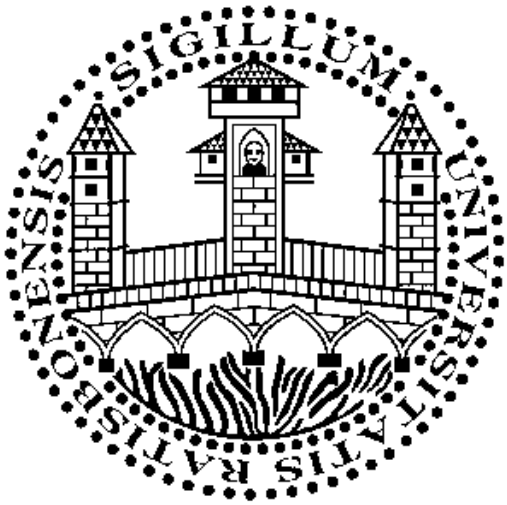
Stereoselective synthesis of biologically relevant dihydropyridines and pyrans via ring-expansion of monocyclopropanated heterocycles



Dissertation

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Meiner Familie

und

Jonas

TABLE OF CONTENT

Abkürzungsverzeichnis

Ac	acetate
acac	acetylacetone
AcOH	acetic acid
AIBN	Azobisisobutyronitrile
Ar	aryl
BDNF	brain derived neurotrophic factor
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
BnOH	benzyl alcohol
brsm.	based in recovered starting material
^{t}Bu	*tert*-butyl
Bz	benzyl
CDI	carbonyldiimidazol
^{13}C-NMR	carbon NMR
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo-[5.4.0]undec-7-en
DCC	N-N‘-dicyclohexyl-carbodiimide
DCM	dichloromethane
DFT	Density functional theory
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPP-4	dipeptidylpeptidase 4
dr	diasteromeric ratio
E	electrophile
EA	ethyl acetate
ee	enantiomeric eccess
e.g.	for example
equiv	equivalents
Et	ethyl
et al.	and others (co-authors)
EtOH	ethanol
EWG	electron weak group
GABA	γ-Aminobutyric acid
h	hour(s)
Hal	halogen
^{1}H-NMR	proton NMR
HPLC	high performance liquid chromatography
HRMS	high resolution mass
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
i.e.	“id est”
LA	Lewis acid
LED	light emitting diods
LG	leaving group
LRMS	low resolution mass
λ_{max}	max. UV-vis wavelength
M	molar (moles per liter)

*m*CPBA	*meta*-chlorperbenzoic acid
MDA	3,4-Methylenedi-oxyamphetamine
Me	methyl
MeCN	acetonitrile
MHz	Megahertz
MeOH	methanol
MOM	methoxymethyl acetal
Ms	mesyl
MW	microwave irradiation
2D-NMR	2-dimensional nuclear magnetic resonance
NAS	*N*-acetylserotonin
NBS	*N*-Bromsuccinimide
*n*Bu	*n*-butyl
n-BuOH	*n*-butanol
n.d.	not dertermined
NEt_3	triethylamine
NGF	nerve groth factor
NIS	*N*-Iodsuccinimide
NMR	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
PAF	platelet-activation factor
Pg	protecting group
Ph	phenyl
ppm	parts per million
^{i}Pr	*iso*-propyl
^{i}PrOH	*iso*-propanol
PTAB	phenyltrimethyl-ammonium
p-TsOH	*para*-toluenesulfonic acid
R	arbitrary residue
rac	racemic
TBAB	tetra-*n*-butylammonium bromide
TBDMS	*tert*-butyyldimethylsilyl ether
TBS	*tert*-butyldimethylsilyl ether
TCPTTL	tetrakis[*N*-tetrachloro-phthaloyl-(*S*)-*tert*-leucinate
rt	room temperature
t	time
T	temperature
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl ether
TPCP	tetrakis((*S*,*R*)-1-(4-phe-nyl(phenyl))-2,2-diphenylcyclopropane-carboxylate
Ts	tosyl
TS	transition state
X	heteroatom

1 Introduction

1.1 The importance of six-membered heterocycles in physiological systems and natural products

Six-membered heterocyclic systems are a key structural motif in a vast amount of different physiologically active compounds.[1] For instance, piperidine and pyran derivatives can be found in various natural products and drug targets or are commonly used as pharmaceuticals for the treatment of different diseases.[2] A selection of representative *N*- and *O*-heterocyclic drug targets and natural products is presented (Figure 1).

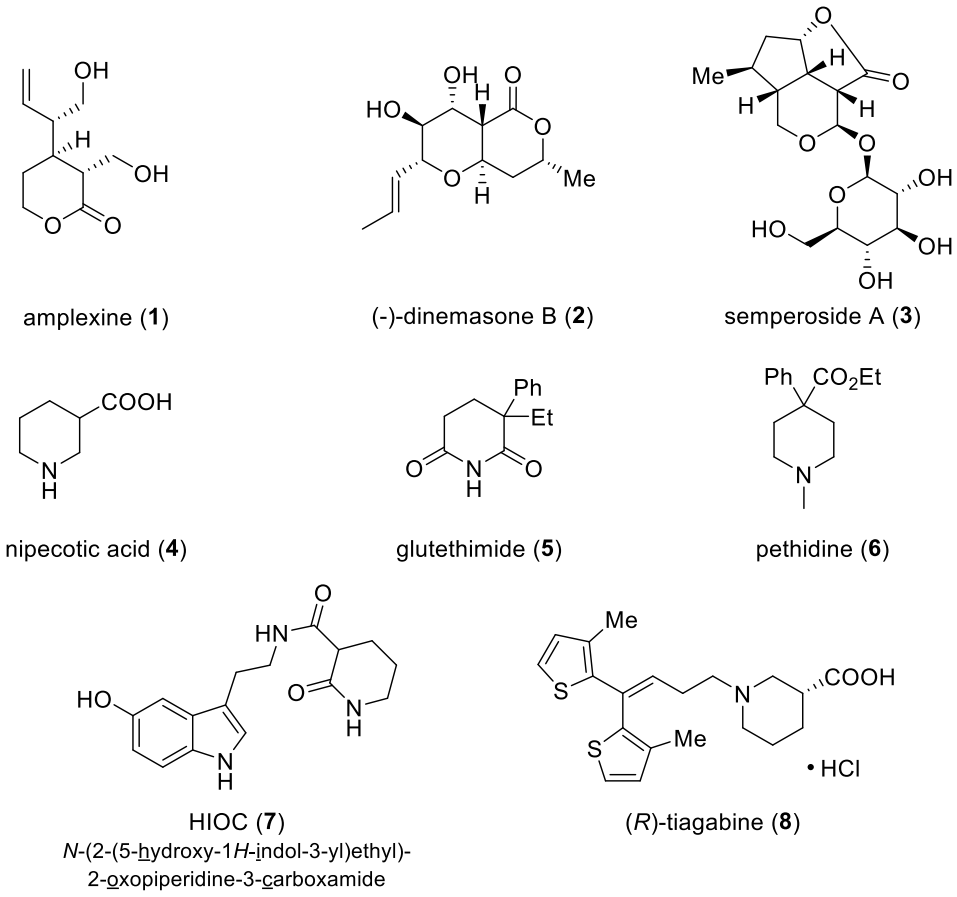


Figure 1. Important representatives of pyran and piperidine containing drug targets and natural products.

Likewise, pyrans are key constituents in natural products and display various biological activities. Amplexine (**1**) which was isolated from *tachia grandiflora* showed potential

antimalarial and anticancer activities.[3] Furthermore, it was found that (-)-Dinemasone B (**2**) is a natural antibiotic that was isolated from fungus *dinemasporium strigosum* and showed antibacterial, antifungal, and anti-algae activities.[4] Finally, semperoside A (**3**) belongs to the class of iridoide glycosides which are characterized by a cyclopenta[*c*]pyran core and was isolated from *gelsemium sempervirens*.[5] Besides pyran based natural products, the piperidine core structure is found in various biologically active compounds and drug targets. Nipecotic acid (**4**), being a potent inhibitor of neural and glial gamma-aminobutyric acid (GABA) uptake, is widely used in scientific research.[6] Together with (*R*)-tiagabine (**8**), which is a nipecotic acid (**1**) derivative being able to cross the blood-brain barrier due to its lipophilic anchor, it is involved in the treatment of epilepsy.[7,8] The latter specifically inhibits the uptake of said neurotransmitter GABA into astrocytes and neurons and generally does not interfere with other antiepileptic drugs making **8** relevant for add-on therapy.[9] Glutethimide (**5**) which belongs to the class of sedatives is an alternative to barbiturates.[10] It was found that **5** is involved in the adrenal secretion of both cortisol and aldosterone triggering a metabolic pathway ultimately resulting in some lowering of blood pressure.[11] Furthermore, pethidine (**6**) is known as an analgesic which was also used as premedication in anesthesia.[12,13] Finally, the *N*-acetylserotonin derivative *N*-[2-(5-hydroxy-1*H*-indl-3-yl)ethyl]-2-oxopiperidine-3-carboxamide (HIOC, **7**) acts as a selective TrkB receptor agonist and is a lead compound for the development of novel neuroprotectants for neurodegenerative disease treatment, e. g. Alzheimer's.[14–17]

Due to their wide range of application in the synthesis of drug targets and natural products, establishing new methods which provide highly functionalized piperidine and pyran derivatives affordably and straightforwardly is imperative. Especially for the synthesis of new pethidine (**6**), tiagabine (**8**), and HIOC (**7**) analogs a pool of highly functionalized piperidine and pyrans can contribute to the progress in the development of those drug targets. Despite much success, the piperidine and pyran structure motif remains a demanding challenge for organic synthesis, especially, due to the scarcity of *ex-chiral* pool precursors.[18] An excellent setup for the synthesis of required highly functionalized piperidines and pyrans *via* a stereoselective ring-expansion is offered by monocyclopropanated furans and pyrroles but only a few examples are reported until today.

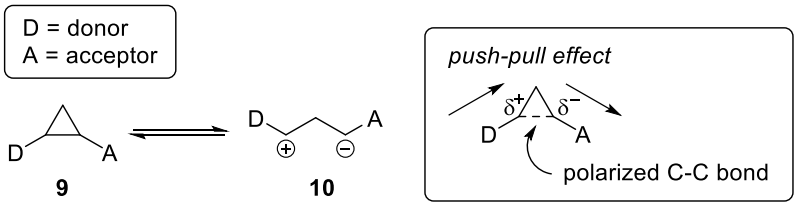
To establish new methodologies for the ring-expansion of monocyclopropanated heterocycles the particular reactivity of donor-acceptor substituted cyclopropane

derivatives has to be examined carefully. In general, donor-acceptor cyclopropane derivatives can be accomplished by several efficient and often enantioselective procedures and have emerged as important intermediates for the synthesis of complex molecules *via* selective cyclopropane ring-opening.[19] Typical reactions that involve donor-acceptor substituted cyclopropane derivatives are reactions with nucleophiles or electrophiles, rearrangements, and cycloadditions.[20,21,22] Manipulations of donor-acceptor cyclopropanated heterocycles, especially in five- and six-membered ring-systems can be categorized into two main types of reactions: the selective cleavage of the exo- or the endocyclic cyclopropane carbon-carbon bond. In the following an overview of important advantages in the selective cleavage of exo- and endocyclic cyclopropane carbon-carbon bonds in monocyclopropanated five- and six-membered heterocycles are presented and their role in natural product synthesis and drug design is emphasized.

1.2 Selective carbon-carbon bond cleavages in donor-acceptor cyclopropanes

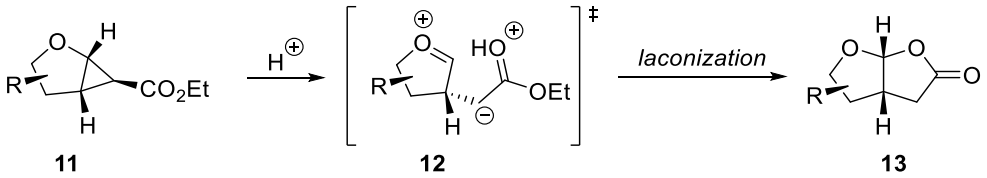
1.2.1 Exocyclic carbon-carbon bond cleavage in monocyclopropanated heterocycles

The unique structure motif of cyclopropanes is ubiquitous and various natural products contain this three-membered carbocycle as a subunit.[23] Also in modern organic chemistry cyclopropanes, especially donor-acceptor substituted cyclopropanes, are widely utilized due to their special reactivity.[24] In comparison to typical carbon-carbon bonds, the one between the donor- and acceptor substituted carbon atom can be cleaved heterolytically.[25,26] The resulting negative charge is stabilized by the acceptor while the positive charge is stabilized by the donor which enables various transformations (Scheme 1).[18,20,25,27]



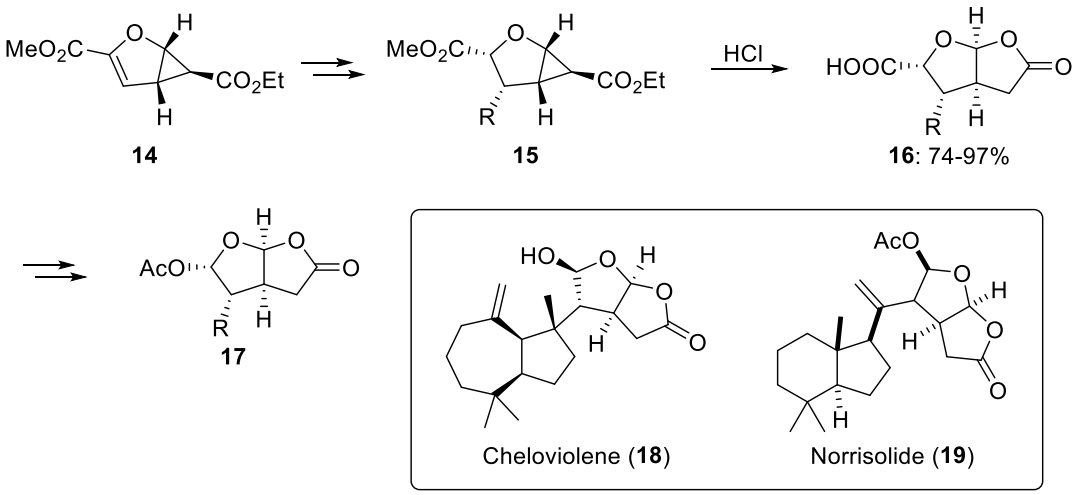
Scheme 1. Heterolytic carbon-carbon bond cleavage in donor-acceptor substituted cyclopropanes **9**.[24]

Formerly underinvestigated donors and acceptors are nowadays utilized in current research and offer additional possibilities for enantioselective transformations.[24,28] Thus, the selective exocyclic ring-opening in monocyclopropanated heterocycles became an important tool in the total synthesis of various natural products. One of the most powerful methods is an acid-induced exocyclic ring-opening which was utilized by Kim *et al.*[29] to access fused tetrahydrofuran-γ-lactones. They showed that the selective exocyclic cyclopropane bond cleavage in substrates of type **11** was possible *via* an acid-mediated pathway. Activation of the ester moiety triggered an exocyclic carbon-carbon bond cleavage and a subsequent lactonization which resulted in bicyclic substrate **13**. (Scheme 2).[29]



Scheme 2. Proposed mechanism of the acid-induced exocyclic ring-opening lactonization of furan derivatives **11**.[29]

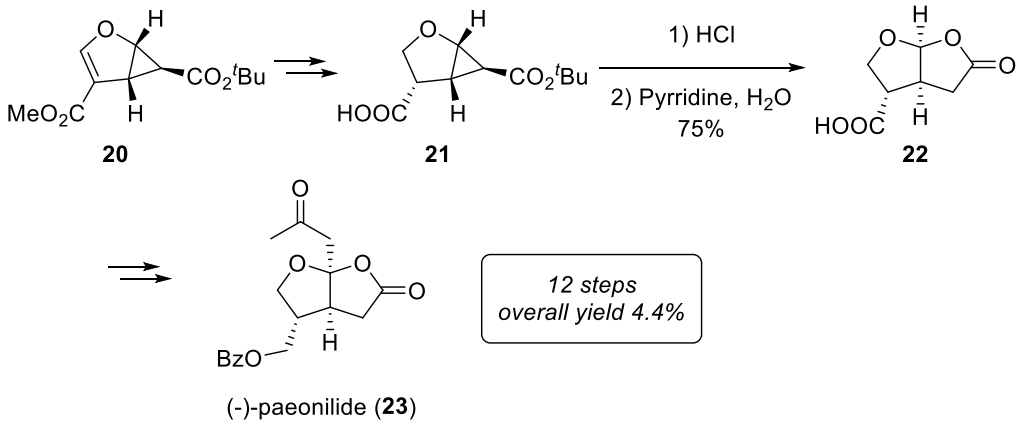
Our group utilized this acid-mediated exocyclic carbon-carbon bond cleavage to access configurationally pure 5-oxofuro[2,3-b]-furans **17** starting from cyclopropanated furan derivative **14**. The structure motif of **17** was found in various natural products such as spongiane diterpenoid Cheloviolene (**18**) or Norrisolide (**19)**. The total synthesis of the latter was published by Granger *et al.* and follows a similar pathway (Scheme 3).[30–32]



Scheme 3. Synthesis of the 5-oxofuro[2,3-b]-furan framework **17** being present in various natural products such as Cheloviolene (**18**) and Norrisolide (**19**); R = H, Aryl, Alkyl.[30,31]

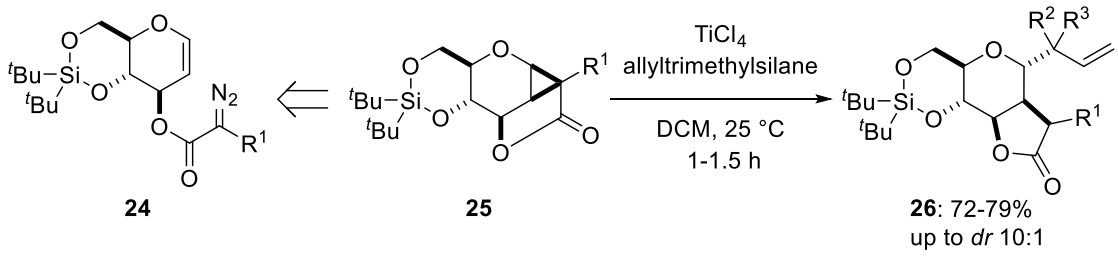
A similar approach was used by our group to synthesize the unnatural enantiomer **23** of (+)-paeonilide (Scheme 4).[33] The monoterpenoid (+)-paeonilide, which was isolated from *Paeonia delavayi* belonging to the class of ginkgolides, showed selective inhibition of the platelet aggregation induced by PAF (platelet-activating factor) with an IC_{50} value of 8 µg mL^{-1}.[34] Starting from 3-furoic acid the synthesis of the unnatural enantiomer **23** was achieved within 12 steps involving the acid-induced exocyclic ring-opening lactonization as a crucial step in an overall yield of 4.4%. Unfortunately,

biological testings revealed the inactivity of **23** against the PAF receptor which highlights the unique character of (+)-paeonilide (Scheme 4).[33]



Scheme 4. Total synthesis of (-)-paeonilide (**23**) within 12 steps and an overall yield of 4.4%.[33]

In addition to the Brønsted acid-mediated pathway, it is known that also Lewis acids can mediate the exocyclic carbon-carbon bond cleavage in donor-acceptor cyclopropanated heterocycles. Yu *et al.* described a direct stereoselective allylation of dihydropyran-derived donor-acceptor cyclopropanes with allylsilanes and stannanes.[35] The required starting materials **25** were provided by copper-catalyzed intramolecular cyclopropanation of glycal derived diazoacetates **24** (Scheme 5).[36]

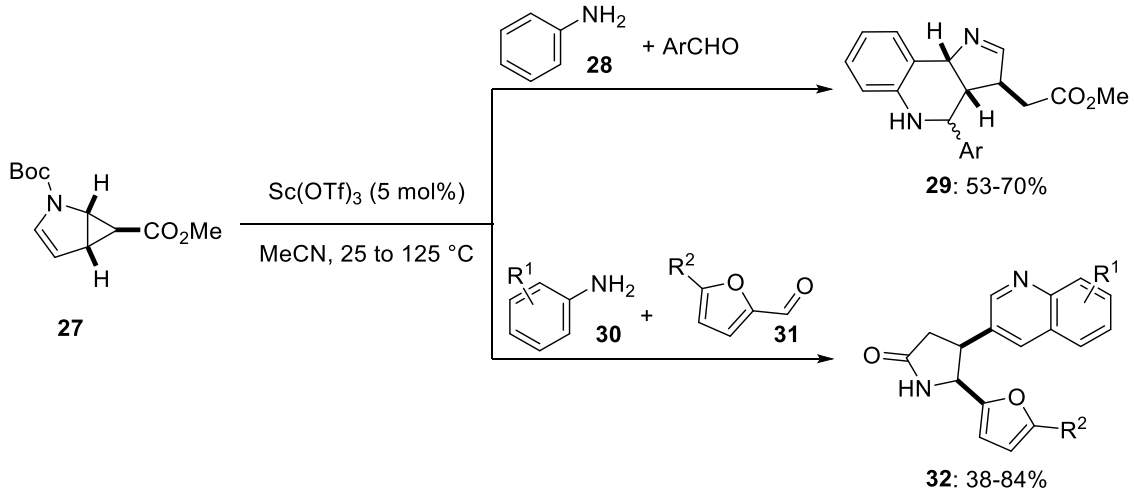


Scheme 5. Lewis-acid mediated allylation of glycal-derived donor-acceptor cyclopropanes **25**; only the major diastereomere **26** is shown; R^1 = H, SiMe, SiVinyl; R^2 = H, Me; R^3 = H, Me.[35,36]

In complete analogy to the described Brønsted-acid activation, the selective exocyclic ring-opening was achieved with $TiCl_4$ as Lewis acid which gave access to tricyclic systems **26** in good yield after trapping the intermediate with various substituted

allyltrimethylsilanes. This methodology contributed to the synthesis of C(2)-branched sugars which are potent glucosidase inhibitors.[37]

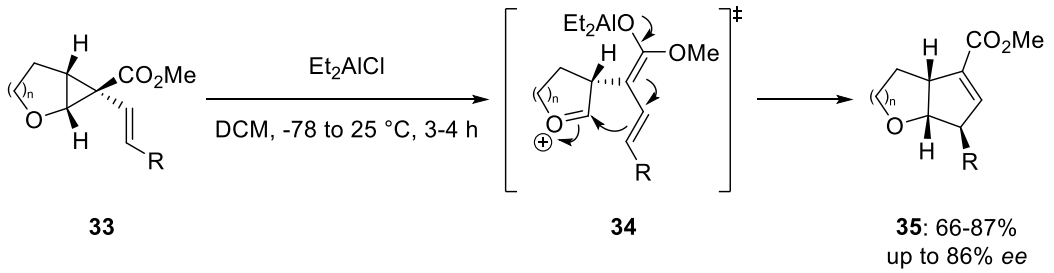
Furthermore, the powerful Lewis acid mediated exocyclic ring-opening in donor-acceptor cyclopropanes was also applied to the synthesis of tricyclic imines **29** or pyrrolidones **32**. A multicomponent approach for their synthesis starting from cyclopropanated *N*-Boc pyrrole derivative **27** was published by our group (Scheme 6).[38]



Scheme 6. A multicomponent approach for the synthesis of tricyclic imines **29** and *cis*-substituted pyrrolidones **32**.[38]

The selective exocyclic bond cleavage in **27** was the initiation step for a subsequent Povarov reaction,[39] a cycloaddition with *in situ* generated aldimines which resulted in tricyclic imines **29** in yields up to 70% or in the stereoselective formation of biologically interesting pyrrolidones **32** in comparable yields if furfural derivatives **31** were applied.

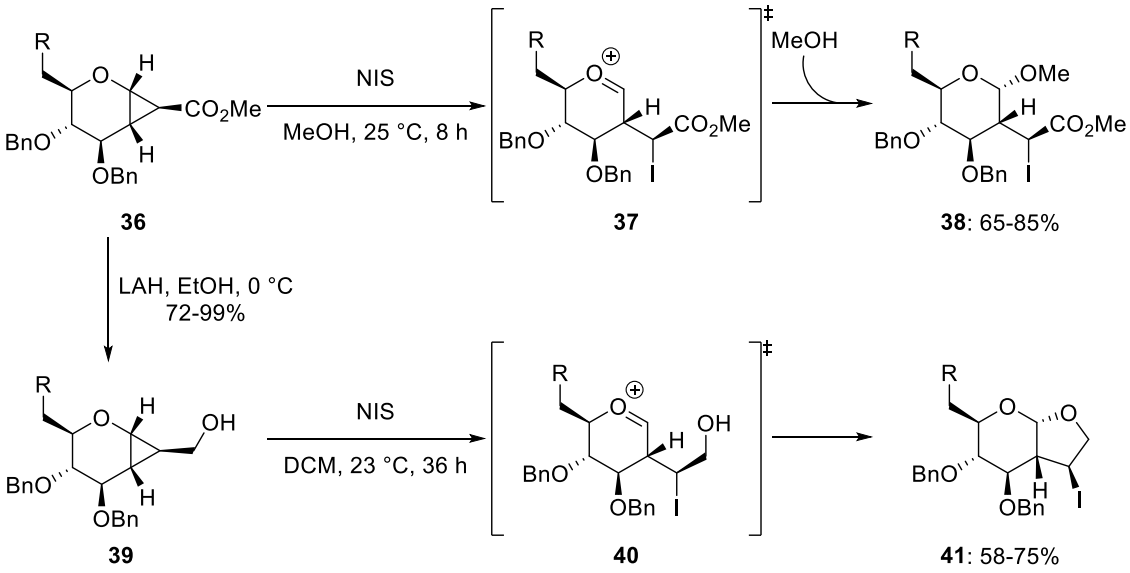
Besides the Lewis acid induced Povarov cycloaddition, it is known that Lewis acids can also mediate intramolecular cycloadditions in donor-acceptor cyclopropanes.[40] Especially for cycloadditions in vinyl cyclopropanes **33** towards fused cyclopentanoid terpenes, it turned out to be a powerful tool. Similar to the Povarov cycloaddition, the key step is the selective exocyclic cyclopropane bond cleavage which is initiated by Et_2AlCl as Lewis acid and is followed by a subsequent cyclization which gives fused cyclopentanes **35** up to 87% yield. Remarkably, the products were obtained in perfect diastereoselectivity and an enantiomeric excess up to 86% *ee* (Scheme 7).[41]



Scheme 7. Lewis acid induced ring-expansion of donor-acceptor vinylcyclopropanes **33**; R = Ph, Me; n = 1, 2.[41]

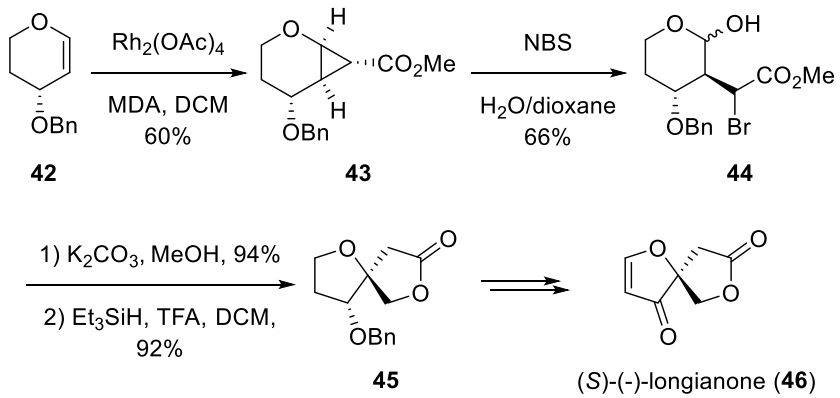
This transformation is interesting for organic chemists since a polycyclic core structure is found in many natural products such as Retigeranic acid, but the dia- and enantioselective synthesis of highly functionalized polycyclic systems is still challenging.[42] Recently, Wu *et al.* successfully extended the scope of the vinyl cyclopropane rearrangement to tetracyclic, pentacyclic, or polycyclic substrates since they were able to improve the Rh(II)-catalyzed cyclopropanation to complex vinyl diazoacetates.[43]

Furthermore, an efficient Rh(II)-catalyzed cyclopropanation of sugar derivative was also the decisive step for the synthesis of perhydrofuro[2,3-b]pyrans **41** or C(2)-branched sugar derivatives **38** being precursors for glycol-amino acids (Scheme 8).[44–46]



Scheme 8. Selective exocyclic ring-opening of 1,2-cyclopropanated sugar derivatives **36**; R = H, OH, OTBDMS, OBn.[45,46]

The key step for the synthesis of the biologically relevant substrates was elegantly solved by offering an electrophile which triggered the exocyclic carbon-carbon bond cleavage to generate the oxonium ion **37** which was subsequently trapped by a nucleophile. In the special case, when the ester moiety in **36** was reduced to the corresponding alcohol a rearrangement to the perhydrofuro[2,3-b]pyrans **41** was observed since the formed oxonium ion **40** was intramolecularily trapped. In both approaches, the products were obtained as single diastereomer and in yields up to 85%.[45–47] In addition to the synthesis of C(2)-branched sugars, this synthetic procedure was applied in the synthesis of unnatural C(2)-amino acid nucleosides.[48] An extension of the approach to the synthesis of sugar fused γ-butyro-lactones by applying NBS in an aqueous solution was published recently in literature.[49] Remarkably, this improvement allowed the total synthesis of (*S*)-(-)-longianone (**46**) which was found as a bacterial metabolite in *Pseudomonas syringae* (Scheme 9).[50]

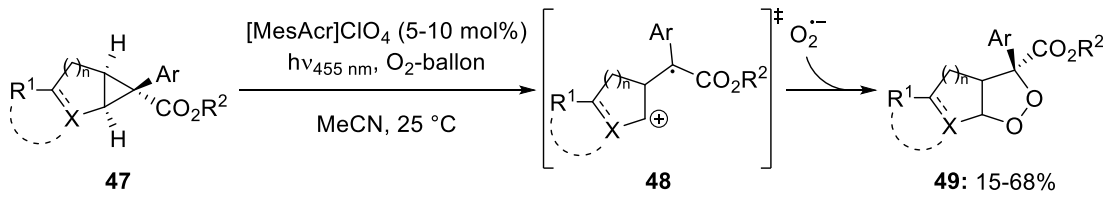


Scheme 9. Synthesis of (*S*)-(-)-longianone (**46**) *via* an NBS mediated pathway.[50]

The main difference to previous work was the use of NBS in an aqueous solution to achieve the ring-opening which resulted in semi-acetal **44.** After treating the semi-acetal **44** with K_2CO_3, a spiro-cyclization was observed which finally allowed the synthesis of (*S*)-(-)longianone (**46**).

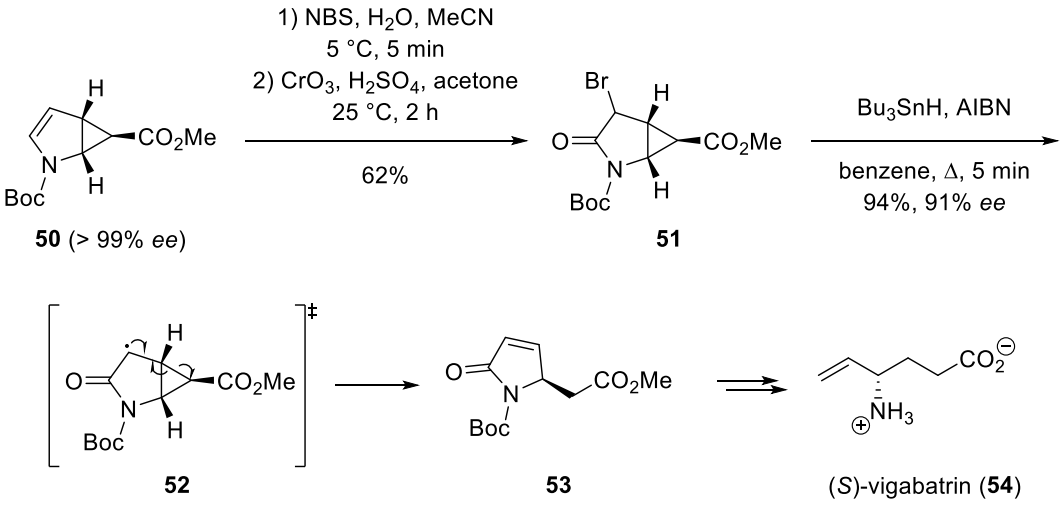
In contrast to the initiation of the exocyclic bond cleavage *via* activation of the ester moiety or offering an electrophile, it was also possible to perform a photooxidation resulting in cyclic endoperoxides **49**. Pioneering work in acyclic systems was done by Yoon *et al.* and was improved by our group to structurally complex fused hetero- and

carbocycles with [MesAcr]ClO_4 as the catalyst which gave access to endoperoxides **49** (Scheme 10).[51,52]



Scheme 10. Visible light mediated oxidative ring-expansion of anellated cyclopropanes **47** to fused endoperoxides **49**; X = CH, O, NR; R^1 = H, Aryl, Alkyl; R^2 = Me, Octyl.[52]

Photooxidation of the aryl-group in **47** initiated the exocyclic bond cleavage which resulted in radical cation **48**. The cation was stabilized by the neighboring heteroatom or π-system whereas the radical was stabilized by the push-pull interaction between the ester and aryl group. Intermediate **48** was trapped by $O_2^{\cdot -}$ which resulted in endoperoxides **49** in good yield after radical-recombination. Additionally, various functional groups were tolerated and the obtained products showed promising biological activities against *Plasmodium falciparum*.[52] Also radical intermediates, especially cyclopropyl methyl radicals,[53] are known to undergo a rapid ring-opening.[54] An elegant example was established by our group in the synthesis of (*S*)-vigabatrin (**54**) starting from cyclopropanated pyrrole **50** (Scheme 11).[22]



Scheme 11. Synthesis of (*S*)-vigabatrin (**54**) starting from **50** *via* a cyclopropyl methyl radical-mediated pathway.[22]

After derivatization of **50**, they obtained the brominated lactam **51** which was radically debrominated resulting in cyclopropyl methyl radical **52**. Radical **52** underwent a smooth exocyclic ring-opening to form **53** in excellent yield and enantioselectivity. After additional steps, unsaturated lactam **53** was successfully converted to (*S*)-vigabatrin (**54**), being an irreversible inhibitor for GABA-T used in the therapy of epilepsy.[22,55]

1.2.2 Ring-expansion of monocyclopropanated heterocycles *via* selective endocyclic carbon-carbon bond cleavage

In contrast to the well established exocyclic carbon-carbon bond cleavage in donor-acceptor cyclopropanated heterocycles, the selective cleavage of the endocyclic carbon-carbon bond remains challenging.[56] The presented examples for the exocyclic ring-opening implicates already that the endocyclic bond cleavage is the less favored reaction if donor-acceptor substituted monocyclopropanated heterocycles are concerned. To circumvent this problem and to achieve an endocyclic bond cleavage, a reversed electron flow in **55** has to be generated to polarize the endocyclic carbon-carbon bond which gives access to substrates of type **56** (Figure 2).

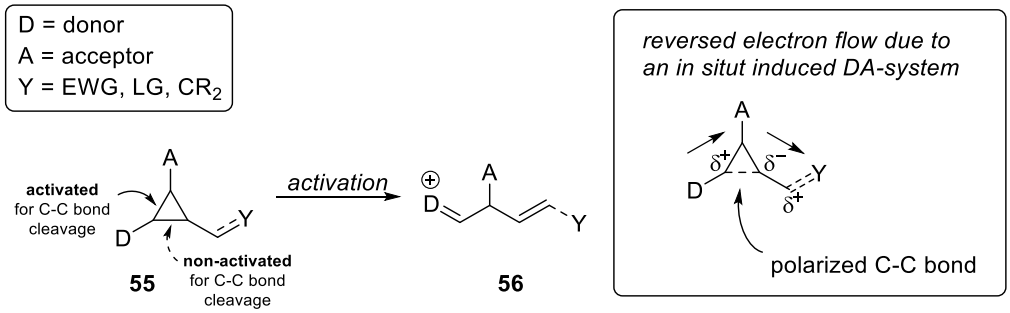
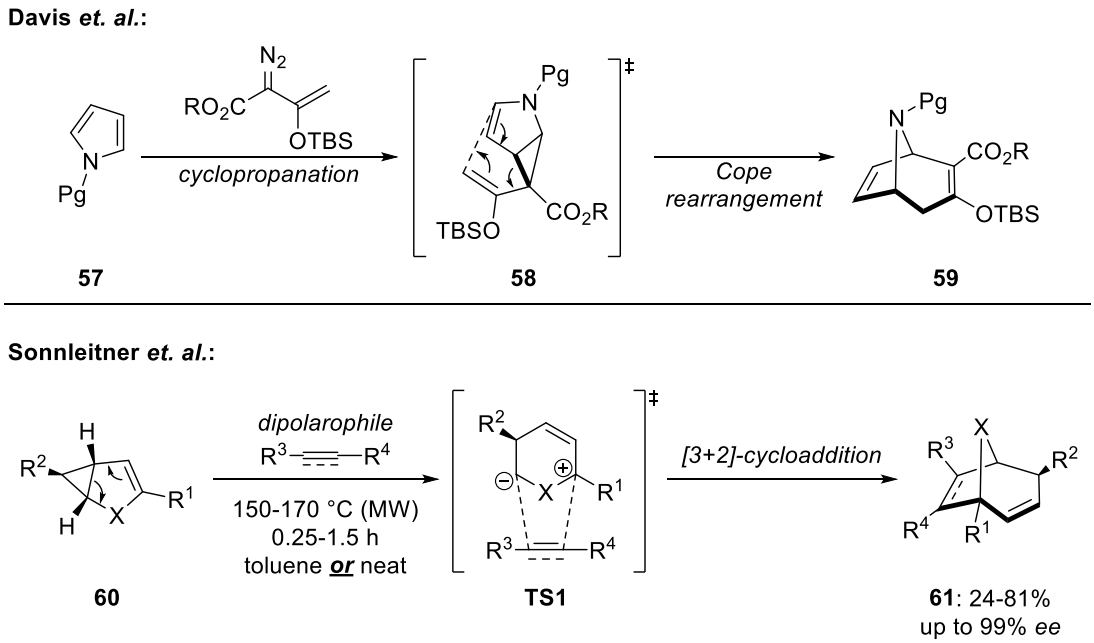


Figure 2. *In situ* induced donor-acceptor system (DA-system) by different activation methods to achieve a reversed electron flow and to access a selective cleavage of the non-activated carbon-carbon; EWG = electron weak group; LG = leaving group.

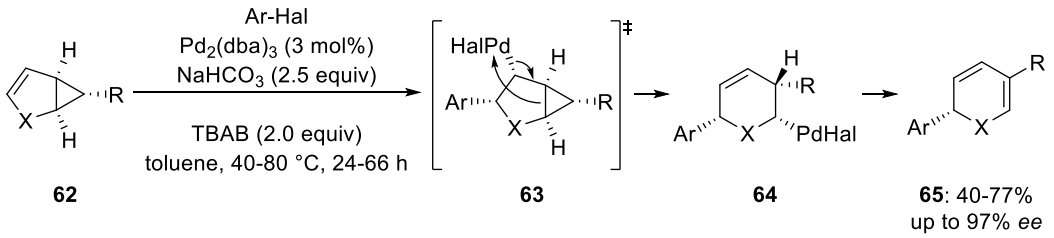
In literature, only a few opportunities for the polarization of this non-activated carbon-carbon bond in monocyclopropanated systems are known. An elegant example for the application of the endocyclic bond cleavage is the synthesis of tropane derivatives. The initial work for this approach was done in the 1970s by Fowler and co-workers. They reported that homopyrrole can undergo cycloadditions under thermal activation with suitable dipolarophiles to form bicyclic seven-membered ring systems.[57] After improvement of the initial methodology to homofuran by Herges and Ugi,[58] mechanistic studies by Klärner[59] and Yu[60] revealed a possible reaction mechanism. Finally, this type of ring-expansion was utilized by Davies *et al.* and our group for the synthesis of tropanes starting from readily available cyclopropanated pyrroles and furans (Scheme 12).[61–66],[67]



Scheme 12. Stereoselective synthesis of tropanes **59** or **61** starting from monocyclopropanated heterocycles **58** or **60**.[61–66],[67]

Even if both approaches gave access to tropane derivatives, the main difference is the generation of the tropane core. Davies *et al.* utilized a Cope-rearrangement of vinyl cyclopropanes **58** *via* an exocyclic cyclopropane bond-cleavage while our group achieved the tropane systems *via* a [3+2]-cycloaddition. Within a short sequence we were able to stereoselectively synthesize an oxo- and aza-bicyclo-[3.2.1] and [2.2.2]-scaffold **61** which was found to be highly relevant for natural products and drug targets such as atropine, scopolamine, or (*R*)-(-)-cocaine. As a key step, a 1,3-dipole in **TS1** was generated under microwave-irradiation by a retro-electrocyclic 6π-ring-opening of monocyclopropanated furans and pyrroles **60** which was efficiently trapped by various dipolarophiles to receive bridged seven-membered ring-systems **61** up to 81% yield in perfect enantioselectivity.[61–66],[67]

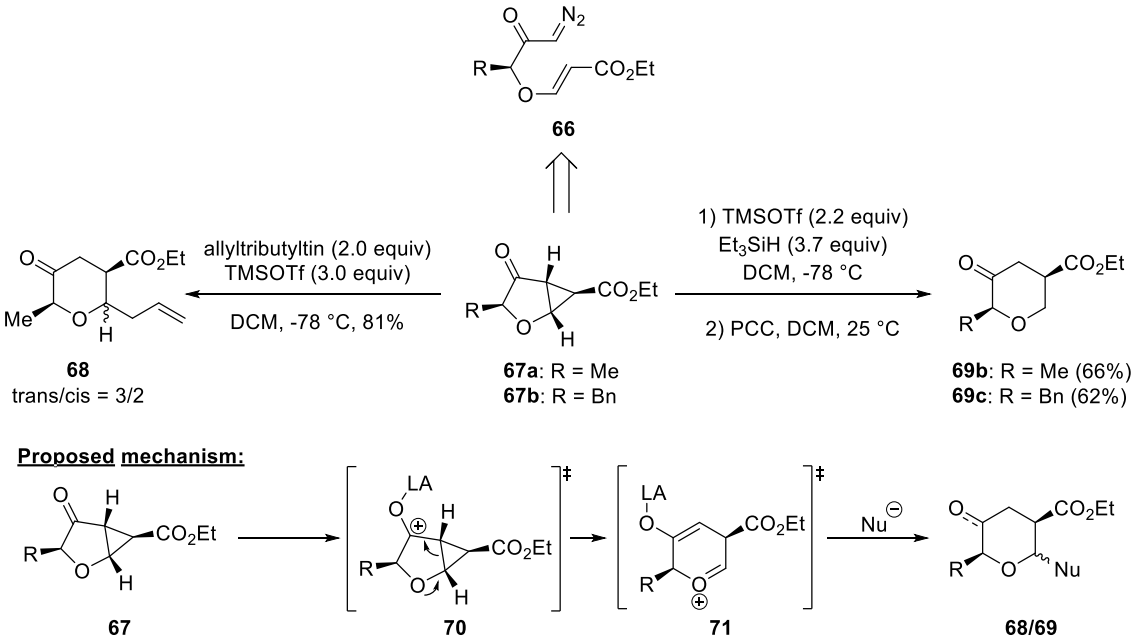
Besides the microwave-assisted [3+2]-cycloaddition, our group also found that a palladium-catalyzed Heck cross-coupling of monocyclopropanated heterocycles with aryl halides is a possibility to access a ring-expansion in **62** *via* selective cleavage of the non-activated endocyclic carbon-carbon bond (Scheme 13).[56]



Scheme 13. Regio- and stereoselective synthesis of functionalized six-membered heterocycles **65** *via* Heck coupling of monocyclopropanated furans and pyrroles **62**; X = O, NBoc; R = CO_2Me, CO_2Et, $CO_2{}^tBu$, CH_2OH; Hal = Br, I; used reagents for X = O: $Pd(OAc)_2$ (5 mol%), KOAc (2.5 equiv). [56]

It is well known that migration of PdHal can induce a ring-opening in vinyl cyclopropane derivatives.[68] This particular methodology was utilized to access the ring expansion of monocyclopropanated furans and pyrroles **62**. After oxidative addition of the PdAr to the remaining double bond in **62**, migration of PdHal was observed which induced the cleavage of the endocyclic cyclopropane bond and formed six-membered heterocycles **65** in good yield and perfect enantioselectivity.[56]

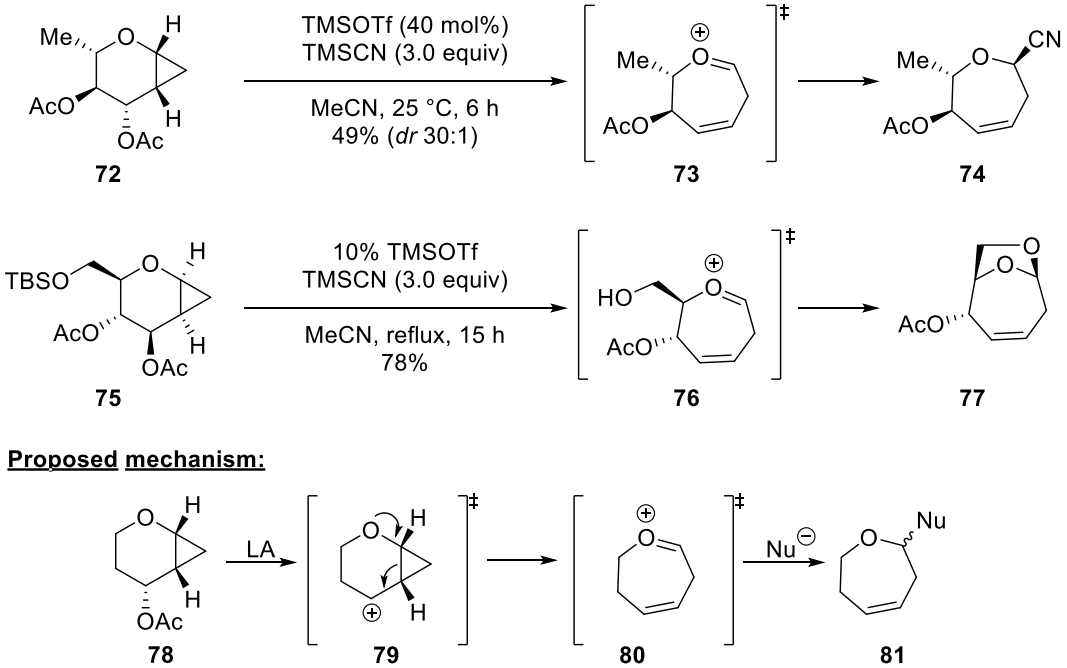
Furthermore, a ring-expansion can also be achieved by activation of cyclopropafuranones **67** with lewis-acids which was established by Gharpure and coworkers. They showed, that pyrans **68** or **69** were synthesized *via* lewis acid activation of the ketone moiety in **67** which results in the endocyclic cyclopropane bond cleavage (Scheme 14).[69]



Scheme 14. Lewis acid mediated ring-opening of cyclopropafuranons **67** established by Gharpure and co-workers.[69]

They achieved the opening with TMSOTf as lewis-acid which resulted in an *in situ* generated cyclopropylmethyl cation type intermediate **70** which triggered the selective endocyclic carbon-carbon bond cleavage. The resulting oxonium ion **71** was immediately trapped by a nucleophile giving pyran **68** or **69** in good yield. The required starting material **67** was obtained by intramolecular cyclopropanation of enantiopure lactic acid with $Cu(acac)_2$ as the catalyst. Notably, it was shown that the initial stereochemistry was successfully transferred to the product **69** if triethyl silane was used as the nucleophile. In contrast, nucleophilic trapping with allyltributyltin provided pyran **68** as a diastereomeric mixture (*dr* 1.5:1). Sridhar *et al.* a few years later made use of this method to achieve *in situ* glycosylation of unnatural sugar derivatives.[70]

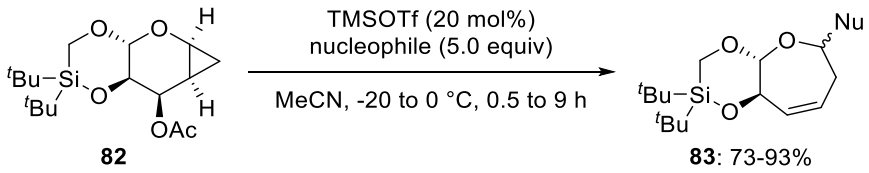
This type of Lewis acid induced ring-expansion of monocyclopropanated heterocycles was also applied in the synthesis of oxepanes.[71] Until the beginning of the 1990's only a few was known about the synthesis of oxepanes from carbohydrate-derived cyclopropanes.[72] In the mid-1990's Hoberg and coworkers investigated the first facile method for the ring-expansion of carbohydrate-derived cyclopropanes to access highly functionalized oxepanes (Scheme 15).[73]



Scheme 15. Synthesis of oxepanes **74** and **77** *via* a lewis-acid mediated ring-expansion of sugar derived monocyclopropanated heterocycles.[73]

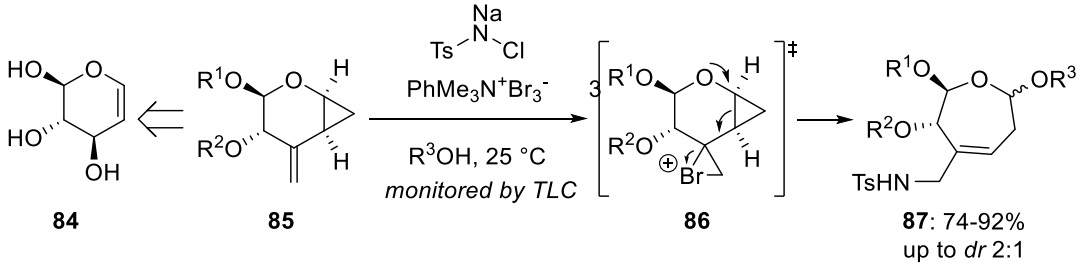
They were able to perform the cleavage of the endocyclic carbon-carbon bond by Lewis acid activation and abstraction of the acetal group in **72** to afford a cationic intermediate of type **79** which was supposed to rearrange to oxonium ion **73**. Nucleophilic trapping with TMSCN afforded oxepane **74** in 49% yield with good diastereoselectivity if precursor **72** was applied. Remarkably, when cyclopropanated pyran **75** was treated with TMSOTf, intramolecular trapping of the oxonium ion **76** was observed yielding the bridged oxepane **77** in 79% yield as a single compound. It was successfully demonstrated that the skeleton of naturally occurring seven-membered ring systems can be provided in good yield and perfect diastereoselectivity.[73,74]

Further research by Hoberg *et al.* allowed the expansion of the scope by applying various silanes as nucleophiles while readily available glycal-derived cyclopropane **82** served as a model substrate to afford oxepanes **83** in excellent yield (Scheme 16).[75,76]



Scheme 16. Expanded scope of the lewis-acid mediate oxepane synthesis established by Hoberg and co-workers; Nu = TMSR, Et_3SiH, TMS-alkyl, TBS-enolate.[75]

Latest research showed that *in situ* generated donor-acceptor cyclopropanes can also be generated by transformations of the carbon-carbon double bond in vinyl cyclopropanes. Ganesh *et al.* introduced an exo-methylene group in sugar-derived cyclopropanes which gave access to the corresponding seven-membered ring-systems **86** (Scheme 17).[77]



Scheme 17. A facile approach to oxepanes **87** *via* a **σ**-Ferrier rearrangement of carbohydrate derived vinylcyclopropanes **85**; R^1 = TBS, alkyl; R^2 = Bn, alkyl; R^3 = Me, ^{n}Bu, ^{i}Pr.[77]

The required precursor **85** was obtained after a cascade of OH-protection, cyclopropanation, oxidation, and Wittig-reaction starting from **84**. Treating **85** with chloramine T and phenyltrimethylammonium tribromide (PTAB, $PhMe_3N^+Br_3^-$) in the respective alcohol gave access to highly functionalized oxepane **87**. Formation of the interhalogen compound TsN^-Br^+ by the reaction of chloramine-T and PTAB enabled the electrophilic addition of Br^+ to the vinyl cyclopropane **85** resulting in bromonium ion related intermediate **86**. Opening of the bromonium ion **86** the ring-expansion was achieved *via* a σ-Ferrier rearrangement resulting in a seven-membered oxonium ion. The cationic intermediate was trapped by the alcohol giving highly functionalized oxepanes **87** up to 92% as diastereomeric mixtures.[77]

With recent advances made in the selective transformation of donor-acceptor substituted monocyclopropanated heterocycles, this research area appears to get exciting in future. There are abundant methods for the synthesis of monocyclopropanated heterocycles starting from readily available substrates. Until now, it was successfully demonstrated that the exocyclic cyclopropane bond cleavage is a powerful tool for the diastereo- and enantioselective synthesis of natural products or biologically relevant substrates. The exocyclic opening was achieved *via* Brønsted- or lewis-acid mediated, NIS or NBS induced, photooxidative or radical pathways. In contrast, the ring-expansion of donor-acceptor substituted monocyclopropanated heterocycles *via* the selective endocyclic carbon-carbon bond cleavage is rather challenging since the exocyclic ring-opening is the categorically favored transformation. To get access to the ring-expansion an *in situ* generated donor-acceptor cyclopropane has to be utilized which was achieved by a microwave-assisted, lewis-acid mediated, Pd-catalyzed or bromonium ion induced pathway until today. Even if promising methods were reported, the selective ring-expansion of monocyclopropanated heterocycles, however, has yet to be developed to its fullest extent, and the application to natural products and drug targets is in early stages. Thus, with the ease of access to these molecules, new developments and uses should be possible in the future.

2 Main Part

2.1 Stereoselective ring-expansion of monocyclopropanated heterocycles

2.1.1 Cyclopropylcarbinyl cation as key intermediate in the stereoselective ring-expansion of cyclopropane derivatives

Among carbocationic systems, the cyclopropylcarbinyl cation **88** which is the most extensively investigated carbon derived cation attracted great attention and many prominent chemist contributed to the development of its particular chemistry.[78] Various calculations revealed that the cyclopropylcarbinyl cation **88** can equilibrate with its energetically equal cyclobutyl cation **89** at low temperatures. In contrast, both cations can rearrange irreversibly to the homoallylic cation **91** at elevated temperatures**.** Additionally, nucleophilic trapping experiments showed that a mixture of products **90**, **92** and **93** were obtained which supported the proposed behavior of the cyclopropylmethyl cation **88.** (Scheme 18).[79,80–82]

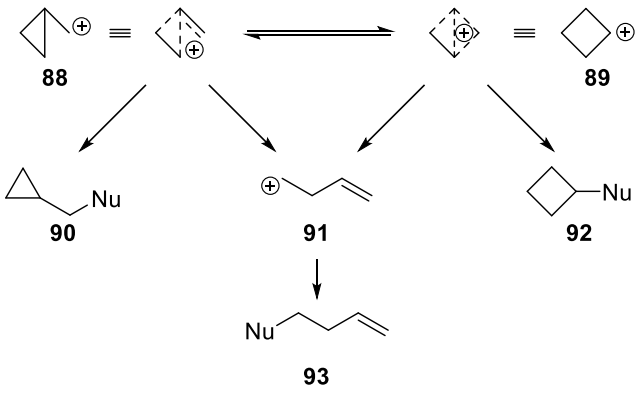
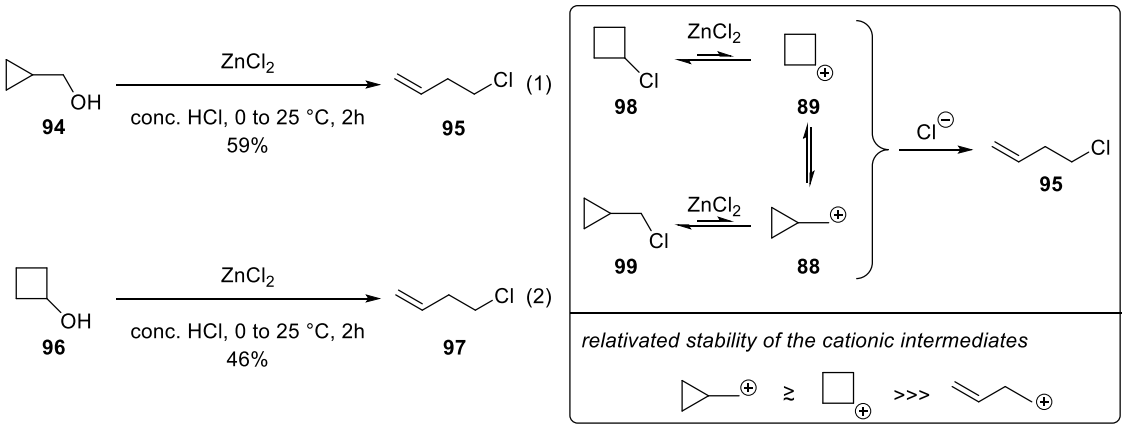


Figure 3. Proposed behavior of the cyclopropylcarbinyl cation **88** and nucleophilic trapping of the formed intermediates.

These calculations and assumptions were experimentally confirmed by Roberts *et al.* by converting the cyclopropylcarbinol **94** and cyclobutanol **96** to the allylcarbinyl chloride **95.** Treating of **98** and **99** with $ZnCl_2$ in concentrated HCl afforded allylcarbinyl chloride **95** in moderate yield. These results were explained by the before mentioned equilibration between cyclopropylcarbinyl cation **88** and cyclobutyl

cation **89** after acid-mediated solvolysis of the starting material which, finally, resulted exclusively in allylcarbinyl chloride **95** (Scheme 18).[83]



Scheme 18. Synthesis of allylcarbinyl chloride **95** starting from cyclopropylcarbinol **94** and cyclobutanol **96** and mechanistic explanation of the allylcarbinyl chloride **95** formation in regard to the relative stability of the cationic intermediates.

Additionally, the transformation of the allylcarbinyl chloride **95** to **98** or **99** was not possible which was explained by the relative stability of the observed intermediates whereas the allylcarbinyl cation **91**, in comparison, is much more stable than **88** and **89**. Until today, utilizing the particular reactivity of the cyclopropylcarbinyl cation **88** has gained a lot of attention in organic chemistry and, besides an Au(I)- or Cu(II)- catalyzed pathway,[81],[84] the method of choice for the generation of the reactive cationic intermediate is the solvolysis of substituted cyclopropylcarbinol derivatives.[80,82,85] An excellent setup for the application of this method is a stereoselective ring-expansion is offered by monocyclopropanated furans and pyrroles **100**. We envisaged that the typically non-activated endocyclic carbon-carbon bond, indeed, can be selectively cleaved if a cyclopropylcarbinyl related cation **101** is generated from **100** (Figure 4).

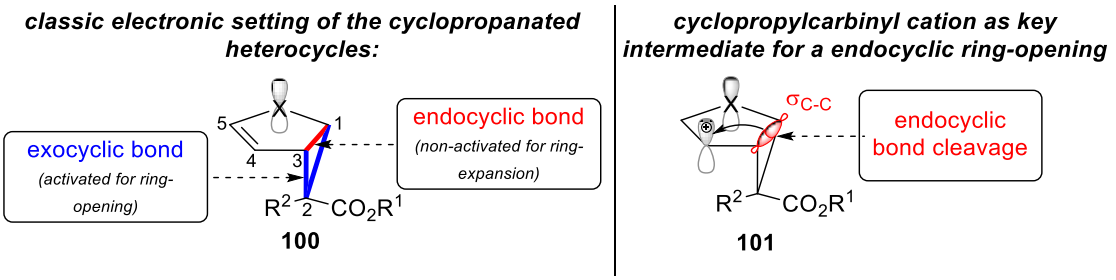
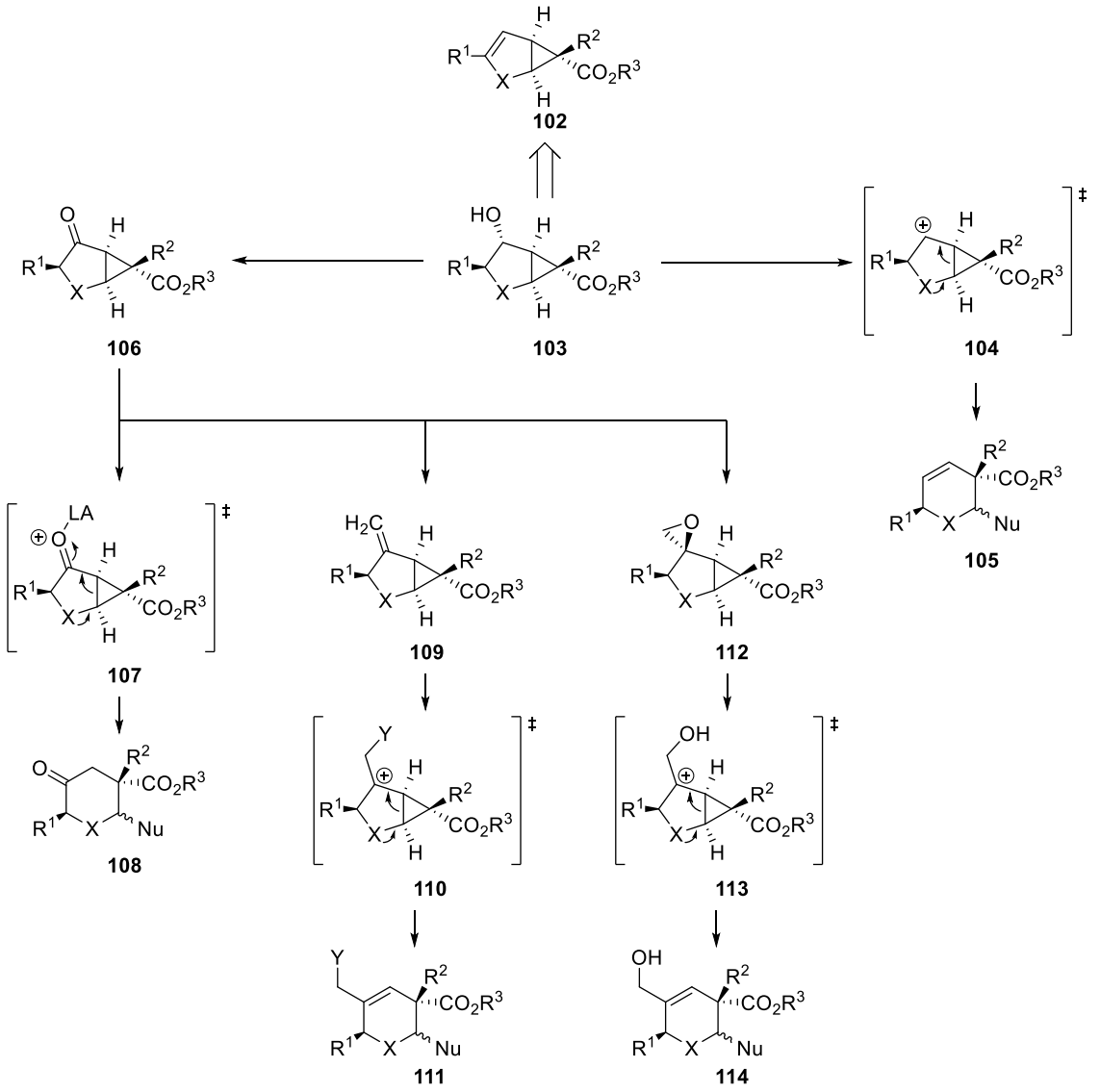


Figure 4. Analysis of the electronic properties in **100** and the envisaged selective endocyclic bond cleavage in **101**.

Cyclopropylcarbinol derivatives **103** which were assumed to be potent precursors in order to generate cyclopropylcarbinyl cations of type **101** can be provided by e.g. a hydroboration of **102**. These starting materials **103** can either be directly applied in the ring-expansion utilizing the solvolytic release of the hydroxy group or, after oxidation to the corresponding ketone **106,** activation of the ketone with lewis acids or ylids can give access to further pathways. Lewis acid activation of ketones **106** results in substrates of type **108,** while the treatment of **106** with phosphorous- or sulfur-ylids enables the synthesis of **109** and **112**. Substrates **109** and **112** are offering the opportunity to achieve a ring-expansion *via* manipulations of the vinylcyclopropane moiety in **109** or the opening of vinylcyclopropane epoxide in **112** (Scheme 19).

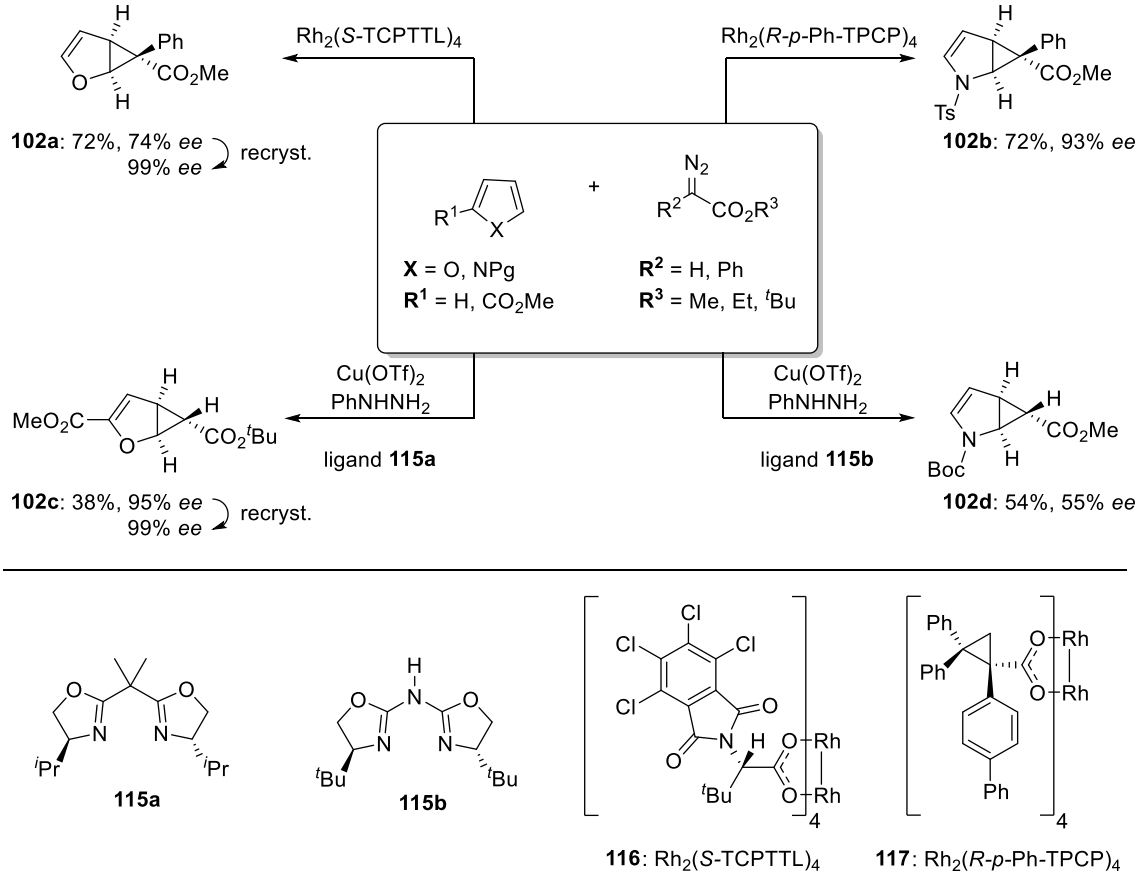


Scheme 19. Potential pathways for the ring-expansion starting from hydroxylated monocyclopropanated furans or pyrroles **103**.

All described pathways are featuring a cyclopropylcarbinyl cation which results in the desired six-membered heterocycles **105**, **108**, **111** and **114** after a selective endocyclic bond cleavage and nucleophilic trapping of the intermediate. Establishing these methods can provide highly functionalized and biologically and pharmaceutically relevant six-membered heterocycles. To explore these potential pathways, the transformation of the monocyclopropanated heterocycles to their corresponding cycloporopylcarbinol derivatives **103**, starting from cyclopropanated furan and pyrrole derivatives **102**, was established first.

2.1.2 Rh(II)- and Cu(I)-catalyzed cyclopropanation of furans and pyrroles

Coal, natural gas and petroleum are known to be the main raw materials for energy production but also for the chemical industry.[86] Today the most promising sources for the synthesis of fine chemicals are renewable resources since fossil resources are extremely limited.[87,88] Indeed, there are methods known making the synthesis of furan derivatives from hemicellulose profitable.[89] These obtained furan and, additionally, pyrrole derivatives are suitable substrates for an asymmetric monocyclopropanation with diazo compounds by e.g. Rh(II)- or Cu(I)-catalysis.[38,87,89,90] This is an extensively explored type of reaction and a selection of relevant monocyclopropanated heterocycles **102** for the investigation of a stereoselective ring-expansion is given in the following (Scheme 20).



Scheme 20. Selected examples for Cu(I)- and Rh(II)-catalyzed cyclopropanation of furan and pyrrole derivatives.[91–94]

Our group found that Cu(I)-complexes with a C2-symmetric chiral bis(oxazoline) **115a** or aza-bis(oxazoline) ligand **115b** turned out to be powerful for the regio- and enantioselective cyclopropanation of furan and pyrrole giving **102c** and **102d** in moderate to excellent enantiomeric excess which could be increased to 99% *ee* in case of furan derivative **102c**.[91,94] A very efficient cyclopropanation of furan with a phenyl diazo compound was published by Lehner *et al.* and Fu *et al.* where they used Rh_2(*S*-TCPTTL) (**116**) or Rh_2(*R*-*p*-Ph-TPCP)$_4$ (**117**) as chiral catalysts. Remarkably, the synthesis was conducted with extremely low catalyst loading and the products **102a** and **102b** were obtained in good enantioselectivity. Additionally, recrystallization of furan based derivative **102a** resulted in 99% *ee*.[92,93]

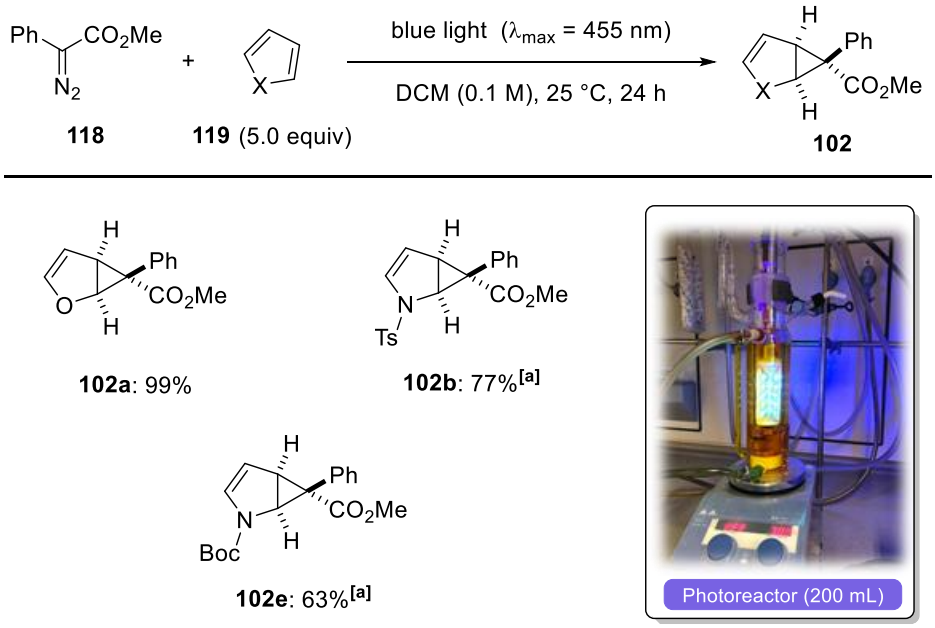
Because of the remarkable regio-, diastereo- and enantioselectivity of the Cu(I)- and Rh(II)-cyclopropanation of furans and pyrroles with various diazo acetates, these substrates served as potent starting materials for the investigation of the stereoselective ring-expansion of monocyclopropanated heterocycles. Additionally, the starting materials for the cyclopropanes were readily available by inexpensive renewable resources making this method environmentally feasible.

2.1.3 Visible light mediated cyclopropanation

In addition to the well explored Cu(I)- and Rh(II)- catalyzed cyclopropanation of heterocycles, Davies *et al.* established an alternative, metal-free procedure for the racemic synthesis of cyclopropanated compounds *via* a photolysis of aryl diazo acetates. They observed that electron rich arenes undergo a selective C-H activation, whereas electron deficient arenes such as *N*-Boc pyrrole are exclusively cyclopropanated with perfect diastereoselectivity (*dr* > 20:1). They proposed, that diazo acetates undergo photolysis by irradiation with blue light (λ_{max} = 460-490 nm) forming a singlet carbene after extrusion of N_2 to afford products of cyclopropanation and O-H, N-H and C-H insertions.[95]

Since the monocyclopropanation of *N*-Boc pyrrole is hardly possible by Cu(I)- or Rh(II)-catalysis due to the favored double cyclopropanation,[96] instead, the required pyrrole derived cyclopropane **102b** was easily provided by the published photochemical

approach. Additionally, it was aimed for an expansion of the published substrate scope to further heteroaromatic substrates including up-scaling experiments (Scheme 21).

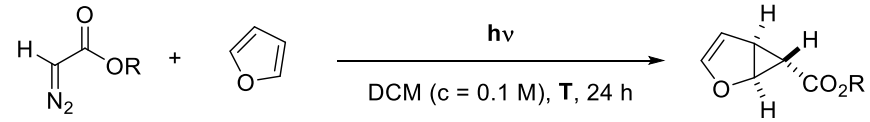


Scheme 21. Visible light mediated cyclopropanation of heterocycles **119**; [a] scale-up: 4.12-28.4 mmol of **118** were applied to yield 1.17 g of **102b** and 5.63 g of **102e**.

In analogy to the published cyclopropanation of *N*-Boc pyrrole, furan was used as starting material and the reaction was conducted at 1 mmol scale affording almost quantitative yield of the desired product **102a**. Due to the successful transformation of furan to the corresponding cyclopropane derivative **102a**, the reaction was up-scaled to 20 mmol using a photoreactor (Scheme 21; capacity: 200 mL). Unfortunately, only 12% of the expected product **102a** was isolated from a complex reaction mixture. This observation might be caused by the, in comparison to the usual one-LED setup, higher light intensity emitted by the built-in LEDs of the used photoreactor. In contrast, when the photocyclopropanation of *N*-Boc pyrrole was run on a 28.4 mmol scale, the cyclopropane derivative **102e** was obtained in 63% yield. Additionally, the cyclopropanation of *N*-Ts pyrrole was conducted on 4.12 mmol scale and gave 77% of the desired cyclopropane derivative **102b**. To avoid double cyclopropanation, it was indispensable to use the heteroarene in five-folded excess. Remaining starting material was re-isolated by distillation or column chromatography.

To improve the photocyclopropanation, as a next step, the tolerance of diazo compounds **120** missing the phenyl substituent in the cyclopropanation of furan (**119a**) were tested (Table 1).

Table 1. Screening of potential conditions for the application of diazoesters **120** in the photo induced cyclopropanation of furan (**119b**).



120a: R = Et **119a** (5.0 equiv) **121a**: R = Et
120b: R = ^{t}Bu **121b**: R = ^{t}Bu

entry	R	hν [nm]	T [°C]	results
1	CO_2Et	455	25	decomposition
2	$CO_2{}^tBu$	455	25	decomposition
3	CO_2Et	455	0	decomposition
4	CO_2Et	403	0	decomposition
5	$CO_2{}^tBu$	403	0	50%

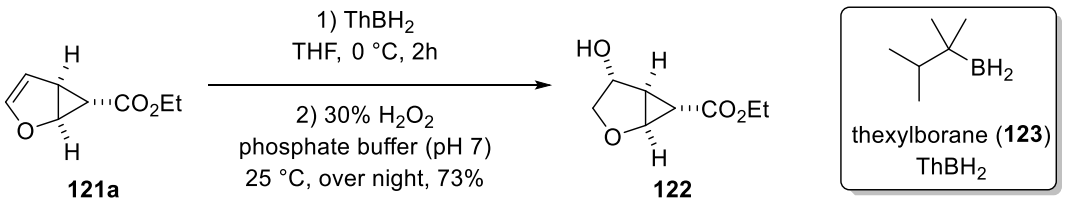
For a first attempt, diazo compounds bearing an ethyl ester **120a** (Table 1, entry 1) or *tert*-butyl ester **120b** (Table 1, entry 2) were irradiated with blue light (λ_{max} = 455 nm) at ambient temperature in order to perform a cyclopropanation of furan (**119a**). After 24 h complete conversion of the starting material **120** was achieved but only decomposition was observed in both cases. Since previous research in our group showed that cyclopropanes **121** are very unstable, the next test reaction was conducted at 0 °C but again only decomposition was observed (Table 1, entry 4). Davies *et al.*[95] showed that the UV-Vis absorption A_{max} of diazo acetates **120** is, in comparison to methyl phenyl diazoacetate **118** (A_{max} = 400 – 460 nm), shifted to the UV-region (A_{max} = 340 – 420 nm). Thus, a UV-LED (λ_{max} = 403 nm) was applied which led to decomposition when ethyl diazo acetate **120a** was used (Table 1, entry 5). In contrast, 50% of the expected product **121b** was received using the *tert*-butyl diazo acetate **120b** (Table 1, entry 6). Unfortunately, the product **121b** decomposed rapidly making purification and analytic measurements hardly possible. Nevertheless, the structure was

confirmed by ^{1}H-NMR and MS-spectrometry. Due to the extremely unstable products and poor yield the optimization was not pursued.

To sum up, the photo-mediated cyclopropanation offered a rather cheap and environmentally feasible alternative to the metal-catalyzed method. Especially cyclopropanated pyrrole derivatives **102b** and **102e** were provided on gram-scale. Further optimization of this method might be achieved by adopting this procedure to a flow-reactor. That might enable the gram-scale synthesis of cyclopropanated furan derivatives **102a**. Additionally, there is also the possibility to improve the yield of pyrrole derivatives **102b** and **102e**. Additionally, access to the cyclopropanation utilizing diazo acetates missing the phenyl moiety can be achieved since the cyclopropanation itself was successful but cooling and purification turned out to be challenging under the batch conditions. Further investigation on this project is already ongoing in our group.

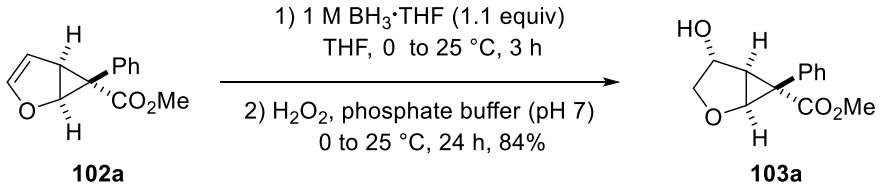
2.1.4 Diastereoselective synthesis of hydroxylated cyclopropanated heterocycles

The cyclopropylcarbinol derivatives were described as potent precursors for the stereoselective ring-expansion of monocyclopropanated heterocycles, thus, a hydroxylation of the cyclopropanated furan and pyrrole derivatives was essential. For this purpose, the hydroboration of these substrates was investigated since it is known that the addition of borane proceeds regioselective if vinylethers[97] or enamines[98,99] are applied as substrates. Monn *et al.* made use of a hydroboration of **121a** with *in situ* generated, sterically demanding thexylborane (**123**) in their synthesis of heterobicyclic amino acids (Scheme 22).[100]



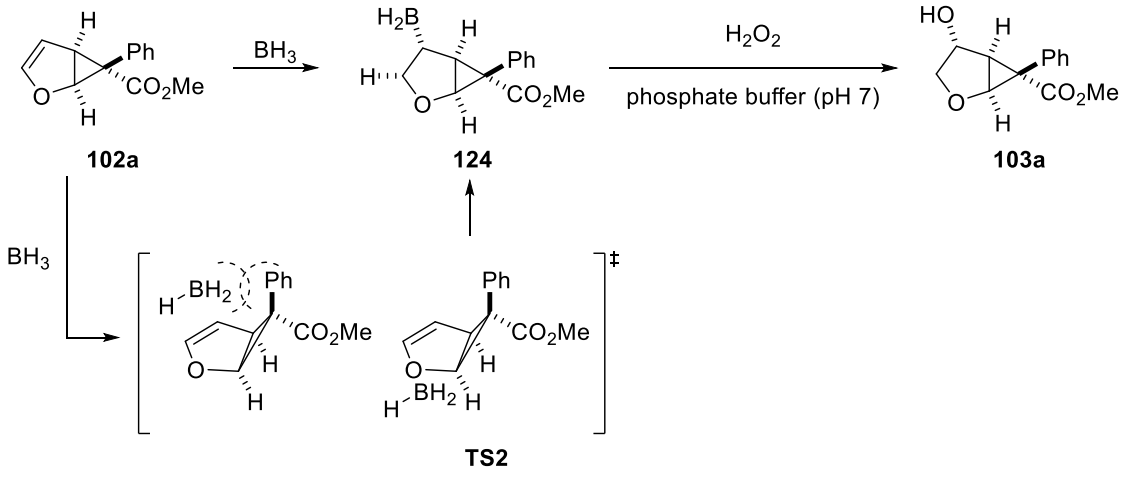
Scheme 22. Established hydroboration of **121a** utilizing thexylborane (**123)** in the synthesis of heterobicyclic aminoacids published by Monn and co-workers.[100]

The hydroboration established by Monn *et al.* provided the cyclopropylcarbinol derivative **122** as single diastereomere in good yield which emphasizes the suitability of the hydroboration in case of synthesizing the required hydroxylated precursors.[100] Consequently, cyclopropanated furan **102a** was tested in the hydroboration (Scheme 23).



Scheme 23. Regio- and diastereoselective hydroboration of **102a** with BH_3·THF as reagent.

For the sake of simplicity, furan **102a** was treated with a commercial available 1 M BH_3·THF-solution in a first test reaction. Indeed, the expected product **103a** was obtained in excellent yield of 84% and relative stereochemistry was assigned by 2D-NMR spectroscopy. Due to the particular β-selectivity of the borane addition to the carbon-carbon double bond in vinyl ethers which is a key structure motif in cyclopropanated furan **102a**, the borane addition resulted exclusively in the β-adduct **124** (Scheme 24). [101]

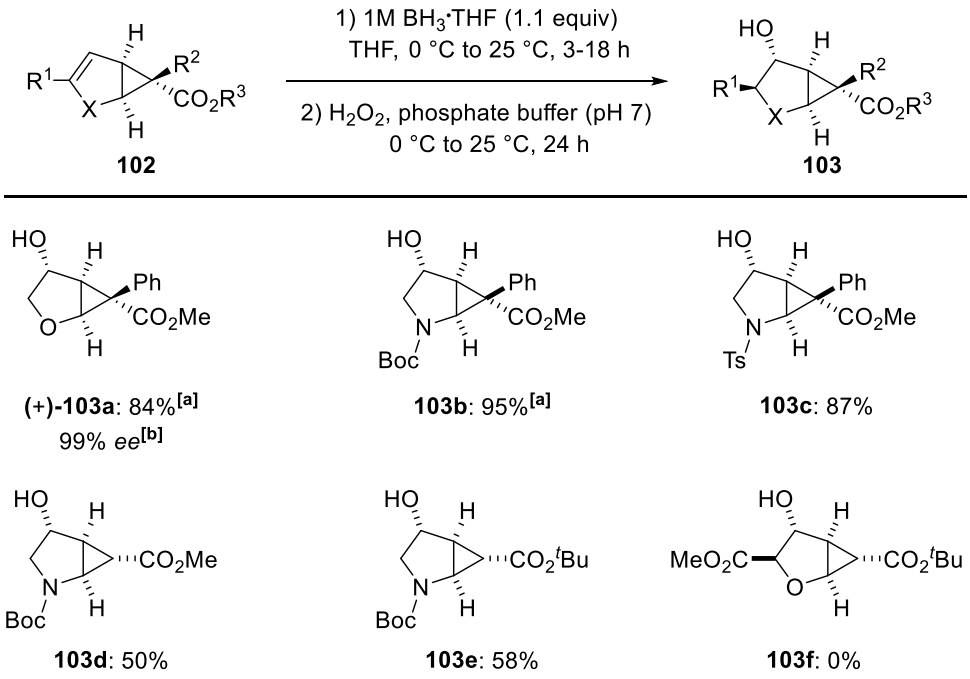


Scheme 24. Directing effects observed in the hydroboration of cyclopropane derivative **102a**.

Additionally, the diastereoselectivity of this transformation can be explained by the sterically demanding cyclopropane moiety blocking the concave side of the molecule.

As consequence, the borane addition occurs predominantly from the less hindered convex side of the molecule and is assumed to proceed through **TS2** forming exclusively hydroxylated furan derivative **103a** after aqueous workup.

With these conditions in hands, the scope of the hydroboration was extended whereupon cyclopropanated pyrroles and furans **102** served as starting materials (Scheme 25).



Scheme 25. Substrate scope of the established hydroboration; [a] scale-up: 20.0 mmol of **(*rac*)-102a** and 7.0 mmol of **102e** were applied to yield 3.95 g of **(*rac*)-103a** and 2.21 g of **103b**; [b] determined by chiral HPLC.[1]

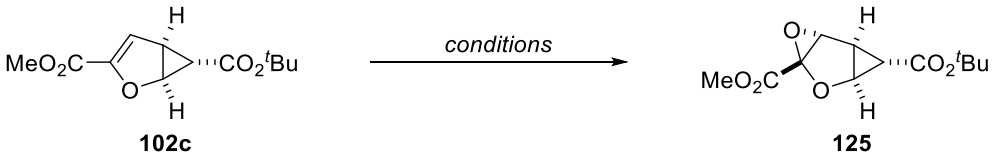
Besides the model substrate **102a**, also the *N*-Boc pyrrole **102e** and *N*-Ts pyrrole **102b** bearing a phenyl-substituent at the cyclopropane moiety gave the desired alcohols **103b** and **103c** in excellent yield. In case of cyclopropanes **102d** and **102f** the yield dropped significantly since the products **103d** and **103e** turned out to be rather unstable. Furthermore, the desired hydroboration of **102c** to afford **103e** was not feasible since a hydroboration at electronic deficient carbon-carbon double bonds e.g. acrylates[102] is not possible under these conditions. In contrast, the diastereoselectivity of this

[1] The results for the synthesis of **103a** and **103b** are taken from the Bachelor thesis of A. Tiefel, 2019, Universität Regensburg (supervised by R. Eckl).

hydroboration allowed the synthesis of the enantiopure alcohol **(+)-103a** if enantiopure cyclopropane **102a** was used as starting material. Additionally, the scalability of this procedure was demonstrated by synthesizing **(*rac*)-103a** and **103b** on gram-scale and the stereochemistry was proved by 2D-NMR spectroscopy. Noteworthy, the proposed β-selectivity during the borane addition was also observed when pyrrole derivatives were used which can be explained by the directing effect of the nitrogen atom in enamines[99] which is similar to the selectivity displayed by vinyl ethers.

Since the hydroboration usually requires an electron rich carbon-carbon double bond to yield in a successful product formation, the epoxidation is known to be more versatile.[103] Additionally, the possibility is offered to adjust the required conditions to particular synthetic and electronic problem. In the following, a suitable pathway for the epoxidation of **102c** was established (Table 2).

Table 2. Screening of suitable reaction conditions for the epoxidation of cyclopropane derivative **102c**.



102c **125**

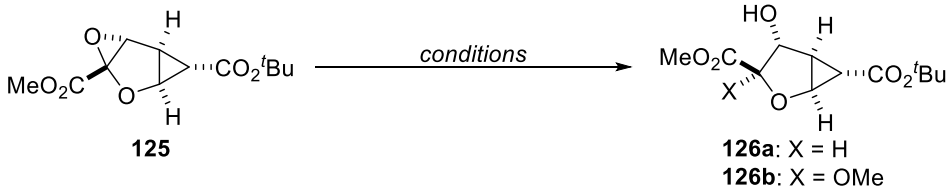
entry	peroxide	base	solvent	T [°C]	t [h]	results
1	H_2O_2	NaOH	DCM/MeOH (1:1)	25	24	decomposition
2	^{t}BuOOH	DBU	-	0	24	no conversion
3	*m*CPBA	$NaHCO_3$	DCM	25	24	traces
4	*m*CPBA	$NaHCO_3$	DCM	70	24	75%
5	Oxone	$NaHCO_3$	acetone/water (1:1)	0	3	95%

From the received results of the established hydroboration, the carbon-carbon double bond in **102c** was revealed as electron-poor due to the attached ester moiety. In accordance to literature,[104] nucleophilic conditions using NaOH and H_2O_2 as reagents were applied but only decomposition of the starting material was observed (Table 2, entry 1). Furthermore, using *tert*-butylhydroperoxide and DBU as published[105] resulted in no conversion of **102c** (Table 2, entry 2). Switching to electrophilic conditions,[106] *m*CPBA and $NaHCO_3$ gave traces of product at ambient temperature (Table 2, entry 3)

and 75% of the expected product **125** at 70 °C (Table 2, entry 4). Since up-scaling with *m*CPBA as reagent turned out to be challenging, dimethyldioxirane,[107] was tested as reagent. Surprisingly, the electrophilic epoxidation with *in situ* generated dimethyldioxirane resulted in almost quantitative epoxidation of **102c** (Table 2, entry 5)**.** Notably, the synthesis of **125** on gram-scale was also possible. Additionally, the product was formed diastereoselective and the relative stereochemistry was assigned by 2D-NMR spectroscopy. The diastereoselective product formation can be explained by the sterically blocked concave side of the molecule, thus, the epoxidation exclusively proceeded from the less hindered convex side of the molecule as it was already observed in the established hydroboration.

Since the alcohol was required for further transformations, the opening of the obtained epoxide **125** was investigated next by testing nucleophilic and electrophilic strategies for its opening (Table 3).

Table 3. Investigation of suitable conditions for the selective opening of epoxide **125**.



125

126a: X = H
126b: X = OMe

entry	X	reagent	solvent	T [°C]	t [min]	yield [%]
1	H	$Sc(OTf)_3$ (10 mol%)	DCM	25	60	0[a]
2	H	$LiAlH_4$	THF	0	10	0[a]
3	H	Pd/C (5 mol%), 30 bar H_2	EA	25	180	25
4	H	Pd/C (20 mol%), 30 bar H_2	EA	25	180	36
5	OMe	Amberlyst 15® (20 w/w%)	MeOH	25	15	99

[a] decomposition of the starting material.

As a first assumption, the epoxide **125** was activated with $Sc(OTf)_3$ as lewis acid[108] but only decomposition of the epoxide **125** was observed (Table 3, entry 1). Testing a reduction[109] of **125** with $LiAlH_4$ resulted also in decomposition of the starting material (Table 3, entry 2). Hydrogenation with Pd(0) on char coal, being a mild method for the reduction of epoxides,[110] gave 25% of product **126a** with 5 mol% catalyst (Table 3,

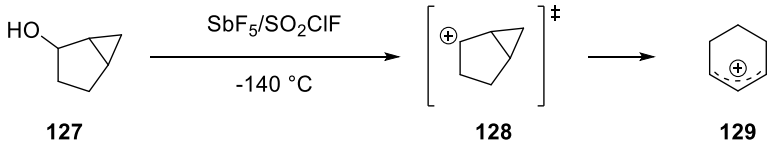
entry 3) and 36% with 20 mol% of Pd(0) (Table 3, entry 4). In contrast, when epoxide **125** was treated with the acidic ion exchange resin Amberlyst 15® which is known as powerful tool for a heterogeneous epoxide opening[111] afforded the expected alcohol **126b** in almost quantitative yield with MeOH as solvent after 15 min at ambient temperature (Table 3, entry 5). Additionally, product **126b** was obtained as single diastereomere which was caused by the blocked concave side as mentioned in case of the hydroboration and epoxidation.

The investigation of the hydroboration, epoxidation and epoxide opening of cyclopropanated furans and pyrroles allowed the synthesis of various hydroxylated monocyclopropanated furan and pyrrole derivatives which turned out to be potent precursors for the development of a stereoselective ring-expansion giving rise promising pharmaceutical relevant pyran, diydropyridine and tetrahydropyridine derivatives. The development of the ring-expansion *via* a stereoselective endocyclic cyclopropane bond cleavage is described in the following.

2.1.5 Microwave-assisted ring-expansion

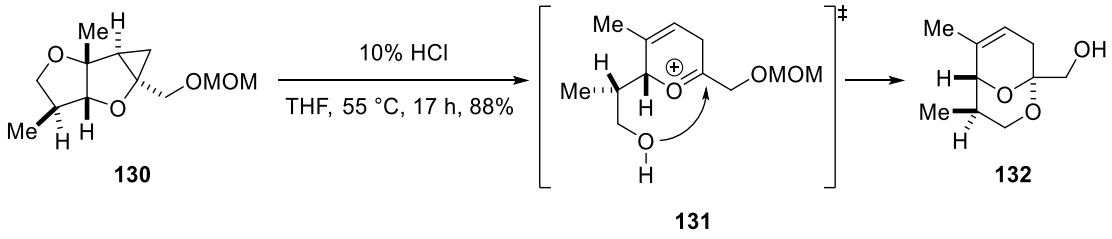
2.1.5.1 Studies towards a ring-expansion starting from hydroxylated monocyclopropanated furan and pyrrole derivatives

After activation, hydroxy groups are known to be excellent leaving groups and are commonly used in nucleophilic substitutions or elimination reactions.[112] Additionally, they can be utilized in the activation of a cyclopropane moiety to generate a cyclopropylcarbinyl cation. Especially in bicyclic systems of type **127**, the desired ring-expansion featuring a cyclopropylcarbinyl cation **128** can be achieved as it was shown by Olah *et al.* in the 1980's (Scheme 26).[113]



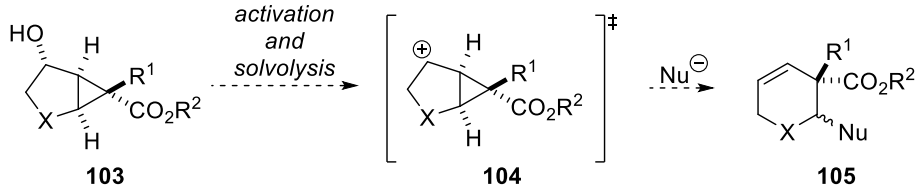
Scheme 26. Solvolytic ionization of bicyclo[3.1.0]hexan-2-ol (**127**) in super acid SbF_5/SO_2ClF forming allylic ion **129** *via* the cyclopropylcarbinyl cation **128** as key intermediate.

They carried out studies on the ionization of bicyclo[3.1.0]hexan-2-ol (**127**) in super acids such as SbF_5/SO_2ClF to achieve a solvolysis of **127** forming the cationic intermediate **128**. The rearrangement to allylic ion **129** was independent from the applied acid and could not even be prevented in any case. Detection of the allylic cation **129** was done by NMR-spectroscopy, additionally, they pointed out that trapping of the cation **129** might be possible by nucleophiles.[113] An example for the elegant integration of the ring-expansion including the intramolecular trapping of the cation was published by Ireland *et al.* in their total synthesis of Monensin. (Scheme 27).[114]



Scheme 27. Application of an acid-mediated ring-expansion in the synthesis of Monensin precursor **132**.[114]

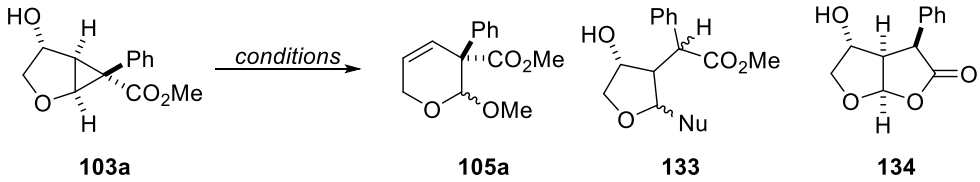
Acidic activation of **130** using 10% HCl in THF mediated the solvolytic rearrangement towards oxonium ion **131**. The cationic intermediate **131** was intramolecular trapped by the released side chain to form bridged pyran **132** in excellent yield. Those results emphasized that a ring-expansion of monocyclopropanated heterocycles, indeed, is possible *via* a solvolytic pathway and also various functional groups might be tolerated during the reaction. With these results in mind, the transformation was adopted to our cyclopropanated furan and pyrrole derivatives **103** (Scheme 28).



Scheme 28. Strategy for a solvolytic ring-expansion of hydroxylated monocyclopropanated heterocycles **103.**

We suggested that the release of the hydroxy group generates the cyclopropylcarbinyl cation of type **104** which is supposed to rearrange to the six-membered heterocycle and is then immediately trapped by a nucleophile to yield **105**. To confirm this hypothesis, a screening was conducted while hydroxylated furan derivative **103a** served as model substrate (Table 4).

Table 4. Screening of suitable conditions for a (lewis) acid-mediated ring-expansion of furan derivative **103a**.

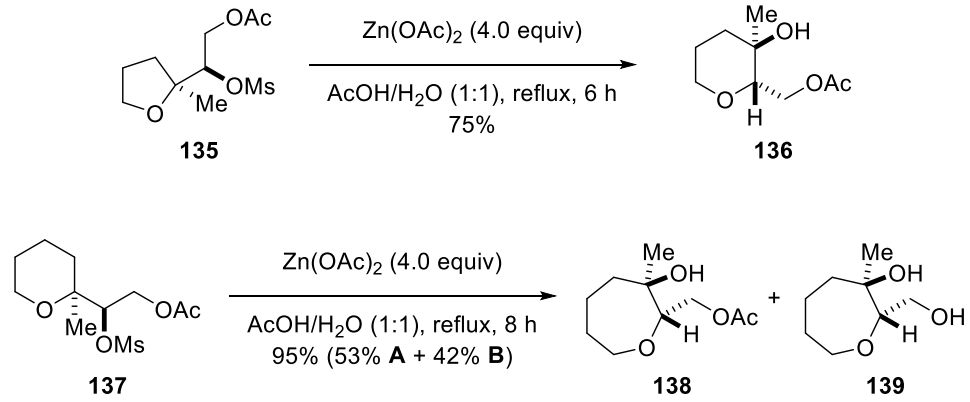


entry	reagent	solvent	T [°C]	t [h]	results
1	10% HCl	THF/MeOH (2:1)	55	24	complex mixture; traces of **134**
2	TFA, Et_3SiH	DCM	0	24	complex mixture
3	H_2SO_4	MeOH	25	24	32% **133** (X = OMe)
4	$BF_3{\cdot}Et_2O$, Et_3SiH	DCM	-78	20	83% **133** (X = H)

As a first test reaction, the same conditions as reported by Ireland *et al.*[114] were applied. Treating **103a** with 10% HCl in THF/MeOH resulted mainly in a complex reaction mixture but also **134** was formed in traces after a reaction time of 24 h at 55 °C (Table 4, entry 1). It is known that donor-acceptor cyclopropanated furan derivatives can undergo a selective exocyclic carbon-carbon bond cleavage by activation of the acceptor moiety under acidic conditions resulting in bicyclic compounds such as **134** which are precursors for paeonilide derivatives as it was published earlier by our group.[33] Furthermore, when TFA was used in combination with triethylsilane as hydride source only a complex mixture was received after 20 h at 0 °C (Table 4, entry 2). In contrast, when sulfuric acid was applied as a much stronger acid in MeOH, suddenly, an exocyclic carbon-carbon bond opening forming **133** in 32% was observed (Table 4, entry 3). Since none of the tested conditions triggered the transformation of interest, finally, starting material **103a** was treated with $BF_3{\cdot}Et_2O$ in order to test a potential lewis-acid mediated pathway. Unfortunately, an exocyclic carbon-carbon bond cleavage was observed providing **133** in 83% as mixture of several diastereomers (Table 4, entry 4). This type of acid-mediated exo-cyclic cyclopropane bond cleavage in donor-acceptor cyclopropanes is known and it is explained by the activation of the ester moiety favoring the cleavage of the exocyclic cyclopropane bond.[115] Consequently, a selective endocyclic carbon-carbon bond cleavage in substrates of type **103a** turned out to be not accessible under acidic conditions. Thus, this problem has to be circumvented by establishing a milder, acid free pathway to trigger the ring-expansion of interest.

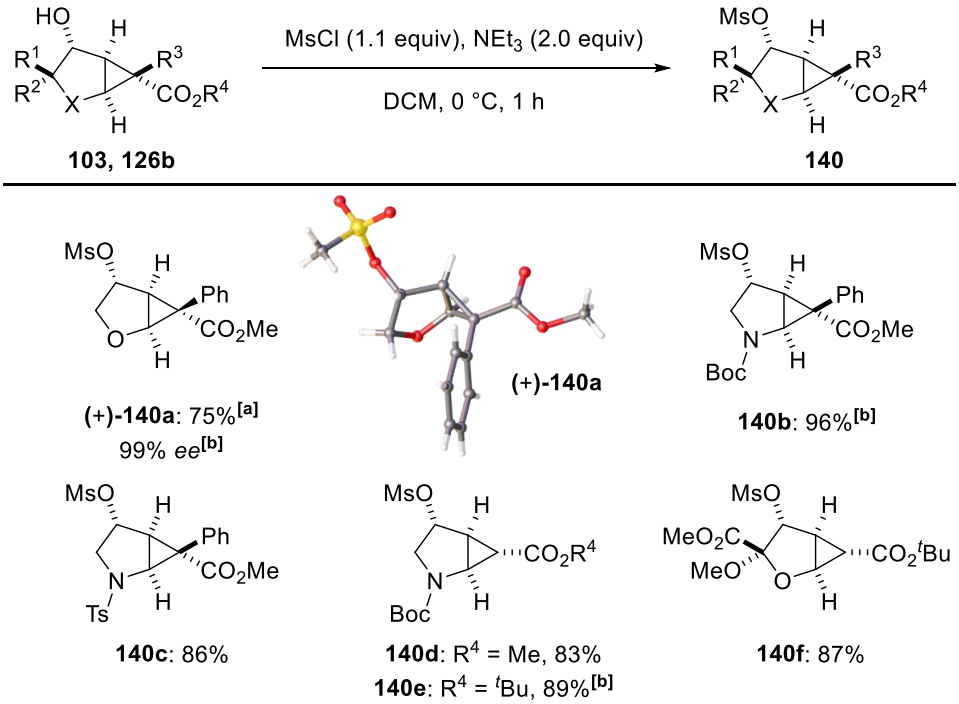
2.1.5.2 Development of a stereoselective ring-expansion via a endocyclic bond-cleavage utilizing mesylates as potent precursors

The previous results indicated that the formation of the cyclopropylcarbinyl cation being the key intermediate for the ring-expansion was not successful *via* the acidic activation of the hydroxyl group. Consequently, a synthetic transformation of the hydroxyl group was essential to convert the poor leaving group into a good leaving group. A promising opportunity was the transformation of the alcohol moiety to a mesylate which is a prominent leaving group and was utilized e.g. in nucleophilic substitutions in classic and also modern organic synthesis.[116] A notable example was published by Nakata *et al.* who used mesylated precursors **135** and **137** in a $Zn(OAc)_2$ mediated ring-expansion of cyclic ethers giving access to *tetra*-hydropyrane **136** and oxepanes **138** and **139** in good to excellent yield (Scheme 29).[117–119]



Scheme 29. Stereoselective synthesis of *tetra*-hydropyran **136** and oxepanes **138** and **139** *via* a $Zn(OAc)_2$ mediated pathway utilizing mesylated precursors.[117–119]

They demonstrated that mesylates, indeed, are excellent leaving groups to generate cationic intermediates which were the key intermediate to achieve the ring-expansion. Thus, mesylates were elected as reasonable precursors for the ring-expansion of monocyclopropanated heterocycles. The required scope of mesylates **140** was synthesized from the hydroxylated furan and pyrrole derivatives **103** based on procedures from Apsel *et al.*[120] and Dai *et al.*[121] which were optimized and improved with regard to the particular synthetic project (Scheme 30).



