Heck-type coupling of cyclopropanated pyrroles: Synthesis of 6-aryl substituted nipecotic acid derivatives

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An dieser Stelle möchte ich Herrn Prof. Dr. Oliver Reiser für die Überlassung des interessanten Themas und die Unterstützung während der gesamten Arbeit danken.

Rodzicom

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aryl
ax	axial
Bn	benzyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
boc	*t*-butoxycarbonyl
Bu	butyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
d	days
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
1,2-DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAEA	2-diethylaminoethylamine
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
dr	diastereomeric ratio
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
eq	equatorial
equiv	equivalent
Et	ethyl
Flu	9-fluorenylmethyl
Fmoc	9-fluorenylmethoxycarbonyl
HPLC	high-pressure liquid chromatography
HRMS	high-resolution mass spectrometry
IR	infrared spectroscopy
LED	light-emitting diode
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
m.p.	melting point
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
MW	microwaves
MTBE	methyl *t*-butyl ether
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nos	4-nitrobenzenesulfonyl
Nu	nucleophile
o-NBSA	*o*-nitrobenzenesulfonyl azide
Pg	protecting group
Ph	phenyl
Pin	pinacol
PMP	4-methoxyphenyl

Pr	propyl
Ps	phenylsulfonyl
PTC	phase transfer catalysis
quant.	quantitative yield
Ra-Ni	Raney nickel
R_f	retention factor in chromatography
rOe	rotating-frame Overhauser effect
T3P	propanephosphonic acid anhydride
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TCE	2,2,2-trichloroethyl
TES	triethylchlorosilane
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFP	tris(2-furyl)phosphine
THF	tetrahydrofuran
β-TIC	tetrahydroisoquinoline-4-carboxylic acid
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TLC	thin-layer chromatography
Ts	*p*-toluenesulfonyl
TS	transition state
wt%	percentage by weight

Contents

I Background and aim of the work

For many years the group of Prof. Reiser at the University of Regensburg conducts research on the application of bicycles **1** (Figure 1) as synthetic building blocks. The utility of these substrates results from the presence of a donor-acceptor cyclopropane ring, an enamine double bond as well as the well-defined geometry of the molecule ensuring high facial selectivity of the transformations.[1]

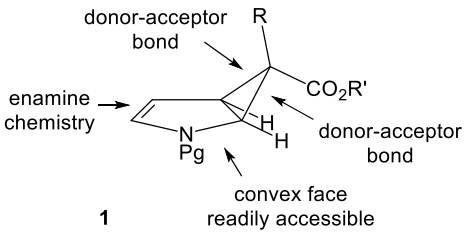
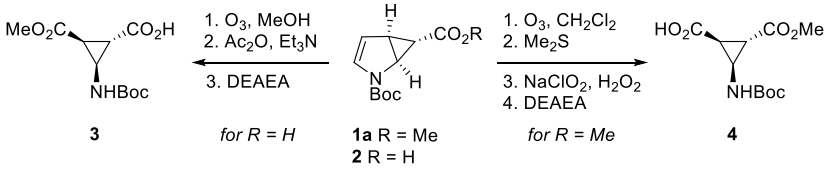


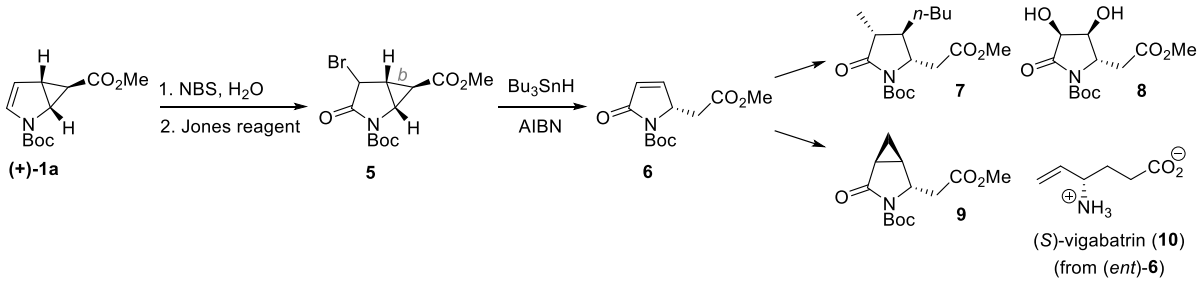
*Figure 1. Monocyclopropanated pyrroles **1**.*

Initially, the studies on compounds **1** focused on their conversion into aminocyclopropanecarboxylic acids **3** and **4** (Scheme 1).[2,3] Some of the peptides modified with these products served as organocatalysts,[4] while the others showed high selectivity and affinity towards G-protein coupled receptors.[5–7]



*Scheme 1. Transformations of 2-azabicyclo[3.1.0]hex-3-enes **1a** and **2** into aminocyclopropanecarboxylic acids **3** and **4**.*

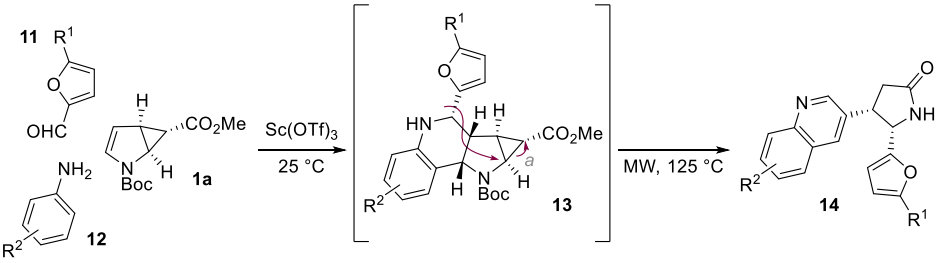
Further works resulted in the development of a method for the preparation of pyrrolidinones such as **7**-**9** (Scheme 2).[8] For this purpose, pyrrole **1a** was first transformed into bromoketone **5**, which under the influence of tributyltin hydride underwent selective cyclopropane ring-opening on bond *b*. Compounds **7**-**9** were obtained from the resulting 3-pyrrolin-2-one **6** by simple derivatizations of the double bond. Pyrrolinone *ent*-**6** was also successfully converted into an antiepileptic agent (*S*)-vigabatrin.



*Scheme 2. Synthesis of 3-pyrrolin-2-one **6** and its further transformations.*

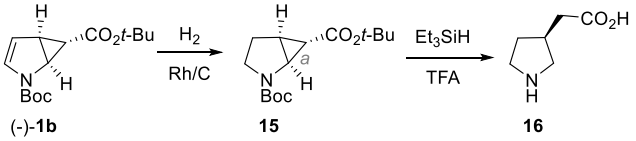
Subjected to the reaction with furancarbaldehyde **11** and aniline **12** in the presence of $Sc(OTf)_3$ at 25 °C, 2-azabicyclo[3.1.0]hex-3-ene **1a** formed, in turn, adduct **13**, which upon raising the temperature of the process to 125 °C rearranged to *cis*-disubstituted pyrrolidinone

14 (Scheme 3).[9] The latter step begins with the selective opening of the cyclopropane bond *a* with concurrent 1,4-shift of the furan moiety.



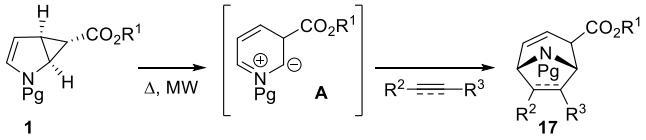
Scheme 3. Synthesis of cis*-4,5-disubstituted pyrrolidinones **14**.*

The facile cleavage of bond *a* was also exploited in the synthesis of homo-β-proline (**16**) (Scheme 4).[10]



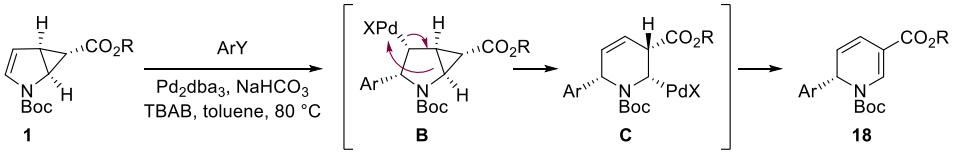
*Scheme 4. Synthesis of homo-β-proline (**16**).*

On the other hand, under microwave heating bicycle **1** underwent 6π-electrocyclic ring-opening to form 1,3-dipole **A**, which could be trapped with various dipolarophiles providing tropane derivatives **17**.[11]



Scheme 5. Synthesis of tropanes via *a 6π-electrocyclic ring-opening/Huisgen [3+2]-cycloaddition cascade of bicycles **1**.*

Finally, Pd-catalysed coupling of cyclopropane **1** with aryl halides yielded corresponding 1,2-dihydropyridines **18** (Scheme 6).[12] The observed reaction outcome may be rationalized by the fact that the initial Heck-adduct **B** can undergo neither β-dehydropalladation nor reductive elimination, and thus the catalytic cycle may proceed further only *via* the [1,3] migration of Pd, leading to six-membered species **C**.



*Scheme 6. Synthesis of 1,2-dihydropyridines **18*** via *Heck-type coupling of bicycles **1** with aryl halides.*

The latter work constituted the starting point for my doctoral project. Since in many of the reported examples yields of the products were only moderate, and the time required to achieve full conversion rather long (at least 24 h), my task was to develop a more efficient

procedure for Heck-type arylation of enecarbamates **1**. Motivation to undertake these efforts was the broad applicability of 1,2-dihydropyridines as building blocks in organic synthesis as well as the significance of α-aryl-substituted piperidine derivatives in medicinal chemistry and pharmacy. In the further part of my work, I was going to investigate Heck reactions involving 6,6-*gem*-disubstituted 2-azabicyclo[3.1.0]hex-3-enes (Figure 1, R ≠ H). These substrates are more challenging since the organopalladium intermediate analogous to **C** cannot undergo β-dehydropalladation. Thus, it was necessary to find a nucleophile capable of trapping species **C**, thereby enabling the closure of the catalytic cycle. Following these works, I planned to examine the reactivity of the obtained products. Selected examples from the synthesised piperidine derivatives should be then incorporated into peptides for conformational studies.

Bearing in mind the utility of bicycles **1**, I decided additionally to investigate cyclopropanation of several substituted pyrrole derivatives that had not been previously employed in this transformation. As a complementary approach to access novel 2-azabicyclo[3.1.0]hex-3-enes, I envisioned functionalization of the double bond in the synthesised bicycles.

II Literature overview

II 1 Introduction

Piperidine-3-carboxylic acid (nipecotic acid, **19**; Figure 2) constitutes a structural motif of many pharmacologically relevant compounds. An important example of such derivatives is an antiepileptic drug from the group of γ-aminobutyric acid (GABA) reuptake inhibitors, tiagabine (**20**), available on the market as Gabitril® or Cephalon®.[13–15] In recent years, many related compounds were synthesised, among them SK&F-89976A (**21**),[14,16] NO711 (**22**),[14] and DDPM-2571 (**23**)[17] gave the most promising results in biological studies. Nipecotic acid (**19**) itself also exhibits significant *in vitro* activity as an inhibitor of GABA uptake, but due to the highly hydrophilic, zwitterionic character cannot cross the blood-brain barrier and consequently is nearly inactive *in vivo*.[15,18]

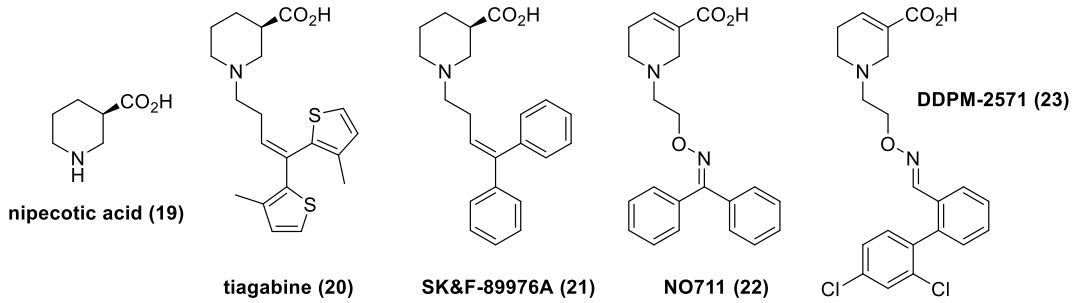


Figure 2. Nipecotic acid and its derivatives synthesised as GABA uptake inhibitors.

Other examples of piperidine-3-carboxylic acids of pharmacological interest are compounds **24**-**27** (Figure 3). The first of them was synthesised as a potential antihypertensive agent acting as a direct inhibitor of renin.[19] Derivative **25** decreases the activity of phosphoinositide-dependent protein kinase-1 (PDK1), which was recently proposed as a biological target in the therapy of cancer.[20] Also the next compound (**26**) was developed as an anticancer agent, but its molecular mechanism of action relies on the inhibition of epidermal growth factor receptor-2 (HER-2) sheddase.[21] Finally, avacopan (**27**) constitutes a first-in-class selective antagonist of complement 5a receptor (C5aR) and is currently in advanced clinical development for the treatment of ANCA-associated vasculitis.[1,[22,23]]

[1] Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are a group of autoimmune diseases characterised by inflammation and necrosis of blood vessels.

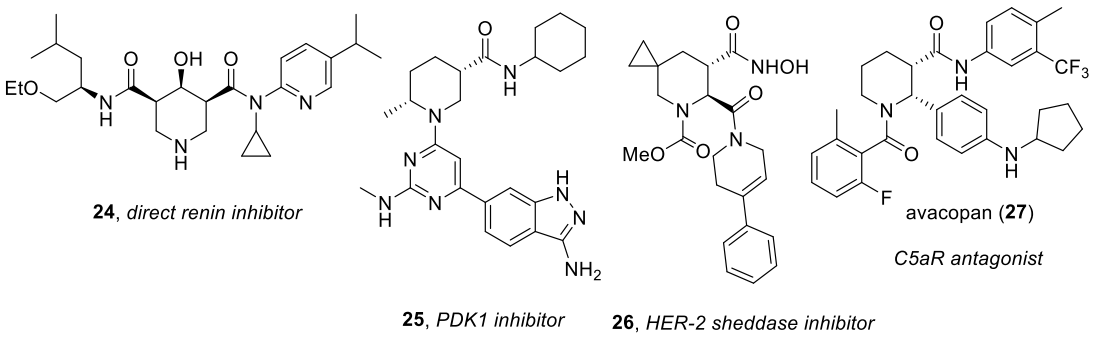


Figure 3. Pharmacologically relevant piperidine-3-carboxylic acids.

Although the isolation of nipecotic acid (**19**, Figure 2) from a natural source was not reported to date, its simple derivatives **28** (Figure 4) as well as unsaturated analogues **29** and **30** were identified in extracts obtained from areca nuts.[24] Siastatine B (**31**), a potent neuraminidase inhibitor, was, in turn, discovered in the culture filtrate of one of the *Streptomyces* strains.[25] Moreover, nipecotic acid motif may be recognized in the ring systems of numerous alkaloids represented in Figure 4 by ergometrine (ergonovine; **32**) – an ergot alkaloid used to treat postpartum haemorrhage.[26]

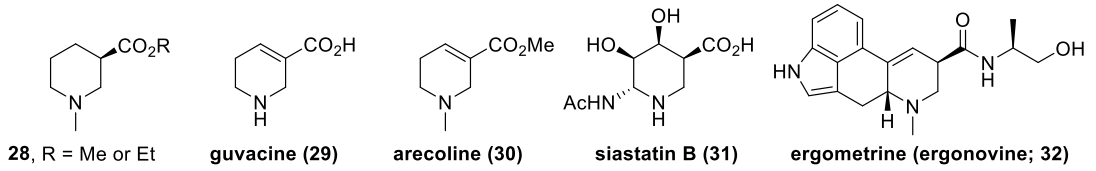


Figure 4. Natural products containing nipecotic acid structural motif.

Similarly to other groups of non-proteinogenic cyclic amino acids,[27–37] compound **19** (Figure 2) and its derivatives play an important role in peptide chemistry.[38–43] Incorporation of such rigid subunits into a molecule restricts its conformational flexibility as well as allows to induce particular structural motifs. These changes often result in increased selectivity and affinity of the ligand towards its biological target. Another important feature of peptides modified with non-proteinogenic residues is higher proteolytic stability.

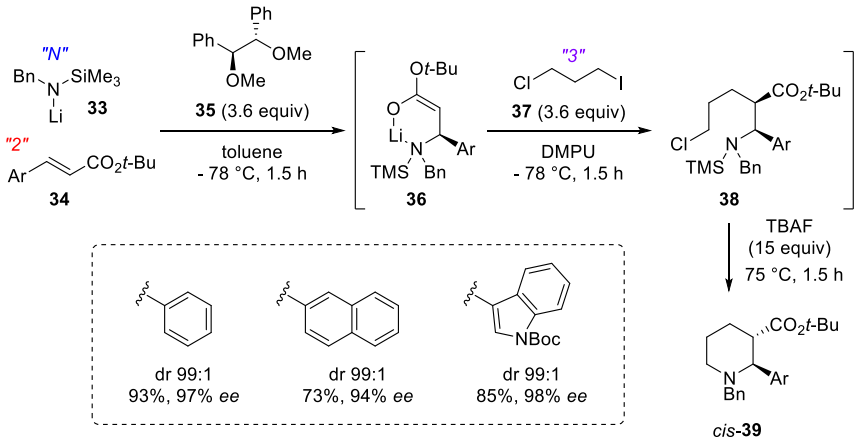
The significance of nipecotic acids in various fields of science stimulated the development of methods for their synthesis. These studies resulted in the discovery of manifold interesting protocols featuring high chemical as well as stereochemical yields. Selected works published over the last 10 years are presented below, whereby the sections are organized according to the position and the degree of the substitution of the piperidine ring. Earlier reports were discussed i.a. in the following reviews.[44–47]

II 2 Synthesis of piperidine-3-carboxylic acid derivatives

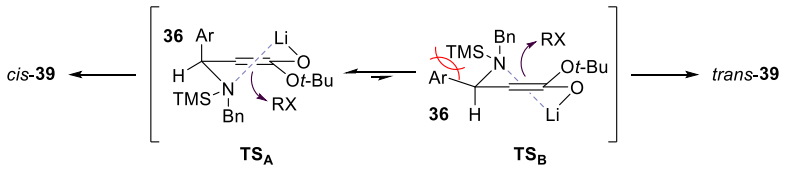
II 2.1. Monosubstituted piperidine-3-carboxylic acids

C-2-substituted nipecotic acids

In 2012, Harada and co-workers presented a one-pot method for the preparation of 2,3-disubstituted piperidines **39** based on the so-called [*N*+2+3] cyclization strategy (Scheme 7).[48,49] The first step of the synthesis constituted conjugate addition of lithium amide **33** to α,β-unsaturated ester **34** mediated by chiral diether **35**. Consecutive alkylation of the generated enolate **36** with 1-chloro-3-iodopropane (**37**) provided compound **38**, which under the influence of TBAF underwent an intramolecular S_N2 reaction. The corresponding piperidines *cis*-**39** were obtained as single diastereomers in excellent yields and enantioselectivities. The observed diastereoselectivity of the alkylation of enolate **36** was attributed to higher stability of transition state **TS$_A$** as compared to conformer **TS$_B$** (Scheme 8).

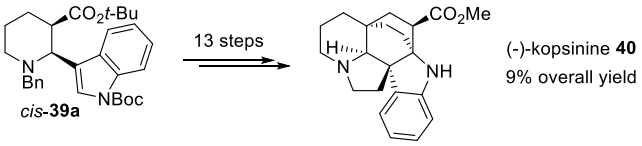


Scheme 7. Synthesis of cis*-piperidines* cis*-**39** by an asymmetric one-pot [N+2+3] cyclization.*



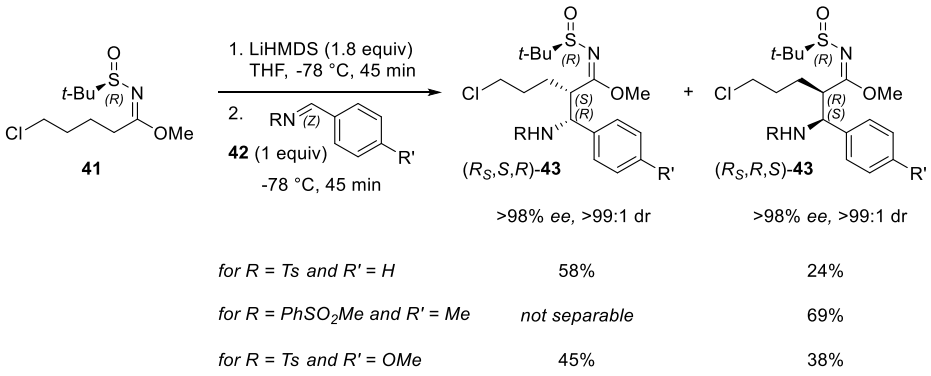
*Scheme 8. Transition states explaining the observed diastereoselectivity of alkylation of enolate **36**.*

To demonstrate the utility of the developed protocol in the synthesis of advanced piperidine derivatives, the authors transformed product **39a** into (−)-kopsinine (**40**)[48] (Scheme 9) – indole alkaloid first isolated from the rain-forest tree *Kopsia Longiflora* Merr.[50–53]

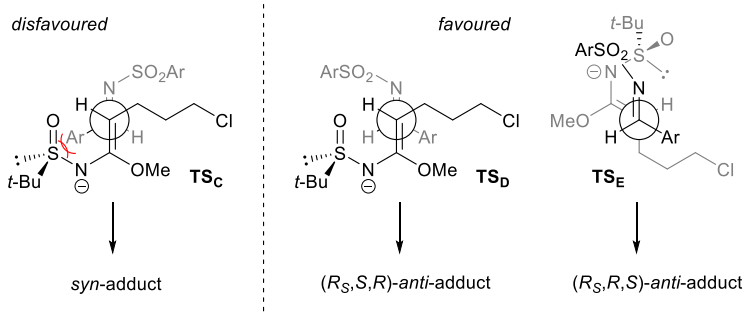


*Scheme 9. Structure of (-)-kopsinine (**40**).*

Another approach enabling the preparation of 2-aryl-substituted piperidine-3-carboxylates was published by the group of Prof. Mangelinckx.[54] The key step of this method constituted Mannich-type reaction of chiral δ-chloro-*N*-*tert*-butanesulfinyl-substituted imidates **41** with aldimines **42** (Scheme 10). Under the optimized conditions, the transformation proceeded with excellent *anti*-diastereoselectivity (*anti*/*syn* >99:1) and moderate control of the absolute stereochemistry. Overall yields of the isolated (R_S,*S*,*R*)- and (R_S,*R*,*S*)-adducts **43** ranged from 69% to 83%. Interestingly, the addition of *para*-methoxy-substituted imine provided (R_S,*R*,*S*)-imidate as a major product, whereas other investigated substrates preferentially formed *anti*-isomer with the opposite absolute configuration at carbon atoms. The stereochemical outcome of the process was rationalized with transition states **TS$_C$**-**TS$_E$** (Scheme 11). Due to the steric repulsion between the sulfinyl group of the generated enolate and the arylsulfonyl protection of imine **42**, transition state **TS$_C$**, leading to *syn*-adducts, should have higher energy than **TS$_D$** and **TS$_E$**.

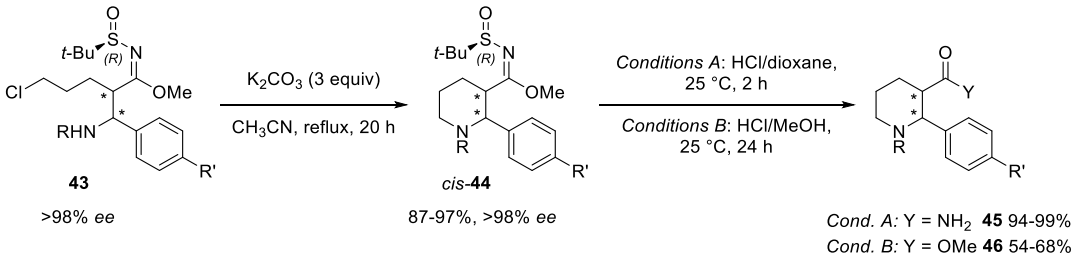


*Scheme 10. Synthesis of piperidine precursors **43**.*



*Scheme 11. Transition states proposed for addition of imidates **41** to aldimines **42**.*

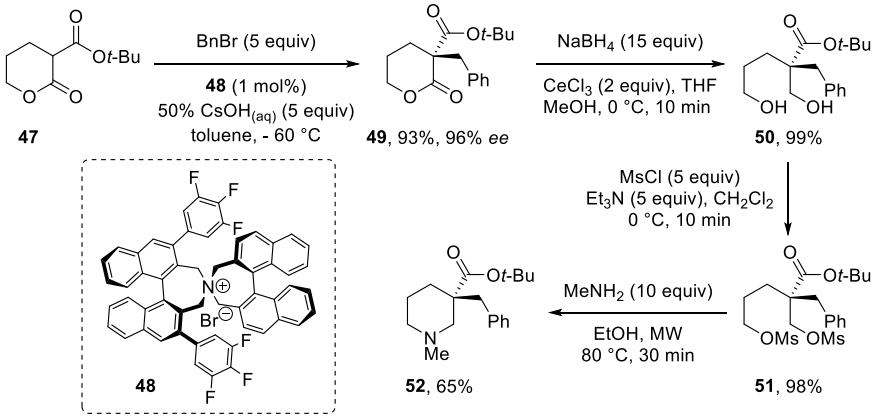
The obtained imidates **43** were then cyclized using K_2CO_3 as a base providing the desired piperidines **44** in very good to excellent yields (87–97 %; Scheme 12).[54] *tert*-Butylsulfinyl moiety in heterocycles **44** could be subsequently removed employing HCl in dioxane to give the corresponding amides **45**. The use of MeOH as solvent allowed, by contrast, the preparation of esters **46**.



*Scheme 12. Cyclization of imidates **43** to piperidines **44** as well as preparation of amides **45** and esters **46**.*

C-3-Substituted nipecotic acids

An interesting protocol allowing the synthesis of 3-alkyl-piperidine-3-carboxylates with high optical purity was proposed by Ha and co-workers (Scheme 13).[55] The basis of this approach constituted the developed by the authors method for enantioselective α-benzylation and α-allylation of α-*tert*-butoxycarbonyllactones **47** under phase-transfer catalytic conditions. As they demonstrated with compound **49**, the resulting products may be converted into piperidine derivatives by selective reduction with $NaBH_4$, dimesylation, and finally amination with methylamine.



*Scheme 13. Enantioselective α-benzylation of lactone **47** and the conversion of the resulting product **49** into piperidine **52**.*

C-4-Substituted nipecotic acids

Among the title nipecotic acid derivatives, of particular interest of synthetic chemists are those in which the C-4-substituent is an aryl residue. These compounds constitute useful intermediates in the preparation of pharmacologically relevant 4-arylpiperidines including antidepressants (-)-paroxetine (**53**; Paxil®, Seroxat®) and femoxetine (**54**, Figure 5).

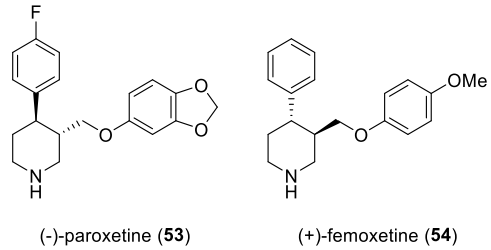
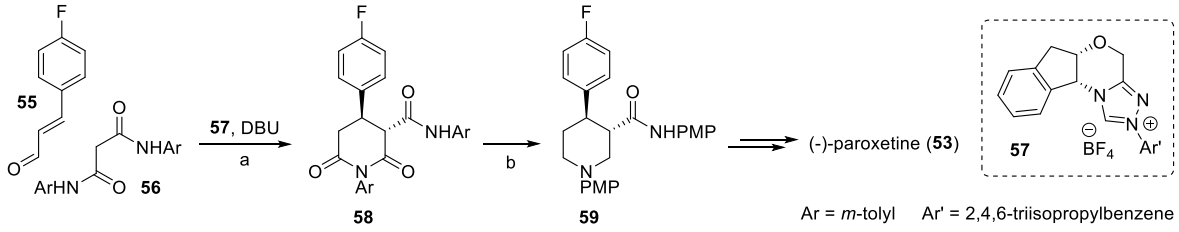


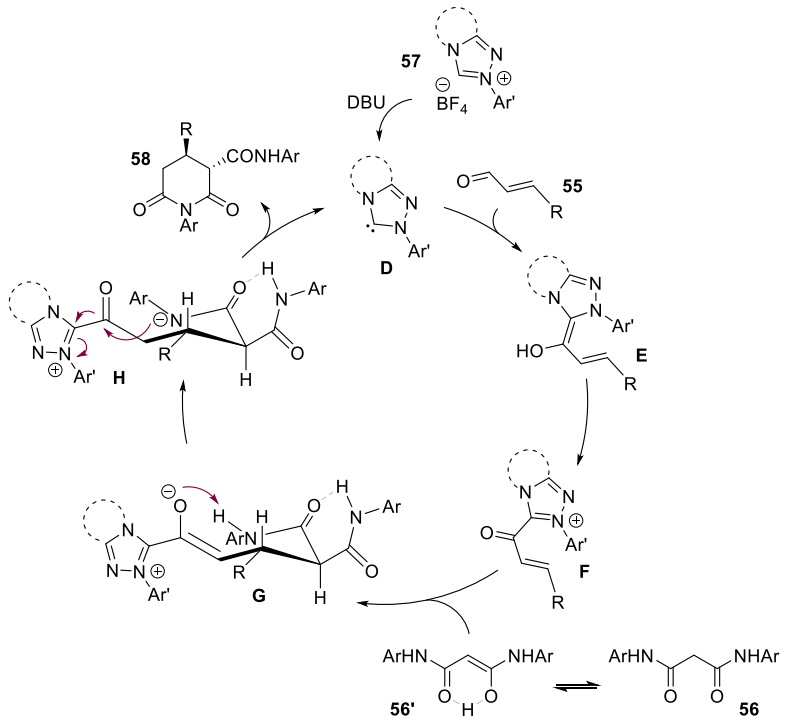
Figure 5. Structures of (-)-paroxetine and (+)-femoxetine.

For example, nipecotamide **59** served as a (-)-paroxetine precursor in the approach proposed by Guin (Scheme 14).[56] In this strategy, piperidine ring was constructed *via* formal [3+3] annulation between enal **55** and malonamide **56**. The transformation was catalysed by *N*-heterocyclic carbene generated from azolium salt **57** and carried out under oxidative conditions. The resulting glutarimide **58** was isolated in excellent enantioselectivity (97% *ee*) and very good yield (72%). Following the exchange of *N*-protecting groups, imide carbonyl functions were selectively reduced using $LiAlH_4$ at 25 °C affording derivative **59**.



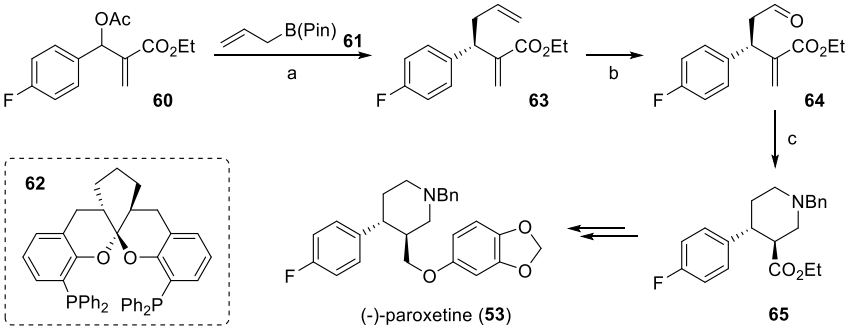
*Scheme 14. Synthesis of nipecotamide **59**. Conditions: (a) enal **55** (2 equiv), malonamide **56** (1 equiv), precatalyst **57** (15 mol%), DBU (20 mol%), 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (1.5 equiv), 4 Å MS, THF, 0 °C, 48 h, 72%, 97%* ee. *(b) $PMPNH_2$ (8 equiv), LiCl (10 mol%), THF, 160 °C, 72 h, 51%, 96%* ee. *(c) $LiAlH_4$ (8 equiv), THF, 25 °C, 12 h, 55%, 95%* ee.

The mechanism proposed for the reaction leading to imide **58** begins with the formation of carbene **D**, which subsequently undergoes nucleophilic addition to enal **55** (Scheme 15).[56] Oxidation of the resulting Breslow intermediate **E** affords azolium ion **F**. This species reacts then with diamide **56** to give enolate **G**. Formation of the final product proceeds through intermediate **H**.



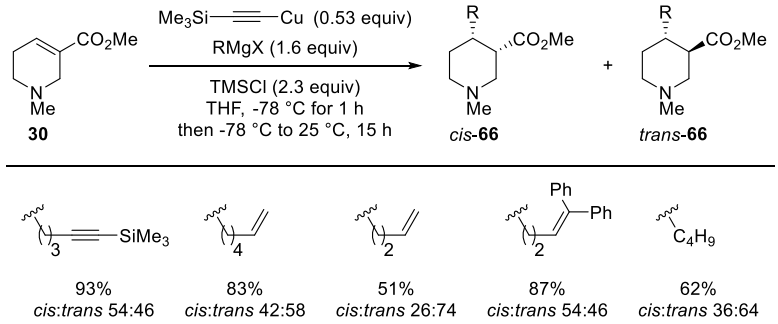
*Scheme 15. The mechanism proposed for the reaction between enal **55** and malonamide **56**.*

4-Fluorophenyl nipecotic acid ester **65** was, in turn, one of the intermediates in the synthesis of paroxetine designed by Wang and co-workers (Scheme 16).[57] The key step of this approach constituted asymmetric allylation of Morita-Baylis-Hillman-adduct **60** with allyl pinacolatoboronate **61**. The reaction was conducted in the presence of the palladium complex of spiroketal-based chiral diphosphine **62** (SKP) and delivered the corresponding diene in 85% yield and 97% *ee*. The more electron-rich double bond in product **63** was then oxidatively cleaved to give aldehyde **64**. Reductive amination of this compound followed by intramolecular conjugate addition provided piperidine-3-carboxylate **65**.



*Scheme 16. Synthesis of nipecotic acid derivative **65**. Conditions: (a) **61** (1.2 equiv), $[Pd(C_3H_5)Cl]_2$, **62** (1.25 mol%), CsF, CH_2Cl_2, 25 °C, 17 h, 85%, 97%* ee. *(b) i)* m*-CPBA (1.5 equiv), CH_2Cl_2, 0 °C→25 °C, 17 h; ii) HIO_5 (1.2 equiv), THF-H_2O (3:1), 0 °C, 1 h, 68% over two steps. (c) i) $BnNH_2$ (3 equiv), $NaBH_3CN$ (5 equiv), AcOH, MeOH, 25 °C, 17 h; ii) KO*t*-Bu (3 equiv),* t*-BuOH (1.5 equiv), toluene, 25 °C, 1 h, 65% over two steps.*

An example of a work describing the synthesis of nipecotic acid derivatives comprising an aliphatic residue at C-4 constitutes, by contrast, the publication by Hellenbrandt and co-workers.[58] The approach presented by the authors was based on the conjugate addition of organomagnesium cuprates to alkaloid arecoline (**30**; Scheme 17). The process was carried out in THF in the presence of TMSCl, and the desired organometallic reagents generated from the corresponding Grignard compound and copper(I) (trimethylsilyl)acetylide. The target piperidines **66**, containing an alkyl, an alkenyl, or a TMS-protected-alkynyl substituent, were obtained in very good to excellent overall yields and 54:46-26:74 diastereomeric ratios.



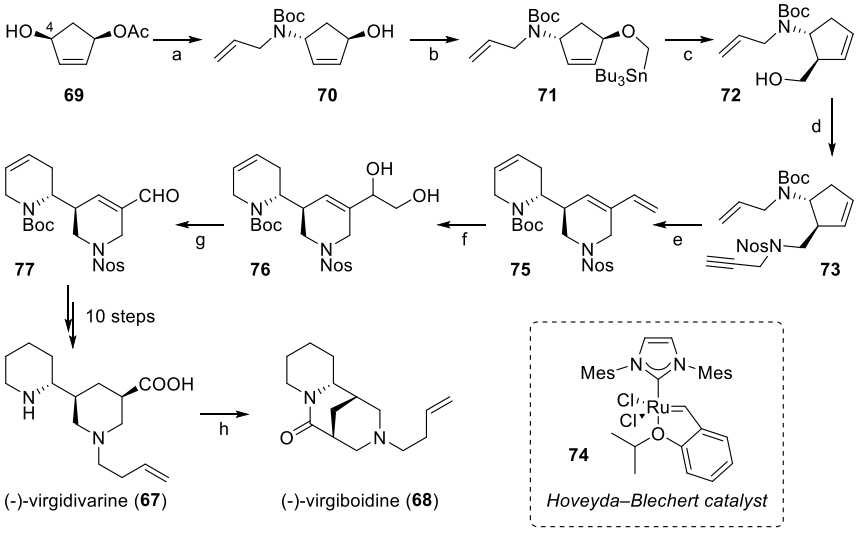
*Scheme 17. Conjugate addition of organomagnesium cuprates to arecoline **30**.*

C-5-Substituted nipecotic acids

Virgidivarine (**67**)[59,60] and its derivative virgiboidine (**68**)[61] are dipiperidine alkaloids discovered in 1982 by van Eijk and de Kok in the leaves of African Leguminosae *Virgilia divaricata* and *Virgilia oroboides* (Scheme 18). The first total synthesis of these compounds was, in turn, accomplished by Kress and co-workers in 2016.[62] The developed approach was based on intramolecular ene-ene-yne ring-rearrangement metathesis (RRM). To prepare precursor **73**, the authors first transformed acetate **69** in four steps into alcohol **70**. The inversion of the configuration at C-4 was achieved during the installation of the amine moiety. Carbocycle **70** was then alkylated with iodomehyltributultin to afford compound **71** in 90 % yield. Upon treatment with *n*-BuLi, this product underwent [2,3] sigmatropic rearrangement (Wittig–Still rearrangement) providing cyclopentene **72**. The reaction of derivative **72** with Nos-protected propargylamine under Mitsunobu conditions furnished the desired carbamate **73**.

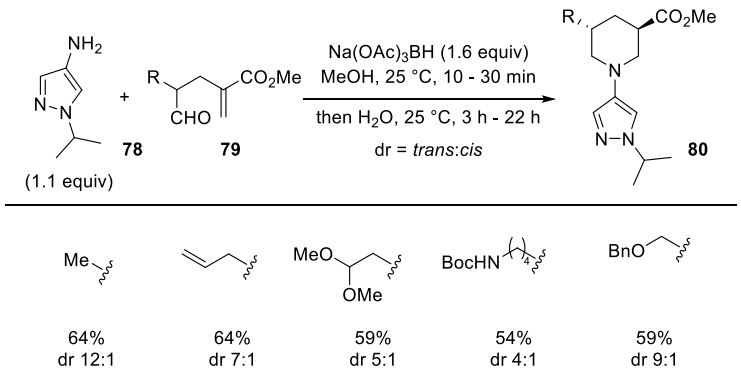
Precursor **73** was subsequently exposed to various metathesis catalysts (Scheme 18).[62] The highest yield of dipiperidine **75** was achieved when the reaction was performed in the presence of complex **74** (5 mol%) under atmosphere of ethylene. Metathesis product **75** was next subjected to Sharpless dihydroxylation followed by cleavage of the resulting glycol **76** with $NaIO_4$. The target molecule **67** was obtained from aldehyde **77** in further 10 steps.

Construction of piperidino-quinolizidine system in virgiboidine (**68**) was accomplished by EDC-mediated intramolecular formation of amide bond within virgidivarine **67**.



*Scheme 18. Synthesis of virgidivarine (**67**) and its conversion into virgiboidine (**68**). Conditions: (a) i) allylNHNos (1 equiv), PPh_3 (2.5 equiv), DIAD (2 equiv), THF, 0 °C → 25 °C, 98%; ii) PhSH (1 equiv), K_2CO_3 (3 equiv), DMF, 60 °C, 96%; iii) Boc_2O (1 equiv), MeOH, 60 °C, 94%; iv) KCN (2.5 mol%), MeOH, 25 °C, 97%. (b) KH (2.2 equiv), ICH_2SnBu_3 (1.2 equiv), dibenzo-18-crown-6 (0.5 mol%), THF, 25 °C, 90%. (c)* n-*BuLi (1.1 equiv), THF, –100 °C → –60 °C → 25 °C, 74%; (d) C_3H_3NHNos (1 equiv), PPh_3 (2.5 equiv), DIAD (2 equiv), THF, 0 °C → 25 °C, 82%. (e) Hoveyda–Blechert catalyst (**74**; 5 mol%), ethylene (1 atm, balloon), CH_2Cl_2, 40 °C, 83%. (f) AD-mix-β,* t-*BuOH/H_2O (1:1), 0 °C, 48% (87% brsm). (g) $NaIO_4/SiO_2$, MeCN/EtOAc, 96%. (h) EDC (1.1 equiv),* N-*methylmorpholine (5 equiv), EtOH, 25 °C, 29%.*

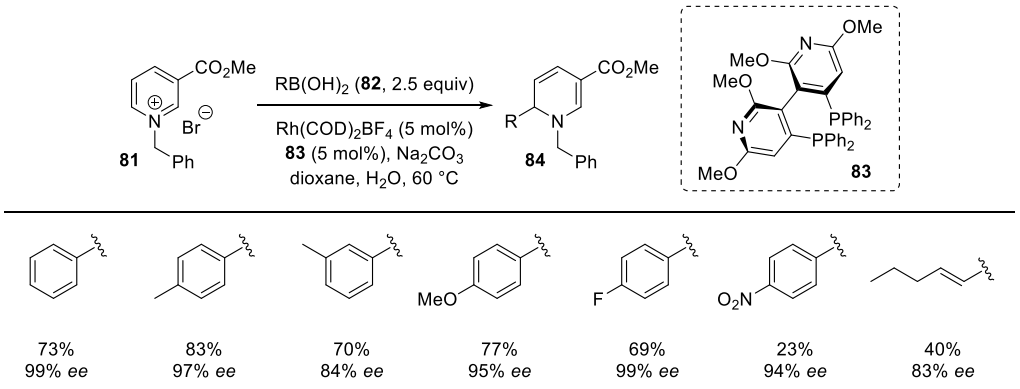
Last year, a group of Merck scientists disclosed a method for the preparation of *N*-(hetero)aryl piperidines based on reductive amination/aza-Michael reaction sequence.[63] Among the presented examples, there were also several 5-substituted nipecotic acid derivatives. To obtain these compounds, the authors first reacted aldehydes **79** with amine **78** in MeOH in the presence of sodium triacetoxyborohydride (Scheme 19). The resulting products were directly, without isolation, cyclized providing *trans*-piperidines **80** in moderate to good yields and with high diastereoselectivities. The latter transformation could be achieved by simply adding water to the reaction mixture. It is worthwhile to mention that the use of ketones instead of aldehydes **79** allowed the preparation of analogous 6-substituted piperidine-3-carboxylates.



*Scheme 19. Synthesis of piperidines **80** by reductive amination/aza-Michael reaction sequence - selected examples.*

C-6-Substituted nipecotic acids

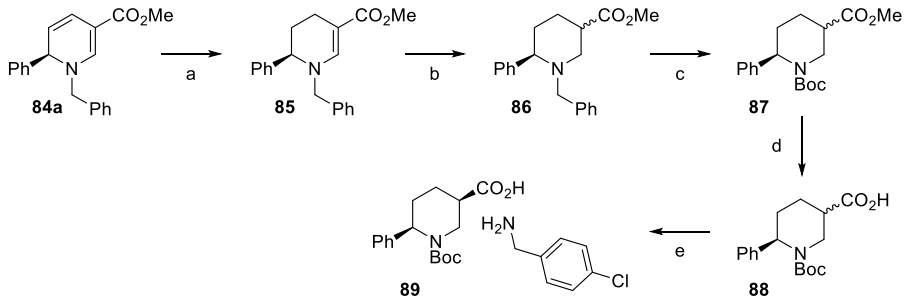
In 2011, Nadeau and co-workers described an enantioselective addition of boronic acids **82** to nicotinate salt **81** leading to 1,2-dihydropyridines **84** (Scheme 20).[64] The optimized conditions encompassed the use of $Rh(COD)_2BF_4$ and bisphosphine ligand **83**. Phenylboronic acid as well as *para*-substituted substrates afforded the corresponding products in high enantioselectivities (94−97% *ee*) and in most cases very good yields. An exception constituted the reaction partner containing a nitro group, which reacted in only 23% yield. The researchers could also prepare dihydropyridines comprising an *ortho*-substituted aryl moiety or an alkenyl chain, although in lower optical purities.



*Scheme 20. Enantioselective addition of boronic acids **82** to* N*-benzylnicotinate bromide **81** - selected examples.*

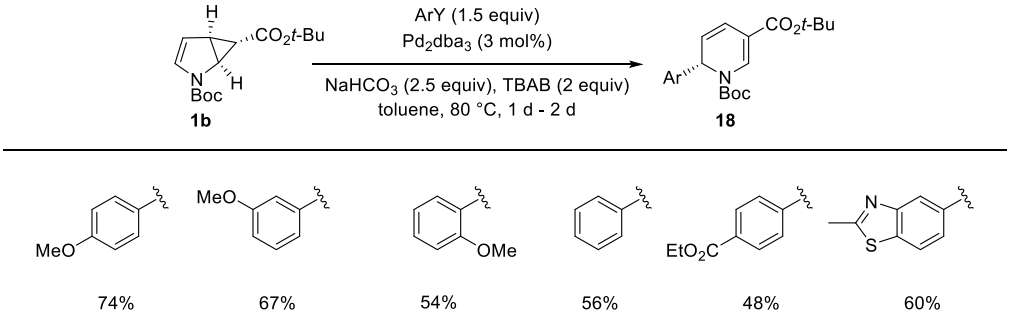
The possibility of employing the obtained products in the synthesis of piperidines was investigated with compound **84a** (Scheme 21).[64] Accordingly, hydrogenation of dihydropyridine **84a** in the presence of $Pd(OH)_2/C$ furnished the corresponding vinylogous carbamate **85**. This product was subsequently subjected to the reduction with sodium cyanoborohydride to afford a 1:1 mixture of *trans*- and *cis*-esters **86**. After the exchange of the benzyl protection to a Boc group, the diastereomers were treated with NaOMe, which allowed to epimerize the ester moiety toward the equatorial position. The remaining *trans*-isomer was

removed upon conversion of the resulting acid **88** into the corresponding 4-chlorobenzylammonium salt **89**.



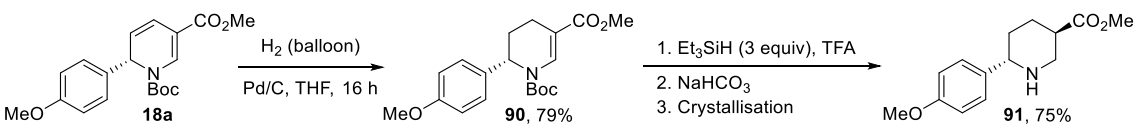
*Scheme 21. Synthesis of phenyl-substituted piperidine **89** from compound **84a**. Conditions: (a) H_2 (45 psi), $Pd(OH)_2/C$, EtOH, 25 °C, 18 h. (b) $NaBH_3CN$ (1.2 equiv), MeOH, AcOH, 25 °C, 3 h. (c) Boc_2O (1.2 equiv), Et_3N (1 equiv), H_2 (45 psi), $Pd(OH)_2/C$, EtOH, 25 °C, 18 h. (d) NaOMe (2.2 equiv), MeOH, H_2O (6 equiv), 60 °C, 18 h. (e) 4-chlorobenzylamine (1 equiv), Et_2O; recrystallization EtOAc/hexane, 80%* ee *and 49% yield over 5 steps.*

As I already mentioned, also our group reported the synthesis of 6-aryl-1,6-dihydropyridine-3-carboxylates (Scheme 22).[12] The proposed approach was based on ring expansion of cyclopropanated pyrroles **1** under Heck-coupling conditions. Arylation of bicycle **1b** could be successfully performed with a variety of substituted and unsubstituted aryl halides, although the use of electron-deficient substrates led to only moderate results. We also showed that the process tolerated not only *para*- but also *meta*- and *ortho*-isomers. Importantly, the developed ring expansion proceeded without racemization, as demonstrated with the reaction of optically pure derivative (-)-**1b**.



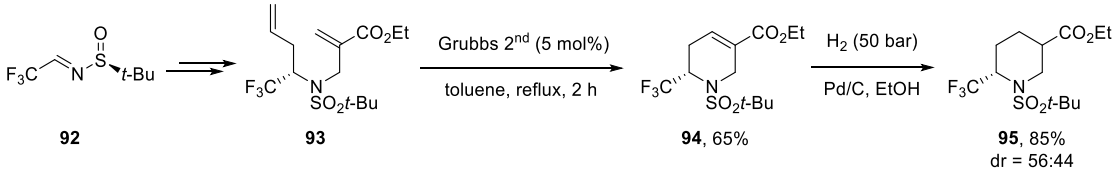
*Scheme 22. Pd-catalysed arylation of monocyclopropanated pyrrole **1b** with aryl halides – selected examples.*

The protocol for the reduction of double bonds in products **18** was developed using compound **18a** as a model substrate (Scheme 23).[12] Thus, enecarbamate **90**, resulting from the catalytic hydrogenation of derivative **18a**, was treated with Et_3SiH and trifluoroacetic acid to provide *trans*-piperidine **91** in 75% yield.



*Scheme 23. Transformation of 1,2-dihydropyridine **18a** into nipecotic acid derivative **91**.*

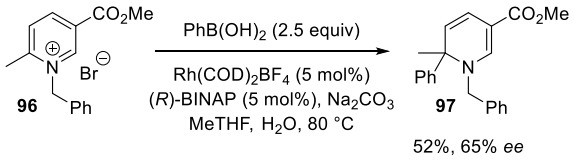
On the other hand, Hao and co-workers reported the synthesis of trifluoromethylated tetrahydropyridine **94** by ring-closing-metathesis of aminodiene **93** (Scheme 24).[65] The transformation was performed using Grubbs 2nd generation catalyst and proceeded in 65% yield. Compound **94** was then subjected to catalytic hydrogenation yielding the corresponding piperidine **95** in 85% yield as a ca 1:1 mixture of diastereomers. Substrate **93** was prepared in three steps from readily available *N*-*tert*-butanesulfinyl-(3,3,3)-trifluoroacetaldimine (**92**).



*Scheme 24. Synthesis of trifluoromethylated piperidine **95**.*

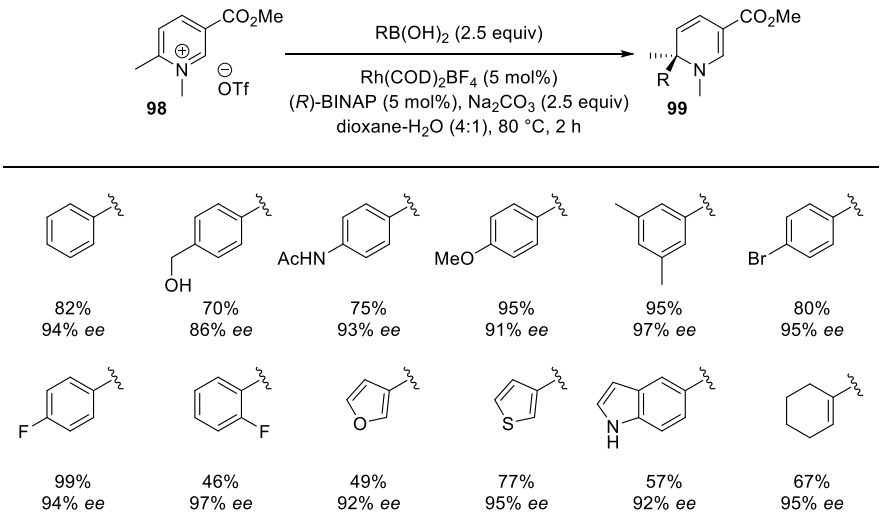
II 2.2. Polysubstituted piperidine-3-carboxylic acids

As I described in the previous section, Nadeau and co-workers developed a method for the synthesis of enantio-enriched 1,2-dihydropyridines based on the addition of boronic acids **82** to nicotinate salt **81** (Scheme 20).[64] In the same work, the authors presented one example of an analogous process involving 6-methyl-substituted pyridine **96** (Scheme 25). Employing (*R*)-BINAP as a ligand, they were able to obtain the desired product **97**, albeit in moderate optical purity (65% *ee*) and only 52% yield.



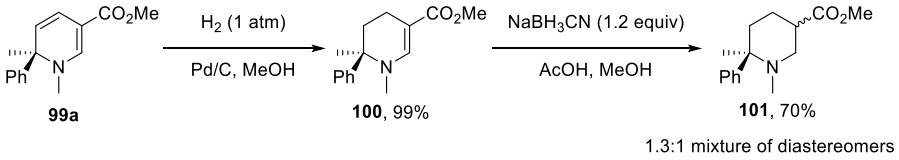
*Scheme 25. Addition of phenylboronic acid to salt **96**.*

Recently, the group of Prof. Karimov showed that much better results may be achieved with analogous triflate **98** as a substrate and using dioxane instead of MeTHF (Scheme 26).[66] Under the optimized conditions, the reaction of nicotinate **98** with phenylboronic acid proceeded in 84% yield and 94% *ee*. Furthermore, the researchers successfully employed a variety of other aromatic boronic acids as well as a vinylic substrate. The corresponding dihydropyridines **99** were obtained in high optical purities and generally very good yields.



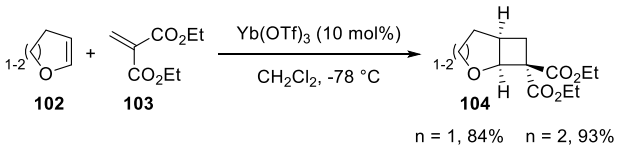
*Scheme 26. Addition of boronic acids to salt **98** – selected examples.*

The authors also demonstrated several derivatizations of the obtained products.[66] For instance, catalytic hydrogenation of dihydropyridine **99a** followed by treatment of the resulting vinylogous carbamate **100** with sodium cyanoborohydride furnished the corresponding nipecotic acid derivative **101** as a 1.3:1 mixture of diastereomers (Scheme 27).

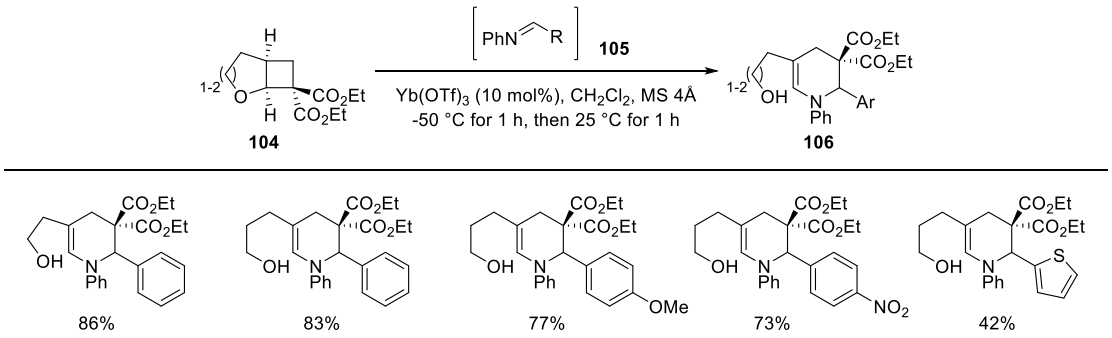


*Scheme 27. Transformation of dihydropyridine **99a** into piperidine 3-carboxylate **101**.*

A distinctive approach for the preparation of polysubstituted nipecotic acid derivatives was presented by the research group conducted by Pagenkopf. The authors developed a method for the synthesis of 2-alkoxy-1,1-cyclobutane diesters **104** and subsequently subjected the obtained products to cycloadditions with *in situ* generated imines **105** (Scheme 28).[67] Interestingly, both the synthesis of substrates **104** and their conversion into heterocycles **106** proceeded most efficiently in the presence $Yb(OTf)_3$. The corresponding tetrahydropyridines **106** were isolated in moderate to very good yields (Scheme 29).

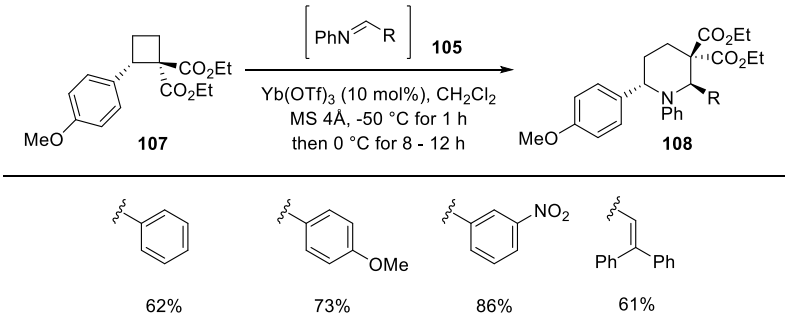


*Scheme 28. $Yb(OTf)_3$-catalysed synthesis of cyclobutanes **104**.*



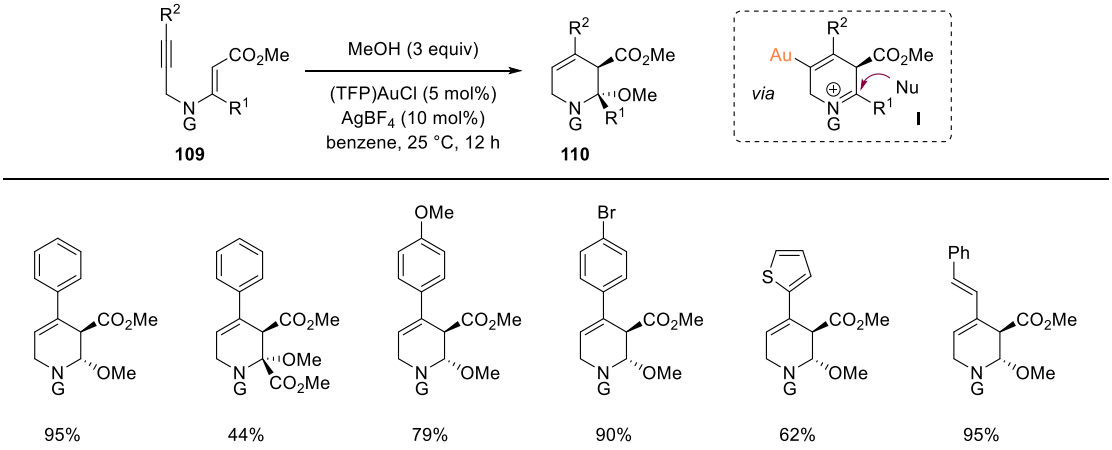
*Scheme 29. $Yb(OTf)_3$-catalysed formal [4+2] cycloaddition of cyclobutanes **104** with imines **105** - selected examples.*

The authors could also successfully extend the developed methodology to cyclobutanes with carbon-donating groups **107** (Scheme 30).[67] Cycloadditions of imines **105** to these products proceeded with complete diastereoselectivity affording the corresponding 2,6-*trans*-piperidines **108** in the yields ranging from 59% to 84%.



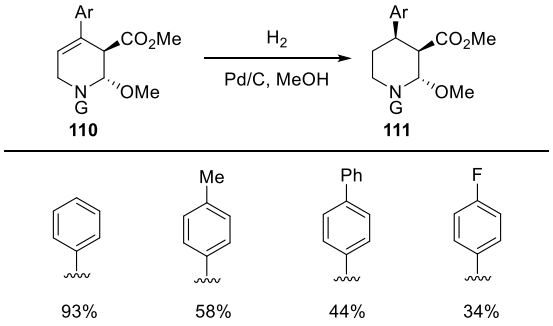
*Scheme 30. Synthesis of piperidines **108** from cyclobutanes **107** and imines **105** – selected examples.*

Nipecotic acid derivatives may be also conveniently synthesised by cycloisomerization of enynes. An example of such transformation was presented this year by Matouš and co-workers.[68] The scientists exposed β-propargylamino acrylic derivatives **109** to (TFP)AuCl/$AgBF_4$ in the presence of MeOH to obtain the corresponding tetrahydropyridines **110** (Scheme 31). The formation of these products may be rationalized by nucleophilic trapping of the intermediary iminium ion **I**. Most of the substrates bearing an aryl residue at the triple bond provided the corresponding product in good or very good yield. The few exceptions encompassed derivatives containing a 3,4-dichloro- or an NO_2-substituted phenyl ring. Lower yield was also observed for enyne with R^1 = CO_2Me. In the case of R^1 = alkyl or aryl, the cyclization led, in turn, to 1,2-dihydropyridines instead of adducts **110**. On the other hand, the strategy could be successfully extended to alken-1-yl derivatives, which yielded the expected products **110** in moderate to excellent yields. Substrates comprising a 1,3-diyne motif were, however, not tolerated.



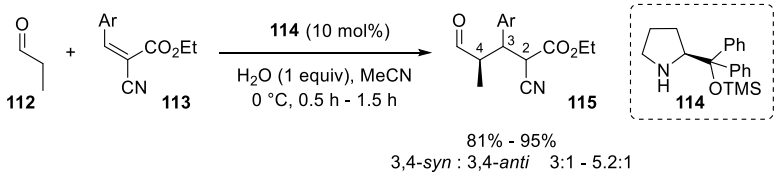
*Scheme 31. Cycloisomerization of enynes **109** – selected examples. G =* p*-methoxybenzenesulfonyl.*

Several aryl-substituted tetrahydropyridines were then subjected to catalytic hydrogenation using Pd/C as a catalyst and MeOH as a solvent (Scheme 32).[68] While all reactions proceeded with complete diastereoselectivity, the yields significantly varied and ranged from satisfactory 34% (for the fluorine-containing substrate) to excellent 93% (for the piperidine with an unsubstituted phenyl ring).

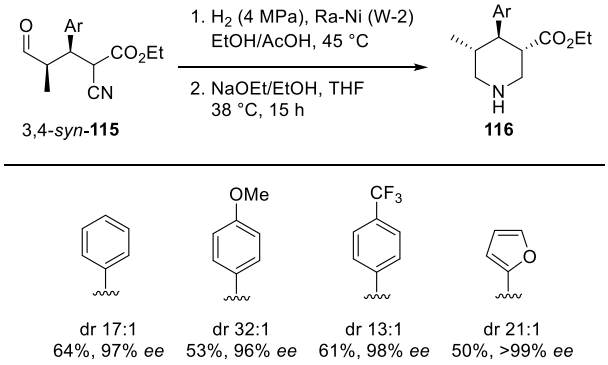


*Scheme 32. Catalytic hydrogenation of tetrahydropyridines **110**. G =* p*-methoxybenzenesulfonyl.*

Hayashi disclosed, in turn, a method for the preparation of enantiomerically pure 3,4,5-trisubstituted piperidines *via* asymmetric Michael reaction between propanal (**112**) and α-cyano α,β-unsaturated esters **113** followed by a reduction/cyclization cascade (Scheme 33).[69] The conjugate addition was performed in the presence of diphenylprolinol silyl ether **114** (Hayashi–Jørgensen catalyst) and proceeded with good 3,4-*syn* stereoselectivity. Overall yields of the products ranged from 81% to 95%. 3,4-*Syn* adduct, which further existed as a mixture of C-2 diastereomers, was separated from 3,4-*anti* isomer by column chromatography and then subjected to hydrogenation in the presence of activated Raney Nickel (Scheme 34). Subsequent epimerization at C-3 of the resulting piperidine using sodium ethoxide provided thermodynamically favoured isomer **116** in 50-66% yield. In all examples, this product was obtained in high optical purity, ranging from 90% to >99% *ee*.

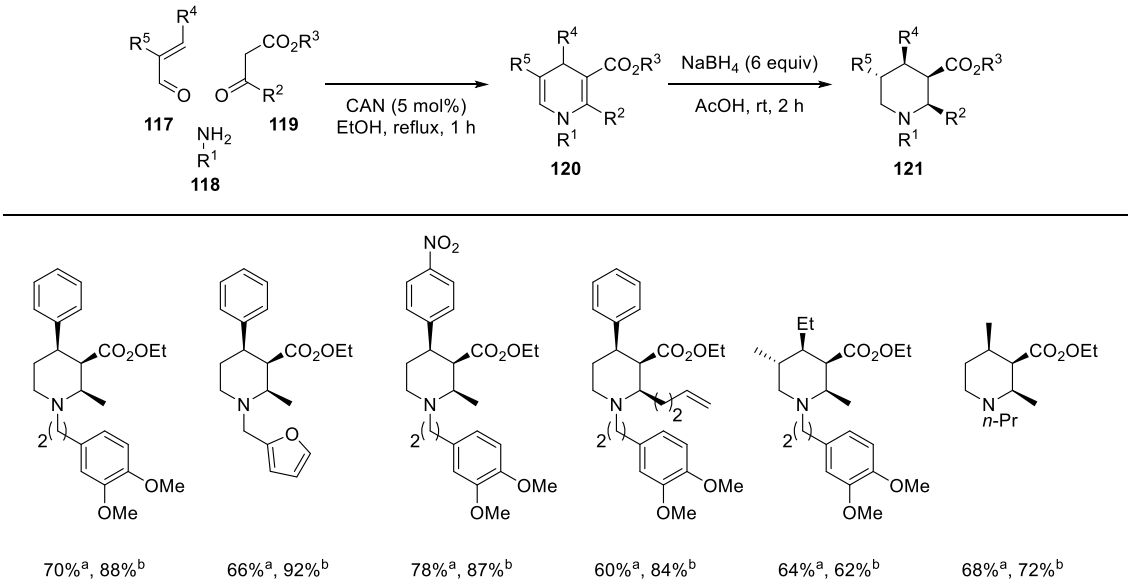


*Scheme 33. Diphenylprolinol silyl ether **114**-mediated asymmetric conjugate addition of propanal (**112**) and α-cyano α,β-unsaturated esters **113**.*



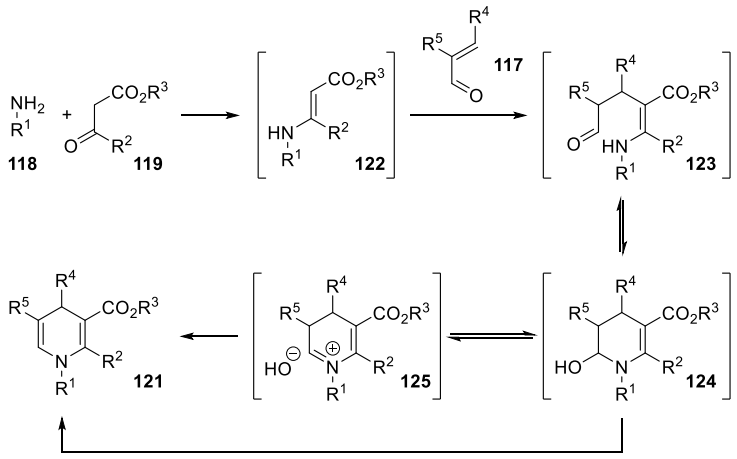
*Scheme 34. Conversion of adducts 3,4-*syn*-**115** into piperidines **116**.*

In recent years, appeared also several publications describing the synthesis of polysubstituted piperidine-3-carboxylates *via* multicomponent reactions. One of them is the work presented by the group of Prof. Menéndez.[70] The authors reacted amines **118** with α,β-unsaturated aldehydes **117** and β-dicarbonyl compounds **119** in the presence of cerium(IV) ammonium nitrate (CAN) obtaining 1,4-dihydropyridine-3-carboxylates **120** (Scheme 35). The reduction of these products with $NaBH_4$ proceeded with complete diastereoselectivity, and the corresponding piperidines **121** (bearing up to five substituents) were isolated in good to very good yields.



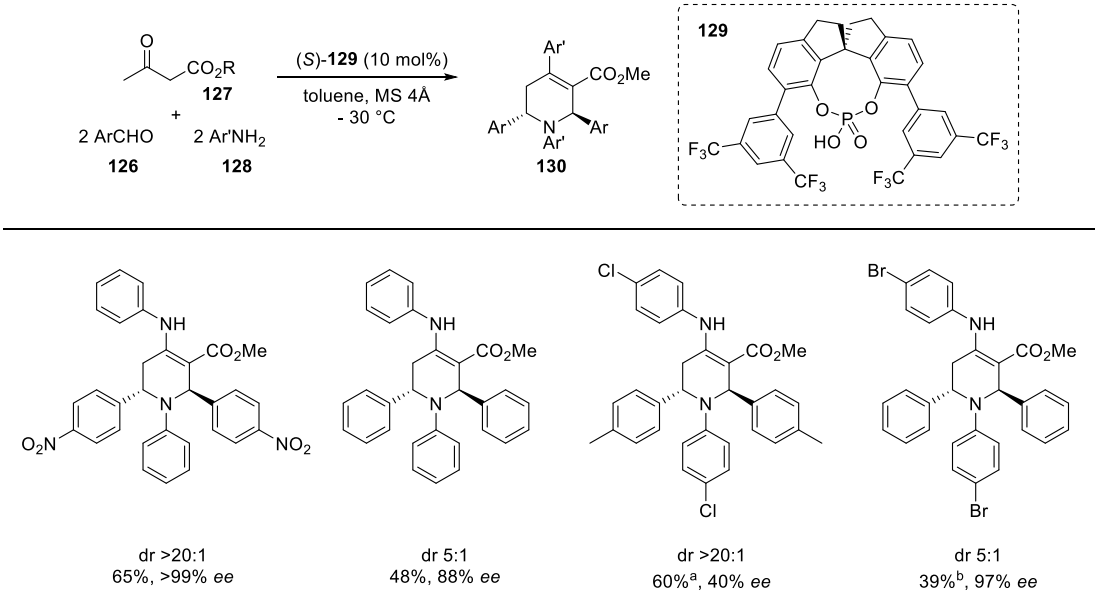
*Scheme 35. Synthesis of piperidine-3-carboxylates **121** by the group of Prof. Menéndez. [a] Yield of dihydropyridine **120**. [b] Yield of $NaBH_4$ reduction of dihydropyridine **120**.*

According to the authors, the three-component reaction begins with the formation of β-enaminone **122**, which then undergoes Michael addition to aldehyde **117** (Scheme 36).[70] The 6-*exo*-*trig* cyclization of the resulting intermediate **123** affords enaminoester **124**. Dehydration of this compound, which may also proceed *via* iminium ion **125**, provides the corresponding tetrahydropyridine **121**.



Scheme 36. Mechanism of 1,4-dihydropyridine formation proposed by Menéndez and co-workers.

Li presented, in turn, an organocatalytic asymmetric reaction between aromatic aldehydes **126**, β-ketoesters **127**, and anilines **128** leading to tetrahydropyridines **130** (Scheme 37).[71] The authors found that this pseudo five-component process may be efficiently catalysed by chiral SPINOL-phosphoric acid **129**. Transformations involving electron-deficient aldehydes provided the desired products in moderate yields and with good to excellent diastereoselectivities. The enantiomeric excesses ranged from 85% to >99%, whereby *para*-substituted substrates performed better than *meta*- and *ortho*-isomers. While benzaldehyde also turned out to be a suitable reaction partner, more electron-rich 4-methylbenzaldehyde did not react under the standard conditions. The corresponding product could be, however, obtained upon increasing the reaction temperature and the catalyst loading, although in low optical purity. On the other hand, the introduction of a bromine atom onto the aniline aromatic ring resulted in a noticeable improvement of the stereoselectivity with only a small effect on the reaction yield.



*Scheme 37. Organocatalytic multicomponent reaction of aromatic aldehydes **126**, anilines **128**, and β-ketoesters **127** leading to tetrahydropyridines **130** – selected examples.*

III Results and discussion

The central part of my Ph.D. project concerned the expansion of the cyclopropane ring in 2-azabicyclo[3.1.0]hex-3-enes under Heck-reaction conditions. Continuing the studies on this transformation conducted in our group, I set out to develop a procedure for the arylation of substrates **1** which would be more efficient than the initial one. In the next step, I planned to investigate analogous reactions involving *gem*-disubstituted cyclopropanes. Motivation to undertake these works was the broad applicability of the resulting dihydro- and tetrahydropyridines as building blocks in organic synthesis as well as the significance of α-aryl-substituted piperidine derivatives in medicinal chemistry and pharmacy. Following determination of scope and limitations of the developed protocols, I was going to examine the reactivity of the obtained products. Selected from the prepared derivatives should be then employed for the preparation of model peptides for conformational studies.

My research tasks encompassed also the synthesis of novel 2-azabicyclo[3.1.0]hex-3-enes by cyclopropanation of substituted pyrrole derivatives as well as investigations on functionalization of the double bond in the prepared bicycles.

III 1 Cyclopropanation of pyrrole derivatives

The first part of my work concerned cyclopropanation of pyrroles with diazoesters. Besides the synthesis of 2-azabicyclo[3.1.0]hex-3-enes derived from *N*-Boc pyrrole (**131**), I was going to investigate reactions involving substituted derivatives **132**-**138** (Figure 6).

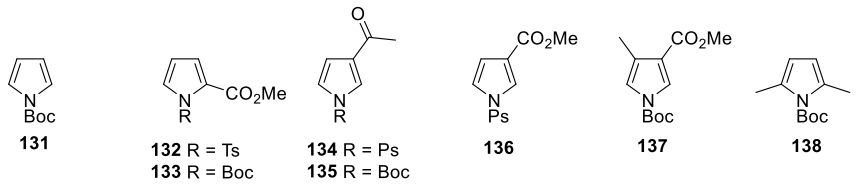
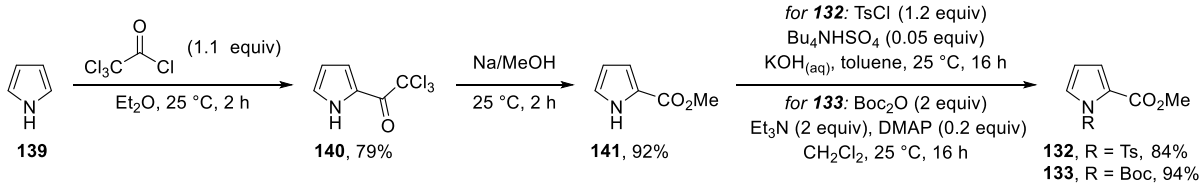


Figure 6. Prepared pyrrole derivatives.

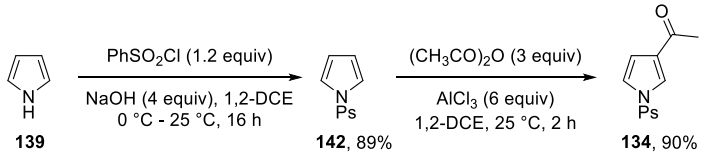
Compounds **131** and **138** (Figure 6) were prepared by Boc-protection of commercially available heteroarenes using the standard synthetic procedure.

The synthesis of methyl 2-pyrrolecarboxylates **132** and **133** commenced with acylation of pyrrole (**139**) with trichloroacetyl chloride in Et_2O (Scheme 38). The resulting derivative **140** was subsequently treated with NaOMe in MeOH to give ester **141**.[72] Protection of this product with a tosyl or a Boc-group provided the desired compounds **132** and **133**.



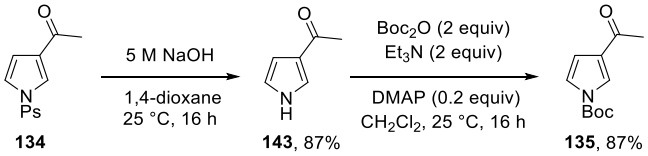
*Scheme 38. Synthesis of esters **132** and **133**.*

The method employed to prepare substrate **134** was based on the fact that a strong electron-withdrawing group on pyrrole nitrogen, such as phenylsulfonyl in heteroarene **142**, directs aromatic electrophilic substitution to the 3-position (Scheme 39). Precursor **142** was obtained in the reaction of pyrrole (**139**) with phenylsulfonyl chloride in 89% yield. Friedel-Crafts acetylation of compound **142** was performed in 1,2-dichloroethane using $AlCl_3$ as a Lewis acid and proceeded in 90% yield.[73,74]



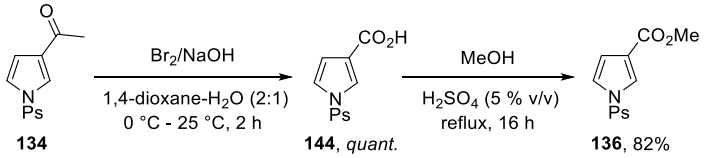
*Scheme 39. Synthesis of 3-acetyl-*N*-(phenylsulfonyl)pyrrole **134**.*

Although β-acetylation of pyrrole may be also successfully performed using other types of arylsulfonyl protecting groups, I choose the phenylsulfonyl one due to the possibility of its easy removal under basic conditions. Thus, the treatment of compound **134** with NaOH in a water/1,4-dioxane mixture yielded derivative **143** in 87% yield (Scheme 40).[73] The obtained product was subsequently protected with a Boc-group employing a standard procedure.



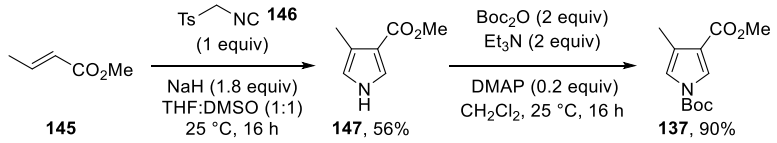
*Scheme 40. Synthesis of 3-acetyl-*N*-Boc-pyrrole **135**.*

Ester **136** was synthesised from derivative **134** *via* haloform reaction (Scheme 41). For this purpose, I added a freshly prepared solution of hypobromite to a cooled solution of substrate **134** to obtain quantitatively carboxylic acid **144**. Heating of this product in MeOH in the presence of H_2SO_4 provided the desired compound **136** in 82%.[75,76]



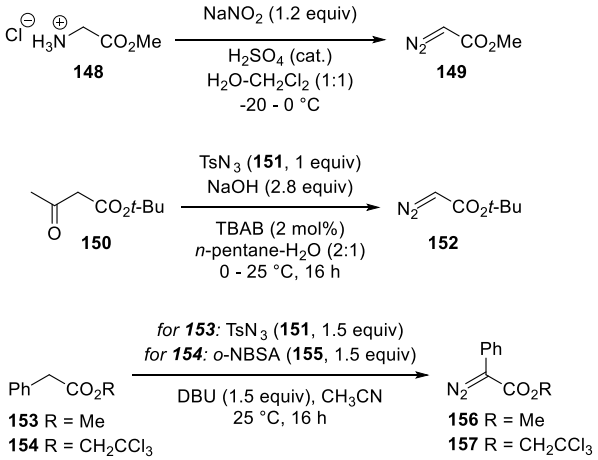
Scheme 41. Synthesis of methyl N*-(phenylsulfonyl)pyrrole-3-carboxylate **136**.*

To prepare 3,4-disubstituted derivative **137** I employed a method for pyrrole synthesis proposed by Van-Leusen.[77] It is based on [3+2] cycloaddition of tosylmethyl isocyanides (TosMICs) to electron-deficient olefins. Performing the reaction of isocyanide **146** with methyl crotonate (**145**) under the conditions presented in Scheme 42, I obtained heteroarene **147** in 56% yield.[78] Target compound **137** was prepared by the reaction of pyrrole **147** with Boc-anhydride.



*Scheme 42. Synthesis of 3,4-disubstituted pyrrole **137**.*

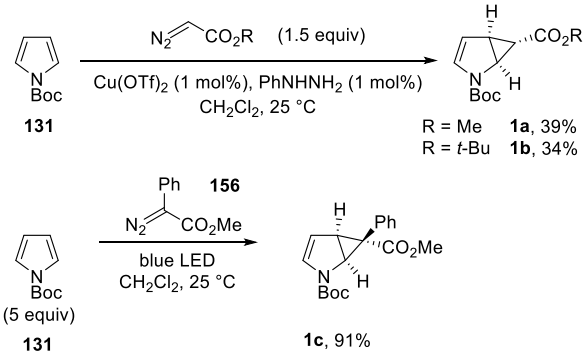
Following the synthesis of pyrrole derivatives, I prepared diazoesters **149**, **152**, **156**, and **157** (Scheme 43). Methyl diazoacetate (**149**) was obtained by treatment of glycine ester hydrochloride **148** and sodium nitrite with sulfuric acid.[79] Compounds **152**, **156**, **157** were, in turn, prepared by Regitz diazo transfer using either tosyl azide (**151**) or *o*-nitrobenzenesulfonyl azide (**155**) as a donor of a diazo group. The reaction of the first of them with *tert*-butyl acetoacetate (**150**) was performed in a biphasic system aqueous NaOH solution/pentane using TBAB as a phase-transfer catalyst.[80] To synthesize methyl phenyldiazoacetate (**156**), I subjected ester **153** to the reaction with reagent **151** in acetonitrile in the presence of DBU.[81] Diazo compound **157** was prepared analogously from *o*-NBSA (**155**) and substrate **154**.[82]



*Scheme 43. Synthesis of diazoesters **149**, **152**, **156**, and **157**.*

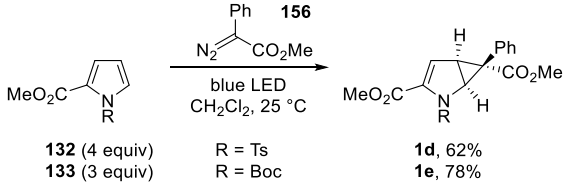
With all substrates in hand, I commenced the synthesis of 2-azabicyclo[3.1.0]hex-3-enes. Cyclopropanations with methyl and *tert*-butyl diazoacetates were performed using a catalytic system composed of copper(II) triflate and phenylhydrazine. For aryldiazoacetates, I employed rhodium complexes or the photocatalytic protocol.[83]

In the first order, I prepared bicycles **1a**,[84] **1b**,[10] and **1c**[83] according to the literature procedures (Scheme 44).



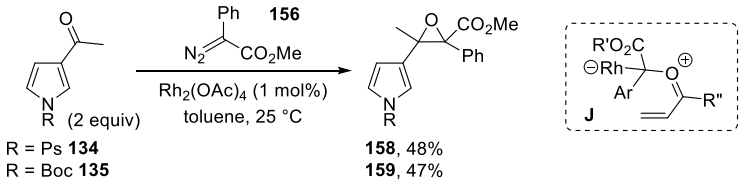
Scheme 44. Cyclopropanation of N*-Boc pyrrole (**131**).*

Esters **132** and **133** may be cyclopropanated with aryldiazoacetates in very good yields and with high enantioselectivities using Rh_2(*R-p*-PhTPCP)$_4$ as a catalyst.[85] Since for my work I did not need optically pure substrates, to avoid the use of expensive Rh-complexes, I decided to attempt the photocatalytic approach (Scheme 45). It turned out that this method allows obtaining bicycle **1d** in 62% yield. Its *N*-Boc analogue **1e** was, in turn, isolated in 78% yield.



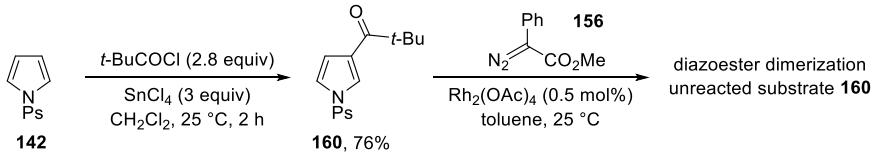
*Scheme 45. Cyclopropanation of methyl 2-pyrrolecarboxylates **132** and **133**.*

Further experiments focused on cyclopropanation of 3-acetyl pyrroles **134** and **135**. Unfortunately, attempted reactions of these substrates with *tert*-butyl diazoacetate in the presence of Cu(OTf)$_2$ were unsuccessful, and I observed only dimerization of the diazo compound. Rh-Catalysed decomposition of methyl phenyldiazoacetate (**156**) in the presence of pyrrole **134** furnished, in turn, epoxide **158** instead of the desired cyclopropane (Scheme 46). Processes of this type are known in the literature and are assumed to proceed *via* ylides of type **J**.[86,87] Since the reactivity of pyrroles in cyclopropanation reactions decreases with the increase of the electron-withdrawing character of the nitrogen protecting group, I decided to replace the phenylsulfonyl moiety in substrate **134** with the *tert*-butoxycarbonyl one. Disappointingly, also in the case of *N*-Boc pyrrole **135** the formation of the desired 2-azabicyclo[3.1.0]hex-3-ene was not observed.



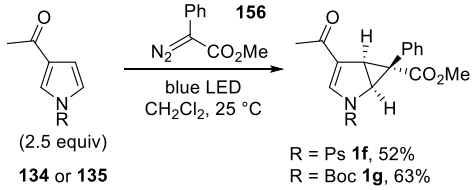
*Scheme 46. Attempted cyclopropanation of 3-acetyl pyrroles **134** and **135**.*

It has become of my interest if increasing the steric bulk around the ketone carbonyl group, for example by replacing the methyl moiety with *tert*-butyl one, would suppress the formation of epoxide and consequently allow the cyclopropanation to occur. Thus, I synthesised compound **160** analogously to ketone **134**, i.e. by the reaction of 1-(phenylsulfonyl)pyrrole (**142**) with pivaloyl chloride (Scheme 47). Indeed, epoxidation of derivative **160** did not proceed, but, unfortunately, the desired cyclopropane was also not obtained.



*Scheme 47. Synthesis of pyrrole **160** and attempted cyclopropanation.*

Given the failure of the transition-metal-catalysed reactions, I attempted to perform cyclopropanation in a photochemical variant. Gratifyingly, irradiation of the CH_2Cl_2-solution of phenyldiazoacetate **156** and substrate **134** with blue light afforded the desired bicycle **1f** in 52% yield (Scheme 48). Analogous reaction of *N*-Boc derivative **135** proceeded even in slightly better yield of 63%. In neither of the experiments, the formation of epoxide was observed. It should be added that such a process is feasible under the employed conditions.[83]



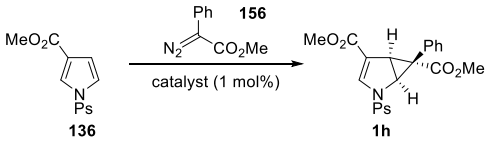
*Scheme 48. Photocatalytic cyclopropanation of pyrrole derivatives **134** and **135**.*

In the further part of my work, I investigated cyclopropanation of ester **136** with phenyldiazoacetate **156**. The first experiment was conducted in the presence of $Rh_2(OAc)_4$ in toluene at 50 ℃ (Table 1, entry 1). The elevated temperature of performing the reaction was due to the poor solubility of pyrrole **136** in the employed solvent. It turned out that under these conditions cyclopropanation of **136** proceeds but in low yield. Changing the solvent to CH_2Cl_2, in which both derivative **136** and the catalyst are better soluble, allowed to improve the initial

result to 24% (entry 2). The use of THF (entry 3) or replacing $Rh_2(OAc)_4$ with $Rh_2(DOSP)_4$ (entry 4) caused, in turn, that the cyclopropanation did not occur.

Since in all these experiments I observed the formation of significant amounts of products resulting from dimerization of the diazo compound, in the next attempt, I added the diazoester solution with a lower rate (1 drop/20 s; Table 1, entry 5). Unfortunately, neither this modification nor an attempt to improve the efficiency of cyclopropanation by increasing the concentration of pyrrole did result in the awaited improvement (entries 6 and 7). Likewise, the reaction performed at 40 °C proceeded with the yield comparable to that achieved at 25 °C. Changing the stoichiometry had, in turn, a detrimental effect on the process outcome (entry 8).

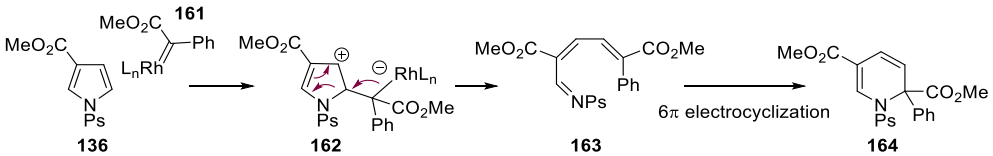
*Table 1. Cyclopropanation of pyrrole-3-carboxylate **136** with methyl phenyldiazoacetate (**156**)*[a]



No.	Catalyst	**136**:**156**	Solvent	Temp. [°C]	Yield[b] [%]
1	$Rh_2(OAc)_4$	1:2	toluene	50	8
2	$Rh_2(OAc)_4$	1:2	CH_2Cl_2	25	24
3	$Rh_2(OAc)_4$	1:2	THF	25	-
4	$Rh_2(DOSP)_4$	1:2	CH_2Cl_2	25	-
5[c]	$Rh_2(OAc)_4$	1:2	CH_2Cl_2	25	20
6[d]	$Rh_2(OAc)_4$	1:2	CH_2Cl_2	25	22
7	$Rh_2(OAc)_4$	1:2	CH_2Cl_2	40	27
8	$Rh_2(OAc)_4$	1.1:1	CH_2Cl_2	25	15

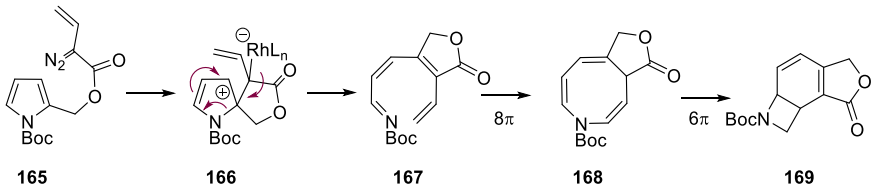
[a] Reactions were performed on 1 mmol scale using 1 mol% of the catalyst. Diazoester was dissolved in 2 mL of the solvent and added to the solution of pyrrole **136** in 2 mL of the solvent with the rate of 1 drop/10 s.
[b] Isolated by column chromatography.
[c] Diazoester solution was added with the rate of 1 drop/20 s.
[d] Pyrrole was dissolved in 1 mL of the solvent.

The reactions conducted in the presence of $Rh_2(OAc)_4$ provided additionally another product in a ca 1:1 ratio with the target bicycle **1h**. Surprisingly, the collected analytical data were in agreement with structure **164** (Scheme 49).



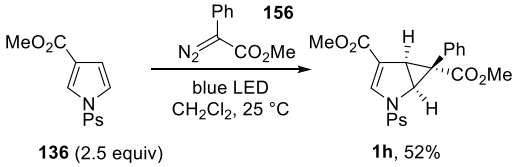
*Scheme 49. Plausible mechanism for the formation of dihydropyridine **164**.*

Since this part of my work aimed at the preparation of bicyclic cyclopropanes, I did not investigate the pathway on which compound **164** forms. Nevertheless, it may be supposed that the mechanism involves the ring-opening of the initially formed zwitterionic intermediate **162**, followed by 6π electrocyclization of the resulting azatriene **163** (Scheme 49). A similar explanation assuming the intermediacy of zwitterionic species was proposed by the group of Prof. Davies to explain the formation of 7-azabicyclo[4.2.0]octadiene **169** from pyrrole derivative **165** (Scheme 50).[88] In this case, intermediate **167** resulting from the opening of the pyrrole ring underwent successive 8π and 6π electrocyclizations.



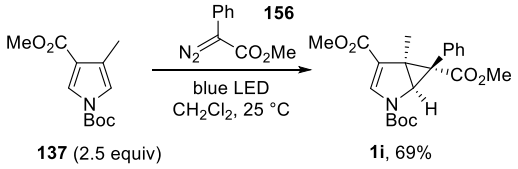
*Scheme 50. Formation of 7-azabicyclo[4.2.0]octadiene **169** from pyrrole derivative **165**.*

Among the investigated protocols for the synthesis of bicycle **1h**, the most efficient one turned out to be the photochemical cyclopropanation of pyrrole **136** (Scheme 51). This reaction proceeded in 52% yield. As expected, the formation of dihydropyridine **164** was not observed.



*Scheme 51. Photocatalytic cyclopropanation of pyrrole derivative **136**.*

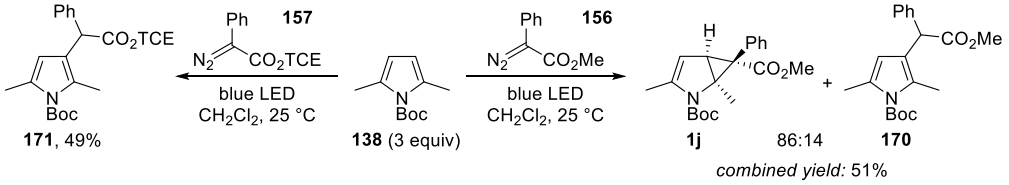
The photochemical approach also allowed successful preparation of bicycle **1i**, which was isolated in 69% yield (Scheme 52).



*Scheme 52. Photocatalytic cyclopropanation of pyrrole derivative **137**.*

Contrary to the reactions of other pyrrole derivatives, photochemical cyclopropanation of 2,5-dimethyl-substituted substrate **138** gave a noticeable amount of alkylation product (**170**), whereby the ratio of compound **170** to cyclopropane **1j** was equal to 14:86 (Scheme 53). Unfortunately, attempts to separate these substances were unsuccessful. The tendency to form alkylated pyrrole derivatives in the reaction with substrate **138** was even more pronounced in

the case of diazoester **157**. This compound afforded heteroarene **171** in 49%, whereas the desired cyclopropane was not observed.



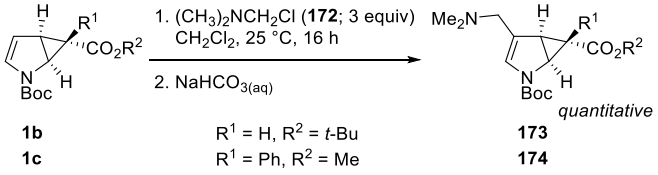
*Scheme 53. Photolysis of diazo compounds **156** and **157** in the presence of* N*-Boc-2,5-dimethylpyrrole (**138**).*

III 2 Functionalization of monocyclopropanated pyrroles

III 2.1. Transformations based on aminomethylenanation

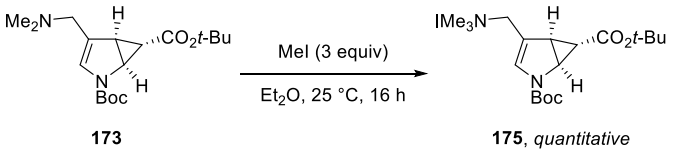
The next part of the studies dealt with the functionalization of synthesised 2-azabicyclo[3.1.0]hex-3-enes. First, I attempted to perform aminomethylenanation of enecarbamates **1b** and **1c** with dimethyl(methylene)ammonium chloride (**172**; Böhme's salt).[89,90] The utility of processes of this type arises mainly from the possibility of further transformations of the introduced side-chain *via* nucleophilic substitution of dialkylamino moiety. Although dimethyl(methylene)ammonium ions may be also generated *in situ* (e.g. Mannich-type conditions),[91–93] I decided to employ a preformed salt since this approach significantly reduces the risk of side-reactions: the use of acids is not necessary, and a higher concentration of the electrophile allows performing transformations under milder conditions and in a shorter time.[94]

Thus, salt **172** was added to a solution bicycle **1b** or **1c** in dry CH_2Cl_2, and after 16 h of stirring, the reactions were worked-up with saturated solution of $NaHCO_3$ (Scheme 54). To my delight, the desired products **173** and **174** were formed in quantitative yields.



*Scheme 54. Reactions of enecarbamates **1b** and **1c** with dimethyl(methylene)ammonium iodide **172**.*

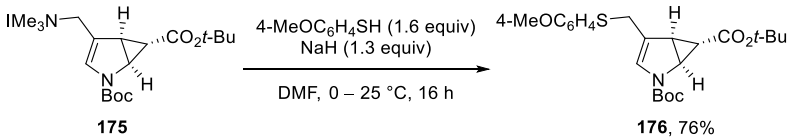
The possibility of further transformations of the introduced substituent was examined with compound **173**. To facilitate nucleophilic substitution, dimethylamino group was first quaternized using MeI (Scheme 55).



173 **175**, *quantitative*

*Scheme 55. Methylation of amine **173**.*

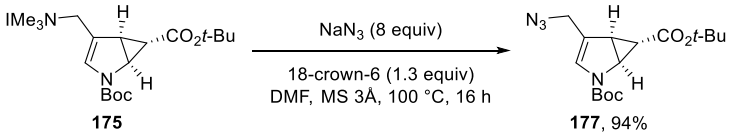
Salt **175** was subsequently subjected to the reaction with 4-methoxythiophenolate (Scheme 56). For this purpose, I dissolved substrate **175** in DMF and then added the solution of the nucleophile in the same solvent. The expected product **176** was obtained in 76% yield.



175 **176**, 76%

*Scheme 56. Reaction of substrate **175** with 4-methoxythiophenolate.*

Next, I investigated the possibility of displacing trimethylamine moiety in salt **175** with an azide group.[95–97] After several unsuccessful attempts, I found that the desired product **177** may be obtained in very good yield of 94% when a mixture of substrate **175**, NaN_3, and 18-crown-6 in DMF is heated to 110 °C over 16 h (Scheme 57). The use of crown ether was essential for the substitution to proceed.

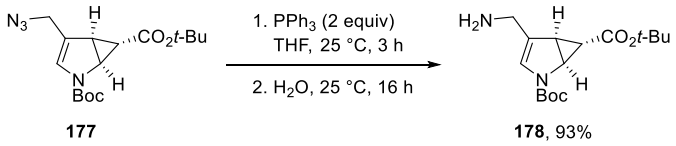


175 **177**, 94%

*Scheme 57. Reaction of salt **175** with NaN_3.*

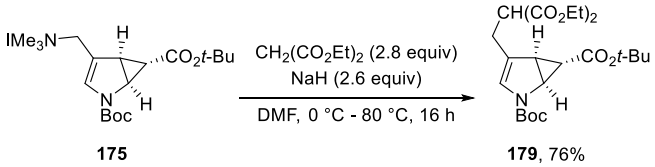
The utility of organic azides results among others from the possibility of their easy conversion into corresponding amines. This transformation may be achieved for example by catalytic hydrogenation[95,97,98] or *via* Staudinger reaction.[99–102] The latter method features high chemoselectivity allowing reduction of N_3 group i.a. in the presence of the double bond.[100,102]

To evaluate the feasibility of reduction of azide **177** under Staudinger conditions, I subjected this substrate to the reaction with PPh_3 in THF (Scheme 58). After TLC had indicated the complete disappearance of the starting pyrroline, I added to the reaction mixture water and continued the stirring for 16 h. As a result of the described experiment, I obtained the desired amine **178** in 93% yield.



*Scheme 58. Staudinger reduction of azide **177**.*

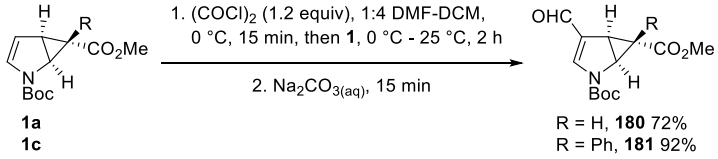
Next, I examined the reactivity of salt **175** towards sodium diethyl malonate. It turned out that heating the solution of both substrates and 18-crown-6 in DMF to 90 °C for 16 h furnished compound **179** in 76% yield (Scheme 59). Conducting the reaction analogously but omitting the crown ether, I observed low conversion of salt **175**.



*Scheme 59. Reaction of substrate **175** with sodium diethyl malonate.*

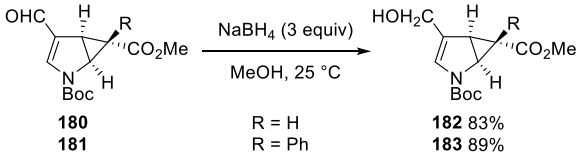
III 2.2. Transformations based on formylation

In the further part of my work, I investigated transformations of aldehydes **180** and **181**. These compounds were obtained by formylation of enecarbamates **1a** and **1c** with Vilsmeier reagent generated *in situ* from DMF and oxalyl chloride.[12] The first product was isolated in 72% yield, whereas the second one in 92% yield (Scheme 60).



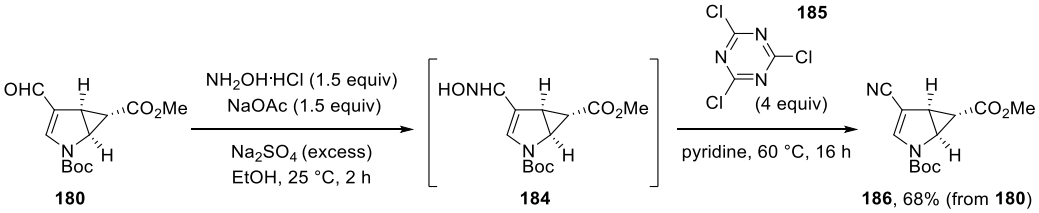
*Scheme 60. Vilsmeier-Haack formylation of enecarbamates **1a** and **1c**.*

Derivatives **180** and **181** were then treated with $NaBH_4$ in MeOH which allowed selective reduction of the aldehyde group (Scheme 61). Alcohols **182** and **183** were obtained in 83% and 89% yield, respectively.



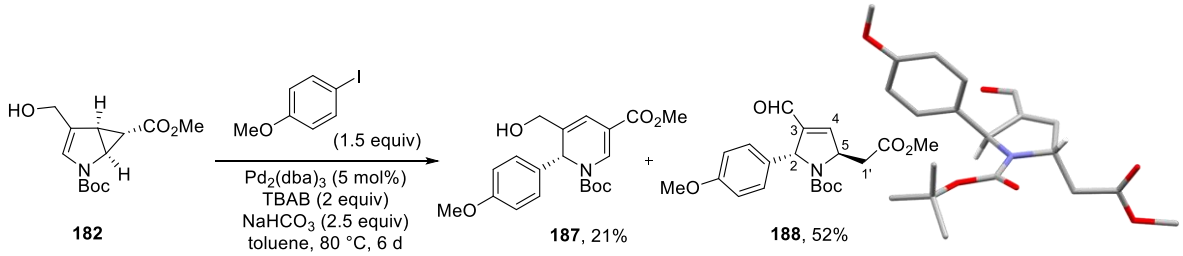
*Scheme 61. Reduction of aldehydes **180** and **181** to the corresponding alcohols.*

The next experiment aimed at the conversion of aldehyde **180** into the corresponding nitrile. Among many methods developed for this transformation,[103–108] I choose the one based on dehydration of intermediary aldoxime with cyanuric chloride (**185**).[109,110] Its advantages encompass the easy availability of all reagents and the relatively mild conditions of the process. Thus, substrate **180** was dissolved in EtOH, followed by the addition of hydroxylamine hydrochloride and sodium acetate (Scheme 62). After 2 h, the reaction was worked-up, and the residue obtained after the removal of the solvent was treated with reagent **185** in pyridine. As a result of this experiment, I obtained the desired product **186** in 68% yield.



*Scheme 62. Conversion of aldehyde **180** into nitrile **186**.*

To exemplify the possible applications of the obtained products, I employed them in Heck reaction with 4-methoxyiodobenzene using the previously established procedure.[12] Interestingly, arylation of alcohol **182** gave as major product aldehyde **188**, whereby the structure of this compound was proven by roentgenographic analysis (Scheme 63). As illustrated in Figure 7, high-temperature NMR measurements confirmed that the doubling of signals observed at 25 °C results from the presence of rotamers and not diastereomers.



*Scheme 63. Arylation of enecarbamate **182**. X-Ray structure of aldehyde **188**.*

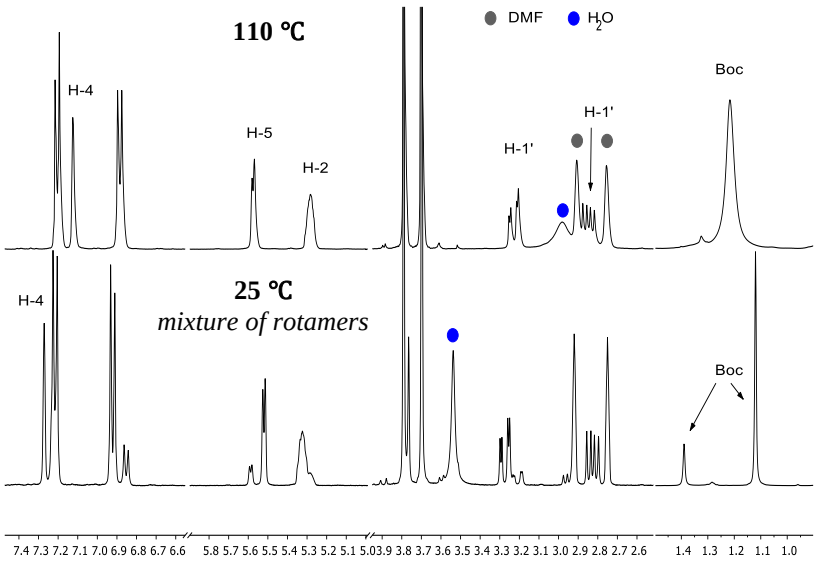
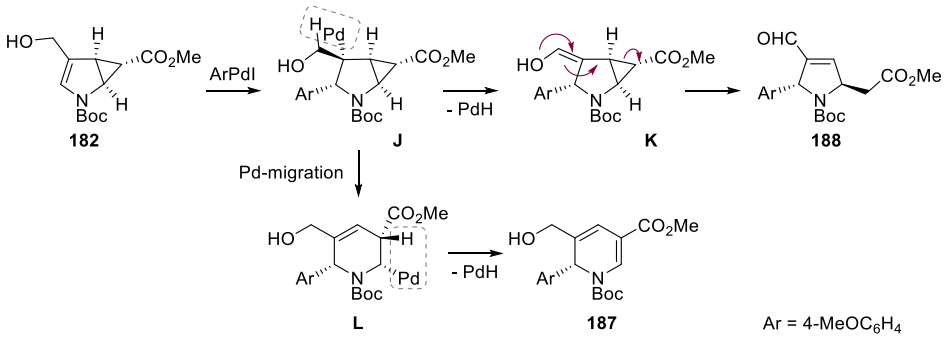


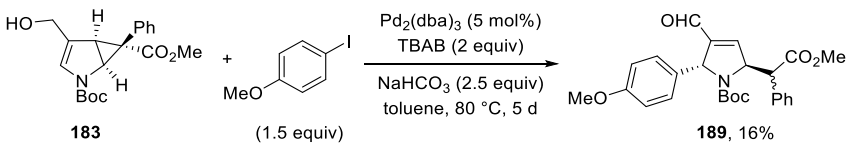
*Figure 7. Comparison of ^{1}H NMR spectra of compound **188** measured in DMF-d_7 at 25 ℃ and 110 ℃. Coalescence of signals with increasing the temperature indicates the presence of rotamers.*

The outcome of the arylation of substrate **182** may be easily understood considering that the initially formed organopalladium intermediate **J** may undergo β-hydride elimination involving hydrogen atom of the side chain (Scheme 64). The resulting enol **K** tautomerizes subsequently to the aldehyde form (**188**) through the opening of the cyclopropane ring. The fact that aldehyde **188** constituted the major product of the arylation of substrate **182** suggests that dehydropalladation of adduct **J** is faster than Pd-migration leading to species **L**.



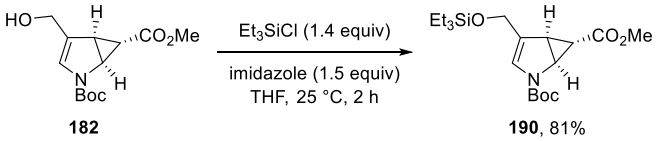
*Scheme 64. Mechanism explaining the formation of products **187** and **188**.*

Analogous 2-aryl-3-formyl-3-pyrroline **189** was also obtained in the reaction of substrate **183**, although in low yield and together with a significant amount of side-products.

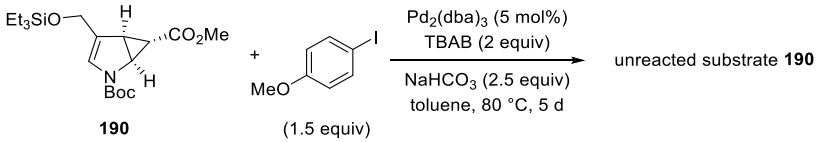


*Scheme 65. Arylation of enecarbamate **183**.*

The interesting outcome of the arylation of alcohols **182** and **183** prompted me to check what will happen if the possibility of enolization is suppressed by protecting of the hydroxyl group. For this purpose, I prepared compound **190** by the reaction of substrate **182** with triethylsilyl chloride (Scheme 66). The process was conducted in the presence of imidazole in THF and proceeded in 81% yield. Product **190** turned, however, out to be unreactive under the employed reaction conditions, most probably due to the steric hindrance of the side chain (Scheme 67).

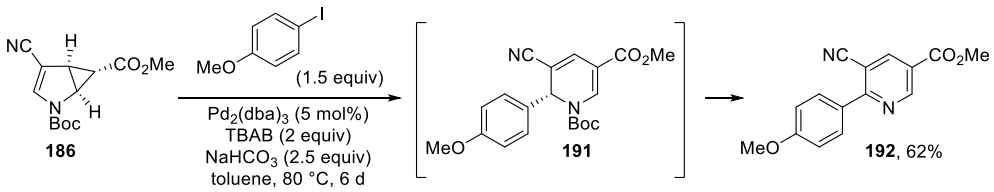


*Scheme 66. Protection of alcohol **182** with triethylsilyl group.*



*Scheme 67. Attempted arylation of derivative **190**.*

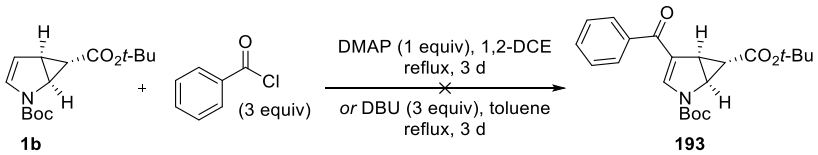
Finally, I conducted the coupling of 4-methoxyiodobenzene with nitrile **186** (Scheme 68). As a result, I obtained pyridine **192** in 62% yield. This reaction outcome may be explained by *in situ* oxidation of the initially formed 1,2-dihydropyridine **191**.



*Scheme 68. Arylation of nitrile **186**.*

III 2.3. Attempts on acylation and transformations of 4-acetyl-2-azabicyclo[3.1.0]hex-3-ene

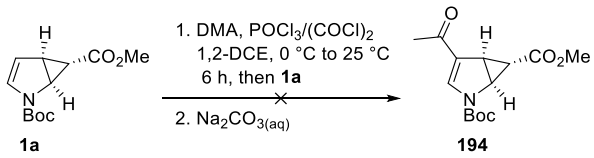
Following the studies on the reactivity of aldehydes **180** and **181**, I turned my attention to acylation of bicycles **1**. Conducted previously in our group attempts to perform this transformation using acyl chlorides in the presence of a Lewis acid resulted in cyclopropane ring-opening and consequently aromatization of the substrate. Therefore, I decided to try an alternative approach based on nucleophilic catalysts such as DMAP. To evaluate its applicability in acylation of monocyclopropanated pyrroles, I employed benzoyl chloride as a model electrophile and 1,2-DCE as a solvent (Scheme 69). Disappointingly, refluxing the reaction mixture for 3 days did not result in any visible conversion of bicycle **1b**. Likewise, the reaction did not proceed in the presence of DBU.



*Scheme 69. Attempted benzoylation of substrate **1b**.*

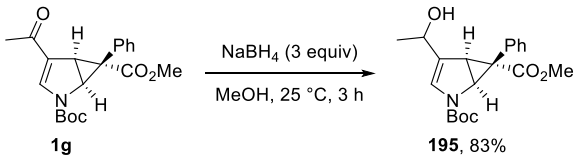
As next, I attempted to perform acylation in a microwave reactor. In this series of experiments, I employed besides benzoyl chloride also acetyl chloride and acetyl anhydride as electrophiles. The used solvents were toluene, 1,2-DCE, and pyridine, whereas the reaction temperatures ranged from 40°C to 150 °C. Unfortunately, also these attempts were fruitless.

The success of Vilsmeier-Haack formylation of substrates **1** suggested that acylation may be possible under analogous conditions. To verify this hypothesis, I subjected substrate **1a** to the reactions with Vilsmeier reagent generated from dimethylacetamide, whereby in one experiment I used for this purpose $POCl_3$ and in the second one oxalyl chloride (Scheme 70). Regardless of the employed method, at 25 °C I did not observe conversion of the substrate, whereas increasing the temperature resulted in aromatization. Given the difficulties in acylation of bicycles **1** on the one hand and the synthetic utility of synthesised amines **173**, **174**, and aldehydes **180** and **181** on the other, I did not undertake further attempts on this transformation.

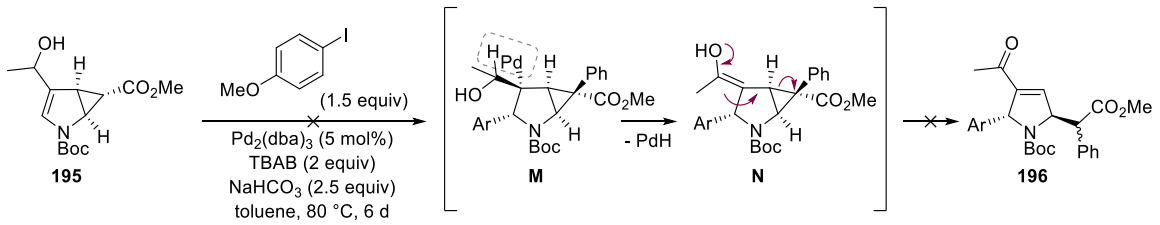


*Scheme 70. Attempted Vilsmeier-Haack acylation of bicycle **1a**.*

Nevertheless, I could obtain 4-acetyl-2-azabicyclo[3.1.0]hex-3-ene **1g** by photochemical cyclopropanation of 3-acetyl pyrrole **135** (see paragraph III 1). To exemplify further transformations of this product, I subjected it to the reduction with $NaBH_4$ (Scheme 71). As a result, I obtained alcohol **195** in 83% yield. This compound was then used in Heck reaction with 4-iodoanisole. Based on the results obtained for derivatives **182** and **183**, I expected formation of pyrroline **196** (Scheme 72). Disappointingly, substrate **195** turned out to be unreactive under the employed conditions.



*Scheme 71. Reduction of compound **1g** with $NaBH_4$.*

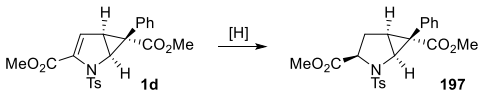


*Scheme 72. Expected outcome of the coupling of alcohol **195** with 4-methoxyiodobenzene.*

III 2.4. Hydrogenation of azabicyclo[3.1.0]hex-3-ene-3-carboxylates **1d** and **1e**

Continuing the works, I focused on the reactivity of cyclopropanated pyrrole-2-carboxylates. In the first order, I undertook an attempt to reduce the double bond in substrate **1d** (Table 2).

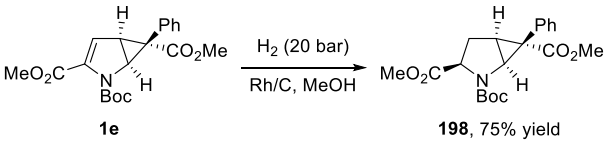
*Table 2. Reduction of the double bond in substrate **1d***



No.	Conditions	Result
1	Pd/C (10 wt%), MeOH, H_2 (balloon), 25 °C, 16 h	no conversion
2	Rh/C (10 wt%), MeOH, H_2 (balloon), 25 °C, 16 h	no conversion
3	PtO_2 (10 wt%), EtOH, H_2 (balloon), 25 °C, 3 d	no conversion
4	$RhCl(PPh_3)_3$ (10 wt%), acetone, H_2 (balloon), 25 °C, 2 weeks	no conversion
5	Pd/C (10 wt%), MeOH, H_2 (40 bar), 8 h	no conversion
6	Rh/C (10 wt%), MeOH, H_2 (40 bar), 8 h	**197**, 63%
7	$[RhCl(cod)]_2$ (1 mol%), Cs_2CO_3 (10 mol%), *i*-PrOH, 60 °C, 16 h	no conversion

The experiments in which compound **1d** was exposed to normal hydrogen pressure in the presence of a catalyst such as Pd/C, Rh/C, PtO_2, or Wilkinson's catalyst were unsuccessful (Table 2; entries 1-4). The formation of bicycle **197** was also not observed, using Pd/C and upon increasing the hydrogen pressure to 40 bars (entry 5). Changing the catalyst to Rh/C allowed, however, to obtain product **197** in good, 63%, yield (entry 6). Additionally, I attempted to reduce the double bond under transfer-hydrogenation conditions, but in this case, I could only recover the unreacted substrate (entry 7).

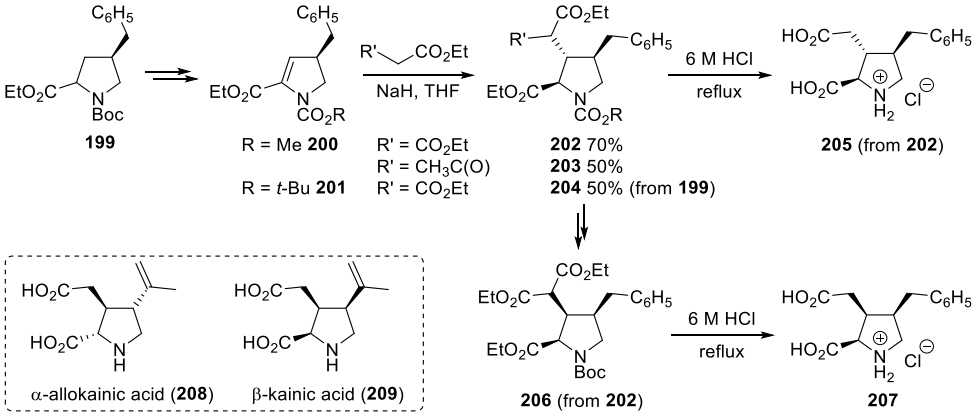
The conditions developed for *N*-Ts-protected derivative **1d** could be successfully adapted to its *N*-Boc analogue **1e**. As shown in Scheme 73, product **198** was obtained in 75% yield.



*Scheme 73. Hydrogenation of bicycle **1e**.*

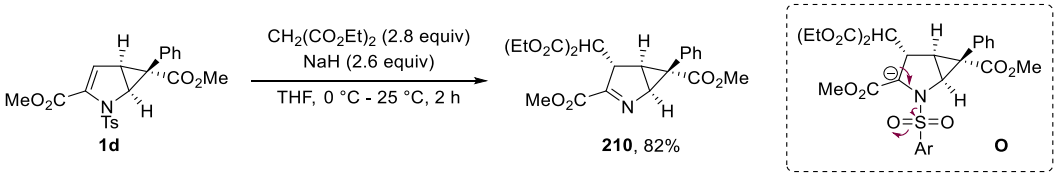
III 2.5. Nucleophilic addition to cyclopropanated esters of pyrrole

Surveying the literature concerning the reactivity of cyclic enecarbamates, I found the works by Rubio's group describing the additions of carbon nucleophiles to 4-benzyl-2,3-didehydroprolinates **200** and **201** (Scheme 74).[111,112] The researchers showed that these transformations proceed stereoselectively in good yields, and to demonstrate the synthetic utility of the developed methodology they obtained kainoids **205** and **207**. Pyrrolidinedicarboxylic acids of this type receive much research interest[113–119] due to their interesting biological activities above all their neuroexcitatory effect.[120–122] The possible synthetic applications of the resulting products prompted me to examine if also cyclopropanated esters of pyrrole may react as Michael acceptors.



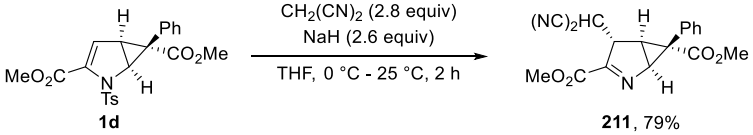
*Scheme 74. Michael additions to 4-benzyl-2,3-didehydroprolinates **200** and **201**.*

I began this part of my research with the reaction between alkene **1d** and enolate of diethyl malonate. Following the procedure proposed by Rubio's group,[111,112] I first treated malonic ester with NaH in dry THF at 0 °C and then added substrate **1d** dissolved in the same solvent (Scheme 75). As a result of this experiment, I obtained imine **210** in 82%. Although the formation of this product seems surprising at first glance, it may be easily explained by the loss of *p*-toluenesulfinate by intermediary anion **O**.



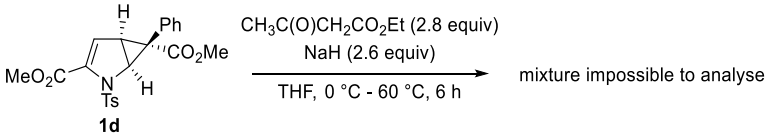
*Scheme 75. Addition of malonic ester enolate to substrate **1d**.*

Encouraged with the positive result, I subjected substrate **1d** to the analogous reaction with malononitrile (Scheme 76). Also this transformation proceeded smoothly to furnish the expected imine **211** in 79% yield.



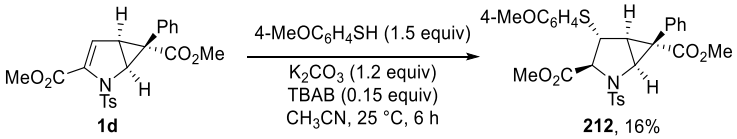
*Scheme 76. Reaction of malonnitrile with substrate **1d**.*

Reaction of ester **1d** with ethyl acetoacetate required, by contrast, heating to proceed and provided an inseparable mixture of several products (Scheme 77). The collected analytical data did not allow to state if it contains the desired adducts.



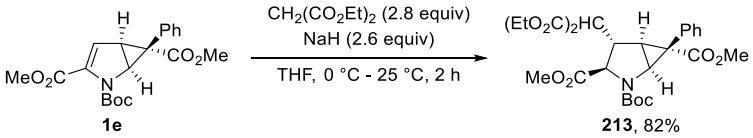
*Scheme 77. Attempted addition of ethyl acetoacetate to ester **1d**.*

Continuing the studies on the reactivity of pyrroline **1d** towards nucleophiles, I attempted to adapt the employed procedure to 4-methoxythiophenol. Additions of *S*-nucleophiles to 2,3-dehydroproline derivatives are known in the literature.[123–125] Unfortunately, in the investigated example I observed solely the opening of the cyclopropane ring leading to a mixture of pyrroles. These compounds were also major products of the reaction performed under phase-transfer-catalytic conditions but in this case, I could also isolate a small amount of adduct **212** (Scheme 78).



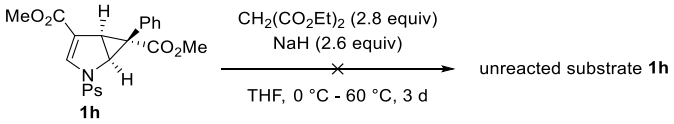
*Scheme 78. Addition of 4-methoxythiophenolate to substrate **1d**.*

To investigate the influence of nitrogen protecting group on the outcome of Michael addition to cyclopropanated pyrrole-2-ester, I conducted a reaction of *N*-Boc derivative **1e** with diethyl malonate (Scheme 79). As a result of this experiment, I obtained adduct **213** in 82% yield.



*Scheme 79. Addition of malonic ester enolate to substrate **1e**.*

Next, I decided to examine if also ester **1h** will undergo Michael addition with enolate of malonic ester (Scheme 80). Disappointingly, even prolonged heating of the reaction mixture did not result in any visible conversion of substrate **1h**.



*Scheme 80. Attempted addition of enolate of malonic ester to enecarbamate **1h**.*

The configuration on the newly created stereogenic centres in products **210-213** was assigned based on NOESY experiments. For illustration, in Figure 8 I presented key correlations observed for compounds **210** and **213**. Accordingly, the attachment of the malonic ester moiety on the *exo* face of bicycles **210** and **213** was indicated by nOe's between H-4 and aromatic protons, as well as between H-2' and H-5. In the spectrum of adduct **213**, I additionally observed cross-peaks between signals of protons of pyrrolidine ester methyl group and protons of phenyl residue as well as between signals of protons H-2' and H-3 - this suggested *trans* alignment of substituents at C-3 and C-4. The configuration on C-3 could be also recognized based on the chemical shift (3.12) of methyl protons of the ester group indicating its *endo* position where it is shielded by the ring current of the phenyl substituent.

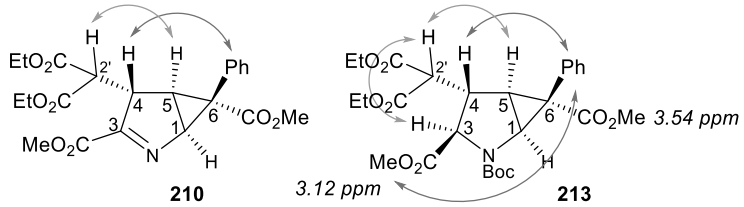
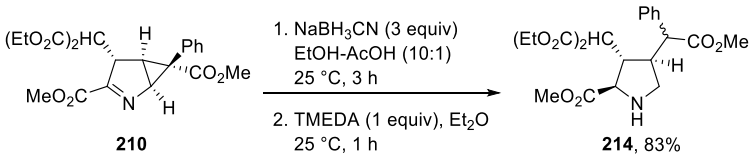


*Figure 8. Key correlations in the NOESY spectra of compounds **210** and **213**. Chemical shifts are given for major rotamer.*

Products resulting from the presented nucleophilic addition to substrates **1d** and **1e** constitute useful building blocks. It may be supposed that deprotection of the nitrogen atom will result in opening of the cyclopropane ring.[126,127] To confirm this, I subjected iminoester **210** to the reduction with $NaBH_3CN$ in EtOH-AcOH mixture (Scheme 81).[128] In order to cleave amine-borane complex formed under the employed conditions, I treated crude products with TMEDA.[129] As a result, I obtained the expected amines **214** as a mixture of diastereomers.



*Scheme 81. Reduction of iminoester **210** with $NaBH_3CN$.*

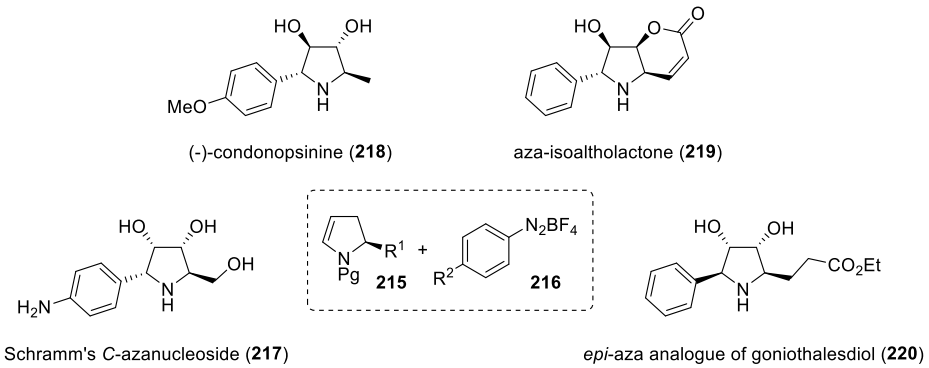
III 3 Ring expansion of monocyclopropanated pyrroles

III 3.1. Arylation of 2-azabicyclo[3.1.0]hex-3-ene-6-carboxylates with diazonium salts

My next research aim was to develop a more efficient protocol for the synthesis of 1,2-dihydropyridines **18** from bicycles **1**. I envisaged that this may be achieved by employing aryl-diazonium salts as coupling partners.

Pd-catalysed arylation of alkenes employing the above reagents is often referred to as Heck-Matsuda coupling and features mild conditions, short reaction times, and no necessity of using air- and moisture- sensitive phosphine ligands.[130–133] These properties result from the ease with which diazonium salts undergo oxidative addition to palladium and the high reactivity of the resulting cationic intermediate. Another advantage of using diazonium salts is their ready availability from the corresponding anilines.

Among an array of interesting publications on Heck-Matsuda coupling, a particularly important role in my research played the studies on endocyclic enecarbamates **215** conducted by the group of Prof. Correia. The authors found that arylations of the substrates of this type with diazonium tetrafluoroborates **216** proceed most efficiently in CH_3CN in the presence of Pd-dibenzylideneacetone complexes (Pd_2dba_3 or $Pddba_2$) and using NaOAc as a base. The utility of the developed methodology was demonstrated i.a. with the synthesis of Schramm's antiprotozoal *C*-azanucleoside **217**,[134] (-)-codonopsinine (**218**),[135] as well as compounds **219** and **220** that may be considered as nitrogen analogues of biologically active styryllactones (Scheme 82).[136]



*Scheme 82. Synthetic applications of Heck-Matsuda arylation of endocyclic enecarbamates **215** presented by Correia.*

I commenced the studies on the arylation of monocyclopropanated pyrroles with a series of reactions between substrate **1b** and 4-methoxybenzenediazonium tetrafluoroborate (**216a**). The first experiment was conducted under conditions related to those proposed by Correia,[134–136] whereby $Pddba_2$ was used in an amount of 10 mol% and the diazonium salt in a 1.3-fold excess (Table 3; entry 1). It turned out that the coupling proceeded already at 25 °C to provide 58% of the desired 1,2-dihydropyridine **18a**$^{t\text{-Bu}}$ together with 7% of the product of double arylation. To avoid the formation of the latter compound, in the next reactions I employed a lower number of equivalents of salt **216a** (entries 2-4). The best result of 93% was obtained for 1.05 equiv (entry 3).

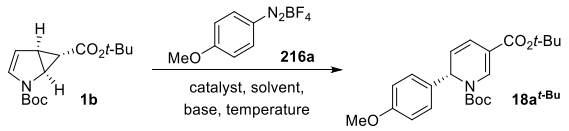
Next, I screened several other catalysts commonly used in Heck-Matsuda arylation. Replacement of $Pddba_2$ with Pd_2dba_3 led to a similar, but slightly worse result of 87% (Table 3; entry 5). Palladium sources such as $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, $PdCl_2$ turned out to be significantly less effective giving the desired product in the yields not exceeding 72% (entries 6-8). Likewise, the use of MeOH, acetone, CH_2Cl_2, or THF as a solvent had a detrimental effect on the process outcome (entries 9-12). Coupling performed in PhCN proceeded, in turn, in 87% yield which constituted a comparable result to that achieved using CH_3CN (compare entries 3 and 13). The fact that arylation of substrate **1b** was efficient only in nitrile solvents may be attributed to their ability to stabilize cationic palladium intermediates formed in the course of the reaction.[130,132,137]

Many protocols for Heck-Matsuda coupling employ sterically hindered, non-nucleophilic pyridine bases which are 2,6-di-*tert*-butyl-pyridine and its 4-methyl congener.[138–140] In my studies, I tested the second of them and obtained the desired derivative **18a**$^{t\text{-Bu}}$ in very good, 86%, yield (Table 3; entry 14). The application of Na_2CO_3 caused, in turn, a decrease in the product amount to 44% (entry 15). Although Heck-Matsuda reactions can be sometimes performed in the absence of a base,[141–143] in the case of the investigated process its presence turned out to be essential, and the performed control experiment provided only a trace amount of product **18a**$^{t\text{-Bu}}$ (entry 16).

The next reaction was carried out at 45 °C, whereas other parameters were identical with those presented in entry 3 (Table 3). However, this modification did not have any significant influence on the process outcome (entry 17).

In the last part of the model studies, I investigated the possibility of decreasing the catalyst loading. It turned out that in the presence of 5 mol% of Pd the coupling proceeded in high, but considerably lower than the best one yield of 82% (Table 3; entry 18).

*Table 3. Arylation of enecarbamate **1b** with 4-methoxybenzenediazonium tetrafluoroborate (**216a**)*[a]



No.	Catalyst	Equiv of **216a**	Solvent	Base[b]	Temp. [°C]	Yield[c] [%]
1	$Pddba_2$ (10 mol%)	1.3	CH_3CN	NaOAc	25	58
2	$Pddba_2$ (10 mol%)	1.1	CH_3CN	NaOAc	25	91
3	$Pddba_2$ (10 mol%)	1.05	CH_3CN	NaOAc	25	93
4	$Pddba_2$ (10 mol%)	0.67	CH_3CN	NaOAc	25	70
5	Pd_2dba_3 (5 mol%)	1.05	CH_3CN	NaOAc	25	87
6	$Pd(OAc)_2$ (10 mol%)	1.05	CH_3CN	NaOAc	25	72
7	$PdCl_2$ (10 mol%)	1.05	CH_3CN	NaOAc	25	50
8	$Pd(PhCN)_2Cl_2$ (10 mol%)	1.05	CH_3CN	NaOAc	25	52
9	$Pddba_2$ (10 mol%)	1.05	MeOH	NaOAc	25	trace
10	$Pddba_2$ (10 mol%)	1.05	acetone	NaOAc	25	20
11	$Pddba_2$ (10 mol%)	1.05	CH_2Cl_2	NaOAc	25	<15
12	$Pddba_2$ (10 mol%)	1.05	THF	NaOAc	25	<15
13	$Pddba_2$ (10 mol%)	1.05	PhCN	NaOAc	25	87
14	$Pddba_2$ (10 mol%)	1.05	CH_3CN	DTBMP	25	86
15	$Pddba_2$ (10 mol%)	1.05	CH_3CN	Na_2CO_3	25	44
16	$Pddba_2$ (10 mol%)	1.05	CH_3CN	-	25	trace
17	$Pddba_2$ (10 mol%)	1.05	CH_3CN	NaOAc	45	90
18	$Pddba_2$ (5 mol%)	1.05	CH_3CN	NaOAc	45	82

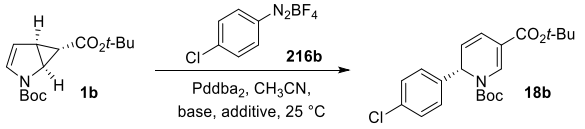
[a] Reactions were performed on 0.5 mmol scale using 3 mL of the solvent for 14 h. [b] 3 equiv for NaOAc and Na_2CO_3, 1.5 equiv for DTBMP. [c] determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Further experiments revealed that the conditions optimized for reagent **216a** are not suitable for electron-deficient diazonium salts – these substrates formed the corresponding dihydropyridines in only moderate yields and together with a noticeable amount of by-products. However, when in the reaction of cyclopropane **1b** with 4-chlorobenzenediazonium tetrafluoroborate (**216b**) I replaced NaOAc with DTBMP, the product yield increased from 53% to 67% (compare entries 1 and 2, Table 4). The amount of the base could be reduced to 1 equivalent without any significant effect on the process outcome (entry 3). Unsuccessful were, in turn, attempts to use proton sponge or $CaCO_3$ (entries 4 and 5).

Further improvement over the results from entries 2 and 3 brought the introduction of Bu_4NHSO_4 into the reaction system. Under the conditions modified in this way, the coupling proceeded in 86% yield (Table 4; entry 6). The process outcome remained virtually unaffected

after changing the ratio of **216b**:**1b** from 1.1 to 0.67 (entry 7). The next experiment confirmed, in turn, that the use of DTBMP in excess is not necessary (entry 8). The arylation could be also successfully conducted in the presence of Bu_4NBF_4, however, the achieved result was not as good as in the case of analogous hydrogensulfate (compare entries 6 and 9). In contrast, attempts to employ Bu_4NBr or Bu_4NCl resulted in fast decomposition of the diazonium salt, and the obtained mixture contained unreacted starting material (entries 10 and 11). The next coupling was performed according to protocol 6, with the exception that the amount of Pd was decreased to 5 mol%. As a result of this attempt, I obtained product **18b** in lower, yet fully satisfying yield of 70% (entry 12).

*Table 4. Arylation of enecarbamate **1b** with 4-chlorobenzenediazonium tetrafluoroborate (**216b**)*[a]

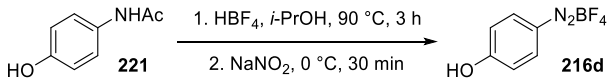


No.	Pd amount	Equiv of **216b**	Base	Additive[b]	Yield[c] [%]
1	10 mol%	1.1	NaOAc (3 equiv)	-	53
2	10 mol%	1.1	DTBMP (1.5 equiv)	-	67
3	10 mol%	1.1	DTBMP (1 equiv)	-	65
4	10 mol%	1.1	proton sponge	-	-
5	10 mol%	1.1	$CaCO_3$	-	<10
6	10 mol%	1.1	DTBMP (1 equiv)	Bu_4NHSO_4	86
7	10 mol%	0.67	DTBMP (1 equiv)	Bu_4NHSO_4	85
8	10 mol%	1.1	DTBMP (2 equiv)	Bu_4NHSO_4	87
9	10 mol%	1.1	DTBMP (1 equiv)	Bu_4NBF_4	70
10	10 mol%	1.1	DTBMP (1 equiv)	Bu_4NCl	-
11	10 mol%	1.1	DTBMP (1 equiv)	Bu_4NBr	-
12	5 mol%	1.1	DTBMP (1 equiv)	Bu_4NHSO_4	70

[a] Reactions were performed on 0.5 mmol scale for 14 h using 3 mL of the solvent. [b] 2 equiv [c] determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

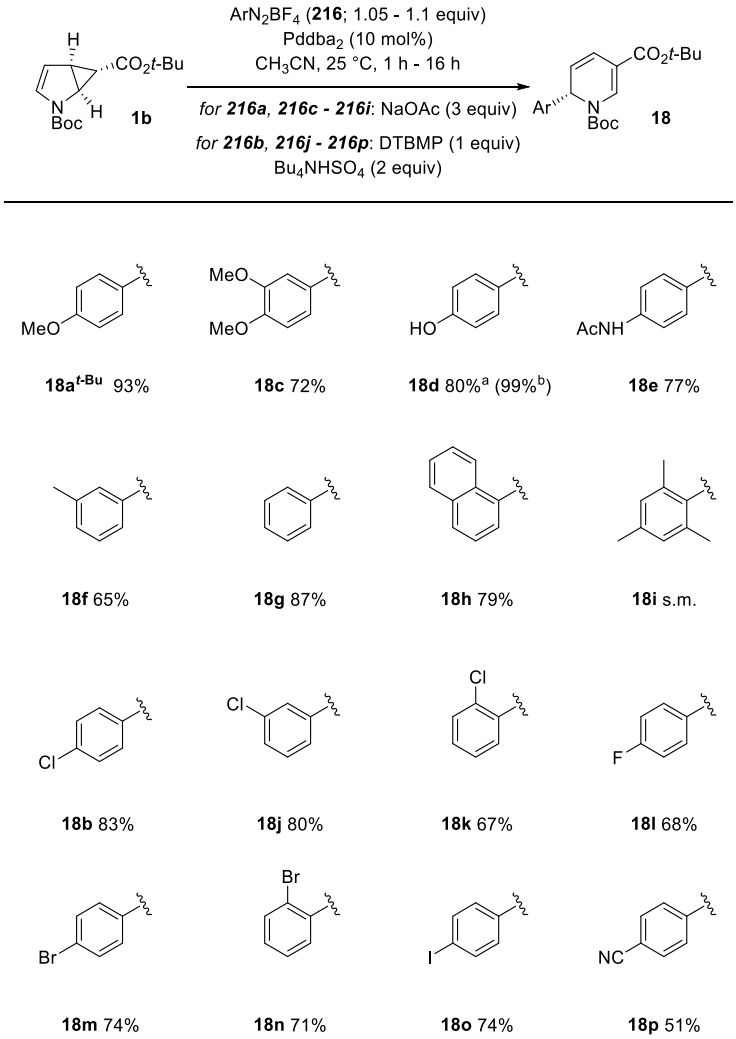
Given the results obtained for tetrafluoroborates **216a** and **216b**, I decided to investigate the scope of the process using two sets of conditions. Arylations with diazonium salts bearing an electron-donating group (**216a**, **216c** – **216f**, **216i**) or containing an unsubstituted aromatic ring (**216g**, **216h**) were performed in the presence of NaOAc (conditions from entry 3, Table 3). For electron-deficient tetrafluoroborates (**216b**, **216j**-**216p**), I employed DTBMP in combination with Bu_4NHSO_4 (conditions from entry 6, Table 4). Similarly to model substrates **216a** and **216b**, most of the investigated diazonium salts were prepared directly from the

corresponding anilines by diazotization employing $NaNO_2$ and HBF_4. The only exception constituted 4-phenoldiazonium salt synthesised according to a one-pot procedure from 4-acetamidophenol (**221**; Scheme 83).[144]



*Scheme 83. Synthesis of 4-phenoldiazonium salt **216d**.*

*Scheme 84. Arylation of enecarbamate **1b** with aryldiazonium tetrafluoroborates **216**.*



[a] Product of double arylation (**18d***, see experimental part) was obtained in 15% yield. [b] Reaction was performed using 0.5 mmol of salt **216d** and 0.75 mmol (1.5 equiv) of cyclopropanated pyrrole **1b**. Yield based on tetrafluoroborate **216d**.

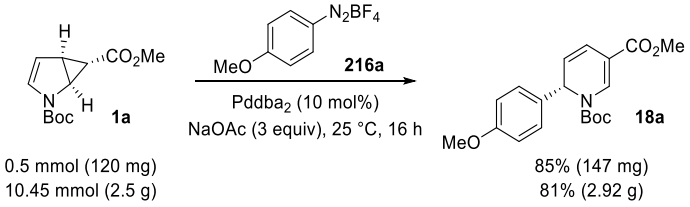
s.m. = starting material

Diazonium salts containing electron-donating groups in *para* (**216a**, **216d**, **216e**) and/or *meta* position (**216c**, **216f**) provided the corresponding 1,2-dihydropyridies **18a$^{t\text{-Bu}}$**, **18c-f** in good to excellent yields (65% - 93%; Scheme 84). The coupling with phenol derivative **216d**

gave, however, additionally a noticeable amount of double arylation product (15%), and therefore I decided to repeat this experiment but employing pyrroline **1b** in excess (1.5 equiv). As a result, I obtained the desired derivative **18d** in nearly quantitative yield. Benzendiazonium (**216g**) and 1-naphtalenediazonium (**216h**) tetrafluoroborates also proved to be effective arylating agents, yielding compounds **18g** and **18h** in 87% and 79% yield, respectively. In contrast, coupling was not observed for sterically highly demanding 2,4,6-trimethyl-substituted salt **216i**.

The reaction tolerated not only chloro-substituent but also all other halogens. Arylations with 4-bromo- and 4-iodobenzendiazonium tetrafluoroborates (**216m** and **216o**) proceeded in identical, 74%, yield, whereas the use of 4-fluoro analogue **216l** led to a slight decrease in the product amount (68%). In the series of chlorobenzenediazonium salts, *para* and *meta* isomers exhibited similar reactivity (83% and 80%, respectively) and performed better than the more congested *ortho*-chlorinated substrate **216k** (67%). Interestingly, an analogous difference in the efficiency of the coupling was not observed for *para*- and *ortho*-bromo-substituted salts **216m** and **216n**. These electrophiles afforded the corresponding products in comparable yields, equal to 74% and 71%, respectively. Finally, derivative **18p**, containing a *para*-cyano-substituted phenyl ring, could be synthesised in 51% yield.

Next, I investigated the scalability of the process. For this purpose, I conducted two reactions between cyclopropane **1a** and 4-methoxybenzenediazonium tetrafluoroborate (**216a**): in the first experiment, I employed 0.5 mmol of the substrate and in the second one - 10.45 mmol (Scheme 85). Gratifyingly, not only the yields of both transformations but also the reaction times were comparable.



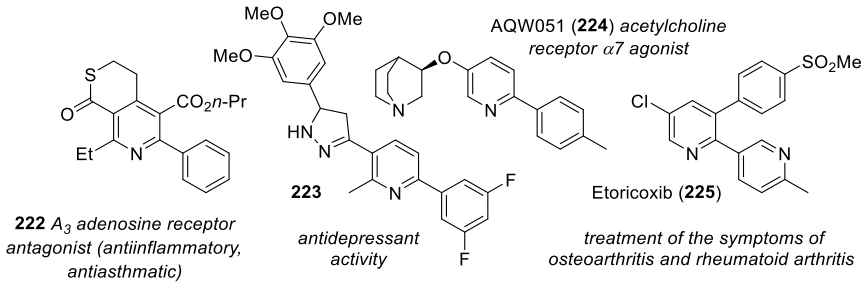
*Scheme 85. Scalability of arylation of bicycles **1** with diazonium salts.*

III 3.2. Transformations of 1,2-dihydropyridines **18**

Having determined the scope and the limitations of the developed procedure, I studied the reactivity of the synthesised 1,2-dihydropyridines **18**.

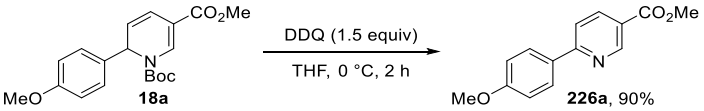
Oxidation to pyridines

A useful application of 1,2-dihydropyridines resulting from the presented Heck reaction would be the synthesis of corresponding arylpyridines. Compounds of this type play an important role in pharmaceutical (Scheme 86)[145–149] and material sciences[150–153] as well as serve as ligands in transition-metal-based catalysts.[154–156] At the same time, traditional protocols for the preparation of derivatives like **222-225**, based on cross-coupling of suitable pyridine precursor, suffer from harsh conditions and limited group tolerance.[157–161]



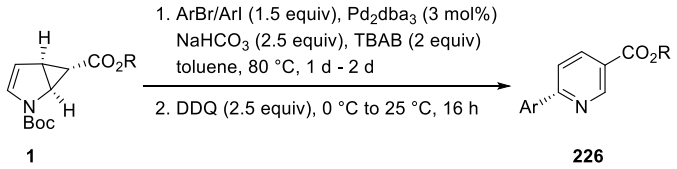
Scheme 86. Biologically active 2-arylpyridines.

A method chosen by me to transform substrate **18a** into compound **226a** employed DDQ as an oxidant.[162,163] Thus, I added this reagent to a cooled solution of derivative **18a** in THF and stirred the resulting mixture for 2 h (Scheme 87). Extractive work-up followed by column chromatography provided pyridine **226a** in 90% yield.



*Scheme 87. Oxidation of 1,2-dihydropyridine **18a**.*

Importantly, the described oxidation method could be then combined with Heck arylation of substrates **1** into a one-pot protocol (Scheme 88).[12,164]

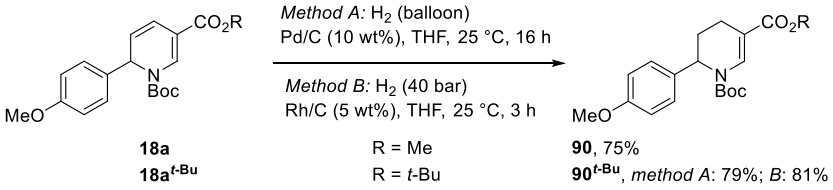


*Scheme 88. One-pot synthesis of 2-arylpyridines **226** from monocyclopropanated pyrroles **1**.*

Reduction of double bonds

Further experiments concerned addition reactions to the double bonds of the obtained 1,2-dihydropyridines **18**. In the first order, I investigated hydrogenation using derivatives **18a** and **18a$^{t\text{-Bu}}$** as model compounds.

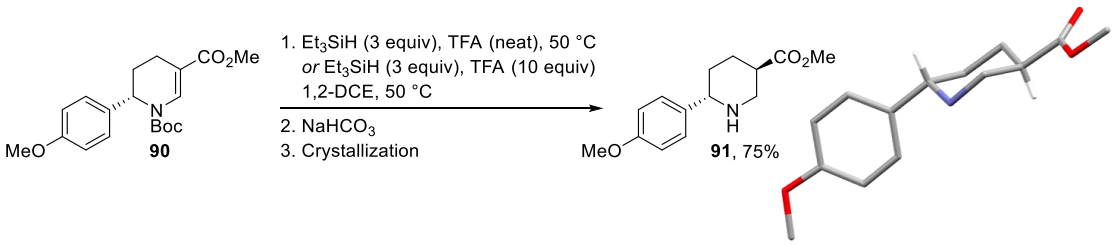
It turned out that substrates **18a** and **18a$^{t\text{-Bu}}$** exposed to hydrogen in the presence of Pd/C formed regioselectively tetrahydropyridines **90** and **90$^{t\text{-Bu}}$** in 75% and 79% yield, respectively (Scheme 89). An equally well result while shortening the reaction time was achieved with Rh/C as a catalyst at 40 bar of hydrogen pressure.



*Scheme 89. Catalytic hydrogenation of substrates **18a** and **18a$^{t\text{-Bu}}$**.*

Subsequent attempts to reduce also enecarbamate double bond in dihydropyridines **18a** and **18a$^{t\text{-Bu}}$** employing higher hydrogen pressures (up to 60 bar) and/or other transition-metal based catalysts (PtO_2, $Pd(OH)_2/C$, Raney nickel, Crabtree's catalyst) unfortunately failed yielding corresponding tetrahydropyridines together with various amount of by-products. Likewise, the experiments in which isolated compound **90** was treated with $NaBH_3CN$ or $NaBH_4$ were unsuccessful.

