Synthesis of 8-Aza- and 8-Oxabicyclo[3.2.1]octanes via [3+2]-Cycloadditions of cyclopropanated Furan and Pyrrole Derivatives

Dissertation

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Für meine Familie

und

Johannes

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Abbreviations

Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
Boc	*tert*-butyloxycarbonyl
BPR	back pressure regulator
brine	saturated NaCl solution
Bu	butyl
^{t}Bu	*tert*-butyl
^{t}BuOH	*tert*-butanol
BzCl	benzoyl chloride
°C	degrees Celsius
cal.	calculated
CCR5	C-C chemokine receptor type 5
cm^{-1}	wavenumbers
CMT	2-carbomethoxy-tropinone
^{13}C NMR	carbon NMR
CP	cyclopropane
COPD	chronic obstructive pulmonary disease
crm	complex reaction mixture
d	day (s)
2D	2-dimensional
DACH	(1*R*,2*R*) diamino-cyclohexane
DAT	dopamine transporter
DBU	1,8-diazabicyclo-[5.4.0]undec-7-en
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-*H*	diisobutylaluminium hydride
DMAD	dimethyl acetylene-dicarboxylate
DMAP	4-dimethylaminopyridine
DMC	demethylcantharidin
DMF	dimethylformamide
DMP	Dess-Martin-periodane
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
EA	ethyl acetate
ee	enantiomeric eccess
e.g.	for example
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
et al.	and others (co-authors)
Et_2O	diethyl ether
EtOH	ethanol

EWG	electron withdrawing group
FDA	Food and Drug Administration
gem	geminal
h	hour(s)
HIV	human immuno-deficiency viruses
^{1}H NMR	proton NMR
HPLC	high performance liquid chromatography
HRMS	high resolution mass
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LED	light emitting diods
LRMS	low resolution mass
λ_{max}	max. UV-vis wavelength
M	molar (moles per liter)
18-MC	(–)-18-methoxy-coronaridine
*m*CPBA	*meta*-chlorperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
m.p.	melting point
MS	mass spectrometry
Ms	mesyl
MW	microwave irradiation
nAChR	nicotinic acetylcholine receptor
NBS	*N*-bromosuccinimide
nc	no conversion
nd	not determined
nm	nanometer(s)
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
OAc	acetate
PCC	pyridinium chlorochromate
PE	petroleum ether
Pg	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
PP2A	protein phosphatase 2A
ppm	parts per million
R	arbitrary residue
rac	racemic
RCM	ring closing metathesis
R_f	retention factor
R_T	residence time
SAR	structure-activity relationships
t	time
T	temperature
TEA	triethylamine

Tf	triflate	t_r	retention time
TFA	trifluoroacetic acid	Ts	*p*-toluenesulfonyl
THF	tetrahydrofuran	TS	transition state
TLC	thin layer chromatography	VCP	vinylcyclopropane
TMG	tetramethylguanidine	X	heteroatom

A Introduction

1 8-Azabicyclo[3.2.1]octanes

Tropane alkaloids, being characterized by a *N*-methyl-8-azabicyclo[3.2.1]octane core **1**, serve as key motifs in drug design due to their unique biological activities (Figure 1).[1] More than 300 compounds of this large class of secondary metabolites have been obtained by isolation from different plant families including *Solanaceae*, *Erythroxylaceae*, *Convolvulaceae*, *Proteaceae*, *Rhizophoraceae*, *Brassicaceae*, and *Euphorbiaceae*.[2]
Often tropane alkaloids are esters of 3β-tropanole (**2**, pseudotropine) or 3α-tropanole (**3**, tropine). Tropinone (**4**) is an ideal prochiral substrate for enantioselective desymmetrization reactions.[3] 8-Azabicyclo[3.2.1]octane comprising an unmethylated nitrogen bridge is generally referred to as nortropane (**5**).[4]

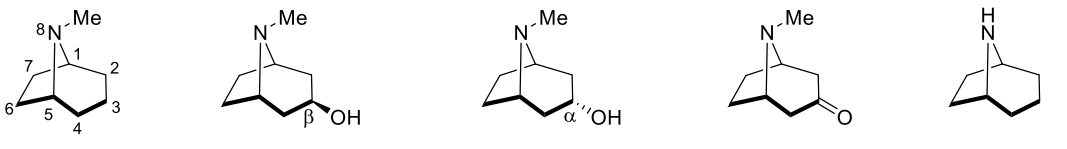
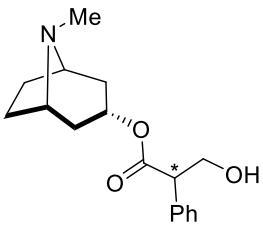


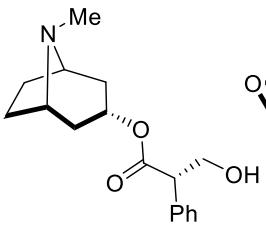
Figure 1. Structures of tropanes.

Important representatives of this class are atropine (**6**), hyoscyamine (**7**), scopolamine (**8**), (*R*)-(−)-cocaine (**9**), (+)-ferruginine (**10**) and calystegine C_2 (**11**) (Figure 2). These tropane alkaloids are named after the respective first plant from which they were extracted: e.g., atropine (**6**) was extracted from *Atropa belladonna* (the deadly nightshade) and hyoscyamine (**7**) from *Hyoscyamus niger* (the black henbane).[5]
Although the illustrated compounds have the same core structure, they differ greatly in their chemical as well as pharmacological properties. For instance, (*R*)-(−)-cocaine (**9**) acts as a reuptake inhibitor of the three monoamine transporters serotonin, dopamine and noradrenalin,[3b,6] whereas atropine (**6**), hysoamine (**7**) and scopolamine (**8**) are competitive muscarinic receptor antagonists.[7] Alterations of these transporter functions may play a role in diseases like Parkinson and Alzheimer.[7c,8] (*Ent*)-(**10**) acts as a potent agonist for the nicotinic acetylcholine receptor (nAChR).[9] Calystegines such as **11** belong to the class of glycoalkaloids and impact rhizosphere ecology as nutritional sources for soil microorganisms and as glycosidase inhibitors.[10]
Furthermore, 8-oxabicyclo[3.2.1]octanes, structural mimics of tropane alkaloids, have attracted great attention in the design of medications for cocaine abuse due to their promising dopamine transporter inhibitor properties.[8b,11]

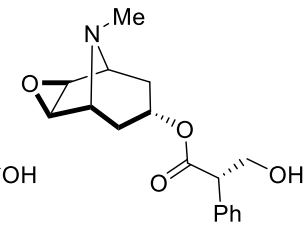
Atropa belladonna[1]



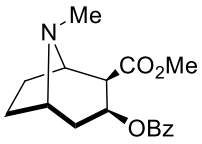
atropine (**6**)



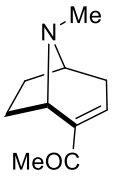
hyoscyamine (**7**)



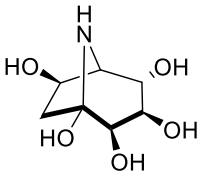
scopolamine (**8**)



(*R*)-(–)-cocaine (**9**)



(+)-ferruginine (**10**)



calystegine C_2 (**11**)

Hyoscyamus niger [2]

Figure 2. Important representatives of naturally occurring (nor)tropane alkaloids.

Due to the remarkable biological activities of the tropane alkaloids, 8-azabicyclo[3.2.1]octane is the central structural motif of a variety of pharmaceutically important, synthetically or semi-synthetically produced agents (Figure 3): Scopolamine butylbromide (**12**), sold under the brand name Buscopan®, is an anticholinergic agent to treat abdominal pain.[12] It is a semisynthetic derivative of scopolamine (**8**) with a butylbromide moiety attached at the nitrogen to prevent passage across the blood-brain-barrier, resulting in fewer systemic side effects.[13] Ipratropium (**13**, Atrovent®), oxitropium (**14**, Oxivent®), and tiotropium (**15**, Srivasso®) are marketed anticholinergics for the treatment of chronic obstructive pulmonary disease (COPD), an inflammatory lung disease characterized by airflow blockage and breathing-related problems, and asthma.[14] Ipratropium bromide (**13**) is a quaternary ammonium analogue of atropine (**6**)[15] while oxitropium (**14**) is an *N*-ethyl analogue that is pharmacologically equivalent to **13**.[16] In contrast to the short-acting muscarinic antagonists **13** and **14**, tiotropium (**15**) was the first long-acting anticholinergic drug.[16-17] Trospium chloride (**16**) is used to treat overactive bladder and COPD.[18] Benztropine (**17**, brand name: Cogentin®) is an anticholinergic/antihistamine agent that atypically blocks the dopamine transporter in addition to the muscarinic acetylcholine receptor. It is used as a medicine to treat symptoms of Parkinson's disease.[19]

[1] https://commons.wikimedia.org/wiki/File:Atropa_bella-donna0.jpg; author: Kurt Stüber, 2004 (accessed on 16.06.2021).

[2] https://commons.wikimedia.org/wiki/File:Hyoscyamus_niger_0003.JPG; author: H. Zell, 2009 (accessed on 16.06.2021).

The development of new drugs like CCR5 antagonists for the Human Immunodeficiency Virus (HIV) has still a high research priority. In 2005, Pfizer discovered a potent antagonist for the CCR5 receptor, containing a 8-azabicyclo[3.2.1]octane core structure.[20] Maraviroc (**18**), sold under the trade name Celsentri® (outside the United States), was approved by the FDA in 2007 for the treatment of HIV.[21]

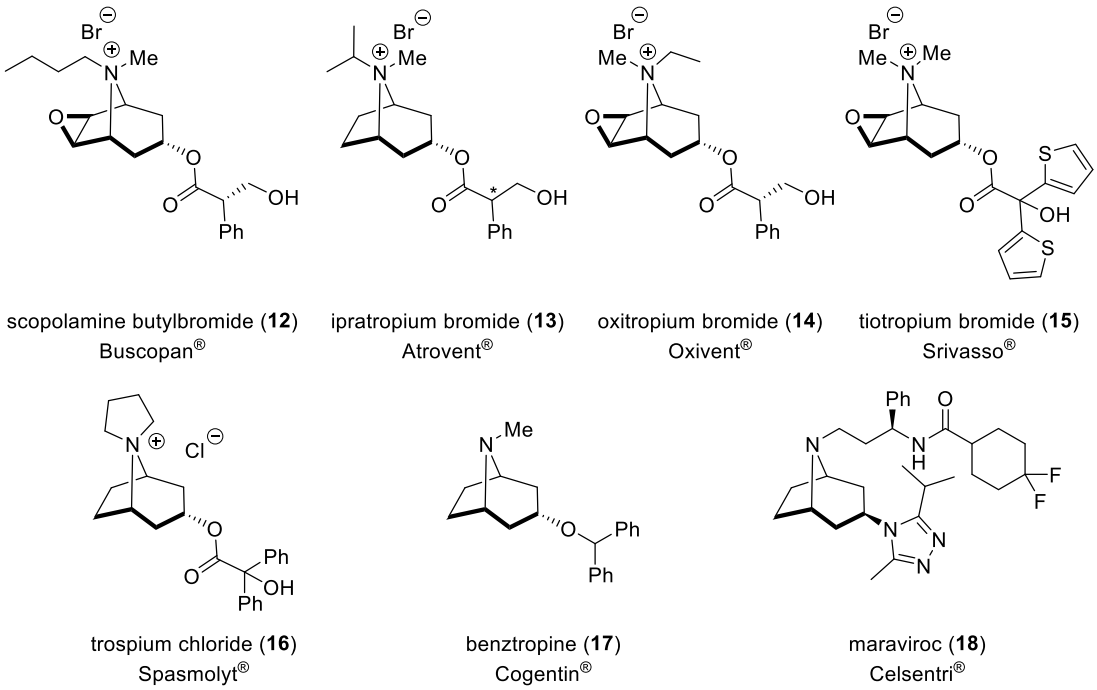


Figure 3. Pharmaceutical products based on tropane alkaloids.

In summary, anticholinergic agents containing a tropane scaffold represent the current standard of care for the treatment of asthma, COPD, and motion sickness. Despite the developed synthetic congeners depicted in figure 3, being more effective and safer, there remains a large unmet medical need for more selective agents[4] that exploit the other versatile chemical properties of bioactive tropane alkaloids in addition to anticholinergics.[7a] For example, novel derivatives of calystegines or cocaine are also promising drug candidates in the field of glucosidase inhibitors and cocaine antagonists, respectively. Therefore, new efficient methodologies for the enantioselective synthesis of the 8-azabicyclo[3.2.1]octane scaffold are highly attractive within the industrial and academic research communities. The key step for the efficient synthesis of novel tropane alkaloids and analogues is the construction of bridged seven-membered rings containing the appropriate functionalities, and a number of elegant solutions has been presented to this challenging problem.[2b,3b,22] These approaches can be classified into different categories: 1) enantioselective desymmetrization of achiral tropinone derivatives[3a], 2) chiral auxiliaries or enantioselective catalysis,[3a] 3) enantioenriched starting materials.

[3b,23] The most recent examples reported to date will be disclosed in the following, using starting materials from the chiral pool.

2 Enantioselective synthesis of 8-azabicyclo[3.2.1]octane derivatives starting from the chiral pool

Naturally occurring enantiopure building blocks are often used to construct the tropane framework with all required stereochemical information.[3b] An overview of recently prepared 8-azabicyclo[3.2.1]octanes from the chiral pool is presented in table 1, including the enantiomerically pure starting materials, the key step of the synthetic routes, and the pharmacological properties of the (nor)tropane derivatives. The widely used strategies to access the tropane scaffold starting from the chiral pool are ring closing metathesis (RCM) and cycloaddition reactions. Calystegines are the most common tropane alkaloids derived from enantiomerically pure building blocks due to their structural similarity to monosaccharides.[10b,23-24] They are iminosugars which have medicinal potential in the treatment of diseases such as diabetes, HIV, cancer, influenza and lysosomal storage disorder.[25] Therefore, the demand for the synthesis of calystegines and novel derivatives characterized by a polyhydroxylated nortropane scaffold has received increased attention in recent years. Important representatives of iminosugars with glucosidase inhibitor properties of the class of piperidines like 1-deoxynojirimycin (**19**), iosfagomine (**20**), noeuromycin (**21**) and Miglitol (**22**, anti-diabetic drug) are shown in figure 4 which share their biological activity with bicyclic iminosugars like calystegine B_2 (**23**).

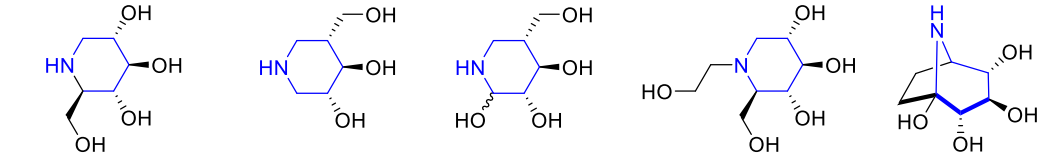
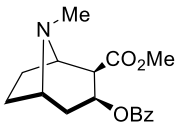
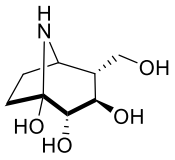
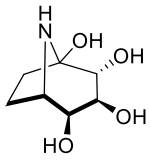
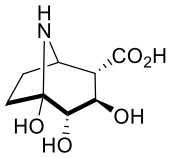
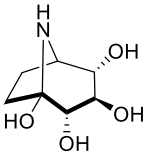
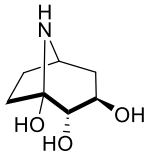
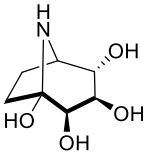
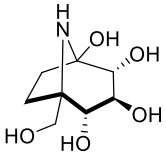
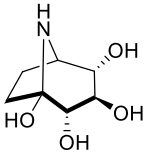
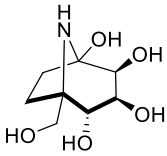
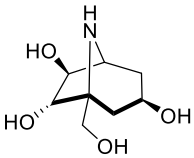
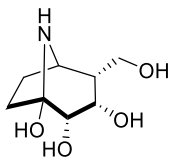


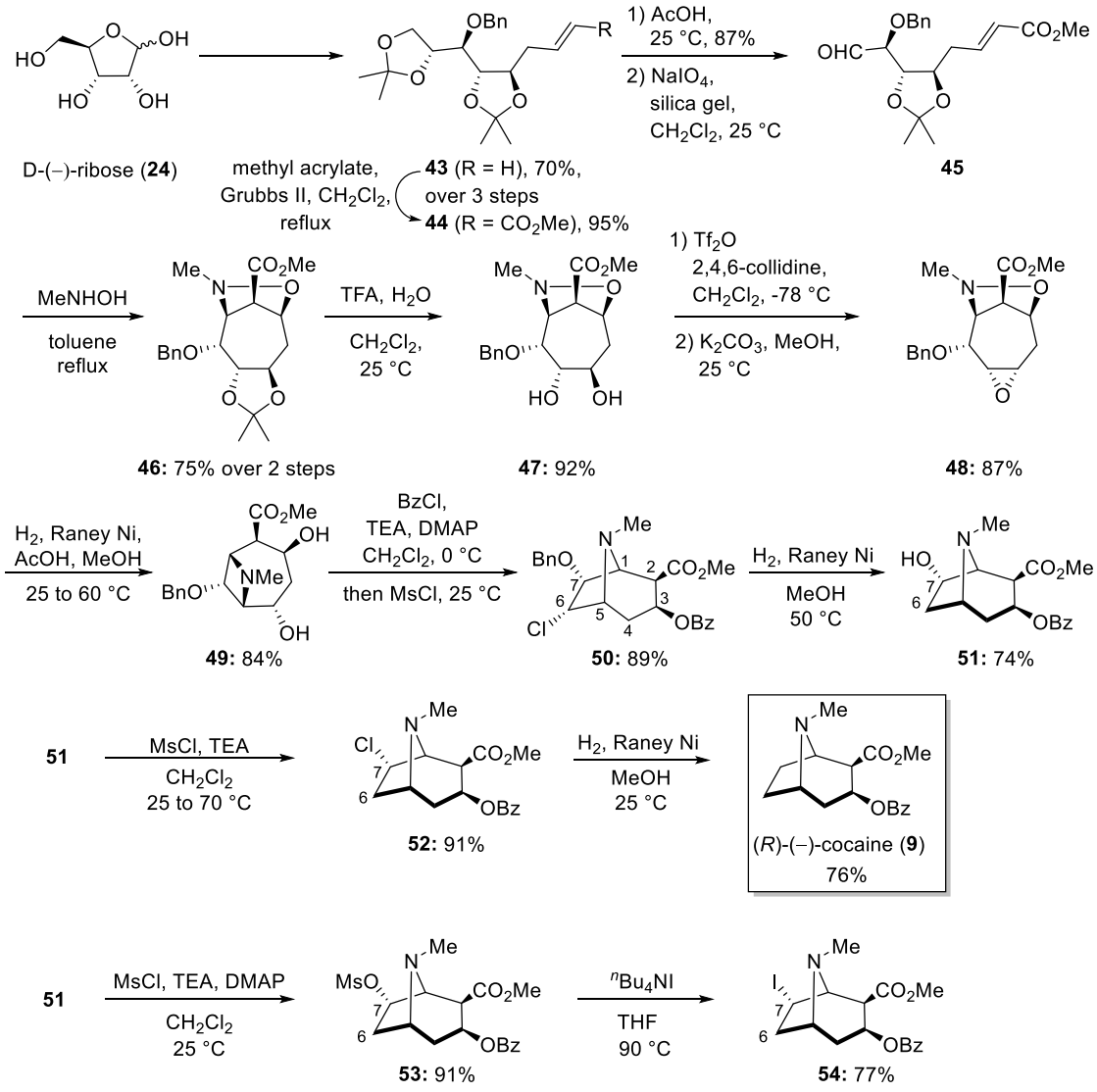
Figure 4. Glucosidase inhibitors with structure of iminosugars.

Therefore, the development of hybrids of piperidines and calystegines has attracted attention for novel medicines in the field of glucosidase inhibitors. The synthetic routes to the (nor)tropanes shown in table 1 are described in more detail in the following section.

Table 1. Overview of (nor)tropanes accessed from the chiral pool.

entry	(nor)tropane	chiral pool/ scheme/ **biological activity**	entry	(nor)tropane	chiral pool/ scheme/ **biological activity**
1[22i]	 (*R*)-(−)-cocaine (**9**) 15 steps, 13%	D-ribose (**24**) scheme 1 intra. cyclo-addition **DAT inhibitor**	7[26]	 noeurostegine **(33)** 22 steps, 1.8%	levoglucosan (**34**) scheme 7 RCM **glucosidase inhibitor (β)**
2[27]	 *ent*-calystegine B_4 (**25**), 13 steps, 2%	L-tartrate (**26**) scheme 2 nitro-Michael/aldol reaction	8[28]	 *uronic*-noeurostegine (**35**) 24 steps, 1.5%	levoglucosan (**34**) scheme 8 RCM **glucuronidase inhibitor (β)**
3[29]	 calystegine B_2 (**23**) 11 steps, 27%	D-xylose derivative (**27**) scheme 3 NHK **glucosidase inhibitor (β)**	9[30]	 calystegine A_3 (**36**) 17 steps, 5.1%	2-deoxy-D-glucose (**37**) scheme 9 RCM
4[29]	 calystegine B_3 (**28**) 11 steps, 19%	L-arabino-pyranose **29** scheme 4 NHK	10[31]	 nojiristegine (**38**) 21 steps, 2.7%	methyl α-D-glucopyranoside (**39**) scheme 10 RCM
5[32]	 calystegine B_2 (**23**) 10 steps, 19%	α-D-xylo-pyranoside (**30**) scheme 5 RCM **glucosidase inhibitor (β)**	11[31]	 *manno*-nojiristegine (**40**) 21 steps, 1.6%	methyl α-D-manno-pyranoside (**41**) scheme 11 RCM
6[33]	 labystegine (**31**) 42% from nitrone **77**	D-xylo-furanose (**32**) scheme 6 intra. cyclo-addition **glucosidase inhibitor (α)**	12[34]	 *galacto*-noeurostegine (**42**), 21 steps, 1%	levoglucosan (**34**) scheme 12 RCM **galacto-cerebrosidase inhibitor**

Shing *et al.* demonstrated the synthesis of (*R*)-(–)-cocaine (**9**) starting from the chiral pool from inexpensive D-(–)-ribose (**24**) in 15 steps with 13% overall yields, as shown in scheme 1.[22i] D-(–)-ribose (**24**) was readily converted to alkene **43** in three steps.[35] Cross metathesis of **43** by Grubbs II catalyst afforded α,β-unsaturated ester **44** which was transformed through acid hydrolysis and glycol cleavage oxidation to aldehyde **45**. Cycloadduct **46** was prepared *via* an *endo*-selective intramolecular nitrone-alkene cycloaddition of aldehyde **45** with MeNHOH as key step of the synthesis.

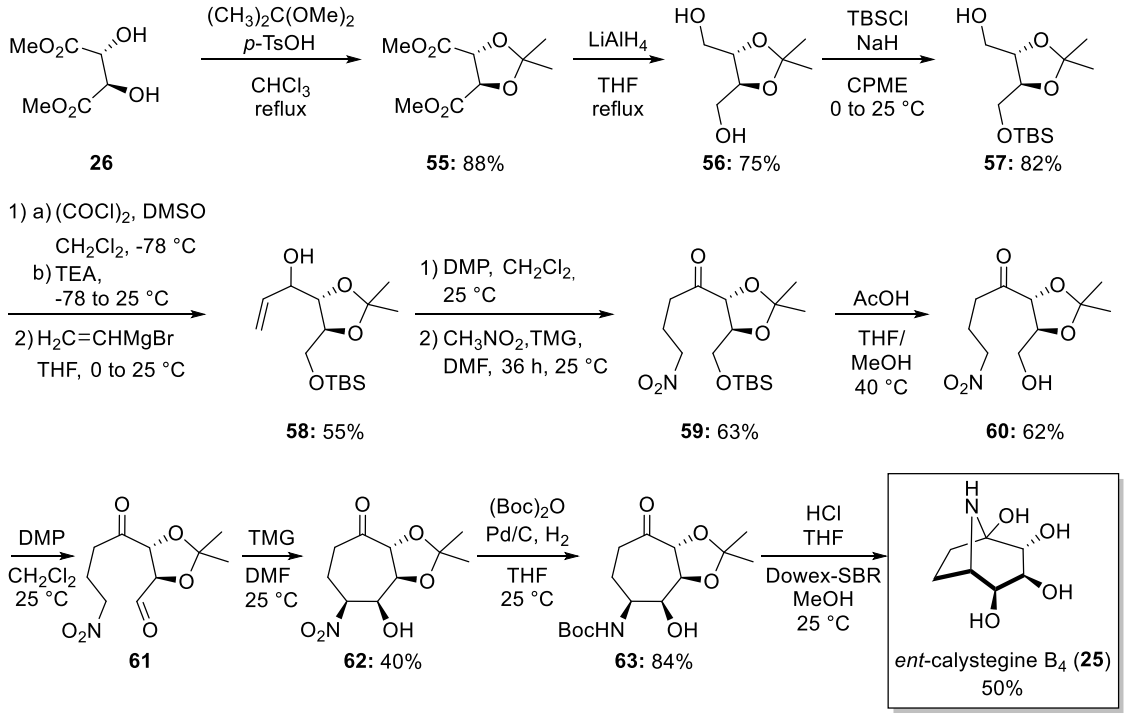


Scheme 1. Enantioselective synthesis of C6/C7 and C7 cocaine analogues.

Azetidine-diol **49** was formed by hydrolysis, esterification, and Raney-Nickel mediated hydrogenolysis. Benzoylation of **49**, followed by mesylation furnished 8-azabicyclo[3.2.1]octane **50**. (7*S*)-hydroxy cocaine (**51**) was prepared by hydrogenolysis of **50** in the presence of Raney Ni. Mesylation of alcohol **51** gave

(7*S*)-chloro-cocaine (**52**), which was finally converted to (*R*)-(–)-cocaine (**9**) *via* Raney Ni mediated hydrogenolysis. Moreover, C6,C7 cocaine analogues **53-54** were provided by this synthetic strategy.[22i] Analogues of cocaine are in great demand in the research of antagonists or partial agonists for the treatment of cocaine addiction, which is a worldwide problem. C6/C7 tropane analogues are still underexplored and rarely accessible as they often require novel total syntheses compared to the tremendous studies on C2/C3 analogues, which are readily derived from (*R*)-(–)-cocaine (**9**).[3b,22i]

A chiral pool total synthesis of *ent*-calystegine B_4 (**25**) was carried out from commercially available chiral L-dimethyl tartrate (**26**) in 13 steps (Scheme 2).[27] Tartrate (**26**) was converted to acetal **55**, followed by reduction, monoprotection, Swern oxidation and addition of vinylmagnesium to furnish compound **58**. Oxidation and 1,4-addition gave **59**, which was deprotected on the primary alcohol group and oxidized to an aldehyde **61**.

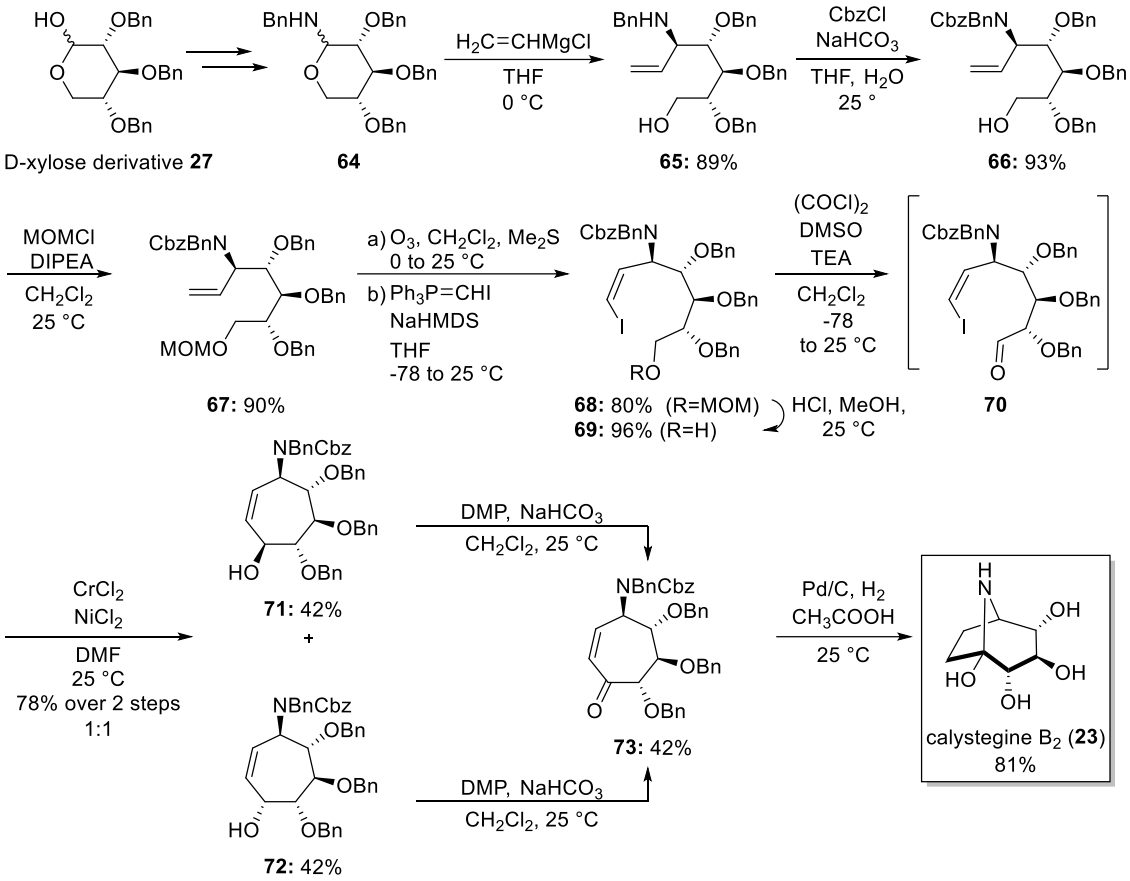


Scheme 2. Total synthesis of *ent*-calystegine B_4 (**25**) *via* nitro-Michael/aldol reaction.

Polyhydroxylated nitrocycloheptanone **62** was subsequently obtained *via* stereoselective intramolecular nitroaldol reaction of aldehyde **61**. The conversion of **62** to *N*-Boc protected amino cycloheptane **63** was performed under pressurized hydrogenation conditions in the presence of Boc_2O. Global deprotection of **63** under acidic conditions afforded *ent*-calystegine B_4 salt which was converted to **25** by treatment with Dowex acidic resin in MeOH.

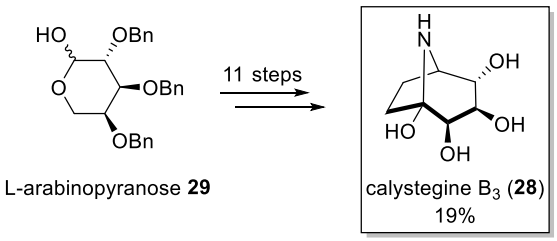
Wang *et al.* developed a synthesis towards calystegine B_2 (**23**), which is one of the most powerful representatives of calystegines, in 11 steps in an excellent overall yield of 27%

from readily available D-xylose derivative **27** (Scheme 3).[29] The key transformation in the synthesis of calystegine B_2 (**23**) involved the construction of cycloheptanone **71/72** *via* an intramolecular Nozaki-Hiyama-Kishi (NHK) reaction of **70**. The latter was prepared from ozonolysis of **67**, followed by Stork olefination as essential steps.



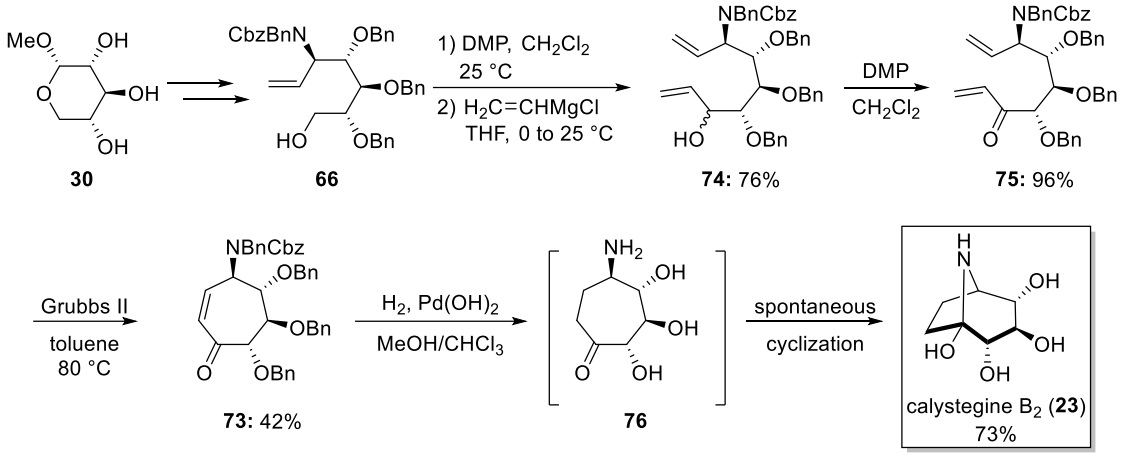
Scheme 3. Synthesis of calystegine B_2 (**23**) *via* intramolecular NHK reaction.

In analogous way, calystegine B_3 (**28**) was synthesized from L-arabinopyranose **29** in 11 steps in an overall yield of 19% (Scheme 4).



Scheme 4. Starting material for the synthesis of calystegine B_3 (**28**) *via* intramolecular NHK reaction.

Underlin *et al.* also described the total synthesis of calystegine B_2 (**23**) from commercially available methyl α-D-xylopyranoside (**30**) in over 10 steps in an overall yield of 19% (Scheme 5).[32]



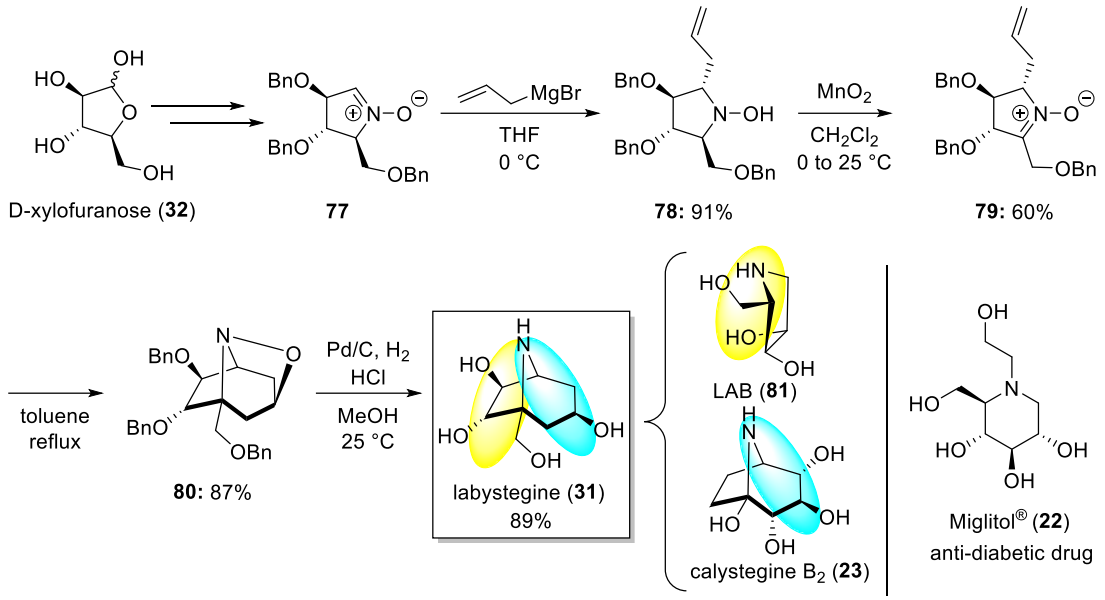
Scheme 5. Synthesis of calystegine B_2 (**23**) from methyl α-D-xylopyranoside (**30**).

The central cycloheptenone **73** was formed through a stereoselective nucleophilic addition of vinyl magnesium bromide, DMP oxidations and an intramolecular ring-closing metathesis with Grubbs II catalyst. The final step included reduction of the alkene moiety in **73**, followed by global deprotection with Pearlman's catalyst, resulting in spontaneous cyclization of **76** to calystegine B_2 (**23**).

In recent years, the research focus in the field of calystegines has been further extended to the investigation of hybrids between bicyclic iminosugars (e.g., potent calystegine B_2 (**23**)) and piperidines or pyrrolidines. The ethylene bridge present in calystegines is expected to optimize stability limitations of potent piperidines (e.g., noeuromycin (**21**)).[34b] Furthermore, the aim was to selectively modify the inhibitor properties of the hybrids based on the inhibition moieties of the fragment (pyrrolidines, piperidines).[33]

Kato *et al.* reported the design and synthesis of labystegine (**31**), a new class of nortropane-type iminosugar, which is a hybrid of α-1-C-alkylated 1,4-dideoxy-1,4-imino-L-arabinitol (**81**, LAB) and calystegine B_2 (**23**) (Scheme 6).[33] The novel compounds were developed based on molecular dynamics calculations and molecular docking studies. Labystegine (**31**) was prepared starting from sugar-derived cyclic nitrone **77** *via* intramolecular [3+2]-cycloaddition reaction as key step. Nitrone **77**, obtained from D-xylofuranose (**32**)[36], reacted with allyl Grignard reagent to furnish hydroxylamine **78** as single diastereomer. The oxidation of the latter with MnO_2 gave nitrone **79**. The cycloadduct **80** was generated as single product by heating of **79**. Finally, catalytic hydrogenolysis accomplished labystegine (**31**). Biological evaluation identified

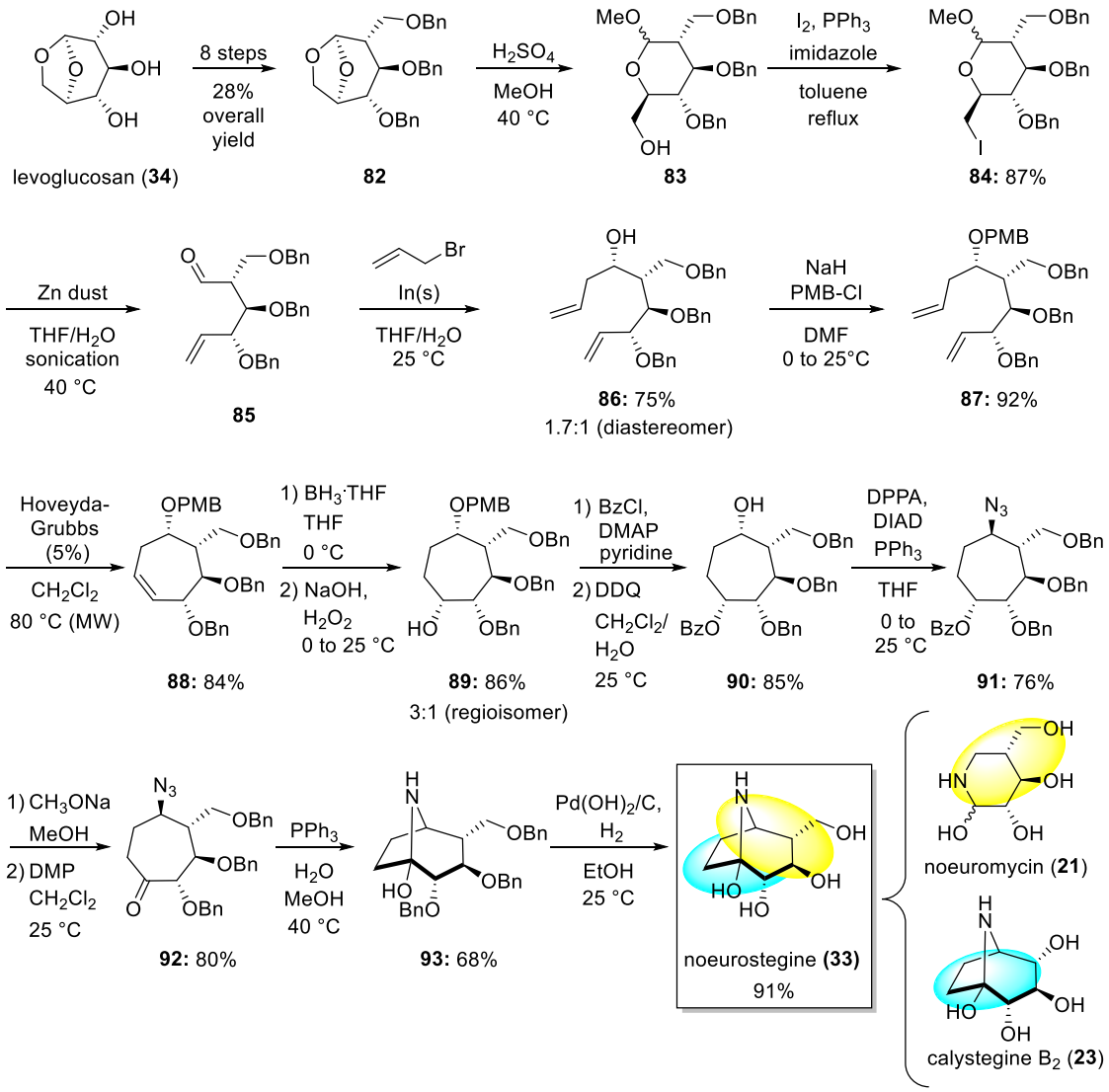
labystegine (**31**) as potent inhibitor of intestinal α-glucosidases, which was 10-fold more potent compared to Miglitol® (**22**), an antidiabetic drug.[33]



Scheme 6. Synthesis of labystegine (**31**) from sugar-derived D-xylofuranose (**32**) *via* intramolecular 1,3-dipolar cycloaddition.[33]

The synthesis of noeurostegine (**33**), a hybrid of noeuromycin (**21**) and the stable as well as selective β-glucosidase inhibitor calystegine B_2 (**23**) (Scheme 7) was described by Rasmussen *et al*.[26] Noeuromycin (**21**) is a potent, albeit unstable and unselective inhibitor of glycosidases.[37] The novel hybride nortropane **33** was synthesized from levoglucosan (**34**) in 22 steps, using **82** as key synthetic intermediate derived in eight steps from biomass derived **34**. Acid-catalyzed methanolysis of **82**, followed by iodination furnished halide **84,** which was converted to aldehyde **85** by zinc-mediated fragmentation. Subsequently, Barbier reaction was carried out to afford homoallylic alcohols **86**, which were protected as *p*-methoxybenzyl ether **87**. Cycloheptene **88** was generated by Hoveyda-Grubbs catalyst-mediated ring closing metathesis. Hydroboration/oxidation of the alkene **88** led to alcohol **89**, and the latter was protected, subsequently reacted with DDQ to give **90**. The nitrogen atom was introduced by nucleophilic substitution of the alcohol in **90** with an azide under Mitsunobu conditions to produce azido cycloheptane **91**. Removal of the benzoyl ester by Zemplen diacylation and oxidation with DMP to ketone **92** was successfully carried out. Finally, noeurostegine (**33**) was obtained *via* Staudinger reduction and catalytic hydrogenolysis. Noeurostegine (**33**) is a potent, competitive inhibitor of almond and *Thermotoga maritima* β-glycosidase, while yeast α-glucosidase was not inhibited, making noeurostegine (**33**) a highly selective inhibitor. Moreover, **33** was evaluated as an inhibitor of glucocerebrosidase

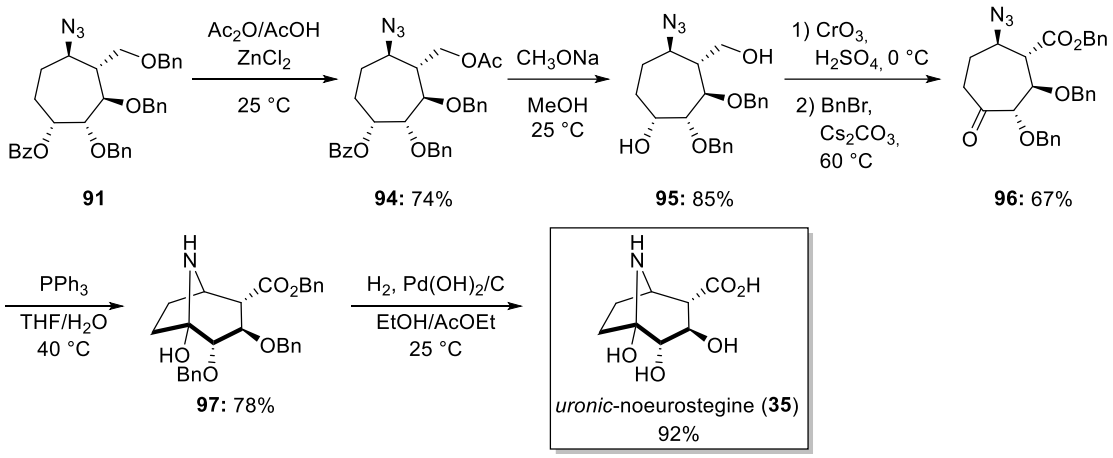
(GCase), while *N*-butyl and *N*-nonyl noeurostegine derivatives did not possess inhibitory properties for human GCase.[38]



Scheme 7. Synthesis of noeurostegine (**33**) from levoglucosan (**34**) in 22 steps.

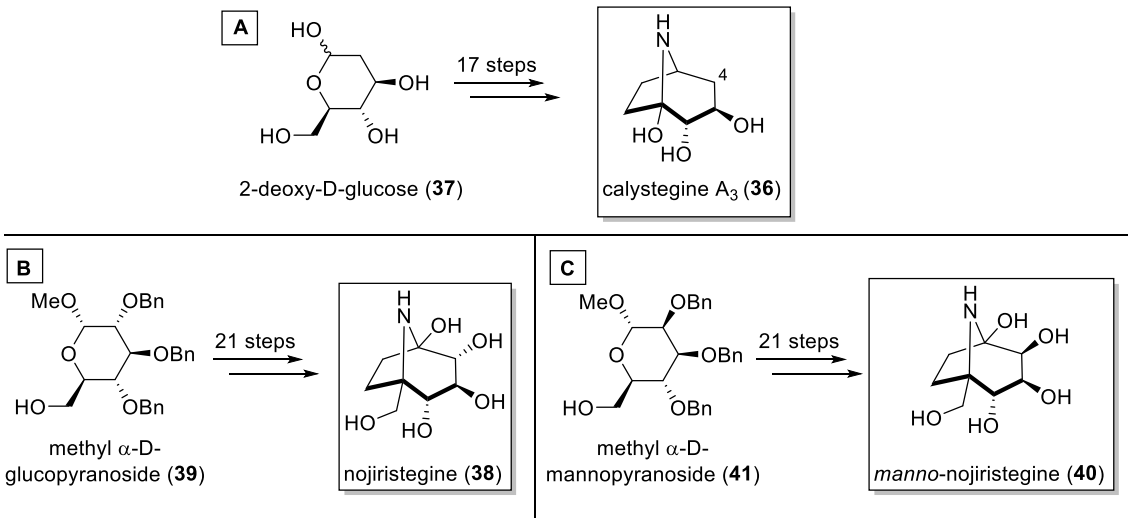
Due to the promising biological activity of noeurostegine (**33**), *uronic*-noeurostegine (**35**), possessing a carboxylic acid moiety, was prepared in 24 steps starting from levoglucosan (**34**).[28] The target compound **35** was obtained using azido cycloheptane **91** as key intermediate (Scheme 8) accessible *via* cross metathesis as described above in the synthesis of noeurostegine (**33**) from levoglucosan (**34**, Scheme 7). Azido cycloheptane **91** was selectively acetolysed to acetate **94,** followed by removal of acetyl and benzoyl group to **95**. Oxidation of **95** by Jones reagent gave keto carboxylic acid **96**, which was subsequently protected with benzyl bromide. The azide of **96** was reduced by Staudinger reaction to cyclize spontaneously to azabicyclo[3.2.1]octane **97**, which finally afforded the desired *uronic*-noeurostegine (**35**) after debenzylation with Pearlman's

catalyst. *Uronic*-noeurostegine (**35**) has been found to be a competitive and potent bacterial β-glucuronidase inhibitor. Therefore, calystegine derivative **35** could play a crucial role in the treatment of colon cancer as it was recently found that glucuronidase inhibitors can alleviate harmful side effects of the chemotherapeutic agent CPT-11.[39]



Scheme 8. Synthesis of *uronic*-noeurostegine (**35**) as a potent bacterial β-glucuronidase inhibitor.

Inspired by their previous work on the synthesis of new calystegine derivatives (Scheme 7), Rasmussen *et al.* also synthesized the naturally occurring nortropane iminosugar calystegine A_3 (**36**), which is deoxygenated in C4 position, in 17 steps from 2-deoxy-D-glucose (**37**, Scheme 9 A).[30]

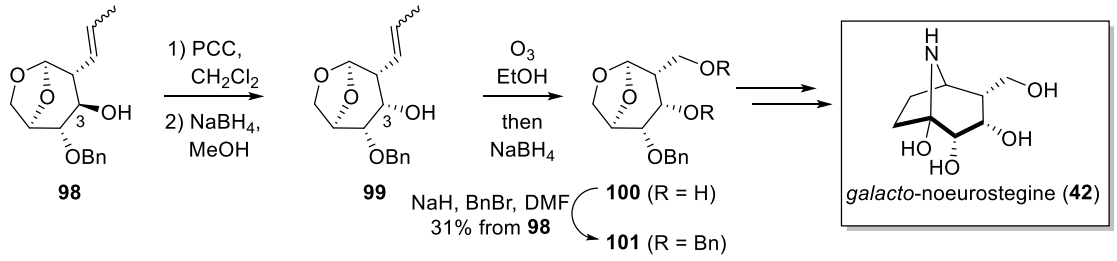


Scheme 9. Starting materials for the syntheses of calystegine A_3 (**36**), nojiristegine (**38**) and *manno*-nojiristegine (**40**).

Moreover, the syntheses of novel nortropane derivatives, nojiristegine (**38**) from methyl α-D-glucopyranoside (**39**) (Scheme 9 B) and *manno*-nojiristegine (**40**) from methyl

α-D-mannopyranoside (**41**, Scheme 9 C) were established based on the synthesis of noeurostegine (**33**, Scheme 7).[31] Both analogues possess only weak glycosidase inhibitor properties.[31]

In 2015, Salamone *et al.* demonstrated the synthesis of *galacto*-noeurostegine (**42**) with the same strategy previously described (Scheme 7) in 21 steps (Scheme 10).[34a] *Galacto*-configuration in **42** was prepared by epimerisation of the C3 position of the alcohol **98,** derived from readily available levoglucosan (**34**). An oxidation with PCC yielded ketone, which was reduced with hydride to the inverted alcohol at C3 position. The subsequent reactions steps were identical to those described above with noeurostegine (**33**, Scheme 7). In 2021, the bicyclic form of *galacto*-noeurostegine (**42**) has proved to be potent inhibitor of β-glucosidase as well as galactocerebrosidase which could be a promising drug for pharmacological chaperone therapy of patients with Krabbe disease.[34b]



Scheme 10. Synthesis of *galacto*-noeurostegine (**42**) as β-glycosidase inhibitor.

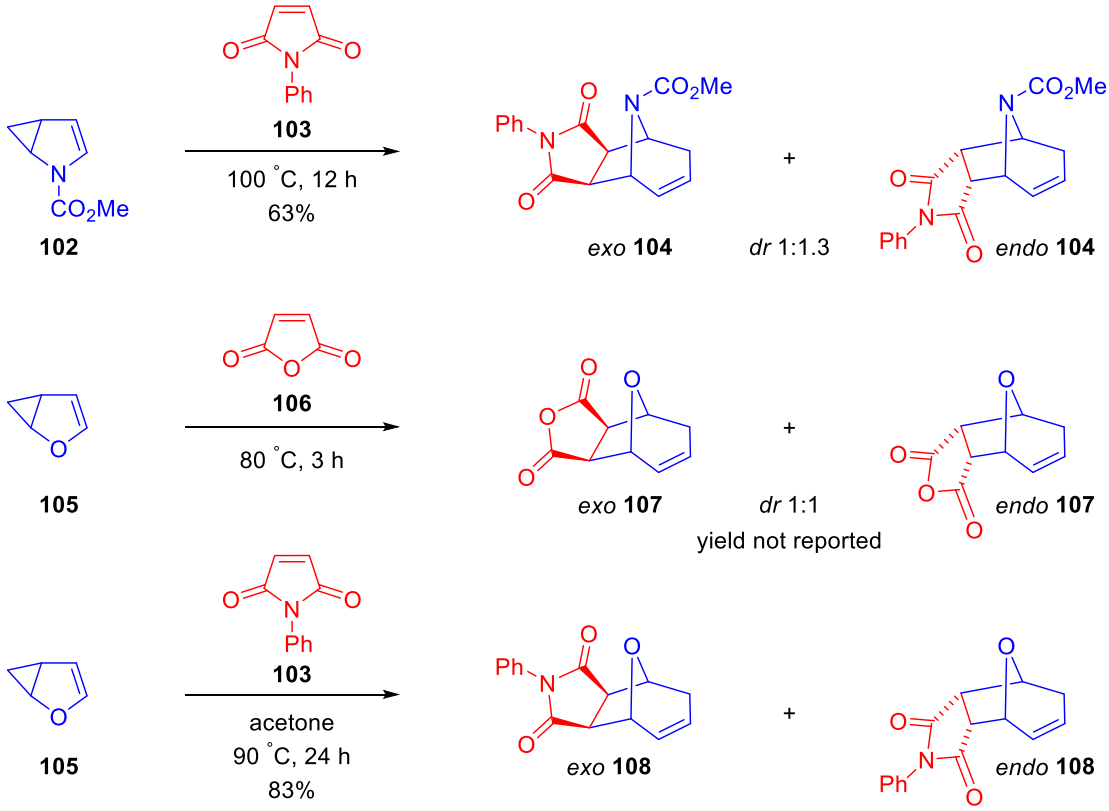
In conclusion, research on the chemistry and pharmacology of tropane alkaloids has already led to the development of various drugs with anticholinergic activity in pharmaceutical industries, while the design and synthesis of calystegine analogues has received less attention for a long time. Recent studies on the synthesis and pharmacology of new calystegine derivatives disclosed above demonstrated the remarkable properties of this family of bicyclic iminosugars. In the future, more efficient synthetic procedures for the enantioselective synthesis to access bicyclic seven-membered ring systems for novel calystegines with diverse functionalities, in particular hydroxyl groups, using enantioselective catalysis or chiral auxiliaries are desirable in addition to the chiral pool total syntheses described in this chapter. Furthermore, hydroxylated analogues (e.g., dihydroxylated nortropanes) which do not belong to the calystegines per definition, but nevertheless possess promising biological activity as demonstrated by the example of (–)-Bao Gong Teng A (**153**, see chapter 2.2)[10b,40], should be developed for structure-activity relationships (SAR) studies.

B Main part

1 Microwave-assisted [3+2]-cycloadditions with cyclopropanated heterocycles

1.1 Precedent studies

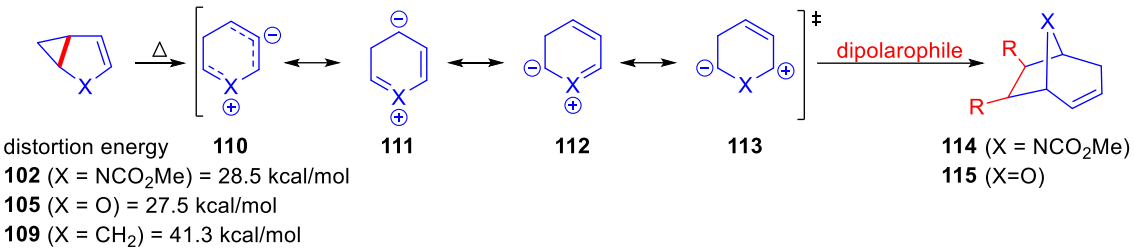
In the 1970s, Fowler *et al.* reported that homo-pyrrole **102** can undergo cycloaddition reactions with suitable dipolarophiles under thermal activation to form bicyclic seven-membered ring systems (Scheme 11).[41] Thereafter, Herges and Ugi[42] described an analogous cycloaddition reaction of homo-furan **105** with activated dipolarophiles like maleic anhydride (**106**) and *N*-phenylmaleimide (**103**), followed by elegant mechanistic studies by Klärner at high pressure.[43]



Scheme 11. Previous [3+2]-cycloadditions with homo-pyrrole **102** and homo-furan **105**.[42-43]

In 2013, a mechanistic study of metal-free [3+2]-cycloadditions of homo-pyrrole **102** and homo-furan **105** was reported by Yu *et al*.[44] They conclude by using density functional theory (DFT) calculations that the low distortion energies are the main reason why cyclopropanated pyrrole **102** and furan **105** can easily rearrange under thermal conditions to a reactive 1,3-dipole **113** in the transition state (TS) and therefore are able to undergo [3+2]-cycloadditions (Scheme 12). The distortion energy is the energy

required to distort the dipolarophile and dipole to their geometries in the transition state but without their interaction.[45]

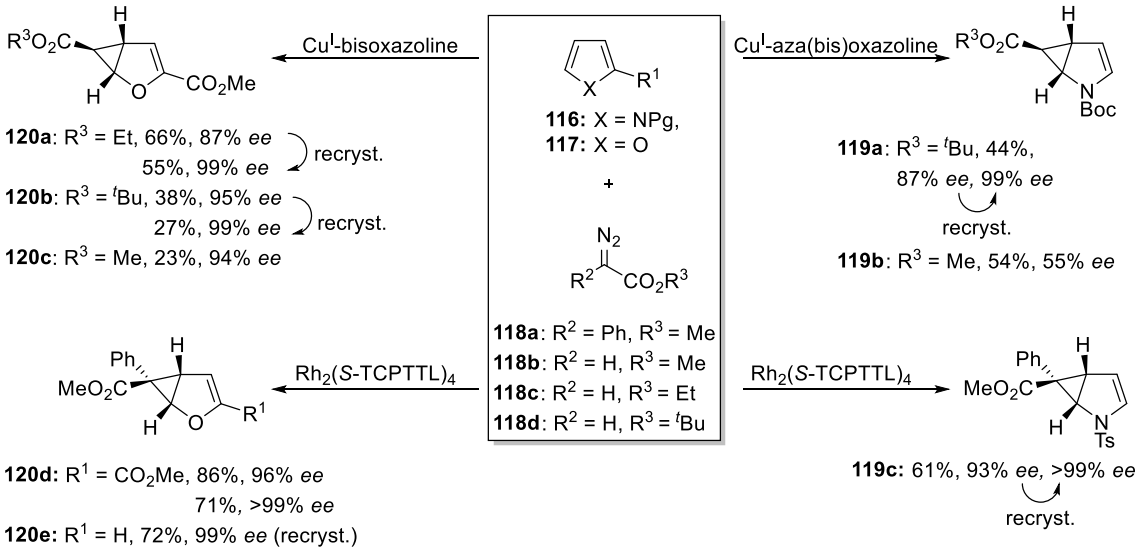


Scheme 12. Distortion energies of 1,3-dipoles in their transition states calculated by DFT.[44]

The distortion energy of homo-pyrrole **102** is 28.5 kcal/mol, and of homo-furan **105** is 27.5 kcal/mol, whereas the distortion energy of bicyclo[3.1.0]hex-2-ene **109** is 41.3 kcal/mol, which leads to difficult formation of a 1,3-dipole **113** of the latter. Therefore, only special vinyl cyclopropanes (VCPs), which are attached to heteroatoms like nitrogen and oxygen, can be used in metal-free [3+2]-cycloaddition reactions.[44] This type of reaction provides access to bicyclic seven-membered ring systems, representing a particularly valuable extension of conventional cycloadditions to four-, five-, and six-membered rings. Nevertheless, given the limited substrate scope and low or unreported product yields, this type of reaction is still an underexplored area in organic synthesis.[46] Moreover, the cycloadditions have been carried out only with racemic starting materials, and applications of the prepared cycloadducts for the synthesis of natural products or analogues were not reported. This thesis focused on the microwave-assisted 6π-electrocyclic ring-opening / [3+2]-cycloaddition cascade of monocyclopropanated pyrroles and furans towards the synthesis of 8-aza- and 8-oxabicyclo[3.2.1]octanes. Therefore, various cyclopropanated heterocycles were desirable, which are described in the following chapter.

1.2 Monocyclopropanated heterocycles as precursors for 1,3-dipoles[3]

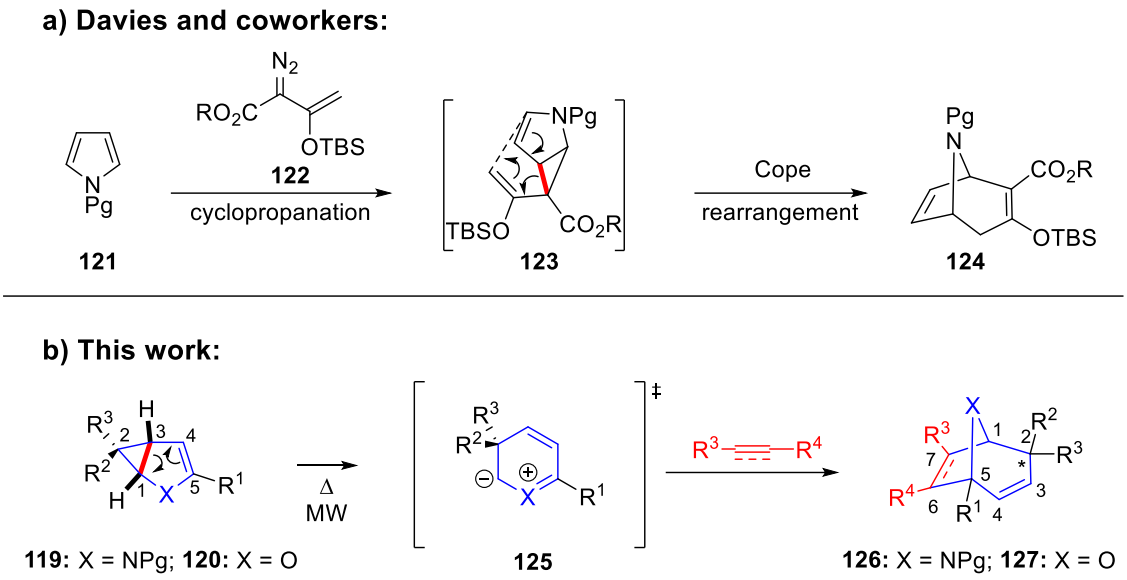
The regio-, diastereo-, and enantioselective cyclopropanation of pyrrole **116** and furan **117** with various diazo compounds **118a-d**, established by Reiser *et al.,* allows access to diverse cyclopropanes (Scheme 13).[47] These are valuable starting materials for the cycloadditions described in the previous section since the compounds can be prepared enantiomerically pure starting from inexpensive, renewable resources and their substitution pattern enables the introduction of various substituents into the seven-membered ring system. The absolute stereochemistry of these cyclopropanes depends on the chiral ligand used, as a consequence both enantiomers are easily accessible.



Scheme 13. Precedent literature of enantioselective cyclopropanation of pyrrole **116** and furan **117** with different diazo compounds **118a**-**d**.

Such cyclopropanated heteroycles **119**-**120** have been proven to be of great synthetic value, being associated with the facile cleavage of the activated, *exocyclic*, donor-acceptor substituted cyclopropane bonds.[47e-h,48] In the context of the synthesis of tropanes, this reactivity was most elegantly exploited by Davies and coworkers with the cyclopropanation of pyrroles **121** by vinyldiazoacetates **122** followed by a Cope rearrangement (Scheme 14 a).[22d,f,49]

[3] This chapter is partially based on C. M. Sonnleitner, S. Park, R. Eckl, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.*, **2020,** *59*, 18110.



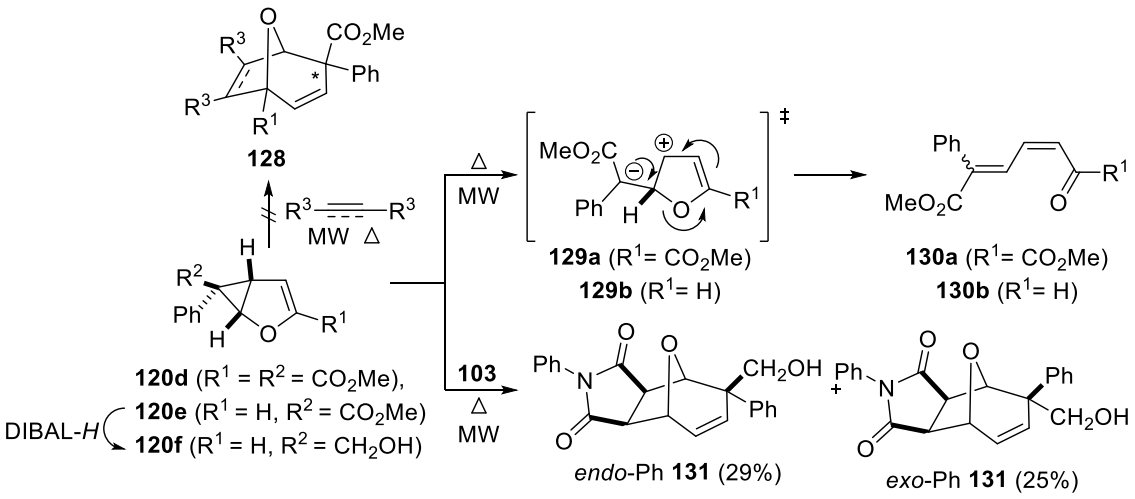
Scheme 14. Strategies to tropanes *via* cyclopropanated pyrroles and furans.

In contrast, examples for the ring-opening of the unactivated, *endocyclic* cyclopropane bond in **119** or **120** are rare.[50] Nevertheless, we reasoned that the transition state of a 6π-electrocyclic reaction leading to a transient 1,3-dipol **125** could outcompete the typical ring-opening pathway of the *exocyclic* cyclopropane bond *via* the push-pull system present through the heteroatom donor and the ester group on the cyclopropane moiety. Trapping of **125** with dipolarophiles in a Huisgen [3+2]-cycloaddition[51] would then give direct access to complex 8-azabicyclo[3.2.1]octanes **126** and 8-oxabicyclo[3.2.1]octanes **127** (Scheme 14, b).[8b]

1.3 [3+2]-Cycloadditions with *gem*-disubstituted cyclopropanes

The initial cycloaddition reactions were carried out with *gem*-disubstituted cyclopropanated furan derivatives **120d-e** and *N*-phenylmaleimide (**103**), maleic anhydride (**106**), diethyl acetylenedicarboxylate or (*E*)-1,2-bis(phenylsulfonyl)ethene.[52] However, the first attempts to prepare cycloadduct **128** were not successful since only isomeric dienes **130a**-**b** were observed under thermal conditions (Scheme 15). Wenkert, Reiser, and Davies *et al*. reported that furan derivatives undergo unravelling of heterocycles resulting in the corresponding isomeric diene(s). [47b,i,49c] Davies *et al.* proposed that the formation of these dienes involves a zwitterionic intermediate.[49c] The proposed formation of a zwitterionic intermediate like **129a,b** under thermal conditions led to a complex mixture of isomeric dienes **130a,b**. In order to circumvent the formation

of dienes, the appropriate choice of cyclopropyl substituents was crucial to change the reactivity of the cyclopropane ring due to the electronic and steric properties of the attached substituents. A less electron-withdrawing group like CH_2OH instead of an ester moiety at the cyclopropane ring was expected to minimize the formation of dienes due to its destabilizing effect on the zwitterionic intermediate. Therefore, reduction of the ester group in cyclopropane **120e** to alcohol **120f** using DIBAL-*H* was performed, and the desired alcohol **120f** was obtained as a single diastereomer (Scheme 15). Notably, the reactivity of **120f** was changed by reduction of the ester functionality, and the microwave-assisted [3+2]-cycloaddition with *N*-phenylmaleimide (**103**) afforded separable *endo*-Ph **131** and *exo*-Ph **131** in an overall yield of 54% after 1.5 h at 170 °C under microwave irradiation. Structure assignments for **131** were based on ^{1}H NMR and 2D NMR spectra. Indeed, no ring-opening products were observed, however, reactions of **120f** with other dipolarophiles led to decomposition.[52]



Scheme 15. First attempts of [3+2]-cycloadditions.[52]

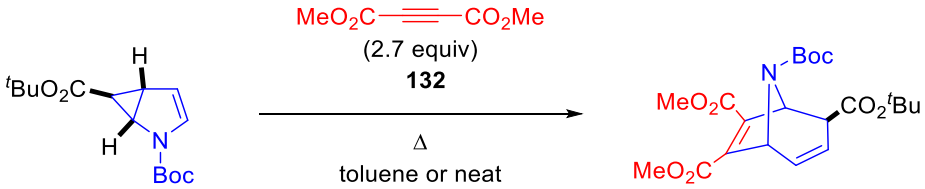
These studies have shown that the substitution pattern of the cyclopropane ring has a high impact on its reactivity. Cyclopropanated furans **120d,e** with phenyl and an ester substituent on the cyclopropyl ring have proven to be unsuitable for cycloaddition reaction due to electronic effects (zwitterionic intermediate) or steric congestion (two sterically demanding substituents attached at the cyclopropane moiety). To investigate the influence of various cyclopropyl substituents on [3+2]-cycloadditions, the next reactions were carried out with mono-substituted cyclopropanes, described in the upcoming chapter.

1.4 [3+2]-Cycloadditions with mono-substituted cyclopropanes[4]

1.4.1 [3+2]-Cycloadditions with cyclopropanated pyrroles

Cyclopropanated pyrrole **119a** and dimethyl acetylenedicarboxylate (**132**, DMAD) were used to examine the [3+2]-cycloaddition with mono-substituted cyclopropanes, which indeed proved to be suitable (Table 2) in contrast to *gem*-disubstituted cyclopropanated furans (Scheme 15). Appreciable reaction rates were only observed well above 100 °C (Table 2, entry 1), giving rise to the cycloadduct **133a** as single, *exo*-diastereomer in 70% yield upon conventional heating at 150 °C for 24 hours (Table 2, entry 2). A dramatic acceleration of the reaction rate was observed upon changing to microwave heating, affording **133a** in 77% yield in a reaction time of only one hour (Table 2, entry 3), which could be further shortened to 0.5 h / 81% yield when running the reaction neat (Table 2, entry 4).[8b]

Table 2. Optimization of the reaction conditions.



119a **133a**

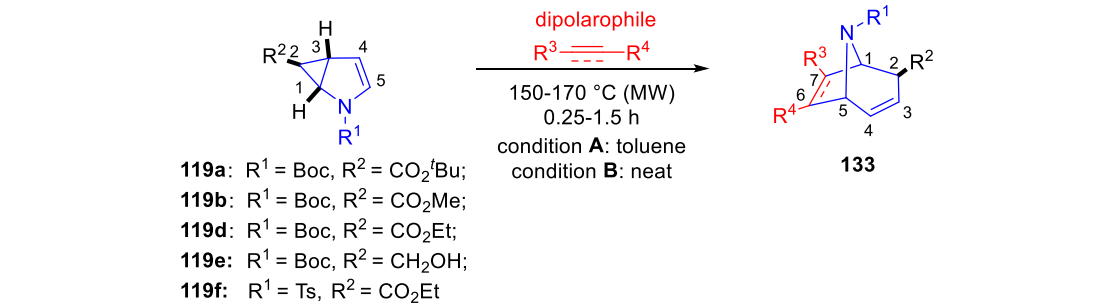
entry	solvent	T [°C]	time [h]	yield [%]
1	toluene	100	24	no conversion
2	toluene	150	24	70
3[a]	toluene	150	1	77
4[a]	**neat**	**150**	**0.5**	**81**

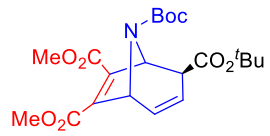
[a] Microwave irradiation was used.

With the optimal reaction conditions established, in collaboration with Dr. S. Park[53], the scope of the reaction with monocyclopropanated pyrroles was investigated (Scheme 16). Depending on the aggregation state of the dipolarophile, the reaction was performed in minimal amounts of toluene (A, solid dipolarophile) or in the absence of solvent (B, liquid dipolarophile). Keeping subsequent functionalizations of adducts of type **133a** in mind,

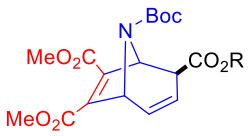
[4] This chapter is partially based on C. M. Sonnleitner, S. Park, R. Eckl, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.*, **2020,** *59*, 18110.

we established with the synthesis of **133a-f** that different combinations of ester groups stemming from **119** or the acetylenedicarboxylate as well as common nitrogen protecting groups (Ts, Boc) are amenable for this process. Enantiomerically pure **119a,** and **119b** gave rise to **(+)-133a** and **(–)-133k** without any observable erosion of enantiopurity.

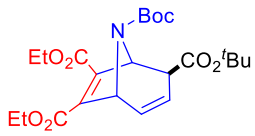




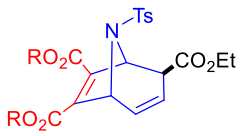
(+)-133a: 81%[a], 99% *ee*, **B**



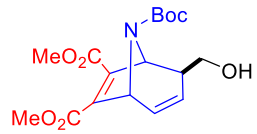
133b: R = Me, 74%[a], **B**
133c: R = Et, 72%[a], **B**



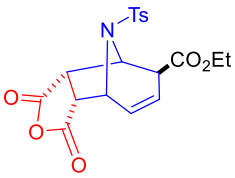
133d: 64%[b], **B**



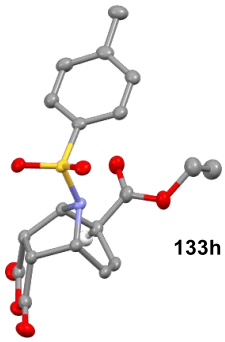
133e: R = Me, 70%[c], **B**
133f: R = Et, 61%[b], **B**



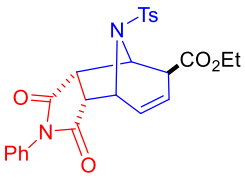
133g: 75%[d], **B**



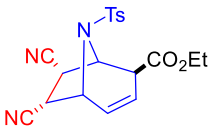
133h: 79%[b],[e], **A**



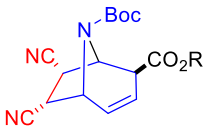
133h



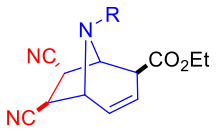
133i: 64%[b],[e], **A**



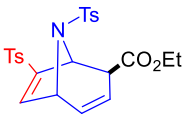
133j: 61%, **A**



133k: R = Me, **A** *endo* **(–)-133*k*** 38%, 99% *ee, exo* **(–)-133k**: 33% 98% *ee*
133l: R = Et, **A** *endo* **133l**: 29%, *exo* **133l**: 33%



133m: R = Boc, 80%[f],[g], *dr* 4.5:1, **A**
133n: R = Ts, 69%[b],[f],[g], *dr* 3.0:1, **B**



133o: 24%[g],[h], ratio 4.0:1, **A**

Scheme 16. Substrate scope of [3+2]-cycloadditions for the synthesis of 8-azabicyclo[3.2.1]octanes **133**: 0.3-1 mmol **119**, dipolarophile (2.7 equiv); [a] Scale-up: 4.39 mmol **119a** were employed to yield 1.54 g of **133a**; 4.18 mmol **119b** were employed to yield 1.18 g of **133b;** 4.03 mmol **119d** were employed to yield 1.15 g of **133c**; [b] Synthesized by Dr. S. Park; [c] 170 °C; [d] 100 °C; [e] 1 h, 1.1 equiv of dipolarophile; [f] Major diastereomer shown; [g] Combined isolated yield of two diastereomers; [h] Major regioisomer shown.

Furthermore, the cycloadducts **133a**, **133b**, and **133c** were prepared on gram scale, demonstrating the value of the developed protocol for synthetic applications. Starting from **119e** in which the ester moiety on C2 was changed to an alcohol was also well tolerated giving rise to cycloadduct **133g**, again as single, *exo*-diastereomer in 75% yield. Notably, in this case of a donor cyclopropane the reaction proceeded already at 100 °C, which could be either due to reduced steric congestion in the ring-opening / cycloaddition process or to more favorable electronics in the cycloaddition with an electron-deficient dipolarophile. Switching from alkyne to alkene based cycloaddition partners was also well tolerated: Starting from pyrrole **119f**, maleic anhydride afforded **133h** and *N*-phenylmaleimide **133i** in 79% and 64% yield, respectively, both with perfect *endo*-control of the approaching dipolarophile and *exo*-placement of the ester moiety, which was unambiguously established by X-ray structure analysis of **133h**[53]. Moreover, maleonitrile was successfully used as a dipolarophile in the cycloaddition with **119f** and afforded *endo* cycloadduct **133j** exclusively. The reaction with unsymmetrical dipolarophiles such as fumaronitrile or tosylacetylene gave the corresponding cycloadducts **133m** and **133o** in a *ratio* of 4.5:1 and 4.0:1, respectively. The tropane skeleton in **133m** could be fully assigned by ^{1}H NMR and 2D NMR. The coupling constants for protons H1 and H5 adjacent to the bridging nitrogen were indicative of the *exo* and *endo* relationship to H7 and H6. The spectroscopic data of **133m** are in agreement with the related tropane **140d** (*vide infra*) data, for which an X-Ray structure was obtained. The structure assignment for cycloadduct **133o** was based on ^{1}H NMR and 2D NMR.[8b]

The [3+2]-cycloaddition of cyclopropanated pyrrole **119** with acetylene (**136**) would lead to particularly attractive tropane **134**, a potential precursor to (*R*)-(–)-cocaine (**9**) which serves as a lead compound in drug discovery (Figure 5). Unfortunately, cycloadditions with the unsubstituted acetylene cannot be carried out due to the large electron density.[54]

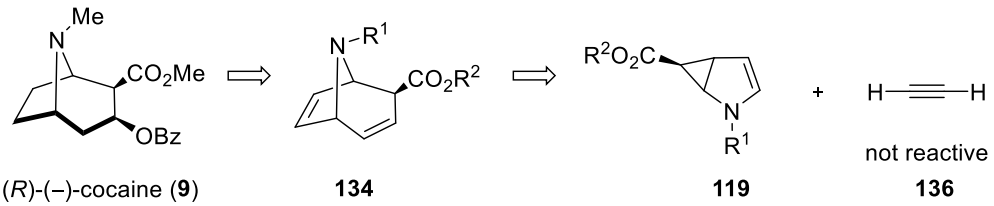
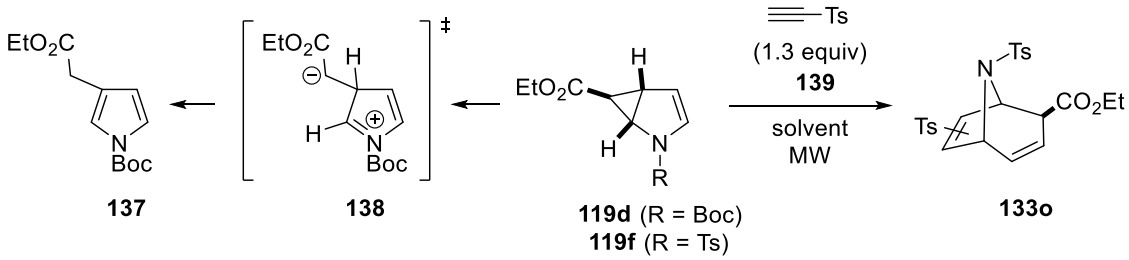


Figure 5. Retrosynthesis of (*R*)-(–)-cocaine (**9**).

Therefore, the use of suitable acetylene equivalents such as tosylacetylene (**139**) is desirable since the attached substituents can be removed after the cycloaddition

reaction. However, regarding the low yields of the cycloaddition reaction with tosylacetylene described above (**133o**, Scheme 16), further studies were carried out (Table 3).

Table 3. Cycloadditions of cyclopropane **119d** and **119f** with tosylacetylene (**139**).



entry	CP	solvent	T [°C]	time [h]	product	yield [%]	conversion [%]
1	**119d**	toluene	150 → 160	45 → 45	**137**	nd	100
2	**119d**	toluene	90	150	**137**	nd	100
3	**119f**	toluene	180	15	**133o**	22[a]	100
4	**119f**	toluene	100	180	crm	-	100
5	**119f**	toluene	150	45	**133o**	20[b]	53
6	**119f**	toluene	150	60	**133o**	20[b]	100
7[c]	**119f**	toluene	150	30	**133o**	24[a]	100
8[d]	**119f**	toluene	150	60	**133o**	13[b]	100
9	**119f**	MeOH	150	45	crm	-	100
10	**119f**	DMF	150	45	crm	-	100

CP=cyclopropane; nd=not determined; crm=complex reaction mixture. [a] Isolated yield; [b] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard; [c] 2.7 Equiv of **139** was used; [d] CuI (2.0 equiv) was added.

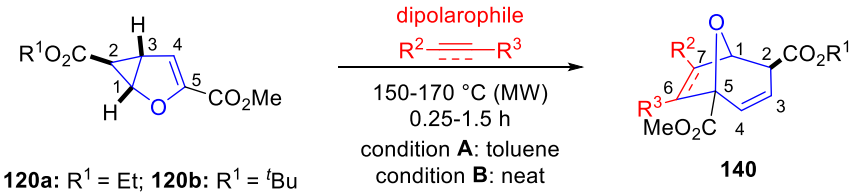
Since the cycloadditions with *N*-Boc protected cyclopropanated pyrrole **119d** and tosylacetylene **139** were not successful as only rearomatization to pyrrole **137** was observed (Table 3, entry 1 and 2), the screening of the reaction was carried out with the more stable *N*-Ts protected cyclopropanated pyrrole **119f**. The reaction of cyclopropane **119f** with **139** in toluene under microwave condition for 15 min at 180 °C led to the product in low yields (Table 3, entry 3), but full conversion of the starting material was observed, which indicates that milder reactions conditions were required due to thermal decomposition. Hence, various reaction temperatures were screened to optimize the [3+2]-cycloaddition. However, lowering the temperature to 100 °C led to a complex mixture (Table 3, entry 4), whereas 150 °C furnished cycloadduct **133o** after 45 min in 20% yield (Table 3, entry 5). Prolonging the reaction time to 60 min at 150 °C resulted in further decomposition of cyclopropane **119f** (Table 3, entry 6). Next, subjecting cyclopropane **119f** with 2.7 equivalents of tosylacetylene (**139**) afforded cycloadduct **133o** in 24% yield after 30 min (Table 3, entry 7). The reaction of **119f** and alkyne **139** with copper(I) iodide (2 equiv) under the same reaction conditions as entry 6 led to the product **133o** in lower yields (Table 3, entry 8). Copper(I) iodide was added to determine whether the copper(I) acetylide that forms with dipolarophile **139** increases the overall yield of the reaction. Switching the solvent to MeOH (Table 3, entry 9) or DMF (Table 3, entry 10) was unsuccessful.

In summary, the [3+2]-cycloadditions with acetylene synthon **139** afforded the cycloadduct in only low yields. A potential issue may arise from the acidity of the terminal alkyne **139** which could cause side reactions, e.g., rearomatization. To avoid this side reaction, the acidic hydrogen of the alkyne **139** should be replaced by other substituents. Unfortunately, also other acetylene synthons failed for the cycloaddition (see experimental part, Table 27). Moreover, the low yields observed with tosylacetylene (**139**), pointing to the requirement of strongly electron-poor dipolarophiles for the title reaction.

1.4.2 [3+2]-Cycloadditions with cyclopropanated furans

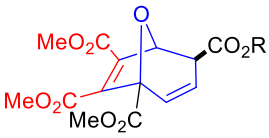
Further expanding the scope to cyclopropanated furans **120a,b** provides access to 8-oxabicyclo[3.2.1]octanes **140** (Scheme 17), being also key motifs in biologically active compounds.[11,55] In contrast to *gem*-disubstituted cyclopropanes **120d**-**e** (see chapter 1.3), no ring-opening dienes were observed. DMAD **132** was again identified as

a suitable dipolarophile, resulting in the corresponding cycloadducts **140a** and **140b** as single, *exo* diastereomers in 71% and 75% yield, respectively.

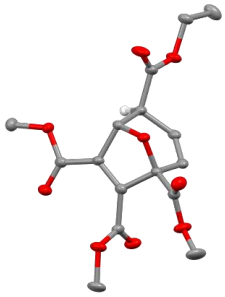


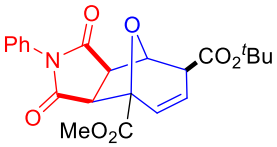
120a: R^1 = Et; **120b:** R^1 = ^{t}Bu

140

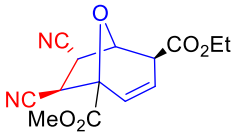


(+)-140a: R = Et 71%[a], 99% *ee*, **B**
140b: R = ^{t}Bu 75%, **B**

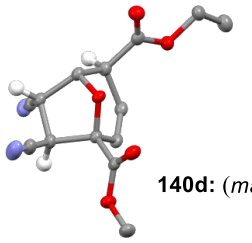




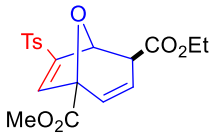
140c: 72% [b],[c] *dr* 2.9:1, **A**



140d: *dr* 3.7:1, 50%, 99% *ee* (*major*) [b], 23% (*major* and *minor*), **A**



140d: (*major*)



140e: 46%, **A**

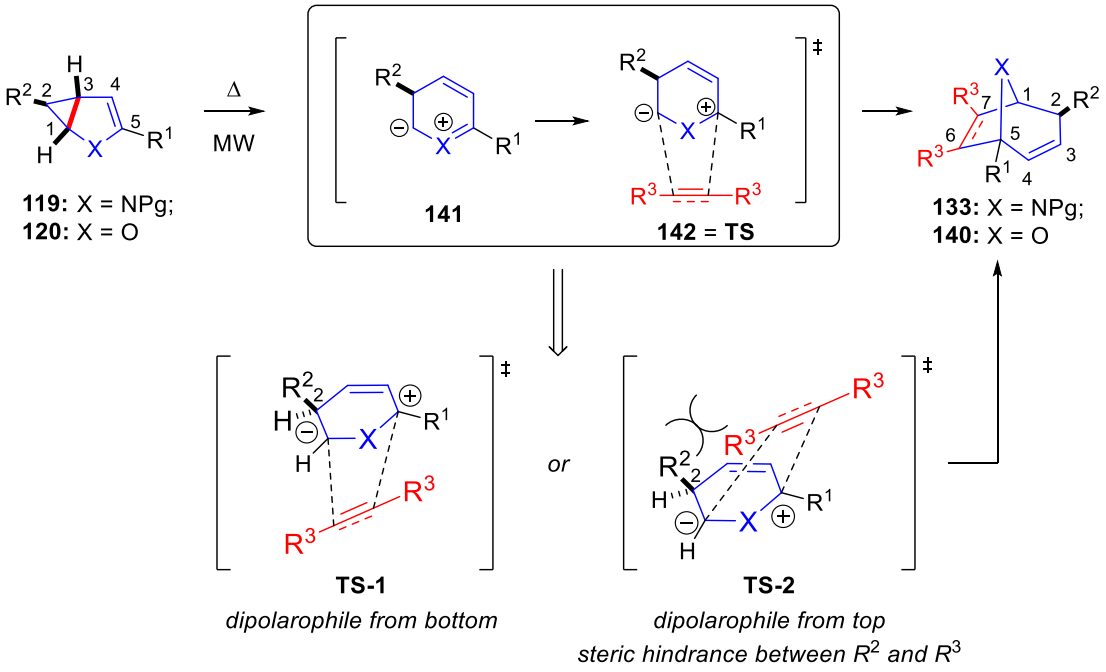
Scheme 17. Substrate scope of [3+2]-cycloadditions for the synthesis of 8-oxabicyclo[3.2.1]octanes **140**: 0.4-2.7 mmol **120**, dipolarophile (2.7 equiv); [a] Scale-up: 7.87 mmol **(−)-120a** were employed to yield 1.98 g of **(+)-140a**; [b] Major diastereomer shown. [c] Combined isolated yield of two diastereomers.

Enantiomerically pure cycloadduct (+)-**140a** (>99% *ee*, confirmed by X-ray analysis) could be obtained as a single stereoisomer in gram quantities using (−)-**120a**, highlighting once more the scalability of the developed protocol. Additionally, enantiomerically pure (–)-**120a** gave access to (–)-**140d** (*major*). The reaction between cyclopropanated furan derivative **120a** and *N*-phenylmaleimide gave rise to **140c** (72%, *dr* 2.9:1), from which *major* diastereomer could be isolated in pure form. Structure assignments for *exo*/*endo* **140c** were based on ^{1}H NMR and 2D NMR spectra. The *endo* and *exo* stereochemistry can be deduced from differences in the coupling constant of the bridgehead proton H1 to the *exo* or *endo* proton H7. Coupling of **120a** and fumaronitrile resulted in **140d** (73%, *dr* 3.7:1), from which the *major*, presumably sterically favored diastereomer was isolated in pure form (50% yield). Finally, the cycloaddition of tosylacetylene with **120a** was performed, giving rise to single regioisomer **140e** in 46% yield most likely a consequence of the ester group in the

bridgehead position, which was unambiguously assigned by ^{1}H NMR and 2D NMR spectroscopy.[8b] Compared to the cyclopropanated pyrroles **119**, longer reaction times or higher reaction temperatures were required to prepare the desired 8-oxabicyclo[3.2.1]octanes **140**.