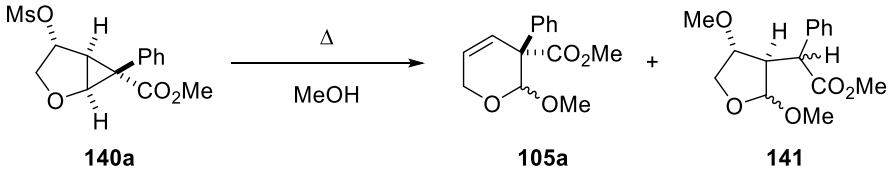
Scheme 30. Synthesis of precursors **140** by mesylation of alcohols **103** or **126b**; [a] scale-up: 5.51 mmol of ***(rac)*-103a** and 5.61 mmol of **103b** were applied to yield 1.23 g of ***(rac)*-140a** and 2.21 g of **140b**; [b] determined by chiral HPLC by analyzing the corresponding alcohol **(+)-103a** (X-Ray crystallography confirmed the absolute stereochemistry of **(+)-140a** and the corresponding alcohol **(+)-103a**).[2]

In each particular case, the expected product was obtained in excellent yield after easy purification by washing the crude product with methanol. The synthesis of ***(rac)*-140a** and **140b** were conducted on gram-scale, additionally, **(+)-140a** was synthesized enantiopure by starting with **(+)-103a** and the structure was confirmed by single X-Ray crystallography. With these compounds in hand, a screening of suitable reaction conditions at various temperatures with MeOH as solvent was conducted (Table 5). As a first test reaction, precursor **140a** was stirred in MeOH for 4 d at ambient temperature but no conversion of the starting material was observed (Table 5, entry 1). In order to achieve full conversion of the starting material, the following reactions were investigated in a microwave oven. It is known that heating under microwave irradiation is more efficient in comparison to conventional heating since e.g. reaction times can be reduced.[122] Heating of **140a** to 40 °C for 8 h resulted in no conversion since the poor solubility of **140a** in methanol at low temperatures prohibited the transformation (Table 5, entry 2). Suddenly, traces of product were observed after heating **140a** to 60

[2] The results for the synthesis of **140a** and **140b** are taken from the Bachelor thesis of A. Tiefel, 2019, Universität Regensburg (supervised by R. Eckl).

°C for 3 h (Table 5, entry 3) whereupon running the reaction at 80 °C for 1 h resulted in full conversion of the starting material (Table 5, entry 4). After purification, 55% of the expected product **105a** was obtained as epimeric mixture (*dr* 2.4:1), but additionally, an exocyclic ring-opening to **141** has occurred to an almost equal extend (Table 5, entry 4).

Table 5. Screening of suitable reaction conditions for an endocyclic ring-opening using mesylate **140a** as precursor.

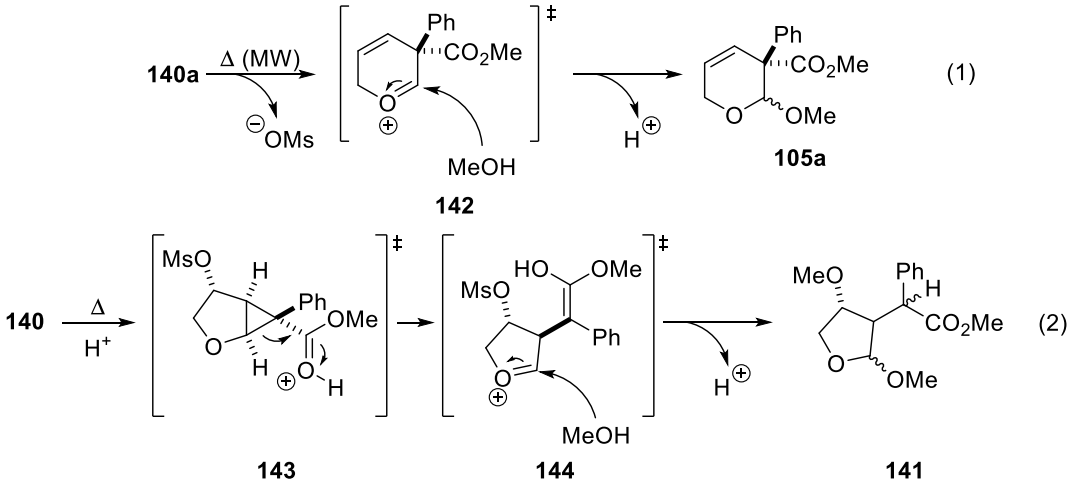


140a **105a** **141**

entry	heating method	T [°C]	t [h]	results
1	-	25	96	no conversion[a]
2	MW	40	8	no conversion[a]
3	MW	60	3	traces of **150a**
4	MW	80	1	55% **105a** (*dr* 2.4:1) + 45% **141**

[a] **140a** occurred to be hardly soluble in MeOH.

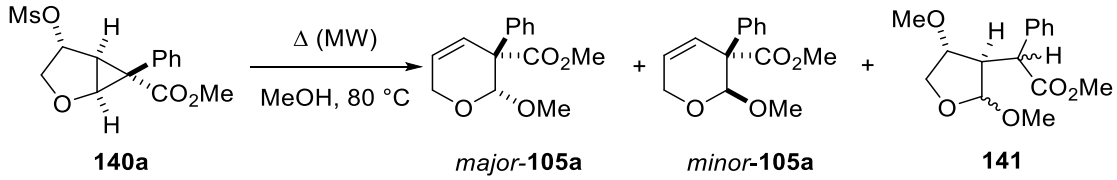
As expected, utilizing the solvolysis of mesylates turned out to be the key for a successful stereoselective ring-expansion of monocyclopropanated furans and pyrroles. Unfortunately, the endocyclic ring-opening competed with the exocyclic cyclopropane carbon-carbon bond cleavage. Mechanistic considerations, in accordance to literature,[33,115] were consulted to analyze the observed side-reaction (Scheme 31).



Scheme 31. Mechanistic considerations of the observed ring-expansion and side-reaction in the conversion of **140a** in MeOH under microwave irradiation.

At first, the leaving group in **140a** was solvolytically released under thermal conditions initiating the rearrangement to oxonium ion **142** featuring a cyclopropylmethyl cation as key intermediate. This intermediate **142** was then nucleophilically trapped by MeOH resulting in the desired product **105a**. We suspected that the formation of methyl sulfonic acid in the course of the reaction will be sufficient to activate the ester group to cause the undesired exocyclic ring-opening. In turn, intermediate **144** resulted from the exocyclic bond cleavage which is than trapped by MeOH giving **141**. To prohibit the exocyclic ring-opening a non-nucleophilic base was added in order to trap the *in situ* generated traces of acid. To confirm this hypothesis, K_2CO_3 was chosen as base for the following screening (Table 6).

Table 6. Screening of suitable reaction conditions with K_2CO_3 as non-nucleophilic base.[3]



140a *major*-**105a** *minor*-**105a** **141**

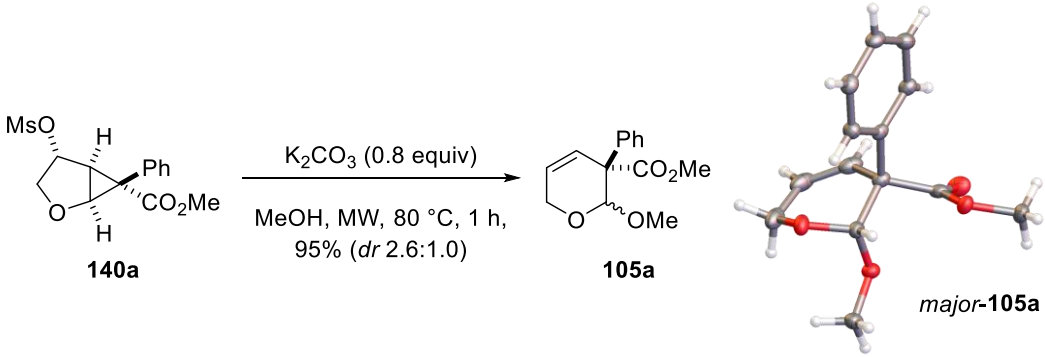
entry	base[a]	equivalents	t [h]	yield of 105a	yield of 141
1	-	-	1	55% (*dr* 2.4:1);	45%
2	K_2CO_3	2.0	1	58% (*dr* 2.8:1)	-
3	K_2CO_3	1.2	1	81% (*dr* 2.5:1)	-
4	K_2CO_3	1.0	1	90% (*dr* 2.6:1)	-
5	K_2CO_3	0.8	1	95% (*dr* 2.6:1)	-
6	K_2CO_3	0.5	1	90% (*dr* 2.6:1);	traces
7[b]	K_2CO_3	0.8	6	76% (*dr* 2.6:1)	

[a] non-nucleophilic base was added if stated; [b] reaction was conducted under conventional heating.

As it was shown, heating of **140a** in MeOH without base resulted in an approximately 1:1 mixture of **105a** and **141** (Table 6, entry 1). Indeed, adding 2.0 equivalents of K_2CO_3 completely suppressed the formation of **141** and the desired pyran **105a** was obtained in 58% yield after 1 h under microwave irradiation (Table 6, entry 2).

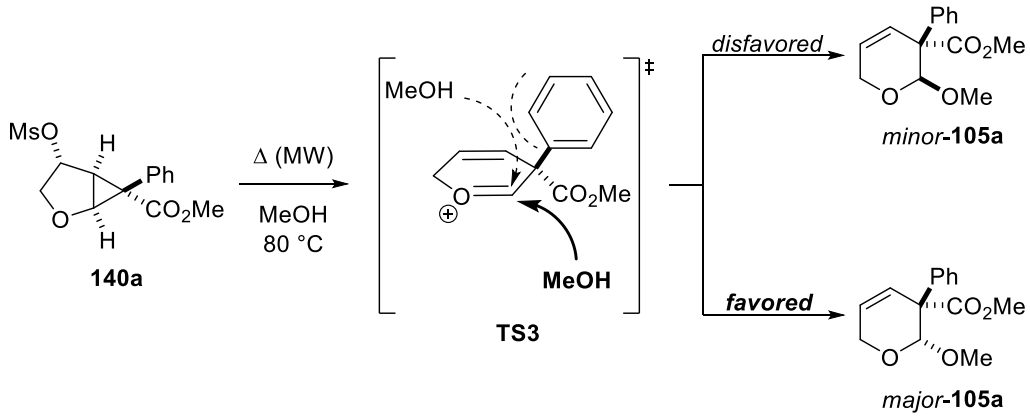
[3] Results are taken from the Bachelor thesis of A. Tiefel, 2019, Universität Regensburg (supervised by R. Eckl).

Decreasing the amount of K_2CO_3 from 2.0 to 0.8 equivalents resulted in almost quantitative yield of the expected product and the formation of typical epimers at the anomeric was observed (Table 6, entry 5). The limit was reached by 0.5 equivalents of K_2CO_3 which still afforded 90% of the desired product but additionally traces of the side product **141** were observed (Table 6, entry 6). The benefit of microwave irradiation became apparent by comparison to conventional heating, when only 76% of **105a** were isolated even at an extended reaction time of 6 h (Table 6, entry 7). Furthermore, the structure of the received product **105a** was confirmed by single crystal X-Ray crystallography (Scheme 32).



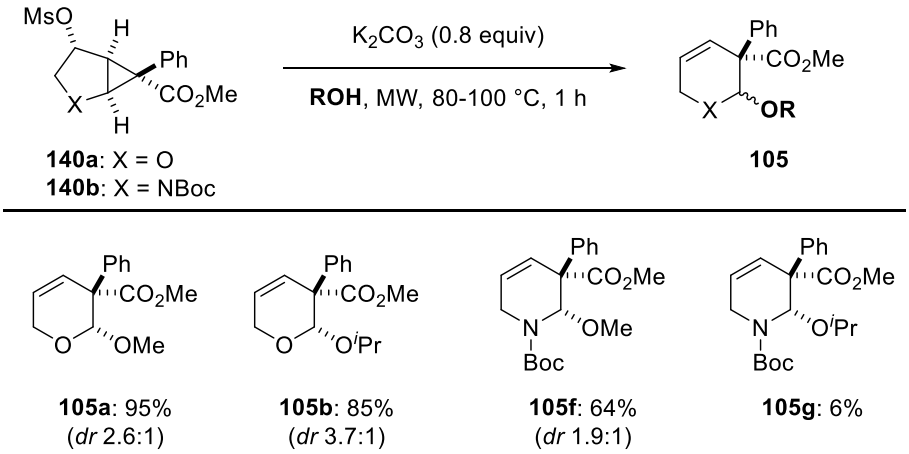
Scheme 32. Single crystal X-Ray crystallography of pyran **105a**.

To explain the formation of the epimers, it was assumed that the mechanism proceeded through a planar oxonium ion which enabled the nucleophilic attack of MeOH from the top or bottom in **TS3**. In contrast to the ester group, the more sterically demanding phenyl substituent blocked the upper side, thus, the favored nucleophilic attack occured from the bottom. Hence, the phenyl substituent and the nucleophile are pointing to opposite directions (Scheme 33).



Scheme 33. Mechanistic considerations for the formation of epimers *major*-**105a** and *minor*-**105a** during the ring-expansion of **140a** by analyzing **TS3**.

With the optimized reaction conditions in hands, the substrate scope of the stereoselective ring-expansion was extended to *N*-Boc pyrrole derivative **140b** utilizing various alcohols as solvents (Scheme 34).



Scheme 34. Studies towards an extended substrate scope with **140a** and **140b** as starting materials; in all examples the major diastereomere is shown.[4]

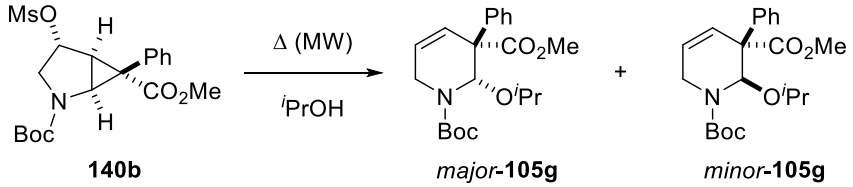
Besides the successful ring-expansion of **140a** with MeOH as solvent conducting the reaction in *i*PrOH afforded **105b** in 85% yield with a diastereomeric ratio of *dr* 3.7:1. Direct correlation between the steric demand of the nucleophile and the diastereomeric ratio was observed. Moving to *N*-Boc pyrrole derivative **140b** the combination of K_2CO_3 and microwave irradiation was also successful. However, a raise of the reaction temperature to 100 °C was necessary for full conversion to obtain **105f** in 64% yield. Finally, using **140b** in combination with *i*PrOH as solvent, the yield decreased drastically and the desired product **105g** was obtained in 6%. In the latter case, careful analysis of the crude ^{1}H-NMR raised the suspicion that Boc-deprotection and further side-reactions occurred which indicated that there are still traces of acid. This observation can be explained by the poor solubility of K_2CO_3 in *i*PrOH since it is a more unpolar solvent than MeOH.

Consequently, K_2CO_3 was replaced by an organic non-nucleophilic base. Therefore, DBU was chosen as organic base since it is soluble in most organic solvents. The

[4] The results are taken from the Bachelor thesis of A. Tiefel, 2019, Universität Regensburg (supervised by R. Eckl).

following screening was investigated by treating *N*-Boc-pyrrole **140b** with DBU in *i*PrOH as solvent and the optimized reaction conditions were applied (Table 7).

Table 7. Alternative screening for suitable reaction conditions for the ring-expansion of *N*-Boc pyrrole derivative **140b** replacing K_2CO_3 with DBU.[5]



140b *major*-**105g** *minor*-**105g**

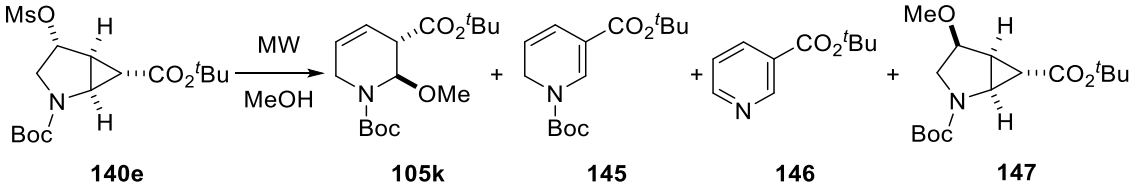
entry	base	equivalents	T [°C]	t [h]	yield
1	K_2CO_3	0.8	100	1.0	6% (*dr* 3.1:1)
2	DBU	0.8	120	1.5	40% (*dr* 3:1)
3	DBU	1.05	120	1.5	79% (*dr* 3:1)
4	DBU	1.2	120	1.5	99% (*dr* 3:1)
5	DBU	2.0	120	1.5	77% (*dr* 3.2:1)

In comparison to the ring-expansion of **140a** using 0.8 equivalents of K_2CO_3 as base (Table 6, entry1), an improvement was found switching to DBU which immediately afforded the desired product **105g** in 40% yield (Table 7, entry 2). This maintained the hypothesis that the low yield was caused by solubility issues of K_2CO_3. Due to this promising result the amount of DBU was increased stepwise to 2.0 equivalents (Table 7, entry 3-5). It turned out that 1.2 equivalents of DBU allowed the synthesis of dihydropyridine **105g** in almost quantitative yield (Table 7, entry 4). Additionally, the observed formation of epimers (*dr* 3:1) was independent from the applied amount of base as it was observed with **140a** as starting material.

To gain access to a versatile methodology also precursors lacking the phenyl group were applied in the microwave-assisted ring-expansion to examine the influence of the quaternary cyclopropane carbon. For this purpose the optimized reaction conditions with DBU as base were applied while **140e** served as starting material (Table 8).

[5] The results are taken from the Bachelor thesis of A. Tiefel, 2019, Universität Regensburg (supervised by R. Eckl).

Table 8. Microwave-assisted ring-expansion of *N*-Boc pyrrole **140e**.



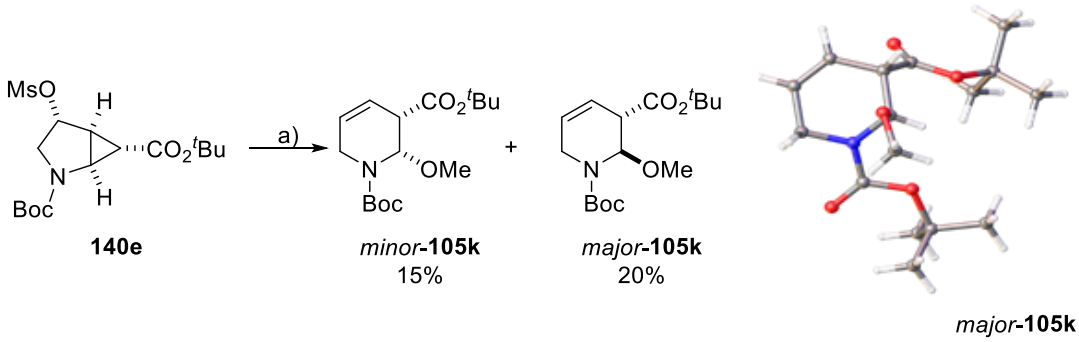
140e **105k** **145** **146** **147**

entry	base	T [°C]	t [h]	yield [%]			
				105k[e]	**145**	**146**	**147**
1[a]	DBU	100	1	-	35	17	16
2[b]	2,6-Lutidine	100	1	-	50	7	12
3	2,6-Lutidine	80	1	17[d] (*dr* 1.3:1)	*n.d.*	*n.d.*	18
4	2,6-Lutidine	60	8	35[d] (*dr* 1.3:1)	-	26	20
5[c]	2,6-Lutidine	50	144	39[d] (*dr* 1.3:1)	-	26	26

[a] determined by ^{1}H-NMR with 1,1,2,2-tetrachloroethane as internal standard; [b] determined by ^{1}H-NMR with 1,3,5-trioxane as internal standard; [c] reaction performed under N_2 atmosphere without MW-irradiation and the yield of **105k** was determined by ^{1}H-NMR with 1,3,5-trioxane as internal standard; [d] isolated yield after column chromatography; [e] major diastereomere is shown.

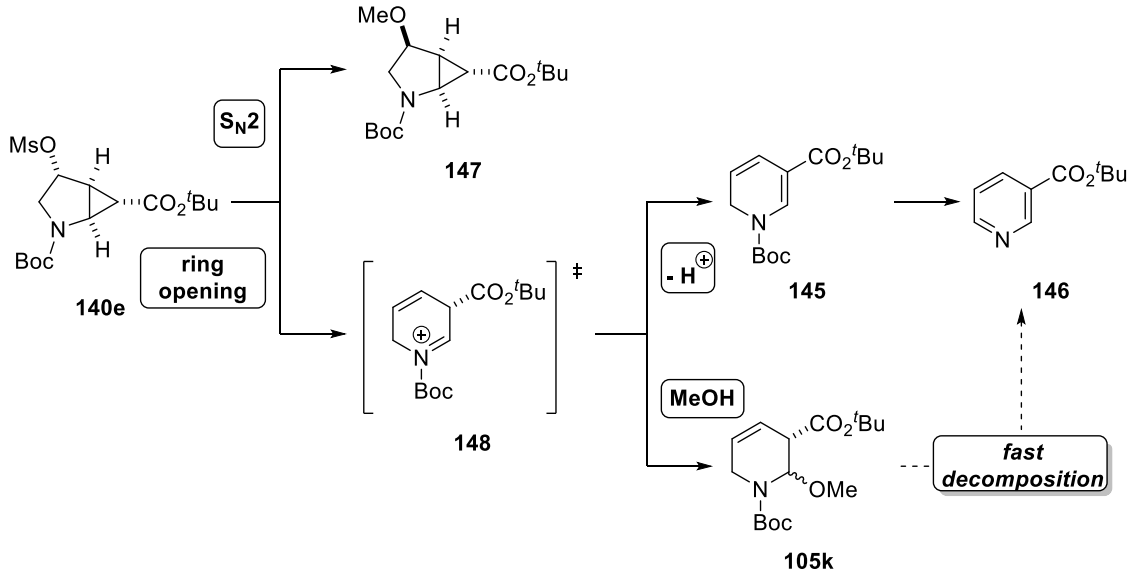
As first test reaction, the optimized conditions were applied for the conversion of precursors **140e** (Table 8, entry 1). After 1 h at 100 °C under microwave irradiation with DBU as base the formation of 35% (*dr* 1.3:1) of 6*H*-pyridine **145**, 17% of nicotinate **146** and 16% substitution product **147** were observed. This result indicated that the used base might has been too strong and caused the formation of 6*H*-pyridine **145** by deprotonation at the α-carbon next to the ester moiety. Subsequently **145** was partially oxidized resulting in nicotinate **146**. Thus, 2,6-Luthidine (pk_a = 6.6)[123] which is a much weaker base than DBU (pk_a = 13.5)[124] was used in the next reaction but similar observations were made as described in the latter (Table 8, entry 2). Since eliminations are favored at higher temperatures, the following reactions temperature was decreased stepwise. At 80 °C, 17% of the desired product **105k** was obtained after 1 h under microwave irradiation but the side reactions were still present (Table 8, entry 3). The best result was achieved at 60 °C providing the desired product **105k** in 35% yield with a diastereomeric ratio of *dr* 1.3:1 after 8 h but the side reactions

were again not prevented (Table 8, entry 4). Last, decreasing of the temperature to 50 °C under conventional heating afforded the expected product **105k** in 39% yield even at an extended reaction time of 6 d (Table 8, entry 5). Noteworthy, the diastereomers were separated by flash column chromatography and crystallization of the major diastereomere *major*-**105k** confirmed the assumed structure by single crystal X-Ray crystallography and mass analysis (Scheme 35).



Scheme 35. Best reaction conditions (Table 8, entry 4) for the ring-expansion of **140e** forming **105k**; conditions: a) 2,6-Luthidine (1.2 equiv), MeOH, MW, 60 °C, 8 h, 35% (*dr* 1:1.3).

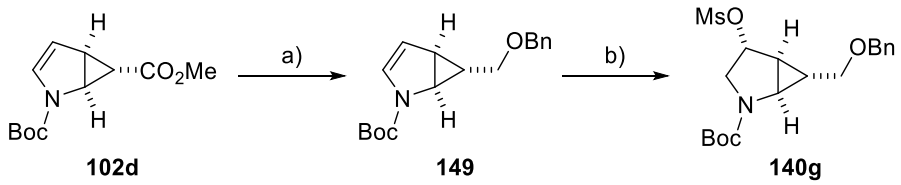
Characterization of the product was hardly possible since it was not stable in solution. However, the structure could be proved by HRMS and ^{1}H-NMR. In the next step, the different potential reaction pathways were analyzed in order to subsequently prevent the side reactions (Scheme 36).



Scheme 36. Analysis of the side reactions observed within the synthesis of product **150k**.

On the one hand, precursor **140e** can undergo a nucleophilic substitution forming **147** at elevated temperatures. On the other hand, the transformation of **140e** follows the expected pathway resulting in the iminium ion **148**. From this intermediate, there are again two possible reaction pathways leading to the formation of the expected product **105k** after a nucleophilic attack of methanol or the spontaneous or base-mediated elimination resulting in the 6*H*-pyridine **145**. In turn, the 6*H*-pyridine **145** is unstable and, therefore, undergoes a rapid oxidation forming the more stable nicotinate **146** which makes the isolation of **145** hardly possible. Additionally, the fast decomposition of **105k** in solution turned out to be a further problem. Unfortunately, the obtained results pointed out that the formation of 6*H*-pyridine **145** was independent from the added bases, thus, the most challenging side reaction was still not controllable.

The last possibilities to prevent the elimination pathway was reducing the CH-acidity of the α-proton next to the ester moiety in by reduction of the ester moiety to a primary alcohol or changing the electron weak *N*-Boc group to a free amine or alkylated tertiary amine. As a first attempt, the conversion of the ester moiety to a benzylated primary alcohol was investigated and cyclopropanated pyrrole derivative **102d** served as model substrate (Scheme 37).



102d **149** **140g**

Scheme 37. Synthesis of precursors **140g** *via* the established hydroboration-mesylation protocol starting from *N*-Boc pyrrole derivative **102d**; a) *i.* $LiAlH_4$ (1.0 equiv), THF, 0 to 25 °C, 21 h; *ii.* BnBr (1.05 equiv), NaH (1.5 equiv), DMF, 0 to 25 °C, 5 h, 46%; b) *i.* 1 M BH_3·THF (1.1 equiv), H_2O_2 (30 equiv), phosphate buffer (pH 7), THF, 0 to 25 °C, 2 d.

Reduction of the monocyclopropanated pyrrole **102d** was carried out as it is known in literature to receive the required alcohol.[94] Due to its known lability, the alcohol was subsequently treated with benzyl bromide and sodium hydride to obtain a benzyl protected alcohol **149** in 46% yield over two steps.[125] Without further purification **149** was converted to precursor **140g** *via* the established hydroboration followed by mesylation of the introduced hydroxyl group with methansulfonyl chloride**.** Even if the reaction protocol itself was reliable, not only benzylated pyrrole **149** turned out to be

rather unstable also isolation and purification of the mesylated precursor **140g** was not feasible since it decomposed rapidly at ambient temperature. Also cooling of the substrate in the freezer did not prevent the rapid decomposition. Therefore, it was almost impossible to run any further reaction with mesylate **140g** as starting material.
Consequently, this pathway was discarded and the only way left was the Boc-deprotection in order to decrease the electron deficient character at the nitrogen atom. To test the Boc-deprotection, precursor **140b** was chosen as model substrate because all elimination pathways during the ring-expansion were excluded due to the quaternary cyclopropane carbon (Table 9).

Table 9. Studies towards a Boc-deprotection in pyrrole derivative **140b**.

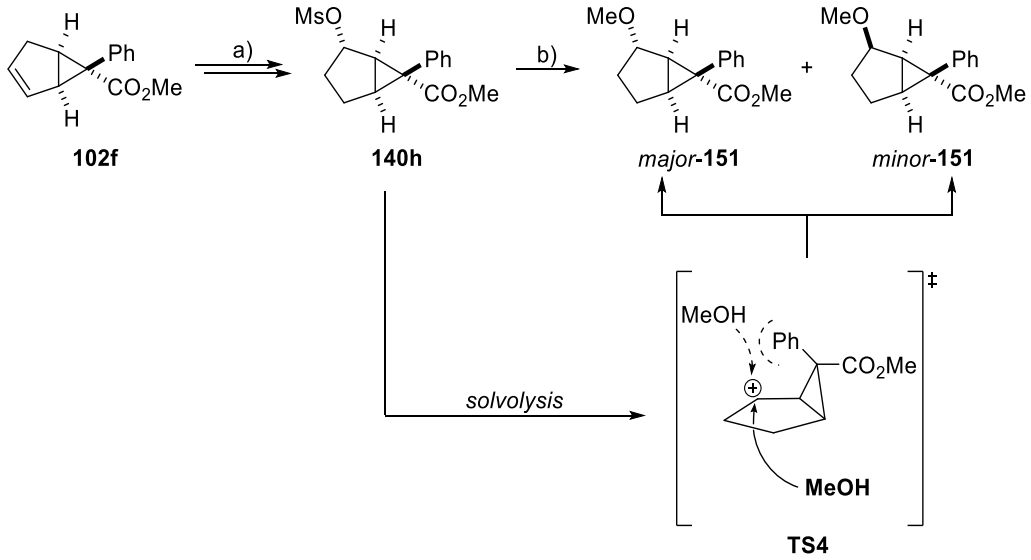
140b **150** **105f**

entry	reagent	solvent	T [°C]	t [h]	workup	results
1	TFA	DCM	25	3	evaporation	decomposition
2	TFA	DCM	0	5	evaporation	decomposition
3	HCl (4 M)	EA	25	3	evaporation	decomposition
4	K_3PO_4	MeOH	120	1	extraction	71% **105f**

In a first step, typical Boc-cleavage conditions were used starting with TFA in DCM.[126] Neither conducting the cleavage at ambient temperature (Table 9, entry1), nor at 0 °C (Table 9, entry 2) gave the expected product **150.** Instead, decomposition of the starting material was observed. Applying a protocol published by Coleman *et al.*[127] resulted also in decomposition after treating **140b** with a 4 M HCl in ethyl acetate at ambient temperature (Table 9, entry 3). Also a milder conditions[128] using K_3PO_4 in MeOH under microwave irradiation at 120 °C was not successful and resulted, as expected, in 71% yield of dihydropyridine **105f** (Table 9, entry 4). These results clearly indicated that also the Boc-deprotection is not the method of choice to access suitable precursors for the ring-expansion. Since the deprotection did not work with the phenyl substituted cyclopropane **140b** it was assumed that the deprotection of **140e** lacking the

phenyl group would cause similar problems. Consequently, the microwave-assisted ring-expansion of monocyclopropanated heterocycles turned out to be limited to cyclopropanes with a quaternary cyclopropane carbon which prohibited any elimination pathways.

Finally, also the influence of the heteroatom on the ring-expansion was examined. Besides the possibility of a radical induced ring-expansion of monocyclopropanated cyclopentadiene derivatives, it is also known that the selective endocyclic carbon-carbon bond cleavage is affordable *via* the cationic pathway.[78,129] Both types of transformations are resulting in a cyclohexane derivative. In order to test the cationic pathway involving the generation of the cyclopropylcarbinyl cation, cyclopropanated cyclopentadiene **102f** which was synthesized in accordance to literature served as model substrate.[130] It was selected as a promising test substrate to reveal the role of the heteroatom during the ring-expansion because it is based on a carbocyclic core structure but showed the same substitution pattern as the initially used cyclopropanated furans and pyrroles. The required mesylate **140h** was obtained after allylic oxidation,[131] Pd(0)-catalyzed hydrogenation and mesylation in an overall yield of 94%. Subjecting the carbocyclic derivative **140h** to the optimized reaction conditions, no ring-opening but rather direct substitution to **151** was observed (Scheme 38).



Scheme 38. Microwave-assisted ring-expansion of monocyclopropanted cyclopentadiene **140h**; a) *i.* SeO_2 (1.1 equiv), 1,4-dioxane, MW, 130 °C, 1 h, 98%; *ii.* Pd/C (10 w/w%), 60 bar H_2, EA, 25 °C, 2 h, 100%; *iii.* MsCl (1.1 equiv), NEt_3 (2.0 equiv), DCM, 0 °C, 1 h, 96%; b) DBU (2.5 equiv), MeOH, MW, 100 °C, 30 min, 66% (*dr* 3.7:1).[6]

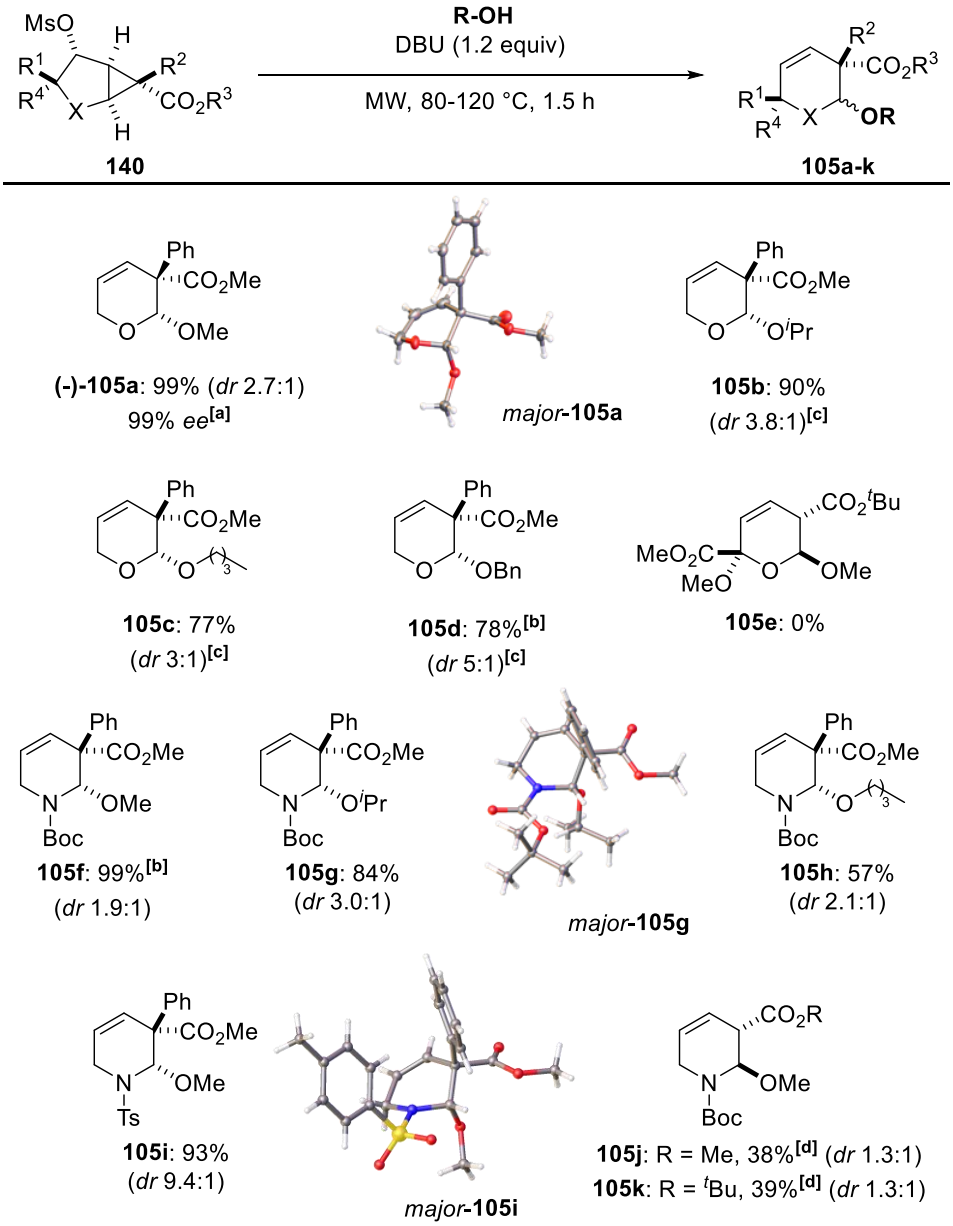
[6] The results were provided by Sebastian Fischer, *ongoing PhD-Thesis* (AK Reiser, Universität Regensburg).

Instead, after 30 min at 100 °C under microwave irradiation nucleophilic substitution of the mesyl group was observed giving product **151** in 66% yield and as diastereomeric mixture (*dr* 3.7:1). The structure and the stereochemistry of the product were assigned by 2D-NMR spectroscopy. The partial retention of stereochemistry in **151** clearly indicated that the reaction has proceeded *via* a S_N1 pathway and, thus, through the cationic intermediate **TS4**. In literature, there are few examples present which clearly show that the favored transformation of such substrates is a solvent dependent S_N1- or S_N2-reaction.[132] Especially, electron withdrawing substituents promote nucleophilic substitutions of the leaving group at C4.[133] Kinetic studies done by Mazur revealed that, in general, the ring-opening of the cyclopropylcyarbinyl cation gives the allylicarbinyl system with a rate constant at 50 °C of 7.5×10^{-6} s^{-1} which supported the experimental results observed in the conversion of **140h**.[83,134] Nevertheless, the ring-expansion of cyclopropanated carbocycles, indeed, are accessible by employing precursors with electron donating substituents at the cyclopropane moiety which are supporting the endocyclic carbon-carbon bond cleavage.[135] In heterocyclic precursors **140a-g** the heteroatom acts as electron donating group which enables the desired ring-expansion *via* the selective endocyclic carbon-carbon bond cleavage and clearly emphasized the exigency of the heteroatom.

In summary, promising reaction conditions for a microwave-assisted ring-expansion of monocyclopropanated furans and pyrroles were established. Even if the method is limited to heterocyclic cyclopropane derivatives bearing a quaternary carbon at the cyclopropane moiety, the desired six-membered heterocycles were provided in excellent yields. In the following a reasonable substrate scope was synthesized and further optimization of the method gave access to a versatile protocol.

2.1.5.3 Substrate scope of the microwave-assisted ring-expansion

With the optimized conditions in hands, a reasonable substrate scope was synthesized. Besides methanol, other alcohols such as *i*PrOH, *n*-BuOH, or BnOH could be employed as solvents in the ring-opening of **140**, giving rise to the corresponding pyrans or dihydropyridines **105** (Scheme 39).



Scheme 39. Microwave-assisted ring-expansion of **140** (0.3-2.8 mmol); combined isolated yield of two diastereomeres is given and the major diastereomer is shown; [a] determined by chiral HPLC by analyzing the epimeric mixture; [b] Scale-up: 4.02 mmol of **140a** and 4.86 mmol of **140b** were employed to yield 1.22 g of **105d** and 1.68 g of **105f**; [c] diastereomeres were isolated in pure form (see SI for details); [d] 2,6-Lutidine (1.2 equiv), MeOH, MW, 60 °C, 16 h.

When the furan derived precursor **140a** was applied, various pyran derivatives **105a-d** were received in excellent yield up to 99% and the structure of **105a** was confirmed by single crystal X-Ray crystallography. Additionally, the diastereomeric ratio was improved by using bulky alcohols and in case of **105b-d** the diastereomers were easily separated. If enantiopure starting material **(+)-140a** was used, the initial *ee*-value could be successfully transferred to the corresponding product **(-)-105a**. Furthermore, an electron withdrawing substituent at C5-position decreased the mandatory electron donating character of the adjacent heteroatom which prohibited the conversion of the starting material **140e** to the expected pyran derivative **105e**. By switching to the *N*-Boc pyrrole derived precursors **140b-d**, similar results with respect to yield and diastereoselectivity were obtained and the structures of **105g** and **105i** were proved by single crystal X-Ray crystallography. If **140b** was used as starting material, the expected piperidine derivatives **105g** and **105h** were obtained in good yield, whereupon **105f** could be isolated in almost quantitative yield.[7] Furthermore, the use of the *N*-tosyl derived precursor **105c** led to a successful product formation in 93% yield. Since the *N*-Ts-pyrrole cyclopropane **102b** can be synthesized in an enantiopure manner by Rh(II)-catalysis published by *Davies et al.*[92] the established ring-expansion can be conducted under retention of the stereochemistry as it was shown in the case of the furan derived precursor **(+)-105a**. The transformations proceeded generally in high yields with the exception of **105j** and **105k**, which was found to be unstable, suffering from elimination and oxidation ultimately leading to pyridine derivatives.

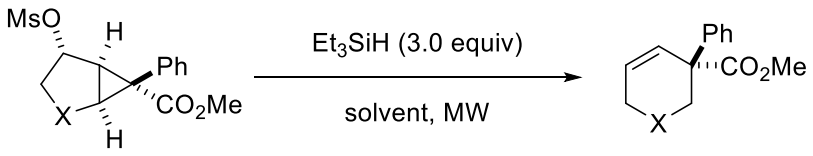
Even if the established protocol provided the pyran and dihydropyridine derivatives in excellent yield, it turned out to be extremely limited in terms of starting materials and employed nucleophiles. Nevertheless, the reaction worked in unpolar alcohols which made a change to an inert polar aprotic solvent reasonable. Aiming to extend the scope of the process to nucleophiles that cannot be employed as solvent, we improved the established microwave-assisted ring-expansion as described in the following.

[7] The results for synthesis of **105f-h** are taken from the Bachelor thesis of A. Tiefel, 2019, Universität Regensburg (supervised by R. Eckl).

2.1.5.4 Development of a versatile ring-expansion of cyclopropanated furans enabling various couplings

Until now, the established ring-expansion gave promising results which might enable further development reaching a universal methodology allowing different types of couplings which would give access to a pool of chiral pyrans and dihydropyridines. To confirm this hypothesis, the applied conditions were chosen to design the simplest result as possible. On account of this consideration, precursor **140a** was selected as model substrate and triethylsilane provided a hydride as nucleophile. Different polar aprotic solvents in combination with different temperatures were screened to reveal suitable conditions (Table 10).

Table 10. *In situ* reduction starting from **140a** as potential model for the development of a versatile methodology.



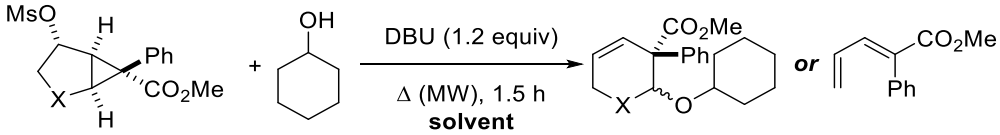
140a **105l**

entry	X	solvent	T [°C]	T [h]	results
1	O	THF	80	1.5	no conversion
2	O	THF	120	1.5	no conversion
3	O	DMF	80	1.0	no conversion
4	O	DMF	100	1.0	partial conversion
5	O	DMF	120	3.0	67%
6	NBoc	DMF	120	3.0	complex mixture

Interestingly, starting with THF at 80 °C (Table 10, entry 1) or at 120 °C (Table 10, entry 2) resulted in no conversion of the starting material **140a**. Thus, THF itself seemed not to be polar enough to launch the reaction. As consequence, THF was replaced by DMF and different temperatures were screened beginning with 80 °C (Table 10, entry 3) and 100 °C (Table 10, entry 4) but only partial conversion was

observed in the latter. Finally, conducting the ring-expansion of **140a** at 120 °C resulted in 67% yield of the expected product **105l** after 3 h. In contrast, the ring-expansion of pyrrole derived precursor **140b** resulted in a complex mixture under these conditions after 3 h. With these promising results in hands, a second screening was carried out and triethylsilane was replaced by a more complex nucleophile, additionally, different polar aprotic solvents were tested. Again, furan derived mesylate **140a** served as starting material and cyclohexanol (**152**) was applied as nucleophile (Table 11).

Table 11. Studies towards the use of complex alcohols in the established protocol including the screening of the solvent and the required amount of nucleophile.



140a: X = O
140b: X = NBoc
140c: X = NTs

152 (**x** equiv)

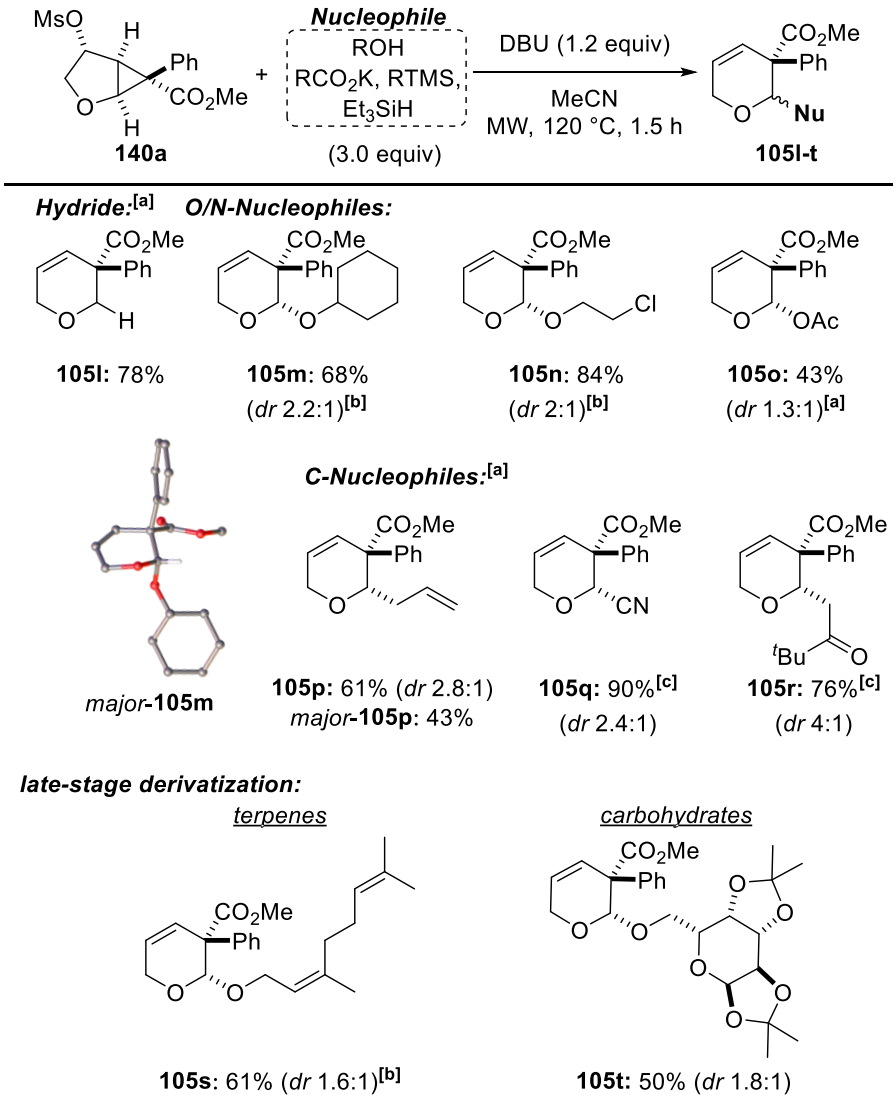
105

153

entry	X	solvent	equivalents of 15	T [°C]	Yield 105 [%]
1	O	THF	5.0	120	no conversion
2	O	DMF	5.0	120	51 (**153**)
3	O	MeCN	5.0	120	69
4	O	MeCN	1.2	120	44
5	O	MeCN	3.0	120	66
6	O	MeCN	10.0	120	74
7	NBoc	MeCN	3.0	150	34
8	NTs	MeCN	3.0	150	29

First, different polar-aprotic solvents were tested revealing MeCN as a suitable solvent (Table 11, entry 3) affording the desired product **105m** in 69% yield. In contrast, with THF (Table 11, entry 1) no conversion of **140a** was observed. Using DMF (Table 11, entry 2) yielded in **153** which was formed under acidic conditions since DBU seemed to has reacted with DMF under microwave irradiation as it was observed by Ramírez-

Jiménez and co-workers.[136] The solvent screening was followed by applying different amounts of the nucleophile **152**. Initially, 5.0 equivalents of **152** were used and the amount was varied from 1.2 up to 10.0 equivalents whereupon 3.0 equivalents resulted in 66% yield of the expected product **105m** which turned out to be synthetically and ecologically worthwhile (Table 11, entry 4). Switching to *N*-Boc-pyrrole derived precursors **140b** and **140c** only low yields of the desired products were achieved (Table 11, entry 7-8). Due to these results, it was focused on the furan derived precursors **140a** while various nucleophiles that cannot be employed as solvent were applied in order to extend the substrate scope (Scheme 40).



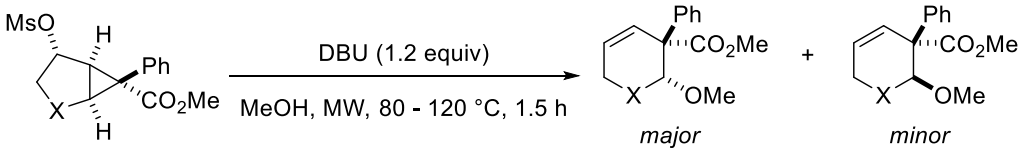
Scheme 40. Microwave-assisted ring-expansion of **140a** (0.32 mmol); combined isolated yield of two diastereomeres is given and the major diastereomer is shown [a] no base was necessary; [b] diastereomeres were isolated in pure form (see SI for details); [c] reaction time of 4 h.

Using 2-chloroethan-1-ol gave 84% of expected product **105n** which demonstrated the selectivity of the methodology concerning further nucleophilic pathways. In case of **105m** and **105n** the diastereomers were readily separated. Single crystal X-Ray crystallography of the separated major diastereomere *major*-**105m** confirmed the assumption that the nucleophilic attack at the planar oxonium ion occurs predominantly *trans* to the phenyl group due to steric reasons. Furthermore, it was possible to use carboxylates as nucleophiles providing **105o** in moderate yield of 43%. Additionally, it was possible to perform an *in situ* reduction of the oxonium ion with triethylsilane as the reducing agent giving **105l** in 78% yield. Switching to carbon nucleophiles gave access to a new product class which enabled a carbon-carbon bond formation during the ring-expansion. Reactions with an enol, allyl or cyanide gave the expected products **105p-r** up to 90% yield, whereupon 43% of the major diastereomere *major*-**105p** was separated. Finally, a late-stage derivatization was achieved opening up the possibility of synthesizing functionalized terpenes **105s** and unnatural glycosides **105t**. Notably, the diastereomers of the geraniol derivative **105s** were separated and it was demonstrated that 74% (2.2 equiv) of unreacted geraniol could be re-isolated. In general, typical epimers were obtained at the anomeric center which could be readily separated in most cases.

In summary, the initially established protocol of the microwave-assisted ring-expansion of monocyclopropanated heterocycles was successfully expanded to a generalized method with MeCN as the polar-protic solvent of choice, thus, allowing the introduction of more complex alcohols, carboxylic acids, hydride or various C-nucleophiles, additionally, the late-stage derivatization of sugars and terpenes was demonstrated. Finally, the microwave-assisted ring-expansion became a powerful and versatile tool for the synthesis of highly functionalized six-membered heterocycles. In the following DFT-calculations were considered to confirm the proposed mechanism and to explain the selectivity of the microwave-assisted ring-expansion of monocyclopropanated heterocycles.

2.1.5.5 Mechanistic considerations – computational studies

The established stereoselective ring-expansion of monocyclopropanated furans and pyrroles is an elegant method to provide highly functionalized and versatile pyrans and diydropyridines on gram-scale. So far, the best results were obtained applying DBU as base and MeOH as solvent which resulted in almost quantitative yield of the desired products under microwave irradiation (Scheme 41).



140a: X = O
140b: X = NBoc
140c: X = NTs

105a: X = O, 99% (*dr* 2.6:1)
105f: X = NBoc, 99% (*dr* 1.9:1)
105j: X = NTs, 93% (*dr* 9.4:1.0)

Scheme 41. Best results obtained in the ring-expansion of monocyclopropanated furans and pyrroles **140a-c**.

In order to explain the product formation and the diastereoselectivity, mechanistic considerations were made and DFT-calculations utilizing furan derived precursor **140a** as the model substrate was used to propose a possible reaction mechanism.[8] The calculations were performed on a B3LYP/6-31+G(d,p) level of theory in the gas phase using the Gaussian09 Rev. E.01 software package.[137–147,148] Therefore, the transformation was divided in two parts: the formation of the oxonium ion and the nucleophilic trapping of the intermediate. First, the formation of the oxonium ion was considered (Figure 5). In the first step the calculations revealed an activation barrier of 55.5 kcal/mol which can be overcome by thermal activation. The transition state shows a concerted opening of the cyclopropane moiety and the release of the mesylate group. The stabilized oxonium ion intermediate shows an energy 19.5 kcal/mol higher than the substrate molecule. A stabilization seems to be achieved by intermolecular interactions between the oxonium ion and the mesylate.

[8] The DFT-calculations were provided from Daniel Schmidhuber (AK Rehbein, Universität Regensburg).

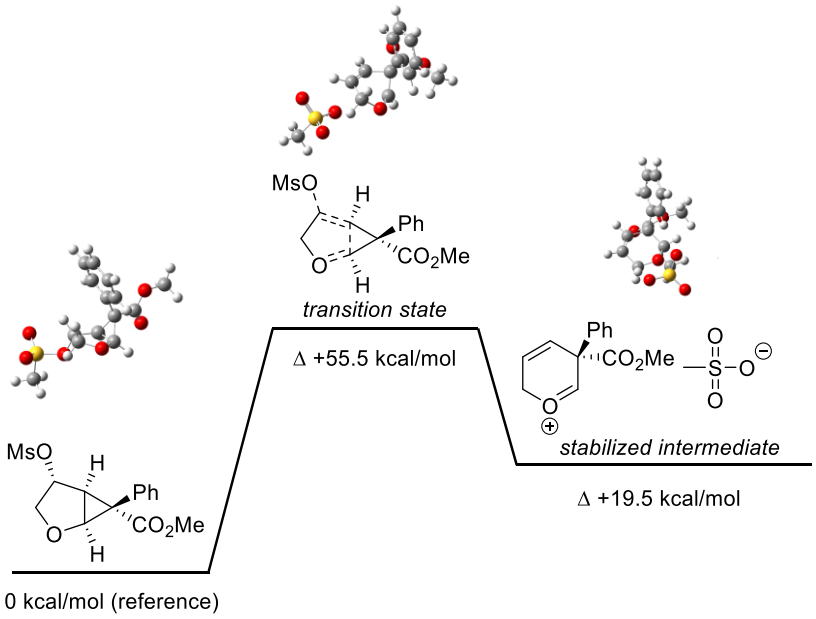


Figure 5. Reaction profile of the oxonium ion formation obtained by calculations on a B3LYP/6-31+G(d,p) level of theory in the gas phase; the oxonium ion intermediate is stabilized by intermolecular interaction with the mesylate group.

To obtain more information about the possible stabilizing effect of the solvent, further calculations will have to be carried out in the future. Finally, the oxonium ion is trapped by a nucleophile and the formation of two diastereomers was observed (Figure 6).

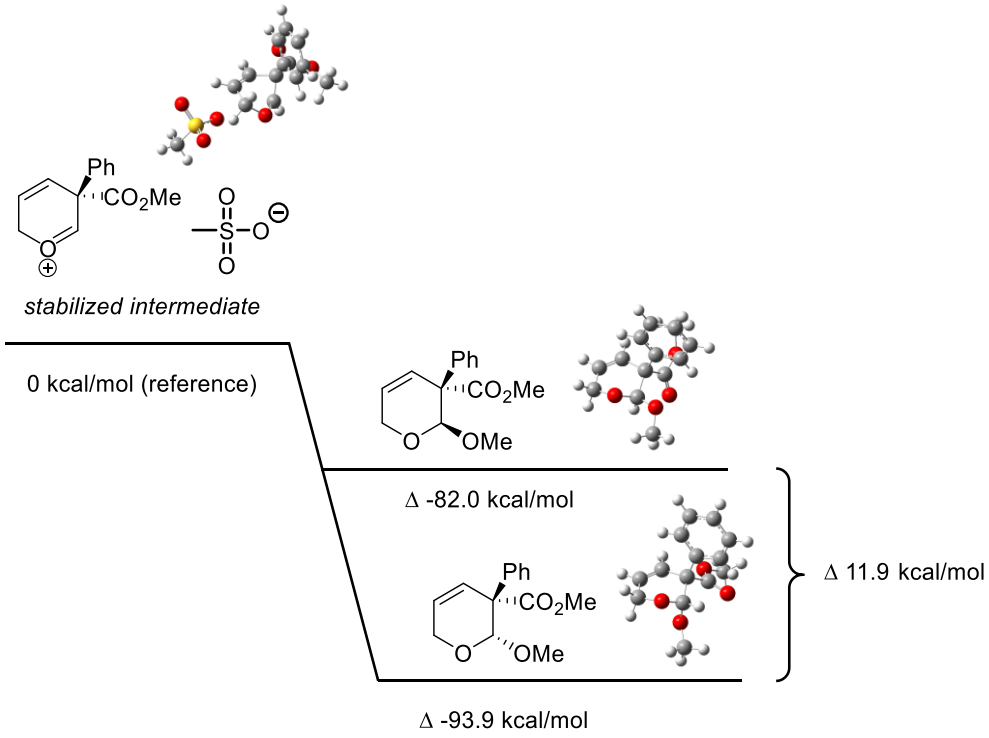
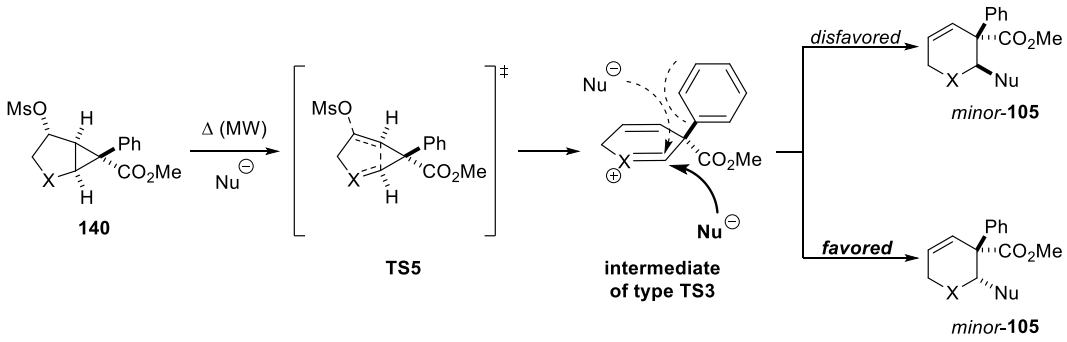


Figure 6. DFT-calculations concerning the nucleophilic trapping of the stabilized intermediate by methanolate on a B3LYP/6-31+G(d,p) level of theory in the gas phase.

Besides sterical reasons, the major diastereomer is also energetically more favored due to an energetic difference between minor and major diastereomer of Δ 2.3 kcal/mol. These calculations are consistent with the obtained experimental results.

In summary, a generalized mechanism for the microwave-assisted ring-expansion of monocyclopropanated furans and pyrroles can be postulated by taking the DFT-calculations into account. Furthermore, the proposed mechanism is not limited to the transformation using the respective alcohol as solvent, it is also valid for the established generalized protocol which allowed the use of external nucleophiles in an inert solvent (Scheme 42).

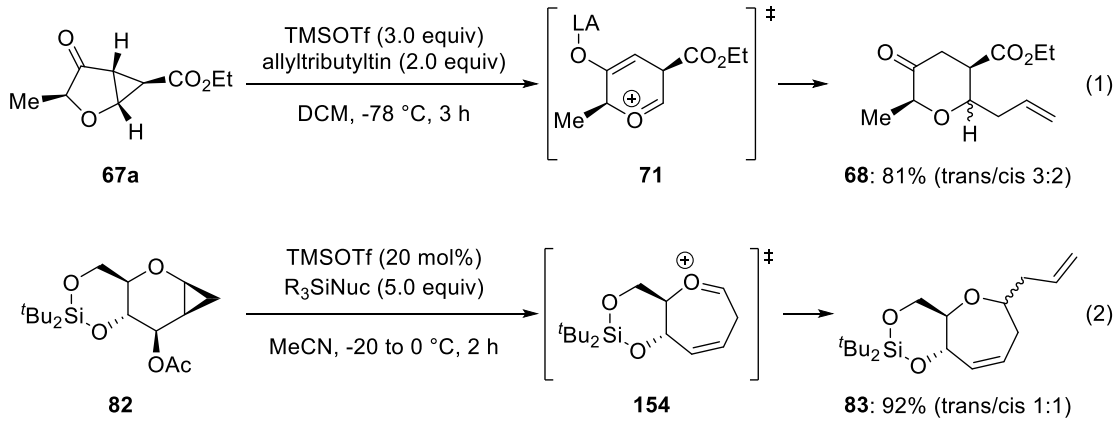


Scheme 42. Proposed mechanism for the microwave-assisted ring-expansion based on computational studies.

2.1.6 Stereoselective acidic endocyclic cyclopropane bond cleavage

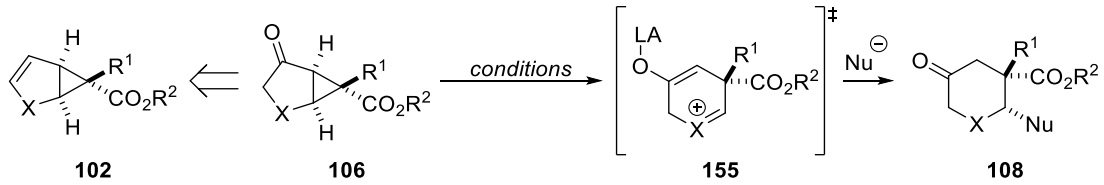
2.1.6.1 Lewis acid mediated approach

Besides the established microwave-assisted ring-expansion, it is known that monocyclopropanated furans can undergo a ring-expansion *via* lewis acid activation of the ketone moiety in **67a**. This method was published by Gharpure *et al*. where they showed that TMSOTf is a suitable lewis acid for the ring-expansion of interest (Scheme 43, equation (1)).[69] Earlier, a similar approach was established by Hoberg *et al*. for the ring-expansion of sugar derived cyclopropanes **82** in their synthesis of seven-membered oxacycles by abstracting –OAc as leaving group *via* lewis acid activation (Scheme 43, equation (2)).[75] In both examples the transformation resulted in a diastereomeric mixtures, however, the products were obtained in good to excellent yield.



Scheme 43. Examples of a stereoselective lewis-acid mediated ring-expansion of cyclopropane derivatives.[69,75]

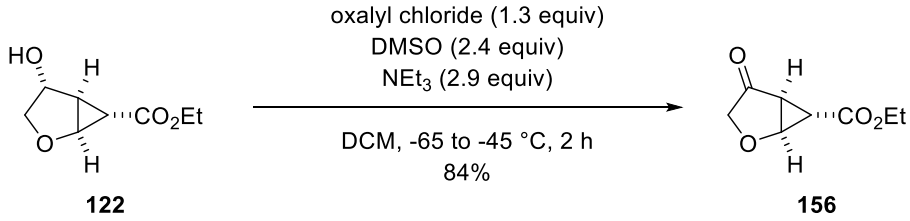
Since this type of opening remained an underexplored topic and due to the fact, that the established hydroboration offered an extended scope of suitable starting materials, the methodology should be expanded. Additionally, it was questioned if this protocol can be improved to get access to a diastereoselective pathway (Scheme 44).



Scheme 44. Planned synthetic improvement of the lewis acid mediated ring-expansion of precursors **106**.

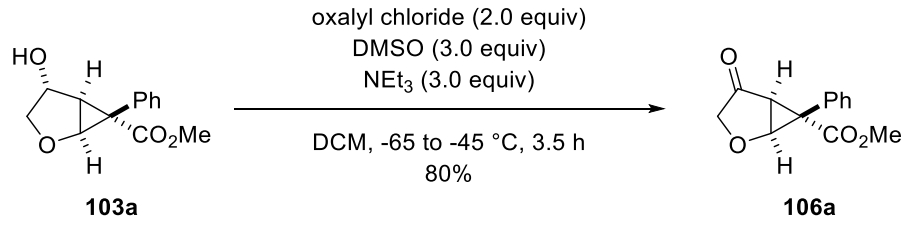
2.1.6.2 Synthesis of promising ketones by Swern-Oxidation

For the synthesis of ketones starting from secondary alcohols several different conditions such as the oxidation with dichromate, CrO_3/pyridine (Collins reagent), Dess-Martin periodane, CrO_3/H_2SO_4/acetone (Jones-Oxidation) or DMSO/oxalyl chloride (Swern-Oxidation) are commonly used in organic synthesis.[149] Monn *et al*. showed that the oxidation of **122** is easily accessible by Swern Oxidation giving **156** in good yield (Scheme 45).[100]



Scheme 45. Swern-Oxidation of hydroxylated furan **122** established by Monn *et al*. to access ketone **156**.[100]

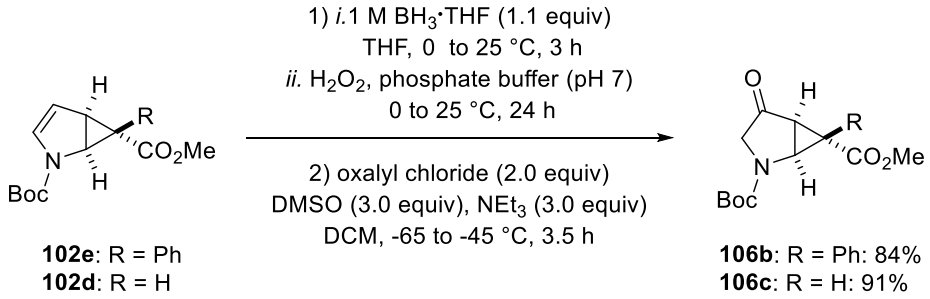
Since the starting material used by Monn *et al.* showed the same core structure,[100] their procedure was directly adapted to **103a** as the starting material. After optimizing the amount of applied reagents, full conversion was achieved, hence, 80% of desired ketone **106a** was isolated after 3.5 h (Scheme 48).



Scheme 46. Synthesis of ketone **106a** *via* Swern-Oxidation starting from **103a** applying the conditions published by Monn and co-workers.[100]

Furthermore, the same optimized conditions were successfully applied to the transformation of cyclopropanated *N*-Boc pyrrole derivatives **103b** and **103d** to their corresponding ketones **106b** and **106c**. In contrast to the example using furan derivative **103a** as precursor, it was directly started from cyclopropanes **102d** or **102e** since the hydroxylated cyclopropanated pyrrole derivatives, especially **103d**, turned out to be rather unstable on silica gel during purification *via* column chromatography.

Consequently, after hydroboration the alcohols were immediately oxidized to the corresponding ketones **106b** or **106c** without further purification (Scheme 47).

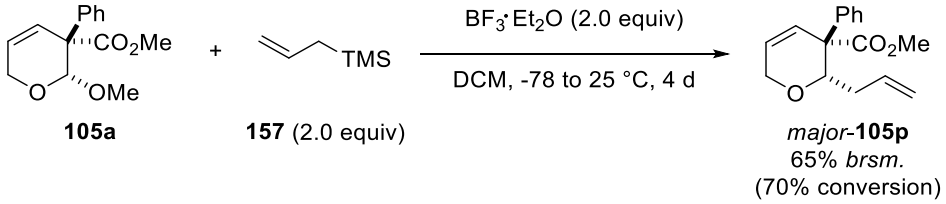


Scheme 47. Synthesis of pyrrole derived ketones **106b** and **106c** *via* Swern-Oxidation; the yields are given over two steps.

Finally, ketone **106b** was received in 84% yield, whereas the synthesis of **106c** resulted in 91% yield. These compounds served as staring materials for expanding the lewis-acid mediated pathway of *tetra*-substituted cyclopropanes and *N*-Boc-pyrrole derivatives.

2.1.6.3 Studies towards a diastereoselective Lewis acid mediated ring-expansion

The plan of improving the lewis acid mediated ring-expansion to achieve a diastereoselective protocol was supported by an established derivatization of pyran **105a** which resulted in a diastereoselective product formation (Scheme 48.)

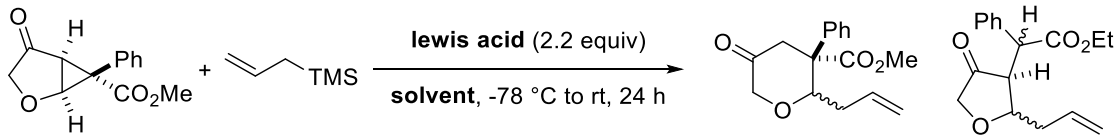


Scheme 48. Diastereoselective lewis acid mediated allylation of pyran **105a**.

Pyran **105a** was activated with BF_3 as lewis acid and **157** was applied as nucleophile which gave exclusively allylated pyran *major*-**105p** in 65% yield (*brsm.*). The stereochemistry of the product was assigned by 2D-NMR spectroscopy. The diastereoselectivity of this reaction was mainly caused by the sterically demanding

phenyl group attached to the adjacent quaternary carbon center. Due to this observation, it was questioned if the pathway established by Gharpure *et al.*[69] can be improved to get access to a diastereoselective method with phenyl substituted cyclopropanated heterocycles. To confirm this hypothesis, the conditions of the BF_3-mediated derivatization of pyran **105a** and the procedure of Gharpure *et al.*[69] were combined (Table 12).

Table 12. Screening of potential reaction conditions for a diastereoselective ring-expansion of **106a**.

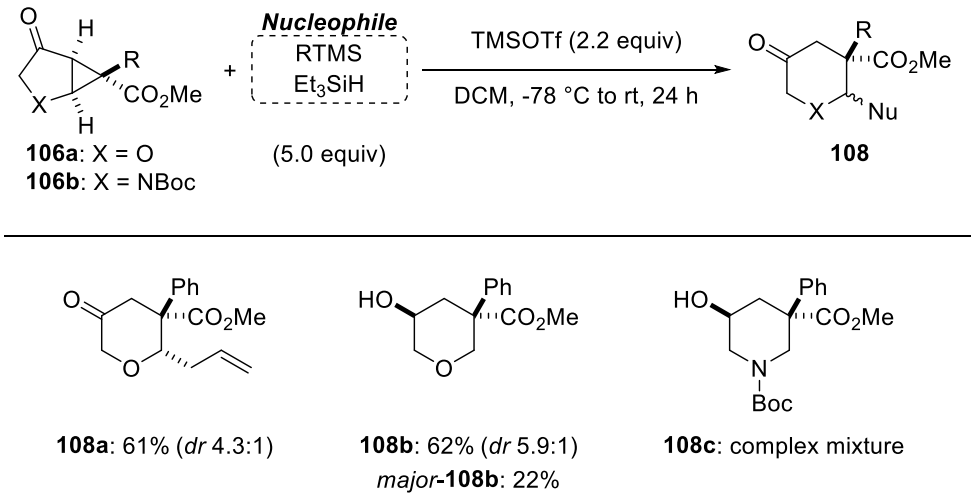


106a **157** (5.0 equiv) **108a** **158**

entry	lewis acid	solvent	yield of 108a
1	$BF_3 \cdot Et_2O$	DCM	traces of **158**
2	TMSOTf	DCM	61% (*dr* 4.3:1)
3	TMSOTf	MeCN	58% (*dr* 4:1)

Thus, $BF_3 \cdot Et_2O$ was applied as lewis acid in combination with trimethylallylsilane as the nucleophile in DCM at -78 °C (Table 12, entry 1). Even after 24 h, mostly unconverted starting material was *re*-isolated, additionally, the formation of **158** *via* an exocyclic opening in traces was observed. When TMSOTf was used as a stronger lewis acid, the desired product **108a** was obtained in 61%. Unfortunately the product **108a** was obtained as diastereomeric mixture (*dr* 4.3:1) (Table 12, entry 2). Employing MeCN as solvent did not result in the desired diastereoselective product formation as it would have been expected from the initially obtained results (Table 12, entry 3). Unfortunately, the screening resulted only in an improved diastereomeric ratio of product **108a** but the initial hypothesis could not be confirmed. Due to those results, developing a diastereoselective pathway seems to be not possible *via* a lewis-acid mediated protocol.

Nevertheless, the substrate scope of the protocol was expanded applying new furan derived precursors. Additionally, the ring-expansion was also conducted with *N*-Boc pyrrole derivative **106b** (Scheme 49).



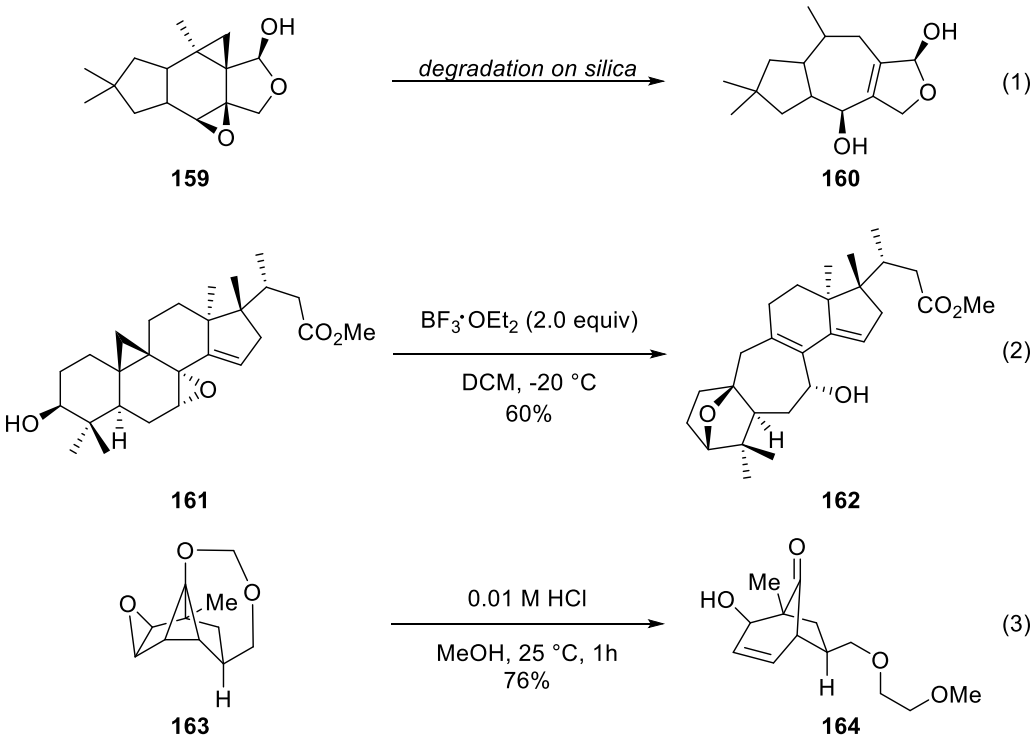
Scheme 49. Expansion of the substrate scope using the lewis acid mediated pathway; only the major diastereomere is shown.

Besides the allylated product **108a** which was obtained in 61% yield (*dr* 4.3:1), it was also possible to convert the starting material **106a** with triethylsilane as the nucleophile to pyran derivative **108b** in 62% yield (*dr* 5.9:1) and 22% of pure *major*-**108b** were separated. In this particular case, the diastereomers are arising from the hydroxyl group which is formed during the opening by reduction of the *in situ* formed enol to the alcohol since triethylsilane was used in five-folded excess. In contrast, using the *N*-Boc-pyrrole derivative **106b** as precursor only a complex reaction mixture was obtained. It is known from peptide chemistry that the Boc-protection group is easily cleaved by TMSOTf.[150] Thus, this methodology seemed to be a promising method for the synthesis of pyrane derivatives starting from furan based precursors, whereupon the conditions turned out to be too harsh for the ring-expansion of *N*-Boc-pyrrole derivatives.

Besides pyran derivatives, especially highly functionalized pyridines and piperidines have attracted great attention in organic chemistry and are present in various drug targets. Studies towards a successful ring-expansion of monocyclopropanated furans and pyrroles under acidic conditions are presented in the following.

2.1.6.4 Ring-expansion of vinylcyclopropane epoxides

In addition to the ring-expansion of monocyclopropanated heterocycles *via* the activation of the ketone moiety, there are also few examples present showing that reactions with vinylcyclopropane epoxides are able to trigger a ring-opening of cyclopropanes. Besides a radical type reaction,[151] the opening of the vinylcyclopropane epoxides is achieved by Brønsted or Lewis acids (Scheme 50).

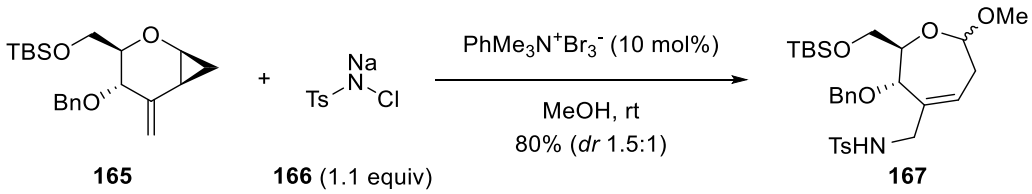


Scheme 50. Selected examples for the ring-expansion of cyclopropanated carbocycles *via* acidic activation of vinylcyclopropane epoxides.

In 1984, Sterner *et al.* were the first who observed the ring-expansion of vinylcyclopropane epoxides giving cyclic allyl alcohol **160** during purification of velutinal esters **159** (isolated from the mushroom species *Lactarius*) on silica but the yield remained unreported (Scheme 50, equation (1)).[152] The same type of transformation was utilized by Corey *et al.* in their natural product synthesis of glycinolepin to access the desired ring-expansion of vinylcyclopropane epoxide **161** by lewis-acid activation giving seven-membered carbocycle **162** in moderate yield (Scheme 50, equation (2)).[14] Latest research confirmed that the ring-expansion *via* vinylcyclopropane epoxides is a powerful tool for the synthesis of seven-membered carbocycles.[153] Also in bridged systems such as **163** this method can easily be applied

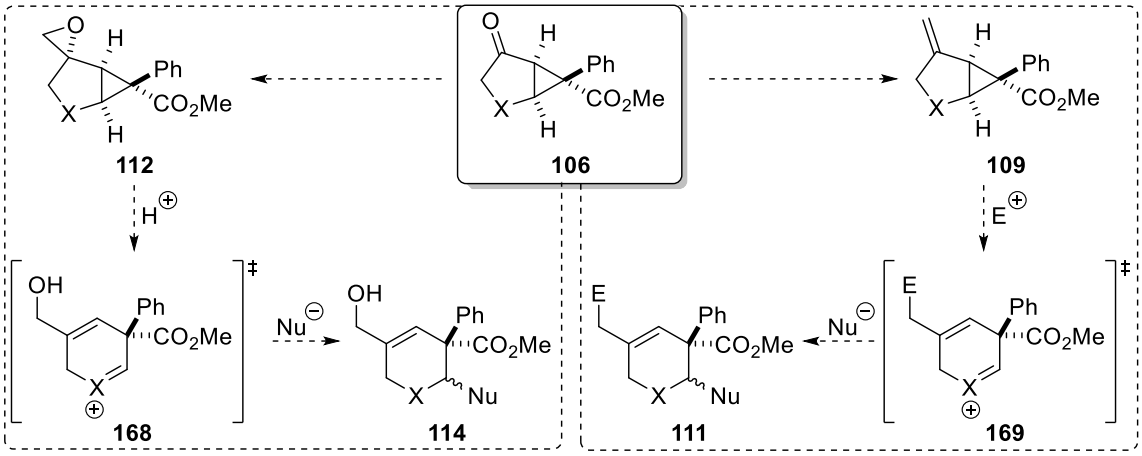
to obtain **164** in good yield after activation of the epoxide by Brønsted acids as it was published by Penkett *et al.* (Scheme 50, equation (3)).[154]

Besides this smart acidic ring-opening of vinylcyclopropane epoxides, *exo*-methylene groups can also be utilized to achieve a ring-expansion of monocyclopropanated heterocycles by cleaving the endocyclic carbon-carbon bond. A meaningful example was published by Ganesh *et al.* where they developed a α-Ferrier ring-expansion of carbohydrate derived vinyl cyclopropanes **165**. By an electrophilic addition to the *exo*-methylene group, mediated by chloramine T (**166**) and a phase-transfer catalyst, they got access to oxepane analogues **167** as epimeric mixtures in good yield (Scheme 51).[155]



Scheme 51. α-Ferrier ring-expansion of carbohydrate derived vinyl cyclopropanes **165**.[155]

Both methods were found to induce a selective endocyclic carbon-carbon bond cleavage in cyclopropanes, hence, enabling the ring-expansion of monocyclopropanated heterocycles. Since the oxidation of the hydroxylated furans and pyrroles gave the corresponding ketones **106** in excellent yield it seemed worthwhile to apply the presented alternative reaction pathways to precursor **103** or **112** which should be accessible from ketones **106**. (Scheme 52)

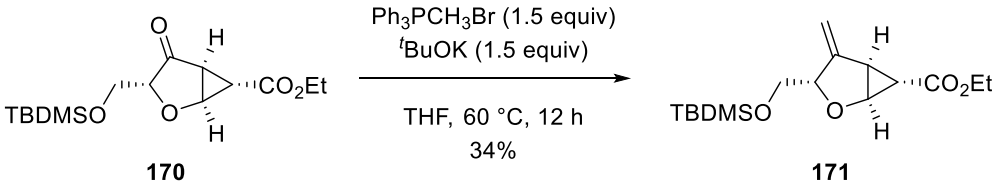


Scheme 52. Potential pathways for a selective ring-expansion of ketones **106** by inducing the endocyclic carbon-carbon bond cleavage *via* activation of vinylcyclopropane epoxide **112** or an *exo*-methylene group in **109**.

On the one hand, converting the ketone moiety in **106** to an *exo*-methylene group by a Wittig reaction with phosphorous ylides might give access to a type of α-Ferrier ring-expansion as it was published by Ganesh *et al*.[155] *via* an electrophilic addition to the *exo*-methylene group. The resulting intermediate **169** can then be trapped by a nucleophile giving rise to **111**. On the other hand, using sulfur ylides in the Corey-Chaykovsky reaction allows the transformation of ketone **106** to spiro-epoxides **112**. With the presented literature in mind, applying typical conditions for an epoxide opening might trigger the desired ring-expansion which would yield in products of type **114**. To confirm this hypothesis, ketones **106** were applied in a Wittig- or Corey-Chaykovsky-reaction to obtain suitable model substrates for developing these ring-expansion pathways.

2.1.6.5 Synthesis of suitable precursors

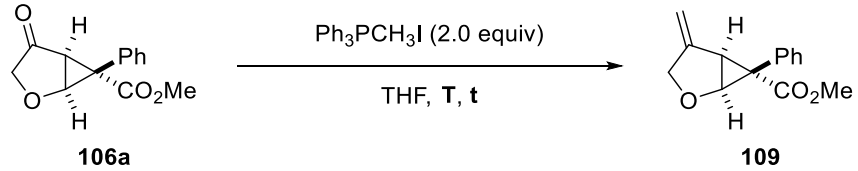
As a first attempt, a Wittig reaction should be conducted to introduce an *exo*-methylene group. In literature, a similar conversion is already known which was published by Kim *et al.* (Scheme 53).[29]



Scheme 53. Wittig reaction on furan derived cyclopropanes **170** established by Kim and co-workers.[29]

They applied a sugar derived monocyclopropanated furan derivative **170** which was treated with an *in situ* generated phosphorous ylide to achieve the transformation of the ketone moiety to an *exo*-methylene group. After 12 h at 60 °C they obtained the desired product **171** in low yield of 34%. The reported low yield in this particular Wittig reaction already suggested that this type of reaction might not be the most promising pathway for the synthesis of the required precursors. Nevertheless, a screening was investigated starting with the conditions published by Kim *et al.*[29] (Table 13).

Table 13. Screening of suitable reaction conditions for the Wittig-reaction with **106a** as precursor.

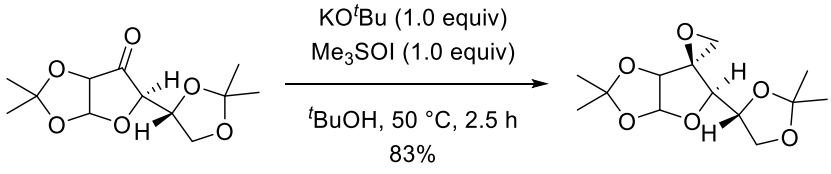


entry	base	equivalents	T [°C]	t [h]	yield
1	^{t}BuOK	1.5	25 to 60	24	no conversion
2	*n*BuLi	1.8	25	0.33	27%
3	*n*BuLi	1.8	0	0.33	28%

Running the first test reaction as reported by Kim *et al.*[29] resulted in no conversion at 25 °C. Also increasing the temperature to 60 °C resulted in no conversion of the starting material (Table 13, entry 1). Changing the base from ^{t}BuOK to *n*BuLi led to full conversion at 25 °C, but only 27% of the expected product **109** was isolated

(Table 13, entry 2). Also decreasing the temperature to 0 °C did not improve the yield of **109** (Table 13, entry 3). Due to the low yield, the Wittig reaction turned out to be not promising for the synthesis of the required precursors in acceptable yield.

Consequently, it was focused on the synthesis of vinylcyclopropane epoxides *via* a Corey-Chaykovsky reaction involving *in situ* generated sulfur ylides as reagents. A promising example for this type of reaction is given by Soler *et al*. in their synthesis of functionalized sugars (Scheme 54).[156]

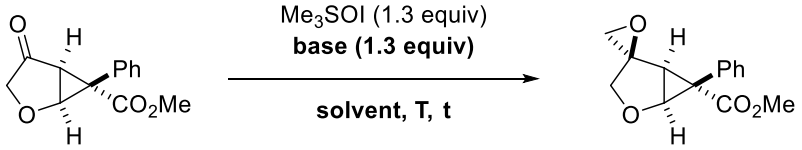


172 **173**

Scheme 54. Example for a successful application of the Corey-Chaykovsky in the synthesis of spiro-epoxide **173**.[156]

They treated ketone **172** with Me_3SOI and KO^{t}Bu to obtain the epoxide **173** in good yield after 2.5 h at 50 °C. Since the core structure in **172** is comparable to furan derived ketone **106a** the screening was started with the reported conditions (Table 14).

Table 14. Screening of suitable reaction conditions for a Corey-Chaykovsky reaction affording vinylcyclopropane epoxide **112a**.



106a **112a**

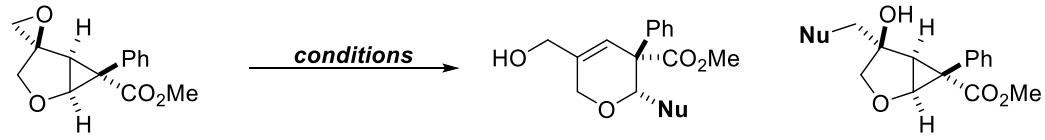
entry	base	solvent	T [°C]	t [h]	results[a]
1	KO^{t}Bu	^{t}BuOH	50	72	no conversion
2	KO^{t}Bu	DMSO	50	72	no conversion
3	NaH	DMSO	0 → 25	20	full conversion

[a] the yield remained unreported since the product was directly applied in the following ring-expansion.

Unfortunately, the reported conditions using KO^{t}Bu as base in *tert*-butanol resulted in no conversion of the starting material **106a** after 72 h at 50 °C (Table 14, entry 1). Since KO^{t}Bu seemed to be hardly soluble under these conditions the solvent was changed to

DMSO, however, no conversion was observed even if KO^{t}Bu was completely dissolved (Table 14, entry 2). Due to this result, it seemed obvious that the applied base was too weak and was replaced by NaH immediately (Table 14, entry 3). Finally, the desired epoxide **112a** was obtained after 20 h at 25 °C. Additionally, the structure was confirmed by 2D-NMR spectroscopy and HRMS. Then, epoxide **112a** was directly applied in the screening of the ring-expansion without further purification since it turned out to be rather unstable. Consequently, the yields in the following screening are given over two steps (Table 15).

Table 15. Studies towards the ring-expansion of vinylcyclopropane epoxide **112a** under acidic conditions.



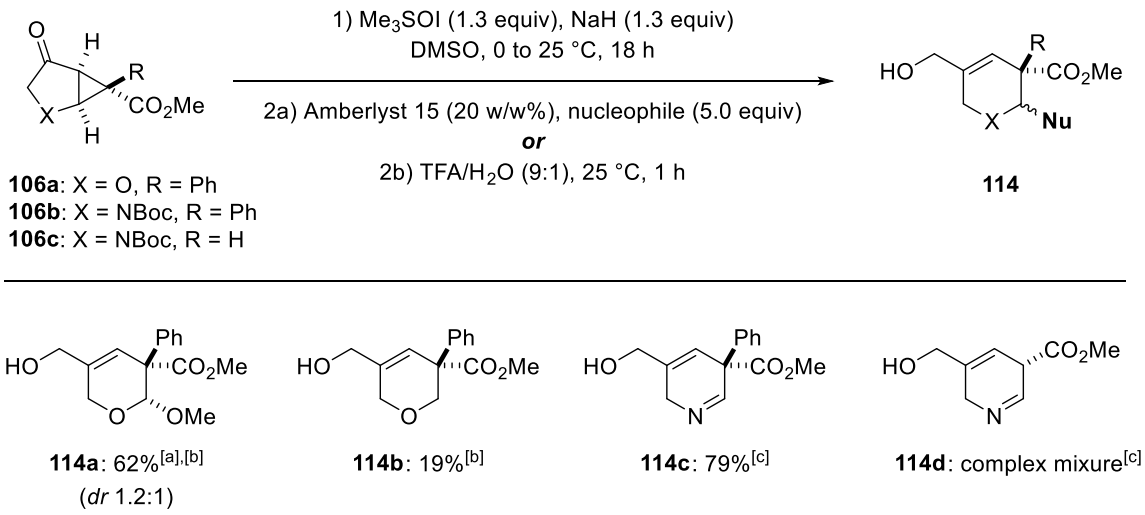
112a **114a**: Nu = OMe **114b**: Nu = H **174**

entry	acid[a]	solvent	Nu	T [°C]	t [h]	results[c]
1	Amberlyst 15	MeOH	MeOH	0	24	34% **114a** (*dr* 2.1:1), 7% **174**
2	Amberlyst 15	MeOH	MeOH	25	0.5	56% **114a** (*dr* 3.5:1), 16% **174**
3	Amberlyst 15	MeCN	MeOH	25	1	62% **114a** (*dr* 1.2:1)
4[b]	Amberlyst 15	MeCN	Et_3SiH	25	1	complex mixture
5[b]	TMSOTf	MeCN	Et_3SiH	25	0.5	19**% 114b**

In case of **114** only the major diastereomere is shown; [a] 20 w/w% Amberlyst 15 or 1.1 equiv of TMSOTf were used; [b] 5.0 equiv of required nucleophile were applied; [c] yield is given over two steps.

As a first test reaction, the opening was conducted in MeOH and Amberlyst 15 was used as acidic resin which initially gave 34% yield of the expected ring-opening product **114a** as epimeric mixture (*dr* 2.1:1) after 24 h at 0 °C (Table 15, entry 1). Additionally, formation of side product **174** was observed. Running the same reaction at 25 °C gave the expected product **114a** in 56% yield (*dr* 3.5:1) after 30 min but also the amount of side product **174** was increased (Table 15, entry 2). The formation of the side product **174** can be explained by a simple nucleophilic opening of epoxide **114a** by MeOH. This nucleophilic opening was prevented by applying MeOH as external nucleophile in five-

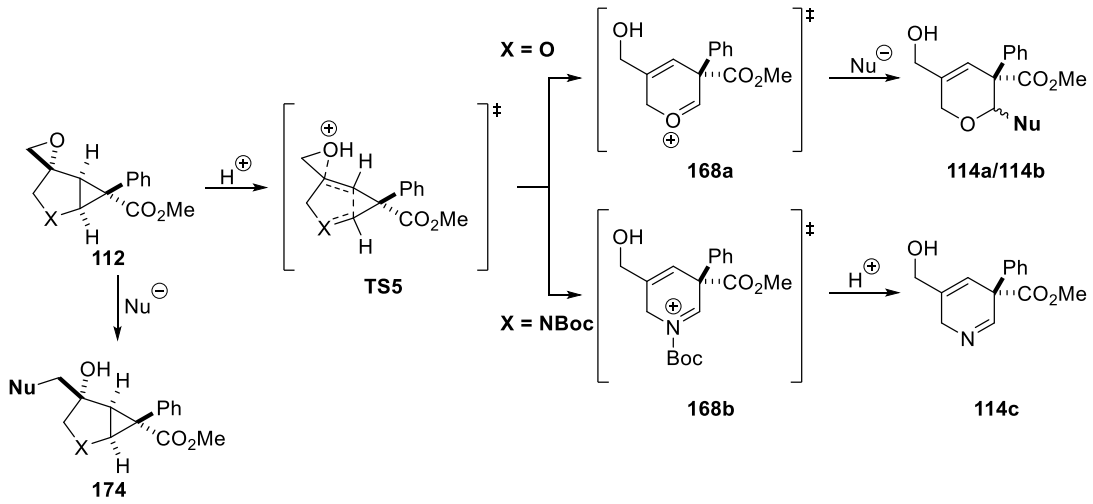
folded access while MeCN served as a solvent (Table 15, entry 3). Finally, the expected ring-opening product **114a** was received in 62% yield as epimeric mixture (*dr* 1.2:1) and the stereochemistry was in accordance with the observations during the microwave-assisted ring-expansion. Additionally, the assumption was proved by 2D-NMR spectroscopy. When the nucleophile was replaced by Et_3SiH as hydride source to perform an *in situ* reduction only a complex reaction mixture was received after 1 h at ambient temperature (Table 15, entry 4). In contrast, when TMSOTf was used as lewis acid instead, the expected product **114b** was obtained in 19% yield after 30 min at 25 °C (Table 15, entry 5). In summary, a protocol for the transformation of furan derived ketone **106a** *via* a Corey-Chaykovsky epoxidation followed by the ring-expansion under acidic conditions was established. With this procedure in hand a reasonable substrate scope was synthesized and, in addition to the furan derived precursor **106a,** the protocol was also applied to *N*-Boc pyrrole based ketones **106b** and **106c** (Scheme 55).



Scheme 55. Synthesis of a reasonable substrate scope applying furan and *N*-Boc pyrrole derivatives **106** as precursors; [a] only the major diastereomere is shown; [b] conditions 2a) were applied; [c] conditions 2b) were applied.

Besides the synthesis of the pyrans **114a** and **114b** which was already described in Table 15, the established method was applied to *N*-Boc pyrrole derivatives **106b** and **106c**. In contrast to the ring-expansion of furan derived epoxide **112a**, the activation of the corresponding epoxides of **106b** or **106c** was performed with typical conditions for a Boc-deprotection. Treating the corresponding epoxide of ketone **106b** with a 9:1 mixture of TFA/water at ambient temperature gave access to the expected six-

membered imine **114c** in 79% yield as single diastereomere. Unfortunately, performing the reaction with ketone **106c** under the same conditions resulted in a complex reaction mixture. To explain the observations during the established acid-mediated ring-expansion of monocyclopropanated furans and pyrroles, some mechanistic considerations in accordance to the received DFT-calculations for the mechanism of the microwave-assisted ring-expansion were made (Scheme 56).



Scheme 56. Proposed mechanism for the acid-mediated ring-expansion furan and pyrrole derived epoxides **112**.

The side reaction which was observed during the screening can be explained by the nucleophilic attack at the sterically less hindered carbon at the epoxide forming **174**. That competing reaction was prevented by drastically reducing the amount of nucleophile. Thus, the observed pathway was the ring-expansion which was initiated by acidic activation of epoxide **112** and proceeded exclusively through transition state **TS5**. In case of furan derived precursor **112a** the oxonium ion **168a** was formed which was trapped by the added nucleophile. In contrast, when *N*-Boc pyrrole **112b** was used as starting material the iminium ion **168b** was formed which underwent smooth Boc-deprotection under acidic conditions and resulted in dihydropyridine **114c**.

In conclusion, the established acid-mediated ring-expansion is limited to precursors with a quaternary cyclopropane carbon as it was already observed during the microwave-assisted ring-expansion. Nevertheless, pyran **114a** and dihydropyridine **114c** were synthesized in good yields and are potent precursors for various drug targets as it will be shown in the following derivatizations.

2.2 Targeted transformation of pyrans and dihydropyridines

2.2.1 Dihydroxypiperidines and their role as diabetes mellitus drug

Diabetes mellitus is known as a metabolic disease and is based on an abnormal glucose metabolism which is attended by long-term complications. It is characterized by hyperglycemia caused by defects in insulin secretion, insulin action or by a combination of both. Typically, the permanent increased blood sugar level causes long-term damage, dysfunction and failure of various organs, for example eyes, kidney, heart, nerves and blood vessels. The disease diabetes mellitus can be mainly categorized in two forms: type 1 and type 2. Type 1 is caused by an absolute insulin deficiency and is an autoimmune disease. In contrast, diabetes mellitus type 2, which is the most common type of diabetes mellitus, mainly results from a resistance of cells to insulin action.[157] Within the last decades, metformin has become the preferred first-line glucose-lowering drug in the treatment of diabetes mellitus type 2 and delays the uptake of glucose from the intestines.[158] Besides the medication with metformin, there are further opportunities for the treatment of diabetes mellitus type 2. An innovative and promising method is the development of dipeptidyl peptidase 4 (DPP-4) inhibitors since DPP-4 inhibitors enhance the body´s own ability to control to blood-glucose level. [159] In general, α-glucosidase inhibitors are another promising possibility to control and slow down the glucose uptake from the intestines.[160] Since diabetes is a lifelong disease the development of new therapies is essential and piperidine based drug targets seem to be promising and are already used in clinical practice.[161,162] Thus, it was sensible to develop new piperidine based drug targets. For example, Kasturi *et al.* showed that 3,4-dihydroxypiperidines of type **175** and **176** exhibit excellent α-glucosidase inhibitory activity and are potent anti-diabetic targets (Figure 7).[162]

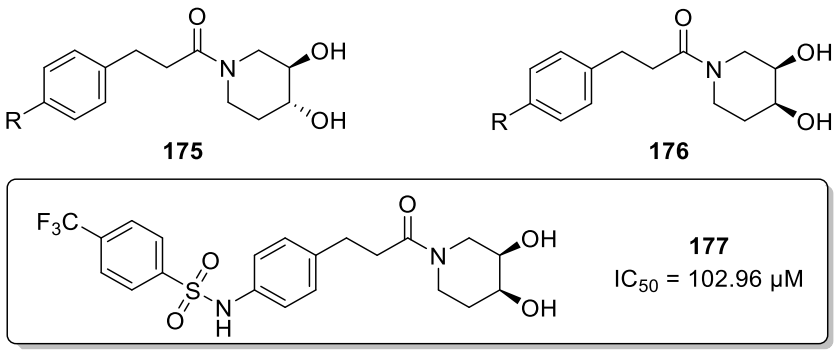
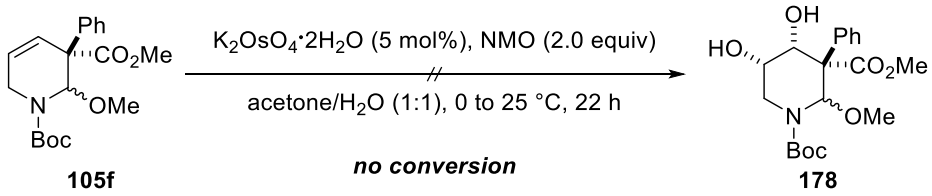


Figure 7. Potent *cis*-/*trans*-3,4-dihyroxypiperidines as promising α-glucosidase inhibitors.[162]

All their reported substrates **175** and **176** possess the same core structure and differ in the *para*-substituent at the phenyl moiety. Among all tested 3,4-dihydroxypiperidines, the *cis*-derivatives, especially substrate **177** (IC_{50} = 102.96 µM), showed the best inhibitory activities against the α-glucosidase enzyme.[162]

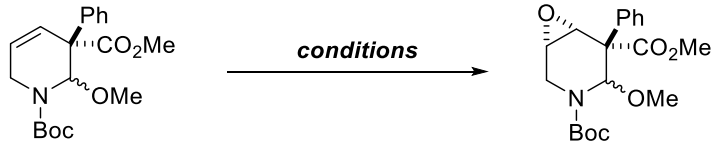
Since further structural modification of these substrates is required to achieve potent anti-diabetic drug targets, the dihydropyridines provided by the established selective ring-expansion of monocyclopropanated pyrroles were applied in the transformation to dihydroxypiperidines. As a first attempt, substrate **105f** was tested in a dihydroxylation of the remaining carbon-carbon double bond using K_2OsO_4 as catalyst and *N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant to give rise to the required dihydroxylated piperidine derivative **178** (Scheme 57).



Scheme 57. K_2OsO_4 catalyzed dihydroxylation of *tetra*-hydropyridine **178**.

The chosen conditions were used in the conversion of compounds bearing similar structure motifs,[67,163] but no conversion was obtained after 22 h. Since the dihydroxylation of this sterically demanding substrate seemed to be hardly accessible, different conditions for an epoxidation of **105f** were tested to circumvent this problem (Table 16). Due to the ester moiety in **105f** an electron-poor character of the double-bond was assumed. Thus, nucleophilic conditions using formic acid and H_2O_2 as reagents were chosen for the epoxidation but only decomposition was observed because Boc-deprotection and hydrolysis of the acetal-moiety might have led to various side-reactions (Table 16, entry 1). Switching form a nucleophilic to an electrophilic epoxidation with *in situ* generated dimethyldioxirane (DMDO) using Oxone® and $NaHCO_3$ as reagents also yielded in no conversion of the starting material (Table 16, entry 2). Since DMDO is known to be explosive, heating of this reaction was not possible, thus, *m*CPBA was applied instead (Table 16, entry 3-4). At 0 °C and 25 °C no reaction was observed (Table 16, entry 4) but heating to 50 °C (Table 16, entry 5) resulted in full conversion of the starting material and quantitative yield of the desired epoxide **179**. The structure of **179** was confirmed by NMR-spectroscopy and HRMS.

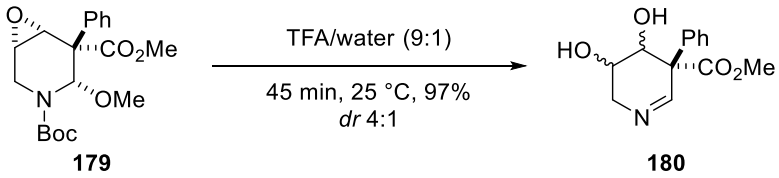
Table 16. Screening of suitable reaction conditions for the epoxidation of **105f**.



105f **179**

entry	reagents	solvent	T [°C]	t [h]	results
1	H_2O_2/formic acid (1:1)	-	25	48	decomposition
2	Oxone® (5.0 equiv) $NaHCO_3$ (15 equiv)	DCM	0 → 25	48	no conversion
3	*m*CPBA (4.0 equiv)	DCM	0 → 25	48	no conversion
4	*m*CPBA (4.0 equiv)	DCM	50	24	quantitative

Since a diastereomeric mixture, arising from the anomeric center of the staring material, was used in the epoxidation and due to the additional rotamers caused by the Boc-protecting group, analysis of the stereochemistry in **179** *via* NMR-spectroscopy was hardly possible. In accordance to previous results, it was assumed that epoxidation occurred exclusively from the sterically less hindered side, hence, the epoxide was introduced anti to the phenyl substituent. To get access to the required diol **178**, the opening of the epoxide under acidic conditions was carried out (Scheme 59).

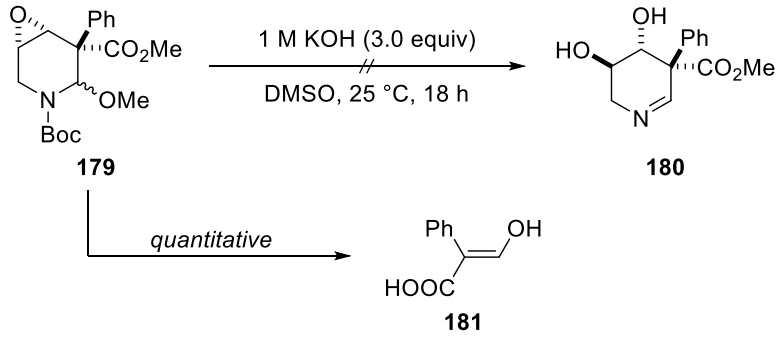


179 **180**

Scheme 58. Acid-mediated epoxide opening giving rise to diols **180**.