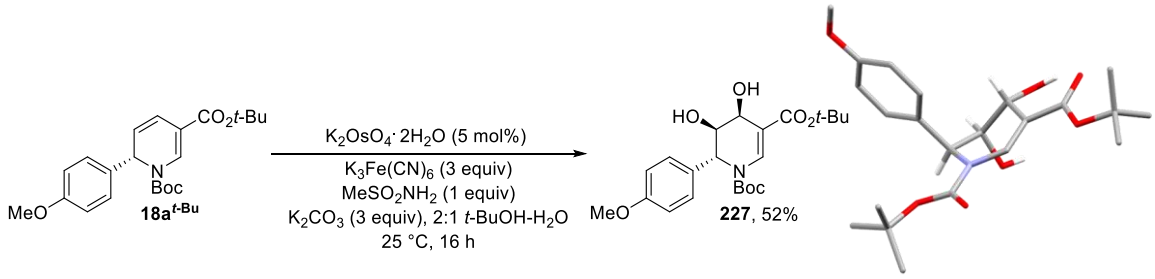
The next evaluated procedure encompassed the use of Et_3SiH/TFA as a reducing system.[165] The reaction was conducted at 50 °C for 3 h and subsequently worked up with an aqueous $NaHCO_3$ solution (Scheme 90). Gratifyingly, as a result of this experiment, I obtained the desired methyl 6-arylnipecotinate **91**, whereby this compound was formed as a ca 8:2 mixture of diastereomers. Crystallization of the crude products from MeOH yielded the major of them in 75% yield. Based on the obtained crystal structure, this compound was identified as the more thermodynamically stable *trans*-diastereomer. The subsequent experiment revealed that when 1,2-DCE is used as a solvent, the amount of the acid may be decreased to 10 equiv.



*Scheme 90. Reduction of tetrahydropyridine **90** and X-Ray structure of the obtained product **91**.*

Dihydroxylation

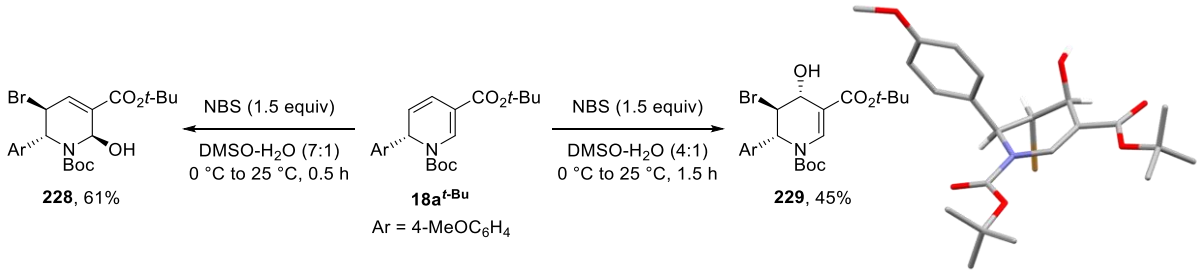
The next envisioned transformation of substrate **18a$^{t\text{-Bu}}$** was *cis*-dihydroxylation. The method employed for this purpose involved the use of K_2OsO_4 as a non-volatile OsO_4 precursor in combination with $K_3Fe(CN)_6$ as a co-oxidant (Scheme 91).[166] The process was conducted in the presence of K_2CO_3 and $MeSO_2NH_2$ in a *t*-BuOH-H_2O solvent system. From the post-reaction mixture, I isolated one product whose spectral data suggested that dihydroxylation occurred regioselectively on the less substituted double-bond. This assignment was unequivocally confirmed by roentgenographic analysis of the grown crystal. The obtained crystal structure also revealed that the addition took place on the site of the molecule opposite the aryl substituent.



*Scheme 91. Dihydroxylation of 1,2-dihydropyridine **18a$^{t\text{-Bu}}$** and X-Ray structure of diol **227**.*

Bromohydrination

Undertaken in the following part of the work attempts on bromohydrination of diene **18a$^{t\text{-Bu}}$** using NBS-H_2O system revealed that the regioselectivity of this process depends on the employed reaction conditions (Scheme 92). The transformation performed in a 7:1 mixture DMSO-H_2O yielded 1,4-bromohydrin **228** in 61% yield. Increasing the content of water caused that 1,2-adduct **229** started to form, and for DMSO-H_2O ratio equal to 4:1, this product constituted the major regioisomer. Unfortunately, the use of a higher amount of water led to a significant decrease in the solubility of substrate **18a$^{t\text{-Bu}}$** resulting in its incomplete conversion. Searching for conditions allowing a more efficient synthesis of 3-bromo-4-hydroxy-1,2,3,4-tetrahydropyridine **229**, I examined mixtures of water with several other organic solvents (THF, DMF, DME, MeCN, acetone). Disappointingly, product **229** was formed in these reactions in a small amount or was not detected at all.

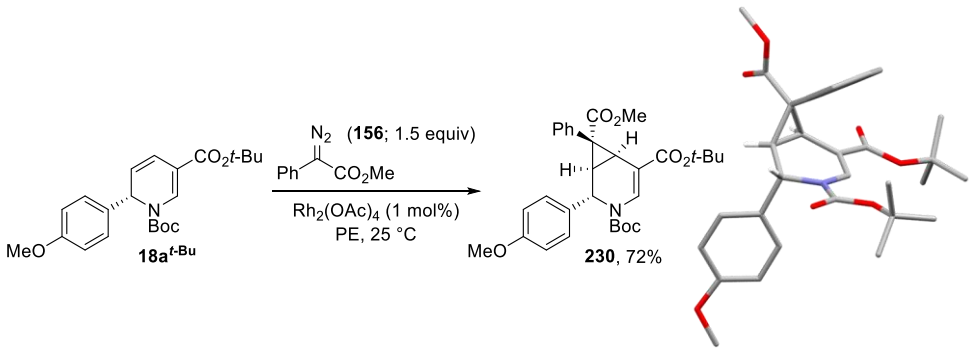


*Scheme 92. Bromohydrination of 1,2-dihydropyridine **18a**$^{t\text{-}Bu}$ and X-Ray structure of 1,2-adduct **229**.*

In the case of 1,2-isomer **229**, I was able to obtain a crystal suitable for roentgenographic analysis (Scheme 92). The collected data were in agreement with the approach of NBS from the face of the double bond opposite the aryl group, analogously as it was observed for OsO_4 in dihydroxylation reaction (*vide supra*).

Cyclopropanation

In the next experiment, a solution methyl phenyldiazoacetate (**156**) in petroleum ether was slowly added to a mixture of dihydropyridine **18a**$^{t\text{-}Bu}$ and $Rh_2(OAc)_4$ in the same solvent (Scheme 93). As a result of this attempt, I obtained selectively bicycle **230** in 72% yield. The structural assignment of this compound was unequivocally confirmed by X-Ray crystallography.

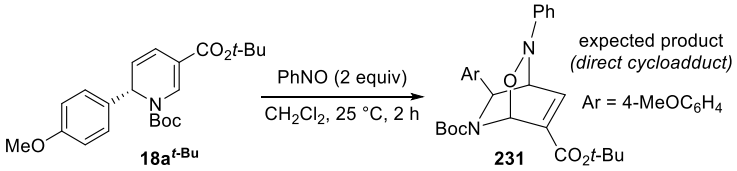


*Scheme 93. Cyclopropanation of 1,2-dihydropyridine **18a**$^{t\text{-}Bu}$ and X-Ray structure of the obtained product **230**.*

Nitroso Diels-Alder reaction

1,2-Dihydropyridines may also participate as a 4-carbon component in various types of [4+2] cycloadditions.[167] An important example of such transformations constitutes nitroso Diels–Alder (NDA) reaction in which the role of a dienophile is played by a nitroso-compound.[168–171] This process allows regio- and stereoselective installment of nitrogen and oxygen functionalities on the piperidine ring and at the same time features mild reaction conditions and broad functional group tolerance.

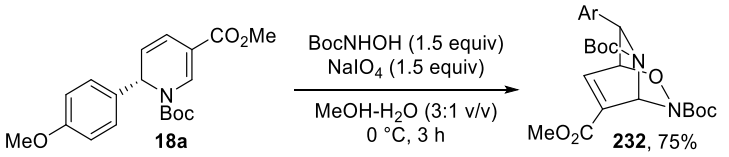
I commenced the attempts on performing an NDA reaction on 1,2-dihydropyridine **18a**$^{t\text{-Bu}}$ using nitrosobenzene as a dienophile. Based on the previous reports,[172–175] I expected that the addition will proceed with the regioselectivity shown in Scheme 94, giving the so-called *direct* isomer **231**. Unfortunately, the generated cycloadduct turned out to be prone to undergo a *retro*-Diels-Alder reaction which hampered its purification. The liability of products formed in reactions between nitrosoarenes and 1,2-dihydropyridines is, however, a known problem in the literature.[172,174]



Scheme 94. Cycloaddition of 1,2-dihydropyridine ***18a***$^{t\text{-Bu}}$ *with nitrosobenzene.*

Therefore, I turned my attention to acyl nitroso dienophiles. Reactions of these substrates with 1,2-dihydropyridines proceed with the regioselectivity opposite to that observed for nitrosoarenes to afford significantly more stable inverse cycloadducts.[170,176] The difference in the behaviour of aryl and acyl nitroso compounds was explained by both electronic and steric factors.[177] Due to the very high reactivity, acyl nitroso derivatives are generated *in situ*, most commonly through oxidation of the corresponding hydroxamic acid.[168] Other useful precursors of these reaction partners are nitrile oxides and 9,10-dimethylanthracene adducts.[178]

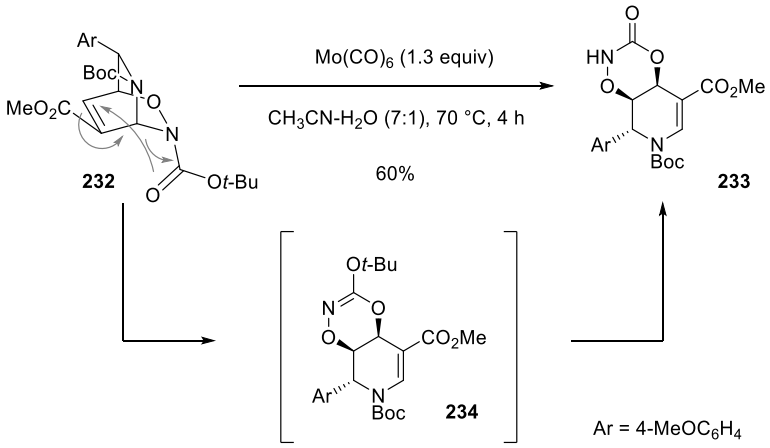
The dienophile chosen by me for the studies was *N*-Boc nitrosoformate. Thus, I treated a mixture of 1,2-dihydropyridine **18a** and *tert*-butyl hydroxycarbamate in a 3:1 MeOH-H_2O solvent system with $NaIO_4$ (Scheme 95).[179] As a result of this experiment, I obtained cycloadduct **232** in 75% yield.



Scheme 95. Cycloaddition of N*-Boc nitrosoformate to 1,2-dihydropyridine* ***18a****.*

Almost all synthetic applications of nitroso Diels-Alder reaction involve reductive cleavage of N-O bond in prepared cycloadducts. Reagents[180] commonly used for this purpose encompass zinc in acetic acid,[181] molybdenum hexacarbonyl,[182] titanium(III) salts,[183] or samarium diiodide.[184] N-O bond may be also cleaved by catalytic hydrogenation[185] or under photocatalytic conditions.[186]

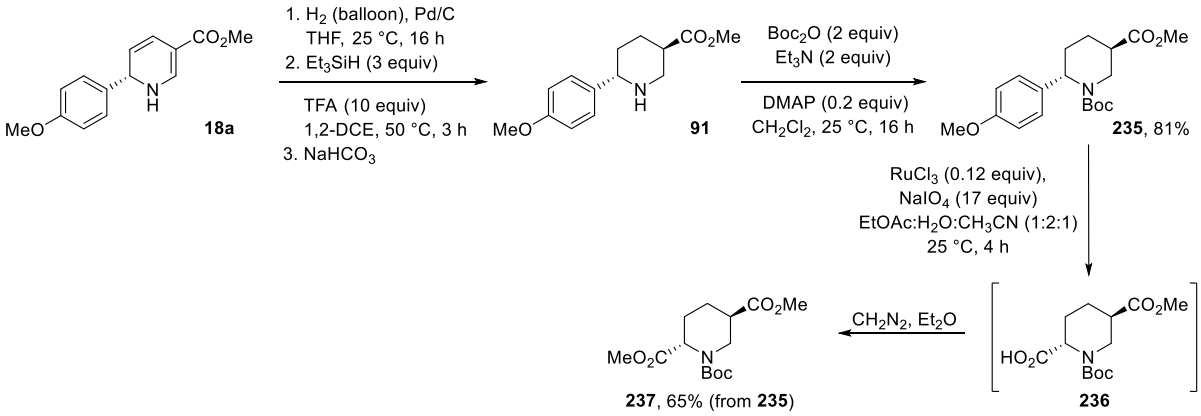
The method I decided to test involved the use of $Mo(CO)_6$. Thus, I heated the mixture of this reagent and cycloadduct **232** in wet CH_3CN to 70 °C, and after 3 hours I observed full-conversion of the substrate (Scheme 96). Interestingly, the analytical data of the isolated product were in agreement with structure **233**. Formation of bicycles analogous to compound **233** from cycloadducts generated from 1,2-dihydropyridines and carbamate-nitroso compounds has been, however, observed also by other authors, and its plausible mechanism involves formal [3.3]-sigmatropic rearrangement and subsequent hydrolysis of the resulting 5,6-dihydro-1,4,2-dioxazine.[177,187] This proposal strongly supports the isolation of intermediates of type **234** in the case of related benzoyl-carbamate-derived substrates.[177,187]



*Scheme 96. Rearrangement of cycloadduct **232**.*

Oxidation of aryl moiety

Another possible application of the prepared 1,2-dihydropyridines **18** constitutes the synthesis of pipecolic acid derivatives by oxidation of the aryl moiety, for example using $RuCl_3$-$NaIO_4$ system. Before performing this transformation, it was, however, necessary to reduce both double bonds and to protect the nitrogen atom with a group that would be stable under the oxidation conditions (Scheme 97). Such protection is i.a. *tert*-butyloxycarbonyl. Conversion of derivative **235** into acid **236** was carried out in an EtOAc-CH_3CN-H_2O mixture at 25 °C.[188] The product was, however, not isolated but directly converted into the corresponding methyl ester in the reaction with diazomethane. As a result of this oxidation-methylation sequence, I obtained the desired derivative **237** in 65% yield.

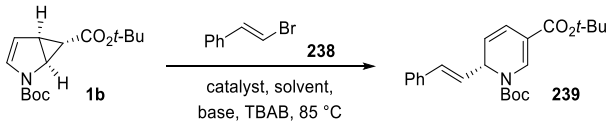


*Scheme 97. Synthesis of diester **237**.*

III 3.3. Vinylation of enecarbamate **1b**

Continuing the works on Pd-catalysed ring expansion of substrates **1**, I undertook an attempt to extend this methodology on vinylic coupling partners. For this purpose, I conducted several reactions between enecarbamate **1b** and β-bromostyrene (**238**; Table 5).

*Table 5. Vinylation of enecarbamate **1b** with β-bromostyrene (**238**)*[a]



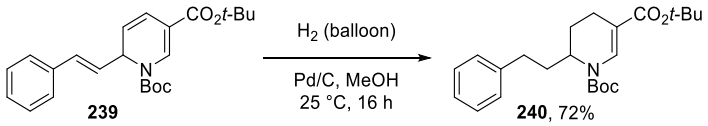
No.	Catalyst	Solvent	Base	Yield[b] [%]
1	Pd_2dba_3 (5 mol%)	DMF	$NaHCO_3$	33
2	Pd_2dba_3 (5 mol%)	CH_3CN	$NaHCO_3$	<15[c]
3	Pd_2dba_3 (5 mol%)	CH_3CN/H_2O	$NaHCO_3$	30
4	Pd_2dba_3 (5 mol%)	DMF	Cs_2CO_3	<15[c]
5	$Pd(OAc)_2$ (10 mol%)	DMF	$NaHCO_3$	29
6	$Pd(OAc)_2$ (10 mol%)	CH_3CN/H_2O	$NaHCO_3$	30
7	$Pd(PPh_3)_2Cl_2$ (10 mol%)	DMF	$NaHCO_3$	trace[c]
8	$PdCl_2$ (10 mol%), dppp (30 mol%)	DMF	$NaHCO_3$	trace[c]
9	$PdCl_2$ (10 mol%), dppf (30 mol%)	DMF	$NaHCO_3$	34[d]
10	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10 mol%)	DMF	$NaHCO_3$	42

[a] Reactions were performed on 0.5 mmol scale using 2.5 equiv of bromide **238**, 2.5 equiv of the base, 2 equiv of TBAB, and 3 mL of the solvent. [b] determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] mainly unreacted substrate **1b** according to NMR of the crude reaction mixture. [d] 2 equiv of bromide **238** were added after 2 d.

The obtained results were, however, little satisfying – the reactions were slow (3 - 7 d), resulted in the formation of a significant amount of by-products, and the highest achieved yield of the desired compound **239** was equal to 42% (Table 5; entry 10). Nevertheless, these initial

studies confirmed that vinylation of enecarbamates **1** is possible and may serve as the basis for further optimization.

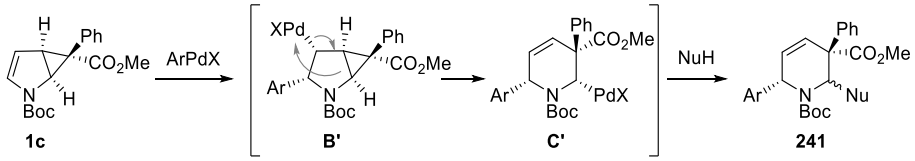
To illustrate the possible synthetic applications of 2-vinyl-1,2-dihydropyridines, I subjected compound **239** to catalytic hydrogenation (Scheme 98). As a result of this attempt, I obtained derivative **240** in 72% yield.



*Scheme 98. Catalytic hydrogenation of 1,2-dihydropyridine **239**.*

III 3.4. Ring-expansion of 6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate **1c**

Having completed the studies on Heck-type coupling of cyclopropane **1b**, I turned my attention to its *gem*-disubstituted congener **1c**. As I already mentioned, this substrate turned out to be inert under the initial Heck-coupling conditions, which was explained with the formation of organopalladium species **C'** unable to undergo either β-hydride elimination or reductive elimination (Scheme 99).[12] According to this proposal, the use of a suitable nucleophile should allow the synthesis of tetrahydropyridines **241**.

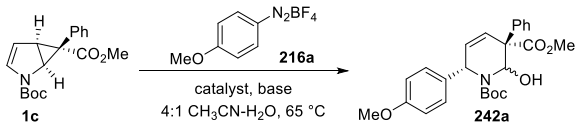


*Scheme 99. Arylation of enecarbamate **1c** in the presence of a nucleophile.*

A role of such a trapping reagent could play for instance water introduced to the reaction mixture. To verify this hypothesis, I subjected substrate **1c** to the reactions with 4-methoxybenzenediazonium tetrafluoroborate (**216a**) in a 4:1 CH_3CN-H_2O mixture using the catalytic system developed for analogous arylation of cyclopropane **1b** (see paragraph III 3.1). The choice of diazonium salts as coupling partners for these studies was associated with the cationic character of formed intermediates facilitating their reaction with nucleophiles.

In the case of the experiments performed at 25 °C and 45 °C, I could only recover unreacted substrate **1c**. Increasing the reaction temperature to 65 °C resulted, however, in full conversion of the substrate, and from the resulting mixture, I isolated expected lactamols **242a** in 65% overall yield (Table 6; entry 1). Encouraged with this positive result, I undertook the optimization of the conditions for arylation of enecarbamate **1c**.

*Table 6. Arylation of enecarbamate **1c** with 4-methoxybenzenediazonium tetrafluoroborate (**216a**)*[a]



No.	Catalyst	Equiv of **216a**	Solvent	Base (equiv)	Additive	Yield[b] [%]
1	$Pddba_2$	1.3	CH_3CN-H_2O 4:1	NaOAc (3)	-	65
2	$Pddba_2$	1.3	CH_3CN-H_2O 4:1	NaOAc (1)	-	54
3	$Pddba_2$	1.3	CH_3CN-H_2O 4:1	DTBMP (1)	-	85
4	$Pddba_2$	1.3	CH_3CN-H_2O 4:1	2,6-lutidine (3)	-	-
5	$Pddba_2$	1.3	CH_3CN-H_2O 4:1	Cy_2NMe (3)	-	-
6	$Pd(OAc)_2$	1.3	CH_3CN-H_2O 4:1	DTBMP (1)	-	64
7	$Pdtfa_2$	1.3	CH_3CN-H_2O 4:1	DTBMP (1)	-	53
8	$Pddba_2$	1.1	CH_3CN-H_2O 4:1	DTBMP (1)	-	90
9	$Pddba_2$	1.1	CH_3CN-H_2O 4:1	DTBMP (1)	Bu_4NHSO_4	68
10	$Pd(OAc)_2$	1.1	CH_3CN-H_2O 4:1	DTBMP (1)	Bu_4NHSO_4	55

[a] Reactions were performed on 0.5 mmol scale using 10 mol% of the catalyst and 3 mL of a 4:1 CH_3CN-H_2O mixture. [b] Isolated by column chromatography.

Since organopalladium intermediate **C'** may also undergo a competing reaction with acetate anion, the next arylation was carried out employing a lower amount of NaOAc (Table 6; entry 2). This modification led, however, to a worse result of 54%. A better idea turned out to be the use of DTBMP as a base which allowed to obtain the target compound **242a** in 85% yield (entry 3). Furthermore, the reaction proceeded with virtually complete diastereoselectivity. In contrast, coupling was not observed in the presence of 2,6-lutidine or Cy_2NMe (entries 4, 5). In the next experiments, I investigated the possibility of employing Pd(II) sources such as $Pd(OAc)_2$ and $Pdtfa_2$ (entries 6, 7). Similarly to the case of cyclopropane **1b**, catalysts of this type were not as effective as $Pddba_2$ giving product **242a** in 64% and 53% yield, respectively. On the other hand, changing the number of equivalents of the employed diazonium salt from 1.3 to 1.1 resulted in an improvement of the results to 90% (entry 8). The attempt to further enhance the efficiency of the process by introducing Bu_4NHSO_4 into the reaction system was, however, unsuccessful (entry 9). For comparison, I conducted an analogous experiment using $Pd(OAc)_2$ (entry 10). Also in this case, the yield of the obtained product was lower than that achieved with $Pddba_2$.

The structure of the obtained diastereomer was assigned based on the spectral data, and the final proof provided X-ray analysis of the obtained crystal. The NMR measurements were conducted at elevated temperature since the existence of the analyte as a mixture of rotamers caused doubling and significant broadening of the signals in the spectra recorded at 25 ℃. The influence of conditions on the shape of the NMR signals is illustrated in Figure 9.

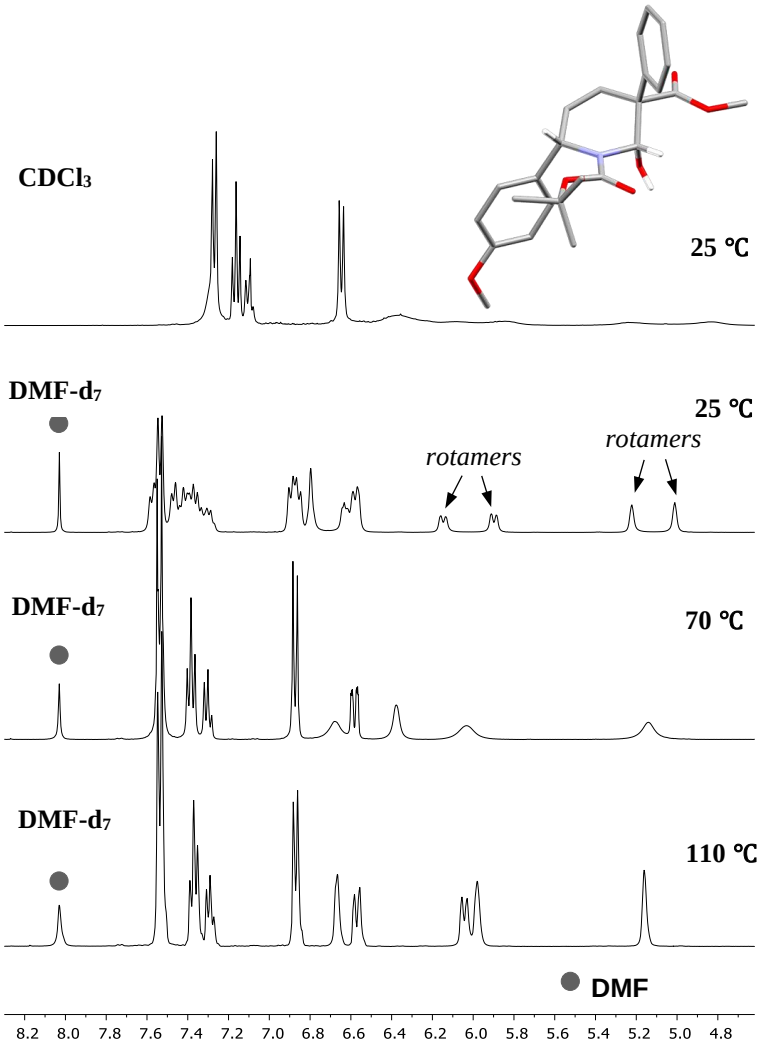
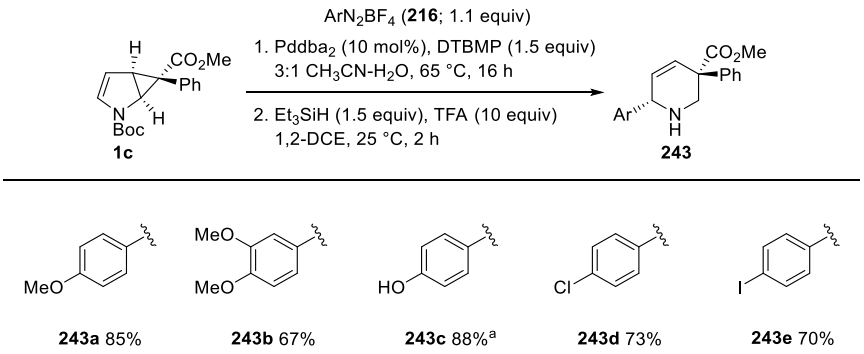


*Figure 9. Comparison of ^{1}H NMR spectra of compound 2,6-*syn*-**242a** measured under different conditions.*

Unlike in the case of compound **242a**, purification of other hemiaminals turned out to be difficult which resulted i.a. from their tendency to undergo dehydration under the reaction conditions. Therefore, I decided to subject the product mixture to reduction with Et_3SiH/TFA directly after the work-up.

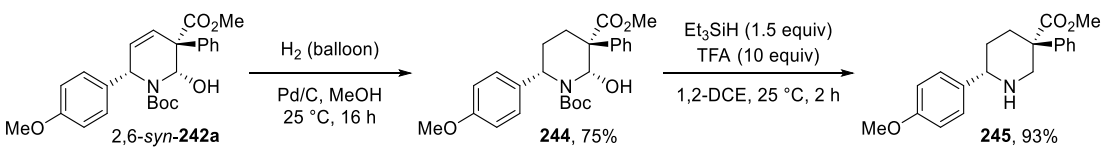
*Scheme 100. Arylation of substrate **1c** with diazonium salts **216**.*



[a] Reaction was performed using 0.5 mmol of 4-phenoldiazonium tetrafluoroborate (**216d**) and 0.75 mmol (1.5 equiv) of cyclopropanated pyrrole **1c**. Yield based on salt **216d**.

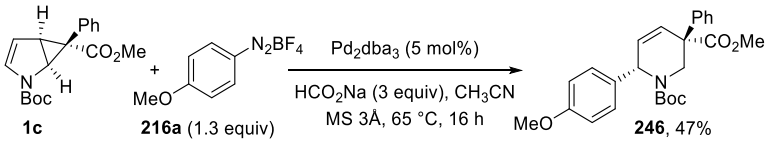
Whereas model 4-methoxybenzenediazonium tetrafluoroborate (**216a**) subjected to the developed reaction sequence furnished the corresponding product **243a** in 85% yield, the use of 3,4-dimethoxy-substituted coupling partner led to a somewhat worse result of 67% (**243b**; Scheme 100). Gratifyingly, 4-phenoldiazonium salt turned out not only to be a suitable substrate but also provided the desired tetrahydropyridine **243c** in very good yield of 88%. The latter experiment was, however, performed using pyrroline **1c** in excess. Employed to 4-chloro- and 4-iodobenzendiazonium tetrafluoroborates, the protocol allowed, in turn, the synthesis of derivatives **243d** and **243e** in 73% and 70% yield, respectively. In contrast, reactions with benzendiazonium and 1-naphtalenediazonium salts were unsuccessful. This may be associated with the lower thermal stability of unsubstituted diazonium tetrafluoroborates.

Products resulting from the developed ring-expansion of bicycle **1c** may be easily transformed into corresponding piperidines. For instance, hydrogenation of hemiaminal 2,6-*syn*-**242a** in the presence of Pd/C gave the expected heterocycle **244** in 75% yield (Scheme 101). Treatment of this compound with TFA in the presence of Et_3SiH provided derivative **245** in 93% yield. It should be noted that maintaining the described order of steps was essential for the successful synthesis of piperidine **245** – attempted hydrogenation of derivative **243a** under standard conditions furnished only a low amount of product, which was most likely due to the poisoning of Pd-catalyst.



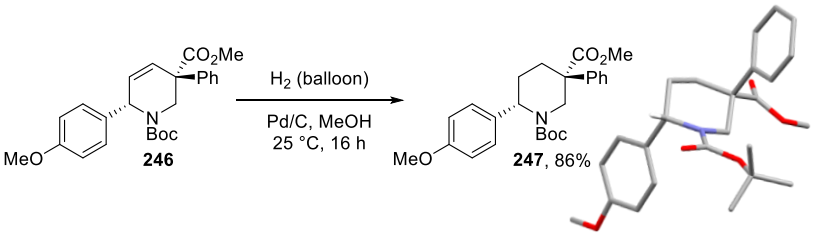
*Scheme 101. Transformation of lactamol 2,6-*syn*-**242a** into piperidine **245**.*

To demonstrate the possibility of trapping intermediate **C'** with other nucleophiles, I subjected enecarbamate **1c** to the reaction with 4-methoxybenzenediazonium tetrafluoroborate (**216a**) in the presence of sodium formate. This salt should serve not only as a hydride donor but also as a base. As shown in Scheme 102, the performed experiment provided the desired tetrahydropyridine **246** in 47% yield. Maintaining anhydrous reaction conditions was necessary to avoid the formation of lactamols **242a**.



*Scheme 102. Coupling of substrate **1c** with 4-methoxybenzenediazonium tetrafluoroborate (**216a**) in the presence of HCO_2Na.*

The structure of the obtained derivative **246** was assigned based on NMR studies. This assignment was confirmed by X-ray analysis of hydrogenation product **247** (Scheme 103).



*Scheme 103. Hydrogenation of compound **246**. X-Ray structure of the obtained product **247**.*

III 4 Application of 6-aryl-piperidine-3-carboxylic acids in peptides – initial results

As I noted in section II 1, nipecotic acids constitute useful building blocks for the preparation of peptides. The influence of the parent compound (**19**; Figure 2) on the conformation of a peptide backbone was studied by the group of Prof. Gellman.[39–41,189] On the basis of the spectral data, the authors found that dipeptide composed of two different enantiomers of nipecotic acid (**248**; Figure 10) formed in CH_2Cl_2 solution a reverse turn stabilized by a 12-membered ring hydrogen bond. In contrast, a structural preference of this type was not observed either for homochiral diastereomer **249** or derivatives **250** containing an acyclic β-amino acid in the first position.

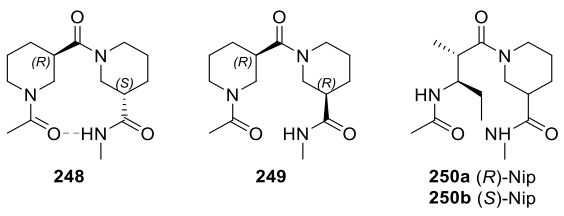


Figure 10. Model dipeptides studied by Gellman and co-workers. Dashed lines symbolise hydrogen bonds.

Each stereoisomer of dinipecotic acid moiety was subsequently evaluated for its ability to induce formation of an antiparallel β-sheet structure. For this purpose, the researchers synthesised a range of model tetrapeptides such as compounds **251** (Figure 11).[39–41,189] The spectral data revealed that both heterochiral dinipecotic acid segments are compatible with hydrogen bonds between the attached strand residues, although the (*R*,*S*)-configured subunit is more effective as a hairpin inducer than its (*S*,*R*)-isomer. As expected, neither of the homochiral diastereomers promotes β-sheet formation.

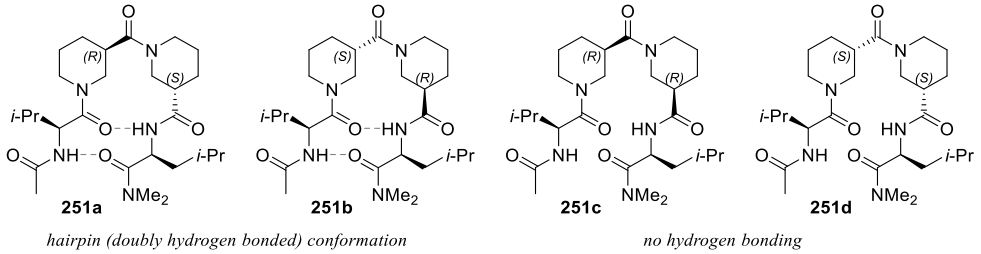


*Figure 11. Tetrapeptides **251** containing dinipecotic acid segment studied by Gellman and co-workers. Dashed lines symbolise hydrogen bonds.*

The obtained results served then as a basis for the design of semisynthetic ribonuclease A.[38] The scientist proved that the replacement of two native turn residues (Asn113-Pro114) with (*R*,*S*)-dinipecotic acid segment not only does not influence the catalytic activity of the enzyme but also enhances its conformational stability.

In the literature, there is also a work published by Bucci and describing peptides **253** modified with compound **252** (β-TIC; Figure 12).[190] The chemists stated that molecules comprising (*R*)-enantiomer of this rigid scaffold assumed in solution two different turn conformations in a 1:1 ratio. For the first of them (**253a^{E}**), they proposed a 12-membered ring hydrogen bond connecting the carbonyl group of alanine with the amine function of valine. The second conformation (**253a^{Z}**) was, in turn, stabilized by the interaction between NH of valine and C=O of the Fmoc moiety. Peptide comprising (*S*)-β-TIC existed, by contrast, as a mixture of three conformers in a ratio of 1:0.6:0.1. The authors characterized only the two major isomers, but neither of them adopted a preferred conformation.

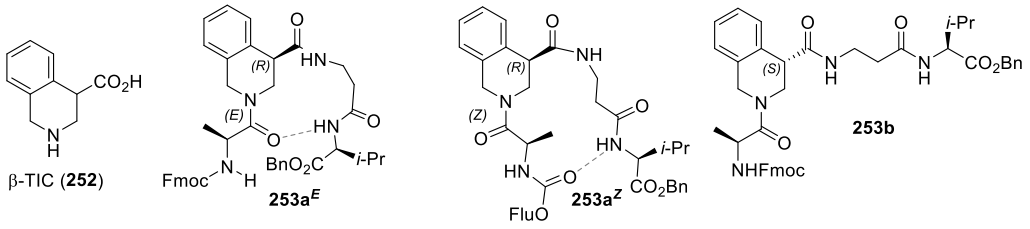
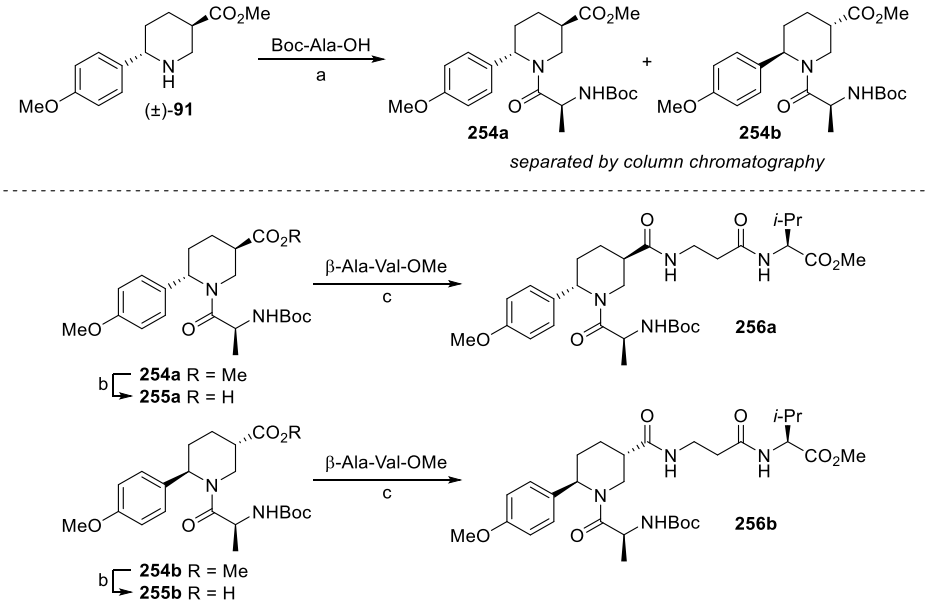


*Figure 12. Tetrapeptides **253** containing β-TIC analysed by Bucci and co-workers. Dashed lines symbolise hydrogen bonds.*

The results reported by Bucci[190] prompted us to investigate whether analogous oligopeptides **256** comprising derivative **91** will show similar behaviour and adopt a turn structure (Scheme 104). We supposed that the aryl substituent of compound **91** will not only ensure the rigidity of the piperidine ring but also restrict *E-Z* isomerisation about the tertiary amide bond. The synthesis of peptides **256** as well as the NMR studies was conducted by Francesco Feola (cooperation with the group of Prof. Gelmi, University of Mailand).[191] The synthetic strategy he followed commenced with the coupling of alanine with racemic derivative **91**. After the separation by column chromatography, diastereomers **254** were subjected to hydrolysis with LiOH, and the resulting acids **255** were subsequently coupled with β-Ala-Val-OMe moiety.[2]



*Scheme 104. Synthesis of model tetrapeptides **256a** and **256b**. Conditions: (a) Boc-Ala-OH (1.1 equiv), EDCCl (1.1 equiv), Oxyma (1.1 equiv), DIPEA (1.1 equiv), CH_2Cl_2, 25 °C, 48 h; 73% overall yield. (b) LiOH (3 equiv), 1:1 THF-H_2O, 25 °C, 3 h; **255a** 95%, **255b** 98%. (c) β-Ala-Val-OMe (1.1 equiv), EDCCl (1.1 equiv), Oxyma (1.1 equiv), DIPEA (1.1 equiv), CH_2Cl_2, 25 °C, 48 h; **256a** 75%, **256b** 72%.*

The collected analytical data confirmed our hypothesis that **91**-β-Ala dipeptide may act as a turn inducer.[191] For the first investigated diastereomer of compound **256**, we observed the formation of two turn-conformations in a ca 6:4 ratio (**256a**$^{\boldsymbol{Z}}$ and **256a**$^{\boldsymbol{E}}$; Figure 13). Variable temperature NMR experiments indicated that in both of them amine proton of alanine was involved in a strong hydrogen-bond (low $\Delta\delta/\Delta T$ for NH of alanine). In the case of the second tetrapeptide (**256b**), one of the detected conformers significantly predominated, and only this species was characterised. The pattern of the observed rOe signals resembled that exhibited by

[2] Absolute configuration of the residue of **91** in compounds **254**-**256** was tentatively assigned.

isomer **256a^{Z}**. The relatively high Δδ/ΔT value determined for NH of alanine suggested, however, only moderate stability of this conformation.

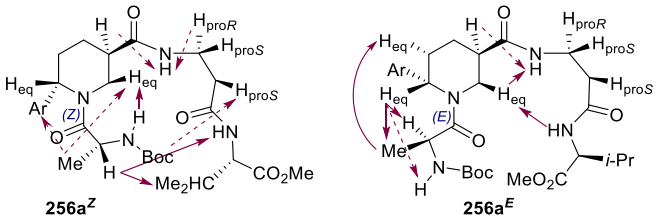
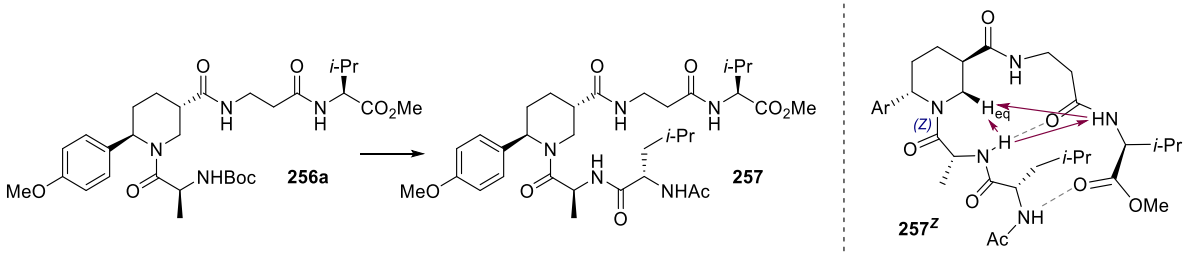


*Figure 13. Conformations proposed for tetrapeptide **256a**. Arrows indicate diagnostic rOe's.*

To determine whether elongation of a peptide chain will influence the distribution of tertiary amide rotamers, Feola prepared pentapeptide **257** (Scheme 105). NMR data indicated that again two isomers were present in a 6:4 ratio. Contrary to the case of precursor **256a**, the major of them was, however, identified as *Z* rotamer. This preference resulted most probably from the fact that only such configuration of the tertiary amide allowed the formation of an additional hydrogen bond.

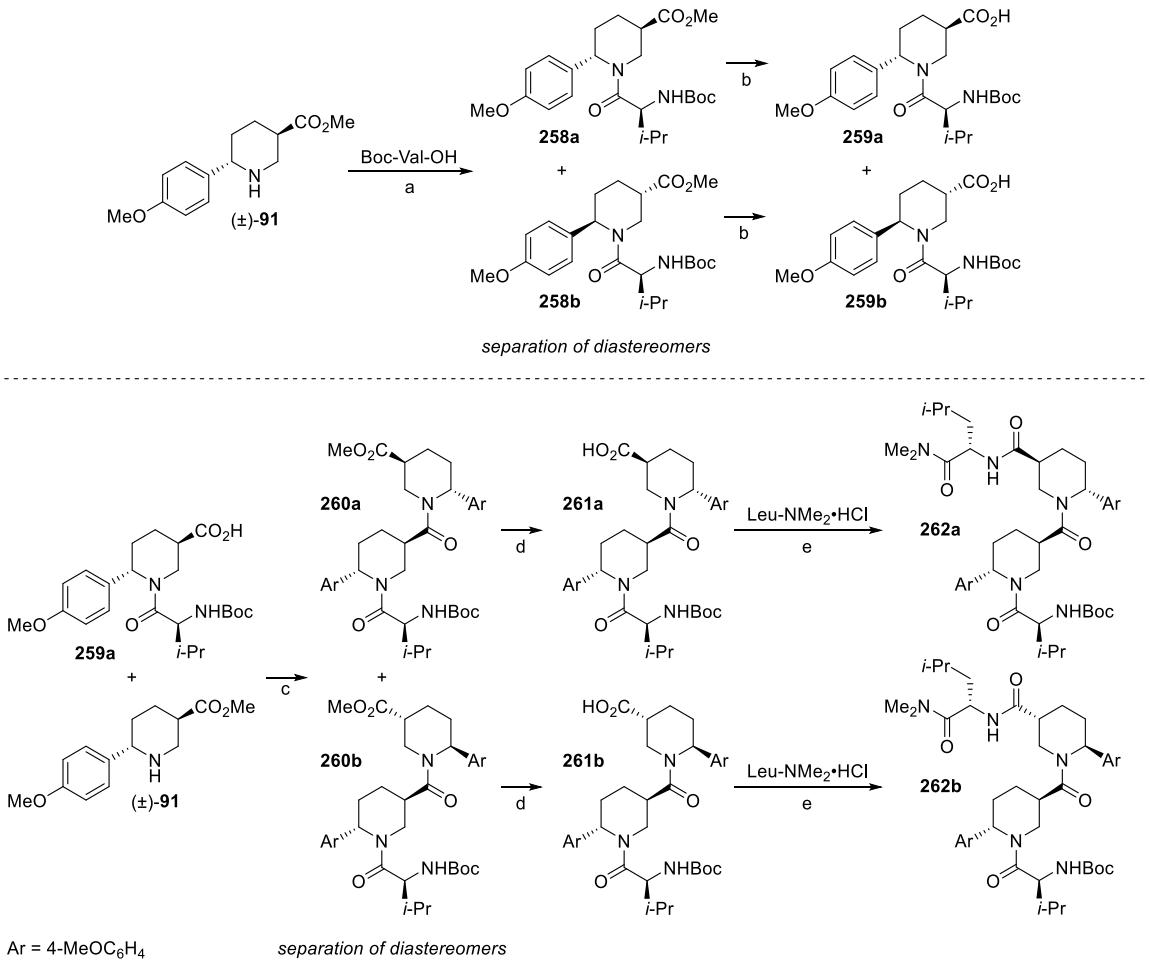


*Scheme 105. Synthesis of pentapeptide **257** and structure postulated for the major conformer (**257^{Z}**). Conditions: (i) TFA-CH_2Cl_2 1:1, 25 °C, 2 h; (ii) Ac-Leu-OH (2 equiv), T3P (1.2 equiv), DIPEA (1.2 equiv), CH_2Cl_2, 25 °C, 48 h, 65% over 2 steps. Arrows indicate diagnostic rOe's, whereas dashed lines symbolise hydrogen bonds.*

Continuing the studies on the application of 6-aryl-piperidine-3-carboxylic acids in peptides, I decided to prepare oligoamides **262** (Scheme 106), analogous to compounds **251** described by Gellman (compare Figure 11).[40] Specifically, I focused on the synthesis of diastereomers differing in the configuration of the second residue of **91**. Similarly to Feola, I planned to perform the synthesis employing derivative **91** in a racemic form and separate diastereomeric products after each reaction with an optically pure substrate.

Thus, the preparation of model tetrapeptides **262** started with the coupling of derivative **91** with *N*-Boc-Valine (Scheme 106). For this purpose, I employed EDC as an activating agent, Oxyma as an additive, and DIPEA as a base. The resulting diastereomers **258a** and **258b** were separated by column chromatography and then hydrolysed using LiOH. Further transformations were conducted only with acid **259a**. Coupling with the second molecule of amine **91** was performed under conditions similar to those employed in the first step. The resulting products

260 were subsequently converted into the corresponding acids **261**, which, in turn, were coupled with Leu-NMe_2. The latter step was carried out in CH_2Cl_2, in the presence of EDCCl, HOBt, and DIPEA.



*Scheme 106. Synthesis of model tetrapeptides **262a** and **262b**. Conditions: (a) Boc-Val-OH (1.1 equiv), EDCCl (1.2 equiv), Oxyma (1.2 equiv), DIPEA (1.2 equiv), CH_2Cl_2, 25 °C, 48 h; **258a** 49%, **258b** 34%. (b) LiOH (3 equiv), 1:1 THF-H_2O, 25 °C, 3 h; **259a** 96%, **259b** 97%. (c) **91** (1.1 equiv), EDCCl (1.2 equiv), Oxyma (1.2 equiv), DIPEA (1.2 equiv), CH_2Cl_2, 25 °C, 48 h; **260a** 46%, **260b** 41%. (d) LiOH (3 equiv), 1:1 THF-H_2O, 25 °C, 3 h. (e) Leu-NMe_2·HCl (1.3 equiv), EDCCl (1.4 equiv), HOBt (1.4 equiv), DIPEA (2.8 equiv), CH_2Cl_2, 25 °C, 48 h; **262a** 69% (over 2 steps), **262b** 76% (over 2 steps).*

The obtained peptides were characterized by NMR spectroscopy using both 1D and 2D techniques. The common feature of all spectra recorded in $CDCl_3$ at 25 °C was the presence of several sets of signals belonging to various rotamers of the analyte. That the observed species are rotamers and not diastereomers could be easily recognized from negative NH/NH and CH/CH cross-peaks in NOESY/ROESY spectra. Furthermore, spatial proximities between protons belonging to different rotameric forms were detected.[192]

The most important conclusion drawn from the spectral data of dipeptides **258** and **259** was the axial orientation of piperidine substituents. Such arrangement was indicated by low values of vicinal coupling constants of H-3 and H-6 as well as the pattern of the nOe signals. Diagnostic cross-peaks included those connecting H-2_{ax} with H_{ortho} and the latter protons with H-4_{ax} (Figure 14).

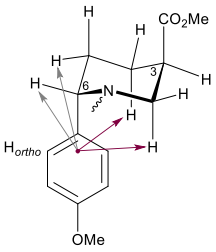


Figure 14. nOe's of aromatic protons

Dipeptides **258**, **259** adopt thus a chair conformation inverted to that observed for unprotected amine **91**, in which aryl and ester moieties occupied equatorial positions (Figure 15 *left*, compare Scheme 90). This change in the conformational behaviour may be attributed to minimization of pseudo allylic 1,3-strain related to the partial double bond character of the amide bond.[193–198]

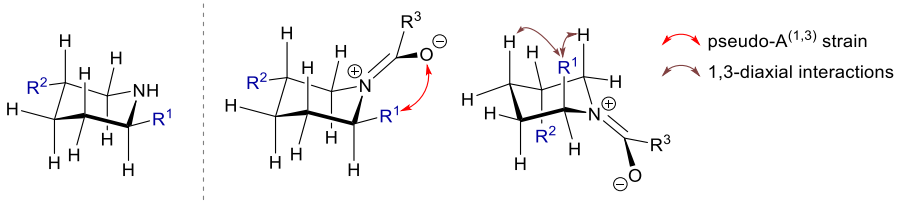


Figure 15. Pseudo allylic 1,3-strain: the steric interference between NC(O) moiety and an equatorial C-2 substituent on piperidine ring causes that an axial orientation of the latter is energetically favourable despite 1,3-diaxial interactions.

Whereas the configuration of the second residue of **91** in synthesized tri- and tetrapeptides was assigned tentatively, the stereochemistry of the first of them was proven by the crystal structure of compound **259b** (Figure 16). These data also confirmed the predicted conformation of the heterocyclic ring.

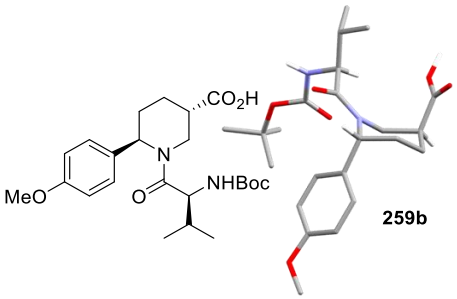


*Figure 16. Crystal structure of compound **259b**.*

^{1}H NMR spectrum of tripeptide **260a** revealed that one of the four possible tertiary amide rotamers was present in a considerably higher amount. An important observation for this species was the difference in chemical shifts of corresponding H-6 and H-2, suggesting an opposite configuration of amide bonds (Figure 17). Proton H-6 resonating at higher field showed spatial proximity with CH_{α} and H-3 of valine, which supported its assignment to *E*-rotamer. The attachment of the second to the third amino acid residue manifested, in turn, in cross-peaks

between H-6^2 and H-3^1 as well as the latter proton and H-2^2_{eq}. On the other hand, intraresidue nOe's between protons of the aryl ring and H-2_{ax} as well as the singlet-like shape of H-3 and H-6 signals suggested that the conformation of the piperidine rings was similar to that postulated for dipeptides. Due to the overlap of H-4 and H-5 resonances, it was, however, not possible to verify this hypothesis.

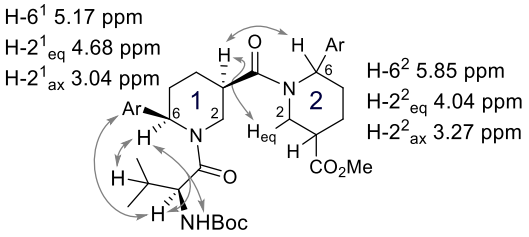


*Figure 17. Selected nOe observed for peptide **260a** and chemical shifts of piperidine α-protons.*

Differently from compound **260a**, diastereomer **260b** exhibited a comparable preference for two conformations. Because of this fact, the assignment of the observed signals was difficult; even the analysis of nOe effects did not help. For example, irradiation of α-proton of valine of one isomer caused a response of H-6 of each rotamer. Based on the comparison of chemical shifts of piperidine α-protons,[3] it could be, however, supposed that these species differ in the configuration of both tertiary amide bonds.

To get the first information about the conformational preferences of tetrapeptides **262**, I measured their IR spectra in diluted CH_2Cl_2 solution. Specifically, I analysed N-H stretch bands to confirm respectively exclude the formation of interstrand hydrogen bonds. In the first case, N-H stretching maxima would appear in a region between 3250 and 3400 cm^{-1}, whereas in the second one - in a range of 3400-3500 cm^{-1}.[39,41,189]

The fragments of IR spectra recorded for tetrapeptides **262** are presented in Figure 18, and as can be seen, both compounds exhibited a maximum in the non-hydrogen bonded region, at around 3420 cm^{-1}. Absorption close to this wavenumber is typical for N-H groups participating in a so-called "C_5" interaction - a weak intraresidue NH···O=C interaction with unfavourable geometry of functional groups.[40]

[3] e.g. H-6^1 5.87 ppm/4.76 ppm and H-6^2 5.70ppm/5.18 ppm

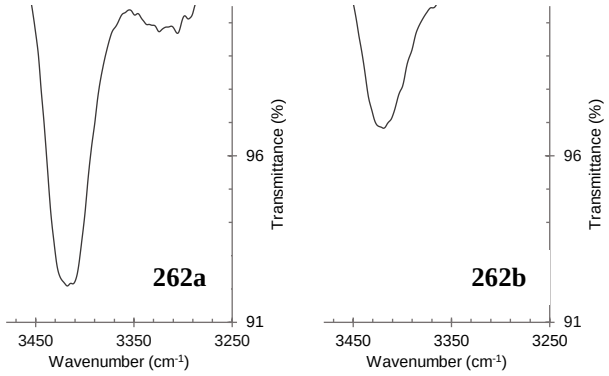


*Figure 18. NH stretch region of IR spectra of tetrapeptides **262** measured in CH_2Cl_2 at room temperature (1 mM solutions). Compound **262a**: maximum at 3418 cm^{-1}; Compound **262b**: maximum at 3419 cm^{-1}.*

Further studies were conducted by NMR spectroscopy. These measurements showed that neither of the peptides did assume a single, well-defined conformation. In the case of oligoamide **262a**, one isomer predominated, although its content in the overall pool of conformers was lower than 50%. Signals assigned to amide protons of this species appeared at 6.47 ppm (Leu) and 5.39 ppm (Val), evidencing the absence of hydrogen bonds. The similarity of chemical shifts of piperidine protons to the values determined for **260a** suggested, in turn, an identical configuration of the tertiary amide subunits in both products. Consistent with this assignment, nOe contacts were observed between H-3^1 and H-2^2_{eq}, the last proton and H-2^1_{ax}, as well as between H-2^1_{ax} and H-3^2. Spatial proximities between nonadjacent residues were not detected. The data collected so far allow, however, to draw only some initial conclusions about conformational preferences of compound **262a**, and their detailed interpretation requires support by computational methods. These studies are currently in progress (cooperation with the group of Prof. Gelmi, University of Mailand).

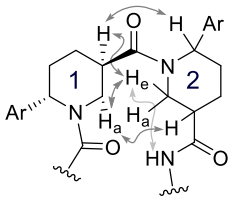


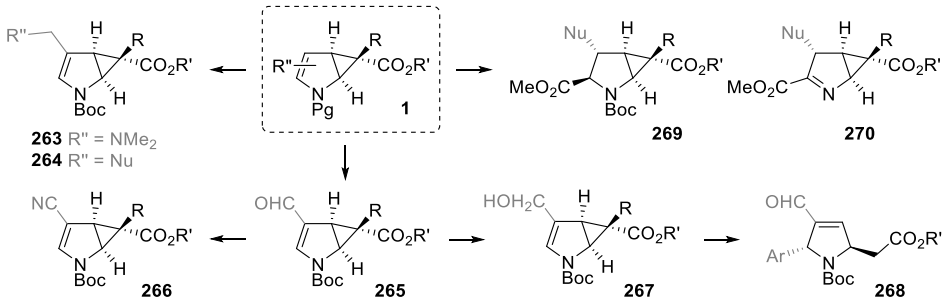
*Figure 19. Key nOe's between residues of **91** in **262a**.*

Also the explanation of the observed behaviour of diastereomer **262b** requires analysis by theoretical methods. NMR and IR data allow, however, to exclude the formation of interstrand hydrogen bonds. Furthermore, the comparison of spectra recorded for **262b** to that acquired for tripeptide **260b** revealed that leucine residue has little effect on the conformational preferences of Val-**91**-**91** scaffold. Analogous similarity was observed between **262a** and **260a** (*vide supra*).

IV Summary

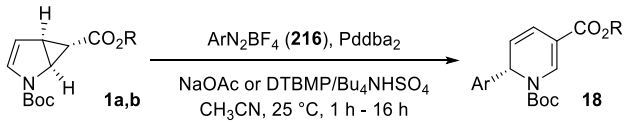
The present thesis concerns the synthesis and the reactivity of monocyclopropanated pyrroles **1** (Scheme 107), in particular their application in Heck reaction.

In the first part of the work, I prepared a range of 2-azabicyclo[3.1.0]hex-3-enes **1** *via* cyclopropanation of the corresponding heteroarenes and then examined transformations of the remaining double bond. Through the reaction with Böhme's salt, I obtained amines **263** (Scheme 107). These products were subsequently further functionalised by nucleophilic substitution on the side chain. Vilsmeier reaction of substrate **1** delivered, in turn, compounds **265**. The aldehyde functionality was then selectively reduced to alcohol as well as transformed into a nitrile moiety. Interestingly, the coupling of derivative **267** with 4-methoxyiodobenzene provided not only the expected dihydropyridine but also aldehyde **268**. Moreover, I demonstrated that cyclopropanated pyrrole-2-carboxylates may react as Michael acceptors. Whereas additions to *N*-Boc protected substrate afforded the expected products **269**, *N*-Ts-analogue formed imionoesters **270**.



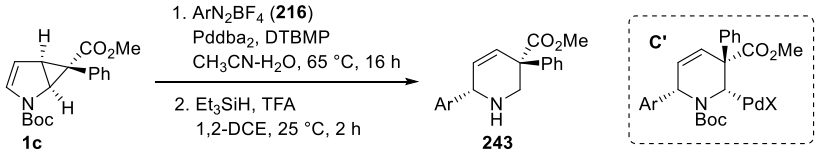
*Scheme 107. Investigated transformations of bicycles **1**.*

Next, I focused on the development of a more efficient procedure for conversion of bicycles **1** into the corresponding 6-aryl-1,6-dihydropyridine-3-carboxylates **18** (Scheme 108). It turned out that this aim may be achieved by employing aryldiazonium salts **216** as coupling partners. The optimal conditions of the process depended on the electronic properties of the substrate: while reactions with electron-reach and unsubstituted tetrafluoroborates proceed best in CH_3CN in the presence of $Pddba_2$ and NaOAc, in the case of electron-deficient salts higher yields were obtained using DTBMP as a base in combination with Bu_4NHSO_4 as an additive. Employing the optimized protocol, I synthesized an array of 1,2-dihydropyridines in the yields ranging from 51% to nearly quantitative. Notably, the reaction tolerated phenoldiazonium salt as well as iodo- and bromo-substituted electrophiles. The utility of the synthesised compounds was demonstrated in transformations such as dihydroxylation, bromohydrination, and cycloaddition.



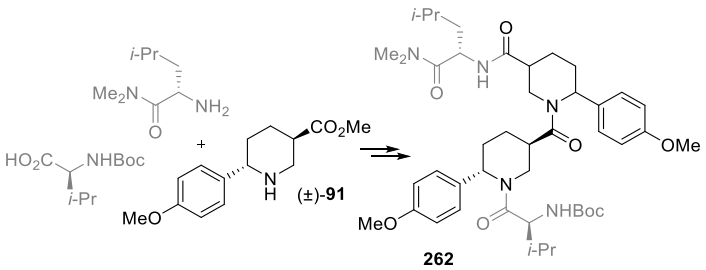
*Scheme 108. Arylation of bicycles **1** with aryldiazonium tetrafluoroborates **216**.*

Further works dealt with the ring expansion of 6,6-*gem*-disubstituted 2-azabicyclo[3.1.0]hex-3-ene **1c** (Scheme 109). In the case of this substrate, the generated six-membered organopalladium intermediate (**C'**) cannot undergo β-hydride elimination. Therefore, it was necessary to find a nucleophile that would be able to trap species **C'** thereby enabling the closure of the catalytic cycle. These studies established that substrate **1c** may be converted into the corresponding piperidine derivatives when the reaction with diazonium salts is performed in the presence of water. To simplify the isolation of the resulting lactamols, I decided to subject crude products to the reduction with Et_3SiH/TFA system directly after the work-up. The investigation on the reaction scope revealed that both electron-reach and halogen-substituted diazonium salts are tolerated. In contrast, the attempts to employ unsubstituted reaction partners were unsuccessful.



*Scheme 109. Arylation of bicycle **1c** with aryldiazonium tetrafluoroborates (**216**).*

Finally, I prepared model tetrapeptides **262** containing two consecutive residues of **91** (Scheme 110). The synthesis was conducted using racemic derivative **91**, and the diastereomeric products were separated after each coupling. Contrary to analogous oligoamides comprising nipecotic acid (piperidine-3-carboxylic acid),[40] neither of the studied peptides **262** adopted β-hairpin structure. This difference may be attributed to the preference of residues of **91** for axial orientation of the substituents. Computational studies aiming at a detailed explanation of the conformational behaviour of the synthesized compounds are currently in progress.

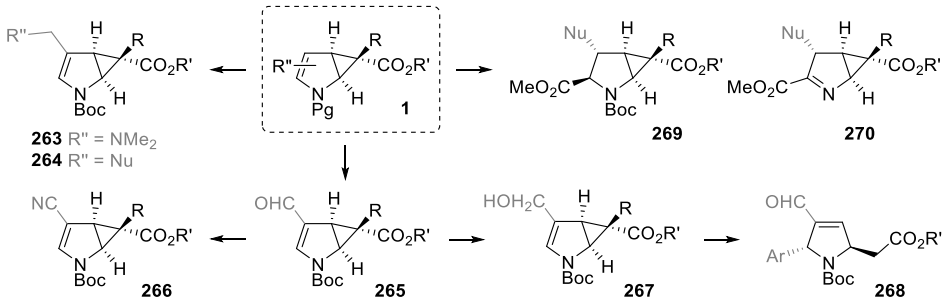


*Scheme 110. Model tetrapeptides **262**.*

V Zusammenfassung

Die vorliegende Dissertation befasst sich mit der Synthese und Reaktivität der cyclopropanierten Pyrrole **1** (Schema 1), insbesondere deren Anwendung in der Heck Reaktion.

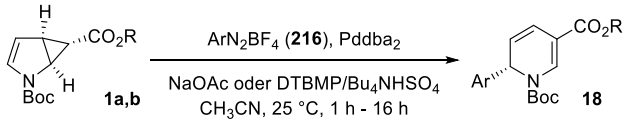
Im ersten Teil der Arbeit stellte ich eine Reihe von 2-Azabicyclo[3.1.0]hex-3-enen **1** durch die Cyclopropanierung der entsprechenden Heteroarene her, und danach untersuchte ich Transformationen der verbliebenen Doppelbindung (Schema 1). In der Reaktion mit Böhme Salz erhielt ich Amine **263**, die ich anschließend durch nukleophile Substitution an der Seitenkette weiter funktionalisierte. Die Vilsmeier Reaktion von Edukten **1** lieferte wiederum Verbindungen **265**. Die Aldehydfunktion wurde dann selektiv zum Alkohol reduziert sowie in eine Nitrilgruppe umgewandelt. Interessanterweise, lieferte die Kupplung des Derivats **267** mit 4-Methoxyiodbenzol nicht nur das erwartete Dihydropyridin, sondern auch den Aldehyd **268**. Darüber hinaus habe ich gezeigt, dass cyclopropanierte Pyrrol-2-carboxylate als Michael-Akzeptoren reagieren können. Während die Additionen an das *N*-Boc-geschützte Edukt zu den erwarteten Produkten **269** führten, bildete das *N*-Ts-Analogon den Imionoester **270**.



*Schema 1. Transformationen von Bizyklen **1**.*

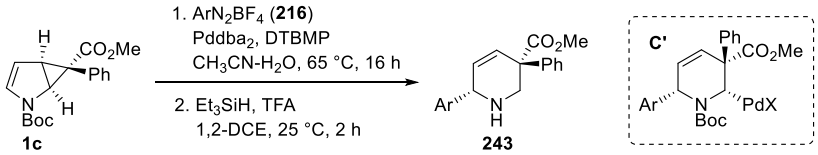
Als nächstes, konzentrierte ich mich auf die Entwicklung einer effizienteren Prozedur zur Umwandlung von Bizyklen **1** in entsprechende 6-Aryl-1,6-dihydropyridin-3-carboxylate **18** (Schema 2). Es stellte sich heraus, dass dieses Ziel durch den Einsatz von Aryldiazoniumsalzen als Kupplungspartner erreicht werden kann. Die optimalen Bedingungen des Prozesses hingen von dem elektronischen Charakter des Substrats ab: während Reaktionen mit elektronenreichen und unsubstituierten Tetrafluorboraten am besten in Gegenwart von $Pddba_2$ und NaOAc in CH_3CN abliefen, wurden im Fall der elektronarmen Salze höhere Ausbeuten unter Verwendung von DTBMP als Base in Kombination mit Bu_4NHSO_4 als Additiv erreicht. Mittels des optimierten Protokolls synthetisierte ich eine Reihe von 1,2-Dihydropyridinen **18** in Ausbeuten von 51% bis nahezu quantitativ. Bemerkenswert, tolerierte die Reaktion Phenoldiazoniumsalz sowie Iod- und Brom-substituierte Elektrophile. Der Nutzen der hergestellten Verbindungen

wurde anhand Transformationen wie Dihydroxylierung, Bromhydrinierung und Cycloaddition demonstriert.



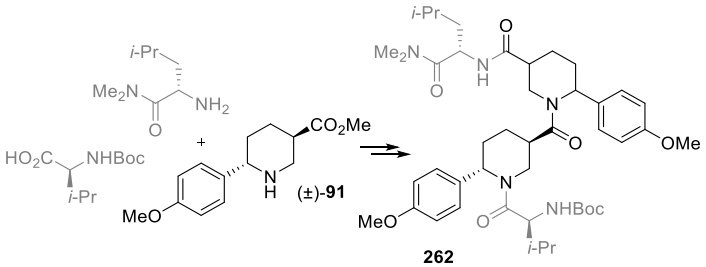
*Schema 2. Arylierung von Bizyklen **1** mit Aryldiazoniumsalzen **216**.*

Weitere Arbeiten befassten sich mit der Ringexpansion von 6,6-*gem*-disubstituiertem 2-Azabicyclo[3.1.0]hex-3-en **1c**. Im Fall dieses Substrates kann das generierte sechsgliedrige Organopalladiumintermediat **C'** keine β-Hydrideliminierung eingehen. Deswegen war es notwendig ein Nukleophil zu finden, das durch das Abfangen des Spezies **C'** die Schließung des katalytischen Zyklus ermöglichen würde. Diese Studien ergaben, dass das Edukt **1c** in die entsprechenden Piperidinderivate umgewandelt werden kann, wenn die Reaktion mit Diazoniumsalzen in Gegenwart von Wasser durchgeführt wird. Um die Isolierung der resultierenden Lactamole zu vereinfachen, habe ich beschlossen, Rohprodukte direkt nach der Aufarbeitung mit dem Et_3SiH/TFA-System zu reduzieren. Die Untersuchung der Substratbreite zeigte, dass sowohl elektronenreiche als auch halogensubstituierte Diazoniumsalze toleriert werden. Die Versuche unsubstituierte Reaktionspartner zu verwenden waren dagegen erfolglos.



*Schema 3. Arylierung von Bizyklus **1** mit Aryldiazoniumsalzen **216**.*

Schließlich stellte ich Modelltetrapeptide **262** her, die zwei aufeinanderfolgende Reste von **91** enthielten. Die Synthese wurde unter Verwendung des racemischen Derivats **91** durchgeführt, und die diastereomeren Produkte wurden nach jeder Kupplung chromatographisch getrennt. Im Gegensatz zu analogen Oligoamiden von Nipecotinsäure (3-Piperidincarbonsäure),[40] nahm keines der untersuchten Peptide **262** eine β-Haarnadelstruktur an. Dieser Unterschied kann auf die Präferenz von Resten von **91** für eine axiale Orientierung der Substituenten zurückgeführt werden. Derzeit werden Computerstudien durchgeführt, die eine detaillierte Erklärung des konformationellen Verhaltens der synthetisierten Verbindungen zum Ziel haben.



*Schema 4. Modelltetrapeptide **262.***

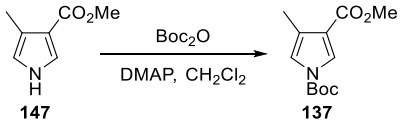
VI Experimental part

General Information

Air- and moisture-sensitive reactions were conducted in oven-dried glassware under an atmosphere of nitrogen. Commercially available chemicals were used as received. Dry solvents were prepared according to the standard procedures. Column chromatography was performed using silica gel (230-400 mesh; Merck). Analytical thin layer chromatography (TLC) was carried out on Silica gel 60 F254 aluminium plates (Merck). Visualization was achieved with UV light (λ = 254 nm or 366 nm) and common dip stains (cerium ammonium molybdate, ninhydrin, potassium permanganate, or vanillin). NMR spectra were measured on Bruker Avance 300 (300 MHz), Bruker Avance III HD 400 (400 MHz), and Bruker Avance III 600 TCI Cryo (600 MHz) spectrometers. Chemical shifts are quoted on the δ scale, ppm, with the solvent signal as the internal standard (^{1}H NMR: $CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm, DMF-d_7: 8.03 ppm, methanol-d_4: 3.31 ppm; ^{13}C NMR: $CDCl_3$: 77.16 ppm, C_6D_6: 128.06 ppm, DMF-d_7: 163.15 ppm, methanol-d_4: 49.00 ppm). Multiplicities for ^{1}H NMR signals are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) are given in Hertz (Hz). Infrared spectra (IR) are described in cm^{-1} and were recorded on a Biorad Excalibur FTS 3000 spectrophotometer or a Varian FT-IR-Spectrometer Scimitar 800. High resolution mass spectra (HRMS) were obtained on Thermoquest Finnigan TSQ 7000, Finnigan MAT 95, Varian MAT 311A, or Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS and are reported in *m/z*. Melting points (m.p.) were determined with OptiMelt MPA 100 apparatus and are uncorrected. Optical rotations [α] were measured on Perkin Elmer 241 polarimeter at λ = 589 nm (Na D-line) in a 1.0 dm measuring cell in $CHCl_3$. X-ray analyses were performed on Agilent Technologies SuperNova or Agilent GV1000 diffractometer.

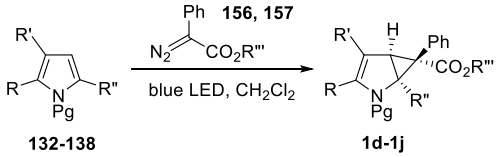
Compounds **1a**,[84] **1b**,[10] **1c**,[83] *tert*-butyl-1*H*-pyrrole-1-carboxylate (**131**),[199] methyl 1-tosyl-1*H*-pyrrole-2-carboxylate (**132**),[72,200] 1-(*tert*-butyl) 2-methyl 1*H*-pyrrole-1,2-dicarboxylate (**133**),[201] 1-(1-(phenylsulfonyl)-1*H*-pyrrol-3-yl)ethan-1-one (**134**),[73,202] *tert*-butyl 3-acetyl-1*H*-pyrrole-1-carboxylate (**135**),[73,203,204] methyl 1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (**136**),[75,76] *tert*-butyl 2,5-dimethyl-1*H*-pyrrole-1-carboxylate (**138**),[205] methyl 4-methyl-1*H*-pyrrole-3-carboxylate (**147**),[78] methyl diazoacetate (**149**),[79] tosyl azide (**151**),[206] *tert*-butyl diazoacetate (**152**),[80] *ortho*-nitrobenzenesulfonyl azide (**155**),[207] methyl phenyldiazoacetate (**156**),[81] 2,2,2-trichloroethyl 2-diazo-2-phenylacetate (**157**),[82] 2,2-dimethyl-1-(1-(phenylsulfonyl)-1*H*-pyrrol-3-yl)propan-1-one (**160**),[208] diazonium salts **216**,[144,164,209,210] *tert*-butyl *N*-hydroxycarbamate,[211] and β-bromostyrene (**238**)[212] were synthesised following the previously reported procedures and their analytical data were consistent with those published in the literature.

Preparation of pyrrole 137



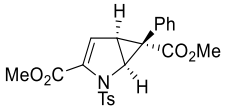
Methyl 4-methyl-1*H*-pyrrole-3-carboxylate (**147**; 918 mg, 6.6 mmol) and DMAP (81 mg, 0.66 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (23 mL), and a solution of Boc_2O (1.73 g, 7.92 mmol, 1.2 equiv) in the same solvent (10 mL) was slowly added at 25 °C. The mixture was stirred at 25 °C until complete consumption of substrate **147** (TLC control; 16 h). Thereafter, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel. Compound **137** was obtained as colorless crystals (1.42 g, 90%). **M.p.** = 68.4-70.0 °C; $\mathbf{R_f}$ = 0.53 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.79 – 7.74 (m, 1H), 7.00 – 6.94 (m, 1H), 3.81 (s, 3H), 2.26 – 2.21 (m, 3H), 1.59 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.2, 148.3, 125.8, 123.3, 118.7, 118.3, 84.7, 51.2, 28.1, 11.8. **IR** (film) *ν*: 3131, 2997, 2952, 1744, 1707, 1584, 1521, 1480, 1402, 1342, 1245, 1156, 1115, 984, 842, 775, 686 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{12}H_{17}NO_4Na$ [M + Na^+] 262.1050. Found 262.1053.

General procedure for photochemical cyclopropanation of pyrrole derivatives - preparation of compounds 1d-1j, 170, 171



A Schlenk flask containing a magnetic stirring bar was charged with pyrrole derivative **132-138** (2.5-5 mmol, 2.5-5 equiv), aryldiazoacetate **156** or **157** (1 mmol), CH_2Cl_2 (5 mL) and then closed with a Teflon-sealed cap equipped with a glass rod. The rod was connected to a 455 nm LED lamp. The reaction mixture was irradiated at 25 °C until TLC indicated complete consumption of the diazo compound. Thereafter, the solution was transferred into a round-bottom flask, the reaction vessel was thoroughly rinsed with CH_2Cl_2, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography to give compounds **1d-1j**, **170**, **171**.

Dimethyl (1*S,5*S**,6*R**)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (1d)**

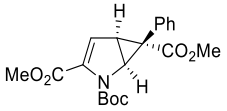


Obtained according to the general procedure using 4 equiv of methyl *N*-Ts-pyrrole-2-carboxylate (**132**).

Yield: 256 mg (62%); colorless crystals; **m.p.** = 128.1-130.0 °C; $\mathbf{R_f}$ = 0.32 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.82 – 7.78 (m, 2H), 7.41 – 7.34 (m, 2H), 7.20 – 7.11 (m, 3H), 6.98 – 6.90 (m, 2H), 6.04 (d, *J* = 2.5 Hz, 1H), 4.79 (d, *J* = 5.8 Hz, 1H), 3.62 (s, 3H), 3.54 (s, 3H), 3.12 (dd, *J* = 5.8, 2.5 Hz, 1H), 2.47 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 172.8, 161.2, 144.8, 135.8, 134.5, 132.2, 129.8, 129.6, 128.2, 127.9, 127.7, 123.5, 53.1, 52.2, 51.8, 36.4, 30.0, 21.8. **IR** (film) *ν*: 2952, 1715, 1595, 1498, 1435, 1361, 1320, 1260, 1226, 1167, 1062, 995, 809,

708, 671 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{22}NO_6S$ [M + H^+] 428.1162. Found 428.1172.

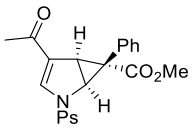
2-(*tert*-Butyl) 3,6-dimethyl (1*S,5*S**,6*R**)-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,3,6-tricarboxylate (1e)**



Obtained according to the general procedure using 3 equiv of methyl *N*-Boc-pyrrole-2-carboxylate (**133**).

Yield: 291 mg (78%); wax; $\mathbf{R_f}$ = 0.31 (15% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.39 – 7.10 (m, 5H), 5.77 (d, *J* = 2.7 Hz, 1H), 4.75 (d, *J* = 6.2 Hz, 1H), 3.63 (s, 3H), 3.47 (s, 3H), 3.29 (dd, *J* = 6.2, 2.7 Hz, 1H), 1.47 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 173.5, 161.4, 151.5, 135.4, 132.4, 130.2, 128.0, 127.5, 117.3, 82.9, 52.9, 51.8, 49.6, 36.2, 29.3, 28.1. **IR** (film) *v*: 2978, 1711, 1435, 1368, 1234, 1148, 1085, 962, 772, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{23}NO_6Na$ [M + Na^+] 396.1418. Found 396.1426.

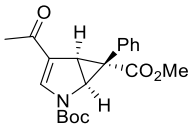
Methyl (1*S,5*S**,6*R**)-4-acetyl-6-phenyl-2-(phenylsulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (1f)**



Obtained according to the general procedure using 2.5 equiv of 3-acetyl-1-(phenylsulfonyl)pyrrole (**134**).

Yield: 208 mg (52%); colorless crystals; **m.p.** = 203.0-204.9 °C; $\mathbf{R_f}$ = 0.19 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.92 – 7.83 (m, 2H), 7.75 – 7.56 (m, 3H), 7.24 – 7.00 (m, 5H), 6.83 – 6.78 (m, 1H), 4.60 (dd, *J*=6.8, 1.5, 1H), 3.63 – 3.50 (m, 4H), 2.13 – 2.06 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 193.0, 173.0, 139.1, 137.7, 134.4, 131.9, 130.0, 129.9, 128.3, 128.0, 127.4, 125.4, 53.1, 52.2, 36.7, 28.1, 26.3. **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{19}NO_5SNa$ [M + Na^+] 420.0876. Found 420.0874.

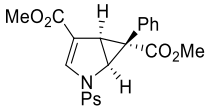
2-(*tert*-Butyl) 6-methyl (1*S,5*S**,6*R**)-4-acetyl-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (1g)**



Obtained according to the general procedure using 2.5 equiv of 3-acetyl-*N*-Boc-pyrrole (**135**).

Yield: 226 mg (63%); colorless crystals; **m.p.** = 147.6-149.3 °C; $\mathbf{R_f}$ = 0.14 (15% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.27 – 7.16 (m, 3H), 7.14 – 6.60 (m, 3H), 4.77 – 4.56 (m, 1H), 3.69 – 3.53 (m, 4H), 2.16 – 2.03 (m, 3H), 1.67 – 1.44 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 193.2, 173.3, 173.1, 150.5, 139.7, 138.7, 131.9, 130.7, 128.3, 127.9, 123.8, 123.7, 83.9, 52.8, 49.6, 36.6, 35.4, 29.4, 29.3, 28.2, 26.1. **IR** (film) *v*: 3086, 2982, 2952, 1700, 1648, 1573, 1431, 1372, 1334, 1245, 1156, 1133, 984, 842, 746 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{23}NO_5Na$ [M + Na^+] 380.1468. Found 380.1467.

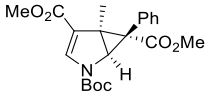
Dimethyl (1*S,5*S**,6*R**)-6-phenyl-2-(phenylsulfonyl)-2-azabicyclo[3.1.0]hex-3-ene-4,6-dicarboxylate (1h)**



Obtained according to the general procedure using 2.5 equiv of methyl 1-(phenylsulfonyl)pyrrole-3-carboxylate (**136**).

Yield: 216 mg (52%); colorless crystals; **m.p.** = 172.3-173.4 °C; $\mathbf{R_f}$ = 0.43 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$)*:* 7.89 – 7.83 (m, 2H), 7.73 – 7.66 (m, 1H), 7.63 – 7.56 (m, 2H), 7.26 – 7.19 (m, 3H), 7.15 – 7.08 (m, 2H), 6.85 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.62 (dd, *J* = 6.9, 1.6 Hz, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.49 (dd, *J* = 6.8, 0.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 173.2, 164.3, 139.1, 137.8, 134.2, 132.0, 129.9, 129.7, 128.4, 128.0, 127.3, 115.7, 53.1, 52.6, 51.9, 37.4, 27.7. **IR** (film) *v*: 2952, 1707, 1588, 1498, 1435, 1372, 1331, 1118, 1036, 984, 746 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{19}NO_6SNa$ [M + Na^+] 436.0825. Found 436.0828.

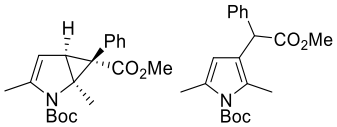
2-(*tert*-Butyl) 4,6-dimethyl (1*S,5*S**,6*S**)-5-methyl-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,4,6-tricarboxylate (1i)**



Obtained according to the general procedure using 2.5 equiv of methyl *N*-Boc-4-methylpyrrole-3-carboxylate (**137**).

Yield 267 mg (69%); colorless crystals; **m.p.** = 155.8-157.5 °C; $\mathbf{R_f}$ = 0.30 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.25 – 7.04 (m, 5H), 6.94 – 6.65 (m, 1H), 4.81 – 4.60 (m, 1H), 3.70 (s, 3H), 3.63 (s, 3H), 1.72 (s, 3H), 1.63 – 1.43 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 171.6, 164.9, 150.6, 139.4, 139.0, 132.6, 131.6, 128.2, 127.7, 116.4, 83.2, 52.7, 51.3, 41.5, 34.7, 28.2, 13.5. **IR** (film) *v*: 3097, 2989, 1689, 1588, 1435, 1398, 1323, 1230, 1156, 1126, 969, 928, 876, 705 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{26}NO_6$ [M + H^+] 388.1755. Found 388.1756.

2-(*tert*-Butyl) 6-methyl (1*S,5*S**,6*R**)-1,3-dimethyl-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (1j) and *tert*-butyl 3-(2-methoxy-2-oxo-1-phenylethyl)-2,5-dimethyl-1*H*-pyrrole-1-carboxylate (170)**

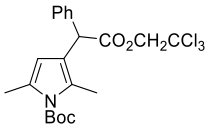


Obtained according to the general procedure using 3 equiv of *N*-Boc-2,5-dimethylpyrrole (**138**).

Characterized as a mixture (**1j**:**170** = 86:14). Yield: 175 mg (51%); yellowish oil; $\mathbf{R_f}$ = 0.36 (10% Et_2O/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ:* 7.38 – 7.08 (m, $5H_{1j}$ + $5H_{170}$), 5.94 (s, $1H_{170}$), 4.92 – 4.77 (m, $1H_{1j}$ + $1H_{170}$), 3.70 (s, $3H_{170}$), 3.58 (s, $3H_{1j}$), 3.12 – 2.97 (m, $1H_{1j}$), 2.34 (s, $3H_{170}$), 2.33 (s, $3H_{170}$), 1.90 (s, $3H_{1j}$), 1.65 – 1.40 (m, $12H_{1j}$+ $9H_{170}$). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ:* 173.3, 172.8, 152.0, 150.4, 142.6, 138.9, 133.0, 132.7, 130.4, 128.5, 128.2, 127.5, 127.3, 127.0, 126.9, 119.6, 111.2, 105.8, 83.4, 81.2, 56.9, 52.4, 52.2, 48.6, 40.1, 37.2, 28.4,

28.1, 17.0, 16.6, 15.7, 13.4. **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{26}NO_4$ [M + H^+] 344.1856. Found for **1j** 344.1866. Found for **170** 344.1861.

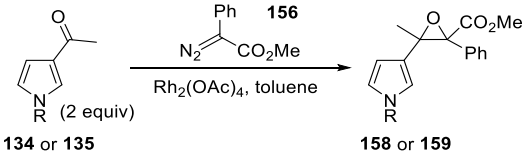
2-(*t*ert-Butyl) 6-(2,2,2-trichloroethyl) (1*S,5*S**,6*R**)-1,3-dimethyl-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (171)**



Obtained according to the general procedure using 3 equiv of *N*-Boc-2,5-dimethylpyrrole (**138**).

Yield: 225 mg (49%); yellowish oil; $\mathbf{R_f}$ = 0.35 (2% EtOAc/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ:* 7.41 – 7.19 (m, 5H), 6.03 – 6.01 (m, 1H), 5.03 (s, 1H), 4.85 – 4.73 (m, 2H), 2.38 (s, 6H), 1.60 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ:* 171.2, 150.5, 138.1, 130.6, 128.7, 128.3, 128.0, 127.4, 118.8, 111.2, 94.9, 83.6, 74.4, 48.5, 28.5, 28.2, 16.6, 13.5. **IR** (film) *v*: 2978, 2930, 1737, 1603, 1547, 1454, 1323, 1252, 1118, 1033, 775, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{25}Cl_3NO_4$ [M + H^+] 460.0844. Found 460.0845.

Synthesis of epoxides 158 and 159



To a mixture of pyrrole **134** or **135** (2 mmol, 2 equiv) and $Rh_2(OAc)_4$ (2 mg, 5 μmol, 1 mol%) in dry toluene (2 mL) was added by a syringe pump (addition rate: 1 drop/10 s) a solution of methyl phenyldiazoacetate (**156**; 176 mg, 1 mmol) in the same solvent (2 mL) at 25 °C under the atmosphere of nitrogen. After completion of the addition, the reaction mixture was stirred for an additional 30 min and subsequently filtered through a pad of Celite®. The residue obtained after the removal of the solvent was chromatographed on silica gel to give epoxide **158** or **159**.

Methyl 3-methyl-2-phenyl-3-(1-(phenylsulfonyl)-1*H*-pyrrol-3-yl)oxirane-2-carboxylate (158)

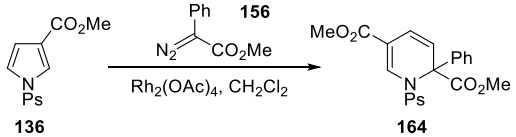
Yield: 189 mg (48%); colorless oil; $\mathbf{R_f}$ = 0.29 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.91 – 7.83 (m, 2H), 7.65 – 7.57 (m, 3H), 7.56 – 7.49 (m, 2H), 7.40 – 7.32 (m, 3H), 7.21 – 7.15 (m, 1H), 7.15 – 7.08 (m, 1H), 6.34 – 6.27 (m, 1H), 3.30 (s, 3H), 1.28 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 168.2, 138.9, 134.1, 133.4, 129.6, 128.7, 128.4, 128.1, 127.4, 127.0, 121.2, 118.5, 112.5, 71.3, 63.9, 52.0, 19.3. **IR** (film) *v*: 3004, 2952, 1737, 1446, 1372, 1174, 1059, 757, 727, 686 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{19}NO_5SNa$ [M + Na^+] 420.0876. Found 420.0882.

***tert*-Butyl 3-(3-(methoxycarbonyl)-2-methyl-3-phenyloxiran-2-yl)-1*H*-pyrrole-1-carboxylate (159)**

Yield: 169 mg (47%); colorless oil; $\mathbf{R_f}$ = 0.24 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.67 – 7.61 (m, 2H), 7.42 – 7.33 (m, 3H), 7.26 – 7.23 (m, 1H), 7.21 – 7.14 (m, 1H), 6.23 – 6.18 (m, 1H), 3.59 (s, 3H), 1.59 (s, 9H), 1.33 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 168.7,

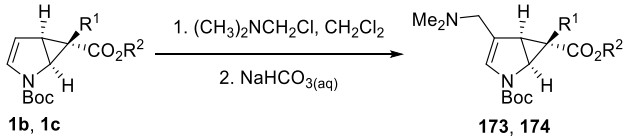
148.6, 133.9, 128.6, 128.4, 127.4, 126.2, 120.4, 118.1, 110.5, 84.1, 71.2, 64.4, 52.2, 28.1, 19.5. **IR** (film) *v*: 2982, 1737, 1450, 1252, 1152, 973, 772, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{24}NO_5$ [M + H^+] 358.1649. Found 358.1657.

Synthesis of dimethyl 2-phenyl-1-(phenylsulfonyl)-1,2-dihydropyridine-2,5-dicarboxylate (164)



To a solution of pyrrole **136** (531 mg, 2 mmol, 2 equiv) and $Rh_2(OAc)_4$ (2 mg, 5 µmol, 1 mol%) in dry CH_2Cl_2 (2 mL) was added by a syringe pump (addition rate: 1 drop/10 s) a solution of methyl phenyldiazoacetate (**156**; 176 mg, 1 mmol) in the same solvent (2 mL) at 25 °C under the atmosphere of nitrogen. After completion of the addition, the reaction mixture was stirred for an additional 30 min and subsequently filtered through a pad of Celite®. The residue obtained after the removal of the solvent was chromatographed on silica gel using EtOAc/PE to give compound **164** (100 mg, 24%) as a yellow oil. $\mathbf{R_f}$ = 0.35 (10% acetone/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ:* 8.02 (t, *J* = 1.1 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.24 – 7.06 (m, 5H), 7.04 – 6.93 (m, 2H), 6.49 (dd, *J* = 9.9, 1.2 Hz, 1H), 5.34 (dd, *J* = 9.9, 0.9 Hz, 1H), 3.96 (s, 3H), 3.80 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ:* 169.4, 165.4, 139.5, 138.4, 135.5, 132.9, 130.7, 128.8, 128.4, 127.7, 126.6, 122.8, 118.8, 104.7, 70.9, 53.6, 51.9. **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{20}NO_6S$ [M + H^+] 414.1006. Found 414.1007.

Aminomethylenetion of enecarbamates 1b and 1c with Böhme′s salt - preparation of compounds 173 and 174



To an intensively stirred solution of cyclopropanated pyrrole **1b** or **1c** (2.5 mmol) in dry CH_2Cl_2 (10 mL) was added *N*,*N*-dimethylmethyleneiminium chloride (**172**, Böhme′s salt; 702 mg, 7.5 mmol, 3 equiv) under an atmosphere of nitrogen at 25 °C. The reaction was conducted at the same temperature for 16 h and then quenched with a saturated solution of $NaHCO_3$ (10 mL). After the separation of the phases, the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo* yielding compound **173** or **174** as a white solid.

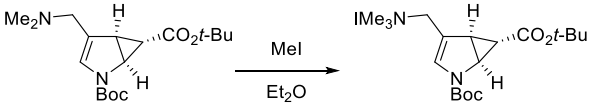
Di-*tert*-butyl (1*S,5*R**,6*S**)-4-((dimethylamino)methyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (173)**

Yield: 846 mg, *obtained quantitatively*; white solid; **m.p.** = 78.5-80.5 °C; $\mathbf{R_f}$ = 0.36 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 6.54 – 6.21 (m, 1H), 4.49 – 4.01 (m, 1H), 3.13 – 2.89 (m, 2H), 2.84 – 2.61 (m, 1H), 2.21 (s, 6H), 1.49 (s, 9H), 1.42 (s, 9H), 0.98 – 0.85 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 172.32, 172.01, 151.47, 151.16, 126.79, 126.41, 122.68, 81.60, 80.89, 57.21, 45.51, 44.75, 44.39, 32.62, 31.79, 28.40, 28.29, 24.27, 24.18. **IR** (film) *v*: 3123, 2974, 2933, 2810, 2758, 1700, 1413, 1364, 1297, 1152, 1014, 831, 760 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{18}H_{31}N_2O_4$ [M + H^+] 339.2278. Found 339.2274.

2-(*tert*-Butyl) 6-methyl (1*S,5*S**,6*R**)-4-((dimethylamino)methyl)-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (174)**

Yield: 931 mg, *obtained quantitatively*; white solid; **m.p.** = 95.6-97.2 °C; $\mathbf{R_f}$ = 0.19 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.36 – 7.09 (m, 5H), 6.04 (s, 0.4H), 5.88 (s, 0.6H), 4.72 (dd, *J* = 6.8, 1.2 Hz, 0.6H), 4.62 (dd, *J* = 6.8, 1.2 Hz, 0.4H), 3.67 – 3.57 (m, 3H), 3.42 – 3.27 (m, 1H), 3.23 – 3.08 (m, 1H), 2.80 – 2.67 (m, 1H), 2.22 (s, 6H), 1.61 (s, 3.6H), 1.47 (s, 5.4H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 174.0, 173.8, 151.5, 151.3, 132.1, 131.9, 131.5, 131.3, 128.1, 128.0, 127.7, 127.5, 127.5, 119.7, 119.5, 81.9, 81.6, 57.5, 57.4, 52.6, 52.6, 49.6, 49.4, 45.7, 45.6, 40.4, 39.3, 30.6, 30.2, 28.5, 28.3. **IR** (film) *v*: 3116, 2986, 2766, 1703, 1402, 1349, 1245, 1159, 1025, 984, 954, 760, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{28}N_2O_4Na$ [M + Na^+] 395.1941. Found 395.1946.

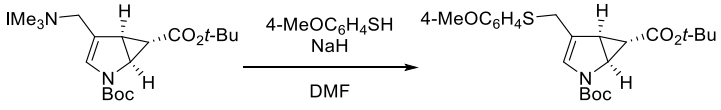
Preparation of 1-((1*S,5*R**,6*S**)-2,6-bis(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hex-3-en-4-yl)-*N*,*N*,*N*-trimethylmethanaminium iodide (175)**



173 **175**

Compound **173** (855 mg) was dissolved in dry Et_2O (10 mL) and MeI (1.08 g, 476 μL, 7.58 mmol, 3 equiv) was added under the nitrogen atmosphere at 25 °C. The reaction mixture was intensively stirred at the same temperature for 12 h. Afterwards, the solid formed was filtered off, washed with dry Et_2O, and dried under vacuum to give salt **175** (1.21 g, *quant*.) as colorless crystals. **M.p.** = 151.0-152.9 °C; $\mathbf{R_f}$ = 0.21 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.03 (s, 1H), 4.69 – 4.05 (m, 3H), 3.36 – 3.22 (m, 9H), 2.88 – 2.74 (m, 1H), 1.36 (s, 9H), 1.28 (s, 9H), 0.83 – 0.69 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 170.46, 149.94, 136.29, 109.87, 109.54, 82.94, 81.52, 64.21, 52.89, 45.34, 33.32, 32.57, 27.86, 22.89. **IR** (film) *v*: 2997, 2933, 1715, 1618, 1476, 1413, 1364, 1293, 1230, 1156, 1029, 954, 872, 757 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{33}N_2O_4$ [M^+] 353.2435. Found 353.2436.

Preparation of di-*tert*-butyl (1*S,5*R**,6*S**)-4-(((4-methoxyphenyl)thio)methyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (176)**

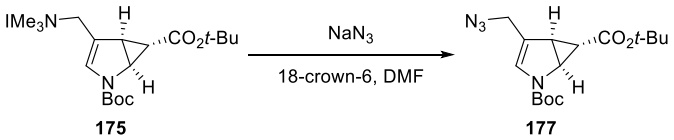


175 **176**

A suspension of NaH (31 mg of 60% dispersion in mineral oil, 0.779 mmol, 1.3 equiv) in dry DMF (3 mL) was cooled to 0 °C, and 4-methoxythiophenol (134 mg, 118 μL, 0.959 mmol, 1.6 equiv) was added. The resulting mixture was stirred at the same temperature for 30 min. Thereafter, a solution of salt **175** (288 mg, 0.600 mmol) in DMF (2 mL) was slowly added, the cooling bath was removed, and the stirring was continued for 16 h. The reaction was then quenched with saturated solution of NH_4Cl, poured into water, followed by extraction with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. Purification of the residue obtained after the removal of the solvents gave compound **176** (197 mg, 76%) as colorless crystals. **M.p.** = 147.0-149.0 °C; $\mathbf{R_f}$ = 0.39 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.40 – 7.28 (m, 2H), 6.93 – 6.70 (m, 2H), 6.38 – 6.00 (m, 1H), 4.38 – 4.10 (m, 1H),

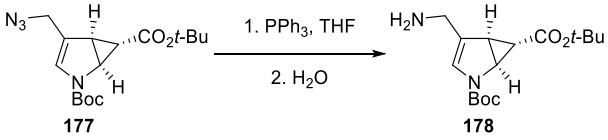
3.79 (s, 3H), 3.70 – 3.50 (m, 2H), 2.83 – 2.62 (m, 1H), 1.53 – 1.35 (m, 18H), 0.91 – 0.76 (m, 1H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 172.32, 171.95, 159.43, 151.22, 151.03, 134.58, 134.18, 126.24, 126.06, 125.77, 121.22, 121.10, 114.65, 81.68, 80.94, 55.41, 44.42, 44.15, 35.07, 34.97, 32.52, 31.60, 28.36, 28.32, 24.28 (*signal doubling due to rotamers*). **IR** (film) *v*: 3105, 2967, 1700, 1592, 1495, 1435, 1390, 1327, 1230, 1152, 1059, 980, 928, 746, 708 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{35}N_2O_5S$ [M + NH_4^+] 451.2261. Found 451.2262.

Preparation of di-*tert*-butyl (1*S,5*R**,6*S**)-4-(azidomethyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (177)**



A flask equipped with a magnetic stirring bar was charged with salt **175** (829 mg, 1.73 mmol), NaN_3 (898 mg, 13.81 mmol, 8 equiv), 18-crown-6 (593 mg, 2.24 mmol, 1.3 equiv), molecular sieves 3Å, then flushed with nitrogen followed by addition of dry DMF (12 mL). The reaction mixture was heated to 100 °C for 16 h. At the end of this time, the solution was diluted with EtOAc (100 mL), filtered, washed with brine (3 x 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. Removal of the solvents under reduced pressure and subsequent column chromatography of the obtained residue yielded product **177** (543 mg, 94%) as colorless crystals. **M.p.** = 95.5-97.4 °C; $\mathbf{R_f}$ = 0.26 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 6.78 – 6.32 (m, 1H), 4.55 – 4.12 (m, 1H), 4.04 – 3.84 (m, 2H), 2.89 – 2.54 (m, 1H), 1.51 (s, 9H), 1.44 (s, 9H), 1.06 – 0.93 (m, 1H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 172.02, 171.70, 151.20, 150.95, 128.40, 128.00, 118.78, 82.21, 81.25, 49.01, 44.66, 44.39, 31.87, 30.89, 28.36, 28.27, 23.65 (*signal doubling due to rotamers*). **IR** (film) *v*: 3131, 2978, 2937, 2095, 1696, 1633, 1416, 1364, 1252, 1148, 1021, 835, 760 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{16}H_{24}N_4O_4Na$ [M + Na^+] 359.1690. Found 359.1689.

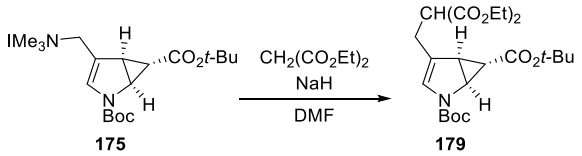
Preparation of di-*tert*-butyl (1*S,5*R**,6*S**)-4-(aminomethyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (178)**



A solution of azide **177** (585 mg, 1.74 mmol) and PPh_3 (912 mg, 3.48 mmol, 2 equiv) in THF (8 mL) was stirred at 25 °C for 3 h. Thereafter, water (0.5 mL) was added, and the stirring was continued for 16 h. The post-reaction mixture was then diluted with EtOAc, poured into water, and the phases were separated. The aqueous layer was washed with an additional portion of EtOAc. After the combined organic extracts were dried over anhydrous Na_2SO_4, the solvent was removed, and the residue was subjected to column chromatography eluting with MeOH/CH_2Cl_2 to furnish amine **178** as a waxy solid (504 mg, 93%). $\mathbf{R_f}$ = 0.35 (10% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, methanol-d_4) *δ:* 6.54 – 6.32 (m, 1H), 4.31 – 4.09 (m, 1H), 3.42 (s, 2H), 2.88 – 2.69 (m, 1H), 1.51 (s, 9H), 1.46 (s, 9H), 1.03 – 0.94 (m, 1H). **^{13}C NMR** (101 MHz, methanol-d_4) *δ:* 173.6, 152.7, 127.3, 125.5, 82.9, 82.8, 82.1, 45.3, 45.0, 39.8, 32.9, 32.0, 28.5, 28.4, 25.0. **IR** (film) *v*: 2978, 2930, 1700, 1633, 1476, 1409, 1368, 1297, 1141,

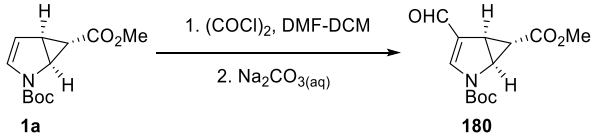
1111, 1021, 947, 831, 760 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{16}H_{26}N_2O_4Na$ [M + Na^+] 333.1785. Found 333.1782.

Synthesis of di-*tert*-butyl (1*S,5*R**,6*S**)-4-(3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (179)**



A mixture of NaH (26 mg of 60% dispersion in mineral oil, 0.649 mmol, 1.3 equiv) and 18-crown-6 (172 mg, 0.649 mmol, 1.3 equiv) in dry DMF (4 mL) was cooled to 0 °C, and diethylmalonate (112 mg, 107 µL, 0.699 mmol, 1.4 equiv) was added. The resulting solution was stirred at the same temperature for 30 min. Thereafter, salt **175** (240 mg, 0.500 mmol) dissolved in DMF (2 mL) was slowly added, the cooling bath was removed, and the reaction vessel was placed in an oil bath preheated to 90 °C. The stirring was continued for 16 h. The reaction mixture was then cooled down to ambient temperature, diluted with EtOAc (80 mL), poured into water (150 mL), and the phases were separated. The aqueous one was washed with two additional portions of EtOAc (2 x 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Column chromatography of the resulting residue yielded compound **179** together with an undefined impurity as a colorless oil. The yield was calculated based on the NMR spectrum (197 mg, 76%). $\mathbf{R_f}$ = 0.21 (20% Et_2O/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 6.46 – 6.04 (m, 1H), 4.36 – 4.14 (m, 5H), 3.61 – 3.51 (m, 1H), 2.86 – 2.72 (m, 2H), 2.65 – 2.56 (m, 1H), 1.50 – 1.40 (m, 18H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.87 – 0.82 (m, 1H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 172.0, 168.8, 168.7, 151.1, 125.7, 120.9, 81.7, 81.0, 61.8, 61.7, 61.7, 51.3, 49.6, 44.5, 44.1, 31.9, 28.4, 28.3, 27.7, 24.1, 14.2, 14.2 (*signal doubling due to rotamers*). **IR** (film) *v*: 2982, 1707, 1405, 1368, 1297, 1141, 1029, 947, 835, 760 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{36}NO_8$ [M + H^+] 454.2435. Found 454.2436.

Preparation of 2-(*tert*-butyl) 6-methyl (1*S,5*R**,6*S**)-4-formyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (180)**[164]

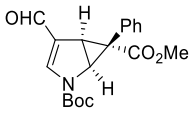


Oxalyl chloride (1.02 g, 8.02 mmol, 1.2 equiv, 688 µL) was introduced dropwise to a vigorously stirred mixture of DMF (13 mL) and CH_2Cl_2 (52 mL) at 0 °C under the atmosphere of nitrogen. The stirring was continued at the same temperature for 15 min before a solution of bicycle **1a** (1.6 g; 6.68 mmol) in CH_2Cl_2 (13 mL) was added. The mixture was allowed to warm to ambient temperature and then left for 2 h. After that time, the reaction was quenched with saturated Na_2CO_3 solution, stirred for 15 min, followed by addition of water (250 mL) and CH_2Cl_2 (50 mL). The phases were separated and the aqueous one was extracted with an additional portion of CH_2Cl_2 (100 mL). The combined organic layers were then washed three times with water (3 x 150 mL). After drying over anhydrous Na_2SO_4, the solvent was removed under diminished pressure. Column chromatography of the obtained residue eluting with EtOAc/PE delivered compound **180** as a colorless oil (1.29 g, 72%). $\mathbf{R_f}$ = 0.12 (30% EtOAc/PE); **^{1}H NMR** (400

MHz, $CDCl_3$) *δ:* 9.50 (s, 1H), 7.35 (br s, 1H), 4.40 (br s, 1H), 3.64 (s, 3H), 3.13 (dd, *J* = 6.8, 2.9 Hz, 1H), 1.50 (s, 9H), 1.03 – 1.00 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 184.6, 172.1, 149.8, 144.2, 126.7, 84.3, 52.2, 44.8, 28.1, 26.7, 21.8. **IR** (film) *ν*: 2982, 1718, 1662, 1580, 1409, 1353, 1279, 1208, 1141, 1029, 980, 913, 835, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{13}H_{17}NO_5Na$ [M + Na^+] 290.0999. Found 290.1005.

The analytical data are in good accordance with those reported in the literature.[164]

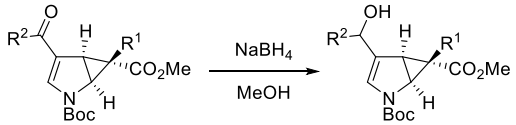
2-(*tert*-Butyl) 6-methyl (1*S,5*S**,6*R**)-4-formyl-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (181)**



Obtained analogously to compound **180** using bicycle **1c** (1.4 g, 4.43 mmol), oxalyl chloride (675 mg, 5.32 mmol, 1.2 equiv, 456 µL), DMF (9 mL), and CH_2Cl_2 (45 mL).

Yield: 1.4 g (92%); colorless crystals; **m.p.** = 183.0-184.6 °C; **R_f** = 0.30 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 9.39 (s, 1H), 7.25 – 7.17 (m, 3H), 7.12 – 6.73 (m, 3H), 4.85 – 4.56 (m, 1H), 3.69 – 3.53 (m, 4H), 1.74 – 1.31 (m, 9H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 185.2, 172.9, 150.1, 145.2, 144.6, 131.8, 130.3, 128.4, 128.0, 124.9, 84.3, 52.9, 49.8, 34.8, 33.7, 29.5, 28.1 (*signal doubling due to rotamers*). **IR** (film) *ν*: 2986, 2956, 2825, 1707, 1666, 1580, 1498, 1413, 1338, 1249, 1211, 1148, 977, 842, 746, 708 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{21}NO_5Na$ [M + Na^+] 366.1312. Found 366.1312.

Preparation of alcohols 182, 183 and 195



180, **181** or **1g** → **182**, **183** or **195**

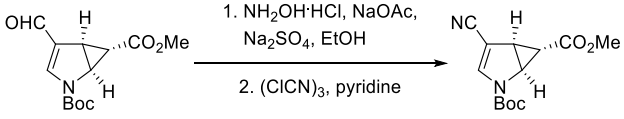
Compound **180**, **181**, or **1g** (2 mmol) was dissolved in dry methanol (3 mL) and $NaBH_4$ (114 mg, 3 mmol, 1.5 equiv) was added in one portion at 0 °C. The reaction was allowed to warm to 25 °C, and the stirring was continued until complete consumption of the starting material (TLC monitoring). Next, saturated solution of NH_4Cl (3 mL) was slowly added, and the mixture was poured into water (50 mL). The product was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel to furnish compound **182**, **183**, or **195**.

2-(*tert*-Butyl) 6-methyl (1*S,5*R**,6*S**)-4-(hydroxymethyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (182).** Yield: 445 mg (83%); colorless oil; **R_f** (30% acetone/PE) 0.39; **^{1}H NMR** (400 MHz, methanol-d_4) *δ:* 6.59 – 6.40 (m, 1H), 4.71 (s, 1H), 4.37 – 4.13 (m, 3H), 3.69 (s, 3H), 2.88 – 2.79 (m, 1H), 1.51 (s, 9H), 1.13 – 1.08 (m, 1H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, methanol-d_4) *δ:* 174.6, 152.4, 126.6, 126.2, 82.9, 58.8, 52.4, 45.3, 45.2, 33.1, 32.1, 28.5, 23.7 (*signal doubling due to rotamers*). **HRMS** (ESI-TOF) m/z calcd for $C_{13}H_{19}NO_5Na$ [M + Na^+] 292.1153. Found 292.1155.

2-(*tert*-Butyl) 6-methyl (1*S,5*S**,6*R**)-4-(hydroxymethyl)-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (183).** Yield: 616 mg (89%); colorless crystals; **m.p.** = 154.4-156.2 °C; $\mathbf{R_f}$ = 0.23 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.32 – 7.13 (m, 5H), 6.14 – 5.93 (m, 1H), 4.77 – 4.58 (m, 1H), 4.27 – 4.14 (m, 2H), 3.66 – 3.59 (m, 3H), 3.41 – 3.34 (m, 1H), 1.87 – 1.71 (m, 1H), 1.65 – 1.42 (m, 9H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.0, 173.8, 151.5, 151.3, 132.1, 131.9, 131.4, 131.2, 128.2, 128.1, 127.7, 127.6, 127.3, 127.0, 121.5, 121.5, 82.2, 81.9, 59.4, 59.3, 52.8, 52.7, 49.7, 49.6, 40.1, 38.9, 30.1, 29.8, 28.4, 28.3 (*signal doubling due to rotamers*). **IR** (film) *v*: 3504, 2982, 2937, 2878, 1707, 1681, 1416, 1390, 1245, 1152, 1033, 977, 846, 708 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{23}NO_5Na$ [M + Na$^+$] 368.1468. Found 368.1470.

2-(*tert*-Butyl) 6-methyl 4-(1-hydroxyethyl)-6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (195). Yield: 670 mg (93%); colorless crystals; **m.p.** = 141.1-142.6 °C; $\mathbf{R_f}$ = 0.23 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.30 – 7.14 (m, 5H), 6.19 – 5.82 (m, 1H), 4.75 – 4.55 (m, 1H), 4.50 – 4.37 (m, 1H), 3.65 – 3.55 (m, 3H), 3.49 – 3.25 (m, 1H), 1.62 – 1.41 (m, 9H), 1.39 – 1.27 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 193.2, 173.3, 173.1, 150.5, 139.7, 138.7, 131.9, 130.7, 128.3, 127.9, 123.8, 123.7, 83.9, 52.8, 49.6, 36.6, 35.4, 29.4, 29.3, 28.2, 26.1. **IR** (film) *v*: 3504, 2982, 2937, 2878, 1707, 1681, 1416, 1390, 1245, 1152, 1033, 977, 846, 708 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{25}NO_5Na$ [M + Na$^+$] 382.1625. Found 382.1621.

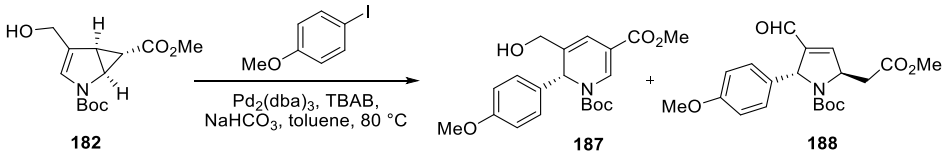
Preparation of 2-(*tert*-butyl) 6-methyl (1*S,5*R**,6*S**)-4-cyano-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (186)**



180 **186**

To a solution of aldehyde **180** (466 mg, 1.65 mmol) in EtOH (20 mL) were added hydroxylamine hydrochloride (172 mg, 2.47 mmol, 1.5 equiv), NaOAc (203 mg, 2.47 mmol, 1.5 equiv), and solid Na_2SO_4 (excess) at 25 °C. After stirring for 2 h at the same temperature, the reaction mixture was diluted with EtOAc (150 mL) and washed with brine (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4. Next, the residue obtained after the removal of the solvents was taken up into pyridine (30 mL), cyanuric chloride (1.22 g, 6.6 mmol, 4 equiv) was added, and the resulting solution was heated to 60 °C for 16 h. After that time, the mixture was cooled to ambient temperature, diluted with toluene (200 mL) followed by washing with brine (2 x 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated. Purification of the crude product by column chromatography gave the title compound as colorless crystals (298 mg, 68%). **M.p.** = 117.2-119.0 °C; $\mathbf{R_f}$ = 0.64 (30% acetone/PE); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.31 – 7.07 (m, 1H), 4.63 – 4.29 (m, 1H), 3.72 (s, 3H), 3.03 (dd, J = 7.0, 2.7 Hz, 1H), 1.52 (s, 9H), 1.18 – 1.13 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 171.86, 149.46, 141.87, 115.18, 93.08, 84.51, 52.50, 44.39, 31.82, 30.74, 28.16, 20.91. **IR** (film) *v*: 3120, 2986, 2952, 2214, 1715, 1588, 1435, 1398, 1282, 1182, 1148, 1029, 984, 846, 764 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{13}H_{16}N_2O_4Na$ [M + Na$^+$] 287.1002. Found 287.1002.

Arylation of enecarbamate 182 with 4-methoxyiodobenzene - synthesis of compounds 187 and 188

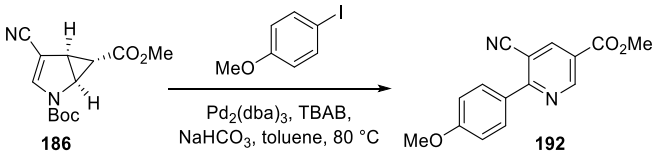


A flask equipped with a magnetic stirring bar was charged with cyclopropanated pyrrole **182** (385 mg, 1.43 mmol), $NaHCO_3$ (300 mg, 3.57 mmol, 2.5 equiv), TBAB (922 mg, 2.86 mmol, 2 equiv), 4-methoxyiodobenzene (502 mg, 2.14 mmol, 1.5 equiv), and Pd_2dba_3 (65 mg, 71 µmol, 5 mol%), flushed with nitrogen followed by addition of dry toluene (15 mL). The mixture was stirred at 25 ℃ for 5 min, and then the reaction vessel was placed in an oil bath preheated to 80 ℃. The coupling was conducted until TLC indicated the complete conversion of the cyclopropane. Thereafter, the mixture was cooled down to ambient temperature, diluted with EtOAc, and filtered through a pad of Celite®. The residue obtained after the removal of the solvents was chromatographed on silica gel eluting with an EtOAc/PE mixture to provide compounds **187** and **188**.

1-(*tert*-Butyl) 3-methyl 5-(hydroxymethyl)-6-(4-methoxyphenyl)pyridine-1,3(6*H*)-dicarboxylate (187). Yield: 113 mg (21%); colorless oil; $\mathbf{R_f}$ = 0.27 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.92 (br s, 1H), 7.36 – 7.23 (m, 2H), 6.84 – 6.78 (m, 2H), 6.54 (br s, 1H), 5.76 (br s, 1H), 4.09 – 3.93 (m, 2H), 3.80 – 3.75 (m, 6H), 1.48 – 1.40 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.4, 159.7, 152.0, 135.2, 132.9, 128.9, 116.0, 114.0, 107.1, 83.6, 63.8, 57.1, 55.4, 51.6, 28.2 (*one quaternary carbon could not be detected*). **IR** (film) *ν*: 3437, 2978, 1703, 1607, 1510, 1238, 1148, 1033, 992, 760 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{26}NO_6$ [M + H^+] 376.1755. Found 376.1759.

***tert*-Butyl (2*R**,5*R**)-3-formyl-5-(2-methoxy-2-oxoethyl)-2-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (188).** Yield: 280 mg (52%); colorless crystals; **m.p.** = 129.9-131.8 ℃; $\mathbf{R_f}$ = 0.36 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, DMF-d_7, 110 ℃) *δ:* 9.67 (s, 1H), 7.26 – 7.18 (m, 2H), 7.18 – 7.10 (m, 1H), 6.96 – 6.85 (m, 2H), 5.59 (d, *J* = 5.0 Hz, 1H), 5.35 – 5.25 (m, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.25 (dd, *J* = 15.5, 3.9 Hz, 1H), 2.87 (dd, *J* = 15.5, 8.1 Hz, 1H), 1.39 – 1.14 (m, 9H). **^{13}C NMR** (101 MHz, DMF-d_7; *mixture of rotamers*) *δ:* 189.1, 188.9, 171.9, 171.7, 160.2, 160.0, 154.1, 153.0, 148.0, 147.5, 145.7, 145.3, 134.9, 133.9, 129.6, 129.5, 114.4, 114.3, 80.8, 80.3, 66.9, 62.9, 62.6, 56.0, 55.9, 52.3, 38.7, 37.4, 28.8, 28.5. **IR** (film) *ν*: 2982, 2840, 1718, 1677, 1510, 1461, 1387, 1301, 1245, 1200, 1152, 1033, 865, 816 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{25}NO_6Na$ [M + Na^+] 398.1574. Found 398.1575.

Methyl 5-cyano-6-(4-methoxyphenyl)nicotinate (192)

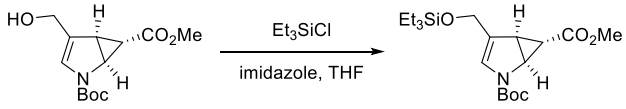


Compound **192** was obtained analogously to derivatives **187** and **188** from nitrile **186** (125 mg, 0.473 mmol).

Yield: 79 mg (62%); colorless crystals; **m.p.** = 123.2-125.1 ℃; $\mathbf{R_f}$ = 0.36 (5% Et_2O/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 9.35 (d, *J* = 2.1 Hz, 1H), 8.61 (d, *J* = 2.1 Hz, 1H), 8.08 – 8.00 (m,

2H), 7.09 – 7.02 (m, 2H), 4.00 (s, 3H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 164.2, 163.4, 162.3, 153.4, 143.4, 131.1, 128.9, 123.4, 117.5, 114.5, 106.4, 55.6, 53.0. **IR** (film) *v*: 3086, 2956, 2840, 2229, 1726, 1588, 1521, 1394, 1297, 1252, 1227, 1182, 1148, 1029, 995, 842, 775 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{15}H_{13}N_2O_3$ [M + H^+] 269.0921. Found 269.0924.

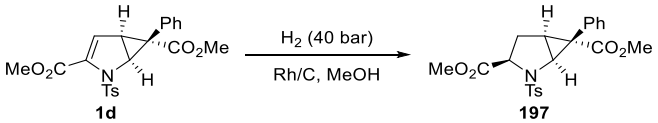
Synthesis of 2-(*tert*-butyl) 6-methyl (1*S,5*R**,6*S**)-4-(((triethylsilyl)oxy)methyl)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (190)**



182 **190**

To a solution of alcohol **182** (776 mg, 2.88 mmol) and imidazole (294 mg, 4.32 mmol, 1.5 equiv) in dry DMF (15 mL) was added dropwise TESCl (608 mg, 4.03 mmol, 676 μL, 1.4 equiv) at 0 °C. The resulting mixture was stirred until complete disappearance of the starting material (TLC monitoring). Then, the reaction solution was poured into water (250 mL), diluted with EtOAc (100 mL), and the layers were separated. The aqueous phase was extracted with an additional portion of EtOAc (100 mL). The combined organic extracts were washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/PE to provide compound **190** as a colorless oil (899 mg, 81%). $\mathbf{R_f}$ = 0.29 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 6.63 – 6.17 (m, 1H), 4.61 – 4.03 (m, 3H), 3.70 – 3.63 (m, 3H), 2.82 – 2.73 (m, 1H), 1.52 – 1.45 (m, 9H), 1.08 – 1.00 (m, 1H), 0.99 – 0.89 (m, 9H), 0.66 – 0.51 (m, 6H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 173.6, 173.3, 151.4, 151.2, 125.2, 124.9, 81.7, 59.2, 51.9, 44.7, 44.6, 32.3, 31.1, 28.4, 23.0, 6.9, 6.8, 4.6 (*signal doubling due to rotamers*). **IR** (film) *v*: 2956, 1711, 1409, 1364, 1293, 1152, 980, 794, 727 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{33}NO_5SiNa$ [M + Na^+] 406.2020. Found 406.2023.

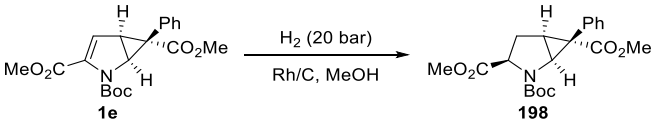
Preparation of dimethyl (1*S,3*R**,5*S**,6*R**)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hexane-3,6-dicarboxylate (197)**



1d **197**

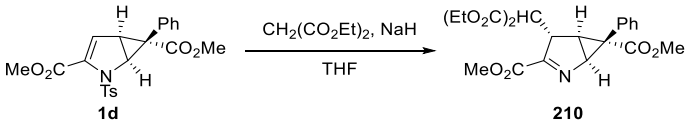
A mixture of bicycle **1d** (60 mg, 0.140 mmol) and Rh/C (3 mg, 5 wt%) in MeOH (3 mL) was intensively stirred under H_2 (40 bar) for 8 h. Next, the suspension was filtered through a short pad of Celite® and the solvent was removed. The residue was chromatographed on silica gel using an EtOAc/PE mixture to give compound **197** as a waxy solid (49 mg, 63%). $\mathbf{R_f}$ = 0.25 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.88 – 7.80 (m, 2H), 7.44-7.35 (m, 2H), 7.34-7.26 (m, 3H), 7.16 – 7.08 (m, 2H), 4.60 – 4.43 (m, 1H), 4.27 – 4.14 (m, 1H), 3.56 (s, 3H), 3.19 (s, 3H), 2.60 – 2.45 (m, 5H), 2.26 – 2.16 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 171.8, 170.0, 144.4, 135.1, 133.2, 130.0, 129.7, 128.3, 128.1, 128.0, 66.4, 53.4, 52.9, 52.3, 39.9, 30.6, 29.2, 21.8. **IR** (film) *v*: 3027, 2960, 2926, 1771, 1737, 1707, 1599, 1498, 1435, 1357, 1297, 1252, 1096, 1029, 954, 887, 820, 749, 671 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{23}NO_6SNa$ [M + Na^+] 452.1138. Found 452.1143.

2-(*tert*-Butyl) 3,6-dimethyl (1*S,3*R**,5*S**,6*R**)-6-phenyl-2-azabicyclo[3.1.0]hexane-2,3,6-tricarboxylate (198)**



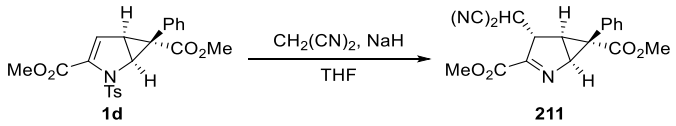
The title compound was obtained analogously to bicycle **197** from substrate **1e** (60 mg, 0.161 mmol) using 5 mg of Rh/C and 5 mL of MeOH. Hydrogen pressure was equal to 20 bars. Yield: 45 mg (75%); wax; $\mathbf{R_f}$ = 0.21 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.40 – 7.19 (m, 5H), 4.66 – 4.36 (m, 1H), 4.25 – 4.10 (m, 1H), 3.59 – 3.50 (m, 3H), 3.11 (s, 3H), 2.76 – 2.65 (m, 1H), 2.65 – 2.56 (m, 1H), 2.19 – 2.08 (m, 1H), 1.59 – 1.32 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 172.1, 171.8, 170.5, 169.9, 154.0, 153.9, 132.9, 130.7, 130.6, 128.3, 128.2, 127.9, 127.7, 81.0, 80.8, 63.8, 63.2, 52.7, 52.6, 52.1, 51.9, 51.8, 51.7, 41.4, 40.7, 30.6, 29.4, 29.2, 28.6, 28.1, 28.0. **IR** (film) *v*: 2967, 1722, 1692, 1439, 1398, 1368, 1230, 1133, 1036, 999, 854, 757, 705 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{26}NO_6$ [M + H$^+$] 376.1755. Found 376.1755.

Synthesis of dimethyl (1*S,4*S**,5*S**,6*R**)-4-(1,3-diethoxy-1,3-dioxopropan-2-yl)-6-phenyl-2-azabicyclo[3.1.0]hex-2-ene-3,6-dicarboxylate (210)**



Diethylmalonate (268 mg, 1.67 mmol, 2.8 equiv, 255 µL) was added dropwise to an intensively stirred suspension of NaH (62 mg of 60% dispersion in mineral oil, 1.55 mmol of NaH, 2.6 equiv) in dry THF (4 mL) at 0 °C. After stirring for 30 min at the same temperature, a solution of ester **1d** (255 mg, 0.597 mmol) in THF (2 mL) was added. The reaction vessel was removed from the cooling bath and left at 25 °C for 3 h. Thereafter, the reaction was quenched with saturated NH_4Cl solution, the resulting mixture was diluted with water (150 mL) and EtOAc (70 mL), and the phases were separated. The aqueous one was extracted with two additional portions of EtOAc (2 x 70 mL). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated, and the residue was subjected to column chromatography to furnish compound **210** as a yellowish oil (212 mg, 82%). $\mathbf{R_f}$ = 0.23 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.34 – 7.00 (m, 5H), 4.62 (dd, *J* = 4.6, 3.0 Hz, 1H), 4.31 – 4.10 (m, 4H), 4.10 (d, *J* = 4.1 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.27 (ddd, *J* = 4.1, 3.0, 1.3 Hz, 1H), 2.92 (dd, *J* = 4.6, 1.3 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 171.8, 167.9, 167.6, 167.2, 161.3, 133.0, 129.2, 128.4, 127.9, 62.1, 62.0, 61.8, 53.0, 52.8, 51.0, 50.5, 42.2, 34.9, 14.2, 14.1. **IR** (film) *v*: 2982, 2956, 1718, 1610, 1439, 1349, 1241, 1178, 1103, 1029, 854, 738, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{25}NO_8K$ [M + K$^+$] 470.1212. Found 470.1214.

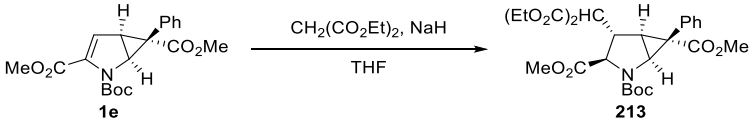
Dimethyl (1*S,4*S**,5*S**,6*R**)-4-(dicyanomethyl)-6-phenyl-2-azabicyclo[3.1.0]hex-2-ene-3,6-dicarboxylate (211)**



Obtained analogously to compound **210** from ester **1d** (100 mg, 0.234 mmol) using malononitrile (40 mg, 0.608 mmol, 2.6 equiv), NaH (22 mg of 60% dispersion in mineral oil; 0.538 mmol, 2.3 equiv), and dry THF (4 mL).

Yield: 91 mg (79%); yellow solid; **m.p.** = 145.6-147.6 °C; $\mathbf{R_f}$ = 0.33 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.36 – 7.25 (m, 3H), 7.20 – 6.92 (m, 2H), 4.96 (dd, *J* = 4.5, 2.9 Hz, 1H), 4.72 (d, *J* = 3.8 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.19 (td, *J* = 3.8, 2.9, 1.0 Hz, 1H), 3.01 (dd, *J* = 4.5, 1.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 170.6, 162.9, 160.9, 132.8, 128.8, 128.6, 127.9, 111.0, 110.0, 61.8, 53.5, 53.5, 51.3, 42.9, 32.9, 25.0. **IR** (film) *v*: 3064, 2967, 2919, 2259, 1715, 1614, 1498, 1443, 1353, 1256, 1197, 1100, 962, 850, 798, 708 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{18}H_{15}N_3O_4Na$ [M + Na^+] 360.0955. Found 360.0955.

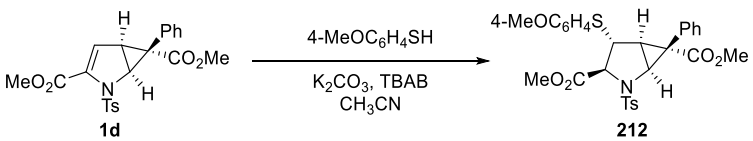
2-(*tert*-Butyl) 3,6-dimethyl (1*S,3*R**,4*S**,5*S**,6*R**)-4-(1,3-diethoxy-1,3-dioxopropan-2-yl)-6-phenyl-2-azabicyclo[3.1.0]hexane-2,3,6-tricarboxylate (213)**



Obtained analogously to compound **210** from ester **1e** (212 mg, 0.568 mmol) using diethylmalonate (236 mg, 1.48 mmol, 2.6 equiv, 225 µL), NaH (52 mg of 60% dispersion in mineral oil, 1.31 mmol, 2.3 equiv), and dry THF (5 mL).

Yield: 248 mg (82%); yellowish oil; $\mathbf{R_f}$ = 0.44 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.41 – 7.28 (m, 5H), 4.57 – 4.42 (m, 1H), 4.33 – 4.11 (m, 5H), 3.73 – 3.67 (m, 1H), 3.60 – 3.51 (m, 3H), 3.18 – 3.08 (m, 3H), 3.04 (ddd, *J* = 7.8, 6.5, 1.5 Hz, 1H), 2.59 – 2.53 (m, 1H), 1.56 – 1.34 (m, 9H), 1.33 – 1.26 (m, 6H) (*signal doubling due to rotamers*). **^{13}C NMR** (101 MHz, CD_3CN) *δ:* 172.3, 172.2, 170.5, 170.0, 168.7, 168.6, 168.5, 168.4, 154.4, 154.4, 133.9, 132.0, 129.8, 129.2, 128.7, 81.6, 81.6, 68.7, 68.4, 62.8, 62.7, 55.1, 55.0, 53.1, 52.5, 52.3, 52.3, 51.9, 43.4, 42.3, 42.1, 41.8, 34.6, 33.6, 28.6, 28.3, 14.4, 14.3 (*signal doubling due to rotamers*). **IR** (film) *v*: 2956, 2926, 1703, 1435, 1398, 1368, 1249, 1141, 1029, 969, 801, 705 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{27}H_{35}NO_{10}Na$ [M + Na^+] 556.2153. Found 556.2153.

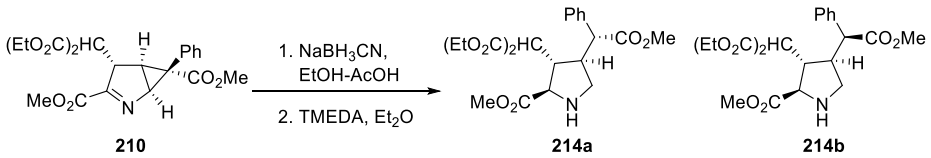
Synthesis of dimethyl (1*S,3*S**,4*R**,5*S**,6*R**)-4-((4-methoxyphenyl)thio)-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hexane-3,6-dicarboxylate (212)**



Ester **1d** (124 mg, 0.290 mmol) was added to a vigorously stirred mixture of 4-methoxythiophenol (61 mg, 0.435 mmol, 54 µL, 1.5 equiv), K_2CO_3 (48 mg, 0.348 mmol, 1.2 equiv), and TBAB (14 mg, 44 µmol, 0.15 equiv) in CH_3CN (4 mL) at 25 °C. The reaction was

conducted at the same temperature until complete consumption of the starting material (TLC monitoring, 6 h). Thereafter, the solids were filtered off, the filtrate was diluted with EtOAc (40 mL) and sequentially washed with 1M HCl (100 mL), water (100 mL), and finally brine (100 mL). Following drying of the organic layer over anhydrous Na_2SO_4, the solvents were removed under reduced pressure. Compound **212** was isolated by preparative TLC using EtOAc/PE mixture as a colorless oil (27 mg, 16%). $\mathbf{R_f}$ = 0.22 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.84 – 7.76 (m, 2H), 7.42 – 7.26 (m, 7H), 7.18 – 7.07 (m, 2H), 6.86 – 6.78 (m, 2H), 4.35 (d, *J* = 5.6 Hz, 1H), 4.19 (d, *J* = 7.3 Hz, 1H), 3.85 (dd, *J* = 5.6, 1.2 Hz, 1H), 3.81 (s, 3H), 3.55 (s, 3H), 3.17 (s, 3H), 2.59 (dd, *J* = 7.3, 1.1 Hz, 1H), 2.50 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 171.3, 168.2, 160.4, 144.5, 136.2, 134.7, 133.0, 130.0, 129.5, 128.5, 128.3, 128.2, 122.5, 115.0, 72.6, 55.5, 53.0 (2C overlapped), 52.5, 49.8, 39.8, 36.0, 21.8. **IR** (film) *v*: 2952, 2922, 1715, 1592, 1495, 1435, 1357, 1245, 1163, 1096, 1025, 962, 816, 701, 664 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{29}H_{29}NO_7S_2Na$ [M + Na^+] 590.1278. Found 590.1284.

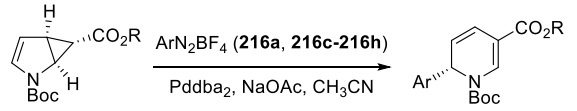
Synthesis of compounds 214



210 **214a** **214b**

To a solution of adduct **210** (50 mg, 0.115 mmol) in a 10:1 EtOH-AcOH mixture (3 mL) was added $NaBH_3CN$ (73 mg, 0.346 mmol, 3 equiv). The reaction was conducted for 2 h at 25 °C under nitrogen atmosphere. Thereafter, the process was quenched with aqueous NH_3 (32%), the mixture was poured into water (50 mL), and the organic materials were extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Next, the residue was dissolved in Et_2O (1.5 mL), followed by addition of TMEDA (13 mg, 0.115 mmol, 1 equiv, 17 µL). The resulting mixture was stirred for 1 h at 25 °C, and then the precipitate formed was filtered off. Column chromatography of the residue obtained after the removal of the solvents eluting with an EtOAc/PE system afforded compounds **214a** and **214b** as a ca 1:1 mixture (42 mg, 83%). Analytical sample of **214a** was obtained by preparative TLC (EtOAc/PE). Stereochemistry was assigned tentatively. Colorless oil; $\mathbf{R_f}$ = 0.52 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ*: 7.36 – 7.23 (m, 5H), 4.28 – 4.19 (m, 4H), 4.07 (d, *J* = 3.4 Hz, 1H), 3.87 – 3.83 (m, 1H), 3.74 (s, 3H), 3.68 – 3.60 (m, 4H), 2.96 – 2.74 (m, 3H), 2.63 (dd, *J* = 11.1, 5.7 Hz, 1H), 1.32 – 1.26 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.1, 173.7, 168.7, 168.7, 137.4, 128.9, 128.5, 127.9, 63.7, 61.9, 61.8, 55.3, 54.4, 52.6, 52.3, 50.5, 46.8, 46.3, 14.2, 14.2. **IR** (film) *v*: 2982, 2956, 1726, 1435, 1372, 1200, 1156, 1029, 913, 861, 731 cm^{-1}. **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{30}NO_8$ [M + H^+] 436.1966. Found 436.1971. *For **214b**:* $\mathbf{R_f}$ = 0.48 (50% EtOAc/PE); **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{30}NO_8$ [M + H^+] 436.1966. Found 436.1971.

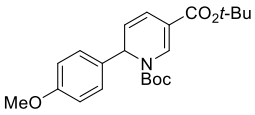
Arylation of cyclopropanated pyrroles with diazonium salts 216a, 216c-216h: synthesis of 1,2-dihydropyridines 18a, 18a$^{t\text{-Bu}}$, 18c-18h



1a or **1b** — **18a**, **18a$^{t\text{-Bu}}$**, **18c-18h**

A flask equipped with a magnetic stirring bar was charged with cyclopropanated pyrrole **1a** or **1b** (0.5 mmol) and NaOAc (123 mg, 1.5 mmol, 3 equiv), flushed with nitrogen, followed by addition of dry CH_3CN (3 mL). When the starting material had completely dissolved, to the resulting solution was added in one portion at 25 °C a mixture of $Pddba_2$ (29 mg, 50 µmol, 10 mol%) and diazonium tetrafluoroborate **216** (0.525 mmol, 1.05 equiv). The reaction was conducted at the same temperature until TLC indicated complete conversion of the cyclopropane. After dilution with EtOAc, the mixture was filtered through a pad of Celite®, and the solvent was removed. The product was purified by column chromatography eluting with an EtOAc/PE, acetone/PE, or Et_2O/PE mixture.

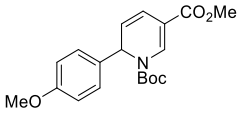
Di-*tert*-butyl 6-(4-methoxyphenyl)pyridine-1,3(6*H*)-dicarboxylate (18a$^{t\text{-Bu}}$)



Yield: 180 mg (93%); yellowish oil; $\mathbf{R_f}$ = 0.39 (7% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.89 (br s, 1H), 7.34 – 7.21 (m, 2H), 6.86 – 6.80 (m, 2H), 6.42 (d, *J* = 9.9 Hz, 1H), 5.69 (br s, 1H), 5.55 (dd, J = 9.9, 5.3 Hz, 1H), 3.77 (s, 3H), 1.53 – 1.37 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.2, 159.4, 152.3, 134.7, 134.3, 128.2, 121.5, 118.8, 113.9, 108.7, 83.1, 80.2, 57.1, 55.3, 28.4, 28.1. **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{29}NO_5Na$ [M + Na^+] 410.1938. Found 410.1938.

The spectral data are in good accordance with those reported in the literature.[12]

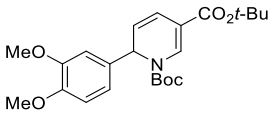
1-(*tert*-Butyl) 3-methyl 6-(4-methoxyphenyl)pyridine-1,3(6*H*)-dicarboxylate (18a)



Yield: *from 120 mg (0.5 mmol) of **1a**:* 147 mg (85%), *from 2.5g (10.45 mmol) of **1a**:* 2.92 g (81%); yellowish oil; $\mathbf{R_f}$ = 0.34 (10% acetone/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.97 (br s, 1H), 7.36 – 7.18 (m, 2H), 6.88 – 6.78 (m, 2H), 6.47 (d, *J* = 9.9 Hz, 1H), 5.72 (br s, 1H), 5.58 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.79 – 3.75 (m, 6H), 1.43 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.3, 159.5, 152.1, 135.5, 134.2, 128.2, 121.7, 118.5, 113.9, 107.2, 83.3, 56.6, 55.3, 51.5, 28.0. **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{23}NO_5Na$ [M + Na^+] 368.1468. Found 368.1465.

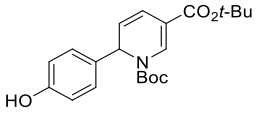
The spectral data are in good accordance with those reported in the literature.[12]

Di-*tert*-butyl 6-(3,4-dimethoxyphenyl)pyridine-1,3(6*H*)-dicarboxylate (18c)



Yield: 151 mg (72%); yellowish oil; $\mathbf{R_f}$ = 0.21 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.87 (br s, 1H), 6.97 – 6.75 (m, 3H), 6.43 (d, *J* = 9.9 Hz, 1H), 5.71 (br s, 1H), 5.56 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.86 – 3.79 (m, 6H), 1.54 – 1.36 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.1, 152.3, 149.0, 148.8, 134.7 (2C overlapped), 121.2, 119.3, 119.1, 111.1, 110.2, 108.8, 83.1, 80.2, 56.8, 56.0, 55.9, 28.3, 28.0. **IR** (film) *v*: 2978, 2937, 1700, 1640, 1592, 1513, 1461, 1368, 1238, 1137, 1029, 850, 734 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{31}NO_6Na$ [M + Na^+] 440.2044. Found 440.2043.

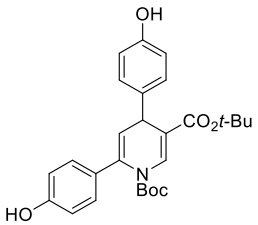
Di-*tert*-butyl 6-(4-hydroxyphenyl)pyridine-1,3(6*H*)-dicarboxylate (18d)



Arylation was performed under slightly modified conditions, i.e. employing 0.5 mmol of 4-hydroxybenzenediazonium tetrafluoroborate (**216d**) and 0.75 mmol (1.5 equiv) of monocyclopropanated pyrrole **1b**. Yield based on tetrafluoroborate **216d**.

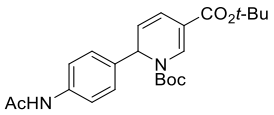
Yield: 187 mg, *obtained quantitatively*; yellowish oil; $\mathbf{R_f}$ = 0.40 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.93 (br s, 1H), 7.31 (br s, 1H), 7.22 – 7.10 (m, 2H), 6.81 – 6.70 (m, 2H), 6.40 (d, *J* = 9.9 Hz, 1H), 5.66 (br s, 1H), 5.54 (dd, *J* = 9.9, 5.2 Hz, 1H), 1.54 – 1.36 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.0, 156.4, 152.4, 135.2, 133.6, 128.2, 121.9, 118.2, 115.4, 108.5, 83.4, 80.9, 56.9, 28.3, 28.0. **IR** (film) *v*: 3373, 2974, 2933, 1722, 1696, 1595, 1513, 1476, 1390, 1342, 1245, 1133, 1081, 1006, 906, 831, 775, 716 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{28}NO_5$ [M + H^+] 374.1962. Found 374.1968.

Di-*tert*-butyl 4,6-bis(4-hydroxyphenyl)pyridine-1,3(4*H*)-dicarboxylate (18d*)



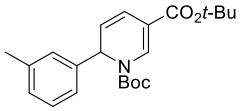
Yield: 35 mg (15%); yellowish oil; $\mathbf{R_f}$ = 0.56 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 8.13 (s, 1H), 7.15 – 7.02 (m, 4H), 6.76 – 6.66 (m, 4H), 5.92 (br s, 2H), 5.25 (d, *J* = 6.5 Hz, 1H), 4.44 (d, *J* = 6.5 Hz, 1H), 1.42 (s, 9H), 1.23 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.5, 155.6, 154.7, 151.0, 136.2, 136.2, 135.8, 130.8, 128.9, 127.6, 116.5, 115.6 (2C overlapped), 115.1, 83.6, 81.1, 39.1, 28.3, 27.7. **IR** (film) *v*: 3377, 2978, 2933, 1685, 1610, 1513, 1454, 1346, 1249, 1144, 1044, 910, 828, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{27}H_{31}NO_6Na$ [M + Na^+] 488.2044. Found 488.2043.

Di-*tert*-butyl 6-(4-acetamidophenyl)pyridine-1,3(6*H*)-dicarboxylate (18e)



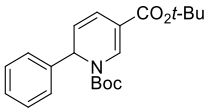
Yield: 159 mg (77%); yellowish oil; $\mathbf{R_f}$ = 0.50 (30% acetone/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ*: 8.51 – 8.36 (m, 1H), 7.90 (br s, 1H), 7.54 – 7.43 (m, 2H), 7.29 – 7.18 (m, 2H), 6.37 (d, *J* = 10.0 Hz, 1H), 5.67 (br s, 1H), 5.51 (dd, *J* = 10.0, 5.3 Hz, 1H), 2.11 (s, 3H), 1.53 – 1.31 (m, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ*: 169.0, 165.4, 152.2, 138.2, 137.6, 134.9, 127.2, 121.3, 119.8, 118.6, 108.5, 83.3, 80.5, 56.5, 28.3, 27.9, 24.4. **IR** (film) *v*: 3310, 2978, 2933, 1722, 1696, 1603, 1532, 1368, 1245, 1129, 1077, 906, 842, 723 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{30}N_2O_5Na$ [M + Na^+] 437.2047. Found 437.2048.

Di-*tert*-butyl 6-(*m*-tolyl)pyridine-1,3(6*H*)-dicarboxylate (18f)



Yield: 121 mg (65%); yellowish oil; $\mathbf{R_f}$ = 0.42 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.96 (br s, 1H), 7.23 – 7.05 (m, 4H), 6.39 (dt, *J* = 9.9, 1.3 Hz, 1H), 5.70 (br s, 1H), 5.56 (dd, *J* = 9.9, 5.2 Hz, 1H), 2.33 (s, 3H), 1.53 – 1.32 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.2, 152.3, 142.5, 138.3, 135.0, 128.7, 128.6, 127.1, 123.5, 121.5, 118.7, 108.6, 83.1, 80.2, 57.9, 28.4, 28.0, 21.5. **IR** (film) *v*: 2978, 2930, 1722, 1696, 1640, 1588, 1476, 1387, 1338, 1245, 1126, 1077, 1010, 906, 850, 764, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{30}NO_4$ [M + H^+] 372.2169. Found 372.2177.

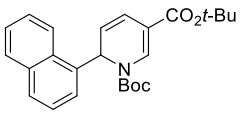
Di-*tert*-butyl 6-phenylpyridine-1,3(6*H*)-dicarboxylate (18g)



Yield: 156 mg (87%); yellow foam; $\mathbf{R_f}$ = 0.31 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.89 (br s, 1H), 7.33 – 7.13 (m, 5H), 6.34 (d, *J* = 9.9 Hz, 1H), 5.67 (br s, 1H), 5.51 (dd, *J* = 9.9, 5.2 Hz, 1H), 1.49 – 1.21 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.1, 152.3, 142.5, 134.9, 128.7, 128.0, 126.5, 121.4, 118.8, 108.7, 83.2, 80.3, 57.8, 28.4, 28.0. **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{27}NO_4Na$ [M + Na^+] 380.1832. Found 380.1836.

The spectral data are in good accordance with those reported in the literature.[12]

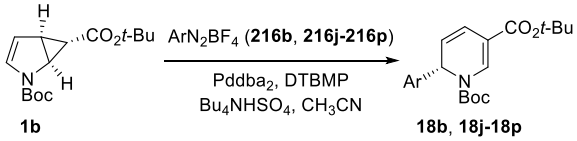
Di-*tert*-butyl 6-(naphthalen-1-yl)pyridine-1,3(6*H*)-dicarboxylate (18h)



Yield: 161 mg (79%); yellowish oil; $\mathbf{R_f}$ = 0.41 (5% acetone/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 8.22 (br s, 1H), 8.15 – 8.04 (m, 1H), 7.91 – 7.85 (m, 1H), 7.81 – 7.75 (m, 1H), 7.59 – 7.41 (m, 4H), 6.69 – 6.46 (m, 1H), 6.32 (dt, *J* = 10.1, 1.5 Hz, 1H), 5.73 (dd, *J* = 10.1, 4.8 Hz, 1H), 1.60 – 0.95 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.1, 152.3, 140.3, 135.2, 133.7, 129.0,

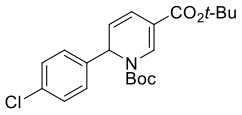
128.7, 128.1, 126.6, 126.0, 125.8, 122.9, 122.3, 121.3, 118.1, 107.7, 83.1, 80.3, 54.8, 28.4, 27.7. **IR** (film) *v*: 2974, 2933, 1692, 1648, 1599, 1513, 1476, 1405, 1368, 1331, 1271, 1129, 1077, 947, 902, 846, 775, 712 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{25}H_{29}NO_4Na$ [M + Na^+] 430.1989. Found 430.1986.

Arylation of cyclopropanated pyrroles with diazonium salts 216b, 216j-216p: synthesis of 1,2-dihydropyridines 18b, 18j-18p



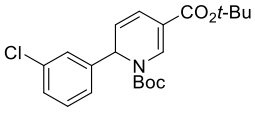
Reactions were performed analogously as above, except that Bu_4NHSO_4 (340 mg, 1 mmol, 2 equiv) was used as an additive and NaOAc was replaced with DTBMP (103 mg, 0.5 mmol, 1 equiv).

Di-*tert*-butyl 6-(4-chlorophenyl)pyridine-1,3(6*H*)-dicarboxylate (18b)



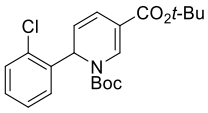
Yield: 163 mg (83%); yellow oil; $\mathbf{R_f}$ = 0.43 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.89 (br s, 1H), 7.40 – 7.16 (m, 4H), 6.41 (d, *J* = 9.9 Hz, 1H), 5.71 (br s, 1H), 5.52 (dd, *J* = 9.9, 5.3 Hz, 1H), 1.54 – 1.33 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 152.0, 140.8, 134.7, 133.8, 128.9, 128.1, 120.8, 119.3, 108.7, 83.4, 80.4, 57.0 + 55.7, 28.4, 28.0 (*signal doubling due to rotamers*). **IR** (film) *v*: 2978, 2933, 1722, 1696, 1640, 1592, 1491, 1387, 1342, 1238, 1126, 1077, 1010, 962, 906, 850, 738 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{26}ClNO_4Na$ [M + Na^+] 414.1443. Found 414.1444.

Di-*tert*-butyl 6-(3-chlorophenyl)pyridine-1,3(6*H*)-dicarboxylate (18j)



Yield: 157 mg (80%); yellowish oil; $\mathbf{R_f}$ = 0.37 (10% Et_2O/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.92 (br s, 1H), 7.36 – 7.16 (m, 4H), 6.43 (d, *J* = 9.9 Hz, 1H), 5.72 (br s, 1H), 5.54 (dd, *J* = 9.9, 5.2 Hz, 1H), 1.55 – 1.32 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 152.1, 144.3, 134.8, 134.5, 130.1, 128.2, 126.8, 124.8, 120.6, 119.5, 108.7, 83.5, 80.5, 57.4, 28.4, 28.0. **IR** (film) *v*: 2978, 2933, 1722, 1700, 1640, 1592, 1476, 1387, 1338, 1238, 1126, 1077, 1010, 910, 846, 738, 693 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{27}ClNO_4$ [M + H^+] 392.1623. Found 392.1621.