1.4.3 Mechanistic aspects of [3+2]-cycloadditions with cyclopropanated heterocycles

The [3+2]-cycloaddition reactions proceeded in all cases with complete facial selectivity in that the incoming dipolarophile and the ester group at C2 orient *anti* to each other (TS-1, Scheme 18), resulting in the *exo*-orientation of the latter. In case of alkene dipolarophiles, high *endo*-control of the latter was observed in the pyrrole series (**133h, 133i,** and **133j**), while in the furan series, the *exo*-orientation was preferred (**140c**) (see chapter 1.4.1 and 1.4.2), being a consequence of the different steric demand of the heteroatom bridge (O *vs. N*-Ts). The approach reported here allows the introduction of various substituents with stereoselective control at the tropane skeleton, in particular at C6/C7 positions, comparing well to other approaches, which often require multistep synthesis.



Scheme 18. Stereochemical model for the [3+2]-cycloadditions of **119** and **120**. Adapted from Dr. Saerom Park.[53]

As above-mentioned, the [3+2]-cycloadditions were successfully performed with strongly electron-poor dipolarophiles. Indeed, electron-neutral or electron-rich dipolarophiles failed to undergo the reaction sequence (see experimental part, Table 26 and Table 27). This could be a consequence of the dipole **141** generated *via* electrocyclic ring-opening, which is an azomethine ylide **143** or in the case of cyclopropanated furans, a carbonyl ylide **144** (Figure 6).

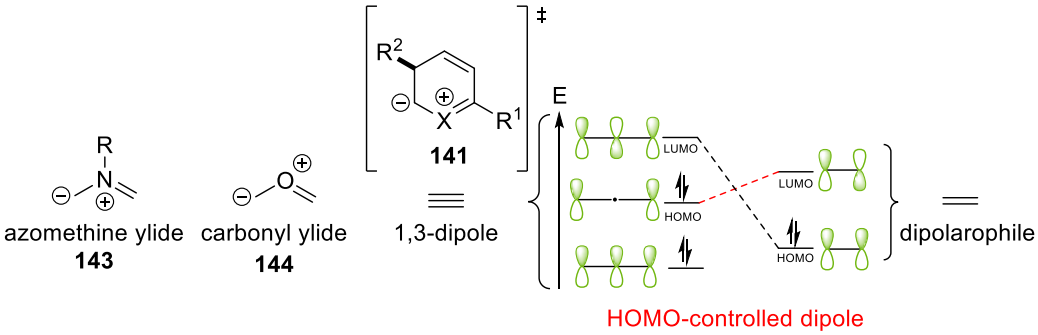


Figure 6. Classification of [3+2]-cycloadditions of azomethine ylides and carbonyl ylides according to frontier molecular orbitals of the 1,3-dipole.[51d]

In 1,3-dipolar cycloadditions, these ylides **143** and **144** generally react as a HOMO-controlled dipole (nucleophilic) as they are electron-rich. To minimize the HOMO-LUMO energy gap, the LUMO of the dipolarophile can be lowered by electron-withdrawing groups on the dipolarophile. This is in accordance with the observed reactivity of the 1,3-dipole **141** with electron-poor dipolarophiles in contrast to the failed reactions with neutral or electron-rich dipolarophiles. In addition, electron-donating groups attached to the HOMO-controlled dipole result in higher reactivity, which is also consistent with the increased reactivity of the donor cyclopropane **119e** at 100 °C in contrast to normally required activation temperature of 150 °C.

1.5 Microwave flow [3+2]-cycloaddition reaction

Microwave irradiation has become a widely applied heating method in organic synthesis due to its advantages such as energy transfer instead of heat transfer, material selectivity and non-contacting heating. Therefore, microwave heating often results in higher yields and purities of products in shorter reaction times compared to conventional heating.[56] The results of the microwave-assisted [3+2]-cycloadditions with cyclopropanated heterocycles are in accordance with the aforementioned advantages, e.g., dramatic acceleration of the reaction rate was observed upon changing from conventional heating to microwave heating. However, microwave-assisted synthesis suffers from challenging scale up by the limited penetration depth and irradiation power of microwaves. The combination of flow synthesis (e.g., large surface to volume ratio) and microwave heating technologies could solve scale up issues as shown in recent publications.[56h,i,57] The Diels-Alder reaction of acetylenedicarboxylates and furans was already demonstrated using a microwave flow reactor.[56i] Therefore, the microwave-assisted [3+2]-cyclo-addition reaction of cyclopropanated pyrrole **119a** with alkyne **132** was investigated in a large-scale microwave flow reactor (Figure 7[5]) in cooperation with Dr. Joshua Barham (University of Regensburg). Large amounts of cyclopropane **119a** (~35 g) have been required for the optimization of the synthesis in the microwave flow reactor. In addition, the cyclopropanation of heterocycles with diazo esters in flow is currently ongoing in the Reiser- and Barham group.

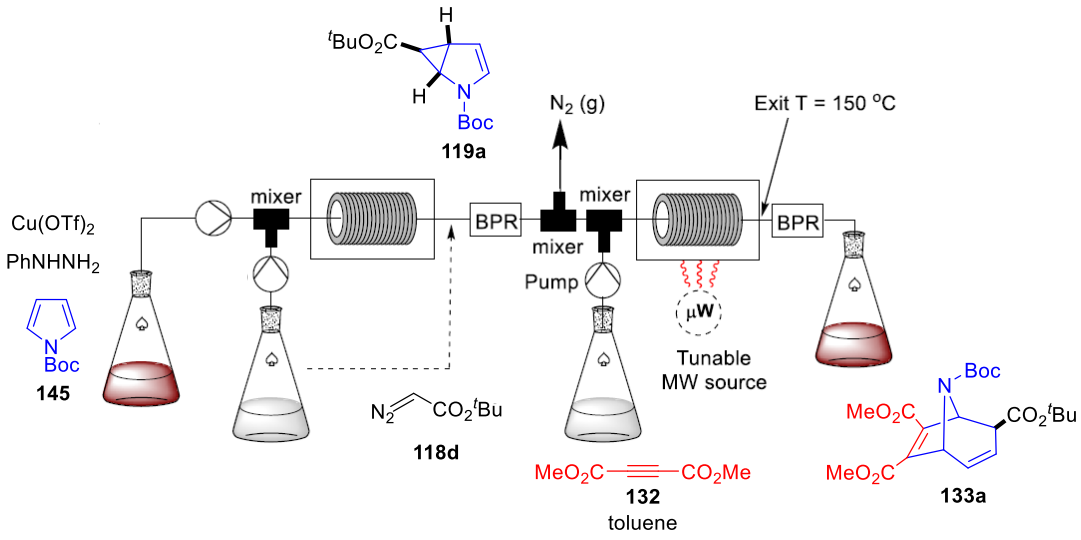


Figure 7. Cyclopropanation and [3+2]-cycloaddition using a continuous-flow (MW) apparatus. Adapted from Dr. Joshua Barham.

[5] The graphic was designed by Dr. Joshua Barham.

A commercially available microwave flow reactor[56i] was employed as illustrated in figure 8 (see experimental part for details). The analytics (HPLC method) were carried out by Michal Domanski (Master student of Barham group, University of Regensburg).

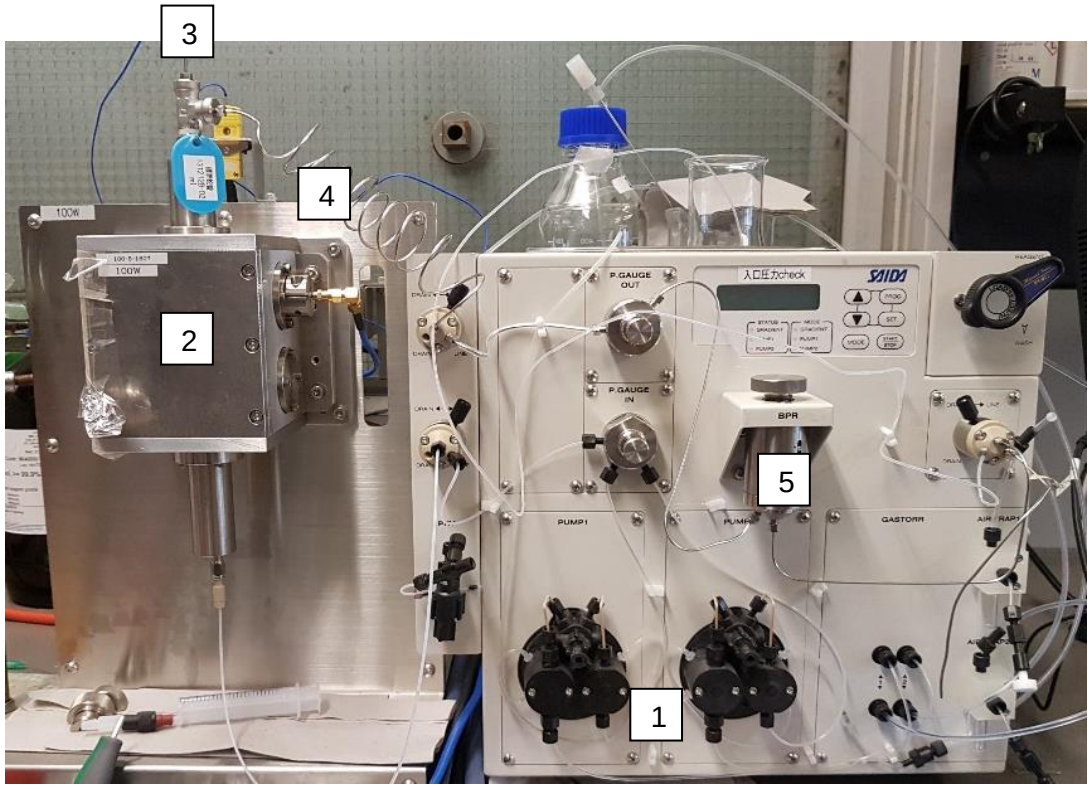
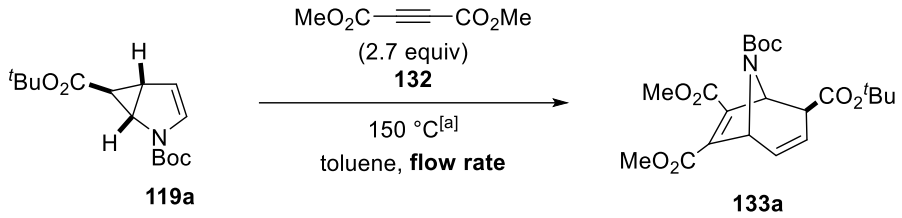


Figure 8. 100 W MW flow reactor consisting of 1) pump unit, 2) 100 W MW cavity, 3) reactor exit temperature probe 'Saida', 4) cooling coil, 5) adjustable back pressure regulator (BPR).

The first microwave flow reaction was performed with a 0.5 M solution of cyclopropane **119a** and DMAD **132** in toluene at 150 °C in a 100 W reactor in single-pass mode (Table 4). A residence time (R_T: time spent in the heated reactor tube) of 3.1 min gave the best conversion of cyclopropane **119a** (46%) and the desired cycloadduct **133a** was obtained in 31% yield (Table 4, entry 1). The screening of the flow rate showed that under these conditions a higher flow rate than 0.8 mL/min led to almost no conversion of starting material **119a** resulting in only traces of the desired cycloadduct **133a** (Table 4, entry 2 and 3).

Table 4. Attempts of microwave flow reaction in a 100 W reactor in single-pass mode.



119a **133a**

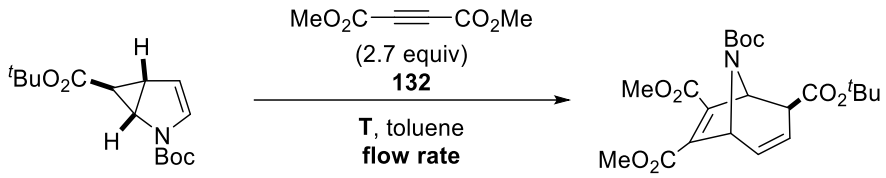
entry	flow rate [mL/min]	R_T [min]	yield [%][b]	conversion [%][b]	selectivity [%]
1	0.8	3.1	31	46	67
2	2.0	1.3	4	12	33
3	4.0	0.6	-	8	-

All reactions used 100 W MW flow reactor setup; 2.5 mL helical tube; 0.5 M cyclopropane **119a** in toluene as solvent; R_T = residence time; BPR rated to 3.0 MPa. [a] Reaction temperature measured at the reactor tube exit upon reaching steady state; [b] Yield and conversion determined by HPLC (Michal Domanski).

The next flow reactions were performed in a 250 W reactor with a 5.2 mL helical tube instead of a 2.5 mL reactor tube of the 100 W reactor to increase conversion due to twice the residence time. To increase the conversion, the flow rate and temperature were screened using a 0.25 M solution of cyclopropane **119a** in toluene to be material conservative (Table 5) since high amounts of cyclopropane **119a** were required in single-pass mode. The discrepancy between yield and conversion for 0.8 and 1.0 ml/min at 150/155 °C using the 250 W reactor (Table 5, entry 1 and 2) is much larger than with the 100 W reactor described above (Table 4, entry 1). On the one hand, the temperature distribution in the 250 W reactor could be more uneven at this low flow rate, resulting in overheating and gas evolution indicating burning of the starting material **119a** or product **133a**. To reach the exit temperature of 150 °C, temperatures greater than the latter are required in the center of the flow path. However, these higher temperatures (exact temperature in the center cannot be measured) led to decomposition of the cyclopropane **119a** or cycloadduct **133a**, which was observed by gas evolution. One possible reason for this could be the *tert*-butyl ester cleavage at higher temperatures. On the other hand, the difference in the concentration (0.25 M /250 W *vs.* 0.5 M/100 W) may also cause the poor selectivity. The low concentrations may result in a decreased reaction rate resulting in decomposition of cyclopropane **119a**. Moreover, increasing the temperature at the same flow rate led to a higher conversion, however not to the desired cycloadduct **133a** (Table 5, entry 3-6). The most promising single-pass condition (Table 5, entry 2) afforded

cycloadduct **133a** in 38% yield at a flow rate of 1.0 mL/min at 155 °C, however only 55% of the conversion resulted in the desired cycloadduct **133a**. In summary, diluted concentrations resulted in poor selectivity in the 250 W reactor.

Table 5. Attempts of microwave flow reaction in a 250 W reactor in single-pass mode.



119a **133a**

entry	flow rate [mL/min]	R_T [min]	T[a] [°C]	yield [%][b]	conversion [%]	selectivity [%]
1	0.8	6.5	150	11	73	15
2	1.0	5.2	155	38	69	55
3	2.0	2.6	150	7	10	70
4	2.0	2.6	170	22	30	73
5	2.0	2.6	175	26	40	65
6	2.0	2.6	190	33	67	49

All reactions used 250 W MW flow reactor setup; 5.2 mL helical tube; 0.25 M cyclopropane **119a** in toluene as solvent R_T = residence time; BPR rated to 3.0 MPa. [a] Reaction temperature measured at the reactor tube exit upon reaching steady state; [b] Yield and conversion determined by HPLC (Michal Domanski).

The following [3+2]-cycloaddition reactions were run in recycle mode to achieve full conversion and be more material-conservative (Figure 9). The 100 W reactor was chosen due to the better temperature distribution compared to the 250 W reactor as discussed above. The recycling reaction with a 0.5 M solution of cyclopropane **119a** in toluene and DMAD **132** was performed at 150 °C with a flow rate of 1.4 mL/min (Figure 9a), however the conversion was drastically reduced, 47% yield was obtained after a reaction time of 1.5 h, while 71% of the conversion can be attributed to cycloadduct **133a**. To further improve the yield and selectivity, concentration could play a crucial role. Unfortunately, increasing the concentration of the reaction mixture from 0.5 M to 1.0 M at the same flow rate and temperature resulted in rapid heating due to the much greater microwave absorption. The result was overheating (observed gas evolution at the start of the reaction) and therefore, a large discrepancy between conversion and yield (Figure 9b). Since recycling was used the achievable yield was

limited due to the decomposition of cyclopropane by overshooting of the temperature from the beginning, which could be circumvented by using single-pass method with the optimized conditions. Overheating could be avoided by using a higher flow rate. Switching to a flow rate of 3.4 mL/min indeed prevented the overshoot of the temperature, but the conversion was drastically reduced (Figure 9c). The 1,3-dipole has to react with alkyne **132** in the short time (R_T = 44 s) that the reaction mixture was heated up to 150 °C in the microwave cavity, otherwise it will begin to decompose (see batch experiments Table 6). Therefore, an increasing discrepancy between conversion and yield was observed as the reaction time progressed. In a final attempt, a higher concentration of alkyne **132** was used to increase the conversion of cyclopropane **119a** to cycloadduct **133a** before competing with its decomposition. Using 10 equivalents of alkyne **132** and running the cycloaddition reaction at a flow rate of 1.4 mL/min at 150 °C successfully afforded the desired cycloadduct **133a** in 70% yield after 20 minutes. The productivity was improved to 4.4 g/h (Figure 9d).

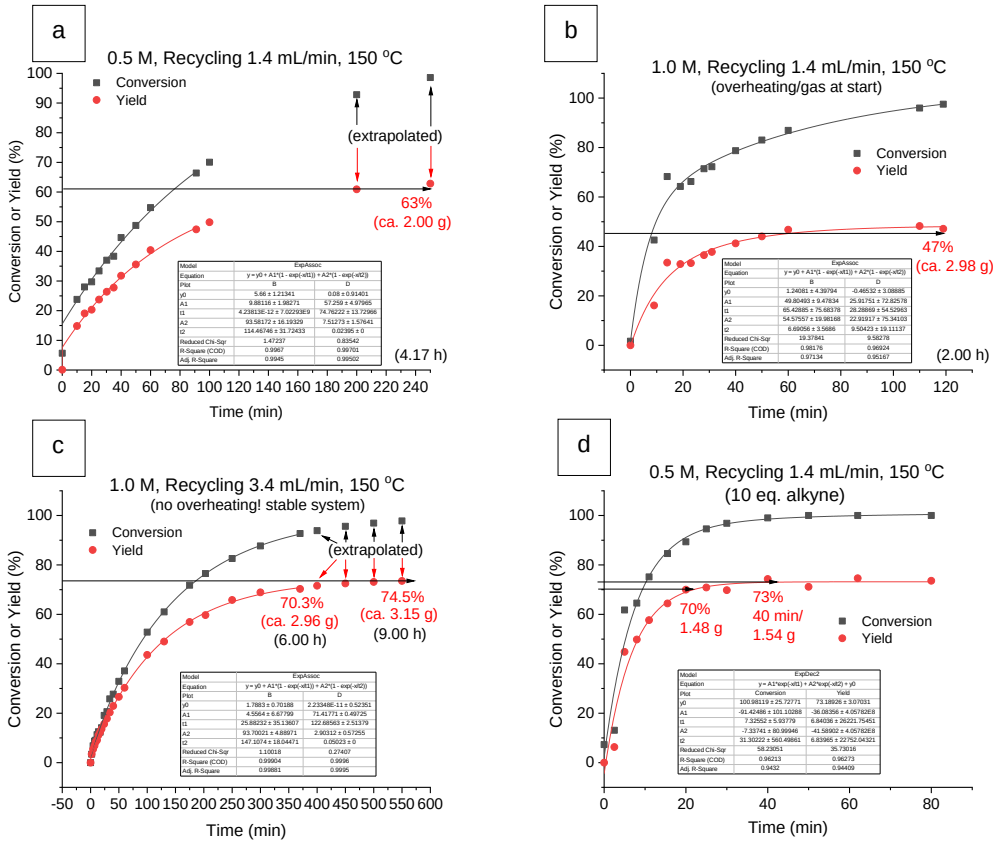
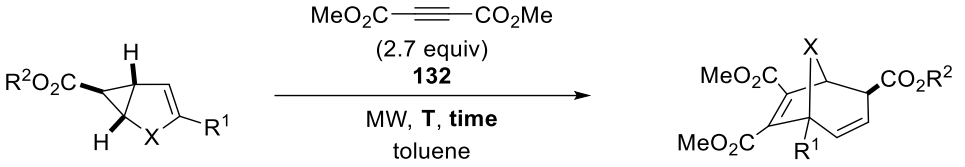


Figure 9. [3+2]-cycloadditions of **119a** with alkyne **132** using different concentrations and flow rates in recycle mode.[6]

[6] The diagrams were made by Dr. Joshua Barham.

In summary, gas evolution was observed several times during [3+2]-cycloadditions under continuous MW flow synthesis, indicating that the temperature in the center was much higher than the exit temperature. As a result, the cyclopropane **119a** or cycloadduct **133a** decomposed, which was also confirmed by the discrepancy of conversion and yield. The gas evolution could indicate cleavage of the *tert*-butyl ester or *N*-Boc protecting group due to the high temperatures in the center. To verify decomposition due to overheating, batch control experiments were carried out at a higher temperature (Table 6). Cyclopropane **119a** partially decomposed at a microwave temperature of 200 °C without the addition of alkyne **132**, demonstrating that cyclopropane **119a** decomposed when no reactant partner was present (Table 6, entry 1). This result was in accordance with the large discrepancy between yield and conversion during flow experiments using low concentrations. Using standard neat conditions at an elevated temperature of 200 °C, the cycloaddition of **119a** with DMAD led to complete decomposition of the cyclopropane **119a**/cycloadduct **133a** (Table 6, entry 2). Switching of the *N*-Boc- to the *N*-Ts protecting group could be promising, if the observed decomposition occurred due to the cleavage of the *N*-Boc or *tert*-butyl ester group. However, the cycloaddition of the *N*-Ts protected cyclopropane **119f** afforded cycloadduct **133e** in only 39% yield, although full conversion of cyclopropane **119f** was observed (Table 6, entry 3). This clearly showed that the *N*-Boc protecting group or the *tert*-butyl ester were not crucial for the decomposition at higher temperatures. The cycloaddition with a 0.5 M reaction mixture furnished cycloadduct **133a** in 33% yield compared to the complete decomposition under neat conditions (Table 6, entry 4). Reducing the reaction time from 30 to 5 min at 200 °C resulted in a further significant increase in yield to 72% (Table 6, entry 5). This would suggest that decomposition could be avoided in flow experiments by increasing the flow rate, but this was not successful in flow due to the reduced conversion as described above. With a 0.5 M reaction mixture or a 1 M reaction mixture, the same results were observed at a temperature of 200 °C (Table 6, entry 6). In contrast, the best yield was obtained at a reaction temperature of 150 °C under neat conditions with a reaction time of 30 min (Table 6, entry 7). Full conversion was not achieved using a 0.5 M reaction mixture (Table 6, entry 8), but was improved by addressing a 1 M reaction mixture (Table 6, entry 9). Finally, the reaction with cyclopropanated furan **120a** was carried out at 200 °C under neat conditions leading to the desired cycloadduct in a moderate yield of 53% despite full conversion (Table 6, entry 10). Nevertheless, this showed the tendency that the reaction with cyclopropanated furans **120** tolerated the thermal conditions better than the cycloadditions with cyclopropanated pyrroles **119**.

Table 6. Batch control experiments.



119a (X = NBoc, R^1 = H, R^2 = ^{t}Bu)
119f (X = NTs, R^1 = H, R^2 = Et)
120a (X = O, R^1 = CO_2Me, R^2 = Et)

133a (X = NBoc, R^1 = H, R^2 = ^{t}Bu)
133e (X = NTs, R^1 = H, R^2 = Et)
140a (X = O, R^1 = CO_2Me, R^2 = Et)

entry	CP	toluene	T [°C]	time [min]	product	yield [%][a]	conversion [%][a]
1[b]	**119a**	0.5 M	200	30	**133a**	-	41
2	**119a**	-	200	30	**133a**	-	100
3	**119f**	-	200	30	**133e**	39	100
4	**119a**	0.5 M	200	30	**133a**	33	100
5	**119a**	0.5 M	200	5	**133a**	72	100
6	**119a**	1 M	200	5	**133a**	71	100
7	**119a**	-	150	30	**133a**	81[c]	100
8	**119a**	0.5 M	150	30	**133a**	58	62
9	**119a**	1 M	150	30	**133a**	76	87
10	**120a**	-	200	30	**140a**	53	100

Reactions were performed on a 0.3-0.5 mmol scale using 2.7 equivalents of dipolarophile **132**, CP=cyclopropane. [a] Determined *via* NMR using 1,3,5-trimethoxybenzene as an internal standard; [b] Reaction was carried out without alkyne [c] Isolated yield.

In conclusion, the batch reactions at higher temperatures are consistent with the observed decomposition of starting material **119a** and cycloadduct **133a** in the microwave flow reactor. Switching to other cyclopropanes with similar required activation temperature of 150 °C will not provide any benefit, as batch results showed that decomposition occurred here as well, albeit at a lower rate. As an outlook, the flow reaction with the donor cyclopropane **119e** could be promising since the cycloaddition already took place at a moderate temperature of 100 °C and thus high temperatures and probably decomposition could be avoided. The cyclopropanation in flow is currently under investigation and could lead to very large amounts of cyclopropane to perform the [3+2]-cycloadditions in the microwave flow reactor with the best conditions in single-pass mode.

2 Derivatizations of 8-aza- and 8-oxabicyclo[3.2.1]octanes at C3/C4 positions

2.1 Isomerization of the C3-C4 double bond – ferruginine analogues

Azabicyclic derivatives are an eminent class of heterocyclic molecular scaffolds which can be found in many natural products with numerous biological and neurochemical activities.[2a,9b,c,e,58] (+)-Ferruginine (**10**), a member of the tropane alkaloid family, was isolated from *Darlingiana Ferruginea*[59] and *D. Darlingiana*[60] (Figure 10). Its unnatural enantiomer (−)-ferruginine (**147**) and (−)-norferruginine (**148**) were found to be potent agonists for the nicotinic acetylcholine receptors (nAChRs) and serve as lead compounds for the development of medications for various diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's disease.[9] (+)-Anatoxin-a (**146**), characterized by a 9-azabicyclo[4.2.1]nonane skeleton which can be considered as a higher homologue of (−)-norferruginine (**148**)**,** was isolated from *Anabaena flos-aquae* and is one of the most potent nicotinic agonists known for nAChR.[9e,61]

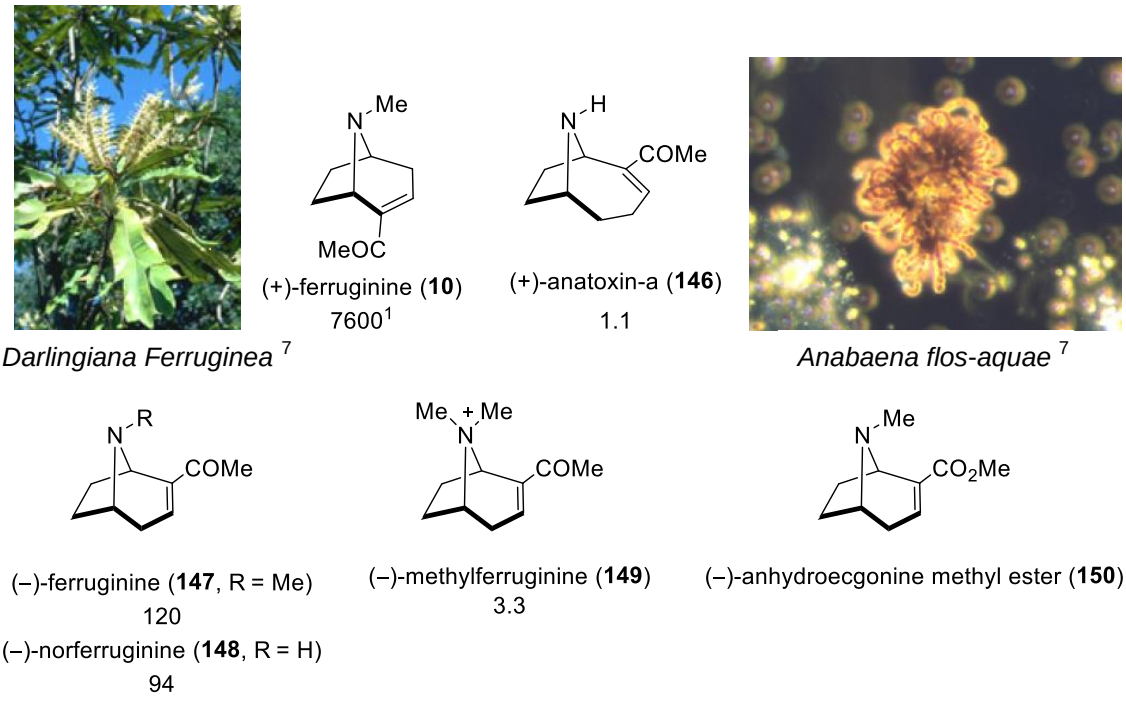


Figure 10. Alkaloid nAChR ligands ([1]affinity values: K_i [nM]; inhibition of ligand binding to nicotinic ($\alpha_4\beta_2$) receptors) and (−)-anhydroecgonine methyl ester (**150**).

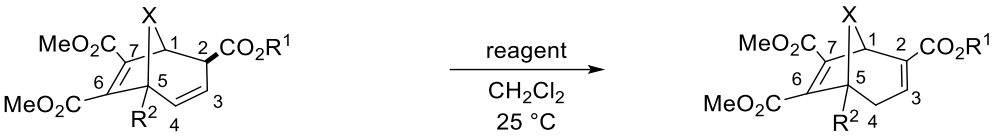
[7] Reprinted by permission from Springer nature license: Springer Nature, *Cellular and Molecular Neurobiology*, Nicotinic Agonists, Antagonists, and Modulators From Natural Sources, J. W. Daly, Copyright, **2004**.

Notably, *N*,*N*-dimethylation decreased the potency of (+)-anatoxin-a (**146**) 10000-fold whereas the potency of (−)-norferruginine (**148**) increased 30-fold (Figure 10; K_i values).[9d] Therefore, the design and synthesis of novel ferruginine analogues is desirable to contribute to the studies of the structure-activity relationships (SAR) at the nAChR. Moreover, the introduction of new substituents into the 8-azabicyclo[3.2.1]octane scaffold could improve selectivity and affinity combined with reduced toxicity, leading to useful therapeutic agents. The biological activity of these compounds originates from the nitrogen atom and a π-system (conjugated ketone group) together with a suitable spatial arrangement, since in the rigid bicyclic framework the nitrogen atom is forced to a precise distance from the π-system.[62] Moreover, structural related (−)-anhydroecgonine methyl ester bearing a 2-carbomethoxy group (**150**, Figure 10) serves as an important intermediate in the synthesis of new tropanes.[22d,f,49b,63]

The [3+2]-cycloadditions provided 8-azabicyclo[3.2.1]octanes **133**, which already contain the core structure of (−)-ferruginine (**147**) as well as (−)-anhydroecgonine methyl ester (**150**), making the synthesis of new analogues a promising synthetic target. In addition, oxabicyclic analogues can be prepared starting from 8-oxabicyclo[3.2.1]-octanes **140** to investigate the role of the bridgehead atom, as studies with cocaine have already shown that also its oxa derivatives possess biological activity.[11a,c,64]

Therefore, a desirable postfunctionalization is the isomerization of the C3-C4 double bond to the conjugated C2/C3 position (Table 7). The isomerization of the C3-C4 double bond of the bicyclic seven-membered ring system **140** to the thermodynamically favored enone **151** was first observed during purification by column chromatography with silica, whereas with flash silica no isomerization products were formed. However, attempts for silica and acid mediated isomerization of **140a** resulted only in partial isomerization to **151a** (Table 7, entry 1 and 2). Base-promoted isomerization of the double bond through an enolate intermediate could also afford αβ-unsaturated ester **151a**. Indeed, using triethylamine (TEA) as the reagent, enone **151a** was obtained after 5 h in quantitative yield (Table 7, entry 3), which could be further optimized to a reaction time of 30 min (Table 7, entry 4). Cycloadduct **140b** bearing a *tert*-butyl ester group at C2 position was also well tolerated giving rise to enone **151b** in quantitative yield (Table 7, entry 5). The choice of different combinations of ester groups was crucial for selective postfunctionalizations (see chapter 3.1). In an analogous way, enones **152a** and **152b** were obtained in the nitrogen series in excellent yields (Table 7, entry 6 and 7).

Table 7. Isomerization of the C3-C4 double bond.



140a (X = O, R^1 = Et, R^2 = CO_2Me),
140b (X = O, R^1 = ^{t}Bu, R^2 = CO_2Me),
133a (X = NBoc, R^1 = ^{t}Bu, R^2 = H),
133c (X = NBoc, R^1 = Et, R^2 = H)

151 (X = O)
152 (X = NBoc)

entry	X	R^1	R^2	reagent	time [h]	product	yield [%]
1	O	Et	CO_2Me	HCOOH[a]	6	-	nc
2	O	Et	CO_2Me	HCOOH, silica	120	**151a**	nd[b]
3	O	Et	CO_2Me	TEA (1.3 equiv)	5	**151a**	quant.
4	O	Et	CO_2Me	TEA (1.3 equiv)	0.5	**151a**	quant.
5	O	^{t}Bu	CO_2Me	TEA (1.3 equiv)	0.5	**151b**	quant.
6	*N*-Boc	^{t}Bu	H	TEA (1.3 equiv)	2	**152a**	quant.
7	*N*-Boc	Et	H	TEA (1.3 equiv)	2	**152b**	99%

Reactions were performed on a 0.3-1.3 mmol scale; nc=no conversion; nd=not determined. [a] HCOOH was used as solvent; [b] Only partial conversion was observed.

The structure of isomerized cycloadduct **152a** was unambiguously assigned by X-ray crystallography (Figure 11).

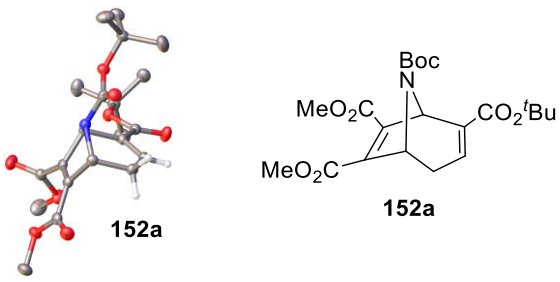


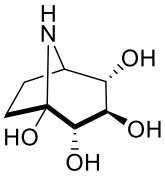
Figure 11. X-Ray structure of enone **152a**.

The isomerization of the double bond yielded attractive compounds **151-152** containing the core structure of (−)-anhydroecgonine methyl ester (**150**) and (–)-ferruginine (**147**) which demonstrates the utility of this synthetic transformation. These analogues possess additional substituents at the C6/C7 positions, which are still unknown due to their challenging introduction and therefore the influence on the biological activity is still unknown. Using *N*-Boc protecting group allows its facile cleavage which was shown with derivative **220** and the exchange to *N*-Me group is also possible (see chapter 2.7). Furthermore, the isomerized products were used for the synthesis of novel Pt(II) compounds as potential anticancer drugs in chapter 3.

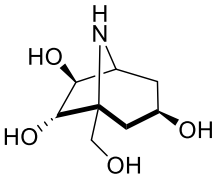
2.2 Dihydroxylation reactions – hydroxylated nortropanes

Calystegines, containing a polyhydroxylated nortropane ring system, are a class of naturally occurring imino sugar mimetics[65] first isolated from *Calystegia sepium* in 1988 (Figure 12).[66] They have been classified into three types depending on the number of hydroxyl groups attached to the nortropane ring system: **A** (three OH groups), **B** (four OH groups) and **C** (five OH groups).[23-24] Several calystegines impact rhiszosphere ecology as nutritional sources for soil microorganism and exhibit potent glycosidase inhibitory properties.[10b] Therefore, they are lead compounds in the treatment of viral diseases[67], cancer[68], diabetes[69] and lysosomal storage disorders[70]. Calystegine B_2 (**23**) is a potent and specific inhibitor of β-glycosidase (Figure 12).[10a,65b,71]

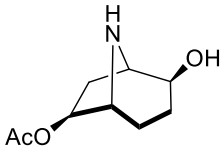
Calystegia sepium[8]



calystegine **B**$_2$ (**23**)



3(*S*)-hydroxy-labystegine (**31**)



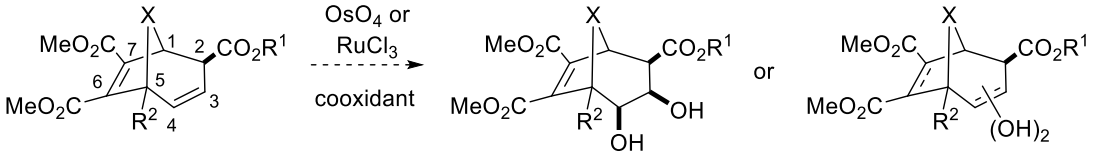
(–)-Bao Gong Teng A (**153**)

Figure 12. Hydroxylated nortropane alkaloids.

The synthesis of calystegines and novel derivatives has attracted great attention. Various derivatives were developed, such as labystegine (**31**), a hybrid iminosugar of

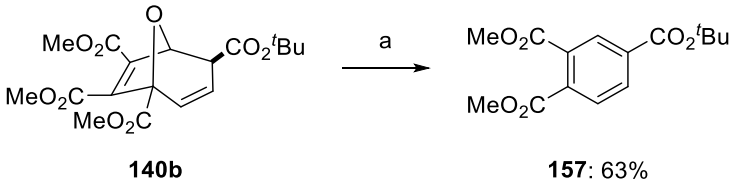
[8] https://commons.wikimedia.org/wiki/File:Calystegia_sepium_sepium_-_top_(aka).jpg, author: André Karwath aka Aka, 2005 (accessed on 16.06.2021).

LAB and calystegine (for synthesis see introduction), which represents a promising new class of nortropane-type iminosugar with potential to treat postprandial hyperglycemia (Figure 12).[33] In recent years, much effort was devoted to the synthesis of calystegines, whereas much less attention was drawn to the synthesis of dihydroxytropanes such as (–)-Bao Gong Teng A (**153**)[72], but also hydroxylated nortropane alkaloids are known for their biological activity.[40b,73] (–)-Bao Gong Teng A (**153**) exhibits hypertensive and miotic activities, therefore it has been used in clinics for the treatment of glaucoma.[40a]
In this thesis, highly functionalized 8-aza- **133** and 8-oxabicyclo[3.2.1]octanes **140** were exploited as precursors for the synthesis of hydroxylated tropane analogues *via* various postfunctionalizations. For example, dihydroxylation is a promising way to introduce hydroxyl groups that could lead to very attractive hydroxylated tropanes (Scheme 19). Due to the different electronic nature of the double bonds in the bicyclic seven-membered rings **154**, the dihydroxylation reaction should occur first selectively at the C3-C4 double bond since the C6-C7 double bond is electron-deficient.



Scheme 19. Planned dihydroxylation reactions.

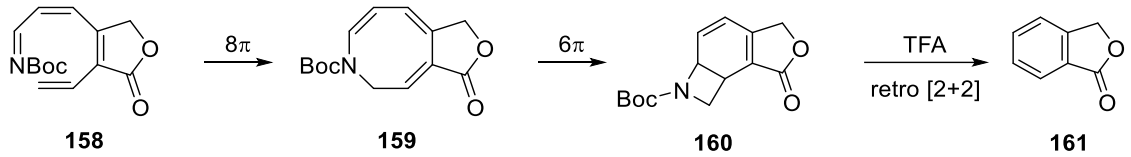
An *exo*-diol **155** will be most likely formed, because of the sterically less-hindered convex side. Initially, dihydroxylations were performed with 8-oxabicyclo[3.2.1]octane **140b**, and then 8-azabiyclo[3.2.1]octane **133** was also investigated to identify differences in the reactivity profile due to the heteroatom bridge.



Scheme 20. First attempt for dihydroxylation of 8-oxabicyclo[3.2.1]octane **140b**. Conditions: a) K_2CO_3 (3.0 equiv), $K_3[Fe(CN)_6]$ (3.0 equiv), $K_2[OsO_4]\cdot 2H_2O$ (1 mol%), ^{t}BuOH/H_2O, 25 °C, 21 h, 63%.

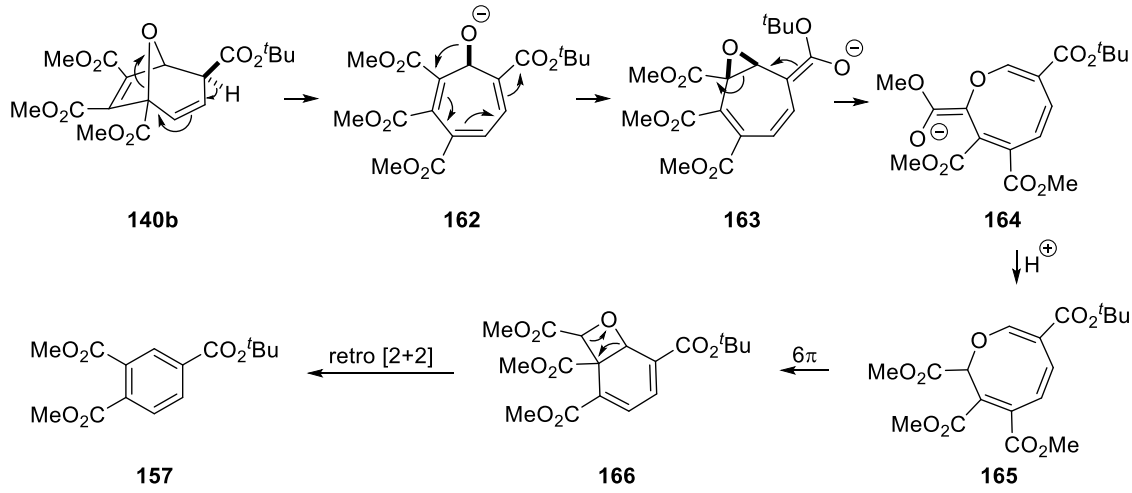
The dihydroxylation reaction of 8-oxabicyclo[3.2.1]octane **140b** with $K_2[OsO_4]\cdot 2H_2O$[74] and K_2CO_3 furnished an unexpected aromatic compound **157** in 63% yield instead of the desired diol (Scheme 20), probably *via* a base-assisted rearrangement, which was also

formed in the following epoxidation chapter 2.4 with base. Davies *et al.* observed an aromatization of cycloadduct **158** to compound **161** (Scheme 21). They proposed an aromatization of **158** *via* 8π/6π-electrocyclizations to **160**, followed by a retro [2+2]-cycloaddition to give the aromatic compound **161**.[75]



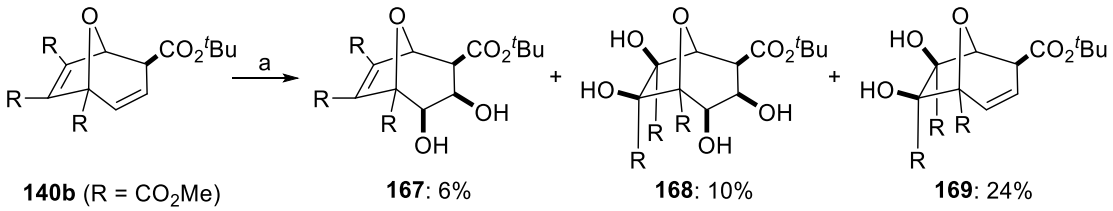
Scheme 21. Proposed mechanism of aromatization of **158** reported by Davies *et al*.[75]

The aromatization of **140b** may proceed in a similar manner to the proposed mechanism of Davies *et al*. Deprotonation of the acidic proton adjacent to the *tert*-butyl ester of cycloadduct **140b** resulted in a ring-opening of the ether bridge leading to compound **162** (Scheme 22). The formation of an epoxide **163**, followed by further rearrangements, led to oxocine **165**. A 6π electrocyclization of the latter afforded **166**, which accomplished an aromatic compound **157** *via* a retro [2+2]-cycloaddition.



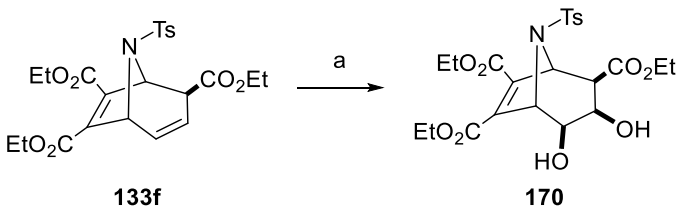
Scheme 22. Proposed mechanism for aromatization of cycloadduct **140b.**

In a next approach, $RuCl_3 \cdot 3H_2O$[76] was used for dihydroxylation of **140b**, which unfortunately gave a complex mixture of diols **167**, **168**, and **169** (Scheme 23). Notably, diol **169** was the *major* product, although tetrasubstituted, electron-deficient double bonds are not prone to undergo dihydroxylation reactions preferentially over electron-rich double bonds. Due to the poor selectivity and hence, low synthetic value, the dihydroxylation of 8-oxabicyclo[3.2.1]octane **140b** was not pursued further.



Scheme 23. Attempt for stereoselective dihydroxylation of 8-oxabicyclo[3.2.1]octane **140b**. Conditions: a) $RuCl_3 \cdot 3H_2O$ (0.06 equiv), $NaIO_4$ (1.5 equiv), H_2O/CH_3CN, 0 to 25°C, 3 h.

Next, dihydroxylation of 8-azabicyclo[3.2.1]octanes **133** will be examined in more detail, as the selectivity might be altered by the heteroatom bridge. To accomplish the diol, the dihydroxylation of *N*-Ts protected azabicycle **133f** was carried out using $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ as co-oxidant[48e,76-77] in the Reiser group by Dr. S. Park (Scheme 24).[53] The *exo*-diol **170** was obtained as a single diastereomer in moderate yield. The stereochemistry of the diol **170** was determined by 2D NMR analysis.

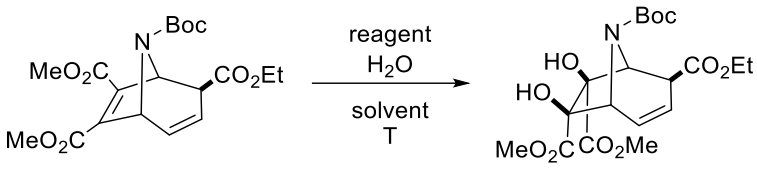


Scheme 24. Dihydroxylation of *N*-Ts protected 8-azabicyclo[3.2.1]octane **133f** by Dr. S. Park. Conditions: a) $RuCl_3 \cdot 3H_2O$ (0.06 equiv), $NaIO_4$ (1.5 equiv), H_2O, CH_3CN, 0 to 25°C, 2 d, 47%.[53]

Switching to the *N*-Boc protected azabicycle **133c**, dihydroxylation was also performed with $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ as co-oxidant (Table 8, entry 1). In contrast to the previously described dihydroxylation, *exo*-diol **171** was obtained selectively as the *major* product, however the rest was an inseparable complex mixture.

Hence, in a next attempt, $K_2OsO_4 \cdot 2H_2O$ and NMO as co-oxidant[78] were used for the dihydroxylation, resulting in **171** as a single diastereomer in 35% yield (Table 8, entry 2). The reaction time was reduced to 1 h to accomplish diol **171** in 48% yield (Table 8, entry 3). Cooling to 0 °C afforded the *exo*-diol **171** in moderate yield, the most promising conditions, as recrystallization furnished pure diol in 43% yield (Table 8, entry 4).

Table 8. Dihydroxylation of *N*-Boc protected 8-azabicyclo[3.2.1]octane **133c**.

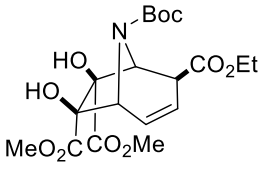


133c **171**

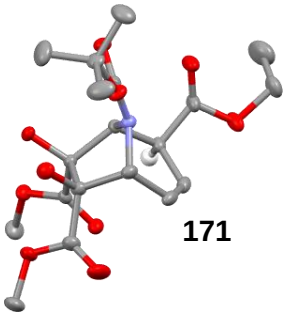
entry	reagent	solvent	T [°C]	time [h]	171 [%]
1	$RuCl_3 \cdot 3H_2O$ (0.07 equiv), $NaIO_4$ (1.5 equiv)	CH_3CN	25	50	32[a] [b]
2	$K_2OsO_4 \cdot 2H_2O$ (0.05 equiv), NMO (2.0 equiv)	acetone	25	2.5	35[b]
3	$K_2OsO_4 \cdot 2H_2O$ (0.05 equiv), NMO (2.0 equiv)	acetone	25	1	48[c]
4	$K_2OsO_4 \cdot 2H_2O$ (0.05 equiv), NMO (2.0 equiv)	acetone	0	12	43[d]

Reactions were performed on a 0.3 mmol scale. [a] 83% Conversion; [b] Isolated yield; [c] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard; [d] Recrystallization from diethyl ether.

The structure of the unusual *exo*-diol **171** was unambiguously determined by X-ray crystallography (Figure 13).



171

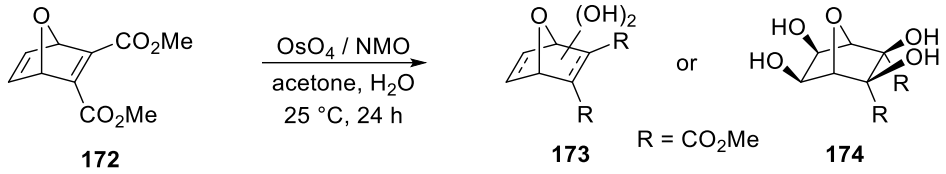


171

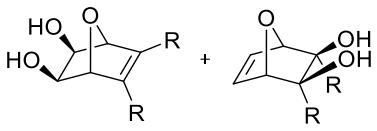
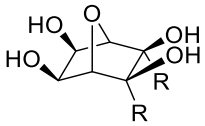
Figure 13. X-Ray structure of *exo*-diol **171**.

In general, dihydroxylations of electron-rich double bonds are preferred over electron-deficient, tetrasubstituted double bonds,[79] which has been clearly demonstrated by dihydroxylations of norbornene derivatives, e.g., oxanorbornene **172** (Table 9).[80]

Table 9. Precedent studies of dihydroxylation of oxanorbornene **172** with electron-deficient double bond.[80]



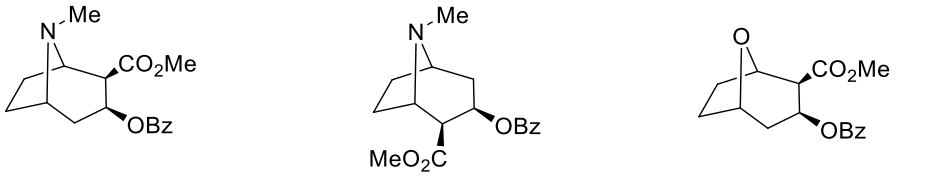
172 **173** **174**

entry	NMO [equiv]	product
1	1.0	 **173a:** 95% **173b:** 5%
2	2.0	 **174:** 83%

172 was treated with catalytic amount of OsO_4 in the presence of NMO (1.0 equiv), resulting in *exo*-diol **173a** and *exo*-diol **173b** in 95% and 5% yield, respectively (Table 9, entry 1). The use of two equivalents of NMO gave **174** in 83% yield (Table 9, entry 2).
In summary, the dihydroxylation reactions of 8-oxabicyclo[3.2.1]octane **140b** led to rearrangement (Scheme 20) or was nonselective (Scheme 23). The latter could be a consequence of steric congestions due to the additional methyl ester group at C5 position compared to 8-azabicyclo[3.2.1]octane **133**. Moreover, the dihydroxylation reactions have shown that the heteroatom bridge (O *vs. N*-Ts *vs. N*-Boc) had a great influence on the reactivity of the double bonds. Selective dihydroxylation of the electron-deficient, tetrasubstituted C6-C7 double bond of the *N*-Boc protected cycloadduct **133c** yielded *exo*-diol **171**, while using *N*-Ts protected cycloadduct **133f** accomplished *exo*-diol **170** *via* dihydroxylation of C3-C4 double bond, which represented a remarkable result. By choosing the *N*-protecting group, it was possible to achieve different selectivity's and thus hydroxylated nortropanes are accessible by this synthesis, which, as described in the beginning of this chapter, are promising derivatives due to their potential biological activity.

2.3 Hydroboration reactions – cocaine analogues

(*R*)-(–)-Cocaine (**9**) is one of the most commonly known representative of the tropane alkaloid class due to its remarkable activity as a reuptake inhibitor of the neurotransmitters noradrenaline, serotonin, and especially dopamine (Figure 14).[3b,6] Alterations of the dopamine transporter function may play a role in diseases like Parkinson and Alzheimer.[7c,8a] Its enantiomer, (*S*)-(+)-cocaine (**175**) is comparatively less potent[81] and is rapidly metabolized.[22g,82]



(*R*)-(–)-cocaine (**9**) (*S*)-(+)-cocaine (**175**) (*R*)-(–)-oxa-norcocaine (**176**)

Figure 14. (*R*)-(–)-Cocaine (**9**), its enantiomer (*S*)-(+)-cocaine (**175**) and (*R*)-(–)-oxa-norcocaine (**176**).

The pharmacological mechanism of action of (*R*)-(–)-cocaine (**9**) involves binding to the dopamine transporter (DAT), which is accompanied by blockade of presynaptic reuptake (Figure 15).[6e,83] The extracellular concentration of the neurotransmitter dopamine increases rapidly in the synaptic cleft with a resultant enhanced activation of postsynaptic receptors.[6c,84] The reinforcing and stimulant effects lead to cocaine abuse as a narcotic drug, a worldwide medical problem. To date, there is no effective medication for cocaine dependence.[6d,22g,i,84]

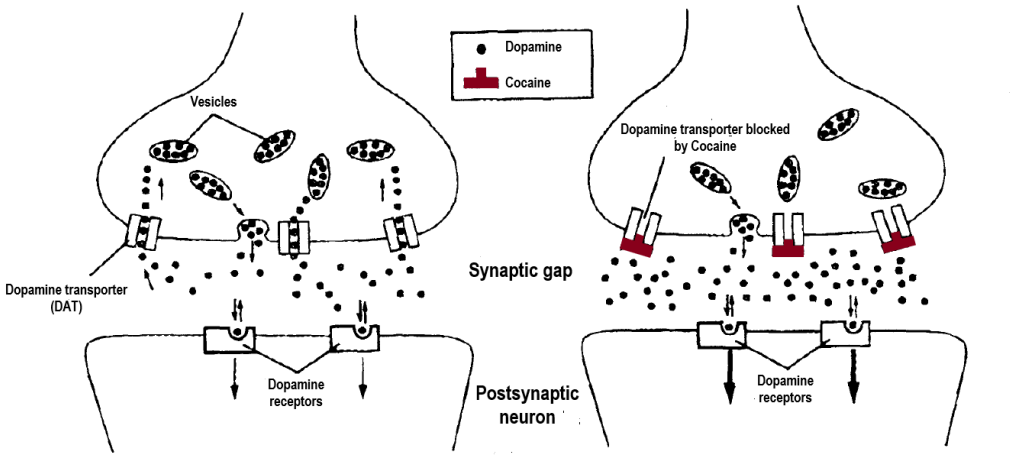
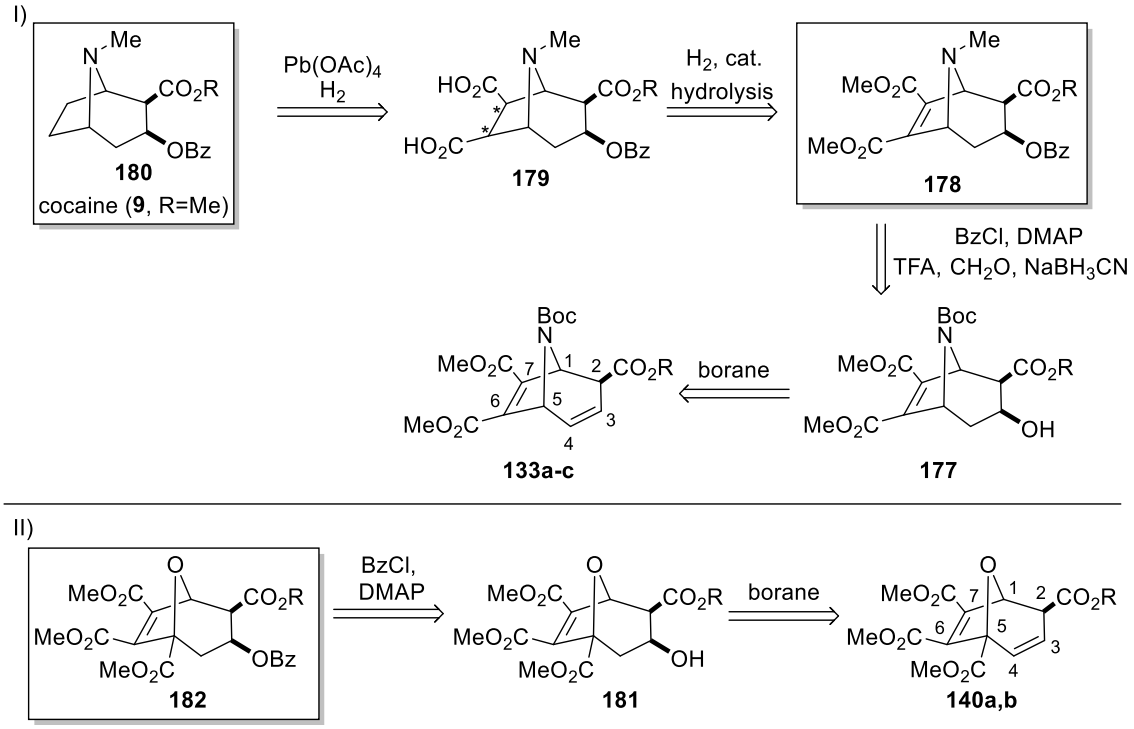


Figure 15. A dopaminergic synapse under normal conditions (left) and cocaine inhibition of dopamine transporter (right). Adapted from Kuhar *et al.*[83b]

However, using morphine as an example, research has already shown that simple modifications of the opiate led to an antagonist that can be used for effective therapy of opiate addiction.[55a,85] For the treatment of cocaine abuse, the development of cocaine analogues as potential antagonists or partial agonists is of special interest.[22g,55c] Antagonists prevent cocaine from binding to the dopamine transporter, allowing dopamine to re-enter the presynapse. [55b,d] In addition, 8-oxabicyclo[3.2.1]octanes, structural mimics of tropane alkaloids, have attracted considerable attention in the development of drugs for cocaine abuse due to their promising properties as dopamine transporter inhibitors. [11,64,86] The major difficulty in the synthesis of cocaine and its analogues is the construction of the bridged seven-membered rings containing the appropriate functionalities. On the one hand, it is synthetically challenging to introduce the *cis* relationship between substituents at the C2/C3 position, and on the other hand, most cocaine analogues are prepared starting from (*R*)-(–)-cocaine (**9**).[6d,22g,j] For this reason, C6/C7 substituted analogues are still relatively unexplored.[22g,i,55a-c] The 8-azabicyclo[3.2.1]octanes **133** and 8-oxabicyclo[3.2.1]octanes **140** bearing various substituents at the C6/C7 positions of the tropane ring system are particularly attractive for the synthesis of new cocaine analogues due to their already present core structure of cocaine as depicted in scheme 25. To synthesize new cocaine analogues, the introduction of an *exo* hydroxyl group at C3 position is crucial. This can be realized *via* hydroboration of the electron-rich double bond at the C3/C4 position of the cycloadducts. Previous studies of hydroboration with cycloadducts bearing maleic anhydride such as **133h** have already shown that they tend to undergo unselective ring-opening reactions.[52-53] Therefore, the focus was directed on cycloadducts **133a-c** or **140a,b** prepared *via* (3+2)-cycloadditions with alkynes as single diastereomers to avoid stability problems due to the maleic anhydride. A proposed retrosynthetic strategy towards C6/C7 substituted cocaine analogue **178** involves hydroboration of **133a-c**, followed by benzoylation (**177**) and reductive amination (Scheme 25, I). The total synthesis of cocaine (**9**) can be accomplished *via* hydrogenation/hydrolysis of **178**, subsequent oxidative decarboxylation with $Pb(OAc)_4$ (**179**) and finally hydrogenation of the double bond (Scheme 25, I). In analogous way, the synthetic route to oxa-analogues **182** should be investigated (Scheme 25, II). Since the hydroboration of **133a-c**/**140a,b** can lead to regioisomeres or diastereomers, various sterically hindered organoboranes should be examined. Boranes such as 9-BBN, thexylborane ($ThBH_2$), catecholborane (HBCat) or chiral hydroboration reagents such as diisopinocampheylborane (Ipc_2BH) are suitable organoboranes.[87] Nevertheless, the hydroboration should preferably proceed from the sterically less-hindered convex side and the boron adds preferentially at the C3 position due to the steric demand of the nitrogen or oxygen bridge.

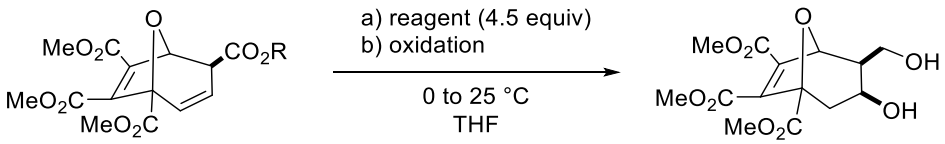


Scheme 25. Retrosynthesis of cocaine analogue **178**, cocaine (**9**), and oxa-norcocaine **182**.

The first attempt of hydroboration using BH_3·THF as borane reagent, followed by basic oxidative workup only led to decomposition of cycloadduct **140b** (Table 10, entry 1), most likely due to the hydrolysis of the attached methyl esters. In order to circumvent strongly basic conditions, a neutral oxidation with a phosphate buffer (pH 7.2) was performed.[87b] The hydroboration of **140b** with BH_3·THF using neutral oxidation conditions were successfully executed, but simultaneously the reduction of *tert*-butyl ester at C2 position to the corresponding alcohol **183** was observed (Table 10, entry 2). Since borane generally does not reduce ester groups it was assumed that first hydrolysis of the acid labile *tert*-butyl ester to the carboxylic acid occurred, followed by its reduction with BH_3·THF to the alcohol. Diol **183** was isolated in 36% yield as single diastereomer, which was unambiguously assigned by ^{1}H NMR and 2D NMR spectroscopy. Unfortunately, the exchange of the *tert*-butyl ester to the ethyl ester did not prevent the reduction of the ester at C2 position (Table 10, entry 3). Noteworthy, no reduction of the attached ethyl ester groups at C6/C7 positions of cycloadduct **140** was observed in previous studies[52] in contrast to the reduction of the ethyl ester at C2 position of cycloadduct **140a**. This result showed that the ester at C2 position is prone for hydrolysis/reduction with BH_3·THF. Next, subjecting cycloadduct **140a** with 1.1 equivalents of BH_3·THF resulted in no conversion of the starting material (Table 10, entry 4). Subsequently, the reaction with cycloadduct **140b** was performed on a 1.4 mmol scale which led to an inseparable complex mixture of diastereomers (Table 10, entry 5). Therefore, $(Ipc)_2BH$ and 9-BBN

were used as less reactive borane reagents, however only starting material was recovered (Table 10, entry 6 and 7).

Table 10. Attempts for hydroboration of 8-oxabicyclo[3.2.1]octanes **140**.

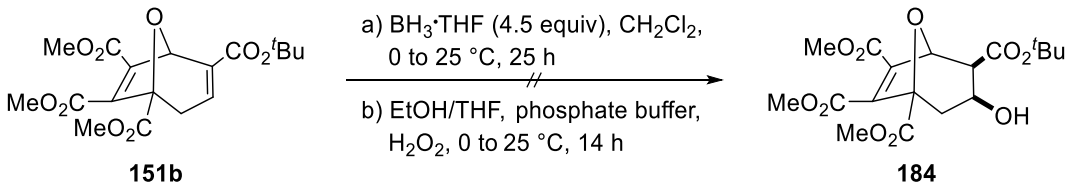


140a (R = Et), **140b** (R = ^{t}Bu) **183**

entry	R	reagent	oxidation	time [h]	observation
1	^{t}Bu	BH_3·THF	basic	a) 7; b) 14	crm
2	^{t}Bu	BH_3·THF	neutral[a]	a) 7; b) 15	**183** (36%)
3	Et	BH_3·THF	neutral[a]	a) 6; b) 14	**183** (31%)
4[b]	Et	BH_3·THF	neutral[a]	a) 22; b) 24	nc
5[c]	^{t}Bu	BH_3·THF	neutral[a]	a) 7; b) 14	crm
6	^{t}Bu	$(Ipc)_2BH$	neutral[a]	a) 24; b) 26	nc
7	Et	9-BBN	neutral[a]	a) 25; b) 26	nc

Reactions were performed on a 0.2-0.4 mmol scale; crm=complex reaction mixture; nc=no conversion. [a] Neutral oxidative workup: EtOH:THF (1:1), phosphate buffer (pH 7.2), H_2O_2; [b] 1.1 Equiv BH_3·THF was used; [c] Reaction was performed on a 1.4 mmol scale using 2.0 equiv of BH_3·THF.

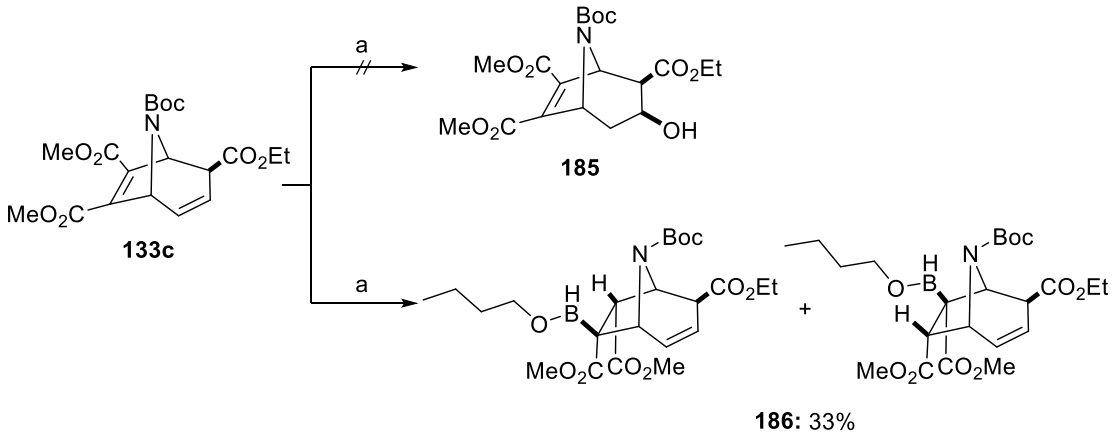
Hydroboration–oxidation of the isomerized cycloadduct **151b** using the best BH_3·THF conditions (Table 10, entry 2) was investigated in a next experiment. Unfortunately, no conversion of the starting material **151b** was observed (Scheme 26). Notably, the hydrolysis/reduction of the *tert*-butyl ester at C2 position of isomerized bicyclic compound **151b** did not occur, in contrast to the results described above with cycloadducts **140a,b**.



Scheme 26. Attempt for hydroboration of isomerized cycloadduct **151b**.

In conclusion, hydroboration attempts of 8-oxabicyclo[3.2.1]octanes **140a,b** afforded diol **183** in low yields. In addition, it was shown that the reaction was nonselective on a larger scale and therefore has no further applicability.

In the nitrogen series, 8-azabicyclo[3.2.1]octane **133c** was subjected to the hydroboration reaction to obtain the desired alcohol **185**. Azabicyclic compound **133c** was treated with BH_3·THF, but instead of the expected product **185**, an inseparable mixture of **186** was obtained in 33% yield with 25% recovered starting material (Scheme 27). The neutral oxidation conditions probably did not lead to the cleavage of the borane.

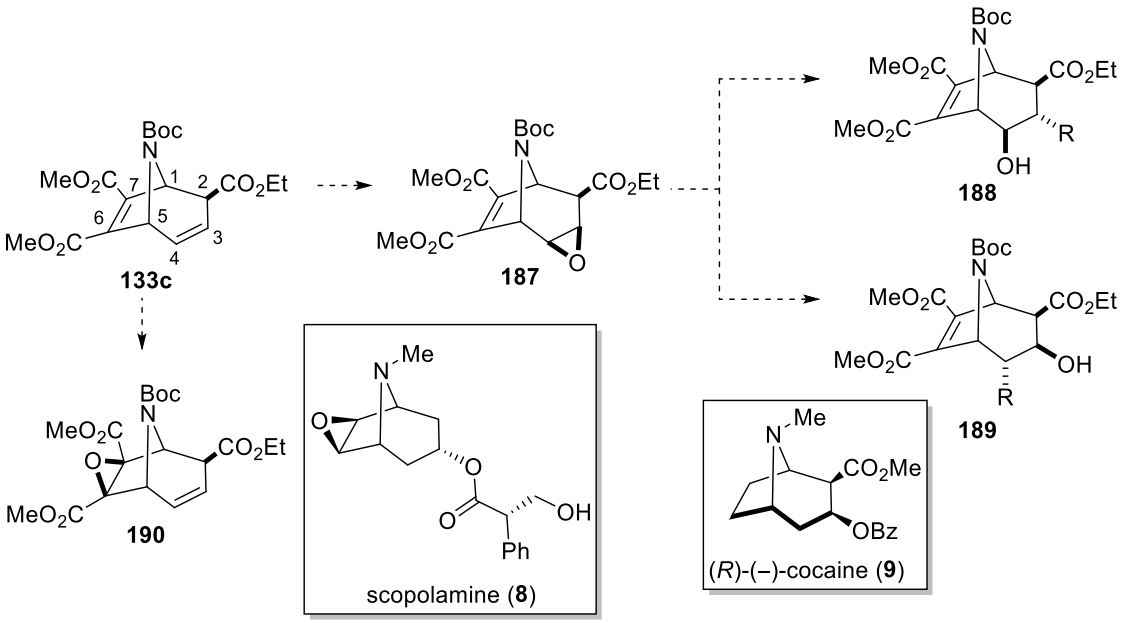


Scheme 27. Attempt for hydroboration of 8-azabicyclo[3.2.1]octane **133c**. Conditions: a) *(i)* BH_3·THF (4.5 equiv), CH_2Cl_2, 0 to 25 °C, 24 h, *(ii)* EtOH/THF, phosphate buffer, H_2O_2, 0 to 25 °C, 7.5 h, 33%, 75% conversion.

The change in reactivity from 8-oxa- **140a,b** to 8-azabicyclo[3.2.1]octanes **133c** could arise from the different steric demand of the heteroatom bridge (O *vs. N*-Boc). Hydroboration occurred from the sterically less-hindered convex side at the electron-deficient C6-C7 double bond. This was also in accordance with the results of dihydroxylation of *N*-Boc protected cycloadducts which proceeded selectively at the C6-C7 double bond (see chapter 2.2). In the following chapter, further postfunctionalizations to synthesize new cocaine analogues were pursued such as epoxidation/epoxide opening.

2.4 Epoxidation reactions

Epoxides are important structural motifs that are versatile chiral building blocks in organic synthesis due to their high reactivity, stereospecificity, and regioselectivity in ring-opening processes. Moreover, oxiranes are found in many biologically active compounds, such as scopolamine (**8**) (Scheme 28), which have pharmaceutical applications (e.g., Buscopan®, see introduction chapter 1, figure 3).[88] Therefore, the epoxidation of the C3-C4 or C6-C7 double bond of **133c** represents another useful transformation, especially when aiming to hydroxylated tropanes **188** or **189** *via* regioselective ring-opening of epoxide **187**. Hydroxylated (nor)tropanes are promising target structures since, as described in the previous chapter, they occur in numerous biologically active compounds (see chapter 2.2)[10b,72] Therefore, regioselective epoxide opening to either **188** with respect to (–)-Bao Gong Teng A (**153**, see chapter 2.2) or azabicycle **189** as a promising precursor for the synthesis of new cocaine analogues, would be of great synthetic value. Moreover, the epoxidation/epoxide ring-opening of 8-oxabicyclo[3.2.1]octanes **140** (structural mimics of tropane alkaloids) a common structural motif found in many natural products and biologically significant compounds has been investigated.[89] Epoxides and hydroxylated oxabicycles serve as interesting synthetic building blocks for potential bioactive molecules.[90]



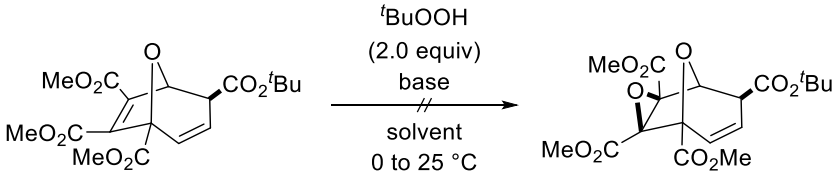
Scheme 28. Planned synthesis of hydroxylated (nor)tropane derivatives.

The epoxidation of C=C bonds is generally categorized into two classes: Electrophilic epoxidation applied for electron-rich double bonds, while nucleophilic epoxidation is used for electron-deficient double bonds.[91] Therefore, the nucleophilic epoxidation should

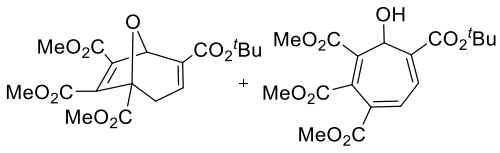
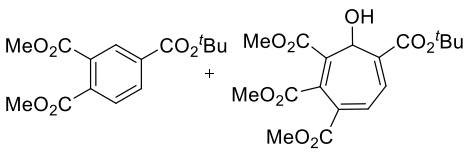
occur selectively at the C6-C7 double bond of **133** or **140** with nucleophilic reagents, while the electrophilic epoxidation takes place on the C3-C4 double bond with electrophilic reagents (Scheme 28).

In the following, nucleophilic epoxidation[92] of the C6-C7 double bond of 8-oxabicyclo[3.2.1]octane **140b** was investigated using *tert*-butyl hydroperoxide (^{t}BuOOH) in the presence of base[93] (Table 11). The treatment of **140b** with DBU and ^{t}BuOOH did not yield the desired epoxide **191** but led to a mixture of isomerized cycloadduct **151b** and ring-opened product **192** (Table 11, entry 1). Unfortunately, the next attempt of nucleophilic epoxidation of cycloadduct **140b** with ^{t}BuOOH and $NaHCO_3$ [94] was also not successful. Aromatic compound **157** was obtained in 30% yield as well as seven-membered ring **192** in 10% yield (Table 11, entry 2). Comparison of the crude ^{1}H NMR spectra with a *ratio* of **157**:**192**=1:2 to the isolated yield (**157**:**192**=3:1) indicated that the compound **192** was not stable on column chromatography.

Table 11. Attempts of nucleophilic epoxidation of C6-C7 double bond of **140b**.



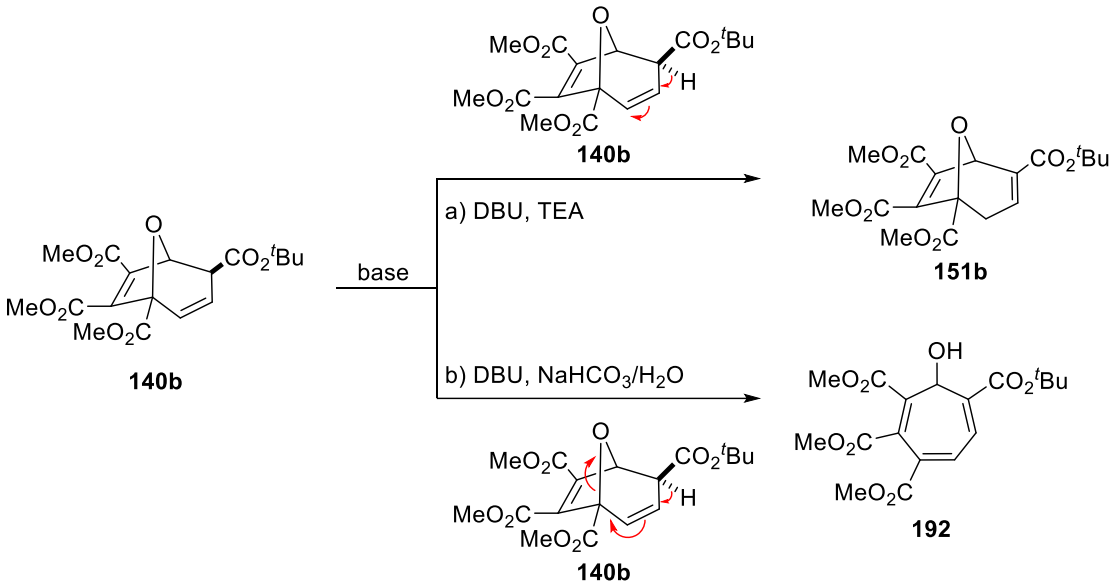
140b **191**

entry	base	solvent	time [h]	observation[a]
1	DBU (1.1 equiv)	CH_2Cl_2	1.5	 **151b:** 31% **192:** 25%
2	$NaHCO_3$	MeOH/ H_2O	40	 **157:** 30% **192:** 10%

Reactions were performed on a 0.3 mmol scale. [a] Isolated yield *via* column chromatography.

The proposed mechanism to enone **151b** involves abstraction of the proton by the base DBU, resulting in isomerization of the double bond (Scheme 29, a), as already observed with TEA (see chapter 2.1), while **192** was formed by opening of the ether-bridge (Scheme 29, b). In contrast, an aromatic compound **157** was obtained using $NaHCO_3$ in

MeOH/H_2O, which was also afforded by a dihydroxylation reaction under basic conditions in the presence of H_2O, a postulated mechanism being described in chapter 2.2 (Scheme 22). Control experiments showed that these reactions were exclusively base-mediated.



Scheme 29. Base-induced reactions: (a) isomerization of the C3-C4 double bond to **151b**; (b) opening of the ether-bridge to **192**.

In conclusion, depending on the base, rearrangements occurred that completely prevented the nucleophilic epoxidation of C6-C7 double bond of 8-oxa-bicyclo[3.2.1]octane **140b**. Nevertheless, the obtained ring-opened product **192** is an attractive framework for the synthesis of tropones by oxidation of the alcohol to the corresponding carbonyl moiety. Further optimization studies are required to increase the yield and selectivity of the reaction, such as investigating the influence of various bases (e.g., LDA) and purification methods. Tropone **193** and its related tropolones **194**-**196** exhibit a broad range of biological activity, such as antibacterial[95], antifungal[96], anti-HIV[97], anti-malarial[98] and anticancer[99] activity (Figure 16).

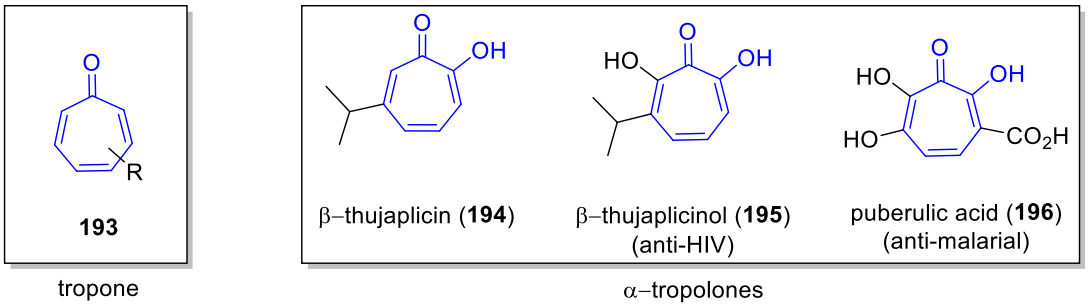
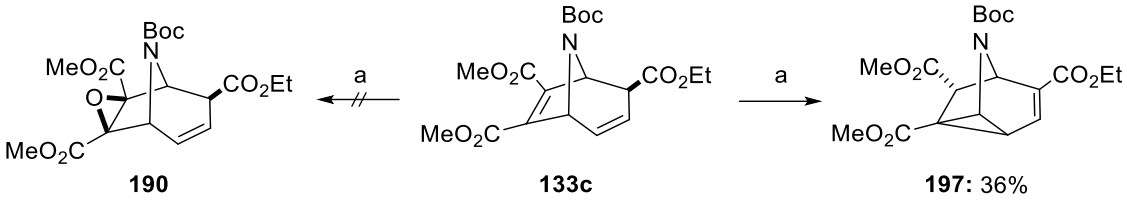


Figure 16. Structures of relevant tropones and α-tropolones.

Therefore, the development of new tropolones by selective reduction of the ester groups of the seven-membered ring **192** to the corresponding alcohols would be desirable in the future.

Particularly promising with respect to scopolamine (**8**) would be the nucleophilic epoxidation of 8-azabicyclo[3.2.1]octane **133** (Scheme 30). The nucleophilic epoxidation of C6-C7 double bond in **133c** with hydrogen peroxide under basic condition did not yield the desired epoxide **190**. Instead, a rearrangement to 6-azatricyclo[3.2.1.$0^{2,7}$]octane **197** took place (Scheme 30), which was also observed upon hydrolysis as well as dehalogenation and is therefore discussed in chapter 2.8. The low yields indicated that under basic conditions hydrolysis of the methyl esters occurred.



190 **133c** **197:** 36%

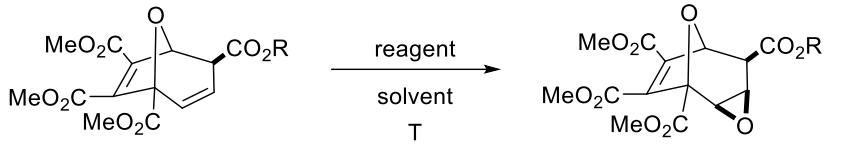
Scheme 30. Base-mediated rearrangement of **133c** to 6-azatricyclo[3.2.1.$0^{2,7}$]octane **197**. Conditions: a) NaOH (1.2 equiv), H_2O_2 (5.4 equiv), CH_2Cl_2/MeOH (1:1), 25 °C, 3 h, 36%.

In summary, nucleophilic epoxidations of the C6-C7 double bond in 8-aza- and 8-oxabicyclo[3.2.1]octanes **133**, **140** were not successful, due to base-mediated rearrangements. Nevertheless, depending on the bridgehead atom (O *vs. N*-Boc) of the bicyclo[3.2.1]octanes and base, the rearrangements led to complex and interesting scaffolds such as 6-azatricyclo[3.2.1.$0^{2,7}$]octane **197**.

As described at the beginning of the chapter, in addition to the nucleophilic epoxidation, electrophilic epoxidation of the C3-C4 double bond using various reagents such as peracids could also lead to valuable compounds. Previous attempts to epoxidize the C3-C4 double bond of maleic anhydride bearing cycloadducts, e.g., **133h** failed,[52-53] thus, cycloadducts **140a-b** and **133c** were used as model substrate for further studies. In a first approach, the epoxide was prepared starting from cycloadduct **140b** using a mixture of TFAA and hydrogen peroxide[100] to generate the peracid *in situ*, resulting in selective epoxidation of the more electron-rich C3-C4 double bond. However, the *exo*-epoxide **198b** was only obtained in a low yield of 14% with 46% recovered starting material **140b** (Table 12, entry 1). Using performic acid[101], the yield was slightly improved to 47%, but full conversion of the starting material **140b** was observed (Table 12, entry 2). This observation indicated that undesirable side reactions, such as hydrolysis of the methyl esters during basic workup, occurred. Therefore, no basic workup was included in a next set of experiments, leading to the desired epoxide **198b**

in 75% yield (Table 12, entry 3). The analogous treatment of **140a** with HCOOOH gave rise to **198a** in 63% yield (Table 12, entry 4). Moreover, the epoxidation reaction was performed using the organic peracid *m*-CPBA, which is safe and easy to handle.

Table 12. Screening of epoxidation of 8-oxabicyclo[3.2.1]octanes **140a,b** with different reagents.



140a (R = Et); **140b** (R = ^{t}Bu) **198a** (R = Et); **198b** (R = ^{t}Bu)

entry	R	reagent	solvent	T [°C]	time [h]	product	yield [%]
1	^{t}Bu	TFAA, H_2O_2	CH_2Cl_2	0 to 25	22	**198b**	14[a]
2	^{t}Bu	HCOOH, H_2O_2[b]	HCOOH	25	17	**198b**	47
3	^{t}Bu	HCOOH, H_2O_2[c]	HCOOH	25	39	**198b**	75
4	Et	HCOOH, H_2O_2	HCOOH	0 to 25	32	**198a**	63
5	Et	*m*-CPBA[d]	CH_2Cl_2	25	144	**198a**	70[e]
6	Et	*m*-CPBA[d]	CH_2Cl_2	50	18	**198a**	89
7	^{t}Bu	*m*-CPBA[d]	CH_2Cl_2	50	20	**198b**	85

Reactions were performed on a 0.2 mmol scale. [a] 54% Conversion, isolated yield *via* column chromatography; [b] Basic workup; [c] Neutral workup; [d] 3.5 Equiv was used; [e] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard.

Epoxidation with 3.5 equivalents of *m*-CPBA furnished the desired epoxide **198a** in 70% yield, but a drawback was the long reaction time (Table 12, entry 5). Therefore, the reactions were next carried out at an elevated temperature of 50 °C, which indeed drastically reduced the reaction times and afforded the epoxides **198a,b** in excellent yields (Table 12, entry 6 and 7).

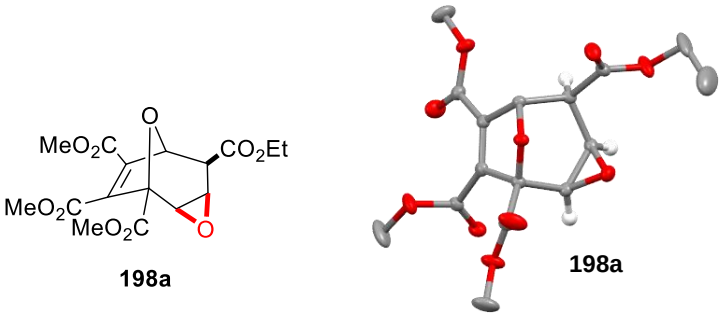
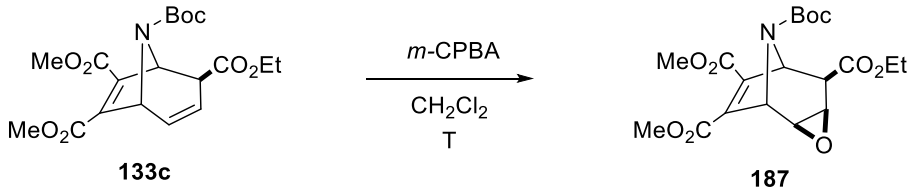


Figure 17. X-Ray structure of *exo*-epoxide **198a**.

The reactions selectively led to the *exo*-epoxides, since the convex side of the bicyclic seven-membered ring system has been sterically favored. *Exo*-epoxide **198a** was unambiguously assigned by X-ray crystallography (Figure 17). In all cases, the epoxidations proceeded regioselectively at the less substituted, electron-rich C3-C4 double bond.

Furthermore, the epoxidation of the C3-C4 double bond in 8-azabicyclo[3.2.1]octane **133c** was investigated using *m*-CPBA as epoxidation reagent (Table 13). After stirring for 47 h with 2.0 equivalents of *m*-CPBA, epoxide **187** was isolated in 49% yield as single diastereomer with 28% recovered starting material (Table 13, entry 1).

Table 13. Screening of epoxidation of 8-azabicyclo[3.2.1]octane **133c** with *m*-CPBA.



entry	*m*-CPBA [equiv]	T [°C]	time [h]	yield [%]
1	2.0	25	47	49[a]
2	5.4	25	47	80[b]
3	4.0	25	72	99
4	4.0	50	24	74[b]

Reactions were performed on a 0.3-0.8 mmol scale. [a] 72% Conversion, isolated yield *via* column chromatography; [b] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard.

Increasing the *m*-CPBA equivalents to 5.4 provided the desired epoxide **187** after 47 h in 80% yield (Table 13, entry 2). Excellent yields were obtained after 3 d using 4.0 equivalents of *m*-CPBA (Table 13, entry 3). To reduce the reaction time, the temperature was increased to 50 °C, which, however, lead to a decreased yield of 74% (Table 13, entry 4). The structure of the *exo*-epoxide **187** was confirmed by X-ray diffraction analysis (Figure 18).

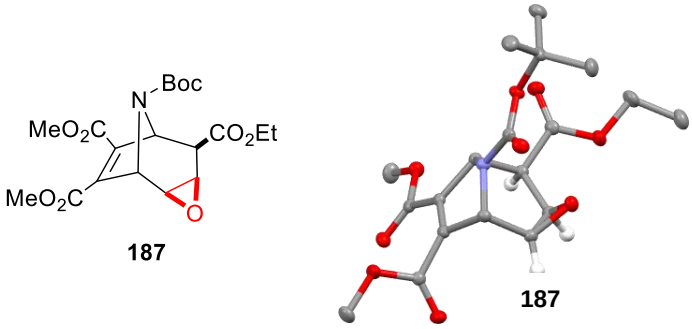


Figure 18. X-Ray structure of epoxide **187**.