To get access to diol **180**, epoxide **179** was treated with a mixture of TFA and water (9:1) at ambient temperature. After 45 min, diol **180** was received in almost quantitative yield, additionally, the acetal moiety was also hydrolyzed to the corresponding imine. Contrary to expectations, the product was obtained as diastereomeric mixture (*dr* 4:1) which can be explained by different facts. On the one hand, the diastereomers were already formed in the previous epoxidation and the opening of the epoxide proceeded stereoselectively. On the other hand, the epoxide **179** was formed stereoselectively but

the opening of the epoxide **179** resulted in *cis*- and *trans*-diols. No matter what the correct explanation is, the stereochemistry could not be identified since single crystal X-Ray analysis was not successful and 2D-NMR spectroscopy led to no explicit statement about the stereochemistry in **179** or **180**. To circumvent these arising difficulties during the acid catalyzed epoxide opening, a nucleophilic opening was tested next because less side reactions were expected to occur. Additionally, the opening itself is assumed to proceed more selective because the regioselectivity of the epoxide opening is highly influence by sterics (Scheme 60).



Scheme 59. Nucleophilic epoxide opening of **179** using 1 M KOH in DMSO as reagent.

The nucleophilic opening of the epoxide **179** was carried out with 1 M KOH in DMSO at 25 °C. After 18 h full conversion of the starting material was observed but the desired diol **180** was not obtained at all. Instead, a rearrangement was observed which resulted exclusively in acrylic acid **181**.

Due to the large number of unavoidable side reactions in the electrophilic and nucleophilic epoxide opening and the possibly unselective epoxide formation, a selective synthesis of dihydroxypiperidines *via* this synthetic pathway is hardly possible. Consequently, in the following it was focused on further derivatizations to access potent drug targets with a pyran or dihydropyridine core.

2.2.2 Serotonin derivatives as potential drug targets in Alzheimer's disease

Neurodegenerative diseases are a growing issue in an aging population. In addition, risk factors such as diet or physical activity play a decisive role. In principle, neurodegenerative diseases are based on the loss of function, breakdown and death of neurons.[164] The most common neurodegenerative disorder is the Alzheimer's disease which makes up two third of all dementia cases. In the course of the disease, neurons lose their function, especially in the hyppocampus.[165] Latest research showed that irregularities in neuronal expression of neurotrophins are involved in various neurodegenerative processes, especially in Alzheimer's.[15]

Neurotrophins promote neural development, synaptic plasticity, maintenance of the adult nervous system, learning and memory.[166] The most important neurotrophins including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4) are agonists for tropomysin-related receptors (TrkA, TrkB, TrkC) and p75NTR receptor. In contrast to the p75NTR receptor, which is responsible for cell death, the Trk-receptors primarily support cell growth and cell survival. Exemplary, decreased levels of NGF which is an agonist for the TrkA receptor in the basal forebrain results in reduction of nerve fibers density, cell atrophy and down-regulation of transmitter-associated enzymes (acetyltransferase, acetylcholinesterase), thus, a decrease of cholinergic transmission can be observed. In comparison, the BDNF/TrkB signaling pathway plays a more important role in developing therapies for Alzheimer's disease. The level of BDNF in the brain of patients is decreased which promotes the biosynthesis of β-amyloid peptide. This peptide accumulates in the brain and contributes to neurodegeneration. The reason for the decreasing BDNF level in the hippocampus is that the associated mRNA level drops in Alzheimer's patients, i.e. the protein biosynthesis of BDNF decreases.[167] Thus, the BDNF/TrkB signaling pathway possess a protective role against Alzheimer's disease related pathogenesis.[168] Consequently, the maintenance of the BDNF/TrkB signaling pathway by developing efficient synthetic agonist for the TrkB receptor offers a promising opportunity in the development of therapies for Alzheimer's disease.

Latest research showed that several serotonin derivatives, such as *N*-acetyl serotonin (NAS, **182**) and *N*-[2-(5-hydroxy-1*H*-indl-3-yl)ethyl]-2-oxopiperidine-3-carboxamide (HIOC, **7**), are potent agonists for the TrkB receptor (Figure 8).

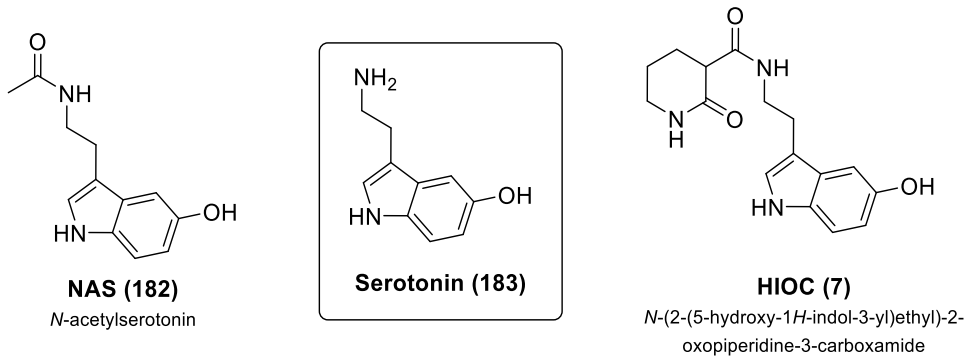


Figure 8. Serotonin derivatives NAS (**182**) and HIOC (**7**) as potent TrkB agonists.

Thereby, HIOC (**7**) was discovered as very potent agonist being selective for the TrkB receptor. It is more stable than NAS (**182**) which was determined by its higher half-life of ~4 h. In contrast, NAS (**182**) depicts a half-life-time of ~30 min under the same conditions. The increased stability is caused by the bulkiness of the 2-oxopiperidine-3-carboxyamide group blocking the hydrolysis of the amide moiety in HIOC (**7**) compared to the acetyl group in NAS (**182**). Additionally, HIOC (**7**) can pass the blood-brain-barrier (BBB) whereupon BDNF has a poor BBB penetration capability.[17,169]

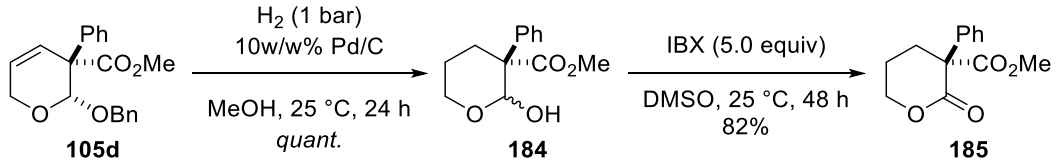
This stresses the role of HIOC (**7**) as a lead compound for the development of neuroprotectants and, therefore, it is indispensable to synthesize new derivatives particularly with regard to its sterically demand and additional functional groups.

2.2.2.1 Synthesis of promising HIOC building blocks

Developing the efficient ring-expansion of monocyclopropanated furan and pyrrole derivatives gave access to interesting building blocks. Using our established method, various δ-lactam and δ-lactone precursors can be provided on gram-scale and also as enantiopure compounds.

We envisaged that the benzyl protected six-membered heterocycle **105d** can easily be converted to a δ-lactone *via* debenzylation followed by oxidation to afford a building block for an oxygen analog of HIOC. First, the corresponding O/O-semi acetal **184** was

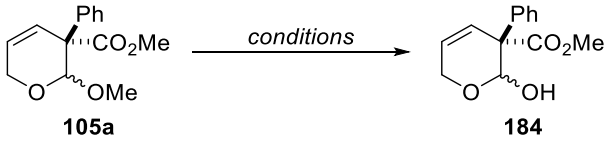
synthesized *via* a Pd(0)-catalyzed benzyl-deprotection and was then oxidized to δ-lactone **185** (Scheme 61).



Scheme 60. Benzyl deprotection of **105d** by hydrogenolysis with Pd(0) as catalyst and the synthesis of lactone **185** by oxidation with IBX.

At first, pyran **105d** was hydrogenated under Pd(0)-catalysis in MeOH applying atmospheric H_2-pressure to obtain semi-acetal **184** in quantitative yield after 24 h. According to Taniguchi *et al.*,[170] semi-acetal **184** was subsequently oxidized by 2-iodoxybenzoic acid (IBX) to give δ-lactone **185** in 82% yield after 48 h. Surprisingly, the debenzylation turned out to be challenging because the reaction was not reproducible. Consequently, this turned out to be a non-reliable pathway for the synthesis δ-lactone **185** even if the subsequent oxidation of **184** with IBX was successful. As an alternative pathway, pyran **105a** was assumed to undergo a hydrolysis forming the desired semi-acetal **184** under acidic conditions (Table 17).

Table 17. Acidic hydrolysis of pyran **105a** giving access to semi-acetal **184**.

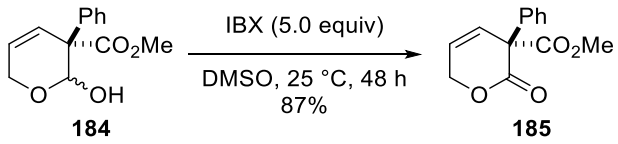


entry	conditions	T [°C]	t [h]	yield [%]
1	THF/HCl (2:1)	25	72	0[a]
2	*p*-TsOH (1.5 equiv), THF/H_2O (1:1)	25	72	0[a]
3	TFA/H_2O (1:9)	50	72	0[a]
4	TFA/H_2O (9:1)	50	0.75	75 (*dr* 1:1)

[a] no conversion of starting material.

Acid-mediated hydrolysis of pyran derived acetals is an established research topic and for a fist test reaction similar conditions as it was published by Bergkemper *et al.* were

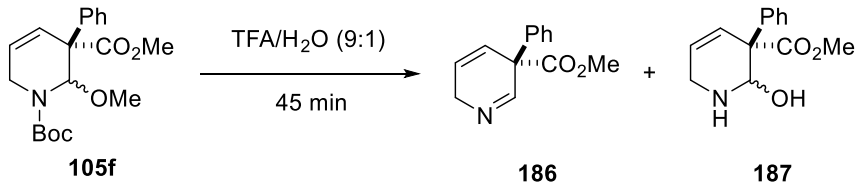
tested.[171] Hydrolysis of the acetal **105a** was neither possible with HCl (Table 17, entry 1) nor with *p*-toluene sulfonic acid (Table 17, entry 2) at 25 °C. Even after 72 h no conversion of the starting material was observable. This result suggested that harsher reaction conditions were required. Therefore, conditions for a TFA mediated hydrolysis, in accordance to Tada *et al.*,[172] were applied. Using a mixture of TFA in water (1:9) at 50 °C resulted in no conversion after 72 h (Table 17, entry 3). Finally, using a more concentrated mixture of TFA and water (9:1) as solvent afforded the desired product **184** in 75% yield within a short reaction time of 45 min (Table 17, entry 4). Additionally, epimerization of the anomeric was observed which resulted in a 1:1 mixture from an initial epimeric ratio *dr* 2.7:1. Finally, the obtained semi-acetal **184** was transferred to its corresponding lactone **185** by oxidation with IBX in 87% yield. Hence, a new building block for an oxygen analog of HIOC was obtained (Scheme 62).



Scheme 61. Oxidation of semi-acetal **184** with IBX as oxidant giving access to lactone **185**.

With the aim of synthesizing new and more sterically demanding piperidine based derivatives that could also serve as HIOC building blocks, the established pathway for the synthesis of lactone **185** should be adapted to dihydropyridine **105f** (Table 18).

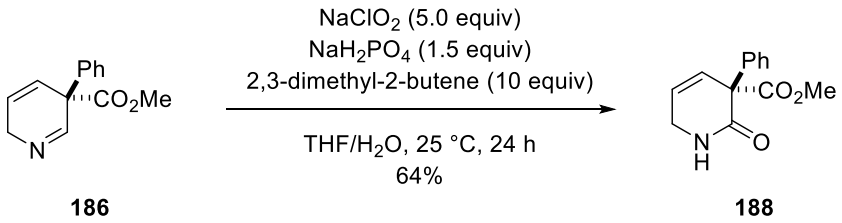
Table 18. Acidic hydrolysis of *N/O*-acetal **105f** resulting in the cyclic imine **186**.



entry	T [°C]	yield of 186 [%]
1	50	90
2	25	94
3	0	88

For a first attempt, the established conditions (Table 17, entry 4) were applied for the synthesis of semi-acetal **186** with **105f** as starting material. Contrary to expectations, applied acidic conditions using a TFA/water (9:1) mixture resulted not in semi-acetal **187** but gave access to 90% of cyclic imine **186** after 45 min. Variation of the reaction temperature from 50 to 0 °C was carried out revealing 25 °C as optimal temperature for the hydrolysis of **105f** yielding in 94% of imine **186** (Table 18, entry 2). The phenomenon of imine formation from a N/O-acetal was also observed by Wels *et al.* in the synthesis of benzodiazepines.[173]

The obtained cyclic imine **186** turned out to be an extremely useful substrate since it offered various possibilities for synthetic transformations. With the synthesis of HIOC derivatives in mind, the obtained cyclic imine **186** was oxidized to its corresponding lactam **188** (Scheme 63).



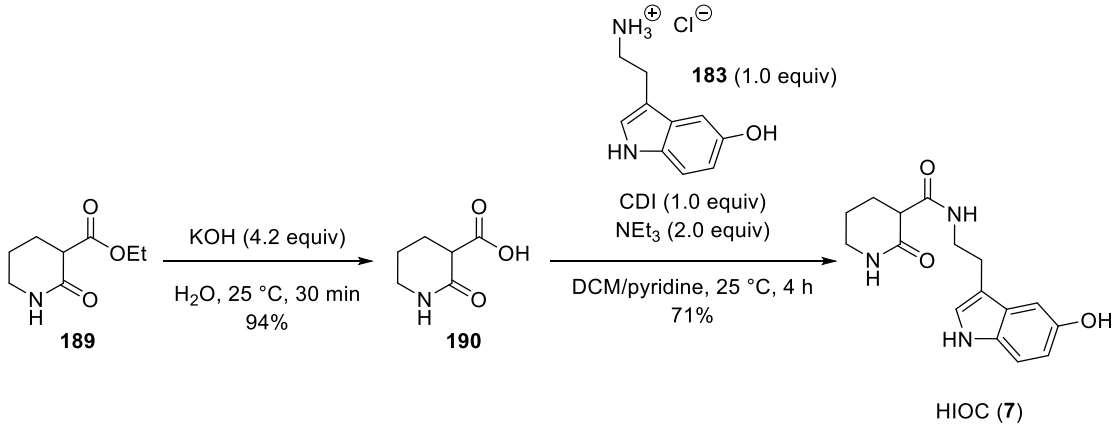
Scheme 62. Oxidation of imine **186** with $NaClO_2$ as oxidant forming lactam **188**.

In accordance to Scott *et al.*[174] and Mohamed *et al.*[175] the reaction was carried out with $NaClO_2$ as oxidant in THF/H_2O at 25 °C. After 24 h lactam **188** was isolated in moderate yield of 64%.

Finally, this established transformation of the six-membered heterocycles obtained after the microwave-assisted ring expansion turned out to be a powerful tool for the synthesis of lactones and lactams. Additionally, there is the possibility to expand the amount of potential building blocks since the remaining carbon-carbon double bond in **105a** and **105f** offers various opportunities for further functionalization giving access to a pool of suitable building blocks for HIOC-analogs.

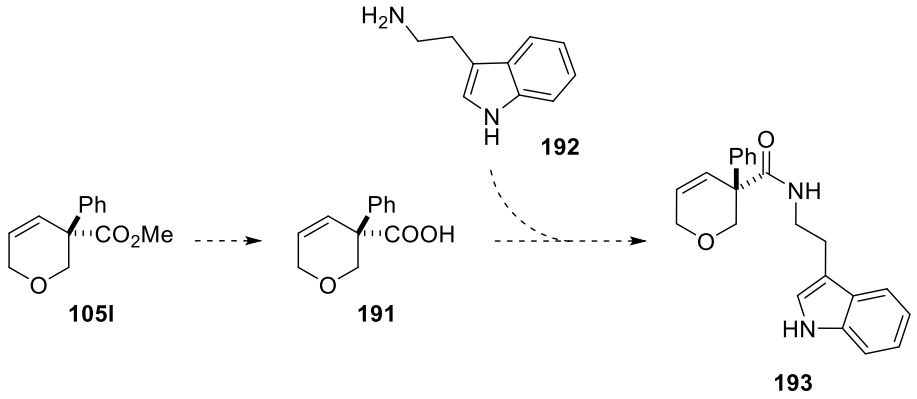
2.2.2.2 Synthesis of a phenyl-substituted HIOC analog

HIOC (**7**) was identified as potent activator of the TrkB receptor in mammalian neurons. Setterholm *et al.*[176] published the only total synthesis of HIOC (**7**) starting from commercially available ester **189** on gram-scale. They reported a chemoselective *N*-acetylation of serotonin (**183**) giving directly HIOC (**7**) in 71% yield without the use of any protective groups in the acylation step after hydrolysis of ester **189** under basic conditions (Scheme 64).[176]



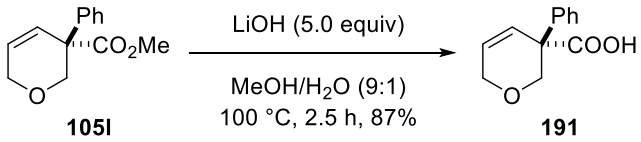
Scheme 63. Synthesis of HIOC (**7**) by direct *N*-acylation of serotonin (**183**).

If HOC is once bound to the receptor, the resistance against hydrolysis of the six-membered heterocycle is known to be decisive for its biological activity. Thus, it should be demonstrated that the sterically bulky and hydrolysis resistant model substrate **105l** can be coupled to serotonin after initial saponification to afford HIOC analog **193.** The synthesis was investigated as published by Setterholm *et al.*[176] with the difference that the less expansive tryptamine (**192**) being related to serotonin was applied as coupling partner while pyran **105l** served as model substrate. (Scheme 64)



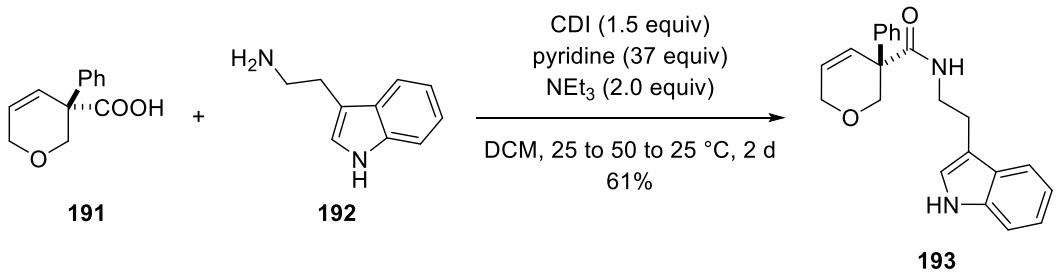
Scheme 64. Planned synthetic pathway affording HIOC analogue **193** by coupling of pyran **191** to tryptamine (**192**).

Before the coupling to tryptamine (**192**) could be carried out, the methyl ester of the model substrate **105l** had to be hydrolyzed. For this purpose, pyran **105l** was treated with LiOH in aqueous MeOH to give the desired acid **191** in 87% after 2.5 h at 100 °C (Scheme 65).



Scheme 65. LiOH mediated ester hydrolysis affording free carboxylic acid **191**.

Subsequently, the coupling of the free carboxylic acid **191** to tryptamine (**192**) was carried out using the conditions of Setterholm *et al.*[176] in order to get access to sterically more demanding HIOC analogues (Scheme 66).



Scheme 66. Synthesis of HIOC analogue **193** *via* coupling of pyran **191** to tryptamine (**192**).

To afford HIOC analogue **193**, pyran **191** was converted first to its active ester *in situ* using carbonyldiimidazole (CDI) within 22 h at 25 °C followed by 3 h at 50 °C. Then, the coupling partner tryptamine (**192**) was added to give HIOC analogue **193** in 61% yield after 24 h at 25 °C.

In summary, the HIOC analogue **193** was obtained in an overall yield of 26% within five steps starting from cyclopropanated furan derivative **102a.** This example showed that sterically demanding six-membered heterocycles, indeed, can be coupled to tryptamine (**193**) and consequently also the coupling to serotonin (**183**) should be accessible. Correspondingly, further substrates provided in this work can be used in the synthesis of new HIOC analogs which, compared to HIOC, could serve as potent TrkB agonists due to the sterically demanding groups.

2.2.3 (*R*)-Tiagabine – a selective GABA uptake inhibitor

Epilepsy is one of the oldest known and most common neurological disease affecting humans of all ages.[177] The disorder is characterized by recurring seizures, the cause of which is not readily apparent.[178] To gain control over this disease, the majority of patients are treated with antiepileptic drugs, however, in some cases the disease cannot be treated despite the best possible medication.[179] A major problem with anti-epileptic drugs is that in many cases the medication does not work due to their poor adherence.[180] This non-adherence leads to loss of seizure control, thus, the patient's quality of life is significantly reduced.[181]

Among antiepileptic drugs, tiagabine (**8**) is known as a drug target with a exactly defined mechanism of action, additionally, pharmacodynamics and pharmacokinetics are well-examined and it does not interfere with other drugs enabling an add-on therapy with tiagabine (**8**).[7,182] Tiagabine is structurally related to nipecotic acid (**4**) but is able to cross the blood-brain-barrier due to an additionally attached lipophilic anchor (Figure 9).[9]

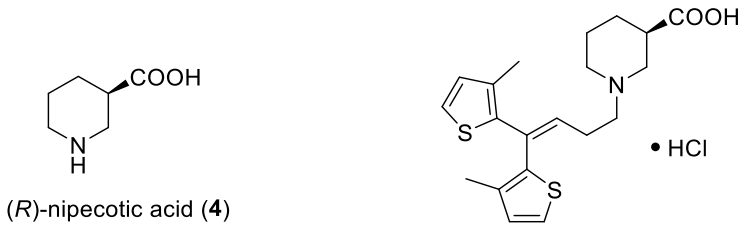
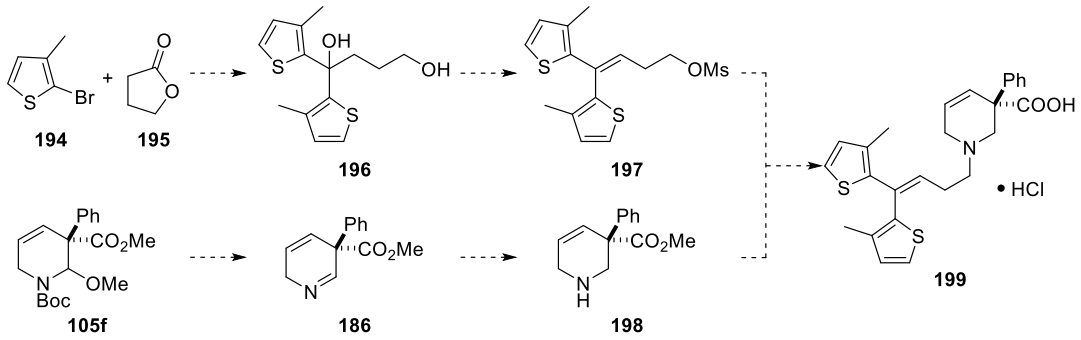


Figure 9. Chemical structures of (*R*)-nipecotic acid (**4**) and antiepileptic drug (*R*)-tiagabine (**8**).

From a pharmacological point of view, tiagabine (**8**) prevents the reuptake of γ-aminobutyric acid (GABA) in neurons and glia by inhibiting GABA transporter GAT-1.[8,183] The resulting elevated synaptic GABA level in turn reduces neuronal excitability and, thus, the probability of seizures gets minimized.[7] Due to the promising effect of tiagabine (**8**) as an antiepileptic drug, it is sensible to further develop this compound and to synthesize new tiagabine derivatives.

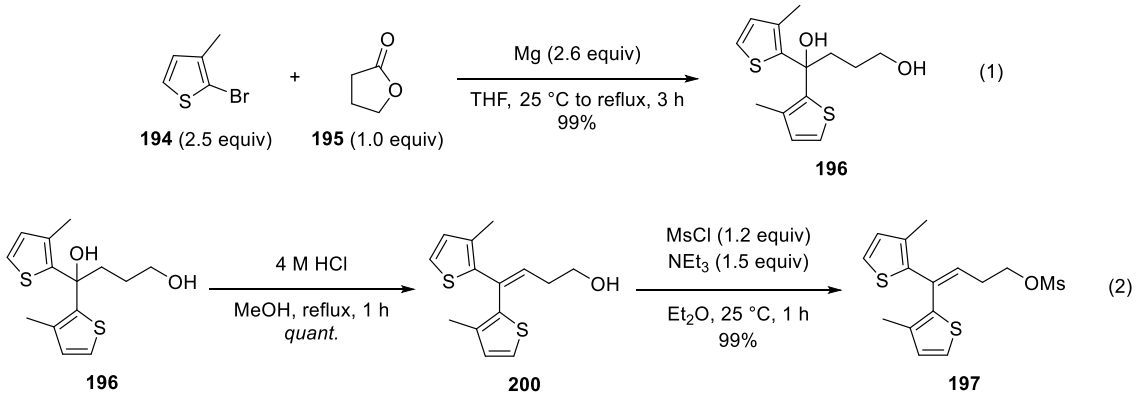
In 1993 the first total synthesis of tiagabine (**8**) was published by Andersen *et al.* starting from commercially available 2-bromo-3-methylthiophen (**194**) within five steps revealing tiagabine as anticonvulsant drug candidate.[184] Additionally, they varied the aromatic substituents attached at the lipophilic anchor and found that methyl-substituted thiophene showed the best biological activity among all tested aromatic groups [184] This

synthetic approach was improved by Song *et al.*[185] in 2013. Their improved synthetic pathway served as template for the synthesis of a new tiagabine analog **199** which differs in the substitution pattern at the piperidine moiety (Scheme 67).



Scheme 67. Theoretical synthesis of tiagabine analogue **199** by coupling of *tetra*-hydropyridine **198** to anchor **197**.

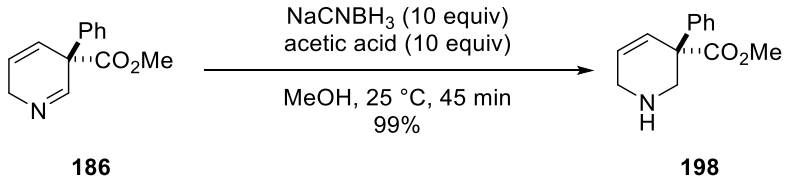
To gain access to the new tiagabine derivative **199**, the lipophilic anchor **197** had to be synthesized first. The synthesis of mesylate **197** was carried out starting from thiophene **194** and γ-butyrolactone (**195**) as published (Scheme 68).[185]



Scheme 68. Synthesis of anchor **197** *via* Grignard-reaction, elimination and mesylation.

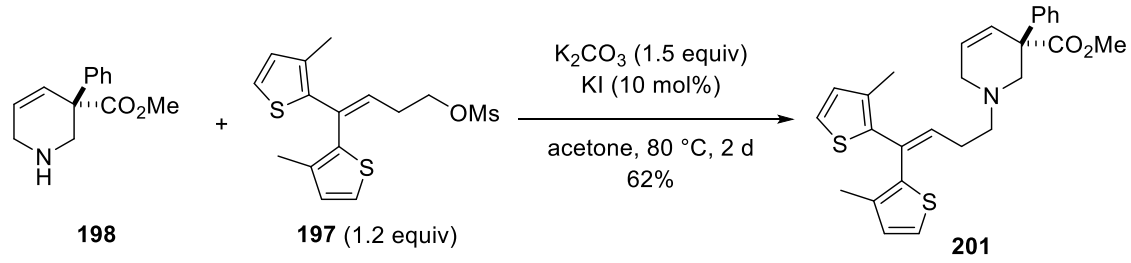
In the first step, a Grignard-reaction between 2-bromo-3-methylthiophen (**194**) and γ-butyrolactone (**195**) was carried out giving diol **196** in 99% yield under reflux conditions after 3 h (Scheme 68, equation 1). Then, an acid catalyzed elimination with 4 M HCl in MeOH afforded alcohol **200** in quantitative yield which was subsequently converted to the required precursor **197** in 99% yield after 1 h by mesylation of the alcohol **200** with MsCl and NEt_3 as reagents (Scheme 68, equation 2).

Since the acid-mediated hydrolysis of acetal **105f** resulted in the formation of cyclic imine **186** in 94% yield (Table 18, entry 2), a reduction of the imine moiety was established to get access to piperidine **198** (Scheme 69).



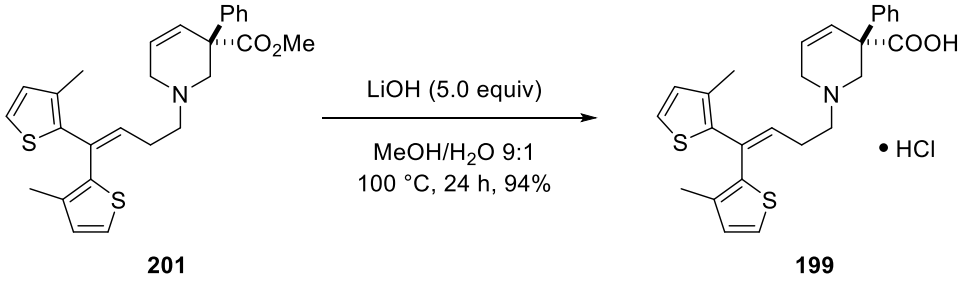
Scheme 69. Reduction of **186** with $NaCNBH_3$ giving access to *tetra*-hydropyridine **198**.

In literature it is well known that sodium cyanoborohydrid ($NaCNBH_3$) is a mild reagent applied in the selective reduction of imines to its corresponding free amine.[186–188] Thus, cyclic imine **186** was treated with $NaCNBH_3$ and acetic acid in MeOH to obtain amine **198** in almost quantitative yield after a short reaction time of 45 min. As next step, the coupling of the lipophilic anchor **197** to *tetra*-hydropyridine derivative **198** was performed (Scheme 70).



Scheme 70. Synthesis of tiagabine derivative **201** *via* coupling of *tetra*-hydropiperidine **198** to **197**.

In comparison to the known procedure,[185] it was necessary to increase the temperature to 80 °C to achieve a successful product formation giving adduct **201** in 62% after 2 d. Finally, ester hydrolysis in **201** was conducted under basic conditions using LiOH in a mixture of MeOH/water (9:1) at 100 °C to get access to tiagabine derivative **199** in 94% yield after 24 h (Scheme 71).



Scheme 71. Basic ester-hydrolysis of **201** affording tiagabine derivative **199**.

In conclusion, the new tiagabine derivate **199** was synthesized in seven steps starting from monocyclopropanated pyrrole **102b** in an overall yield of 53%. It was shown, that also bulky nipecotic acid derivatives were tolerated in the coupling to the lipophilic anchor **197**. Additionally, the remaining carbon-carbon double bond in amine **198** or tiagabine precursor **201** offered various opportunities for further derivatization which could enable access to a completely new class of tiagabine derivatives. These new tiagabine derivatives may have the potential to contribute to the further development of anti-epileptic drugs.

2.2.4 Pethidine derivatives – new synthetic opioids

Opium is the dried milky juice of the unripe seed capsule of the poppy (*papaver somniferum*) which contains several alkaloids. The most important alkaloids in opium which are known to relive pain are morphine (**202**), codeine (**203**) and thebaine (**204**). Among the extensively explored G-protein coupled μ-, δ- and κ-opioid receptors in the central nervous system, morphine (**202**) behaves as agonists at the μ-opioid receptor which induces analgesia (Figure 10).[189]

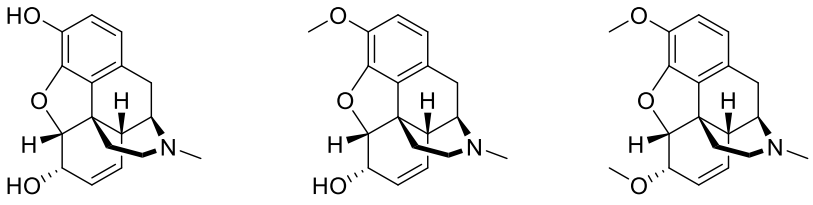


Figure 10. Most important alkaloids morphine (**202**), codeine (**203**) and thebaine (**204**) isolated from *papaver somniferum.*

Nowadays there are also various inexpensively synthesized substrates known which also show morphine-like activities and are therefore called *opioids*. Particularly noteworthy is pethidine (**6**) which is a prototype of phenylpiperidine based opioids, a group which also includes fentanyl (**207**) being used as a pain medication and is applied together with other medications in anesthesia. Pethidine (**6**) is pharmacologically related to atropine (**206**) and was first synthesized in 1939 by Eiselb and Schaumann.[190]

Pethidine (**6**) and fentanyl (**207**) were found to be μ-opioid receptor agonists, additionally, pethidine (**6**) and its derivatives can inhibit the dopamine and monamine transporter in the same manner as cocaine (Figure 11).[13,191]

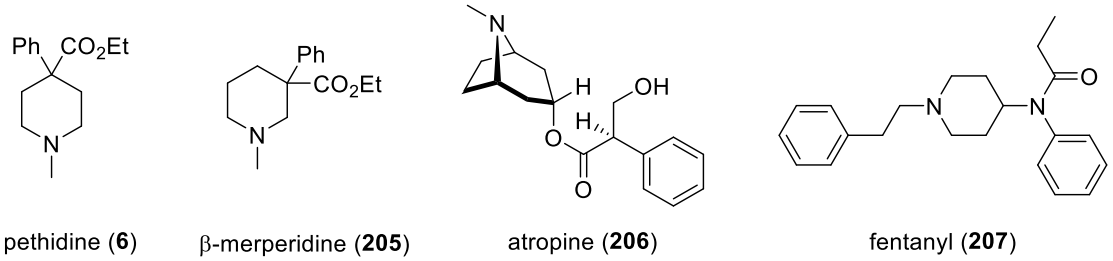
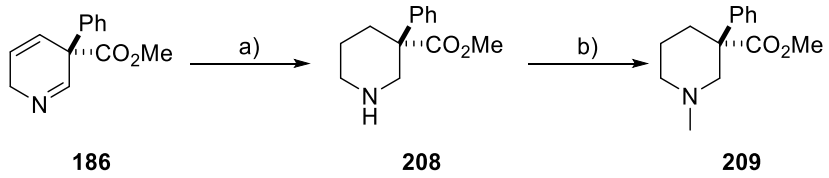


Figure 11. Pethidine (**6**) and β-merperidine (**205**), atropine (**206**) and fentanyl (**207**) as representative examples for synthetic opioids.

These days pethidine (**6**) (trade name: Demerol®) has almost completely disappeared from human medicine and is only used as a local anesthetic during childbirth.[192] Even though pethidine (**6**) is a very effective analgesic, studies have shown that the dangerous side-effects and risk of addiction of opioids have also been observed with pethidine (**6**). Even worse, the side-effect profile is unpredictable and, additionally, it turned out to be the only analgesic agent that negatively affects mood.[193] In contrast to pethidine (**6**), its structural analogue β-merperidine (**205**) was found to be also a potent active analgesticum which is less toxic and has a lower risk to cause addiction and, thus, was assumed to be a promising alternative to pethidine (**6**).[194] In order to increase the biologically activity of β-merperidine (**205**) different variations on the *N*-protecting group and an additional methyl group next to the piperidine nitrogen were already established but they revealed as unsuitable in increasing the biological activity. In contrast, introducing a *meta*-hydroxy group at the phenyl moiety increased the biological activity.[195,196] During all conducted biological testings, one common rule has been revealed: the more similar the derivative is to morphine, the more active it is.[197]

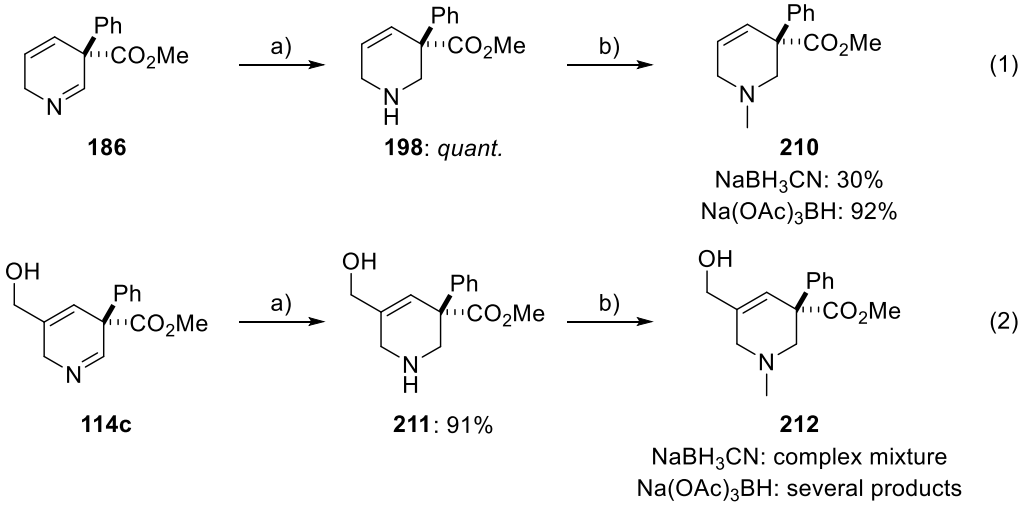
Due to the fact that phenylated dihydropyridines and tetrahydropyridines which are promising β-merperidine precursors were easily accessible by the established selective ring-expansion of monocyclopropanated pyrroles, the possibility of synthesizing new β-

merperidine derivatives was offered. As a first synthesis plan cyclic imine **186** should be converted to β-merperidine derivative **209** (Scheme 73).



Scheme 72. Synthesis of β-merperidine analog **209**; a) Pd/C (10 mol%), 40 bar H_2, MeOH, 25 °C, 2 h, 64%; b) 37% aq. CH_2O (6.2 equiv), $NaBH_3CN$ (3.0 equiv), MeCN, 25 °C, 1 h, 73%.

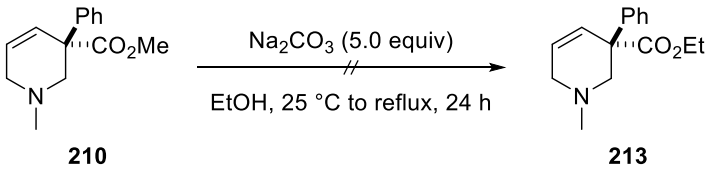
Hydrogenation of unsaturated imine **186** with 10 mol% Pd(0) under hydrogen atmosphere (p = 40 bar) resulted in the hydrogenation of the carbon-carbon double bond and the reduction of the imine moiety giving free amine **208** in 64% yield. According to Cheng *et al.*[198] reductive amination of **208** was performed with formaldehyde and $NaBH_3CN$ as reducing agent which afforded the expected analog **209** in 73% yield.
In literature it is known that an imine moiety can be selectively reduced in presence of an carbon-carbon double bond.[186–188] Consequently, a more versatile core structure can be obtained which offers the possibility of further modification (Scheme 74).



Scheme 73. Studies towards the synthesis of new β-merperidine analogues; a) $NaBH_3CN$ (10.0 equiv), CH_3COOH (10.0 equiv), MeOH, 45 min, 25 °C; b) 37% aq. CH_2O (6.2 equiv), $NaBH_3CN$ (3.0 equiv) or $Na(OAc)_3BH$ (3.0 equiv), MeCN, 25 °C, 1 h.

In the first step imines **186** and **114c** were chemoselectively reduced applying $NaBH_3CN$ in excess which afforded the corresponding free amines **198** and **211** in 91% or quantitative yield (Scheme 74, equation (1) and (2)). As it was shown in the synthesis of **209**, reductive amination of the free amines **198** and **211** was carried out under the same conditions. Unfortunately, only the formation of a complex mixture in the reductive amination of amine **211** was observed and in case of **198** only 30% of the desired product **210** was obtained. In comparison to the synthesis of saturated β-merperidine derivative **209** the carbon-carbon double bound seemed to be the reason for the inefficient or even failing product formation. Thus, a milder reducing agent was required to achieve successful product formation. According to Abdel-Magid *et al.*,[199] sodium triacetoxyborohydride ($Na(OAc)_3BH$) was claimed as extremely mild and selective reducing agent used in reductive aminations, additionally, various ketones and amines were tolerated. Consequently, $Na(OAc)_3BH$ was tested in the reductive amination of **211** which resulted again in an inseparable mixture of several products which has been caused by isomerization of the carbon-carbon double bond (Scheme 74, equation (2)). In contrast, using amine **198** as starting material gave access to 92% of the methylated amine **210** (Scheme 74, equation (1)). For further investigations, unsaturated β-merperidine derivative **210** served as model substrate.

MacDonald *et al.*[197] reported also some variations of the ester moiety in pethidine. Biological testing revealed that only the ethyl ester showed promising analgesic properties. Thus, a transesterification from methyl to ethyl ester in **211** was essential to synthesize potent substrates. As a first test reaction, a mild direct transesterification published by Liang *et al.*[200] applied in the synthesis of isogalactofagomine was tested (Scheme 75).

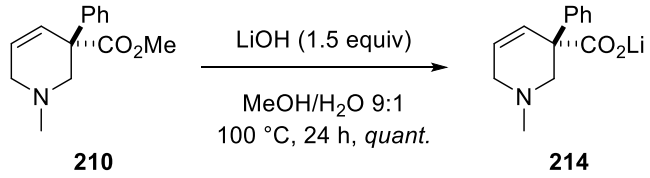


210 **213**

Scheme 74. Direct transesterification applying basic conditions.

The transesterification was tested under basic conditions in EtOH but no conversion was observed after 24 h neither at 25 °C nor under reflux conditions. Already the

established synthesis of HIOC analogue **199** showed that harsher reaction conditions for the conversion of the ester attached to the quaternary carbon were required. Thus, the ester was saponificated to circumvent the direct transesterification (Scheme 76).

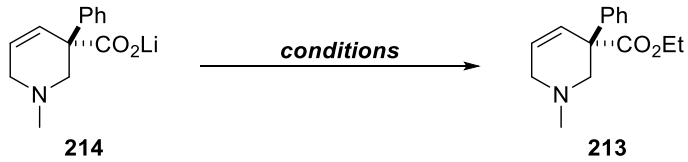


210 **214**

Scheme 75. Saponification of **210** under basic conditions resulting in carboxylate **214**.

First, the ester hydrolysis was performed with LiOH as base at ambient temperature but no conversion was observed. Heating of the reaction mixture to reflux afforded the lithium salt **214** in quantitative yield after 24 h. With this compound in hands, different conditions for the esterification of the lithium salt **214** were tested next (Table 19).

Table 19. Screening of reaction conditions for the esterification of **214**.



214 **213**

entry	conditions	yield [%]
1	DCC (1.2 equiv), DMAP (10 mol%), EtOH (20 equiv),	no conversion
2	$SOCl_2$ (33 equiv), EtOH, 100 °C, 4.5 h	58

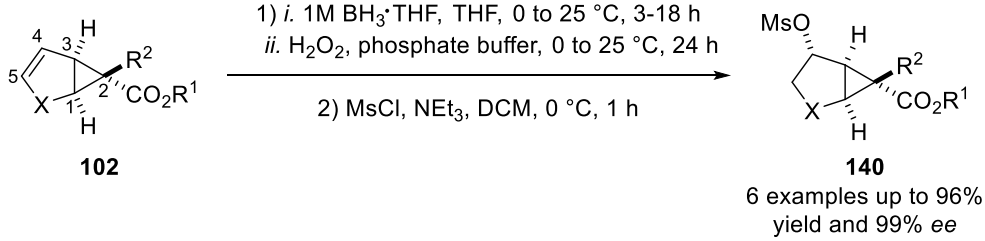
As a first test reaction, the esterification was carried out under mild conditions in accordance to Neises *et al.*[201] using DCC and DMAP as coupling reagents but no conversion of the starting material was observed (Table 19, entry 1). In contrast, applying thionyl chloride in large excess in EtOH afforded the expected β-merperidine derivative **213** in 58% yield after 4.5 h at 100 °C (Table 19, entry 2). Finally, hydrogenation of the carbon-carbon double bond would provide β-merperidine (**205**), however, other functionalizations would result in biologically more interesting products since there is only one example form Lawson *et al.*[196] for derivatizations at the piperidine core known.

To sum up, it was shown that dihydropyridines provided by the stereoselective ring-expansion of monocyclopropanated pyrroles, indeed, can be converted into promising β-merperidine based targets. Noteworthy, all transformations afforded the substrates in excellent yield, thus, the β-merperidine derivative **213** was synthesized in an overall yield of 45% within 8 steps. Remarkably, the carbon-carbon double **213** was stable under the established conditions which offered various possibilities for late-stage derivatizations allowing structural modification with regard to optimizing the biological activity.

2.3 Summary/Zusammenfassung

2.3.1 Summary

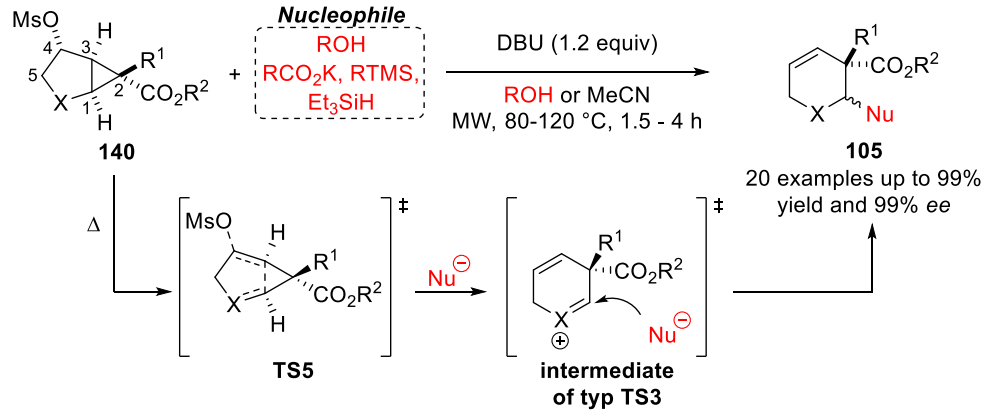
The present thesis deals with the stereoselective, scalable and metal-free ring-expansion of monocyclopropanated pyrroles and furans leading to value-added, highly functionalized dihydropyridine and pyran derivatives. Featuring a cyclopropylcarbinyl cation rearrangement as the key step, the selective cleavage of the unactivated endocyclic cyclopropane carbon-carbon bond is achieved. The established protocols benefit from versatility, scalability and their short reaction times under environmentally benign conditions. Targeted transformations of the so obtained six-membered heterocycles give access to versatile building blocks with high relevance for drug synthesis. The required monocyclopropanated heterocycles **102** were readily prepared by Cu(I) or Rh(II)-catalyzed or by a light-mediated cyclopropanation in racemic or enantiopure form. Aiming at the introduction of a leaving group at C4 to generate a cyclopropylmethyl cation, we were pleased to see that hydroboration followed by mesylation gave rise to **140a-e**, while **140f** was accessible from **102c** by epoxidation, acidic epoxide-opening and mesylation (Scheme 76).



Scheme 76. Synthesis of precursors **140** starting from monocyclopropanated heterocycles **102**.

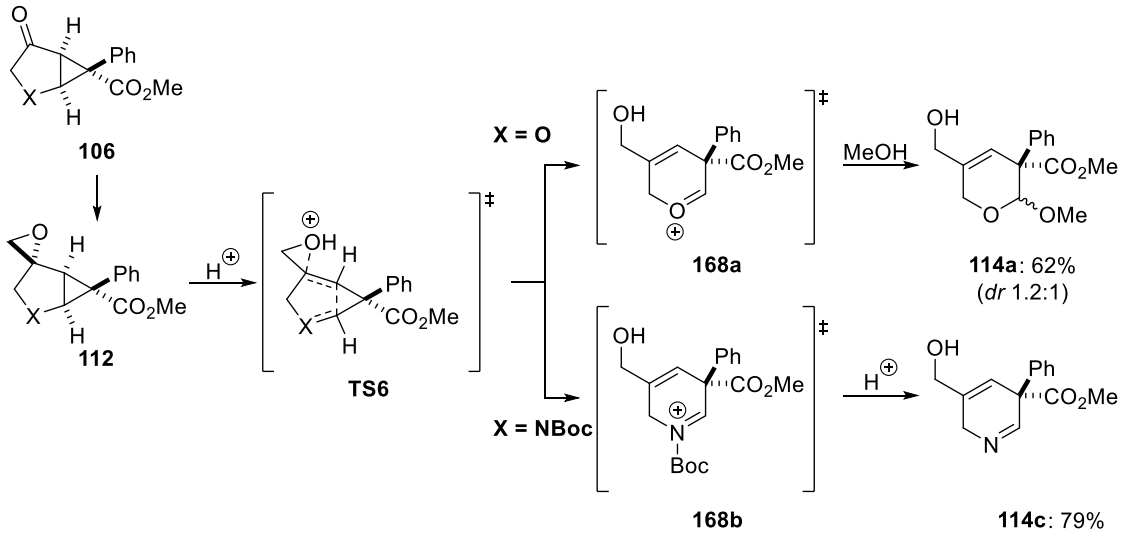
The perfect diastereoselectivity observed can be explained by the exclusive functionalization of the bicycle **102** from the convex side, being confirmed by NMR analysis and single X-Ray crystallography. As a first attempt towards a ring-expanstion, **140a** was heated to 80 °C under microwave irradiation (Table 6, entry 1) and indeed gave rise to the desired pyran **105a** (55% yield), but additionally, a exocyclic ring-opening to **141** had occurred to an almost equal extent (45% yield). We suspected that the formation of methyl sulfonic acid in the course of the reaction will be sufficient to activate the ester group to cause the undesired exocyclic ring-opening. An improvement of the initial reaction conditions was found by adding DBU as non-nucleophilic base

being able to trap *in situ* formed traces of acid which allowed the synthesis of various six-membered heterocycles with different alcohols as solvent (Scheme 77).



Scheme 77. Microwave-assisted ring-expansion of monocyclopropanated furans and pyrroles **140** giving access to six-membered heterocycles **105**.

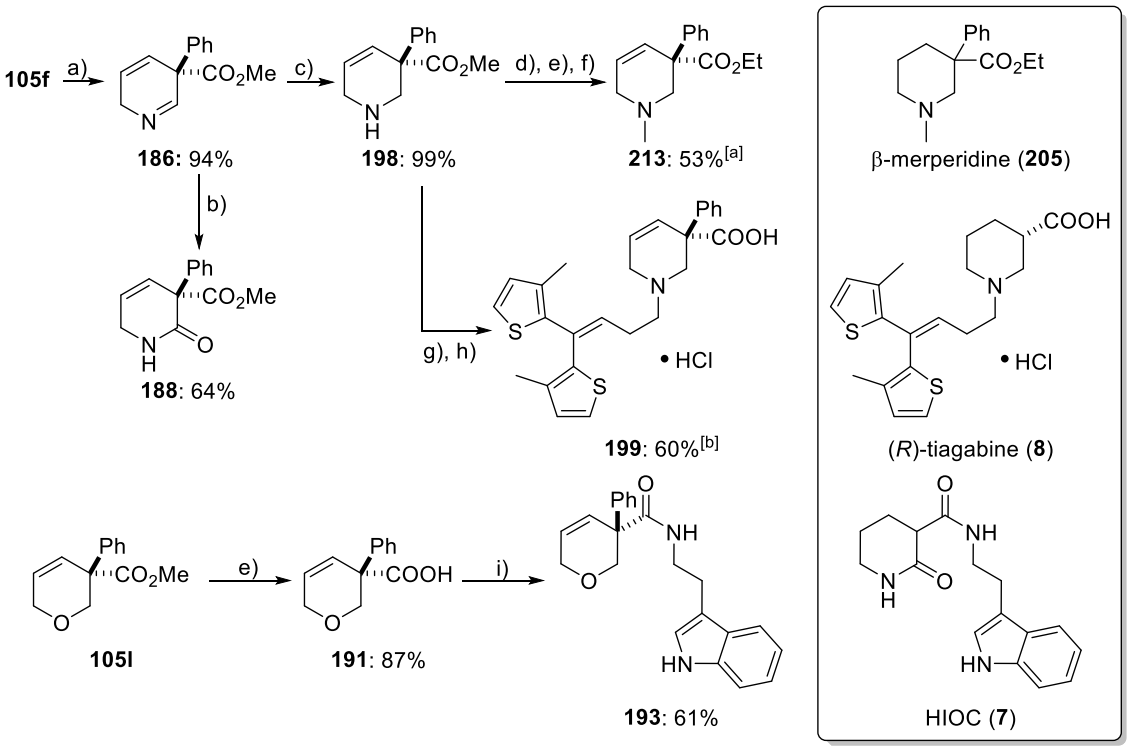
To extend the scope of the process to nucleophiles that cannot be employed as solvent, we found that the reaction proceeds effectively in MeCN, thus allowing the introduction of more complex alcohols, carboxylic acids, hydride or various C-nucleophiles. Additionally, a late-stage derivatization of terpenes and carbohydrates was possible. Generally the ring-expansion products were provided in high yields. Typically, epimers at the anomeric center were obtained, which could be readily separated in most cases. Aiming at an alternative to mesylates **140**, we explored vinylcyclopropane epoxides **112** which were readily obtained *via* a Corey-Chaykovsky-Epoxidation of **106** (Scheme 78).



Scheme 78. Acid-mediated ring-expansion of vinylcyclopropane epoxides **112** being accessible *via* a Corey-Chaykovsky-epoxidation of ketones **106** (for synthetic details see experimental part).

Treating the *in situ* generated vinylcyclopropane epoxides **112** with Amberlyst 15® in methanol or TFA in water (9:1) enabled the expected ring-expansion featuring the cyclopropylmethyl cation of type **TS6** as key intermediate. Notably and contrasting the formation of **141** under acidic conditions (Table 6, entry 1), no exocyclic cyclopropane ring opening was observed, suggesting the epoxide functionality to be superior than a mesylate or ester for activation by protonation.

Finally, the variability of the obtained pyran and dihydropyridine derivatives was demonstrated by targeted transformation which provided new derivatives of potent drug targets. With a view to synthetic opioid β-merperidine (**205**), epilepsy drug (*R*)-tiagabine (**8**) and neuroprotectant HIOC (**7**) dihydropyridine **105f** and pyran **105l** were converted to analogues of these drug targets (Scheme 79).

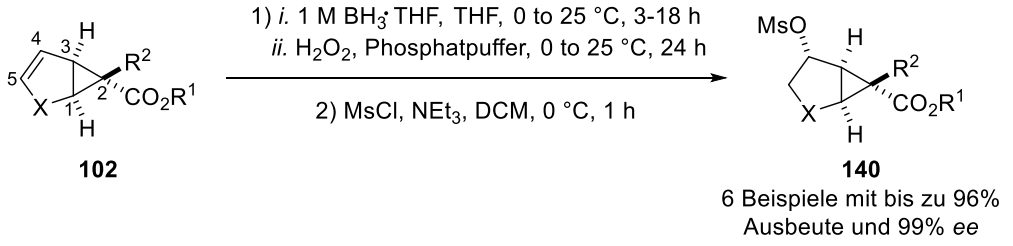


Scheme 79. Targeted derivatization of **105f** and **105l**; [a] yield is given over three steps; [b] yield is given over two steps; conditions: a) TFA/H_2O (9:1), 25 °C, 45 min; b) $NaClO_2$ (5.0 equiv), NaH_2PO_4 (1.5 equiv), 2,3-dimethyl-2-butene (10 equiv), THF/H_2O, 25 °C, 24 h; c) $NaBH_3CN$ (10 equiv), CH_3COOH (10.0 equiv), MeOH, 45 min, 25 °C; d) 37% aq. CH_2O (6.2 equiv), $Na(OAc)_3BH$ (3.0 equiv), MeCN, 25 °C, 1.5 h; e) LiOH (5.0 equiv), MeOH/H_2O (9:1), 100 °C, 2.5 h; f) 2 M $SOCl_2$, EtOH, 100 °C, 4.5 h; g) 4,4-bis(3-methylthiophen-2-yl)but-3-en-1-yl methanesulfonate (1.2 equiv), K_2CO_3 (1.5 equiv), KI (10 mol%), 80 °C, 48 h; h) LiOH (5.0 equiv), MeOH/H_2O (9:1), 100 °C, 24 h; i) *i.* CDI (1.5 equiv), DCM, 25 to 50 °C, 27 h; *ii*. tryptamine (1.02 equiv), pyridine (46 equiv), 25 °C, 24 h.

Hydrolysis of the *N/O*-acetal **105f** under acidic conditions gave access to cyclic imine **186** in high yield (94%), which could be chemoselectively oxidized to the corresponding δ-lactam **188**. On the other hand, chemoselective reductions of **186** are possible, giving rise to **198** or, following methylation and transesterification to β-merperidine derivative **213**. Coupling of **198** to a lipophilic anchor followed by saponification provided tiagabine derivative **199**. Finally, substrates **188** and **105l** are potent precursors for the synthesis of HIOC derivatives. If HIOC is once bound to the receptor, the resistance against hydrolysis of the six-membered heterocycle is known to be decisive for its biological activity. Thus, it was demonstrated that the sterically bulky and hydrolysis resistant model substrate **105l** could, indeed, be coupled to the serotonin related tryptamine after initial saponification within two high-yielding steps to afford HIOC analogue **193**.

2.3.2 Zusammenfassung

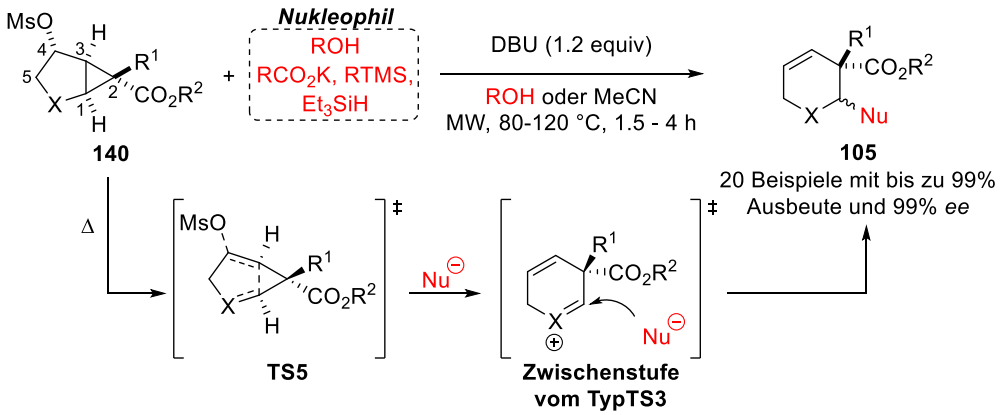
Die vorliegende Arbeit beschäftigt sich mit der stereoselektiven, im großen Maßstab durchführbaren und metallfreien Ringerweiterung von monocyclopropanierten Pyrrolen und Furanen. Deren Entwicklung ermöglichte die Herstellung von synthetisch interessanten und hoch funktionalisierten Dihydropyridin- und Pyranderivaten. Die selektive Spaltung der nichtaktivierten endocyklischen Cyclopropanbindung wird dabei durch das Erzeugen eines Cyclopropylcarbinylkations und der dadurch initiiert Umlagerung erreicht. Die entwickelte sehr umweltfreundliche Reaktionsführung profitiert von ihrer Variabilität in Bezug auf die Ansatzgröße und die verwendeten Startmaterialien, sowie von kurzen Reaktionszeiten. Durch anschließende anwendungsorientierte Umsetzung der erhaltenen sechsgliedringen Heterozcyclen können variable pharmazeutisch relevante Bausteine hergestellt werden.
Die für die Ringerweiterung notwendigen monocyclopropanierten Heterocyclen **102** wurden mittels einer Cu(I)-/Rh(II)-katalysierten oder einer photochemische Cyclopropanierung in razemischer oder enantiomerenreiner Form hergestellt. Um ein Kation in C4-Position durch das Abspalten einer Abgangsgruppe erzeugen zu können, wurden als Startmaterialien die Mesylate **140a-e** über eine Reaktionssequenz, bestehend aus einer Hydroborierung gefolgt von einer Mesylierung, hergestellt. Des Weiteren konnte das Startmaterial **140f** durch eine Epoxidierung, gefolgt von einer sauren Epoixdöffnung und Mesylierung synthetisiert werden (Schema 1).



Schema 1. Synthese der Startmaterialien **140** ausgehend von den monocyclopropanierten Heterocyclen **102**.

Die Diastereoselektivität, die in der Reaktion beobachtet werden konnte, kann damit erklärt werden, dass die Funktionalisierung des Bicyclus **102** exklusiv über die konvexe Seite erfolgt. Dies konnte ebenfalls durch NMR-Spektroskopie und X-Ray Kristallstrukturanalyse bestätigt werden. Als erste Testreaktion zur Ringerweiterung wurde das Startmaterial **140a** in einem Mikrowellenofen auf 80 °C erhitzt

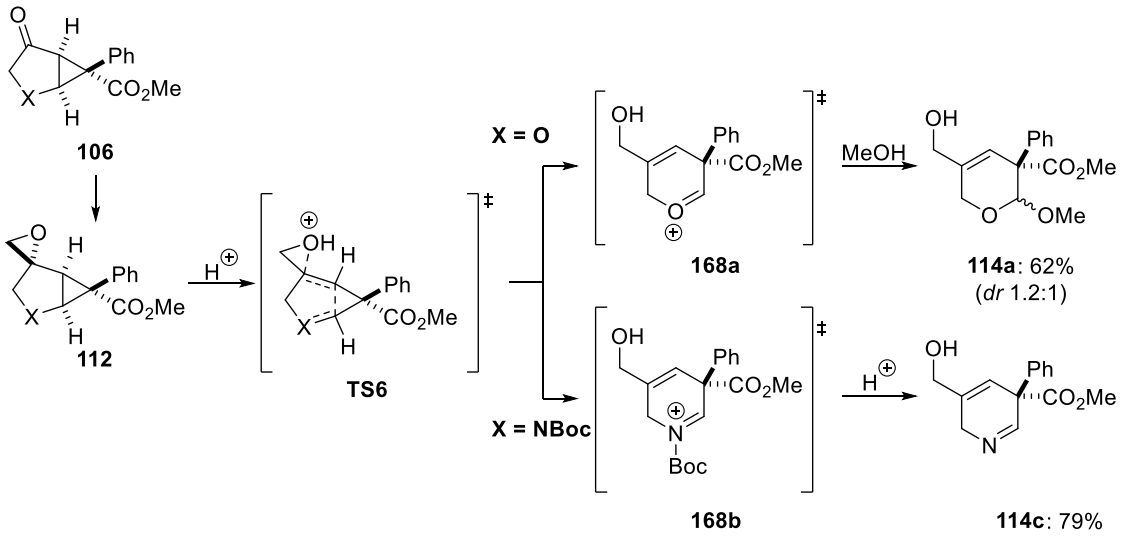
(Tabelle 6, Eintrag 1). Überraschenderweise wurde auf Anhieb das erwartete Pyran **105a** (55% Ausbeute) erhalten. Jedoch wurde dabei auch eine exocyclische Ringöffnung beobachtet, die das Produkt **141** in ähnlicher Menge (45% Ausbeute) lieferte. Es wurde angenommen, dass die während der Reaktion freigesetzte Methansulfonsäure für die unerwartete Nebenreaktion verantwortlich war, indem diese die Estergruppe in **140a** aktivierte und dadurch eine exocyclische Ringöffnung ermöglichte. Diese Nebenreaktion konnte durch den Zusatz von DBU als nicht-nukleophile Base verhindert werden, sodass die Synthese von verschiedensten funktionalisierten sechsgliedrigen Heterocyclen möglich wurde. Außerdem konnten diverse Alkohole als Lösungsmittel verwendet werden (Schema 2).



Schema 2. Mikrowellenunterstützte Ringerweiterung von monocyclopropanierten Furanen und Pyrrolen **140** zur Synthese von sechsgliedrigen Heterocyclen **105**.

Des Weiteren wurde die entwickelte Methodik so optimiert, dass auch Nukleophile, die nicht als Lösungsmittel verwendet werden konnten, zum Einsatz kommen konnten. Diese Optimierung wurde erreicht, indem die bisherigen polar-protischen Lösungsmittel, die zugleich als Nukleophil dienten, durch MeCN als inertes, polar-aprotisches Lösungsmittel eingesetzt wurden. Nun konnten auch Nukleophile wie komplexe Alkohole, Carbonsäuren, Hydride oder verschiedene C-Nukleophile verwendet werden. Zusätzlich wurde durch den Wechsel zu MeCN als Lösungsmittel auch die Derivatisierung von Terpenen und Zucker ermöglicht. Insgesamt wurden die Produkte der Ringerweiterung in hohen Ausbeuten erhalten. Allerdings handelte es sich meist um Mischungen von Epimeren, die jedoch in den meisten Fällen gut voneinander getrennt werden konnten.

Zusätzlich zu den Mesylaten **140** wurden auch Vinylcyclopropanepoxide **112** als potentielle Startmaterialien untersucht. Diese wurden über eine Corey-Chaykovsky-Epoxidierung ausgehend von Ketonen **106** hergestellt (Schema 3).

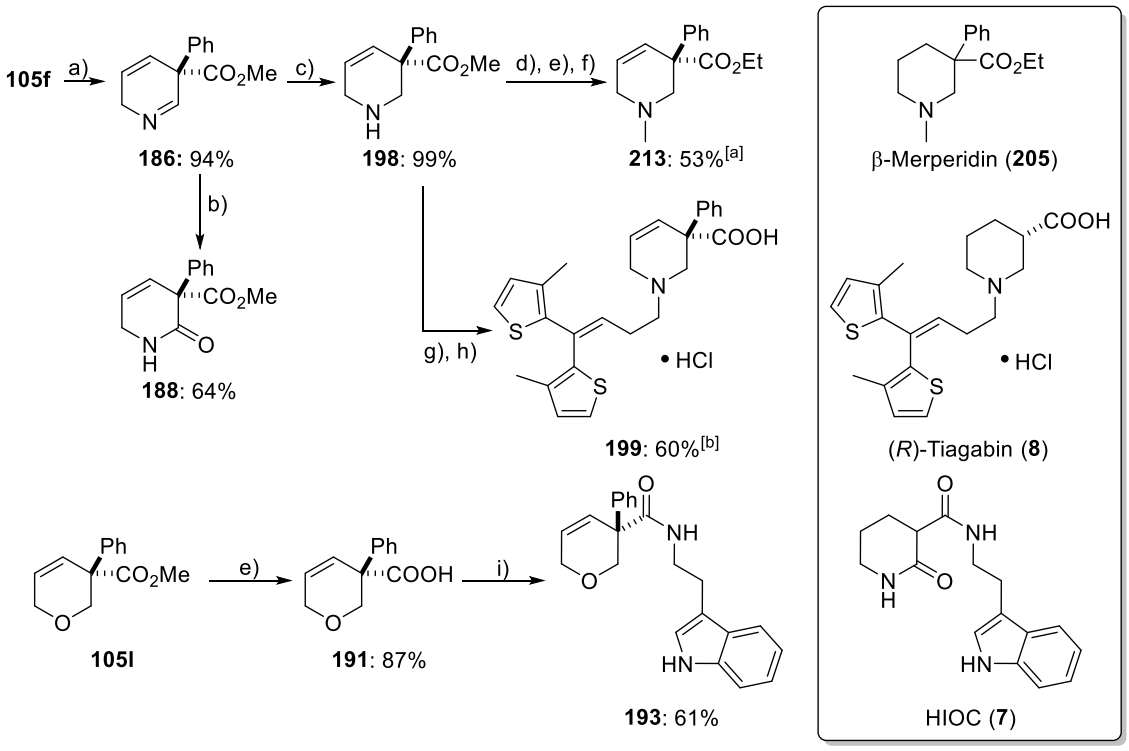


Schema 3. Säureinduzierte Ringerweiterung von Vinylcyclopropanen **112**; (synthetische Details sind dem experimentellen Teil zu entnehmen).

Die Aktivierung der *in situ* generierten Vinylcyclopropane **112** mit Amberlyst 15® in Methanol oder mit TFA in Wasser (9:1) induzierte die Ringerweiterung über ein Cyclopropylmethylkation vom Typ **TS6**. Im Gegensatz zur mikrowellenunterstützten Ringerweiterung, wurde die unerwünschte, säurekatalysierte Bildung des Ringöffnungsprodukts **141** durch einen exocyclischen Bindungsbruch in diesem Fall nicht beobachtet. Dies bedeutet, dass die Epoxidöffnung in **112** und der damit verbundene endocyclische Bindungsbruch vergleichsweise schneller abläuft und dadurch die exocyclische Ringöffnung vollständig unterdrückt wurde.

Abschließend wurde gezeigt, dass die dargestellten Pyran- und Dihydropyridinderivate durch anwendungsorientierte Derivatisierungen in neue Analoga des Opioids β-Merperidin (**205**), des Epilepsie-Wirkstoffes (*R*)-Tiagabin (**8**) und des Neuroprotektivums HIOC (**7**) überführt werden konnten. Dabei dienten das Dihydropyridin **105f** und das Pyran **105l** als Modellsubstrate (Schema 4). Hydrolyse des *N/O*-Acetals **105f** unter sauren Bedingungen lieferte das cyclische Imin **186** in hoher Ausbeute (94%). Dieses konnte chemoselektiv oxidiert werden, wodurch das δ-Laktam **188** erhalten wurde. Des Weiteren konnte das Imin **186** chemoselektiv zum

korrespondierenden freien Amin **198** reduziert werden, welches nach anschließender Methylierung und Umesterung in das β-Merperidinderivat **213** überführt wurde. Zudem konnte das freie Amin **198** an einen lipophilen Anker gekoppelt werden, sodass nach anschließender basischer Verseifung das Tiagabinderivat **199** hergestellt werden konnte. Des Weiteren sind die Modellsubstrate **188** und **105l** vielversprechende Vorläufersubstrate für die Synthese neuer HIOC-Derivate. Ausschlaggebend für dessen biologische Aktivität ist die Hydrolysebeständigkeit der Amidbindung zwischen dem Serotonin und dem Heterocyclus im HIOC (**7**). Deshalb wurde gezeigt, dass das sterisch anspruchsvolle und hydrolysebeständige Pyran **105l** nach einer Esterspaltung an das mit dem Serotonin verwandte Tryptamin gekoppelt werden kann. Das HIOC Derivat **193** konnte dementsprechend in zwei Schritten in guten Ausbeuten synthetisiert werden (Schema 4).



Schema 4. Anwendungsorientierte Derivatisierung der Substrate **105f** und **105l**; [a] die Ausbeute ist auf drei Schritte bezogen; [b] die Ausbeute ist auf zwei Schritte bezogen; Reaktionsbedingungen: a) TFA/H_2O (9:1), 25 °C, 45 min; b) $NaClO_2$ (5.0 equiv), NaH_2PO_4 (1.5 equiv), 2,3-Dimethyl-2-buten (10 equiv), THF/H_2O, 25 °C, 24 h; c) $NaBH_3CN$ (10 equiv), CH_3COOH (10 equiv), MeOH, 45 min, 25 °C; d) 37% aq. CH_2O (6.2 equiv), $Na(OAc)_3BH$ (3.0 equiv), MeCN, 25 °C, 1.5 h; e) LiOH (5.0 equiv), MeOH/H_2O (9:1), 100 °C, 2.5 h; f) 2 M $SOCl_2$, EtOH, 100 °C, 4.5 h; g) 4,4-Bis(3-methylthiophen-2-yl)but-3-en-1-yl methanesulfonat (1.2 equiv), K_2CO_3 (1.5 equiv), KI (10 mol%), 80 °C, 48 h; h) LiOH (5.0 equiv), MeOH/H_2O (9:1), 100 °C, 24 h; i) *i.* CDI (1.5 equiv), DCM, 25 → 50 °C, 27 h; *ii*. Tryptamin (1.02 equiv), Pyridin (46 equiv), 25 °C, 24 h.

3 Experimental Part

3.1 General Aspects

Moisture sensitive reactions were performed in flame-dried glassware and under nitrogen atmosphere. Commercially available chemicals were used as purchased and anhydrous solvents were prepared according to standard procedures. Thin layer chromatography (TLC) was performed with precoated aluminium sheets (ALUGRAM® Xtra SIL G/UV$_{254}$ from MACHEREY-NAGEL GmbH & Co. KG, thickness 0.2 mm). Visualization was accomplished by UV light (λ=254 nm) and common dip stain (vanillin, potassium permanganate or ninhydrin solution). Column chromatography was performed with silica gel (Merck Geduran Si 60, 0.063-0.200 mm particle size) and flash silica gel 60 (Merck Geduran Si 60, 0.040-0.063 mm particle size). Microwave-assisted experiments were carried out on an Anton Paar Monowave 300 reactor. ^{1}H NMR- and ^{13}C NMR-spectra were recorded on Bruker Avance 300 (300 MHz) and Bruker Avance III 400 (400 MHz) NMR spectrometer. The spectra were recorded in $CDCl_3$ (δ = 7.26 ppm) or D_2O (δ = 4.67 ppm) and therefore the chemical shifts for ^{1}H NMR were reported as δ, parts per million (ppm), relative to the signal of $CHCl_3$. Spectra were evaluated in 1st order and the coupling constants (*J*) are described in Hertz (Hz). Splitting patterns for the spin multiplicity were described in abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet. The chemical shifts for ^{13}C-NMR were reported as δ, parts per million (ppm), relative to the signal of $CHCl_3$ (δ = 77.16 ppm). High resolution mass spectra (HRMS) were obtained on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000 or Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS and are reported in *m/z*. The analysis was done by the Central Analytical Laboratory (University Regensburg). Infrared spectra (IR) were measured on a Biorad Excalibur FTS 3000 spectrophotometer and are reported in cm^{-1}. X-ray analysis was performed on Agilent Technologies SuperNova, Agilent Technologies SuperNova E (Mova) or Oxford Diffraction Gemini R Ultra. Analytical high-performance liquid chromatography (HPLC) was conducted on a Varian 920-LC chromatograph equipped with Diode Array detector. Phenomenex Lux Cellulose-1 and Amylose-1 served as chiral stationary phase and mixtures of *n*-heptane and *i*PrOH were used for elution. Optical rotations $[\alpha]_D^{20}$ were determined using Perkin Elmer 241

polarimeter at λ = 589 nm (sodium-*d*-line) in a 1.0 dm measuring cell and the specified solvent. As irradiation device served blue light emitting diodes (LED, 3 W, λ_{max} = 455 nm) produced by LUXEON.

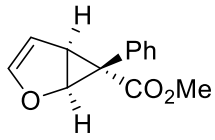
3.2 Synthesis of compounds

Following compounds were already on stock in our laboratories:

Ethyl 2-diazoacetate (**120a**), *tert*-butyl 2-diazoacetate (**120b**), methyl 2-diazoacetate (**120c**), methyl 2-diazo-2-phenylacetate (**118**), furan (**119a**), *N*-Boc-pyrrole (**119b**), *N*-Ts-pyrrole (**119c**), methyl furan-2-carboxylate (**119d**), Rh_2(S-TCPTTL)$_4$ (**116**), (*S*,*S*)-*i*Pr-BOX (**115a**), Cu(OTf)$_2$.

3.3 Synthesis of starting materials

methyl-(1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate ((-)-102a):

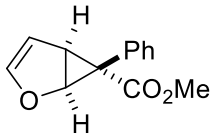


The synthesis was conducted according to a literature procedure.[93] A flame dried 250 mL Schlenk-flask was charged with furan (**119a**) (16.0 mL, 0.22 mmol, 2.0 equiv) and with chiral catalyst Rh_2(S-TCPTTL)$_4$ (**116**) (6.65 mg, 11.0 µmol, 0.001 mol%) under a nitrogen atmosphere. Then, methyl 2-diazo-2-phenylacetate (**118**) (19.4 g, 0.11 mol, 1.0 equiv) was added to the stirred solution *via* a syringe pump using a flow rate of 22 mL/h at 0 °C within 1h. The syringe was attached *via* a septum equipped with an additional cannula for pressure equalizing. After the addition of the diazo-compound, the reaction mixture was stirred for another 5 min until completion of the reaction was achieved. The solvent was removed under reduced pressure to obtain the crude product. Afterwards, the obtained residue was purified by column chromatography using *n*-hexanes and ethyl acetate (95:5) as eluent. The product **(-)-102a** (14.0 g, 64.7 mmol, 59%, *ee* >99% *ee*) was received as white crystalline solid.

Measured analytical data is in accordance to literature:[93]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.16 (m, 5H), 5.91 (dd, *J* = 2.6, 0.8 Hz, 1H), 5.23 (t, *J* = 2.6 Hz, 1H), 5.14 (dd, *J* = 5.6, 0.8 Hz, 1H), 3.62 (s, 3H), 3.31 (dd, *J* = 5.6, 2.7 Hz, 1H). **HPLC analysis** (Phenomenex Lux Cellulose-1, *n*-heptane/*i*PrOH 99:1. Flow 1.0 mL/min): t_r = 8.45 min (major peak).

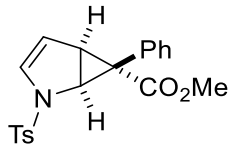
methyl-(1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate ((*rac*)-102a):



Under air, a pressure tube was charged with furan (**119a**) (364 µL, 5.00 mmol, 5.0 equiv), methyl 2-diazo-2-phenylacetate (**118**) (176 mg, 1.00 mmol, 1.0 equiv) and DCM (10 mL, c = 0.1 M). The reaction mixture was irradiated with a blue LED (λ_{max} = 455 nm) at 25 °C for 24 h. Finally, the solvent and remaining furan were evaporated under reduced pressure to obtain the clean product **(*rac*)-102a** (210 mg, 969 µmol, 97%) as white solid.

Analytical data was identical with those reported for the enantiomer **(-)-102a**.

methyl (1*S*,5*S*,6*R*)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (102b):



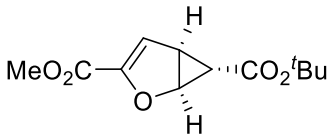
The synthesis was conducted according to a literature procedure.[95] At first, a pressure tube was charged with methyl 2-diazo-2-phenylacetate (**118**) (725 mg, 4.12 mmol, 1.0 equiv) and *N*-Ts-pyrrole (**119c**) (4.55 g, 20.6 mmol, 5.0 equiv) dissolved in DCM (40 mL; c = 0.1 M solution of the diazo compound in DCM). The reaction mixture was irradiated with blue light (λ_{max} = 455 nm) for 24 h and then concentrated under reduced

pressure. After purification by column chromatography using *n*-hexanes and ethyl acetate (gradient: 9:1 to 3:1) the clean product **102b** (1.17 g, 3.17 mmol, 77%) was received as white solid.

Measured analytical data is in accordance to literature:[92]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 – 7.67 (m, 2H), 7.36 – 7.31 (m, 2H), 7.28 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 5.95 (dd, *J* = 3.9, 1.5 Hz, 1H), 5.28 (dd, *J* = 3.9, 2.5 Hz, 1H), 4.53 (dd, *J* = 6.6, 1.4 Hz, 1H), 3.60 (s, 3H), 3.14 (dd, *J* = 6.6, 2.5 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.6, 144.4, 134.9, 132.5, 130.8, 130.4, 130.0, 127.8, 127.4, 127.2, 111.3, 52.8, 52.2, 38.7, 28.0, 21.6. **HRMS:** (ESI-MS) *m/z* calculated for $C_{20}H_{19}NO_4S$ $[M+H]^+$: 370.1108, found 370.1116.

6-(tert-butyl)-3-methyl-(1S,5S,6S)-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (102c):



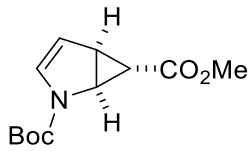
The synthesis was conducted according to a literature procedure.[202] All steps were performed in flame-dried glassware and under a nitrogen atmosphere. First, the copper-catalyst was prepared in a separate flask. $Cu(OTf)_2$ (192 mg, 0.53 mmol, 0.01 equiv.) and the chiral ligand (*S*,*S*)-*i*Pr-BOX (**115a**) (291 mg, 1.09 mmol, 0.02 equiv.) were dissolved in 5 mL dry DCM and stirred for 30 min. In the meantime, a 250 mL flask was charged with methyl furan-2-carboxylate (**119d**) (6.50 g, 51.5 mmol, 1.0 equiv.) and dry DCM (10 mL). The solution was cooled to 0 °C and the prepared blue solution of the chiral copper-catalyst was added to the reaction mixture. Phenyl hydrazine (53 µL, 0.53 mmol, 0.01 equiv.) was added to the mixture to reduce the copper-catalyst from Cu^{II} to the catalytic active Cu^{I}-species. To the reaction mixture **120b** in DCM (94.7 g of an 11.24 w% solution, 74.81 mmol, 1.45 equiv.) was added with a syringe pump (flow rate: 1.3 mL/h) to the stirred reaction mixture. Then the conducted reaction was stirred at 0 °C until the whole diazo-compound was added to the reaction mixture. After completion of the reaction as judged by TLC, the mixture was filtered through a

plug of basic alumina (Al_2O_3) and washed with DCM (400 mL). The solvent of the filtrate was evaporated under reduced pressure to obtain the crude product. This residue was purified by column chromatography using *n*-hexanes and ethyl acetate (95:5) as eluent. Afterwards, the product was purified again by recrystallization from *n*-hexanes to obtain the pure product **102c** as white crystals. (4.23 g, 17.61 mmol, 34%)

Measured analytical data is in accordance to literature:[202]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 2.9 Hz, 1H), 4.89 (dd, *J* = 5.3, 1.0 Hz, 1H), 3.80 (s, 3H), 2.78 (dt, *J* = 5.5, 2.8 Hz, 1H), 1.44 (s, 9H), 1.07 (dd, *J* = 2.7, 1.0 Hz, 1H).

2-(*tert*-butyl) 6-methyl (1*S*,5*S*,6*S*)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (102d):

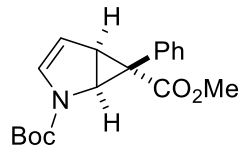


The synthesis was conducted according to a literature procedure.[94] All the steps were performed in flame-dried glassware and under a nitrogen atmosphere. First, *N*-Boc-pyrrole (**119b**) (16.7 mL, 100 mmol, 1.0 equiv) and $Cu(OTf)_2$ (220 mg, 609 µmol, 0.2 equiv) were dissolved in dry DCM (10 mL). Phenyl hydrazine (60.0 µL, 609 µmol, 0.2 equiv) was added to the mixture to reduce the copper-catalyst from Cu^{II} to the catalytic active Cu^{I}-species. To the reaction mixture methyl 2-diazoacetate (**120c**) in DCM (49.4 g of a 9.25 w/w% solution, 45.7 mmol, 1.5 equiv) was added with a syringe pump (flow rate: 1.3 mL/h) to the stirred reaction mixture at room temperature until the whole diazo-compound was pumped into the reaction mixture. After completion of the reaction as judged by TLC, the mixture was filtrated through a plug of basic alumina (Al_2O_3) and washed with DCM (400 mL). The solvent of the filtrate was evaporated under reduced pressure to obtain the crude product. This residue was purified by column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain the clean product **102d** (4.96 g, 20.7 mmol, 68%) as white solid.

In the proton NMR signal doubling and broadening due to rotamers is observed. Measured analytical data is in accordance to literature:[94]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 – 6.31 (m, 1H), 5.43 – 5.25 (m, 1H), 4.54 – 4.17 (m, 1H), 3.77 – 3.54 (m, 4H), 2.88 – 2.68 (m, 1H), 1.51 – 1.43 (m, 10H), 0.99 – 0.88 (m, 1H).

2-(*tert*-butyl) methyl-(1*S*,5*S*,6*R*)-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (102e):

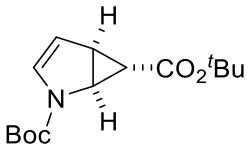


The synthesis was conducted according to a literature procedure.[95] A photo reactor (capacity: 190 mL) was charged with *N*-Boc-pyrrole (**119b**) (23.7 g, 142 mmol, 5.0 equiv) and the diazo-compound **118** (5.00 g, 28.4 mmol, 1.0 equiv) in DCM (c = 0.16 M of diazo-compound in DCM). The reactor was irradiated with blue light (λ_{max} = 455 nm) for 24 h. After the reaction was finished, the solvent was evaporated under reduced pressure. Remaining *N*-Boc-pyrrole (**119b**) was recovered by a distillation under reduced pressure (27 mbar, bp: 91 °C). Afterwards, the obtained residue was recrystallized from methanol to obtain the clean product **102e** (5.63 g, 17.9 mmol, 63%) as white crystals.

In the proton NMR signal doubling and broadening due to rotamers is observed. Measured analytical data is in accordance to literature:[95]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 – 7.19 (m, 3H), 7.17 – 7.06 (m, 2H), 6.21 – 5.88 (m, 1H), 5.30 – 5.00 (m, 1H), 4.78 – 4.54 (m, 1H), 3.64 – 3.56 (m, 3H), 3.37 – 3.27 (m, 1H), 1.63 – 1.39 (m, 9H).

di-*tert*-butyl (1*S*,5*S*,6*S*)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (102f):



The synthesis was conducted according to a literature procedure.[94] All the steps were performed in flame-dried glassware and under a nitrogen atmosphere. First, *N*-Boc-pyrrole (**119b**) (13.5 mL, 80.7 mmol, 1.0 equiv) and $Cu(OTf)_2$ (293.0 mg, 0.81 mmol, 0.1 equiv) were dissolved in 10 mL dry DCM. Phenyl hydrazine (80.0 µL, 0.81 mmol, 0.1 equiv) was added to the mixture to reduce the copper-catalyst from Cu^{II} to the catalytic active Cu^{I}-species. To the reaction mixture *tert*-butyl 2-diazoacetate (**120b**) in DCM (166 g of a 10.37 w/w% solution, 121 mmol, 1.5 equiv) was added with a syringe pump (flow rate: 1.3 mL/h) to the stirred reaction mixture at room temperature until the whole diazo-compound was pumped into the reaction mixture. After completion of the reaction as judged by TLC, the mixture was filtrated through a plug of basic alumina (Al_2O_3) and washed with 400 mL distilled DCM. The solvent of the filtrate was evaporated under reduced pressure to obtain the crude product. This residue was purified by column chromatography using *n*-hexanes and ethyl acetate (93:7) as eluent to obtain the clean product **102f** (5.66 g, 20.1 mmol, 25%) as yellowish solid.

In the proton NMR signal doubling and broadening due to rotamers is observed. Measured analytical data is in accordance to literature:[94]

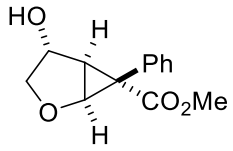
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.69 – 6.35 (m, 1H), 5.49 – 5.27 (m, 1H), 4.47 – 4.13 (m, 1H), 2.87 – 2.63 (m, 1H), 1.51 (s, 9H), 1.44 (s, 1H), 0.97 – 0.75 (m, 1H).

3.3.1 Hydroboration of monocyclopropanated heterocycles

General procedure A– Hydroboration (*GP-A*):

All steps were performed in flame-dried glassware and under nitrogen atmosphere. The cyclopropane derivative **102** (1.0 equiv) was dissolved in a certain amount of dry THF and cooled to 0 °C. A 1 M solution of BH_3·THF (1.1 equiv) was added dropwise to the stirred solution. Then, the reaction mixture was stirred at 0 °C until completion of BH_3-addition was achieved. Afterwards, H_2O_2 (35 w%, 30 equiv) was added dropwise followed by the addition phosphate buffer (pH 7, containing 1 M KH_2PO_4 and 1 M K_2HPO_4) at 0 °C. The mixture was stirred for 14 h while warming to 25 °C. After completion, the reaction was cooled again to 0 °C and was slowly quenched with saturated $Na_2S_2O_3$. The quenched reaction was then extracted with ethyl acetate and the combined organic layers were washed once with half saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to obtain the crude product which was purified by flash column chromatography to obtain the clean product **103**.

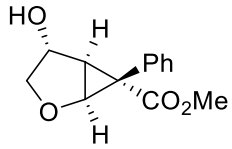
methyl (1*S*,4*R*,5*R*,6*R*)-4-hydroxy-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate ((*rac*)-103a):



According to *GP-A*, **(*rac*)-103a** was prepared from cyclopropanated furan derivative **(*rac*)-102a** (4.00 g, 20.0 mmol, 1.0 equiv) and a 1 M BH_3·THF solution (22.0 mL, 22.0 mmol, 1.1 equiv) in dry THF (20 mL). After completion of BH_3 addition (3 h), H_2O_2 solution (40.0 mL, 35 w%, 600 mmol, 30 equiv) followed by phosphate buffer (40 mL) were added dropwise at 0 °C. After extraction with ethyl acetate (3x100 mL), flash column chromatography using *n*-hexanes and ethyl acetate (3:2) as eluent afforded the clean product **(*rac*)-103a** (3.95 g, 16.9 mmol, 84%) as colorless liquid.

R_f = 0.56 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.41 – 7.26 (m, 5H), 4.64 (d, *J* = 5.2 Hz, 1H), 4.26 (dd, *J* = 5.4, 1.2 Hz, 1H), 3.64 (dt, *J* = 10.7, 1.3 Hz, 1H), 3.58 (s, 3H), 2.74 (dd, *J* = 5.3, 1.1 Hz, 1H), 2.53 (dd, *J* = 10.7, 5.3 Hz, 1H), 2.36 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.7, 131.9, 131.0, 128.6, 127.9, 78.1, 72.8, 68.8, 52.6, 37.8, 36.0. **IR:** ν[cm^{-1}] = 3350, 2952, 1718, 1674, 1431, 1230, 1066. **HRMS:** (APCI-MS) *m/z* calculated for $C_{13}H_{14}O_4$ $[M+H]^+$: 235.0965, found 235.0967.

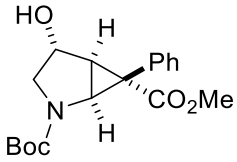
methyl (1*S*,4*R*,5*R*,6*R*)-4-hydroxy-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate ((+)-103a):



According to *GP-A,* (+)-**103a** was prepared from cyclopropanated furan derivative **(-)-102a** (1.00 g, 4.64 mmol, 1.0 equiv) and a 1 M BH_3·THF solution (5.1 mL, 5.1 mmol, 1.1 equiv) in dry THF (5 mL). After completion of BH_3 addition (3 h), H_2O_2 solution (9.3 mL, 35 w%, 0.14 mol, 30 equiv) followed by phosphate buffer (9 mL) were added dropwise at 0 °C. After extraction with ethyl acetate (3x50 mL), flash column chromatography using *n*-hexanes and ethyl acetate (3:2) as eluent afforded the clean product **(+)-103a** (764 mg, 3.26 mmol, 70%, 99% *ee*) as colorless liquid.

NMR and IR were identical with those reported for the racemate **103a**; **HRMS:** (APCI-MS) *m/z* calculated for $C_{13}H_{14}O_4$ $[M+H]^+$: 235.0965, found 235.0968. **HPLC analysis** (Phenomenex Lux Cellulose-1, *n*-heptane/*i*PrOH 7:3. Flow 0.5 mL/min): t_r = 10.52 min (major peak), 99% *ee*; $[\alpha]_D^{20}$ + 41.0 ° (*c* 1.0, $CHCl_3$).

2-(*tert*-butyl) 6-methyl (1*S*,4*R*,5*S*,6*R*)-4-hydroxy-6-phenyl-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (103b):

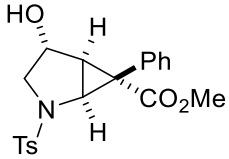


According to *GP-A*, **103b** was prepared from cyclopropanated pyrrole derivative **102e** (2.21 g, 7.00 mmol, 1.0 equiv) and a 1 M BH_3·THF solution (7.7 mL, 7.7 mmol, 1.1 equiv) in dry THF (15 mL). After completion of BH_3 addition (3 h), H_2O_2 solution (14 mL, 35 w%, 0.21 mol, 30 equiv) followed by phosphate buffer (15 mL) were added dropwise at 0 °C. After extraction with ethyl acetate (3x50 mL), flash column chromatography using *n*-hexanes and ethyl acetate (3:2) as eluent afforded the clean product **103b** (2.21 g, 6.63 mmol, 95%) as colorless liquid.

In the proton and carbon NMR signal doubling and broadening due to rotamers is observed.

R_f = 0.53 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.31 – 7.24 (m, 3H), 7.21 – 7.09 (m, 2H), 4.31 – 4.12 (m, 2H), 3.59 – 3.46 (m, 3H), 3.24 – 3.07 (m, 1H), 2.71 – 2.64 (m, 1H), 2.35 – 2.17 (m, 1H), 1.92 – 1.72 (m, 1H), 1.54 – 1.33 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.6, 171.3, 155.2, 154.2, 132.2, 131.9, 131.2, 130.7, 128.8, 128.7, 128.1, 127.9, 80.7, 80.2, 71.4, 70.3, 56.0, 55.8, 52.7, 52.6, 48.3, 48.0, 37.9, 37.0, 36.9, 36.8, 28.5, 28.3. **IR:** ν[cm^{-1}] = 3381, 2978, 1718, 1654, 1495, 1420, 1136. **HRMS:** (EI-MS) *m/z* calculated for $C_{18}H_{23}NO_5$ $[M+H]^+$: 334.1649, found 334.1650.

methyl (1*S*,4*R*,5*S*,6*R*)-4-hydroxy-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hexane-6-carboxylate (103c):

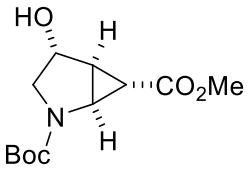


According to *GP-A*, **103c** was prepared from cyclopropanated pyrrole derivative **102b** (600 mg, 1.62 mmol, 1.0 equiv) and a 1 M BH_3·THF solution (1.8 mL, 1.8 mmol,

1.1 equiv) in dry THF (3 mL). After completion of BH_3 addition (3 h), H_2O_2 solution (3.3 mL, 35 w%, 49 mmol, 30 equiv) followed by phosphate buffer (3.3 mL) were added dropwise at 0 °C. After extraction with ethyl acetate (3x50 mL), flash column chromatography using *n*-hexanes and ethyl acetate (3:2) as eluent afforded the clean product **103c** (485 mg, 1.25 mmol, 77%) as white solid.

R_f = 0.18 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **mp =** 149 – 151 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.81 – 7.71 (m, 2H), 7.38 – 7.26 (m, 7H), 4.35 (d, J = 6.2 Hz, 1H), 4.18 (d, *J* = 5.2 Hz, 1H), 3.59 (s, 3H), 3.20 (dt, *J* = 12.9, 1.1 Hz, 1H), 2.57 (dd, *J* = 6.2, 1.3 Hz, 1H), 2.44 (s, 3H), 2.00 (dd, *J* = 13.1, 5.3 Hz, 1H), 1.61 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.3, 144.0, 136.2, 131.3, 130.8, 130.0, 128.7, 128.1, 127.2, 71.6, 57.4, 52.9, 50.4, 36.4, 35.2, 21.6. **IR:** ν[cm^{-1}] = 3500, 3064, 3030, 2956, 2363, 1715, 1342, 1249, 1163, 1118, 816, 708, 667. **HRMS:** (ESI-MS) *m/z* calculated for $C_{20}H_{21}NO_5S$ $[M+H]^+$: 388.1213, found 388.1221.

2-(*tert*-butyl) 6-methyl (1*S*,*4R*,5*S*,6*S*)-4-hydroxy-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (103d):



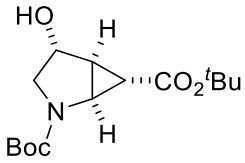
According to *GP-A*, **103d** was prepared from cyclopropanated pyrrole derivative **102d** (1.00 g, 4.18 mmol, 1.0 equiv) and a 1 M BH_3·THF solution (4.6 mL, 4.6 mmol, 1.1 equiv) in dry THF (5 mL). After completion of BH_3 addition (24 h), H_2O_2 solution (8.4 mL, 35 w%, 1.3 mmol, 30 equiv) followed by phosphate buffer (8.4 mL) were added dropwise at 0 °C. After extraction with ethyl acetate (3x50 mL), flash column chromatography using *n*-hexanes and ethyl acetate (3:2) as eluent afforded the clean product **103d** (533 mg, 2.07 mmol, 50%) as colorless liquid.

In the proton and carbon NMR signal broadening due to rotamers is observed.

R_f = 0.17 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.46 (d, *J* = 5.2 Hz, 1H), 4.00 (s, 1H), 3.66 (s, 3H), 3.59 (d, *J* = 13.2 Hz,

1H), 3.08 (dd, *J* = 13.2, 5.3 Hz, 1H), 2.44 (s, 1H), 2.31 – 2.19 (m, 1H), 1.67 (dd, *J* = 3.9, 1.6 Hz, 1H), 1.45 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.0, 154.6, 80.7, 70.9, 53.2, 52.0, 43.1, 31.2, 28.4, 22.9. **IR:** ν[cm^{-1}] = 3407, 2978, 1674, 1394, 1275, 1163, 1118, 1085, 954, 850, 753, 719. **HRMS:** (APCI-MS) *m/z* calculated for $C_{12}H_{19}NO_5$ $[M+H]^+$: 258.1336, found 258.1338.

di-tert-butyl (1S,4R,5S,6S)-4-hydroxy-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (103e):



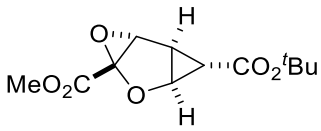
According to *GP-A*, **103e** was prepared from cyclopropanated pyrrole derivative **102f** (2.06 g, 7.32 mmol, 1.0 equiv) and a 1 M BH_3·THF solution (10.0 mL, 10.0 mmol, 1.1 equiv) in dry THF (20 mL). After completion of BH_3 addition (24 h), H_2O_2 solution (14.7 mL, 220 mmol, 30.0 equiv) followed by phosphate buffer (15 mL) were added dropwise at 0 °C. After extraction with ethyl acetate (3x50 mL), flash column chromatography using *n*-hexanes and ethyl acetate (3:2) as eluent afforded the clean product **103e** (1.30 g, 4.34 mmol, 59%) as colorless liquid.

In the proton and carbon NMR signal broadening due to rotamers is observed.

R_f = 0.31 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 4.47 – 4.37 (m, 1H), 4.03 – 3.77 (m, 1H), 3.55 (d, J = 13.1 Hz, 1H), 3.20 (bs, 1H), 3.03 (dd, J = 13.1, 5.3 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.53 (dd, J = 3.9, 1.7 Hz, 1H), 1.43 (s, 9H), 1.40 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 169.7, 154.7, 81.2, 80.5, 70.9, 53.4, 42.8, 31.0, 28.4, 28.1, 24.2. **HRMS:** (ESI-MS) *m/z* calculated for $C_{15}H_{25}NO_5$ $[M+H]^+$: 300.1805, found 300.1810. **IR:** ν[cm^{-1}] = 3414, 2978, 2937, 1700, 1416, 1367, 1297, 1256, 1156, 1122, 969, 936, 842, 768, 723.

3.3.2 Epoxidation and epoxide opening

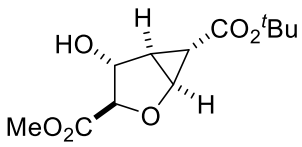
7-(*tert*-butyl) 4-methyl (1*S*,2*S*,4*S*,6*S*,7*S*)-3,5-dioxatricyclo[4.1.0.02,4]heptane-4,7-dicarboxylate (125):



At first, cyclopropanated furan **102c** (1.00 g, 4.16 mmol, 1.0 equiv) was dissolved in acetone (150 mL) and diluted with water (150 mL). Afterwards, $NaHCO_3$ (5.2 g, 62 mmol, 15 equiv) was added and the resulting mixture was cooled to 0 °C. Then, Oxone® (12.8 g, 20.8 mmol, 5.0 equiv) was added in portions and the mixture was stirred for 3 h until completion of TLC. The remaining residue was filtered and the filtrate was extracted with ethyl acetate (3x100 mL). For quenching, the combined organic layers were washed with $Na_2S_2O_5$ (100 mL, 5 w/w%) followed by brine. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the clean product **125** (1.01 g, 3.94 mmol, 95%) as colorless oil which crystallized in the fridge.

R_f = 0.53 (*n*-hexanes/ethyl acetate = 3:1, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.12 (t, *J* = 0.7 Hz, 1H), 4.06 (dt, *J* = 5.6, 1.0 Hz, 1H), 3.82 (s, 3H), 2.67 (dd, *J* = 5.6, 3.9 Hz, 1H), 1.97 (dd, *J* = 3.9, 1.2 Hz, 1H), 1.42 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 168.3, 164.0, 83.4, 81.8, 65.1, 62.7, 53.4, 28.6, 28.0, 27.7. **IR:** ν[cm^{-1}] = 2989, 1752, 1707, 1450, 1368, 1193, 1137, 883. **HRMS:** (EIC-MS) *m/z* calculated for $C_{12}H_{16}O_6$ $[M+NH_4]^+$: 274.1285, found 274.1288.

6-(*tert*-butyl) 3-methyl (1*S*,3*R*,4*R*,5*R*,6*S*)-4-hydroxy-2-oxabicyclo[3.1.0]hexane-3,6-dicarboxylate (126a):

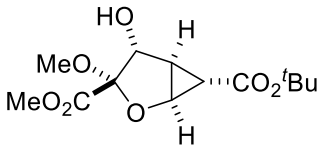


At first, the epoxide **125** (102 mg, 400 µmol, 1.0 equiv) was dissolved in ethyl acetate (2 mL) and the catalyst Pd/C (169 mg, 5 w/w%, 78 µmol, 20 mol%) was added to the solution. The reaction mixture was stirred for 3 h under H_2 atmosphere applying 30 bar

pressure. Afterwards, the reaction mixture was filtered and the solvent was evaporated to obtain the crude product. Purification was achieved by flash column chromatography using a mixture of *n*-hexanes and ethyl acetate (gradient: 3:1 to 3:2) to obtain the clean product **126a** (36.8 mg, 142 µmol, 36%) as colorless oil.

R_f = 0.38 ((*n*-hexanes/ethyl acetate = 3:2, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.68 – 4.62 (m, 2H), 4.42 (dd, J = 5.1, 1.1 Hz, 1H), 3.76 (s, 2H), 3.12 (bs, 1H), 2.18 (t, J = 4.7 Hz, 1H), 1.69 (dd, J = 4.1, 1.1 Hz, 1H), 1.39 (s, 7H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.5, 169.3, 88.1, 81.4, 76.7, 66.5, 52.7, 31.0, 28.0, 24.7. **HRMS:** (APCI-MS) *m/z* calculated for $C_{12}H_{18}O_6$ $[M+NH_4]^+$: 276.1442, found 276.1445. **IR:** ν[cm^{-1}] = 3459, 2978, 1711, 1405, 1368, 1308, 1208, 1156, 1111, 1066, 962, 939, 872, 839, 768, 734.

6-(*tert*-butyl) 3-methyl (1*S*,3*R*,4*R*,5*R*,6*S*)-4-hydroxy-3-methoxy-2-oxabicyclo[3.1.0] hexane-3,6-dicarboxylate (126b):



To a solution of epoxide **125** (268 mg, 1.0 mmol, 1.0 equiv) in MeOH (13 mL) an catalytic amount of Amberlyst® 15 (53 mg, 20 w/w%) was added. The suspension was stirred for 15 min at 25 °C. After completion, the reaction mixture was filtered and the solvent was evaporated to obtain the clean product **126b** (298 mg, 1.0 mmol, *quant.*) as colorless oil which was used without further purification.

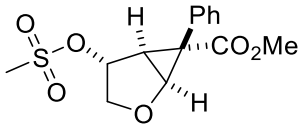
R_f = 0.27 (*n*-hexanes/ethyl acetate = 2:1, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.45 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.25 (s, 1H), 3.77 (s, 3H), 3.15 (s, 3H), 2.93 (bs, 1H), 2.11 (dd, *J* = 5.2, 4.0 Hz, 1H), 2.04 (dd, *J* = 4.0, 1.2 Hz, 1H), 1.37 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 169.3, 167.0, 112.4, 81.3, 78.4, 65.9, 52.9, 51.7, 28.6, 28.1, 25.8. **IR:** ν[cm^{-1}] = 3481, 2978, 2840, 1752, 1715, 1457, 1394, 1372, 1282, 1156, 1096, 992, 876, 842, 719. **HRMS:** (ESI-MS) *m/z* calculated for $C_{13}H_{20}O_7$ $[M+H]^+$: 289.1282, found 289.1284.

