Endocyclic ring opening of cyclopropanated piperidines: An approach to the asymmetric total synthesis of Meptazinol

Dissertation

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Meiner Familie

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Abbreviations

Ac	acetate	EDG	electron donating group
(h)AChE	(human) acetylcholinesterase	ee	enantiomeric excess
ADH	alcoholdehydrogenase	EI	electron ionisation
AIDS	acquired immunodeficiency syndrome	equiv	equivalents
aq.	aquatized	ESI	electrospray ionisation
Ar	aryl	Et	ethyl
atm	atmosphere	EWG	electron withdrawing group
BChE	butyrylcholinesterase	FC	flash column
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl	FTIR	Fourier-transform infrared spectroscopy
Bn	benzyl	g	gram
Boc	*tert*-butyloxycarbonyl	h	hours
Bu	butyl	Hal	halogen
c	concentration	HFIP	hexafluoroisopropanol
calc.	calculated	HMDS	bis(trimethylsilyl)amide
CAN	cer(IV)-ammoniumnitrate	HOMO	highest occupied molecular orbital
cat.	catalyst	HPLC	high performance liquid chromatography
conc.	concentrated	HRMS	high resolution mass spectrometry
conv.	conversion	^{i}	iso
cym	cymol	IC_{50}	inhibitory concentration
d	days	IR	infrared spectroscopy
DABCO	1,4-diazabicyclo[2.2.2]octane	KRED	ketoreductase
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	L	liter
DCM	dichloromethane	LUMO	lowest unoccupied molecular orbital
de	diastereomeric excess	*m*	*meta*
DFT	density functional theory	*m*CPBA	*m*-chloroperoxybenzoic acid
DIPE	diisopropylether	Me	methyl
DKR	dynamic kinetic resolution	MIC_{50}	minimum inhibitory concentration
DMA	dimethylacetamide	min	minute
DMF	dimethylformamide	ML_n	metal-ligand$_{number}$
DMSO	dimethylsulfoxide	mp	melting point
DPEN	diphenylethylenediamine	Ms	mesyl
dr	diastereomeric ratio	MW	microwave
EA	ethyl acetate		

NAD(P)	nicotinamide adenine dinucleotide (phosphate)		Tf	triflyl
NBS	*N*-bromosuccinimide		TFA	trifluoroacetic acid
(h)NK$_1$(R)	(human) neurokinin 1 (receptor)		THF	tetrahydrofurane
NMO	*N*-methylmorpholine *N*-oxide		TLC	thin layer chromatography
NMP	*N*-methyl-2-pyrrolidone		TMP	tetramethylpiperidide
NMR	nuclear magnetic resonance		TMS	trimethylsilane
Nu	nucleophile		TOF	turn over frequency
o	*ortho*		Tol	toluene
p	*para*		TPP	5,10,15,20-tetraphenyl-21H,23H-porphine
PDE	phosphodiesterase		Ts	tosyl
PE	petrolether		wt	weight
PG	protecting group		X	halide
pH	*pondus hydrogenii*			
Ph	phenyl			
PMB	*p*-methyoxybenzyl			
ppm	parts per million			
Pr	propyl			
PS	*pseudomonas cepacia*			
psi	pound-force per square inch			
R	residue			
Red-Al	sodium bis(2-methoxyethoxy)aluminum dihydride			
R$_f$	retardation factor			
RNA	ribonucleic acid			
S	solvent			
SAR	structure activity relationship			
(h)SERT	(human) serotonin transporter			
t	*tert*			
TBAB	tetrabutylammonium bromide			
TBAF	tetrabutylammonium fluoride			
TBS	*tert*-butyldimethylsilyl			
temp.	temperature			

1 Introduction

1.1 Azepanes as key-motif in biological active compounds

Azepanes, characterized as saturated seven membered azacycloalkanes, belong to the class of heteromonocycles. Although less common as their five and six membered analogues, they still serve as key-building block of numerous biological active compounds and approved drugs.[1] Their properties range from the treatment of psychiatric disorders such as Alzheimer's disease, schizophrenia, and anxiety to activity against cancer, tuberculosis, or AIDS.
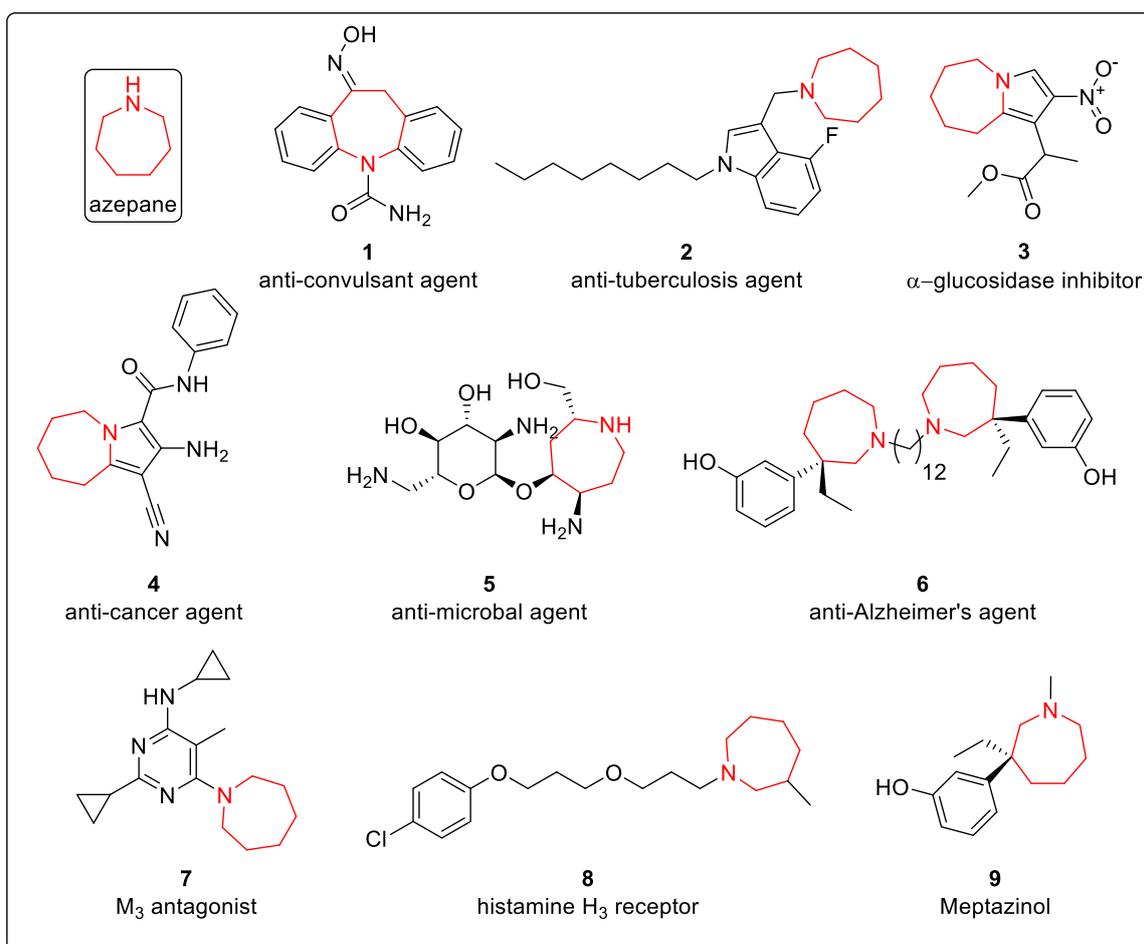
Figure 1: Representatives of Azepane containing biologically active compounds.

Compound **1** was found to be highly effective as anti-convulsant agent while bearing little side effect potential and therefore low toxicity.[2] Dick and co-workers synthesized a series of indol containing amphiphilic compounds to test the growth inhibition on *M. tuberculosis.* Azepane **2** showed the highest potency with $MIC_{50} = 2$ µM.[3] In addition, **3** is highly effective as non-sugar-type α-glucosidase inhibitor with $IC_{50} = 8$ µM which is an 25-fold increase compared to the standard drug 1-deoxynojirimycin.[4] Even to cancer, one of humans biggest threats,

azepanes could provide a solution. Belal revealed the excellent effects of **4** to liver, breast and colon cancer cell lines with IC$_{50}$ values in the nM range.[5] Furthermore, azepane-glycosides such as **5** could find utility as antibiotics. Barluenga et al. discovered their interference with the bacterial decoding site of RNA and thereby the inhibition of bacterial translation of *S. aureus* in vitro.[6] Through SAR optimization Provins et al. discovered **7** and related compounds as dual M$_3$ antagonists and PDE4 inhibitors which could lead to a new class of drugs possing bronchodilating and anti-inflammatory properties for a treatment of COPD (Chronic Obstructive Pulmonary Disease).[7] High activity as H$_3$ histamine receptor (K$_i$ = 3.2 nM) was found in Azepane **8**. The neurotransmitter histamin plays an important role in mammalian brains regulating vigilance, attention, sleep, and weight. Application could be found in the treatment of narcolepsy, attention-deficit hyperactivity disorder, schizophrenia or Alzheimer's disease.[8] Compound **6** known as bis-(-)-nor-meptazinol belongs to the same class of drugs with similar properties. It expresses high inhibition against AChE and BChE (AChE ≥3.9 nM; BChE ≥ 10 nM) and the thereby induced amyloid-β aggregation, making it a promising candidate for Alzheimer's disease treatment as well.[9] The importance of Meptazinol **9** as the key compound of the following dissertation will be highlighted in the next chapter.

1.2 Meptazinol

Developed at John Wyeth & Brother Limited,[10] Meptazinol **9** entered the human pharmaceutical market as a racemic mixture in the 1980s for use as an analgesic, majorly in the treatment of labor pain[11] due to its little side effects in terms of dependency and respiratory depression.[12] Besides that, vigilance impairments are much less observed compared to other opioid-type analgesics making Meptazinol a preferred drug for the treatment of patents advanced age, in anesthesia or emergency medicine.[13] Its properties are based on its partial agonism at the µ1 opioid receptor as well as its activity as an acetylcholinesterase (AChE) inhibitor,[11] particularly in its (-) enantiomeric form (hAChE = 6.02 µM).[14] Meptazinols core structure can be found in a variety of biologically active compounds as shown in Figure 2. Although the key moiety remains, these substances differ in their pharmacological properties. While **10** is a candidate for analgesic use,[15] **11** can serve as a monoamine reuptake inhibitor with potential in anxiety or attention deficit-hyperactivity disorder therapy.[16]
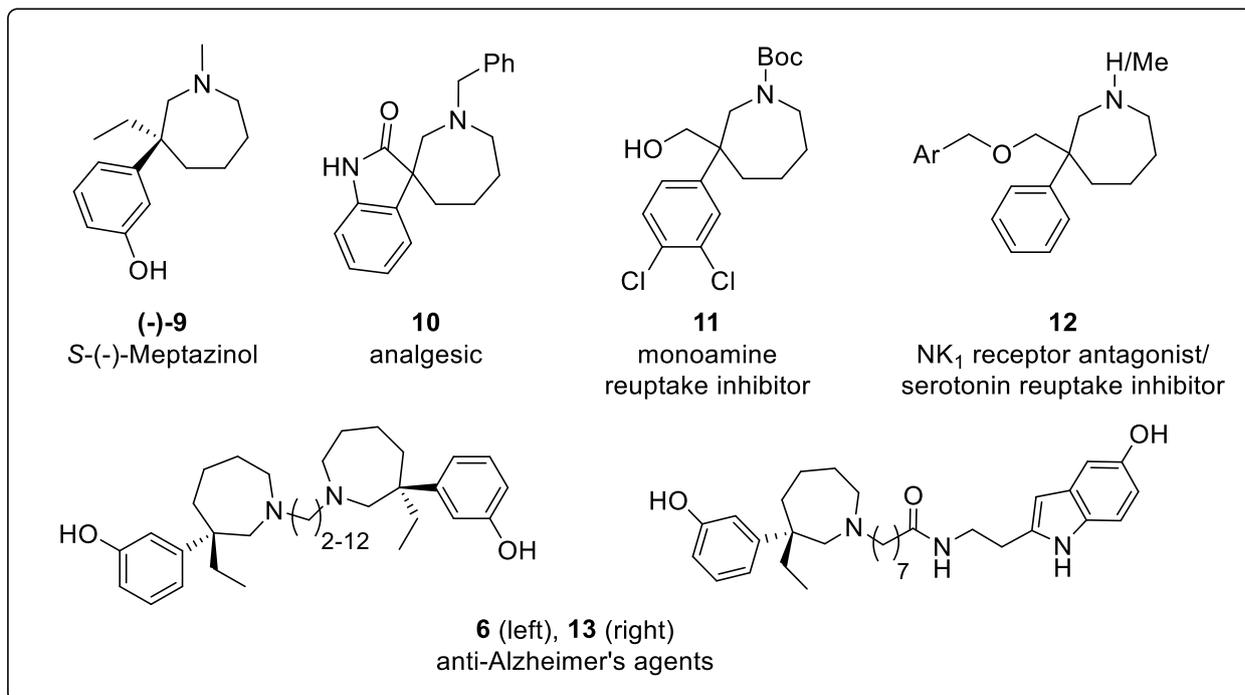
Figure 2: Representatives of C3-quarternary azepanes.

Ether derivatives **12** were shown to be potent dual NK_1R antagonist ($hNK_1R \geq 16$ nM) -SERT inhibitors ($hSERT \geq 140$ nM) that may find utility as antidepressants.[17] Furthermore, S-(-)-Meptazinol-melatonin hybrids **13** show similar effects ($AChE \geq 310$ nM; $BChE \geq 290$ nM) as the already mentioned Bis-(-)-nor-Meptazinol **6**.[14]

Several racemic syntheses of Meptazinol were reported in the past decades. The first route to an unsubstituted phenyl derivative of Meptazinol was developed by Testa et al. back in 1964.[18] Based on this, Meptazinol could be synthesized *via* a 9 step-cyclization approach in an overall yield of 23% (scheme 1).[19] Within 3 steps **15** was generated from *m*-methoxybenzaldehyde **14** in a yield of 75%. A substitution reaction with methyl-4-iodobutanoate and the following nitrile reduction gave rise to the amine-ester **17** that could be cyclized to the lactame **18** in high yields. The lactam was than reduced to the secondary amine to build the azepane core structure using $LiAlH_4$ as reagent. Refluxing **19** in conc. aq. HBr solution cleaved the arylic ether in good yields of 82%. The reaction of **20** with formaldehyde and the reduction of the formed tertiary amide gave afterwards rise to the final product.
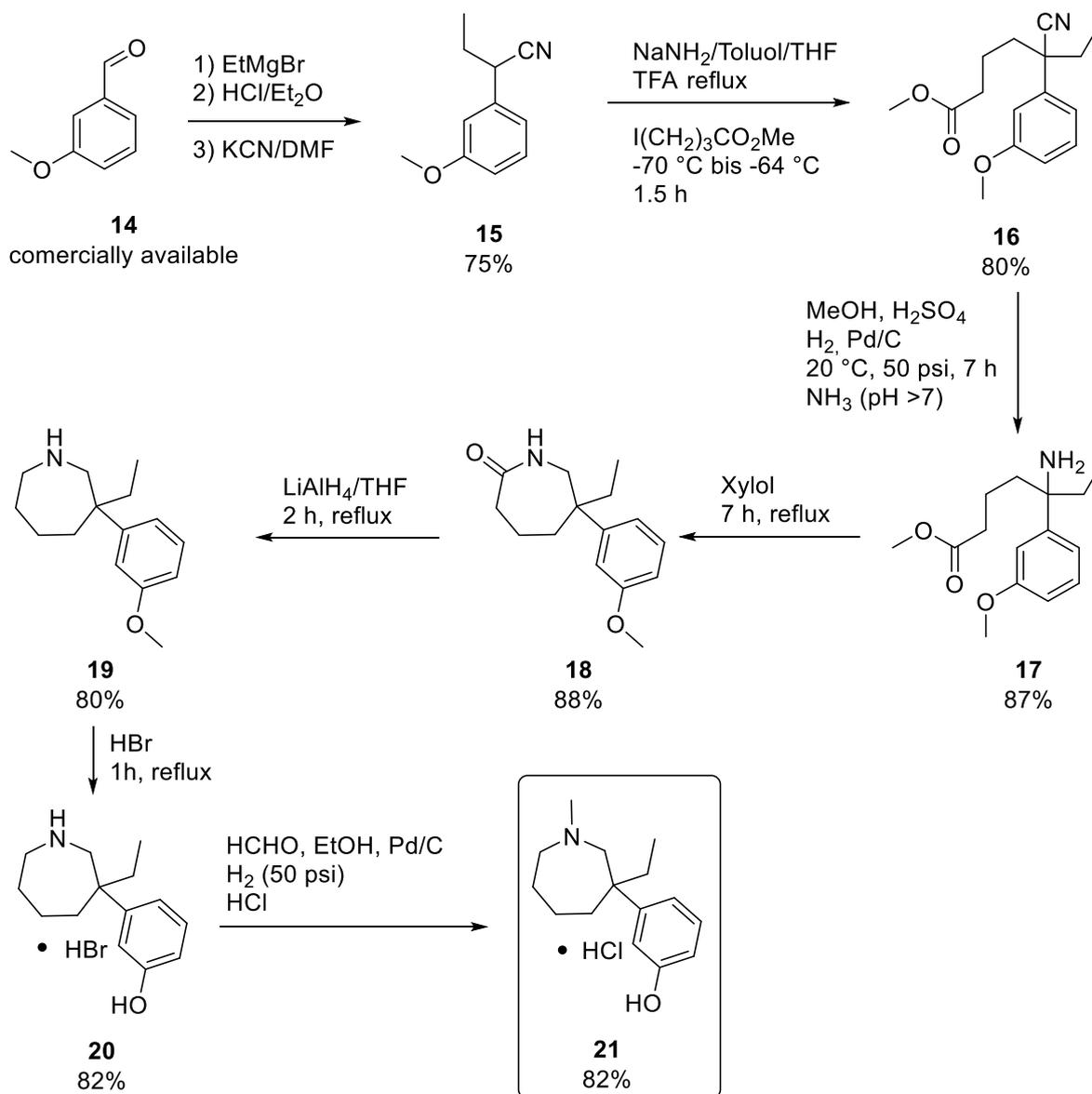
Scheme 1: First synthesis of Meptazinol by Bradley et al. based on the work of Testa et al.

The industrial adoption of this synthesis was impeded by its unpractical reaction conditions e.g., -80 °C and liquid ammonia as solvent. Furthermore, the long reaction sequence resulted in a low overall yield which fluctuated strongly.[19] Therefore, Bradley et al. investigated new synthesis pathways starting from caprolactam **22**. Caprolactam offers two important moieties as they appear in the final meptazinol: The seven-membered ring and the tertiary methylamine. Its carbonyl function gives the possibility to insert sidechains at the C3-position *via* enolate chemistry. Bradley et al, managed to implement both sidechains in a one-pot reaction which resulted in a strongly simplified synthesis with only three steps. The synthesis is closed by the carbonyl reduction followed by the ether cleavage, both high yielding.
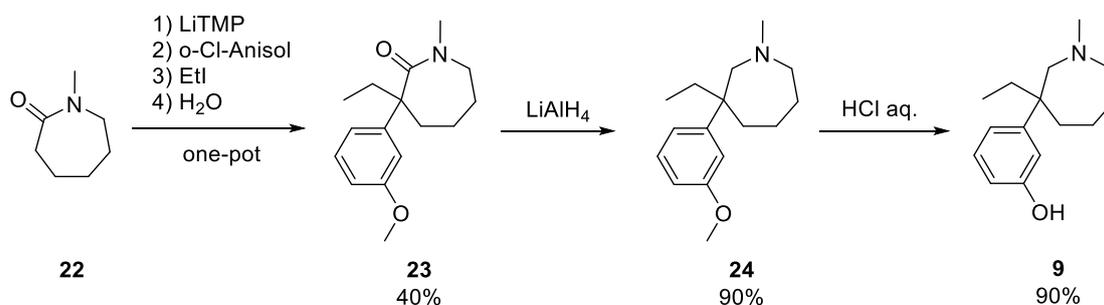
Scheme 2: Three-step synthesis of Meptazinol by Bradley et al.

Dissatisfied with the low yield of the initial step, giving an overall yield of 32%, Bradley et al. tried to implement the sidechains sequentially. Unlike the previous synthesis the aryl moiety was now inserted as alkyloxycyclohexenone and aromatised later. Depending on the insertion order these new pathways gave overall yields of 38% - 53%.
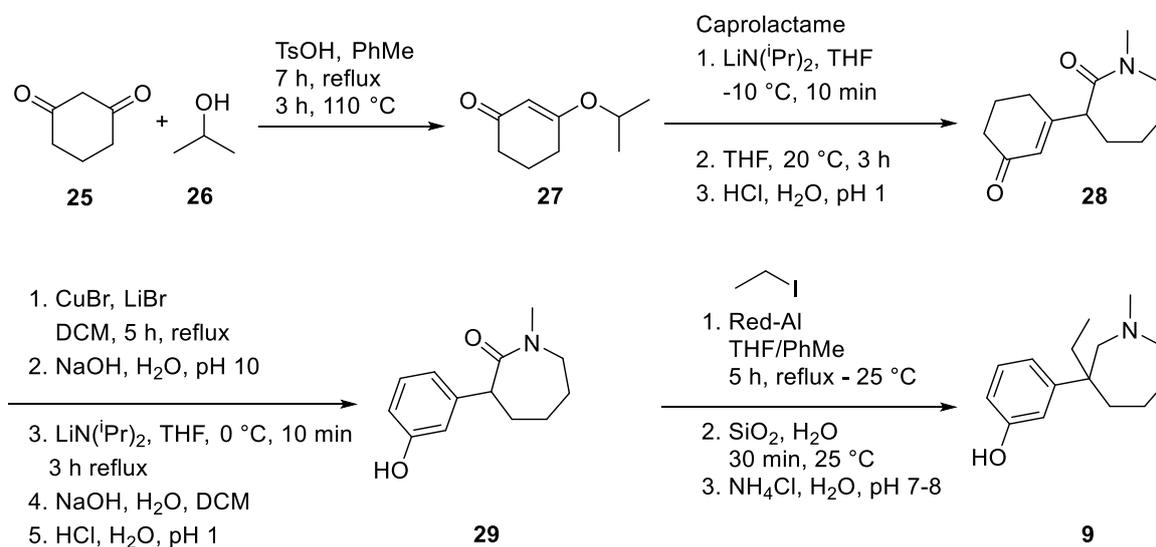
Scheme 3: Synthesis of Meptazinol by Zheng et al. based on the work of Bradley et al.

Taking the same approach Zheng et al. tried to optimize this synthesis, mainly focussing on the reagents (Scheme 3). The overall yield could not be enhanced (39%).[20]

Just as many chiral substances the two enantiomers of Meptazinol differ greatly in their pharmacological properties. The acetylcholinesterase inhibition, responsible for its analgesic effect, mainly goes back to the *S*-(-)-Meptazinol.[21] While investigating the respiratory effects, Cowlrick and Shepperson were able to prove that *S*-(-)-Meptazinol decreased the CO_2 level in rats while the *R*-enantiomer induced an increase.[12] However, the positive effects of Meptazinol in connection with strong blood loss seems to go back to the *R*-(+)-enantiomer.[22] The interest in Meptazinol derived drugs increased steadily over the past decades (Figure 2) and with it the demand for enantiomerically pure Meptazinol. Therefore different separation strategies were

implemented like the crystallization with tartaric acid,[23] reversed phase HPLC[24] and capillary electrophoresis.[25] Although the compound was made accessible enantiomerically pure through these methods, a racemic synthesis and laborious separation remains inefficient and points up the need for an asymmetric synthesis.

1.3 Donor-acceptor-cyclopropanes in the synthesis of heterocycles

In the history of chemistry cyclopropanes have been exploited in a variety that probably no other functionality can match. Even though their syntheses are manifold, transition metal catalysis is one of the most efficient and diverse. Copper,[26] palladium,[27] rhodium,[28] gold,[29] zinc,[30] ruthenium,[31] iron,[32] nickel,[33] cobald,[34] and even titanium[35] were used in the synthesis of cyclopropanes. However, these metals can be toxic, expensive or their use problematic in terms of their respective conditions e.g. water-, air-, base-sensitivity. Transition metal free pathways to cyclopropanes are given by the use of light,[36] lewis base,[37] lewis acid[38] or ylides.[39]

Since cyclopropanes are part of numerous natural or synthetic products their construction is surely important. But of much higher interest is their use as precursor for various transformations which all go hand in hand with some kind of ring opening. This lively reactivity is contrary to the sluggish reactivity of other carbocycles. Explanations can be provided by several models. The most intuitive one is the ring strain model. Quaternary substituted carbon molecules are usually tetrahedron shaped with the carbon centred in the middle and the substituents making up the corners, placed by the electrostatic repulsion of the binding electrons leading to an optimal angle between the bonds of 109.5°. The cyclopropane shape requires an angle of 60° between the sp^3-orbitals resulting in high strain. As a consequence of the cyclopropanes planar structure, all substituents are eclipsed to each other enhancing the repulsion further leading to a total ring strain of 27.5 kcal/mol. If this value is compared to cyclobutanes ring strain of 26.5 kcal/mol the sole explanation of cyclopropanes reactivity by ring strain gets questionable, since the 90° angles in cyclobutene should reduce the strain dramatically and cyclobutanes do not react the same way even though their driving force is comparable.[40] The Forster-Coulsin-Moffit model treats the cyclopropane ring building bonds as 22° bent from its direct axes.[41] This results in an 20% decreased overlap of the orbitals which is seen as the reason of the increased reactivity. The explanation of the bent character is found in the sp^5 hybridisation of the C-C bond building orbitals. The high p-proportion would also explain similarities between the reactivity of olefins and cyclopropanes.[40] Experimental

evidence for the Forster-Coulsin-Moffit model was found in X-ray crystallographic studies. Indeed deformation density was found outside the linear bond axis,[42] and shorter C-C bond lengths were observed.[43]
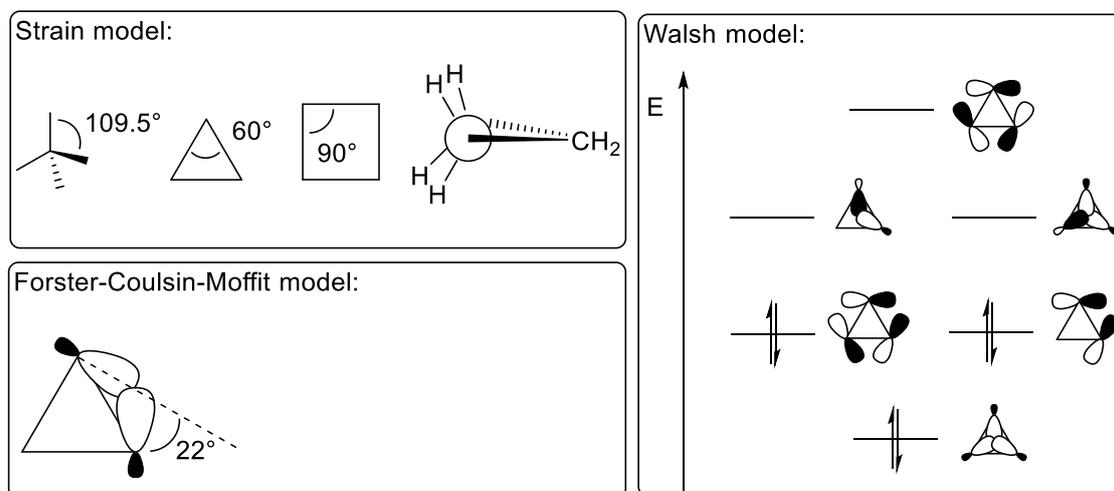

Figure 3: Cyclopropane-bonding models.

Even though the Forster-Coulsin-Moffit model rationalizes some behaviour of cyclopropanes, the reactivity of cyclopopanes with electron donating/withdrawing substituents and the electron density in the middle of the ring is not sorted out. Walsh used the molecular orbital theory to describe the bonding of cyclopropanes in his model.[44] According to him the cyclic bonds in cyclopropanes are built from six sp^2 and p-like orbitals distributed to four energy levels. The energetic lowest molecular orbital is formed by three sp^2 orbitals overlapping in the middle of the ring explaining the electron density found there. Two HOMO orbitals with dominant binding interaction are formed by either two or three centred p-orbitals giving the bond a π-like character. This explains the olefine type reactivity of cyclopropanes as well as the mesomeric interaction with electron withdrawing or donating substituents. The next highest energy level is occupied by two LUMO orbitals formed by two or three centred sp^2-oribtals which interact dominantly destructive. The molecular orbital with the highest energy is made up of three p-orbitals interacting solely anti-binding. As mentioned above this model addresses the interaction with substituents and the electron density in the ring centre but also brought up the concept of σ-aromaticity, since the orbitals have p-character, the six electrons are spread across all three carbon atoms and their number follow the Hückel rule. This aromaticity could add stabilization to the system and explain the low strain energy compared to cyclobutene which does not follow the 4n+2 rule.[40] The truth about the electron bonding in cyclopropanes is probably somewhere in between these models. Whether one or the other is used often depends on users' preference or the problem that is discussed.

With a better understanding of the cyclopropanes bonding character typical reactions of donor-acceptor-cyclopropanes are presented herewith. Rearrangements of cyclopropanes can be driven by the formation of radicals, carbenes, metal insertions, organo catalysis as well as positive or negative charges.[45] Especially if cyclopropanes are donor-acceptor substituted charges play a crucial role in the activation as they can be stabilized simply by the respective substituent.
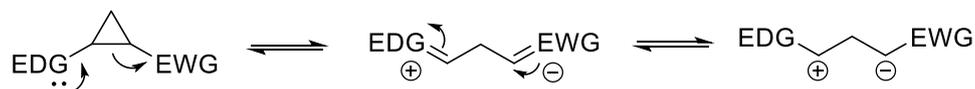
Scheme 4: General reactivity of donor-acceptor substituted cyclopropanes.

The easiest way to introduce a positive charge is by acid catalysis as utilized in plenty transformations. The group of Reissig were able to synthesize aldehyde esters from TMSO-, ester-substituted cyclopropanes with simultaneous ring cleavage making use of Et$_3$NHF or TBAF as Brønsted acid.[46] With compound **33** baring a hydroxy group, as intramolecular nucleophile, furan derivative **35** could be synthesized directly.[47]
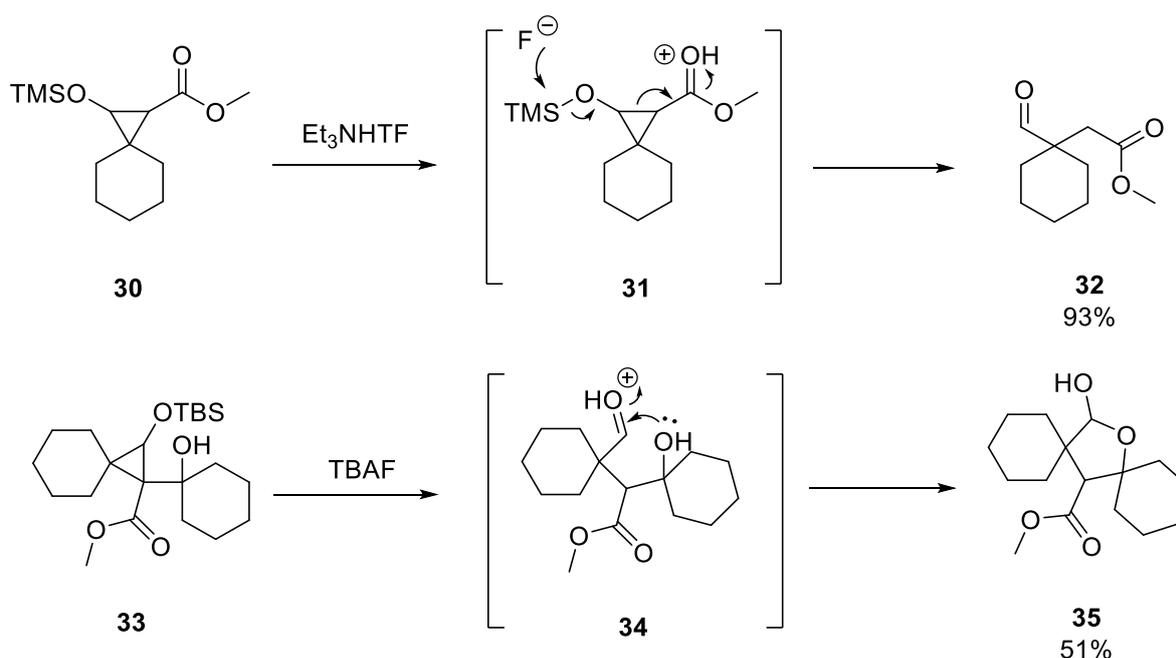
Scheme 5: Synthesis of aldehyde esters and furane derivatives by ring opening of TMSO-, ester substituted cyclopropanes.

Pohlhaus et al. published a similar reaction in 2008, where lewis-acid catalysis is used to cleave the cyclopropane α to a malonic ester heterolytically, followed by dipolar cycloaddition of aldehydes to form furan derivatives.[48]
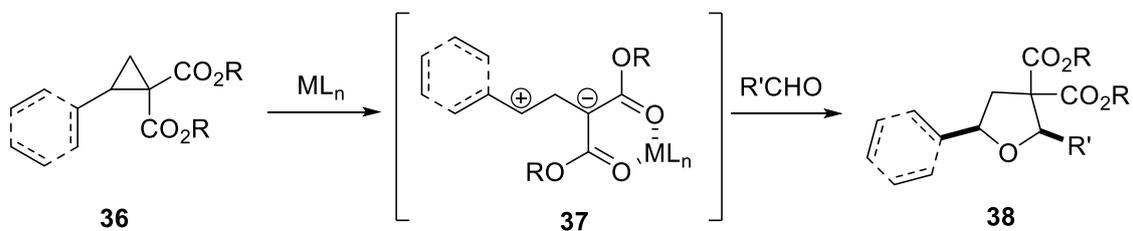
Scheme 6: Lewis-acid catalyzed ring cleavage of cyclopropanes: Synthesis of furanes.

Depending on the lewis-acid, diastereoselectivity es well as yields were excellent. Taking bicyclic cyclopropanes as starting materials, Pohlhaus et al. were able to synthesize benzofuran derivatives.

Although less obvious, bases can catalyze this type of transformations as well. Sasaki et al. reported a carbanion-induced [3+2] annulation of donor-acceptor cyclopropanes taking LiHMDS as base and a tosylgroup α to the cyclopropane as auxiliary.[49] Noteworthy is the simple removal of the auxiliary without an extra step by minor adjustments of the reaction conditions and substituents.
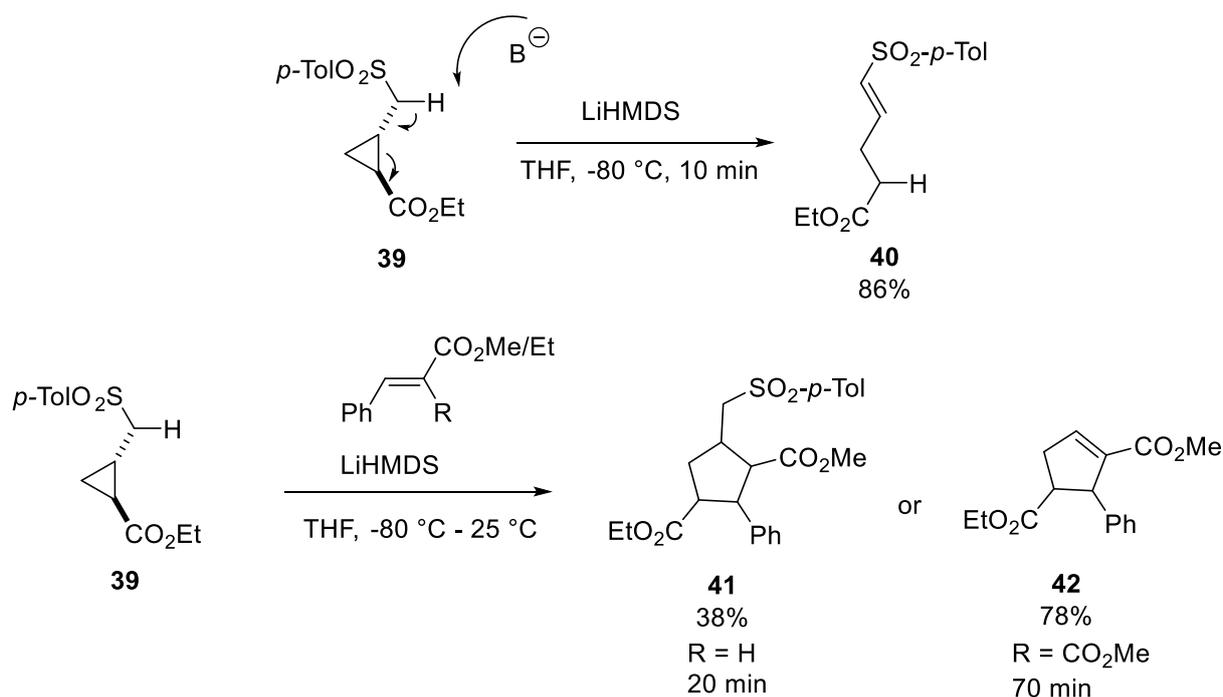
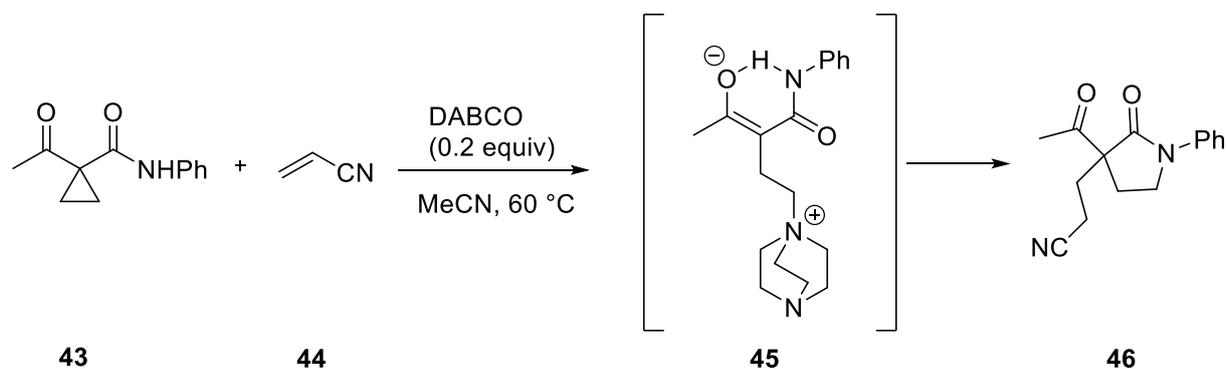*Scheme 7: Base induced ring opening of cyclopropanes.*

With the tosyl-auxiliary attached to the same carbon atom, the α-hydrogen is acidic enough to be deprotonated by the LiHMDS base. The carbanion acts now as electron donor and the esters group as acceptor leading to the ring opening of the cyclopropane. If polarized olefines are present in the reaction mixture the dipolar intermediate can be trapped and cyclopentane

derivatives are formed. Two ester groups on the trapping olefine and prolonged reaction times lead to a subsequent cleavage of the auxiliary.

A lewis-base catalyzed ring opening of cyclopropanes was described by Liu and co-workers.[50] Trapping of intermediates with electron poor olefines led to the synthesis of γ-lactams with 16 examples and yields up to 98%.

Scheme 8: Lewis-base catalyzed ring opening of cyclopropanes. Synthesis of γ-lactams.

DABCO was used as electron donating catalyst to start the cycle by a nucleophilic attack to the cyclopropane. If no trapping olefine is present, Liu and co-workers manged to isolate the dipolar intermediate **45** in 100% yield. If electron poor olefines like **44** are added, the reaction continues with a Michael type addition followed by a proton transfer generating an amide anion. Product **46** forms by aza-cyclization *via* nucleophilic substitution and elimination of the DABCO catalyst.

A different approach for the activation of cyclopropanes is the use of organo-catalysts. The group of Jørgensen showed impressively how chiral amines can be used in the synthesis of cyclobutanes from cyclopropanes by the transformation of an aldehyde in β-position to an electron donating enamine.[51]
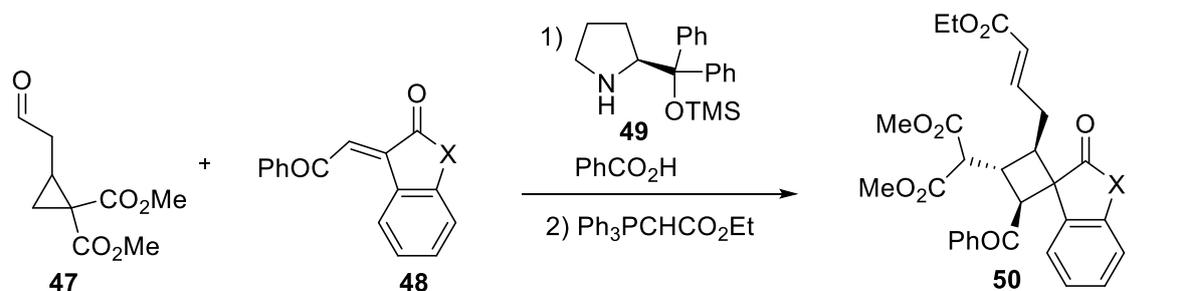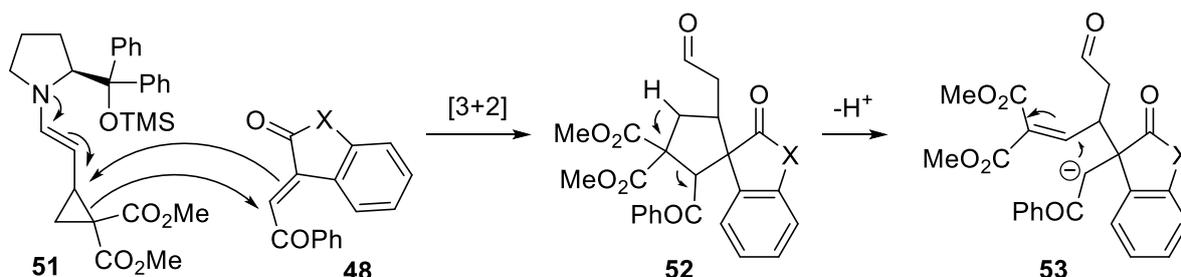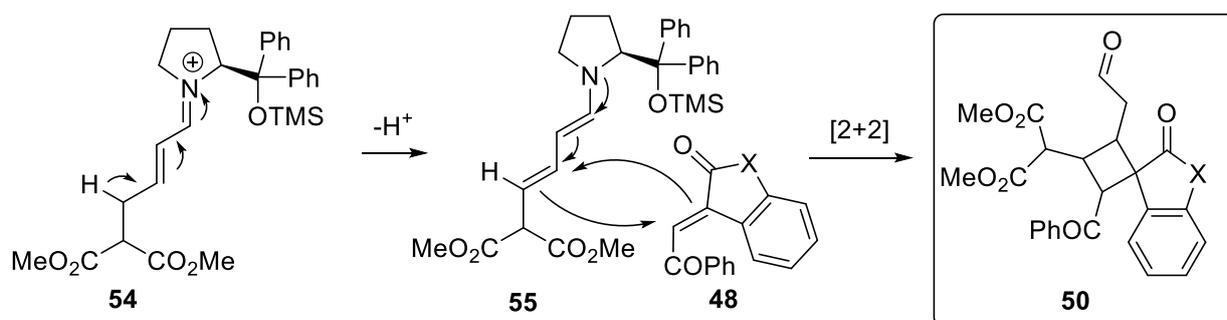
Scheme 9: Organo-catalyzed ring opening of cyclopropanes. Synthesis of cyclobutanes.

Instead of [3+2] cycloaddition, which would give rise to cyclopentanes like **41**, Jørgensen observed the formation of spiro-annulated cyclobutanes. Two plausible mechanisms were proposed. The first one assumes that the reaction starts with the desired [3+2] cycloaddition and a rearrangement occurs afterwards, driven by three electron withdrawing functionalities and proton abstraction. The other mechanism is proposed as a second enamine formation, leading to **55** after the initial cyclopropane opening which is followed by a [2+2] cycloaddition.

In the previous examples polarized olefines were often used as trapping reagents after cyclopropanes were opened to force cycloadditions. If the acceptor moiety is replaced by leaving groups, the negative charge can leave the molecule and nucleophiles can attack to furnish the product. This concept was first successfully applied by Hoberg and co-workers.[52] As an acetate itself is not sufficiently strong as leaving group, lewis-acid activation was required to generate **58** *via* nucleophilic trapping of **57** with TMSCN.
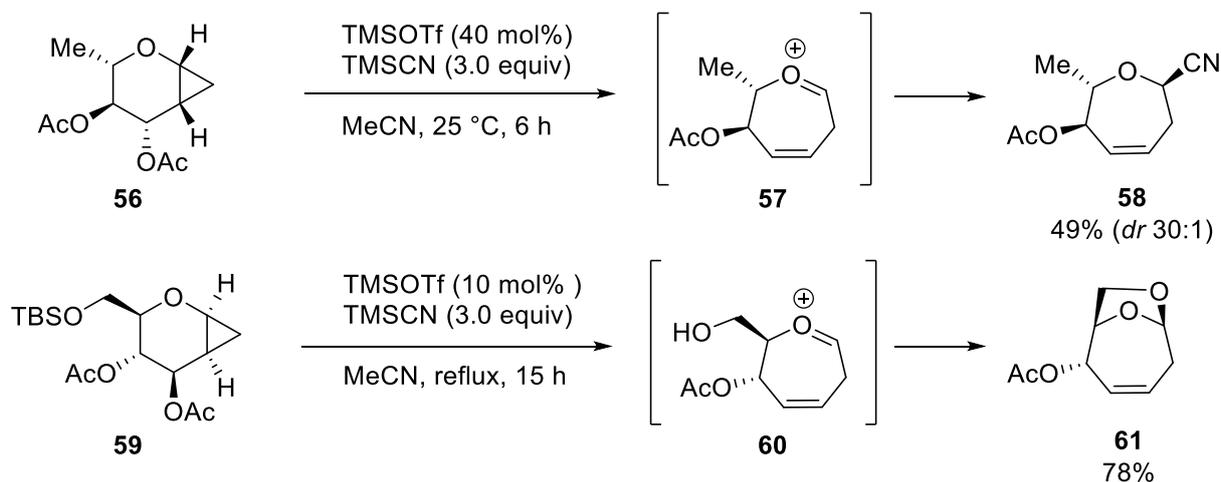
Scheme 10: Synthesis of oxepanes via endocyclic ring opening of cyclopropanes triggered by activated leaving groups.

Using cyclopropane **59**, **61** is formed in good yields of 78% by an intra-molecular nucleophilic attack of the deprotected alcohol. Eckl et al. transferred this concept to cyclopropanated furans and pyrrols.[53] By replacing the acetate with a more powerful mesylate leaving group, they were able to synthesize a wide scope of ring enlarged products without additional acid activation. However, elevated temperatures of 80 °C – 120 °C were required and conveniently applied by microwave irradiation.
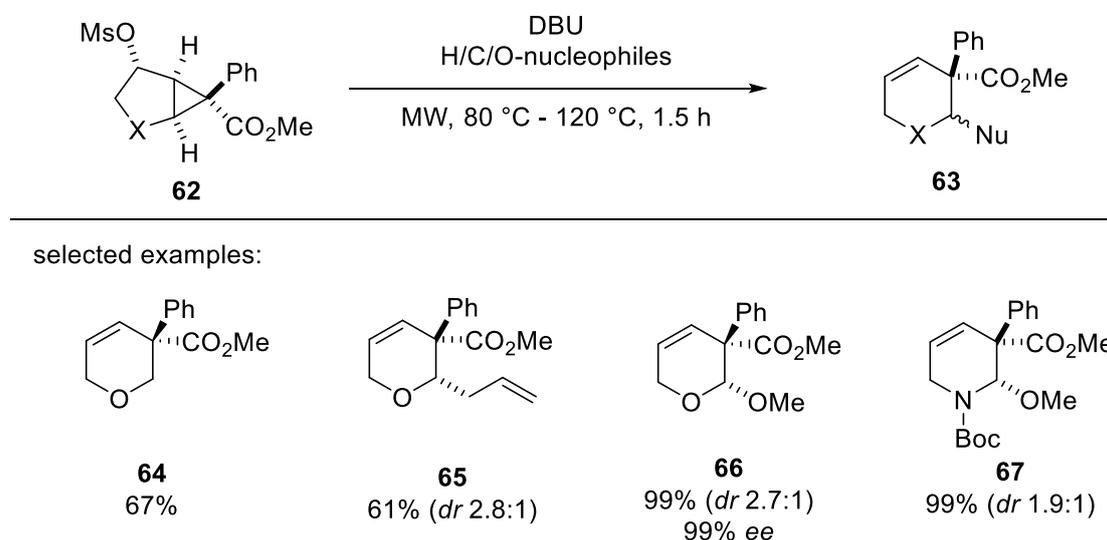
Scheme 11: Endocyclic ring enlargement of cyclopropanated furans and pyrrols.

Hydrogen, carbon, and oxygen nucleophiles turned out to be good coupling partners. If enantiomerically pure starting materials are used, chirality is transferred completely to the product as **66** shows.

2 Main part

2.1 Suitable starting materials in the synthesis of azepanes from cyclopropanes

The aim of this dissertation was to develop new pathways to azepanes starting from cyclopropanes while using all their advantages. Straightforward, fast, and easy synthesis. Approachable with all kinds of chemistry depending on substrates' special needs. Availability of stereoselective synthesis and a wide range of activation possibilities. Suitable starting materials were seen in cyclopropanated piperidines as the nitrogen atom can act as electron donating group. The implementation of an acceptor group to the opposite should give enough activation to drive the ring enlargement to the desired azepanes.
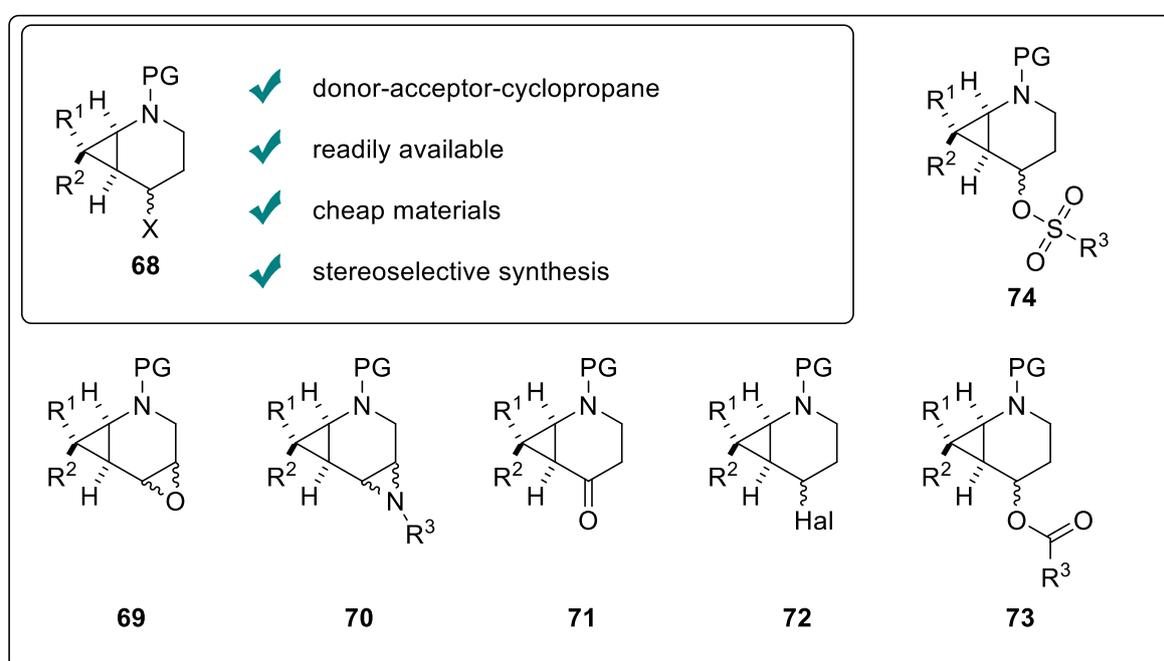
Figure 4: Requirements and possible candidates for a suitable starting material.

Materials that would fulfill these requirements are shown in Figure 4. While the nitrogen would always act as electron donating group the electron acceptor could possibly be an epoxide, aziridine, ketone, halogen, ester, or sulfonic acid ester. Since no records of these compounds were present in literature, the development of fast, stereoselective syntheses of such compounds from cheap reagents was the first task to achieve during this work.

2.2 Synthesis of novel hetero-atom bridged azepanes from donor-acceptor-cyclopropanes by epoxide or aziridine activation

Former work in our group on the synthesis of azepanes and other hetero- and carbocycles *via* Heck-coupling driven ring enlargements,[54] used cyclopropanated 1,2-dihydropyridines as substrates. The remaining double bond of these vinyl cyclopropanes was used for the oxidative addition of palladium to trigger endocyclic ring enlargements. Unfortunately yields of these reactions were rather low and the synthesis of the starting material by copper catalysis problematic. Nevertheless, these cyclopropanes would suit perfectly as starting point for the synthesis of aziridines **76** and epoxides **79** as donor-acceptor-cyclopropanes if the cyclopropanation could be improved.
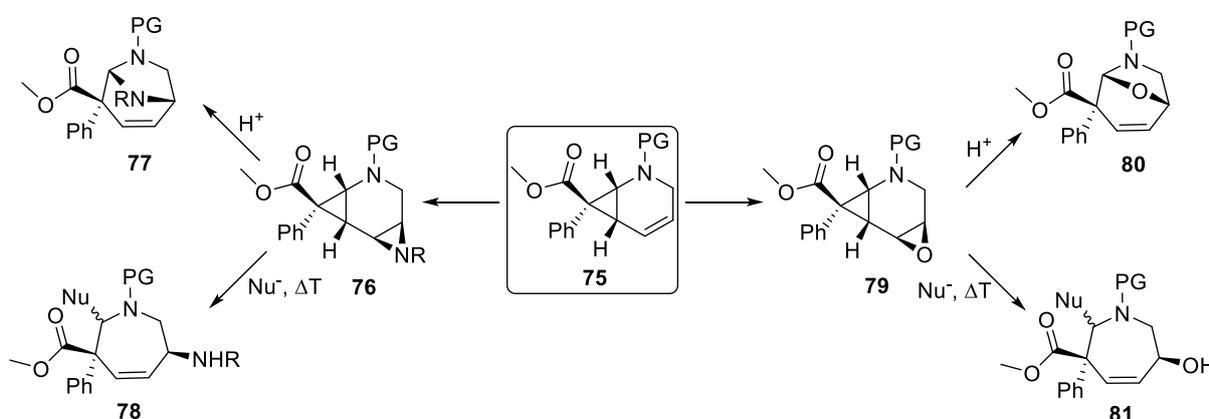
Figure 5: Aziridines and epoxids as starting material to novel monocyclic and bridged azepanes.

Research in the synthesis of Ritalin derivatives by our group in collaboration with the group of Prof. Dr. Huw Davies showed that very similar cyclopropanes can be synthesized more effectively by rhodium catalysis starting from tetrahydropyridines.[55] These cyclopropanated piperidines were also synthesized highly enantioselective (up to ee = 95%) with chiral catalysts. If this reaction could be applied on 1,2-dihydropyridines as well, subsequent aziridination or epoxidation could provide the required compounds. From there at least two interesting transformations are conceivable. An acid catalyzed activation of the respective heteroatom could start a cascade of two ring openings leading to an iminium ion. Form there intramolecular trapping by the N/O-group or trapping with an added nucleophile could lead to new interesting azepanes with defined stereochemistry.

2.2.1 Synthesis of cyclopropane **87**

Following Fowlers procedure, carbamate protected 1,2-dihydropyridines can be easily obtained in gram scale by one step from pyridine.[56] Pyridine and fine crushed $NaBH_4$ dissolved in EtOH is therefore cooled to -78 °C while phenyl chloroformate is added within 1 h. After additional reaction time of 16 h at 25 °C the product was isolated in 86% yield.
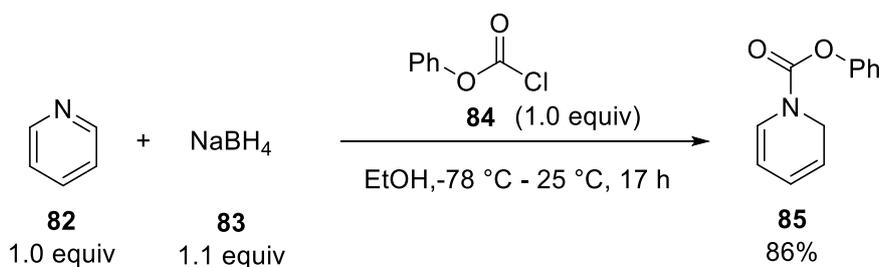
Scheme 12: Synthesis of 1,2-dihydropyridine 85.

With 1,2-dihydropyridine **85** in hand, several chiral rhodium catalysts were tested on its cyclopropanation. It was assumed that sterically more demanding catalysts could favour the double bond at 3,4-position **88** over the double bond at 5,6-position **87**. However, only product **87** was observed with all catalysts tested. The product was formed as single diastereomer according to NMR and HPLC analysis. Going in line with previous observations on heterocycle cyclopropanation, the aryl group is concave oriented as X-ray analysis of **90** proves.

Table 1: Studies on the rhodium catalyzed cyclopropanation of 1,2-dihydropyridines.
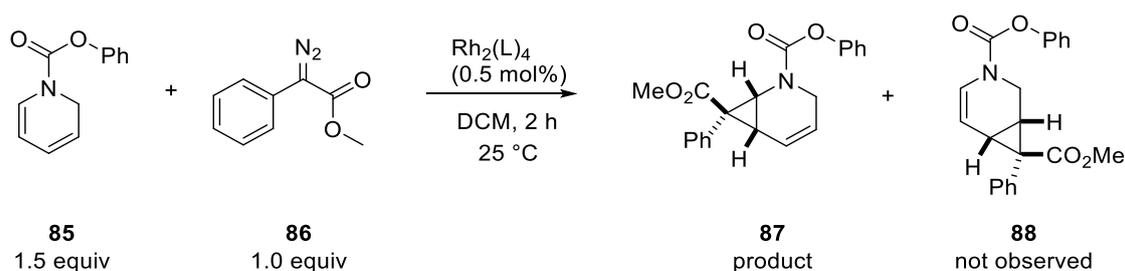
entry	catalyst	yield [%]	*ee* [%]
1	Rh₂(*R*-2Cl-5Br-TPCP)₄	86	15
2	Rh₂(*S*-4-Br-TPCP)₄	75	8
3	Rh₂(*S*-TCPPTL)₄	85	39
4	Rh₂(*R*-DOSP)₄	70	69
5	Rh₂(*R*-TCPTAD)₄	100	36
6	Rh₂(OAc)₄	80	-
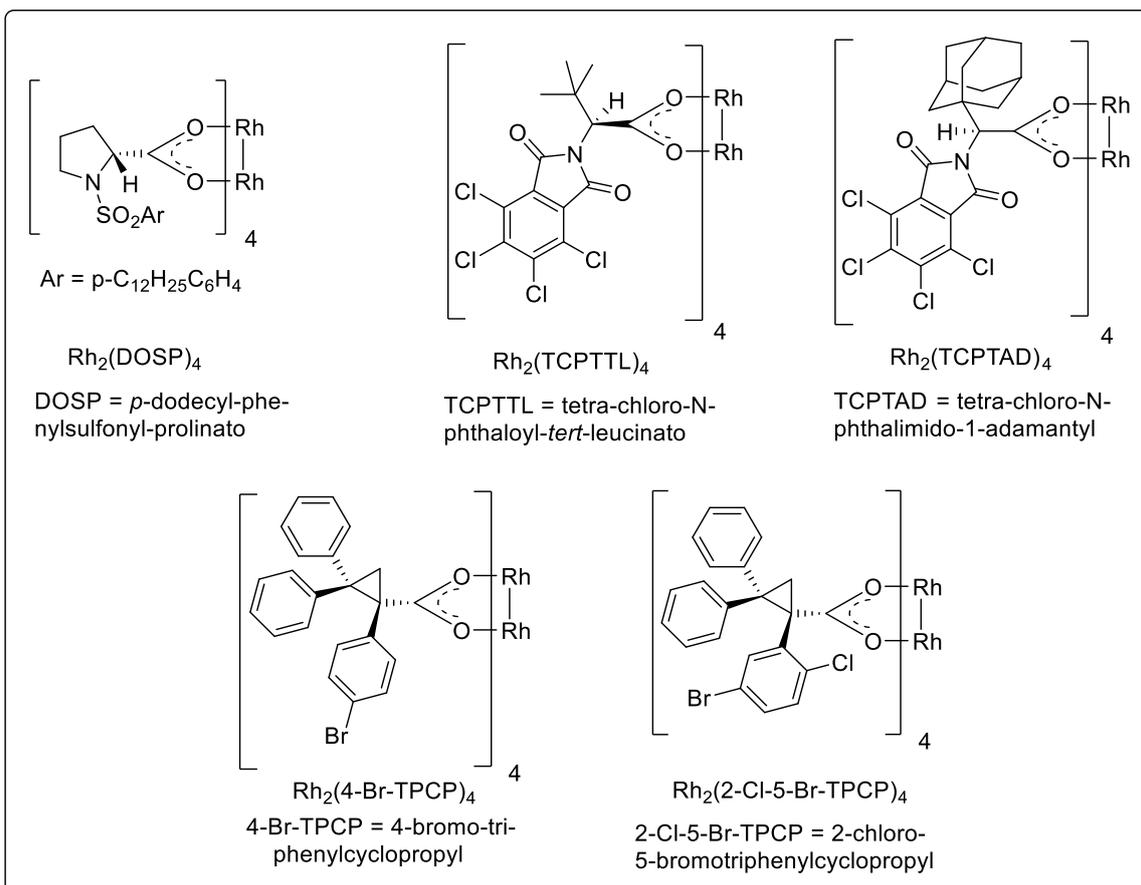
Figure 6: Structure of rhodium catalysts.

The tested rhodium catalysts were developed by the group of Prof. Dr. Huw Davies for enantioselective cyclopropanation and C-H insertion chemistry and are therefore usually highly active for this kind of reactions. Only 0.5 mol% catalyst loading was required, and short reaction times were sufficient to give high yields of 70%-100%. In the case of Rh_2OAc_4 (entry 6) also gram scale experiments were performed where the high yield of 80% did not break down. The reaction time is determined by addition rate of the diazo ester. Lower rates can result in higher yields by prevention of dimerization reactions. For the catalysts that gave lower yields a decreased addition rate could be useful. Unfortunately, enantioselectivity was considerably lower compared to previous observations by cyclopropanations of tetrahydropyridines. In line, on the other hand, is that the highest ee was obtained using $Rh_2(R\text{-DOSP})_4$ with a value of 69%. For increased selectivity adjustments on reaction temperatures could be investigated. Lower temperatures in the range of 0 °C to -40 °C often give better results. Also higher temperatures can enhance the selectivity as the group of Davies observed it while studying cyclopropanations on pyrrols.[57] Because of collaborational reasons, these catalysts were unavailable after the initial experiments and temperature screening could not be conducted.

2.2.2 Synthesis of epoxide **89** and subsequent transformation to 8-oxa-6-azabicyclo[3.2.1]octanes

Once cyclopropane **87** was synthesized in high yields, epoxidation of the remaining double bond was the next achievement to be made to gain the desired donor-acceptor-cyclopropane. *In situ* generated dimethyldioxirane from oxone in an acetone:water mixture under basic conditions[58] led to a clean generation of the desired epoxide in good yields of 81%. Upscaling to gram scale however led to a decreased yield of 41%. Refluxing compound **89** in EtOAc under acidic conditions indeed gave the oxygen bridged azepane **90** in an excellent yield of 94%. The structure was proved by crystallographic analysis.
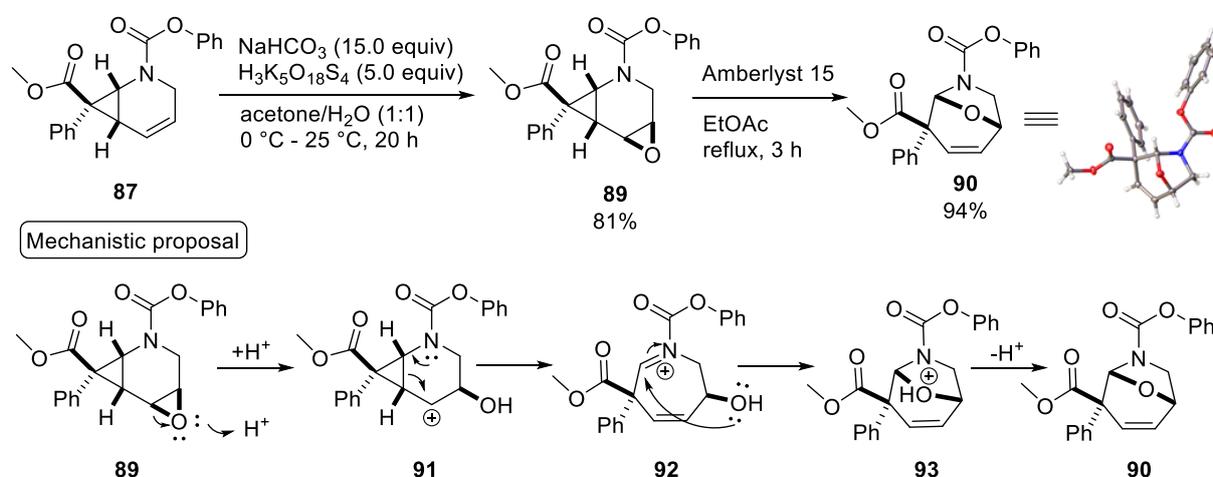
*Scheme 13: Synthesis of O-bridged azepane **90** and mechanistic proposal.*

The mechanism of this reaction is proposed as follows. Under acidic conditions the epoxide is protonated leading to the carbocationic intermediate **91**. The rearrangement of electrons is leading to the endocyclic ring opening and the cation is stabilized as iminium ion. The hydroxy group can now act as nucleophile to form the final product **90** after proton elimination. It was further tested if the addition of MeOH as external nucleophile would give non bridged products like **94**. But even if MeOH acts as cosolvent in a ratio of 1:1 with EtOAc only **90** was formed. Cyclopropane **95** which would arise from a nucleophilic attack to the epoxide without ring-opening was not observed as well. Unfortunately, as the alcohol in **95** could be converted to a leaving group to drive the endocyclic ring opening in a later stage. In order to enhance the nucleophilic strength NaOMe was prepared *in situ* and used as nucleophile. Neither of the desired products formed, rather the protecting group was substituted from Ph to Me. With 30 mol% CAN as lewis acid and nBu$_4$NBr in refluxing MeCN bicyclic product **90** was formed.[59]
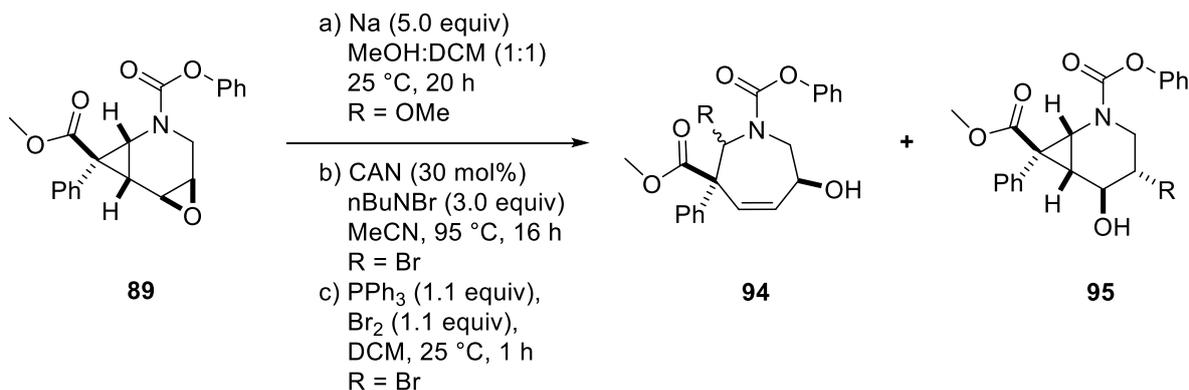
Scheme 14: Nucleophilic opening of epoxide 89.

The same outcome was observed using PPh$_3$ and Br$_2$.[60] This leads us to the conclusion that driving force to **90** is very high and Brønsted as well as Lewis acids are able to catalyze this reaction. As strong nucleophiles go along with one sort of acid the direct way to **110** is prohibited. Another way to these molecules could be the cleavage of the hemiaminal ether moiety and will be discussed in chapter 2.2.4.

2.2.3 Derivatizations of **90**

There is little known about 8-oxa-6-azabicyclo[3.2.1]octanes and their examples in literature a only a few. Nevertheless, these few examples show that this structural motive is biologically interesting. Preusser et al. reported three alkaloids found in the skin gland secretion of the amphibia *Salamandra maculosa*. They serve the animal as protection from infection of the moist skin by bacteria or molds. In agar-diffusion test the antimicrobial activity of the so called samandarine **96**, samandarone **97** and samandaridine **98** was proven.[61] Isolated from the colonial zoanthid *Zoanthus sp.*, Norzoanthamine **99** decreases interleukin-6 production. It was proven that if used on mice, bone weight and density increases making it a potential drug for osteoporosis treatment.[62] Inoue et al. discovered that most of its activity goes back to the 8-oxa-6-azabicyclo[3.2.1]octane moiety **100** which is reducing the complexity of a synthetic approach to this potential osteoporosis drug a lot.[63] The parent compound of a class of alkaloids containing indanobenzazepine is called Ribasine **101** and was isolated from *Fumariaceae* plants by Boente et al. Unfortunately, there is still little known about biological effects of this compound.[64]
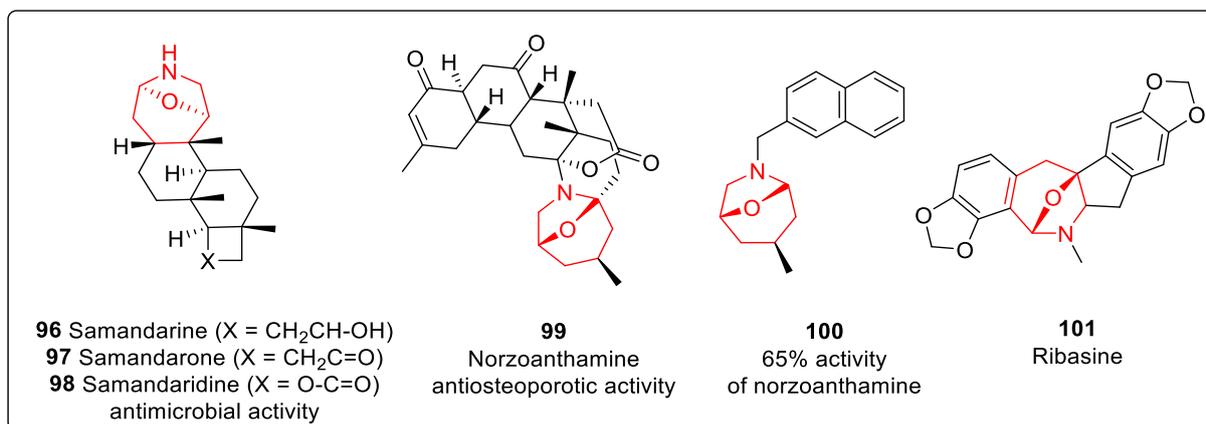
Figure 7: Interesting examples of 8-oxa-6-azabicyclo[3.2.1]octanes.

To widen the small library of this bicyclic system common double bond derivatizations were performed on **90** (scheme 15). Hydrogenation was achieved in excellent yield of 96% at atmospheric pressure with Pd/C catalysis. Several attempts on the synthesis of halohydrines failed. Whether using NBS for mild conditions or elemental Br_2 at 25 °C or elevated temperatures up to 70 °C no reaction was observed. In order to investigate potential pathways to Samandarine type molecules, Diels-Alder-reactions were carried out. Using cyclopentadiene at 25 °C did not lead to any reaction. Microwave assisted heating to 150 °C also had no impact on this. Therefore, the diene was switched to Danishefsky's as electron rich diene. Microwave assisted heating to 200 °C again did not lead to any conversion of the substrate.
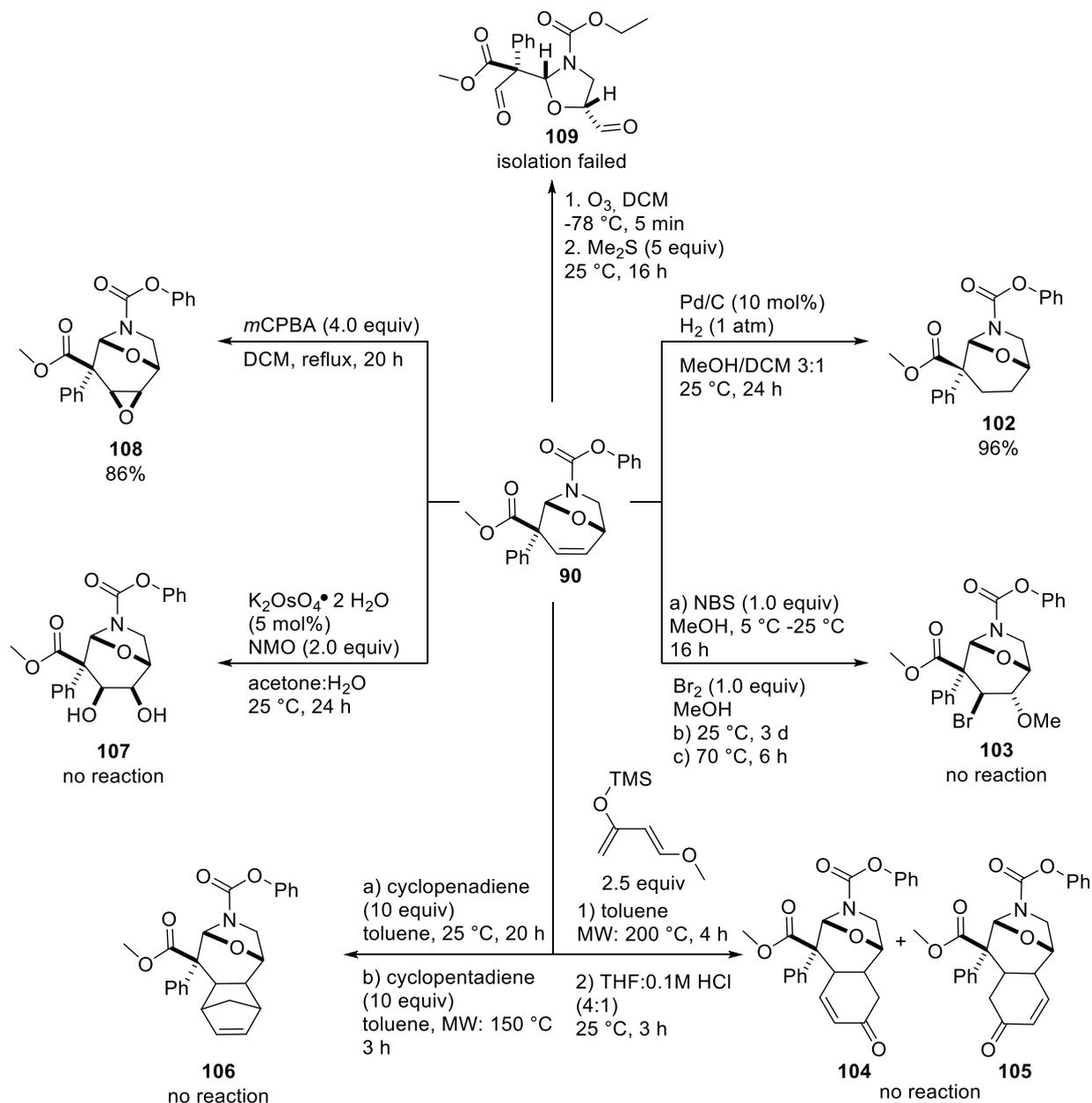
Scheme 15: Double bond functionalization of 90.

As the double bond of **90** is neither electron poor nor electron rich in combination with sterically demanding sidechains nearby, the substrate is probably too inactive as dienophile. Osmium catalyzed dihydroxylation was carried out next. Unfortunately, the formation of **107** was not observed. Epoxidation using *m*CPBA did lead to **108** as single diastereomer in a good yield of 86%. The epoxide is thereby convex oriented. Lastly the double bond was cleaved by ozonolysis leading to highly functionalized, stereo controlled oxazolidine **109**. Even though the crude NMR-analysis is indicating full conversion with a high content of desired product, isolation of the product failed due to its instability.

2.2.4 Cleavage of hemiaminal ether 90 for the synthesis of azepanes

As we concluded at the end of chapter 2.2.2 the direct synthesis of azepanes through epoxides is prohibited by the strong driving force to compound **90**. However, there are several procedures available in literature for the cleavage of this so called hemiaminal ether functionality. Starting with the conditions used by Taniguchi et al. for the cleavage of hemiacetals having BF_3 as Lewis acid and Et_3SiH as H$^-$ source, no reaction was observed after 20 h.[65] Harsh acidic conditions under elevated temperatures (entry 2) did not result in any conversion of starting material. Following the procedure of Fuentes et al. $NaCNBH_4$ was tested under harsh, mild and non-acidic conditions (entry 3-5).[66] Once more no reaction was observed in all cases.