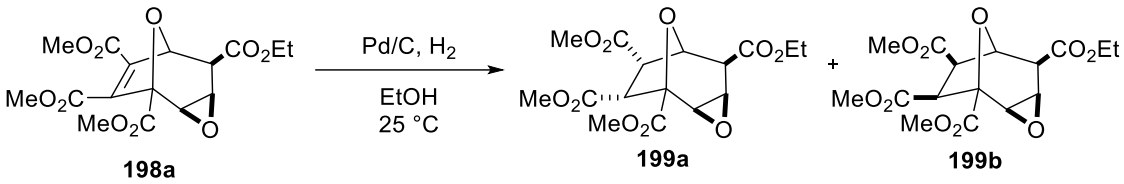
The stereoselective electrophilic epoxidation of C3-C4 double bond of 8-oxa- **140a,b** and 8-azabicyclo[3.2.1]octanes **133c** was successfully performed, leading to valuable intermediates **198a,b** and **187** for ring-opening reactions which will be discussed in the next chapter.

2.5 Epoxide ring-opening reactions – tropanoles

The prepared *exo*-epoxides **198a,b** and **187** are versatile building blocks to undergo selective ring-opening reactions. The reductive opening of epoxides is a powerful strategy to obtain the corresponding alcohols,[102] which are particularly attractive with regard to the synthesis of cocaine analogues and hydroxylated nortropanes. Catalytic hydrogenation over Pd/C is one method to open epoxides to alcohols, but a problem of regioselectivity may arise. In a first attempt, epoxide **198a** was hydrogenated under atmospheric pressure with Pd/C, however, only partial conversion was observed (Table 14, entry 1). To achieve full conversion, the pressure was increased to 10 bar (Table 14, entry 2). An inseparable diastereomeric mixture of hydrogenated *endo* cycloadduct **199a** and *exo* cycloadduct **199b** was formed after 1 h in 66% yield with a diastereomeric ratio of 1:5.3. The *endo* cycloadduct **199a** was received as the *major* product due to the hydrogenation occurring from the sterically less-hindered convex side. Since only hydrogenation of the double bond was observed, a pressure of 40 bar was

applied, however, the same results were observed (Table 14, entry 3), demonstrating the stability of the epoxide under these reductive conditions.

Table 14. Attempts for epoxide opening of **198a** *via* hydrogenolysis.



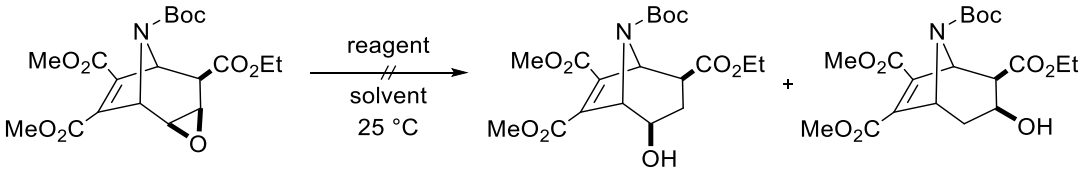
198a **199a** **199b**

entry	Pd/C [mol%]	time [h]	p(H_2) [bar]	*dr* 199a/199b	yield [%]
1	1.0	3	1	partial conversion	nd[a]
2	1.0	1	10	5.3:1	66[b]
3	10	22	40	3.6:1	71[c]

Reactions were performed on a 0.1-0.3 mmol scale; nd=not determined. [a] Estimated from TLC; [b] Isolated yield *via* column chromatography; [c] Determined *via* NMR using 2,2,4,4-tetra-chloroethane as an internal standard.

According to Shi *et al.,*[103] the epoxide opening of a similar structural unit was accomplished by reduction with $NaBH_3CN$ in the presence of $ZnCl_2$.

Table 15. Attempts for epoxide ring-opening of **187**.



187 **200a** **200b**

entry	reagent	solvent	time [h]	observation
1	$NaBH_3CN$ (3.0 equiv), $ZnCl_2$ (3.0 equiv)	CH_2Cl_2/THF (10:1)	22	nc
2	SmI_2 (4.0 equiv)	THF/H_2O (9:1)	0.5	crm

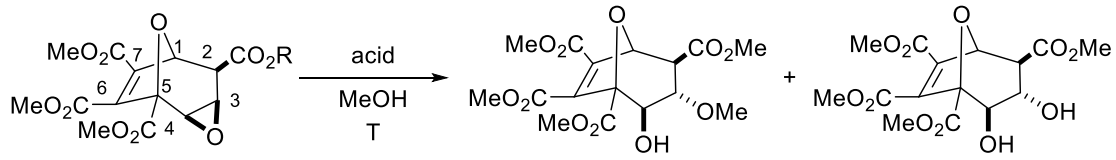
Reactions were performed on a 0.1-0.2 mmol scale, nc=no conversion, crm=complex reaction mixture.

Thus, the synthetic protocol was applied for nucleophilic epoxide opening of **187**. Unfortunately, the epoxide proved to be inert upon treatment with this mild reducing agent (Table 15, entry 1).

SmI_2 selectively reduces epoxides under mild reaction conditions in the presence of esters.[102] According to a literature procedure[104], SmI_2 in THF/H_2O was used to introduce the desired hydroxyl group, but regioselectivity could be a problem, since two possible isomers **200a** and **200b** can be formed. However, the reaction yielded further by-products besides the expected alcohols **200a,b** (Table 15, entry 2).

Another efficient method for the ring-opening of epoxides represents the addition of nucleophiles under acidic or basic conditions.[105] This strategy leads to 1,2 disubstituted products, which can form valuable new tropane analogues. First attempts for acidic epoxide opening were performed with cycloadduct **198b** and Amberlyst® in MeOH.[106]

Table 16. Acid-catalyzed epoxide opening of **198a,b** with MeOH.



198a (R = Et); **198b** (R = ^{t}Bu) **201** **202**

entry	R	acid	T [°C]	time [h]	observation	conversion [%]
1	^{t}Bu	Amberlyst®	25	17	nc[a]	0
2	^{t}Bu	Amberlyst®	70	5.5	hydrolysis of ^{t}Bu	nd
3	Et	H_2SO_4	25	19	nc[a]	0
4	Et	H_2SO_4	70	2	**201** (25%), **202** (9%)[b]	100[c]
5	Et	H_2SO_4	70	38	**201** (37%), **202** (13%)[d]	100

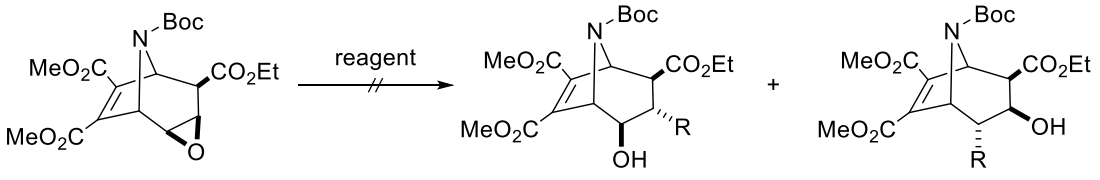
Reactions were performed on a 0.2-0.3 mmol scale; nd=not determined; nc=no conversion. [a] Estimated from TLC; [b] Isolated yield; [c] 14% Transesterification of starting material; [d] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard.

At 25 °C no conversion of the starting material **198b** was observed, whereas at an elevated temperature of 70 °C only partial hydrolysis of the *tert*-butyl ester occurred

without formation of any desired ring-opening product (Table 16, entry 1 and 2). Therefore, the starting material was changed to **198a** bearing a less acid labile ethyl ester instead of *tert*-butyl ester. When the reaction was catalyzed by H_2SO_4 at 25 °C only starting material was recovered (Table 16, entry 3). Applying higher temperature gave 1,2 disubstituted cycloadduct **201** and diol **202** in 25% and 9% yield, respectively, with transesterification of the respective ethyl- to the methyl ester occurring in both cases (Table 16, entry 4). Prolonging the reaction time to 38 h led to full conversion of starting material **198a** without significantly enhancing the desired product formation (Table 16, entry 5). In summary, higher temperatures were required for acid-catalyzed epoxide opening, which unfortunately led to hydrolysis of the ester at C2 position. Therefore, ring-opening product **201** was obtained in poor yields and moreover, diol **202** was formed. Nevertheless, it was noteworthy that the opening by nucleophilic attack occurred selectively at the C3 position adjacent to the ester and no evidence for nucleophilic attack at the C4 position was observed. The selectivity is probably achieved by steric hindrance of the rigid bicyclic scaffold. This regioselective nucleophilic ring-opening at C3 position is in accordance with the product outcome of the halohydrin formation which is described in chapter 2.6.

Since the previous chapters have already shown that the reactivity of 8-oxa- to 8-azabicyclo[3.2.1]octane can vary substantially, the acid-catalyzed opening of **187** in MeOH was performed in a next attempt. Unfortunately, the acidic conditions only led to the deprotection of the *N*-Boc group (Table 17, entry 1).

Table 17. Attempts for acid-catalyzed epoxide opening of **187**



187

203a (R = Br); **204a** (R = OMe) **203b** (R = Br); **204b** (R = OMe)

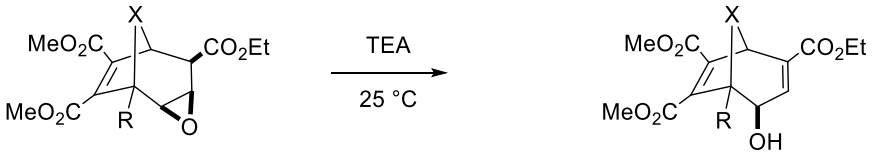
entry	reagent	R	solvent	T [°C]	time [h]	observation
1	H_2SO_4 (1.0 equiv)	OMe	MeOH	25 to 60	1.5 to 2.5	*N*-Boc deprotection
2	HBr (49 equiv)	Br	-	25	2	decomposition

Reactions were performed on a 0.1 mmol scale.

Baylis and Thomas *et al.* reported a selective epoxide ring-opening of a similar structure to 8-azabicyclo[3.2.1]octane **187** using HBr.[107] However, treatment of **187** with HBr led to decomposition of the starting material, which could be attributed to the different nitrogen protecting group compared to Baylis and Thomas (*N*-CO_2Me) (Table 17, entry 2).

In the following, facile deprotonation at C2 position of the cycloadduct with base was envisaged to induce selective epoxide ring-opening. The isomerization of the C3-C4 double bond of 8-oxabicyclo[3.2.1]octane **140a,b** and 8-azabicyclo[3.2.1]octane **133a,c** occurred with TEA in quantitative yield due to the acidic proton at C2 position (see chapter 2.1, table 7). Therefore, in a first attempt the epoxide opening of **187** was performed with TEA in CH_2Cl_2, however, only starting material was recovered (Table 18, entry 1). Next, the solvent was changed to THF/H_2O, resulting in the desired allylic alcohol **205** after 24 h in 33% yield (Table 18, entry 2). Reducing the reaction time to 17 h gave allylic alcohol **205** in 62% yield (Table 18, entry 3).

Table 18. Base-induced epoxide opening of **187** or **198a** with TEA.



187 (X = NBoc, R = H); **198a** (X = O, R = CO_2Me) **205** (X = NBoc, R = H); **206** (X = O, R = CO_2Me)

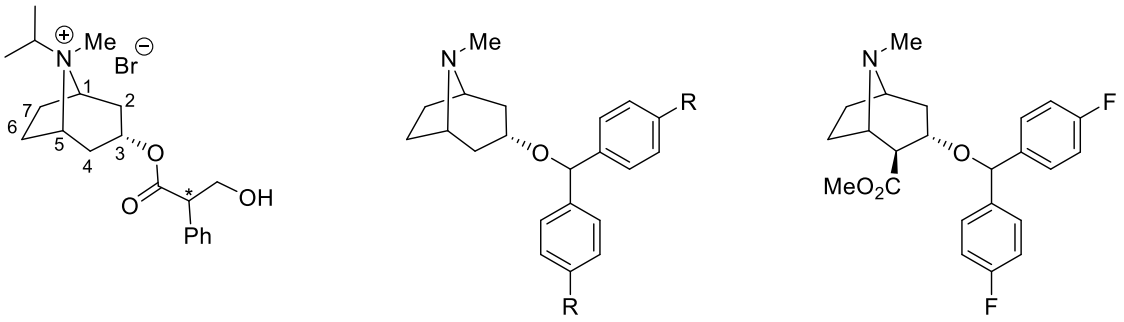
entry	X	R	solvent	time [h]	product	yield [%]
1	*N*-Boc	H	CH_2Cl_2	24	**205**	nc[a]
2	*N*-Boc	H	THF/H_2O	24	**205**	33[b]
3	*N*-Boc	H	THF/H_2O	17	**205**	62[c]
4[d]	*N*-Boc	H	-	-	**205**	77[b]
5[d]	O	CO_2Me	-	-	**206**	64[b]

Reactions were performed on a 0.1-0.5 mmol scale; no conversion=nc. [a] Determined by ^{1}H NMR analysis of the crude mixture; [b] Isolated yield *via* column chromatography; [c] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard; [d] Flash column chromatography, 1% TEA.

Notably, the epoxide opening was successfully achieved by simple flash column chromatography using 1% TEA, allowing purification during the reaction, and the allylic alcohol **205** was obtained in 77% yield as single diastereomer (Table 18, entry 4). This reaction was also successfully applied to the 8-oxabicyclo[3.2.1]octane **198a** (Table 18, entry 5). The synthesized allylic alcohols **205**-**206** are versatile chiral building blocks for the synthesis of various compounds with significant biological relevance. As already described at the beginning of this chapter, **205** is a promising derivative since the *exo* hydroxyl group was selectively introduced at C4 position (enantiomerically pure cycloadducts: C4 or C2 position accessible) as in Bao Gong Teng A (**153**), demonstrating the value of the developed synthetic protocol (see also chapter 2.2, figure 12). In addition, the allylic alcohol **205** allows further diversifications, for example to polyhydroxylated nortropanes *via* subsequent dihydroxylation. The oxidation of the alcohol in **206** to tropinones or oxidation/subsequent opening of the ether bridge of **206** to tropones/tropolones (see chapter 2.4, figure 16) could lead to further scaffolds found in natural products and medicinal active compounds.

2.6 Halohydrin formation – tropine analogues

Neurologically active natural products such as atropine (**6**) or scopolamine (**8**) bearing *endo* substituents at C3 position are lead compounds in drug design (see introduction, Figure 2). Ipratropium bromide (**13**) is a derivative of atropine which is commercially sold as Atrovent® to treat symptoms of chronic obstructive pulmonary disease (COPD) and asthma (Figure 19).[108] This hydrophilic atropine analogue **13** is not able to pass the blood-brain-barrier due to the attached quaternary amine, therefore, reduced side effects occur by blocking of muscarinic receptors in contrast to atropine (**6**).[7c] Further medications with new tropane analogues have been developed like anti-Parkinsonian benztropine (**17**, trade name: Cogentin®).[109] The flourosubstituted phenyl groups in the benztropine derivative **207** improved the dopamine transporter affinity. Diflouropine (**208**, O-620), a benztropine analogue reported by Meltzer *et al.* proved to be a potent and selective dopamine reuptake inhibitor bearing an additional 2-carbomethoxy group. Remarkably, **208** represents a unique example among the tropane-derived dopamine reuptake inhibitors because the *S*-enantiomer is the potent and selective ligand for the DAT, unlike all other tropanes, e.g., the *S*-enantiomer of natural (*R*)-(−)-cocaine, which is inactive.[8a,84]



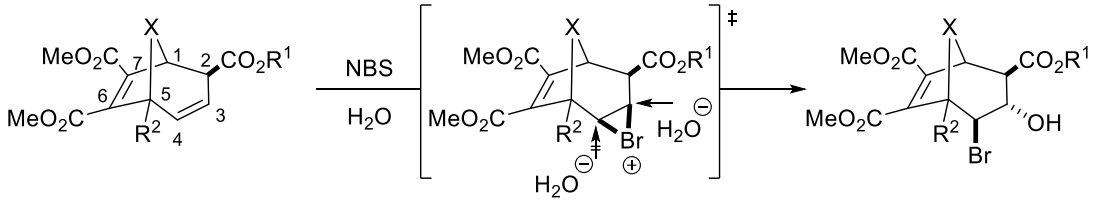
ipratropiumbromide (**13**)
Atrovent®

benztropine (**17**, R = H), Cogentin®
4,4-difluorobenztropine (**207**, R = F)

difluoropine (**208**)
O-620

Figure 19. Biologically active synthetic derivatives of tropanes containing *endo* substituents at C3.

3-Tropine (*cf* introduction, Figure 2, **3**) is a key building block in the synthesis of pharmacologically important tropane alkaloids, especially to those with substituents at C3 position, as described above. Therefore, a stereospecific addition of NBS to the C3-C4 double bond in 8-aza- and 8-oxabicyclo[3.2.1]octanes **154** was an envisaged route to access 3-tropine analogues **210** (Scheme 31), which may also be a potential precursor for novel cocaine analogues. It was assumed in accordance with the diastereoselective epoxidation, the bromonium ion **209** is initially formed from the sterically favoured convex side, followed by nucleophilic attack from the inner, concave side at C3 position, giving rise to **210**, since this selectivity has already been observed for acid-catalyzed epoxide ring-opening with MeOH (Table 16).



154 (X = O; NBoc)

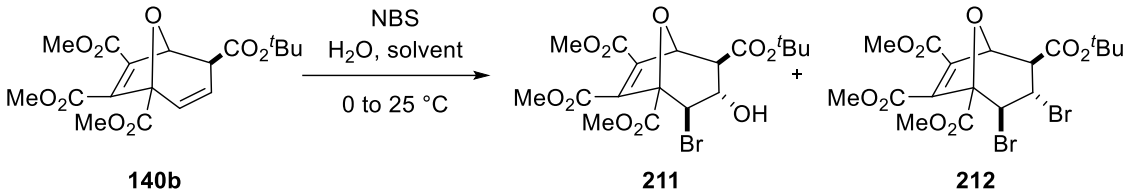
209 (X = O; NBoc)

210 (X = O; NBoc)

Scheme 31. Synthesis of tropine analogues **210** *via* halohydrin formation of **154**.

The halohydrin formation of 8-oxabicyclo[3.2.1]octane **140b** was screened by using different solvents, NBS concentrations and reaction temperatures (Table 19). The first attempt was performed with cycloadduct **140b** and NBS in THF/H_2O (1:1) at 25 °C (Table 19, entry 1). The desired halohydrin **211** and a dibromo-substituted product **212** were obtained after 44 h in 20% and 8% yield, respectively, with 43% recovered starting material.

Table 19. Halohydrin formation of 8-oxabicyclo[3.2.1]octane **140b** with NBS.



140b **211** **212**

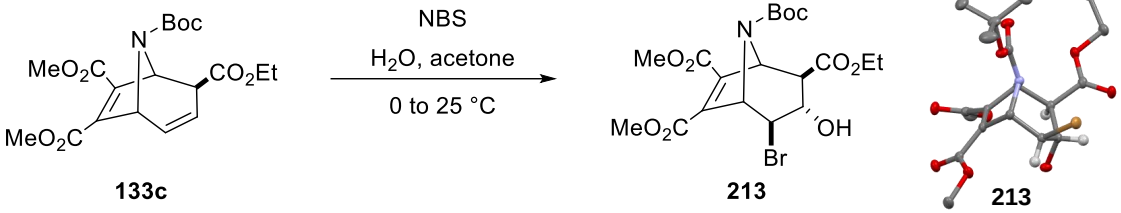
entry	NBS [equiv]	solvent	time	yield 211[%]	yield 212 [%]	conversion [%]
1	1.1	THF	44 h	20[a]	8[a]	57
2[b]	1.1	THF	44 h	5[a]	4[a]	82
3	3.0	THF	44 h	22[a]	19[a]	93
4	3.0	acetone	44 h	23[c]	-	57
5	3.0	acetone	7 d	78[d]	-	100

Reactions were performed on a 0.3-0.5 mmol scale. [a] Isolated yield; [b] 50 °C; [c] Isolated yield, *ratio* crude ^{1}H NMR **140b**:**211**=1.1:1; [d] Extraction with diethyl ether to remove succinimide.

Heating to 50 °C for 2 d did not improve the yield of halohydrin **211** (Table 19, entry 2). A higher conversion of cycloadduct **140b** was achieved with 3.0 equivalents of NBS at 25 °C (Table 19, entry 3) but still with poor yield and selectivity. These results indicated that the halohydrin was not stable under the applied reaction conditions or during purification by column chromatography. Shimizu *et al.* reported that THF could be incompatible with NBS, which may lead to undesired side reactions.[110] To optimize the halohydrin formation, the solvent was changed to acetone/H_2O. Performing the reaction in acetone/H_2O furnished the product in 23% yield with 43% recovered starting material (Table 19, entry 4). Notably, the formation of the bromine addition by-product **212** was completely prevented in acetone/H_2O. Comparison of the crude ^{1}H NMR with a *ratio* of **140b**:**211**=1.1:1 to the isolated yield (**140b**:**211**=1.9:1) indicated that the compound **211** was not stable on column chromatography. Full conversion was achieved with a prolonged reaction time of 7 d, providing **211** in 78% yield as single diastereomer (Table 19, entry 5).

Next, the halohydrin formation was examined with 8-azabicyclo[3.2.1]octane **133c** in acetone/H_2O using different amounts of NBS to afford halohydrin **213** (Table 20).

Table 20. Halohydrin formation of 8-azabicyclo[3.2.1]octane **133c** with NBS.



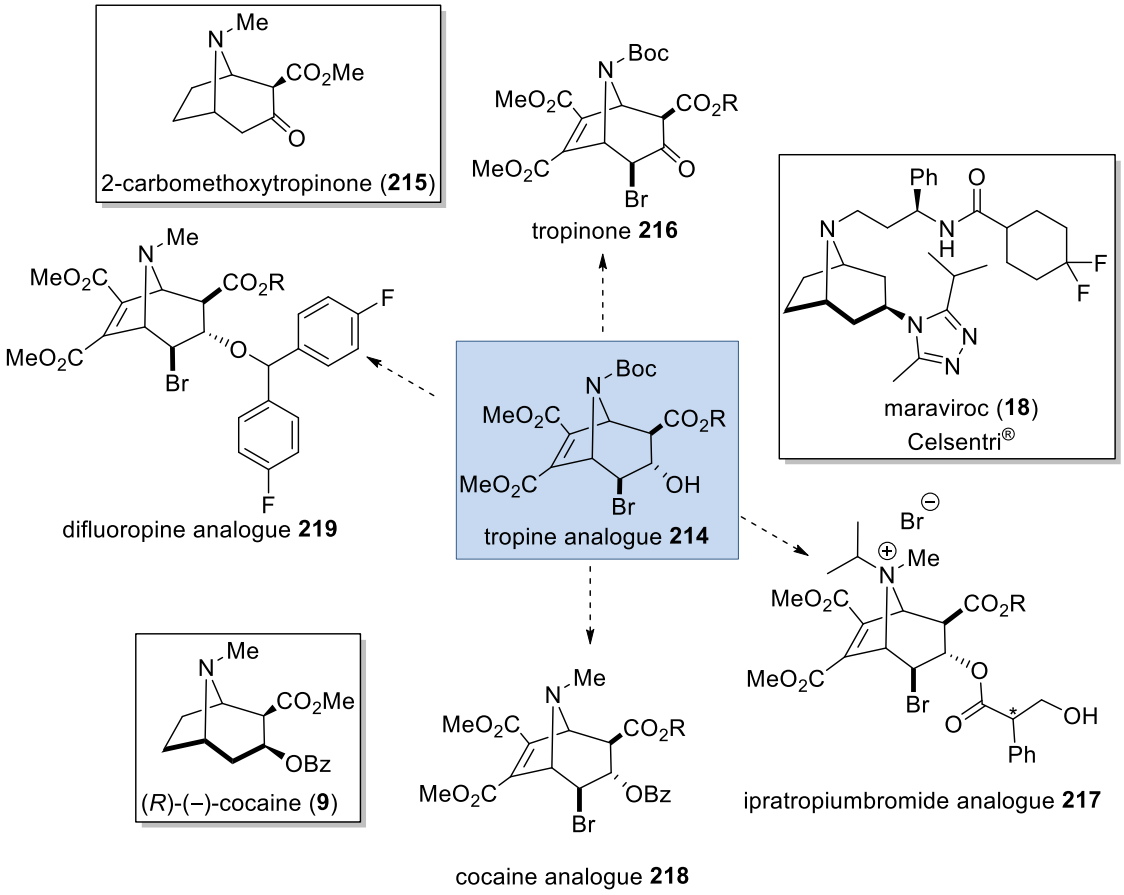
133c **213** **213**

entry	NBS [equiv]	time [h]	yield [%]	conversion [%]
1[a]	2.7	48	34[b]	74
2[a]	4.0	48	64	100
3[c]	4.0	48	87[d]	100
4[c]	2.0	24	82	100

[a] 0.3 mmol scale; [b] Isolated yield, *ratio* crude **133c**:**213**=1:2.3; [c] 1.6 mmol Scale; [d] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard.

In a first approach, the desired halohydrin **213** was prepared using 2.7 equivalents of NBS, and purified by column chromatography, but as observed with the previous halohydrin **211**, the cycloadduct **213** was unstable, which was confirmed by the low isolated yield of 34% with 26% recovered starting material (Table 20, entry 1) compared to the *ratio* of **133c**:**213**=1:2.3 of crude ^{1}H NMR. In a second attempt, the reaction was conducted with 4.0 equivalents of NBS and the halohydrin **213** was obtained in 64% yield (Table 20, entry 2). Upscaling of the reaction improved the yield (Table 20, entry 3) and finally 2.0 equivalents led to the desired product **213** after only 24 h in 83% yield (Table 20, entry 4). The absolute stereochemistry of the halohydrin **213** was confirmed by X-ray crystallography (Table 20).

The established halohydrin formation of **140b** as well as **133c** generated two new stereocenters in one step and proceeded completely diastereoselectively, since the convex side of the bicyclic seven-membered ring is sterically favored, and regioselectively at C3 position probably due to steric reasons of the rigid bicyclic scaffold.



Scheme 32. Tropine analogue **214** as a potential precursor for various transformations.

As illustrated in Scheme 32, tropine analogue **214** is a potential precursor for a lot of further transformations. The alcohol group in **214** could be oxidized to 3-tropinone analogue **216,** a central structural unit, as demonstrated with 2-carbomethoxytropinone (**215**, CMT), a commonly used intermediate in numerous syntheses of tropane analogues. In addition, 3-tropinone analogues are also used for the synthesis of maraviroc (**18**), an anti-HIV drug.[111]. Moreover, the synthesis of novel ipratropiumbromide analogue **217** or difluoropine analogue **219** bearing methyl esters at C2, C6, C7 positions may have relevance for new SAR studies. Since diflouropine (**208**, O-620), as described above, a potent and selective dopamine reuptake inhibitor with additional anticholinergic and antihistaminergic effects, bears a 2-carbomethoxy group, halohydrin **214** with the ester group at C2 position has the appropriate functionalities for conversion into new potentially active derivatives. In this thesis, the focus was on the synthesis of the core structure of cocaine (**9**) from halohydrin **213** (Table 12), including the introduction of the benzoate group at C3 and replacement of the *N*-Boc to *N*-Me protecting group, as described in the next chapter.

2.7 Synthesis of C6/C7 cocaine analogues

In this chapter, the aim was to access the desired cocaine pharmacophore (Figure 20) by functional group transformations of the obtained halohydrins. On the basis of SAR data, a pharmacophore model for (*R*)-(–)-cocaine (**9**) with DAT was proposed by Carroll *et al.*[6c] Cocaine ligands require a basic amino group most prominently *N*-Me for electrostatic or hydrogen-bonding. At the C2 position the presence of at least one or two additional hydrogen bond acceptor sites of the two oxygens of the 2β-carbomethoxy group of cocaine is crucial. Moreover, a hydrophobic pocket accommodates benzoyl as well as phenyl groups at C3 position is essential for cocaine binding.[6c]

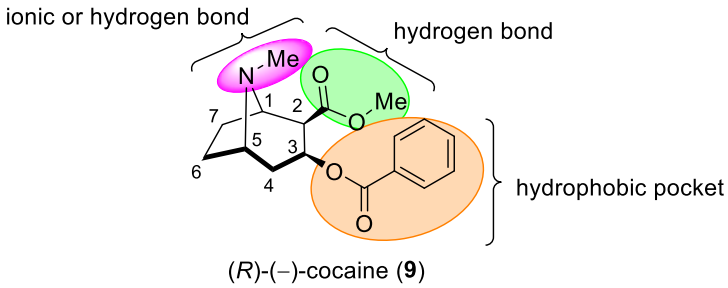
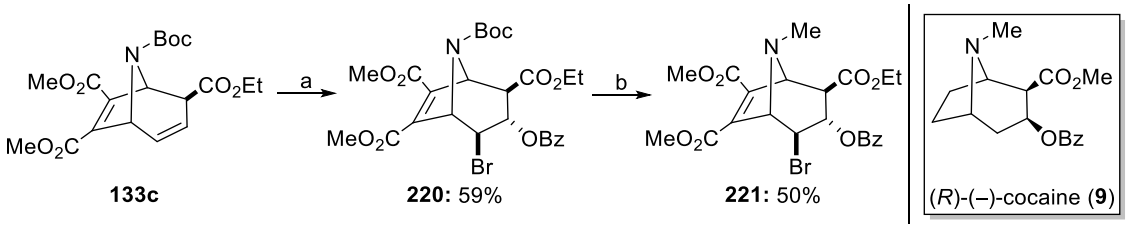


Figure 20. Schematic representation of putative interactions of (*R*)-(–)-cocaine (**9**) with DAT.[6c]

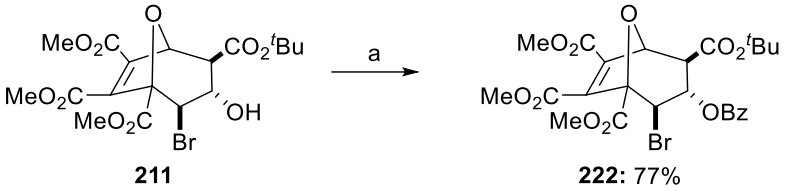
Therefore, benzoylation reaction was performed to introduce the benzoyl functionality, which is important for the biological activity of the natural product (*R*)-(–)-cocaine (**9**) due to the aromatic π-system.[6c] Since the purification after halohydrin formation was challenging, the halohydrins were subsequently converted into the benzoates. Therefore, cycloadduct **133c** was transferred to halohydrin, followed by treatment with benzoyl chloride, DMAP and TEA to obtain benzoate **220** in 59% yield over two steps (Scheme 33).



133c **220:** 59% **221:** 50%

Scheme 33. Synthesis of cocaine analogue **221**. Conditions: a) (*i*) NBS (2.0 equiv), acetone/H_2O (3:1 v/v), 0 to 25 °C, 21 h; (*ii*) BzCl (1.5 equiv), DMAP (0.5 equiv), TEA (5.0 equiv), CH_2Cl_2, 25 °C, 8 h, 59%; b) *(i)* TFA (33 equiv), CH_2Cl_2, 25 °C, 1.5 h; (*ii*) 37% aq CH_2O (6.0 equiv), $NaBH_3CN$ (3.0 equiv), MeCN, 25 °C, 1 h, 50%.

Finally, deprotection of the *N*-Boc protecting group of **220** with TFA, followed by reductive amination with $NaBH_3CN$[22h] demonstrated the exchange of the *N*-Boc to *N*-Me protecting group as typically found in natural products, especially in cocaine.
In summary, a successful synthetic strategy has been established for the preparation of a novel, highly substituted cocaine analogue **221** containing all relevant functionalities of cocaine (**9**) with additional methyl esters at C6,C7, which are still unknown at these positions due to their challenging introduction, but are generally found prominently in tropane alkaloids. Postfunctionalizations of the C6,C7 positions are demonstrated in chapter 3.1 using compound **133a**.



211 **222:** 77%

Scheme 34. Synthesis of oxa-cocaine analogue **222**. Conditions: a) BzCl (1.5 equiv), DMAP (0.5 equiv), TEA (2.0 equiv), CH_2Cl_2, 0 to 25 °C, 24 h, 77%.

Further studies of the cocaine pharmacophore showed that structural mimics of cocaine such as 8-oxabicyclo[3.2.1]octanes possess also promising dopamine transporter inhibitor properties and thus the nitrogen bridge head of cocaine ligands is not essential for its action.[11] Therefore, in analogous way, benzoylation of halohydrin **211** was carried out to access benzoate **222** in 77% yield (Scheme 34). This synthesis route established a novel C6,C7 substituted oxa-cocaine analogue **222**. Moreover, the bromo analogues are valuable precursors for further diversification *via* transformations of the bromine (see chapter 2.8) to synthesize potential biologically active compounds**.**

2.8 Dehalogenation reactions – isoquinuclidine and 6-azatricyclo[3.2.1.$0^{2,7}$]-octanes

The 2-azabicyclo[2.2.2]octane skeleton **223** (isoquinuclidines) is prominently found in many natural and pharmaceutical products: a representative example is ibogaine (**224**), a natural indole alkaloid found in *Tabernanthe iboga,*[112] being an important lead structure in the development of analgesia with anti-addictive properties (Figure 21).[113] Chemical modifications of ibogaine (**224**) have already led to the discovery of very potent analogues with distinct activity profiles. (–)-18-Methoxycoronaridine (**225**, 18-MC), an

iboga alkaloid congener, was found to be a selective antagonist of α3β4 nicotinic receptors reported by Glick *et al*.[114]

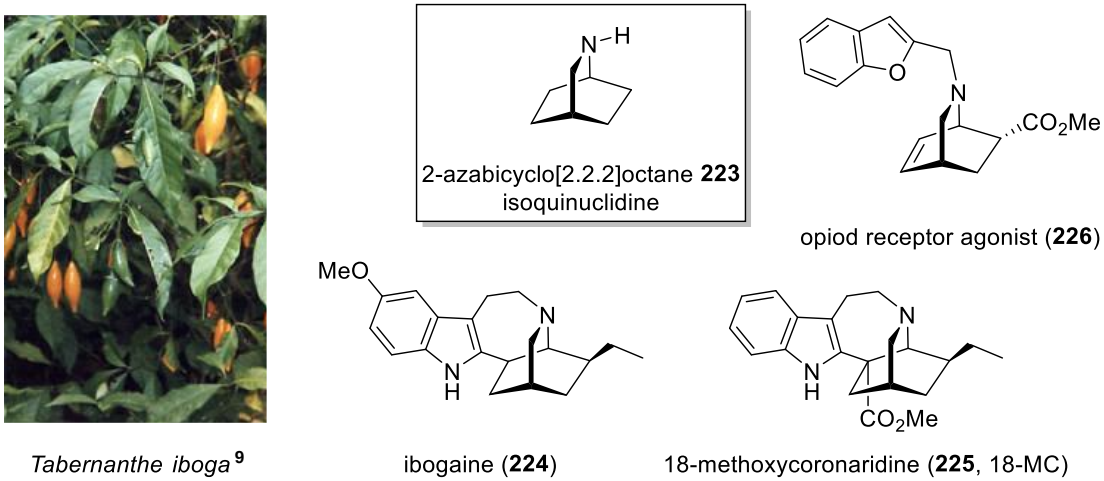
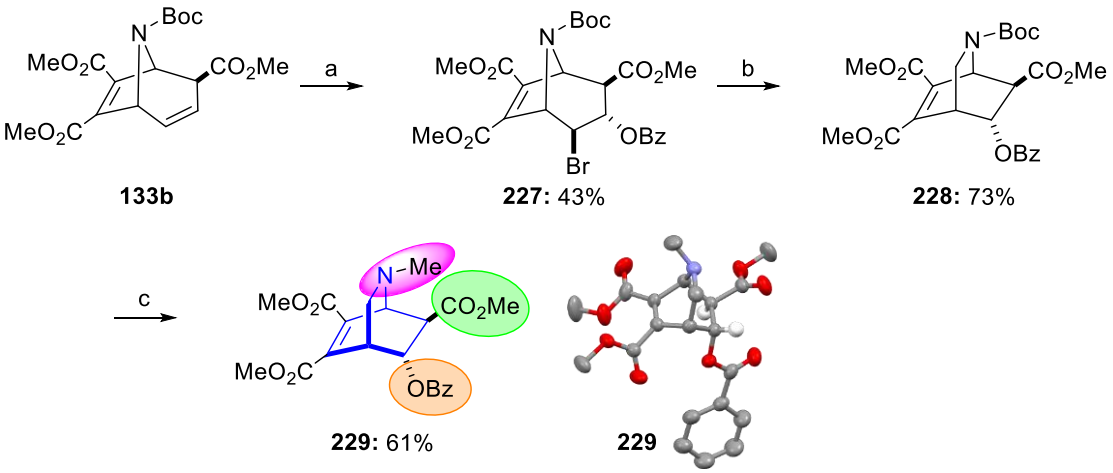


Figure 21. Structure of isoquinuclidines.

Replacing the indole ring with a benzofuran moiety resulted in the ibogaine analogue **226**, a dual μ-opioid and κ-opioid receptor agonist.[115] The development of enantioselective routes to isoquinuclidines **223** has therefore attracted considerable interest however, only few asymmetric syntheses to functionalized isoquinuclidines have been reported.[113d,116]

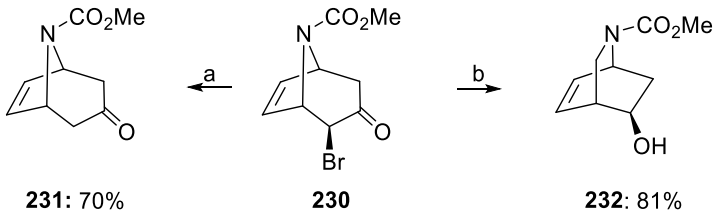
Inspired by a radical homoallylic rearrangement of 8-azabicyclo[3.2.1]octane reported by Hodgson *et al.*[116h], the synthesis of isoquinuclidine (2-azabicyclo[2.2.2]octane) was envisaged by applying radical conditions to the novel radical precursor **227**. The latter was readily rearranged to isoquinuclidine **228** by treatment with AIBN/Bu_3SnH upon which a homoallylic radical rearrangement to **228** took place (Scheme 35). Removing *N*-Boc protecting group by addition of TFA, followed by reductive amination with $NaBH_3CN$ yielded isoquinuclidine derivative **229** in 61% yield, which was unambiguously assigned by X-ray crystallography.

[9] https://commons.wikimedia.org/w/index.php?curid=358702; author: CiXeL, 2005 (accessed on 08.06.2021).



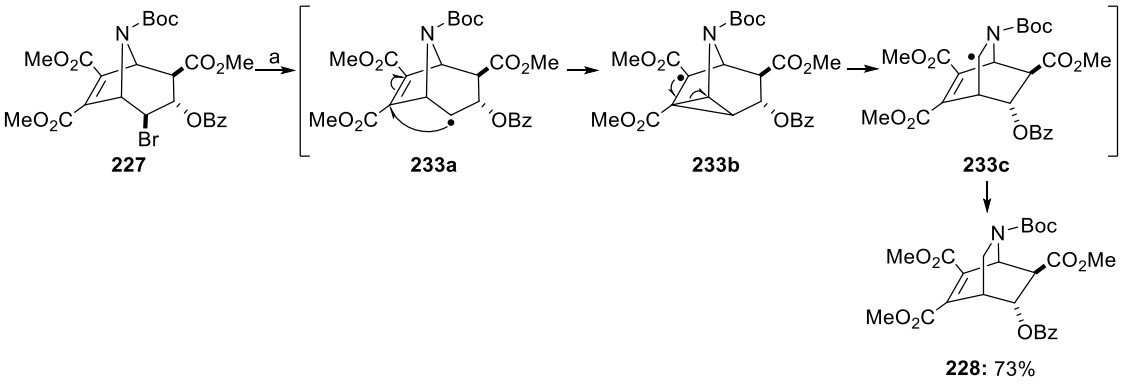
Scheme 35. Isoquinuclidine synthesis by homoallylic radical rearrangement of **227**. Conditions: a) *(i)* NBS (4.0 equiv), acetone/H_2O (4:1 v/v), 0 to 25 °C, 3 d; *(ii)* BzCl (1.5 equiv), DMAP (0.5 equiv), TEA (5.0 equiv), CH_2Cl_2, 25 °C, 15 h, 43%; b) azobisisobutyronitrile (AIBN) (0.1 equiv), Bu_3SnH (1.6 equiv), benzene, reflux, 5 h, 73%; c) *(i)* TFA (33 equiv), CH_2Cl_2, 25 °C, 1 h, *(ii)* 37% aq CH_2O (11 equiv), $NaBH_3CN$ (8.2 equiv), MeCN, 25 °C, 1.5 h, 61%.

Hodgson *et al*. reported a radical rearrangement of 8-azabicyclo[3.2.1]octane **230** under similar conditions as in the previously described reaction (Scheme 36).[116h,117] Remarkably, treatment of **230** with AIBN/Bu_3SnH did not result in the planned isoquinuclidine subunit, but dehalogenation to **231** occurred. It was suggested that the generated radical species was capto-stabilized by the α-keto group. Thus, reduction of the keto group in α-bromoketone **230** to a hydroxyl group was carried out, and indeed, subsequent radical rearrangement furnished isoquinuclidine **232**.



Scheme 36. Synthesis of isoquinuclidine **232** *via* homoallylic radical rearrangement by Hodgson *et al*. Conditions: a) AIBN (0.1 equiv), Bu_3SnH (1.5 equiv), toluene, reflux, 2 h, 70%; b) $NaBH_4$, EtOH, -30 to 25 °C, then $NaBH_4$, 15% Bu_3SnH, AIBN (0.1 equiv), EtOH, reflux, 81%.[116h]

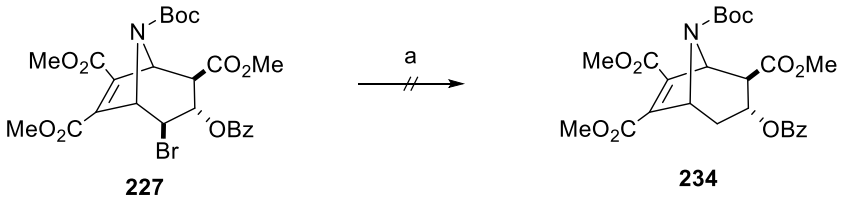
Hodgson *et al.* proposed a mechanism for the radical rearrangement of 8-azabicyclo[3.2.1]octanes to isoquinuclidines (2-azabicyclo[2.2.2]octanes),[116h] which is illustrated with cycloadduct **227** in scheme 37. First, radical **233a** was generated, which then cyclized transannular to **233b**, followed by ring-opening to α-nitrogen stabilized radical **233c**. Finally, isoquinuclidine **228** was obtained in 73% yield.



Scheme 37. Mechanism of homoallylic radical rearrangement of **227**. Conditions: a) AIBN (0.1 equiv), Bu_3SnH (1.6 equiv), benzene, reflux, 5 h, 73%.

In summary, a complex isoquinuclidine **229** bearing substituents like cocaine was prepared by a radical rearrangement (Scheme 35), resulting in a combination of isoquinuclidine scaffold and cocaine substituents (Figure 20). Compared to the biological active isoquinuclidines depicted in figure 21, the compound **228** also possesses promising carbomethoxy groups and cleavage of Boc group to **229** was already successfully demonstrated. Various isoquinuclidine derivatives could be synthesized enantiomerically pure starting from readily available enantiopure cyclopropanated pyrroles in the future. Therefore, the developed protocol is particularly interesting, since asymmetric preparation of novel isoquinuclidine derivatives is especially challenging and still limited as mentioned above. Moreover, Hodgson *et al.* has demonstrated that the adjacent substituent of the bromide has a high impact on the product outcome of the radical reaction, therefore, the oxidation of the alcohol to the ketone is desirable to obtain dehalogenation product without rearrangement.

A method for the removal of halogen was investigated using a metal catalyst under mild reaction conditions. In a first attempt, $PdCl_2$ has been employed as a homogenous catalyst with Et_3SiH[118] for the dehalogenation of alkyl bromide **227** (Scheme 38), however, a complex mixture was formed.

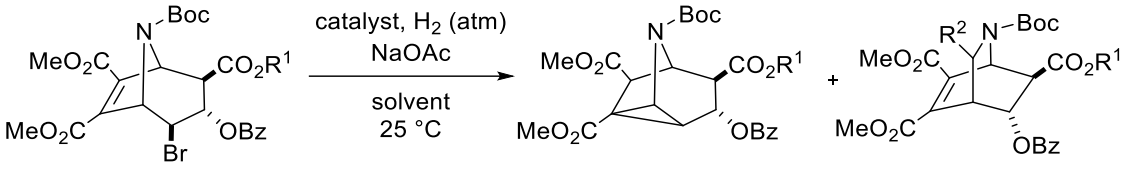


Scheme 38. Dehalogenation of **227** with $PdCl_2$ and Et_3SiH. Conditions: a) $PdCl_2$ (5 mol%), Et_3SiH (2.6 equiv), Et_2O, 25 °C, 3 h.

Pd/C has been used as an efficient heterogenous catalyst for reductive dehalogenation with H_2, while Raney nickel is often deactivated by the release of halide ions. The reactions were carried out in the presence of a base to neutralize haloacids formed during dehalogenation, since halogens and hydrogen ions can poison metallic catalysts. Furthermore, it should be noted that the rate of catalytic hydrogenolysis is generally slower for alkyl halides than for aryl halides.[119]

Dehalogenation of the cycloadduct **227** with Pd/C and NaOAc at ambient pressure did not furnish the expected dehalogenation product. Instead, 6-azatricyclo[3.2.1.$0^{2,7}$]octane **235a** was identified as the *major* product by 2D NMR analysis, accompanied by the occurrence of an isoquinuclidine side product **236a** isolated in 10% yield (Table 21, entry 1). The side product **236a** was formed by a nucleophilic attack of the solvent EtOH, resulting in the isoquinuclidine structural motif already formed by the radical rearrangement described above. Due to the same retention value of product **235a** and starting material **227**, full conversion of the reaction was difficult to detect. Therefore, the reaction time was reduced to 3 h, however, full conversion of the starting material **227** was not observed. It is notable that the selectivity was improved (*ratio* of 11:1) and the 6-azatricyclo[3.2.1.$0^{2,7}$]octane **235a** was isolated in 64% yield (Table 21, entry 2). Performing the reaction for 4 h resulted in full conversion, however, the amount of by-product had been increased (Table 21, entry 3). To examine the influence of the base, the dehalogenation was carried out without NaOAc, which resulted in no conversion of the cycloadduct **227**, clearly indicating the importance of base to avoid deactivation of the catalyst (Table 21, entry 4). To exclude the rearrangement to azatricyclooctane **235a** without H_2, it was omitted in the next reaction, but only starting material **227** was recovered (Table 21, entry 5). Hydrogenation at 40 bar in an autoclave afforded comparable results to those obtained at ambient pressure (Table 21, entry 6). Notably, the change of cycloadduct **227** to **220** gave **235b**/**236b** in a *ratio* of 16:1, demonstrating that selectivity was improved due to the sterically demanding ethyl ester instead of methyl ester at the C2 position of the cycloadduct **235a** (Table 21, entry 7). A screening of different solvents was neither successful with EA nor with Et_2O, resulting in a complex mixture (Table 21, entry 8 and 9). Finally, dehalogenation of **227** was carried out with Raney Ni in MeOH to afford 6-azatricyclo[3.2.1.$0^{2,7}$]octane **235a** in 63% yield and isoquinuclidine **236c** bearing a methoxy group in 14% yield (Table 21, entry 10). The *ratio* of product to by-product was poor compared to the previous results, suggesting that the chosen solvent also had an influence, MeOH is sterically less demanding than EtOH and therefore can attack more easily as a nucleophile.

Table 21. Reductive dehalogenation reactions of 8-azabicyclo[3.2.1]octane **227** or **220**.



227 (R^1 = Me)
220 (R^1 = Et)

235a (R^1 = Me)
235b (R^1 = Et)

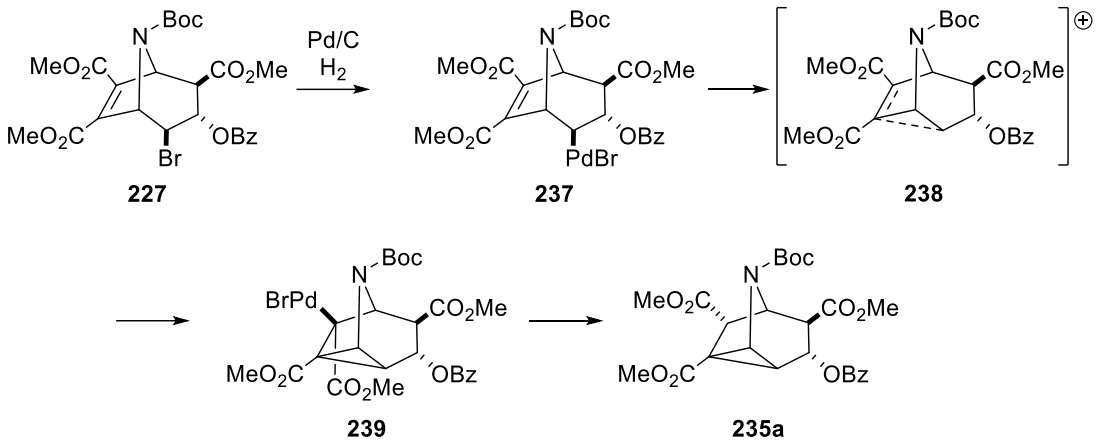
236a (R^1 = Me, R^2 = OEt)
236b (R^1 = Et, R^2 = OEt)
236c (R^1 = Me, R^2 = OMe)

entry	R^1	solvent	catalyst	time [h]	*ratio* 235:236[a]	235 [%]	R^2	236 [%]
1	Me	EtOH	Pd/C[b]	8	8.5:1	76	OEt	10
2	Me	EtOH	Pd/C [b]	3	11:1[c]	64	OEt	-
3	Me	EtOH	Pd/C [b]	4	5.6:1	80	OEt	14
4[d]	Me	EtOH	Pd/C [e]	3	nc	-	OEt	-
5[f]	Me	EtOH	Pd/C [e]	3	nc	-	OEt	-
6[g]	Me	EtOH	Pd/C [e]	2.5	6:1	nd	OEt	nd
7[h]	Et	EtOH	Pd/C [b]	4.5	16:1	66	OEt	4
8	Me	EA	Pd/C [e]	8	crm	-	OEt	-
9	Me	Et_2O	Pd/C [e]	1.5	crm	-	OEt	-
10[i]	Me	MeOH	Raney Ni	2.5	4.4:1	63	OMe	14

Reactions were performed on a 0.1-0.6 mmol scale. nc=no conversion; nd=not determined; crm=complex reaction mixture. [a] Determined by ^{1}H NMR analysis of the crude mixture; [b] 10 mol%; [c] *ratio* **227**:**236**=1:7.9 determined by analysis of crude ^{1}H NMR; [d] Without NaOAc; [e] 20 mol%; [f] Without hydrogen; [g] p(H_2) = 40 Bar; [h] 1 mmol; [i] Pyridine was used instead of NaOAc.

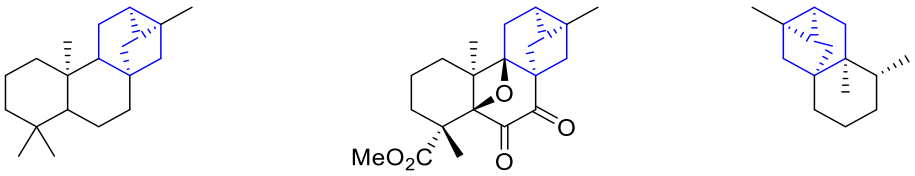
A proposed mechanism for homoallylic rearrangement includes C-Br bond activation by Pd/C (**237**), followed by formation of a non-classical ion **238** as a cationic intermediate (Scheme 39). Finally, dehalogenation with Pd/C and H_2 afforded azatricycle **235a**. Using sterically bulky alcohols (e.g., 2-propanol) as solvents and sterically demanding substituents at C2 position of the cycloadduct, such as ethyl or *tert*-butyl ester, formation of the by-product **236** could be suppressed in future work. This homoallylic

rearrangement induced *via* Pd/C activation serves as a new strategy towards azatricyclooctanes **235.**



Scheme 39. Proposed mechanism of homoallylic rearrangement of **227** to azatricyclooctane **235a**.

Homoallylic rearrangements as described above have already been observed in norbornene systems leading to nortricyclenes.[120] These are more stable compared to the olefine norbornene and predominated in reactions with cationic intermediates. In the studies of norbornyl systems to nortricycles, homoallylic rearrangement occurred by solvolysis in contrast to the Pd-induced homoallylic rearrangement of 8-azabicyclo[3.2.1]octanes **220** and **227** under mild conditions to azatricycles **235**. The tricyclo[3.2.1.$0^{2,7}$]octane scaffold is prominently found in its carbocyclic version in several natural products[121] including (–)-trachylobane (**240**)[122], (–)-mitrephorone A (**241**)[123], and sesquiterpenoid (–)-ishwarane (**242**)[124] (Figure 22).



(–)-trachylobane (**240**) (–)-mitrephorone A (**241**) (–)-ishwarane (**242**)

Figure 22. Natural products containing tricyclo[3.2.1.$0^{2,7}$]octane scaffold.

To date, the 6-azatricyclo[3.2.1.$0^{2,7}$]octane scaffolds such as **235a** are still limited accessible[125] due to their challenging synthesis. Since many complex azacyclic compounds are known for their biological activity, the azatricycles, which can also be prepared enantiomerically pure, are potential candidates for testing their pharmacological properties.

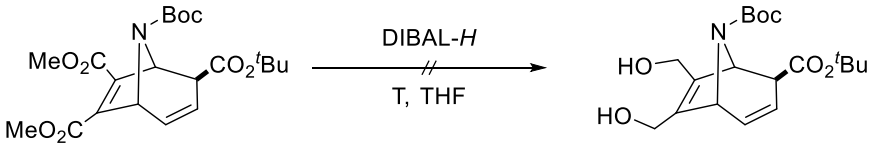
3 Derivatizations of 8-aza- and 8-oxabicyclo[3.2.1]octanes at C6/C7 positions

3.1 Derivatizations of methyl ester groups at C6/C7 positions

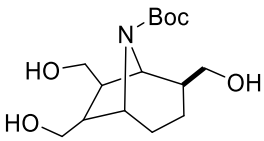
The previous chapter focused on the derivatization of the C3/C4 positions of the bicyclic seven-membered ring systems, whereas in the following chapter the selective derivatization of the C6/C7 positions will be discussed. Addressing the lack of using electron-neutral or donating dipolarophiles that can be used in the [3+2]-cycloaddition reactions, also manipulations of the methyl ester groups in **133a** were investigated.

The selective reduction of methyl ester groups in **133a** to the corresponding diol **243** was first attempted with DIBAL-*H*. A screening of the temperature and equivalents of DIBAL-*H* was carried out in THF (Table 22).

Table 22. Attempts for the selective reduction of methyl ester moieties in **133a** with DIBAL-*H*.



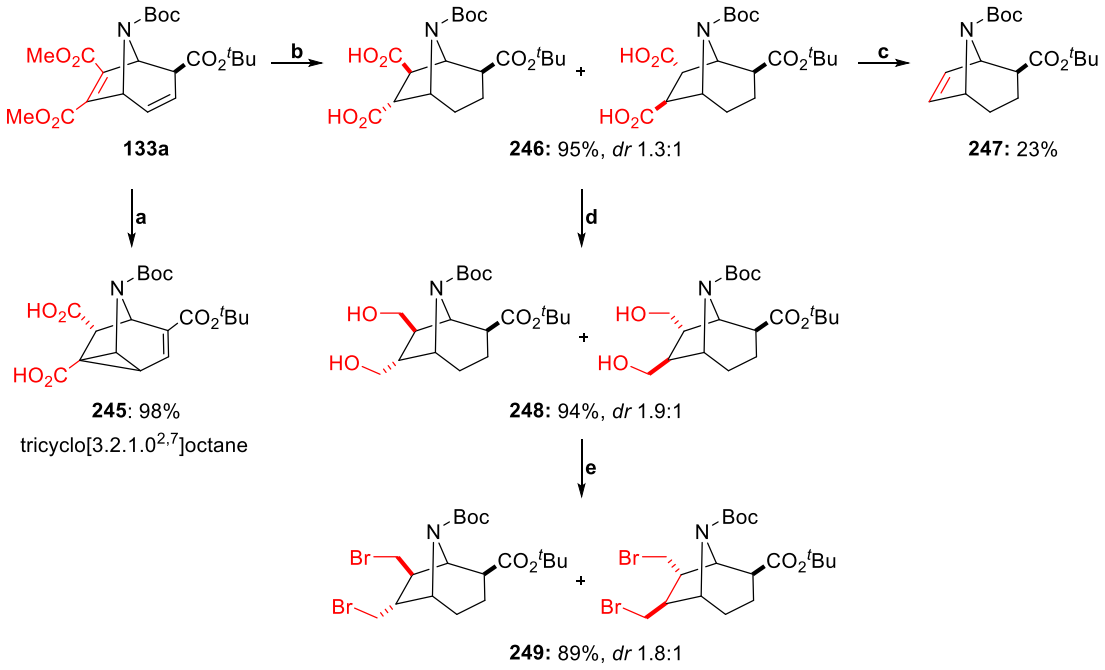
133a **243**

entry	DIBAL-*H* [equiv]	T [°C]	time [h]	observation[a][b]
1	5	-78	3	crm
2	5	0	0.25	crm
3	8	0	0.25	crm
4	4 → 2	0 to 25	30	 **244:** 20%

Reactions were performed on a 0.1-0.3 mmol scale; crm=complex reaction mixture. [a] Determined by analysis of the crude ^{1}H NMR; [b] Full conversion was observed.

Unfortunately, using an excess of 5 equivalents of DIBAL-*H* at -78 °C resulted in a complex reaction mixture (Table 22, entry 1). Analysis of the crude ^{1}H NMR showed that a mixture of aldehydes and alcohols was formed. In addition, the *tert*-butyl ester moiety was reduced preferentially while the methyl ester groups were only partially reduced. To prevent the formation of aldehydes, the temperature was raised to 0 °C (Table 22,

entry 2). Indeed, then no aldehydes were observed, however, the methyl esters were still only partially reduced even at higher temperature. Finally, to completely reduce the methyl esters, 8 equivalents of DIBAL-*H* were used (Table 22, entry 3). This resulted in further reduction products due to the isomerization and reduction of the double bond. To minimize these side reactions, DIBAL-*H* was added in two portions (Table 22, entry 4). This prevented the formation of by-products, however, still only partial reduction of the methyl ester groups was observed. Nevertheless, completely reduced compound **244** was isolated in low yields. In summary, DIBAL-*H* was not suitable for the desired selective derivatization, therefore other transformations were considered. A further alternative selective conversion of the methyl ester groups at C6/C7 positions in **133a** was realized *via* their direct saponification to the corresponding acids **246**, followed by the reduction of the acids with BH_3·THF to the corresponding diol. The hydrolysis of the methyl esters of **133a** was performed with NaOH solution in THF, but instead of the desired product, 6-azatricyclo[3.2.1.$0^{2,7}$]octane **245** was received in excellent yield (Scheme 40).

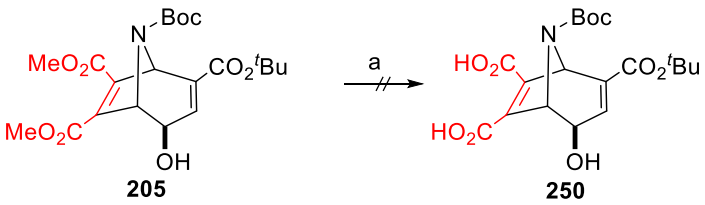


Scheme 40. Derivatizations of **133a**. Conditions: a) NaOH (2.0 equiv), THF, 0 to 25 °C, 5.5 h, then HCl, 0 °C, 98%; b) (i) H_2, Pd/C (10 mol%), EtOH/THF (1:4 v/v), p(H_2) = 60 bar, 25 °C, 4 h, (ii) NaOH (2.0 equiv), THF, 0 to 25°C, 4 h, then HCl, 0 °C, 95%; c) $Pb(OAc)_4$ (2.4 equiv), C_5H_5N, 67 °C, 6 h, 23%; d) BH_3·THF (6.5 equiv), THF, 0 to 25 °C, 24 h, 94%; e) (i) MsCl (2.2 equiv), TEA (4.0 equiv), CH_2Cl_2, 0 °C, 2 h, (ii) LiBr (13 equiv), THF, reflux, 9 h, 89%.

Notably, this process was base-mediated in contrast to the formation of this species during dehalogenations with palladium on charcoal and H_2 *via* carbocation

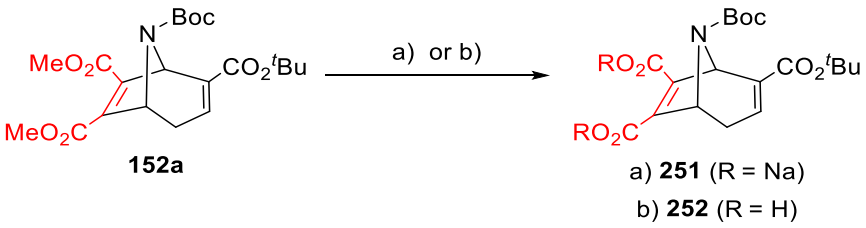
rearrangement (*cf.* scheme 39). As already described in the previous chapter, this tricyclo[3.2.1.$0^{2,7}$]octane scaffold is prominently found in its carbocyclic version in several natural products. Achieving saponification without rearrangement to **245**, hydrogenation followed by saponification gave rise to **246** in excellent yield, however, an equilibration to the sterically less-hindered *trans*-arrangement of the carboxylic acid groups had taken place as well. Such a base-mediated isomerization occurred also with structural similar compounds.[126] Subsequent lead tetraacetate degradation of **246** gave rise to **247,** moreover, the carboxylic acids **246** can be reduced to alcohols **248** and further transformed to the corresponding bromides **249** as shown in scheme 40 below.

To circumvent the isomerization to the *trans* acid **246** and to prevent the rearrangement to tricyclooctanes **245**, the saponification of allylic alcohol **205** was carried out (Scheme 41). Cycloadduct **205** was treated with NaOH and the corresponding salt was formed after 3.5 h in quantitative yield. The acidic work-up to get the diacid **250** resulted in decomposition, most likely due to the attached alcohol group, which is prone to elimination reactions under acidic conditions.



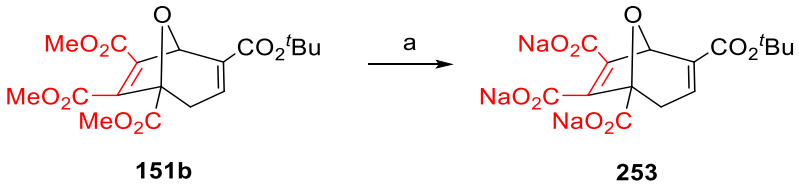
Scheme 41. Hydrolysis of allylic alcohol **205**. Conditions: a) NaOH (2.0 equiv), THF, 0 to 25 °C, 3.5 h, then HCl, 0 °C.

The isomerization product **152a** could also be a potential precursor to obtain the diacid **252** (Scheme 42). Ester hydrolysis with NaOH indeed furnished salt **251** in quantitative yield as single diastereomer while hydrolysis with NaOH followed by acidic work-up resulted in the desired acid **252** in 98% yield without any observable rearrangement product such as tricyclooctane or *trans* isomerization of the diacid.



Scheme 42. Hydrolysis of enone **152a**. Conditions: a) NaOH (2.0 equiv), THF, 0 to 25 °C, 3.5 h, quant.; b) NaOH (2.0 equiv), THF, 0 to 25 °C, 3.5 h, then HCl, 0 °C, 97%.

Moreover, hydrolysis of 8-oxabicyclo[3.2.1]octane **151b** yielded salt **253** in quantitative yield as single diastereomer (Scheme 43).



151b **253**

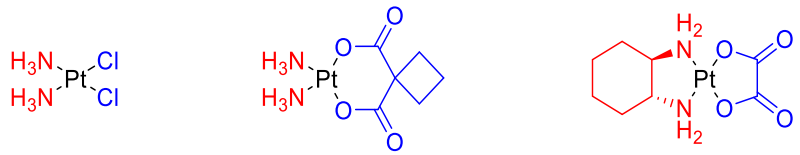
Scheme 43. Hydrolysis of enone **151b**. Conditions: a) NaOH (2.0 equiv), THF, 0 °C, 2 h, quant.

In summary, several postfunctionalizations of the 8-aza- **133a/152a** and 8-oxabicyclo[3.2.1]octanes **151b** at the C6/C7 position were achieved, which can be used for further transformations, e.g., the prepared salts **251**/**253** represented valuable precursors for the synthesis of novel Pt(II) complexes (see chapter 3.2.2). The synthesis of Pt(II) compounds will be discussed in the following chapters.

3.2 Synthesis of bicyclic platinum(II) complexes

3.2.1 Synthesis of diamine ligand *via* reduction of nitrile groups

Platinum(II) complexes, more precisely *cis*-diamminedichloroplatinum(II) (cisplatin **254**), is one of the most effective antitumor agent and therefore essential in the chemotherapy (Figure 23).[127] The anticancer activity of cisplatin (**254**) was discovered in the 1960 by Rosenberg.[128] The worldwide approved second-generation and third-generation platinum drugs are diammine(1,1-cyclobutadicarboxylato)platinum(II) (carboplatin **255**) and (1*R*,2*R*)-(diaminocyclohexane)oxalate-platinum(II) (oxaliplatin **256**).[129]



cisplatin (**254**) carboplatin (**255**) oxaliplatin (**256**)

Figure 23. Platinum-based anticancer drugs: cisplatin (**254**), carboplatin (**255**) and oxaliplatin (**256**).

These Pt(II) drugs **257** are all electronically neutral, square planar and possess two cis oriented ammine or chelating diamine ligands and two cis oriented chloride ligands or

chelating ligands that are attached to platinum by oxygen donors (Figure 24).[130] The am(mine) ligands are inert, non-leaving group ligands whereas the dianionic fragments form the semilabile leaving group ligands, allowing platinum to bind to the DNA, the major target of these complexes. The non-leaving group ligands determine the type of DNA lesion, resulting in the resistance profile. In contrast, the leaving group ligands play a key role in the reaction kinetics and toxicity profile.[131]

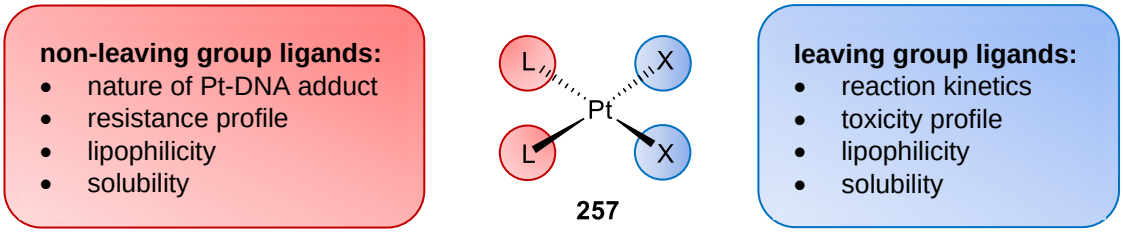


Figure 24. Basic structure of platinum(II)-based chemotherapeutic agents. Adapted from *Johnstone et al.*[130]

Platinum-based chemotherapeutic agents inhibit effective the replication of DNA as the platinum atom of these complex binds covalently to the purine bases in DNA to form 1,2- or 1,3 intra- and interstrand crosslinks (Figure 25). These DNA adducts induce cellular responses, such as replication inhibition, transcription inhibition, cell-cycle arrest, DNA repair and cellular apoptosis.[127b,132] However, the use of Pt drugs in clinical treatment is limited due to major drawbacks such as high toxicity, severe side effects[133] and drug resistance.[134]

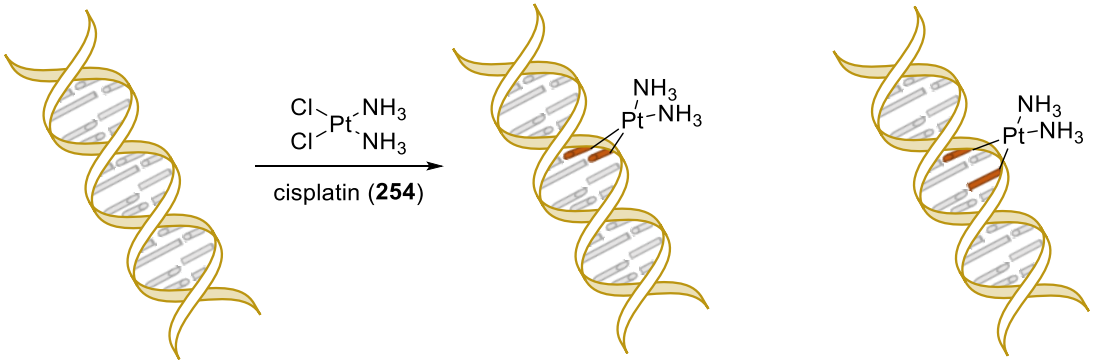


Figure 25. Formation of cisplatin-DNA adducts.

To overcome the drawbacks of cisplatin (**254**) such as toxicity due to the ease with which leaving groups are aquated, carboplatin (**255**) was developed by modification of the leaving group to bidentate dicarboxylate in place of the two chloride ligands, resulting in slower release of the leaving groups, and reduced toxicity. Carboplatin (**255**) is used as

standard therapy for ovarian cancer[135] and higher dosage[136] can be administered due to the less toxic agent[137] whereas cisplatin (**254**) is still used for testicular, head and neck cancer.[138] Unfortunately, the same non-leaving ammine group ligands in carboplatin (**255**) lead to cross-resistance to cisplatin (**254**). The replacement of the two ammine groups by (1*R*,2*R*)-diaminocyclohexane (DACH) led to the development of oxaliplatin (**256**), the third-generation platinum drug which is used to treat colorectal cancer (Figure 23). Noteworthy, this platinum complex has unique anticancer properties as it was the first drug which was capable to overcome cisplatin resistance.[139] Some Pt(II) anticancer agents are approved regionally such as nedaplatin (**258**) in Japan, heptaplatin (**259**) in Korea and, lobaplatin (**260**) in China (Figure 26).[127c] Lobaplatin (**260**) has a seven-membered ring structure (1,2-bis(aminomethyl)cyclobutane) that forms the non-leaving group and lactic acid functions as leaving group.[140] Few examples showed that seven-membered platinacycles have better antiproliferative activities compared to their smaller analogues.[141] The examples are still limited due to their challenging synthesis.

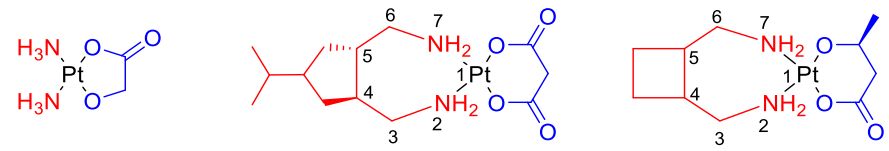
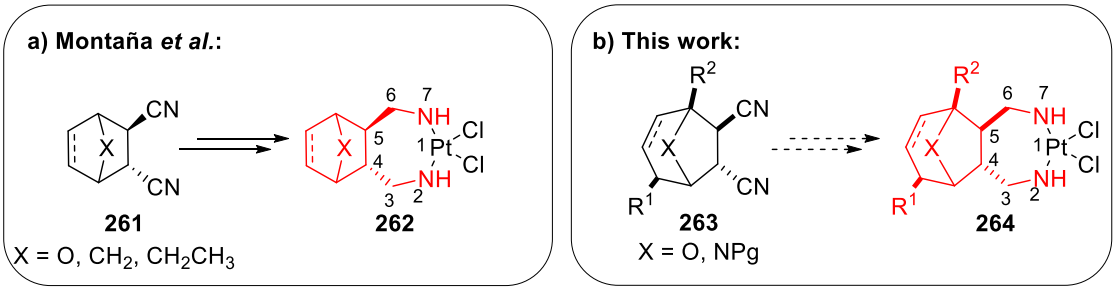


Figure 26. Regionally approved platinum-based anticancer drugs.

Despite the success of platinum-based drugs used in 70% of all cancer treatments, drug resistance and severe side effects remain the most serious and challenging limitations.[142] Therefore, it is still highly demanded to study structure-activity relationships of new platinum complexes to improve tumour selectivity and to overcome acquired resistance.

Due to the striking anticancer activity of oxaliplatin (**256**), which has a diamino ligand attached to a six-membered carbocycle (DACH ligand), Montaña *et al*. investigated the synthesis of cis-platinum(II) complexes **262** with amine ligands containing a carbocyclic or oxabicyclic scaffold (Scheme 44a).[143] These complexes with a seven-membered platinacycle were designed to modulate flexibility, steric hindrance, and lipophilicity of the diamine carrier ligand. Indeed, the complexes **262** have promising anticancer activity and lower resistance factors than cisplatin (**254**). Nevertheless, the main problem of these complexes was their low water solubility which limited their clinical application.[143-144]

The novel bicyclic seven-membered ring systems **263** represent an ideal precursor for the synthesis of novel amine ligands **264** (Scheme 44b), as they have equally trans nitrile functionalities compared to the bicycles **261** prepared in the previous work of Montaña *et al*. (Scheme 44a). Therefore, the new 8-oxa- and 8-azatropanes **263** prepared *via* cycloadditions with fumaronitrile should be converted by reductions to the amines **264**. The introduction of hydrophilic functional groups on such bicyclic seven-membered rings **264** could improve the water solubility, leading to highly attractive target molecules.

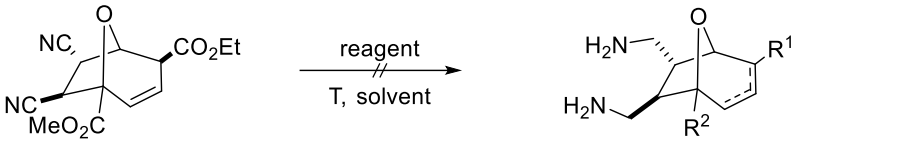


Scheme 44. Strategies to promising Pt(II) complexes with bicyclic amine ligands.

The selective reduction of the nitrile groups in *major* **140d** to amines **265** with $LiAlH_4$ was not successful (Table 23, entry 1 and 2). $LiAlH_4$ was a too strong reducing agent for all functional groups present. Almost all ester groups were reduced under these conditions resulting in a complex reaction mixture. Gowda *et al.* reported a simple and rapid reduction of aliphatic nitriles by using Raney nickel and hydrazinium monoformate.[145] The application of this reduction protocol did not lead to any conversion of the starting material *major* **140d** even after 3 days (Table 23, entry 3). To avoid the side reactions caused by $LiAlH_4$, $NaBH_4$ was used as a milder reducing agent, however, $NaBH_4$ itself generally cannot reduce nitriles to amines. It requires the addition of transition metal salts such as $CoCl_2$ and $NiCl_2$ to $NaBH_4$ to facilitate the reduction of nitriles to amines.[146] The reduction of *major* **140d** with $CoCl_2 \cdot 6H_2O$ and $NaBH_4$ in MeOH did not lead to the formation of the product **265** (Table 23, entry 4). Next, according to a literature procedure[146c], Boc_2O was added to protect the free amines formed by reduction due to their potentially high reactivity. The reduction of *major* **140d** with $NiCl_2 \cdot 6H_2O$, $NaBH_4$ and Boc_2O led to traces of an inseparable mixture of partially reduced product and isomerized compound **266** in 10% yield (Table 23, entry 5). Furthermore, starting material and isomerized starting material *major* **140d** were isolated as an inseparable mixture in 59% yield. In conclusion, the double bond in *major* **140d** caused issues during reduction of the nitriles to the amines since its isomerization increased the number of potential products. To minimize isomerization products, functionalization, e.g., by dihydroxylation, hydrogenation or targeted isomerization may prevent these side reactions. An advantage

of hydrogenation is that a saturated cycloadduct could be more stable than the unsaturated one.

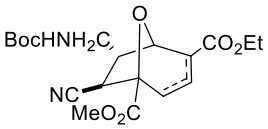
Table 23. Attempts for reduction of nitriles in *major* **140d** to amines **265**.



major **140d**

265

R^1 = CH_2OH, CO_2Et; R^2 = CH_2OH, CO_2Me

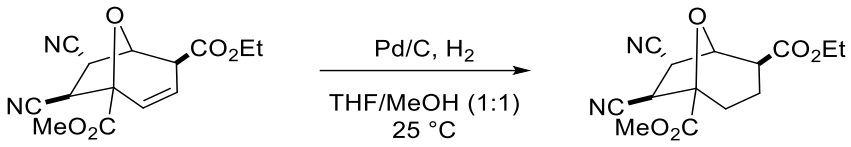
entry	reagent	solvent	T [°C]	time [h]	observation	conversion [%]
1	$LiAlH_4$[a]	THF	0	1	crm	100
2	$LiAlH_4$[a]	THF	-78	1	crm	100
3	Raney Ni, N_2H_4, HCOOH	HCOOH	25	72	nc	nd
4	$CoCl_2$ (4 equiv), $NaBH_4$[a]	MeOH	0	0.25	crm	100
5	$NiCl_2 \cdot 6H_2O$[b], $NaBH_4$[a], Boc_2O[a]	MeOH	0	2	 **266:** 10%	59[c]

Reactions were performed on a 0.1-0.6 mmol scale; crm=complex reaction mixture; nc=no conversion; nd=not determined. [a] 10 equiv was used; [b] 0.1 equiv was used; [c] Isomerization of the starting material was observed.

Therefore, the removal of the double bond *via* hydrogenation by Pd/C and H_2 was attempted (Table 24). The hydrogenation of *major* **140d** was performed with various amounts of Pd/C under different pressures. Hydrogenation with 10 mol% palladium on charcoal at 25 bar H_2 in the autoclave afforded the desired product **267** in 26% yield but full conversion of the starting material was observed (Table 24, entry 1). These data suggest that undesired side reactions, e.g., unselective partial reductions of the nitrile group, occurred. To minimize the unselective reductions, the reaction was carried out under atmospheric pressure (Table 24, entry 2). However, similar results were obtained.

Finally, the hydrogenation with 1 mol% Pd/C under atmospheric pressure gave the hydrogenated product **267** in 22% yield with 62% conversion of the starting material (Table 24, entry 3).

Table 24. Hydrogenation of the double bond in *major* **140d**.

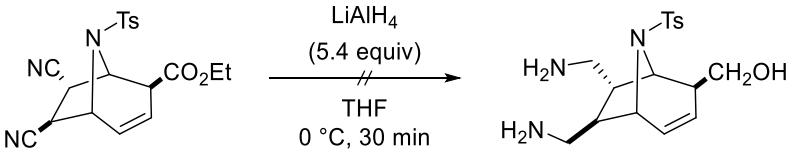


major **140d** **267**

entry	Pd/C [mol%]	time [h]	p(H_2) [bar]	product [%]	conversion [%]
1	10	4.5	25	26[a]	100
2	10	2.5	1	24[a]	100
3	1	4.5	1	22[b]	62[b][c]

Reactions were performed on a 0.3 mmol scale. [a] Isolated yield; [b] Determined *via* NMR using 2,2,4,4-tetrachloroethane as an internal standard; [c] Isomerization of the double bond of SM occurred after addition of internal standard.

In summary, the desired hydrogenated product **267** was only accessible in low yield, since, in addition to the hydrogenation of the double bond, the partial hydrogenation of nitriles already led to mixtures of imines or of primary, secondary, and tertiary amines. Montaña *et al.* reported that the oxygen-bridged compounds were particularly labile and formed by-products in all synthesis steps, especially during reduction with $LiAlH_4$, which led to low yields. Therefore, using compound **133n**[53] could be beneficial due to the *N*-Ts heteroatom bridge as well as its single ester functionality compared to *major* **140d** bearing two ester groups.



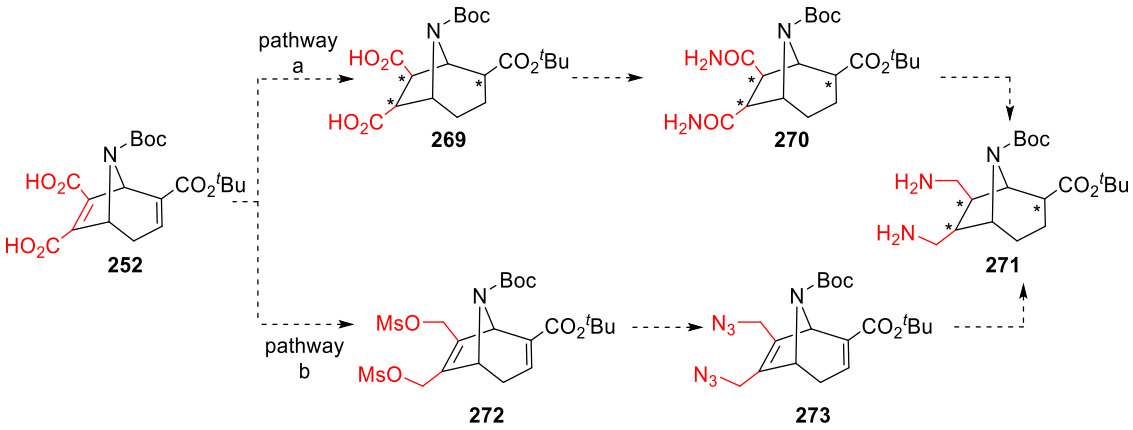
133n **268**

Scheme 45. Reduction of the nitriles in 8-azabicyclo[3.2.1]octane **133n** with $LiAlH_4$.

Unfortunately, the reduction of the nitriles in **133n** with $LiAlH_4$ did not yield the desired amine **268** (Scheme 45). In accordance with the above-described results the reduction with $LiAlH_4$ induced various side reactions due to its strong reducing properties.

3.2.2 Synthesis of diamine ligand *via* transformation of acids

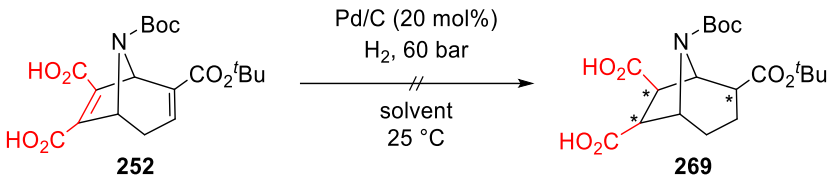
Since the synthesis of amine ligands **264** *via* the reduction of nitriles was not successful, the readily available acid **252** was considered as a potential precursor to amine ligand **271**. One synthesis involves hydrogenation of the diacid **252** followed by conversion of **269** to the carboxylic acid amide **270** and finally reduction to the diamine **271** (Scheme 46, pathway a). Another synthetic route to the desired amine **271** could take place *via* the synthesis of the mesylate **272** which is then converted into the corresponding azide **273** followed by the reduction to **271** (Scheme 46, pathway b). This amine ligand **271** could then be converted to novel Pt(II) complexes.



Scheme 46. Synthetic strategy towards amine **271** starting from diacid **252.**

To realize the synthetic pathway of the amine **271** *via* the formation of carboxylic acid amides **270**, first the double bonds in **252** were hydrogenated. Therefore, typical hydrogenation conditions were tested with Pd/C at 60 bar H_2 in EtOH/THF (Table 25, entry 1) as used in the previous chapter (see chapter 3.1, Scheme 40). Unfortunately, no conversion of the starting material **252** was observed. Due to the different polarity of the diacid **252** compared to cycloadduct **133a** used in the above-described hydrogenations, different solvents typically used for the hydrogenation of compounds bearing diacids[147] were screened. Unfortunately, the hydrogenations in MeOH or dioxane gave a complex reaction mixture (Table 25, entry 2 and 3).

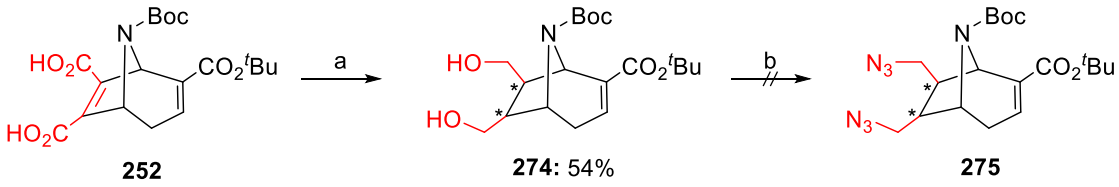
Table 25. Hydrogenation of the double bonds in **252**.



entry	solvent	time [h]	observation[a]
1	EtOH/THF (1:4)	7	nc
2	MeOH	24	crm
3	dioxane	24	crm

Reactions were performed on a 0.2 mmol scale; nc=no conversion; crm=complex reaction mixture. [a] Determined by analysis of crude ^{1}H NMR.

Therefore, the synthesis route *via* azides **275** was considered to prepare amine ligand **271** (Scheme 47). The reduction of the diacid **252** with BH_3·THF resulted in additional reduction of the tetrasubstituted double bond and yielded diol **274** in 54% yield with a diastereomeric ratio of 3.8:1. Due to the overlapping of rotamers and diastereomers the new stereochemistry of the diol **274** could not be determined by ^{1}H NMR and 2D NMR.



Scheme 47. Synthesis route to azides **275**. Conditions: a) BH_3·THF (6.5 equiv), THF, 0 to 25 °C, 24 h, 54%, *dr* 3.8:1; b) (i) MsCl (2.2 equiv), TEA (4.0 equiv), CH_2Cl_2, 0 °C, 4 h, (ii) NaN_3 (4.0 equiv), DMF, reflux, 25 h.

Then attempts for conversion of the diol **274** to the azide **275** *via* the mesylate were conducted. The mesylate was confirmed by HRMS and crude ^{1}H NMR. Unfortunately, subsequent treatment with NaN_3 led to a complex reaction mixture, the desired azide **275** was only observed in traces. In conclusion, the synthesis of amine ligands proved to be very difficult regardless of starting from nitriles or acids. Therefore, the following chapter focuses on the synthesis of platinum(II) drugs bearing bicyclic dicarboxylate as leaving group.

3.2.3 Synthesis of platinum(II) complexes bearing bicyclic dicarboxylate as leaving group

The focus has so far been on the synthesis of an amine carrier ligand for the development of new platinum based anticancer drugs. In the following chapter, the modification of the leaving group is investigated. The application of bioactive ligands as leaving groups is promising for the development of novel platinum complexes. Such complexes can have a dual mechanism of action, on the one hand through the biologically active ligand and on the other hand through the Pt pharmacophore. Cantharidin (**276**)**,** an active terpenoid toxin mainly produced by blister beetles (*hycleus lugens*)[148], has inhibitory activity on protein phosphatase 2A (PP2A)[149] The bicyclic compound has been used in the traditional Chinese medicine (TCM) to treat tumours, but the major drawback is its toxicity (Figure 27).[150] Demethylcantharidin (DMC, **277**) and endothall, the hydrolysed, ring-opened derivative of DMC, are analogues of cantharidin (**276**) with reduced side effects but exhibit similar effective inhibitors of PP2A.[149d] Studies have shown that the inhibition of protein phosphatase could be a key step in the development of new anticancer agents.[151]

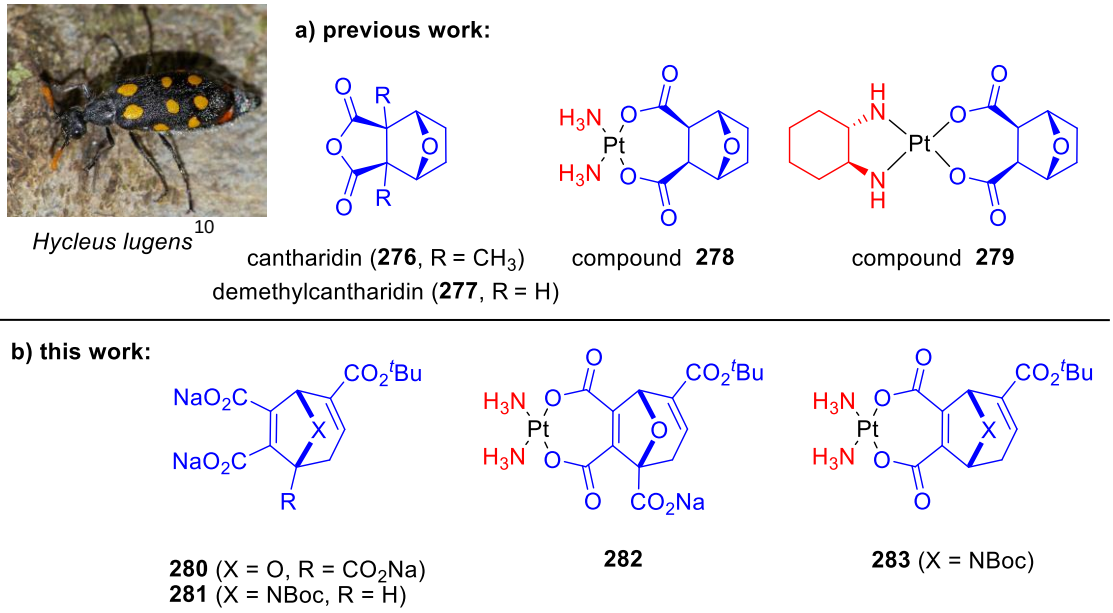


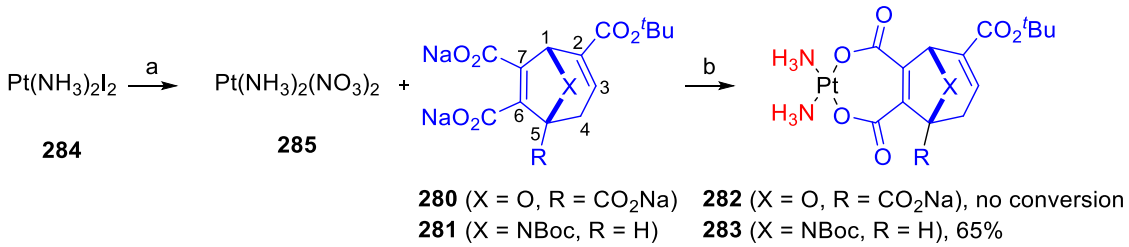
Figure 27. Chemical structures of demethylcantharidin **277**, TCM-Pt-compounds **278**-**279** and novel planned platinum(II) compounds **282**-**283**.