3.3.3 Activation of the hydroxylated cyclopropane derivatives

General procedure B – Mesylation (*GP-B*):

At first, respective alcohol **103** (1.0 equiv) was dissolved in DCM and NEt_3 (2.0 equiv) was added. The solution was cooled to 0 °C and MsCl (1.1 equiv) was added dropwise to the vigorously stirred solution. After 1 h, the reaction was quenched with 1 M HCl (15 mL) and the obtained layers were separated. The organic layer was washed with 1 M HCl (15 mL), 2 M NaOH (20 mL) and brine (50 mL). Then, the organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Purification of the residue was achieved by adding a small amount of MeOH (2 mL) to obtain a suspension which was placed in the sonicator for 15 min followed by cooling in the freezer for 3 h. Finally, the precipitate was isolated by filtration and washing with cold MeOH to obtain the product **140**.

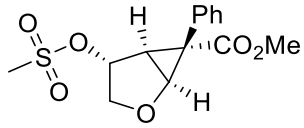
methyl (1*S*,4*R*,5*S*,6*R*)-4-((methylsulfonyl)oxy)-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate ((*rac*)-140a):



According to *GP-B*, alcohol **(*rac*)-103a** (1.29 g, 5.51 mmol, 1.0 equiv) was dissolved in DCM (46 mL), then NEt_3 (1.5 mL, 11 mmol, 2.0 equiv) and MsCl (0.47 mL, 6.1 mmol, 1.1 equiv) were added. After extraction and evaporation of the solvent, the crude product was purified to obtain **(*rac*)-140a** (1.23 g, 3.94 mmol, 75%) as white solid.

R_f = 0.29 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **mp** = 92 °C. **^{1}H NMR (400 MHz, $CDCl_3$** δ = 7.42 – 7.28 (m, 5H), 5.08 (d, *J* = 4.3 Hz, 1H), 4.72 (d, *J* = 5.2 Hz, 1H), 3.91 (dt, *J* = 11.9, 1.2 Hz, 1H), 3.60 (s, 3H), 3.07 (s, 3H), 2.95 (dd, *J* = 5.2, 1.2 Hz, 1H), 2.63 (dd, *J* = 11.9, 5.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 170.7, 131.0, 130.8, 129.0, 128.3, 80.2, 75.5, 69.0, 52.8, 38.8, 36.2, 35.0. **IR:** ν[cm^{-1}] = 3027, 2948, 1722, 1435, 1349, 1245, 1170, 1085, 965, 936. **HRMS:** (EI-MS) *m/z* calculated for $C_{14}H_{16}O_6S$ $[M+H]^+$: 313.0740, found 313.0742.

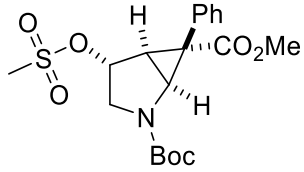
methyl (1*S*,4*R*,5*S*,6*R*)-4-((methylsulfonyl)oxy)-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate ((+)-140a):



According to *GP-B*, enantiopure alcohol **(+)-103a** (553 mg, 2.36 mmol, 1.0 equiv) was dissolved in DCM (20 mL), then NEt_3 (0.66 mL, 4.73 mmol, 2.0 equiv) and MsCl (0.20 mL, 2.58 mmol, 1.1 equiv) were added. After extraction and evaporation of the solvent, the crude product was purified to obtain **(+)-140a** (530 mg, 1.70 mmol, 72%) as white solid.

NMR, IR and melting point were identical with those reported for the racemate **(*rac*)-140a.** $[\alpha]_D^{20}$ + 64.1°(*c* 1.0, $CHCl_3$). **HRMS:** (EI-MS) *m/z* calculated for $C_{14}H_{16}O_6S$ $[M+H]^+$: 313.0740, found 313.0746.

2-(*tert*-butyl) 6-methyl (1*S*,4*R*,5*S*,6*R*)-4-((methylsulfonyl)oxy)-6-phenyl-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (140b):



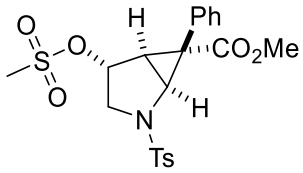
According to *GP-B*, the alcohol **103b** (1.87 g, 5.61 mmol, 1.0 equiv) was dissolved in DCM (47 mL), then NEt_3 (1.6 mL, 11. mmol, 2.0 equiv) and MsCl (0.48 mL, 6.2 mmol, 1.1 equiv) were added. After extraction and evaporation of the solvent, the crude product was purified to obtain **140b** (2.21 g, 5.37 mmol, 96%) as white solid.

In the proton and carbon NMR signal doubling and broadening due to rotamers is observed.

R_f = 0.38 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **mp** = 121–124 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.40 – 7.30 (m, 3H), 7.30 – 7.15 (m, 2H), 5.18 – 5.10 (m, 1H), 4.41 – 4.23 (m, 1H), 3.66 – 3.56 (m, 3H), 3.56 – 3.40 (m, 1H), 3.11 – 3.01 (m, 3H), 3.00 – 2.89 (m, 1H), 2.06 – 1.90 (m, 1H), 1.59 – 1.38 (m, 9H). **^{13}C NMR**

(101 MHz, $CDCl_3$): δ = 170.7, 170.5, 154.5, 153.7, 131.3, 131.1, 130.5, 129.2, 129.1, 128.5, 128.4, 81.2, 80.8, 78.9, 78.0, 53.8, 53.3, 53.0, 52.9, 48.4, 48.0, 38.94, 38.91, 37.3, 37.0, 35.3, 34.1, 28.5, 28.3. **IR:** ν[cm^{-1}] = 2978, 1700, 1402, 1357, 1234, 1170, 1126, 962, 910. **HRMS:** (EI-MS) *m/z* calculated for $C_{19}H_{25}NO_7S$ $[M+H]^+$: 412.1424, found 412.1426.

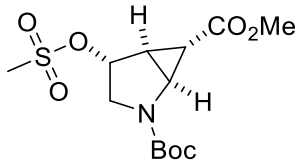
methyl (1*S*,4*R*,5*S*,6*R*)-4-((methylsulfonyl)oxy)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0] hexane-6-carboxylate (140c):



According to *GP-B*, alcohol **103c** (455 mg, 1.17 mmol, 1.0 equiv) was dissolved in DCM (10 mL), then NEt_3 (0.33 mL, 2.4 mmol, 2.0 equiv) and MsCl (0.10 mL, 1.3 mmol, 1.1 equiv) were added. After extraction and evaporation of the solvent, the crude product was purified to obtain **140c** (469 mg, 1.01 mmol, 86%) as white solid.

R_f = 0.25 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **mp** = 96-97 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.82 – 7.72 (m, 2H), 7.40 – 7.26 (m, 7H), 4.95 (d, *J* = 5.1 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 3.61 (s, 3H), 3.53 – 3.44 (m, 1H), 2.79 (s, 3H), 2.76 (dd, *J* = 6.2, 1.6 Hz, 1H), 2.45 (s, 3H), 2.08 (dd, *J* = 14.5, 5.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 170.6, 144.0, 135.8, 130.5, 130.4, 129.9, 129.1, 128.5, 127.4, 78.4, 55.1, 53.2, 50.7, 38.5, 35.1, 33.8, 21.6. **IR:** ν[cm^{-1}] = 3030, 2956, 2259, 1718, 1599, 1498, 1450, 1349, 1252, 1163, 1111, 1006, 954, 913, 880, 816, 731, 708, 667. **HRMS:** (ESI-MS) *m/z* calculated for $C_{21}H_{23}NO_7S_2$ $[M+H]^+$: 466.0989, found 466.0994.

2-(*tert*-butyl) 6-methyl (1*S*,4*R*,5*S*,6*S*)-4-((methylsulfonyl)oxy)-2-azabicyclo[3.1.0] hexane-2,6-dicarboxylate (140d):

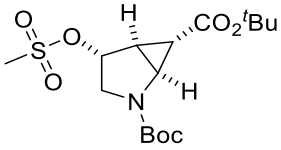


According to *GP-B*, alcohol **103d** (485 mg, 1.89 mmol, 1.0 equiv) was dissolved in DCM (16 mL), then NEt_3 (0.53 mL, 3.8 mmol, 2.0 equiv) and MsCl (0.16 mL, 2.1 mmol, 1.1 equiv) were added. After extraction and evaporation of the solvent, the clean product **140d** (522 mg, 1.56 mmol, 83%) was obtained as colorless oil.

In the proton and carbon NMR signal broadening due to rotamers is observed.

R_f = 0.24 (*n*-hexanes/ethyl acetate = 3:2, stained in $KMnO_4$). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 5.31 (d, *J* = 5.2 Hz, 1H), 4.11 (s, 1H), 3.91 (d, *J* = 14.5 Hz, 1H), 3.69 (s, 3H), 3.22 (dd, *J* = 14.3, 5.3 Hz, 1H), 3.09 (s, 3H), 2.59 – 2.43 (m, 1H), 1.77 (dd, *J* = 3.8, 1.8 Hz, 1H), 1.47 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 169.9, 153.9, 81.2, 78.6, 52.2, 50.8, 43.2, 38.9, 28.8, 28.3, 22.9. **IR:** ν[cm^{-1}] = 2982, 1700, 1416, 1364, 1305, 1170, 1122, 962, 902, 857, 787, 731. **HRMS:** (ESI-MS) *m/z* calculated for $C_{13}H_{21}NO_7S$ $[M+H]^+$: 336.1111, found 336.1112.

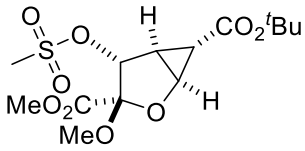
di-*tert*-butyl (1*S*,4*R*,5*S*,6*S*)-4-((methylsulfonyl)oxy)-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (140e):



According to *GP-B*, the alcohol **103e** (1.2 g, 4.0 mmol, 1.0 equiv) was dissolved in DCM (35 mL), NEt_3 (1.1 mL, 8.0 mmol, 2.0 equiv) and MsCl (440 µL, 4.4 mmol, 1.1 equiv) were added. After extraction and evaporation of the solvent, the crude product was obtained as a yellowish solid. The crude product was purified following the general procedure to obtain the clean product **140e** (1.34 g, 3.55 mmol, 89%) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.30 (d, J = 5.1 Hz, 1H), 4.18 – 3.94 (m, 1H), 3.89 (d, J = 14.4 Hz, 1H), 3.19 (dd, J = 14.3, 5.3 Hz, 1H), 3.09 (s, 3H), 2.38 (s, 1H), 1.66 (dd, J = 3.8, 1.8 Hz, 1H), 1.47 (s, 9H), 1.44 (s, 9H).**^{13}C NMR (101 MHz, $CDCl_3$):** δ = 168.6, 154.0, 81.7, 81.0, 78.6, 51.0, 42.9, 38.9, 28.3, 28.1, 24.0. **HRMS:** (EI-MS) *m/z* calculated for $C_{16}H_{27}NO_7S$ $[M+H]^+$: 378.1581, found 378.1586. **IR:** ν[cm^{-1}] = 2978, 2937, 1700, 1476, 1416, 1364, 1304, 1282, 1156, 1122, 1047, 962, 902, 861, 790, 734. **R_f** = 0.17 (*n*-hexanes/ethyl acetate = 3:1, Vanillin).

6-(*tert*-butyl) 3-methyl (1*S*,3*S*,4*R*,5*S*,6*S*)-3-methoxy-4-((methylsulfonyl)oxy)-2-oxabicyclo[3.1.0]hexane-3,6-dicarboxylate (140f):



According to *GP-B*, alcohol **126b** (288 mg, 1.00 mmol, 1.0 equiv) was dissolved in DCM (8.4 mL), then NEt_3 (0.28 mL, 2.0 mmol, 2.0 equiv) and MsCl (85 µL, 1.1 mmol, 1.1 equiv) were added. After extraction and evaporation of the solvent, the crude product was purified to obtain **140f** (318 mg, 868 µmol, 87%) as white solid.

R_f = 0.39 (*n*-hexanes/ethyl acetate = 3:2; stained in $KMnO_4$). **mp** = 120-121 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 5.07 (s, 1H), 4.60 (dd, *J* = 5.1, 1.2 Hz, 1H), 3.84 (s, 3H), 3.24 (s, 3H), 3.04 (s, 3H), 2.35 (dd, *J* = 5.1, 3.9 Hz, 1H), 2.21 (dd, *J* = 3.9, 1.3 Hz, 1H), 1.44 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 168.3, 165.2, 110.4, 84.0, 81.9, 66.1, 53.2, 51.9, 38.8, 28.1, 26.7, 26.1. **IR:** ν[cm^{-1}] = 2982, 2941, 1759, 1707, 1402, 1368, 1323, 1286, 1156, 1096, 1018, 988, 820, 772, 716. **HRMS:** (ESI-MS) *m/z* calculated for $C_{14}H_{22}O_9S$ $[M+Na]^+$: 389.0877, found 389.0880.

3.4 Microwave-assisted ring expansion

General procedure C – Conditions I (*GP-C-I*):

Mesylated precursor **140** (1.0 equiv) was dissolved in respective alcohol (1.5 mL) and DBU (1.2 equiv) was added. Then, the reaction mixture was heated (80 – 120 °C) for 1.5 h under microwave irradiation. After completion of the reaction, as judged by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and the mixture was washed with water (2x20 mL). The aqueous layer was re-extracted with ethyl acetate (2x20 mL), followed by washing the combined organic layers with brine and drying over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to obtain the crude product **105a-k** which was purified by flash column chromatography.

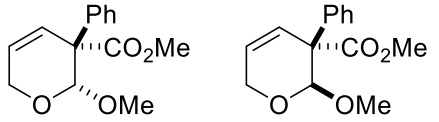
General procedure C – Conditions II (*GP-C-II*):

Mesylated precursor **140a** (1.0 equiv) was dissolved in dry MeCN (2 mL) and respective nucleophile (3.0 equiv) followed by DBU (1.2 equiv) were added. Then, the reaction mixture was heated to 120 °C for 1.5 h under microwave irradiation. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 mL) and the mixture was washed with water (2x20 mL). The aqueous layer was re-extracted with ethyl acetate (2x20 mL), followed by washing the combined organic layers with brine and drying over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to obtain the crude product **105m-n/105s-t** which was purified by flash column chromatography.

General procedure C – Conditions III (*GP-C-III*):

Mesylated precursor **140a** (1.0 equiv) was dissolved in dry MeCN (2 mL) and respective nucleophile (3.0 equiv) was added. Then, the reaction mixture was heated to 120 °C for 4 h under microwave irradiation. After completion of the reaction, as judged by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and the mixture was washed with water (2x20 mL). The aqueous layer was re-extracted with ethyl acetate (2x20 mL), followed by washing the combined organic layers with brine and drying over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure to obtain the crude product **105l/105o-r** which was purified by flash column chromatography.

methyl (2*R*,3*R*)-2-methoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*S*,3*R*)-2-methoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate ((*rac*)-105a):



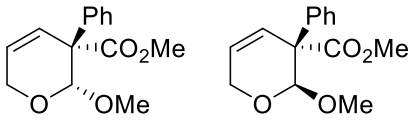
major-(***rac*)-105a** *minor*-(***rac*)-105a**

According to *GP-C-I*, mesylated precursor **(*rac*)-140a** (865 mg, 2.77 mmol, 1.0 equiv) was dissolved in MeOH (13 mL) and DBU (0.50 mL, 3.3 mmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 80 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 2.7:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain an inseparable mixture of *major*- and *minor*-**(*rac*)-105a** (680 mg, 2.74 mmol, *dr* 2.7:1, 99%) as colorless oil crystallizing in the freezer.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.53 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.50 – 7.44 (m, 2H), 7.38 – 7.23 (m, 5H), 6.38 – 6.31 (m, 1H), 6.19 – 6.13^{minor} (m, 0.38H), 6.09^{minor} (ddd, *J* = 10.4, 2.9, 2.0 Hz, 0.36H), 5.95 (dddd, *J* = 10.5, 3.2, 1.9, 0.6 Hz, 1H), 5.38 – 5.35^{minor} (m, 0.37H), 5.34 – 5.32 (m, 1H), 4.30 – 4.01 (m, 2.84H), 3.74 (s, 3H), 3.70^{minor} (s, 1.12H), 3.53 (s, 3H), 3.30^{minor} (s, 1.11H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.6^{minor}, 171.9, 139.8, 138.2^{minor}, 128.7, 128.3, 127.8^{minor}, 127.3, 127.0, 126.9, 125.1, 124.6, 123.9^{minor}, 100.9, 100.2^{minor}, 59.7 ^{minor}, 59.2, 56.6^{minor}, 56.5, 54.5^{minor}, 54.3, 52.5^{minor}, 52.3. **IR:** ν[cm^{-1}] = 2948, 2840, 1730, 1495, 1439, 1379, 1245, 1111, 1059, 701. **HRMS:** major diastereomer (acquisition time 5.104 – 5.126 min): (APCI-MS) *m/z* calculated for $C_{14}H_{16}O_4$ $[M+H]^+$: 249.1121, found 249.1124; minor diastereomer (acquisition time 5.063 – 5.085 min): (APCI-MS) *m/z* calculated for $C_{14}H_{16}O_4$ $[M+H]^+$: 249.1121, found 249.1128.

methyl (2*R*,3*R*)-2-methoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*S*,3*R*)-2-methoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate ((-)-105a):

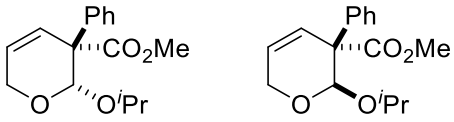


major-**(-)-105a** *minor*-**(-)-105a**

According to *GP-C-I*, enantiopure mesylated precursor **(+)-140a** (156 mg, 500 µmol, 1.0 equiv) was dissolved in MeOH (2.3 mL) and DBU (90 µL, 600 µmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 80 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 2.7:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain to obtain an inseparable mixture of *major* and *minor* **(-)-105a** (111 mg, 449 µmol, *dr* 2.7:1, 90%, >99% *ee*) as colorless oil.

NMR and IR were identical with those reported for the racemate **(*rac*)-105a**; **HPLC analysis** (Amylose-1, *n*-heptane/*i*PrOH 99:1. Flow 0.5 mL/min): t_r = 17.20 min (major epimer), t_r = 24.43 min (minor epimer), >99% *ee*; $[\alpha]_D^{20}$ – 143.4 ° (*c* 1.0, $CHCl_3$). **HRMS:** major diastereomer (acquisition time 5.099 – 5.103 min): (APCI-MS) *m/z* calculated for $C_{14}H_{16}O_4$ $[M+H]^+$: 249.1121, found 249.1124; minor diastereomer (acquisition time 5.058 – 5.077 min): (APCI-MS) *m/z* calculated for $C_{14}H_{16}O_4$ $[M+H]^+$: 249.1121, found 249.1126.

methyl (2*S*,3*R*)-2-isopropoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-isopropoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105b):



major-**105b** *minor*-**105b**

According to *GP-C-I*, mesylated precursor **140a** (101 mg, 324 µmol, 1.0 equiv) was dissolved in *i*PrOH (1.5 mL) and DBU (60 µL, 400 µmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 100 °C under microwave irradiation for 1.5 h. After

isolation of the crude product (*dr* 3.8:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (gradient: 14:1 to 9:1) as eluent to obtain major diastereomer *major*-**105b** (64.1 mg, 232 µmol, 72%) and the minor diastereomer *minor*-**105b** (16.3 mg, 59.0 µmol, 18%) both as colorless oils.

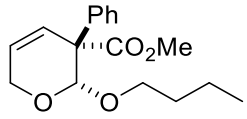
Major diastereomer major-**105b**:

R_f = 0.60 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.50 – 7.44 (m, 2H), 7.37 – 7.30 (m, 2H), 7.28 – 7.22 (m, 1H), 6.33 (dq, *J* = 10.5, 2.2 Hz, 1H), 5.91 (ddd, *J* = 10.6, 2.8, 1.9 Hz, 1H), 5.51 (d, *J* = 1.5 Hz, 1H), 4.29 (dt, *J* = 16.6, 1.9 Hz, 1H), 4.07 (ddd, *J* = 16.6, 3.3, 2.2 Hz, 1H), 3.98 (h, *J* = 6.2 Hz, 1H), 3.72 (s, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.0, 140.3, 128.6, 127.2, 126.9, 125.0, 124.9, 98.1, 71.1, 59.2, 54.6, 52.1, 23.3, 21.6. **IR:** ν[cm^{-1}] = 3053, 2974, 2855, 1737, 1498, 1435, 1379, 1238, 1103, 1051, 977, 697. **HRMS:** (APCI-MS) *m/z* calculated for $C_{16}H_{20}O_4$ $[M+H]^+$: 277.1434, found 277.1435.

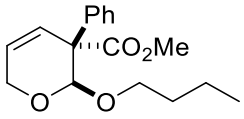
Minor diastereomer minor-**105b**:

R_f = 0.54 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.35 – 7.23 (m, 5H), 6.15 (dq, *J* = 10.4, 2.0 Hz, 1H), 6.07 (ddd, *J* = 10.4, 2.8, 1.8 Hz, 1H), 5.48 (d, *J* = 1.2 Hz, 1H), 4.29 (dt, *J* = 16.7, 2.1 Hz, 1H), 4.12 (ddd, *J* = 16.7, 3.1, 1.8 Hz, 1H), 3.74 – 3.61 (m, 4H), 1.07 (d, *J* = 6.2 Hz, 3H), 0.65 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.8, 138.7, 128.03, 127.97, 127.11, 127.09, 124.1, 97.7, 71.4, 59.6, 54.8, 52.4, 23.1, 21.1. **IR:** ν[cm^{-1}] = 3030, 2974, 2363, 1737, 1599, 1495, 1450, 1241, 1111, 1044, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{16}H_{20}O_4$ $[M+H]^+$: 277.1434, found 277.1437.

methyl (2*S*,3*R*)-2-butoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-butoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105c):



major-**105c**



minor-**105c**

According to *GP-C-I*, mesylated precursor **140a** (101 mg, 322 µmol, 1.0 equiv) was dissolved in 1-butanol (1.5 mL) and DBU (60 µL, 400 µmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 100 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 3:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (95:5) as eluent to obtain the major diastereomer *major*-**105c** (55.7 mg, 192 µmol, 60%) and the minor diastereomer *minor*-**105c** (16.0 mg, 55.1 µmol, 17%) both as colorless oils.

Major diastereomer major-**105c**:

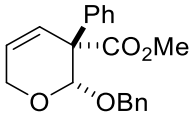
R_f = 0.61 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.42 – 7.37 (m, 2H), 7.26 (ddd, *J* = 7.8, 6.8, 1.2 Hz, 2H), 7.21 – 7.14 (m, 1H), 6.30 – 6.22 (m, 1H), 5.85 (ddd, *J* = 10.5, 3.3, 1.9 Hz, 1H), 5.34 (d, *J* = 1.4 Hz, 1H), 4.17 (dt, *J* = 16.8, 2.1 Hz, 1H), 3.99 (ddd, *J* = 16.6, 3.2, 2.2 Hz, 1H), 3.73 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.64 (s, 3H), 3.50 (dt, *J* = 9.8, 6.7 Hz, 1H), 1.59 – 1.41 (m, 2H), 1.37 – 1.23 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.0, 140.1, 128.6, 127.2, 126.9, 124.89, 124.86, 99.4, 68.8, 59.2, 54.3, 52.1, 31.5, 19.3, 13.8. **IR:** ν[cm^{-1}] = 2956, 2870, 1737, 1495, 1435, 1379, 1241, 1111, 1059, 984, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{17}H_{22}O_4$ $[M+H]^+$: 291.1591, found 291.1594.

Minor diastereomer minor-**105c**:

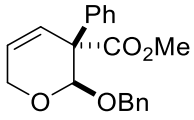
R_f = 0.55 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.34 – 7.19 (m, 5H), 6.13 (dq, *J* = 10.7, 1.8 Hz, 1H), 6.05 (ddd, *J* = 10.4, 3.0, 1.8 Hz, 1H), 5.38 (s, 1H), 4.22 (dt, *J* = 16.6, 2.1 Hz, 1H), 4.09 (ddd, *J* = 16.7, 3.0, 1.9 Hz, 1H), 3.68 (s, 3H), 3.60 (dt, *J* = 9.9, 6.2 Hz, 1H), 3.27 (dt, *J* = 9.9, 6.5 Hz, 1H), 1.32 – 1.16 (m, 2H), 1.01 – 0.79 (m, 2H), 0.66 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.7, 138.5, 128.1, 127.9, 127.1, 127.0, 124.0, 98.8, 68.5, 59.5, 54.6, 52.4, 31.1, 18.8, 13.6. **IR:** ν[cm^{-1}] = 2956, 2870, 1733, 1599, 1495, 1435, 1238,

1118, 1062, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{17}H_{22}O_4$ $[M+H]^+$: 291.1591 found 291.1591.

methyl (2*S*,3*R*)-2-(benzyloxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-(benzyloxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105d):



major-**105d**



minor-**105d**

According to *GP-C-I*, the mesylated precursor **140a** (1.25 g, 4.02 mmol, 1.0 equiv) was dissolved in BnOH (19 mL) and DBU (0.72 mL, 4.8 mmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 120 °C for 1.5 h under microwave irradiation. The reaction mixture was diluted with ethyl acetate (50 mL) and the mixture was washed with water (2x50 mL). The aqueous layer was back-extracted with ethyl acetate (2x50 mL), followed by washing the combined organic layer with brine and drying over Na_2SO_4. After filtration, ethyl acetate was evaporated under reduced pressure to obtain the crude product dissolved in BnOH. To remove remaining BnOH, a distillation under reduced pressure heating to 100 °C was applied obtaining the crude product. After isolation of the crude product (*dr* 5:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain the major diastereomer *major*-**105d** (1.02 g, 3.14 mmol, 78%) and minor diastereomer *minor*-**105d** (202 mg, 623 µmol, 16%) both as colorless oils.

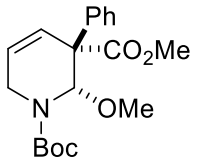
Major diastereomer major-**105d**:

R_f = 0.59 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.47 – 7.43 (m, 2H), 7.38 – 7.22 (m, 8H), 6.36 (dtd, *J* = 10.6, 2.3, 1.5 Hz, 1H), 5.97 – 5.89 (m, 1H), 5.54 (d, *J* = 1.5 Hz, 1H), 4.84 (d, *J* = 12.1 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.28 (dt, *J* = 16.7, 2.2 Hz, 1H), 4.11 (ddd, *J* = 16.7, 3.1, 2.2 Hz, 1H), 3.63 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.9, 140.0, 137.4, 128.7, 128.3, 128.1, 127.8, 127.3, 126.9, 124.9, 124.8, 98.5, 70.3, 59.5, 54.3, 52.2. **IR:** ν[cm^{-1}] = 3030, 2948, 2855, 1737, 1599, 1498, 1450, 1241, 1107, 1062, 701. **HRMS:** (ESI-MS) *m/z* calculated for $C_{20}H_{20}O_4$ $[M+H]^+$: 325.1434, found 325.1440.

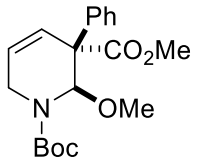
Minor diastereomer minor-**105d**:

R_f = 0.50 (*n*-hexanes/ethyl acetate = 3:1, stained in Vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.37 – 7.24 (m, 6H), 7.19 – 7.11 (m, 2H), 6.79 – 6.73 (m, 2H), 6.23 – 6.17 (m, 1H), 6.10 (ddd, *J* = 10.5, 3.2, 1.8 Hz, 1H), 5.50 (d, *J* = 1.3 Hz, 1H), 4.67 (d, *J* = 12.6 Hz, 1H), 4.45 (d, *J* = 12.6 Hz, 1H), 4.29 (dt, *J* = 17.0, 2.1 Hz, 1H), 4.16 (ddd, *J* = 16.7, 3.1, 1.9 Hz, 1H), 3.70 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.5, 138.5, 137.5, 128.3, 128.1, 127.8, 127.29, 127.27, 127.21, 127.1, 123.8, 97.9, 69.8, 59.5, 54.5, 52.5. **IR:** ν[cm^{-1}] = 3030, 2948, 2855, 1733, 1599, 1498, 1450, 1238, 1111, 1051, 701. **HRMS:** (ESI-MS) *m/z* calculated for $C_{20}H_{20}O_4$ $[M+H]^+$: 325.1434, found 325.1436.

1-(*tert*-butyl) 3-methyl (2*S*,3*R*)-2-methoxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate/ 1-(*tert*-butyl) 3-methyl (2*R*,3*R*)-2-methoxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (105f):



major-**105f**



minor-**105f**

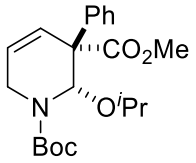
According to *GP-C-I*, the mesylated precursor **140b** (2.00 g, 4.86 mmol, 1.0 equiv) was dissolved in MeOH (23 mL) and DBU (0.87 mL, 5.8 mmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 120 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 1.9:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain to obtain an inseparable mixture of *major*- and *minor*-**105f** (1.68 g, 4.83 mmol, *dr* 1.9:1, 99%) as colorless oil.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

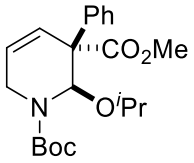
R_f = 0.47 (*n*-hexanes/ethyl acetate = 3:1, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.50 – 7.18 (m, 9.65H), 6.52^{minor} (dq, *J* = 10.5, 2.2 Hz, 0.52H), 6.42 (dq, *J* = 10.5, 2.2 Hz, 1H), 6.24^{minor} (d, *J* = 1.5 Hz, 0.53H), 6.05 (ddd, *J* = 10.5, 3.7, 2.6 Hz, 1H), 5.92 – 5.84 (m, 1.67H), 4.16 (ddd, *J* = 18.7, 3.6, 2.6 Hz, 1H), 3.98^{minor} (dt, *J* =

18.5, 3.1 Hz, 0.55H), 3.75 (s, 3H), 3.71^{minor} (s, 1.53H), 3.61 – 3.49 (m, 1.51H), 3.38^{minor} (s, 1.44H), 3.36 (s, 3H), 1.39^{minor} (s, 4.69H), 1.30 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.0^{minor}, 171.8, 155.1^{minor}, 154.0, 139.3^{minor}, 138.4, 128.5^{minor}, 128.4, 127.6^{minor}, 127.4, 127.3, 126.80, 126.76^{minor}, 125.0^{minor}, 124.9, 123.9, 123.4^{minor}, 86.6, 84.1^{minor}, 80.6^{minor}, 80.5, 56.5, 56.3^{minor}, 56.1^{minor}, 56.0, 52.49, 52.47^{minor}, 52.3^{minor}, 40.7^{minor}, 39.6, 28.2^{minor}, 28.1. **IR:** ν[cm^{-1}] = 3086, 2978, 1737, 1700, 1450, 1402, 1365, 1241, 1163, 1074, 977, 865, 697. **HRMS:** major diastereomer (acquisition time 6.428 – 6.532 min): (ESI-MS) *m/z* calculated for $C_{19}H_{25}NO_5$ $[M+Na]^+$: 370.1625, found 370.1629; minor diastereomer (acquisition time 6.374 – 6.428 min): (ESI-MS) *m/z* calculated for $C_{19}H_{25}NO_5$ $[M+Na]^+$: 370.1625, found 370.1628.

1-(*tert*-butyl) 3-methyl (2*S*,3*R*)-2-isopropoxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate/ 1-(*tert*-butyl) 3-methyl (2*R*,3*R*)-2-isopropoxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (105g):



major-**105g**



minor-**105g**

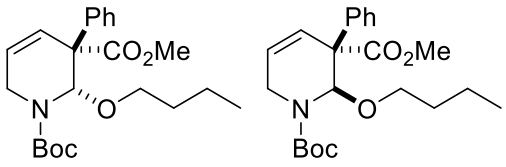
According to *GP-C-I*, mesylated precursor **140b** (131 mg, 319 µmol, 1.0 equiv) was dissolved in *i*PrOH (1.5 mL) and DBU (60 µL, 400 µmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 120 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 3:1) following *GP-C-I*, it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain an inseparable mixture of *major*- and *minor*-**105g** (100 mg, 267 µmol, *dr* 2:1, 85%) as colorless oil .

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.58 (*n*-hexanes/ethyl acetate = 3:1, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.51 – 7.41 (m, 3H), 7.33 – 7.18 (m, 5H), 6.52^{minor} (dq, *J* = 10.4, 2.1 Hz, 0.47H), 6.45 – 6.38 (m, 1.42H), 6.07 (d, *J* = 1.4 Hz, 1H), 6.03 (ddd, *J* = 10.5, 3.7, 2.4

Hz, 1H), 5.86^{minor} (ddd, *J* = 10.4, 3.6, 2.6 Hz, 0.49H), 4.16 (ddd, *J* = 18.5, 3.7, 2.5 Hz, 1H), 3.99^{minor} (ddd, *J* = 18.4, 3.7, 2.6 Hz, 0.50H), 3.82^{minor} (p, *J* = 6.1 Hz, 0.52H), 3.76 – 3.67 (m, 5.27H), 3.61^{minor} (dt, *J* = 18.4, 2.4 Hz, 0.62H), 3.53 (dt, *J* = 18.5, 2.4 Hz, 1H), 1.39^{minor} (s, 4H), 1.30 (s, 9H), 1.20 (d, *J* = 6.1 Hz, 3H), 1.17^{minor} (d, *J* = 6.1 Hz, 1.42H), 1.15 – 1.11 (m, 4.35H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.1^{minor}, 171.8, 154.8^{minor}, 153.7, 139.7^{minor}, 138.7, 128.5^{minor}, 128.3, 127.49, 127.47^{minor}, 127.1^{minor}, 126.9, 125.4^{minor}, 124.7, 124.2, 123.2^{minor}, 83.0, 81.2^{minor}, 80.4^{minor}, 80.3, 70.5^{minor}, 69.5, 56.6^{minor}, 52.2, 40.8^{minor}, 39.6, 28.2^{minor}, 28.1, 23.2^{minor}, 23.1, 21.7^{minor}, 21.1. **IR:** ν[cm^{-1}] = 3027, 2971, 1737, 1703, 1599, 1491, 1390, 1245, 1170, 1051,977, 693. **HRMS:** major diastereomer (acquisition time 3.327 – 3.397 min): (ESI-MS) *m/z* calculated for $C_{21}H_{29}NO_5$ $[M+Na]^+$: 398.1938, found 398.1941; minor diastereomer (acquisition time 3.397 – 3.464 min): (ESI-MS) *m/z* calculated for $C_{21}H_{29}NO_5$ $[M+Na]^+$: 398.1938, found 398.1941.

1-(*tert*-butyl) 3-methyl (2*S*,3*R*)-2-butoxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate/ 1-(*tert*-butyl) 3-methyl (2*R*,3*R*)-2-butoxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (105h):



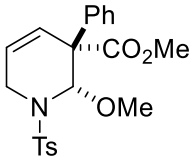
major-**105h** *minor*-**105h**

According to *GP-C-I,* mesylated precursor **140b** (134 mg, 326 µmol, 1.0 equiv) was dissolved in 1-butanol (1.5 mL) and DBU (60 µL, 400 µmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 120 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 2.1:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain an inseparable mixture of *major*- and *minor*-**105h** (72.7 mg, 187 µmol, *dr* 2:1, 57%) as colorless oil.

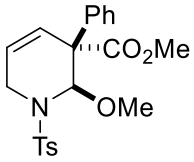
In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.61 (*n*-hexanes/ethyl acetate = 3:1, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.47 – 7.37 (m, 3H), 7.30 – 7.13 (m, 5H), 6.48^{minor} (dq, *J* = 10.4, 2.1 Hz, 0.49H), 6.38 (dq, *J* = 10.5, 2.1 Hz, 1H), 6.28^{minor} (d, *J* = 1.5 Hz, 0.50H), 5.99 (ddd, *J* = 10.5, 3.7, 2.5 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.82^{minor} (ddd, *J* = 10.4, 3.6, 2.6 Hz, 0.51H), 4.12 (ddd, *J* = 18.5, 3.7, 2.6 Hz, 1H), 3.94^{minor} (ddd, *J* = 18.3, 3.6, 2.6 Hz, 0.53H), 3.70 (s, 3H), 3.66^{minor} (s, 1.54H), 3.57^{minor} (dt, *J* = 18.4, 2.4 Hz, 0.54H), 3.53 – 3.39 (m, 4H), 1.57 – 1.44 (m, 3H), 1.37^{minor} (s, 4.62H), 1.34 – 1.23 (m, 12.18H), 0.92 – 0.82 (m, 4.71H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.0^{minor}, 171.8, 155.0^{minor}, 153.9, 139.6^{minor}, 138.6, 128.5^{minor}, 128.3, 127.5^{minor}, 127.4, 127.1^{minor}, 126.8, 125.2^{minor}, 124.7, 124.1, 123.2^{minor}, 84.8, 82.5^{minor}, 80.43^{minor}, 80.37, 68.4^{minor}, 68.0, 56.4, 56.0^{minor}, 52.32, 52.27^{minor}, 40.7^{minor}, 39.6, 31.5^{minor}, 31.3, 28.2^{minor}, 28.1, 19.4, 19.3^{minor}, 13.84, 13.77^{minor}. **IR:** ν[cm^{-1}] = 2960, 2870, 1737, 1700, 1450, 1394, 1241, 1167, 1081, 977, 734, 697. **HRMS:** inseparable mixture of two diastereomers: (ESI-MS) *m/z* calculated for $C_{22}H_{31}NO_5$ $[M+Na]^+$: 412.2094, found 412.2099.

methyl (2*S*,3*R*)-2-methoxy-3-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine-3-carboxylate/ methyl (2*R*,3*R*)-2-methoxy-3-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine-3-carboxylate (105i):



major-**105i**



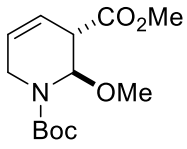
minor-**105i**

According to *GP-C-I*, mesylated precursor **140c** (235 mg, 504 µmol, 1.0 equiv) was dissolved in methanol (2.5 mL) and DBU (90 µL, 610 mmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 120 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 9.4:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (9:1) as eluent to obtain to obtain an inseparable mixture of *major*- and *minor*-**105i** (189 mg, 471 µmol, *dr* 9.1:1, 93%) as colorless oil.

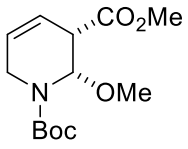
In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.42 (*n*-hexanes/ethyl acetate = 2:1, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.84 – 7.78^{minor} (m, 0.17H), 7.53 – 7.47 (m, 2H), 7.40 – 7.27 (m, 4H), 6.97 – 6.90 (m, 2H), 6.84 – 6.78 (m, 2H), 6.45 (dq, *J* = 10.5, 2.1 Hz, 1H), 6.17 – 6.11^{minor} (m, 0.11H), 6.01 – 5.90 (m, 2.19H), 3.77 (s, 3H), 3.72 (dt, *J* = 17.2, 2.3 Hz, 1.12H), 3.59^{minor} (s, 0.29H), 3.57 (s, 3H), 3.28 (ddd, *J* = 17.1, 3.8, 2.5 Hz, 1H), 3.07^{minor} (s, 0.25H), 2.41^{minor} (s, 0.25H), 2.32 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.6^{minor}, 171.2, 143.6^{minor}, 143.3, 138.5, 138.2^{minor}, 136.4^{minor}, 135.4, 129.33^{minor}, 129.26, 128.8, 128.7^{minor}, 128.5^{minor}, 128.0, 127.8, 127.7^{minor}, 127.5, 126.8^{minor}, 124.8^{minor}, 124.5, 124.4^{minor}, 123.7, 88.1, 86.2^{minor}, 57.6^{minor}, 57.4, 57.0^{minor}, 56.9, 52.6, 52.5^{minor}, 40.5, 40.4^{minor}, 21.5^{minor}, 21.4. **IR:** ν[cm^{-1}] = 3056, 2952, 2837, 2363, 1737, 1595, 1495, 1446, 1334, 1241, 1156, 1070, 943, 887, 813, 734, 701, 664. **HRMS:** (ESI-MS) *m/z* calculated for $C_{21}H_{23}NO_5S$ $[M+H]^+$: 402.1370, found 402.1371.

1-(*tert*-butyl) 3-methyl (2*R*,3*S*)-2-methoxy-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate/ 1-(*tert*-butyl) 3-methyl (2*S*,3*S*)-2-methoxy-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (105j):



major-**105j**



minor-**105j**

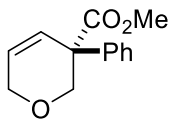
According to *GP-C-I*, mesylated precursor **140d** (231 mg, 690 µmol, 1.0 equiv) was dissolved in MeOH (3.2 mL) and 2,6-lutidine (96 µL, 830 µmol, 1.2 equiv) was added. Then, the reaction mixture was heated to 60 °C for 16 h under microwave irradiation. After isolation of the crude product (*dr* 1.3:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (gradient: 14:1 to 9:1) as eluent to obtain an inseparable mixture of *major*- and *minor*-**105j** (71.7 mg, 264 µmol, *dr* 1.2:1, 38%) as colorless oil.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Additionally, signal broadening due to rotamers is observed.

R_f = 0.59 (*n*-hexanes/ethyl acetate = 3:2, stained in $KMnO_4$). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 6.00 – 5.62 (m, 3H), 4.36 – 4.03 (m, 1H), 3.79 – 3.65 (m, 3H), 3.62 – 3.43

(m, 1H), 3.42 – 3.30 (m, 1H), 3.30 – 3.24 (m, 3H), 1.54 – 1.41 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 170.5, 170.4, 154.9, 154.5, 154.3, 125.7, 125.6, 124.4, 124.0, 119.8, 119.3, 118.9, 81.43, 81.36, 81.0, 80.6, 80.5, 80.1, 55.7, 55.5, 55.3, 54.9, 52.2, 52.1, 52.0, 46.4, 46.2, 45.8, 45.5, 40.3, 40.1, 39.4, 38.9, 28.4, 28.31, 28.27, 28.1. **IR:** ν[cm^{-1}] = 2978, 2851, 1741, 1700, 1439, 1405, 1368, 1260, 1156, 118, 1074, 977, 943, 857, 824, 775, 682. **HRMS:** major diastereomer (acquisition time 2.463 – 2.542 min): (ESI-MS) *m/z* calculated for $C_{13}H_{21}NO_5$ $[M+Na]^+$: 294.1312, found 294.1311; minor diastereomer (acquisition time 2.343 – 2.413 min): (ESI-MS) *m/z* calculated for $C_{13}H_{21}NO_5$ $[M+Na]^+$: 294.1312, found 294.1311.

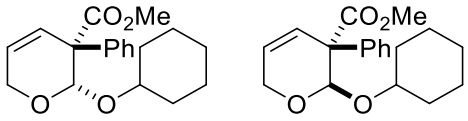
methyl (*R*)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105l):



According to *GP-C-III*, mesylated precursor **140a** (100 mg, 320 µmol, 1.0 equiv) and Et_3SiH (153 µL, 961 µmol, 3.0 equiv) were used. The mixture was heated to 120 °C for 1.5 h under microwave irradiation. After isolation of the crude product, it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain the product **105l** (54.5 mg, 250 µmol, 78%) as colorless oil.

R_f = 0.41 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.40 – 7.21 (m, 5H), 6.27 (dtd, *J* = 10.3, 2.2, 1.1 Hz, 1H), 6.08 (ddd, *J* = 10.3, 3.0, 2.3 Hz, 1H), 4.49 (dd, *J* = 11.3, 1.1 Hz, 1H), 4.30 – 4.10 (m, 2H), 3.74 (s, 3H), 3.62 (d, *J* = 11.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.1, 139.7, 128.8, 128.5, 127.5, 126.7, 126.3, 72.2, 65.4, 52.5, 51.5. **IR:** ν[cm^{-1}] = 3030, 2982, 2952, 2825, 1730, 1599, 1491, 1435, 1379, 1238, 1156, 1088, 1047, 1018, 984, 924, 887, 828, 764, 697. **HRMS:** (APCI-MS) *m/z* calculated for $C_{13}H_{14}O_3$ $[M+H]^+$: 219.1016, found 219.1019.

methyl (2*S*,3*R*)-2-(cyclohexyloxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-(cyclohexyloxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105m):



major-**105m** *minor*-**105m**

According to *GP-C-II*, mesylated precursor **140a** (102 mg, 325 µmol, 1.0 equiv), cyclohexanol (102 µL, 981 µmol, 3.0 equiv) and DBU (58 µL, 390 mmol, 1.2 equiv) were used. After isolation of the crude product (*dr* 2.2:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain the *major*-**105m** (46.3 mg, 146 µmol, 45%) and minor diastereomer *minor*-**105m** (23.6 mg, 74.6 µmol, 23%) both as colorless oils.

Major diastereomer major-**105m**:

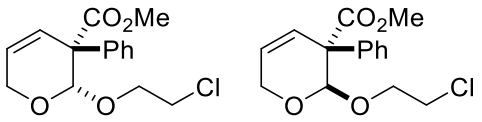
R_f = 0.61 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.51 – 7.43 (m, 2H), 7.34 (ddt, *J* = 8.3, 6.6, 0.8 Hz, 2H), 7.28 – 7.20 (m, 1H), 6.33 (dtd, *J* = 10.5, 2.2, 1.4 Hz, 1H), 5.91 (ddd, *J* = 10.6, 3.3, 1.8 Hz, 1H), 5.56 (d, *J* = 1.7 Hz, 1H), 4.29 (dt, *J* = 16.6, 2.1 Hz, 1H), 4.05 (ddd, *J* = 16.6, 3.2, 2.1 Hz, 1H), 3.71 (s, 3H), 3.69 – 3.60 (m, 1H), 2.00 – 1.84 (m, 2H), 1.81 – 1.65 (m, 2H), 1.64 – 1.05 (m, 6H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 172.1, 140.3, 128.6, 127.1, 126.9, 125.0, 124.9, 97.8, 76.8, 59.3, 54.5, 52.1, 33.5, 31.6, 25.6, 24.3, 24.1. **IR:** ν[cm^{-1}] = 3086, 2930, 2851, 1733, 1580, 1498, 1443, 1368, 1252, 1156, 1111, 1062, 965, 913, 869, 798, 768, 731. **HRMS:** (ESI-MS) *m/z* calculated for $C_{19}H_{24}O_4$ $[M+H]^+$: 317.1747, found 317.1746.

Minor diastereomer minor-**105m**:

R_f = 0.55 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.35 – 7.21 (m, 5H), 6.15 (dq, *J* = 10.4, 1.7 Hz, 1H), 6.07 (ddd, *J* = 10.4, 3.0, 1.6 Hz, 1H), 5.51 (d, *J* = 1.3 Hz, 1H), 4.28 (dt, *J* = 16.6, 2.0 Hz, 1H), 4.09 (ddd, *J* = 16.6, 3.0, 1.8 Hz, 1H), 3.71 (s, 3H), 3.53 – 3.38 (m, 1H), 1.76 – 1.63 (m, 1H), 1.56 – 1.45 (m, 1H), 1.38 – 0.91 (m, 8H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 172.8, 138.8, 128.0, 127.9, 127.11, 127.09, 124.1, 96.9, 75.5, 59.5, 54.7, 52.4, 33.1, 30.4, 25.5, 23.5, 22.9. **IR:** ν[cm^{-1}] = 3056, 2933, 2855, 1737, 1599, 1498, 1450, 1379, 1241, 1148, 1107,

1059, 969, 869, 798, 769, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{19}H_{24}O_4$ $[M+H]^+$: 317.1747, found 317.1754.

methyl (2*S*,3*R*)-2-(2-chloroethoxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-(2-chloroethoxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105n)



major-**105n** *minor*-**105n**

According to *GP-C-II*, mesylated precursor **140a** (100 mg, 320 µmol, 1.0 equiv), 2-chloroethan-1-ol (64 µL, 961 µmol, 3.0 equiv) and DBU (58 µL, 384 mmol, 3.0 equiv) were used. After isolation of the crude product (*dr* 2:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain *major*-**105n** (50.8 mg, 171 µmol, 54%) and *minor*-**105n** (28.5 mg, 96.0 µmol, 30%) both as colorless oils.

Major diastereomer major-**105n**:

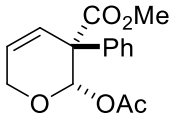
R_f = 0.42 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.49 – 7.43 (m, 2H), 7.38 – 7.31 (m, 2H), 7.29 – 7.24 (m, 1H), 6.40 – 6.31 (m, 1H), 5.95 (ddd, *J* = 10.6, 3.3, 2.0 Hz, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 4.29 (dt, *J* = 16.7, 2.2 Hz, 1H), 4.10 (ddd, *J* = 16.8, 3.2, 2.2 Hz, 1H), 4.04 (dt, *J* = 11.3, 5.7 Hz, 1H), 3.90 (dt, *J* = 11.2, 6.0 Hz, 1H), 3.75 (s, 3H), 3.66 (t, *J* = 5.7 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.7, 139.7, 128.7, 127.4, 126.8, 124.9, 124.5, 99.8, 69.1, 59.6, 54.2, 52.4, 42.5. **IR:** ν[cm^{-1}] = 3056, 2952, 2855, 1733, 1599, 1495, 1431, 1383, 1327, 1301, 1241, 1111, 1081, 1059, 973, 921, 872, 798, 734, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{15}H_{17}ClO_4$ $[M+H]^+$: 297.0888, found 297.0881.

Minor diastereomer minor-**105n**:

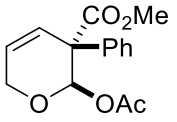
R_f = 0.36 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.36 – 7.24 (m, 5H), 6.14 (dq, *J* = 10.4, 1.8 Hz, 1H), 6.08 (ddd, *J* = 10.4, 2.9, 1.8 Hz, 1H), 5.46 (s, 1H), 4.30 (dt, *J* = 16.7, 2.0 Hz, 1H), 4.16 (ddd, *J* = 16.7, 2.8, 1.8 Hz, 1H), 3.83 (dt, *J* = 11.1, 6.2 Hz, 1H), 3.71 (s, 3H), 3.58 (dt, *J* = 11.1, 6.1 Hz,

1H), 3.31 (td, *J* = 6.1, 2.5 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.5, 138.0, 128.2, 127.7, 127.4, 127.2, 123.8, 99.2, 69.0, 60.0, 54.6, 52.5, 42.1. **IR:** ν[cm^{-1}] = 3030, 2952, 2855, 1733, 1685, 1618, 1495, 1435, 1245, 1148, 1118, 1066, 921, 872, 798, 742, 671. **HRMS:** (APCI-MS) *m/z* calculated for $C_{15}H_{17}ClO_4$ $[M+NH_4]^+$: 314.1154, found 314.1164.

methyl (2*S*,3*R*)-2-acetoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/
methyl (2*R*,3*R*)-2-acetoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105o):



major-**105o**



minor-**105o**

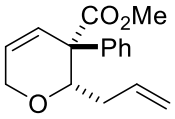
According to *GP-C-III*, mesylated precursor **140a** (101 mg, 323 µmol, 1.0 equiv) and potassium acetate (95.2 mg, 970 µmol, 3.0 equiv) were used. The mixture was heated to 120 °C for 1.5 h under microwave irradiation. After isolation of the crude product (*dr* 1.3:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain to obtain an inseparable mixture of *major*- and *minor*-**105o** (38.2 mg, 138 µmol, *dr* 1.3:1, 43%) as colorless oil.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

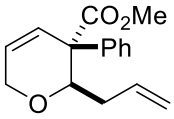
R_f = 0.32 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.50 – 7.42 (m, 2H), 7.38 – 7.27 (m, 6H), 6.82^{minor} (d, *J* = 1.3 Hz, 0.56H), 6.77 (d, *J* = 1.6 Hz, 1H), 6.43 (dq, *J* = 10.7, 2.2 Hz, 1H), 6.23^{minor} (dq, *J* = 10.5, 2.0 Hz, 0.62H), 6.14^{minor} (dt, *J* = 10.5, 2.5 Hz, 0.63H), 6.02 (dt, *J* = 10.7, 2.6 Hz, 1H), 4.37 – 4.11 (m, 3.43H), 3.74^{minor} (s, 1.77H), 3.71 (s, 3H), 2.09 (s, 3H), 1.72^{minor} (s, 1.84H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.8^{minor}, 171.1, 169.4, 168.8^{minor}, 138.6, 137.2^{minor}, 128.8, 128.4, 127.8, 127.7, 127.4, 127.0, 126.9, 125.1, 124.3, 123.8, 92.6, 91.5^{minor}, 60.7^{minor}, 60.5, 53.5^{minor}, 53.2, 52.7^{minor}, 52.4, 20.8, 20.4^{minor}. **IR:** ν[cm^{-1}] = 2960, 2907, 3012, 2863, 1748, 1720, 1595, 1490, 1439, 1372, 1245, 1215, 1152, 1118, 1059, 1014, 977, 947, 880, 857, 798, 768, 738, 701. **HRMS:** major diastereomer (acquisition time 5.757 – 5.784 min): (APCI-MS) *m/z* calculated for $C_{15}H_{16}O_5$ $[M+NH_4]^+$: 294.1336,

found 294.1343; minor diastereomer (acquisition time 5.732 – 5.757 min): (APCI-MS) *m/z* calculated for $C_{15}H_{16}O_5$ $[M+NH_4]^+$: 294.1336, found 294.1342.

methyl (2*S*,3*R*)-2-allyl-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-allyl-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105p):



major-**105p**



minor-**105p**

According to *GP-C-III*, mesylated precursor **140a** (100 mg, 320 µmol, 1.0 equiv) and allyltrimethylsilane (153 µL, 961 µmol, 3.0 equiv) were used. The mixture was heated to 120 °C for 2 h under microwave irradiation. After isolation of the crude product (*dr* 2.8:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain the *major* diastereomer *major*-**105p** (35.5 mg, 137 µmol, 43%) and an inseparable mixture of *major* and *minor*-**105p** (14.7 mg, 56.9 µmol, *dr* 1.9:1, 18%) both as colorless oils.

Major diastereomer major-**105p**:

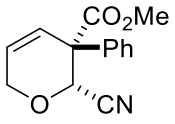
R_f = 0.50 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.41 – 7.35 (m, 2H), 7.31 (ddd, *J* = 7.7, 2.6, 1.6 Hz, 3H), 6.18 (dt, *J* = 10.2, 2.2 Hz, 1H), 6.05 (ddd, *J* = 10.2, 3.0, 2.0 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.09 – 4.96 (m, 2H), 4.41 – 4.21 (m, 2H), 3.79 (dd, *J* = 10.5, 2.4 Hz, 1H), 3.77 (s, 3H), 2.90 (dddt, *J* = 15.2, 10.6, 7.0, 1.3 Hz, 1H), 2.27 (ddq, *J* = 15.2, 6.4, 1.6 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.1, 140.4, 136.3, 128.9, 128.6, 127.32, 127.29, 127.27, 116.2, 81.4, 65.2, 55.0, 52.0, 33.9. **IR:** ν[cm^{-1}] = 3064, 3034, 2952, 2840, 1733, 1640, 1599, 1495, 1431, 1383, 1230, 1200, 1129, 1074, 1003, 913, 835, 798, 764, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{16}H_{18}O_3$ $[M+H]^+$: 259.1329, found 259.1334.

Mixture of major-**105p** and *minor*-**105p**:

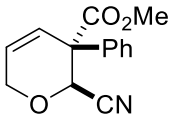
In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f (*major*) = 0.50 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **R_f (*minor*)** = 0.55 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.38 – 7.25 (m, 6H), 7.24 – 7.19 (m, 2H), 6.17 – 6.11 (m, 1.49H), 6.09 (dt, *J* = 10.3, 1.9 Hz, 1H), 6.01^{major} (ddd, *J* = 10.2, 3.0, 2.0 Hz, 0.52H), 5.89 – 5.67 (m, 1.54H), 5.05 – 4.95 (m, 3H), 4.38 – 4.14 (m, 4H), 3.77 (s, 3H), 3.74^{major} (s, 1.59H), 2.86^{major} (dddt, *J* = 15.1, 10.6, 7.0, 1.3 Hz, 0.57H), 2.31 – 2.18 (m, 1.57H), 1.57 – 1.47 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.7, 172.1^{major}, 140.4^{major}, 137.8, 136.3^{major}, 135.9, 128.9, 128.6, 128.4, 128.2, 128.1, 127.4, 127.3, 127.29, 127.27, 127.0, 116.3, 116.2^{major}, 81.4^{major}, 77.8, 65.2^{major}, 64.7, 55.5, 55.0^{major}, 52.3, 52.0^{major}, 36.0, 33.9^{major}. **IR:** ν[cm^{-1}] = 3075, 2952, 2837, 1733, 1640, 1495, 1435, 1238, 1133, 1070, 1025, 916, 83, 794, 746, 701. **HRMS:** major diastereomer (acquisition time 5.410 – 5.412 min): (APCI-MS) *m/z* calculated for $C_{16}H_{18}O_3$ $[M+NH_4]^+$: 259.1329, found 259.1336; minor diastereomer (acquisition time 5.435 – 5.439 min): (APCI-MS) *m/z* calculated for $C_{16}H_{18}O_3$ $[M+NH_4]^+$: 259.1329, found 259.1335.

methyl (2*R*,3*R*)-2-cyano-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/
methyl (2*S*,3*R*)-2-cyano-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105q):



major-**105q**



minor-**105q**

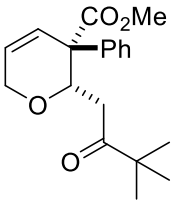
According to *GP-C-III*, mesylated precursor **140a** (100 mg, 320 µmol, 1.0 equiv) and TMSCN (130 µL, 961 µmol, 3.0 equiv) were used. The mixture was heated to 120 °C under microwave irradiation for 4 h. After isolation of the crude product (*dr* 2.4:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain an inseparable mixture of *major*- and *minor*-**105q** (70.1 mg, 288 µmol, *dr* 2.4:1, 90%) as colorless oil.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

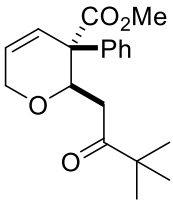
R_f = 0.35 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.47 – 7.30 (m, 7H), 6.41 (dtd, *J* = 10.6, 2.4, 1.0 Hz, 1H), 6.30^{minor} (dtd, *J*

= 10.6, 2.2, 1.1 Hz, 0.42H), 6.23 – 6.13 (m, 1.44H), 5.56^{minor} (d, *J* = 1.0 Hz, 0.39H), 5.07 (d, *J* = 1.0 Hz, 1H), 4.54 – 4.43 (m, 1.48H), 4.38 – 4.25 (m, 1.50H), 3.82 (s, 3H), 3.75^{minor} (s, 1.18H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.1^{minor}, 170.3, 137.3, 135.3^{minor}, 129.3, 129.1, 129.0, 128.5, 128.0, 127.4, 126.8, 126.6, 124.7, 123.8^{minor}, 115.9, 114.7^{minor}, 69.4^{minor}, 68.9, 63.7, 62.7^{minor}, 53.8, 53.2^{minor}, 53.1, 53.0^{minor}. **IR:** ν[cm^{-1}] = 3060, 3034, 2956, 2848, 1733, 1599, 1495, 1450, 1241, 1144, 1092, 977, 902, 864, 798, 764, 738, 701. **HRMS:** major diastereomer (acquisition time 5.595 – 5.599 min): (APCI-MS) *m/z* calculated for $C_{14}H_{13}NO_3$ $[M+H]^+$: 244.0968, found 244.0969; minor diastereomer (acquisition time 5.605 – 5.632 min): (APCI-MS) *m/z* calculated for $C_{14}H_{13}NO_3$ $[M+H]^+$: 244.0968, found 244.0968.

methyl (2*S*,3*R*)-2-(3,3-dimethyl-2-oxobutyl)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxy-late/ methyl (2*R*,3*R*)-2-(3,3-dimethyl-2-oxobutyl)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105r):



major-**105r**



minor-**105r**

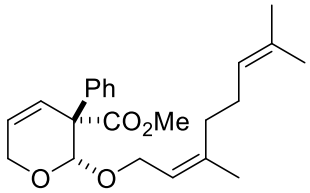
According to *GP-C-III*, mesylated precursor **140a** (102 mg, 326 µmol, 1.0 equiv) and ((3,3-dimethylbut-1-en-2-yl)oxy)trimethylsilane (211 µL, 977 µmol, 3.0 equiv) were used. The mixture was heated to 120 °C for 4 h under microwave irradiation. After isolation of the crude product (*dr* 4:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain an inseparable mixture of *major*- and *minor*-**105r** (78.0 mg, 247 µmol, *dr* 4:1, 76%) both as colorless oil.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

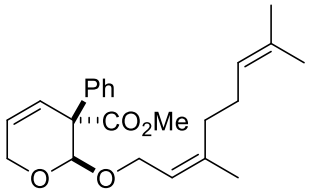
R_f = 0.47 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.40 – 7.16 (m, 7H), 6.16 – 5.99 (m, 2.46H), 4.66^{minor} (dd, *J* = 9.7, 1.7 Hz, 0.25H), 4.39 – 4.17 (m, 2.51H), 4.13 (dd, *J* = 9.8, 1.7 Hz, 1H), 3.79 – 3.73 (m, 3.72H), 3.63 (dd, *J* = 17.6, 9.8 Hz, 1H), 2.68^{minor} (dd, *J* = 17.2, 1.7 Hz, 0.25H), 2.35 (dd, *J* =

17.6, 1.8 Hz, 1H), 2.03^{minor} (dd, *J* = 17.2, 9.7 Hz, 0.27H), 1.05 (s, 9H), 0.99^{minor} (s, 2.23H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ = 213.9, 212.8^{minor}, 173.4^{minor}, 172.4, 139.6^{minor}, 137.9, 129.5, 128.8, 128.3, 128.1, 128.0, 127.6, 127.42, 127.35, 127.1, 78.6, 74.1^{minor}, 66.9, 65.7^{minor}, 55.2, 55.1^{minor}, 52.3^{minor}, 52.0, 44.2, 44.1^{minor}, 39.7^{minor}, 37.0, 26.2^{minor}, 26.1. **IR:** ν[cm^{-1}] = 3030, 2967, 2829, 1737, 1710, 1599, 1476, 1364, 1297, 1230, 1141, 1103, 831, 798, 753, 701. **HRMS:** inseparable mixture of both diastereomer: (APCI-MS) *m/z* calculated for $C_{19}H_{24}O_4$ $[M+H]^+$: 317.1747, found 317.1751.

methyl (2*S*,3*R*)-2-(((*Z*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-(((*Z*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (105s):



major-**105s**



minor-**105s**

According to *GP-C-II,* mesylated precursor **140a** (101 mg, 325 µmol, 1.0 equiv), geraniol (169 µL, 974 µmol, 3.0 equiv) and DBU (58 µL, 390 µmol, 3.0 equiv) were used. After isolation of the crude product (*dr* 1.6:1), it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (14:1) as eluent to obtain *major*-**105s** (48.8 mg, 132 µmol, 41%) and *minor*-**105s** (23.4 mg, 63.2 µmol, 20%) both as colorless oils.

Major diastereomer major-**105s**:

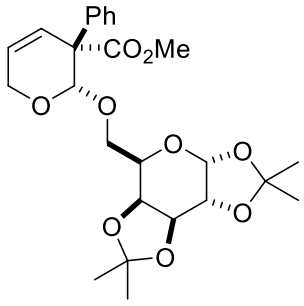
R$_f$ = 0.59 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (300 MHz, CDCl$_3$):** δ = 7.51 – 7.43 (m, 2H), 7.39 – 7.21 (m, 3H), 6.34 (dq, *J* = 10.6, 2.1 Hz, 1H), 5.93 (ddd, *J* = 10.6, 3.3, 1.9 Hz, 1H), 5.47 (d, *J* = 1.5 Hz, 1H), 5.40 – 5.28 (m, 1H), 5.17 – 5.05 (m, 1H), 4.36 – 3.98 (m, 4H), 3.72 (s, 3H), 2.17 – 1.99 (m, 4H), 1.68 (s, 3H), 1.66 (d, *J* = 1.4 Hz, 3H), 1.60 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$):** δ = 172.0, 140.7, 140.1, 131.7, 128.6, 127.2, 126.9, 125.0, 124.9, 123.9, 120.0, 98.2, 64.9, 59.3, 54.3, 52.2, 39.7, 26.4, 25.7, 17.7, 16.4. **IR:** ν[cm^{-1}] = 3030, 2926, 2855, 1737, 1670, 1495,

1435, 1379, 1327, 1241, 1148, 1103, 1062, 869, 835, 798, 764, 734, 667. **HRMS:** (APCI-MS) *m/z* calculated for $C_{23}H_{30}O_4$ $[M+NH_4]^+$: 388.2482, found 388.2483.

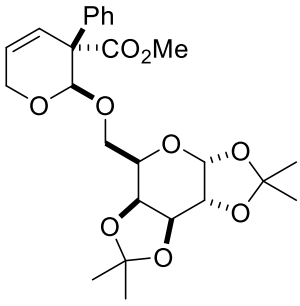
Minor diastereomer minor-**105s**:

R_f = 0.53 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.36 – 7.21 (m, 5H), 6.18 (dq, *J* = 10.4, 1.9 Hz, 1H), 6.08 (ddd, *J* = 10.3, 3.1, 1.8 Hz, 1H), 5.48 (d, *J* = 1.2 Hz, 1H), 5.11 – 5.00 (m, 1H), 4.98 – 4.89 (m, 1H), 4.32 – 4.09 (m, 2H), 4.08 – 3.91 (m, 2H), 3.69 (s, 3H), 2.07 – 1.84 (m, 4H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.59 (s, 3H), 1.44 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 172.7, 141.1, 138.5, 131.6, 128.2, 128.0, 127.2, 127.0, 124.0, 123.8, 119.8, 97.4, 64.7, 59.5, 54.4, 52.5, 39.5, 26.4, 25.7, 17.7, 16.2. **IR:** ν[cm^{-1}] = 3027, 2926, 2855, 1737, 1670, 1495, 1435, 1379, 1238, 1148, 1111, 1036, 991, 928, 869, 835, 798, 738, 701, 675. **HRMS:** (APCI-MS) *m/z* calculated for $C_{23}H_{30}O_4$ $[M+NH_4]^+$: 388.2482, found 388.2488.

Methyl (2*S*,3*R*)-3-phenyl-2-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy)-3,6-dihydro-2*H*-pyran-3-carboxy-late/ methyl (2*R*,3*R*)-3-phenyl-2-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetra-hydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy)-3,6-dihydro-2*H*-pyran-3-carboxylate (105t):



major-**105t**



minor-**105t**

According to *GP-C-II*, mesylated precursor **140a** (101 mg, 324 µmol, 1.0 equiv), 1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose (253 mg, 973 µmol, 3.0 equiv) and DBU (58 µL, 389 µmol, 3.0 equiv) were used. After isolation of the crude product (*dr* 1.5:1),, it was purified by flash column chromatography using *n*-hexanes and ethyl acetate (5:1) as eluent to obtain to obtain an inseparable mixture of *major*- and *minor*-**105t** (77.3 mg, 162 µmol, *dr* 1.8:1, 50%) as colorless oil.

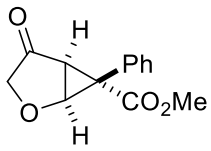
In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.65 (*n*-hexanes/ethyl acetate = 1:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.48 – 7.43 (m, 2H), 7.36 – 7.21 (m, 7H), 6.31 (dq, *J* = 10.6, 2.0 Hz, 1H), 6.16 – 6.11^{minor} (m, 0.57H), 6.08^{minor} (ddd, *J* = 10.4, 3.0, 1.5 Hz, 0.57H), 5.91 (ddd, *J* = 10.6, 3.2, 1.9 Hz, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 5.50^{minor} (d, *J* = 1.1 Hz, 0.48H), 5.48 (d, *J* = 1.6 Hz, 1H), 5.41^{minor} (d, *J* = 5.0 Hz, 0.47H), 4.59 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.40 – 4.34 (m, 1H), 4.34 – 4.32^{minor} (m, 0.55H), 4.31 – 4.28 (m, 1.37H), 4.28 – 4.25^{minor} (m, 0.46H), 4.25 – 4.21 (m, 1.39H), 4.18^{minor} (dd, *J* = 5.0, 2.3 Hz, 0.52H), 4.11^{minor} (ddd, *J* = 16.7, 3.0, 1.6 Hz, 0.61H), 4.08 – 4.03 (m, 1H), 4.02 – 3.99 (m, 1H), 3.96 (dd, *J* = 10.6, 6.0 Hz, 1H), 3.81 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.76 – 3.73^{minor} (m, 0.57H), 3.72 (s, 3H), 3.70^{minor} (s, 1.42H), 3.64 – 3.58^{minor} (m, 0.58H), 3.52^{minor} (dd, *J* = 9.4, 7.8 Hz, 0.52H), 3.28^{minor} (dd, *J* = 8.0, 1.8 Hz, 0.50H), 1.53 (s, 3H), 1.45^{minor} (s, 1.80H), 1.44 (s, 3H), 1.36^{minor} (s, 1.63H), 1.32 (s, 6H), 1.28^{minor} (s, 1.47H), 1.20^{minor} (s, 1.45H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.5^{minor}, 171.9, 140.0, 138.6^{minor}, 128.6, 128.1, 127.9, 127.24, 127.19, 127.1, 126.9, 125.0, 124.5, 123.8^{minor}, 109.2, 108.8^{minor}, 108.6, 108.3^{minor}, 100.2, 99.1^{minor}, 96.3, 96.2^{minor}, 71.1, 71.0^{minor}, 70.71, 70.6, 70.4, 70.3, 70.1, 59.5, 59.3^{minor}, 54.5^{minor}, 54.3, 52.5^{minor}, 52.3, 26.1^{minor}, 26.03, 26.00, 25.9^{minor}, 25.0, 24.9^{minor}, 24.5, 24.4^{minor}. **IR:** ν[cm^{-1}] = 2986, 2937, 1732, 1599, 1495, 1450, 1379, 1245, 1211, 1170, 1111, 1062, 999, 910, 798, 768, 731, 701. **HRMS:** major diastereomer (acquisition time 3.113 – 3.180 min): (ESI-MS) *m/z* calculated for $C_{25}H_{32}O_9$ $[M+Na]^+$: 499.1939, found 499.1949; minor diastereomer (acquisition time 3.035 – 3.093 min): (ESI-MS) *m/z* calculated for $C_{25}H_{32}O_9$ $[M+Na]^+$: 499.1939, found 499.1941.

3.5 Lewis- and Brønsted-acid mediated ring-expansion

3.5.1 Synthesis of suitable ketones

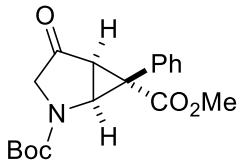
methyl (1*S*,5*S*,6*R*)-4-oxo-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (106a):



All steps were performed in flame dried glassware and under nitrogen atmosphere. At first DMSO (1.2 mL, 16.9 mmol, 3.0 equiv.) was diluted with dry DCM (3.2 mL) and cooled to -65 °C. Then, oxalyl chloride (900 µL, 10.5 mmol, 2.0 equiv) dissolved in DCM (8 mL) was added to the reaction mixture within 15 min. The mixture was stirred for additional 10 min at -65 °C. In the meantime alcohol **103a** (1.23 g, 5.25 mmol, 1.0 equiv) was dissolved in dry DCM (3.7 mL) and was then added dropwise to the stirred solution at -65 °C within 15 min. After 15 min, NEt_3 (2.20 mL; 15.8 mmol, 3.0 equiv) was added dropwise at -65 °C to the reaction mixture which was subsequently warmed to -45 °C. After full consumption of the starting material (1 h), the mixture was diluted with DCM (50 mL) and the organic layer was washed with 2 M HCl (2x50 mL). Then, the aqueous layer was extracted with DCM (3x25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the crude product which was purified by flash column chromatography using *n*-hexanes and ethyl acetate (gradient: 5:1 to 3:2) to obtain the clean product **106a** (975 mg, 4.20 mmol, 80%) as yellowish oil.

R_f = 0.68 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.36 (qd, *J* = 5.7, 5.2, 1.9 Hz, 5H), 5.08 (d, *J* = 4.6 Hz, 1H), 3.82 (dd, *J* = 17.8, 1.4 Hz, 1H), 3.63 (s, 3H), 3.09 (dd, *J* = 4.6, 1.4 Hz, 1H), 2.68 (d, *J* = 17.8 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 207.2, 169.8, 131.5, 130.4, 128.8, 128.5, 72.4, 72.2, 53.1, 40.2, 38.8. **IR:** ν[cm^{-1}] = 3064, 3034, 2956, 2919, 1748, 1718, 198, 1435, 1357, 1327, 1305, 1241, 1126, 1066, 977, 954, 865, 787, 749, 701, 675. **HRMS:** (EI-MS) *m/z* calculated for $C_{13}H_{12}O_4$ $[M]^+$: 232.0730, found 232.0731.

2-(*tert*-butyl) 6-methyl (1*S*,5*S*,6*R*)-4-oxo-6-phenyl-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (106b):



According to *GP-A*, **106b** was prepared from cyclopropanated pyrrole derivative **102e** (879 mg, 2.79 mmol, 1.0 equiv) and a 1 M BH_3·THF solution (3.10 mL, 3.10 mmol, 1.1 equiv) in dry THF (10 mL). After completion of BH_3 addition (3 h), H_2O_2 solution (5.60 mL, 35 w%, 83.6 mmol, 30 equiv) followed by phosphate buffer (6 mL) were added dropwise at 0 °C. After extraction with ethyl acetate (3x50 mL) and evaporation of the solvent the crude product was obtained as yellowish oil which was used without further purification.

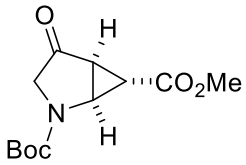
All steps were performed in flame dried glassware and under nitrogen atmosphere. At first DMSO (600 µL, 8.45 mmol, 3.0 equiv.) was diluted with dry DCM (2.5 mL) and was cooled to -65 °C. Then, oxalyl chloride (480 µL, 5.60 mmol, 2.0 equiv) dissolved in DCM (5 mL) was added to the reaction mixture within 15 min. The mixture was stirred for additional 10 min at -65 °C. In the meantime the crude alcohol **103b** was dissolved in dry DCM (3 mL) and was then added dropwise to the stirred solution at -65 °C within 15 min. After 15 min, NEt_3 (1.20 mL; 8.61 mmol, 3.0 equiv) was added dropwise at -65 °C to the reaction mixture which was subsequently warmed to -45 °C. After full consumption of the starting material (2 h), the mixture was diluted with DCM (50 mL) and the organic layer was washed with 2 M HCl (2x50 mL). Then, the aqueous layer was extracted with DCM (3x25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the crude product which was purified by automatic flash column chromatography using *n*-hexanes and ethyl acetate (gradient: 95:5 to 21:4 PE/EA) to obtain the clean product **106b** (670 mg, 2.02 mmol, 72%) as yellowish oil

In the proton and carbon NMR signal doubling and broadening due to rotamers is observed.

R_f = 0.48 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.37 – 7.23 (m, 6H), 4.67 – 4.54 (m, 1H), 3.66 – 3.59 (m, 3H), 3.59 – 3.46

(m, 1H), 3.20 – 3.12 (m, 1H), 2.43 – 2.22 (m, 1H), 1.63 – 1.34 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 203.4, 202.9, 169.8, 169.6, 154.3, 153.1, 131.3, 131.0, 130.9, 130.6, 129.0, 128.9, 128.8, 128.6, 81.5, 81.2, 54.2, 53.8, 53.2, 53.1, 50.19, 50.16, 41.3, 41.1, 40.1, 39.5, 28.4, 28.2. **IR:** ν[cm^{-1}] = 3064, 2978, 2930, 1752, 1700, 1498, 1435, 1394, 1238, 1163, 1129, 1074, 965, 917, 861, 768, 734, 705. **HRMS:** (ESI-MS) *m/z* calculated for $C_{18}H_{21}NO_5$ $[M+H]^+$: 332.1492, found 332.1497.

2-(*tert*-butyl) 6-methyl (1*S*,5*S*,6*S*)-4-oxo-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate (106c):



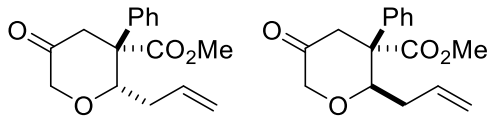
All steps were performed in flame dried glassware and under nitrogen atmosphere. At first DMSO (670 µL, 9.43 mmol, 3.0 equiv.) was diluted with dry DCM (2.5 mL) and was cooled to -65 °C. Then, oxalyl chloride (540 µL, 6.30 mmol, 2.0 equiv) dissolved in DCM (9 mL) was added to the reaction mixture within 15 min. The mixture was stirred for additional 10 min at -65 °C. In the meantime alcohol **103d** (810 mg, 3.15 mmol, 1.0 equiv) was dissolved in dry DCM (6 mL) and was then added dropwise to the stirred solution at -65 °C within 15 min. After 15 min, NEt_3 (1.30 mL, 9.43 mmol, 3.0 equiv) was added dropwise at -65 °C to the reaction mixture which was subsequently warmed to -45 °C afterwards. After full consumption of the starting material (2 h), the mixture was diluted with DCM (50 mL) and the organic layer was washed with 2 M HCl (2x50 mL). Then, the aqueous layer was extracted with DCM (3x25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the crude product which was purified by automatic flash column chromatography using *n*-hexanes and ethyl acetate (gradient: 95:5 to 21:4 PE/EA) to obtain the clean product **106c** (727 mg, 2.85 mmol, 91%) as yellowish oil.

In the proton and carbon NMR signal doubling and broadening due to rotamers is observed.

R_f = 0.38 (*n*-hexanes/ethyl acetate = 3:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.42 – 4.16 (m, 1H), 3.83 – 3.71 (m, 1H), 3.68 – 3.58 (m, 3H), 3.57 – 3.47 (m, 1H), 2.61 – 2.49 (m, 1H), 2.30 – 2.13 (m, 1H), 1.45 – 1.32 (m, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 202.7, 202.5, 168.6, 153.6, 81.3, 52.4, 51.9, 45.0, 33.5, 32.8, 28.2, 27.7. **IR:** ν[cm^{-1}] = 2978, 1759, 1707, 1439, 1394, 1372, 1320, 1264, 1170, 1122, 1059, 984, 910, 869, 768. **HRMS:** (ESI-MS) *m/z* calculated for $C_{12}H_{17}NO_5$ $[M+H]^+$: 256.1179, found 256.1180.

3.5.2 Lewis-acid mediated ring-expansion

methyl (2*S*,3*R*)-2-allyl-5-oxo-3-phenyltetrahydro-2*H*-pyran-3-carboxylate/ methyl (2*R*,3*R*)-2-allyl-5-oxo-3-phenyltetrahydro-2*H*-pyran-3-carboxylate (108a):



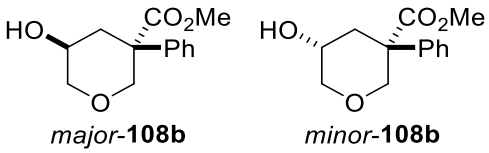
major-**108a** *minor*-**108a**

All steps were performed under nitrogen atmosphere and in flame dried glassware. At first, ketone **106a** (72.0 mg, 310 µmol, 1.0 equiv.) and allyltrimethylsilane (246 µL, 1.55 mmol, 5.0 equiv.) were dissolved in dry DCM (13 mL). The mixture was cooled to -78 °C and TMSOTf (124 µL, 682 µmol, 2.2 equiv.) was added dropwise to the stirred solution. The mixture was stirred for 30 min at -78 °C and was allowed to warm to ambient temperature afterwards. After 20 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution (15 mL) and the reaction mixture was extracted with ethyl acetate (3x25 mL). The combined organic layers were washed once with brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the crude product. Afterwards the residue was purified by automatic flash column chromatography (gradient: 14:1 to 9:1 PE/EA) to obtain the product as colorless oil consisting an inseparable mixture of *major*-**108a** and *minor*-**108a** (52.1 mg, 190 µmol, 61%, *dr* 4.3:1).

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.41 (*n*-hexanes/ethyl acetate = 3:1; stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.41 – 7.27 (m, 4H), 7.22 – 7.16 (m, 2H), 5.93 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.87 – 5.78^{minor} (m, 0.18H), 5.18 – 5.04 (m, 2.25H), 4.79^{minor} (t, *J* = 7.0 Hz, 0.16H), 4.39 (dd, *J* = 7.3, 4.9 Hz, 1H), 4.27 (dd, *J* = 17.0, 1.7 Hz, 1H), 4.11^{minor} (d, *J* = 9.1 Hz, 0.28H), 4.07 (d, *J* = 17.0 Hz, 1H), 3.80 (s, 3H), 3.72^{minor} (s, 0.67H), 3.39^{minor} (d, *J* = 16.8 Hz, 0.24H), 3.16 (ddd, *J* = 17.0, 1.7, 0.9 Hz, 1H), 2.90^{minor} (d, *J* = 16.9 Hz, 0.20H), 2.64 (d, *J* = 17.0 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.21 – 2.13^{minor} (m, 0.46H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 205.5^{minor}, 204.4, 173.6^{minor}, 172.5, 139.9, 137.1^{minor}, 135.3, 134.1^{minor}, 129.1, 128.8^{minor}, 128.0^{minor}, 127.6, 126.8^{minor}, 126.3, 117.5^{minor}, 117.0, 81.1, 78.2^{minor}, 73.8, 69.6^{minor}, 57.6, 55.5^{minor}, 53.0^{minor}, 52.6, 50.5, 42.8^{minor}, 34.7, 31.5^{minor}. **IR:** ν[cm^{-1}] = 3068, 2952, 2863, 1726, 1640, 1498, 1435, 1372, 1338, 1290, 1223, 1174, 1096, 1040, 988, 842, 757, 701. **HRMS:** major diastereomer (acquisition time 5.955 – 5.957 min): (APCI-MS) *m/z* calculated for $C_{16}H_{18}O_4$ $[M+H]^+$: 275.1278, found 275.1277; minor diastereomer (acquisition time 5.985 – 6.043 min): (APCI-MS) *m/z* calculated for $C_{16}H_{18}O_4$ $[M+H]^+$: 275.1278, found 275.1278.

methyl (3*R*,5*S*)-5-hydroxy-3-phenyltetrahydro-2*H*-pyran-3-carboxylate/ methyl (3*R*,5*R*)-5-hydroxy-3-phenyltetrahydro-2*H*-pyran-3-carboxylate (108b):



major-**108b** *minor*-**108b**

All steps were performed under nitrogen atmosphere and in flame dried glassware. At first, the ketone **106a** (232 mg, 1.00 mmol, 1.0 equiv.) and Et_3SiH (400 µL, 2.20 mmol, 2.2 equiv.) were dissolved in dry DCM (13 mL). The mixture was cooled to -78 °C and TMSOTf (640 µL, 4.00 mmol, 4.0 equiv.) was added dropwise to the stirred solution. The mixture was stirred for 20 h and was allowed to warm to ambient temperature. Then, saturated $NaHCO_3$ solution (15 mL) was added and the reaction mixture was extracted with ethyl acetate (3x25 mL). The combined organic layers were washed once with brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the crude product. Afterwards the residue was purified by automatic flash column chromatography (gradient: 3:2 to 1:2 PE/EA) to obtain *major*-**108b** (51.1 mg, 216 µmol, 22%) and a mixture of *major*- and *minor*-**108b** (95.0 mg, 402 µmol, 40%) as colorless oils.

Major diastereomer major-**108b**:

R_f = 0.44 (*n*-hexanes/ethyl acetate = 1:3, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.31 – 7.18 (m, 5H), 4.60 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.96 (ddd, *J* = 10.5, 5.0, 2.0 Hz, 1H), 3.93 – 3.84 (m, 1H), 3.63 (s, 3H), 3.38 (d, *J* = 11.3 Hz, 1H), 3.05 (dd, *J* = 10.4, 9.6 Hz, 1H), 2.96 (ddt, *J* = 12.5, 4.5, 2.2 Hz, 1H), 2.32 (s, 1H), 1.68 (dd, *J* = 12.5, 10.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.8, 138.8, 128.9, 127.8, 125.7, 73.0, 72.6, 64.4, 52.7, 51.5, 40.6. **IR:** ν[cm^{-1}] = 3407, 3064, 2956, 2855, 1730, 1599, 1498, 1446, 1230, 1148, 1066, 969, 932, 872, 775, 731, 697. **HRMS:** (EI-MS) *m/z* calculated for $C_{13}H_{16}O_4$ $[M+H]^+$: 236.1043, found 236.1046.

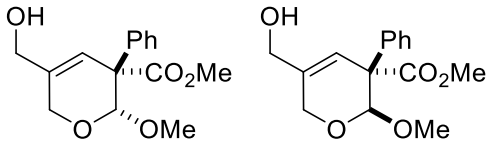
Mixture of major-**108b** and *minor*-**108b**:

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f (*major*) = 0.44 (*n*-hexanes/ethyl acetate = 1:3, stained in vanillin). **R_f (*minor*)** = 0.35 (*n*-hexanes/ethyl acetate = 1:3, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.32 – 7.17 (m, 6H), 4.61 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.40^{minor} (dd, *J* = 11.6, 1.9 Hz, 0.19H), 3.96 (ddd, *J* = 10.5, 5.1, 1.9 Hz, 1H), 3.89 (tt, *J* = 9.9, 4.4 Hz, 1H), 3.82 – 3.73^{minor} (m, 0.42H), 3.68^{minor} (ddd, *J* = 11.7, 4.2, 1.6 Hz, 0.23H), 3.62 (s, 3H), 3.60^{minor} (s, 0.63H), 3.57^{minor} (dd, *J* = 11.6, 2.6 Hz, 0.22H), 3.37 (d, *J* = 11.3 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.97 (ddt, *J* = 12.5, 4.4, 2.2 Hz, 1H), 2.69 – 2.54 (m, 1H), 2.22^{minor} (dd, *J* = 14.0, 3.8 Hz, 0.20H), 2.14 – 2.08^{minor} (m, 0.25H), 1.68 (dd, *J* = 12.4, 10.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 178.3^{minor}, 175.6, 139.9, 138.8^{minor}, 128.91^{minor}, 128.87, 127.8^{minor}, 127.6, 125.8, 125.7^{minor}, 73.1, 73.0^{minor}, 72.7, 72.6^{minor}, 64.6^{minor}, 64.4, 52.8, 48.8^{minor}, 40.7^{minor}, 38.5. **IR:** ν[cm^{-1}] = 3444, 3030, 2956, 2926, 2855 1730, 1603, 1498, 1446, 1241, 1148, 1096, 1025, 947, 880, 835, 772, 738, 667. **HRMS:** major diastereomer (acquisition time 5.564 – 5.567 min): (APCI-MS) *m/z* calculated for $C_{13}H_{16}O_4$ $[M+H]^+$: 237.1121, found 237.1121; minor diastereomer (acquisition time 5.625 – 5.628 min): (APCI-MS) *m/z* calculated for $C_{13}H_{16}O_4$ $[M+H]^+$: 237.1120, found 237.1120.

3.5.3 Brønsted-acid induced endocyclic ring-expansion

methyl (2*R*,3*R*)-5-(hydroxymethyl)-2-methoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate methyl/ (2*S*,3*R*)-5-(hydroxymethyl)-2-methoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (114a):



major-**114a** *minor*-**114a**

At first, a Schlenk-flask was charged with Me_3SOI (127 mg, 576 µmol, 1.3 equiv) and NaH (13.8 mg, 576 µmol, 1.3 equiv). After cooling to 0 °C, DMSO (2 mL) was added dropwise resulting in a suspension which was stirred for 30 min at 25 °C. To the clear solution ketone **106a** (89.3 mg, 385 µmol, 1.0 equiv) dissolved in DMSO (2 mL) was added dropwise and stirring was continued for 18 h at 25 °C. Then, the mixture was diluted with water (30 mL) and the aqueous layer was extracted with diethyl ether (3x20 mL). The combined organic layers were washed with water (2x20 mL), brine (20 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude epoxide which was used without further purification.

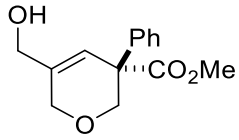
To access pyran **114a**, the obtained epoxide was dissolved in MeCN (2 mL) and Amberlyst 15 (20 w/w%, 10 mg) followed by MeOH (78.0 µL, 1.92 mmol, 5.0 equiv) were added to the stirred solution at 25 °C. After 30 min, the mixture was filtered and the solvent was evaporated to obtain the crude product. Purification of the crude product was achieved by flash column chromatography using *n*-hexanes and ethyl acetate (gradient: 3:1 to 3:2 PE/EA) to yield pure product **114a** (65.7 mg, 236 µmol, 61%, *dr* 1.2:1) as colorless oil consisting of two inseparable diastereomers.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.24 (*n*-hexanes/ethyl acetate = 3:2; stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.44 – 7.40 (m, 2H), 7.37 – 7.30 (m, 4H), 7.30 – 7.23 (m, 3H), 6.28 (q, *J* = 1.6 Hz, 1H), 6.12^{minor} (q, *J* = 1.6 Hz, 0.76H), 5.38^{minor} (d, *J* = 1.1 Hz, 0.77H), 5.34 (d, *J* = 1.3 Hz, 1H), 4.29 – 4.10 (m, 7H), 3.73 (s, 3H), 3.69^{minor} (s, 2.29H), 3.51 (s, 3H), 3.29^{minor} (s, 2.29H), 1.75 (bs, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 172.5^{minor}, 172.0,

139.8, 138.6, 138.2^{minor}, 135.6, 128.7, 128.4^{minor}, 127.4^{minor}, 127.3, 126.9^{minor}, 126.7, 120.8, 119.5^{minor}, 100.5, 100.1^{minor}, 63.9, 63.7^{minor}, 59.8^{minor}, 59.5, 56.5, 55.4^{minor}, 52.6^{minor}, 52.4. **IR:** ν[cm^{-1}] = 3440, 3060, 3001, 2930, 2855, 1730, 1603, 1498, 1435, 1245, 1156, 1115, 1059, 932, 842, 783, 749, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{15}H_{18}O_5$ [M+H]$^+$: 279.1227, found 279.1229.

Methyl (*R*)-5-(hydroxymethyl)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (114b):



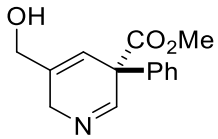
At first, a Schlenk-flask was charged with Me_3SOI (114 mg, 519 µmol, 1.3 equiv) and NaH (12.5 mg, 520 µmol, 1.3 equiv). After cooling to 0 °C, DMSO (2 mL) was added dropwise resulting in a suspension which was stirred for 30 min at 25 °C. To the clear solution ketone **106a** (80.4 mg, 346 µmol, 1.0 equiv) dissolved in DMSO (2 mL) was added dropwise and stirring was continued for 18 h at 25 °C. Then, the mixture was diluted with water (30 mL) and the aqueous layer was extracted with diethyl ether (3x20 mL). The combined organic layers were washed with water (2x20 mL), brine (20 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude epoxide which was used without further purification.

To access pyran **114b** the obtained epoxide was dissolved in dry MeCN (2 mL) and Et_3SiH (280 µL, 1.75 mmol, 5.0 equiv) was added to the stirred solution at 25 °C. Then, TMSOTf (70 µL, 387 µmol, 1.1 equiv) were added dropwise to the stirred solution. After 30 min, the mixture was filtered and the solvent was evaporated to obtain the crude product. Purification of the crude product was achieved by flash column chromatography using *n*-hexanes and ethyl acetate (3:2) to give the clean product **114b** (16.3 mg, 65.6 µmol, 19%) as colorless oil.

R_f = 0.19 (*n*-hexanes/ethyl acetate = 3:2, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.39 – 7.22 (m, 4H), 6.23 (s, 1H), 4.48 (d, *J* = 11.3 Hz, 1H), 4.30 – 4.13 (m, 4H), 3.73 (s, 3H), 3.61 (d, *J* = 11.3 Hz, 1H), 1.95 (bs, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.2, 139.7, 139.4, 128.8, 127.6, 126.3, 122.2, 72.2, 66.0, 63.7, 63.7, 52.5, 51.3. **IR:** ν[cm^{-1}] = 3437, 3060, 3027, 2926, 2855, 1730, 1603, 1495, 1450, 1387,

1238, 1189, 1159, 1111, 1021, 988, 878, 846, 746, 701. **HRMS:** (APCI-MS) *m/z* calculated for $C_{14}H_{16}O_4$ $[M+H]^+$: 249.1121, found 249.1119.

methyl (*R*)-5-(hydroxymethyl)-3-phenyl-3,6-dihydropyridine-3-carboxylate (114c):



At first, a Schlenk-flask was charged with Me_3SOI (138 mg, 628 µmol, 1.3 equiv) and NaH (15.1 mg, 628 µmol, 1.3 equiv). After cooling to 0 °C, DMSO (3 mL) was added dropwise resulting in a suspension which was stirred for 30 min at 25 °C. To the clear solution ketone **106b** (160 mg, 483 µmol, 1.0 equiv) dissolved in DMSO (3 mL) was added dropwise and stirring was continued for 18 h at 25 °C. Then, the mixture was diluted with water (30 mL) and the aqueous layer was extracted with diethyl ether (3x20 mL). The combined organic layers were washed with water (2x20 mL), brine (20 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude epoxide which was used without further purification.

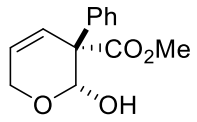
Then, the obtained epoxide was treated with a 9:1 TFA/water mixture (1 mL). The resulting solution was stirred for 1 h at 25 °C. Afterwards, the reaction mixture was neutralized with sat. $NaHCO_3$ solution. The reaction mixture was extracted with DCM (4x25 mL) and the combined organic layers were washed with sat. $NaHCO_3$ solution (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the crude product. Purification of the crude product was achieved by automatic flash column chromatography using DCM and MeOH (gradient: 99:1 to 95:5 DCM/MeOH) to give the clean product **114c** (83.1 mg, 339 µmol, 70%) as brownish oil.

R_f = 0.25 (DCM/MeOH = 19:1, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 8.16 (s, 1H), 7.45 – 7.39 (m, 2H), 7.38 – 7.31 (m, 1H), 7.26 – 7.22 (m, 1H), 6.17 (s, 1H), 4.37 – 4.16 (m, 4H), 3.84 (s, 3H), 2.67 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.5, 159.3, 139.4, 136.8, 129.2, 127.8, 126.6, 118.9, 118.8, 64.3, 53.2, 52.8, 49.8. **IR:** ν[cm^{-1}] = 3280, 3027, 2952, 2926, 2855, 1733, 1655, 1599, 1491, 1435, 1249, 1156, 1028, 954, 828, 757, 701. **HRMS:** (EIC-MS) *m/z* calculated for $C_{14}H_{15}NO_3$ $[M+H]^+$: 246.1125, found 246.1125.

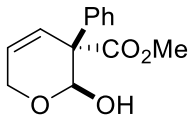
3.6 Synthesis of pharmacological relevant compounds

3.6.1 HIOC related compounds

methyl (2*R*,3*R*)-2-hydroxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate/ methyl (2*S*,3*R*)-2-hydroxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (184):



major-**184**



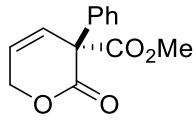
minor-**184**

At first, acetal **105a** (0.25 g, 1.0 mmol, 1.0 equiv) was dissolved in TFA/H_2O (1 mL, 9:1). The reaction mixture was stirred and heated to 50 °C for 45 min and was subsequently neutralized with saturated $NaHCO_3$ solution. Then, the mixture was extracted with DCM (3x15 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude product (*dr* 3.9:1). After purification by flash column chromatography using *n*-hexanes and ethyl acetate (3:2) as eluent, an inseparable mixture of *major*- and *minor*-**184** (0.16 g, 0.70 mmol, *dr* 4.1:1, 69%) was obtained as colorless oil.

In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.38 (*n*-hexanes/ethyl acetate = 3:2; stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.41 – 7.27 (m, 6.46H), 6.18 – 6.02 (m, 2.55H), 5.70^{minor} (s, 0.26H), 5.42 (s, 1H), 4.91 (s, 1H), 4.50 – 4.34 (m, 2.35H), 4.27^{minor} (dt, *J* = 17.2, 1.9 Hz, 0.27H), 3.79 (s, 3H), 3.75^{minor} (s, 0.74H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 174.0, 172.6^{minor}, 138.4, 136.7^{minor}, 128.8, 128.6, 128.2, 127.9, 127.83, 127.79, 126.8, 126.4, 124.3, 98.3, 93.4^{minor}, 64.9, 61.7^{minor}, 55.9^{minor}, 55.0, 52.63, 52.56^{minor}. **IR:** ν[cm^{-1}] = 3440, 3056, 2952, 2855, 1733, 1599, 1495, 1435, 1245, 1140, 1062, 902, 865, 764, 701. **HRMS:** major diastereomer (acquisition time 1.888 – 1.942 min): (ESI-MS) *m/z* calculated for $C_{13}H_{14}O_4$ $[M+Na]^+$: 257.0784, found 257.0785; minor diastereomer (acquisition time 1.739 – 1.784 min): (ESI-MS) *m/z* calculated for $C_{13}H_{14}O_4$ $[M+Na]^+$: 257.0784, found 257.0784.

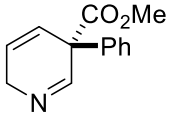
methyl (*S*)-2-oxo-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (185):



To a solution of semi-acetal **184** (120 mg, 511 µmol, 1.0 equiv) in DMSO (3 mL), 2-iodoxybenzoic acid (IBX) (716 mg, 2.56 mmol, 5.0 equiv) was added. The mixture was stirred at 25 °C for 48 h. Then, saturated $Na_2S_2O_3$ (30 mL) was added and the quenched mixture was extracted with diethyl ether (4x15 mL). The combined organic layer was washed once with brine (30 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the clean product **185** (101 mg, 437 µmol, 87%) as yellowish oil.

R_f = 0.33 (*n*-hexanes/ethyl acetate = 3:2, stained in $KMnO_4$). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.43 – 7.30 (m, 5H), 6.38 – 6.22 (m, 2H), 5.05 – 4.74 (m, 2H), 3.81 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 169.6, 166.9, 135.9, 128.5, 128.4, 128.1, 127.0, 124.8, 68.5, 59.3, 53.5. **IR:** ν[cm^{-1}] = 3030, 2956, 1722, 1599, 1495, 1450, 1398, 1230, 1156, 1085, 1018, 835, 801, 742, 693. **HRMS:** (EI-MS) *m/z* calculated for $C_{13}H_{12}O_4$ $[M]^{\cdot+}$: 232.0730, found 232.0725.

methyl (*R*)-3-phenyl-3,6-dihydropyridine-3-carboxylate (186):

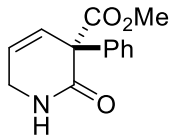


Cyclic acetal **105f** (434 mg, 1.25 mmol, 1.0 equiv) was dissolved in TFA/H_2O (1 mL, 9:1) and was stirred at 25 °C for 45 min. Subsequently, the reaction mixture was quenched with saturated $NaHCO_3$ solution until a pH of 8-9 was reached. The mixture was then diluted with DCM (25 mL), the phases were separated and the organic layer was extracted with DCM (3x25 mL). The combined organic layers were washed once with saturated $NaHCO_3$ (25 mL), brine (25 mL) and dried over Na_2SO_4. After filtration, the solvent was evaporated to obtain the clean product **186** (254 mg, 1.25 mmol, 94%) as brownish oil.

R_f = 0.40 (*n*-hexanes/ethyl acetate = 1:1+ 1% NEt_3, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 8.12 (s, 1H), 7.41 – 7.35 (m, 2H), 7.33 – 7.27 (m, 1H), 7.25 – 7.21

(m, 2H), 6.20 – 6.09 (m, 2H), 4.32 – 4.13 (m, 2H), 3.80 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.5, 159.0, 139.6, 129.1, 127.7, 126.6, 126.2, 124.0, 52.7, 52.0, 49.0. **IR:** ν[cm^{-1}] = 3027, 2952, 2892, 2840, 1730, 1674, 1644, 1245, 1047, 701. **HRMS:** (EI-MS) *m/z* calculated for $C_{13}H_{13}NO_2$ $[M]^+$: 215.0941, found 215.0939.

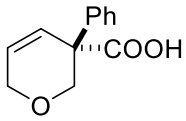
methyl (*R*)-2-oxo-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (188):



To a mixture of 2,3-dimethylbut-2-ene (472 µL, 3.98 mmol, 10 equiv) and $NaClO_2$ (180 mg, 2.00 mmol, 5.0 equiv) in THF (2 mL) a 1 M NaH_2PO_4 solution (600 µL, 600 µmol, 1.5 equiv) was added. Subsequently, the imine **186** (85.6 mg, 398 µmol, 1.0 equiv) dissolved in THF (2 mL) was added dropwise to the stirred solution. After complete addition of the imine **186**, the reaction mixture was stirred for 24 hours at 25 °C. Then, the reaction mixture was diluted with ethyl acetate (30 mL) and the phases were separated. The organic layer was washed once with brine (20 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude product which was recrystallized from refluxing ethyl acetate to give the pure product **188** (58.9 mg, 255 µmol, 64%) as white solid.

R_f = 0.33 (DCM/MeOH = 19:1, stained in vanillin). **mp** = 161 – 163 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.45 – 7.39 (m, 2H), 7.38 – 7.27 (m, 3H), 6.86 – 6.66 (m, 1H), 6.16 – 6.10 (m, 1H), 6.09 – 6.04 (m, 1H), 4.10 – 3.93 (m, 2H), 3.79 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 171.0, 168.0, 138.0, 128.4, 128.2, 127.8, 126.5, 123.2, 59.2, 53.2, 43.5. **IR:** ν[cm^{-1}] = 3194, 3060, 2948, 1722, 1681, 1490, 1327, 1230, 1200, 1036, 831, 801, 738, 693. **HRMS:** (ESI-MS) *m/z* calculated for $C_{13}H_{13}NO_3$ $[MH]^+$: 232.0968, found 232.0967.

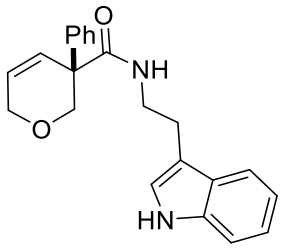
(*R*)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylic acid (191):



Ester **105l** (68.3 mg, 313 µmol, 1.0 equiv) was dissolved in MeOH/water (6 mL, 9:1) and LiOH (37.5 mg, 1.56 µmol, 5.0 equiv) was added. The reaction mixture was refluxed at 100 °C for 2.5 h. Afterwards, the mixture was diluted with water (30 mL) and was then extracted with DCM (2x20 mL) to remove organic impurities. Then, the aqueous layer was acidified with 1 M HCl reaching pH 2 and then extracted with ethyl acetate (3x25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the clean product **191** (55.4 mg, 271 µmol, 87%) as colorless oil.

R_f = 0.36 (*n*-hexanes/ethyl acetate = 3:2 + 1% formic acid, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.37 (d, *J* = 3.8 Hz, 4H), 7.34 – 7.28 (m, 1H), 6.29 (dtd, *J* = 10.3, 2.3, 1.1 Hz, 1H), 6.13 (ddd, *J* = 10.3, 3.0, 2.2 Hz, 1H), 4.48 (dd, *J* = 11.4, 1.1 Hz, 1H), 4.31 – 4.13 (m, 2H), 3.64 (d, *J* = 11.4 Hz, 1H), 3.49 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 177.3, 139.0, 129.0, 128.9, 127.8, 126.4, 126.3, 71.9, 65.4, 51.2. **IR:** ν[cm^{-1}] = 3146, 3079, 2907, 2855, 1737, 1595, 1491, 1454, 1379, 1238, 1200, 1148, 1107, 1074, 1014, 988, 887, 842, 805, 764, 723, 701. **HRMS:** (ESI-MS) *m/z* calculated for $C_{12}H_{12}O_3$ $[MH]^+$: 205.0859, found 205.0862.