Table 2: Conditions for the cleavage of hemiaminal ether 90.
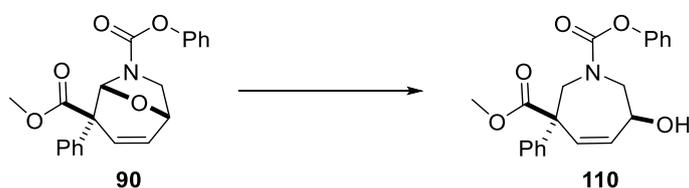
entry	conditions	observation
1	$BF_3 \cdot OEt_2$ (2.0 equiv), Et_3SiH (2.0 equiv), DCM, -78 °C – 25 °C, 20 h	no reaction
2	$TFA:H_2O$ (9:1), 50 °C, 1 h	no reaction
3	H_2SO_4, $NaCNBH_3$ (1.5 equiv), MeOH:MeCN (1:1), 25 °C, 20 h	no reaction
4	HOAc, $NaCNBH_3$ (1.5 equiv), MeOH:MeCN (1:1), 25 °C, 20 h	no reaction
5	$NaCNBH_3$ (1.5 equiv), MeOH:MeCN (1:1), 25 °C, 20 h	no reaction

Since no successes were achieved in the cleavage of the oxygen bridge, the focus was turned towards the synthesis of N-bridged analogues.

2.2.5 Synthesis of aziridine **76** for the subsequent transformation to N-bridged azepanes

In line with their oxygen bridged counterparts, this bicyclic aminal structure called diazabicyclo[3.2.1]octane is discussed very little in literature. Just a few molecules of its type are reported and in fact only one patent is dealing with its biological properties. Cheng et al. observed that compound **111** and derivatives show T-lymphocyte proliferation for a better human immunity and could be used in the treatment of immunocompromised diseases.[67]

111
activity in immunotherapy
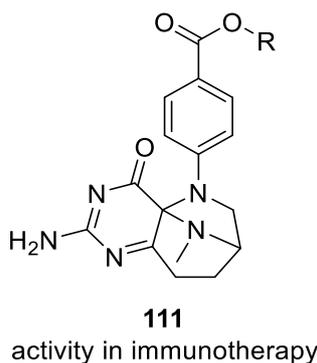
Figure 8: Biologically active diazabicyclo[3.2.1]octane.

Nevertheless, new molecules of this type could bear unknown properties, especially if all stereocenters could be controlled. Therefore, several aziridination reactions were carried out to get **76** as donor-acceptor cyclopropane for the transformation to diazabicyclo[3.2.1]octane **77**. Following the procedure established by the group of Sharpless,[68] chloramine-T should add to the C-C- double bond by Br$^-$ catalysis. However, even after 3 d reaction time no conversion was observed (entry 1). Switching the halogen source to I_2 or NBS gave the same result (entry 2-3). Next an Cu(II) mediated aziridination developed by the group of Falck was tested.[69] Hydroxylamine-O-sulfonic acid (HOSA) is used as a source of nitrogen in this reaction. The reaction requires basic conditions and 1,10-phenantroline as ligand for the copper (entry 4). Once more no conversion of starting material was observed. Finally, the approach was shifted towards implementation of an iodo azide,[70] with a following rearrangement to N-phosphorylated aziridine by PPh$_3$, which could be reduced to the desired aziridine by LiAlH$_4$.[71] Unfortunately this synthetic procedure resulted in an unanalysable mixture of products.

Table 3: Studies on the synthesis of tricyclic aziridines.
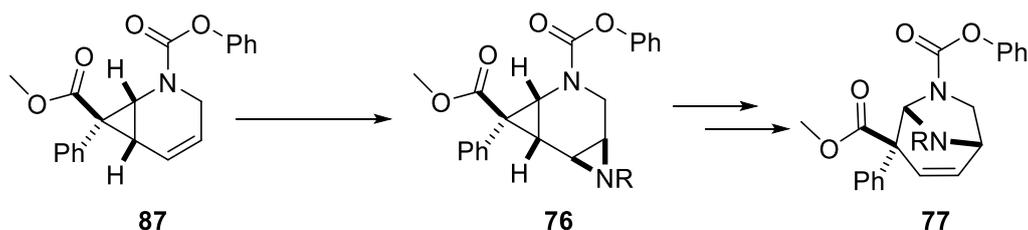
entry	R =	conditions	observation
1	Ts	Chloramine-T (1.1 equiv), PhMe₃NBr₃ (10 mol%), MeCN, 3 d	no reaction
2	Ts	Chloramine-T (1.1 equiv), I₂ (10 mol%), MeCN, 3d	no reaction
3	Ts	Chloramine-T (1.1 equiv), NBS (10 mol%), MeCN, 25 °C, 3 d	no reaction
4	H	HOSA (1.5 equiv.), pyridine (1.5 equiv), CuCl₂ (10 mol%), 1,10-phenantroline (10 mol%), HFIP, 0 °C – 25 °C, 3.5 h	no reaction
5	H	1. NaN₃ (5.0 equiv), ICl (2.5 equiv), MeCN, 6 d 2. PPh₃ (1.0 equiv), toluene, 25 °C, 20 h	complex mixture

Because all synthetic approaches to aziridine **76** failed, the planned rearrangement to **77** could not be accomplished. The focus was turned towards the synthesis of other donor-acceptor-cyclopropanes with either a keto group or an activated alcohol leaving group.

1.3 Synthesis of new cyclopropanated piperidines with donor/leaving-acceptor substitution for the synthesis of chiral azepanes

Having made the first achievements with the synthesis of **90** and its derivatives by endocyclic ring opening of donor-epoxide-acceptor-cyclopropanes, the seek started for new substrates featuring other types of acceptor groups as previously shown in figure 4. Since the synthesis of aziridines failed, the focus turned to ketones as classical moiety for this type of rearrangements (see introduction). In addition, ketones can be converted to alcohol-leaving groups easily to give more types of staring materials to explore. As first substrate **114** should be synthesized following exactly the procedure developed by Lopez-Rodriguez, Dominguez and Perez-Castells.[72] After the synthesis of piperidinon **113** from 4-methoxy-pyridine cyclopropanation should be achieved using sulfur-ylides. Unfortunately, results deviated much from the reports. **113** could be synthesized in 28% but in far lower yields compared to the 69% obtained by Lopez-Rodriguez et al. Cyclopropanation with sulfur ylides did not work out at all. Instead of 52% yield only traces of products were observed after multiple attempts. Whether heating was applied by microwave irradiation following the procedure or conventional heating with oil bath, DBU is added right before heating is applied or together with the ylide **114** was not formed in isolable amounts. However, the conversion of the ylide was observed but not its binding to the substrate.
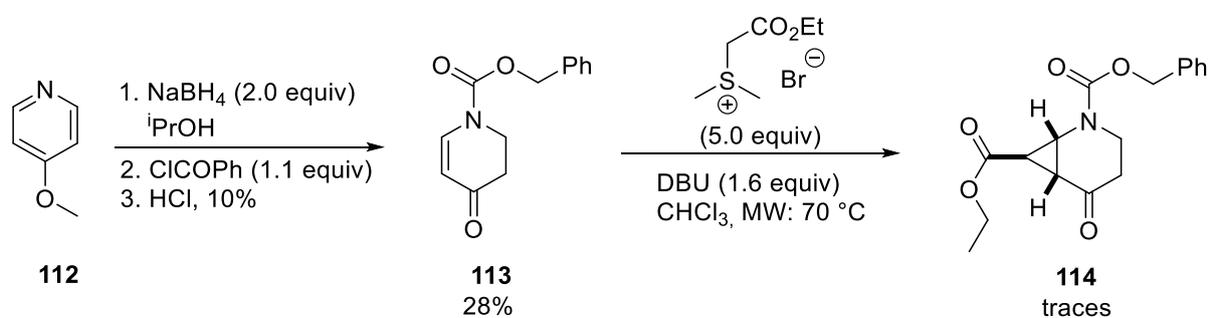
Scheme 16: Synthesis of donor-ketone-acceptor-cyclopropanes following the procedure of Lopez-Rodriguez et al.

Another disadvantage of this route is the high price of 4-methoxy-pyridine **112**. A synthetic sequence with multiple steps as the synthesis of azepanes will require could be very cost intensive. Therefore, a similar piperidinone **118** was synthesized from cheap piperidinone **115** in 2-3 steps. The sequence starting with an acetal protection of the ketone and subsequent bromination in α-position was conducted high yielding and in multigram scale following literature procedures.[73–75] By heating of **116** under basic condition HBr is eliminated next to form the double bond in **117**. With an acidic workup the acetal protection group is removed to

form **118** directly. Nevertheless, initial investigations required **117** to be isolated for use as substrate in cyclopropanations. Inspired by Lopez-Rodriguez et al.'s research, sulfur ylide cylopropanation was conducted with Ph-ethyl ester-ylides and H-ethyl ester ylides using their conditions. Again, none of these reactions resulted in the formation of cyclopropanes. Cyclopropanantion with diazo esters using rhodium catalysis, usually a reliably way for these reactions, did not give product **120** as well. Next to Rh$_2$(OAc)$_4$, Rh$_2$(R-TCPTAD)$_4$ known as extremely active catalyst was employed. Reasoning is seen in the sterically shielding of both sides by the acetal protecting group so the carbene bound to the catalyst cannot be transferred to the double bond.
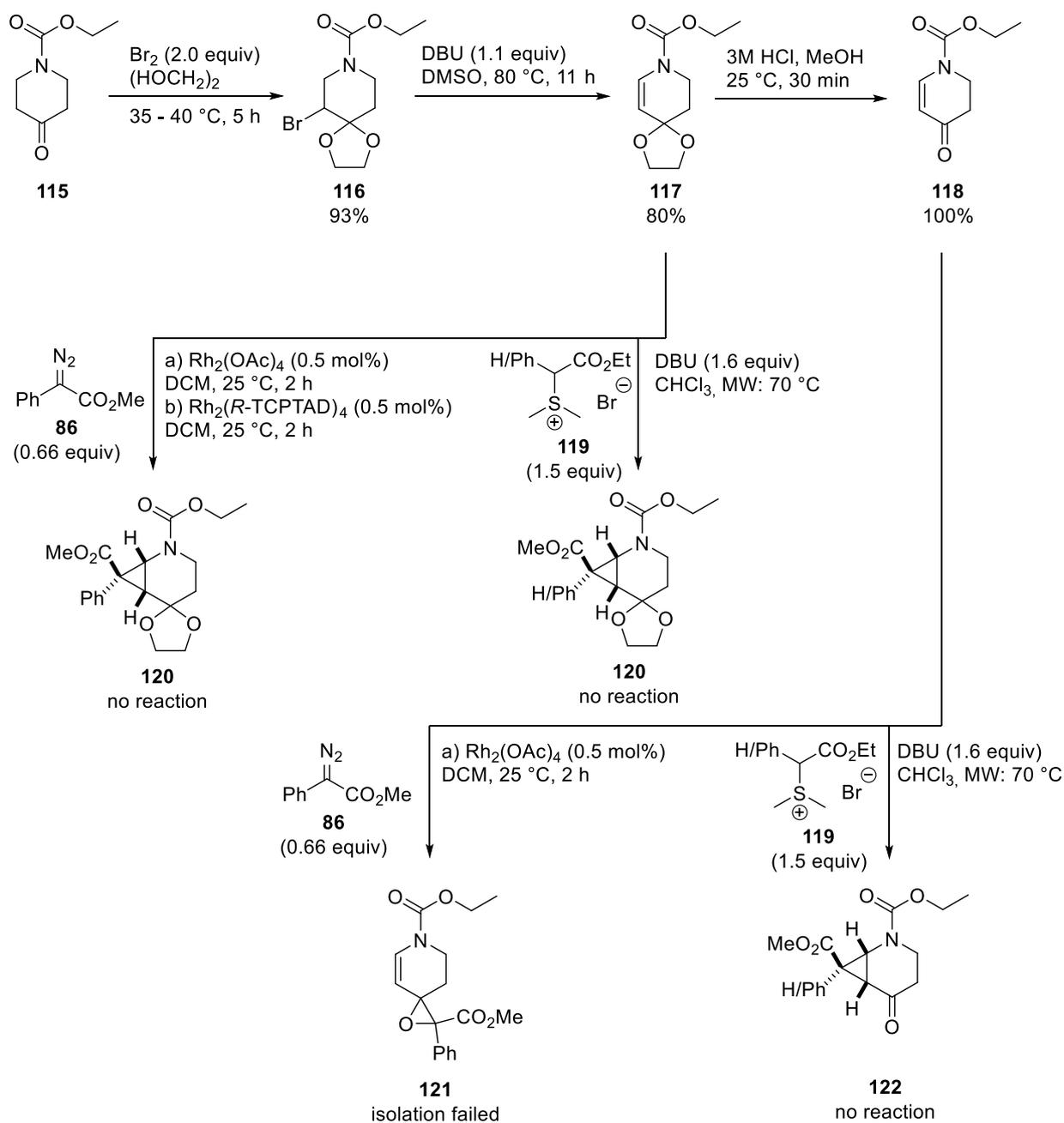
Scheme 17: Seek for new donor-acceptor cyclopropanes.

By removal of the acetal protecting group the C-C double bond should be better accessible however reports of rhodium-carbene complexes forming epoxides with ketones can be found in literature making epoxides a potential by-product.[76] **118** was now used as substrate and sulfur ylides as well as rhodium catalyzed conversion of diazo esters were tested as cyclopropanation procedures. Once again, sulfur ylides did not lead to the formation of cyclopropanes. The rhodium catalyzed reaction instead gave a new product. After analysis of the crude reaction mixture and in accordance with the reactivity of this substrates as it is reported, epoxide **121** is the product that formed most likely. Regrettably, isolation of the product failed due to instability. After the failed synthesis of donor-ketone-acceptor cyclopropanes efforts were shifted to the synthesis of cyclopropanes with alcohol leaving groups in α-position. Taking the procedure of Luche's sodiumborohydride/ceriumtrichloride reduction alcohol **123** was easily obtained in excellent yields and multi gram scale.[77–79] At this point direct cyclopropanation of **123** using rhodium catalysis was conducted. Unfortunately, instead of the desired product **127** only a complex mixture of products was observed.
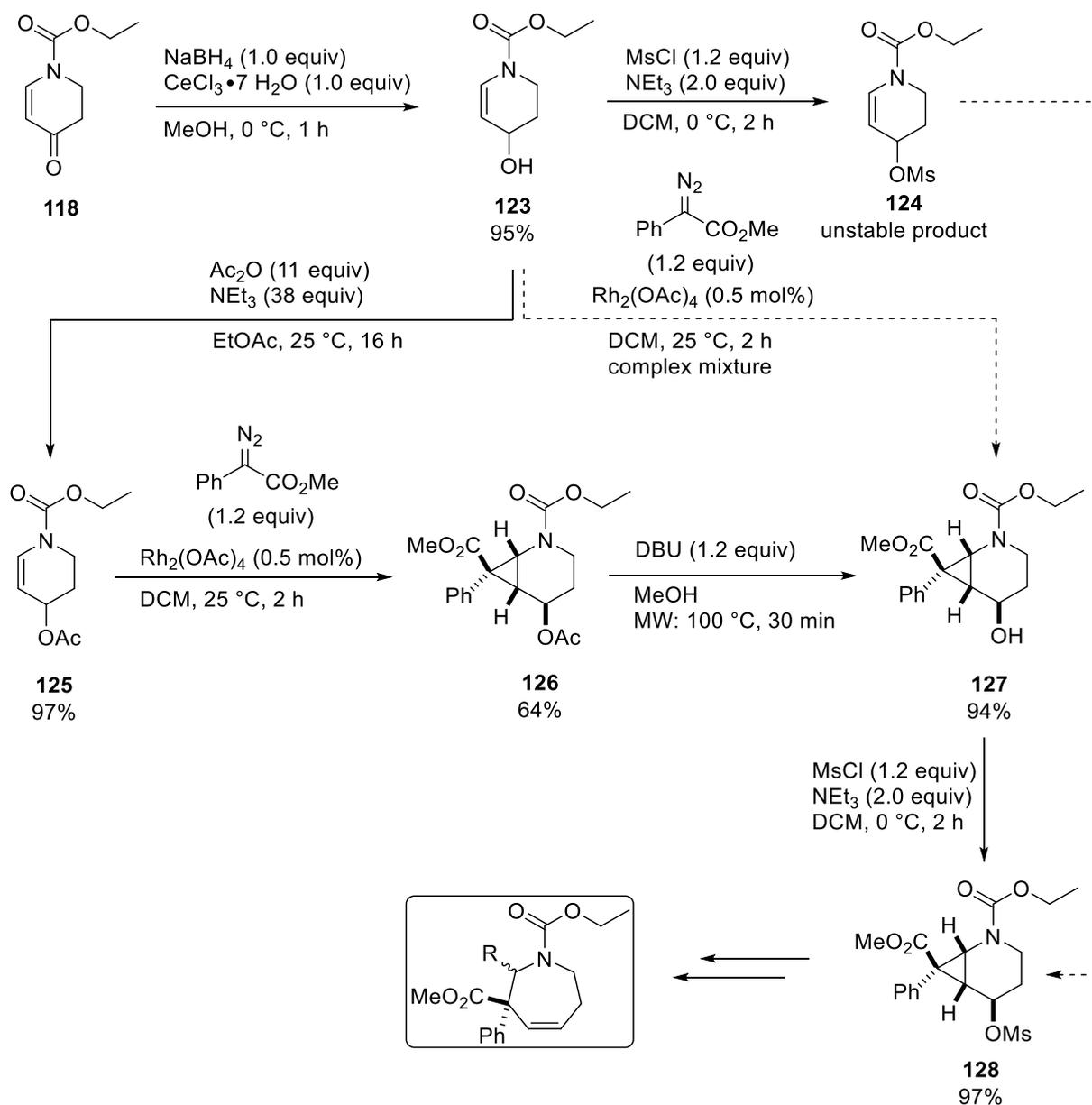
Scheme 18: Seek for new donor-acceptor-cyclopropanes with alcohol leaving groups.

One possible product could be a rhodium catalyzed OH insertion leading to ethers as it was observed in foregoing research.[80] However, this hypothesis was not proved by isolation of this kind of products. Nevertheless, it was decided to protect the free alcohol to decrease its reactivity and create a cleaner reaction. Recalling the work by Robert Eckl in the synthesis of piperidines and pyrans from donor-acceptor cyclopropanes,[53] showing that mesylate leaving groups are a perfect trigger for the ring expansion (see scheme 11), the implementation of a mesyl group as alcohol protecting group and acceptor group of a from it resulting cyclopropane seemed to be an efficient strategy. The synthesis of **124**, however, failed due to its instability resulting from the strong electronic push-pull system put up by the nitrogen and the strong leaving group bridged by the C-C double bond. In search for a more stable alcohol protection

123 was acetylated which gave **125** in good yields of 97%. At this point rhodium catalyzed cyclopopanation with methyl 2-diazo-2-phenylacetate was finally successful giving rise to **126** in a yield of 64% as a single diastereomer. Last the acetate protecting group was replaced in 2 steps. The alcohol was deprotected in excellent yields by refluxing under basic conditions followed by mesylation using MsCl as reagent. With **126** and **128** two substrates were found that fulfil the requirements. Cheap and scalable synthesis, donor-acceptor substituted cyclopropane and the possibility of a stereoselective approach. Therefore, the endocyclic ring opening was investigation on both substrates as it will be discussed later on.

1.4 Enantioselective synthesis of donor-acceptor-cyclopropanes **126** and **128**

1.4.1 Concept behind the enantioselective approach to 3,3-substituted azepanes

In analogy to any other stereoselective synthesis one of the following requirements needs to be met in order to obtain the product in a specified chiral settlement. The first option is to use a molecule from the chiral pool as starting material. The chiral pool is defined as summary of all enantiomerically pure from nature available compounds. This option is usually favoured as many of these compounds are commercially available, rather cheap and 100% enantiomerically pure. Using these compounds allows to fall back to classic chemistry that usually does not rely on expensive catalysts. The second option is to start from a prochiral starting material and a subsequent conversion to the specific enantiomer by enantioselective reactions. In the past decades basic research in chemistry focused on the implementation of enantioselective alternatives to almost every classic reaction. But in comparison to the chiral pool strategy this approach has some major drawbacks. First of all, these reactions require enantiomerically pure chiral catalysts that are often expensive. Moreover, the enantioselectivity is usually strongly dependent on the substrate and highly enantioenriched products are not guaranteed. The third way to single enantiomers goes over chiral resolution. The concept of chiral resolution benefits from the difference in reaction speed of enantiomers from a racemic sample with chiral catalyst. This concept often uses enzymes as catalysts as they are highly specialized in the conversion of specific enantiomers. A special case of the chiral resolution concept is known as dynamic kinetic resolution (DKR) where the remaining enantiomer is racemising and over time 100% conversion to the desired enantiomerically pure product can be achieved.

Applying these concepts to the priorly elaborated synthetic sequence to **126** and **128**, raises the question at which point selectivity can be covered and maintained. Taking advantage of the diastereoselective rhodium catalyzed cyclopropanation where the aryl moiety is oriented concave and the ester convex while the carbene attack takes place from the sterically unhindered side, a stereoselective synthesis of **126** and so **128** can be put down by having alcohol **123** in enantiomerically pure form. Unfortunately, there is no compound from the chiral pool that could serve as starting material to form **126**. However, enantioselective reductions of **118** to **123** or chiral resolutions during esterification to **125** could be applied and will be discussed in the following. If the stereocenter of interest at the C3-position could be preserved during ring opening the (S)-alcohol **(-)-123** would lead to (*R*)-azepanes and the (*R*)-form **(+)-123** to **(S)-129** respectively.
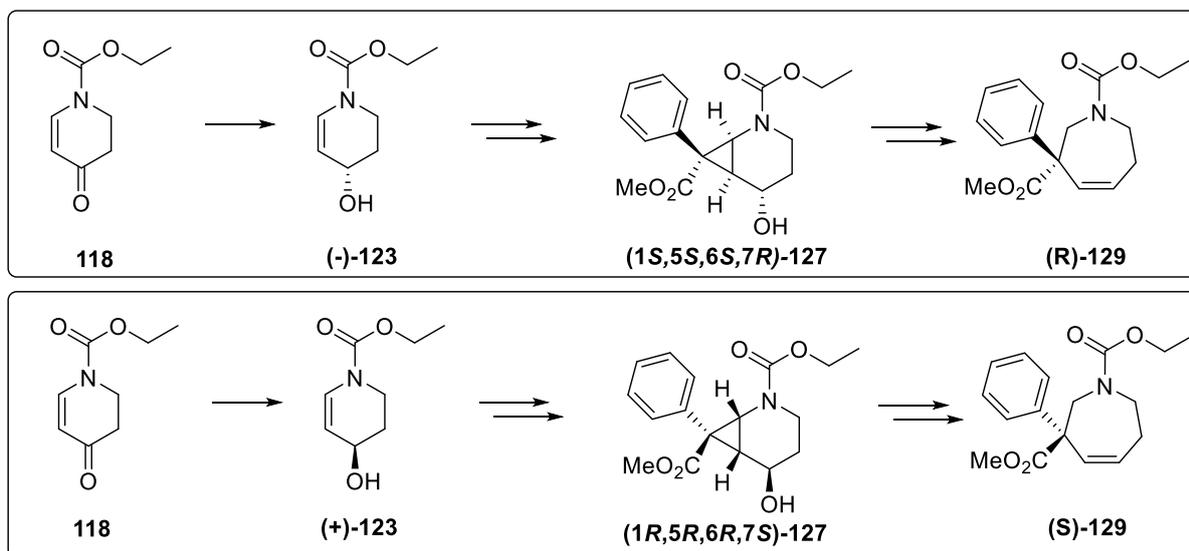
Scheme 19: Stereoselective synthesis of C3-substituted azepanes: the concept.

1.4.2 Common enantioselective reduction

1.4.2.1 The Corey-Bakshi-Shibata reduction

First published in 1987 under the headline "Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications"[81] their reaction from this date known as CBS reduction became the number one synthetic tool to chiral alcohols from ketones. Based on the work of Itsuno, who first achieved enantioselective reductions of prochiral ketones with chiral amino alcohols as catalyst and BH_3 as reducing agent,[82] Corey, Bakshi and Shibata developed their oxazaborolidine catalyst from abundant proline which had the advantage of a large scope, high selectivity and predictability through an understood mechanism. In the same year they improved their catalyst by adding a methyl group to the boron which added much stability and removed sensibility to air and moisture. Furthermore, its synthesis was much easier.[83] Although, several derivatives of this catalyst were reported over the years, most of them with different alkyl or aryl substituents at the boron, the Me-CBS catalyst remained the most popular one.[84]
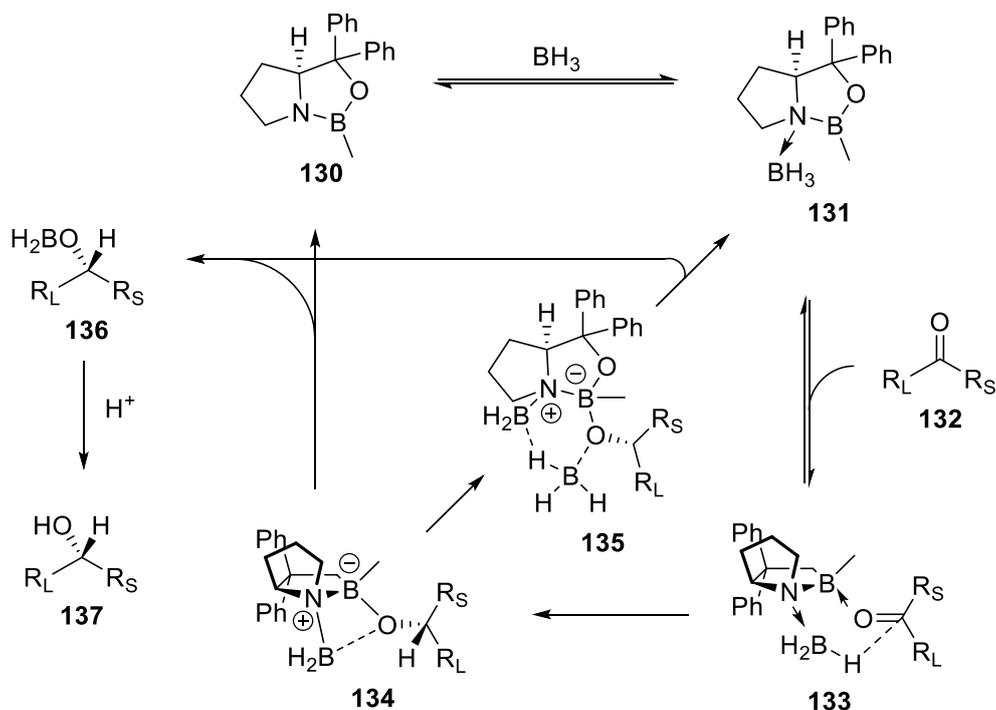
Scheme 20: Mechansism of CBS-reduction.

By looking at the mechanism the product configuration can be easily determined. The mechanism starts by the formation of a lewis-acid-base complex between the oxazaborolidine and BH_3. A second lewis-acid-base complex is forming afterwards between the substrate ketone and the boron atom resulting in a 6-membered cyclic arrangement. The large residue R_L will point away from the catalyst blocked by the steric repulsion of the proline cycle (bold) setting the final configuration. At this stage the hydride transfer occurs leading to intermediate **134**. From there two pathways could follow. The first one proposes an intermediate **135** where a second BH_3 is adding as lewis acid/base leading to the direct formation of BH_3 adduct **131** with a release of **136**. The second pathways directly generate **136** while the catalyst goes back to its initial form. The final product arises by acid catalyzed cleavage of borane **136**.[84]

Next to alkylic or arylic ketones, also α,β-unsaturated carbonyls can be selectively reduced by this method. The applications of the CBS-reduction are uncountable, nevertheless a few are shown in the following due to their similarity to the substrate of interest **118**. Reddy, Padhi and Mohapatra used the CBS reduction for their stereoselective synthesis of the core of Penostatin B.[85]
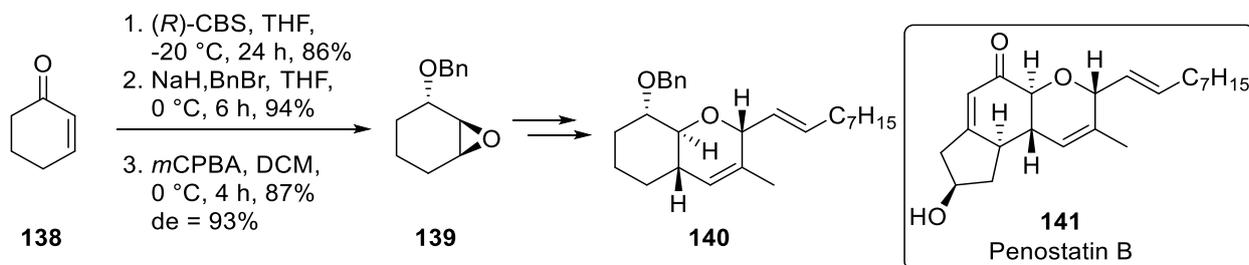
Scheme 21: CBS-reduction in the synthesis of Penostatin B.

The reduction of cyclic α,β-unsaturated carbonyl **138** was achieved with the standard Me-CBS catalyst in THF-solution at -20 °C within 24 h. A substrate even more related to **118** was selectively reduced by Knapp et al. during their synthesis of XylNAc-Isofagomine.[86] The 4-oxo-3,4-dihydropyridine **142** only differs to **118** in its protection group. After testing a variety of conditions, the best selectivity with an ee of 74% was achieved taking catecholborane as reducing agent and a mixture of DCM, CCl$_4$ and toluene as solvent at a temperature of -78 °C. Unsatisfied with the enantioselectivity, Knapp et al. introduced bromine to the carbonyls α-position using NBS to have sterically more differentiated flanking groups. Using this method, the ee could be enhanced to 89% but for the price of a prolonged reaction sequence caused by the introduction and removal of the bromine in yields of 85% and 71% respectively.
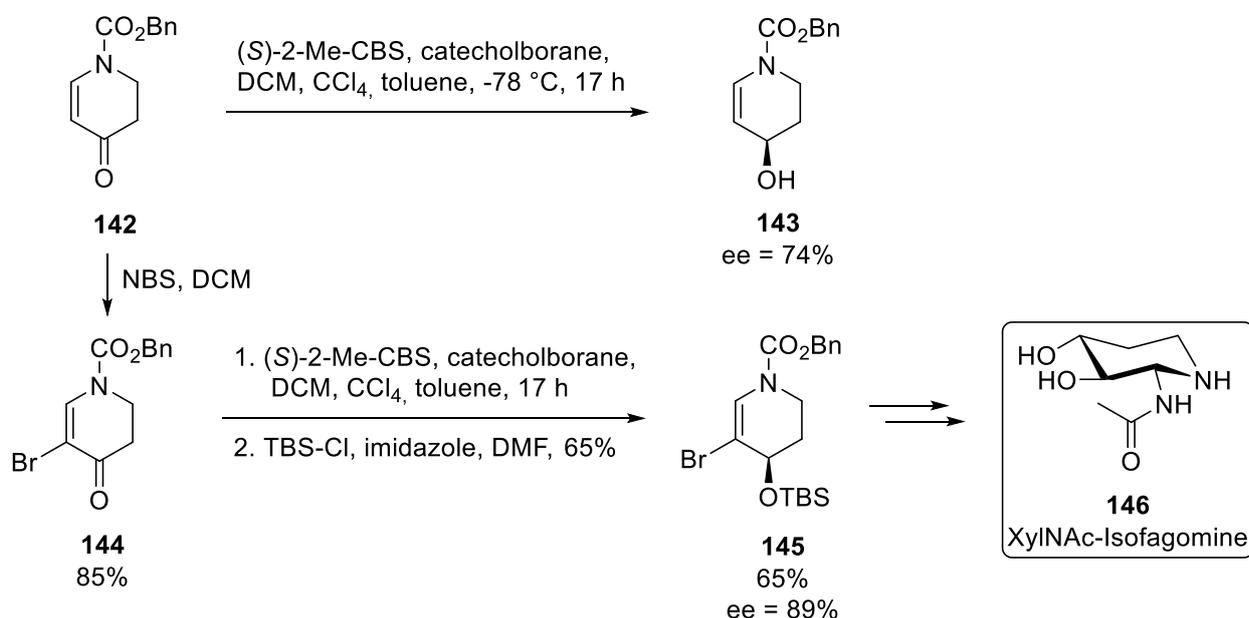
Scheme 22: CBS reduction in the synthesis of XylNAc-Isofagomine.

With this data in mind the CBS reduction of **118** should be feasible but enantioselectivity could be problematic. Therefore, a broad screening should be conducted for best results.

1.4.2.2 Enantioselective hydrogenations

Next to CBS-reductions, enantioselective hydrogenations provide tools for the stereoselective synthesis of alcohols from carbonyls. In fact, the first asymmetric catalyst ever developed was used for enantioselective hydrogenation and was made from $PdCl_2$ absorbed and reduced on silk.[87] From there on a long history of developments starts leading to homogeneous catalysts primarily based on platinum group metals bearing chiral ligands coordinating through heteroatoms like P, N, O and S or formation of cyclopentadienyl complexes. Especially for rhodium, one of the most used metals in asymmetric hydrogenations, numerous investigations were made, and computational data was collected on which the following mechanism is proposed.[88]
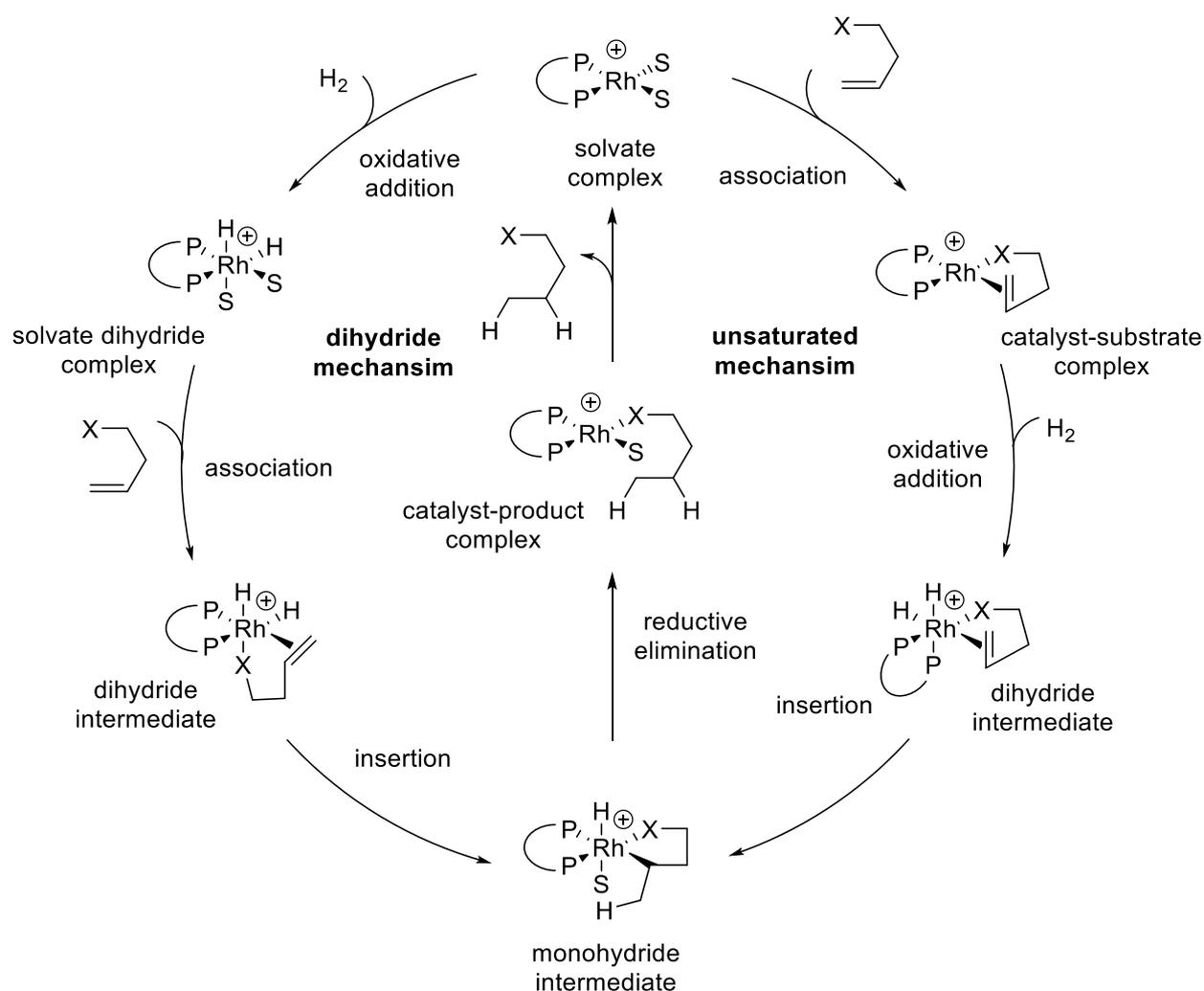
Scheme 23: Catalytic cycle of rhodium based homogeneous hydrogenation.

Starting from the solvate complex the catalytic cycle splits into two pathways which differ primarily in their order of oxidative addition and substrate association. If oxidative addition of

hydrogen occurs first a solvate dihydride complex is build giving this pathway the name "dihydride mechanism". Afterwards the solvent molecules are replaced by the substrate during the association step to give rise to the dihydride intermediate in which the substrate is bound to the metal core through the olefine moiety in a η^2-coordination as well through a heteroatom. If ketones or imines are hydrogenated the end-on η^1-coordination can compete with η^2-coordination.[89] At this stage chiral ligands also place the substrate into the right position depending on substrates' steric demands to transfer the hydrogen from the correct side in the insertion step. The monohydride intermediate now undergoes reductive elimination by formation of the catalyst-product complex. The catalytic cycle is closed by product release. The second pathway called the "unsaturated mechanism" starts with substrate association to build up the unsaturated catalyst-substrate complex from which the mechanism's name origins. This is followed by the oxidative addition of hydrogen to come to the dihydride intermediate. From now on both pathways merge. Since both pathways only differ in their order of association and oxidative addition, respectively, and the same product is formed, whether the one or the other occurs in which situation is hard to determine.

As previously broached, the selectivity of these hydrogenations is induced by chiral ligands. Depending on their sterics and the coordination number only specific areas of the catalyst's active center are approachable. A tool for fast predictions and explanations is provided by the so called "quadrant model".
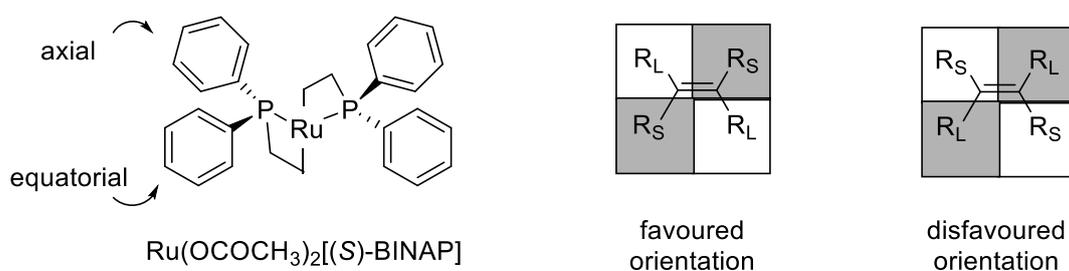
Figure 9: Quadrant model for asymmetric hydrogenations.

In figure 9 the quadrant model for Ru(OCOCH$_3$)$_2$[(*S*)-BINAP] is shown.[90] The structure is simplified for clarity. The two protuberant phenyl groups prohibit access to two quadrants of the open side of the catalyst. This is reflected in the quadrant models to the left that shows the favoured orientation for a substrate as one where large moieties are placed unhindered.

When it comes to asymmetric hydrogenation of ketones, Noyoris catalyst is probably the most famous system used in this space. Although Ru[BINAP] complexes are able to do ketone

hydrogenation as well, they usually require any kind of heteroatom as anchoring group as shown in the catalytic cycle above. This drawback has been overcome by Noyori using ethylendiamine as additional ligand in a basic solution of isopropanol.[91] Using this system he was able to do asymmetric hydrogenations on aromatic ketones without heteroatom anchors in yields up to 99% and ee up to 97%. After these initial investigations, he observed even better results by using prepared pre-catalysts where diamines are already bound to the centered ruthenium which accelerated the TOF.[92] These catalytic systems proved chemoselectivity towards ketones and imines leaving alkenes unreacted. By the use of chiral diamines, the enantioselectivity could be enhanced even further for some substrate classes. Even though many derivatives of Noyoris catalyst were developed over the past years, **149** crystalized out as one of the most dominant representatives of modern Noyori catalysts.
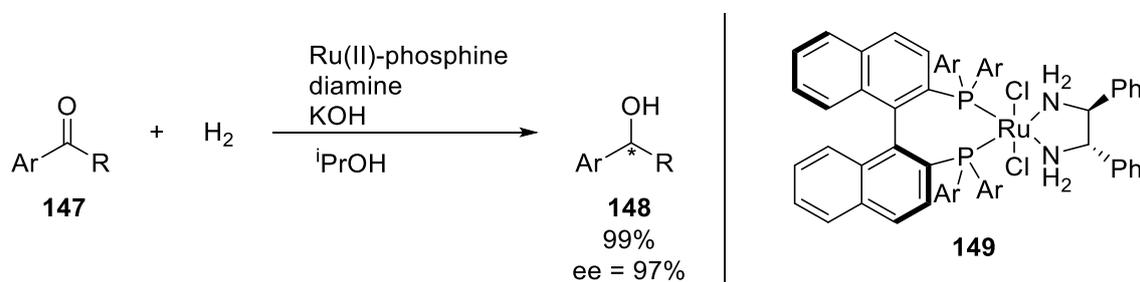
Scheme 24: left: Initial investigations on asymmetric hydrogenations of aryl-ketones by Noyori; right: representative modern catalyst.

The scope of ruthenium catalyzed hydrogenations is wide and contains aromatic, heteroaromatic, cyclopropyl, dialkyl, amino, α-alkoxy and olefinic ketones. Therefore, these systems were also tested on the substrate of interest **118** and discussed later on.

1.4.2.3 Enantioselective enzymatic reductions

Alcohol dehydrogenases (ADH) are responsible for the reversible oxidation of alcohols to aldehydes or ketones, or the reduction back to alcohols, respectively. They appear in prokaryotic as well as eukaryotic cells, in plants and mammals.[93] Having prochiral ketones as substrate they often show high enantioselectivity during the reduction due to their special folding. One of their key characteristics is the requirement of NAD(P)H/NAD(P)$^+$ as cofactor which serves as fuel for the reaction and takes up the released or donates the required hydrogen which makes it necessary in stochiometric amounts (see scheme 25).
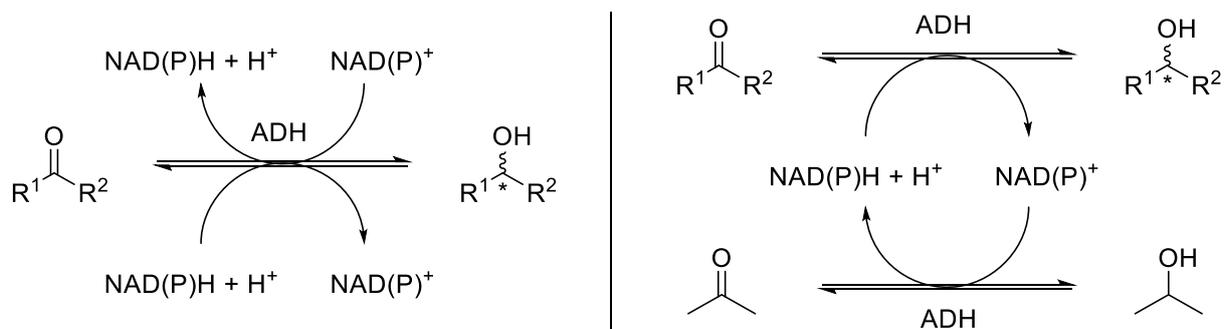
Scheme 25: left: working principle of ADH; right: cofactor recycling mechanism.

Since these cofactors are pricy, cofactor recycling systems were implemented. This is usually achieved by a second reaction that counteracts the main reaction. If ketones should be reduced to the alcohol, a cheap sacrificial alcohol will be oxidized e.g., ^{i}PrOH. This can be done by the same ADH that is responsible for the reduction of the target substrate but can also be another enzyme with respective sacrificial molecules as long as the required cofactors matches.[93] Taking advantage of this process, Kosjek et al. achieved the selective reduction of α,β-unsaturated carbocycle **150** in 97% conversion, 95% ee and 99% dr.[94] The enzymes used for this purpose are unnatural enzymes developed by Codexis (former Biocatalytics Inc.).
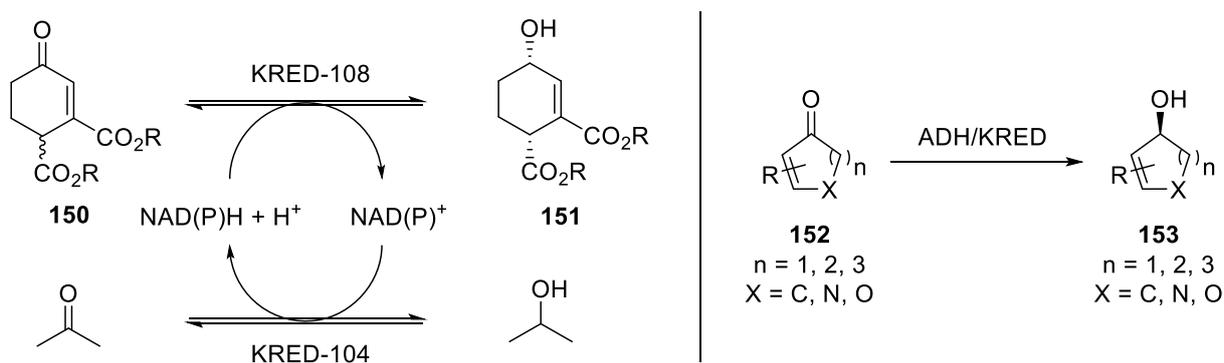
*Scheme 26: Reduction of **150** and **152** using enzyme catalysis by Moore et al.*

Using similar systems the same group around Moore converted five, six and seven membered carbo and heterocycles with and without substituents to their corresponding alcohols in enantiomeric excess up to 99%.[95] Unfortunately substrate **118** was not tested during their investigations and finding the right enzyme for a specific substrate can be like searching for a needle in a haystack. Nevertheless, these results highly encourage the use of enzyme catalysis for the synthesis of **123**.

1.4.2.4 Enzymatic acetylation and kinetic resolution

The fact that enzymes are very specified to certain substrates can be a disadvantage when looking for the right ADH for reduction purposes. However, some enzymes can distinguish even between enantiomers leading to a rapid conversion of one over the other. This effect is known as kinetic resolution. Kinetic resolutions principally can appear in all kinds of catalyzed reactions and can deal with chemo, regio or stereoselectivity. When it comes to separation of enantiomers, lipase catalyzed acetylation or hydrolysis is a wide used concept in organic chemistry.[96] E.g., in the asymmetric synthesis of Loxoprofen, Bhuniya and Nanda applied it to a racemic mixture of alcohol **154** to obtain the (*S*)-acetate **155** in 98% ee.[97] The major drawback of this approach is that the maximum yield is capped at 50% if the selectivity is perfect. The dynamic kinetic resolution provides an escape from this dilemma. Depending on the substrate it can be possible to induce racemisation while the kinetic resolution is conducted. The remaining enantiomer is racemising while the favoured enantiomer is converted to the desired product until full conversion is achieved.
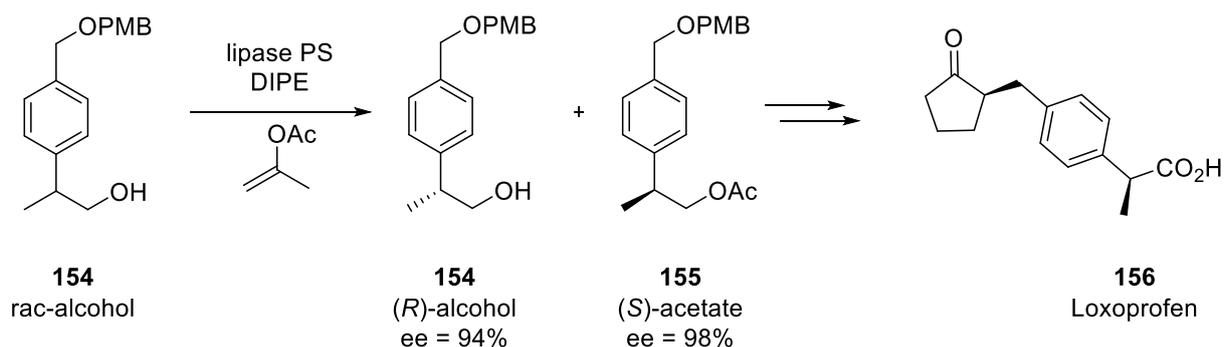
*Scheme 27: Enzymatic kinetic resolution of **154** in the synthesis of Loxoprofen.*

Particularly prone to this concept are substrates with acid or base labile stereocenters. If special catalysts are used even unactivated dialkyl alcohols can be racemised like the group around Bäckvall showed. While a special ruthenium catalyst is racemising the starting material, lipase B isolated from *candida antarctica* produced the desired acetate in high yields and excellent selectivity.[98] Selected examples are shown in scheme 28. Among more than 30 examples there are dialkyl substrates like **160**, tertiary amines as **161,** vinyl alcohols **162** and aryl alcohols **163**.
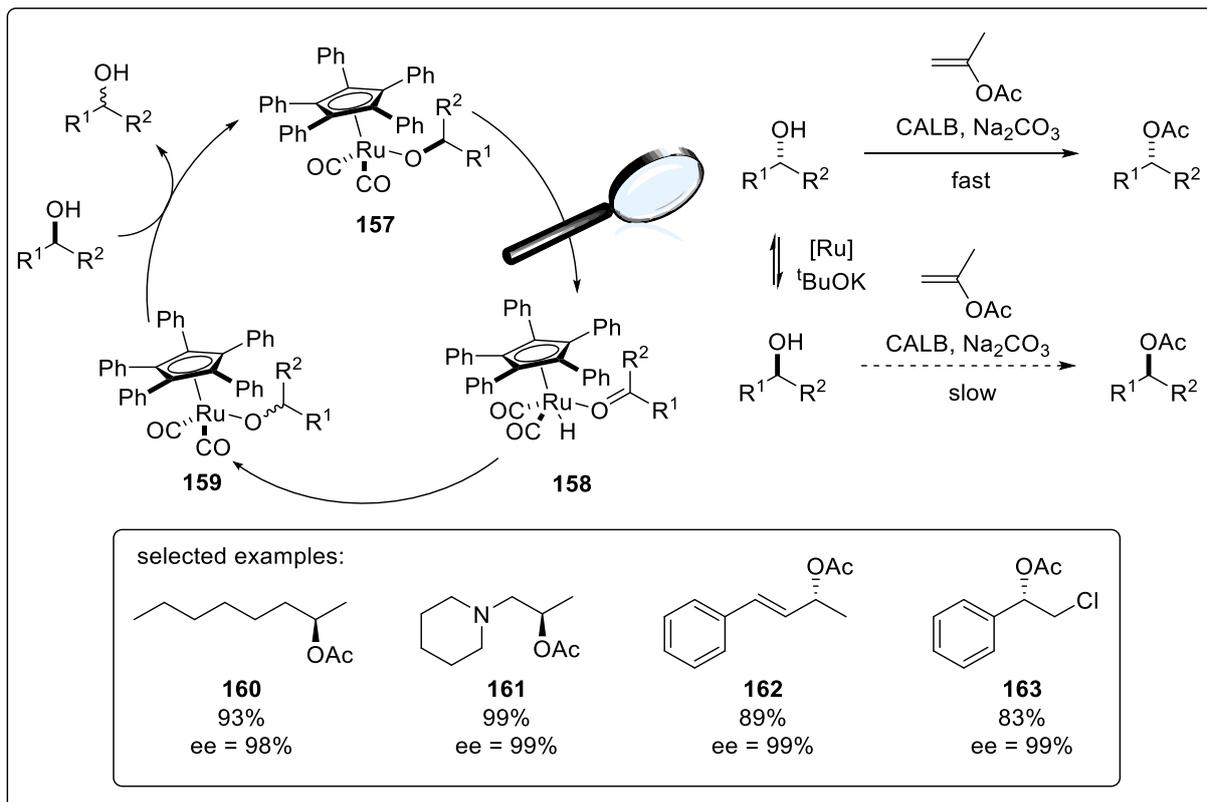
Scheme 28: Concept of chemoenzymatic DKR by Bäckvall; selected examples from substrate scope.

If a selective lipase for **118** can be found, Bäckvalls chemoenzymatic dynamic kinetic resolution could provide a good method to increase yields since amines and vinyl alcohols are tolerated.

1.4.3 Enantioselective synthesis of **123**

Starting with the CBS-reduction the above concepts were applied on **118** and **123** respectively to set the stereocenter at the C4 position. A broad screening was conducted to fit the reaction to the substrate and aim for the best selectivity. At first the three common reducing agents were tested (see table 4).

Table 4: CBS-screening: reducing agents.
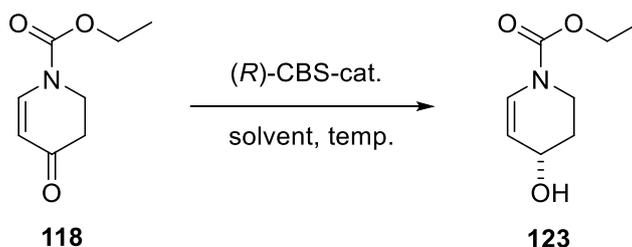
entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3 \cdot THF$	1.0	THF	-78, 0, 25, 50, 100	10 mol%	No reaction
2	$BH_3 \cdot Me_2S$	1.0	THF	-78	10 mol%	Clean reaction (TLC) Conversion: 70% ee = 13%
3	Catecholborane	1.0	THF	-78	10 mol%	Side products ee = 0%

The screening was started with the following conditions. 1.0 equivalents of reducing agents were added dropwise within 1 min to a solution of **118** and 10 mol% catalyst in THF at a temperature of -78 °C. The best result was obtained with $BH_3 \cdot Me_2S$ complex as hydrogen source (entry 2). The TLC as well as the NMR analysis showed a clean reaction towards the desired product, however the conversion was not complete, and the selectivity was poor with an ee of 13%. For time management reasons the product was not isolated during this screening stage and the product seemed to be instable showing decomposition peaks depending on the time until NMR measurements can be taken, what makes NMR yield using internal standard impossible. The reactions were therefore ranked on the conversion and appearing side-products next to decomposition peaks. Catecholborane as common reducing agent for CBS reductions gave next to the desired product multiple other products (entry 3). HPLC analysis showed that the reduction with catecholborane proceeds not selective. Using the $BH_3 \cdot THF$ complex no reaction took place (entry 1). Therefore, the temperature was elevated stepwise from -78 °C to 0 °C, 25 °C, 50 °C and lastly to 100 °C without changes to the educt. With $BH_3 \cdot Me_2S$ complex identified as best reducing agent, the screening was continued by exploration of the reaction

temperature. As the reaction proceeds very fast and is finished within 5 min but the conversion was not complete, the amount of reducing agent was raised to 2.2 equivalents, which led to a full conversion of **118** without additional by-products. Elevation of the reaction temperature from -78 °C to -25 °C (entry 2) only improved the enantioselectivity minorly but indicated the direction towards higher temperatures. At a temperature of 0 °C the selectivity already showed and ee of 23% (entry 3).

Table 5: CBS-screening: temperature.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3 \cdot Me_2S$	1.0	THF	-78	10 mol%	Conversion: 70% ee = 13%
2	$BH_3 \cdot Me_2S$	2.2	THF	-25	10 mol%	Full conversion ee = 15%
3	$BH_3 \cdot Me_2S$	2.2	THF	0	10 mol%	Full conversion ee = 23%
4	$BH_3 \cdot Me_2S$	2.2	THF	25	10 mol%	Side products ee = 23%

An even higher temperature of 25 °C did not better the selectivity but side products appeared instead. For this reason, 0 °C was chosen as optimal reaction temperature to go with. In the next stage, for CBS-reductions commonly used solvents were tested (table 6).

Table 6: CBS-screening: solvent.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3 \cdot Me_2S$	2.2	THF	0	10 mol%	ee = 23%
2	$BH_3 \cdot Me_2S$	2.2	toluene	0	10 mol%	ee = 41%
3	$BH_3 \cdot Me_2S$	2.2	DCM	0	10 mol%	decomposition

Changing THF with toluene led to a strong enhancement of selectivity with and ee of 41%. In contrast the reduction in DCM resulted in a messy reaction where neither educt nor the desired product could be observed through NMR analysis. With toluene as solvent of choice the screening was pursued with a slow addition experiment (table 7). Therefore, the reducing agent was diluted in 1 mL toluene and added dropwise within 1 hour with the help of a syringe pump. The slow addition should give the catalyst enough time to complete the cycle before the next reducing agent is added and through this selectivity should rise. Unfortunately, the effect was rather small and almost neglectable as the ee only improved from 41% to 43%.

*Table 7: CBS-screening. BH₃•Me₂S diluted in 1mL toluene, 1 h dropwise addition.*

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	BH₃•Me₂S	2.2	toluene	0	10 mol%	ee = 43%

Since the slow addition experiment did not give the expected result, the screening was continued with fast addition of reducing agent for a faster and simpler reaction setup. The next factor to be examined was the catalyst loading (table 8). Great improvements of enantioselectivity were observed by increasing the loading to 30 mol%. The ee could be raised through this to 57% (entry 2). Bringing up the catalyst loading even further to 100% only minorly enhanced the selectivity to 61% (entry 3). Even though 61% ee would be the best result so far, such a high consumption of catalyst cannot be justified economically making a catalyst loading of 30 mol% the condition of choice.

Table 8: CBS-screening: cat. loading.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	BH₃•Me₂S	2.2	toluene	0	10 mol%	ee = 41%
2	BH₃•Me₂S	2.2	toluene	0	30 mol%	ee = 57% isolated yield = 81%
3	BH₃•Me₂S	2.2	toluene	0	100 mol%	ee = 61%

Finally (*R*)-*o*-Tolyl-CBS catalyst was tested under the optimal conditions as well, which resulted in a poor selectivity of 17% (table 9, entry 2). Even though the conditions were optimized on the Me-CBS catalyst and a second optimization on the o-tolyl-CBS would likely improve its performance, this result is too far from 57% to justify the effort.
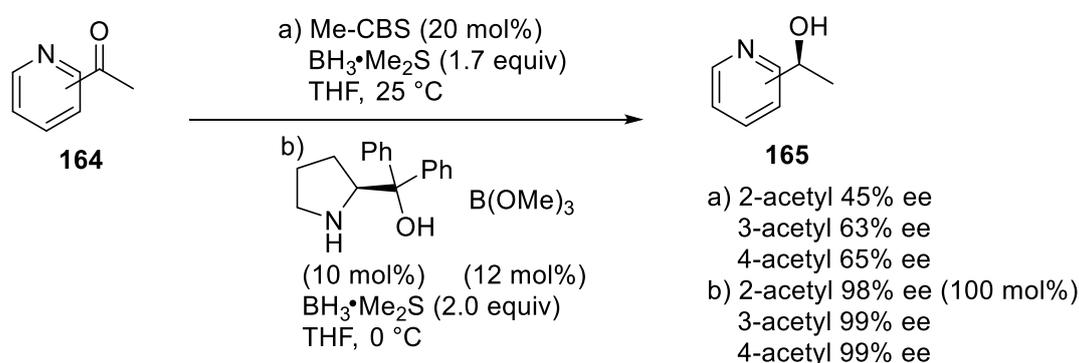
Scheme 29: CBS-reductions on substituted pyridines by Masui and Shiori.

Inspired by the work of Masui and Shiori[99] and independently Kawanami and Yanagita[100] who improved enantioselectivity in CBS reductions of nitrogen containing substrates and α,β-

enones, respectively, by *in-situ* preparation of the CBS catalyst, this method was tested on substrate **118**.
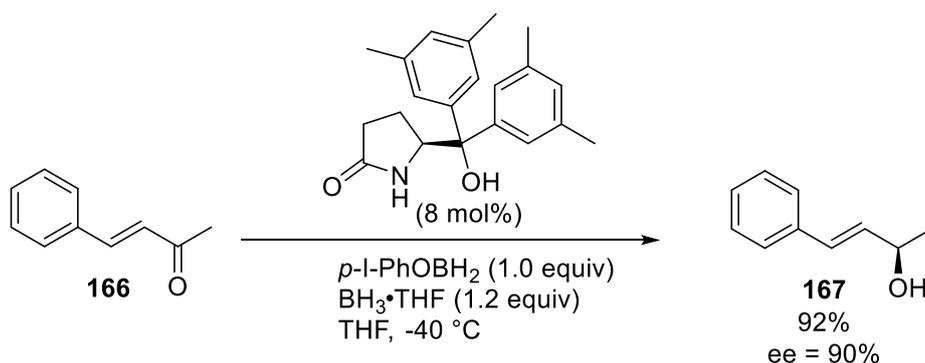
*Scheme 30: CBS reducion on α,β-enone **166** developed by Kawanami and Yanagita.*

As it can be taken from table 9 entry 3 and 4, the in-situ preparation of the CBS catalyst after the protocol of Masui and Shiori lead to a strong decrease of enantioselectivity. Performing the reaction in toluene lead to a low selectivity of ee = 11%. Changing the solvent to THF gave racemic results.

Table 9: CBS-screening: catalyst.

| entry	reducing agent	equiv	solvent	temp. [°C]	catalyst	cat. loading	result
1	$BH_3 \cdot Me_2S$	2.2	toluene	0	(R)-Me-CBS	30 mol%	ee = 57%
2	$BH_3 \cdot Me_2S$	2.2	toluene	0	(R)-o-Tolyl-CBS	30 mol%	ee = 17%
3	$BH_3 \cdot Me_2S$	2.2	toluene	0	(S)-Diphenyl(pyrrolidin-2-yl)methanol, B(OMe)₃	30 mol%	ee = 11%
4	$BH_3 \cdot Me_2S$	2.2	THF	0	(S)-Diphenyl(pyrrolidin-2-yl)methanol, B(OMe)₃	30 mol%	ee = 2%

Although, brought optimization efforts for CBS-reduction of **118** to **123** lead to an acceptable selectivity of ee = 57% with an isolated yield of 81%, the selectivity was tried to be enhanced further by using the method of asymmetric hydrogenation. As mentioned previously Ru(BINAP) complexes and Noyori's catalytic system are among the most used and promising catalyst for this type of reaction and were therefore examined initially. Using (R)-Ru(OAc)₂BINAP as catalyst with a loading of 1 mol% no reduction occurred and the starting material could be fully isolated after a reaction time of 16 h whether a H_2-pressure of 1 atm or 75 bar was applied (scheme 31, a and b). Subjection of **118** to Noyori`s conditions (scheme 31, c) lead to the same result after 16 h reaction time.
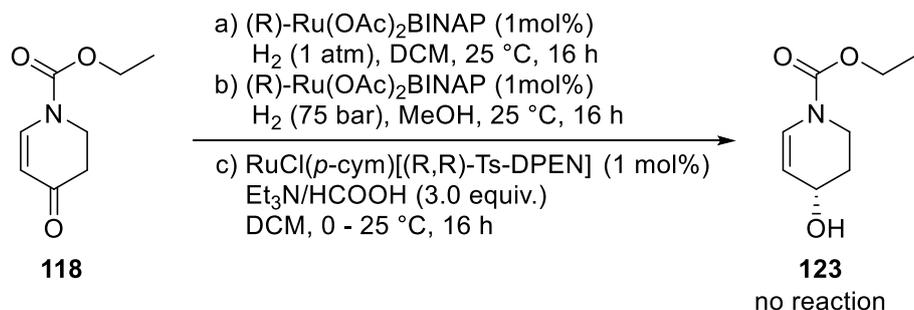
Scheme 31: Ru(BINAP) and Noyoris' catalyst in asymmetric hydrogenations.

Unfortunately, these most common homogeneous hydrogenation techniques were not applicable to compound **118**. Nevertheless, there are numerous protocols available in literature, presenting asymmetric hydrogenation catalysts. Compared to the substrates investigated in the presented scientific work, a hydrogenation protocol developed by Kolcsár, Fülöp and Szöllösi, where Ru incorporated in chitosan as natural chiral ligand is used as heterogeneous asymmetric catalyst turned out to be a promising candidate.[101] As starting point for the following study a catalyst loading of 5% ruthenium in a mixture of H_2O and ^iPrOH, cooled to 0 °C, inspired by the optimal conditions in Kolscár's work, was chosen. These conditions lead to a low conversion of <5% after a reaction time of 24 h. HPLC analysis determined an enantioselectivity of 14% ee.

*Table 10: Ru-chitosan catalysed enantioselective transfer hydrogenation.*
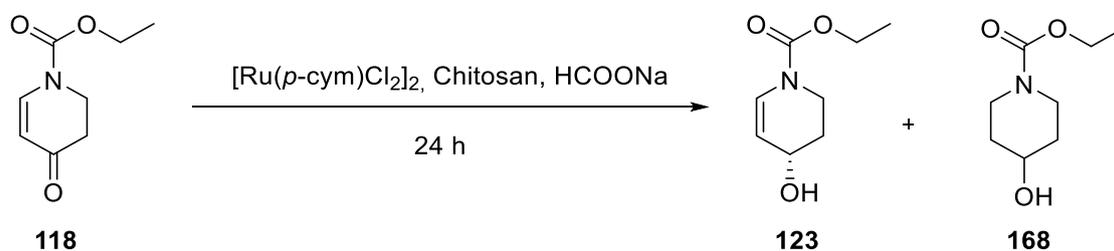
entry	solvent	temp. [°C]	cat. loading	conversion	123:168	ee
1	H_2O: ^iPrOH (4:1)	0	5%	<5%	n.d.	ee = 14%
2	H_2O: ^iPrOH (4:1)	25	5%	30%	1:1.6	ee = 64%
3	H_2O: ^iPrOH (4:1)	50	5%	100%	1:3.5	ee = 65%
4	H_2O: ^iPrOH (4:1)	25	10%	75%	1:1.1	ee = 62%
5	H_2O: MeOH (4:1)	25	5%	25%	1:1.5	ee = 56%
6	H_2O: EtOH (4:1)	25	5%	25%	1:1.1	ee = 55%
7	H_2O: DMF (4:1)	25	5%	25%	1:1.9	ee = 61%

In order to increase the low conversion, the temperature was elevated to 25 °C (entry 2) and subsequently to 50 °C (entry 3) which resulted in 30% and 100% conversion, respectively.

Delighted, a major increase in enantioselectivity to 64% was observed at a temperature of 25 °C, but without additional rise at 50 °C. In the course of higher conversion, the double hydrogenated by-product **168** was observed in high amounts. At 25 °C the ratio of **123** to **168** was already at 1:1.6 which worsened to 1:3.5 if the temperature was elevated to 50 °C. In an attempt to circumvent low conversions and the formation of the undesired product **168** the catalyst loading was enhanced to 10% keeping a temperature of 25 °C (entry 4). Although, the enantioselectivity was comparable to the one observed in entry 2 and 3 and the conversion indeed was already at 75% after 24 h, the product ratio was still at 1:1.1. Further enhancement of catalyst loading hand in hand with lower reaction times was seen economically unacceptable. Finally, ^{i}PrOH was substituted by MeOH, EtOH and DMF as cosolvents leading to similar results in terms of conversion, product ratio and enantioselectivity (entry 5-7). Since all tested asymmetric hydrogenations either produced large amounts of over hydrogenated products or did not react at all, investigations in this area were stopped and the focus was shifted to enzymatic reductions.

Encouraged by the work of Moore et al.[95] (see chapter 1.4.2.4 for more information) several alcohol dehydrogenases were tested in their capability of reducing compound **118**. NAD$^+$ was used as cofactor in catalytic amounts of 2 mol%. As cofactor recycling system lactat dehydrogenase in combination with L-lactat was employed. Both dehydrogenases were used in an amount of 1.0 mg / 1.0 mol of **118**. As solvent an aqueous K_3PO_4 buffer system provided a pH-neutral medium which was checked throughout the reaction by a pH-meter.

*Table 11: Enzymatic reductions of **118**.*
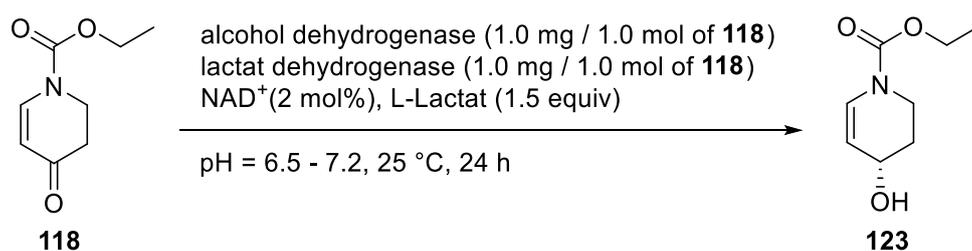
entry	ADH	Yield
1	Saccharomyces cerevisiae	no reaction
2	Equine, recombinant, expressed in E. coli	no reaction
3	Agarose from baker's yeast (S. cerevisiae)	no reaction
4	Fresh baker's yeast (no additional additives)	no reaction

Three ADHs were subjected to the conditions described above (entry 1-3). Unfortunately, none of them showed any activity in converting compound **118**. In a last attempt fresh baker's yeast was added to an aqueous solution of **118** and stirred for 24 h (entry 4) following literature examples[102] who observed highly selective reduction of cyclic ketones by this method. Again, no reaction was observed. Further investigations in enzymatic reductions were stopped as no more enzymes were available. Although, all tested ADHs were unactive on substrate **118**, other enzymes could still work perfectly for this purpose. An effective screening of ADHs and KREDs could be provided by special tool kits that are commercially available.

After encountering issues with reactivity, chemoselectivity and enantioselectivity under a variety of reaction types and conditions with compound **118**, the initial sequence to compound **125** was inverted. Therefore, the enantioselective reduction of the ketone to the alcohol should occur prior to the elimination of an α-positioned bromine to break the symmetry of the molecule and allow catalysts an easier differentiation. The new synthesis was started by α-bromination of piperidinone **115** to form **169** in a very good yield of 96%.
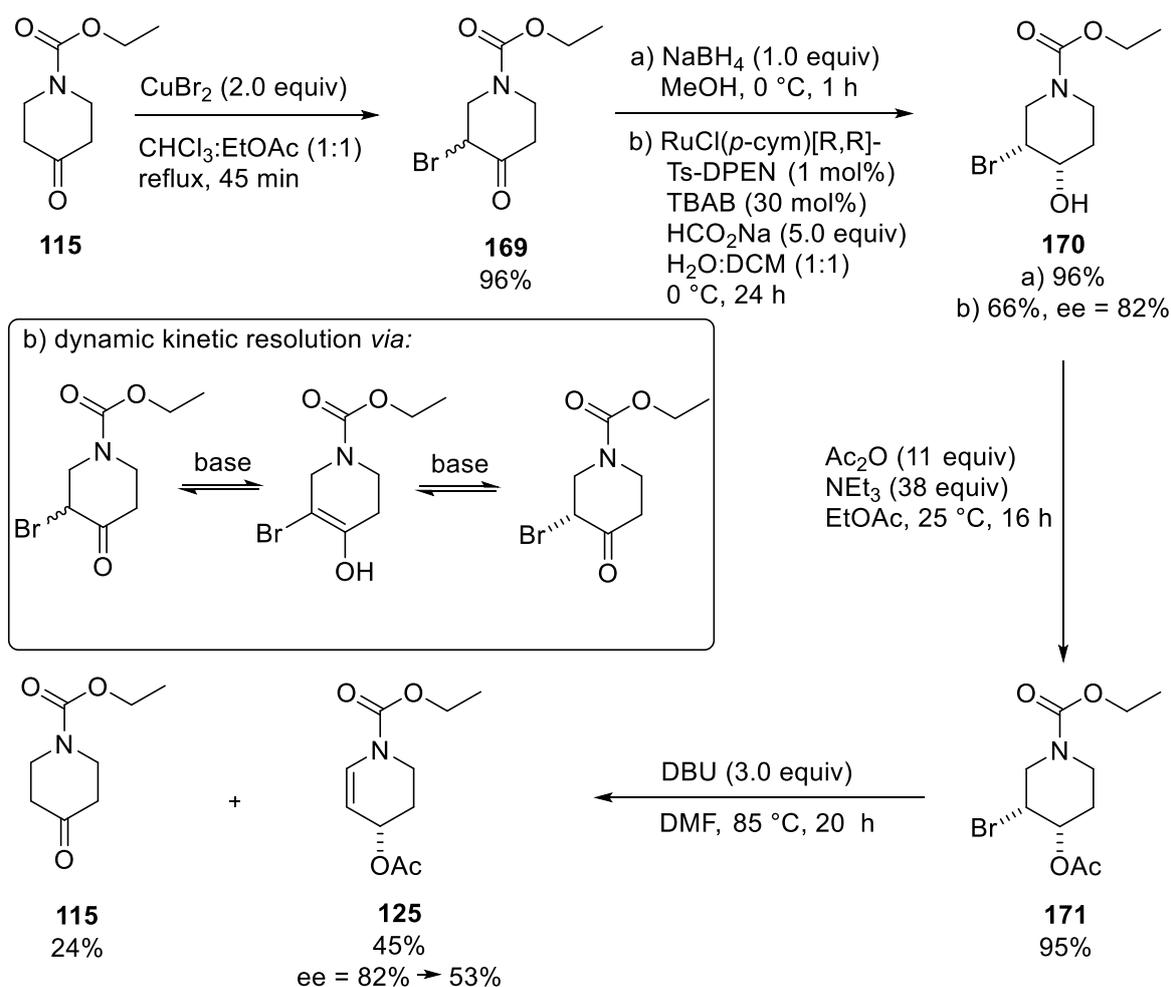
Scheme 32: Inverted synthesis of enantioenriched 125.

Because **169** bears already one stereocenter the following reduction needs to differentiate between the two enantiomers of the starting material featuring a kinetic resolution. The main problem kinetic resolutions have in common is their capped yield at 50% which can be circumvented by racemisation of the remaining enantiomer (for more details see chapter 1.4.2.4). Drawing benefit from the strong acidity of an α-bromine-ketone and the basic conditions of a Noyori-type asymmetric hydrogenation, Ros et al. developed a procedure for a dynamic kinetic resolution giving them halohydrins in high yields, diastereoselectivity and enantioselectivity.[103] Once racemic halohydrin **170** was prepared in excellent yield and diastereoselectivity by reduction with NaBH$_4$, **170** was prepared enantioselectively. The dynamic kinetic resolution was conducted through addition of 1 mol% of RuCl(*p*-cym)[*R,R*]-Ts-DPEN, 30 mol% TBAB and HCO$_2$Na as reducing agent to **170** in a H$_2$O:DCM biphasic system (table 12). Five hours reaction time at a temperature of 25 °C resulted in a yield and selectivity of 66% each (entry 1).

*Table 12: Optimisation study on the DKR to halohydrin **170**.*
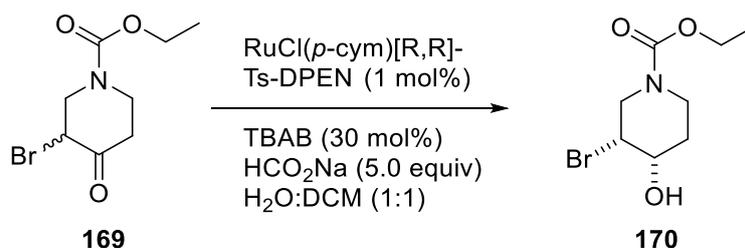
entry	reaction time	temp.	yield	ee
1	5 h	25 °C	66%	66%
2	1 d	25 °C	66%	76%
3	3 d	25 °C	66%	76%
4	1 d	0 °C	66%	82%

Prolonging the reaction time to 24 h enhanced the selectivity to 76% ee but without effects to the yield (entry 2). Even longer reaction times did not affect yields or selectivity (entry 3). Keeping the reaction time at 24 h with a lower temperature brought the selectivity up to 82% ee. As water is part of the reaction medium a lower temperature could not be applied. Further optimization was postponed until **125** was successfully synthesized from the enantioenriched **170** without bigger loses in yields or enantiomeric excess. The next step towards the synthesis of **125** was the acetylation of the alcohol which worked well in 95% yield employing the regular method. The elimination of HBr was conducted under a temperature of 85 °C in DMF with an

addition of DBU as base. Indeed, the desired product **125** was formed in 45% yield, however, 24% of piperidinone **115** was observed as by-product arising from a poor regioselectivity of H$^+$ abstraction during the elimination step. On top of that comes a loss in enantiomeric excess from 82% to 53%. This major loss in chiral information along with the low yield makes the inverted sequence inferior compared to the pathways investigated before.