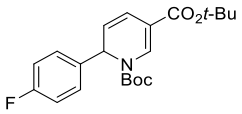
Di-*tert*-butyl 6-(2-chlorophenyl)pyridine-1,3(6*H*)-dicarboxylate (18k)



Yield: 131 mg (67%); yellowish oil; $\mathbf{R_f}$ = 0.40 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 8.10 (br s, 1H), 7.40 – 7.29 (m, 2H), 7.30 – 7.13 (m, 2H), 6.29 (dt, *J* = 10.1, 1.5 Hz, 1H),

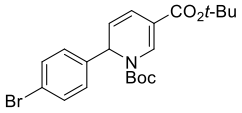
6.17 (d, *J* = 4.8 Hz, 1H), 5.77 – 5.53 (m, 1H), 1.55 – 1.21 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 152.1, 141.6, 135.0, 129.4, 128.8, 127.9, 126.7, 119.8, 118.5, 108.0, 83.3, 80.3, 55.5, 28.4, 27.8 (*one carbon could not be detected*). **IR** (film) *v*: 2978, 2933, 1737, 1700, 1491, 1457, 1394, 1290, 1245, 1148, 1066, 1018, 895, 768 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{26}ClNO_4Na$ [M + Na^+] 414.1443. Found 414.1444.

Di-*tert*-butyl 6-(4-fluorophenyl)pyridine-1,3(6*H*)-dicarboxylate (18l)



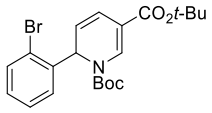
Yield: 128 mg (68%); yellowish oil; $\mathbf{R_f}$ = 0.18 (5% Et_2O/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.90 (br s, 1H), 7.39 – 7.26 (m, 2H), 7.06 – 6.93 (m, 2H), 6.43 (d, *J* = 9.9 Hz, 1H), 5.73 (br s, 1H), 5.54 (dd, *J* = 9.9, 5.3 Hz, 1H), 1.57 – 1.34 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 162.51 (d, J_{CF} = 246.3 Hz), 152.1, 138.2, 134.7, 128.6, 121.1, 119.2, 115.50 (d, J_{CF} = 21.4 Hz), 108.7, 83.3, 80.4, 56.6, 28.4, 28.0. **IR** (film) *v*: 2978, 2933, 1722, 1700, 1640, 1603, 1506, 1387, 1342, 1234, 1126, 1010, 906, 835, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{27}FNO_4$ [M + H^+] 376.1919. Found 376.1919.

Di-*tert*-butyl 6-(4-bromophenyl)pyridine-1,3(6*H*)-dicarboxylate (18m)



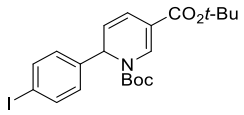
Yield: 162 mg (74%); yellow oil; $\mathbf{R_f}$ = 0.48 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.90 (br s, 1H), 7.50 – 7.38 (m, 2H), 7.27 – 7.12 (m, 2H), 6.42 (d, *J* = 9.9 Hz, 1H), 5.71 (br s, 1H), 5.53 (dd, *J* = 9.9, 5.3 Hz, 1H), 1.55 – 1.30 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 152.0, 141.2, 134.7, 131.8, 128.4, 122.0, 120.7, 119.4, 108.8, 83.5, 80.4, 57.3 + 56.0, 28.4, 28.1 (*signal doubling due to rotamers*). **IR** (film) *v*: 2978, 2933, 1722, 1696, 1640, 1588, 1484, 1387, 1342, 1238, 1126, 1074, 1006, 906, 850, 734 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{26}BrNO_4Na$ [M + Na^+] 458.0937. Found 458.0939.

Di-*tert*-butyl 6-(2-bromophenyl)pyridine-1,3(6*H*)-dicarboxylate (18n)



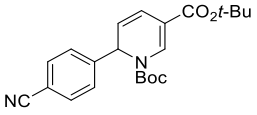
Yield: 155 mg (71%); yellowish oil; $\mathbf{R_f}$ = 0.37 (10% Et_2O/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.87 (br s, 1H), 7.30 – 7.24 (m, 1H), 7.16 – 7.10 (m, 1H), 7.07 – 7.02 (m, 1H), 6.91 – 6.83 (m, 1H), 6.05 (dt, *J* = 10.1, 1.5 Hz, 1H), 5.96 – 5.82 (m, 1H), 5.56 – 5.34 (m, 1H), 1.31 – 0.96 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.0, 152.2, 143.3, 135.1, 132.8, 129.1, 128.6, 126.8, 119.8, 119.2, 118.5, 108.1, 83.4, 80.4, 58.0, 28.4, 27.9. **IR** (film) *v*: 2978, 2933, 1730, 1700, 1644, 1599, 1465, 1390, 1338, 1241, 1126, 1077, 1006, 910, 850, 753 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{26}BrNO_4Na$ [M + Na^+] 458.0937. Found 458.0941.

Di-*tert*-butyl 6-(4-iodophenyl)pyridine-1,3(6*H*)-dicarboxylate (18o)



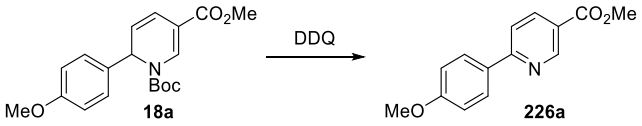
Yield: 179 mg (74%); yellowish oil; $\mathbf{R_f}$ = 0.43 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.89 (br s, 1H), 7.69 – 7.60 (m, 2H), 7.14 – 7.02 (m, 2H), 6.41 (d, *J* = 9.9 Hz, 1H), 5.69 (br s, 1H), 5.52 (dd, *J* = 9.9, 5.3 Hz, 1H), 1.58 – 1.27 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 164.9, 152.0, 141.7, 137.8, 134.7, 128.6, 120.6, 119.4, 108.7, 93.7, 83.4, 80.4, 56.8, 28.3, 28.0. **IR** (film) *v*: 2974, 2930, 1722, 1696, 1640, 1588, 1480, 1387, 1342, 1238, 1126, 1077, 1006, 962, 906, 850, 816, 775, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{26}INO_4Na$ [M + Na^+] 506.0799. Found 506.0799.

Di-*tert*-butyl 6-(4-cyanophenyl)pyridine-1,3(6*H*)-dicarboxylate (18p)



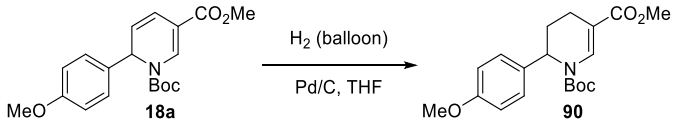
Yield: 97 mg (51%); yellowish oil; $\mathbf{R_f}$ = 0.29 (25% Et_2O/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.90 (br s, 1H), 7.65 – 7.56 (m, 2H), 7.48 – 7.36 (m, 2H), 6.43 (d, *J* = 9.9 Hz, 1H), 5.79 (br s, 1H), 5.52 (dd, *J* = 9.9, 5.3 Hz, 1H), 1.56 – 1.31 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 164.7, 151.8, 146.7, 134.7, 132.7, 127.1, 119.9 (2C overlapped), 118.7, 111.8, 108.7, 83.8, 80.6, 56.5, 28.3, 28.0. **IR** (film) *v*: 2978, 2933, 2229, 1722, 1696, 1640, 1592, 1368, 1238, 1126, 1081, 1006, 910, 850, 760, 712 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{26}N_2O_4Na$ [M + Na^+] 405.1785. Found 405.1788.

Synthesis of methyl 6-(4-methoxyphenyl)nicotinate (226a)



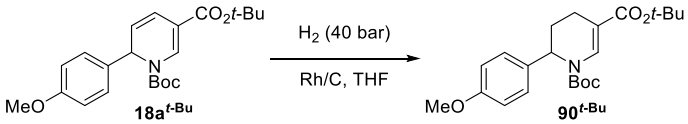
A solution of dihydropyridine **18a** (200 mg, 0.579 mmol) in THF (2.5 mL) was cooled to 0 °C and DDQ (197 mg, 0.869 mmol, 1.5 equiv) dissolved in the same solvent (1.5 mL) was added. The resulting mixture was stirred at 0 °C until TLC indicated complete conversion of the starting material (2 h). Thereafter, water (30 mL) and EtOAc (30 mL) were added, the phases were separated and the aqueous one was extracted with two additional portions of EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. Column chromatography eluting with EtOAc/PE provided pyridine **226a** as colorless crystals (127 mg, 90%). **M.p.** = 161.8-163.4 °C; $\mathbf{R_f}$ = 0.40 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 9.23 (d, *J* = 0.2 Hz, 1H), 8.29 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.08 – 7.99 (m, 2H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.08 – 6.93 (m, 2H), 3.96 (s, 3H), 3.87 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.1, 161.4, 160.6, 151.1, 137.9, 131.0, 128.9, 123.6, 119.0, 114.4, 55.5, 52.4. **IR** (film) *v*: 2952, 1715, 1592, 1513, 1431, 1286, 1249, 1111, 1018, 954, 828, 783, 738 cm^{-1}; **HRMS** (EI) m/z calcd for $C_{14}H_{13}NO_3$ ($M^{+\cdot}$) 243.0890. Found 243.0887.

Synthesis of 1-(*tert*-butyl) 3-methyl 6-(4-methoxyphenyl)-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (90)



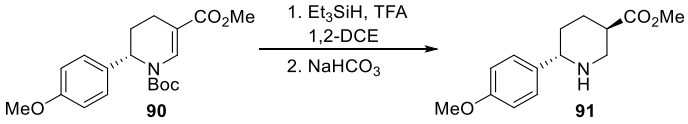
To a solution of 1,2-dihydropyridine **18a** (200 mg, 0.579 mmol) in THF (6 mL) Pd/C (20 mg, 10 wt%) was added, and the mixture was vigorously stirred under hydrogen at 25 ℃. After the reaction was completed (TLC control; 16 h), the catalyst was filtered off. The solvent was removed and the resulting residue was chromatographed on silica gel eluting with EtOAc/PE to afford compound **90** as a white solid (151 mg, 75%). **M.p.** = 83.8-85.8 ℃; $\mathbf{R}_f$ = 0.26 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 8.28 (br s, 1H), 7.00 – 6.91 (m, 2H), 6.82 – 6.74 (m, 2H), 5.25 (br s, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 2.41 – 2.29 (m, 1H), 2.06 – 1.94 (m, 1H), 1.95 – 1.73 (m, 2H), 1.36 (br s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 167.8, 158.6, 151.8, 135.9, 133.5, 126.3, 113.8, 107.4, 82.4, 55.1, 54.3, 51.2, 27.9, 27.3, 16.5. **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{25}NO_5Na$ [M + Na^+] 370.1625. Found 370.1631.

Synthesis of di-*tert*-butyl 6-(4-methoxyphenyl)-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (90$^{t\text{-Bu}}$)



A mixture of dihydropyridine **18a$^{t\text{-Bu}}$** (60 mg, 0.155 mmol) and Rh/C (3 mg, 5 wt%) in THF (3 mL) was intensively stirred under H_2 (40 bar, autoclave) for 2 hours. Next, the suspension was filtered through a short pad of Celite® and the solvent was removed. The residue was chromatographed on silica gel using an EtOAc/PE mixture to give compound **90$^{t\text{-Bu}}$** as a white solid (49 mg, 81%). **M.p.** = 117.2-118.9 ℃; $\mathbf{R}_f$ = 0.33 (7% EtOAc/PE); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ:* 8.22 (s, 1H), 7.03 – 6.98 (m, 2H), 6.85 – 6.80 (m, 2H), 5.23 (s, 1H), 3.77 (s, 3H), 2.34 (d, *J* = 16.7 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.94 – 1.87 (m, 1H), 1.84 – 1.75 (m, 1H), 1.51 – 1.26 (m, 18H); **^{13}C NMR** (101 MHz, DMF-d_7, 80 ℃) *δ:* 167.2, 160.0, 152.9, 135.8, 135.0, 127.5, 115.1, 110.4, 83.1, 80.3, 56.1, 55.3, 28.9, 28.5, 28.2, 17.8. **IR** (film) *ν*: 2974, 2933, 1718, 1636, 1513, 1386, 1245, 1126, 1036, 902, 831, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{31}NO_5Na$ [M + Na^+] 412.2094. Found 412.2103.

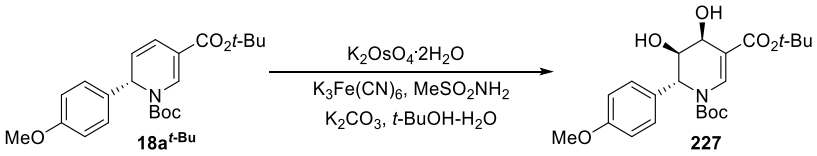
Preparation of methyl-6-(4-methoxyphenyl)piperidine-3-carboxylate (91)



To a solution of **90** (200 mg, 0.576 mmol) in 1,2-DCE (3 mL) TFA (656 mg, 5.76 mmol, 441 µL, 10 equiv) and Et_3SiH (201 mg, 1.73 mmol, 276 µL, 3 equiv) were added, and the mixture was stirred at 50 ℃ for 3 hours. The reaction was quenched by saturated $NaHCO_3$ solution (30 mL), the phases were separated and the aqueous one was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was

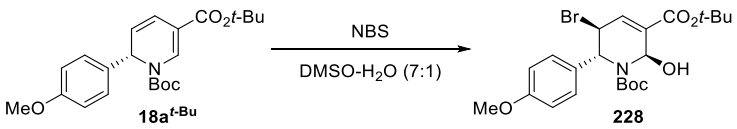
evaporated under reduced pressure (the excess of triethylsilane was removed under high vacuum at 60 °C). Crystallization of crude products from methanol afforded piperidine **91** (35 mg, 75%) as colorless crystals. **M.p.** = 80.2-81.2 °C; $\mathbf{R_f}$ = 0.26 (5% MeOH/CH_2Cl_2); **^{1}H NMR** *δ:* 7.34 – 7.21 (m, 2H), 6.95 – 6.75 (m, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.53 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.41 (ddd, *J* = 11.6, 4.0, 1.9 Hz, 1H), 2.87 (t-like, *J* = 11.4 Hz, 1H), 2.57 (tt, *J* = 11.6, 4.0 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.85 (dq, *J* = 13.0, 3.2 Hz, 1H), 1.74 – 1.59 (m, 2H), 1.52 (tdd, *J* = 13.0, 11.0, 3.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.8, 158.8, 136.9, 127.7, 113.8, 60.8, 55.3, 51.7, 49.4, 42.3, 33.9, 28.3. **IR** (film) *v*: 3332, 2997, 2941, 2837, 1722, 1610, 1513, 1454, 1301, 1245, 1159, 1111, 1036, 999, 835, 790 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{14}H_{19}NO_3$ [M + H$^+$] 250.1365. Found 250.1370.

Synthesis of 1-(*tert*-butyl) 3-butyl (4*S,5*R**,6*R**)-4,5-dihydroxy-6-(4-methoxyphenyl)-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (227)**



To an intensively stirred mixture of *t*-BuOH (1 mL) and water (1 mL) were added at 25 °C $MeSO_2NH_2$ (33 mg, 0.351 mmol, 1 equiv), $K_3Fe(CN)_6$ (347 mg, 1.05 mmol, 3 equiv), K_2CO_3 (146 mg, 1.05 mmol, 3 equiv), followed by $K_2OsO_4{\cdot}2H_2O$ (6.5 mg, 17.6 µmol, 5 mol%). After 20 min, a solution of dihydropyridine **18a$^{t\text{-Bu}}$** (136 mg, 0.351 mmol) in *t*-BuOH (1 mL) was added dropwise at the same temperature. The reaction was conducted for 16 h and then quenched by the addition of solid Na_2SO_3 (221 mg, 1.75 mmol, 5 equiv). After stirring for additional 30 min, the resulting mixture was diluted with CH_2Cl_2 (20 mL) and water (20 mL), the phases were separated, and the aqueous one was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. Column chromatography eluting with acetone/PE provided diol **227** as yellowish crystals (77.4 mg, 52%). **M.p.** = 114-116 °C; $\mathbf{R_f}$ = 0.24 (15% EtOAc/PE); **^{1}H NMR** (400 MHz, DMF-d_7, 80 °C) *δ:* 8.16 (s, 1H), 7.19 – 7.11 (m, 2H), 7.02 – 6.90 (m, 2H), 5.11 (d, *J* = 4.8 Hz, 1H), 4.30 (dd, *J* = 3.7, 0.9 Hz, 1H), 4.00 (dd, *J* = 4.8, 3.7 Hz, 1H), 3.82 (s, 3H), 1.54 (s, 9H), 1.38 (s, 9H). **^{13}C NMR** (101 MHz, DMF-d_7, 80 °C) *δ:* 167.8, 160.4, 153.2, 137.0, 132.8, 128.0, 115.3, 110.2, 83.5, 81.2, 71.8, 63.6, 61.8, 56.2, 28.9, 28.4. **IR** (film) *v*: 3362, 2978, 2881, 1722, 1655, 1513, 1461, 1394, 1249, 1137, 1092, 910, 872 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{31}NO_7Na$ [M + Na$^+$] 444.1993. Found 444.1992.

Preparation of di-*tert*-butyl (2*R,5*S**,6*R**)-5-bromo-2-hydroxy-6-(4-methoxyphenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (228)**



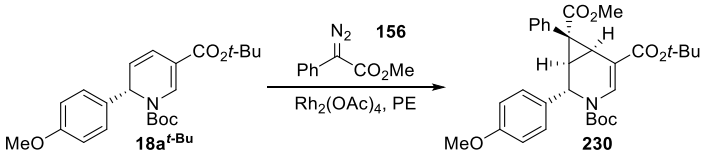
To an intensively stirred solution of dihydropyridine **18a$^{t\text{-Bu}}$** (72 mg, 0.185 mmol) in a DMSO-H_2O mixture (3 mL; 7:1 v/v) NBS (49 mg, 0.278 mmol, 1.5 equiv) was slowly added at 0 °C. Subsequently, the cooling bath was removed, and the reaction mixture was left for 30 min. After that time, the solution was diluted with EtOAc (20 mL), poured into water, and the phases were separated. The aqueous layer was then washed with two additional portions of EtOAc (2 x 10

mL). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by preparative TLC afforded bromohydrin **228** as a colorless oil (55 mg, 61%). The stereochemistry of **228** was assigned based on NOESY experiments and the crystal structure of compound **229**. $\mathbf{R_f}$ = 0.36 (15% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.38 – 7.31 (m, 2H), 7.08 (d, *J* = 5.9 Hz, 1H), 6.87 – 6.78 (m, 2H), 6.28 (br s, 1H), 5.76 (br s, 1H), 5.06 (d, *J* = 5.9 Hz, 1H), 3.77 (s, 3H), 1.52 (s, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 164.1, 159.2, 155.0, 134.3, 133.1, 131.8, 129.0, 113.9, 82.5, 81.9, 71.2, 58.9, 55.3, 44.5, 28.4, 28.2. **IR** (film) *v*: 3470, 2978, 2933, 1689, 1610, 1513, 1457, 1368, 1249, 1156, 1025, 753 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{30}BrNO_6Na$ [M + Na^+] 506.1149. Found 506.1147.

Preparation of di-*tert*-butyl (4*R,5*R**,6*R**)-5-bromo-4-hydroxy-6-(4-methoxyphenyl)-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (229)**

To an intensively stirred solution of dihydropyridine **18a$^{t\text{-Bu}}$** (51 mg, 0.132 mmol) in a DMSO-H_2O mixture (6 mL; 4:1 v/v) NBS (35 mg, 0.197 mmol, 1.5 equiv) was slowly added at 0 °C. Subsequently, the cooling bath was removed and the reaction mixture was left for 30 min. After that time, the solution was diluted with EtOAc (25 mL), poured into water, and the phases were separated. The aqueous layer was then washed with two additional portions of EtOAc (2 x 10 mL), the combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/PE) afforded compound **229** as colorless crystals (29 mg, 45%). **M.p.** = 113.0-113.7 °C; $\mathbf{R_f}$ = 0.14 (15% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 8.38 (br s, 1H), 7.14 – 7.05 (m, 2H), 6.89 – 6.80 (m, 2H), 5.59 (br s, 1H), 4.76 – 4.63 (m, 2H), 3.77 (s, 3H), 1.54 – 1.41 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 166.2, 159.3, 151.6, 135.4, 129.1, 126.9, 114.5, 108.4, 83.8, 81.0, 66.6, 59.8, 55.3, 49.9, 28.4, 28.0. **IR** (film) *v*: 3411, 2978, 2937, 1726, 1674, 1640, 1513, 1454, 1368, 1271, 1133, 1029, 772 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{22}H_{30}BrNO_6Na$ [M + Na^+] 506.1149. Found 506.1149.

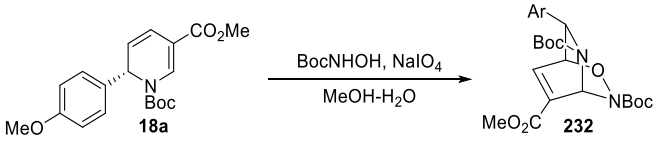
Preparation of 3,5-di-*tert*-butyl 7-methyl (1*R,2*S**,6*S**,7*R**)-2-(4-methoxyphenyl)-7-phenyl-3-azabicyclo[4.1.0]hept-4-ene-3,5,7-tricarboxylate (230)**



A solution of methyl phenyldiazoacetate (**156**; 72 mg, 0.408 mmol, 1.5 equiv) in dry petroleum ether (1.5 mL) was added using a syringe pump (addition rate:1 drop/10 s) to a vigorously stirred mixture of dihydropyridine **18a$^{t\text{-Bu}}$** (105 mg, 0.272 mmol) and $Rh_2(OAc)_4$ (3.6 mg, 8.2 μmol, 3 mol%) in the same solvent (1.5 mL) at 25 °C under an atmosphere of nitrogen. After the addition was completed, the resulting mixture was left for additional 30 min and then the solvent was evaporated. Column chromatography eluting with Et_2O/PE afforded derivative **230** as colorless crystals (105 mg, 72%). **M.p.** = 150.9-151.8 °C; $\mathbf{R_f}$ = 0.41 (20% EtOAc/PE); **^{1}H**

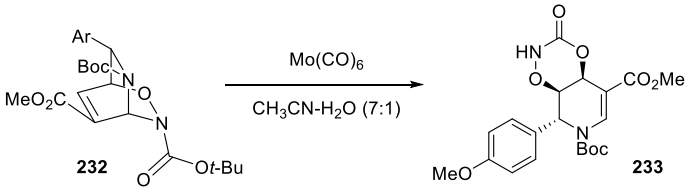
NMR (400 MHz, DMF-d_7, 80 °C) *δ:* 7.47 (s, 1H), 7.40 – 7.26 (m, 7H), 7.00 – 6.95 (m, 2H), 5.64 (s, 1H), 3.83 (s, 3H), 3.61 (s, 3H), 2.92 (dd, *J* = 9.8, 0.9 Hz, 1H), 2.71 (dd, *J* = 9.8, 0.7 Hz, 1H), 1.59 (s, 9H), 1.29 (s, 9H). **^{13}C NMR** (101 MHz, C_6D_6, 70 °C) *δ:* 172.1, 166.4, 159.9, 150.8, 135.1, 134.9, 133.8, 131.2, 128.6, 128.1, 127.6, 114.6, 108.2, 81.8, 79.8, 54.9, 52.0, 50.9, 40.95, 36.6, 28.4, 27.9, 24.2. **IR** (film) *v*: 2974, 2937, 1718, 1689, 1644, 1510, 1368, 1234, 1170, 1141, 988, 705 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{31}H_{37}NO_7Na$ [M + Na^+] 558.2462. Found 558.2466.

Preparation of 3,5-di-*tert*-butyl 8-methyl (1*S,4*R**,6*R**)-6-(4-methoxyphenyl)-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-3,5,8-tricarboxylate (232)**



To a solution of *tert*-butyl *N*-hydroxycarbamate (54 mg, 0.461 mmol, 1.2 equiv) in a MeOH-H_2O mixture (2 mL, 1:1 v/v) was added a methanolic solution (2 mL) of dihydropyridine **18a** (133 mg, 0.384 mmol), followed by $NaIO_4$ (99 mg, 0.461 mmol, 1.2 equiv) at 0 °C. After stirring for 2 hours at the same temperature, the resulting mixture was diluted with CH_2Cl_2 (30 mL), poured into water, and the phases were separated. The aqueous layer was then washed with two additional portions of CH_2Cl_2 (20 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using an EtOAc/PE mixture to give cycloadduct **232** as a yellowish oil (138 mg, 75%). $\mathbf{R_f}$ = 0.32 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.06 – 6.70 (m, 6H), 5.15 – 4.95 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 1.49 – 1.15 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 162.0, 159.3, 156.3, 153.8 + 153.3, 135.6 + 134.8, 135.4, 129.6 +128.8, 127.5, 114.2 + 113.9, 83.4, 82.0 + 81.4, 77.9, 57.8 + 57.4, 56.5, 55.3, 52.5, 28.2, 28.06 (*signal doubling due to rotamers*). **IR** (film) *v*: 2978, 2937, 1707, 1614, 1513, 1439, 1368, 1245, 1156, 1033, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{27}H_{32}N_2O_8Na$ [M + Na^+] 499.2159. Found 499.2055.

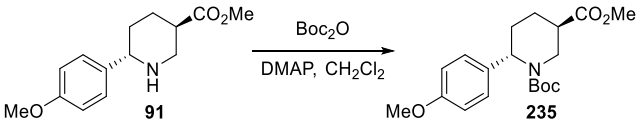
Preparation of *tert*-butyl (4a*R,8*R**,8a*R**)-5-methoxy-8-(4-methoxyphenyl)-3-oxo-2,3,8,8a-tetrahydropyrido[4,3-e][1,4,2]dioxazine-7(4a*H*)-carboxylate (233)**



To an intensively stirred solution of cycloadduct **232** (67 mg, 0.129 mmol) in a 7:1 MeCN-H_2O mixture (8 mL) $Mo(CO)_6$ (44 mg, 0.168 mmol, 1.3 equiv) was added in one portion at 25 °C. The resulting suspension was then heated to 75 °C, and the stirring was continued for 4 h. After that time, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/PE) yielded **233** as a yellowish oil (33 mg, 60%). $\mathbf{R_f}$ = 0.11 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 8.45 (s, 1H), 7.10 – 7.02 (m, 2H), 6.88 – 6.81 (m, 2H), 5.43 (s, 1H), 5.22 (d, *J* = 8.3 Hz, 1H), 4.37 – 4.26 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 1.41 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.7, 160.4, 159.7, 151.2, 139.7, 127.7, 127.3, 114.7, 103.7, 84.4, 65.9, 63.0, 55.4, 54.1, 51.8, 27.9. **IR** (film) *v*: 3250, 2956,

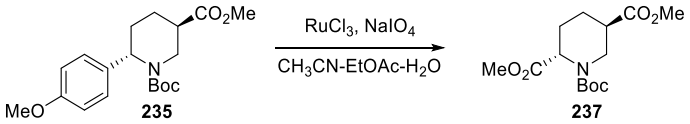
1767, 1707, 1636, 1513, 1439, 1238, 1144, 1010, 977, 753 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{25}N_2O_8$ [M + H^+] 421.1605. Found 421.1612.

Preparation of 1-(*tert*-butyl) 3-methyl (3*R,6*S**)-6-(4-methoxyphenyl)piperidine-1,3-dicarboxylate (235)**



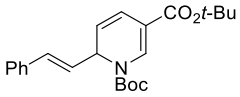
To a vigorously stirred solution of piperidine **91** (431 mg, 1.73 mmol) and DMAP (21 mg, 0.173 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL) Boc_2O (566 mg, 2.6 mmol, 1.5 equiv) dissolved in the same solvent (5 mL) was slowly added at 25 °C. After 16 h, the mixture was combined with a portion of silica gel, and the solvent was removed. Column chromatography eluting with Et_2O/PE afforded compound **235** as a white solid (491 mg, 81%). **M.p.** = 72.8-74.4 °C; $\mathbf{R_f}$ = 0.31 (35% Et_2O/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ:* 7.15 – 7.04 (m, 2H), 6.90 – 6.78 (m, 2H), 5.40 – 5.23 (m, 1H), 4.42 (dq, *J* = 13.8, 1.6 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 2.96 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.48 (dq, *J* = 5.6, 2.8 Hz, 1H), 2.18 – 1.93 (m, 3H), 1.76 – 1.57 (m, 1H), 1.49 – 1.35 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ:* 173.9, 158.3, 155.3, 131.8, 127.5, 114.0, 79.6, 55.2, 52.3, 51.8, 40.5, 39.0, 28.4, 24.3, 20.7. **IR** (film) *v*: 2982, 2952, 2840, 1722, 1677, 1610, 1513, 1439, 1409, 1364, 1323, 1252, 1163, 1029, 932, 760 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{28}NO_5$ [M + H^+] 350.1962. Found 350.1959.

Preparation of 1-(*tert*-butyl) 2,5-dimethyl (2*S,5*R**)-piperidine-1,2,5-tricarboxylate (237)**



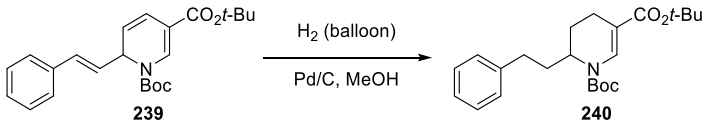
Piperidine **235** (315 mg, 0.901 mmol) dissolved in EtOAc (12 mL) was added dropwise to an intensively stirred solution of $NaIO_4$ (6.46 g, 15.33 mmol, 17 equiv) and $RuCl_3$ (hydrate, Ru 36%; 62 mg, 0.108 mmol, 0.12 equiv) in a CH_3CN-H_2O mixture (36 mL, 1:2 v/v) at 25 °C. The reaction was conducted at the same temperature for 4 h during which time a white precipitate formed. Thereafter, the solids were filtered off, and the resulting filtrate was diluted with water (60 mL), followed by extraction with EtOAc (5 x 40 mL). The combined organic phases were then dried over anhydrous Na_2SO_4. The residue obtained after the removal of the solvents was taken up into Et_2O (10 mL), and to the resulting mixture, an ethereal solution of freshly prepared diazomethane was slowly introduced at 0 °C. The addition was continued until a yellow color persisted. The mixture was subsequently washed with saturated $NaHCO_3$ solution (20 mL), the organic layer was dried over anhydrous Na_2SO_4, and the solvents were evaporated. Column chromatography of crude product using an EtOAc/PE mixture afforded diester **237** as a colorless oil (176 mg, 65%). $\mathbf{R_f}$ = 0.33 (20% EtOAc/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ:* 5.15 – 4.49 (m, 1H), 4.48 – 4.24 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.26 – 3.03 (m, 1H), 2.59 (s, 1H), 2.18 – 1.82 (m, 3H), 1.59 – 1.35 (m, 10H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 173.5, 172.3, 155.4, 80.4, 54.7+53.3, 52.2, 51.9, 42.5 + 41.9, 38.5, 28.4, 23.2, 22.1 (*signal doubling due to rotamers*). **IR** (film) *v*: 2956, 1737, 1689, 1416, 1364, 1338, 1245, 1208, 1148, 1118, 1021, 936, 880, 772 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{14}H_{23}NO_6Na$ [M + Na^+] 324.1418. Found 324.1416.

Preparation of di-*tert*-butyl (*E*)-6-styrylpyridine-1,3(6*H*)-dicarboxylate (239)



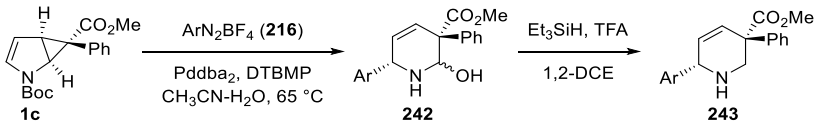
A flask equipped with a magnetic stirring bar was charged with cyclopropanated pyrrole **1b** (141 mg, 0.5 mmol), $NaHCO_3$ (105 mg, 1.25 mmol, 2.5 equiv), TBAB (322 mg, 1 mmol, 2 equiv), β-bromostyrene (**238**; 229 mg, 1.25 mmol, 2.5 equiv), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (41 mg, 50 μmol, 10 mol%), flushed with nitrogen, followed by addition of dry DMF (3 mL). The mixture was stirred at 25 °C for 5 min, and then the reaction vessel was placed in an oil bath preheated to 80 °C. The coupling was conducted for 3 days. Thereafter, the mixture was cooled down to ambient temperature, water and EtOAc were added, and the phases were separated. The aqueous one was extracted with two additional portions of EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvents were removed. Column chromatography of the resulting residue eluting with an EtOAc/PE mixture provided compound **239** as a yellowish oil (81 mg, 42%). $\mathbf{R_f}$ = 0.19 (5% Et_2O/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.86 (br s, 1H), 7.48 – 7.21 (m, 5H), 6.64 – 6.44 (m, 2H), 6.20 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.56 (dd, *J* = 9.7, 5.6 Hz, 1H), 5.41 (br s, 1H), 1.59 – 1.54 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 165.2, 152.2, 136.5, 134.6, 131.5, 128.7, 128.1, 126.8, 126.3, 120.8, 118.9, 109.7, 83.1, 80.3, 54.8, 28.4, 28.2. **IR** (film) *ν*: 2974, 2933, 1722, 1700, 1640, 1584, 1476, 1390, 1342, 1245, 1141, 1077, 965, 850, 731, 693 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{29}NO_4Na$ [M + Na^+] 406.1989. Found 406.1992.

Synthesis of di-*tert*-butyl 6-phenethyl-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (240)



To a solution of 1,2-dihydropyridine **239** (100 mg, 0.261 mmol) in MeOH (3 mL) Pd/C (20 mg, 10 wt%) was added and the mixture was intensively stirred under hydrogen at 25 °C. After the reaction was completed (TLC monitoring), the catalyst was filtered off. The solvent was evaporated, and the obtained residue was chromatographed on silica gel to provide compound **240** as a yellowish oil (73 mg, 72%). $\mathbf{R_f}$ = 0.34 (5% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 8.42 – 7.81 (m, 1H), 7.40 – 7.19 (m, 5H), 4.72 – 3.95 (m, 1H), 2.82 – 2.70 (m, 1H), 2.63 (ddd, *J* = 13.8, 10.5, 6.4 Hz, 1H), 2.46 (dd, *J* = 17.6, 5.4 Hz, 1H), 2.28 – 2.14 (m, 1H), 2.04 (ddd, *J* = 13.8, 4.0, 2.1 Hz, 1H), 1.95 – 1.66 (m, 3H), 1.61 – 1.52 (m, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 167.2, 151.8, 141.6, 134.5, 128.5, 128.4, 126.1, 108.3, 82.2, 79.8, 50.7 + 50.0, 33.2, 32.4, 28.4, 28.3, 23.3, 17.1 (*signal doubling due to rotamers*). **IR** (film) *ν*: 2974, 2930, 1715, 1633, 1476, 1390, 1342, 1245, 1137, 902, 850, 734, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{33}NO_4Na$ [M + Na^+] 410.2302. Found 410.2301.

Arylation of cyclopropanated pyrrole 1c with diazonium salts: synthesis of lactamols 242 and 1,2,3,6-tetrahydropyridines 243



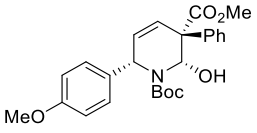
Coupling

A reaction vessel containing a solution of cyclopropanated pyrrole **1c** (158 mg, 0.5 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (154 mg, 0.75 mmol, 1.5 equiv) in a 4:1 CH_3CN-H_2O mixture (3 mL) was placed in an oil bath preheated to 65 °C, followed by addition of a mixture of $Pddba_2$ (29 mg, 50 µmol, 10 mol%) and diazonium tetrafluoroborate (0.550 mmol, 1.1 equiv). The stirring was continued at the same temperature until TLC indicated complete consumption of the starting cyclopropane **1c**. Next, the mixture was diluted with EtOAc, poured into water, and the phases were separated. The aqueous layer was washed with an additional portion of EtOAc. After the combined organic extracts were dried over anhydrous Na_2SO_4, the solvent was removed. The resulting residue was then filtered through a pad of silica gel eluting with EtOAc/PE to remove most of the impurities. The formation of lactamols **242** was confirmed by MS analysis.

Reduction

Products resulting from the previous step were dissolved in dry 1,2-DCE (5 mL), followed by sequential addition of TFA (570 mg, 5 mmol, 383 µL, 10 equiv) and Et_3SiH (87 mg, 0.750 mmol, 120 µL, 1.5 equiv) at 25 °C. The reaction mixture was stirred at the same temperature for 2 h. After that time, the excess of the acid was neutralized using a saturated solution of $NaHCO_3$, the phases were separated, and the aqueous one was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under diminished pressure (the excess of triethylsilane was removed under high vacuum at 60 °C). Tetrahydropyridines **243** were purified either by crystallization from Et_2O or by column chromatography.

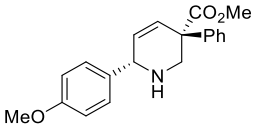
1-(*tert*-Butyl) 3-methyl (2*S,3*R**,6*S**)-2-hydroxy-6-(4-methoxyphenyl)-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (2,6-*syn*-242a)**



Isolated by column chromatography after the coupling step. Yield: 197 mg (90%); colorless crystals; **m.p.** = 140.4-142.2 °C; $\mathbf{R_f}$ = 0.22 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, DMF-d_7, 110 °C) *δ:* 7.58 – 7.50 (m, 4H), 7.41 – 7.24 (m, 3H), 6.91 – 6.83 (m, 2H), 6.71 – 6.63 (m, 1H), 6.62 – 6.53 (m, 1H), 6.10 – 6.00 (m, 1H), 5.98 (br s, 1H), 5.16 (br s, 1H), 3.84 – 3.77 (m, 3H), 3.80 – 3.73 (m, 3H), 1.28 – 1.20 (m, 9H). **^{13}C NMR** (101 MHz, DMF-d_7, 70 °C) *δ:* 173.1, 159.9, 154.8, 140.9, 135.9, 130.9, 130.0, 129.5, 128.4, 128.3, 125.1, 114.3, 80.7, 77.9, 58.4, 56.6, 56.1, 52.9, 28.7. **IR** (film) *ν*: 3407, 2974, 1737, 1670, 1610, 1513, 1461, 1394, 1349, 1241, 1163,

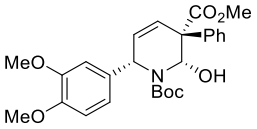
1059, 1033, 954, 842, 757, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{25}H_{30}NO_6$ [M + H^+] 440.2068. Found 440.2071.

Methyl (3*R,6*S**)-6-(4-methoxyphenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (243a)**



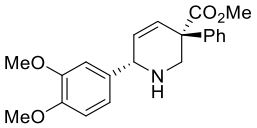
Yield: *from 100 mg (0.228 mmol) of the isolated lactamol 2,6*-syn-***242a**:* 69 mg (94%); *from cyclopropanated pyrrole* **1c**: 138 mg (85%); white solid; **m.p.** = 108.0-109.6 °C; $\mathbf{R_f}$ = 0.29 (2% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.42 – 7.33 (m, 2H), 7.34 – 7.22 (m, 5H), 6.93 – 6.85 (m, 2H), 6.35 (ddd, *J* = 10.2, 2.5, 1.5 Hz, 1H), 6.17 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.45 (t-like, *J* = 2.3 Hz, 1H), 3.87 – 3.78 (m, 4H), 3.77 (s, 3H), 2.88 (d, *J* = 13.2 Hz, 1H), 1.94 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.6, 159.2, 141.7, 134.8, 134.0, 128.9 (2C overlapped), 128.3, 127.3, 126.3, 114.1, 57.6, 55.4, 53.7, 52.5, 51.5. **IR** (film) *v*: 3340, 2960, 2800, 1722, 1610, 1510, 1439, 1361, 1286, 1241, 1200, 1092, 1044, 973, 939, 865, 831, 798, 775, 682 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{22}NO_3$ [M + H^+] 324.1594. Found 324.1599.

1-(*tert*-Butyl) 3-methyl (2*S,3*R**,6*S**)-6-(3,4-dimethoxyphenyl)-2-hydroxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (242b)**



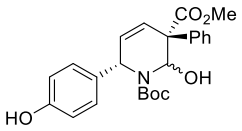
yellowish oil; $\mathbf{R_f}$ = 0.16 (50% EtOAc/PE); **HRMS** (ESI-TOF) m/z calcd for $C_{26}H_{32}NO_7$ [M + H^+] 470.2173. Found 470.2175.

Methyl (3*R,6*S**)-6-(3,4-dimethoxyphenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (243b)**



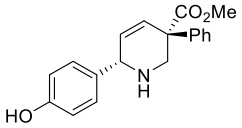
Yield: 119 mg (67%); yellowish crystals; **m.p.** = 110.4-112.1 °C; $\mathbf{R_f}$ = 0.21 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.42 – 7.24 (m, 5H), 6.92 – 6.80 (m, 3H), 6.36 (dt, *J* = 10.2, 2.4, 1.5 Hz, 1H), 6.17 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.47 (t-like, *J* = 2.2 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.82 (dd, *J* = 13.1, 1.5 Hz, 1H), 3.76 (s, 3H), 2.89 (d, *J* = 13.1 Hz, 1H), 2.41 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.6, 149.2, 148.7, 141.5, 135.0, 133.7, 128.9, 128.4, 127.4, 126.3, 119.7, 111.3, 111.2, 57.8, 56.1, 56.0, 53.6, 52.5, 51.4. **HRMS** (ESI-TOF) m/z calcd for $C_{21}H_{24}NO_4$ [M + H^+] 354.1700. Found 354.1706.

1-(*tert*-Butyl) 3-methyl (3*R,6*S**)-2-hydroxy-6-(4-hydroxyphenyl)-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (242c)**



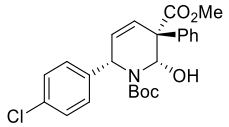
inseparable mixture of diastereomers; white solid; $\mathbf{R_f}$ = 0.40 (30% acetone/PE); **HRMS** (ESI-TOF) m/z calcd for $C_{24}H_{27}NO_6Na$ [M + Na^+] 448.1731. Found 448.1730.

Methyl (3*R,6*S**)-6-(4-hydroxyphenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (243c)**



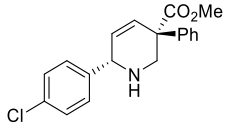
Yield: 136 mg (88%); white solid; **m.p.** = 185.0-186.9 °C; $\mathbf{R_f}$ = 0.44 (5% $MeOH/CH_2Cl_2$); **^{1}H NMR** (400 MHz, methanol-d_4) *δ:* 7.50 – 7.33 (m, 5H), 7.34 – 7.25 (m, 2H), 6.94 – 6.85 (m, 2H), 6.62 (ddd, *J* = 10.6, 2.6, 1.2 Hz, 1H), 6.29 (dd, *J* = 10.6, 2.2 Hz, 1H), 5.09 (t, *J* = 2.4 Hz, 1H), 4.15 (d, *J* = 13.1 Hz, 1H), 3.82 (s, 3H), 3.39 (d, *J* = 13.1 Hz, 1H). **^{13}C NMR** (101 MHz, methanol-d_4) *δ:* 173.40, 160.42, 140.02, 131.53, 130.43, 129.63, 129.57, 128.65, 127.34, 125.79, 117.09, 57.36, 53.87, 51.01, 49.57. **IR** (film) *v*: 3083, 2967, 1730, 1655, 1517, 1443, 1364, 1267, 1185, 1141, 1021, 828; 701 cm^{-1}; **HRMS** (EI) m/z calcd for $C_{19}H_{19}NO_3$ ($M^{+\cdot}$) 309.1359. Found 309.1348.

1-(*tert*-Butyl) 3-methyl (2*S,3*R**,6*S**)-6-(4-chlorophenyl)-2-hydroxy-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (242d)**



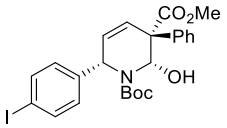
$\mathbf{R_f}$ = 0.41 (20% EtOAc/PE); **HRMS** (ESI-TOF) m/z calcd for $C_{24}H_{26}ClNO_5Na$ [M + Na^+] 466.1392. Found 466.1393.

Methyl (3*R,6*S**)-6-(4-chlorophenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (243d)**



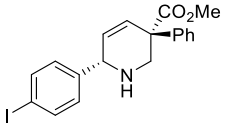
Yield: 120 mg (73%); colorless crystals; **m.p.** = 123.9-125.9 °C; $\mathbf{R_f}$ = 0.46 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.42 – 7.24 (m, 9H), 6.37 (dt, *J* = 10.2, 2.5, 1.5 Hz, 1H), 6.13 (dd, *J* = 10.2, 2.1 Hz, 1H), 4.50 (t-like, *J* = 2.3 Hz, 1H), 3.82 (dd, *J* = 13.1, 1.5 Hz, 1H), 3.77 (s, 3H), 2.90 (d, *J* = 13.1 Hz, 1H), 2.50 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.5, 141.3, 140.6, 133.7, 132.8, 129.3, 129.0, 129.0, 128.8, 127.5, 126.3, 57.5, 53.4, 52.7, 51.4. **IR** (film) *v*: 3336, 2956, 1722, 1580, 1491, 1446, 1282, 1245, 1208, 1092, 1014, 861, 794, 731, 701 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{19}ClNO_2$ [M + H^+] 328.1099. Found 328.1104.

1-(*tert*-Butyl) 3-methyl (2*S,3*R**,6*S**)-2-hydroxy-6-(4-iodophenyl)-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (242e)**



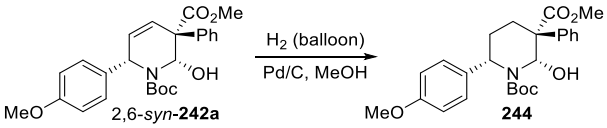
R*f* = 0.45 (30% EtOAc/PE); **HRMS** (ESI-TOF) m/z calcd for $C_{24}H_{26}INO_5Na$ [M + Na^+] 558.0748. Found 558.0755.

Methyl (3*R,6*S**)-6-(4-iodophenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (243e)**



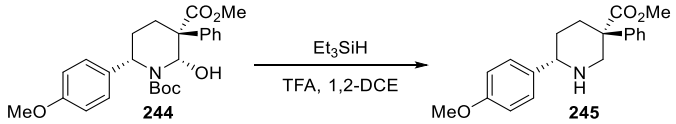
Yield: 146 mg (70%); yellowish crystals; **m.p.** = 127.5-129.3 °C; **R*f*** = 0.56 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.73 – 7.61 (m, 2H), 7.41 – 7.32 (m, 2H), 7.34 – 7.23 (m, 3H), 7.13 – 7.04 (m, 2H), 6.36 (ddd, *J* = 10.2, 2.5, 1.4 Hz, 1H), 6.11 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.43 (t-like, *J* = 2.3 Hz, 1H), 3.81 (dd, *J* = 13.1, 1.4 Hz, 1H), 3.76 (s, 3H), 2.87 (d, *J* = 13.1 Hz, 1H), 1.83 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.5, 142.3, 141.5, 137.9, 133.0, 129.8, 128.9, 128.9, 127.4, 126.3, 93.2, 57.7, 53.5, 52.6, 51.5. **IR** (film) *ν*: 3332, 2952, 1722, 1584, 1476, 1446, 1398, 1241, 1208, 1088, 1006, 939, 850, 824, 731, 697 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{19}H_{19}INO_2$ [M + H^+] 420.0455. Found 420.0459.

Preparation of 1-(*tert*-butyl) 3-methyl (2*S,3*R**,6*S**)-2-hydroxy-6-(4-methoxyphenyl)-3-phenylpiperidine-1,3-dicarboxylate (244)**



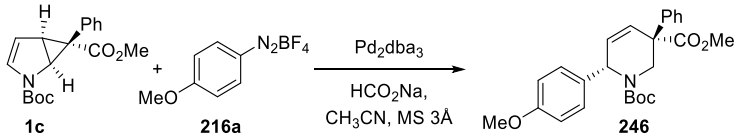
To a solution of substrate 2,6-*syn*-**242a** (200 mg, 0.455 mmol) in MeOH (5 mL) Pd/C (20 mg, 10 wt%) was added, and the mixture was intensively stirred under hydrogen at 25 °C. After TLC indicated the complete consumption of the substrate, the catalyst was filtered off. The solvent was removed under reduced pressure, and the resulting residue was chromatographed on silica gel to afford compound **244** as a white solid (151 mg; 75%). **M.p.** = 144.4-146.1 °C; **R*f*** = 0.50 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.47 – 7.40 (m, 2H), 7.39 – 7.21 (m, 5H), 6.86 – 6.79 (m, 2H), 6.63 (d, *J* = 4.9 Hz, 1H), 4.98 (d, *J* = 6.7 Hz, 1H), 3.91 (br s, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 2.65 (td, *J* = 13.9, 3.3 Hz, 1H), 2.14 (dt, *J* = 14.3, 4.0 Hz, 1H), 1.90 (d, *J* = 14.3 Hz, 1H), 1.67 (tdd, *J* = 13.9, 7.1, 3.3 Hz, 1H), 1.37 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 173.9, 158.3, 156.0, 139.9, 136.2, 128.9, 128.1, 127.2, 126.6, 113.6, 81.3, 76.6, 55.3, 54.9, 53.6, 52.2, 28.3, 24.9, 23.1. **IR** (film) *ν*: 3452, 3384, 2960, 1737, 1659, 1614, 1513, 1457, 1394, 1368, 1245, 1159, 1066, 1029, 962, 865, 753, 705 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{25}H_{31}NO_6Na$ [M + Na^+] 464.2044. Found 464.2043.

Preparation of methyl (3*R,6*S**)-6-(4-methoxyphenyl)-3-phenylpiperidine-3-carboxylate (245)**



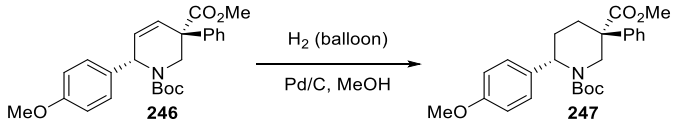
To a solution of compound **244** (151 mg, 0.342 mmol) in dry 1,2-DCE (3 mL) were added TFA (390 mg, 3.42 mmol, 262 µL, 10 equiv) and Et_3SiH (60 mg, 0.513 mmol, 82 µL, 1.5 equiv) at 25 °C. The reaction mixture was stirred at the same temperature for 2 h. After that time, the excess of the acid was neutralized using saturated solution of $NaHCO_3$, the phases were separated, and the aqueous one was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under diminished pressure. The excess of triethylsilane was removed under high vacuum at 60 °C. Crystallization of the crude product from Et_2O provided piperidine **245** (103 mg, 93%) as a white solid. **M.p.** = 120.9-122.8 °C; $\mathbf{R_f}$ = 0.51 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.33 – 7.11 (m, 7H), 6.82 – 6.69 (m, 2H), 3.91 (dd, *J* = 12.3, 2.7 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.52 (dd, *J* = 11.4, 2.7 Hz, 1H), 2.84 (d, *J* = 12.3 Hz, 1H), 2.76 – 2.65 (m, 1H), 1.97 – 1.73 (m, 3H), 1.66 – 1.51 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 175.1, 158.8, 141.9, 136.6, 128.8, 127.8, 127.4, 125.8, 113.9, 60.2, 55.4, 55.1, 52.4, 50.5, 33.7, 32.5. **IR** (film) *v*: 3347, 2948; 2818, 1722, 1614, 1513, 1439, 1305, 1211, 1115, 1029, 869, 828, 727 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{20}H_{24}NO_3$ [M + H^+] 326.1751. Found 326.1757.

Synthesis of 1-(*tert*-butyl) 3-methyl (3*R,6*S**)-6-(4-methoxyphenyl)-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (246)**



A flask equipped with a magnetic stirring bar was charged with cyclopropanated pyrrole **1c** (158 mg, 0.5 mmol), HCO_2Na (102 mg, 1.5 mmol, 3 equiv), activated MS 3Å, flushed with nitrogen, followed by addition of dry CH_3CN (3 mL). The reaction vessel was then placed in an oil bath preheated to 65 °C. When the starting material had completely dissolved, to the resulting solution, a mixture of Pd_2dba_3 (23 mg, 25 µmol, 5 mol%) and 4-methoxybenzenediazonium tetrafluoroborate (**216a**; 144 mg, 0.650 mmol, 3 equiv) was added in one portion. The reaction was conducted at the same temperature until TLC indicated complete conversion of the cyclopropane (16 h). Thereafter, the mixture was cooled down, diluted with EtOAc, the solids were filtered off, and the solvent was removed. The product was purified by column chromatography eluting with an EtOAc/PE mixture to afford compound **246** as a yellowish oil (100 mg, 47%). $\mathbf{R_f}$ = 0.30 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.46 – 7.21 (m, 7H), 6.97 – 6.78 (m, 2H), 6.75 – 5.20 (m, 3H), 4.80 – 4.17 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.56 – 3.32 (m, 1H), 1.43 – 0.97 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 173.4, 159.2, 154.2, 140.0, 132.0, 130.9, 129.2, 128.5, 127.8, 127.4, 127.1, 113.9, 79.5, 55.3, 53.4, 52.7, 52.6, 46.4, 27.9. **IR** (film) *v*: 2930, 1726, 1677, 1610, 1510, 1454, 1420, 1308, 1245, 1159, 1044, 880, 820, 757, 705 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{25}H_{29}NO_5Na$ [M + Na^+] 446.1938. Found 446.1941.

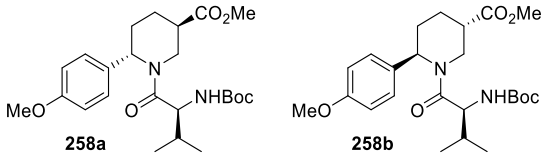
Preparation of 1-(*tert*-butyl) 3-methyl (3*R,6*S**)-6-(4-methoxyphenyl)-3-phenylpiperidine-1,3-dicarboxylate (247)**



A mixture of tetrahydropyridine **246** (100 mg, 0.234 mmol) and Pd/C (10 mg, 10 wt%) in MeOH (3 mL) was intensively stirred under H_2 (balloon) for 16 hours. Next, the suspension was filtered through a short pad of Celite® and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel using an EtOAc/PE mixture to give compound **247** as a white solid (86 mg, 86%). **M.p.** = 165.6-167.6 °C; $\mathbf{R_f}$ = 0.21 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ:* 7.60 – 7.52 (m, 2H), 7.40 – 7.31 (m, 2H), 7.31 – 7.22 (m, 1H), 7.17 – 7.09 (m, 2H), 6.94 – 6.85 (m, 2H), 5.37 – 5.15 (m, 1H), 4.99 (d, *J* = 14.3 Hz, 1H), 3.81 (s, 3H), 3.53 (s, 3H), 3.11 (d, *J* = 14.3 Hz, 1H), 2.57 – 2.44 (m, 1H), 2.19 – 2.08 (m, 1H), 2.01 (td, *J* = 13.8, 3.0 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.47 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ:* 174.6, 158.5, 155.5, 138.5, 131.4, 128.6, 127.7, 127.5, 127.2, 114.2, 80.4, 55.4, 52.4, 51.8, 49.9, 43.8, 28.5, 28.0, 23.5. **IR** (film) *v*: 2971, 2881, 1730, 1692, 1614, 1513, 1446, 1416, 1364, 1327, 1234, 1167, 1133, 1066, 1033, 958, 846, 731, 693 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{25}H_{32}NO_5$ [M + H^+] 426.2275. Found 426.2278.

Synthesis of dipeptides 258a and 258b

The solution of *N*-Boc-Val (192 mg, 0.882 mmol, 1.1 equiv) in CH_2Cl_2 (16 mL) was cooled to 0 °C followed by addition of Oxyma (137 mg, 0.963 mmol, 1.2 equiv) and EDCCl (185 mg, 0.963 mmol, 1.2 equiv). The cooling bath was removed, and the mixture was stirred for 1 h at 25 °C. After re-cooling of the reaction solution to 0 °C, amine **91** (200 mg, 0.802 mmol) was added followed by DIPEA (124 mg, 168 µL, 0.963 mmol, 1.2 equiv). The coupling was conducted at 25 °C for 48 h. Then, the mixture was diluted to 100 mL with CH_2Cl_2 and sequentially washed with $KHSO_4$ (5% solution, 3 x 30 mL), saturated solution of $NaHCO_3$ (3 x 30 mL), and finally with brine (1 x 30 mL). The organic layer was dried over Na_2SO_4. The residue obtained after the removal of the solvent was chromatographed on silica gel to provide compounds **258a** and **258b**.

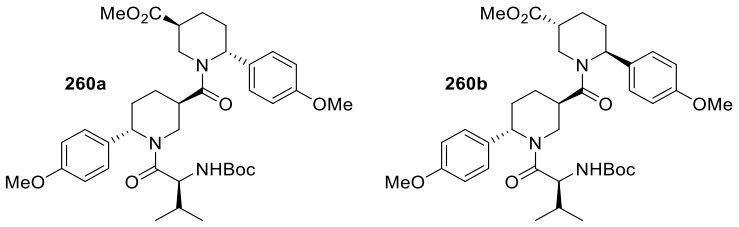


Methyl (3*R*,6*S*)-1-((*tert*-butoxycarbonyl)-L-valyl)-6-(4-methoxyphenyl)piperidine-3-carboxylate (258a). Yield: 177 mg (49%); colorless oil; $\mathbf{R_f}$ = 0.31 (20% acetone/PE); **^{1}H NMR** (600 MHz, $CDCl_3$; *major rotamer*) *δ:* 7.11 – 7.03 (m, 2H), 6.88 – 6.80 (m, 2H), 5.93 – 5.80 (m, 1H), 5.55 (d, *J* = 8.6 Hz, 1H), 4.97 – 4.87 (m, 1H), 4.13 (d, *J* = 14.1 Hz, 1H), 3.78 – 3.75 (m, 3H), 3.73 (s, 3H), 3.19 (dd, *J* = 14.1, 3.8 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.25 – 2.11 (m, 2H), 2.02 – 1.79 (m, 3H), 1.42 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.91 – 0.81 (m, 3H); (*minor rotamer*) *δ:* 7.11 – 7.03 (m, 2H), 6.88 – 6.80 (m, 2H), 5.36 (d, *J* = 9.2 Hz, 1H), 5.22 – 5.04 (m, 1H), 4.97 – 4.87 (m, 1H), 4.46 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.78 – 3.75 (m, 3H), 3.65 (s, 3H), 2.76 (dd, *J* = 14.0, 4.2 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.36 – 2.26 (m, 1H), 2.10 – 2.03 (m, 1H), 2.02 – 1.79 (m, 2H), 1.79 – 1.66 (m, 1H), 1.34 (s, 9H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.81 (m, 3H). **^{13}C**

NMR (151 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 173.6, 172.9, 172.4, 171.6, 158.8, 158.5, 155.8, 155.6, 130.6, 129.5, 127.7, 127.4, 114.4, 114.2, 79.2, 79.1, 55.3, 55.1, 54.7, 54.5, 52.4, 51.9, 50.0, 42.1, 39.8, 38.8, 38.5, 32.2, 31.7, 28.4, 28.3, 24.4, 23.9, 21.2, 20.7, 20.1, 19.6, 16.9, 16.2. **IR** (film) *v*: 3414, 2963, 1711, 1636, 1513, 1431, 1390, 1249, 1163, 1036, 850 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{24}H_{36}N_2O_6Na$ [M + Na^+] 471.2466. Found 471.2469. $[\alpha]_D^{20}$ = -98.2 (10 mg/mL).

Methyl (3*S*,6*R*)-1-((*tert*-butoxycarbonyl)-L-valyl)-6-(4-methoxyphenyl)piperidine-3-carboxylate (258b). Yield: 123 mg (34%); colorless oil; $\mathbf{R_f}$ = 0.30 (30% acetone/PE); **^{1}H NMR** (400 MHz, $CDCl_3$; *major rotamer*) *δ:* 7.16 – 6.73 (m, 4H), 5.77 – 5.68 (m, 1H), 5.23 – 5.06 (m, 1H), 4.60 – 4.43 (m, 2H), 3.77 – 3.72 (m, 3H), 3.71 – 3.60 (m, 3H), 3.31 (d, *J* = 14.3 Hz, 1H), 2.62 – 2.50 (m, 1H), 2.30 – 1.63 (m, 5H), 1.45 – 1.39 (m, 9H), 1.05 – 0.60 (m, 6H); (*minor rotamer*) *δ:* 7.16 – 6.73 (m, 4H), 5.35 – 5.29 (m, 1H), 5.26 – 5.02 (m, 1H), 4.97 – 4.76 (m, 1H), 4.39 – 4.22 (m, 1H), 3.77 – 3.72 (m, 3H), 3.71 – 3.60 (m, 3H), 3.01 – 2.91 (m, 1H), 2.62 – 2.50 (m, 1H), 2.30 – 1.63 (m, 5H), 1.45 – 1.39 (m, 9H), 1.05 – 0.60 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, *mixture of rotamers*) *δ:* 173.4, 172.8, 158.3, 156.0, 131.1, 130.3, 127.5, 114.2, 79.5, 55.3, 51.9, 50.8, 42.4, 39.3, 38.8, 30.6, 28.4, 26.2, 24.8, 20.5, 19.8, 17.8, 17.3. **IR** (film) *v*: 3310, 2960, 1703, 1636, 1513, 1435, 1364, 1290, 1245, 1163, 1036, 831 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{24}H_{36}N_2O_6Na$ [M + Na^+] 471.2466. Found 471.2472. $[\alpha]_D^{20}$ = 73.0 (10 mg/mL).

Methyl 1-((3*R*,6*S*)-1-((*tert*-butoxycarbonyl)-L-valyl)-6-(4-methoxyphenyl)piperidine-3-carbonyl)-6-(4-methoxyphenyl)piperidine-3-carboxylates (260)



Tripeptides **260a** and **260b** were obtained analogously to compounds **258** from acid **259a** (145 mg, 0.334 mmol) and amine **91** (92 mg, 0.367 mmol, 1.1 equiv) using 57 mg of Oxyma (0.400 mmol, 1.2 equiv), 77 mg of EDCCl (0.400 mmol, 1.2 equiv), 52 mg of DIPEA (70 µL, 0.400 mmol, 1.2 equiv), and 10 mL of CH_2Cl_2. Absolute stereochemistry of the second residue of **91** could not be unequivocally assigned.

Tripeptide 260a. Yield: 102 mg (46%); colorless oil; $\mathbf{R_f}$ = 0.42 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$; *major rotamer*) *δ:* 7.23 – 6.68 (m, 8H), 5.92 – 5.79 (m, 1H), 5.36 (d, *J* = 9.4 Hz, 1H), 5.21 – 5.10 (m, 1H), 4.68 (d, *J* = 13.8 Hz, 1H), 4.51 – 4.40 (m, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 3.84 – 3.54 (m, 9H), 3.42 – 3.30 (m, 1H), 3.27 (d, *J* = 14.0 Hz, 1H), 3.11 – 2.99 (m, 1H), 2.54 – 2.43 (m, 1H), 2.36 – 1.65 (m, 9H), 1.37 (s, 9H), 1.03 – 0.71 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 173.6, 173.3, 172.6, 158.8, 158.4, 156.0, 155.4, 130.6, 130.3, 128.3, 128.1, 127.5, 127.3, 114.3, 114.3, 79.1, 55.4, 55.4, 55.3, 55.0, 52.0, 49.5, 41.8, 39.9, 38.4, 33.7, 32.3, 28.4, 24.9, 24.3, 21.1, 20.9, 19.8, 17.2. **IR** (film) *v*: 3403, 2960, 1707, 1633, 1513, 1431, 1364, 1245, 1163, 1036, 1014, 913, 846, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{37}H_{52}N_3O_8$ [M + H^+] 666.3749. Found 666.3766. $[\alpha]_D^{20}$ = -9.0 (10 mg/mL).

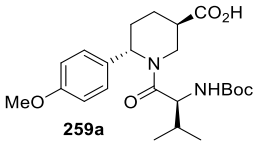
Tripeptide 260b. Yield: 90 mg (41%); colorless oil; $\mathbf{R_f}$ = 0.33 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.29 – 6.61 (m, 8H), 6.21 – 3.85 (m, 6H), 3.85 –

3.55 (m, 9H), 3.55 – 2.38 (m, 4H), 2.38 – 1.57 (m, 9H), 1.59 – 1.20 (m, 9H), 1.11 – 0.64 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, *mixture of rotamers*) *δ:* 173.7, 173.3, 172.5, 158.7, 158.4, 155.9, 155.4, 132.6, 131.0, 130.6, 127.6, 127.3, 114.2, 114.0, 78.9, 78.7, 55.3, 55.3, 54.5, 52.1, 51.7, 48.9, 42.7, 41.8, 39.9, 38.6, 34.5, 32.5, 31.9, 28.4, 24.9, 24.2, 21.9, 21.6, 21.2, 20.9, 20.2, 19.7, 17.3, 16.5. **IR** (film) *v*: 3362, 2960, 1715, 1618, 1513, 1435, 1364, 1249, 1178, 1036, 831 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{37}H_{51}N_3O_8Na$ $[M + Na]^+$ 688.3568. Found 688.3586. $[\alpha]_D^{20}$ = -62.4 (10 mg/mL).

Hydrolysis of methyl esters 258a and 258b

Peptide **258a** or **258b** was dissolved in a 1:1 THF-water mixture at 25 °C, and LiOH (3 equiv) was added in one portion. The reaction was conducted at the same temperature and monitored by TLC. After the complete disappearance of the starting material, the mixture was concentrated to half of its volume and acidified using $KHSO_4$ (1 M solution in H_2O) to pH 3 (indicator paper). Afterwards, the product was extracted from the aqueous phase with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Products **259a** and **259b** were used in the next step without further purification.

(3*R*,6*S*)-1-((*tert*-Butoxycarbonyl)-L-valyl)-6-(4-methoxyphenyl)piperidine-3-carboxylic acid (259a)

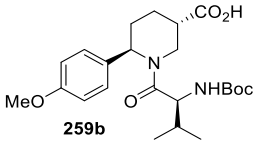


259a

Obtained from **258a** (462 mg, 1.03 mmol) as a white solid (429 mg, 96%).

R_f = 0.39 (5% $MeOH/CH_2Cl_2$); **^{1}H NMR** (400 MHz, $CDCl_3$; *major rotamer*) *δ:* 10.71 (br s, 1H), 7.13 – 7.03 (m, 2H), 6.94 – 6.80 (m, 2H), 5.91 – 5.83 (m, 1H), 5.63 (d, *J* = 9.0 Hz, 1H), 5.05 – 4.97 (m, 1H), 4.14 (d, *J* = 14.0 Hz, 1H), 3.80 – 3.74 (m, 3H), 3.20 (dd, *J* = 14.0, 3.9 Hz, 1H), 2.66 – 2.53 (m, 1H), 2.37 – 1.68 (m, 5H), 1.43 (s, 9H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.90 – 0.83 (m, 3H); (*minor rotamer*) *δ:* 10.71 (br s, 1H), 7.13 – 7.03 (m, 2H), 6.94 – 6.80 (m, 2H), 5.59 – 5.48 (m, 1H), 5.26 – 5.15 (m, 1H), 4.93 (d, *J* = 13.7 Hz, 1H), 4.54 – 4.45 (m, 1H), 3.80 – 3.74 (m, 3H), 2.85 – 2.67 (m, 1H), 2.66 – 2.53 (m, 1H), 2.37 – 1.68 (m, 5H), 1.35 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 – 0.83 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 177.2, 176.4, 172.9, 171.8, 158.8, 158.5, 156.0, 155.7, 130.6, 129.4, 127.7, 127.4, 114.4, 114.2, 79.5, 79.3, 55.3, 55.2, 54.8, 54.7, 50.3, 42.1, 39.4, 38.8, 38.5, 32.1, 31.5, 28.4, 28.3, 24.5, 24.0, 20.8, 20.7, 20.0, 19.7, 17.0, 16.3. **IR** (film) *v*: 3310, 2967, 2933, 1715, 1636, 1513, 1439, 1364, 1245, 1163, 1092, 1014, 917, 731 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{34}N_2O_6Na$ $[M + Na^+]$ 457.2309. Found 457.2311. $[\alpha]_D^{20}$ = -75.5 (10 mg/mL).

(3*S*,6*R*)-1-((*tert*-Butoxycarbonyl)-L-valyl)-6-(4-methoxyphenyl)piperidine-3-carboxylic acid (259b)

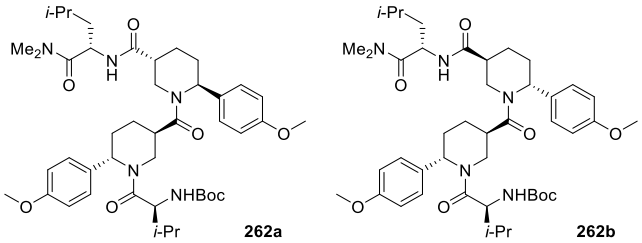


259b

Obtained from **258b** (244 mg, 0.544 mmol) as a white solid (229 mg, 97%).

R_f = 0.35 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$; *major rotamer*) *δ:* 10.17 (br s, 1H), 7.24 – 6.70 (m, 4H), 5.84 – 5.71 (m, 1H), 5.43 (d, *J* = 9.8 Hz, 1H), 4.69 – 4.52 (m, 2H), 3.88 – 3.70 (m, 3H), 3.32 (d, *J* = 13.9 Hz, 1H), 2.63 (s, 1H), 2.41 – 1.69 (m, 5H), 1.52 – 1.38 (m, 9H), 1.04 – 0.69 (m, 6H); (*minor rotamer*) *δ:* 10.17 (br s, 1H), 7.24 – 6.70 (m, 4H), 6.37 (d, *J* = 10.1 Hz, 1H), 5.61 – 5.49 (m, 1H), 5.00 (d, *J* = 13.8 Hz, 1H), 4.35 – 4.22 (m, 1H), 3.88 – 3.70 (m, 3H), 3.02 (d, *J* = 13.8 Hz, 1H), 2.63 (s, 1H), 2.41 – 1.69 (m, 5H), 1.52 – 1.38 (m, 9H), 1.04 – 0.69 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; *mixture of rotamers*) 178.3, 177.4, 173.7, 173.5, 158.8, 158.4, 156.2, 131.5, 130.2, 127.5, 114.3, 79.7, 79.3, 55.7, 55.4, 51.0, 42.5, 39.3, 39.0, 38.8, 30.7, 28.4, 26.1, 25.0, 20.5, 19.9, 19.7, 18.2. **IR** (film) *v*: 3295, 2967, 2930, 1700, 1595, 1513, 1457, 1364, 1290, 1238, 1163, 1036, 1014, 828 cm^{-1}; **HRMS** (ESI-TOF) m/z calcd for $C_{23}H_{34}N_2O_6Na$ [M + Na^+] 457.2309. Found 457.2313. $[\alpha]_D^{20}$ = 56.0 (10 mg/mL).

Preparation of tetrapeptides 262a and 262b



262a **262b**

Methyl esters **260a** and **260b** were converted into the corresponding acids using a procedure analogous to that described for dipeptides, and the formation of compounds **261a** and **261b** was confirmed by mass spectrometry. **HRMS** (ESI-TOF) m/z calcd for $C_{36}H_{49}N_3O_8Na$ [M + Na^+] 674.3412. Found for **261a** 674.3426. Found for **261b** 674.3423. The crude product was then placed in a flask equipped with a magnetic stirring bar, Leu-NMe_2·HCl (1.6 equiv) and HOBt·H_2O (1.40 equiv) were added, whereupon the reaction vessel was flushed with nitrogen. The solid mixture was dissolved in dry CH_2Cl_2 (c**261**0.2 M). Next, EDCCl (1.4 equiv) and DIPEA (dropwise) were added, and the stirring was continued at 25 °C for 2 h. After that time, the mixture was diluted with additional CH_2Cl_2 and sequentially washed with 10% aqueous (w/v) citric acid, saturated $NaHCO_3$, and finally brine. The organic layer was dried over anhydrous Na_2SO_4. The residue obtained after the removal of the solvent was chromatographed on silica gel eluting with MeOH/CH_2Cl_2 to provide compound **262a** or **262b**.

Tetrapeptide 262a*:* obtained from **260a** (120 mg, 0.180 mmol); yield after two steps 98 mg (69%), colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$; *major rotamer*) *δ:* 7.23 – 6.95 (m, 4H), 6.95 – 6.71 (m, 4H), 6.54 – 6.43 (m, 1H), 5.84 – 5.77 (m, 1H), 5.43 – 5.36 (m, 1H), 5.20 – 5.11 (m, 1H), 5.00 – 4.94 (m, 1H), 4.75 (d, *J* = 14.1 Hz, 1H), 4.52 – 4.44 (m, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 3.90 – 3.73 (m, 6H), 3.49 – 3.41 (m, 1H), 3.27 (d, *J* = 13.4 Hz, 1H), 3.12 – 2.84 (m, 8H),

2.52 – 2.41 (m, 1H), 2.27 – 0.66 (m, 32H). **HRMS** (ESI-TOF) m/z calcd for $C_{44}H_{65}N_5O_8Na$ [M + Na^+] 814.4725. Found 814.4738. $[\alpha]_D^{20}$ = 3.8 (10 mg/mL).

Tetrapeptide 262b*:* obtained from **260b** (110 mg, 0.165 mmol); yield after two steps 99 mg (76%); colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$; *mixture of rotamers*) *δ:* 7.21 – 6.71 (m), 5.89 – 5.31 (m), 5.24 – 4.50 (m), 4.46 – 3.93 (m), 3.87 – 3.59 (m), 3.54 – 0.37 (m). **HRMS** (ESI-TOF): m/z calcd for $C_{44}H_{66}N_5O_8$ [M + H^+] 792.4906. Found 792.4920. $[\alpha]_D^{20}$ = -77.4 (10 mg/mL).

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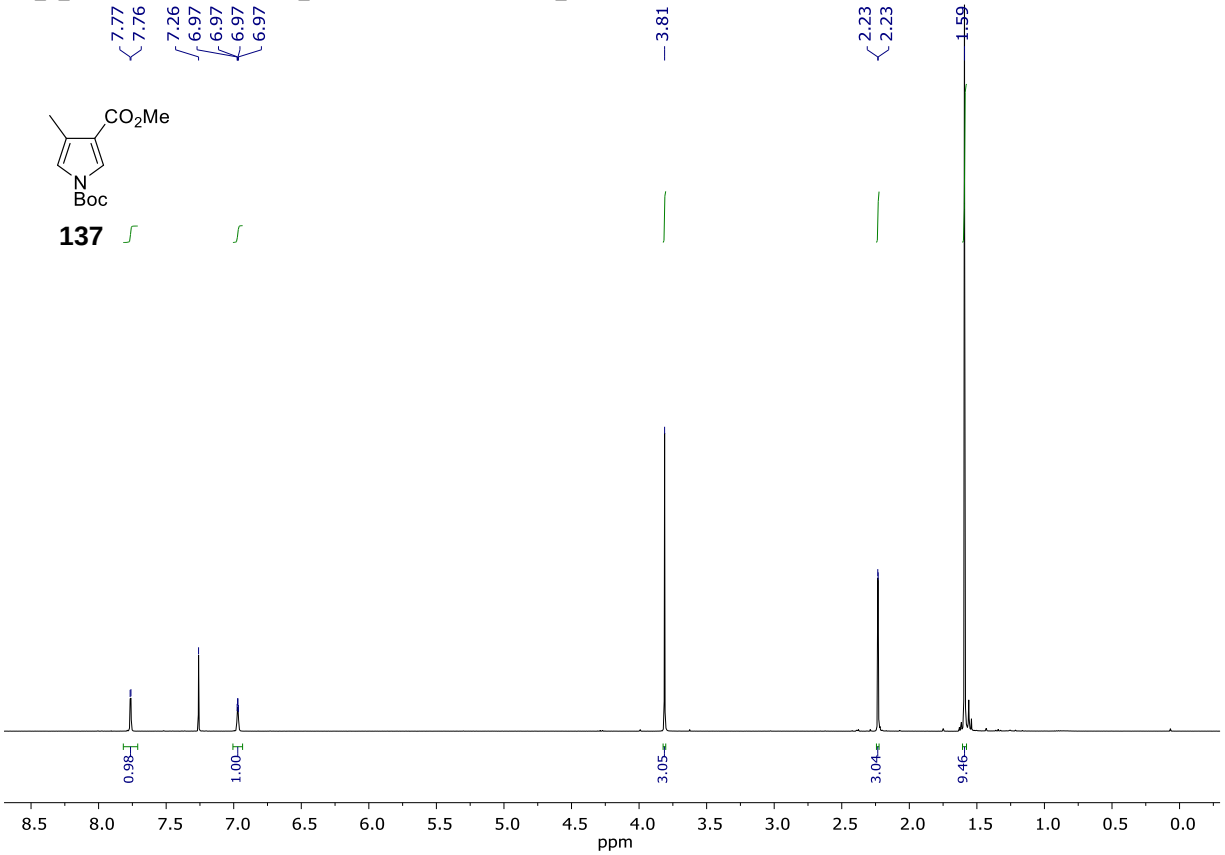
Appendix 1. Copies of NMR spectra



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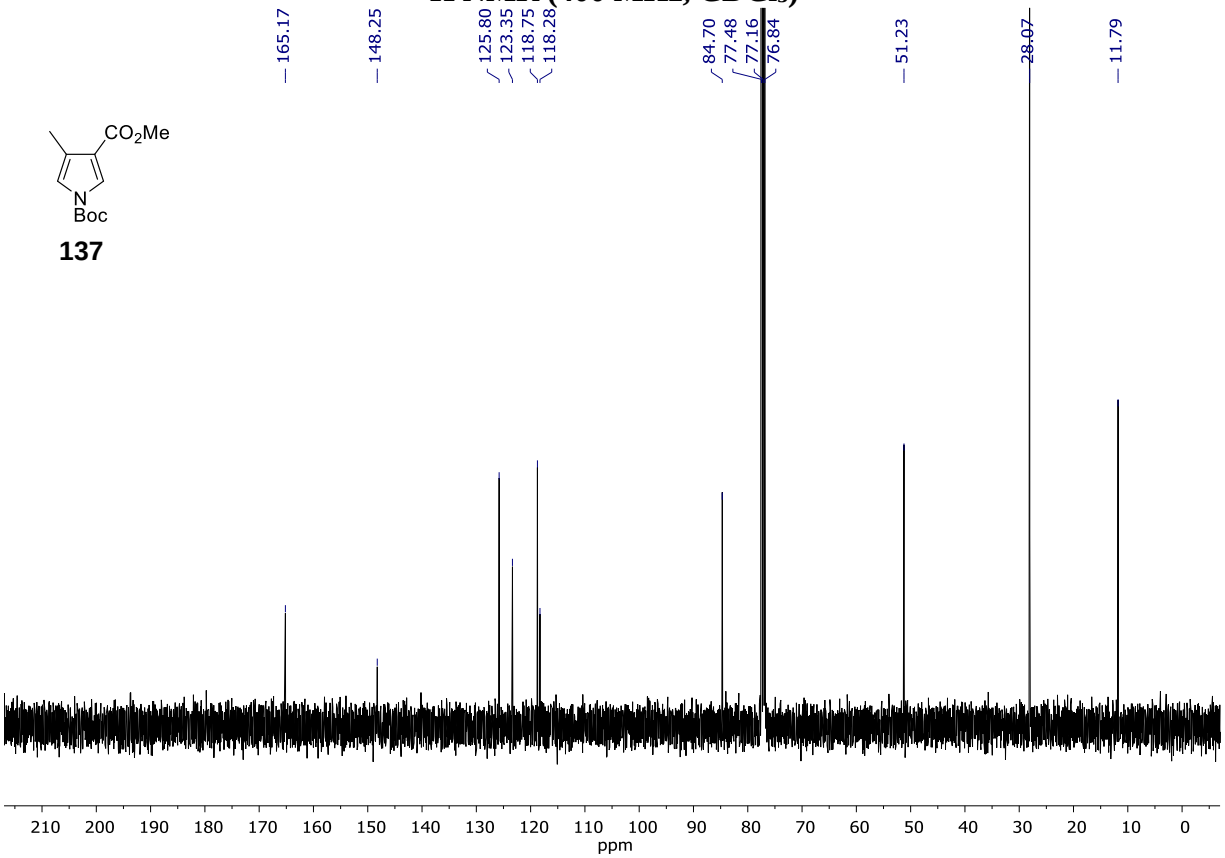

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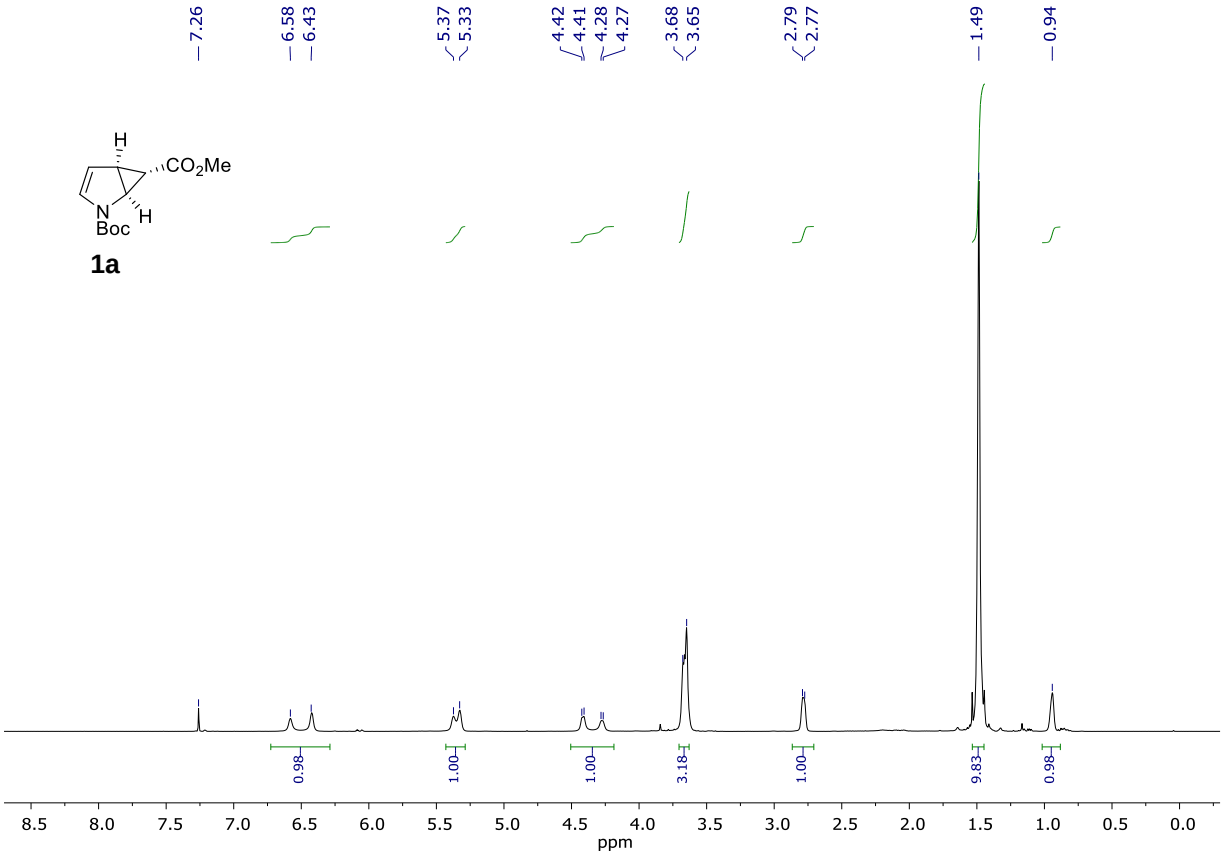

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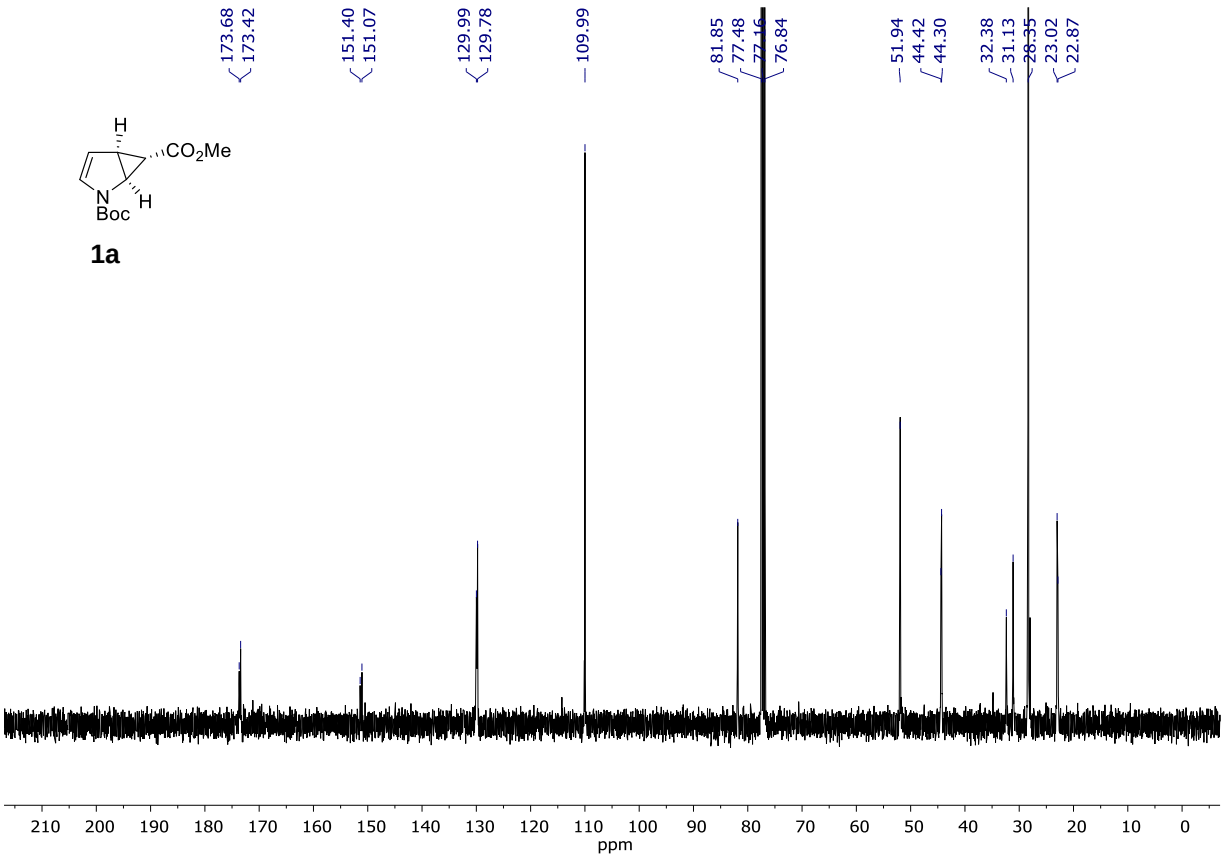

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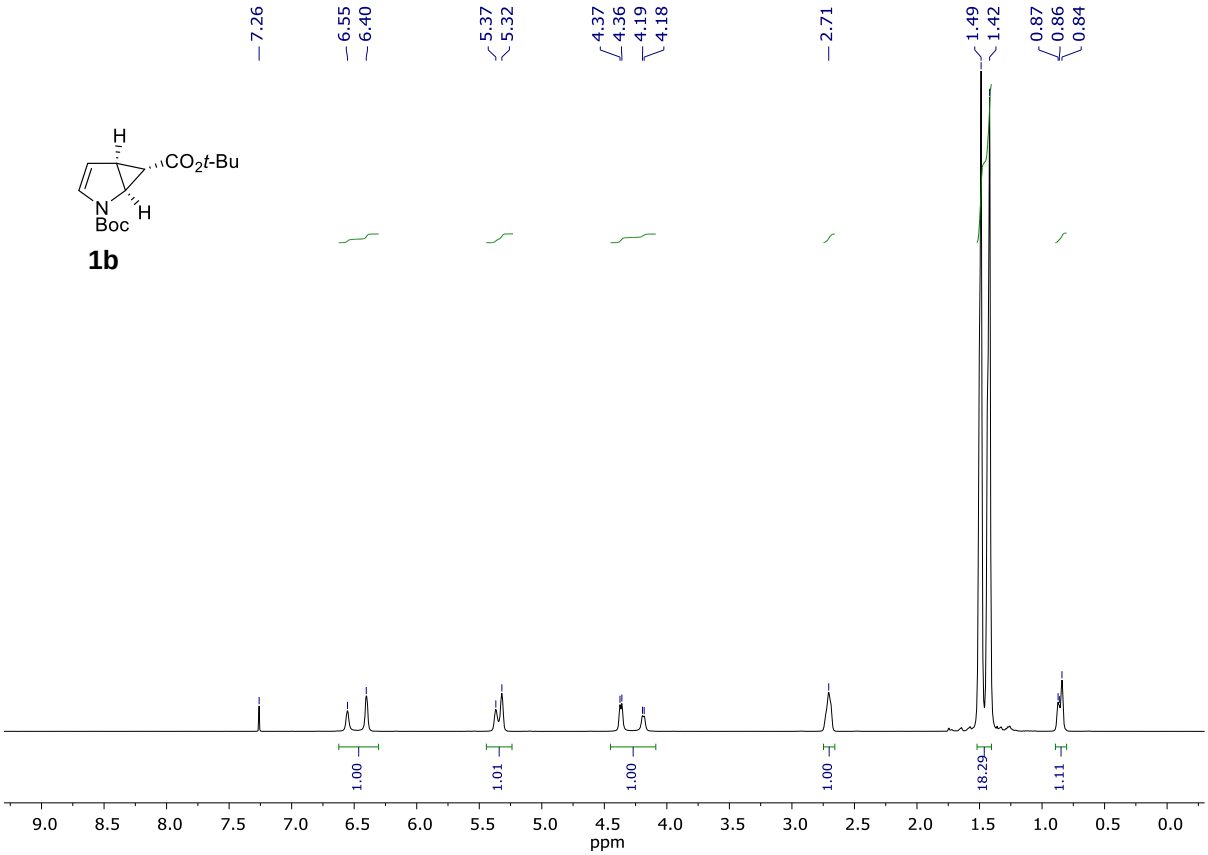

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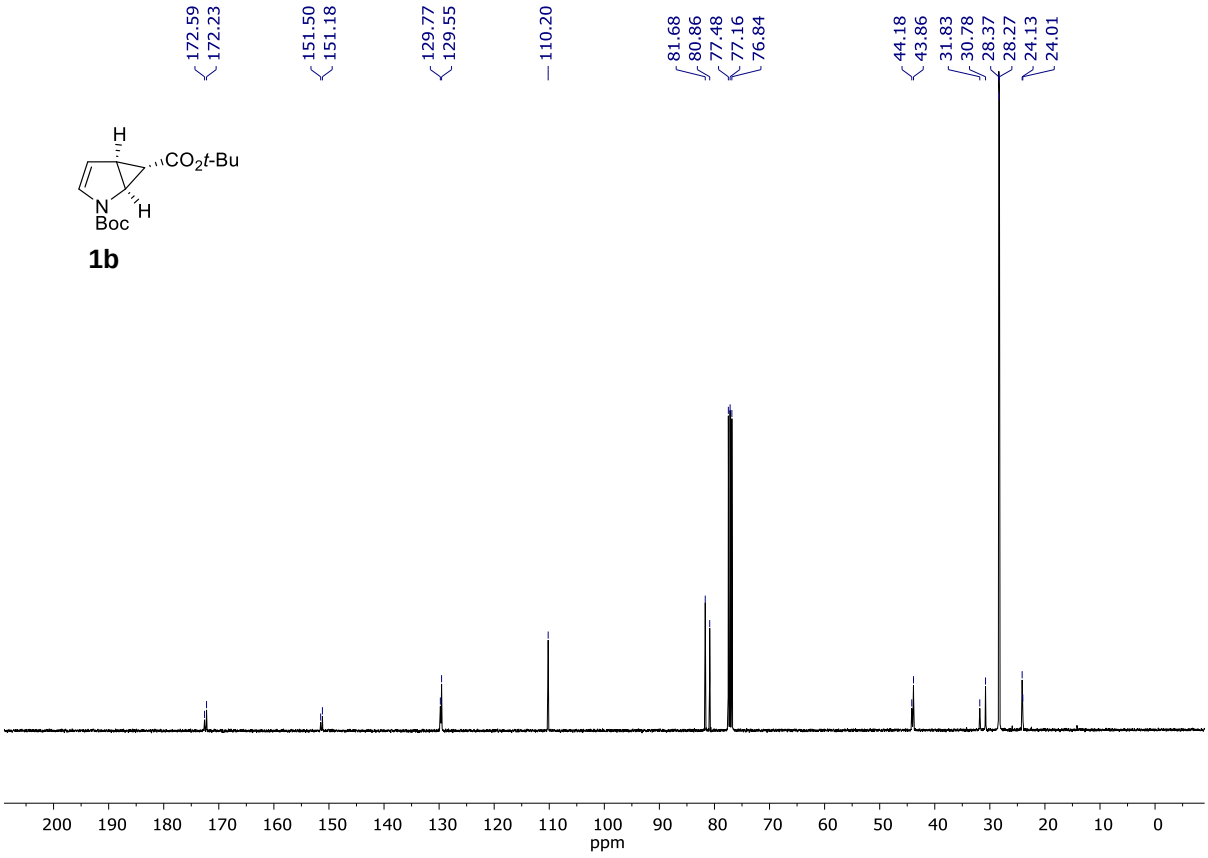

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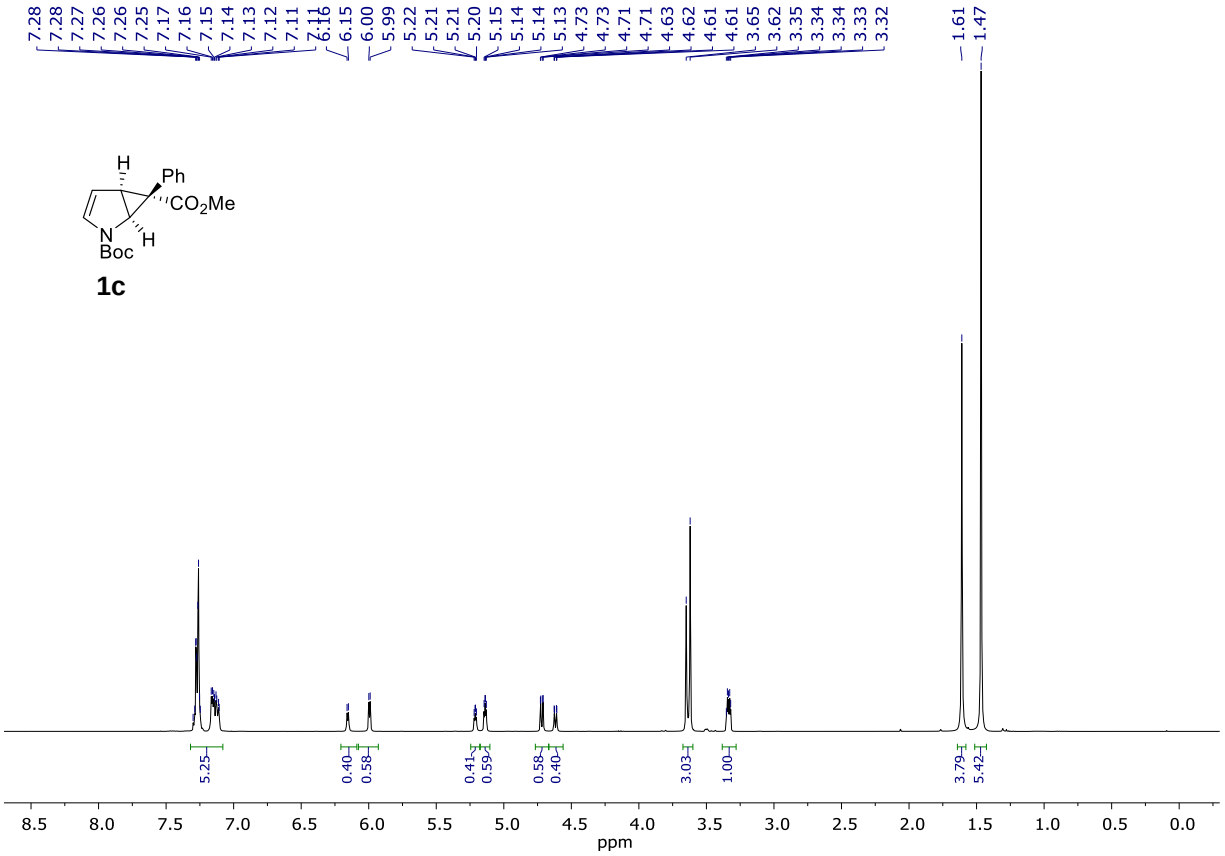

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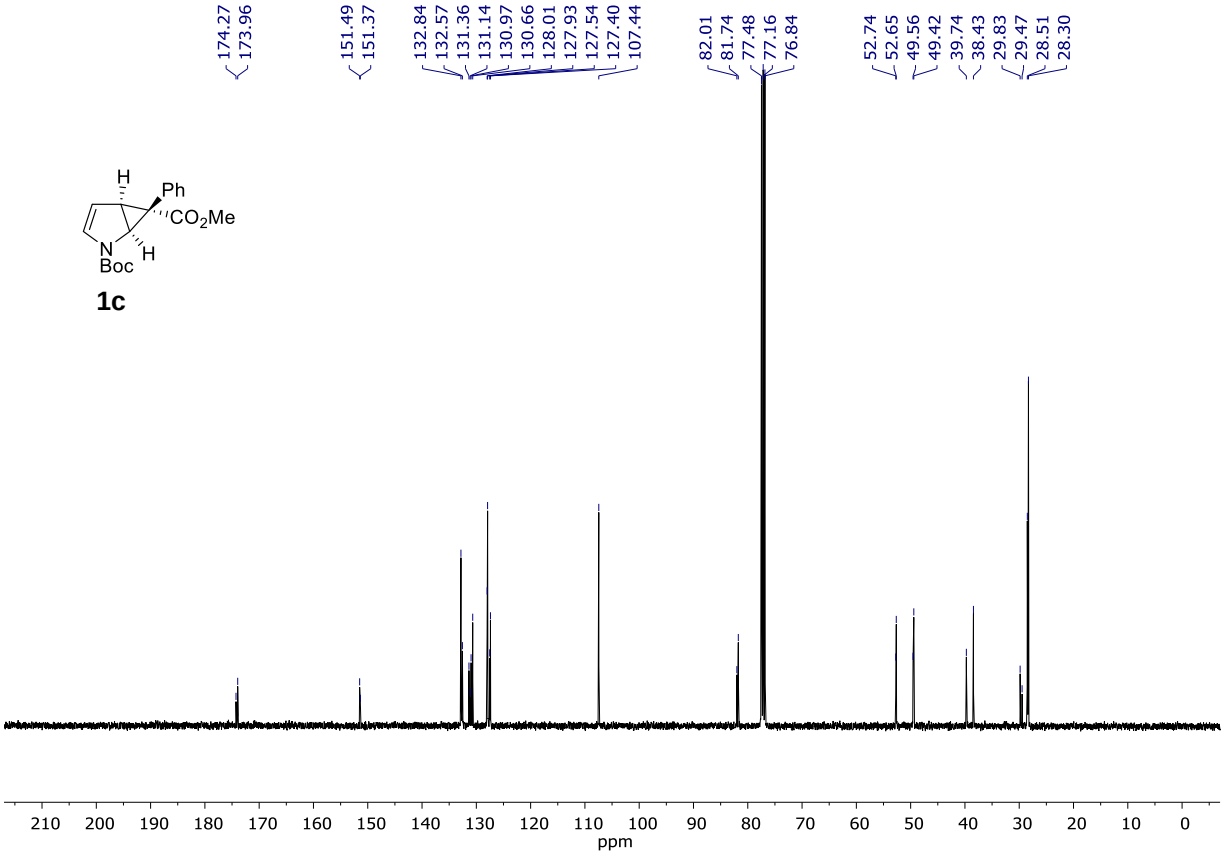

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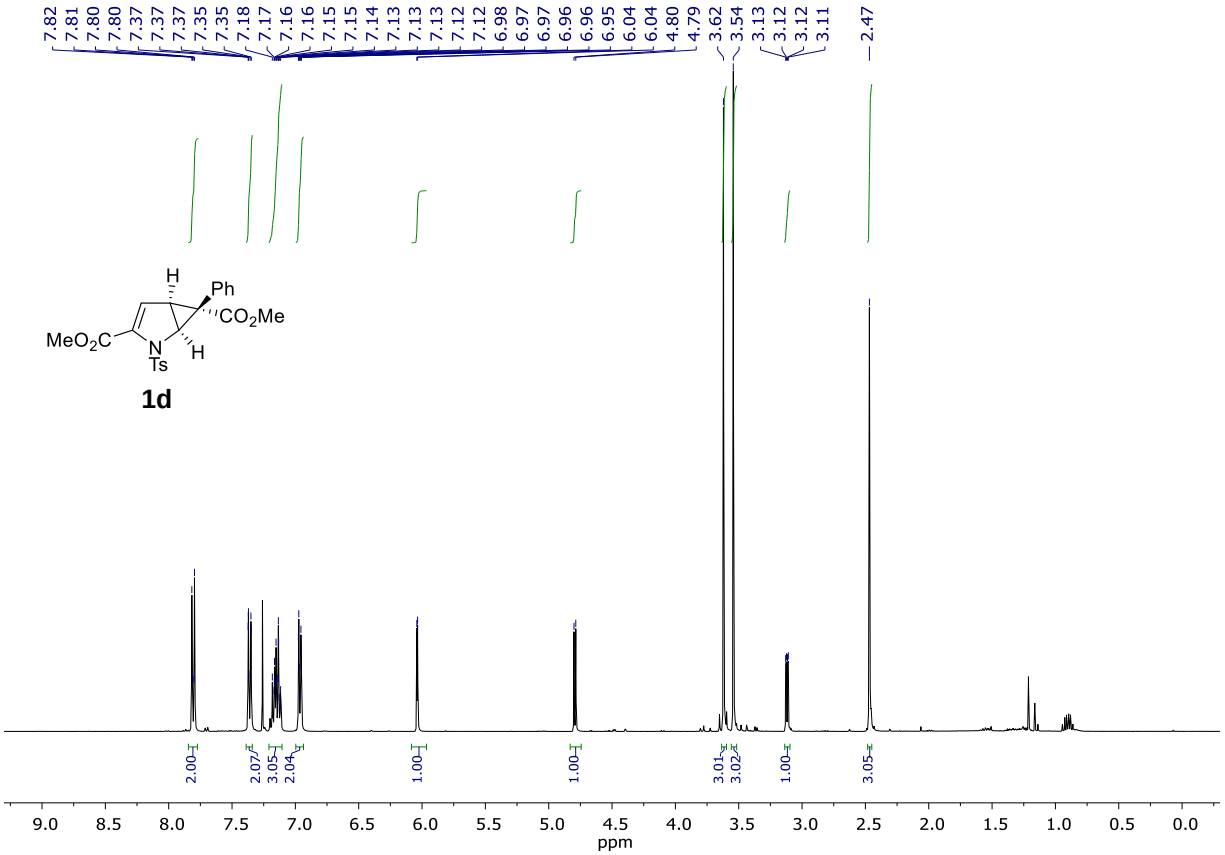

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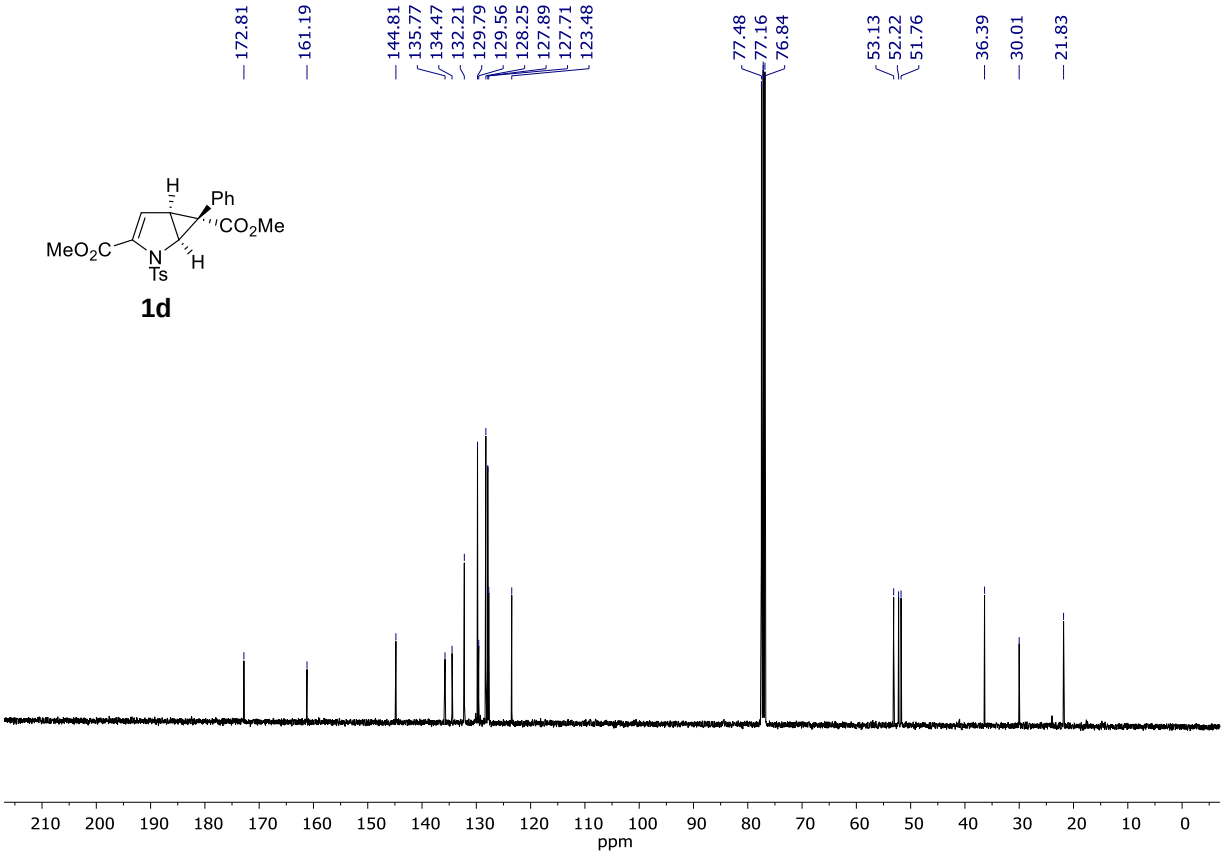

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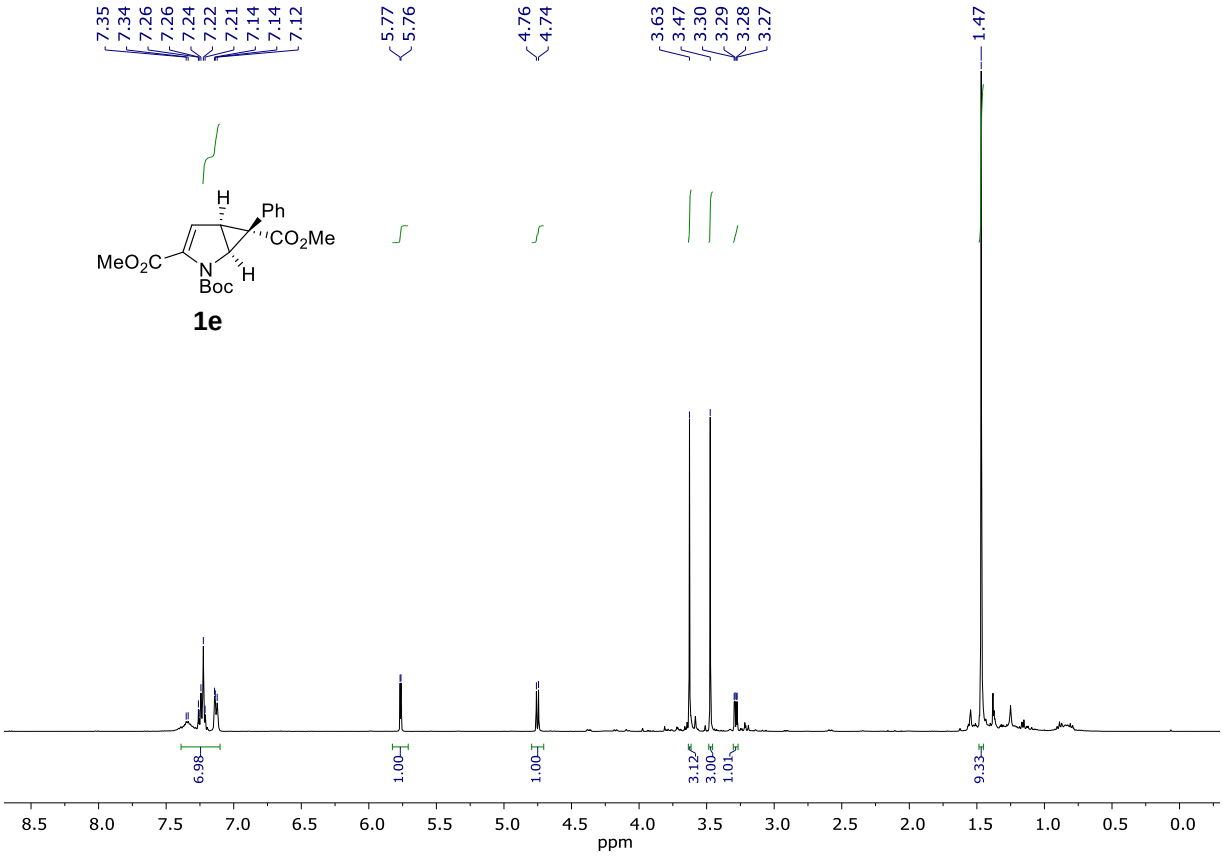

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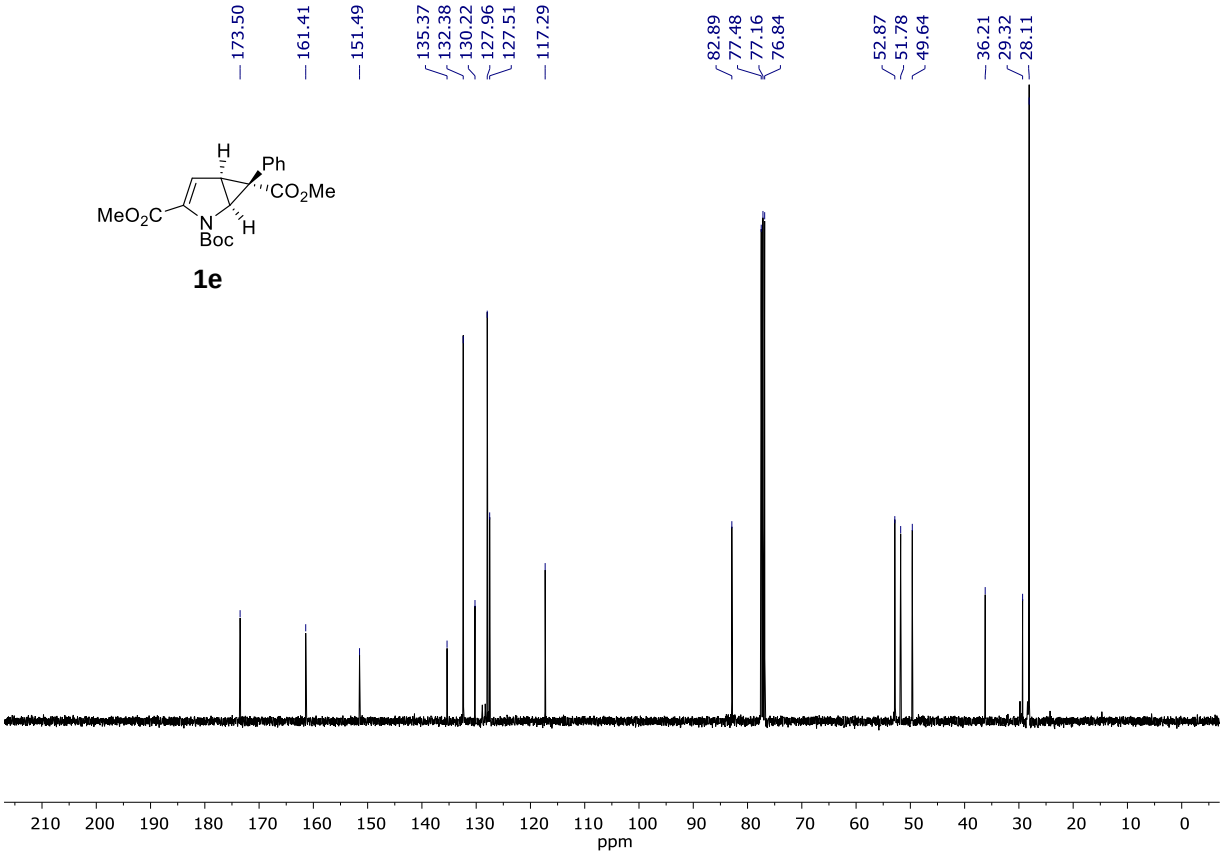

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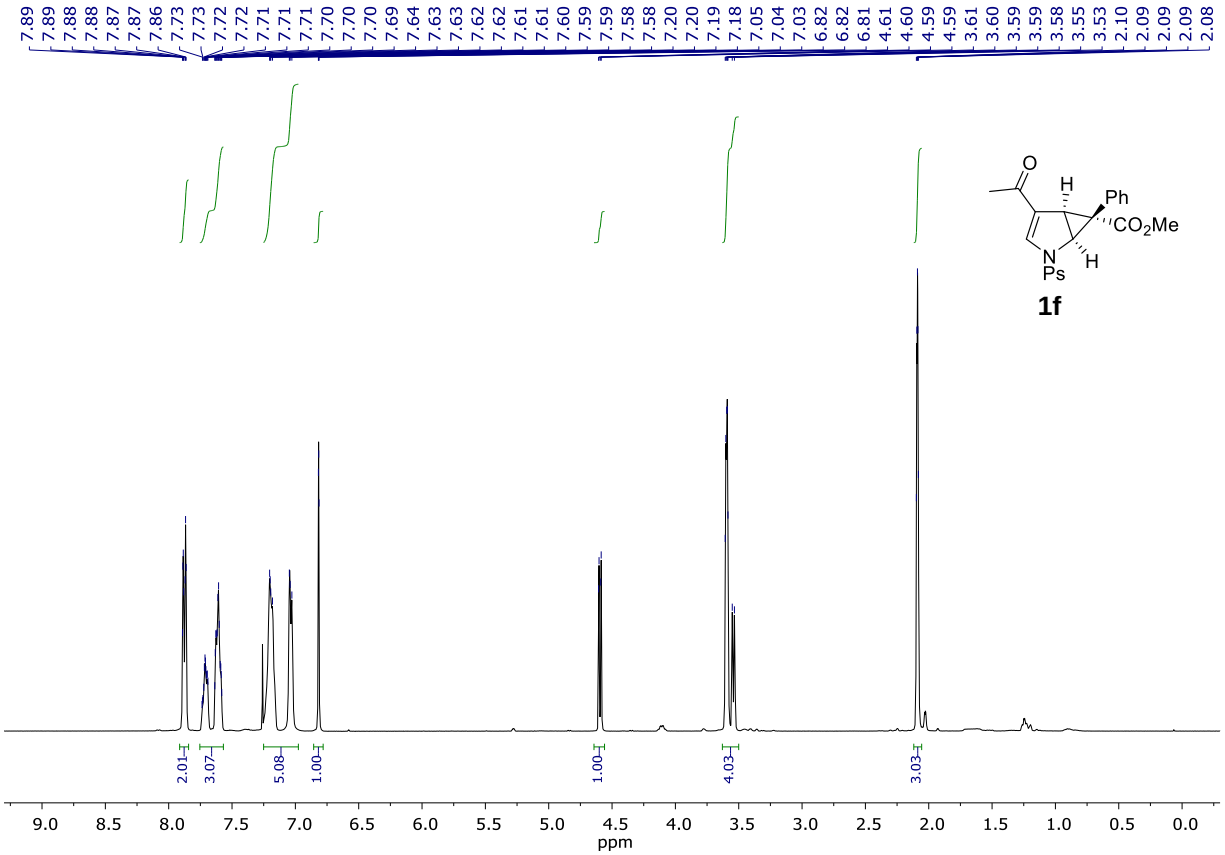

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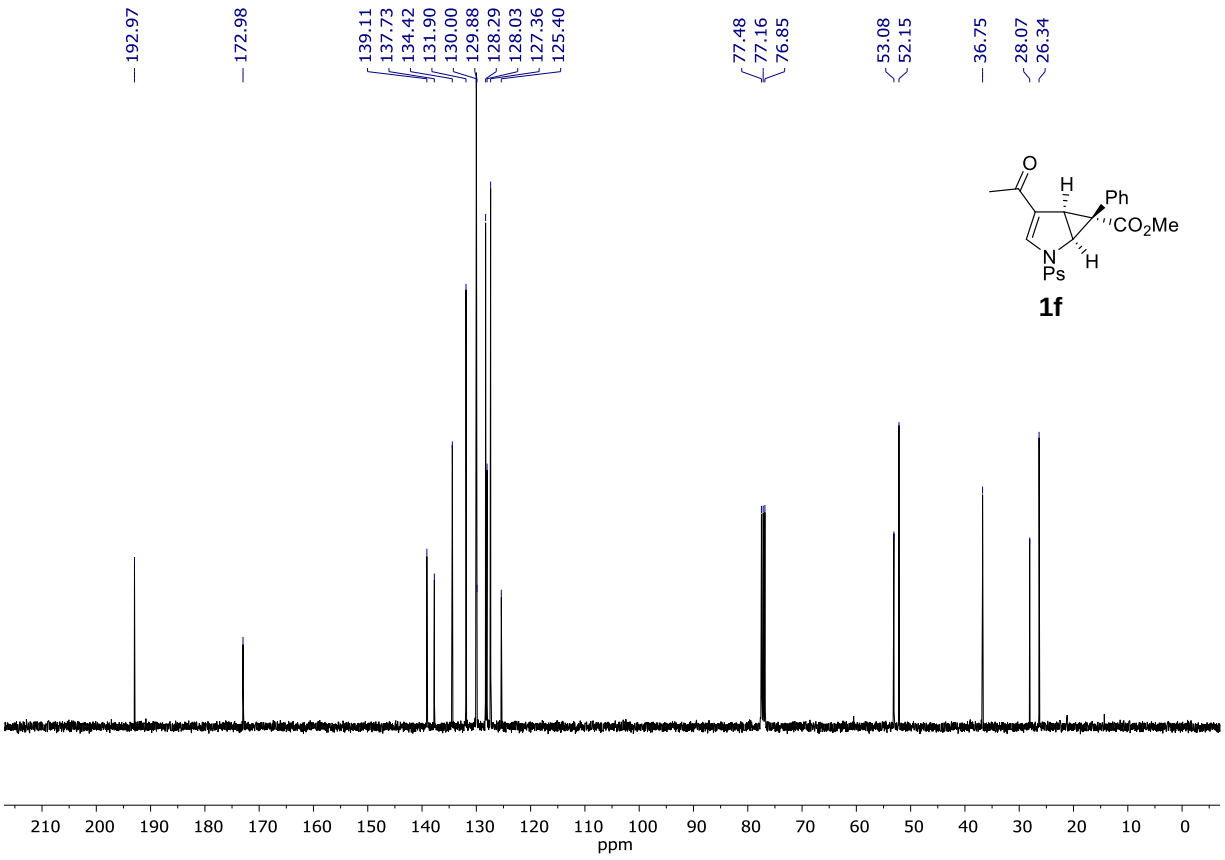

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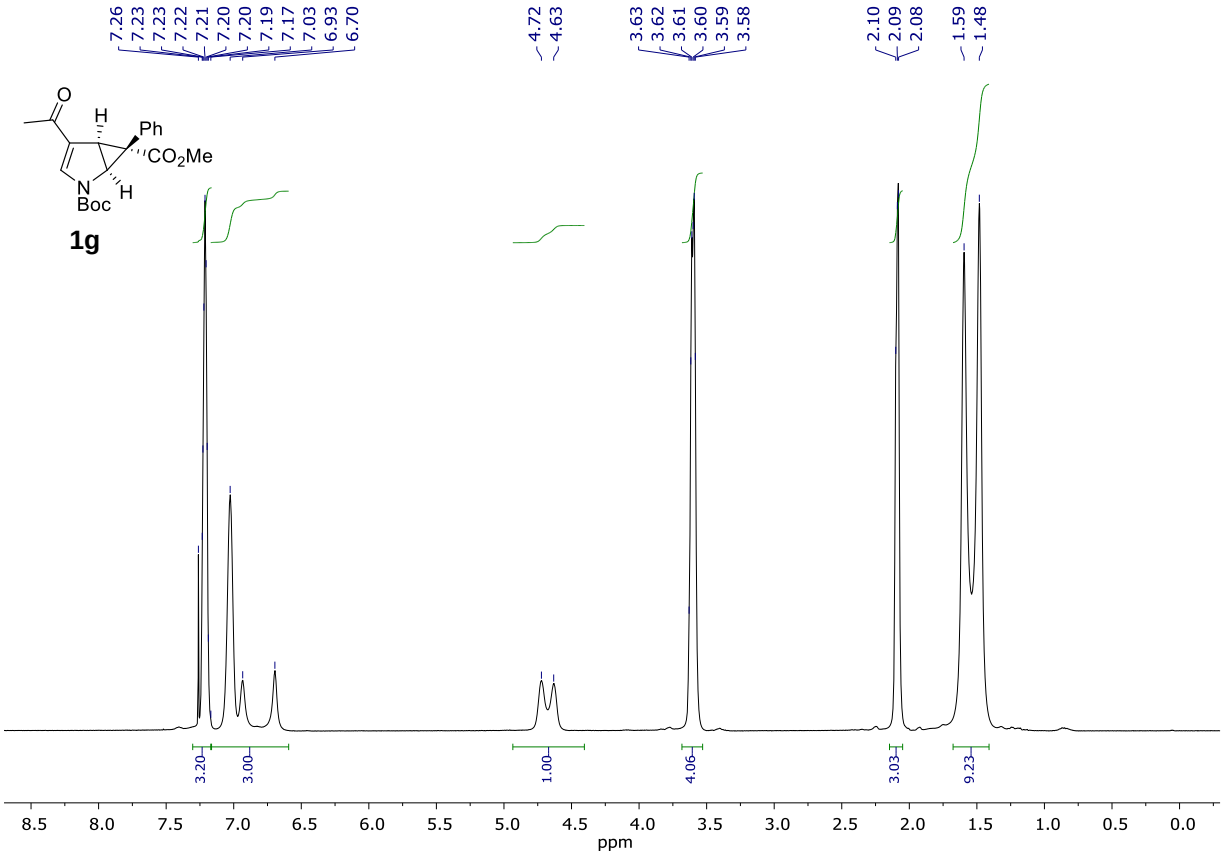

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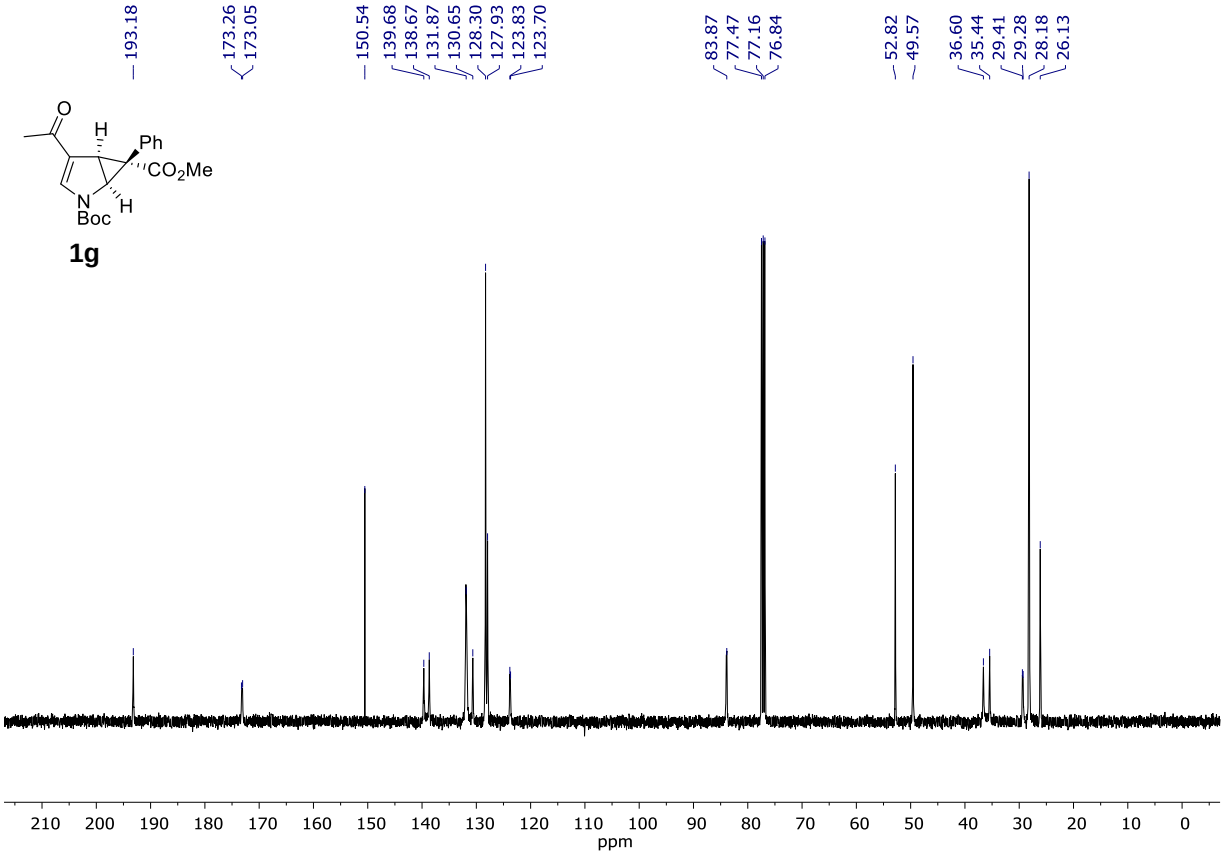

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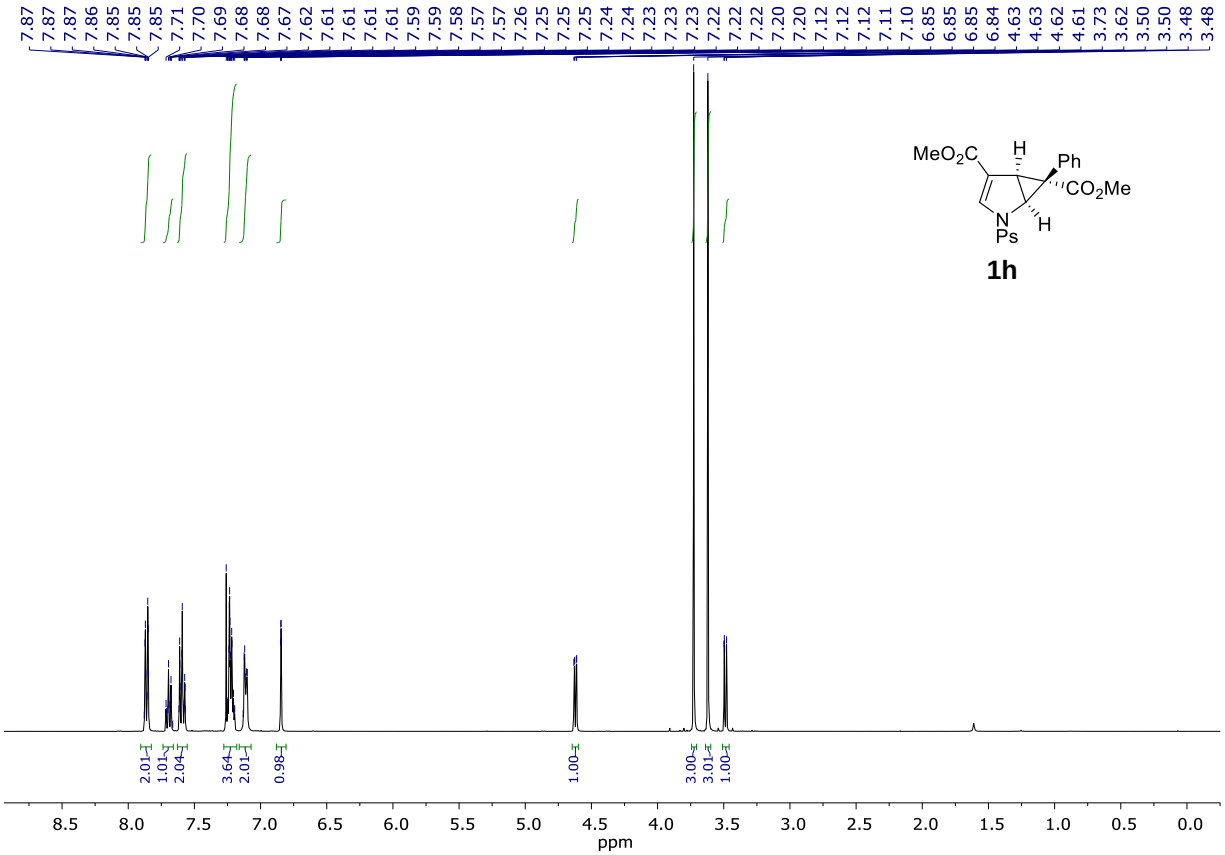

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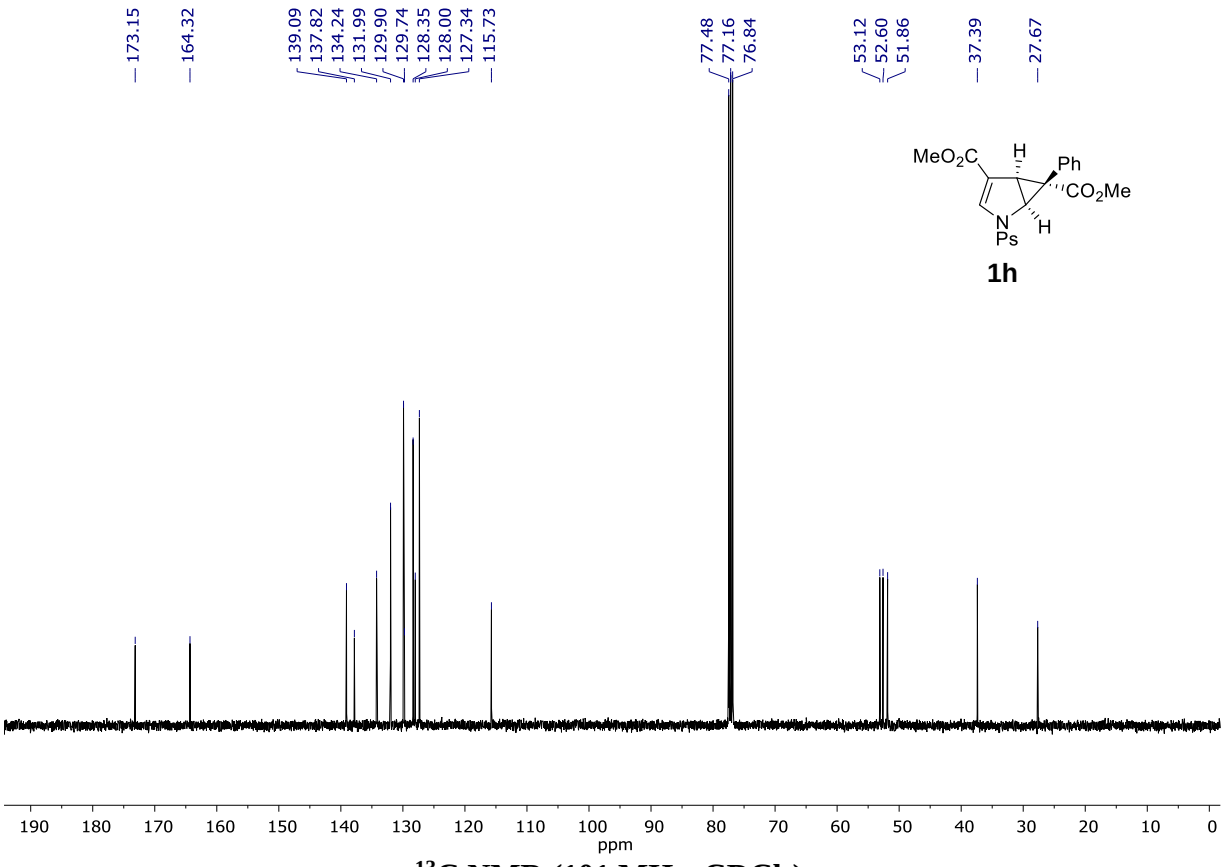

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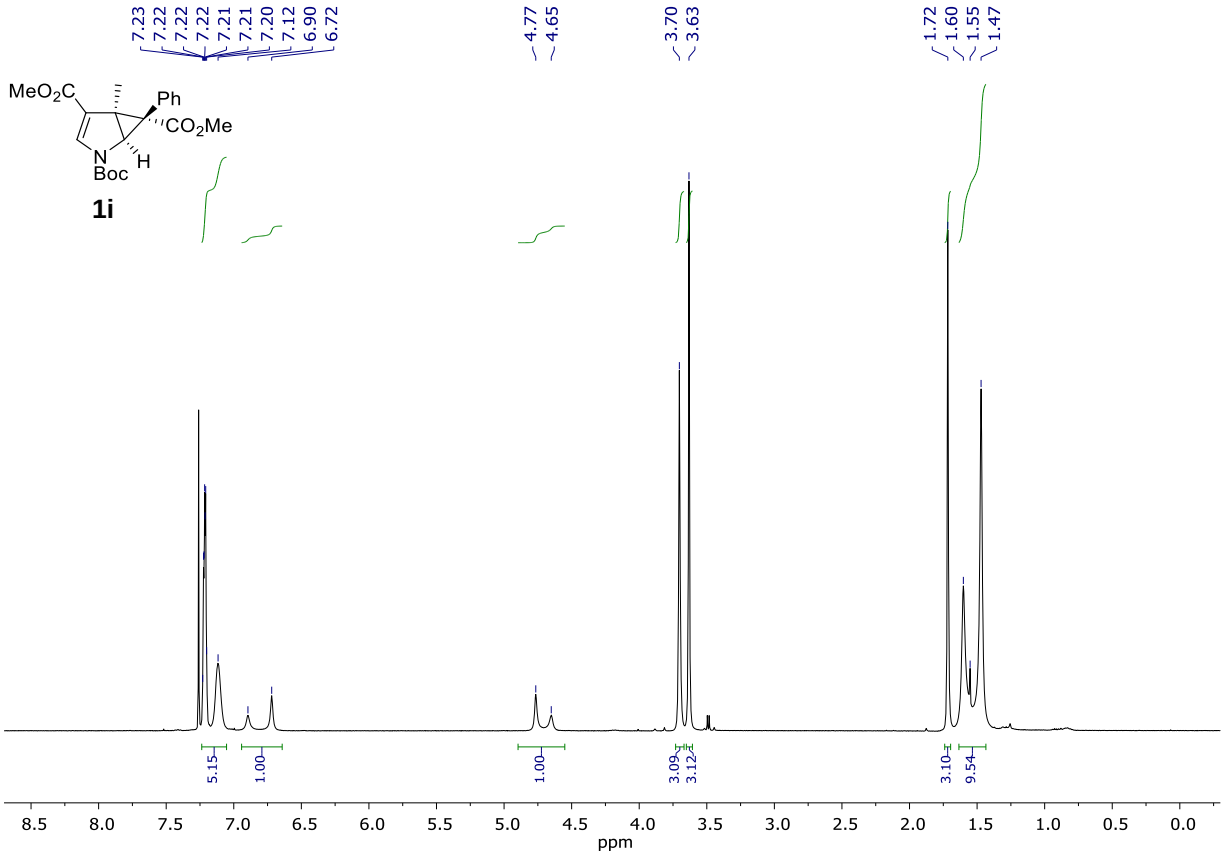

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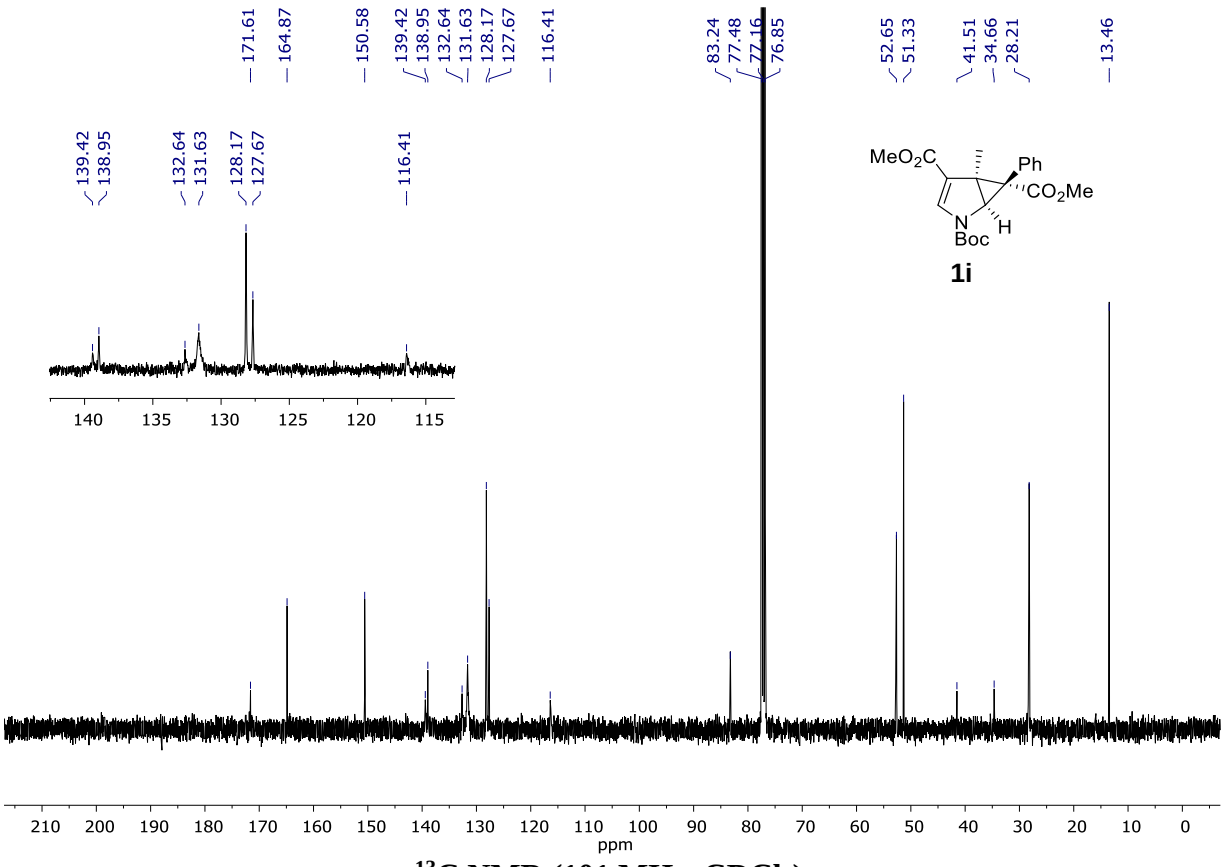

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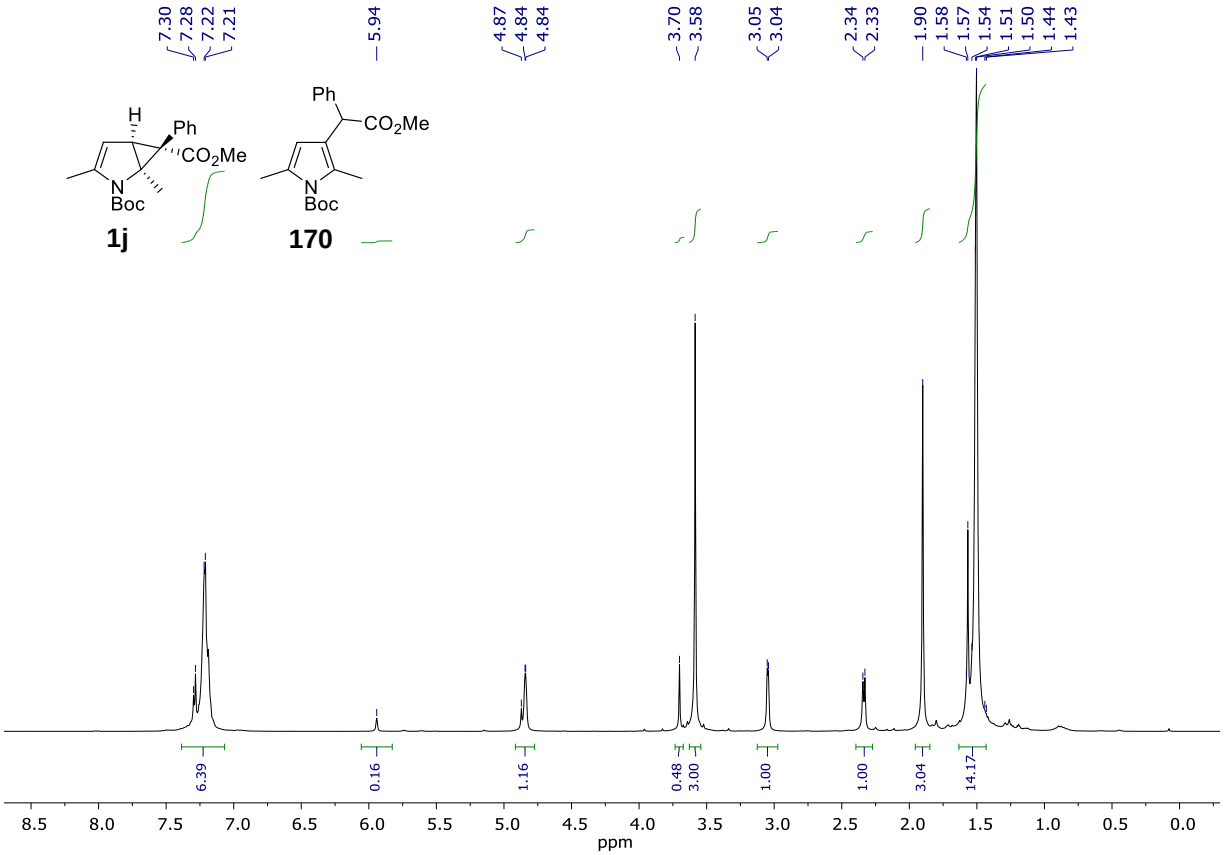

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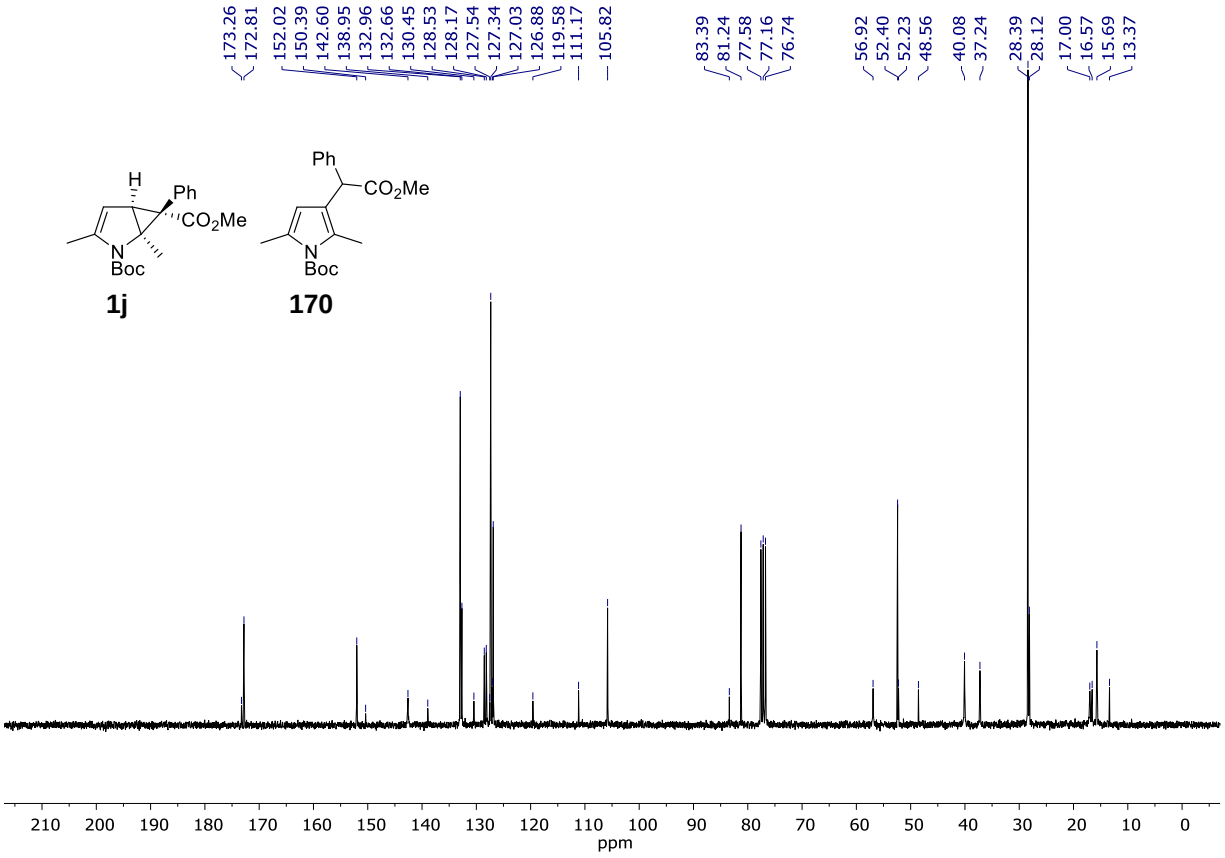

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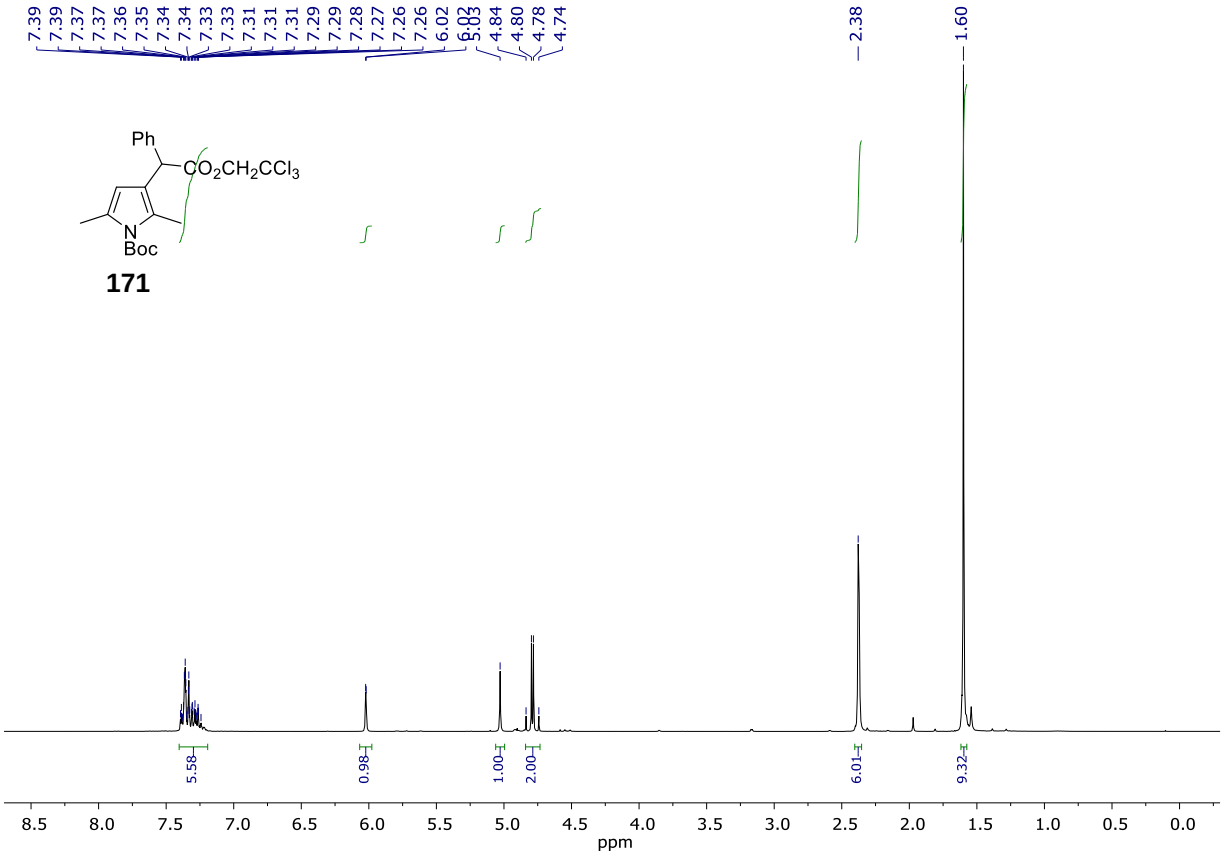