(*R*)-*N*-(2-(1*H*-indol-3-yl)ethyl)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxamide (193):



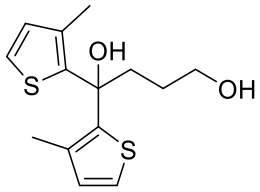
All steps were performed in flame dried glassware and under nitrogen atmosphere. At first, carboxylic acid **191** (52.8 mg, 259 µmol, 1.0 equiv) was dissolved in dry DCM (5 mL) and CDI (62.9 mg, 388 µmol, 1.5 equiv) was added. The mixture was stirred for 24 h at 25 °C and finally heated to 50 °C for additional 3 h. Afterwards, pyridine

(958 µL, 11.9 mmol, 46 equiv), followed by tryptamine (42.3 mg, 264 µmol, 1.02 equiv) and NEt_3 (72.1 µL, 517 µmol, 2.0 equiv) were added. The resulting mixture was stirred at 25 °C for 24 h. Then, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using DCM and MeOH (99:1 + 1% NEt_3) as eluent to obtain the clean product **193** (54.7 mg, 158 µmol, 61%) as yellowish oil.

R_f = 0.52 (DCM/MeOH = 19:1 + 1% NEt_3, stained in vanillin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 8.37 (d, *J* = 28.6 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.25 (m, 5H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.88 – 6.82 (m, 1H), 6.28 (q, *J* = 6.2 Hz, 1H), 6.09 (dt, *J* = 10.4, 1.8 Hz, 1H), 5.98 (dt, *J* = 10.3, 2.4 Hz, 1H), 4.46 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.17 – 4.06 (m, 2H), 3.64 (dp, *J* = 19.9, 6.6 Hz, 2H), 3.55 (dd, *J* = 11.4, 1.0 Hz, 1H), 2.97 (td, *J* = 6.8, 3.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.2, 140.6, 136.4, 129.0, 128.7, 127.41, 127.37, 127.3, 127.1, 122.3, 122.0, 119.3, 118.7, 112.7, 111.3, 72.4, 65.3, 51.8, 40.2, 25.2. **IR:** ν[cm^{-1}] = 3407, 3314, 3056, 2926, 2855, 2359, 1648, 1521, 1457, 1342, 1267, 1230, 1152, 1088, 1010, 746, 701. **HRMS:** (ESI-MS) *m/z* calculated for $C_{22}H_{22}N_2O_2$ $[MH]^+$: 347.1754, found 347.1756.

3.6.2 (*R*)-Tiagabine derivatives

1,1-bis(3-methylthiophen-2-yl)butane-1,4-diol (196):

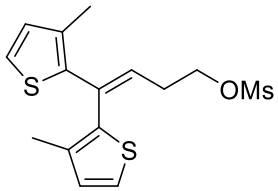


Diol **196** was synthesized according to literature.[185] Magnesium (220 mg, 9.06 mmol, 2.6 equiv) was suspended in dry THF (3 mL) and 2-bromo-3-methylthiphene (981 µL, 8.71 mmol, 2.5 equiv) in dry THF (5 mL) was added dropwise to maintain the temperature below 35 °C. After 1 h of stirring at 25 °C, the reaction mixture was cooled to 0 °C and 4-butyrolactone (266 µL, 3.48 mmol, 1.0 equiv) in dry THF (2 mL) was added slowly to the stirred reaction mixture. Then, the mixture was refluxed for 2 h and was poured into saturated NH_4Cl (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3x50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude product. For purification, the crude product was washed with pentane to give the clean product **196** (975 mg, 3.45 mmol, 99%) as white solid.

Analytical data is in accordance to literature:[185]

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.05 (d, *J* = 5.0 Hz, 2H), 6.77 (d, *J* = 5.1 Hz, 2H), 4.07 (t, *J* = 6.9 Hz, 2H), 2.62 (t, *J* = 7.8, 6.7 Hz, 2H), 2.14 (p, *J* = 7.0 Hz, 2H), 2.04 (d, *J* = 13.9 Hz, 1H), 1.96 (s, 6H).

4,4-bis(3-methylthiophen-2-yl)but-3-en-1-yl methanesulfonate (197):



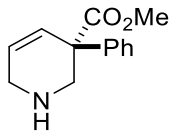
Mesylate **197** was synthesized according to literature.[185] The diol **196** (500 mg, 1.77 mmol, 1.0 equiv) was dissolved in MeOH (4 mL) and 4 M HCl (1 mL) was added to the solution. Then, the mixture was refluxed for 1 h and was then cooled to 25 °C.

The solution was transferred to a separation funnel, diluted with Et_2O (30 mL) and saturated K_2CO_3 solution was added. After separation of the layers, the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude product as yellowish oil which was used without further purification. To the crude product dissolved in Et_2O (6 mL) was added $MeSO_2Cl$ (158 µL, 2.04 mmol, 1.15 equiv) and NEt_3 (358 µL, 2.57 mmol, 1.45 equiv). The mixture was stirred for 1 h at 25 °C. Afterwards, the reaction mixture was quenched with 1 M HCl (15 mL) and the obtained layers were separated. The organic layer was washed with 1 M HCl (15 mL), 2 M NaOH (20 mL) and brine (50 mL). Then, the organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to obtain the clean product **197** (600 mg, 1.75 mmol, 99%) as yellowish oil.

Analytical data is in accordance to literature:[185]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 5.2 Hz, 1H), 7.09 (d, *J* = 5.1 Hz, 1H), 6.87 (d, *J* = 5.1 Hz, 1H), 6.78 (d, *J* = 5.1 Hz, 1H), 6.04 (t, *J* = 7.3 Hz, 1H), 4.29 (t, *J* = 6.6 Hz, 2H), 3.00 (s, 3H), 2.60 (q, *J* = 6.8 Hz, 2H), 2.05 (s, 3H), 2.02 (s, 3H).

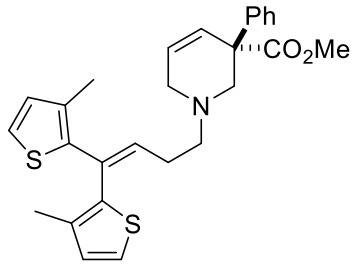
methyl (*R*)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (198)



Imine **186** (89.7 mg, 417 µmol, 1.0 equiv) was dissolved in MeOH (10 mL) followed by addition of $NaBH_3CN$ (261 mg, 4.17 mmol, 10 equiv) and acetic acid (240 µL, 4.20 mmol, 10.0 equiv). After 45 min at 25 °C, the reaction was finished and poured into a separation funnel. Then, the solution was diluted with DCM (20 mL) and washed with saturated $NaHCO_3$ (30 mL) and the aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the clean product **198** (90.0 mg, 414 µmol, 99%) as brownish oil.

R_f = 0.30 (DCM/MeOH = 19:1, stained in $KMnO_4$). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.39 – 7.21 (m, 5H), 6.20 (dq, *J* = 10.3, 1.8 Hz, 1H), 6.12 (dt, *J* = 10.3, 2.8 Hz, 1H), 3.74 – 3.65 (m, 4H), 3.37 (t, *J* = 2.4 Hz, 2H), 2.80 (d, *J* = 13.4 Hz, 1H), 2.17 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 174.4, 141.7, 131.0, 128.7, 127.3, 127.2, 126.3, 53.5, 52.4, 51.2, 44.4. **IR:** ν[cm^{-1}] = 3343, 3030, 2952, 2922, 2840, 1726, 1599, 1491, 1446, 1241, 1208, 1088, 1018, 828, 701. **HRMS:** (ESI-MS) *m/z* calculated for $C_{13}H_{15}NO_2$ $[MH]^+$: 218.1176, found 218.1172.

methyl (*R*)-1-(4,4-bis(3-methylthiophen-2-yl)but-3-en-1-yl)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (201):

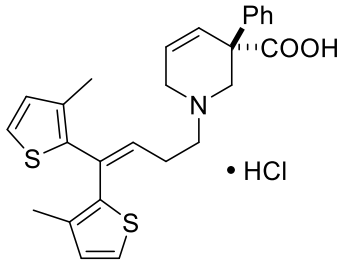


In a dry pressure tube, tetrahydropyridine **198** (50.8 mg, 234 µmol, 1.0 equiv) was dissolved in acetone (5 mL) and K_2CO_3 (48.5 mg, 351 µmol, 1.5 equiv), KI (3.9 mg, 24 µmol, 10 mol%) and mesylate **197** (96.1 mg, 281 mg, 1.2 equiv) were added to the stirred solution. The mixture was heated to 80 °C for 2 days. Then, the precipitate was filtered off, washed with Et_2O and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography using *n*-hexanes and ethyl acetate (3:1 + 1% NEt_3) as eluent to afford the clean product **201** (67.0 mg, 145 µmol, 62%) as colorless oil.

R_f = 0.45 (*n*-hexanes/ethyl acetate = 3:1, stained in ninhydrin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.31 (d, *J* = 3.4 Hz, 4H), 7.25 – 7.22 (m, 1H), 7.21 (d, *J* = 5.1 Hz, 1H), 7.04 (d, *J* = 5.1 Hz, 1H), 6.84 (d, *J* = 5.1 Hz, 1H), 6.76 (d, *J* = 5.1 Hz, 1H), 6.16 – 6.11 (m, 1H), 6.07 (t, *J* = 7.3 Hz, 1H), 5.99 (ddd, *J* = 10.0, 4.1, 2.4 Hz, 1H), 3.70 (s, 3H), 3.47 (d, *J* = 11.4 Hz, 1H), 3.14 (dd, *J* = 16.6, 3.6 Hz, 1H), 2.84 (dt, *J* = 16.5, 2.5 Hz, 1H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.43 – 2.31 (m, 3H), 2.04 (s, 3H), 2.00 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.9, 141.6, 139.8, 135.41, 135.35, 133.6, 133.5, 131.1, 129.6, 128.6, 128.0, 127.8, 127.5, 127.2, 126.2, 124.3, 122.6, 59.8, 57.1, 53.6, 52.4,

52.3, 27.3, 14.9, 14.4. **IR:** ν[cm^{-1}] = 3042, 2922, 2859, 2807, 2751, 1733, 1655, 1599, 1495, 1431, 1364, 1241, 1204, 1141, 1036, 1006, 910, 865, 816, 697. **HRMS:** (ESI-MS) *m/z* calculated for $C_{27}H_{29}NO_2S_2$ $[MH]^+$: 464.1712, found 464.1716.

(3*R*)-1-(4,4-bis(3-methylthiophen-2-yl)but-3-en-1-yl)-3-carboxy-3-phenyl-1,2,3,6-tetrahydropyridin-1-ium chloride (199):

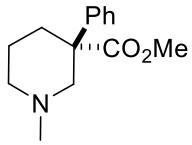


Ester **201** (38.5 mg, 83.0 µmol, 1.0 equiv) was dissolved in MeOH/water (2 mL, 9:1) and LiOH (9.9 mg, 415 µmol, 5.0 equiv) was added. The reaction mixture was refluxed at 100 °C for 24 h. Afterwards, the solvent was evaporated to obtain the crude product as yellowish oil. The residue was dissolved in DCM (3 mL) and 1 M HCl (10 mL) was added. The mixture was stirred for 1 h at 25 °C. Then, the mixture was extracted with DCM (4x20 mL) and the combined organic layers were washed with 1 M HCl, brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Finally, the clean product was washed with a 1:1 mixture of *n*-hexanes and *i*-PrOH to give **199** (37.9 mg, 78.0 µmol, 94%) as yellowish oil.

mp = 108 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.28 (m, 4H), 7.25 – 7.22 (m, 1H), 7.16 (d, *J* = 5.0 Hz, 1H), 7.05 (d, *J* = 5.0 Hz, 1H), 6.82 (d, *J* = 5.0 Hz, 1H), 6.74 (d, *J* = 5.1 Hz, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 6.01 (q, *J* = 7.1 Hz, 2H), 4.27 – 4.08 (m, 1H), 3.85 – 3.70 (m, 1H), 3.40 – 3.18 (m, 2H), 3.11 – 2.96 (m, 1H), 2.74 – 2.62 (m, 2H), 2.61 – 2.50 (m, 1H), 2.00 (s, 3H), 1.95 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.4, 139.0, 138.3, 136.1, 134.5, 133.9, 131.5, 131.3, 130.1, 129.0, 128.8, 128.1, 126.7, 124.7, 123.4, 57.4, 56.0, 51.9, 50.7, 24.9, 14.9, 14.5. **IR:** ν[cm^{-1}] = 3332, 3056, 2922, 2855, 1718, 1603, 1491, 1446, 1383, 1249, 1208, 1103, 1033, 1006, 910, 727. **HRMS:** (ESI-MS) *m/z* calculated for $C_{26}H_{27}NO_2S_2$ $[MH]^+$: 450.1556, found 450.1557.

3.6.3 Pethidine analogues

methyl (*R*)-1-methyl-3-phenylpiperidine-3-carboxylate (209):



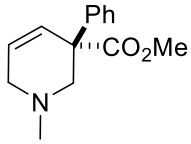
At first, cyclic imine **186** (100 mg, 466 µmol, 1.0 equiv) was dissolved in MeOH (3 mL) and Pd/C (49.6 mg, 46.6 µmol, 10 mol%, 10 w% Pd on charcoal) was added. The reaction mixture was stirred for 2 h under 40 bar H_2 atmosphere at 25 °C. After completion, the reaction mixture was filtered and the solvent was evaporated. The residue was diluted with DCM (20 mL) and washed with 1 M HCl (3x20 mL). After treating the combined aqueous layers with saturated $NaHCO_3$ solution (pH 10-11), it was extracted with DCM (3x20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL) and with brine (30 mL). Afterwards, the organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the crude product as brownish oil.

In the second step, the crude product was dissolved in MeCN (5 mL) and formaldehyde solution (215 µL, 37 w/w%, 2.87 mmol, 6.25 equiv) was added followed by the addition of $NaBH_3CN$ (87.9 mg, 1.40 mmol, 3.0 equiv). The reaction mixture was stirred at 25 °C for 1 h. Then, the reaction mixture was acidified (pH 6) with acetic acid and was again stirred at 25 °C for 30 min. Afterwards, the mixture was neutralized with ammonia (pH 9) and diluted with DCM (30 mL) and saturated $NaHCO_3$ solution (30 mL). The phases were separated and the aqueous layer was extracted with DCM (4x15 mL) followed by washing the combined organic layers with brine. After drying the organic layer over Na_2SO_4 and filtration, the solvent was evaporated under reduced pressure to obtain the crude product. Finally, the crude product was purified by flash column chromatography using *n*-hexanes and ethyl acetate (1:2 + 1% NEt_3) as eluent to afford product **209** (50.6 mg, 217 µmol, 47%) as colorless oil.

R_f = 0.21 (*n*-hexanes/ethyl acetate = 1:2, stained in ninhydrin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.41 – 7.36 (m, 2H), 7.32 (ddd, *J* = 7.9, 6.7, 1.2 Hz, 2H), 7.27 – 7.21 (m, 1H), 3.67 (s, 3H), 3.53 – 3.41 (m, 1H), 2.84 – 2.64 (m, 1H), 2.61 – 2.48 (m, 1H), 2.38 – 2.21 (m, 4H), 2.08 – 1.91 (m, 1H), 1.89 – 1.74 (m, 1H), 1.73 – 1.55 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 174.7, 141.8, 128.5, 127.1, 125.9, 62.8, 55.7, 52.3, 50.8, 46.8,

32.4, 23.4. **IR:** ν[cm^{-1}] = 3060, 3027, 2945, 2840, 2784, 1730, 1610, 1498, 1446, 1379, 1297, 1230, 1200, 1152, 1066, 1021, 969, 820, 768, 701. **HRMS:** (EI-MS) *m/z* calculated for $C_{14}H_{19}NO_2$ $[M]^{\cdot+}$: 233.1403, found 233.1406.

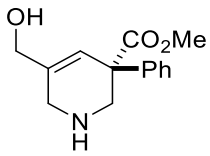
methyl (*R*)-1-methyl-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (210):



Free amine **198** was dissolved in MeCN (5 mL) and a formaldehyde solution (110 µL, 37 w/w% 1.46 mmol, 6.15 equiv) was added followed by the addition of $Na(OAc)_3BH$ (151 mg, 714 µmol, 3.0 equiv). The reaction mixture was stirred at 25 °C for 1.5 h. Afterwards, the mixture was diluted with DCM (30 mL) and saturated $NaHCO_3$ solution (30 mL). The phases were separated and the aqueous layer was extracted with DCM (5x15 mL) followed by washing the combined organic layers with brine. After drying the organic layer over Na_2SO_4 and filtration, the solvent was evaporated under reduced pressure to obtain the clean product **210** (50.7 mg, 219 µmol, 92%) as yellowish oil.

R_f = 0.38 (*n*-hexanes/ethyl acetate = 1:2 + 1% NEt_3, stained in ninhydrin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.36 – 7.26 (m, 5H), 6.19 – 6.12 (m, 1H), 6.02 (ddd, *J* = 10.1, 4.1, 2.4 Hz, 1H), 3.71 (s, 3H), 3.43 (d, *J* = 11.5 Hz, 1H), 3.15 (ddt, *J* = 16.7, 4.2, 1.4 Hz, 1H), 2.76 (dt, *J* = 16.6, 2.5 Hz, 1H), 2.35 (s, 3H), 2.31 (d, *J* = 11.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.9, 141.6, 128.7, 128.0, 127.2, 126.9, 126.1, 62.1, 54.3, 53.5, 52.4, 45.7. **IR:** ν[cm^{-1}] = 3034, 2948, 2840, 2792, 1730, 1599, 1495, 1450, 1375, 1241, 1208, 1152, 1115, 1055, 973, 865, 790, 753, 697. **HRMS:** (EI-MS) *m/z* calculated for $C_{14}H_{17}NO_2$ $[M]^{\cdot+}$: 231.1254, found 231.1255.

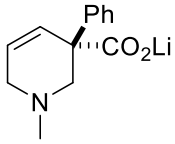
methyl (*R*)-5-(hydroxymethyl)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (211)



Imine **114c** (207 mg, 845 µmol, 1.0 equiv) was dissolved in MeOH (10 mL) followed by addition of $NaBH_3CN$ (531 mg, 8.45 mmol, 10 equiv) and acetic acid (483 µL, 8.45 mmol, 10.0 equiv). After 45 min at 25 °C, the reaction was finished and poured into a separation funnel. Then, the solution was diluted with DCM (20 mL), washed with saturated $NaHCO_3$ (30 mL) and the aqueous layer was extracted with DCM (3x20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and the solvent was evaporated to obtain the clean product **211** (194 mg, 208 µmol, 93%) as brownish oil.

R_f = 0.55 (DCM/MeOH = 9:1, stained in ninhydrin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.45 – 7.18 (m, 5H), 6.18 (s, 1H), 4.19 (s, 2H), 3.71 (s, 4H), 3.49 – 3.35 (m, 2H), 2.78 (d, *J* = 13.4 Hz, 1H), 2.10 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 174.2, 141.4, 141.2, 128.8, 127.4, 126.2, 122.5, 64.9, 53.2, 52.5, 51.1, 44.9. **IR:** ν[cm^{-1}] = 3317, 3060, 3027, 2952, 2922, 2844, 1722, 1599, 1491, 1439, 1245, 1178, 1081, 1021, 910, 865, 731. **HRMS:** (ESI-MS) *m/z* calculated for $C_{14}H_{17}NO_3$ $[MH]^+$: 248.1281, found 248.1289.

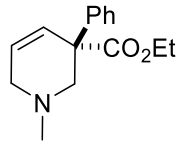
lithium (*R*)-1-methyl-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (214):



Ester **210** (20.6 mg, 89.1 µmol, 1.0 equiv) was dissolved in a 9:1 mixture of MeOH/water (2 mL) and LiOH (10.7 mg, 445 µmol, 5.0 equiv) was added. The reaction mixture was refluxed at 100 °C for 2.5 h. Afterwards, the solvent was evaporated to obtain the clean product **214** (33.0 mg, 89.1 µmol, *quant.*) as brownish solid.

mp = 121 °C. **^{1}H NMR (400 MHz, D_2O):** δ = 7.25 – 7.09 (m, 5H), 6.05 – 5.89 (m, 1H), 5.78 – 5.64 (m, 1H), 2.92 – 2.82 (m, 1H), 2.73 – 2.53 (m, 3H), 2.05 – 1.94 (m, 3H). **^{13}C NMR (101 MHz, D_2O):** δ = 181.1, 144.2, 129.3, 128.5, 126.6, 126.6, 125.6, 61.4, 54.9, 53.6, 44.7. **IR:** ν[cm^{-1}] = 3317, 3027, 2922, 2855, 1592, 1491, 1446, 1402, 1301, 1256, 1148, 1085, 984, 861, 831, 746, 697. **HRMS:** (ESI-MS) *m/z* calculated for $C_{13}H_{15}NO_2$ $[MH]^+$: 218.1176, found 218.1182.

ethyl (*R*)-1-methyl-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (213):



At first, carboxylate **214** (46.0 mg, 206 µmol, 1.0 equiv) was dissolved in EtOH (5 mL) and a 2 M $SOCl_2$ solution (3.4 mL) was added slowly. Then, the reaction mixture was heated to 100 °C and refluxed for 4.5 h. The resulting mixture was quenched with saturated $NaHCO_3$ solution and extracted with DCM (4x30 mL). The combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressured. The residue was purified by flash column chromatography using DCM and MeOH (99:1 + 1% NEt_3) as eluent to obtain the clean product **213** (29.3 mg, 119 µmol, 58%) as yellowish oil.

R_f = 0.38 (DCM/MeOH = 19:1 + 1% NEt_3, stained in ninhydrin). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 7.30 – 7.24 (m, 4H), 7.23 – 7.17 (m, 1H), 6.10 (dt, *J* = 10.0, 2.2 Hz, 1H), 5.96 (ddd, *J* = 10.1, 4.1, 2.5 Hz, 1H), 4.23 – 4.06 (m, 2H), 3.35 (d, *J* = 11.4 Hz, 1H), 3.08 (dd, *J* = 16.7, 3.7 Hz, 1H), 2.72 (dt, *J* = 16.6, 2.6 Hz, 1H), 2.33 – 2.25 (m, 4H), 1.14 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 173.4, 141.9, 128.6, 127.8, 127.1, 127.1, 126.2, 62.0, 61.1, 54.4, 53.4, 45.7, 14.0. **IR:** ν[cm^{-1}] = 3056, 3027, 2956, 2926, 2855, 1730, 1495, 1450, 1372, 1241, 1178, 1118, 1029, 910, 842, 731, 701. **HRMS:** (EI-MS) *m/z* calculated for $C_{15}H_{19}NO_2$ $[M]^{\cdot+}$: 245.1410, found 245.1410.

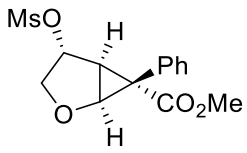
4 Computational Studies

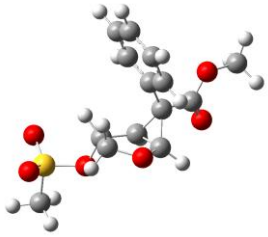
All calculations were performed with the Gaussian09 Rev. E.01 software package on the high performance computing cluster of the University of Regensburg.[9] The calculations were carried out on a B3LYP/6-31+G(d,p) level of theory.[137–147] Stationary points were confirmed as ground or transition states with the computation of the harmonic vibrational frequencies and evaluating the number of imaginary frequencies (0 for ground state, 1 for transition state). Further confirmation of the TS being associated to the reaction coordinate of interest was obtained by visualization of the imaginary frequency. Reported energies are unscaled Gibbs free energies that include a zeropoint energy correction and are based on the frequency calculations within the harmonic oscillator approximation.

[9] Gaussian 09, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

Ground state optimizations

GS1





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C	-0.14726300	-1.08858600	0.12616600
C	-1.18869600	0.01226500	0.14578400
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O	-2.47635100	-0.68577000	0.21160800
C	-4.97292800	-1.18387500	-0.15326000
S	-3.76382000	0.11057200	-0.43574600
O	-3.54090600	0.28980300	-1.87198400
O	-4.07487900	1.27876000	0.39123300
C	2.23978300	-1.82601600	-0.15732700
O	1.91153600	-3.00024400	-0.11635100
O	3.46460300	-1.41391200	-0.53317400
C	4.39485500	-2.45506400	-0.89152500
C	1.82679900	0.70915100	0.00254900
C	2.50509100	1.40819400	1.01083400
C	2.98319700	2.69967500	0.77921100
C	2.79077500	3.30825100	-0.46450600
C	2.11931100	2.61739600	-1.47710200
C	1.64020100	1.32652500	-1.24322200
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H	-0.38051300	-2.00861800	-0.39662400
H	-1.18518000	0.65257300	-0.73952900
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H	-5.03186900	-1.37330000	0.91845000
H	5.31260600	-1.93647000	-1.16658000
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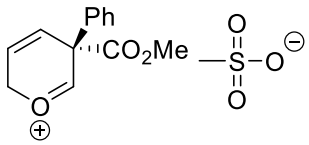
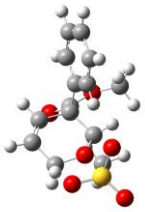
H	4.01028300	-3.03558700	-1.73326900
H	2.64769900	0.94046800	1.97996300
H	3.50407600	3.23124600	1.57049100
H	3.16054400	4.31375600	-0.64323200
H	1.96721700	3.08209500	-2.44701800
H	1.12496900	0.78973000	-2.03581400

Zero-point correction= 0.287768 (Hartree/Particle)
Thermal correction to Energy= 0.307859
Thermal correction to Enthalpy= 0.308803
Thermal correction to Gibbs Free Energy= 0.236245
Sum of electronic and zero-point Energies= -1392.325492
Sum of electronic and thermal Energies= -1392.305401
Sum of electronic and thermal Enthalpies= -1392.304457
Sum of electronic and thermal Free Energies= -1392.377015

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	193.184	74.536	152.710

INT1





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C	-0.67678400	-2.85379700	0.32353600
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H	1.34249100	-0.97260200	2.38799300
O	-1.54288200	0.35509100	-1.06802200
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S	-3.02518200	0.11152300	-0.39835900
O	-2.91900900	-0.86763900	0.68810700
O	-3.96441100	-0.10602900	-1.49633800
C	2.07700500	-0.03921800	-0.01862000
C	2.94622800	0.82154700	0.67007300
C	4.29579900	0.90595100	0.32059800
C	4.80458800	0.12464400	-0.71911700
C	3.95360300	-0.75323600	-1.39439300
C	2.60522800	-0.84224700	-1.04099400
C	0.08334400	1.11137200	1.10207600
O	-0.37193500	1.11483100	2.22440600
O	0.16170700	2.29640400	0.45491300
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H	-1.71553600	-2.84321800	0.66911300
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H	-3.28039500	2.47629900	-0.48802600
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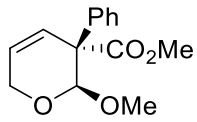
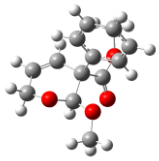
H	1.97565300	-1.56186600	-1.55546800
H	0.79213000	3.56375400	-0.98234100
H	1.33920800	1.89443700	-1.25316200
H	-0.37160800	2.33064000	-1.55497600

Zero-point correction= 0.285921 (Hartree/Particle)
Thermal correction to Energy= 0.306276
Thermal correction to Enthalpy= 0.307220
Thermal correction to Gibbs Free Energy= 0.236702
Sum of electronic and zero-point Energies= -1392.296300
Sum of electronic and thermal Energies= -1392.275946
Sum of electronic and thermal Enthalpies= -1392.275002
Sum of electronic and thermal Free Energies= -1392.345520

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	192.191	76.995	148.418

SUBS1_high





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C	2.66987100	-1.56568400	1.22894900
C	1.45684600	-0.87244600	1.28512000
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O	-1.27337000	1.99604800	-1.51285600
O	0.51273400	2.75306800	-0.49165200
C	1.70075400	2.67564500	0.31600400
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H	3.40517200	-1.08397700	-2.05497500
H	4.32481100	-2.17863400	-0.01410500
H	3.05356800	-2.04803000	2.12360500
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H	1.97682700	3.71479000	0.50272500
H	1.54172600	2.16324100	1.26436500
H	2.49730100	2.17232000	-0.23562600
H	-1.74290700	-2.07852300	-3.16055200
H	-2.68026200	-2.46521400	-1.69034100
H	-2.94591900	-0.90936500	-2.54689200

Zero-point correction= 0.277529 (Hartree/Particle)
Thermal correction to Energy= 0.294408
Thermal correction to Enthalpy= 0.295352
Thermal correction to Gibbs Free Energy= 0.233141
Sum of electronic and zero-point Energies= -843.736899
Sum of electronic and thermal Energies= -843.720019
Sum of electronic and thermal Enthalpies= -843.719075
Sum of electronic and thermal Free Energies= -843.781286

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
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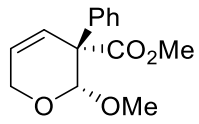
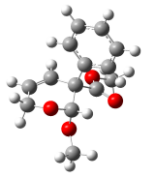
SUBS1_low





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C	-1.03361700	-0.80462700	-0.73871500
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C	2.13258900	-0.69774500	0.93324100
C	3.49853700	-0.84712600	0.67589400
C	4.04644800	-0.37809800	-0.51843600
C	3.21445700	0.24499800	-1.45232200
C	1.85147200	0.39878200	-1.19291900
C	-0.60127200	1.54464200	-0.00711700
O	-0.72172300	2.01247200	-1.12167900
O	-0.72220600	2.27941900	1.11445200
C	-1.00975900	3.67891400	0.92070000
O	-2.38366400	-0.41289000	-0.68331900
C	-3.15052900	-0.82284000	-1.81267000
H	-1.43070900	-1.85448600	2.92093200
H	-0.92440200	-3.52555900	1.05841800
H	-2.48536400	-2.75082900	0.74111700
H	-0.63685200	-0.68317100	-1.75143500
H	-0.44270100	0.33811300	2.48429300
H	1.72282800	-1.08073500	1.86067200
H	4.13054100	-1.33522600	1.41260800
H	5.10723100	-0.49596200	-0.72031800
H	3.62510700	0.61652400	-2.38702000
H	1.22446800	0.89968200	-1.92267900
H	-1.07341400	4.10111300	1.92313600
H	-0.20930300	4.15470700	0.34943700
H	-1.95539500	3.79991000	0.38772500
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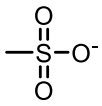
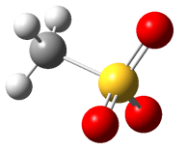
Zero-point correction= 0.277944 (Hartree/Particle)
Thermal correction to Energy= 0.294844
Thermal correction to Enthalpy= 0.295788
Thermal correction to Gibbs Free Energy= 0.232799
Sum of electronic and zero-point Energies= -843.755491
Sum of electronic and thermal Energies= -843.738591

Sum of electronic and thermal Enthalpies= -843.737647
Sum of electronic and thermal Free Energies= -843.800637

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	185.017	63.596	132.573

mesylate





C	1.65383000	0.00191600	0.00004100
S	-0.17554100	-0.00009000	-0.00000200
O	-0.54417300	-1.44963700	-0.02698400
O	-0.54755100	0.70047800	1.26831000
O	-0.54754100	0.74719200	-1.24136800
H	1.99985700	1.03798300	0.01931900
H	1.99997000	-0.49945900	-0.90680100
H	1.99996800	-0.53284700	0.88760400

Zero-point correction= 0.049788 (Hartree/Particle)
Thermal correction to Energy= 0.054952
Thermal correction to Enthalpy= 0.055896
Thermal correction to Gibbs Free Energy= 0.021387
Sum of electronic and zero-point Energies= -663.764118
Sum of electronic and thermal Energies= -663.758954
Sum of electronic and thermal Enthalpies= -663.758010
Sum of electronic and thermal Free Energies= -663.792519

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	34.483	17.714	72.630

methoxy

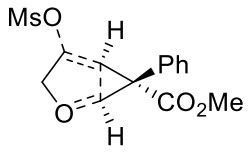
C	-0.54384400	0.00003400	-0.00002000
O	0.79717500	0.00003800	-0.00001800
H	-1.03848200	1.00072500	0.23585500
H	-1.03819200	-0.29642900	-0.98456400
H	-1.03766400	-0.70480400	0.74897300

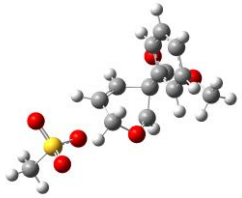
Zero-point correction= 0.034986 (Hartree/Particle)
Thermal correction to Energy= 0.037895
Thermal correction to Enthalpy= 0.038839
Thermal correction to Gibbs Free Energy= 0.012735
Sum of electronic and zero-point Energies= -115.080535
Sum of electronic and thermal Energies= -115.077627
Sum of electronic and thermal Enthalpies= -115.076683
Sum of electronic and thermal Free Energies= -115.102786

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	23.779	6.919	54.940

Transition state optimizations

TS1





C	-0.90252000	-0.41166100	0.66516000
C	-0.02561900	0.57288200	0.99131000
C	0.35013100	0.98667400	-0.96466100
C	-0.80111100	-1.01482600	-0.69702000
O	-0.31145700	0.04166100	-1.58251800
C	1.26690000	0.73102100	0.14248500
H	0.17553200	1.98712600	-1.35788000
H	-0.14696000	1.25513500	1.82333000
O	-2.94893700	0.86589800	-0.01652200
C	-5.58913200	0.56534300	-0.04421000
S	-3.97954100	-0.24355800	0.06681600
O	-3.93017400	-0.93580700	1.38763200
O	-3.87507100	-1.16555300	-1.10719900
C	2.19187500	-0.48797600	0.13662600
C	2.71684700	-0.92384200	1.36273000
C	3.58105000	-2.01719100	1.41033500
C	3.92471000	-2.69444800	0.23582700
C	3.40333900	-2.26726000	-0.98640700
C	2.54442100	-1.16473800	-1.03869700
C	2.02545400	2.00279400	0.61539900
O	1.83987400	2.47847700	1.70884100
O	2.92113600	2.58043000	-0.20799200
C	3.33547400	2.06026300	-1.48326600
H	-1.65695300	-0.79894800	1.34876500
H	-0.11864200	-1.87488500	-0.71215500
H	-1.78126600	-1.28604600	-1.10935400
H	-6.35396200	-0.21115500	0.00910900
H	-5.68239500	1.25724500	0.79394500
H	-5.64264200	1.09548300	-0.99601300
H	2.44431500	-0.40927600	2.27972000
H	3.98266200	-2.34177700	2.36528700
H	4.59161700	-3.55020200	0.27487900
H	3.65956200	-2.78960500	-1.90319600
H	2.14790100	-0.84661600	-1.99793100
H	3.87836500	2.87897100	-1.95494400
H	3.99532900	1.20164400	-1.34875800
H	2.48631900	1.78677200	-2.11545100

Zero-point correction= 0.282778 (Hartree/Particle)

Thermal correction to Energy= 0.303465
Thermal correction to Enthalpy= 0.304409
Thermal correction to Gibbs Free Energy= 0.231219
Sum of electronic and zero-point Energies= -1392.242114
Sum of electronic and thermal Energies= -1392.221427
Sum of electronic and thermal Enthalpies= -1392.220483
Sum of electronic and thermal Free Energies= -1392.293673

	E (Thermal) KCal/Mol	CV Cal/Mol-Kelvin	S Cal/Mol-Kelvin
Total	190.427	76.183	154.042

ν_{imag} = -229.60 cm^{-1}

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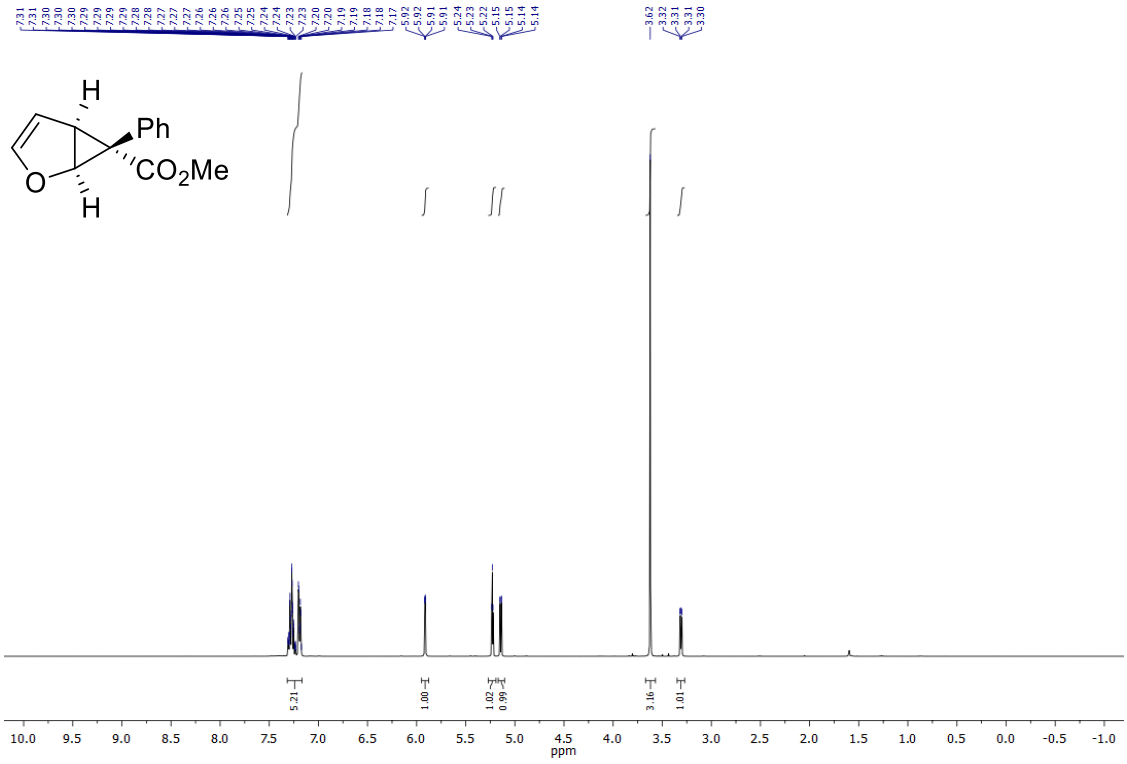
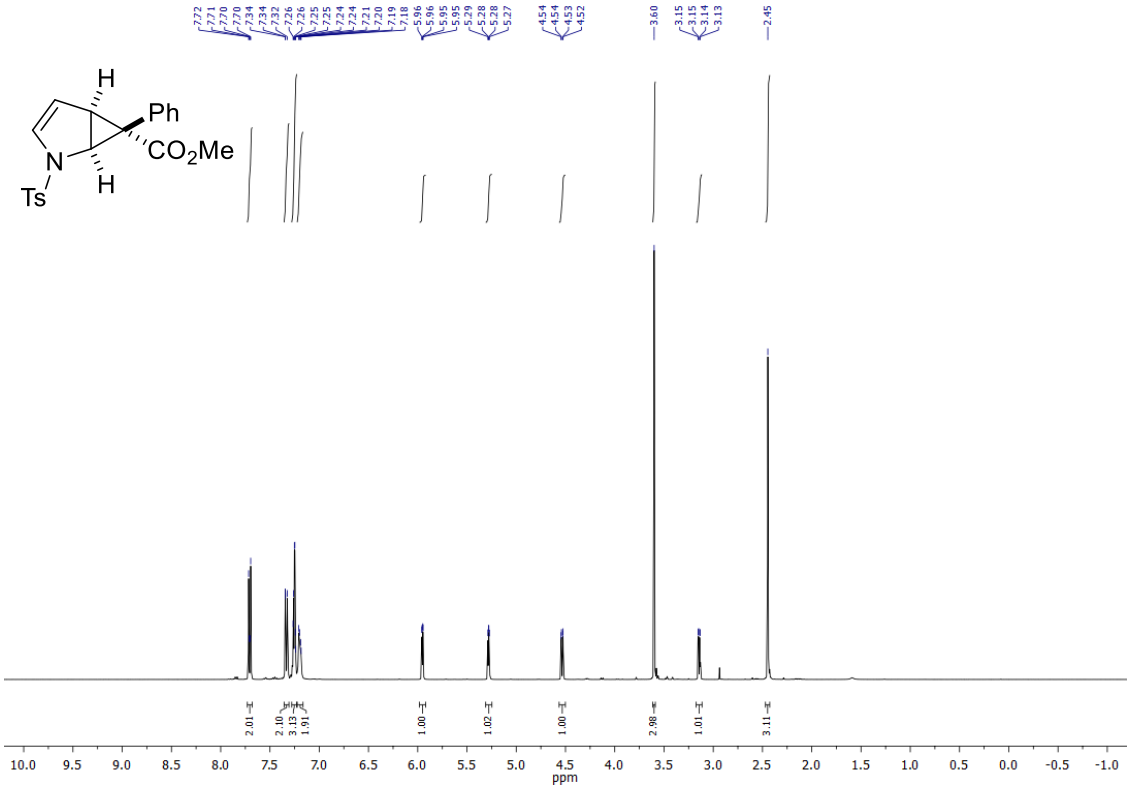
6 Appendix

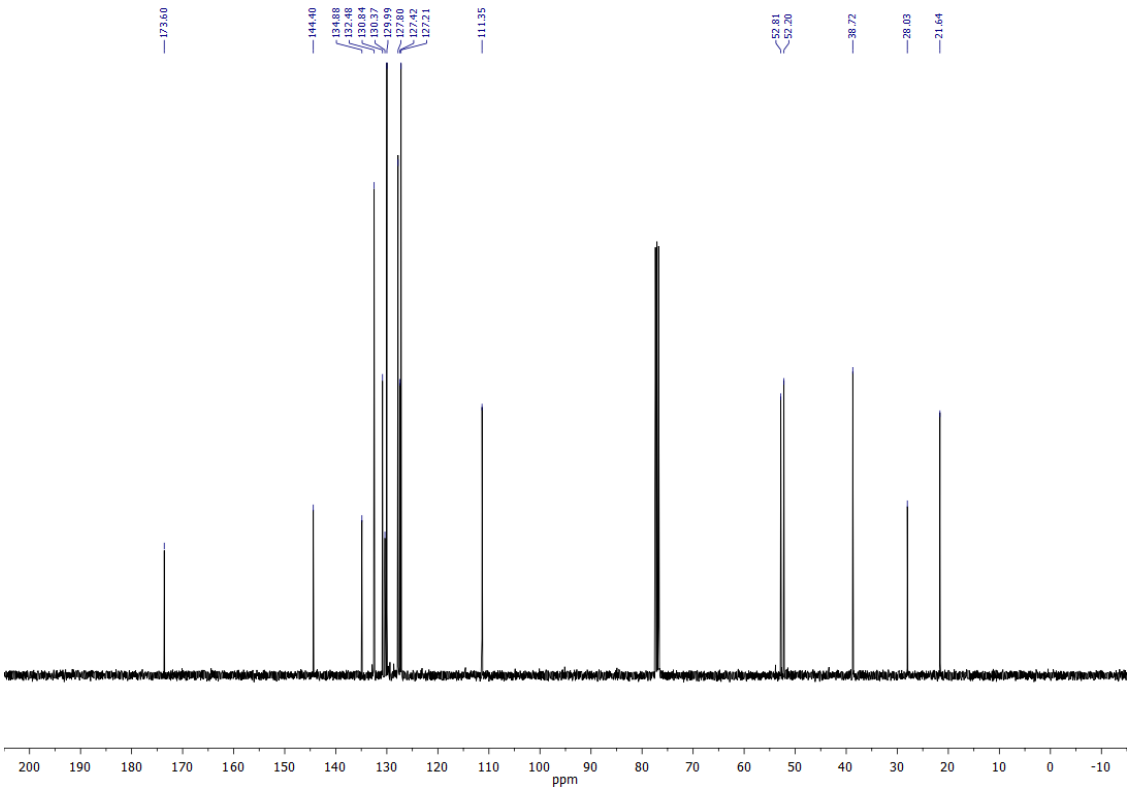
6.1 Copies of NMR spectra

Compound **(-)-102a**: ^{1}H-NMR (400 MHz, $CDCl_3$)

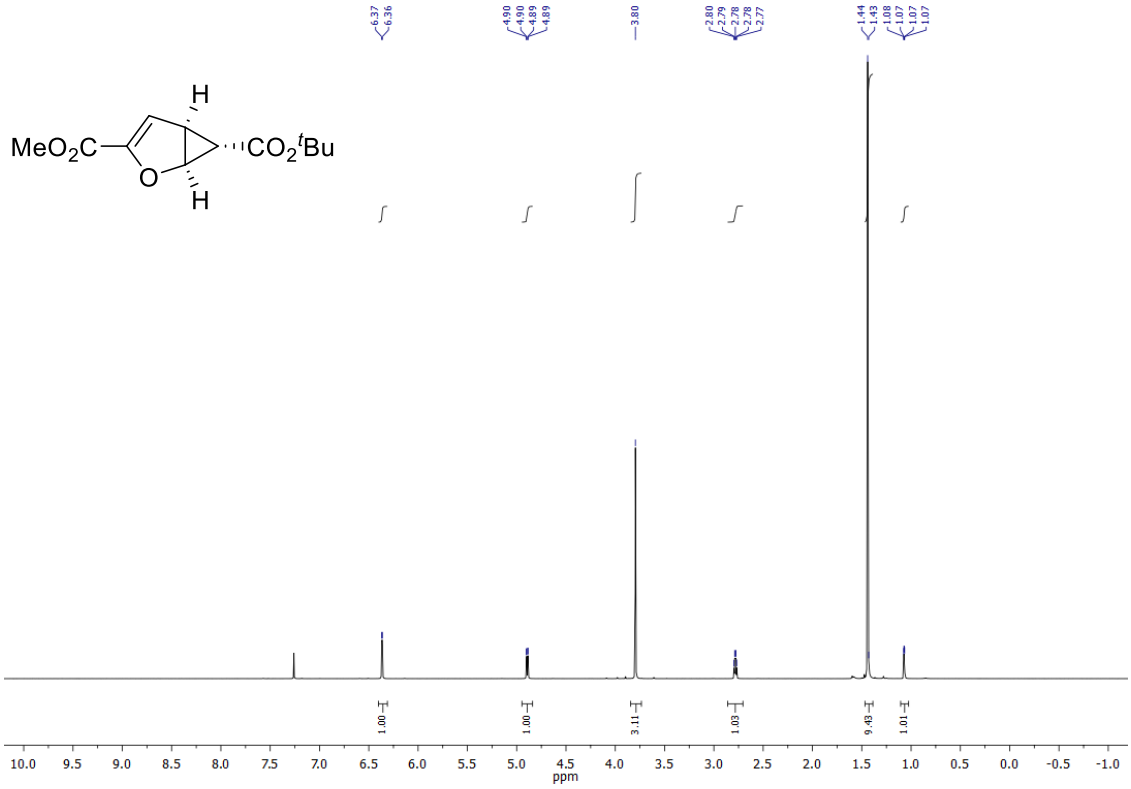


Compound **102b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

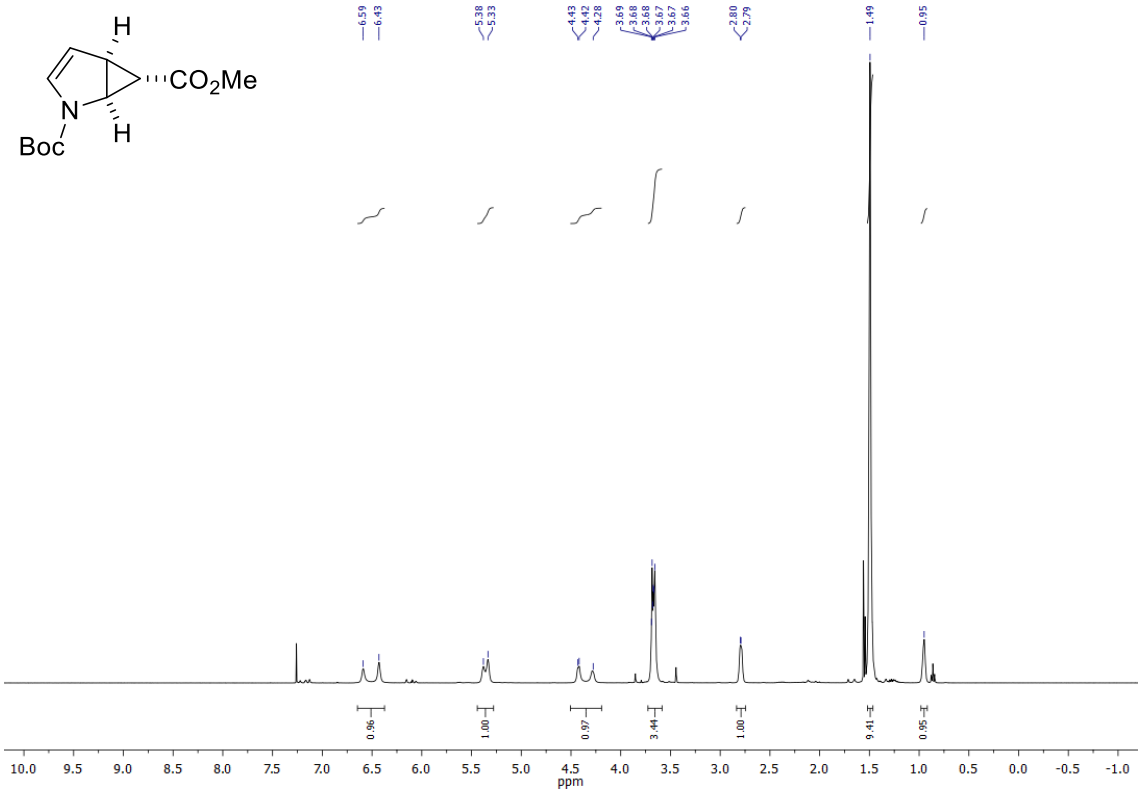




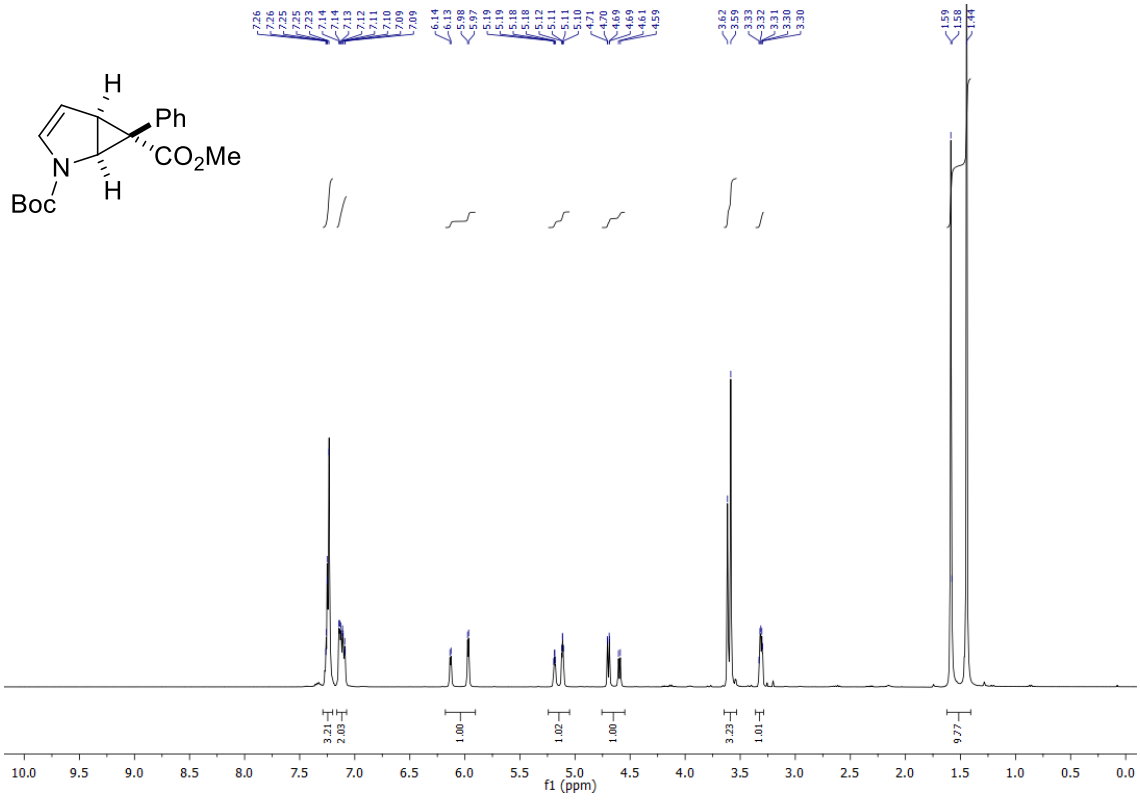
Compound **102c**: ^{1}H-NMR (400 MHz, $CDCl_3$)



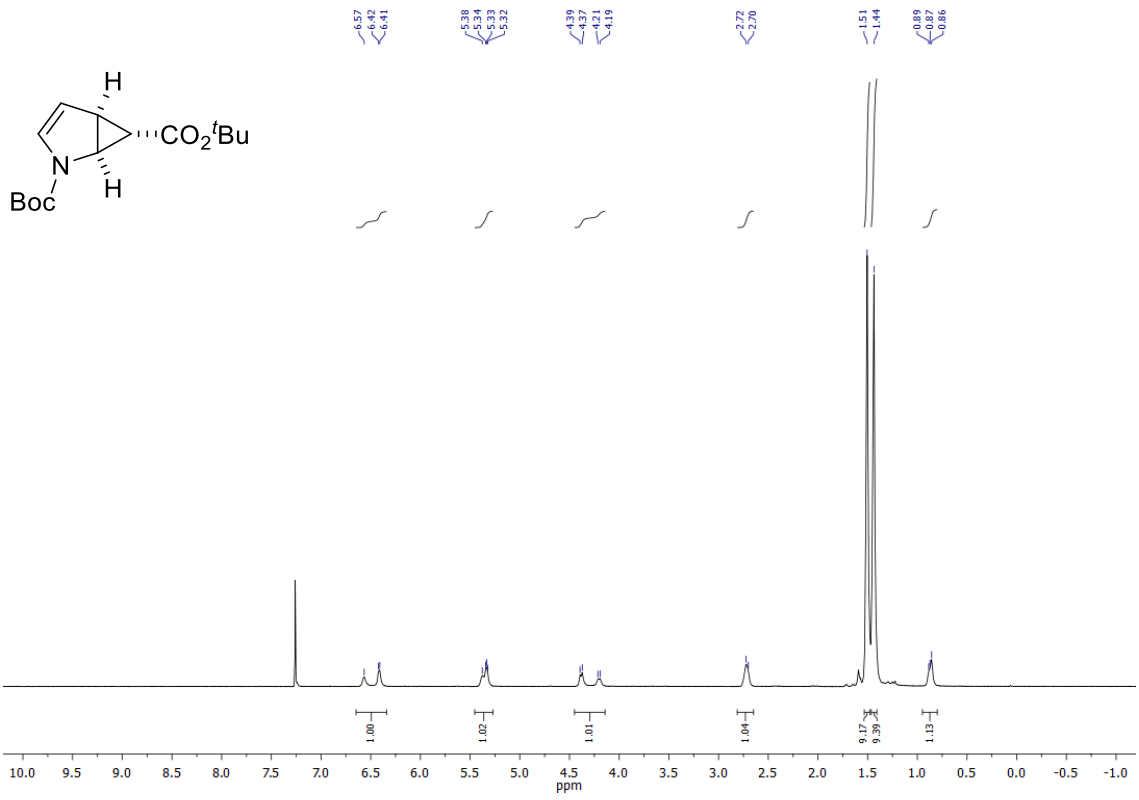
Compound **102d**: ^{1}H-NMR (400 MHz, $CDCl_3$)



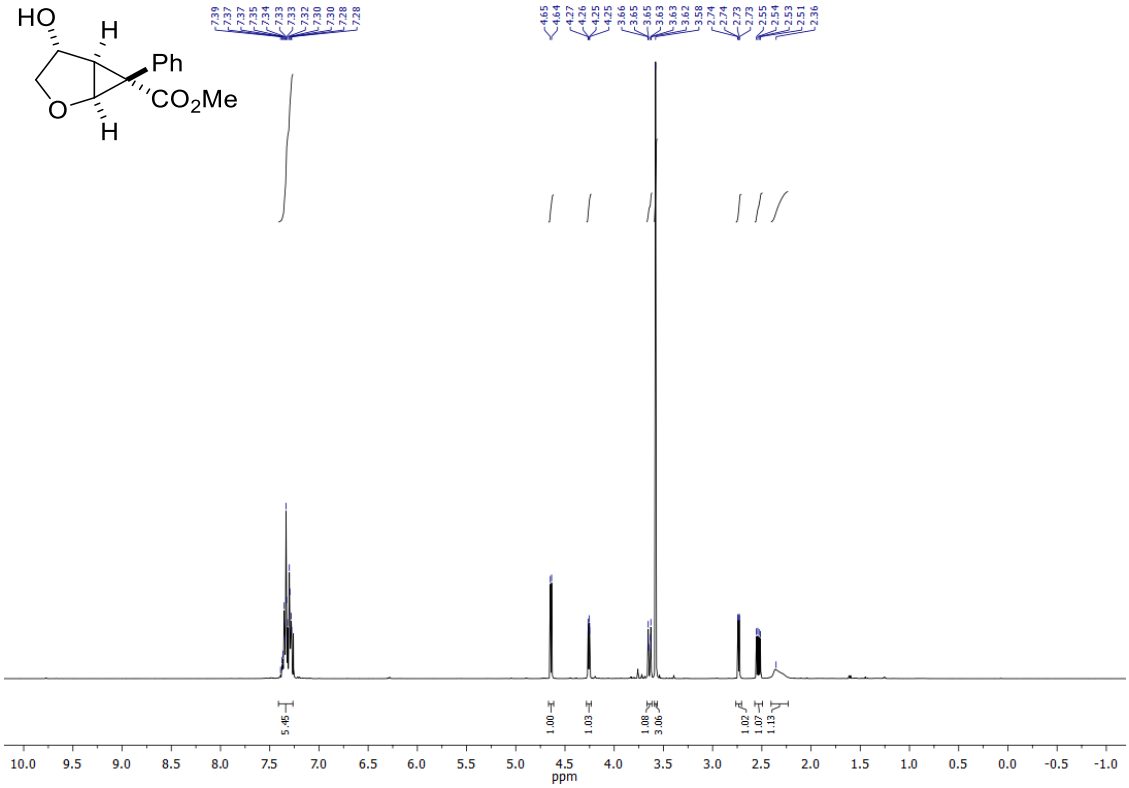
Compound **102e**: ^{1}H-NMR (400 MHz, $CDCl_3$)

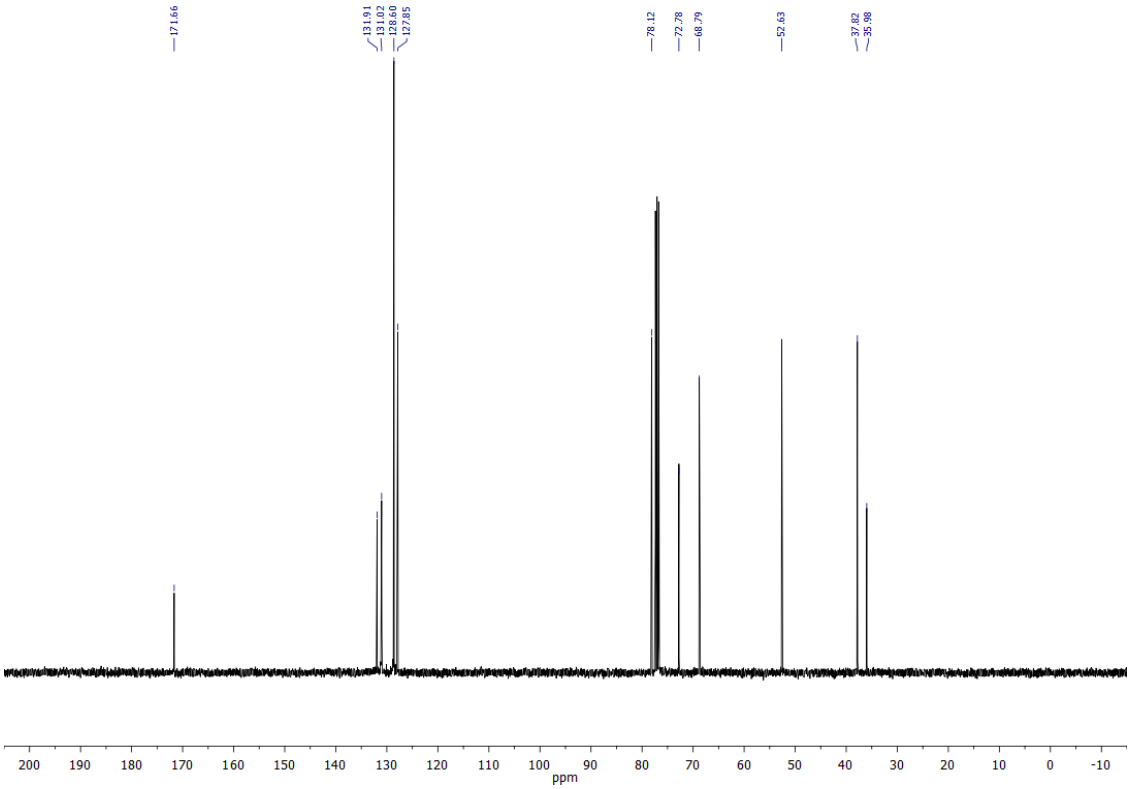


Compound **102f**: ^{1}H-NMR (300 MHz, $CDCl_3$)

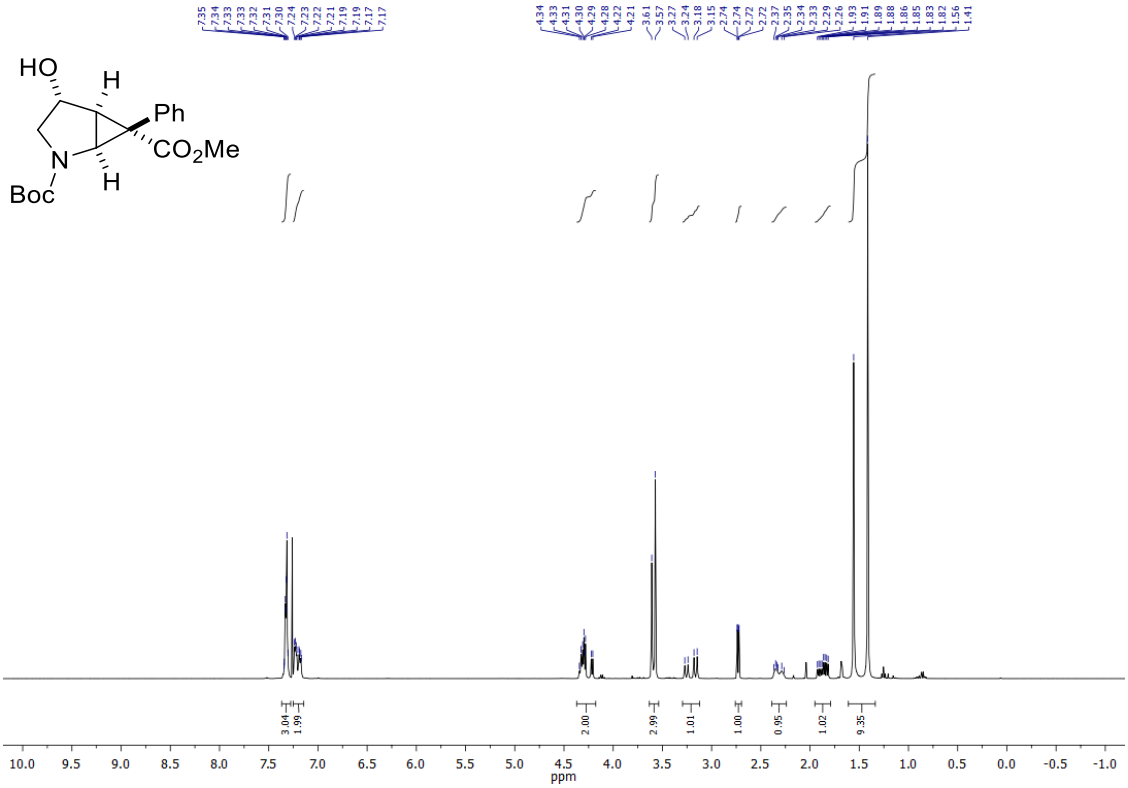


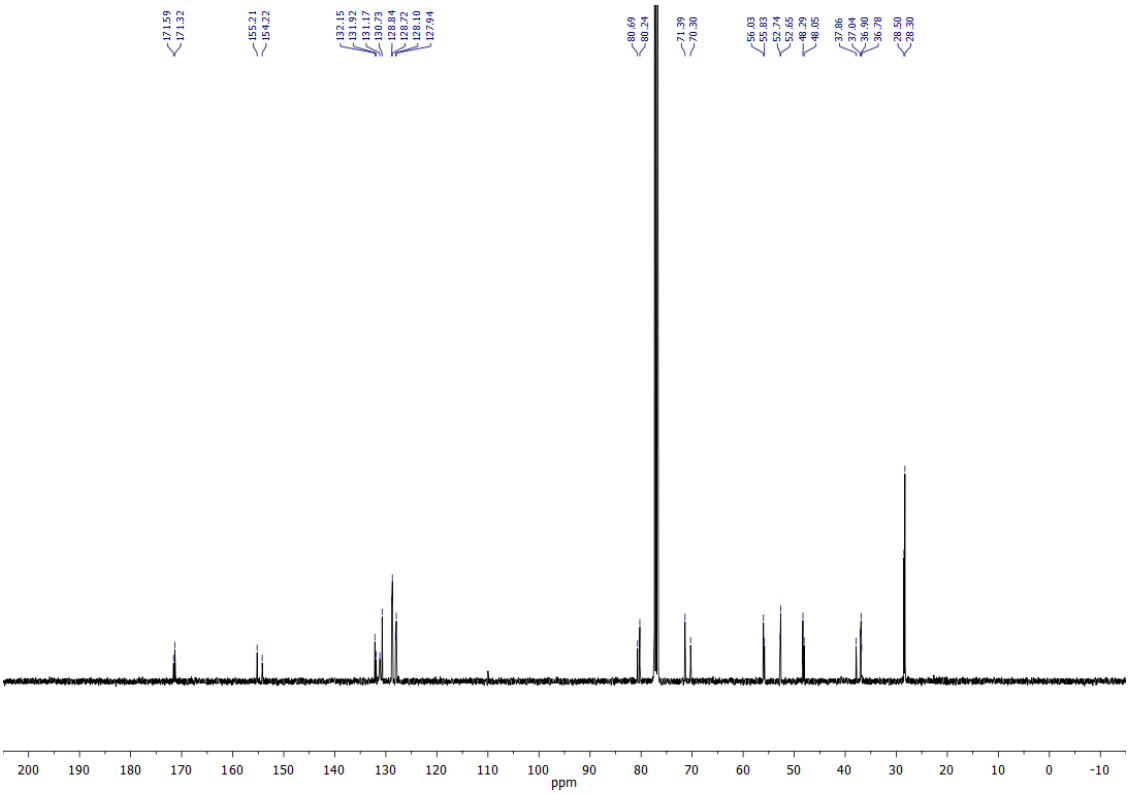
Compound **(*rac*)-103a**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



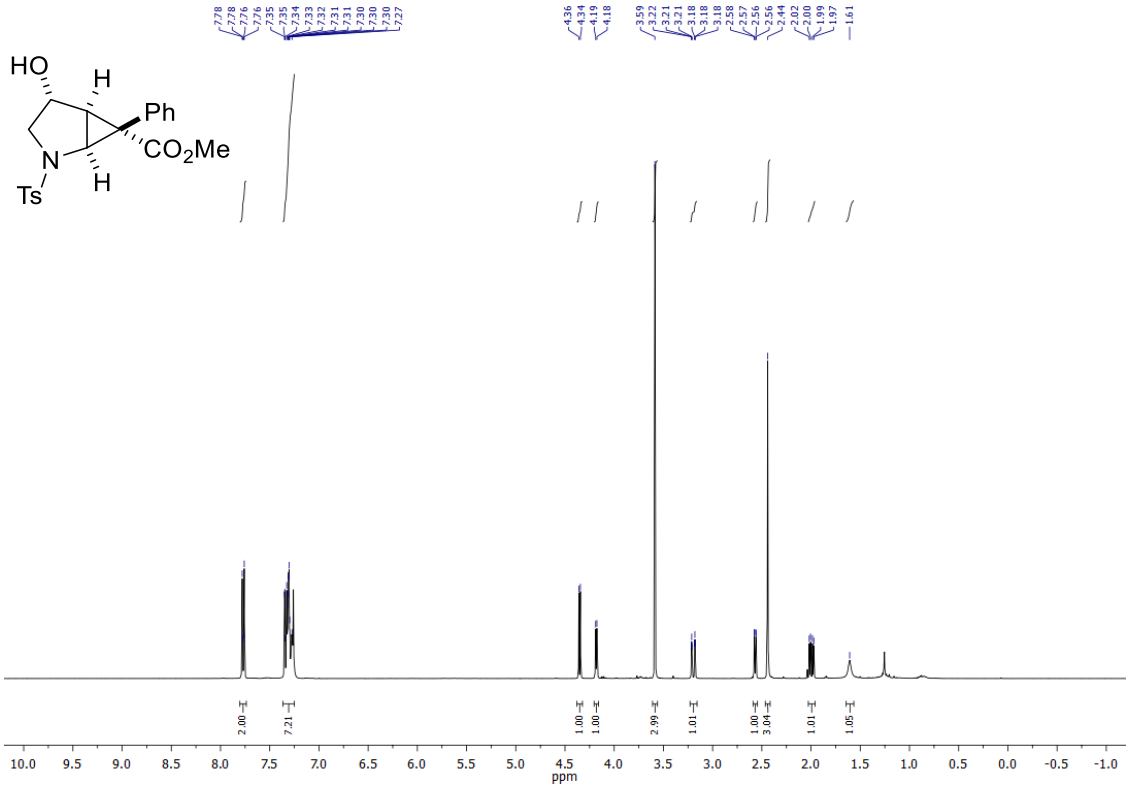


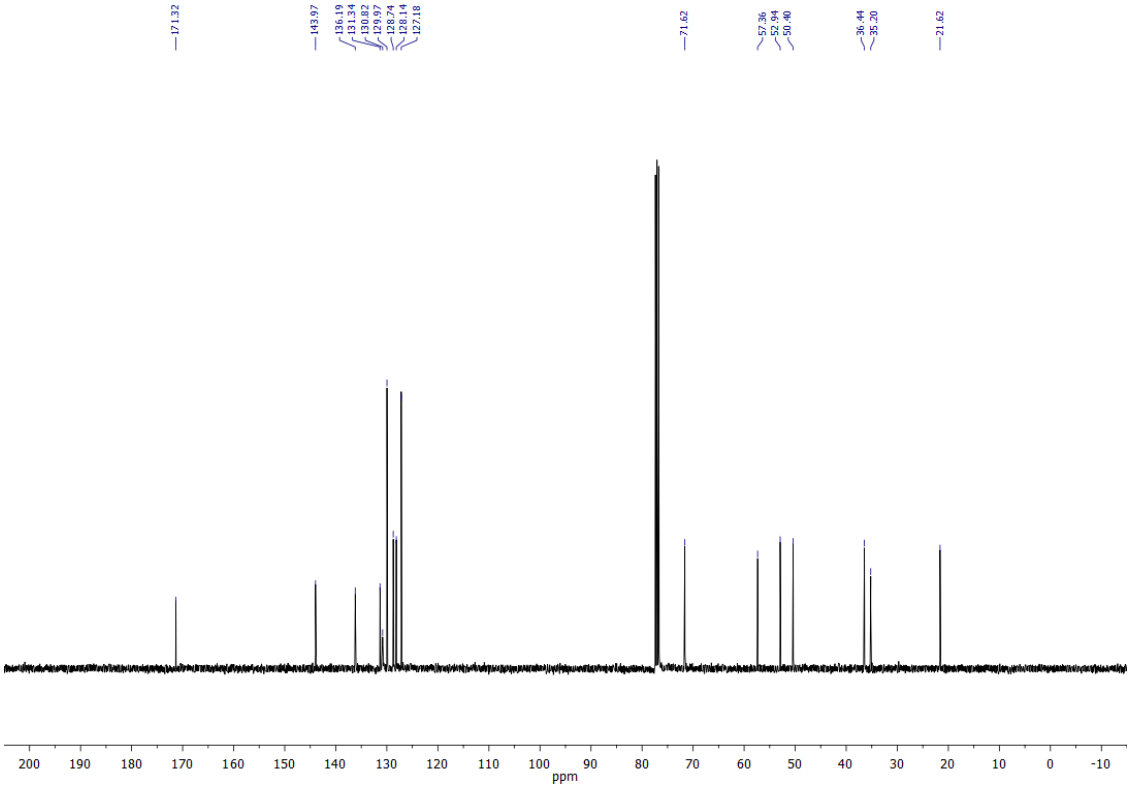
Compound **103b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



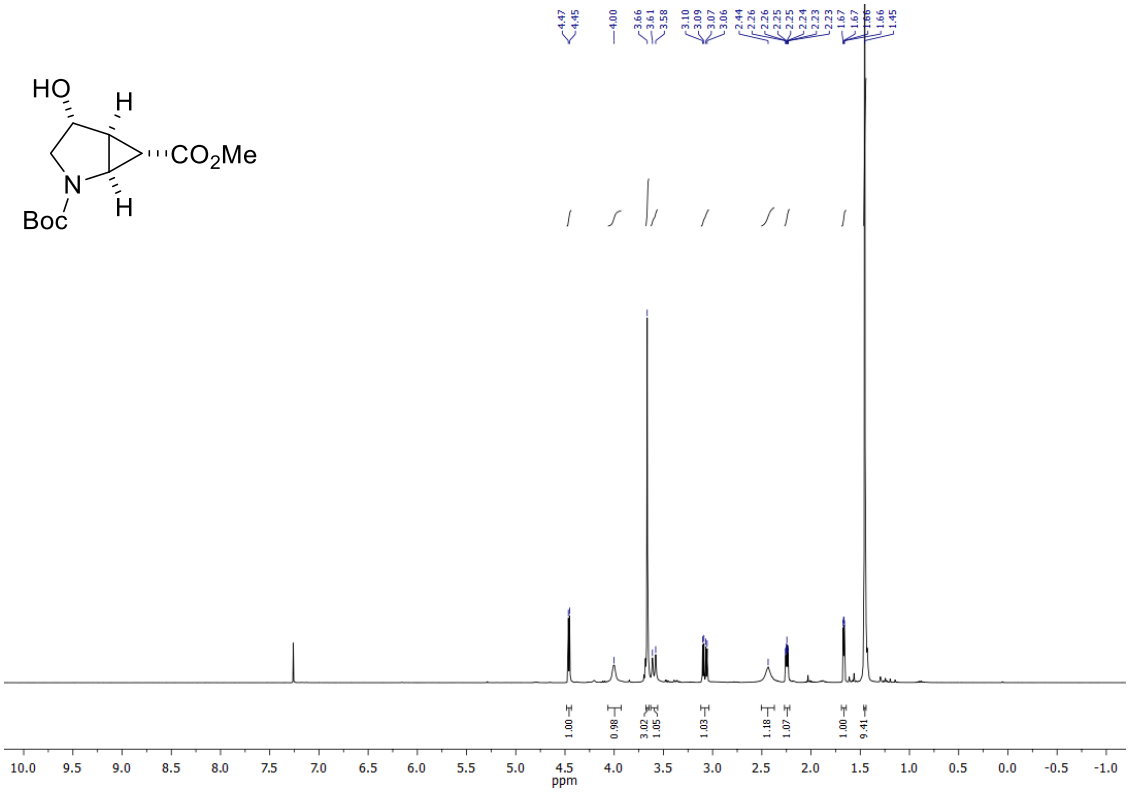


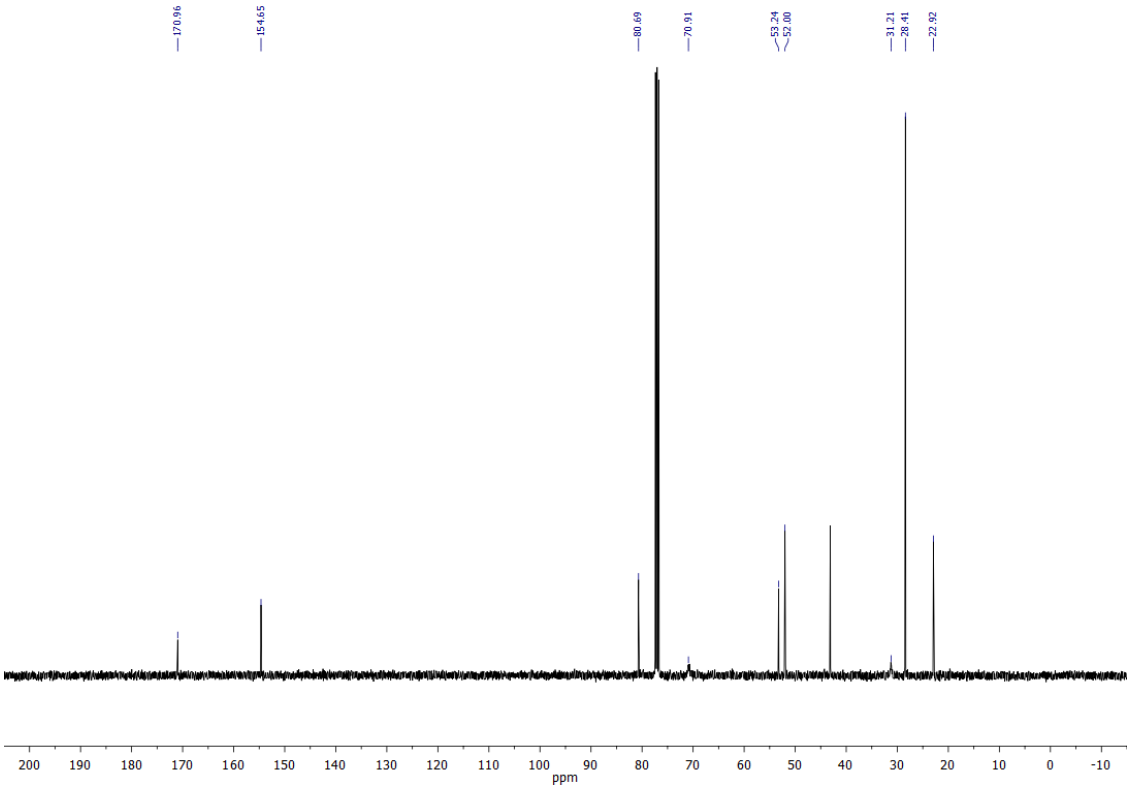
Compound **103c**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



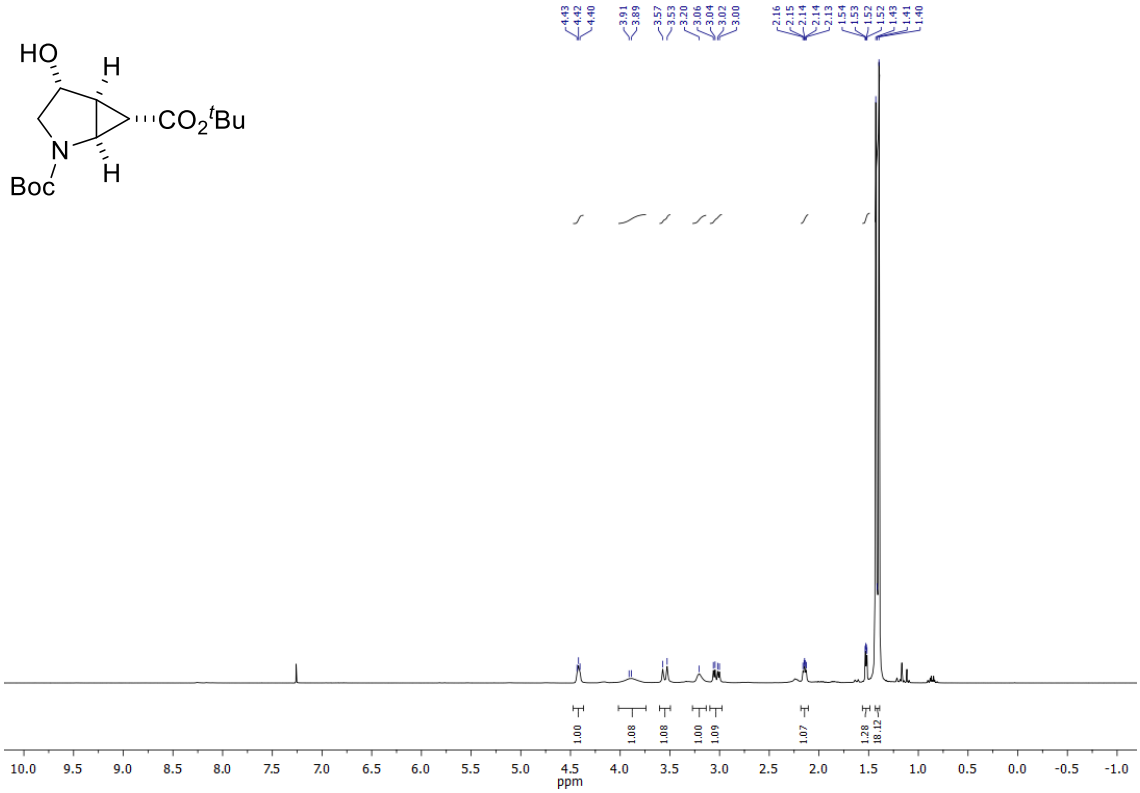


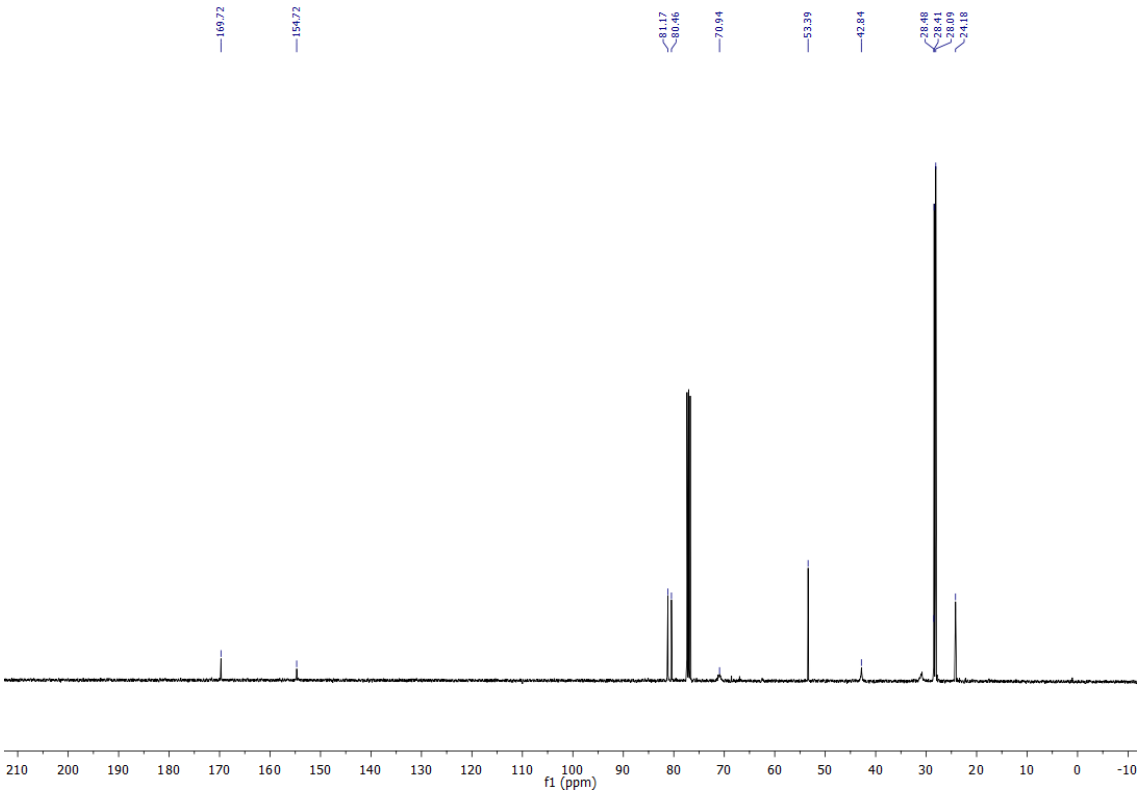
Compound **103d**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



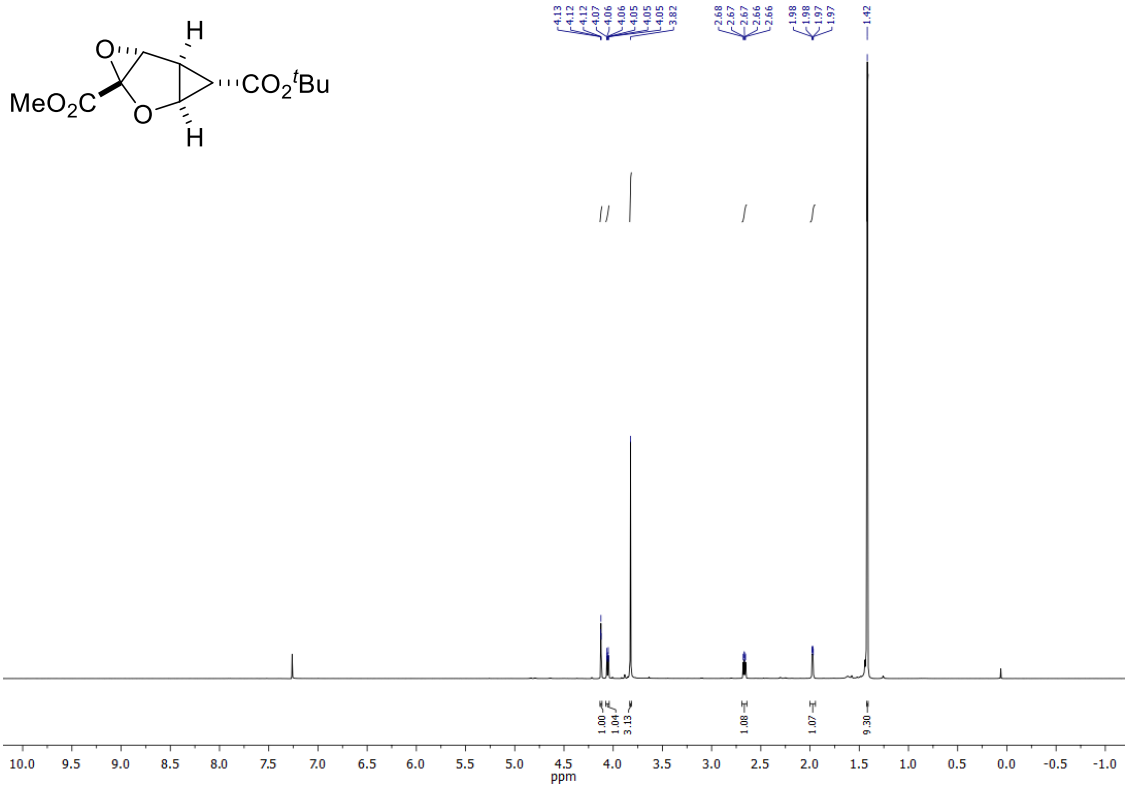


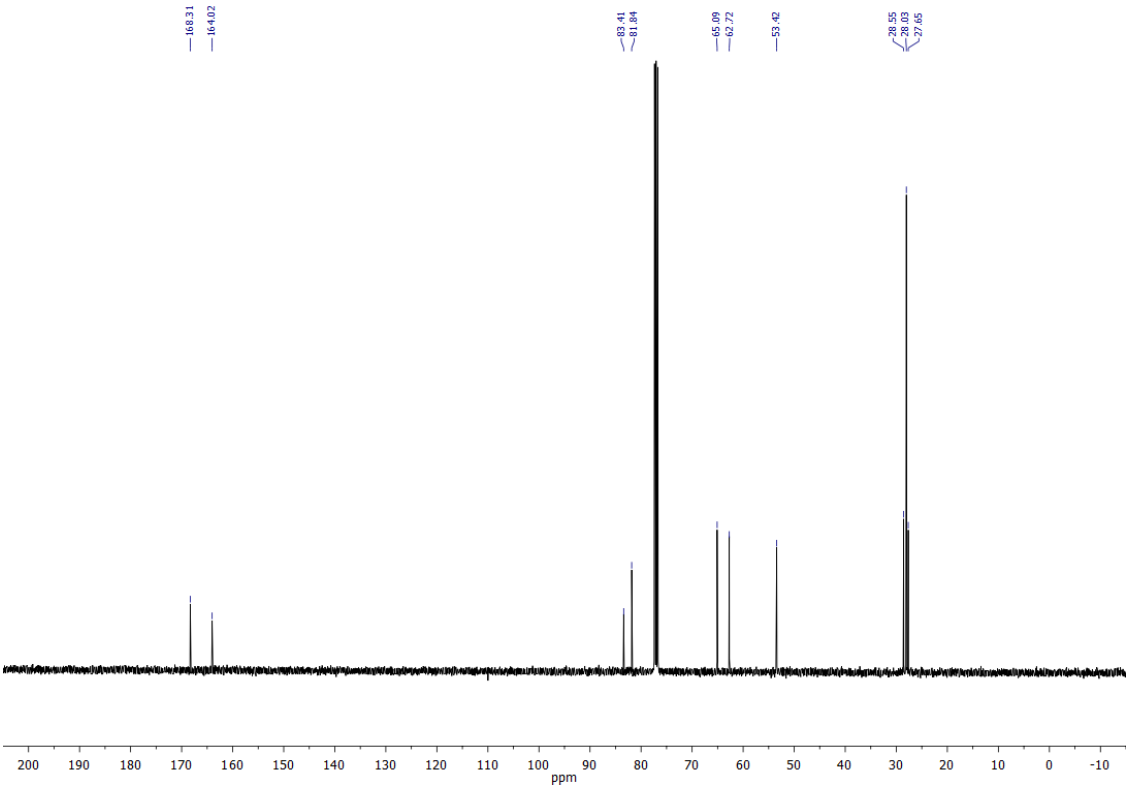
Compound **103e**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



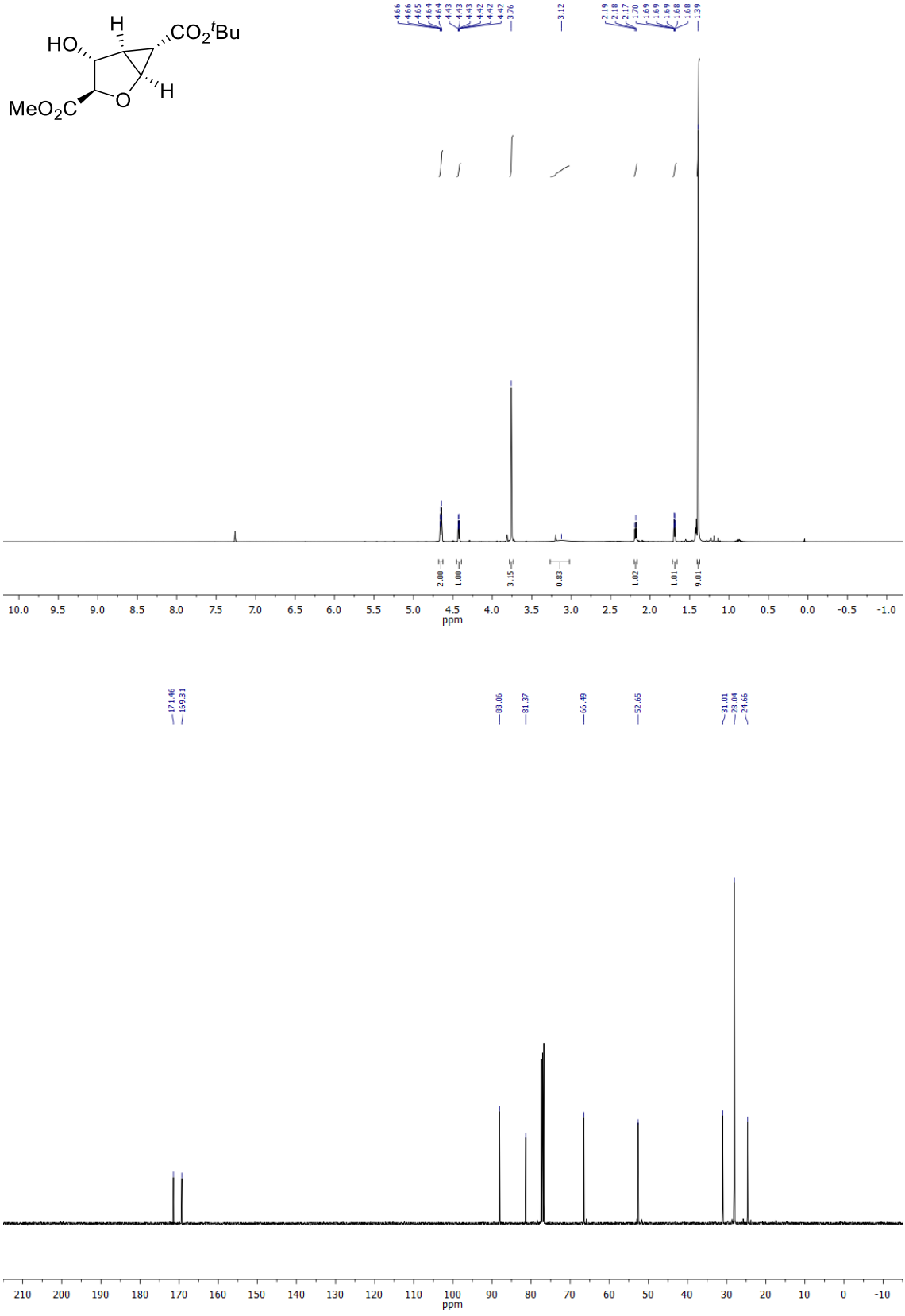


Compound **125**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

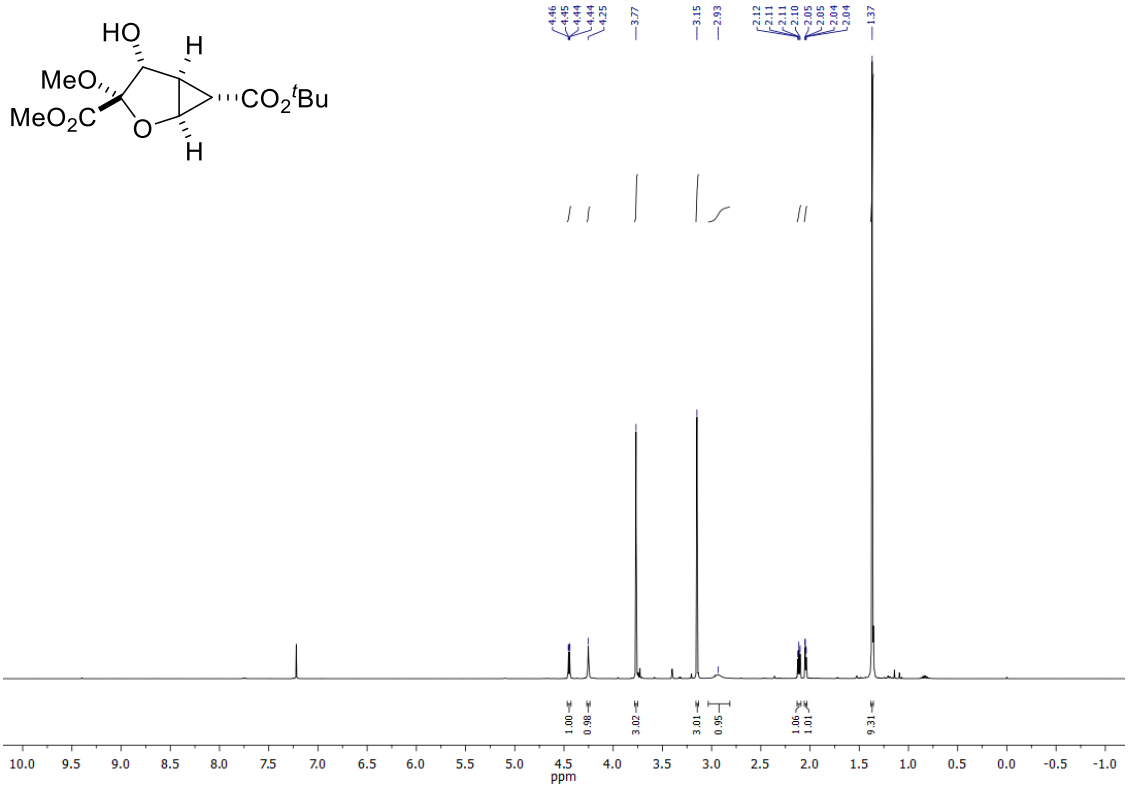


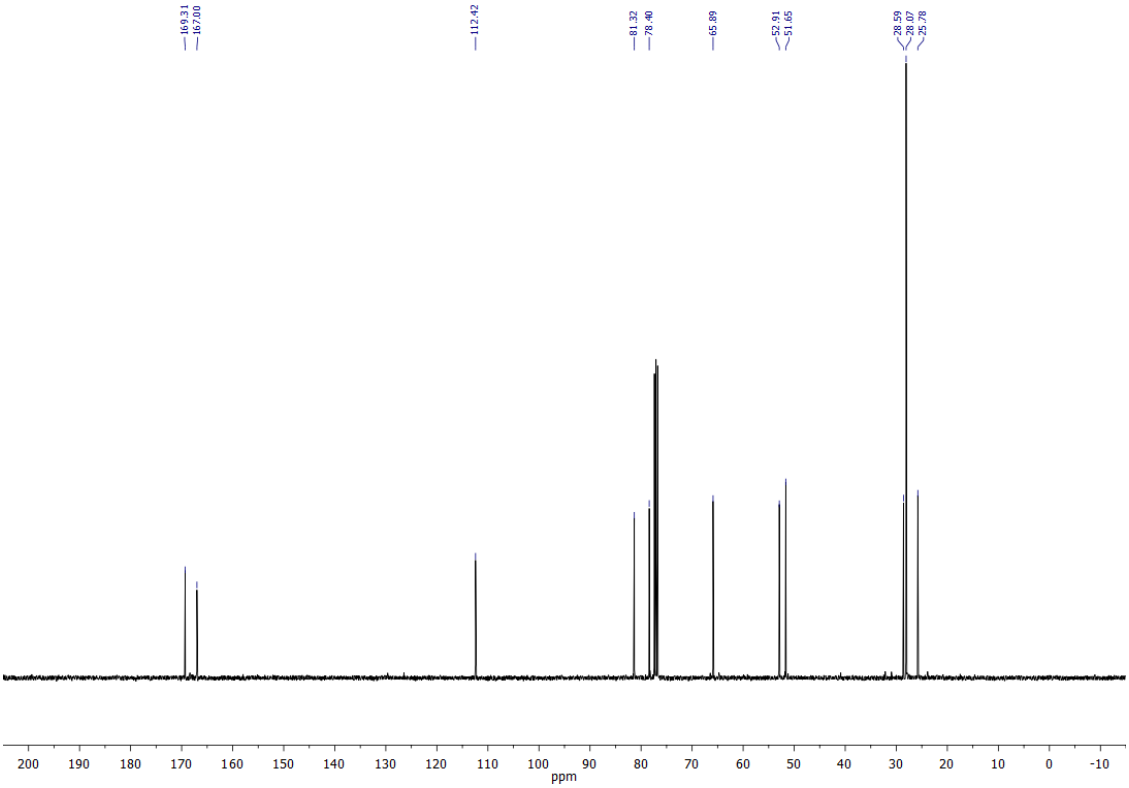


Compound **126a**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

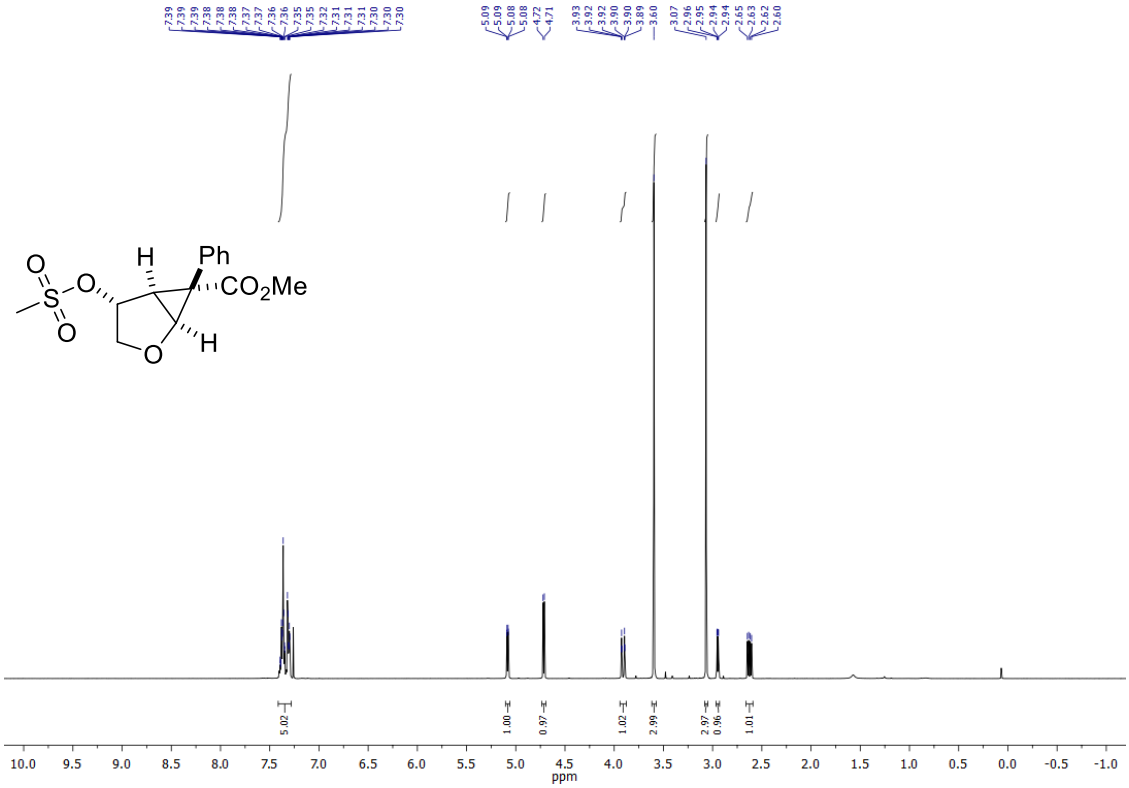


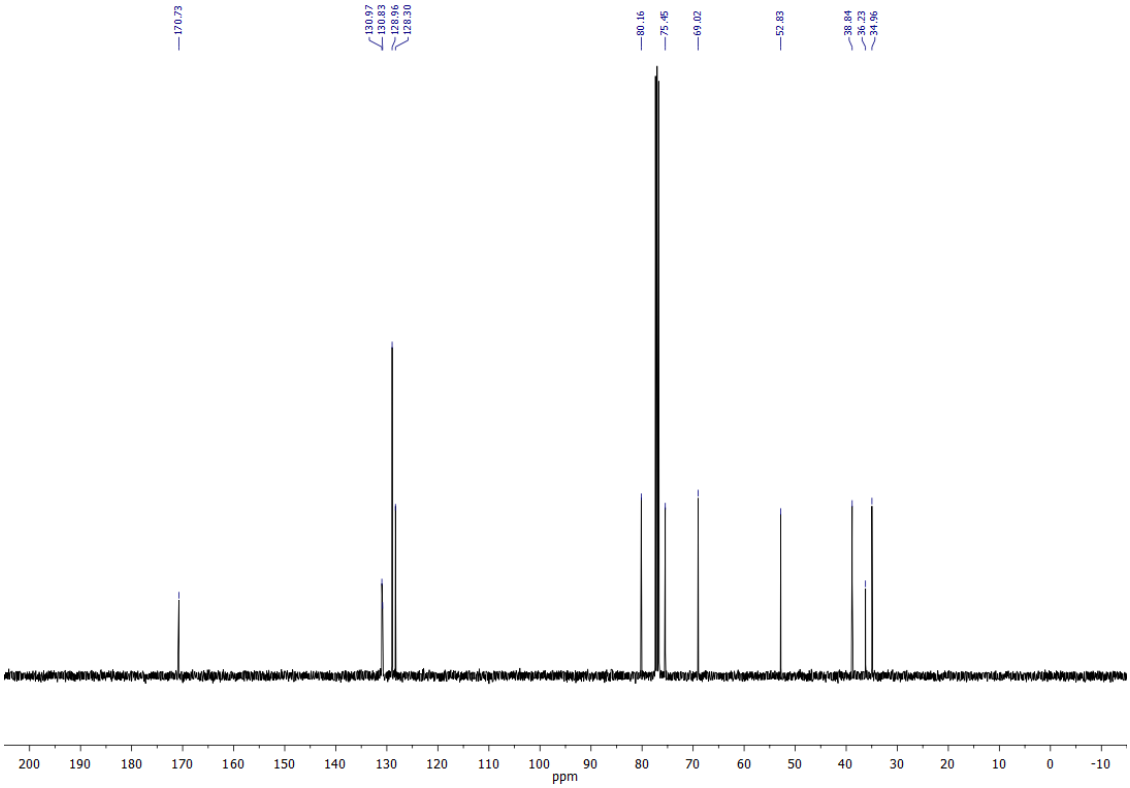
Compound **126b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