[10] https://commons.wikimedia.org/wiki/File:Blister_Beetle_(Hycleus_lugens)_(11890956313).jpg; author: Bernard DUPONT, 2013 (accessed on 16.06.2021).

Therefore, the 7-oxabicyclo[2.2.1]hepante-2,3-carboxylic acid anhydride (**277**) was incorporated into the platinum(II) drug framework as a bioactive leaving group.[152] The TCM-based platinum compounds **278** and **279** proved to be highly cytotoxic, lack of Pt cross-resistance and the inhibitory activity of PP2A remained. A unique dual mechanism of action of the Pt-based anticancer drugs was demonstrated: (i) the platination of DNA by the Pt-am(m)ine ligand and (ii) inhibition of PP2A by the diacid form of DMC that is slowly released.[152-153]

In this thesis, the developed 8-oxa- and 8-azabicyclo[3.2.1]octane scaffolds **280**, **281** were considered as possible leaving group ligands due to their potential biological activity as well as their structural similarity to DMC/endothall. The bicyclic seven-membered ring systems are unique with their substituents at C6,C7 positions. Installing carboxylic acid groups makes them ideal precursors for the synthesis of novel platinum anticancer drugs. Incorporation of 8-oxabicyclo[3.2.1]octanes **280** into the platinum(II) scaffold would lead to higher homologue **282** compared to 7-oxabicyclo[2.2.1]heptane **278** which already contain the core structure of the DMC-Pt anticancer drugs. Moreover, the influence of the double bond next to the diacid ligand at C6/C7 attached to the platinum atom can be examined. Such complexes are still rather unexplored and only examples with aromatic compounds exist. [154]

According to a literature procedure[152], $Pt(NH_3)_2I_2$ **284** was prepared from K_2PtCl_4 with KI, followed by the reaction with $AgNO_3$ to obtain $Pt(NH_3)_2(NO_3)_2$ **285** in water. The bicyclic salts **280-281** were prepared by [3+2]-cycloadditions, isomerizations and finally saponifications as described in the previous chapters. The reaction of 8-oxabicyclo[3.2.1]octane **280** and $Pt(NH_3)_2(NO_3)_2$ **285** did not lead to any conversion of the starting material **280** (Scheme 48). In contrast, Pt(II) compound **283** was successfully synthesized by reaction of ligand **281** with $Pt(NH_3)_2(NO_3)_2$ **285** in water in 65% yield.



Scheme 48. Attempts for the synthesis of novel platinum(II) complexes. Conditions: a) $AgNO_3$, H_2O, 24 h, 25 °C, b) 24 h, 25 °C.

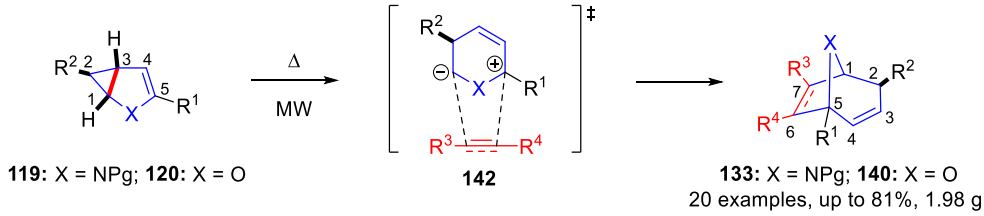
The 8-oxabicyclo[3.2.1]octane **280** appeared to be unreactive which might be a consequence of the different steric demand of the oxygen derivative **280** bearing an ester

moiety at C5 position compared to the aza analogue **281**. Therefore, further synthesis protocols should be tested and the reaction time extended.

In conclusion, the successful design and synthesis of a novel platinum(II) drug **283** was realized. In future, the preparation of 8-aza- or 8-oxabicyclo[3.2.1]octane-integrated Pt(II) complexes with various am(m)ine groups in particular the Pt-DACH moiety will be desirable. Moreover, the synthesis of acid ligands should be expanded to derivatives of the bicyclic seven-membered ring system described above. Recently, a novel strategy to overcome tumour resistance involves nano-delivery of Pt(IV) and demethylcantharidin with polymeric micelles.[155] Therefore, the synthesis of Pt(IV) with axial ligands remains promising.

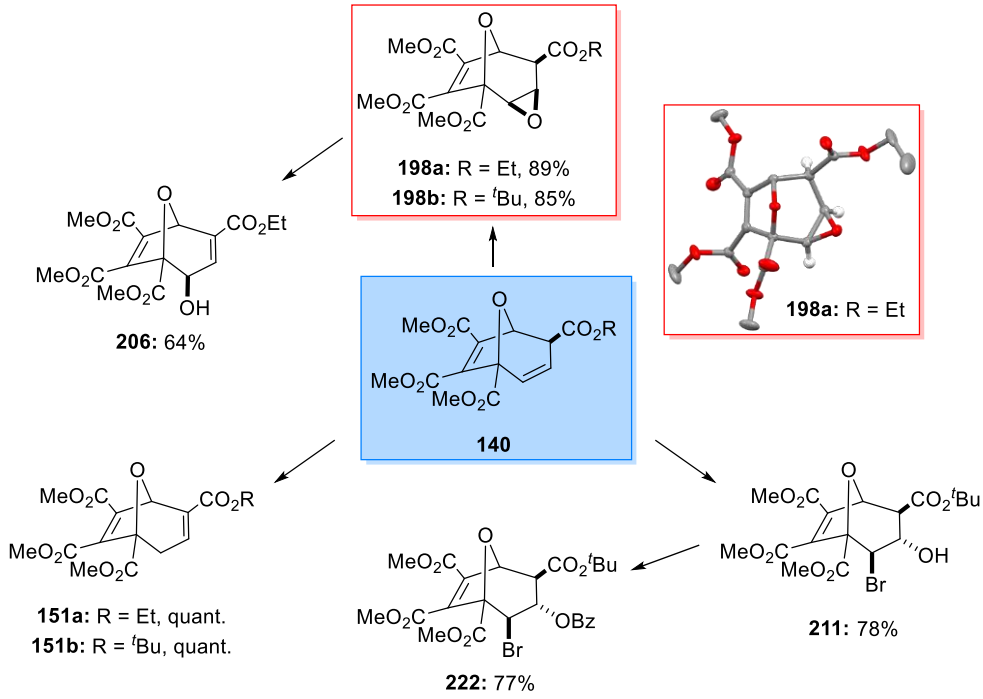
C Summary

The present thesis deals with the synthesis of 8-aza- and 8-oxabicyclo[3.2.1]octanes **133**, **140** *via* a microwave-assisted, stereoselective 6π-electrocyclic ring-opening / [3+2]-cycloaddition cascade of monocyclopropanated pyrrole and furan derivatives **119**, **120** with electron-poor dipolarophiles (**142**, red) (Scheme 49).



Scheme 49. Synthetic strategy to 8-aza- and 8-oxabicyclo[3.2.1]octanes **133, 140** *via* microwave-assisted [3+2]-cycloadditions of 2-aza- and 2-oxa-bicyclo[3.1.0]-hex-3-enes **119, 120**.

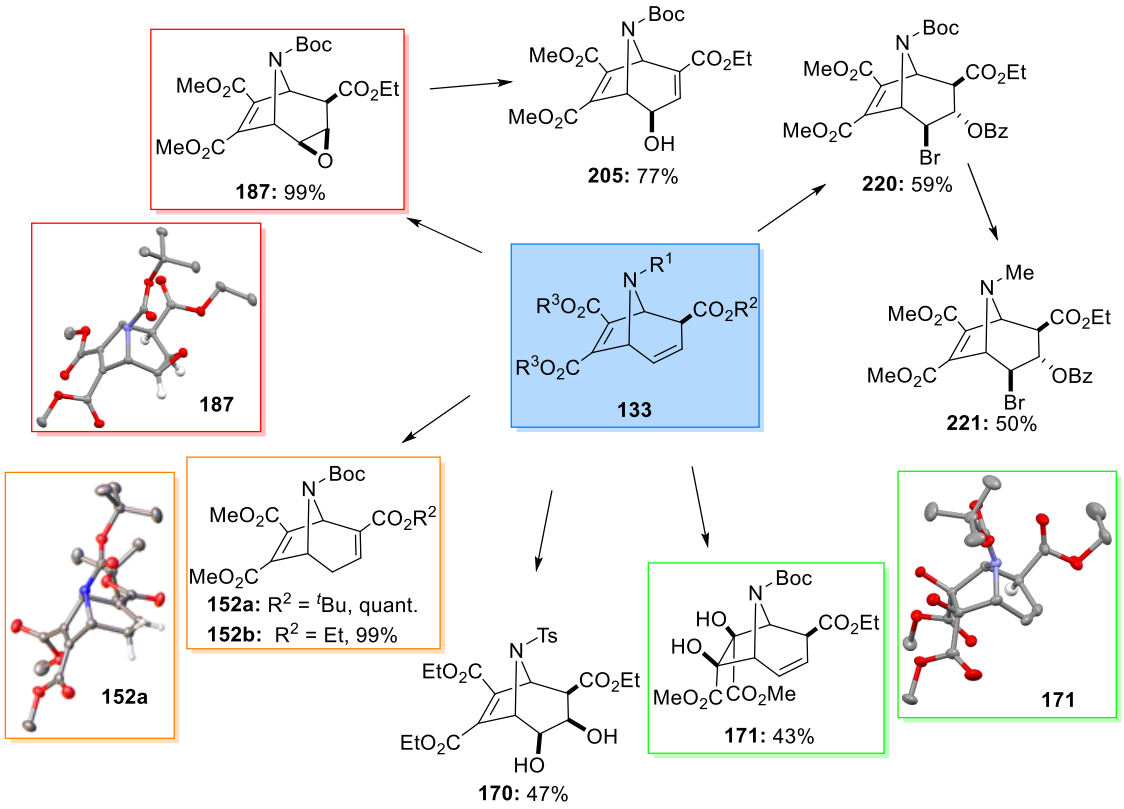
The key step of this transformation is a thermally induced selective cleavage of the non-activated, endocyclic C1-C3 cyclopropane bond in 2-aza- or 2-oxabicyclo[3.1.0]-hex-3-enes **119**, **120**, resulting in 1,3-dipoles (**142**, blue) which can be trapped with suitable dipolarophiles (**142**, red). Starting from pyrroles or furans, 8-aza- and 8-oxabicyclo-[3.2.1]octanes **133**, **140** are accessible in two steps (cyclopropanation/cycloaddition) in diastereo- and enantioselective pure form, being versatile building blocks for the synthesis of pharmaceutically relevant targets.



Scheme 50. Derivatization reactions of the 8-oxabicyclo[3.2.1]octane framework **140**.

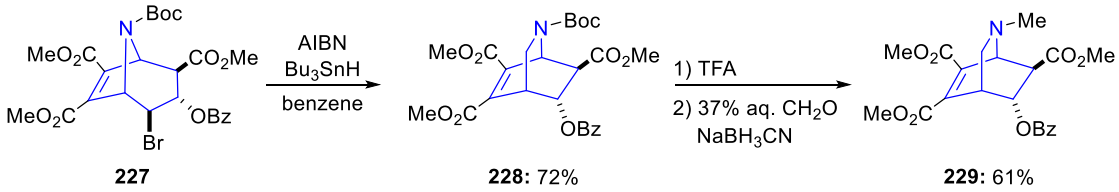
Furthermore, various postfunctionalizations of the scaffolds obtained are possible (Scheme 50, 51), allowing their further diversifications. Epoxidation of 8-oxabicyclo-[3.2.1]octane **140a** with *m*CPBA occurred selectively from the less-hindered convex side to give *exo*-epoxide **198a** in 89% yield, which was further converted under basic conditions to allylic alcohol **206** in 64% yield (Scheme 50). In turn, the isomerization of the C3/C4 double bond in **140** to the thermodynamically favored enone **151** was quantitatively achieved under basic conditions with TEA. Bromohydrin formation of **140b** with NBS in the presence of water, followed by esterification with BzCl proceeded with remarkable diastereoselectivity to **222**.

In an analogous way, derivatives **152, 187, 205** and **220** were obtained in the nitrogen series in excellent yields (Scheme 51). Deprotection and reductive amination[22h] of **220** in one pot to **221** demonstrated the exchange of the *N*-Boc protecting group to *N*-Me as typically found in natural products (*cf* Scheme 2). Dihydroxylation of **133c** in the presence of K_2OsO_4/NMO in acetone/water proceeded in moderate yield but surprisingly, furnished exclusively *exo*-diol **171** as single diastereomer. In contrast, the dihydroxylation of **133f** with $RuCl_3 \cdot 3H_2O$, and $NaIO_4$ resulted selectively in diol **170**[53] These alcohols have potential for the synthesis of calystegine analogues being polyhydroxylated nortropane alkaloids (*cf* Scheme 1).



Scheme 51. Derivatization reactions of the 8-azabicyclo[3.2.1]octane framework **133**.

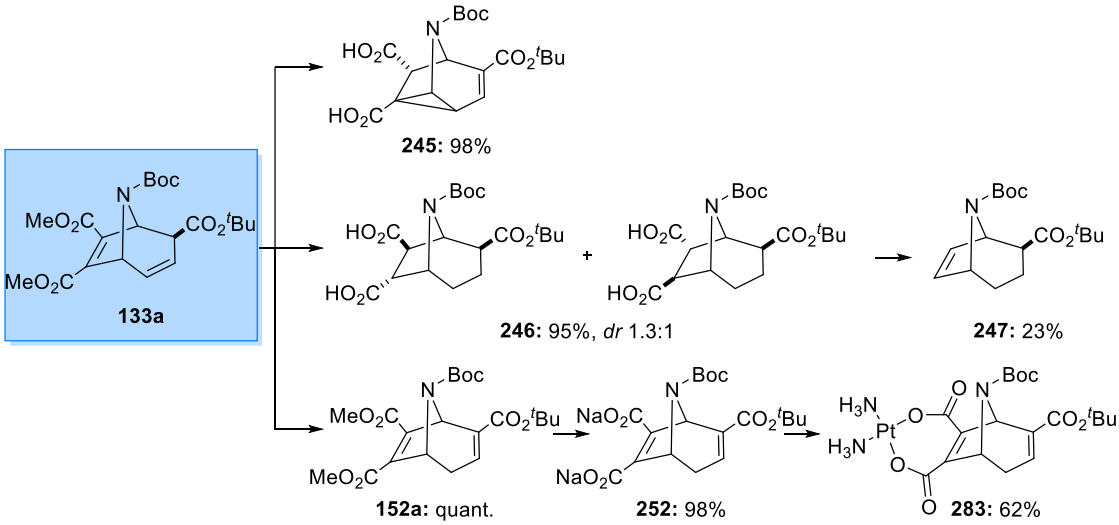
Furthermore, the tropane scaffold can also be readily rearranged to the isoquinuclidine scaffold[117] by subjecting bromo compounds such as **227** to AIBN/Bu_3SnH upon which a homoallylic radical rearrangement to **228** took place (Scheme 52). Deprotection and reductive amination of **228** yielded **229**, which was unambiguously confirmed by X-ray.



227 **228:** 72% **229:** 61%

Scheme 52. Isoquinuclidine synthesis by homoallylic radical rearrangement.

Finally, addressing the lack of using electron-neutral or donating dipolarophiles that can be used in the reaction cascade, manipulations of the methyl ester groups in **133a** were desirable (Scheme 53). Direct saponification of **133a** gave rise to 6-azatricyclo-[3.2.1.$0^{2,7}$]octane **245**, a scaffold that is prominently found in its carbocyclic version in several natural products.[121b]

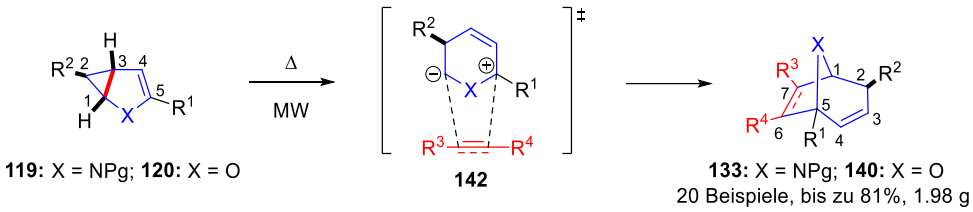


Scheme 53. Derivatization reactions of 8-azabicyclo[3.2.1]octane framework **133a** at C6/C7 position.

Hydrogenation followed by saponification afforded **246** in excellent yield, however, an equilibration to the sterically less-hindered *trans*-arrangement of the carboxylic acid groups had taken place as well. Subsequent lead tetraacetate degradation of **246** furnished **247**. The successful synthesis of a novel, potentially antitumor Pt(II) compound **283** was realized by complexation of $Pt(NH_3)_2(NO_3)_2$ with ligand **252** obtained from isomerized cycloadduct **152a** by saponification.

D Zusammenfassung[11]

Die vorliegende Arbeit befasst sich mit der Synthese von 8-Aza- und 8-Oxabicyclo[3.2.1]octanen **133**, **140** über eine mikrowellenunterstützte, stereoselektive 6π-elektrocyclische Ringöffnungs- / [3+2]-Cycloadditionskaskade von monocyclopropanierten Pyrrol- und Furanderivaten **119**, **120** mit elektronenarmen Dipolarophilen (**142**, rot) (Schema 1).

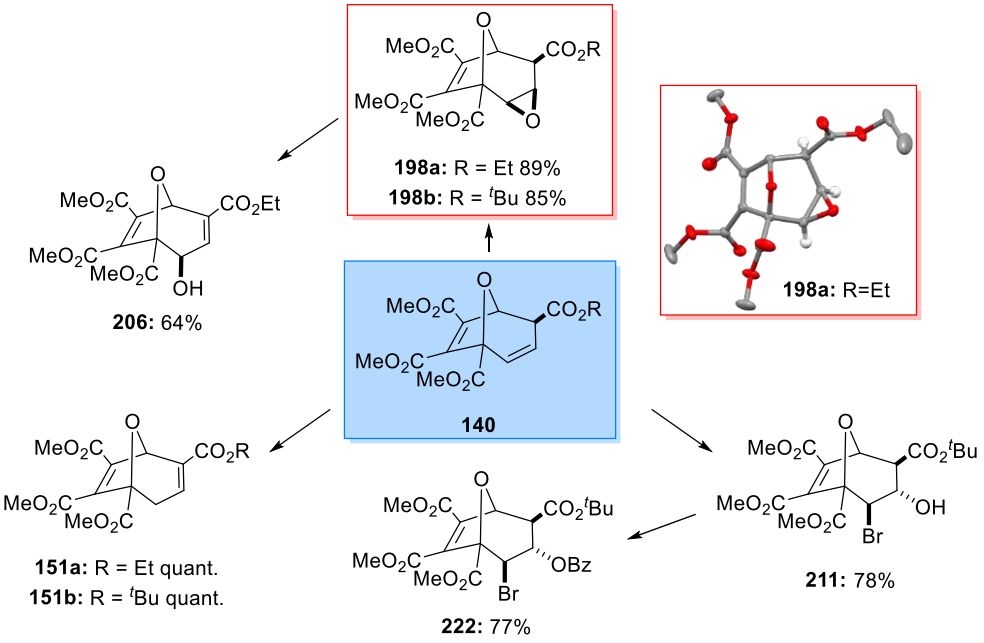


Schema 1: Darstellung von 8-Aza- und 8-Oxabicyclo[3.2.1]octanen **133, 140** über mikrowellenunterstützte [3+2]-Cycloadditionen von 2-Aza- und 2-Oxa-Bicyclo[3.1.0]-hex-3-enen **119, 120**.

Der Schlüsselschritt dieser Synthese ist die thermisch induzierte selektive Öffnung der nicht aktivierten, endocyclischen C1-C3 Cyclopropanbindung in 2-Aza- oder 2-Oxabicyclo[3.1.0]-hex-3-enen **119**, **120**, zu 1,3-Dipolen (**142**, blau), die mit geeigneten Dipolarophilen (**142**, rot) abgefangen werden können. Ausgehend von Furanen oder Pyrrolen sind 8-Aza- und 8-Oxabicyclo[3.2.1]octane **133**, **140** in zwei Schritten (Cyclopropanierung/Cycloaddition) in diastereo- und enantioselektiver Reinform zugänglich, die vielseitige Bausteine für die Synthese pharmazeutisch relevanter Zielmoleküle darstellen.

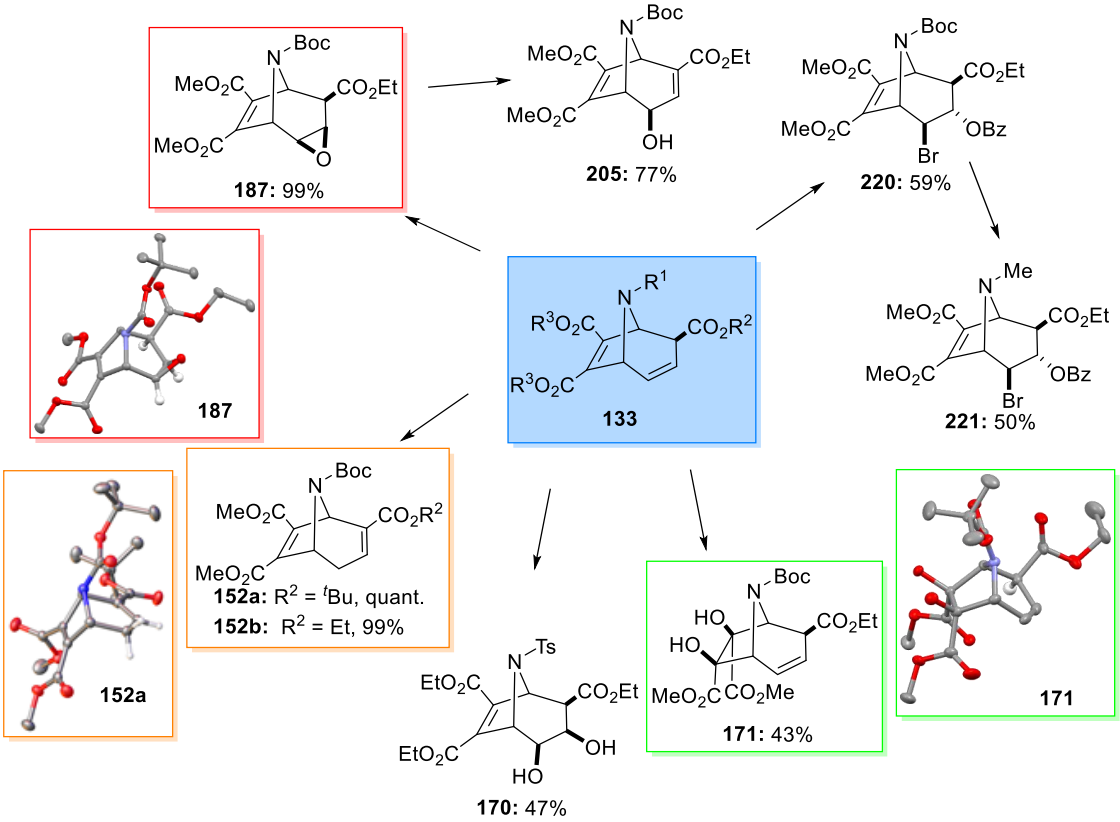
Darüber hinaus sind verschiedene Postfunktionalisierungen der erhaltenen Siebenringsysteme möglich (Schema 2, 3), wodurch weitere Diversifizierungen zugänglich werden. Die Epoxidierung von 8-Oxabicyclo[3.2.1]octan **140** mit *m*CPBA erfolgte selektiv von der weniger gehinderten konvexen Seite und lieferte *exo*-Epoxid **198a** in 89% Ausbeute, welches unter basischen Bedingungen weiter zum Allylalkohol **206** in 64% Ausbeute umgewandelt wurde (Schema 2). Die Isomerisierung der C3/C4-Doppelbindung in **140a-b** zum thermodynamisch begünstigten Enon **151a-b** konnte unter basischen Bedingungen mit TEA quantitativ erzielt werden.

[11] Summary/Zusammenfassung are partially based on C. M. Sonnleitner, S. Park, R. Eckl, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.*, **2020,** *59*, 18110; in cooperation with Dr. S. Park[54]



Schema 2: Derivatisierungsreaktionen der 8-Oxabicyclo[3.2.1]octan-Grundstruktur **140**.

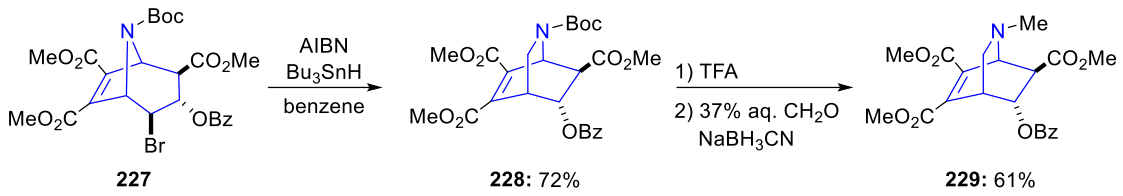
Die Bromhydrin-Bildung von **140b** mit NBS in Gegenwart von Wasser und die anschließende Veresterung mit BzCl verlief mit bemerkenswerter Diastereoselektivität und resultierte in **222**. In analoger Weise wurden in der Stickstoffreihe Derivate **152**, **187,** **205** und **220** in ausgezeichneten Ausbeuten erhalten (Schema 3).



Schema 3: Derivatisierungsreaktionen der 8-Azabicyclo[3.2.1]octan-Grundstruktur **133**.

Die Entschützung und reduktive Aminierung[22h] von **220** zu **221** in einem Schritt demonstrierte den Austausch der *N*-Boc- zur *N*-Me Schutzgruppe, wie sie typischerweise in Naturstoffen zu finden ist (vgl. Schema 2). Die Dihydroxylierung von **133c** in Gegenwart von K_2OsO_4/NMO in Aceton-Wasser verlief in mäßiger Ausbeute, resultierte aber überraschenderweise ausschließlich in *exo*-Diol **171** als einziges Diastereomer.

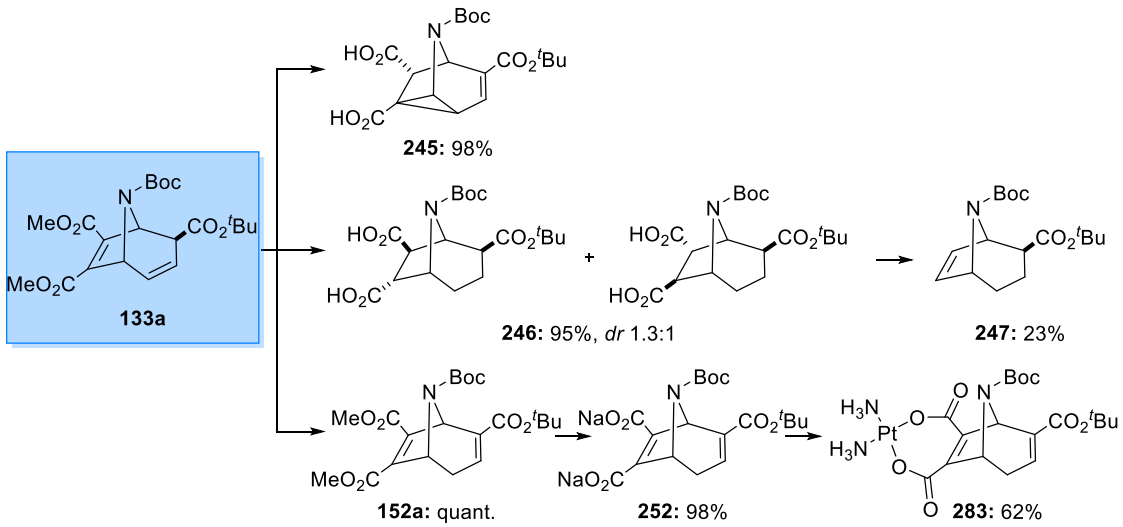
Im Gegensatz dazu führte die Dihydroxylierung von **133f** mit $RuCl_3 \cdot 3H_2O$ und $NaIO_4$ selektiv zum Diol **170**.[53] Bei diesen Alkoholen handelt es sich um potentielle Vorläuferstrukturen in der Synthese von Calystegin-Analoga, bei denen es sich um polyhydroxylierte Nortropanalkaloide handelt (vgl. Scheme 2).



227 **228:** 72% **229:** 61%

Schema 4: Isochinuclidin Synthese durch homoallylische Radikalumlagerung.

Weiterhin konnte das Tropan-Grundgerüst leicht in den Isochinuclidin-Grundbaustein[116h,117] transformiert werden, indem eine Umsetzung von Bromverbindungen wie **227** und AIBN/Bu_3SnH erfolgte, die in einer homoallylischen Radikalumlagerung zu **228** resultierte (Schema 4). Die Entschützung und reduktive Aminierung von **228** lieferte Isoquinuclidin Derivat **229**, das durch Röntgenstrukturanalyse bestätigt wurde.



Schema 5: Derivatisierungsreaktionen der 8-Azabicyclo[3.2.1]octan-Grundstruktur **133a** an der C6/C7 Position.

Da sich sowohl elektronenneutrale als auch elektronenreiche Dipolarophile für die angeführte Cycloaddition nicht als tauglich erwiesen, wurden Derivatisierungen der Methylestergruppen in **133a** angestrebt (Schema 5). Die direkte Verseifung von **133a** resultierte in der Bildung von 6-Azatricyclo[3.2.1.$0^{2,7}$] **245**, einem Gerüst, dessen Grundstruktur in seiner carbocyclischen Form in Naturstoffen vertreten ist.[121b]

Die Hydrierung mit anschließender Verseifung führte zu **246** in ausgezeichneter Ausbeute, jedoch unter Äquilibrierung zum sterisch weniger anspruchsvollem *trans*-Produkt. Die anschließende Oxidation der Dicarbonsäure **246** mit Bleitetraacetat ergab **247**. Darüber hinaus wurde die Synthese einer neuen, potentiell antitumoralen Pt(II) Verbindung **283** durch Komplexierung von $Pt(NH_3)_2(NO_3)_2$ mit dem Liganden **252**, der aus dem isomerisierten Cycloaddukt **152a** durch Verseifung gewonnen wurde, realisiert.

E Experimental part

1 General information

All moisture sensitive reactions were performed in flame-dried glassware under nitrogen atmosphere. Commercially available chemicals were used as purchased. Dry solvents were prepared according to standard procedures. Analytical thin layer chromatography was performed on Silica gel 60 F254 aluminium plates (Merck). Visualization was accomplished using UV-irradiation (λ = 254 nm), vanillin/sulfuric acid solution, potassium permanganate solution, bromocresol green or Seebach's stain. Column chromatography was carried out on silica gel Merck Geduran 60 (0.063-0.200 mm) and flash silica gel Merck Geduran Si 60 (0.040-0.063 mm). Furthermore, purification by flash system was performed with silica gel (Merck, 0.040-0.063 mm) on a Reveleris® X2 Flash System (Büchi). Melting points were recorded on Stanford Research Systems OptiMelt MPA 100 Automated melting point system. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz and Bruker Avance 400 MHz spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of $CHCl_3$ at 7.26 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the signal of $CHCl_3$ at 77.2 ppm and TMS as an internal standard. Coupling constants (*J*) are given in Hertz (Hz). The following notations indicate the multiplicity of the signals: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartet, td = triplet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dddd = doublet of doublet of doublet of doublets and m = multiplet. ^{13}C NMR: (+) = primary/tertiary, (−) = secondary, (q) = quaternary carbon. The assignment resulted from DEPT, COSY, HSQC, HMBC and NOESY experiments. FTIR was carried out on a spectrometer equipped with a Diamon Single Reflection ATR-SYSTEM. The samples were prepared as thin films. Mass spectra were recorded at the Central Analytical Laboratory at the Department of Chemistry of the University of Regensburg on Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS. Optical rotations [α] were determined using Perkin Elmer 241 polarimeter at λ = 589 nm (sodium-*d*-line) in a 1.0 dm measuring cell and the specified solvent. X-ray analysis was performed on Agilent Technologies SuperNova and Agilent Technologies GV 1000 at the crystallography laboratory of the University of Regensburg. Analytical high-performance liquid chromatography (HPLC) was conducted on a Varian 920-LC chromatograph equipped with Diode Array detector. Phenomenex Lux Cellulose-1, Phenomenex Lux Cellulose-2, Chiracel AS-H, Chiracel OJ-H and Chiralpak AS-H served as chiral stationary phase and mixtures of *n*-heptane and *i*-PrOH were used for elution. The HPLC yields of the screening of microwave flow reactions was conducted on a

Agilent 1260 Infinity system equipped with Diode Array detector. Nucleosil C18 served as stationary phase and mixtures of H_2O and MeCN.
Microwave irradiation experiments were carried out using an Anton Paar Monowave 300 reactor.

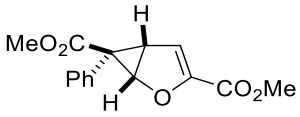
2 Experimental procedures and analytical data

Following compounds were synthesized according to literature procedures and spectroscopic data matched well with those reported:

4-methylbenzenesulfonyl azide[156], Rh_2(*S*-TCPTTL)$_4$[157], furan-2-carboxylic acid methyl ester[158], 2,2-bis((4*S*)-(–)-4-isopropyloxazoline) propane[159], 1-tosyl-1*H*-pyrrole[160], *tert*-butyl-1*H*-pyrrole-1-carboxylate (**145**)[161], methyl 2-diazo-2-phenylacetate (**118a**)[162], methyl 2-diazoacetate (**118b**)[163], ethyl 2-diazoacetate (**118c**)[164], *tert*-butyl diazoacetate (**118d**)[165], ethynyl *p*-tolyl sulfone[166], compounds **(−)-119a**[47g], **(−)-119b**[47g], **119e**[167], **120a**[47j], **120b**[47j], **133n**[53], $Pt(NH_3)_2I_2$[152].

Synthesis of cyclopropanes

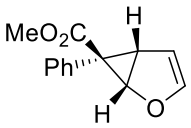
dimethyl (1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (120d)



Methyl furan-2-carboxylate (6.18 g, 5.2 mL, 49.0 mmol, 2.0 equiv) and $Rh_2(OAc)_4$ (6.7 mg, 15.2 µmol, 0.06 mol%) were dissolved in dry PE (30 mL) under nitrogen atmosphere. Within 1 h a solution of diazo ester **118a** (4.32 g, 4.7 mL, 24.5 mmol, 1.0 equiv) in dry PE (15 mL) was added dropwise *via* syringe pump at 25 °C. After addition, the reaction mixture was stirred for 5 min. The precipitated solids were filtered off and washed with PE and the crude product was recrystallized from methanol. The target compound **120d** (5.36 g, 19.5 mmol, 79%) was obtained as a colorless solid.[52]

Spectroscopic data matched well with those reported in literature.[47i]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 – 7.17 (m, 5H), 6.11 (d, *J* = 3.0 Hz, 1H), 5.23 (d, *J* = 5.4 Hz, 1H), 3.64 (s, 3H), 3.61 (s, 3H), 3.37 (dd, *J* = 5.4, 3.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.1 (q), 158.8 (q), 148.9 (q), 132.3 (+), 129.6 (q), 128.1 (+), 127.7 (+), 114.1 (+), 71.1 (+), 52.9 (+), 52.1 (+), 39.5 (+), 28.5 (q).

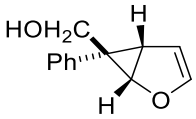
methyl (1*S*,5*S*,6*R*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (120e)



Furan (10.0 g, 8.47 mL, 49.0 mmol, 2.0 equiv) and Rh_2(*S*-TCPTTL)$_4$ (3.3 mg, 1.67 µmol, 0.07 mol%) were dissolved in dry PE (25 mL) under nitrogen atmosphere. Within 1 h a solution of diazo ester **118a** (4.32 g, 4.7 mL, 24.5 mmol, 1.0 equiv) in dry PE (15 mL) was added dropwise *via* syringe pump at 25 °C. After addition, the reaction mixture was stirred for another 5 min. The solvent was evaporated and the crude product was purified by silica gel column chromatography (5% EA:PE) to obtain the target compound **120e** (4.45 g, 20.6 mmol, 84%) as a colorless solid.[52]

Spectroscopic data matched well with those reported in literature.[47i]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 – 7.23 (m, 3H), 7.21 – 7.14 (m, 2H), 5.90 (dd, *J* = 2.6, 0.8 Hz, 1H), 5.22 (t, *J* = 2.6 Hz, 1H), 5.13 (dd, *J* = 5.6, 0.8 Hz, 1H), 3.61 (s, 3H), 3.30 (dd, *J* = 5.6, 2.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.9 (q), 147.4 (+), 132.7 (+), 130.7 (q), 127.8 (+), 127.3 (+), 104.0 (+), 70.8 (+), 52.6 (+), 39.3 (+), 27.3 (q).

((1*S*,5*S*,6*S*)-6-phenyl-2-oxabicyclo[3.1.0]hex-3-en-6-yl) methanol (120f)



DIBAL-*H* (1 M solution in cyclohexene, 495 mg, 3.48 mL, 3.48 mmol, 2.5 equiv) was added dropwise to a solution of ester **120e** (301 mg, 1.39 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 0 °C under nitrogen atmosphere. After stirring for 30 min at 0 °C, CH_2Cl_2 (10 mL) was added and subsequently stirred for additional 15 min at 0 °C. Then a saturated $KNaC_4H_4O_6{\cdot}4H_2O$ solution (6 mL) was added at 25 °C. After stirring for 1 h at 25 °C, additional saturated $KNaC_4H_4O_6{\cdot}4H_2O$ solution (25 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification of the crude product by silica gel column chromatography (17 → 50% EA:PE) yielded **120f** (130 mg, 690 µmol, 50%) as a yellowish solid.[52]

R_f = 0.38 (PE:EA = 3:1; UV, vanilin); **m.p.** = 74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.20 (m, 5H, overlapping with solvent signal), 5.82 (dd, *J* = 2.7, 0.8 Hz, 1H), 5.09 (t, *J* = 2.7 Hz, 1H), 4.67 (dd, *J* = 5.9, 0.8 Hz, 1H), 3.60 (d, *J* = 11.5 Hz, 1H), 3.46 (d, *J* = 11.5 Hz, 1H), 2.58 (dd, *J* = 5.8, 2.7 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 145.9 (+), 134.5 (q), 131.9 (+), 128.2 (+), 127.1 (+), 103.5 (+), 68.4 (–), 67.1 (+), 31.6 (+), 28.0 (q); **IR** $\tilde{\nu}$ [cm^{-1}]: 3269, 3027, 2926, 2899, 1592, 1495, 1446, 1320, 1156, 1029, 992, 936, 880, 805, 768, 693; **HRMS** (EI): calcd. for $C_{12}H_{12}O_2$ ($M^{+\cdot}$), m/z = 188.0832; found 188.0835.

General procedures for cyclopropanations (GP-1, GP-2):

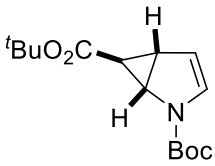
General procedure 1 (GP-1): Racemic cyclopropanation of pyrroles

A flame-dried schlenk flask was charged with $Cu(OTf)_2$ (0.01 equiv) and dry CH_2Cl_2 (5-10 mL) under nitrogen atmosphere. Pyrrole (1.0 equiv) was dissolved in dry CH_2Cl_2 (42-60 mL) and the $Cu(OTf)_2$ solution was added at 25 °C. Subsequently, phenylhydrazine (0.01 equiv) was added. Afterwards, diazoester (1.5 equiv) in CH_2Cl_2 was added dropwise to the reaction mixture *via* syringe pump (addition rate: 1 drop/10 s). The reaction mixture was filtered through a plug of basic Al_2O_3 and washed with CH_2Cl_2 (800 mL). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to obtain cyclopropane. Recrystallization from pentane yielded pure cyclopropane **119** as a colorless solid.

General procedure 2 (GP-2): Enantioselective cyclopropanation of furans

A flame-dried schlenk flask was charged with $Cu(OTf)_2$ (0.01 equiv), 2,2-bis((4*S*)-(–)-4-isopropyloxazoline) propane (0.02 equiv) and dry CH_2Cl_2 (10 mL) under nitrogen atmosphere and was stirred for 30 min at 25 °C. The $Cu(OTf)_2$ solution was transferred to a solution of furan-2-carboxylic acid methyl ester (1.0 equiv) at 0 °C under nitrogen atmosphere. Phenylhydrazine (0.01 equiv) was added and diazoester **118** (1.5 equiv) in CH_2Cl_2 was added dropwise *via* syringe pump (addition rate: 1 drop/10 s). The mixture was warmed to 25 °C, filtrated through a plug of basic Al_2O_3 and washed with CH_2Cl_2 (800 mL). The solvent was evaporated and purification of the crude product by silica gel column chromatography yielded compound **120** as a colorless solid.

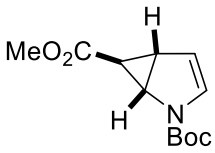
di-*tert*-butyl (1*S*,5*S*,6*S*)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (119a)



According to **GP-1,** $Cu(OTf)_2$ (260 mg, 719 µmol, 0.01 equiv) in dry CH_2Cl_2 (5 mL) was added to solution of *tert*-butyl-1*H*-pyrrole-1-carboxylate **145** (12.0 g, 12 mL, 71.9 mmol, 1.0 equiv) in dry CH_2Cl_2 (45 mL). Phenylhydrazine (77.7 mg, 70.7 µL, 719 µmol, 0.01 equiv) and *tert*-butyl 2-diazoacetate (**118d**, 112 g, 13.7 wt%, 108 mmol, 1.5 equiv) in CH_2Cl_2 were added and the crude product was purified by silica gel column chromatography (2 → 10% EA:PE) to obtain cyclopropane **119a** as a yellowish solid. Recrystallization from pentane yielded pure cyclopropane **119a** (6.50 g, 23.1 mmol, 32%) as a colorless solid.

Spectroscopic data matched well with those reported in literature.[47g]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.66 – 6.31 (m, 1H), 5.45 – 5.22 (m, 1H), 4.45 – 4.07 (m, 1H), 2.80 – 2.63 (m, 1H), 1.50 (s, 9H), 1.44 (s, 9H), 0.93 – 0.76 (m, 1H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.4 (q), 172.1 (q), 151.3 (q), 151.0 (q), 129.6 (+), 129.4 (+), 110.0 (+), 81.5 (q), 80.7 (q), 44.0 (+), 43.7 (+), 31.7 (+), 30.6 (+), 28.2, (+) 28.1 (+), 24.0 (+) (signal doubling due to rotamers).

2-(*tert*-butyl) 6-methyl (1*S*,5*S*,6*S*)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (119b)

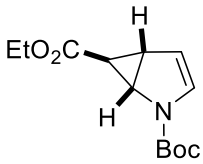


According to **GP-1**, $Cu(OTf)_2$ (224 mg, 619 µmol, 0.01 equiv) in dry CH_2Cl_2 (5 mL) was added to a solution of *tert*-butyl 1H-pyrrole-1-carboxylate **145** (10.4 g, 10.4 mL, 61.9 mmol, 1.0 equiv) in dry CH_2Cl_2 (45 mL). Phenylhydrazine (67.0 mg, 61 µL, 619 µmol, 0.01 equiv) and methyl 2-diazoacetate (**118b**, 9.30 g, 8.20 wt%, 92.9 mmol, 1.5 equiv) in CH_2Cl_2 were added and the crude product was purified product by silica gel column chromatography (10% EA:PE) to obtain cyclopropane **119b** (8.42 g, 35.2 mmol,

57%) as a yellowish oil. Recrystallization from pentane yielded pure cyclopropane **119b** (6.10 g, 25.5 mmol, 41%) as a colorless solid.

Spectroscopic data matched well with those reported in literature.[47g]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 – 6.31 (m, 1H), 5.45 – 5.17 (m, 1H), 4.53 – 4.17 (m, 1H), 3.75 – 3.53 (m, 3H), 2.88 – 2.67 (m, 1H) 1.48 (s, 9H), 1.01 – 0.88 (m, 1H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.5 (q), 173.3 (q), 151.2 (q), 150.9 (q), 129.8 (+), 129.6 (+), 109.8 (+), 81.7 (q), 51.8 (+), 44.3 (+), 44.2 (+), 32.2 (+), 31.0 (+), 28.2 (+), 22.9 (+), 22.7 (+) (signal doubling due to rotamers).

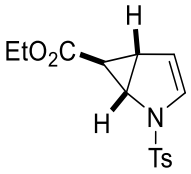
2-(*tert*-butyl) 6-ethyl (1*S*,5*S*,6*S*)-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (119d)[8b]



According to **GP-1**, $Cu(OTf)_2$ (482 mg, 1.33 mmol, 0.01 equiv) in dry CH_2Cl_2 (5 mL) was added to a solution of *tert*-butyl-1*H*-pyrrole-1-carboxylate **145** (22.3 g, 22.3 mL, 133 mmol, 1.0 equiv) in dry CH_2Cl_2 (42 mL). Phenylhydrazine (144 mg, 131 µL, 1.33 mmol, 0.01 equiv) and ethyl 2-diazoacetate (**118c**, 22.8 g, 9.73 wt%, 200 mmol, 1.5 equiv) in CH_2Cl_2 were added and the crude product was purified by silica gel column chromatography (17% EA:PE) to obtain cyclopropane **119d** (14.0 g, 55.3 mmol, 42%) as a yellowish oil. Recrystallization from pentane yielded pure cyclopropane **119d** (10.9 g, 43.1 mmol, 32%) as a colorless solid.

R_f = 0.78 (PE:EA = 2:1; $KMnO_4$, vanillin); **m.p.** = 43 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.71 – 6.28 (m, 1H), 5.45 – 5.23 (m, 1H), 4.44 – 4.21 (m, 1H), 4.16 – 4.04 (m, 2H), 2.88 – 2.62 (m, 1H), 1.48 (s, 9H), 1.26 – 1.20 (m, 3H), 0.97 – 0.85 (m, 1H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.2 (q), 172.9 (q), 151.3 (q), 151.0 (q), 129.8 (+), 129.6 (+), 109.9 (+), 81.7 (q), 60.6 (–), 44.3 (+), 44.1 (+), 32.2 (+), 31.0 (+), 28.3 (+), 23.1 (+), 23.0 (+), 14.3 (+) (signal broadening and doubling due to rotamers); **IR $\tilde{\nu}$** [cm^{-1}]: 3097, 3049, 2982, 2940, 2904, 1700, 1588, 1474, 1461, 1398, 1342, 1262, 1249, 1167, 1141, 1044, 1013, 939, 937, 902, 831, 814, 764, 729, 719; **HRMS** (ESI): calcd. for $C_{13}H_{19}NO_4$ $(M+H)^+$, m/z = 254.1387; found 254.1391.

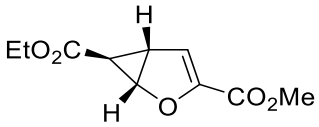
ethyl (1*S*,5*S*,6*S*)-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate (119f)[8b]



According to **GP-1**, $Cu(OTf)_2$ (361 mg, 998 µmol, 0.01 equiv) in dry CH_2Cl_2 (10 mL) was added to a solution of 1-tosyl-1*H*-pyrrole (22.1 g, 99.8 mmol, 1.0 equiv) in dry CH_2Cl_2 (60 mL). Phenylhydrazine (108 mg, 98 µL, 998 µmol, 0.01 equiv) and ethyl 2-diazoacetate (**118c**, 17.1 g, 10.7 wt%, 150 mmol, 1.5 equiv) in CH_2Cl_2 were added and the crude product was purified by silica gel column chromatography (10 → 17% EA:PE) to obtain cyclopropane **119f** (10.5 g, 34.2 mmol, 34%) as a colorless solid.

R_f = 0.36 (PE:EA = 5:1; $KMnO_4$, vanillin); **m.p.** = 66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.33 (d, *J* = 3.9 Hz, 1H), 5.45 (dd, *J* = 3.9, 2.7 Hz, 1H), 4.22 – 3.98 (m, 3H), 2.70 (dt, *J* = 6.1, 2.6 Hz, 1H), 2.44 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.48 – 0.43 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.2 (q), 144.5 (q), 133.7 (q), 130.5 (+), 130.1 (+), 127.6 (+), 113.8 (+), 61.0 (−), 45.4 (+), 31.6 (+), 21.8 (+), 21.1 (+), 14.4 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 3124, 2986, 2907, 1715, 1588, 1495, 1446, 1402, 1379, 1346, 1290, 1163; **HRMS** (ESI): calcd. for $C_{15}H_{17}NO_4S$ $(M+H)^+$, m/z = 308.0951; found 308.0957.

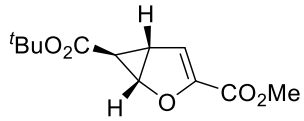
6-ethyl 3-methyl (1*S*,5*S*,6*S*)-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (120a)



According to **GP-2**, 2,2-bis((4*S*)-(–)-4-isopropyloxazoline) propane (743 mg, 2.79 mmol, 0.02 equiv) was added to a solution of $Cu(OTf)_2$ (504 mg, 1.39 mmol, 0.01 equiv) in dry CH_2Cl_2 (10 mL). The $Cu(OTf)_2$ solution was added to furan-2-carboxylmethylester (17.6 g, 14.9 mL, 139 mmol, 1.0 equiv) at 0°C. Then phenylhydrazine (151 mg, 1.39 mmol, 0.01 equiv) and the diazo ester **118c** (135 g, 17.7 wt%, 209 mmol, 1.5 equiv) in dry CH_2Cl_2 were added and the crude product was purified by silica gel column chromatography (9 → 20% EA:PE) to obtain the pure cyclopropane **120a** (16.0 g, 75.5 mmol, 54%) as a colorless solid.

Spectroscopic data matched well with those reported in literature.[47j]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 2.9 Hz, 1H), 4.94 (dd, *J* = 5.3, 1.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.84 (dt, *J* = 5.5, 2.8 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.13 (dd, *J* = 2.7, 1.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 171.8 (q), 159.5 (q), 149.2 (q), 116.2 (+), 67.6 (+), 61.1 (–), 52.3 (+), 32.0 (+), 21.5 (+), 14.2 (+);

6-(*tert*-butyl) 3-methyl (1*S*,5*S*,6*S*)-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (120b)[47j]

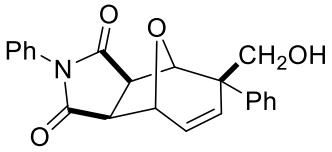


According to **GP-2**, 2,2-bis((4*S*)-(–)-4-isopropyloxazoline) propane (1.04 g, 3.90 mmol, 0.02 equiv) was added to a $Cu(OTf)_2$ (705 mg, 1.95 mmol, 0.01 equiv) in dry CH_2Cl_2 (10 mL). The $Cu(OTf)_2$ solution was added to furan-2-carboxylic acid methyl ester (24.6 g, 20.8 mL, 195 mmol, 1.0 equiv). Phenylhydrazine (211 mg, 192 µL, 1.95 mmol, 0.01 equiv) and *tert*-butyl 2-diazoacetate (**118d**, 41.6 g, 13.5 wt%, 293 mmol, 1.5 equiv) in CH_2Cl_2 were added and the crude product was purified by silica gel column chromatography (6% EA:PE) to obtain cyclopropane **120b** (14.1 g, 58.7 mmol, 30%) as a colorless solid.

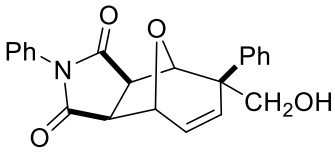
Spectroscopic data matched well with those reported in literature.[47j]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 2.9 Hz, 1H), 4.89 (dd, *J* = 5.3, 1.1 Hz, 1H), 3.80 (s, 3H), 2.78 (dt, *J* = 5.5, 2.8 Hz, 1H), 1.44 (s, 9H), 1.07 (dd, *J* = 2.7, 1.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.0 (q), 159.6 (q), 149.1 (q), 116.4 (+), 81.5 (q), 67.4 (+), 52.2 (+), 31.6 (+), 28.1 (+), 22.5 (+).

[3+2]-Cycloaddition reactions

(3a*R*,4*R*,5*S*,8*R*,8a*S*)-5-(hydroxymethyl)-2,5-diphenyl-4,5,8,8a-tetrahydro-4,8-epoxycyclohepta[c]pyrrole-1,3(2H,3aH)-dione (*endo*-Ph 131)
(3a*R*,4*R*,5*R*,8*R*,8a*S*)-5-(hydroxymethyl)-2,5-diphenyl-4,5,8,8a-tetrahydro-4,8-epoxycyclohepta[c]pyrrole-1,3(2H,3aH)-dione (*exo*-Ph 131)



endo-Ph **131** (29%)



exo-Ph **131** (25%)

A microwave vial was equipped with alcohol **120f** (112 mg, 597 µmol, 1.0 equiv), *N*-phenylmaleimide (**103**, 279 mg, 1.61 mmol, 2.7 equiv) and xylene (0.4 mL). The reaction mixture was heated in a microwave cavity for 1.5 h at 170 °C and the solvent was evaporated under reduced pressure. Purification of the crude product by flash system (33 → 50% EA:PE) yielded *endo*-Ph **131** (62.9 mg, 174 µmol, 29%) as a colorless solid and *exo*-Ph **131** (53.5 mg, 148 µmol, 25%) as a colorless oil.

***endo*-Ph 131: R_f** = 0.28 (PE:EA = 1:1; $KMnO_4$); **m.p.** = 198 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.50 – 7.19 (m, 10H), 6.37 (dd, *J* = 9.9, 4.2 Hz, 1H), 5.93 (dd, *J* = 9.9, 1.9 Hz, 1H), 4.97 (d, *J* = 4.2, 1H), 4.91 (d. *J* = 1.8 Hz, 1H), 4.08 (d, *J* = 11.3, 1H), 4.04 (d, *J* = 11.3, 1H), 4.00 (d, *J* = 7.4, 1H), 3.58 (d, *J* = 7.3, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 177.5 (q), 177.4 (q), 176.0 (q), 142.53 (q), 142.50 (q), 131.8 (q), 130.80 (+), 130.77 (+), 129.3 (+), 129.0 (+), 128.9 (+), 128.4 (+), 127.5 (+), 127.4 (+), 126.6 (+), 86.2 (+), 76.3 (+), 66.0 (–), 54.0 (+), 49.2 (q), 46.6 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3474, 1498, 1383, 1178, 1029, 962, 876, 753, 697; **HRMS** (ESI): calcd. for $C_{22}H_{19}NO_4$ $(M+NH_4)^+$, m/z = 379.1652; found 379.1652;

***exo*-Ph 131: R_f** = 0.49 (PE:EA = 1:1; $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.47 – 7.34 (m, 8H), 7.24 – 7.21 (m, 2H), 6.43 (dd, *J* = 10.1, 4.5 Hz, 1H), 6.18 (dd, *J* = 10.1, 1,9 Hz, 1H), 5.15 (br. s, 1H), 5.00 (d, *J* = 4.5 Hz, 1H), 4.01 (d, *J* = 10.9, 1H), 3.86 (d, *J* = 10.9, 1H), 3.42 (d, *J* = 7.5, 1H), 3.14 (d, *J* = 7.5, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 176.7 (q), 175.5 (q), 138.9 (q), 131.7 (q), 131.5 (+), 129.4 (+), 129.2 (+), 128.8 (+), 128.3 (+), 127.9 (+), 126.9 (+), 126.3 (+), 85.1 (+), 75.9 (+), 70.6 (–), 53.4 (+), 49.8 (q), 47.6 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3474, 3060, 2959, 2878, 1778, 1711, 1599, 1498, 1387, 1193, 1130, 1036, 977, 895, 839, 753, 701 **HRMS** (ESI): calcd. for $C_{22}H_{19}NO_4$ $(M+Na)^+$, m/z = 384.1206; found 384.1206.

General procedures for dipolar cycloaddition (GP-3a, GP-3b):

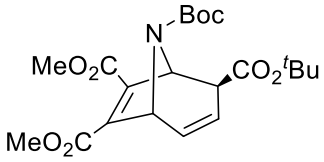
General procedure 3 (GP-3): Conditions I

A microwave vial equipped with a magnetic stirring bar was charged with cyclopropane **119a-d, 119e-f, 120a-b** (1.0 equiv) and dipolarophile (2.7 equiv). The mixture was stirred for 15-30 min at 150-170 °C under microwave irradiation. The solution was concentrated under reduced pressure and crude product was purified by column chromatography using EA:PE as eluent.

General procedure 4 (GP-4): Conditions II

A microwave vial equipped with a magnetic stirring bar was charged with cyclopropane **119b ,119d**, **119f, 120a-b** (1.0 equiv), dipolarophile (1.1-2.7 equiv) and toluene. The mixture was stirred for 0.25-1.5 h at 150-170 °C under microwave irradiation. The solution was concentrated under reduced pressure and crude product was purified by column chromatography using EA:PE as eluent.

2,8-di-*tert*-butyl 6,7-dimethyl (1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7,8-tetracarboxylate ((+)-133a)

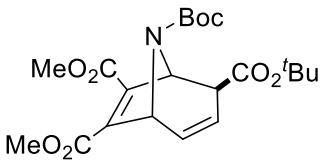


According to **GP-3**, **(+)-133a** was prepared from cyclopropane **(−)-119a** (103 mg, 365 µmol, 1.0 equiv) and DMAD (140 mg, 120 µL, 987 µmol, 2.7 equiv). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash system (5 → 13% EA:PE) to afford cycloadduct **(+)-133a** (125 mg, 295 µmol, 81%, 99% *ee*) as a colorless solid.

R_f = 0.58 (PE:EA = 3:1; UV, $KMnO_4$); **m.p.** = 51 °C; **HPLC analysis:** 99% *ee* (Phenomenex Lux Cellulose-2, *n*-heptane/*i*-propanol 90:10, 1.0 mL/min, 215 nm): t_r = 7.82 min; $[\alpha]_D^{20}$ = +73.2 (c = 1.0 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.35 (ddd, *J* = 9.6, 5.3, 2.1 Hz, 1H), 5.67 (ddd, *J* = 9.6, 3.9, 1.8 Hz, 1H), 5.53 (dt, *J* = 1.8, 0.9 Hz, 1H), 5.19 – 4.70 (m, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.09 (ddd, *J* = 3.8, 2.1, 1.0 Hz, 1H),

1.49 (s, 9H), 1.45 (s, 9H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.0 (q), 163.5 (q), 162.8 (q), 152.6 (q), 148.7 (q), 138.3 (q), 130.6 (+), 124.7 (+), 82.0 (q), 80.9 (q), 62.0 (+), 58.8 (+), 52.57 (+), 52.55 (+), 43.3 (+), 28.3 (+), 28.1 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2982, 1707, 1640, 1435, 1312, 1256, 1156, 1081, 1025, 947, 846, 783; **HRMS** (ESI): calcd. for $C_{21}H_{29}NO_8$ $(M+H)^+$, m/z = 424.1966, found 424.1969.

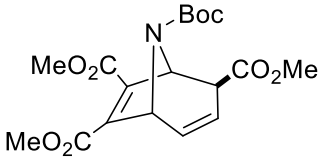
2,8-di-*tert*-butyl 6,7-dimethyl (1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7,8-tetracarboxylate (133a)



According to **GP-3**, **133a** was prepared from cyclopropane **119a** (1.24 g, 4.39 mmol, 1.0 equiv) and DMAD (1.68 g, 1.45 mL, 11.9 mmol, 2.7 equiv). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash system (5 → 13% EA:PE) to afford cycloadduct **133a** (1.54 g, 3.64 mmol, 83%) as a colorless solid.

NMR, m.p. and IR data were identical with those reported for the enantiomer **(+)-133a**.

8-(*tert*-butyl) 2,6,7-trimethyl (1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7,8-tetracarboxylate (133b)

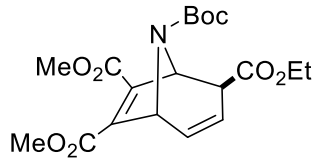


According to **GP-3**, **133b** was prepared from cyclopropane **119b** (1.00 g, 4.18 mmol, 1.0 equiv) and DMAD (1.60 g, 1.38 mL, 11.3 mmol, 2.7 equiv). The mixture was heated

for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash system (6 → 20% EA:PE) to afford cycloadduct **133b** (1.18 g, 3.09 mmol, 74%) as a yellowish oil.

R_f = 0.56 (PE:EA = 2:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.37 (ddd, *J* = 10.1, 5.3, 2.0 Hz, 1H), 5.66 (ddd, *J* = 9.7, 3.8, 1.8 Hz, 1H), 5.47 – 5.41 (m, 1H), 5.11 – 4.71 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.22 – 3.05 (m, 1H), 1.40 (s, 9H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.5 (q), 163.1 (q), 162.6 (q), 152.2 (q), 148.6 (q), 137.6 (q), 131.3 (+), 124.0 (+), 81.0 (q), 61.8 (+), 58.3 (+), 52.5 (+), 42.0 (+), 28.2 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2956, 1700, 1640, 2435, 1435, 1394, 1312, 1249, 1163, 1118, 1077, 1025, 947, 857, 760; **HRMS** (ESI): calcd. for $C_{18}H_{23}NO_8$ $(M+NH_4)^+$, m/z = 399.1762, found 399.1762.

8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7,8-tetracarboxylate (133c)

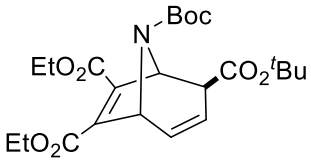


According to **GP-3**, **133c** was prepared from cyclopropane **119d** (1.02 g, 4.03 mmol, 1.0 equiv) and DMAD (1.55 g, 1.33 mL, 10.9 mmol, 2.7 equiv). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash system (6 → 15% EA:PE) to afford cycloadduct **133c** (1.15 g, 2.91 mmol, 72%) as a yellowish oil.

R_f = 0.62 (PE:EA = 2:1; $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.38 (ddd, *J* = 9.7, 5.2, 2.1 Hz, 1H), 5.69 (ddd, *J* = 9.6, 3.7, 1.8 Hz, 1H), 5.55 – 5.42 (m, 1H), 5.13 – 4.72 (m, 1H), 4.26 – 4.15 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.14 (ddd, *J* = 3.5, 2.2, 0.9 Hz, 1H), 1.42 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9 (q), 163.2 (q), 162.6 (q), 152.3 (q), 149.0 (q), 137.8 (q), 131.1 (+), 124.1 (+), 80.9 (q), 61.7 (+), 61.5 (–), 58.4 (+), 52.5 (+), 42.2 (+), 28.1 (+), 14.1 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2982, 1703, 1640, 1435, 1390,

1249, 1163, 1118, 1077, 1028, 947, 887, 857, 760; **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_8$ $(M+H)^+$, m/z = 418.1472; found 418.1474.

2,8-di-*tert*-butyl 6,7-diethyl (1*S*,2*S*,5*R*)-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7,8-tetracarboxylate (133d)[12][53]

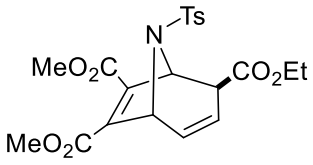


According to **GP-3**, **133d** was prepared from cyclopropane **119a** (56.0 mg, 199 µmol, 1.0 equiv) and DEAD (140 mg, 86 µL, 537 µmol, 2.7 equiv). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash column chromatography (5 → 13% EA:PE) to afford cycloadduct **133d** (57.9 mg, 130 µmol, 64%) as a colorless oil.

R_f = 0.30 (PE:EA = 5:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.34 (ddd, *J* = 9.6, 5.3, 2.1 Hz, 1H), 5.66 (ddd, *J* = 9.6, 3.9, 1.8 Hz, 1H), 5.50 (dt, *J* = 1.8, 0.9 Hz, 1H), 5.17 – 4.70 (m, 1H), 4.40 – 4.16 (m, 4H), 3.09 (ddd, *J* = 3.4, 2.2, 0.9 Hz, 1H), 1.48 (s, 9H), 1.44 (s, 9H), 1.35 – 1.27 (m, 6H) (signal broadening due to rotamers); **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.0 (q), 163.1 (q), 162.5 (q), 152.4 (q), 138.1 (q), 135.0 (q), 130.7 (+), 124.6 (+), 81.8 (q), 80.8 (q), 62.0 (+), 61.6 (–), 61.5 (–), 58.6 (+), 43.2 (+), 28.2 (+), 28.0 (+), 14.0 (+) (signal broadening due to rotamers); **IR $\tilde{\nu}$** [cm^{-1}]: 2982, 2937, 1707, 1640, 1476, 1457, 1392, 1368, 1305, 1252, 1159, 1115, 1077, 1033, 869, 844, 775; **HRMS** (ESI): calcd. for $C_{23}H_{33}NO_8$ $(M+H)^+$, m/z = 452.2279, found 452.2281.

[12] Synthesized by Dr. Saerom Park.

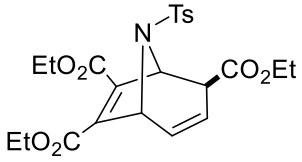
2-ethyl 6,7-dimethyl (1*S*,2*S*,5*R*)-8-tosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7-tricarboxylate (133e)[53]



According to **GP-3**, **133e** was prepared from cyclopropane **119f** (102 mg, 332 µmol, 1.0 equiv) and DMAD (127 mg, 110 µL, 896 µmol, 2.7 equiv). The mixture was heated for 15 min at 170 °C under microwave irradiation. The crude product was purified by flash system (16 → 41% EA:PE) to afford cycloadduct **133e** (105 mg, 234 µmol, 70%) as a colorless oil.

R_f = 0.43 (PE:EA = 2:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.64 – 7.60 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.35 (ddd, *J* = 9.5, 5.8, 2.1 Hz, 1H), 5.71 (ddd, *J* = 9.5, 4.0, 1.6 Hz, 1H), 5.44 – 5.40 (m, 1H), 4.85 (dd, *J* = 5.8, 1.1 Hz, 1H), 4.26 – 4.14 (m, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 3.16 (ddd, *J* = 3.7, 2.1, 1.0 Hz, 1H), 2.38 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.0 (q), 162.6 (q), 161.8 (q), 147.8 (q), 144.2 (q), 135.4 (q), 134.3 (q), 130.2 (+), 129.9 (+), 128.0 (+), 124.4 (+), 64.5 (+), 61.9 (–), 61.5 (+), 52.41 (+), 52.36 (+), 43.5 (+), 21.6 (+), 14.1 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 2982, 2956, 2931, 2856, 1711, 1644, 1599, 1439, 1349, 1287, 1245, 1163, 1126, 1088, 1022, 1021, 965, 936, 857, 816, 782, 753, 706, 690; **HRMS** (ESI): calcd. for $C_{21}H_{23}NO_8S$ $(M+H)^+$, m/z = 450.1217, found 450.1211.

triethyl (1*S*,2*S*,5*R*)-8-tosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2,6,7-tricarboxylate (133f)[13][53]

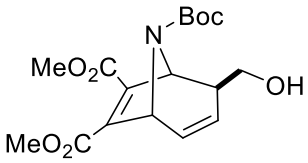


[13] Synthesized by Dr. Saerom Park.

According to **GP-4**, **133f** was prepared from cyclopropane **119f** (123 mg, 400 µmol, 1.0 equiv) and diethyl acetylenedicarboxylate (200 µL, 212 mg, 1.25 mmol, 3.0 equiv) in toluene (0.4 mL). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash system (5 → 13% EA:PE) to afford cycloadduct **133f** (115 mg, 240 µmol, 61%) as a colorless oil.

R_f = 0.38 (PE:EA = 2:1; UV; $KMNO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.66 – 7.57 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.35 (ddd, *J* = 9.5, 5.8, 2.1 Hz, 1H), 5.71 (ddd, *J* = 9.5, 3.9, 1.6 Hz, 1H), 5.41 (q, *J* = 1.3 Hz, 1H), 4.83 (dd, *J* = 5.8, 1.1 Hz, 1H), 4.27 – 4.06 (m, 6H), 3.16 (ddd, *J* = 3.5, 2.2, 1.1 Hz, 1H), 2.36 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.18 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.0 (q), 162.3 (q), 161.4 (q), 147.4 (q), 143.9 (q), 135.2 (q), 134.3 (q), 130.2 (+), 129.9 (+), 127.9 (+), 124.3 (+), 64.6 (+), 61.9 (–), 61.54 (+), 61.47 (–), 61.4 (–), 43.5 (+), 21.6 (+), 14.1 (+), 14.0 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 2982, 2933, 2908, 1711, 1640, 1599, 1447, 1446, 1394, 1370, 1353, 1286, 1241, 1163, 1091, 1081, 1036, 965, 938, 910, 855, 816, 735, 705, 687; **HRMS** (ESI): calcd. for $C_{23}H_{27}NO_8S$ $(M+Na)^+$, m/z = 500.1349; found 500.1350.

8-(*tert*-butyl) 6,7-dimethyl (1*R*,4*S*,5*S*)-4-(hydroxymethyl)-8-azabicyclo[3.2.1]octa-2,6-diene-6,7,8-tricarboxylate (133g)

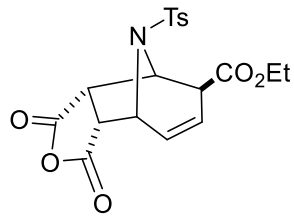


According to **GP-3**, **133g** was prepared from cyclopropane **119e** (96.0 mg, 454 µmol, 1.0 equiv) and DMAD (174 mg, 150 µL, 1.23 mmol, 2.7 equiv). The mixture was heated for 30 min at 100 °C under microwave irradiation. The crude product was purified by flash system (3 → 40% EA:PE) to afford cycloadduct **133g** (120 mg, 340 µmol, 75%) as a colorless oil.

R_f = 0.31 (PE:EA = 1:1; $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.33 (ddd, *J* = 9.7, 5.1, 1.9 Hz, 1H), 5.46 (ddd, *J* = 9.6, 3.6, 1.8 Hz, 1H), 5.18 – 5.07 (m, 1H), 4.97 – 4.74 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.71 – 3.58 (m, 1H), 2.53 – 2.33 (m, 2H), 1.46 (s, 9H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.3 (q), 162.7 (q), 152.3 (q), 147.3 (q), 138.1 (q), 131.0 (+), 127.5 (+), 81.1 (q), 63.6 (–), 60.4 (+),

58.4 (+), 52.5 (+), 52.4 (+), 40.4 (+), 28.3 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3437, 2978, 1700, 1640, 1431, 1367, 1327, 1260, 1163, 1118, 1077, 1033, 943, 861, 757, 731; **HRMS** (ESI): calcd. for $C_{17}H_{23}NO_7$ $(M+H)^+$, m/z = 354.1547; found 354.1547.

ethyl (3*aS*,4*S*,5*S*,8*R*,8*aR*)-1,3-dioxo-9-tosyl-3,3a,4,5,8,8a-hexahydro-1*H*-4,8-epiminocyclohepta[c]furan-5-carboxylate (133h)[14][53]

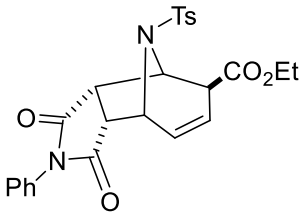


According to **GP-4**, **133h** was prepared from cyclopropane **119f** (307 mg, 1.00 mmol, 1.0 equiv) and maleic anhydride (108 mg, 1.10 mmol, 1.1 equiv) in toluene (2 mL). The mixture was heated for 1 h at 150 °C under microwave irradiation. The crude mixture was filtered through a short plug of silica gel and the solvent was removed under reduced pressure to afford the desired cycloaddition product **133h** (320 mg, 789 µmol, 79%) as a colorless solid.

R_f = 0.10 (PE:EA = 3:1, UV); **m.p.** = 155 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.77 – 7.70 (m, 2H), 7.36 – 7.28 (m, 2H), 6.13 (ddd, *J* = 9.6, 5.8, 1.8 Hz, 1H), 5.94 (ddd, *J* = 9.6, 4.5, 1.4 Hz, 1H), 5.14 (dq, *J* = 8.4, 1.6 Hz, 1H), 4.82 (ddd, *J* = 7.2, 5.9, 1.6 Hz, 1H), 4.18 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.10 – 3.90 (m, 2H), 3.83 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.49 (dt, *J* = 4.5, 1.8 Hz, 1H), 2.44 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.6 (q), 168.8 (q), 167.5 (q), 145.0 (q), 134.9 (q), 129.9 (+), 128.5 (+), 128.1 (+), 126.3 (+), 61.7 (–), 58.7 (+), 56.02 (+), 55.99 (+), 50.4 (+), 45.1 (+), 21.7 (+), 13.9 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2989, 1864, 1774, 1722, 1595, 1446, 1368, 1325, 1308, 1259, 1242, 1221, 1208, 1185, 1156, 1088, 1021, 1006, 987, 917, 902, 857, 813, 763, 719, 667; **HRMS** (ESI): calcd. for $C_{19}H_{19}NO_7S$ $(M+H)^+$, m/z = 406.0955; found 406.0955.

[14] Synthesized by Dr. Saerom Park.

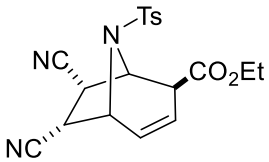
ethyl (3a*S*,4*R*,5*S*,8*R*,8a*R*)-1,3-dioxo-2-phenyl-9-tosyl-1,2,3,3a,4,5,8,8a-octahydro-4,8-epiminocyclohepta[c]pyrrole-5-carboxylate (133i)[15][53]



According to **GP-4**, **133i** was prepared from cyclopropane **119f** (154 mg, 501 µmol, 1.0 equiv) and *N*-phenylmaleimide (95.4 mg, 551 µmol, 1.1 equiv) in toluene (0.5 mL). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash column chromatography (33% EA:PE) to afford cycloadduct **133i** (154 mg, 320 µmol, 64%) as a colorless solid.

R_f = 0.29 (PE:EA = 2:1; UV); **m.p.** = 71 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.83 – 7.74 (m, 2H), 7.52 – 7.36 (m, 3H), 7.36 – 7.29 (m, 2H), 7.19 – 7.09 (m, 2H), 6.13 (ddd, *J* = 9.7, 5.8, 1.8 Hz, 1H), 5.95 (ddd, *J* = 9.6, 4.4, 1.4 Hz, 1H), 5.19 (dq, *J* = 8.3, 1.5 Hz, 1H), 4.97 – 4.79 (m, 1H), 4.11 – 3.78 (m, 4H), 3.53 (dt, *J* = 4.3, 1.7 Hz, 1H), 2.44 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 174.7 (q), 173.2 (q), 169.3 (q), 144.6 (q), 135.6 (q), 131.3 (q), 129.8 (+), 129.3 (+), 129.1 (+), 128.6 (+), 128.0 (+), 126.3 (+), 125.7 (+), 61.6 (–), 58.3 (+), 56.0 (+), 54.4 (+), 49.5 (+), 45.1 (+), 21.7 (+), 14.0 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 2982, 1707, 1595, 1498, 1457, 1579, 1353, 1327, 1304, 1185, 1156, 1088, 1049, 1029, 932, 906, 862, 817, 735, 717, 691, 664; **HRMS** (ESI): calcd. for $C_{25}H_{24}N_2O_6S$ $(M+H)^+$, m/z = 481.1428; found 481.1432.

ethyl (1*R*,2*S*,5*R*,6*R*,7*S*)-6,7-dicyano-8-tosyl-8-azabicyclo[3.2.1]oct-3-ene-2-carboxylate (133j)



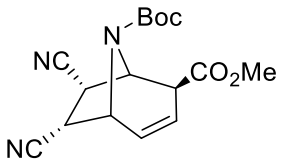
[15] Synthesized by Dr. Saerom Park.

According to **GP-4**, **133j** was prepared from cyclopropane **119f** (144 mg, 469 µmol, 1.0 equiv) and maleonitrile (98.8 mg, 1.26 mmol, 2.7 equiv) in toluene (0.3 mL). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product was purified by flash system (5 → 21% EA:PE) to afford *endo* **133j** (110 mg, 285 µmol, 61%) as a colorless solid.

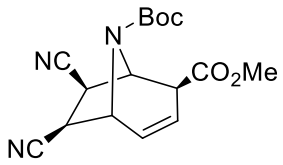
R_f = 0.52 (PE:EA = 3:2; UV, $KMNO_4$); **m.p.** = 174 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 – 7.65 (m, 2H), 7.40 – 7.27 (m, 2H), 6.28 (ddd, *J* = 9.6, 5.9, 1.9 Hz, 1H), 6.05 (ddd, *J* = 9.6, 4.5, 1.4 Hz, 1H), 5.12 (dq, *J* = 7.5, 1.5 Hz, 1H), 4.73 (td, *J* = 5.7, 1.5 Hz, 1H), 3.97 (ddd, *J* = 13.6, 10.8, 7.3 Hz, 2H), 3.84 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.75 (dd, *J* = 10.9, 5.5 Hz, 1H), 3.61 (dd, *J* = 4.2, 2.0 Hz, 1H), 2.44 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.6 (q), 145.3 (q), 134.7 (q), 129.9 (+), 128.7 (+), 128.0 (+), 125.5 (+), 115.9 (q), 115.0 (q), 61.8 (–), 58.8 (+), 56.3 (+), 46.5 (+), 40.7 (+), 35.3 (+), 21.7 (+), 13.9 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 2248, 1730, 1595, 1446, 1327, 1293, 1208, 1159, 1088, 1029, 980, 939, 898, 816, 760, 708, 664; **HRMS** (ESI): calcd. for $C_{19}H_{19}N_3O_4S$ $(M+Na)^+$, m/z = 408.0988; found 408.0987.

8-(*tert*-butyl) 2-methyl (1*R*,2*S*,5*R*,6*R*,7*S*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*endo* (–)-133k)

8-(*tert*-butyl) 2-methyl (1*R*,2*S*,5*R*,6*S*,7*R*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*exo* (–)-133k)



endo **(–)-133k**



exo **(–)-133k**

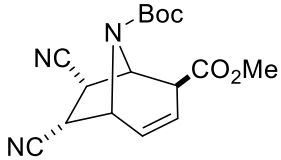
According to **GP-4**, **(–)-133k** was prepared from cyclopropane **(−)-119b** (150 mg, 627 µmol, 1.0 equiv) and maleonitrile (132 mg, 1.69 mmol, 2.7 equiv) in toluene (0.3 mL). The mixture was heated for 15 min at 150 °C under microwave irradiation. The crude product (diastereomeric ratio of *dr* 1:1) was purified by flash system (4 → 20% EA:PE) to afford *endo* **(–)-133k** (74.8 mg, 236 µmol, 38%, 99% *ee*) as a colorless solid and *exo* **(–)-133k** (66.1 mg, 208 µmol, 33%, 98% *ee*) as a colorless oil.

***endo* (–)-133k:** R_f = 0.52 (PE:EA = 3:2; $KMNO_4$); **m.p.** = 153 °C; **HPLC analysis:** 99% *ee* (Chiralcel OJ-H, *n*-heptane/*i*-propanol 70:30, 0.5 mL/min, 215 nm): t_r = 31.61 min; $[\alpha]_D^{20}$ = -132.3 (c = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.31 (ddd, *J* = 9.8, 5.4, 1.9 Hz, 1H), 6.07 (ddd, *J* = 9.8, 4.3, 1.5 Hz, 1H), 5.22 (dq, *J* = 7.6, 1.3 Hz, 1H), 4.79 (t, *J* = 5.6 Hz, 1H), 3.78 (dd, *J* = 10.9, 7.7 Hz, 1H), 3.75 (s, 3H), 3.55 (dt, *J* = 4.4, 1.5 Hz, 1H), 3.42 (dd, *J* = 10.8, 5.6 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9 (q), 152.0 (q), 129.2 (+), 125.5 (+), 116.0 (q), 115.2 (q), 82.3 (q), 56.0 (+), 53.7 (+), 52.7 (+), 45.1 (+), 39.6 (+), 35.4 (+), 28.1 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2978, 2251, 1737, 1700, 1394, 1342, 1260, 1163, 1118, 731; **HRMS** (ESI): calcd. for $C_{16}H_{19}N_3O_4$ $(M+Na)^+$, m/z = 340.1268; found 340.1271.

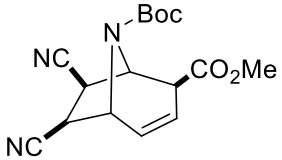
***exo* (–)-133k:** R_f = 0.29 (PE:EA = 3:2; $KMNO_4$); **HPLC analysis:** 98% *ee* (Phenomenex Lux Cellulose-1, *n*-heptane/*i*-propanol 70:30, 0.5 mL/min, 215 nm): t_r (*major*) = 42.56 min, t_r (*minor*) = 24.21 min; $[\alpha]_D^{20}$ = -60.0 (c = 1.0 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.23 – 6.08 (m, 1H), 5.82 (dd, *J* = 9.6, 4.1 Hz, 1H), 5.42 – 5.23 (m, 1H), 5.16 – 4.77 (m, 1H), 3.74 (s, 3H), 3.54 (d, *J* = 8.5 Hz, 1H), 3.36 (d, *J* = 8.3 Hz, 1H), 3.12 – 3.01 (m, 1H), 1.47 (s, 9H) (signal doubling and broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.3 (q), 152.1 (q), 129.9 (+), 124.2 (+), 123.9 (+), 117.2 (q), 116.6 (q), 82.3 (q), 59.4 (+), 58.6 (+), 57.4 (+), 56.4 (+), 52.7 (+), 48.6 (+), 48.3 (+), 41.4 (+), 38.4 (+), 37.5 (+), 28.0 (+) (signal doubling and broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 2930, 2244, 1733, 1670, 1394, 1338, 1238, 1156, 1118, 1066; **HRMS** (ESI): calcd. for $C_{16}H_{19}N_3O_4$ $(M+Na)^+$, m/z = 340.1268; found 340.1268.

8-(*tert*-butyl) 2-methyl (1*R*,2*S*,5*R*,6*R*,7*S*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*endo* 133k)

8-(*tert*-butyl) 2-methyl (1*R*,2*S*,5*R*,6*S*,7*R*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*exo* 133k)



endo **133k**



exo **133k**

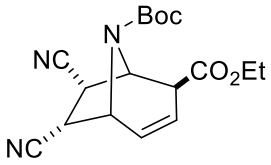
According to **GP-4**, **133k** was prepared from cyclopropane **119b** (158 mg, 660 µmol,

1.0 equiv) and maleonitrile (139 mg, 1.78 mmol, 2.7 equiv) in toluene (0.3 mL). The mixture was heated for 15 min at 150 °C under microwave irradiation. The crude product (diastereomeric ratio of *dr* 1:1) was purified by flash system (4 → 20% EA:PE) to afford *endo* **133k** (76.4 mg, 241 µmol, 36%) as a colorless solid and *exo* **133k** (70.0 mg, 221 µmol, 33%) as a colorless oil.

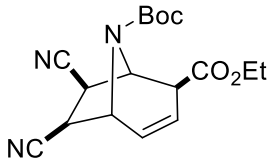
NMR, m.p. and IR data were identical with those reported for the enantiomers **(–)-133k**.

8-(*tert*-butyl) 2-ethyl (1*R*,2*S*,5*R*,6*R*,7*S*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*endo* 133l)

8-(*tert*-butyl) 2-ethyl (1*R*,2*S*,5*R*,6*S*,7*R*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*exo* 133l)



endo **133l**



exo **133l**

According to **GP-4**, **133l** was prepared from cyclopropane **119d** (154 mg, 608 µmol, 1.0 equiv) and maleonitrile (128 mg, 1.64 mmol, 2.7 equiv) in toluene (0.3 mL). The mixture was heated for 15 min at 150 °C under microwave irradiation. The crude product (diastereomeric ratio of *dr* 1:1) was purified by flash system (12 → 17% EA:PE) to afford *endo* **133l** (59.2 mg, 179 mol, 29%) and *exo* **133l** (66.0 mg, 199 µmol, 33%) both as a colorless oil.

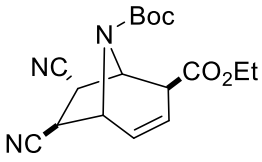
***endo* 133l: R_f** = 0.57 (PE:EA = 3:2; $KMNO_4$); **1H NMR** (400 MHz, $CDCl_3$) δ = 6.31 (ddd, *J* = 9.8, 5.4, 1.9 Hz, 1H), 6.08 (dddd, *J* = 9.8, 4.4, 1.6, 0.7 Hz, 1H), 5.30 – 5.21 (m, 1H), 4.80 (t, *J* = 5.5 Hz, 1H), 4.29 – 4.12 (m, 2H), 3.76 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.54 (d, *J* = 4.6 Hz, 1H), 3.39 (dd, *J* = 10.8, 5.6 Hz, 1H), 1.43 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 169.4 (q), 152.1 (q), 129.0 (+), 125.7 (+), 115.98 (q), 115.96 (q), 115.19 (q), 115.17 (q), 82.3 (q), 61.8 (–), 56.0 (+), 53.8 (+), 45.3 (+), 39.6 (+), 35.4 (+), 28.1 (+), 14.1 (+) (signal doubling and broadening due to rotamers); **IR $\tilde{\nu}$** [cm^{-1}]: 3060, 2982, 2248, 1409, 1737, 1670, 1476, 1409, 1368, 1355, 1252, 1174, 1118, 1033,

958, 861, 820, 753, 690; **HRMS** (ESI): calcd. for $C_{17}H_{21}N_3O_4$ $(M+Na)^+$, m/z =354.1424; found 354.1428.

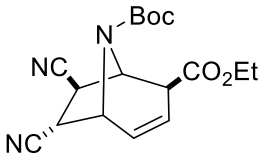
***exo* 133l: R_f** = 0.25 (PE:EA = 3:2; $KMNO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 6.20 – 6.06 (m, 1H), 5.82 (ddd, *J* = 9.7, 4.4, 1.6 Hz, 1H), 5.49 – 5.26 (m, 1H), 5.15 – 4.81 (m, 1H), 4.27 – 4.13 (m, 2H), 3.53 (d, *J* = 8.4 Hz, 1H), 3.35 (d, *J* = 8.4 Hz, 1H), 3.04 (dt, *J* = 3.8, 1.7 Hz, 1H), 1.48 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H) (signal doubling and broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 168.7 (q), 152.0 (q), 129.6 (+), 124.3 (+), 123.4 (+), 117.1 (q), 116.5 (q), 82.2 (q), 61.8 (–), 59.39 (+), 58.44 (+), 57.3 (+), 56.4 (+), 48.6 (+), 41.4 (+), 38.2 (+), 37.5 (+), 27.9 (+), 14.0 (+) (signal doubling and broadening due to rotamers); **IR $\tilde{\nu}$** [cm^{-1}]: 2982, 2933, 2248, 1726, 1457, 1394, 1338, 1308, 1256, 1189, 1118, 939, 854, 772, 670; **HRMS** (ESI): calcd. for $C_{17}H_{21}N_3O_4$ $(M+Na)^+$, m/z =354.1424; found 354.1426.

8-(*tert*-butyl) 2-ethyl (1*R*,2*S*,5*R*,6*S*,7*S*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*major* 133m)

8-(*tert*-butyl) 2-ethyl (1*R*,2*S*,5*R*,6*R*,7*R*)-6,7-dicyano-8-azabicyclo[3.2.1]oct-3-ene-2,8-dicarboxylate (*minor* 133m)



major **133m**



minor **133m**

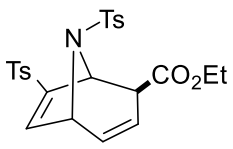
According to **GP-4**, **133m** was prepared from cyclopropane **119d** (102 mg, 403 µmol, 1.0 equiv) and fumaronitrile (85.0 mg, 1.09 mmol, 2.7 equiv) in toluene (0.3 mL). The mixture was heated for 1 h at 150 °C under microwave irradiation. The crude product (diastereomeric ratio of *dr* 4.5:1) was purified by flash system (12 → 19% EA:PE) to afford *major* **7j** (25.4 mg, 76.7 µmol, 19%) and inseparable mixture of *major* and *minor* **133m** (81.2 mg, 245 µmol, 61%, *dr* 3.2:1) both as a colorless oil.