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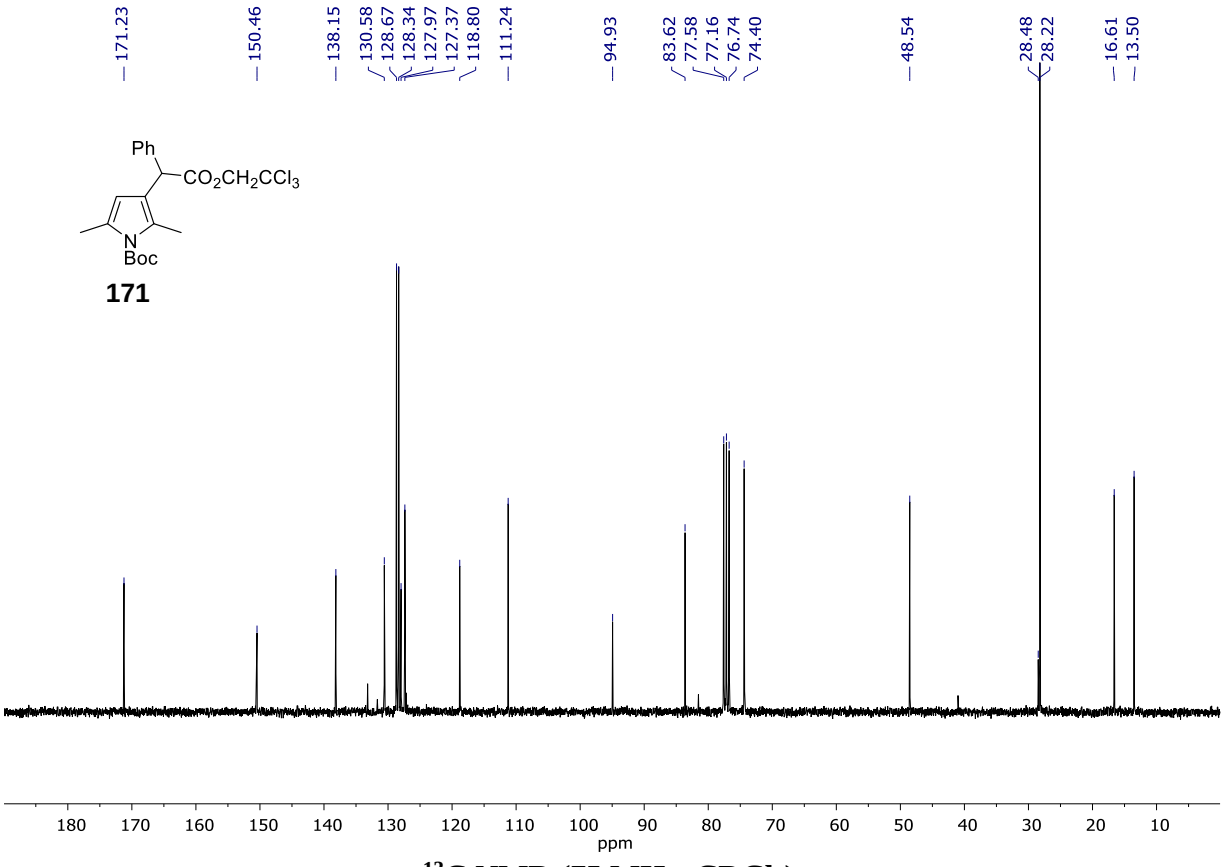

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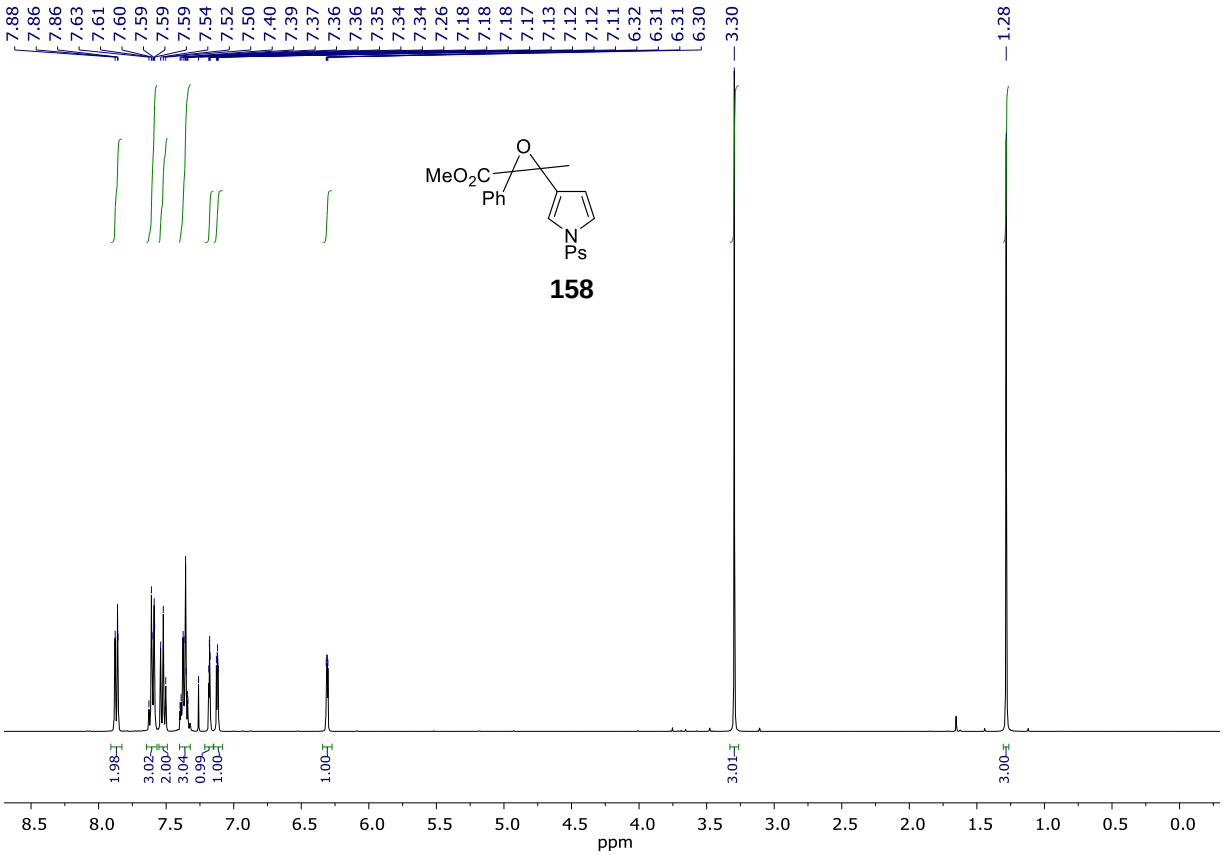

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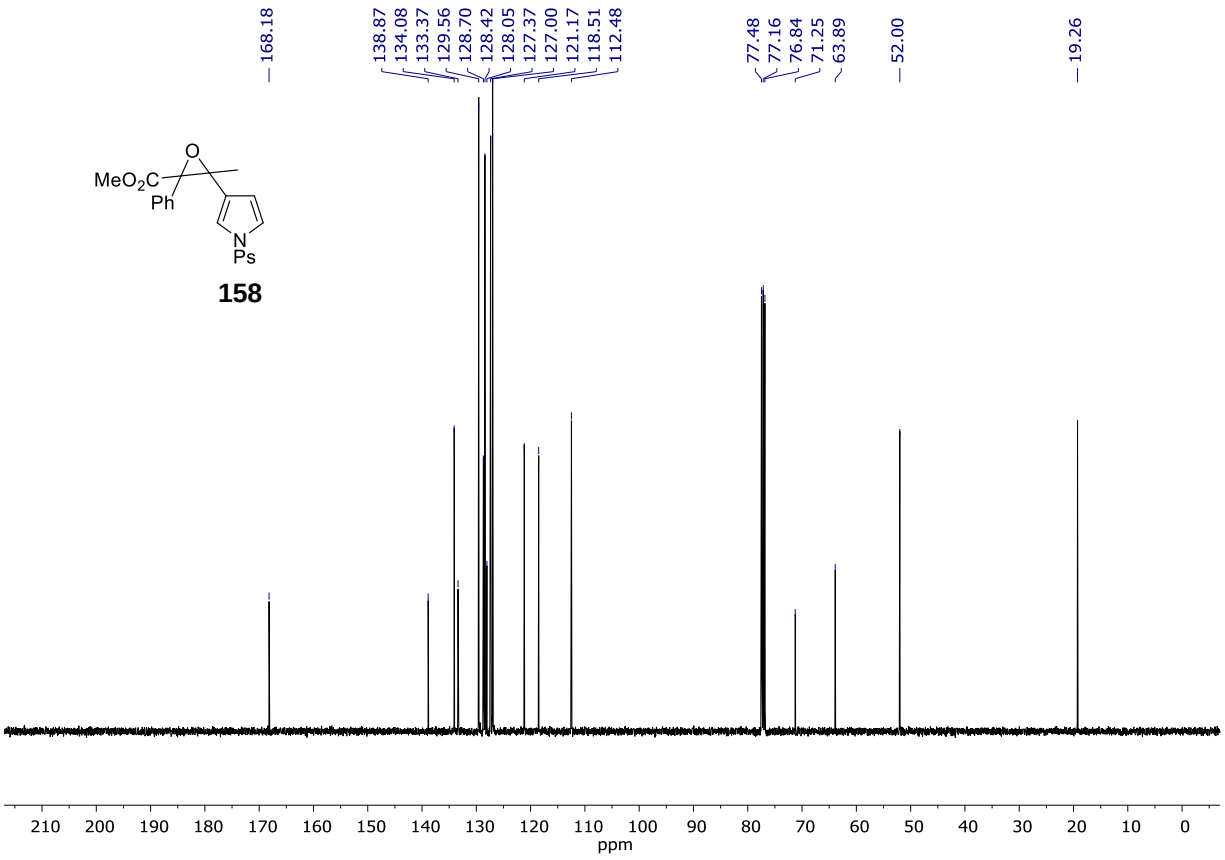

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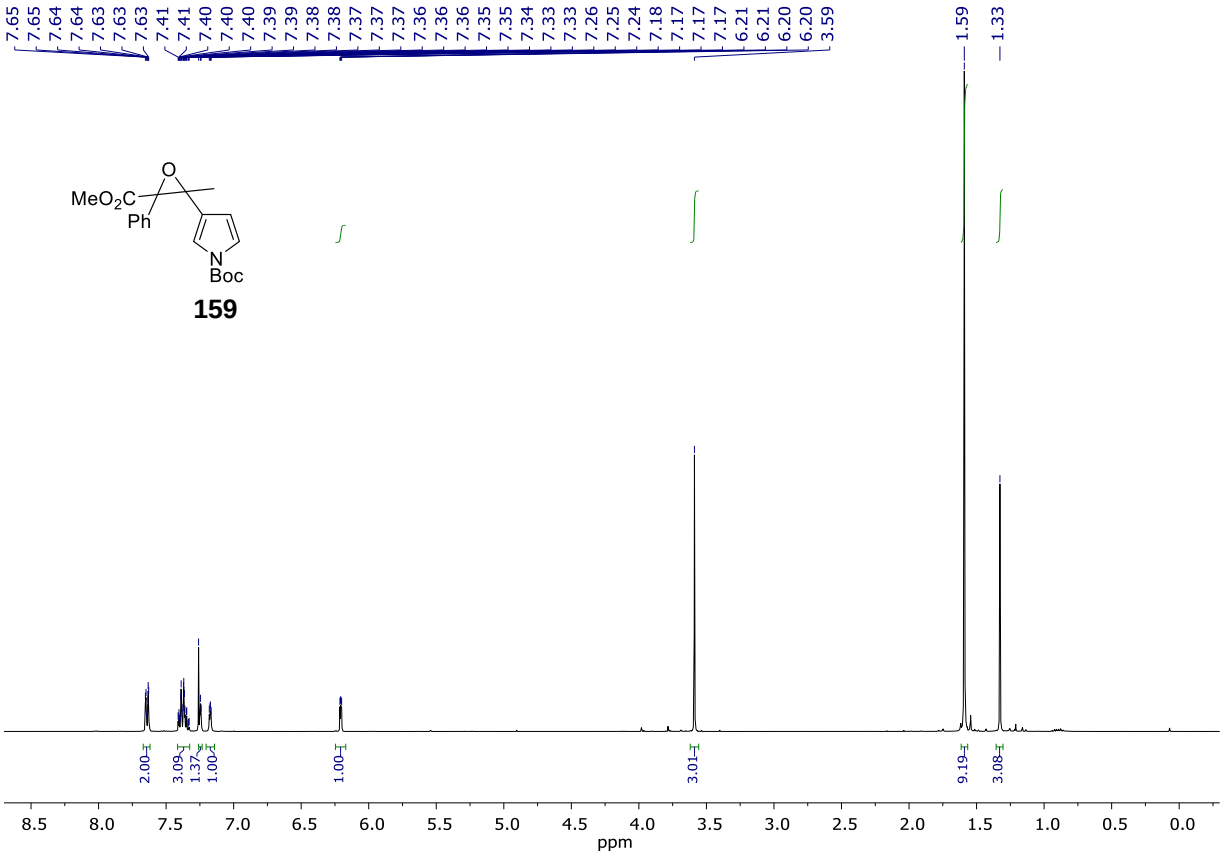
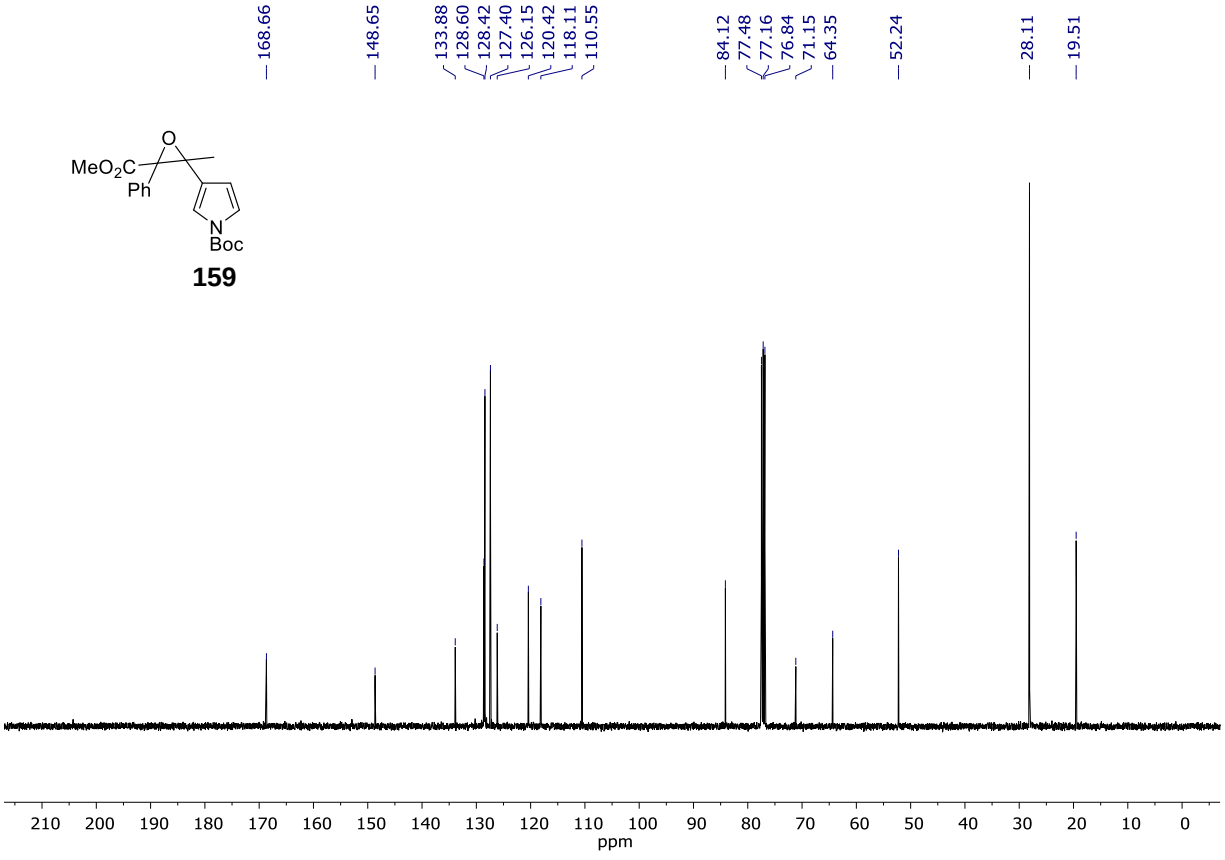


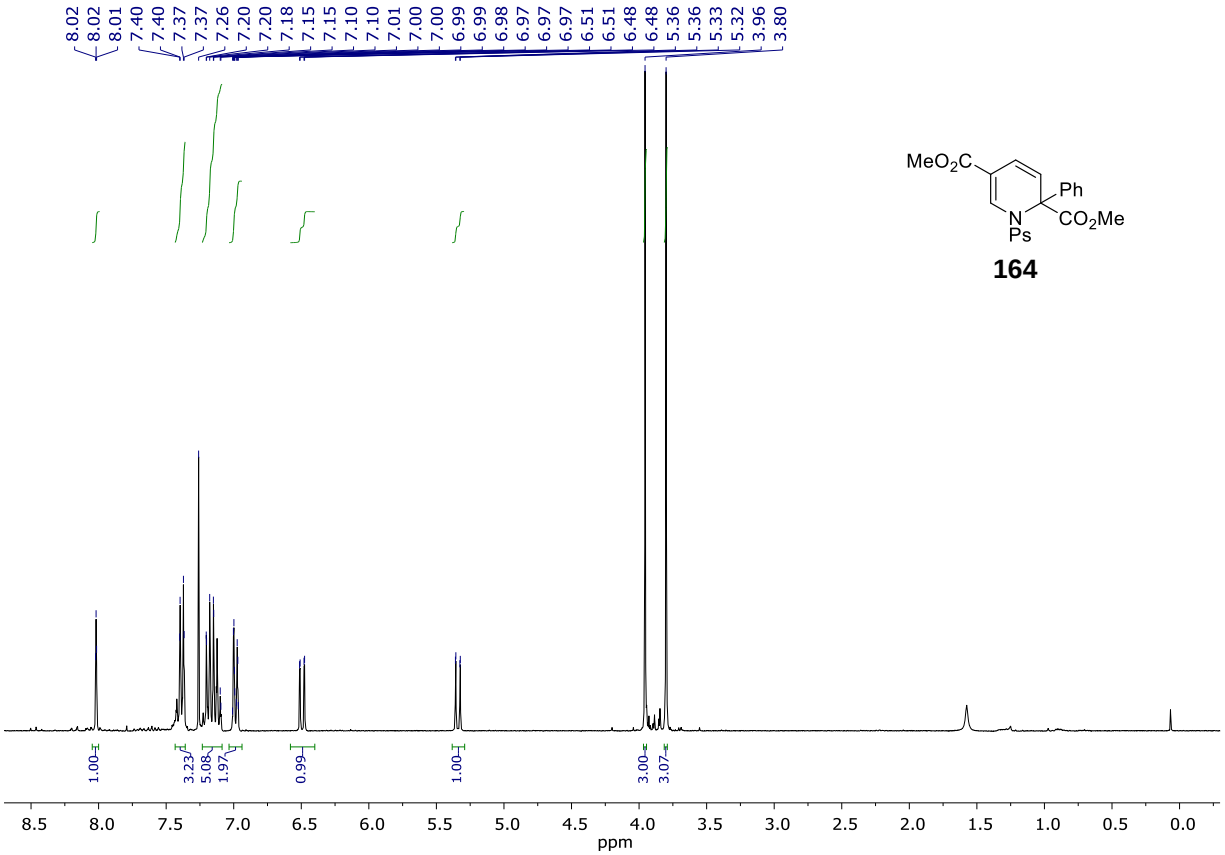
159

^{1}H NMR (400 MHz, $CDCl_3$)



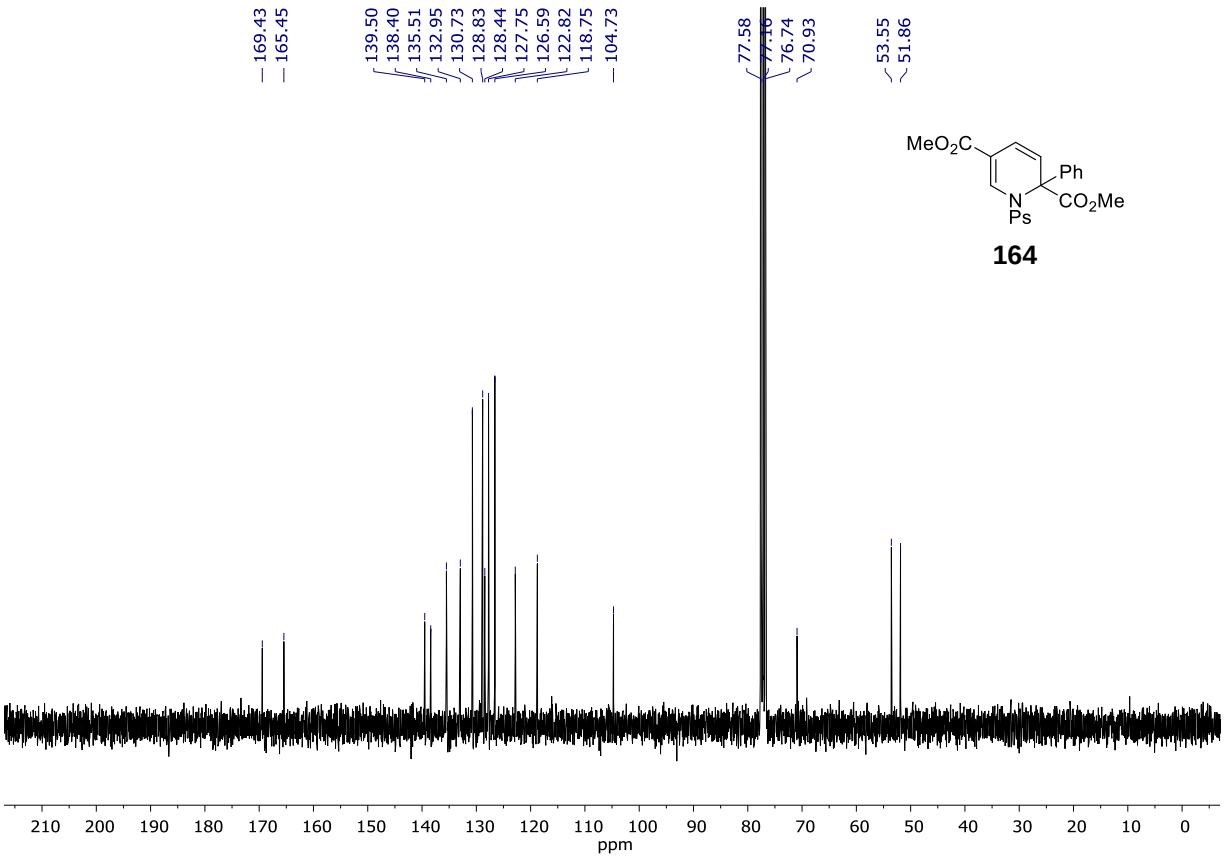
159

^{13}C NMR (101 MHz, $CDCl_3$)



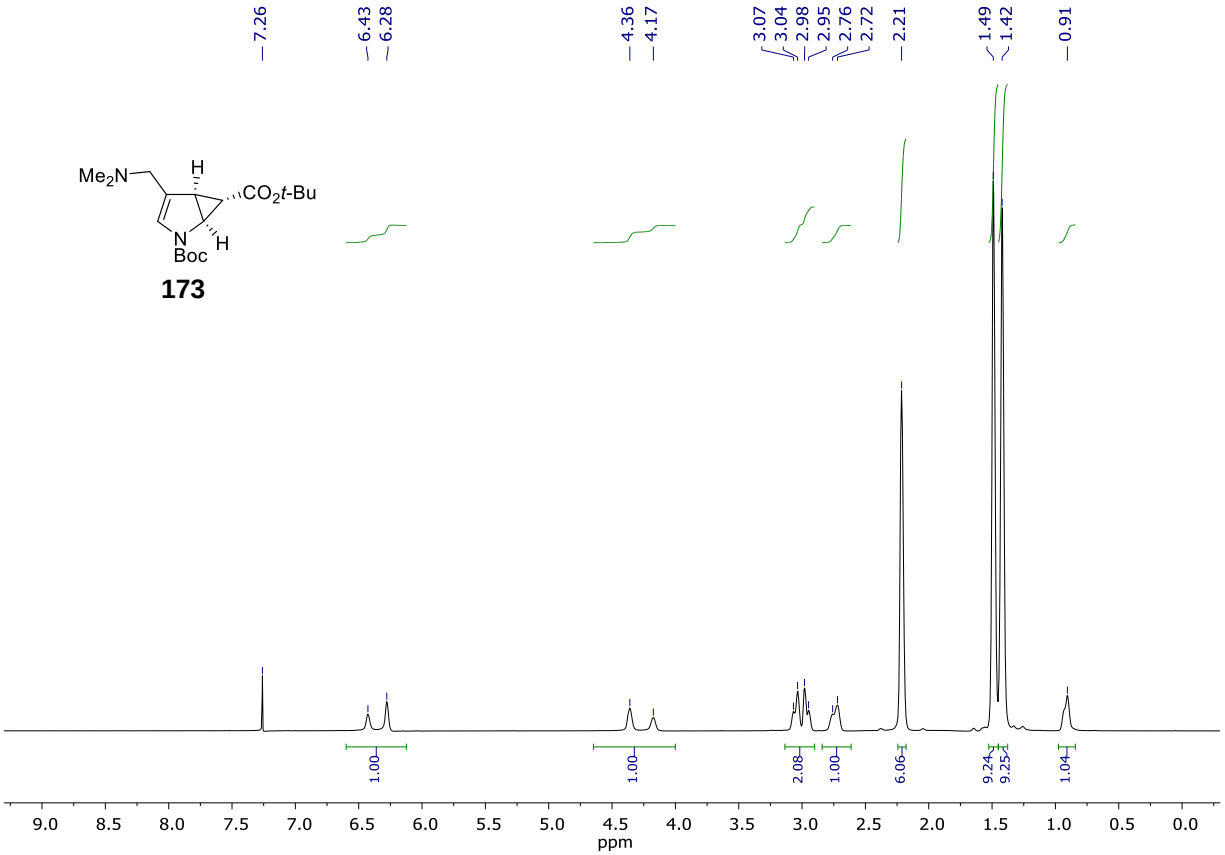
164

^{1}H NMR (300 MHz, $CDCl_3$)



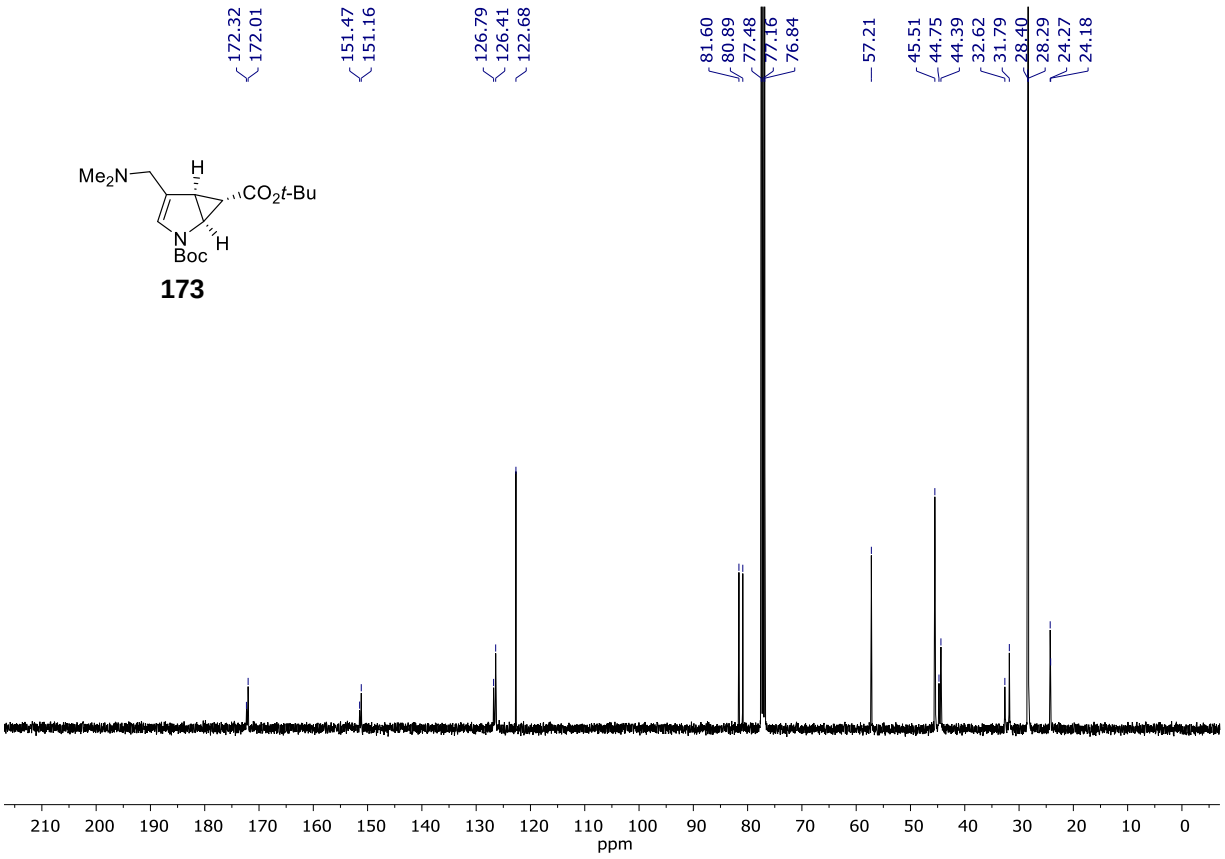
164

^{13}C NMR (75 MHz, $CDCl_3$)



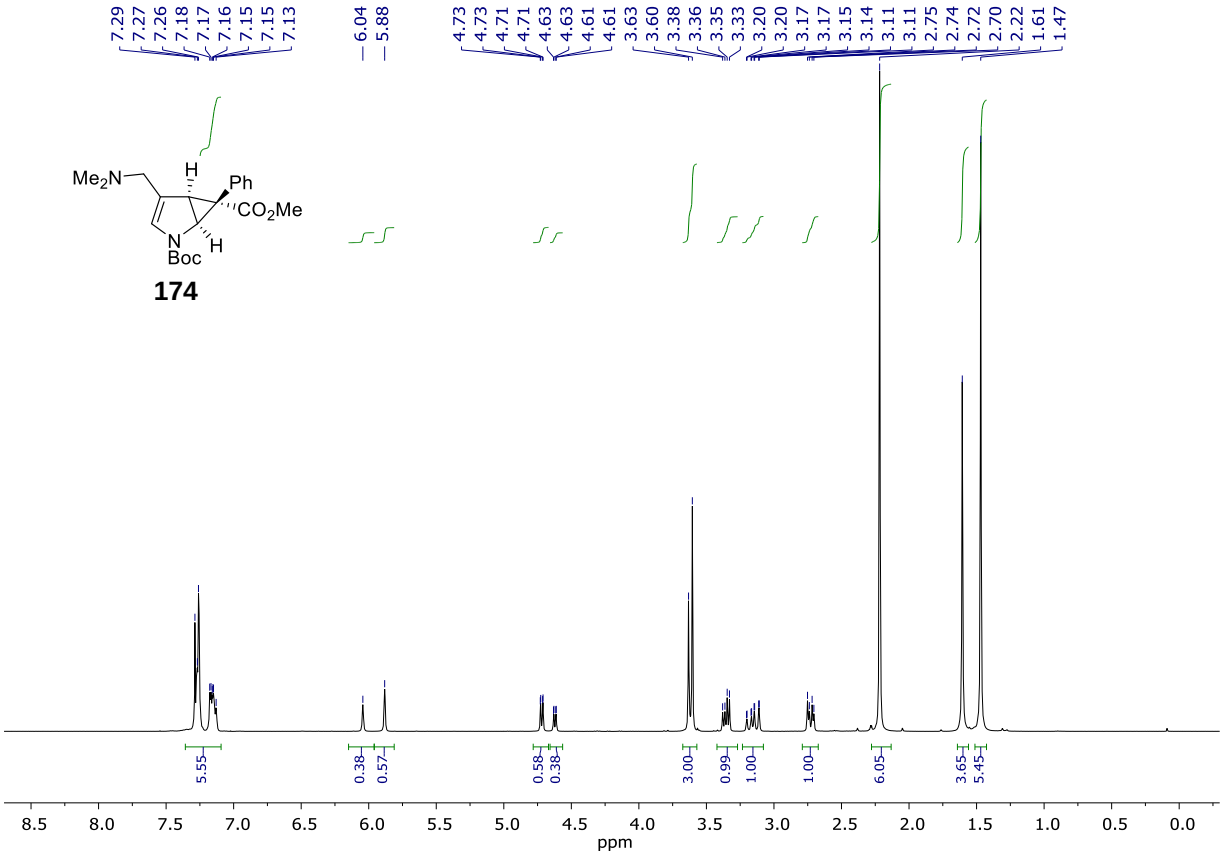
173

^{1}H NMR (400 MHz, $CDCl_3$)



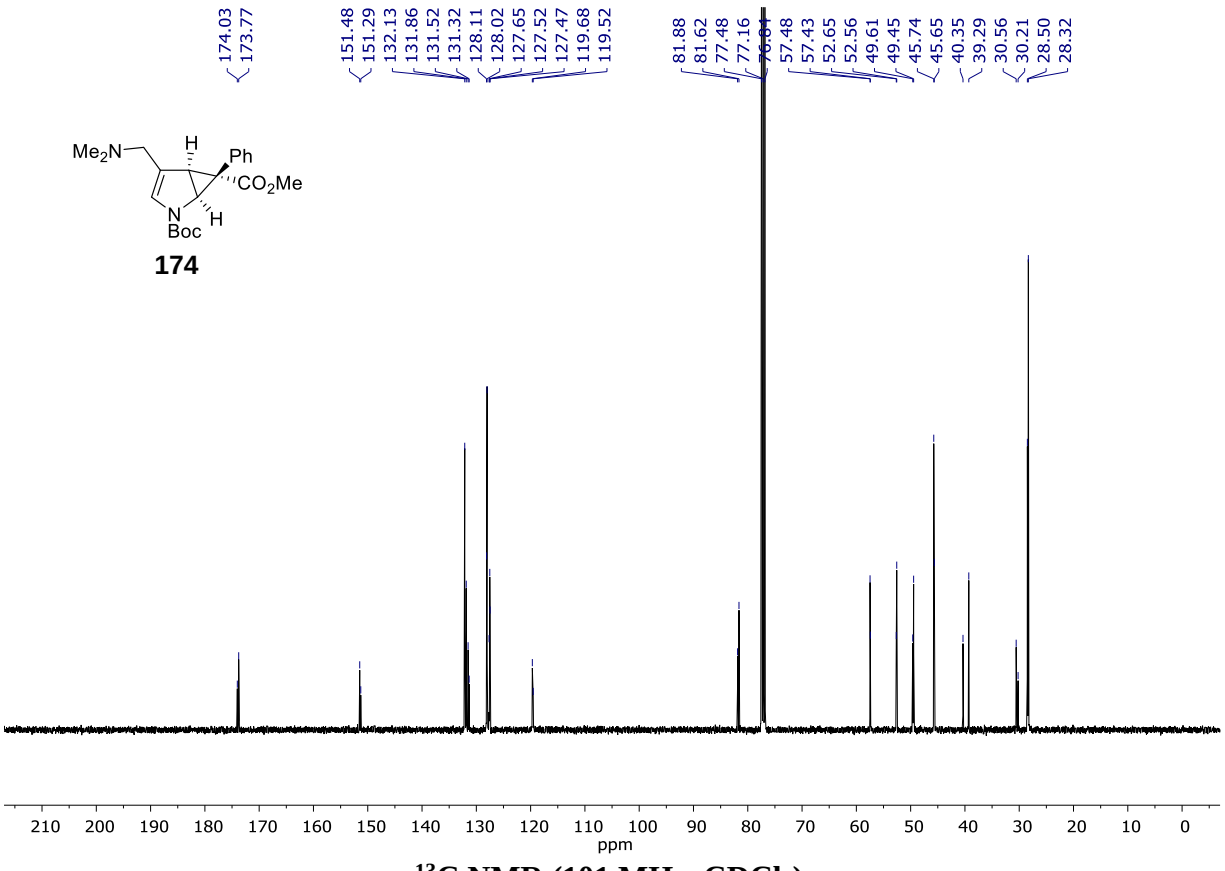
173

^{13}C NMR (101 MHz, $CDCl_3$)



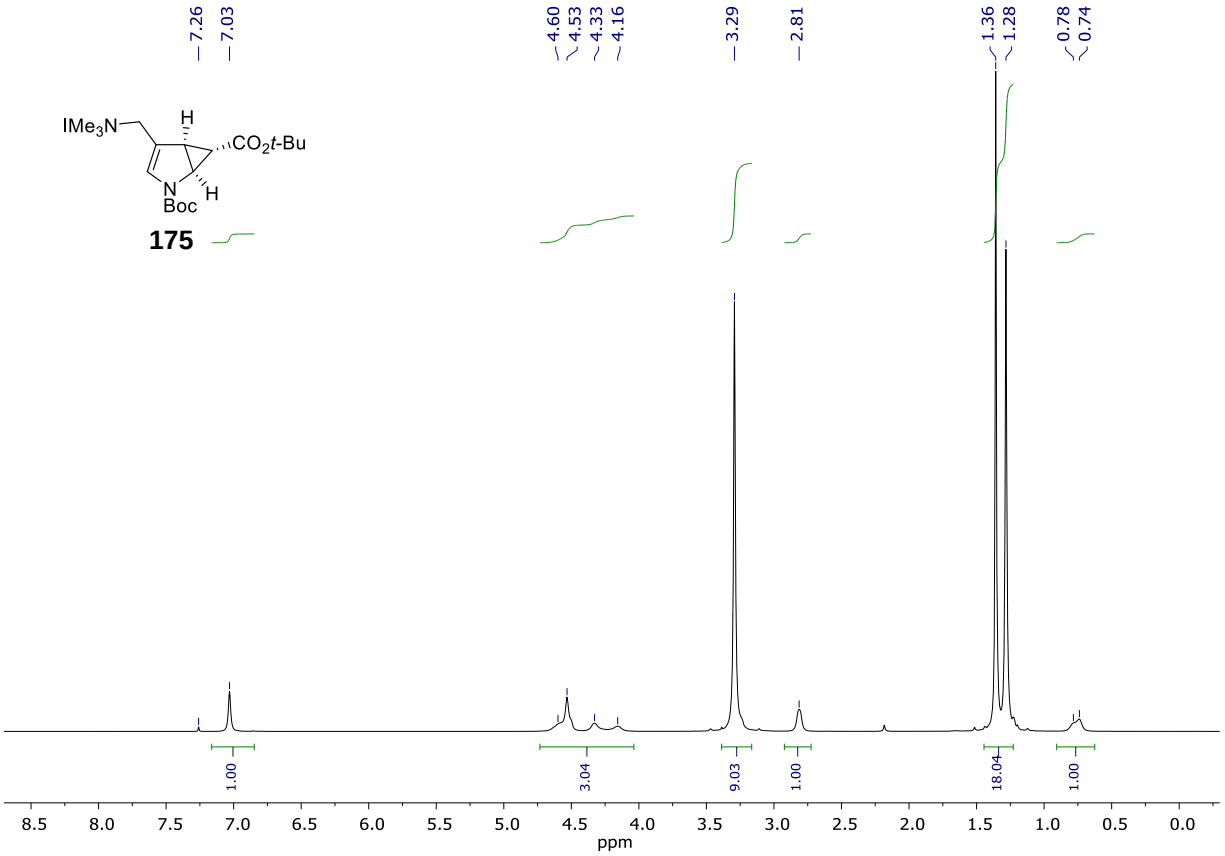
174

^{1}H NMR (400 MHz, $CDCl_3$)

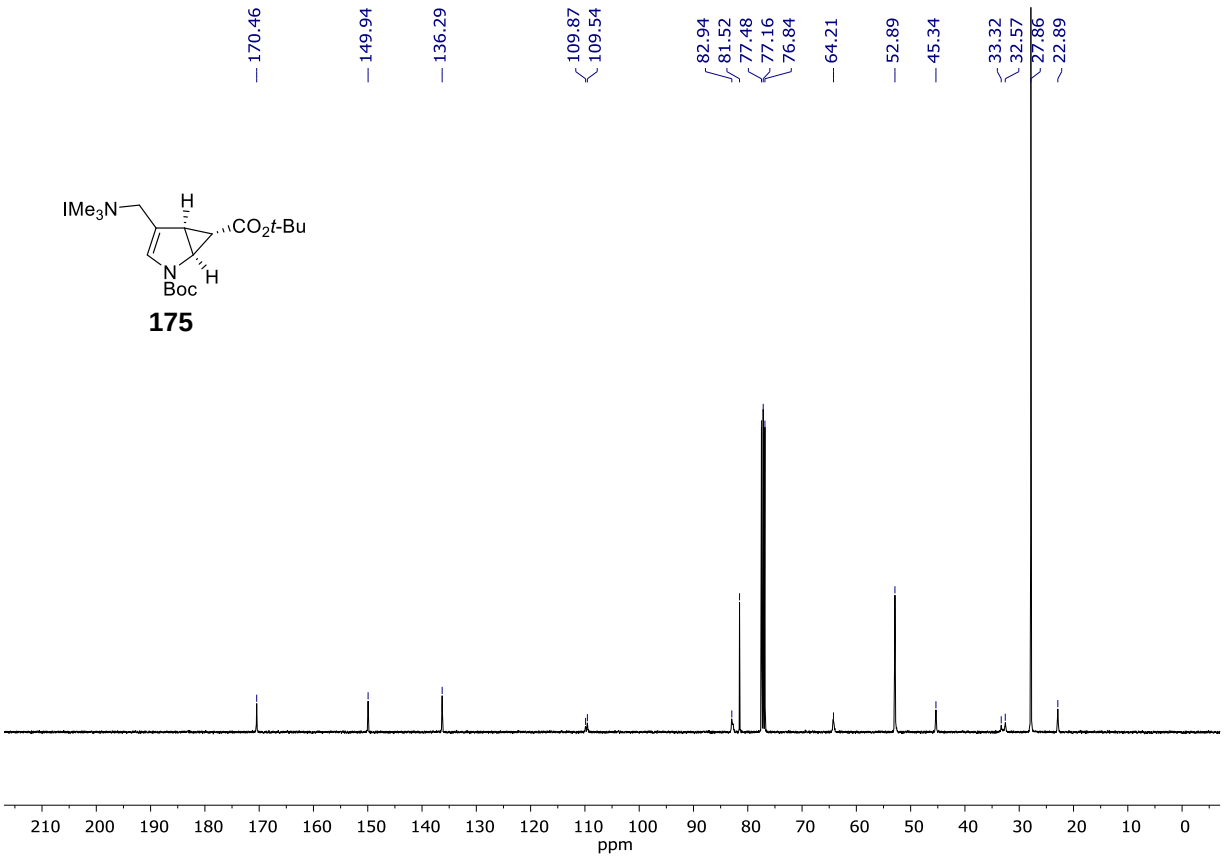


174

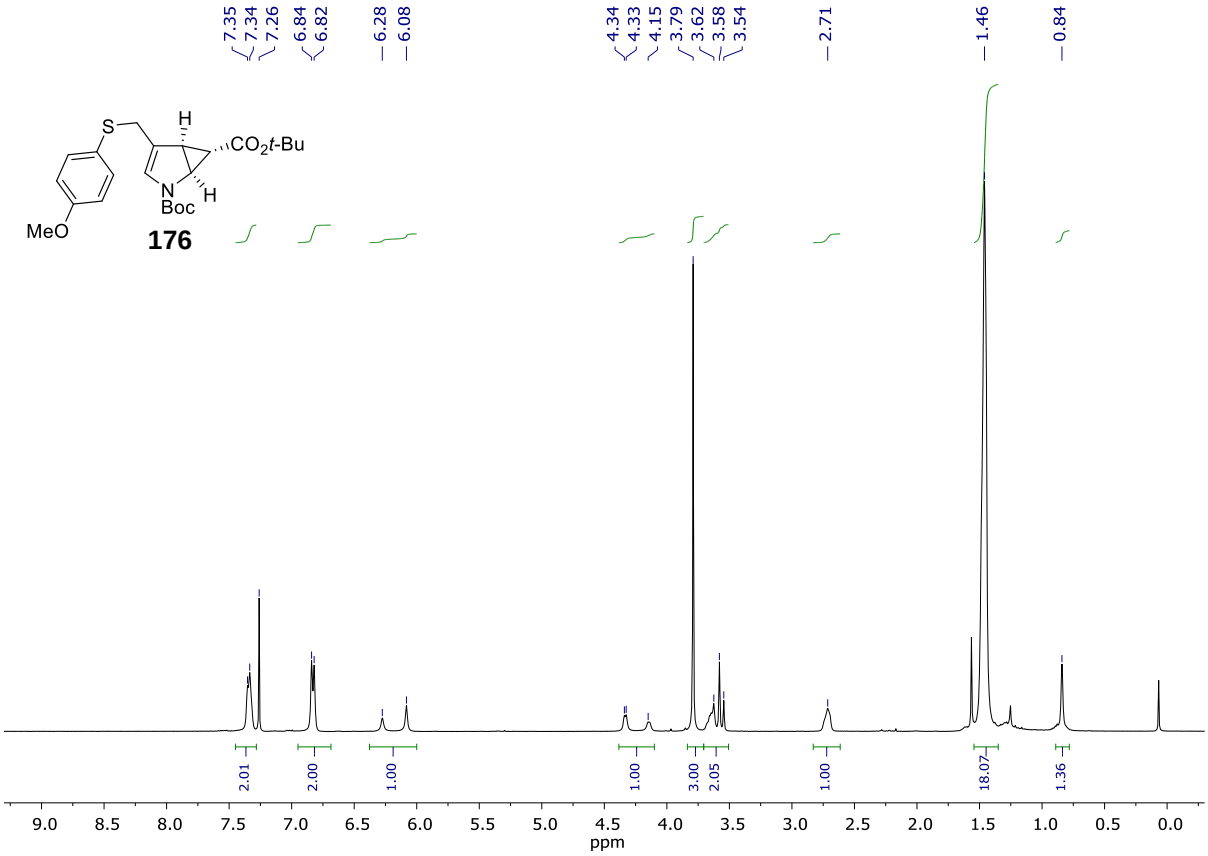
^{13}C NMR (101 MHz, $CDCl_3$)



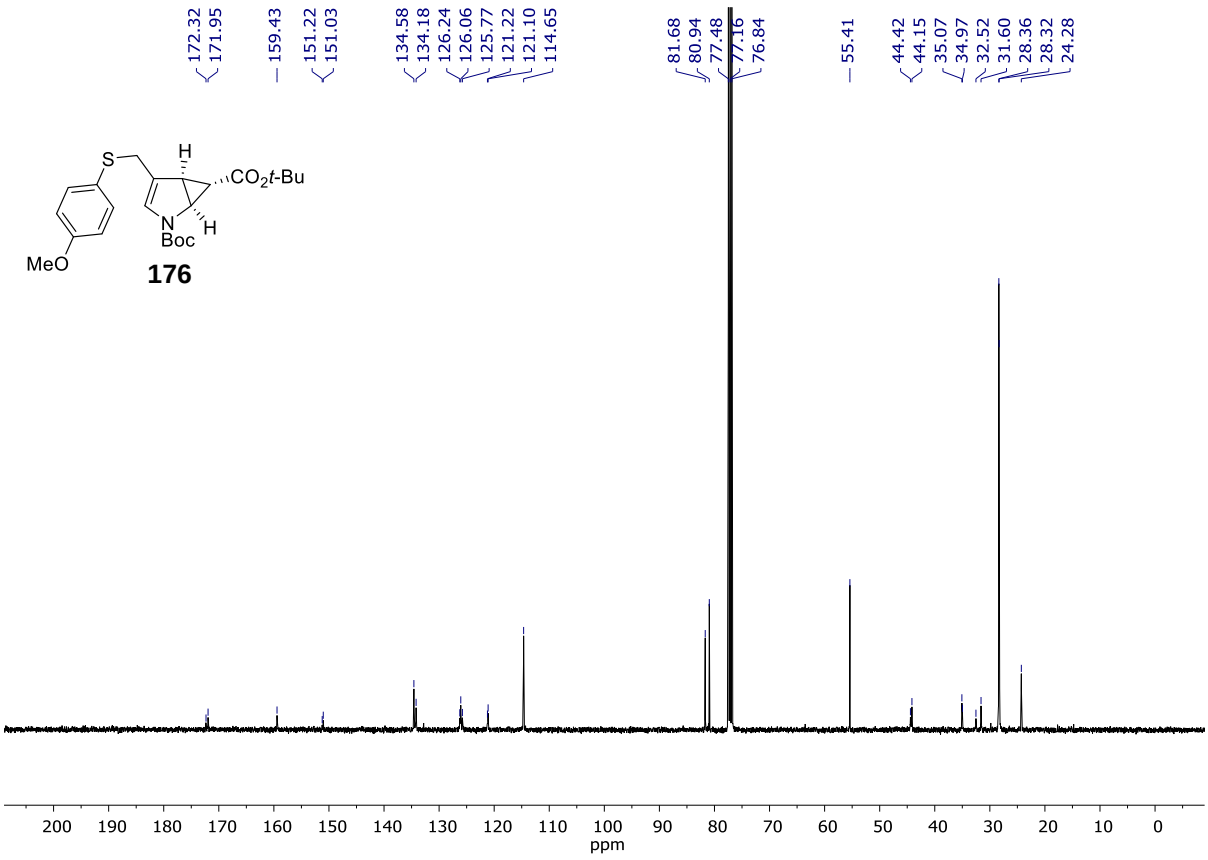
^{1}H NMR (400 MHz, $CDCl_3$)



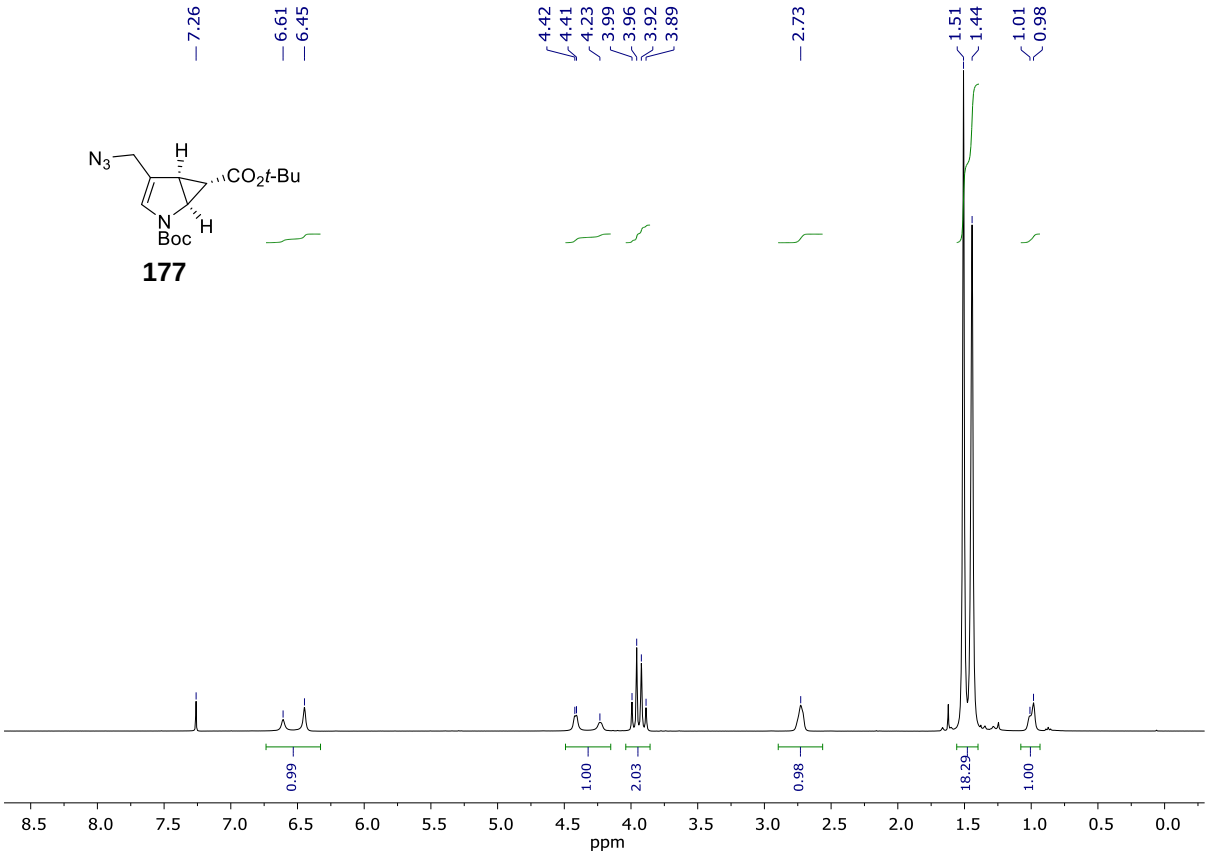
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)

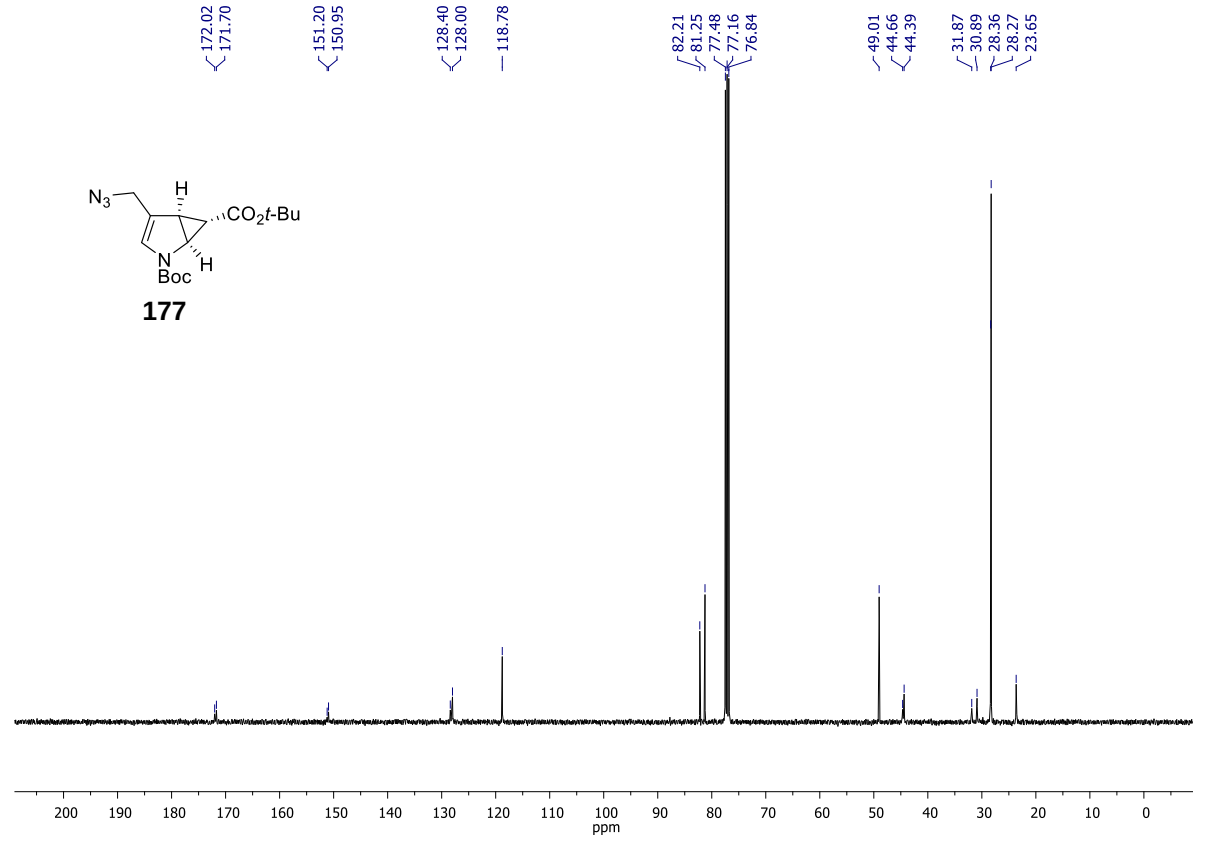


^{13}C NMR (101 MHz, $CDCl_3$)



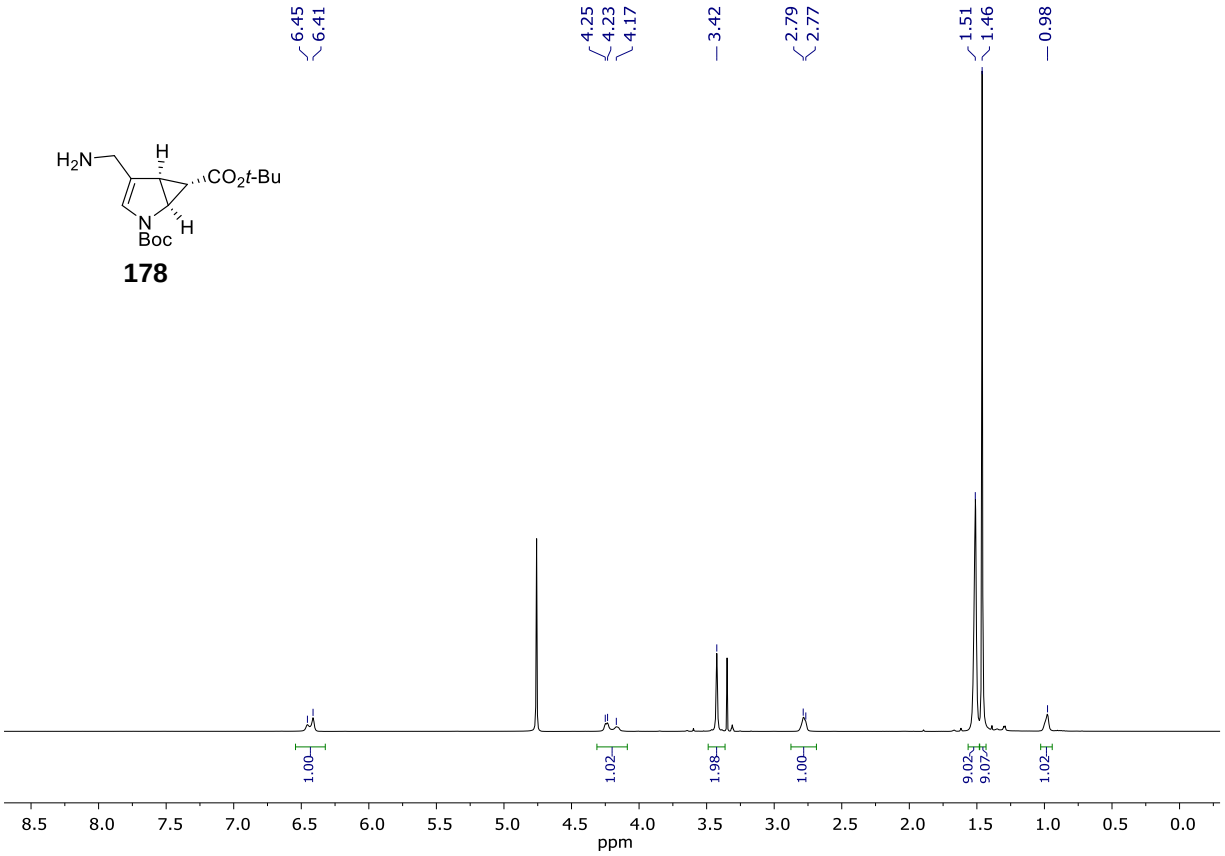
177

^{1}H NMR (400 MHz, $CDCl_3$)



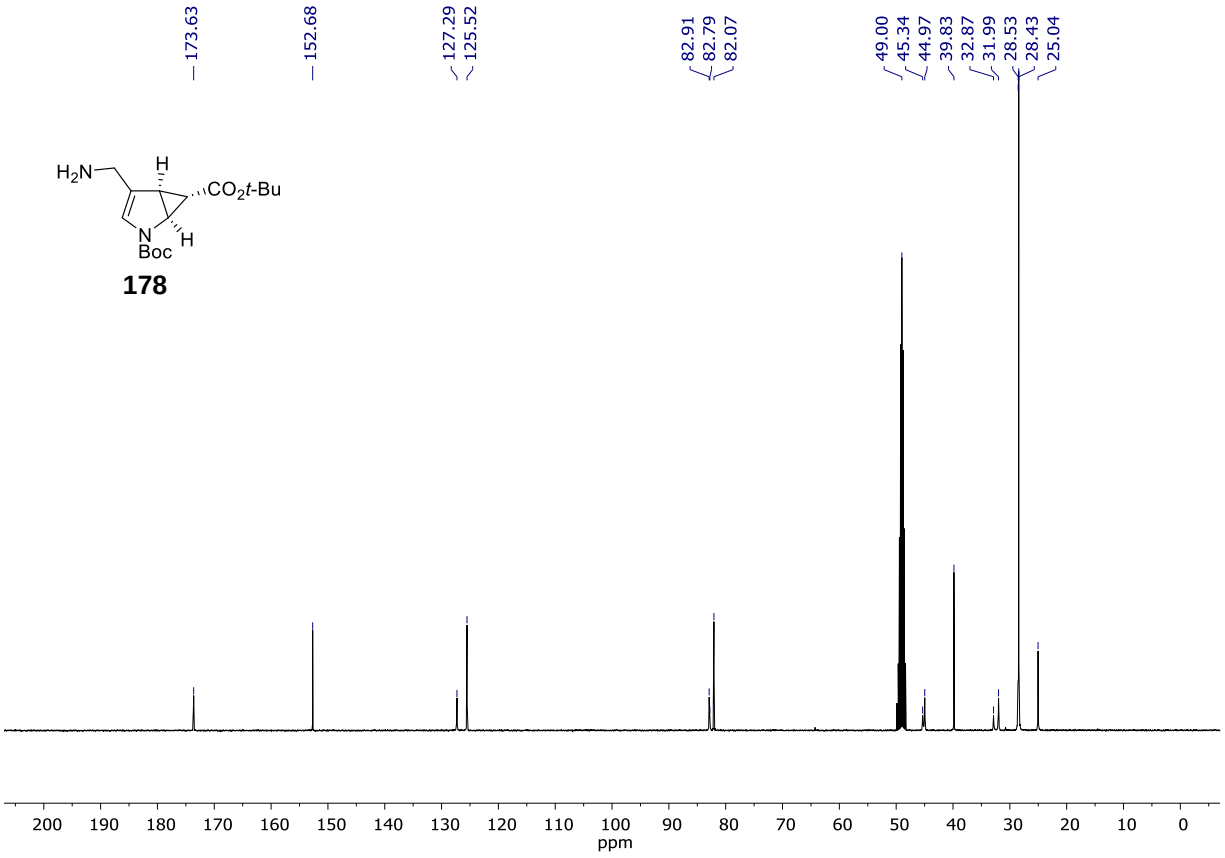
177

^{13}C NMR (101 MHz, $CDCl_3$)



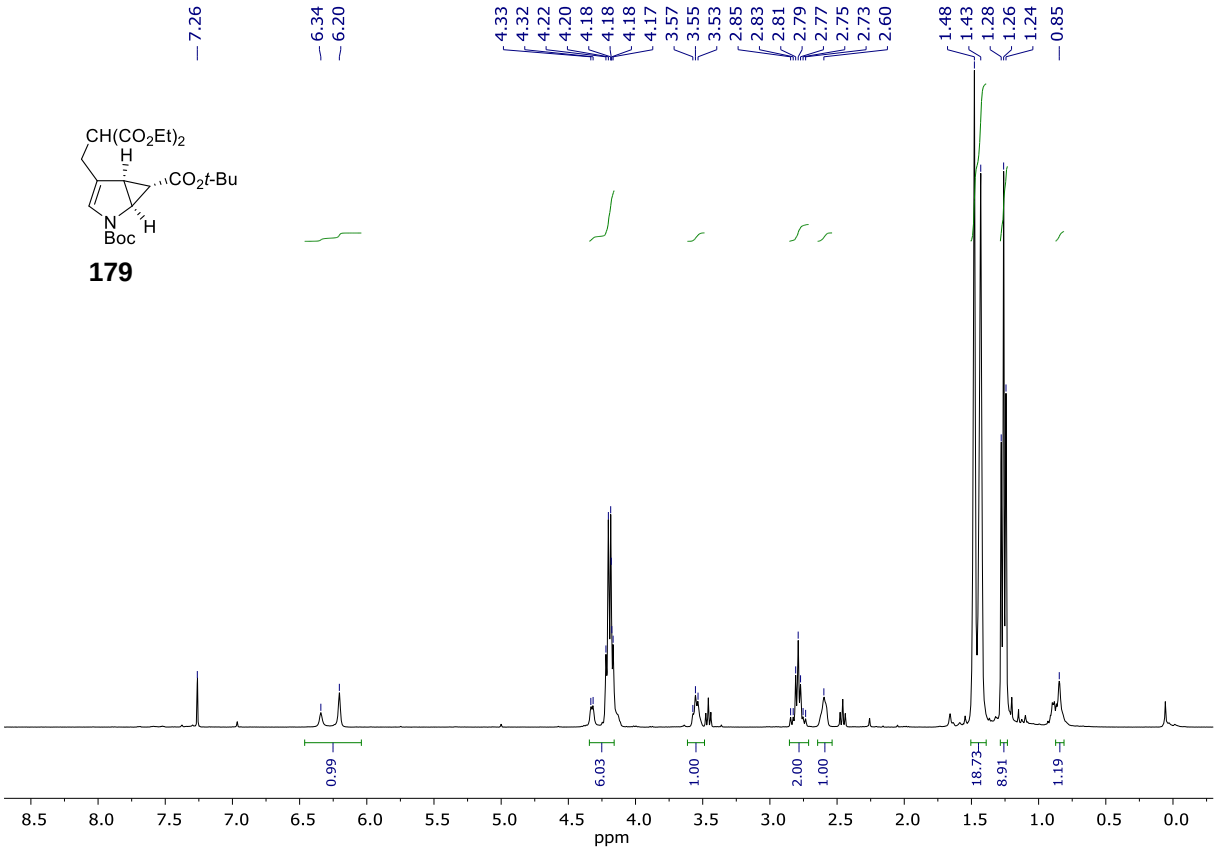
178

^{1}H NMR (400 MHz, methanol-d_4)



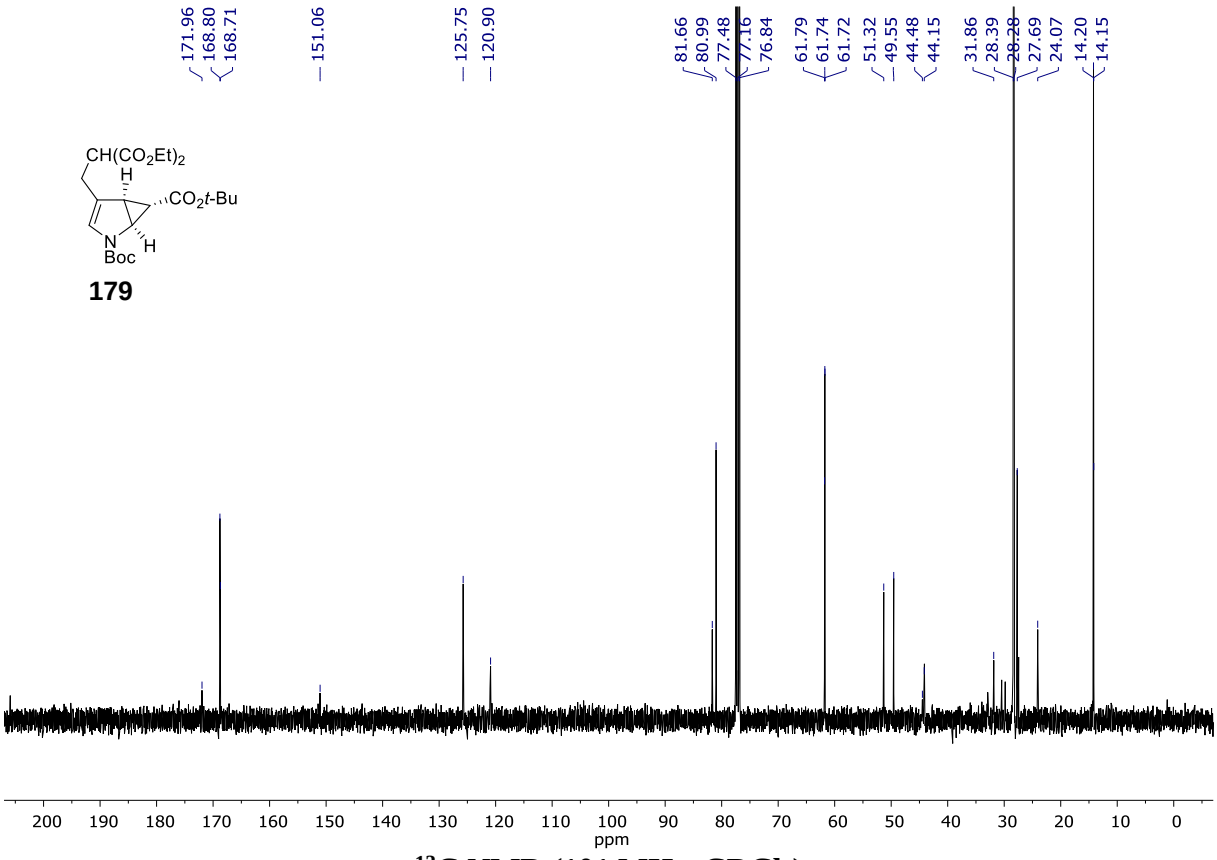
178

^{13}C NMR (101 MHz, methanol-d_4)



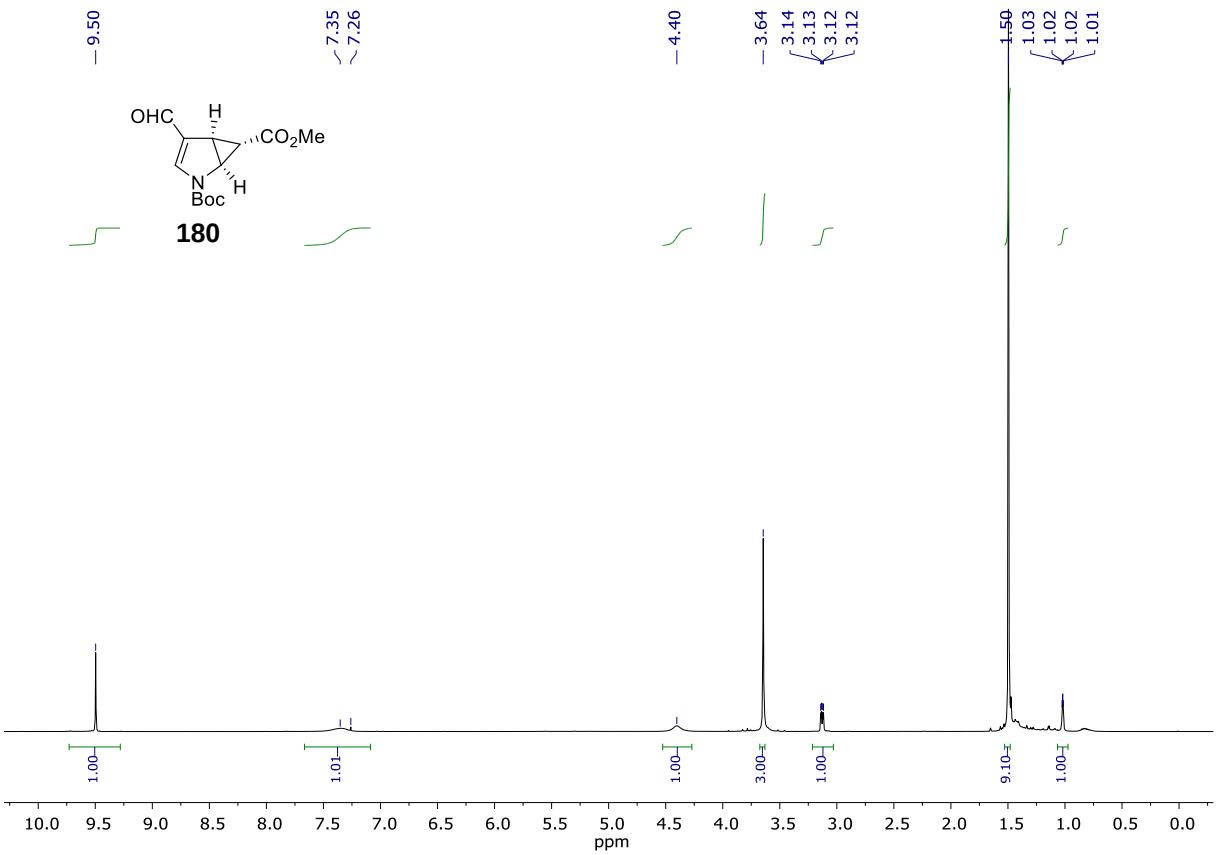
179

^{1}H NMR (400 MHz, $CDCl_3$)

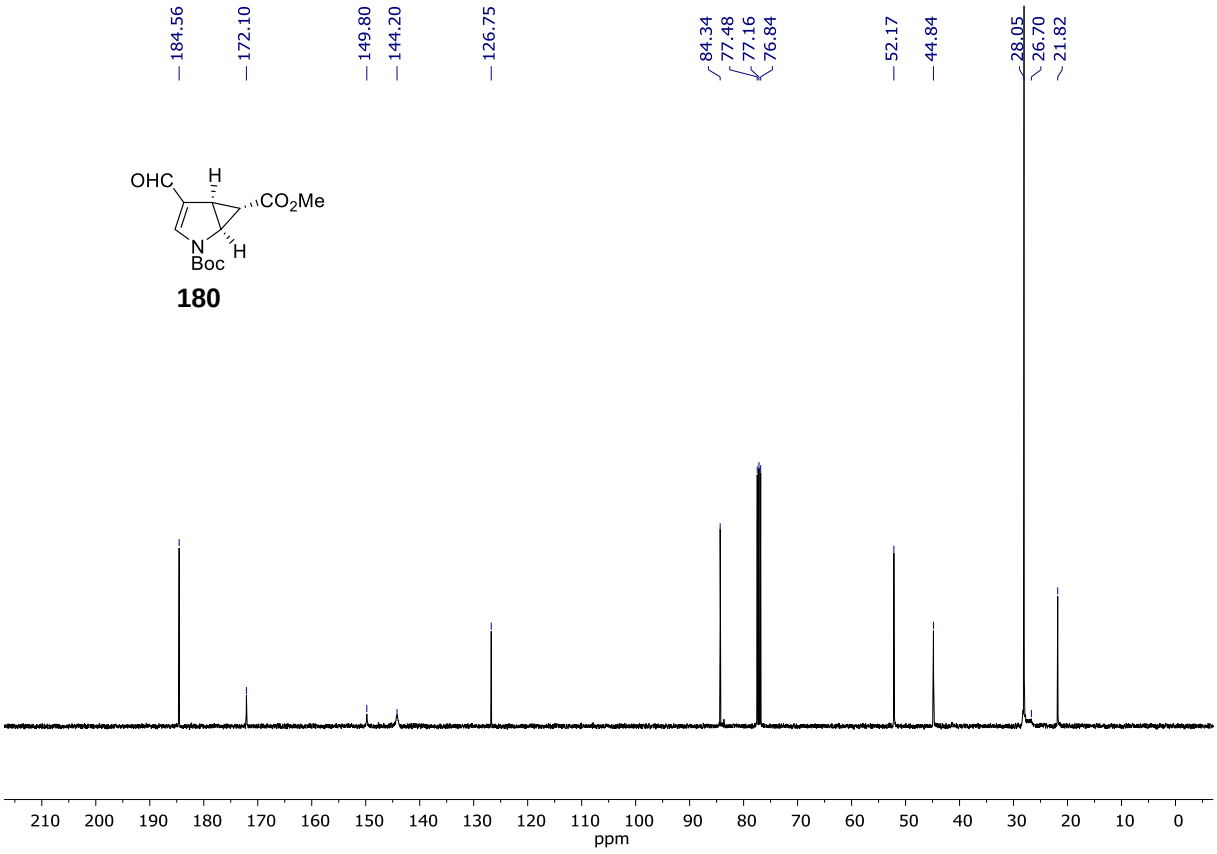


179

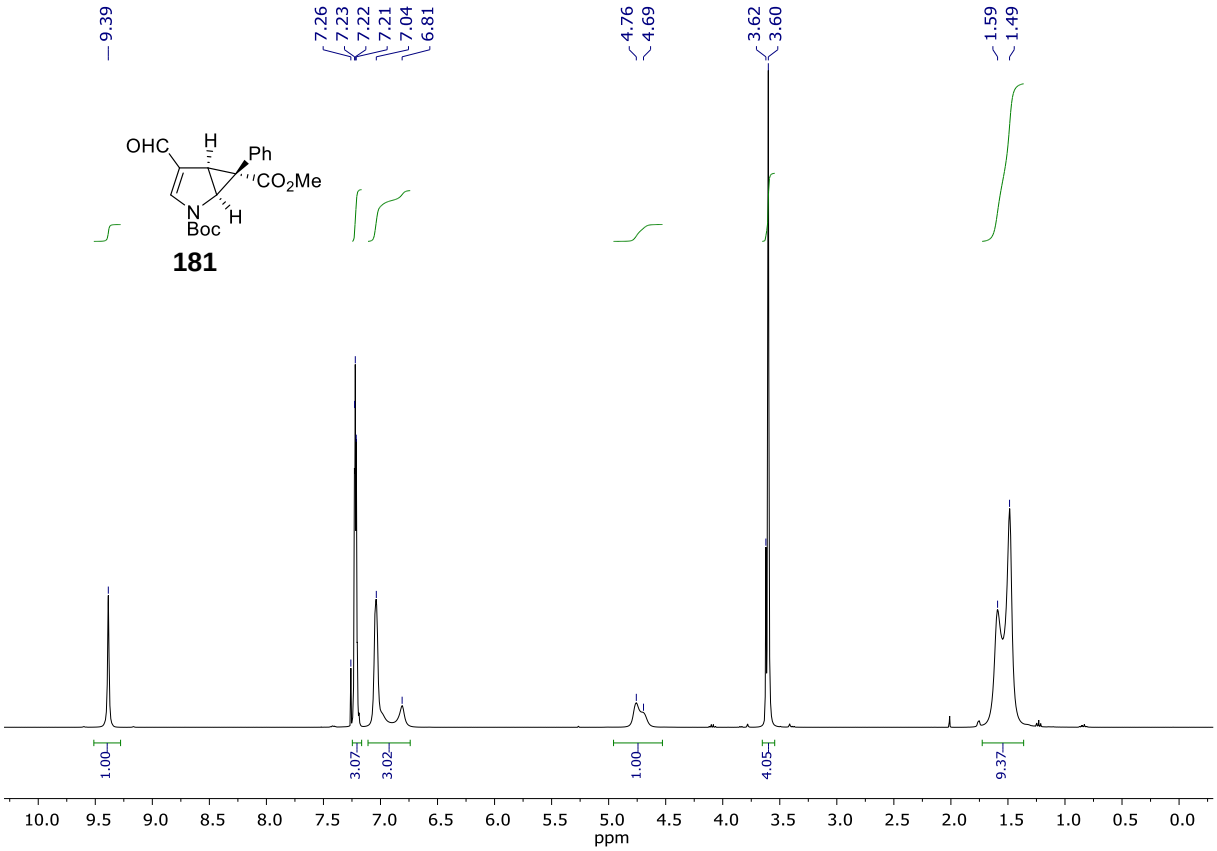
^{13}C NMR (101 MHz, $CDCl_3$)



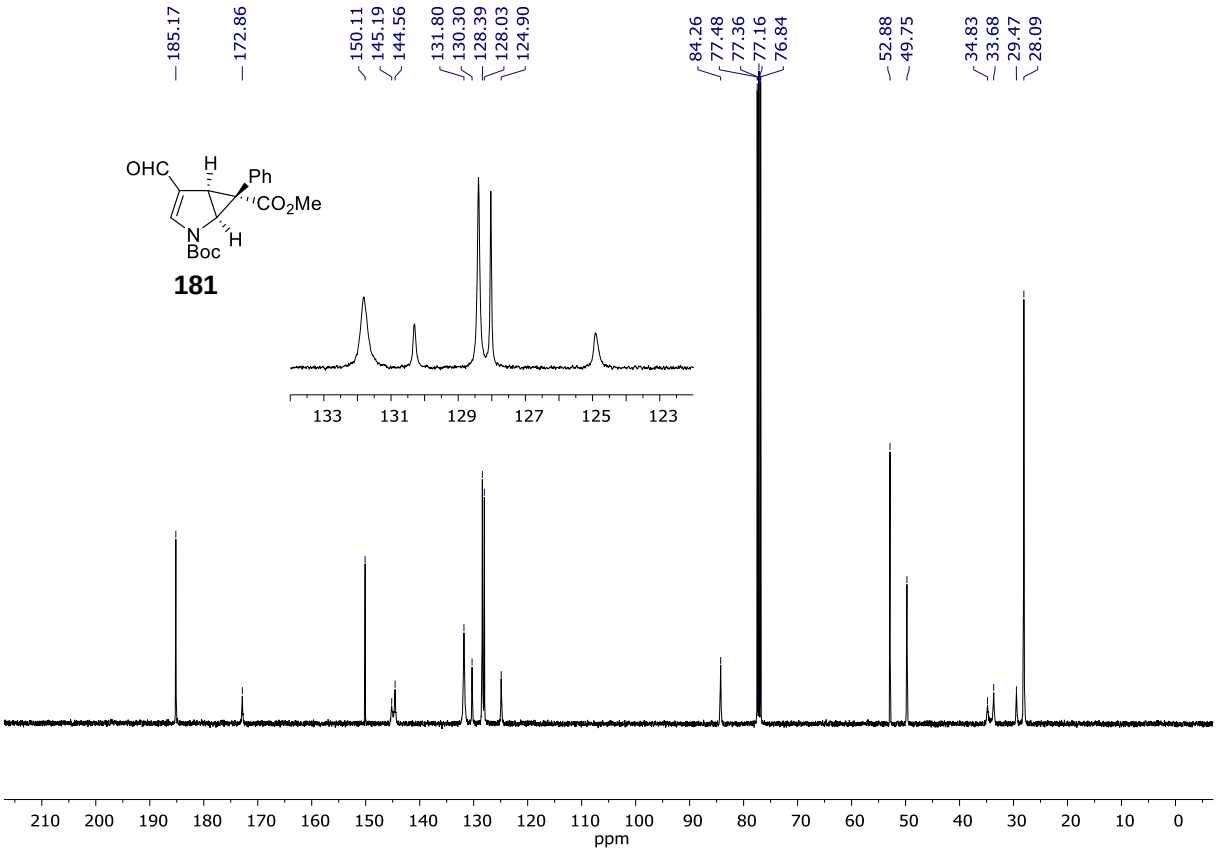
^{1}H NMR (400 MHz, $CDCl_3$)



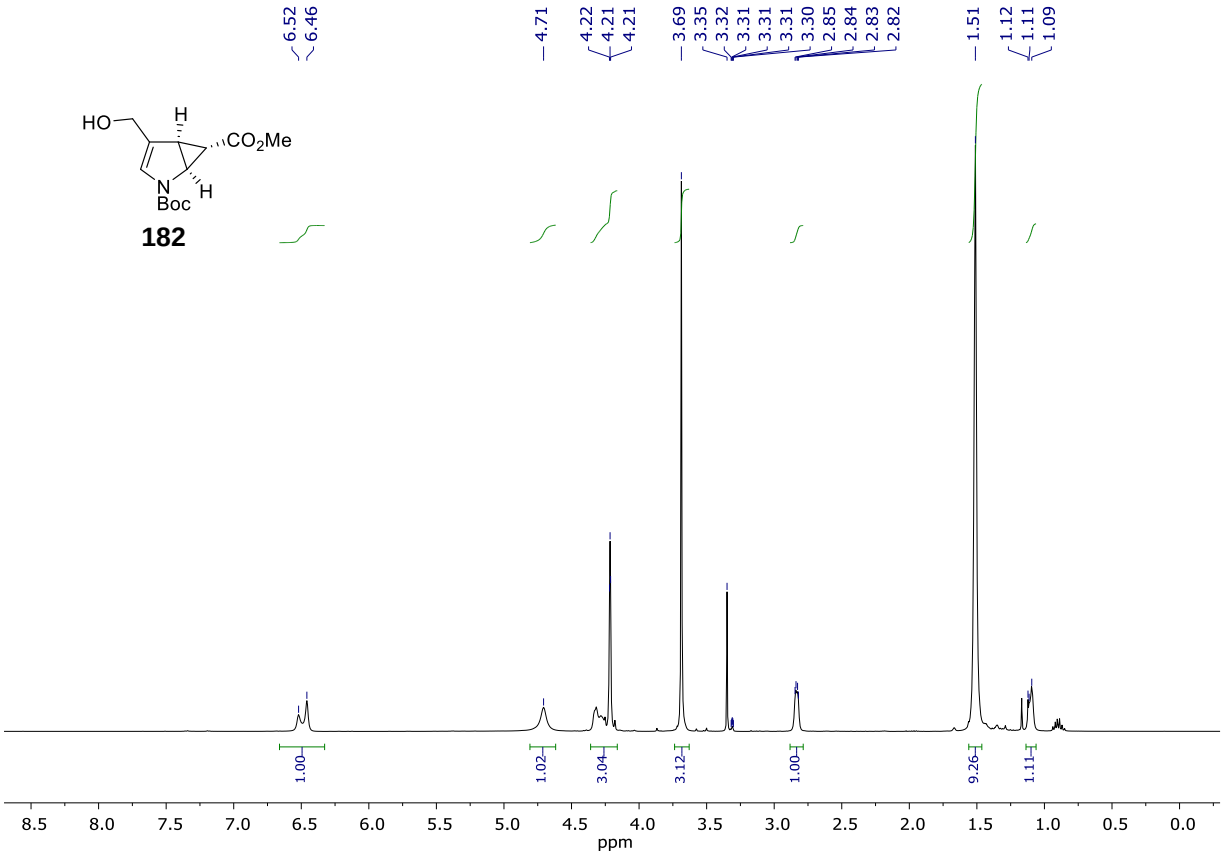
^{13}C NMR (101 MHz, $CDCl_3$)



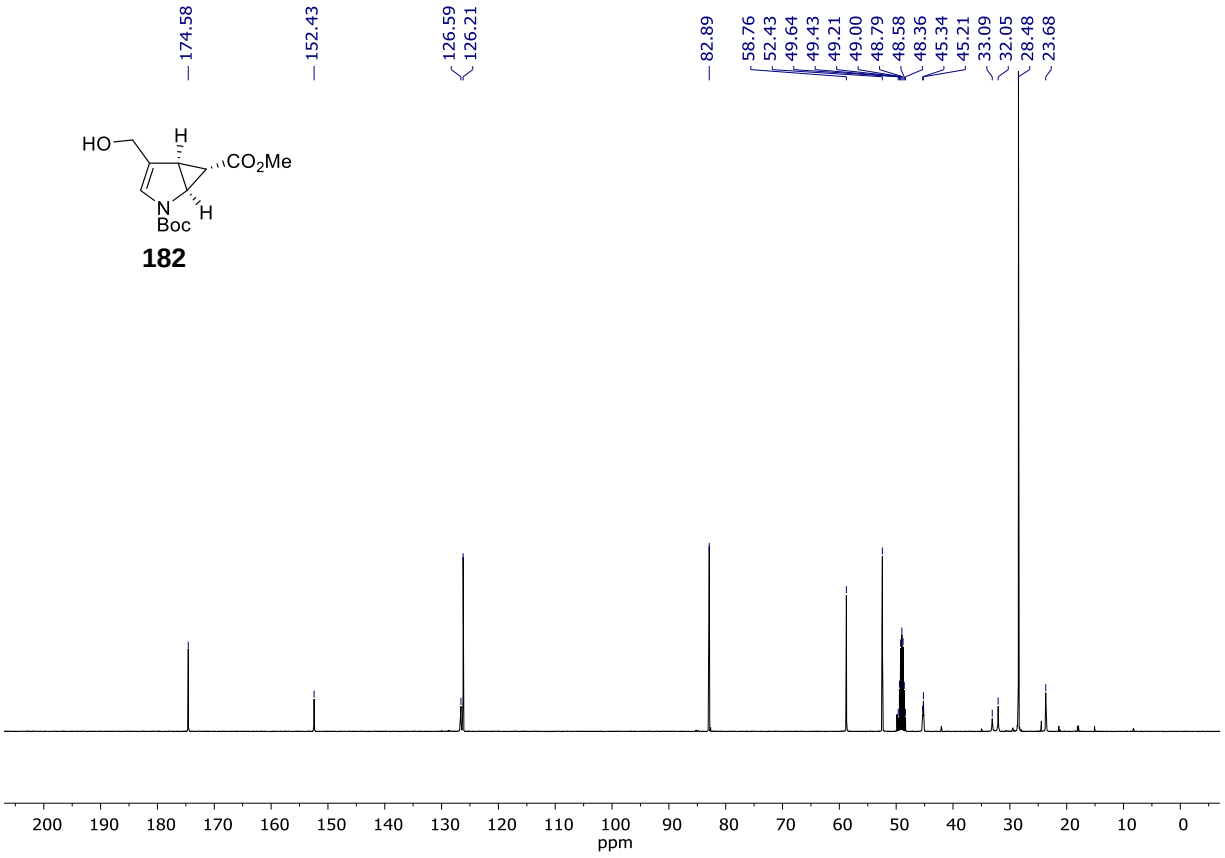
^{1}H NMR (400 MHz, $CDCl_3$)



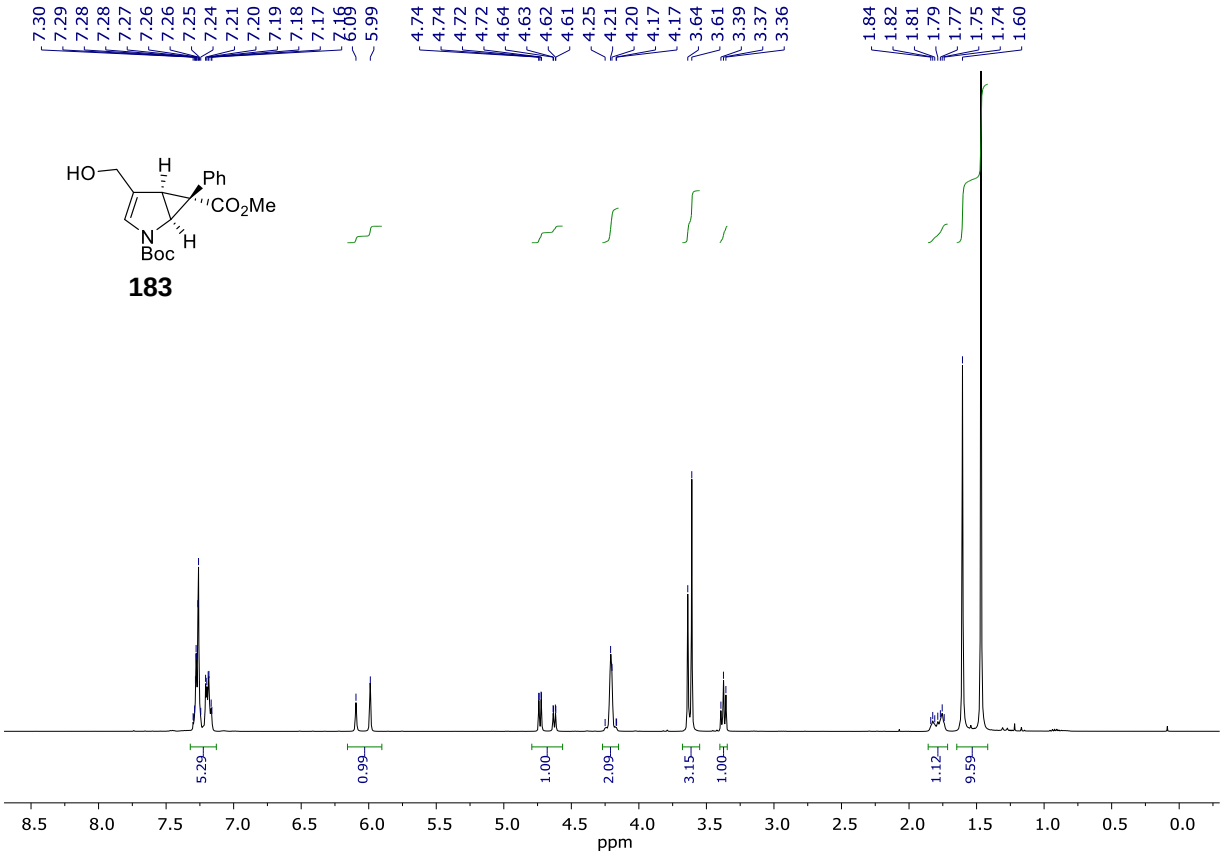
^{13}C NMR (101 MHz, $CDCl_3$)



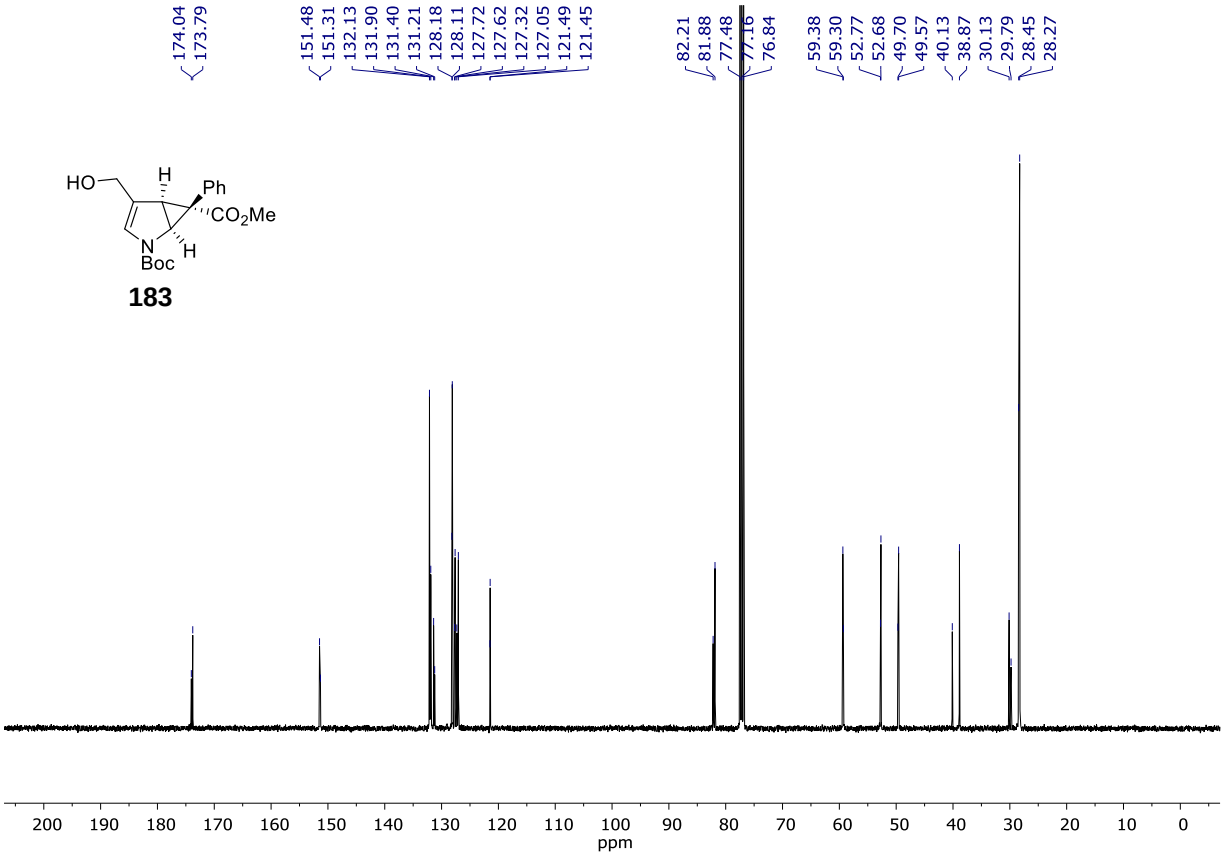
^{1}H NMR (400 MHz, methanol-d_4)



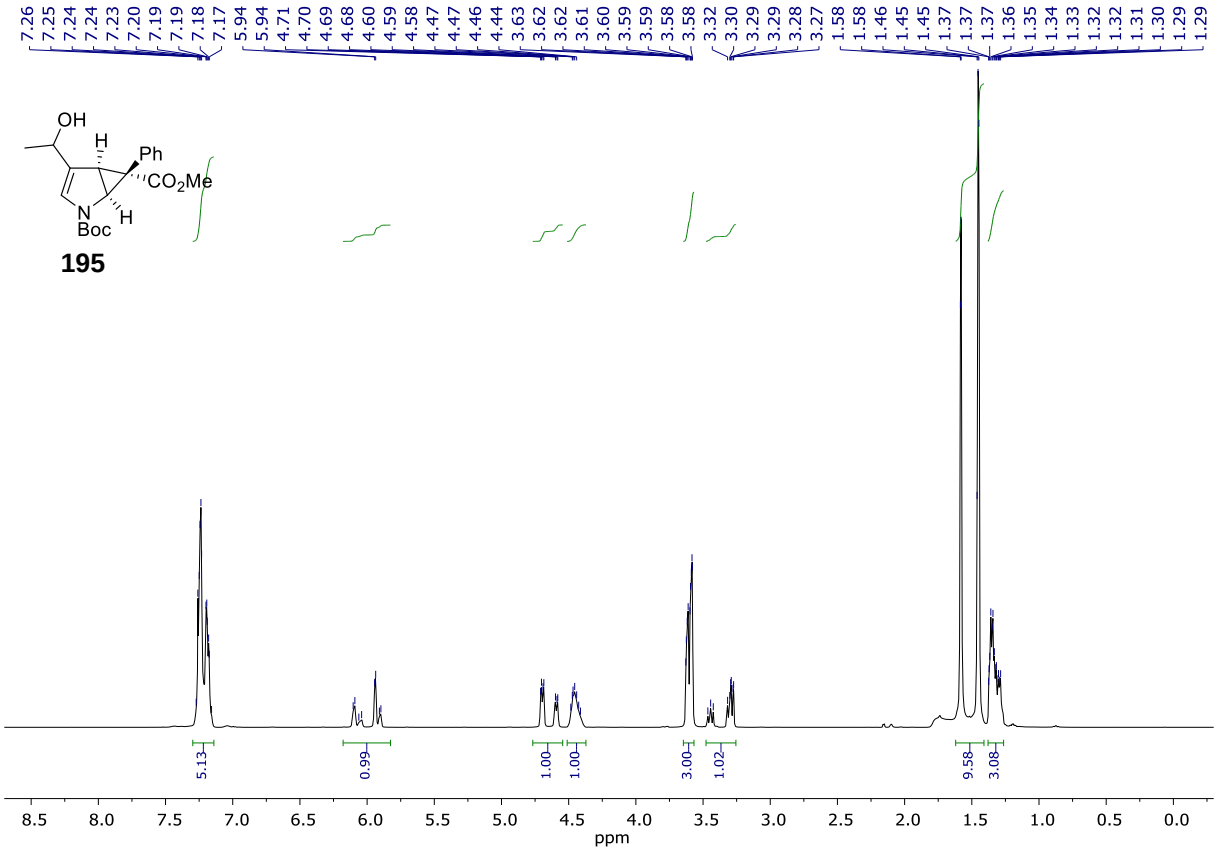
^{13}C NMR (101 MHz, methanol-d_4)



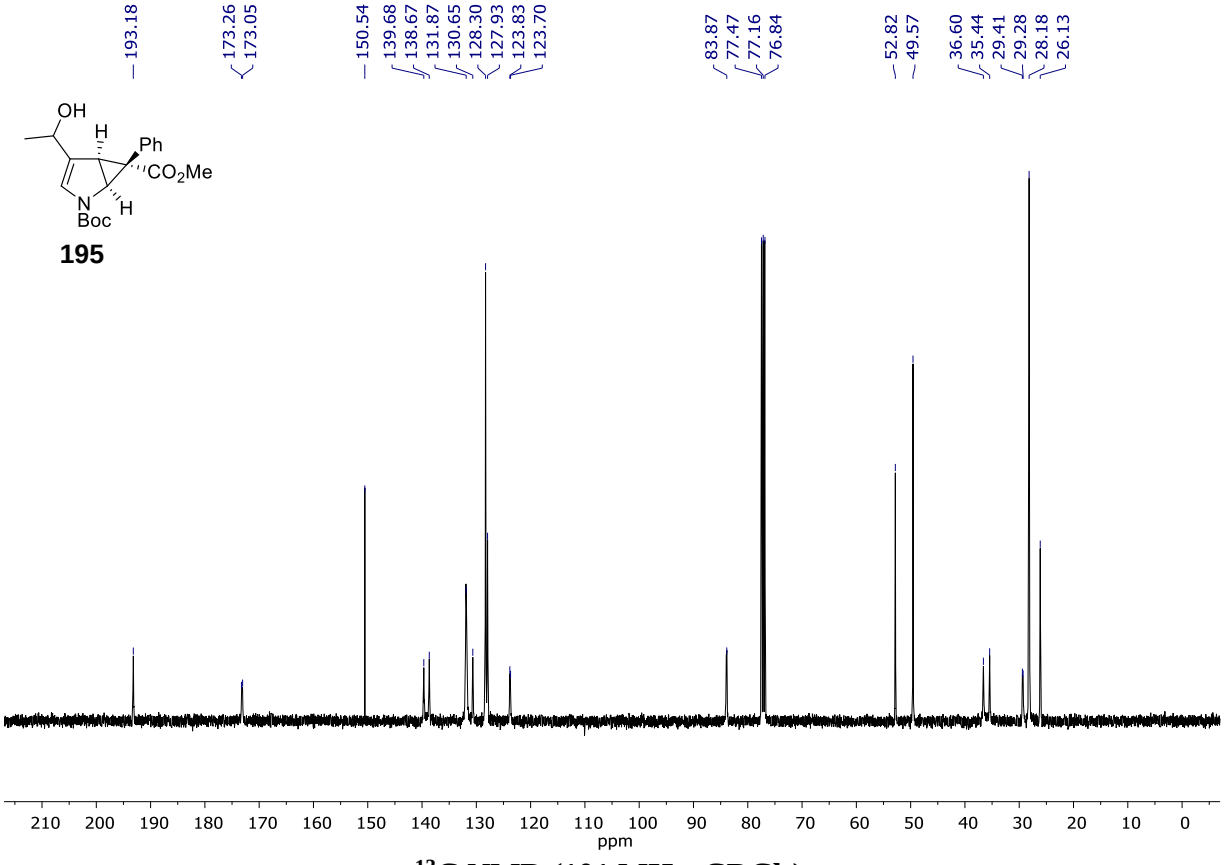
^{1}H NMR (400 MHz, $CDCl_3$)



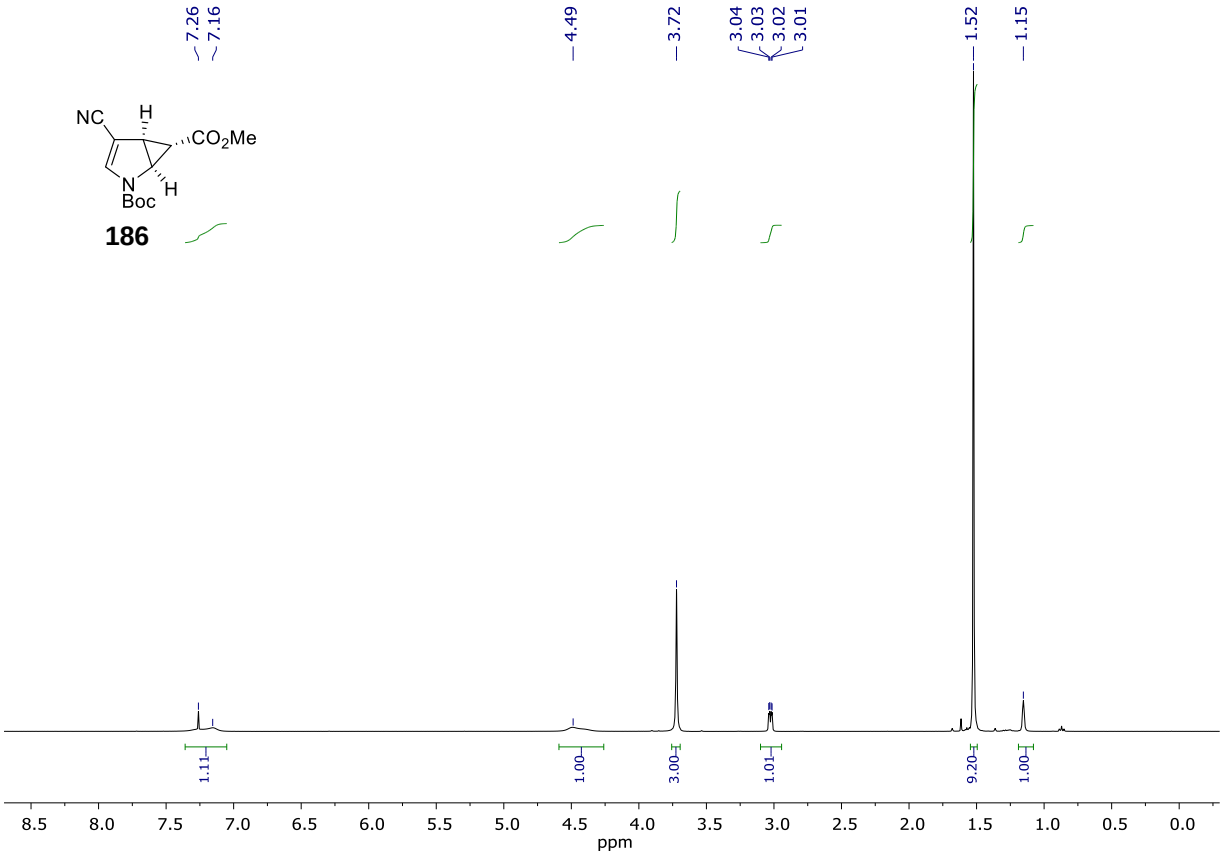
^{13}C NMR (101 MHz, $CDCl_3$)



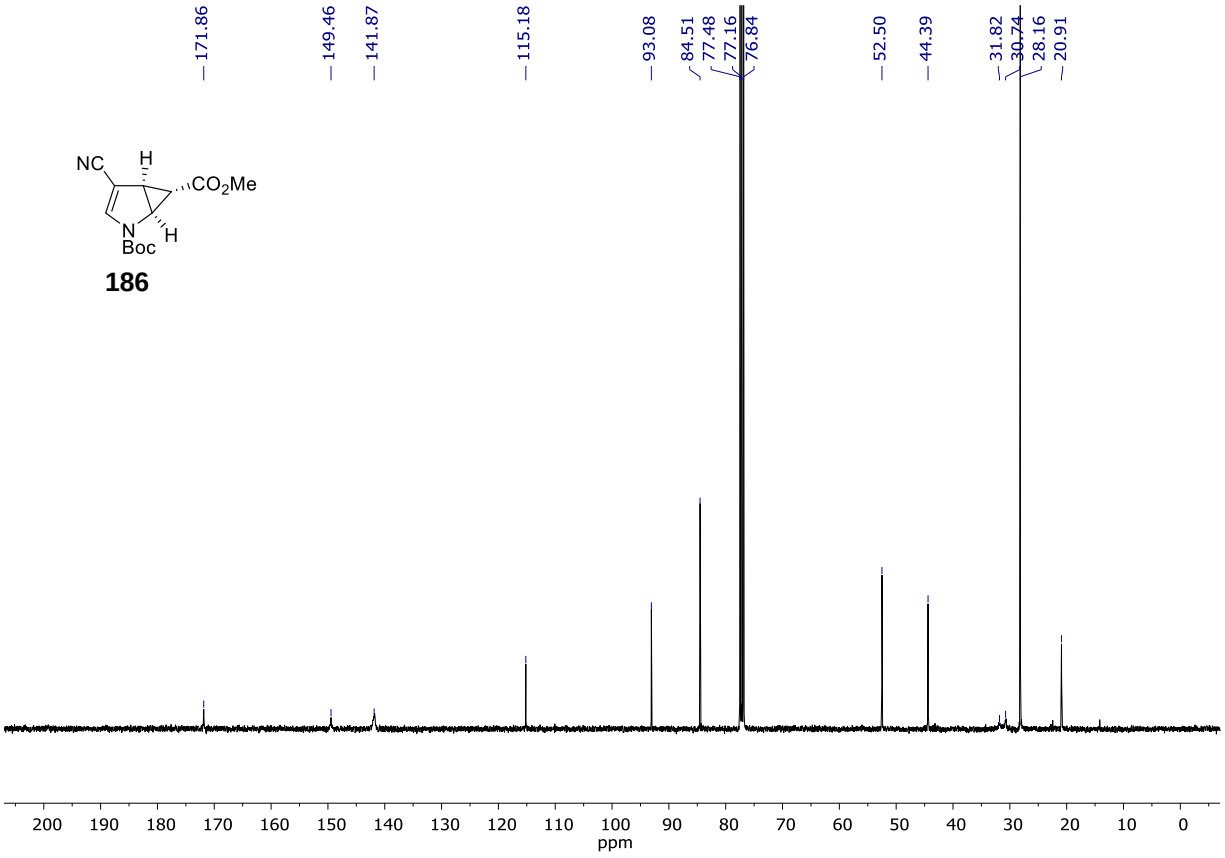
^{1}H NMR (400 MHz, $CDCl_3$)



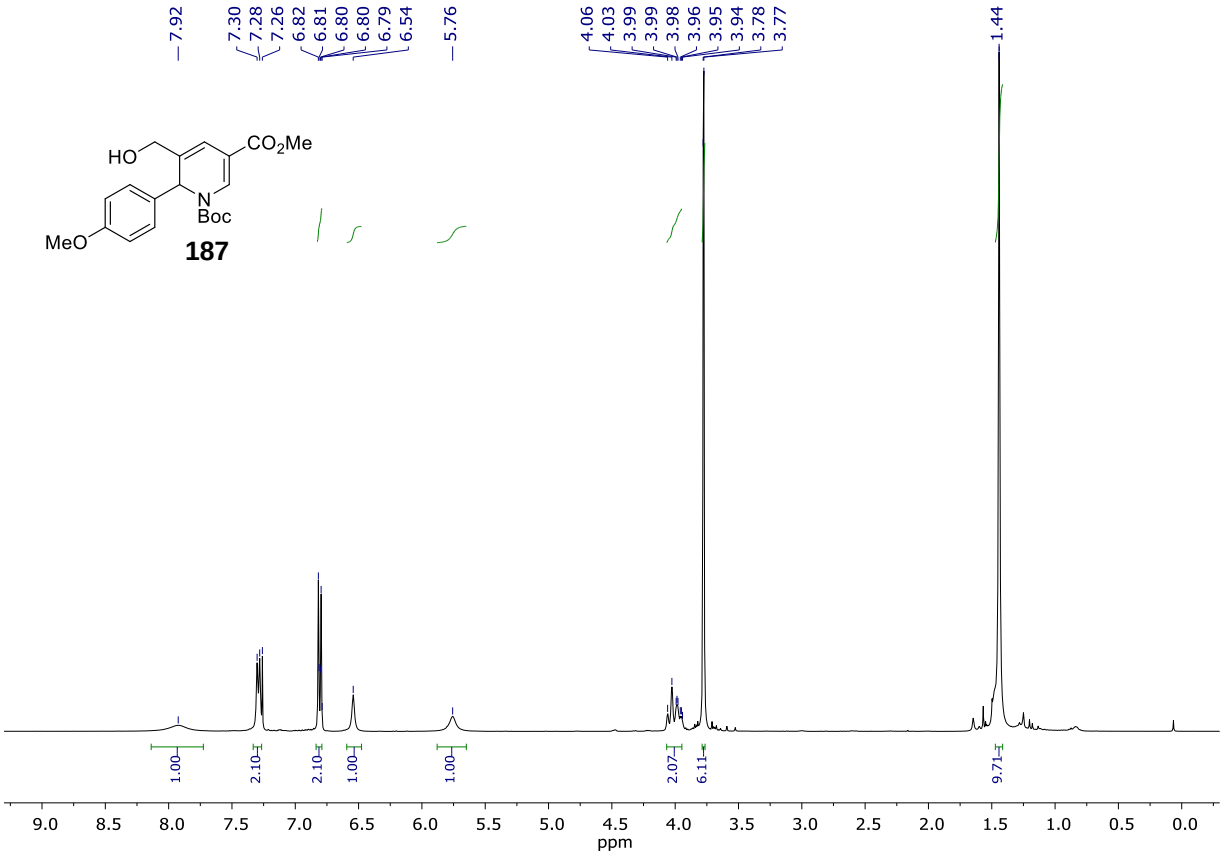
^{13}C NMR (101 MHz, $CDCl_3$)



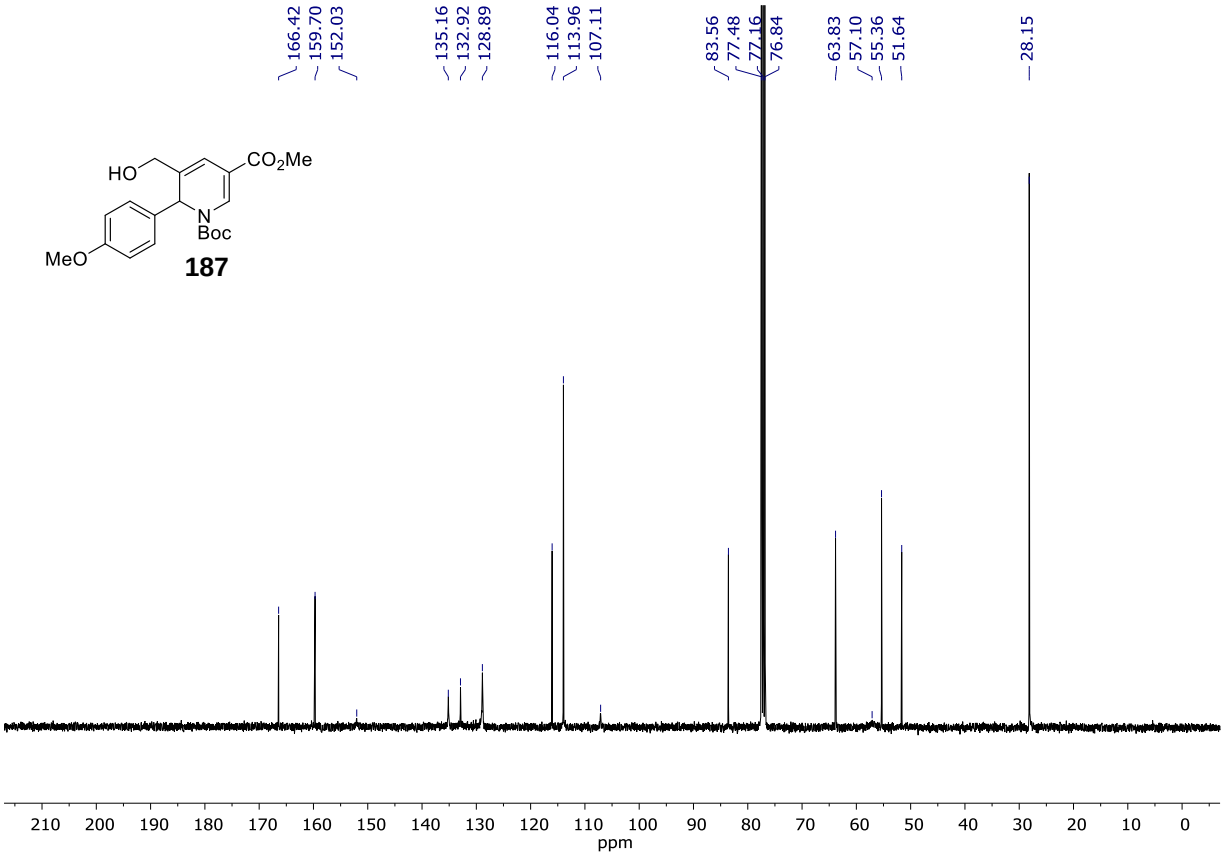
^{1}H NMR (400 MHz, $CDCl_3$)



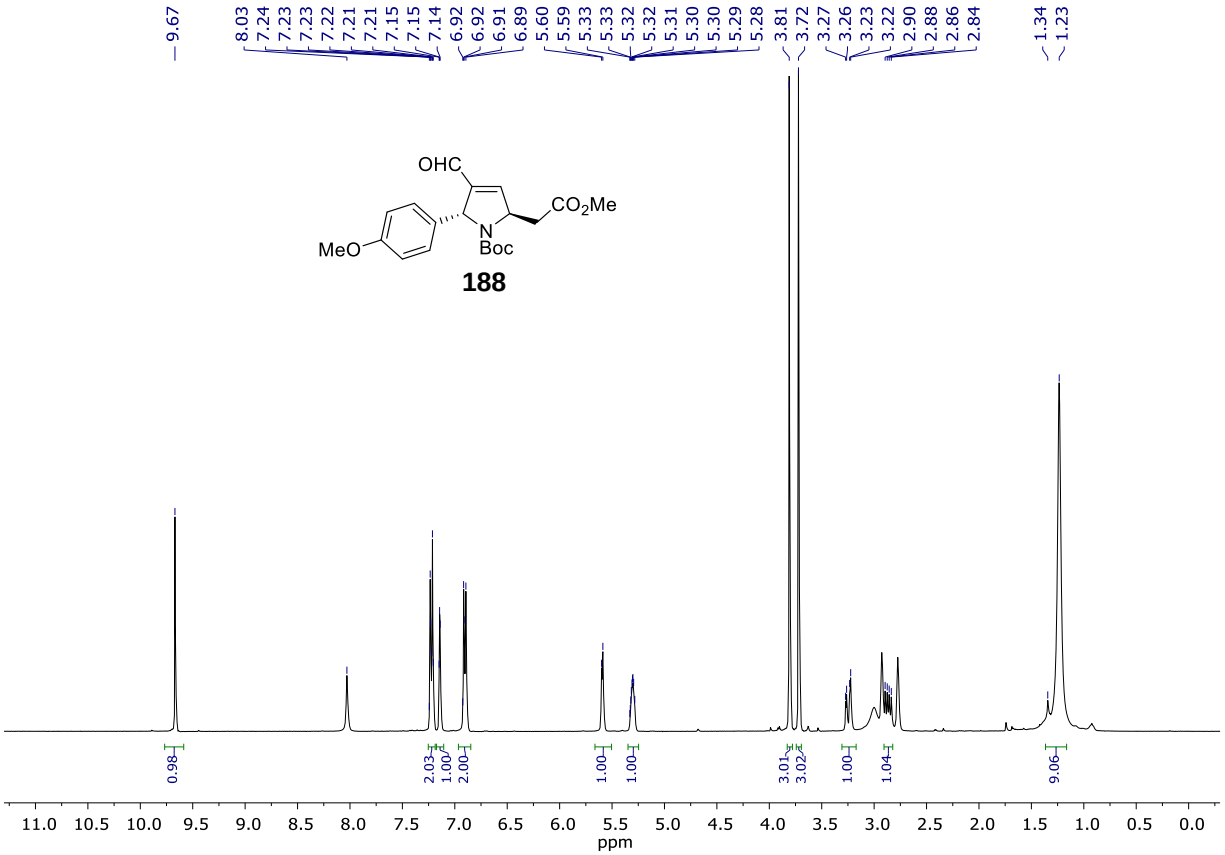
^{13}C NMR (101 MHz, $CDCl_3$)



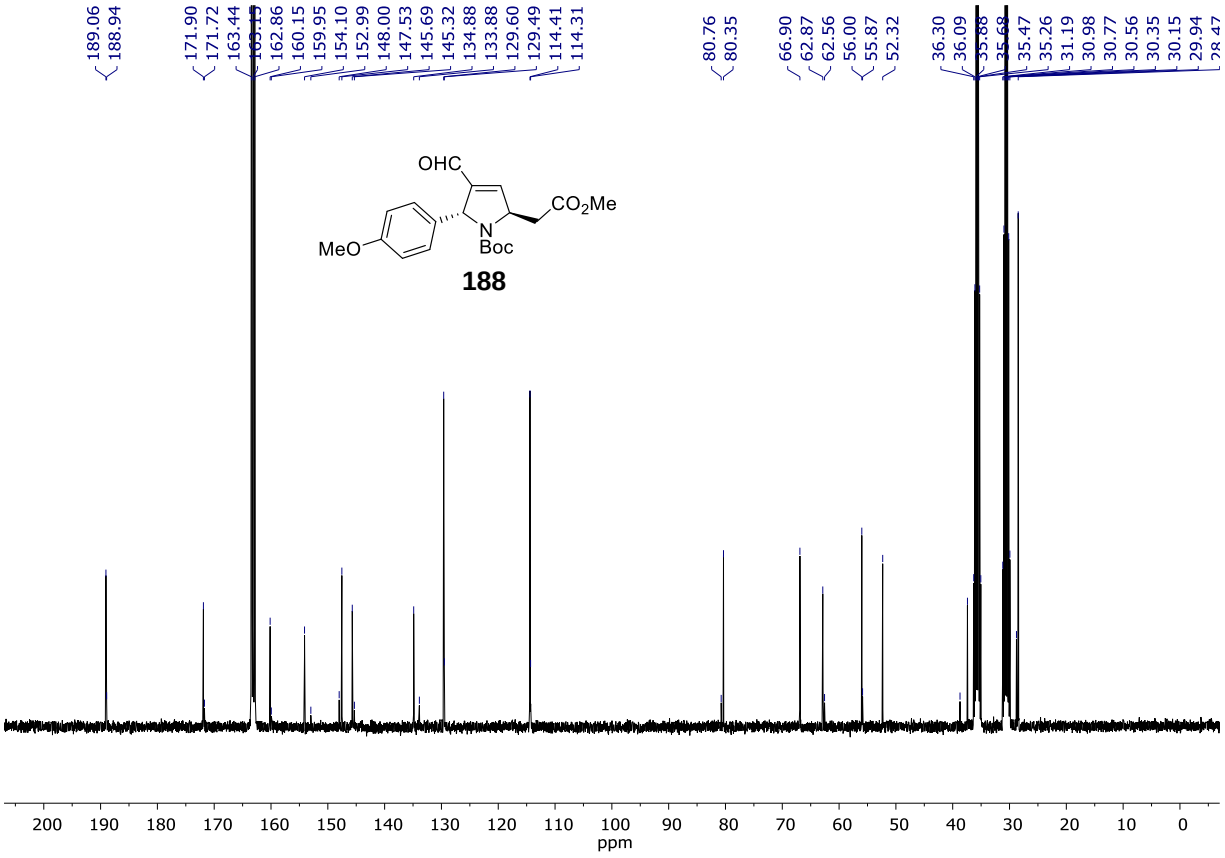
^{1}H NMR (400 MHz, $CDCl_3$)



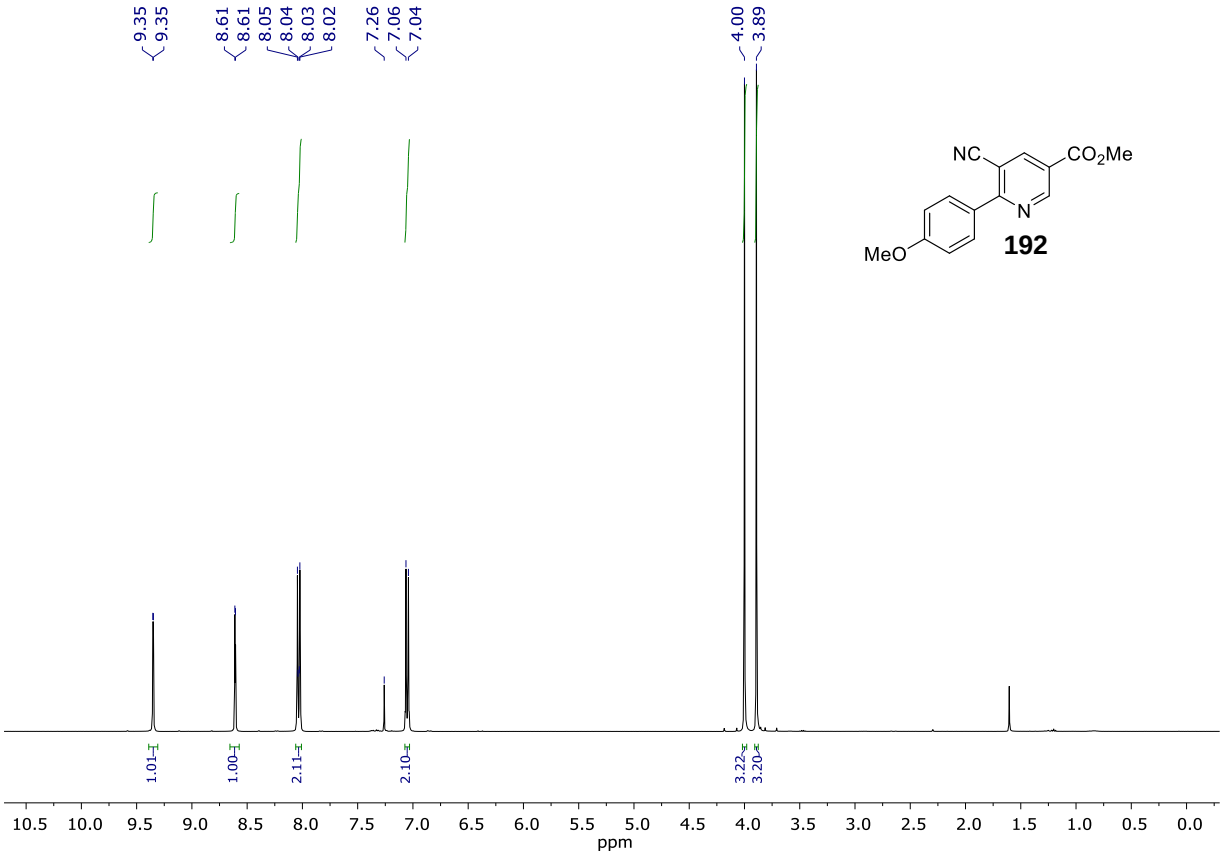
^{13}C NMR (101 MHz, $CDCl_3$)



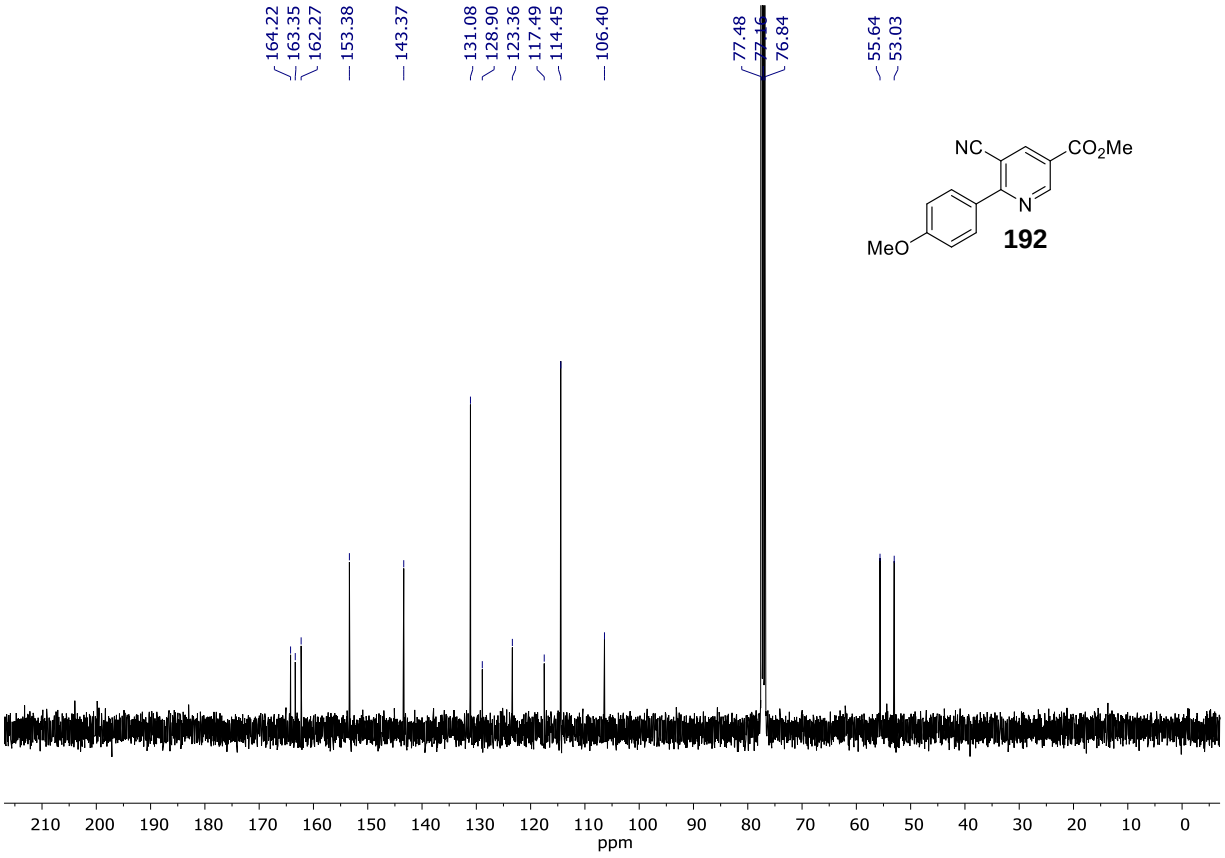
^{1}H NMR (400 MHz, DMF-d$_7$, 110 °C)



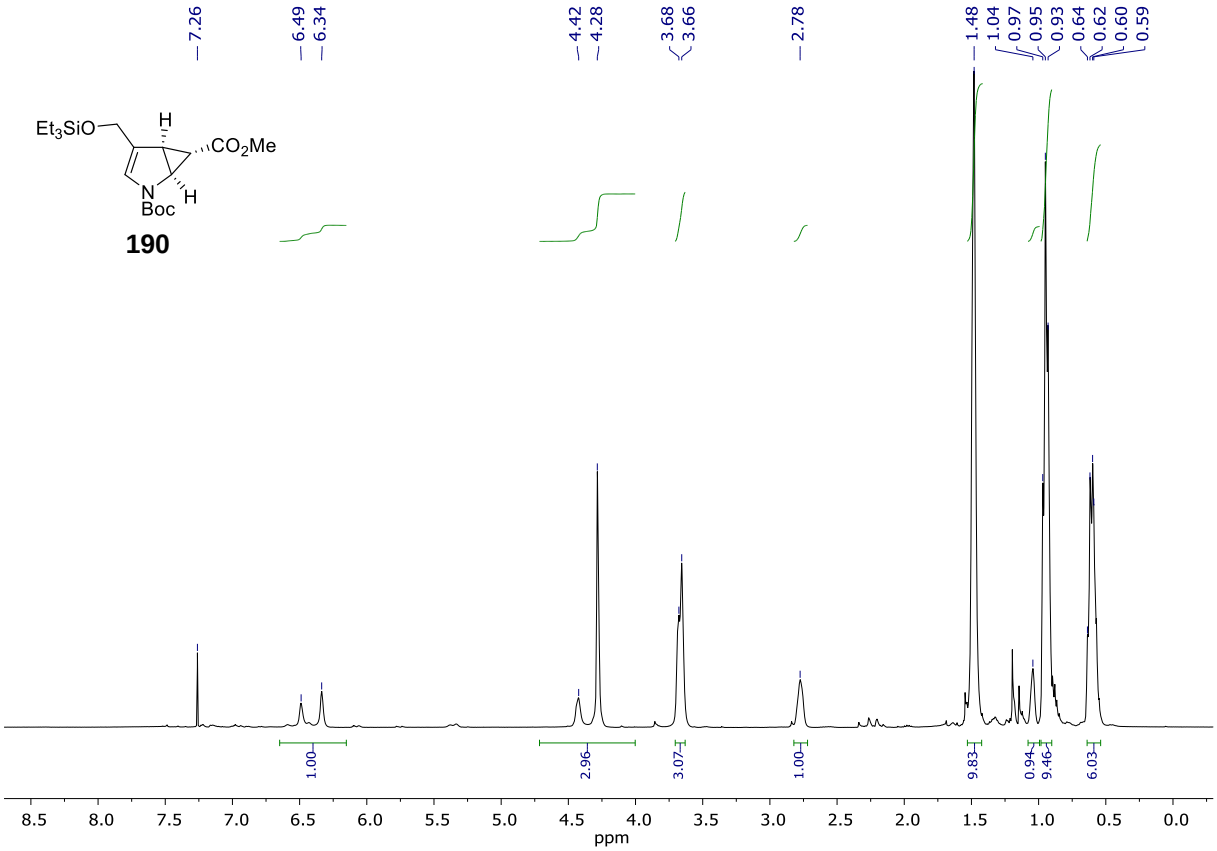
^{13}C NMR (101 MHz, DMF-d$_7$)



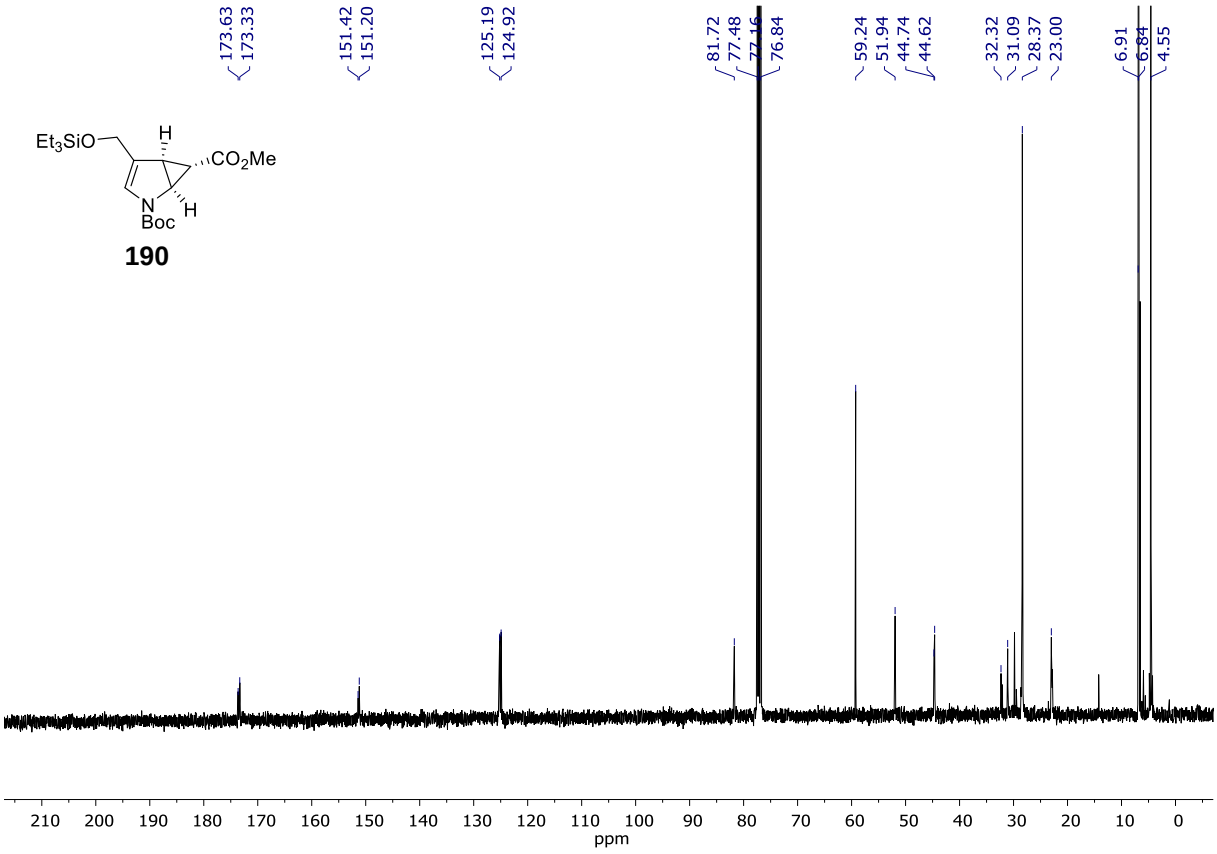
^{1}H NMR (400 MHz, $CDCl_3$)



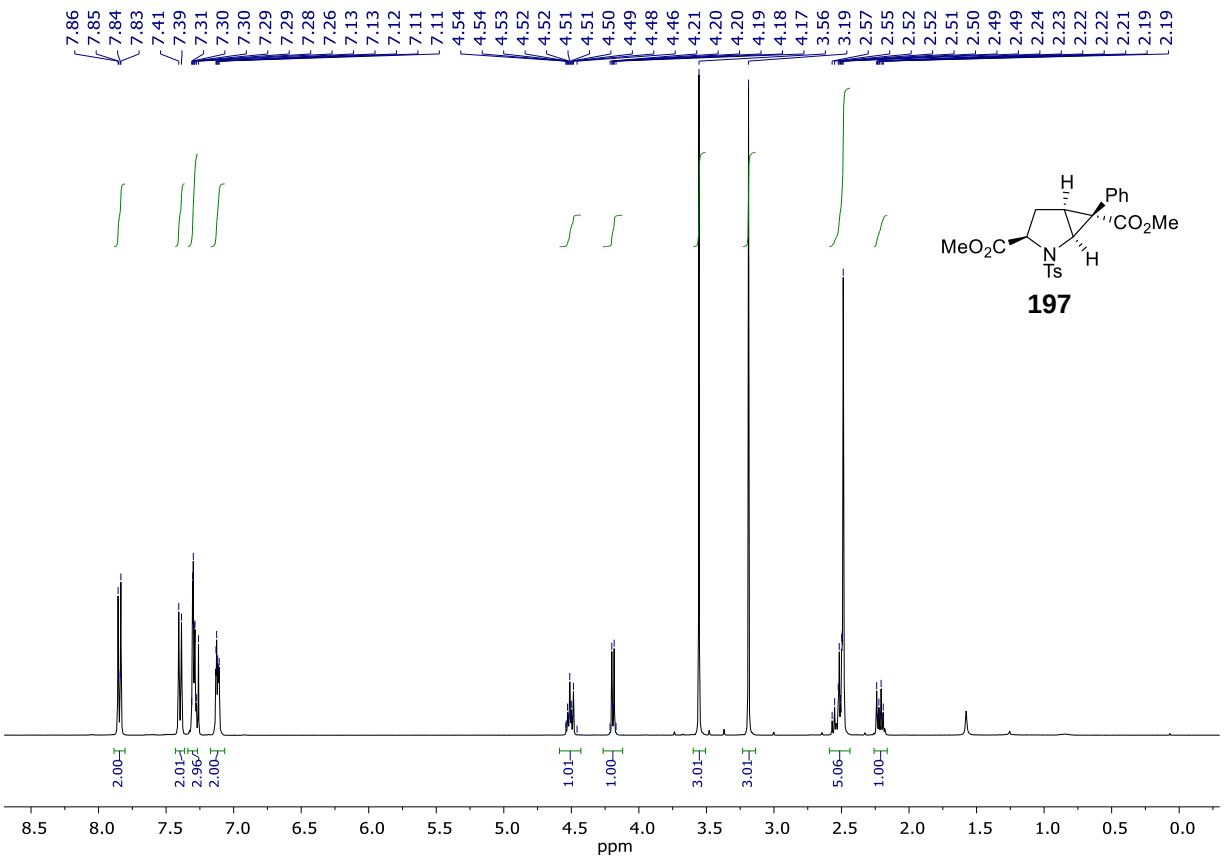
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)

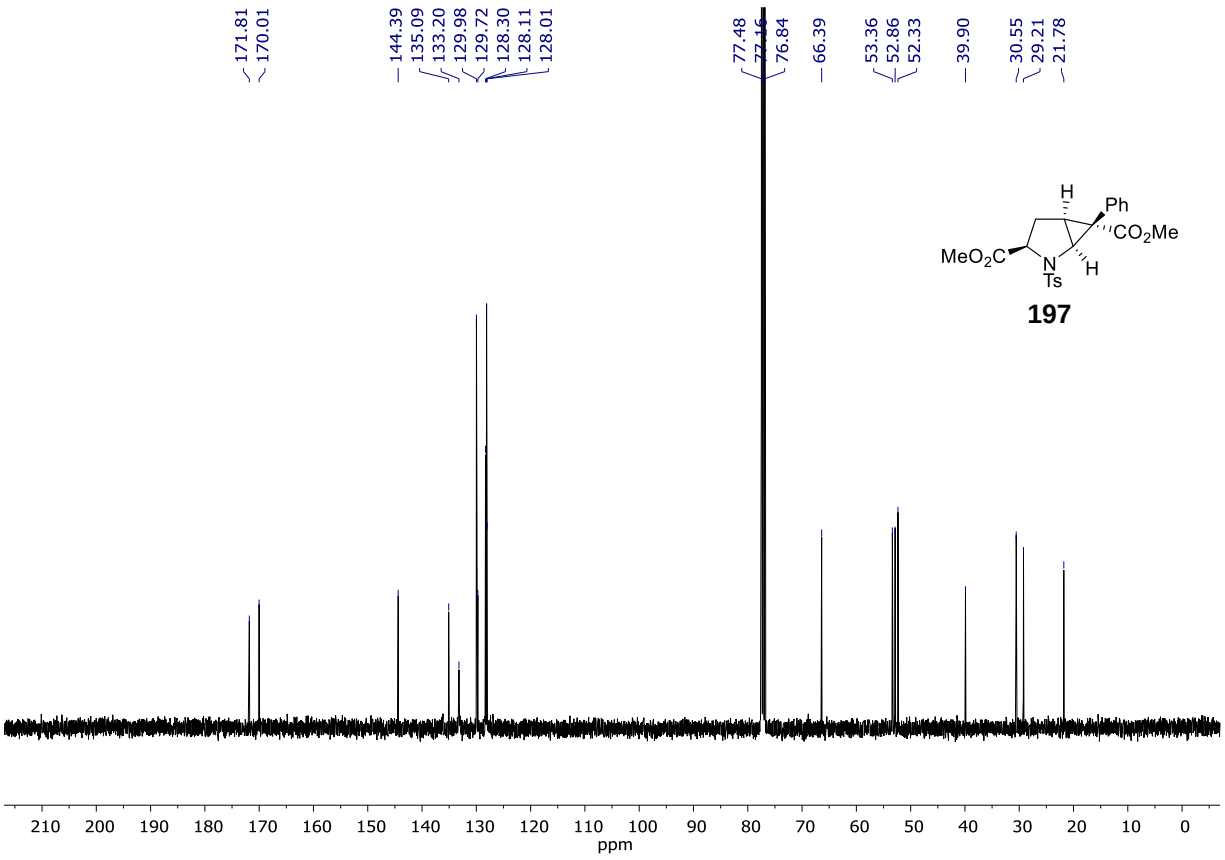


^{13}C NMR (101 MHz, $CDCl_3$)



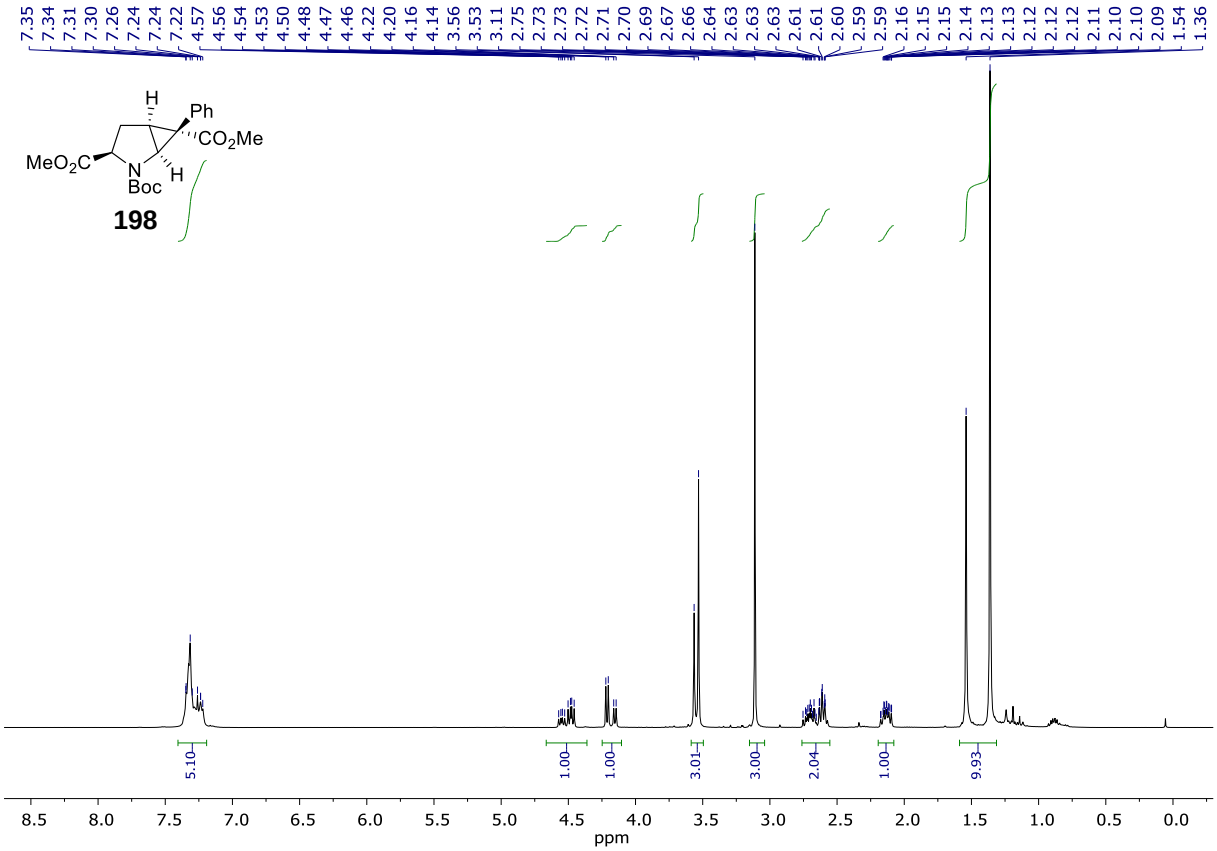
197

^{1}H NMR (400 MHz, $CDCl_3$)