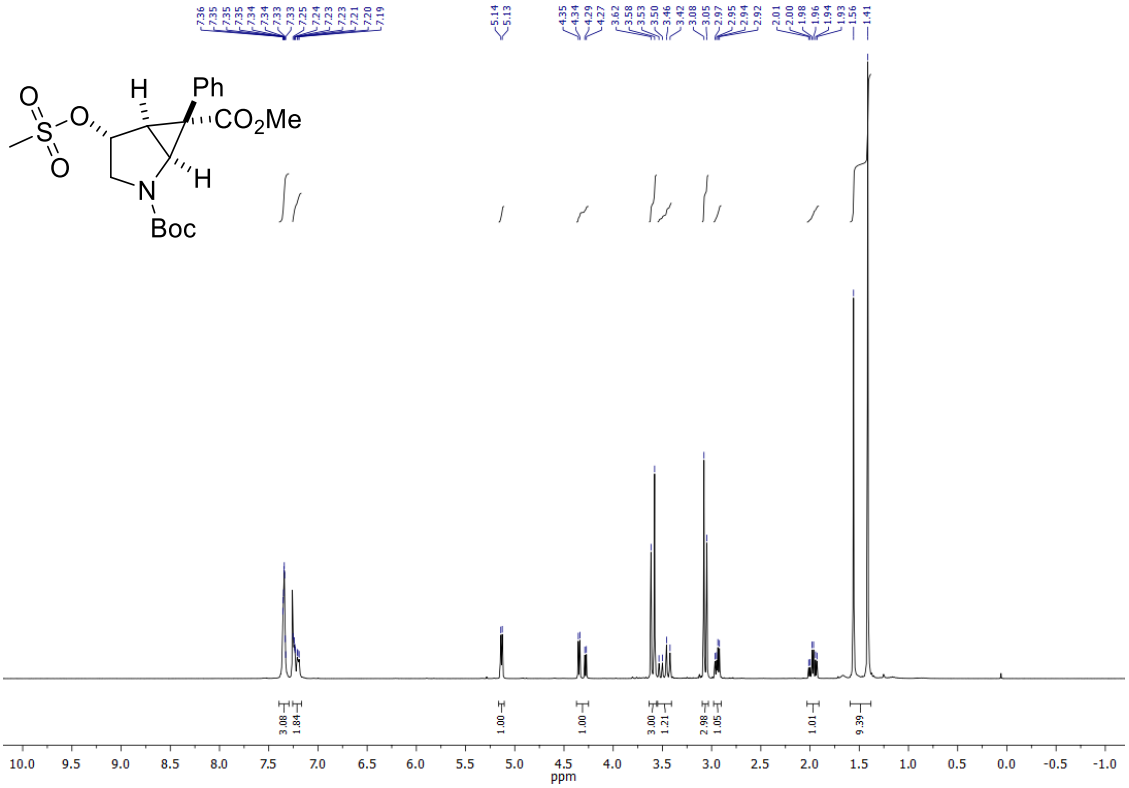


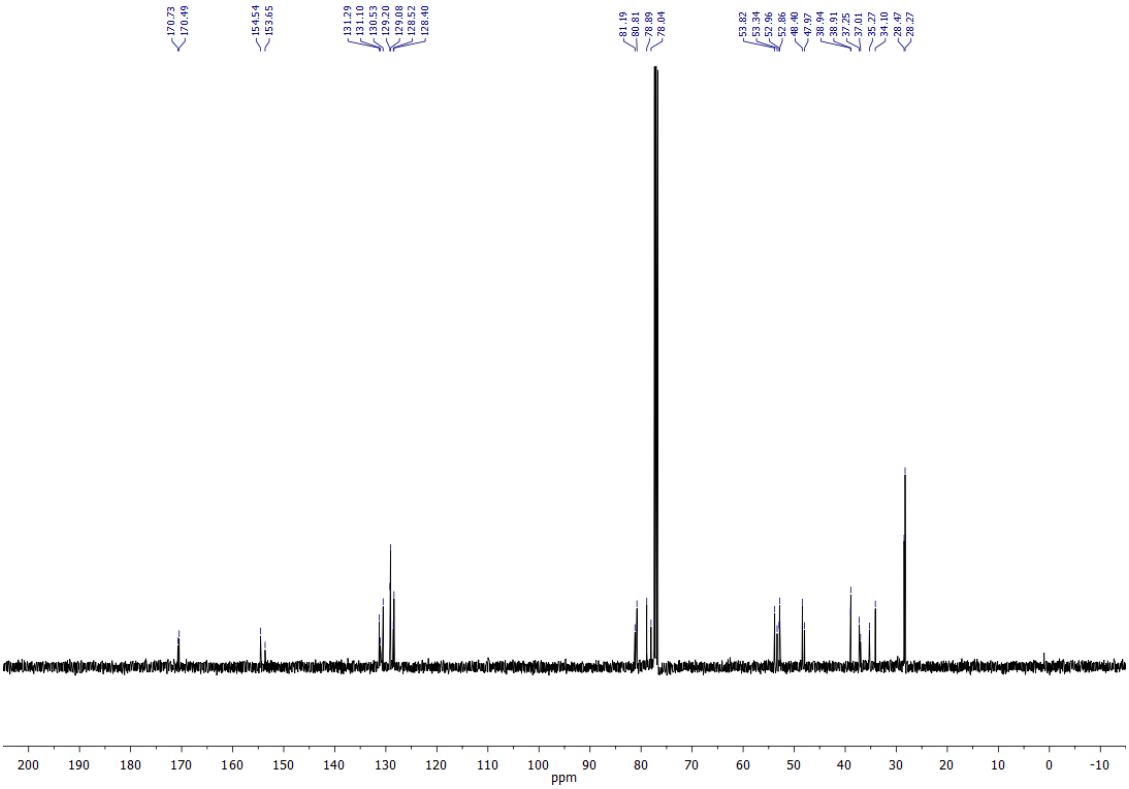
Compound **(*rac*)-140a**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



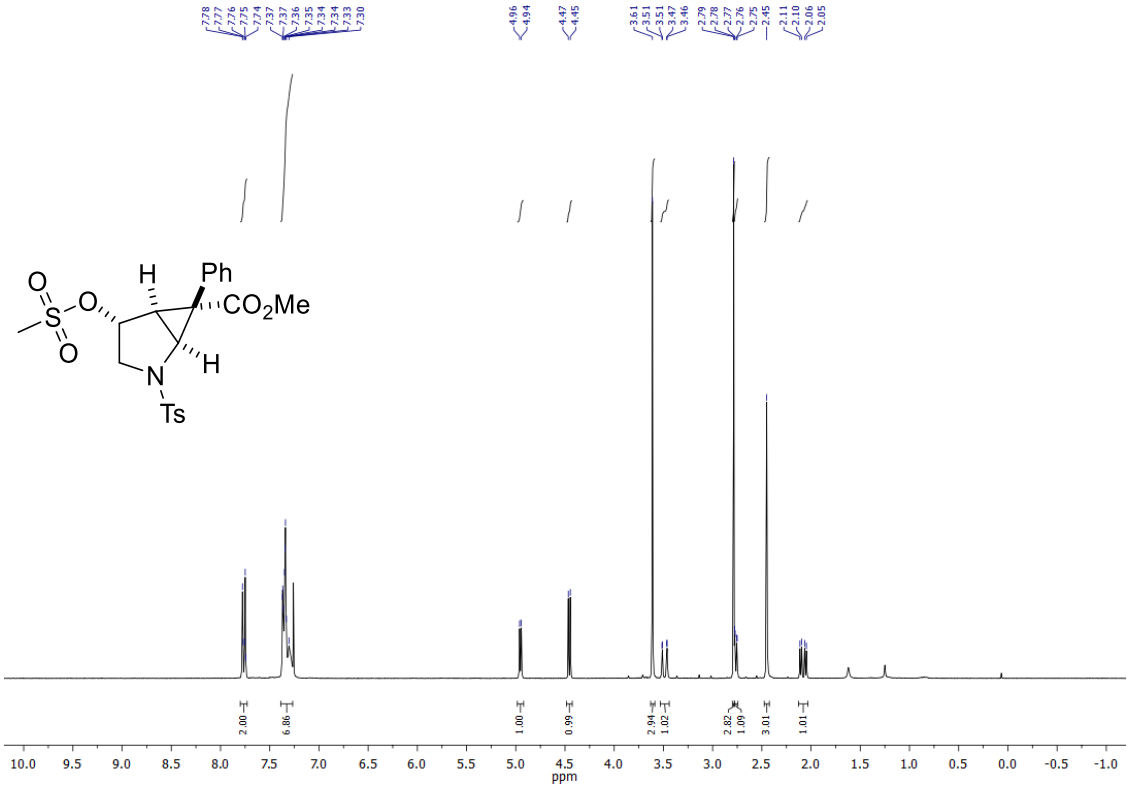


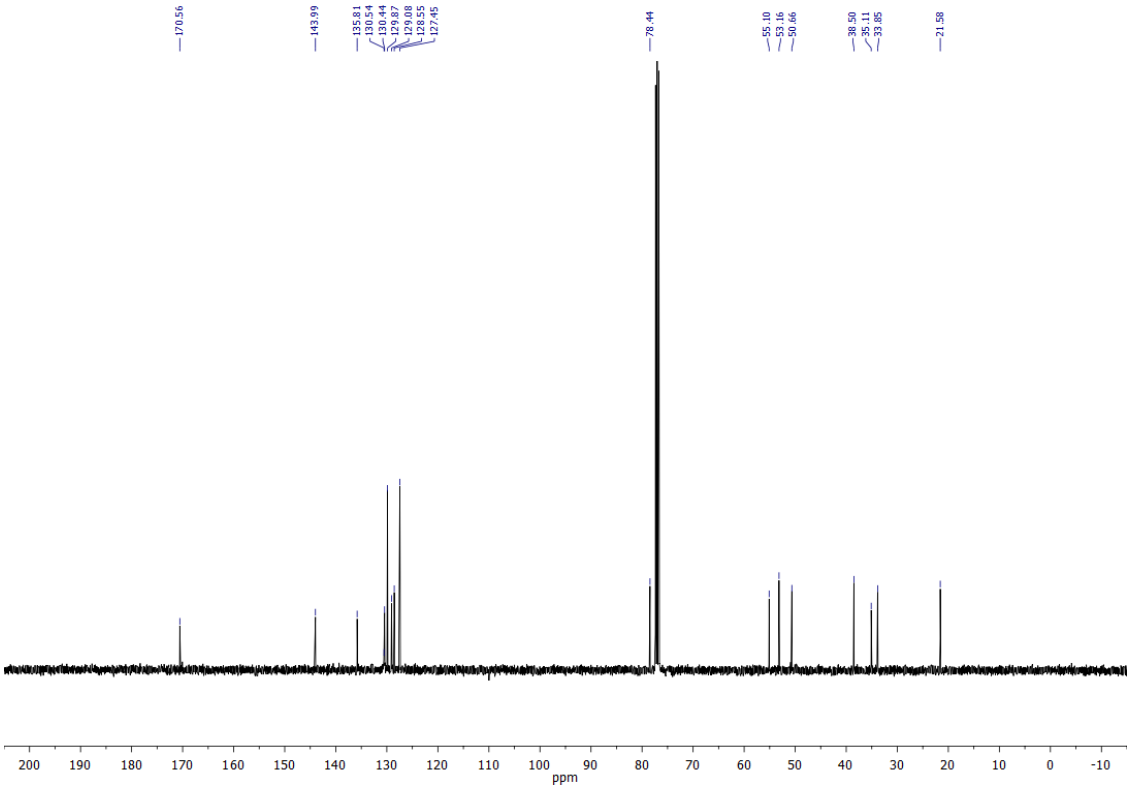
Compound **140b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



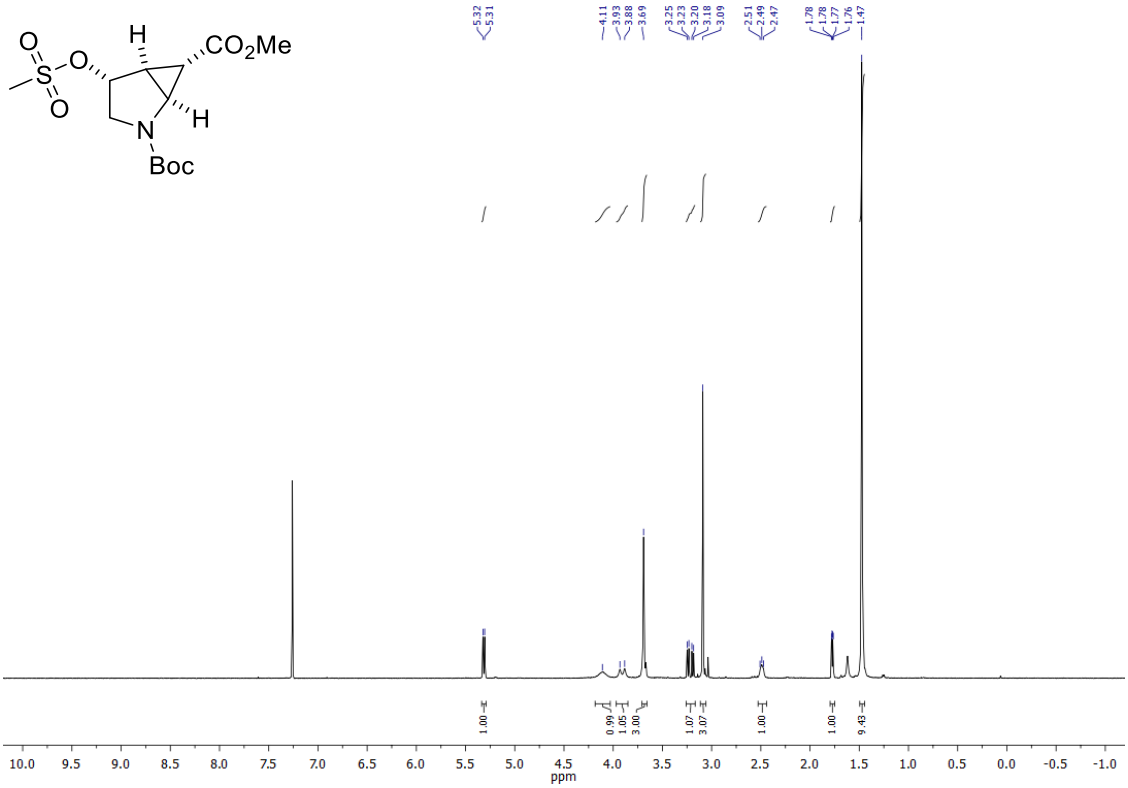


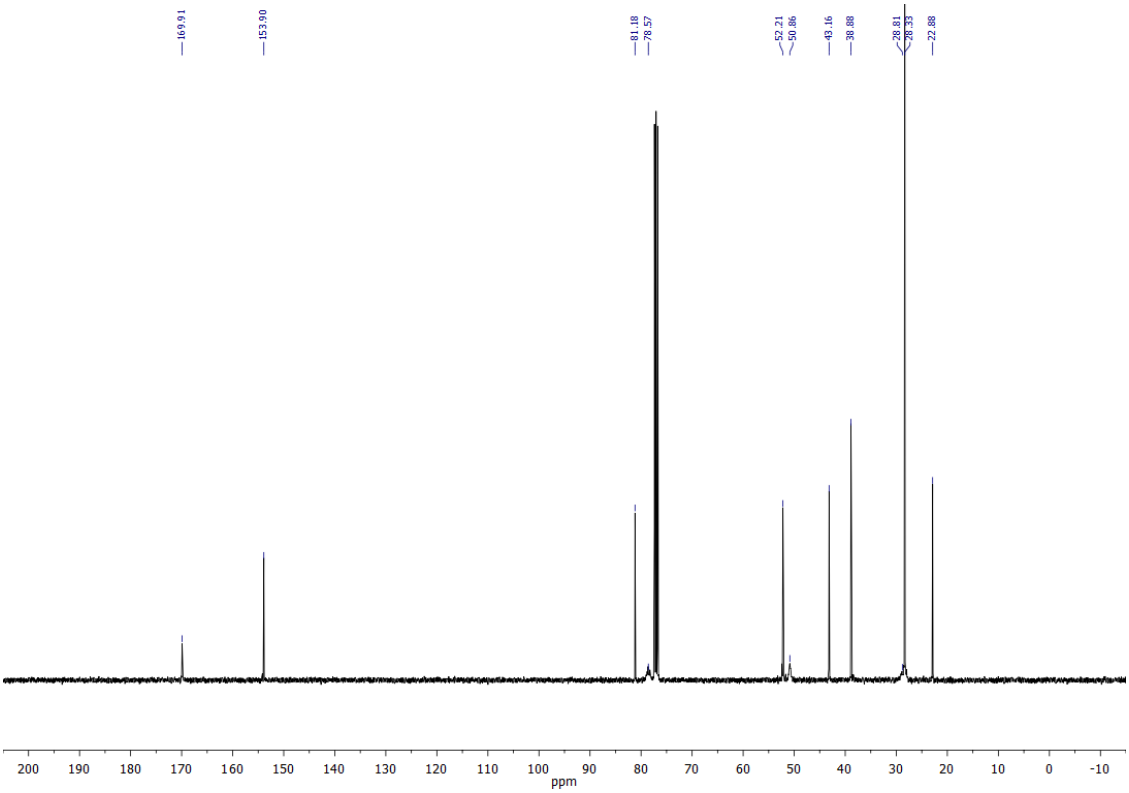
Compound **140c**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



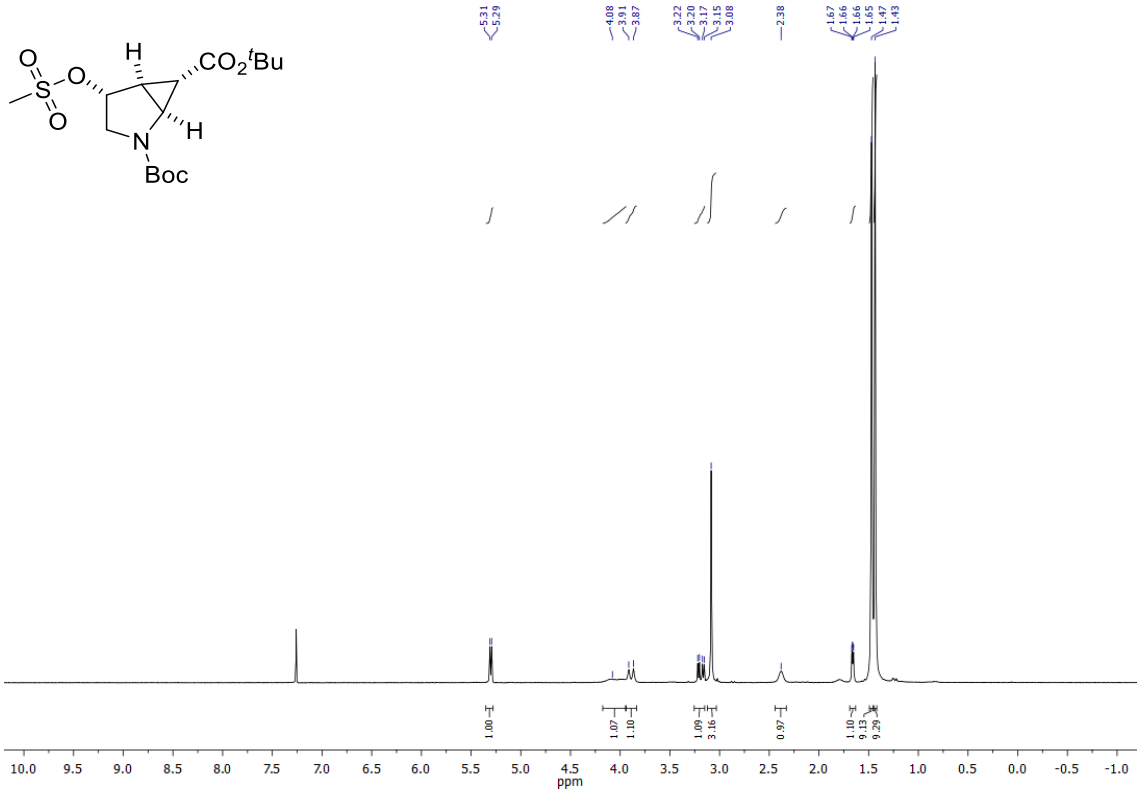


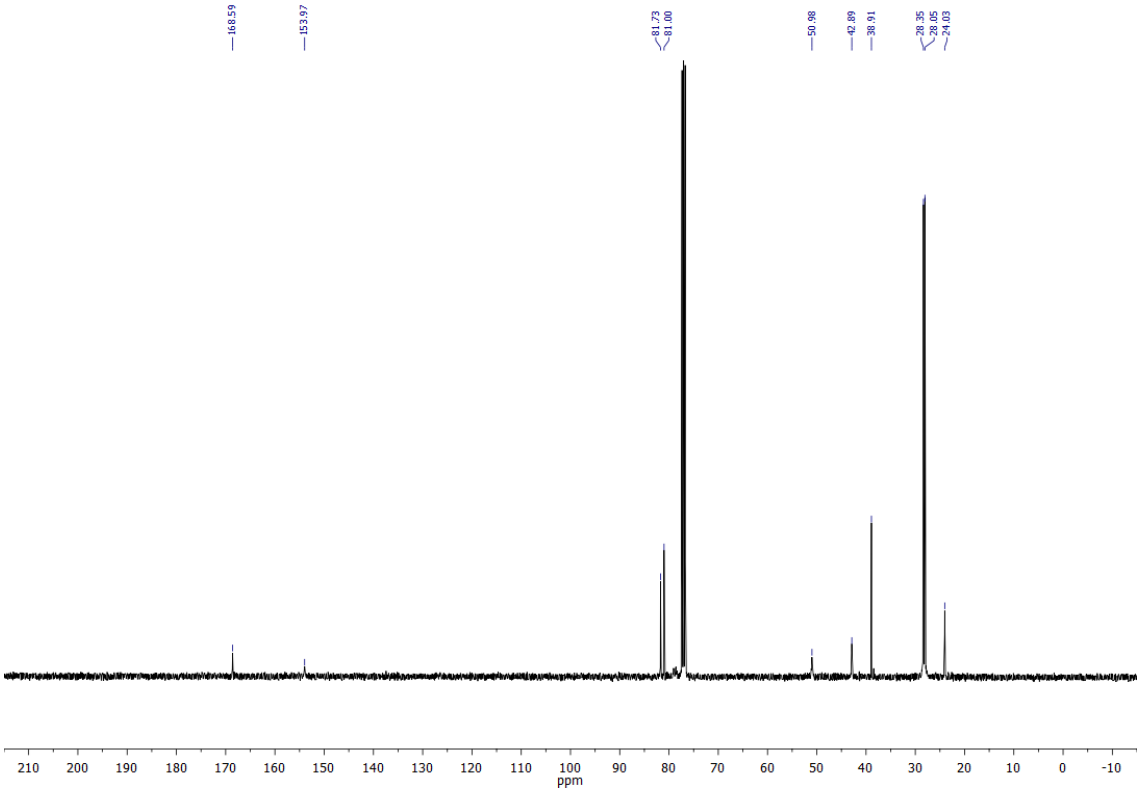
Compound **140d**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



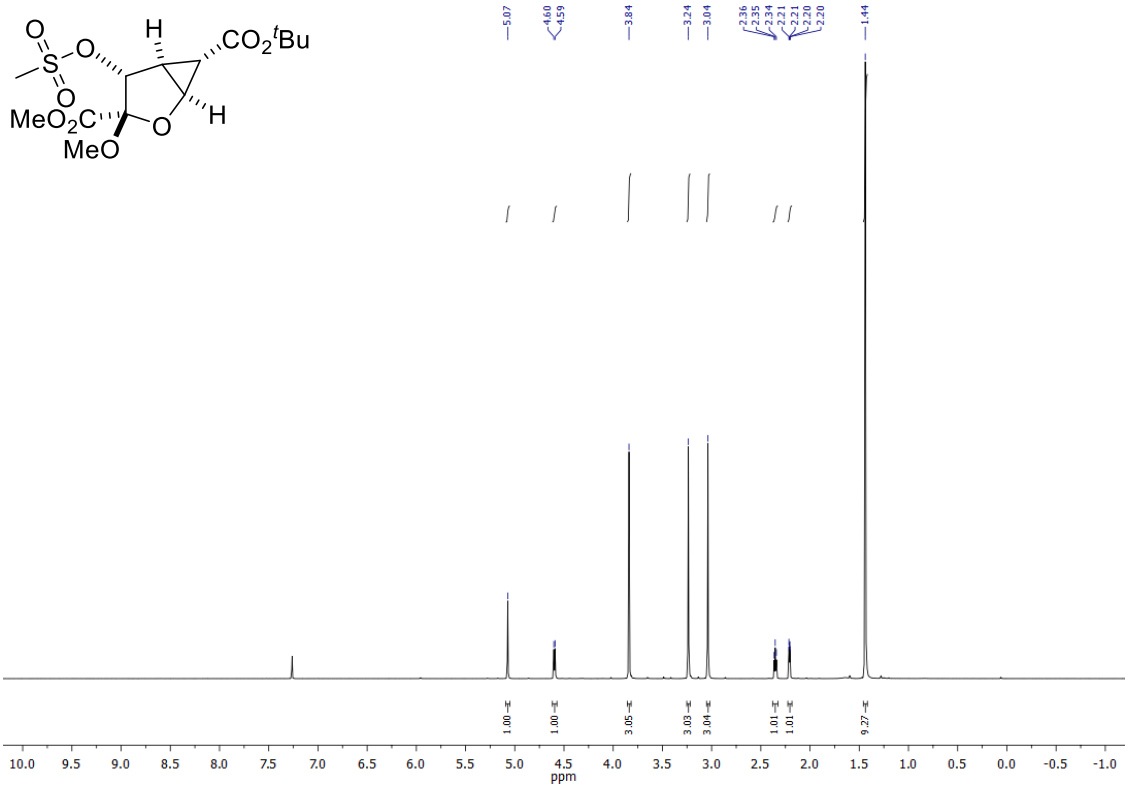


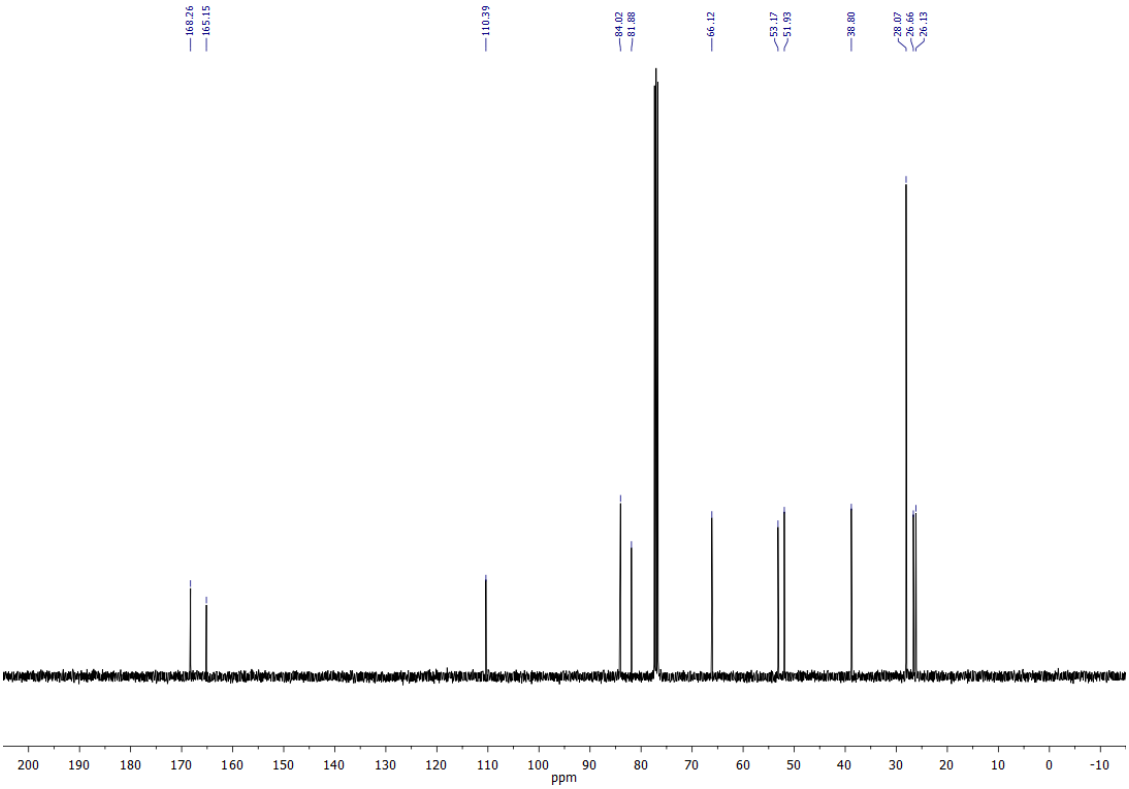
Compound **140e**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



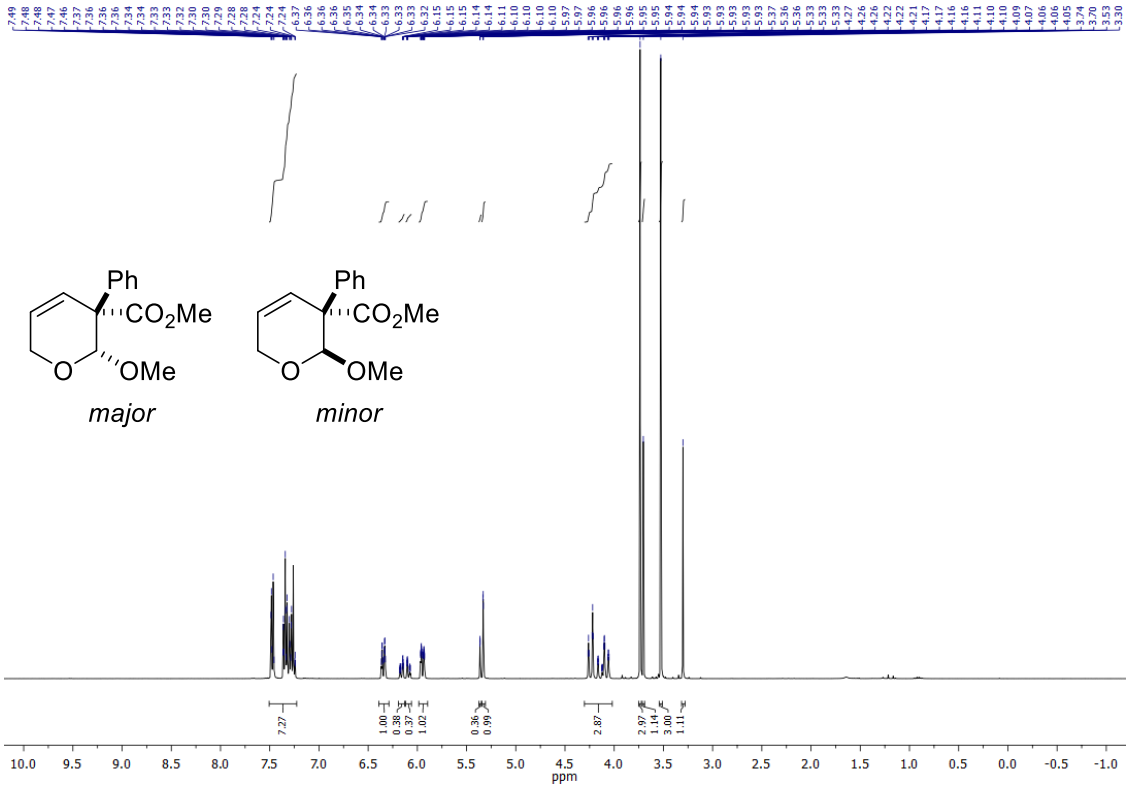


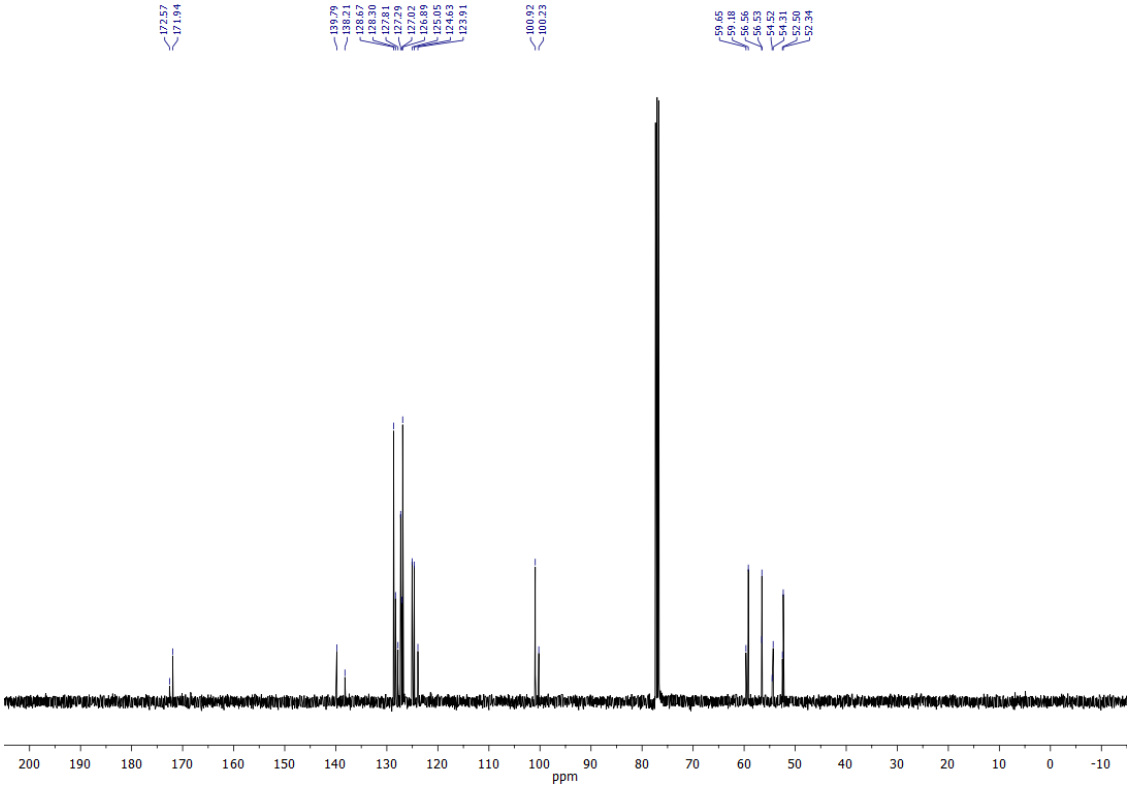
Compound **140f**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



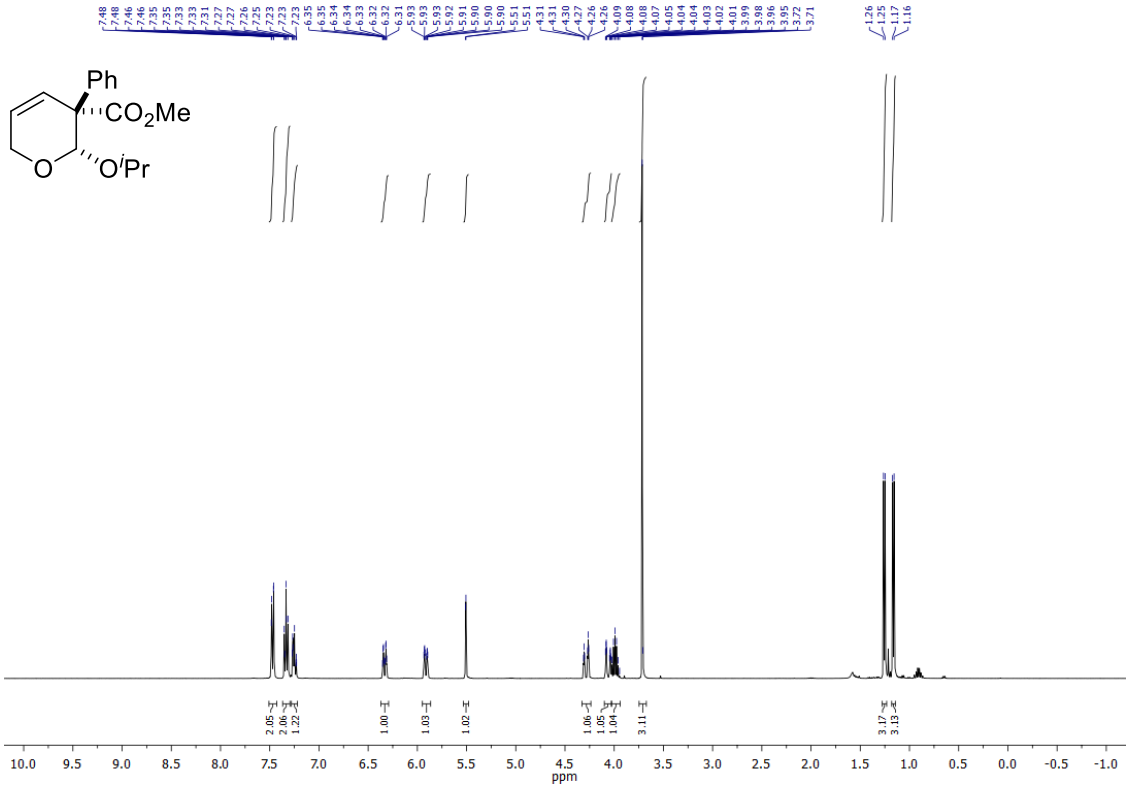


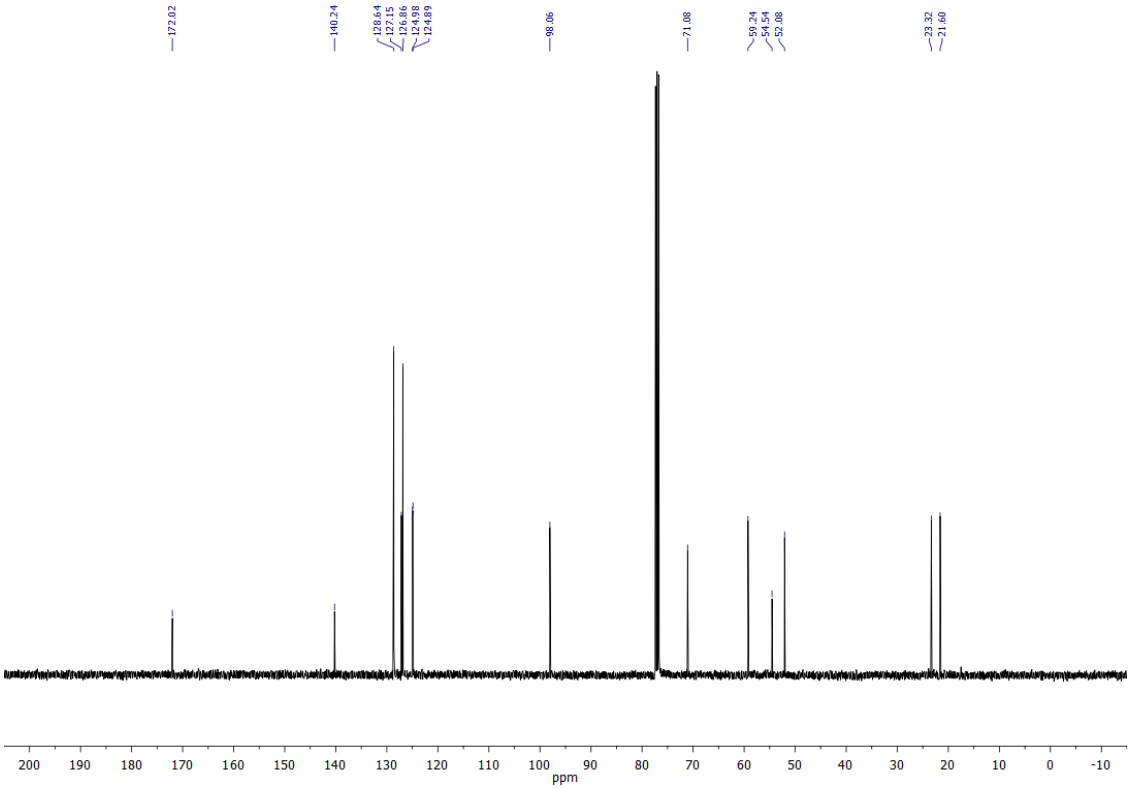
Compound **(*rac*)-105a**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



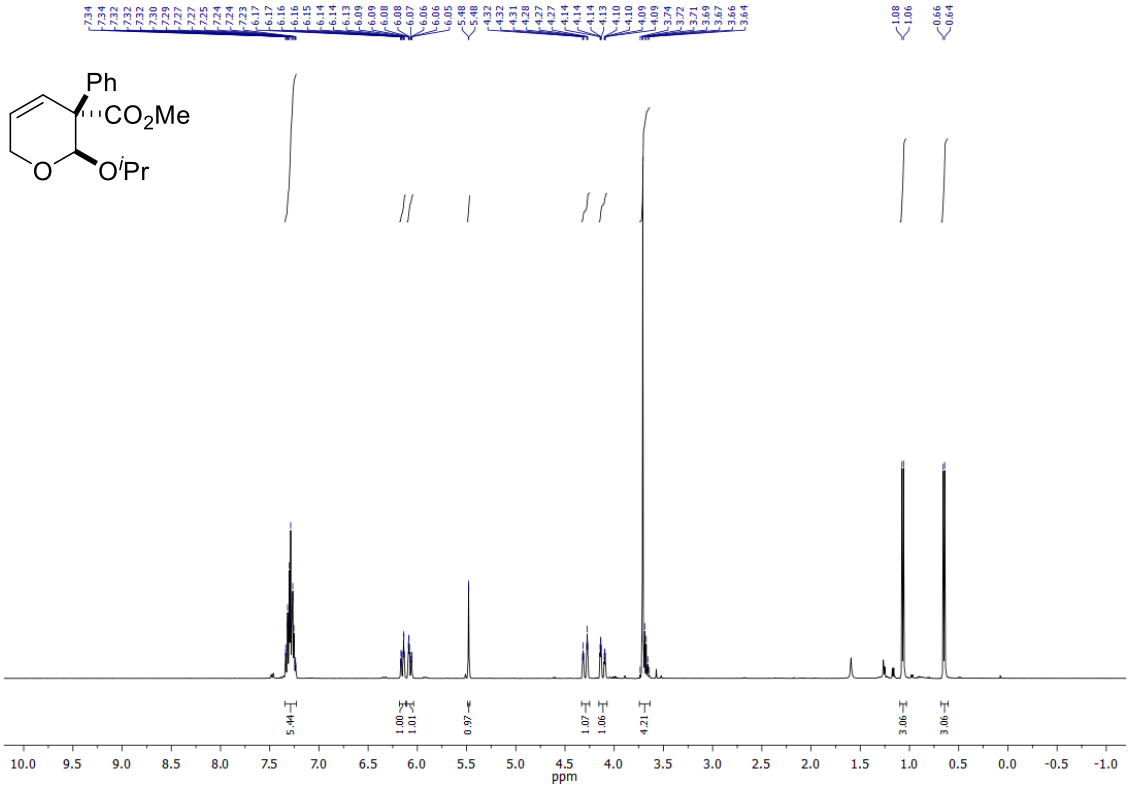


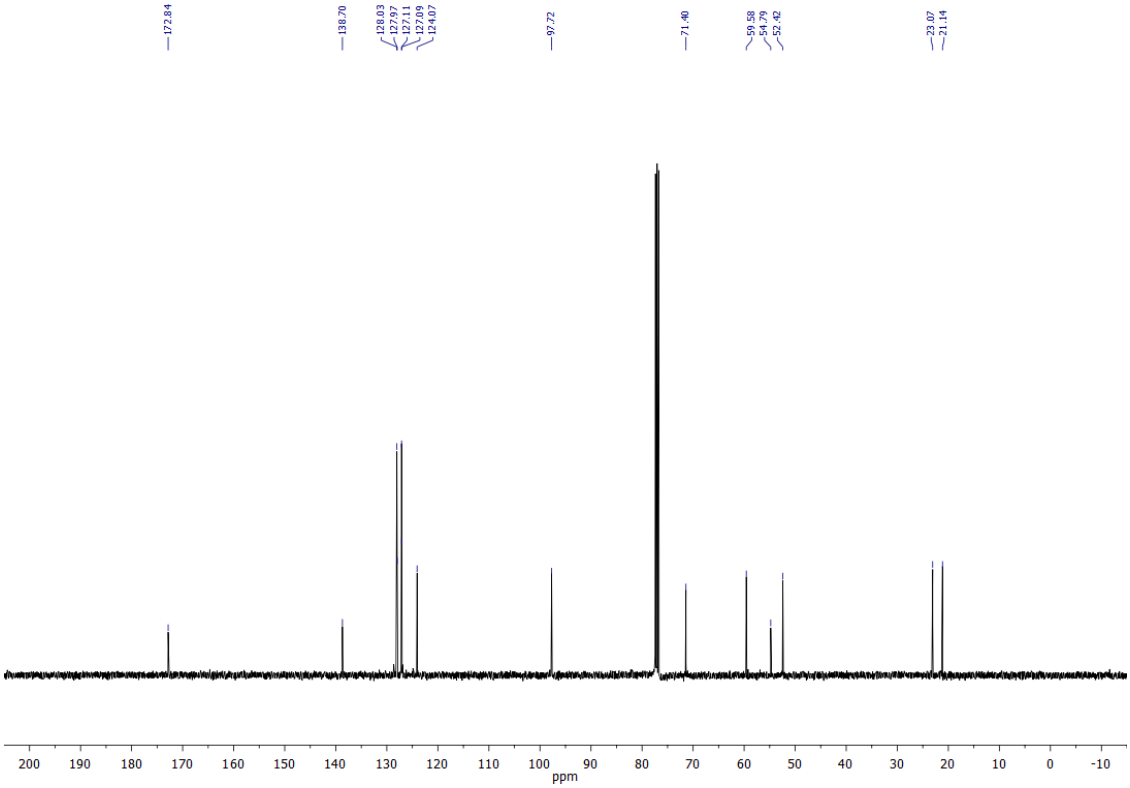
Compound *major*-**105b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



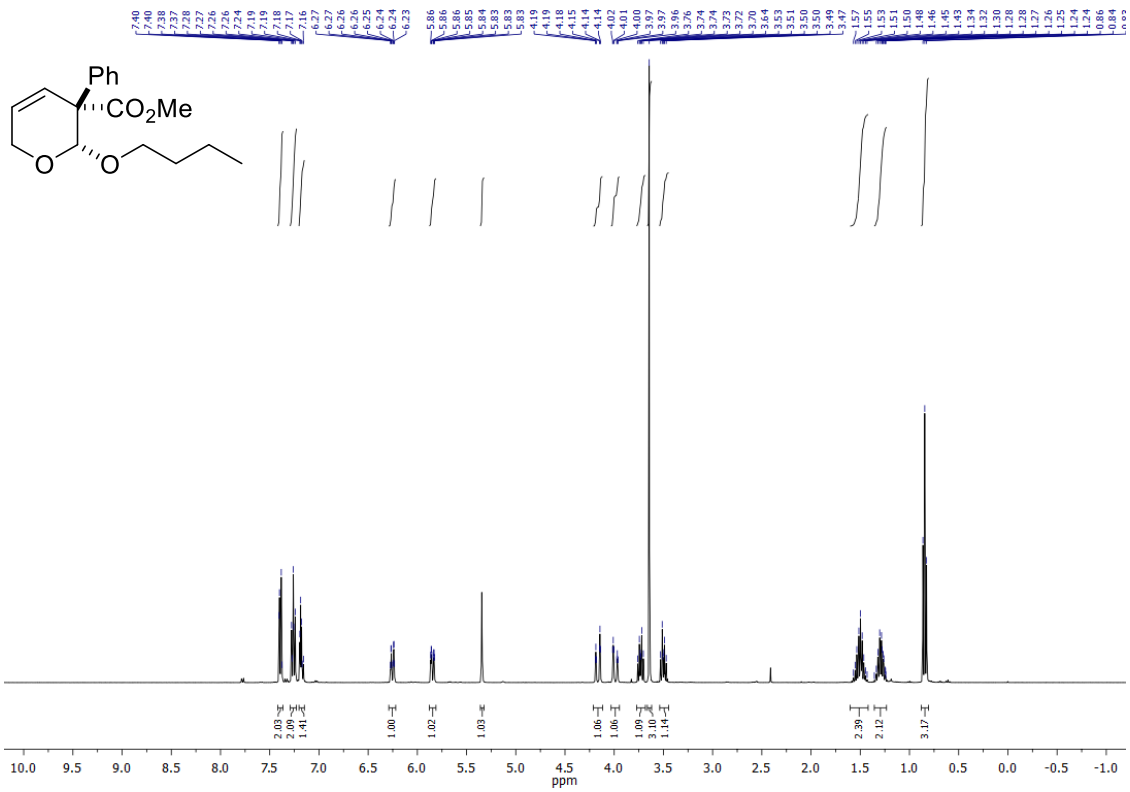


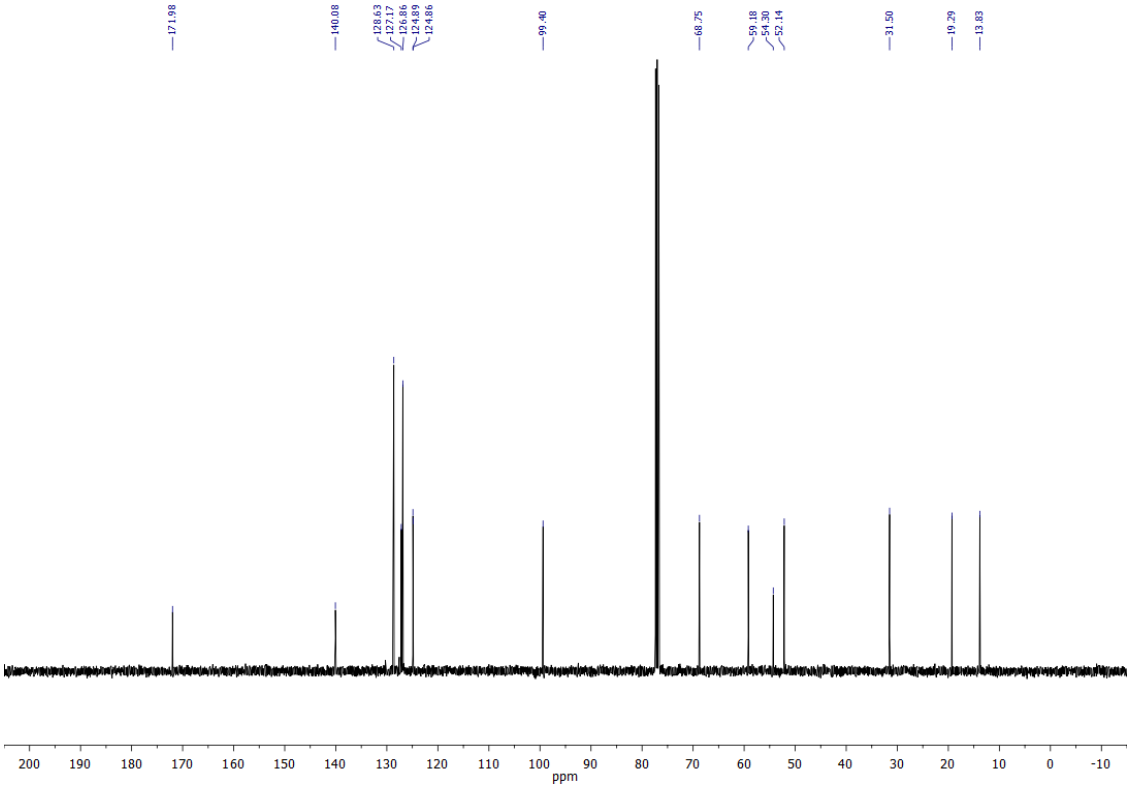
Compound *minor*-**105b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



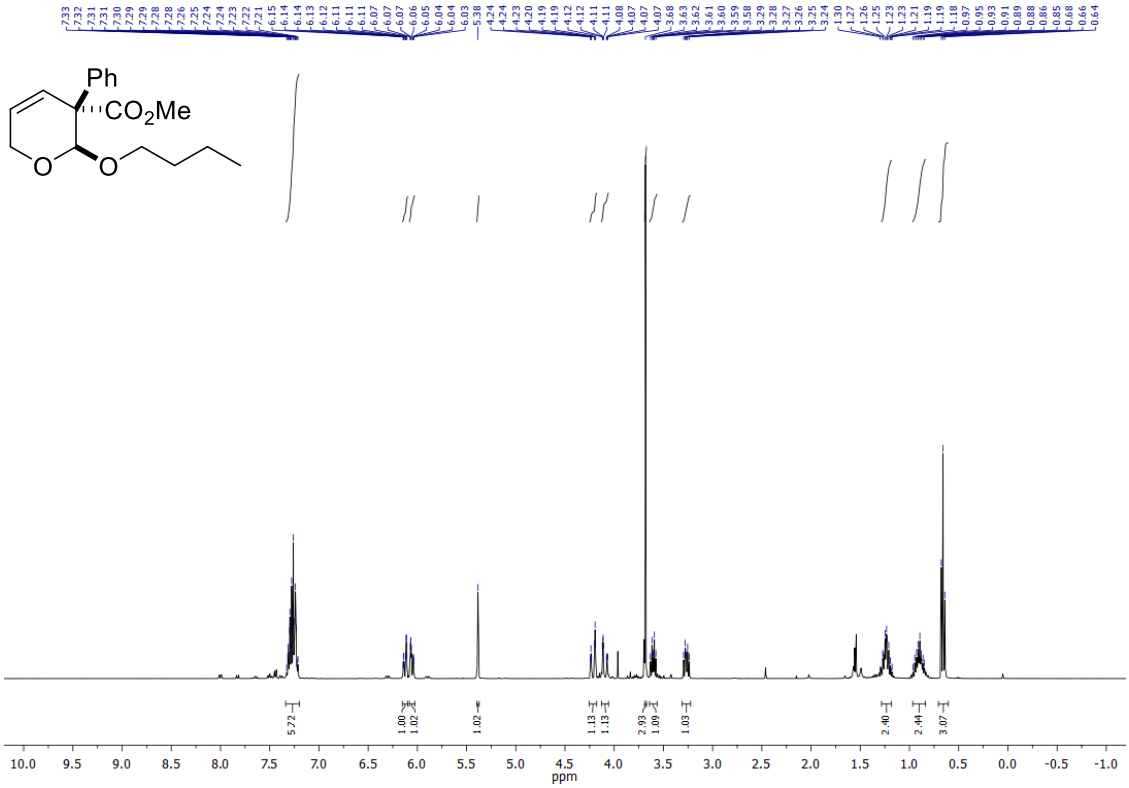


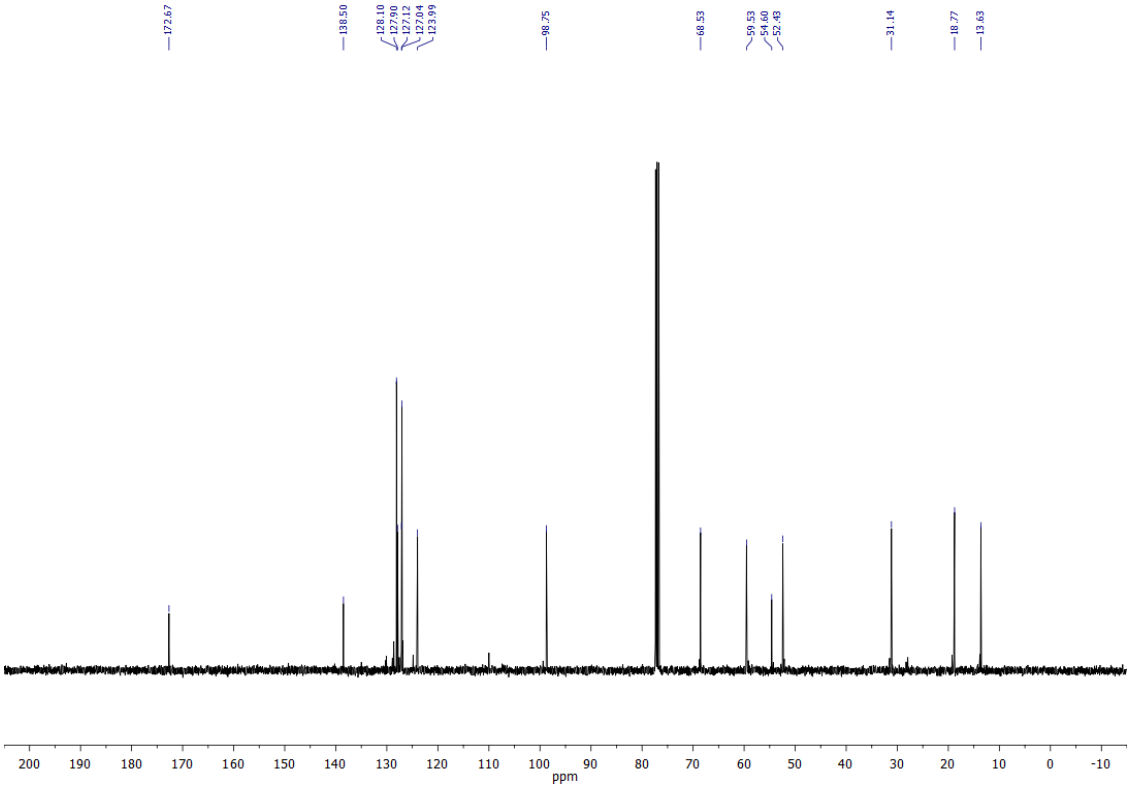
Compound *major*-**105c**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



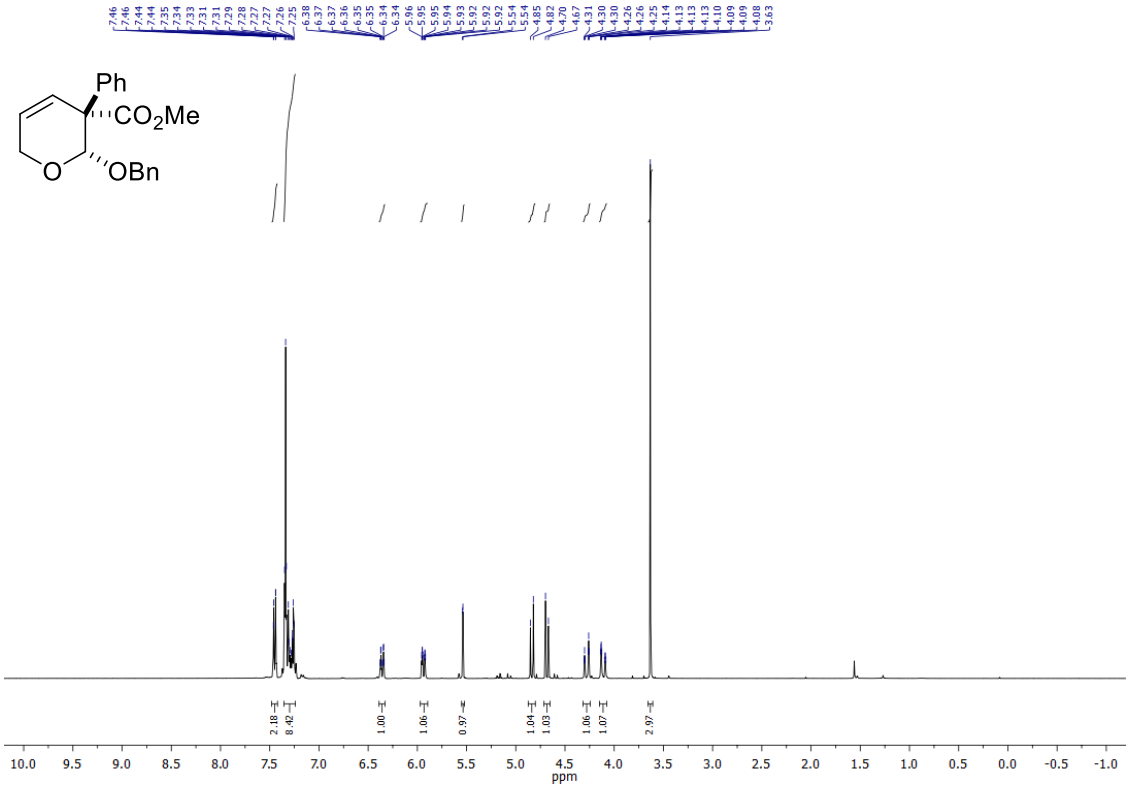


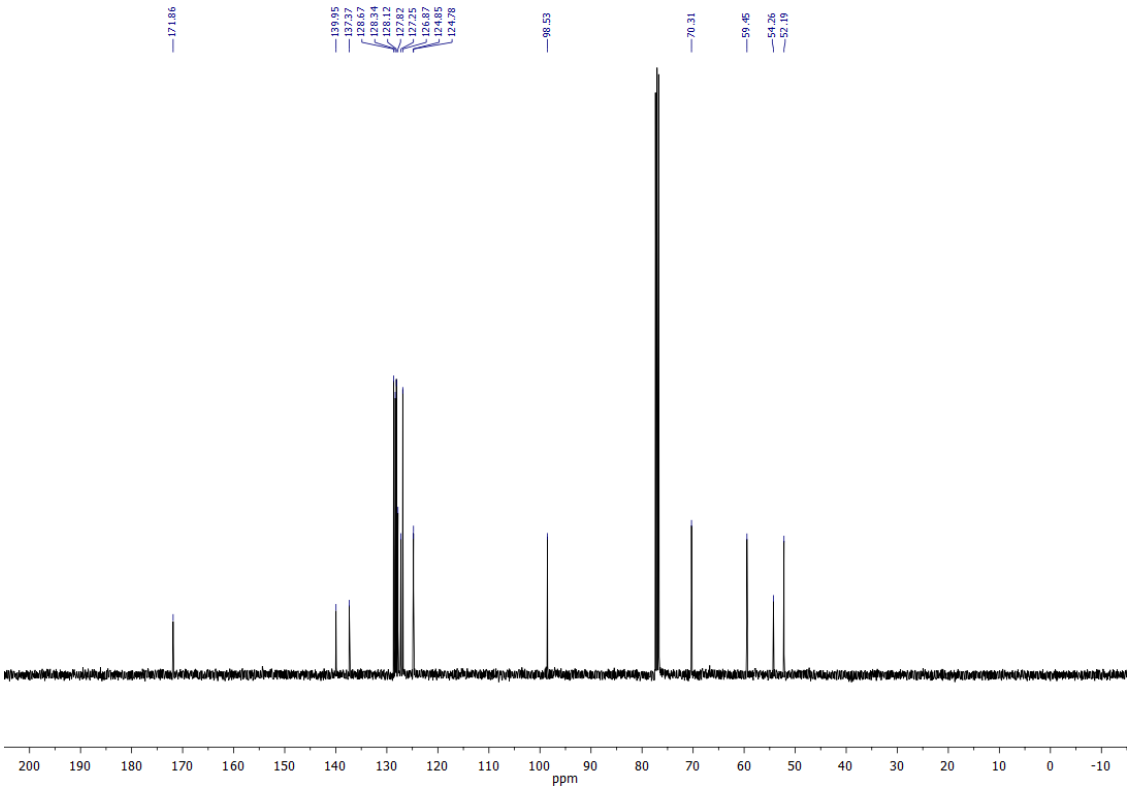
Compound *minor*-**105c**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



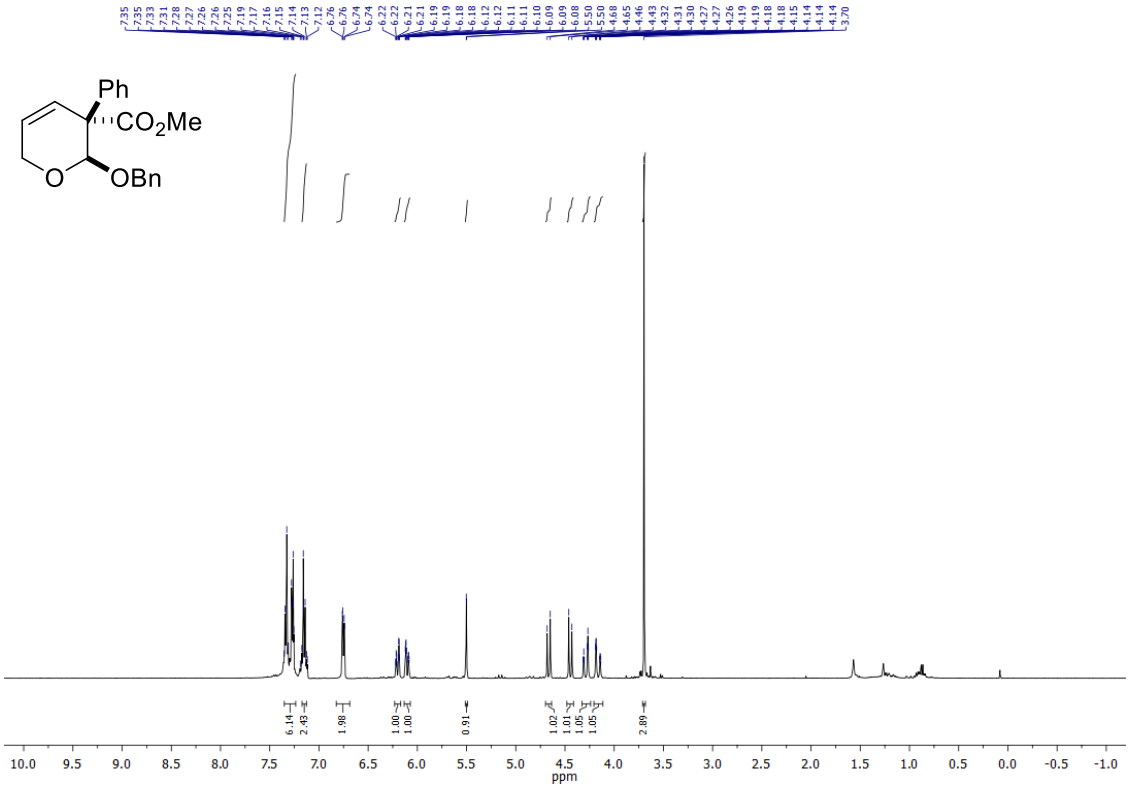


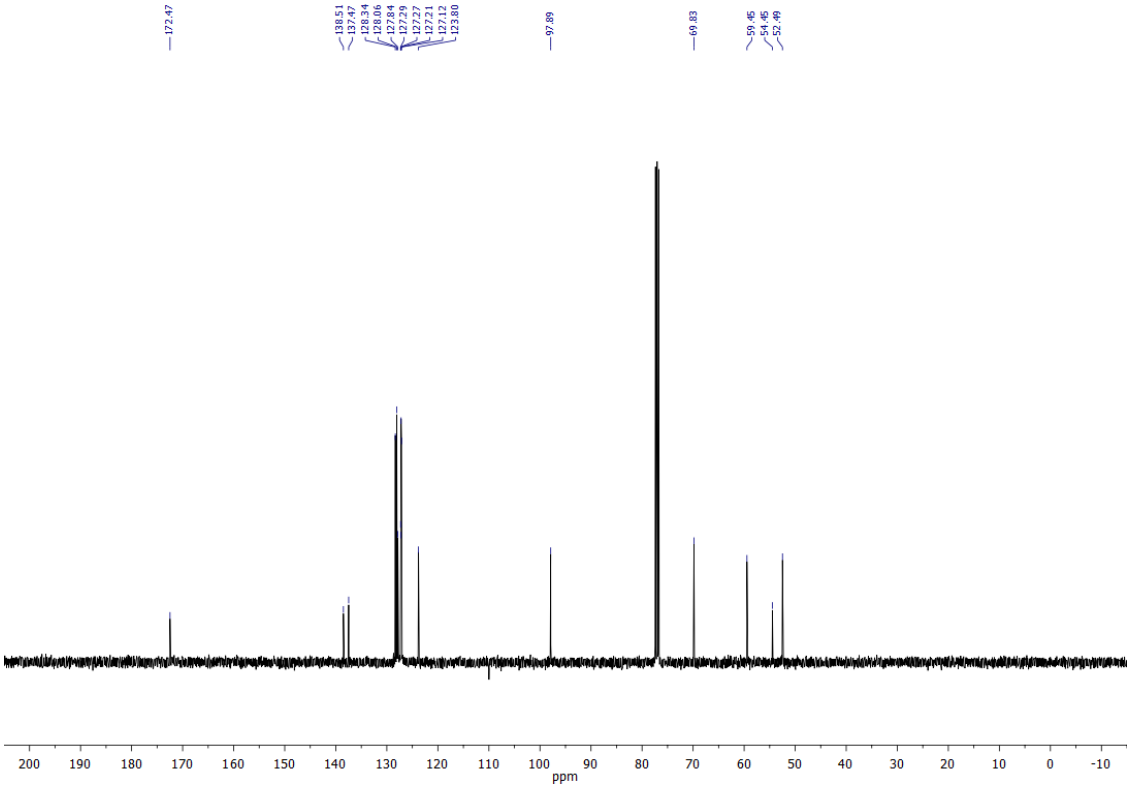
Compound *major*-**105d**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



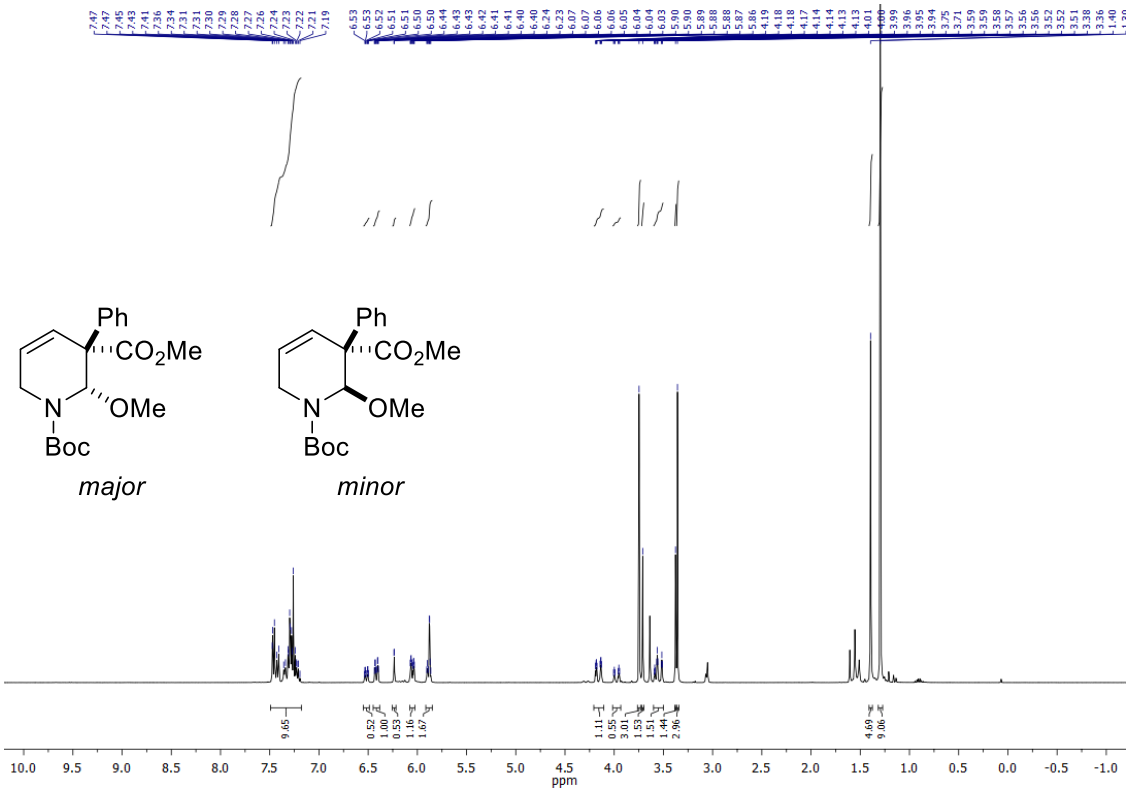


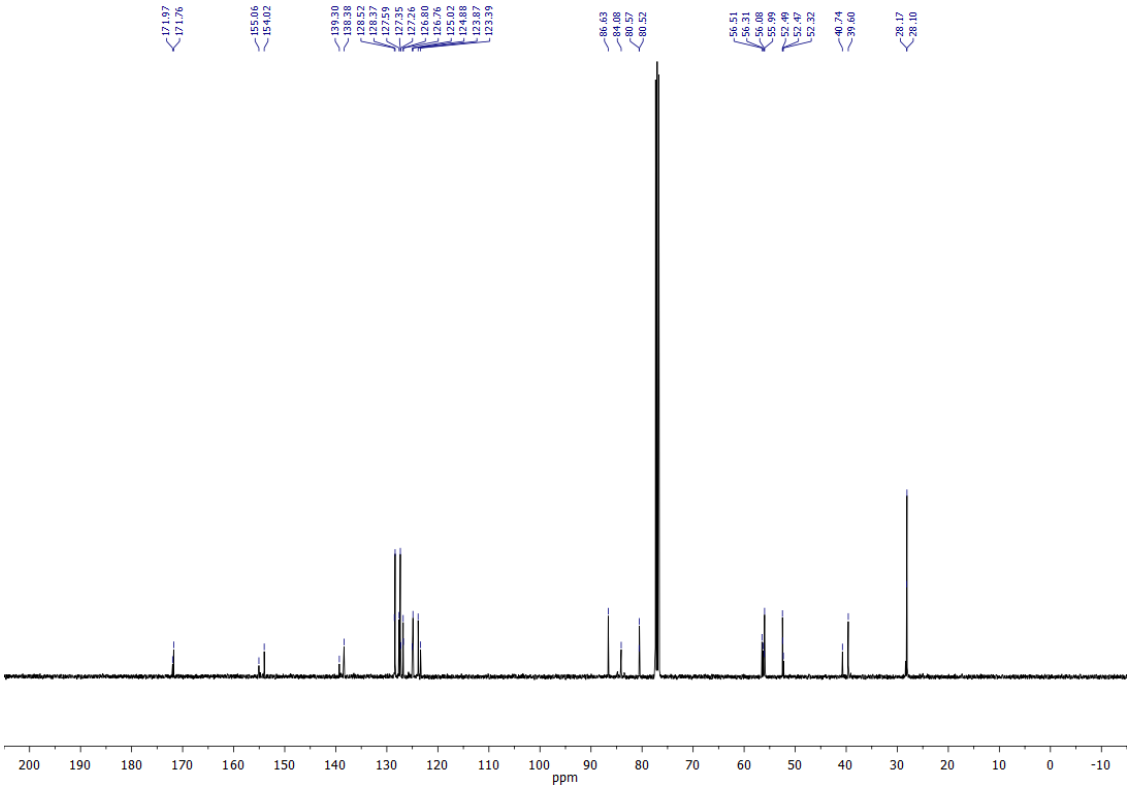
Compound *minor*-**105d**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



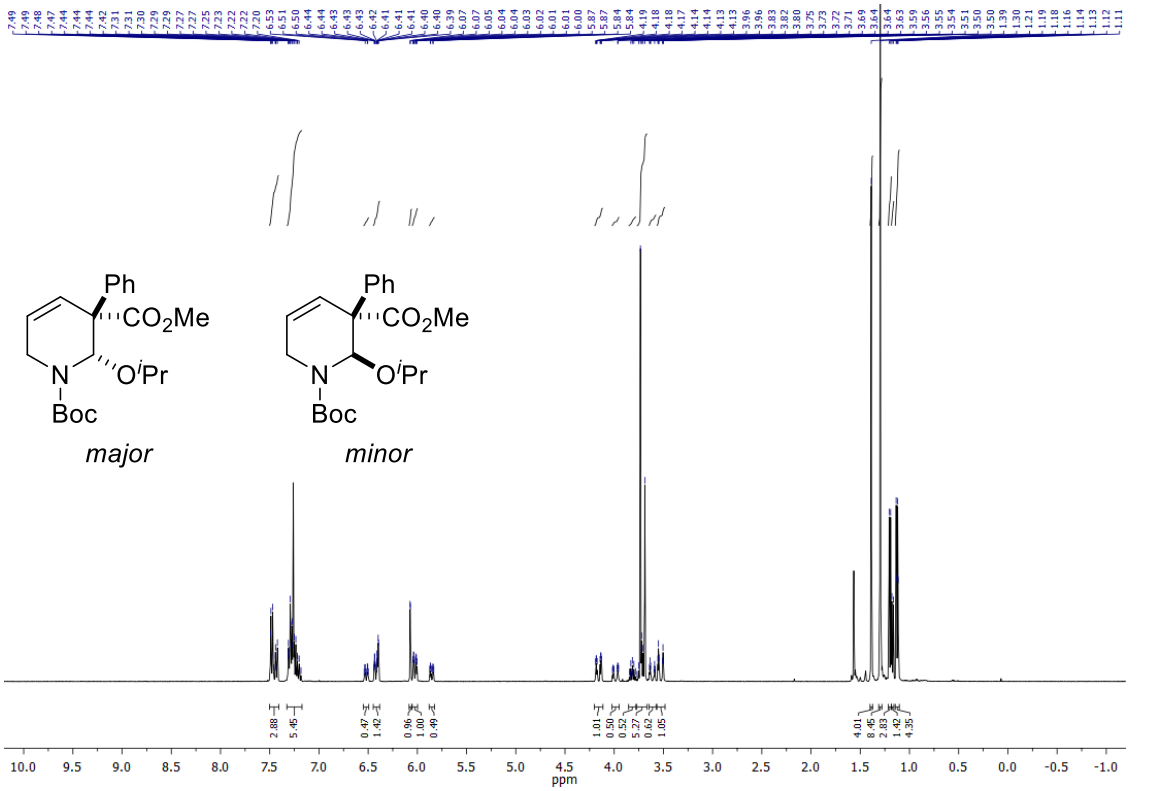


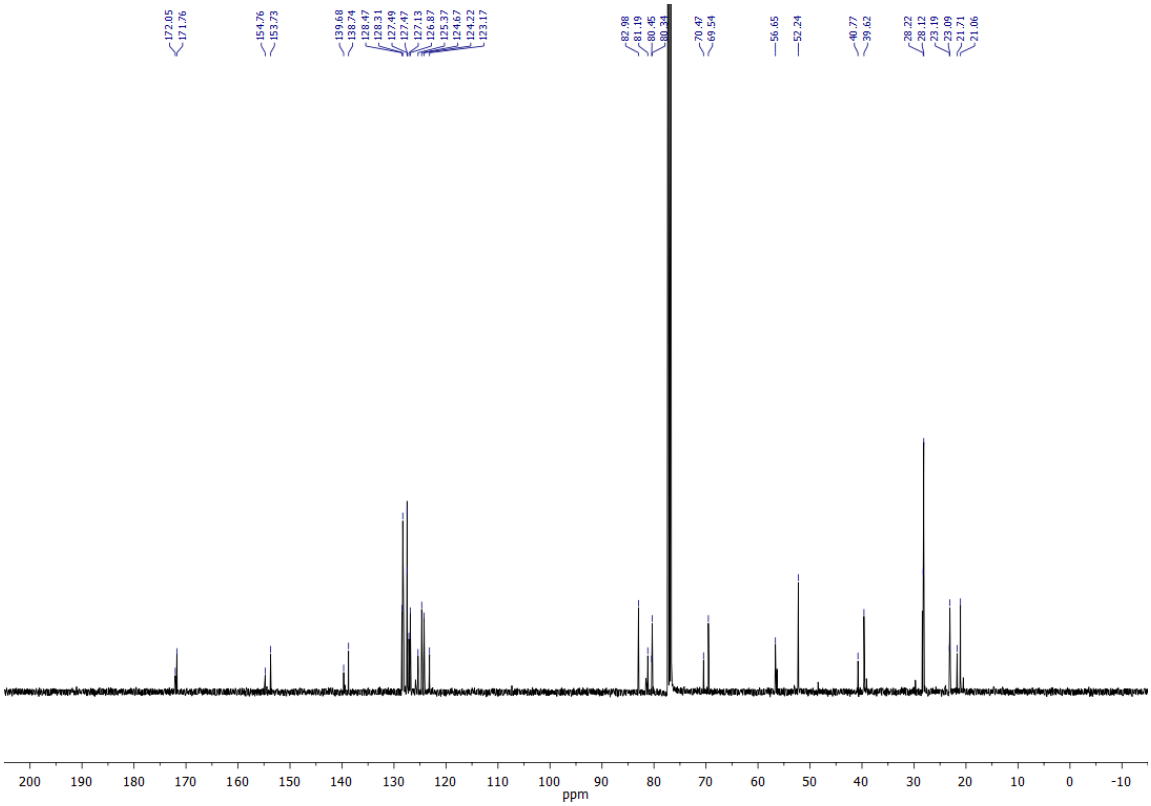
Compound **105f**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



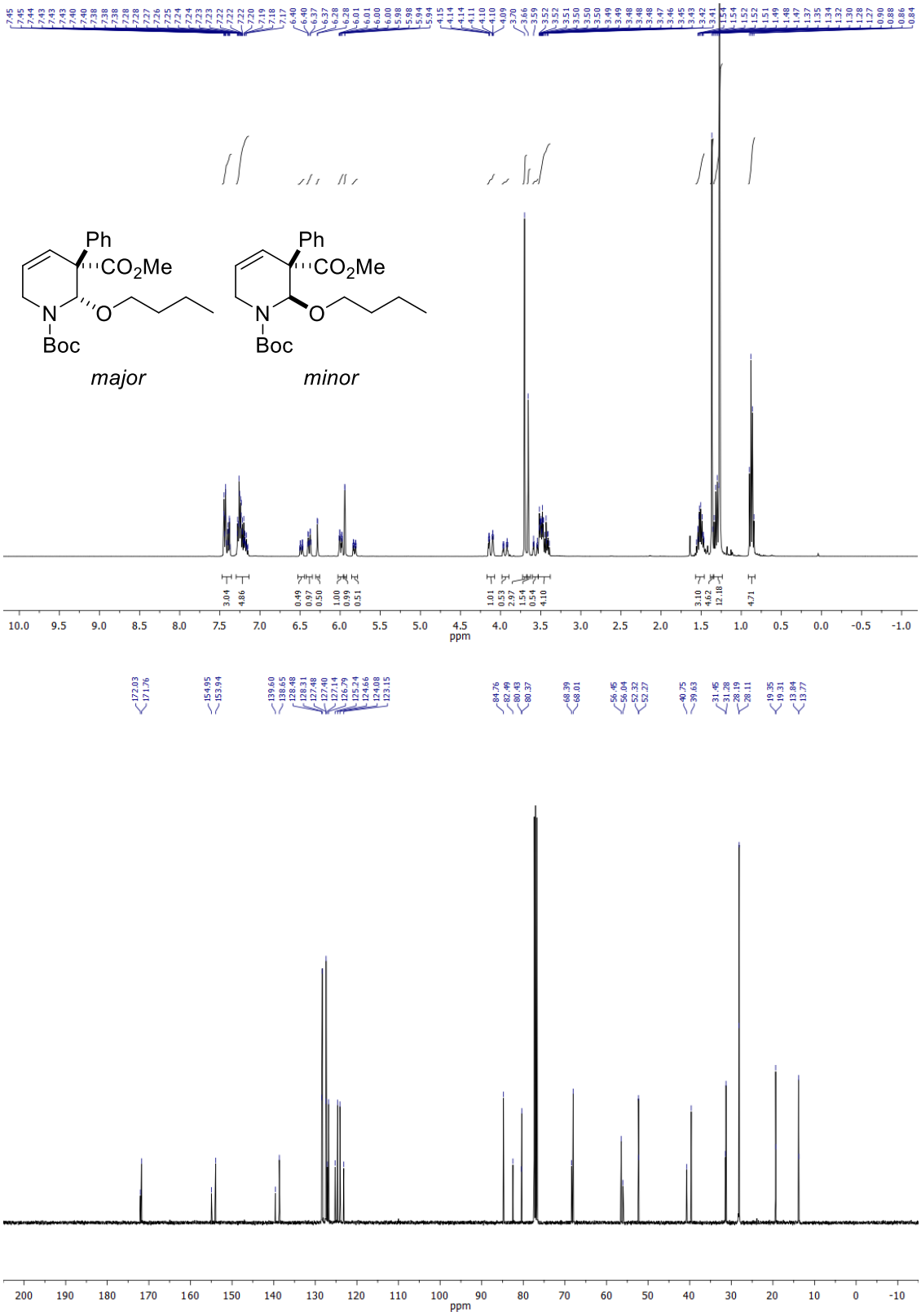


Compound **105g**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

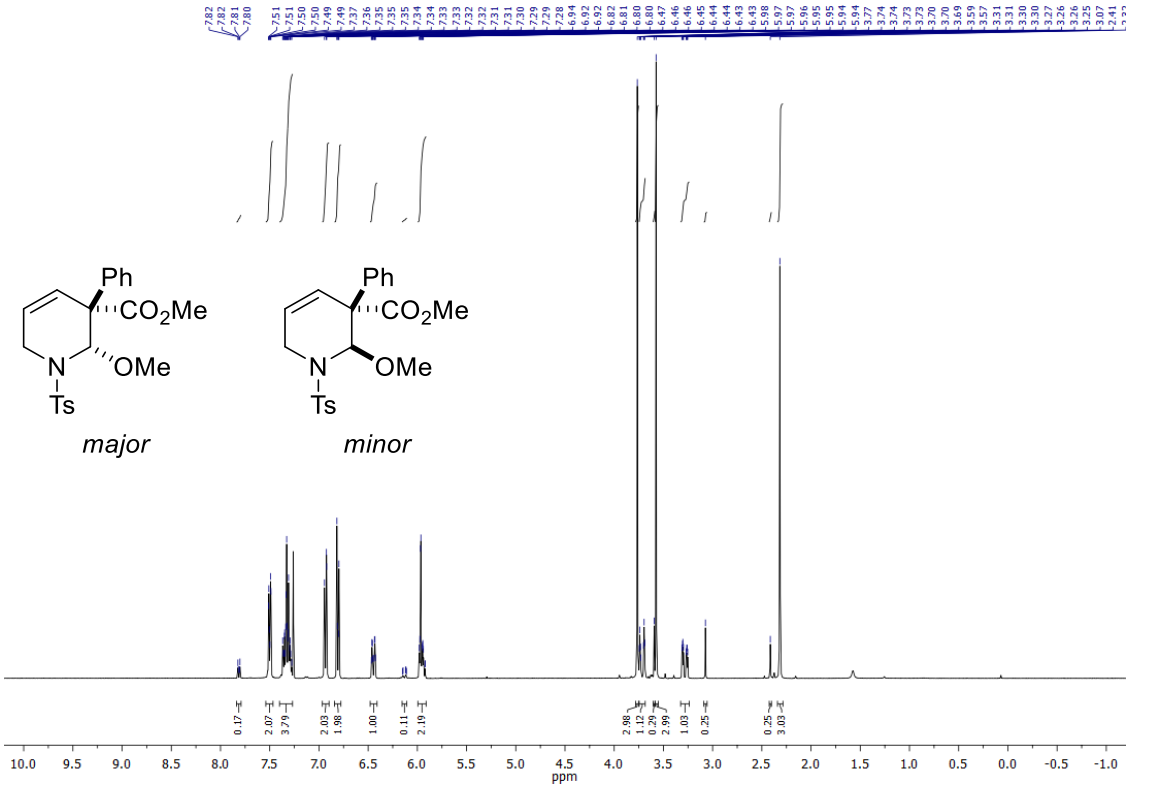


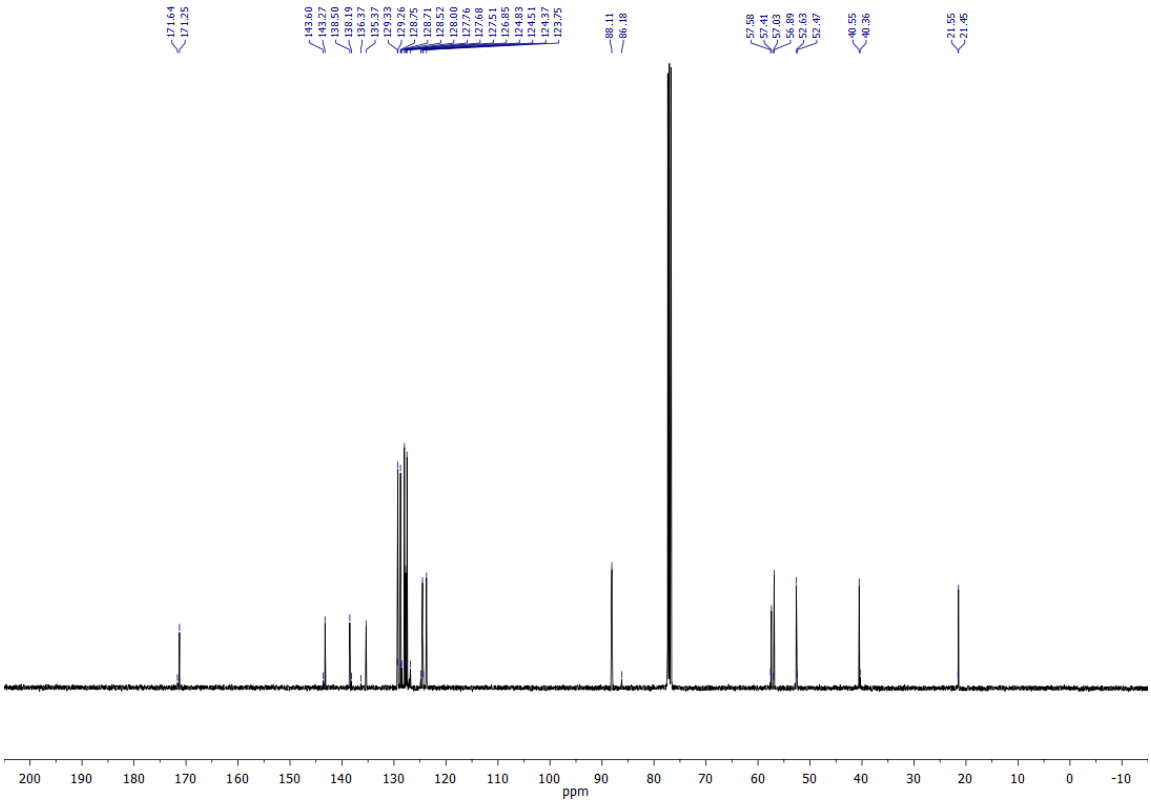


Compound **105h**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

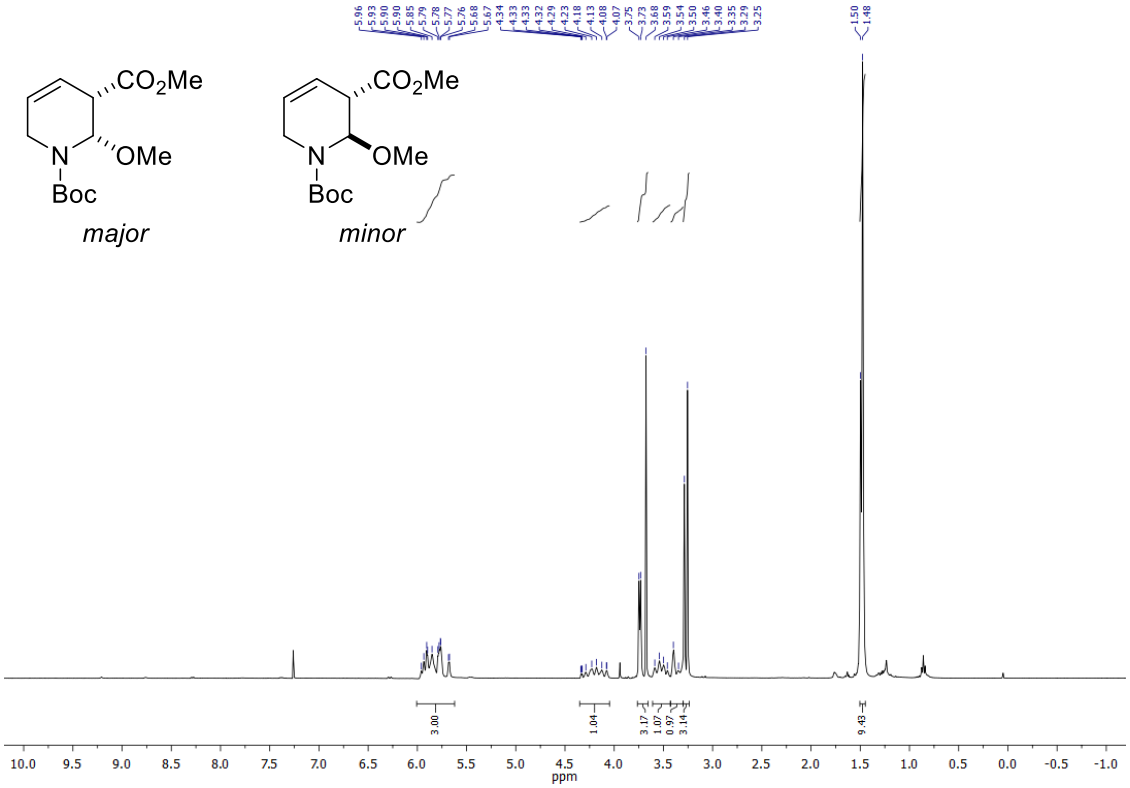


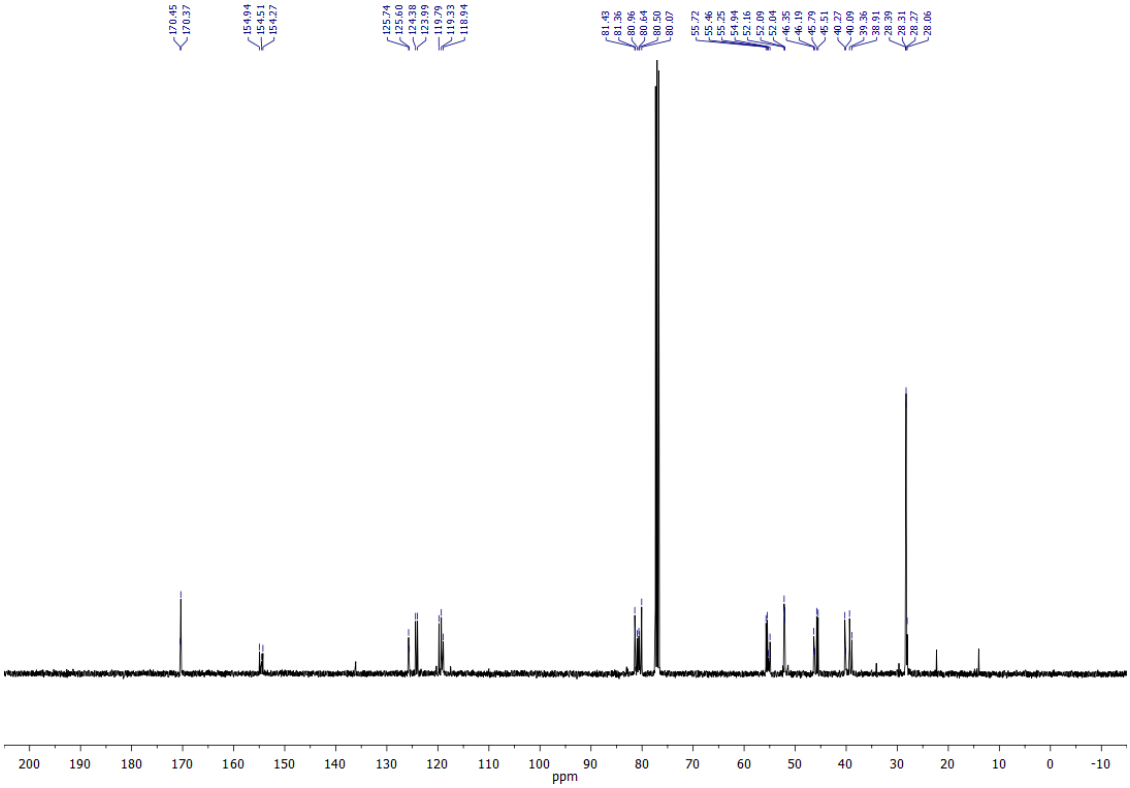
Compound **105i**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



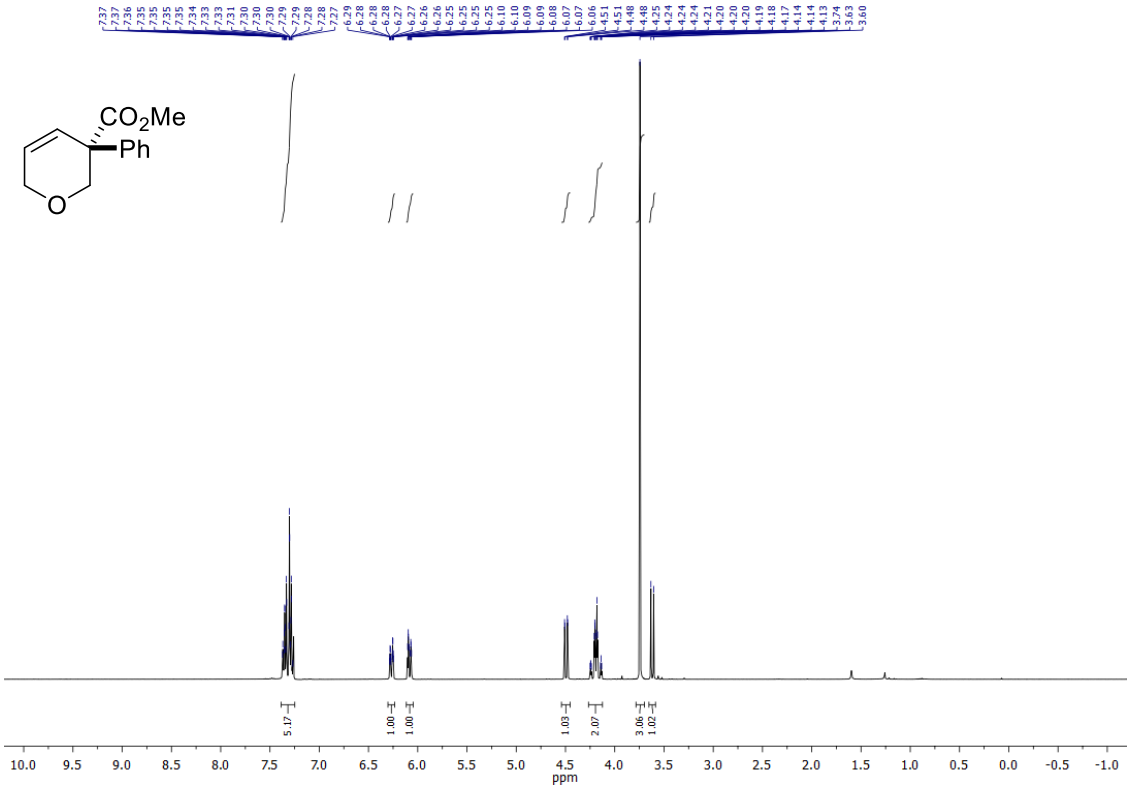


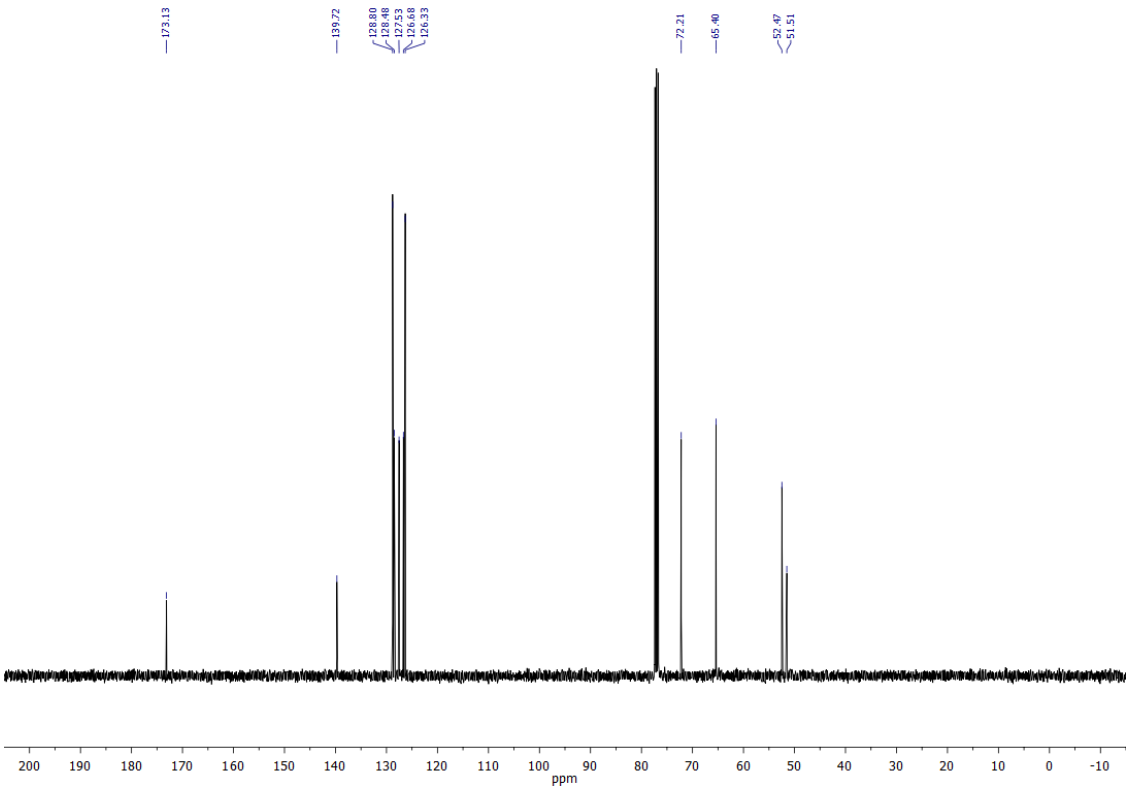
Compound **105j**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