R_f = 0.45 (PE:EA = 3:1; $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*major* **133m**) = 6.20 (ddd, *J* = 9.8, 5.5, 1.9 Hz, 1H), 5.96 (ddd, *J* = 9.6, 4.3, 1.5 Hz, 1H), 5.50 – 5.30 (m, 1H), 5.01 – 4.69 (m, 1H), 4.32 – 4.10 (m, 2H), 3.65 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.46 (dt, *J* = 4.5,

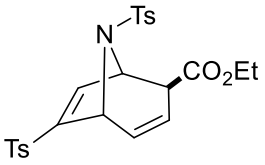
1.5 Hz, 1H), 3.34 (d, *J* = 3.6 Hz, 1H), 1.46 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*major* **133m**) = 169.3 (q), 152.2 (q), 129.8 (+), 125.1 (+), 118.0 (q), 117.2 (q), 82.6 (q), 62.0 (–), 57.1 (+), 55.9 (+), 45.1 (+), 41.4 (+), 37.1 (+), 28.1 (+), 14.2 (+) (signal broadening due to rotamers); *major* **133m**: **IR** $\tilde{\nu}$ [cm^{-1}]: 2982, 2937, 2248, 1707, 1476, 1394, 1372, 1334, 1260, 1163, 1118, 1085, 1036, 977, 910, 760, 723; **HRMS** (ESI): calcd. for $C_{17}H_{21}N_3O_4$ $(M+Na)^+$, m/z = 354.1424; found 354.1424 (*major* **133m** t_r = 2.424-2.474 min); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*minor* **133m**) = 6.26 (dddd, *J* = 9.8, 5.5, 2.1, 0.9 Hz, 1H), 5.98 – 5.91 (m, 1H)*, 5.28 – 5.24 (m, 1H), 4.96 – 4.75 (m, 1H)*, 4.25 – 4.13 (m, 2H)*, 3.29 (dd, *J* = 7.0, 5.6 Hz, 1H), 3.18 (dd, *J* = 7.0, 1.4 Hz, 1H), 3.08 (dt, *J* = 3.8, 1.6 Hz, 1H), 1.44 (s, 9H)*, 1.29 – 1.25 (m, 3H)* (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*minor* **133m**) = 168.8 (q), 152.4 (q), 129.0 (+), 125.0 (+), 118.2 (q), 116.2 (q), 82.5 (q), 61.9 (–), 59.7 (+), 54.4 (+), 48.8 (+), 42.0 (+), 38.3 (+), 28.0 (+)*, 14.1 (+)* (signal broadening due to rotamers; *these signals are overlapping with major diastereomer); **HRMS** (ESI): calcd. for $C_{17}H_{21}N_3O_4$ $(M+Na)^+$, m/z = 354.1424; found 354.1423 (*minor* **133m** t_r = 2.483-2.520 min).

ethyl (1*S*,2*S*,5*R*)-7,8-ditosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2-carboxylate (*major* 133o)

ethyl (1*S*,2*S*,5*R*)-6,8-ditosyl-8-azabicyclo[3.2.1]octa-3,6-diene-2-carboxylate (*minor* 133o)



major **133o**

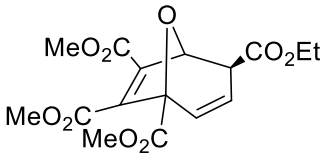


minor **133o**

According to **GP-4**, **133o** was prepared from cyclopropane **119f** (252 mg, 818 µmol, 1.0 equiv) and tosylacetylene (399 mg, 2.21 mmol, 2.7 equiv) in toluene (0.3 mL). The mixture was heated for 30 min at 150 °C under microwave irradiation. The crude product (diastereomeric ratio of *dr* 4.0:1) was purified by flash system (17 → 25% EA:PE) to afford *major* **133o** (30.0 mg, 61.5 µmol, 8%) as a colorless solid and mixture of *major* and *minor* **133o** (62.3 mg, 128 µmol, 16%, *dr* 1.7:1) as a colorless oil.

R_f = 0.46 (PE:EA = 2:1; $KMnO_4$); **m.p.** = 49 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*major* **133o**) = 7.64 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 2.3 Hz, 1H), 6.23 (ddd, *J* = 9.5, 5.7, 2.1 Hz, 1H), 5.71 (ddd, *J* = 9.5, 4.0, 1.6 Hz, 1H), 5.35 (bs, 1H), 4.73 (dd, *J* = 5.8, 2.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.27 (ddd, *J* = 3.5, 2.1, 1.0 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*major* **133o**) = 168.8 (q), 148.0 (+), 145.3 (q), 143.9 (q), 142.3 (q), 135.8 (q), 134.7 (q), 130.04 (+), 129.8 (+), 128.9 (+), 128.2 (+), 127.8 (+), 125.6 (+), 62.2 (+), 61.8 (–), 60.0 (+), 44.7 (+), 21.8 (+), 21.6 (+), 14.1(+); *major* **133o**: **IR $\tilde{\nu}$** [cm^{-1}]: 3060, 2982, 2926, 1737, 1595, 1450, 1353, 1305, 1230, 1152, 1096, 1040, 969, 731, 645; **HRMS** (ESI): calcd. for $C_{24}H_{25}NO_6S_2$ $(M+Na)^+$, m/z = 510.1016; found 510.1015 (*major* **133o** t_r = 2.926-2.972 min);**^{1}H NMR** (400 MHz, $CDCl_3$): δ (*minor* **133o**) = 7.53 – 7.49 (m, 2H), 7.35 – 7.31 (m, 4H)*, 7.18 (d, *J* = 8.1 Hz, 2H), 6.25 (d, *J* = 2.5 Hz, 1H), 6.14 (ddd, *J* = 9.5, 5.7, 2.1 Hz, 1H), 5.54 (ddd, *J* = 9.5, 3.9, 1.5 Hz, 1H), 5.20 (d, *J* = 1.1 Hz, 1H), 4.81 (d, *J* = 5.7 Hz, 1H), 4.21 – 4.11 (m, 2H)*, 2.88 (ddd, *J* = 3.5, 2.1, 0.9 Hz, 1H), 2.46 (s, 3H), 2.40 (s, 3H)*, 1.29 – 1.22 (m, 3H)*; **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*minor* **133o**) = 169.0 (q), 155.5 (q), 145.4 (q), 144.0 (q), 135.6 (q), 134.9 (+), 134.4 (q), 131.7 (+), 130.02 (+), 129.9 (+), 128.3 (+), 127.9 (+), 122.5 (+), 62.7 (+), 62.0 (–), 58.9 (+), 42.9 (+), 21.8 (+)*, 21.6 (+)*, 14.1 (+)* (*these signals are overlapping with *major* diastereomer); **HRMS** (ESI): calcd. for $C_{24}H_{25}NO_6S_2$ $(M+Na)^+$, m/z = 510.1016; found 510.1015 (*major* and *minor* **133o** t_r = 2.926-2.972 min).

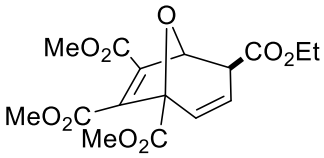
4-ethyl 1,6,7-trimethyl (1*R*,4*S*,5*S*)-8-oxabicyclo[3.2.1]octa-2,6-diene-1,4,6,7-tetracarboxylate ((+)-140a)



According to **GP-3**, **(+)-140a** was prepared from cyclopropane **(−)-120a** (1.67 g, 7.87 mmol, 1.0 equiv) and DMAD (3.02 g, 2.60 mL, 21.3 mmol, 2.7 equiv). The mixture was heated for 30 min at 170 °C under microwave irradiation. The crude product was purified by flash system (6 → 37% EA:PE) to afford cycloadduct **(+)-140a** (1.98 g, 5.59 mmol, 71%, 99% *ee*) as a colorless solid.

R_f = 0.21 (PE:EA = 3:1; $KMnO_4$); **m.p.** = 64 °C; **HPLC analysis:** 99% *ee* (Chiralcel AS-H, *n*-heptane/*i*-propanol 90:10, 1.0 mL/min, 215 nm): t_r (*major*) = 18.96 min, t_r (*minor*) = 24.37 min; $[\alpha]_D^{20}$ = +128.7 (c = 1.0 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.59 (dd, *J* = 9.8, 2.3 Hz, 1H), 5.89 (ddd, *J* = 9.8, 4.2, 1.9 Hz, 1H), 5.76 (d, *J* = 1.8 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.02 (dd, *J* = 4.0, 2.1 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.5 (q), 166.7 (q), 162.2 (q), 162.0 (q), 150.2 (q), 134.7 (q), 130.7 (+), 124.1 (+), 86.1 (q), 80.7 (+), 61.9 (–), 53.2 (+), 52.9 (+), 52.7 (+), 40.6 (+), 14.2 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2989, 2960, 1722, 1655, 1439, 1368, 1260, 1193, 1144, 1029, 850, 727, 667; **HRMS** (ESI): calcd. for $C_{16}H_{18}O_9$ $(M+H)^+$, m/z = 355.1024; found 355.1032.

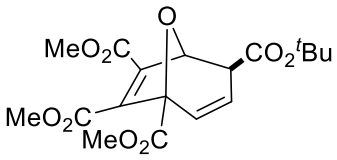
4-ethyl 1,6,7-trimethyl (1*R*,4*S*,5*S*)-8-oxabicyclo[3.2.1]octa-2,6-diene-1,4,6,7-tetracarboxylate (140a)



According to **GP-3**, **140a** was prepared from cyclopropane **120a** (215 mg, 1.01 mmol, 1.0 equiv) and DMAD (389 mg, 335 µL, 2.74 mmol, 2.7 equiv). The mixture was heated for 30 min at 170 °C under microwave irradiation. The crude product was purified by flash system (6 → 37% EA:PE) to afford cycloadduct **140a** (250 mg, 706 µmol, 70%) as a colorless solid.

NMR, m.p. and IR data were identical with those reported for the enantiomer **(+)-140a**.

4-(*tert*-butyl) 1,6,7-trimethyl (1*R*,4*S*,5*S*)-8-oxabicyclo[3.2.1]octa-2,6-diene-1,4,6,7-tetracarboxylate (140b)

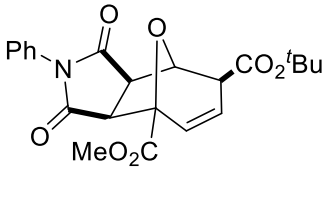


According to **GP-3**, **140b** was prepared from cyclopropane **120b** (607 mg, 2.53 mmol, 1.0 equiv) and DMAD (969 mg, 836 µL, 6.82 mmol, 2.7 equiv). The mixture was heated for 30 min at 170 °C under microwave irradiation. The crude product was purified by flash system (6 → 37% EA:PE) to afford cycloadduct **140b** (726 mg, 1.90 mmol, 75%) as a colorless oil.

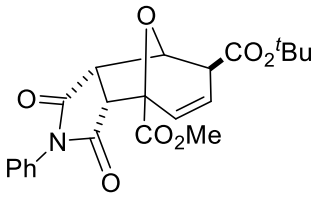
R_f = 0.62 (PE:EA = 2:1; $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.57 (dd, *J* = 9.8, 2.3 Hz, 1H), 5.84 (ddd, *J* = 9.8, 4.1, 1.9 Hz, 1H), 5.70 (d, *J* = 1.8 Hz, 1H), 3.81 (s, 6H), 3.79 (s, 3H), 2.93 (ddd, *J* = 4.1, 2.3, 0.7 Hz, 1H), 1.47 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 168.4 (q), 166.8 (q), 162.11 (q), 162.08 (q), 149.6 (q), 135.2 (q), 130.3 (+), 124.5 (+), 85.9 (q), 82.4 (q), 80.7 (+), 53.1 (+), 52.7 (+), 52.6 (+), 41.3 (+), 28.0 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 1722, 1651, 1439, 1245, 1200, 1148, 1077, 1006, 731; **HRMS** (ESI): calcd. for $C_{18}H_{22}O_9$ $(M+H)^+$, m/z = 383.1337; found 383.1336.

7-(*tert*-butyl) 4-methyl (3a*S*,4*R*,7*S*,8*R*,8a*R*)-1,3-dioxo-2-phenyl-2,3,3a,7,8,8a-hexahydro-4,8-epoxycyclohepta[c]pyrrole-4,7(1*H*)-dicarboxylate (*major* 140c)

7-(*tert*-butyl) 4-methyl (3a*R*,4*R*,7*S*,8*R*,8a*S*)-1,3-dioxo-2-phenyl-2,3,3a,7,8,8a-hexahydro-4,8-epoxycyclohepta[c]pyrrole-4,7(1*H*)-dicarboxylate (*minor* 140c)



major **140c**



minor **140c**

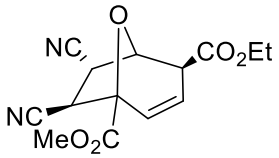
According to **GP-4**, **140c** was prepared from cyclopropane **120b** (100 mg, 416 µmol, 1.0 equiv) and *N*-phenylmaleimide (195 mg, 1.12 mmol, 2.7 equiv) in toluene (1 mL). The

mixture was heated for 1.5 h at 150 °C under microwave irradiation. The crude product (diastereomeric ratio of *dr* 2.9:1) was purified by flash column chromatography (33% EA:PE) to afford inseparable mixture of *major* and *minor* **140c** (124 mg, 299 µmol, 72%, *dr* 2.8:1) as a colorless solid. Recrystallization from toluene led to separation of pure *major* **140c** (47 mg, 114 µmol, 27%) as a colorless solid.

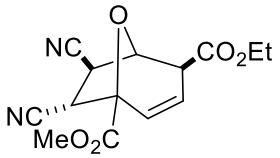
R_f = 0.23 (PE:EA = 1:1; $KMnO_4$); **m.p.** = 144 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*major* **140c**) = 7.51 – 7.36 (m, 3H), 7.29 – 7.27 (m, 2H, overlapping with solvent signal), 6.55 (dd, *J* = 9.9, 2.1 Hz, 1H), 5.98 (ddd, *J* = 9.9, 4.5, 1.6 Hz, 1H), 5.49 (bs, 1H), 3.86 (s, 3H), 3.79 (d, *J* = 7.5 Hz, 1H), 3.36 (dd, *J* = 7.5, 1.0 Hz, 1H), 2.93 (ddd, *J* = 4.5, 2.1, 0.7 Hz, 1H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*major* **140c**) = 175.3 (q), 172.8 (q), 168.2 (q), 167.4 (q), 131.41 (+), 131.36 (q), 129.2 (+), 129.0 (+), 126.4 (+), 123.8 (+), 83.0 (q), 82.5 (q), 79.5 (+), 57.5 (+), 53.1 (+), 50.3 (+), 47.1 (+), 28.1 (+); *major* **140c**: **IR** $\tilde{\nu}$ [cm^{-1}]: 2974, 1711, 1372, 1204, 1156, 1096, 1070, 846, 731; **HRMS** (ESI): calcd. for $C_{22}H_{23}NO_7$ $(M+H)^+$, m/z = 414.1547; found 414.1548 (*major* **140c** t_r = 2.636-2.644 min); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*minor* **140c**) = 7.44 – 7.36 (m, 3H)*, 7.22 – 7.17 (m, 2H), 6.41 (dd, *J* = 10.0, 2.1 Hz, 1H), 6.11 (ddd, *J* = 10.0, 4.6, 1.7 Hz, 1H), 5.48 (dd, *J* = 9.1, 1.4 Hz, 1H)*, 4.11 (dd, *J* = 9.6, 8.6 Hz, 1H), 3.96 (d, *J* = 9.5 Hz, 1H), 3.91 (s, 3H), 3.27 (dd, *J* = 4.7, 2.1 Hz, 1H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*minor* **140c**) = 174.4 (q), 171.5 (q), 168.5 (q), 168.0 (q), 131.36 (q)*, 129.3 (+), 129.1 (+), 127.9 (+), 126.32 (+), 126.30 (+), 82.3 (q), 80.7 (q), 76.7 (+), 57.8 (+), 53.4 (+), 49.7 (+), 43.2 (+), 28.0 (+)* (*these signals are overlapping with major diastereomer); **HRMS** (ESI): calcd. for $C_{22}H_{23}NO_7$ $(M+H)^+$, m/z = 414.1547; found 414.1552 (*minor* **140c** t_r = 2.686-2.732 min).

4-ethyl 1-methyl (1*R*,4*S*,5*R*,6*R*,7*R*)-6,7-dicyano-8-oxabicyclo[3.2.1]oct-2-ene-1,4-dicarboxylate (*major* (–)-140d)

4-ethyl 1-methyl (1*R*,4*S*,5*R*,6*S*,7*S*)-6,7-dicyano-8-oxabicyclo[3.2.1]oct-2-ene-1,4-dicarboxylate (*minor* 140d)



major (–)-**140d**



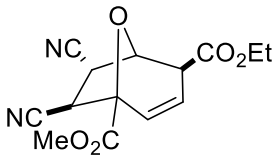
minor **140d**

According to **GP-4**, **140d** was prepared from cyclopropane **(−)-120a** (566 mg, 2.67 mmol, 1.0 equiv) and fumaronitrile (562 mg, 7.20 mmol, 2.7 equiv) in toluene (0.5 mL). The mixture was heated for 15 min at 170 °C under microwave irradiation. The crude mixture (diastereomeric ratio of *dr* 3.7:1) was recrystallized from toluene to obtain pure *major* **(–)-140d** (390 mg, 1.34 mmol, 50%, 99% *ee*) as a colorless solid. The filtrate was concentrated under reduced pressure. The residue was purified by flash system (17 → 20% EA:PE) to afford inseparable mixture of *major* and *minor* **140d** (181 mg, 624 µmol, 23%, *dr* 1:1) as a colorless solid.

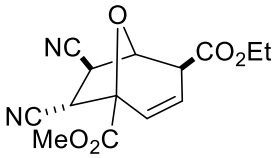
R_f = 0.47 (PE:EA = 2:1, $KMnO_4$); **m.p.** = 165 °C; **HPLC analysis:** 99% *ee* (Chiralpak AS-H, *n*-heptane/*i*-propanol 50:50, 0.5 mL/min, 215 nm): t_r = 25.61 min; $[\alpha]_D^{20}$ = -31.4 (c = 1.0 in $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ (*major* **(–)-140d**) = 6.33 (dd, *J* = 9.8, 2.0 Hz, 1H), 6.19 (ddd, *J* = 9.8, 4.7, 1.6 Hz, 1H), 5.57 (d, *J* = 7.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 3.87 (dd, *J* = 8.0, 3.5 Hz, 1H), 3.75 (d, *J* = 3.5 Hz, 1H), 3.35 (dd, *J* = 4.7, 1.8 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ (*major* **(–)-140d**) = 168.5 (q), 166.2 (q), 128.9 (+), 125.5 (+), 116.4 (q), 115.9 (q), 84.0 (q), 76.3 (+), 62.16 (–), 53.8 (+), 45.0 (+), 43.3 (+), 36.6 (+), 14.1 (+); *major* **(–)-140d**: **IR** $\tilde{\nu}$ [cm^{-1}]: 3086, 2993, 2251, 1759, 1722, 1439, 1327, 1264, 1193, 1111, 1085, 1028, 839, 887, 731; **HRMS** (ESI): calcd. for $C_{14}H_{14}N_2O_5$ $(M+Na)^+$, m/z = 313.0795; found 313.0798 (*major* **(–)-140d** t_r = 1.866-1.870 min); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*minor* **140d**) = 6.42 (dd, *J* = 9.9, 2.0 Hz, 1H), 6.23 – 6.14 (m, 1H)*, 5.48 – 5.42 (m, 1H), 4.31 – 4.18 (m, 2H)*, 3.91 (s, 3H), 3.62 (d, *J* = 7.4 Hz, 1H), 3.38 – 3.31 (m, 1H)*, 3.01 (dd, *J* = 4.8, 2.0 Hz, 1H), 1.32 – 1.26 (m, 3H)*; **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*minor* **140d**) = 168.0 (q), 166.1 (q), 127.9 (+), 125.1 (+), 117.1 (q), 114.8 (q), 81.9 (q), 79.5 (+), 62.22 (–), 53.9 (+), 46.9 (+), 45.9 (+), 38.1 (+), 14.1 (+)* (*these signals are overlapping with major diastereomer); **HRMS** (ESI): calcd. for $C_{14}H_{14}N_2O_5$ $(M+Na)^+$, m/z = 313.0795; found 313.0796 (*minor* **140d** t_r = 1.913-2.005 min).

4-ethyl 1-methyl (1*R*,4*S*,5*R*,6*R*,7*R*)-6,7-dicyano-8-oxabicyclo[3.2.1]oct-2-ene-1,4-dicarboxylate (*major* 140d)

4-ethyl 1-methyl (1*R*,4*S*,5*R*,6*S*,7*S*)-6,7-dicyano-8-oxabicyclo[3.2.1]oct-2-ene-1,4-dicarboxylate (*minor* 140d)



major **140d**

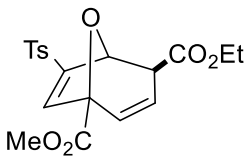


minor **140d**

According to **GP-4**, **140d** was prepared from cyclopropane **120a** (268 mg, 1.26 mmol, 1.0 equiv) and fumaronitrile (266 mg, 3.41 mmol, 2.7 equiv) in toluene (0.25 mL). The mixture was heated for 15 min at 170 °C under microwave irradiation. The crude mixture (diastereomeric ratio of *dr* 3.6:1) was recrystallized from toluene to obtain pure *major* **140d** (179 mg, 1.26 mmol, 49%) as a colorless solid. The filtrate was concentrated under reduced pressure. The residue was purified by flash system (17 → 20% EA:PE) to afford inseparable mixture of *major* and *minor* **140d** (80.7 mg, 278 µmol, 22%, *dr* 1:1) as a colorless solid.

NMR, m.p. and IR data were identical with those reported for the enantiomer **(–)-140d**.

4-ethyl 1-methyl (1*R*,4*S*,5*S*)-6-tosyl-8-oxabicyclo[3.2.1]octa-2,6-diene-1,4-dicarboxylate (140e)

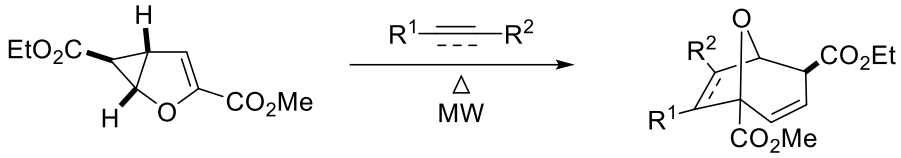


According to **GP-4**, **140e** was prepared from cyclopropane **120a** (109 mg, 514 µmol, 1.0 equiv) and tosylacetylene (250 mg, 1.39 mmol, 2.7 equiv) in toluene (0.2 mL). The mixture was heated for 30 min at 160 °C under microwave irradiation. The crude product was purified by flash system (8 → 35% EA:PE) to afford cycloadduct **140e** (92.0 mg, 234 µmol, 46%) as a colorless oil.

R_f = 0.50 (PE:EA = 3:2; $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.30 (s, 1H), 6.37 (dd, *J* = 9.7, 2.2 Hz, 1H), 5.89 (dddd, *J* = 9.7, 4.1, 2.0, 0.8 Hz, 1H), 5.54 (d, *J* = 1.8 Hz, 1H), 4.29 – 4.14 (m, 2H), 3.81 (s, 3H), 3.22 (dd, *J* = 3.9, 2.4 Hz, 1H), 2.45 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.3 (q), 167.4 (q), 147.2 (+), 145.7 (q), 144.0 (q), 135.6 (q), 130.3 (+), 130.1 (+), 128.1 (+), 125.1 (+), 85.5 (q), 79.5 (+), 61.9 (–), 53.2 (+), 41.5 (+), 21.7 (+), 14.1 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 3086, 2982, 2926, 1733, 1595, 1439, 1402, 1368, 1305, 1215, 1148, 1118, 1025, 969, 943, 880, 816, 671; **HRMS** (ESI): calcd. for $C_{19}H_{20}O_7S$ $(M+H)^+$, m/z = 393.1003; found 393.1003.

Screening of various dipolarophiles with different electronic distributions

Table 26. Screening of cycloaddition with various dipolarophiles and monocyclopropanated furan **120a**.



120a **140**

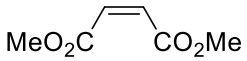
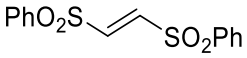
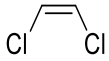
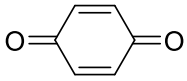
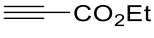
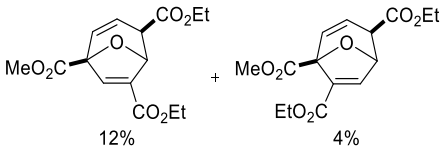
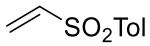
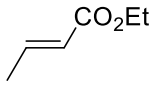
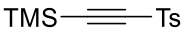
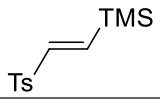
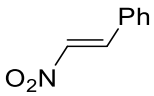
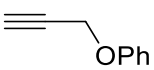
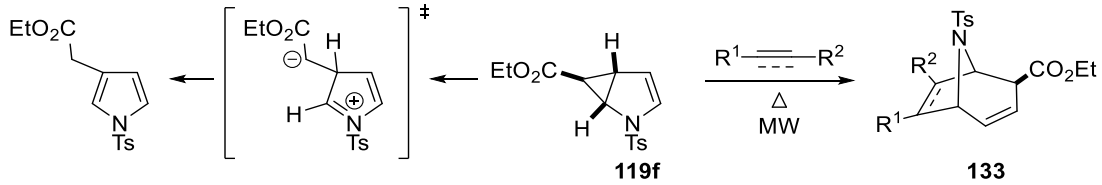
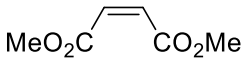
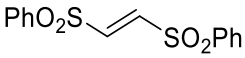
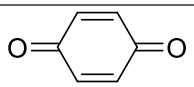
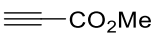
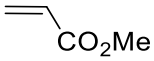
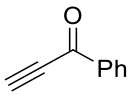
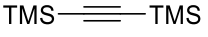
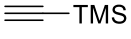
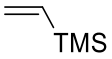
entry	R^1—≡—R^2	T [°C]	time [h]	product
1		170	1	partial conversion
2		150	0.5	-
3		150 → 170	2.5	complex mixture
4		150	1.5	complex mixture
5		170	1	 12% 4%
6		150	3	no conversion
7		150 → 180	2.5	no conversion
8		150 → 170	2	complex mixture
9		170	0.5	complex mixture
10		150 → 170	1 → 1	decomposition
11		150 → 160	1 → 2	no conversion
12		170	1.5	no conversion
13		150	3	no conversion
14		170	1	decomposition

Table 27. Screening of cycloaddition with various dipolarophiles and monocyclopropanated pyrrole **119f**.[53]16



entry	R^1—≡—R^2	T [°C]	time [h]	product
1		180	0.25	rearomatization
2		200	1	rearomatization
3		135	0.25	-
4		150	1	rearomatization
5		100 → 130	0.25 → 1	no conversion
6		150	1	-
7		180	1	-
8		150	1	rearomatization
9		150	0.5	rearomatization
10		150 → 200	1	rearomatization

[16] Screening carried out by Dr. Saerom Park.

Cooperation Barham group, University of Regensburg:

Microwave flow reactor and reactor tubes for [3+2]-cycloadditions

Details of the MW flow reactor, designed by SAIDA FDS Inc. have been described in previous publications.[56i] The reactor consists of a pump unit, a MW generator, a resonant cavity (100 W: 8 cm x 8 cm x 10 cm; 250 W: 8 cm x 8 cm x 20 cm), a helical tubular borosilicate glass tube reactor (channel i.d. 6.0 mm, channel i.d. 3.6 mm, coil i.d. 20.0 mm, internal volume in the resonant cavity: 100 W: 2.5 mL; 250 W: 5.2 mL), and a power controller. The MW generator is a solid-state device which generates a uniform electromagnetic field within the resonant cavity. The tuning of the irradiation frequency used a technology which adjusts the frequency for detected electric power in the resonator to be maximized. The device output is up to 100 W or 250 W in the 2.4 - 2.5 GHz frequency range. Irradiation power, reflected power, internal reactor exit temperature and reaction mixture pressure are monitored and controlled in real time. A back-pressure regulator (BPR, rated to 3.0 MPa), fitted after the helical tube reactor, maintains the reaction mixture pressure.[57c] The adjustable back pressure regulator (BPR) was set to ensure pressures between 2.0 and 3.0 MPa. For HPLC yields an aliquot of reaction mixture of known volume and concentration was collected.

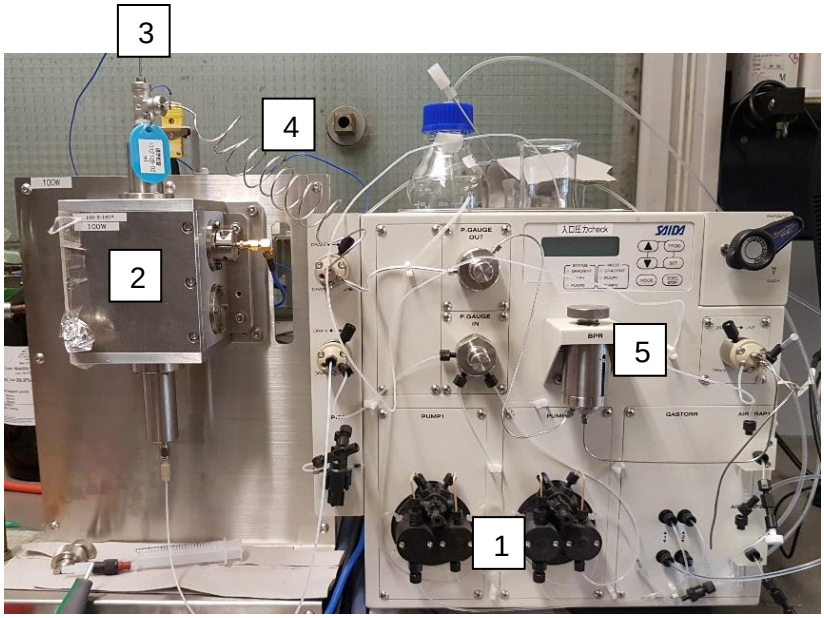


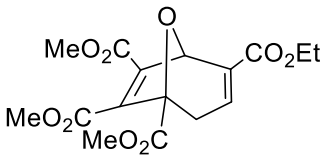
Figure 28. *100 W MW flow reactor consisting of 1) pump unit, 2) 100 W MW cavity, 3) reactor exit temperature probe 'Saida', 4) cooling coil, 5) adjustable back pressure regulator (BPR).*

HPLC quantification method

The analytics were carried out by Michal Domanski member of the Barham group. For a screening of the microwave flow [3+2]-cycloaddition reactions HPLC yields were determined. HPLC chromatograms were compared with authentic standards at defined concentrations for purposes of quantification.

Derivatization reactions

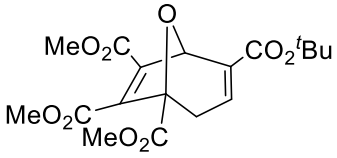
4-ethyl 1,6,7-trimethyl (1*R*,5*S*)-8-oxabicyclo[3.2.1]octa-3,6-diene-1,4,6,7-tetracarboxylate (151a)



8-Oxatropane **140a** (120 mg, 339 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1 mL). Then TEA (44.6 mg, 61 µL, 449 µmol, 1.3 equiv) was added and the reaction mixture was stirred for 30 min at 25 °C. The solvent was removed under reduced pressure and product **151a** (120 mg, 337 µmol, quant.) was obtained as a yellowish oil.

R_f = 0.21 (PE:EA = 3:1; $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.83 (t, *J* = 3.6 Hz, 1H), 5.59 (s, 1H), 4.27 – 4.15 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.14 – 3.03 (m, 1H), 2.57 (ddd, *J* = 20.2, 4.0, 1.0 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 168.0 (q), 163.4 (q), 162.3 (q), 161.8 (q), 147.5 (q), 137.0 (+), 136.0 (q), 133.2 (q), 86.6 (q), 78.1 (+), 61.0 (–), 53.2 (+), 52.66 (+), 52.65 (+), 28.6 (–), 14.2 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 2960, 1711, 1640, 1439, 1372, 1334, 1297, 1241, 1141, 1088, 1018, 988, 939, 872, 820; **HRMS** (ESI): calcd. for $C_{16}H_{18}O_9$ $(M+Na)^+$, m/z = 377.0843; found 377.0843.

4-(*tert*-butyl) 1,6,7-trimethyl (1*R*,5*S*)-8-oxabicyclo[3.2.1]octa-3,6-diene-1,4,6,7-tetracarboxylate (151b)

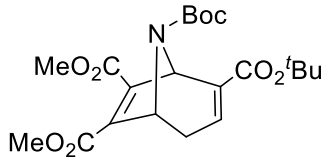


8-Oxatropane **140b** (104 mg, 273 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.4 mL). Then TEA (36.5 mg, 50 µL, 361 µmol, 1.3 equiv) was added and the reaction mixture

was stirred for 30 min at 25 °C. The solvent was removed under reduced pressure and product **151b** (104 mg, 273 µmol, quant.) was obtained as a yellowish oil.

R_f = 0.32 (PE:EA = 3:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.70 (ddd, *J* = 4.0, 3.3, 0.8 Hz, 1H), 5.51 (t, *J* = 1.0 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.04 (ddd, *J* = 20.0, 3.3, 1.4 Hz, 1H), 2.50 (dd, *J* = 20.1, 4.0 Hz, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 168.1 (q), 162.6 (q), 162.3 (q), 162.0 (q), 147.9 (q), 135.9 (+), 135.6 (q), 134.4 (q), 86.6 (q), 81.4 (q), 78.3 (+), 53.2 (+), 52.62 (+), 52.59 (+), 28.6 (–), 28.0 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2982, 2956, 1722, 1640, 1439, 1368, 1252, 1152, 1092, 1010, 943, 876, 846, 753; **HRMS** (ESI): calcd. for $C_{18}H_{22}O_9$ $(M+NH_4)^+$, m/z = 400.1602; found 400.1600.

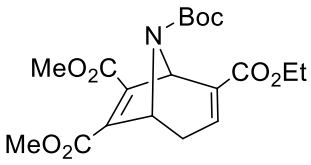
2,8-di-*tert*-butyl 6,7-dimethyl (1*S*,5*R*)-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7,8-tetracarboxylate (152a)



8-azatropane **133a** (542 mg, 1.28 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3 mL). Then TEA (172 mg, 237 µL, 1.70 mmol, 1.3 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. The solvent was removed under reduced pressure and product **152a** (541 mg, 541 µmol, quant.) was obtained as a colorless solid.

R_f = 0.57 (PE:EA = 3:2; UV, $KMnO_4$); **m.p.** = 107°C, **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.61 – 6.50 (m, 1H), 5.37 – 5.11 (m, 1H), 4.89 (d, *J* = 5.6 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.96 – 2.72 (m, 1H), 2.16 (dd, *J* = 20.1, 3.9 Hz, 1H), 1.42 (s, 9H), 1.37 (s, 9H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9 (q), 162.8 (q), 162.5 (q), 152.9 (q), 152.4 (q), 149.6 (q), 147.9 (q), 136.0 (+), 135.1 (q), 134.0 (q), 80.9 (q), 80.7 (q), 58.7 (+), 57.8 (+), 52.3 (+), 52.2 (+), 28.1 (+), 27.9 (+), 26.48 (–), 25.46 (–) (signal doubling and broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2978, 1700, 1640, 1364, 1249, 1156, 1081, 1025, 977, 749; **HRMS** (ESI): calcd. for $C_{21}H_{29}NO_8$ $(M+H)^+$, m/z = 424.1966; found 424.1974.

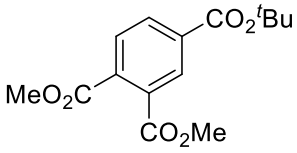
8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,5*R*)-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7,8-tetracarboxylate (152b)



8-azatropane **133c** (283 mg, 716 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL). Then TEA (94.2 mg, 130 µL, 930 µmol, 1.3 equiv) was added and the reaction mixture was stirred for 2 h at 25 °C. The solvent was removed under reduced pressure and product **152b** (280 mg, 709 µmol, 99%) was obtained as a yellowish oil.

R_f = 0.62 (PE:EA = 2:1; $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.70 – 6.61 (m, 1H), 5.40 – 5.25 (m, 1H), 4.93 (d, *J* = 5.5 Hz, 1H), 4.23 – 4.13 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.01 – 2.72 (m, 1H), 2.23 (dd, *J* = 20.3, 3.8 Hz, 1H), 1.40 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 163.8 (q), 162.9 (q), 162.6 (q), 152.8 (q), 147.8 (q), 137.1 (+), 135.6 (q), 134.8 (q), 81.0 (q), 60.8 (–), 58.6 (+), 57.9 (+), 52.43 (+), 52.36 (+), 28.2 (+), 25.9 (–), 14.2 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 1707, 1640, 1439, 1368, 1252, 1118, 1156, 1080, 1029, 943, 857, 783; **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_8$ $(M+Na)^+$, m/z = 418.1472; found 418.1475.

4-(*tert*-butyl) 1,2-dimethyl benzene-1,2,4-tricarboxylate (157)

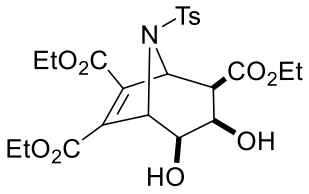


$K_3[Fe(CN)_6]$ (268 mg, 815 µmol, 3.0 equiv), K_2CO_3 (113 mg, 815 µmol, 3.0 equiv), $K_2[OsO_4]\cdot 2H_2O$ (1.0 mg, 2.72 µmol, 1 mol%) and cycloadduct **140b** (104 mg, 272 µmol, 1.0 equiv) were added to a solution of H_2O/^{t}BuOH (1:1, 10 mL). After stirring for 21 h at 25 °C, Na_2SO_3 (205 mg, 1.63 mmol, 6.0 equiv) was added and stirred for further 30 min at 25 °C. The phases were separated and the aqueous phase was extracted with EA (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After purification of the crude product by flash column

chromatography (66% EA:PE) aromatic compound **157** (50.0 mg, 170 µmol, 63%) was obtained as a colorless solid.

R_f = 0.63 (PE:EA = 3:1, UV); **m.p.** = 128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 1.7, 0.5 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.74 (dd, *J* = 8.0, 0.5 Hz, 1H), 3.92 (s, 6H), 1.60 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 167.6 (q), 167.3 (q), 164.0 (q), 135.4 (q), 134.5 (q), 132.0 (+), 131.7 (q), 130.0 (+), 128.8 (+), 82.3 (q), 52.9 (+), 52.8 (+), 28.1 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2986, 2930, 2855, 1715, 1577, 1487, 1431, 1394, 1368, 1320, 1282, 1249, 1170, 1115, 1070, 969, 749, 697; **HRMS** (ESI): calcd. for $C_{15}H_{18}O_6$ $(M+Na)^+$, m/z = 317.0996; found 317.0995.

triethyl (1*S*,2*R*,3*R*,4*S*,5*S*)-3,4-dihydroxy-8-tosyl-8-azabicyclo[3.2.1]oct-6-ene-2,6,7-tricarboxylate (170)[17][53]



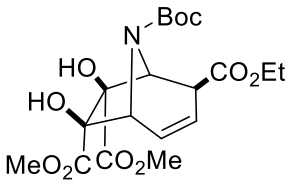
According to literature procedure[76], to a vigorously stirred solution of the cycloaddition product **133f** (137 mg, 287 µmol, 1.0 equiv) in MeCN (1.7 mL) was added a solution of $RuCl_3 \cdot 3H_2O$ (4 mg, 17.7 µmol, 6 mol%) and $NaIO_4$ (95.0 mg, 444 µmol, 1.6 equiv) in H_2O (0.3 mL) at 0 °C. The mixture was allowed to warm to 25 °C and stirred for 2 d. Then the suspension was filtered through a short plug of silica gel, which was washed with EA. Concentration of the filtrate and purification by flash column chromatography (33% EA:PE) yielded diol **170** (69.0 mg, 135 µmol, 47%) as a colorless oil.

R_f = 0.25 (PE:EA = 2:1; UV); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.66 – 7.57 (m, 2H), 7.29 – 7.22 (m, 2H, overlapping with solvent signal), 5.03 (dd, *J* = 2.6, 1.1 Hz, 1H), 4.86 (s, 1H), 4.32 – 4.11 (m, 6H), 3.98 (bs, 1H), 3.85 (bs, 1H), 3.32 (dd, *J* = 6.3, 2.6 Hz, 1H), 2.39 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.26 – 1.20 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.1 (q), 161.4 (q), 161.1 (q), 144.5 (q), 138.9 (q), 137.3 (q), 133.9 (q), 130.1 (+), 127.7 (+), 68.8 (+), 65.8 (+), 65.1 (+), 64.9 (+), 62.6 (–), 61.9 (–), 61.8 (–), 46.3 (+),

[17] Synthesized by Dr. Saerom Park.

21.6 (+), 14.1 (+), 14.02 (+), 13.99 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3440, 2982, 1700, 1394, 1364, 1256, 1163, 1025, 931, 880, 723; **HRMS** (ESI): calcd. for $C_{23}H_{29}NO_{10}$ $(M+Na)^+$, m/z = 534.1404; found 534.1400.

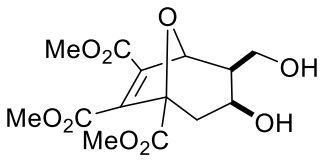
8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,2*S*,5*R*,6*R*,7*S*)-6,7-dihydroxy-8-azabicyclo[3.2.1]oct-3-ene-2,6,7,8-tetracarboxylate (171)



To a solution of cycloadduct **133c** (121 mg, 306 µmol, 1.0 equiv) in acetone (1.5 mL) and H_2O (1.2 mL) was added NMO (82.7 mg, 612 µmol, 2.0 equiv) followed by $K_2OsO_4 \cdot 2H_2O$ (6 mg, 15 µmol, 5 mol%) at 0 °C. The reaction mixture was stirred for 12 h at 0 °C. Then the reaction mixture was filtered through a short plug of silica and the solvent was removed under reduced pressure. Recrystallization from diethyl ether yielded diol **171** (57.0 mg, 137 µmol, 43%) as a colorless solid.

R_f = 0.55 (PE:EA = 1:2; Seebach's stain, $KMnO_4$); **m.p.** = 131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.30 – 6.19 (m, 1H), 5.85 – 5.73 (m, 1H), 5.16 – 4.99 (m, 1H), 4.97 – 4.84 (m, 1H), 4.77 – 4.54 (m, 2H), 4.22 – 4.09 (m, 2H), 3.76 (s, 3H), 3.67 (s, 3H), 3.15 – 2.93 (m, 1H), 1.43 (s, 9H), 1.28 – 1.22 (m, 3H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.9 (q), 170.8 (q), 170.3 (q), 169.7 (q), 169.4 (q), 154.3 (q), 128.6 (+), 128.5 (+), 124.5 (+), 124.4 (+), 89.1 (q), 88.4 (q), 85.6 (q), 84.8 (q), 81.0 (q), 80.9 (q), 67.2 (+), 65.7 (+), 62.1 (+), 61.6 (–), 61.4 (–), 60.7 (+), 53.3 (+), 53.2 (+), 52.4 (+), 52.3 (+), 45.2 (+), 45.0 (+), 28.1 (+), 14.2 (+), 14.1 (+) (signal doubling due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3295, 2978, 1744, 1670, 1413, 1368, 1334, 1279, 1163, 1126, 1059, 1025, 962, 921, 861, 701, 675; **HRMS** (ESI): calcd. for $C_{19}H_{27}NO_{10}$ $(M+H)^+$, m/z = 430.1708; found 430.1713.

trimethyl (1*R*,3*S*,4*S*,5*S*)-3-hydroxy-4-(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-6-ene-1,6,7-tricarboxylate (183)

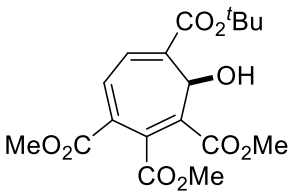


BH_3·THF (1 M solution in THF, 261 mg, 3.0 mL, 3.04 mmol, 4.5 equiv) was added to a solution of cycloadduct **140a** (239 mg, 344 µmol, 1.0 equiv) in dry THF (14 mL) at 0 °C under nitrogen atmosphere and was stirred for 6 h at 25 °C. Then the mixture was basified to a neutral pH value with $NaHCO_3$. A 1:1 mixture of EtOH:THF (1.4 mL), phosphate buffer pH 7.2 (1.4 mL) and H_2O_2 (1.4 mL of a 33% aqueous solution) was added to the mixture. After stirring for 14 h the aqueous phase was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated and purification of the crude product by flash column chromatography (5% MeOH:CH_2Cl_2) yielded compound **183** (68.1 mg, 206 µmol, 31%) as a colorless oil.

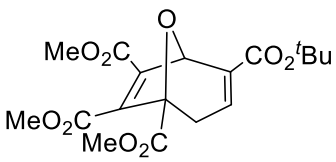
R_f = 0.10 (PE:EA = 1:1; UV, $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.13 (d, *J* = 1.5 Hz, 1H), 4.27 – 4.16 (m, 2H), 3.92 (dd, *J* = 11.2, 4.7 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.81 (s, 3H), 2.47 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.31 (q, *J* = 6.4, 5.9 Hz, 1H), 2.02 (dd, *J* = 13.3, 10.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.7 (q), 163.1 (q), 161.3 (q), 141.6 (q), 137.1 (q), 88.9 (q), 82.5 (+), 66.1 (+), 62.2 (–), 53.1 (+), 52.8 (+), 52.7 (+), 39.5 (+), 33.9 (–); **IR** $\tilde{\nu}$ [cm^{-1}]: 3403, 2960, 2922, 2851, 1722, 1655, 1439, 1230, 1144, 1066, 701, 783, 738; **HRMS** (ESI): calcd. for $C_{14}H_{18}O_9$ $(M+Na)^+$, m/z = 353.0843; found 353.0843.

5-(*tert*-butyl) 1,2,3-trimethyl (*R*)-4-hydroxycyclohepta-2,5,7-triene-1,2,3,5-tetracarboxylate (192)

4-(*tert*-butyl) 1,6,7-trimethyl (1*R*,5*S*)-8-oxabicyclo[3.2.1]octa-3,6-diene-1,4,6,7-tetracarboxylate (151b)



192



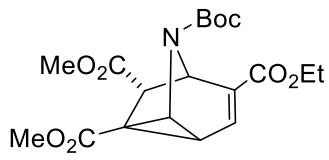
151b

DBU (43.5 mg, 43 µL, 286 µmol, 1.1 equiv) was added to a solution of *tert*-butyl hydroperoxide (5.5 M in decan, 46.8 mg, 94 µL, 519 µmol, 1.1 equiv) in dry CH_2Cl_2 (2 mL). After stirring for 20 min at 25 °C, a solution of cycloadduct **140b** (99.3 mg, 260 µmol, 1.0 equiv) in CH_2Cl_2 (1.1 mL) was added at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C then the reaction was quenched with saturated NH_4Cl solution (20 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (33% EA:PE). Isomerized product **151b** (31 mg, 81.1 µmol, 31%) and seven-membered ring **192** (25.2 mg, 65.9 µmol, 25%) were obtained both as a colorless oil.

151b: $\mathbf{R_f}$ = 0.32 (PE:EA = 3:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.70 (ddd, *J* = 4.0, 3.3, 0.8 Hz, 1H), 5.51 (t, *J* = 1.0 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.04 (ddd, *J* = 20.0, 3.3, 1.4 Hz, 1H), 2.50 (dd, *J* = 20.1, 4.0 Hz, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.1 (q), 162.6 (q), 162.3 (q), 162.0 (q), 147.9 (q), 135.9 (+), 135.6 (q), 134.4 (q), 86.6 (q), 81.4 (q), 78.3 (+), 53.2 (+), 52.62 (+), 52.59 (+), 28.6 (–), 28.0 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2982, 2956, 1722, 1640, 1439, 1368, 1252, 1152, 1092, 1010, 943, 876, 846, 753; **HRMS** (ESI): calcd. for $C_{18}H_{22}O_9$ $(M+NH_4)^+$, m/z = 400.1602; found 400.1600.

192: $\mathbf{R_f}$ = 0.21 (PE:EA = 3:1, UV); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.17 (s, 1H), 7.86 (s, 1H), 5.84 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.72 (s, 3H), 1.59 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.4 (q), 167.0 (q), 166.9 (q), 165.8 (q), 142.3 (q), 134.6 (q), 133.4 (q), 131.5 (q), 131.3 (+), 129.7 (+), 83.6 (q), 71.3 (+), 53.0 (+), 52.94 (+), 52.93 (+), 28.1 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3474, 2956, 1722, 1439, 1372, 1252, 1200, 1159, 1111, 1021, 969, 753; **HRMS** (ESI): calcd. for $C_{18}H_{22}O_9$ $(M+H)^+$, m/z = 383.1337; found 383.1340.

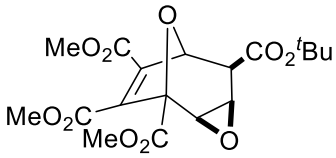
6-(*tert*-butyl) 4-ethyl 1,8-dimethyl (5*R*,7*R*,8*S*)-6-azatricyclo[3.2.1.0^{2,7}]oct-3-ene-1,4,6,8-tetracarboxylate (197)



To a solution of cycloadduct **133c** (106 mg, 267 µmol, 1.0 equiv) in CH_2Cl_2/MeOH (1:1, 0.2 mL), H_2O_2 (35 w%, 49.1 mg, 126 µL, 1.44 mmol, 5.4 equiv) was slowly added. Then 2M NaOH (12.8 mg, 160 µL, 321 µmol, 1.2 equiv) was added and the reaction mixture was stirred for 2 h 50 min at 25 °C. Afterwards, the reaction mixture was poured into CH_2Cl_2 (30 mL), washed with brine (15 mL) and the organic phase was dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded 6-azatricyclo[3.2.1.$0^{2,7}$]octane **197** (38.0 mg, 96.1 µmol, 36%) as a yellowish oil.

R_f = 0.62 (PE:EA = 2:1; $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 6.5, 2.1 Hz, 1H), 5.37 – 5.19 (m, 1H), 4.32 – 4.10 (m, 3H), 3.74 (s, 3H), 3.57 (s, 3H), 3.49 (d, *J* = 6.0 Hz, 1H), 3.00 (ddd, *J* = 6.7, 5.8, 1.0 Hz, 1H), 1.38 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.7 (q), 168.7 (q), 162.9 (q), 154.4 (q), 135.2 (+), 127.5 (q), 81.6 (q), 60.8 (–), 53.0 (+), 52.8 (+), 52.1 (+), 43.3 (+), 42.6 (+), 31.5 (q), 28.2 (+), 24.6 (+), 14.4 (+) (signal broadening due to rotamers); **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_8$ $(M+H)^+$, m/z = 396.1653; found 396.1652.

5-(*tert*-butyl) 1,7,8-trimethyl (1*S*,2*R*,4*R*,5*R*,6*S*)-3,9-dioxatricyclo[4.2.1.$0^{2,4}$]non-7-ene-1,5,7,8-tetracarboxylate (198b)

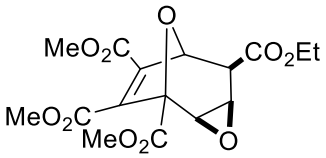


Cycloadduct **140b** (114 mg, 298 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4 mL) and *m*-CPBA (180 mg, 1.04 mmol, 3.5 equiv) was added at 25 °C. The reaction mixture was stirred for 20 h at 50 °C. The reaction was quenched with saturated aqueous sodium thiosulfate and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with saturated $NaHCO_3$ (2 x 20 mL), brine (2 x 20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the epoxide **198b** (101 mg, 254 µmol, 85%) was obtained as a colorless oil.

R_f = 0.22 (PE:EA = 3:1; UV, $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.55 (dd, *J* = 1.4, 0.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.76 (d, *J* = 3.9 Hz, 1H), 3.48 (ddd, *J* = 5.3, 3.9, 1.5 Hz, 1H), 2.71 (dd, *J* = 5.2, 0.6 Hz, 1H), 1.53 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.8 (q), 166.4 (q), 162.1 (q), 161.8 (q), 143.4 (q), 139.6 (q), 86.0 (q),

82.7 (q), 80.3 (+), 53.3 (+), 53.0 (+), 52.9 (+), 50.2 (+), 47.8 (+), 38.7 (+), 28.1 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 1726, 1655, 1439, 1372, 1241, 1200, 1151, 1074, 1029, 984, 902, 846, 757, 708; **HRMS** (ESI): calcd. for $C_{18}H_{22}O_{10}$ $(M+Na)^+$, m/z = 421.1105; found 421.1107.

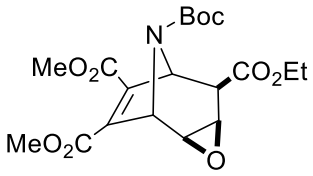
5-ethyl 1,7,8-trimethyl (1*S*,2*R*,4*R*,5*R*,6*S*)-3,9-dioxatricyclo[4.2.1.$0^{2,4}$]non-7-ene-1,5,7,8-tetracarboxylate (198a)



Cycloadduct **140a** (113 mg, 318 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4 mL) and *m*-CPBA (193 mg, 1.12 mmol, 3.5 equiv) was added at 25 °C. The reaction mixture was stirred for 18 h at 50 °C. The reaction was quenched with saturated aqueous sodium thiosulfate and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed with saturated $NaHCO_3$ (2 x 20 mL), brine (2 x 20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product (117 mg, 316 µmol, 99%) was obtained as a yellowish oil. Recrystallization from diethyl ether afforded pure product **198a** (105 mg, 283 µmol, 89%) as a colorless solid.

R_f = 0.32 (PE:EA = 3:2; UV, $KMnO_4$); **m.p.** = 91 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.59 (s, 1H), 4.40 – 4.21 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.78 (d, *J* = 3.9 Hz, 1H), 3.53 (ddt, *J* = 5.3, 3.9, 1.2 Hz, 1H), 2.79 (d, *J* = 5.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 168.7 (q), 166.2 (q), 162.1 (q), 161.6 (q), 143.8 (q), 138.9 (q), 86.1 (q), 80.2 (+), 62.0 (–), 53.4 (+), 53.1 (+), 52.9 (+), 50.3 (+), 47.6 (+), 38.2 (+), 14.2 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 1722, 1655, 1435, 1297, 1260, 1193, 1141, 1081, 1029, 980, 910, 842, 790, 712; **HRMS** (ESI): calcd. for $C_{16}H_{18}O_{10}$ $(M+H)^+$, m/z = 371.0973; found 371.0973.

9-(*tert*-butyl) 5-ethyl 7,8-dimethyl (1*S*,2*S*,4*R*,5*R*,6*S*)-3-oxa-9-azatricyclo-[4.2.1.0^{2,4}]non-7-ene-5,7,8,9-tetracarboxylate (187)

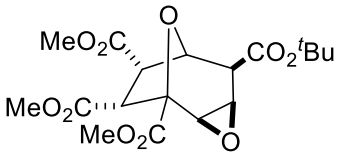


Cycloadduct **133c** (327 mg, 826 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (15 mL). Then *m*-CPBA (285 mg, 1.65 mmol, 2.0 equiv) was added at 25 °C. After stirring for 1 d, additional *m*-CPBA (285 mg, 1.65 mmol, 2.0 equiv) was added and the reaction was stirred for further 2 d at 25 °C. The reaction was quenched with saturated aqueous sodium thiosulfate. Then the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (3 x 30 mL), brine (2 x 30 mL) and were dried over Na_2SO_4. The solvent was removed under reduced pressure and epoxide **187** (336 mg, 816 µmol, 99%) was obtained as a colorless solid.

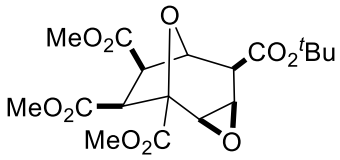
R_f = 0.39 (PE:EA = 3:2; UV, $KMnO_4$); **m.p.** = 122 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.40 – 5.28 (m, 1H), 5.23 – 4.89 (m, 1H), 4.40 – 4.16 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.52 – 3.34 (m, 1H), 3.35 – 3.24 (m, 1H), 2.77 (d, *J* = 4.5 Hz, 1H), 1.43 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.9 (q), 168.8 (q), 163.0 (q), 162.4 (q), 152.6 (q), 152.1 (q), 142.2 (q) 142.1 (q), 141.7 (q), 140.6 (q), 80.8 (q), 61.5 (–), 59.8 (+), 59.7 (+), 58.8 (+), 58.0 (+), 52.7 (+), 49.2 (+), 46.9 (+), 38.8 (+), 38.0 (+), 28.1 (+), 14.1 (+) (signal broadening and doubling due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2989, 2956, 2904, 1730, 1696, 1651, 1416, 1349, 1267, 1223, 1197, 1118, 1036, 954, 891, 764, 727, 686; **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_9$ $(M+H)^+$, m/z = 412.1602; found 412.1610.

5-(*tert*-butyl) 7,8-dimethyl (1*S*,2*R*,4*R*,5*R*,6*R*,7*S*,8*R*)-3,9-dioxatricyclo[4.2.1.0^{2,4}]nonane-5,7,8-tricarboxylate (major 199a)

5-(*tert*-butyl) 7,8-dimethyl (1*S*,2*R*,4*R*,5*R*,6*R*,7*R*,8*S*)-3,9-dioxatricyclo[4.2.1.0^{2,4}]nonane-5,7,8-tricarboxylate (minor 199b)



major **199a**

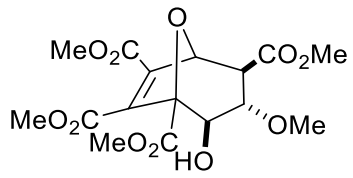


minor **199b**

Epoxide **198b** (33.0 mg, 82.8 µmol, 1.0 equiv) was dissolved in EtOH (1.6 mL). Then 10% Pd/C (34.5 mg, 10 w%, 32.4 µmol, 10 mol%) was added and the flask was charged with H_2 for 2.5 h at 25 °C. Only partial conversion was observed. Therefore, the reaction mixture was transferred in a vial which was placed in an autoclave and sealed. Then the autoclave was pressurized to 10 bar with H_2 and the solution was stirred for 40 min at 25 °C. The reaction mixture was filtered and the solvent removed under reduced pressure. Purification of the crude product by flash column chromatography (25 → 50% EA:PE) yielded inseparable mixture of *endo* and *exo* product **199a-b** (22 mg, 55.0 µmol, 66%, *dr* 5.1:1) both as a colorless oil.
In the proton NMR the signals of both diastereomers are overlapping.

R_f = 0.52 (PE:EA = 3:2; UV, $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*major* **199a**) = 5.17 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.88 (d, *J* = 4.0 Hz, 1H), 3.85 (s, 3H), 3.83 – 3.74 (m, 2H), 3.71 (s, 3H), 3.70 (s, 3H), 3.50 (ddd, *J* = 5.6, 4.1, 1.7 Hz, 1H), 2.78 (d, *J* = 5.2 Hz, 1H), 1.51 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*major* **199a**) = 170.6 (q), 168.9 (q), 168.6 (q), 168.4 (q), 82.24 (q), 80.21 (q), 76.6 (+), 53.4 (+), 53.2 (+), 52.4 (+), 52.3 (+), 50.3 (+), 50.0 (+), 47.3 (+), 41.5 (+), 28.2 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 2855, 1737, 1439, 1372, 1331, 1297, 1208, 1159, 1074, 980; **HRMS** (ESI): calcd. for $C_{18}H_{24}O_{10}$ $(M+Na)^+$, m/z = 423.1262; found 423.1262 (*major* **199a** t_r = 5.010-5.131 min); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (*minor* **199b**) = 5.12 (t, *J* = 1.8 Hz, 1H), 3.87 (s, 1H), 3.85 (s, 6H)*, 3.83 – 3.74 (m, 3H)*, 3.56 (ddd, *J* = 7.1, 3.9, 2.1 Hz, 1H), 3.41 (d, *J* = 3.8 Hz, 1H), 3.37 (dd, *J* = 7.5, 2.4 Hz, 1H), 2.74 (d, *J* = 5.3 Hz, 1H), 1.51 (s, 9H)* (*these signals are overlapping with major diastereomer); **HRMS** (ESI): calcd. for $C_{18}H_{24}O_{10}$ $(M+Na)^+$, m/z = 423.1262; found 423.1261 (*minor* **199b** t_r = 5.198-5.325 min).

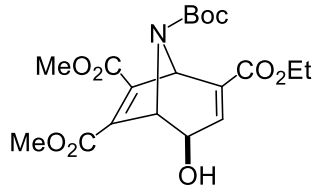
tetramethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-2-hydroxy-3-methoxy-8-oxabicyclo[3.2.1]oct-6-ene-1,4,6,7-tetracarboxylate (201)



Cycloadduct **198a** (75.0 mg, 202 µmol, 1.0 equiv) was dissolved in MeOH (4 mL). Then H_2SO_4 (22 mg, 12 µL, 223 µmol, 1.1 equiv) was added and the reaction mixture was stirred for 19 h at 25 °C. Afterwards, the mixture was heated for 3 h at 70 °C. EA (5 mL) and brine (5 mL) were added and the aqueous layer was extracted with EA (3 x 5 mL). The combined organic phases were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (45 → 56% EA:PE) to afford cycloadduct **201** (20.0 mg, 52 µmol, 25%) as a colorless oil.

R_f = 0.21 (PE:EA = 3:2; UV, $KMNO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.33 (t, *J* = 1.4 Hz, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.18 (dt, *J* = 11.3, 1.2 Hz, 1H), 3.89 – 3.87 (m, 4H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.39 (s, 3H), 2.96 (d, *J* = 1.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.4 (q), 166.6 (q), 163.3 (q), 160.9 (q), 143.2 (q), 135.2 (q), 92.9 (q), 80.6 (+), 78.8 (+), 64.4 (+), 57.9 (+), 53.2 (+), 53.1 (+), 52.8 (+), 52.6 (+), 45.7 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3440, 2960, 2851, 1722, 1659, 1439, 1260, 1200, 1156, 1021, 917, 820, 731; **HRMS** (ESI): calcd. for $C_{16}H_{20}O_{11}$ $(M+Na)^+$, m/z = 411.0898; found 411.0898.

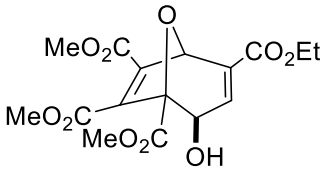
8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,4*R*,5*S*)-4-hydroxy-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7,8-tetracarboxylate (205)



Flash column chromatography (25% EA:PE + 1% TEA) of epoxide **187** (336 mg, 816 µmol, 1.0 equiv) resulted in allylic alcohol **205** (259 mg, 630 µmol, 77%) as a colorless oil.

R_f = 0.41 (PE:EA = 3:2; UV, $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.71 – 6.60 (m, 1H), 5.56 – 5.33 (m, 1H), 5.13 – 5.04 (m, 1H), 4.40 – 4.15 (m, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 1.44 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.7 (q), 162.6 (q), 162.3 (q), 155.5 (q), 150.0 (q), 137.7 (+), 137.1 (q), 135.8 (q), 82.3 (q), 65.2 (+), 64.9 (+), 61.3 (–), 59.8 (+), 52.58 (+), 52.56 (+), 28.2 (+), 14.2 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3440, 2982, 1711, 1435, 1394, 1372, 1323, 1252, 1163, 1118, 1088, 1040, 951, 921, 775; **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_9$ $(M+H)^+$, m/z = 412.1602; found 412.1600.

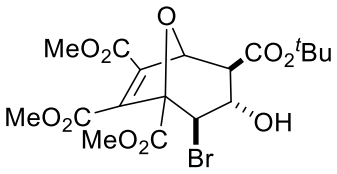
4-ethyl 1,6,7-trimethyl (1*S*,2*R*,5*S*)-2-hydroxy-8-oxabicyclo[3.2.1]octa-3,6-diene-1,4,6,7-tetracarboxylate (206)



Flash column chromatography (33 → 50% EA:PE + 1% TEA) of epoxide **198a** (87.0 mg, 246 µmol, 1.0 equiv) resulted in allylic alcohol **206** (58.0 mg, 157 µmol, 64%) as a colorless oil.

R_f = 0.28 (PE:EA = 1:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.70 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.70 (d, *J* = 0.8 Hz, 1H), 4.60 – 4.44 (m, 1H), 4.37 – 4.16 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 2.73 (s, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4 (q), 163.12 (q), 163.05 (q), 160.8 (q), 147.1 (q), 139.6 (q), 137.8 (q), 135.6 (+), 92.1 (q), 77.9 (+), 63.5 (+), 61.4 (–), 53.2 (+), 53.0 (+), 52.7 (+), 14.2 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3478, 2960, 1726, 1651, 1439, 1275, 1162, 1059, 1021; **HRMS** (ESI): calcd. for $C_{16}H_{18}O_{10}$ $(M+H)^+$, m/z = 371.0973; found 371.0973.

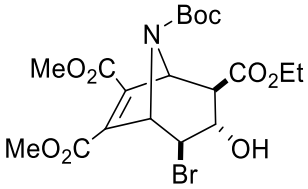
4-(*tert*-butyl) 1,6,7-trimethyl (1*R*,2*R*,3*S*,4*S*,5*S*)-2-bromo-3-hydroxy-8-oxabicyclo[3.2.1]oct-6-ene-1,4,6,7-tetracarboxylate (211)



To a stirred solution of cycloadduct **140b** (188 mg, 492 µmol, 1.0 equiv) in acetone (2 mL) and H_2O (0.7 mL) NBS (263 mg, 1.48 µmol, 3.0 equiv) was added in portions within 45 min at 0 °C under exclusion of light. The reaction mixture was allowed to warm to 25 °C and stirred for 7 d at 25 °C. The reaction was quenched with saturated aqueous sodium metabisulfite until the initial yellow color had faded. Acetone was removed under reduced pressure. Then the residue was redissolved in diethyl ether and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with H_2O (2 x 30 mL), brine (2 x 30 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded halohydrin **211** (185 mg, 386 µmol, 78%) as a colorless oil.

R_f = 0.34 (PE:EA = 3:2; UV, $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.70 (s, 1H), 5.05 (d, *J* = 5.0 Hz, 1H), 4.49 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.00 (d, *J* = 5.4 Hz, 1H), 2.66 (s, 1H), 1.51 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.9 (q), 166.0 (q), 164.0 (q), 160.9 (q), 142.7 (q), 138.1 (q), 90.2 (q), 82.6 (q), 80.2 (+), 72.7 (+), 53.29 (+), 53.25 (+), 52.8 (+), 47.5 (+), 45.2 (+), 28.0 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3511, 2960, 1722, 1662, 1439, 1152, 1047, 1018, 969, 854, 753; **HRMS** (ESI): calcd. for $C_{18}H_{23}BrO_{10}$ $(M+H)^+$, m/z = 479.0547; found 479.0546.

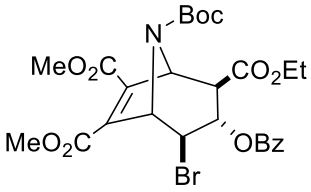
8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,2*R*,3*S*,4*S*,5*S*)-4-bromo-3-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-2,6,7,8-tetracarboxylate (213)



To a stirred solution of cycloadduct **133c** (502 mg, 1.27 mmol, 1.0 equiv) in acetone/H_2O (2.4 mL; 3:1 v/v) NBS (454 mg, 2.55 mmol, 2.0 equiv) was added in portions within 1 h at 0 °C under exclusion of light. The reaction mixture was allowed to warm up to 25 °C and stirred for 21 h at 25 °C. The reaction was quenched with saturated aqueous sodium metabisulfite until the initial yellow color had faded. Acetone was removed under reduced pressure. Then the residue was redissolved in diethyl ether and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with H_2O (2 x 30 mL), brine (2 x 30 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded halohydrin **213** (514 mg, 1.04 mmol, 82%) as a colorless oil.

R_f = 0.57 (PE:EA = 3:2; UV, $KMNO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.59 – 5.38 (m, 1H), 5.34 – 5.05 (m, 1H), 4.86 – 4.73 (m, 1H), 4.35 – 4.14 (m, 3H), 3.86 – 3.81 (m, 6H), 3.10 – 2.92 (m, 1H), 2.95 – 2.84 (m, 1H), 1.45 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H) (signal broadening due to rotamers); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 169.7 (q), 163.2 (q), 162.7 (q), 152.7 (q), 144.2 (q), 140.5 (q), 81.4 (q), 73.1 (+), 65.4 (+), 61.7 (–), 59.9 (+), 52.8 (+), 47.7 (+) (overlap of two carbons), 28.2 (+), 14.2 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3519, 2982, 1707, 1435, 1368, 1327, 1241, 1159, 1081, 1025, 747; **HRMS** (ESI): calcd. for $C_{19}H_{26}BrNO_9$ $(M+Na)^+$, m/z = 514.0683; found 514.0683.

8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,2*R*,3*S*,4*S*,5*S*)-3-(benzoyloxy)-4-bromo-8-azabicyclo[3.2.1]oct-6-ene-2,6,7,8-tetracarboxylate (220)

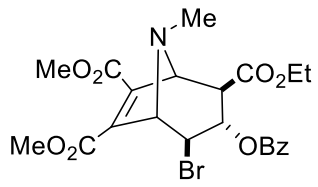


To a stirred solution of cycloadduct **133c** (641 mg, 1.62 mmol, 1.0 equiv) in acetone/H_2O (3 mL; 3:1 v/v) NBS (577 mg, 3.24 mmol, 2.0 equiv) was added in portions within 45 min at 0 °C under exclusion of light. The reaction mixture was allowed to warm up to 25 °C and stirred for 21 h at 25 °C. The reaction was quenched with saturated aqueous sodium metabisulfite until the initial yellow color had faded. Acetone was removed under reduced pressure. Then the residue was redissolved in diethyl ether and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed

with H_2O (2 x 30 mL), brine (2 x 30 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded halohydrin **213** (confirmed by X-ray analysis, *vide infra*) as a colorless oil. To a solution of halohydrin **213** in CH_2Cl_2 (9 mL) benzoyl chloride (342 mg, 280 µL, 2.43 mmol, 1.5 equiv), TEA (820 mg, 1.12 mL, 8.10 mmol, 5.0 equiv) and DMAP (89.1 mg, 729 µmol, 0.5 equiv) were added. After stirring for 8 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (5 mL). The reaction mixture was washed with saturated aqueous $NaHCO_3$ (5 x 10 mL) and brine (10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude product by flash system (10 → 15% EA:PE) yielded compound **220** (571 mg, 957 µmol, 59%) as a colorless oil.

R_f = 0.35 (PE:EA = 3:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.94 – 7.81 (m, 2H), 7.61 – 7.49 (m, 1H), 7.43 – 7.37 (m, 2H), 6.13 – 6.01 (m, 1H), 5.77 – 5.45 (m, 1H), 5.45 – 5.04 (m, 1H), 4.45 – 4.35 (m, 1H), 4.33 – 4.13 (m, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 3.23 – 3.03 (m, 1H), 1.47 (s, 9H), 1.33 (t, *J* = 7.0 Hz, 3H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.3 (q), 164.5 (q), 162.8 (q), 162.5 (q), 152.8 (q), 143.4 (q), 140.6 (q), 133.5 (+), 129.7 (+), 129.0 (q), 128.4 (+), 81.5 (q), 73.3 (+), 65.3 (+), 62.0 (–), 60.0 (+), 52.54 (+), 52.50 (+), 45.2 (+), 43.2 (+), 28.2 (+), 14.2 (+) (signal broadening due to rotamers); **IR $\tilde{\nu}$** [cm^{-1}]: 2982, 1711, 1651, 1439, 1368, 1323, 1241, 1159, 1085, 1025, 992, 947, 857, 767, 712; **HRMS** (ESI): calcd. for $C_{26}H_{30}BrNO_{10}$ $(M+H)^+$, m/z = 596.1126; found 596.1129.

2-ethyl 6,7-dimethyl (1*S*,2*R*,3*S*,4*S*,5*S*)-3-(benzoyloxy)-4-bromo-8-methyl-8-azabicyclo[3.2.1]oct-6-ene-2,6,7-tricarboxylate (221)

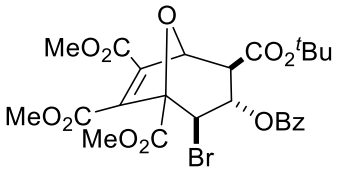


Cycloadduct **220** (229 mg, 384 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4 mL) and TFA (1.44 g, 970 µL, 12.7 mmol, 33 equiv) was added dropwise at 25 °C. After stirring for 1.5 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ was added dropwise. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed

with brine (25 mL) and dried over Na_2SO_4. Then the solvent was removed under reduced pressure and the crude amine was obtained as a yellowish oil. To a solution of crude amine and formaldehyde (70.3 mg, 176 µL, 2.34 mmol, 6.0 equiv) in MeCN 5 mL) was added $NaBH_3CN$ (71.4 mg, 1.14 mmol, 3.0 equiv) and the reaction mixture was stirred for 1 h at 25 °C. The solution was acidified to pH 6 with HOAc and stirred for 1.5 h. After neutralization to pH 9 with NH_3 (25%), the mixture was diluted with CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash system (18 → 39% EA:PE) to afford cycloadduct **221** (98.9 mg, 194 µmol, 50%) as a colorless oil.

R_f = 0.74 (PE:EA = 1:1; UV, $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.97 – 7.84 (m, 2H), 7.60 – 7.48 (m, 1H), 7.45 – 7.33 (m, 2H), 6.09 (t, *J* = 0.9 Hz, 1H), 4.43 – 4.24 (m, 4H), 3.96 (dt, *J* = 2.3, 0.8 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.04 (dd, *J* = 2.3, 1.1 Hz, 1H), 2.43 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.2 (q), 164.7 (q), 164.2 (q), 163.9 (q), 141.0 (q), 139.9 (q), 133.3 (+), 129.8 (+), 129.3 (q), 128.3 (+), 74.6 (+), 72.8 (+), 69.6 (+), 61.8 (–), 52.3 (+), 46.1 (+), 44.6 (+), 41.8 (+), 14.2 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 2952, 1715, 1648, 1435, 1372, 1320, 1245, 1088, 1025, 943, 790, 865, 790, 708; **HRMS** (ESI): calcd. for $C_{22}H_{24}BrNO_8$ $(M+H)^+$, m/z = 510.0758; found 510.0762.

4-(*tert*-butyl) 1,6,7-trimethyl (1*R*,2*R*,3*S*,4*R*,5*S*)-3-(benzoyloxy)-2-bromo-8-oxabicyclo[3.2.1]oct-6-ene-1,4,6,7-tetracarboxylate (222)

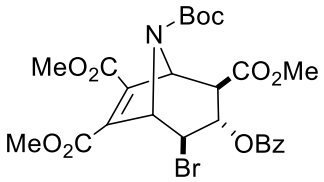


To a solution of halohydrin **211** (184 mg, 384 µmol, 1.0 equiv) in CH_2Cl_2 (3 mL) benzoyl chloride (81.0 mg, 67 µL, 576 µmol, 1.5 equiv), TEA (77.7 mg, 107 µL, 768 µmol, 2.0 equiv) and DMAP (21.1 mg, 173 µmol, 0.5 equiv) were added. After stirring for 12 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (5 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (5 x 20 mL) and brine (30 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure.

Purification of the crude product by flash system (6 → 15% EA:PE) yielded compound **222** (172 mg, 294 µmol, 77%) as a colorless oil.

R_f = 0.55 (PE:EA = 2:1; UV, $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.97 – 7.89 (m, 2H), 7.62 – 7.52 (m, 1H), 7.46 – 7.37 (m, 2H), 6.16 (q, *J* = 1.1 Hz, 1H), 5.80 (t, *J* = 1.3 Hz, 1H), 4.70 (t, *J* = 1.0 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.52 (s, 3H), 2.86 (q, *J* = 1.0 Hz, 1H), 1.56 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8 (q), 165.6 (q), 164.9 (q), 162.4 (q), 161.1 (q), 143.4 (q), 137.1 (q), 133.5 (+), 129.8 (+), 129.1 (q), 128.3 (+), 90.4 (q), 83.3 (q), 80.1 (+), 73.7 (+), 53.3 (+), 52.7 (+), 52.6 (+), 43.7 (+), 43.6 (+), 28.0 (+); **IR $\tilde{\nu}$** [cm^{-1}]: 2956, 2930, 2855, 1774, 1726, 1439, 1372, 1264, 1156, 1088, 1010, 962, 928, 716; **HRMS** (ESI): calcd. for $C_{25}H_{27}BrO_{11}$ $(M+Na)^+$, m/z = 605.0629; found 605.0632.

8-(*tert*-butyl) 2,6,7-trimethyl (1*S*,2*R*,3*S*,4*S*,5*S*)-3-(benzoyloxy)-4-bromo-8-azabicyclo[3.2.1]oct-6-ene-2,6,7,8-tetracarboxylate (227)

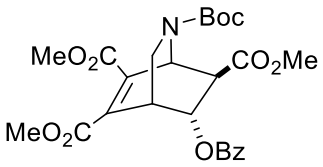


To a stirred solution of cycloadduct **119b** (620 mg, 1.63 mmol, 1.0 equiv) in acetone/H_2O (8 mL; 4:1 v/v), NBS (1.16 g, 6.52 mmol, 4.0 equiv) was added in portions within 45 min at 0 °C under exclusion of light. Subsequently, the ice bath was removed, and the reaction mixture was stirred for 3 d at 25 °C. The reaction was quenched with saturated aqueous sodium metabisulfite until the initial yellow color had faded. Acetone was removed under reduced pressure. Then the residue was redissolved in diethyl ether and the aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with H_2O (2 x 30 mL), brine (2 x 30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude halohydrin was obtained as a colorless oil. To a solution of halohydrin in CH_2Cl_2 (8 mL), benzoyl chloride (344 mg, 282 µL, 2.45 mmol, 1.5 equiv), TEA (825 mg, 1.13 mL, 8.15 mmol, 5.0 equiv) and DMAP (89.6 mg, 734 µmol, 0.5 equiv) were added. After stirring for 15 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (15 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (5 x 20 mL) and brine (30 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure.

Purification of the crude product by flash system (10 → 18% EA:PE) yielded compound **227** (407 mg, 700 µmol, 43%) as a colorless oil.

R_f = 0.58 (PE:EA = 3:2; UV, $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.94 – 7.83 (m, 2H), 7.60 – 7.50 (m, 1H), 7.44 – 7.35 (m, 2H), 6.17 – 6.00 (m, 1H), 5.73 – 5.51 (m, 1H), 5.38 – 5.08 (m, 1H), 4.53 – 4.25 (m, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.22 – 3.05 (m, 1H), 1.48 (s, 9H) (signal broadening due to rotamers); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 168.8 (q), 164.5 (q), 162.8 (q), 162.5 (q), 152.5 (q), 147.0 (q), 141.8 (q), 133.5 (+), 129.7 (+), 129.0 (q), 128.4 (+), 81.6 (q), 73.3 (+), 64.5 (+), 60.1 (+), 52.8 (+), 52.59 (+), 52.56 (+), 45.0 (+), 43.1 (+), 28.2 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2978, 1707, 1651, 1435, 1394, 1323, 1241, 1163, 1085, 1025, 988, 857, 760, 712; **HRMS** (ESI): calcd. for $C_{25}H_{28}BrNO_{10}$ $(M+H)^+$, m/z = 582.0969; found 582.0972.

2-(*tert*-butyl) 5,6,7-trimethyl (1*S*,4*R*,7*R*,8*R*)-8-(benzoyloxy)-2-azabicyclo[2.2.2]oct-5-ene-2,5,6,7-tetracarboxylate (228)

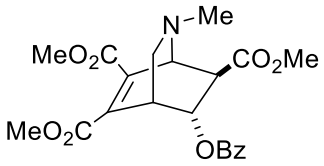


Tributyltin hydride (80.0 mg, 75 µL, 275 µmol, 1.6 equiv) and AIBN (3 mg, 19.7 µmol, 12 mol%) in dry benzene (4 mL) were added to a solution of cycloadduct **227** (98.0 mg, 168 µmol, 1.0 equiv) in dry benzene (7 mL) at reflux under N_2-atmosphere. The reaction mixture was stirred for 5 h at reflux and the solvent was removed under reduced pressure. Then the residue was redissolved in EA (5 mL) and a saturated solution of KF (5 mL) was added. After stirring for 18 h at 25 °C, the white precipitate was removed by filtration. The phases were separated, and the aqueous phase was extracted with EA (3 x 10 mL). The combined organic phases were washed with brine (30 mL) and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (flash silica gel + 10% KF, 10% → 25% EA:PE) to afford cycloadduct **228** (62.0 mg, 123 µmol, 73%) as a colorless oil.

R_f = 0.35 (PE:EA = 3:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.01 – 7.92 (m, 2H), 7.59 – 7.51 (m, 1H), 7.44 – 7.38 (m, 2H), 5.68 – 5.61 (m, 1H), 5.59 – 5.40 (m, 1H),

3.84 (s, 3H), 3.77 (s, 6H), 3.62 – 3.44 (m, 2H), 3.25 – 3.16 (m, 1H), 2.76 – 2.64 (m, 1H), 1.42 (s, 9H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.7 (q), 170.2 (q), 165.9 (q), 165.7 (q), 163.4 (q), 163.2 (q), 154.1 (q), 153.6 (q), 141.1 (q), 140.7 (q), 136.7 (q), 136.4 (q), 133.4 (+), 129.8 (+), 129.3 (q), 128.4 (+), 80.6 (q), 71.7 (+), 71.4 (+), 52.73 (+), 52.65 (+), 52.52 (+), 52.48 (+), 49.9 (+), 48.7 (+), 42.6 (–), 42.2 (–), 38.6 (+), 38.3 (+), 28.3 (+) (signal broadening and doubling due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2956, 1722, 1651, 1439, 1394, 1267, 1174, 1111, 1029, 865, 757, 716; **HRMS** (ESI): calcd. for $C_{25}H_{29}NO_{10}$ $(M+Na)^+$, m/z = 526.1684; found 526.1686.

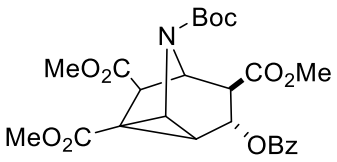
trimethyl (1*S*,4*R*,7*R*,8*R*)-8-(benzoyloxy)-2-methyl-2-azabicyclo[2.2.2]oct-5-ene-5,6,7-tricarboxylate (229)



Cycloadduct **228** (59.0 mg, 117 µmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4 mL) and TFA (441 mg, 296 µL, 3.87 mmol, 33 equiv) was added dropwise at 25 °C. After stirring for 1 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ was added dropwise. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. Then the solvent was removed under reduced pressure and the crude amine was obtained as colorless oil. To a solution of crude amine and formaldehyde (39.6 mg, 99 µL, 1.32 mmol, 11 equiv) in MeCN (5 mL), $NaBH_3CN$ (60.0 mg, 955 µmol, 8.2 equiv) was added and the reaction mixture was stirred for 1 h at 25 °C. The solution was acidified to pH 6 with HOAc and stirred for 1.5 h at 25 °C. After neutralization to pH 9 with NH_3 (25%), the mixture was diluted with CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (40% EA:PE + 1% TEA) to afford cycloadduct **229** (29.6 mg, 70.9 µmol, 61%) as a colorless oil.

R_f = 0.48 (PE:EA 1:1; UV, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.98 – 7.91 (m, 2H), 7.58 – 7.49 (m, 1H), 7.45 – 7.36 (m, 2H), 5.73 (t, *J* = 3.0 Hz, 1H), 4.19 (d, *J* = 2.9 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 3.49 (q, *J* = 2.8 Hz, 1H), 3.34 (dd, *J* = 10.9, 2.0 Hz, 1H), 2.63 (t, *J* = 2.8 Hz, 1H), 2.25 (s, 3H), 2.00 (dd, *J* = 10.9, 3.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.0 (q), 165.8 (q), 165.6 (q), 165.4 (q), 137.8 (q), 137.3 (q), 133.1 (+), 129.74 (q), 129.67 (+), 128.3 (+), 70.8 (+), 58.6 (+), 52.6 (+), 52.52 (+), 52.50 (+), 52.3 (+), 50.8 (–), 44.8 (+), 37.7 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 3004, 2952, 2855, 2803, 1718, 1644, 1435, 1260, 1200, 1144, 1111, 1074, 958, 887, 861, 753, 716; **HRMS** (ESI): calcd. for $C_{21}H_{23}NO_8$ $(M+H)^+$, m/z = 418.1496; found 418.1499.

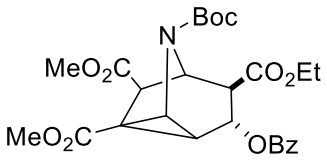
6-(*tert*-butyl) 1,4,8-trimethyl (3*R*,4*R*)-3-(benzoyloxy)-6-azatricyclo[3.2.1.0^{2,7}]octane-1,4,6,8-tetracarboxylate (235a)



To a solution of cycloadduct **227** (67.0 mg, 115 µmol, 1.0 equiv) in EtOH (3 mL), NaOAc (9.4 mg, 115 µmol, 1.0 equiv) and Pd (12.2 mg, 10 w% Pd/C, 11.5 µmol, 10 mol%) were added. The flask was charged with hydrogen and the solution was stirred for 8 h at 25 °C. The reaction mixture was filtrated through a short plug of silica and the solvent was removed under reduced pressure. Cyclopropane **235a** (44.0 mg, 87.4 µmol, 76%) was obtained as a colorless oil.

R_f = 0.60 (PE:EA = 2:1; $KMnO_4$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.07 – 8.00 (m, 2H), 7.60 – 7.52 (m, 1H), 7.47 – 7.39 (m, 2H), 5.98 (t, *J* = 3.3 Hz, 1H), 4.82 (d, *J* = 6.3 Hz, 1H), 4.41 – 4.06 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.66 (d, *J* = 6.4 Hz, 1H), 2.70 – 2.61 (m, 2H), 1.46 (s, 9H); (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.4 (q), 170.2 (q), 169.1 (q), 165.6 (q), 152.4 (q), 133.3 (+), 129.9 (+), 129.6 (q), 128.4 (+), 81.4 (q), 67.2 (+), 53.6 (+), 52.6 (+), 52.5 (+), 52.4 (+), 46.8 (+), 46.4 (+), 43.8 (+), 29.9 (q), 28.2 (+), 22.4 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2956, 1703, 1435, 1368, 1320, 1267, 1167, 1103, 1066, 999, 910, 712; **HRMS** (ESI): calcd. for $C_{25}H_{29}NO_{10}$ $(M+H)^+$, m/z = 504.1864; found 504.1866.

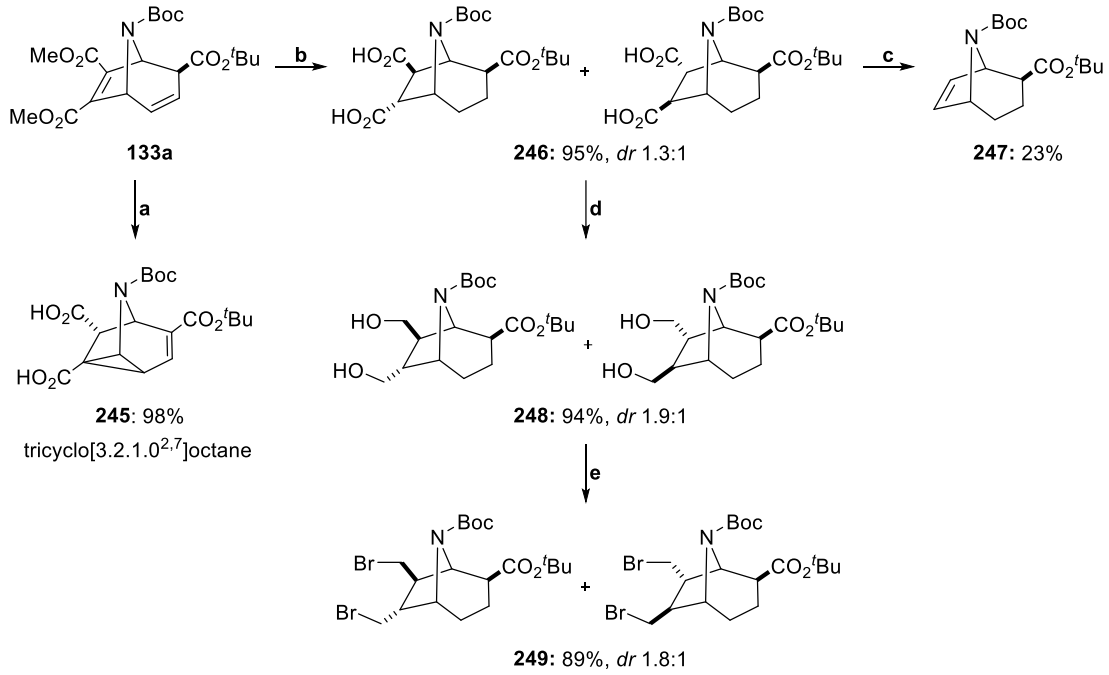
6-(*tert*-butyl) 4-ethyl 1,8-dimethyl (3*R*,4*R*)-3-(benzoyloxy)-6-azatricyclo[3.2.1.0^{2,7}]octane-1,4,6,8-tetracarboxylate (235b)



To a solution of cycloadduct **213** (647 mg, 1.08 mmol, 1.0 equiv) in EtOH (5 mL), NaOAc (89.0 mg, 108 µmol, 1.0 equiv) and Pd (115 mg, 10 w% Pd/C, 108 µmol, 10 mol%) were added. The flask was charged with hydrogen and the solution was stirred for 4.5 h at 25 °C. The reaction mixture was filtrated through a short plug of silica and the solvent was removed under reduced pressure. Cyclopropane **235b** (372 mg, 1.08 mmol, 66%) was obtained as a colorless oil.