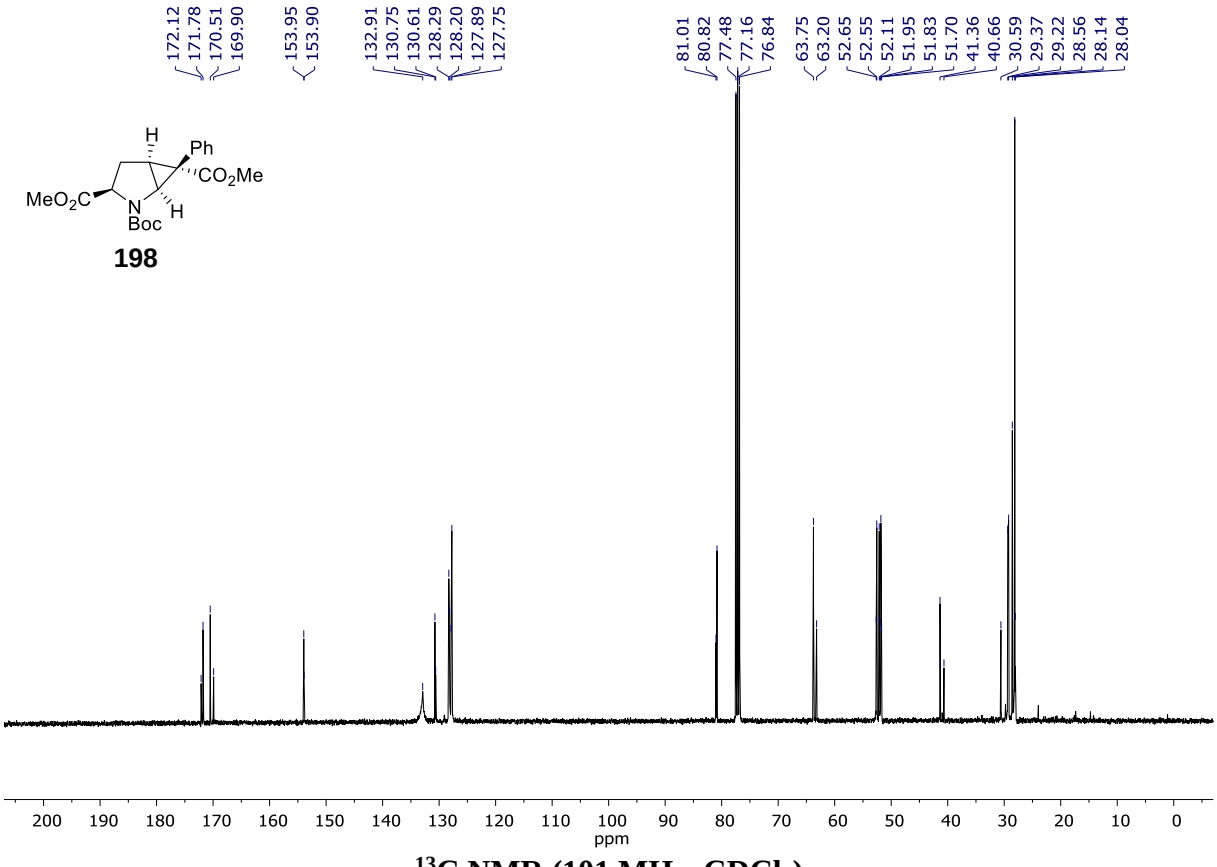


197

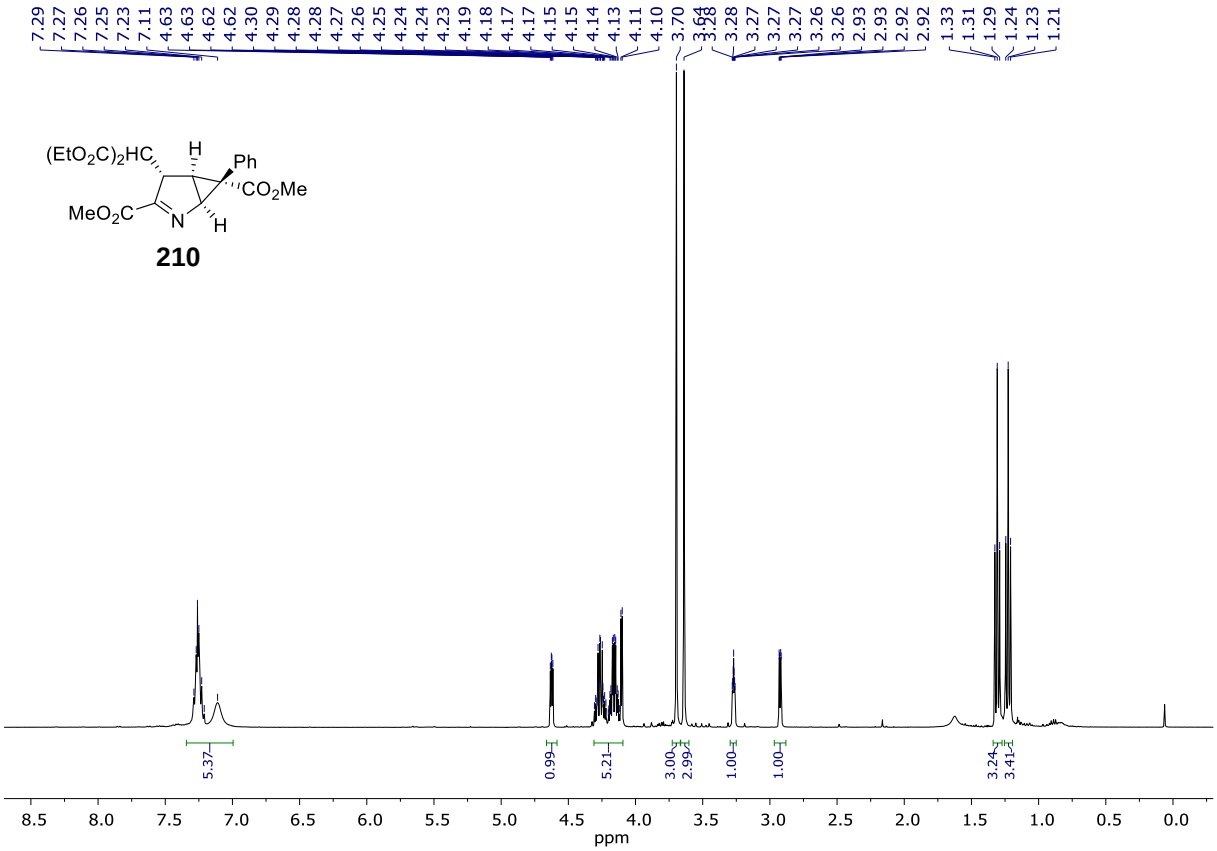
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)

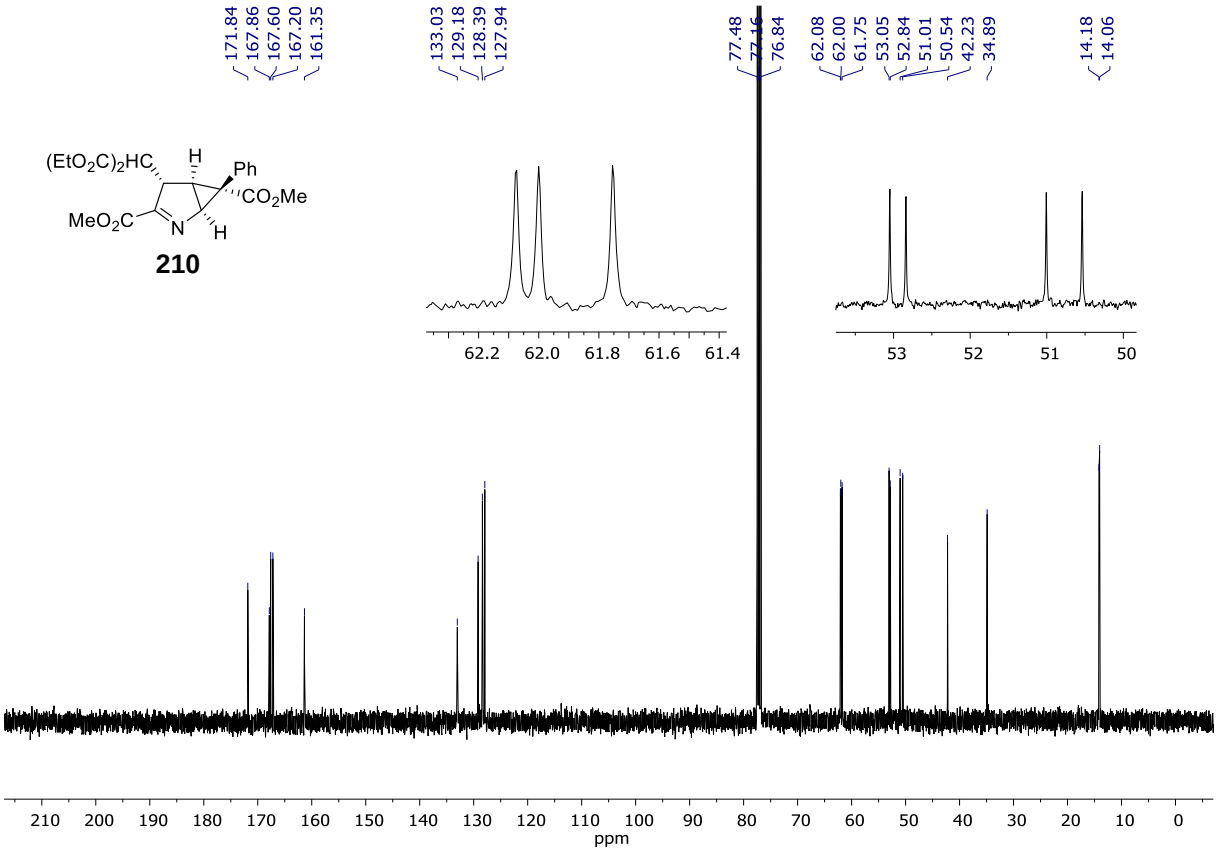


^{13}C NMR (101 MHz, $CDCl_3$)



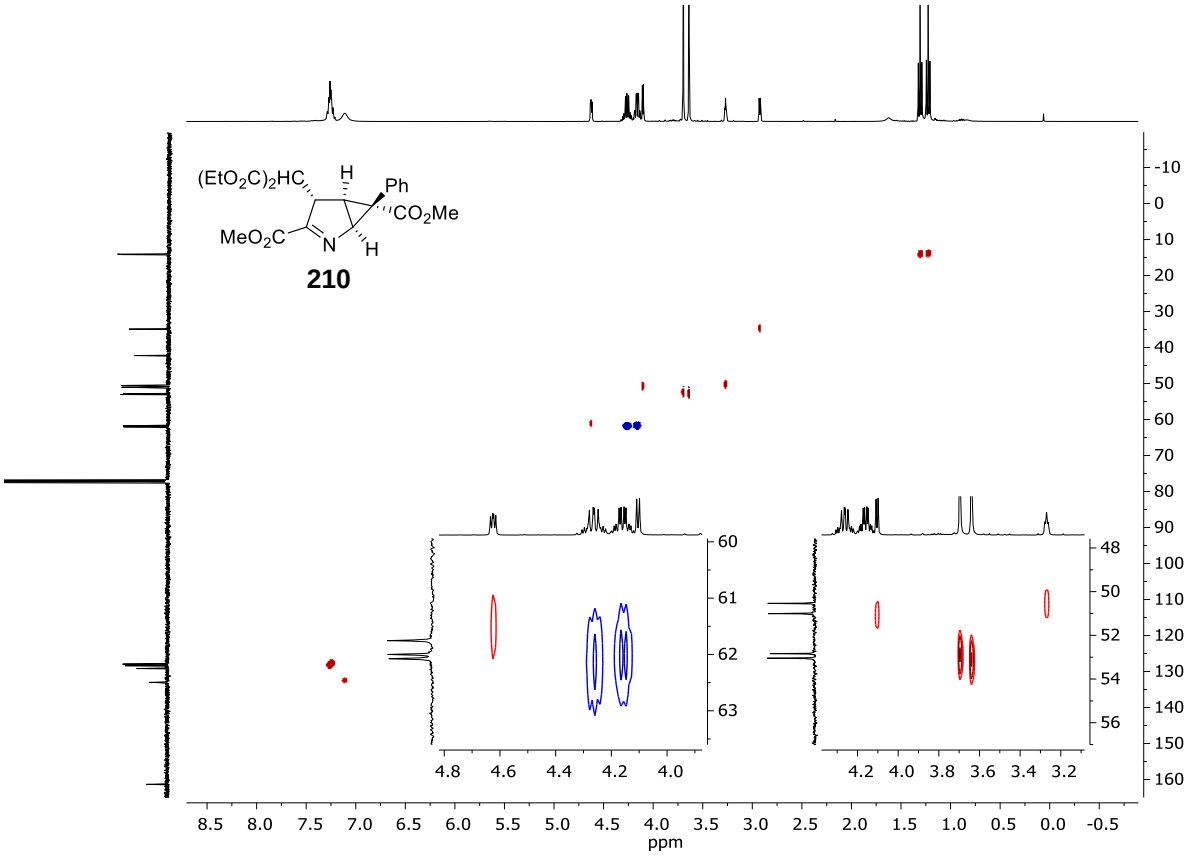
210

^{1}H NMR (400 MHz, $CDCl_3$)

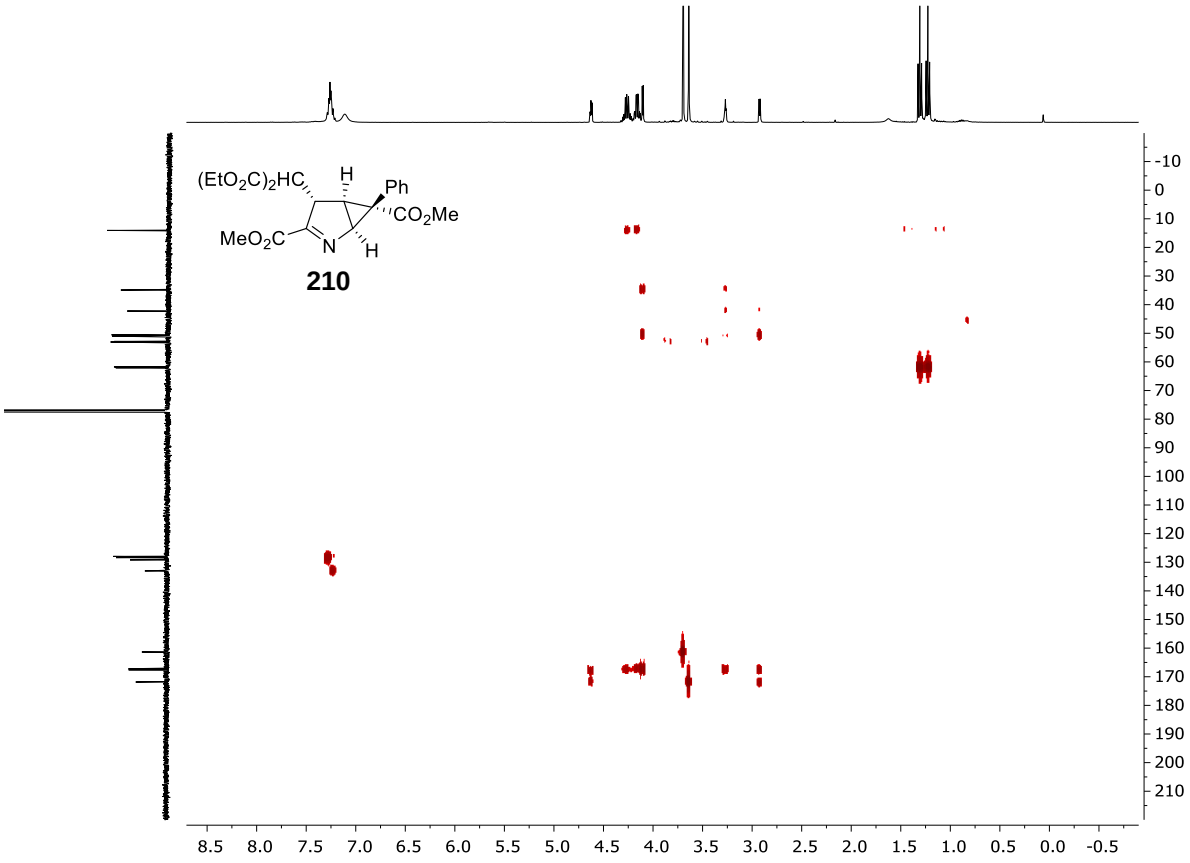


210

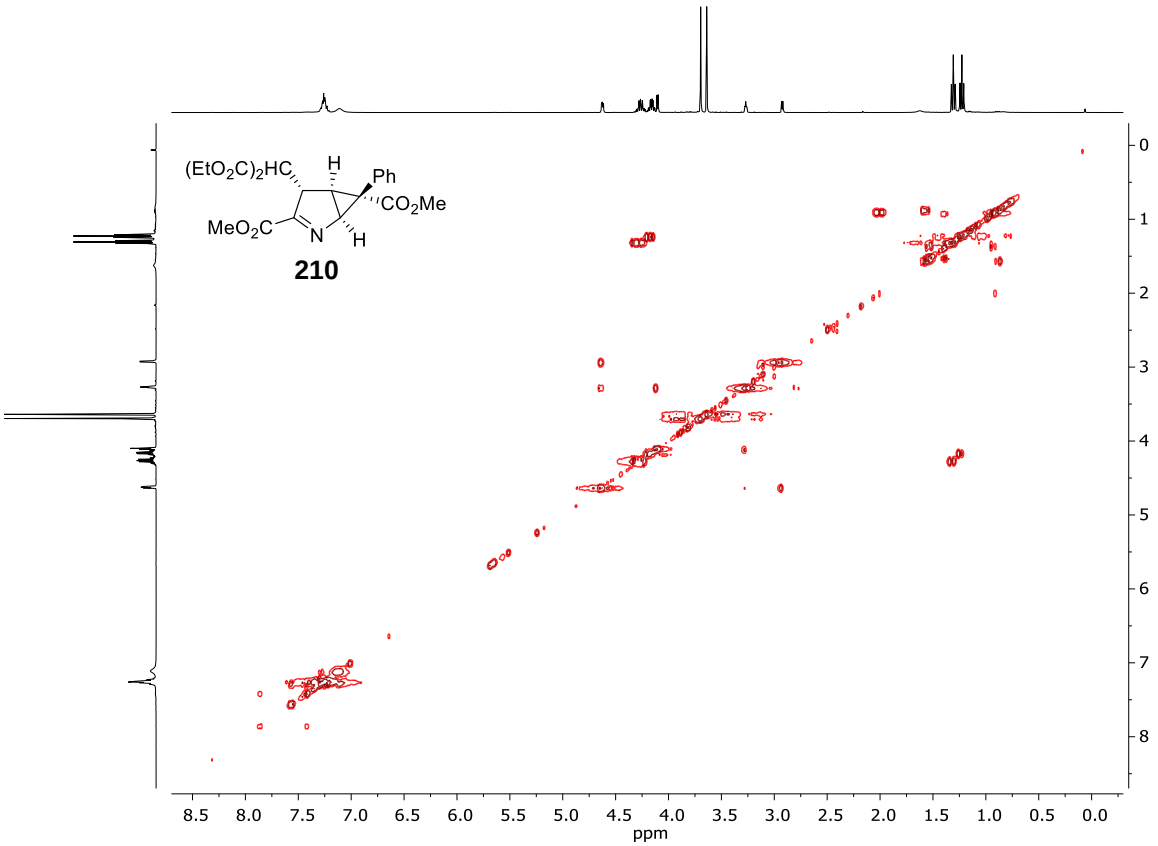
^{13}C NMR (101 MHz, $CDCl_3$)



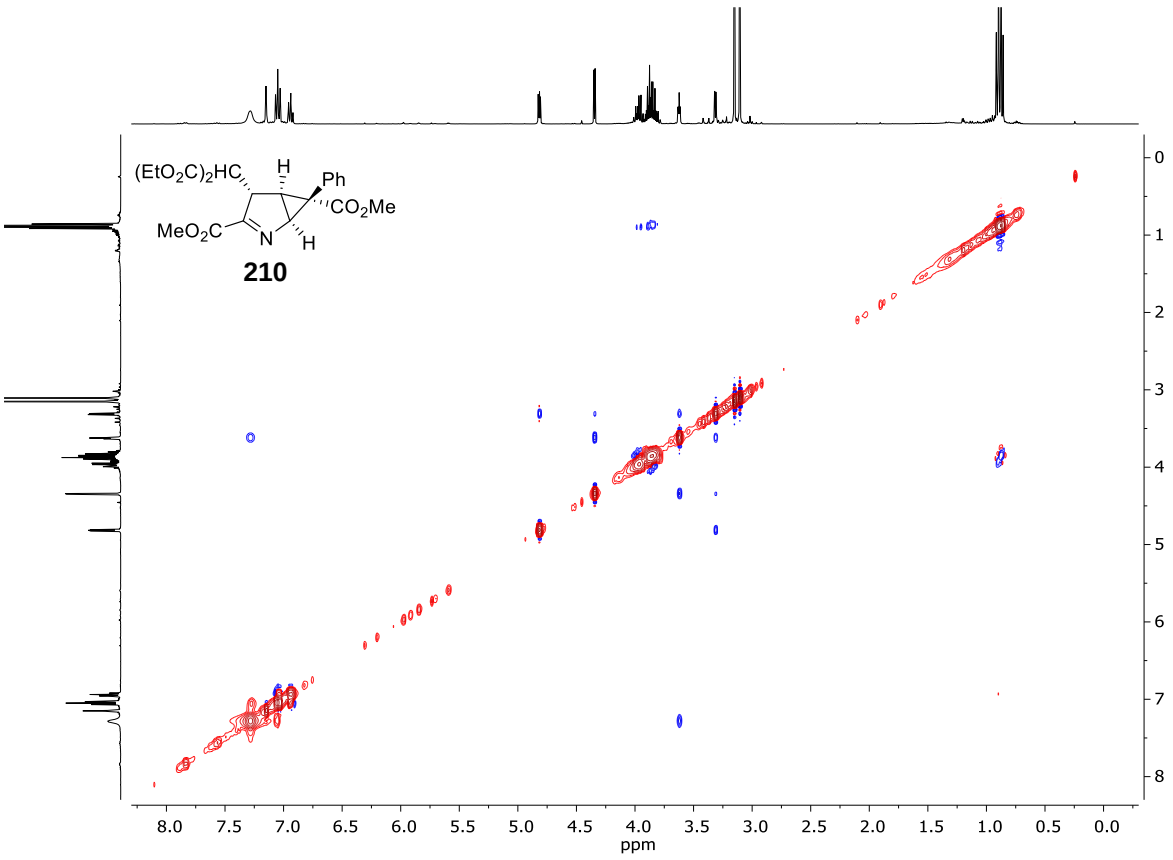
HSQC ((400, 101) MHz, $CDCl_3$)



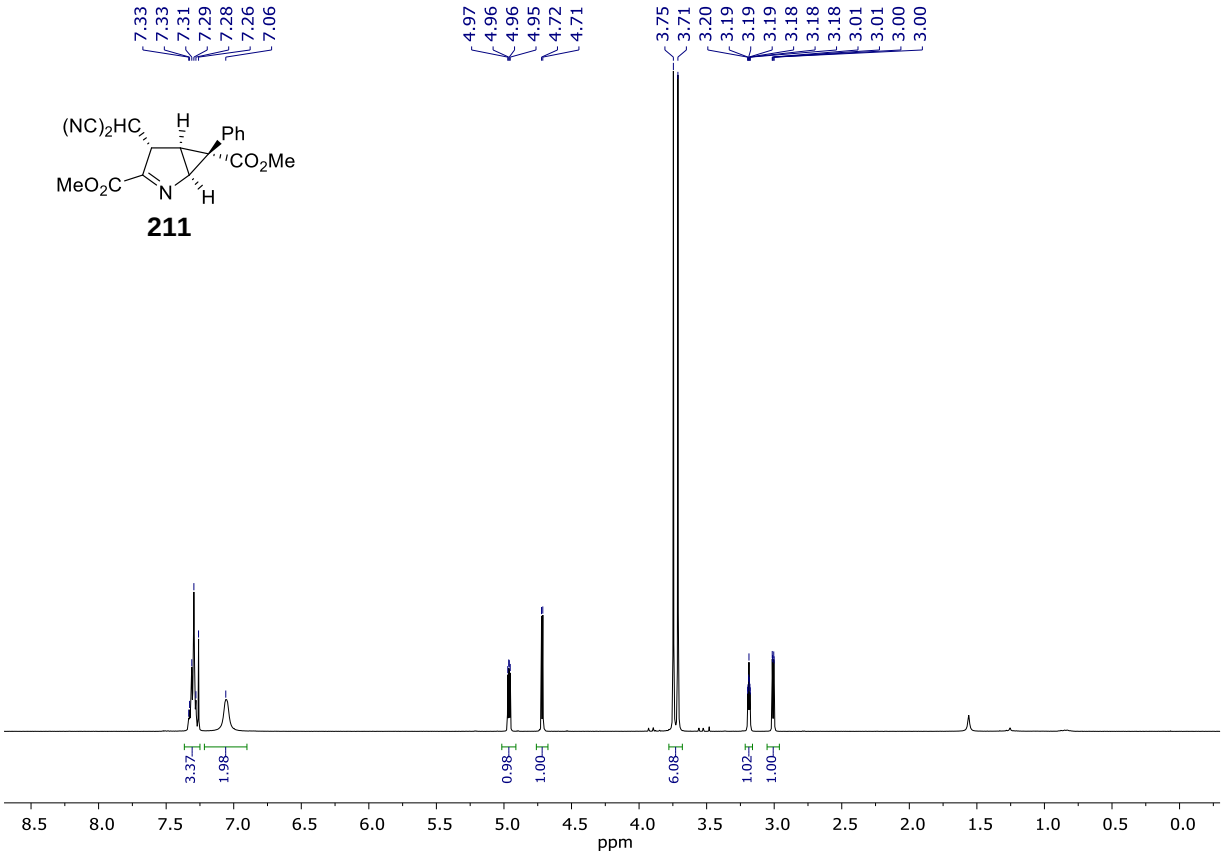
HMBC ((400, 101) MHz, $CDCl_3$)



COSY (400 MHz, $CDCl_3$)

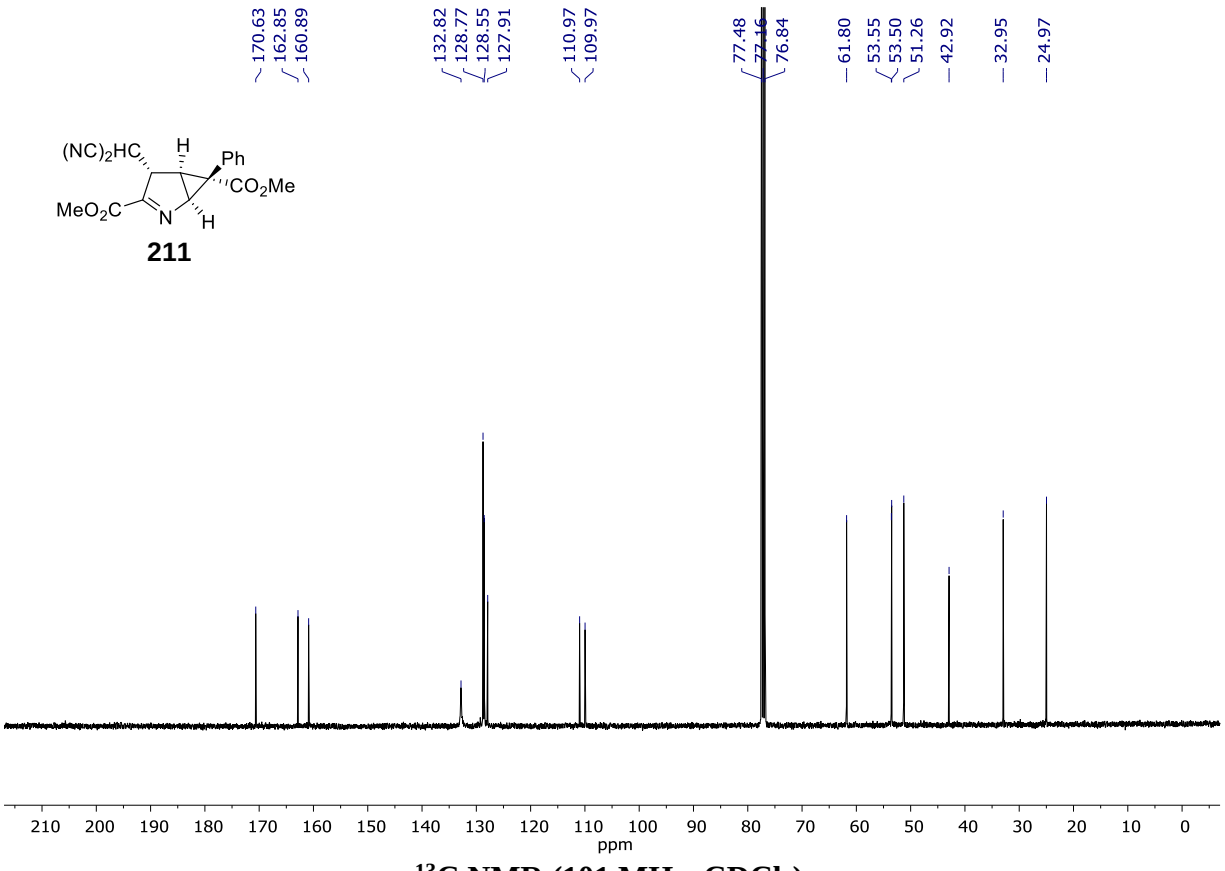


NOESY (400 MHz, C_6D_6)



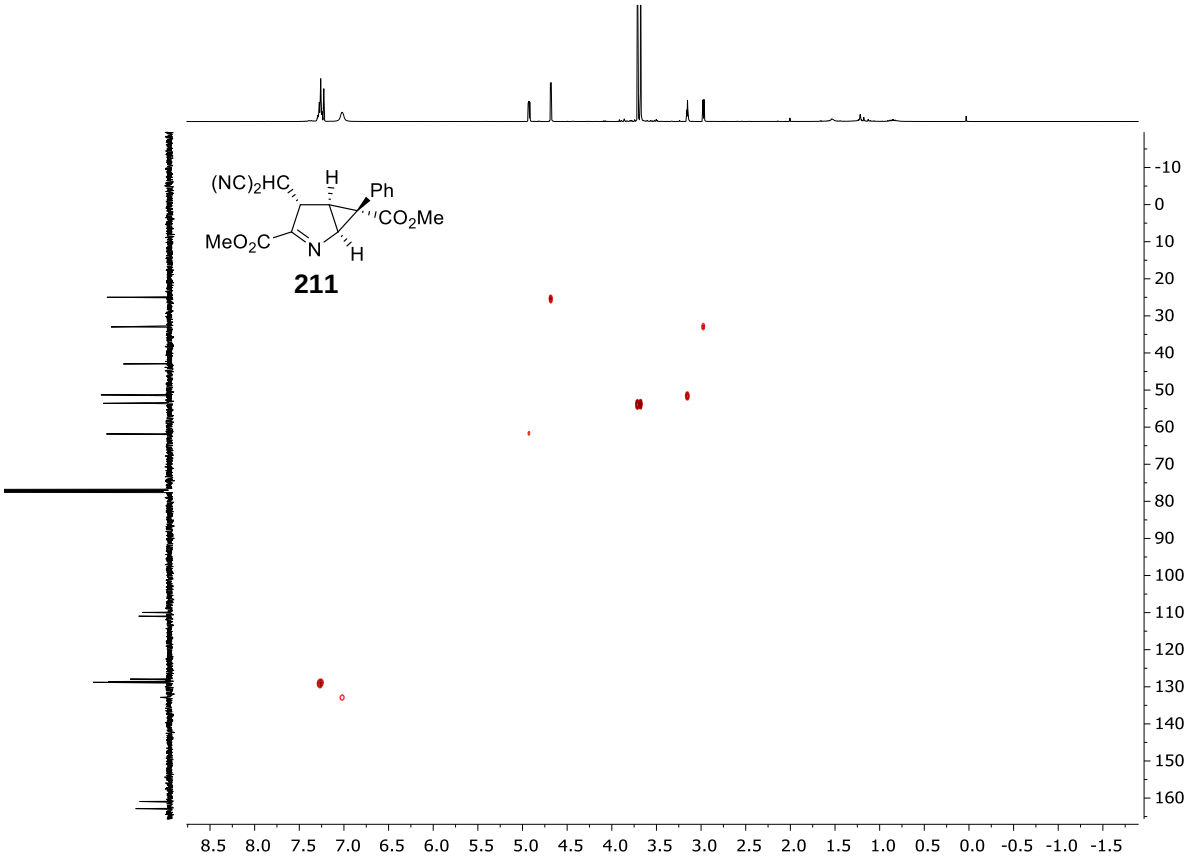
211

^{1}H NMR (400 MHz, $CDCl_3$)

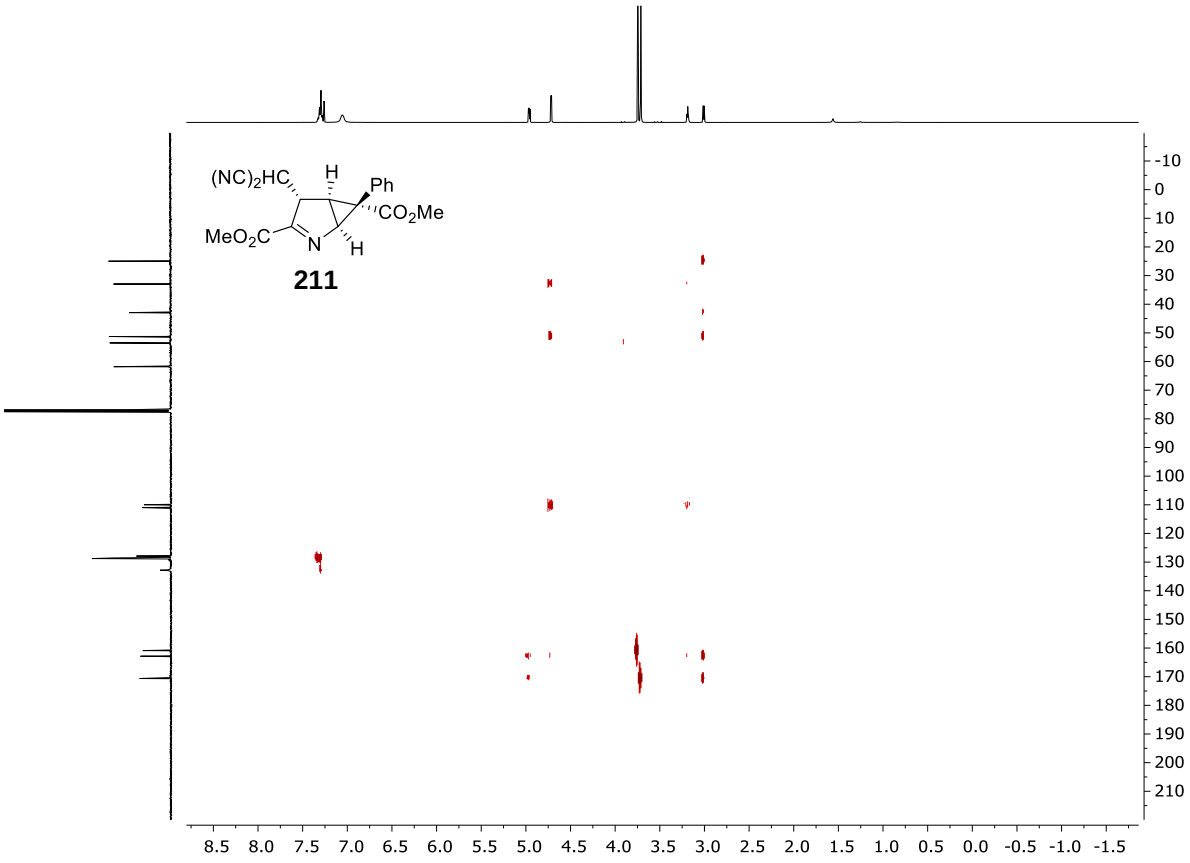


211

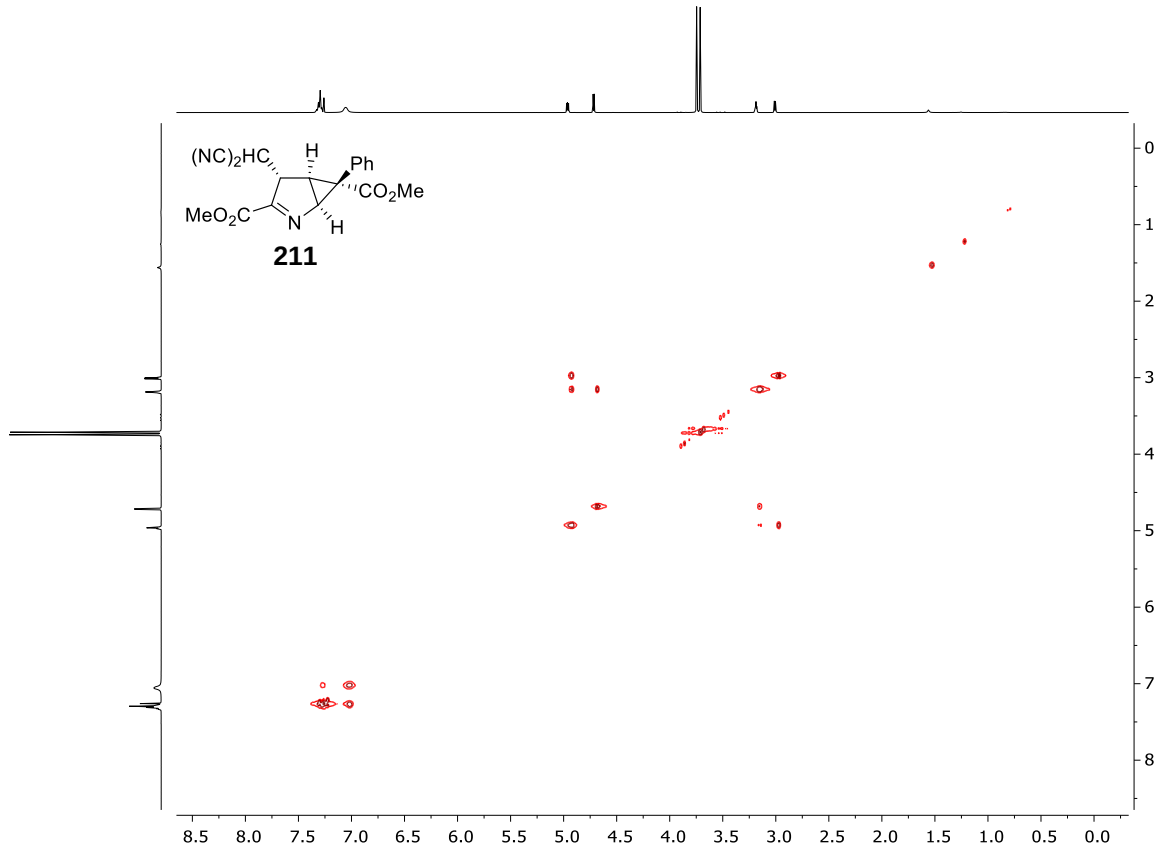
^{13}C NMR (101 MHz, $CDCl_3$)



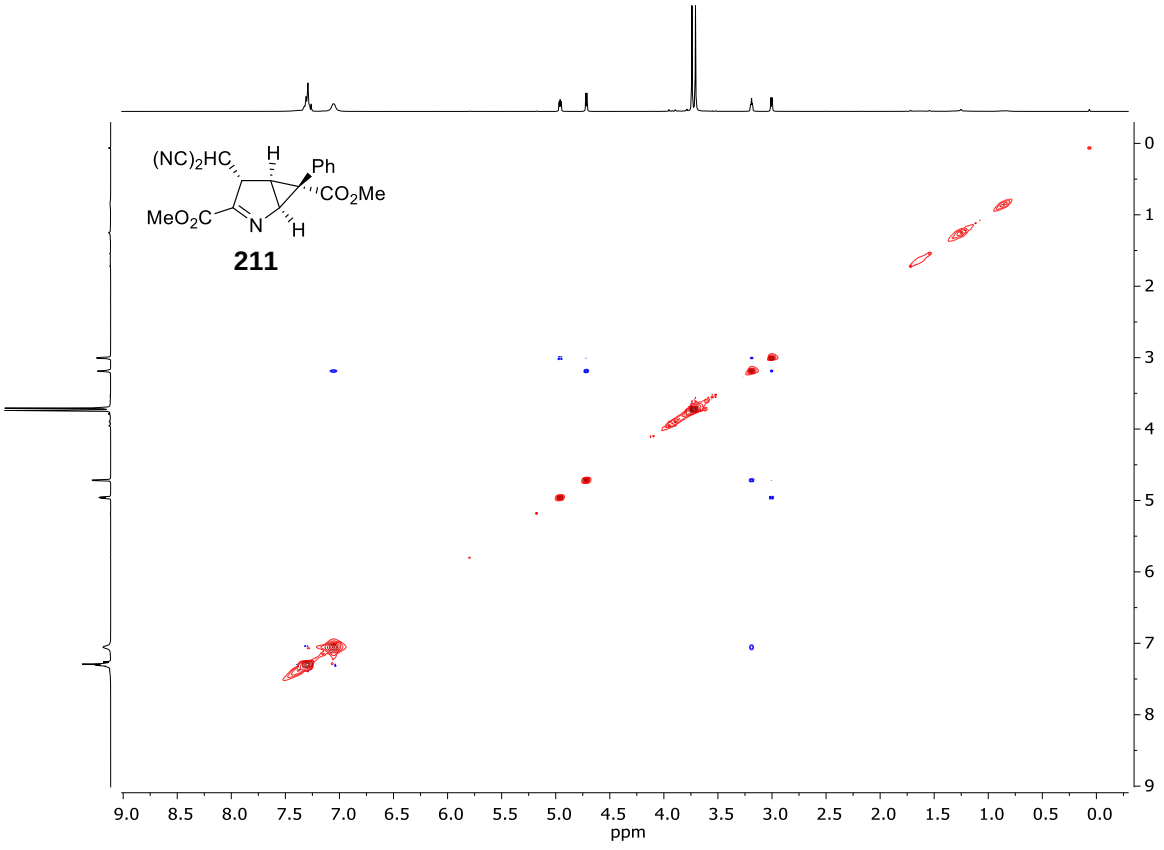
HSQC ((400, 101) MHz, $CDCl_3$)



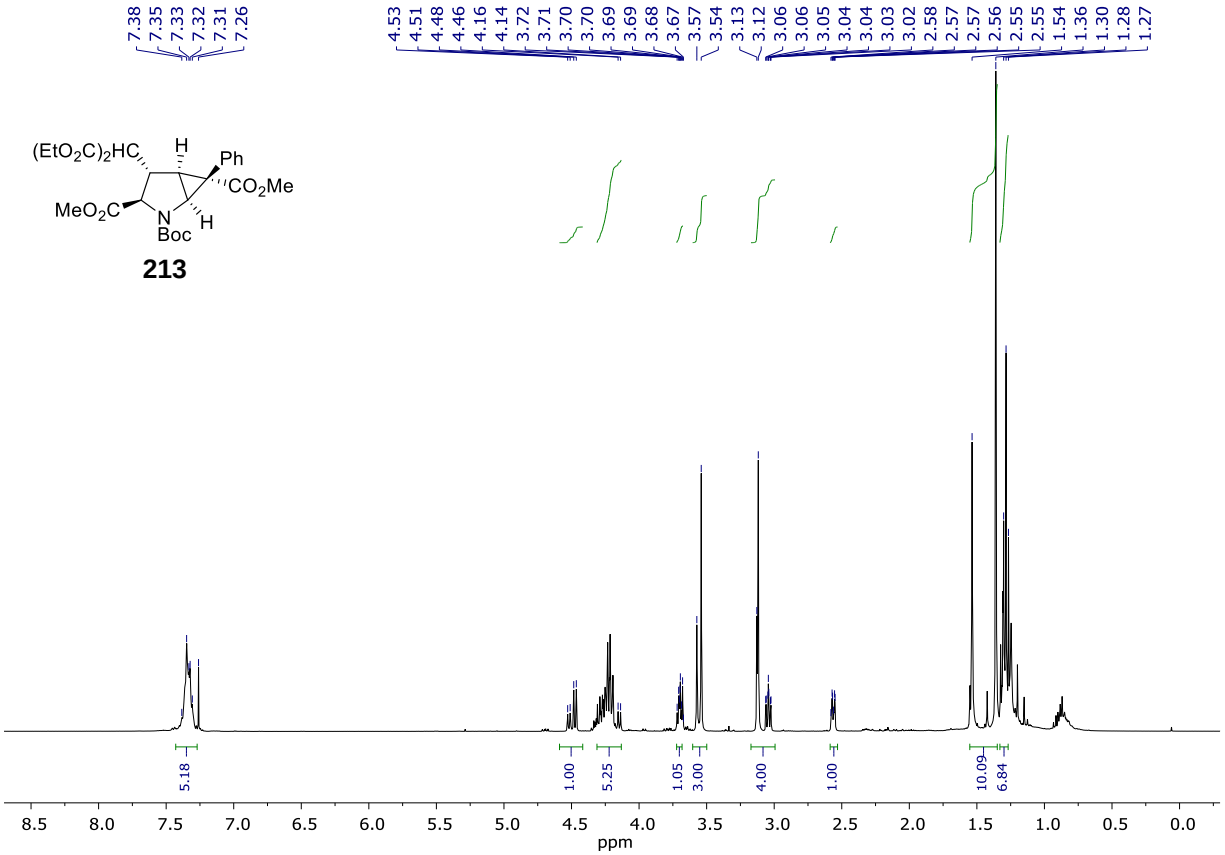
HMBC ((400, 101) MHz, $CDCl_3$)



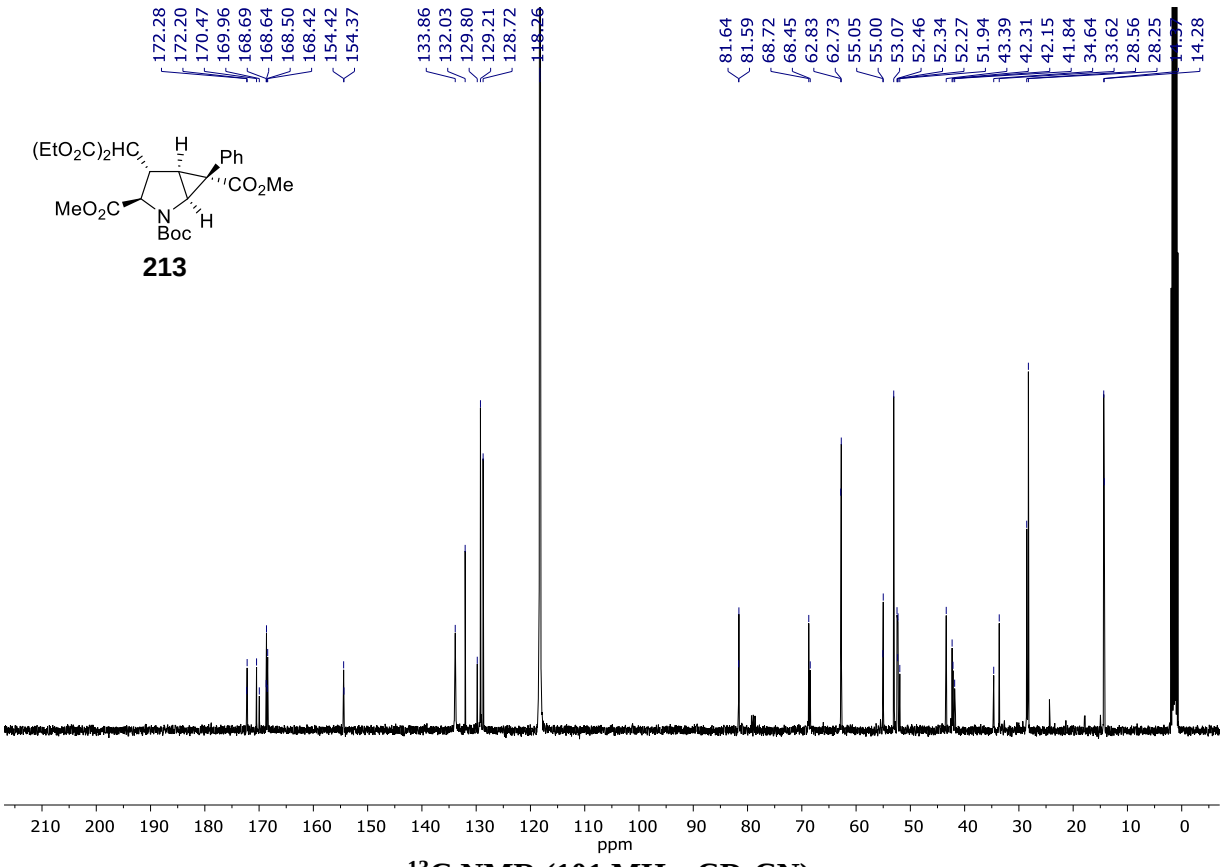
COSY (400 MHz, $CDCl_3$)



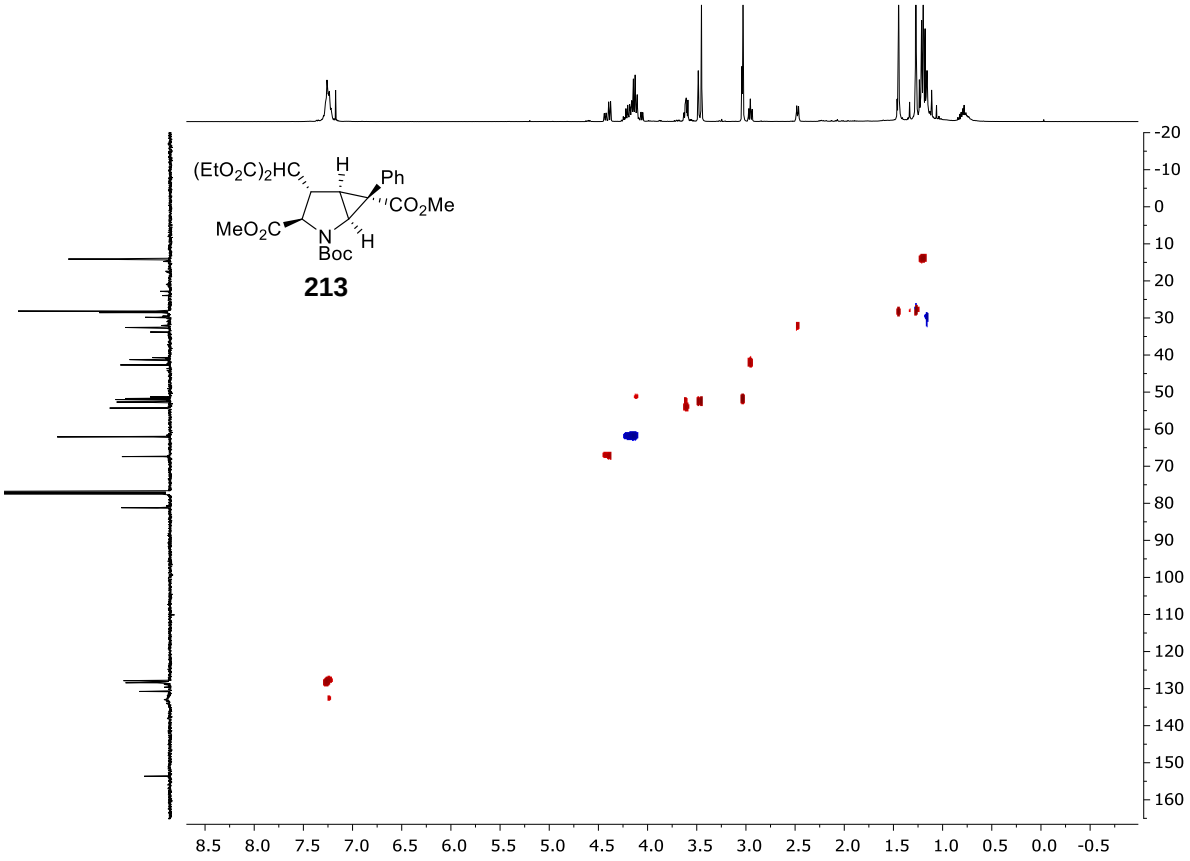
NOESY (400 MHz, $CDCl_3$)



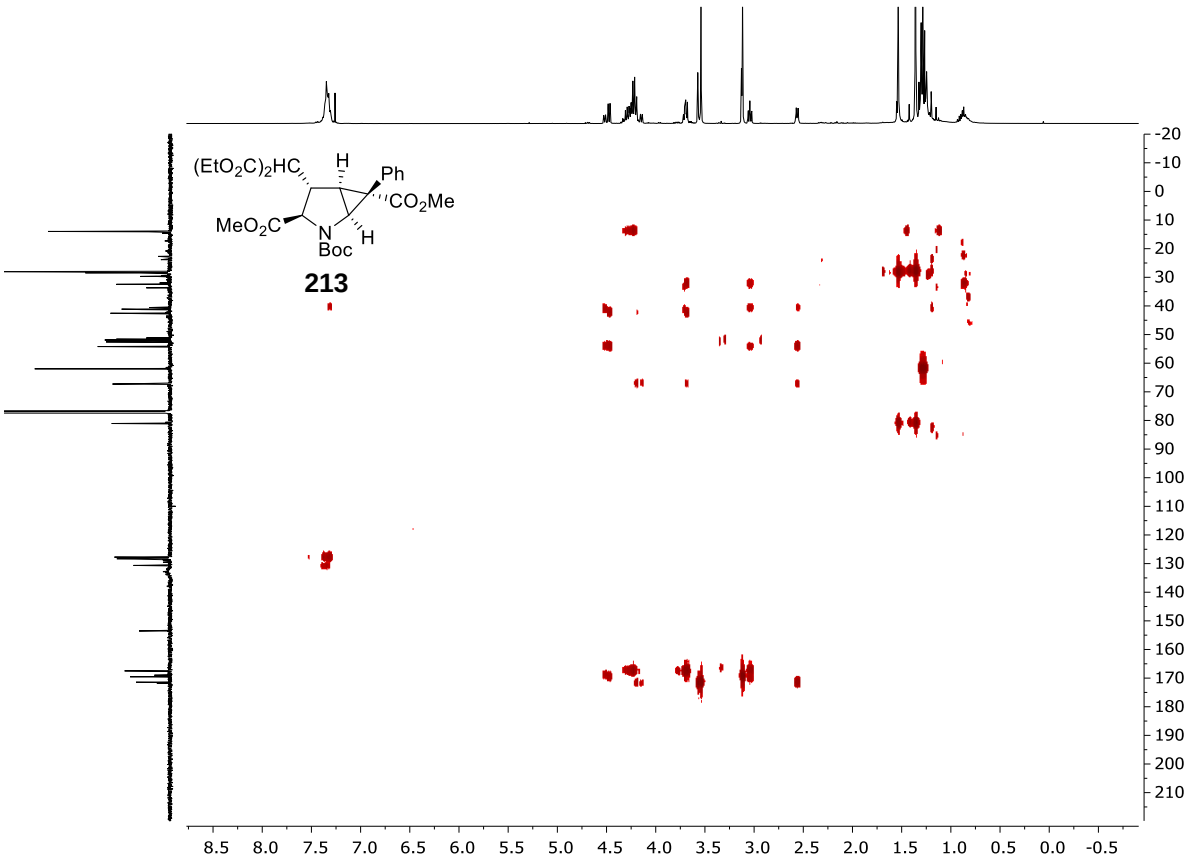
^{1}H NMR (400 MHz, $CDCl_3$)



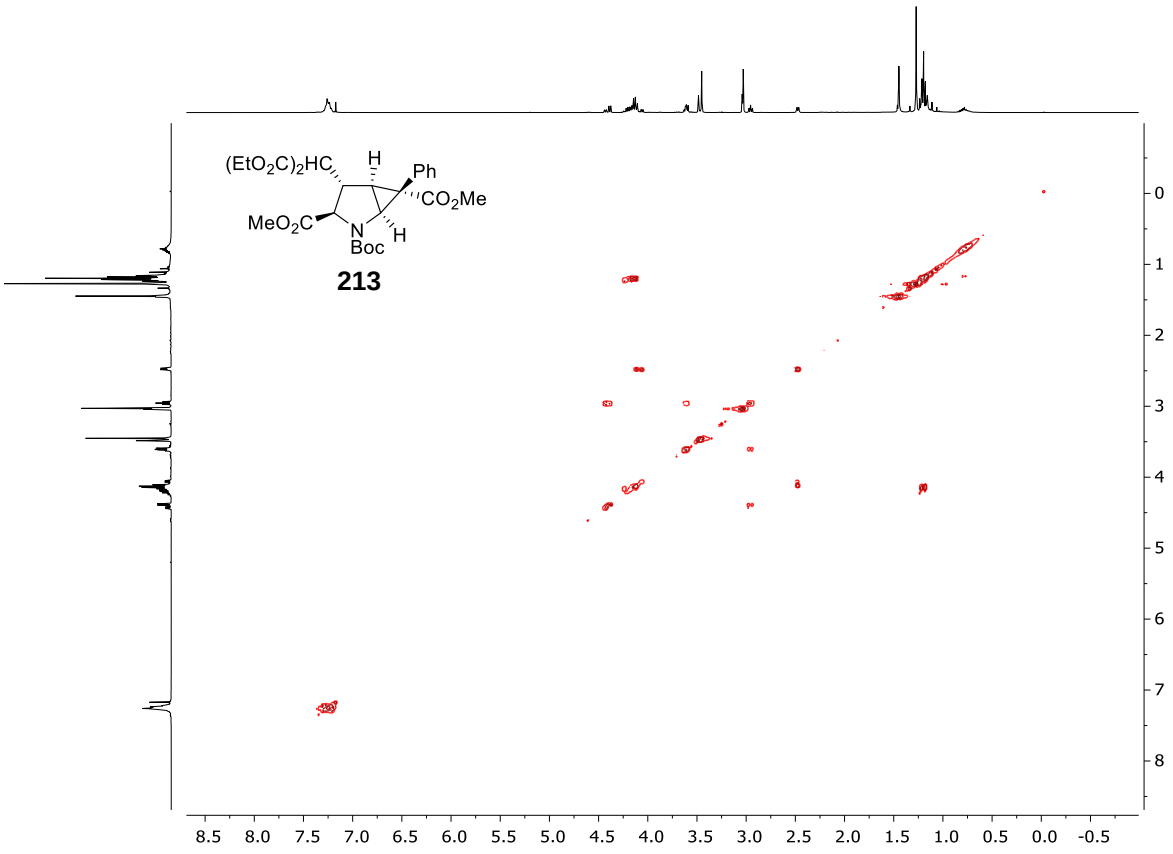
^{13}C NMR (101 MHz, CD_3CN)



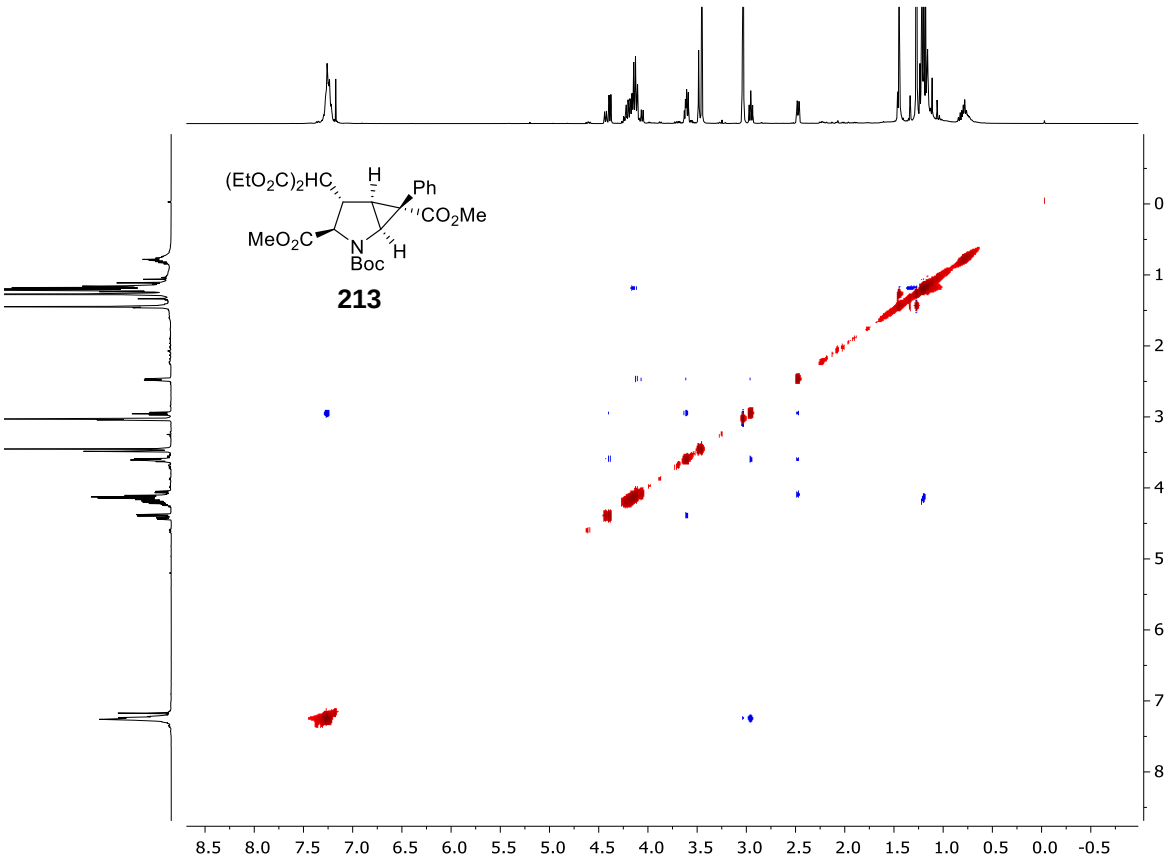
HSQC ((400, 101) MHz, $CDCl_3$)



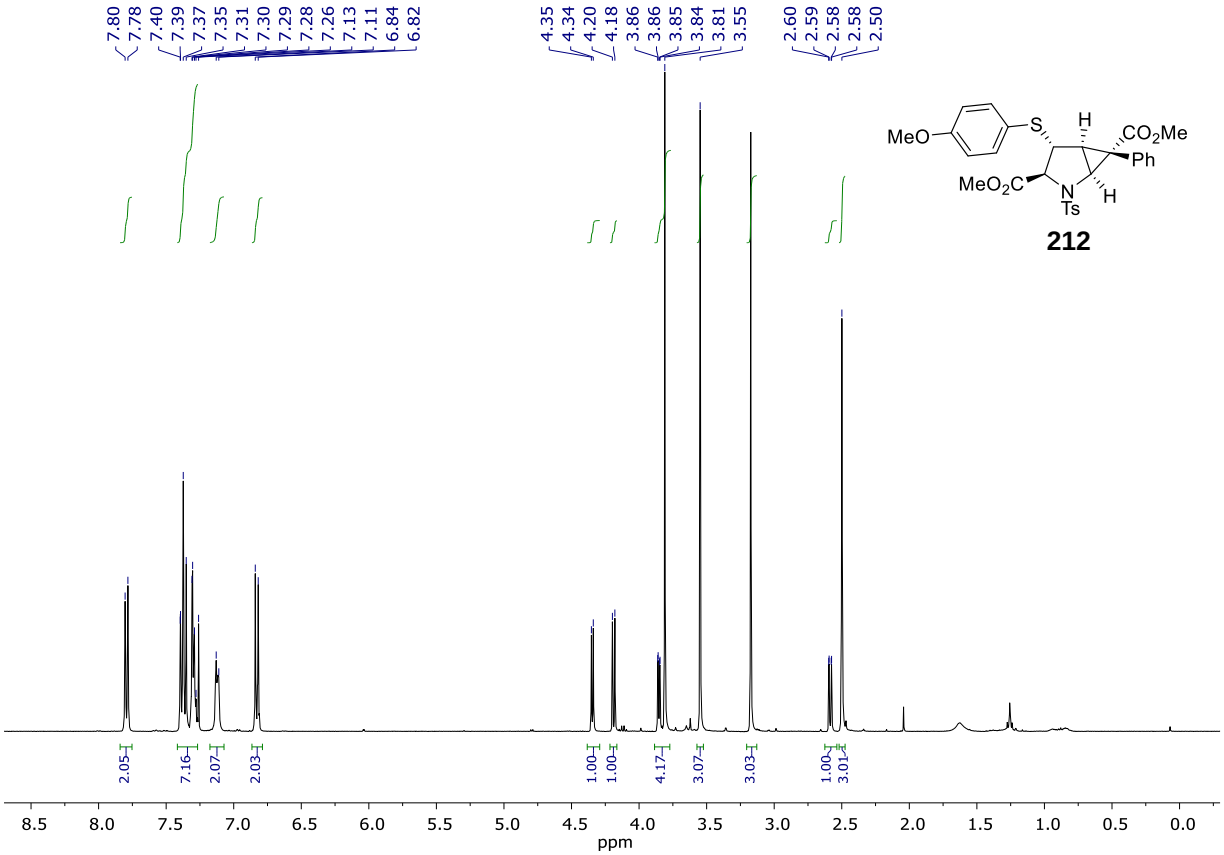
HMBC ((400, 101) MHz, $CDCl_3$)



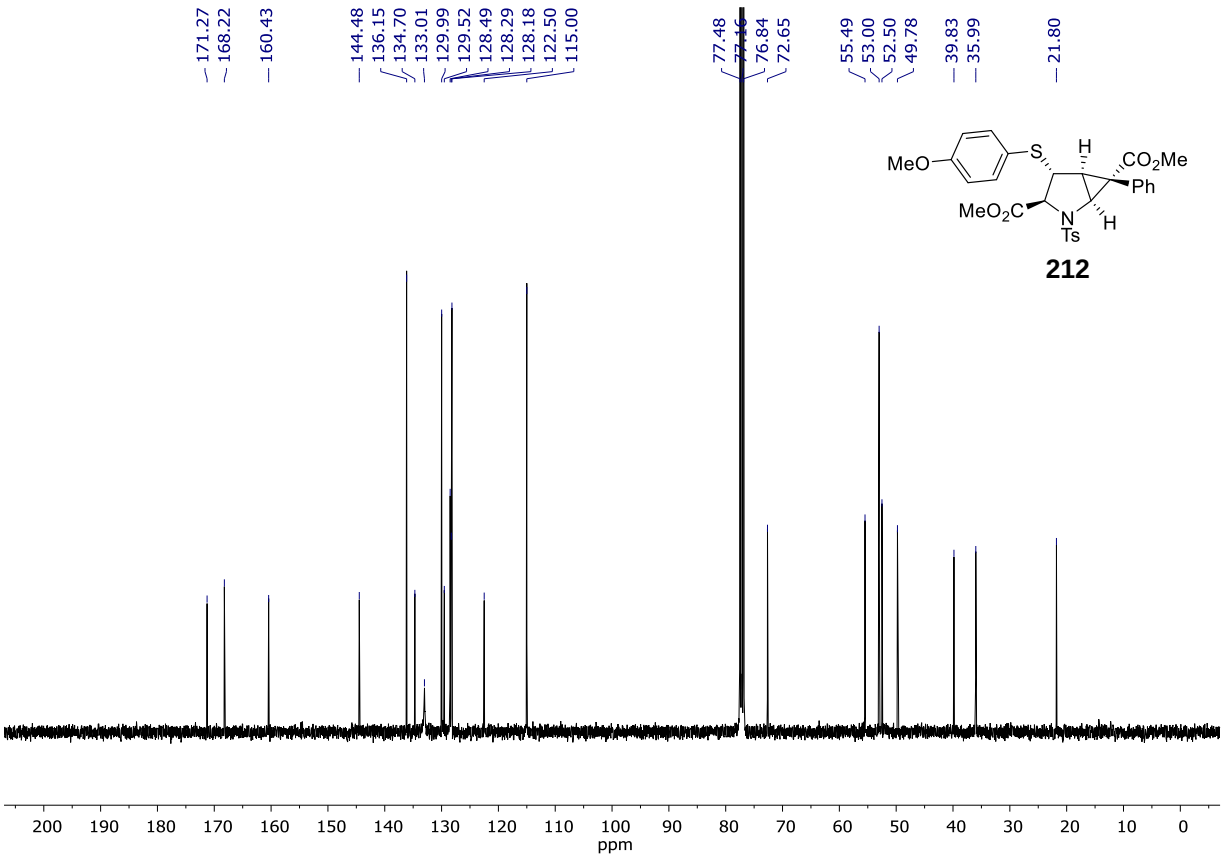
COSY (400 MHz, $CDCl_3$)



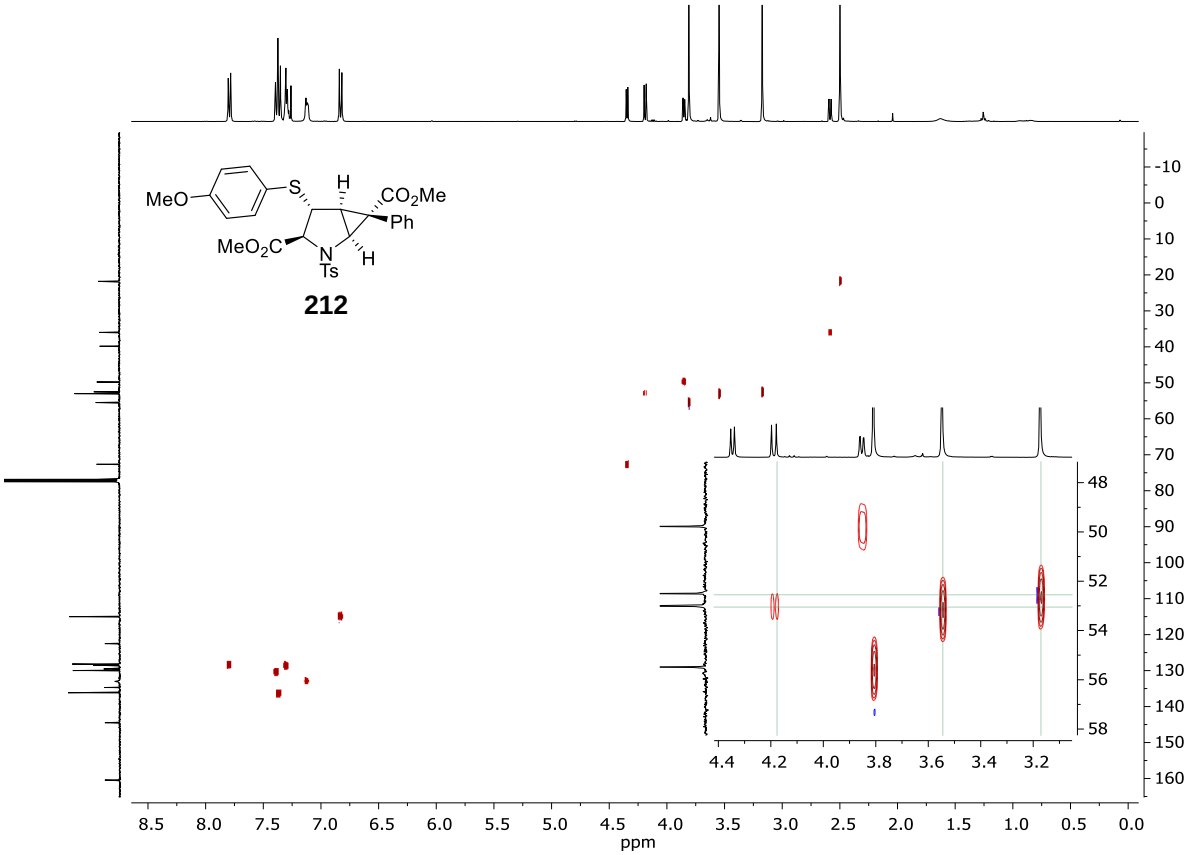
NOESY (400 MHz, $CDCl_3$)



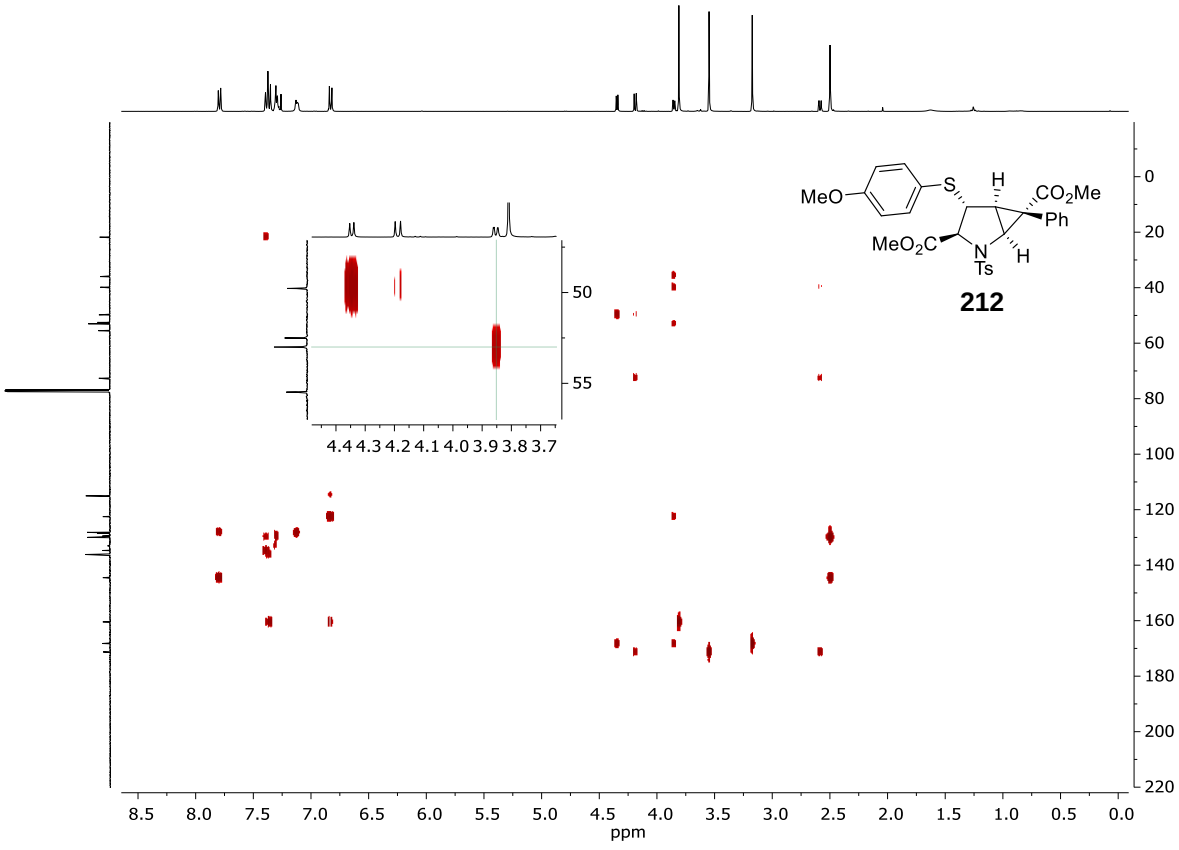
^{1}H NMR (400 MHz, $CDCl_3$)



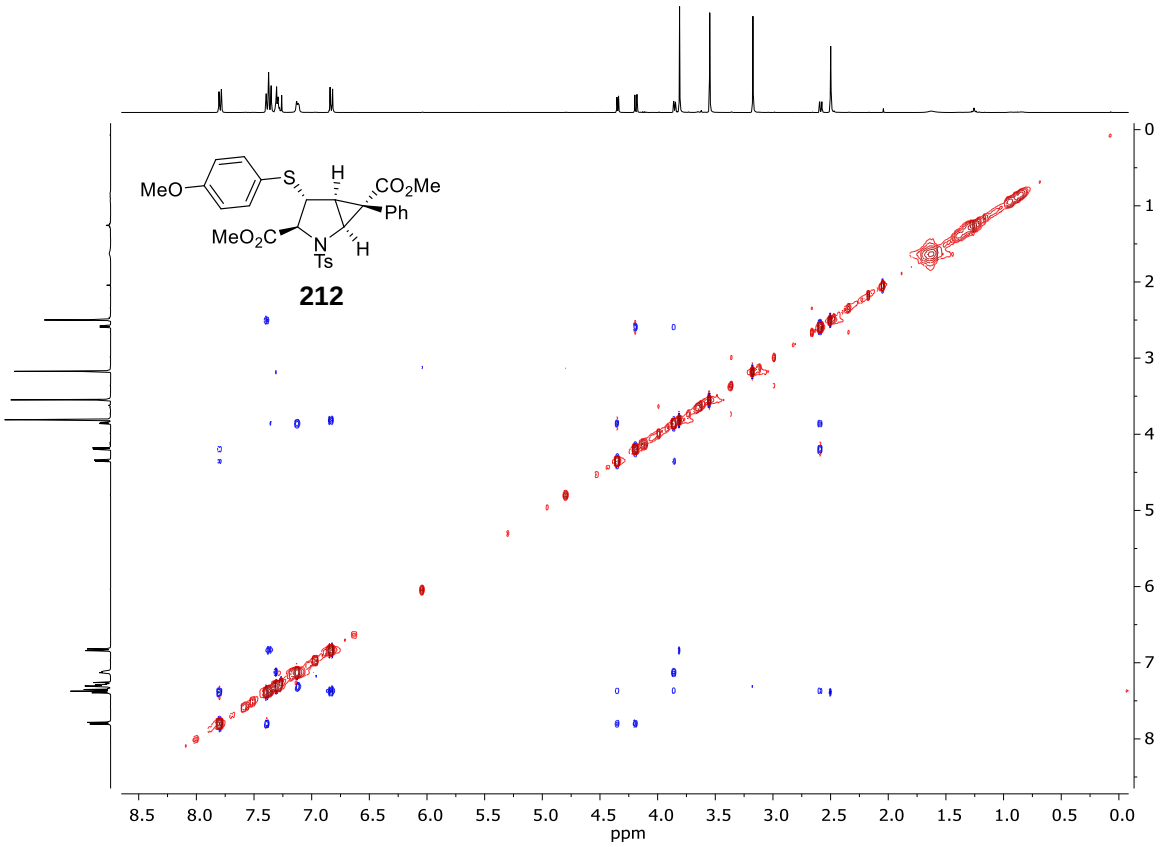
^{13}C NMR (101 MHz, $CDCl_3$)



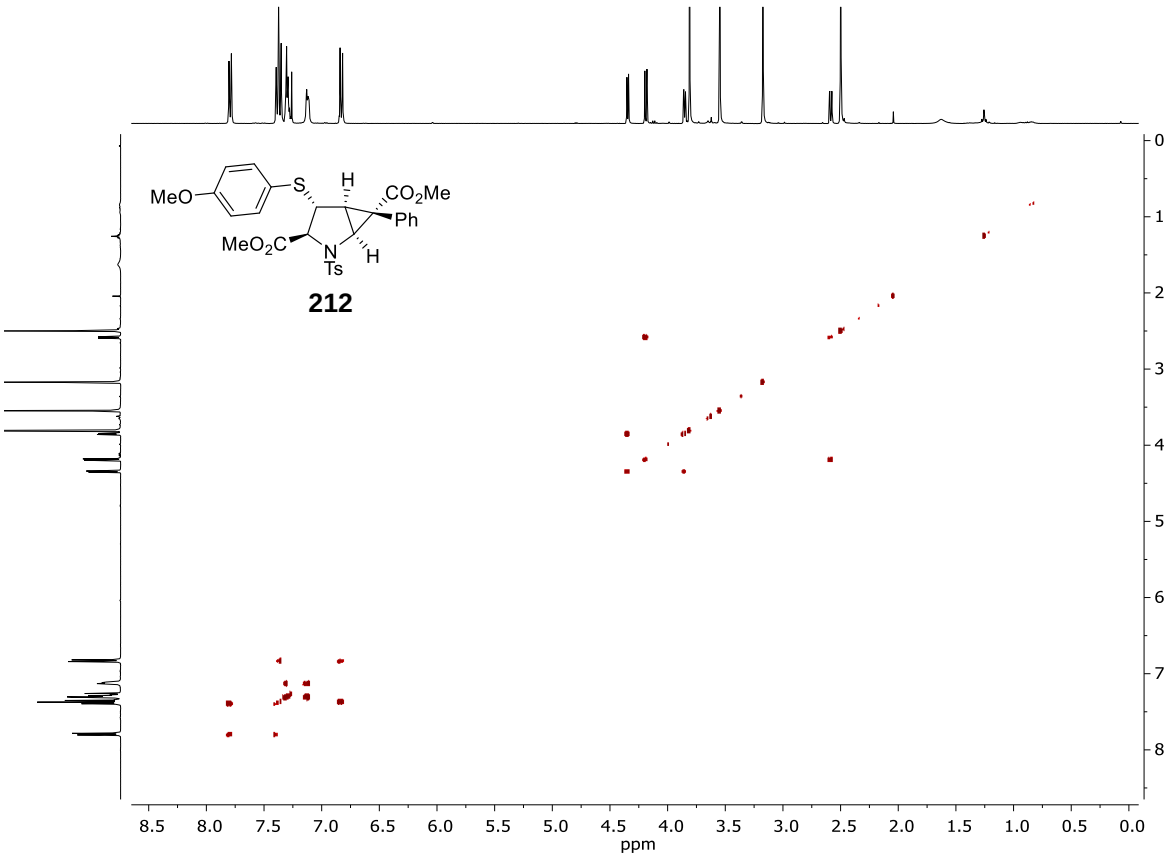
HSQC ((400, 101) MHz, $CDCl_3$)



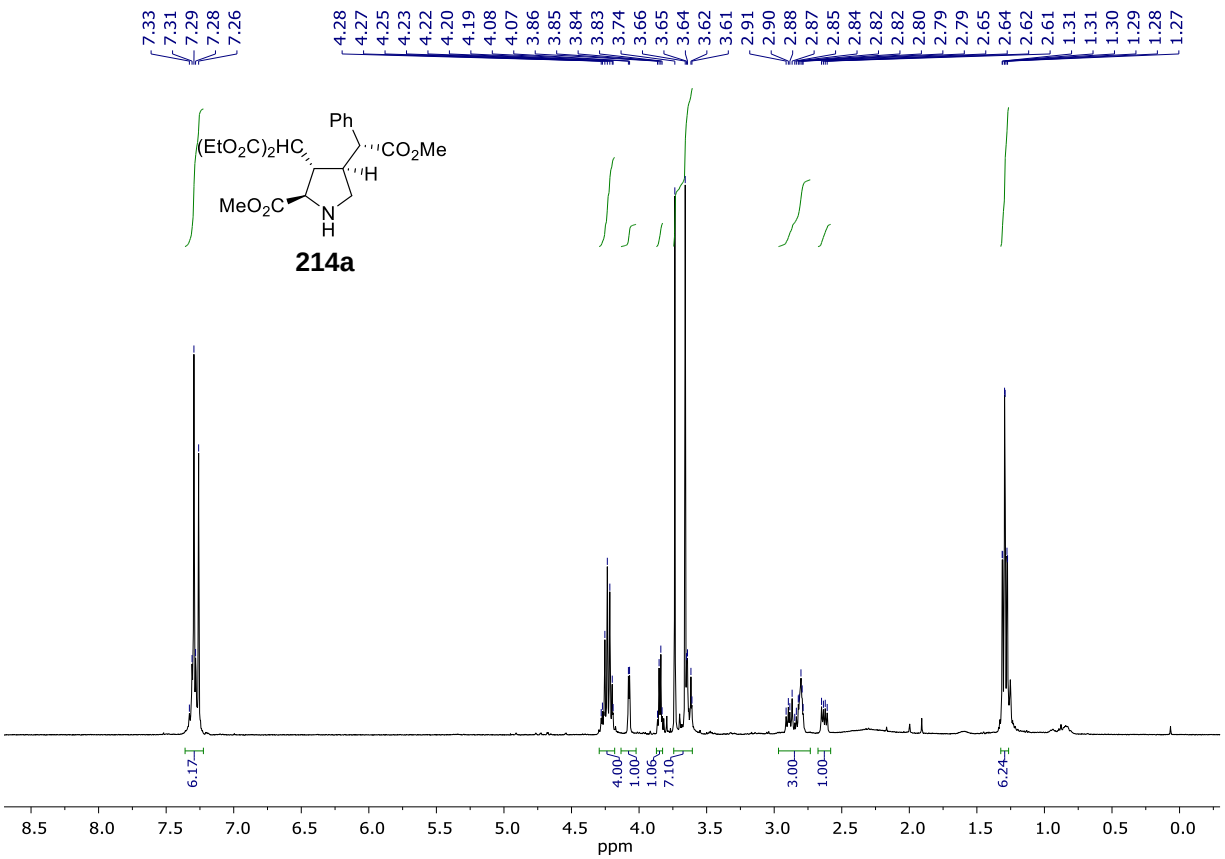
HMBC ((400, 101) MHz, $CDCl_3$)



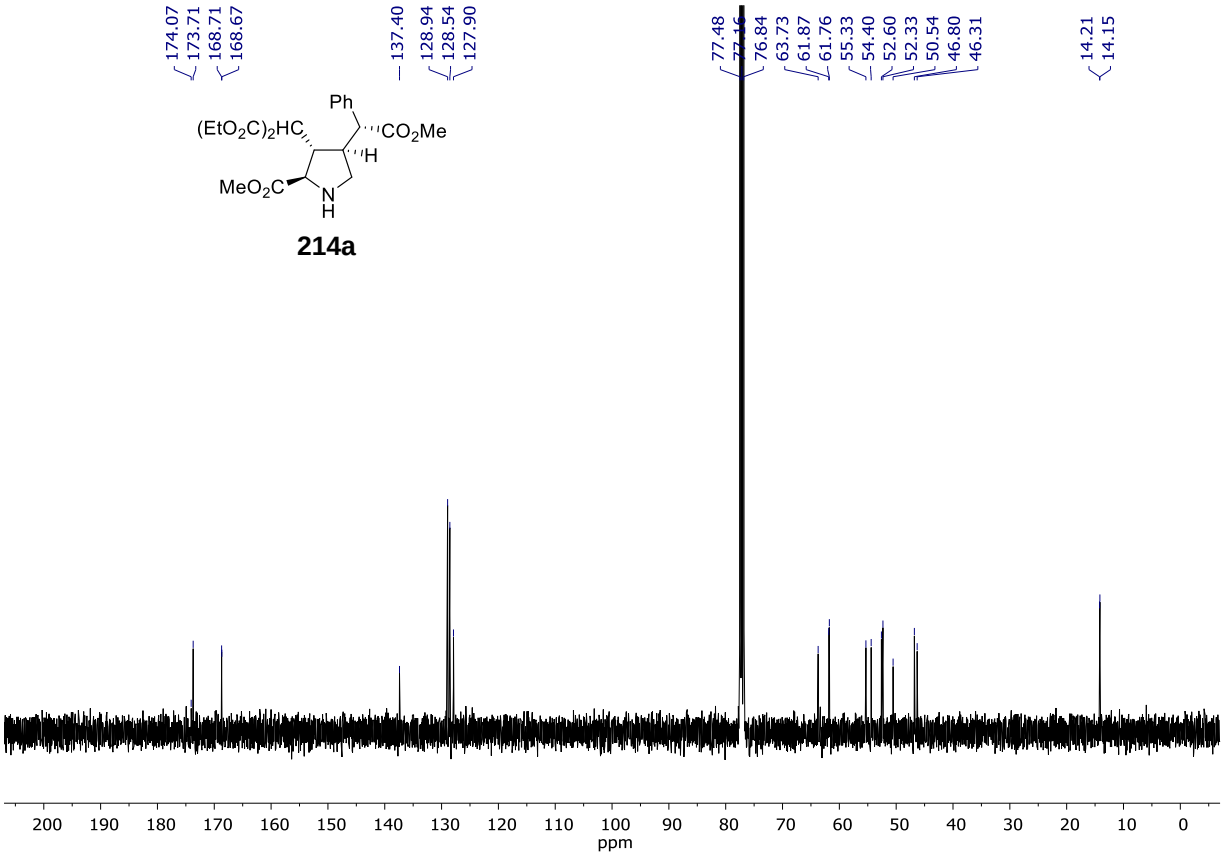
NOESY (400 MHz, $CDCl_3$)



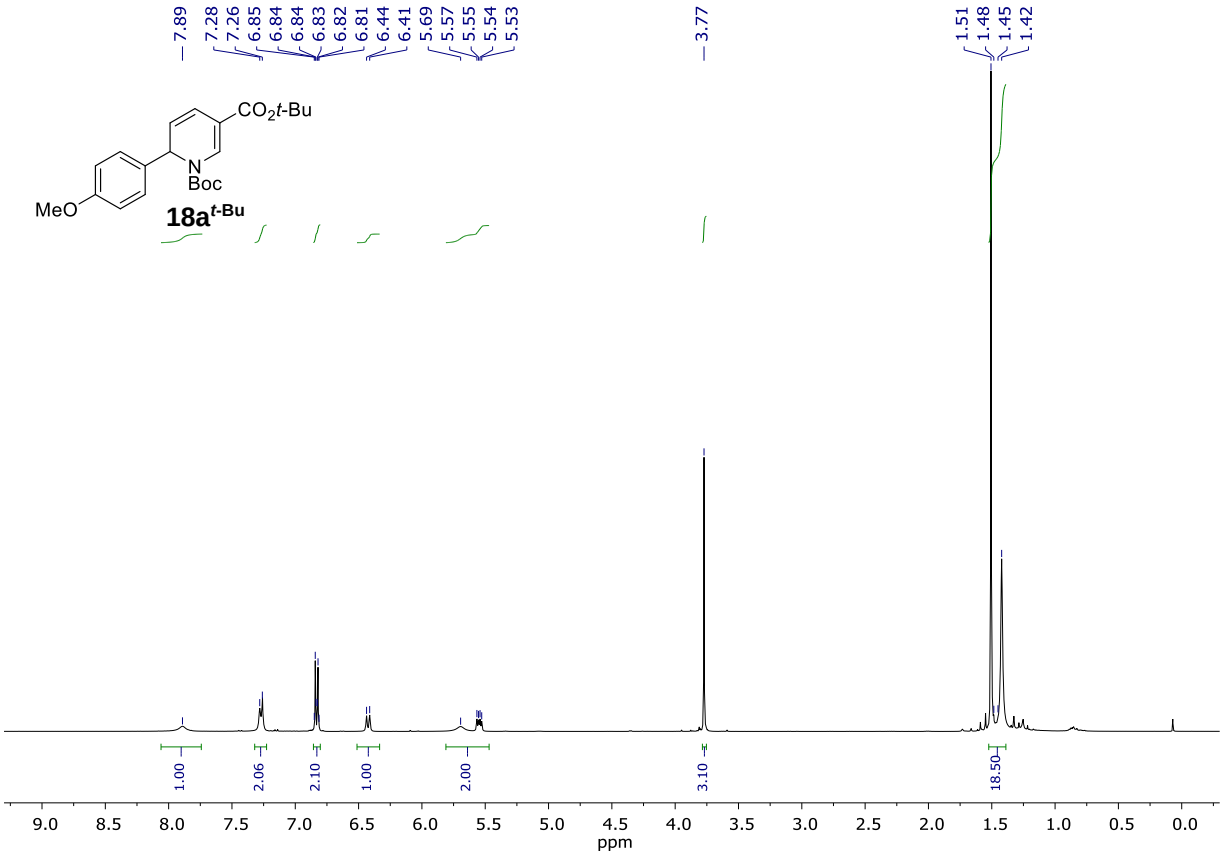
COSY (400 MHz, $CDCl_3$)



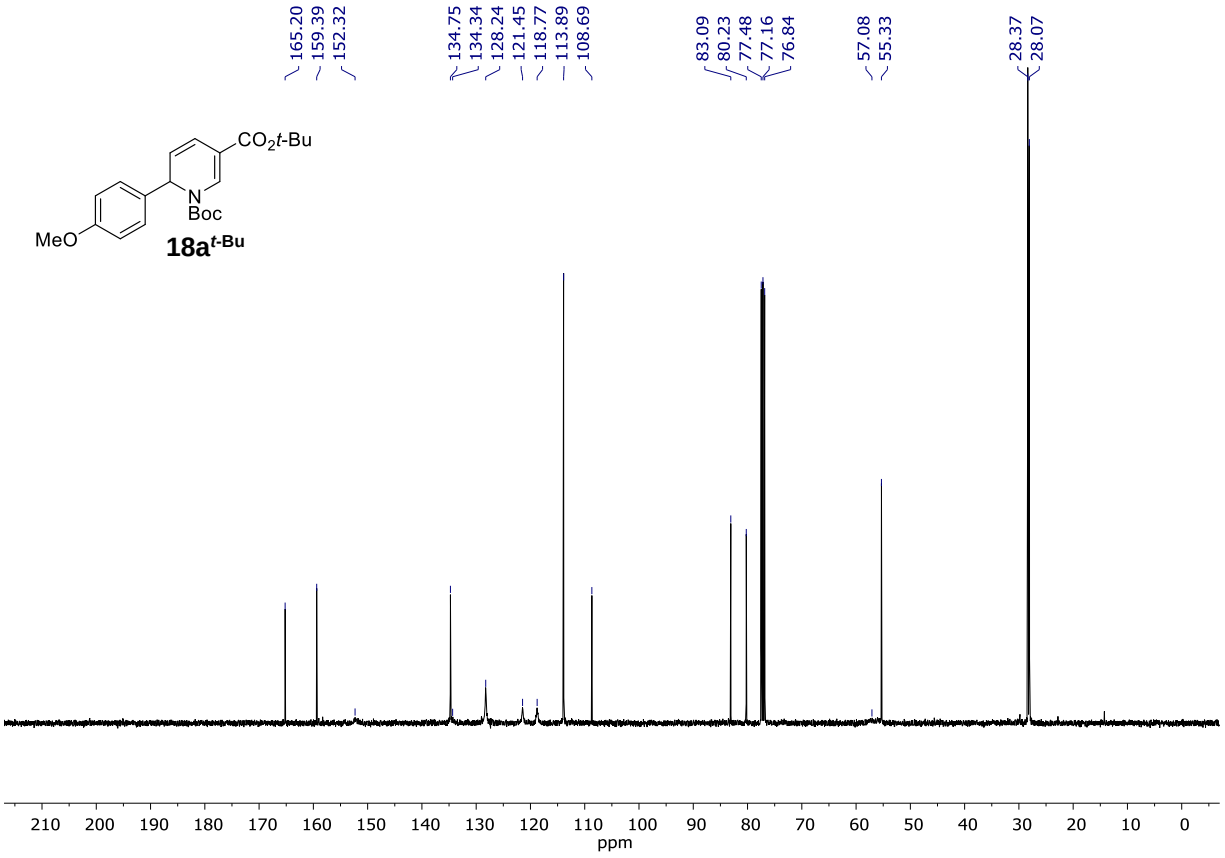
^{1}H NMR (400 MHz, $CDCl_3$)



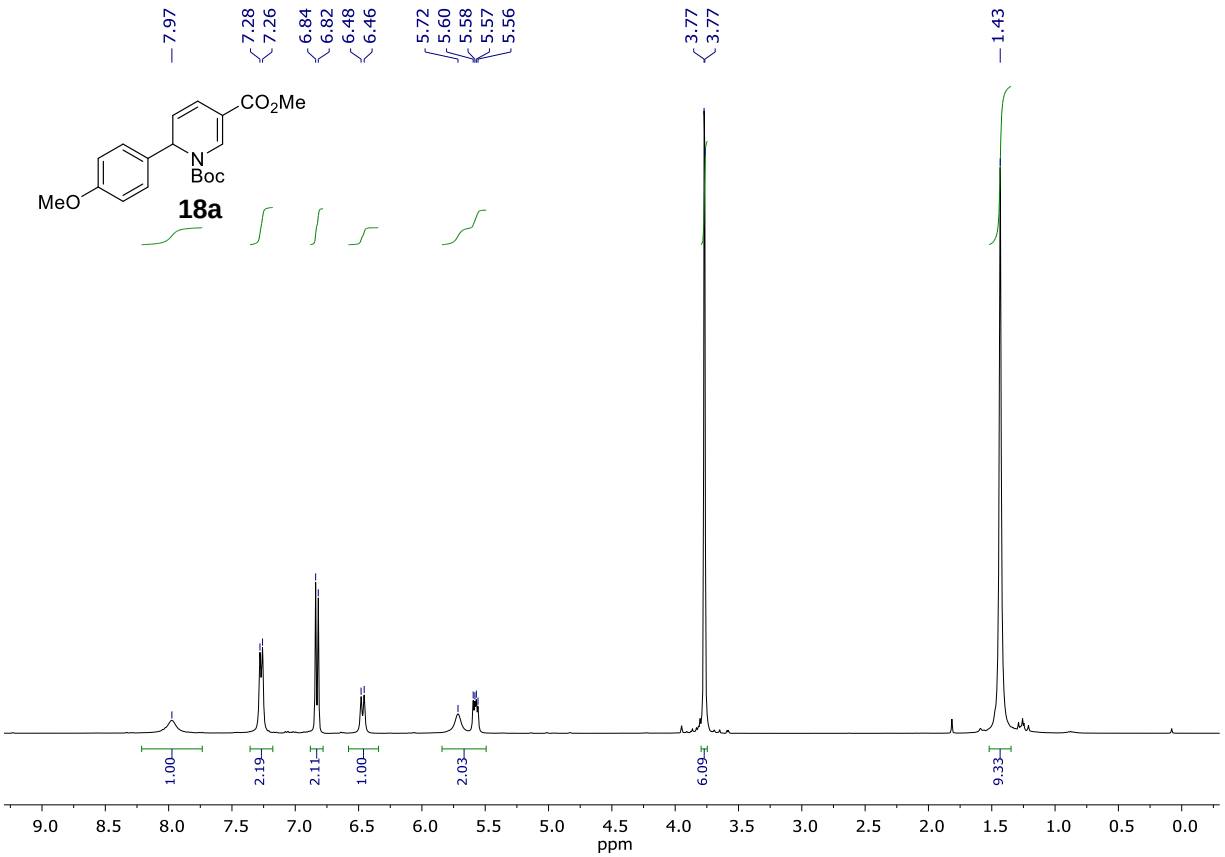
^{13}C NMR (101 MHz, $CDCl_3$)



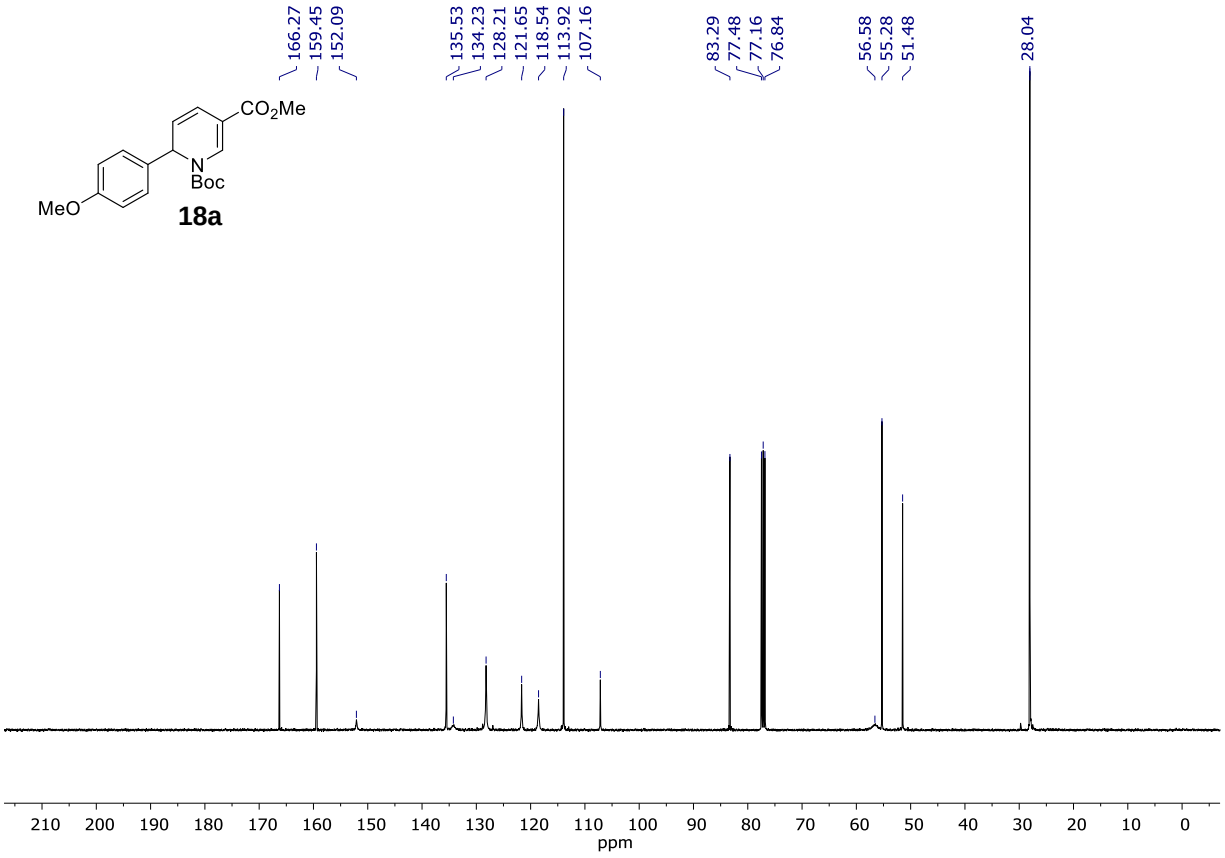
^{1}H NMR (400 MHz, $CDCl_3$)



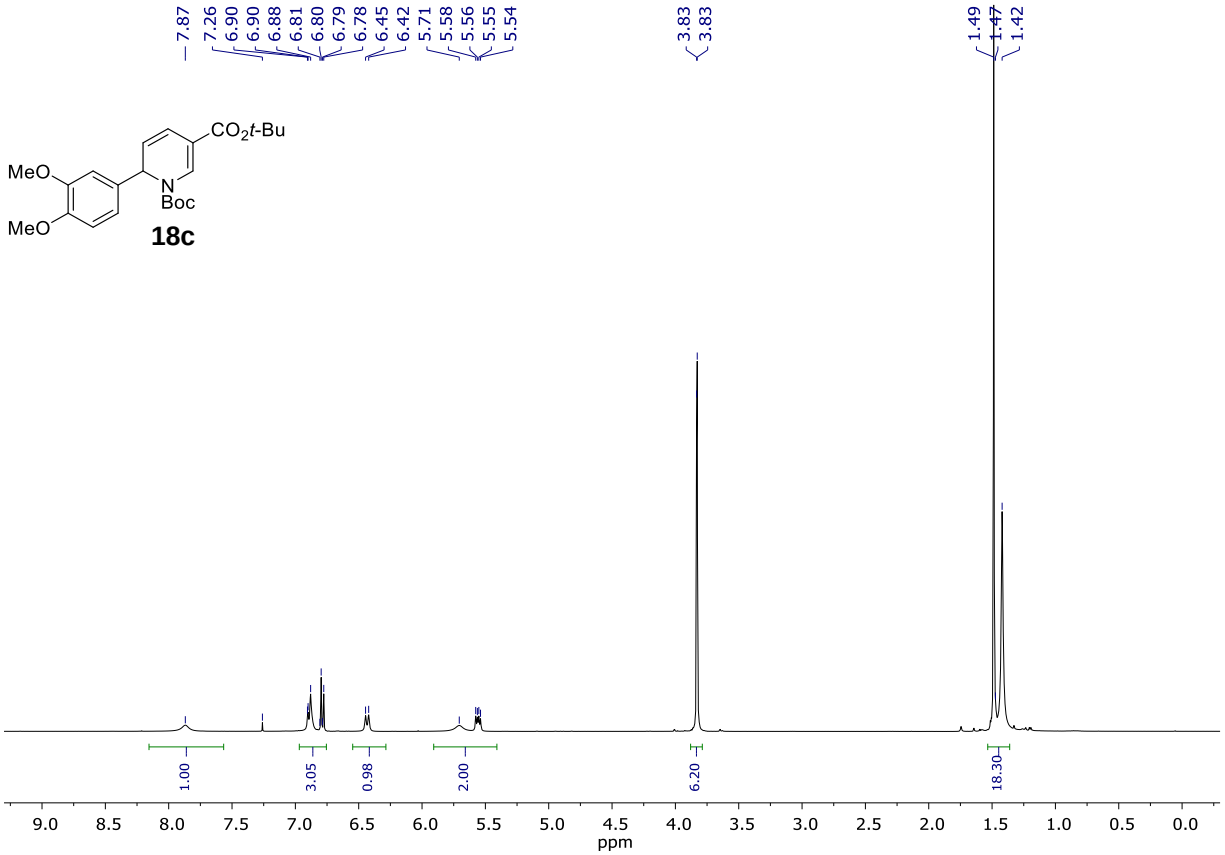
^{13}C NMR (101 MHz, $CDCl_3$)



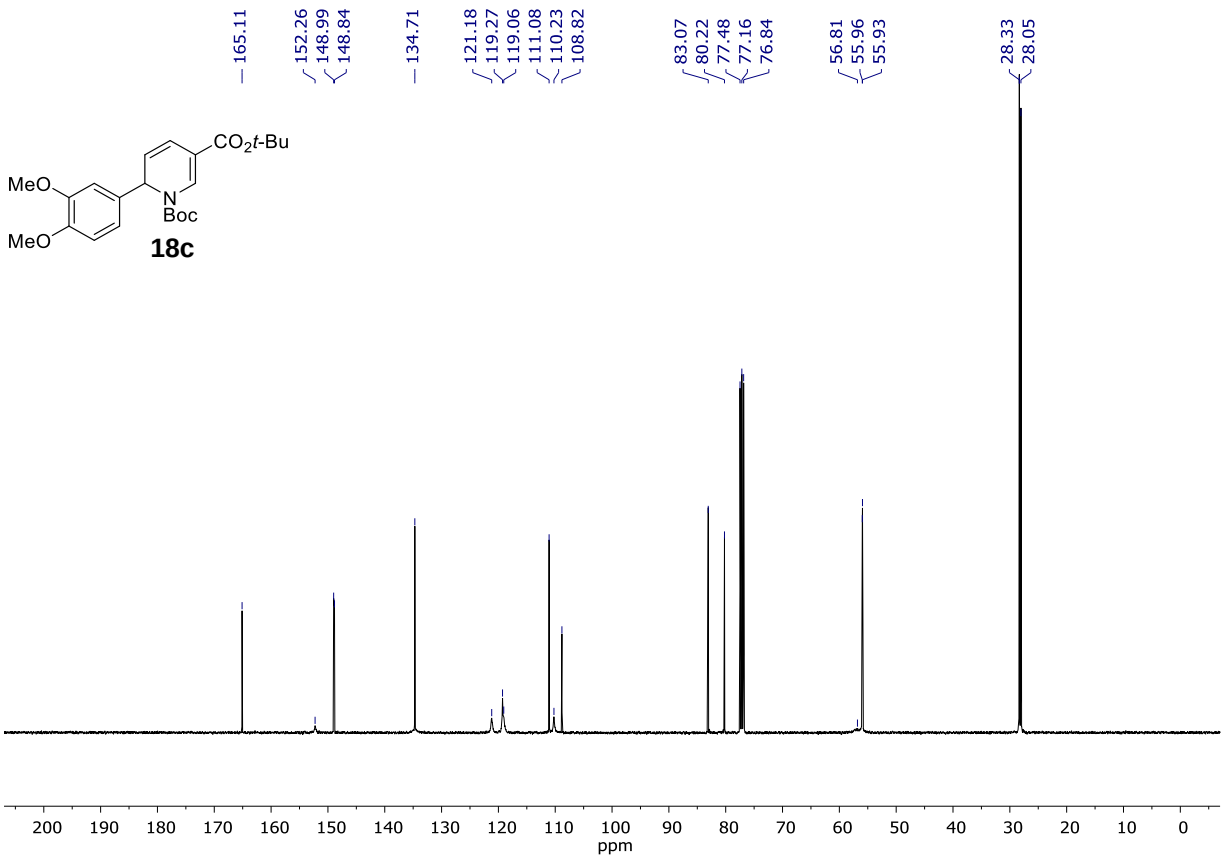
^{1}H NMR (400 MHz, $CDCl_3$)



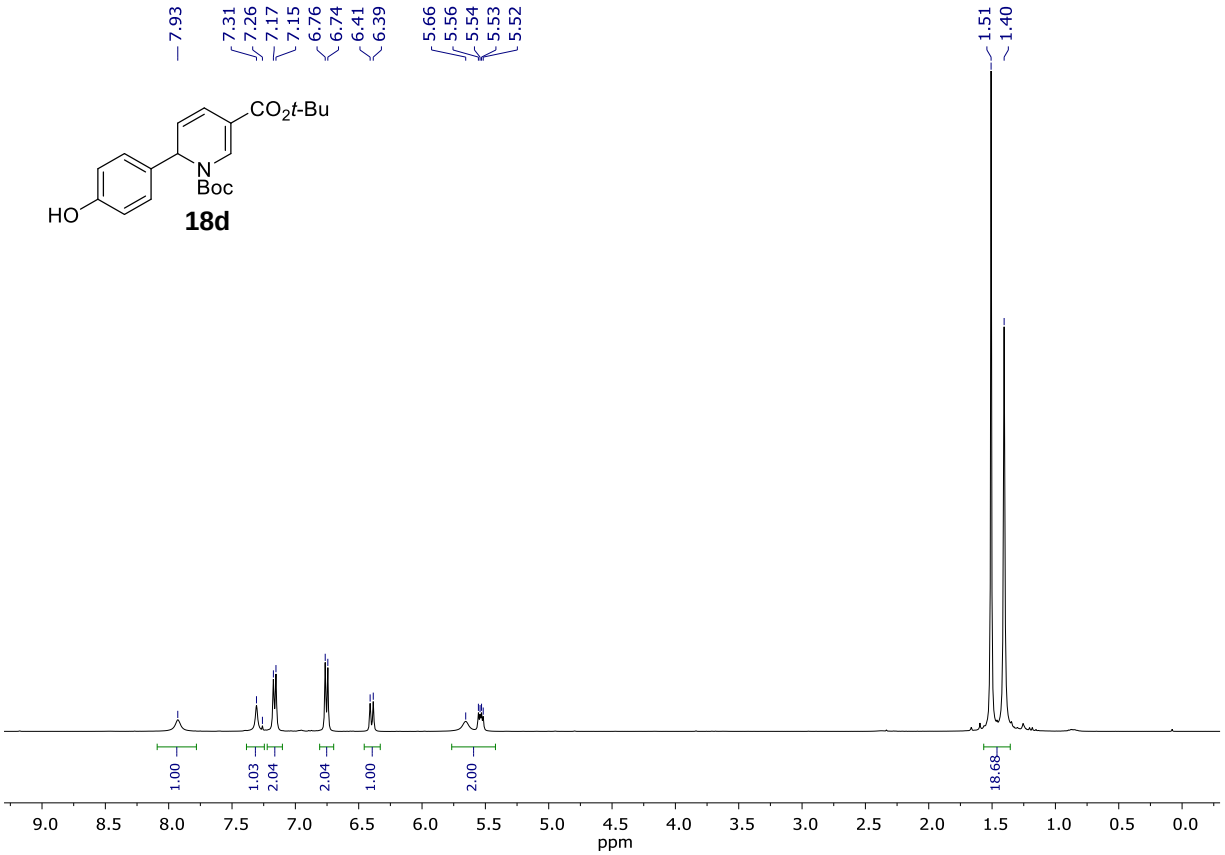
^{13}C NMR (101 MHz, $CDCl_3$)



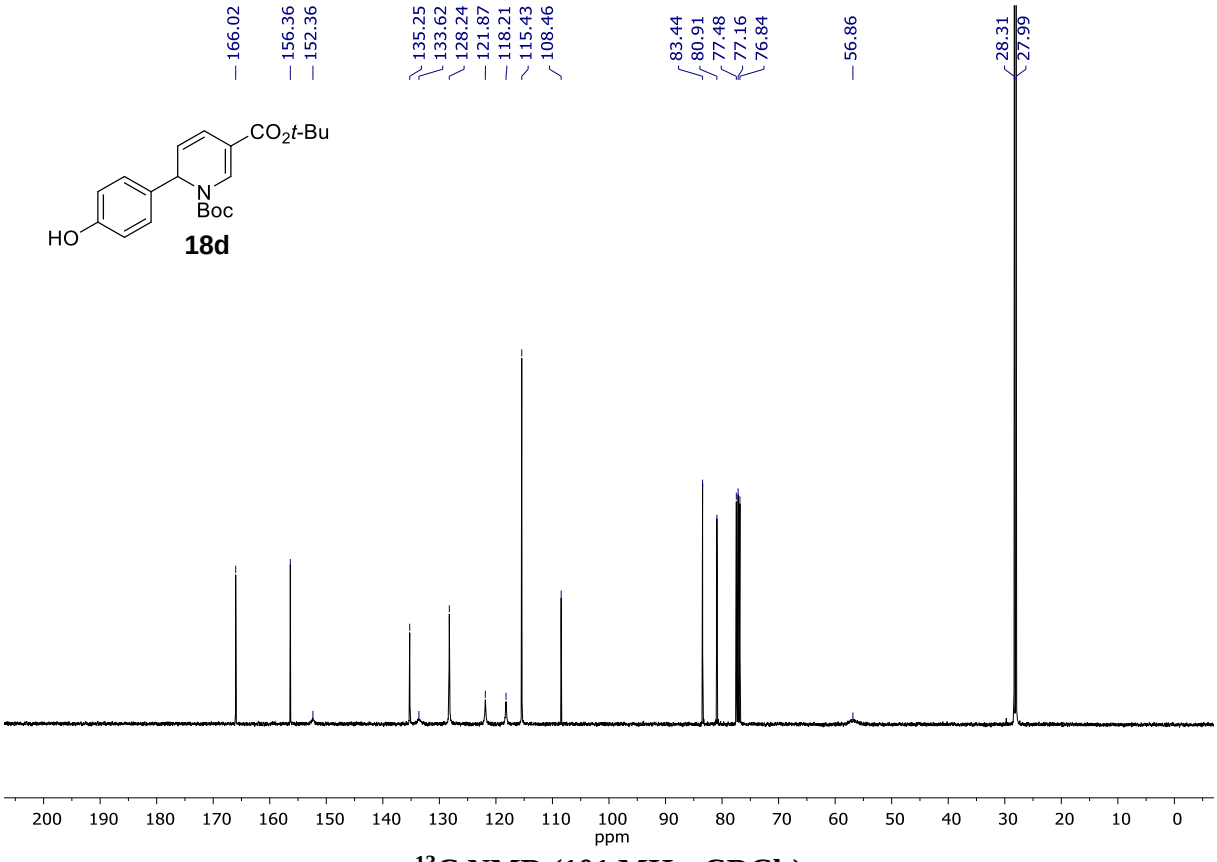
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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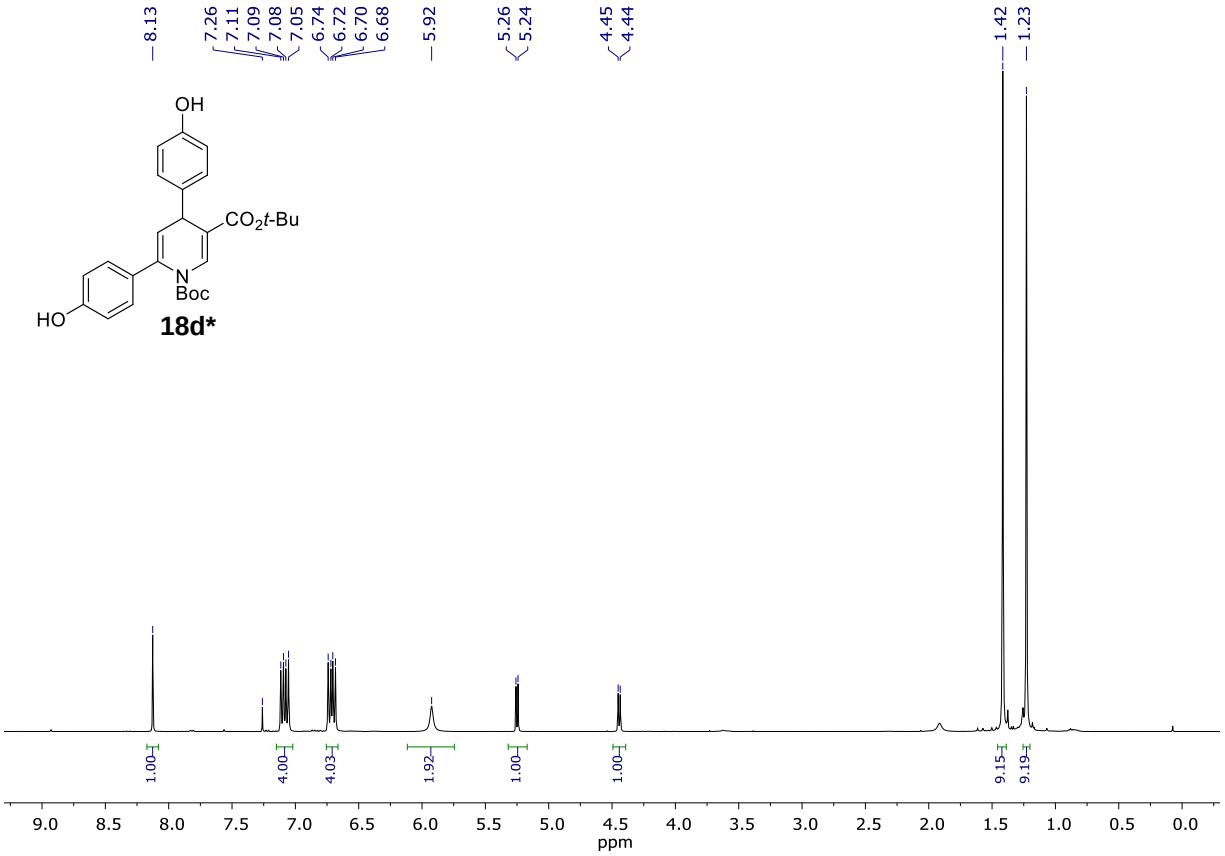

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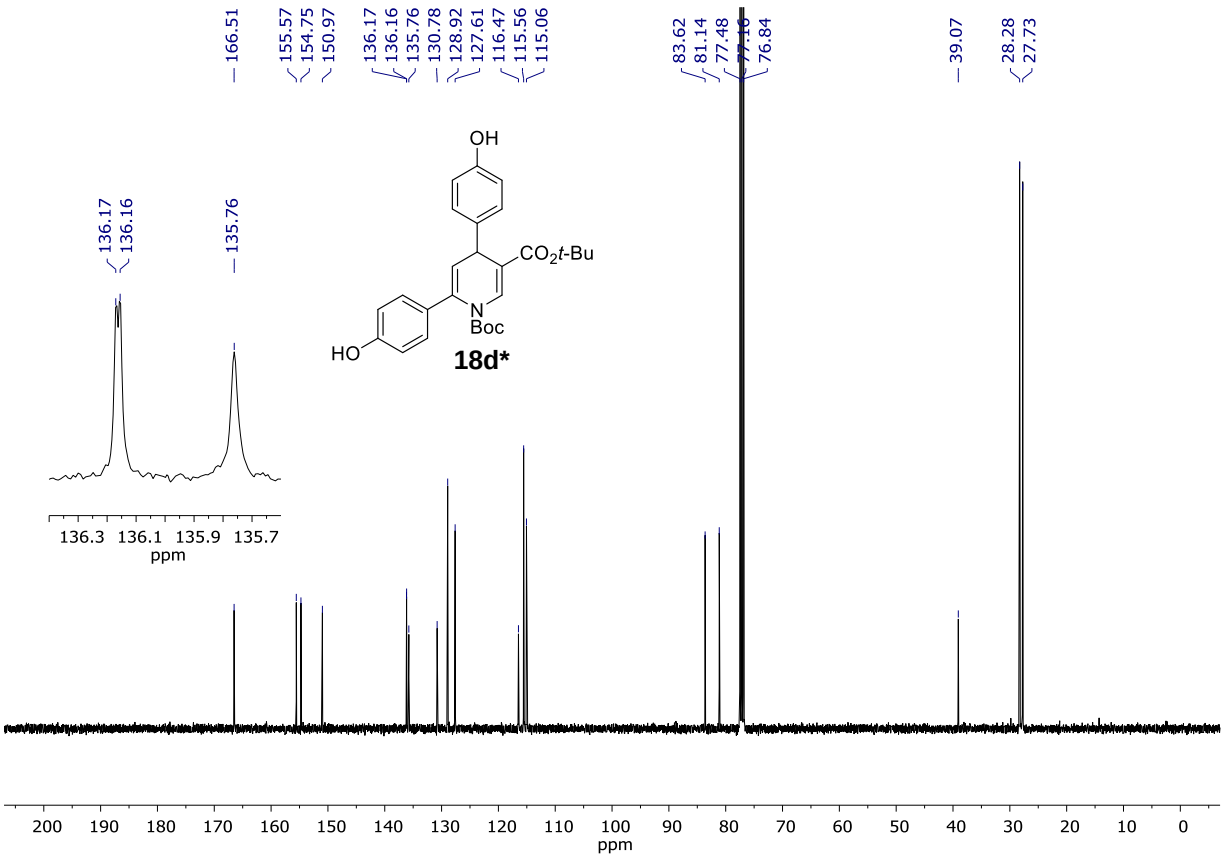
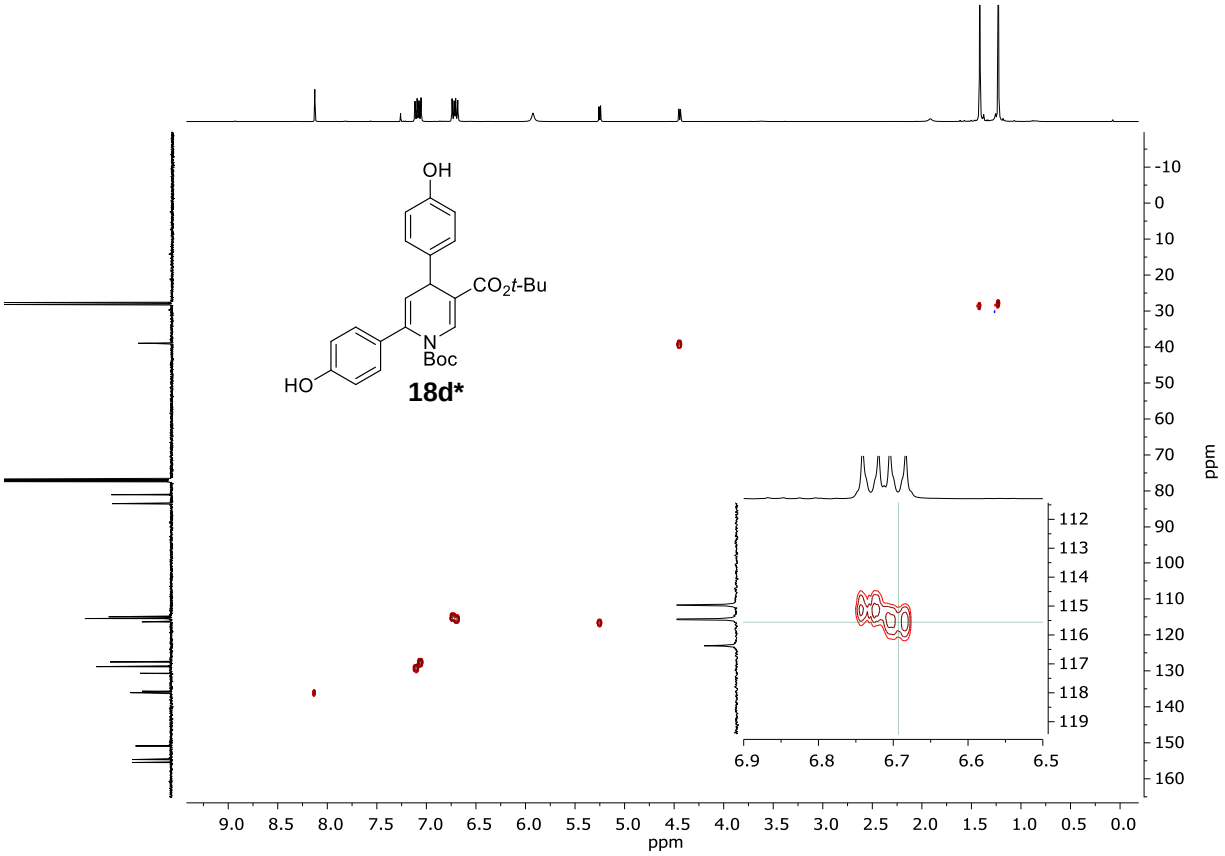
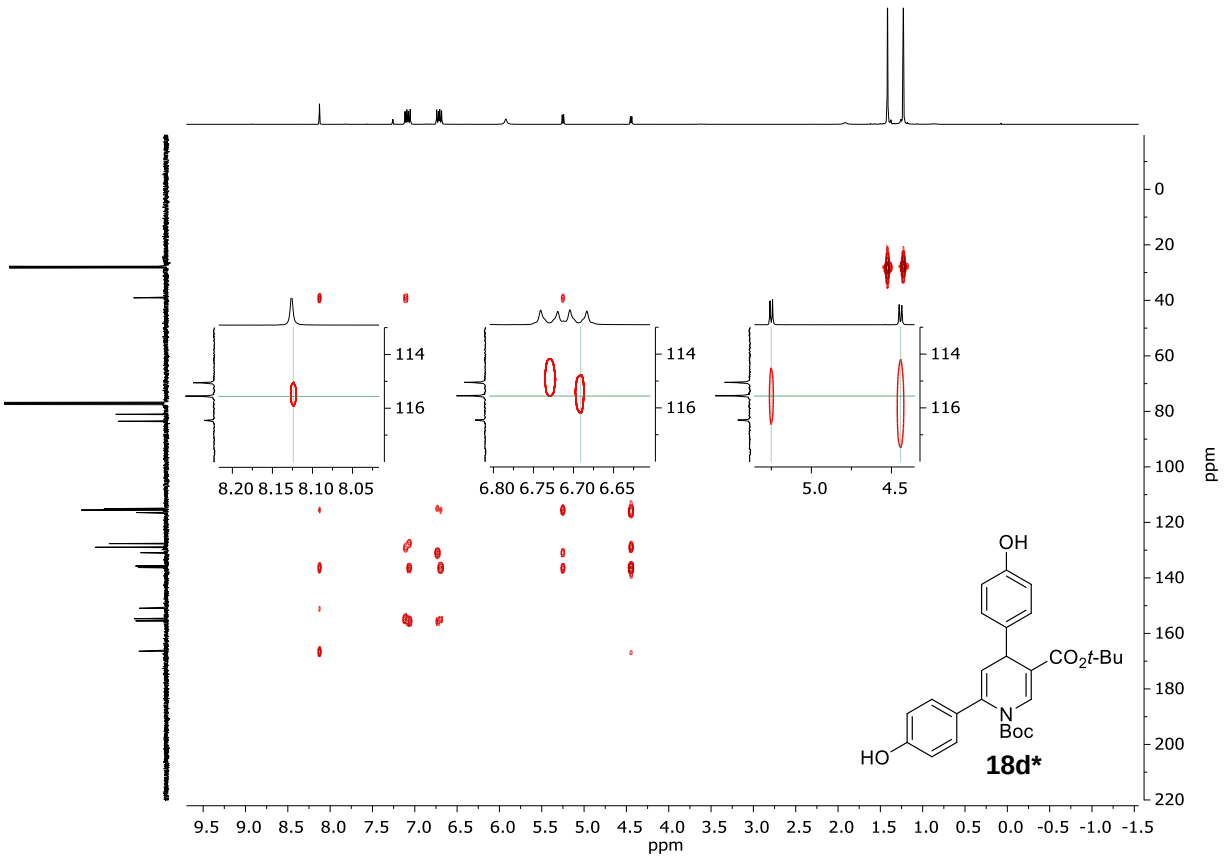


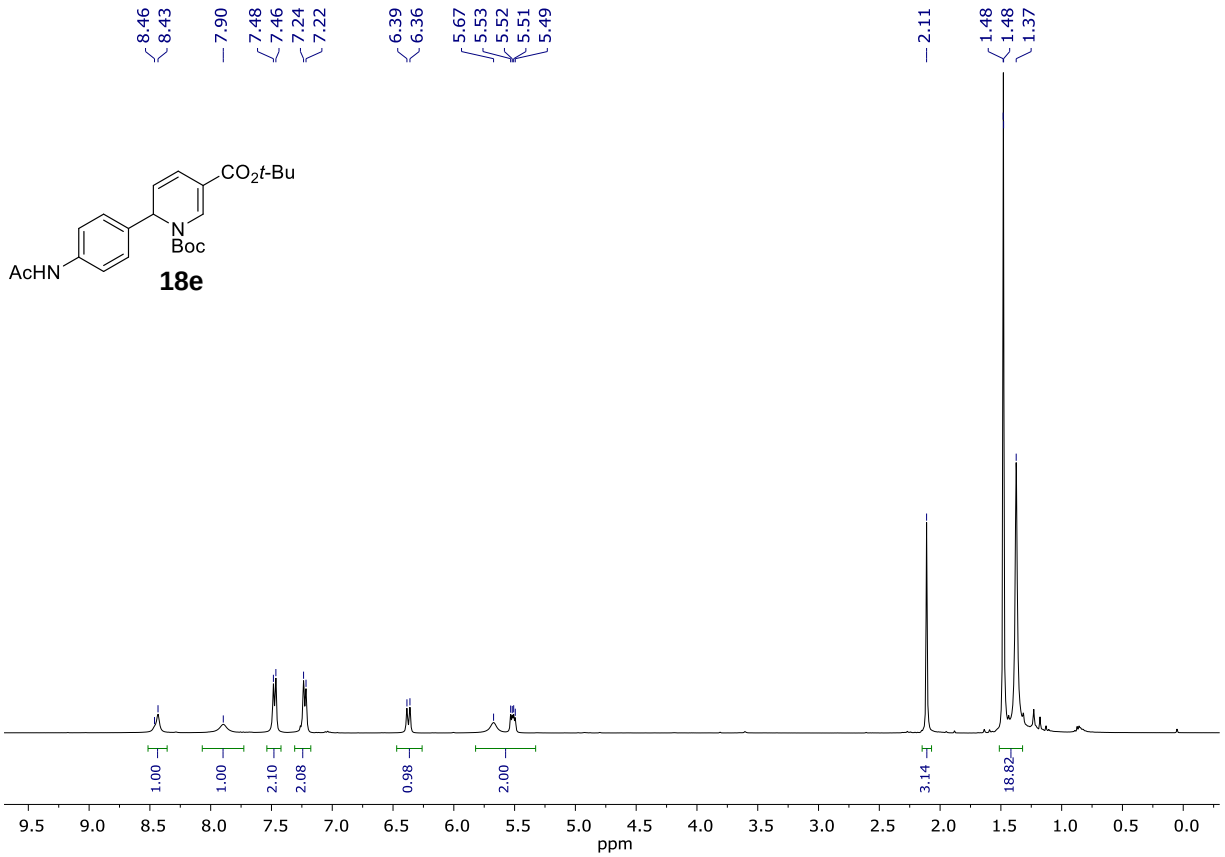
^{13}C NMR (101 MHz, $CDCl_3$)



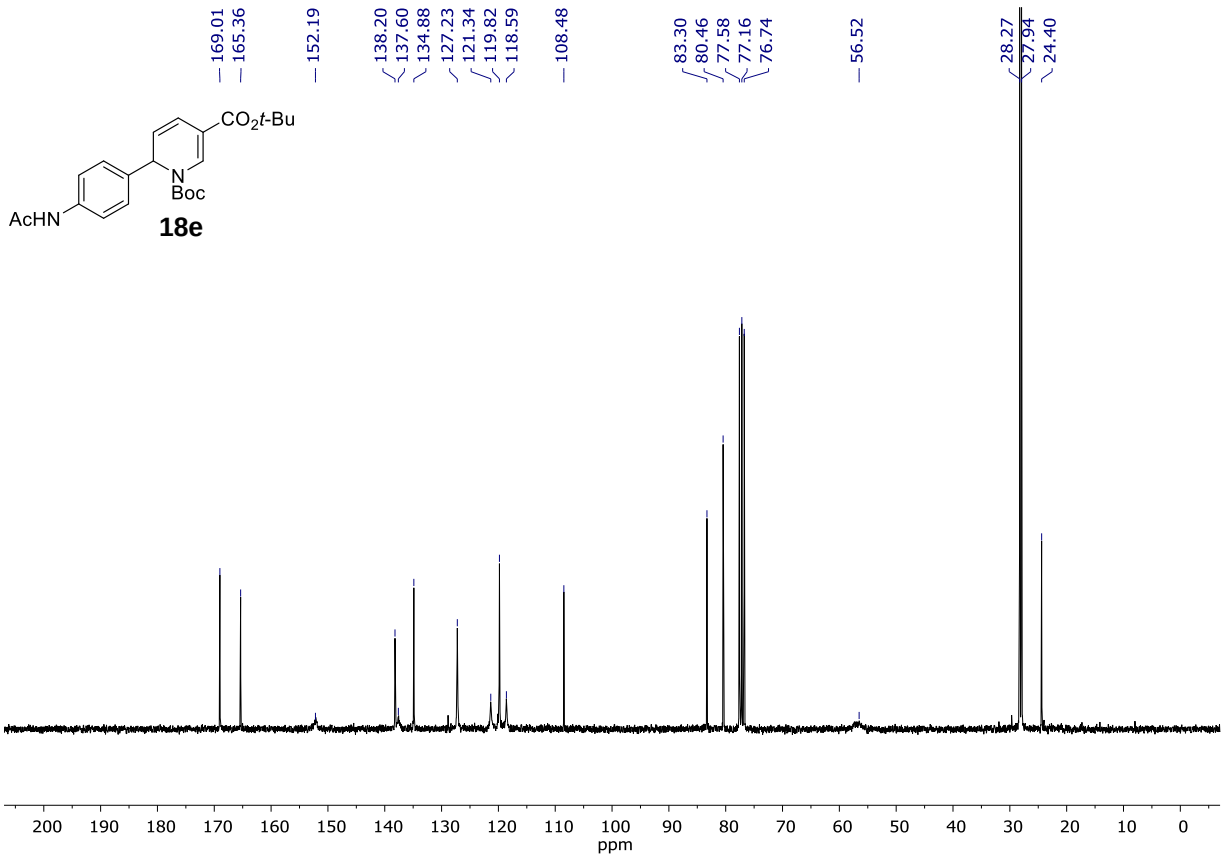
HSQC ((400, 101) MHz, $CDCl_3$)



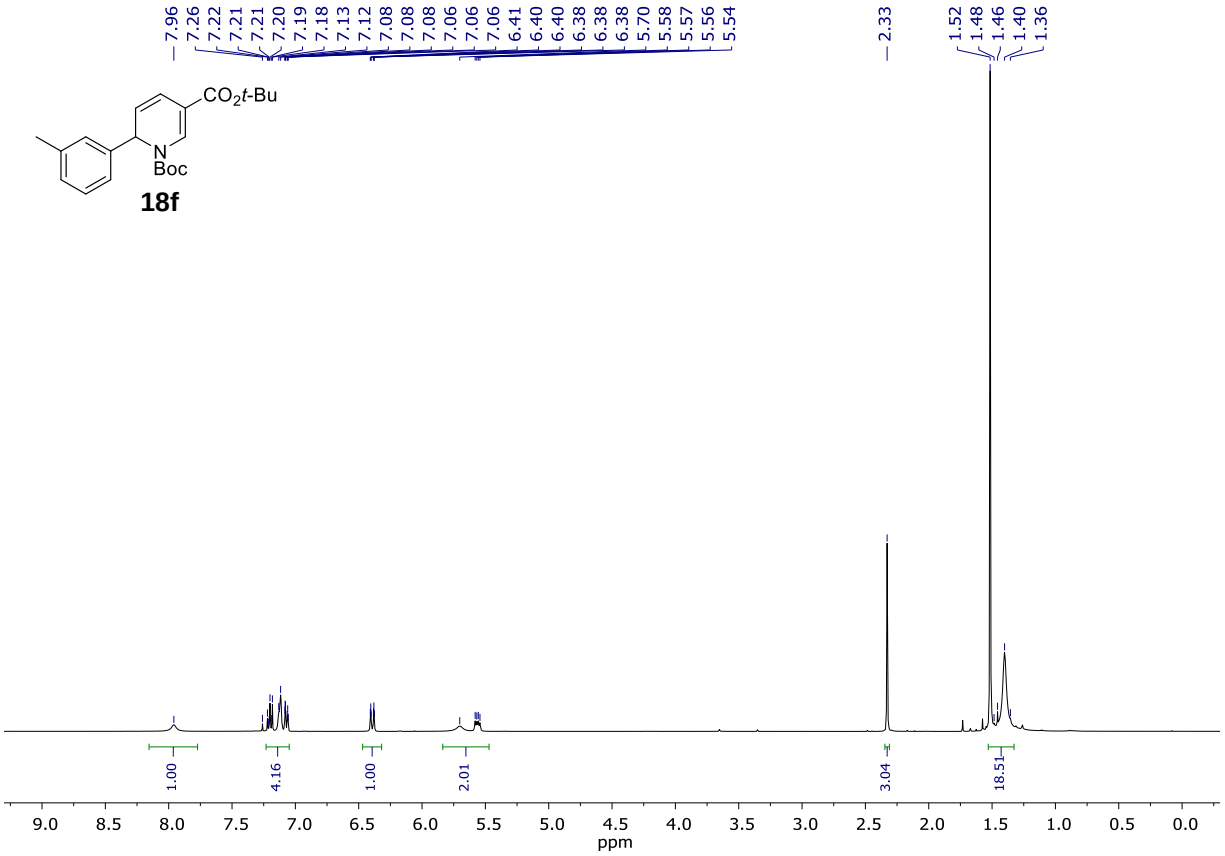
HMBC ((400, 101) MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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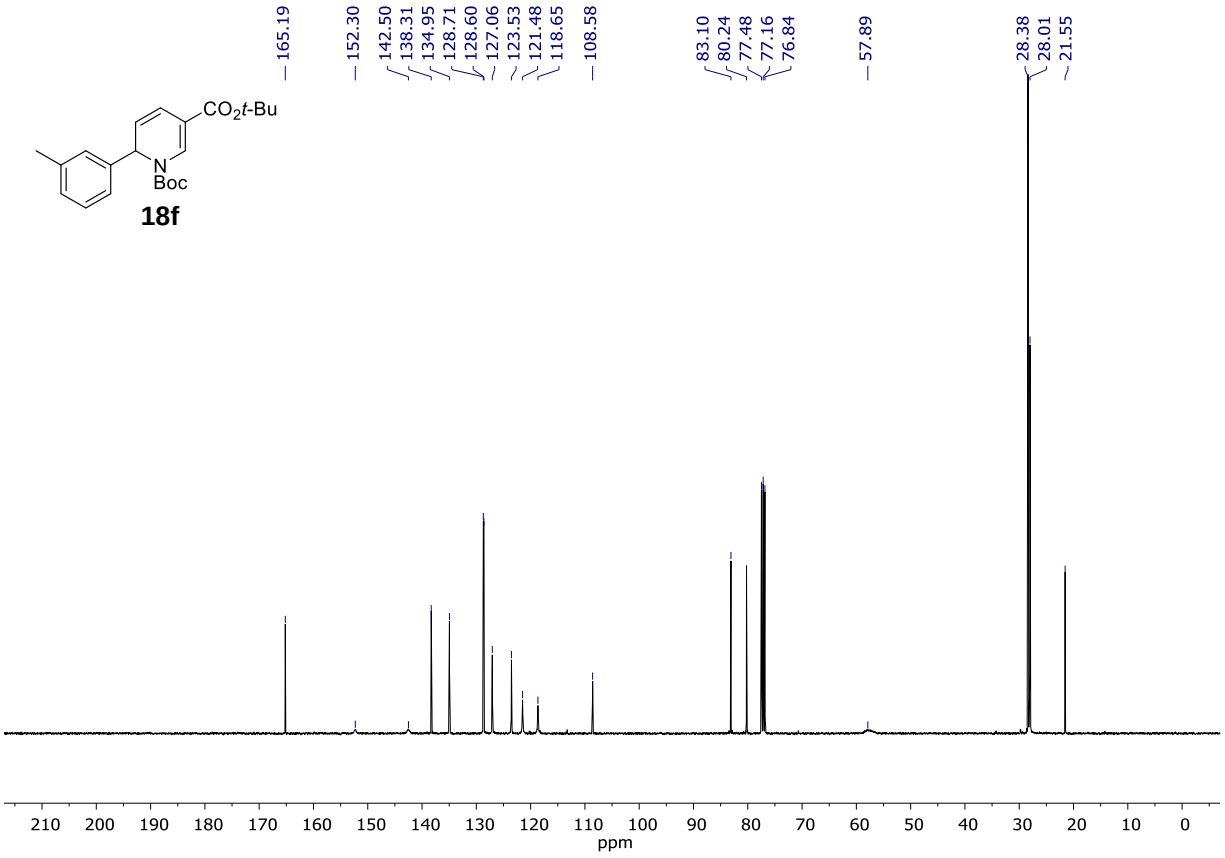
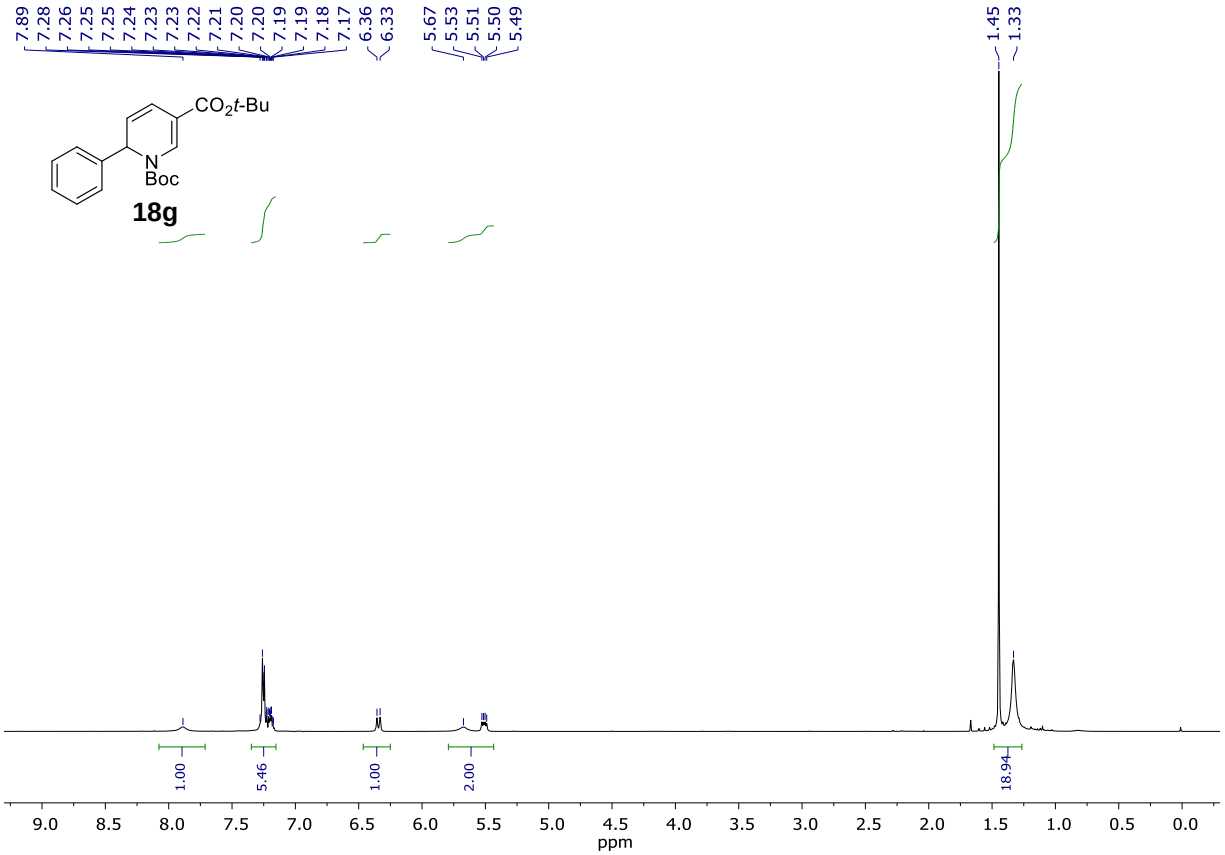


^{13}C NMR (101 MHz, $CDCl_3$)



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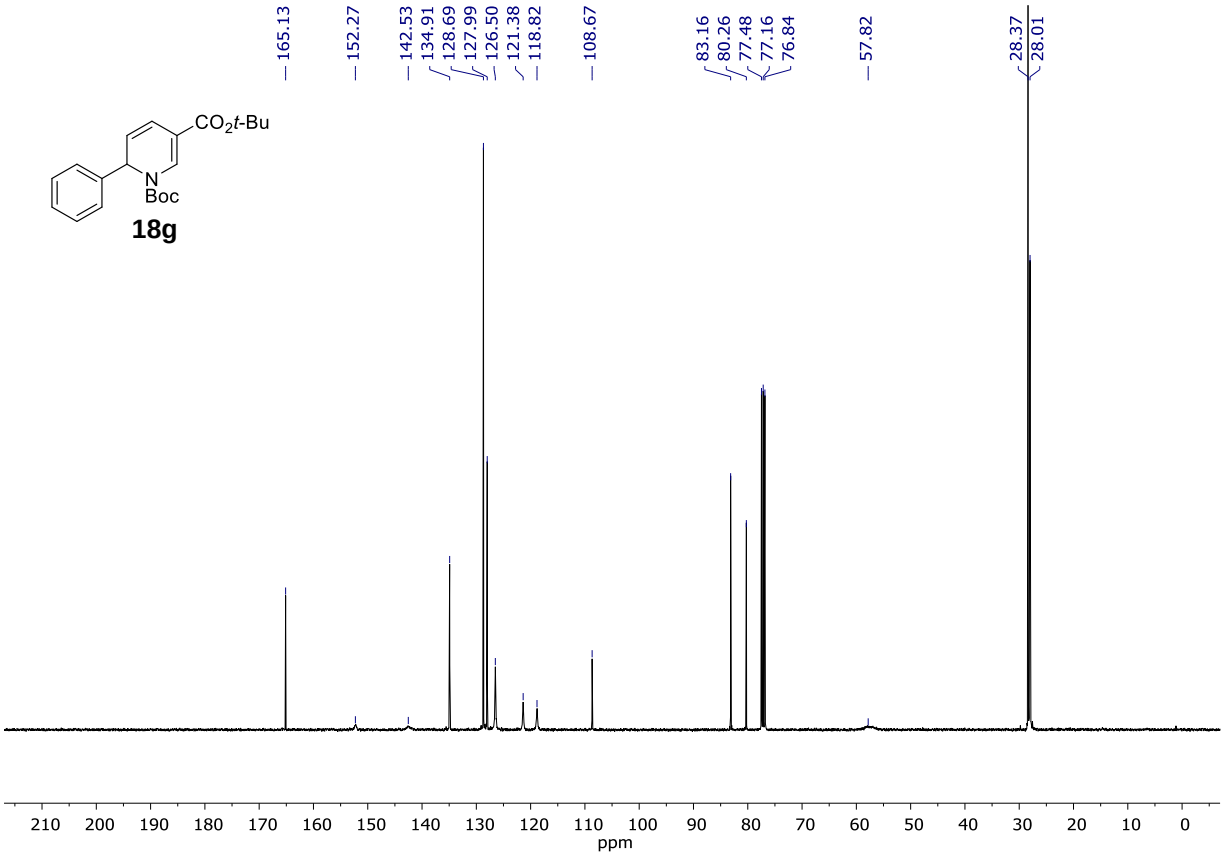
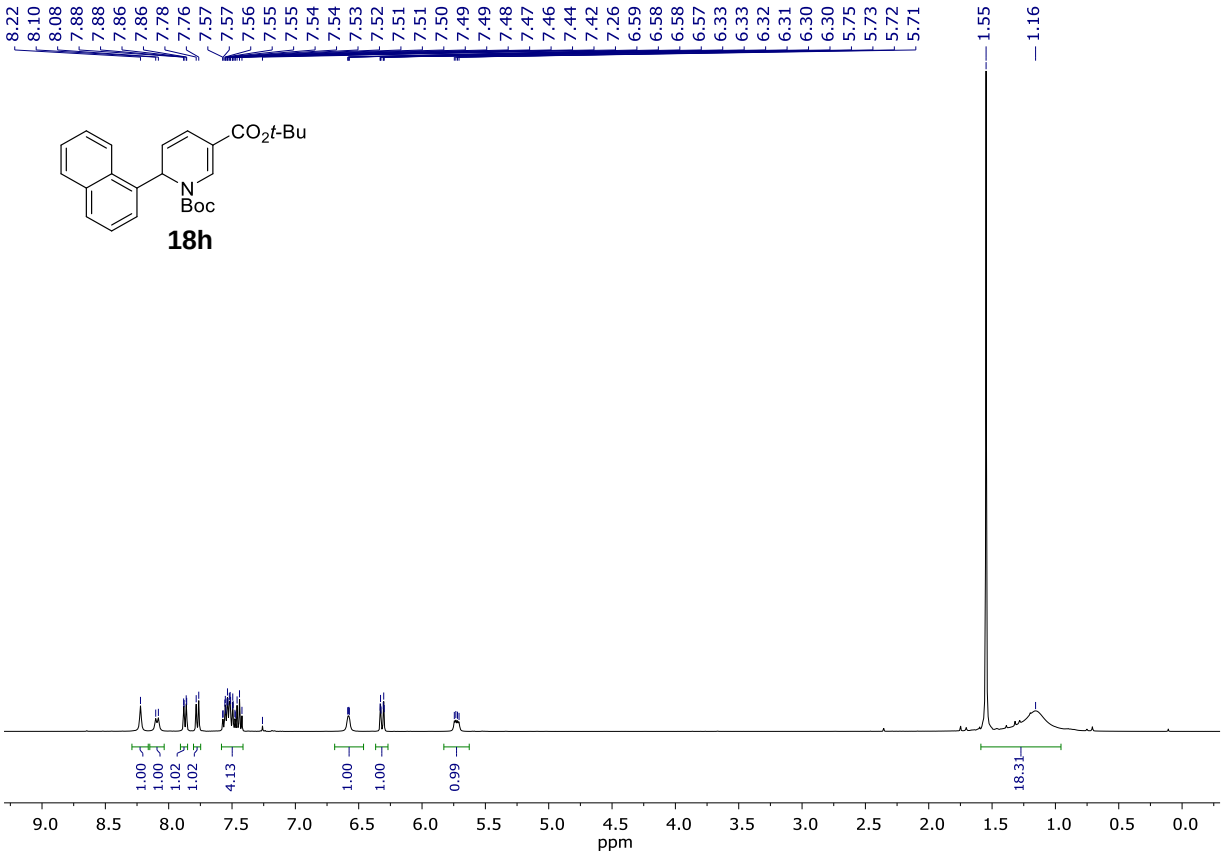
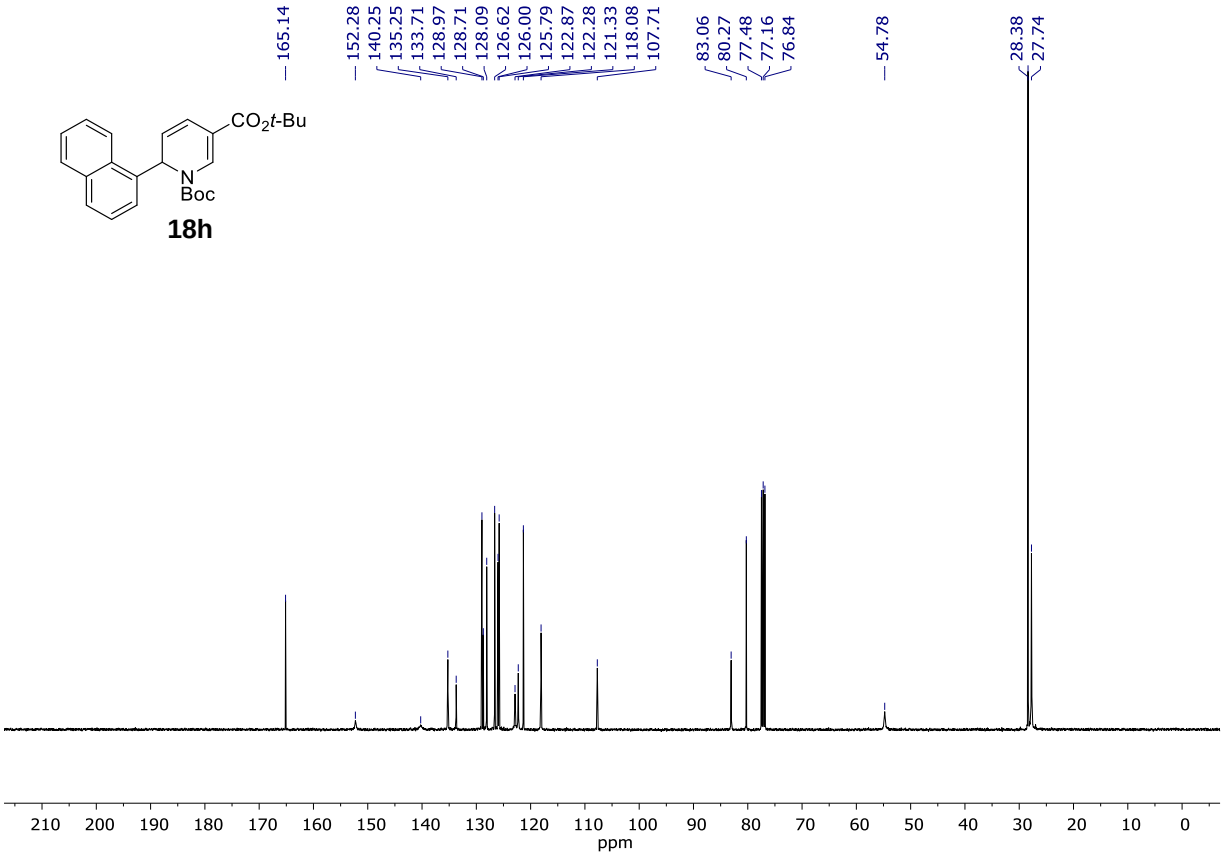