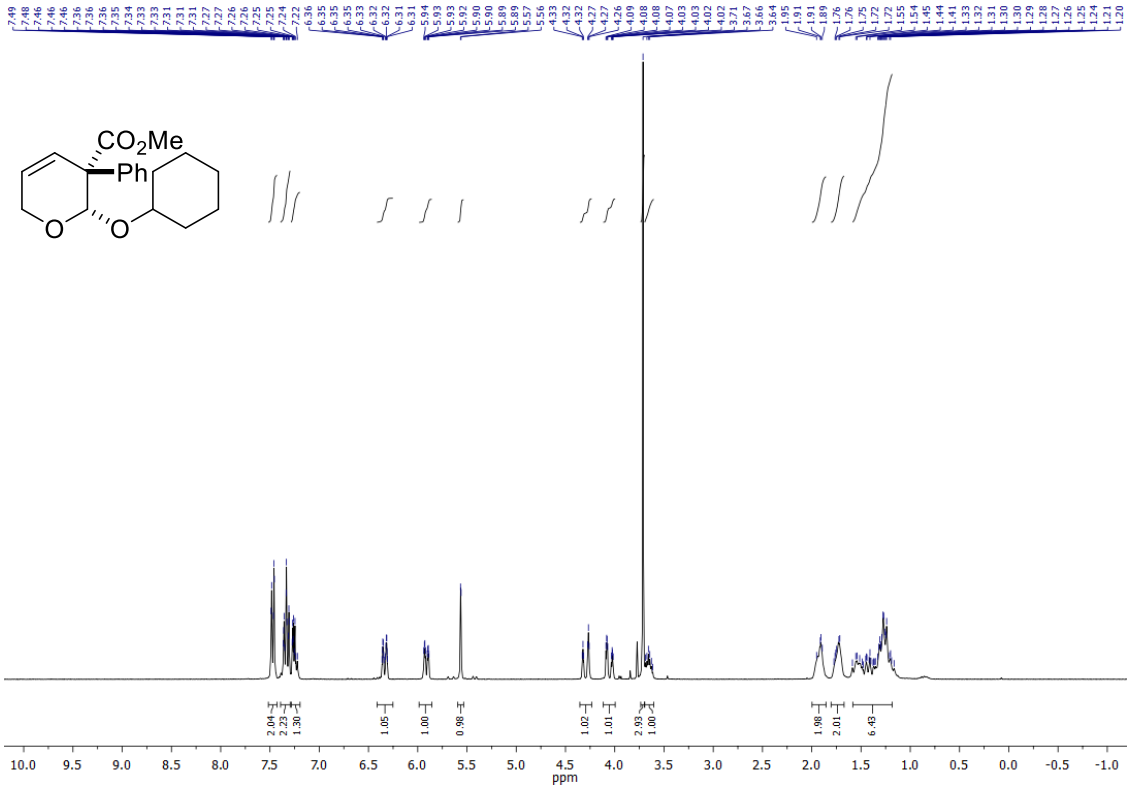


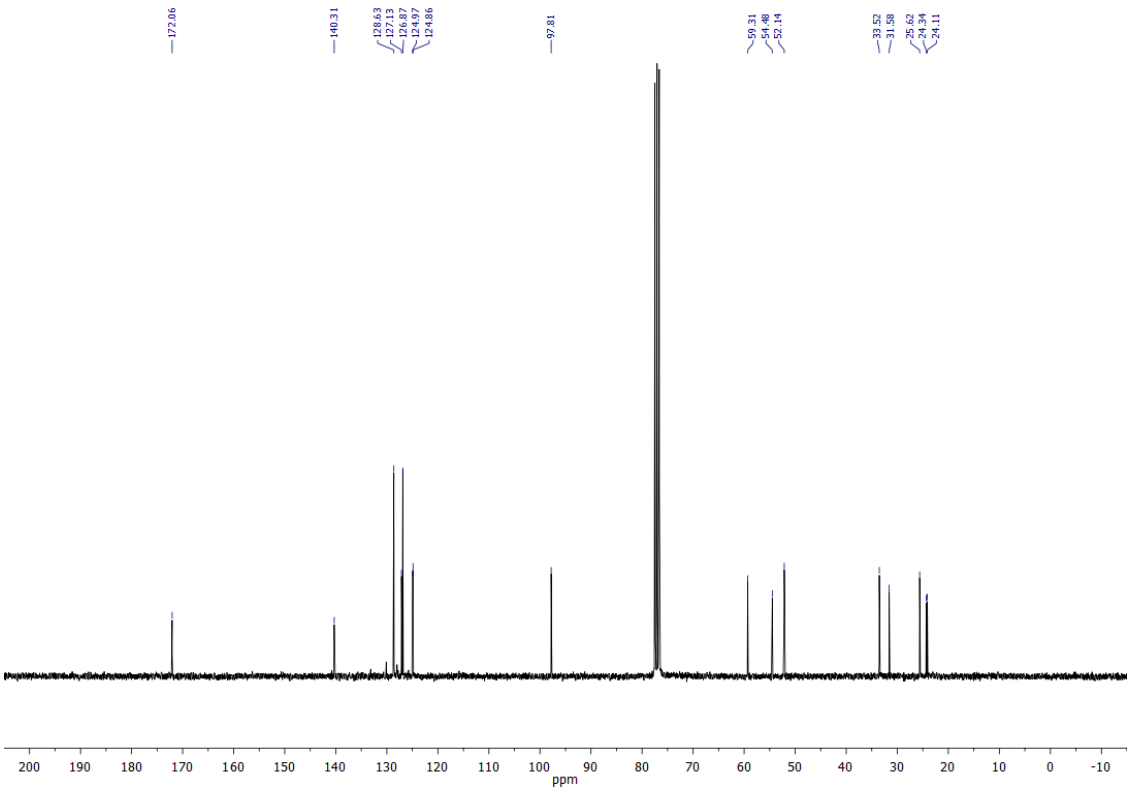
Compound **105l**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



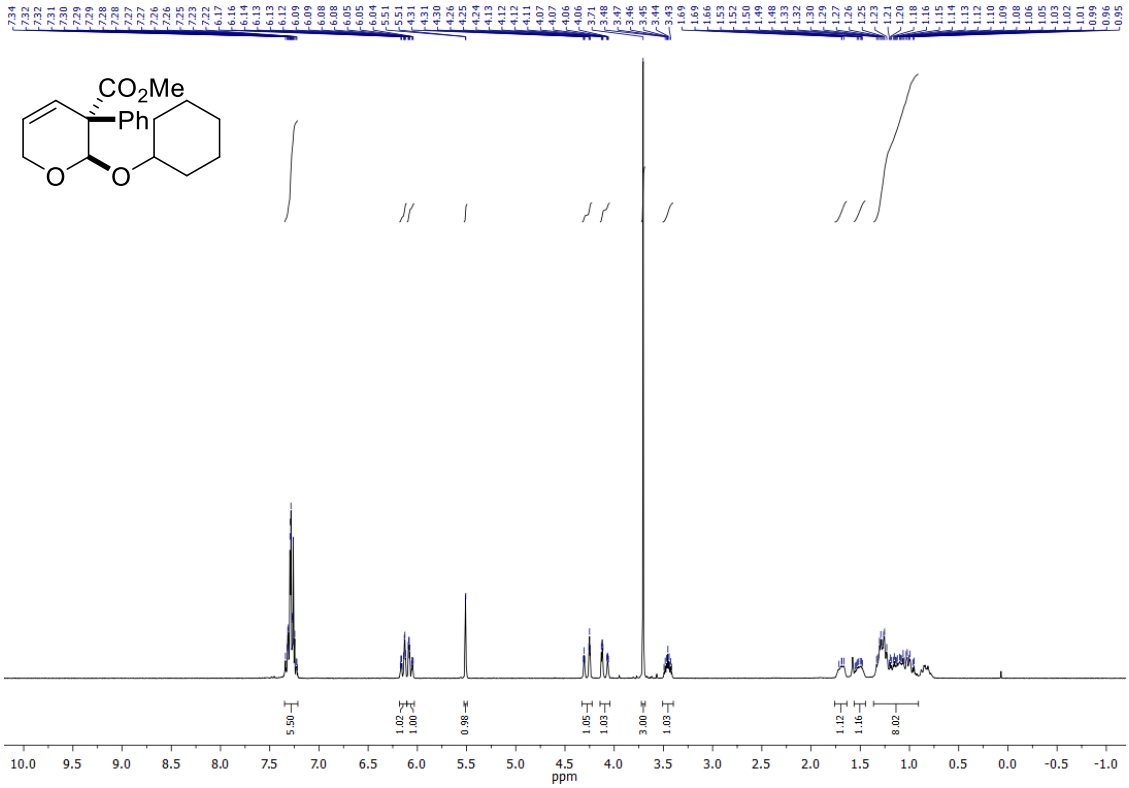


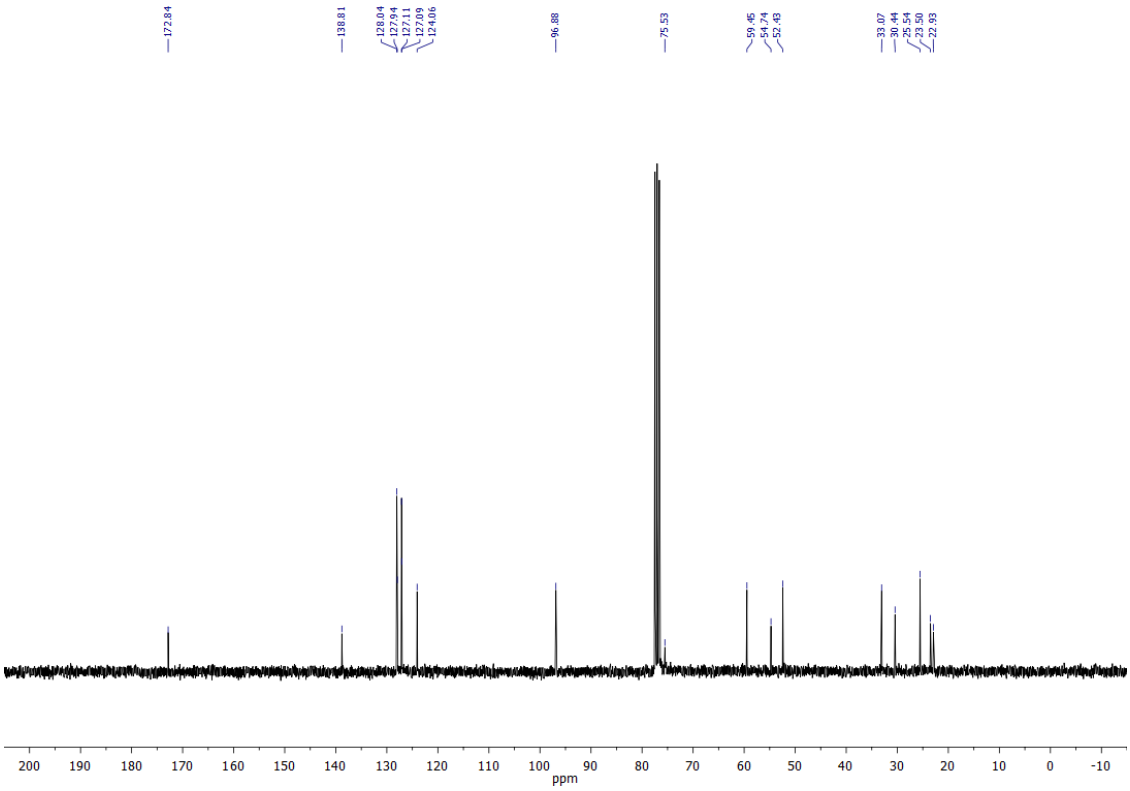
Compound *major*-**105m**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$)



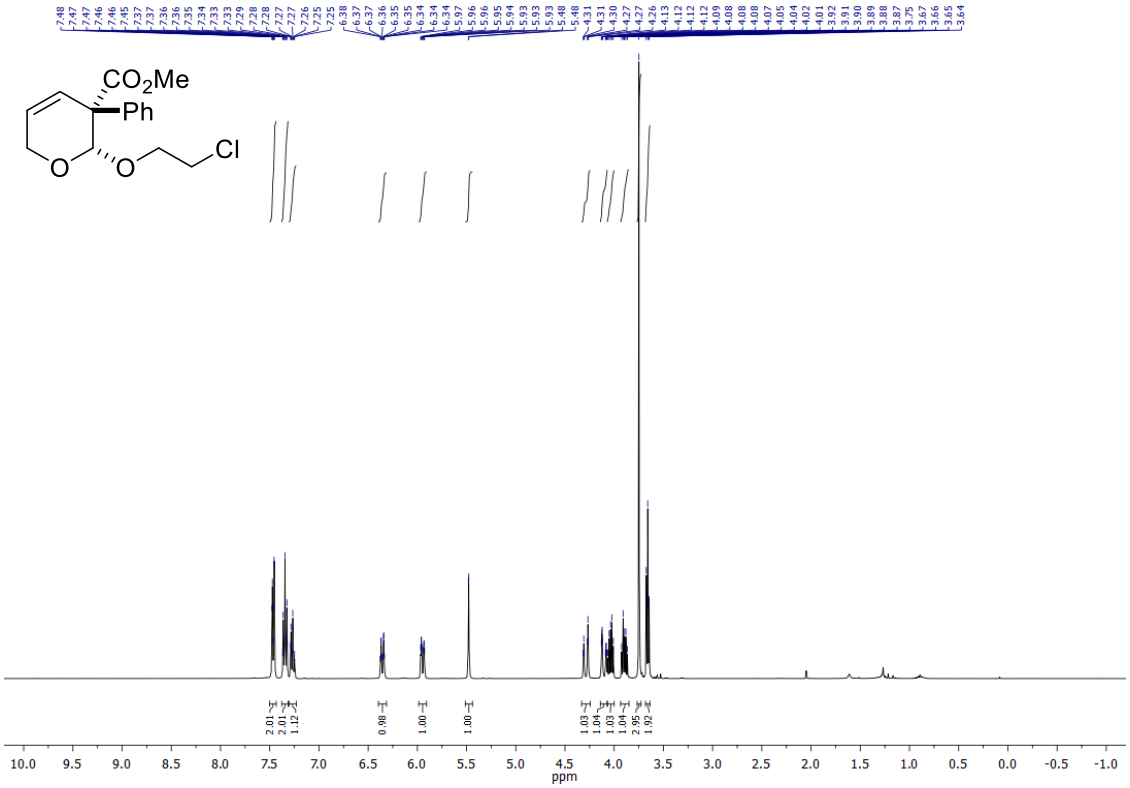


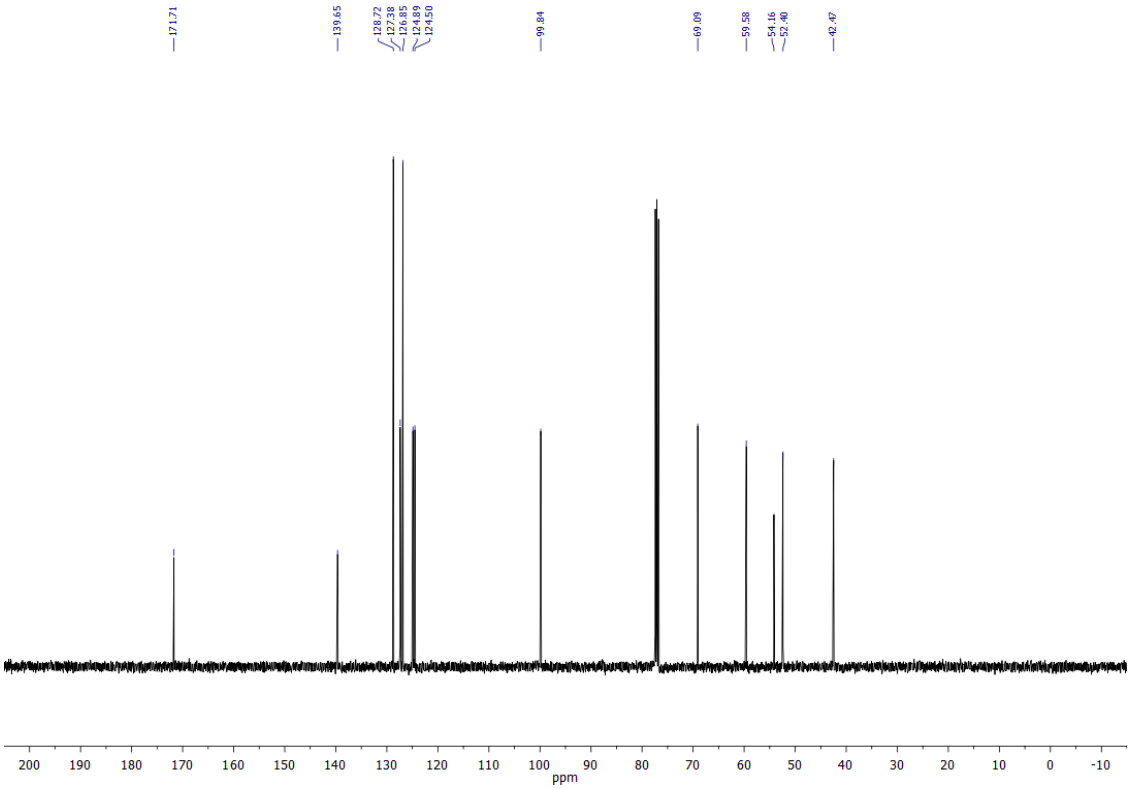
Compound *minor*-**105m**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$)



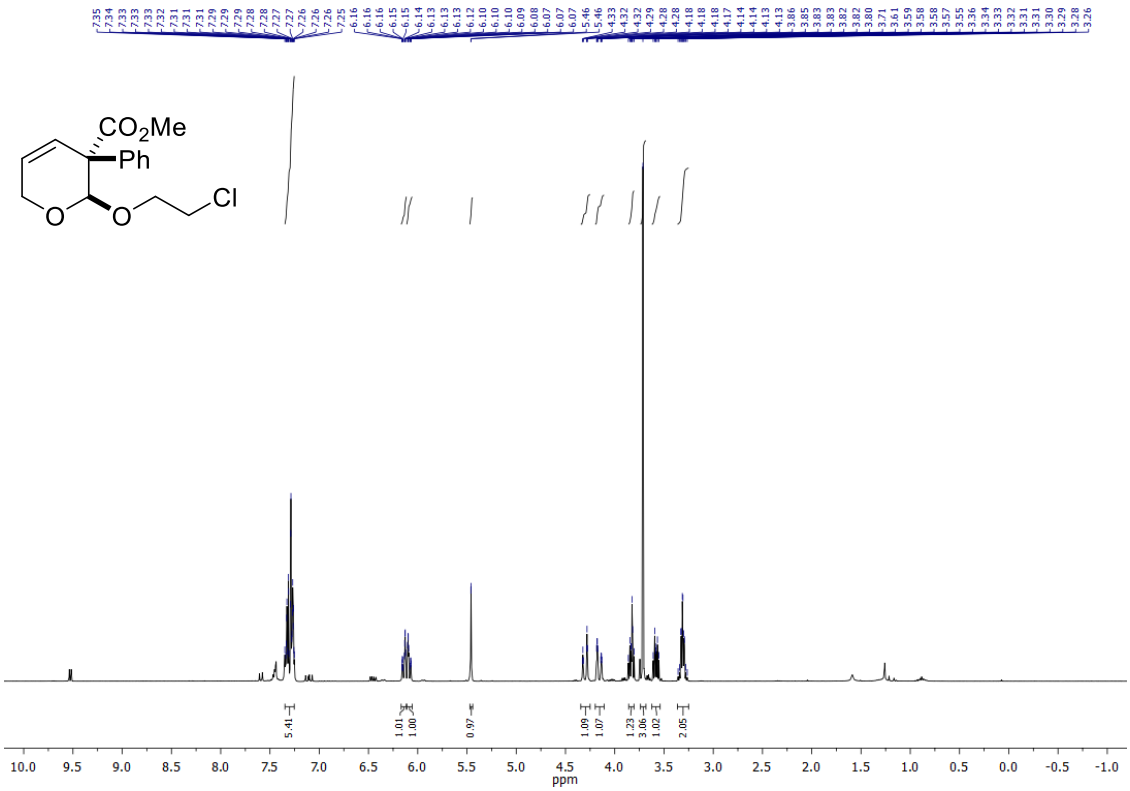


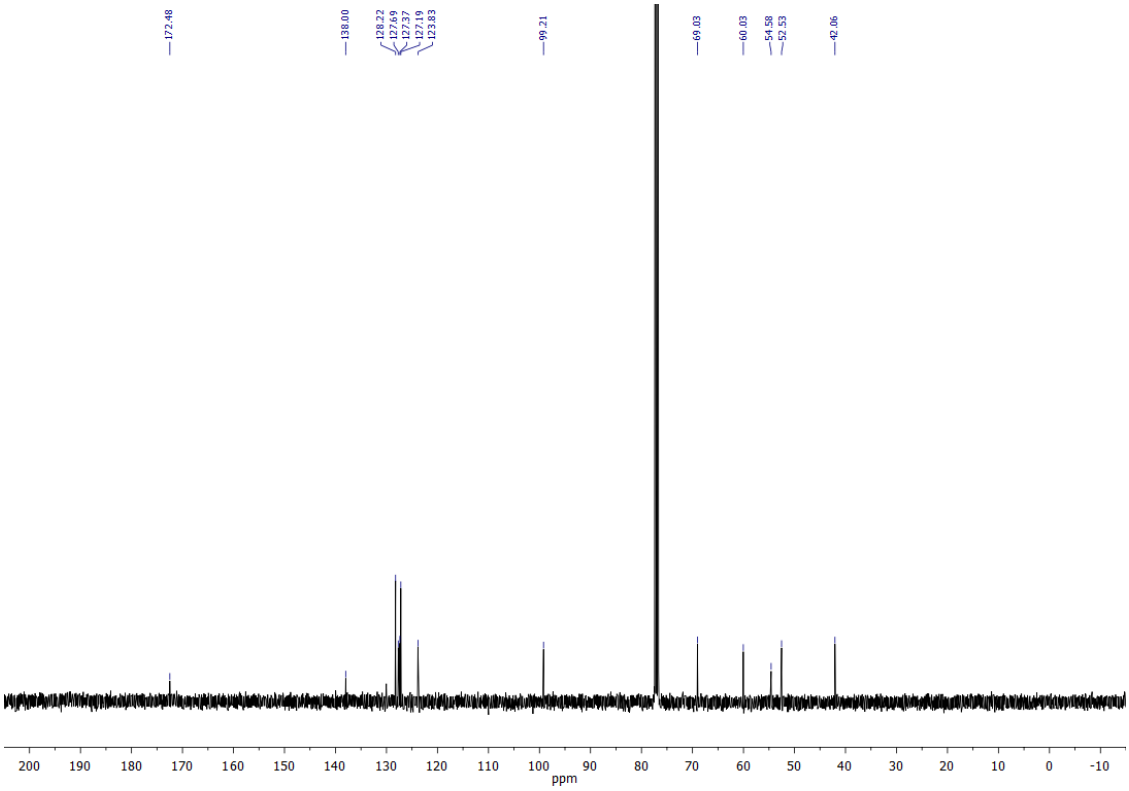
Compound *major*-**105n**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



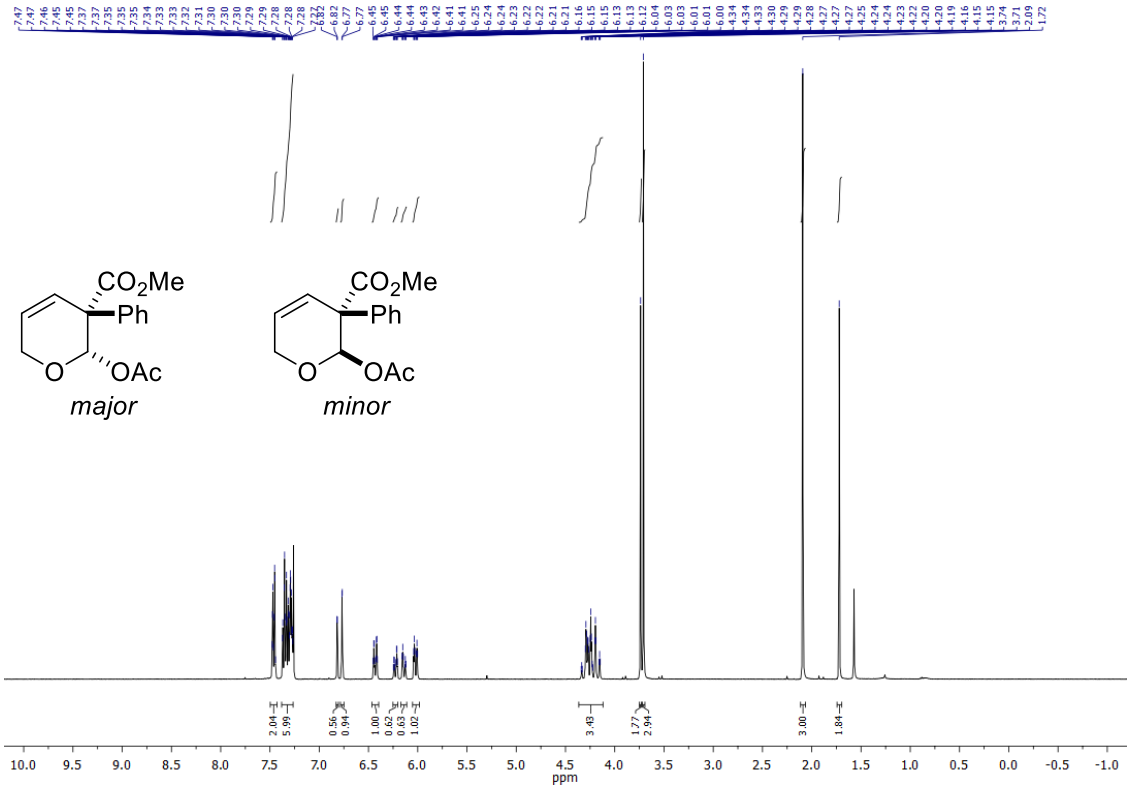


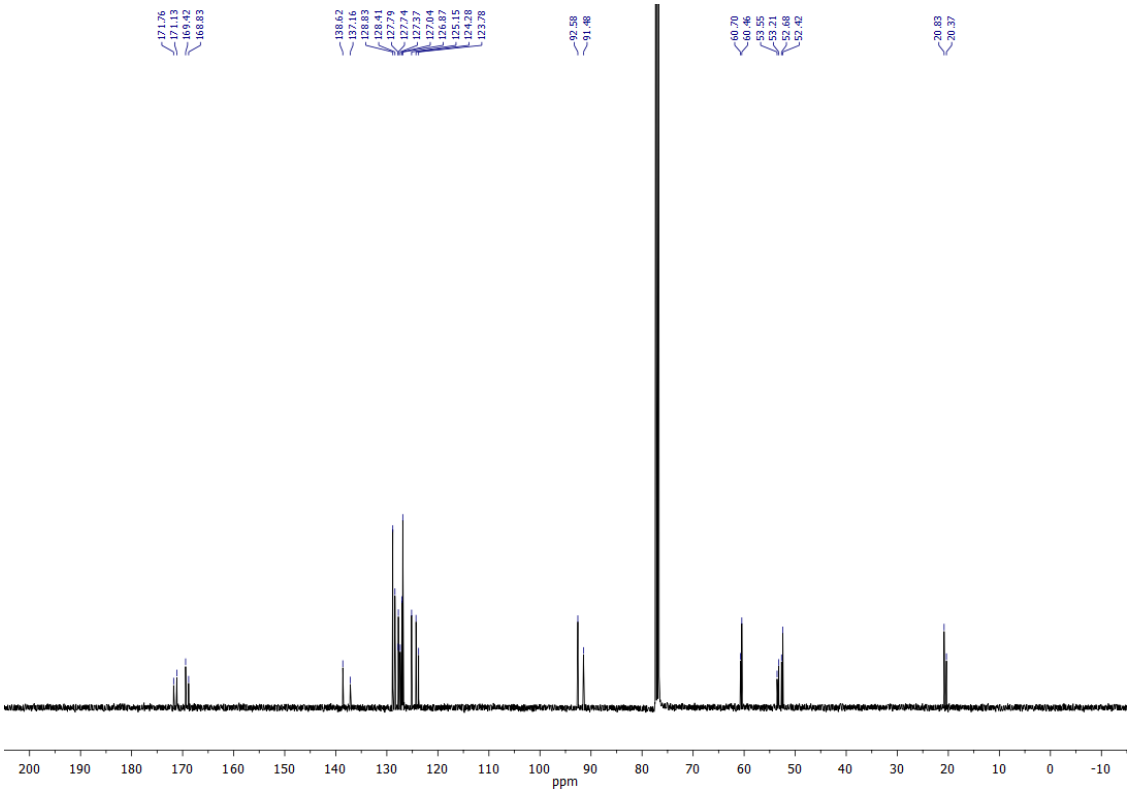
Compound *minor*-**105n**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



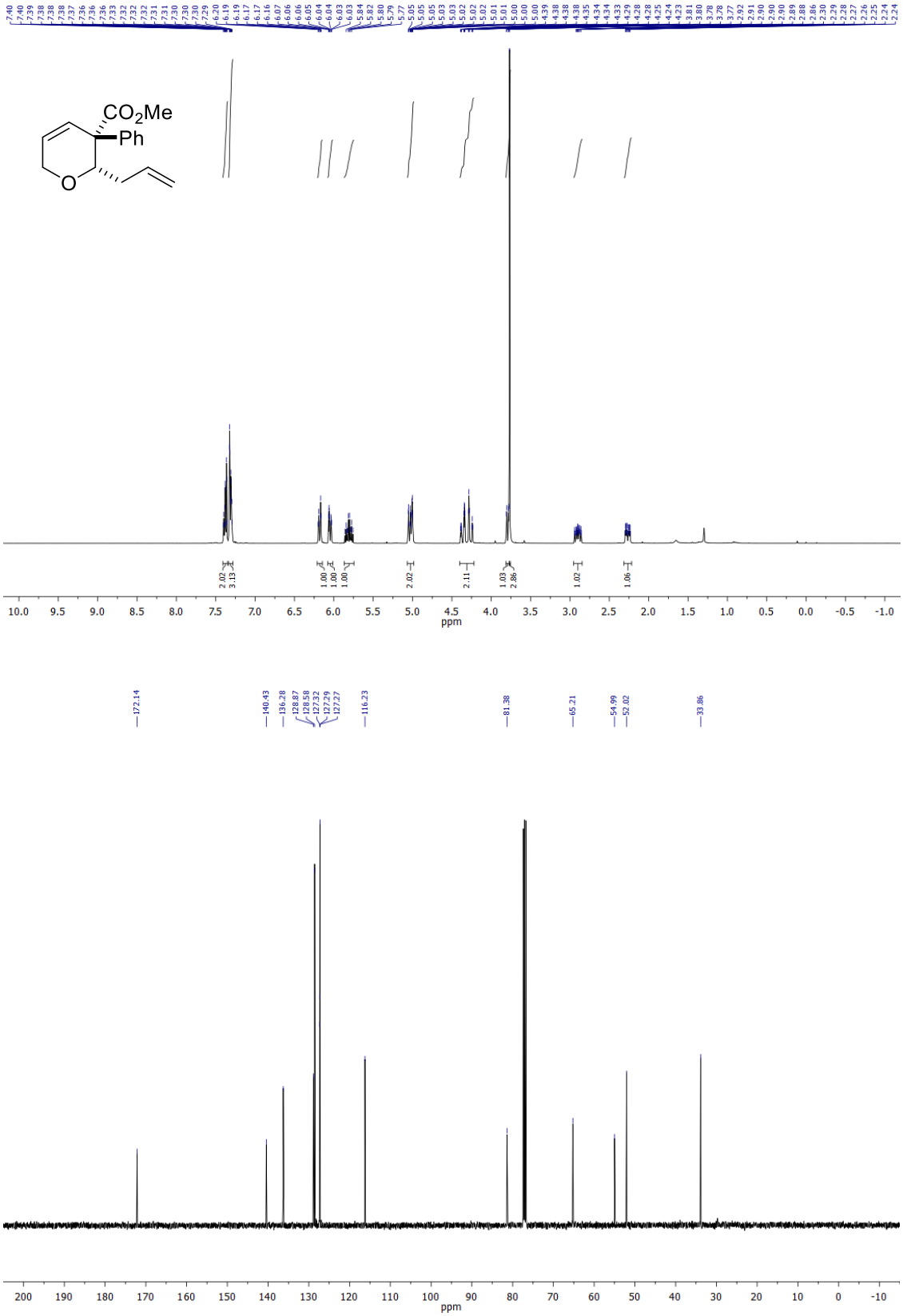


Compound **105o**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

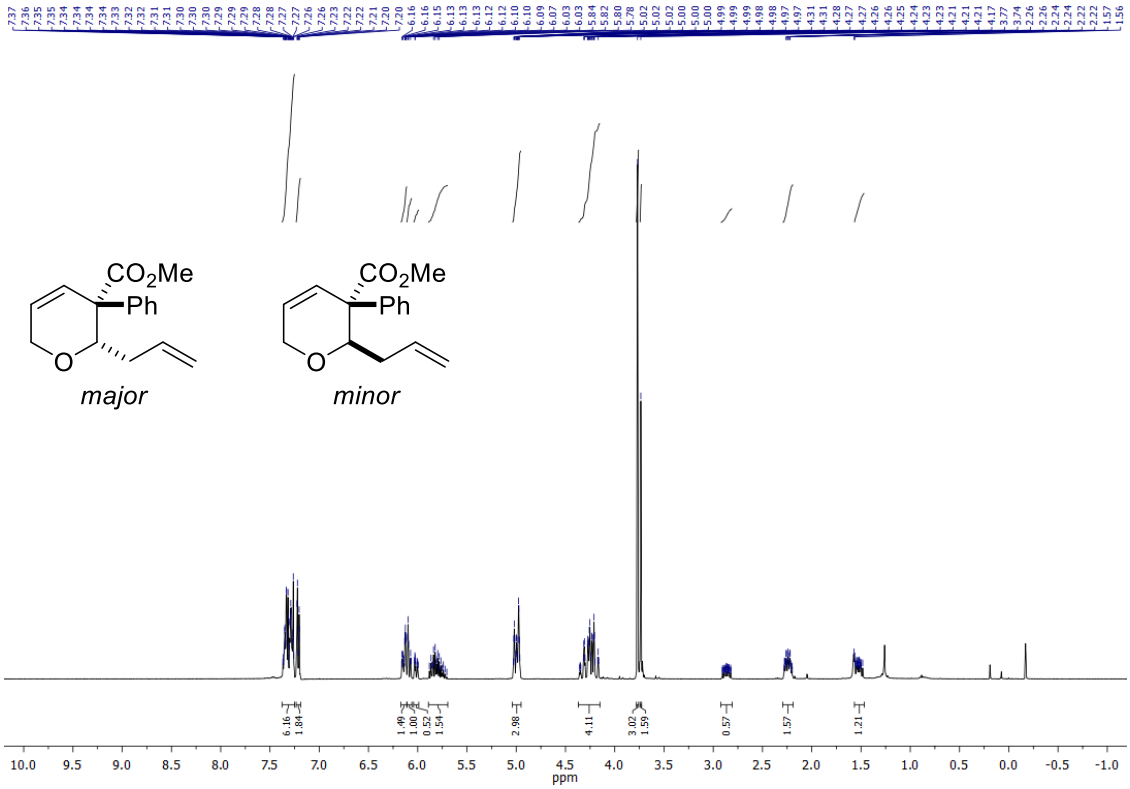


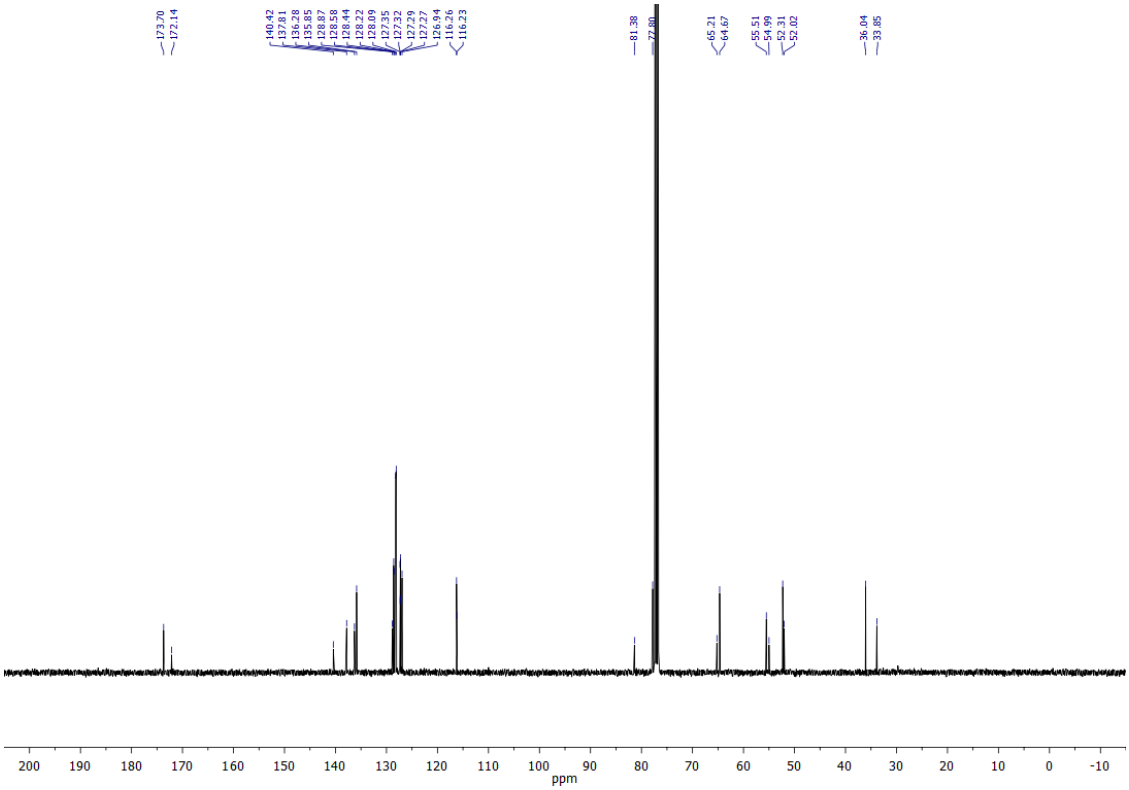


Compound *major*-**105p**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

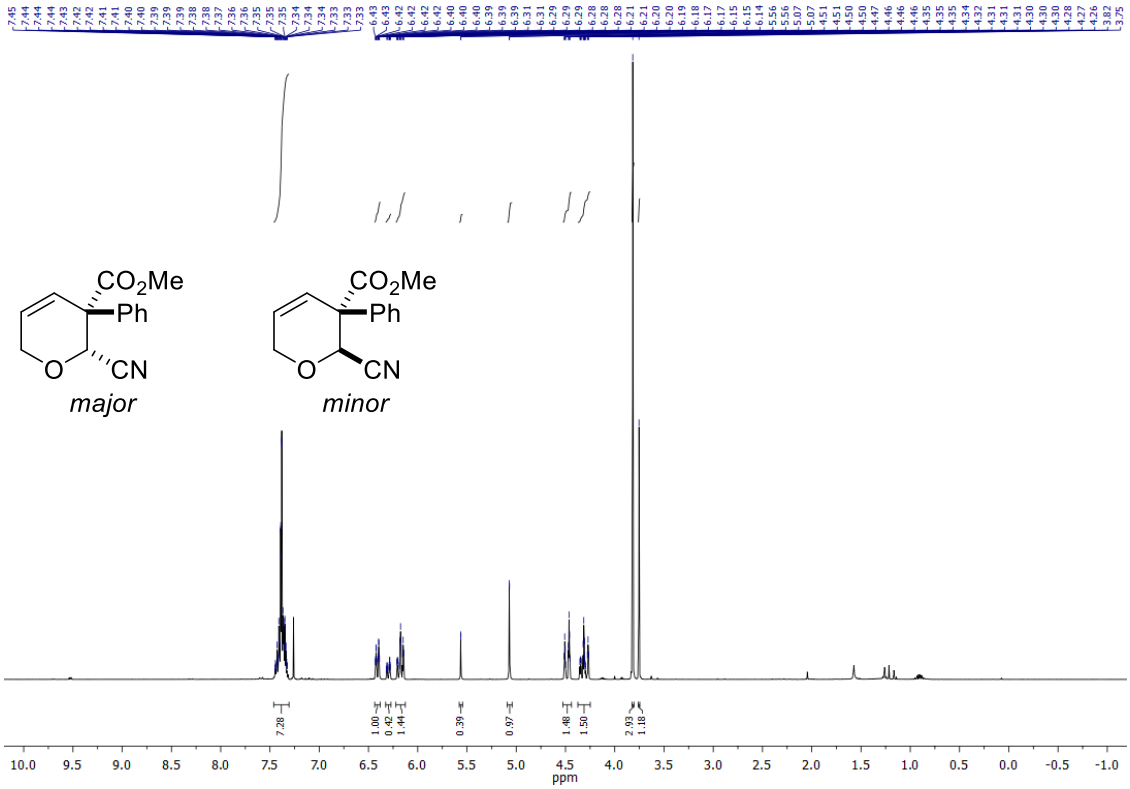


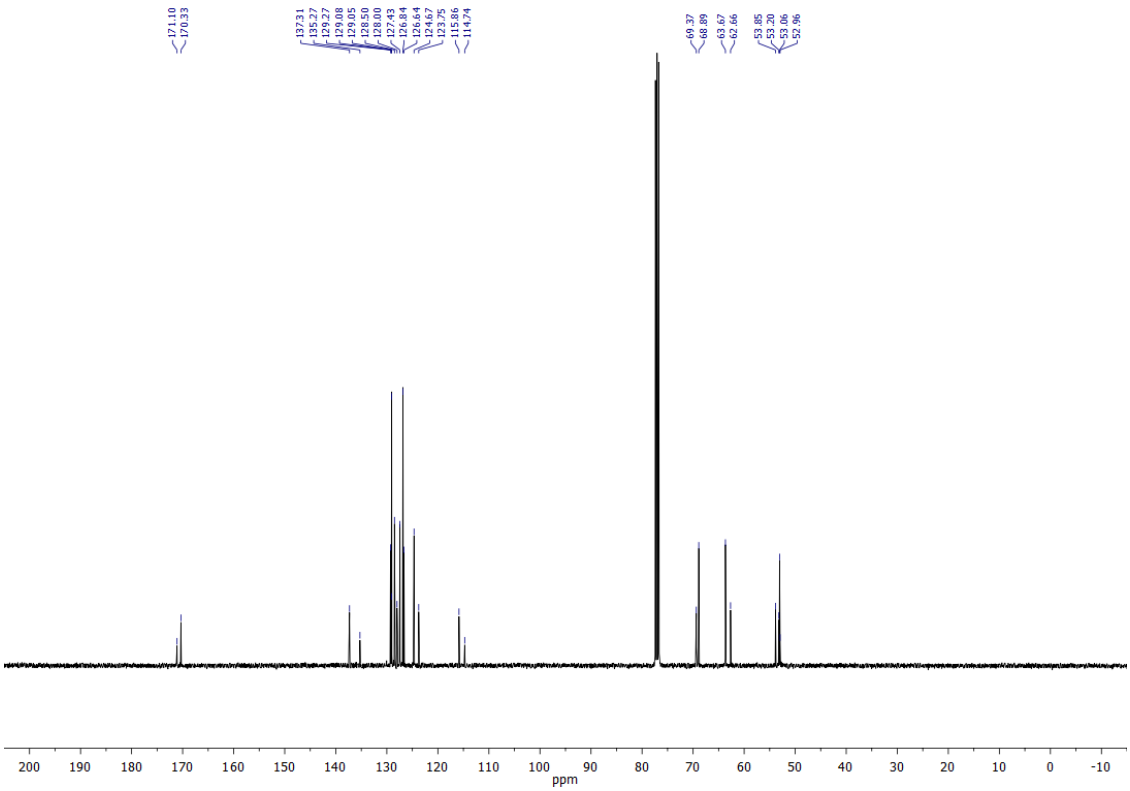
Compound **105p**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



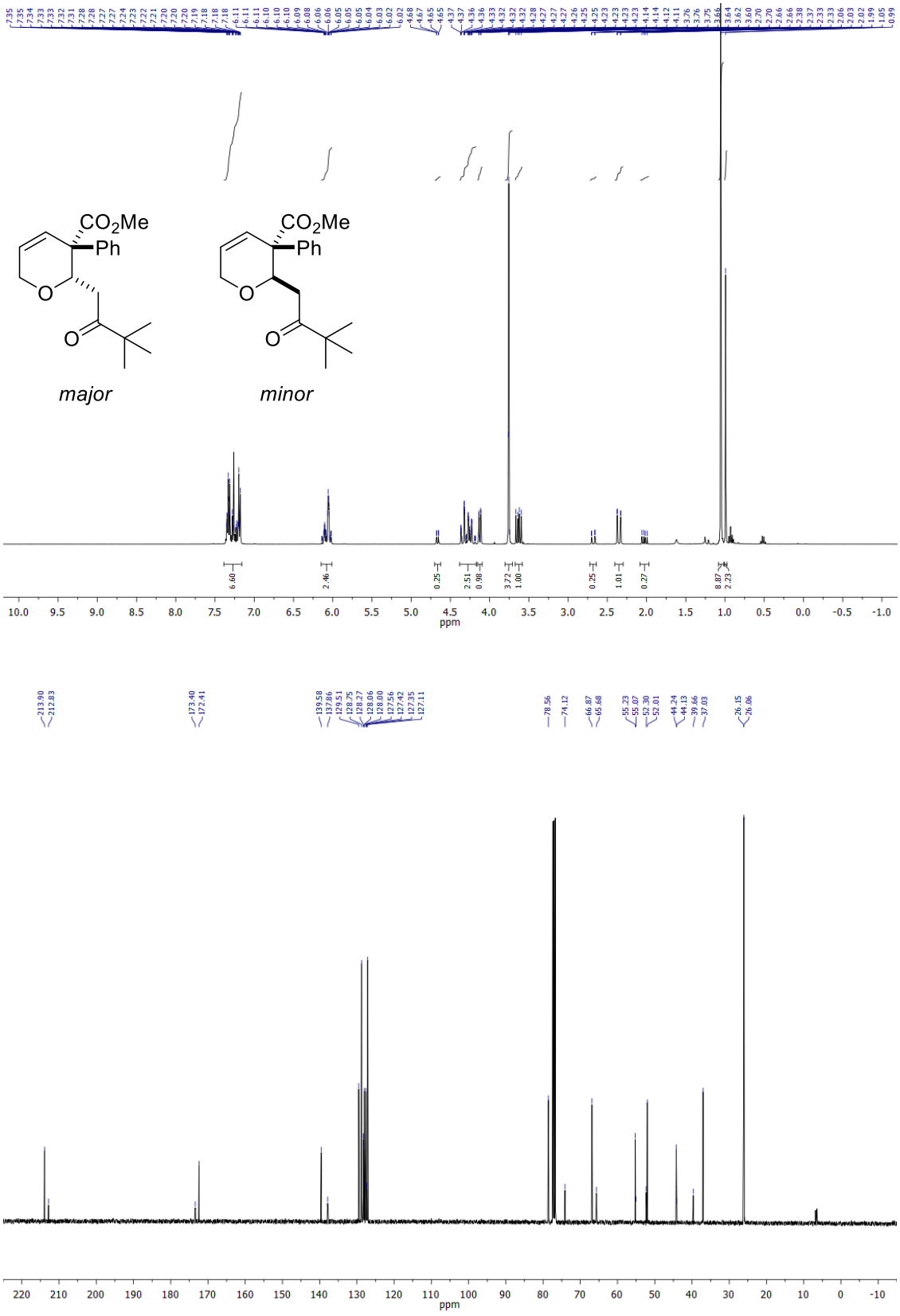


Compound **105q**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

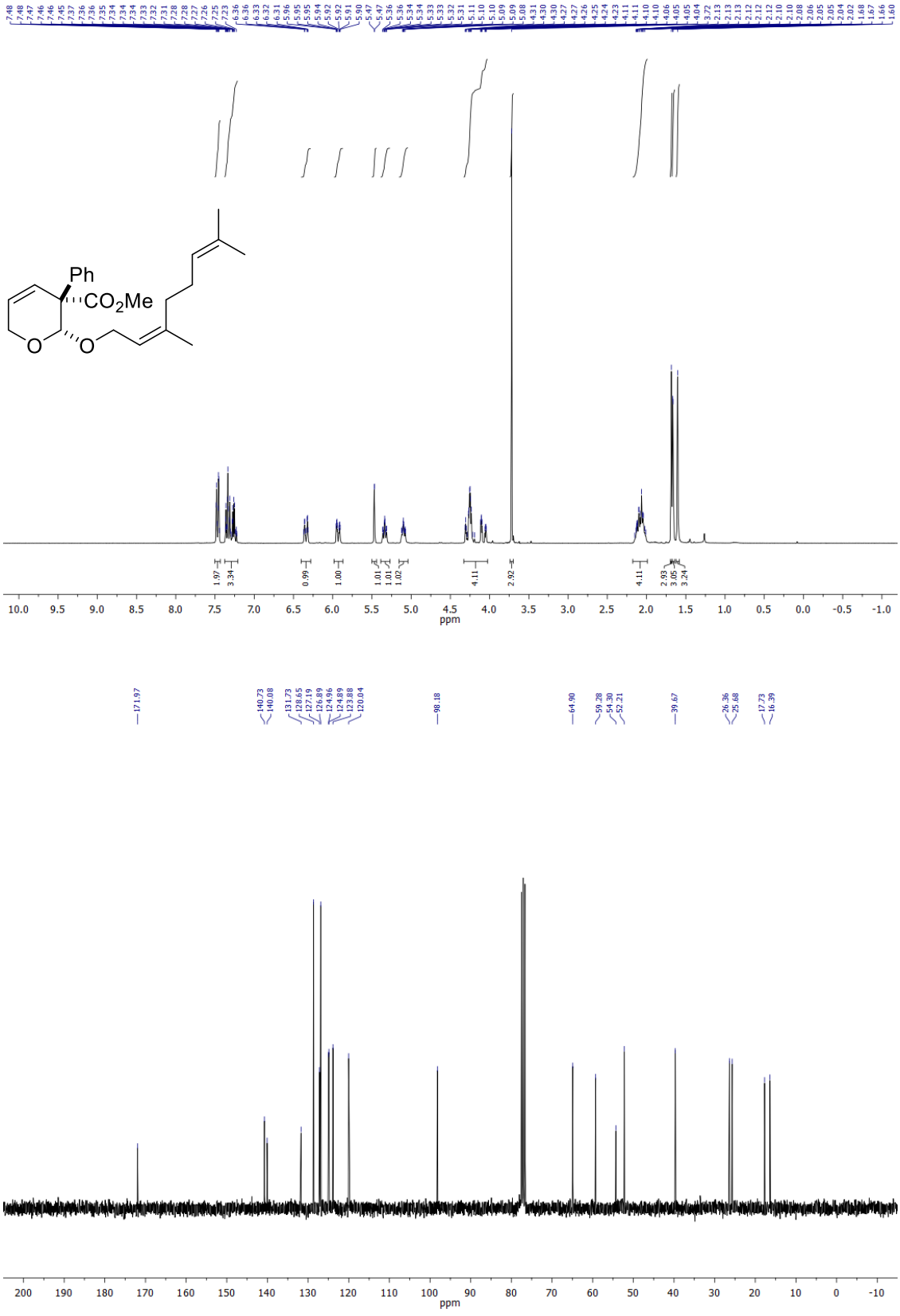




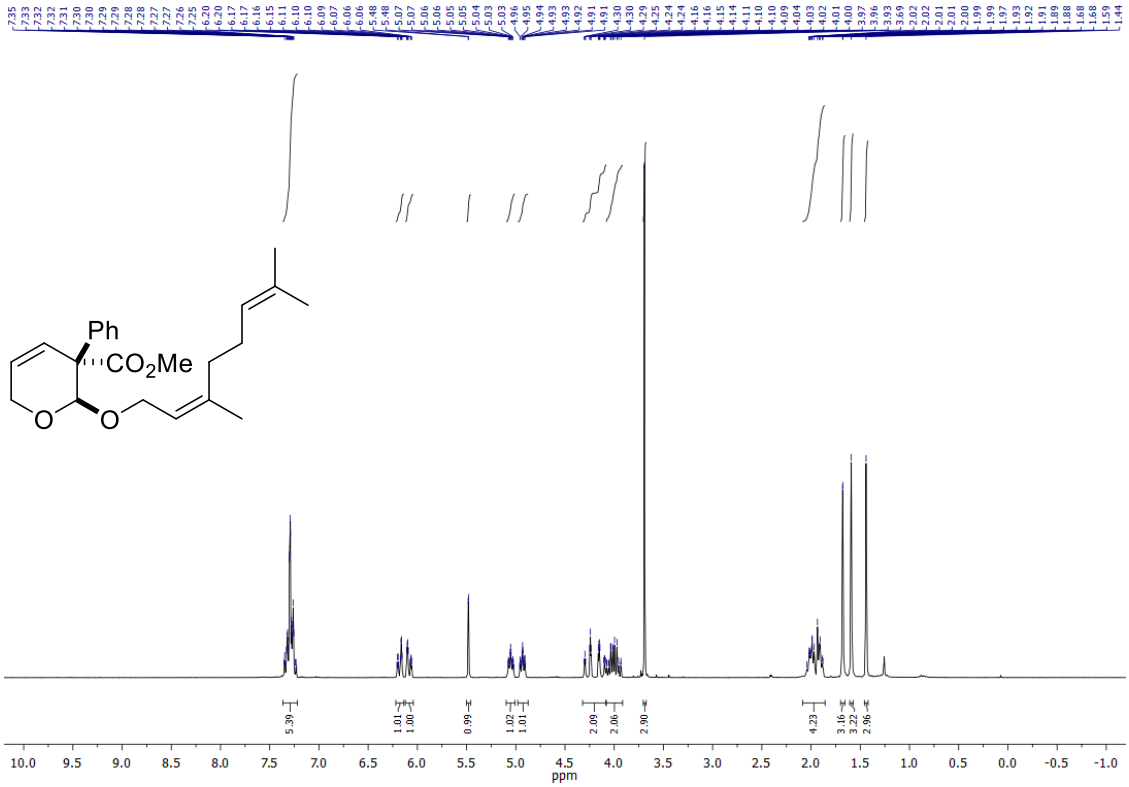
Compound **105r**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

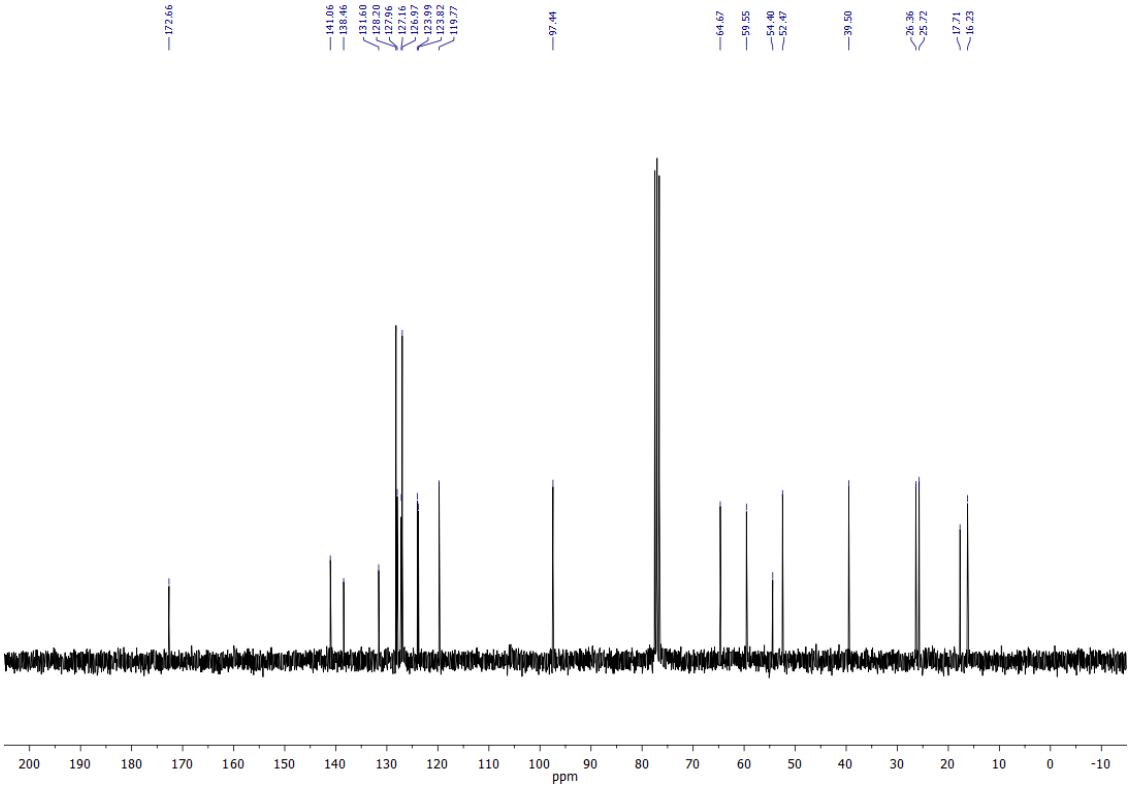


Compound *major*-**105s**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$)

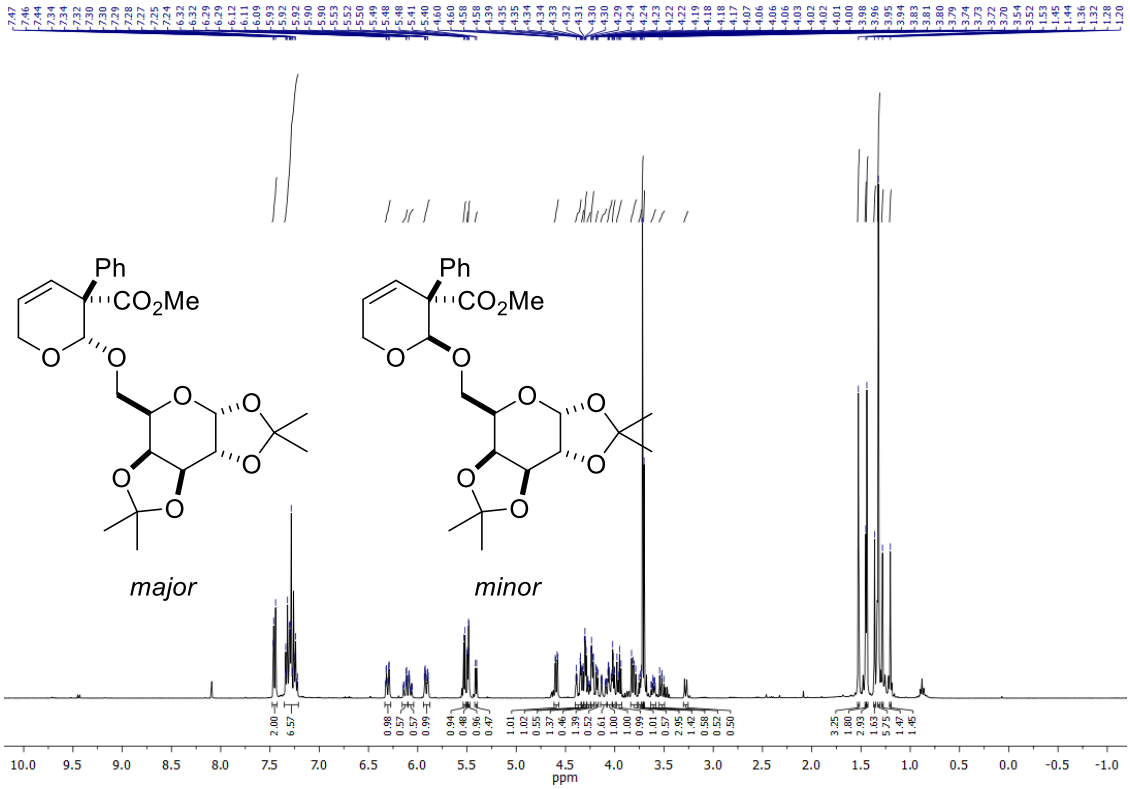


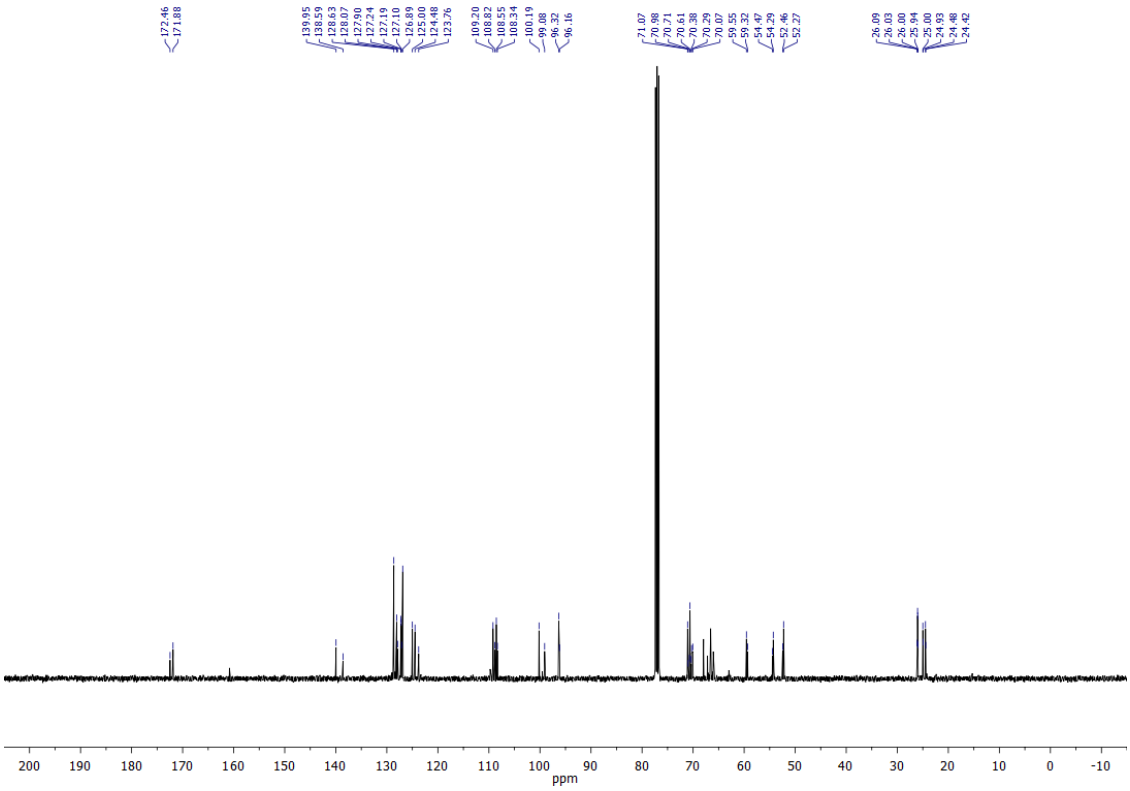
Compound *minor*-**105s**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$)



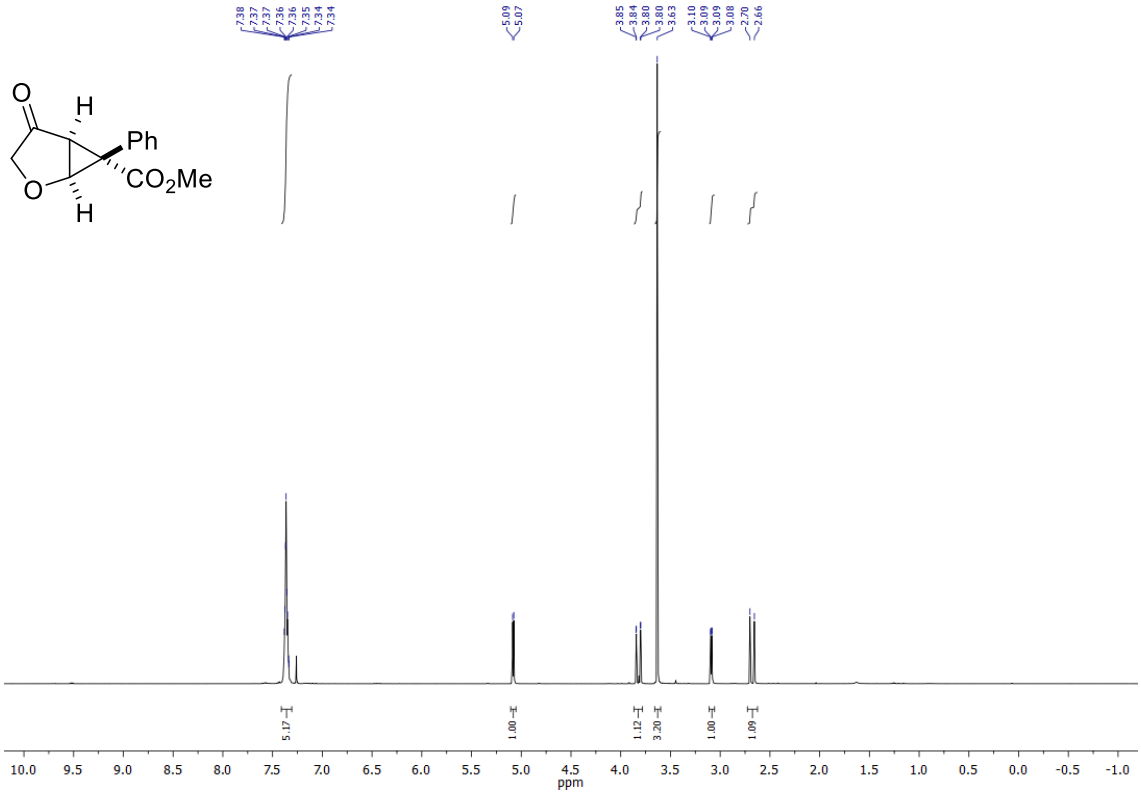


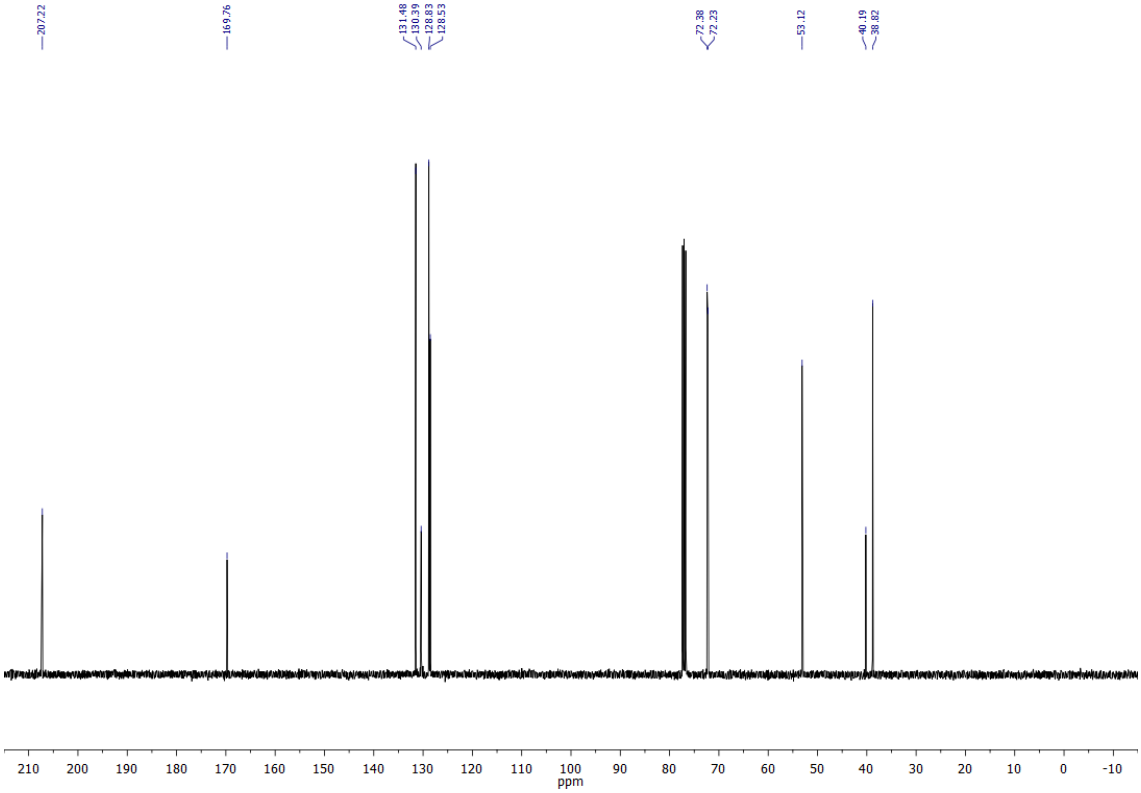
Compound **105t**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



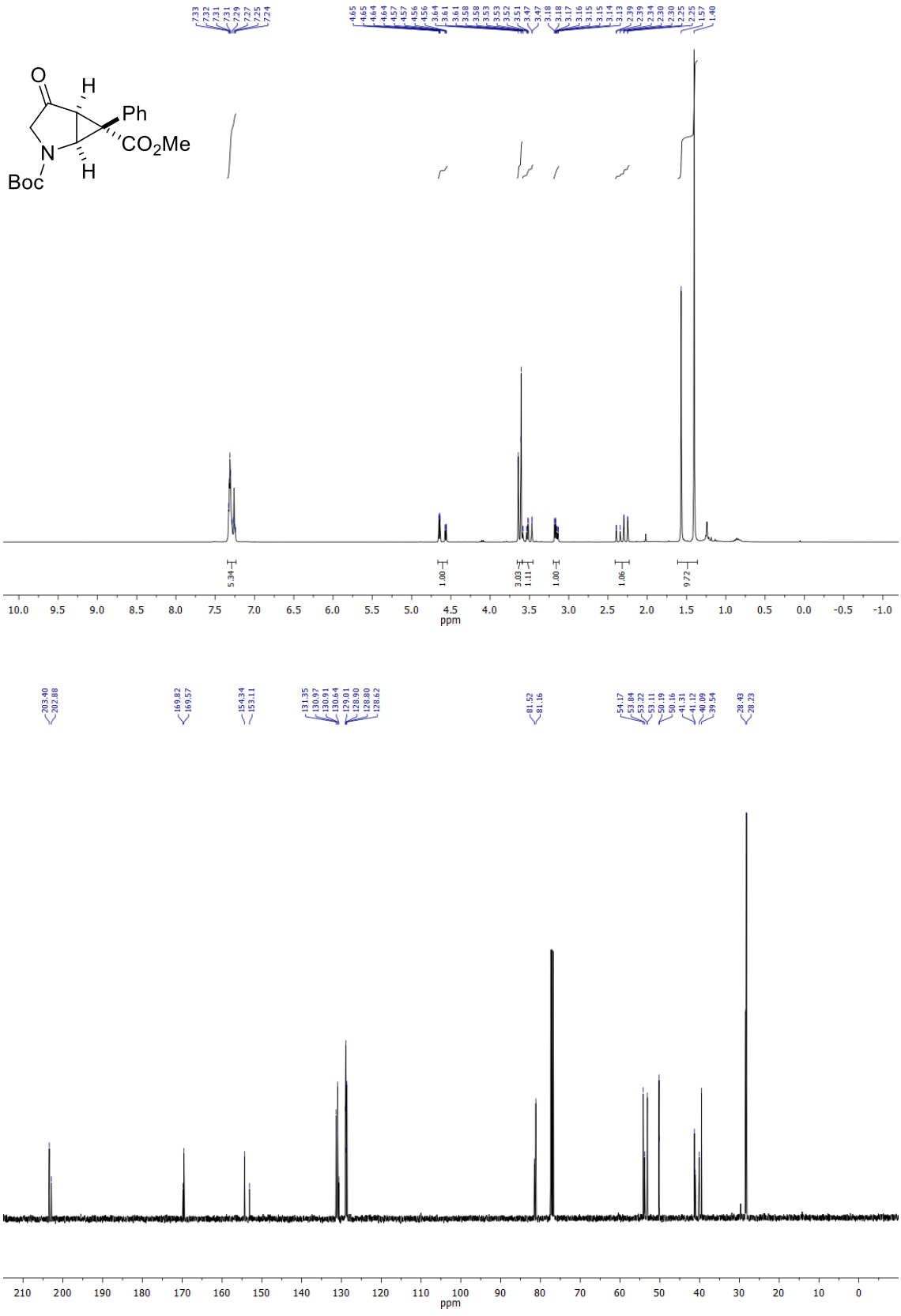


Compound **106a**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

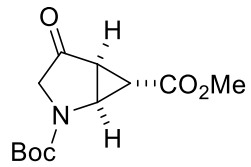


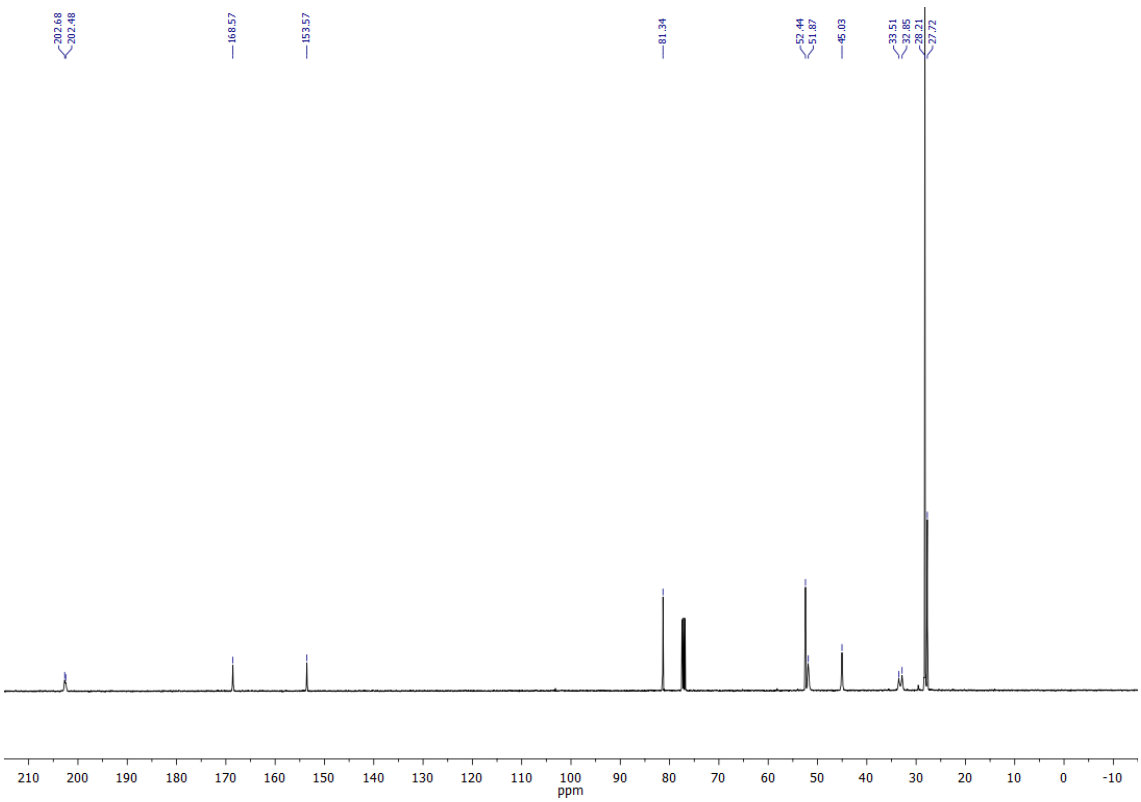


Compound **106b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

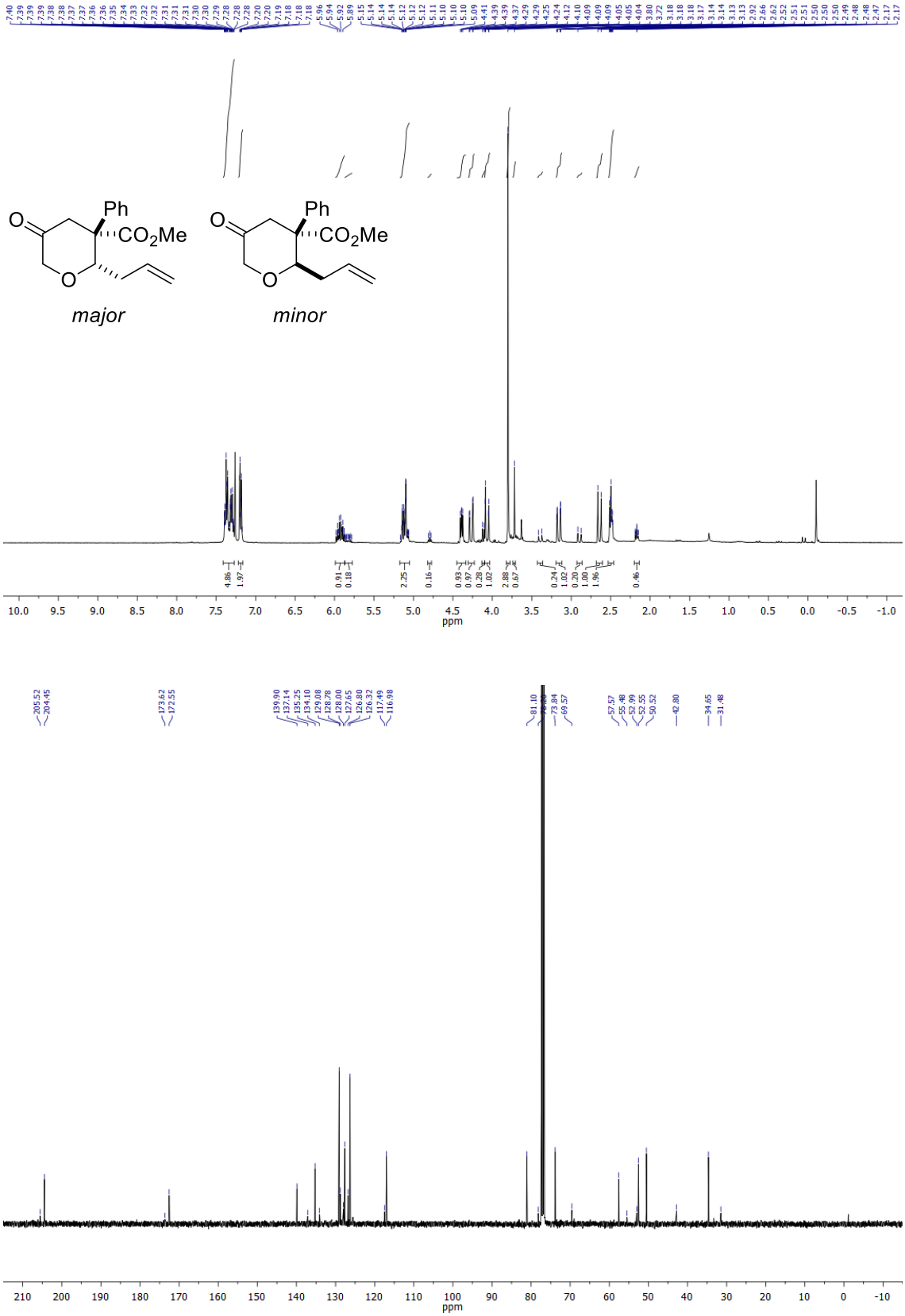


Compound **106c**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

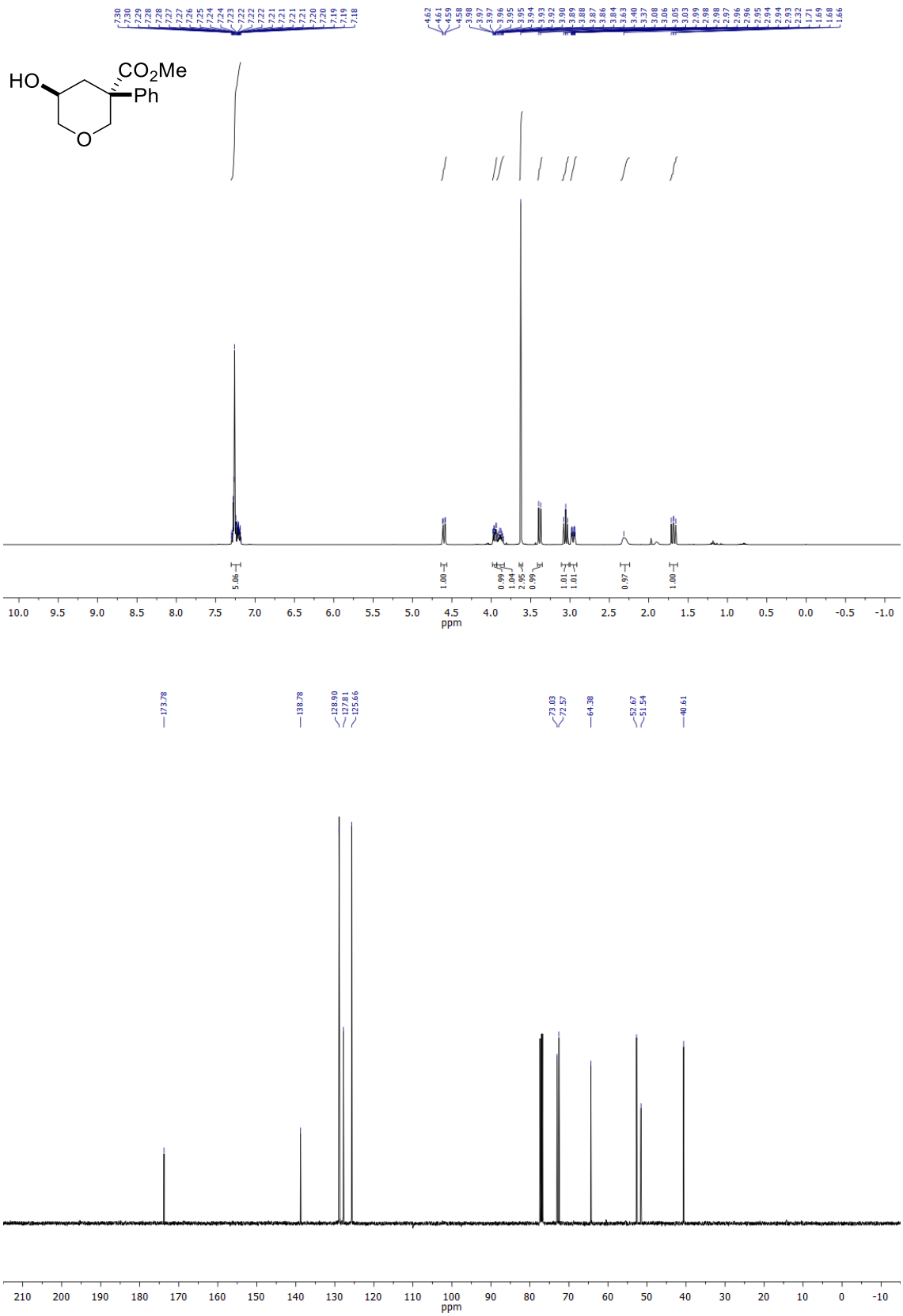




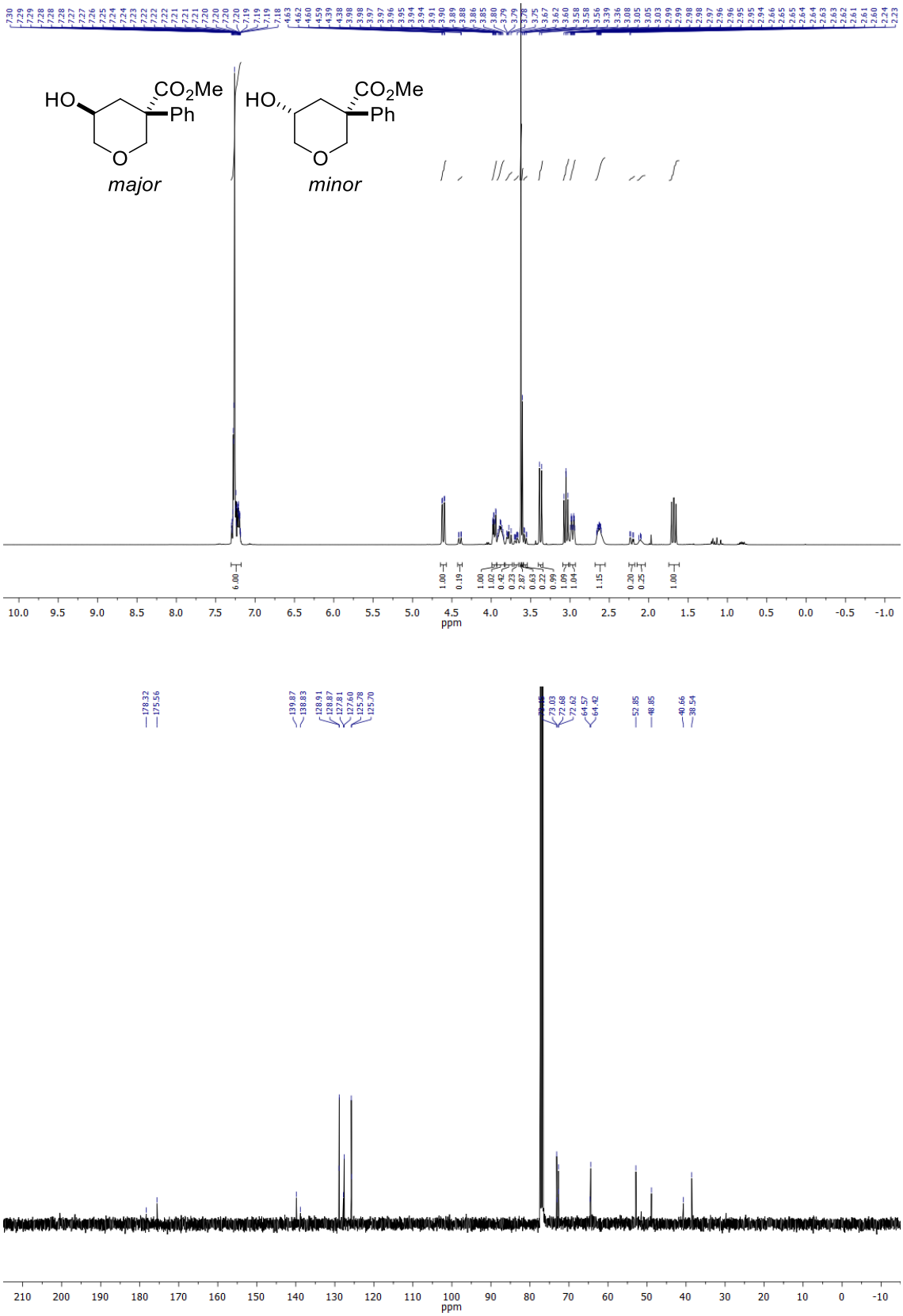
Compound **108a**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



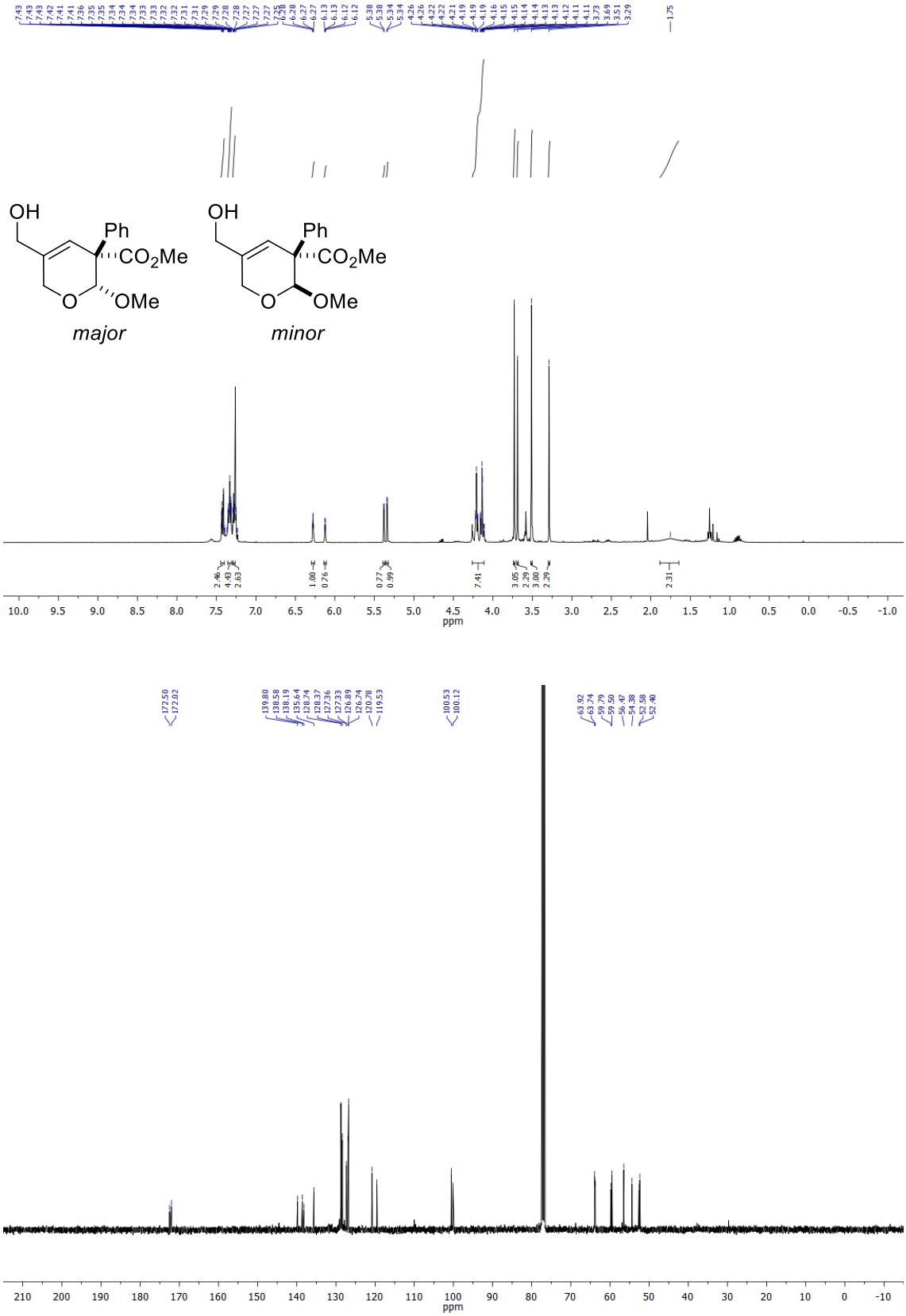
Compound *major*-**108b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



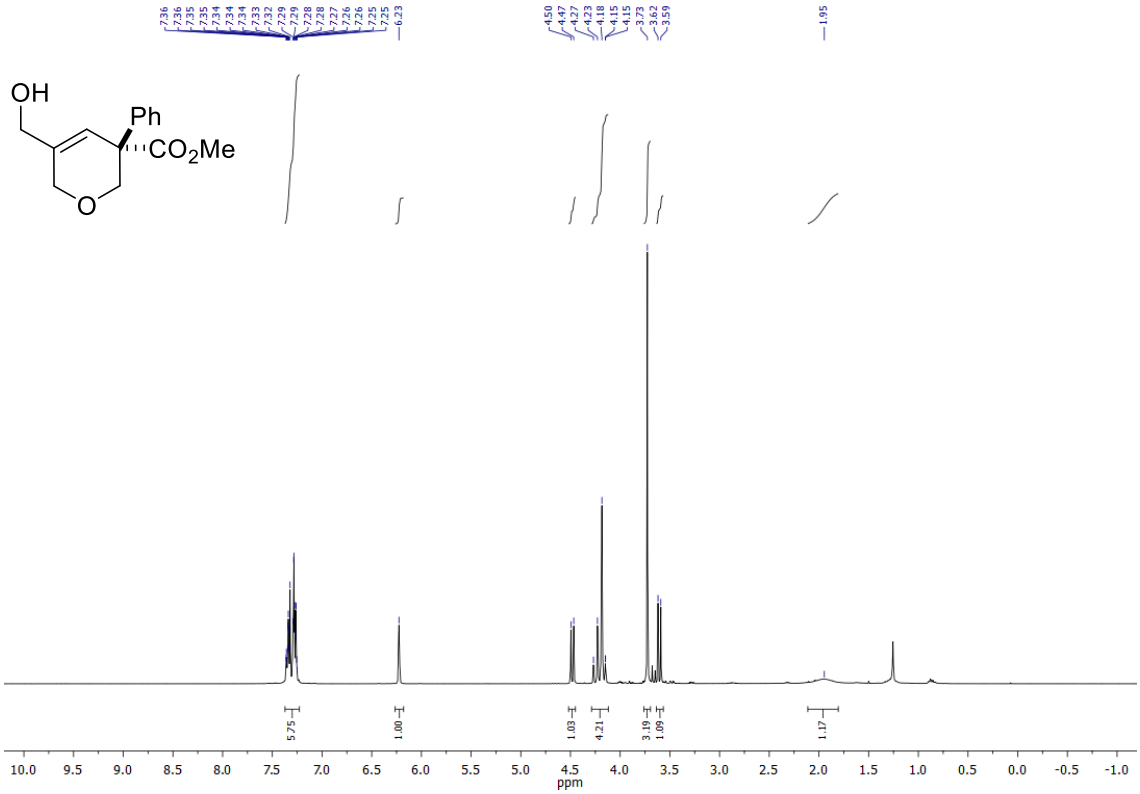
Compound **108b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

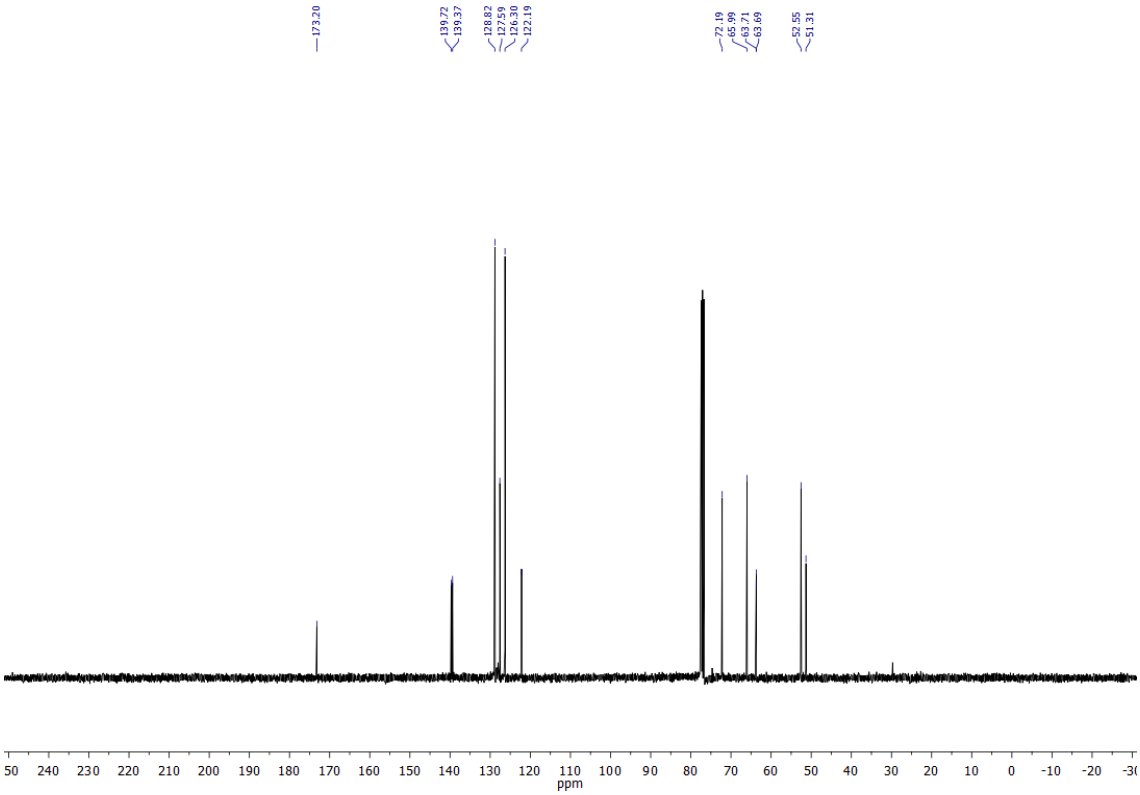


Compound **114a**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

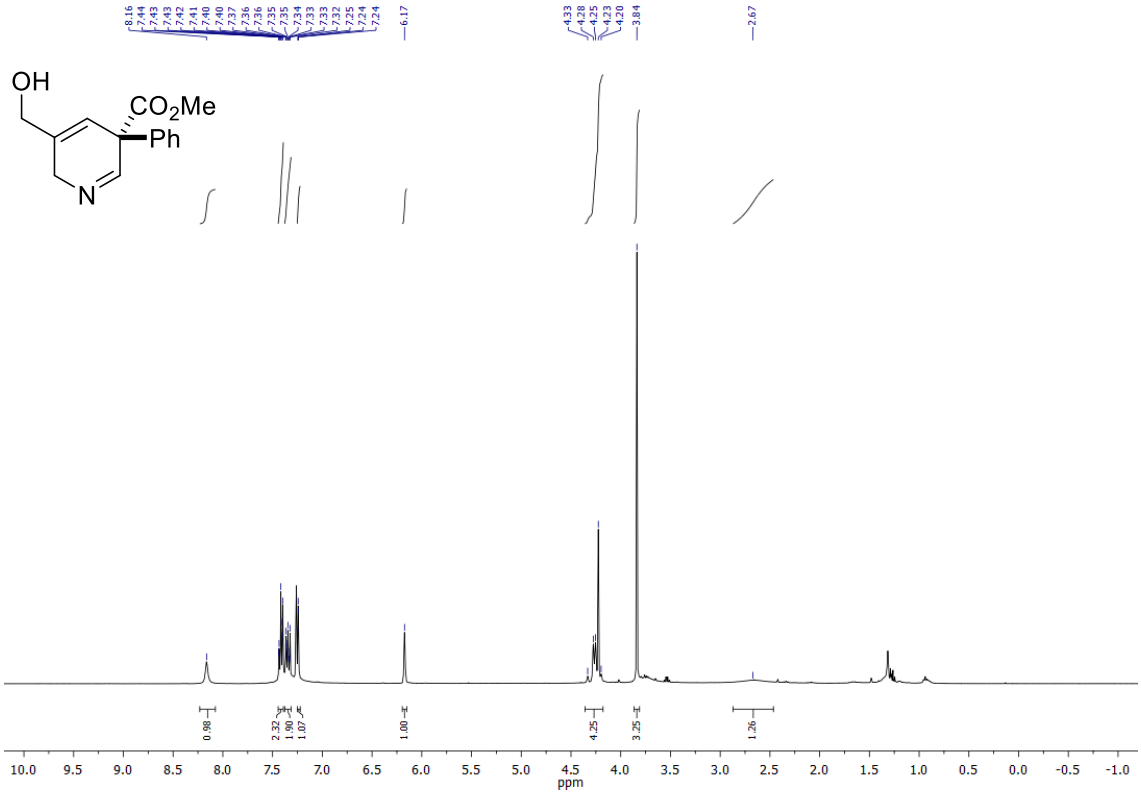


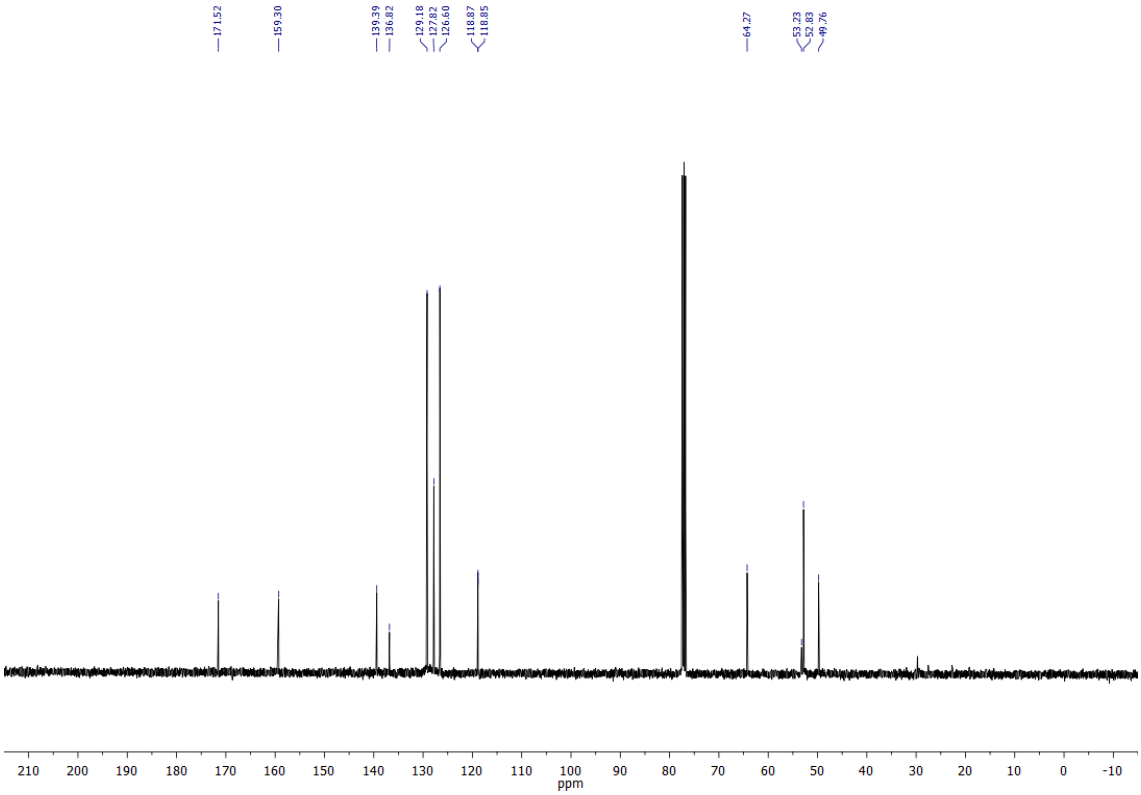
Compound **114b**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