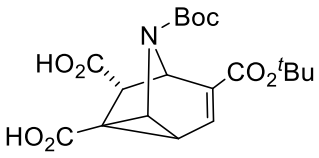
R_f = 0.63 (PE:EA = 2:1; $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.08 – 8.00 (m, 2H), 7.58 – 7.52 (m, 1H), 7.46 – 7.41 (m, 2H), 6.03 – 5.93 (m, 1H) ,4.85 (d, *J* = 5.2 Hz, 1H), 4.28 – 4.13 (m, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.65 (d, *J* = 6.1 Hz, 1H), 2.66 (dd, *J* = 7.6, 3.8 Hz, 1H), 2.64 (t, *J* = 2.5 Hz, 1H), 1.46 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (q), 169.9 (q), 169.2 (q), 165.5 (q), 152.4 (q), 133.2 (+), 129.8 (+), 129.6 (q), 128.3 (+), 81.4 (q), 67.2 (+), 61.7 (–), 53.7 (+), 52.44 (+), 52.39 (+), 46.7 (+), 46.5 (+), 43.9 (+), 29.9 (q), 28.2, 22.5 (+), 14.1 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2982, 1703, 1431, 1368, 1320, 1267, 1167, 1066, 1029, 999, 712; **HRMS** (ESI): calcd. for $C_{26}H_{31}NO_{10}$ $(M+H)^+$, m/z = 518.2021; found 518.2018.

Derivatizations of methyl ester groups at C6/C7 positions in 133a



Scheme 54. Derivatizations of **133a**. Conditions: a) NaOH (2.0 equiv), THF, 0 to 25 °C, 5.5 h, then HCl, 0 °C, 98%; b) *(i)* H_2, Pd/C (10 mol%), EtOH/THF (1:4 v/v), 60 bar, 25 °C, 4 h, *(ii)* NaOH (2.0 equiv), THF, 0 to 25°C, 4 h, then HCl, 0 °C, 95%; c) $Pb(OAc)_4$ (2.4 equiv), C_5H_5N, 67 °C, 6 h, 23%; d) BH_3·THF (6.5 equiv), THF, 0 to 25 °C, 24 h, 94%; e) *(i)* MsCl (2.2 equiv), TEA (4.0 equiv), CH_2Cl_2, 0 °C, 2 h, *(ii)* LiBr (13 equiv), THF, reflux, 9 h, 89%.

(5*R*,7*R*, 8*S*)-4,6-bis(*tert*-butoxycarbonyl)-6-azatricyclo[3.2.1.0^{2,7}]oct-3-ene-1,8-dicarboxylic acid (245)



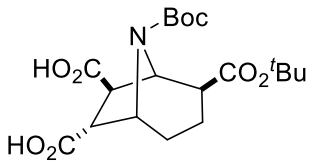
1M NaOH (510 µL, 20.4 mg, 510 µmol, 2.0 equiv) was added dropwise to a solution of cycloadduct **133a** (108 mg, 255 µmol, 1.0 equiv) in THF (2 mL) at 0 °C. Subsequently, the cooling bath was removed and the mixture was stirred for 5.5 h at 25 °C. Then the solvent was removed under reduced pressure and the salt was redissolved in EA and water. The aqueous layer was extracted with EA (3 x 15 mL). Afterwards the pH of the aqueous layer was adjusted to pH 2 by addition of 1M HCl solution. Then the aqueous

layer was extracted with EA (3 x 15 mL) and the combined organic phases were washed with brine (40 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded cycloadduct **245** (99.0 mg, 250 µmol, 98%) as a colorless solid.

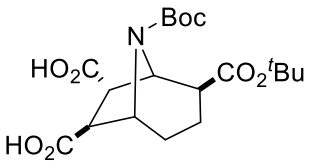
R_f = 0.40 (PE:EA = 1:2; bromocresol green, $KMNO_4$); **m.p.** = 127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.16 (dd, *J* = 6.5, 2.0 Hz, 1H), 5.38 – 5.25 (m, 1H), 4.19 (d, *J* = 5.9 Hz, 1H), 3.51 – 3.48 (m, 1H), 3.03 – 2.95 (m, 1H), 1.47 (s, 9H), 1.41 (s, 9H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 175.4 (q), 173.8 (q), 162.0 (q), 153.9 (q), 134.0 (+), 129.2 (q), 81.8 (q), 81.2 (q), 52.8 (+), 43.7 (+), 42.5 (+), 31.0 (+), 28.11 (q), 28.06 (+), 24.9 (+) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3474, 2978, 2937, 1703, 1621, 1368, 1312, 1282, 1252, 1159, 1111, 1033, 995, 921, 820, 772; **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_8$ $(M+Na)^+$, m/z = 418.1472; found 418.1475.

(1*S*,2*S*,5*R*,6*R*,7*R*)-2,8-bis(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-6,7-dicarboxylic acid (*major 246*)

(1*S*,2*S*,5*R*,6*S*,7*S*)-2,8-bis(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-6,7-dicarboxylic acid (*minor 246*)



major **246**



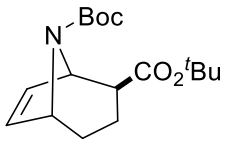
minor **246**

Cycloadduct **133a** (128 mg, 302 µmol, 1.0 equiv) was dissolved in EtOH:THF (3 mL; 1:4 v/v). Then Pd/C (3 mg, 30.2 µmol, 10 mol%, 10w% Pd on charcoal) was added and the reaction mixture was transferred in a vial which was placed in an autoclave and sealed. Then the autoclave was pressurized to 60 bar with H_2 and the solution was stirred for 4 h at 25 °C. The reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was dissolved in THF (2 mL) and a 1M NaOH (604 µL, 24.2 mg, 605 µmol, 2.0 equiv) was added dropwise at 0 °C. Subsequently, the cooling bath was removed and the mixture was stirred for 4 h at 25 °C. After removal of the solvent, the residue was redissolved in EA and water and the phases were separated. The aqueous layer was extracted with EA (3 x 15 mL). Afterwards the pH of the aqueous layer was adjusted to pH 2 by addition of 1M HCl solution. Then the aqueous layer was extracted with EA (3 x 15 mL) and the combined organic phases were

washed with brine (30 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded diastereomeric mixture of compound **246** (115 mg, 287 µmol, 95%, *dr* 1.3:1) as a colorless solid.
In the proton and carbon NMR the signals of both diastereomers are overlapping. Characteristic signals of the minor diastereomer are marked.

R_f = 0.68 (CH_2Cl_2:MeOH = 9:1; bromocresol green, $KMnO_4$); **m.p.** = 173 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 11.09 (s, 4H), 5.15 – 5.05 *minor* (m, 1H), 5.06 – 4.99 (m, 1.32H), 4.83 – 4.47 (m, 2.32H), 3.78 – 3.73 *minor* (m, 1H), 3.70 – 3.63 (m, 1.38H), 3.34 (d, *J* = 6.2 Hz, 1.30H), 3.29 *minor* (d, *J* = 6.1 Hz, 1H), 2.77 *minor* (dd, *J* = 6.0, 2.8 Hz, 1H), 2.65 (dd, *J* = 6.1, 2.9 Hz, 1.31H), 2.06 – 1.91 (m, 4.30H), 1.77 – 1.51 (m, 5.30H), 1.47 – 1.36 (m, 41.91H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 178.7 (q), 177.3 (q), 175.9 (q), 175.44 (q), 171.39 (q), 171.0 (q), 153.4 (q), 81.3 (q), 81.2 (q), 80.9 (q), 59.0 (+); 58.8 (+), 57.7 (+), 56.6 (+), 49.0 (+), 48.8 (+), 48.6 (+), 48.2 (+), 45.9 (+), 41.9 (+), 28.7 (–), 28.2 (+), 27.9 (+), 24.51 (–), 18.12 (–), 18.01 (–) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3440, 2978, 2937, 1700, 1394, 1368, 1312, 1252, 1156, 1051, 1010, 943, 850, 757, 705; **HRMS** (ESI): calcd. for $C_{19}H_{29}NO_8$ $(M+H)^+$, m/z = 400.1966; found 400.1969 (*major* **246** t_r = 5.763-5.829 min); **HRMS** (ESI): calcd. for $C_{19}H_{29}NO_8$ $(M+H)^+$, m/z = 400.1966; found 400.1967 (*minor* **246** t_r = 5.829-5.908 min).

di-*tert*-butyl (1*R*,2*S*,5*R*)-8-azabicyclo[3.2.1]oct-6-ene-2,8-dicarboxylate (247)



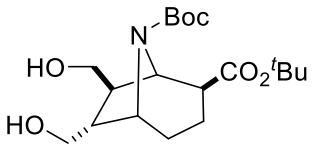
To a solution of compound **246** (90.7 mg, 227 µmol, 1.0 equiv) in dry pyridine (2.5 mL) was added $Pb(OAc)_4$ (141 mg, 318 µmol, 1.4 equiv) at 0 °C under N_2-atmosphere. Then the reaction temperature was gradually raised to 67 °C. After 3 h, additional $Pb(OAc)_4$ (101 mg, 227 µmol, 1.0 equiv) was added at 0 °C and the reaction mixture was stirred for 3 h at 67 °C. At 0 °C water (5 mL) was added and the mixture was filtrated through a short plug of celite. Then the aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with 5% HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) and dried over Na_2SO_4. The solvent was

removed under reduced pressure and the crude product was purified by flash system (2 → 7% EA:PE) to afford cycloadduct **247** (16.3 mg, 52.7 µmol, 23%) as a colorless oil.

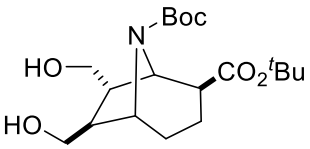
R_f = 0.70 (PE:EA = 3:1; Vanillin, $KMNO_4$); **^{1}H NMR** (400 MHz, DMF-d_7, 333 K): δ = 6.29 (dd, *J* = 5.9, 2.3 Hz, 1H), 6.21 (dd, *J* = 5.9, 2.2 Hz, 1H), 4.98 (t, *J* = 2.4 Hz, 1H), 4.75 – 4.58 (m, 1H), 2.41 (ddd, *J* = 6.3, 2.5, 1.0 Hz, 1H), 1.91 – 1.82 (m, 2H), 1.77 – 1.68 (m, 1H), 1.49 (s, 9H), 1.44 (s, 9H), 1.35 – 1.33 (m, 1H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, DMF-d_7, 333 K): δ = 172.3 (q), 153.7 (q), 133.7 (+), 132.4 (+), 80.3 (q), 79.3 (q), 61.1 (+), 59.7 (+), 40.8 (+), 28.4 (+), 28.1 (+), 22.8 (–), 18.8 (–) (signal broadening due to rotamers); **IR $\tilde{\nu}$** [cm^{-1}]: 2975, 2930, 1730, 1700, 1368, 1312, 1252, 1163, 1051, 1013, 857; **HRMS** (ESI): calcd. for $C_{17}H_{27}NO_4$ $(M+H)^+$, m/z = 310.2013; found 310.2015.

di-*tert*-butyl (1*R*,2*S*,5*R*,6*R*,7*R*)-6,7-bis(hydroxymethyl)-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate (*major* 248)

di-tert-butyl (1*R*,2*S*,5*R*,6*S*,7*S*)-6,7-bis(hydroxymethyl)-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate (*minor* 248)



major **248**



minor **248**

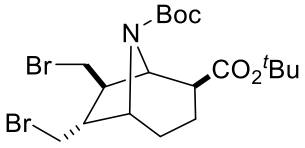
BH_3·THF (1.61 mL, 139 mg, 1.61 mmol, 3.5 equiv) was added dropwise to a solution of compound **246** (184 mg, 461 µmol, 1.0 equiv) in dry THF (4 mL) at 0 °C under N_2-atmosphere. The mixture was then warmed to 25 °C and after 8 h additional BH_3·THF (1.38 mL, 119 mg, 1.38 mmol, 3.0 equiv) was added at 0 °C, then the mixture was stirred for 16 h at 25 °C. Afterwards the reaction mixture was treated with MeOH and the solvent was removed under reduced pressure. The residue was redissolved in MeOH and evaporated in vacuo. This process was repeated three times and purification of the crude product by flash system (1 → 8% MeOH: CH_2Cl_2) afforded diastereomeric mixture of compound **248** (160 mg, 431 µmol, 94%, *dr* 1.9:1) as a colorless oil.

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

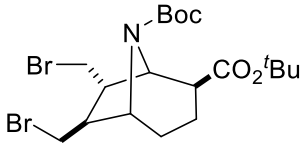
R_f = 0.57 (CH_2Cl_2:MeOH = 9:1; $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.68 – 4.58 *minor*(m, 1H), 4.45 – 4.27 (m, 2.93H), 4.23 – 4.09 (m, 2H), 3.82 – 3.61 (m, 13.62H), 3.36 – 3.20 (m, 3.81H), 2.50 – 2.41 (m, 1.94H), 2.37 – 2.29 *minor*(m, 1H), 2.21 – 1.85 (m, 12.66H), 1.65 – 1.51 (m, 4.35H), 1.43 – 1.36 (m, 53.88H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.4 (q), 172.1 (q), 171.9 (q), 171.6 (q), 154.9 (q), 153.8 (q), 153.3 (q), 81.0 (q), 80.9 (q), 80.64 (q), 80.60 (q), 80.1 (q), 80.0 (q), 79.6 (q), 79.5 (q), 65.8 (–), 65.61 (–), 65.55 (–), 65.5 (–), 61.1 (–), 60.8 (–), 60.6 (–), 59.3 (+), 59.0 (+), 57.5 (+), 57.3 (+), 57.2 (+), 56.7 (+), 56.2 (+), 55.9 (+), 49.3 (+), 45.7 (+), 45.6 (+), 41.6 (+), 28.4 (+), 28.1 (+), 27.9 (+), 23.7 (–), 19.3 (–), 19.2 (–), 19.1 (–), 19.0 (–) (signal broadening and doubling due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3370, 2974, 2930, 2874, 1726, 1662, 1476, 1420, 1364, 1252, 1163, 1115, 1062, 1021, 861, 753; **HRMS** (ESI): calcd. for $C_{19}H_{33}NO_6$ $(M+Na)^+$, m/z = 394.2200; found 394.2201 (*major* **248** t_r = 5.481-5.518 min); **HRMS** (ESI): calcd. for $C_{19}H_{33}NO_6$ $(M+Na)^+$, m/z = 394.2200; found 394.2201 (*minor* **248** t_r = 5.576-5.659 min).

di-*tert*-butyl (1*S*,2*S*,5*R*,6*R*,7*R*)-6,7-bis(bromomethyl)-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate (*major* 249)

di-*tert*-butyl (1*S*,2*S*,5*R*,6*S*,7*S*)-6,7-bis(bromomethyl)-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate (*minor* 249)



major **249**



minor **249**

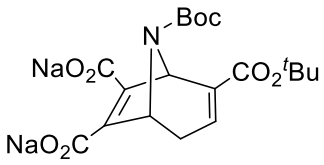
MsCl (50 µL, 74.6 mg, 651 µmol, 2.2 equiv) was added dropwise to a solution of TEA (165 µL, 120 mg, 1.18 mmol, 4.0 equiv) and diol **248** (110 mg, 296 µmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at 0 °C. After stirring for 2 h at 0 °C, 1M HCl (5 mL) was added and the layers were separated. The organic layer was washed with 1M HCl (10 mL), 2M NaOH (10 mL) and brine (10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to obtain the crude mesylate as yellowish solid. The mesylate was dissolved in dry THF (4 mL) and LiBr (334 mg, 3.85 mmol, 13 equiv) was added in one portion at 25 °C under N_2-atmosphere. Then the reaction mixture was heated at reflux for 9 h and was concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (10 mL) and washed with water (4 x 15 mL), brine (15 mL) and dried over Na_2SO_4. Removal of the solvent and purification by flash system (2 → 6%

EA:PE) yielded diastereomeric mixture of *major* and *minor* cycloadduct **249** (131 mg, 264 µmol, 89%, *dr* 1.8:1) as a colorless oil.

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

R_f = 0.63 (PE:EA = 5:1; UV, $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.84 – 4.57 (m, 2.59H), 4.51 – 4.14 (m, 3.26H), 3.76 – 3.61 (m, 2.66H), 3.52 – 3.25 (m, 9.30H), 2.58 (d, *J* = 6.0 Hz, 1H), 2.47 *minor* (dd, *J* = 6.4, 2.7 Hz, 1.79H), 2.39 – 2.15 (m, 3.38H), 2.16 – 1.92 (m, 7.96H), 1.71 – 1.54 (m, 3.83H), 1.47 – 1.40 (m, 51.58H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.8 (q), 171.3 (q), 171.2 (q), 171.0 (q), 154.4 (q), 153.6 (q), 153.2 (q), 152.9 (q), 81.1 (q), 80.8 (q), 80.3 (q), 79.7 (q), 61.5 (+), 60.4 (+), 59.7 (+), 58.3 (+), 57.4 (+), 56.9 (+), 56.2 (+), 51.5 (+), 51.0 (+), 50.8 (+), 50.2 (+), 50.1 (+), 45.3 (+), 40.3 (+), 36.7(–), 36.5 (–), 36.3 (–), 35.9 (--), 30.7 (–), 30.3 (–), 30.0 (–), 29.8 (–), 29.7 (–), 28.3 (+), 28.0 (+), 22.6 (–), 22.4 (–), 21.9 (–), 21.6 (–), 19.2 (–), 19.1 (–) (signal broadening and doubling due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2974, 2928, 1730, 1696, 1394, 1368, 1320, 1256, 1170, 1115, 1036, 865; **HRMS** (ESI): calcd. for $C_{19}H_{31}Br_2NO_4$ $(M+Na)^+$, m/z = 496.0693; found 496.0706 (*major* and *minor* **249** t_r = 7.565-7.660 min).

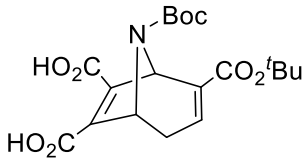
sodium (1*S*,5*R*)-2,8-bis(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate (251)



The isomerized product **152a** (448 mg, 1.06 mmol, 1.0 equiv) was dissolved in THF (4 mL) and a 1M NaOH (84.6 mg, 2.12 mL, 2.12 mmol, 2.0 equiv) was added dropwise at 0 °C. Subsequently, the cooling bath was removed and the mixture was stirred for 3.5 h at 25 °C. Removal of the solvent under reduced pressure yielded salt **251** (463 mg, 1.05 mmol, quant.) as a colorless solid.

m.p. = 198 °C; **^{1}H NMR** (400 MHz, D_2O): δ = 6.75 – 6.68 (m, 1H), 5.15 – 5.00 (m, 1H), 4.78 – 4.67 (m, 1H), 2.88 (d, *J* = 19.2 Hz, 1H), 2.36 (dd, *J* = 20.5, 3.9 Hz, 1H), 1.51 (s, 9H), 1.45 (s, 9H) (signal broadening due to rotamers); **^{13}C NMR** (101 MHz, D_2O): δ = 171.6 (q), 170.6 (q), 165.6 (q), 154.9 (q), 150.2 (q), 138.0 (+), 136.9 (q), 132.8 (q), 82.8 (q), 82.4 (q), 59.8 (+), 57.9 (+), 27.7 (+), 27.3 (+), 26.4 (–) (signal broadening due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 2982, 2937, 1707, 1566, 1313, 1163, 1092, 779; **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_8$ $(M-H)^-$, m/z = 394.1507; found 394.1517.

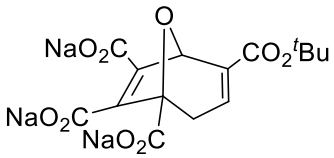
(1*S*,5*R*)-2,8-bis(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylic acid (252)



The cycloadduct **152a** (542 mg, 1.28 mmol, 1.0 equiv) was dissolved in THF (4 mL) and a 1M NaOH (2.56 mL, 102 mg, 2.56 mmol, 2.0 equiv) was added dropwise at 0 °C. Subsequently, the cooling bath was removed and the mixture was stirred for 3.5 h at 25 °C. After removal of the solvent, the residue was redissolved in EA and water and the phases were separated. The aqueous layer was extracted with EA (3 x 15 mL). Afterwards the pH of the aqueous layer was adjusted to pH 2 by addition of 1M HCl solution. Then the aqueous layer was extracted with EA (3 x 15 mL) and the combined organic phases were washed with brine (30 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded compound **252** (490 mg, 1.28 mmol, 97%) as a colorless solid.

R_f = 0.22 (CH_2Cl_2:MeOH = 9:1; bromocresol green, $KMnO_4$); **m.p.** = 157 °C; **^{1}H NMR** (400 MHz, MeOD): δ = 6.65 – 6.57 (m, 1H), 5.44 – 5.30 (m, 1H), 5.00 – 4.89 (m, 1H), 3.02 – 2.75 (m, 1H), 2.38 – 2.07 (m, 1H), 1.51 (s, 9H), 1.44 (s, 9H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, MeOD): δ = 167.3 (q), 166.5 (q), 165.2 (q), 155.2 (q), 150.4 (q), 143.0 (q), 138.5 (q), 137.7 (+), 82.2 (q), 81.8 (q), 60.7 (+), 59.7 (+), 28.6 (+), 28.3 (+), 26.5 (–) (signal broadening and doubling due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3474, 2982, 2930, 1707, 1621, 1372, 1297, 1256, 1163, 1092, 977, 753; **HRMS** (ESI): calcd. for $C_{19}H_{25}NO_8$ $(M-H)^-$, m/z = 394.1507; found 394.1513.

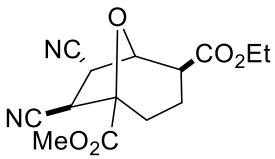
sodium (1*R*,5*S*)-4-(*tert*-butoxycarbonyl)-8-oxabicyclo[3.2.1]octa-3,6-diene-1,6,7-tricarboxylate (253)



The isomerized product **151b** (108 mg, 282 µmol, 1.0 equiv) was dissolved in THF (2 mL) and a 1M NaOH (61.1 mg, 0.84 mL, 847 µmol, 3.0 equiv) was added dropwise at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Removal of the solvent under reduced pressure yielded salt **253** (114 mg, 281 µmol, quant.) as an orange solid.

m.p. = 187 °C; **^{1}H NMR** (400 MHz, D_2O): δ = 6.81 (t, *J* = 3.5 Hz, 1H), 5.36 (s, 1H), 2.85 – 2.69 (m, 2H), 1.51 (s, 9H); **^{13}C NMR** (101 MHz, D_2O): δ = 175.8 (q), 171.5 (q), 170.4 (q), 165.9 (q), 145.8 (q), 138.7 (q), 138.6 (+), 135.8 (q), 88.8 (q), 82.9 (q), 77.9 (+), 30.5 (–), 27.3 (+), **IR** $\tilde{\nu}$ [cm^{-1}]: 2978, 2933, 1692, 1566, 1364, 1144, 1088, 835, 746; **HRMS** (ESI): calcd. for $C_{15}H_{16}O_9$ $(M-H)^-$, m/z = 339.0722; found 339.0730.

4-ethyl 1-methyl (1*R*,4*S*,5*R*,6*R*,7*R*)-6,7-dicyano-8-oxabicyclo[3.2.1]octane-1,4-dicarboxylate (267)

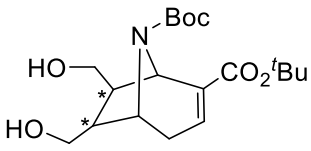


Cycloadduct *major* **140d** (81 mg, 279 µmol, 1.0 equiv) was dissolved in THF:MeOH (4 ml, 1:1) in a glass vial and Pd/C (29.7 mg, 10 w%, 27.9 µmol, 10 mol%) was added. The vial was placed in an autoclave and sealed. Then the autoclave was pressurized to 25 bar with H_2 and the solution was stirred for 4.5 h at 25 °C. The reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash system (13 → 33% EA:PE) to obtain compound **267** (21.6 mg, 73.9 µmol, 26%) as a colorless oil.

R_f = 0.30 (PE:EA = 3:1; $KMNO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.31 (dt, *J* = 7.5, 1.7 Hz, 1H), 4.30 – 4.13 (m, 2H), 3.88 (s, 3H), 3.69 (dd, *J* = 7.4, 6.3 Hz, 1H), 3.57 (d, *J* = 6.2 Hz,

1H), 2.82 (d, *J* = 5.9 Hz, 1H), 2.51 – 2.38 (m, 1H), 2.25 – 2.09 (m, 1H), 2.09 – 1.98 (m, 1H), 1.96 – 1.86 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.0 (q), 168.1 (q), 116.9 (q), 115.3 (q), 87.0 (q), 78.4 (+), 62.0 (–), 53.6 (+), 40.4 (+), 39.8 (+), 36.9 (+), 30.2 (–), 17.1(–), 14.2 (+); **IR** $\tilde{\nu}$ [cm^{-1}]: 2960, 2855, 2251, 1733, 1443, 1372, 1305, 1200, 1092, 1025, 954, 913, 734; **HRMS** (ESI): calcd. for $C_{14}H_{16}N_2O_5$ $(M+H)^+$, m/z = 293.1132; found 293.1138.

di-*tert*-butyl (1*R*,5*R*)-6,7-bis(hydroxymethyl)-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylate (274)



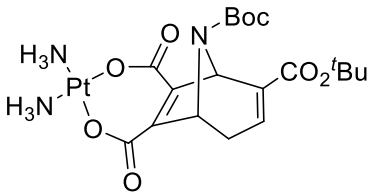
BH_3·THF (130 mg, 1.5 mL, 1.51 mmol, 4.0 equiv) was added dropwise to a solution of compound **252** (149 mg, 377 µmol, 1.0 equiv) in dry THF (3.5 mL) at 0 °C under nitrogen atmosphere. The mixture was then warmed to 25 °C and the mixture was stirred for 5 h at 25 °C. Afterwards the reaction mixture was treated with MeOH and the solvent was removed under reduced pressure. The residue was redissolved in MeOH and evaporated in vacuo. This process was repeated three times and purification of the crude product by flash system (1 → 8% MeOH: CH_2Cl_2) afforded diastereomeric mixture of compound **274** (75.8 mg, 205 µmol, 54%, *dr* 1.9:1) as a colorless oil.

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

R_f = 0.51 (CH_2Cl_2:MeOH = 9:1; $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.84 – 6.73 (m, 3.46H), 6.74 – 6.70 (m, 1H) *minor*, 4.86 – 4.71 (m, 3.12H), 4.43 – 4.37 (m, 1H) *minor*, 4.28 – 4.21 (m, 1H) *minor*, 4.08 – 3.98 (m, 3.46H), 3.72 – 3.40 (m, 18H), 3.25 – 3.02 (m, 10H), 2.95 – 2.57 (m, 11H), 2.36 – 2.31 (m, 1H) *minor*, 2.23 – 2.16 (m, 1H) *minor*, 2.05 – 1.90 (m, 3.56H), 1.64 – 1.61 (m, 1H) *minor*, 1.47 – 1.46 (m, 21H), 1.40 (s, 62H) (signal broadening and doubling due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ (*major* **274**) = 166.1 (q), 154.6 (q), 137.6 (+), 134.8 (q), 81.7 (q), 80.2 (q), 62.4 (–), 59.2 (–), 55.8 (+), 54.7 (+), 50.1 (+), 44.0 (+), 33.8 (–), 28.1 (+), 28.0 (+) (signal broadening and doubling due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3481, 2922, 2855, 1700, 1368, 1256, 1163; **HRMS**

(ESI): calcd. for $C_{19}H_{31}NO_6$ $(M+Na)^+$, m/z = 392.2044; found 392.2042 (*major* **274** t_r = 7.286-7.394 min); **HRMS** (ESI): calcd. for $C_{19}H_{31}NO_6$ $(M+Na)^+$, m/z = 392.2044; found 392.2043 (*minor* **274** t_r = 6.843-6.938 min).

Complex 283



$AgNO_3$ (137 mg, 803 µmol, 2.0 equiv) and $Pt(NH_3)_2I_2$ (194 mg, 402 µmol, 83%) in H_2O (2 mL) were stirred for 24 h at 25 °C under the exclusion of light. After filtration $Pt(NH_3)_2(NO_3)_2$ was obtained in solution. Salt **281** (170 mg, 387 µmol, 1.0 equiv) was added to a solution of $Pt(NH_3)_2(NO_3)_2$ in water and stirred for 24 h at 25 ° under exclusion of light. The solution was filtered, and the orange solid was washed with water (3 mL). Then the solid was redissolved with EA (20 mL) and the solvent was evaporated to obtain the complex **283** (156 mg, 251 µmol, 65%) as an orange solid.

m.p. = 214 °C (decomp. pt); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.85 – 6.25 (m, 1H), 5.65 – 3.30 (m, 8H), 3.22 – 2.44 (m, 2H), 1.55 – 1.32 (m, 18H) (EA could not be removed even after lyophilization, signal broadening due to rotamers); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.4 (q), 165.1 (q), 163.9 (q), 153.7 (q), 149.5 (q), 141.9 (q), 137.6 (q), 136.3 (+), 80.6 (q), 80.3 (q), 59.6 (+, signal overlapping), 29.8 (–), 28.4 (+), 28.2 (+) (signal broadening and overlapping due to rotamers); **IR** $\tilde{\nu}$ [cm^{-1}]: 3250, 2978, 2933, 1700, 1607, 1364, 1300, 1253, 1159, 1088, 1021, 977, 880, 850, 783, 749; **HRMS** (ESI): calcd. for $C_{19}H_{29}N_3O_8Pt$ $(M+H)^+$, m/z = 623.1675; found 623.1685.

F Appendix

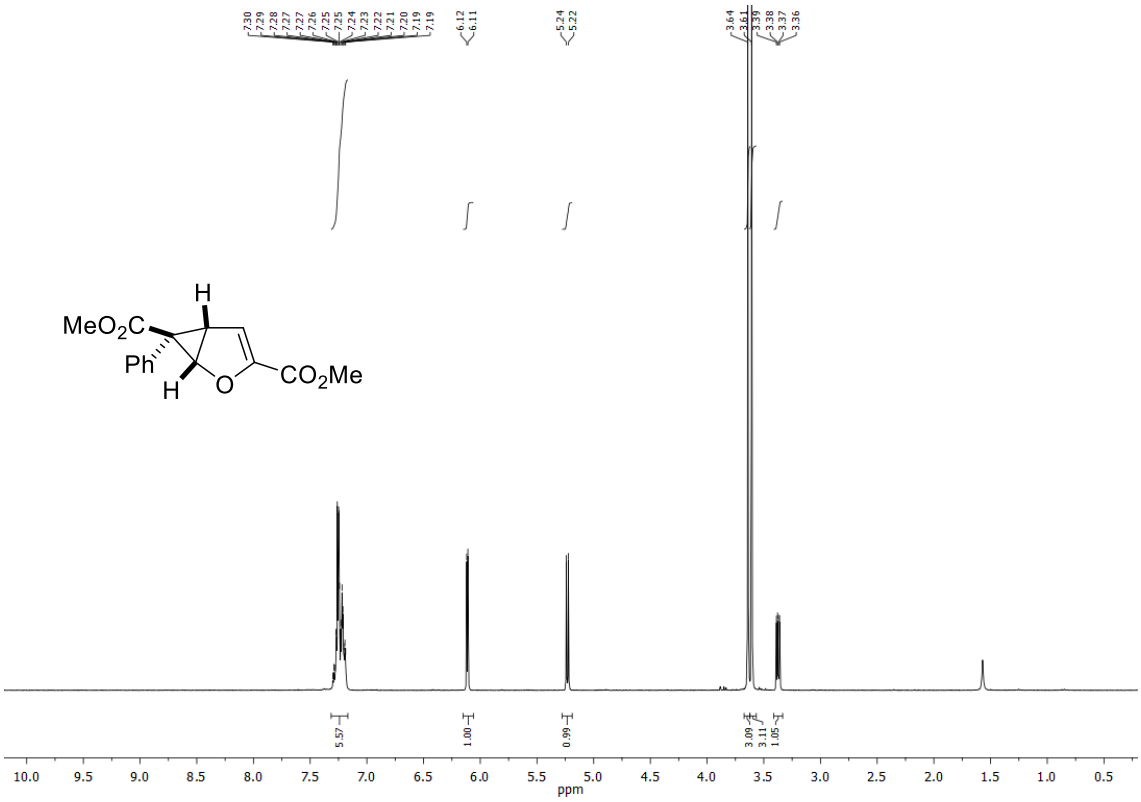
1 NMR spectra

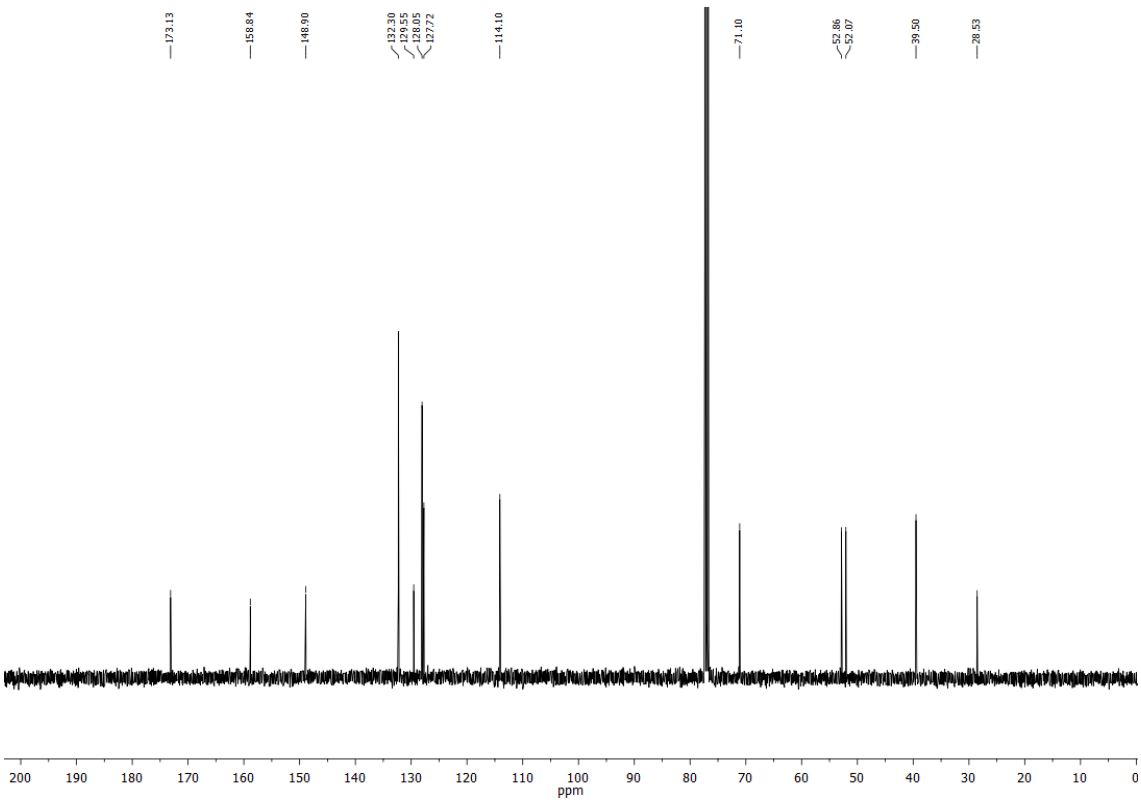
^{1}H NMR spectra: upper image

^{13}C NMR spectra: lower image

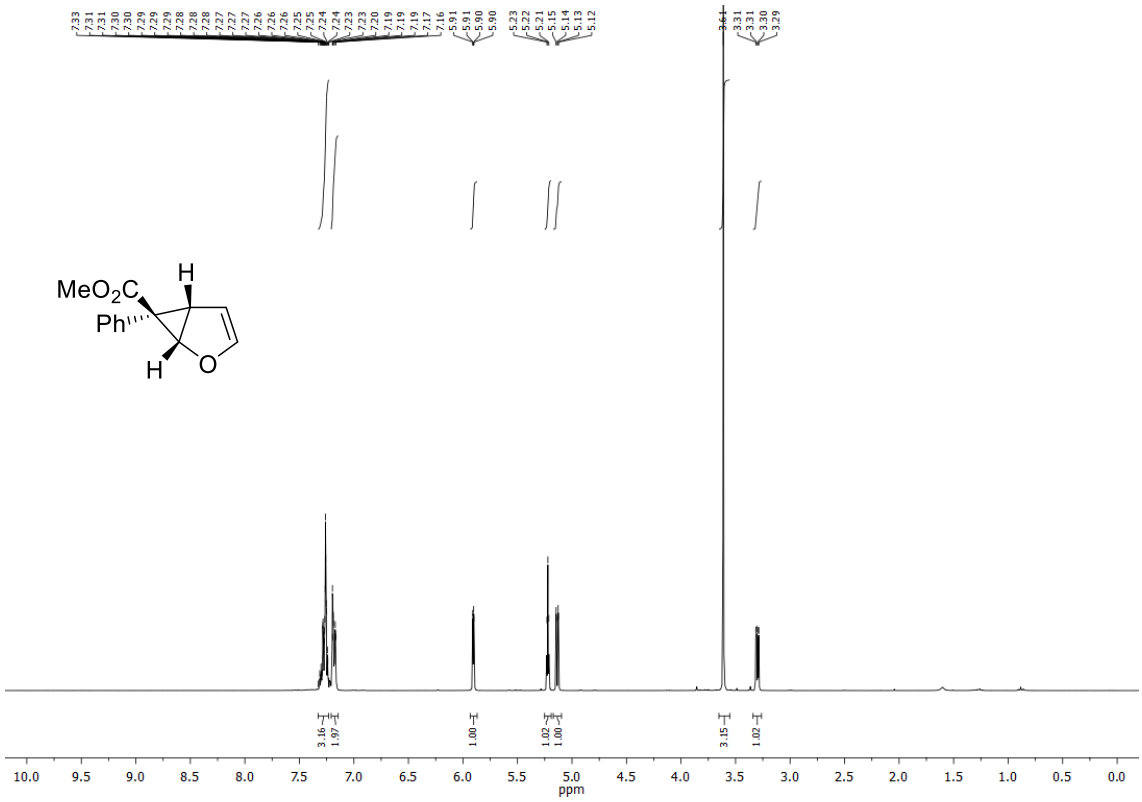
Solvent is given at the spectra.

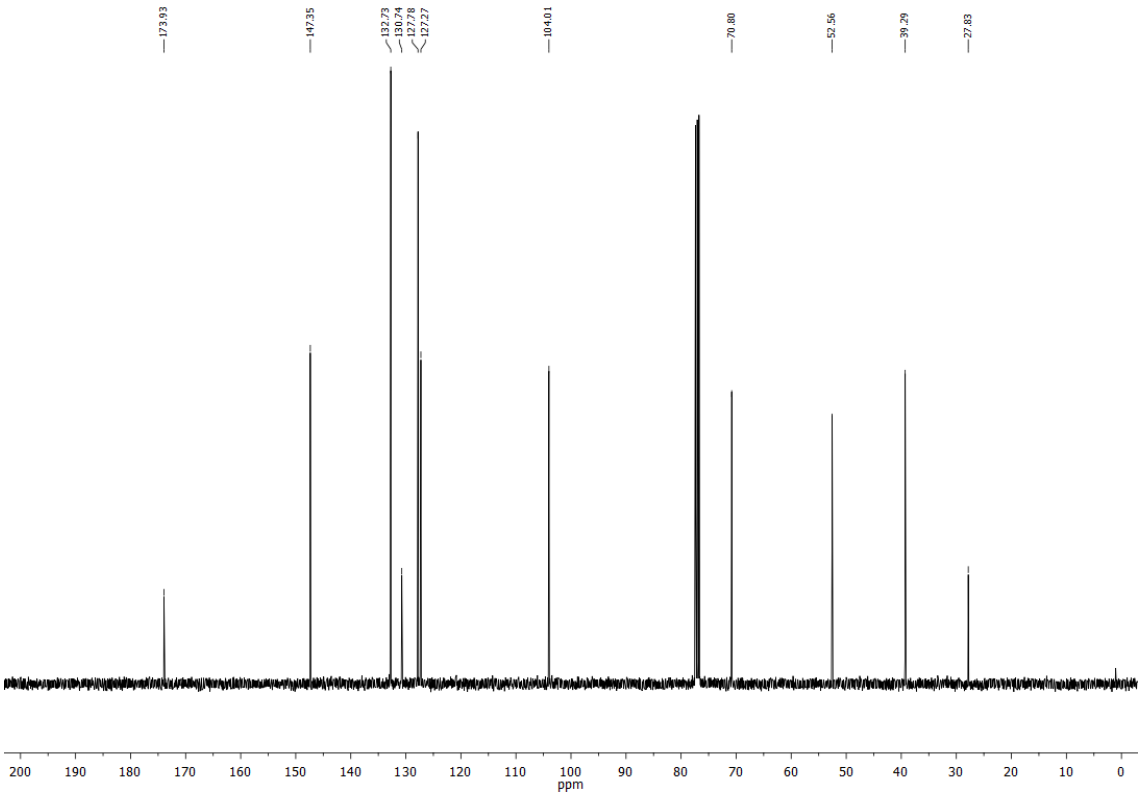
Compound **120d**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



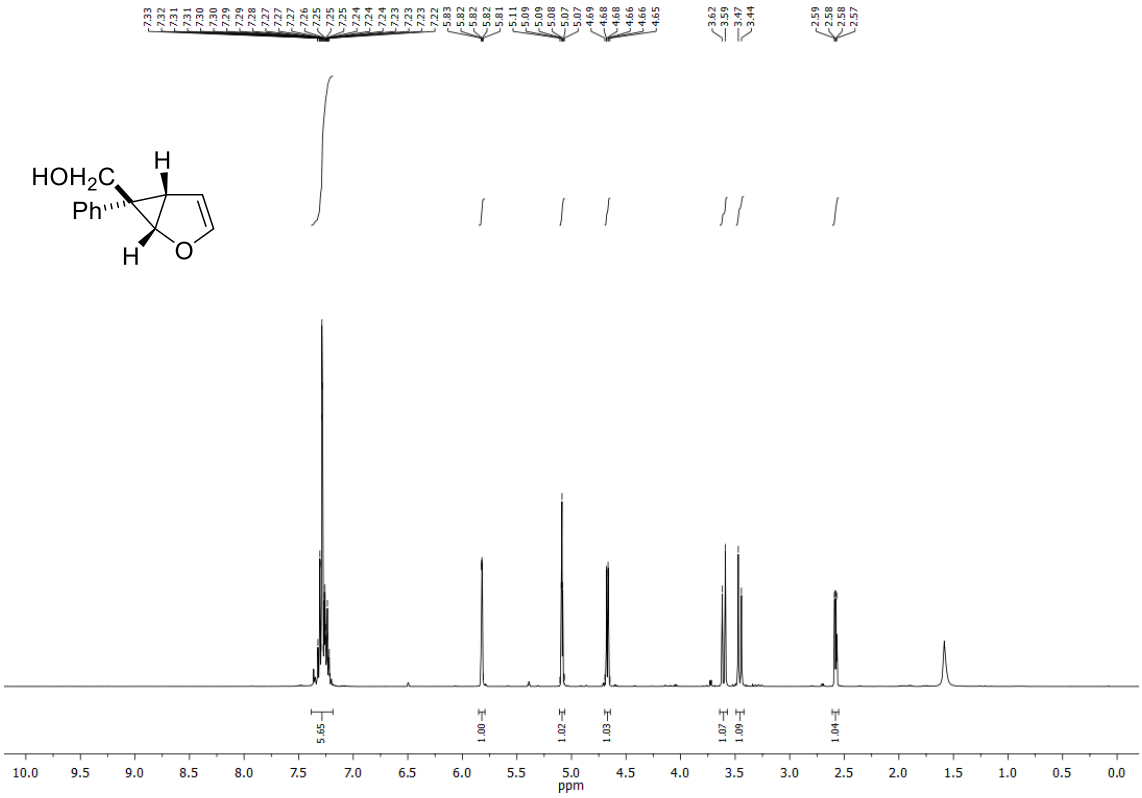


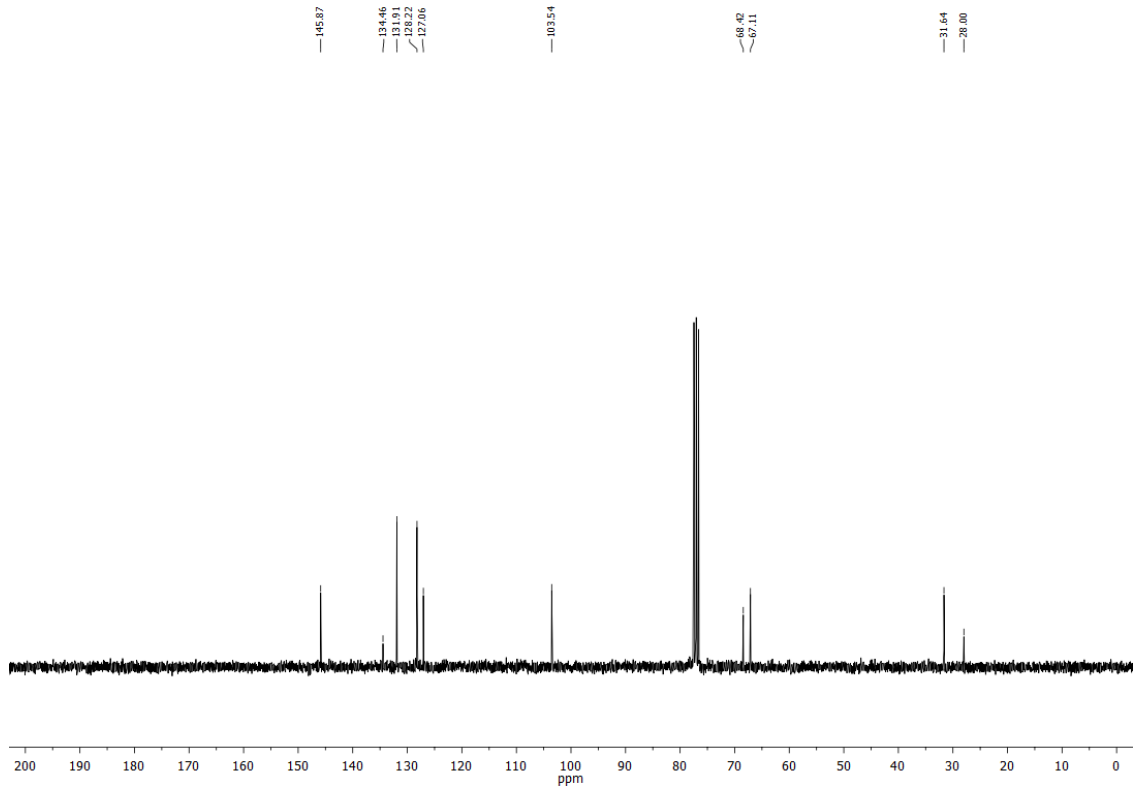
Compound **120e**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



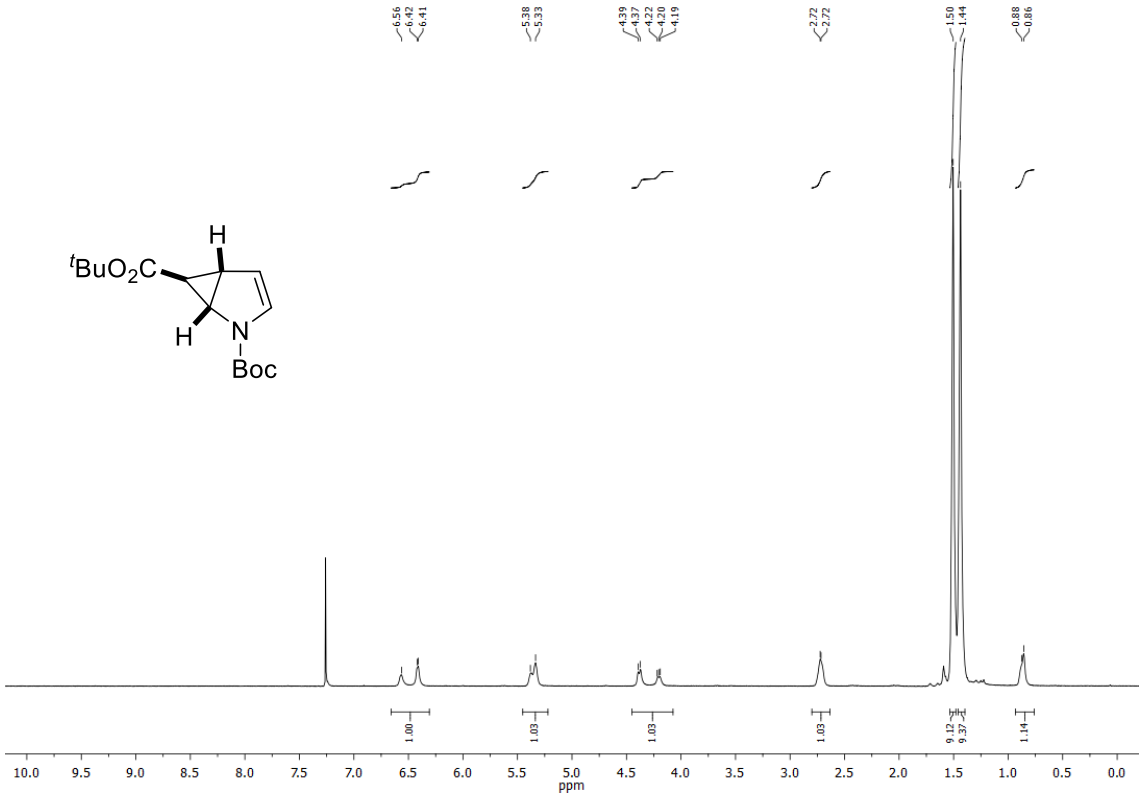


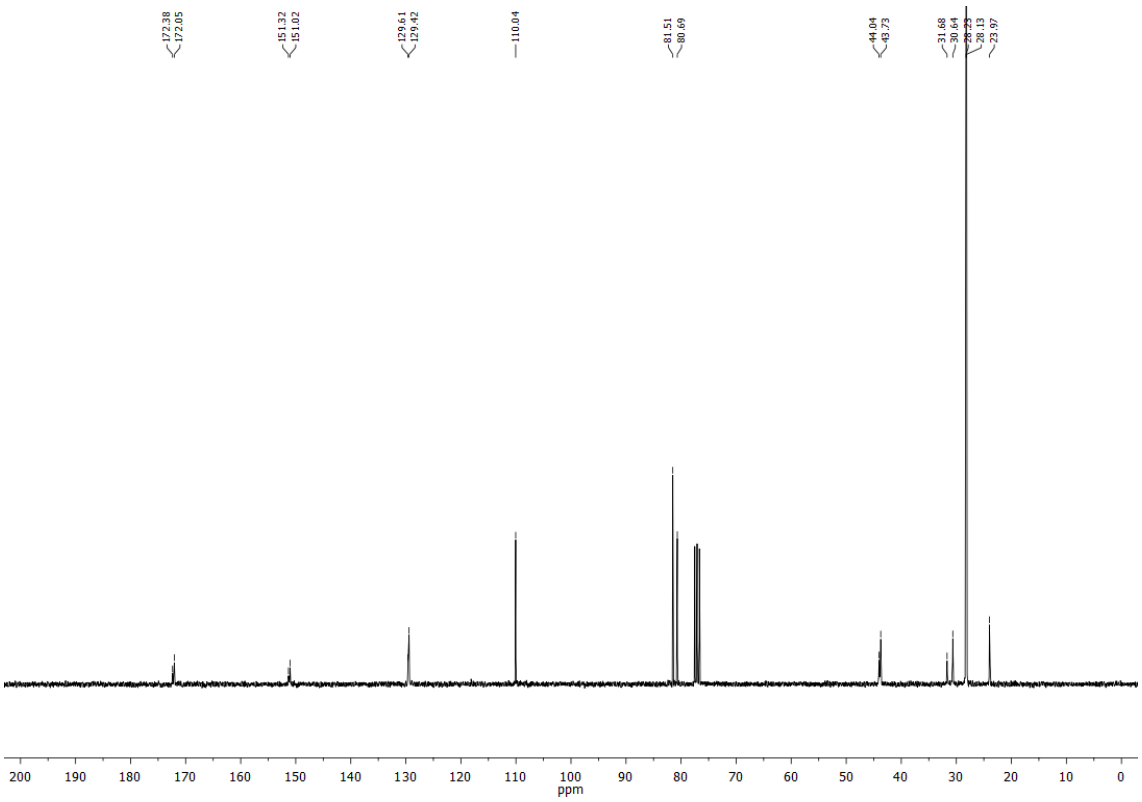
Compound **120f**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



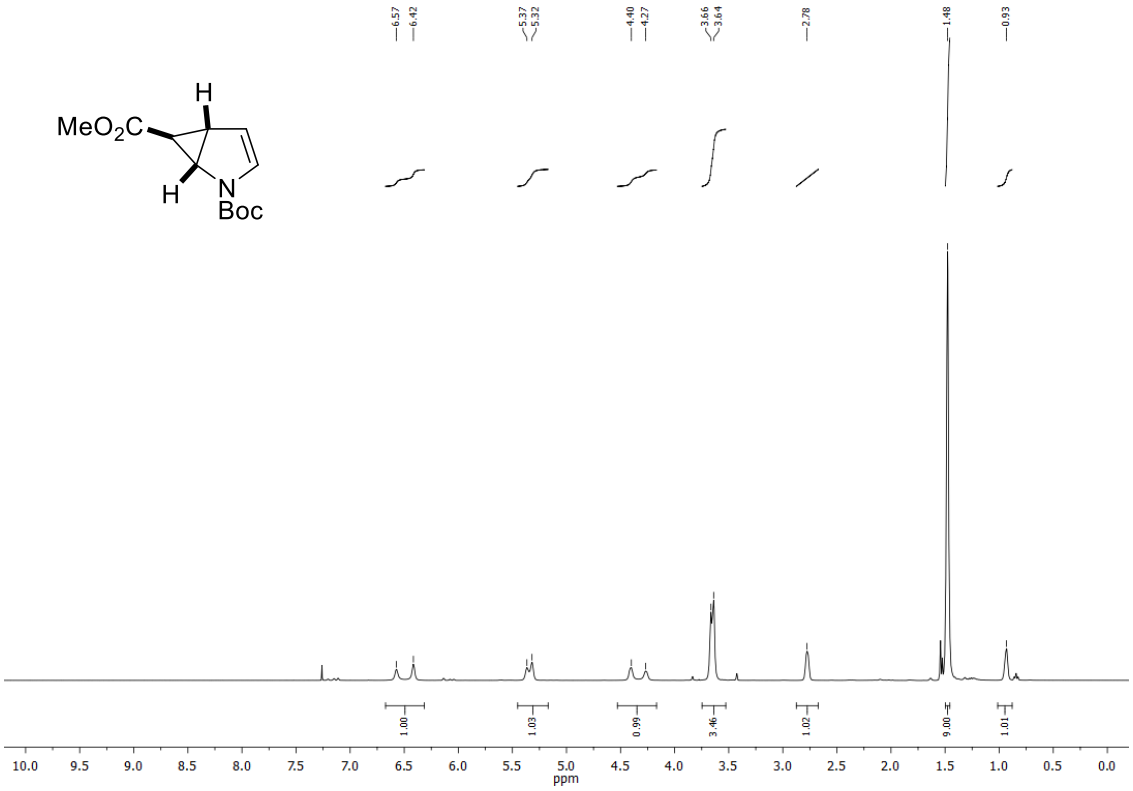


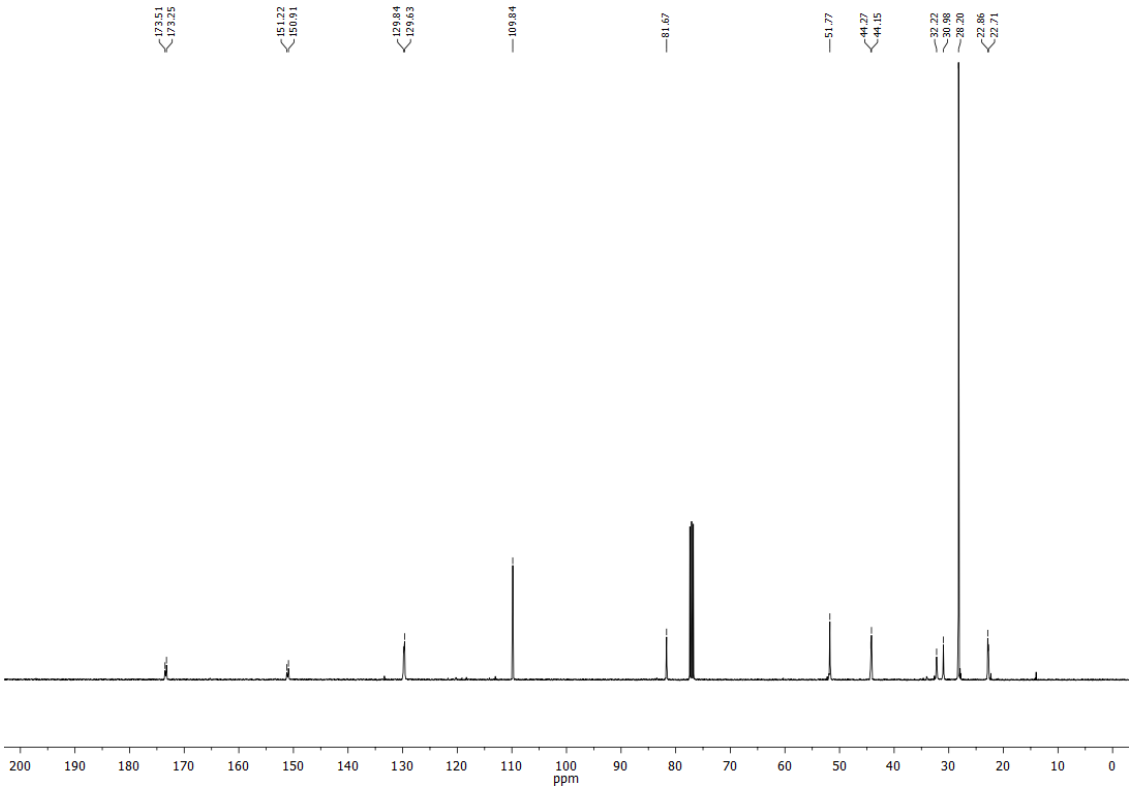
Compound **119a**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



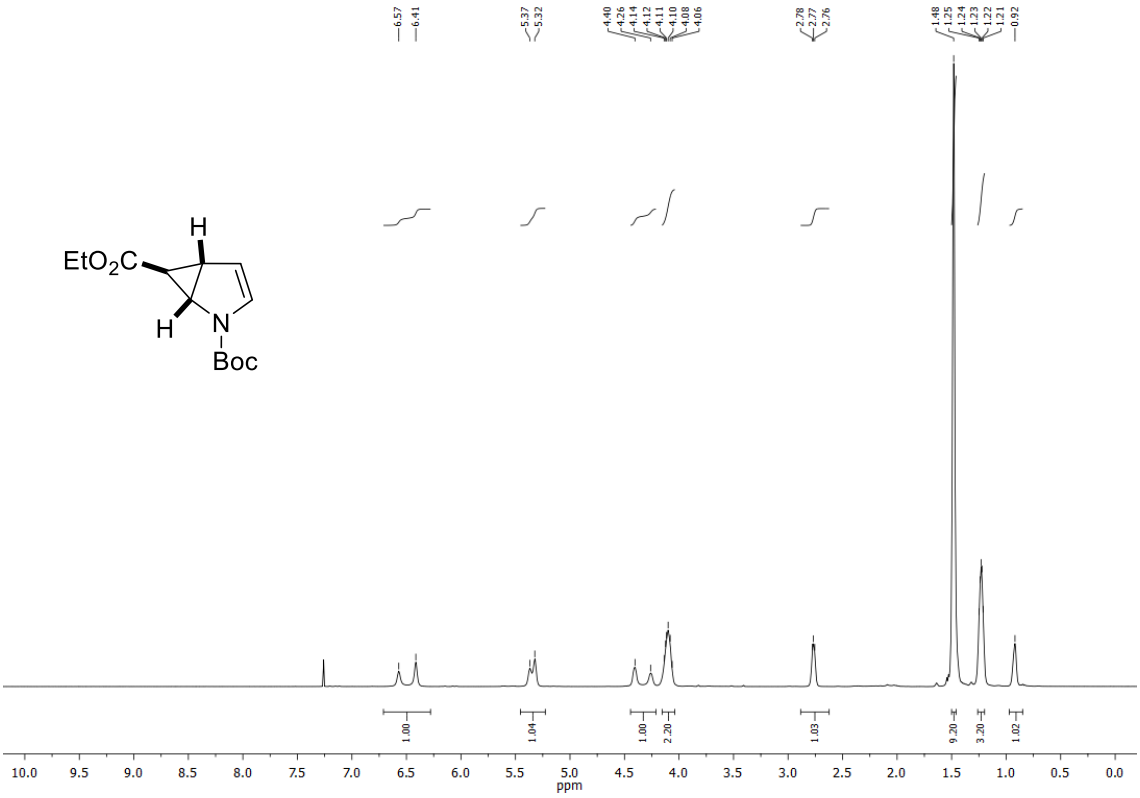


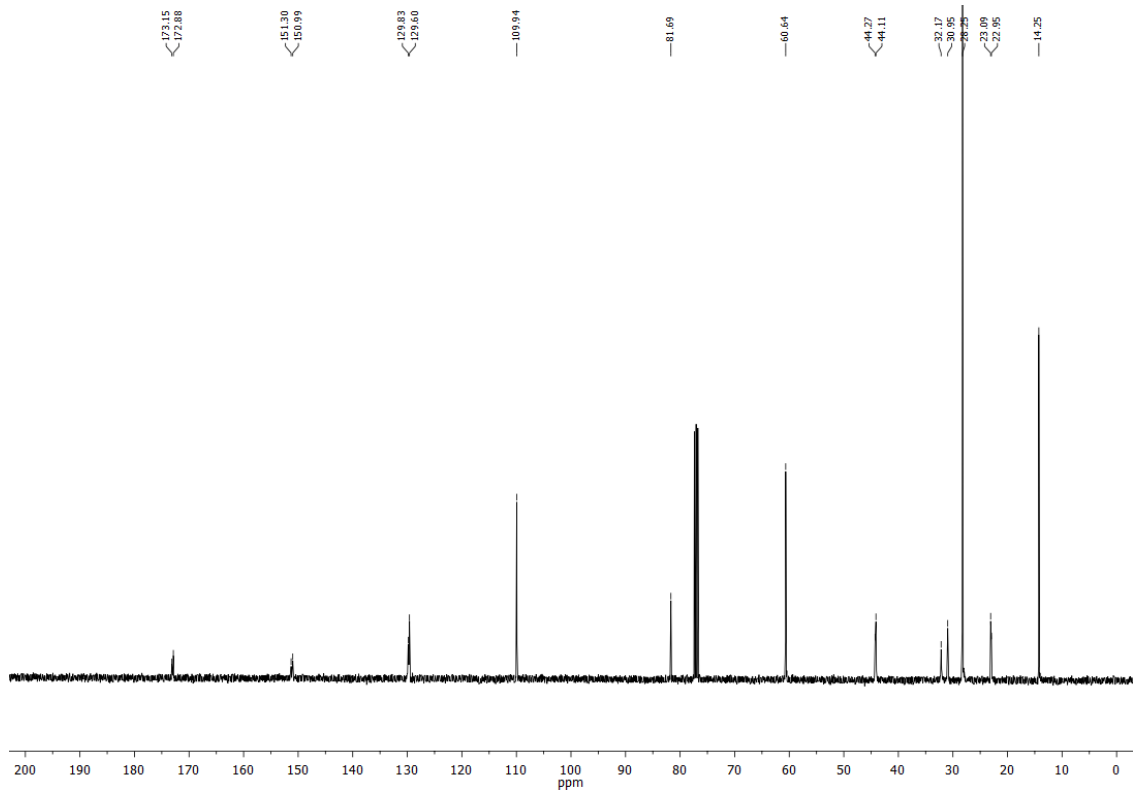
Compound **119b**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



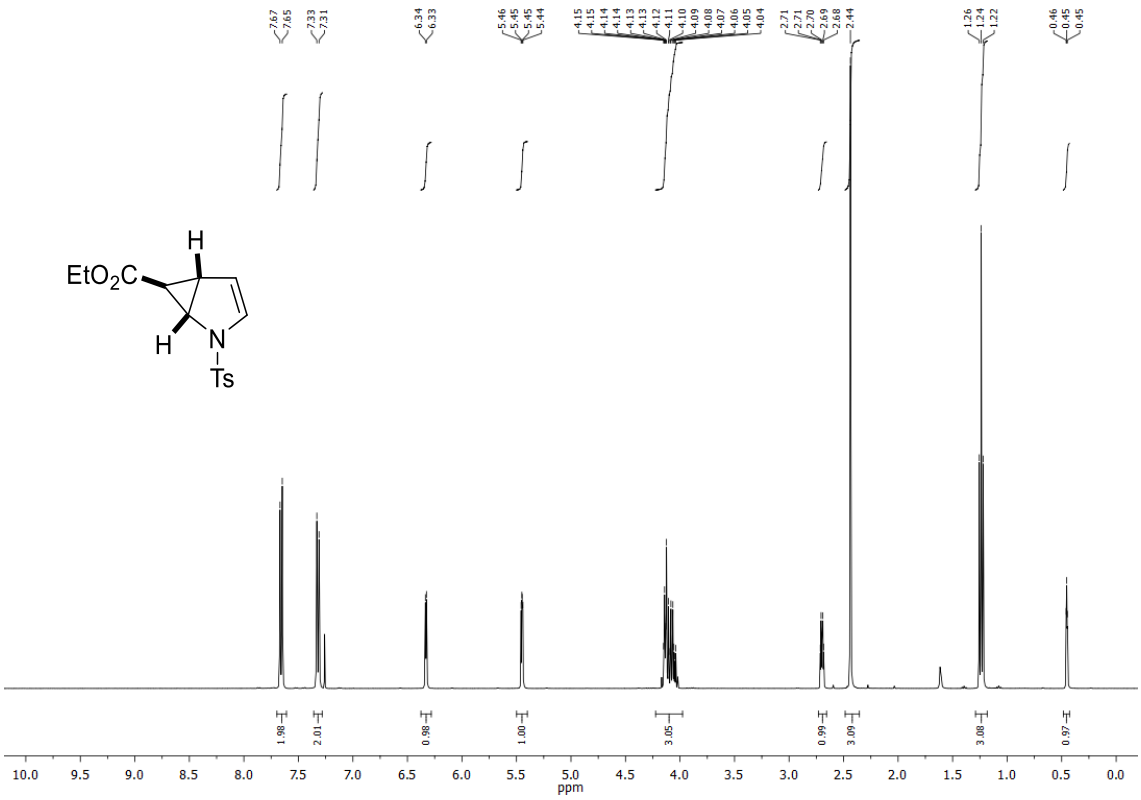


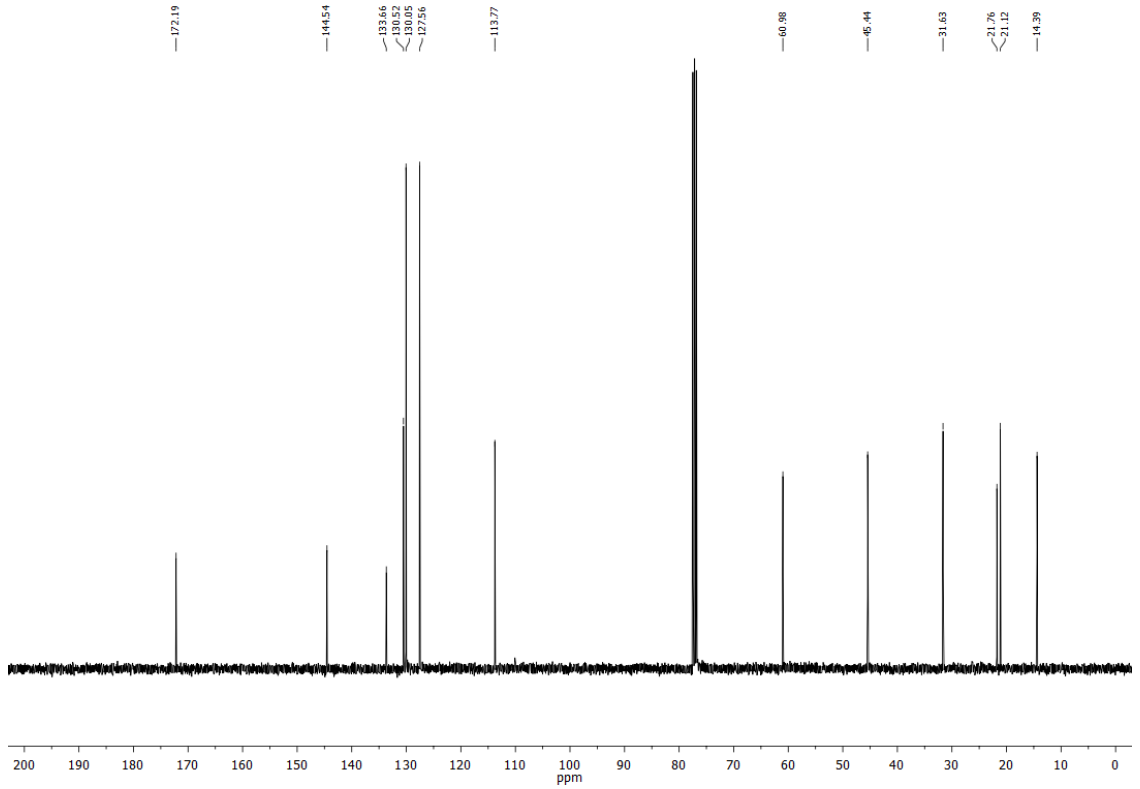
Compound **119d**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



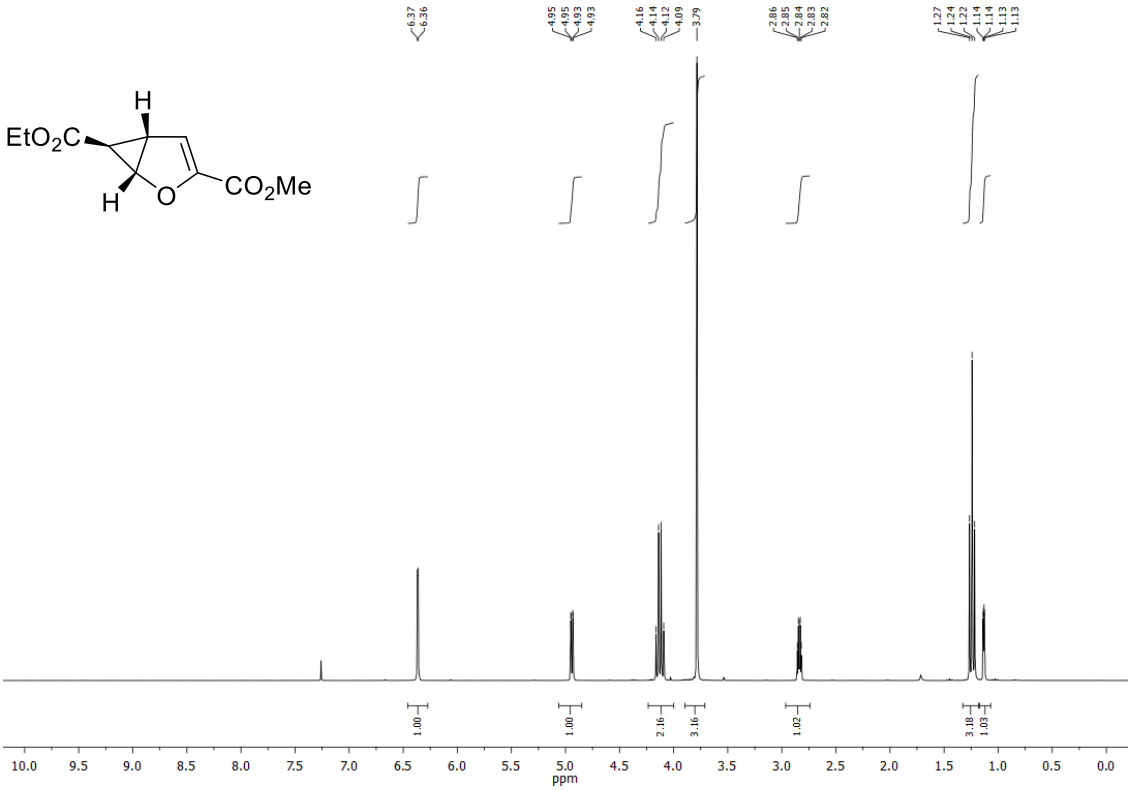


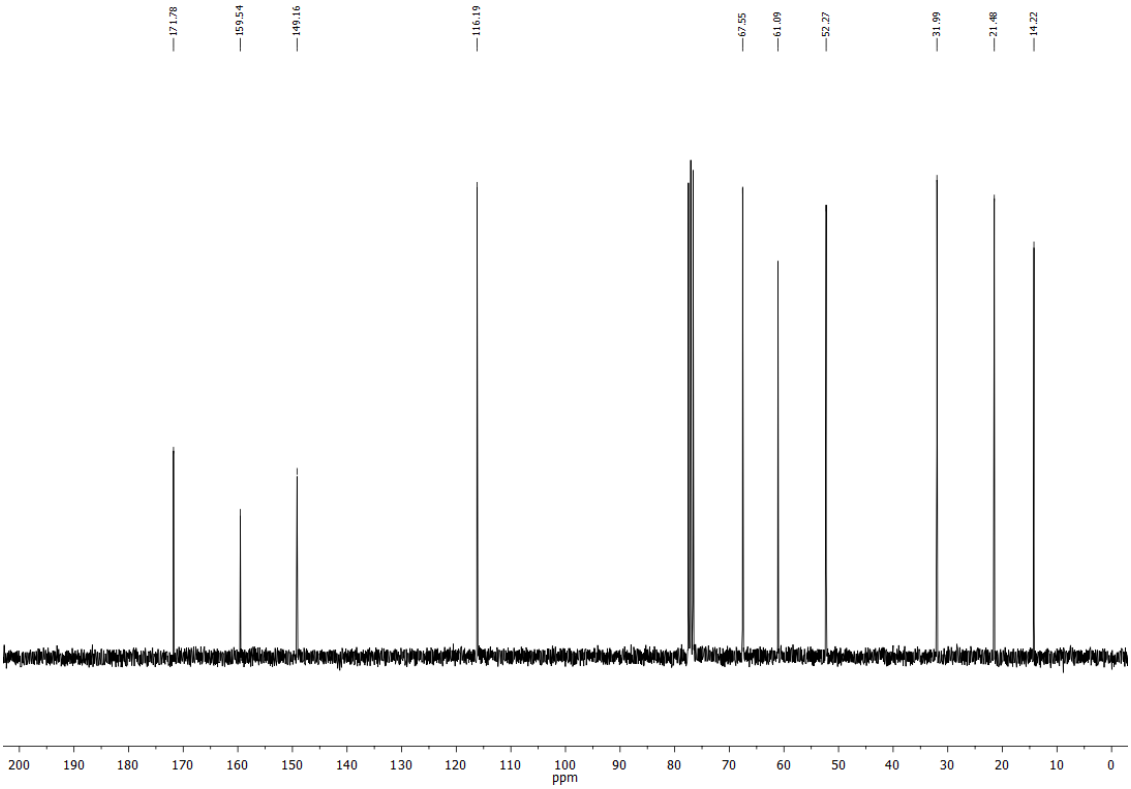
Compound **119f**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



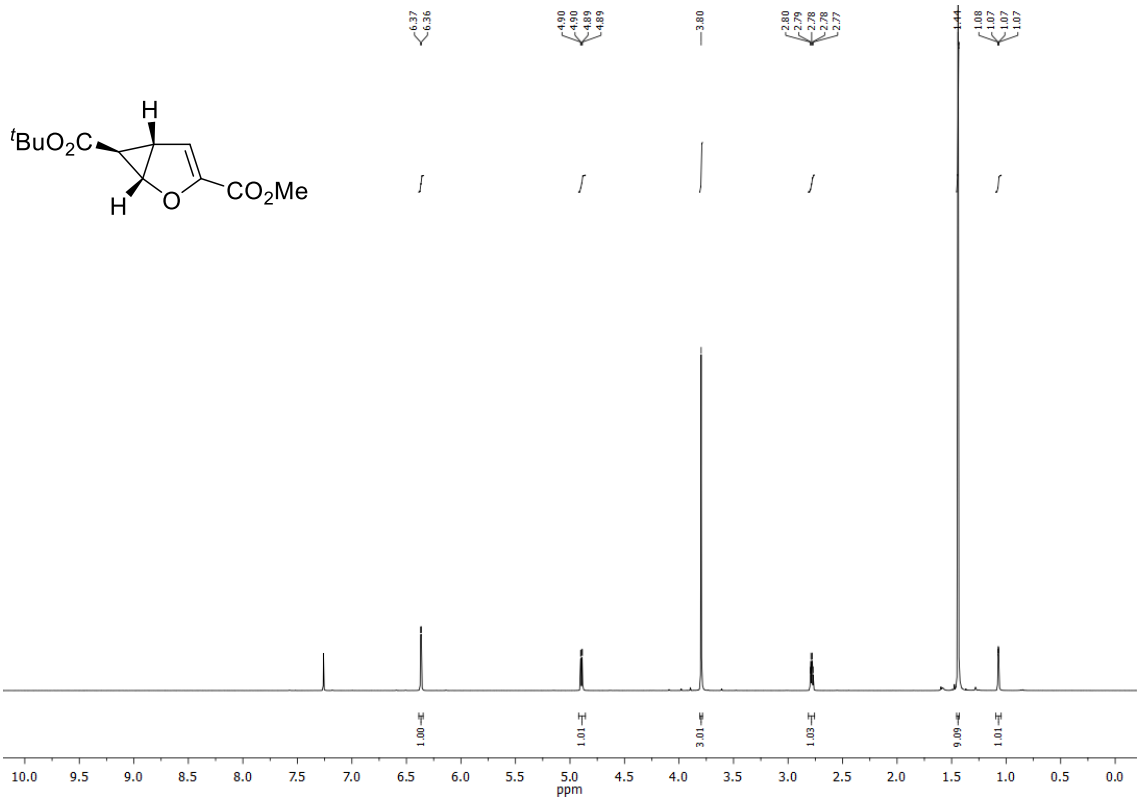


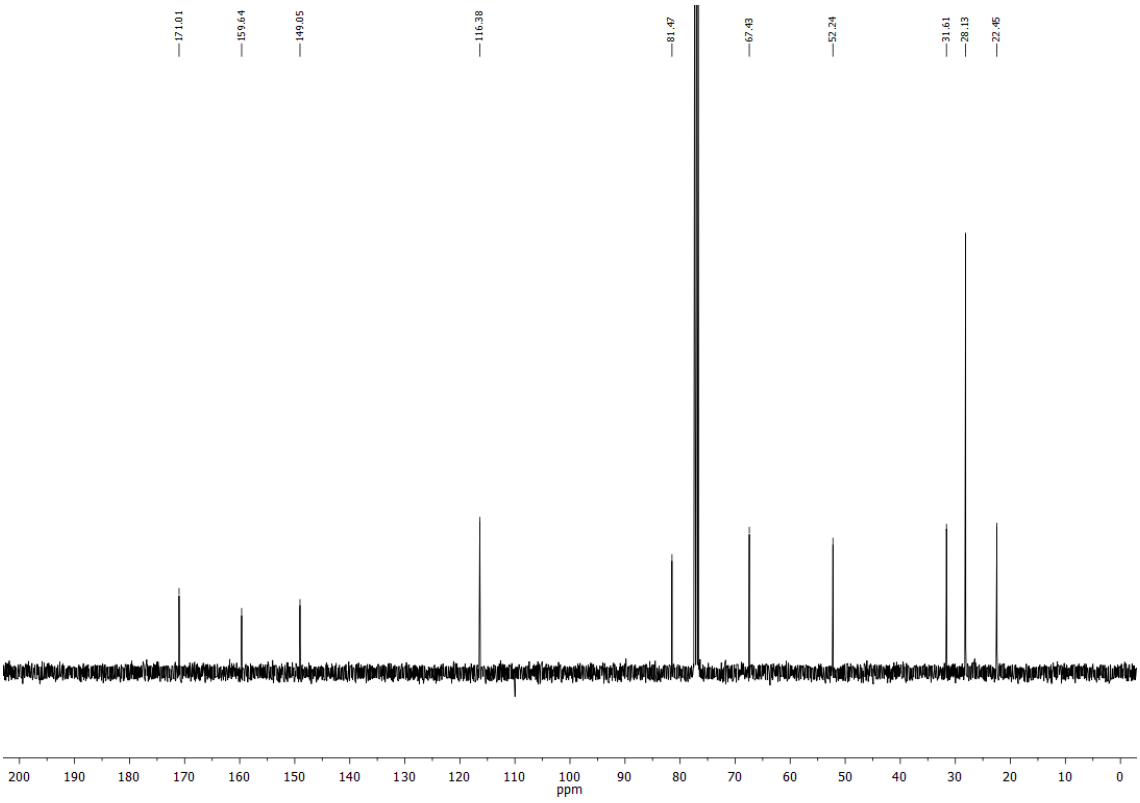
Compound **120a**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



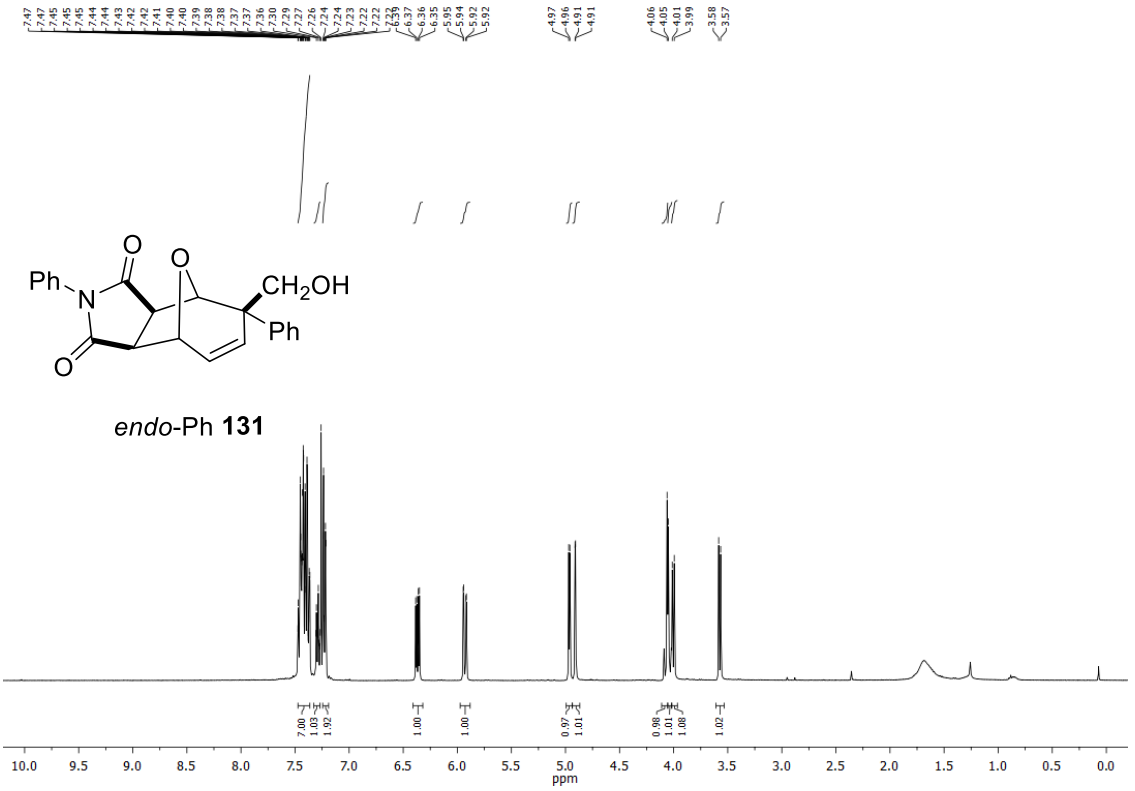


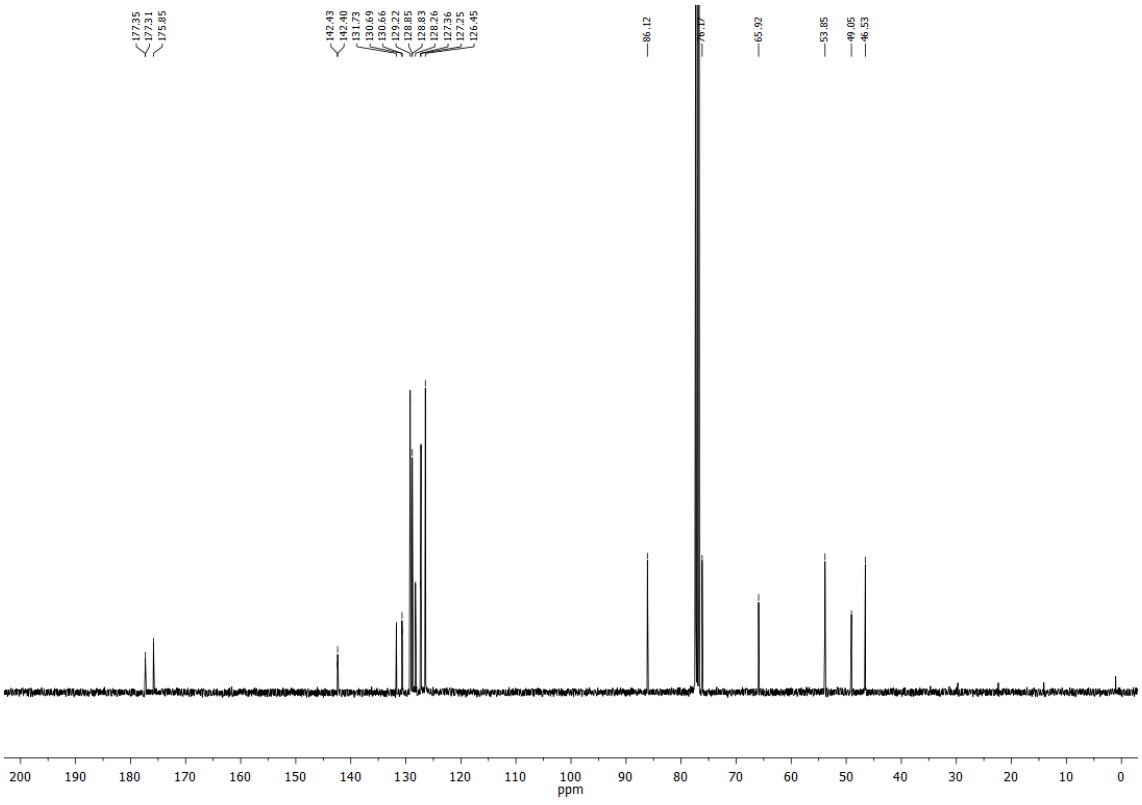
Compound **120b**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



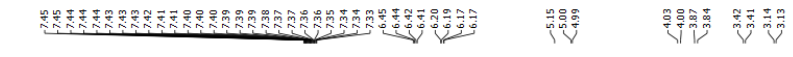


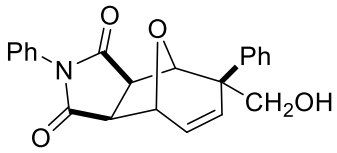
Compound *endo*-Ph **131**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