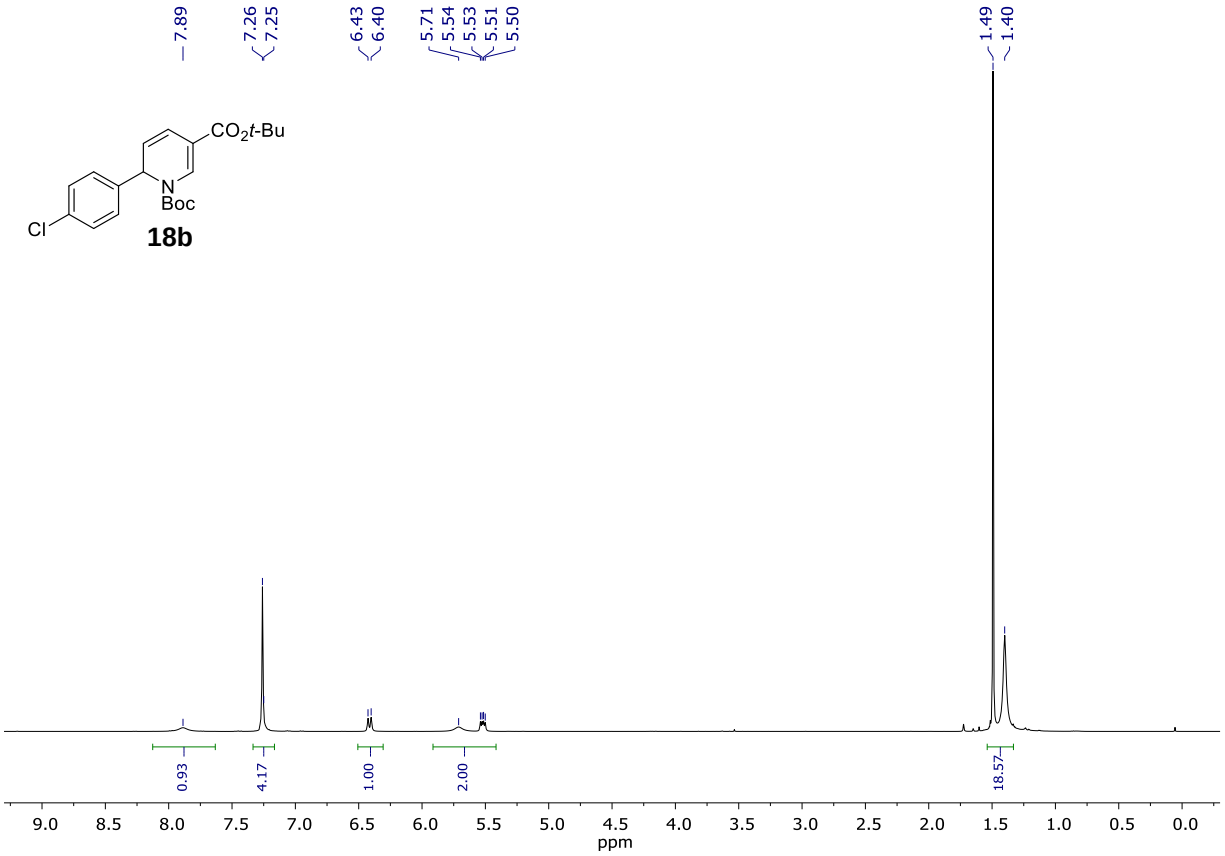
^{13}C NMR (101 MHz, $CDCl_3$)



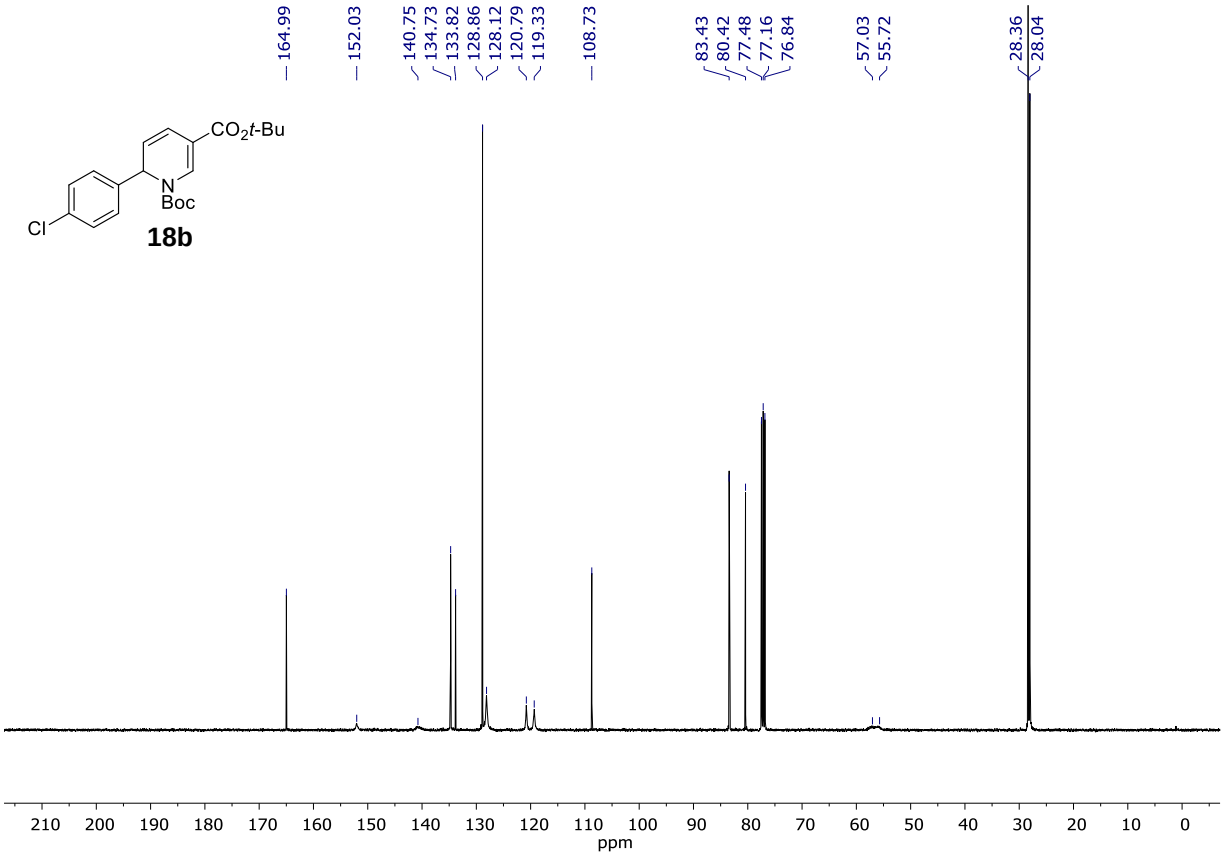
^{1}H NMR (400 MHz, $CDCl_3$)



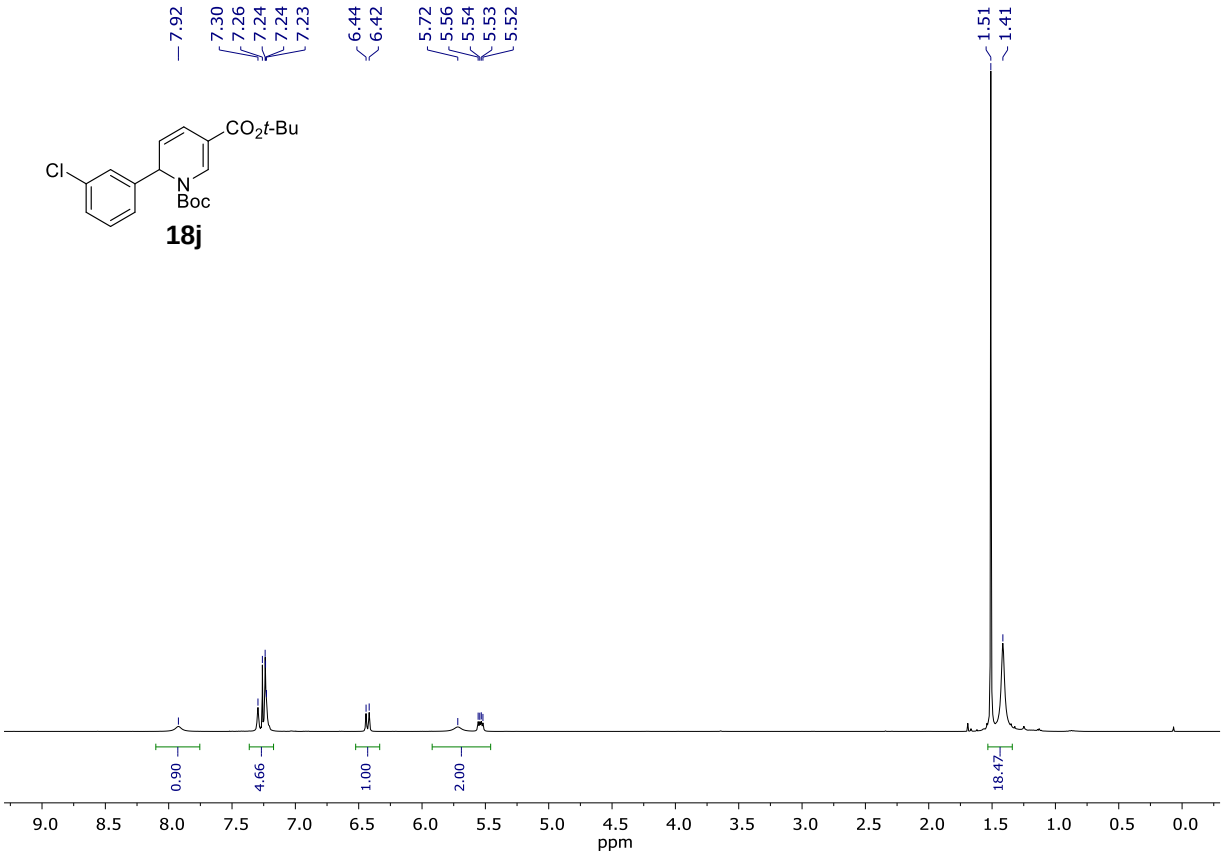
^{13}C NMR (101 MHz, $CDCl_3$)



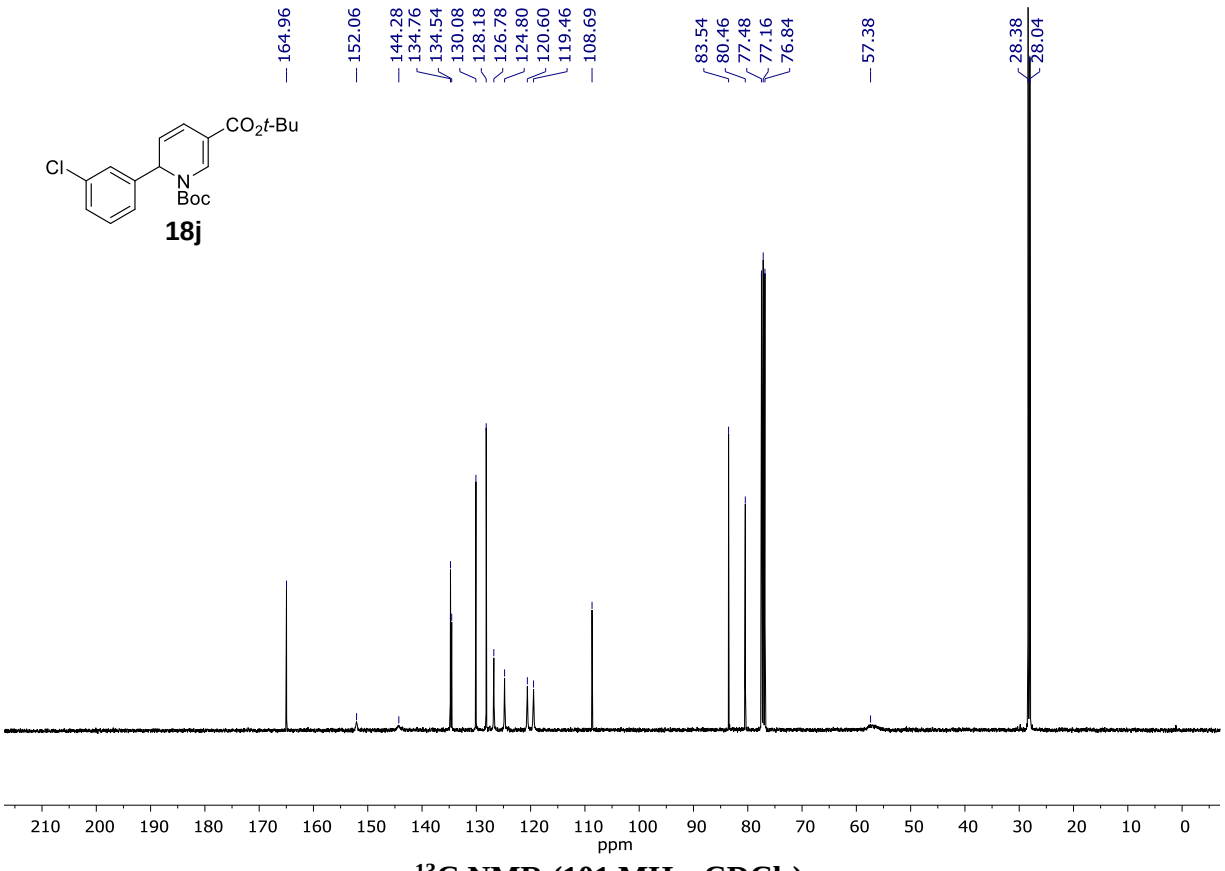
^{1}H NMR (400 MHz, $CDCl_3$)



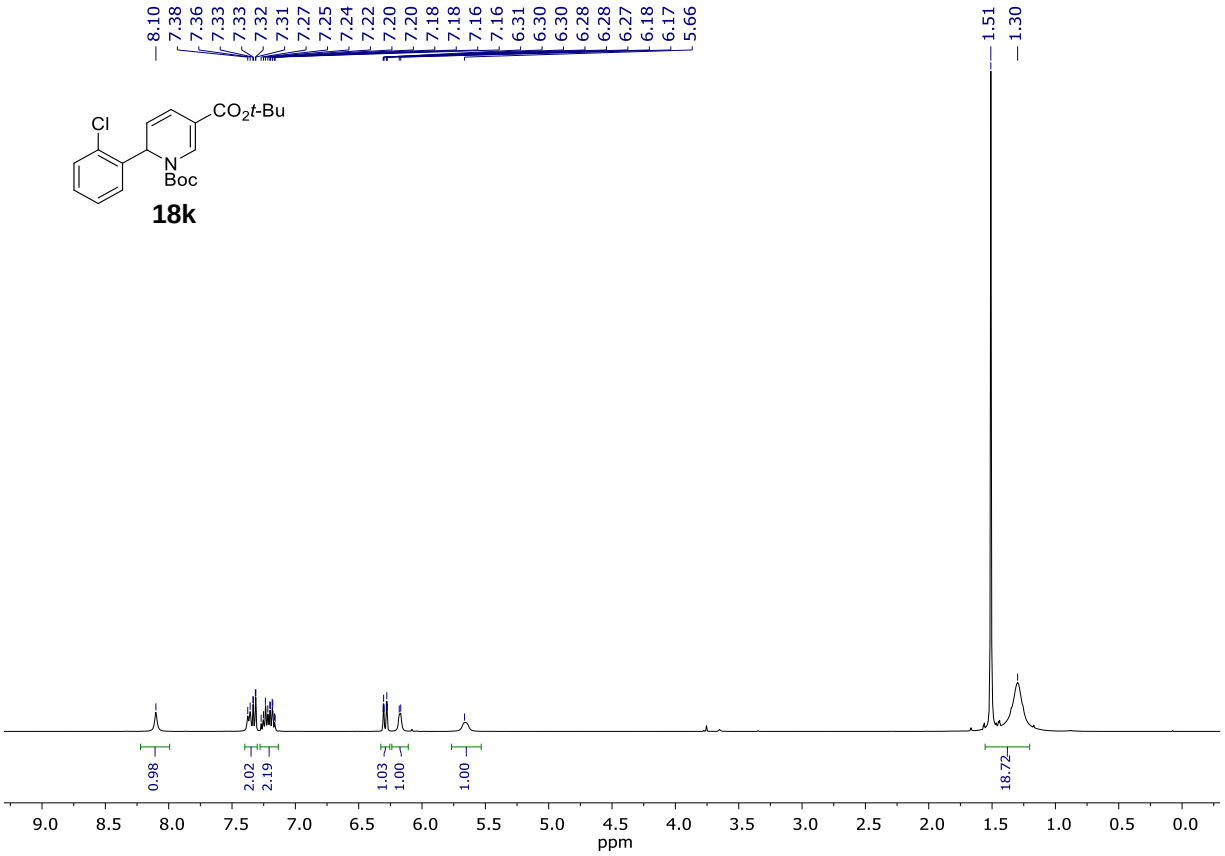
^{13}C NMR (101 MHz, $CDCl_3$)



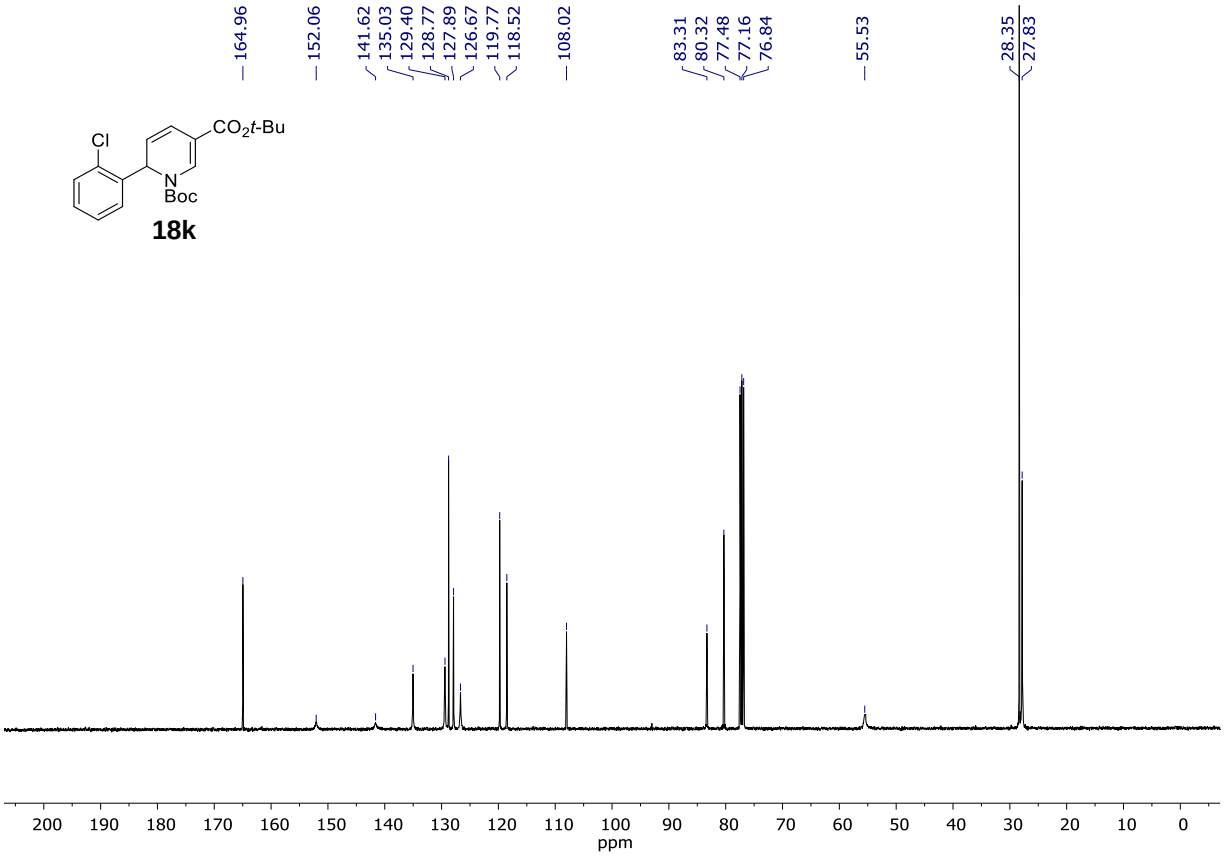
^{1}H NMR (400 MHz, $CDCl_3$)



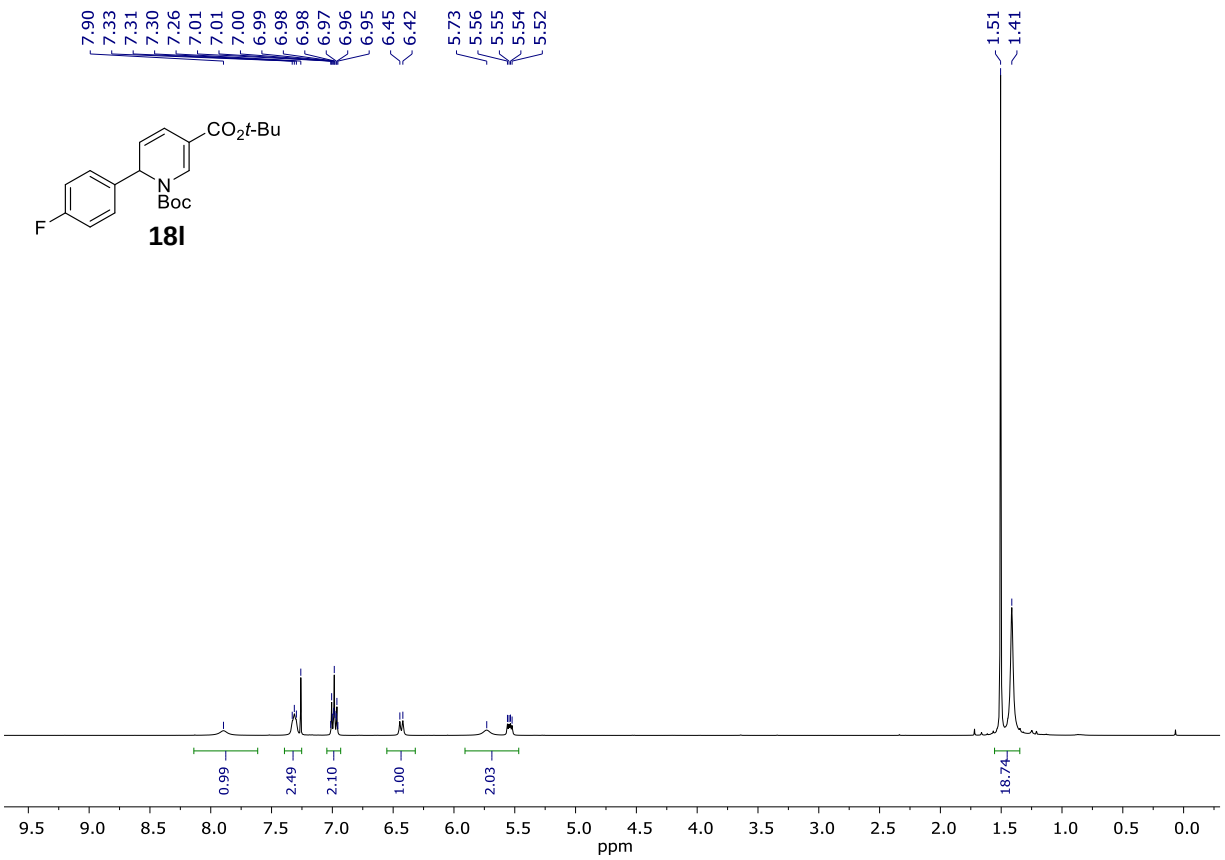
^{13}C NMR (101 MHz, $CDCl_3$)



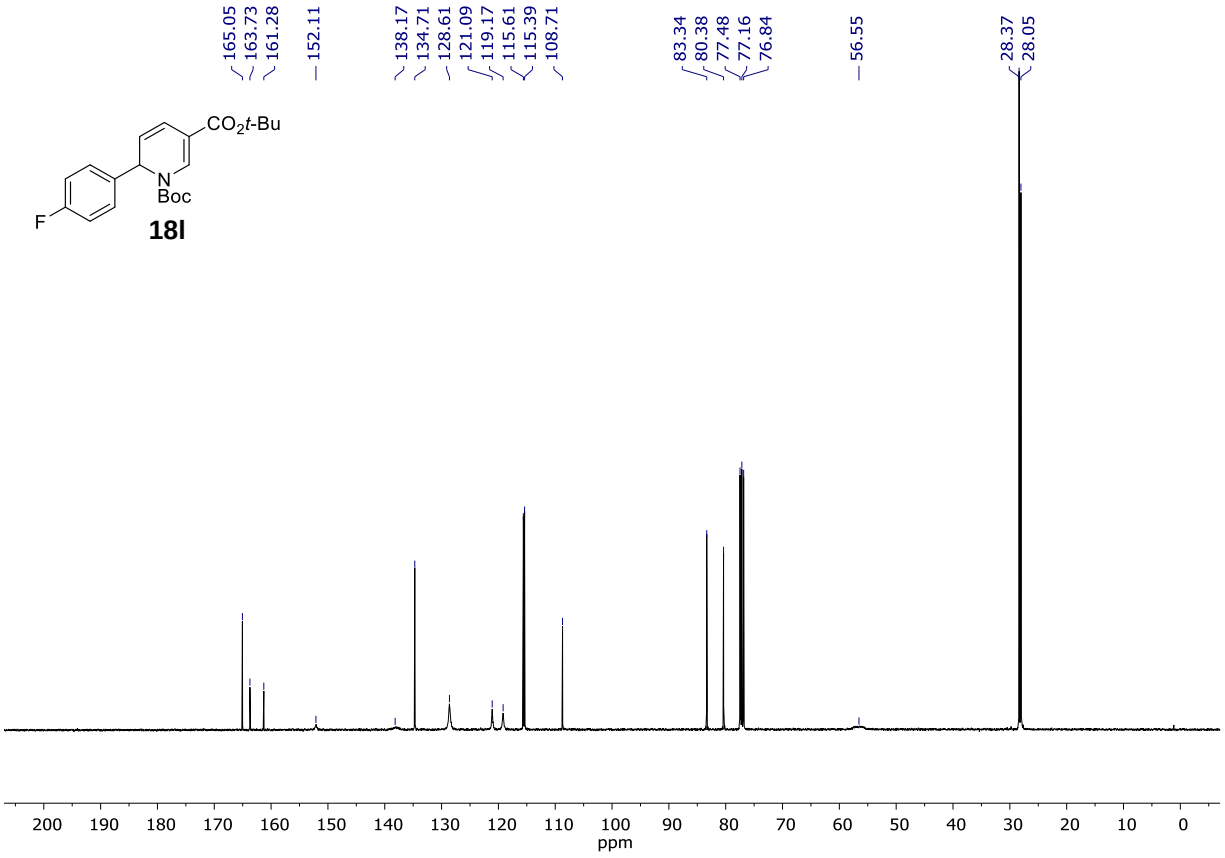
^{1}H NMR (400 MHz, $CDCl_3$)



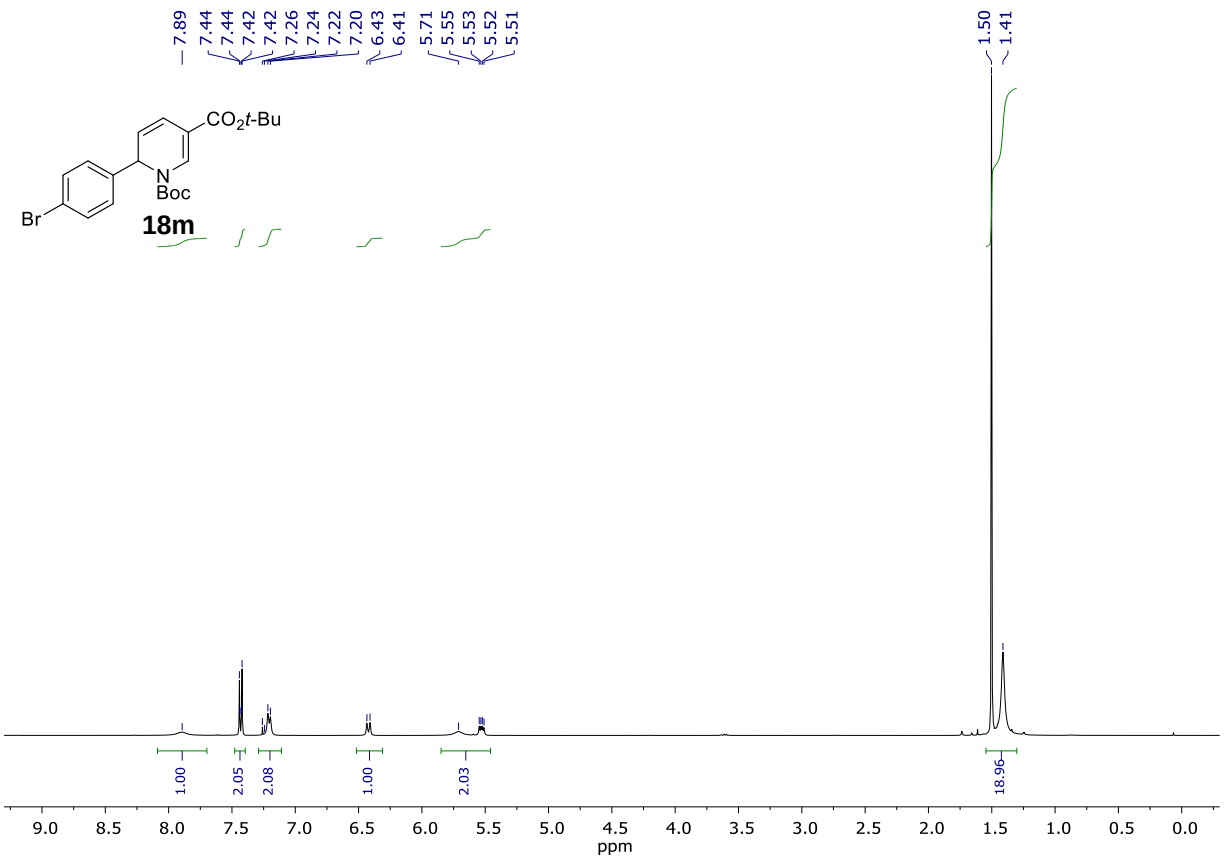
^{13}C NMR (101 MHz, $CDCl_3$)



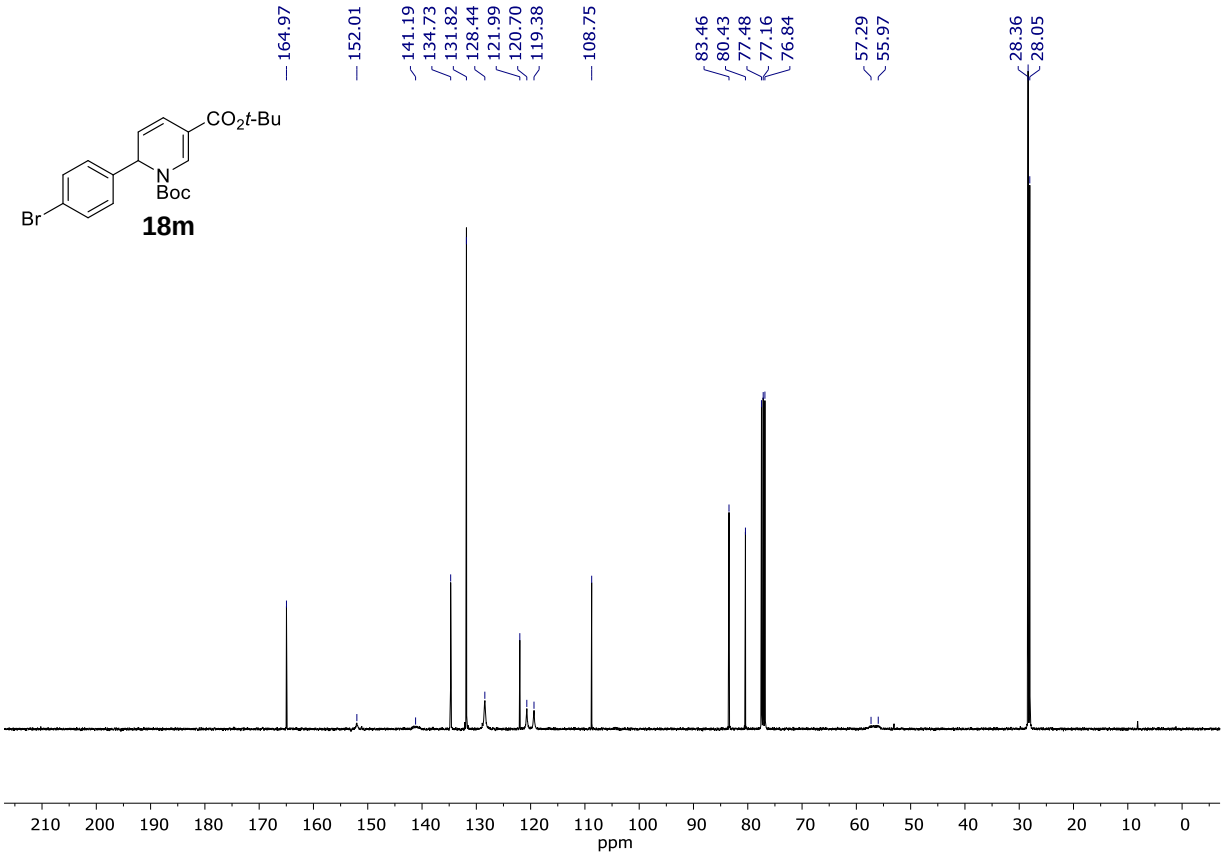
^{1}H NMR (400 MHz, $CDCl_3$)



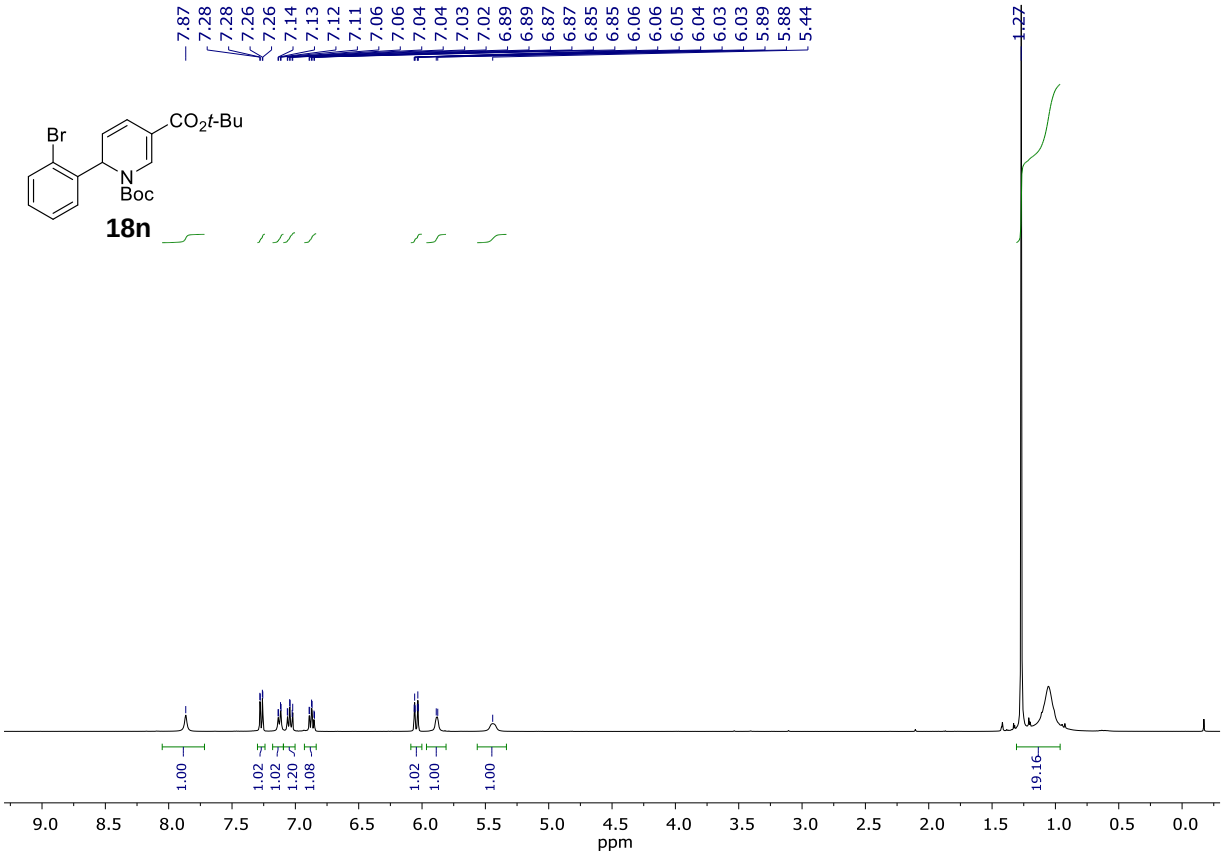
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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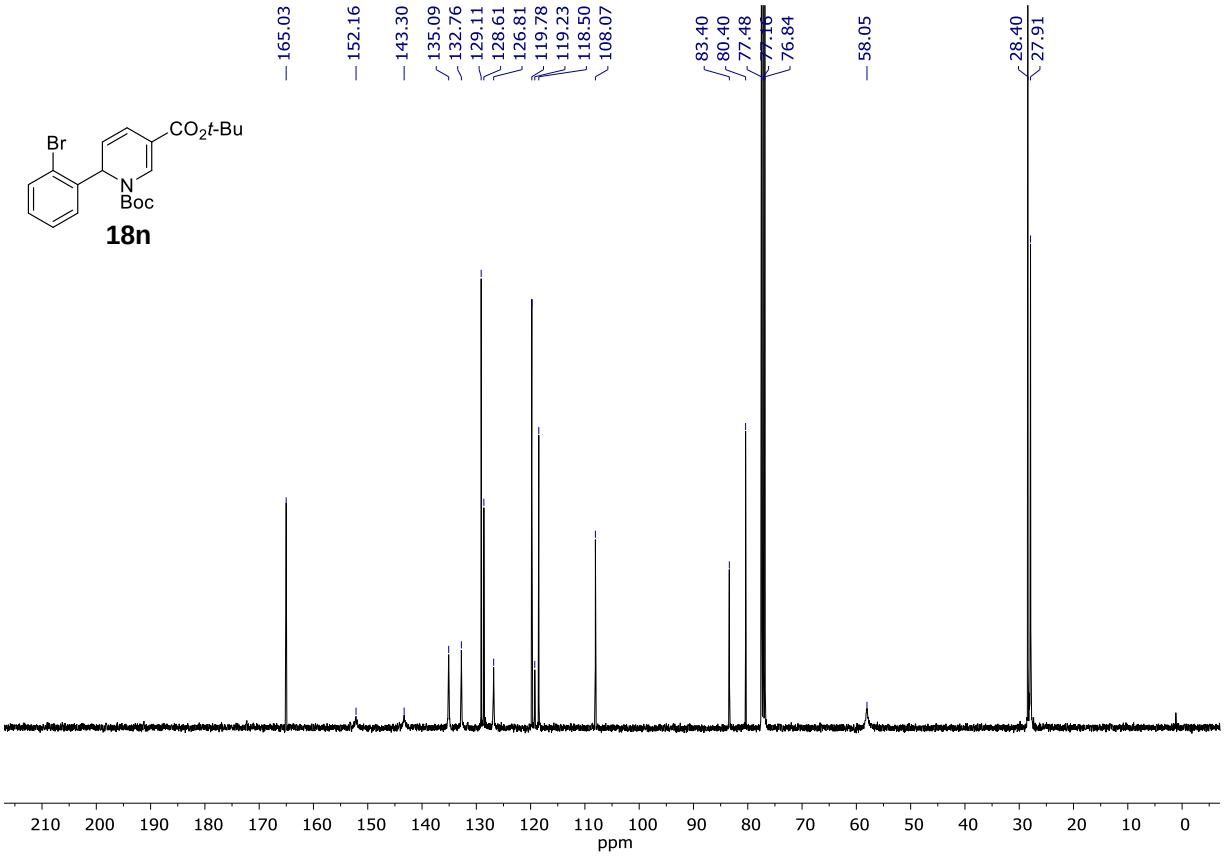
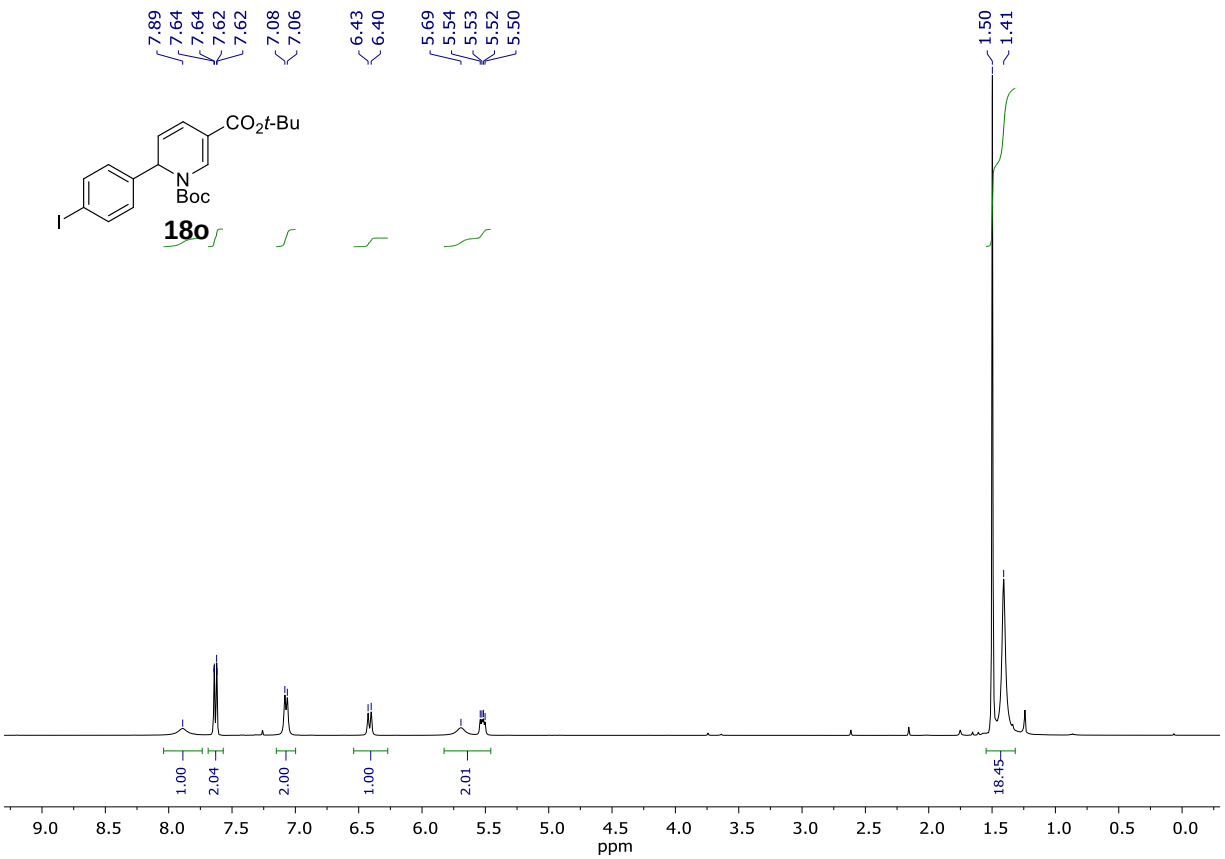


^{13}C NMR (101 MHz, $CDCl_3$)



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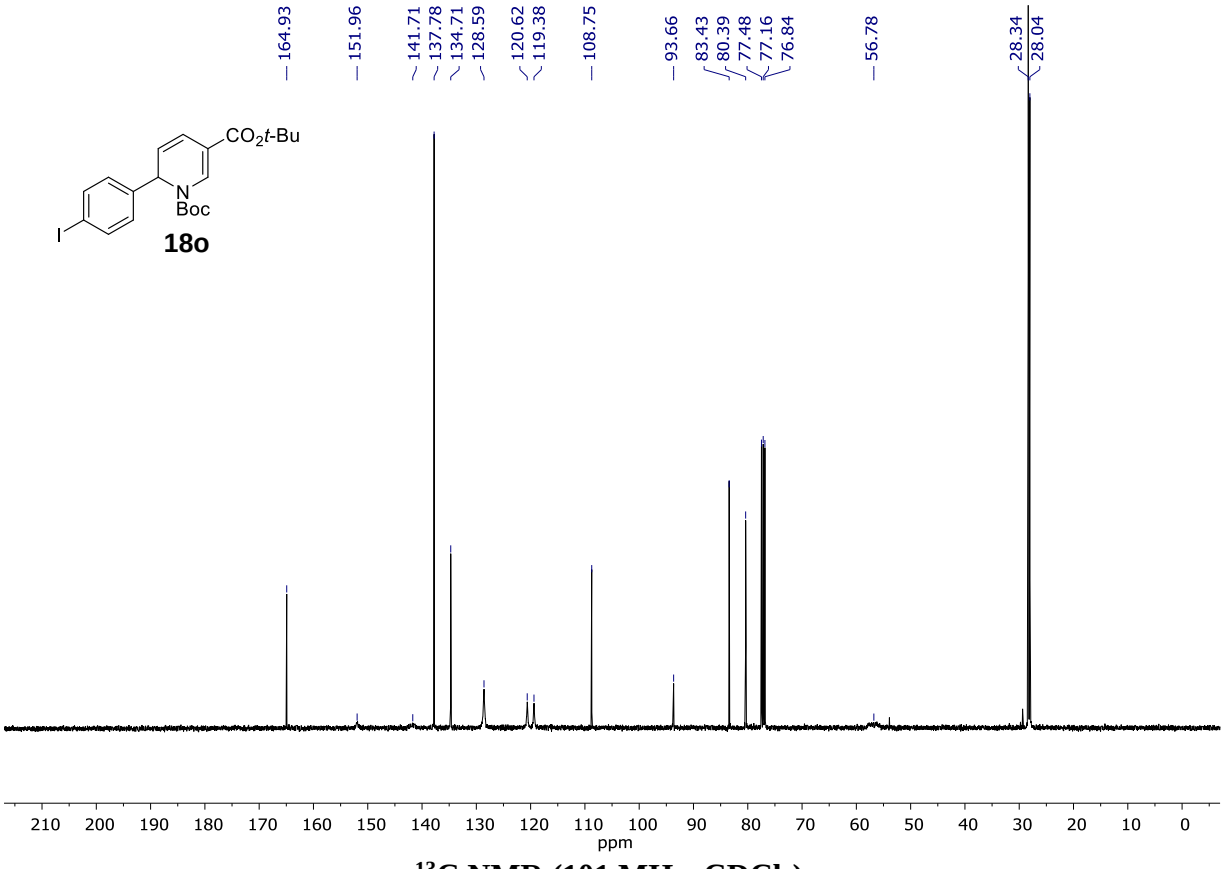

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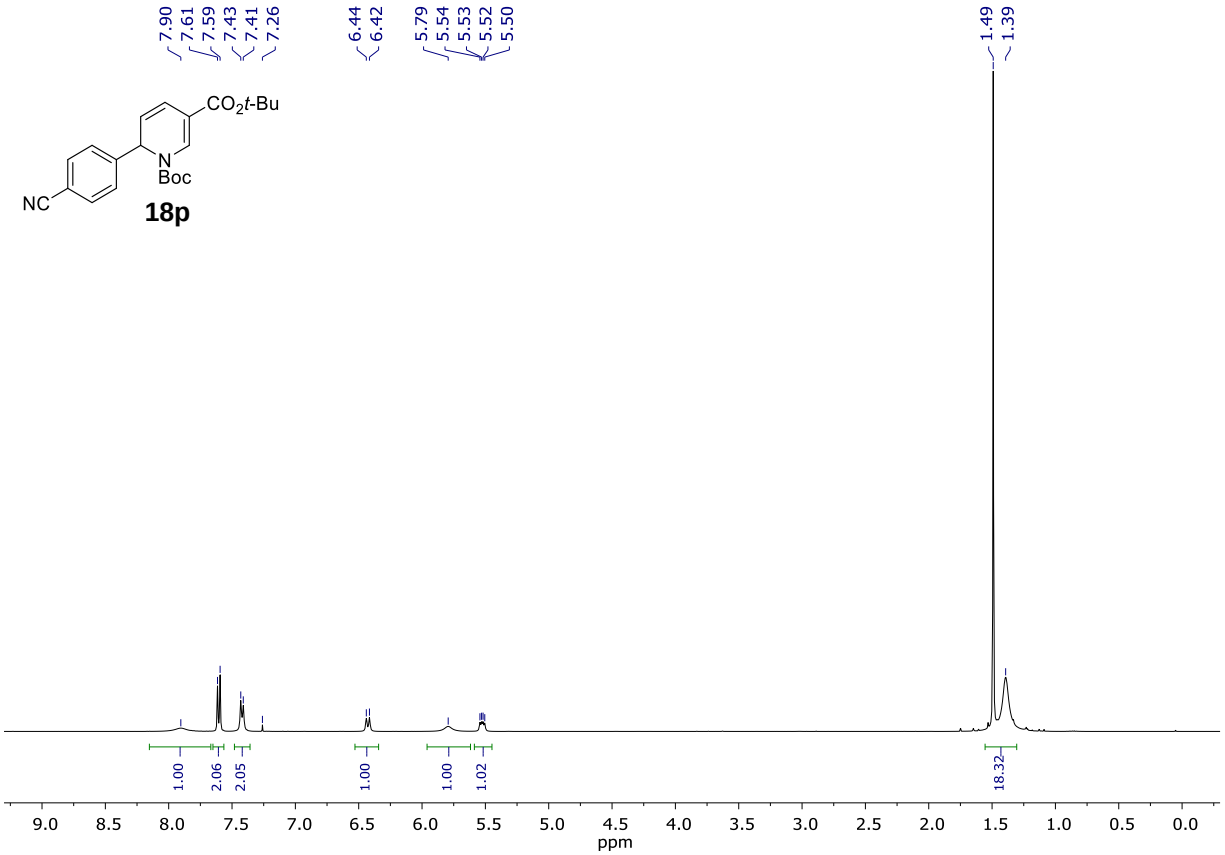

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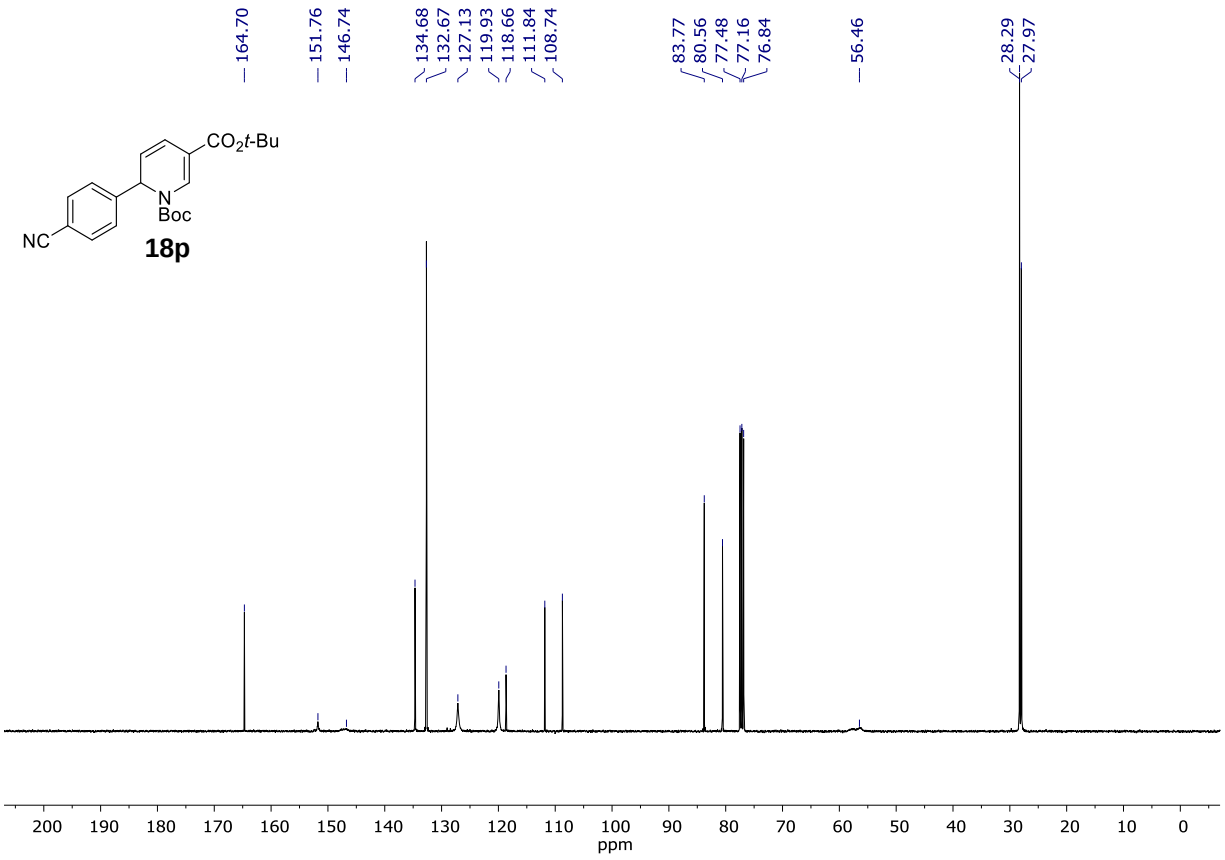
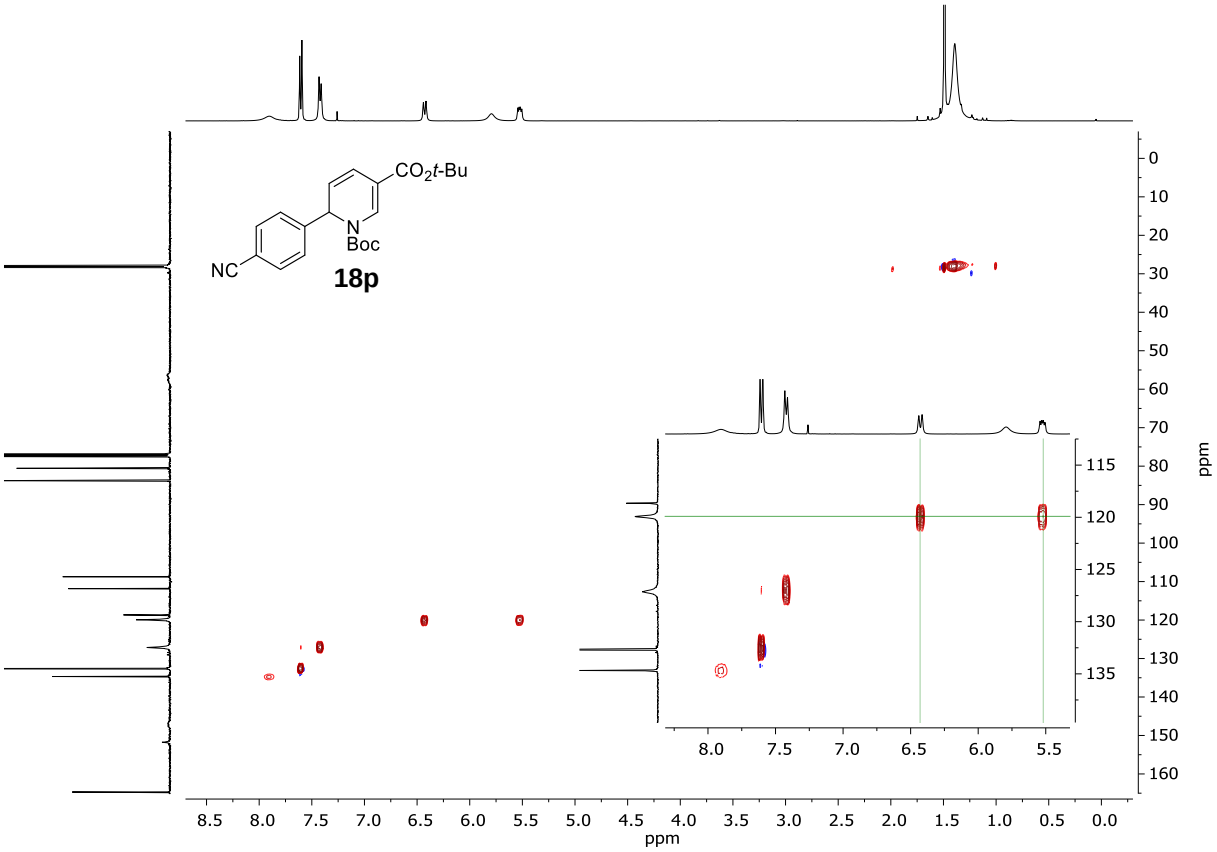
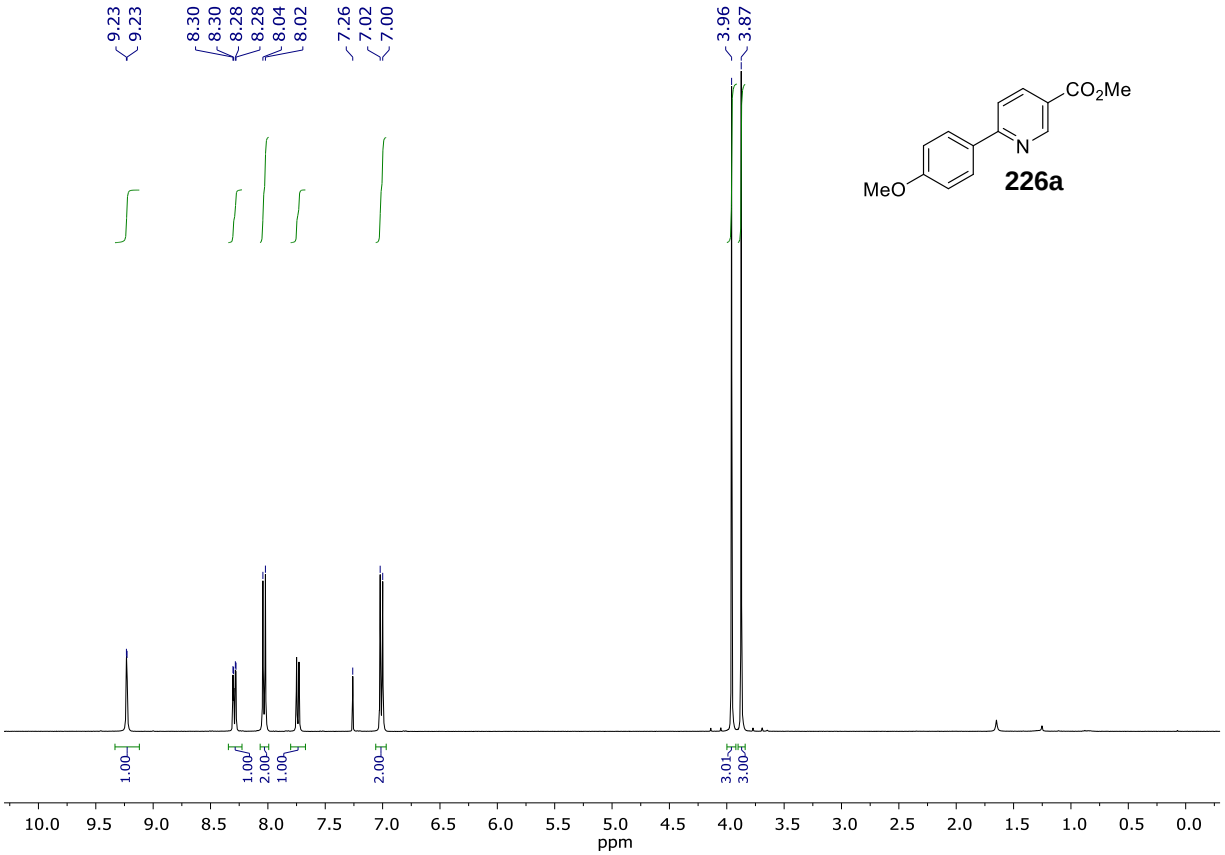


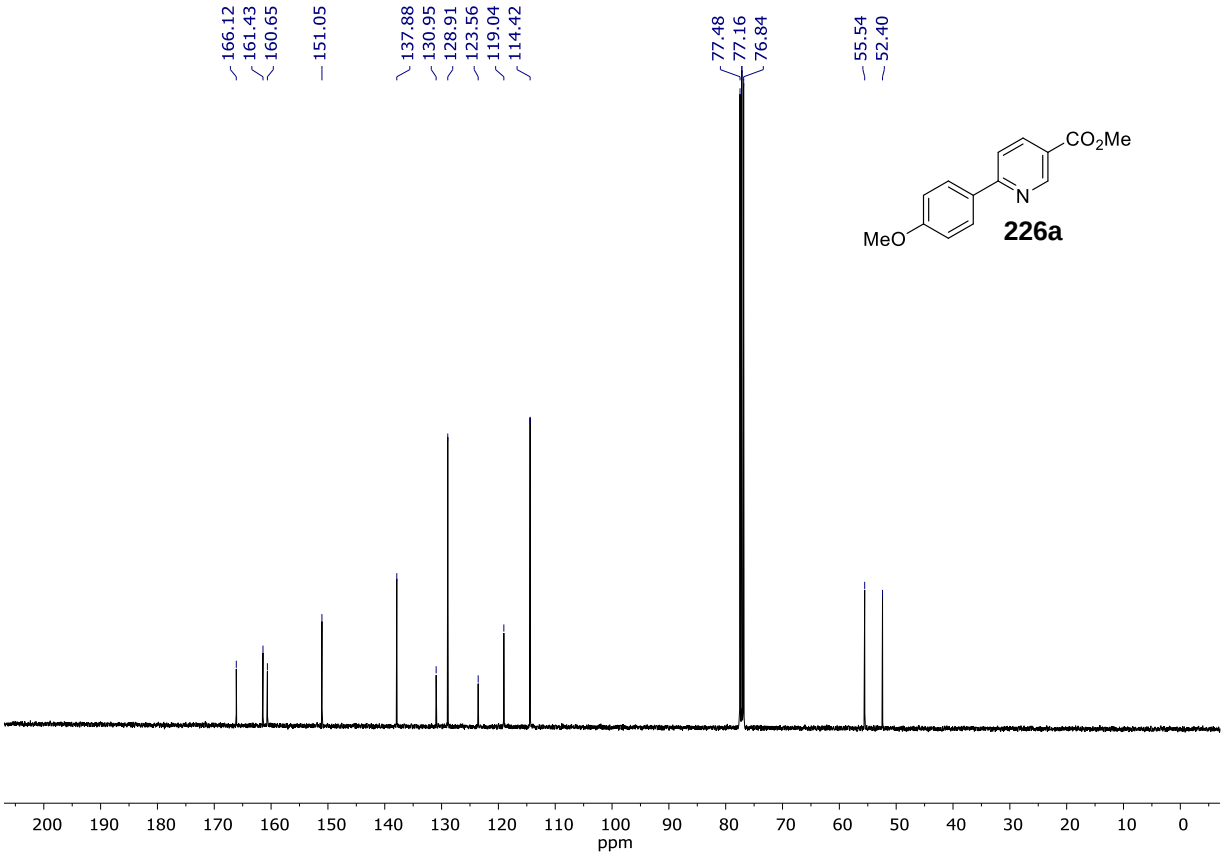
^{13}C NMR (101 MHz, $CDCl_3$)



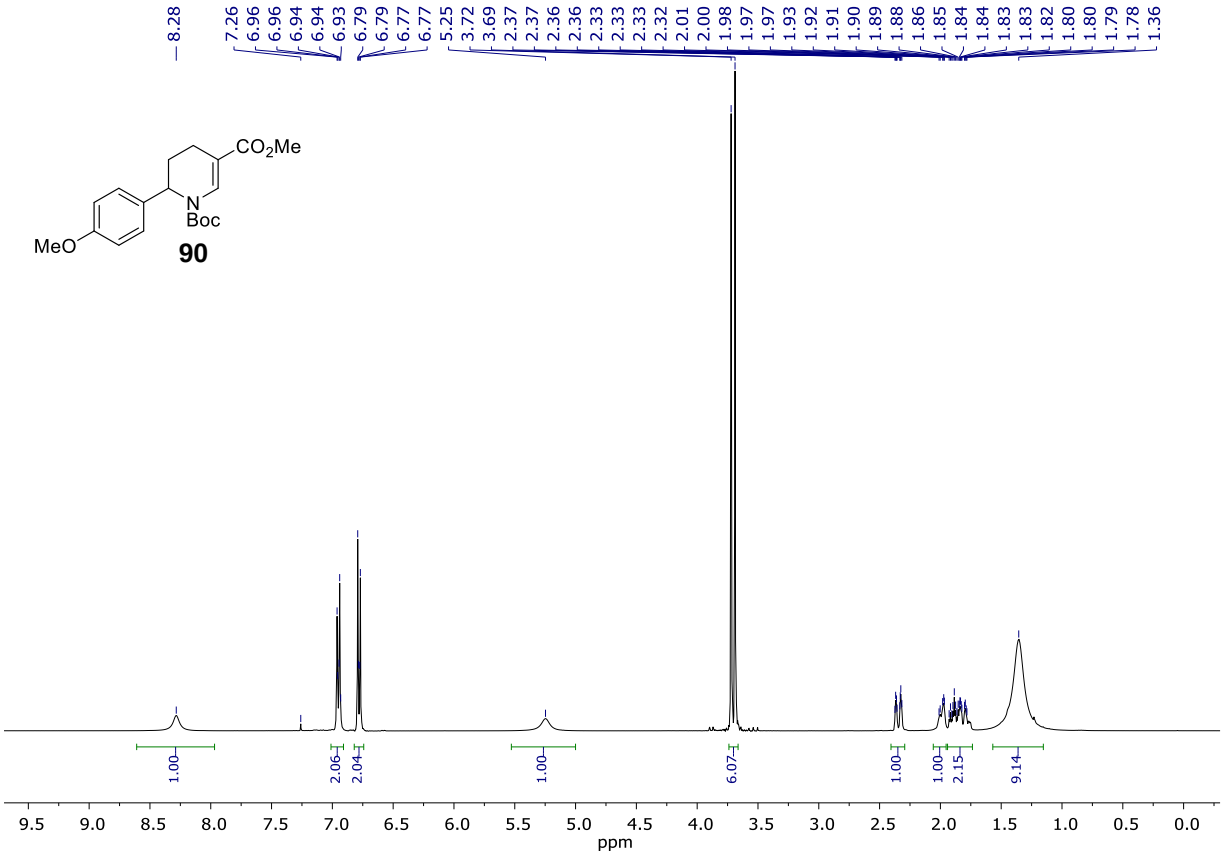
HSQC ((400, 101) MHz, $CDCl_3$)



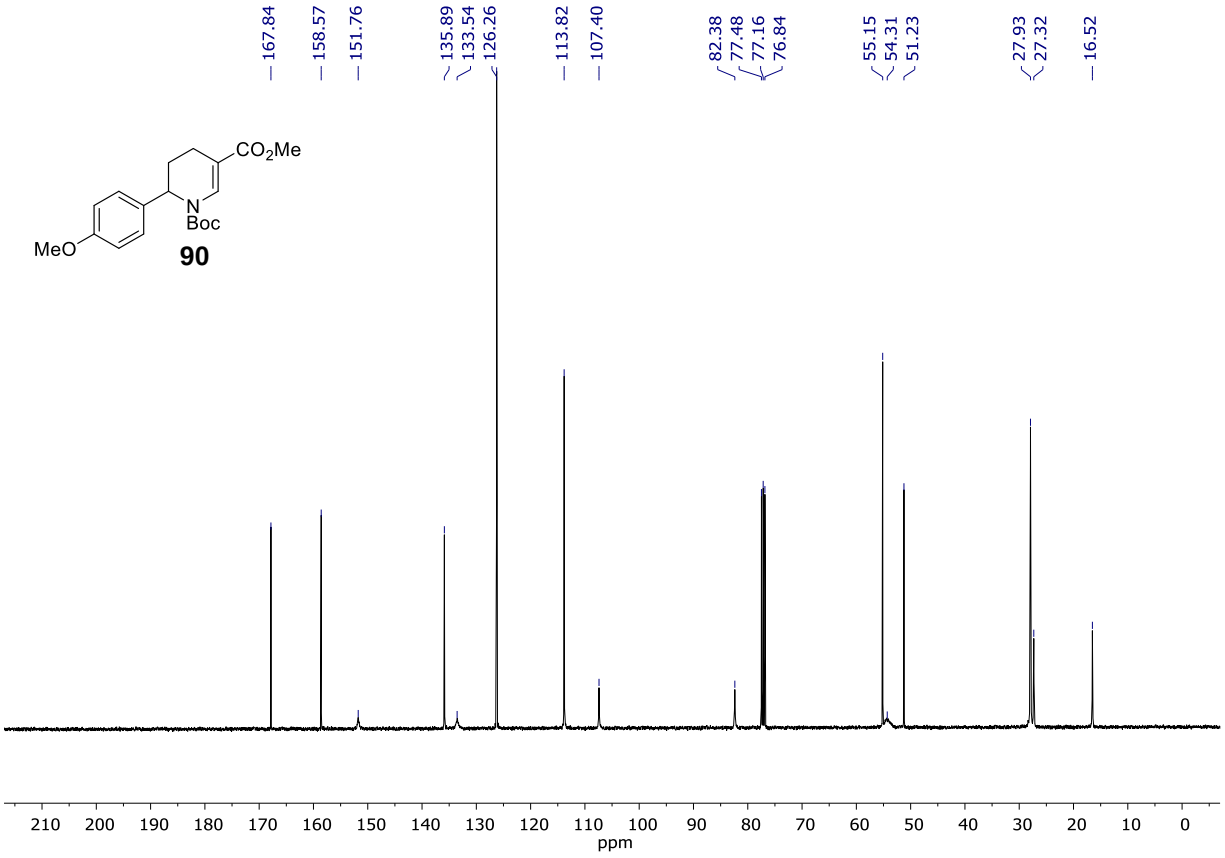
^{1}H NMR (400 MHz, $CDCl_3$)



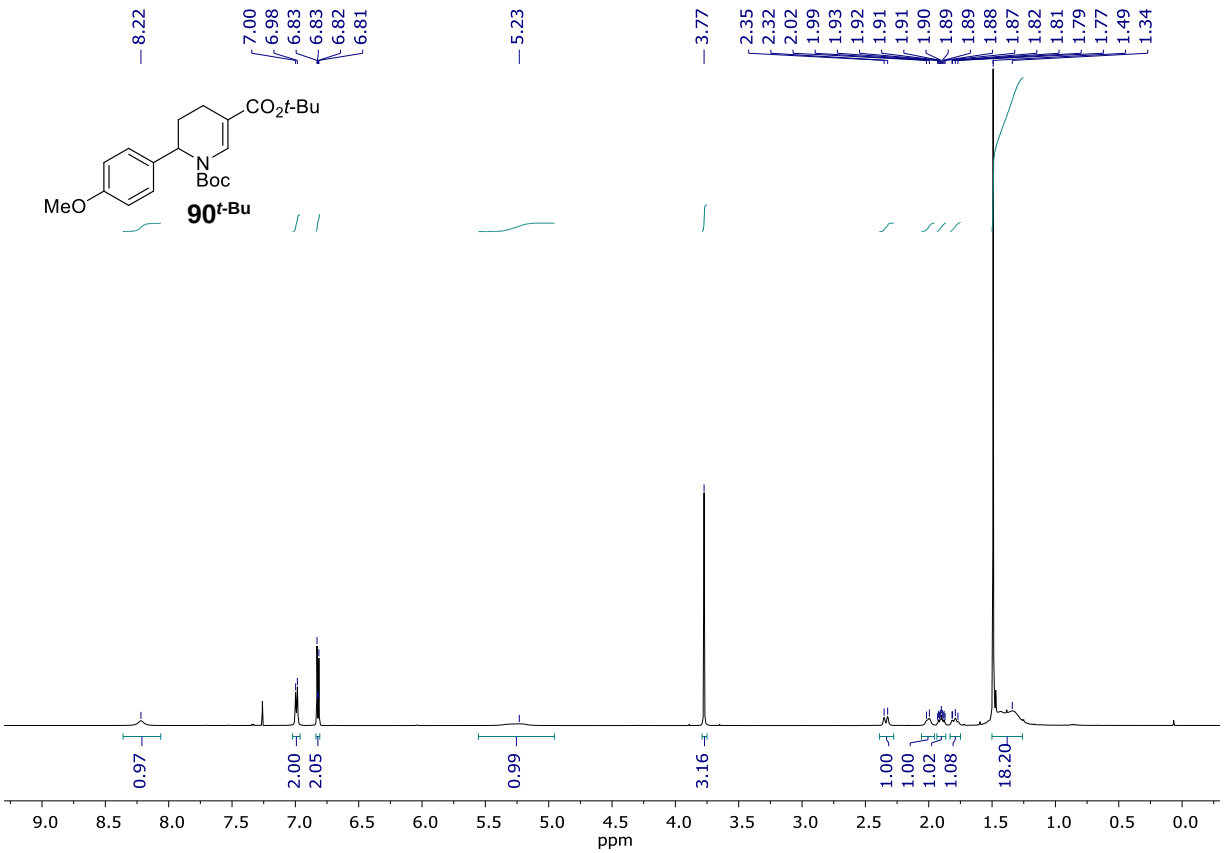
^{13}C NMR (101 MHz, $CDCl_3$)



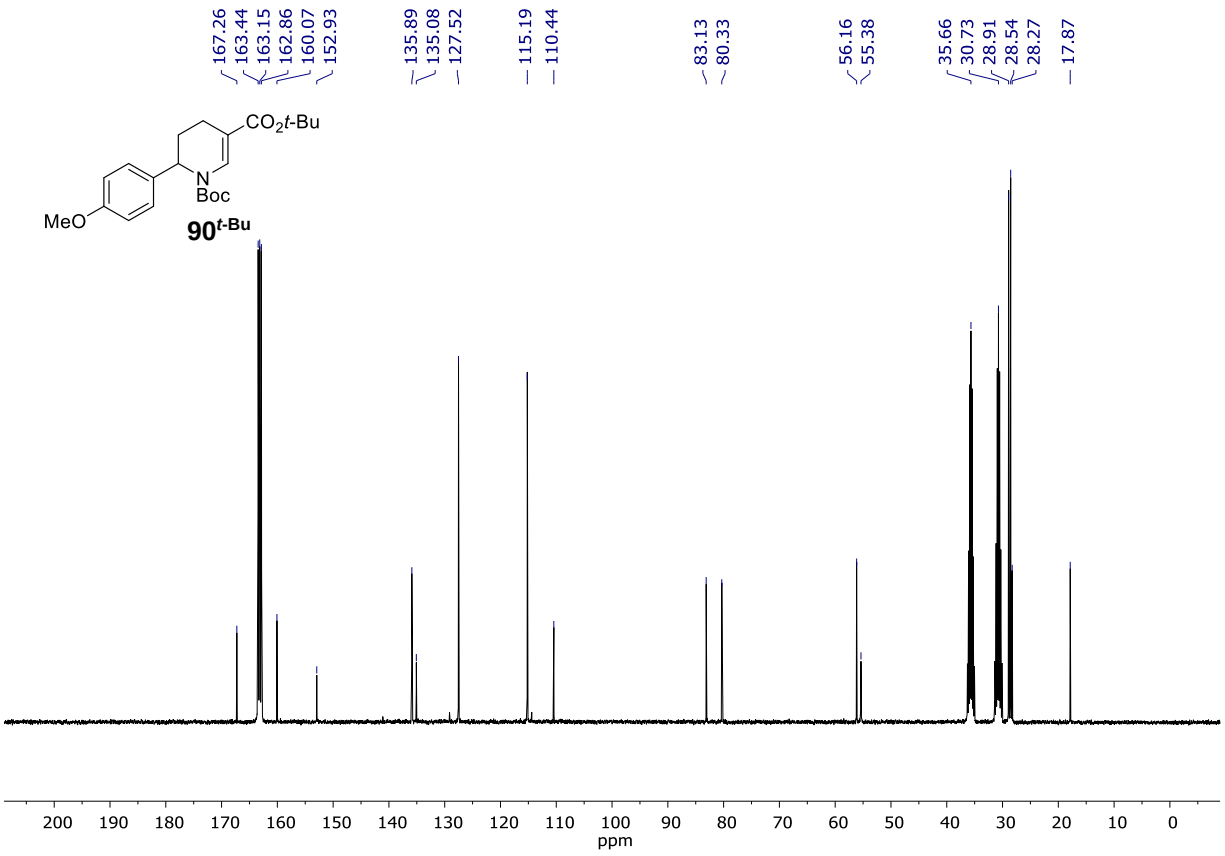
^{1}H NMR (400 MHz, $CDCl_3$)



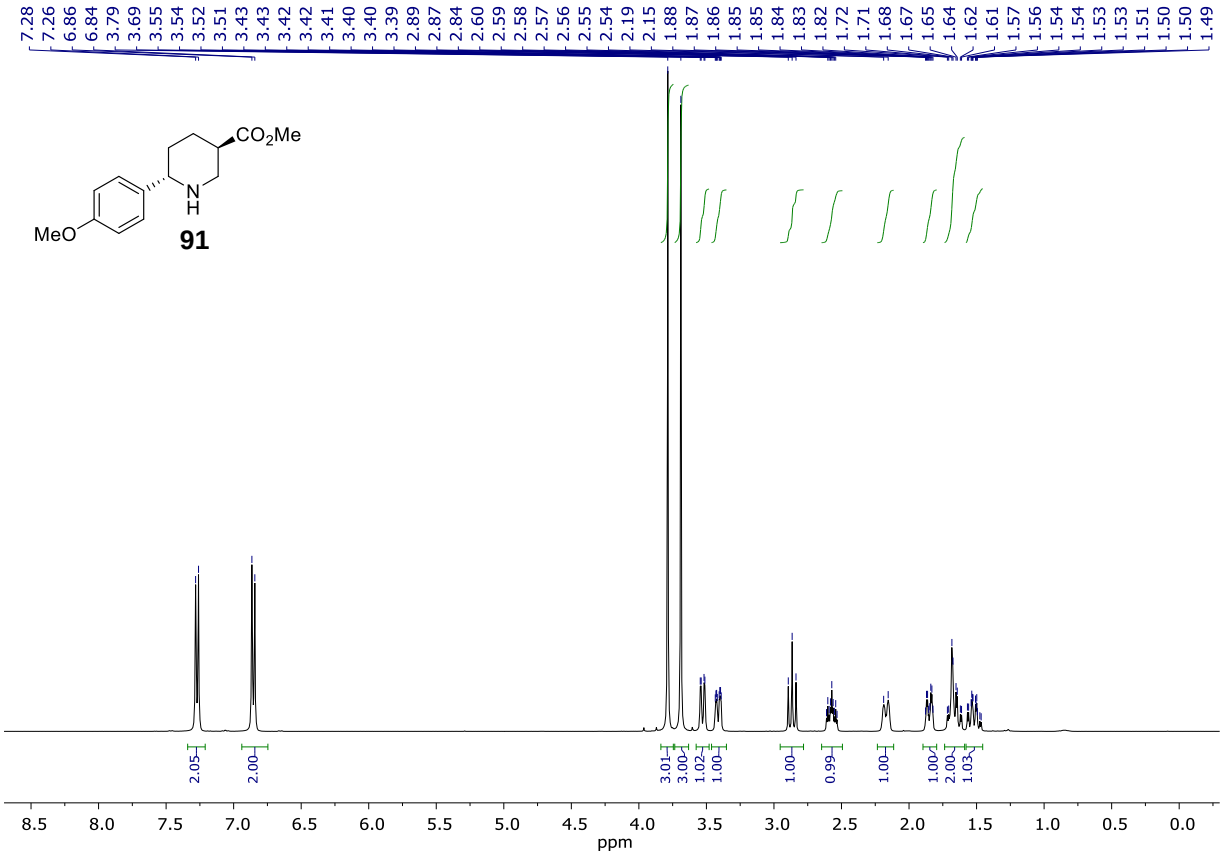
^{13}C NMR (101 MHz, $CDCl_3$)



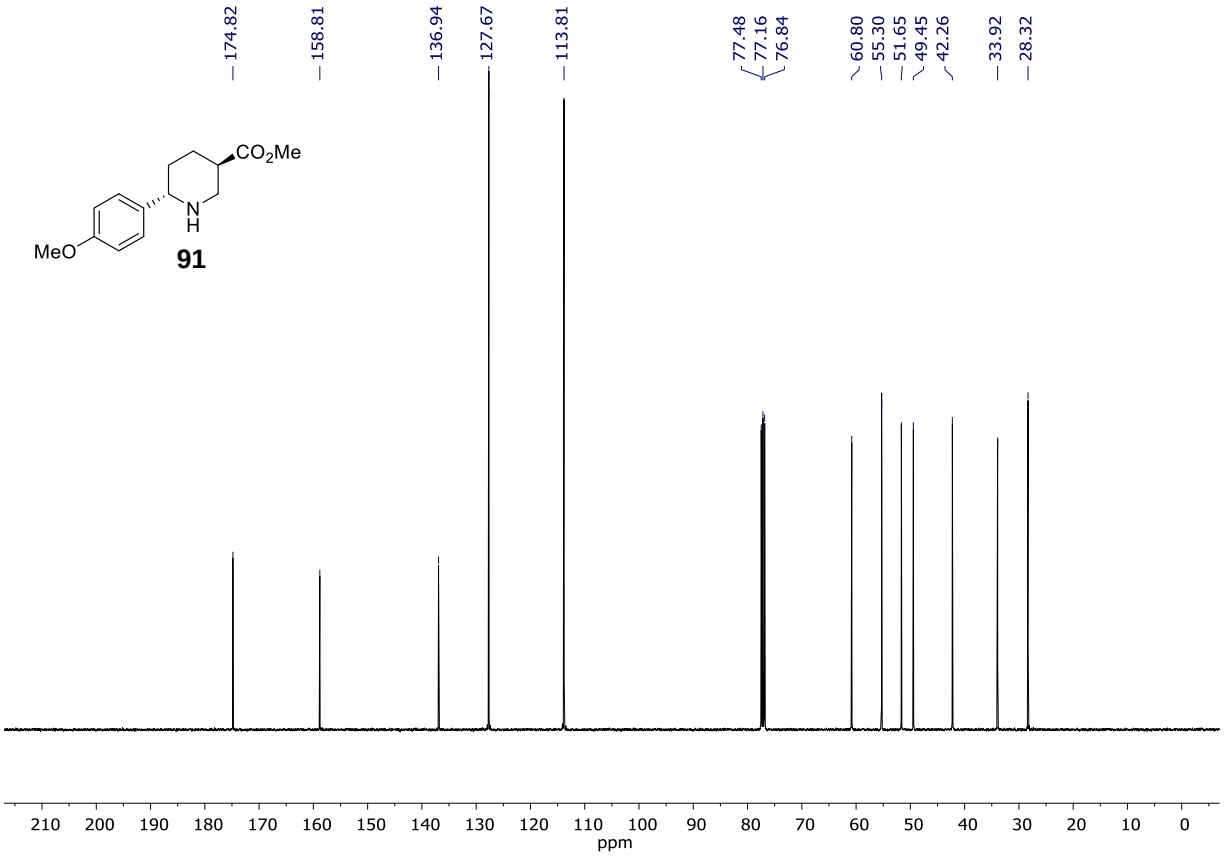
^{1}H NMR (600 MHz, $CDCl_3$)



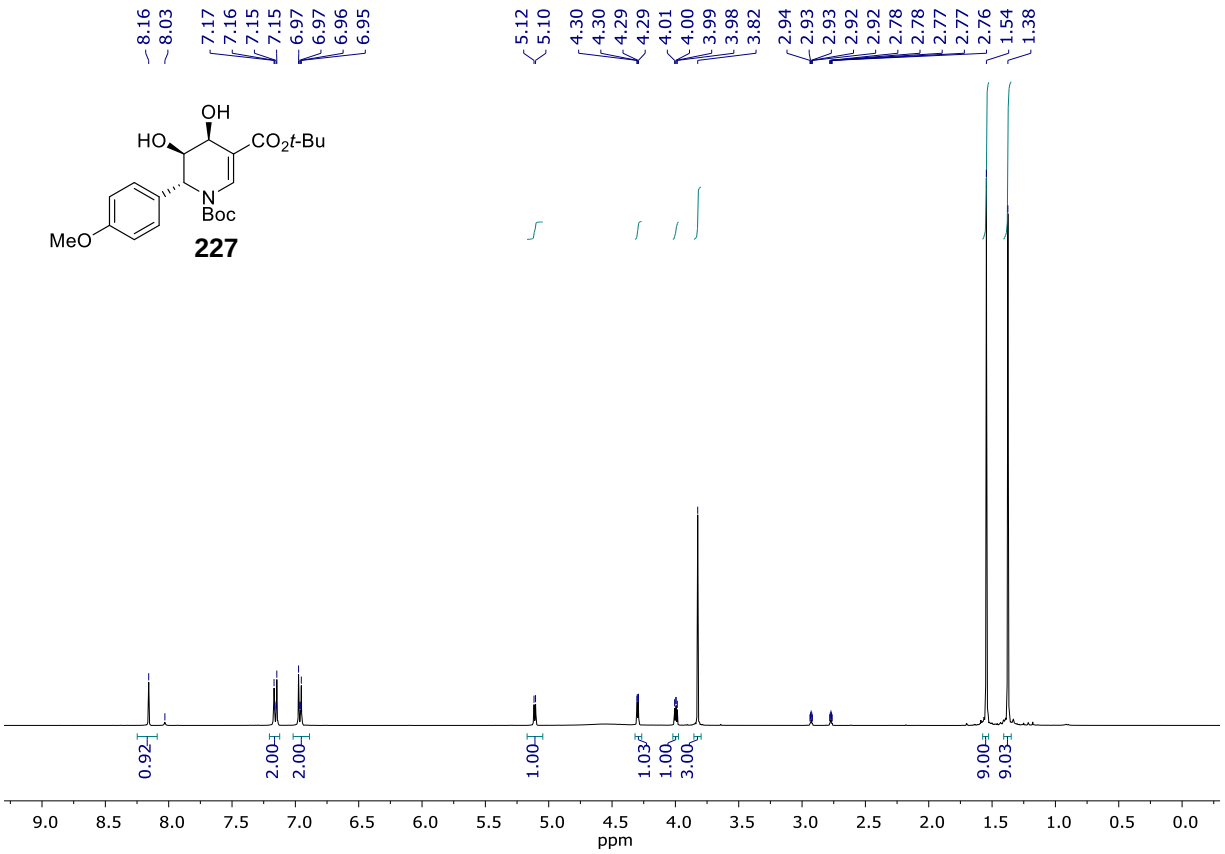
^{13}C NMR (101 MHz, DMF-d_7, 80 °C)



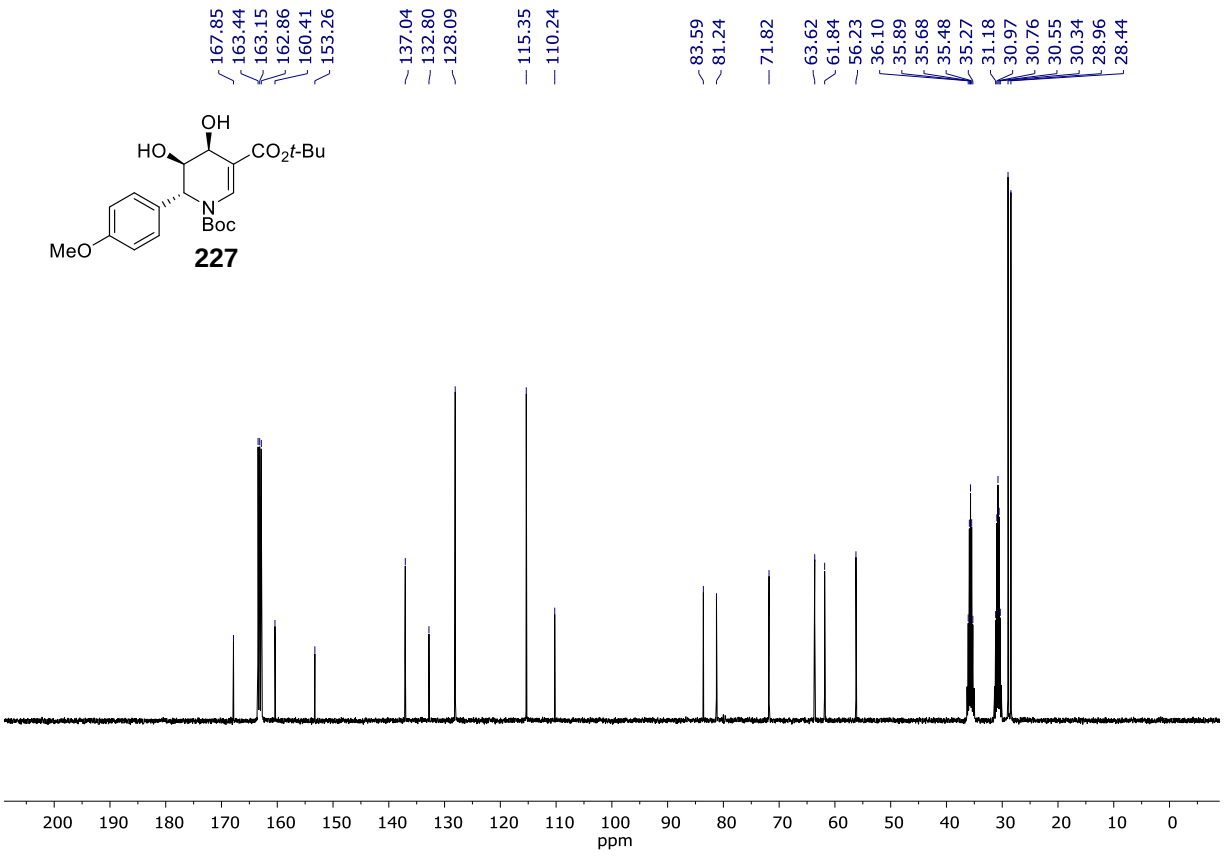
^{1}H NMR (400 MHz, $CDCl_3$)



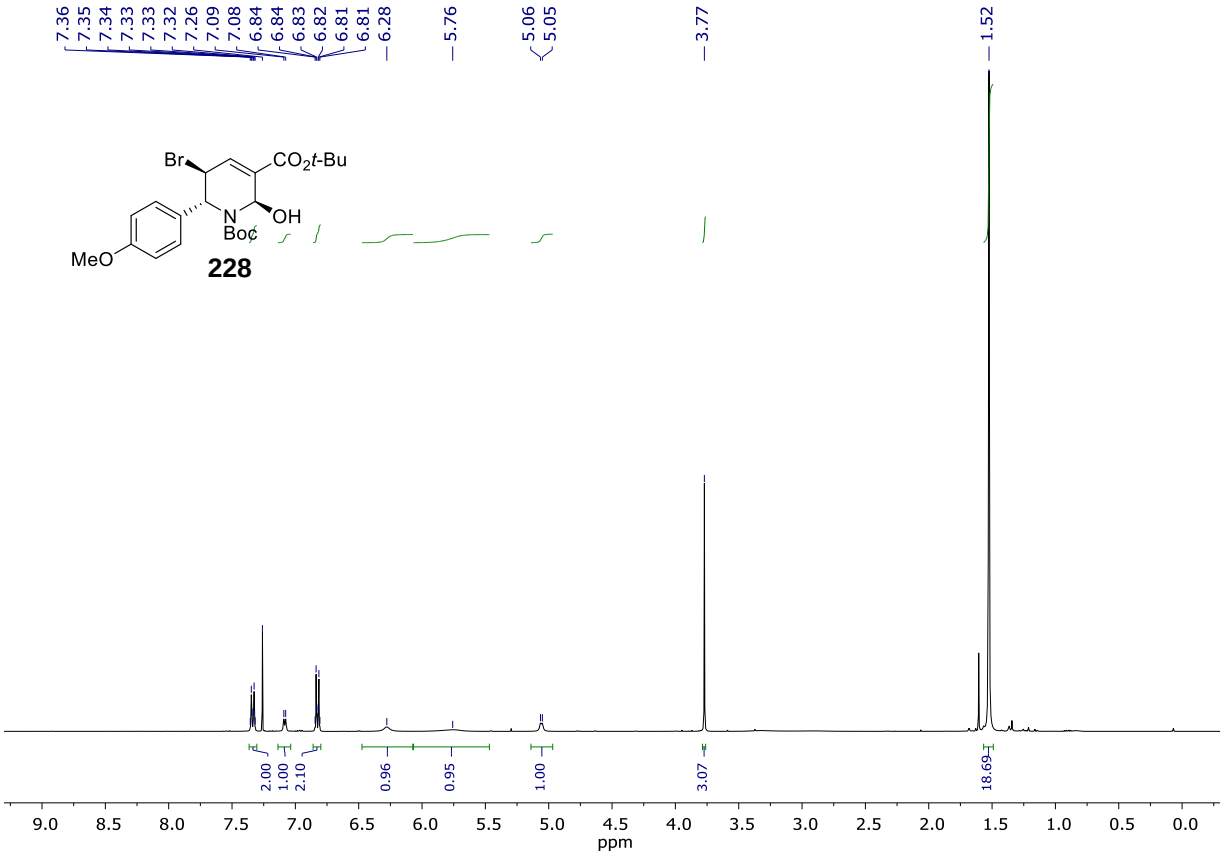
^{13}C NMR (101 MHz, $CDCl_3$)



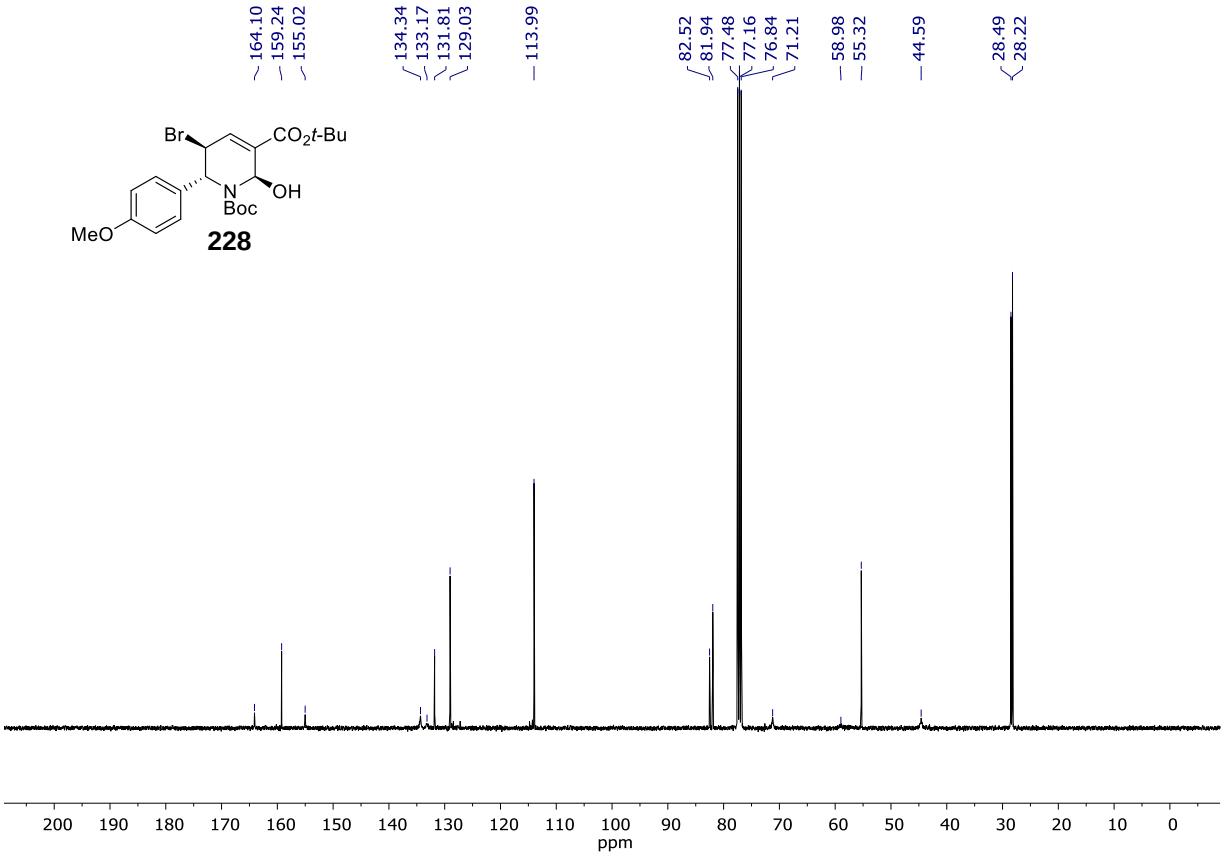
^{1}H NMR (400 MHz, DMF-d$_7$, 80 °C)



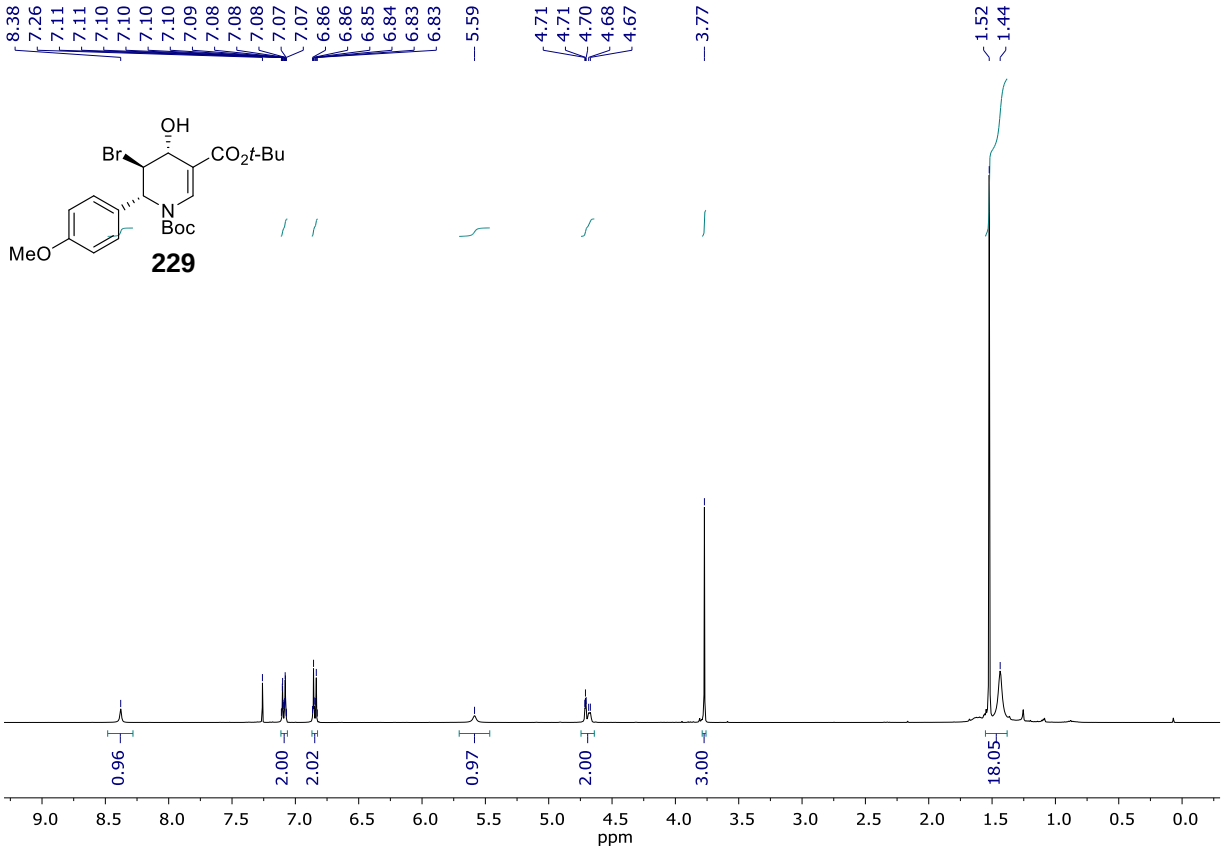
^{13}C NMR (101 MHz, DMF-d$_7$, 80 °C)



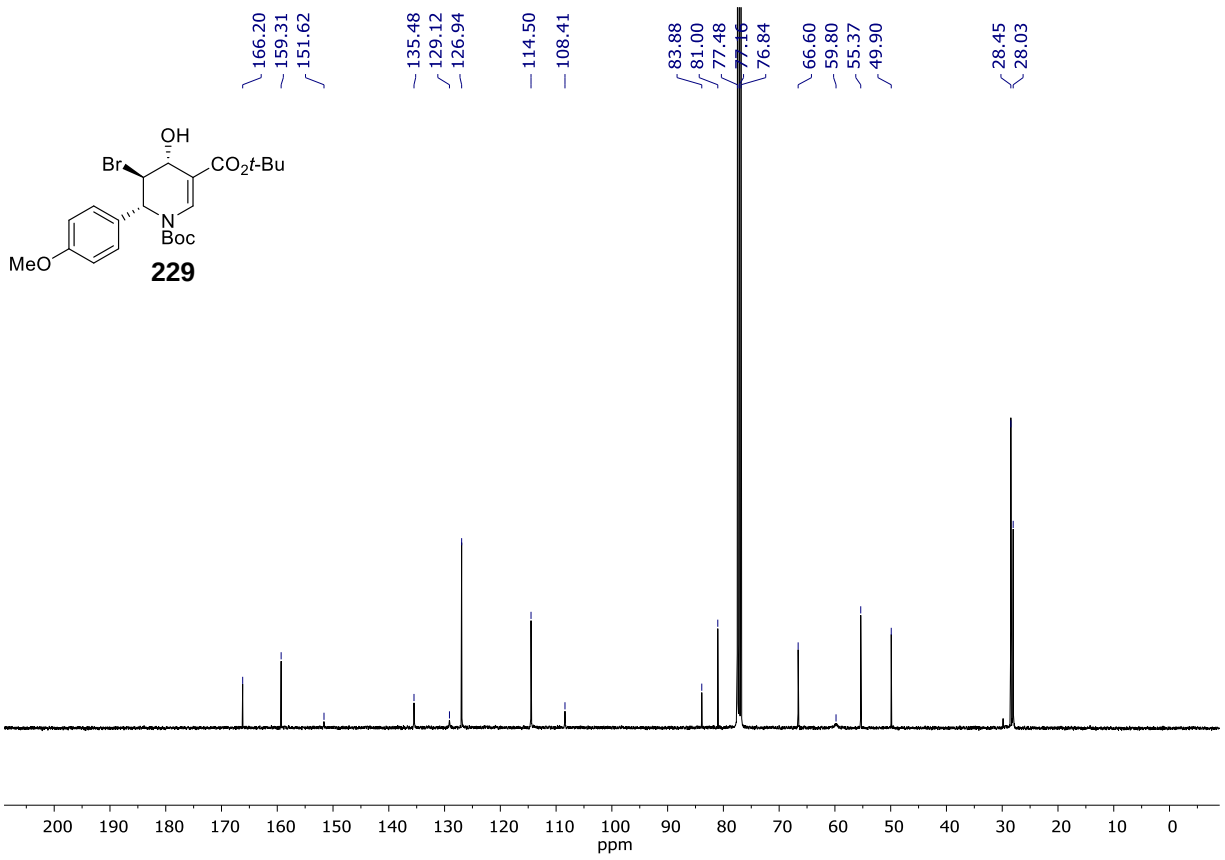
^{1}H NMR (400 MHz, $CDCl_3$)



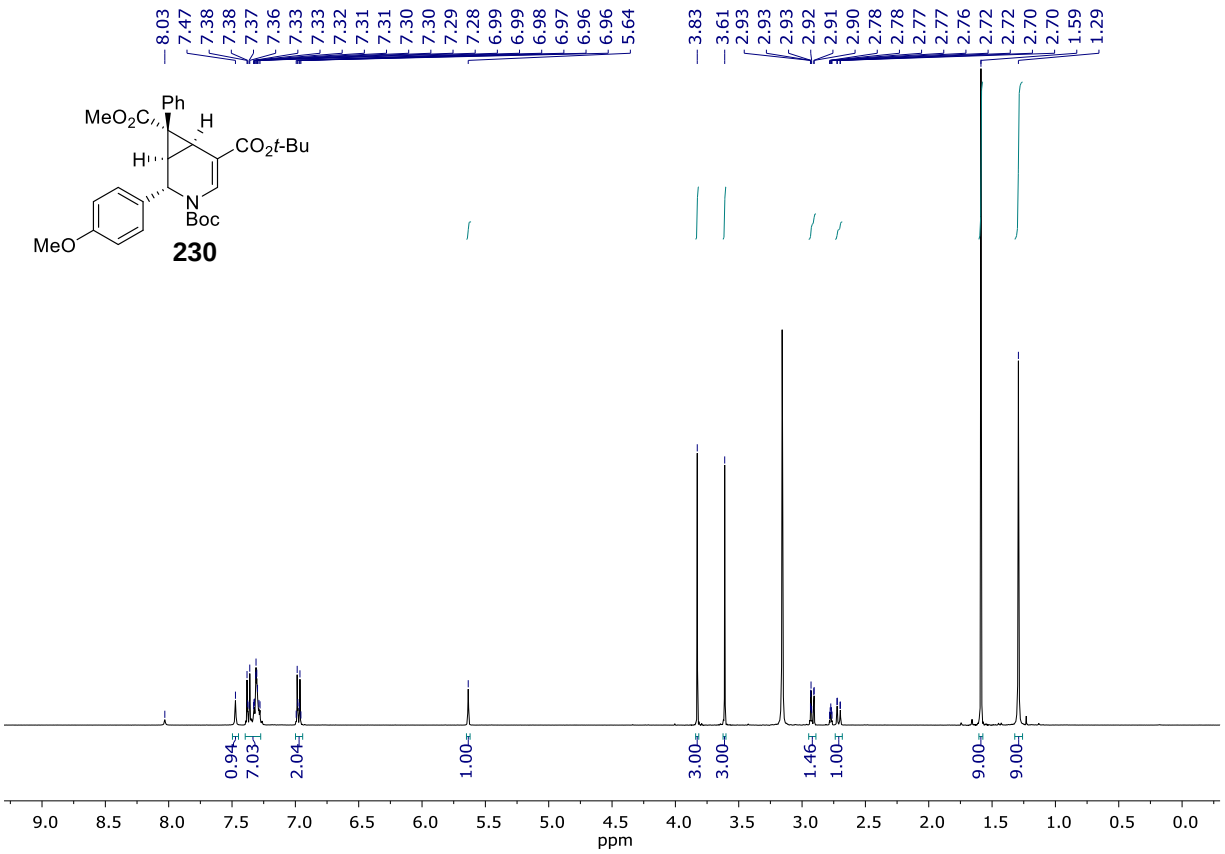
^{13}C NMR (101 MHz, $CDCl_3$)



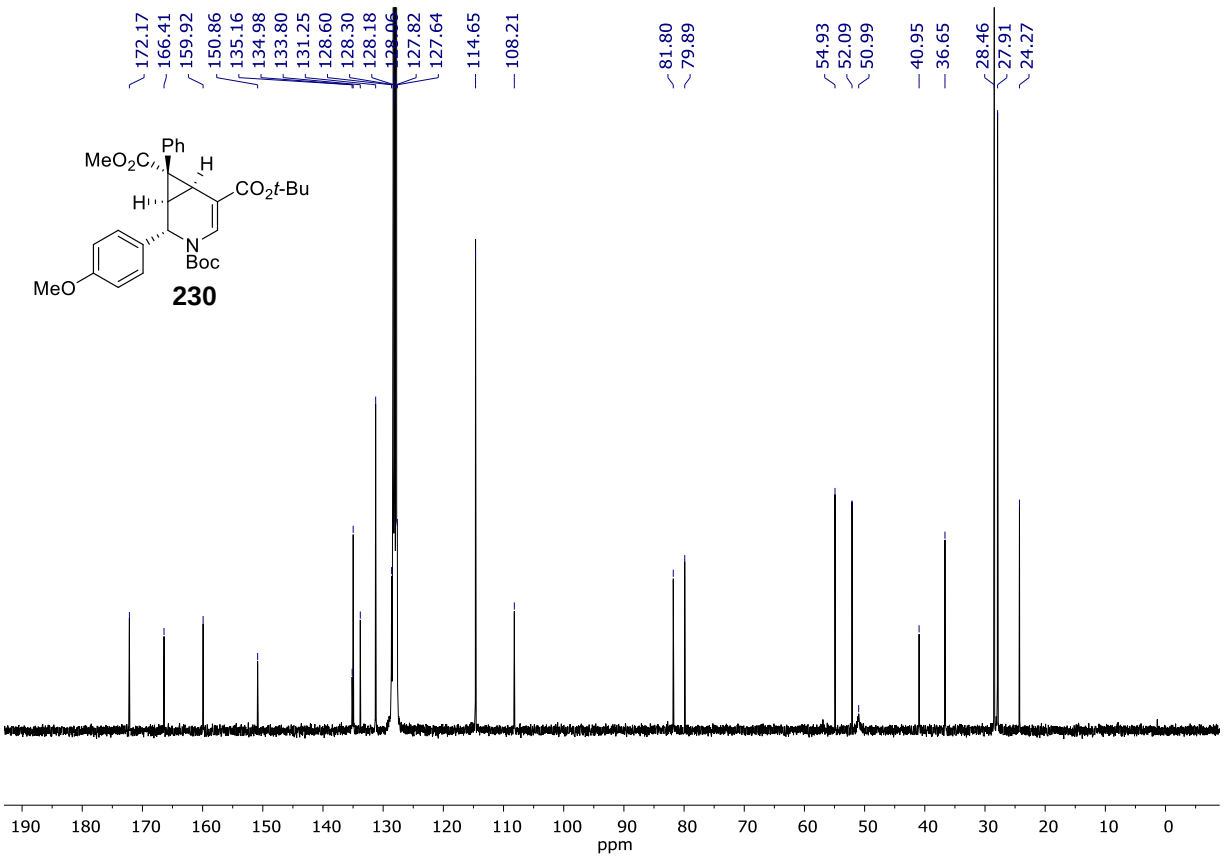
^{1}H NMR (400 MHz, $CDCl_3$)



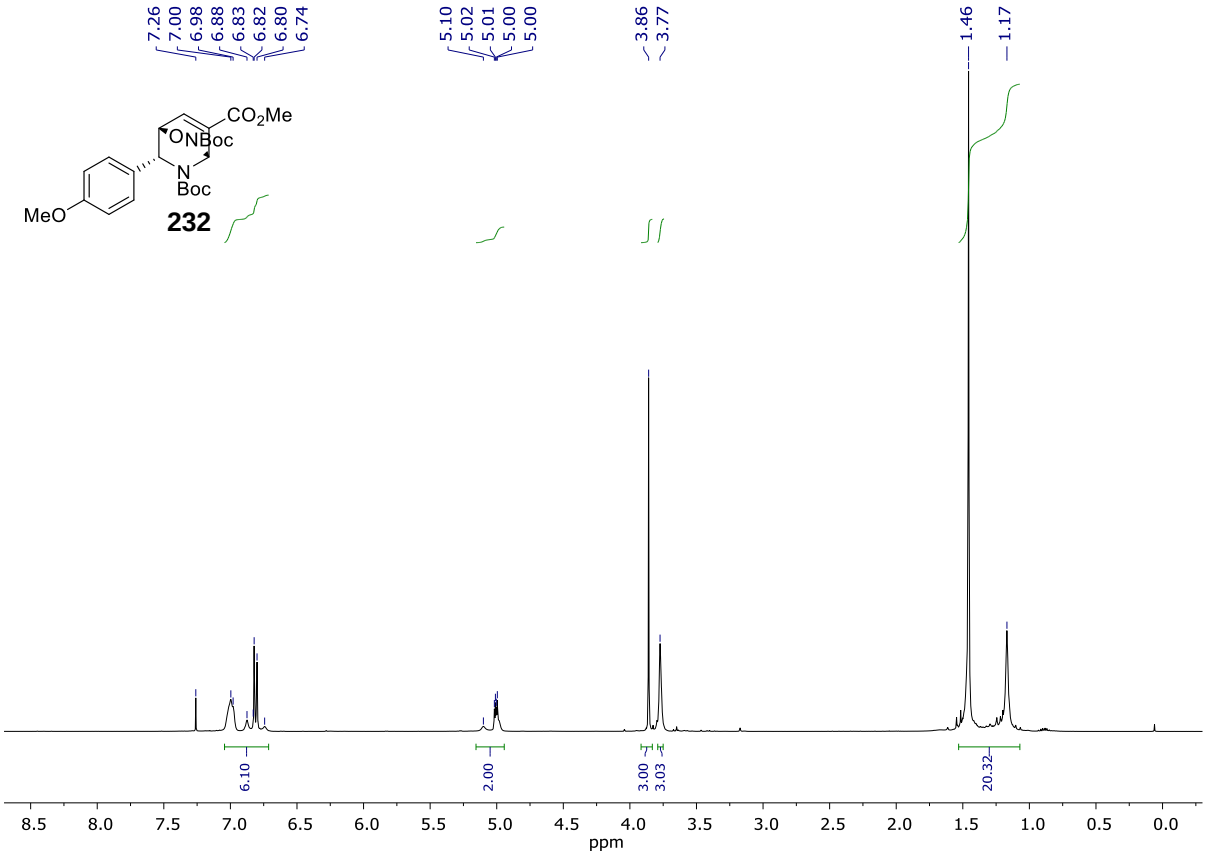
^{13}C NMR (101 MHz, $CDCl_3$)



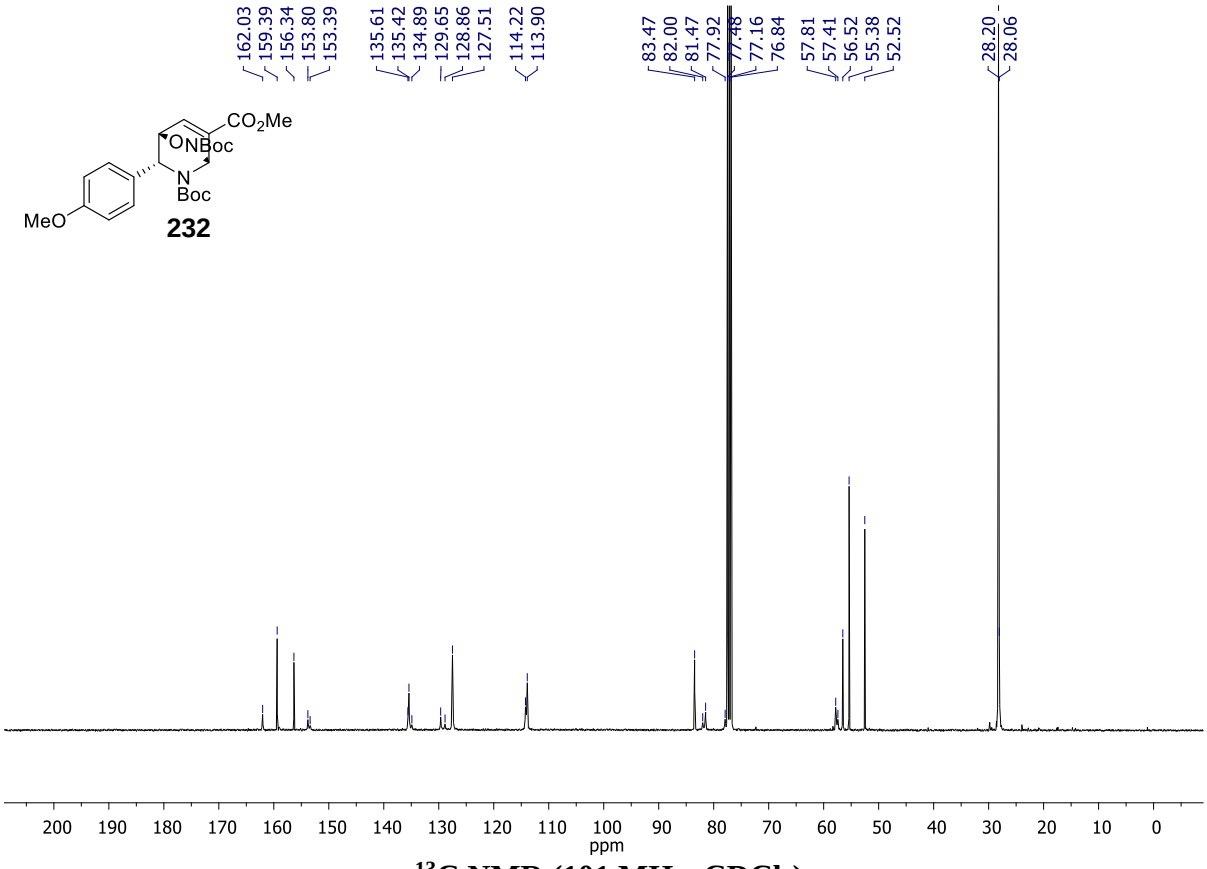
^{1}H NMR (400 MHz, DMF-d$_7$, 80 °C)



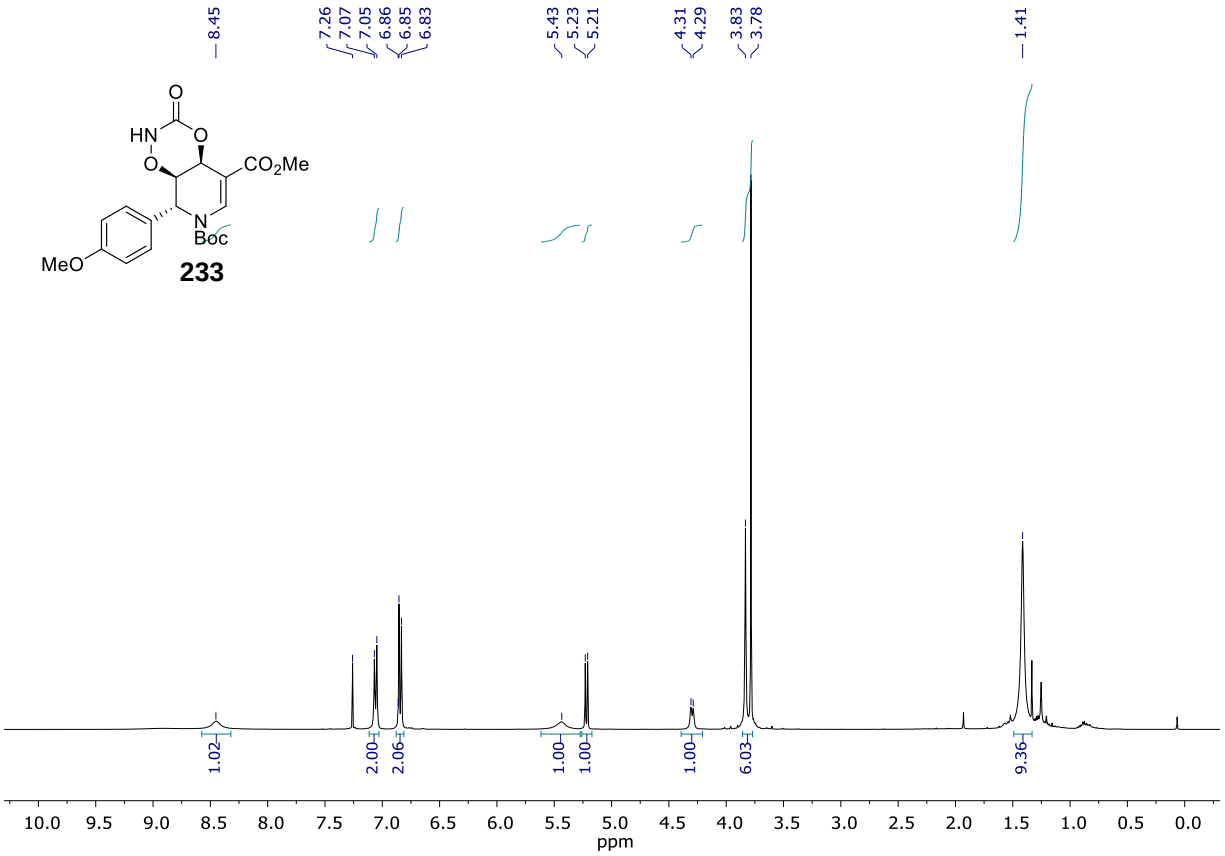
^{13}C NMR (101 MHz, C$_6$D$_6$, 70 °C)



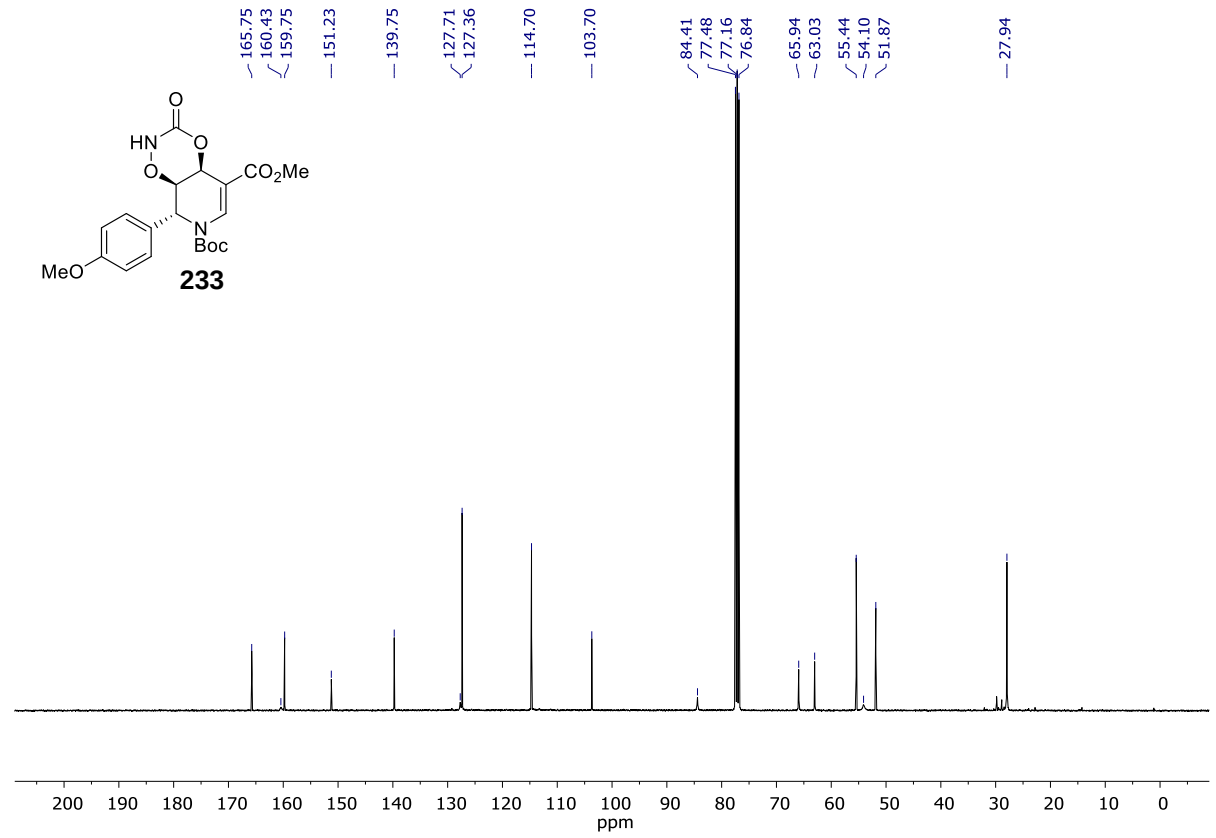
^{1}H NMR (400 MHz, $CDCl_3$)



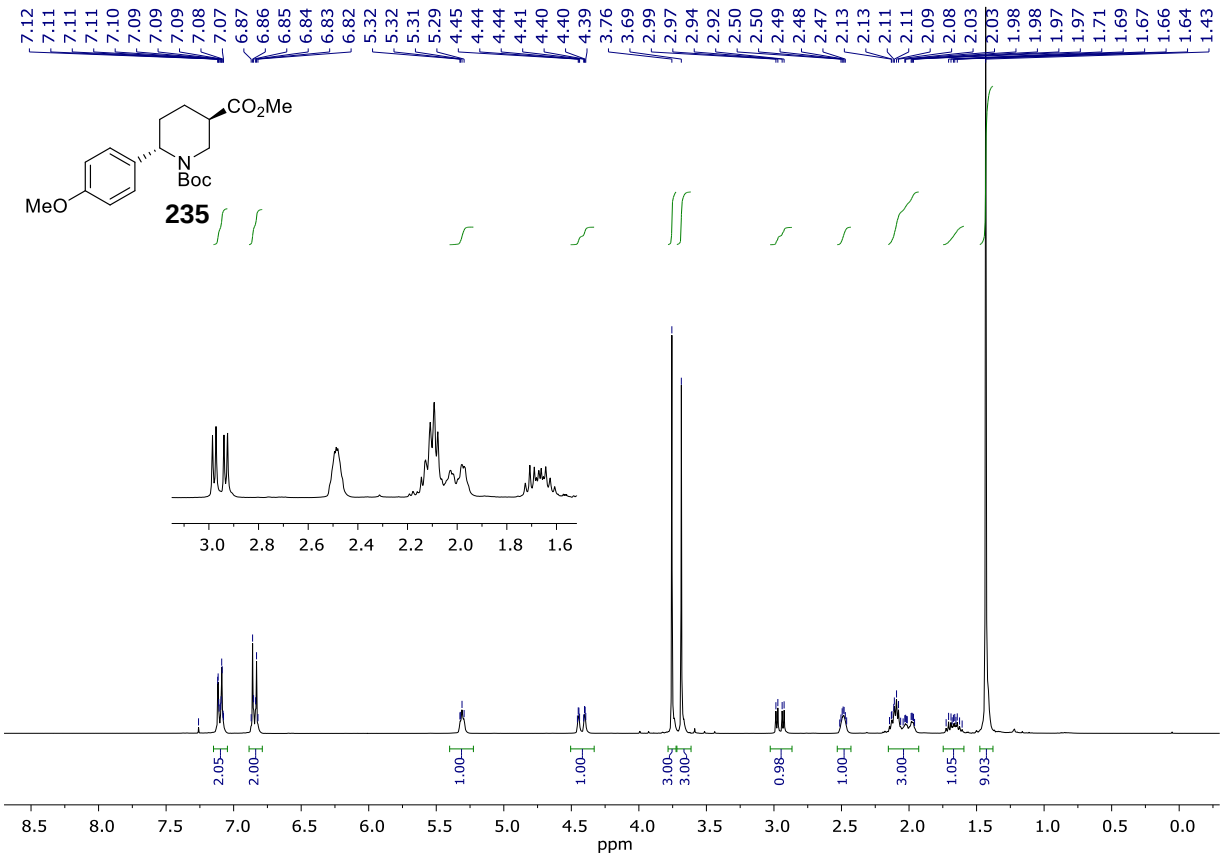
^{13}C NMR (101 MHz, $CDCl_3$)



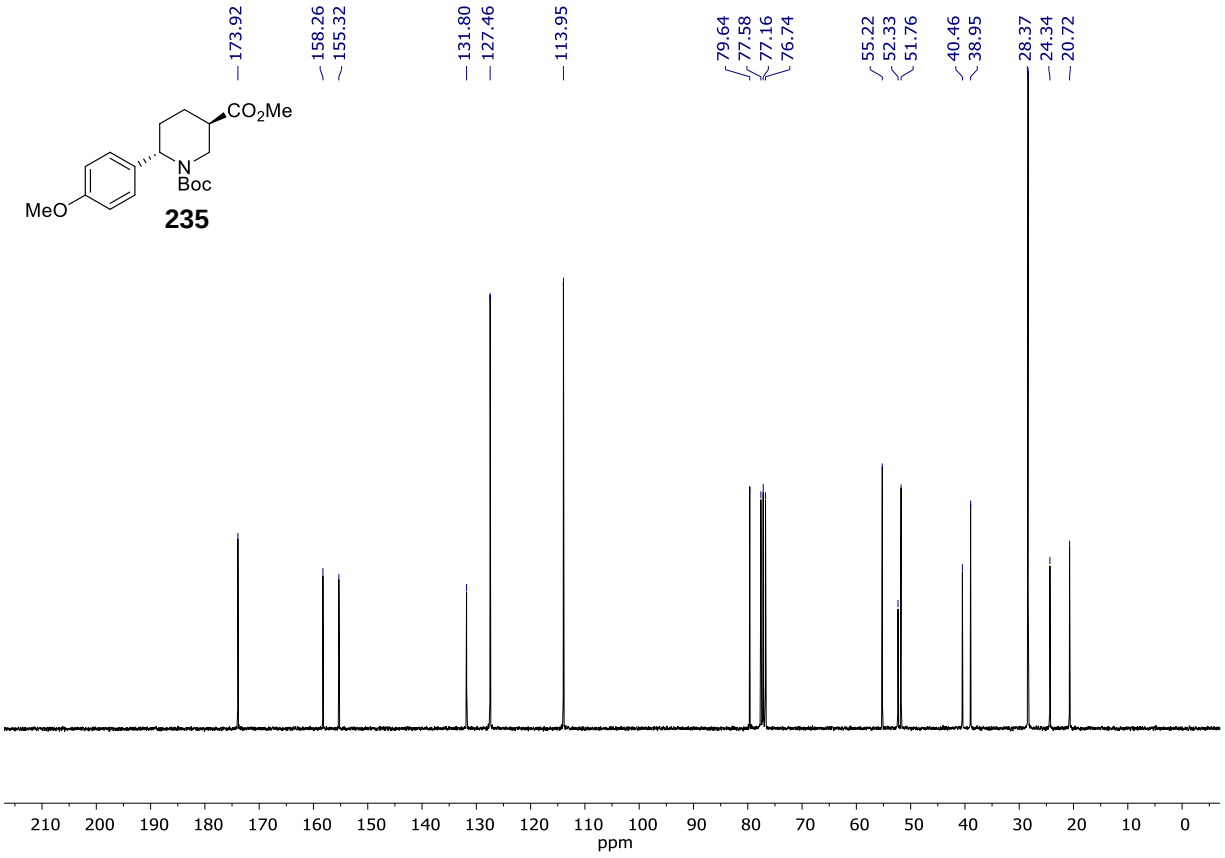
^{1}H NMR (400 MHz, $CDCl_3$)



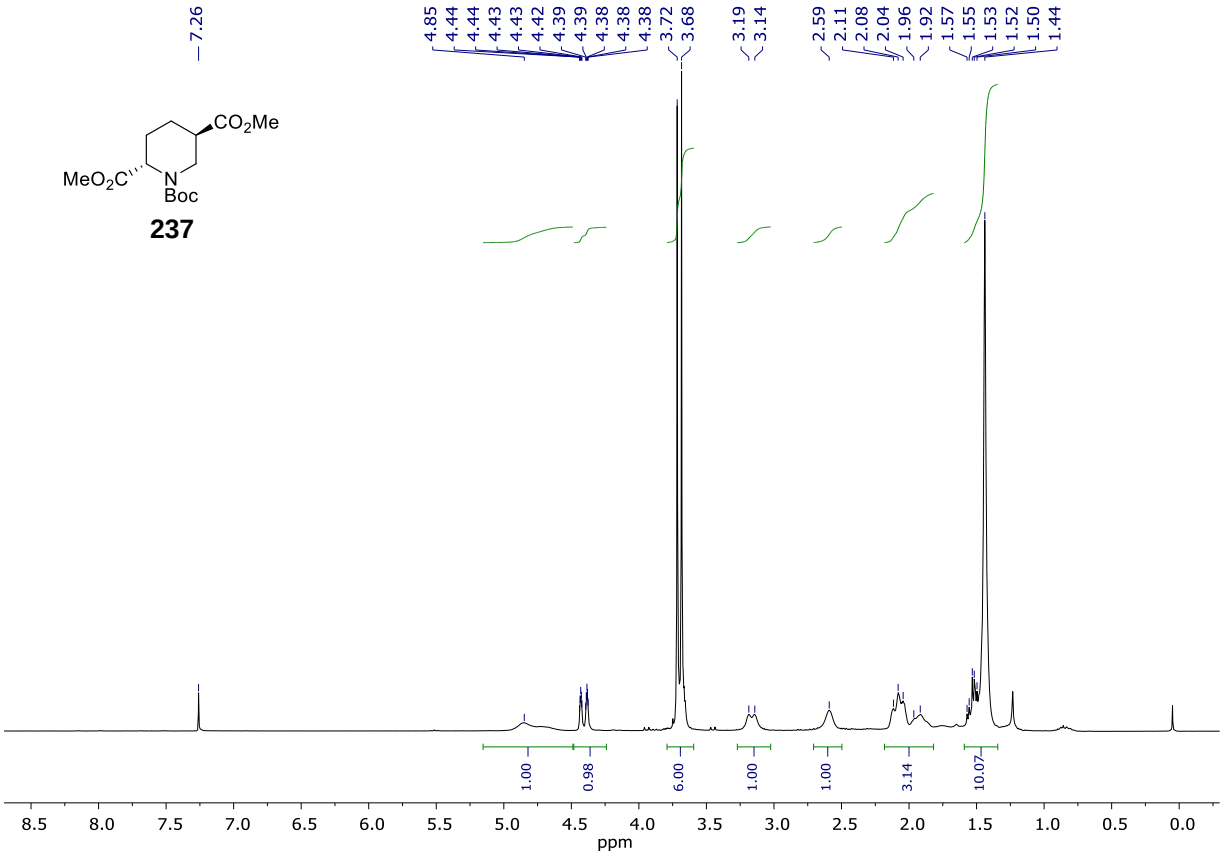
^{13}C NMR (101 MHz, $CDCl_3$)



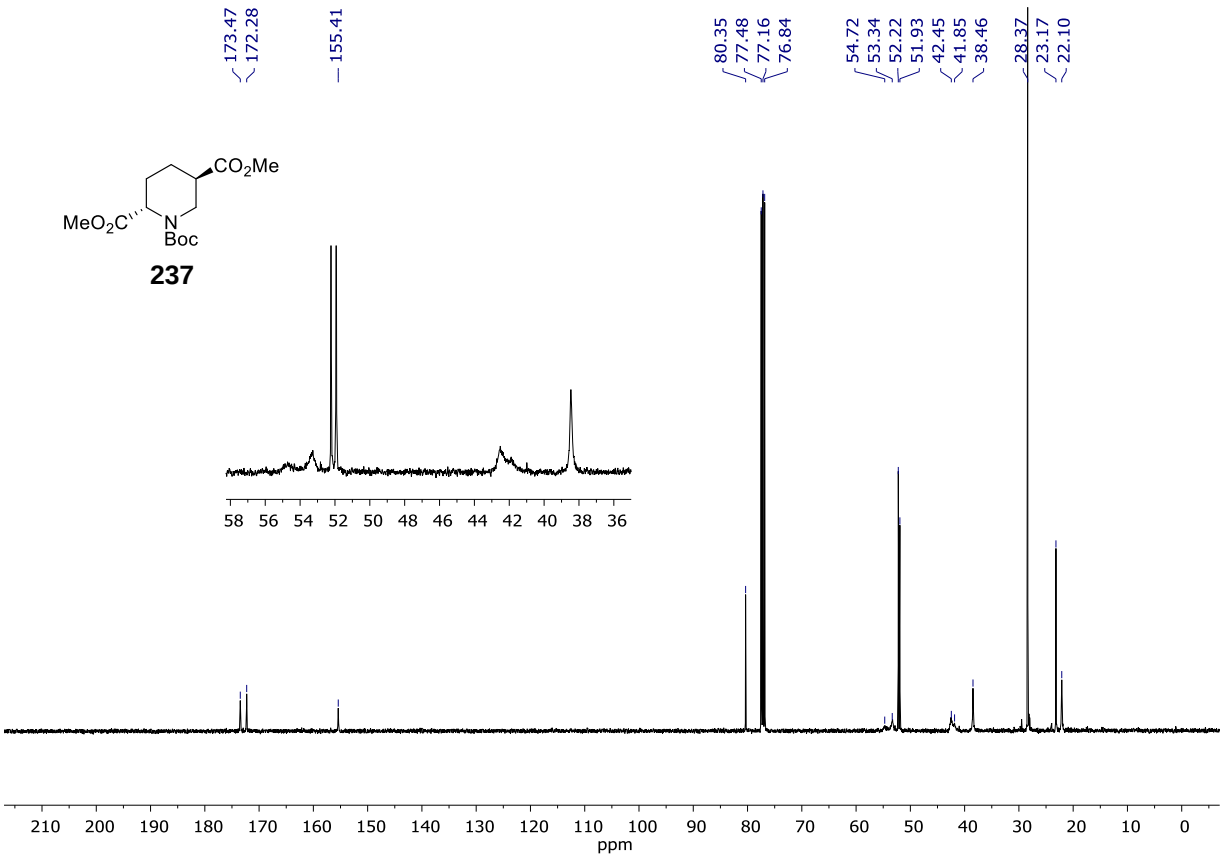
^{1}H NMR (300 MHz, $CDCl_3$)



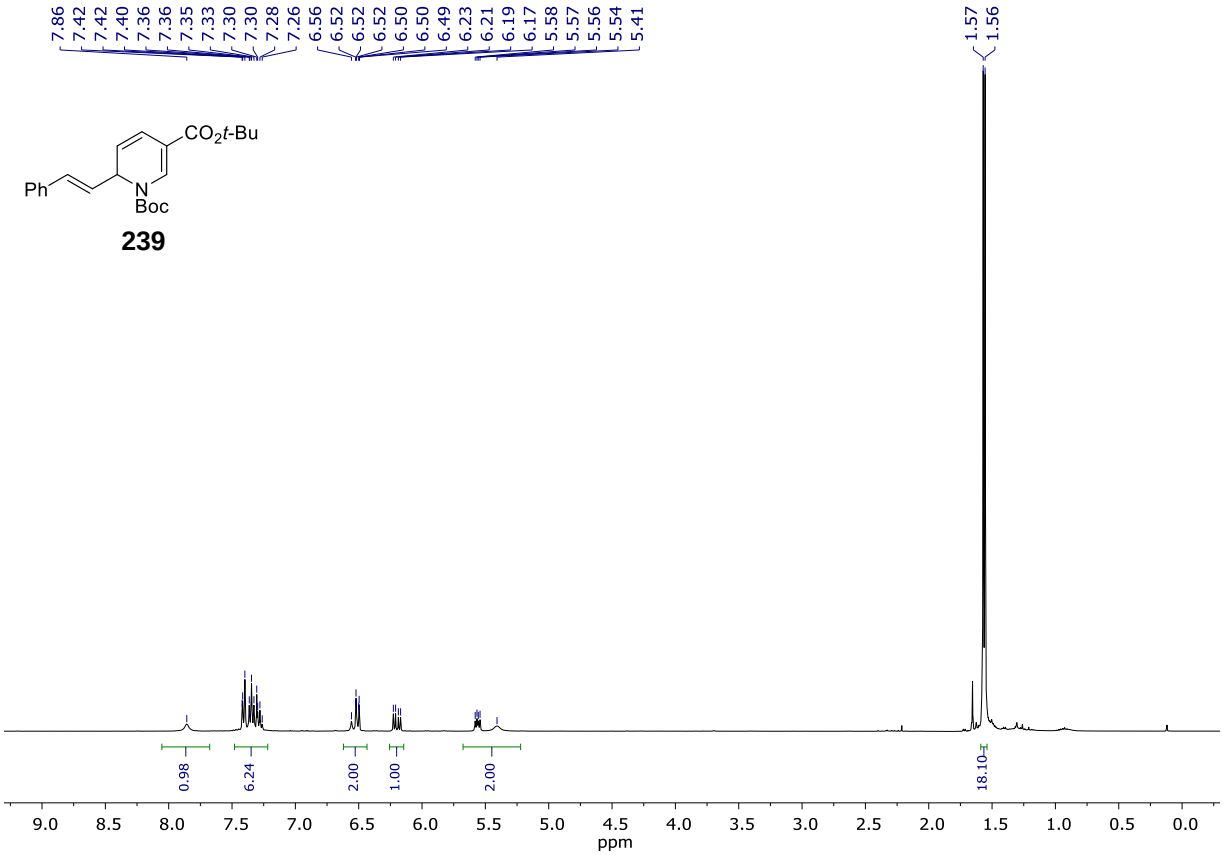
^{13}C NMR (75 MHz, $CDCl_3$)



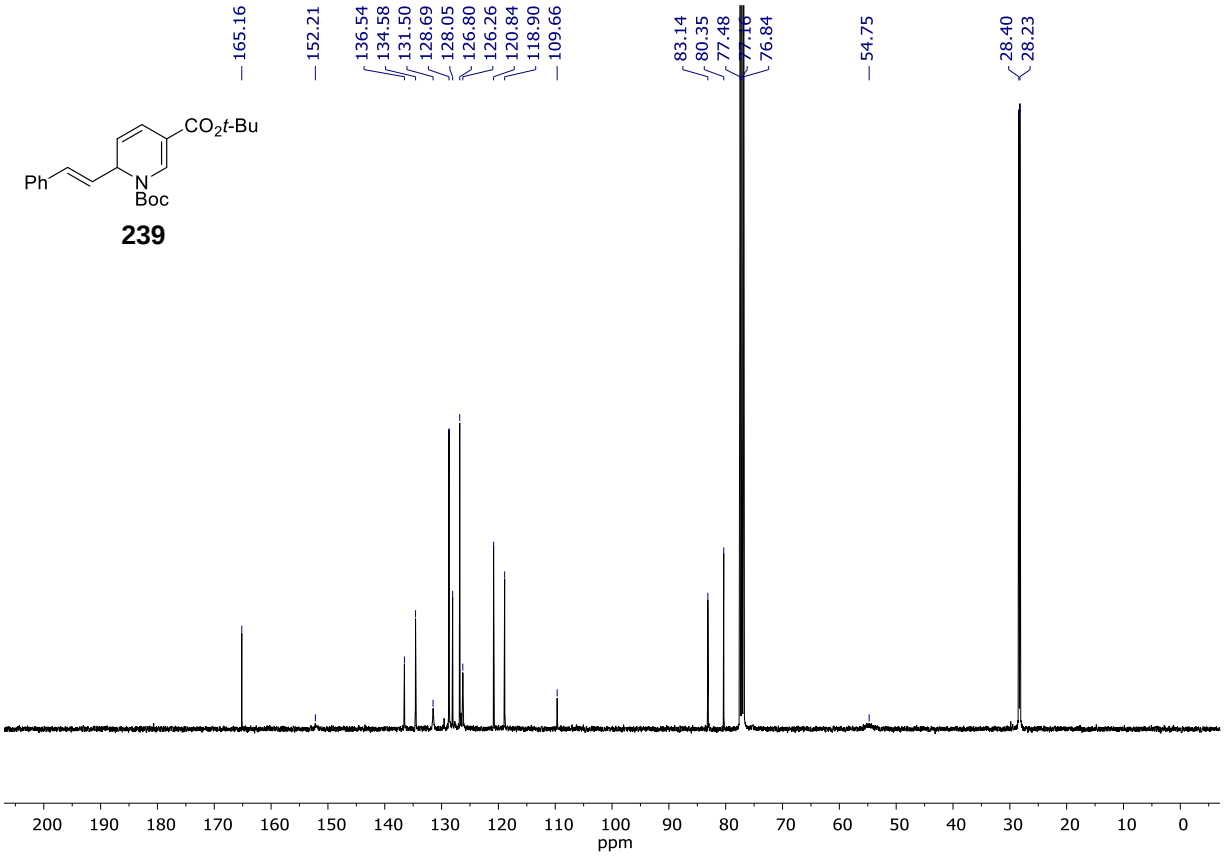
^{1}H NMR (300 MHz, $CDCl_3$)



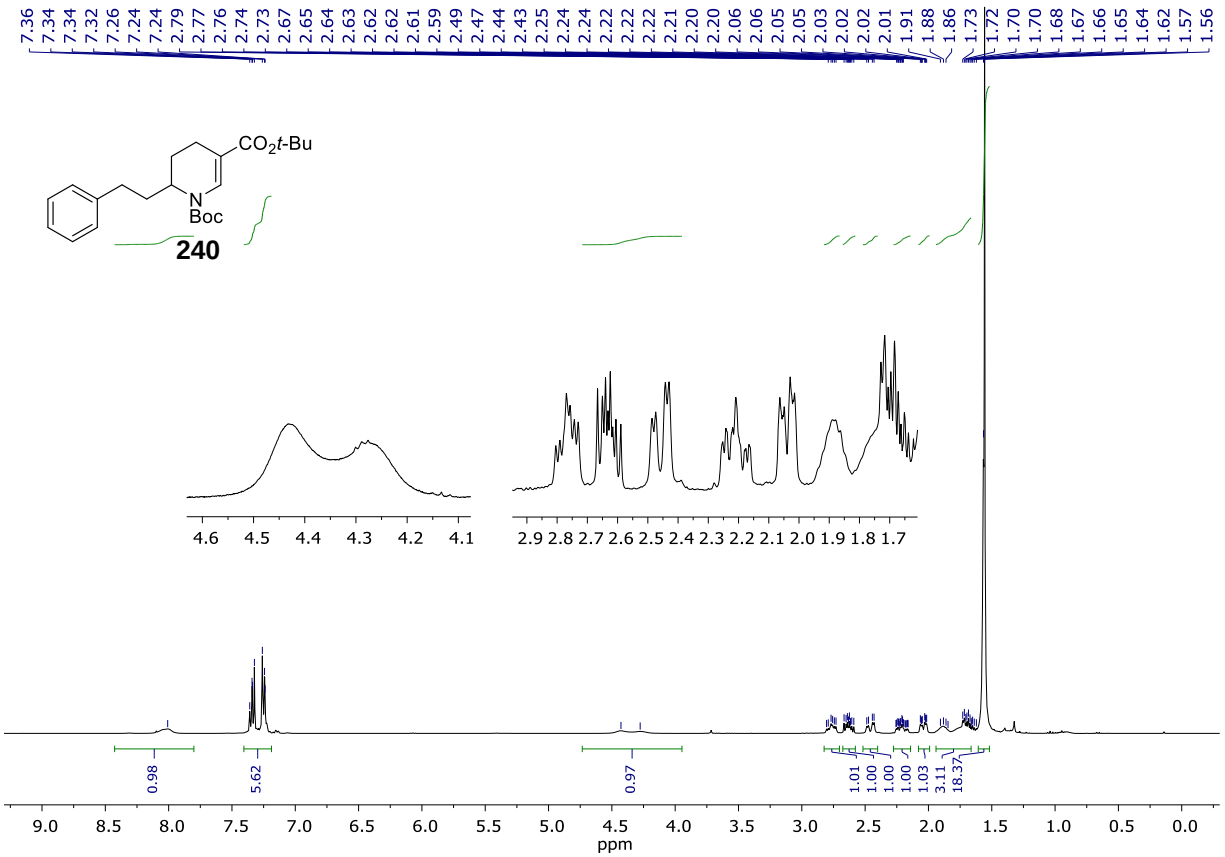
^{13}C NMR (101 MHz, $CDCl_3$)