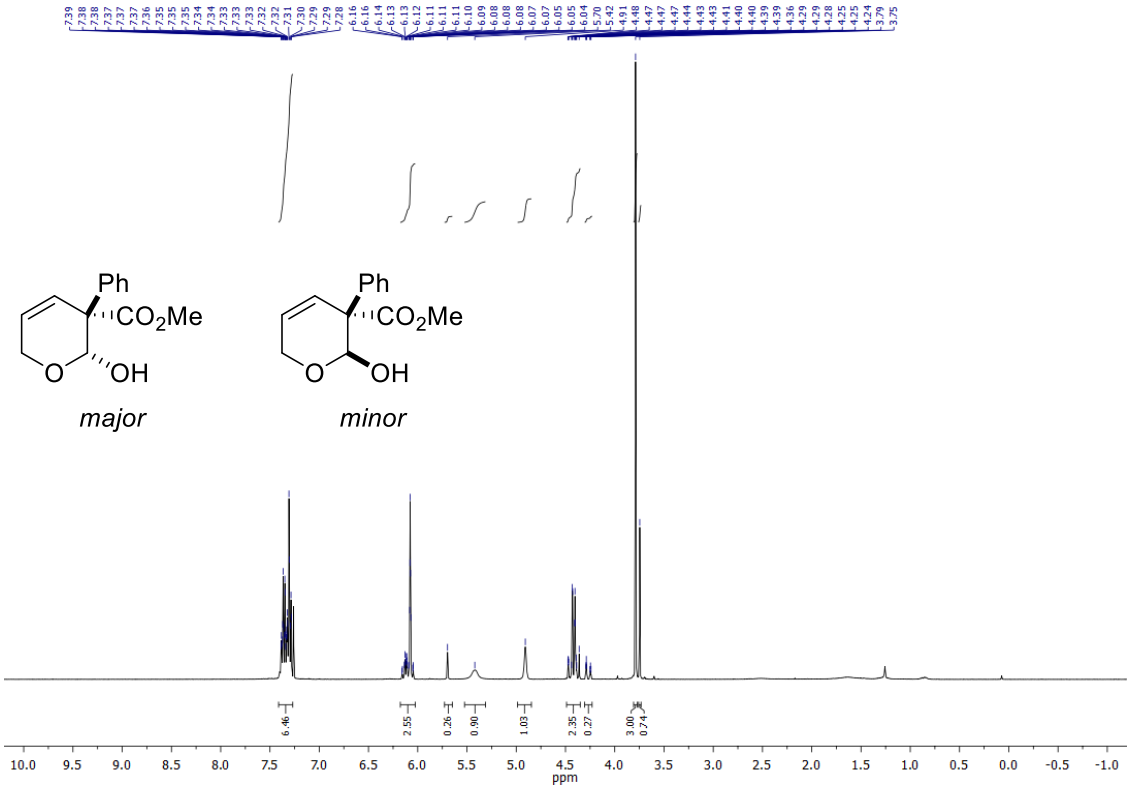


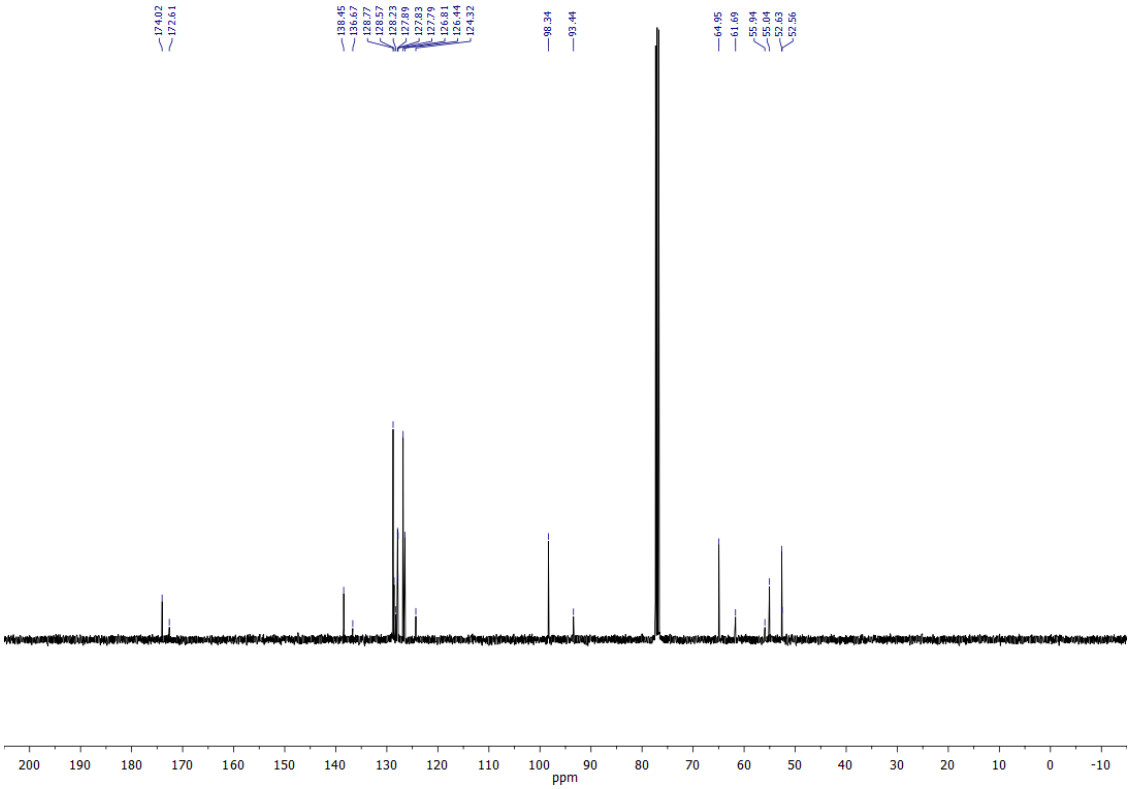
Compound **114c**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



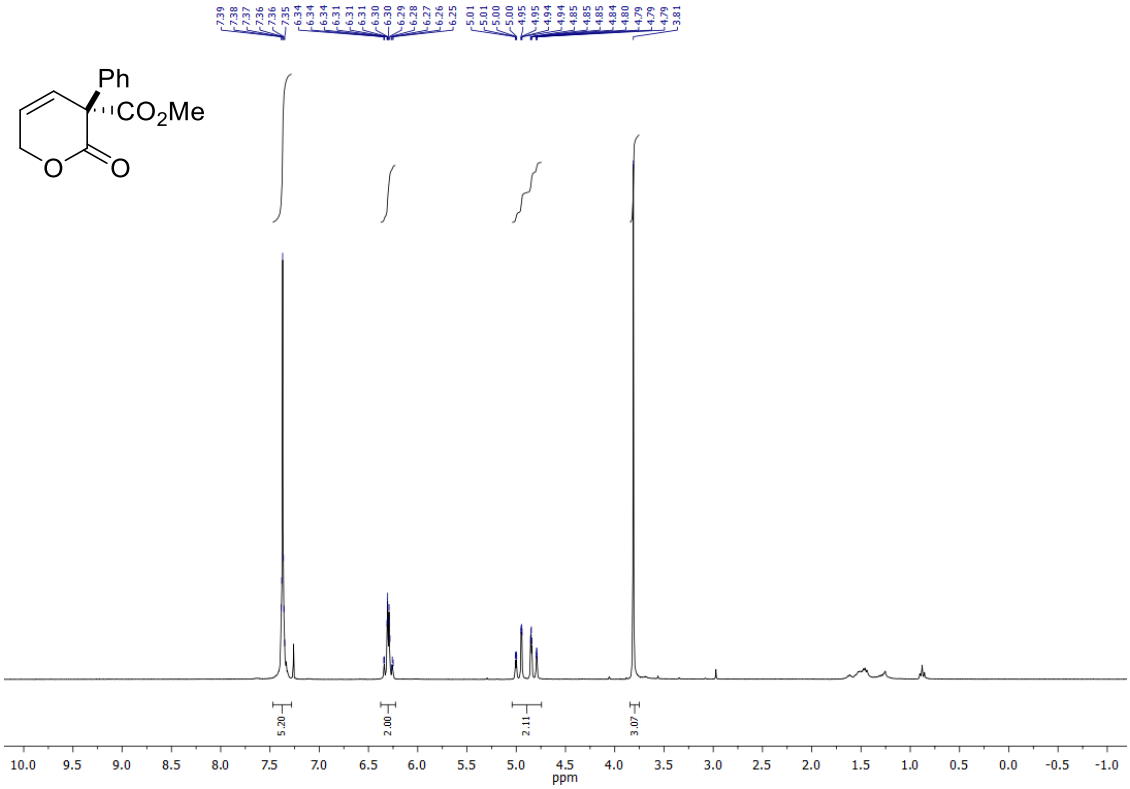


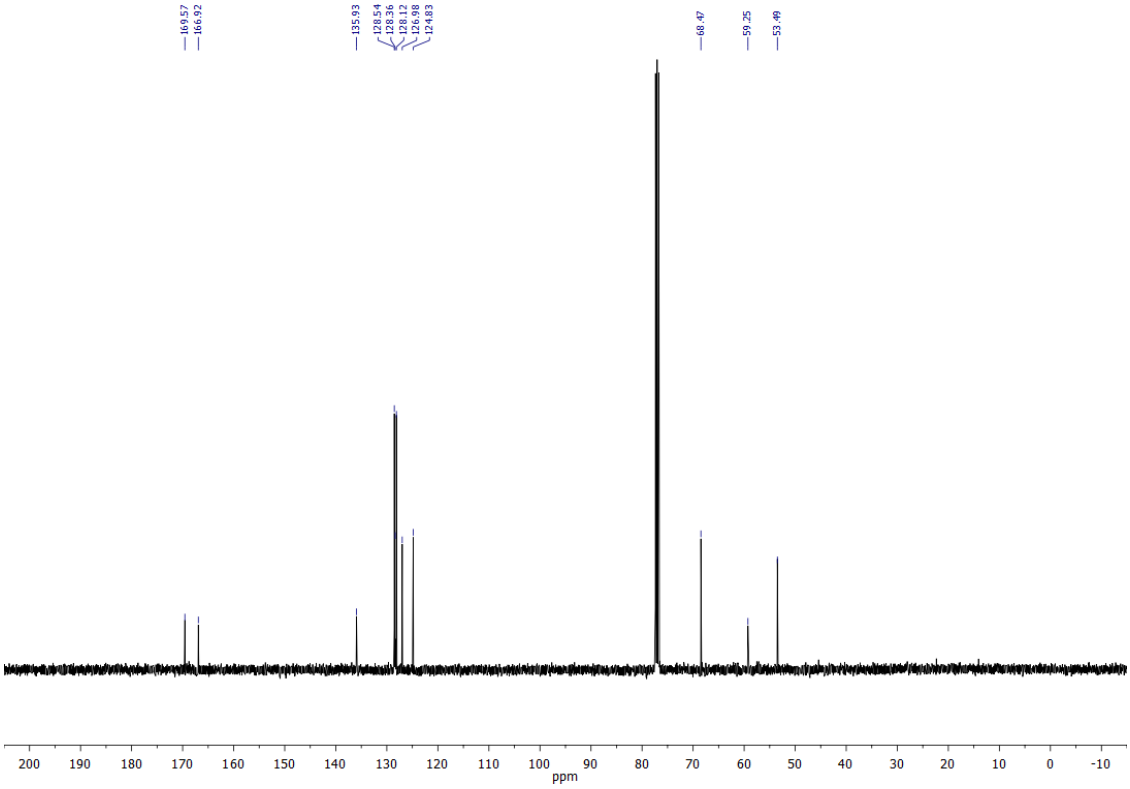
Compound **184**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



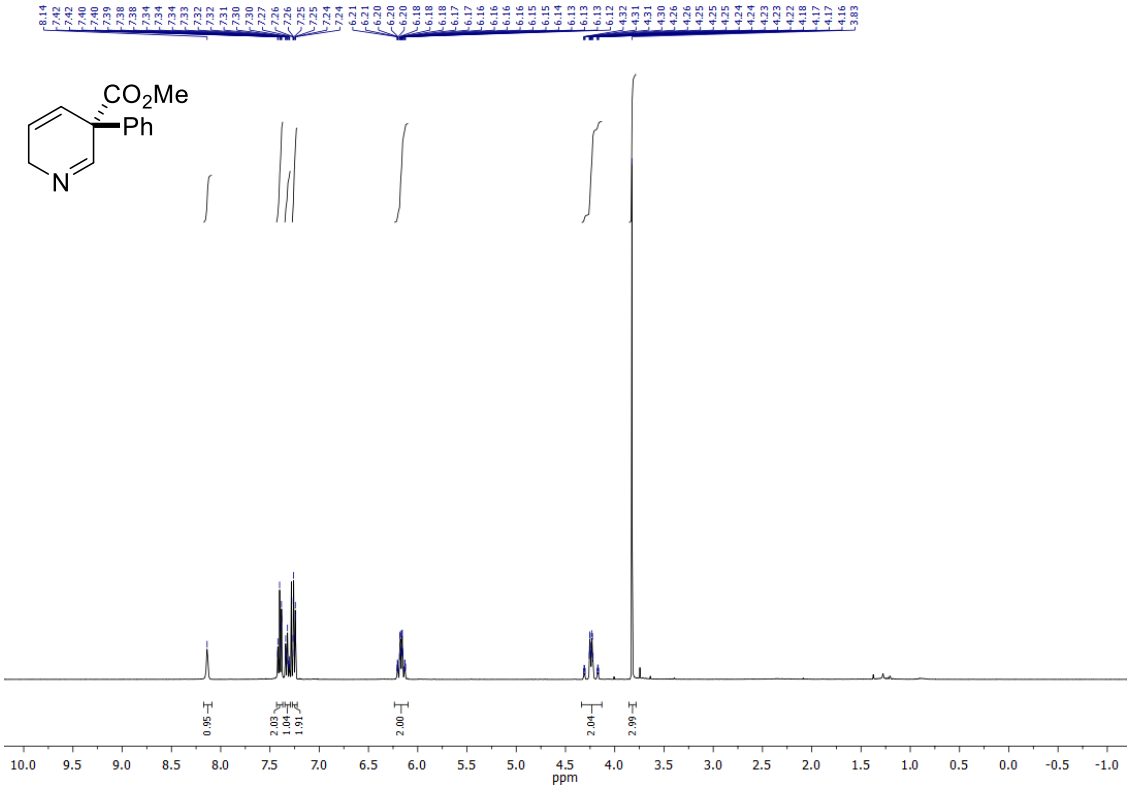


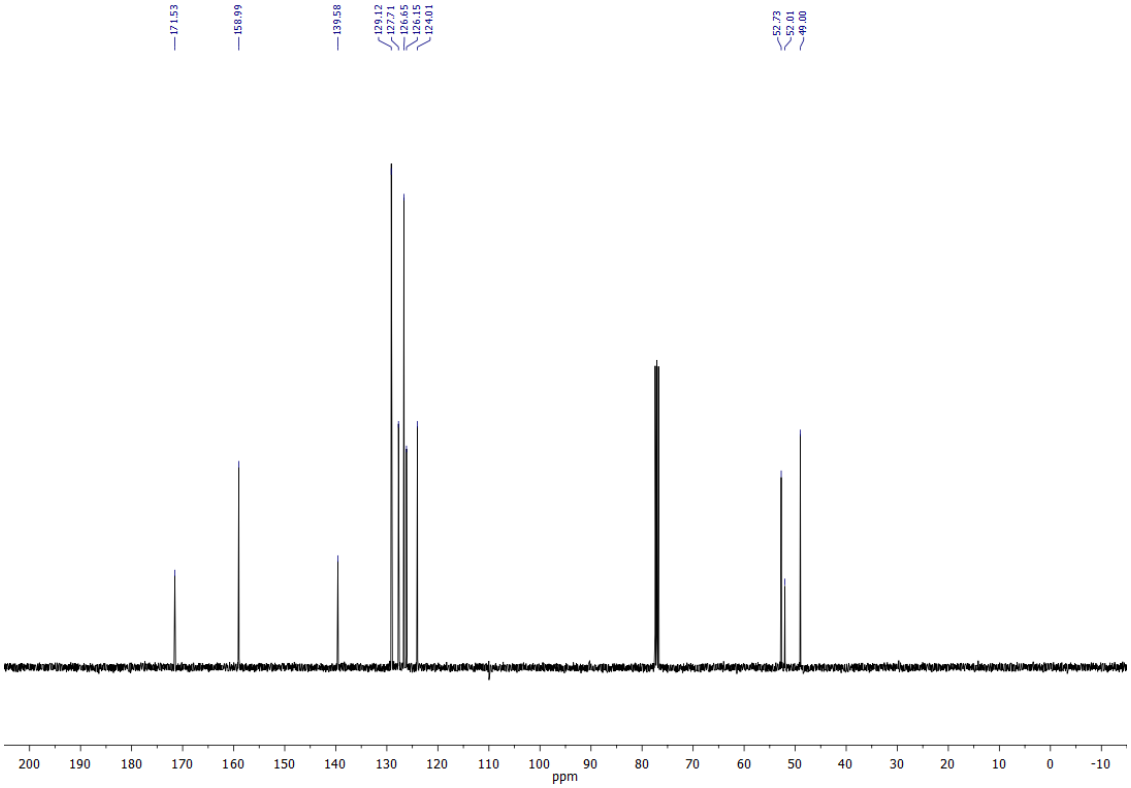
Compound **185**: ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



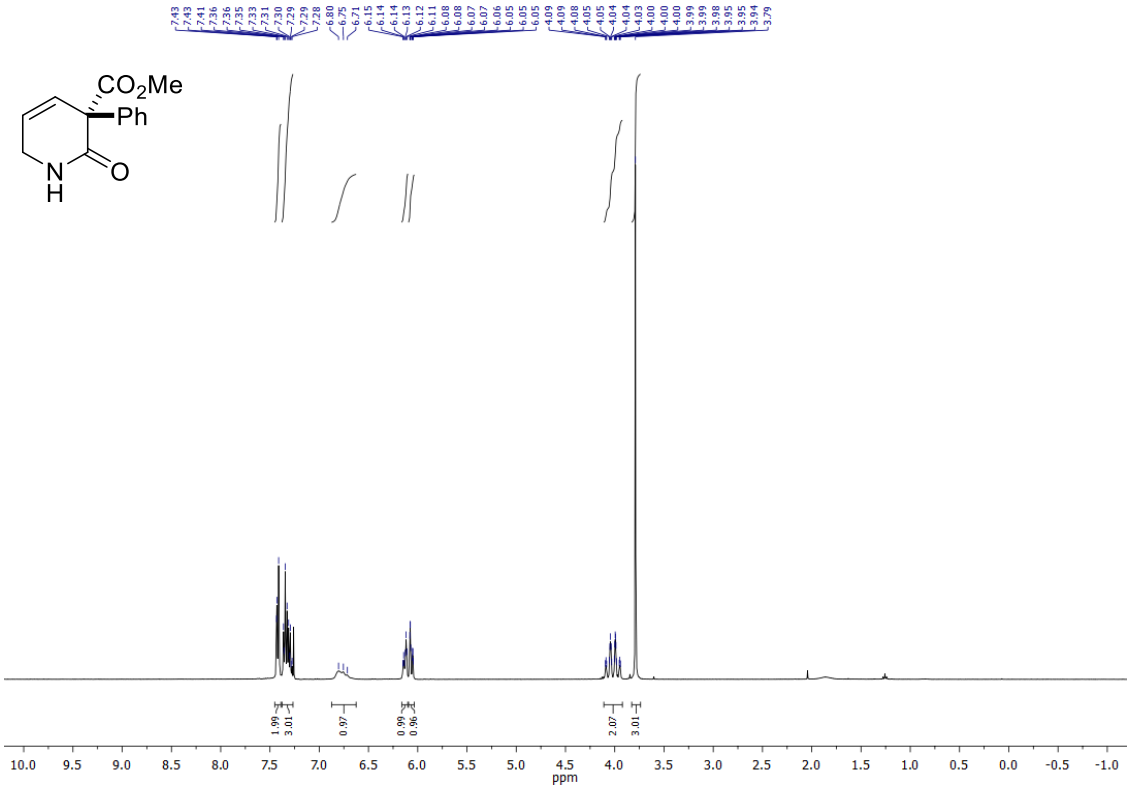


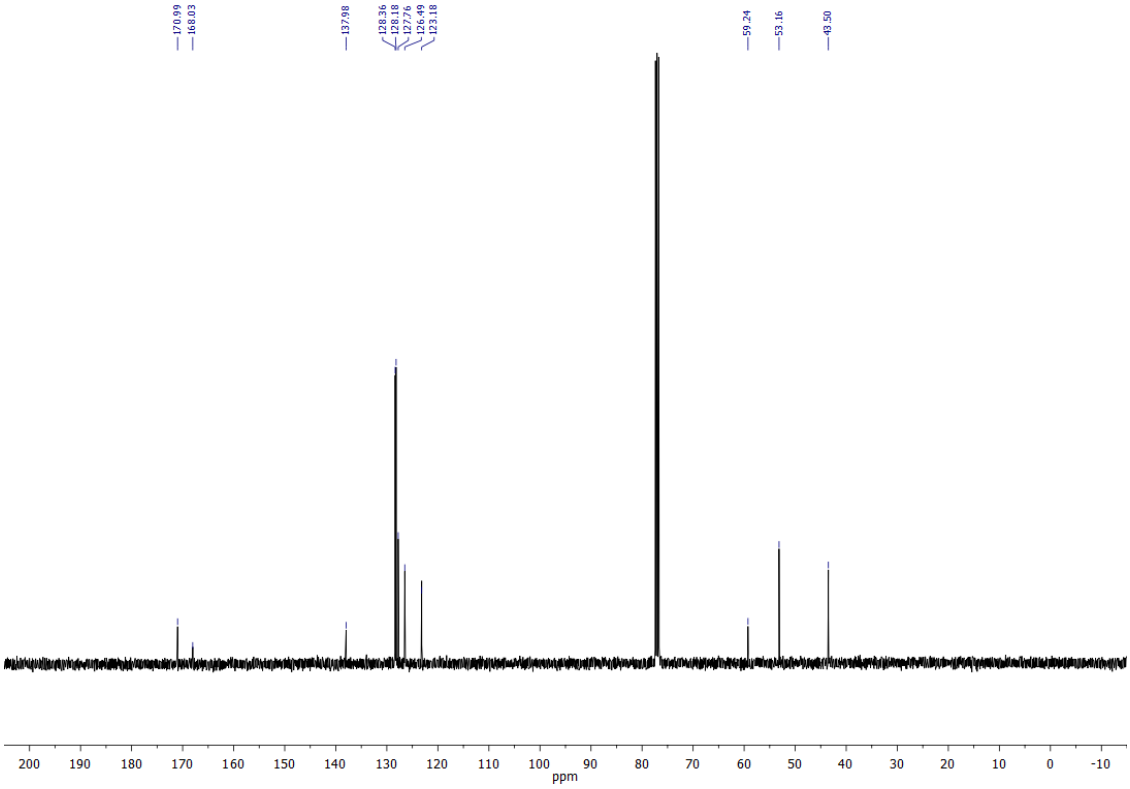
Compound **186**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



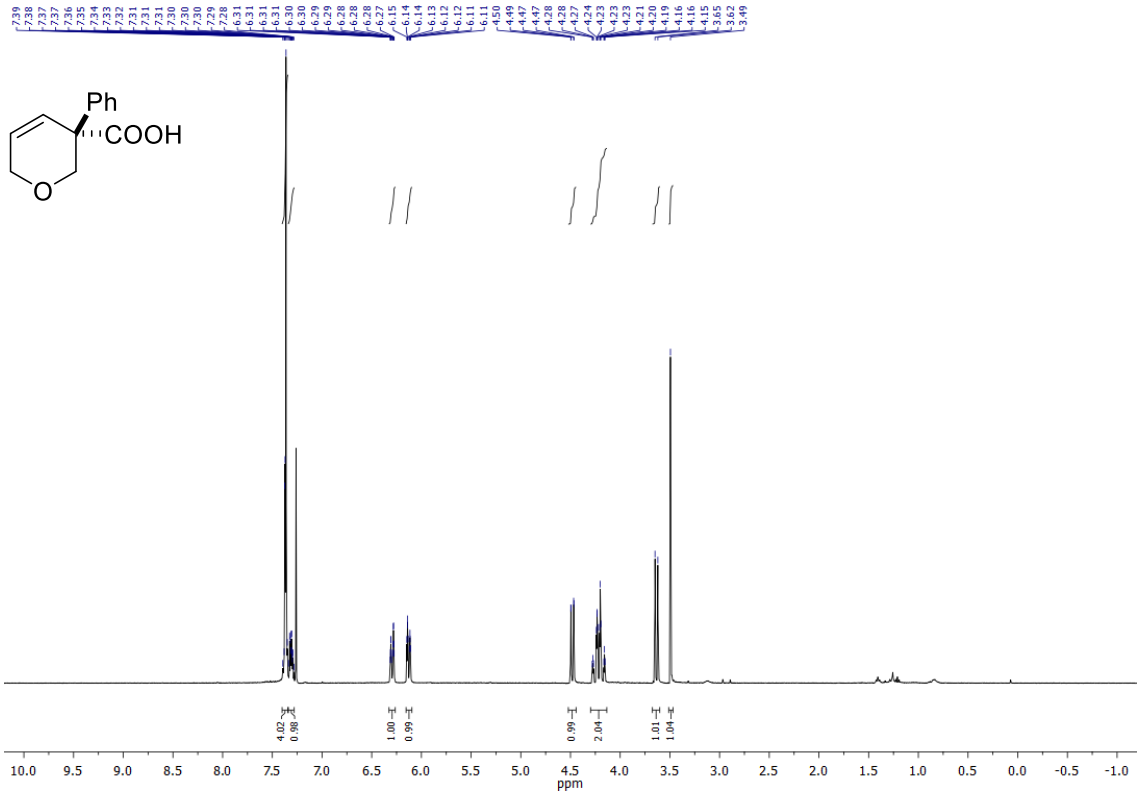


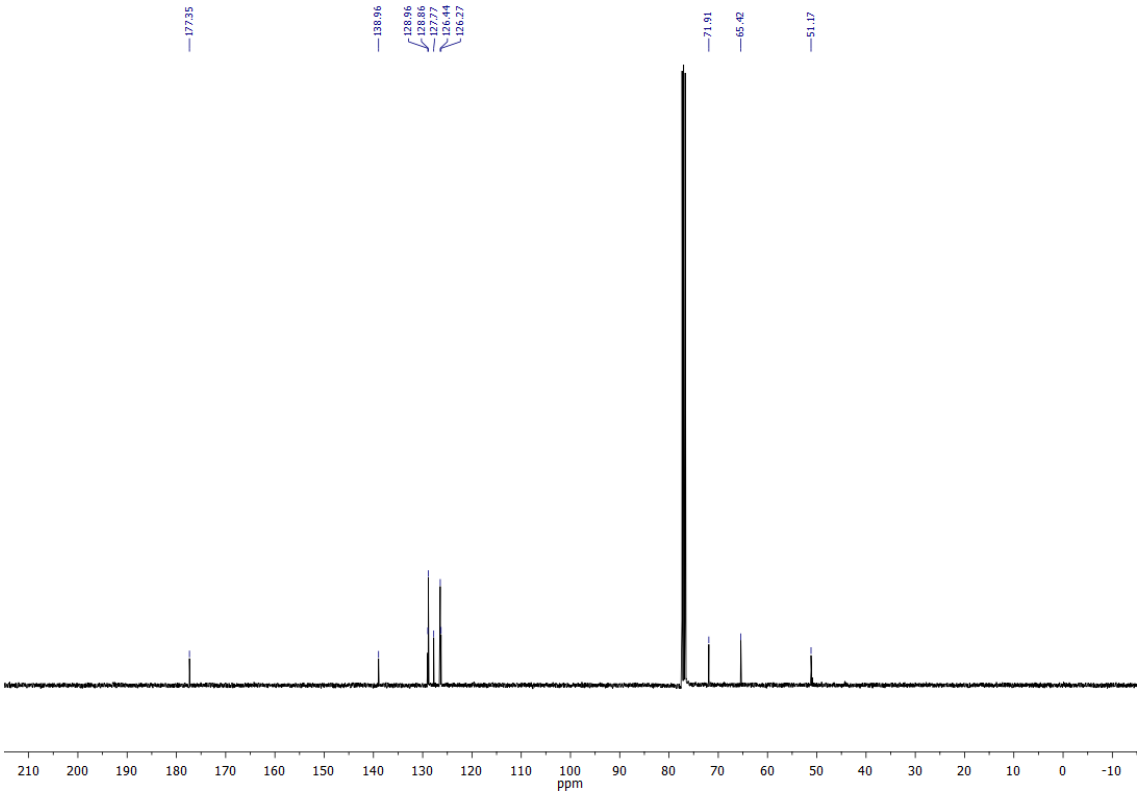
Compound **188**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



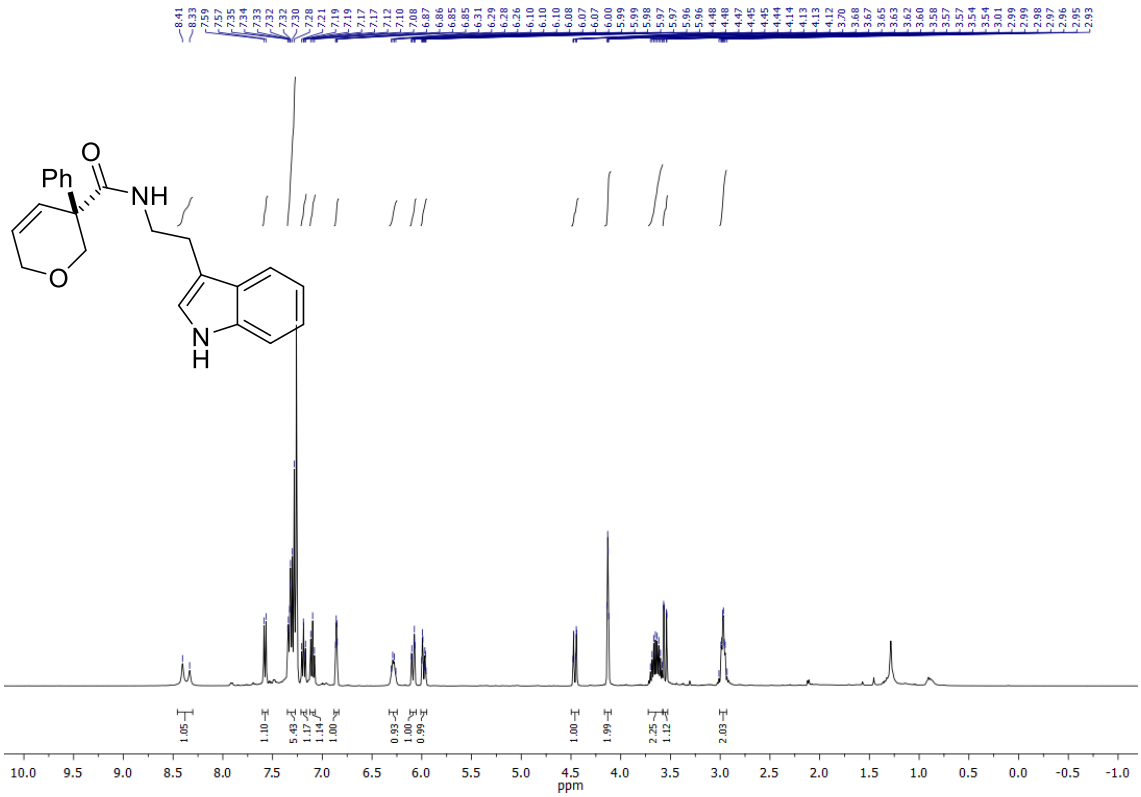


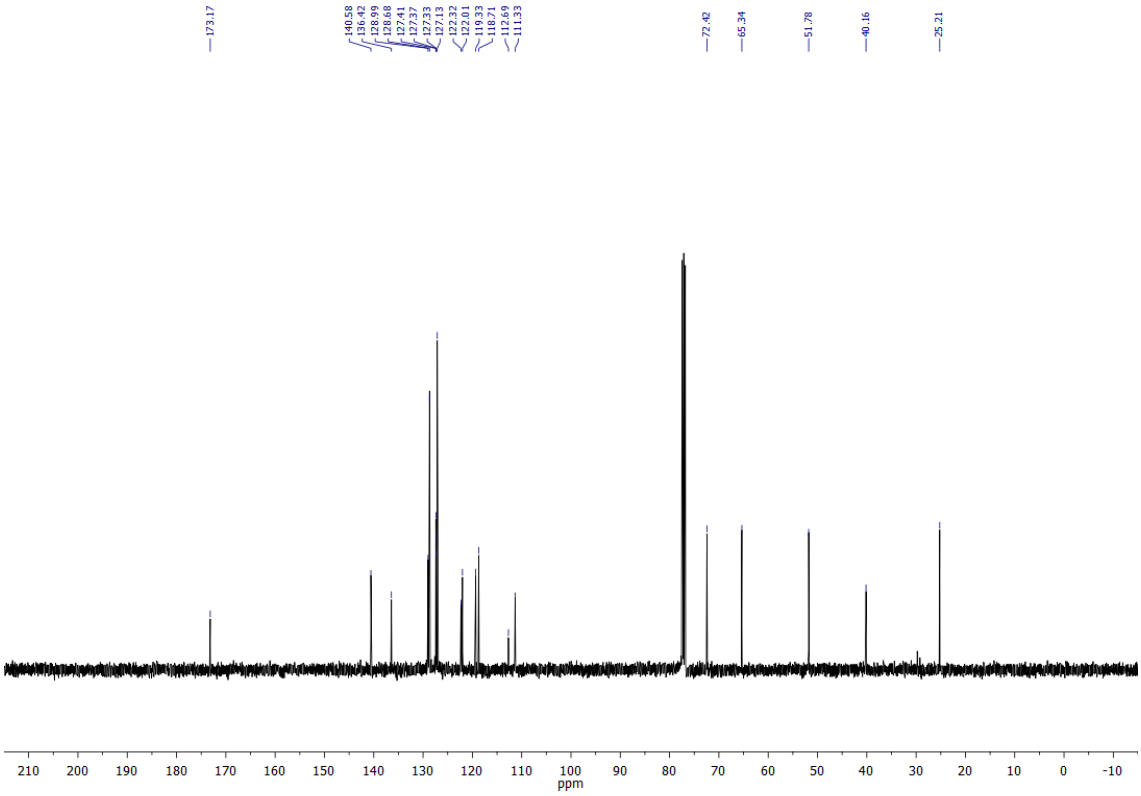
Compound **191**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



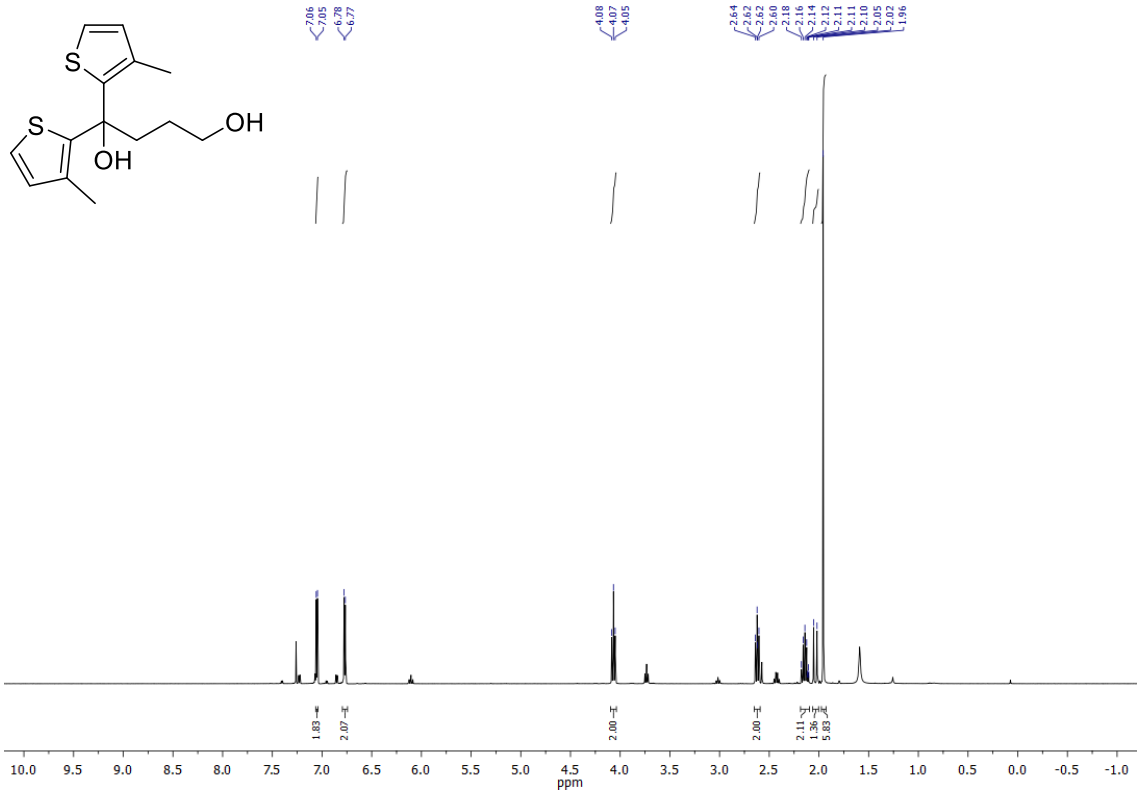


Compound **193**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

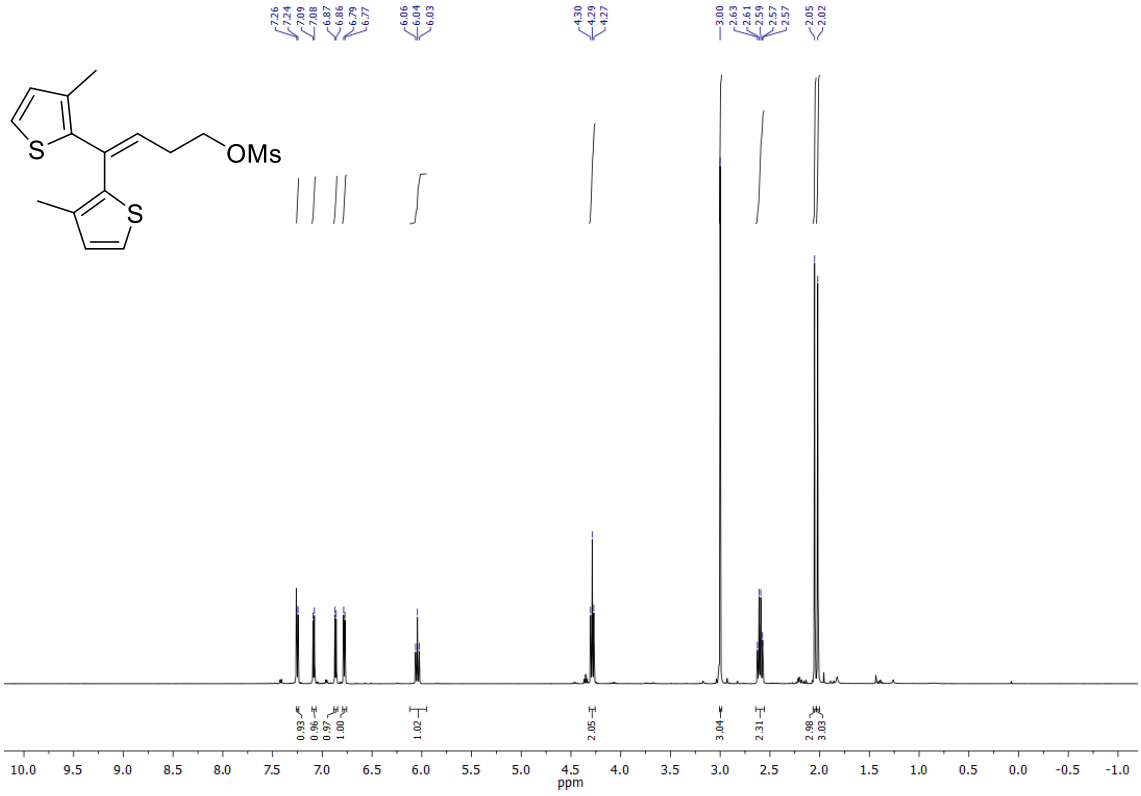




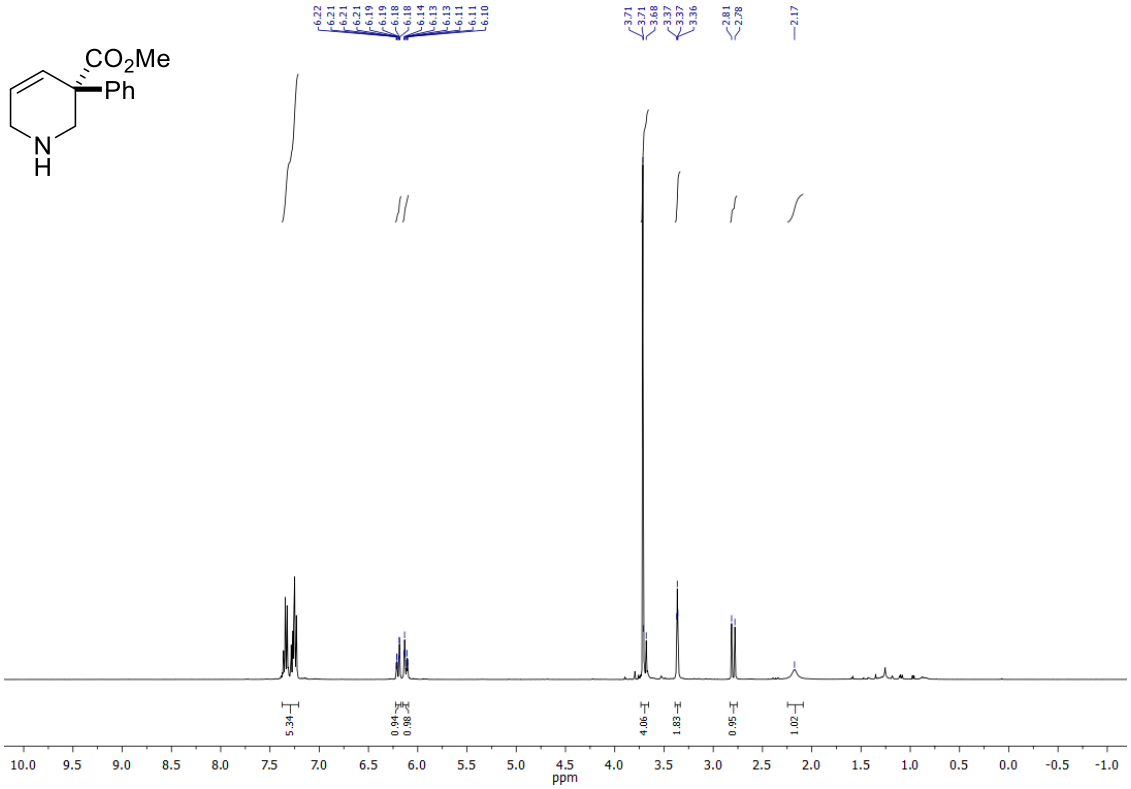
Compound **196**: ^{1}H-NMR (400 MHz, $CDCl_3$)

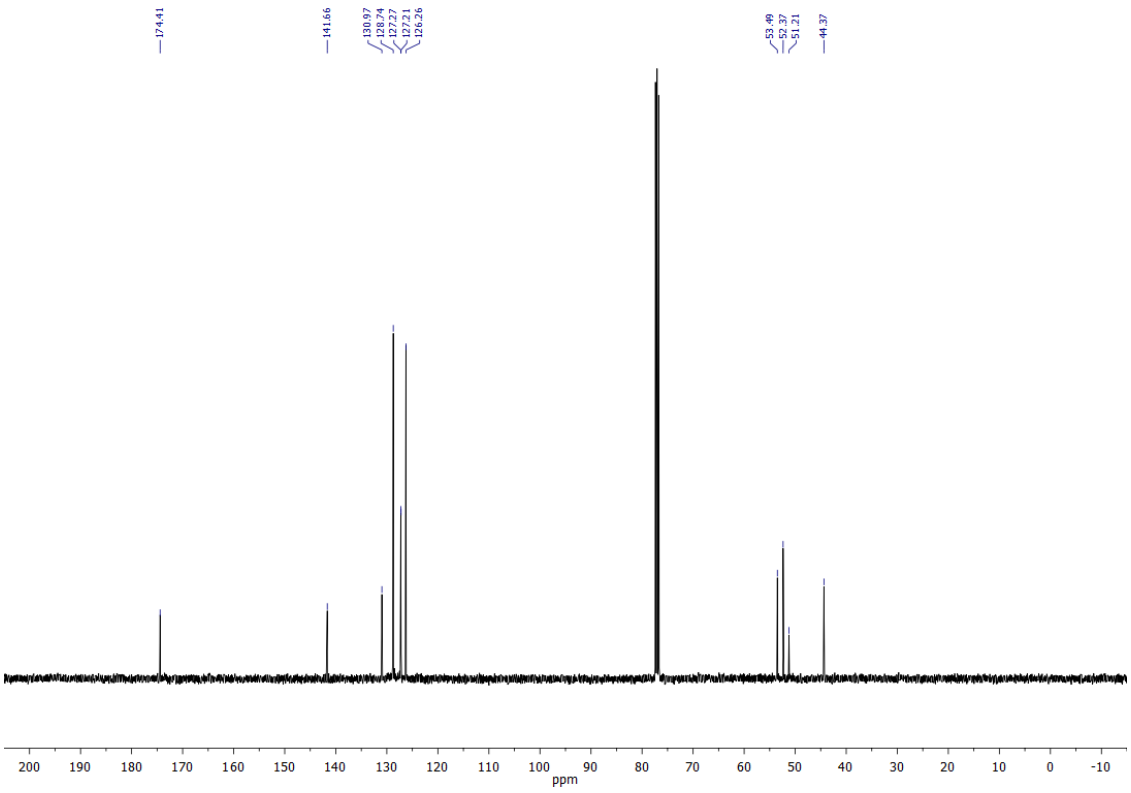


Compound **197**: ^{1}H-NMR (400 MHz, $CDCl_3$)

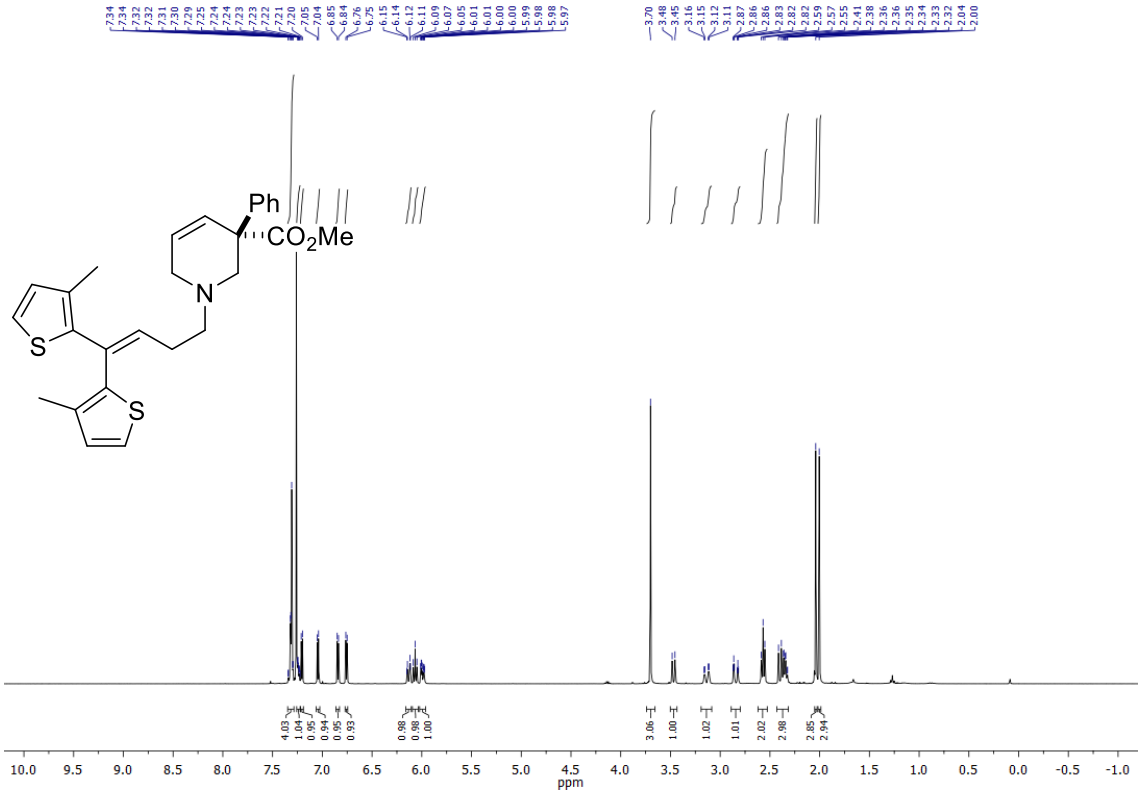


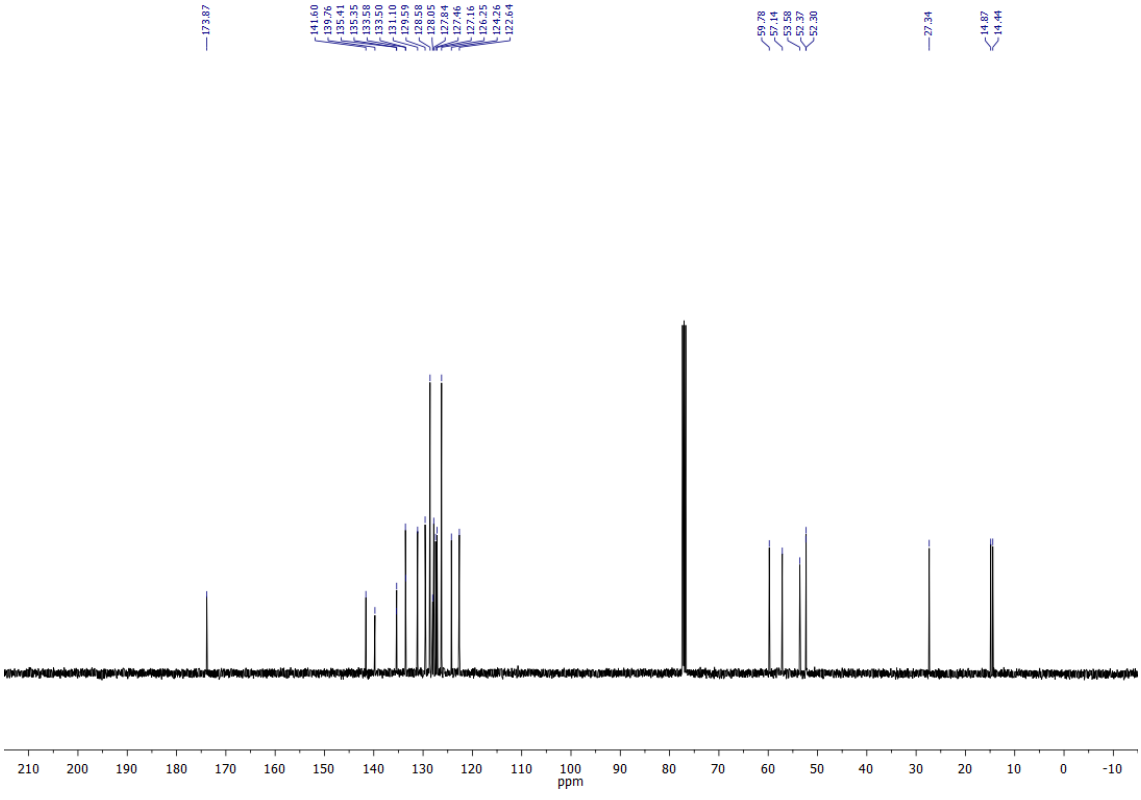
Compound **198**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



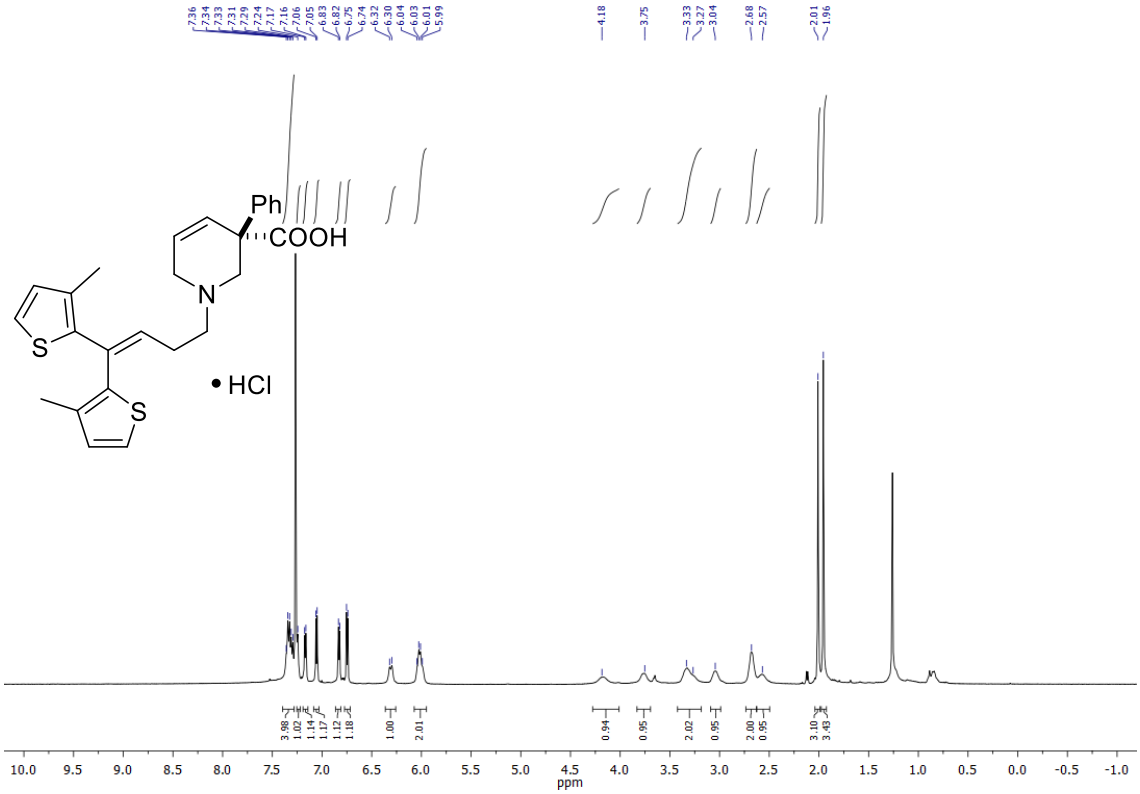


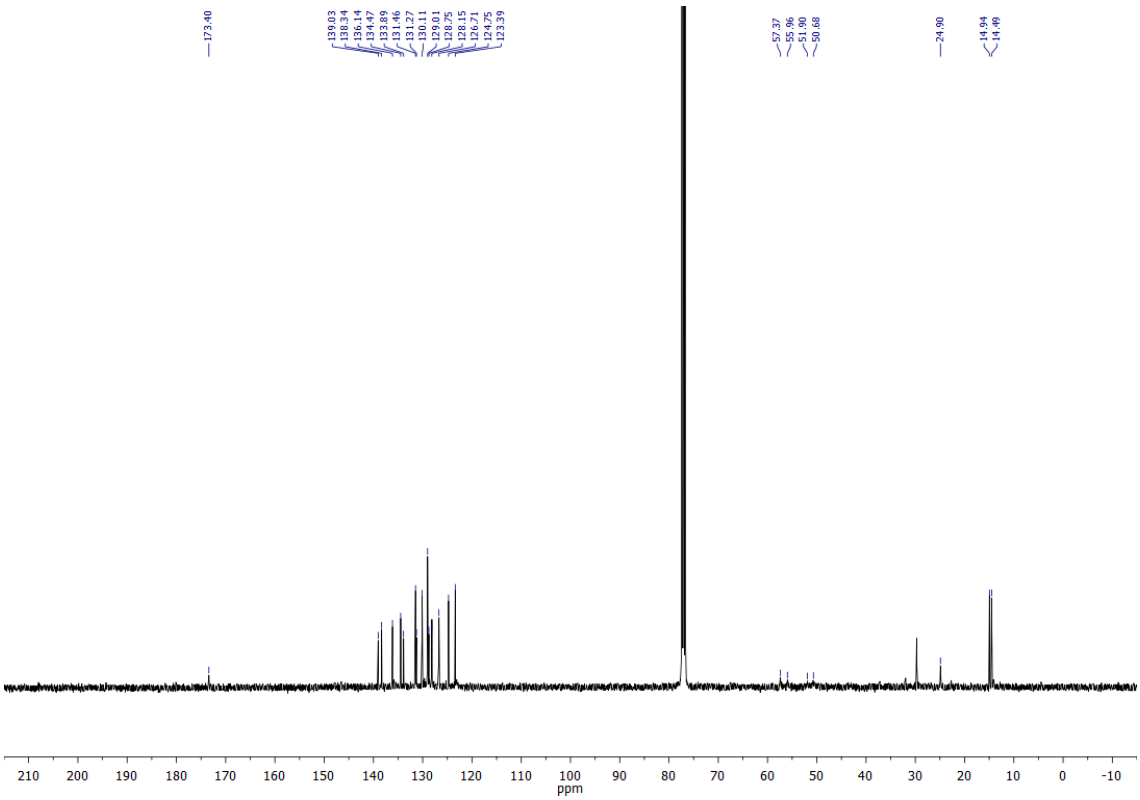
Compound **201**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



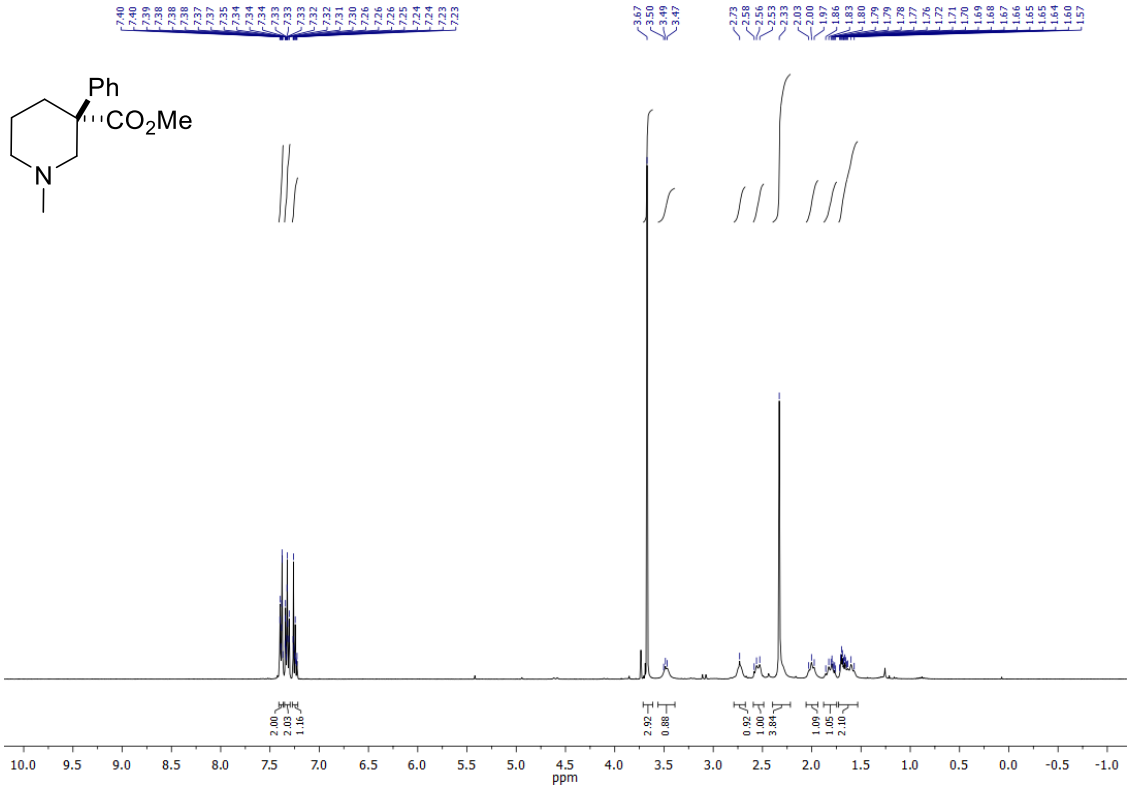


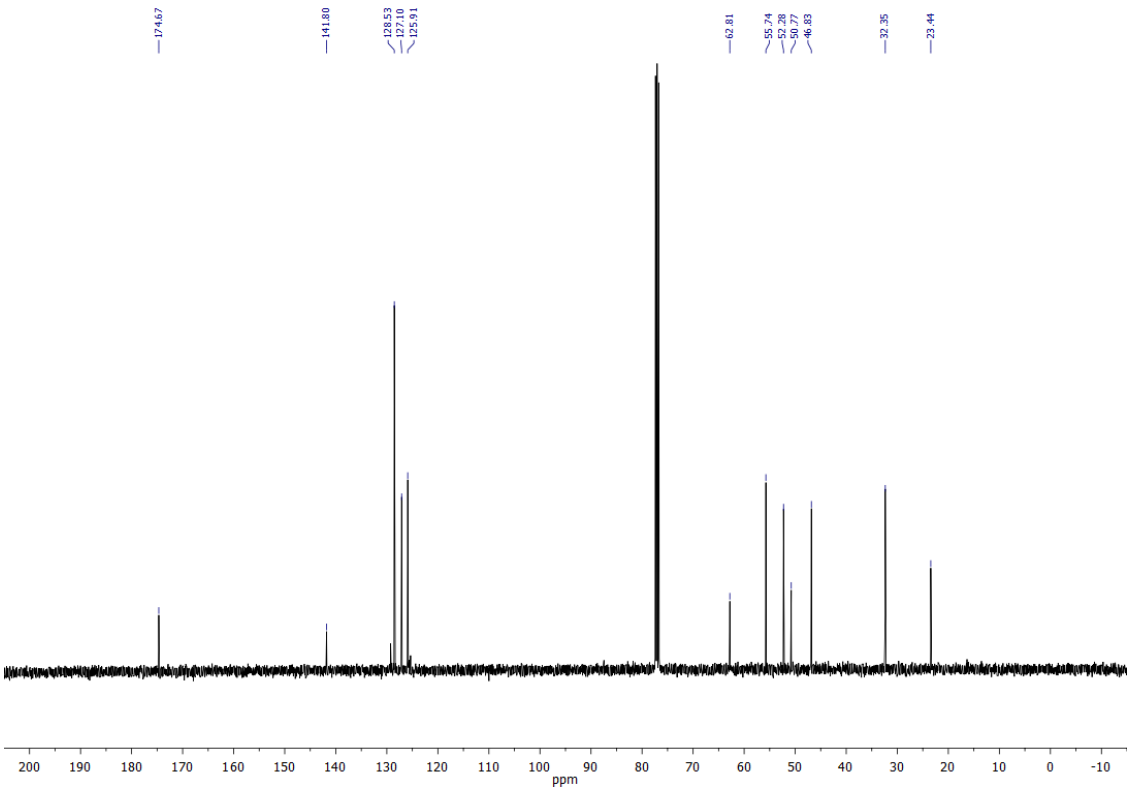
Compound **199**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



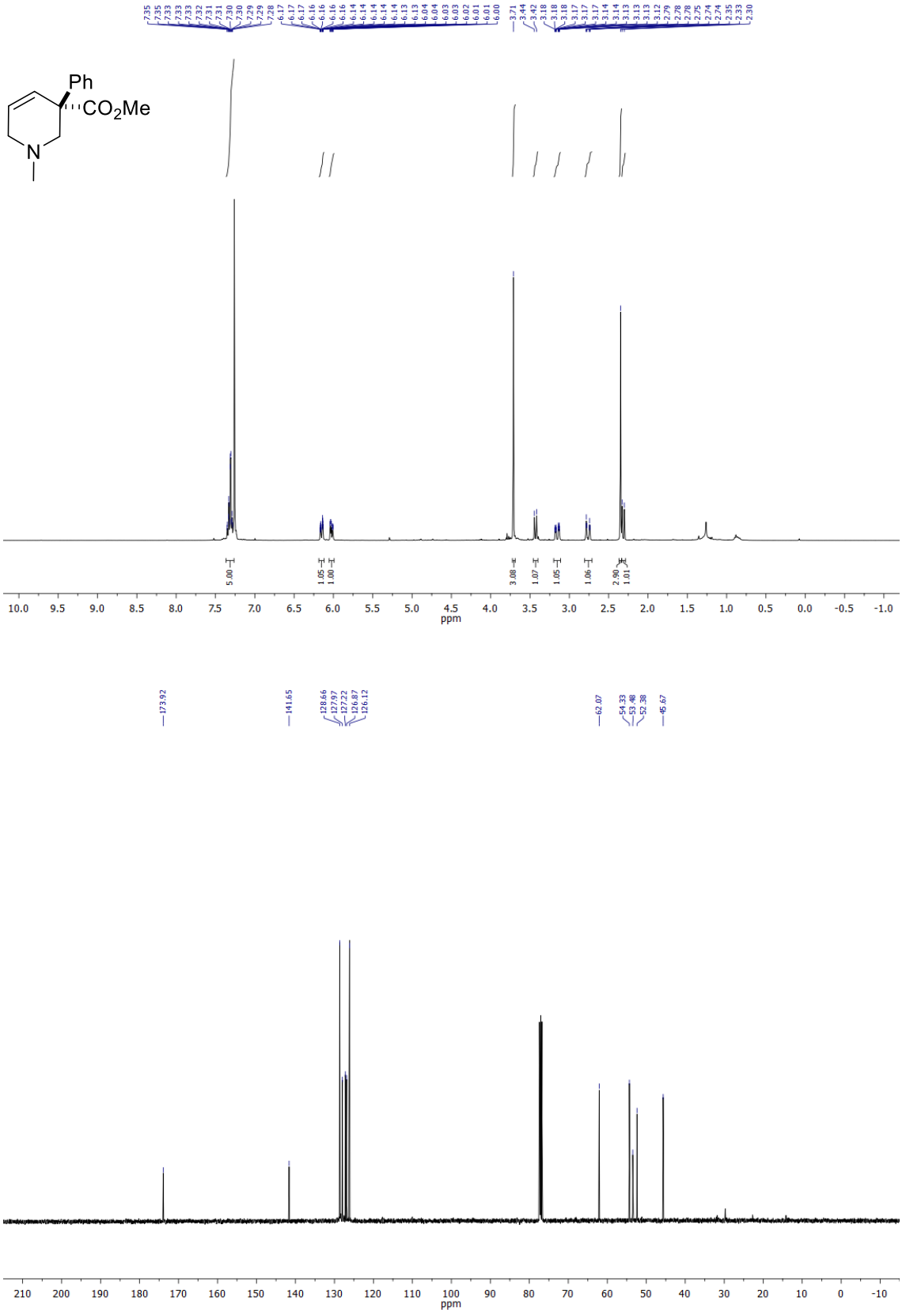


Compound **209**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

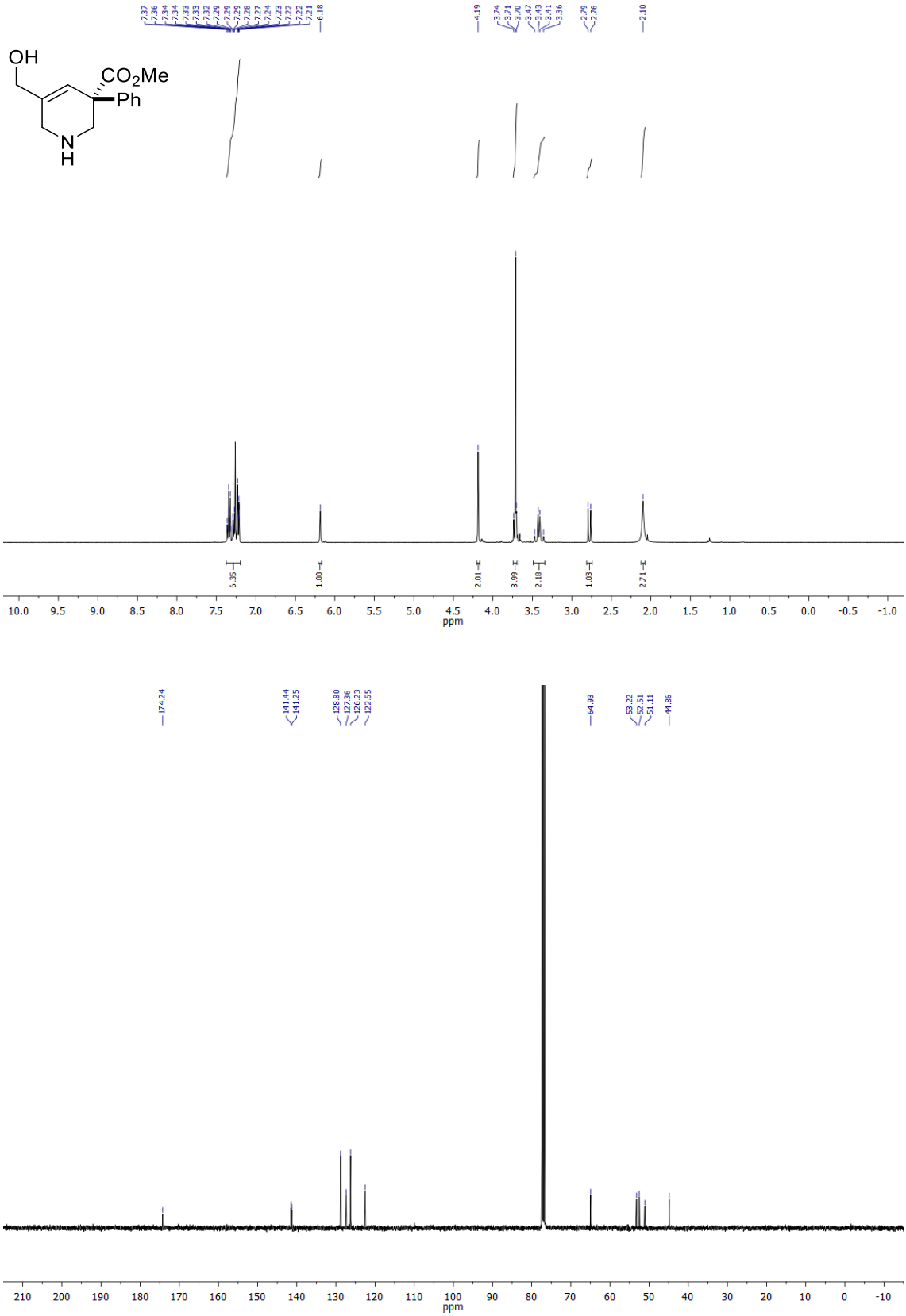




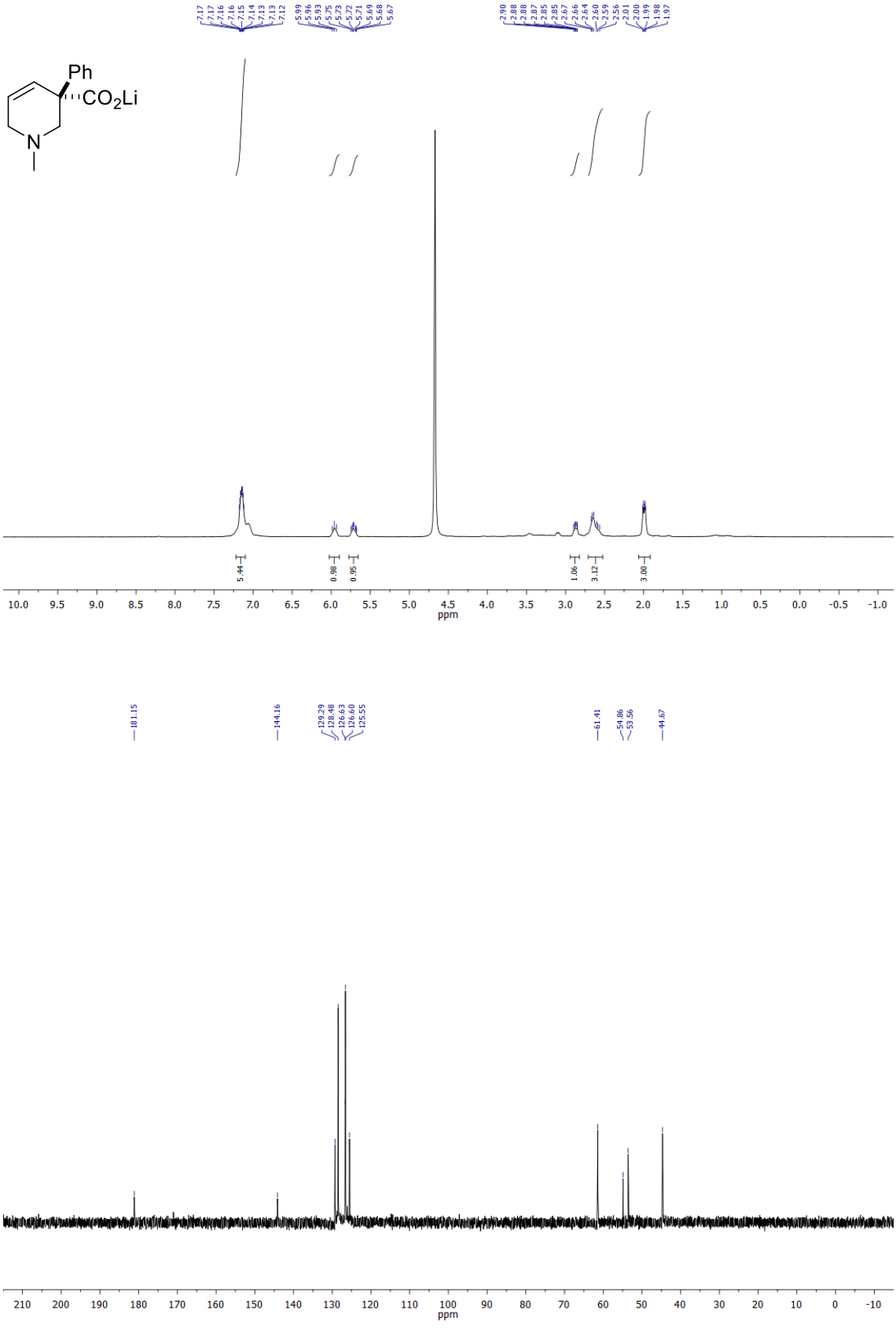
Compound **210**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)



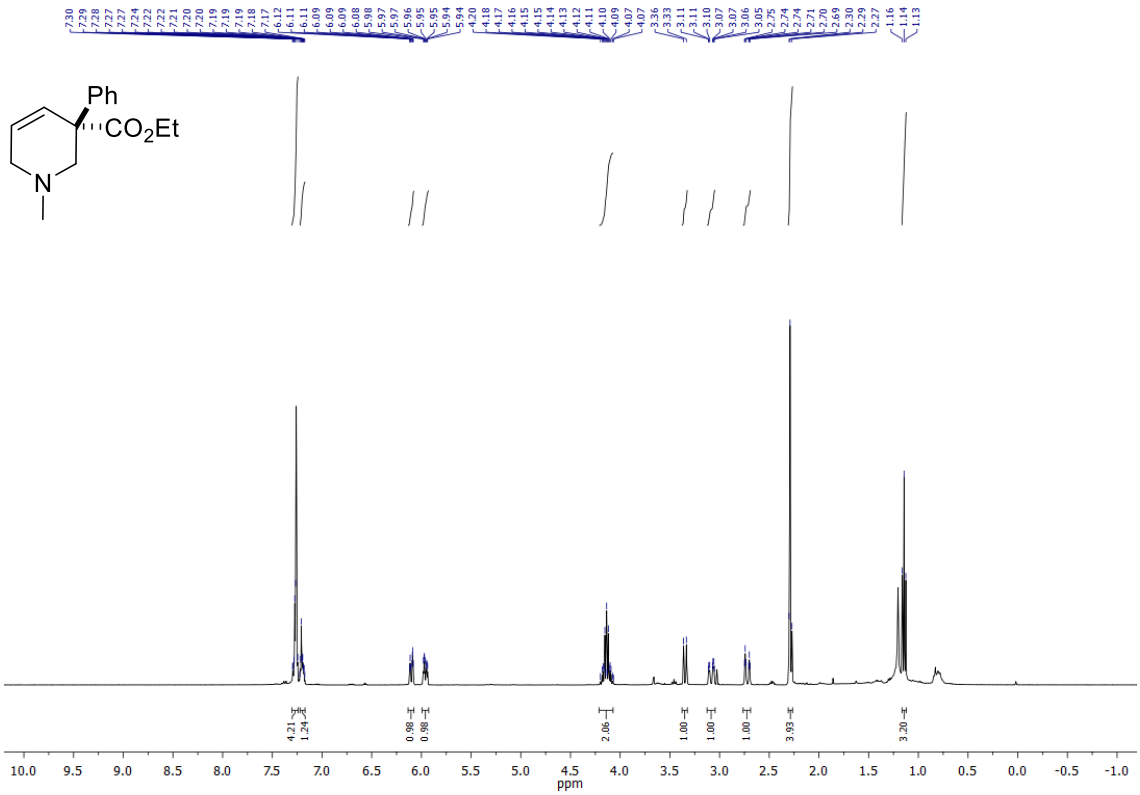
Compound **211**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)

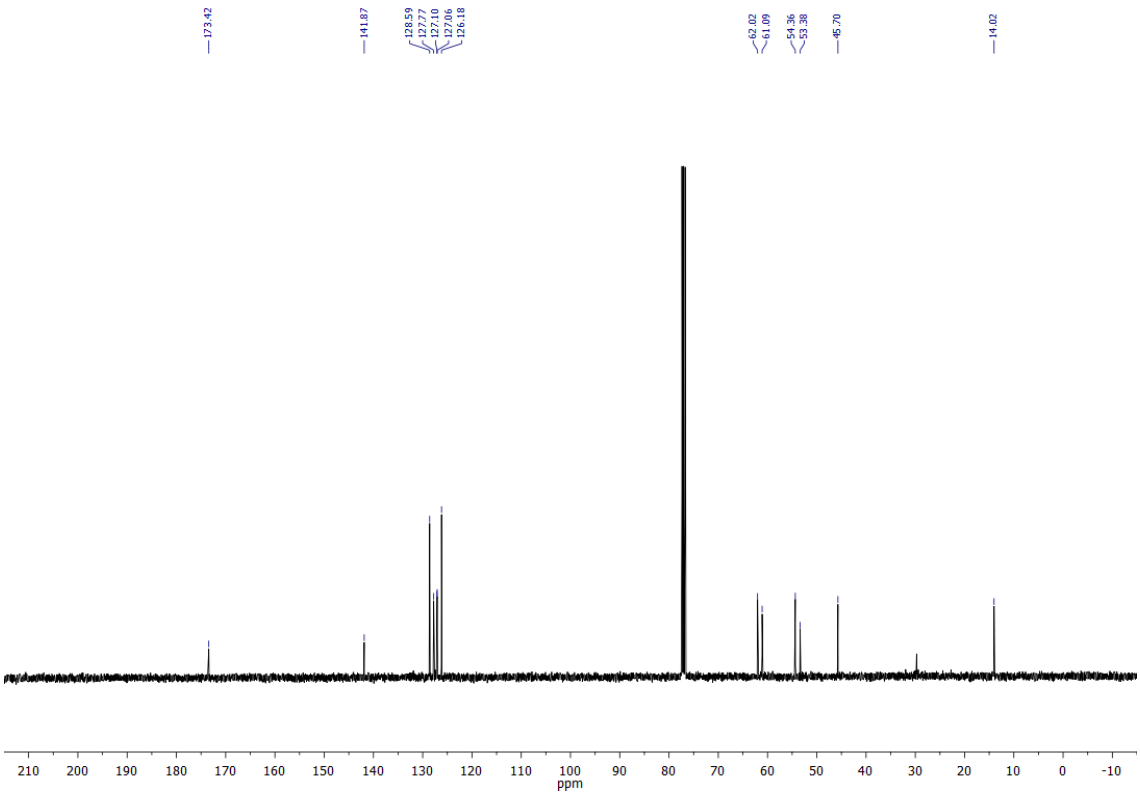


Compound **214**: ^{1}H-NMR (400 MHz, D_2O) and ^{13}C-NMR (101 MHz, D_2O)



Compound **213**: ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$)





6.2 X-Ray

methyl (1*S*,4*R*,5*S*,6*R*)-4-((methylsulfonyl)oxy)-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate ((+)-140a):

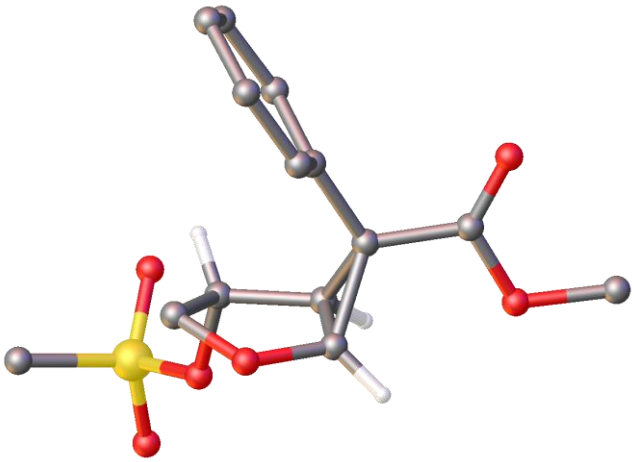


Table 20. Crystal data and structure refinement for **(+)-140a**.

CCDC	
Formula	$C_{14}H_{16}O_6S$
$D_{calc.}$/ g cm^{-3}	1.457
μ/mm^{-1}	2.266
Formula Weight	312.33
Color	clear colourless
Shape	irregular
Size/mm^3	0.37×0.12×0.07
T/K	123.01(10)
Crystal System	monoclinic
Flack Parameter	-0.010(6)
Hooft Parameter	-0.019(4)
Space Group	$P2_1$
a/Å	10.96310(19)
b/Å	8.78833(13)
c/Å	14.8106(2)
α/°	90
β/°	93.9441(15)
γ/°	90

V/Å^3	1423.59(4)
Z	4
Z'	2
Wavelength/Å	1.54184
Radiation type	Cu K_a
$\Theta_{min}/^\circ$	4.042
$\Theta_{max}/^\circ$	73.957
Measured Refl's.	17557
Ind't Refl's	5602
Refl's with I > 2(I)	5543
R_{int}	0.0229
Parameters	383
Restraints	1
Largest Peak	0.213
Deepest Hole	-0.315
GooF	1.050
wR_2 (all data)	0.0634
wR_2	0.0632
R_1 (all data)	0.0241
R_1	0.0238

Methyl (2*R*,3*R*)-2-methoxy-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (*major*-105a):

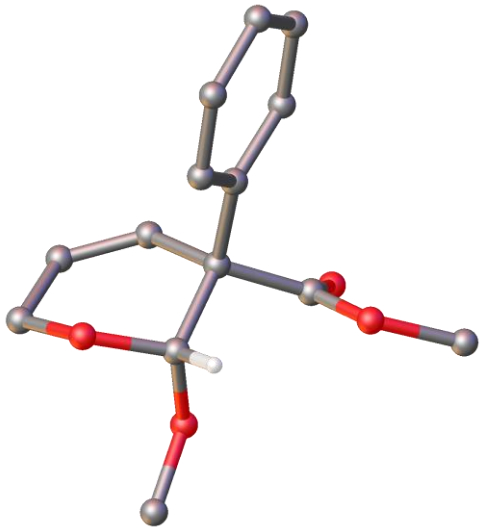


Table 21. Crystal data and structure refinement for *major*-**105a.**

CCDC	
Formula	$C_{14}H_{16}O_4$
$D_{calc.}$/ g cm^{-3}	1.334
μ/mm^{-1}	0.804
Formula Weight	248.27
Colour	clear colourless
Shape	prism
Size/mm^3	0.20×0.08×0.05
T/K	123.01(10)
Crystal System	monoclinic
Flack Parameter	0.00(13)
Hooft Parameter	0.03(11)
Space Group	$P2_1$
a/Å	7.8022(2)
b/Å	7.1103(3)
c/Å	11.3251(3)
α/°	90
β/°	100.437(3)

$\gamma/^{\circ}$	90
V/Å^3	617.88(4)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK$_a$
$\Theta_{min}/^{\circ}$	3.969
$\Theta_{max}/^{\circ}$	73.550
Measured Refl.	6913
Independent Refl.	2362
Reflections with I > 2(I)	2252
R_{int}	0.0322
Parameters	165
Restraints	1
Largest Peak	0.153
Deepest Hole	-0.187
GooF	1.056
wR_2 (all data)	0.0851
wR_2	0.0825
R_1 (all data)	0.0370
R_1	0.0343

1-(*tert*-butyl) 3-methyl (2*S*,3*R*)-2-isopropoxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (*major*-105g):

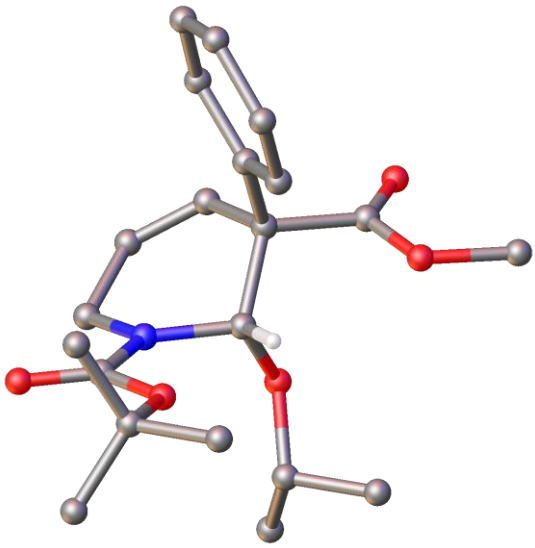


Table 22. Crystal data and structure refinement for *major*-**105g.**

CCDC	
Formula	$C_{21}H_{29}NO_5$
$D_{calc.}$/ g cm^{-3}	1.192
μ/mm^{-1}	0.688
Formula Weight	375.45
Colour	clear colourless
Shape	prism
Size/mm^3	0.15×0.13×0.09
T/K	123.01(10)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	8.57600(19)
b/Å	21.2811(4)
c/Å	11.8109(3)
α/°	90
β/°	103.980(2)
γ/°	90
V/Å^3	2091.73(8)
Z	4

Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K_a
$\Theta_{min}/^{\circ}$	4.155
$\Theta_{max}/^{\circ}$	74.000
Measured Refl.	17887
Independent Refl.	4190
Reflections with I > 2(I)	3692
R_{int}	0.0280
Parameters	271
Restraints	18
Largest Peak	0.269
Deepest Hole	-0.214
GooF	1.029
wR_2 (all data)	0.0982
wR_2	0.0937
R_1 (all data)	0.0422
R_1	0.0369

methyl (2*S*,3*R*)-2-methoxy-3-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine-3-carboxylate (*major*-105i):

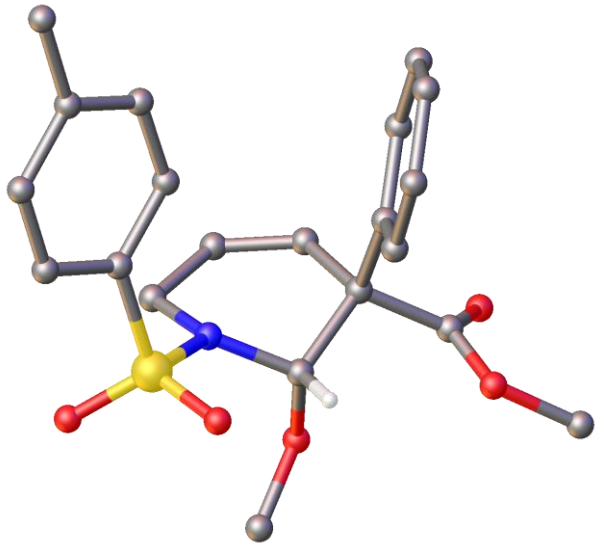


Table 23. Crystal data and structure refinement for *major*-**105i.**

CCDC	
Formula	$C_{21}H_{23}NO_5S$
$D_{calc.}$/ g cm^{-3}	1.356
μ/mm^{-1}	1.743
Formula Weight	401.46
Colour	clear colourless
Shape	prism
Size/mm^3	0.16×0.15×0.05
T/K	123.00(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	17.9322(3)
b/Å	7.55060(10)
c/Å	15.3324(3)
α/°	90
β/°	108.752(2)
γ/°	90
V/Å^3	1965.79(6)
Z	4

Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K_a
$\Theta_{min}/^{\circ}$	5.210
$\Theta_{max}/^{\circ}$	72.929
Measured Refl's.	22005
Ind't Refl's	3892
Refl's with I > 2(I)	3675
R_{int}	0.0218
Parameters	256
Restraints	0
Largest Peak	0.296
Deepest Hole	-0.429
GooF	1.044
wR_2 (all data)	0.0854
wR_2	0.0838
R_1 (all data)	0.0329
R_1	0.0312

di-*tert*-butyl (2*R*,3*S*)-2-methoxy-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (*major*-105k):

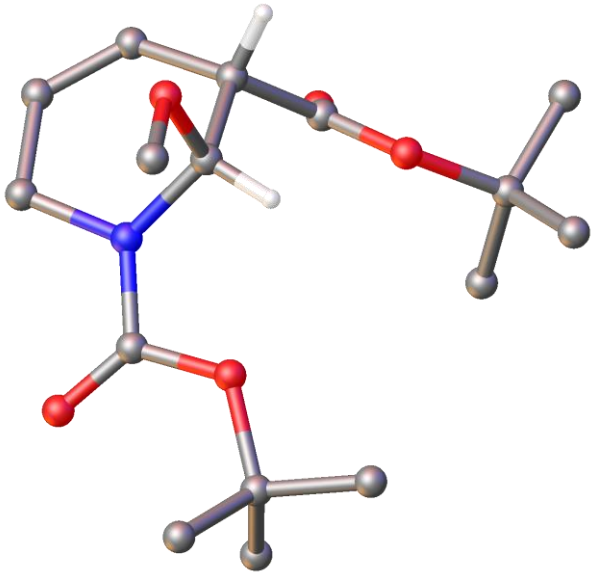


Table 24. Crystal data and structure refinement for *major*-**105k.**

CCDC	
Formula	$C_{16}H_{27}NO_5$
$D_{calc.}$/ g cm^{-3}	1.218
μ/mm^{-1}	0.737
Formula Weight	313.38
Colour	clear colourless
Shape	prism
Size/mm^3	0.12×0.07×0.04
T/K	123.00(10)
Crystal System	triclinic
Space Group	P-1
a/Å	6.14710(10)
b/Å	9.0760(2)
c/Å	15.7119(4)
α/°	99.315(2)
β/°	93.222(2)
γ/°	97.691(2)
V/Å^3	854.52(3)

Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K□
$\Theta_{min}/^{\circ}$	4.991
$\Theta_{max}/^{\circ}$	73.685
Measured Refl's.	20253
Ind't Refl's	3385
Refl's with I > 2(I)	2878
R_{int}	0.0430
Parameters	307
Restraints	0
Largest Peak	0.251
Deepest Hole	-0.181
GooF	1.032
wR_2 (all data)	0.0831
wR_2	0.0788
R_1 (all data)	0.0414
R_1	0.0332

methyl (2*S*,3*R*)-2-(cyclohexyloxy)-3-phenyl-3,6-dihydro-2*H*-pyran-3-carboxylate (*major*-105m):

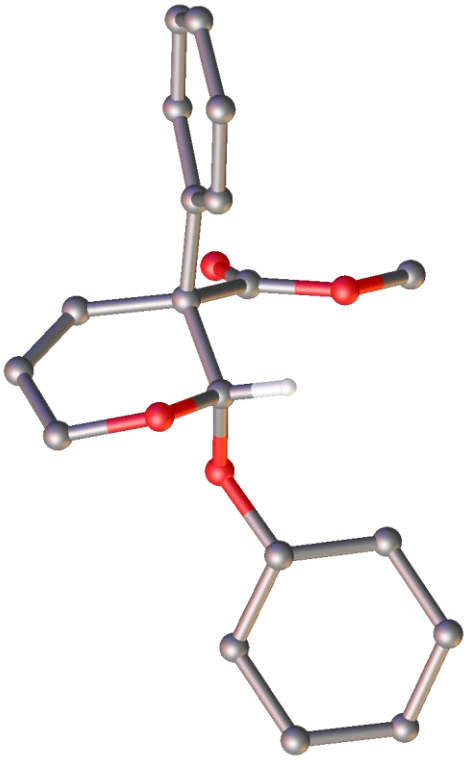


Table 25. Crystal data and structure refinement for *major*-**105m.**

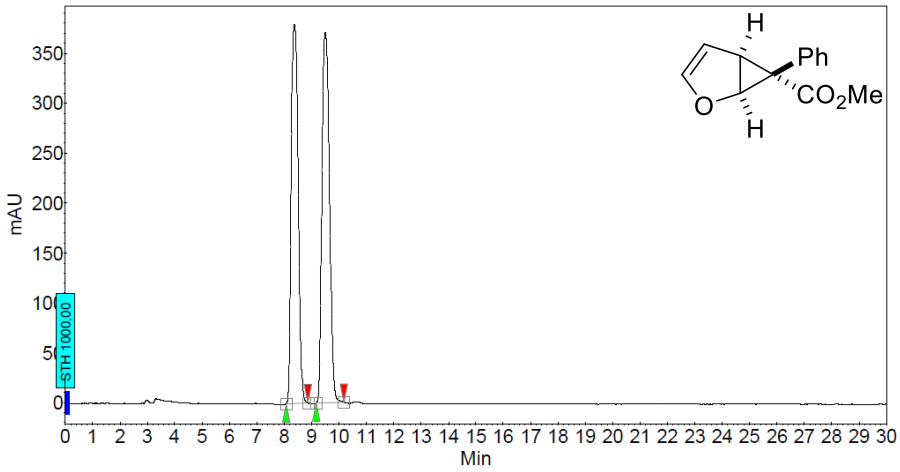
CCDC	
Formula	$C_{19}H_{24}O_4$
$D_{calc.}$/ g cm^{-3}	1.256
μ/mm^{-1}	0.510
Formula Weight	316.38
Colour	clear colourless
Shape	block
Size/mm^3	0.43×0.22×0.14
T/K	122.99(10)
Crystal System	triclinic
Flack Parameter	0.10(11)
Hooft Parameter	0.02(9)
Space Group	*P*1
a/Å	6.24673(18)
b/Å	7.00210(16)

c/Å	19.2630(5)
$\alpha/^{\circ}$	89.993(2)
$\beta/^{\circ}$	89.962(2)
$\gamma/^{\circ}$	83.090(2)
V/Å^3	836.45(4)
Z	2
Z'	2
Wavelength/Å	1.39222
Radiation type	Cu K
$\Theta_{min}/^{\circ}$	4.145
$\Theta_{max}/^{\circ}$	74.620
Measured Refl's.	21960
Ind't Refl's	7211
Refl's with I > 2(I)	7059
R_{int}	0.0345
Parameters	657
Restraints	339
Largest Peak	0.216
Deepest Hole	-0.288
GooF	1.164
wR_2 (all data)	0.1165
wR_2	0.1159
R_1 (all data)	0.0495
R_1	0.0485

6.3 Chiral HPLC

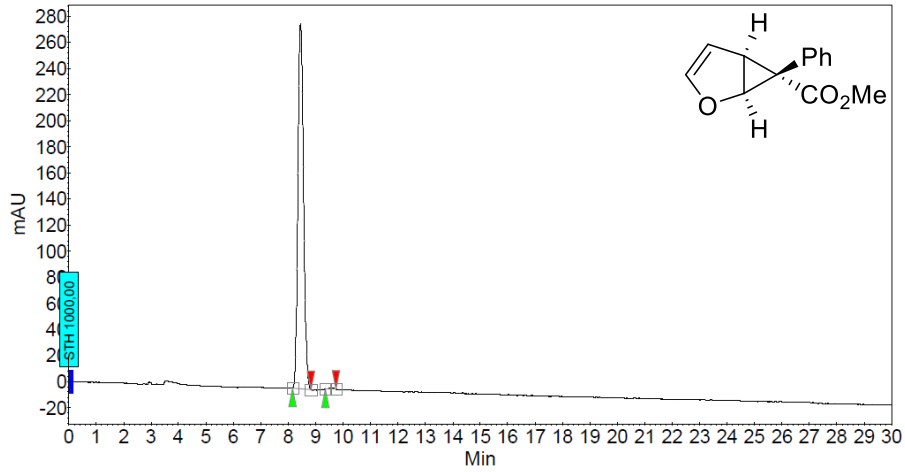
methyl-(1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate ((-)-102a):

Reacemic mixture **(*rac*)-102a:**



Index	Time /min	Area /mAU.min	Area /%
1	8.37	111.3	48.414
2	9.50	118.6	51.586
Total		229.9	100.0

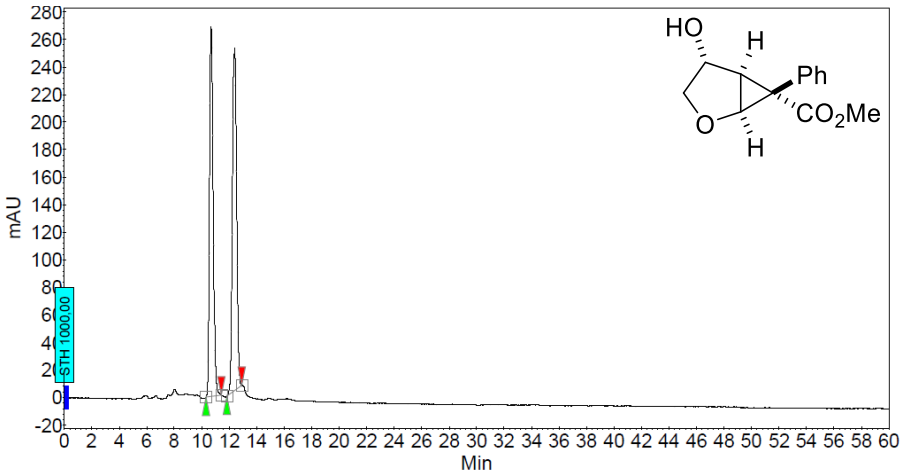
Data for **(-)-102a**:



Index	Time /min	Area /mAU.min	Area /%
1	8.45	67.8	99.592
2	9.57	0.3	0.408
Total		68.1	100.0

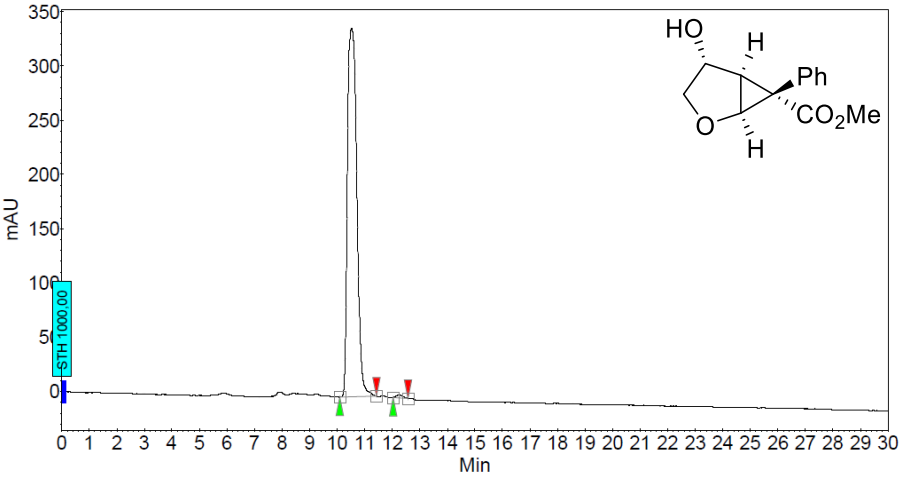
Methyl (1*S*,4*R*,5*R*,6*R*)-4-hydroxy-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate ((+)-103a):

Racemic mixture **(*rac*)-103a***:*



Index	Time /min	Area /mAU.min	Area /%
1	10.69	84.5	49.669
2	12.38	85.7	50.331
Total		170.2	100.0

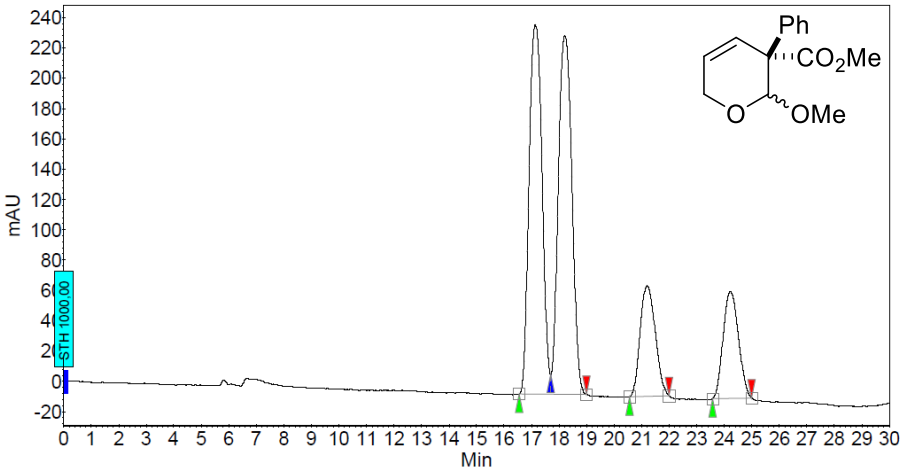
Data for **(+)-103a**:



Index	Time /min	Area /mAU.min	Area /%
1	10.52	133.3	99.447
2	12.26	0.7	0.553
Total		134.0	100.0

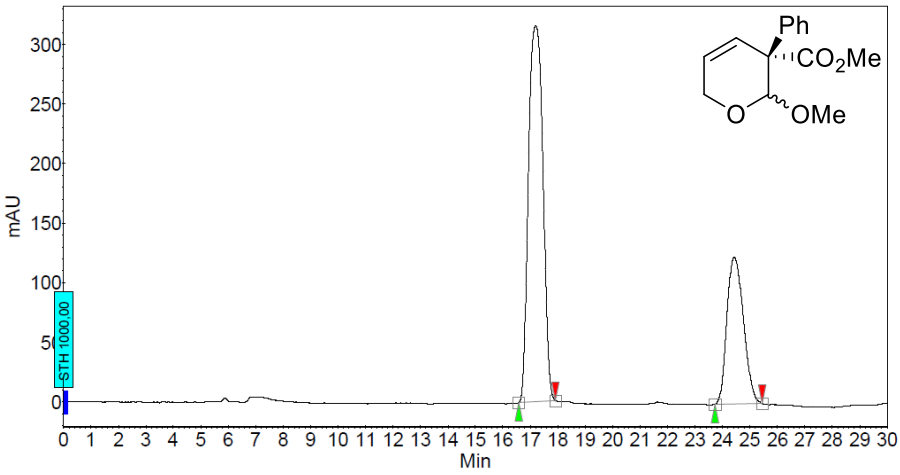
methyl (3*R*)-2-methoxy-3-phenyl-3,6-dihydro-2H-pyran-3-carboxylate ((-)-105a):

Racemic mixture **(*rac*)-105a***:*



Index	Time /min	Area /mAU.min	Area /%
1	17.14	133.6	36.927
2	18.21	135.8	37.538
3	21.20	46.7	12.911
4	24.22	45.7	12.624
Total		361.8	100.0

Data for **(-)-105a**:



Index	Time /min	Area /mAU.min	Area /%
1	17.20	192.9	69.087
2	24.43	86.3	30.913
Total		279.2	100.0

7 Curriculum Vitae

Personal Data

Name	Robert Eckl
Date / place of birth	11.11.1993 in Roding
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Education

01/2018 – 03/2021	PhD (Dr. rer. nat.), Organic Chemistry University of Regensburg Dissertation: Stereoselective synthesis of biologically relevant dihydropyridines and pyrans *via* ring-expansion of mono-cyclopropanated heterocycles
10/2015 – 09/2017	Master of Science (M. Sc.), Chemistry University of Regensburg Master thesis: Asymmetric synthesis of tetrahydrofurans *via* cyclopropanated furans
07/2012 – 09/2015	Bachelor of Science (B. Sc.), Chemistry University of Regensburg Bachelor thesis: Photoinduzierte Decarboxylierungs- und Cyclisierungsreaktionen von *N*-Acyloxyphthalimiden
09/2004 – 06/2012	General Qualification for the University Entrance Joseph-von-Fraunhofer Gymnasium Cham Degree: Allgemeine Hochschulreife

Professional References

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List of Publications

"Stereoselective Synthesis of Tropanes via a Retro-6π Electrocyclic Ring-Opening / Huisgen [3+2]-Cycloaddition Cascade of Monocyclopropanated Heterocycles" (2020)

Carina M. Sonnleitner, Saerom Park, Robert Eckl, Thomas Ertl, Oliver Reiser (C. M. Sonnleitner, S. Park, R. Eckl, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.* **2020**, 18110–18115.)

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Mein größter Dank geht an meine ganze Familie und meine Freunde für ihre unerschütterliche Unterstützung. Mona, Sebi, Ahmed, Maggi, Steffen (aka Sven), Mella und Tim: Ohne euch wäre alles deutlich schwieriger gewesen und das Leben wäre ganz schön langweilig. Danke auch an die ganze George-Family für all die schönen Momente, die ich mit euch an Wochenenden, in Urlauben oder einfach bei einem Glas Sekt und einem Stück Kuchen erleben durfte. Mama, Papa und mein Bruderherz Dominik, ohne euch wäre ich nie so weit gekommen! Ihr habt mich in all der Zeit immer wieder ermutigt und unterstützt. Jonas, dir möchte ich aus tiefsten Herzen danken. Wir haben uns in dieser Zeit kennen und lieben gelernt. Für all deine Unterstützung in der ganzen Zeit kann ich dir nicht genug danken. Du warst derjenige, der mich in schwierigen Situationen aufgefangen hat, der mit mir Erfolge gefeiert hat, mich immer wieder motiviert hat und die gesamte Zeit immer für mich da war. Du bist der Mensch, der in meinem Leben einfach nicht mehr fehlen darf.

Es ist unvorstellbares Glück, eine so große und tolle Familie wie euch zu haben und dafür bin ich unendlich dankbar!

9 Declaration

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

Regensburg, den 15.07.2021

Robert Eckl