As previously discussed in chapter 1.4.2.4, lipase catalysed acetylations are commonly used in kinetic resolutions of chiral alcohols. Taking the conditions used by the group of Bäckvall[98], the alcohol **123** was dissolved in toluene together with prop-1-en-2-yl acetate, Na_2CO_3 and 6 mg lipase / 1 mmol **123** and stirred for 24 h at 25 °C. Three available lipases were tested (table 13).
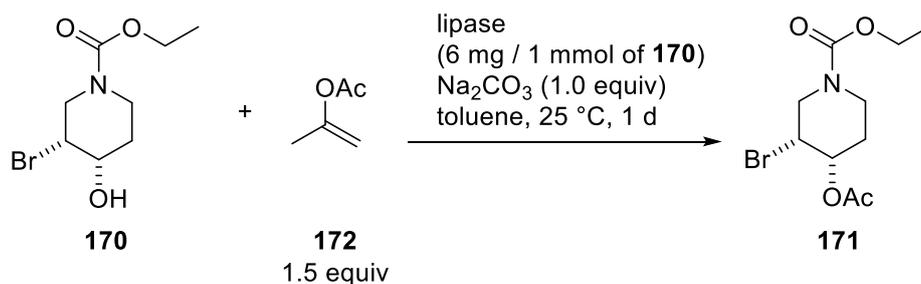
Table 13: Lipase catalysed acetylation of 123.
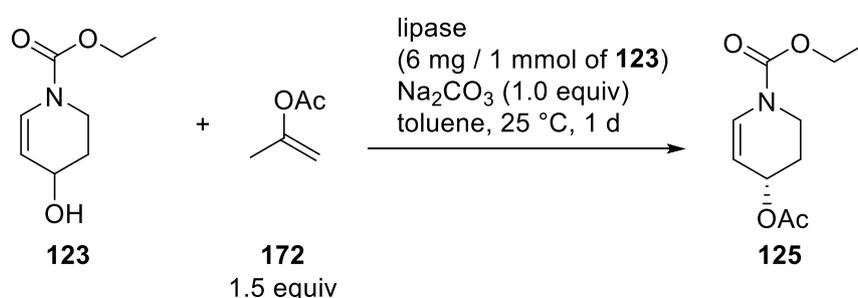
entry	lipase	conversion	ee
1	*Candida antarctica*	67%	0%
2	Porcine pancreas	no reaction	-
3	*Candida rugosa*	no reaction	-

Candida antarctica gave a conversion of 67% to the desired product but with no differentiation of the two starting material enantiomers (entry 1). Lipase from porcine pancreas and *Candida rugosa* were not active on **123** at all (entry 2 and 3).

Next to compound **123**, halohydrin **170** was tested as starting material for lipase catalysed acetalytions as well. Under the same conditions *Candida antarctica*, lipase from porcine pancreas and *Candida rugosa* were applied to the reaction. Unfortunately, none of them showed any activity towards substrate **170**. Since all of the lipase catalysed reaction gave either no reaction or were unselective towards the starting material, Bäckvall's dynamic kinetic resolution with ruthenium catalysed racemisation could not be investigated.

Table 14: Lipase catalysed acetylation of halohydrin 170.

| entry	lipase	conversion	ee
1	*Candida antarctica*	no reaction	-
2	Porcine pancreas	no reaction	-
3	*Candida rugosa*	no reaction	-

Having explored asymmetric hydrogenations with various catalysts, enzymatic reductions employing alcohol dehydrogenases, kinetic as well es dynamic kinetic resolutions with lipase catalysed acetylations and inversions of the starting material synthesis, the CBS reduction still provided the best enantioselectivity with an ee of 57% under the optimum conditions and an isolated yield of 81%.

1.5 Endocyclic ring enlargement of cyclopropanated piperidine 126 and 128

The investigations in the synthesis of donor-acceptor-cyclopropanes for the endocyclic ring enlargement led to 126 and 128 as suitable candidates. As the synthesis of 126 required less steps the focus was turned on this starting material first. Following the footsteps of Hoberg, who was able to perform Lewis acid catalysed endocyclic ring openings on cyclopropanated pyrane-derivatives and subsequent trapping with a variety of nucleophiles,[52,104] his conditions were applied on substrate 126. In analogy to Hobergs reports, 20 mol% of TMSOTf was used as Lewis acid with 5 equiv of 176 as nucleophile mixed at a temperature of -20 °C and slowly warmed to 0 °C. No reaction was observed under these conditions so the amount of TMSOTf was enhanced to 40 mol% and the temperature was gradually elevated until the solvent was refluxing, and TLC analysis showed conversion of starting material. Instead of the desired compound 177 a complex mixture of products was observed which allowed no further analysis. In consequence the nucleophile was changed to Et$_3$SiH, and the reaction temperature was lowered to 0 °C again. To facilitate the reaction the amount of Lewis acid was additionally increased to 2.0 equivalents. After 2 h the complete conversion of starting material was judged by TLC and the reaction was terminated. Instead of the desired azepane 129, minor amounts of

the exocyclic ring opening product **178** was observed which is in line with previous observations in our group on similar compounds treated with Et₃SiH and Lewis acids.[55]

Previous work by Hoberg:
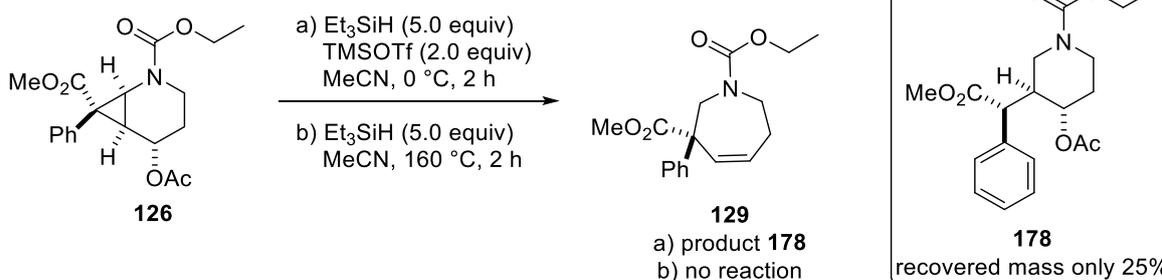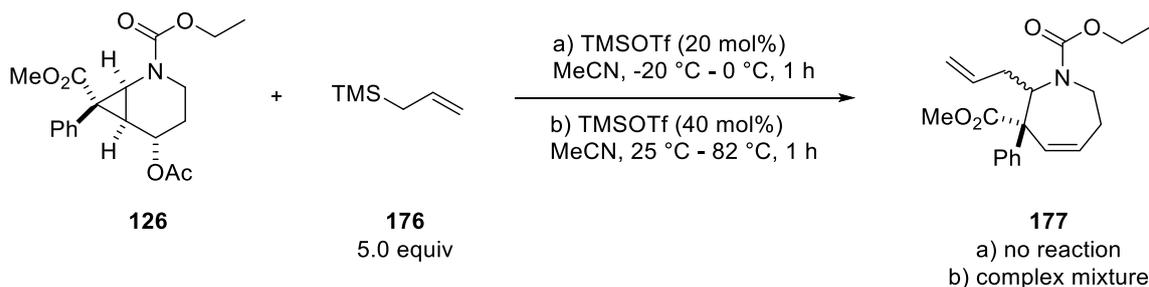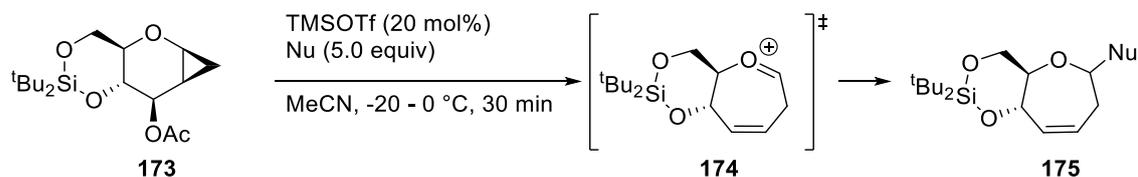
Scheme 33: Lewis acid catalysed ring enlargement to the formation of azepanes.

Counteracting the exocyclic product **178**, the reaction was conducted without Lewis acid and activated by microwave assisted heating up to 160 °C. Unfortunately, no reaction was observed demonstrating the OAc group as too unreactive. Accordingly, the attention was shifted to **128** bearing the more powerful mesylate leaving group as starting material for the endocyclic ring enlargements. To prevent exocyclic ring opening the reaction was performed without addition of acid but with 3.0 equiv of Et₃SiH in MeCN, at 100 °C in a microwave heated vessel. After 1.5 h a full conversion was observed and **129** was isolated in 86% yield proofing the mesylate as optimal leaving group for the ring expansion step. The mechanism is proposed as follows: Activated by heat, the lone-pair of the nitrogen and the mesylate are acting as electronic push-pull system, bridged by the endocyclic cyclopropane bond, leading to the decoupling of the mesylate group and a formation of an iminium ion. The iminium ion is now trapped by a nucleophile to give rise to the product. Next to silanes, alcohols were used as nucleophiles. With MeOH as well as BrCH₂CH₂OH and an addition of DBU, keeping the reaction mixture

basic, **180** and **181** were synthesized in 68% and 45% yield, respectively. For both products two diastereomers were observed in a ratio of 1:1.1.
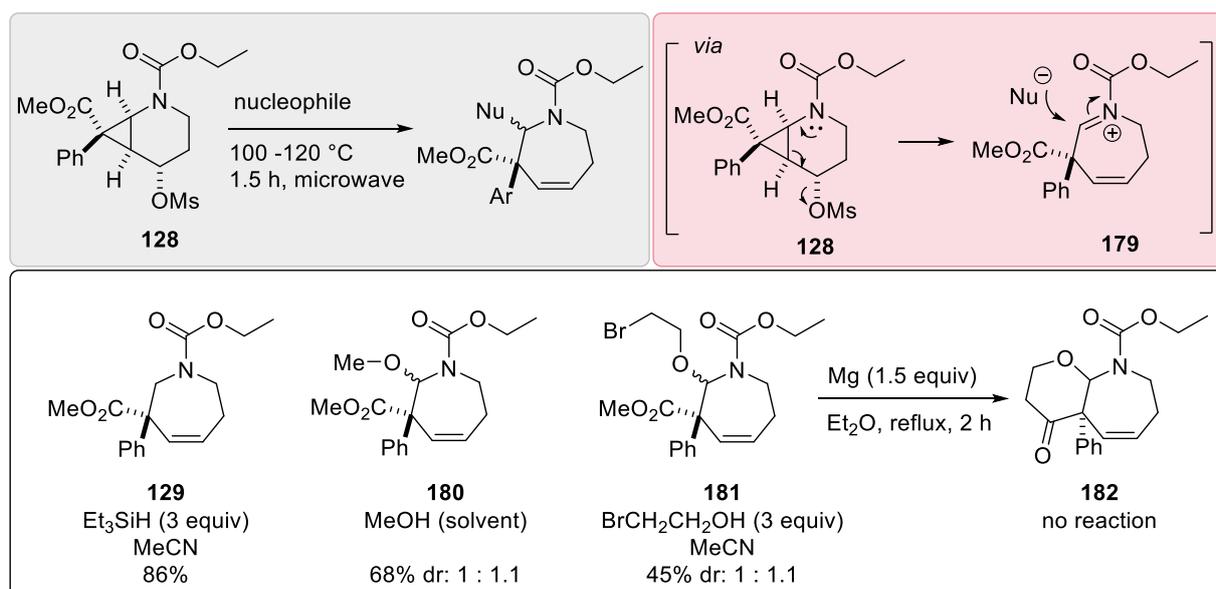

*Scheme 34: Microwave assisted ring enlargement of cyclopropane **128** in the synthesis of azepanes.*

In an attempt to reach bicyclic compound **182**, azepane **181** was subjected to Grignard conditions, but no reaction was observed. In summary the synthesis of azepanes was successful using donor-acceptor-cyclopropanes having a strong mesylate leaving group. Cyclopropanes with acetylate as leaving group did either not react or gave complex product mixtures under the tested conditions.

1.6 Asymmetric total synthesis of (*S*)-Meptazinol

A strong structural relationship between azepane **129** and Meptazinol **9** (see chapter 1.2 for more information) gave the inspiration for its total synthesis. The combination of the newly developed ring enlargement procedure and the enantioselective synthesis of the therefore employed cyclopropanes gives the possibility of a first asymmetric synthesis to this pharmaceutical compound.
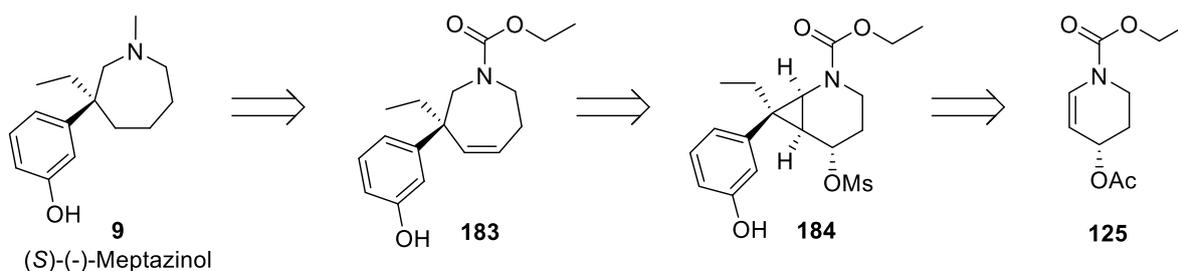
*Scheme 35: Retrosynthetic analysis of (S)-(-)-Meptazinol.*

The first retrosynthetic idea was envisioned as follows: Utilizing the already developed route to enantioenriched compound **125**, a cyclopropanation with a suitable ethyl-aryl diazo compound should provide donor-acceptor-cyclopropane **184**. From this point the elaborated endocyclic ring opening would give rise to azepane **183**, which could be easily transformed to Meptazinol by hydrogenation and carbamate reduction. Aryl-ethyl diazo compounds, however, are very electron rich and accordingly belong to the unstable types of diazo compounds which impacts in fast degradation and dangerous handling. These issues can be partially solved if the diazo is directly prepared from a stable precursor and used immediately. Following a similar procedure from the Davies group,[105] tosylhydrazone **185** was transformed to the ethyl-phenyl diazo compound by oxidation with MnO_2 and used directly in the Rh-catalyzed cyclopropanantion after filtration through celite. Despite multiple attempts having the substrate and rhodium catalyst present during diazo formation or separated, the desired product was not observed but only products arising from diazo dimerization.
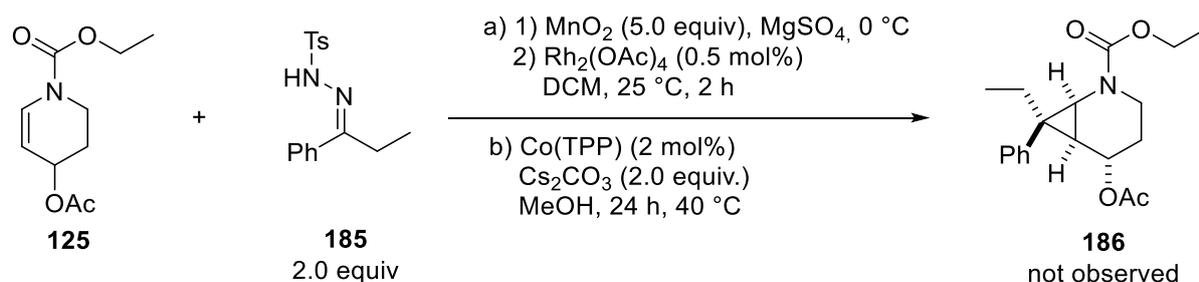
*Scheme 36: Cyclopropanations using alkyl-phenyl-diazo compounds.*

Next to transition metal catalyzed carbene transfer cyclopropanations, tosylhydrazone **185** finds utility in radical cyclopropanations catalyzed by cobalt-porphyrins as demonstrated by the group of Peter Zhang.[106] Reddy et al. applied a similar reaction to *N*-alkyl indoles and pyrrols for the synthesis of polycyclic *N*-heterocycles and cyclopropanes.[34] Based on these promising reports the reaction was carried out with Co(TPP) in a 2 mol% loading at a temperature of 40 °C and a reaction time of 24 h. Instead of cyclopropane **186**, only an acetate deprotection was observed.

Since all cyclopropanations using ethyl diazo compounds failed, α-carbonyl diazo compound **187** was used as more stable carbene precursor. Cyclopropane **188** could successfully be synthesised from **125** using Rh$_2$(OAc)$_4$ as catalyst, on which carbonyl reduction should follow. **188**, however, turned out to be unstable and was rearranging upon purification by column chromatography.
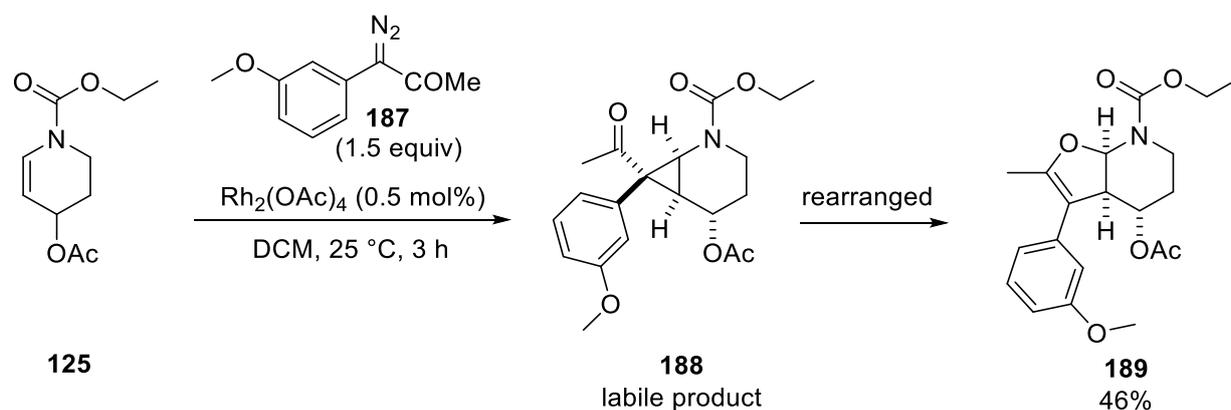
*Scheme 37: Synthesis of cyclopropane **188**.*

The rearranged product was assumed to be the bicyclic structure **189** arising from acid catalyzed exocyclic ring opening and intramolecular nucleophilic oxygen attack. However, purification and exact analysis of **189** failed. Although, the synthesis of **188** was successful, its labile nature prohibited the planned carbonyl reduction and made the use of α-keto diazo compounds impractical. Because neither alky nor α-keto diazo compounds were appropriate for the synthesis of the required donor-acceptor-cyclopropanes, aryl diazo esters were used accepting the drawback of a higher transformation effort to the required ethyl group from the ester.
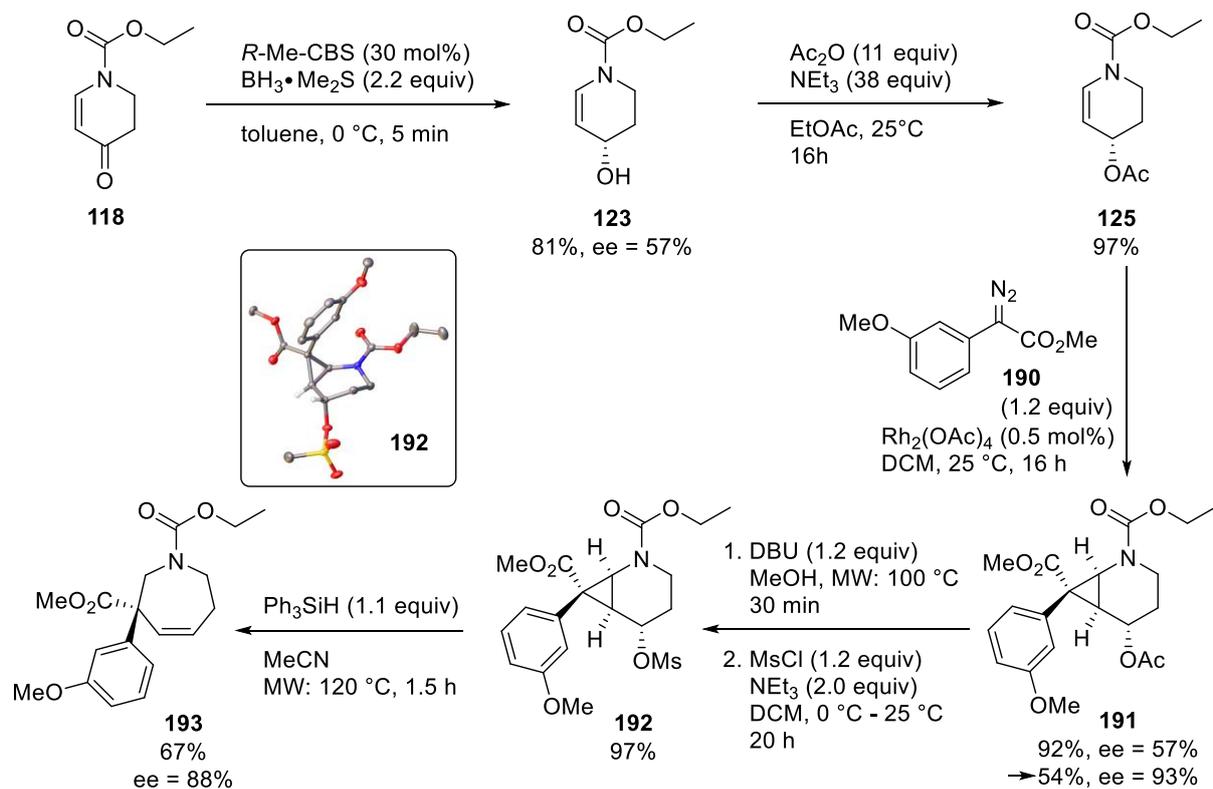
Scheme 38: Synthesis of azepane 193 as intermediate to meptazinol 9.

The synthesis of azepane **193** commenced with the priorly elaborated CBS-reduction, which turned out to be the best way to constitute alcohol **123** in an enantioenriched fashion. After **123** was obtained in 81% yield and 57% ee, the acetylation was required for a clean cyclopropanation in the next step. For the acetylation, acetic anhydride was used as reagent in a basic solution of NEt_3 and EtOAc to give the product **125** in an excellent yield of 97%. Cyclopropane **191** was afterwards synthesized by slow addition of 1.2 equiv of methyl 2-diazo-2-(3-methoxyphenyl)acetate **190** within 16 h to a solution of **125** and 0.5 mol% $Rh_2(OAc)_4$. During cyclopropanation only one diastereomer was formed. At this stage the ee could be enhanced to 93% by recrystallisation. For this purpose, small amounts of MeOH were added to the compound and sonicated. Upon sonication racemic **191** is forming as colourless solid which can be filtered off easily. The remaining solution contains the enantioenriched product. This process comes with a loss of material which drops the yield of the reaction to 54%. At this step the acetyl protection group needs to be changed to the better mesyl leaving group. Deprotection of the alcohol was realized in 30 min by microwave irradiated heating to 100 °C in MeOH and with 1.2 equiv of DBU as base. Afterwards MsCl was used as reagent for mesyl protection under basic conditions induced by addition of 2.0 equiv of NEt_3. After 20 h reaction time **192** could be isolated in 97% overall yield. The last step in the synthesis of **193** was the endocyclic ring opening. Following the priorly elaborated procedure (chapter 1.5) **192** was heated in the

microwave to 120 °C for 1.5 h together with 3.0 equiv Et₃SiH as nucleophile. Although the desired azepane **193** formed, contamination by an unknown by-product was observed which was not to separate from the desired product by any available technique. After a few test reactions, the conditions with lowest contamination were found with Ph₃SiH in a lower stoichiometry giving the desired product in 67% yield but with a small loss in enantiomeric excess (ee = 88%).

As the final challenge towards the synthesis of Meptazinol **9**, the ester group at C3 in **193** had to be transformed into an ethyl group. Considering a substitution strategy, the reduction of the ester to an alcohol, followed by activation and nucleophilic displacement with a C1-synthon would call for a substitution in neopentyl position.
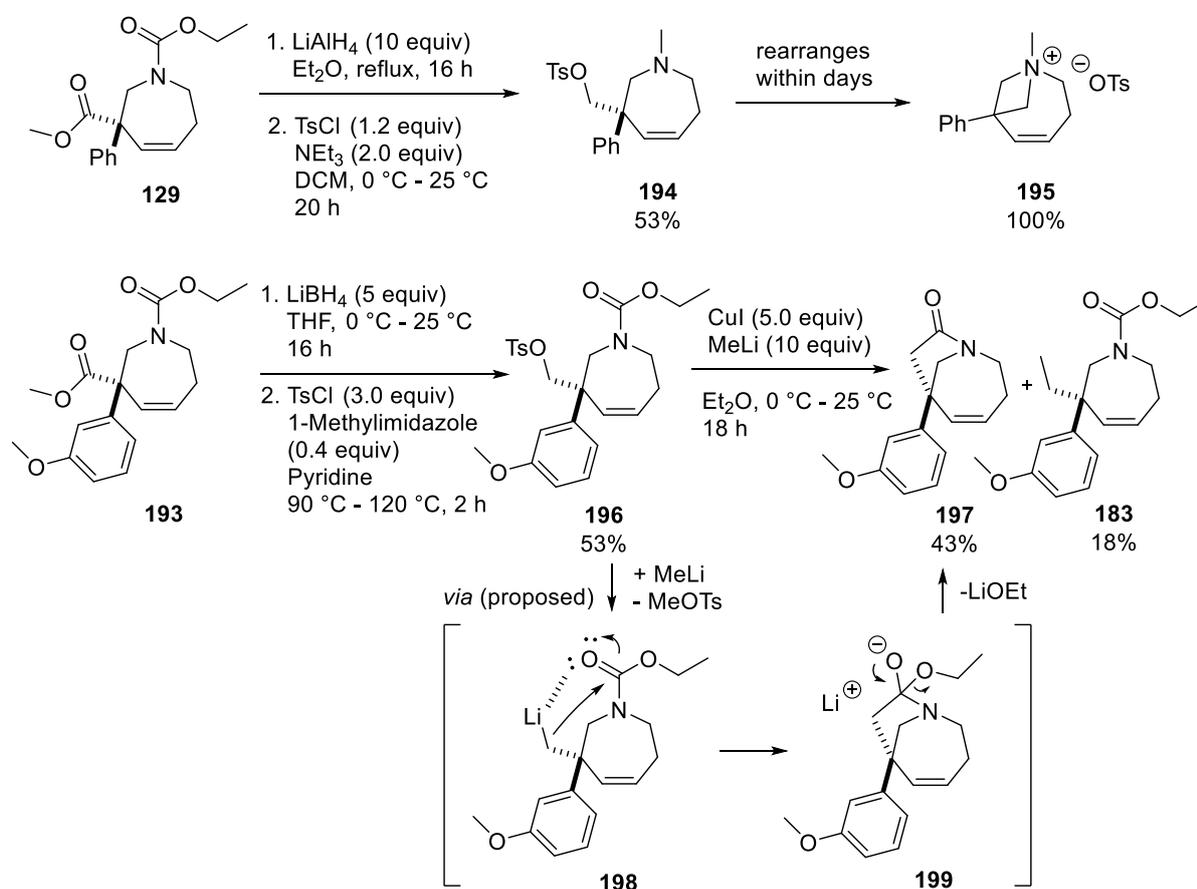

Scheme 39: Substitution approach to the formation of an C3-ethyl side chain.

Taking the lead from Johnson and Dutra who showed that such substitutions are possible for tosylated alcohols with lithium diemthyl cuprate,[107] **129** was transformed *via* reduction with LiAlH₄ followed by tosylation to **194**, which was accompanied by the transformation for the *N*-carbamate to a *N*-Me functionality required for the target compound in an overall yield of 53% (Scheme 39). However, **194** proved to be not amenable for substitution by external

nucleophiles, but rather underwent such a transformation in an intramolecular fashion, giving rise to **195** in quantitative yield. Preserving the carbamate protecting group seemed to be inevitable to impede this intramolecular substitution. By reduction of **193** with LiBH$_4$ followed by tosylation of the sterically shielded alcohol by 1-methylimidazole catalysis[108] gave rise to **196** again in 53% overall yield. The reaction with Me$_2$CuLi indeed yielded the desired azepine **183** in 18% but the bicyclic lactame **197** was the main product, which was presumably formed by lithium tosylate exchange followed by intramolecular cyclization.

Having experienced only medium yields during the tosylation process and side reactions with the alcohol leaving group afterwards, it was tested if the alcohol could be altered to a bromine-leaving group. The first procedure to **201** used PBr$_3$ as bromination agent in a solution of **200** in THF.[109] Although, a product was isolated, it was reviled as an undesired product by mass spectrometry and identification was unsuccessful.
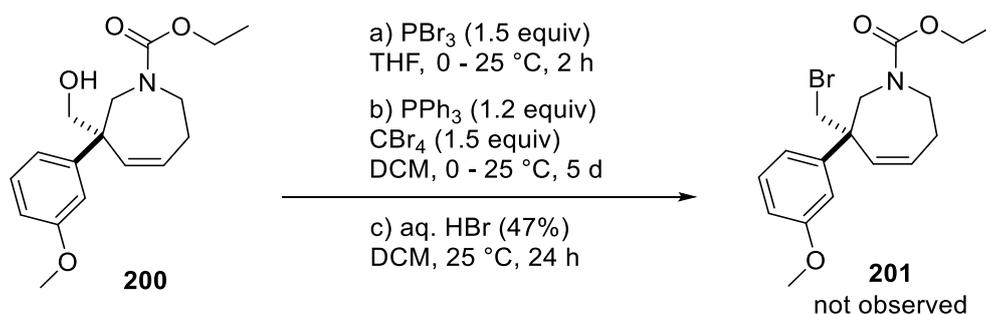
Scheme 40: Alcohol/bromine substitution reactions.

A technique used by Heerding et al. for the substitution of alcohols on nitrogen containing heterocycles uses PPh$_3$ in combination with CBr$_4$ as bromination agent.[110] Application of this protocol on **200** resulted in an unanalyzable mixture of products. Stirring **200** in DCM with addition of conc. HBr resulted in no reaction. In summary all approaches towards **201** failed and subsequent substitutions could not be conducted.

Another way to the required ethyl sidechain was provided by the transformation of the ester to a ketone by Grignard's reaction with a subsequent reduction of the ketone. This reaction however tends to form tertiary alcohols if the substrate is not used over stoichiometrically, an issue that was tried to be overcome by using a variant developed by Kikkawa and Yorifuji which employs basic conditions to stabilize the intermediate ketonic enolate (scheme 41).[111]
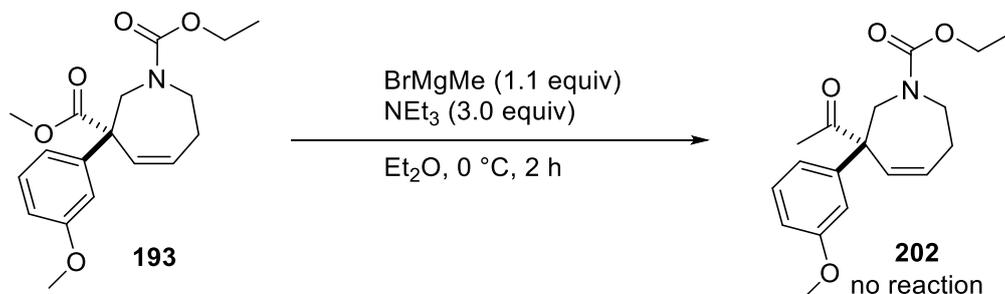
Scheme 41: Synthesis of 202 by Gringard's reaction.

Unfortunately, no reaction was observed most likely to the sterically hindered neopentyl position of the ester group.

Considerably more effective turned out the reduction of **193** to the alcohol **200**, followed by Swern oxidation to aldehyde **203** which was isolated in 88% yield after 12 h reaction time at -65 °C (scheme 42). Subsequent Wittig olefination gave rise to **204** in 80% yield, for which hydrogenation of both alkene moieties was possible in 90% yield by adjusting the hydrogen pressure to 60 bar. Transformation of the *N*-carbamate moiety in **205** to a *N*-methyl group worked extraordinary well with LiAlH$_4$, which allowed the completion of the synthesis to (*S*)-meptazinol **9** by deprotection of the methoxy group upon refluxing **206** in aqueous HBr, as it was already reported in the initial synthesis by Bradley et al.[19] The stereochemical integrity in the course of the transformation starting from **123** to meptazinol **9** was monitored by HPLC analysis as well as by optical rotation comparison of the final product **9** (α_D^{20}= -13.1° (ee = 88%)) lit:[14] (α_D^{20}= -15.1° (ee > 99%)). By deprotection of the methoxy group with BBr$_3$ giving **207** in 94% yield, prior to the transformation of the *N*-carbamate moiety in **205** a fast entry point towards the syntheses of *N*-coupled compounds like **6** and **13** was achieved which were so fare accessible by a transformation of **9** to **207** with a following deprotection to form a secondary amine.[9,14]
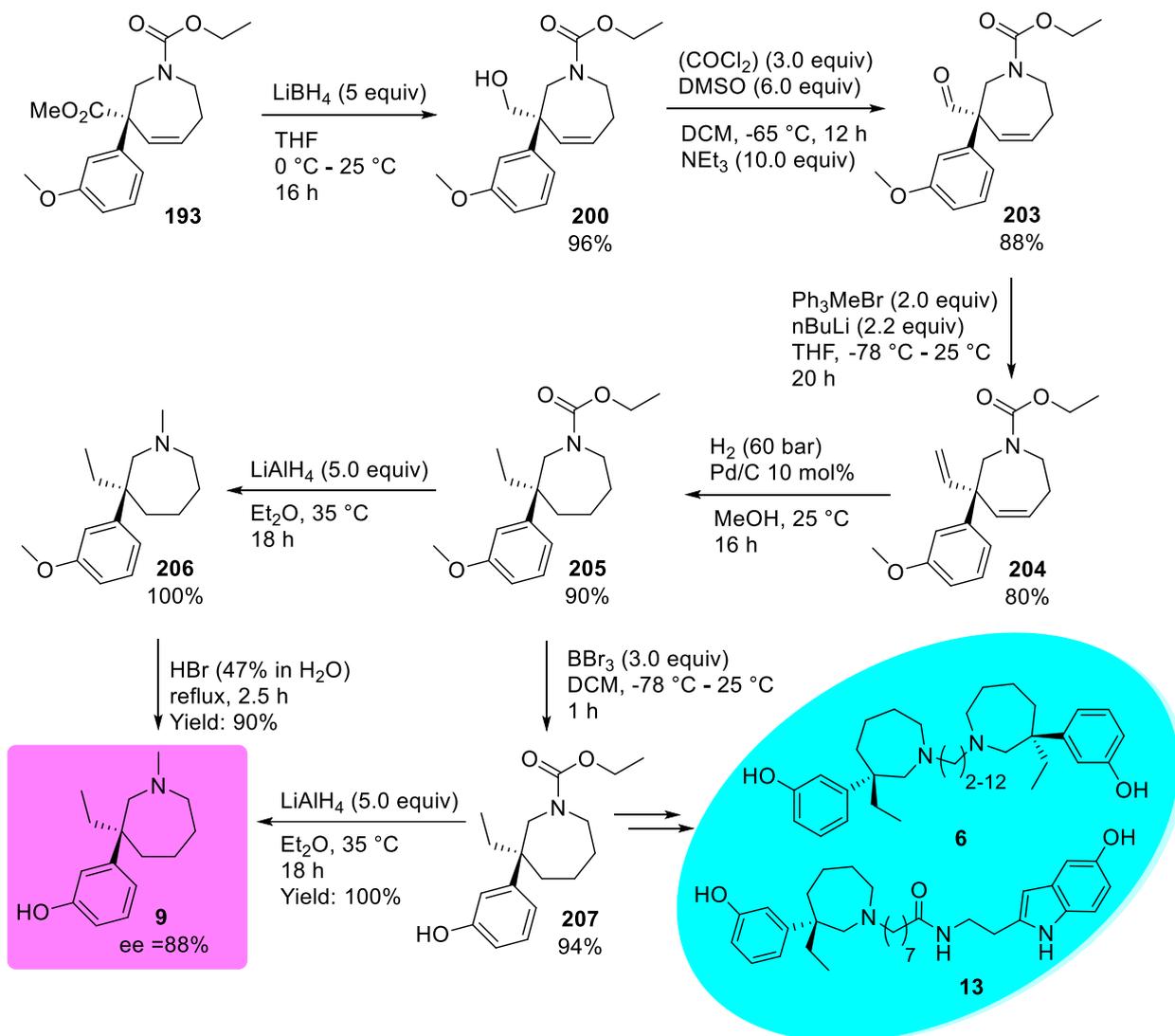
Scheme 42: Synthesis of Meptazinol.

Since many derivatives of Meptazinol **9** were found to be biologically active, entirely new structures were synthesized empowered by possibilities the new approach offered. Next to changes in diazo esters used for the synthesis of the cyclopropanes and different nucleophiles used during endocyclic ring enlargement the synthetic route provides a terminal and an endocyclic double bond for functionalization. As the synthesis of the unsubstituted phenyl azapane **129** requires less expensive starting materials, it was used as starting point for further functionalization rather than **193**.
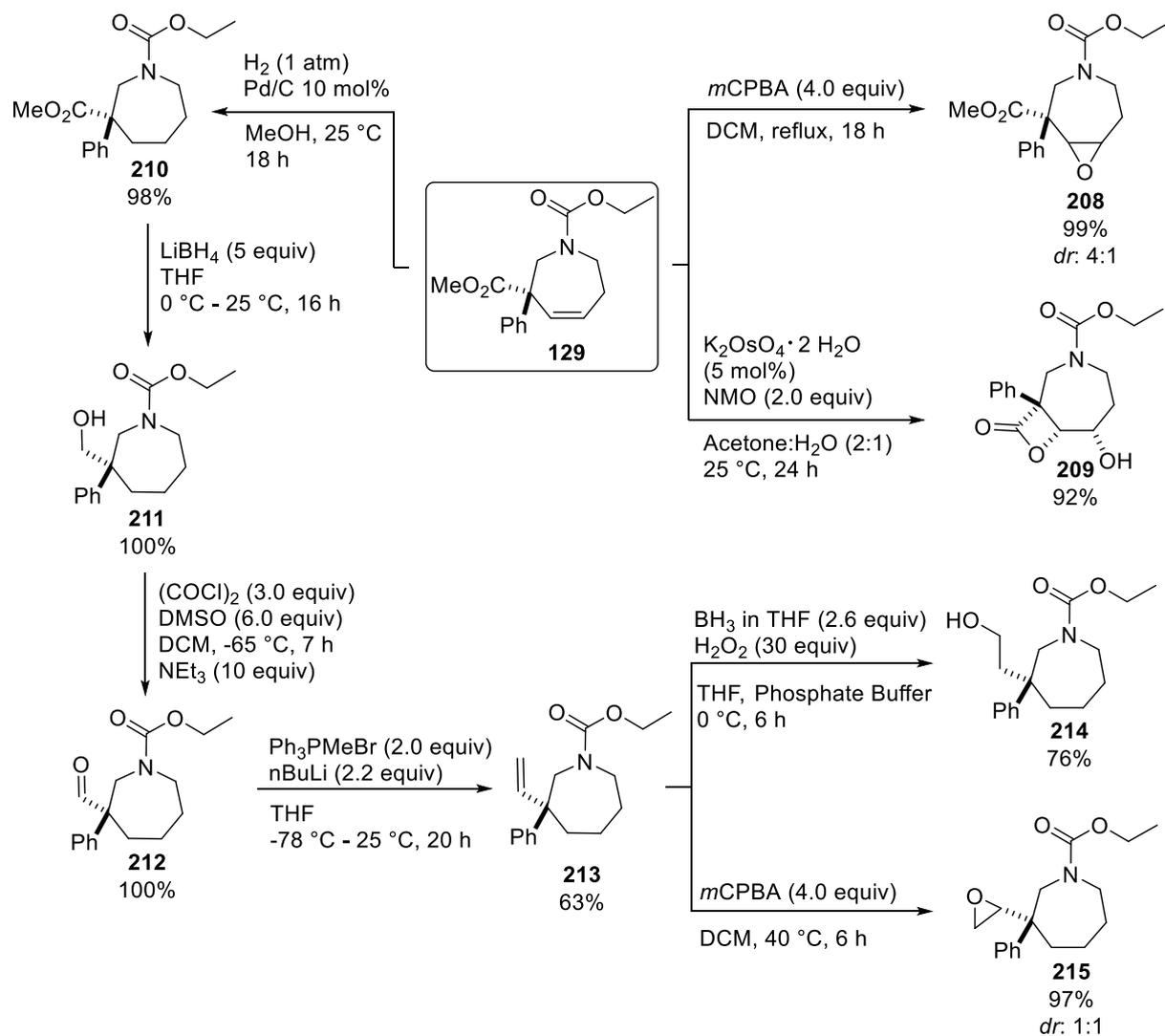
Scheme 43: Double bond derivatizations on 129.

Epoxidation of **129** using 4.0 equiv of *m*CPBA in refluxing DCM gave epoxide **208** in 99% yield in a diastereomeric ratio of 4:1. Dihydroxylation using $K_2OsO_4 \cdot 2\ H_2O$ and 2.0 equiv NMO as oxidation reagents did not give the expected dihydroxy azepane but bicyclic lacton **209** in 92%. Hydrogenation of the double bond was achieved by stirring **129** with Pd/C 10 mol% in MeOH at 25 °C for 18 h under a H_2-atmosphere, giving **210** in 98% yield. With **210** in hand, the priorly elaborated procedure to Wittig olefination was followed to obtain **213** as new starting material for double bond derivatizations. The Swern oxidation of **211** gave rise to **212** in quantitative yields in only 7 h reaction time. From there **213** could be synthesized in 63% yield. **213** was than subjected to hydroboration yielding the terminal alcohol **214** in 76%. Epoxidation with *m*CPBA gave **215** in a yield of 97% and dr = 1:1. Dihydroxylation of the terminal alkane using $K_2OsO_4 \cdot 2\ H_2O$ and NMO gave no reaction.

1.7 Synthesis of azepanes *via* endocyclic ring opening of bicyclic vinyl cyclopropanes triggered by Heck arylation

By the time as Richard F. Heck published his reaction in the year of 1972,[112] palladium catalyzed C-C-coupling reactions were only possible using organomercury, -tin or -lead coupling partners.[113] Exchanging these highly toxic and badly handleable compounds by organohalides led to an enormous thrive of this type of chemistry which resulted in the Nobel prize for Heck in the year 2010. There are numerous applications reported in literature and next to the substrates and the palladium or coupling partner species used, also the conditions can differ widely.[114] The standard Heck reaction, however, requires an olefine, a palladium species in oxidation state zero, an aryl halide and a base. The catalytic cycle starts with the Pd(0) species **216** upon which the aryl halide is binding by oxidative addition and Pd(II) species **218** is formed (scheme 44).
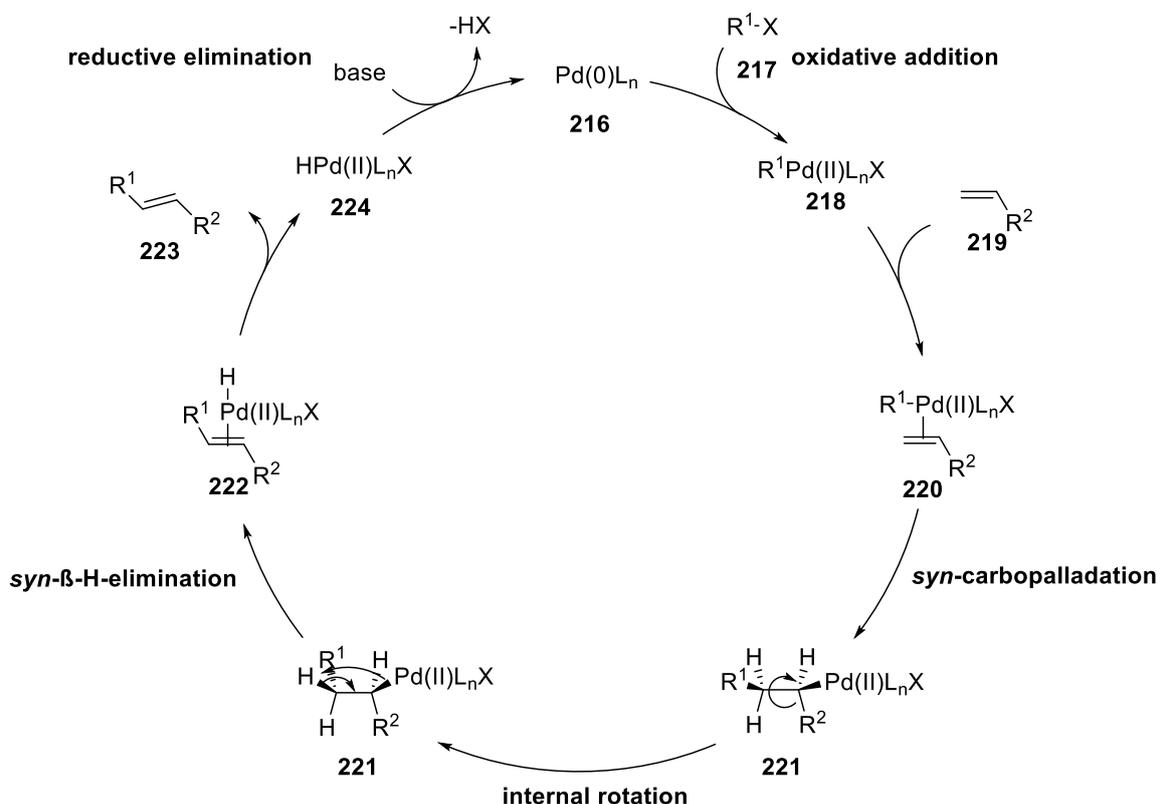
Scheme 44: Catalytic cycle of a standard Heck reaction.

At this stage the olefine is coming close to the catalyst and through *syn*-carbopalladation **221** arises. Now the palladium and the aryl moiety are bond to the substrate and an internal rotation is needed to bring a β-hydride in *syn*-position to the palladium. Upon elimination an olefine is formed again which is released from the catalyst afterwards. To close the catalytic cycle, a base is required that takes up the released halogen acid.

In 2019 the group around Reiser, showed that classical Heck-arylations can trigger the ring opening of cyclopropanes in vinyl position in an endocyclic fashion.[115] Cyclopropanated furans and pyrrols were used as starting materials for the formation of functionalized dihydropyridines, pyridines and 2H-Pyrans. Crucial for the ring opening is the formation of **221** in which the palladium species sits in α-position to the cyclopropane. Lacking a β-hydride in this rigid position, the endocyclic ring opening accompanied by a palladium migration is the only option to terminate the reaction. DFT-calculations showed that this proceeds in a concerted way.[54] An electron donating group on the other side of the cyclopropane is not required. Nevertheless, this method was tested on cyclopropanated piperidines as well and a small scope of azepanes was successfully synthesized. However, yields did not exceed 56% and the carbopalladation proceeded not fully regioselectively which resulted in by-product **227**.
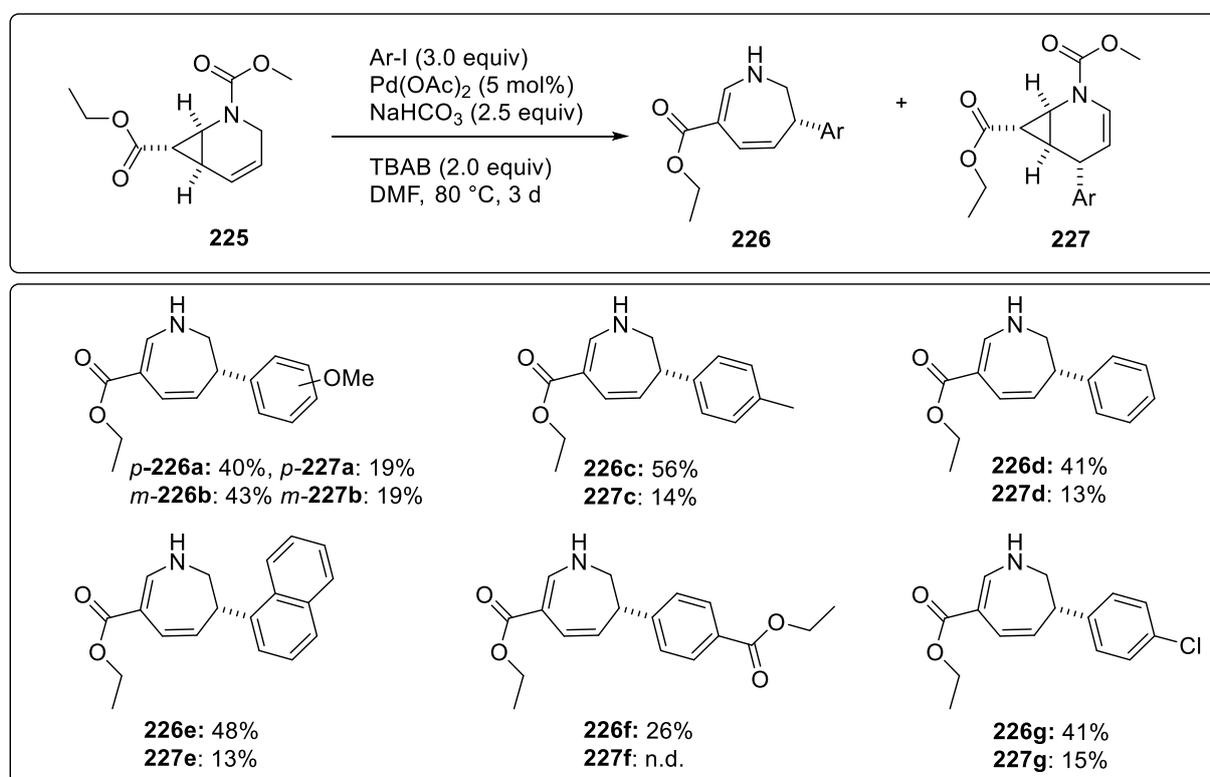
Scheme 45: Heck coupling driven synthesis of azepanes; scope.

The conditions used for the synthesis of the above scope were elaborated by a broad screening of conditions that is summarized in table 15 below. For all screening reactions *p*-MeO-iodobenzene was used as coupling partner. Starting with toluene as solvent and NaHCO$_3$ as base with a reaction time of 24 h at a temperature of 80 °C only Pd(OAc)$_2$ as catalyst showed any conversion (entry 3). Pd$_2$(dba)$_3$, Pd(OAc)$_2$ in combination with PPh$_3$ as ligand and Pd(PPh$_2$)Cl gave no reaction (entry 1,2,4). Pd(OAc)$_2$ however gave three Heck coupling products. Next to by-product **227a**, the desired ring-opened product occurred with and without

protecting group. Later it became apparent that longer reaction times lead to a conversion of the protected **226a** to **226a**. Next to toluene, DMF, THF, MeCN and DMSO were used as solvent (entry 6-9). DMF give the highest yield of 36% of cumulative ring-opened product and was therefore the solvent of choice for further optimization. In the next test-phase NaHCO$_3$ was substituted by KOAc K$_3$PO$_4$, NEt$_3$ and Ag$_2$CO$_3$ but none of them could increase the yields (entry 10-13). Looking at temperature, reaction times and the ratio of cyclopropane to aryl iodide defined 80°, 3 days and a ratio of 1:3 as optimal (entry 14-19).

Table 15: Optimization study on the Heck-arylation driven synthesis of azepanes.

entry	catalyst	solvent	base	time	CP:ArI	temp.	conv.	227a(PG)	226a(PG)	226a
1	Pd$_2$(dba)$_3$	toluene	NaHCO$_3$	24 h	1:1.3	80 °C	n.r.	-	-	-
2	Pd(OAc)$_2$/PPh$_3$ (1:3)	toluene	NaHCO$_3$	24 h	1:1.3	80 °C	n.r.	-	-	-
3	Pd(OAc)$_2$	toluene	NaHCO$_3$	24 h	1:1.3	80 °C	85%	9%	4%	14%
4	Pd(PPh$_2$)Cl$_2$	toluene	NaHCO$_3$	24 h	1:1.3	80 °C	n.r.	-	-	-
5	Pd(OAc)$_2$	toluene	NaHCO$_3$	3 d	1:1.3	40 °C	38%	2%	6%	-
6	Pd(OAc)$_2$	DMF	NaHCO$_3$	24 h	1:1.3	80 °C	100%	11%	25%	25%
7	Pd(OAc)$_2$	THF	NaHCO$_3$	24 h	1:1.3	80 °C	100%	4%	29%	21%
8	Pd(OAc)$_2$	MeCN	NaHCO$_3$	24 h	1:1.3	80 °C	100%	24%	26%	8%
9	Pd(OAc)$_2$	DMSO	NaHCO$_3$	24 h	1:1.3	80 °C	100%	16%	16%	6%
10	Pd(OAc)$_2$	DMF	KOAc	24 h	1:1.3	80 °C	75%	7%	15%	15%
11	Pd(OAc)$_2$	DMF	K$_3$PO$_4$	24 h	1:1.3	80 °C	80%	10%	17%	17%
12	Pd(OAc)$_2$	DMF	NEt$_3$	24 h	1:1.3	80 °C	100%	1%	16%	32%
13	Pd(OAc)$_2$	DMF	Ag$_2$CO$_3$	24 h	1:1.3	80 °C	n.r.	-	-	-
14	Pd(OAc)$_2$	DMF	NaHCO$_3$	3 d	1:1.3	80 °C	100%	-	16%	32%
15	Pd(OAc)$_2$	DMF	NaHCO$_3$	3 d	1:1.3	60 °C	100%	10%	22%	26%
16	Pd(OAc)$_2$	DMF	NaHCO$_3$	2 d	1:1.3	80 °C	100%	4%	19%	30%
17	Pd(OAc)$_2$	DMF	NaHCO$_3$	2 d	5:1	80 °C	-	17%	43%	22%
18	Pd(OAc)$_2$	DMF	NaHCO$_3$	3 d	1:3	80 °C	100%	-	19%	40%
19	Pd(OAc)$_2$	DMF	NaHCO$_3$	3 d	1:5	80 °C	100%	-	16%	29%

Even after these extended optimizations, the yield of the reaction was still moderate and the regioselectivity of the palladium attack was around 2:1 in favour for the ring-opened product. To increase the yield of the desired azepane, a part of this dissertation was dedicated to further optimization and the development of new cyclopropanes.

## 1.7.1 Extended optimization of the Heck coupling driven ring-opening to azepanes

Following the procedure developed by Andrey et al.[116] cyclopropane **225** was synthesized from **228** by slow addition of 1.2 equivalents diazo ethyl ester within 16 h to a solution of 3 mol% (CuOTf)$_2$•benzene complex, priorly mixed with 5 mol% Schiff base. Despite multiple executions without any deviation from the original report, the yield was far lower than 90% and reached only 36%. Mono-cyclopropanation of both available double bonds was observed giving cyclopropane **229** as by-product.
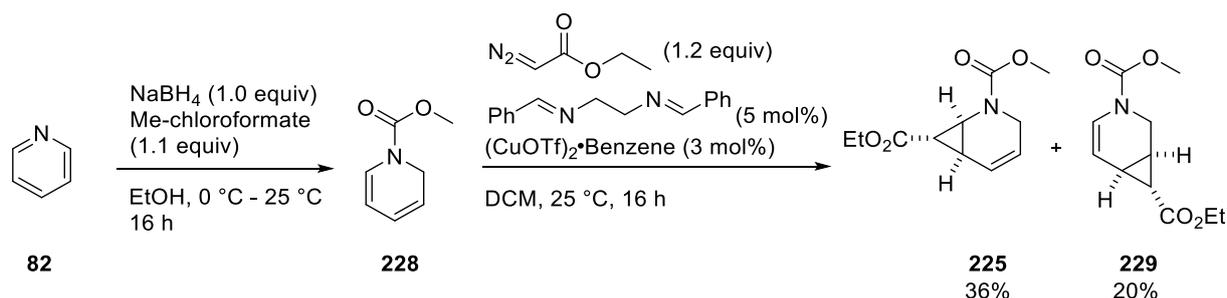
Scheme 46: Synthesis of cyclopropanes as starting material for the consecutive Heck coupling reaction.

The continued screening commenced with an extension of the tested solvents (table 16). A DMF/H$_2$O mixture in a ratio of 9:1 decreased the yield of the desired azepane **226a** by almost 15% while the yield of by-product **227a** stayed in the same range (entry 2). Changing the solvent to NMP (entry 3) or DMA (entry 4) led to a yield-fall for both products. Verification of the Pd(OAc)$_2$/PPh$_3$ system showed that this catalyst can do the reaction as well, if DMF is employed as solvent, but still the yields were inferior to the previously employed Pd(Ac)$_2$ without ligand (entry 4). Substitution of TBABr by TBACl resulted in a decreased yield as well (entry 6). TBAOAc did not give a reaction at all (entry 7). Finally, the catalyst loading was decreased to 1 mol% and 0.1 mol%, respectively, to determine the borders of the reaction. Pd(OAc)$_2$ at 1 mol% loading was not able to fully convert the starting material in 3 days but with a prolonged reaction time, this loading would be sufficient (entry 8). Unfortunately, the ratio between the two major products approached 1:1. Lowering the catalyst loading to 0.1 mol% terminated the reaction (entry 9).

Table 16: Extended optimization study on the Heck-coupling driven synthesis of azepanes.
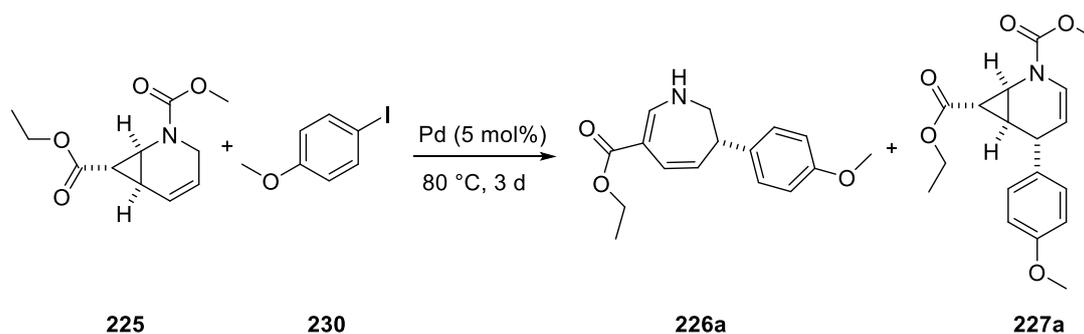
entry	catalyst	solvent	base	additive	conv.	226a	227a
1	Pd(OAc)$_2$	DMF	NaHCO$_3$	TBABr	100%	40%	19%
2	Pd(OAc)$_2$	DMF/H$_2$O (9:1)	NaHCO$_3$	TBABr	100%	25%	17%
3	Pd(OAc)$_2$	NMP	NaHCO$_3$	TBABr	100%	25%	12%
4	Pd(OAc)$_2$	DMA	NaHCO$_3$	TBABr	100%	19%	11%
5	Pd(OAc)$_2$/PPh$_3$ (1:1)	DMF	NaHCO$_3$	TBABr	100%	28%	18%
6	Pd(OAc)$_2$	DMF	NaHCO$_3$	TBACl	100%	22%	16%
7	Pd(OAc)$_2$	DMF	NaHCO$_3$	TBAOAc	n.r.	-	-
8	Pd(OAc)$_2$ (1 mol%)	DMF	NaHCO$_3$	TBABr	86%	17%	16%
9	Pd(OAc)$_2$ (0.1 mol%)	DMF	NaHCO$_3$	TBABr	n.r.	-	-

1.7.2 Matsuda-Heck reaction for the ring-opening of cyclopropanes

Complexes made from transition metals and aryl-diazonium salts were long known in the field of inorganic chemistry[117] before Matsuda introduced them for organic chemists with the first application in this particular field. In 1977 he observed that aryl diazonium salts can replace aryl halides or aryl mercury compounds in palladium catalyzed C-C coupling reactions.[118] From this point a long history of further developments and applications started which revealed numerous advantages over the standard Heck reaction.[119] Contrary to the former process, no stabilizing phosphane ligands are needed eliminating the requirement of water and oxygen free conditions. In addition, the Matsuda-Heck reaction gets along with lower reaction temperatures that may prohibit unwanted side reactions. Full conversions under standard Heck conditions usually require a big excess of one coupling partner over the other. This is often not needed by the use of aryl diazonium salts which is especially important if the coupling partners are hard to obtain and therefore valuable.

The Matsuda-Heck reaction requires a Pd(0)-species as catalyst. Typical Pd-sources are therefore $Pd(OAc)_2$ or $Pd_2(dba)_3$. Often used solvents are MeOH, MeCN, THF and PhCN. Since DMF worked best for the system of interest during the previous studies it was tested as well. If bases are added to push the reaction, NaOAc is the base of choice for the majority of previous applications.

The optimization of the Matsuda-Heck-conditions for the coupling and subsequent ring enlargement of cyclopropane **225** to the desired azepane **226a(PG)** commenced with the search of the optimal Pd(0)-source and the elucidation of a potential base requirement. Therefore, $Pd(OAc)_2$ and $Pd_2(dba)_3$ were used as catalyst with and without the addition of NaOAc and a catalyst loading of 5 mol%. In all cases 4-MeO-phenyl-BF_4 diazonium salt was used in a slight excess of 1.3 equivalents. As solvent MeOH was chosen, and the reactions proceeded in 16 h at a temperature of 25 °C (entry 1-4). **226a(PG)** was assumed as potential product as the milder reaction conditions presumably will not cleave the carbamate protection group. Indeed, the free azepane **226a** was not observed in one of the following reactions. The comparison of $Pd(OAc)_2$ and $Pd_2(dba)_3$ as precatalyst showed no significant difference. Without addition of a base both catalysts showed only a low conversion of starting material after 16 h and a temperature of 25 °C. Converted material diverges into multiple products none of them outstanding. If NaOAc is added, the reaction proceeds very fast as it can be seen by strong release of gas which points towards the consumption of diazonium salt **231**. Although the conversion of starting material **225** elevated, remaining material was observed after workup. The higher conversion however only led to an increased amount of non-analyzable products. Since both pre-catalysts reacted equally so far, further experiments concentrated on $Pd_2(dba)_3$. To increase the conversion, the reaction time was increased to 3 d and in one case the temperature was elevated to 50 °C (entry 5 and 6). Both measures resulted in full consumption of cyclopropane **225**, but again a complex product mixture was obtained. Lastly, a screening of the most common solvents was conducted. Switching to THF gave a lower conversion of approximately 30% again with multiple products (entry 7). A full conversion in combination with complex product mixtures was obtained if MeCN was used (entry 8). PhCN as solvent gave a conversion of 79% without outstanding products. Finally, DMF was tested showing a more promising crude spectrum for the first time.

*Table 17: Optimization study of Matsuda-Heck reaction on cyclopropane 225.*
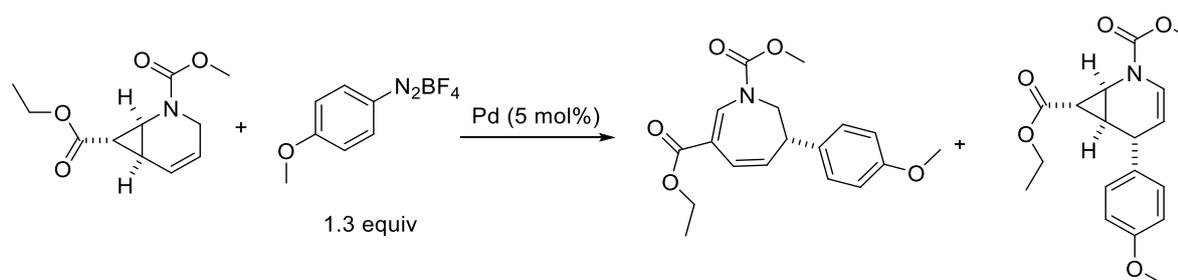
| | 225 | 231 | | | | 226a(PG) | 227a |

entry	catalyst	solvent	base	time	temp.	comment
1	Pd(OAc)$_2$	MeOH	-	16 h	25 °C	low conversion, complex mixture
2	Pd(OAc)$_2$	MeOH	NaOAc	16 h	25 °C	very fast reaction, complex mixture
3	Pd$_2$(dba)$_3$	MeOH	-	16 h	25 °C	low conversion, complex mixture
4	Pd$_2$(dba)$_3$	MeOH	NaOAc	16 h	25 °C	very fast reaction, complex mixture
5	Pd$_2$(dba)$_3$	MeOH	-	3 d	50 °C	full conversion, complex mixture
6	Pd$_2$(dba)$_3$	MeOH	-	3 d	25 °C	full conversion, complex mixture
7	Pd$_2$(dba)$_3$	THF	-	3 d	25 °C	30% conversion, multiple products
8	Pd$_2$(dba)$_3$	MeCN	-	3 d	25 °C	full conversion, complex mixture
9	Pd$_2$(dba)$_3$	PhCN	-	3 d	25 °C	79% conversion, multiple products
10	Pd$_2$(dba)$_3$	DMF	-	3 d	25 °C	85% conversion, **226a(PG)** 14%

Column chromatography and analysis of multiple fractions revealed presumably **226a(PG)** as product. Since the isolated yield was only 14% which is far from the yields obtained by standard Heck-conditions and room for further experiments was small, optimization efforts were stopped.

1.7.3 Heck-coupling driven ring opening of 3,4-cyclopropanated piperidines

The unexpected cyclopropane **229** obtained as by-product in the synthesis of **225** (scheme 46), offers an opportunity in the synthesis of 2,5-substituted azepane **232**. Like **225** it can be used as starting material for the Heck-coupling driven ring expansion. In addition, its double bond is polarized through its enamine nature which would theoretically lead to more regioselectivity during carbopalladation. Application of the standard Heck conditions as optimized for the expansion of **225** only resulted in a complex mixture of products. In an attempt for milder reaction conditions the temperature was lowered to 60 °C and a decreased reaction time of 2 d

was applied. However, only decreased conversion of 37% was observed without selective formation of a particular product.
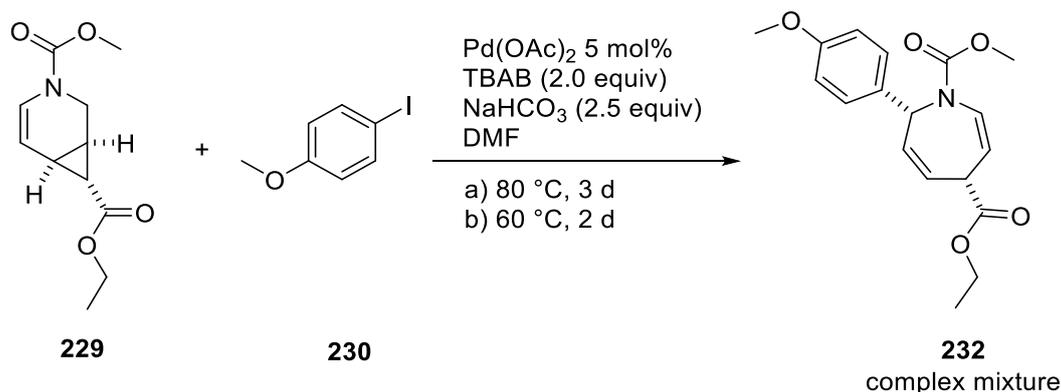
Scheme 47: Ring expansion of 229 using standard Heck conditions.

After the failed synthesis of **232** by standard Heck-conditions the search for a new method led to the oxidative boron Heck-reaction. Oxidative Heck reactions can often be carried out under lower temperatures with high efficiency. In the past better results were observed by Heck-couplings with challenging substrates such es cyclic or sterically demanding olefines. On top of that its high tolerance to functional groups makes it a promising way to explore.[120] The major difference in terms of mechanisms lies in the first step. Instead of an oxidative addition of an aryl halide to a Pd(0)-species, the boronic acid and a Pd(II)-species undergoes a transmetallation. As such O_2 is required after β-H-elimination to reoxidize the so formed Pd(0) to Pd(II) and close the catalytic cycle.

Table 18: Solvent screening for the oxidative Heck-coupling on cyclopropane 229.
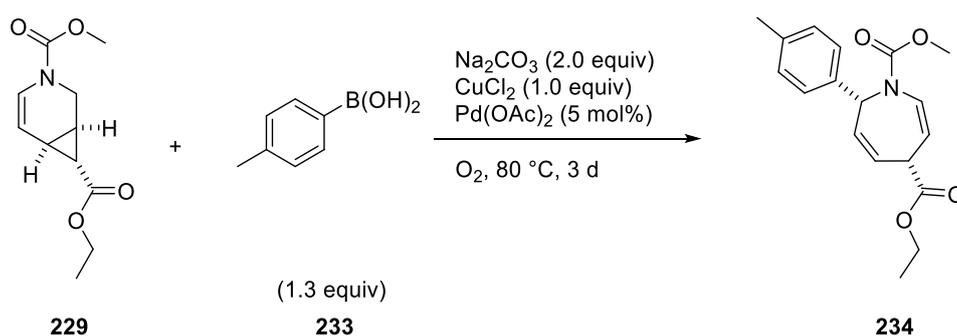
entry	solvent	conversion	comment
1	DMF	66%	dimerization of **233**
2	Dioxan	62%	-
3	NMP	48%	-
4	DMSO	71%	dimerization of **233**
5	MeCN	89%	Complex mixture

The experiments with the oxidative Heck conditions on the cyclopropane **229** were carried out as follows. 1.3 equivalents of *p*-methyl-phenyl boronic acid was dissolved together with the cyclopropane and 2.0 equivalents of Na_2CO_3 as base and 1.0 equivalents of $CuCl_2$ as co-oxidant. $Pd(OAc)_2$ was used as catalyst in a loading of 5 mol%. O_2 was added in a pressure of 1 atm by connection of a balloon to the Schlenk-outlet. All reactions were stirred for 3 days at a temperature of 80 °C. For initial tests a solvent screening was conducted. As typical solvents DMF, dioxane, NMP, DMSO and MeCN were chosen. It is to note that none of the reactions led to a complete conversion of cyclopropane **229**. During the reactions with DMF (entry 1) or DMSO (entry 4) as solvents some dimerization of the boronic acid was observed. Although, by comparison of remaining starting material peaks with an internal standard, conversions of 66% and 48%, respectively, were determined, only small amounts of other molecules could be detected by NMR. Same goes for dioxane or NMP as solvents. Having the reaction run in MeCN gave the highest conversion of 89% in combination with numerous products which none of them was outstanding enough for further analyzation.

1.7.4 New sterically demanding cyclopropanes for regioselective Heck-coupling in the synthesis of azepanes

After an expanded screening of standard Heck-conditions as well as a shift to Matsuda's diazonium salt approach did not improve the yields of the desired azepanes, a sterically customized cyclopropane was considered to control the palladium attack and favour the azepane over a non-ring-opened Heck-coupling product. Therefore, cyclopropanes **235** and **237** were synthesized by the usual copper catalyzed method in 45% yield and 23% yield respectively. The methyl group adjacent to the cyclopropane should block the attack of a big aryl moiety and consecutively promote the formation of **236**.
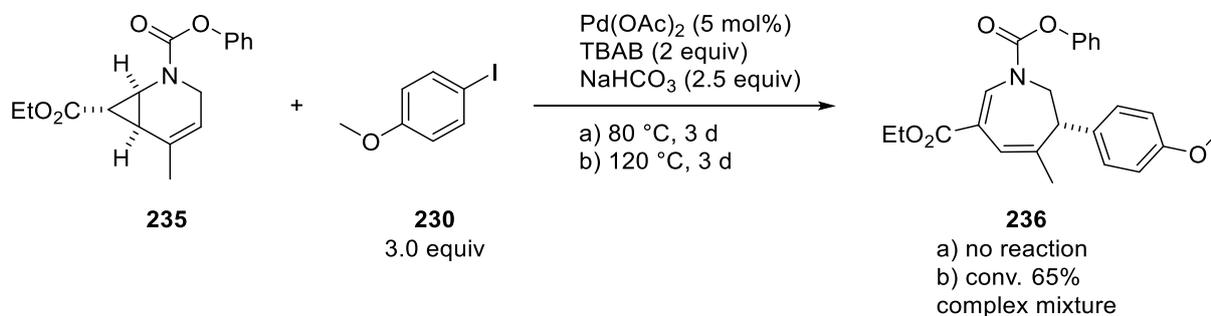
Scheme 48: 4-substituted cyclopropanes for a regioselective Heck-coupling.

Under the optimized standard conditions however no reaction was observed. Elevating the temperature to 120 °C led to a conversion of 65% after 3 d reaction time but only degradation products were observed. As cyclopropane **237** was obtained effortless during the synthesis of **235** it was subjected to both reaction conditions as well. In line with the above reaction no conversion of the starting material was observed at a temperature of 80 °C after 3 d reaction time. A temperature of 120 °C also gave only degradation products.
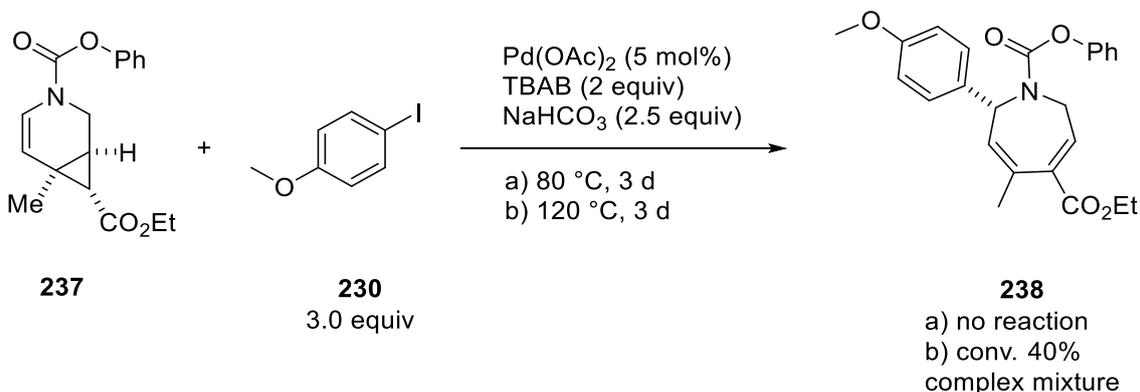
Scheme 49: 4-substituted cyclopropanes for a regioselective Heck-coupling.

In conclusion, all efforts for an improved synthesis of azepanes by Heck-coupling driven ring opening of cyclopropanes failed. Tests of a variety of new solvents or additives did not improve the reaction and the best standard Heck conditions remained as given in table 15 entry 18. Substitution of aryl iodides by diazonium salts under the Matsuda-Heck conditions was unsuccessful since either the reaction was very low in conversion or led to degradation products. Using 3,4-cyclopropanated piperidines as starting material attempting an electronically controlled regioselective carbopalladation resulted in either no reactions or complex product mixtures. The same outcome was observed trying sterically controlled Heck-arylation with 4-methyl substituted cyclopropanes.

3 Summary/Zusammenfassung

3.1 Summary

The presented work deals with the synthesis of azepanes from different types of cyclopropanated piperdines by endocyclic ring-opening. The ring-opening was achieved by either having a donor-acceptor substitution on the cyclopropane moiety together with an acid or heat activation or by employing a unique palladium shift as a consequence of a prior Heck arylation. The utility of the developed methods was underlined by the asymmetric total synthesis of meptazinol, an important drug in the treatment of labor pain and a variety of other use cases.

The research commenced with the synthesis of suitable cyclopropanes. While the donating group was settled in the nitrogen, for the electron accepting moiety multiple options were available. Aiming for a convenient and enantioselective starting material synthesis, an epoxidation of cyclopropane **87** which was accessible by rhodium catalyst cyclopropanation of 1,2-dihydropyridines in good yields and enantiomeric excess up to 69%, was chosen as starting point. The thereof arising donor acceptor cyclopropane **89** was subjected to heat and acid to promote the rearrangement to the ether bridged azepane **90**.
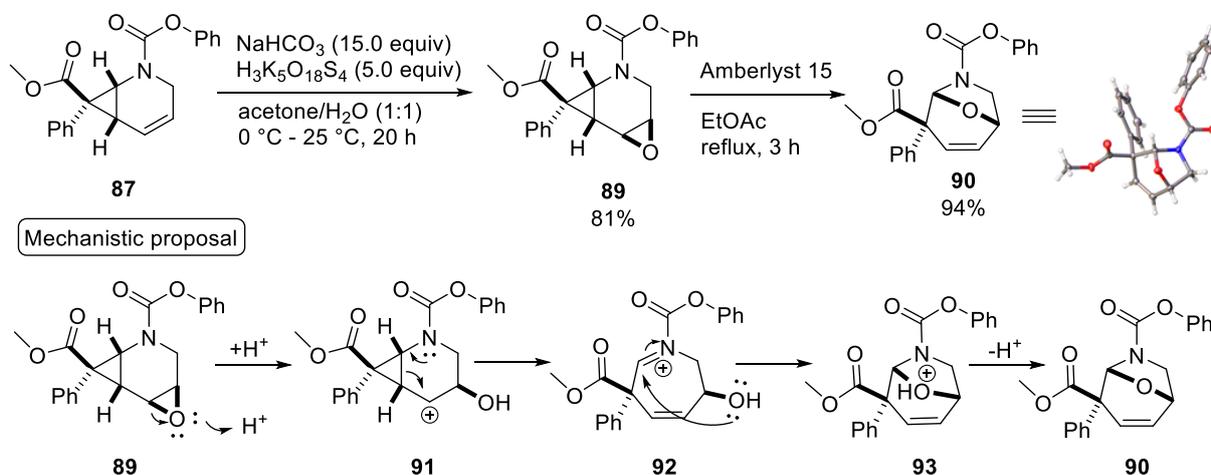
Scheme 50: Synthesis of cyclopropane 89 and its acid catalyzed rearrangement to ether bridged azepane 90.

Double bond derivatization on compound **90** only lead to the desired products in the case of hydrogenation with a yield of 96% and epoxidation with a respective yield of 86%. Osmium tetroxide catalysed dihydroxylation, Diels-Alder reaction with Danishefsky's diene and cyclopentadiene, a variety of halohydrine reactions and ozonolysis gave either no reaction or products that were not to isolate. The cleavage of the bridging ether was unsuccessful, too.

Attemptions in the synthesis of aziridinated cyclopropanes to form nitrogen bridged analogues of **90** failed as well.