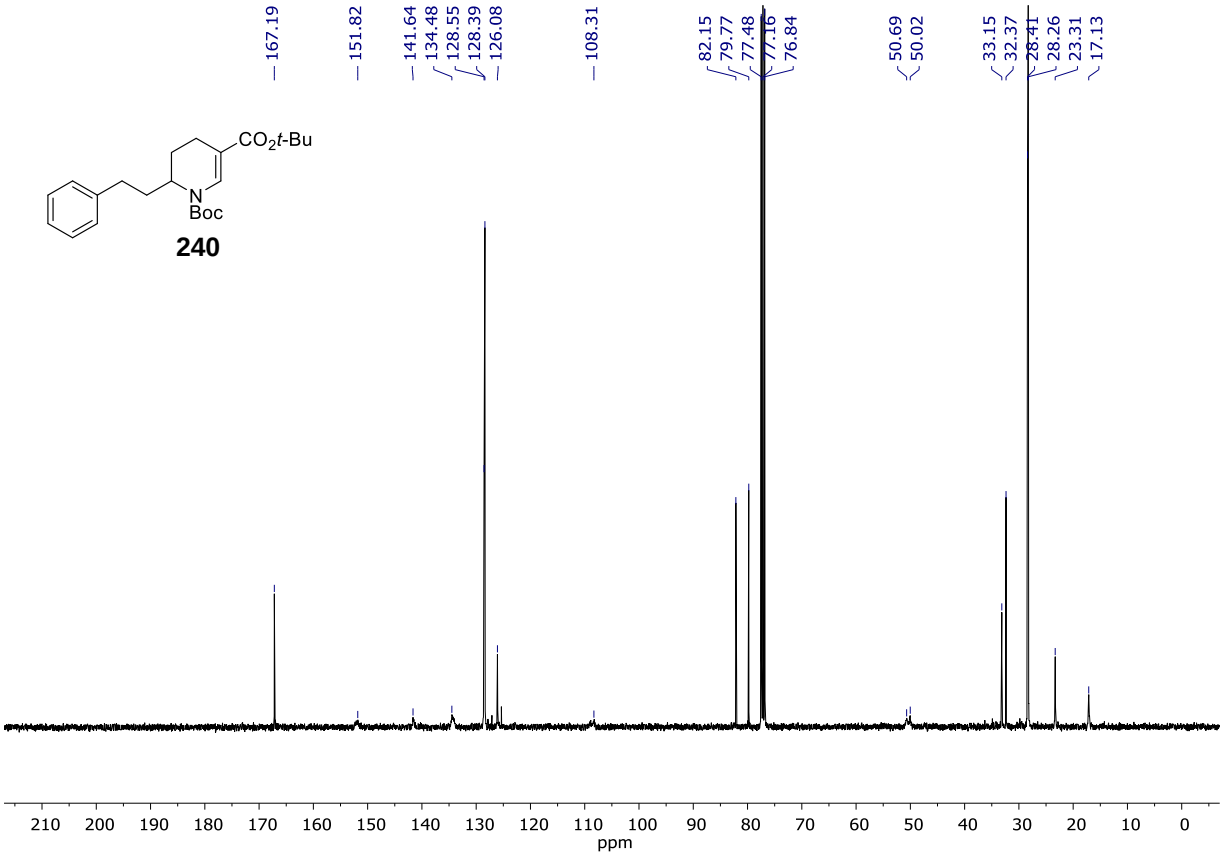
^{1}H NMR (400 MHz, $CDCl_3$)



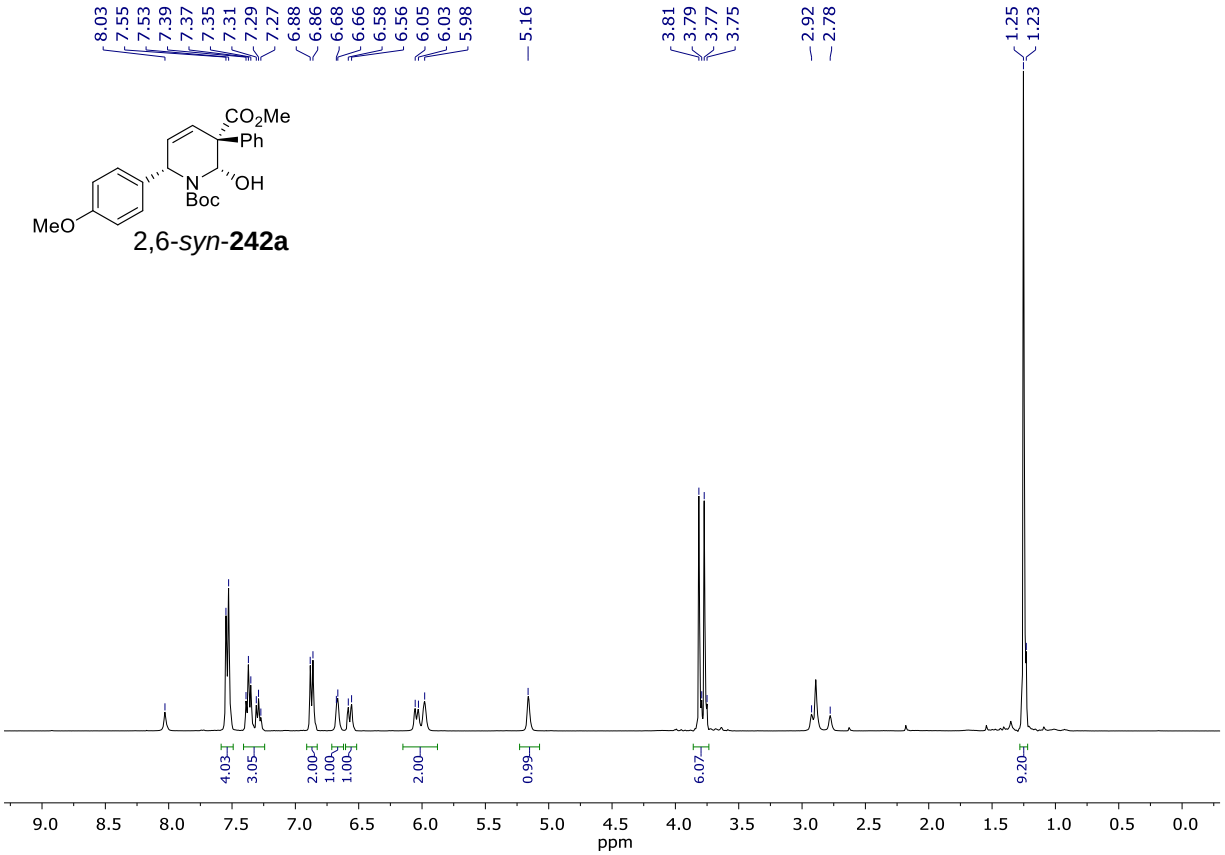
^{13}C NMR (101 MHz, $CDCl_3$)



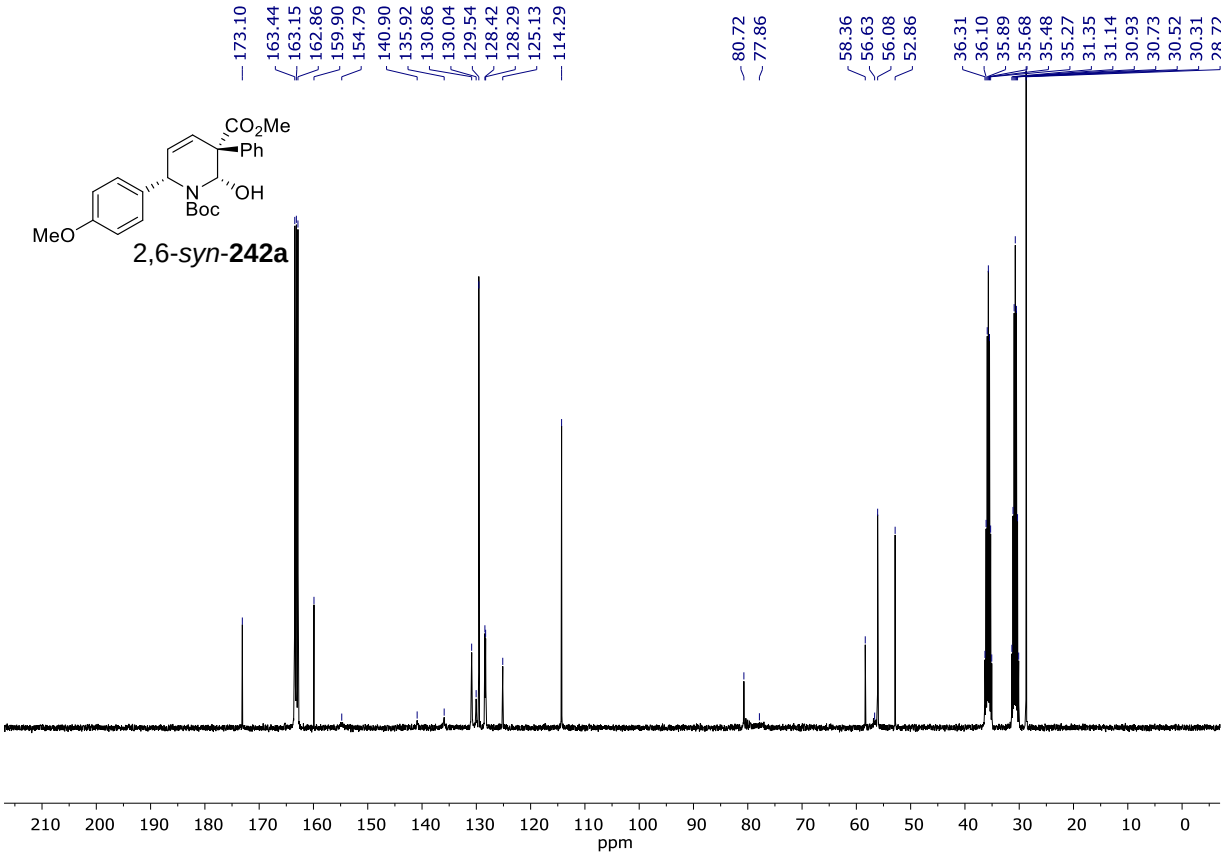
^{1}H NMR (400 MHz, $CDCl_3$)



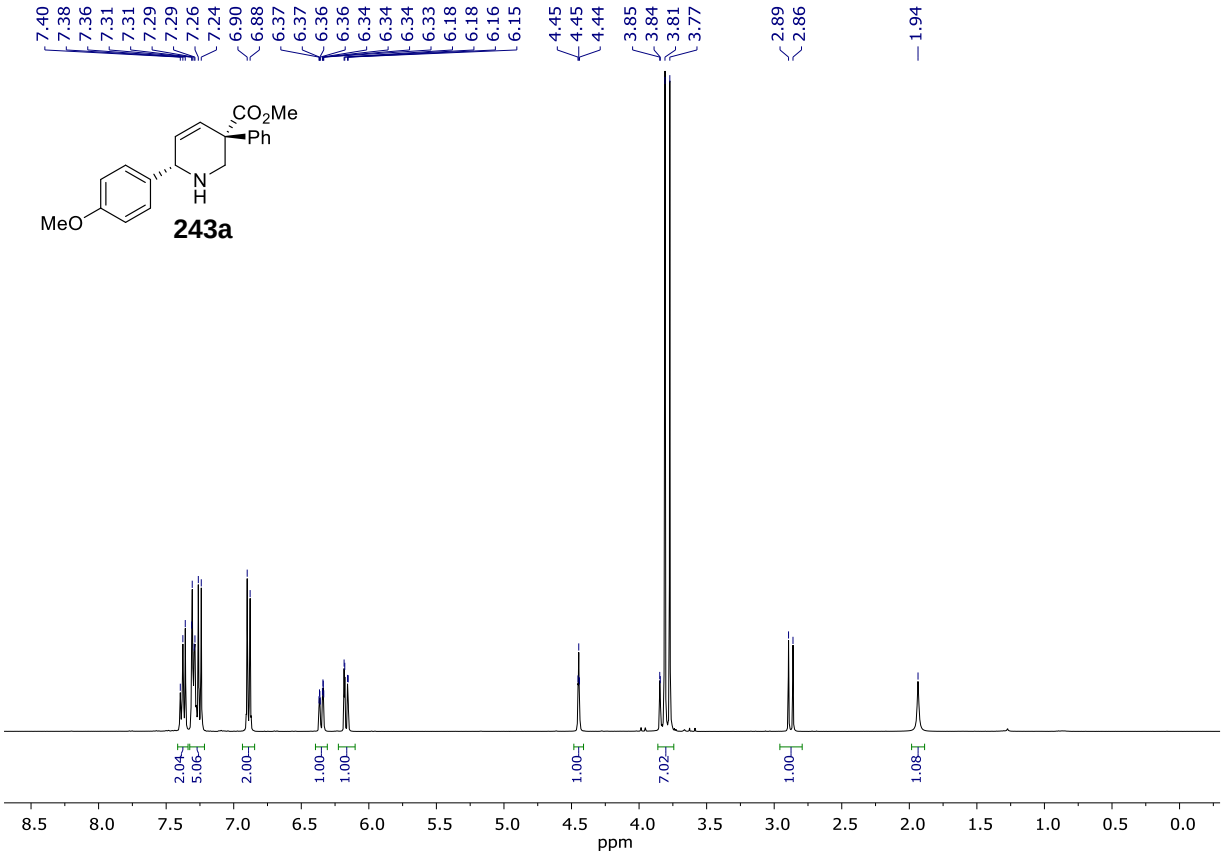
^{13}C NMR (101 MHz, $CDCl_3$)



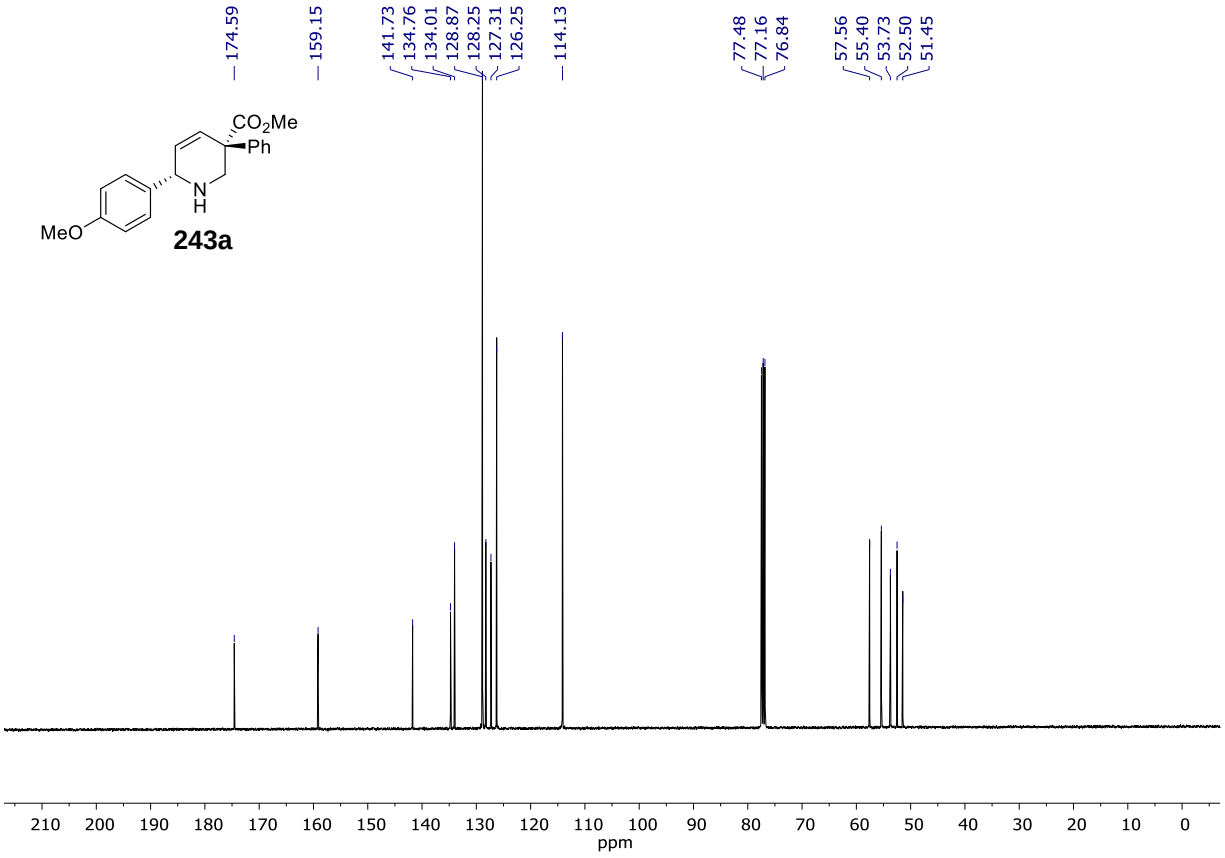
^{1}H NMR (400 MHz, DMF-d$_7$, 110 °C)



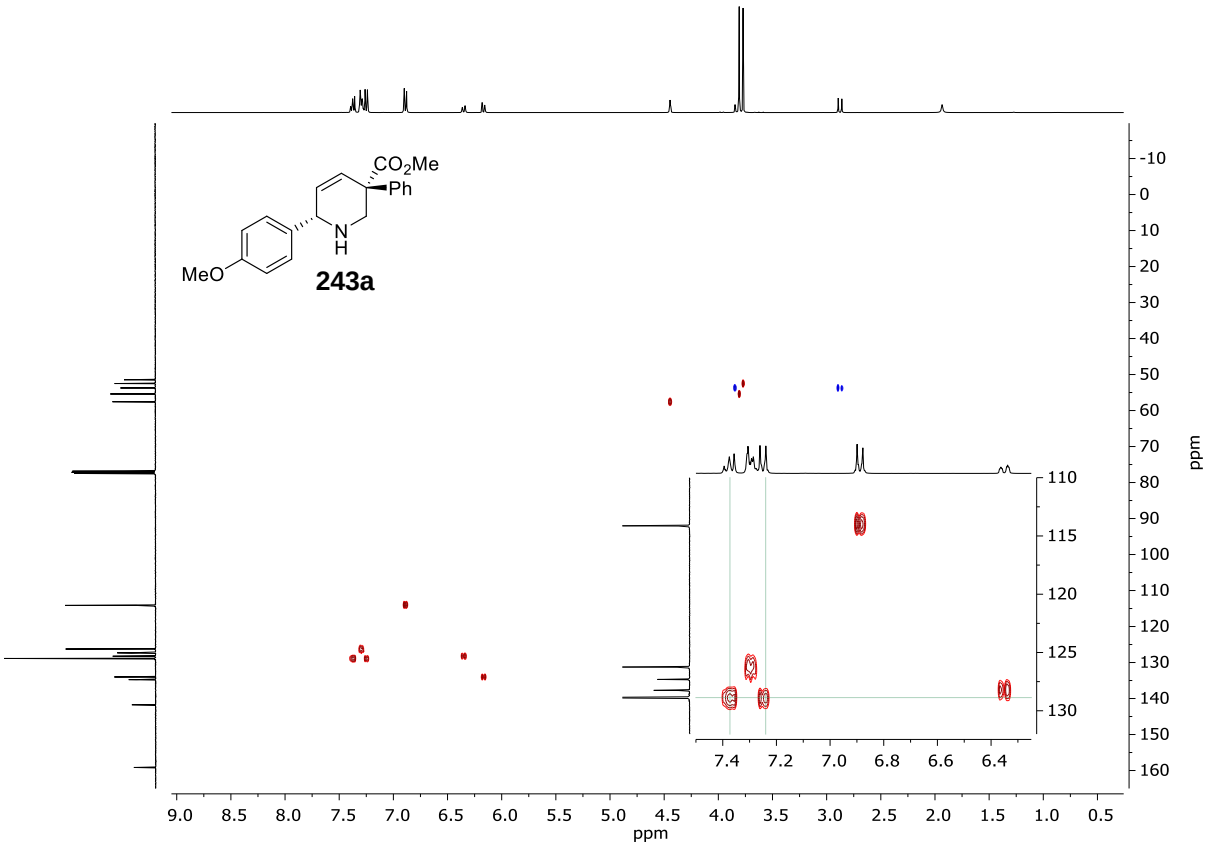
^{13}C NMR (101 MHz, DMF-d$_7$, 70 °C)



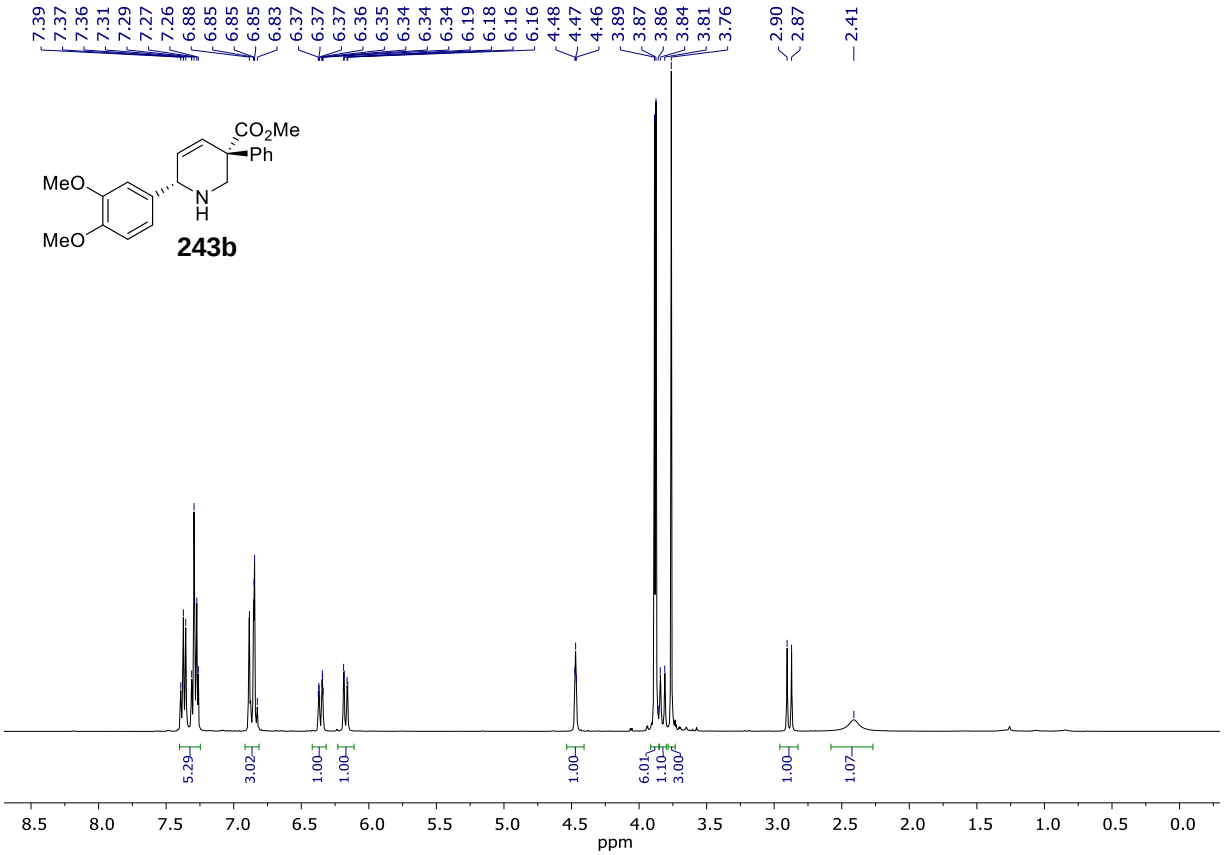
^{1}H NMR (400 MHz, $CDCl_3$)



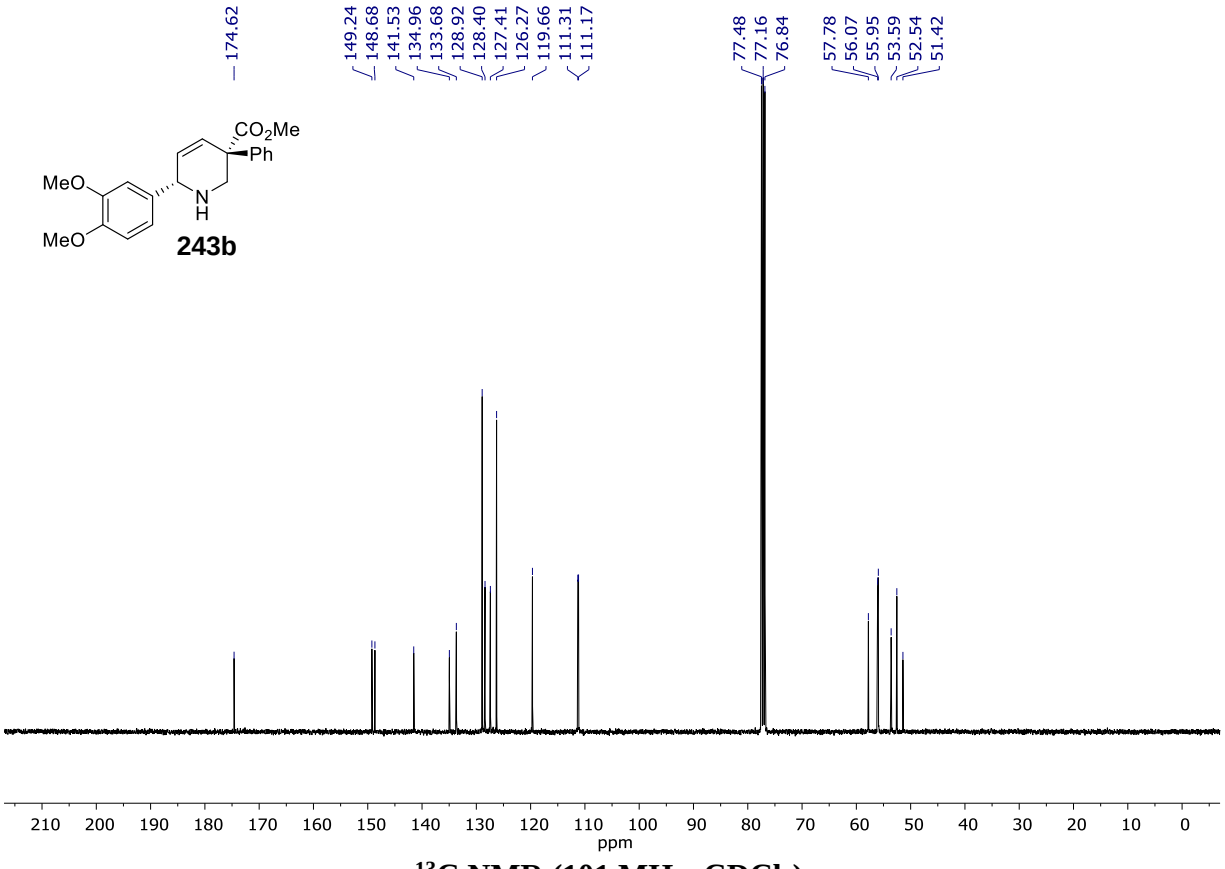
^{13}C NMR (101 MHz, $CDCl_3$)



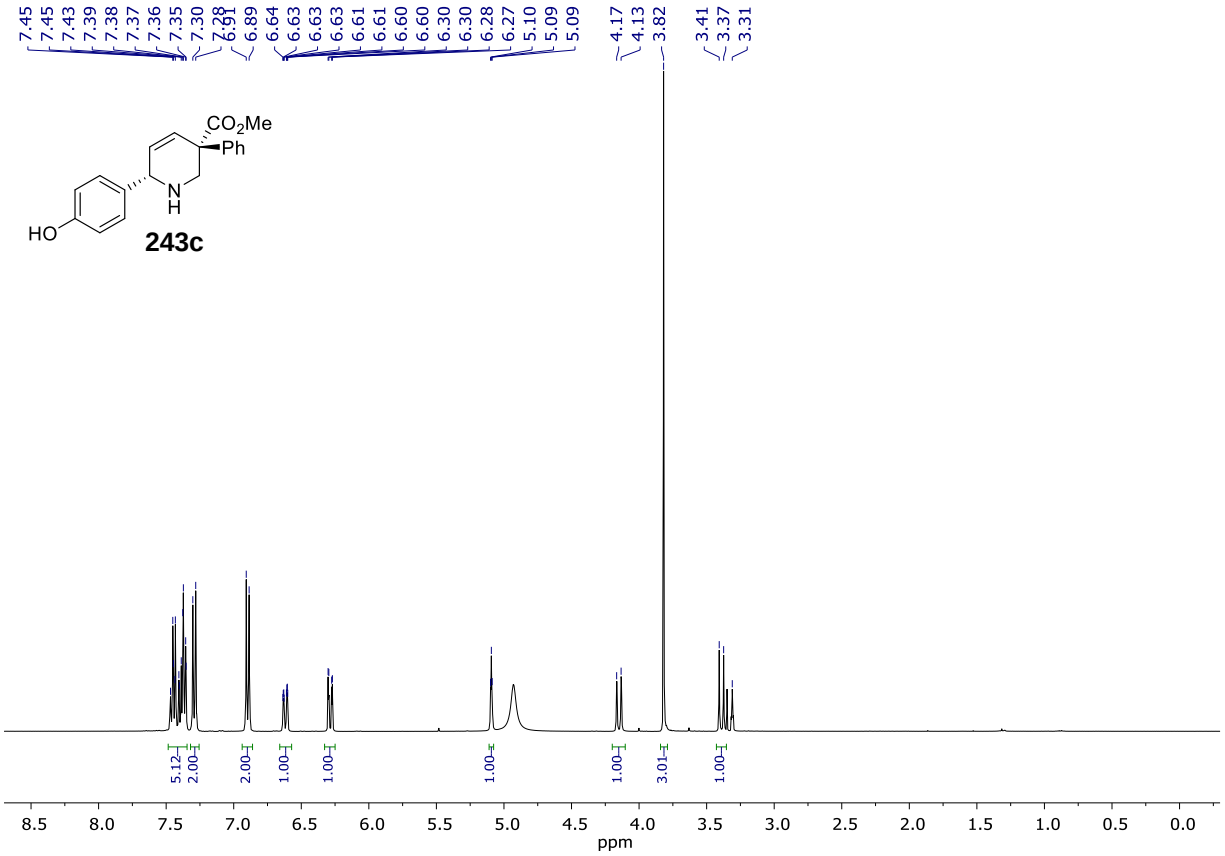
HSQC ((400, 101) MHz, $CDCl_3$)



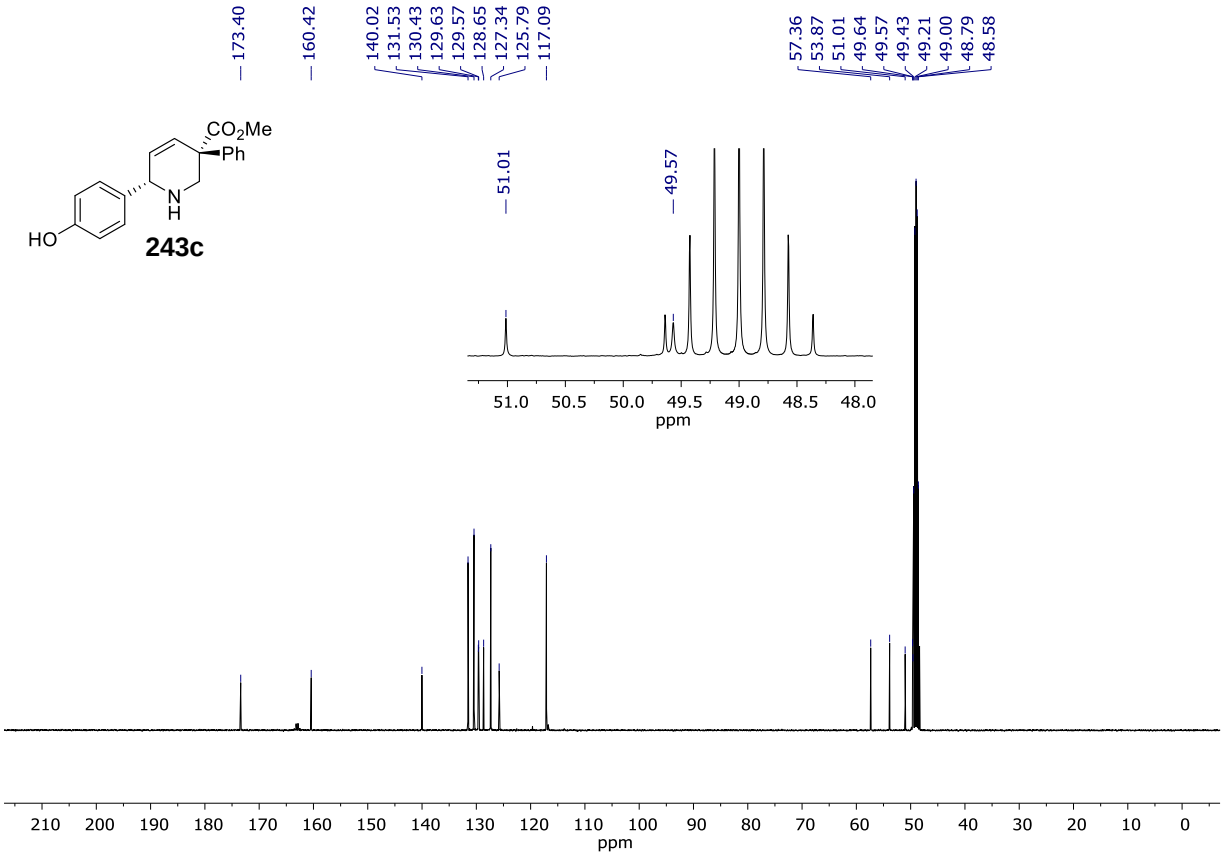
^{1}H NMR (400 MHz, $CDCl_3$)



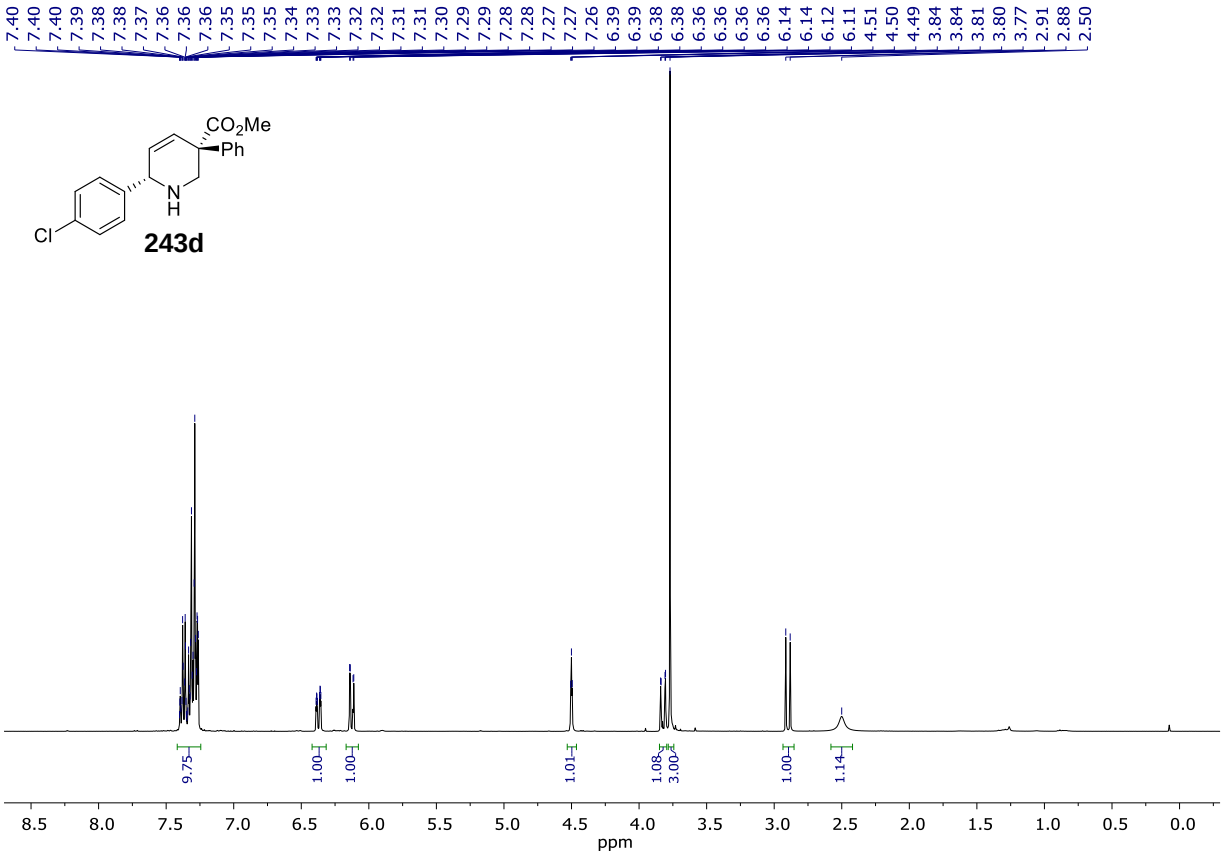
^{13}C NMR (101 MHz, $CDCl_3$)



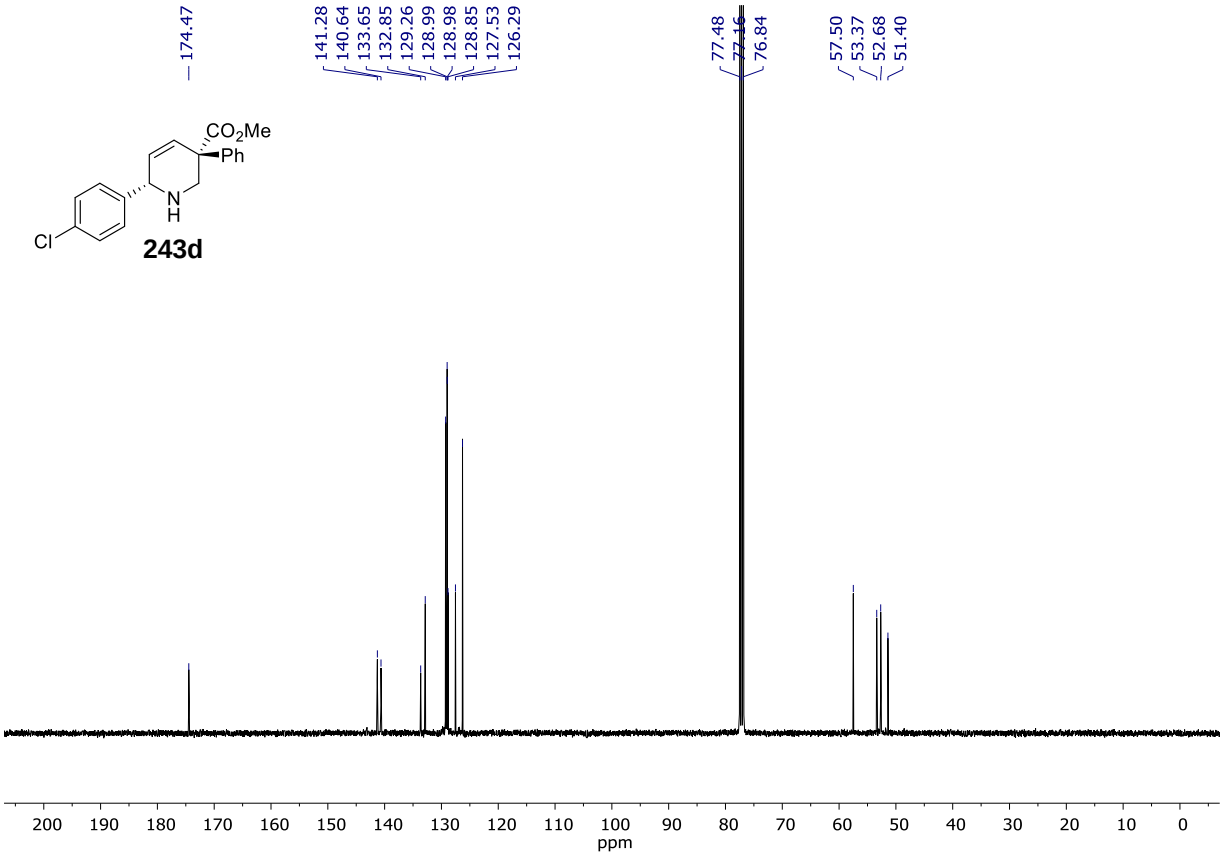
^{1}H NMR (400 MHz, methanol-d_4)



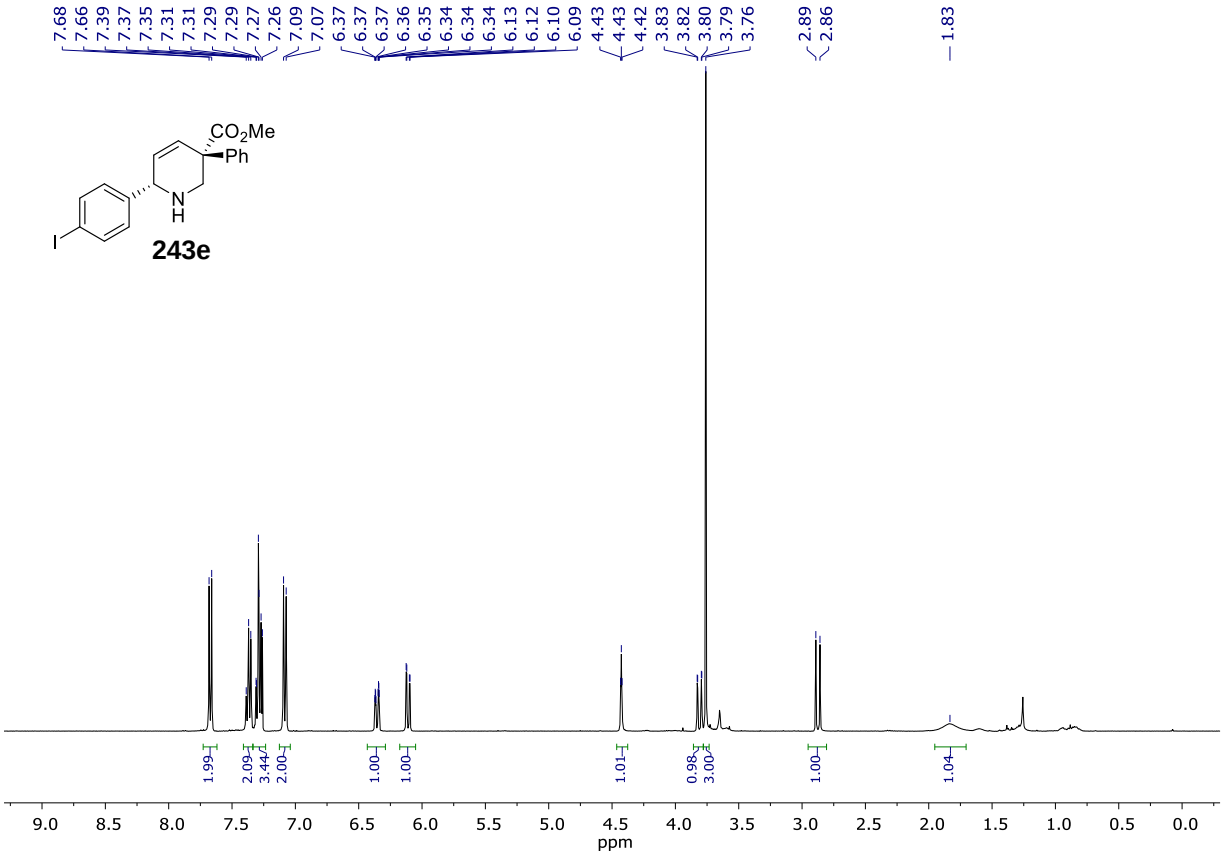
^{13}C NMR (101 MHz, methanol-d_4)



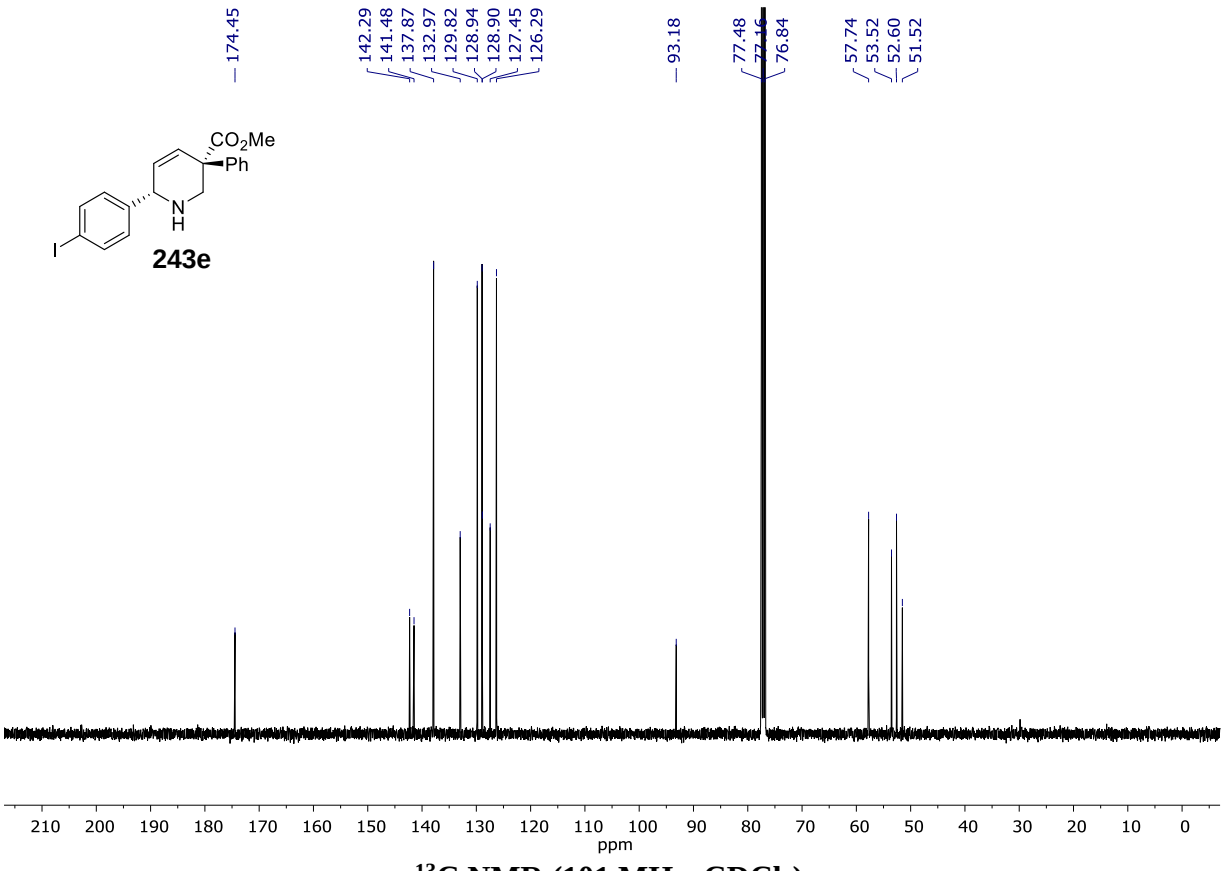
^{1}H NMR (400 MHz, $CDCl_3$)



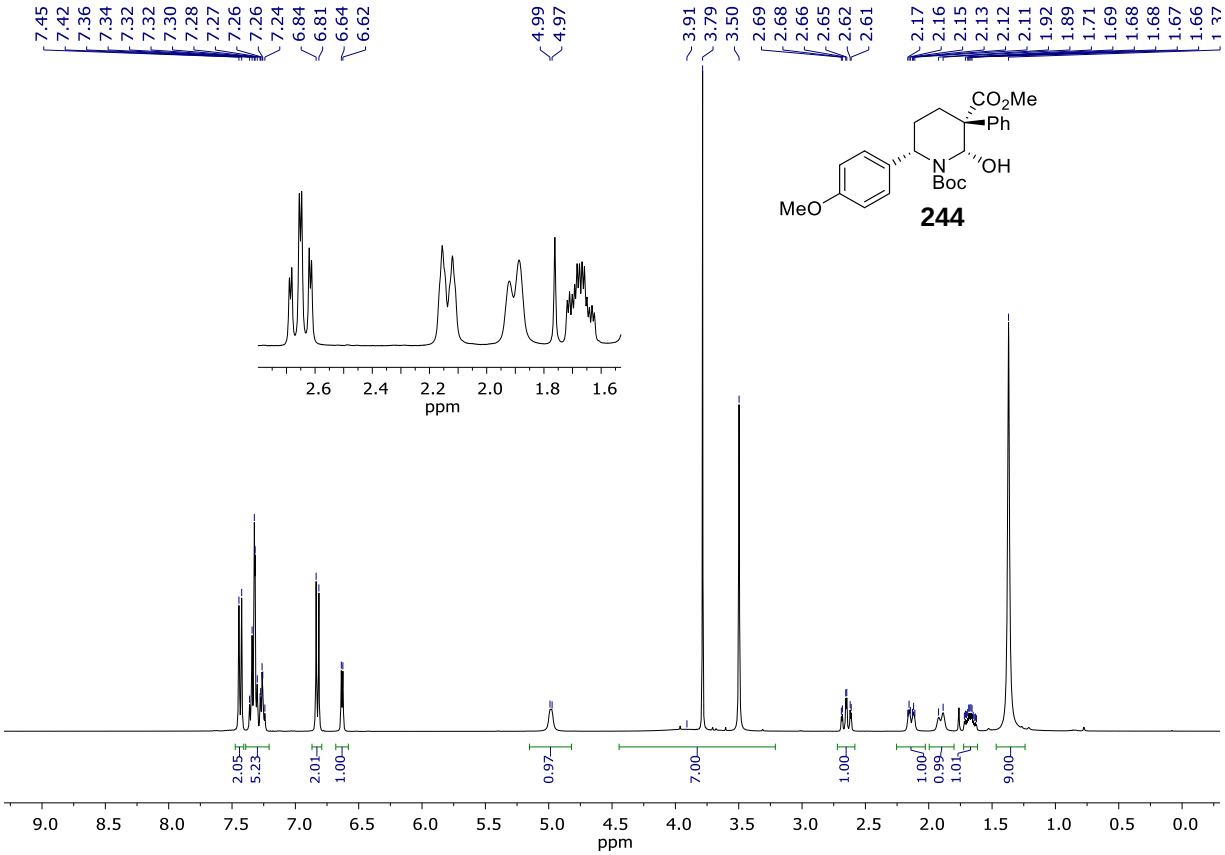
^{13}C NMR (101 MHz, $CDCl_3$)



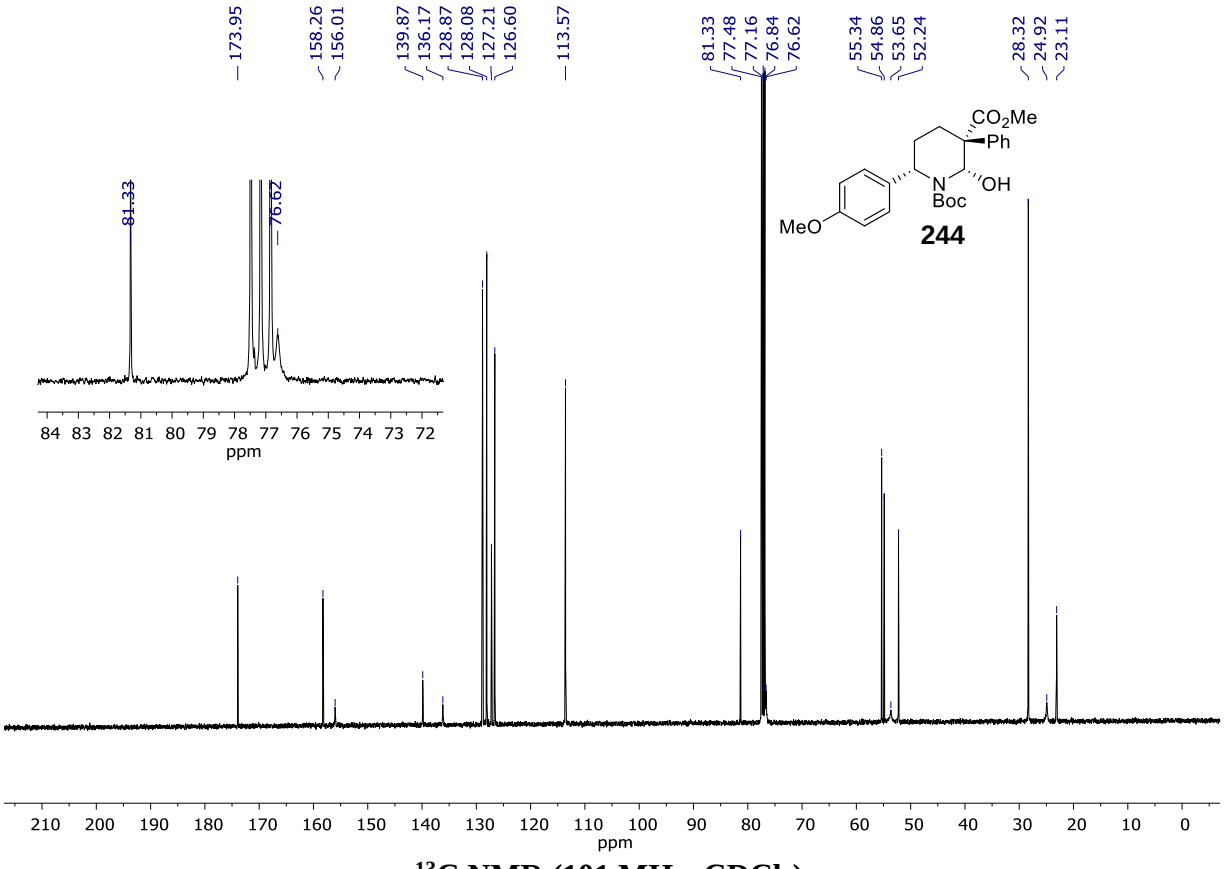
^{1}H NMR (400 MHz, $CDCl_3$)



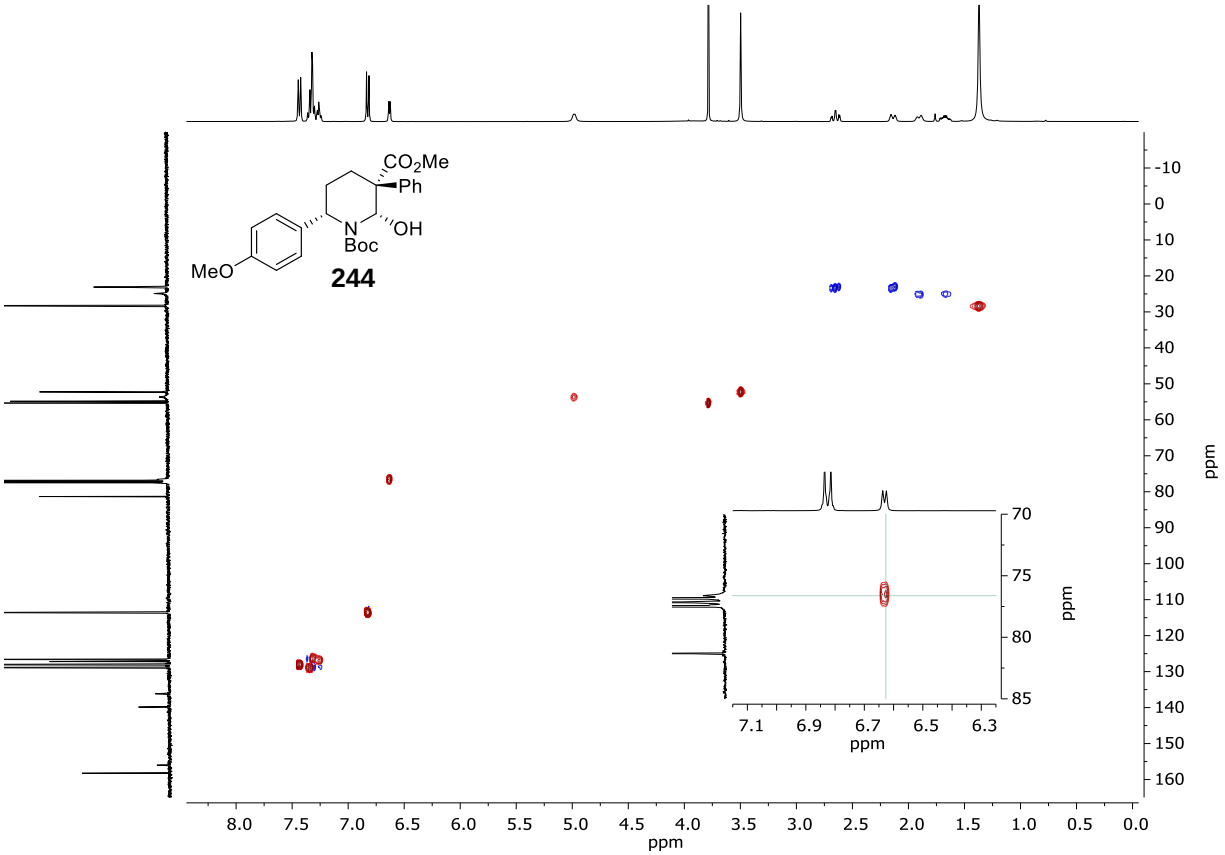
^{13}C NMR (101 MHz, $CDCl_3$)



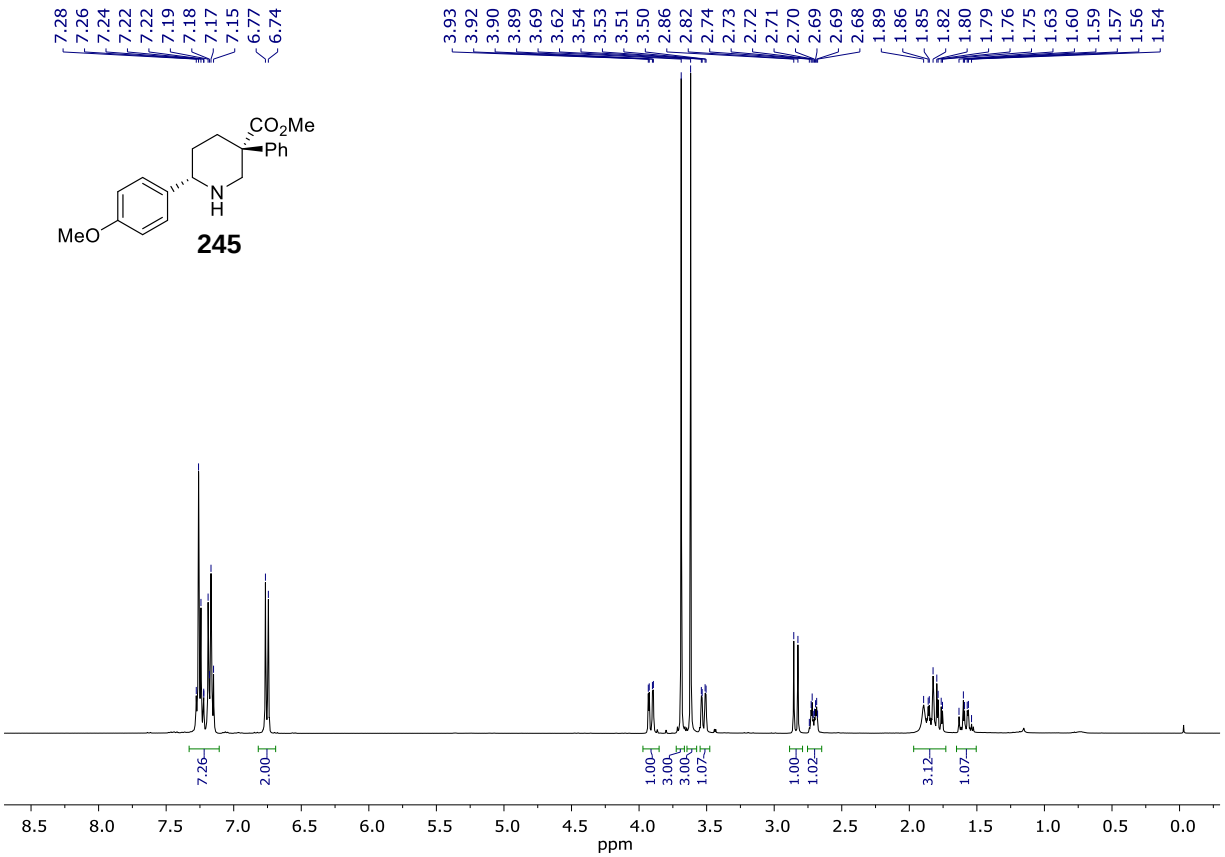
^{1}H NMR (400 MHz, $CDCl_3$)



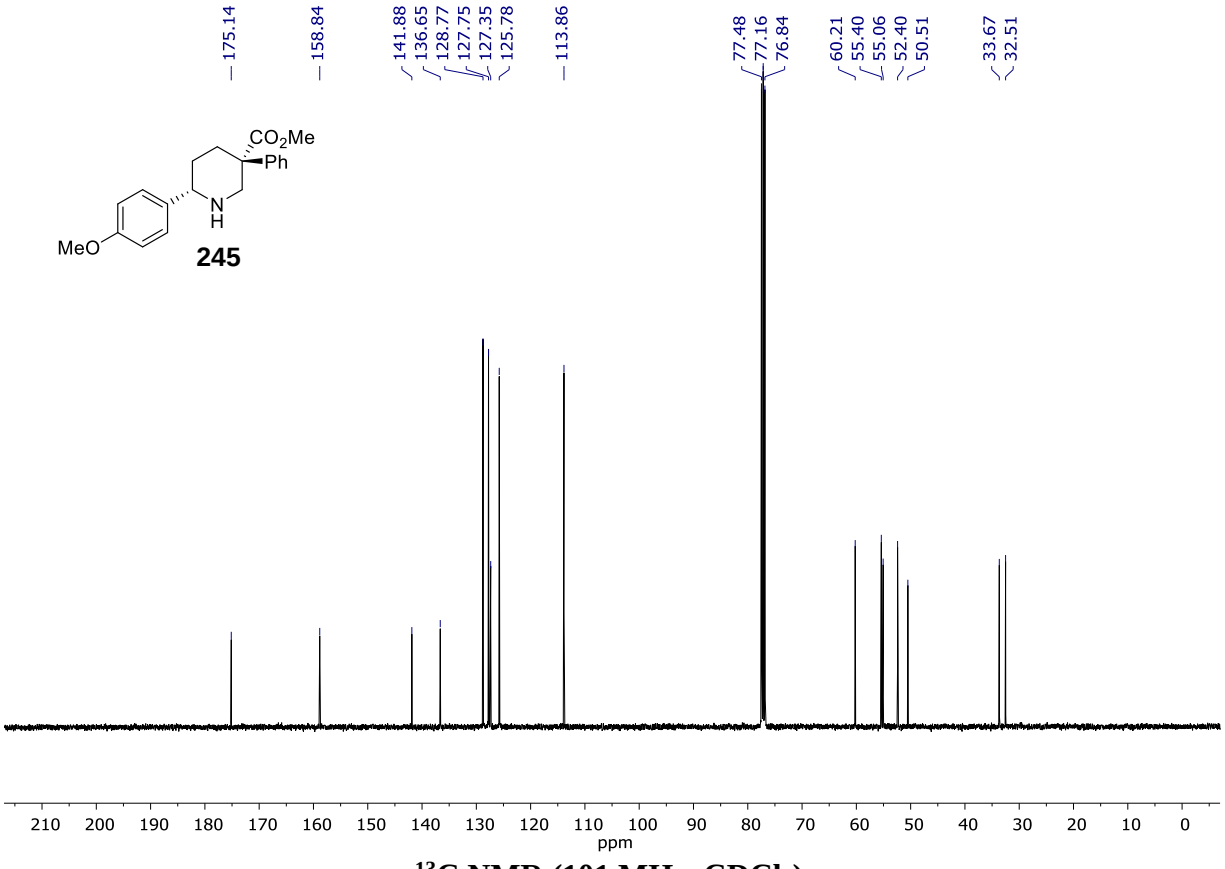
^{13}C NMR (101 MHz, $CDCl_3$)



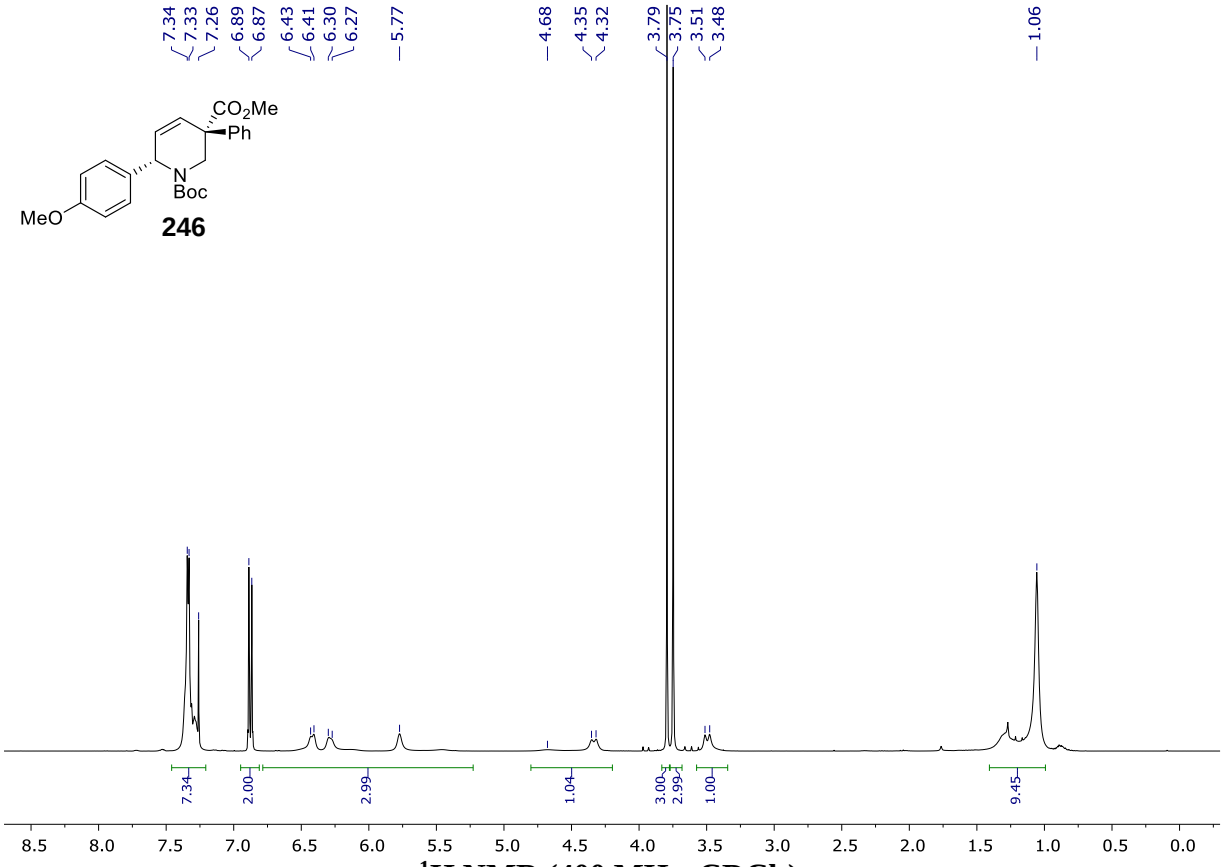
HSQC ((400, 101) MHz, $CDCl_3$)



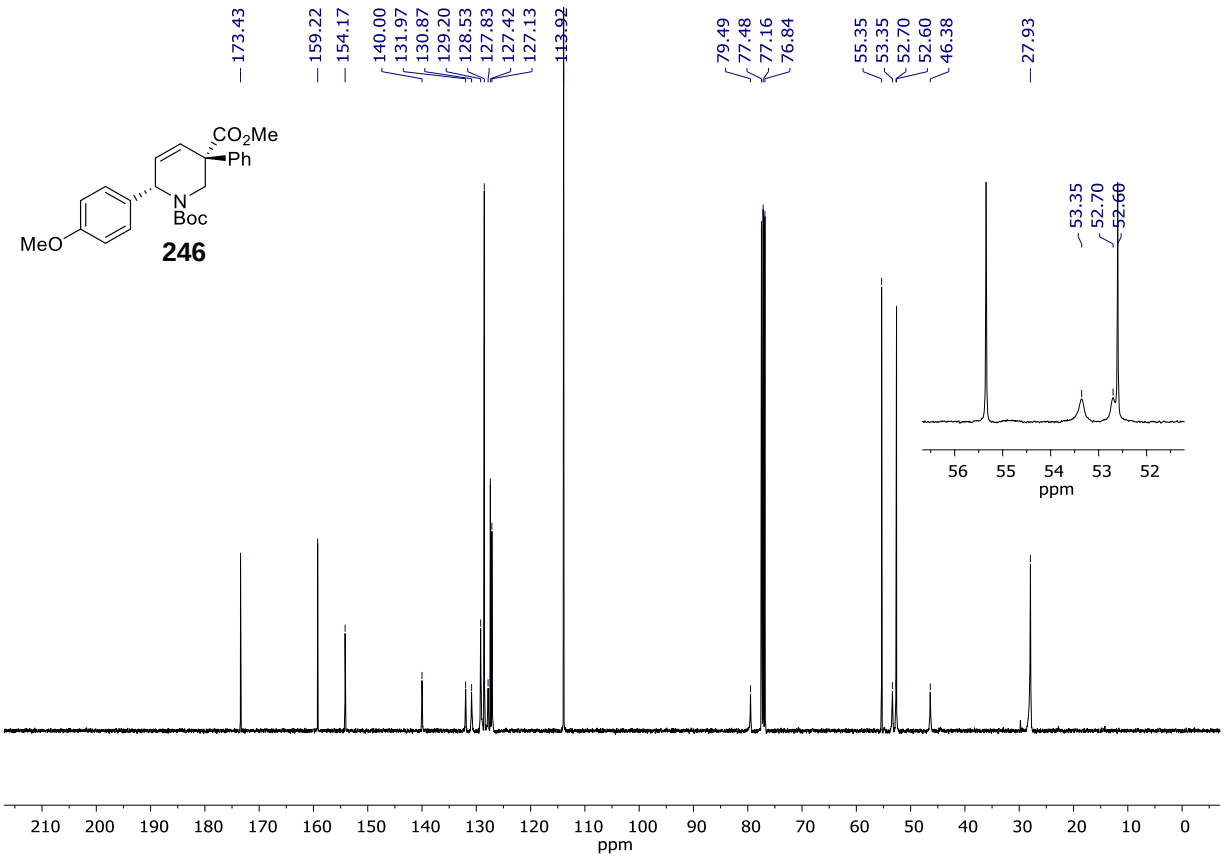
^{1}H NMR (400 MHz, $CDCl_3$)



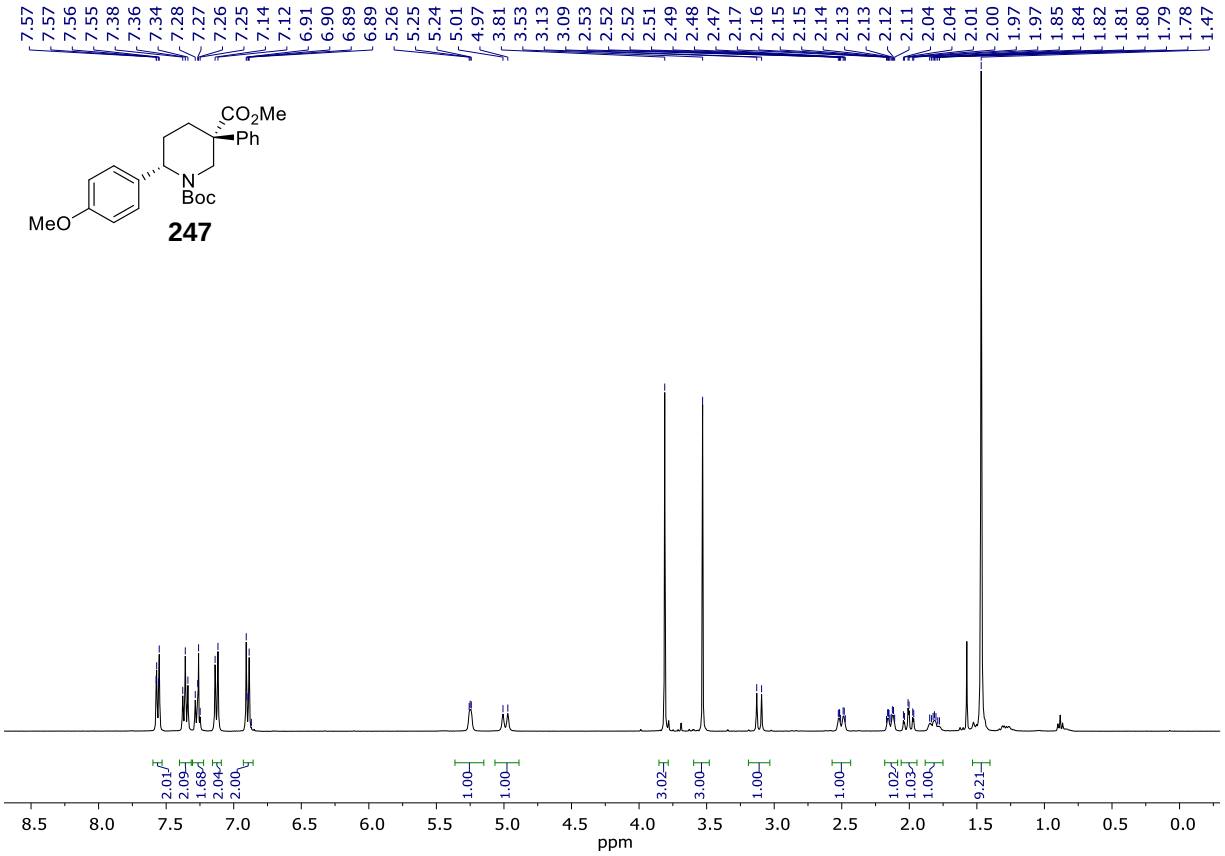
^{13}C NMR (101 MHz, $CDCl_3$)



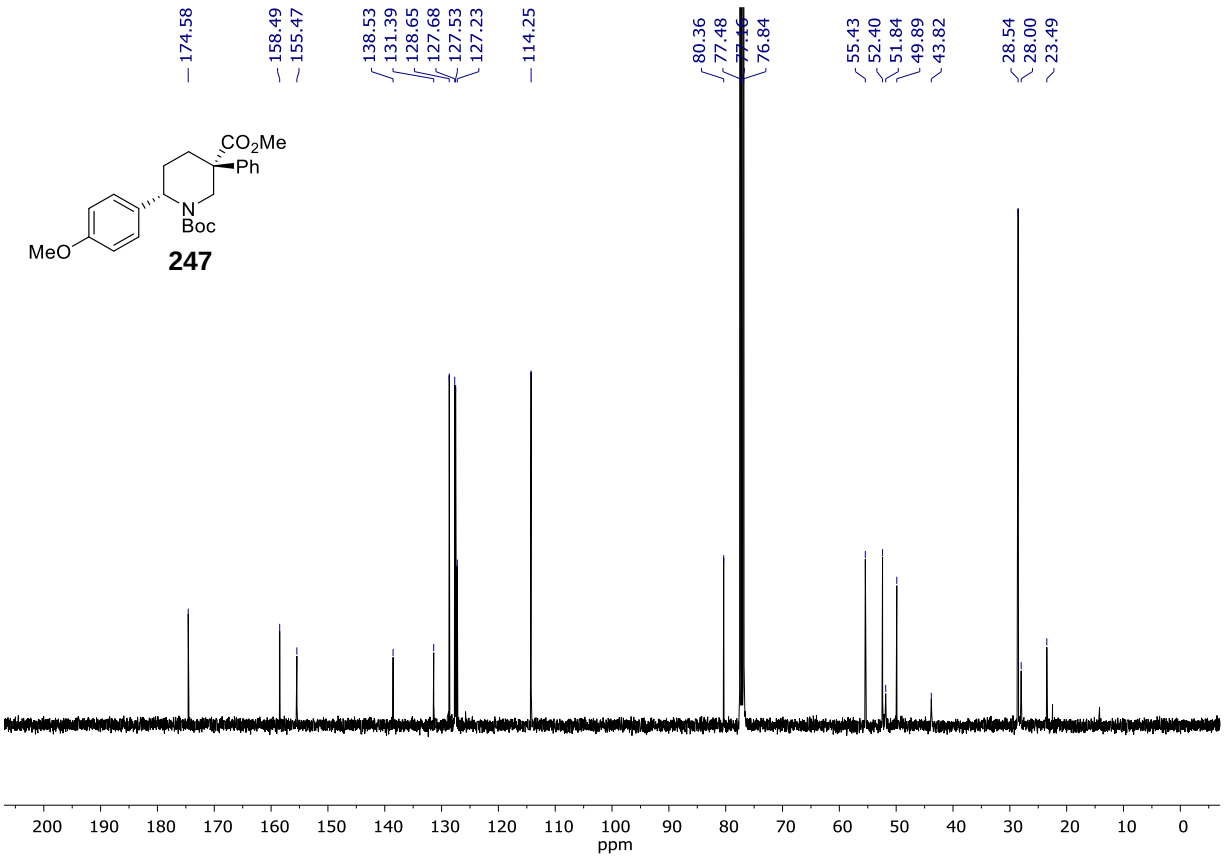
^{1}H NMR (400 MHz, $CDCl_3$)



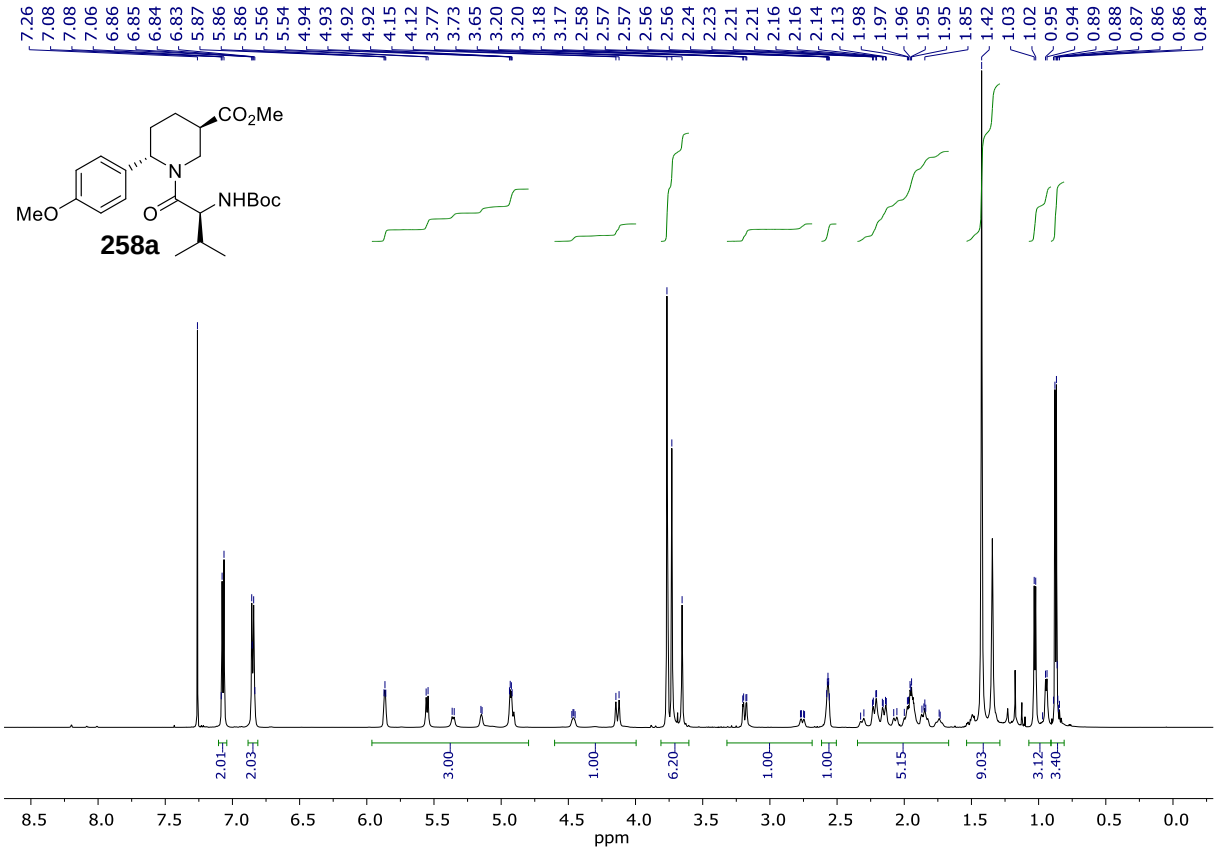
^{13}C NMR (101 MHz, $CDCl_3$)



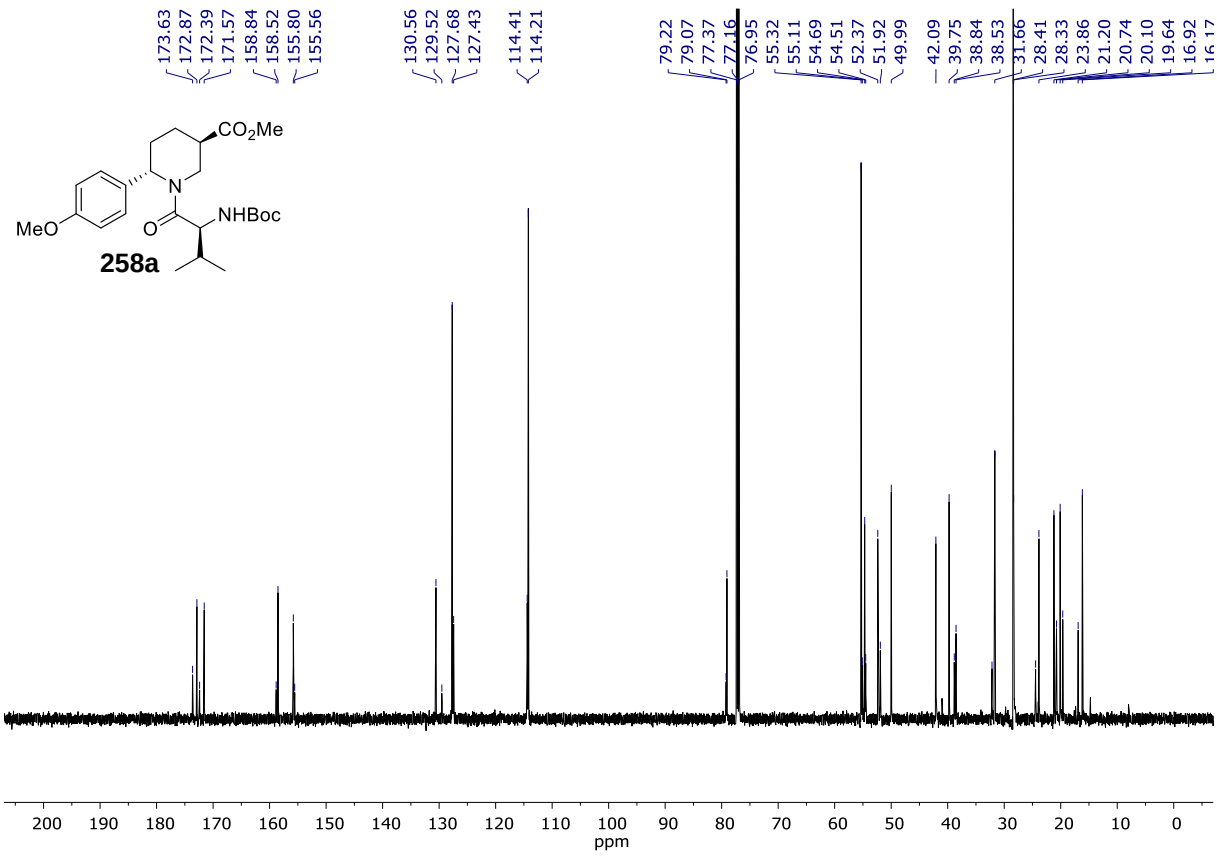
^{1}H NMR (400 MHz, $CDCl_3$)



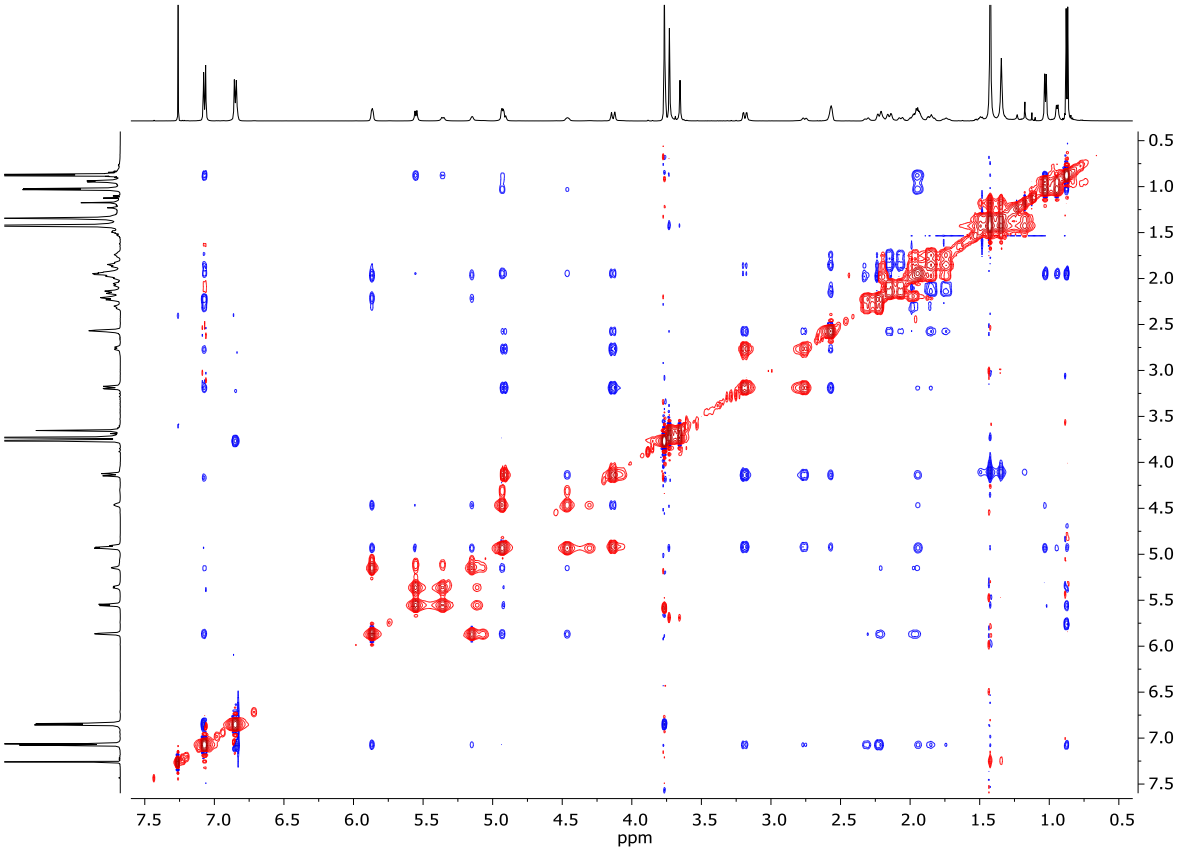
^{13}C NMR (101 MHz, $CDCl_3$)



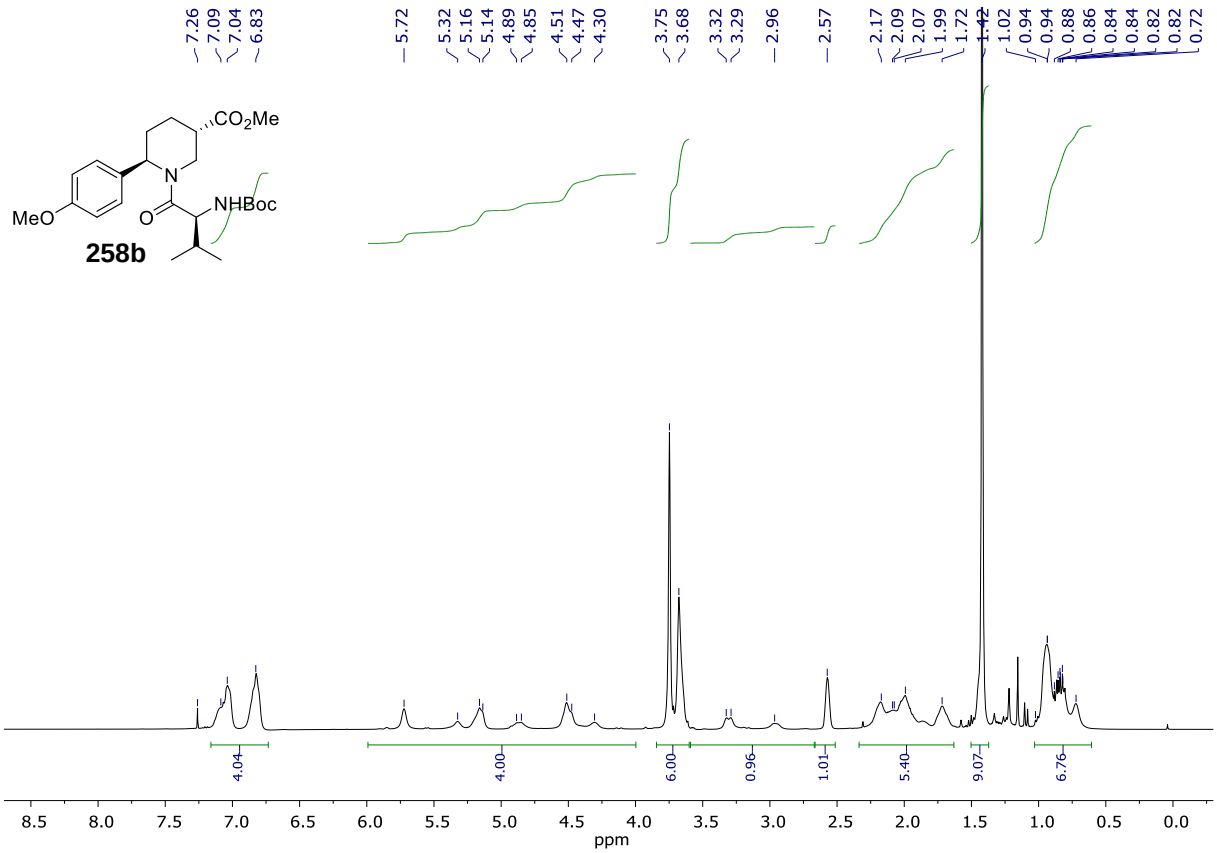
^{1}H NMR (600 MHz, $CDCl_3$)



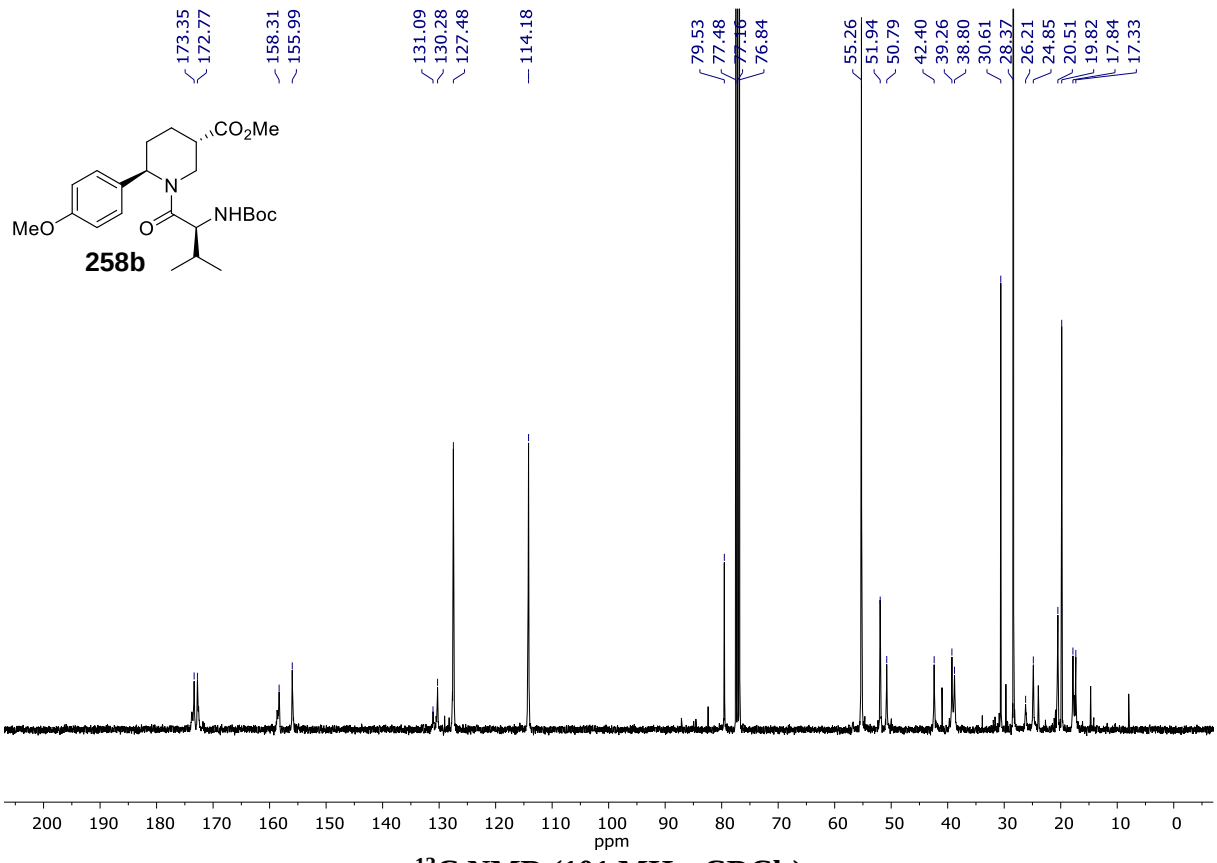
^{13}C NMR (151 MHz, $CDCl_3$)



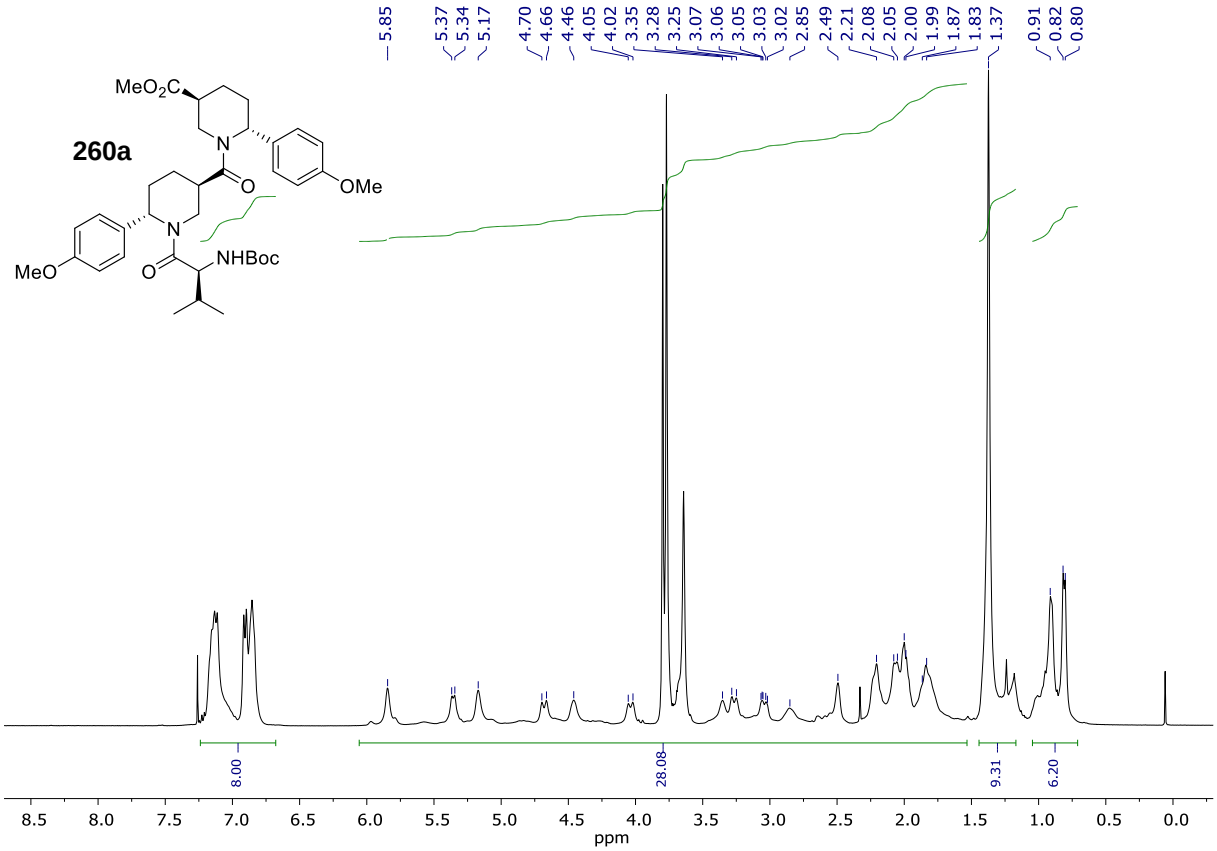
Dipeptide 258a: NOESY (600 MHz, $CDCl_3$)



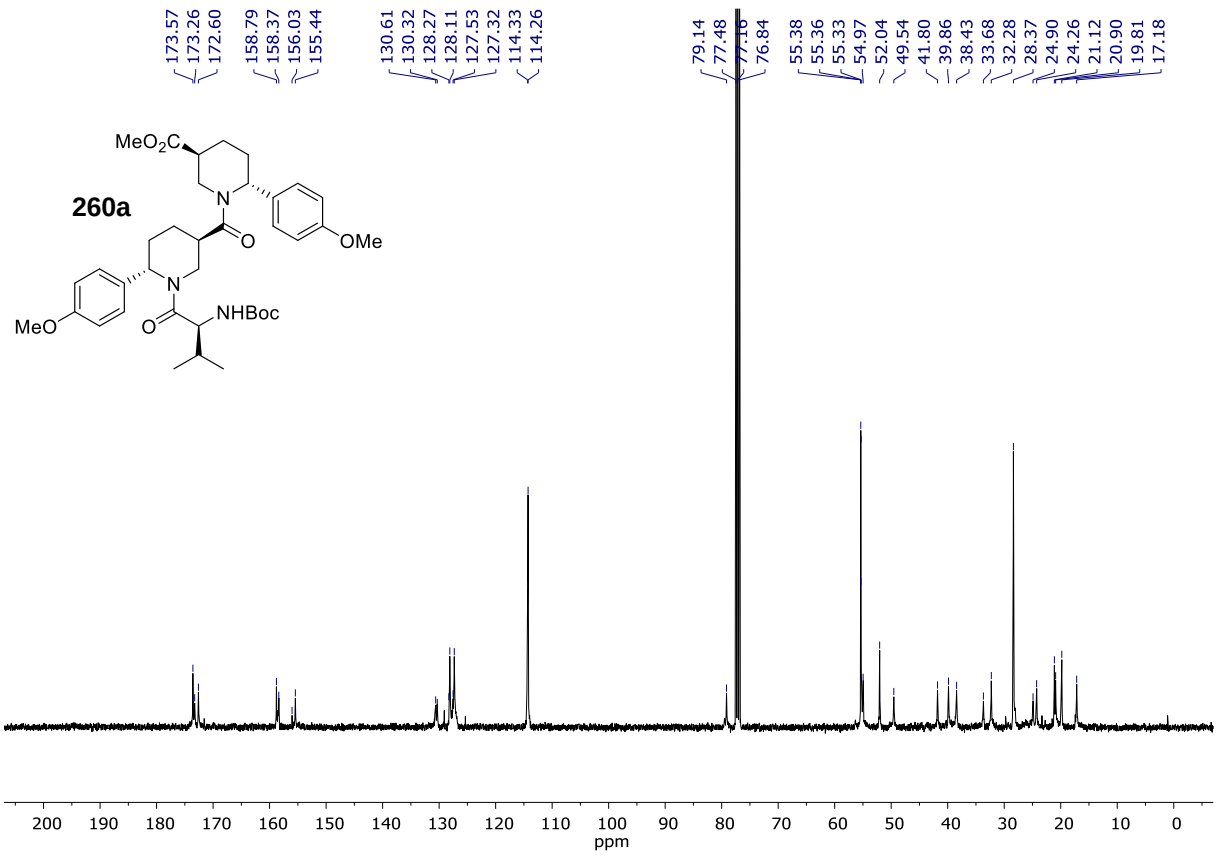
^{1}H NMR (400 MHz, $CDCl_3$)



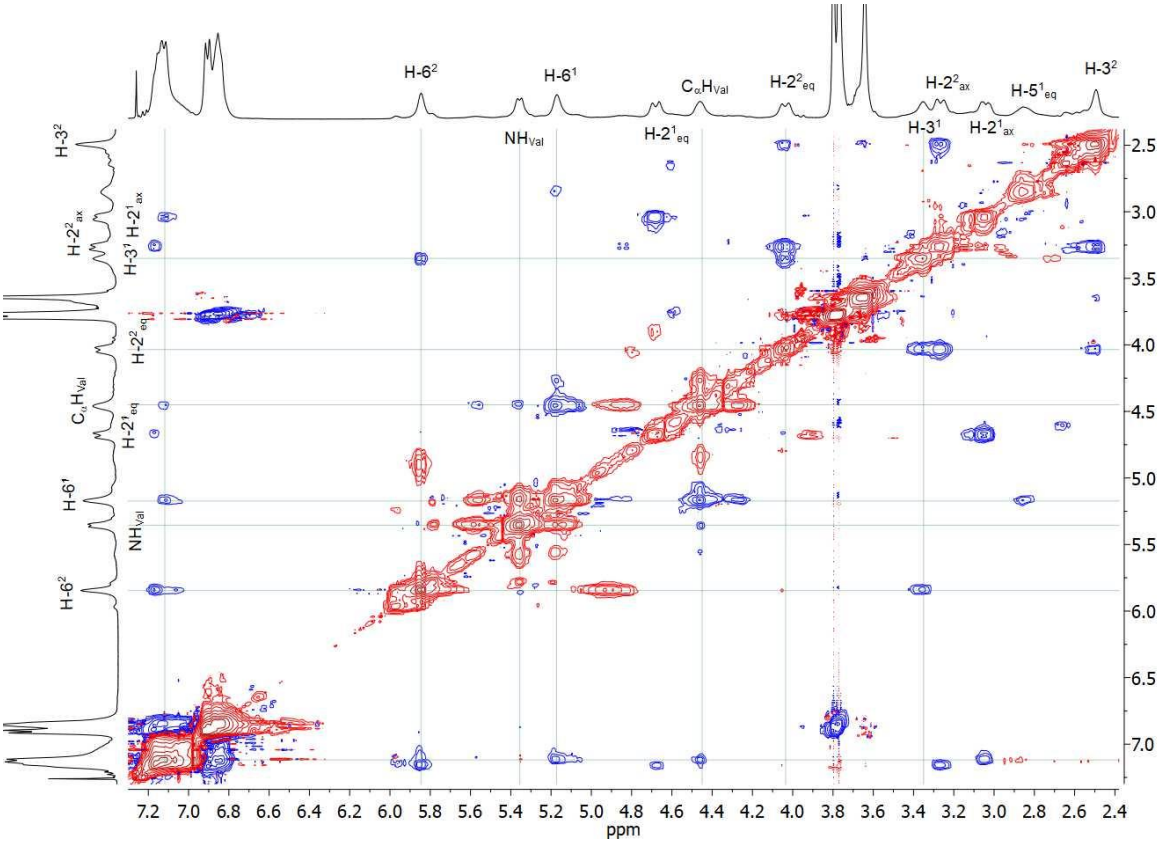
^{13}C NMR (101 MHz, $CDCl_3$)



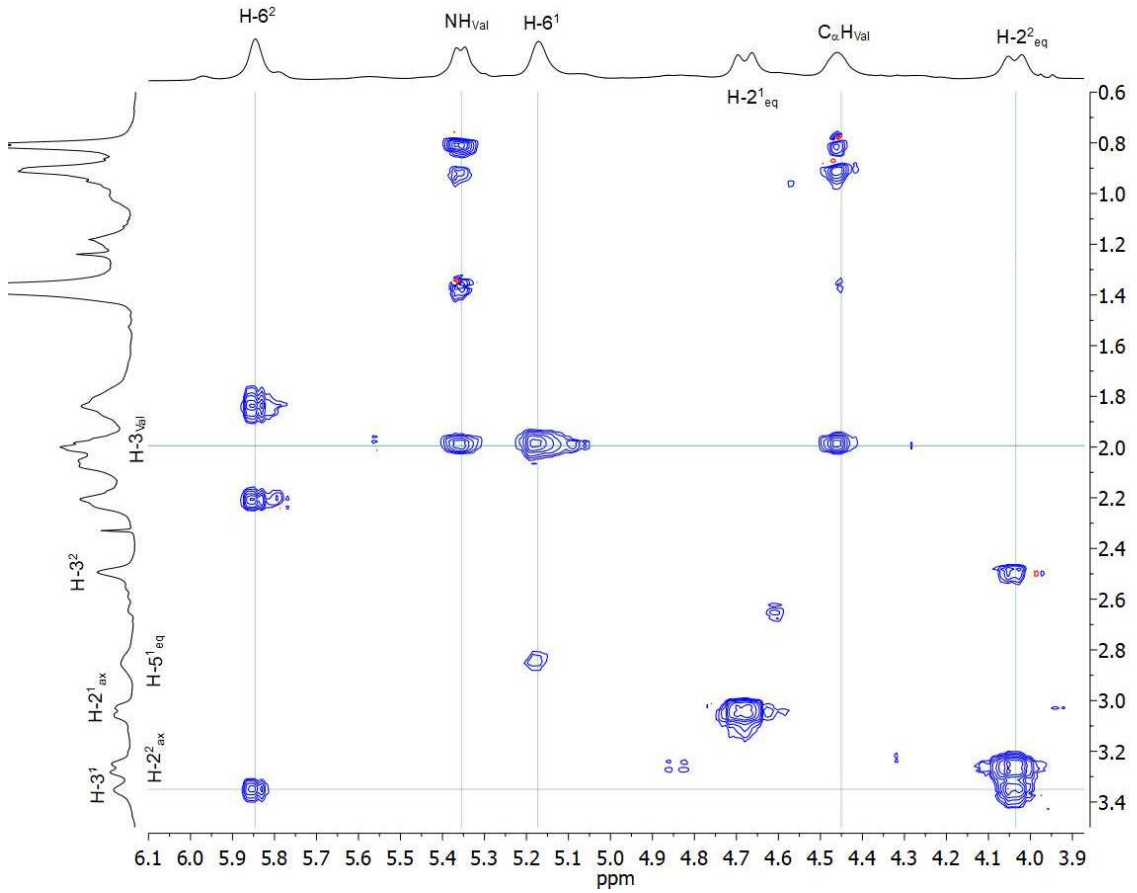
^{1}H NMR (400 MHz, $CDCl_3$)



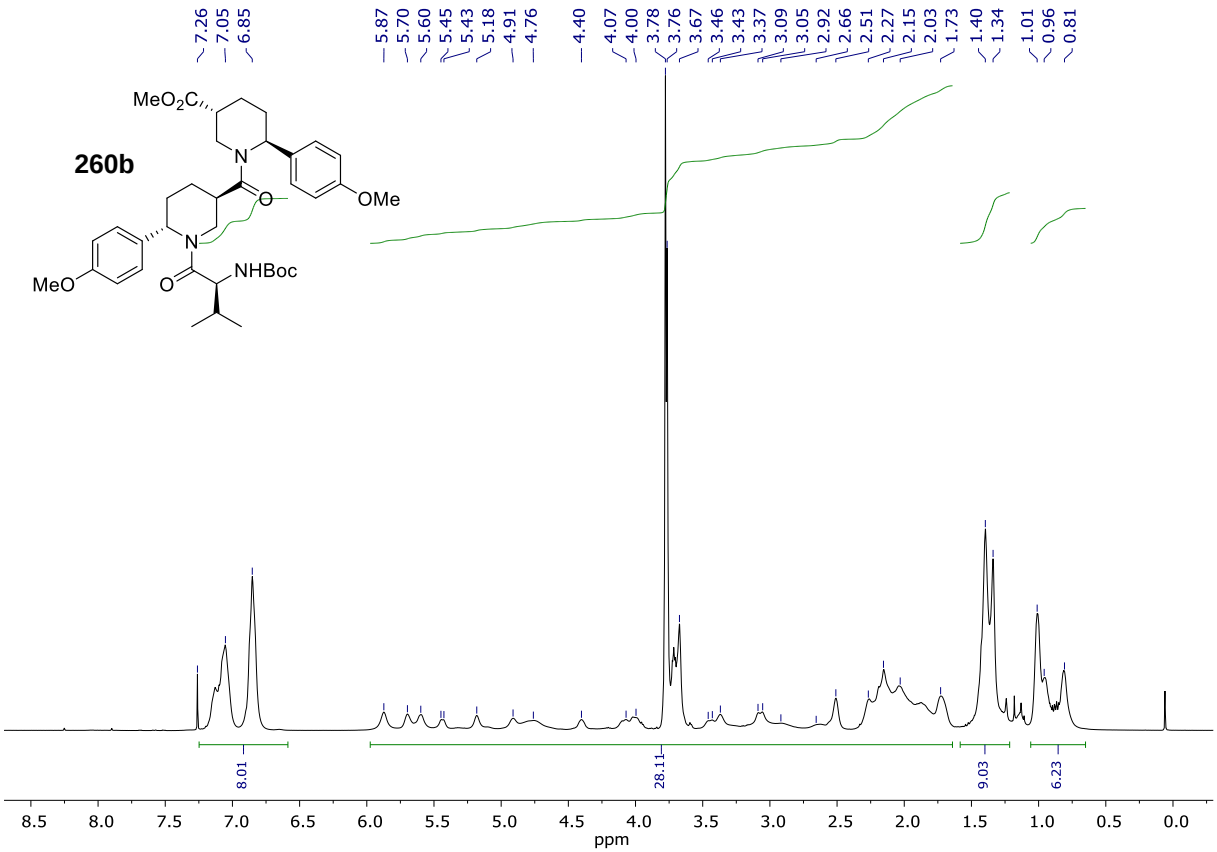
^{13}C NMR (101 MHz, $CDCl_3$)



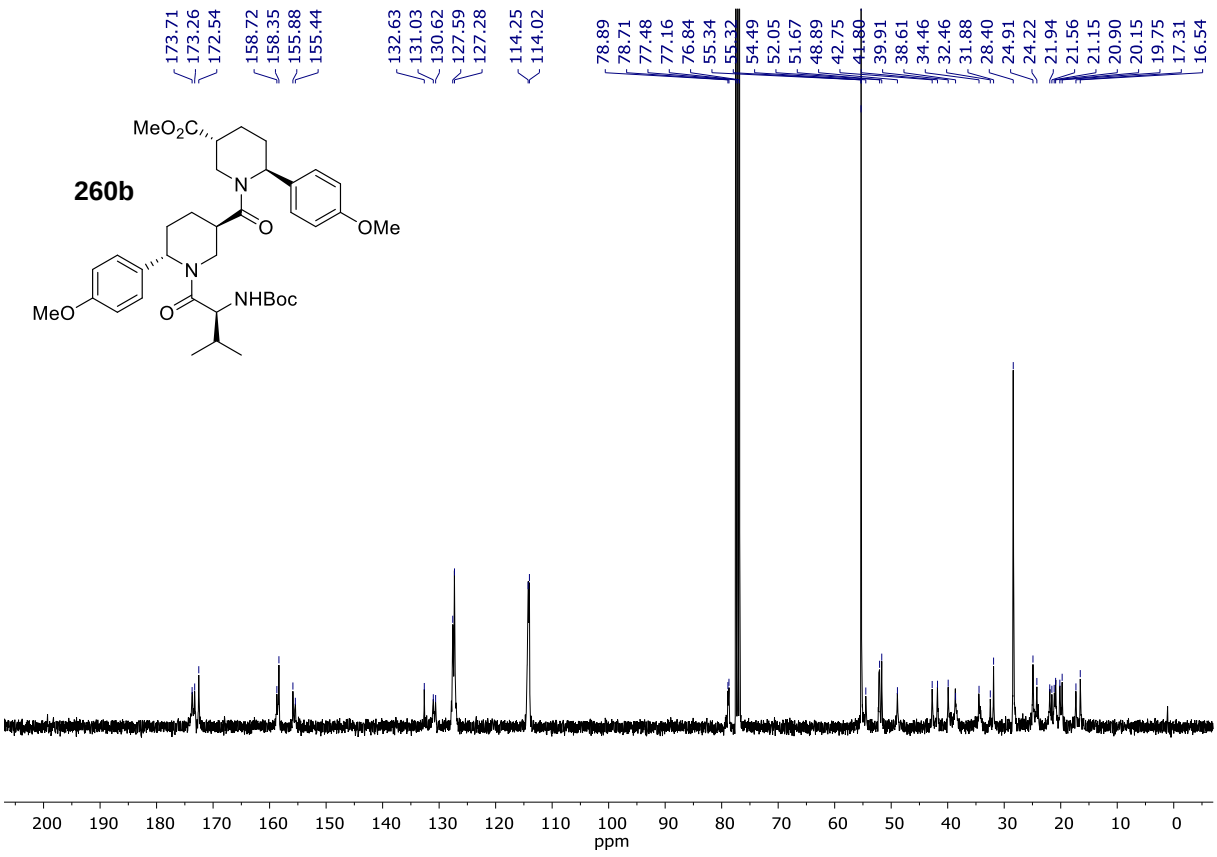
Tripeptide 260a: ROESY (600 MHz, $CDCl_3$)



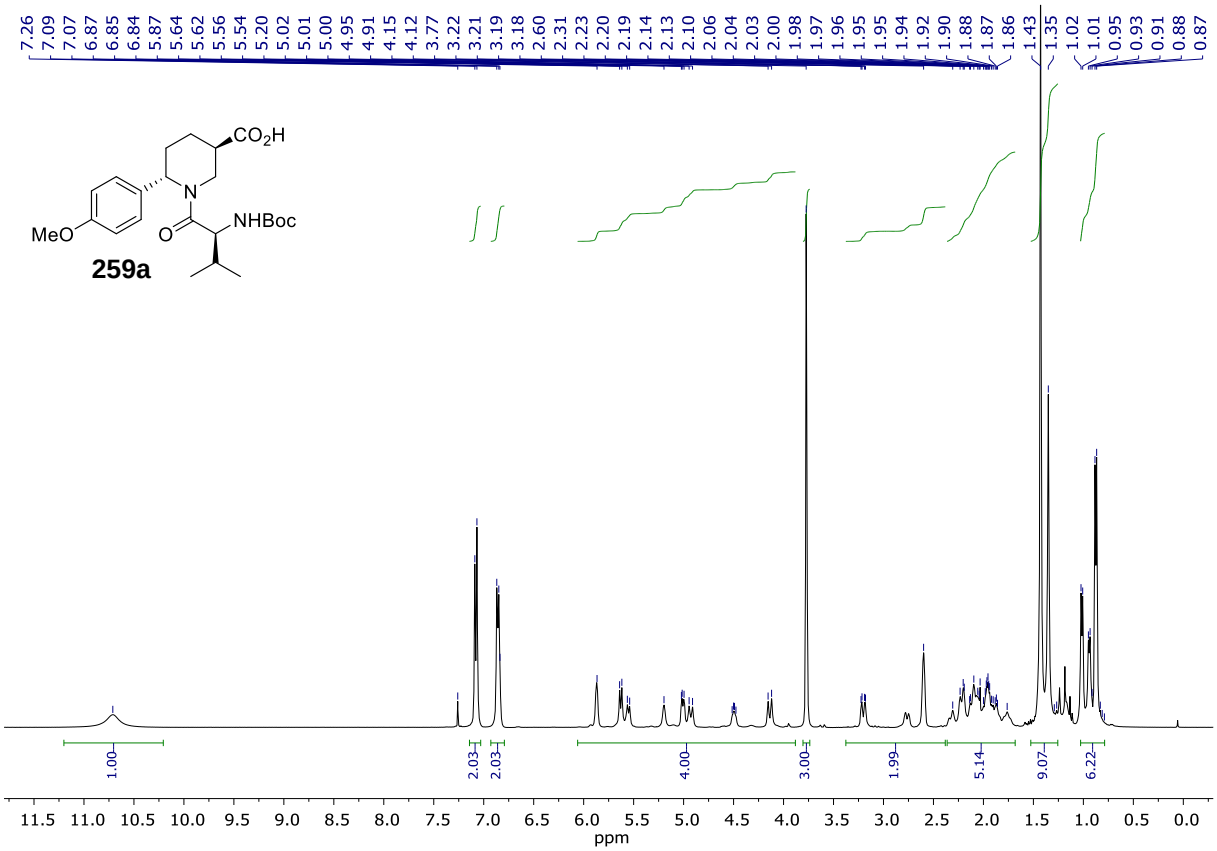
Tripeptide 260a: ROESY (600 MHz, $CDCl_3$)



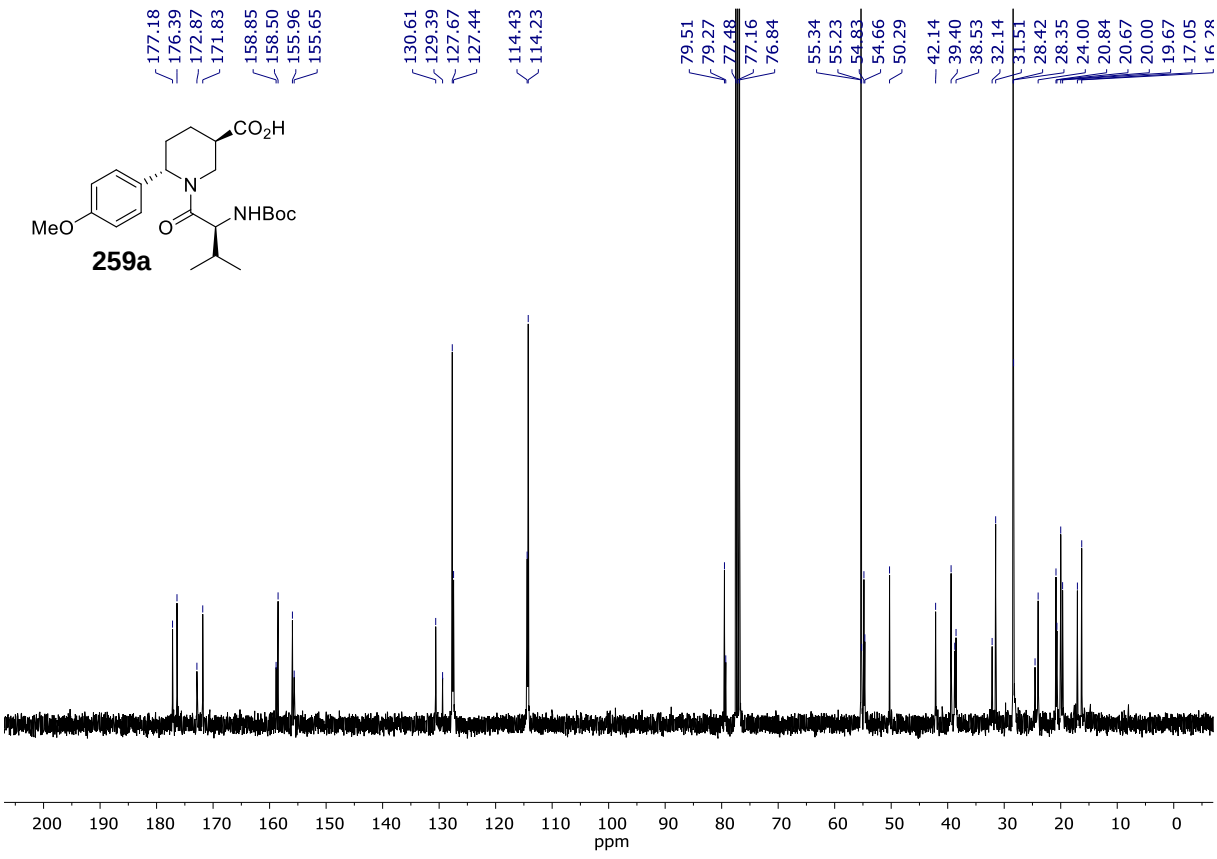
^{1}H NMR (400 MHz, $CDCl_3$)



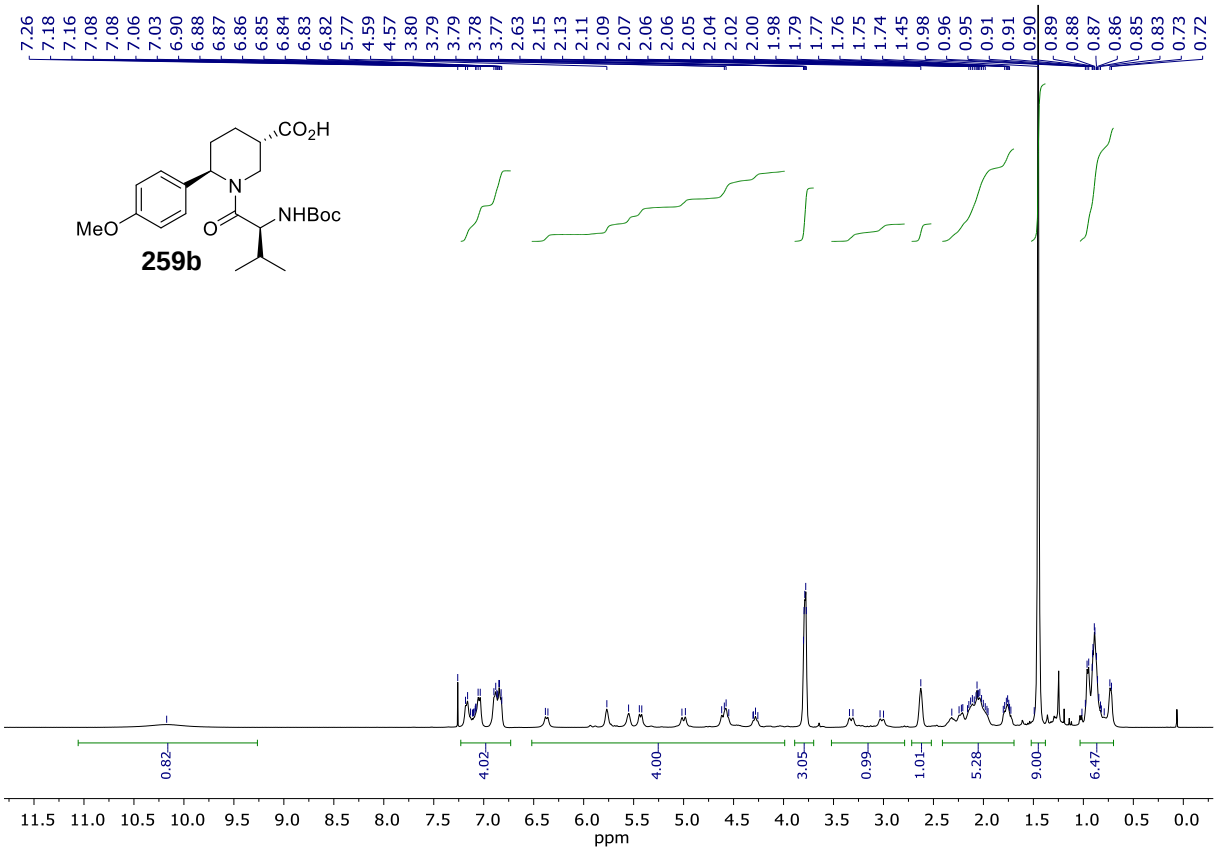
^{13}C NMR (101 MHz, $CDCl_3$)



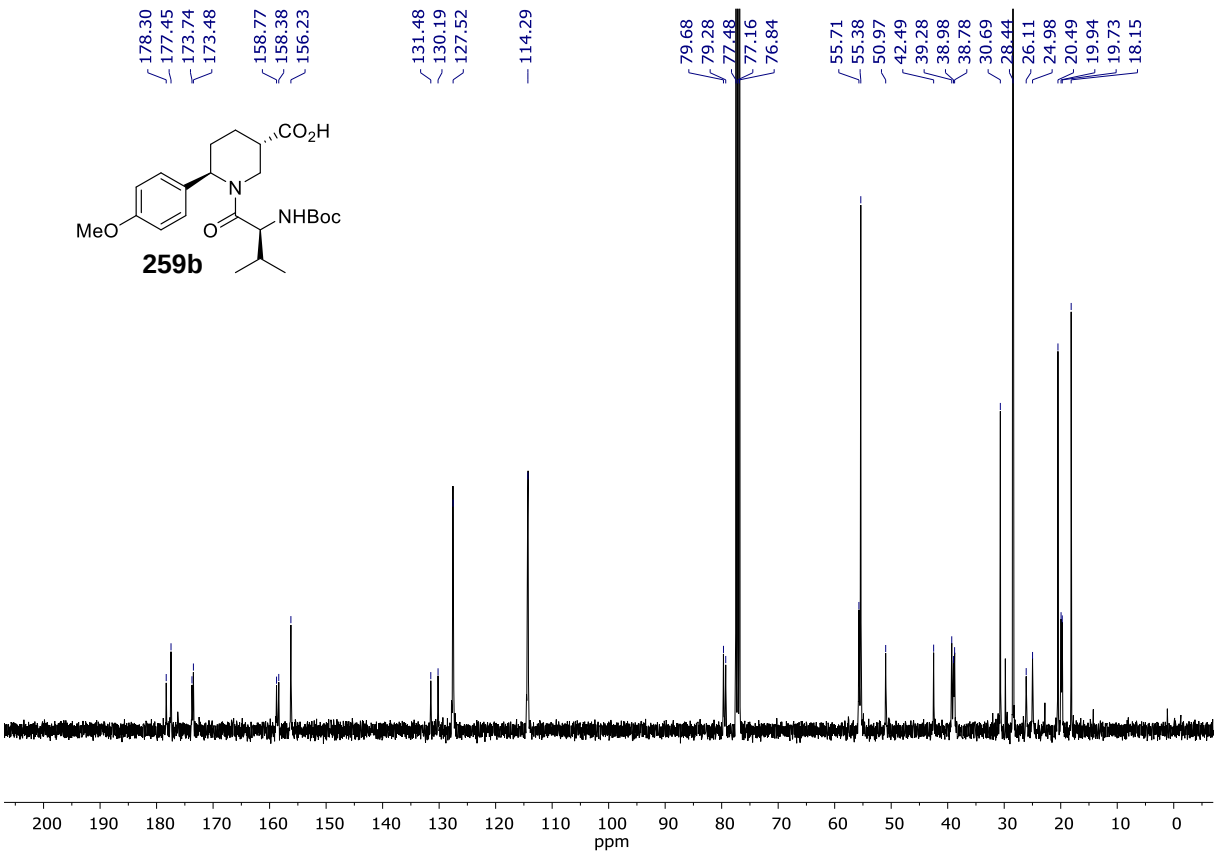
^{1}H NMR (400 MHz, $CDCl_3$)



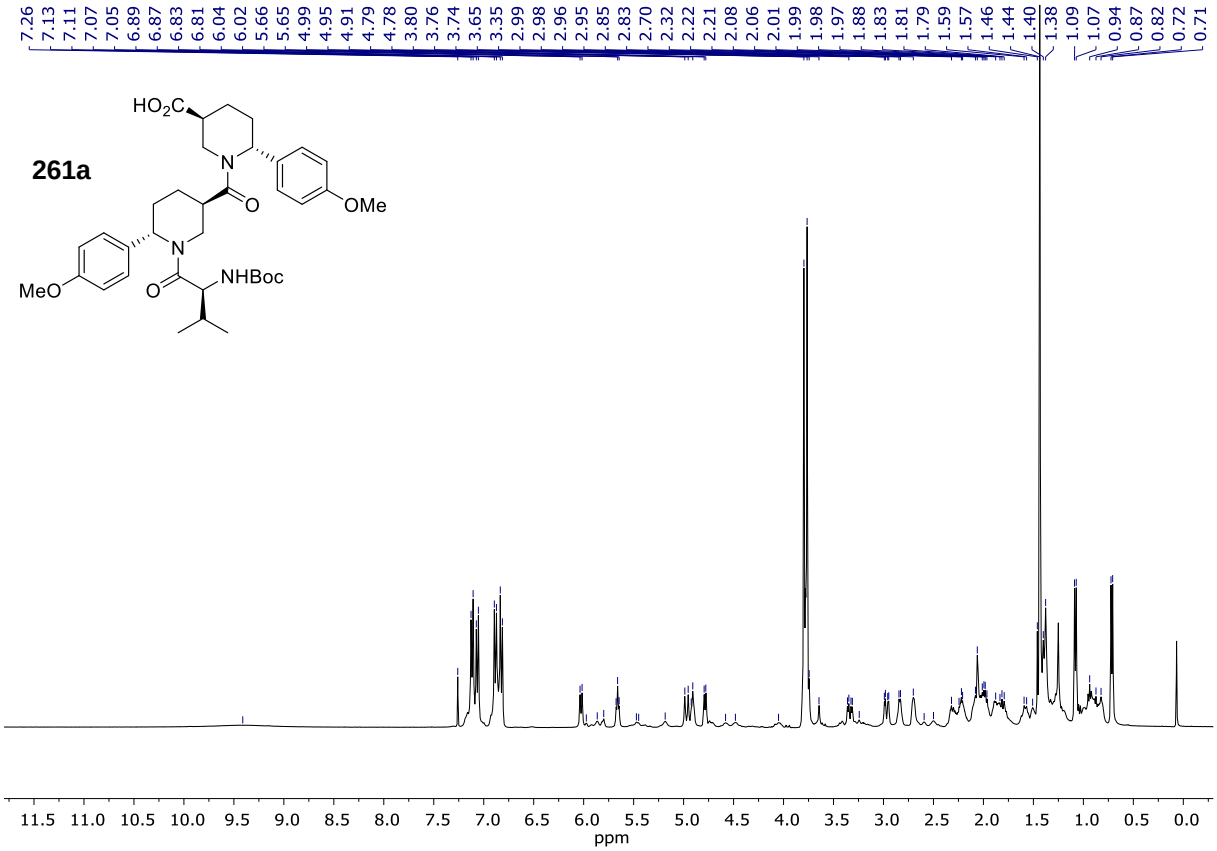
^{13}C NMR (101 MHz, $CDCl_3$)



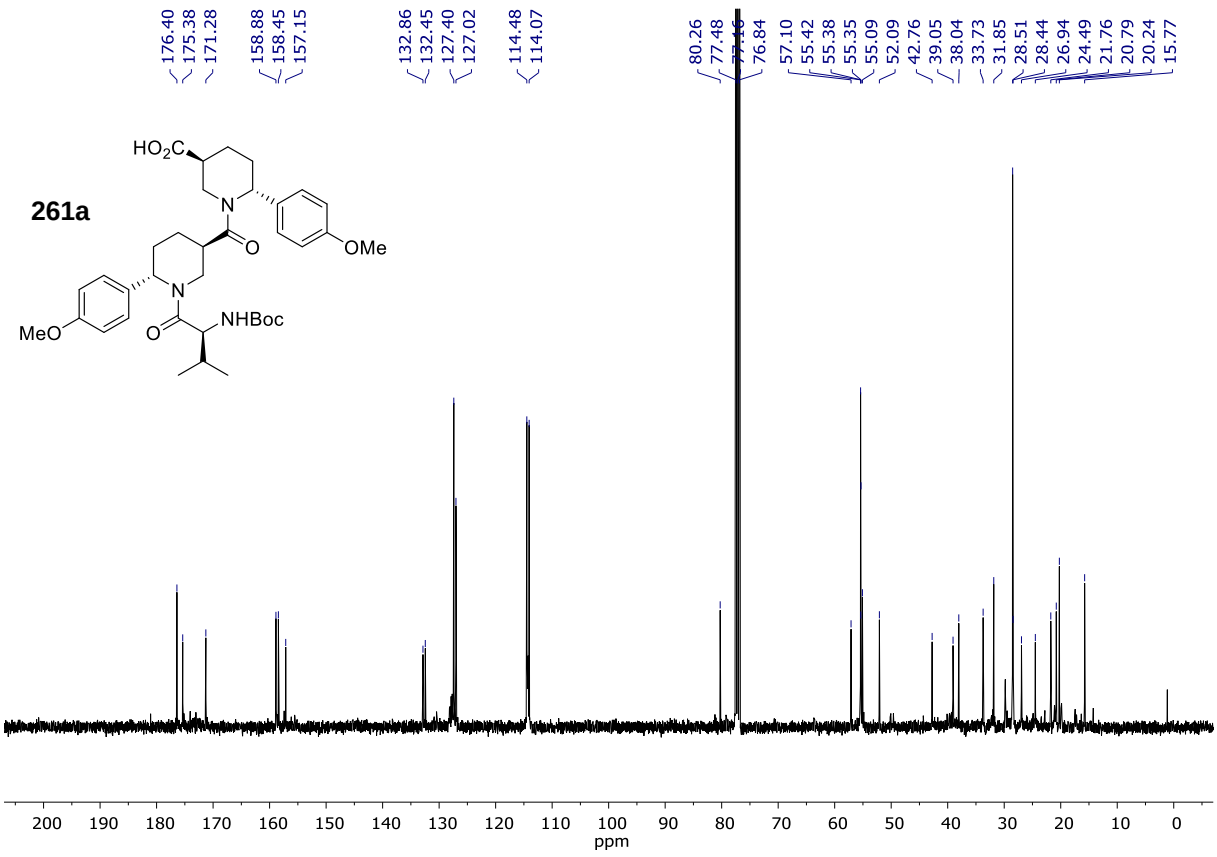
^{1}H NMR (400 MHz, $CDCl_3$)



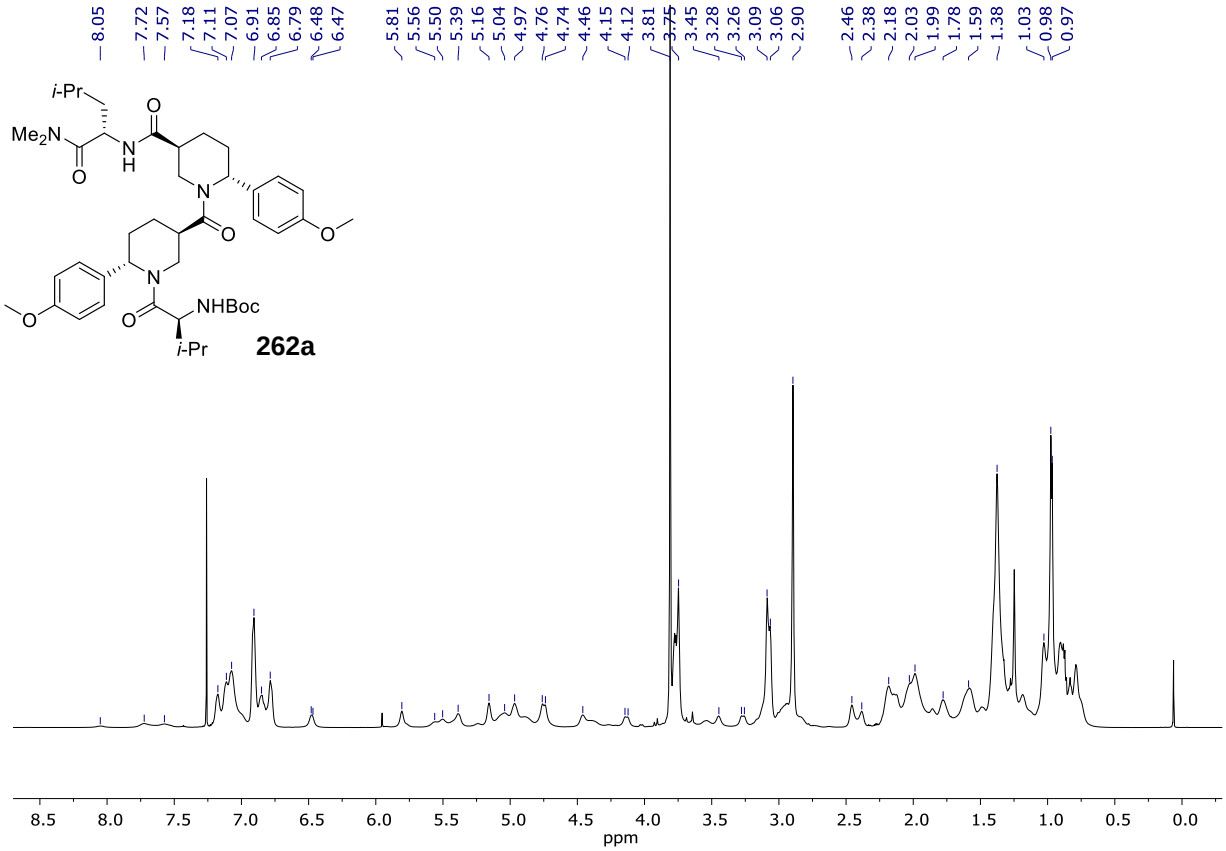
^{13}C NMR (101 MHz, $CDCl_3$)



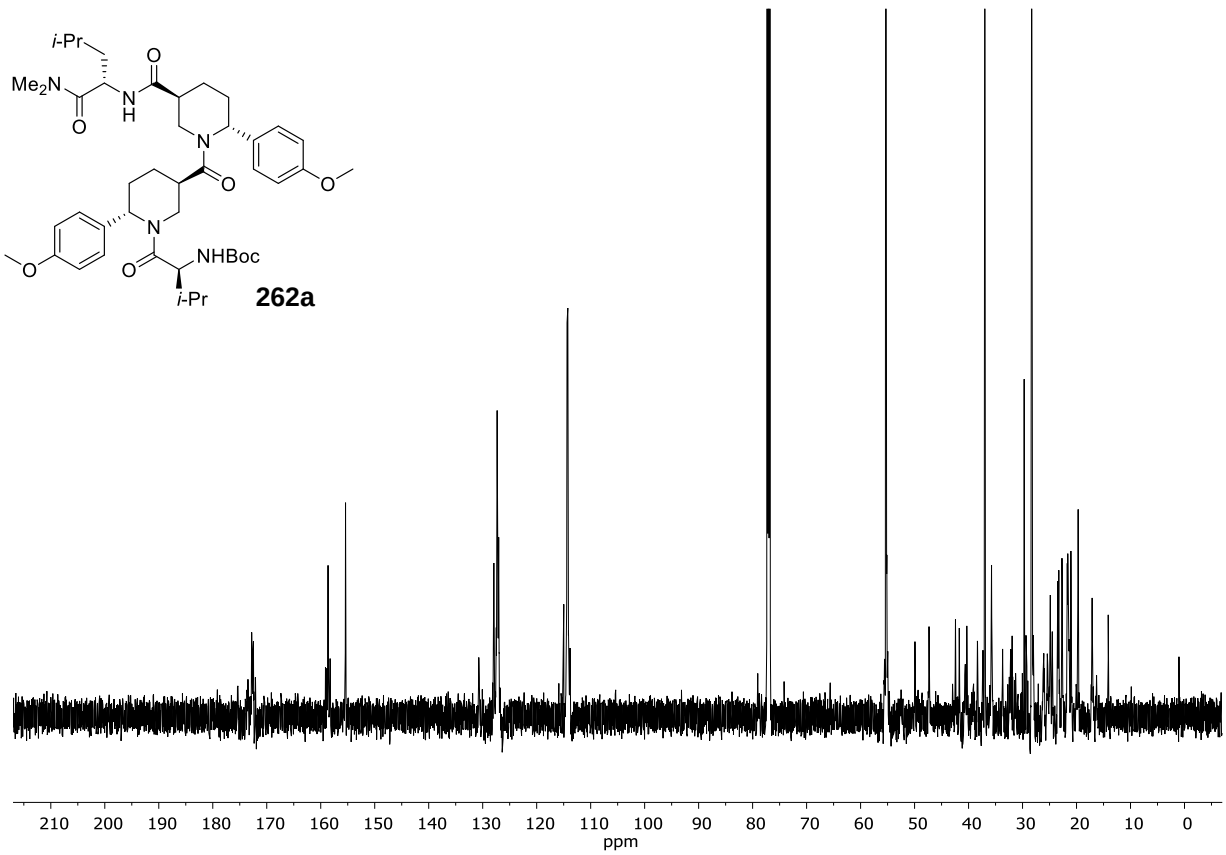
^{1}H NMR (400 MHz, $CDCl_3$)



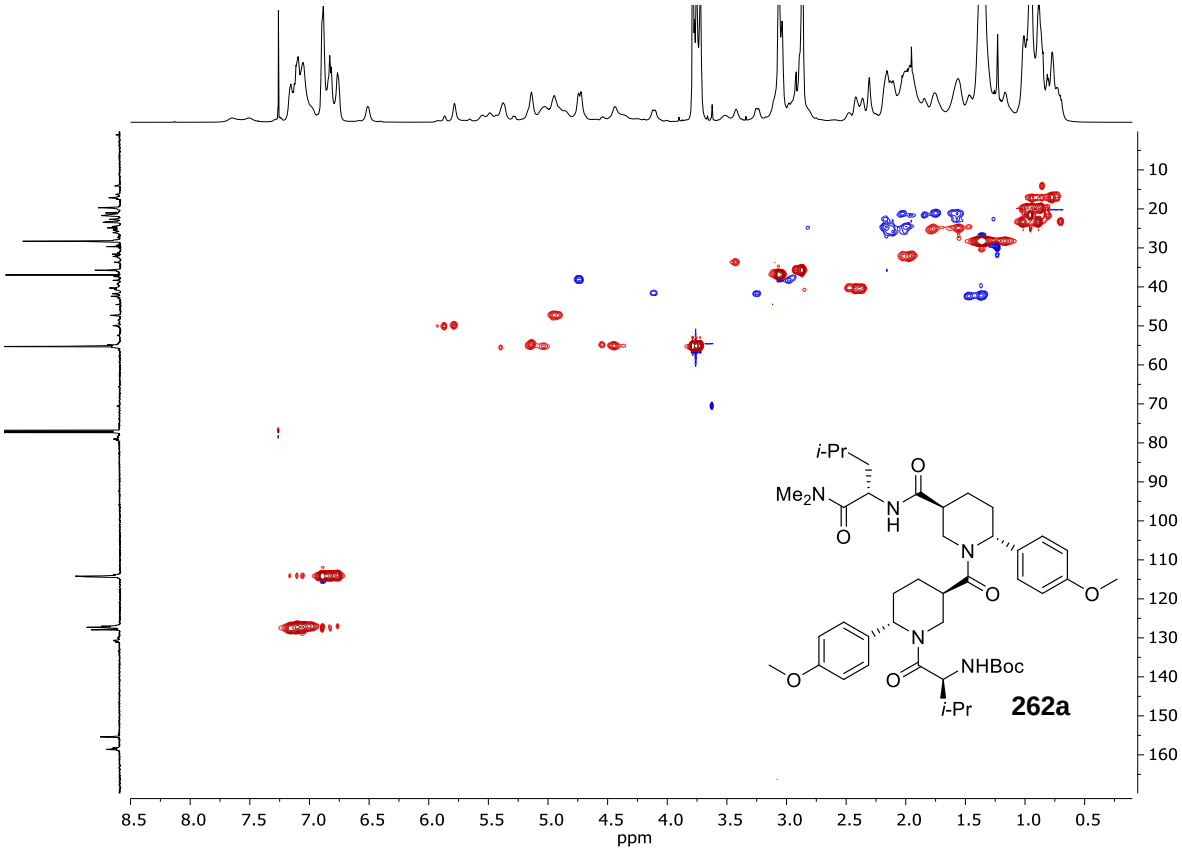
^{13}C NMR (101 MHz, $CDCl_3$)



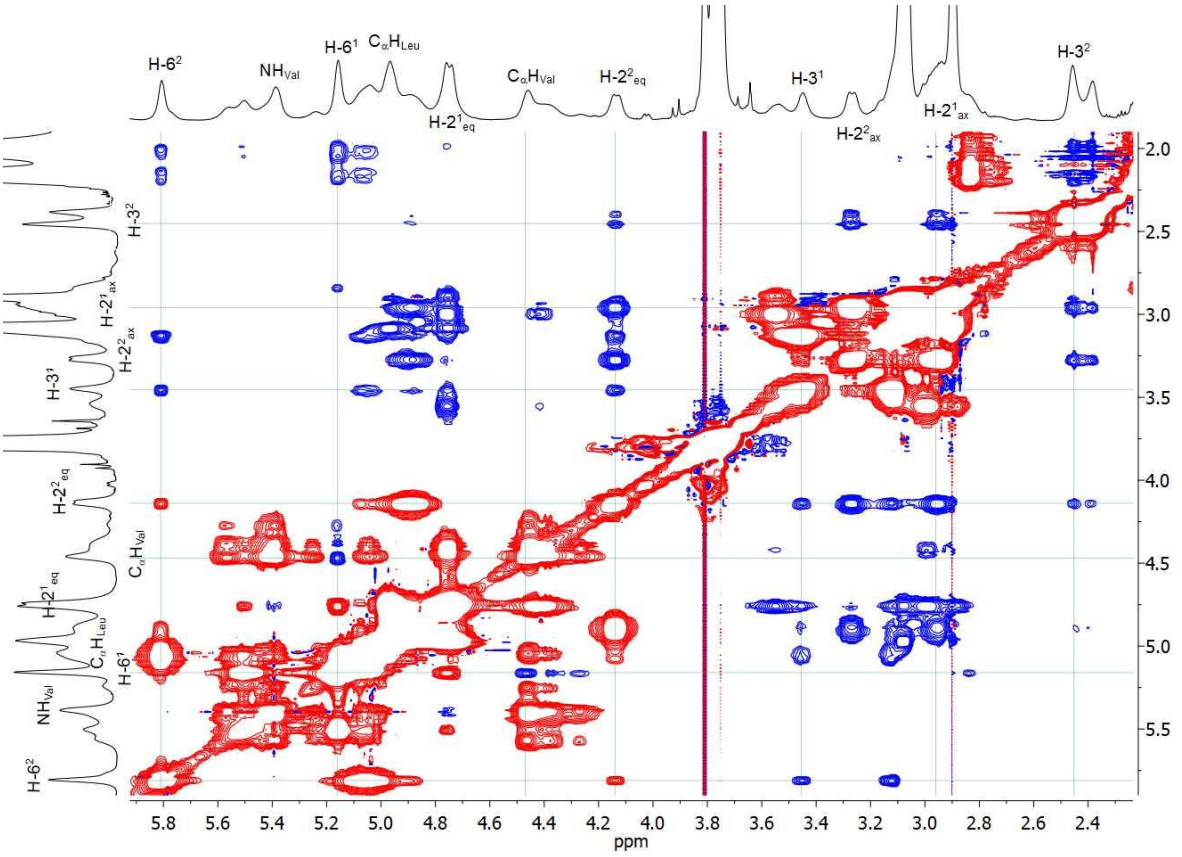
^{1}H NMR (600 MHz, $CDCl_3$)



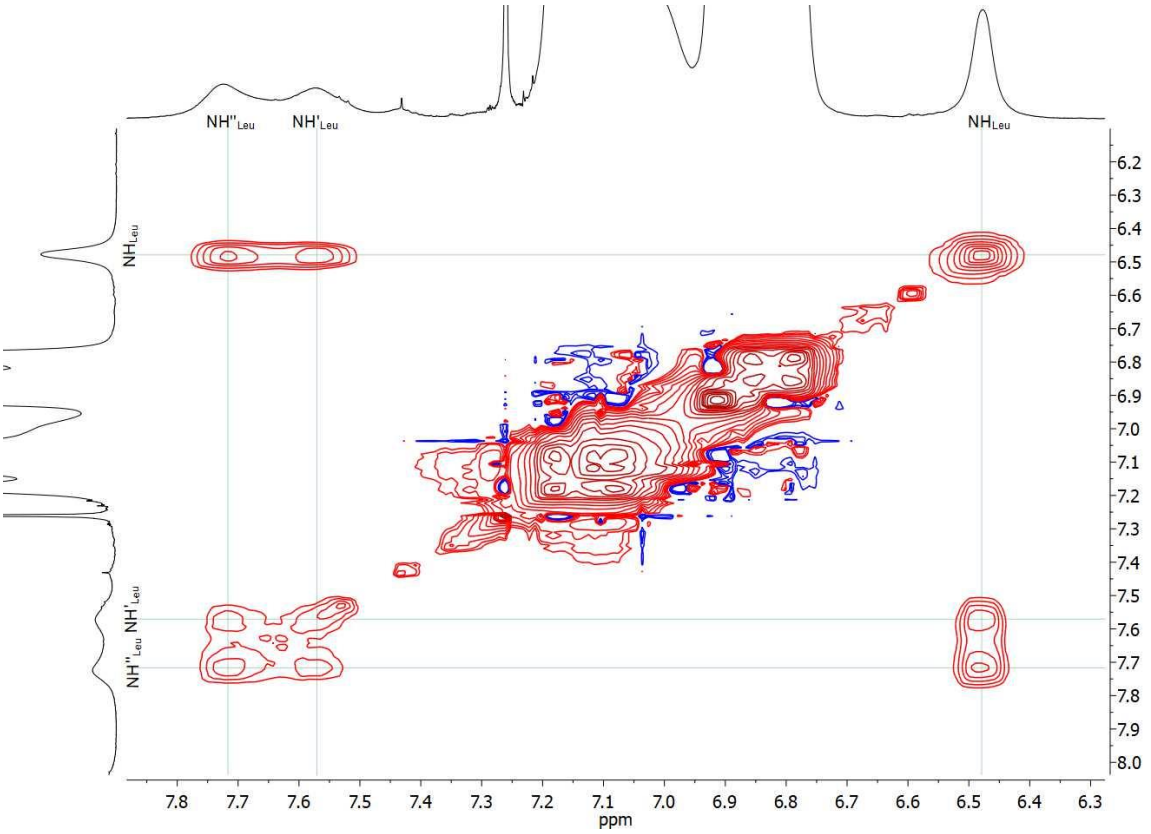
^{13}C NMR (151 MHz, $CDCl_3$)