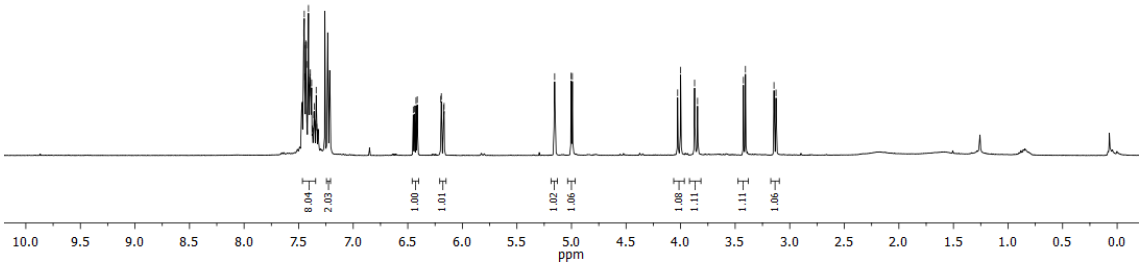


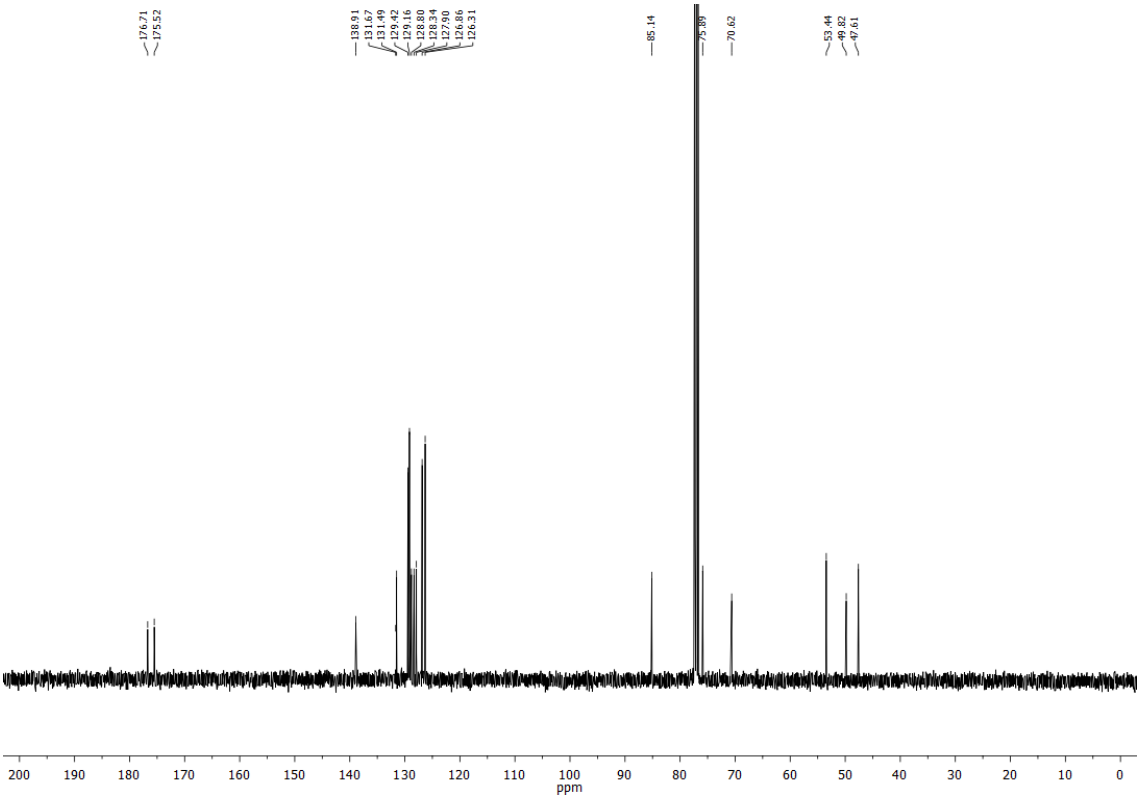
Compound *exo-Ph* **131**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



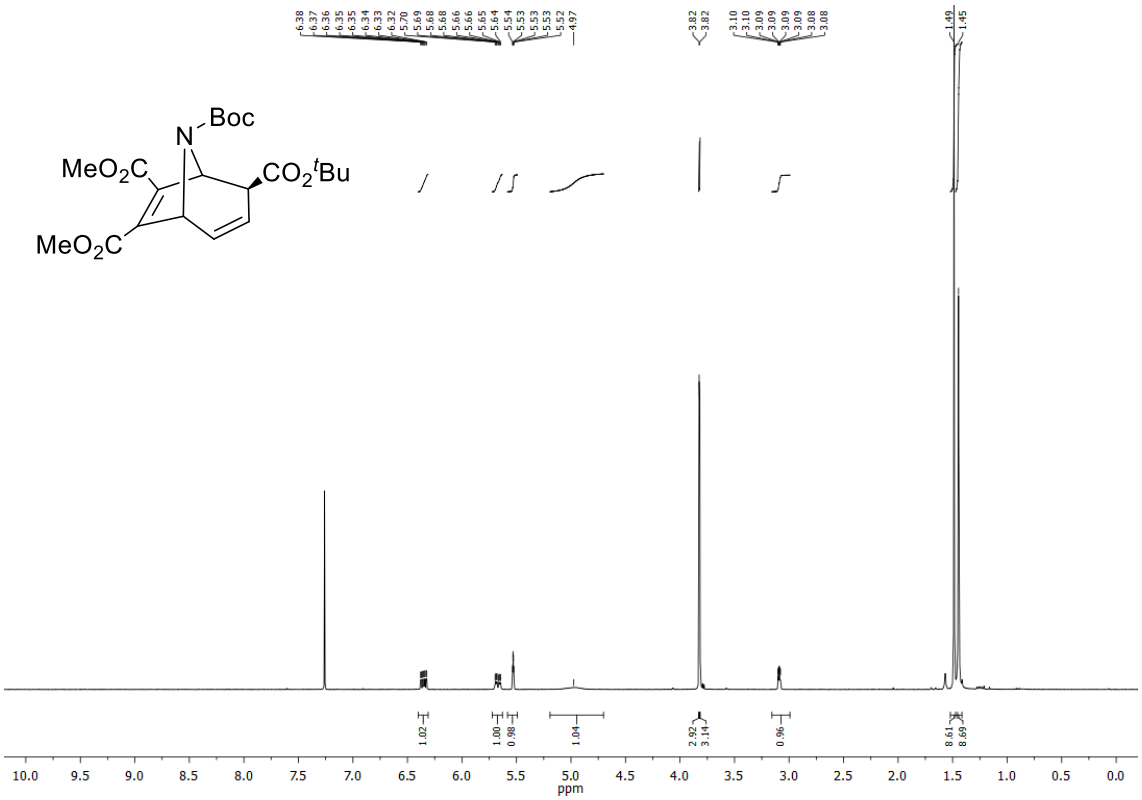


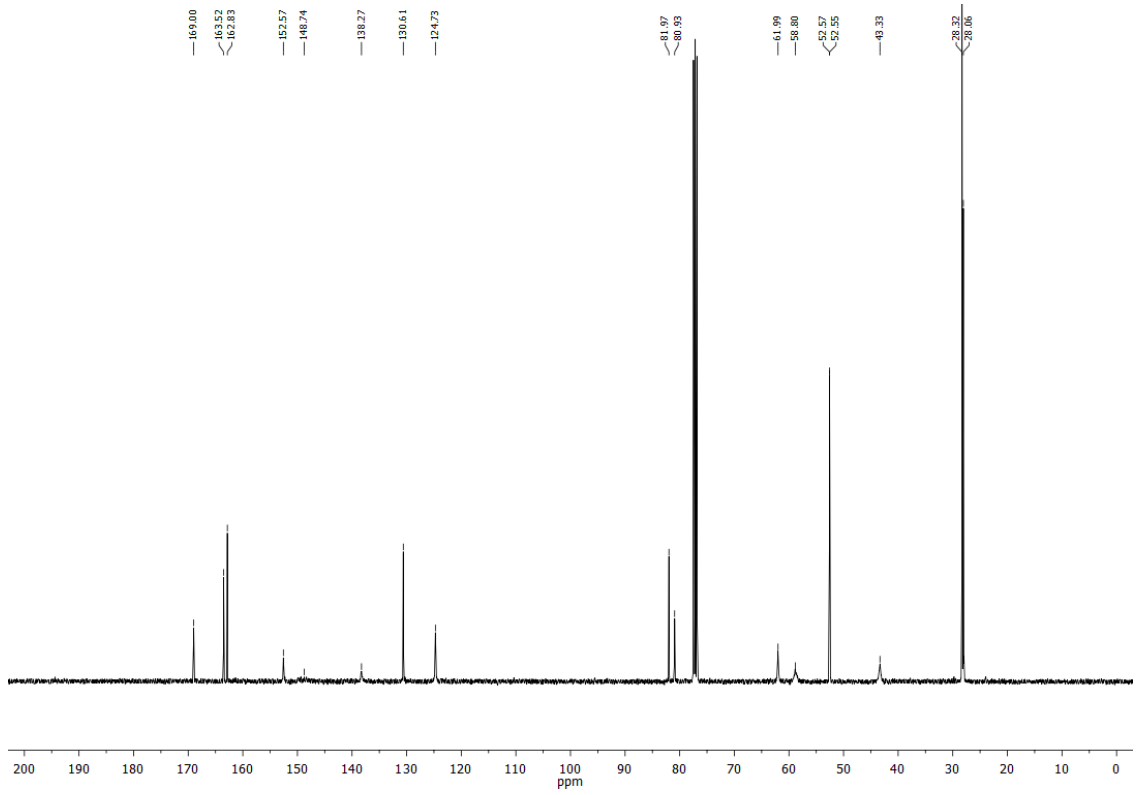
exo-Ph **131**



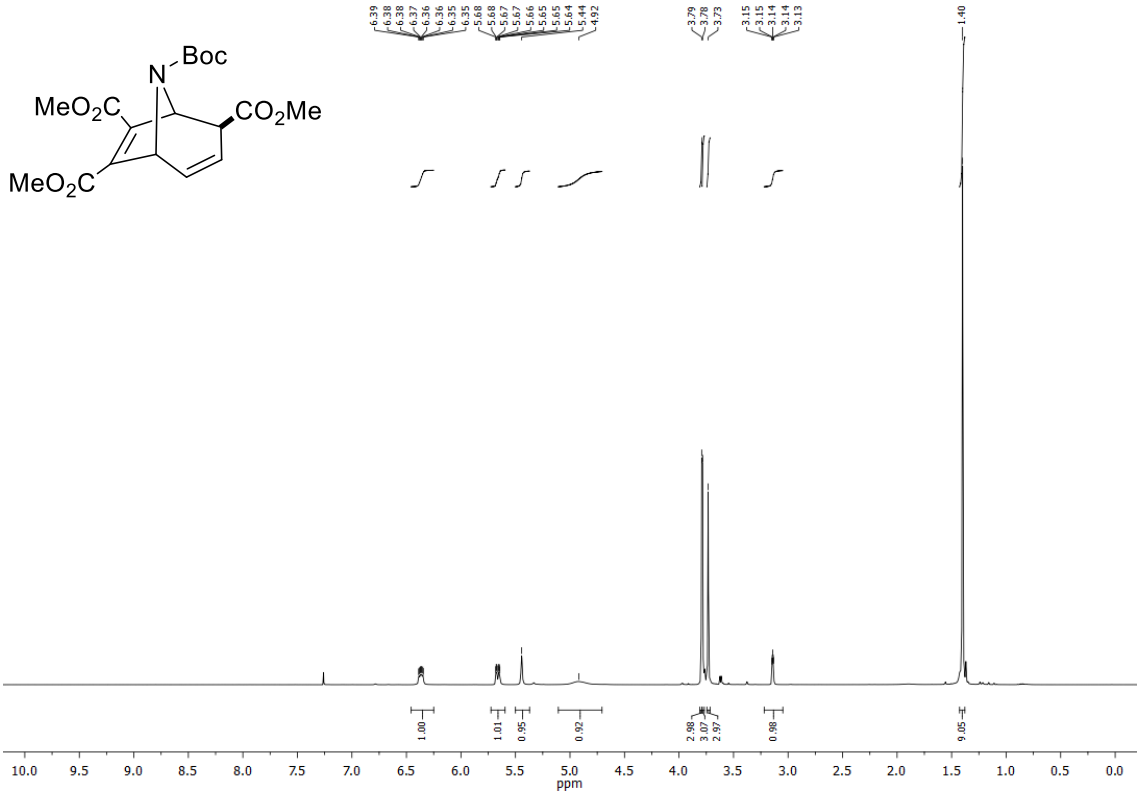


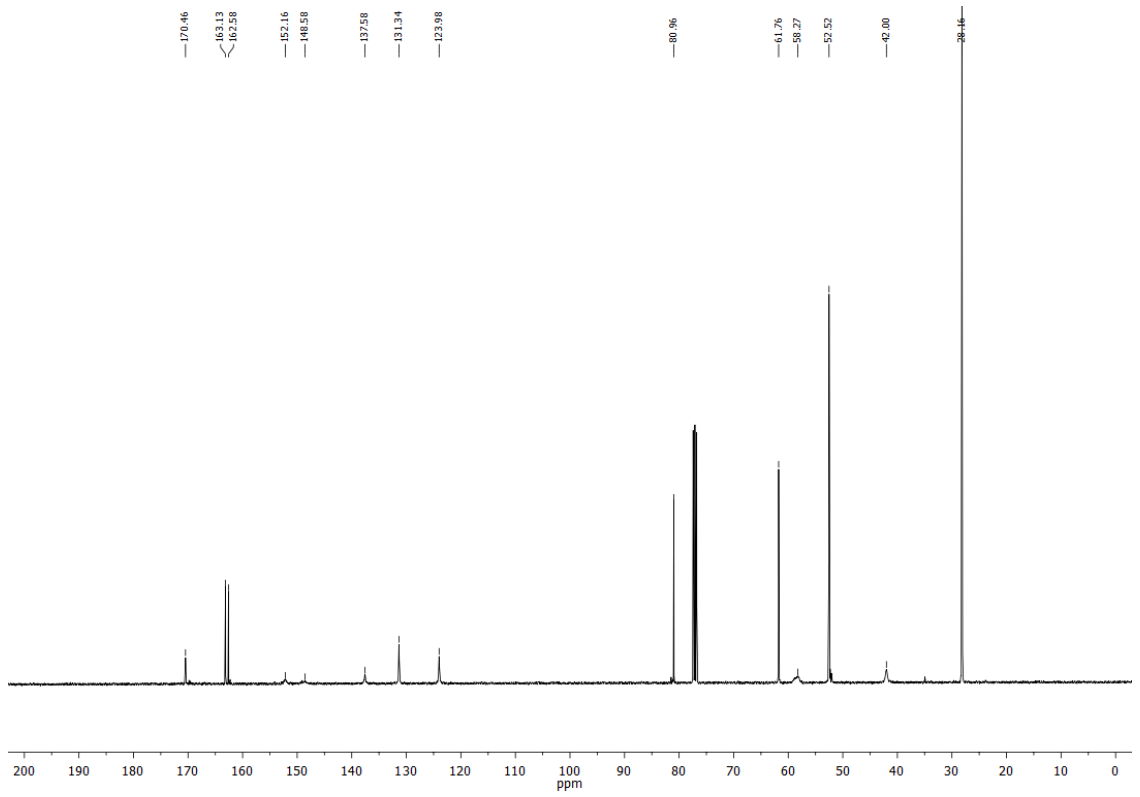
Compound **(+)-133a**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



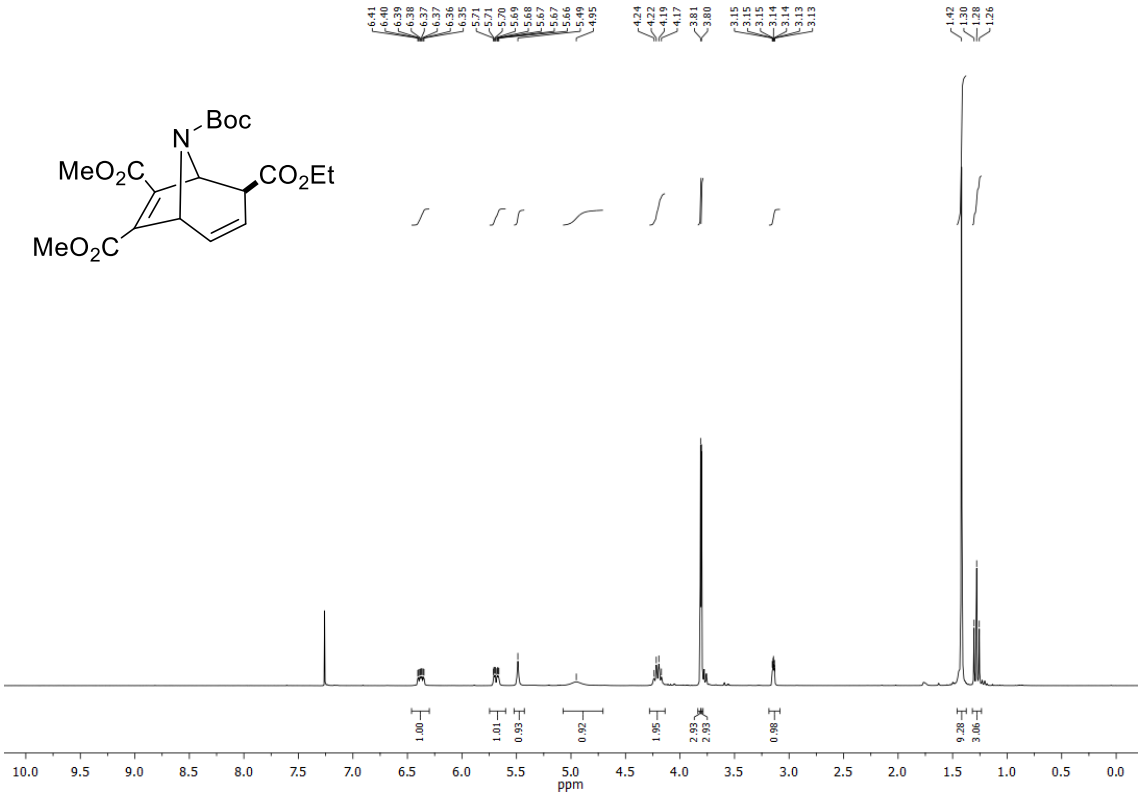


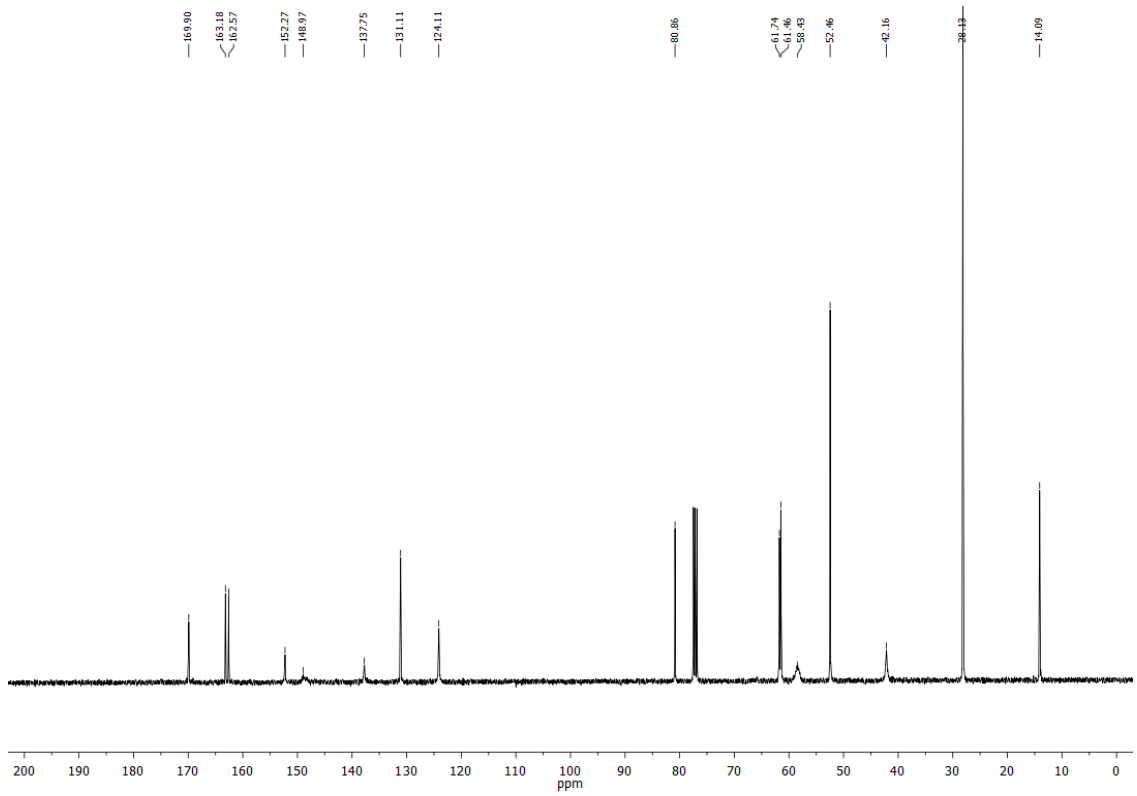
Compound **133b**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



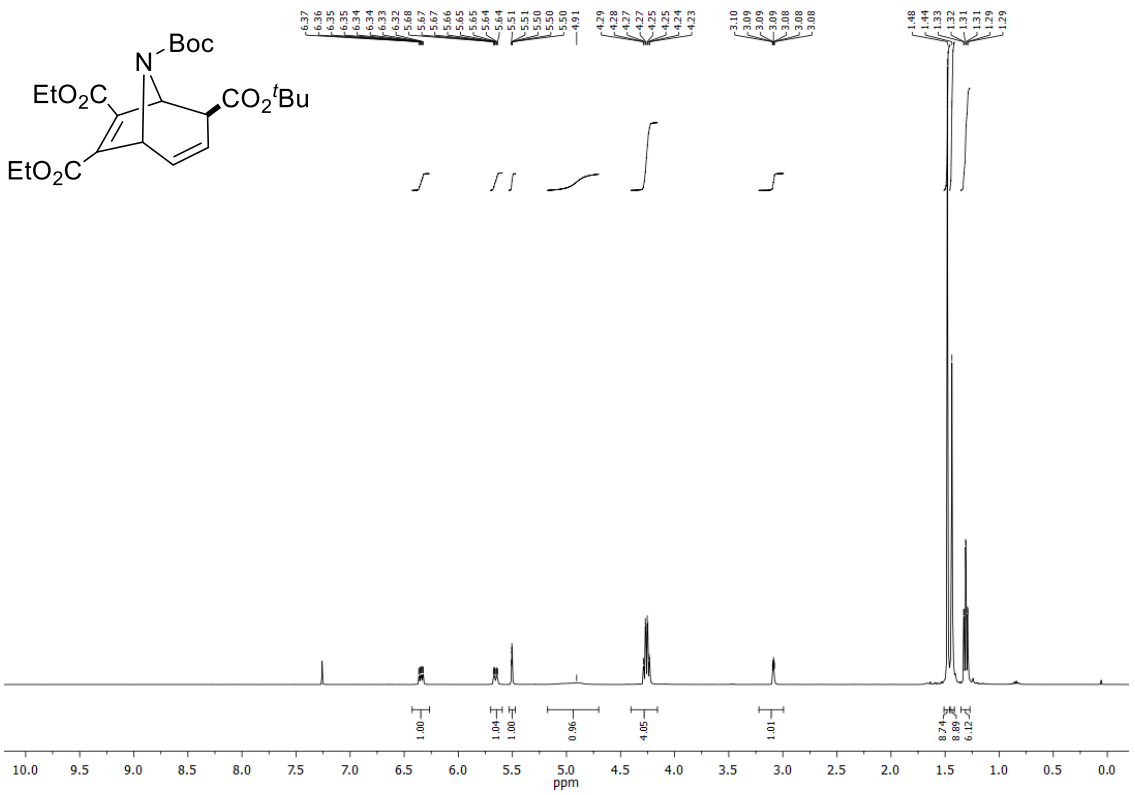


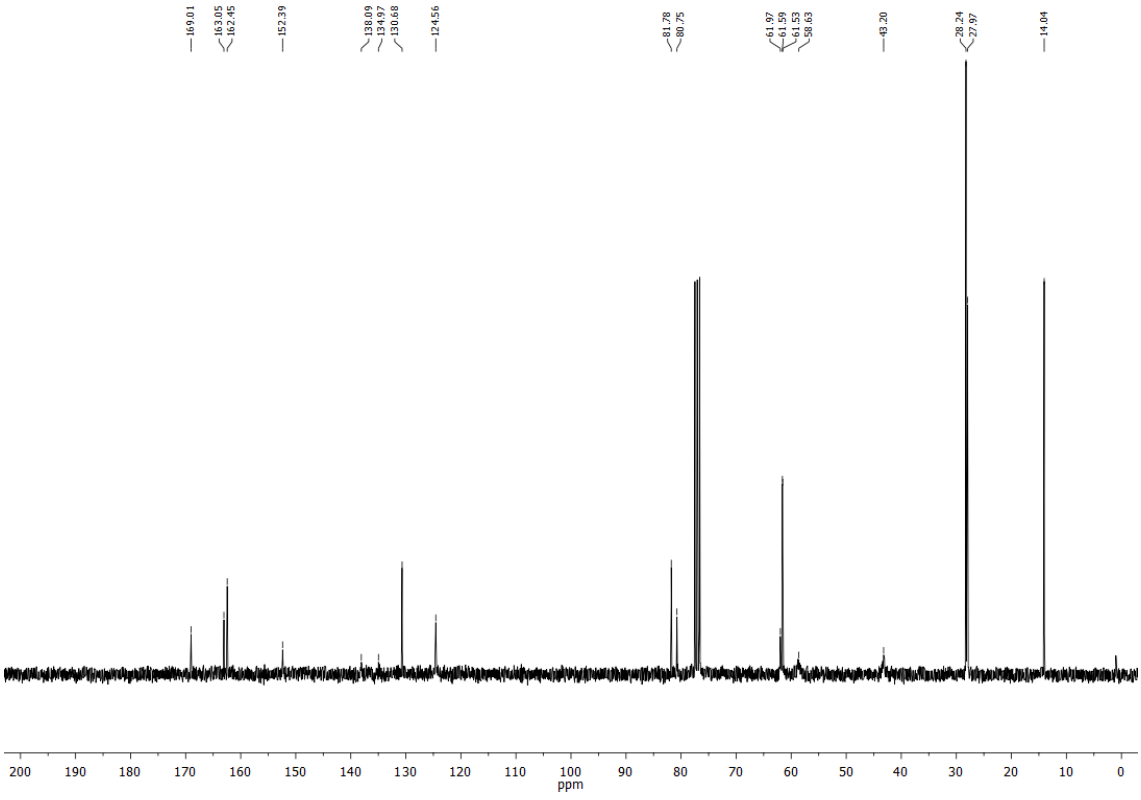
Compound **133c**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



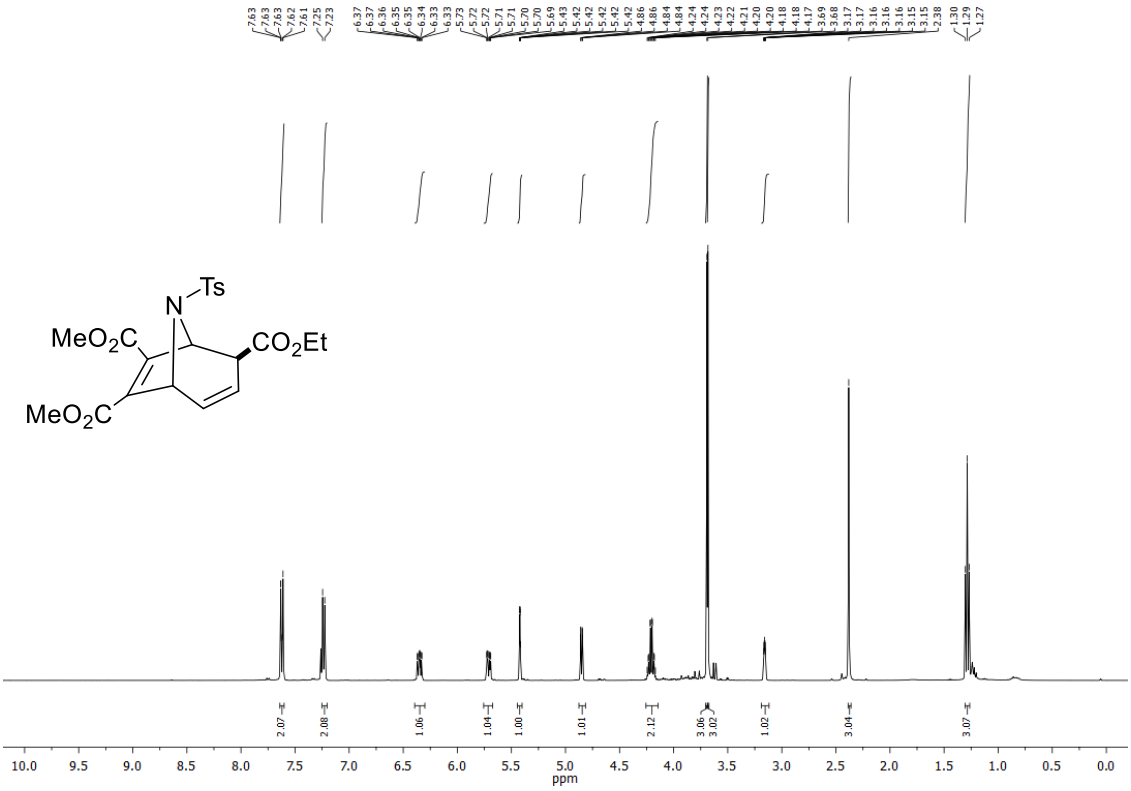


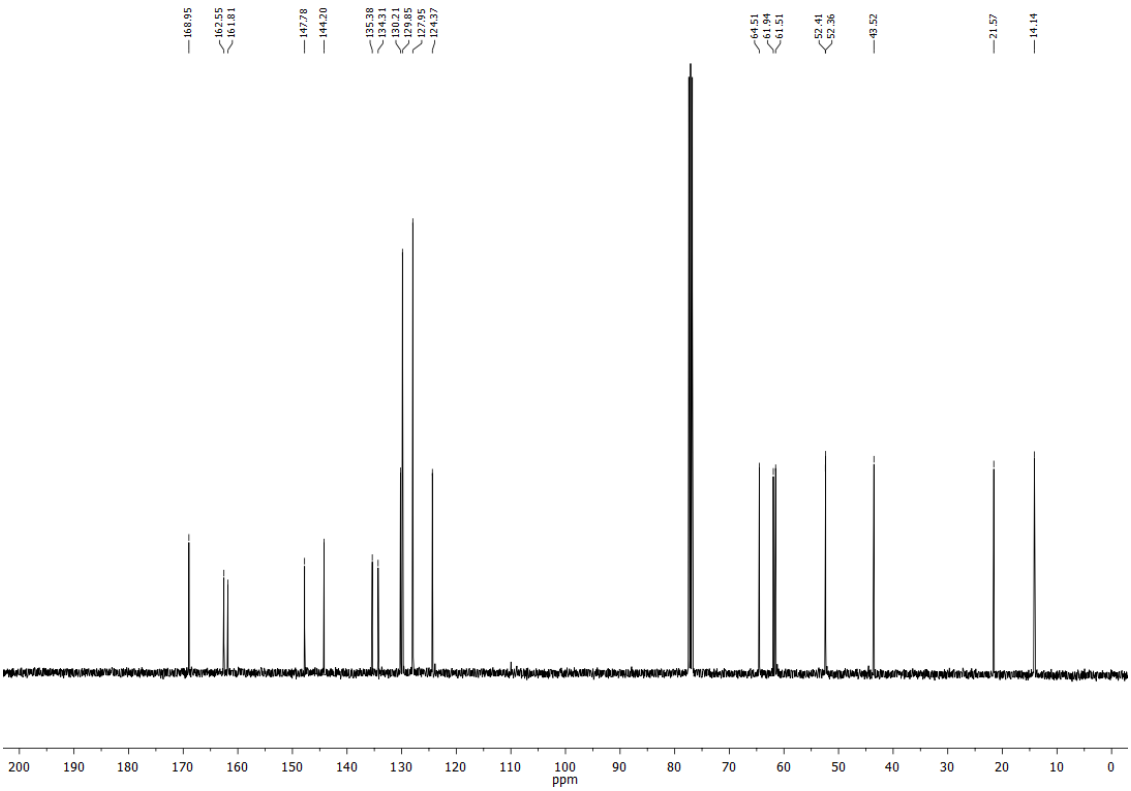
Compound **133d**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



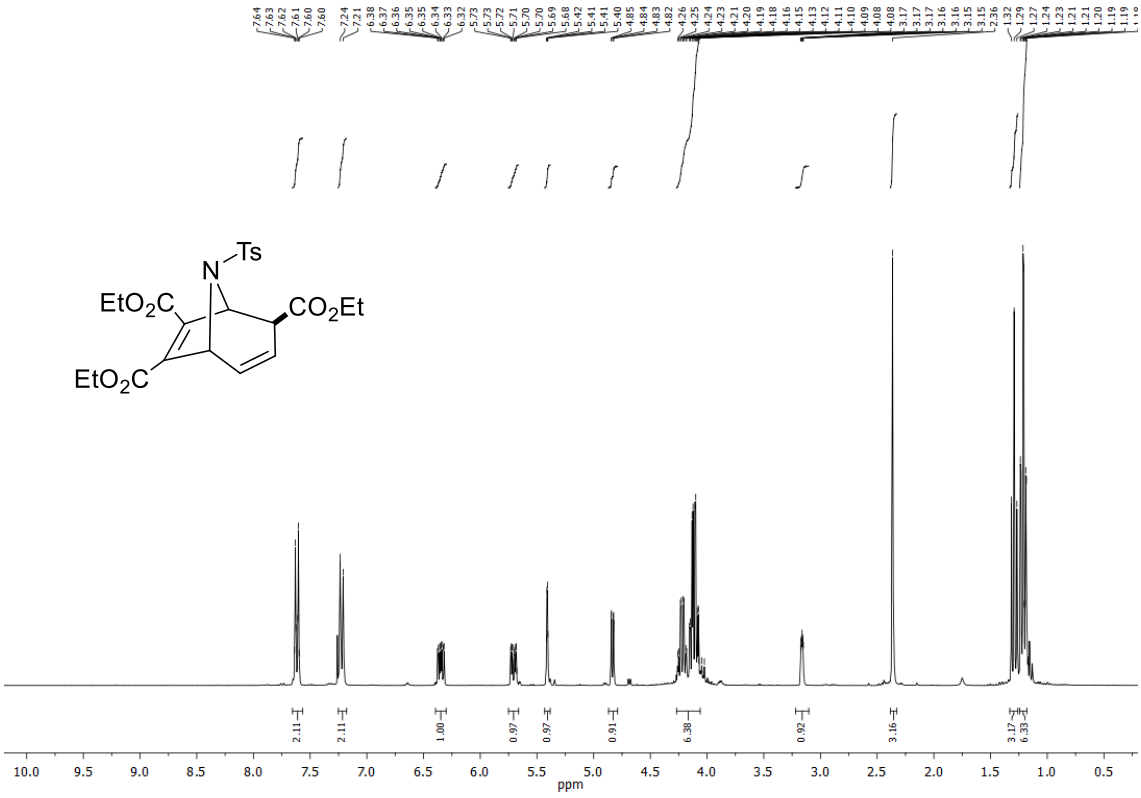


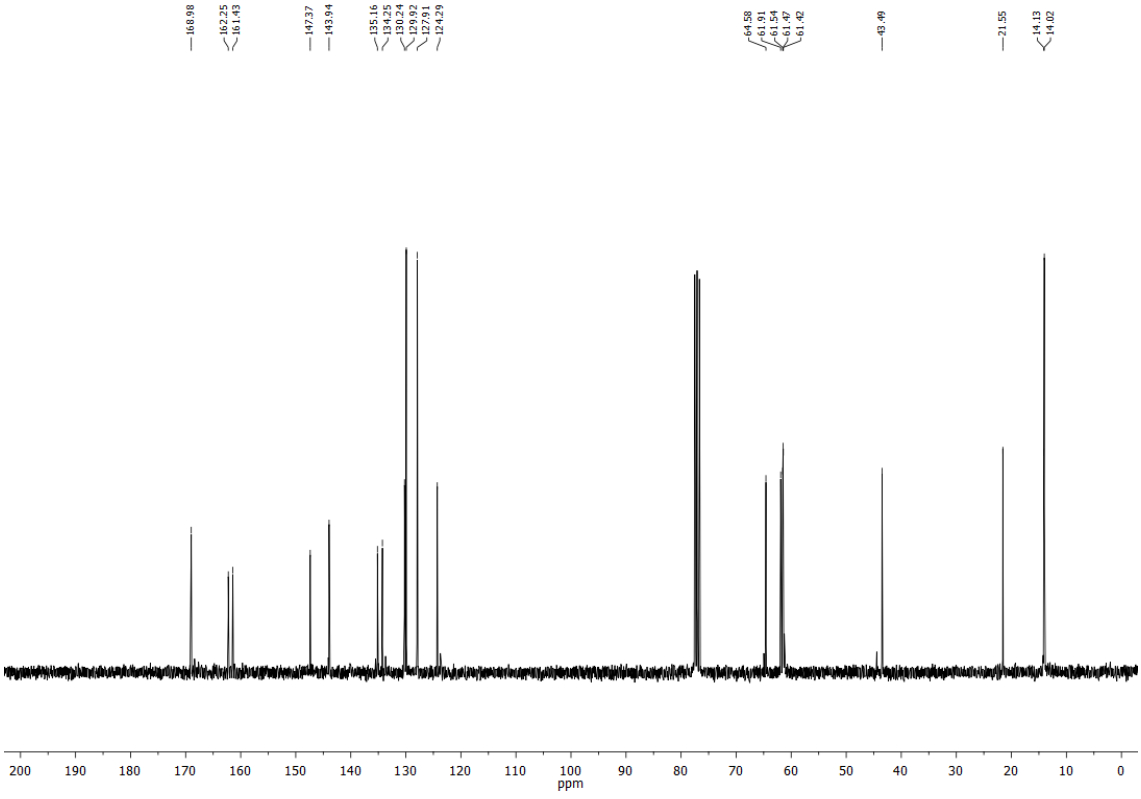
Compound **133e**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



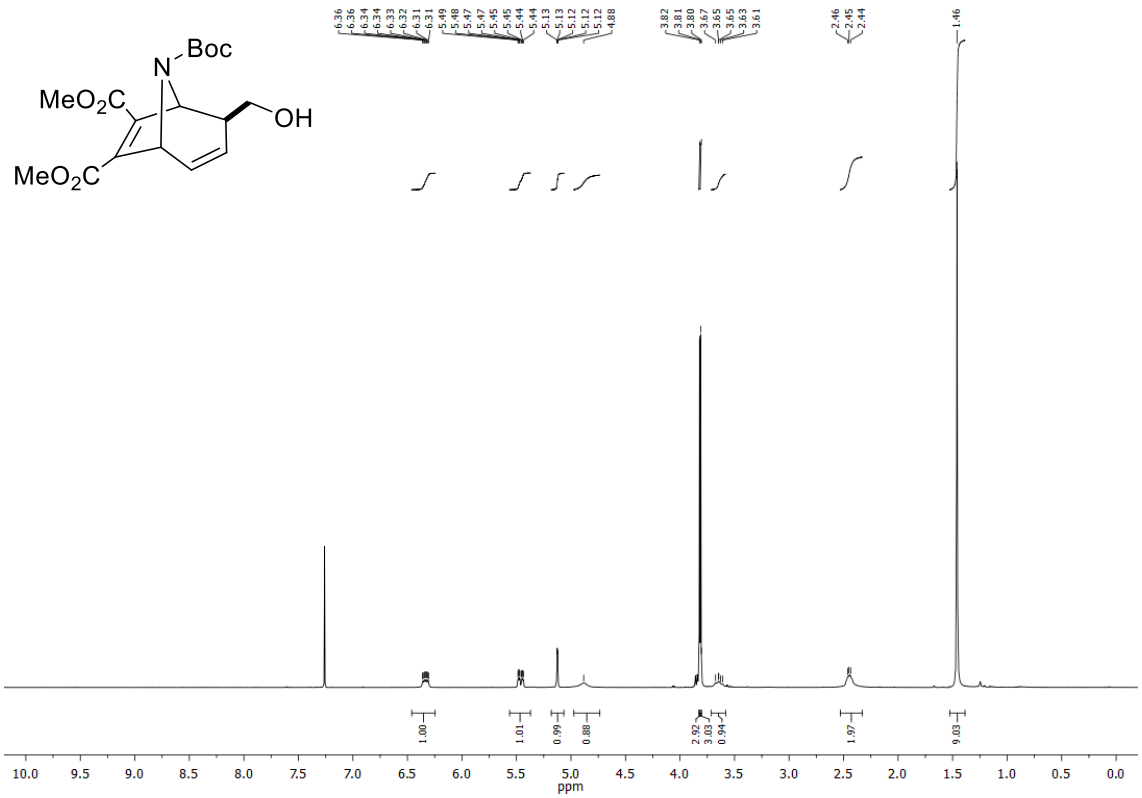


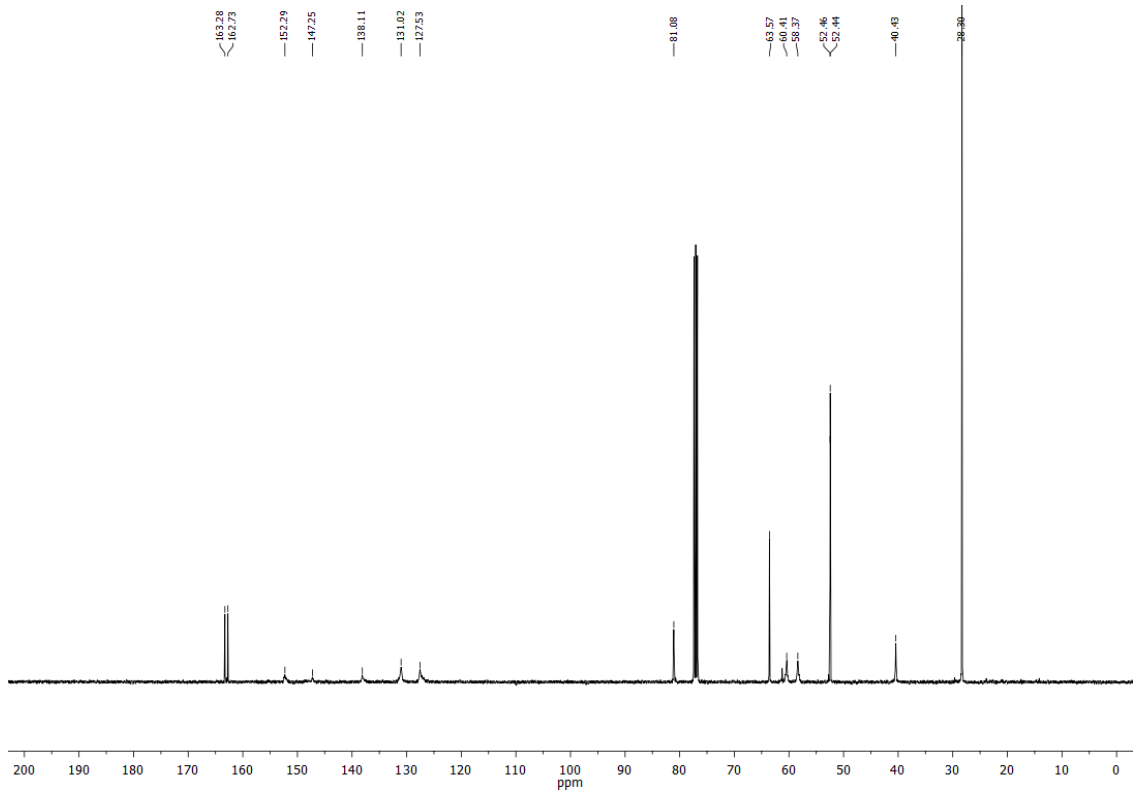
Compound **133f**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



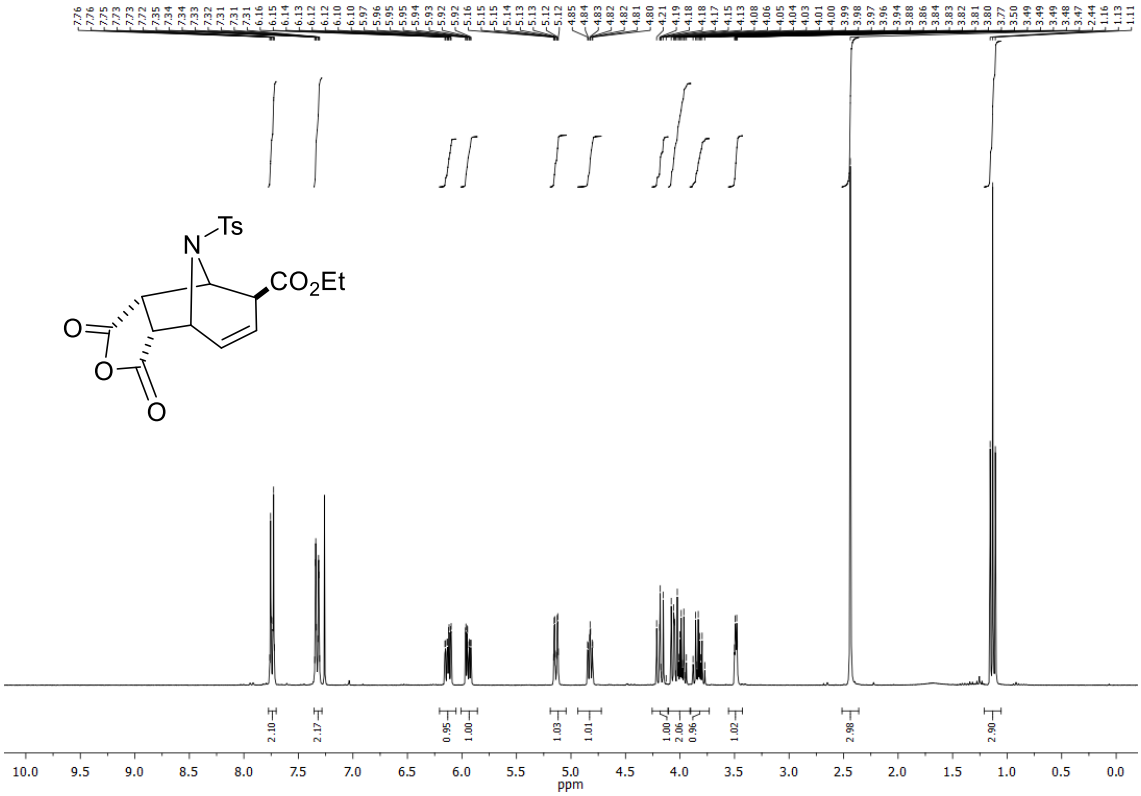


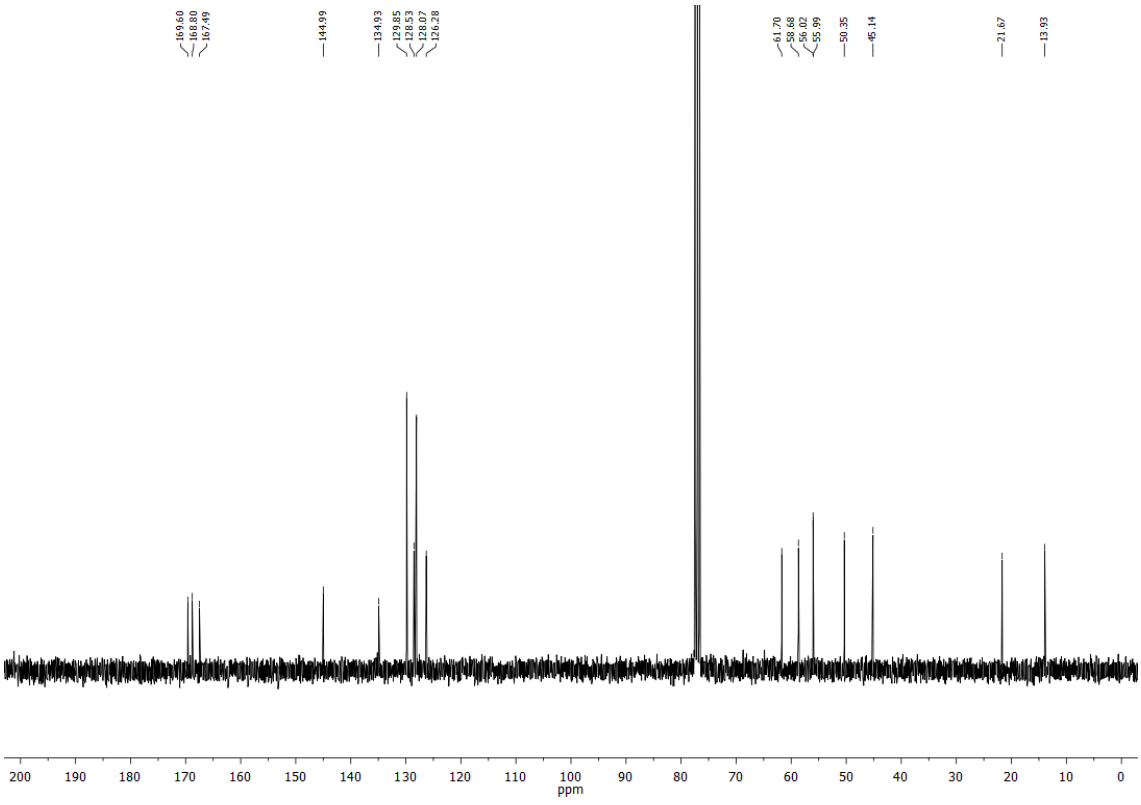
Compound **133g**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



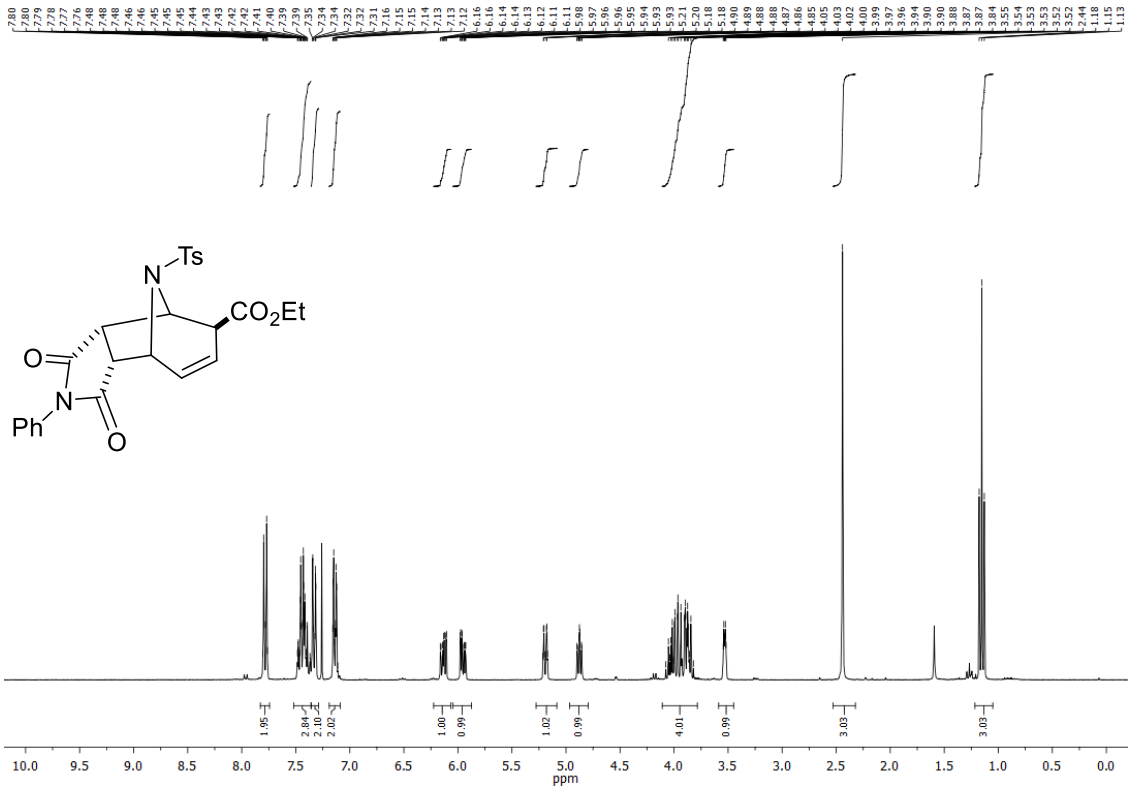


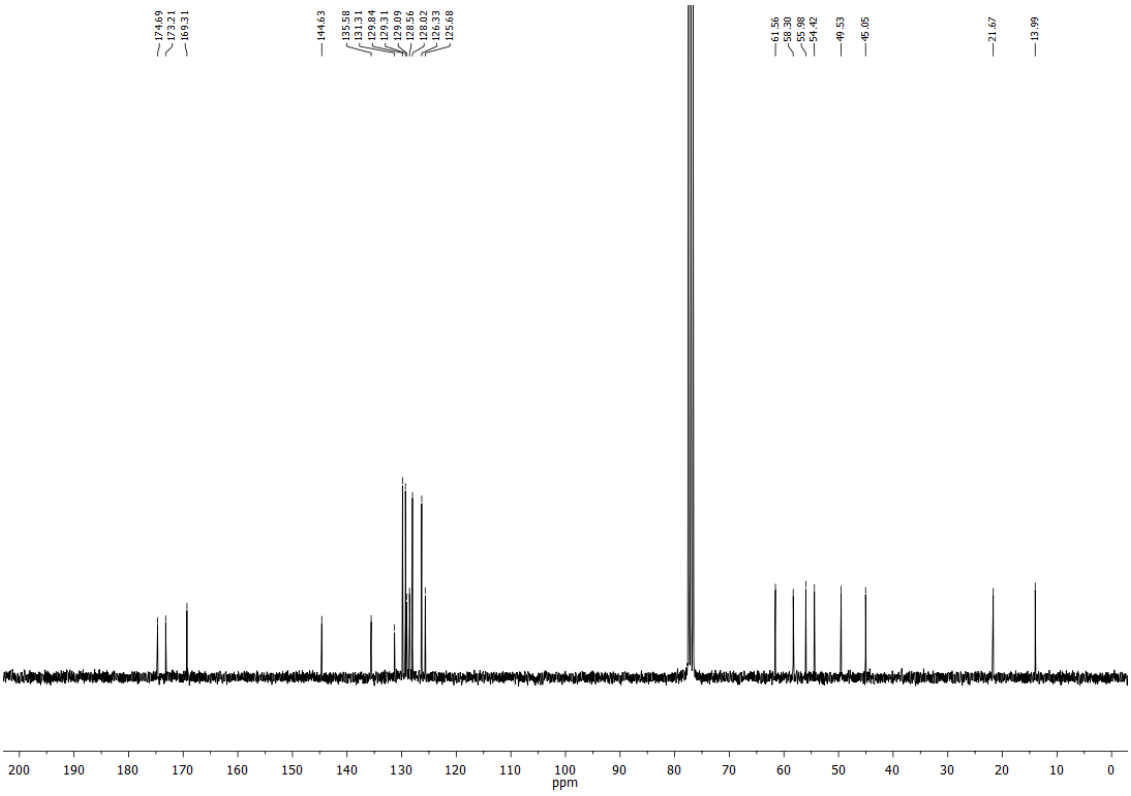
Compound **133h**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



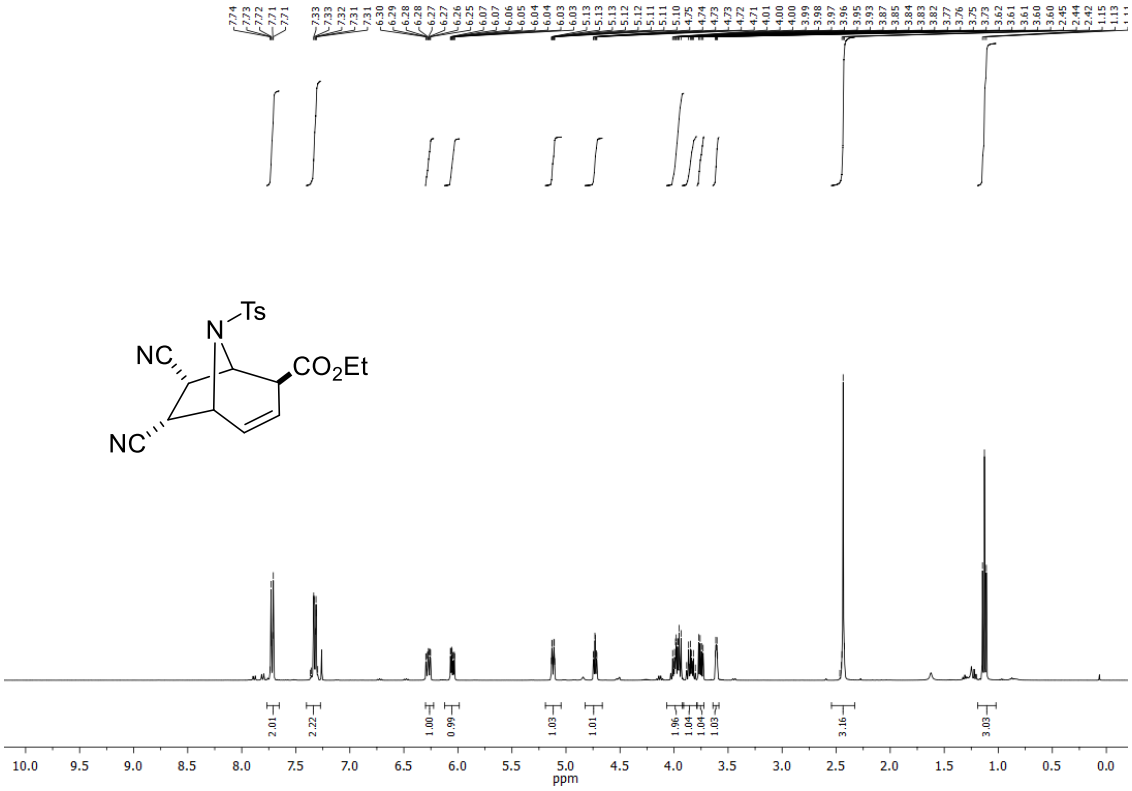


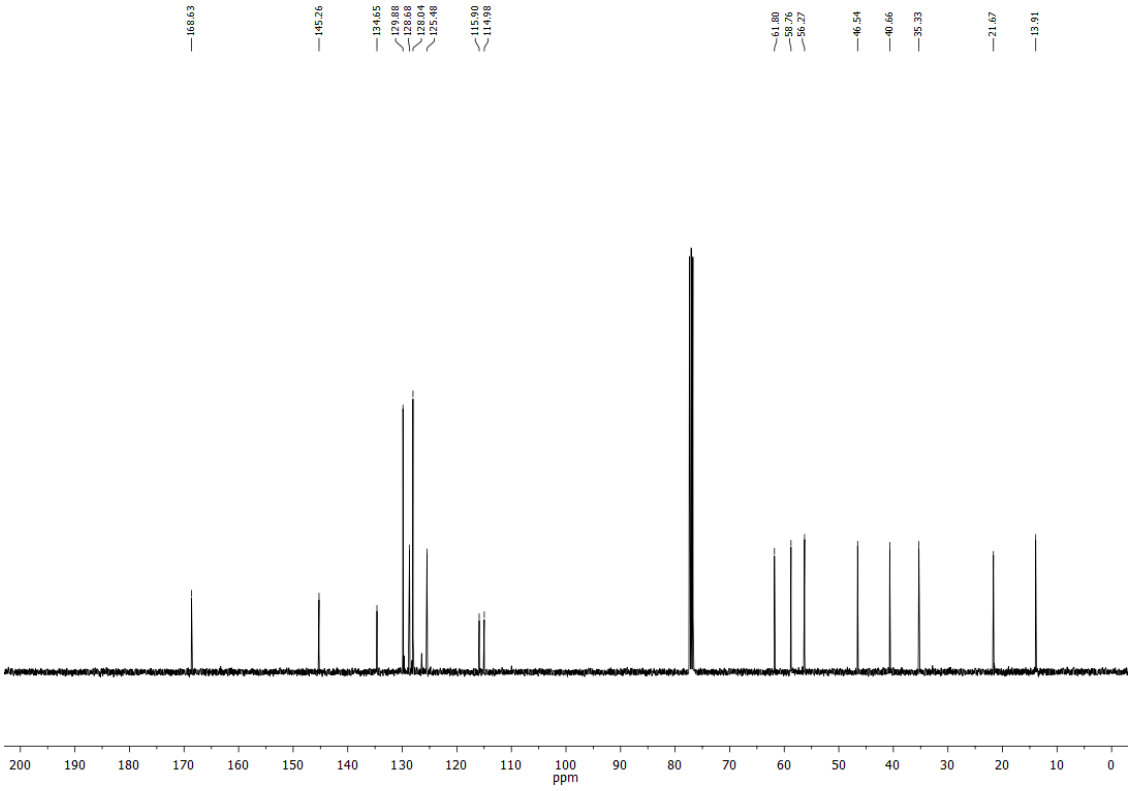
Compound **133i**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



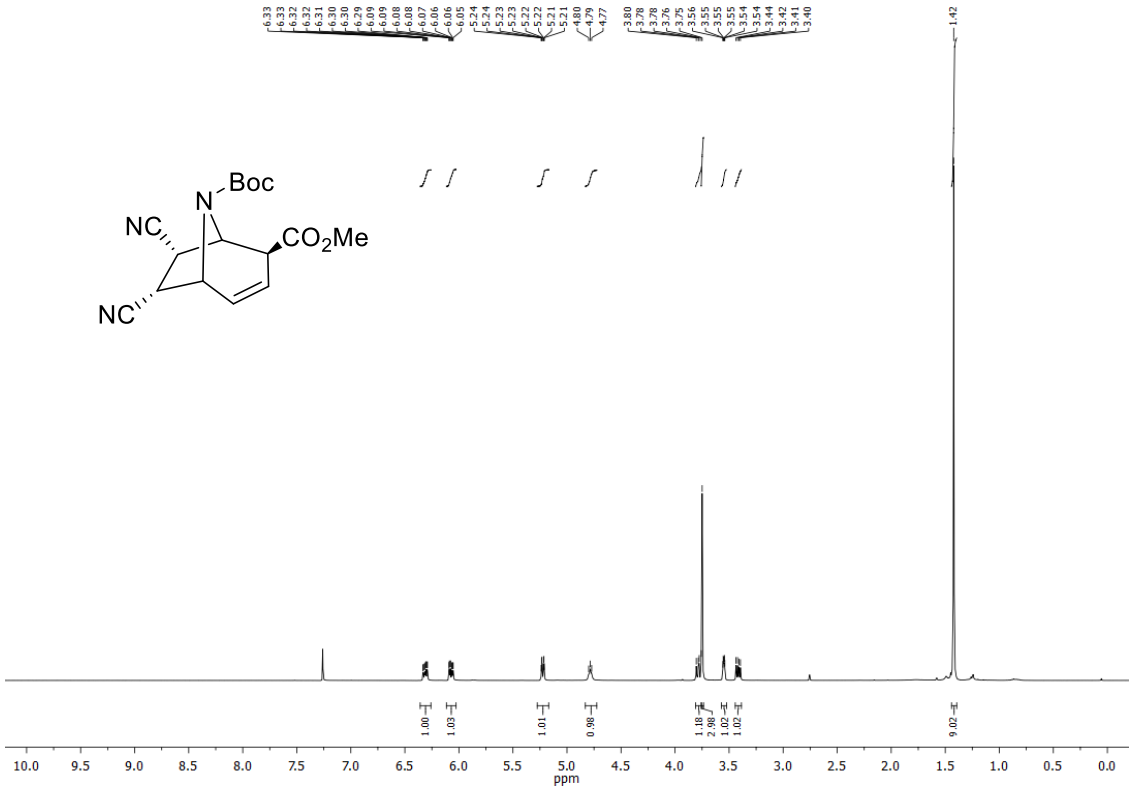


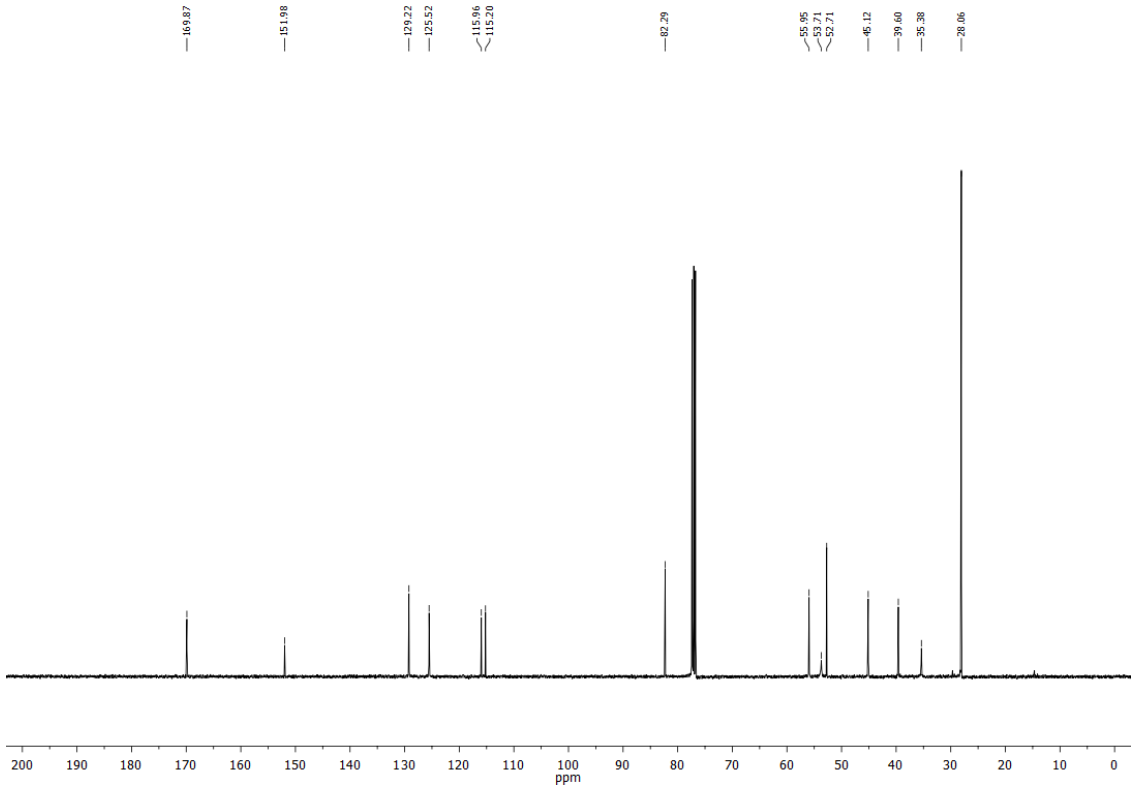
Compound **133j**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



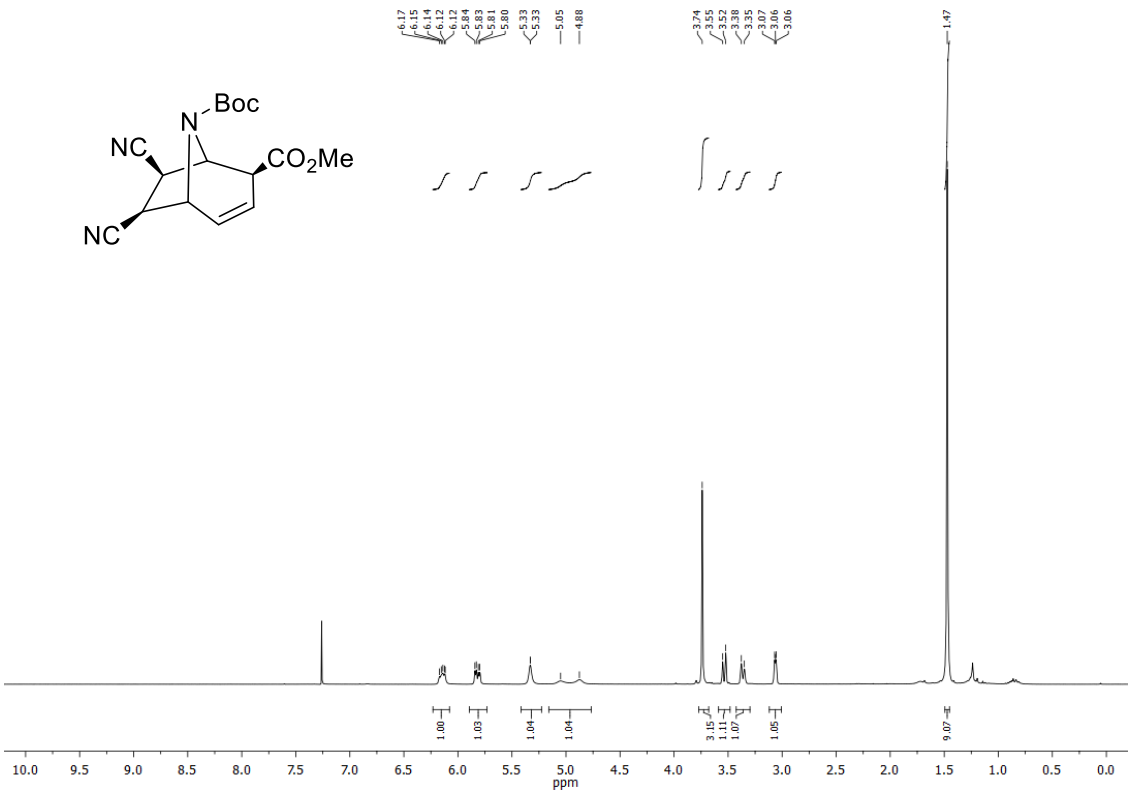


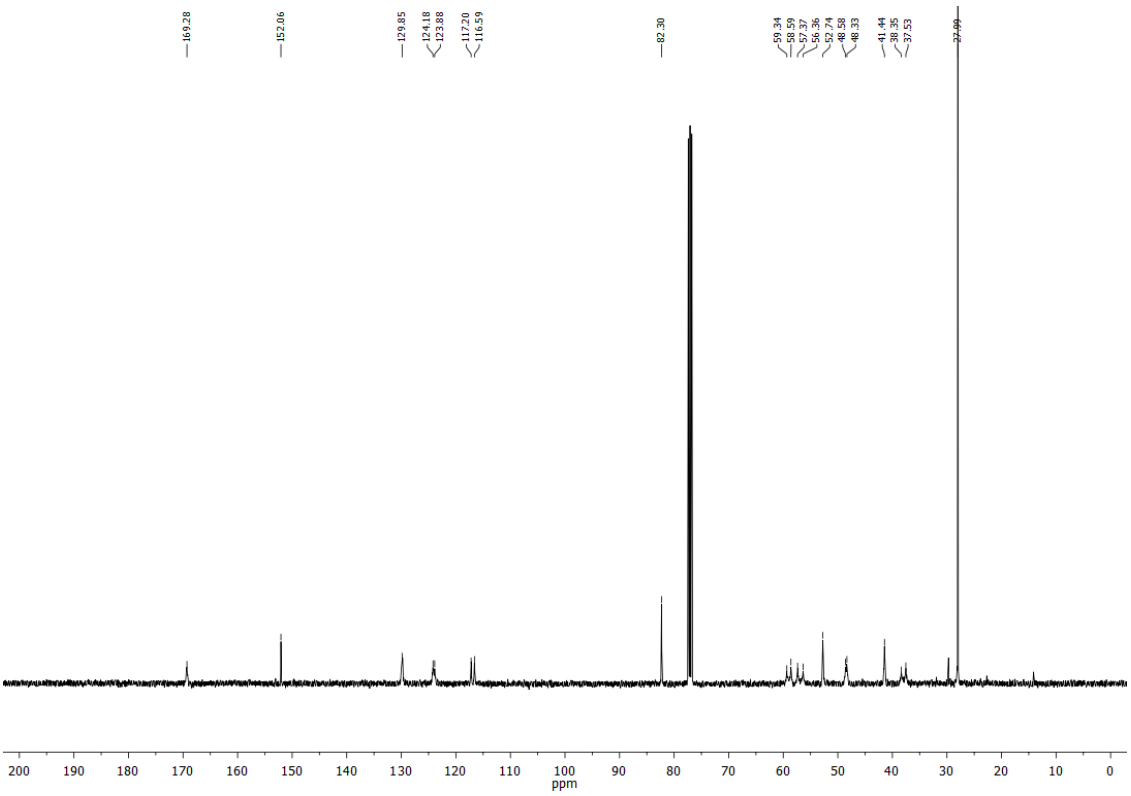
Compound ***endo*** (–)-**133k**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



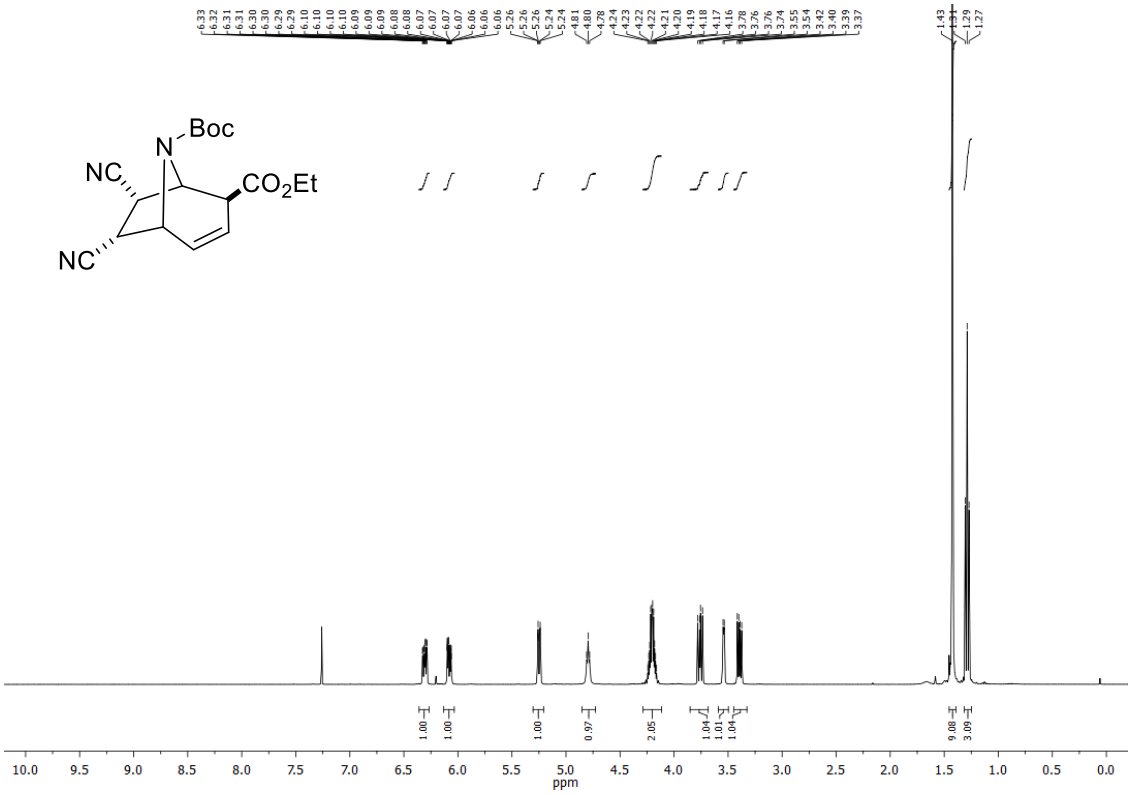


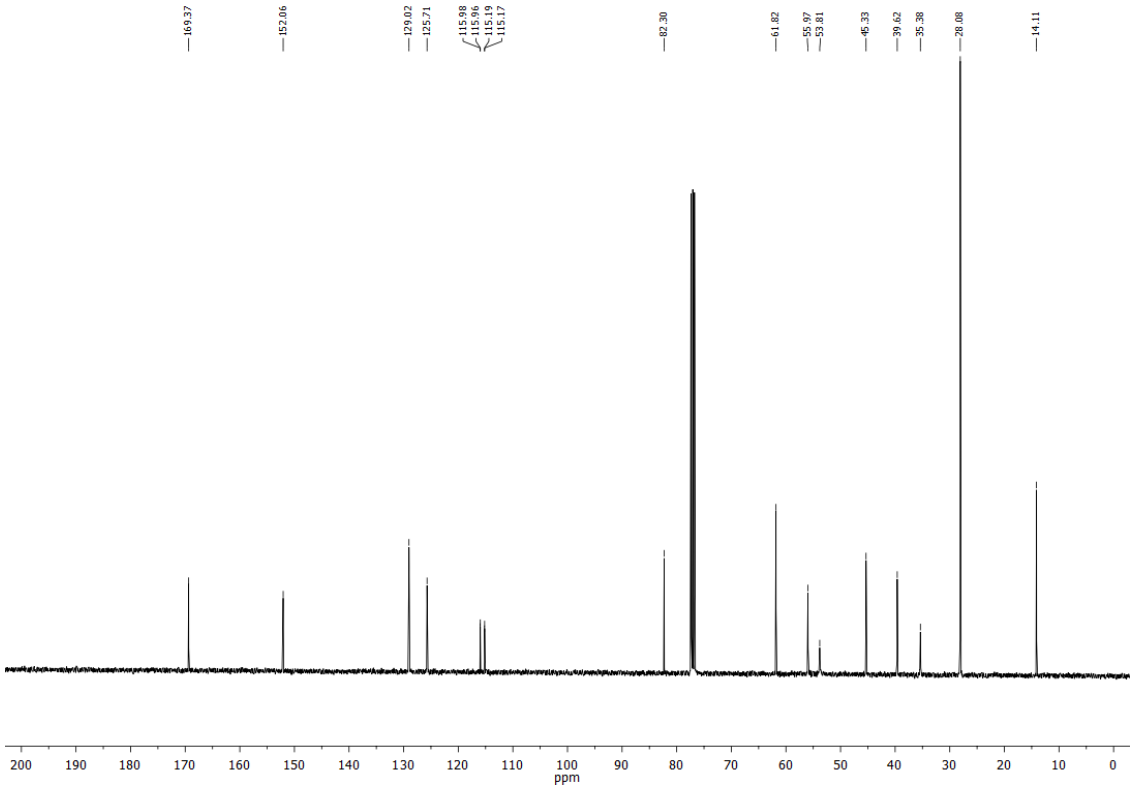
Compound ***exo*** (–)-**133k**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



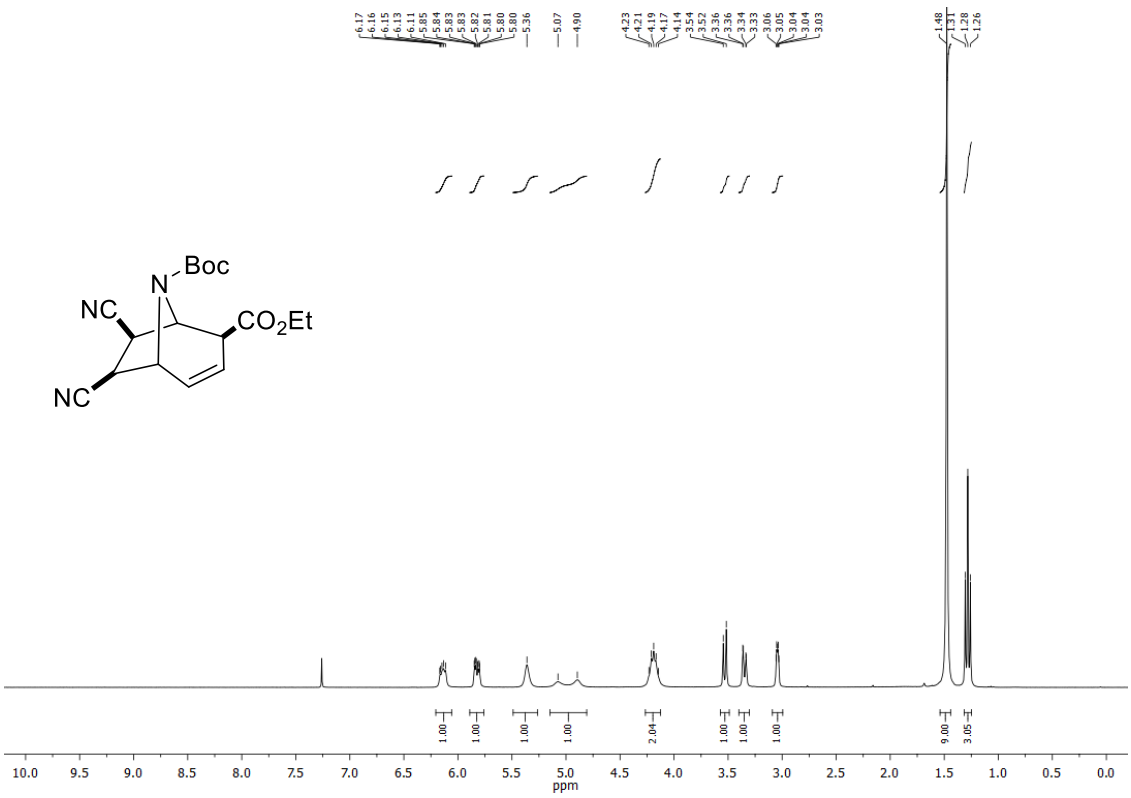


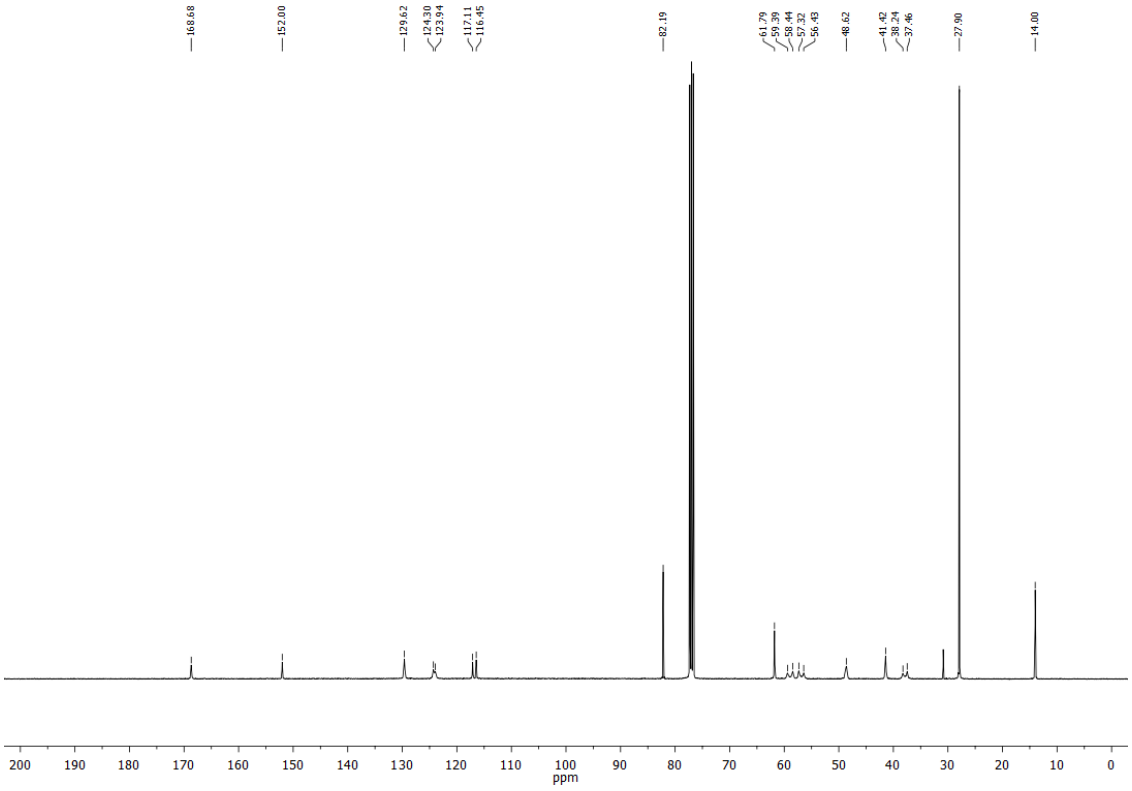
Compound ***endo* 133l**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



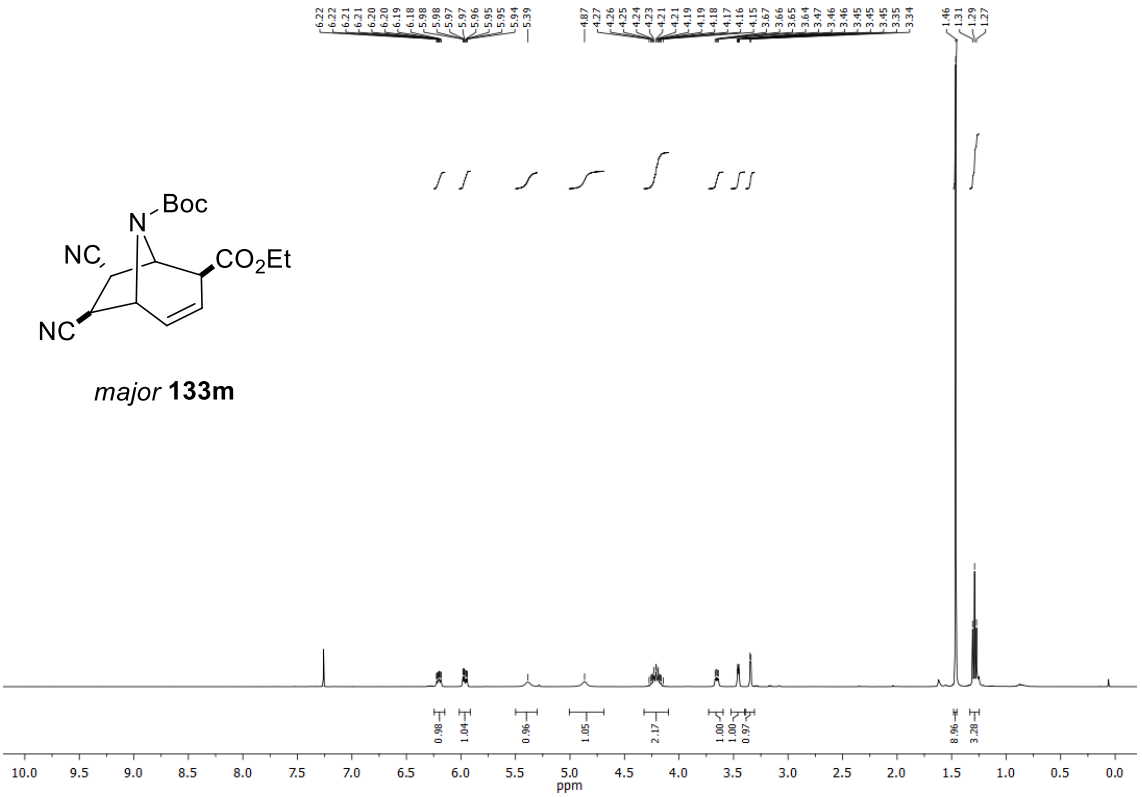


Compound ***exo* 133l**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

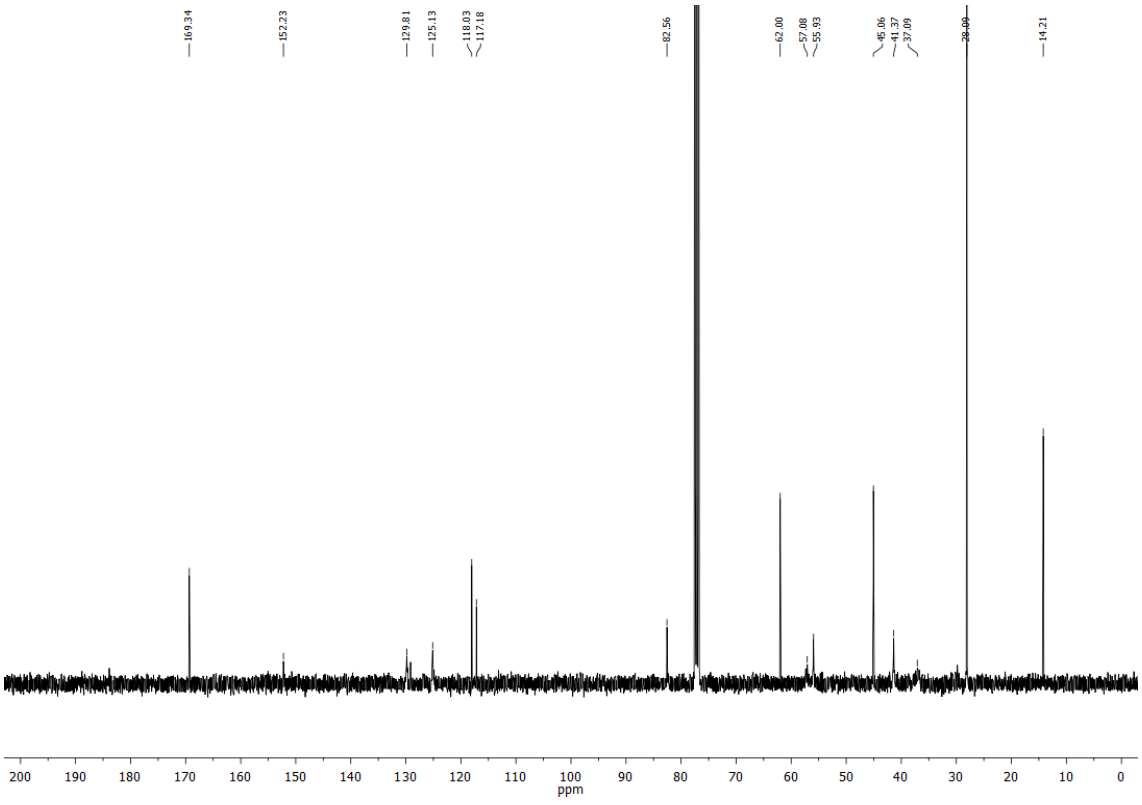




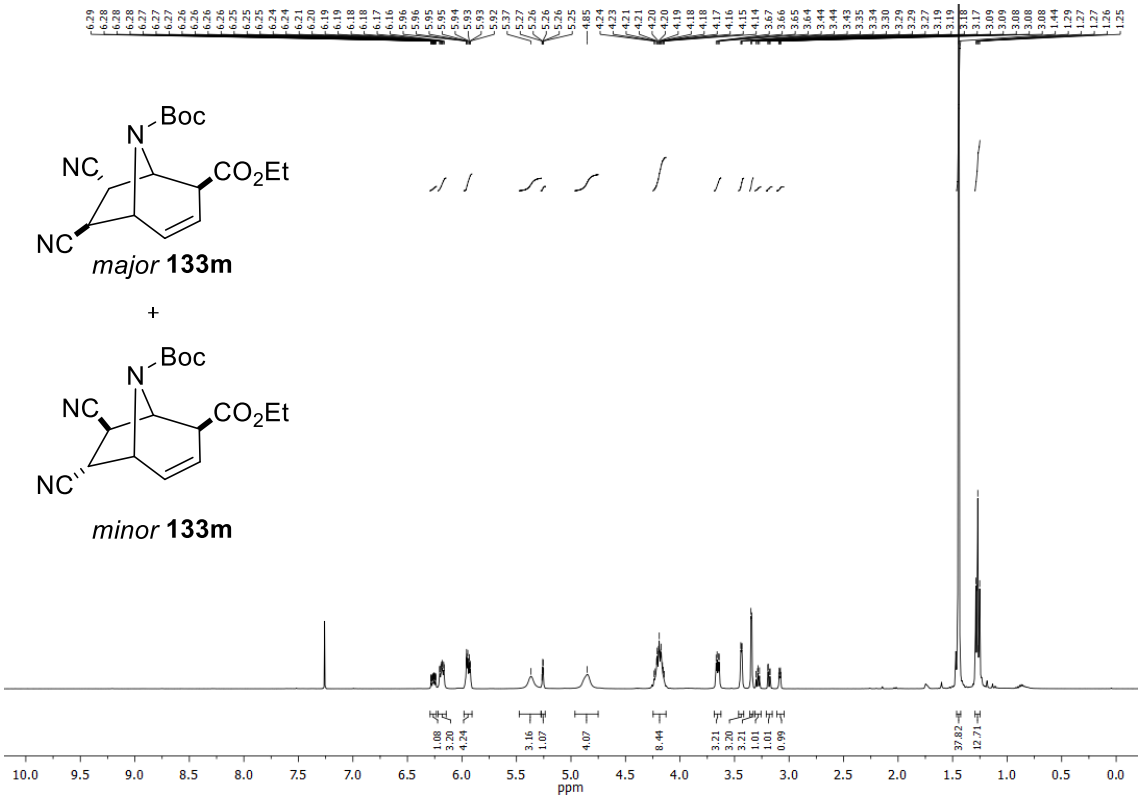
Compound *major* **133m**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