The forgoing observations with oxygen as good acceptor group in form of an epoxide resulted in the idea of the ring enlargement promotion by alcoholic leaving groups. Piperidinone **118** was employed as starting material to be reduced and cyclopropanated in a later step. The reduction was done by NaBH₄ with excellent yields followed by the alcohol protection with Ac₂O.
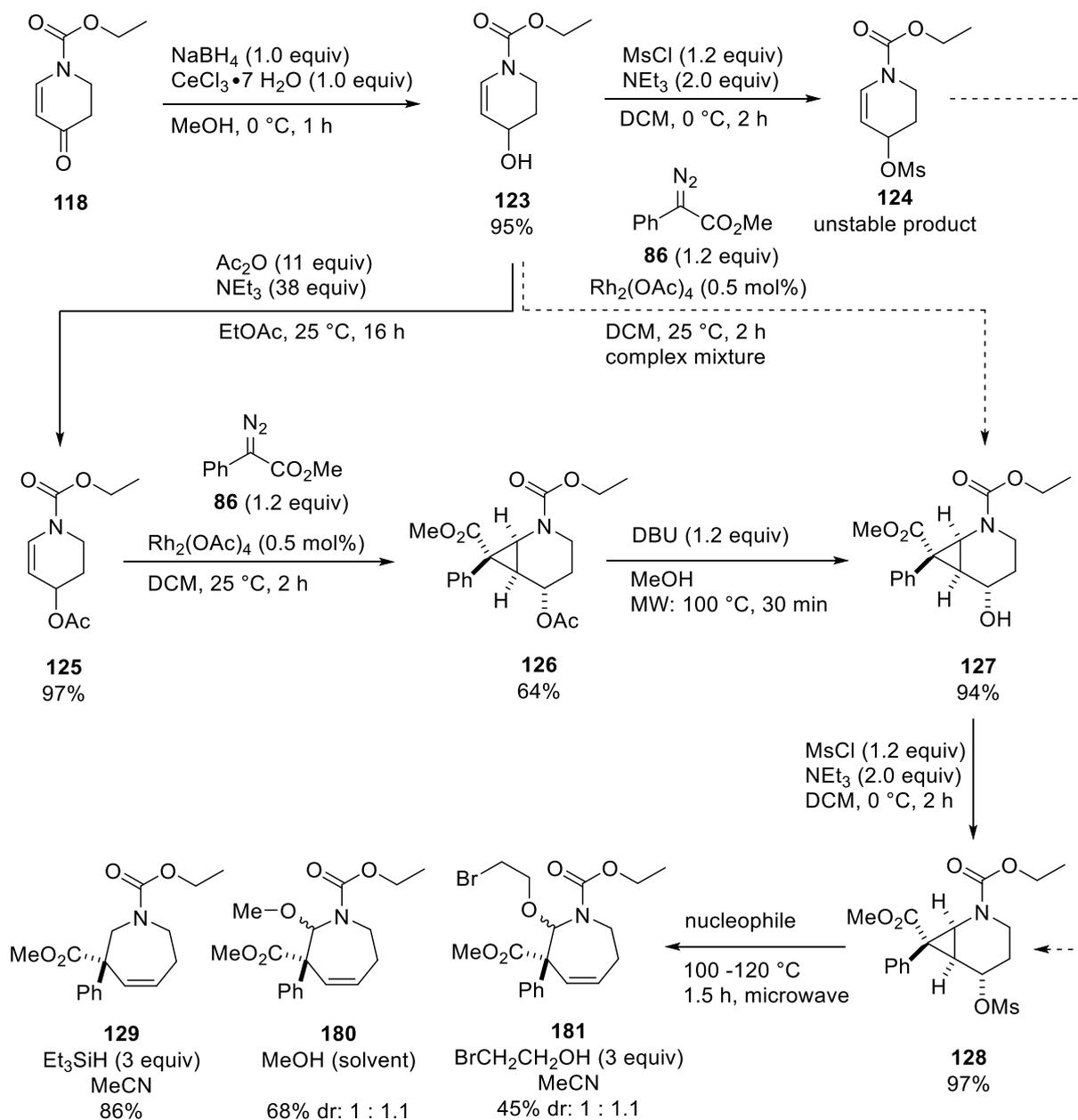
Scheme 51: *Synthesis of new unexplored azepanes from cyclopropanated piperidines featuring alcoholic leaving groups.*

Cyclopropane **126** could afterwards be synthesized by Rh$_2$(OAc)$_4$ catalyzed carben transfer from diazo ester **86**. As ring openings on **126** failed due to the low reactivity of the acetate acceptor group the leaving group was changed. Within two steps the acetyl group was substituted by mesyl which was now powerful enough to undergo a ring enlargement reaction if heated to temperatures above 100 °C in a microwave reactor. To trap the arising iminium ion, hydrides and alcohols served as external nucleophiles. Seeking for a shortened reaction pathway to the required mesyl cyclopropane **128** a direct mesylation of alcohol **123** was carried out revealing the product to be too unstable to handle. A direct cyclopropanation of the very same alcohol resulted in many by-products making the reaction undesirable.

Major similarities of **129** to the synthetic drug Meptazinol **9** inspired the use of this novel transformation for a new and first asymmetric synthesis of this compound. The key to the settled chiral center was seen in a combination of the diastereoselectivity during the cyclopropanation and an enantiomerical pure alcohol derivative **125**. Enantioselective reductions, asymmetric hydrogenation, enzyme catalyzed reductions, lipase mediated acetylation and hydrogenations in combination with dynamic kinetic resolution were applied to obtain **125** enantiomerically pure. The best result was obtained using classical CBS-reductions at a temperature of 0 °C to give alcohol **123** in 57% ee and good yield of 81%.
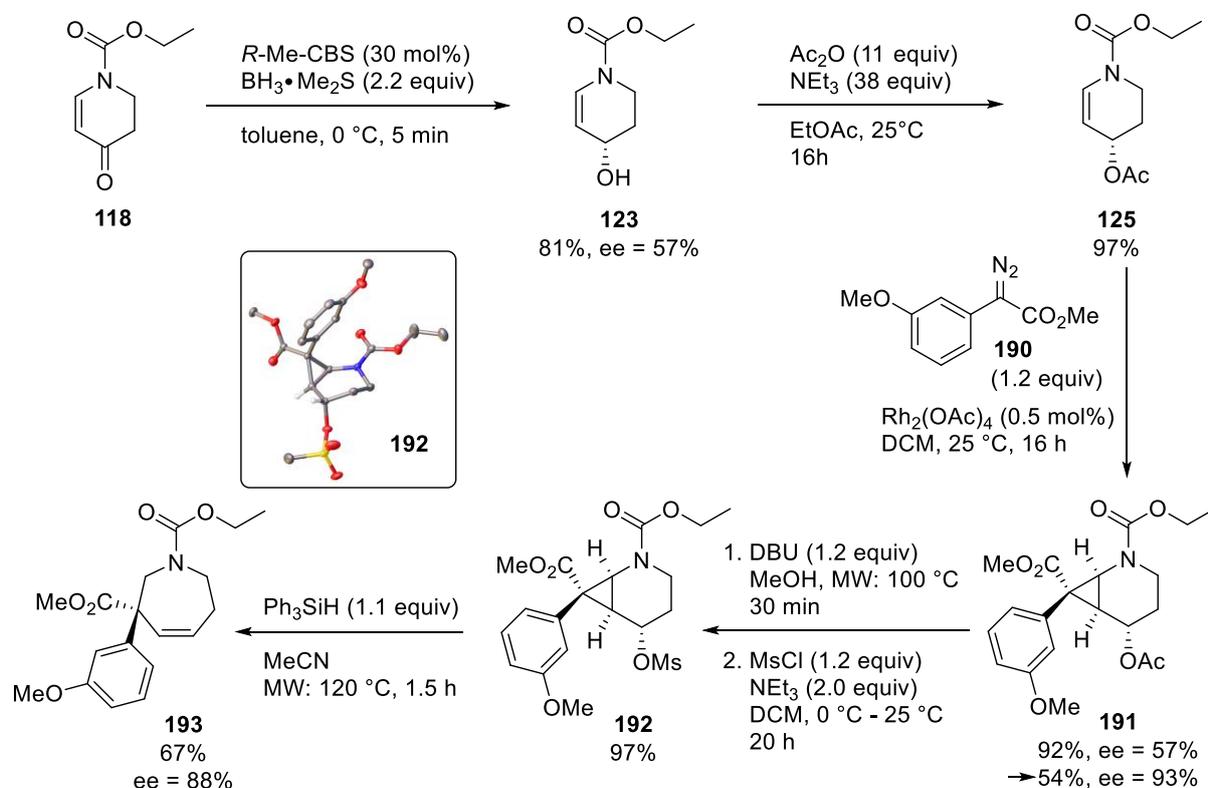
Scheme 52: Asymmetric synthesis of Meptazinol. Step 1-5.

A *m*-methoxy substituted phenyl diazo ester was used in the production of cyclopropane **191** after the alcohol was protected with Ac$_2$O following the previously elaborated procedure. **191** was produced in excellent yield of 92% and could be recrystallized easily to enhance the ee to 93%. The protection group was subsequently changed to a mesyl leaving group in high yield which enabled the ring enlargement to azepane derivative **193**. During this step a minor loss in enantiomeric excess was detected. After observing unwanted products if the ethyl side chain is introduced by substitution techniques, a Wittig olefination was chosen for this purpose. The stage for this was set by selective reduction of the methyl ester to the corresponding alcohol using LiBH$_4$ as mild reducing agent.
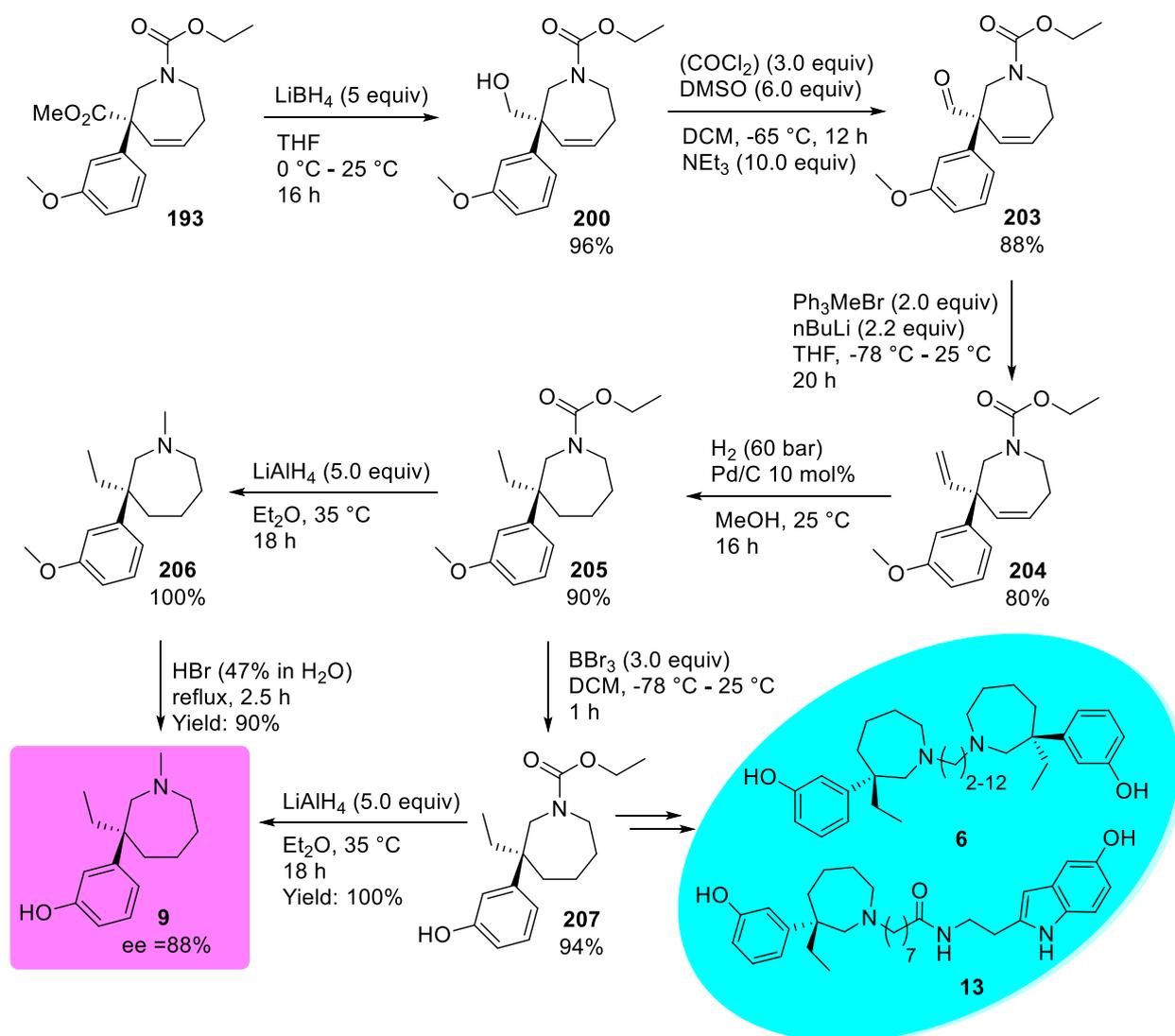
Scheme 53: Asymmetric synthesis of Meptzinol. Step 6-11.

A Swern oxidation of this very alcohol yielded aldehyde **203** in 88%. Wittig's reaction could now add the missing carbon to form compound **204** and the ethyl side chain counting in the ensuing hydrogenation. Having azepane **205** in hand, Meptazinol **9** can be obtained in two steps

via reduction of the carbamate protecting group to form the tertiary amine with LiAlH$_4$ and subsequent ether cleavage by refluxing **206** in concentrated aqueous HBr. Having the ether cleavage to happen first *via* reaction with BBr$_3$, gives compound **207** in high yields which is used for the synthesis of anti-Alzheimer agents **6** and **13**.

Next to donor-acceptor substitution also a unique palladium shift can be used to trigger the endocyclic ring opening of cyclopropanes to form ring enlarged products. In course of this dissertation, this reactivity was employed to synthesize azepanes as a consequence of a forgoing Heck-arylation, as it was done previously in the group of Prof. Dr. Reiser. As prior procedures had the disadvantage of low to medium yields, because of poor regioselectivity of the palladium attack, further optimization was conducted and new procedures together with customized starting materials were tested. Further optimization of the standard Heck conditions in terms of solvents or additive did not lead to better yields. Changing the coupling partner to diazonium salt **231** and a screening of the belonging Matsuda-Heck conditions, only led to low conversion or unselective reactions. Similar observations were made by substitution of the coupling partner by aryl boronic acid **233** with the corresponding oxidative Heck conditions.
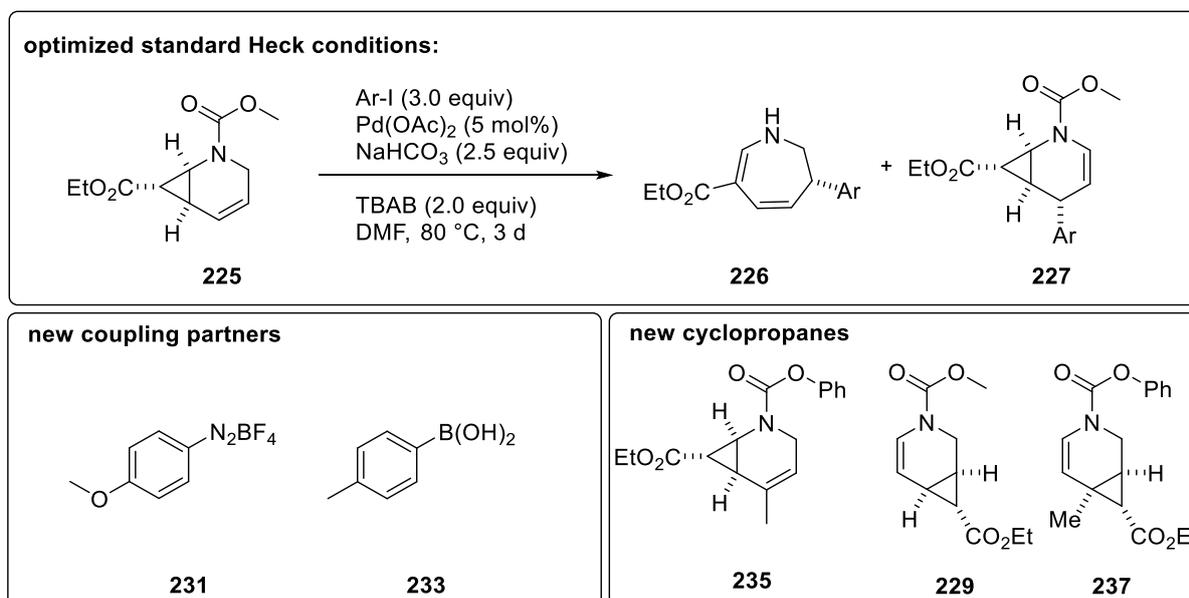
Scheme 54: Optimization strategies on the Heck-coupling driven synthesis of azepanes.

Unsuccessful with different coupling partners, the focus was shifted to the cyclopropanes. Attempting to control the regioselectivity during carbopalladation in a steric fashion, cyclopropane **235** was synthesized bearing a repulsive methyl group. Unfortunately, reactions with this substrate only were observed under harsh conditions leading to decomposition

products. Substrates **229** and **237** which allow arylation only at C2 position to close the catalytic cycle showed the same behaviour.

3.2 Zusammenfassung

Die vorliegende Arbeit beschäftigt sich mit der Synthese von Azepanen aus cyclopropanierten Piperidinen unterschiedlicher Art durch endocyclische Ringöffnung. Diese Ringöffnung wurde entweder durch eine Donor-Akzeptor Substitution am Cyclopropan in Kombination mit Säure oder thermischer Aktivierung erhalten oder durch das Ausnutzen einer einzigartigen Palladium Wanderung, die aus einer vorangegangen Heck Arylierung resultierte. Der Nutzen der entwickelten Methoden wurde durch die daraus hervorgegangene asymmetrische Totalsynthese von Meptazinol unterstrichen, eines wichtigen Medikamentes in der Behandlung von Wehenschmerzen und weiteren Einsatzgebieten.

Die Forschung startete mit der Synthese geeigneter Cyclopropane. Während die Elektronen donierende Gruppe durch das Stickstoffatom festgesetzt war, standen für die Elektronen akzeptierende Einheit mehrere Optionen zur Verfügung. Mit dem Ziel einer bequemen und enantioselektiven Synthese des Startmateriales wurde Cyclopropan **87** durch Epoxidierung und vorangegangener Rhodium-katalysierten Cyclopropanierung in guten Ausbeuten und Enantiomerenüberschuss von bis zu 69% aus 1,2-Dihydropyridinen dargestellt. Das so entstandene Donor-Akzeptor-Cyclopropan **89** wurde Hitze und Säure unterzogen, um die Umstrukturierung zum Ether überbrückten Azepan **90** herbeizuführen.
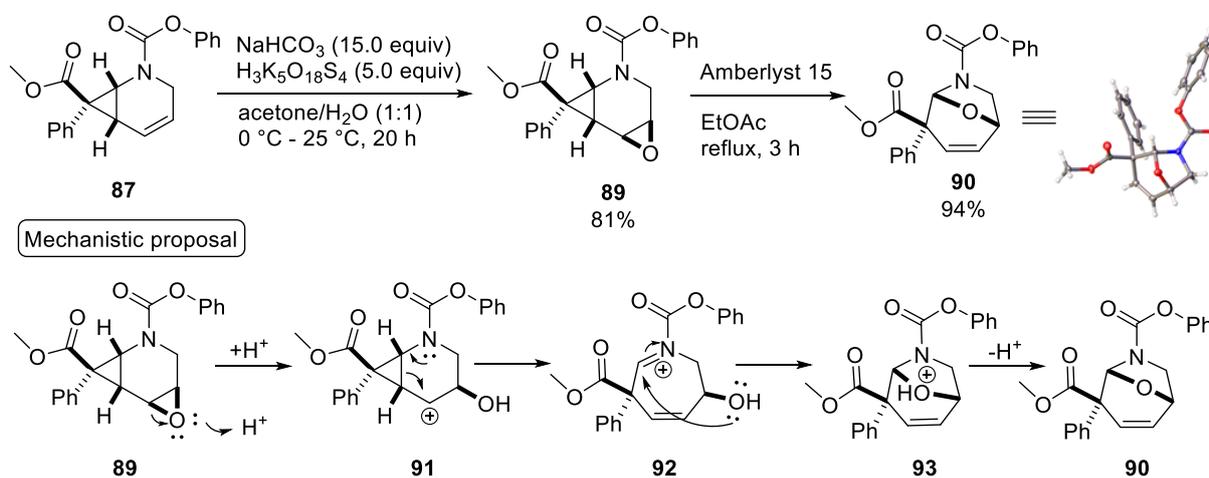
*Schema 1: Synthese von Cyclopropan **89** und die darauffolgende Säure katalysierte Umlagerung zum Ether überbrückten Azepan **90**.*

Derivatisierungen an der Doppelbindung der Verbindung **90** führten nur in den Fällen der Hydrierung mit einer Ausbeute von 96% und der Epoxidierung mit einer Ausbeute von 86% zum erwünschten Produkt. Osmiumtetroxid katalysierte Dihydroxylierung, Diels-Alder Reaktionen am Danishefsky-Dien und Cyclopentadien, unterschiedliche Halohydrin

Reaktionen und Ozonolysen ergaben entweder keine Umsetzung des Startmaterials oder Produkte welche nicht isoliert werden konnten. Unerfolgreich war auch der Bruch der überbrückenden Ether-Bindung. Bemühungen einer Synthese von aziridinierten Cyclopropanen, um Stickstoff überbrückende Analoga von **90** darzustellen schlugen ebenso fehl.

Die vorangegangenen Beobachtungen mit Sauerstoff als gute Akzeptorengruppe in Form eines Epoxides führten dazu alkoholische Abgangsgruppen zur Ringerweiterung in Betracht zu ziehen.
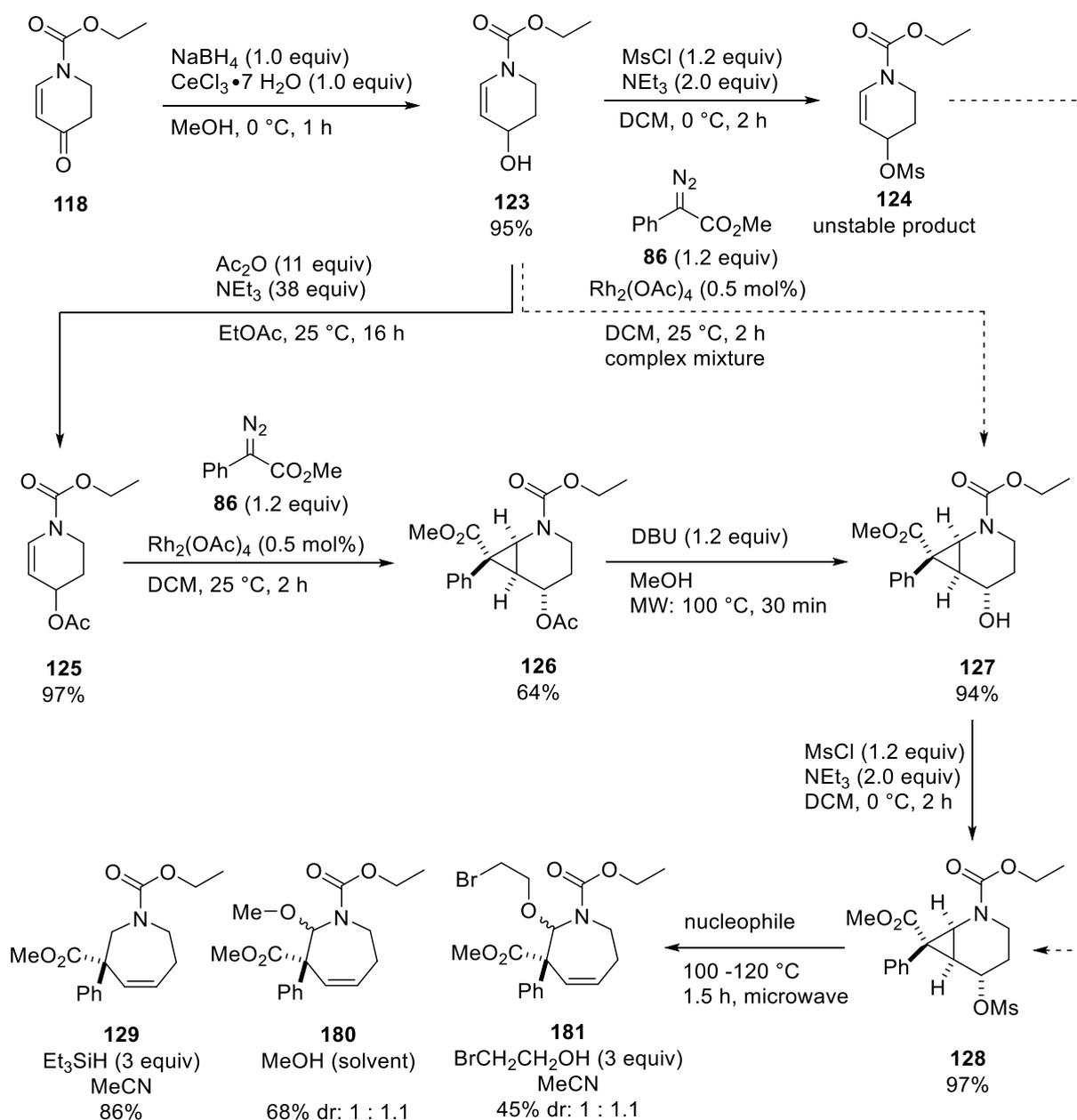
Schema 2: Synthese neuer unerforschter Azepane aus cyclopropanierten Piperidinen durch alkoholische Abgangsgruppen.

Das Piperidinon **118** diente hierfür als Startmaterial für eine Reduktion zum Alkohol und einer späteren Cyclopropanierung. Die Reduktion konnte mit Hilfe von NaBH₄ in exzellenten Ausbeuten erreicht werden, worauf eine Schützung mit Ac₂O folgte. Cyclopropan **126** konnte daraufhin durch Rh₂(OAc)₄ katalysierten Carbentransfer von Diazoester **86** synthetisiert werden. Da die Ringöffnung von **126** aufgrund unzureichender Reaktivität der Acetat Akzeptorgruppe nicht glückte, musste die Abgangsgruppe ausgetauscht werden. Innerhalb zweier Schritte wurde die Acetatgruppe durch eine Mesylgruppe substituiert, welche nun in der Lage war bei Temperaturen von über 100 °C in einem Mikrowellenreaktor, eine Ringöffnung herbeizuführen. Das dabei entstehende Iminiumion konnte durch Hydride und Alkohole welche als Nukleophile dienten abgefangen werden. Auf der Suche nach einem kürzeren Syntheseweg zu dem benötigten Mesyl-Cyclopropan **128**, wurde eine direkte Mesylierung des Alkohols **123** durchgeführt. Das daraus erhaltene Produkt war jedoch zu instabil, um weiterverarbeitet zu werden. Eine direkte Cyclopropanierung des selbigen Alkohols führte zu vielen Nebenprodukten, worauf auch dieser Weg verworfen werden musste.

Große Ähnlichkeiten von **129** zu dem synthetisch hergestellten Medikament Meptazinol **9** inspirierten zu dessen erster asymmetrische Synthese mit Hilfe dieser neuartigen Transformation.
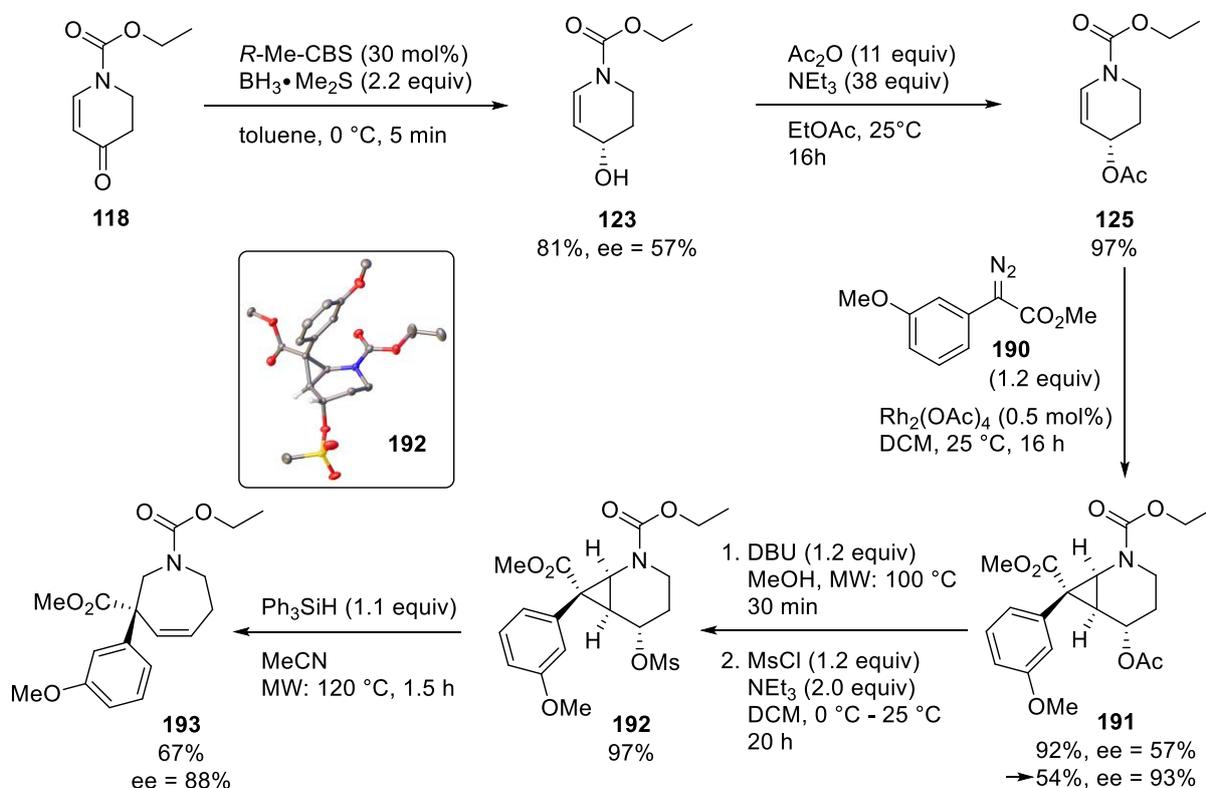
Schema 3: Asymmetrische Synthese von Meptazinol, Schritte 1-5.

Der Schlüssel zur selektiven Festsetzung des Stereozentrums wurden in der Kombination der Diastereoseletivität des Cyclopropanierungsschrittes und eines enantiomerenreinen Alkholderivat **125** gesehen. Daraufhin wurden enantioselektive Reduktionen, asymmetrische Hydrierungen, Enzym katalysierte Reduktionen sowie Lipasen gesteuerte Acylierungen und Hydrierungen in Kombination mit dynamischer kinetischer Resolutionen angewandt, um **125** enantiomerenrein darzustellen. Das Beste Ergebnis wurde durch klassische CBS-Reduktion bei einer Temperatur von 0 °C erzielt, durch welche Alkohol **123** in 57% ee und einer Ausbeute von 81% zur Verfügung stand. Ein *m*-Methoxy subsituierter Phenyldiazoester diente zur Produktion von Cyclopropan **191,** nachdem der Alkohol, der vorher erarbeiteten Vorschrift folgend, geschützt wurde. **191** konnte in einer exzellenten Ausbeute von 92% erhalten und durch Umkristallisierungen einfach auf einen Enantiomerenüberschuss von 93% gebracht werden. Nachfolgend wurde die Schutzgruppe mit der Mesylabgangsgruppe in hoher Ausbeute ausgetauscht, was die Ringerweiterung zu Azepanderivat **193** ermöglichte. Während dieses Prozesses wurden kleine Verluste beim Enantiomerenüberschuss festgestellt. Da bei den Einführungen der Ethyl-Seitenkette mit Hilfe einer Substitution unerwünschte Produkte beobachtet wurden, wurde diese Aufgabe fortfolgend durch eine Wittig Olefinierung bewerkstelligt. Der dazu benötigte Aldehyd **203** wurde durch selektive Reduktion des Methlesters zum Alkohol mit Hilfe von $LiBH_4$ als mildes Reduktionsmittel und einer darauffolgenden Swern-Oxidation in einer Ausbeute von 88% hergestellt.

Schema 4 Asymmetrische Synthese von Meptazinol, Schritte 6-11.

Wittigs' Reaktion konnte nun das fehlende Kohlenstoffatom anbringen, um die Substanz **204** und in Kombination mit der folgenden Hydrierung die Ethyl-Seitenkette darzustellen. Mit Azepan **205** in Händen, wurde Meptazinol **9** in zwei weiteren Schritten, über eine Reduktion der Carbamatschutzgruppe zum tertiären Amin durch LiAlH₄ und einer darauffolgenden Etherspaltung in refluxierender konzentrierter wässriger HBr-Lösung erhalten. Spaltet man dagegen den Ether zuerst durch eine Reaktion mit BBr₃ kommt man in hohen Ausbeuten zur Verbindung **207,** welche zur Synthese von **6** und **13** verwendet wird, zweier Komponenten mit hoher Wirksamkeit gegen die Alzheimererkrankung.

Zusätzlich zu einer Donor-Akzeptor Substitution am Cyclopropan ist auch eine einzigartige Palladium Wanderung in der Lage eine endocyclische Ringerweiterung herbeizuführen. Im Zuge dieser Dissertation wurde ebendiese Reaktivität in Folge einer vorausgehenden Heck-Arylierung zur Synthese von Azepanen angewandt, wie es bereits vorher in der Arbeitsgruppe

von Prof. Dr. Reiser durchgeführt wurde. Da aber vorherige Protokolle die Nachteile von niedrigen bis mittelmäßigen Ausbeuten aufwiesen, als Resultat schwacher Regioselektivität während des Palladium Angriffs, wurde die Optimierung dieser Reaktion erweitert sowie neue Techniken erforscht und Startmaterialien angepasst. In Bezug auf die Standard Heck-Bedingungen wurden die Tests um einige Lösungsmittel und Additive erweitert, welche aber zu keinen besseren Ausbeuten führten. Der Austausch des Kopplungspartners durch das Diazoniumsalz **231** und eine breite Versuchsreihe mit den dazugehörigen Matsuda-Heck Bedingungen erbrachte nur geringe Umsätze oder unselektive Reaktionen. Ähnliche Beobachtungen wurden gemacht, wenn Arylboronsäure **233** unter oxidativen Bedingungen verwendet wurde.
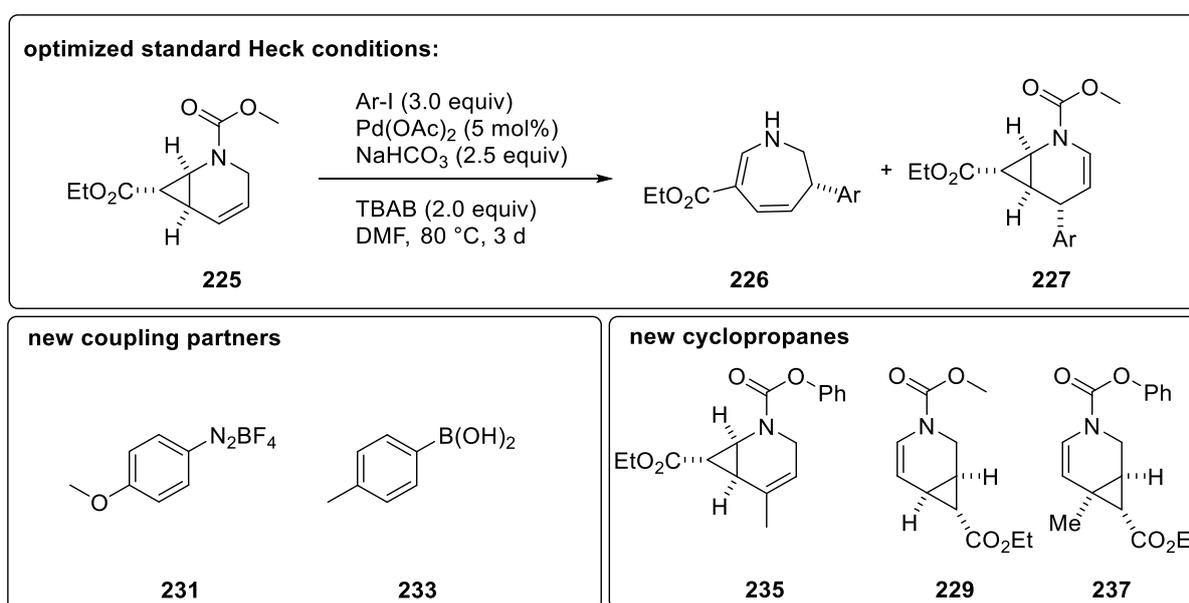
Schema 5: Optimierungsstrategien bei der Heck-Kupplung gesteuerten Synthese von Azepanen.

Aufgrund mangelnder Erfolge mit neuartigen Reaktionsbedingungen wurde der Fokus auf die Anpassung der Cyclopropane gelenkt. Mit dem Versuch die Regioselektivität der Carbopalladierung sterisch zu steuern, wurde Cyclopropan **235** synthetisiert, welches eine abstoßende Methylgruppe aufweist. Unglücklicherweise konnte mit diesem Substrat eine Reaktion nur unter harschen Bedingungen hervorgerufen werden, welche dann zu Zerfallsprodukten führte. Die Cyclopropane **229** und **237,** welche nur eine Arylierung der C2-Position erlauben um einen vollständigen Katalysezyklus durchlaufen zu können zeigen dasselbe Reaktionsverhalten.

4 Experimental Part

4.1 General Information

Solvents and Chemicals

Commercially available chemicals were employed without further purification if not stated otherwise. Reactions with moisture or oxygen sensitive reagents were carried out in flame-dried glass ware under an atmosphere of predried nitrogen. Hexanes (40-60 °C), EtOAc and DCM were distilled before use for column chromatography. Anhydrous solvents were prepared according to standard procedures. Reported yields are referred to isolated compounds if not stated otherwise.

Thin Layer Chromatography (TLC)

TLC was performed on alumina plates coated with silica gel (Merck silica gel 60 F_{254}, d = 0.2 mm). Visualization was accomplished by irradiation with UV-light (λ = 254 nm) or staining with suitable reagents (potassium permanganate, vanillin/sulfuric acid, Seebach's stain).

Column Chromatography

(Flash-) Column chromatography was performed using Merck Geduran 60 (0.063–0.200 mm) or Merck flash silica gel 60 (0.040–0.063 mm).

NMR Spectroscopy

All NMR spectra were measured using a Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz, T = 300 K) or a Bruker Avance III HD 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 101 MHz, T = 300 K). The chemical shifts are reported in δ [ppm] relative to an internal standard, represented by the solvent residual peak, while the coupling constants J are given in Hertz [Hz]. All spectra were analyzed by first order. Abbreviations used for signal multiplicities: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, dq = doublet of quartets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, tdd = triplet of doublet of doublets, ddp = doublet of doublet of pentets, dddd = doublet of doublet of doublet of doublets, dddt = doublet of doublet of doublet of triplets.

Mass Spectrometry

Mass spectrometry was performed by the Central Analytical Department of the University of Regensburg using a Jeol AccuTOF GCX, Agilent Q-TOF 6540 UHD, Finnigan MAT SSQ 710 A or a ThermoQuest Finnigan TSQ 7000. High-resolution mass spectra were measured using atmospheric pressure chemical ionization (APCI), electron ionization (EI) or electrospray ionization (ESI) with a quadrupole time-of-flight (Q-TOF) detector.

IR Spectroscopy

FTIR spectroscopy was carried out on an Agilent Technologies Cary 630 FTIR spectrometer. Solid and liquid compounds were measured neatly, and wave numbers are reported in cm^{-1}.

X-Ray Crystallography

X-ray crystallographic analysis was performed by the Central Analytic Department of the University of Regensburg using an Agilent Technologies SuperNova, an Agilent Technologies Gemini R Ultra, an Agilent GV 50 or a Rigaku GV 50 diffractometer. Suitable crystals were mounted on a Lindemann tube oil and kept at a steady temperature of T = 123 K or T = 100 K during data collection. The structures were solved with the SheIXT (Scheldrick 2015) structure solution program using the Intrinsic Phasing solution method and by using Olex2 as the graphical interface.[2,3] The model was refined with SheIXL using Least Squares minimization.[4]

HPLC

HPLC was performed on a Varian 920-LC with a photodiode array (PDA) detector, using a specified chiral stationary phase.

Optical Rotation

The optical rotation was determined on an Anton Paar MCP 500 polarimeter at 589 nm wavelength (sodium-*d*-line) in a 1.0 dm measuring cell.

Melting Point

Measurements of melting point (mp) were carried out on a SRS MPA 100 – Automated melting point system by OptiMelt using a ramp rate of 1 K/min.

Microwave Reactor

Microwave irradiation experiments were carried out using an Anton Paar Monowave 300 reactor.

4.2 Experimental procedures and analytical data

4.2.1 Synthesis of diazo compounds and carbene precursors

Methyl 2-diazo-2-phenylacetate (86)[121]
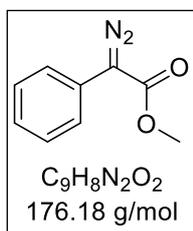
In a flame dried Schlenk-flask tosyl azide (20.52 g, 0.10 mol, 1.4 equiv), and methyl 2-phenylacetate (10.76 g, 0.072 mol, 1 equiv) were dissolved in 90 ml dry acetonitrile. DBU (16.1 mL, 16.44 g, 0.11 mol, 1.5 equiv) was added dropwise within 10 min using a syringe. The solution turned yellow and after 30 min orange. The mixture was stirred for 24 h at 23 °C and the solvent was evaporated under reduced pressure (max. temperature of heating bath 40 °C, blast shield was used). The remaining liquid was dissolved in 150 mL water and extracted with diethyl ether (5x50 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure (max. temperature of heating bath 40 °C, blast shield was used). The crude product was purified by column chromatography (5% EA in PE) to yield 9.68 g (55.4 mmol, 77%) of an orange liquid that forms crystals stored at 0 °C.

$C_9H_8N_2O_2$
176.18 g/mol

^{1}H NMR (400 MHz, CDCl₃) δ 7.52 – 7.45 (m, 2H), 7.42 – 7.35 (m, 2H), 7.22 – 7.15 (m, 1H), 3.87 (s, 3H).

Methyl 2-diazo-2-(3-methoxyphenyl)acetate (190)[122]
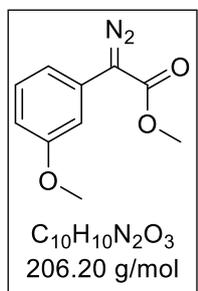
In a flame dried Schlenk-flask tosyl azide (7.70 g, 0.037 mol, 1.4 equiv), and methyl 2-(3-methoxyphenyl)acetate (5.0 g, 0.028 mol, 1.0 equiv) were dissolved in 35 ml dry acetonitrile. DBU (6.22 mL, 6.35 g, 0.042 mol, 1.5 equiv) was added dropwise within 10 min using a syringe. The solution turned yellow and after 30 min orange. The mixture was stirred for 24 h at 25 °C and the solvent was evaporated (max. temperature of heating bath 40 °C, blast shield was used). The remaining liquid was dissolved in 150 mL water and extracted with diethyl ether (5x50 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure (max. temperature of heating bath 40 °C, blast shield was used). Yield: 5.69 g, 0.0276 mol, 99%.

$C_{10}H_{10}N_2O_3$
206.20 g/mol

^{1}H NMR (300 MHz, CDCl₃) δ 7.29 (t, J = 8.1 Hz, 1H), 7.16 (dd, J = 2.5, 1.8 Hz, 1H), 6.98 (ddd, J = 7.9, 1.8, 0.9 Hz, 1H), 6.73 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H).

1-diazo-1-(3-methoxyphenyl)propan-2-one (188)
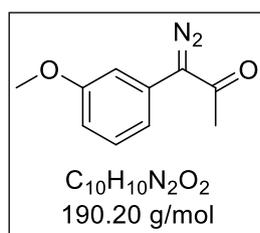
1-(3-methoxyphenyl)propan-2-one (1.1 g, 6.7 mmol, 1.0 equiv) was dissolved together with TsN$_3$ (1.23 mL, 8.04 mmol, 1.2 equiv) in MeCN (10 mL) and cooled to 0 °C. DBU (1.63 mL, 10.72 mmol, 1.6 equiv) was added dropwise within 10 min. The solution was stirred 16 h while it was allowed to warm up to 25 °C. NaH$_4$Cl sat. (25 mL) was added and the mixture was extracted with DCM (3x30 mL). The combined organic phases were washed with brine (30 mL), dried over Na$_2$SO$_4$ and filtered. The solvent was evaporated under reduced pressure to give the crude product which was purified by column chromatography (15% EA in PE). Yield: 1.16 g (6.1 mmol, 91%).

C$_{10}$H$_{10}$N$_2$O$_2$
190.20 g/mol

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31 (t, J = 8.1 Hz, 1H), 7.16 (s, 1H), 7.00 (ddd, J = 7.8, 1.8, 0.9 Hz, 1H), 6.80 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 3.82 (s, 3H), 2.37 (s, 3H).

Ethyl 2-diazoacetate (EX1)
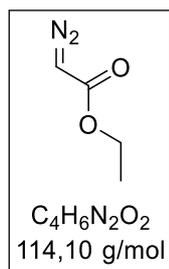
In a 250 mL Schlenk-flask equipped with a heavy stir bar, ethyl glycinate hydrochloride (13.96 g, 0.1 mol, 1 equiv) was dissolved in 25 mL water. DCM (60 mL) was added, and the solution was cooled to 5 °C by adding small amounts of dry ice to a bath of acetone. Ice cold solution of NaNO$_2$ (8.3 g, 0.12 mol, 1.2 equiv) in water (25 mL) was added by a dropping funnel. The mixture was cooled to -20 °C by adding more dry ice to the acetone cooling bath and a solution of sulfuric acid (9.5 g solution with 5 wt%) was added within 3 min. After 10 min the reaction was complete and the ice that was building up in the flask was allowed to melt. Afterwards the mixture was transferred to an extraction funnel and the DCM layer was run into 100 mL of cold NaHCO$_3$ solution (5.3 g NaHCO$_3$ in 98.3 mL water). The aqueous layer was extracted with DCM (75 mL) and the organic phase was combined with the NaHCO$_3$ solution. The bicarbonate/DCM mixture was shacked for 5 min, till all acid was neutralized (checked with pH-paper). Afterwards the organic layer was separated and dried over Na$_2$SO$_4$. The Na$_2$SO$_4$ was filtrated off and the solvent was removed partially under reduced pressure to yield 59.56 g of a yellow solution with 14 wt% product (8.34 g, 73.1 mmol, 73%) in DCM determined by NMR.

C$_4$H$_6$N$_2$O$_2$
114,10 g/mol

^{1}H NMR (300 MHz, CDCl$_3$) δ 4.73 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H).

(2-Methoxy-2-oxo-1-phenylethyl)dimethylsulfonium bromide (EX2)

$C_{11}H_{15}O_2SBr$
291.20 g/mol
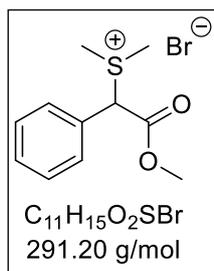
Methyl 2-bromo-2-phenylacetate (500 mg, 2.18 mmol, 1.0 equiv) was dissolved together with Me$_2$S (205 mg, 3.27 mmol, 1.5 equiv) in acetone 5 mL and stirred at 25 °C for 7 d. The solvent was removed under reduced pressure to give the product in 100% yield (635 mg, 2.18 mmol).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.59 – 7.50 (m, 2H), 7.43 – 7.32 (m, 3H), 5.36 (s, 1H), 3.96 (s, 6H), 3.79 (s, 3H).

(2-Ethoxy-2-oxoethyl)dimethylsulfonium bromide (EX3)

$C_6H_{13}O_2SBr$
229.13 g/mol
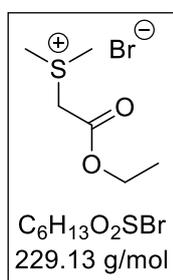
Ethyl 2-bromoacetate (2.22 mL, 20 mmol, 1.0 equiv) was dissolved together with Me$_2$S (1.47 mL, 20 mmol, 1.0 equiv) in acetone (30 mL) and stirred at 25 °C for 3 d. The solid was filtered of and washed with cold acetone to give the product in 24% yield (1.10 g, 4.8 mmol).

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.28 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.50 (s, 6H), 1.32 (t, J = 7.2 Hz, 3H).

4.2.2 Synthesis of 1,2-dihydropydridines

Phenyl pyridine-1(2H)-carboxylate (85) [56]
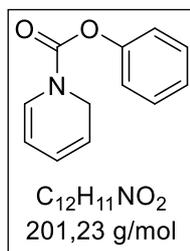
$C_{12}H_{11}NO_2$
201,23 g/mol

In a round bottom flask, pyridine (2.04 mL, 2.00 g, 25 mmol, 1 equiv) and NaBH$_4$ (1.05 g, 28 mmol, 1.1 equiv) were dissolved in 10 mL ethanol at -78 °C. Over 1 h phenyl chloroformate (3.2 mL, 25 mmol, 1 equiv) was added *via* a syringe pump. After addition, the reaction mixture was stirred at 23 °C for 2 h and poured into ice water. The solution was stirred till H$_2$ formation stopped. The aqueous phase was extracted with diethyl ether (3x100 mL) and the combined organic layers were washed with water (3x100 mL) and dried over Na$_2$SO$_4$. After evaporation, the crude product was purified by FC (EA in PE: 5%) to yield 6.28 g product (31.2 mmol, 86%) of a colourless solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.85 (dd, *J* = 36.5, 7.9 Hz, 1H), 5.95 – 5.87 (m, 1H), 5.65 – 5.53 (m, 1H), 5.32 – 5.21 (m, 1H), 4.60 (dd, *J* = 3.8, 2.0 Hz, 1H), 4.46 (dd, *J* = 3.9, 2.0 Hz, 1H).

Phenyl 4-methylpyridine-1(2H)-carboxylate (EX4) [123]

$C_{13}H_{13}NO_2$
215.25 g/mol
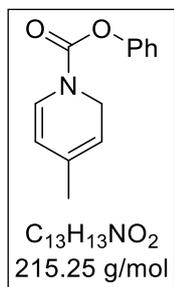
In a round bottom flask, 4-methylpyridine (4.9 mL, 4.7 g, 50 mmol, 1 equiv) and NaBH$_4$ (1.9 g, 50 mmol, 1.0 equiv) were dissolved in 40 mL methanol at -78 °C. Over 1 h phenyl chloroformate (6.25 mL, 50 mmol, 1 equiv) was added *via* a syringe pump. After addition, the reaction mixture was stirred at 23 °C for 2 h and poured into ice water. The solution was stirred till H$_2$ formation stopped. The aqueous phase was extracted with diethyl ether (3x100 mL) and the combined organic layers were washed with water (3x100 mL) and dried over Na$_2$SO$_4$. After evaporation, the crude product was purified by FC (EA in PE: 5%) to yield 5.83 g product (27.1 mmol, 54%) of a colourless liquid. The product should be stored cooled and under N$_2$-atmosphere.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44 – 7.08 (m, 5H), 6.84 (dd, *J* = 20.9, 7.9 Hz, 1H), 5.42 – 5.23 (m, 1H), 5.22 – 5.04 (m, 1H), 4.63 – 4.28 (m, 2H), 1.76 (s, 3H).

Methyl pyridine-1(2H)-carboxylate (228)
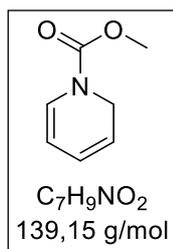
$C_7H_9NO_2$
139,15 g/mol

In a round bottom flask, pyridine (2.04 mL, 2.00 g, 25 mmol, 1 equiv) and NaBH$_4$ (1.05 g, 28 mmol, 1.1 equiv) were dissolved in 10 mL ethanol at -78 °C. Over 1 h methyl chloroformate (1.94 mL, 25 mmol, 1 equiv) was added utilizing a syringe pump. After addition, the reaction mixture was stirred at 23 °C for 2 h and poured into ice water. The solution was stirred till H$_2$ formation stopped. The aqueous phase was extracted with diethyl ether (3x100 mL) and the combined organic layers were washed with water (3x100 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated carefully under reduced pressure as the product is also volatile. The product was stored at 0 °C under nitrogen atmosphere to prevent decomposition. Yield: 1.15 g (8.25 mmol, 33%) of a colourless liquid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.71 (dd, J = 49.2, 7.8 Hz, 1H), 5.93 – 5.71 (m, 1H), 5.64 – 5.39 (m, 1H), 5.14 (dt, J = 13.0, 6.7 Hz, 1H), 4.36 (s, 2H), 3.77 (s, 3H)

4.2.3 Compounds belonging to the synthesis of oxygen bridged azepanes

(±)-7-Methyl 2-phenyl (1S,6S,7R)-7-phenyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (87)

C$_{21}$H$_{19}$NO$_4$
349,39 g/mol
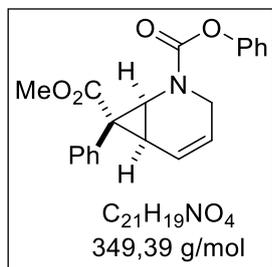
In a 25 mL round bottom flask, phenyl pyridine-1(2H)-carboxylate (**85**) (151 mg, 0.75 mmol, 1.5 equiv) and Rh$_2$(L)$_4$ (0.005 mmol, 0.5 mol%) were brought under inert gas atmosphere and dissolved in 2 mL dry DCM. A solution of methyl 2-diazo-2-phenylacetate (88 mg, 0.5 mmol, 1.0 equiv) in 12 mL DCM was added within 2 h *via* a syringe pump. After complete addition, the reaction mixture was stirred for 30 min and evaporated. The crude product was purified by FC (EA in PE: 10-20% gradient) to yield a colorless oil that solidifies slowly.

Table 19: Catalyst screening on the cyclopropanation of 1,2-dihydropyridine 85.

entry	catalyst	yield [%]	*ee* [%]
1	Rh$_2$(R-2Cl-5Br-TPCP)$_4$	86	15
2	Rh$_2$(S-p-Br-TPCP)$_4$	75	8
3	Rh$_2$(S-TCPPTL)$_4$	85	39
4	Rh$_2$(R-DOSP)$_4$	70	69
5	Rh$_2$(R-TCPTAD)$_4$	100	36
6[a]	Rh$_2$(OAc)$_4$	80	-

a) 10 mmol scale (2.8 g yield)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 – 7.07 (m, 10H), 6.03 (dddt, J = 10.0, 7.3, 4.9, 2.5 Hz, 1H), 5.50 (ddt, J = 19.1, 10.2, 3.4 Hz, 1H), 4.31 (d, J = 8.7 Hz, 1H), 3.87 – 3.48 (m, 4H), 3.13 (ddt, J = 50.6, 18.8, 3.2 Hz, 1H), 2.82 – 2.65 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) (2 Rotamers) δ 172.2, 171.9, 155.6, 154.9, 151.2, 151.1, 132.9, 132.7, 131.8, 131.6, 129.5, 129.4, 128.3, 128.1, 127.6, 127.5, 125.7, 125.6, 124.8, 124.3, 121.8, 121.7, 119.5, 119.0, 52.7, 52.6, 43.3, 42.9, 42.2, 42.1, 41.3, 41.2, 24.7, 24.4.

IR (cm^{-1}): 3049, 2989, 2948, 1707, 1349, 1238, 1200, 1156, 1070, 749, 693.

HRMS (ESI-MS): m/z: MH$^+$ (calc.) = 350.1387, found M$^+$ [C$_{21}$H$_{20}$NO$_4$]$^+$ = 350.1393

R$_f$ (20% EA in PE) = 0.33

mp: 108 °C

$[\alpha]_D^{20}$ = - 267.5 ° (*c* = 1.0, MeOH).

(±)-8-Methyl 6-phenyl (1S,2R,4S,7S,8R)-8-phenyl-3-oxa-6-azatricyclo[5.1.0.0^{2,4}]octane-6,8-dicarboxylate (89)

MeO$_2$C

Ph

C$_{21}$H$_{19}$NO$_5$
365.39 g/mol
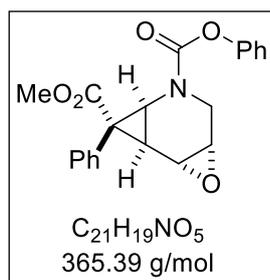
(±)-7-Methyl 2-phenyl 7-phenyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (87) (349.4 mg, 1.0 mmol, 1.0 equiv.) and NaHCO$_3$ (1.26 g, 15.0 mmol, 15 equiv) were dissolved in Acetone:H$_2$O-mixture (1:1, 70 mL) and cooled to 0 °C. H$_3$K$_5$O$_{18}$S$_4$ (3.07 g, 5.0 mmol, 5.0 equiv) was added in portions and the mixture was stirred for 20 h allowing the temperature to rise to 25 °C. The mixture was filtered and extracted with EA (3x50 mL). The combined organic layers were washed with 5 wt% Na$_2$S$_2$O$_5$ solution (50 mL) and brine (50 mL). The organic layer was dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure to give the product as colourless solid. Yield: 295 mg (0.81 mmol, 81%). Upscaling to 3 g (8.57 mmol) of (87) required 2 d reaction time and additional H$_3$K$_5$O$_{18}$S$_4$, NaHCO$_3$ to obtain full conversion. (Yield: 1.35 g, 3.69 mmol, 43%).

^{1}H NMR (400 MHz, CDCl$_3$) (2 Rotamers) δ 7.51 – 7.00 (m, 10H), 4.21 (dd, J = 50.7, 9.3 Hz, 1H), 3.85 – 3.66 (m, 2H), 3.63 (d, J = 12.8 Hz, 3H), 2.97 – 2.79 (m, 2H), 2.36 (ddd, J = 40.2, 15.1, 2.7 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) (2 Rotamers) δ 171.9, 171.6, 155.4, 154.8, 151.0, 150.9, 132.1, 132.1, 131.8, 131.8, 129.5, 129.4, 128.9, 128.7, 128.3, 128.2, 125.8, 125.8, 121.7, 121.6, 53.0, 52.8, 50.3, 50.2, 47.9, 47.8, 41.4, 41.3, 40.4, 40.3, 37.3, 23.8, 23.7.

IR (cm^{-1}): 3056, 2959, 1707, 1595,1498, 1431, 1357, 1249, 1193, 1074.

HRMS (ESI-MS): m/z: MH$^+$ (calc.) = 366.1336, found MH$^+$ [C$_{21}$H$_{20}$NO$_5$]$^+$ = 366.1338.

R$_f$ (25% EA in PE) = 0.23

mp: 145 °C

(±)-4-Methyl 6-phenyl (1S,4S,5R)-4-phenyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4,6-dicarboxylate (90)

MeO$_2$C

Ph

C$_{21}$H$_{19}$NO$_5$
365.39 g/mol
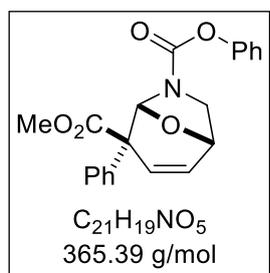
(±)-8-Methyl 6-phenyl 8-phenyl-3-oxa-6-azatricyclo[5.1.0.0^{2,4}]octane-6,8-dicarboxylate (89) (700 mg, 1.92 mmol) was dissolved in EtOAc (100 mL) and Amberlyst 15 (250 mg) was added. The reaction was refluxed for 3.5 h and cooled back to 25 °C. The Amberlyst beads were filtered off and the solvent was evaporated under reduced pressure to give the product as colourless solid. Yield: 654 mg (1.79 mmol, 94%).

¹H NMR (300 MHz, CDCl₃) δ 7.31 (s, 5H), 7.25 – 7.03 (m, 3H), 6.83 – 6.32 (m, 4H), 6.09 (dd, J = 9.9, 2.0 Hz, 1H), 4.87 (t, J = 4.8 Hz, 1H), 3.79 (s, 3H), 3.70 – 3.50 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 172.0, 153.0, 150.3, 137.2, 131.2, 128.9, 128.6, 128.1, 127.4, 127.1, 125.3, 121.3, 89.4, 71.8, 58.1, 52.8, 52.7.

IR (cm⁻¹): 3056, 2952, 2896, 1722, 1495, 1379, 1331, 1241, 1200, 1066, 1036, 943, 865, 753, 690.

HRMS (ESI-MS): m/z: MH⁺ (calc.) = 366.1336, found MH⁺ $[C_{21}H_{20}NO_5]^+$ = 366.1343.

mp: 165 °C

(±)-5-Methyl 7-phenyl (1*R*,2*S*,4*S*,5*R*,6*R*)-5-phenyl-3,9-dioxa-7-azatricyclo[4.2.1.0²,⁴] nonane-5,7-dicarboxylate (108)

$C_{22}H_{21}NO_6$
395.41 g/mol
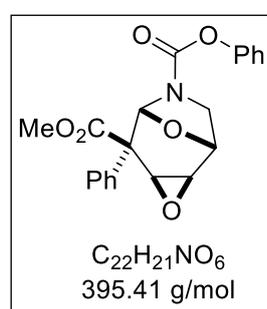
(±)-6-Benzyl 4-methyl 4-phenyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4,6-dicarboxylate (**90**) (100 mg, 0.274 mmol, 1.0 equiv) was dissolved in DCM (5 mL). *m*CPBA (261 mg, 1.10 mmol, 4.0 equiv) was added and the mixture was refluxed for 20 h. DCM (20 mL) was added, and the mixture was washed with 5wt% Na₂S₂O₅ (20 mL), NaHCO₃ (20 mL) and brine (20 mL). The crude product was purified by column chromatography (50% EA in PE) to give the product as colourless solid (R_f = 0.29). Yield: 89.5 mg (0.235 mmol, 86%).

¹H NMR (300 MHz, CDCl₃) δ 7.37 (dd, J = 5.0, 1.9 Hz, 3H), 7.25 – 7.02 (m, 5H), 6.84 – 6.36 (m, 2H), 6.27 – 6.04 (m, 1H), 5.05 – 4.85 (m, 1H), 3.90 (s, 3H), 3.87 – 3.72 (m, 2H), 3.64 (d, J = 9.9 Hz, 1H), 3.46 (dd, J = 3.8, 1.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 171.2, 152.6, 150.1, 136.2, 129.0, 128.8, 128.2, 127.6, 125.5, 121.2, 87.6, 70.7, 55.6, 52.9, 52.4, 51.3, 47.9.

IR (cm⁻¹): 3064, 3030, 2956, 1722, 1495, 1302, 1245, 1193, 943, 913, 869, 734.

HRMS (ESI-MS): m/z: MH⁺ (calc.) = 382.1285, found MH⁺ $[C_{21}H_{20}NO_6]^+$ = 382.1289.

mp: 100 °C

(±)-4-Methyl 6-phenyl (1*S*,4*S*,5*R*)-4-phenyl-8-oxa-6-azabicyclo[3.2.1]octane-4,6-dicarboxylate (102)

MeO$_2$C

Ph

C$_{22}$H$_{23}$NO$_5$
381.43 g/mol
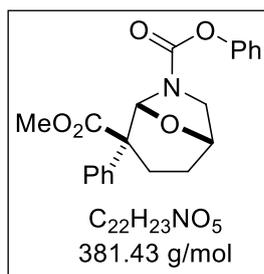
(±)-6-Benzyl 4-methyl 4-phenyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4,6-dicarboxylate (**90**) (200 mg, 0.547 mmol) was dissolved in dry MeOH:DCM solution (3:1) (10 mL) and 10 wt% Pd/C (58 mg, 10 mol%) was added. The mixture was put under H$_2$ atmosphere (1 atm) and stirred for 1 d at room temperature. The solution was filtered through a short celite plug and the solvent was removed under reduced pressure to give the product as colourless solid. Yield: 194 mg (0.527 mmol, 96%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, *J* = 7.4 Hz, 2H), 7.50 – 6.89 (m, 7H), 6.68 – 6.41 (m, 2H), 4.73 (d, *J* = 6.3 Hz, 1H), 3.95 – 3.70 (m,1H), 3.78 (s, 3H), 3.41 (d, *J* = 10.0 Hz, 1H), 2.92 – 2.62 (m, 1H), 2.47 – 2.05 (m, 2H), 1.73 (d, *J* = 14.8 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.6, 152.7, 150.5, 137.1, 129.3, 129.1, 128.4, 127.8, 127.2, 126.9, 125.4, 121.5, 90.4, 74.2, 55.5, 52.6, 49.4, 27.8, 22.9.

IR (cm^{-1}): 3071, 2956, 2989, 1872, 1737, 1490, 1211, 1148, 1040, 891, 690.

HRMS (ESI-MS): m/z: MH$^+$ (calc.) = 368.1492, found MH$^+$ [C$_{21}$H$_{22}$NO$_5$]$^+$ = 368.1499.

mp: 157 °C

4.2.4 Starting materials for the synthesis of α-hydroxy cyclopropanes

Ethyl 6-bromo-1,4-dioxa-8-azaspiro[4.5]decan-8-carboxylate (116)[73–75]

$C_{10}H_{16}BrNO_4$
294,15 g/mol
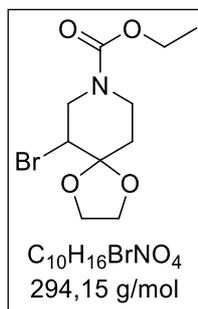
Ethyl 4-oxopiperidin-1-carboxylate (**115**) (14.1 g, 82.5 mmol, 1.0 equiv) was dissolved in dry Et_2O (125 mL) under N_2-atmosphere. At a temperature of 35-40 °C, Br_2 (7.5 mL, 146.5 mmol, 1.78 equiv) was added over a period of 3 h. The solution should always keep a red-brown colour. The mixture was stirred for further 2 h and water free K_2CO_3 (11.7 g, 82.5 mmol, 1.0 equiv) was added afterwards. The solution was stirred until gas evolution stopped. Water (125 mL) was added, and the mixture was extracted with Et_2O (5x150 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (25% EtOAc in PE) to give the pure product in 93% yield (22.7 g, 77.0 mmol).

¹H NMR (300 MHz, CDCl₃) δ 4.28 – 3.90 (m, 8H), 3.77 (dddd, *J* = 13.5, 5.8, 4.4, 1.4 Hz, 1H), 3.56 (bs, 1H), 3.37 (t, *J* = 11.2 Hz, 1H), 2.03 (d, *J* = 13.0 Hz, 1H), 1.73 – 1.57 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 155.1, 106.4, 65.9, 65.8, 61.8, 52.2, 49.0, 41.6, 34.3, 14.7.

Ethyl 4-oxo-3,4-dihydropyridin-1(2H)-carboxylate (118)[73–75]

$C_8H_{11}NO_3$
169.18 g/mol
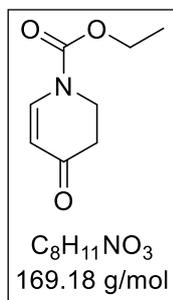
To a solution of ethyl 6-bromo-1,4-dioxa-8-azaspiro[4.5]decan-8-carboxylate (**116**) (22.7 g, 77.0 mmol, 1.0 equiv) in 500 mL DMSO under N_2-athmosphere, DBU (13.1 mL, 87.5 mmol, 1.13 equiv) was added and stirred 12 h at 80 °C. 100 mL water was added afterwards and the mixture was extracted with Et_2O (5x100 mL). The combined organic phases were washed with water (2x50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain 13.15 g (61.6 mmol) of ethyl 1,4-dioxa-8-azaspiro[4.5]dec-6-ene-8-carboxylat in 80% yield. 10.0 g (46.9 mmol) of the crude product was dissolved in MeOH (75 mL) and 3 M HCl solution (5 mL) was added dropwise. The solution was stirred for 30 min at 25 °C. MeOH was removed under reduced pressure and the residue was dissolved in H_2O (100 mL). The mixture was extracted with Et_2O (4x100 mL), and the organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure do give the product in quantitative yields (7.85 g). The product was further purified by vacuum distillation.

^{1}H NMR (400 MHz, CDCl3) δ 7.98 – 7.62 (m, 1H), 5.31 (d, J = 8.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.08 – 3.88 (m, 2H), 2.62 – 2.43 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 193.4, 152.7, 143.5, 107.4, 63.5, 42.5, 35.7, 14.4.

Ethyl 4-hydroxy-3,4-dihydropyridine-1(2H)-carboxylate (123)[75,77–79]

Luche reduction:

$C_8H_{13}NO_3$
171.20 g/mol
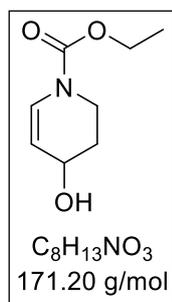
Ethyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (**118**) (3.0 g, 17.5 mmol. 1.0 equiv) and CeCl3•7 H2O (6.57 g, 17.5 mmol, 1.0 equiv) were dissolved in MeOH (25 mL) at 0 °C. Within 15 min fine crushed NaBH4 (0.67 g, 17.5 mmol, 1.0 equiv) was added portionwise. The mixture was stirred for 30 min at 0 °C and quenched with 20 mL H2O. The reaction mixture was extracted with DCM (3x50 mL) and the combined organic phases were dried over Na2SO4. The solvent was evaporated under reduced pressure to yield a colourless oil. Yield: 3.03 g (17.5 mmol, 100%). The product was stored at -18 °C and used without further purification as it is unstable at room temperature.

^{1}H NMR (300 MHz, CDCl3) (2 rotamers) δ 6.92 (dd, J = 31.9, 8.4 Hz, 1H), 5.02 (d, J = 22.0 Hz, 1H), 4.25 – 4.14 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.86 (s, 1H), 3.37 (td, J = 12.8, 12.1, 3.9 Hz, 1H), 2.10 (s, 1H), 1.95 – 1.67 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl3) (2 rotamers) δ 153.7, 153.1, 127.8, 127.4, 107.5, 107.2, 62.2, 60.7, 60.7, 37.7, 37.6, 30.4, 14.5.

CBS-reductions:
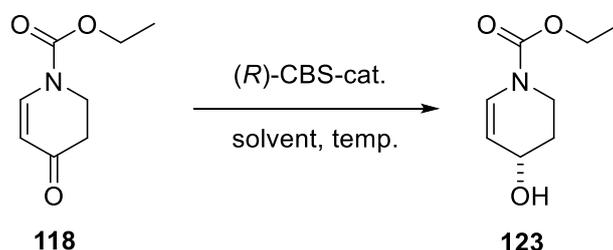
General procedure:[84,86]

In a flame dried Schlenk flask, equipped with a stirring bar and set under N2-atmosphere ethyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (**118**) (50 mg, 0.296 mmol. 1.0 equiv) and CBS-catalyst was dissolved in 1 mL dry solvent. The reducing agent was added and stirred for 5 min. Full conversion was determined by TLC. DCM (5 mL) was added to the reaction mixture and

transferred to a separation funnel. Water (10 mL) was added, and the mixture was extracted with DCM (3x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. HPLC analysis was made without further purification. As the product is decomposing notably until NMR measurements can be taken, yields were not determined during screening stage.

Table 20: CBS-screening: reducing agents.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3 \cdot THF$	1.0	THF	-78, 0, 25, 50, 100	10%	No reaction
2	$BH_3 \cdot Me_2S$	1.0	THF	-78	10%	Clean reaction (TLC) Conversion: 70% ee = 13%
3	Catecholborane	1.0	THF	-78	10%	Side products ee = 0%

Table 21: CBS-screening: temperature.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3 \cdot Me_2S$	1.0	THF	-78	10%	Conversion: 70% ee = 13%
2	$BH_3 \cdot Me_2S$	2.2	THF	-25	10%	Full conversion ee = 15%
3	$BH_3 \cdot Me_2S$	2.2	THF	0	10%	Full conversion ee = 23%
4	$BH_3 \cdot Me_2S$	2.2	THF	25	10%	Side products ee = 23%

Table 22: CBS-screening: solvent.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3 \cdot Me_2S$	2.2	THF	0	10%	ee = 23%
2	$BH_3 \cdot Me_2S$	2.2	toluene	0	10%	ee = 41%
3	$BH_3 \cdot Me_2S$	2.2	DCM	0	10%	decomposition

Table 23: CBS-screening. BH$_3$•Me$_2$S diluted in 1mL toluene, 1 h dropwise addition.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3 \cdot Me_2S$	2.2	toluene	0	10%	ee = 43%

Table 24: CBS-screening: cat. loading.

entry	reducing agent	equiv	solvent	temp. [°C]	cat. loading	result
1	$BH_3•Me_2S$	2.2	toluene	0	10%	ee = 41%
2	$BH_3•Me_2S$	2.2	toluene	0	30%	ee = 57% isolated yield = 81%
3	$BH_3•Me_2S$	2.2	toluene	0	100%	ee = 61%

Table 25:CBS-screening: catalyst.

entry	reducing agent	equiv	solvent	temp. [°C]	catalyst	cat. loading	result
1	$BH_3•Me_2S$	2.2	toluene	0	(*R*)-Me-CBS	30%	ee = 57%
2	$BH_3•Me_2S$	2.2	toluene	0	(*R*)-o-Tolyl-CBS	30%	ee = 17%

Big scale experiment:

In a flame dried Schlenk flask, equipped with a stirring bar and set under N_2-atmosphere ethyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (**118**, 558 mg, 3.33 mmol. 1.0 equiv) and (*R*)-Me-CBS-catalyst in toluene (1.0 mL, 1.0 M, 30 mol%) was dissolved in 20 mL dry toluene. $BH_3•Me_2S$ (0.69 mL, 7.33 mmol, 2.2 equiv) was added dropwise and stirred for 5 min. Full conversion was determined by TLC. DCM (10 mL) was added to the reaction mixture and transferred to a separation funnel. Water (10 mL) was added, and the mixture was extracted with DCM (3x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give the product as colorless oil (494 mg, 2.32 mmol, 81%, ee= 57%).

$[\alpha]_D^{20}$ = - 331 (*c* = 1.0, $CHCl_3$).

Ethyl (*S*)-4-acetoxy-3,4-dihydropyridine-1(2H)-carboxylate (125)
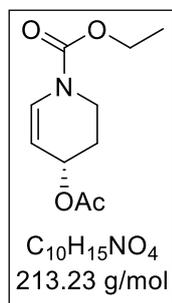
Ethyl (*S*)-4-hydroxy-3,4-dihydropyridine-1(2H)-carboxylate ((**-)-123**, 330 mg, 1.93 mmol, 1.0 equiv) was dissolved in EtOAc (5 mL). NEt_3 (10.1 mL, 38 equiv) were added followed by Ac_2O (2.0 mL, 11 equiv). The mixture was stirred for 20 h at 25 °C and H_2O (10 mL) was added within 20 min. The mixture was extracted with DCM (4x10 mL) and washed with 1 M HCl solution (3x10 mL) and sat. $NaHCO_3$ (2x10 mL). The DCM layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give a yellow liquid. Yield: 399 mg (1.87 mmol, 97%). The product was used without further purification as it decomposes upon column chromatography. Analogously, (±)-**123** (2.86 g, 16.7 mmol) was converted to (±)-**125** (3.47 g, 16.3 mmol, 97%)

$C_{10}H_{15}NO_4$
213.23 g/mol

¹H NMR (400 MHz, CDCl₃) (2 rotamers) δ 7.21 – 6.84 (m, 1H), 5.19 (q, *J* = 4.2 Hz, 1H), 5.03 (d, *J* = 27.4 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.08 – 3.83 (m, 1H), 3.44 – 3.27 (m, 1H), 2.03 (s, 3H), 2.01 – 1.82 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) (2 rotamers) δ 170.4, 170.4, 153.4, 152.9, 129.5, 129.1, 103.2, 102.8, 63.8, 62.2, 38.0, 37.7, 27.3, 21.2, 21.2, 14.5.

IR (cm⁻¹): 2982, 2937, 1711, 1648, 1416, 1372, 1342, 1234, 1118, 1047, 999, 951, 876, 768.

HRMS (EI-MS): m/z: M⁻ (kalk.) = 213.09956, found M⁻ $[C_{10}H_{15}NO_4]^-$ = 213.09897

R$_f$ (15% EA in PE) = 0.28

$[\alpha]_D^{20}$ = - 410.0 ° (*c* = 1.0, CHCl₃).

(±)-Ethyl 3-bromo-4-oxopiperidine-1-carboxylate (169)
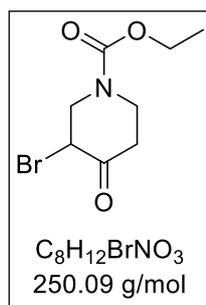
Ethyl 4-oxopiperidine-1-carboxylate (**115**) (2.0 g, 11.6 mmol, 1.0 equiv) was dissolved in a mixture of $CHCl_3$ and EtOAc (1:1) (23 mL) and heated to reflux. $CuBr_2$ (5.2 g, 23.4 mmol, 2.0 equiv) were added while N_2 was bubbled through the solution using a needle. The reaction mixture was stirred for 45 min until the solution lost its green colour and all the dark solid dissolved. The reaction was stopped and cooled down to 25 °C before it was filtered, and the solvent was evaporated. EtOAc (50 mL) was added, and the organic layer was washed with H_2O, $NaHCO_3$ and Brine (30 mL each). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Column chromatography (25%EA in PE) yielded the product in 96% (2.78 g, 11.13 mmol).

$C_8H_{12}BrNO_3$
250.09 g/mol

^{1}H NMR (300 MHz, CDCl$_3$) δ 4.32 (s, 1H), 4.21 – 4.01 (m, 3H), 3.98 – 3.60 (m, 3H), 3.08 – 2.82 (m, 1H), 2.41 (dtd, J = 14.8, 6.2, 1.3 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 199.4, 155.1, 62.3, 50.7, 49.8, 43.4, 38.5, 14.6.

IR (cm^{-1}): 2982, 2933, 1689, 1424, 1301, 1271, 1226, 1103, 1029, 768.

HRMS (EI): m/z M$^+$ (calc.) = 248.99877, found M$^+$ [$C_8H_{12}BrNO_3$]$^+$ = 248.99951

R$_f$ (25% EA in PE) = 0.31

(±)-Ethyl (3R,4S)-3-bromo-4-hydroxypiperidine-1-carboxylate (170)

Method 1:
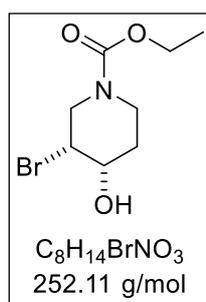
(±)-Ethyl 3-bromo-4-oxopiperidine-1-carboxylate (**169**) (300 mg, 1.2 mmol, 1.0 equiv) was dissolved in MeOH (3 mL) and $NaBH_4$ (42 mg, 1.2 mmol, 1.0 equiv) was added. The reaction was stirred for 1 h at 0 °C bevor it was quenched with sat. NH_4Cl. Water (20 mL) was added, and the mixture was extracted with Et_2O (3x20 mL). The product was obtained as single diastereomer in a yield of 96% (290 mg, 1.15 mmol).