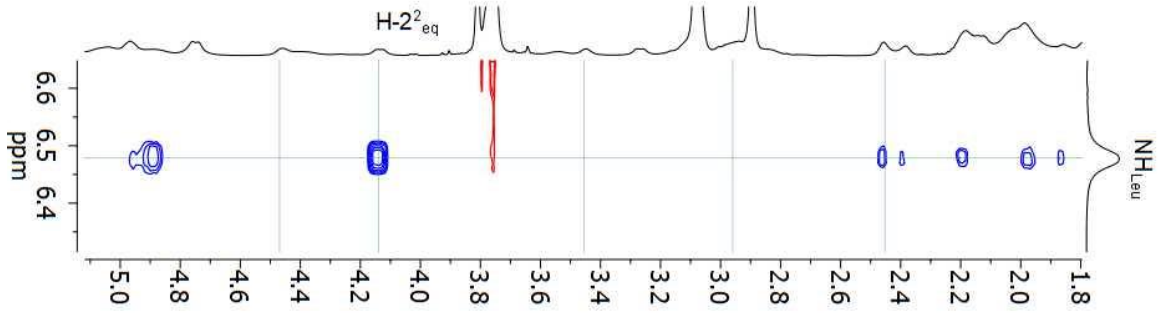
HSQC ((600, 151) MHz, $CDCl_3$)



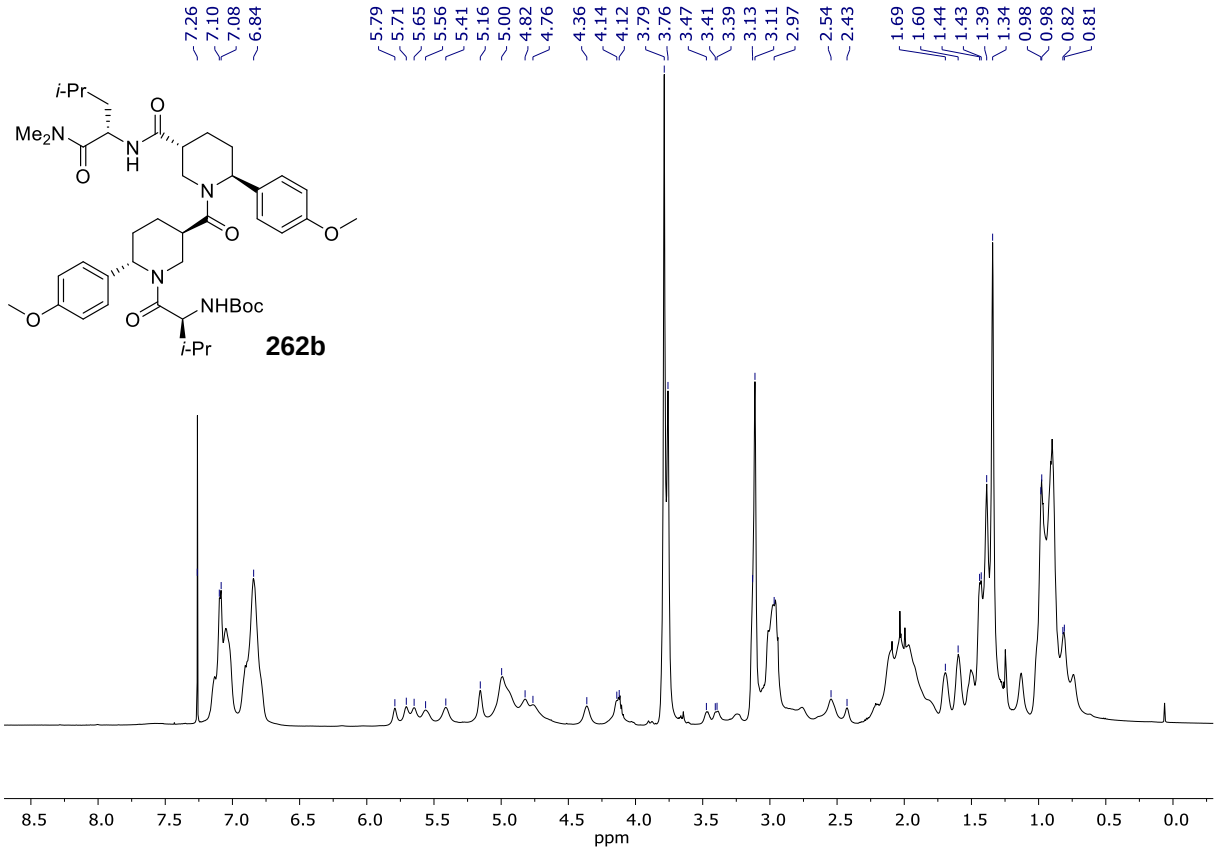
Tetrapeptide 262a: CH/CH region of ROESY spectrum (600 MHz, $CDCl_3$)



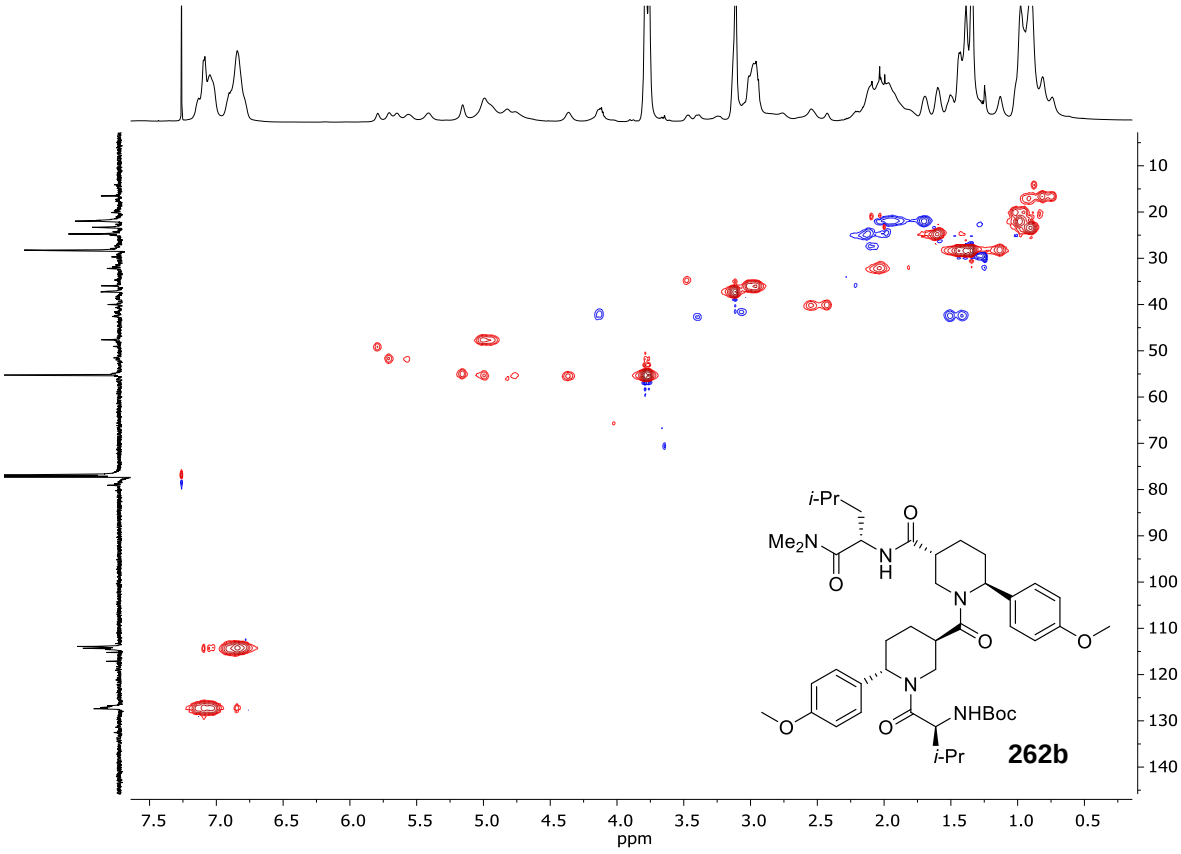
Tetrapeptide 262a: ROESY (600 MHz, $CDCl_3$), NH/NH region



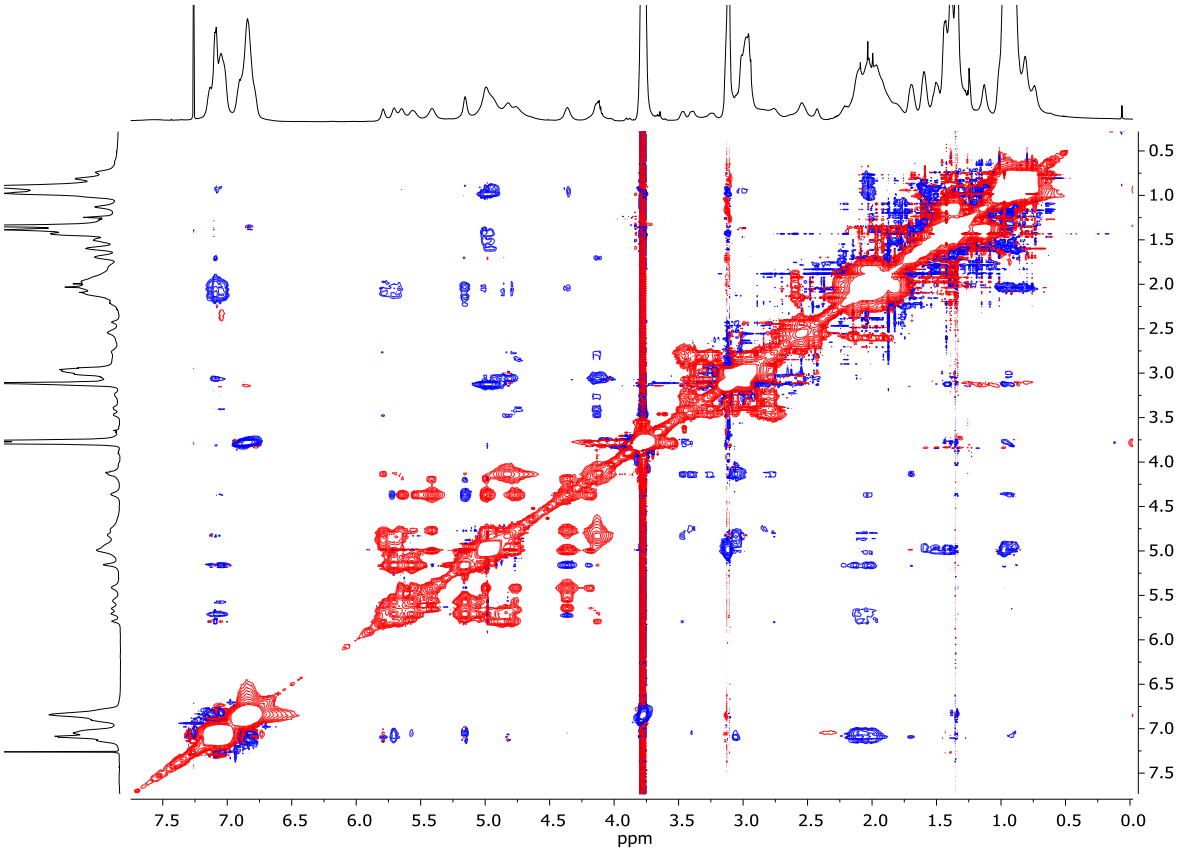
Tetrapeptide 262a: ROESY (600 MHz, $CDCl_3$), NH/CH region



^{1}H NMR (600 MHz, $CDCl_3$)



HSQC ((600, 151) MHz, $CDCl_3$)

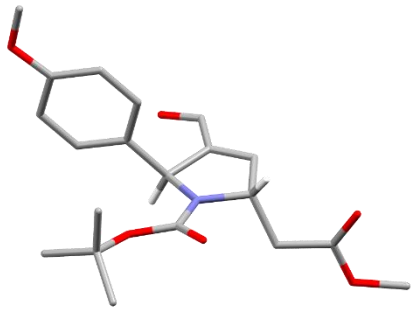


Tetrapeptide 262b: ROESY (600 MHz, $CDCl_3$)

Appendix 2. Crystallographic data

tert-Butyl (2*R**,5*R**)-3-formyl-5-(2-methoxy-2-oxoethyl)-2-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (188)

*Table 7. Crystal data and structure refinement for **188***



Identification code	S040
Empirical formula	$C_{20}H_{25}NO_6$
Formula weight	375.41
Temperature/K	123.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	6.06718(15)
b/Å	9.5680(2)
c/Å	16.9140(4)
α/°	82.356(2)
β/°	85.816(2)
γ/°	86.009(2)
Volume/Å^3	968.77(4)
Z	2
ρ_{calc}g/cm^3	1.287
μ/mm^{-1}	0.787
F(000)	400.0
Crystal size/mm^3	0.183 × 0.091 × 0.062
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.344 to 148.456
Index ranges	-7 ≤ h ≤ 7, -11 ≤ k ≤ 11, -21 ≤ l ≤ 21
Reflections collected	24155
Independent reflections	3907 [R_{int} = 0.0247, R_{sigma} = 0.0135]
Data/restraints/parameters	3907/0/249
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0312, wR_2 = 0.0794
Final R indexes [all data]	R_1 = 0.0340, wR_2 = 0.0817
Largest diff. peak/hole / e Å^{-3}	0.26/-0.21

*Table 8. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **188**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
O(1)	3621.6(11)	3100.3(8)	3547.3(4)	18.16(16)
O(2)	43.0(12)	3867.6(8)	3311.9(4)	21.74(17)
O(6)	7071.7(13)	-2642.2(8)	3099.5(5)	23.79(17)
O(4)	-2346.1(13)	6165.3(8)	997.4(5)	28.13(19)
O(5)	8057.7(13)	2639.5(8)	601.9(5)	27.37(18)
O(3)	-525.5(14)	8093.0(8)	1094.8(5)	27.60(19)
N(1)	2653.9(14)	3661.8(9)	2302.5(5)	17.96(18)
C(5)	1943.7(17)	3555.8(10)	3085.1(6)	16.8(2)

C(16)	6373.3(17)	-1287.3(10)	2819.0(6)	18.7(2)
C(11)	4474.7(17)	3393.0(10)	1095.2(6)	18.6(2)
C(9)	1213.7(17)	4361.2(10)	1689.4(6)	17.8(2)
C(14)	3875.7(17)	529.7(11)	2206.2(6)	20.0(2)
C(7)	-828.0(18)	6713.8(11)	1232.1(6)	20.5(2)
C(15)	4369.5(17)	-890.6(11)	2482.1(6)	20.8(2)
C(10)	2502.6(17)	4030.5(10)	943.1(6)	19.0(2)
C(13)	5338.7(16)	1552.4(10)	2271.8(6)	16.8(2)
C(12)	4812.1(16)	3101.9(10)	1979.3(6)	17.0(2)
C(19)	6169.5(18)	3067.7(11)	473.9(6)	21.9(2)
C(17)	7855.1(17)	-266.3(11)	2886.3(6)	21.3(2)
C(2)	3188.2(18)	2591.3(11)	4401.6(6)	20.7(2)
C(18)	7329.0(17)	1135.1(11)	2618.0(6)	20.3(2)
C(8)	919.9(17)	5954.6(11)	1741.9(6)	20.4(2)
C(3)	5490.7(19)	2150.0(13)	4668.2(7)	27.0(2)
C(20)	5595(2)	-3728.7(11)	3087.2(7)	27.0(2)
C(1)	2135(2)	3767.8(14)	4842.7(7)	34.9(3)
C(4)	1766(2)	1329.6(13)	4475.6(8)	33.9(3)
C(6)	-2137(2)	8942.8(13)	622.9(8)	34.9(3)

*Table 9. Anisotropic Displacement Parameters ($Å^2×10^3$) for **188**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O(1)	15.9(3)	21.8(4)	16.1(4)	-0.7(3)	-0.9(3)	-0.1(3)
O(2)	16.8(4)	25.5(4)	21.7(4)	-1.4(3)	0.5(3)	2.5(3)
O(6)	26.0(4)	14.9(4)	30.4(4)	0.0(3)	-6.4(3)	-0.9(3)
O(4)	27.7(4)	25.6(4)	31.0(4)	0.0(3)	-10.5(3)	0.8(3)
O(5)	23.1(4)	28.1(4)	30.7(4)	-6.8(3)	3.9(3)	-0.4(3)
O(3)	35.8(5)	17.0(4)	29.0(4)	-0.8(3)	-4.2(3)	3.5(3)
N(1)	16.1(4)	19.5(4)	17.4(4)	-1.0(3)	-1.1(3)	3.0(3)
C(5)	18.1(5)	13.3(4)	19.0(5)	-1.2(4)	-1.8(4)	-1.5(4)
C(16)	22.3(5)	15.9(5)	17.5(5)	-2.0(4)	0.3(4)	0.8(4)
C(11)	22.0(5)	15.0(5)	18.6(5)	-1.6(4)	0.5(4)	-3.3(4)
C(9)	17.4(5)	17.0(5)	18.7(5)	-1.0(4)	-3.2(4)	-0.4(4)
C(14)	16.5(5)	20.3(5)	23.3(5)	-3.0(4)	-3.1(4)	-0.1(4)
C(7)	24.8(5)	18.6(5)	17.3(5)	-2.9(4)	1.6(4)	2.7(4)
C(15)	20.0(5)	18.1(5)	25.1(5)	-3.9(4)	-1.5(4)	-4.1(4)
C(10)	22.9(5)	16.1(5)	18.1(5)	-1.2(4)	-2.3(4)	-3.0(4)
C(13)	17.3(5)	16.7(5)	16.1(5)	-2.3(4)	1.3(4)	0.0(4)
C(12)	15.3(5)	16.6(5)	19.0(5)	-3.0(4)	0.5(4)	-1.0(4)
C(19)	25.9(5)	19.1(5)	20.5(5)	-2.6(4)	2.2(4)	-3.4(4)
C(17)	18.3(5)	21.0(5)	24.7(5)	-1.5(4)	-4.9(4)	0.1(4)
C(2)	21.9(5)	22.4(5)	15.9(5)	1.5(4)	-0.1(4)	2.1(4)
C(18)	18.1(5)	18.4(5)	24.7(5)	-2.7(4)	-1.8(4)	-3.6(4)
C(8)	22.4(5)	18.2(5)	21.0(5)	-3.2(4)	-3.7(4)	0.3(4)
C(3)	24.3(6)	32.1(6)	23.5(5)	0.0(5)	-5.6(4)	3.1(5)
C(20)	29.9(6)	16.5(5)	34.5(6)	-1.0(4)	-3.9(5)	-3.5(4)

C(1)	43.4(7)	39.8(7)	20.7(6)	-8.7(5)	-5.0(5)	15.5(6)
C(4)	27.6(6)	29.8(6)	40.4(7)	12.8(5)	-4.0(5)	-5.1(5)
C(6)	43.8(7)	22.7(6)	34.5(7)	3.7(5)	-4.0(5)	10.9(5)

*Table 10. Bond Lengths for **188***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(1)	C(5)	1.3420(12)	C(11)	C(10)	1.3309(15)
O(1)	C(2)	1.4730(12)	C(11)	C(12)	1.5105(14)
O(2)	C(5)	1.2183(13)	C(11)	C(19)	1.4639(14)
O(6)	C(16)	1.3691(12)	C(9)	C(10)	1.4942(14)
O(6)	C(20)	1.4221(13)	C(9)	C(8)	1.5362(14)
O(4)	C(7)	1.2072(14)	C(14)	C(15)	1.3962(15)
O(5)	C(19)	1.2143(14)	C(14)	C(13)	1.3863(14)
O(3)	C(7)	1.3323(13)	C(7)	C(8)	1.5019(14)
O(3)	C(6)	1.4438(14)	C(13)	C(12)	1.5188(13)
N(1)	C(5)	1.3546(13)	C(13)	C(18)	1.3908(14)
N(1)	C(9)	1.4673(13)	C(17)	C(18)	1.3804(15)
N(1)	C(12)	1.4752(12)	C(2)	C(3)	1.5140(15)
C(16)	C(15)	1.3878(15)	C(2)	C(1)	1.5119(16)
C(16)	C(17)	1.3937(14)	C(2)	C(4)	1.5188(16)

*Table 11. Bond Angles for **188***

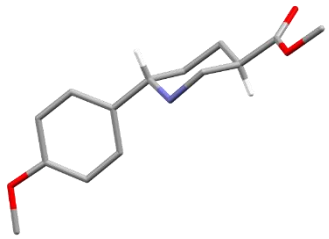
Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(5)	O(1)	C(2)	120.58(8)	O(4)	C(7)	C(8)	125.02(10)
C(16)	O(6)	C(20)	118.01(8)	O(3)	C(7)	C(8)	110.74(9)
C(7)	O(3)	C(6)	115.89(9)	C(16)	C(15)	C(14)	119.37(9)
C(5)	N(1)	C(9)	120.13(8)	C(11)	C(10)	C(9)	111.86(9)
C(5)	N(1)	C(12)	125.84(8)	C(14)	C(13)	C(12)	121.65(9)
C(9)	N(1)	C(12)	114.02(8)	C(14)	C(13)	C(18)	118.56(9)
O(1)	C(5)	N(1)	110.36(8)	C(18)	C(13)	C(12)	119.79(9)
O(2)	C(5)	O(1)	126.67(9)	N(1)	C(12)	C(11)	99.95(8)
O(2)	C(5)	N(1)	122.95(9)	N(1)	C(12)	C(13)	113.74(8)
O(6)	C(16)	C(15)	125.16(9)	C(11)	C(12)	C(13)	113.64(8)
O(6)	C(16)	C(17)	115.02(9)	O(5)	C(19)	C(11)	124.25(10)
C(15)	C(16)	C(17)	119.82(9)	C(18)	C(17)	C(16)	120.02(10)
C(10)	C(11)	C(12)	112.55(9)	O(1)	C(2)	C(3)	102.39(8)
C(10)	C(11)	C(19)	123.75(10)	O(1)	C(2)	C(1)	110.65(9)
C(19)	C(11)	C(12)	123.64(9)	O(1)	C(2)	C(4)	108.60(9)
N(1)	C(9)	C(10)	101.10(8)	C(3)	C(2)	C(4)	111.06(9)
N(1)	C(9)	C(8)	110.47(8)	C(1)	C(2)	C(3)	111.07(10)
C(10)	C(9)	C(8)	112.68(8)	C(1)	C(2)	C(4)	112.58(10)
C(13)	C(14)	C(15)	121.19(10)	C(17)	C(18)	C(13)	121.05(9)
O(4)	C(7)	O(3)	124.20(10)	C(7)	C(8)	C(9)	113.94(8)

*Table 12. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for **188***

Atom	*x*	*y*	*z*	U(eq)
H(9)	-224.54	3939.43	1741.24	21
H(14)	2541.26	794.5	1974.27	24
H(15)	3365.14	-1564.44	2440.6	25
H(10)	1988.61	4244.31	433.7	23
H(12)	5991.5	3666.33	2109.24	20
H(19)	5774.24	3197.54	-53.03	26
H(17)	9198.62	-529.16	3112.11	26
H(18)	8321.11	1810.95	2669.52	24
H(8A)	540.71	6094.52	2294.16	25
H(8B)	2320.81	6373.22	1582.21	25
H(3A)	6122.45	1403.14	4380.48	40
H(3B)	5407.24	1823.83	5230.83	40
H(3C)	6402.19	2943.09	4562.46	40
H(20A)	5279.72	-3789.13	2545.2	40
H(20B)	4243.06	-3515.82	3391.36	40
H(20C)	6264.07	-4614.44	3316.85	40
H(1A)	3035.67	4566.55	4744.14	52
H(1B)	2012.11	3446.89	5405.67	52
H(1C)	687.61	4036.95	4658.31	52
H(4A)	343.91	1627.33	4276.5	51
H(4B)	1579.52	935.43	5026.95	51
H(4C)	2475.36	628.58	4170.19	51
H(6A)	-2002.24	8701.68	87.63	52
H(6B)	-1881.03	9924.26	611.92	52
H(6C)	-3598.67	8767.31	855.26	52

Methyl-6-(4-methoxyphenyl)piperidine-3-carboxylate (91)

*Table 13. Crystal data and structure refinement for **91***



Identification code	R092
Empirical formula	$C_{14}H_{19}NO_3$
Formula weight	249.30
Temperature/K	123.01(10)
Crystal system	monoclinic
Space group	C2/c
a/Å	18.9502(7)
b/Å	7.0518(2)
c/Å	21.3143(7)
α/°	90
β/°	114.296(4)
γ/°	90
Volume/Å^3	2596.02(17)
Z	8
ρ_{calc}g/cm^3	1.276
μ/mm^{-1}	0.726
F(000)	1072.0
Crystal size/mm^3	0.237 × 0.145 × 0.074
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.104 to 148.65
Index ranges	-22 ≤ h ≤ 23, -8 ≤ k ≤ 7, -26 ≤ l ≤ 24
Reflections collected	16486
Independent reflections	2632 [R_{int} = 0.0264, R_{sigma} = 0.0132]
Data/restraints/parameters	2632/0/169
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0358, wR_2 = 0.0919
Final R indexes [all data]	R_1 = 0.0386, wR_2 = 0.0941
Largest diff. peak/hole / e Å^{-3}	0.21/-0.20

*Table 14. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **91**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
O(3)	8375.0(5)	9713.8(12)	7091.3(4)	30.2(2)
O(2)	5162.2(5)	-1854.0(12)	4055.1(5)	37.6(2)
O(1)	4774.1(6)	526.8(13)	3303.4(4)	41.1(2)
N(1)	5993.5(5)	4464.3(13)	4788.9(5)	24.4(2)
C(8)	6902.0(6)	5422.5(15)	5936.0(5)	22.1(2)
C(10)	7971.2(6)	7559.7(16)	6108.4(5)	23.5(2)
C(9)	7468.0(6)	6129.3(16)	5740.9(5)	23.8(2)
C(11)	7912.7(6)	8298.1(16)	6690.0(5)	23.5(2)
C(13)	6860.2(6)	6177.1(17)	6523.6(5)	25.4(2)
C(3)	5776.9(6)	1205.1(15)	4382.8(5)	24.1(2)
C(12)	7358.6(6)	7592.4(17)	6898.6(5)	27.0(2)
C(7)	6346.3(6)	3904.2(15)	5520.0(5)	23.1(2)

C(4)	5397.1(6)	3128.6(15)	4367.3(5)	24.1(2)
C(6)	6741.0(6)	1987.3(15)	5573.0(6)	25.7(2)
C(5)	6178.0(6)	494.9(15)	5122.8(6)	26.2(2)
C(2)	5216.0(6)	-224.3(16)	3917.0(6)	25.7(2)
C(14)	8925.8(7)	10515.9(18)	6875.8(6)	33.6(3)
C(1)	4195.6(9)	-721(2)	2829.3(7)	46.9(4)

*Table 15. Anisotropic Displacement Parameters ($Å^2×10^3$) for **91**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(3)	33.6(4)	30.4(4)	26.5(4)	-4.8(3)	12.3(3)	-5.7(3)
O(2)	37.7(5)	20.8(4)	50.2(5)	2.7(4)	13.8(4)	-3.7(3)
O(1)	51.5(6)	26.4(5)	32.5(4)	-2.2(4)	4.3(4)	-10.0(4)
N(1)	26.0(5)	17.5(5)	25.6(4)	3.0(3)	6.4(4)	1.9(4)
C(8)	22.3(5)	21.2(5)	22.8(5)	4.5(4)	9.3(4)	3.4(4)
C(10)	22.9(5)	26.4(6)	23.0(5)	3.5(4)	11.1(4)	0.7(4)
C(9)	25.9(5)	26.1(6)	21.5(5)	0.1(4)	12.0(4)	2.3(4)
C(11)	24.2(5)	22.9(5)	20.4(5)	2.4(4)	6.4(4)	3.0(4)
C(13)	24.6(5)	30.7(6)	23.8(5)	5.3(4)	12.8(4)	2.0(4)
C(3)	24.6(5)	19.1(5)	30.2(5)	1.8(4)	12.8(4)	1.0(4)
C(12)	30.1(5)	32.4(6)	21.0(5)	0.1(4)	13.0(4)	3.3(5)
C(7)	23.3(5)	22.5(6)	25.5(5)	3.2(4)	12.2(4)	1.2(4)
C(4)	22.9(5)	19.8(5)	27.8(5)	1.6(4)	8.6(4)	1.0(4)
C(6)	25.8(5)	20.9(6)	28.1(5)	6.4(4)	8.6(4)	4.1(4)
C(5)	27.8(5)	18.8(5)	33.1(6)	5.6(4)	13.7(5)	2.8(4)
C(2)	26.2(5)	20.8(5)	34.5(6)	0.0(4)	16.9(5)	1.3(4)
C(14)	34.4(6)	30.5(6)	33.5(6)	-1.0(5)	11.5(5)	-8.1(5)
C(1)	52.1(8)	34.1(7)	41.0(7)	-9.8(6)	5.5(6)	-11.0(6)

*Table 16. Bond Lengths for **91***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(3)	C(11)	1.3708(14)	C(10)	C(9)	1.3877(15)
O(3)	C(14)	1.4195(14)	C(10)	C(11)	1.3903(15)
O(2)	C(2)	1.2010(14)	C(11)	C(12)	1.3900(15)
O(1)	C(2)	1.3382(14)	C(13)	C(12)	1.3805(16)
O(1)	C(1)	1.4442(15)	C(3)	C(4)	1.5295(15)
N(1)	C(7)	1.4745(13)	C(3)	C(5)	1.5264(15)
N(1)	C(4)	1.4615(14)	C(3)	C(2)	1.5044(15)
C(8)	C(9)	1.3925(14)	C(7)	C(6)	1.5264(15)
C(8)	C(13)	1.3927(15)	C(6)	C(5)	1.5245(15)
C(8)	C(7)	1.5077(15)			

*Table 17. Bond Angles for **91***

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(11)	O(3)	C(14)	117.03(9)	C(2)	C(3)	C(4)	112.42(9)
C(2)	O(1)	C(1)	115.62(10)	C(2)	C(3)	C(5)	112.23(9)

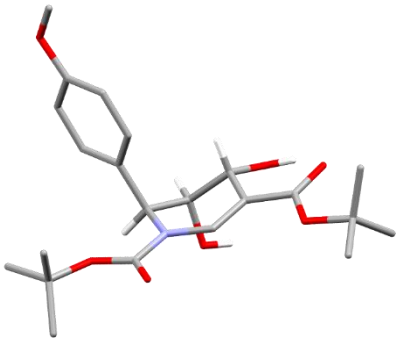
C(4)	N(1)	C(7)	112.14(8)	C(13)	C(12)	C(11)	120.03(10)
C(9)	C(8)	C(13)	117.88(10)	N(1)	C(7)	C(8)	109.55(8)
C(9)	C(8)	C(7)	121.06(9)	N(1)	C(7)	C(6)	108.11(9)
C(13)	C(8)	C(7)	121.06(9)	C(8)	C(7)	C(6)	112.52(8)
C(9)	C(10)	C(11)	119.17(10)	N(1)	C(4)	C(3)	108.68(8)
C(10)	C(9)	C(8)	121.76(9)	C(5)	C(6)	C(7)	111.72(8)
O(3)	C(11)	C(10)	124.35(10)	C(6)	C(5)	C(3)	110.24(9)
O(3)	C(11)	C(12)	115.72(9)	O(2)	C(2)	O(1)	122.42(11)
C(12)	C(11)	C(10)	119.93(10)	O(2)	C(2)	C(3)	125.98(11)
C(12)	C(13)	C(8)	121.23(10)	O(1)	C(2)	C(3)	111.59(9)
C(5)	C(3)	C(4)	110.07(9)				

Table 18. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for ***91***

Atom	***x***	***y***	***z***	**U(eq)**
H(10)	8342.76	8018.65	5967.53	28
H(9)	7509.92	5629.44	5353.86	29
H(13)	6489.7	5719.07	6666	31
H(3)	6179.27	1402.58	4212.5	29
H(12)	7323.61	8073.99	7291.02	32
H(7)	5936.45	3768.38	5684.77	28
H(4A)	5150.58	3588.44	3897.57	29
H(4B)	5004.28	3003.53	4546.23	29
H(6A)	7164.95	2126.47	5433.25	31
H(6B)	6955.29	1566.49	6048.38	31
H(5A)	5793.5	219.4	5301.12	31
H(5B)	6456.47	-667.17	5133.16	31
H(14A)	8663.79	11026.38	6420.43	50
H(14B)	9283.13	9553.17	6873.97	50
H(14C)	9202.99	11510.56	7187.24	50
H(1A)	3914.5	-64.67	2404.24	70
H(1B)	3844.1	-1111.25	3024.86	70
H(1C)	4443.56	-1816.45	2743.6	70
H(1)	5775(9)	5650(20)	4743(8)	40(4)

1-(*tert*-Butyl) 3-butyl (4*S**,5*R**,6*R**)-4,5-dihydroxy-6-(4-methoxyphenyl)-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (227)

*Table 19. Crystal data and structure refinement for **227***



Identification code	R025
Empirical formula	$C_{22}H_{31}NO_7$
Formula weight	421.48
Temperature/K	123.01(11)
Crystal system	trigonal
Space group	R-3c
a/Å	20.7472(2)
b/Å	20.7472(2)
c/Å	55.9713(6)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	20864.8(5)
Z	36
ρ_{calc}g/cm^3	1.208
μ/mm^{-1}	0.742
F(000)	8136.0
Crystal size/mm^3	0.221 × 0.196 × 0.118
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.846 to 150.728
Index ranges	-25 ≤ h ≤ 24, -25 ≤ k ≤ 26, -69 ≤ l ≤ 70
Reflections collected	64951
Independent reflections	4784 [R_{int} = 0.0327, R_{sigma} = 0.0109]
Data/restraints/parameters	4784/0/281
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0331, wR_2 = 0.0873
Final R indexes [all data]	R_1 = 0.0348, wR_2 = 0.0889
Largest diff. peak/hole / e Å^{-3}	0.29/-0.19

*Table 20. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **227**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
O(7)	5433.2(4)	8533.6(4)	7074.4(2)	29.30(17)
O(4)	7697.5(4)	8939.7(4)	7490.3(2)	29.92(17)
O(1)	7247.7(4)	6957.4(4)	7115.9(2)	29.29(17)
O(3)	9406.3(4)	8907.9(4)	6274.5(2)	31.53(17)
O(2)	6037.4(4)	6652.0(4)	7074.8(2)	33.66(18)
O(5)	7650.1(5)	10092.0(4)	7224.2(2)	36.7(2)
O(6)	6322.9(5)	9745.5(4)	7052.5(2)	38.7(2)
N(1)	6973.9(4)	7860.4(4)	7120.7(2)	22.83(17)
C(7)	8182.8(5)	8492.1(5)	6902.3(2)	23.02(19)
C(16)	6480.1(5)	8117.6(5)	7107.5(2)	23.1(2)

C(5)	6691.3(5)	7094.7(5)	7101.4(2)	24.1(2)
C(8)	8930.5(5)	8678.0(5)	6902.2(2)	24.8(2)
C(9)	9324.6(5)	8821.6(6)	6691.3(2)	26.0(2)
C(15)	6687.7(5)	8843.9(5)	7102.9(2)	23.7(2)
C(14)	7506.0(6)	9419.1(5)	7111.8(2)	24.9(2)
C(6)	7786.6(5)	8375.3(5)	7139.2(2)	22.43(19)
C(17)	6141.5(6)	9090.6(6)	7075.0(2)	27.4(2)
C(10)	8974.3(6)	8770.7(5)	6474.2(2)	25.3(2)
C(13)	7921.9(6)	9105.3(5)	7249.7(2)	23.9(2)
C(1)	7144.9(6)	6214.6(5)	7063.6(2)	27.8(2)
C(12)	7844.8(6)	8446.4(6)	6685.0(2)	29.9(2)
C(11)	8230.0(6)	8578.6(6)	6470.2(2)	30.6(2)
C(18)	4813.9(6)	8689.7(6)	7045.7(2)	32.0(2)
C(2)	7939.6(7)	6368.0(7)	7072.4(3)	41.2(3)
C(00P)	9060.4(7)	8858.2(8)	6051.4(2)	39.6(3)
C(19)	4132.9(7)	7918.1(7)	7059.6(3)	43.9(3)
C(21)	4816.3(8)	9173.9(8)	7249.0(3)	47.3(3)
C(20)	4858.8(8)	9026.0(8)	6801.4(2)	46.2(3)
C(4)	6668.4(8)	5673.6(7)	7255.4(3)	50.0(3)
C(3)	6818.1(9)	5973.4(9)	6816.7(3)	53.0(4)

*Table 21. Anisotropic Displacement Parameters ($Å^2×10^3$) for **227**. The Anisotropic displacement factor exponent takes the form: $-2π^2[h^2a^{*2}U_{11}+2hka*b*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O(7)	24.5(4)	24.6(4)	40.9(4)	4.1(3)	0.4(3)	13.8(3)
O(4)	44.5(4)	27.6(4)	23.3(3)	-2.6(3)	-1.8(3)	22.2(3)
O(1)	24.3(3)	18.7(3)	45.1(4)	-7.6(3)	-3.8(3)	10.9(3)
O(3)	32.6(4)	35.6(4)	28.6(4)	1.2(3)	5.0(3)	18.7(3)
O(2)	21.9(4)	19.5(3)	55.2(5)	-1.3(3)	0.7(3)	7.0(3)
O(5)	41.3(5)	20.0(4)	49.8(5)	-10.4(3)	-19.2(4)	16.1(3)
O(6)	34.1(4)	23.0(4)	60.2(5)	4.3(3)	-3.2(4)	15.2(3)
N(1)	19.6(4)	17.2(4)	29.2(4)	-1.9(3)	0.8(3)	7.4(3)
C(7)	20.7(4)	18.5(4)	26.9(5)	-2.9(3)	-1.1(4)	7.6(4)
C(16)	21.2(4)	21.5(4)	25.2(4)	-0.7(4)	1.4(3)	9.6(4)
C(5)	22.9(5)	18.9(4)	28.4(5)	-1.4(4)	1.8(4)	9.0(4)
C(8)	22.7(5)	22.7(5)	28.4(5)	-3.6(4)	-4.4(4)	10.8(4)
C(9)	20.1(4)	23.8(5)	33.8(5)	-2.6(4)	-0.7(4)	10.9(4)
C(15)	23.7(5)	21.1(5)	25.0(5)	-0.4(3)	-0.8(4)	10.1(4)
C(14)	26.7(5)	16.9(4)	27.3(5)	-1.6(4)	-3.9(4)	8.0(4)
C(6)	19.3(4)	18.5(4)	26.5(5)	-2.3(3)	-2.2(3)	7.2(4)
C(17)	28.3(5)	23.5(5)	30.5(5)	1.2(4)	0.1(4)	13.1(4)
C(10)	26.7(5)	20.8(5)	28.3(5)	-0.8(4)	3.1(4)	11.8(4)
C(13)	25.0(5)	19.1(4)	24.3(4)	-2.4(3)	-3.2(4)	8.5(4)
C(1)	29.2(5)	19.3(5)	36.9(5)	-7.7(4)	-4.3(4)	13.5(4)
C(12)	19.8(5)	36.7(6)	30.5(5)	-3.8(4)	-3.2(4)	12.0(4)
C(11)	27.5(5)	37.1(6)	26.1(5)	-3.4(4)	-4.3(4)	15.4(5)

C(18)	27.4(5)	32.6(6)	40.8(6)	6.5(4)	-1.4(4)	18.6(5)
C(2)	31.4(6)	29.4(6)	66.6(8)	-11.4(5)	-4.3(5)	18.0(5)
C(00P)	47.4(7)	50.8(7)	29.1(5)	6.7(5)	5.1(5)	30.8(6)
C(19)	27.6(6)	40.8(7)	60.5(8)	13.5(6)	-2.0(5)	15.0(5)
C(21)	44.5(7)	56.4(8)	56.3(8)	-5.2(6)	-1.1(6)	36.6(7)
C(20)	43.9(7)	44.9(7)	48.7(7)	15.2(6)	-5.7(6)	21.4(6)
C(4)	51.8(8)	37.4(7)	69.1(9)	16.0(6)	14.9(7)	28.4(6)
C(3)	69.6(9)	59.5(9)	49.5(8)	-28.8(7)	-24.0(7)	47.0(8)

*Table 22. Bond Lengths for **227***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(7)	C(17)	1.3405(13)	C(16)	C(15)	1.3446(14)
O(7)	C(18)	1.4825(12)	C(8)	C(9)	1.3812(14)
O(4)	C(13)	1.4100(12)	C(9)	C(10)	1.3927(14)
O(1)	C(5)	1.3226(12)	C(15)	C(14)	1.5110(14)
O(1)	C(1)	1.4755(11)	C(15)	C(17)	1.4664(14)
O(3)	C(10)	1.3703(12)	C(14)	C(13)	1.5251(14)
O(3)	C(00P)	1.4179(14)	C(6)	C(13)	1.5264(13)
O(2)	C(5)	1.2083(13)	C(10)	C(11)	1.3887(15)
O(5)	C(14)	1.4203(12)	C(1)	C(2)	1.5156(15)
O(6)	C(17)	1.2216(13)	C(1)	C(4)	1.5100(17)
N(1)	C(16)	1.3735(12)	C(1)	C(3)	1.5100(16)
N(1)	C(5)	1.3956(12)	C(12)	C(11)	1.3931(15)
N(1)	C(6)	1.4811(12)	C(18)	C(19)	1.5176(16)
C(7)	C(8)	1.3988(14)	C(18)	C(21)	1.5165(18)
C(7)	C(6)	1.5145(13)	C(18)	C(20)	1.5163(16)
C(7)	C(12)	1.3832(14)			

*Table 23. Bond Angles for **227***

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(17)	O(7)	C(18)	120.55(8)	O(7)	C(17)	C(15)	113.87(9)
C(5)	O(1)	C(1)	121.79(8)	O(6)	C(17)	O(7)	123.63(10)
C(10)	O(3)	C(00P)	116.64(9)	O(6)	C(17)	C(15)	122.49(10)
C(16)	N(1)	C(5)	117.88(8)	O(3)	C(10)	C(9)	115.70(9)
C(16)	N(1)	C(6)	121.66(8)	O(3)	C(10)	C(11)	124.37(9)
C(5)	N(1)	C(6)	120.35(8)	C(11)	C(10)	C(9)	119.93(9)
C(8)	C(7)	C(6)	118.87(9)	O(4)	C(13)	C(14)	113.53(8)
C(12)	C(7)	C(8)	118.23(9)	O(4)	C(13)	C(6)	105.69(8)
C(12)	C(7)	C(6)	122.88(9)	C(14)	C(13)	C(6)	110.85(8)
C(15)	C(16)	N(1)	123.59(9)	O(1)	C(1)	C(2)	101.55(8)
O(1)	C(5)	N(1)	108.98(8)	O(1)	C(1)	C(4)	109.54(9)
O(2)	C(5)	O(1)	127.80(9)	O(1)	C(1)	C(3)	109.51(9)
O(2)	C(5)	N(1)	123.22(9)	C(4)	C(1)	C(2)	111.86(10)
C(9)	C(8)	C(7)	121.00(9)	C(4)	C(1)	C(3)	112.68(12)
C(8)	C(9)	C(10)	119.96(9)	C(3)	C(1)	C(2)	111.11(10)
C(16)	C(15)	C(14)	119.22(9)	C(7)	C(12)	C(11)	121.61(10)

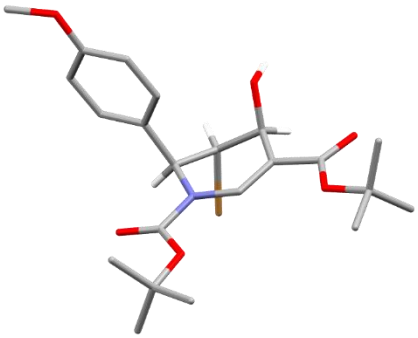
C(16)	C(15)	C(17)	121.52(9)	C(10)	C(11)	C(12)	119.27(9)
C(17)	C(15)	C(14)	119.15(9)	O(7)	C(18)	C(19)	102.45(9)
O(5)	C(14)	C(15)	113.07(9)	O(7)	C(18)	C(21)	110.32(9)
O(5)	C(14)	C(13)	108.02(8)	O(7)	C(18)	C(20)	109.74(10)
C(15)	C(14)	C(13)	109.36(8)	C(21)	C(18)	C(19)	110.68(11)
N(1)	C(6)	C(7)	112.66(8)	C(21)	C(18)	C(20)	113.12(11)
N(1)	C(6)	C(13)	108.80(8)	C(20)	C(18)	C(19)	110.03(10)
C(7)	C(6)	C(13)	112.34(8)				

Table 24. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for ***227***

Atom	***x***	***y***	***z***	**U(eq)**
H(4)	7674.07	9288.06	7550.16	45
H(5)	7322.64	10186.07	7188.34	55
H(16)	5974.47	7770.33	7101.27	28
H(8)	9165.79	8705.44	7046.39	30
H(9)	9823.57	8952.1	6694.25	31
H(14)	7699.46	9530.69	6948.15	30
H(6)	7987.08	8152.31	7249.5	27
H(13)	8456.11	9466.57	7244.58	29
H(12)	7348.24	8324.37	6682.3	36
H(11)	7991.41	8538.72	6325.73	37
H(2A)	8236.21	6749.61	6958.92	62
H(2B)	7948.26	5921.59	7033.83	62
H(2C)	8137.55	6530.12	7229.97	62
H(00A)	9416.2	8978.34	5925.29	59
H(00B)	8877.59	9201.48	6048.71	59
H(00C)	8653.25	8360.99	6029.3	59
H(19A)	4149.26	7615.28	6932.74	66
H(19B)	3691.57	7955.04	7044.26	66
H(19C)	4126.97	7696.03	7210.66	66
H(21A)	4855.01	8968.72	7398.43	71
H(21B)	4362.66	9191.5	7245.96	71
H(21C)	5232.64	9668.12	7231.31	71
H(20A)	5303.66	9503.35	6791.47	69
H(20B)	4432.4	9084.23	6777.85	69
H(20C)	4868.91	8703.45	6680.36	69
H(4A)	6885.47	5863.97	7409.18	75
H(4B)	6639.11	5202.32	7229.3	75
H(4C)	6177.61	5610.46	7249.72	75
H(3A)	6314.45	5875.93	6816.28	79
H(3B)	6824.74	5529.54	6772.73	79
H(3C)	7107.5	6361.47	6704.26	79

Di-*tert*-butyl (4*R**,5*R**,6*R**)-5-bromo-4-hydroxy-6-(4-methoxyphenyl)-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (229)

*Table 25. Crystal data and structure refinement for **229***



Identification code	R048_Wdh
Empirical formula	$C_{22}H_{30}BrNO_6$
Formula weight	484.39
Temperature/K	122.99(13)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	17.1457(3)
b/Å	11.08510(10)
c/Å	13.3111(3)
α/°	90
β/°	111.042(2)
γ/°	90
Volume/Å^3	2361.23(8)
Z	4
ρ_{calc}g/cm^3	1.3625
μ/mm^{-1}	2.676
F(000)	1008.3
Crystal size/mm^3	0.24 × 0.133 × 0.038
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.7 to 149.94
Index ranges	-21 ≤ h ≤ 21, -13 ≤ k ≤ 13, -15 ≤ l ≤ 16
Reflections collected	59974
Independent reflections	4806 [R_{int} = 0.0667, R_{sigma} = 0.0234]
Data/restraints/parameters	4806/0/395
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0286, wR_2 = 0.0695
Final R indexes [all data]	R_1 = 0.0337, wR_2 = 0.0726
Largest diff. peak/hole / e Å^{-3}	0.36/-0.39

*Table 26. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **229**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
Br	2863(12)	6981(9)	5903(10)	33.24(12)
Br(01)	3208.9(4)	6824.5(3)	6147.1(3)	33.24(12)
O(002)	4835.3(6)	8512.8(10)	3780.4(10)	24.5(2)
O(003)	2203.5(7)	9503.3(9)	2901.4(10)	27.6(3)
O(004)	3851.9(8)	4985.8(10)	3881.9(10)	27.5(3)
O(005)	5443.4(7)	6838.3(10)	4685.8(11)	31.4(3)
O(006)	1171.8(7)	8298.3(10)	3036.9(13)	36.5(3)
O(007)	676.5(8)	3513.0(13)	274.3(12)	42.7(3)
N(008)	2523.7(8)	7655.5(11)	3608.3(11)	22.0(3)
C(1)	1870.1(10)	5663.8(14)	2948.9(14)	23.9(3)

C(2)	2183.8(10)	5507.1(15)	2128.1(14)	26.5(3)
C(3)	1774.6(11)	4779.6(16)	1253.0(15)	30.8(4)
C(4)	1035.9(10)	4194.3(15)	1181.8(15)	30.0(4)
C(5)	717.2(11)	4328.7(15)	1991.3(17)	32.4(4)
C(6)	1138.0(10)	5066.4(15)	2864.9(17)	29.6(4)
C(7)	2273.7(10)	6479.6(14)	3914.6(14)	24.1(3)
C(8)	3022.7(10)	5918.8(14)	4806.0(14)	24.3(3)
C(9)	3854.6(10)	5914.6(13)	4620.0(14)	22.6(3)
C(10)	3976.3(10)	7110.1(13)	4173.2(13)	20.8(3)
C(11)	3339.1(9)	7874.6(14)	3722.6(13)	20.4(3)
C(12)	4823.2(10)	7452.0(14)	4244.8(13)	22.2(3)
C(13)	5605.9(10)	9021.7(14)	3687.7(15)	25.4(3)
C(14)	5291.7(13)	10214.4(16)	3122.3(19)	35.3(4)
C(15)	6253.2(13)	9236(2)	4798.7(18)	39.9(5)
C(16)	5910.1(13)	8199.7(17)	2997.0(18)	32.6(4)
C(17)	1888.7(10)	8502.0(14)	3157.5(15)	26.5(4)
C(18)	1656.8(10)	10502.2(15)	2299.7(15)	29.6(4)
C(19)	2282.9(13)	11326.5(18)	2081.5(19)	38.0(5)
C(20)	1028.2(14)	10016(2)	1255.0(19)	44.7(5)
C(21)	1257.3(13)	11097.7(17)	3009.3(19)	37.2(4)
C(22)	-149.6(13)	3067(2)	76(2)	46.0(6)

*Table 27. Anisotropic Displacement Parameters ($Å^2×10^3$) for **229**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{12}**	**U_{13}**	**U_{23}**
Br	44.1(3)	33.15(12)	28.23(14)	-3.73(12)	19.93(17)	-4.37(9)
Br(01)	44.1(3)	33.15(12)	28.23(14)	-3.73(12)	19.93(17)	-4.37(9)
O(002)	19.3(5)	20.2(5)	34.2(6)	0.9(4)	9.8(5)	7.6(5)
O(003)	23.0(5)	15.3(5)	42.3(7)	4.2(4)	9.2(5)	7.4(5)
O(004)	38.2(7)	17.2(5)	28.1(6)	8.7(5)	13.2(5)	3.3(5)
O(005)	25.2(6)	30.3(6)	38.2(7)	9.7(5)	10.9(5)	14.1(5)
O(006)	23.5(6)	24.6(6)	63.8(9)	3.0(5)	18.5(6)	2.7(6)
O(007)	33.7(7)	41.5(7)	44.5(8)	-6.5(6)	3.8(6)	-10.2(6)
N(008)	22.1(6)	13.8(6)	32.4(7)	1.2(5)	12.8(6)	2.2(5)
C(1)	23.0(7)	15.1(7)	34.9(9)	1.8(6)	12.0(7)	4.1(6)
C(2)	22.3(8)	23.8(8)	33.4(9)	-2.3(6)	9.7(7)	2.9(7)
C(3)	27.5(8)	31.1(9)	32.4(10)	1.3(7)	8.9(7)	-0.3(7)
C(4)	25.8(8)	19.7(8)	37.5(10)	2.5(6)	2.7(7)	-0.3(7)
C(5)	24.4(8)	20.7(8)	51.2(12)	-2.3(7)	12.5(8)	2.2(8)
C(6)	26.0(8)	23.6(8)	43.6(11)	-1.2(7)	17.9(8)	2.0(7)
C(7)	26.0(8)	17.2(7)	34.7(9)	-0.8(6)	17.8(7)	2.2(7)
C(8)	34.5(9)	15.8(7)	26.4(9)	-0.5(6)	15.5(7)	1.5(6)
C(9)	28.7(8)	15.6(7)	24.3(8)	4.3(6)	10.6(7)	4.1(6)
C(10)	24.9(7)	17.0(7)	22.1(8)	2.2(6)	10.3(6)	2.6(6)
C(11)	23.7(7)	14.4(7)	24.7(8)	-0.2(6)	10.7(6)	0.3(6)
C(12)	24.5(7)	20.0(7)	22.4(8)	3.4(6)	8.8(6)	3.4(6)
C(13)	21.1(7)	22.5(8)	34.6(9)	-3.7(6)	12.3(7)	0.2(7)

C(14)	37.6(10)	22.0(9)	52.4(13)	-2.8(7)	23.7(10)	4.5(8)
C(15)	30.6(9)	45.3(12)	40.3(12)	-9.0(9)	8.5(9)	-6.9(10)
C(16)	37.5(10)	25.0(9)	42.3(11)	-0.7(8)	22.9(9)	0.2(8)
C(17)	24.1(8)	18.1(7)	37.6(10)	2.0(6)	11.5(7)	-0.7(7)
C(18)	27.7(8)	19.5(8)	37.3(10)	8.7(6)	6.4(7)	6.9(7)
C(19)	42.0(11)	25.2(9)	47.7(12)	8.3(8)	17.3(10)	13.5(9)
C(20)	42.0(11)	39.3(11)	41.2(12)	11.8(9)	0.9(10)	1.6(9)
C(21)	37.8(10)	23.9(9)	50.9(13)	9.3(8)	17.0(10)	2.4(8)
C(22)	34.6(10)	31.7(10)	55.8(14)	-5.8(8)	-3.0(10)	-0.4(10)

*Table 28. Bond Lengths for **229***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Br(01)	C(8)	1.9716(17)	C(4)	C(3)	1.396(2)
O(002)	C(12)	1.3321(19)	C(4)	C(5)	1.380(3)
O(002)	C(13)	1.4820(18)	C(6)	C(5)	1.392(3)
O(003)	C(17)	1.331(2)	C(7)	C(1)	1.520(2)
O(003)	C(18)	1.4857(18)	C(7)	C(8)	1.533(2)
O(004)	C(9)	1.4219(19)	C(8)	Br	1.970(8)
O(005)	C(12)	1.2206(19)	C(9)	C(8)	1.533(2)
O(006)	C(17)	1.203(2)	C(10)	C(9)	1.497(2)
O(007)	C(4)	1.369(2)	C(10)	C(11)	1.342(2)
O(007)	C(22)	1.432(3)	C(12)	C(10)	1.470(2)
N(008)	C(7)	1.4746(19)	C(13)	C(14)	1.521(2)
N(008)	C(11)	1.373(2)	C(13)	C(15)	1.515(3)
N(008)	C(17)	1.399(2)	C(13)	C(16)	1.514(2)
C(1)	C(6)	1.388(2)	C(18)	C(19)	1.515(3)
C(2)	C(1)	1.391(2)	C(18)	C(20)	1.520(3)
C(2)	C(3)	1.383(3)	C(18)	C(21)	1.504(3)

*Table 29. Bond Angles for **229***

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C(13)	O(002)	C(12)	122.52(12)	C(9)	C(10)	C(11)	121.95(14)
C(18)	O(003)	C(17)	121.62(12)	C(9)	C(10)	C(12)	118.53(13)
C(22)	O(007)	C(4)	117.09(18)	C(11)	C(10)	C(12)	119.52(14)
C(7)	N(008)	C(11)	120.76(12)	C(10)	C(11)	N(008)	124.83(14)
C(7)	N(008)	C(17)	116.93(13)	O(005)	C(12)	O(002)	123.99(14)
C(17)	N(008)	C(11)	122.26(13)	C(10)	C(12)	O(002)	112.15(12)
C(6)	C(1)	C(2)	118.09(16)	C(10)	C(12)	O(005)	123.86(14)
C(6)	C(1)	C(7)	118.42(16)	C(14)	C(13)	O(002)	101.78(12)
C(7)	C(1)	C(2)	123.47(14)	C(15)	C(13)	O(002)	109.92(15)
C(3)	C(2)	C(1)	120.80(16)	C(15)	C(13)	C(14)	110.61(16)
C(4)	C(3)	C(2)	120.12(18)	C(15)	C(13)	C(16)	113.31(16)
C(3)	C(4)	O(007)	115.23(17)	C(16)	C(13)	O(002)	109.47(13)
C(5)	C(4)	O(007)	124.71(16)	C(16)	C(13)	C(14)	111.14(16)
C(5)	C(4)	C(3)	120.06(17)	O(006)	C(17)	O(003)	127.69(15)
C(6)	C(5)	C(4)	118.93(16)	N(008)	C(17)	O(003)	110.16(13)

C(5)	C(6)	C(1)	122.00(18)	N(008)	C(17)	O(006)	122.15(15)
C(1)	C(7)	N(008)	112.42(14)	C(19)	C(18)	O(003)	101.51(13)
C(1)	C(7)	C(8)	114.45(13)	C(20)	C(18)	O(003)	109.39(14)
C(8)	C(7)	N(008)	109.06(13)	C(20)	C(18)	C(19)	110.91(18)
C(7)	C(8)	C(9)	116.47(13)	C(20)	C(18)	C(21)	113.40(17)
C(8)	C(9)	O(004)	109.96(13)	C(21)	C(18)	O(003)	109.27(15)
C(8)	C(9)	C(10)	109.38(12)	C(21)	C(18)	C(19)	111.68(16)
C(10)	C(9)	O(004)	109.44(13)				

*Table 30. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for **229***

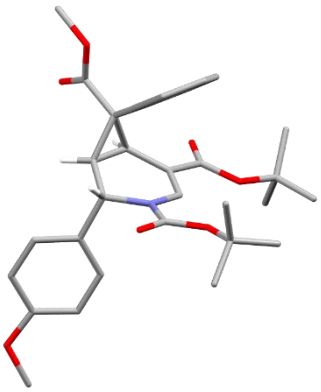
Atom	***x***	***y***	***z***	**U(eq)**
H(004)	4068(14)	4390(20)	4254(19)	41(6)
H(2)	2667(13)	5904(17)	2159(16)	30(5)
H(3)	1979(12)	4667(18)	620(18)	34(5)
H(5)	237(13)	3973(19)	1976(17)	36(5)
H(6)	919(13)	5148(18)	3387(17)	31(5)
H(7)	1866(11)	6636(16)	4209(15)	20(4)
H(8)	2890(11)	5114(17)	4947(15)	24(5)
H(9)	4286(11)	5756(16)	5324(15)	19(4)
H(11)	3434(11)	8605(17)	3457(15)	21(4)
H(14a)	5728(14)	10590(20)	2984(18)	43(6)
H(14b)	4835(15)	10060(20)	2440(20)	44(6)
H(14c)	5105(14)	10740(20)	3590(19)	46(6)
H(15a)	6499(14)	8530(20)	5136(19)	40(6)
H(15b)	6002(14)	9610(20)	5279(19)	44(6)
H(15c)	6694(15)	9750(20)	4738(19)	48(6)
H(16a)	6095(13)	7490(20)	3363(18)	37(6)
H(16b)	6343(14)	8580(20)	2875(18)	39(6)
H(16c)	5453(15)	8052(19)	2310(20)	42(6)
H(19a)	2703(15)	11580(20)	2730(20)	47(7)
H(19b)	2581(14)	10900(20)	1690(19)	46(6)
H(19c)	1994(15)	12020(20)	1710(20)	50(7)
H(20a)	783(15)	10680(20)	800(20)	53(7)
H(20b)	570(15)	9530(20)	1390(19)	48(6)
H(20c)	1313(15)	9520(20)	890(20)	53(7)
H(21a)	1699(16)	11400(20)	3680(20)	55(7)
H(21b)	869(15)	10600(20)	3191(19)	47(6)
H(21c)	935(15)	11760(20)	2650(20)	49(7)
H(22a)	-324(16)	2740(20)	-650(20)	55(7)
H(22b)	-149(15)	2450(20)	610(20)	50(7)
H(22c)	-521(15)	3710(20)	130(20)	54(7)

*Table 31. Atomic Occupancy for **229***

Atom	***Occupancy***	**Atom**	***Occupancy***
Br	0.030(2)	Br(01)	0.970(2)

3,5-Di-*tert*-butyl 7-methyl (1*R**,2*S**,6*S**,7*R**)-2-(4-methoxyphenyl)-7-phenyl-3-azabicyclo[4.1.0]hept-4-ene-3,5,7-tricarboxylate (230)

*Table 32. Crystal data and structure refinement for **230***



Identification code	R042
Empirical formula	$C_{31}H_{37}NO_7$
Formula weight	535.61
Temperature/K	123.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.7904(2)
b/Å	31.2564(5)
c/Å	10.6331(2)
α/°	90
β/°	99.293(2)
γ/°	90
Volume/Å^3	2883.17(10)
Z	4
ρ_{calc}g/cm^3	1.234
μ/mm^{-1}	0.709
F(000)	1144.0
Crystal size/mm^3	0.209 × 0.143 × 0.089
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.89 to 153.12
Index ranges	-11 ≤ h ≤ 11, -38 ≤ k ≤ 38, -9 ≤ l ≤ 13
Reflections collected	33535
Independent reflections	5960 [R_{int} = 0.0415, R_{sigma} = 0.0226]
Data/restraints/parameters	5960/0/360
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0378, wR_2 = 0.0978
Final R indexes [all data]	R_1 = 0.0432, wR_2 = 0.1023
Largest diff. peak/hole / e Å^{-3}	0.27/-0.24

*Table 33. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **230**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
O(1)	3264.1(9)	7303.8(2)	6701.4(8)	18.30(17)
O(7)	6609.5(10)	6549.9(3)	4818.3(9)	22.01(19)
O(6)	6680.1(10)	5824.0(3)	4694.5(8)	23.32(19)
O(2)	1845.8(10)	7000.0(3)	8060.8(8)	23.22(19)
O(3)	5201.3(10)	5629.6(3)	10507.0(8)	26.1(2)
O(4)	2680.1(10)	5609.1(3)	9722.6(9)	30.4(2)
O(5)	-268.8(11)	5077.9(3)	2090.5(9)	29.7(2)
N(1)	4946.7(11)	6159.8(3)	5737.6(9)	15.24(19)
C(7)	4339.1(12)	6539.6(3)	6105.7(10)	14.6(2)
C(6)	3397.6(12)	6559.6(3)	6979.1(10)	15.2(2)

C(10)	4291.4(12)	5741.5(3)	6014.6(10)	15.4(2)
C(5)	2744.5(12)	6970.5(3)	7314.2(10)	15.9(2)
C(8)	3047.2(12)	6173.4(3)	7679.1(10)	15.7(2)
C(18)	6036.5(12)	6094.0(3)	8601.8(10)	15.5(2)
C(26)	6153.2(13)	6152.7(4)	5035.9(11)	17.3(2)
C(24)	3973.3(13)	5710.3(3)	9618.8(11)	17.6(2)
C(9)	3562.1(12)	5755.1(3)	7217.8(10)	15.7(2)
C(11)	3095.9(13)	5583.7(3)	4908.5(11)	16.7(2)
C(19)	7221.0(13)	5833.1(4)	8314.7(11)	18.3(2)
C(17)	4418.0(12)	5931.2(3)	8480.2(10)	15.4(2)
C(23)	6394.5(13)	6504.8(4)	9059.2(11)	19.7(2)
C(12)	2409.9(14)	5843.7(4)	3928.4(11)	20.8(2)
C(20)	8731.4(13)	5980.8(4)	8471.8(11)	21.9(2)
C(13)	1286.7(14)	5687.7(4)	2953.5(12)	22.2(2)
C(2)	2766.2(14)	7743.4(4)	6916.5(11)	20.2(2)
C(14)	833.6(14)	5264.5(4)	2976.5(11)	21.7(2)
C(21)	9074.3(14)	6391.4(4)	8925.6(12)	24.1(3)
C(22)	7904.1(14)	6652.3(4)	9220.5(12)	24.5(3)
C(16)	2651.5(16)	5155.0(4)	4896.0(12)	25.6(3)
C(27)	8012.9(14)	6620.8(4)	4241.2(13)	24.6(3)
C(15)	1527.8(16)	4996.6(4)	3949.9(12)	28.6(3)
C(1)	3745.4(17)	8007.4(4)	6152.6(13)	28.2(3)
C(25)	-886.2(15)	5333.1(4)	1009.0(12)	27.2(3)
C(28)	7837.0(16)	6420.4(5)	2925.5(13)	30.6(3)
C(3)	3126.4(19)	7859.0(4)	8320.5(12)	31.6(3)
C(4)	1068.2(16)	7791.7(4)	6375.9(14)	31.1(3)
C(011)	4898.6(17)	5400.7(5)	11620.3(13)	33.1(3)
C(30)	9398.9(16)	6452.6(5)	5144.9(15)	36.0(3)
C(29)	8049.1(18)	7106.0(5)	4157.0(16)	37.5(3)

*Table 34. Anisotropic Displacement Parameters ($Å^2×10^3$) for **230**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O(1)	21.2(4)	13.5(4)	21.4(4)	-0.2(3)	6.9(3)	1.1(3)
O(7)	20.2(4)	17.3(4)	31.2(5)	-0.4(3)	12.1(3)	-1.0(3)
O(6)	25.6(4)	18.6(4)	27.9(5)	-0.7(3)	10.7(4)	4.2(3)
O(2)	25.6(4)	21.0(4)	25.8(4)	-1.8(3)	12.3(4)	0.5(3)
O(3)	21.2(4)	36.9(5)	19.6(4)	11.5(4)	1.4(3)	-1.1(3)
O(4)	22.1(5)	42.4(5)	26.8(5)	11.2(4)	4.4(4)	-8.8(4)
O(5)	35.2(5)	25.7(5)	23.6(5)	-1.4(4)	-9.5(4)	-7.0(4)
N(1)	15.8(4)	13.6(4)	16.4(4)	-0.1(3)	3.0(3)	-0.3(3)
C(7)	14.3(5)	13.3(5)	15.2(5)	0.4(4)	-0.5(4)	0.4(4)
C(6)	13.7(5)	14.9(5)	16.2(5)	-0.2(4)	0.1(4)	-1.0(4)
C(10)	16.7(5)	12.1(5)	16.8(5)	0.3(4)	0.8(4)	-0.2(4)
C(5)	14.6(5)	17.0(5)	15.6(5)	-0.3(4)	0.6(4)	-1.2(4)
C(8)	13.4(5)	16.8(5)	16.6(5)	0.3(4)	2.0(4)	-0.9(4)
C(18)	15.8(5)	18.9(5)	11.3(5)	2.3(4)	0.8(4)	-1.4(4)

C(26)	16.0(5)	17.7(5)	17.6(5)	0.3(4)	1.0(4)	0.7(4)
C(24)	18.6(5)	16.9(5)	17.3(5)	-0.3(4)	2.8(4)	-1.2(4)
C(9)	15.5(5)	14.6(5)	16.4(5)	0.5(4)	0.7(4)	-2.0(4)
C(11)	18.3(5)	15.4(5)	16.0(5)	-2.3(4)	1.5(4)	0.3(4)
C(19)	18.5(5)	17.4(5)	18.3(5)	0.1(4)	1.2(4)	0.0(4)
C(17)	15.5(5)	16.4(5)	14.1(5)	0.9(4)	2.1(4)	-0.9(4)
C(23)	18.2(5)	21.1(5)	19.8(6)	-2.9(4)	2.8(4)	-0.4(4)
C(12)	23.4(6)	14.6(5)	22.7(6)	0.3(4)	-0.8(5)	-0.3(4)
C(20)	16.7(5)	26.7(6)	22.2(6)	0.7(5)	3.0(4)	2.0(4)
C(13)	23.4(6)	19.4(6)	21.4(6)	1.8(4)	-3.3(5)	2.5(4)
C(2)	27.1(6)	13.4(5)	19.6(6)	-1.6(4)	2.4(4)	2.8(4)
C(14)	22.9(6)	22.0(6)	18.8(6)	-3.8(4)	-0.9(4)	-1.5(4)
C(21)	16.0(5)	29.7(6)	26.4(6)	-0.2(5)	2.5(4)	-5.9(5)
C(22)	22.3(6)	22.0(6)	28.3(6)	-4.7(5)	1.7(5)	-5.6(4)
C(16)	37.8(7)	15.9(6)	19.8(6)	1.7(4)	-5.4(5)	-1.5(5)
C(27)	19.0(6)	26.8(6)	30.4(7)	-0.2(5)	11.3(5)	-2.7(4)
C(15)	41.0(8)	16.3(6)	25.0(6)	0.3(5)	-5.4(5)	-6.6(5)
C(1)	38.7(7)	19.3(6)	26.1(6)	1.5(5)	3.9(5)	-4.2(5)
C(25)	27.1(6)	28.3(6)	22.5(6)	-2.8(5)	-6.9(5)	1.4(5)
C(28)	31.4(7)	35.8(7)	26.7(7)	1.5(5)	11.4(5)	0.8(5)
C(3)	52.2(9)	20.2(6)	21.6(6)	-5.0(5)	3.3(6)	-2.2(5)
C(4)	28.6(7)	32.7(7)	31.6(7)	4.8(5)	3.9(5)	12.6(5)
C(011)	32.6(7)	43.8(8)	23.1(7)	15.1(6)	4.8(5)	-0.3(6)
C(30)	20.9(6)	51.2(9)	35.9(8)	-0.7(6)	4.5(5)	-2.9(6)
C(29)	37.4(8)	28.9(7)	51.6(9)	-1.3(6)	23.7(7)	-10.6(6)

*Table 35. Bond Lengths for **230***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(1)	C(5)	1.3471(13)	C(18)	C(19)	1.3946(16)
O(1)	C(2)	1.4712(13)	C(18)	C(17)	1.4967(15)
O(7)	C(26)	1.3363(14)	C(18)	C(23)	1.3910(16)
O(7)	C(27)	1.4805(14)	C(24)	C(17)	1.4994(15)
O(6)	C(26)	1.2070(14)	C(9)	C(17)	1.5312(15)
O(2)	C(5)	1.2105(14)	C(11)	C(12)	1.3811(16)
O(3)	C(24)	1.3385(14)	C(11)	C(16)	1.3952(16)
O(3)	C(011)	1.4441(15)	C(19)	C(20)	1.3900(16)
O(4)	C(24)	1.2021(15)	C(23)	C(22)	1.3890(17)
O(5)	C(14)	1.3682(14)	C(12)	C(13)	1.3988(16)
O(5)	C(25)	1.4323(15)	C(20)	C(21)	1.3870(18)
N(1)	C(7)	1.3841(14)	C(13)	C(14)	1.3828(17)
N(1)	C(10)	1.4772(13)	C(2)	C(1)	1.5190(17)
N(1)	C(26)	1.3919(15)	C(2)	C(3)	1.5188(17)
C(7)	C(6)	1.3414(16)	C(2)	C(4)	1.5179(18)
C(6)	C(5)	1.4739(15)	C(14)	C(15)	1.3930(17)
C(6)	C(8)	1.4766(15)	C(21)	C(22)	1.3876(18)
C(10)	C(9)	1.5214(15)	C(16)	C(15)	1.3827(17)
C(10)	C(11)	1.5270(15)	C(27)	C(28)	1.5178(19)

C(8)	C(9)	1.4921(15)	C(27)	C(30)	1.5186(19)
C(8)	C(17)	1.5553(15)	C(27)	C(29)	1.5200(19)

*Table 36. Bond Angles for **230***

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(5)	O(1)	C(2)	120.96(9)	C(12)	C(11)	C(16)	118.07(10)
C(26)	O(7)	C(27)	120.28(9)	C(16)	C(11)	C(10)	118.33(10)
C(24)	O(3)	C(011)	115.94(10)	C(20)	C(19)	C(18)	120.80(11)
C(14)	O(5)	C(25)	116.74(10)	C(18)	C(17)	C(8)	121.56(9)
C(7)	N(1)	C(10)	121.47(9)	C(18)	C(17)	C(24)	117.06(9)
C(7)	N(1)	C(26)	121.82(9)	C(18)	C(17)	C(9)	121.57(9)
C(26)	N(1)	C(10)	116.64(9)	C(24)	C(17)	C(8)	112.73(9)
C(6)	C(7)	N(1)	123.03(10)	C(24)	C(17)	C(9)	112.77(9)
C(7)	C(6)	C(5)	121.06(10)	C(9)	C(17)	C(8)	57.81(7)
C(7)	C(6)	C(8)	120.88(10)	C(22)	C(23)	C(18)	120.48(11)
C(5)	C(6)	C(8)	118.00(10)	C(11)	C(12)	C(13)	121.59(11)
N(1)	C(10)	C(9)	111.95(9)	C(21)	C(20)	C(19)	119.92(11)
N(1)	C(10)	C(11)	111.99(9)	C(14)	C(13)	C(12)	119.43(11)
C(9)	C(10)	C(11)	109.01(9)	O(1)	C(2)	C(1)	102.45(9)
O(1)	C(5)	C(6)	112.41(9)	O(1)	C(2)	C(3)	110.79(10)
O(2)	C(5)	O(1)	124.50(10)	O(1)	C(2)	C(4)	109.45(10)
O(2)	C(5)	C(6)	123.09(10)	C(3)	C(2)	C(1)	110.50(10)
C(6)	C(8)	C(9)	116.84(9)	C(4)	C(2)	C(1)	110.55(11)
C(6)	C(8)	C(17)	117.89(9)	C(4)	C(2)	C(3)	112.63(11)
C(9)	C(8)	C(17)	60.28(7)	O(5)	C(14)	C(13)	124.72(11)
C(19)	C(18)	C(17)	121.01(10)	O(5)	C(14)	C(15)	115.60(11)
C(23)	C(18)	C(19)	118.78(10)	C(13)	C(14)	C(15)	119.68(11)
C(23)	C(18)	C(17)	120.15(10)	C(20)	C(21)	C(22)	119.67(11)
O(7)	C(26)	N(1)	110.74(9)	C(21)	C(22)	C(23)	120.36(11)
O(6)	C(26)	O(7)	126.76(11)	C(15)	C(16)	C(11)	121.12(11)
O(6)	C(26)	N(1)	122.50(10)	O(7)	C(27)	C(28)	110.65(10)
O(3)	C(24)	C(17)	111.77(9)	O(7)	C(27)	C(30)	108.85(10)
O(4)	C(24)	O(3)	123.53(11)	O(7)	C(27)	C(29)	101.56(10)
O(4)	C(24)	C(17)	124.68(11)	C(28)	C(27)	C(30)	113.10(11)
C(10)	C(9)	C(17)	122.21(9)	C(28)	C(27)	C(29)	110.94(12)
C(8)	C(9)	C(10)	119.49(9)	C(30)	C(27)	C(29)	111.12(12)
C(8)	C(9)	C(17)	61.91(7)	C(16)	C(15)	C(14)	120.08(11)
C(12)	C(11)	C(10)	123.59(10)				

*Table 37. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **230***

Atom	*x*	*y*	*z*	U(eq)
H(7)	4595.43	6792.7	5730.27	18
H(10)	5134.52	5533	6148.86	18
H(8)	2070.6	6173.34	8012.07	19
H(9)	2871.7	5514.89	7308.81	19
H(19)	6997.69	5557.03	8014.46	22

H(23)	5617.45	6681.98	9258.55	24
H(12)	2701.71	6129.53	3916.37	25
H(20)	9511.07	5804.51	8272.85	26
H(13)	848.55	5867.02	2295.58	27
H(21)	10083.42	6491.35	9031.74	29
H(22)	8131.76	6927.35	9527.74	29
H(16)	3118.89	4972.67	5534.9	31
H(15)	1235.1	4710.96	3963.41	34
H(1A)	4816.66	7956.08	6464.67	42
H(1B)	3522.06	8305.57	6239.67	42
H(1C)	3516.48	7927.35	5270.65	42
H(25A)	-1597.8	5165.04	430.13	41
H(25B)	-62.44	5429.03	586.15	41
H(25C)	-1412.17	5576.15	1285.75	41
H(28A)	7891.35	6114.6	3005.1	46
H(28B)	8649.69	6519.58	2495.01	46
H(28C)	6858.72	6500.21	2444.1	46
H(3A)	2413.21	7716.34	8773.56	47
H(3B)	3035.67	8162.88	8417.61	47
H(3C)	4157.97	7770.98	8657.73	47
H(4A)	897.27	7711.31	5493	47
H(4B)	762.69	8084.1	6455.22	47
H(4C)	470.68	7610.36	6837.65	47
H(01A)	4469.01	5125.39	11370.2	50
H(01B)	4181.68	5560.38	12027.32	50
H(01C)	5844.02	5364.3	12203.38	50
H(30A)	9401.54	6570.68	5978.72	54
H(30B)	10327.38	6534.48	4840.66	54
H(30C)	9344.03	6146.28	5186.73	54
H(29A)	7137.1	7204.95	3614.64	56
H(29B)	8942.88	7193.58	3810.22	56
H(29C)	8090.38	7226.03	4992.88	56

1-(*tert*-Butyl) 3-methyl (2*S**,3*R**,6*S**)-2-hydroxy-6-(4-methoxyphenyl)-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (2,6-*syn*-242a)

*Table 1 Crystal data and structure refinement for 2,6-syn-**242a***

Identification code	S137
Empirical formula	$C_{25}H_{29}NO_6$
Formula weight	439.512
Temperature/K	123.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	11.21817(18)
b/Å	11.7215(2)
c/Å	19.4185(3)
α/°	99.9120(15)
β/°	95.1332(13)
γ/°	108.6042(17)
Volume/Å^3	2355.18(8)
Z	4
ρ_{calc}g/cm^3	1.240
μ/mm^{-1}	0.724
F(000)	939.2
Crystal size/mm^3	0.232 × 0.168 × 0.086
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.14 to 148.44
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 14, -24 ≤ l ≤ 24
Reflections collected	53959
Independent reflections	9376 [R_{int} = 0.0252, R_{sigma} = 0.0144]
Data/restraints/parameters	9376/0/590
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0334, wR_2 = 0.0849
Final R indexes [all data]	R_1 = 0.0370, wR_2 = 0.0881
Largest diff. peak/hole / e Å^{-3}	0.27/-0.17

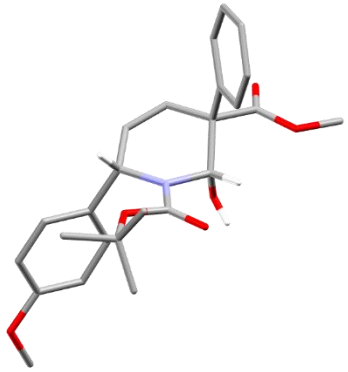


*Table 38. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 2,6-syn-**242a**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
O(2)	3569.3(7)	1486.0(7)	7479.7(4)	24.93(16)
O(4)	1082.3(7)	3624.0(7)	7330.3(4)	27.85(17)
O(10)	5156.6(8)	5923.8(7)	8535.1(4)	28.89(17)
O(8)	4327.1(7)	6785.2(7)	6438.4(4)	27.47(17)
O(9)	2899.9(8)	5428.3(7)	6920.4(4)	31.45(18)
O(3)	4007.2(7)	3457.7(7)	8057.2(5)	32.79(19)
O(12)	3210.1(8)	6311.0(7)	9434.0(4)	34.61(19)
O(6)	416.7(8)	4623.2(8)	8770.3(5)	35.46(19)
O(11)	4986.9(9)	7751.6(8)	10060.2(4)	40.8(2)
O(1)	2201.5(9)	129.6(9)	4386.6(4)	39.7(2)
O(7)	9177.5(8)	5642.6(9)	6170.3(5)	39.6(2)

N(1)	1968.9(8)	2165.2(8)	7650.2(4)	21.35(18)
N(2)	4709.7(8)	6855.6(8)	7589.7(4)	23.85(19)
O(5)	-1400.6(8)	3513.1(9)	8039.4(6)	45.5(2)
C(25)	3257.7(10)	2452.5(9)	7750.6(5)	22.6(2)
C(10)	1452.8(9)	3126.8(9)	7891.2(5)	22.3(2)
C(13)	1150.9(10)	974.5(9)	7204.5(5)	23.1(2)
C(45)	3897.5(10)	6279.7(9)	6973.7(5)	24.2(2)
C(14)	1373.3(10)	776.7(10)	6436.5(5)	23.3(2)
C(4)	502.4(11)	2327.7(9)	8951.1(5)	24.8(2)
C(35)	3490.8(10)	8245.3(10)	8647.6(5)	25.8(2)
C(30)	6874.5(10)	7245.2(10)	7253.8(6)	25.7(2)
C(3)	248.1(10)	2614.6(10)	8221.7(5)	23.8(2)
C(29)	7359.4(10)	7621.5(10)	6663.4(6)	27.3(2)
C(41)	4360.5(10)	6494.7(9)	8245.9(5)	24.9(2)
C(36)	3672.1(11)	9421.0(10)	9033.9(6)	29.3(2)
C(12)	-222.3(10)	765.5(10)	7262.7(6)	28.3(2)
C(2)	-363.1(10)	3615.4(10)	8319.2(6)	28.2(2)
C(32)	6480.0(11)	8567.3(10)	8326.1(6)	28.2(2)
C(34)	4494.9(10)	7650.3(9)	8802.2(5)	25.8(2)
C(31)	5956.3(10)	7797.3(9)	7592.0(6)	25.3(2)
C(17)	1876.0(11)	276.6(11)	5053.5(6)	30.1(2)
C(33)	5838.5(11)	8540.6(10)	8864.0(6)	28.4(2)
C(27)	8446.5(10)	6152.4(11)	6562.0(6)	29.6(2)
C(42)	4294.7(11)	7257.1(10)	9508.1(6)	29.1(2)
C(5)	1709.7(12)	2647.9(11)	9334.2(6)	30.9(2)
C(11)	-641.3(10)	1472.5(10)	7711.3(6)	28.6(2)
C(43)	7222.7(11)	6336.0(11)	7501.0(6)	31.8(2)
C(15)	1151.9(11)	-415.6(10)	6079.6(6)	30.3(2)
C(19)	1826.6(12)	1722.4(11)	6081.1(6)	31.3(2)
C(28)	8146.4(10)	7094.1(11)	6324.1(6)	29.9(2)
C(37)	2758.1(12)	9969.6(11)	8958.3(6)	33.1(3)
C(38)	1637.0(12)	9355.4(11)	8493.8(6)	32.5(3)
C(9)	-546.2(12)	1749.0(11)	9256.5(6)	33.4(3)
C(20)	4904.7(10)	1587.7(10)	7431.3(6)	28.2(2)
C(18)	2085.0(12)	1475.4(11)	5398.0(6)	34.7(3)
C(44)	7993.9(11)	5780.2(11)	7158.7(7)	33.4(3)
C(40)	2371.1(12)	7649.0(11)	8168.4(6)	33.7(3)
C(46)	3598.1(11)	6340.4(11)	5717.3(6)	32.1(3)
C(16)	1382.3(12)	-678.5(11)	5390.7(6)	33.8(3)
C(39)	1455.4(12)	8201.0(12)	8092.2(6)	35.6(3)
C(6)	1863.3(14)	2407.4(12)	10009.6(6)	38.9(3)
C(7)	816.7(15)	1832.4(12)	10301.2(7)	42.7(3)
C(21)	5459.8(13)	2511.9(13)	6985.5(7)	40.5(3)
C(23)	5659.5(12)	1906.5(15)	8163.7(7)	43.1(3)
C(50)	2906.1(15)	5894.8(13)	10075.7(6)	43.6(3)
C(47)	4474.1(14)	7128.4(14)	5299.9(7)	45.5(3)
C(8)	-390.7(15)	1499.9(12)	9922.9(7)	42.7(3)

C(1)	-53.7(15)	5633.9(13)	8938.7(8)	46.3(3)
C(22)	4739.1(14)	289.3(13)	7055.5(9)	49.1(4)
C(26)	9464.9(15)	4657.7(15)	6395.0(10)	53.6(4)
C(49)	3396.7(18)	4996.1(13)	5457.3(7)	54.9(4)
C(24)	2150.9(17)	-1080.1(16)	4070.7(7)	52.8(4)
C(48)	2367.3(14)	6619.5(17)	5715.7(8)	53.0(4)

*Table 39. Anisotropic Displacement Parameters ($Å^2×10^3$) for 2,6-*syn-***242a**. *The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{12}**	**U_{13}**	**U_{23}**
O(2)	23.1(4)	21.6(4)	29.5(4)	8.3(3)	3.5(3)	2.7(3)
O(4)	23.6(4)	30.3(4)	33.9(4)	9.1(3)	7.7(3)	16.7(3)
O(10)	39.1(4)	18.3(4)	25.5(4)	6.7(3)	-1.1(3)	3.8(3)
O(8)	28.2(4)	28.3(4)	21.4(4)	3.0(3)	1.0(3)	7.4(3)
O(9)	31.9(4)	28.2(4)	23.2(4)	-3.3(3)	0.8(3)	4.5(3)
O(3)	23.1(4)	21.7(4)	46.9(5)	4.1(3)	3.7(3)	-2.5(3)
O(12)	44.8(5)	29.0(4)	21.0(4)	0.7(4)	2.4(3)	5.9(3)
O(6)	40.8(5)	28.9(4)	41.5(5)	20.3(4)	5.6(4)	4.2(3)
O(11)	51.5(5)	35.8(5)	23.0(4)	3.6(4)	-5.2(4)	1.8(3)
O(1)	52.5(5)	50.4(5)	21.4(4)	23.4(4)	10.4(4)	8.0(4)
O(7)	35.6(5)	46.6(5)	45.4(5)	22.2(4)	10.0(4)	14.9(4)
N(1)	20.9(4)	19.1(4)	21.7(4)	4.5(3)	2.3(3)	2.8(3)
N(2)	26.0(4)	19.3(4)	21.4(4)	2.0(3)	1.4(3)	3.8(3)
O(5)	24.2(4)	44.1(5)	73.1(7)	13.5(4)	6.5(4)	22.2(5)
C(25)	24.1(5)	20.6(5)	23.3(5)	7.0(4)	4.6(4)	5.3(4)
C(10)	21.3(5)	21.1(5)	24.2(5)	6.4(4)	3.2(4)	5.8(4)
C(13)	25.5(5)	19.1(5)	21.0(5)	3.1(4)	2.3(4)	4.0(4)
C(45)	27.7(5)	20.7(5)	22.1(5)	5.5(4)	3.1(4)	4.4(4)
C(14)	22.0(5)	25.3(5)	20.8(5)	6.1(4)	1.1(4)	4.8(4)
C(4)	34.3(6)	18.2(5)	23.9(5)	11.3(4)	7.6(4)	3.5(4)
C(35)	31.8(5)	22.8(5)	21.1(5)	5.5(4)	5.7(4)	6.5(4)
C(30)	24.1(5)	20.6(5)	26.8(5)	2.0(4)	-1.8(4)	4.2(4)
C(3)	22.4(5)	23.5(5)	25.1(5)	6.2(4)	5.6(4)	6.5(4)
C(29)	25.8(5)	21.6(5)	31.0(5)	3.0(4)	-0.7(4)	9.0(4)
C(41)	30.3(5)	18.7(5)	21.0(5)	3.4(4)	0.7(4)	3.3(4)
C(36)	35.7(6)	24.8(5)	24.3(5)	7.0(4)	4.5(4)	3.5(4)
C(12)	24.5(5)	27.3(5)	24.3(5)	-1.7(4)	2.6(4)	4.0(4)
C(2)	24.7(5)	30.7(6)	34.0(6)	9.9(4)	11.3(4)	14.9(5)
C(32)	28.0(5)	17.9(5)	32.5(6)	2.4(4)	-2.1(4)	3.1(4)
C(34)	31.8(6)	19.2(5)	21.2(5)	4.1(4)	0.4(4)	1.6(4)
C(31)	26.3(5)	18.4(5)	27.5(5)	2.7(4)	0.6(4)	6.4(4)
C(17)	32.1(6)	40.6(6)	19.4(5)	15.0(5)	3.1(4)	6.5(4)
C(33)	32.4(6)	17.7(5)	28.2(5)	4.2(4)	-3.7(4)	-0.5(4)
C(27)	21.7(5)	30.8(6)	33.3(6)	6.6(4)	-0.8(4)	5.9(5)
C(42)	39.1(6)	21.2(5)	23.4(5)	8.5(4)	0.7(4)	1.4(4)
C(5)	36.9(6)	33.5(6)	27.5(5)	18.4(5)	7.0(5)	6.9(5)
C(11)	21.3(5)	32.2(6)	26.8(5)	1.1(4)	4.6(4)	6.6(4)

C(43)	33.6(6)	32.5(6)	31.6(6)	10.9(5)	4.7(5)	13.7(5)
C(15)	37.7(6)	25.3(5)	26.2(5)	7.7(5)	5.8(4)	6.6(4)
C(19)	43.0(6)	25.0(5)	24.3(5)	9.2(5)	5.0(5)	5.7(4)
C(28)	26.2(5)	31.3(6)	29.6(6)	4.9(4)	2.4(4)	10.2(4)
C(37)	43.8(7)	28.4(6)	29.0(6)	13.3(5)	10.5(5)	6.9(4)
C(38)	38.5(6)	37.7(6)	29.3(6)	16.5(5)	12.8(5)	17.5(5)
C(9)	40.6(6)	27.2(6)	30.9(6)	7.8(5)	11.8(5)	6.4(5)
C(20)	24.7(5)	28.5(6)	35.5(6)	12.2(4)	10.2(4)	8.5(5)
C(18)	45.5(7)	33.0(6)	25.8(6)	10.2(5)	7.5(5)	12.2(5)
C(44)	31.2(6)	31.9(6)	40.2(6)	12.1(5)	1.7(5)	15.3(5)
C(40)	37.2(6)	26.6(6)	31.3(6)	6.5(5)	-1.0(5)	2.3(4)
C(46)	36.1(6)	34.2(6)	20.2(5)	5.2(5)	-1.0(4)	6.4(4)
C(16)	45.1(7)	30.1(6)	25.9(5)	14.7(5)	4.6(5)	1.9(4)
C(39)	34.2(6)	36.7(6)	32.5(6)	7.9(5)	-0.3(5)	9.6(5)
C(6)	54.8(8)	43.7(7)	28.3(6)	32.1(6)	3.9(5)	5.7(5)
C(7)	75.6(10)	40.2(7)	26.9(6)	34.3(7)	16.0(6)	13.4(5)
C(21)	42.8(7)	42.1(7)	45.6(7)	17.9(6)	21.8(6)	18.6(6)
C(23)	25.5(6)	63.6(9)	43.8(7)	15.8(6)	5.2(5)	20.0(6)
C(50)	60.5(8)	38.3(7)	24.2(6)	4.1(6)	7.9(5)	10.3(5)
C(47)	50.8(8)	52.6(8)	27.5(6)	6.0(6)	5.6(5)	16.4(6)
C(8)	62.4(9)	34.8(7)	34.5(6)	14.9(6)	21.8(6)	13.1(5)
C(1)	59.6(9)	35.6(7)	59.6(9)	31.0(7)	25.2(7)	15.3(6)
C(22)	43.3(7)	33.7(7)	75.9(10)	20.4(6)	22.3(7)	5.8(7)
C(26)	50.5(8)	53.5(9)	77.0(11)	34.2(7)	24.4(8)	27.7(8)
C(49)	89.7(12)	37.2(7)	28.0(6)	11.6(7)	9.6(7)	0.2(5)
C(24)	81.8(11)	69.0(10)	26.8(6)	50.3(9)	15.7(7)	9.2(6)
C(48)	39.9(7)	74.3(11)	48.0(8)	18.7(7)	-0.8(6)	26.7(8)

*Table 40. Bond Lengths for 2,6-*syn*-**242a***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(2)	C(25)	1.3277(13)	C(35)	C(40)	1.3924(16)
O(2)	C(20)	1.4772(12)	C(30)	C(29)	1.3918(15)
O(4)	C(10)	1.4110(12)	C(30)	C(31)	1.5203(16)
O(10)	C(41)	1.4078(13)	C(30)	C(43)	1.3882(16)
O(8)	C(45)	1.3355(12)	C(3)	C(2)	1.5304(15)
O(8)	C(46)	1.4740(13)	C(3)	C(11)	1.5113(14)
O(9)	C(45)	1.2207(13)	C(29)	C(28)	1.3813(17)
O(3)	C(25)	1.2192(13)	C(41)	C(34)	1.5366(14)
O(12)	C(42)	1.3355(14)	C(36)	C(37)	1.3830(17)
O(12)	C(50)	1.4445(14)	C(12)	C(11)	1.3190(16)
O(6)	C(2)	1.3325(14)	C(32)	C(31)	1.5036(15)
O(6)	C(1)	1.4440(14)	C(32)	C(33)	1.3195(17)
O(11)	C(42)	1.1992(14)	C(34)	C(33)	1.5153(15)
O(1)	C(17)	1.3741(13)	C(34)	C(42)	1.5324(15)
O(1)	C(24)	1.4258(17)	C(17)	C(18)	1.3838(17)
O(7)	C(27)	1.3697(15)	C(17)	C(16)	1.3822(17)
O(7)	C(26)	1.4188(17)	C(27)	C(28)	1.3892(17)

N(1)	C(25)	1.3631(13)	C(27)	C(44)	1.3887(17)
N(1)	C(10)	1.4519(13)	C(5)	C(6)	1.3954(17)
N(1)	C(13)	1.4710(12)	C(43)	C(44)	1.3886(17)
N(2)	C(45)	1.3606(13)	C(15)	C(16)	1.3865(16)
N(2)	C(41)	1.4580(13)	C(19)	C(18)	1.3849(16)
N(2)	C(31)	1.4785(13)	C(37)	C(38)	1.3818(18)
O(5)	C(2)	1.1998(14)	C(38)	C(39)	1.3831(18)
C(10)	C(3)	1.5392(14)	C(9)	C(8)	1.3828(18)
C(13)	C(14)	1.5246(14)	C(20)	C(21)	1.5165(16)
C(13)	C(12)	1.4986(15)	C(20)	C(23)	1.5096(17)
C(14)	C(15)	1.3818(15)	C(20)	C(22)	1.5153(17)
C(14)	C(19)	1.3892(15)	C(40)	C(39)	1.3877(18)
C(4)	C(3)	1.5341(14)	C(46)	C(47)	1.5156(17)
C(4)	C(5)	1.3884(16)	C(46)	C(49)	1.5058(19)
C(4)	C(9)	1.3964(16)	C(46)	C(48)	1.5169(19)
C(35)	C(36)	1.3933(15)	C(6)	C(7)	1.378(2)
C(35)	C(34)	1.5357(16)	C(7)	C(8)	1.383(2)

*Table 41. Bond Angles for 2,6-*syn*-**242a***

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C(20)	O(2)	C(25)	121.75(8)	C(3)	C(2)	O(5)	125.41(11)
C(46)	O(8)	C(45)	121.25(8)	C(33)	C(32)	C(31)	124.83(10)
C(50)	O(12)	C(42)	115.27(9)	C(41)	C(34)	C(35)	113.92(9)
C(1)	O(6)	C(2)	116.66(10)	C(33)	C(34)	C(35)	112.07(9)
C(24)	O(1)	C(17)	116.01(10)	C(33)	C(34)	C(41)	107.48(9)
C(26)	O(7)	C(27)	116.58(10)	C(42)	C(34)	C(35)	106.09(9)
C(10)	N(1)	C(25)	118.34(8)	C(42)	C(34)	C(41)	107.57(8)
C(13)	N(1)	C(25)	119.85(8)	C(42)	C(34)	C(33)	109.57(9)
C(13)	N(1)	C(10)	121.02(8)	C(30)	C(31)	N(2)	112.39(8)
C(41)	N(2)	C(45)	119.14(8)	C(32)	C(31)	N(2)	110.12(9)
C(31)	N(2)	C(45)	120.63(8)	C(32)	C(31)	C(30)	113.91(9)
C(31)	N(2)	C(41)	120.17(8)	C(18)	C(17)	O(1)	116.06(10)
O(3)	C(25)	O(2)	125.41(10)	C(16)	C(17)	O(1)	124.40(11)
N(1)	C(25)	O(2)	110.60(8)	C(16)	C(17)	C(18)	119.54(10)
N(1)	C(25)	O(3)	123.98(10)	C(34)	C(33)	C(32)	121.93(10)
N(1)	C(10)	O(4)	112.09(8)	C(28)	C(27)	O(7)	115.84(10)
C(3)	C(10)	O(4)	106.05(8)	C(44)	C(27)	O(7)	124.49(11)
C(3)	C(10)	N(1)	110.84(8)	C(44)	C(27)	C(28)	119.66(11)
C(14)	C(13)	N(1)	114.57(8)	O(11)	C(42)	O(12)	124.04(10)
C(12)	C(13)	N(1)	110.74(9)	C(34)	C(42)	O(12)	110.76(9)
C(12)	C(13)	C(14)	112.02(8)	C(34)	C(42)	O(11)	125.15(10)
O(9)	C(45)	O(8)	124.59(9)	C(6)	C(5)	C(4)	120.57(11)
N(2)	C(45)	O(8)	110.91(9)	C(12)	C(11)	C(3)	122.22(10)
N(2)	C(45)	O(9)	124.49(9)	C(44)	C(43)	C(30)	121.47(11)
C(15)	C(14)	C(13)	117.85(9)	C(16)	C(15)	C(14)	121.89(11)
C(19)	C(14)	C(13)	124.14(10)	C(18)	C(19)	C(14)	120.74(11)
C(19)	C(14)	C(15)	117.97(10)	C(27)	C(28)	C(29)	120.01(10)

C(5)	C(4)	C(3)	123.84(10)	C(38)	C(37)	C(36)	120.29(11)
C(9)	C(4)	C(3)	117.88(10)	C(39)	C(38)	C(37)	119.22(11)
C(9)	C(4)	C(5)	118.25(10)	C(8)	C(9)	C(4)	121.06(12)
C(34)	C(35)	C(36)	118.44(10)	C(21)	C(20)	O(2)	109.79(9)
C(40)	C(35)	C(36)	117.87(11)	C(23)	C(20)	O(2)	109.99(9)
C(40)	C(35)	C(34)	123.60(10)	C(23)	C(20)	C(21)	112.85(11)
C(31)	C(30)	C(29)	119.91(10)	C(22)	C(20)	O(2)	101.07(9)
C(43)	C(30)	C(29)	118.03(11)	C(22)	C(20)	C(21)	111.18(11)
C(43)	C(30)	C(31)	122.02(10)	C(22)	C(20)	C(23)	111.34(11)
C(4)	C(3)	C(10)	114.34(9)	C(19)	C(18)	C(17)	120.41(11)
C(2)	C(3)	C(10)	106.54(8)	C(43)	C(44)	C(27)	119.53(11)
C(2)	C(3)	C(4)	107.23(8)	C(39)	C(40)	C(35)	120.81(11)
C(11)	C(3)	C(10)	108.30(8)	C(47)	C(46)	O(8)	102.09(9)
C(11)	C(3)	C(4)	110.26(8)	C(49)	C(46)	O(8)	110.41(10)
C(11)	C(3)	C(2)	110.07(9)	C(49)	C(46)	C(47)	111.03(11)
C(28)	C(29)	C(30)	121.23(10)	C(48)	C(46)	O(8)	108.89(10)
N(2)	C(41)	O(10)	112.67(9)	C(48)	C(46)	C(47)	110.40(11)
C(34)	C(41)	O(10)	106.64(8)	C(48)	C(46)	C(49)	113.41(13)
C(34)	C(41)	N(2)	109.19(8)	C(15)	C(16)	C(17)	119.40(11)
C(37)	C(36)	C(35)	121.26(11)	C(40)	C(39)	C(38)	120.51(11)
C(11)	C(12)	C(13)	125.06(10)	C(7)	C(6)	C(5)	120.32(13)
O(5)	C(2)	O(6)	124.32(11)	C(8)	C(7)	C(6)	119.68(12)
C(3)	C(2)	O(6)	110.27(9)	C(7)	C(8)	C(9)	120.11(12)

*Table 42. Torsion Angles for 2,6-*syn*-**242a***

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O(2)	C(25)	N(1)	C(10)	-177.86(8)	N(1)	C(13)	C(14)	C(19)	-27.82(12)
O(2)	C(25)	N(1)	C(13)	-7.91(10)	N(1)	C(13)	C(12)	C(11)	-7.44(11)
O(4)	C(10)	N(1)	C(25)	101.26(9)	N(2)	C(41)	C(34)	C(35)	70.14(9)
O(4)	C(10)	N(1)	C(13)	-68.58(9)	N(2)	C(41)	C(34)	C(33)	-54.65(9)
O(4)	C(10)	C(3)	C(4)	-165.26(7)	N(2)	C(41)	C(34)	C(42)	-172.57(9)
O(4)	C(10)	C(3)	C(2)	-47.00(9)	N(2)	C(31)	C(30)	C(29)	119.97(9)
O(4)	C(10)	C(3)	C(11)	71.37(9)	N(2)	C(31)	C(30)	C(43)	-57.89(10)
O(10)	C(41)	N(2)	C(45)	113.17(9)	N(2)	C(31)	C(32)	C(33)	-10.01(11)
O(10)	C(41)	N(2)	C(31)	-64.17(10)	O(5)	C(2)	C(3)	C(10)	117.90(12)
O(10)	C(41)	C(34)	C(35)	-167.85(8)	O(5)	C(2)	C(3)	C(4)	-119.26(12)
O(10)	C(41)	C(34)	C(33)	67.35(9)	O(5)	C(2)	C(3)	C(11)	0.69(13)
O(10)	C(41)	C(34)	C(42)	-50.57(9)	C(10)	C(3)	C(4)	C(5)	8.41(11)
O(8)	C(45)	N(2)	C(41)	175.55(8)	C(10)	C(3)	C(4)	C(9)	-173.92(9)
O(8)	C(45)	N(2)	C(31)	-7.11(11)	C(10)	C(3)	C(11)	C(12)	28.38(11)
O(9)	C(45)	N(2)	C(41)	-3.33(14)	C(13)	C(14)	C(15)	C(16)	-177.08(10)
O(9)	C(45)	N(2)	C(31)	174.00(11)	C(13)	C(14)	C(19)	C(18)	175.64(11)
O(3)	C(25)	N(1)	C(10)	3.11(13)	C(13)	C(12)	C(11)	C(3)	1.01(14)
O(3)	C(25)	N(1)	C(13)	173.07(10)	C(14)	C(15)	C(16)	C(17)	1.58(14)
O(12)	C(42)	C(34)	C(35)	70.11(10)	C(14)	C(19)	C(18)	C(17)	1.02(14)
O(12)	C(42)	C(34)	C(41)	-52.16(10)	C(4)	C(3)	C(11)	C(12)	-97.42(10)
O(12)	C(42)	C(34)	C(33)	-168.72(9)	C(4)	C(5)	C(6)	C(7)	0.89(13)

O(6)	C(2)	C(3)	C(10)	-62.95(9)	C(4)	C(9)	C(8)	C(7)	0.49(14)
O(6)	C(2)	C(3)	C(4)	59.89(9)	C(35)	C(36)	C(37)	C(38)	0.03(13)
O(6)	C(2)	C(3)	C(11)	179.85(9)	C(35)	C(34)	C(33)	C(32)	-96.49(10)
O(11)	C(42)	C(34)	C(35)	-107.41(13)	C(35)	C(40)	C(39)	C(38)	-0.21(14)
O(11)	C(42)	C(34)	C(41)	130.32(13)	C(30)	C(29)	C(28)	C(27)	1.32(12)
O(11)	C(42)	C(34)	C(33)	13.76(14)	C(30)	C(31)	C(32)	C(33)	-137.32(10)
O(1)	C(17)	C(18)	C(19)	-177.89(11)	C(30)	C(43)	C(44)	C(27)	1.05(13)
O(1)	C(17)	C(16)	C(15)	176.55(12)	C(29)	C(28)	C(27)	C(44)	-2.60(13)
O(7)	C(27)	C(28)	C(29)	176.68(9)	C(41)	C(34)	C(33)	C(32)	29.41(11)
O(7)	C(27)	C(44)	C(43)	-177.79(11)	C(36)	C(37)	C(38)	C(39)	-1.73(13)
N(1)	C(10)	C(3)	C(4)	72.86(9)	C(32)	C(33)	C(34)	C(42)	146.02(11)
N(1)	C(10)	C(3)	C(2)	-168.88(9)	C(5)	C(6)	C(7)	C(8)	-0.38(14)
N(1)	C(10)	C(3)	C(11)	-50.51(9)	C(37)	C(38)	C(39)	C(40)	1.82(13)
N(1)	C(13)	C(14)	C(15)	149.81(9)	C(9)	C(8)	C(7)	C(6)	-0.30(15)

*Table 43. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for 2,6-*syn-***242a***

Atom	***x***	***y***	***z***	**U(eq)**
H(4)	1709(2)	4137(10)	7242(5)	41.8(3)
H(10a)	4852(7)	5176.5(14)	8385(6)	43.3(3)
H(10)	2094.3(9)	3786.0(9)	8244.7(5)	26.8(2)
H(13)	1366.7(10)	339.2(9)	7403.9(5)	27.7(3)
H(29)	7149.7(10)	8239.6(10)	6494.3(6)	32.7(3)
H(41)	3475.9(10)	5934.7(9)	8159.3(5)	29.9(3)
H(36)	4422.0(11)	9844.9(10)	9348.6(6)	35.1(3)
H(12)	-825.8(10)	84.6(10)	6958.9(6)	33.9(3)
H(32)	7318.0(11)	9101.9(10)	8407.1(6)	33.8(3)
H(31)	5796.4(10)	8349.6(9)	7298.0(6)	30.4(3)
H(33)	6222.3(11)	9084.1(10)	9293.6(6)	34.0(3)
H(5)	2422.2(12)	3026.0(11)	9139.0(6)	37.1(3)
H(11)	-1513.3(10)	1261.0(10)	7713.5(6)	34.3(3)
H(43)	6933.0(11)	6093.7(11)	7904.9(6)	38.1(3)
H(15)	839.4(11)	-1060.2(10)	6308.1(6)	36.3(3)
H(19)	1958.0(12)	2530.4(11)	6304.5(6)	37.6(3)
H(28)	8475.3(10)	7369.3(11)	5936.2(6)	35.9(3)
H(37)	2898.7(12)	10755.4(11)	9221.2(6)	39.7(3)
H(38)	1011.8(12)	9714.1(11)	8451.7(6)	39.0(3)
H(9)	-1362.2(12)	1527.5(11)	9007.7(6)	40.0(3)
H(18)	2400.9(12)	2119.1(11)	5169.3(6)	41.6(3)
H(44)	8205.8(11)	5163.2(11)	7327.8(7)	40.1(3)
H(40)	2235.3(12)	6871.2(11)	7896.1(6)	40.4(3)
H(16)	1206.1(12)	-1490.1(11)	5157.5(6)	40.6(3)
H(39)	713.9(12)	7791.6(12)	7768.7(6)	42.7(3)
H(6)	2675.8(14)	2636.2(12)	10264.1(6)	46.7(3)
H(7)	921.7(15)	1668.7(12)	10750.4(7)	51.2(4)
H(21A)	4925(6)	2288(6)	6535(2)	60.7(4)
H(21B)	5509(9)	3318(2)	7223(3)	60.7(4)
H(21C)	6297(4)	2515(7)	6916(5)	60.7(4)

H(23A)	5748(9)	2732(4)	8389(2)	64.6(5)
H(23B)	5223(5)	1343(6)	8438.3(19)	64.6(5)
H(23C)	6487(4)	1847(10)	8129.9(8)	64.6(5)
H(50a)	2143(6)	5185(6)	9967.6(11)	65.4(5)
H(50b)	3595(5)	5682(10)	10281(3)	65.4(5)
H(50c)	2778(10)	6541(4)	10405(2)	65.4(5)
H(47a)	4621(9)	7982.1(15)	5490(4)	68.3(5)
H(47b)	5270(4)	6983(8)	5332(5)	68.3(5)
H(47c)	4086(5)	6919(7)	4813.1(13)	68.3(5)
H(8)	-1099.3(15)	1108.2(12)	10116.9(7)	51.2(4)
H(1A)	-267(10)	5883(7)	8512.2(11)	69.5(5)
H(1B)	-798(6)	5376(3)	9160(5)	69.5(5)
H(1C)	591(4)	6314(4)	9256(5)	69.5(5)
H(22A)	4337(10)	-281.4(16)	7335(3)	73.6(5)
H(22B)	4218(9)	97(4)	6603(3)	73.6(5)
H(22C)	5557.3(16)	230(3)	6991(6)	73.6(5)
H(26a)	9953(10)	4354(8)	6075(4)	80.4(6)
H(26b)	9949(10)	4946(3)	6862(3)	80.4(6)
H(26c)	8687.8(15)	4007(5)	6400(6)	80.4(6)
H(49a)	4188(3)	4855(2)	5548(6)	82.4(6)
H(49b)	2781(9)	4511.5(15)	5700(5)	82.4(6)
H(49c)	3093(12)	4765(3)	4957.8(14)	82.4(6)
H(24A)	2464(11)	-1070(3)	3627(3)	79.2(6)
H(24B)	2668(9)	-1353(5)	4380(3)	79.2(6)
H(24C)	1287(2)	-1632(3)	3993(6)	79.2(6)
H(48a)	1861(5)	6179(9)	6022(5)	79.5(6)
H(48b)	2557.8(14)	7488(2)	5881(6)	79.5(6)
H(48c)	1905(6)	6368(10)	5243.4(14)	79.5(6)

1-(*tert*-Butyl) 3-methyl (3*R**,6*S**)-6-(4-methoxyphenyl)-3-phenyl-3,6-dihydropyridine-1,3(2*H*)-dicarboxylate (247)

*Table 44. Crystal data and structure refinement for **247***

Identification code	S108
Empirical formula	$C_{25}H_{31}NO_5$
Formula weight	425.51
Temperature/K	123.01(10)
Crystal system	triclinic
Space group	P-1
a/Å	8.6885(3)
b/Å	10.3887(4)
c/Å	12.6281(5)
α/°	80.825(3)
β/°	89.457(3)
γ/°	76.064(3)
Volume/Å^3	1091.64(7)
Z	2
ρ_{calc}g/cm^3	1.295
μ/mm^{-1}	0.726
F(000)	456.0
Crystal size/mm^3	0.158 × 0.08 × 0.056
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.094 to 148.32
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 12, -15 ≤ l ≤ 15
Reflections collected	26643
Independent reflections	4377 [R_{int} = 0.0431, R_{sigma} = 0.0237]
Data/restraints/parameters	4377/0/285
Goodness-of-fit on F^2	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0373, wR_2 = 0.0956
Final R indexes [all data]	R_1 = 0.0473, wR_2 = 0.1030
Largest diff. peak/hole / e Å^{-3}	0.29/-0.18

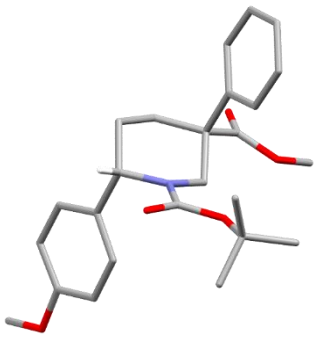


*Table 45. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **247**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
O(1)	-775.4(10)	4898.8(9)	8367.4(7)	26.9(2)
O(2)	-577.2(12)	3092.8(11)	7521.3(8)	36.6(2)
O(4)	4107.4(11)	7752.2(10)	6286.8(8)	33.9(2)
O(3)	2484.0(11)	7894.0(10)	7675.1(7)	31.9(2)
O(5)	7412.1(13)	166.1(11)	9046.1(9)	43.5(3)
N(1)	1141.0(12)	4446.9(11)	7189.0(9)	25.6(2)
C(7)	2126.6(14)	6442.5(13)	6461.5(10)	24.0(3)
C(23)	3030.7(15)	7422.2(13)	6781.8(10)	25.3(3)
C(14)	3187.8(15)	5563.9(14)	5732.4(10)	26.6(3)

C(6)	1817.3(15)	5507.5(13)	7475.2(10)	23.9(3)
C(15)	2471.0(16)	4440.8(14)	5491.7(10)	28.1(3)
C(9)	653.6(16)	8074.5(14)	4881.3(11)	30.1(3)
C(5)	-113.8(15)	4063.0(14)	7681.1(10)	26.9(3)
C(17)	3574.0(16)	2645.1(13)	7149.4(11)	27.9(3)
C(13)	-876.1(15)	7483.8(14)	6374.0(11)	29.5(3)
C(8)	584.5(15)	7327.0(13)	5889.2(10)	25.0(3)
C(2)	-2267.8(15)	4772.4(15)	8886.2(11)	29.0(3)
C(16)	2117.6(15)	3558.1(13)	6512.9(10)	27.1(3)
C(18)	4977.2(16)	2102.8(14)	6670.7(11)	31.3(3)
C(22)	3509.4(17)	2279.4(14)	8259.3(11)	31.9(3)
C(12)	-2231.0(16)	8362.9(15)	5866.8(12)	33.4(3)
C(21)	4791.2(18)	1455.4(15)	8865.0(11)	35.1(3)
C(24)	3273.2(18)	8833.0(15)	8032.4(12)	35.4(3)
C(11)	-2139.6(17)	9112.0(15)	4874.0(12)	34.2(3)
C(19)	6279.5(17)	1265.3(15)	7269.2(12)	34.9(3)
C(10)	-693.8(18)	8965.9(15)	4379.5(11)	34.7(3)
C(1)	-2614.7(17)	5952.8(16)	9492.8(12)	36.6(3)
C(20)	6193.3(18)	957.5(14)	8373.1(12)	34.0(3)
C(3)	-2008.0(18)	3455.0(16)	9655.4(12)	38.5(3)
C(4)	-3560.9(17)	4916.1(18)	8048.3(13)	41.5(4)
C(25)	8926.7(19)	-234.5(18)	8588.7(14)	46.7(4)

*Table 46. Anisotropic Displacement Parameters ($Å^2×10^3$) for **247**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O(1)	23.8(4)	27.5(5)	30.2(5)	-6.0(4)	6.4(3)	-7.0(4)
O(2)	37.1(5)	34.9(6)	44.8(6)	-13.5(5)	11.8(4)	-17.7(5)
O(4)	29.0(5)	32.5(6)	41.0(5)	-3.4(4)	5.3(4)	-11.2(4)
O(3)	37.0(5)	31.3(5)	31.9(5)	-8.4(4)	4.7(4)	-14.6(4)
O(5)	40.9(6)	36.8(6)	40.7(6)	4.8(5)	4.2(5)	6.4(5)
N(1)	24.9(5)	23.2(6)	30.1(5)	-7.4(4)	6.0(4)	-6.5(4)
C(7)	23.4(6)	22.9(6)	24.9(6)	-2.8(5)	2.9(5)	-4.9(5)
C(23)	23.9(6)	21.4(6)	27.5(6)	1.3(5)	-1.9(5)	-2.8(5)
C(14)	25.5(6)	26.4(7)	26.4(6)	-2.4(5)	4.3(5)	-4.5(5)
C(6)	23.7(6)	21.7(6)	25.9(6)	-3.4(5)	2.1(5)	-5.1(5)
C(15)	27.6(6)	28.8(7)	27.3(6)	-7.9(5)	2.4(5)	-3.7(5)
C(9)	29.9(7)	30.7(7)	28.9(7)	-3.6(5)	1.2(5)	-6.4(6)
C(5)	26.0(6)	25.4(7)	29.0(6)	-3.9(5)	2.8(5)	-6.3(5)
C(17)	31.6(7)	20.6(6)	32.2(7)	-4.9(5)	6.4(5)	-7.6(5)
C(13)	27.6(6)	25.5(7)	33.3(7)	-2.0(5)	2.1(5)	-4.1(5)
C(8)	25.9(6)	21.7(6)	27.8(6)	-5.5(5)	-0.6(5)	-5.6(5)
C(2)	21.4(6)	34.2(8)	30.1(7)	-2.7(5)	5.2(5)	-6.2(5)
C(16)	28.2(6)	23.3(7)	31.9(7)	-9.4(5)	5.6(5)	-7.0(5)
C(18)	34.8(7)	27.2(7)	30.7(7)	-3.2(5)	9.3(5)	-6.2(6)
C(22)	35.6(7)	23.9(7)	34.2(7)	-5.6(5)	11.0(6)	-3.3(6)
C(12)	26.3(6)	28.5(7)	43.9(8)	-6.1(6)	1.0(6)	-3.3(6)

C(21)	43.8(8)	26.1(7)	31.7(7)	-1.4(6)	7.2(6)	-3.7(6)
C(24)	42.4(8)	31.0(8)	35.5(7)	-4.7(6)	-4.1(6)	-14.2(6)
C(11)	32.4(7)	25.4(7)	43.0(8)	-5.4(6)	-9.6(6)	-3.0(6)
C(19)	34.1(7)	28.8(8)	38.1(7)	-3.1(6)	11.2(6)	-2.1(6)
C(10)	40.9(8)	29.8(8)	31.2(7)	-0.8(6)	-6.0(6)	-6.8(6)
C(1)	30.2(7)	39.0(9)	39.1(8)	-8.9(6)	9.3(6)	-4.1(6)
C(20)	38.0(7)	22.4(7)	37.1(7)	0.4(6)	3.4(6)	-2.3(6)
C(3)	41.6(8)	38.9(9)	34.4(7)	1.1(6)	7.0(6)	-13.5(7)
C(4)	26.5(7)	52.5(10)	43.8(8)	-6.4(7)	-1.7(6)	-7.0(7)
C(25)	39.2(8)	39.9(9)	50.8(9)	-1.3(7)	1.1(7)	6.0(7)

*Table 47. Bond Lengths for **247***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(1)	C(5)	1.3512(16)	C(9)	C(8)	1.3902(18)
O(1)	C(2)	1.4718(15)	C(9)	C(10)	1.391(2)
O(2)	C(5)	1.2167(16)	C(17)	C(16)	1.5314(19)
O(4)	C(23)	1.2077(16)	C(17)	C(18)	1.3903(19)
O(3)	C(23)	1.3388(16)	C(17)	C(22)	1.3967(19)
O(3)	C(24)	1.4470(16)	C(13)	C(8)	1.3890(18)
O(5)	C(20)	1.3764(18)	C(13)	C(12)	1.3929(19)
O(5)	C(25)	1.4272(19)	C(2)	C(1)	1.516(2)
N(1)	C(6)	1.4604(16)	C(2)	C(3)	1.516(2)
N(1)	C(5)	1.3607(16)	C(2)	C(4)	1.5151(19)
N(1)	C(16)	1.4703(16)	C(18)	C(19)	1.393(2)
C(7)	C(23)	1.5293(18)	C(22)	C(21)	1.381(2)
C(7)	C(14)	1.5420(17)	C(12)	C(11)	1.379(2)
C(7)	C(6)	1.5418(17)	C(21)	C(20)	1.386(2)
C(7)	C(8)	1.5412(17)	C(11)	C(10)	1.384(2)
C(14)	C(15)	1.5193(18)	C(19)	C(20)	1.385(2)
C(15)	C(16)	1.5327(18)			

*Table 48. Bond Angles for **247***

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(5)	O(1)	C(2)	120.34(10)	C(22)	C(17)	C(16)	119.98(12)
C(23)	O(3)	C(24)	115.92(10)	C(8)	C(13)	C(12)	121.08(13)
C(20)	O(5)	C(25)	117.34(11)	C(9)	C(8)	C(7)	119.51(11)
C(6)	N(1)	C(16)	115.90(10)	C(13)	C(8)	C(7)	122.37(11)
C(5)	N(1)	C(6)	124.14(11)	C(13)	C(8)	C(9)	117.97(12)
C(5)	N(1)	C(16)	118.34(11)	O(1)	C(2)	C(1)	101.87(11)
C(23)	C(7)	C(14)	108.17(10)	O(1)	C(2)	C(3)	110.18(11)
C(23)	C(7)	C(6)	109.26(10)	O(1)	C(2)	C(4)	110.38(11)
C(23)	C(7)	C(8)	105.57(10)	C(1)	C(2)	C(3)	110.76(12)
C(6)	C(7)	C(14)	107.79(10)	C(4)	C(2)	C(1)	111.06(12)
C(8)	C(7)	C(14)	113.16(10)	C(4)	C(2)	C(3)	112.14(13)
C(8)	C(7)	C(6)	112.74(10)	N(1)	C(16)	C(15)	107.73(11)
O(4)	C(23)	O(3)	123.17(12)	N(1)	C(16)	C(17)	110.67(10)

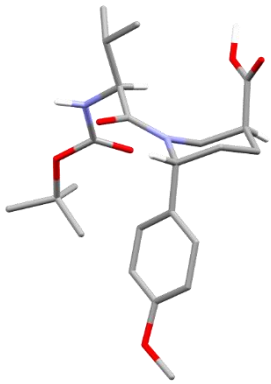
O(4)	C(23)	C(7)	124.44(12)	C(17)	C(16)	C(15)	115.46(11)
O(3)	C(23)	C(7)	112.38(10)	C(17)	C(18)	C(19)	121.85(13)
C(15)	C(14)	C(7)	111.71(10)	C(21)	C(22)	C(17)	121.98(13)
N(1)	C(6)	C(7)	110.79(10)	C(11)	C(12)	C(13)	120.29(13)
C(14)	C(15)	C(16)	112.49(10)	C(22)	C(21)	C(20)	120.05(13)
C(8)	C(9)	C(10)	121.05(13)	C(12)	C(11)	C(10)	119.34(13)
O(1)	C(5)	N(1)	111.20(11)	C(20)	C(19)	C(18)	119.77(13)
O(2)	C(5)	O(1)	124.57(12)	C(11)	C(10)	C(9)	120.27(13)
O(2)	C(5)	N(1)	124.24(12)	O(5)	C(20)	C(21)	115.76(12)
C(18)	C(17)	C(16)	123.09(12)	O(5)	C(20)	C(19)	124.83(13)
C(18)	C(17)	C(22)	116.89(13)	C(19)	C(20)	C(21)	119.41(13)

*Table 49. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for **247***

Atom	***x***	***y***	***z***	**U(eq)**
H(14A)	3331.92	6121.95	5064.07	32
H(14B)	4222.9	5178.09	6080.99	32
H(6A)	2805.91	5107.4	7880.33	29
H(6B)	1091.97	6027.71	7926.18	29
H(15A)	3199.36	3884.51	5065.34	34
H(15B)	1494.73	4829.18	5070.15	34
H(9)	1616.1	7976.84	4537.01	36
H(13)	-950.61	6993.81	7048.25	35
H(16)	1474.5	2980.3	6300.14	33
H(18)	5048.46	2304.77	5930.23	38
H(22)	2574.99	2600.48	8600.5	38
H(12)	-3201.65	8444.93	6199.32	40
H(21)	4713.93	1234.27	9603.44	42
H(24A)	3113.35	9628.77	7501.67	53
H(24B)	4388.28	8426.56	8134.48	53
H(24C)	2841.36	9066.83	8698.05	53
H(11)	-3040.63	9709.59	4539.99	41
H(19)	7203.57	914.22	6928.74	42
H(10)	-622.69	9465.83	3708.93	42
H(1A)	-1751.17	5864.89	9988.99	55
H(1B)	-3574.01	5966.66	9879.1	55
H(1C)	-2738.69	6774.13	8994.4	55
H(3A)	-1797.25	2721.69	9256.17	58
H(3B)	-2941.38	3440.76	10065.61	58
H(3C)	-1120.93	3368.5	10131.36	58
H(4A)	-3583.9	5695.45	7519.61	62
H(4B)	-4567.59	5012.93	8386.22	62
H(4C)	-3350.39	4131.13	7707.99	62
H(25A)	8856.39	-791.72	8062.12	70
H(25B)	9687.7	-729.71	9142.87	70
H(25C)	9254.88	548.38	8253.55	70

(3*S*,6*R*)-1-((*tert*-Butoxycarbonyl)-L-valyl)-6-(4-methoxyphenyl)piperidine-3-carboxylic acid (259b)

*Table 50. Crystal data and structure refinement for **259b***



Identification code	T085
Empirical formula	$C_{24}Cl_{2.5}H_{35.5}N_2O_6$
Formula weight	536.691
Temperature/K	123.15
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.1634(2)
b/Å	12.4846(2)
c/Å	21.8922(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2777.81(9)
Z	4
ρ_{calc}g/cm^3	1.283
μ/mm^{-1}	2.873
F(000)	1143.1
Crystal size/mm^3	0.29 × 0.19 × 0.09
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.08 to 147.6
Index ranges	-12 ≤ h ≤ 10, -14 ≤ k ≤ 15, -26 ≤ l ≤ 24
Reflections collected	16194
Independent reflections	5461 [R_{int} = 0.0216, R_{sigma} = 0.0193]
Data/restraints/parameters	5461/0/350
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0545, wR_2 = 0.1499
Final R indexes [all data]	R_1 = 0.0552, wR_2 = 0.1504
Largest diff. peak/hole / e Å^{-3}	0.34/-0.22
Flack parameter	0.2(6)

*Table 51. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **259b**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.*

Atom	*x*	*y*	*z*	U(eq)
O(001)	4595.7(18)	2932.8(13)	7236.9(8)	35.9(4)
O(002)	5843.5(19)	-889.7(15)	6797.9(8)	40.7(4)
O(003)	8864.7(18)	3528.1(16)	7371.2(8)	43.2(4)
O(004)	8471(2)	2040.2(16)	6800.7(9)	47.1(5)
O(005)	5928(2)	5417.2(16)	4458.4(9)	48.6(5)
O(006)	3771(2)	-1025.4(17)	6461.9(9)	50.3(5)
N(007)	5138.6(19)	1800.4(15)	6484.1(8)	29.4(4)
N(008)	7269(2)	2415(2)	7647.1(9)	37.2(5)
C(009)	5275(2)	2173.6(19)	7058.5(10)	30.6(5)

C(00B)	6031(3)	1063(2)	6165.7(11)	33.1(5)
C(00C)	6234(2)	1652(2)	7506.4(10)	30.6(5)
C(00D)	8236(2)	2614(2)	7226.5(11)	34.7(5)
C(00E)	5656(3)	3662(2)	5763.1(11)	39.3(6)
C(00F)	5300(3)	88(2)	5910.4(10)	34.8(5)
C(00G)	4603(3)	3002.1(19)	5619.9(11)	34.9(5)
C(00H)	4072(2)	2226.7(19)	6096.1(11)	32.9(5)
C(00I)	4870(3)	-664.7(19)	6414.3(11)	35.3(5)
C(00J)	4146(3)	459.2(19)	5512.7(11)	37.5(5)
C(00K)	5444(3)	4600(2)	4813.6(12)	41.2(6)
C(00L)	5493(2)	1322(2)	8095.8(11)	34.9(5)
C(00M)	4242(3)	698(2)	7960.6(12)	39.6(6)
C(00N)	3290(3)	1269(2)	5849.9(12)	36.1(5)
C(00O)	6081(3)	4447(2)	5370.8(11)	38.7(5)
C(00P)	4419(3)	3942(2)	4652.4(13)	47.3(7)
C(00Q)	9915(3)	3944(3)	6977.4(13)	48.5(7)
C(00S)	4005(3)	3141(2)	5054.8(14)	45.9(6)
C(00T)	6402(3)	669(3)	8502.5(14)	60.6(9)
C(00U)	5410(4)	5517(3)	3853.1(14)	62.0(9)
C(00V)	10270(4)	4981(3)	7290.8(18)	68.8(11)
C(00W)	9381(7)	4169(4)	6351.9(18)	107(2)
C(00X)	11047(4)	3200(4)	6990(4)	139(3)

*Table 52. Anisotropic Displacement Parameters ($Å^2×10^3$) for **259b**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{12}**	**U_{13}**	**U_{23}**
O(001)	42.7(9)	31.4(8)	33.7(8)	1.7(7)	-5.4(7)	-6.1(7)
O(002)	51.3(10)	37.9(9)	32.9(8)	7.3(8)	-4.2(8)	6.7(7)
O(003)	37.0(9)	54.9(11)	37.5(9)	-16.9(8)	7.6(8)	-8.2(8)
O(004)	46.6(10)	47.4(10)	47.3(10)	-9.6(9)	17.2(9)	-14.2(9)
O(005)	64.4(13)	46.6(10)	34.7(9)	14.2(10)	6.9(9)	11.3(8)
O(006)	44.6(11)	58.1(12)	48.1(11)	4.7(9)	0.8(9)	24.3(10)
N(007)	30.9(9)	30.9(9)	26.4(9)	1.0(8)	-1.1(8)	1.5(7)
N(008)	30.9(10)	55.1(13)	25.4(9)	-8.7(9)	1.2(8)	-2.9(9)
C(009)	30.4(11)	31.9(11)	29.5(11)	-3.2(9)	0.3(9)	-1.4(9)
C(00B)	34.9(12)	36.0(11)	28.5(11)	6.8(10)	2.3(10)	-0.6(9)
C(00C)	31.4(11)	36.8(12)	23.7(11)	-0.2(9)	0.7(9)	2.7(9)
C(00D)	27.4(11)	47.6(13)	29.1(11)	-1.8(10)	0.7(9)	-0.9(10)
C(00E)	44.1(14)	49.2(14)	24.5(11)	0.7(11)	0.5(10)	-7.8(10)
C(00F)	43.8(13)	35.9(12)	24.6(10)	4.9(11)	0.4(10)	3.5(9)
C(00G)	42.8(13)	29.5(11)	32.3(11)	11.9(10)	-2.8(10)	-3.5(9)
C(00H)	31.6(11)	36.2(12)	30.8(11)	6.2(10)	-4.7(9)	-4.0(9)
C(00I)	44.3(14)	33.2(11)	28.4(11)	7.7(10)	1.9(10)	-1.2(9)
C(00J)	51.3(15)	31.6(12)	29.6(11)	2.3(11)	-8.3(11)	2.1(9)
C(00K)	54.0(15)	35.9(12)	33.6(12)	14.0(12)	4.5(11)	4.2(10)
C(00L)	35.6(12)	42.0(13)	27.1(11)	-2.7(10)	4.4(9)	2.9(10)
C(00M)	40.5(13)	38.5(12)	39.9(13)	-6.6(11)	9.4(11)	0.0(10)

C(00N)	39.6(13)	30.7(11)	38.1(12)	0.7(10)	-7.5(10)	-2.0(10)
C(00O)	44.1(14)	43.8(13)	28.1(11)	-2.8(12)	3.2(10)	-5.8(10)
C(00P)	62.3(18)	41.4(13)	38.2(13)	6.5(13)	-16.7(13)	5.2(11)
C(00Q)	41.8(14)	55.8(16)	47.9(15)	-14.1(13)	17.0(12)	-10.1(13)
C(00S)	53.2(16)	35.0(13)	49.5(15)	2.7(12)	-17.5(13)	2.7(11)
C(00T)	40.9(14)	99(3)	41.8(15)	8.1(16)	5.6(12)	30.9(17)
C(00U)	82(2)	64.9(19)	39.7(15)	28.1(18)	4.4(15)	16.1(14)
C(00V)	67(2)	71(2)	69(2)	-38.2(18)	27.7(18)	-29.1(18)
C(00W)	180(6)	93(3)	49.2(19)	-79(4)	14(3)	7(2)
C(00X)	36.4(19)	76(3)	305(10)	0(2)	52(4)	-18(4)

*Table 53. Bond Lengths for **259b***

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(001)	C(009)	1.236(3)	C(00E)	C(00G)	1.387(4)
O(002)	C(00I)	1.328(3)	C(00E)	C(00O)	1.373(4)
O(003)	C(00D)	1.346(3)	C(00F)	C(00I)	1.514(3)
O(003)	C(00Q)	1.467(3)	C(00F)	C(00J)	1.533(3)
O(004)	C(00D)	1.200(3)	C(00G)	C(00H)	1.521(4)
O(005)	C(00K)	1.374(3)	C(00G)	C(00S)	1.389(4)
O(005)	C(00U)	1.431(4)	C(00H)	C(00N)	1.534(3)
O(006)	C(00I)	1.209(3)	C(00J)	C(00N)	1.525(4)
N(007)	C(009)	1.348(3)	C(00K)	C(00O)	1.394(4)
N(007)	C(00B)	1.468(3)	C(00K)	C(00P)	1.373(4)
N(007)	C(00H)	1.476(3)	C(00L)	C(00M)	1.520(3)
N(008)	C(00C)	1.453(3)	C(00L)	C(00T)	1.520(4)
N(008)	C(00D)	1.369(3)	C(00P)	C(00S)	1.397(4)
C(009)	C(00C)	1.528(3)	C(00Q)	C(00V)	1.510(4)
C(00B)	C(00F)	1.531(4)	C(00Q)	C(00W)	1.499(6)
C(00C)	C(00L)	1.550(3)	C(00Q)	C(00X)	1.479(5)

*Table 54. Bond Angles for **259b***

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C(00Q)	O(003)	C(00D)	120.5(2)	C(00G)	C(00H)	N(007)	111.30(19)
C(00U)	O(005)	C(00K)	117.2(3)	C(00N)	C(00H)	N(007)	107.57(19)
C(00B)	N(007)	C(009)	126.6(2)	C(00N)	C(00H)	C(00G)	116.0(2)
C(00H)	N(007)	C(009)	119.19(19)	O(006)	C(00I)	O(002)	123.7(2)
C(00H)	N(007)	C(00B)	113.98(18)	C(00F)	C(00I)	O(002)	112.2(2)
C(00D)	N(008)	C(00C)	119.7(2)	C(00F)	C(00I)	O(006)	124.1(2)
N(007)	C(009)	O(001)	120.1(2)	C(00N)	C(00J)	C(00F)	111.3(2)
C(00C)	C(009)	O(001)	118.7(2)	C(00O)	C(00K)	O(005)	115.5(3)
C(00C)	C(009)	N(007)	121.1(2)	C(00P)	C(00K)	O(005)	124.8(2)
C(00F)	C(00B)	N(007)	111.9(2)	C(00P)	C(00K)	C(00O)	119.7(3)
C(009)	C(00C)	N(008)	108.54(19)	C(00M)	C(00L)	C(00C)	112.4(2)
C(00L)	C(00C)	N(008)	110.49(19)	C(00T)	C(00L)	C(00C)	109.5(2)
C(00L)	C(00C)	C(009)	109.74(19)	C(00T)	C(00L)	C(00M)	110.3(2)
O(004)	C(00D)	O(003)	126.5(2)	C(00J)	C(00N)	C(00H)	113.0(2)

N(008)	C(00D)	O(003)	109.6(2)	C(00K)	C(00O)	C(00E)	119.9(3)
N(008)	C(00D)	O(004)	123.9(2)	C(00S)	C(00P)	C(00K)	119.6(3)
C(00O)	C(00E)	C(00G)	121.7(2)	C(00V)	C(00Q)	O(003)	102.2(2)
C(00I)	C(00F)	C(00B)	111.56(19)	C(00W)	C(00Q)	O(003)	109.9(3)
C(00J)	C(00F)	C(00B)	109.8(2)	C(00W)	C(00Q)	C(00V)	110.0(3)
C(00J)	C(00F)	C(00I)	112.4(2)	C(00X)	C(00Q)	O(003)	109.4(3)
C(00H)	C(00G)	C(00E)	119.8(2)	C(00X)	C(00Q)	C(00V)	110.1(4)
C(00S)	C(00G)	C(00E)	117.7(3)	C(00X)	C(00Q)	C(00W)	114.6(5)
C(00S)	C(00G)	C(00H)	122.3(2)	C(00P)	C(00S)	C(00G)	121.3(3)

*Table 55. Torsion Angles for **259b***

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O(001)	C(009)	N(007)	C(00B)	167.0(2)	N(007)	C(00B)	C(00F)	C(00J)	53.6(2)
O(001)	C(009)	N(007)	C(00H)	-6.7(3)	N(007)	C(00H)	C(00G)	C(00E)	-34.9(2)
O(001)	C(009)	C(00C)	N(008)	-67.5(2)	N(007)	C(00H)	C(00G)	C(00S)	150.4(2)
O(001)	C(009)	C(00C)	C(00L)	53.3(2)	N(007)	C(00H)	C(00N)	C(00J)	-55.4(2)
O(002)	C(00I)	C(00F)	C(00B)	-49.2(2)	N(008)	C(00C)	C(00L)	C(00M)	168.9(2)
O(002)	C(00I)	C(00F)	C(00J)	-173.0(2)	N(008)	C(00C)	C(00L)	C(00T)	-68.1(3)
O(003)	C(00D)	N(008)	C(00C)	163.33(19)	C(009)	C(00C)	C(00L)	C(00M)	49.2(2)
O(004)	C(00D)	N(008)	C(00C)	-17.2(3)	C(009)	C(00C)	C(00L)	C(00T)	172.3(2)
O(005)	C(00K)	C(00O)	C(00E)	178.9(2)	C(00B)	C(00F)	C(00J)	C(00N)	-51.2(2)
O(005)	C(00K)	C(00P)	C(00S)	-179.5(3)	C(00E)	C(00G)	C(00H)	C(00N)	-158.3(2)
O(006)	C(00I)	C(00F)	C(00B)	131.1(3)	C(00E)	C(00G)	C(00S)	C(00P)	-2.2(3)
O(006)	C(00I)	C(00F)	C(00J)	7.4(3)	C(00E)	C(00O)	C(00K)	C(00P)	-1.9(3)
N(007)	C(009)	C(00C)	N(008)	114.4(2)	C(00F)	C(00J)	C(00N)	C(00H)	54.1(2)
N(007)	C(009)	C(00C)	C(00L)	-124.8(2)	C(00G)	C(00H)	C(00N)	C(00J)	69.9(2)
N(007)	C(00B)	C(00F)	C(00I)	-71.6(2)	C(00G)	C(00S)	C(00P)	C(00K)	0.7(3)

*Table 56. Hydrogen Atom Coordinates (Å×10⁴) and Isotropic Displacement Parameters (Å²×10³) for **259b***

Atom	*x*	*y*	*z*	U(eq)
H(00i)	3691(9)	1108(8)	7677(7)	59.5(8)
H(00j)	4470(3)	8(7)	7776(9)	59.5(8)
H(00k)	3758(10)	576(14)	8341.5(18)	59.5(8)
H(00q)	6640(20)	1(11)	8294(6)	90.9(14)
H(00r)	7200(13)	1082(9)	8588(11)	90.9(14)
H(00t)	5952(11)	500(20)	8887(6)	90.9(14)
H(00u)	5884(19)	6083(16)	3635(5)	93.0(14)
H(00v)	5520(30)	4837(8)	3636(5)	93.0(14)
H(00w)	4473(8)	5700(20)	3874.5(14)	93.0(14)
H(00x)	9495(9)	5447(10)	7308(13)	103.2(16)
H(00y)	10580(30)	4831(3)	7706(6)	103.2(16)
H	10970(20)	5341(13)	7061(8)	103.2(16)
H(00z)	9250(40)	3492(5)	6133(8)	161(3)
H(a)	8540(20)	4540(30)	6387.5(18)	161(3)
H(b)	10000(20)	4620(30)	6127(8)	161(3)
H(00)	11150(40)	2910(40)	7402(8)	209(5)

H(c)	10890(30)	2610(30)	6700(20)	209(5)
H(d)	11849(11)	3587(13)	6880(30)	209(5)
H(00L)	5290(20)	1990(20)	8272(11)	17(5)
H(00H)	3550(30)	2670(20)	6370(14)	37(7)
H(00m)	2920(30)	870(30)	6242(15)	42(8)
H(00a)	6480(30)	1410(20)	5787(13)	33(7)
H(00C)	6650(30)	1080(20)	7298(12)	28(6)
H(00d)	3550(30)	-290(20)	5389(13)	34(7)
H(00b)	6650(30)	840(30)	6436(16)	49(9)
H(00n)	2520(30)	1670(30)	5566(16)	52(9)
H(00P)	3900(30)	4010(30)	4302(16)	50(9)
H(00E)	6080(30)	3600(30)	6133(15)	46(8)
H(00F)	5930(30)	-250(20)	5637(14)	38(7)
H(008)	7140(30)	2920(30)	7920(15)	42(8)
H(00S)	3160(40)	2690(30)	4987(19)	64(11)
H(00O)	6740(40)	4890(30)	5462(18)	67(11)
H(002)	5630(40)	-1450(30)	7117(19)	71(11)
H(00g)	4500(30)	810(30)	5127(14)	42(8)

*Table 57. Solvent masks information for **259b***

Number	X	Y	Z	Volume	Electron count	Content
1	-0.715	0.250	1.000	327.3	82.0	1 $CHCl_3$,1 CH_2Cl_2
2	-0.305	0.750	0.500	327.3	81.9	1 $CHCl_3$,1 CH_2Cl_2

Appendix 3. *Curriculum Vitae*

■ **Personal data:**

Name:	Urszula Klimczak
Date of Birth:	14.06.1992
Address:	Hadamarstraße 30, 93051 Regensburg (Germany)
Telephone:	+491628515064, +48602627857
E-mail:	Urszula.Klimczak@chemie.uni-regensburg.de

■ **Education:**

10.2011-12.2016	University of Warsaw, College of Inter-Faculty Individual Studies in Mathematics and Natural Sciences: chemistry and biotechnology - 06.2014: Bachelor of chemistry (*The application of enzymatic kinetic resolution in the synthesis of non-racemic allylic alcohols*) - 07.2014: Bachelor of biotechnology (*GC-MS analysis of triterpenoids in the leaves and roots of red beet cultivar Red Sphere (*Beta vulgaris *var.* vulgaris *L.*)) - 06.2016: Master of chemistry (*Addition reactions of 4-vinylazetidin-2-ones to aldehydes in the presence of InI, $Pd(PPh_3)_4$ and Brønsted acid: Application to the synthesis of trisubstituted γ-butyrolactones*) - 12.2016: Master of biotechnology (*Triterepene saponins in the leaf beet (*Beta vulgaris *L.) – structure and changes of the content during the vegetation season*)
01.2017-01.2021	PhD studies, University of Regensburg, group of Prof. O. Reiser: asymmetric synthesis of non-proteinogenic pyrrolidine- and piperidine-based amino acids and their application in peptides

■ **Work experience:**

06.2012-11.2016	Internship at the Institute of Organic Chemistry of the Polish Academy of Sciences (Warsaw), group II (Prof. B. Furman): synthesis of *β*- and *γ*-hydroxy *α*-amino acids based on enzymatic kinetic resolution and cyanate-to-isocyanate rearrangement; studies on reactions of non-racemic *β*-lactam-derived *ε*-amino-allylic anions with aldehydes
07.2013-08.2013	Internship at the Institute of Biochemistry and Biophysics of the Polish Academy of Sciences (Warsaw), Department of Lipid Biochemistry (Prof. E. Świeżewska): studies on influence of the double bond stereochemistry of isoprenoids on the susceptibility to oxidation; studies on antioxidative properties of polyisoprenoid alcohols
09.2015-10.2015	Internship at the Medical University of Warsaw, Department of Pharmacognosy and Molecular Basis of Phythotherapy (Prof. M. Naruszewicz):

evaluation of phenolics in aerial parts of *Polygonum bistorta L.*

07.2016-10.2016 Internship at the Institute of Organic Chemistry Ruprecht-Karls-Universität Heidelberg, group of Prof. A. S. K Hashmi:

synthesis of new NAC and NHC gold(I) complexes, gold-catalyzed reactions

■ **Laboratory skills:**

- Fundamental synthetic organic chemistry techniques; methods of isolation and purification of organic compounds
- Instrumental methods: HPLC, GC and UPLC
- Spectroscopic techniques: NMR, IR, MS, UV-Vis, polarimetry

■ **Achievements:**

Publications:

- Szcześniak, P.; Październiok-Holewa, A.; Klimczak, U.; Stecko, S. *J. Org. Chem.* **2014**, *79*, 11700.
- Klimczak, U. K.; Zambroń, B. K. *Chem. Commun. (Camb).* **2015**, *51*, 6796.
- Molińska, E.; Klimczak, U.; Komaszyło, J.; Derewiaka, D.; Obiedziński, M.; Kania, M.; Danikiewicz, W.; Świeżewska, E. *Lipids* **2015**, *50*, 359.
- Klimczak, U.; Staszewska-Krajewska, O.; Zambroń, B. K. *RSC Adv.* **2016**, *6*, 26451.
- Klimczak, U.; Furman, B.; Zambroń, B. 4-Vinyloxyazetidin-2-one, a novel substrate for β-lactam synthesis. In *Beta Lactams: Novel Synthetic Pathways and Applications;* Banik, B. K., Ed. **2016**.
- Klimczak, U.; Woźniak, M.; Tomczyk, M.; Granica, S. *Food Chem.* **2017**, *230*, 281.
- Plata, P.; Klimczak, U.; Zambroń, B. K. *J. Org. Chem.* **2018**, *83*, 14527.
- Yedoyan, J., Wurzer, N., Klimczak, U., Ertl, T., Reiser, O. *Angew. Chem. Int. Ed.* **2019**, 58, 3594; *Angew. Chemie* **2019**, *131*, 3632.

Conferences:

- Klimczak, U., Zambroń, B. *Otrzymywanie i reakcje chiralnych anionów ε-amino-allilowych z aldehydami jako steroselektywana metoda syntezy wysoce sfunkcjonalizowanych alkoholi homoallilowych*, **oral presentation**, Ogólnopolskie Studenckie Mikrosympozjum Chemików III edycja, Bialystok, Poland (12-15.03.2015).
- Mroczek, A., Klimczak, U., Sukiennik, P., Kapusta, I., Kowalczyk, M., Stochmal, A. *Comparison of the triterpenoid content in roots and leaves of red beet (*Beta vulgaris *var.* vulgaris *L.)*, **poster**, Future Trends in Phytochemistry in the global era of agri-food and health II, San Pedro del Pinatar Murcia, Spain (27-30.04.2015).
- Klimczak, U., Zambroń, B. *Otrzymywanie i reakcje chiralnych anionów ε-amino-allilowych z aldehydami jako steroselektywana metoda syntezy wysoce sfunkcjonalizowanych alkoholi homoallilowych*, **poster**, ChemSession'15, Warsaw, Poland (8.05.2015).

- Zambroń, B., Klimczak, U. *Effective 1,5-stereocontrol in Pd(0)/InI promoted reactions of chiral* N-*Ts-4-vinylazetidin-2-ones with aldehydes. An efficient entry to nonracemic semi-protected (3*Z*)-2,6*-anti-*enediols*, **poster**, 16th Tetrahedron Symposium in Berlin, Germany (16-19.06.2015).
- Klimczak, U., Ertl, T., Yedoyan, J., Park, S., Reiser, O. *The application of cyclopropanated pyrroles: the synthesis of nonproteinogenic pyrrolidine- and piperidine-based amino acids*, **poster**, 26th ISHC Congress, Regensburg, Germany (3-8.09.2017).
- Klimczak, U., Yedoyan, J., Reiser, O. *The synthesis of highly functionalized piperidine derivatives* via *Heck coupling of monocyclopropanated pyrroles*, **poster**, ORCHEM 2018, Berlin, Germany (10-12.09.2018).
- Klimczak, U., Yedoyan, J., Reiser, O. *The synthesis of novel nipecotic acid derivatives* via *Heck coupling of monocyclopropanated pyrroles*, **poster**, 8th Austrian Peptide Symposium, Salzburg, Austria (13.12.2018).
- Klimczak, U., Yedoyan, J., Reiser, O. *Heck reaction of cyclopropanated pyrroles – synthesis of novel nipecotic acid derivatives*, **poster**, VIII EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry, Athens, Greece (1-5.09.2019).

■ Other skills:

Languages: German (fluent, both written and spoken)
English (intermediate)
Hungarian (basics)

Computer skills: advanced knowledge of Microsoft Office package, ACD/ChemSketch, ChemDraw, MestReNova, SciFinder, Reaxys, basic knowledge of statistical programs: Statistica, SAS, basic knowledge of Gaussian, basics of Web Page design

■ Research interest:

Asymmetric organic synthesis, synthesis and isolation of natural products and biologically active compounds, mechanisms of organic reactions

Appendix 4. Declaration

Herewith I declare that this thesis is a presentation of my original work, prepared singlehandedly unless otherwise noted. Contributions of others are marked clearly with reference to the literature, license or acknowledgement of collaborative research.