$C_8H_{14}BrNO_3$
252.11 g/mol

^{1}H NMR (300 MHz, CDCl$_3$) δ 4.20 (td, J = 6.3, 2.6 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.93 – 3.84 (m, 1H), 3.82 – 3.59 (m, 2H), 3.46 (t, J = 5.4 Hz, 2H), 2.56 (s, 1H), 1.99 – 1.83 (m, 1H), 1.80 – 1.64 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 155.3, 68.1, 61.7, 55.2, 46.4, 39.1, 31.3, 14.6.

IR (cm^{-1}): 3414, 2982, 2933, 1674, 1431, 1230, 1118, 1036, 969, 910, 727.

HRMS (EI): m/z M$^+$ (calc.) = 251.01516, found M$^+$ [$C_8H_{14}BrNO_3$]$^+$ = 251.01510

R$_f$ (50% EA in PE) = 0.50

Method 2:[103]

(±)-Ethyl 3-bromo-4-oxopiperidine-1-carboxylate (**169**) (250 mg, 1.0 mmol, 1.0 equiv), RuCl(p-cym)[R,R]-Ts-DPEN (1 mol%, 7 mg), TBAB (30 mol%, 97 mg) and HCO_2Na (340 mg, 5.0 mmol, 5 equiv) were dissolved in H_2O/DCM (1:1) (1.5 mL) and stirred. After the respective time was over the water (20 mL) was added and it was extracted with DCM (3x20 mL). After column chromatography (50% EA in PE) the product was obtained as colourless oil.

*Table 26: Dynamic kinetic resolution for the synthesis of **170**. Screening.*

entry	temp. [°C]	time	yield	ee
1	25	5 h	61%	66%
2	25	18h	61%	76%
3	25	3 d	61%	76%
4	0	18 h	66%	82%

(±)-Ethyl (3*R*,4*S*)-4-acetoxy-3-bromopiperidine-1-carboxylate (171)

C$_{10}$H$_{16}$BrNO$_4$
294.15 g/mol
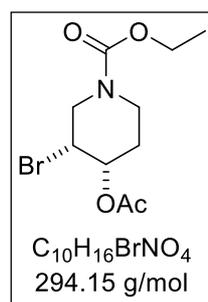
(±)-Ethyl (3*R*,4*S*)-3-bromo-4-hydroxypiperidine-1-carboxylate (**170**) (135 mg, 0.536 mmol) was dissolved in EtOAc (2 mL) and NEt_3 (38 equiv, 2.8 mL) and Ac_2O (0.52 mL, 11 equiv) were added. The reaction was stirred for 24 h at 25 °C and diluted with 10 mL H_2O which was added within 20 min. The aqueous solution was extracted with DCM (4x 20 mL). The combined organic layers were washed with 1M HCl (3x20 mL), and $NaHCO_3$ (2x20 mL). After drying over Na_2SO_4 and filtration, the solvent was evaporated under reduced pressure to give the product is yellowish oil in a yield of 95% (149 mg, 0.507 mmol).

^{1}H NMR (300 MHz, CDCl$_3$) δ 4.95 (s, 1H), 4.25 – 4.18 (m, 1H), 4.08 (qt, J = 6.8, 3.1 Hz, 2H), 3.91 – 3.31 (m, 4H), 2.07 (s, 3H), 2.01 – 1.85 (m, 1H), 1.78 – 1.64 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 170.0, 155.3, 70.2, 61.8, 49.0, 47.5, 40.0, 28.1, 21.0, 14.6.

IR (cm^{-1}): 2982, 2937, 1741, 1700, 1431, 1379, 1234, 1115, 1044.

HRMS (ESI): m/z MH$^+$ (calc.) = 294.0335, found MH$^+$ [C$_{10}$H$_{17}$BrNO$_4$]$^+$ = 294.0339

R$_f$ (50% EA in PE) = 0.77

2-Ethyl 7-methyl (1S,5S,6S,7R)-5-acetoxy-7-(3-methoxyphenyl)-2-azabicyclo[4.1.0] heptane -2,7-dicarboxylate (191)
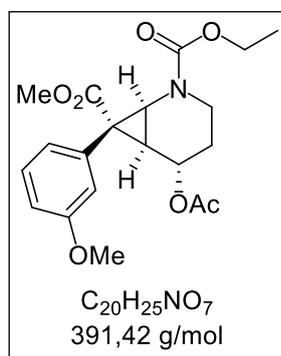
To a solution of ethyl (*S*)-4-acetoxy-3,4-dihydropyridine-1(2H)-carboxylate ((-)-**125**, 265 mg, 1.24 mmol, 1.0 equiv) and Rh$_2$OAc$_4$ (3 mg, 0.5 mol%) in dry DCM (2 mL), methyl 2-diazo-2-(3-methoxyphenyl)acetate (**190**, 308 mg, 1.49 mmol, 1.2 equiv) dissolved in dry DCM (12 mL) was added at 25 °C in a period of 16 h using a syringe pump. The mixture was stirred for 1 h additionally before the solvent was removed under reduced pressure. The residue was purified by column chromatography (20% EA in PE). 416 mg (1.14 mmol, 92%) of the product was isolated as colorless solid. Recrystallization with an ee enhancement from 57% to 93% was achieved by addition of small amounts of MeOH and sonication. The obtained solid product is a racemic crystal while the above solution contains the enantioenriched product (262 mg, 54%). Analogously, (±)-**125** (2.34 g, 10.97 mmol) was converted to (±)-**191** (4.03 g, 10.31 mmol, 94%).

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.28 – 7.20 (m, 1H), 6.97 – 6.72 (m, 3H), 5.24 – 5.08 (m, 1H), 4.27 (dq, *J* = 29.3, 7.1 Hz, 2H), 3.86 – 3.79 (m, 1H), 3.76 (d, *J* = 2.2 Hz, 3H), 3.60 (d, *J* = 6.4 Hz, 3H), 3.09 (m, 2H), 2.39 (ddt, *J* = 17.9, 9.2, 1.4 Hz, 1H), 2.10 (s, 3H), 1.49 – 1.40 (m, 1H), 1.33 (dt, *J* = 24.7, 7.1 Hz, 3H), 0.83 (ddp, *J* = 11.6, 7.7, 3.9 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) (2 rotamers) δ 172.8, 172.6, 170.2, 159.8, 156.9, 156.6, 133.4, 133.2, 129.7, 129.5, 123.9, 123.7, 116.7, 113.8, 64.8, 64.7, 62.0, 61.9, 55.1, 52.9, 41.5, 41.4, 37.4, 37.0, 34.3, 34.0, 28.7, 28.7, 27.3, 27.1, 21.3, 14.8, 14.7.

IR (cm^{-1}): 2956, 2840, 1700, 1603, 1465, 1423, 1379, 1338, 1223, 1156, 1107, 1032, 906, 760, 704.

HRMS (ESI): m/z MH$^+$ (kalk.) = 392.1704, found MH$^+$ [C$_{20}$H$_{26}$NO$_7$]$^+$ = 392.1710

R$_f$ (20% EA in PE) = 0.16

mp: 120 – 121 °C

$[\alpha]_D^{20}$ = - 86.4 ° (*c* = 1.0, CHCl$_3$).

2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-hydroxy-7-(3-methoxyphenyl)-2-azabicyclo [4.1.0]heptane - 2,7-dicarboxylate (EX5)

MeO₂C

C₁₈H₂₃NO₆
349,38 g/mol
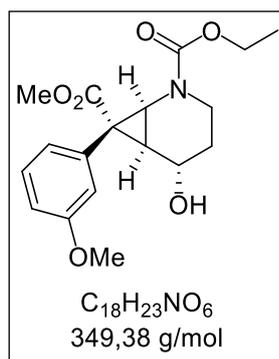
2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-acetoxy-7-(3-methoxyphenyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate ((-)-**191**, 130 mg, 0.33 mmol, 1.0 equiv) and DBU (60 µL, 0.40 mmol, 1.2 equiv) were dissolved in MeOH (2 mL) and stirred for 30 min at 100 °C in a microwave reactor. EtOAc (5mL) was added to the reaction mixture and washed with H₂O (2x5 mL). The aqueous phase was reextracted with EtOAc (3x5 mL) and the combined organic phases were washed with brine (5 mL). The product was isolated as colorless solid (111 mg, 0.32 mol, 97%). Analogously, (±)-**191** (3.29 g, 8.66 mmol) was converted to (±)-**EX5** (3.05 g, 8.66 mmol, quant.).

¹H NMR (300 MHz, CDCl₃) (2 rotamers) δ 7.21 (td, J = 8.1, 4.3 Hz, 1H), 6.94 – 6.60 (m, 3H), 4.25 (dq, J = 29.2, 7.1 Hz, 2H), 4.13 (td, J = 4.2, 3.7, 1.7 Hz, 1H), 3.83 – 3.77 (m, 1H), 3.74 (d, J = 1.3 Hz, 3H), 3.59 (d, J = 8.1 Hz, 3H), 3.20 – 3.03 (m, 2H), 2.53 – 2.28 (m, 2H), 1.40 – 1.24 (m, 1H), 1.31 (dt, J = 24.8, 7.1 Hz, 3H), 0.76 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) (2 rotamers) δ 173.1, 173.0, 159.7, 157.1, 16.7, 133.9, 133.7, 129.6, 129.3, 123.9, 123.7, 116.9, 116.7, 113.9, 113.4, 61.9, 61.8, 61.7, 55.1, 52.8, 41.9, 41.7, 36.9, 36.6, 34.5, 34.2, 31.5, 31.4, 29.9, 29.8, 14.8, 14.7.

IR (cm⁻¹): 3437, 2952, 1685, 1603, 1424, 1342, 1241, 1156, 1107, 1047, 910, 772, 726.

HRMS (ESI): m/z: MH⁺ (calc.) = 350.1598, found MH⁺ [C₁₈H₂₄NO₆]⁺ = 350.1606

R_f (20% EA in PE) = 0.09

mp: 146-148 °C

$[\alpha]_D^{20}$ = - 136.3 ° (c = 1.0, CHCl₃).

2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-7-(3-methoxyphenyl)-5-((methylsulfonyl)oxy)-2-azabicyclo-[4.1.0] heptane-2,7-dicarboxylate (192)

MeO₂C, H
O, O
N
H
ŌMs
OMe

$C_{19}H_{25}NO_8S$
427,47 g/mol
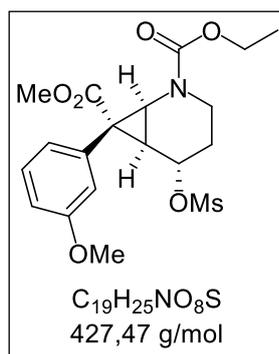
2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-hydroxy-7-(3-methoxyphenyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate ((-)-**EX5**, 99 mg, 0.28 mmol, 1.0 equiv) was dissolved in DCM (5 mL) and cooled to 0 °C. NEt₃ (158 μL, 1.12 mmol, 4.0 equiv) and MsCl (43 μL, 0.56 mmol, 2.0 equiv) were added and stirred for 20 h while slowly warming up to 25 °C. The mixture was washed with 1 M HCl-solution (5 mL), 2 M NaOH-solution (2x5 mL) and brine (5 mL), to give the product as colorless solid (120 mg, quant). Analogously, (±)-**EX5** (2.91 g, 8.33 mmol) was converted to (±)-**192** (3.47 g, 8.12 mmol, 96%) with 2.0 equiv. NEt₃ and 1.2 equiv. MsCl.

¹H NMR (400 MHz, CDCl₃) (2 rotamers) δ 7.38 – 7.13 (m, 1H), 6.92 – 6.60 (m, 3H), 5.26 – 5.03 (m, 1H), 4.27 (dq, *J* = 38.1, 7.1 Hz, 2H), 3.86 (d, *J* = 9.1 Hz, 1H), 3.75 (d, *J* = 2.9 Hz, 3H), 3.61 (d, *J* = 8.7 Hz, 3H), 3.25 – 3.05 (m, 2H), 3.09 (d, *J* = 3.2 Hz, 3H), 2.61 (ddt, *J* = 12.1, 9.1, 1.5 Hz, 1H), 1.65 (dt, *J* = 13.5, 4.2 Hz, 1H), 1.32 (dt, *J* = 31.9, 7.1 Hz, 3H), 0.88 (ddt, *J* = 15.5, 11.2, 4.3 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) (2 rotamers) δ 172.2, 172.1, 160.0, 156.8, 156.4, 133.0, 132.7, 130.0, 129.7, 123.6, 123.4, 116.6, 116.4, 114.4, 114.0, 72.4, 72.3, 62.1, 62.0, 55.1, 53.0, 41.4, 41.2, 39.0, 39.0, 36.7, 36.4, 34.9, 34.5, 28.6, 28.6, 28.5, 28.4, 14.8, 14.7.

IR (cm⁻¹): 2952, 1700, 1603, 1465, 1424, 1334, 1290, 1245, 1170, 1033, 973, 902, 772, 731.

HRMS (ESI): m/z: MH⁺ (calc.) = 428.1374, found MH⁺ [$C_{19}H_{26}NO_8S$]⁺ = 428.1383

R_f (50% EA in PE) = 0.44

mp: 110 -115 °C

$[\alpha]_D^{20}$ = - 82.8 ° (*c* = 1.0, CHCl₃).

(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-acetoxy-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (126)

MeO₂C, H
O, O
N
Ph
H
ŌAc

$C_{19}H_{23}NO_6$
361.39 g/mol
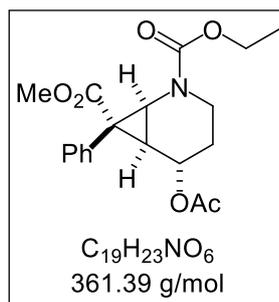
In a Schlenk flask equipped with a septum and a bubbler, (±)-Ethyl 4-acetoxy-3,4-dihydropyridine-1(2H)-carboxylate (**125**) (1.83 g, 8.61 mmol, 1.0 equiv) and Rh₂(OAc)₄ (19 mg, 0.5 mol%) were dissolved in dry DCM (10 mL) at 25 °C. Methyl 2-diazo-2-phenylacetate (**86**) (1.72 g, 10.33 mmol, 1.2 equiv) dissolved in dry DCM (10 mL) was added within 16 h using a syringe pump. After

complete addition the solvent was evaporated under reduced pressure. The product was purified by column chromatography (20% EA in PE) to give the desired product as colourless sticky oil. Yield: 1.98 g (5.48 mmol, 64%).

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.41 – 7.18 (m, 5H), 5.16 (dtd, J = 10.1, 4.2, 1.6 Hz, 1H), 4.42 – 4.12 (m, 2H), 3.83 (dd, J = 9.2, 2.9 Hz, 1H), 3.58 (d, J = 7.8 Hz, 3H), 3.19 – 2.93 (m, 2H), 2.40 (dd, J = 18.2, 9.2 Hz, 1H), 2.09 (s, 3H), 1.46 – 1.24 (m. 1H), 1.32 (dt, J = 25.9, 7.1 Hz, 3H), 0.81 – 0.65 (m, 1H).

^{13}C NMR (75 MHz, CDCl$_3$) (2 rotamers) δ 172.9, 172.7, 170.2, 156.9, 156.6, 132.1, 131.9, 131.7, 131.4, 128.8, 128.6, 127.9, 127.8, 64.7, 64.6, 62.0, 61.8, 52.8, 52.8, 41.6, 41.4, 37.3, 36.9, 34.2, 34.0, 28.6, 27.2, 27.0, 21.3, 14.8, 14.8.

IR (cm^{-1}): 2982, 2881, 1700, 1420, 1379, 1226, 1170, 1111, 1036, 731.

HRMS (ESI): m/z MH$^+$ (calc.) = 362.1598, found MH$^+$ [C$_{19}$H$_{24}$NO$_6$]$^+$ = 362.1601

R$_f$ (25% EA in PE) = 0.25

(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-hydroxy-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (127)

C$_{17}$H$_{21}$NO$_5$
319.36 g/mol
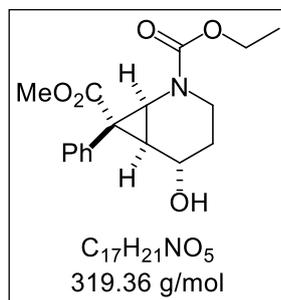
(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-acetoxy-7-phenyl-2-azabicyclo [4.1.0]heptane-2,7-dicarboxylate (**126**) (1.24 g, 3.43 mmol, 1.0 equiv) was dissolved in MeOH (10 mL) and DBU (615 µL, 4.10 mmol, 1.2 equiv) was added. The mixture was heated 30 min to 100 °C using a microwave-reactor. After complete reaction EtOAc (20 mL) was added and the mixture was washed with H$_2$O (2x20 mL). The aqueous layers were combined and back extracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure to give a colourless sticky oil that solidifies upon standing. Yield: 1.10 g (3.43 mmol, 100%).

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.40 – 7.28 (m, 3H), 7.25 – 7.09 (m, 2H), 4.44 – 4.08 (m, 3H), 3.83 (dd, J = 9.2, 2.1 Hz, 1H), 3.59 (d, J = 8.7 Hz, 3H), 3.21 – 2.96 (m, 2H), 2.45 (ddt, J = 13.8, 9.3, 1.5 Hz, 1H), 2.14 (s, 1H), 1.42 – 1.25 (m, 1H), 1.33 (dt, J = 25.5, 7.1 Hz, 3H), 0.81 – 0.62 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) (2 rotamers) δ 173.2, 173.1, 157.1, 156.8, 132.5, 132.4, 131.7, 131.4, 128.7, 128.5, 127.8, 127.7, 62.0, 61.9, 61.8, 52.8, 41.8, 41.7, 36.9, 36.6, 34.5, 34.2, 31.4, 31.4, 29.9, 29.8, 14.8, 14.8.

IR (cm⁻¹): 3440, 2952, 1700, 1420, 1379, 1346, 1245, 1159, 1107, 775, 734.

HRMS (ESI): m/z MH⁺ (calc.) = 320.1492, found MH⁺ [C₁₇H₂₂NO₅]⁺ = 320.1495

R_f (50% EA in PE) = 0.31

mp: 119 °C

(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-((methylsulfonyl)oxy)-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (128)

C$_{18}$H$_{23}$NO$_7$S
397.44 g/mol
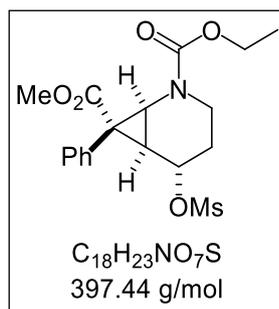
(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-hydroxy-7-phenyl-2-azabicyclo [4.1.0]heptane-2,7-dicarboxylate (**127**) (1.03 g, 3.23 mmol, 1.0 equiv) was dissolved in DCM (30 mL) and cooled to 0 °C. NEt$_3$ (894 µL, 6.46 mmol, 2.0 equiv) and MsCl (300 µL, 3.88 mmol, 1.2 equiv) was added and the mixture was stirred for 1 h at 0 °C. Afterwards 1 M HCl (20 mL) was added. The mixture was washed with 1 M HCl solution, 2 M NaOH solution (20 mL) and Brine (20 mL). The organic layer was dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. The product was crystalized by adding MeOH (2 mL) and sonication to give the product as colourless solid. Yield: 1.23 g (3.10 mmol, 96%).

¹H NMR (400 MHz, CDCl₃) (2 rotamers) δ 7.33 (q, *J* = 6.0, 4.6 Hz, 3H), 7.21 (dd, *J* = 22.4, 6.9 Hz, 2H), 5.14 (dt, *J* = 16.7, 4.0 Hz, 1H), 4.45 – 4.13 (m, 2H), 3.88 (d, *J* = 9.1 Hz, 1H), 3.61 (d, *J* = 9.9 Hz, 3H), 3.21 (ddt, *J* = 20.7, 12.9, 4.5 Hz, 1H), 3.10 (d, *J* = 3.8 Hz, 3H), 3.07 (m, 1H), 2.63 (dd, *J* = 13.0, 9.1 Hz, 1H), 1.64 (d, *J* = 12.2 Hz, 1H), 1.33 (dt, *J* = 33.5, 7.1 Hz, 3H), 0.79 (ddt, *J* = 15.1, 11.3, 3.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) (2 rotamers) δ 172.3, 172.2, 156.8, 156.4, 131.7, 131.5, 131.2, 129.1, 128.9, 128.2, 128.1, 72.3, 72.3, 62.1, 62.0, 53.0, 41.5, 41.3, 39.0, 39.0, 36.6, 36.3, 34.9, 34.6, 28.6, 28.5, 28.5, 28.4, 14.8, 14.7.

IR (cm⁻¹): 2956, 1700, 1420, 1334, 1249, 1170, 1107, 1029, 970, 906, 772, 731.

HRMS (ESI): m/z MH⁺ (calc.) = 398.1268, found MH⁺ [C$_{18}$H$_{24}$NO$_7$S]⁺ = 398.1271

R$_f$ (50% EA in PE) = 0.44

mp: 131 - 138 °C

4.2.6 Cyclopropanes for the Heck-coupling driven synthesis of azepanes

(±)-7-ethyl 2-methyl (1S,6S,7S)-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (225)[116]

(±)-7-ethyl 3-methyl (1R,6R,7R)-3-azabicyclo[4.1.0]hept-4-ene-3,7-dicarboxylate (229)

C₁₁H₁₅NO₄
225.24 g/mol

C₁₁H₁₅NO₄
225.24 g/mol
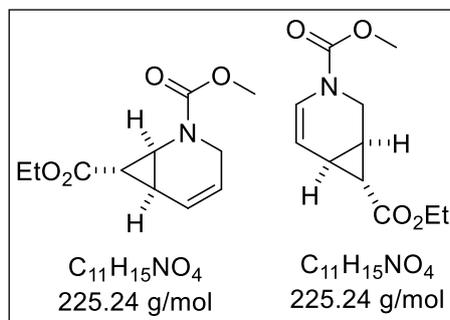
A flame dried Schlenk flask, under nitrogen atmosphere, was charged with [Cu(OTf)]₂ • Benzene (80 mg, 6 mol%) and (1E,1'E)-N,N'-(ethane-1,2-diyl) bis(1-phenyl-methanimine) (114 mg, 0.48 mmol, 10 mol%) and was stirred for 1 h at 25 °C dissolved in DCM (15 mL). Methyl pyridine-(2H)-carboxylate (0.73 g, 525 mmol, 1.0 equiv) dissolved in 2 mL dry DCM was added and the reaction mixture was stirred for 10 min. Within 2 d a solution of ethyl 2-diazoacetate (25.9 g solution (10.4 wt%), 23.6 mmol, 4.5 equiv) was added with the help of a syringe pump. The solvent was evaporated under reduced pressure to yield the crude product. The crude product was purified by FC (EA in PE: 15 - 25%) to yield 538 mg of **225** (2.4 mmol, 46%) and 138 mg of **229** (0.61 mmol, 12%) as yellowish oils.

C₁₁H₁₅NO₄
225.24 g/mol
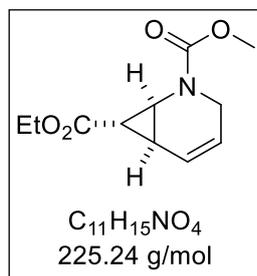
¹H NMR (300 MHz, CDCl₃) (2 rotamers) δ 6.00 (dd, J = 10.0, 4.4 Hz, 1H), 5.85 – 5.51 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.99 – 3.76 (m, 1H), 3.72 (s, 3H), 3.69 – 3.46 (m, 2H), 2.17 – 2.03 (m, 1H), 1.66 – 1.51 (m, 1H), 1.23 (t, J = 6.9 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) (2 rotamers) δ 170.6, 170.5, 157.0, 156.7, 124.9, 123.8, 122.3, 122.0, 60.7, 53.0, 52.8, 40.6, 40.3, 36.7, 36.3, 34.5, 34.2, 21.3, 20.6, 14.2.

C₁₁H₁₅NO₄
225.24 g/mol
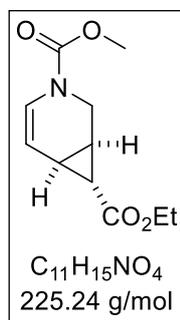
¹H NMR (300 MHz, CDCl₃) (2 rotamers) δ 6.54 (dd, J = 49.6, 8.2 Hz, 1H), 5.26 (s, 1H), 4.19 – 4.00 (m, 3H), 3.73 (s, 3H), 3.34 (dd, J = 29.0, 12.5 Hz, 1H), 2.15 (s, 1H), 1.90 – 1.76 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) (2 rotamers) δ 171.9, 169.7, 124.0, 123.7, 106.7, 106.2, 68.2, 61.0, 60.7, 53.2, 38.5, 38.3, 28.7, 28.3, 26.3, 25.6, 18.4, 14.2.

IR (cm⁻¹): 2982, 3019, 1073, 1446, 1305, 1182, 1044, 749.

HRMS (ESI): m/z MH⁺ (calc.) = 226.1074, found MH⁺ [C₁₁H₁₆NO₄]⁺ = 226.1074

R_f (20% EA in PE) = 0.27

(±)-7-ethyl 2-phenyl (1S,6R,7S)-5-methyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (235)

(±)-7-ethyl 3-phenyl (1S,6R,7S)-6-methyl-3-azabicyclo[4.1.0]hept-4-ene-3,7-dicarboxylate (237)

C$_{17}$H$_{19}$NO$_4$
301.34 g/mol

C$_{17}$H$_{19}$NO$_4$
301.34 g/mol
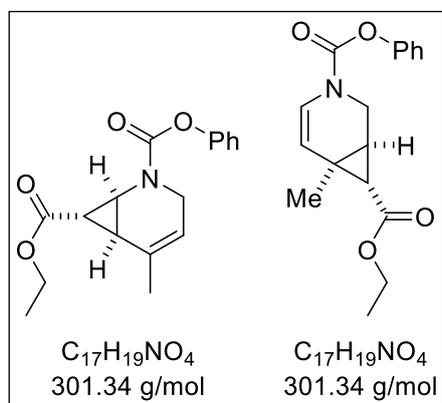
A flame dried Schlenk flask, under nitrogen atmosphere, was charged with [Cu(OTf)]$_2$ • Benzene (38 mg, 3 mol%) and (1E,1'E)-N,N'-(ethane-1,2-diyl) bis(1-phenyl-methanimine) (57 mg, 0.24 mmol, 4.8 mol%) and was stirred for 1 h at 25 °C dissolved in DCM (15 mL). Phenyl 4-methylpyridine-1(2H)-carboxylate (1.08 g, 5 mmol, 1 equiv) dissolved in 2 mL dry DCM was added and the reaction mixture was stirred for 10 min. Within 16 h a solution of ethyl 2-diazoacetate (4.3 mL solution (12 wt%), 0.685 g, 6 mmol, 1.2 equiv) was added with the help of a syringe pump. The solvent was evaporated under reduced pressure to yield the crude product. The crude product was purified by FC (EA in PE: 10%) to yield 542 mg of **235** (1.80 mmol, 36%) and 482 mg of **237** (1.60 mmol, 32%) as colorless solids.

C$_{17}$H$_{19}$NO$_4$
301.34 g/mol
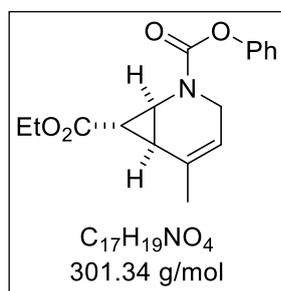
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44 – 7.30 (m, 2H), 7.24 – 7.07 (m, 3H), 5.53 – 5.36 (m, 1H), 4.25 – 4.00 (m, 3H), 3.81 – 3.67 (m, 2H), 2.17 – 2.04 (m, 1H), 1.94 – 1.87 (m, 3H), 1.72 (ddd, J = 10.2, 4.9, 2.7 Hz, 1H), 1.26 (td, J = 7.1, 0.9 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 191.4, 170.8, 130.5, 129.3, 125.4, 121.7, 118.8, 60.9, 41.2, 37.1, 33.9, 25.5, 21.9, 14.3.

HRMS (ESI-MS): m/z: MH$^+$ (kalk.) = 301.1387, found MH$^+$ [C$_{17}$H$_{20}$NO$_4$]$^+$ = 302.1393

R$_f$ (10% EA in PE) = 0.14

mp: 37 °C

C$_{17}$H$_{19}$NO$_4$
301.34 g/mol
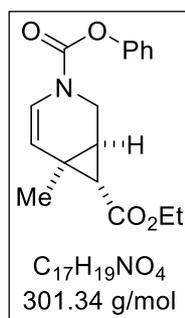
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37 (dd, J = 8.5, 7.2 Hz, 2H), 7.26 – 7.19 (m, 1H), 7.16 – 7.07 (m, 2H), 6.68 (t, J = 7.9 Hz, 1H), 5.36 – 5.13 (m, 1H), 4.34 – 4.20 (m, 1H), 4.16 (tq, J = 7.1, 3.4 Hz, 2H), 3.50 (ddd, J = 68.4, 12.9, 3.2 Hz, 1H), 2.15 (dd, J = 6.4, 2.9 Hz, 1H), 1.95 (dd, J = 5.5, 2.0 Hz, 1H), 1.36 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 170.5, 152.7, 152.3, 150.9, 150.8, 129.4, 125.7, 122.6, 122.3, 121.6, 114.1, 113.8, 60.7, 39.1, 38.5, 33.7, 33.2, 30.7, 30.1, 23.6, 16.7, 14.4.

HRMS (ESI-MS): m/z: MH^+ (kalk.) = 301.1387, found MH^+ $[C_{17}H_{20}NO_4]^+$ = 302.1393

R_f (10% EA in PE) = 0.17

mp: 60 °C

4.2.7 Azepanes towards the synthesis of Meptazinol and derivatives

1-Ethyl 3-methyl (*R*)-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (193)
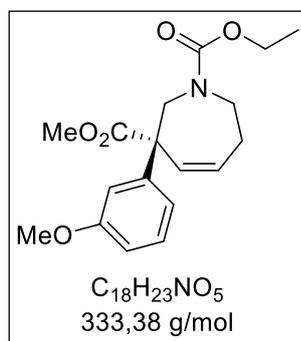
C$_{18}$H$_{23}$NO$_5$
333,38 g/mol

2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-7-(3-methoxyphenyl)-5-((methylsulfonyl)oxy)-2-azabicyclo[4.1.0] heptane-2,7-dicarboxylate ((-)-**192**, 120 mg, 0.28 mmol, 1.0 equiv) and Ph$_3$SiH (94 mg, 0.46 mmol, 1.6 equiv) were dissolved in 2 mL MeCN and heated in a microwave reactor at 120 °C for 90 minutes. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (15% EA in PE) yielding a colorless oil (62 mg, 0.188 mmol, 67%) ee = 88%. Analogously, (±)-**192** (1.66 g, 3.89 mmol) was converted to (±)-**193** (0.87 g, 2.60 mmol, 67%) with 1.1 equiv. PH$_3$SiH.

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.21 (t, *J* = 7.9 Hz, 1H), 6.97 – 6.69 (m, 3H), 6.24 – 5.85 (m, 2H), 4.43 (dd, *J* = 14.9, 1.7 Hz, 1H), 4.11 – 3.85 (m, 2H), 3.77 (d, *J* = 2.8 Hz, 3H), 3.70 (d, *J* = 3.2 Hz, 3H), 3.68 – 3.25 (m, 3H), 2.63 – 2.23 (m, 2H), 1.02 (dt, *J* = 29.7, 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 173.6, 159.5, 156.2, 141.8, 131.4, 131.1, 129.2, 119.6, 113.6, 112.2, 61.1, 59.6, 55.2, 52.6, 50.4, 46.9, 26.0, 14.3.

HRMS (ESI): m/z: MH$^+$ (calc.) = 334.1649, found MH$^+$ [C$_{18}$H$_{24}$NO$_5$]$^+$ = 334.1654

IR (cm^{-1}): 2930, 1730, 1692, 1599, 1465, 1424, 1379, 1349, 1226, 1159, 1114, 947, 768, 731, 697.

R$_f$ (25% EA in PE) = 0.22

$[\alpha]_D^{20}$ = + 5.5 ° (*c* = 1.0, CHCl$_3$).

Ethyl (*R*)-3-(hydroxymethyl)-3 -(3-methoxyphenyl) -2,3,6,7- tetrahydro-1H-azepine-1-carboxylate (200)

C$_{17}$H$_{23}$NO$_4$
305,37 g/mol
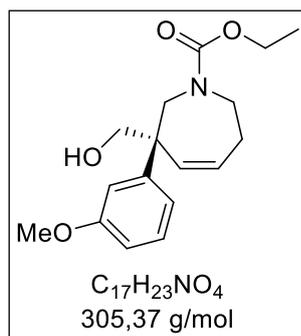
1-Ethyl 3-methyl (*R*)-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate ((+)-**193**, 56 mg, 0.17 mmol, 1.0 equiv) was dissolved in 5 mL dry THF and cooled down to 0 °C. 2M LiBH$_4$ in THF (0.42 mL, 0.84 mmol, 5.0 equiv) was added and the reaction mixture was stirred for 16 hours. It was slowly warmed up to 25°C during that time. 1M HCl was then added to the reaction mixture for

neutralization of LiBH$_4$ and stirred until gas evolution stopped. The solution was transferred to a separating funnel and extracted with EtOAc (3x5 mL) and saturated NaCl-solution (5 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was obtained as a colorless oil (50 mg, 0.164 mmol, 96%). Analogously, (±)-**193** (0.67 g, 2.01 mmol) was converted to (±)-**200** (0.64 g, 2.01 mmol, quant.).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29 – 7.18 (m, 3H), 6.78 (ddd, *J* = 7.8, 2.5, 1.4 Hz, 1H), 5.82 (dt, *J* = 11.9, 5.9 Hz, 1H), 5.44 (dq, *J* = 12.0, 1.5 Hz, 1H), 4.31 – 4.13 (m, 3H), 4.00 – 3.89 (m, 1H), 3.80 (d, *J* = 1.9 Hz, 4H), 3.59 (d, *J* = 12.4 Hz, 1H), 3.37 (dd, *J* = 14.9, 1.1 Hz, 1H), 3.18 (ddd, *J* = 13.3, 7.7, 4.0 Hz, 1H), 2.55 – 2.28 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 159.5, 157.9, 146.1, 135.5, 129.2, 127.6, 119.9, 113.8, 111.8, 65.6, 62.1, 55.2, 53.4, 51.0, 47.7, 27.4, 14.7.

IR (cm^{-1}): 3403, 2933, 2837, 1666, 1580, 1468, 1428, 1252, 1167, 1036, 883, 768, 731.

HRMS (ESI): m/z: MH$^+$ (calc.) = 306.17, found MH$^+$ [C$_{17}$H$_{24}$NO$_4$]$^+$ = 306.1708

R$_f$ (50 % EA in PE) = 0.56

$[\alpha]_D^{20}$ = - 86.5 ° (*c* = 1.0, CHCl$_3$).

Ethyl (R)-3-formyl-3-(3-methoxyphenyl) -2,3,6,7- tetrahydro-1H-azepine-1-carboxylate (203)[124]

303.15 g/mol
C$_{17}$H$_{21}$NO$_4$
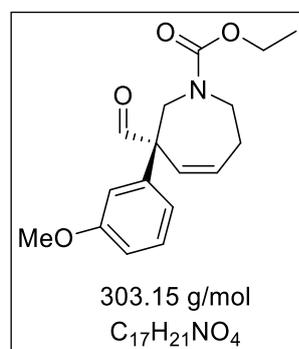
(COCl)$_2$ (34 µL, 0.49 mmol, 3.0 equiv) was dissolved in 1 mL dry DCM and cooled down to -65°C. Then DMSO (55 µL, 0.78 mmol, 6.0 equiv) dissolved in 1 mL dry DCM was added and stirred. After 10 minutes 1-Ethyl 3-methyl (*R*)-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate ((-)-**200**, 40 mg, 0.13 mmol, 1.0 equiv) dissolved in 2 mL dry DCM was added dropwise to the reaction mixture at -65°C, over 20 minutes. After full addition the reaction mixture was stirred further on for 6 hours at -65°C. NEt$_3$ (0.18 mL, 1.3 mmol, 10 equiv) was added and the mixture was slowly warmed up to 25°C in the next 30 minutes. Water (5 mL) was added to the mixture and it was extracted with DCM (3x5 mL). The combined organic layers were washed with 1M HCl solution (5 mL), dried over Na$_2$SO$_4$ and filtered. The solvent was evaporated under reduced pressure. The product was obtained as colorless oil and used without further purification (35 mg, 0.15 mmol, 88%). Analogously, (±)-**200** (0.64 g, 2.01 mmol) was converted to (±)-**203** (0.53 g, 1.76 mmol, 88%).

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 9.48 (d, J = 28.7 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.92 – 6.61 (m, 3H), 6.25 – 6.01 (m, 1H), 5.80 (dd, J = 25.2, 11.7 Hz, 1H), 4.35 – 3.75 (m, 4H), 3.71 (d, J = 2.3 Hz, 3H), 3.59 – 3.15 (m, 2H), 2.48 – 2.25 (m, 2H), 1.02 (dt, J = 30.8, 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) (2 rotamers) δ 197.8, 197.3, 160.0, 156.3, 155.9, 139.0, 138.4, 133.0, 131.8, 129.9, 129.8, 129.2, 127.5, 120.2, 119.9, 114.3, 113.6, 113.1, 112.8, 63.1, 62.8, 61.4, 61.2, 55.2, 49.3, 48.8, 46.7, 46.1, 26.8, 26.8, 14.6, 14.3.

IR (cm^{-1}): 2933, 2837, 2714, 1722, 1688, 1580, 1465, 1423, 1382, 1353, 1289, 1249, 1203, 1167, 947, 906, 768, 731, 701.

HRMS (ESI): m/z: MH$^+$ (calc.) = 304.1543, found MH$^+$ [C$_{17}$H$_{22}$NO$_4$]$^+$ = 304.1545

R$_f$ (15% EA in PE) = 0.30

$[\alpha]_D^{20}$ = - 77.8 ° (c = 1.0, CHCl$_3$).

Ethyl (*S*)-3-(3-methoxyphenyl)-3-vinyl -2,3,6,7- tetrahydro -1H- azepine -1- carboxylate (204)[125–127]

301.39 g/mol
C$_{18}$H$_{23}$NO$_3$
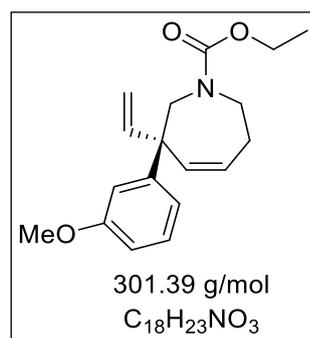
Ph$_3$PMeBr (71 mg, 0.20 mmol, 2.0 equiv) was dissolved in 1 mL dry THF and cooled down to -78 °C. Then 1.6M n-BuLi (140 µL, 0.22 mmol, 2.2 equiv) was added. The solution was stirred at 25 °C for one hour and Ethyl (*R*)-3-formyl-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate ((-)-**203**, 30 mg, 0.10 mmol, 1.0 equiv) dissolved in 3 mL THF was added dropwise to the reaction mixture over 30 minutes. After full addition the reaction mixture was stirred further on for 20 h. The solution was transferred to a separating funnel and brine (5 mL) was added and extracted with EtOAc (3x5 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (15% EA in PE) yielding a colorless oil (24 mg, 0.08 mmol, 80%). Analogously, (±)-**203** (220 mg, 0.73 mmol) was converted to (±)-**204** (123 mg, 0.41 mmol, 56%).

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.23 (t, J = 7.8 Hz, 1H), 7.00 – 6.72 (m, 3H), 6.18 (ddd, J = 28.0, 17.4, 10.7 Hz, 1H), 5.97 (dtd, J = 11.6, 5.8, 1.2 Hz, 1H), 5.68 – 5.52 (m, 1H), 5.29 – 5.07 (m, 2H), 4.20 – 3.82 (m, 4H), 3.78 (d, J = 2.6 Hz, 3H), 3.65 (ddt, J = 15.2, 8.2, 4.0 Hz, 1H), 3.49 – 3.24 (m, 1H), 2.54 – 2.25 (m, 2H), 1.15 (dt, J = 15.9, 7.1 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) (2 rotamers) δ 159.8, 159.5, 156.5, 156.1, 146.5, 146.2, 141.8, 141.5, 136.1, 135.7, 129.6, 129.1, 128.7, 128.4, 119.6, 119.5, 115.4, 115.3, 113.7, 113.3, 111.6, 111.4, 61.2, 61.0, 55.2, 54.7, 54.6, 53.0, 52.9, 47.4, 46.8, 26.5, 14.7, 14.6.

IR (cm⁻¹): 2978, 2933, 2837, 1692, 1580, 1465, 1424, 1379, 1290, 1252, 1204, 1170, 1111, 1029, 995, 917, 880, 768, 731, 701.

HRMS (EI): m/z: M⁺ (calc.) = 301.16725, found M⁺ $[C_{18}H_{23}NO_3]^+$ = 301.16678

R_f (15% EA in PE) = 0.29.

$[\alpha]_D^{20}$ = - 37.5 ° (*c* = 1.0, CHCl₃).

Ethyl (*S*)-3-ethyl-3-(3-methoxyphenyl)azepane-1-carboxylate (205)
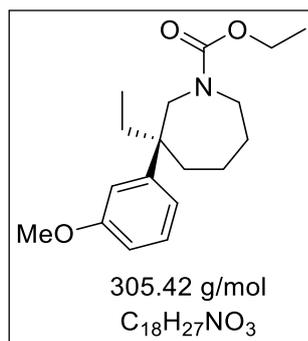
Ethyl (*S*)-3-(3-methoxyphenyl)-3-vinyl-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate ((-)-**204**, 22 mg, 0.073 mmol, 1.0 equiv) was dissolved in 2 mL MeOH. Pd/C 10 wt% (8 mg, 10 mol%) was added to the reaction mixture and H_2 (60 bar) was applied for 16 h. The mixture was filtered over celite and washed thoroughly with Et_2O. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (10% EA in PE) yielding a colorless oil (20 mg, 0.065 mmol, 90%). Analogously, (±)-**204** (98 mg, 0.32 mmol) was converted to (±)-**205** (84 mg, 0.275 mmol, 85%)

305.42 g/mol
$C_{18}H_{27}NO_3$

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.24 (t, *J* = 7.8 Hz, 1H), 6.98 – 6.81 (m, 2H), 6.73 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 4.22 – 3.82 (m, 4H), 3.80 (s, 3H), 3.36 (dd, *J* = 21.7, 14.6 Hz, 1H), 3.10 – 2.85 (m, 1H), 2.13 (td, *J* = 13.0, 12.3, 7.8 Hz, 1H), 1.86 – 1.51 (m, 7H), 1.24 (q, *J* = 6.9 Hz, 3H), 0.56 (q, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) (2 rotamers) δ 159.5, 157.1, 156.6, 147.8, 147.4, 129.0, 119.5, 119.4, 113.8, 113.4, 110.6, 110.0, 61.2, 61.2, 56.6, 56.5, 55.2, 49.7, 48.8, 46.9, 46.6, 35.6, 35.4, 33.8, 32.8, 28.5, 28.2, 22.8, 22.5, 14.8, 14.6, 8.4.

IR (cm^{-1}): 2930, 2878, 1692, 1602, 1469, 1424, 1379, 1252, 1174, 1111, 1051, 772, 705.

HRMS (ESI): m/z: MH$^+$ (calc.) = 306.2064, found MH$^+$ [$C_{18}H_{28}NO_3$]$^+$ = 306.2062

R$_f$ (15% EA in PE) = 0.28

$[\alpha]_D^{20}$ = - 75.1 ° (*c* = 1.0, CHCl$_3$).

(*S*)-3-Ethyl-3-(3-methoxyphenyl)-1-methylazepane (206)
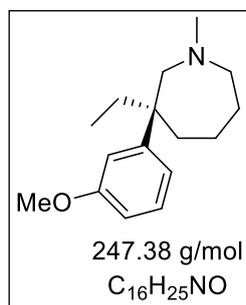
Ethyl (*S*)-3-ethyl-3-(3-methoxyphenyl)azepane-1-carboxylate (**205**) (49 mg, 0.16 mmol, 1.0 equiv) was dissolved in 2 mL dry Et_2O and cooled down to 0 °C. Then LiAlH$_4$ (30 mg, 0.8 mmol, 5.0 equiv) was added portion wise to the reaction mixture. After full addition the reaction mixture was stirred at 40 °C for 18 h. Remaining LiAlH$_4$ was quenched by the addition of 5 mL Et_2O and dropwise 3 mL 10 wt% NaOH. The reaction mixture was filtered over celite and washed multiple times with Et_2O. The solvent was evaporated under reduced pressure and the crude product was obtained as a colourless oil. Yield: 40 mg (0.16 mmol, 100 %).

247.38 g/mol
$C_{16}H_{25}NO$

¹H NMR (300 MHz, CDCl₃) δ 7.31 – 7.13 (m, 1H), 7.00 – 6.83 (m, 2H), 6.72 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 3.80 (s, 3H), 2.85 (d, *J* = 13.9 Hz, 1H), 2.68 – 2.44 (m, 3H), 2.41 (s, 3H), 2.14 (dd, *J* = 14.4, 7.9 Hz, 1H), 1.83 – 1.48 (m, 7H), 0.59 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 159.4, 149.3, 128.9, 119.4, 113.7, 109.7, 68.9, 61.0, 55.1, 49.5, 45.4, 38.0, 34.8, 31.0, 22.4, 8.6.

IR (cm⁻¹): 2930, 2848, 2788, 1603, 1454, 1379, 1290, 1252, 1215, 1178, 1122, 1088, 1055, 977, 872, 819, 775, 701.

HRMS (ESI): m/z: MH⁺ (calc.) = 248.2009, found MH⁺ $[C_{16}H_{26}NO]^+$ = 248.2006

R$_f$ (25% EA in PE) = 0.00

Ethyl (*S*)-3-ethyl-3-(3-hydroxyphenyl)azepane-1-carboxylate (207)

291.39 g/mol
$C_{17}H_{25}NO_3$
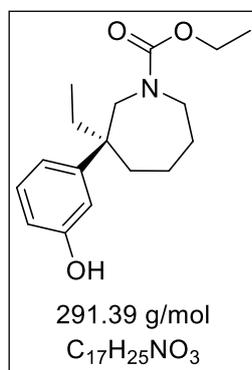
(-)-Ethyl (*S*)-3-ethyl-3-(3-methoxyphenyl)azepane-1-carboxylate ((-)-**205**, 10 mg, 0.033 mmol, 1.0 equiv) was dissolved in dry DCM (1 mL) and cooled to -78 °C. BBr₃ (1 M in DCM) (98 µL, 0.98 mmol, 3.0 equiv) was added. The reaction was stirred 1 h at -78 °C and afterwards warmed up to 25 °C and stirred for 30 min. The reaction mixture was quenched by dropwise addition of sat. NaHCO₃ (2 mL) and extracted with DCM (3x5 mL). The combined organic phases were dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give the product as colorless oil (9 mg, 0.031 mmol, 94%). Analogously, (±)-**205** (80 mg, 0.262 mmol) was converted to (±)-**207** (76 mg, 0.262 mmol, quant.).

¹H NMR (300 MHz, CDCl₃) (2 rotamers) δ 7.17 (t, J = 7.9 Hz, 1H), 6.92 – 6.79 (m, 2H), 6.71 (dd, J = 8.2, 2.3 Hz, 1H), 4.21 – 4.04 (m, 2H), 4.00 – 3.67 (m, 2H), 3.47 (dd, J = 78.7, 14.6 Hz, 1H), 3.13 – 2.92 (m, 1H), 2.27 – 2.03 (m, 1H), 1.82 – 1.53 (m, 7H), 1.24 (q, J = 6.5 Hz, 3H), 0.56 (t, J = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) (2 rotamers) δ 157.4, 156.8, 156.1, 155.9, 148.0, 146.9, 129.1, 118.9, 114.3, 114.1, 112.8, 112.7, 61.6, 61.4, 56.7, 56.2, 49.8, 48.8, 46.8, 46.5, 35.6, 35.3, 34.4, 32.8, 28.4, 27.7, 22.9, 22.4, 14.7, 14.6, 8.4.

IR (cm⁻¹): 3310,2930,2878, 1662, 1584, 1487, 1428, 1260, 1234, 1178, 1111, 1021, 775, 731.

HRMS (EI): m/z: M⁺ (calc.) = 291.18290, found M⁺ $[C_{17}H_{25}NO_3]^+$ = 291.18338

R$_f$ (50% EA in PE) = 0.10

$[\alpha]_D^{20}$ = - 60.1 ° (*c* = 0.9, CHCl₃).

(*S*)-3-(3-Ethyl-1-methylazepan-3-yl)phenol (*S*-(-)-9)

Method 1:

C₁₅H₂₃NO
233.36 g/mol
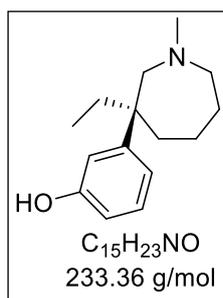
(-)-Ethyl (*S*)-3-ethyl-3-(3-hydroxyphenyl)azepane-1-carboxylate **((-)-207, 9 mg, 0.031 mmol, 1.0 equiv)** was dissolved in 1 mL dry Et₂O and cooled down to 0 °C. Then LiAlH₄ (6 mg, 0.155 mmol, 5.0 equiv) was added to the reaction mixture. After full addition the reaction mixture was stirred at 35 °C for 18 h. Remaining LiAlH₄ was quenched by the addition of 1 mL Et₂O and dropwise 1 mL 10 wt% NaOH. The reaction mixture was filtered over celite and the washed multiple times with Et₂O. The solvent was evaporated under reduced pressure and the crude product obtained as a colorless oil (8 mg, 0.031 mmol, quant). Analogously, (±)-**207** (72 mg, 0.247 mmol) was converted to (±)-**9** (58 mg, 0.247 mmol, quant.)

^{1}H NMR (400 MHz, CDCl₃) δ 7.14 (t, J = 8.0 Hz, 1H), 6.82 (dd, J = 8.1, 1.7 Hz, 2H), 6.68 – 6.59 (m, 1H), 5.02 (s, 1H), 2.97 (d, J = 13.9 Hz, 1H), 2.72 – 2.51 (m, 3H), 2.43 (s, 3H), 2.15 (dd, J = 14.4, 7.4 Hz, 1H), 1.79 – 1.51 (m, 7H), 0.57 (t, J = 7.4 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 156.1, 148.6, 129.1, 118.7, 114.3, 112.7, 68.5, 60.4, 49.0, 45.2, 37.5, 35.1, 29.9, 22.5, 8.5.

IR (cm^{-1}): 3191, 2926, 2855, 2796, 1737, 1584, 1454, 1408, 1338, 1241, 1122, 1066, 913, 872, 782, 731, 705, 667.

HRMS (EI): m/z: M$^+$ (calc.) = 233.17742, found M$^+$ [C₁₅H₂₃NO]$^+$ = 233.17681

R$_f$ (25% EA in PE) = 0.00

$[\alpha]_D^{20}$ = - 14.9 ° (*c* = 0.8, MeOH).

Method 2:[19]

C₁₅H₂₃NO
233.36 g/mol
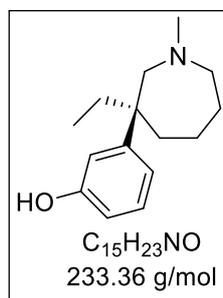
(*S*)-3-Ethyl-3-(3-methoxyphenyl)-1-methylazepane (**206**) (35 mg, 0.14 mmol, 1 equiv) was dissolved in 5 mL 47% HBr in H₂O. The reaction mixture was stirred under reflux for 2 hours. The mixture was cooled to 0 °C and sat. Na₂CO₃ solution was added dropwise until all HBr was quenched. The mixture was transferred to a separating funnel and extracted with DCM (3x20 mL). The combined organic phases were dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure, yielding a colourless oil in 90% (29 mg, 0.126 mmol).

(±)-1-Ethyl 3-methyl (*R*)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (129)
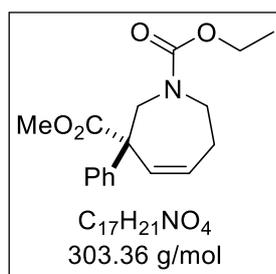
(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-((methylsulfonyl)oxy)-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate ((±)-**128**) (1.0 g, 2.52 mmol, 1.0 equiv) was dissolved in dry MeCN (24 mL) and Et$_3$SiH (1.21 mL, 7.1 mmol, 3.0 equiv) was added. The mixture was heated to 120 °C for 1 h using a microwave-reactor. The reaction was quenched with sat. NaHCO$_3$ solution (20 mL) and extracted with Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. The product was further purified by column chromatography (20% EA in PE) to give the product as colourless oil. Yield: 655 mg (2.16 mmol, 86%).

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.35 – 7.18 (m, 5H), 6.20 – 5.87 (m, 2H), 4.61 – 4.35 (m, 1H), 4.05 – 3.77 (m, 2H), 3.71 (s, 3H), 3.69 – 3.26 (m, 3H), 2.65 – 2.24 (m, 2H), 1.00 (dt, *J* = 33.0, 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) (2 rotamers) δ 173.7, 173.6, 172.1, 156.1, 140.2, 132.2, 131.4, 131.1, 130.7, 128.6, 128.3, 127.3, 127.2, 61.1, 61.0, 59.7, 59.1, 52.5, 52.3, 50.4, 50.0, 47.0, 46.2, 26.0, 25.9, 14.7, 14.3.

IR (cm^{-1}): 3027, 2982, 1730, 1696, 1424, 1379, 1260, 1230, 1178, 1115, 1023, 768.

HRMS (ESI): m/z MH$^+$ (calc.) = 304.1543, found MH$^+$ [C$_{17}$H$_{22}$NO$_4$]$^+$ = 304.1549

R$_f$ (20% EA in PE) = 0.21

(±)-1-Ethyl 3-methyl (3*R*)-2-methoxy-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (180)
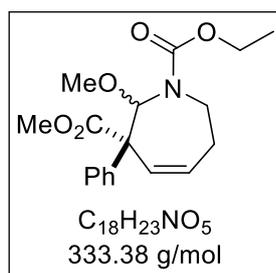
(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-((methylsulfonyl)oxy)-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate ((±)-**128**) (100 mg, 0.28 mmol, 1.0 equiv) was dissolved in dry MeOH (2 mL) and DBU (50 μL, 40 mg, 0.34 mmol, 1.2 equiv) was added. The mixture was heated to 100 °C for 1.5 h using a microwave-reactor. EtOAc (10 mL) was added, and the mixture was washed with water (2x20 mL) and reextracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (10 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure. The product was further purified by column chromatography (15% EA in PE) to give clean product as colourless oil in a diastereomeric ratio of 1:1.1. Yield: 61 mg (0.19 mmol, 68%).

¹H NMR (400 MHz, CDCl₃) (2 diastereomers) δ 7.52 (ddd, *J* = 15.4, 6.9, 1.7 Hz, 2H), 7.30 – 7.18 (m, 3H), 6.64 (s, 0.5H), 6.49 – 6.31 (m, 1.5H), 6.30 – 6.13 (m, 1H), 4.10 – 3.93 (m, 2H), 3.69 (d, *J* = 3.2 Hz, 3H), 3.45 – 3.35 (m, 1.5H), 3.40 (d, *J* = 15.1 Hz, 3H), 3.24 – 3.14 (m, 0.5H), 2.51 – 2.34 (m, 1H), 2.23 – 1.99 (m, 1H), 1.15 (dt, *J* = 63.2, 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) (2 diastereomers) δ 172.9, 172.7, 157.0, 156.1, 137.8, 136.9, 132.2, 131.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.7, 127.6, 127.6, 89.4, 89.1, 62.2, 61.8, 61.7, 61.6, 56.2, 55.9, 52.9, 41.6, 41.2, 27.8, 27.5, 14.6, 14.5.

IR (cm⁻¹): 2982, 2937, 2829, 1733, 1698, 1416, 1375, 1331, 1230, 1115, 1085, 1029, 962, 731.

HRMS (ESI): m/z MNa⁺ (calc.) = 356.1468, found MNa⁺ [C₁₈H₂₃NO₅Na]⁺ = 356.147

R_f (20% EA in PE) = 0.30

(±)-1-Ethyl 3-methyl (3*R*)-2-(2-bromoethoxy)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (181)

Br─CH₂CH₂─O
MeO₂C,,
Ph
C₁₉H₂₄BrNO₅
426.31 g/mol
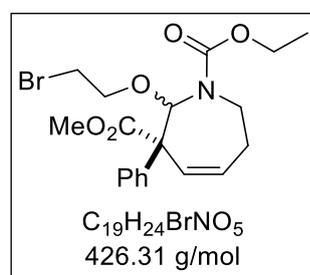
(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-((methylsulfonyl)oxy)-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate **((±)-128)** (100 mg, 0.28 mmol, 1.0 equiv) was dissolved in dry MeCN (2 mL) and DBU (50 µL, 40 mg, 0.34 mmol, 1.2 equiv) was added. 2-Bromoethan-1-ol (60 µL, 106 mg, 0.85 mmol, 3.0 equiv) was added and the mixture was heated to 100 °C for 1 h using a microwave-reactor. After addition of EtOAc (10 mL) the mixture was washed with water (2x20 mL) and reextracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The solvent was evaporated under reduced pressure. The product was further purified by column chromatography (15% EA in PE) to give clean product as colourless oil in a diastereomeric ratio of 1:1.1. Yield: 53 mg (0.125 mmol, 45%).

¹H NMR (400 MHz, CDCl₃) (2 diastereomers) δ 7.51 (ddd, *J* = 13.6, 6.9, 1.6 Hz, 2H), 7.32 – 7.17 (m, 3H), 6.77 (s, 1H), 6.54 (s, 0H), 6.38 (dd, *J* = 32.6, 11.9 Hz, 1H), 6.27 – 6.12 (m, 1H), 4.15 – 3.84 (m, 4H), 3.70 (d, *J* = 2.8 Hz, 3H), 3.61 – 3.39 (m, 3H), 3.20 (dddd, *J* = 62.9, 13.2, 10.2, 2.2 Hz, 1H), 2.67 – 2.45 (m, 1H), 2.25 – 1.99 (m, 1H), 1.16 (dt, *J* = 69.2, 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) (2 diastereomers) δ 172.7, 172.6, 157.1, 155.7, 137.9, 137.1, 132.2, 131.7, 128.4, 128.2, 127.9, 127.8, 127.6, 127.6, 127.5, 127.2, 88.0, 87.7, 68.7, 68.4, 62.0, 61.9, 61.8, 61.6, 53.0, 42.2, 42.0, 30.5, 29.8, 27.6, 27.4, 14.7, 14.5.

IR (cm⁻¹): 2982, 2363, 1733, 1696, 1420, 1375, 1331, 1275, 1230, 1100,1029, 962, 772, 731.

HRMS (ESI): m/z MNa⁺ (calc.) = 448.0730, found MNa⁺ [C₁₉H₂₄NBrO₅Na]⁺ = 448.0726

R$_f$ (15% EA in PE) = 0.26

(±)-(*R*)-(1-methyl-3-phenyl-2,3,6,7-tetrahydro-1H-azepin-3-yl)methanol (EX6)
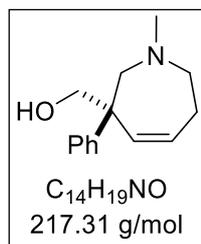
(±)-1-Ethyl 3-methyl (*R*)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (**129**) (310 mg, 1.02 mmol, 1.0 equiv) were dissolved in dry Et$_2$O (20 mL) and cooled to 0 °C. LiAlH$_4$ (388 mg, 10.2 mmol, 10 equiv) was added in portions. After complete addition of LiAlH$_4$ the mixture was refluxed at 40 °C for 20 h. The reaction could cool to room temperature before wet Et$_2$O (4 mL) and 10 wt% NaOH (2 mL) was added slowly till all LiAlH$_4$ was quenched. The mixture was filtered over celite and the cake was washed with Et$_2$O. The solvent was evaporated to yield clean product as colourless oil. Yield: 222 mg (100%, 1.02 mmol).

C$_{14}$H$_{19}$NO
217.31 g/mol

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 (d, *J* = 4.4 Hz, 4H), 7.17 (dt, *J* = 8.6, 4.3 Hz, 1H), 5.92 (ddd, *J* = 11.2, 6.6, 4.0 Hz, 1H), 5.71 (dd, *J* = 12.0, 1.9 Hz, 1H), 5.45 (s, 1H), 4.28 (d, *J* = 10.3 Hz, 1H), 3.84 (d, *J* = 10.3 Hz, 1H), 2.86 (s, 2H), 2.78 (dt, *J* = 11.2, 5.0 Hz, 1H), 2.56 – 2.38 (m, 2H), 2.35 (s, 3H), 2.29 – 2.20 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 144.6, 135.9, 130.4, 128.5, 126.6, 126.4, 72.3, 70.6, 58.7, 49.9, 48.8, 29.5.

IR (cm^{-1}): 3347, 3056, 3023, 2930, 2848, 2803, 2363, 2230, 1446, 1297, 1260, 1055, 910, 798, 727, 697.

HRMS (ESI): m/z MH$^+$ (calc.) = 218.1539, found MH$^+$ [C$_{14}$H$_{20}$NO]$^+$ = 218.1543

R$_f$ (20% EA in PE) = 0.00

(±)-(*R*)-(1-Methyl-3-phenyl-2,3,6,7-tetrahydro-1H-azepin-3-yl)methyl 4-methylbenzene-sulfonate (194)
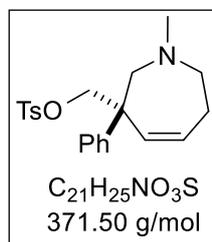
(±)-(*R*)-(1-methyl -3-phenyl-2,3,6,7- tetrahydro-1H-azepin-3-yl)methanol (**EX6**) (118 mg, 0.54 mmol, 1.0 equiv) and NEt$_3$ (150 μL, 110 mg, 1.10 mmol, 2.0 equiv) was dissolved in 2 mL dry DCM and stirred at 0 °C. TsCl (124 mg, 0.65 mmol, 1.2 equiv) was added portionwise. The mixture was allowed to warm up to 25 °C and stirred for 20 h. Water (10 mL) was added, and the mixture was extracted with DCM (3x20 mL). The combined organic layers were washed with 1 M HCl (2x20 mL), NaHCO$_3$ (20 mL) and brine (20 mL) to give the product as colourless oil. Yield 104 mg (0.28 mmol, 53%).

C$_{21}$H$_{25}$NO$_3$S
371.50 g/mol

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74 – 7.62 (m, 2H), 7.32 – 7.16 (m, 7H), 5.91 (dt, J = 11.6, 5.9 Hz, 1H), 5.72 (dt, J = 11.5, 1.4 Hz, 1H), 4.20 (s, 2H), 2.85 (d, J = 12.9 Hz, 1H), 2.66 (d, J = 12.9 Hz, 1H), 2.52 – 2.38 (m, 5H), 2.28 (s, 3H), 2.25 – 1.95 (m, 2H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 144.6, 142.3, 134.7, 132.8, 132.3, 129.7, 128.4, 128.0, 127.0, 126.7, 75.3, 64.9, 57.2, 49.6, 48.6, 28.7, 21.7.

IR (cm^{-1}): 3414, 3027, 2922, 2848, 2803, 1599, 1495, 1450, 1357, 1174, 1122, 954, 813, 764.

HRMS (ESI): m/z MH$^+$ (calc.) = 372.1628, found MH$^+$ [C$_{21}$H$_{26}$NO$_3$S]$^+$ = 372.1635

R$_f$ (50% EA in PE) = 0.17

1-Methyl-6-phenyl-1-azabicyclo[4.1.1]oct-4-en-1-ium-4-methylbenzenesulfonate (195)

C$_{14}$H$_{18}$N$^+$C$_7$H$_7$O$_3$S$^-$
200.30 + 171.19 g/mol
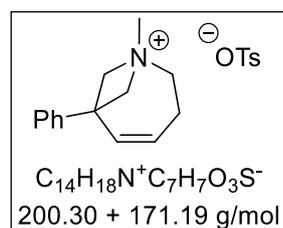
(±)-(R)-(1-Methyl-3-phenyl-2,3,6,7-tetrahydro-1H-azepin-3-yl)methyl 4-methylbenzenesulfonate (**194**) (60 mg, 0.16 mmol) was dissolved in CHCl$_3$ and stirred for 7 days. The solvent was removed under reduced pressure do give the product as colourless oil in quantitative yields. The starting material also rearranges slowly under neat conditions.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, J = 7.9 Hz, 2H), 7.34 – 7.24 (m, 3H), 7.11 (d, J = 7.8 Hz, 2H), 6.93 (d, J = 7.0 Hz, 2H), 5.82 (s, 2H), 4.91 – 4.67 (m, 2H), 4.61 – 4.40 (m, 2H), 3.89 (t, J = 6.5 Hz, 2H), 3.42 (s, 3H), 2.96 (dt, J = 9.5, 4.8 Hz, 2H), 2.31 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 143.7, 142.2, 139.4, 136.6, 129.2, 128.7, 127.6, 126.8, 125.8, 124.7, 74.4, 62.1, 55.8, 43.0, 29.7, 25.0, 21.3.

IR (cm^{-1}): 3444, 3030, 2922, 2855, 1454, 1189, 1118, 1033, 910, 836, 731.

HRMS (ESI): m/z M$^+$ (calc.) = 200.1434, found M$^+$ [C$_{14}$H$_{18}$N]$^+$ = 200.1433

R$_f$ (20% EA in PE) = 0.00

(±)-4-Ethyl 2-methyl (2R)-2-phenyl-8-oxa-4-azabicyclo[5.1.0]octane-2,4-dicarboxylate (208)

C$_{17}$H$_{21}$NO$_5$
319.36 g/mol
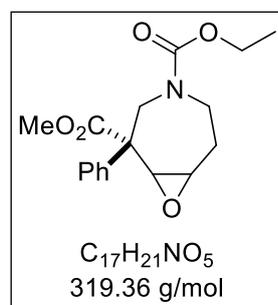
(±)-1-Ethyl 3-methyl (R)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (**129**) (43 mg, 0.141 mmol, 1.0 equiv) and *m*CPBA (195 mg, 0.564 mmol, 4.0 equiv) was dissolved in 25 mL DCM and refluxed for 18 h. The mixture was washed with 5wt% Na$_2$S$_2$O$_5$ (20 mL), NaHCO$_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and evaporated. The crude product was

further purified by column chromatography (15-25% EA in PE) to give the product as colourless oil in 99% yield and dr of 4:1(45 mg, 0.140 mmol).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.49 – 7.27 (m, 4H), 7.25 – 7.16 (m, 1H), 4.66 (d, J = 14.5 Hz, 0.2H), 4.41 (dt, J = 14.9, 1.6 Hz, 0.8H), 4.20 – 3.84 (m, 2H), 3.79 (s, 3H), 3.75 – 3.58 (m, 2H), 3.57 – 3.49 (m, 1H), 3.44 – 3.26 (m, 1H), 3.23 – 3.01 (m, 1H), 2.95 – 2.72 (m, 1H), 2.47 – 2.19 (m, 2H), 0.97 (t, J = 7.1 Hz, 0.6H), 0.79 (t, J = 7.1 Hz, 2.4H).

^{13}C NMR (75 MHz, CDCl$_3$) (major diastereomer) δ 173.2, 155.7, 137.6, 128.6, 127.7, 127.3, 61.0, 60.1, 57.9, 57.3, 52.8, 51.7, 44.0, 28.6, 14.1.

IR (cm^{-1}): 2982, 2952, 1730, 1692, 1469, 1424, 1372, 1271, 1234, 1178, 1115, 984, 947, 701.

HRMS (EI): m/z M$^+$ (calc.) = 319.14142, found M$^+$ [C$_{17}$H$_{21}$NO$_5$]$^+$ = 319.14202

R$_f$ (20% EA in PE) = 016

(±)-1-Ethyl 3-methyl (*R*)-3-phenylazepane-1,3-dicarboxylate (210)
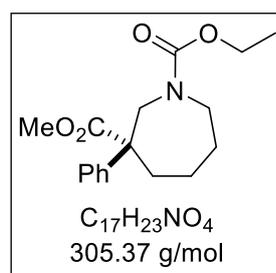
(±)-1-Ethyl 3-methyl (*R*)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (**129**) (516 mg, 1.72 mmol, 1.0 equiv) and Pd/C (10 wt%, 10 mol%, 139 mg) was dissolved in 40 mL MeOH and brought under H$_2$-athmosphere using a balloon. The reaction mixture was stirred for 18 h at 25 °C and filtered over celite. The solvent was evaporated to give the product as colourless oil (508 mg, 1.66 mmol, 98%).

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.31 (d, J = 4.5 Hz, 4H), 7.26 – 7.18 (m, 1H), 4.54 (dd, J = 32.3, 15.0 Hz, 1H), 4.23 – 3.71 (m, 3H), 3.64 (s, 3H), 3.60 – 3.17 (m, 2H), 2.44 – 2.14 (m, 2H), 1.82 – 1.53 (m, 4H), 1.30 – 1.18 (m, 1.5H), 1.00 (t, J = 7.1 Hz, 1.5H).

^{13}C NMR (75 MHz, CDCl$_3$) (2 rotamers) 13C NMR (75 MHz, CDCl3) δ 175.6, 156.5, 156.2, 142.9, 142.8, 128.5, 126.9, 126.3, 61.2, 55.4, 55.1, 54.3, 52.3, 50.5, 49.2, 34.3, 33.3, 28.2, 23.2, 14.7, 14.3.

IR (cm^{-1}): 2933, 2063, 2363, 1730, 1696, 1476, 1424, 1275, 1226, 1200, 1163, 1096, 1036, 772, 701.

HRMS (EI): m/z M$^+$ (calc.) = 305.16216, found M$^+$ [C$_{17}$H$_{23}$NO$_4$]$^+$ = 305.16192

R$_f$ (20% EA in PE) = 0.49

(±)-Ethyl (1*R*,6*S*,7*R*)-6-hydroxy-9-oxo-1-phenyl-8-oxa-3-azabicyclo[5.2.0]nonane-3-carboxylate (209)

C16H19NO5
305.33 g/mol
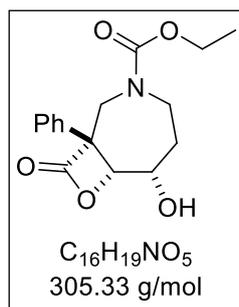
(±)-1-Ethyl 3-methyl (*R*)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (**129**) (75 mg, 0.247 mmol, 1.0 equiv) was dissolved in acetone:water (2:1, 30 mL). NMO (58 mg, 0.5 mmol, 2.0 equiv) and $K_2OsO_4 \cdot 2H_2O$ (5 mg, 5 mol%) were added. The reaction mixture was stirred for 24 h at 25 °C and water (20 mL) was added. The mixture was extracted with EtOAc (3x20 mL) and washed with brine (20 mL). The product was purified by column chromatography (50% EtOAc in PE) to yield a colourless oil. (Yield: 69 mg, 0.226 mmol, 92%)

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 7.63 (dd, *J* = 19.8, 7.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.29 (m, 1H), 4.77 (t, *J* = 3.1 Hz, 1H), 4.64 (d, *J* = 14.8 Hz, 0.5H), 4.38 (d, *J* = 36.3 Hz, 1H), 4.19 (p, *J* = 6.6, 6.2 Hz, 2.5H), 3.98 – 3.81 (m, 1H), 3.74 – 3.60 (m, 0.5H), 3.55 (d, *J* = 14.8 Hz, 0.5H), 3.41 (ddd, *J* = 14.8, 8.0, 4.4 Hz, 0.5H), 3.09 (ddd, *J* = 14.9, 10.1, 4.4 Hz, 0.5H), 2.28 – 1.94 (m, 2H), 1.68 (s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) (2 rotamers) δ 178.2, 177.0, 156.2, 155.1, 134.3, 129.3, 128.8, 128.3, 128.3, 83.2, 82.7, 75.4, 75.3, 62.3, 58.7, 58.3, 55.6, 43.0, 41.7, 31.1, 29.5, 14.7, 14.6.

IR (cm^{-1}): 3437, 2978, 2930, 1767, 1677, 1476, 1428, 1372, 1260, 1223, 1167, 1088, 980, 772, 731.

HRMS (ESI): m/z MH$^+$ (calc.) = 306.1336, found MH$^+$ [C$_{16}$H$_{20}$NO$_5$]$^+$ = 306.134

R$_f$ (50% EA in PE) = 0.29

(±)-Ethyl (*R*)-3-(hydroxymethyl)-3-phenylazepane-1-carboxylate (211)

C16H23NO3
277.36 g/mol
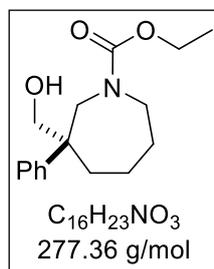
(±)-1-Ethyl 3-methyl (*R*)-3-phenylazepane-1,3-dicarboxylate (**210**) (505 mg, 1.654 mmol, 1.0 equiv) was dissolved in dry THF (40 mL) and cooled to 0 °C. LiBH$_4$ 2 M in THF (4.13 mL, 5.0 equiv) was added and the reaction mixture was stirred for 18 h while allowing it to warm up to 25 °C. Remaining LiBH$_4$ was quenched by dropwise addition of 1 M HCl solution. The mixture was extracted with EtOAc (3x50 mL) and washed with brine (50 mL) to give the product in quantitative yields as colourless oil. (455 mg)

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.42 – 7.29 (m, 4H), 7.25 – 7.17 (m, 1H), 4.41 (d, *J* = 14.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.06 (dt, *J* = 13.9, 5.4 Hz, 1H), 3.69 (d, *J* = 11.9 Hz, 1H), 3.50

(d, J = 12.0 Hz, 1H), 3.23 (d, J = 14.8 Hz, 1H), 2.84 (ddd, J = 13.4, 8.0, 5.3 Hz, 1H), 2.01 (dd, J = 14.9, 9.6 Hz, 1H), 1.87 – 1.44 (m, 6H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 157.9, 145.4, 128.4, 126.5, 126.3, 69.7, 62.0, 53.7, 49.7, 48.3, 34.9, 29.5, 22.8, 14.7.

IR (cm^{-1}): 3463, 2930, 2866, 1666, 1483, 1431, 1383, 1308, 1275, 1219, 1103, 1040, 910, 760, 731.

HRMS (ESI): m/z MH$^+$ (calc.) = 278.1751, found MH$^+$ [C$_{16}$H$_{24}$NO$_3$]$^+$ = 278.1752

R$_f$ (25% EA in PE) = 0.24

(±)-Ethyl (*R*)-3-formyl-3-phenylazepane-1-carboxylate (212)[124]
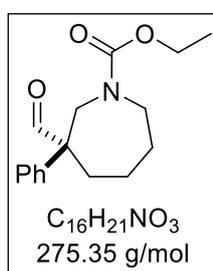
(COCl)$_2$ (0.24 mL, 2.80 mmol, 3 equiv) was dissolved in 5 mL dry DCM and cooled down to -65°C. Then DMSO (0.40 mL, 5.6 mmol, 6 equiv) dissolved in 5 mL dry DCM was added and stirred. After 10 minutes (±)-Ethyl (*R*)-3-(hydroxymethyl)-3-phenylazepane-1-carboxylate (**211**) (0.255 g, 0.92 mmol, 1.0 equiv) dissolved in 10 mL dry DCM was added dropwise to the reaction mixture at -65°C over 10 minutes. After full addition the reaction mixture was stirred further on for 6 h at -65°C. NEt$_3$ (1.3 mL, 9.20 mmol, 10 equiv) was added and the mixture was slowly warmed up to 25°C in the next 30 minutes. Water (30 mL) was added to the mixture and it was extracted with DCM (3x 50 mL). The combined organic layers were washed with 1 M HCl solution and Na$_2$CO$_3$ solution (1:5 saturated Na$_2$CO$_3$:H$_2$O) , dried over Na$_2$SO$_4$ and filtered. The solvent was evaporated under reduced pressure to give the product as colourless oil. Yield: 253 mg, 0.92 mmol, 100%) The product was used without further purification.

^{1}H NMR (300 MHz, CDCl$_3$) (2 rotamers) δ 9.49 (d, J = 55.1 Hz, 1H), 7.33 – 7.10 (m, 5H), 4.52 (dd, J = 60.3, 14.8 Hz, 1H), 4.03 (q, J = 7.0 Hz, 1H), 3.97 – 3.82 (m, 1H), 3.80 – 3.61 (m, 1H), 3.47 (dd, J = 36.8, 14.9 Hz, 1H), 3.15 – 2.91 (m, 1H), 2.24 – 1.92 (m, 2H), 1.78 – 1.41 (m, 4H), 1.16 (t, J = 6.9 Hz, 1.5H), 0.99 (t, J = 7.1 Hz, 1.5H).

^{13}C NMR (75 MHz, CDCl$_3$) (2 rotamers) δ 200.6, 200.0, 156.6, 155.6, 138.8, 138.7, 129.0, 127.5, 127.4, 127.1, 126.9, 61.6, 61.4, 58.9, 58.7, 52.4, 51.9, 50.4, 49.1, 32.1, 30.6, 29.0, 28.9, 22.4, 22.1, 14.7, 14.2. (residues of NEt$_3$ at 45.83, 8.63)

IR (cm^{-1}): 2982, 2933, 2863, 1722, 1689, 1480, 1424, 1308, 1241, 1208, 1115, 1036, 910, 760, 731, 701.

HRMS (ESI): m/z MH$^+$ (calc.) = 276.1594, found MH$^+$ [C$_{16}$H$_{22}$NO$_3$]$^+$ = 276.1597

R$_f$ (25% EA in PE) = 0.38

(±)-Ethyl (*R*)-3-phenyl-3-vinylazepane-1-carboxylate (213)[125–127]

O, O structure — Ph, N, C₁₇H₂₃NO₂, 273.38 g/mol

$C_{17}H_{23}NO_2$

273.38 g/mol
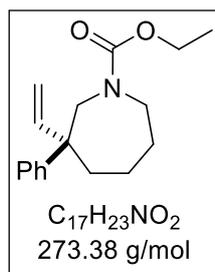
Ph₃MgBr (650 mg, 1.75 mmol, 2 equiv) was dissolved in 5 mL dry THF and cooled down to -78 °C. Then 1.6 M n-BuLi (1.25 mL, 1.96 mmol, 2.2 equiv) was added. The solution was stirred at 25 °C for 1 h and (±)-Ethyl (*R*)-3-formyl-3-phenylazepane-1-carboxylate (**212**) (245 mg, 0.89 mmol, 1.0 equiv) dissolved in 5 mL dry THF was added dropwise to the reaction mixture over 30 minutes. After full addition the reaction mixture was stirred further on for 20 h. The solution was transferred to a separating funnel brine (30 mL) was added and extracted with EtOAc (3x50 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (10% EA in PE) yielding a colourless oil. Yield: 153 mg (0.56 mmol, 63 %).

¹H NMR (400 MHz, CDCl₃) (2 rotamers) δ 7.42 – 7.27 (m, 4H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.09 (ddd, *J* = 22.9, 17.6, 10.8 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 4.93 (dd, *J* = 17.6, 9.8 Hz, 1H), 4.31 – 3.92 (m, 3H), 3.70 (ddd, *J* = 13.0, 7.8, 4.8 Hz, 1H), 3.57 (dd, *J* = 37.6, 14.6 Hz, 1H), 3.21 (ddt, *J* = 60.5, 12.9, 5.6 Hz, 1H), 2.17 – 1.92 (m, 2H), 1.90 – 1.60 (m, 4H), 1.21 (dt, *J* = 32.9, 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) (2 rotamers) δ 157.0, 156.5, 146.0, 145.7, 144.9, 144.7, 128.2, 127.0, 127.0, 126.1, 113.9, 113.6, 61.3, 61.1, 54.9, 54.9, 50.3, 49.8, 49.2, 48.3, 37.3, 37.3, 28.0, 27.6, 23.2, 23.0, 14.8, 14.6.

IR (cm⁻¹): 2982, 2933, 2800, 2248, 1685, 1469, 1424, 1379, 1305, 1215, 1174, 1111, 1025, 910, 760, 727.

HRMS (ESI): m/z MH⁺ (calc.) = 274.1802, found MH⁺ $[C_{17}H_{24}NO_2]^+$ = 274.18

R_f (10% EA in PE) = 0.53

(±)-Ethyl (*R*)-3-(2-hydroxyethyl)-3-phenylazepane-1-carboxylate (214)

O, O structure — HO, N, Ph, C₁₇H₂₅NO₃, 291.39 g/mol

$C_{17}H_{25}NO_3$

291.39 g/mol
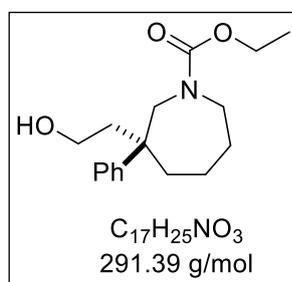
(±)-Ethyl (*R*)-3-phenyl-3-vinylazepane-1-carboxylate (**213**) (43 mg, 0.16 mmol, 1.0 equiv) were dissolved in dry THF (0.4 mL) and cooled to 0 °C. BH₃ in THF (1M, 0.2 mL, 1.3 equiv) was added dropwise and stirred for 2 h, before an additional BH₃ in THF (1M. 0.2 mL, 1.3 equiv) was added and stirred for further 4 h. After that H₂O₂ (0.4 mL, 30 equiv) and phosphate buffer (0.4 mL) were added at 0 °C and stirred for 20 h while the mixture was warmed slowly to 25 °C. The mixture was extracted with EtOAc (3x5 mL) and the organic phase was washed with half conc. $Na_2S_2O_3$ solution

(5 mL) and brine (5 mL). The crude product was purified by column chromatography (15-50% EA in PE) to give the product as a colourless oil. Yield: 35 mg (0.12 mmol, 76%)

^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers) δ 7.41 – 7.28 (m, 4H), 7.25 – 7.17 (m, 1H), 4.43 (d, J = 14.5 Hz, 0.5H), 4.21 – 3.99 (m, 2.5H), 3.97 – 3.80 (m, 1H), 3.51 – 3.18 (m, 3H), 3.13 – 2.90 (m, 1H), 2.34 – 1.84 (m, 4H), 1.82 – 1.52 (m, 5H), 1.29 – 1.21 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) (2 rotamers) δ 157.4, 156.5, 145.5, 145.4, 128.4, 126.5, 126.1, 61.5, 61.3, 59.7, 59.5, 57.1, 55.7, 49.7, 49.2, 45.5, 45.1, 43.0, 42.7, 38.2, 36.1, 28.5, 28.3, 22.5, 22.3, 14.7.

IR (cm^{-1}): 3425, 2930, 2870, 1674, 1472, 1424, 1383, 1275, 1230, 1111, 1036, 768, 701.

HRMS (ESI): m/z MH$^+$ (calc.) = 292.1907, found MH$^+$ [C$_{17}$H$_{26}$NO$_3$]$^+$ = 292.1909

R$_f$ (50% EA in PE) = 0.19

(±)-Ethyl (*R*)-3-((*R*)-oxiran-2-yl)-3-phenylazepane-1-carboxylate (215)

C$_{17}$H$_{23}$NO$_3$
289.38 g/mol
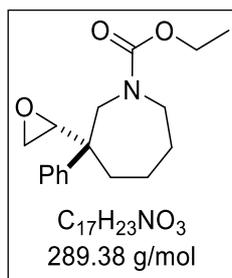
(±)-Ethyl (*R*)-3-phenyl-3-vinylazepane-1-carboxylate (**213**) (63 mg, 0.23 mmol, 1.0 equiv) and *m*CPBA (purity: 70%, 227 mg, 0.92 mmol, 4.0 equiv) was dissolved in 15 mL DCM and refluxed for 6 h. The mixture was washed with 5 wt% Na$_2$S$_2$O$_5$ (20 mL), NaHCO$_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and evaporated. The crude product was further purified by column chromatography (20% EA in PE) to give the product as colourless oil in 97% yield (65 mg, 0.22 mmol) as 2 diastereomers in a ratio of 1:1.

^{1}H NMR (300 MHz, CDCl$_3$) (2 diastereomers, 2 rotamers) δ 7.45 – 7.27 (m, 4H), 7.26 – 7.16 (m, 1H), 4.35 – 3.95 (m, 3H), 3.95 – 3.77 (m, 1H), 3.64 (dd, J = 44.3, 14.7 Hz, 1H), 3.32 – 2.77 (m, 2H), 2.55 (t, J = 4.3 Hz, 1H), 2.36 – 2.05 (m, 2H), 1.92 – 1.50 (m, 4H), 1.34 – 1.18 (m, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) (2 diastereomers, 2 rotamers) δ 156.9, 156.7, 156.3, 156.3, 142.1, 141.5, 128.2, 128.0, 127.4, 127.2, 126.6, 61.4, 61.3, 59.0, 58.8, 58.5, 58.4, 54.0, 53.7, 53.5, 50.4, 49.8, 49.7, 49.2, 46.9, 46.7, 46.5, 46.2, 44.5, 44.4, 44.2, 44.0, 33.0, 32.7, 32.6, 32.3, 29.7, 29.1, 28.9, 28.5, 28.3, 23.0, 22.9, 22.7, 14.8, 14.6, 14.5, 14.2.

IR (cm^{-1}): 3056, 2930, 2870, 1692, 1476, 1424, 1379, 1312, 1271, 1219, 1178, 1111, 1029, 872, 768, 701.

HRMS (ESI): m/z MH$^+$ (calc.) = 290.1751, found MH$^+$ [C$_{17}$H$_{24}$NO$_3$]$^+$ = 290.1751

R$_f$ (20% EA in PE) = 0.23

(±)-Ethyl (R)-3-(3-methoxyphenyl)-3-((tosyloxy)methyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (196)[108]

$C_{24}H_{29}NO_6S$
459.56 g/mol
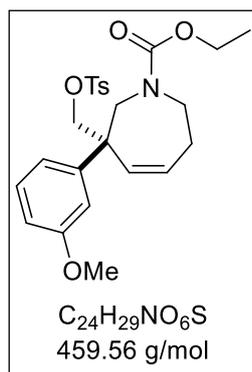
(±)-Ethyl (R)-3-(hydroxymethyl)-3-(3-methoxyphenyl)-2,3,6,7-tetra-hydro -1H-azepine-1-carboxylate (**200**) (180 mg, 0.58 mmol, 1.0 equiv) was dissolved in pyridine (5 mL) and 1-Methylimidazol (20 µL, 0.23 mmol, 0.4 equiv) and TsCl (337 mg, 1.72 mmol, 3.0 equiv) were added. The reaction mixture was stirred at 120 °C for 2 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (20% EA in PE) to give the product as colourless oil. Yield: 142 mg, 0.31 mmol, 53%.

¹H NMR (400 MHz, CDCl₃) (2 rotamers) δ 7.67 (dd, J = 14.6, 7.9 Hz, 2H), 7.30 (t, J = 8.7 Hz, 2H), 7.17 (q, J = 8.4 Hz, 1H), 6.85 – 6.71 (m, 3H), 6.09 – 5.91 (m, 1H), 5.69 (dd, J = 77.4, 11.8 Hz, 1H), 4.25 – 4.09 (m, 2H), 4.08 – 3.96 (m, 1.5H), 3.93 – 3.77 (m, 2H), 3.74 (d, J = 7.2 Hz, 3.5H), 3.56 (dt, J = 12.3, 5.7 Hz, 1H), 3.41 – 3.12 (m, 1H), 2.44 (s, 3H), 2.34 (p, J = 6.0 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) (2 rotamers) δ 159.6, 159.5, 156.4, 155.8, 144.9, 144.7, 142.1, 141.9, 133.4, 132.9, 132.6, 130.9, 130.4, 129.8, 129.8, 129.4, 129.4, 128.0, 119.3, 119.3, 113.8, 113.0, 112.5, 111.9, 75.4, 74.7, 61.5, 61.4, 55.2, 52.0, 51.3, 51.1, 47.0, 46.2, 27.3, 27.0, 21.7, 14.6, 14.5.

IR (cm⁻¹): 2930, 2837, 1692, 1599, 1465, 1424, 1357, 1252, 11174, 1096, 1036, 965, 842, 787, 731.

HRMS (ESI): m/z MH⁺ (calc.) = 460.1788, found MH⁺ [$C_{24}H_{30}NO_6S$]⁺ = 460.179

R_f (20% EA in PE) = 0.13

(±)-(6S)-6-(3-Methoxyphenyl)-1-azabicyclo[4.2.1]non-4-en-8-one (197)

(±)-Ethyl (S)-3-ethyl-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (183)[107]

O

N

C$_{15}$H$_{17}$NO$_2$
243.31 g/mol

O$\diagdown$O$\diagup$

N

OMe

C$_{18}$H$_{25}$NO$_3$
303.40 g/mol
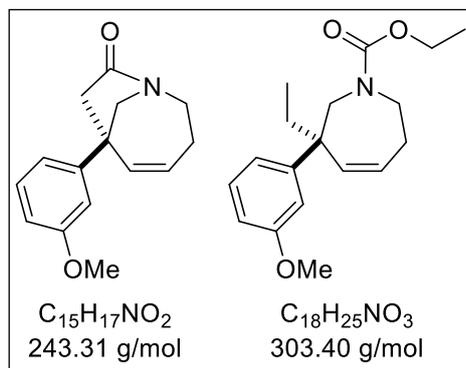
CuI (242 mg, 1.27 mmol, 5.0 equiv) was dissolved in dry Et$_2$O (3 mL) and cooled to 0 °C. MeLi (1.3M in Et$_2$O, 1.72 mL, 10 equiv) was added dropwise within 30 min. (±)-Ethyl (R)-3-(3-methoxyphenyl) -3- ((tosyloxy) methyl)-2,3,6,7-tetrahydro -1H- azepine-1-carboxylate (**196**) (100 mg, 0.22 mmol, 1.0 equiv) was added dissolved in 1 mL Et$_2$O and the mixture was stirred for 18 h while warming up to 25 °C. The mixture was cooled to 0 °C and sat. NH$_4$Cl solution (3 mL) was added and stirred for further 10 min. The mixture was extracted with Et$_2$O (3x20 mL) and the organic layers were washed with brine (20 mL). The organic layers were dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (20% EA in PE) to give two products as colourless oils. Yield (**197**):23 mg, 0.095 mmol, 43%, Yield (**183**) 12 mg, 0.040 mmol, 18%

(±)-(6S)-6-(3-Methoxyphenyl)-1-azabicyclo[4.2.1]non-4-en-8-one (197)

O

N

OMe

C$_{15}$H$_{17}$NO$_2$
243.31 g/mol
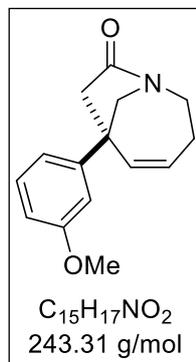
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26 (t, J = 7.9 Hz, 1H), 6.80 (dddd, J = 8.5, 6.9, 2.2, 0.9 Hz, 2H), 6.75 (dd, J = 2.5, 1.7 Hz, 1H), 5.64 (ddd, J = 12.0, 8.9, 3.1 Hz, 1H), 5.47 (dt, J = 11.9, 2.7 Hz, 1H), 4.08 (ddd, J = 13.2, 10.8, 6.9 Hz, 1H), 3.79 (s, 3H), 3.75 (dd, J = 11.2, 3.2 Hz, 1H), 3.35 (dd, J = 11.2, 2.4 Hz, 1H), 3.22 (dd, J = 13.2, 8.2 Hz, 1H), 3.01 (d, J = 14.7 Hz, 1H), 2.79 (dddt, J = 17.0, 11.3, 8.2, 3.2 Hz, 1H), 2.39 (dd, J = 14.7, 3.1 Hz, 1H), 2.21 (ddd, J = 16.3, 8.9, 6.9 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 184.2, 159.9, 142.7, 135.3, 129.8, 124.7, 118.5, 112.8, 112.0, 57.3, 55.3, 54.8, 46.2, 46.2, 24.0.

IR (cm^{-1}): 3004, 2937, 2892, 2836, 1703, 1603, 1487, 1428, 1346, 1371, 1264, 1211, 1170, 1081, 1010, 973, 828, 783, 749, 701.

HRMS (ESI): m/z MH$^+$ (calc.) = 244.1332, found MH$^+$ [C$_{15}$H$_{18}$NO$_2$]$^+$ = 244.1336

R$_f$ (20% EA in PE) = 0.14

(±)-Ethyl (S)-3-ethyl-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (183)

C$_{18}$H$_{25}$NO$_3$
303.40 g/mol
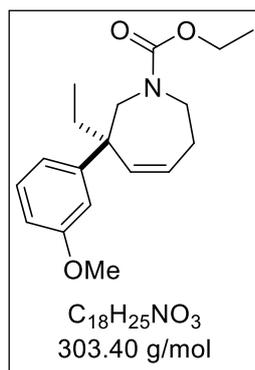
^{1}H NMR (400 MHz, CDCl$_3$) (2 rotamers) δ 7.22 (t, J = 7.9 Hz, 1H), 6.97 – 6.82 (m, 2H), 6.76 – 6.68 (m, 1H), 5.95 (tdd, J = 11.5, 6.2, 4.8 Hz, 1H), 5.77 (dd, J = 38.7, 11.9 Hz, 1H), 4.19 – 3.95 (m, 2H), 3.83 – 3.72 (m, 5H), 3.67 – 3.57 (m, 1H), 3.40 (ddd, J = 13.0, 9.1, 3.5 Hz, 0.5H), 3.21 (ddd, J = 12.8, 9.1, 3.2 Hz, 0.5H), 2.51 – 2.25 (m, 2H), 1.99 – 1.70 (m, 2H), 1.19 – 1.12 (m, 3H), 0.85 – 0.76 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) (2 rotamers) δ 159.5, 159.4, 156.5, 156.2, 146.5, 146.1, 136.9, 136.3, 128.9, 128.5, 128.2, 119.8, 119.6, 114.1, 113.4, 111.2, 110.7, 61.1, 61.0, 55.2, 55.2, 54.9, 54.4, 51.1, 50.8, 47.2, 46.4, 32.8, 31.7, 27.1, 14.7, 14.5, 8.8.

IR (cm^{-1}): 2963, 2930, 2359, 1696, 1603, 1469, 1428, 1379, 1252, 1174, 1118, 1044, 772.

HRMS (ESI): m/z MH$^+$ (calc.) = 304.1907, found MH$^+$ [C$_{18}$H$_{26}$NO$_3$]$^+$ = 304.1909

R$_f$ (20% EA in PE) = 0.70

5 NMR spectra

Methyl 2-diazo-2-phenylacetate (86)

$C_9H_8N_2O_2$
176.18 g/mol

Methyl 2-diazo-2-(3-methoxyphenyl)acetate (190)

$C_{10}H_{10}N_2O_3$
206.20 g/mol

1-diazo-1-(3-methoxyphenyl)propan-2-one (188)
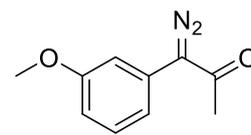
$C_{10}H_{10}N_2O_2$
190.20 g/mol
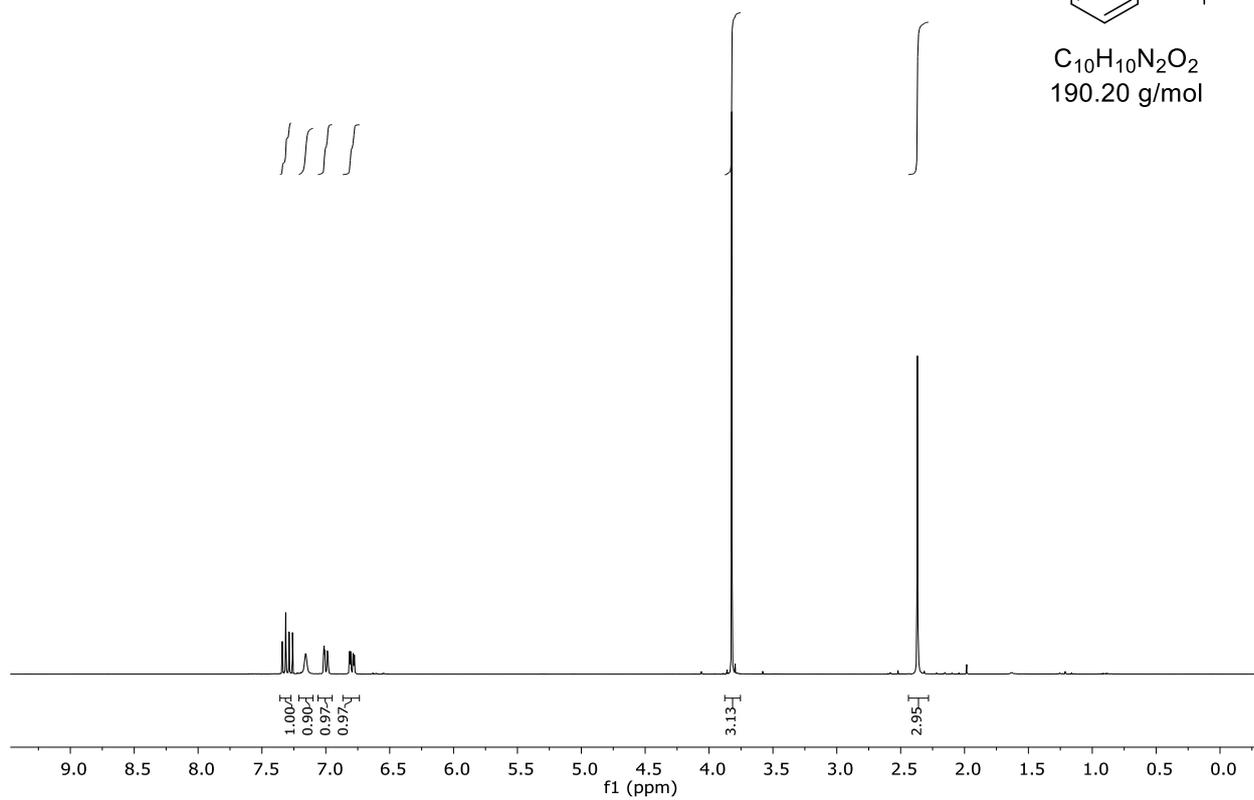
ethyl 2-diazoacetate (EX1)
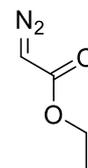
$C_4H_6N_2O_2$
114.10 g/mol
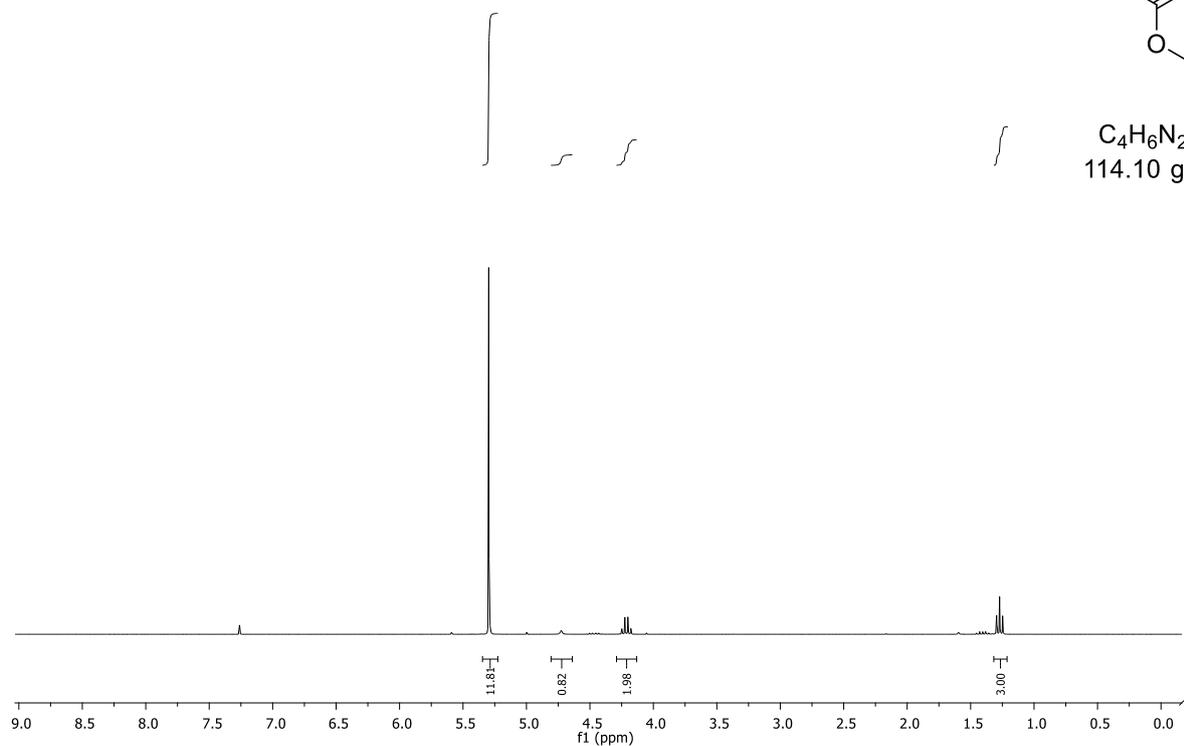
(2-methoxy-2-oxo-1-phenylethyl)dimethylsulfonium bromide (EX2)
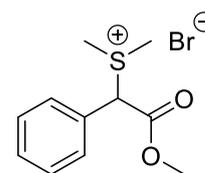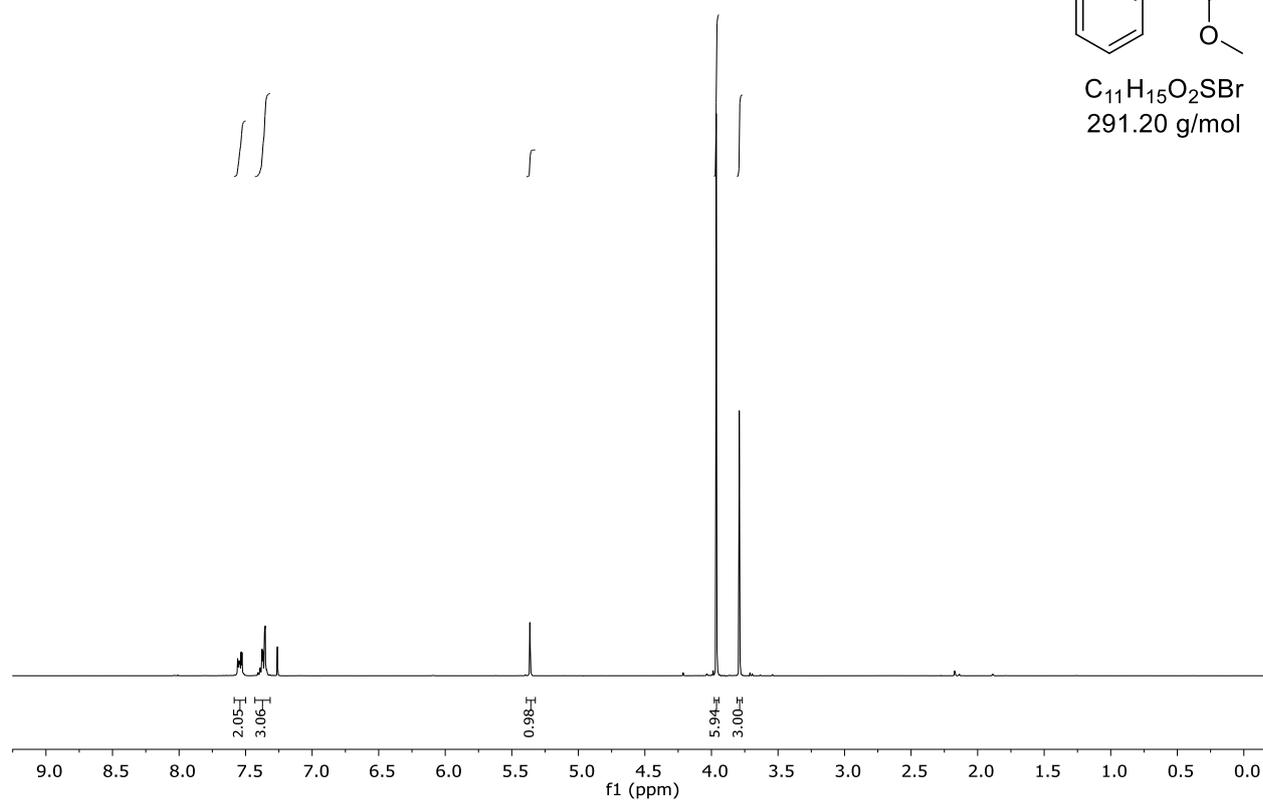
$C_{11}H_{15}O_2SBr$
291.20 g/mol

2.05
3.06
0.98
5.94
3.00

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

(2-ethoxy-2-oxoethyl)dimethylsulfonium bromide (EX3)

$C_6H_{13}O_2SBr$
229.13 g/mol

1.97
2.00
5.88
3.00

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
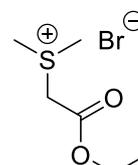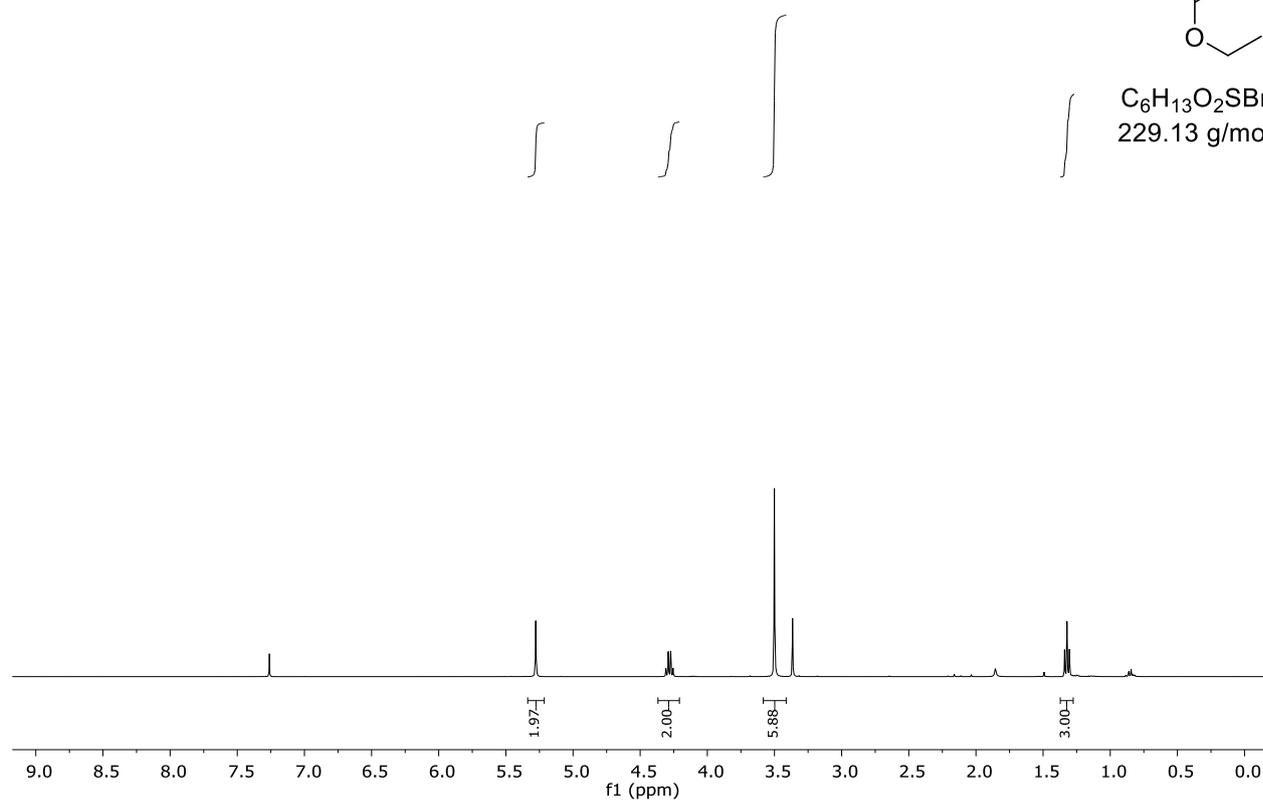
Phenyl pyridine-1(2H)-carboxylate (85)
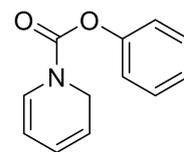
C$_{12}$H$_{11}$NO$_2$
201,23 g/mol
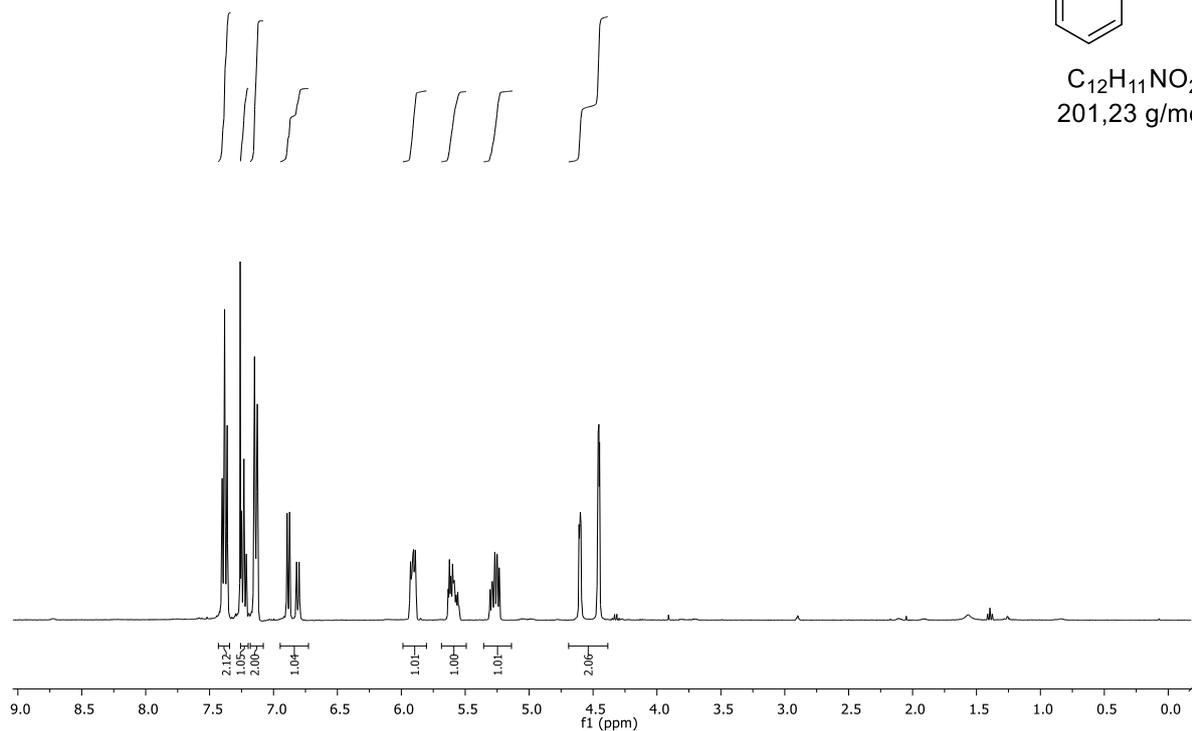
Phenyl 4-methylpyridine-1(2H)-carboxylate (EX4)
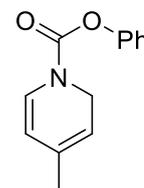
C$_{13}$H$_{13}$NO$_2$
215.25
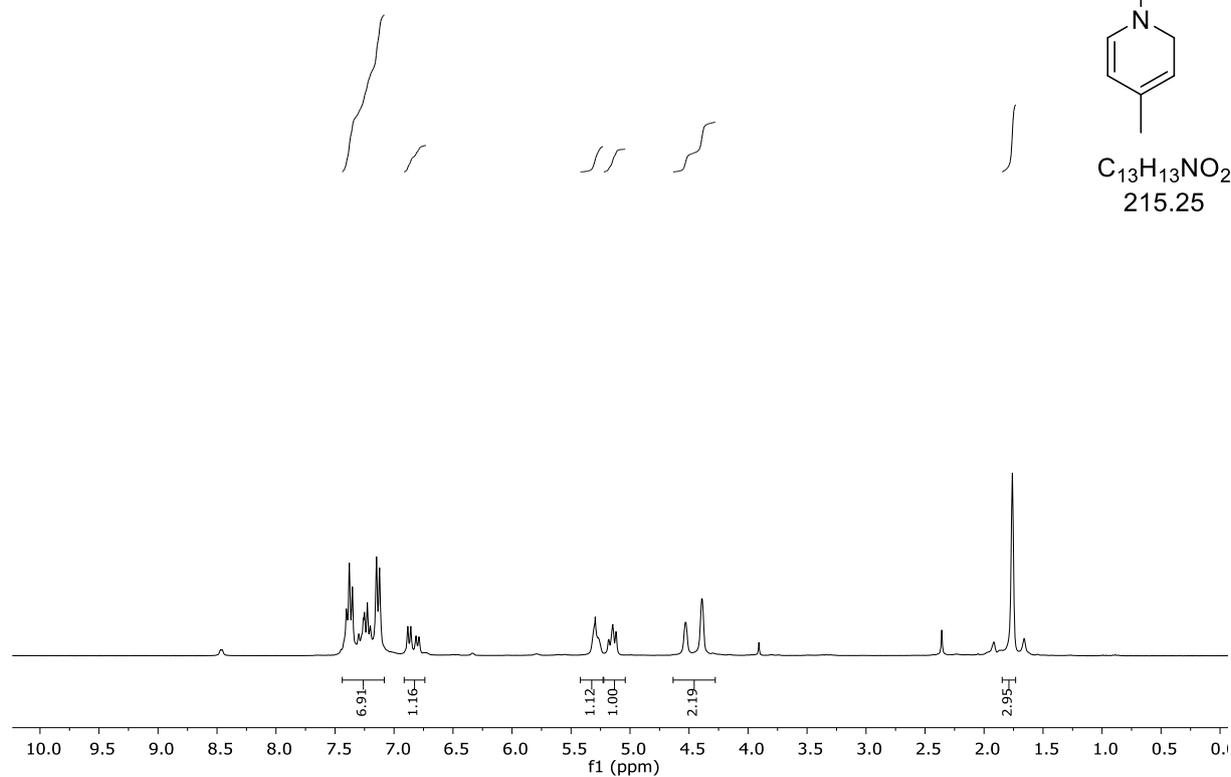
methyl pyridine-1(2H)-carboxylate (228)
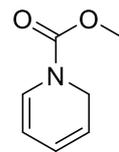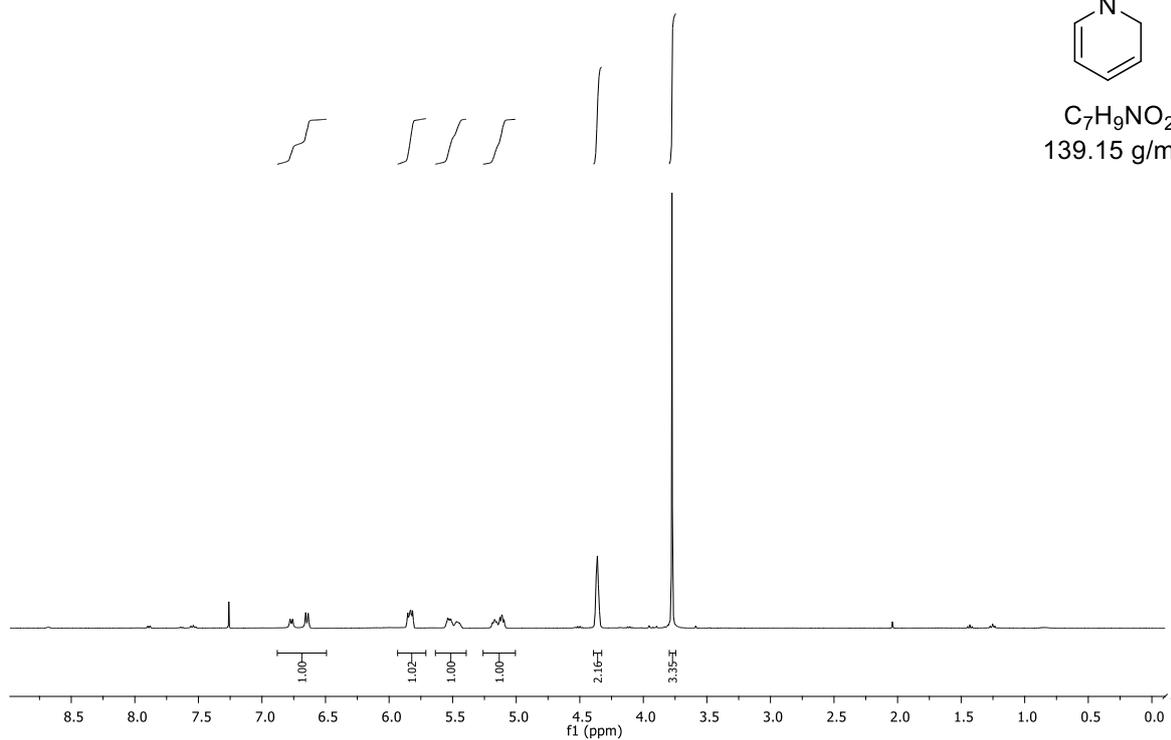
$C_7H_9NO_2$
139.15 g/mol

(±)-7-Methyl 2-phenyl (1S,6S,7R)-7-phenyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (87)
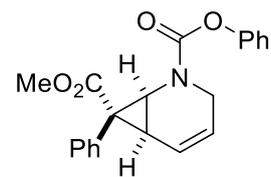
C$_{21}$H$_{19}$NO$_4$
349,39 g/mol

(±)-8-Methyl 6-phenyl (1*S*,2*R*,4*S*,7*S*,8*R*)-8-phenyl-3-oxa-6-azatricyclo[5.1.0.0²,⁴]octane-6,8-dicarboxylate (89)
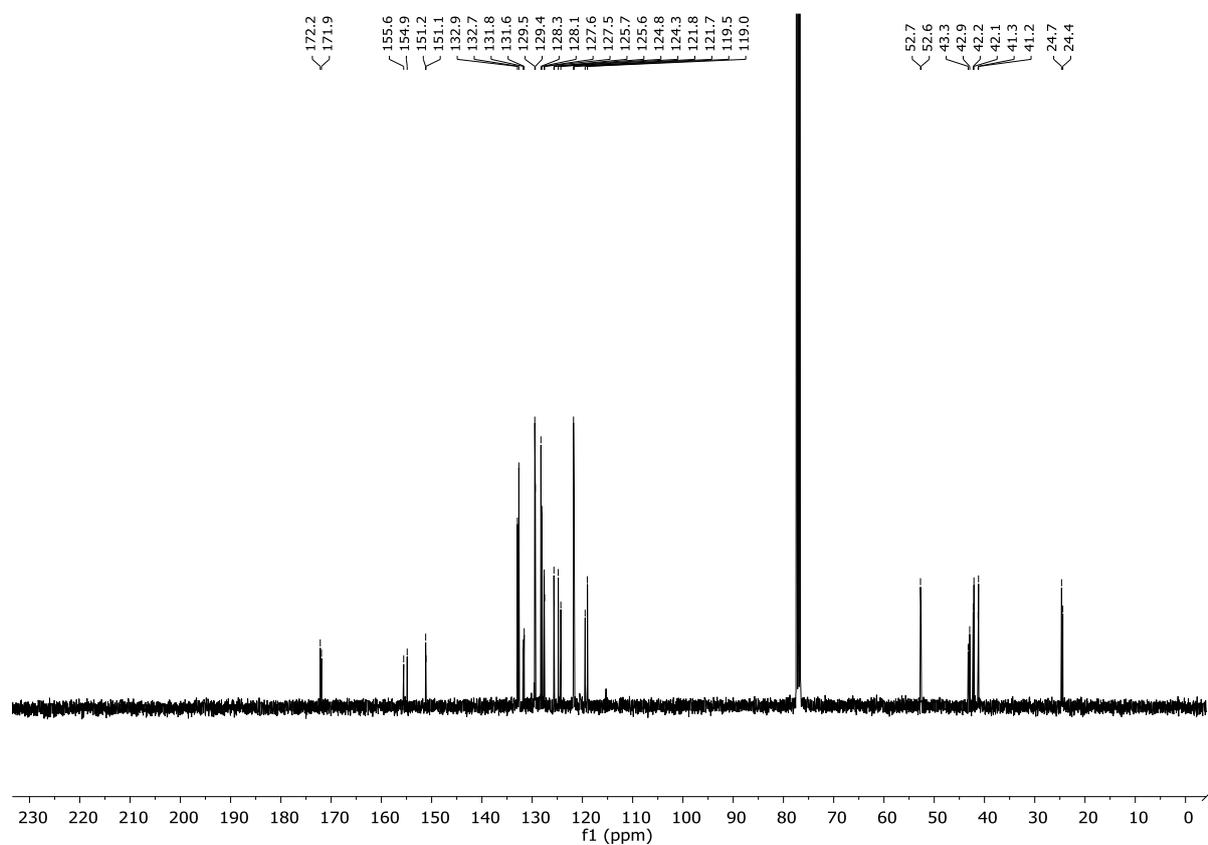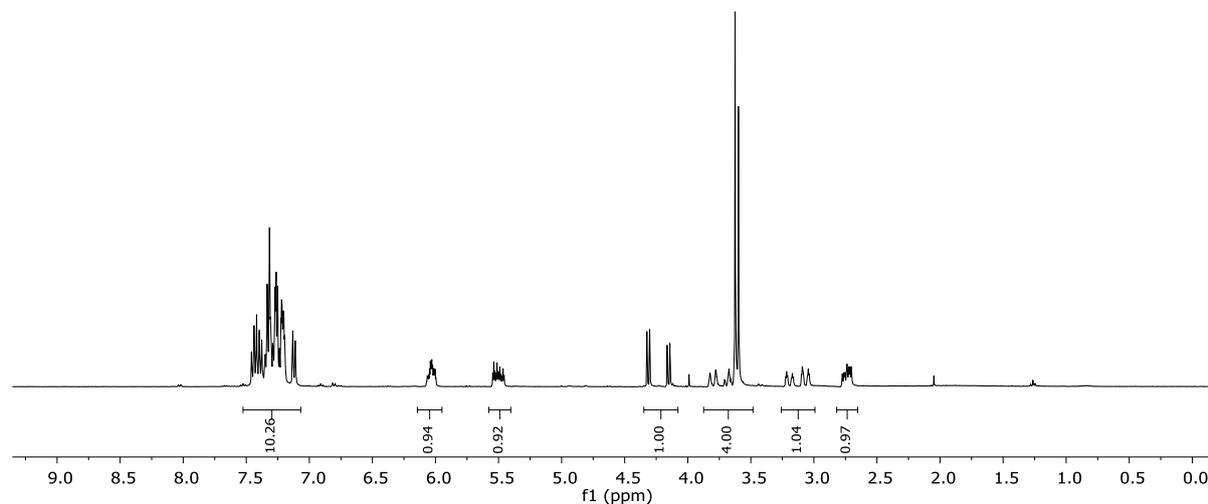
$C_{21}H_{19}NO_5$
365.39 g/mol
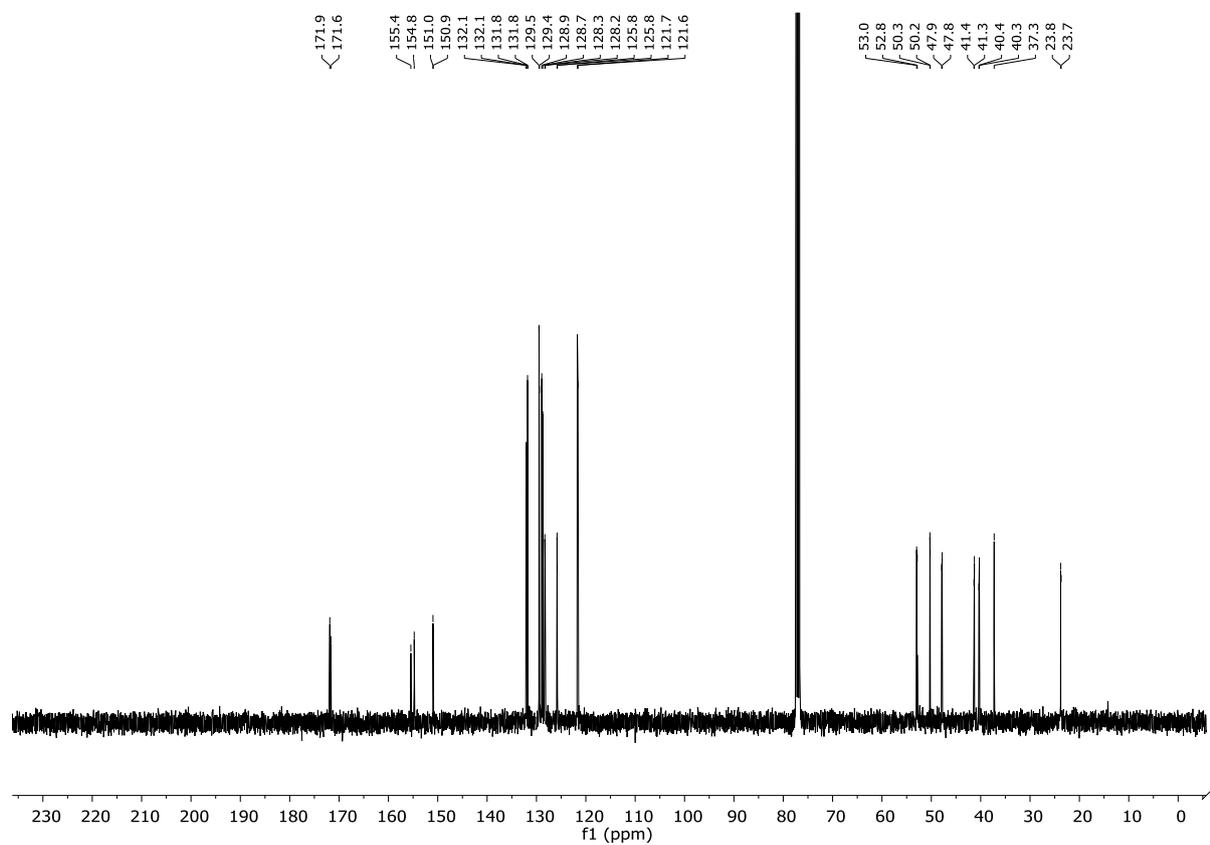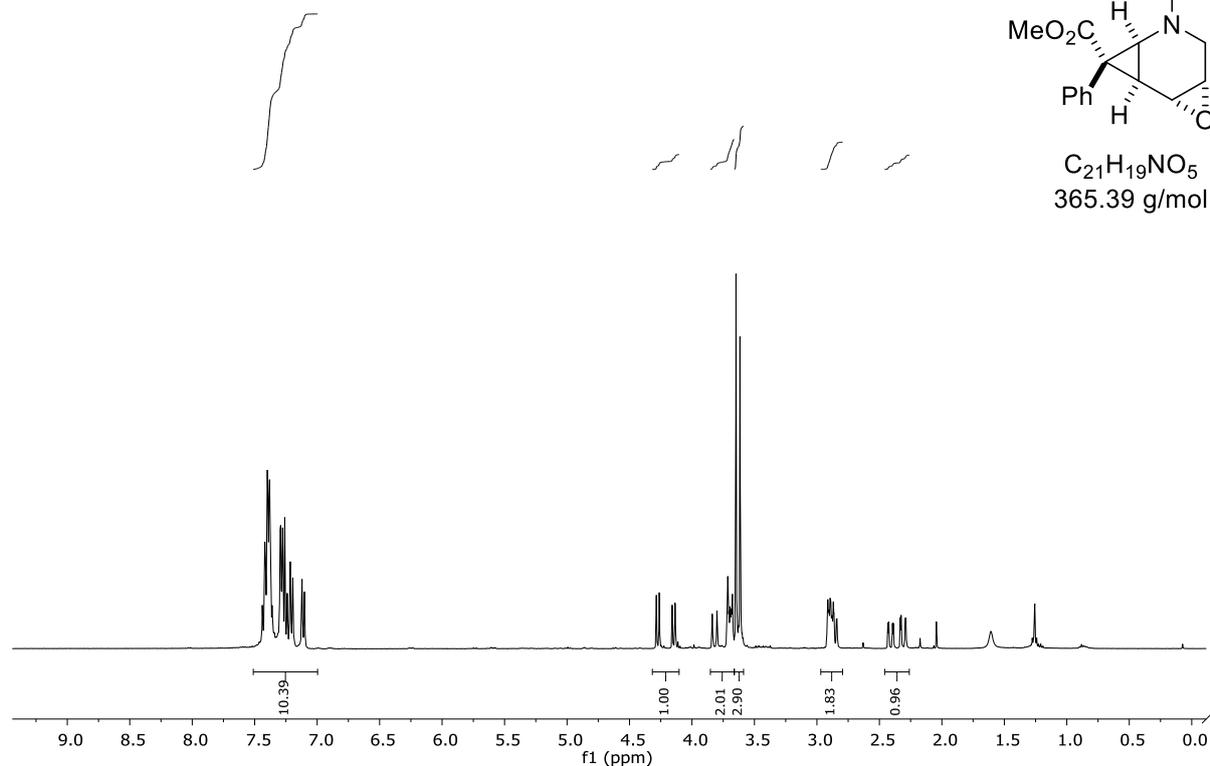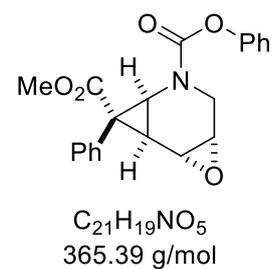
(±)-4-Methyl 6-phenyl (1*S*,4*S*,5*R*)-4-phenyl-8-oxa-6-azabicyclo[3.2.1]oct-2-ene-4,6-dicarboxylate (90)
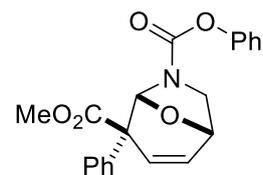
$C_{21}H_{19}NO_5$
365.39 g/mol
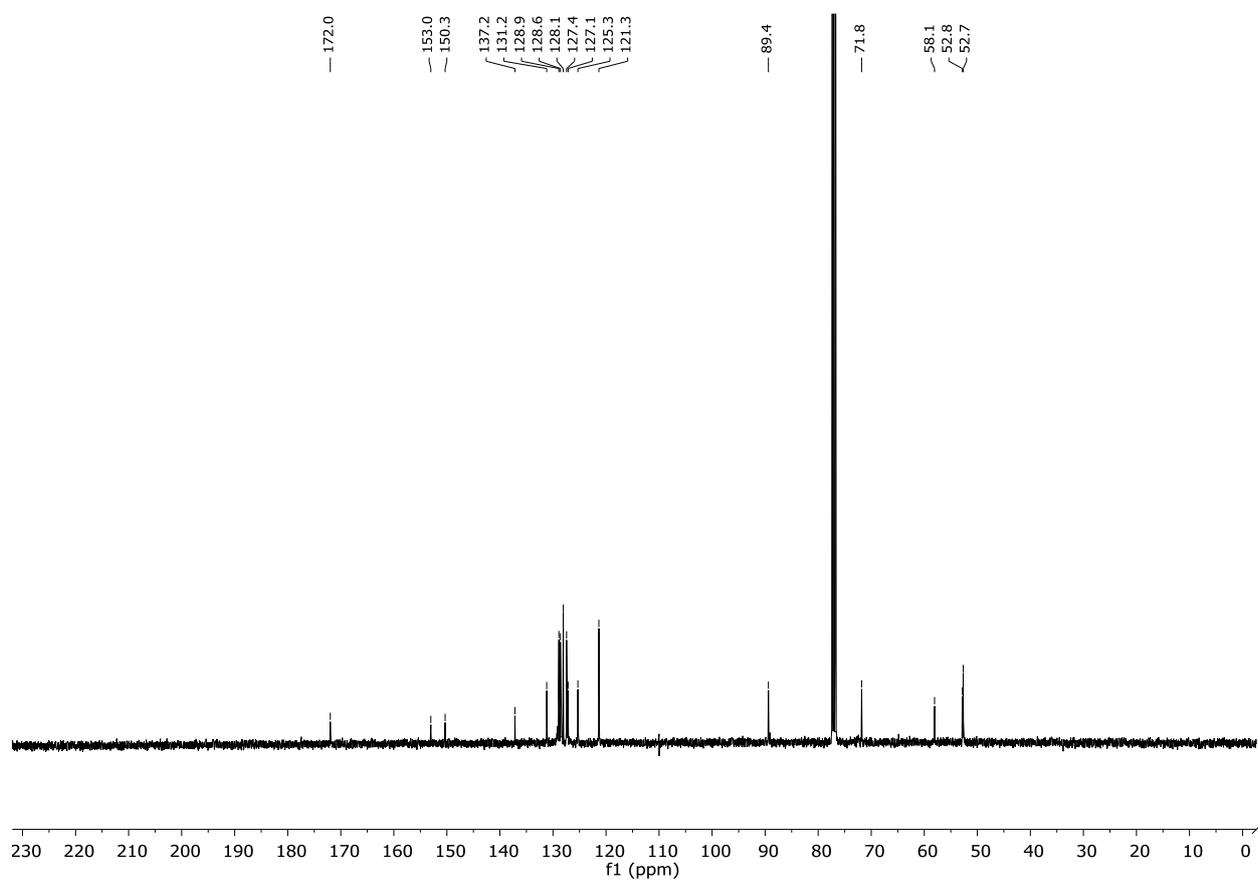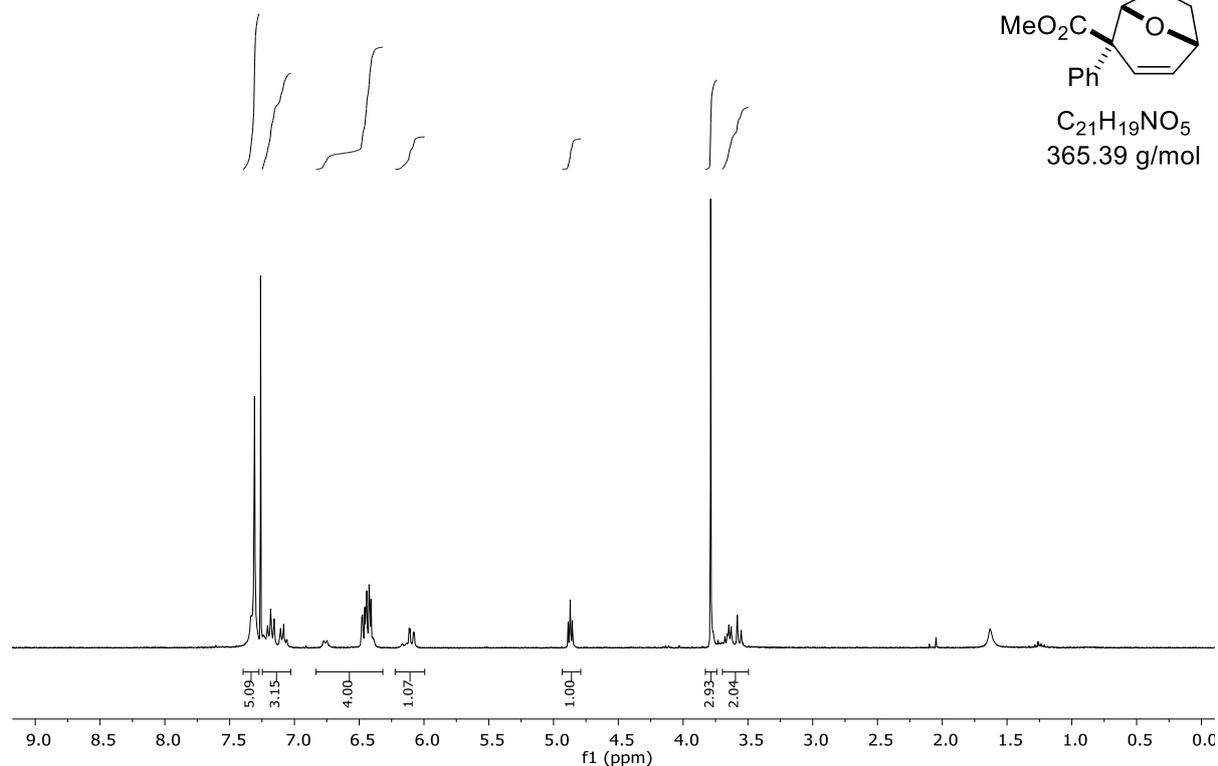
(±)-5-Methyl 7-phenyl (1*R*,2*S*,4*S*,5*R*,6*R*)-5-phenyl-3,9-dioxa-7-azatricyclo[4.2.1.0²,⁴] nonane-5,7-dicarboxylate (108)

$C_{22}H_{21}NO_6$
395.41 g/mol

(±)-4-Methyl 6-phenyl (1*S*,4*S*,5*R*)-4-phenyl-8-oxa-6-azabicyclo[3.2.1]octane-4,6-dicarboxylate (102)

C₂₂H₂₃NO₅
381.43 g/mol
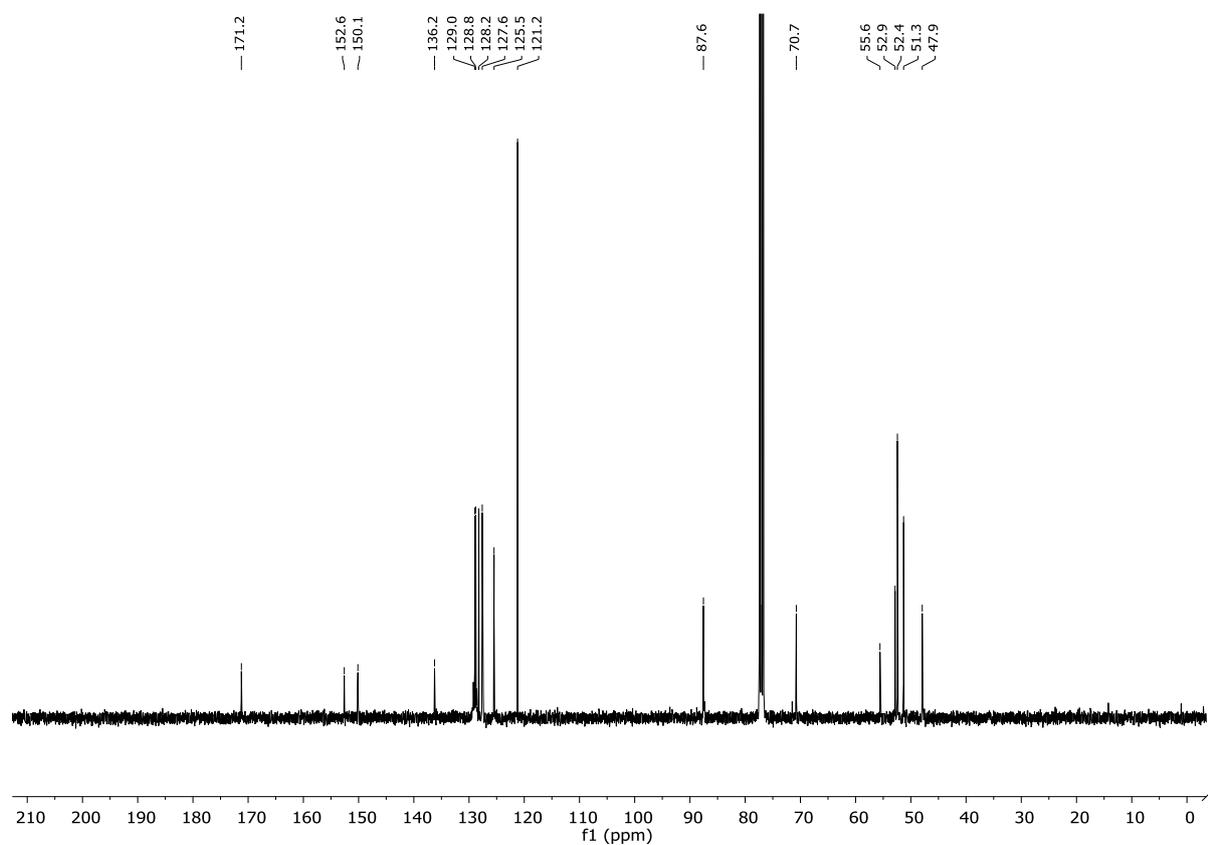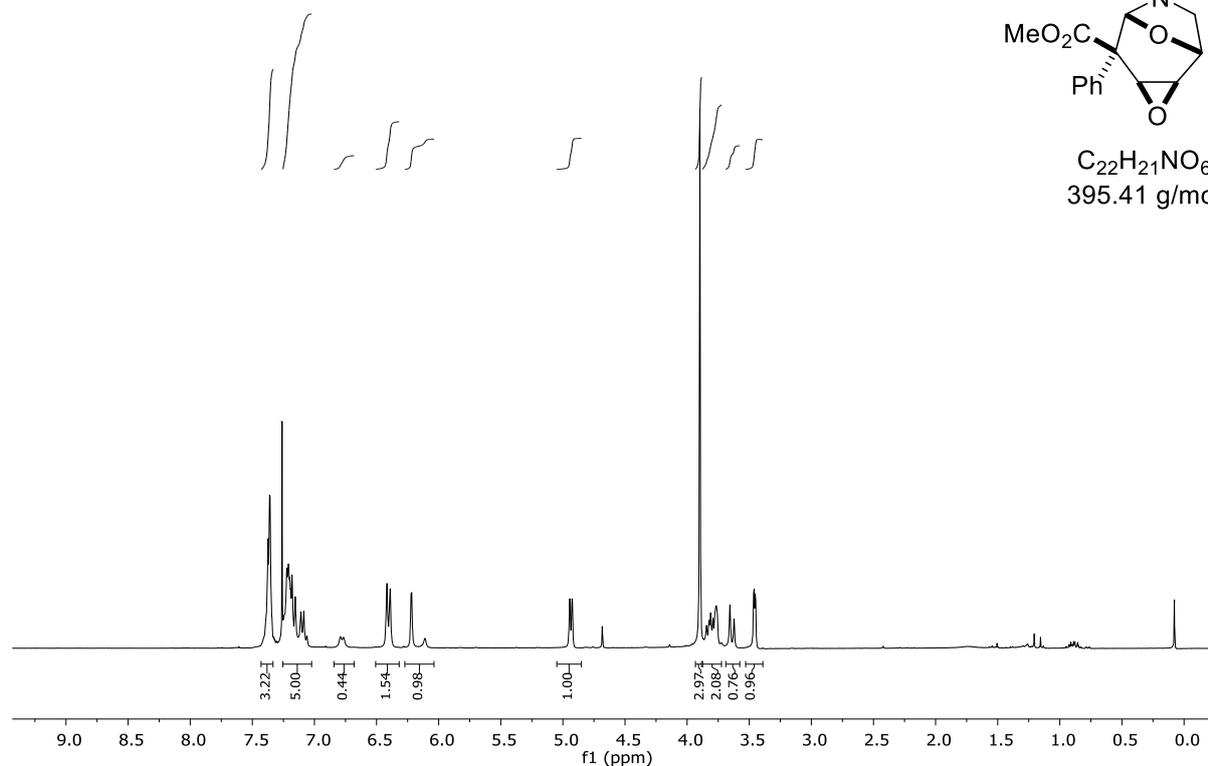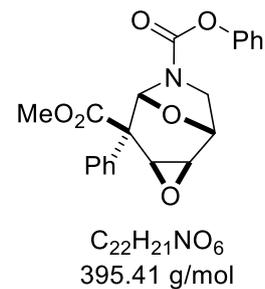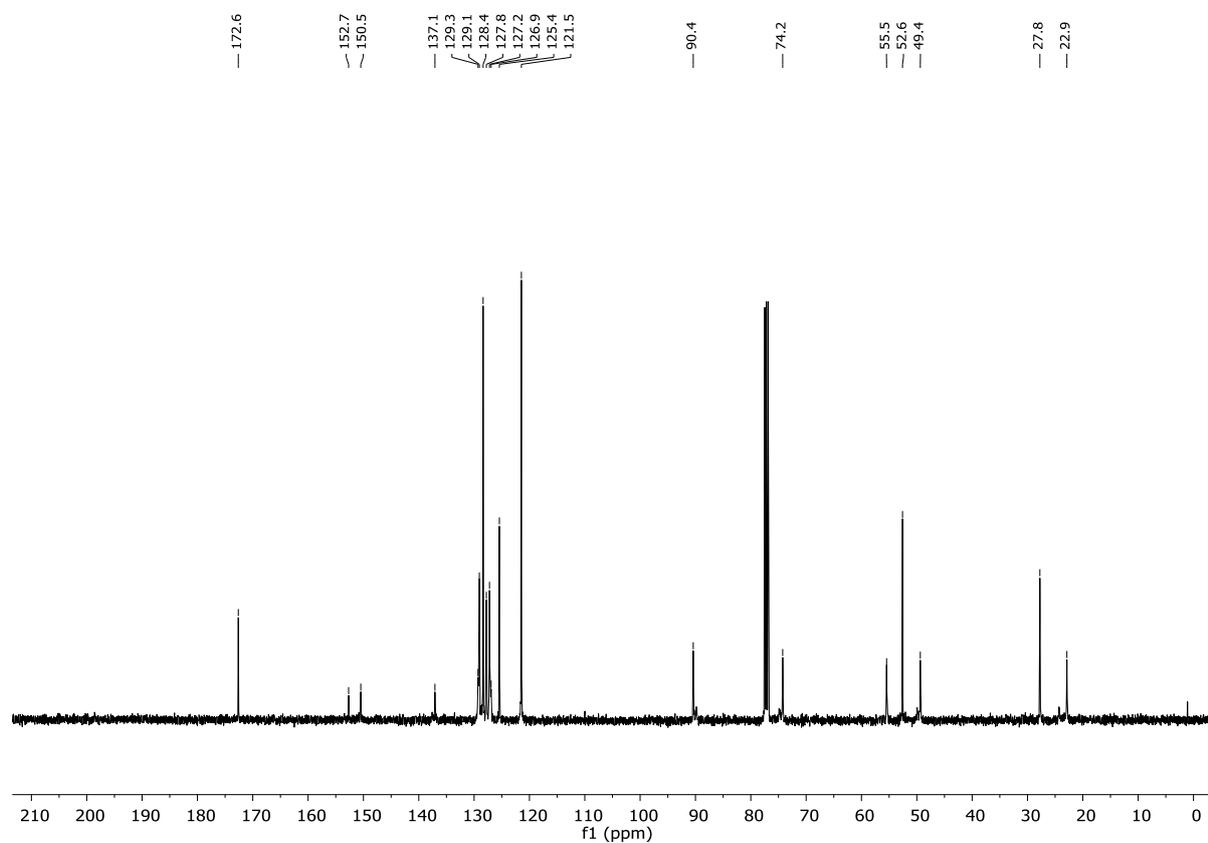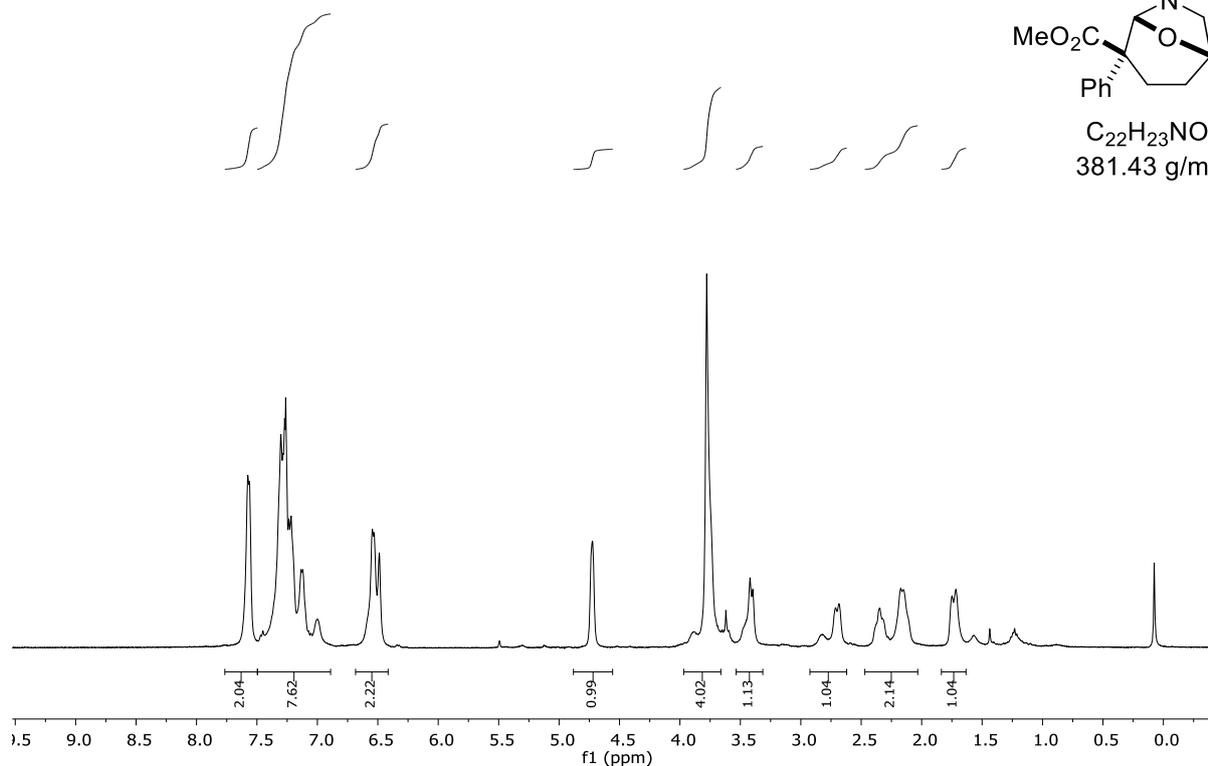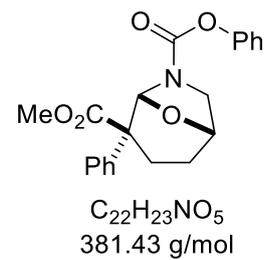
Ethyl 6-bromo-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (116)

C$_{10}$H$_{16}$BrNO$_4$
294,15 g/mol
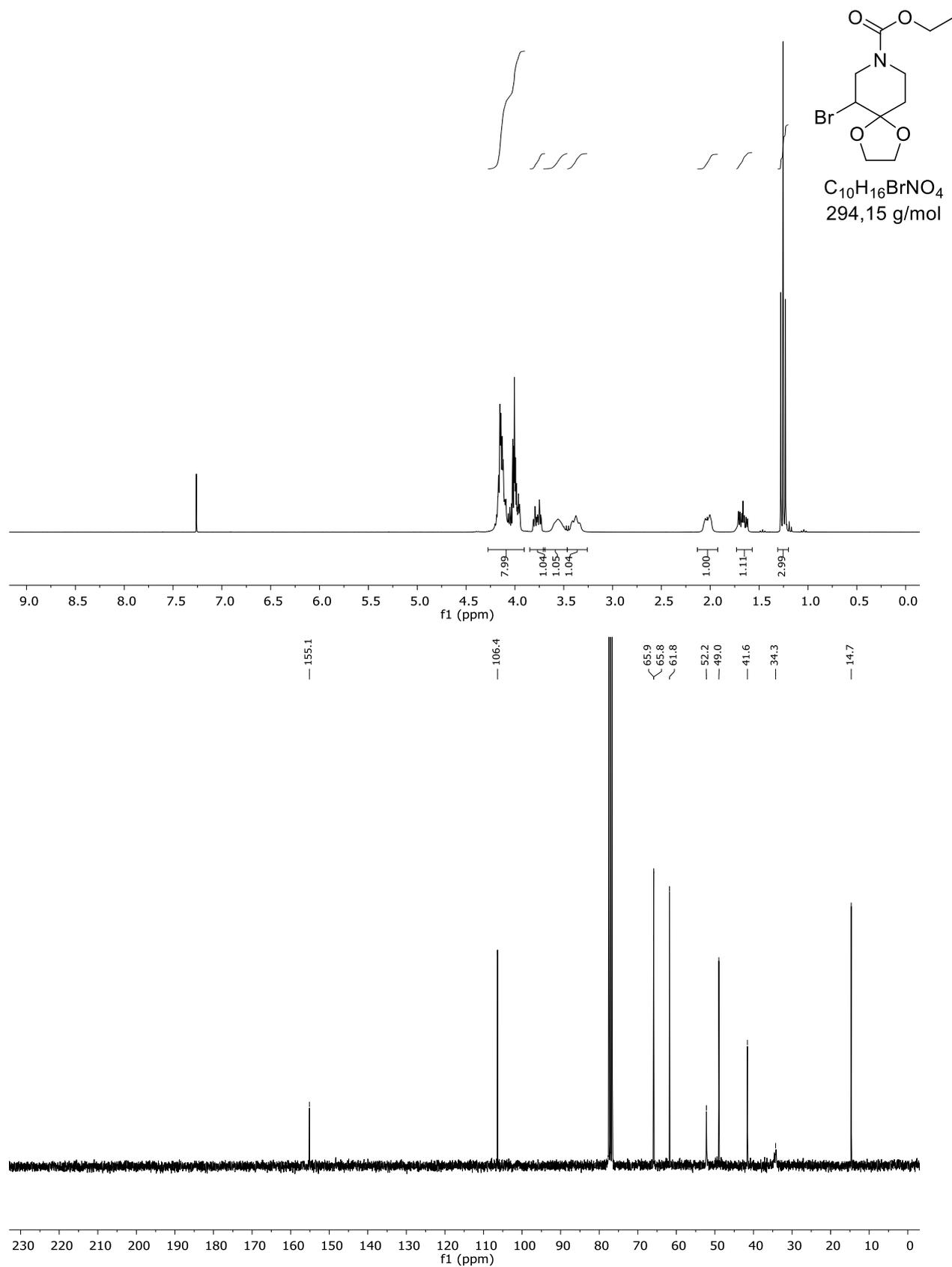
Ethyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (118)
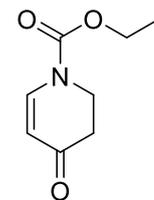
C$_8$H$_{11}$NO$_3$
169.18 g/mol
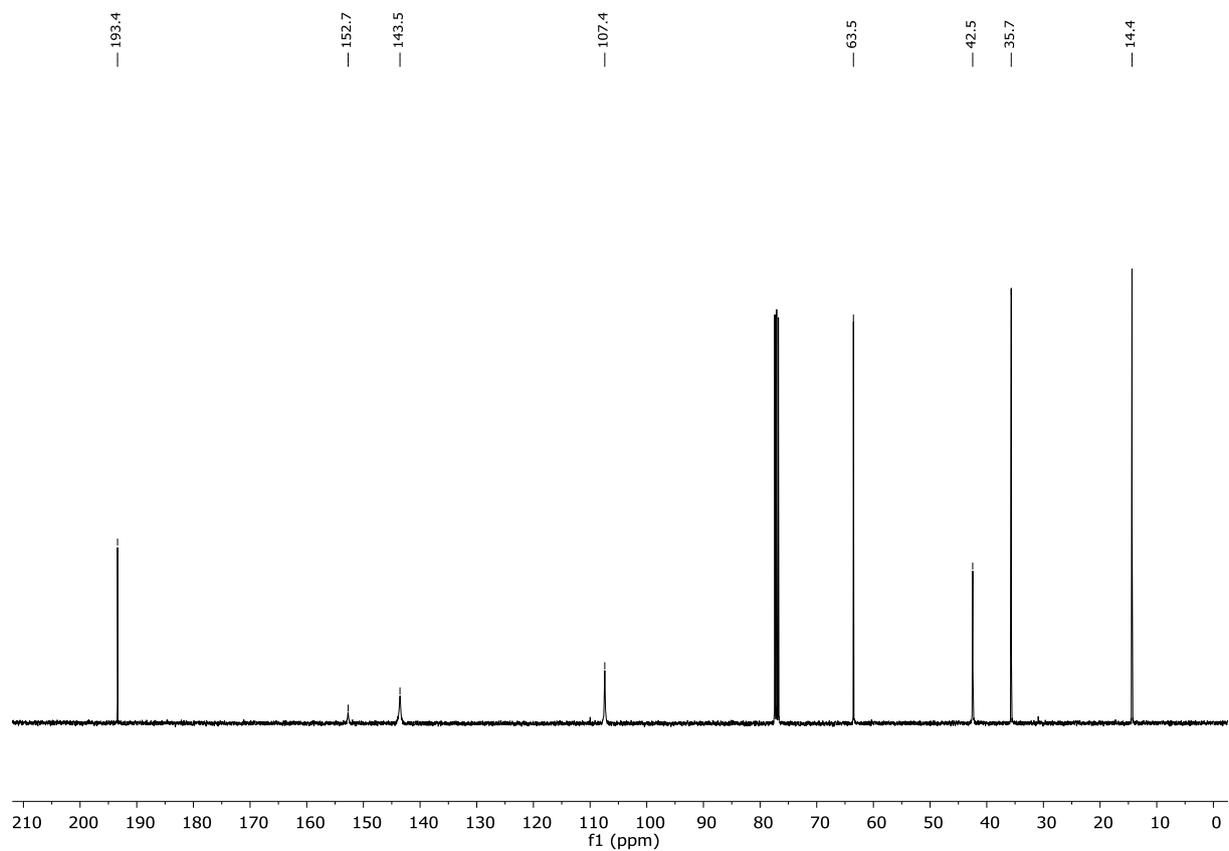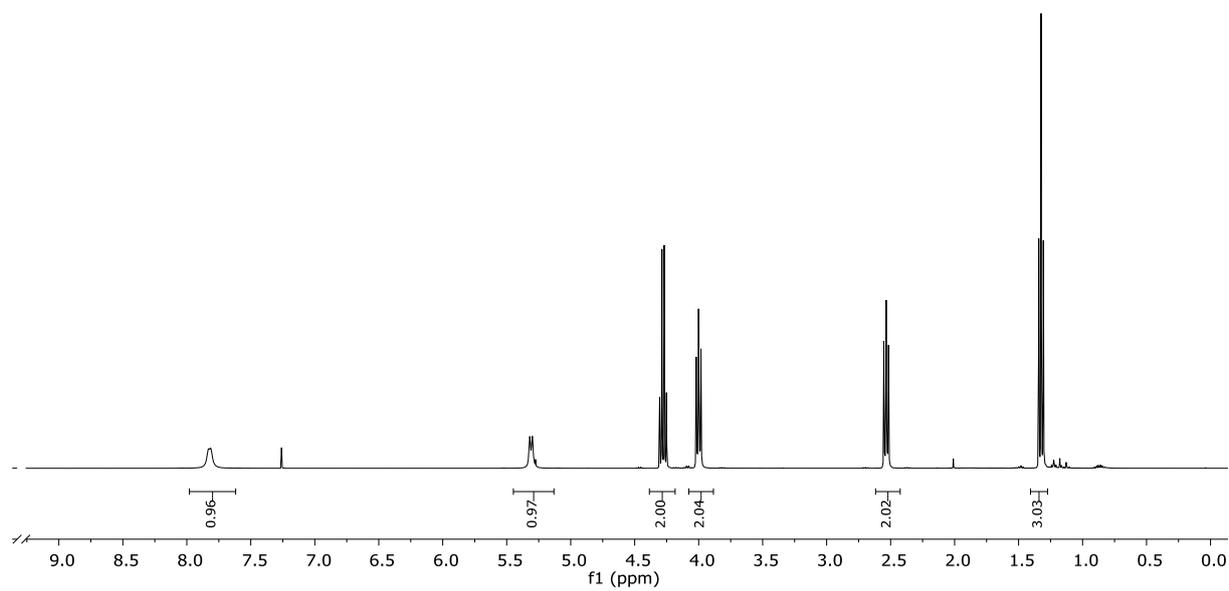
Ethyl (*S*)-4-hydroxy-3,4-dihydropyridine-1(2H)-carboxylate (123)

$C_8H_{13}NO_3$
171.20 g/mol
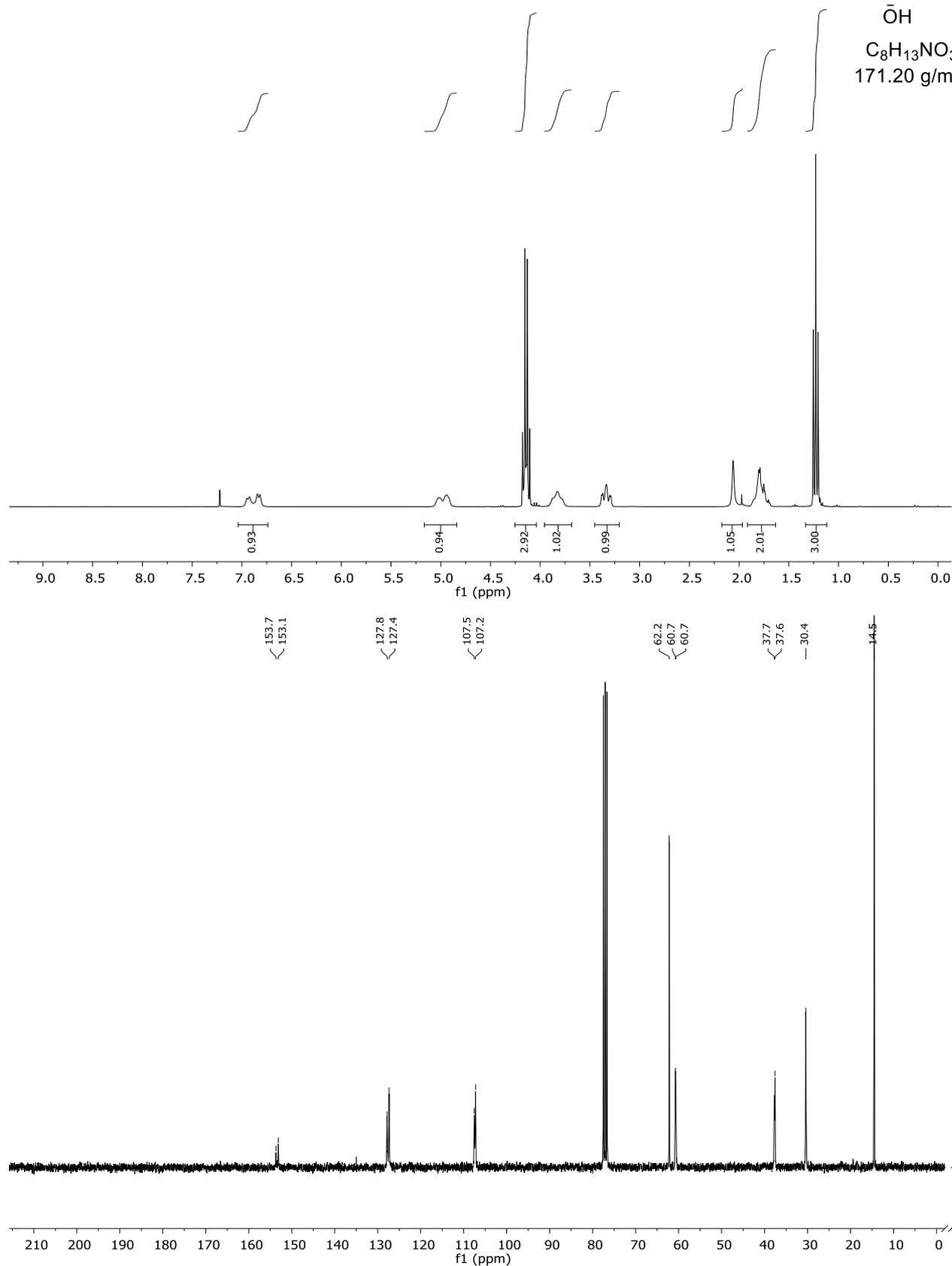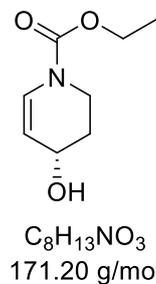
Ethyl (*S*)-4-acetoxy-3,4-dihydropyridine-1(2H)-carboxylate (125)
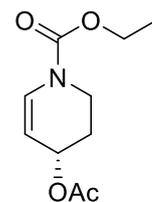
C$_{10}$H$_{15}$NO$_4$
213.23 g/mol
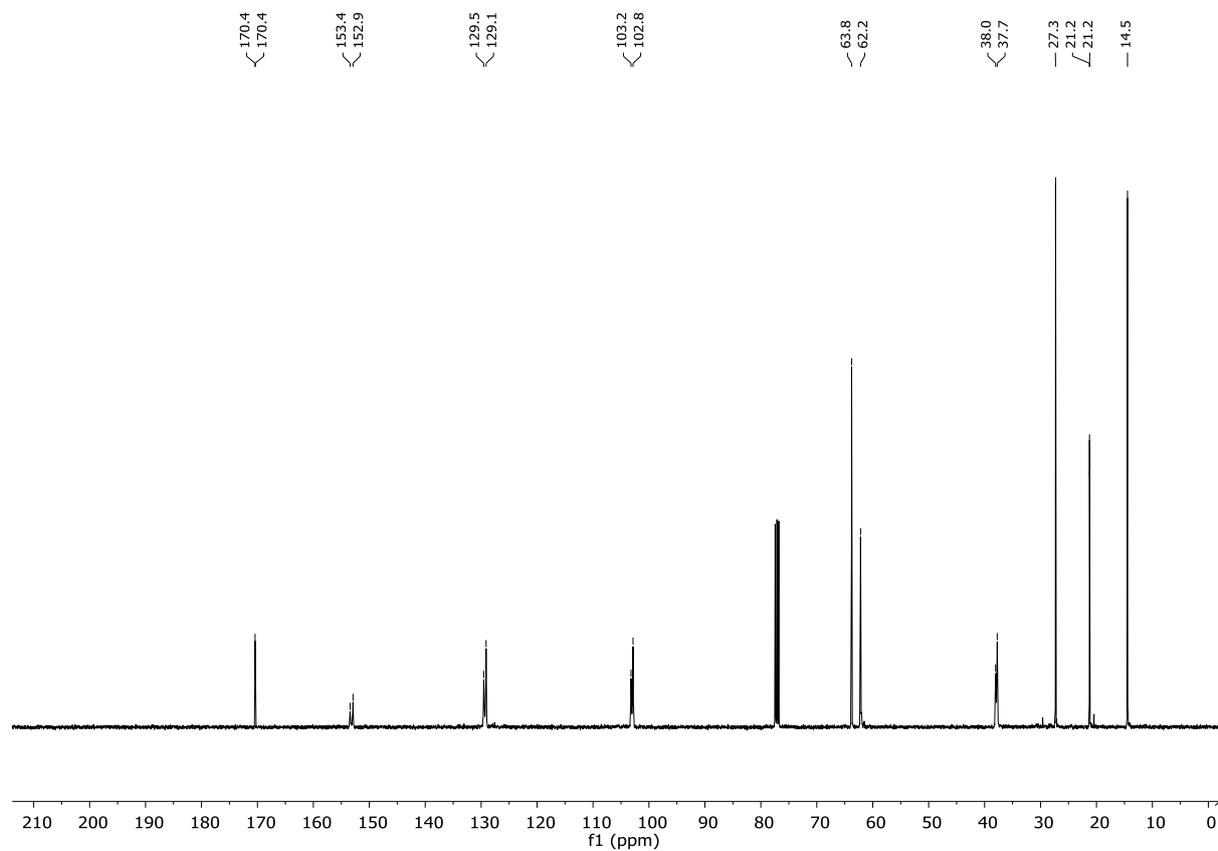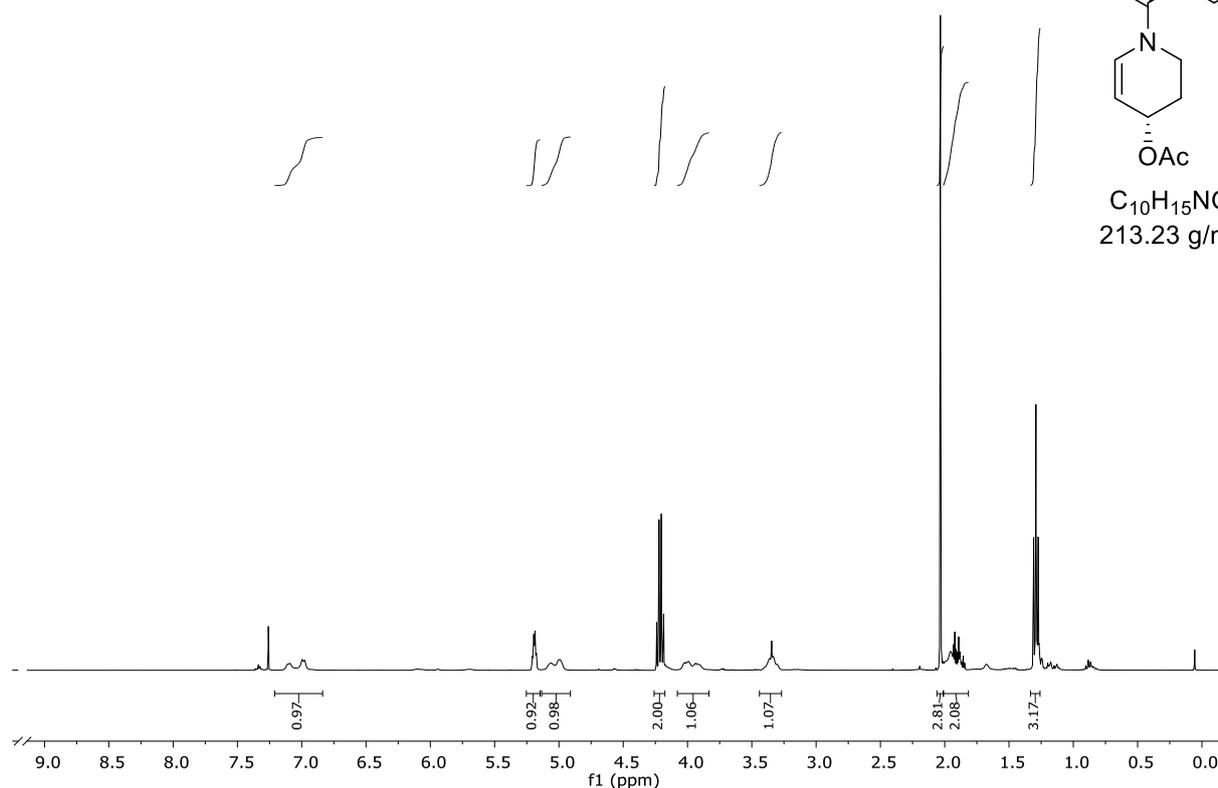
(±)-Ethyl 3-bromo-4-oxopiperidine-1-carboxylate (169)
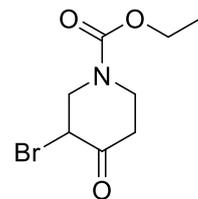
C$_8$H$_{12}$BrNO$_3$
250.09 g/mol
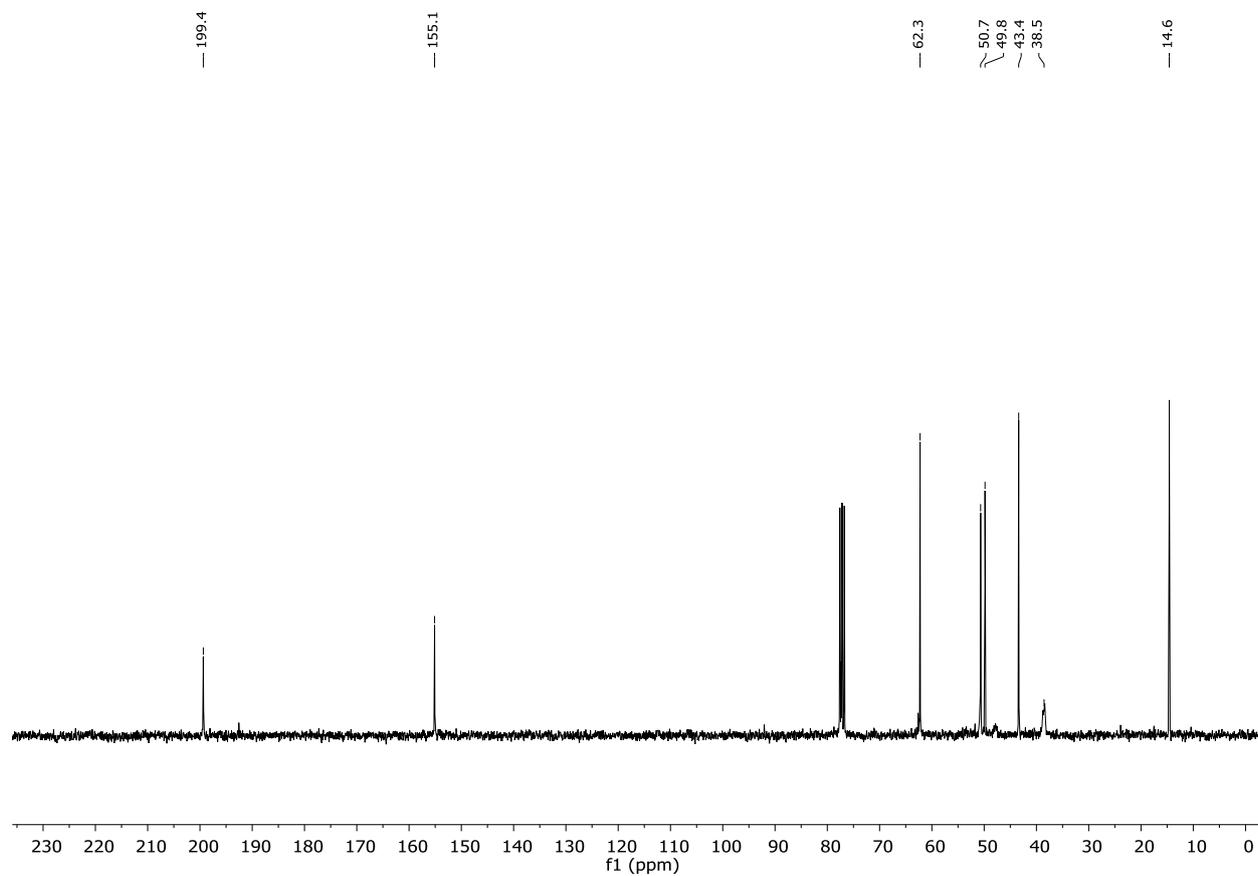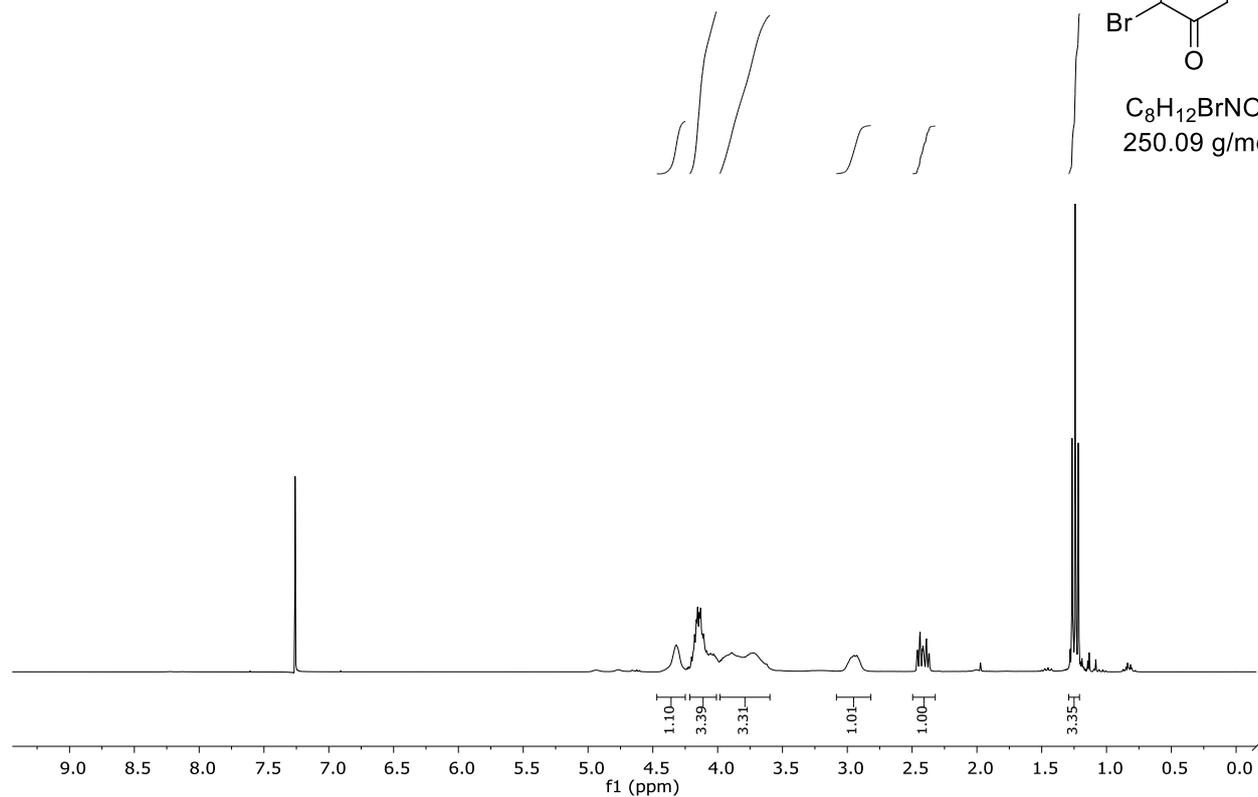
(±)-Ethyl (3*R*,4*S*)-3-bromo-4-hydroxypiperidine-1-carboxylate (170)

$C_8H_{14}BrNO_3$
252.11 g/mol
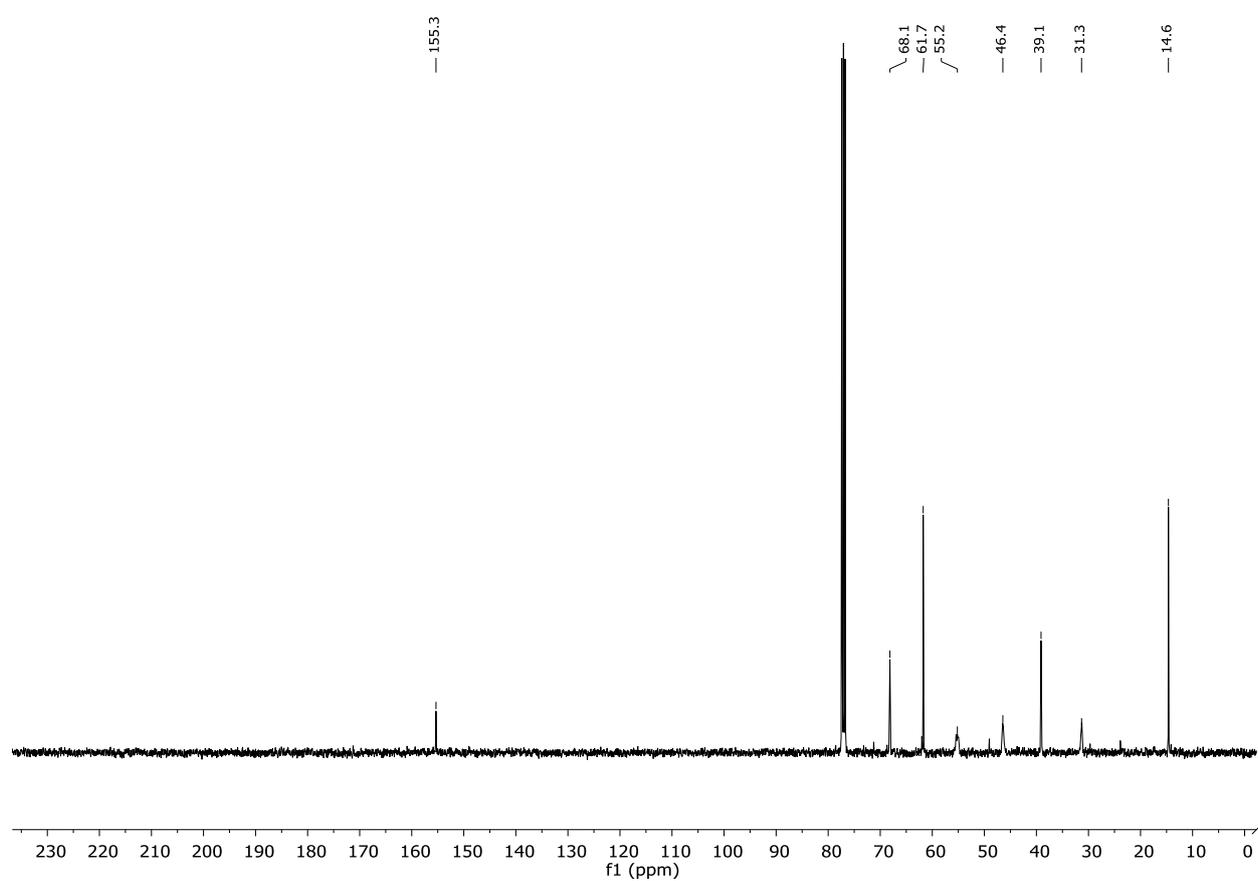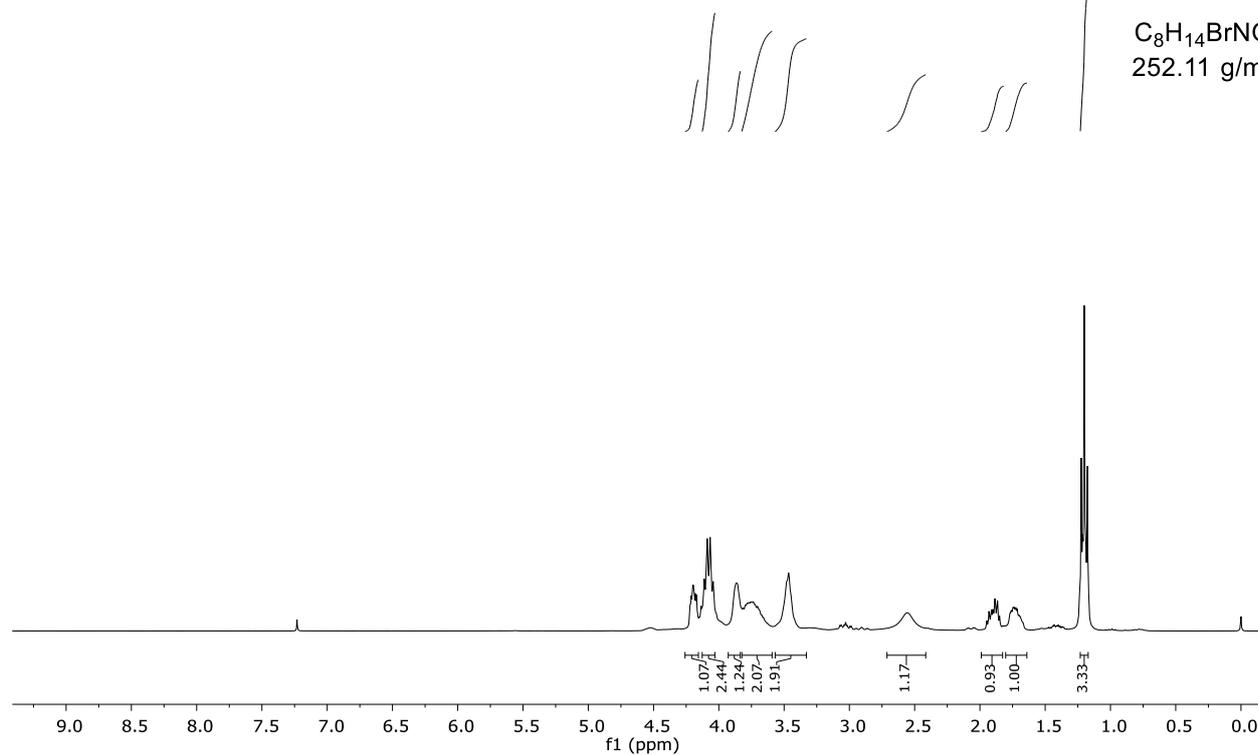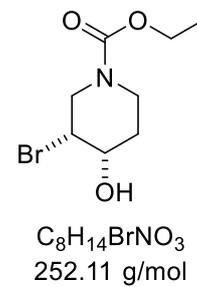
Ethyl (3*R*,4*S*)-4-acetoxy-3-bromopiperidine-1-carboxylate (171)
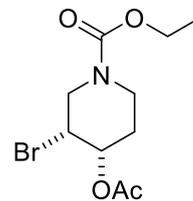
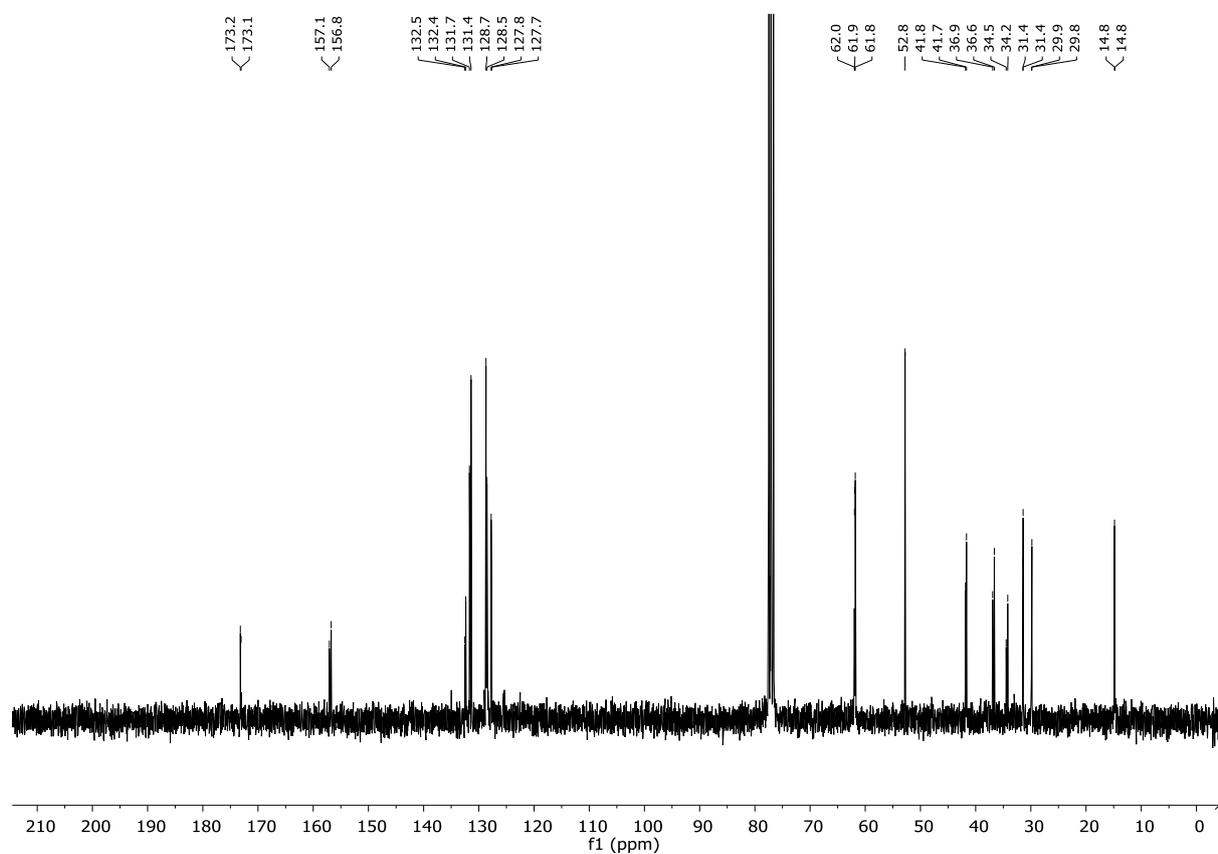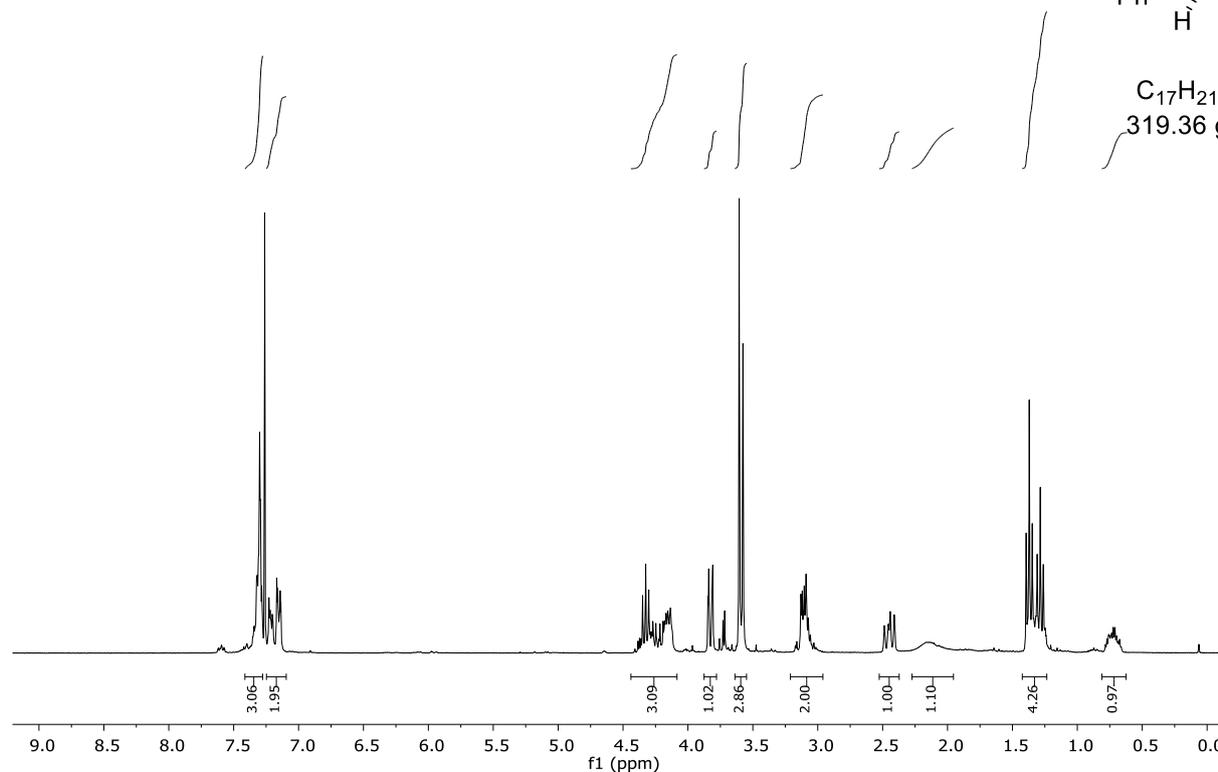$C_{10}H_{16}BrNO_4$
294.15 g/mol

2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-acetoxy-7-(3-methoxyphenyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (191)

C$_{20}$H$_{25}$NO$_7$
391,42 g/mol

2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-hydroxy-7-(3-methoxyphenyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (EX5)

C$_{18}$H$_{23}$NO$_6$
349,38 g/mol

2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-7-(3-methoxyphenyl)-5-((methylsulfonyl)oxy)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (192)

C₁₉H₂₅NO₈S

$C_{19}H_{25}NO_8S$
427,47 g/mol

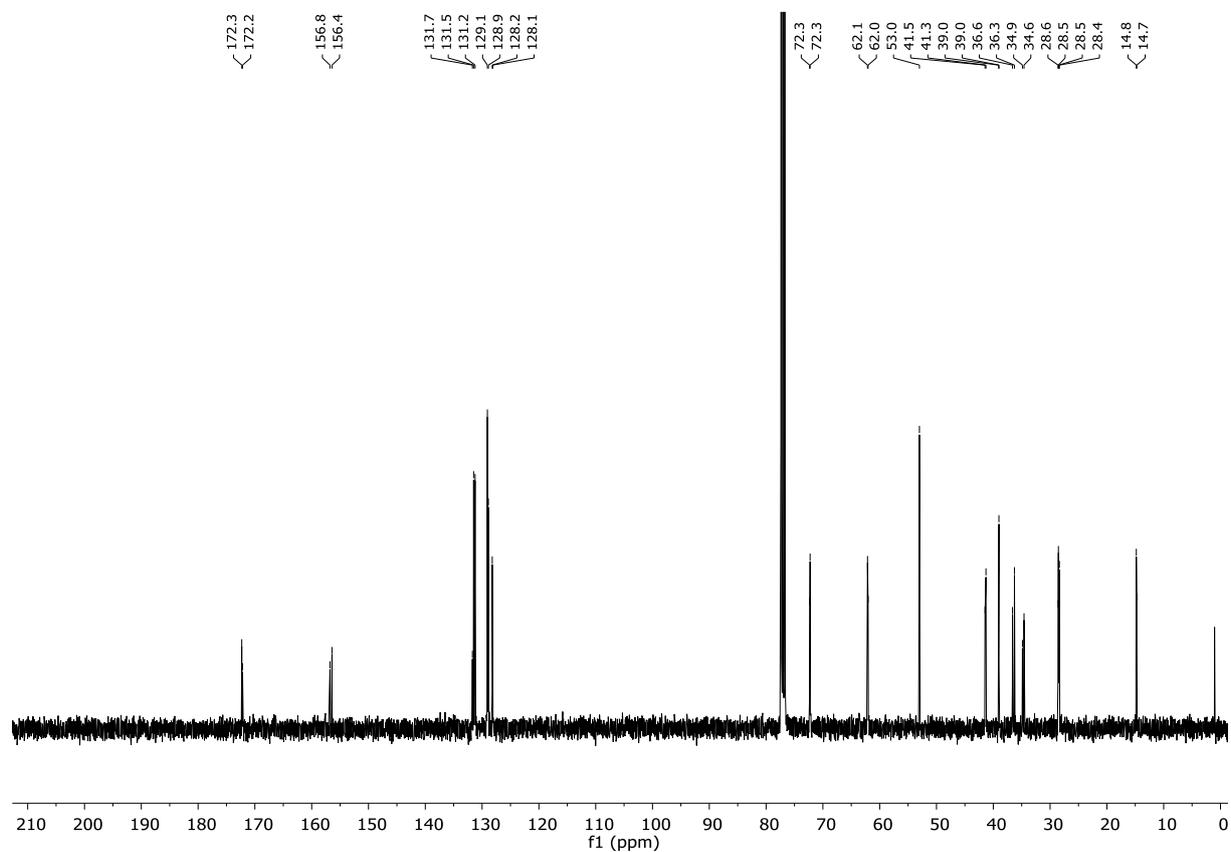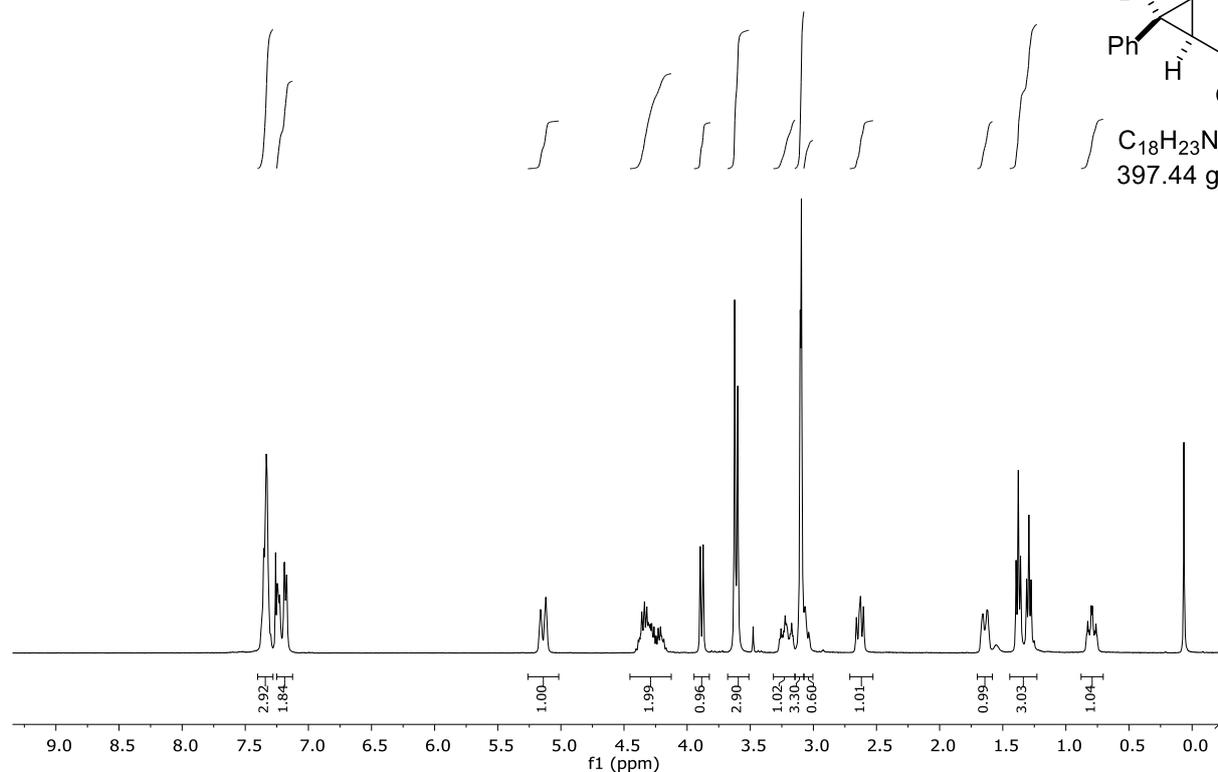# (±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-acetoxy-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate ((±)-126)
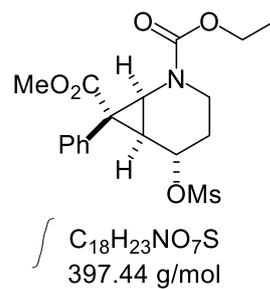

C$_{19}$H$_{23}$NO$_6$
361.39 g/mol

(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-hydroxy-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (127)
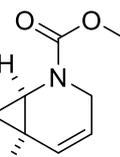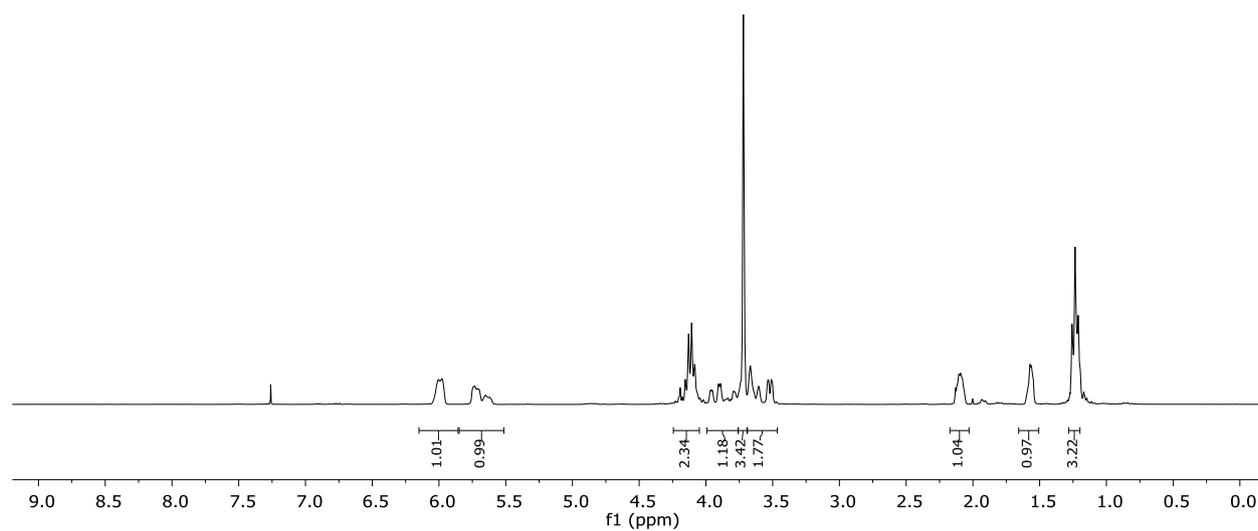
$C_{17}H_{21}NO_5$

319.36 g/mol

(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-((methylsulfonyl)oxy)-7-phenyl-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate ((±)-128)
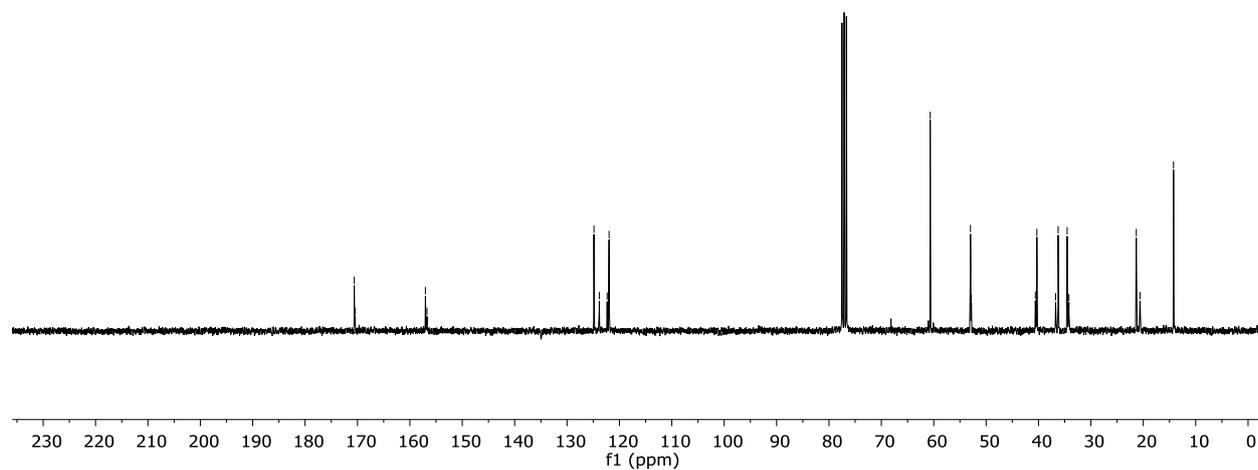
C₁₈H₂₃NO₇S

$C_{18}H_{23}NO_7S$
397.44 g/mol

(±)-7-ethyl 2-methyl (1*S*,6*S*,7*S*)-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (225)

$C_{11}H_{15}NO_4$
225.24 g/mol

(±)-7-ethyl 3-methyl (1R,6R,7R)-3-azabicyclo[4.1.0]hept-4-ene-3,7-dicarboxylate (229)

C$_{11}$H$_{15}$NO$_4$
225.24 g/mol

7-ethyl 2-phenyl (1*S*,6*R*,7*S*)-5-methyl-2-azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (235)

C$_{17}$H$_{19}$NO$_4$
301.34 g/mol

7-ethyl 3-phenyl (1*S*,6*R*,7*S*)-6-methyl-3-azabicyclo[4.1.0]hept-4-ene-3,7-dicarboxylate (237)

1-Ethyl 3-methyl (*R*)-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (193)

C$_{18}$H$_{23}$NO$_5$
333,38 g/mol

Ethyl (*R*)-3-(hydroxymethyl)-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (200)

C$_{17}$H$_{23}$NO$_4$
305,37 g/mol

Ethyl (*R*)-3-formyl-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (203)

303.15 g/mol
C$_{17}$H$_{21}$NO$_4$

Ethyl (*S*)-3-(3-methoxyphenyl)-3-vinyl-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (204)

301.39 g/mol
$C_{18}H_{23}NO_3$

Ethyl (*S*)-3-ethyl-3-(3-methoxyphenyl)azepane-1-carboxylate (205)

305.42 g/mol
$C_{18}H_{27}NO_3$

(±)-Ethyl (*S*)-3-ethyl-3-(3-hydroxyphenyl)azepane-1-carboxylate (207)

291.39 g/mol
$C_{17}H_{25}NO_3$

(*S*)-3-Ethyl-3-(3-methoxyphenyl)-1-methylazepane (206)

247.38 g/mol
$C_{16}H_{25}NO$

(*S*)-3-(3-Ethyl-1-methylazepan-3-yl)phenol (*S*-(-)-9)

C₁₅H₂₃NO
233.36 g/mol

(±)-1-Ethyl 3-methyl (*R*)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (129)

C₁₇H₂₁NO₄
303.36 g/mol

(±)-1-Ethyl 3-methyl (3R)-2-methoxy-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (180)

$C_{18}H_{23}NO_5$

333.38 g/mol

(±)-1-Ethyl 3-methyl (3*R*)-2-(2-bromoethoxy)-3-phenyl-2,3,6,7-tetrahydro-1H-azepine-1,3-dicarboxylate (181)

C$_{19}$H$_{24}$BrNO$_5$
426.31 g/mol

(±)-(*R*)-(1-Methyl-3-phenyl-2,3,6,7-tetrahydro-1H-azepin-3-yl)methanol (EX6)

C$_{14}$H$_{19}$NO
217.31 g/mol
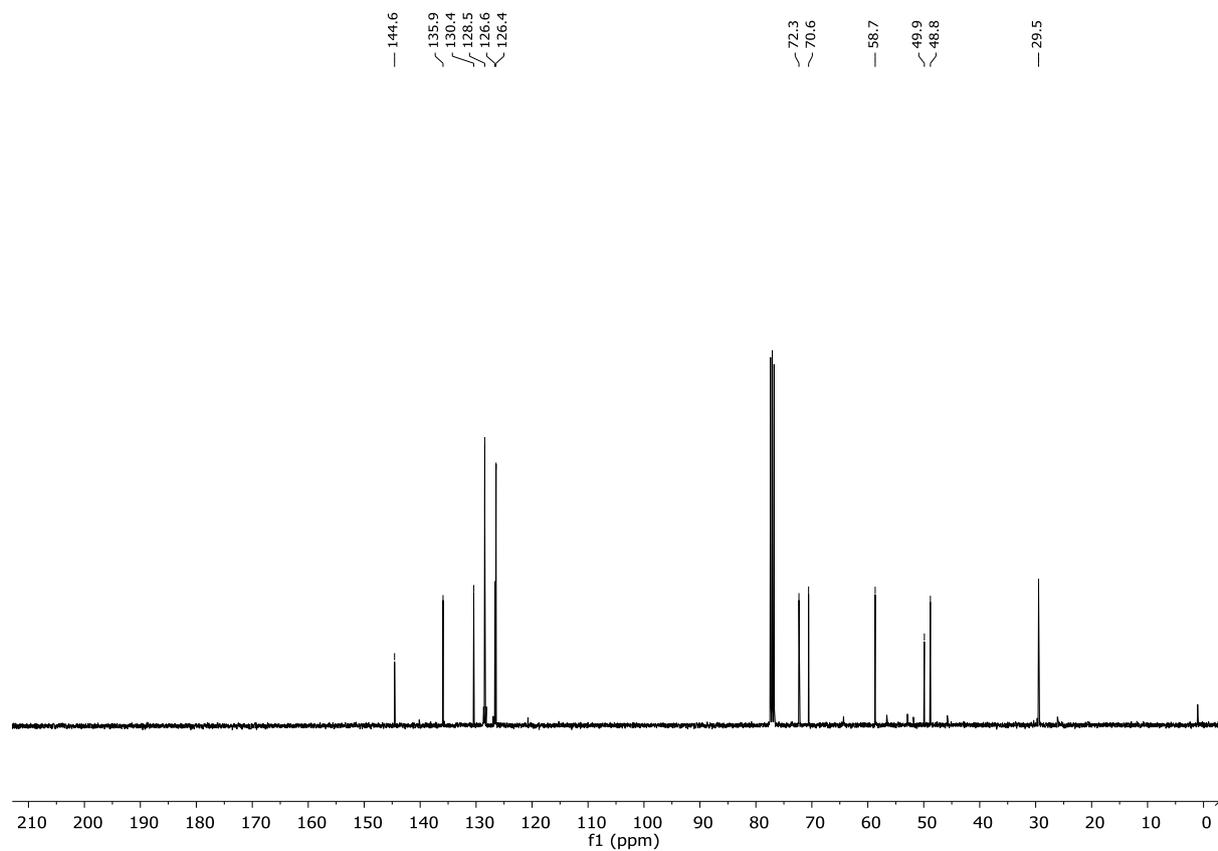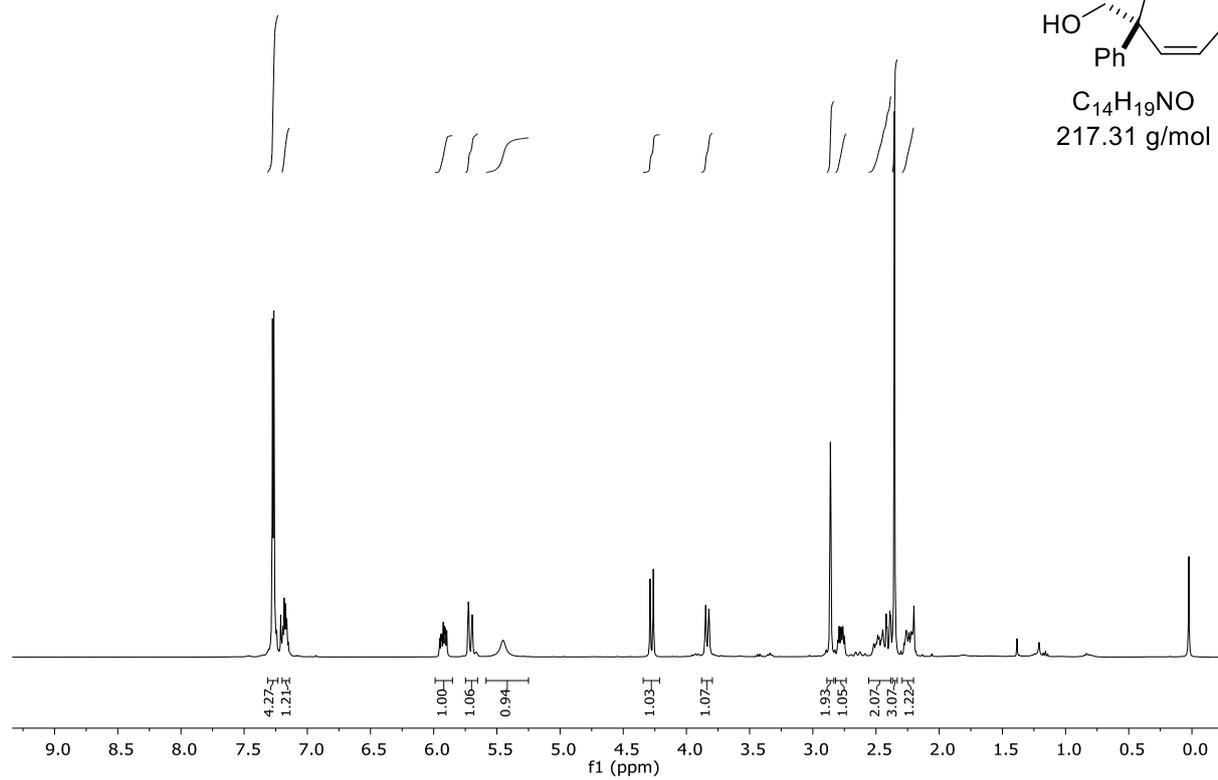
(±)-(*R*)-(1-Methyl-3-phenyl-2,3,6,7-tetrahydro-1H-azepin-3-yl)methyl 4-methylbenzenesulfonate (194)
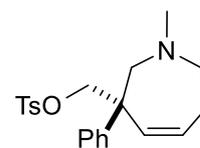
$C_{21}H_{25}NO_3S$
371.50 g/mol
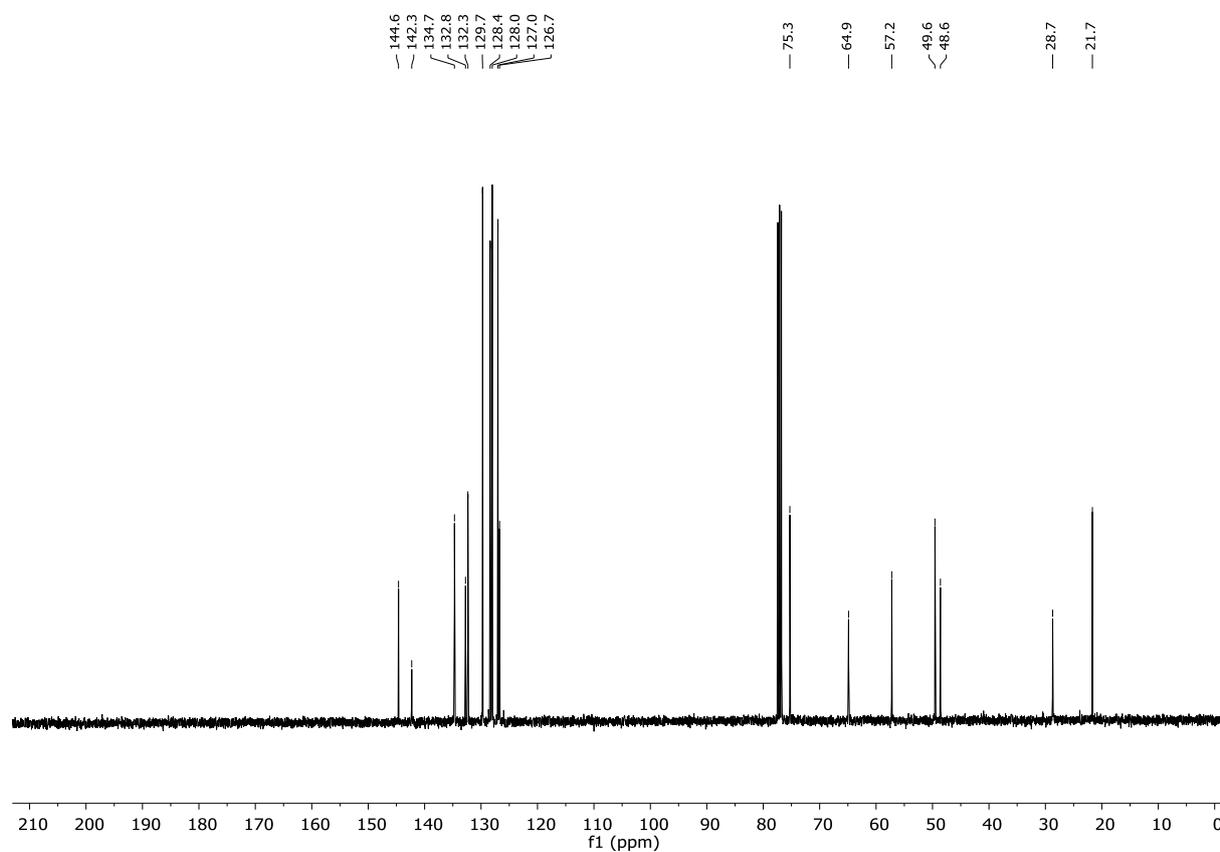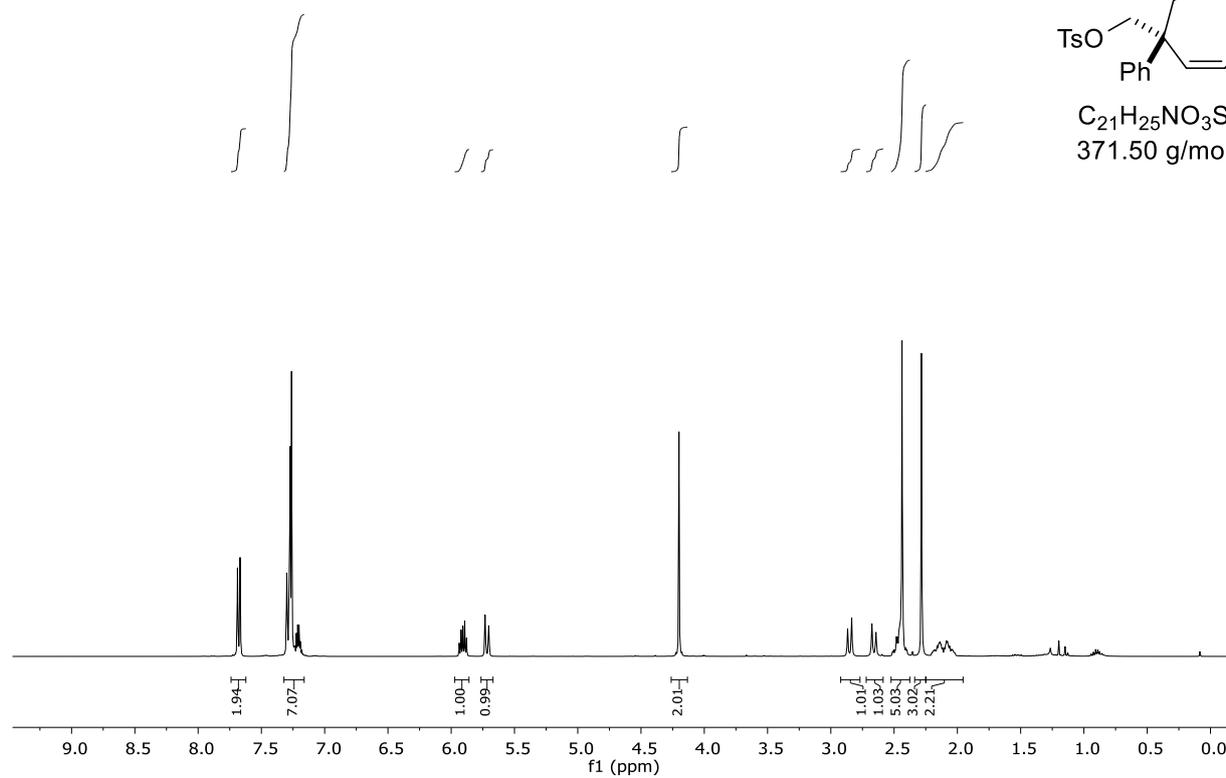
1-Methyl-6-phenyl-1-azabicyclo[4.1.1]oct-4-en-1-ium-4-methylbenzenesulfonate (195)
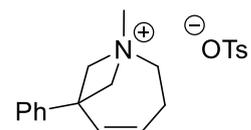
$C_{14}H_{18}N^+C_7H_7O_3S^-$

200.30 + 171.19 g/mol

(±)-4-Ethyl 2-methyl (2*R*)-2-phenyl-8-oxa-4-azabicyclo[5.1.0]octane-2,4-dicarboxylate (208)

$C_{17}H_{21}NO_5$
319.36 g/mol
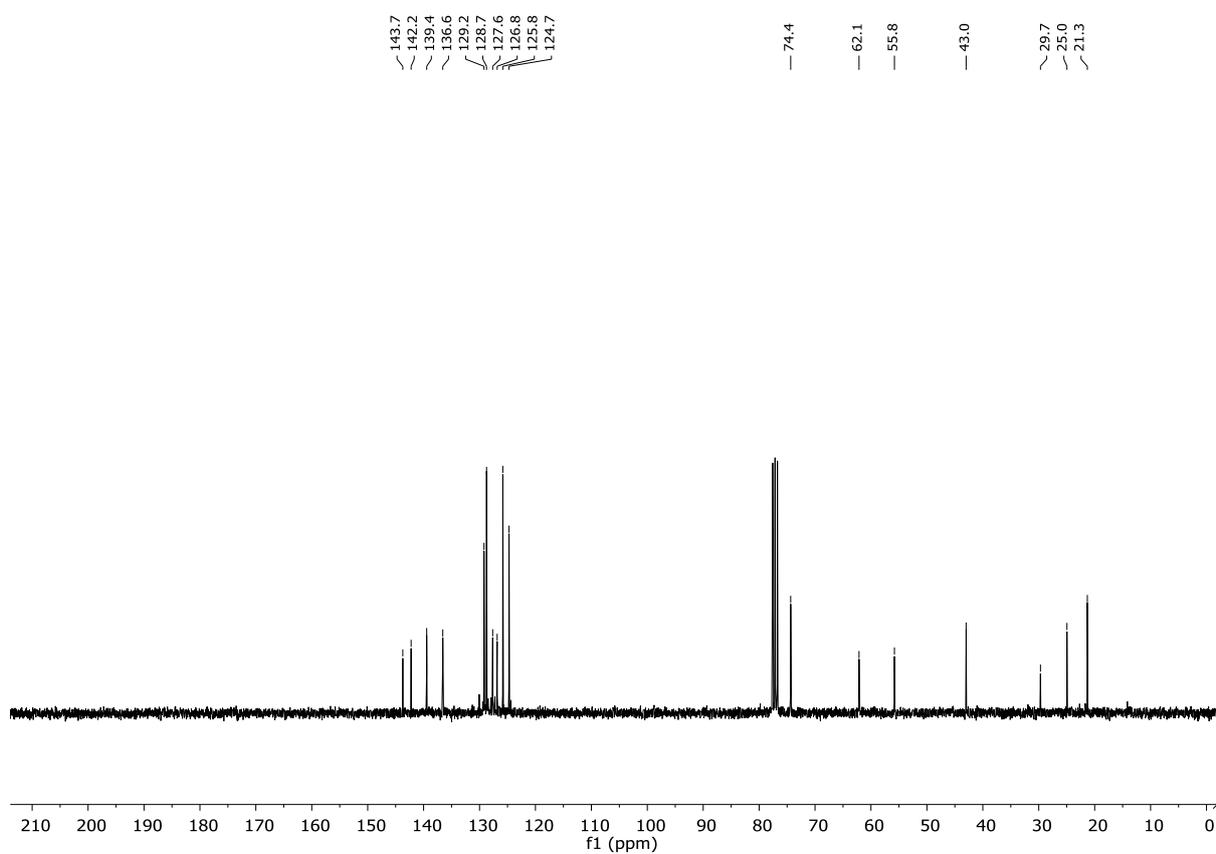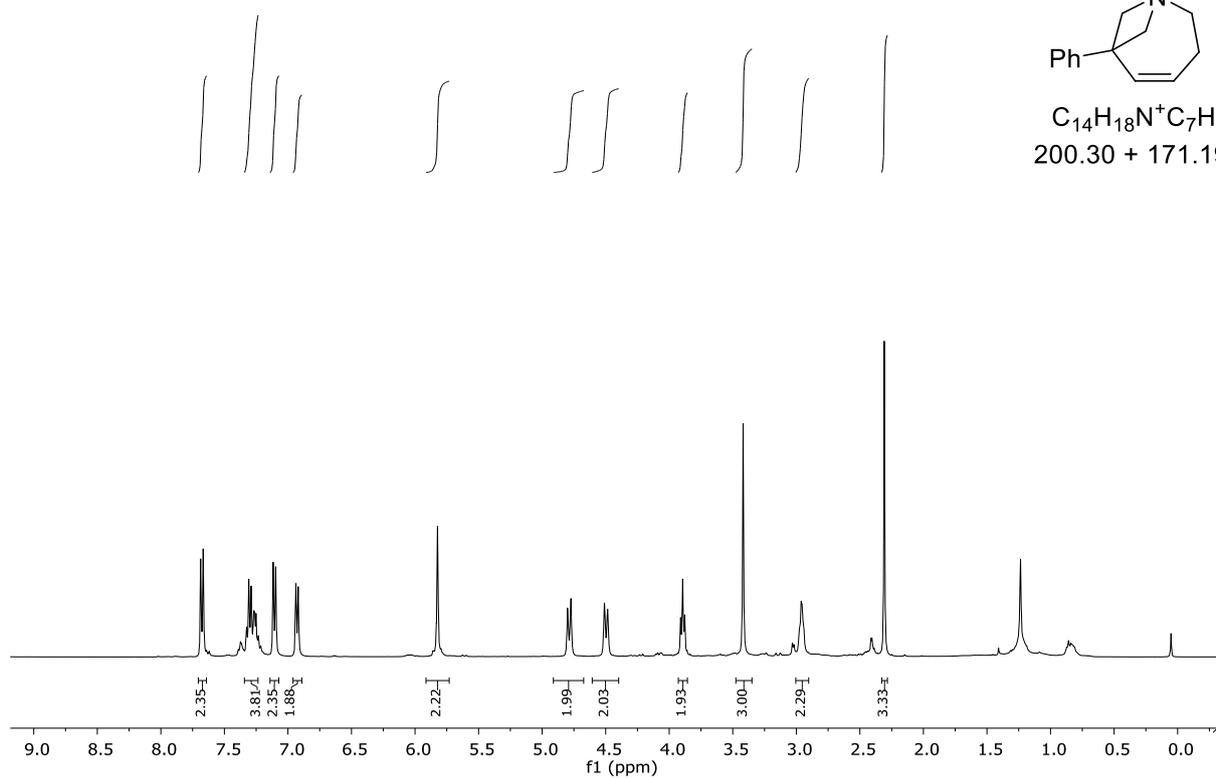
(±)-1-Ethyl 3-methyl (*R*)-3-phenylazepane-1,3-dicarboxylate (210)

C$_{17}$H$_{23}$NO$_4$
305.37 g/mol

(±)-Ethyl (1*R*,6*S*,7*R*)-6-hydroxy-9-oxo-1-phenyl-8-oxa-3-azabicyclo[5.2.0]nonane-3-carboxylate (209)

C$_{16}$H$_{19}$NO$_5$
305.33 g/mol

(±)-Ethyl (*R*)-3-(hydroxymethyl)-3-phenylazepane-1-carboxylate (211)

C$_{16}$H$_{23}$NO$_3$
277.36 g/mol

(±)-Ethyl (*R*)-3-formyl-3-phenylazepane-1-carboxylate (212)

$C_{16}H_{21}NO_3$
275.35 g/mol

(±)-Ethyl (*R*)-3-phenyl-3-vinylazepane-1-carboxylate (213)

C$_{17}$H$_{23}$NO$_2$
273.38 g/mol

(±)-Ethyl (*R*)-3-(2-hydroxyethyl)-3-phenylazepane-1-carboxylate (214)

$C_{17}H_{25}NO_3$
291.39 g/mol

(±)-Ethyl (*R*)-3-((*R*)-oxiran-2-yl)-3-phenylazepane-1-carboxylate (215)

C$_{17}$H$_{23}$NO$_3$
289.38 g/mol

^{1}H NMR (f1, ppm):

Integrations: 3.86, 0.99, 3.00, 0.92, 1.20, 1.88, 0.91, 1.86, 4.48, 3.27

^{13}C NMR peaks: 156.9, 156.7, 156.3, 156.3, 142.1, 141.5, 128.2, 128.0, 127.4, 127.2, 126.6, 61.4, 61.3, 59.0, 58.8, 58.5, 58.4, 54.0, 53.7, 50.4, 49.8, 49.7, 49.2, 46.9, 46.7, 46.5, 46.2, 44.5, 44.4, 44.2, 44.0, 33.0, 32.7, 32.6, 29.7, 29.1, 28.5, 28.3, 23.0, 22.9, 22.7, 14.8, 14.6, 14.5

(±)-Ethyl (*R*)-3-(3-methoxyphenyl)-3-((tosyloxy)methyl)-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (196)

C$_{24}$H$_{29}$NO$_6$S
459.56 g/mol

(±)-(6*S*)-6-(3-methoxyphenyl)-1-azabicyclo[4.2.1]non-4-en-8-one (197)
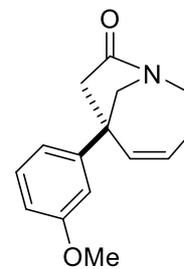
C₁₅H₁₇NO₂
243.31 g/mol
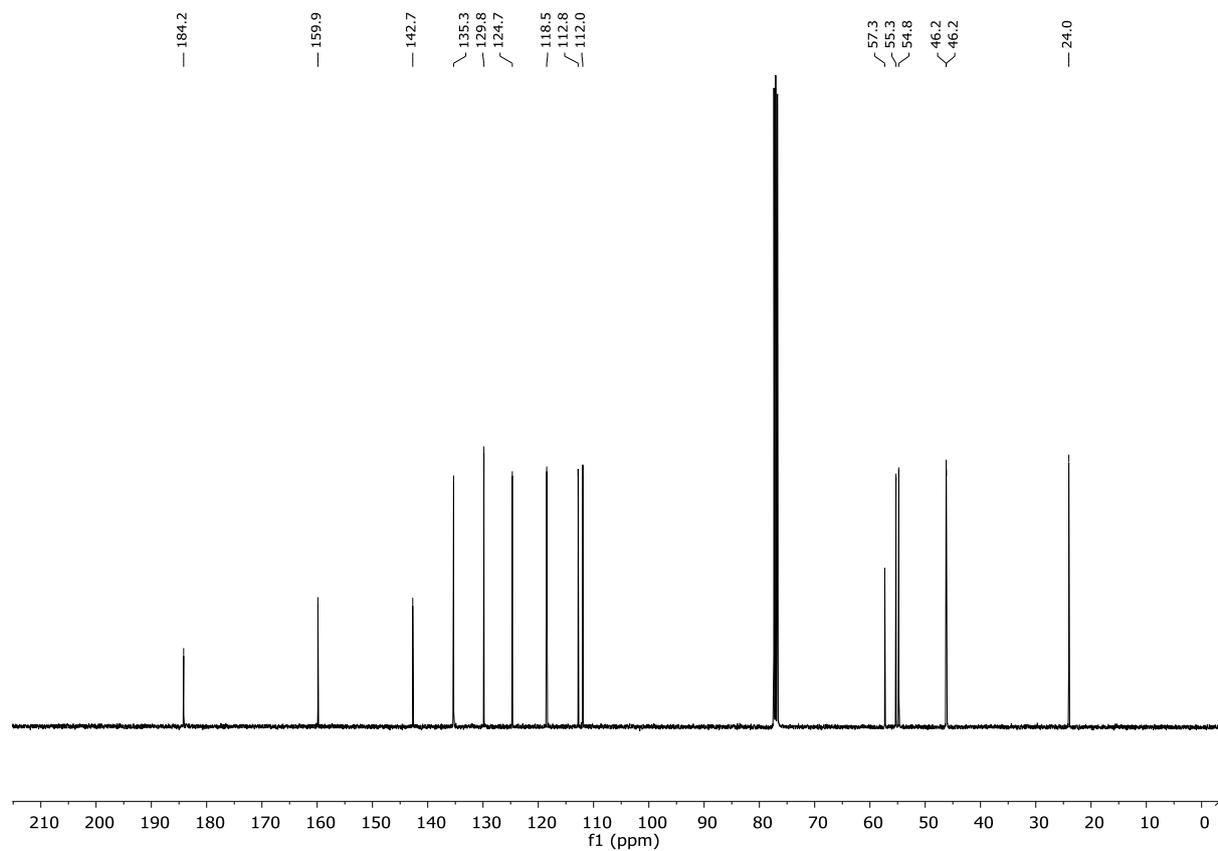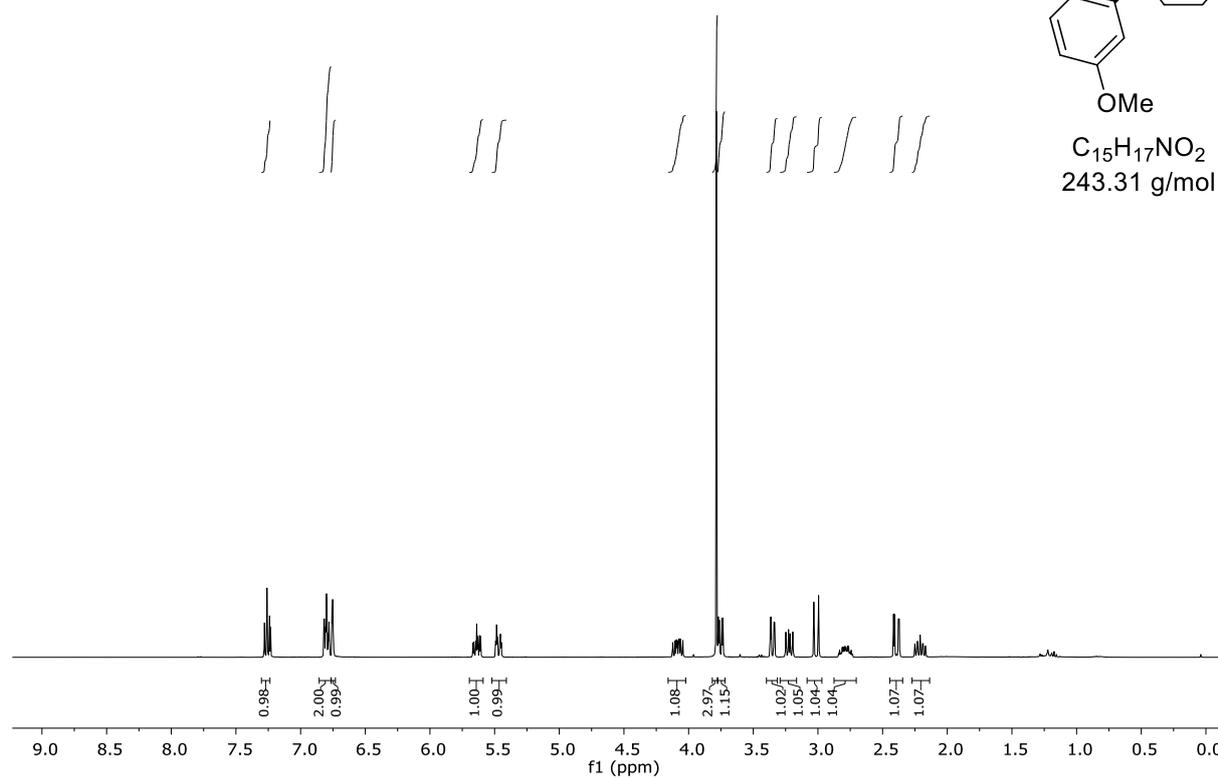
(±)-Ethyl (*S*)-3-ethyl-3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (183)

$C_{18}H_{25}NO_3$
303.40 g/mol
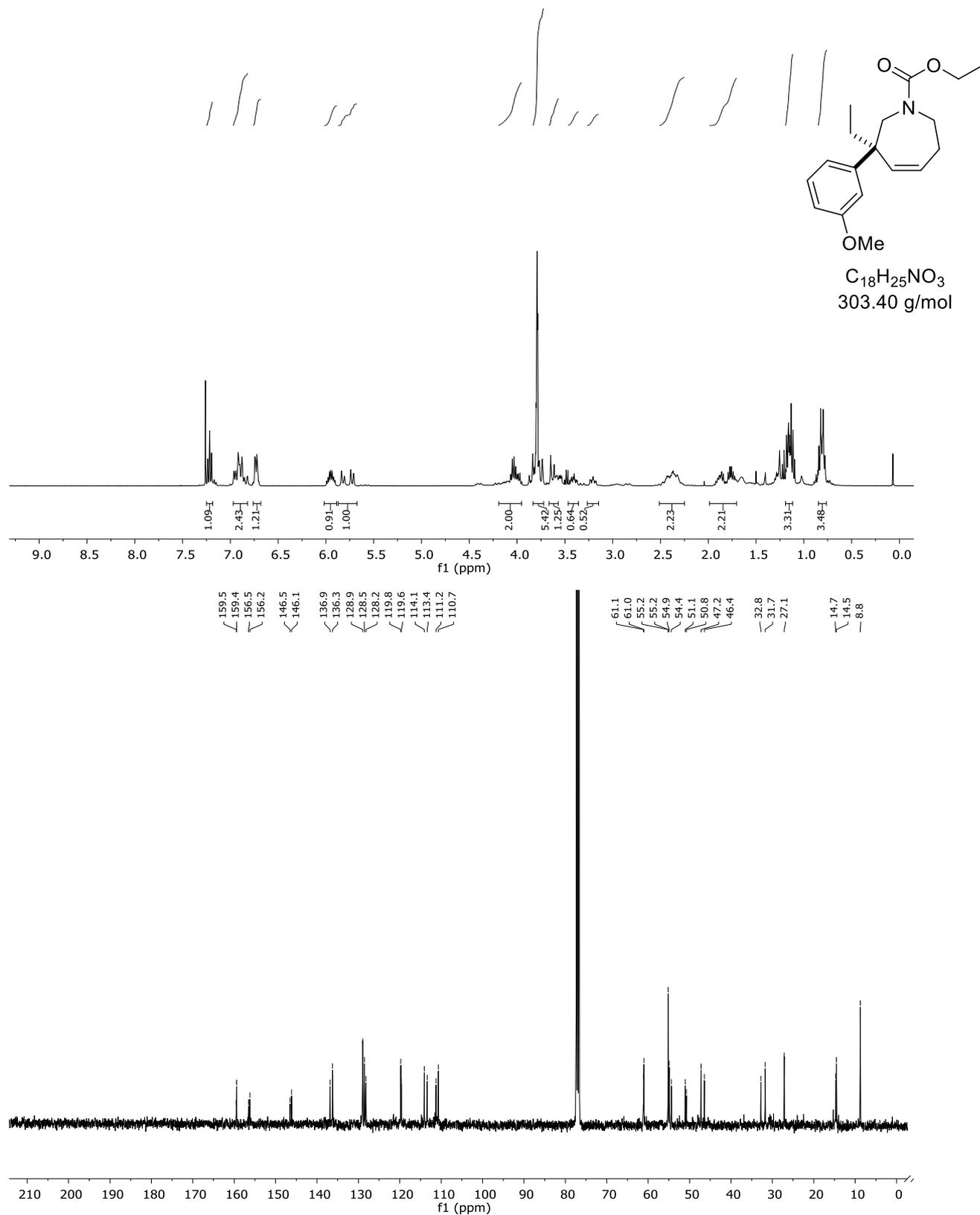
6 X-Ray crystallographic structures

(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-5-hydroxy-7-(3-methoxyphenyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (EX5)

$C_{18}H_{23}NO_6$
349,38 g/mol
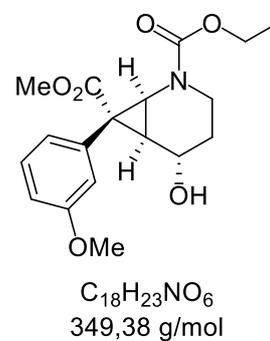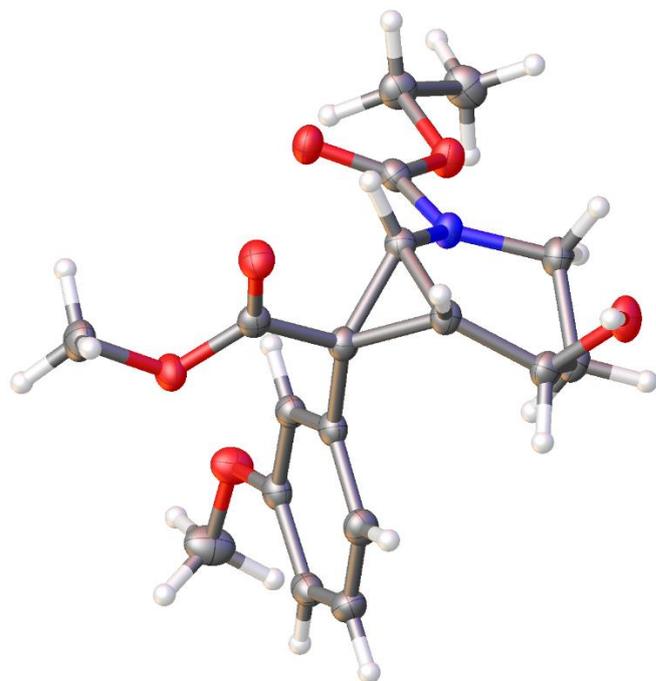
Figure 10: X-Ray crystallographic structure of (±)-2-Ethyl 7-methyl (1S,5S,6S,7R)-5-hydroxy-7-(3-methoxyphenyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (Olex2)

Table 27: Crystal data and structure refinement for EX5

Formula	$C_{18}H_{23}NO_6$
$D_{calc.}$/ g cm^{-3}	1.377
μ/mm^{-1}	0.861
Formula Weight	349.37
Colour	clear colourless
Shape	plate-shaped
Size/mm^3	0.12×0.04×0.04
T/K	123.00(10)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	9.80750(10)
b/Å	14.7859(2)
c/Å	12.0536(2)
α/°	90
β/°	105.324(2)
γ/°	90
V/Å^3	1685.78(4)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu Kα
Θ_{min}/°	4.839
Θ_{max}/°	73.630
Measured Refl's.	19939
Indep't Refl's	3293
Refl's I≥2 σ(I)	2889
R_{int}	0.0247
Parameters	230
Restraints	0
Largest Peak	0.275
Deepest Hole	-0.212
GooF	1.042
wR_2 (all data)	0.0887
wR_2	0.0851
R_1 (all data)	0.0380
R_1	0.0327

Table 28: Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for EX5. Ueq is defined as 1/3 of the trace of the orthogonalised Uij.

Atom	x	y	z	U_{eq}
O5	9120.9(9)	3300.4(6)	6004.3(7)	24.1(2)
O3	6142.5(9)	934.1(6)	5794.2(7)	24.1(2)
O6	8638.0(9)	4791.8(6)	5726.2(7)	23.9(2)
O2	6825.3(9)	936.9(6)	4159.4(7)	25.3(2)
O1	4519.4(10)	3542.8(6)	1825.0(7)	27.5(2)
O4	5958.8(9)	3603.8(6)	8414.4(7)	26.6(2)
N1	7181.1(10)	3771.2(7)	4638.8(8)	19.9(2)
C16	8368.5(12)	3912.2(8)	5492.1(10)	20.4(2)
C4	5064.6(12)	2642.2(8)	5548.8(10)	20.1(2)
C5	5812.2(12)	2996.3(8)	6600.5(10)	20.1(2)
C11	6305.1(12)	1318.7(8)	4837.2(10)	20.3(2)
C6	5105.4(13)	3293.1(8)	7395.2(10)	20.9(3)
C3	5822.8(12)	2282.6(8)	4712.9(10)	19.7(2)
C9	3590.4(13)	2584.9(8)	5297.8(11)	24.0(3)
C2	5506.2(12)	2625.5(8)	3472.3(10)	20.1(2)
C10	6900.0(12)	2853.9(8)	4272.8(10)	19.4(2)
C7	3636.5(13)	3258.1(8)	7137.1(11)	23.2(3)
C1	4450.7(13)	3371.6(8)	2980.5(10)	22.0(3)
C13	6361.0(13)	4484.1(8)	3903.9(11)	23.0(3)
C12	4795.4(13)	4259.8(8)	3635.7(11)	23.5(3)
C8	2893.9(13)	2896.6(9)	6084.5(11)	25.4(3)
C17	9982.9(13)	4986.2(9)	6558.6(11)	26.1(3)
C15	6791.6(14)	50.5(9)	6025.6(12)	28.6(3)
C18	10020.4(15)	5993.0(9)	6762.0(12)	31.2(3)
C14	5301.4(15)	3858.2(11)	9289.9(12)	35.2(3)

*Table 29: Anisotropic Displacement Parameters (×104) for EX5. The anisotropic displacement factor exponent takes the form: -2□2[h2a*2 × U11+ ... +2hka* × b* × U12]*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O5	24.8(4)	22.1(4)	22.4(4)	3.1(3)	0.8(3)	1.0(3)
O3	28.2(4)	19.9(4)	25.1(5)	3.8(3)	8.6(4)	3.0(3)
O6	25.6(4)	19.5(4)	23.3(4)	-1.3(3)	0.5(3)	-2.5(3)
O2	31.5(5)	20.7(4)	24.5(4)	-1.9(3)	8.6(4)	2.8(3)
O1	37.5(5)	24.9(5)	17.1(4)	0.7(3)	1.8(4)	3.3(4)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O4	27.5(5)	31.2(5)	21.4(4)	-7.0(4)	6.8(4)	-4.2(4)
N1	22.0(5)	16.8(5)	19.1(5)	0.4(4)	2.1(4)	0.5(4)
C16	23.2(6)	20.4(6)	18.4(6)	0.8(5)	7.0(5)	-1.3(5)
C4	23.8(6)	16.3(6)	19.8(6)	1.9(4)	5.2(5)	0.8(4)
C5	21.1(6)	18.2(6)	20.8(6)	1.9(4)	5.0(5)	0.0(4)
C11	18.7(5)	20.6(6)	19.6(6)	-1.1(5)	1.8(4)	-2.6(4)
C6	26.6(6)	16.0(6)	19.2(6)	0.9(4)	4.6(5)	-0.6(4)
C3	21.3(6)	18.7(6)	17.8(6)	0.1(4)	3.0(4)	0.2(4)
C9	23.6(6)	25.1(6)	21.5(6)	0.1(5)	2.7(5)	-2.2(5)
C2	22.9(6)	19.2(6)	17.0(6)	-1.2(4)	3.4(5)	0.8(4)
C10	21.8(6)	18.1(6)	18.5(6)	-0.5(4)	5.5(4)	1.0(4)
C7	27.4(6)	20.4(6)	24.3(6)	2.8(5)	11.1(5)	2.4(5)
C1	22.4(6)	23.5(6)	18.0(6)	0.5(5)	1.5(5)	1.5(5)
C13	27.2(6)	18.4(6)	21.8(6)	1.9(5)	3.6(5)	2.2(5)
C12	25.0(6)	21.2(6)	21.9(6)	0.1(5)	2.1(5)	4.7(5)
C8	20.5(6)	27.7(7)	27.8(6)	3.8(5)	6.0(5)	0.8(5)
C17	25.7(6)	27.4(7)	22.5(6)	-3.0(5)	1.7(5)	-4.6(5)
C15	33.2(7)	21.2(6)	31.0(7)	5.4(5)	7.7(5)	4.7(5)
C18	36.4(7)	27.7(7)	28.6(7)	-5.8(5)	6.9(6)	-7.7(6)
C14	34.9(7)	46.5(9)	26.5(7)	-11.0(6)	12.0(6)	-6.3(6)

Table 30: Bond Lengths in Å for EX5.

Atom	Atom	Length/Å
O5	C16	1.2261(15)
O3	C11	1.3329(15)
O3	C15	1.4478(15)
O6	C16	1.3422(15)
O6	C17	1.4594(15)
O2	C11	1.2111(15)
O1	C1	1.4346(14)
O4	C6	1.3701(14)
O4	C14	1.4250(16)
N1	C16	1.3507(15)
N1	C10	1.4303(15)
N1	C13	1.4718(15)
C4	C5	1.3883(16)

Atom	Atom	Length/Å
C4	C3	1.4989(16)
C4	C9	1.3993(17)
C5	C6	1.3935(17)
C11	C3	1.4967(16)
C6	C7	1.3921(17)
C3	C2	1.5311(16)
C3	C10	1.5516(16)
C9	C8	1.3858(18)
C2	C10	1.4888(16)
C2	C1	1.5218(16)
C7	C8	1.3919(18)
C1	C12	1.5237(17)
C13	C12	1.5198(17)
C17	C18	1.5075(18)

Table 31:Bond Angles in ° for EX5.

Atom	Atom	Atom	Angle/°
C11	O3	C15	113.87(9)
C16	O6	C17	115.30(9)
C6	O4	C14	117.63(10)
C16	N1	C10	116.00(10)
C16	N1	C13	124.87(10)
C10	N1	C13	117.61(10)
O5	C16	O6	123.38(11)
O5	C16	N1	123.54(11)
O6	C16	N1	113.08(10)
C5	C4	C3	120.76(10)
C5	C4	C9	119.11(11)
C9	C4	C3	120.06(11)
C4	C5	C6	120.52(11)
O3	C11	C3	112.70(10)
O2	C11	O3	123.57(11)
O2	C11	C3	123.69(11)
O4	C6	C5	115.15(10)
O4	C6	C7	124.31(11)
C7	C6	C5	120.54(11)
C4	C3	C2	122.04(10)

Atom	Atom	Atom	Angle/°
C4	C3	C10	122.70(10)
C11	C3	C4	118.06(10)
C11	C3	C2	112.97(10)
C11	C3	C10	109.08(9)
C2	C3	C10	57.75(7)
C8	C9	C4	119.99(11)
C10	C2	C3	61.81(8)
C10	C2	C1	120.10(10)
C1	C2	C3	124.19(10)
N1	C10	C3	120.26(10)
N1	C10	C2	118.96(10)
C2	C10	C3	60.43(7)
C8	C7	C6	118.64(11)
O1	C1	C2	107.72(10)
O1	C1	C12	106.88(10)
C2	C1	C12	112.84(10)
N1	C13	C12	109.41(10)
C13	C12	C1	111.81(10)
C9	C8	C7	121.18(12)
O6	C17	C18	106.56(10)

Table 32: Torsion Angles in ° for EX5.

Atom	Atom	Atom	Atom	Angle/°
O3	C11	C3	C4	-8.11(15)
O3	C11	C3	C2	-159.60(10)
O3	C11	C3	C10	138.21(10)
O2	C11	C3	C4	173.92(11)
O2	C11	C3	C2	22.42(16)
O2	C11	C3	C10	-39.76(15)
O1	C1	C12	C13	-74.07(12)
O4	C6	C7	C8	-177.71(11)
N1	C13	C12	C1	-61.50(13)
C16	O6	C17	C18	-175.73(10)
C16	N1	C10	C3	99.69(12)

Atom	Atom	Atom	Atom	Angle/°
C16	N1	C10	C2	170.42(10)
C16	N1	C13	C12	-143.86(11)
C4	C5	C6	O4	178.16(10)
C4	C5	C6	C7	-1.45(18)
C4	C3	C2	C10	111.02(12)
C4	C3	C2	C1	2.13(17)
C4	C3	C10	N1	-1.63(16)
C4	C3	C10	C2	-109.90(12)
C4	C9	C8	C7	-0.92(19)
C5	C4	C3	C11	86.25(14)
C5	C4	C3	C2	-124.97(12)
C5	C4	C3	C10	-55.22(16)
C5	C4	C9	C8	1.33(18)
C5	C6	C7	C8	1.86(18)
C11	C3	C2	C10	-98.77(11)
C11	C3	C2	C1	152.34(11)
C11	C3	C10	N1	-146.07(10)
C11	C3	C10	C2	105.66(10)
C6	C7	C8	C9	-0.68(19)
C3	C4	C5	C6	-177.16(11)
C3	C4	C9	C8	178.35(11)
C3	C2	C10	N1	-110.38(11)
C3	C2	C1	O1	176.18(10)
C3	C2	C1	C12	58.45(15)
C9	C4	C5	C6	-0.17(17)
C9	C4	C3	C11	-90.71(14)
C9	C4	C3	C2	58.07(16)
C9	C4	C3	C10	127.81(12)
C2	C3	C10	N1	108.27(12)
C2	C1	C12	C13	44.16(14)
C10	N1	C16	O5	-5.81(17)
C10	N1	C16	O6	174.46(9)
C10	N1	C13	C12	50.82(13)
C10	C3	C2	C1	-108.89(13)
C10	C2	C1	O1	101.62(12)
C10	C2	C1	C12	-16.11(16)
C1	C2	C10	N1	4.85(16)
C1	C2	C10	C3	115.23(12)
C13	N1	C16	O5	-171.35(11)
C13	N1	C16	O6	8.93(16)

Atom	Atom	Atom	Atom	Angle/°
C13	N1	C10	C3	-93.68(13)
C13	N1	C10	C2	-22.95(15)
C17	O6	C16	O5	6.28(16)
C17	O6	C16	N1	-174.00(10)
C15	O3	C11	O2	6.78(16)
C15	O3	C11	C3	-171.19(10)
C14	O4	C6	C5	-175.80(11)
C14	O4	C6	C7	3.79(17)

Table 33: Hydrogen Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for EX5. Ueq is defined as 1/3 of the trace of the orthogonalised Uij.

Atom	x	y	z	U_{eq}
H1	4371.98	3059.63	1445.43	41
H5	6813.55	3036.64	6779.73	24
H9	3066.97	2332.19	4588.23	29
H2	5558.8	2144.19	2902.17	24
H10	7725.87	2511.84	4146.81	23
H7	3150.83	3476.44	7668.44	28
H1A	3475.7	3171.39	2977.03	26
H13A	6653.27	4528.57	3179.94	28
H13B	6543.76	5074.32	4303.55	28
H12A	4243.61	4754	3171.21	28
H12B	4511.9	4217.99	4363.74	28
H8	1891.8	2863.1	5902.03	30
H17A	10781.69	4799.21	6251.81	31
H17B	10050.31	4656.75	7286.2	31
H15A	6389.7	-353.94	5377.6	43
H15B	6611.16	-197.42	6727.4	43
H15C	7813.41	104.85	6128.5	43
H18A	9908.9	6309.78	6029.22	47
H18B	10927.64	6159.7	7292.2	47
H18C	9248.94	6163.95	7096.66	47
H14A	4644.96	4359.09	9014	53
H14B	6026.05	4049.55	9977.3	53
H14C	4780.94	3340.89	9480.67	53

(±)-2-Ethyl 7-methyl (1*S*,5*S*,6*S*,7*R*)-7-(3-methoxyphenyl)-5-((methylsulfonyl)oxy)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (192)

C$_{19}$H$_{25}$NO$_8$S
427,47 g/mol
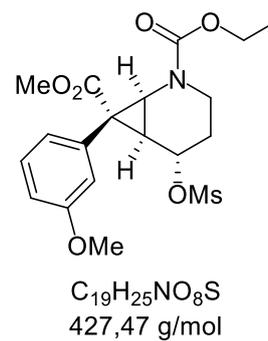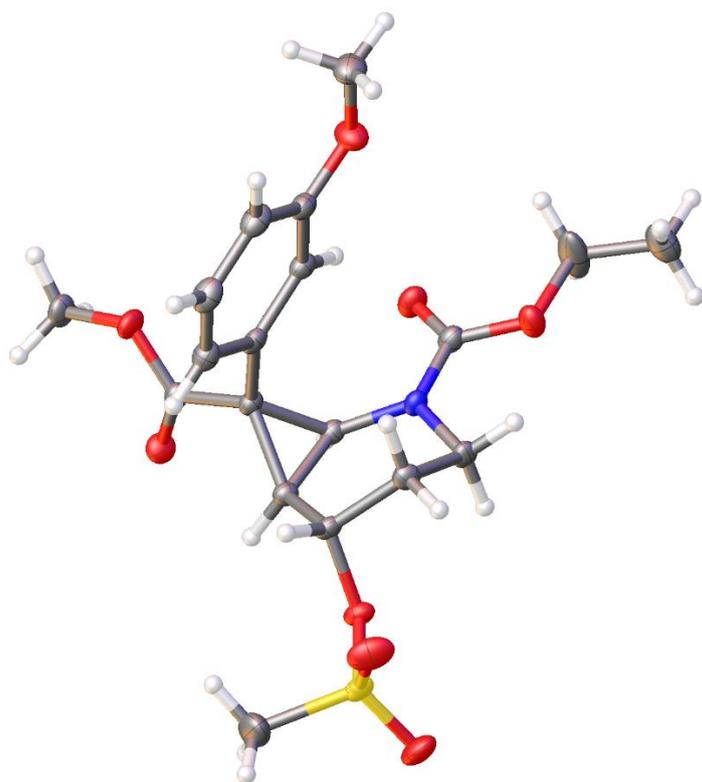
Figure 11: X-Ray crystallographic structure of 192 (Olex2)

Table 34: Crystal data and structure refinement for 192.

Formula	$C_{19}H_{25}NO_8S$
$D_{calc.}$/ g cm^{-3}	1.403
$\square$/mm^{-1}	0.207
Formula Weight	427.46
Colour	clear colourless
Shape	plate
Size/mm^3	0.41×0.28×0.15
T/K	123.00(10)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	9.8923(3)
b/Å	14.7367(4)
c/Å	13.8779(4)
$\square$/°	90
$\square$/°	90.355(3)
$\square$/°	90
V/Å^3	2023.09(10)
Z	4
Z'	1
Wavelength/Å	0.71073
Radiation type	Mo K$_\square$
$\square_{min}$/°	2.888
$\square_{max}$/°	32.528
Measured Refl's.	17312
Indep't Refl's	6674
Refl's I≥2 $\square$(I)	5567
R_{int}	0.0232
Parameters	266
Restraints	0
Largest Peak	0.888
Deepest Hole	-0.414
GooF	1.061
wR_2 (all data)	0.1388
wR_2	0.1309
R_1 (all data)	0.0589
R_1	0.0480

Table 35: Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 192. Ueq is defined as 1/3 of the trace of the orthogonalised Uij.

Atom	x	y	z	U_{eq}
S1	9450.1(4)	7209.0(2)	5164.1(3)	21.66(10)
O3	9115.6(10)	6293.1(7)	5688.7(8)	19.7(2)
O7	6531.1(11)	5055.9(8)	9335.0(7)	21.9(2)
O8	8709.6(11)	5056.8(8)	8907.3(8)	23.0(2)
O5	6832.2(12)	2943.2(7)	6970.7(8)	25.0(2)
O4	6270.6(12)	3076.7(7)	5397.6(8)	25.0(2)
O6	2510.0(11)	4209.9(8)	7109.6(9)	29.0(3)
O2	8224.5(13)	7602.5(9)	4816.8(10)	36.8(3)
O1	10494.4(13)	6997.1(9)	4506.2(9)	32.5(3)
N1	7156.1(12)	4264.4(8)	6171.0(8)	16.9(2)
C4	7809.4(13)	4626.3(9)	6999.8(10)	16.4(2)
C3	8111.0(13)	5615.6(9)	7024.4(10)	16.8(2)
C2	7787.0(13)	6193.5(9)	6163.5(10)	17.1(2)
C5	7025.5(13)	5252.7(9)	7691.7(9)	16.1(2)
C8	3285.9(15)	4948.4(11)	7280.6(10)	20.7(3)
C6	5563.7(14)	5459.1(10)	7556.9(9)	17.3(2)
C13	6831.0(15)	5754.2(9)	5446.1(10)	19.2(3)
C12	7529.4(15)	5123.0(9)	8697.4(10)	17.5(2)
C17	6766.9(15)	3384.5(9)	6231.6(10)	19.5(3)
C7	4659.5(14)	4767.5(10)	7366.0(10)	18.2(3)
C11	5092.5(16)	6346.7(10)	7676.1(11)	22.2(3)
C14	7215.1(16)	4772.5(10)	5266.4(10)	19.8(3)
C10	3718.8(17)	6514.5(11)	7591.1(11)	26.1(3)
C15	6957.5(18)	4859.2(11)	10310.7(10)	25.0(3)
C9	2809.4(16)	5827.6(11)	7389.2(11)	24.8(3)
C16	1087.2(16)	4341.0(13)	7084.5(13)	29.9(3)
C19	5359(2)	1894.5(12)	4434.7(15)	37.0(4)
C1	10103(2)	7876.0(14)	6088.3(16)	44.7(5)
C18	5849(3)	2142.9(12)	5409.5(15)	49.6(6)

Table 36: Anisotropic Displacement Parameters (×104) for 192. The anisotropic displacement factor exponent takes the form: -2□2[h2a*2 × U11+ … +2hka* × b* × U12].

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	26.47(19)	17.12(15)	21.51(18)	2.32(12)	9.70(13)	-1.71(12)
O3	19.7(5)	16.9(4)	22.5(5)	4.1(4)	6.4(4)	0.1(4)
O7	25.1(5)	28.9(5)	11.7(4)	3.4(4)	1.6(4)	0.1(4)
O8	22.5(5)	26.9(5)	19.6(5)	2.5(4)	-3.3(4)	1.7(4)
O5	36.6(6)	19.1(5)	19.2(5)	3.7(4)	5.0(4)	-0.5(4)
O4	38.4(6)	16.4(5)	20.2(5)	0.0(4)	-2.1(4)	-4.9(4)
O6	19.3(5)	30.5(6)	37.2(7)	-6.5(5)	0.8(5)	-0.7(4)
O2	35.6(7)	31.2(6)	43.8(7)	19.9(6)	8.1(6)	5.2(5)
O1	37.0(7)	31.1(6)	29.5(6)	1.1(5)	18.4(5)	-2.2(5)
N1	21.8(5)	16.1(5)	12.9(5)	1.4(4)	2.4(4)	-0.5(4)
C4	16.9(6)	17.1(5)	15.3(6)	1.7(5)	1.6(4)	1.7(5)
C3	17.3(6)	17.4(5)	15.6(6)	1.8(5)	0.7(4)	-0.5(4)
C2	17.4(6)	17.3(6)	16.5(6)	3.4(5)	4.1(5)	0.3(5)
C5	17.0(6)	18.2(6)	13.2(5)	1.3(4)	1.5(4)	0.9(4)
C8	18.3(6)	28.2(7)	15.7(6)	-0.1(5)	2.0(5)	1.5(5)
C6	18.7(6)	21.5(6)	11.7(5)	2.6(5)	2.9(4)	3.1(5)
C13	21.9(6)	18.9(6)	16.9(6)	4.3(5)	0.0(5)	-1.2(5)
C12	22.8(6)	15.3(5)	14.4(6)	0.8(4)	0.9(5)	0.0(5)
C17	23.3(6)	17.6(6)	17.7(6)	0.7(5)	3.8(5)	0.7(5)
C7	18.0(6)	21.7(6)	15.1(6)	2.0(5)	2.1(5)	2.8(5)
C11	26.2(7)	21.0(6)	19.4(6)	1.0(5)	2.8(5)	3.7(5)
C14	26.9(7)	19.3(6)	13.3(6)	2.5(5)	1.6(5)	-3.3(5)
C10	30.0(8)	24.5(7)	23.8(7)	1.4(6)	3.7(6)	10.3(6)
C15	34.5(8)	27.9(7)	12.7(6)	2.8(5)	-1.0(5)	-1.8(6)
C9	22.0(7)	31.8(8)	20.7(7)	2.8(6)	2.0(5)	9.4(6)
C16	19.5(7)	39.5(9)	30.8(8)	-3.1(7)	1.1(6)	-0.2(6)
C19	47.0(11)	24.4(8)	39.5(10)	-3.2(7)	-9.5(8)	-6.0(7)
C1	57.5(13)	36.2(10)	40.6(11)	-15.3(8)	13.4(9)	-21.9(9)
C18	99.3(19)	20.1(8)	29.4(9)	0.6(7)	-4.9(10)	-21.7(10)

Table 37: Bond Lengths in Å for 192.

Atom	Atom	Length/Å
S1	O3	1.5698(10)
S1	O2	1.4252(13)
S1	O1	1.4178(12)
S1	C1	1.737(2)
O3	C2	1.4812(17)
O7	C12	1.3338(18)
O7	C15	1.4451(17)
O8	C12	1.2055(18)
O5	C17	1.2159(17)
O4	C17	1.3339(17)
O4	C18	1.438(2)
O6	C8	1.3520(19)
O6	C16	1.4209(19)
N1	C4	1.4198(17)
N1	C17	1.3554(18)

Atom	Atom	Length/Å
N1	C14	1.4632(17)
C4	C3	1.4885(19)
C4	C5	1.5443(19)
C3	C2	1.5002(18)
C3	C5	1.5195(19)
C2	C13	1.514(2)
C5	C6	1.4883(19)
C5	C12	1.4915(19)
C8	C7	1.389(2)
C8	C9	1.387(2)
C6	C7	1.381(2)
C6	C11	1.399(2)
C13	C14	1.517(2)
C11	C10	1.385(2)
C10	C9	1.382(2)
C19	C18	1.480(3)

Table 38: Bond Angles in ° for 192.

Atom	Atom	Atom	Angle/°
O3	S1	C1	102.86(9)
O2	S1	O3	108.99(7)
O2	S1	C1	109.34(11)
O1	S1	O3	105.42(7)
O1	S1	O2	119.58(8)
O1	S1	C1	109.32(10)
C2	O3	S1	118.80(8)
C12	O7	C15	115.05(12)
C17	O4	C18	114.88(13)
C8	O6	C16	117.14(13)
C4	N1	C14	118.84(11)
C17	N1	C4	115.92(11)
C17	N1	C14	123.76(12)
N1	C4	C3	118.47(11)
N1	C4	C5	120.03(11)
C3	C4	C5	60.10(9)
C4	C3	C2	119.73(11)
C4	C3	C5	61.77(9)

Atom	Atom	Atom	Angle/°
C2	C3	C5	122.47(11)
O3	C2	C3	102.99(10)
O3	C2	C13	107.59(11)
C3	C2	C13	114.23(11)
C3	C5	C4	58.13(9)
C6	C5	C4	122.36(11)
C6	C5	C3	122.77(11)
C6	C5	C12	117.56(12)
C12	C5	C4	109.82(11)
C12	C5	C3	112.46(11)
O6	C8	C7	114.49(13)
O6	C8	C9	125.30(14)
C9	C8	C7	120.19(14)
C7	C6	C5	120.07(12)
C7	C6	C11	119.81(13)
C11	C6	C5	120.03(13)
C2	C13	C14	111.08(12)
O7	C12	C5	112.69(12)
O8	C12	O7	123.62(13)
O8	C12	C5	123.65(13)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O5	C17	O4	124.57(13)	N1	C14	C13	109.62(11)
O5	C17	N1	123.39(13)	C9	C10	C11	121.57(14)
O4	C17	N1	112.00(12)	C10	C9	C8	119.00(14)
C6	C7	C8	120.46(13)	O4	C18	C19	108.63(15)
C10	C11	C6	118.96(14)				

Table 19: Torsion Angles in ° for 192.

Atom	Atom	Atom	Atom	Angle/°
S1	O3	C2	C3	-145.60(9)
S1	O3	C2	C13	93.41(12)
O3	C2	C13	C14	69.52(13)
O6	C8	C7	C6	-178.93(13)
O6	C8	C9	C10	178.05(15)
O2	S1	O3	C2	-29.49(12)
O1	S1	O3	C2	-159.01(10)
N1	C4	C3	C2	-3.09(18)
N1	C4	C3	C5	110.18(13)
N1	C4	C5	C3	-107.62(13)
N1	C4	C5	C6	3.51(19)
N1	C4	C5	C12	147.65(12)
C4	N1	C17	O5	7.4(2)
C4	N1	C17	O4	-174.55(12)
C4	N1	C14	C13	-49.11(17)
C4	C3	C2	O3	-100.46(13)
C4	C3	C2	C13	15.89(18)
C4	C3	C5	C6	-110.45(14)
C4	C3	C5	C12	100.07(12)
C4	C5	C6	C7	46.67(18)
C4	C5	C6	C11	-136.87(14)
C4	C5	C12	O7	-135.04(12)
C4	C5	C12	O8	42.73(18)
C3	C4	C5	C6	111.13(14)
C3	C4	C5	C12	-104.72(12)
C3	C2	C13	C14	-44.14(16)
C3	C5	C6	C7	117.06(15)
C3	C5	C6	C11	-66.47(18)
C3	C5	C12	O7	162.25(11)

Atom	Atom	Atom	Atom	Angle/°
C3	C5	C12	O8	-19.99(19)
C2	C3	C5	C4	109.00(14)
C2	C3	C5	C6	-1.4(2)
C2	C3	C5	C12	-150.93(12)
C2	C13	C14	N1	60.11(15)
C5	C4	C3	C2	-113.27(13)
C5	C3	C2	O3	-174.07(12)
C5	C3	C2	C13	-57.72(17)
C5	C6	C7	C8	177.20(12)
C5	C6	C11	C10	-177.02(13)
C6	C5	C12	O7	11.04(17)
C6	C5	C12	O8	-171.19(13)
C6	C11	C10	C9	-0.2(2)
C12	C5	C6	C7	-94.90(16)
C12	C5	C6	C11	81.56(16)
C17	O4	C18	C19	-178.53(17)
C17	N1	C4	C3	-172.69(12)
C17	N1	C4	C5	-102.66(14)
C17	N1	C14	C13	145.34(13)
C7	C8	C9	C10	-0.6(2)
C7	C6	C11	C10	-0.5(2)
C11	C6	C7	C8	0.7(2)
C11	C10	C9	C8	0.8(2)
C14	N1	C4	C3	20.64(18)
C14	N1	C4	C5	90.67(15)
C14	N1	C17	O5	173.34(14)
C14	N1	C17	O4	-8.6(2)
C15	O7	C12	O8	-2.3(2)
C15	O7	C12	C5	175.42(12)
C9	C8	C7	C6	-0.2(2)
C16	O6	C8	C7	175.56(13)
C16	O6	C8	C9	-3.1(2)
C1	S1	O3	C2	86.47(13)
C18	O4	C17	O5	-2.5(2)
C18	O4	C17	N1	179.47(17)

Table 20: Hydrogen Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for 192. Ueq is defined as 1/3 of the trace of the orthogonalised Uij.

Atom	x	y	z	U_{eq}
H4	8488.64	4233.04	7302.55	20
H3	8962.78	5771.28	7348.58	20
H2	7440.93	6786.35	6365.58	20
H13A	6855.18	6086.66	4843.2	23
H13B	5915.59	5781.42	5690.97	23
H7	4972.32	4176.41	7294.03	22
H11	5691.83	6816.9	7810.33	27
H14A	6598.11	4506.56	4799.67	24
H14B	8121.91	4742.52	5006.33	24
H10	3401.29	7103.38	7671.94	31
H15A	7491.95	4315.49	10316.89	38
H15B	6176.84	4776.16	10708.58	38
H15C	7487.06	5355.42	10554.76	38
H9	1891.54	5952.85	7326.92	30
H16A	857.48	4749.74	6570.4	45
H16B	796.45	4592.9	7686.56	45
H16C	646.26	3768.77	6979.69	45
H19A	6078.78	1966.71	3980.17	55
H19B	4618.01	2281.61	4256.65	55
H19C	5062.89	1274.19	4434.93	55
H1A	9458.96	7912.08	6601.4	67
H1B	10285.43	8474.33	5848.39	67
H1C	10926.16	7610.14	6325.92	67
H18A	5132.02	2060.11	5875.17	60
H18B	6601.9	1757.1	5592.96	60

7 HPLC chromatograms
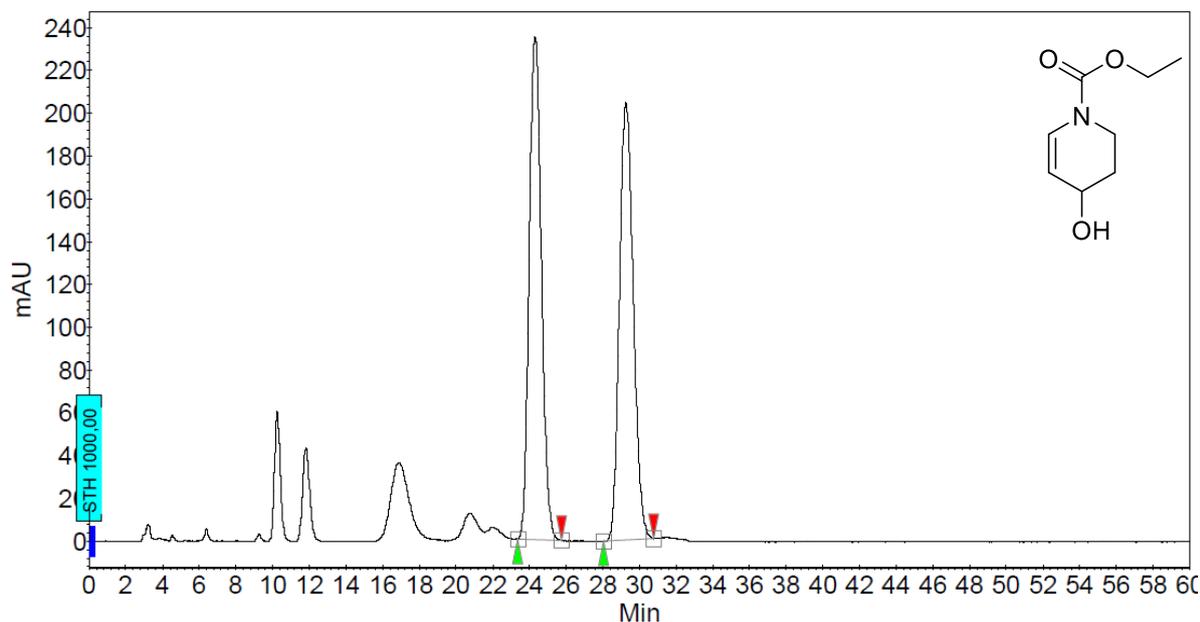
Chiralcel AS-H, n-heptane:ipropanol 97:3, 1.0 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24,31	50,44	235,2	182,7	50,441
2	UNKNOWN	29,26	49,56	204,6	179,5	49,559
Total			100,00	439,9	362,3	100,000
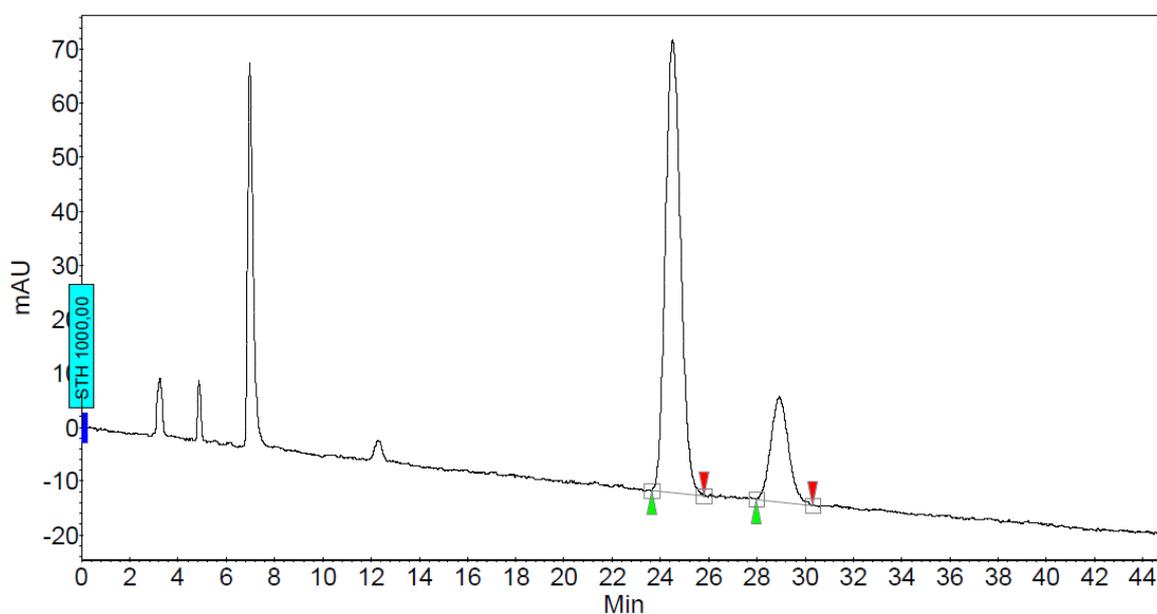
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24,50	78,95	83,9	62,0	78,952
2	UNKNOWN	28,93	21,05	19,5	16,5	21,048
Total			100,00	103,4	78,5	100,000
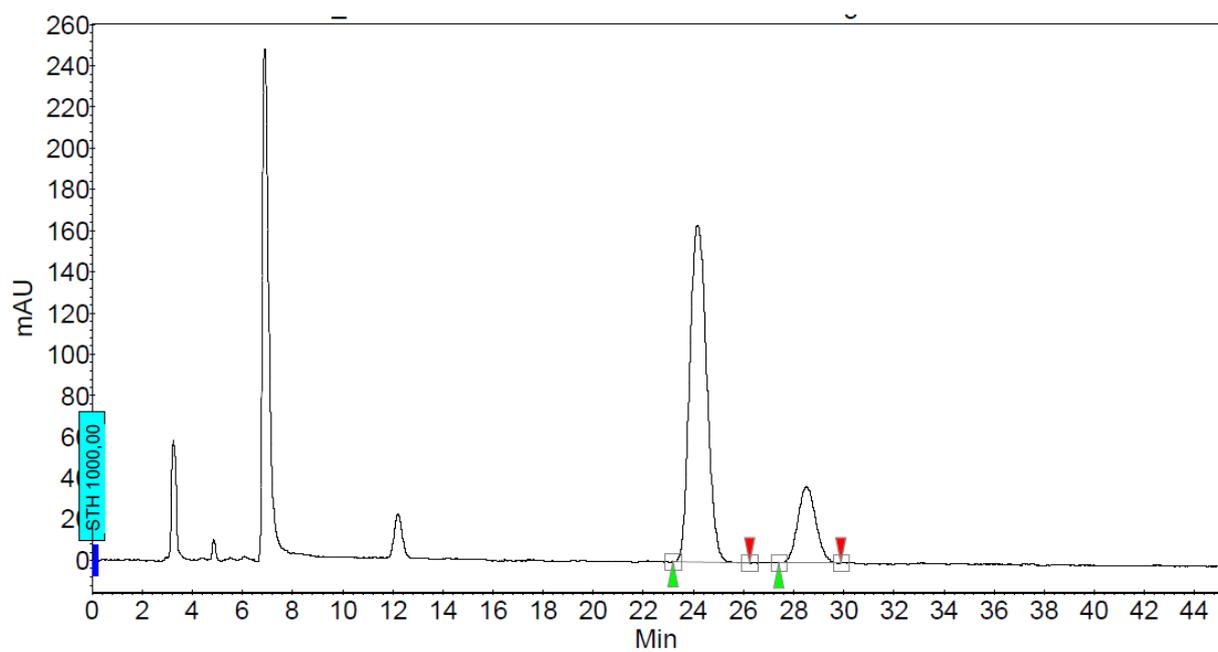
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24,16	80,68	163,8	129,2	80,680
2	UNKNOWN	28,51	19,32	37,0	30,9	19,320
Total			100,00	200,8	160,1	100,000
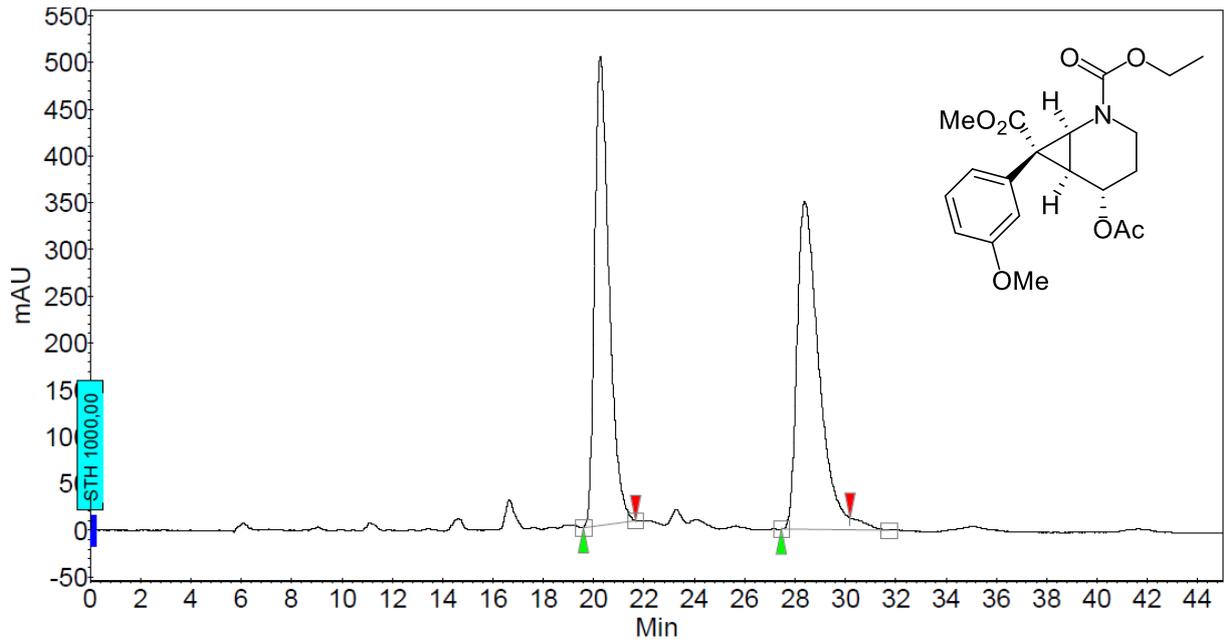
Phenomenex Lux Cellulose-2, n-heptane:^{i}PrOH 80:20, 0.5 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20,26	48,69	500,2	331,5	48,687
2	UNKNOWN	28,38	51,31	351,0	349,3	51,313
Total			100,00	851,2	680,8	100,000
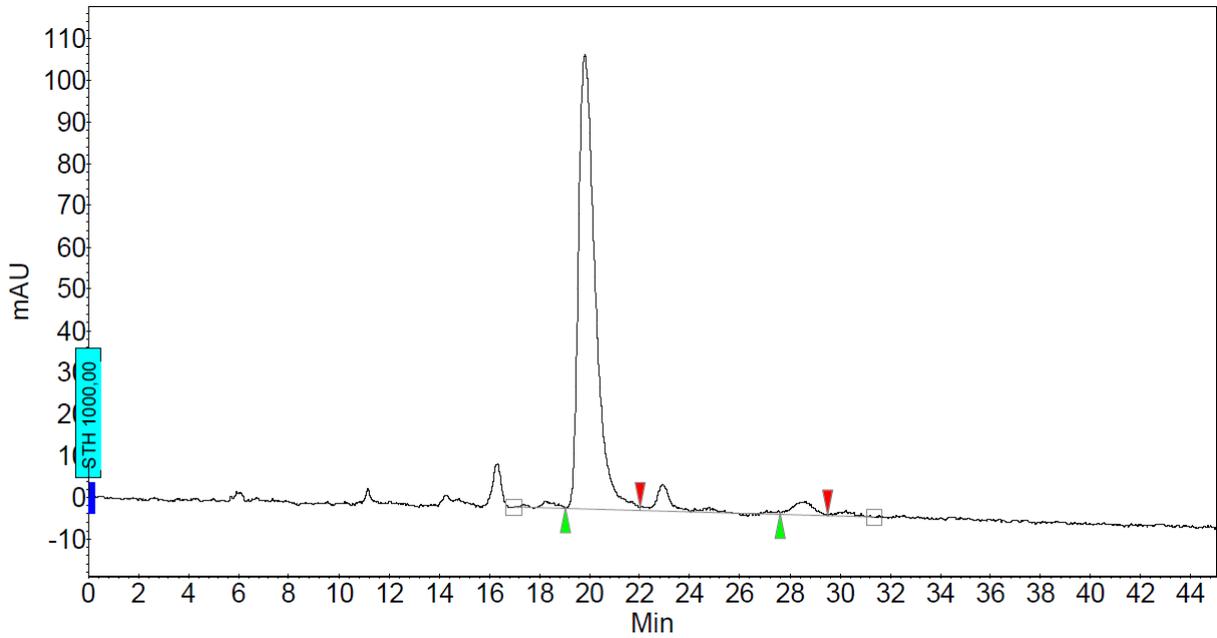
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	19,81	96,41	109,0	84,5	96,413
2	UNKNOWN	28,63	3,59	3,3	3,1	3,587
Total			100,00	112,2	87,6	100,000
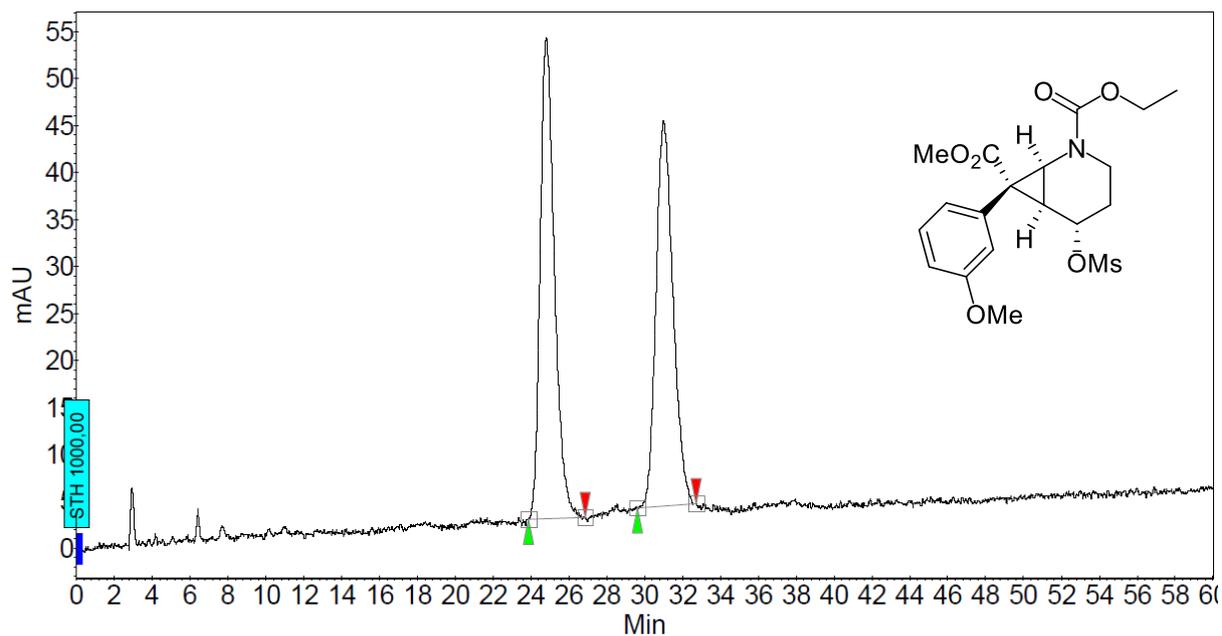
Phenomenex Lux Cellulose-1, n-heptane:^{i}PrOH 90:10, 1.0 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24,80	51,14	51,2	44,5	51,136
2	UNKNOWN	30,99	48,86	41,1	42,6	48,864
Total			100,00	92,3	87,1	100,000
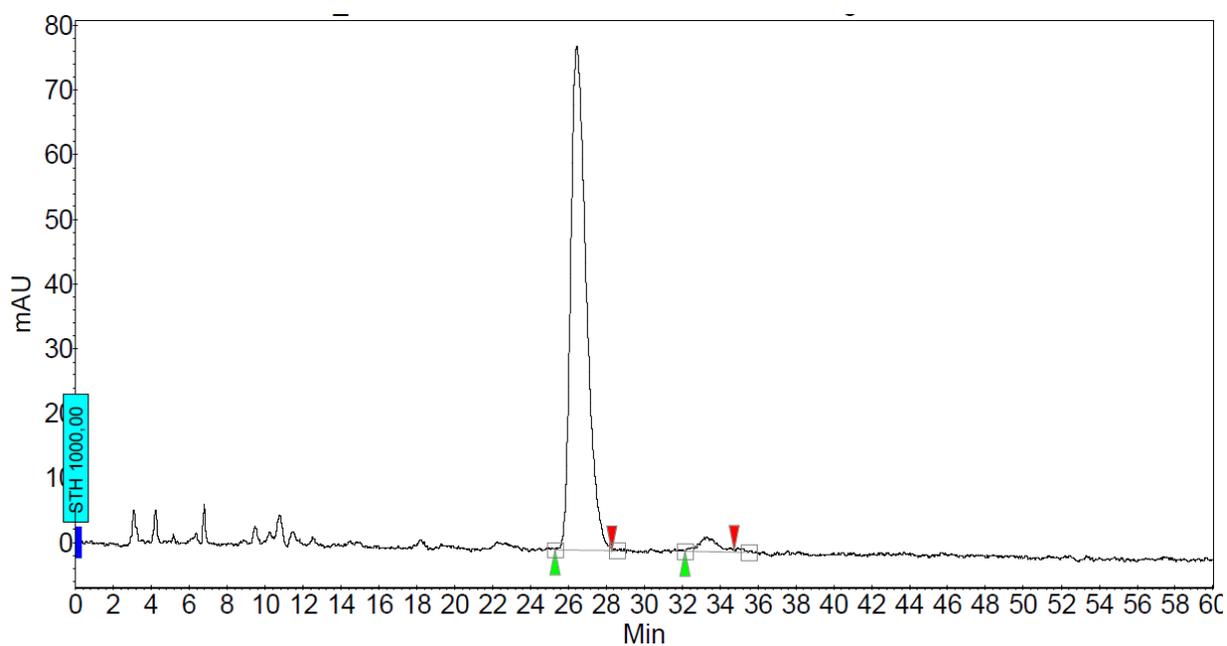
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	26,44	96,75	77,9	74,3	96,750
2	UNKNOWN	33,32	3,25	2,2	2,5	3,250
Total			100,00	80,1	76,8	100,000

Phenomenex Lux Amylose-2, n-heptane: ᶦPrOH 95:5, 1.0 mL/min

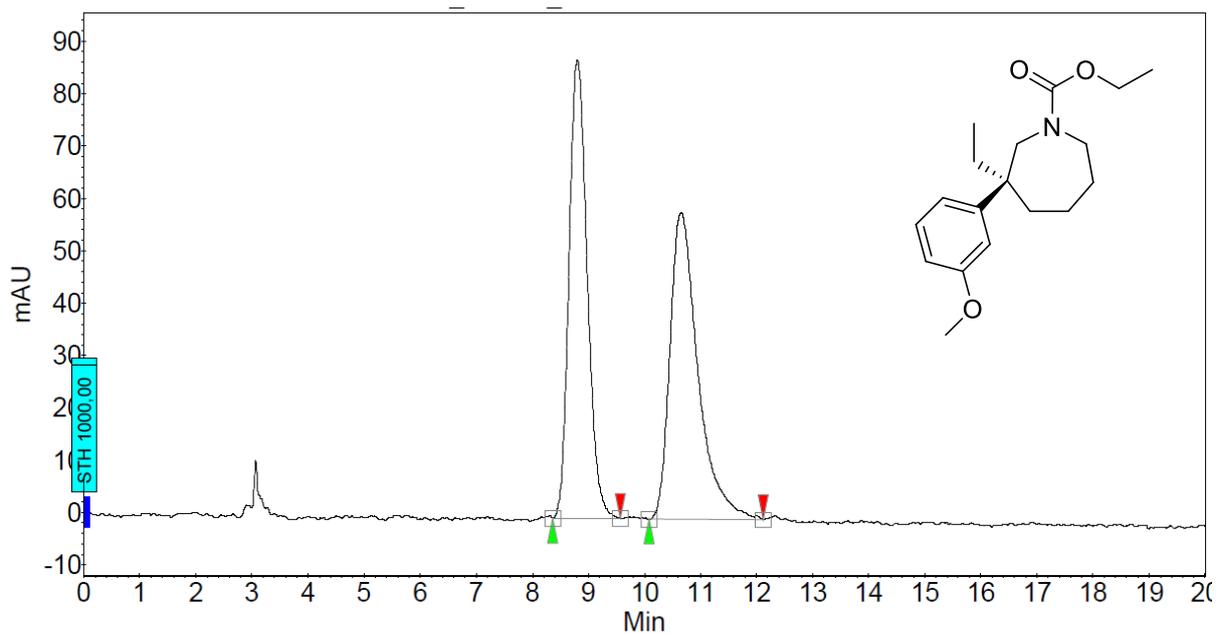| Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8.80	49.46	87.6	33.0	49.456
2	UNKNOWN	10.65	50.54	58.5	33.7	50.544
Total			100.00	146.1	66.6	100.000
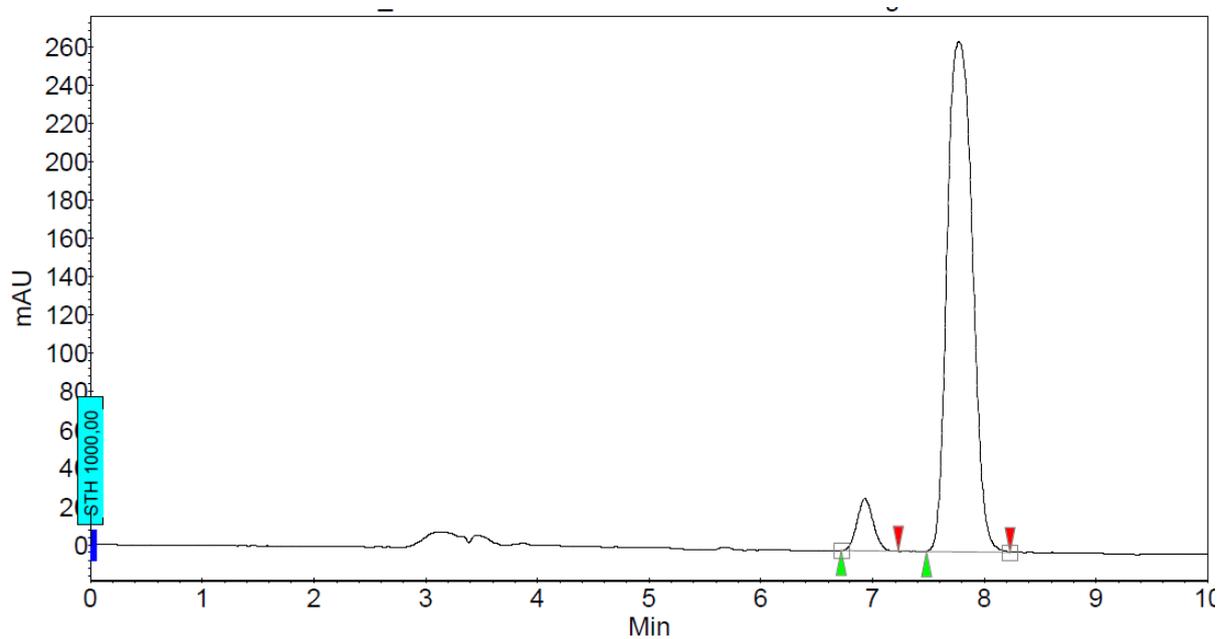
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6.93	6.25	27.3	4.6	6.248
2	UNKNOWN	7.77	93.75	266.1	69.5	93.752
Total			100.00	293.4	74.1	100.000
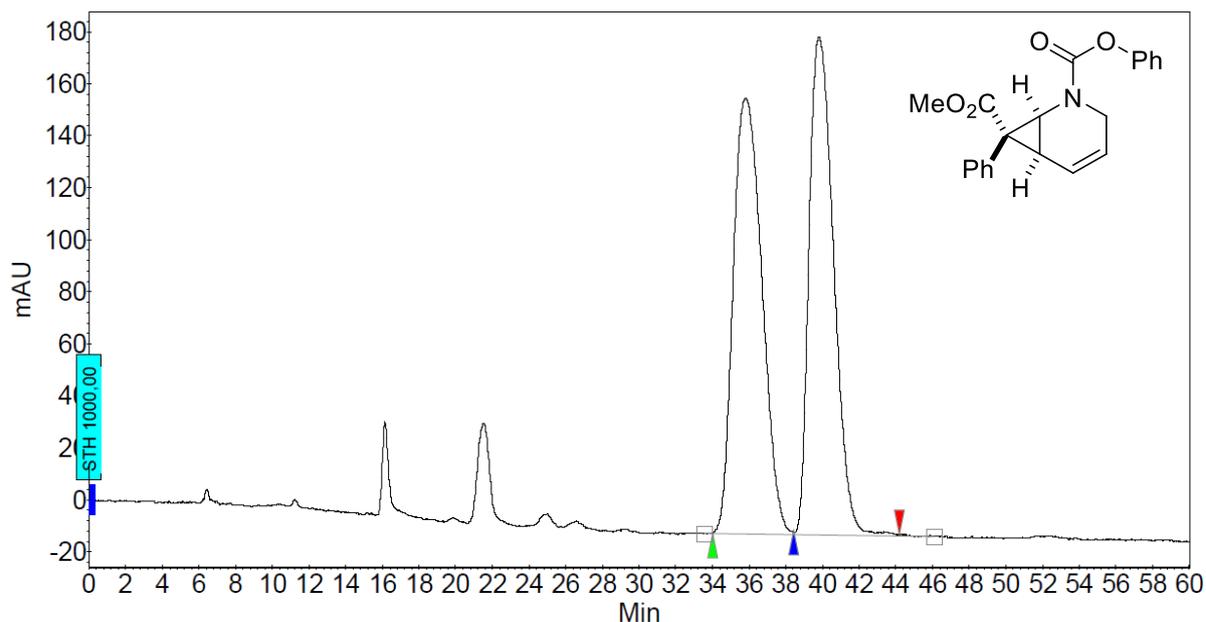
Rh$_2$(OAc)$_4$ Chiralcel AS-H, n-heptane:^{i}PrOH 95:5, 0.5 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	35.78	50.65	167.8	305.3	50.653
2	UNKNOWN	39.81	49.35	191.3	297.4	49.347
Total			100.00	359.1	602.7	100.000
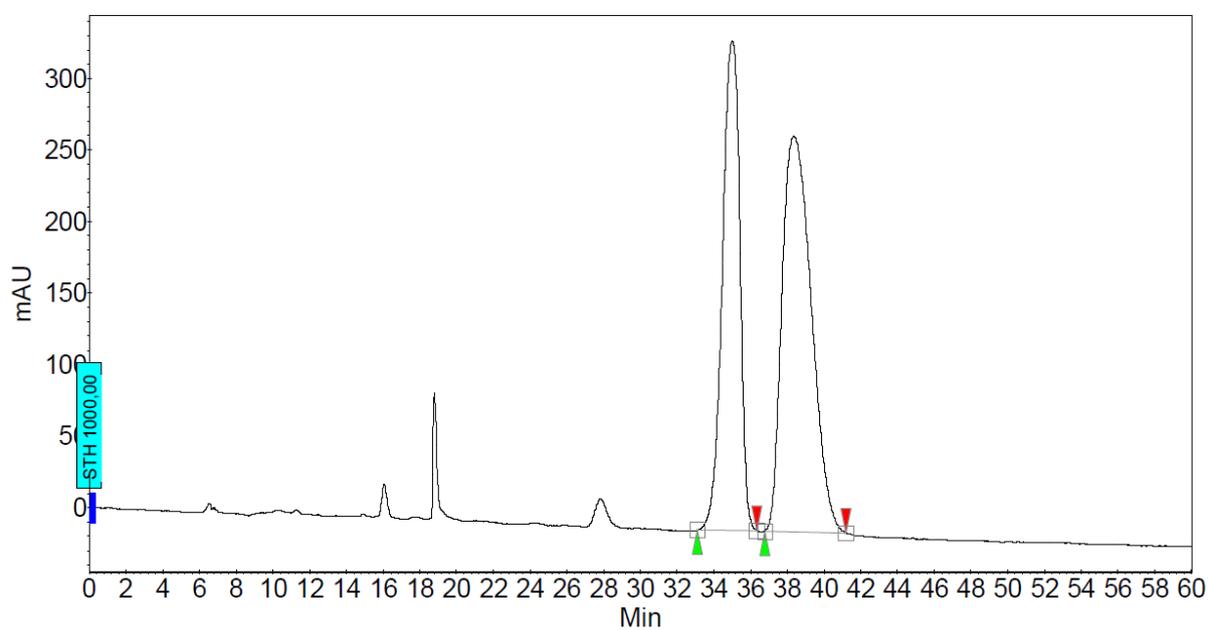
Rh$_2$(*R*-2Cl-5Br-TPCP)$_4$, Chiralcel AS-H, n-heptane:^{i}PrOH 95:5, 0.5 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	34.99	42.53	342.0	378.2	42.533
2	UNKNOWN	38.34	57.47	276.7	511.0	57.467
Total			100.00	618.7	889.3	100.000

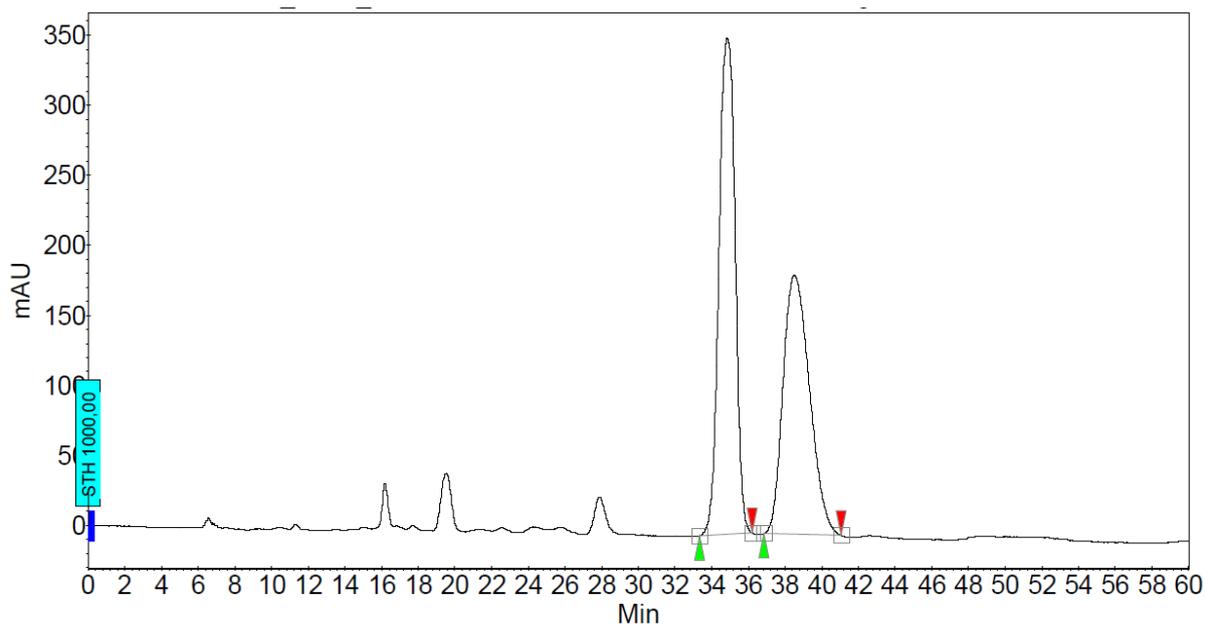Rh$_2$(S-pBr-TPCP)$_4$, Chiralcel AS-H, n-heptane:^{i}PrOH 95:5, 0.5 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	34,85	53,83	354,3	362,1	53,832
2	UNKNOWN	38,50	46,17	185,4	310,6	46,168
Total			100,00	539,7	672,7	100,000
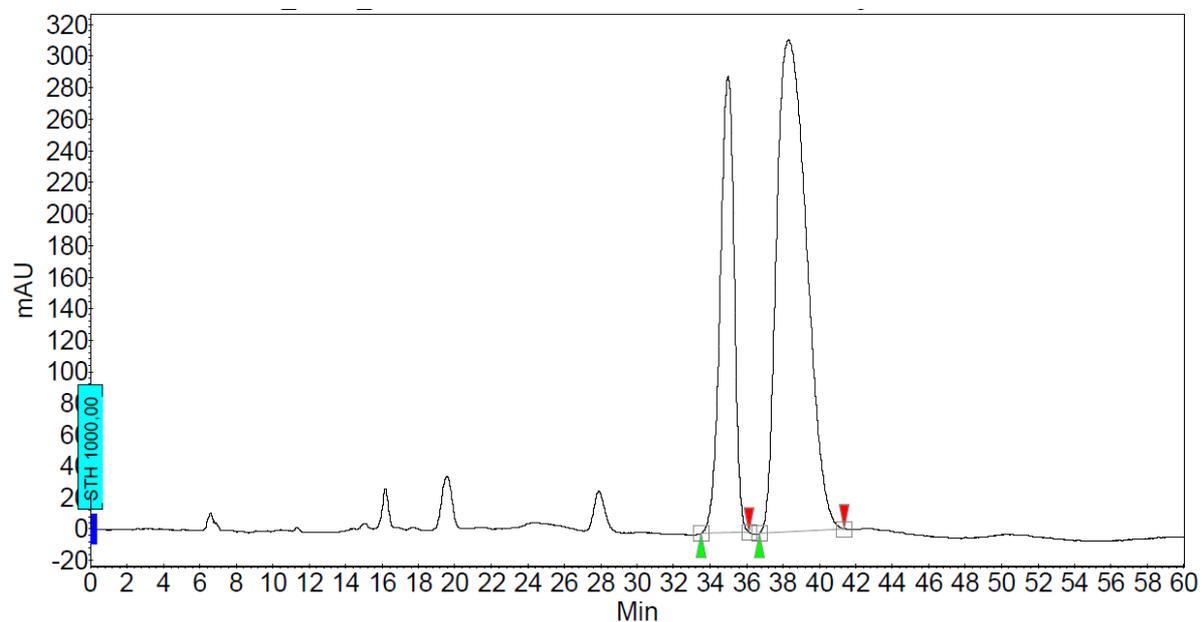
Rh$_2$(S-TCPPTL)$_4$, Chiralcel AS-H, n-heptane:^{i}PrOH 95:5, 0.5 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	34,98	30,40	289,6	260,0	30,397
2	UNKNOWN	38,30	69,60	312,2	595,3	69,603
Total			100,00	601,8	855,3	100,000
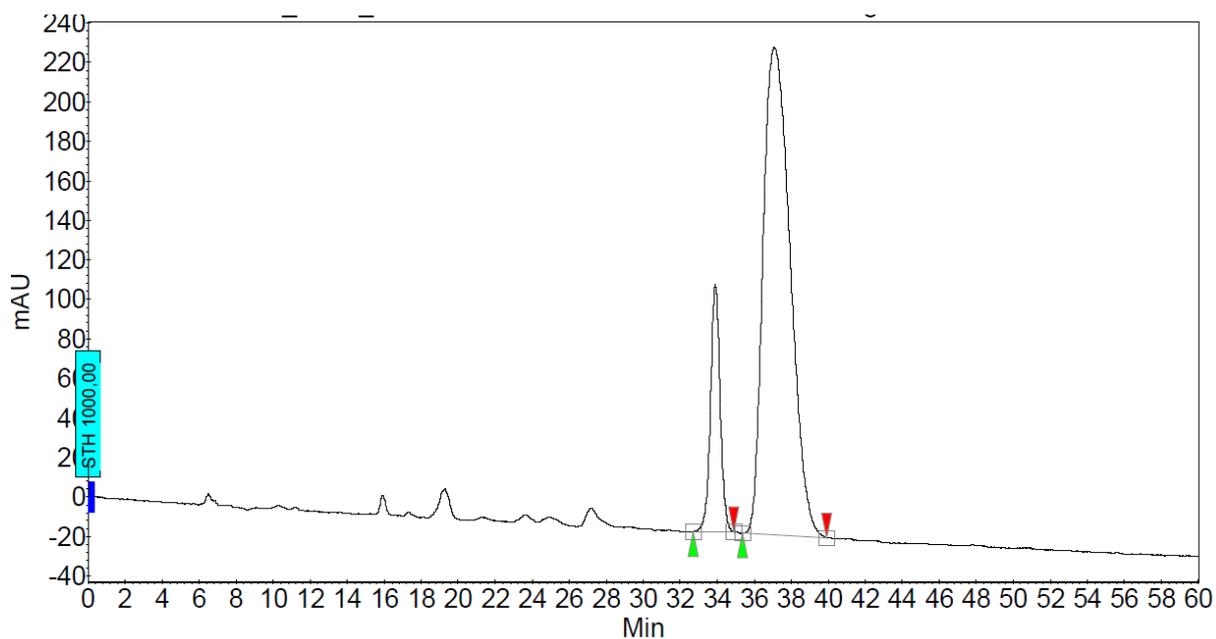
Rh$_2$(R-DOSP)$_4$, Chiralcel AS-H, n-heptane:^{i}PrOH 95:5, 0.5 mL/min

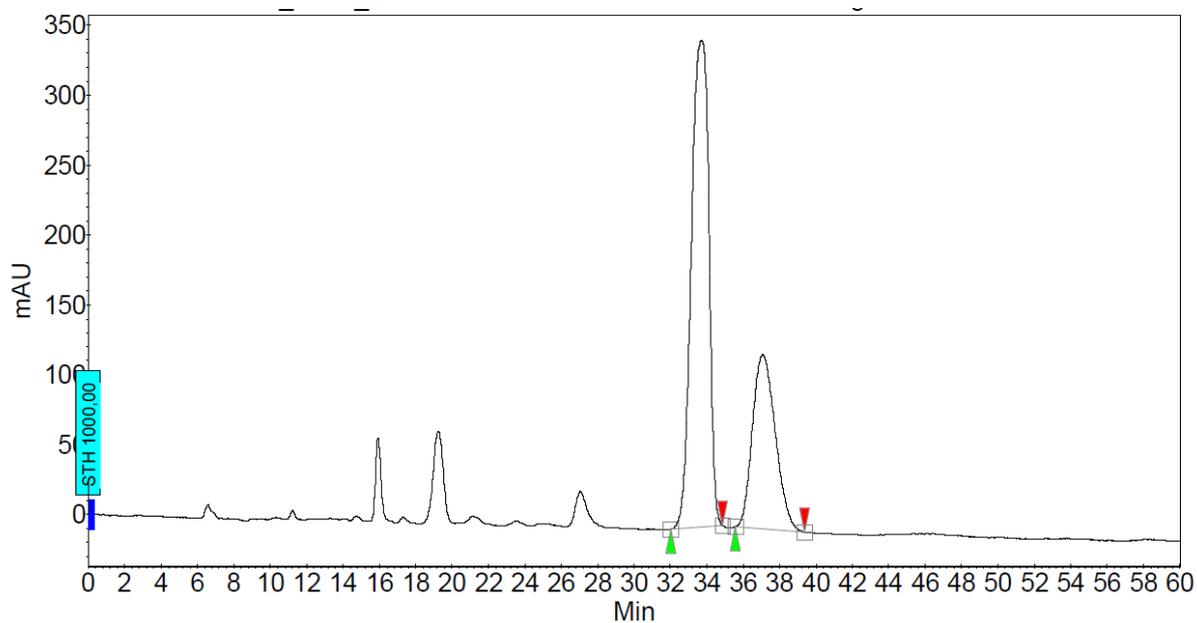| Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	33,89	15,42	125,2	76,1	15,417
2	UNKNOWN	37,09	84,58	246,6	417,5	84,583
Total			100,00	371,8	493,5	100,000

Rh$_2$(R-TCPTAD)$_4$, Chiralcel AS-H, n-heptane:^{i}PrOH 95:5, 0.5 mL/min

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	33,71	68,00	348,2	386,5	67,997
2	UNKNOWN	37,08	32,00	124,6	181,9	32,003
Total			100,00	472,8	568,4	100,000

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9 Curriculum Vitae

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Education ———————————————————————————

12/2018 – 12/2021   <u>PhD (Dr. rer. nat.)</u>, Organic Chemistry
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04/2019 – 04/2021   <u>Bachelor of Science (B. Sc.)</u>, Business-Chemistry
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     Master thesis: Synthesis of Azepanes via Heck-Coupling Driven Ring-Opening of Cyclopropanated Piperidines and the Synthesis of Ritalin™-Analogs via Rhodium Catalyzed Cyclopropanation and C-H Insertion Chemistry

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List of Publications ────────────────────────

"Heck-Type Coupling of Fused Bicyclic Vinylcyclopropanes: Synthesis of 1,2-Dihydropyridines, 2,3-Dihydro-1H-azepines, 1,4-Cyclohexadienes, and 2H-Pyrans" (2021)

N. Wurzer, U. Klimczak, T. Babl, S. Fischer, R. A. Angnes, D. Kreutzer, A. Pattanaik, J. Rehbein, O. Reiser, ACS Catal. **2021**, 11, 12019.

"Functionalization of Piperidine Derivatives for the Site-Selective and Stereoselective Synthesis of Positional Analogues of Methylphenidate" (2020)

W. Liu, T. Babl, A. Röther, O. Reiser, H. M. L. Davies, Chem. Eur. J, **2020**, 26, 4236.

10 Acknowledgement

11 Declaration

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

Regensburg, 10.03.2022

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Tobias Babl