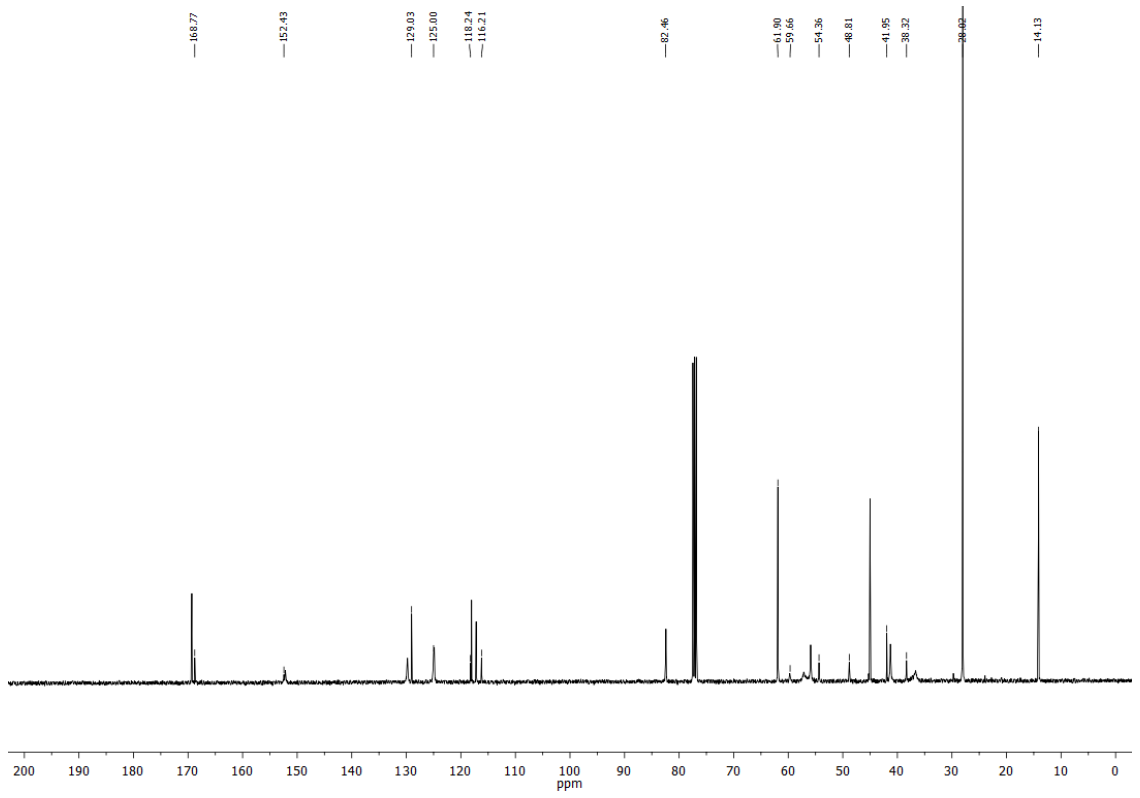


major **133m**

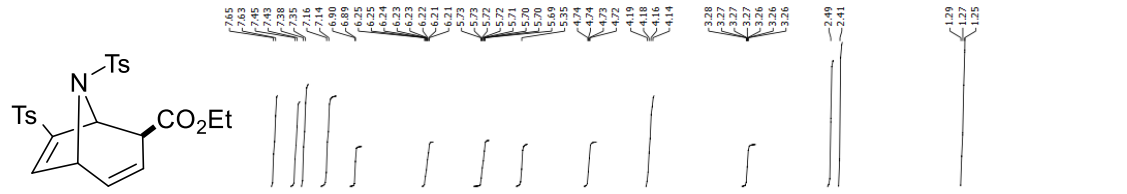


Compound *major and minor* **133m**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

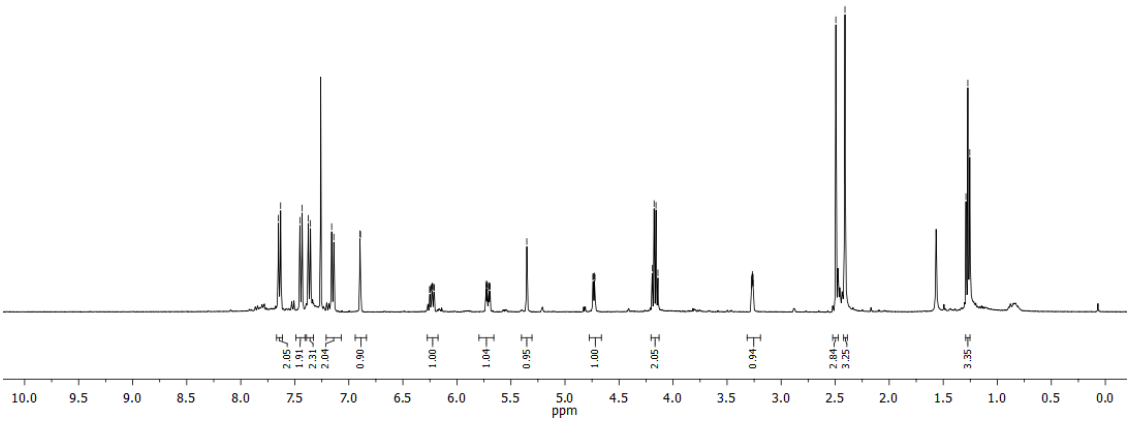


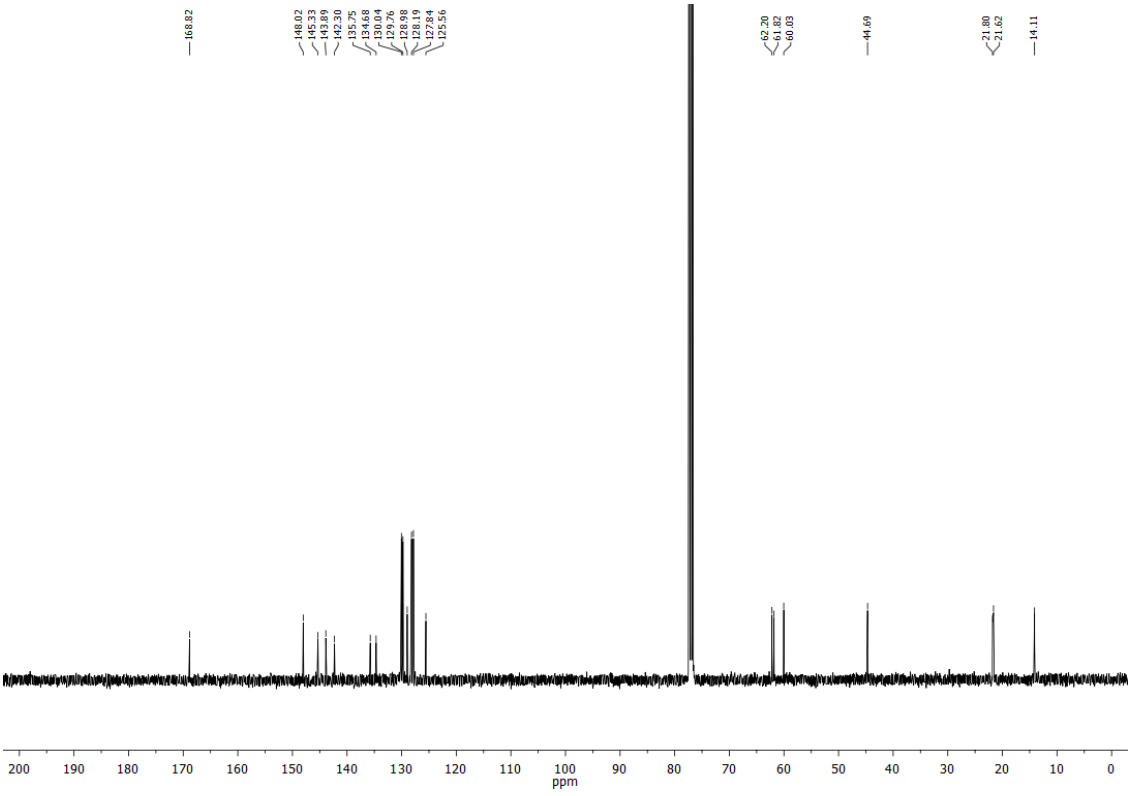


Compound *major* **133o**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

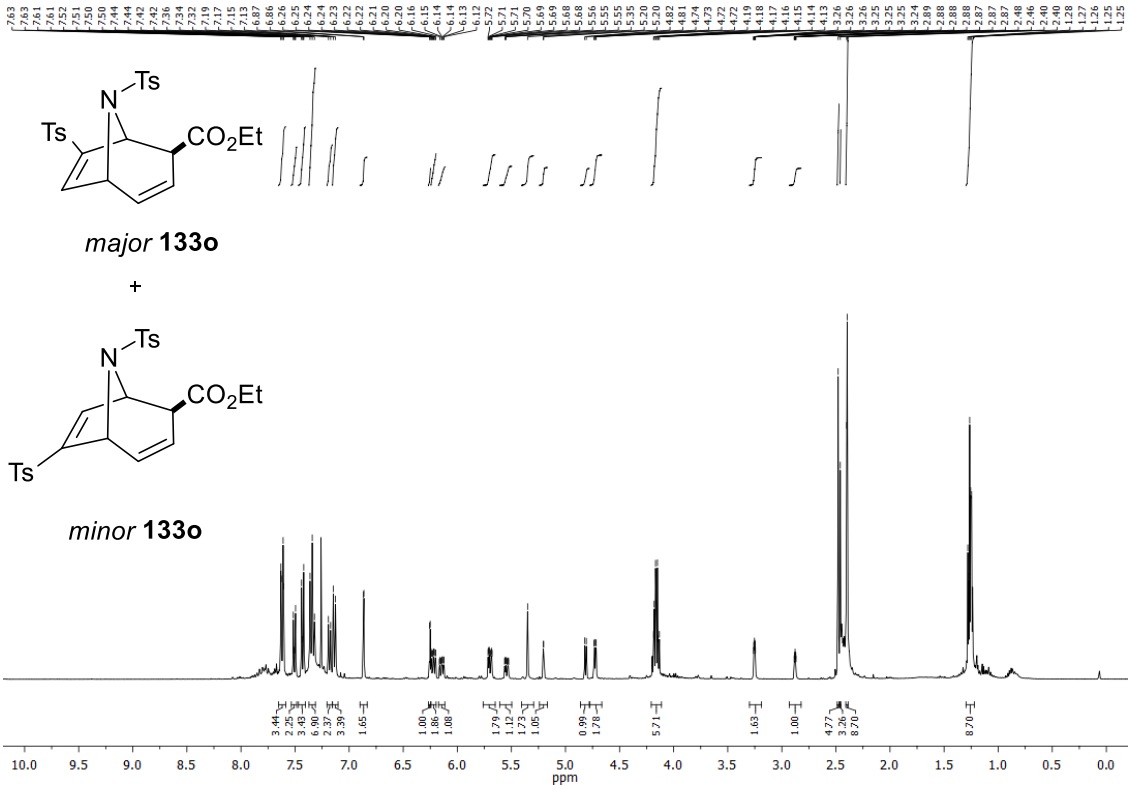


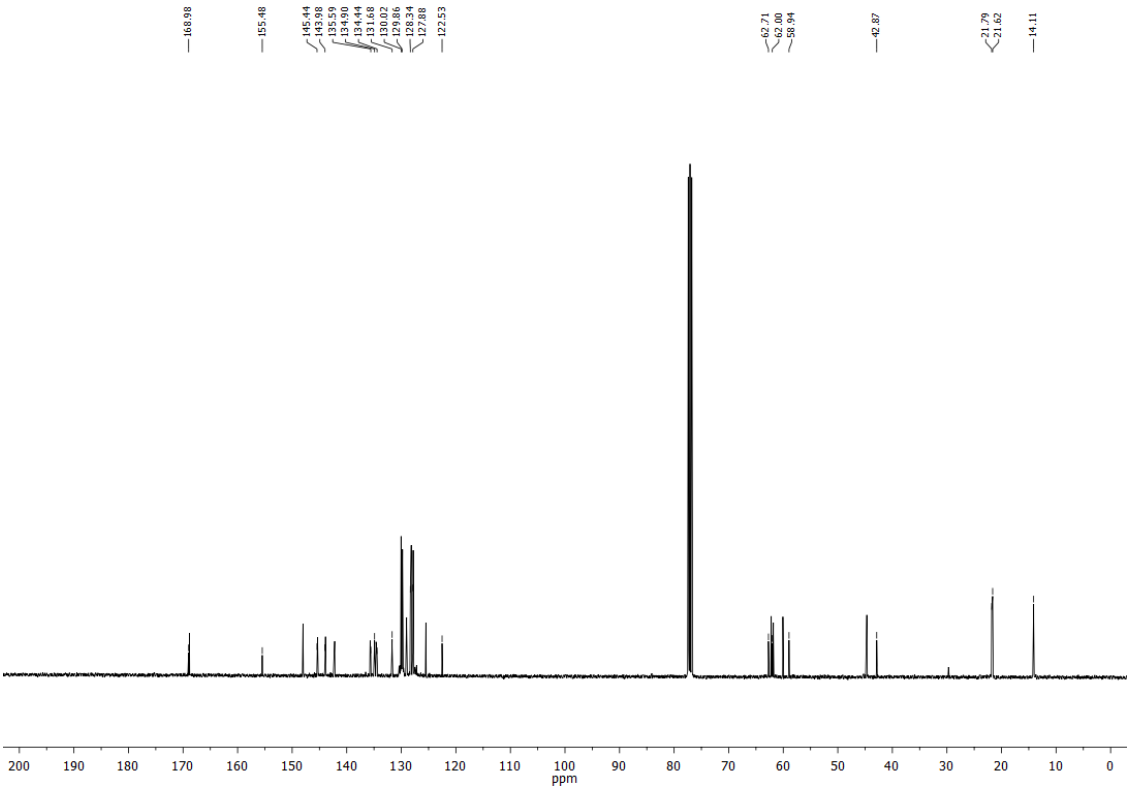
major **133o**



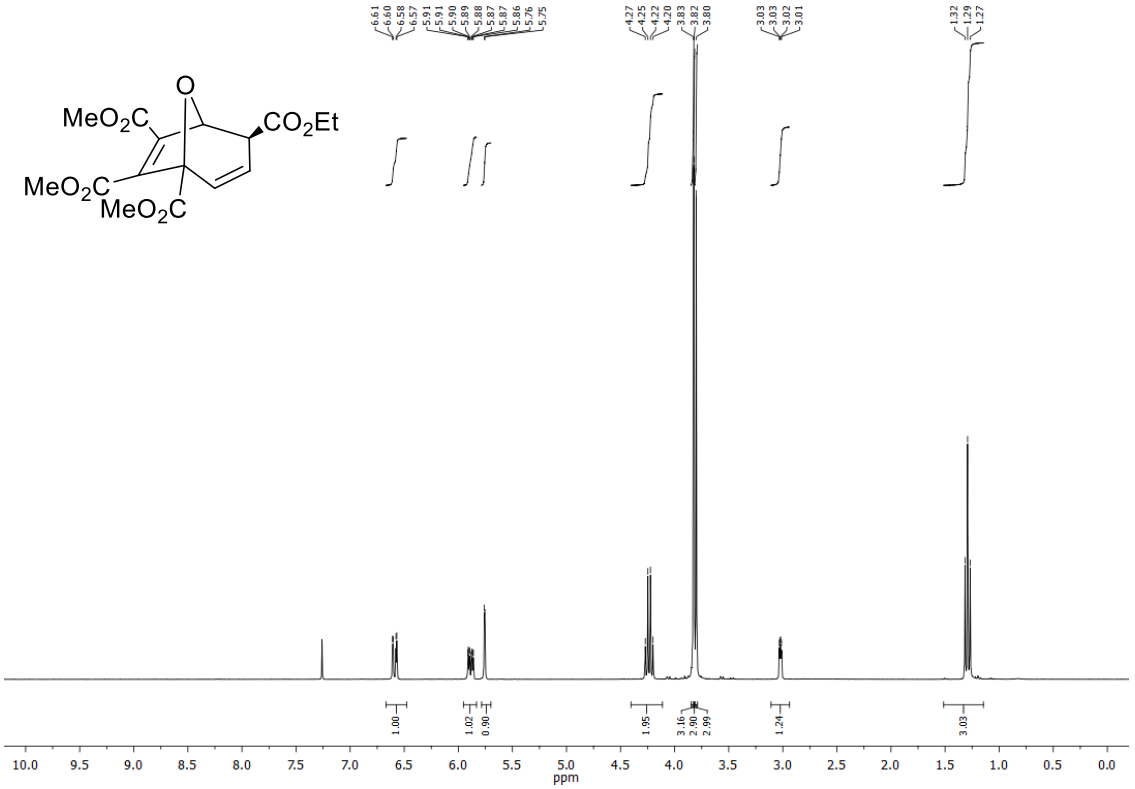


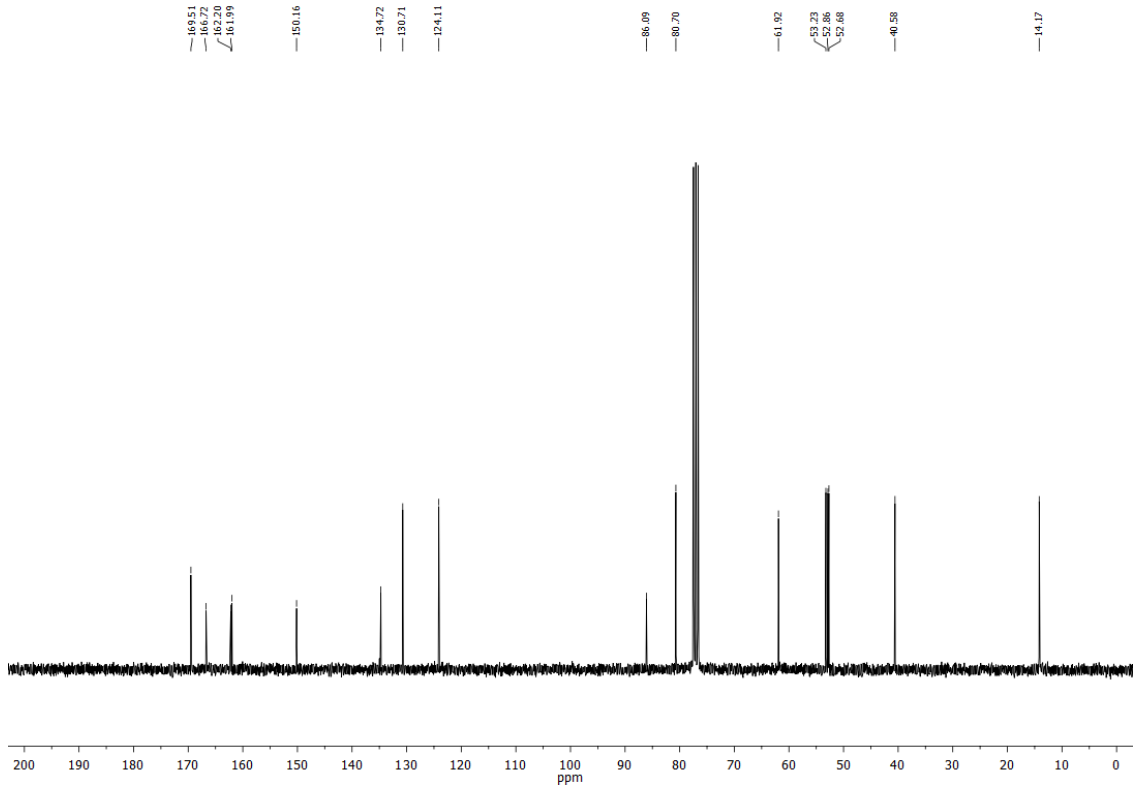
Compound *major* and *minor* **133o**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



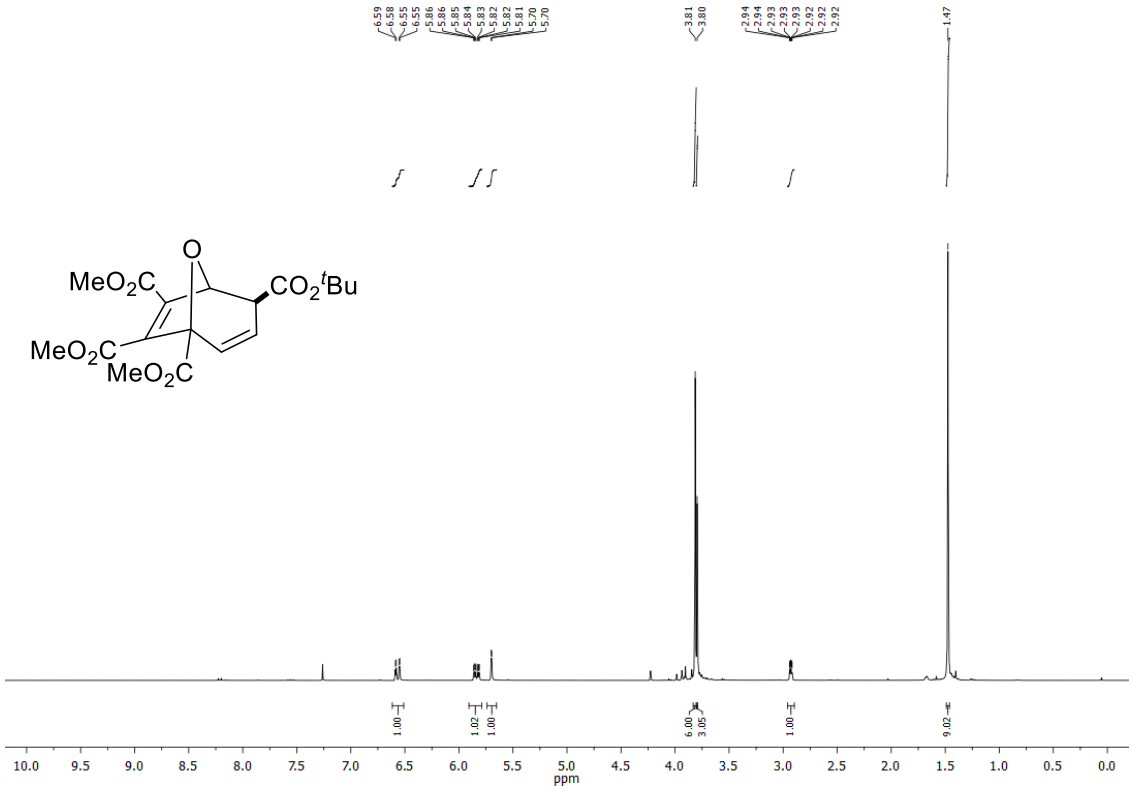


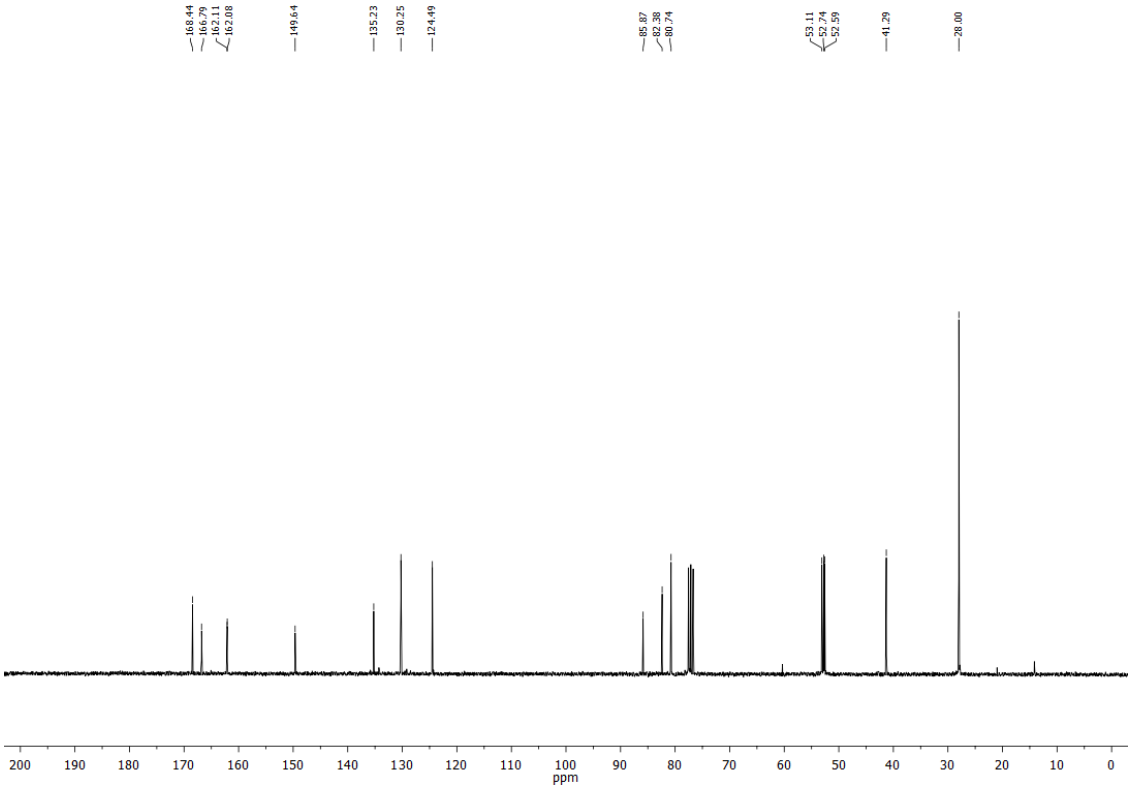
Compound **(+)-140a**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



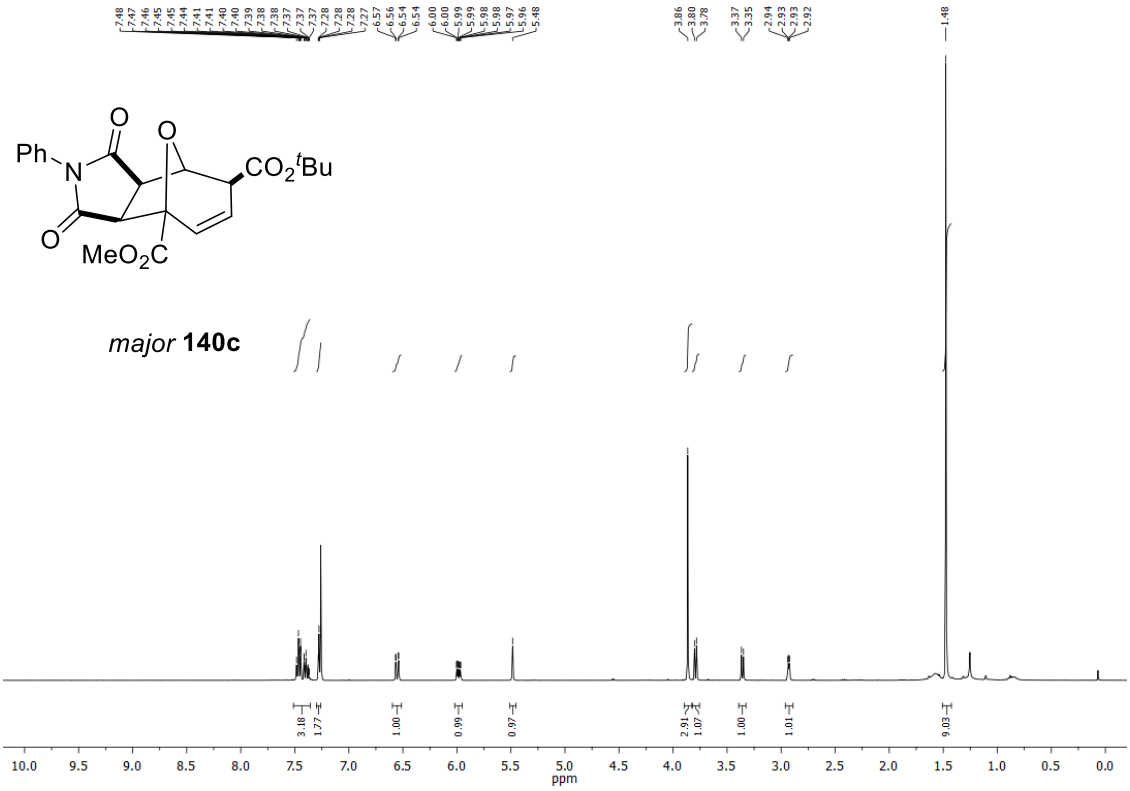


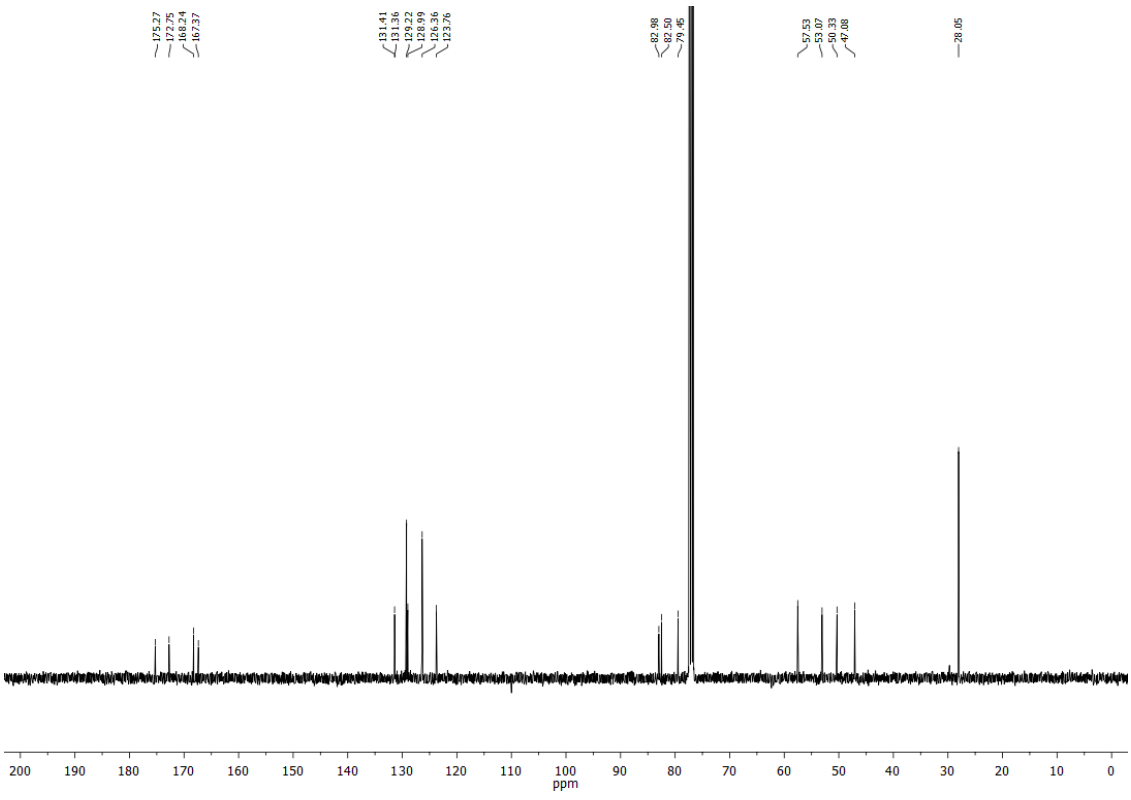
Compound **140b**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



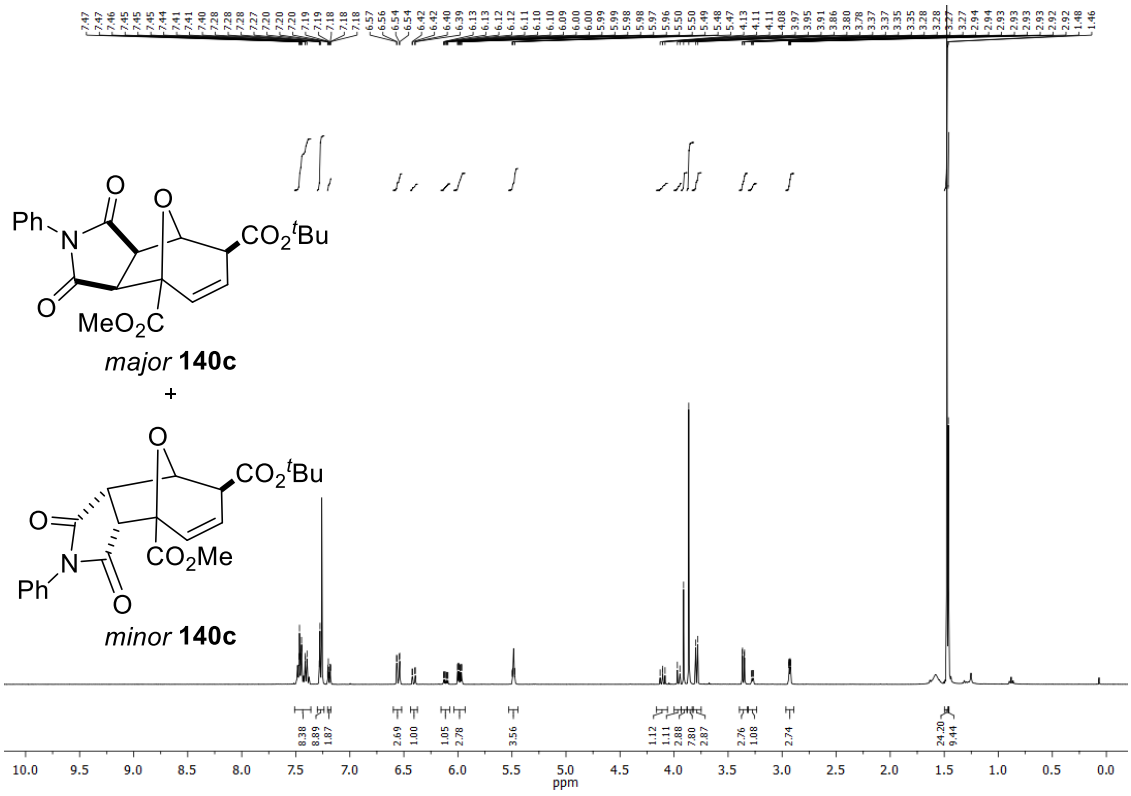


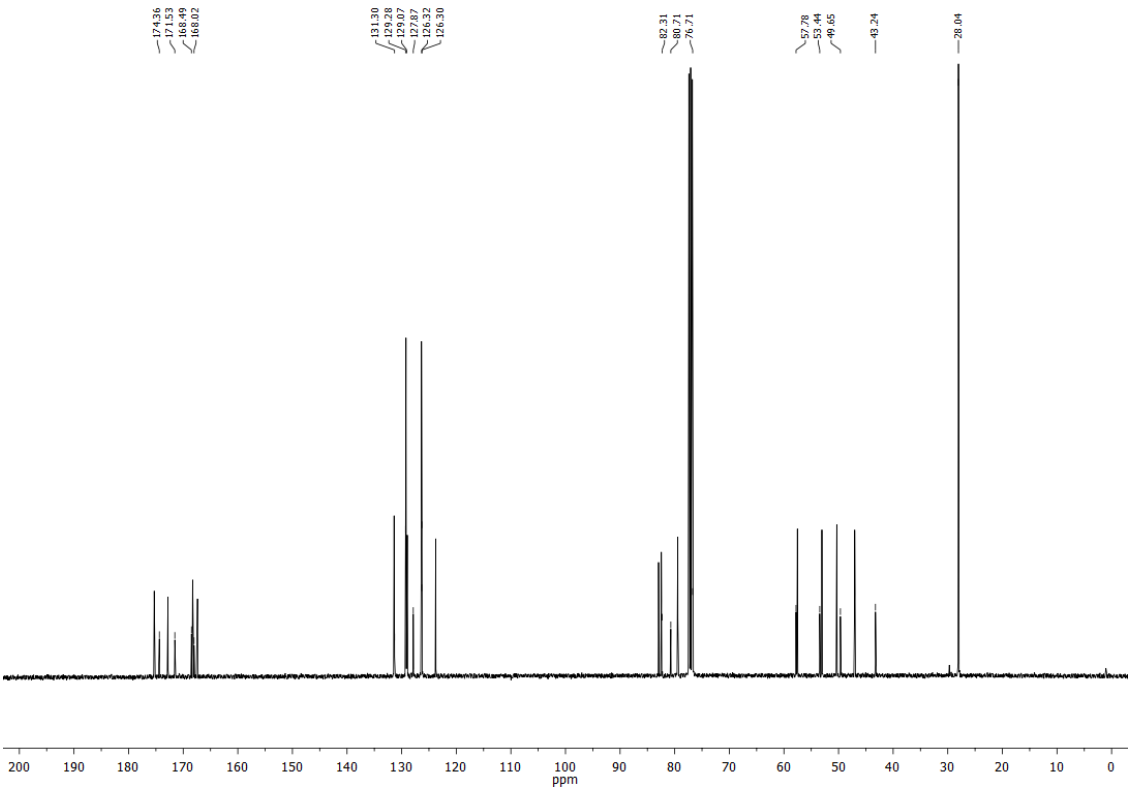
Compound *major* **140c**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



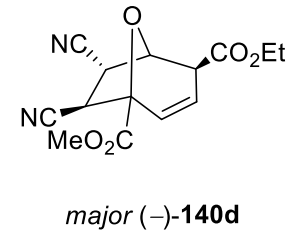


Compound *major* and *minor* **140c**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

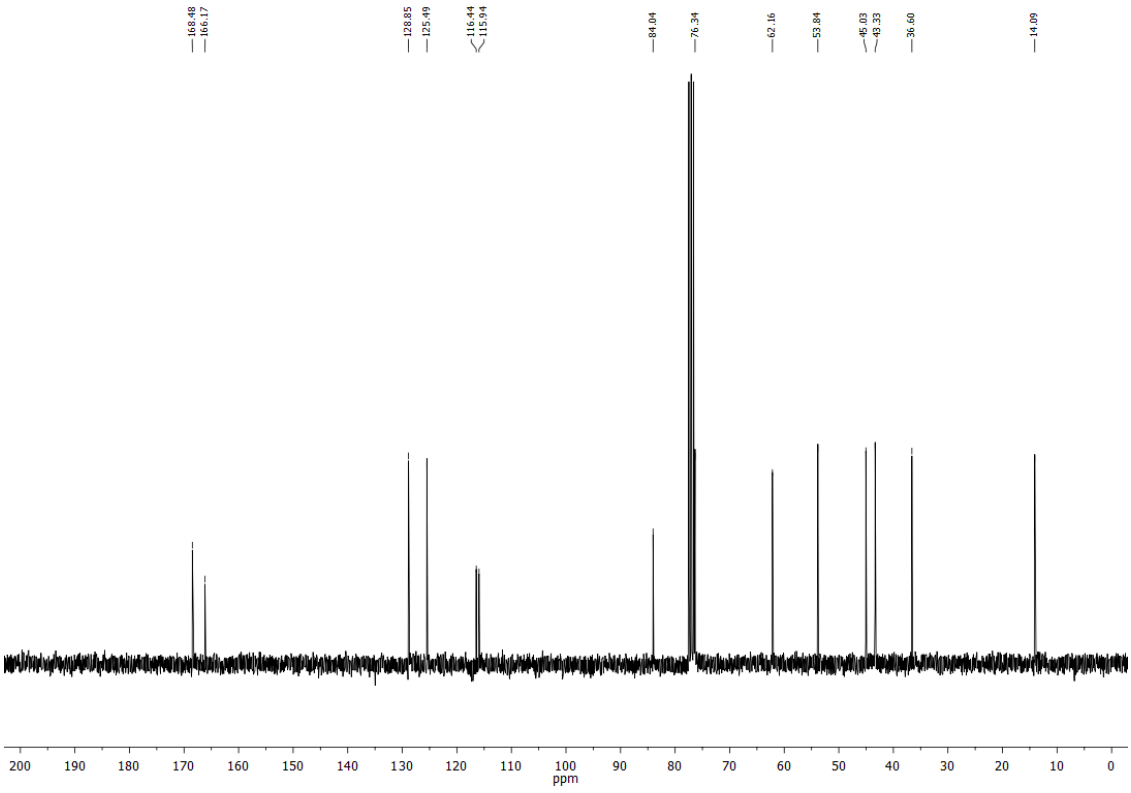




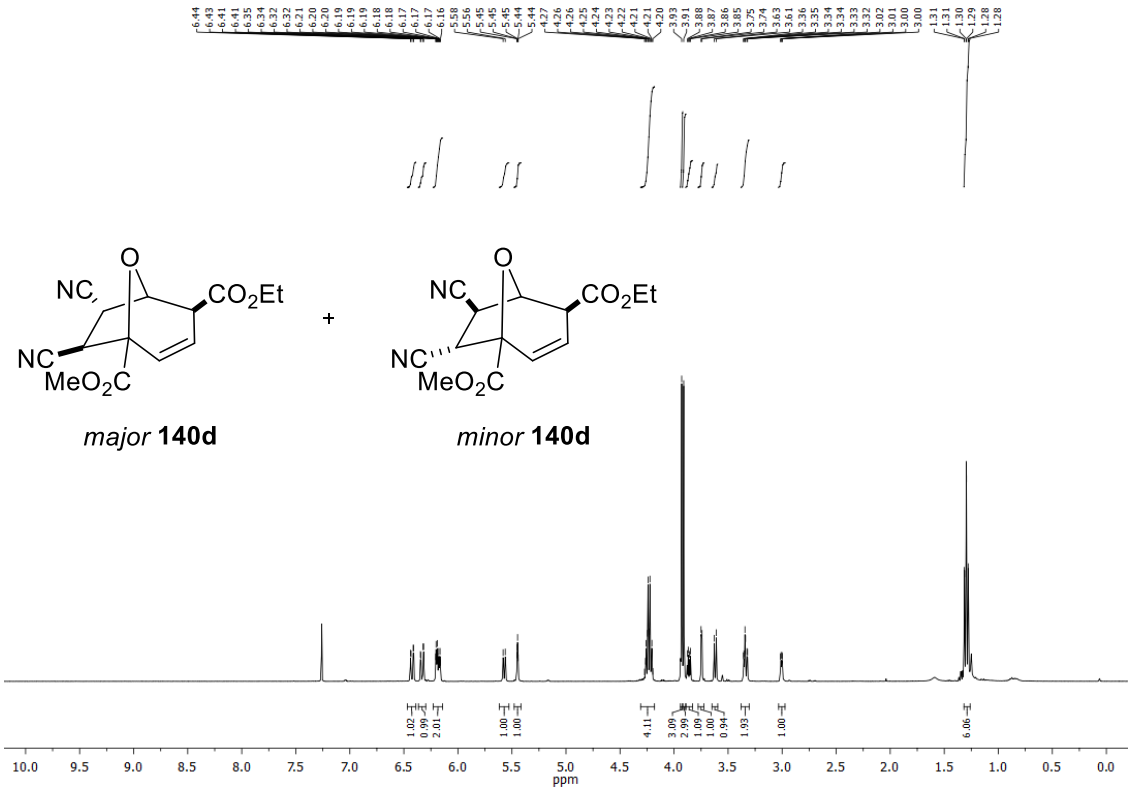
Compound *major* (–)-**140d**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):

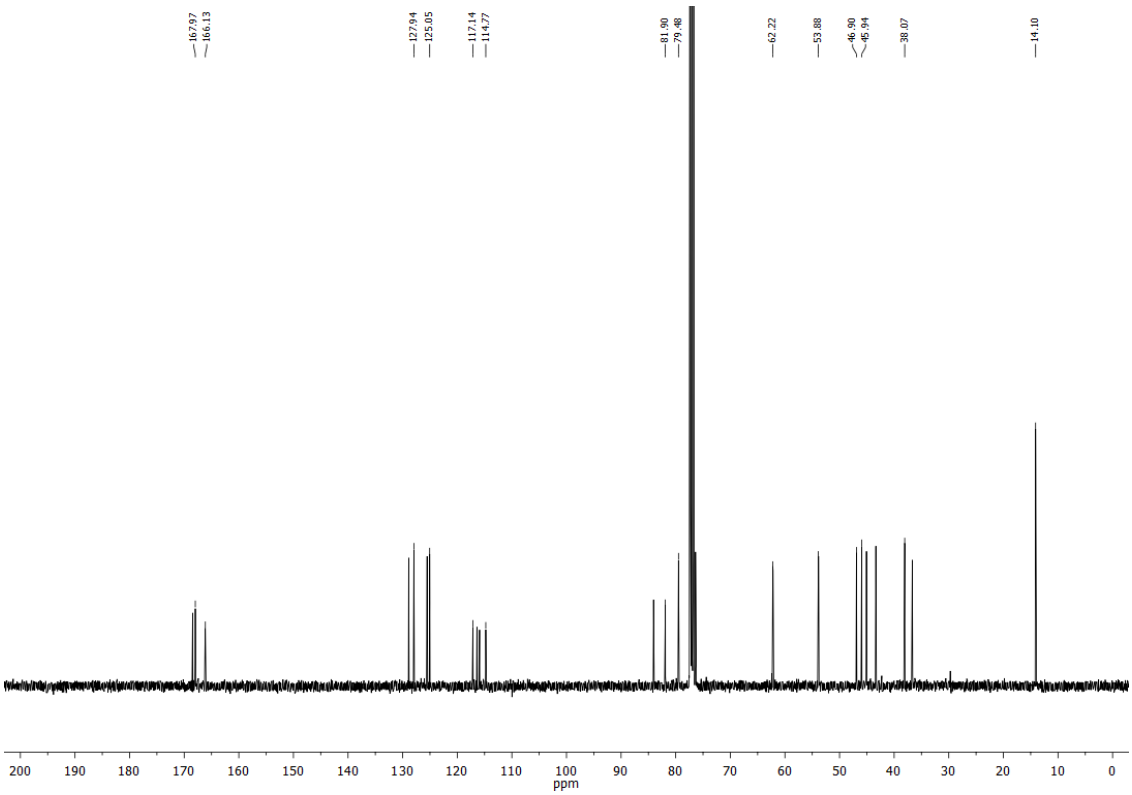


major (–)-**140d**

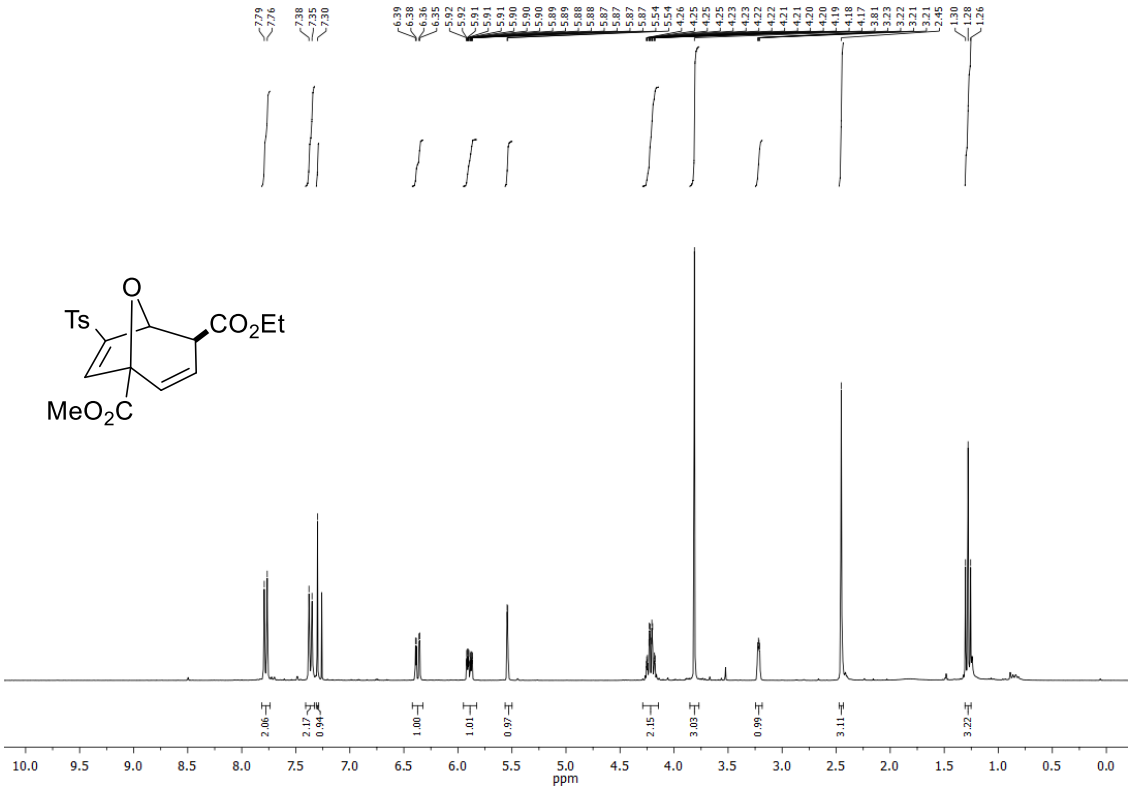


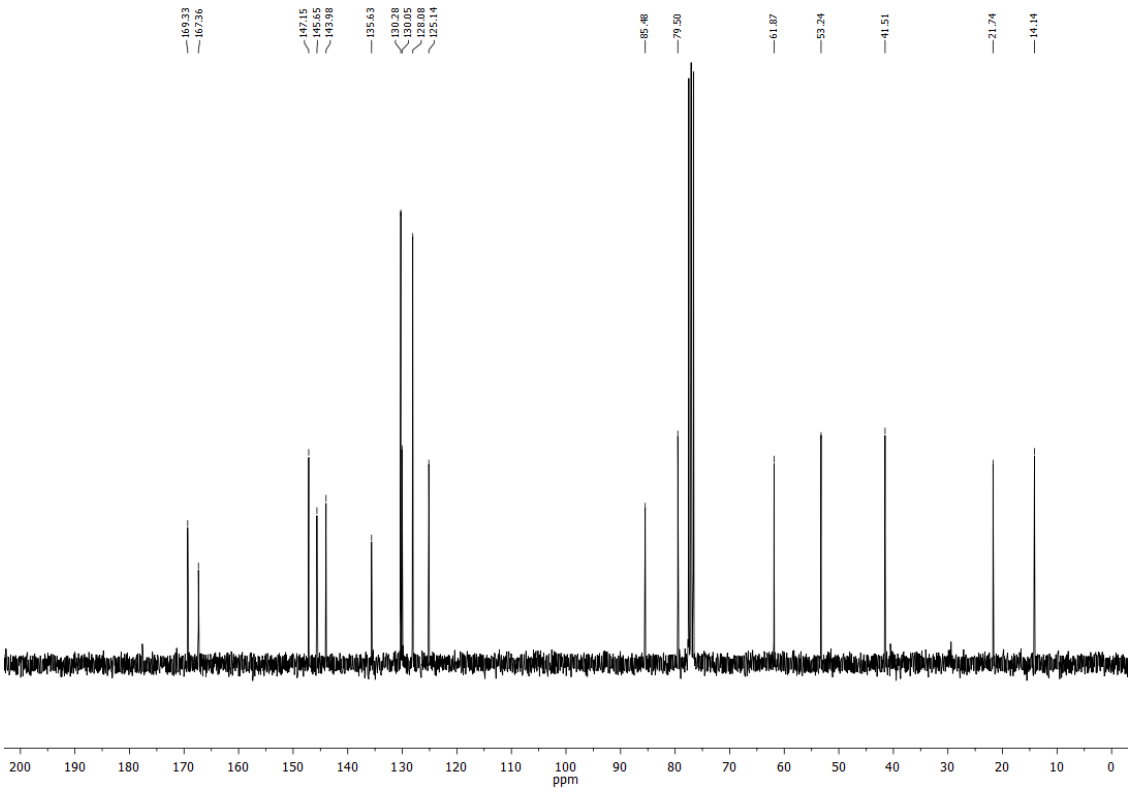
Compound *major* and *minor* **140d**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



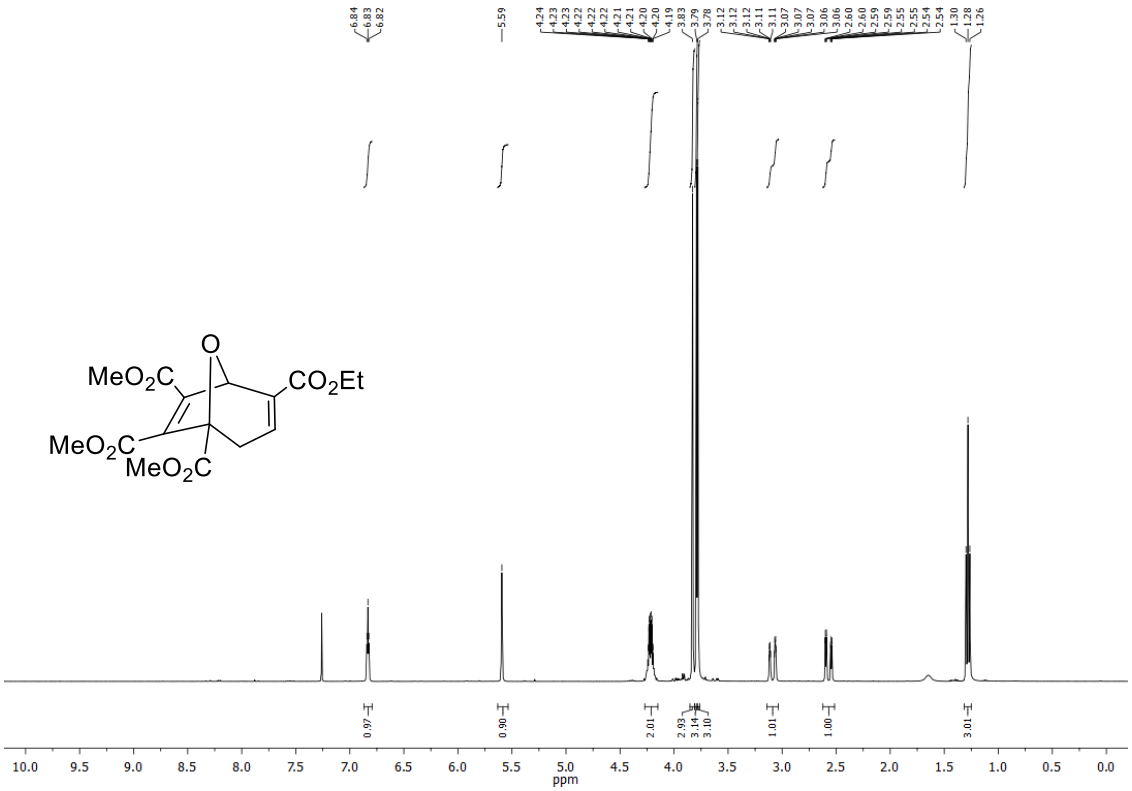


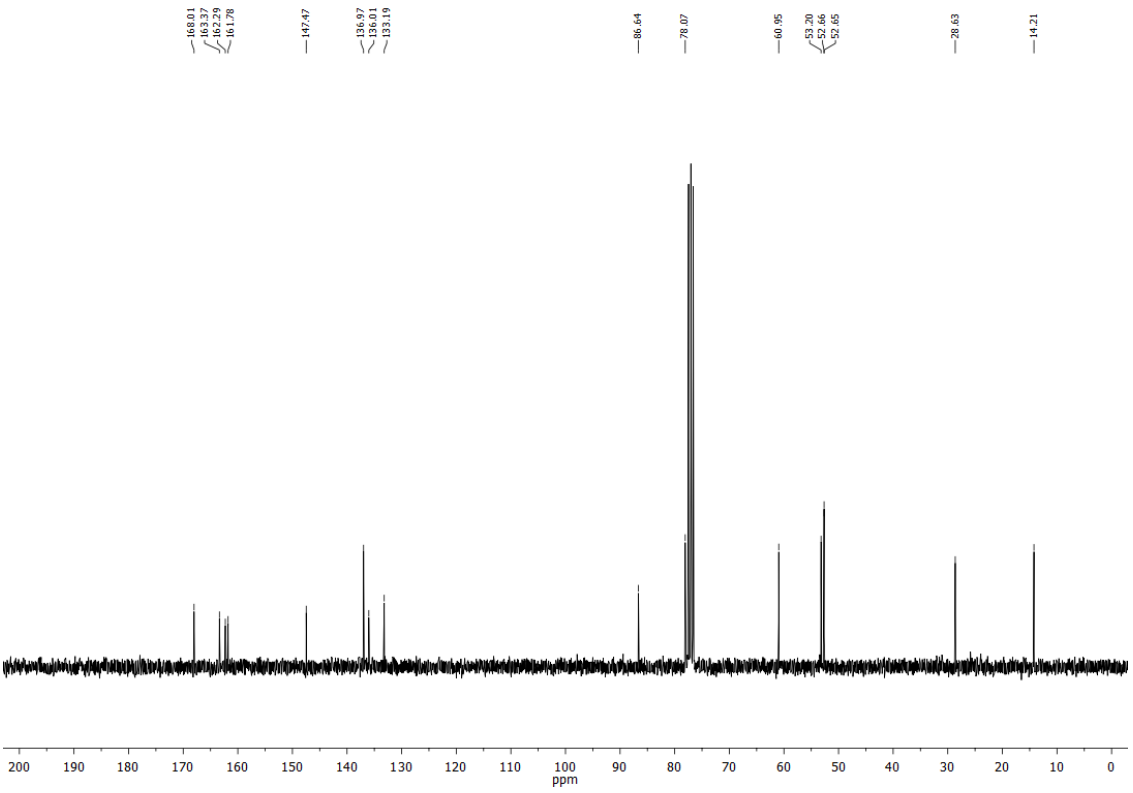
Compound **140e**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



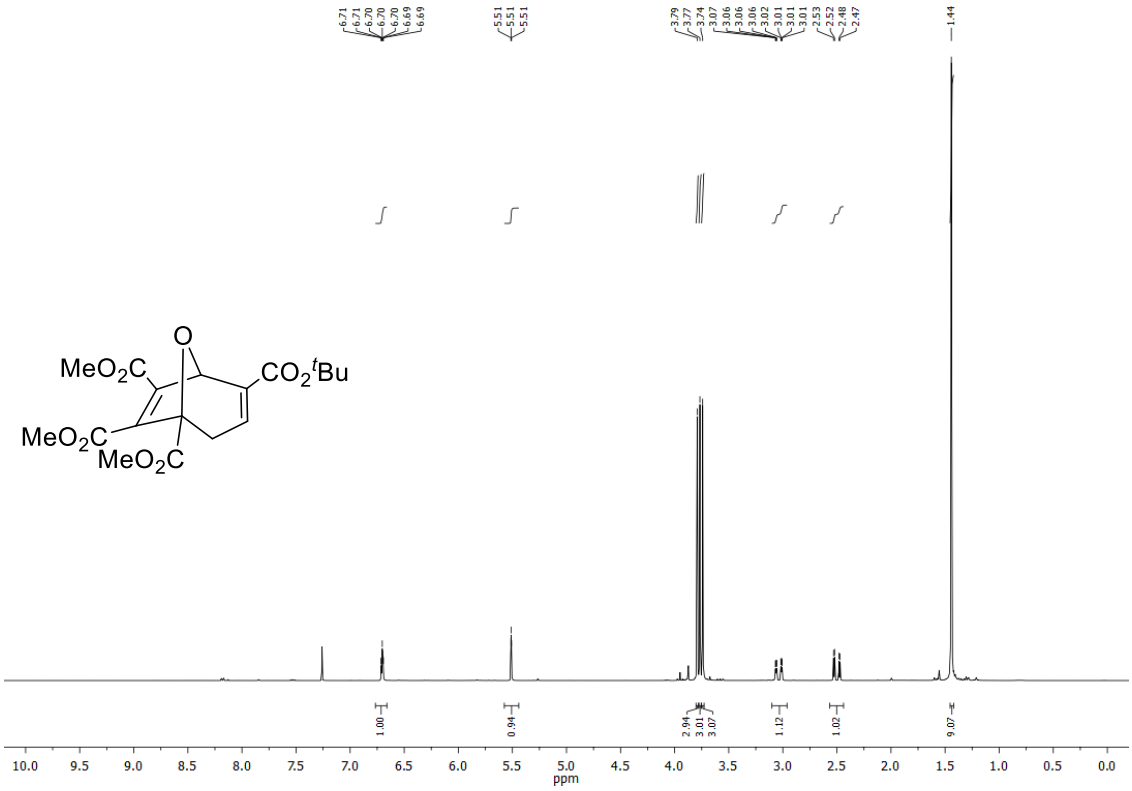


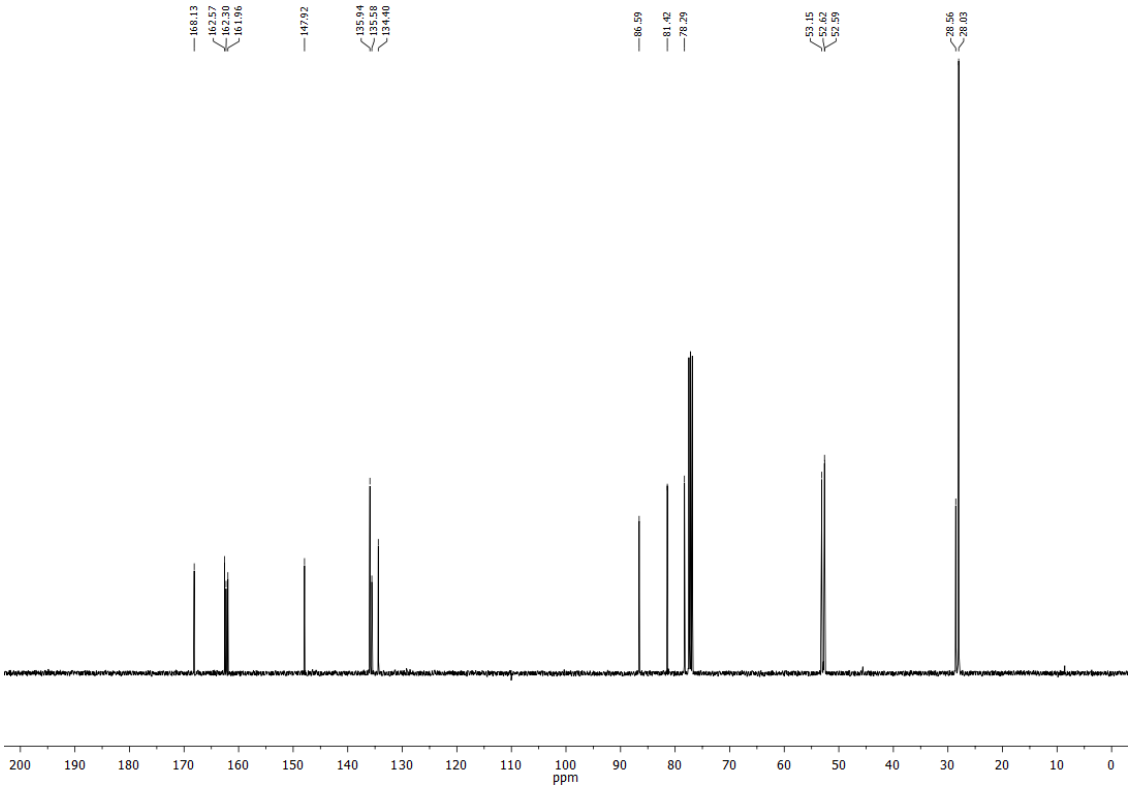
Compound **151a**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



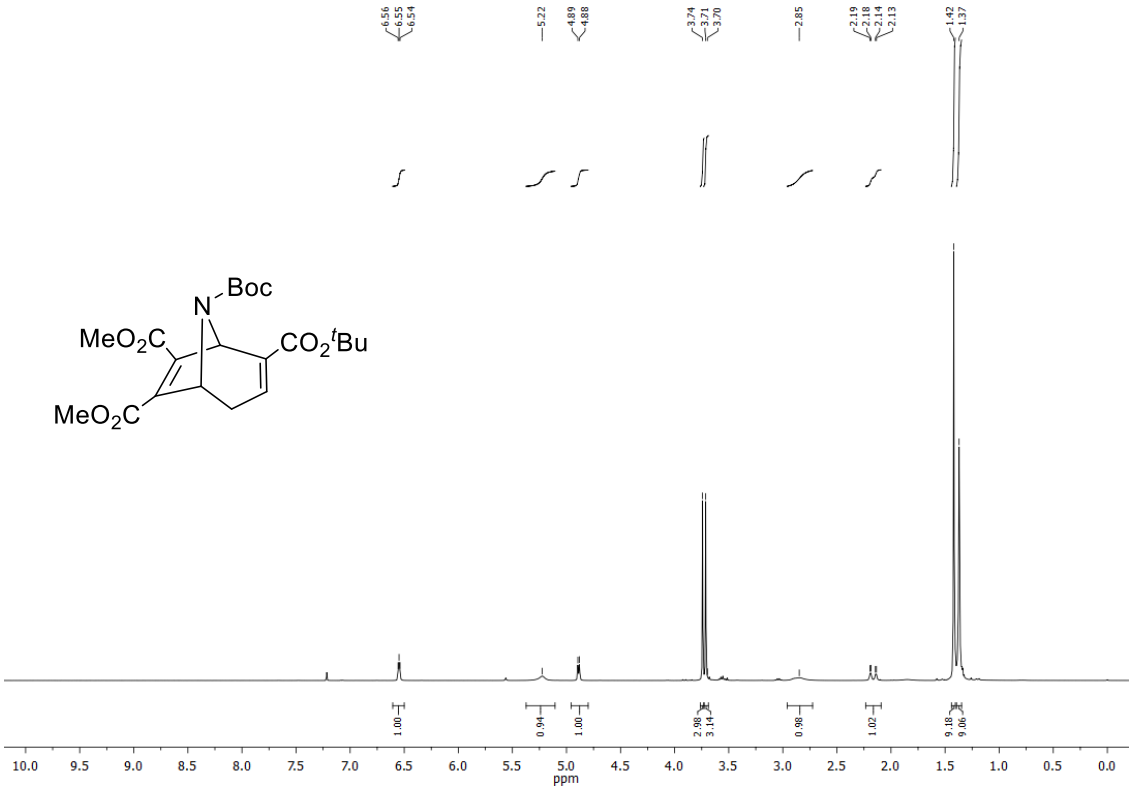


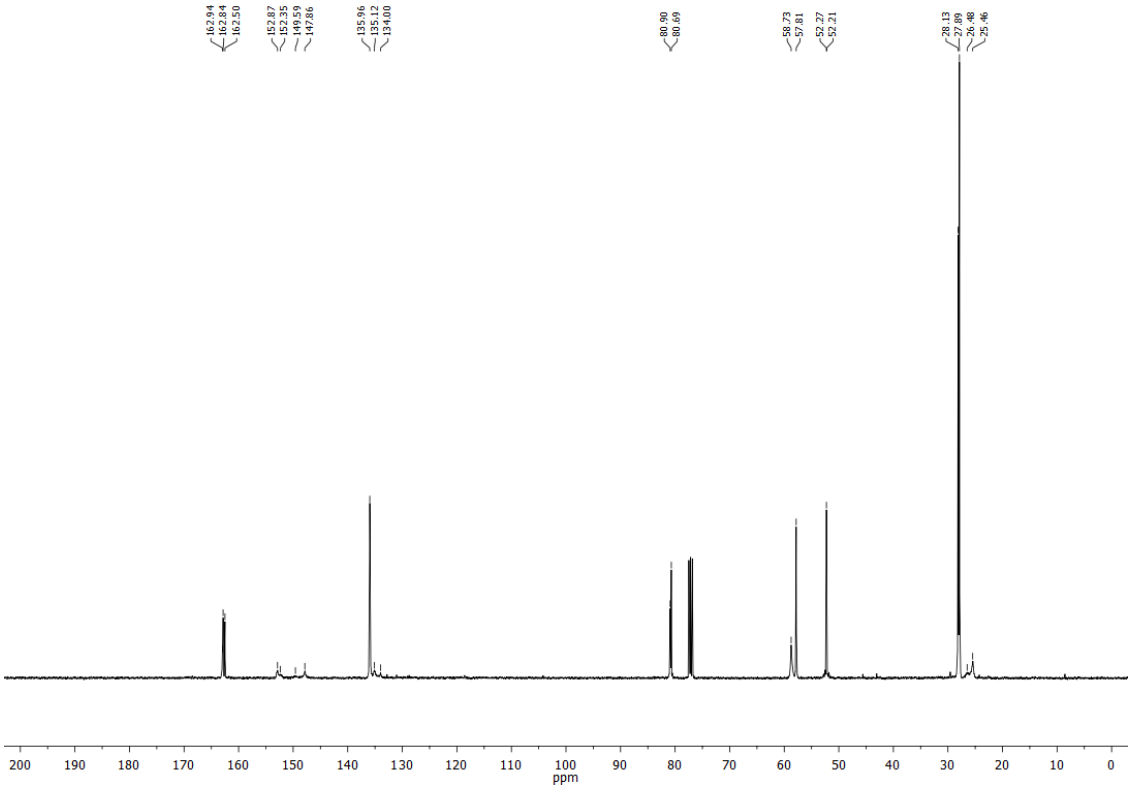
Compound **151b**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



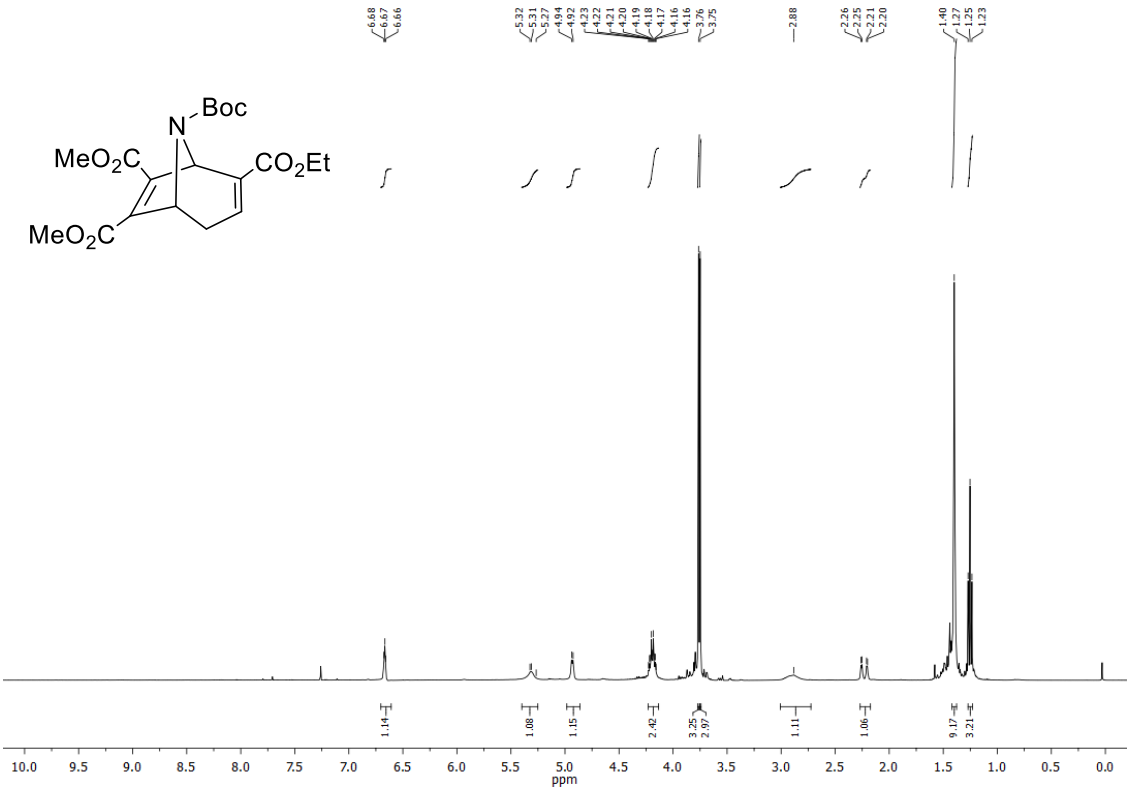


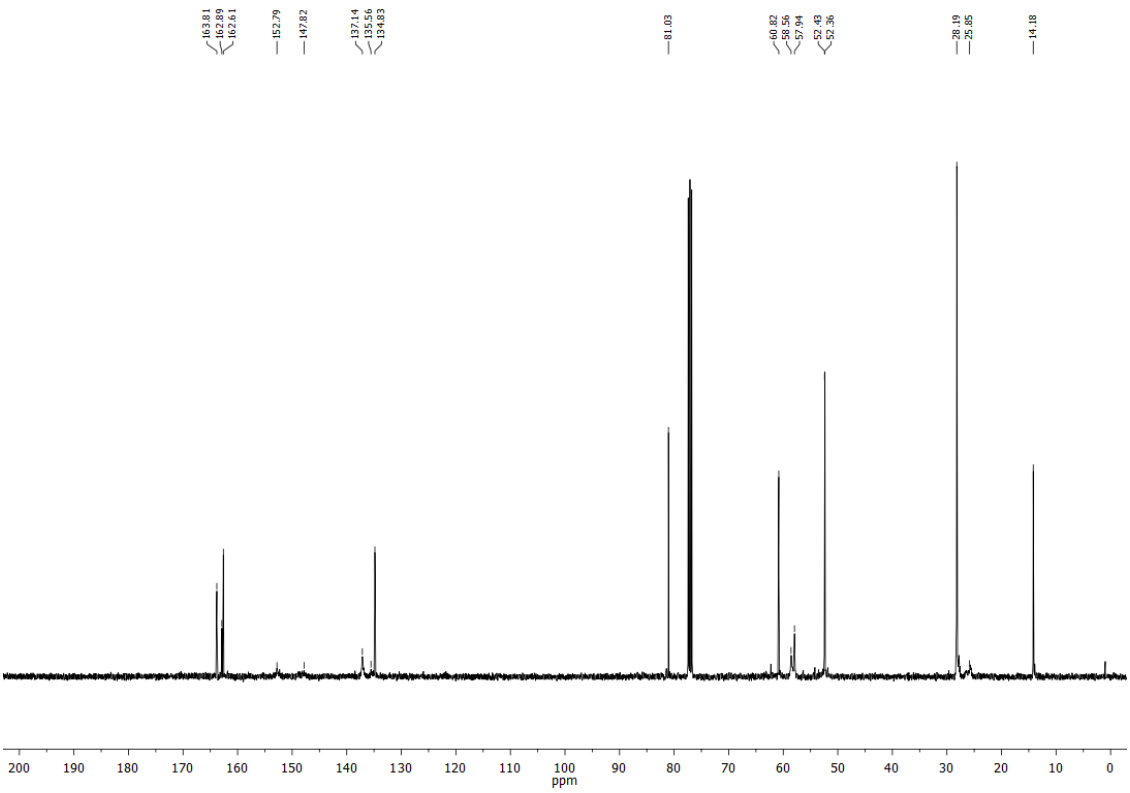
Compound **152a**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



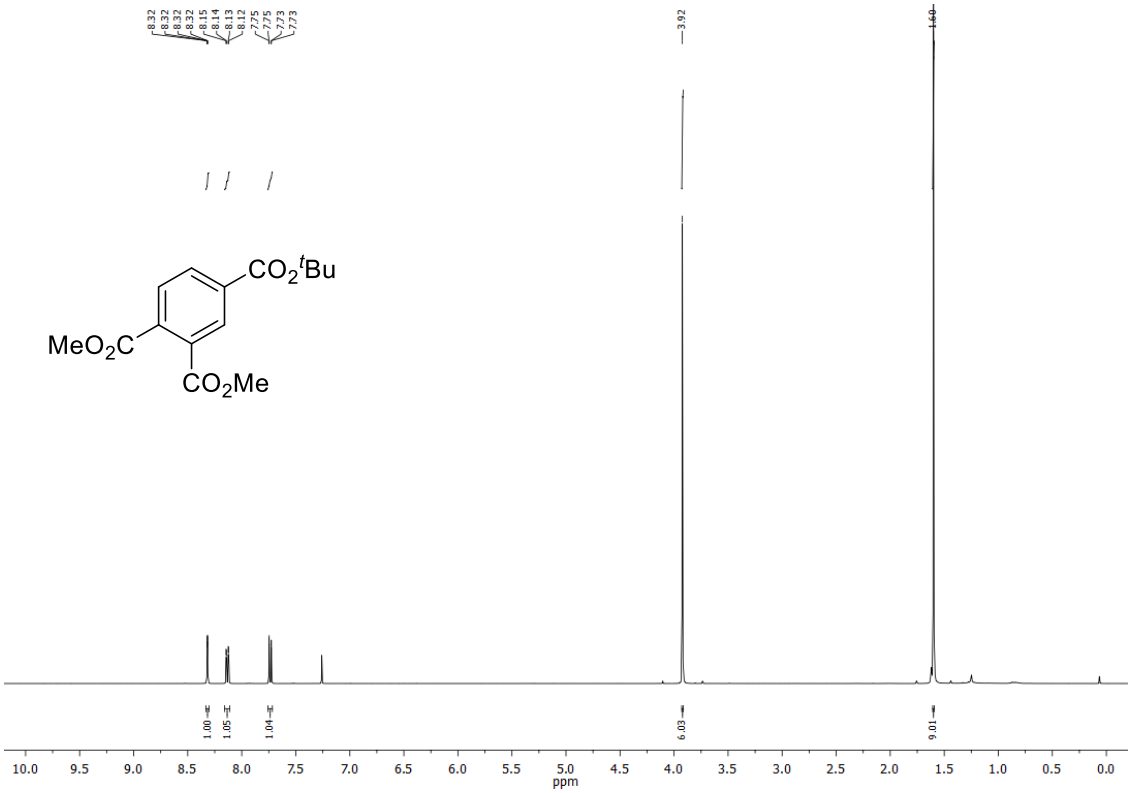


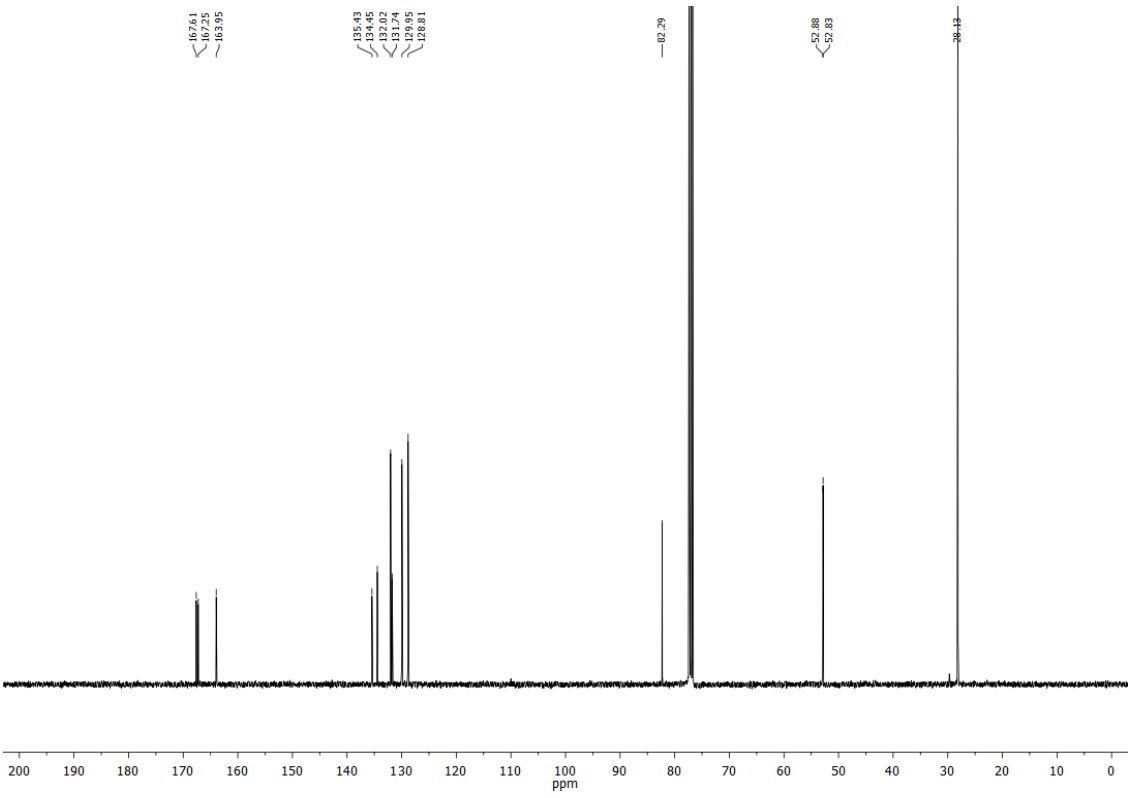
Compound **152b**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



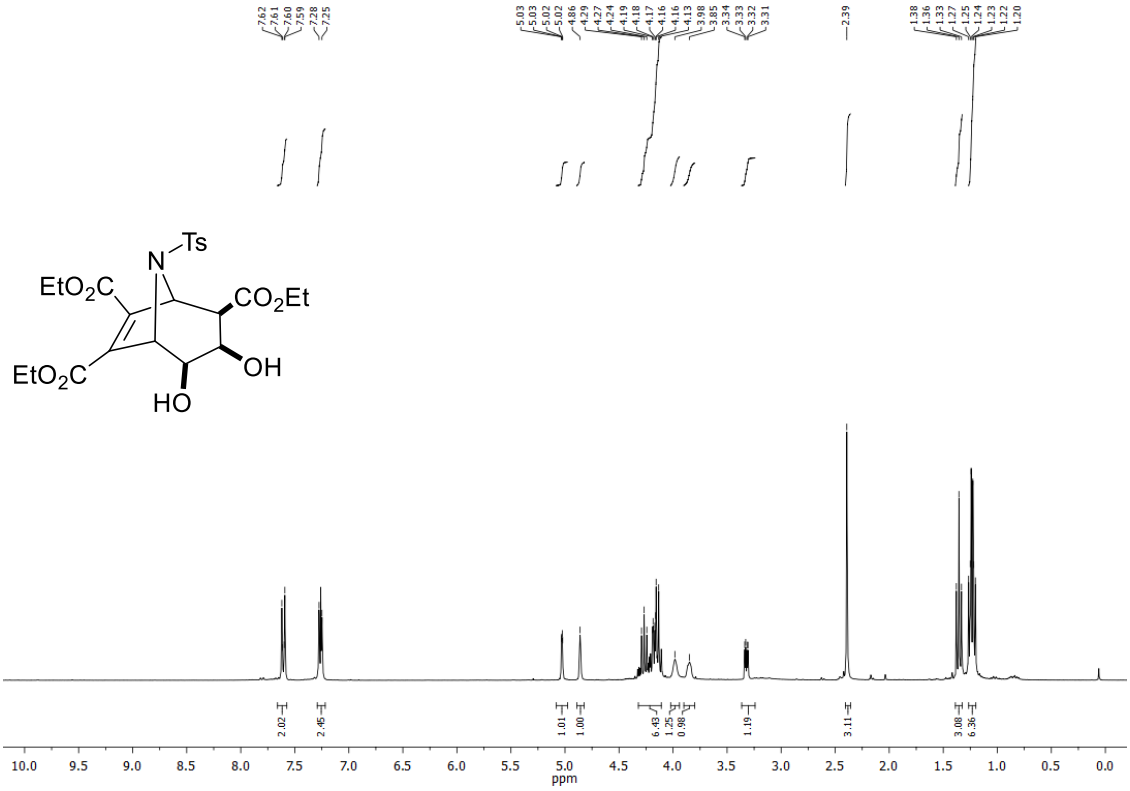


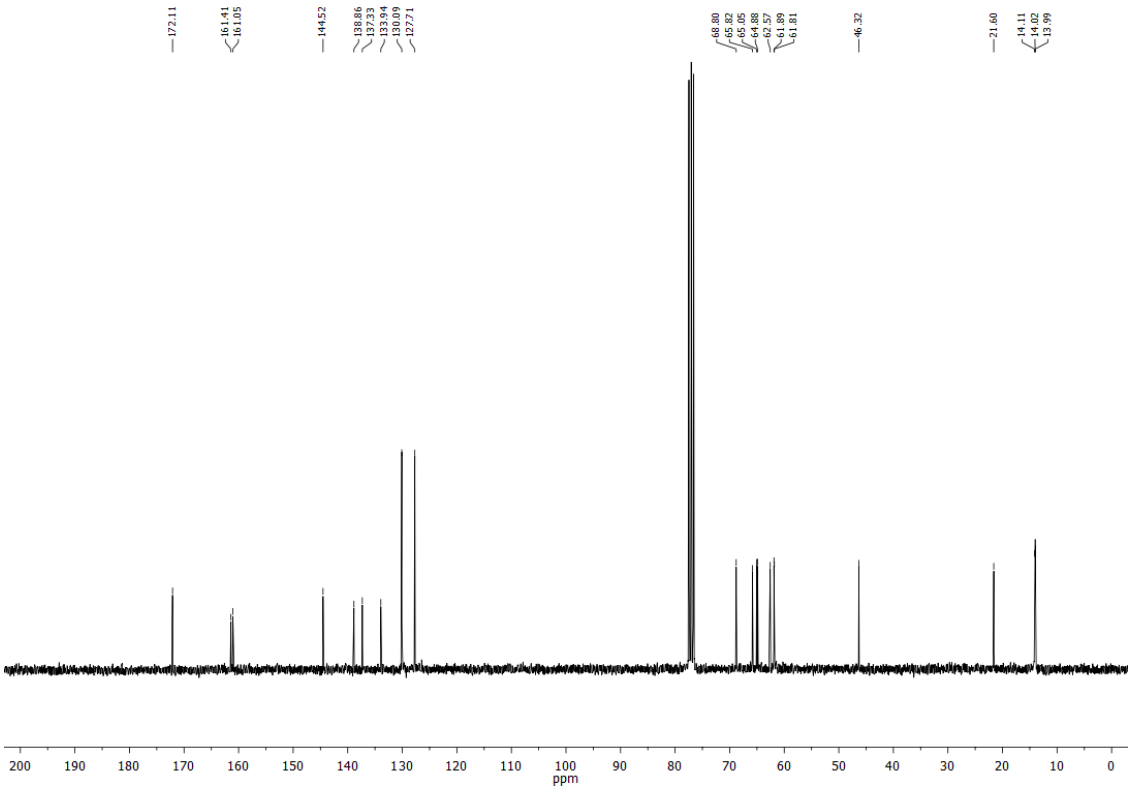
Compound **157**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



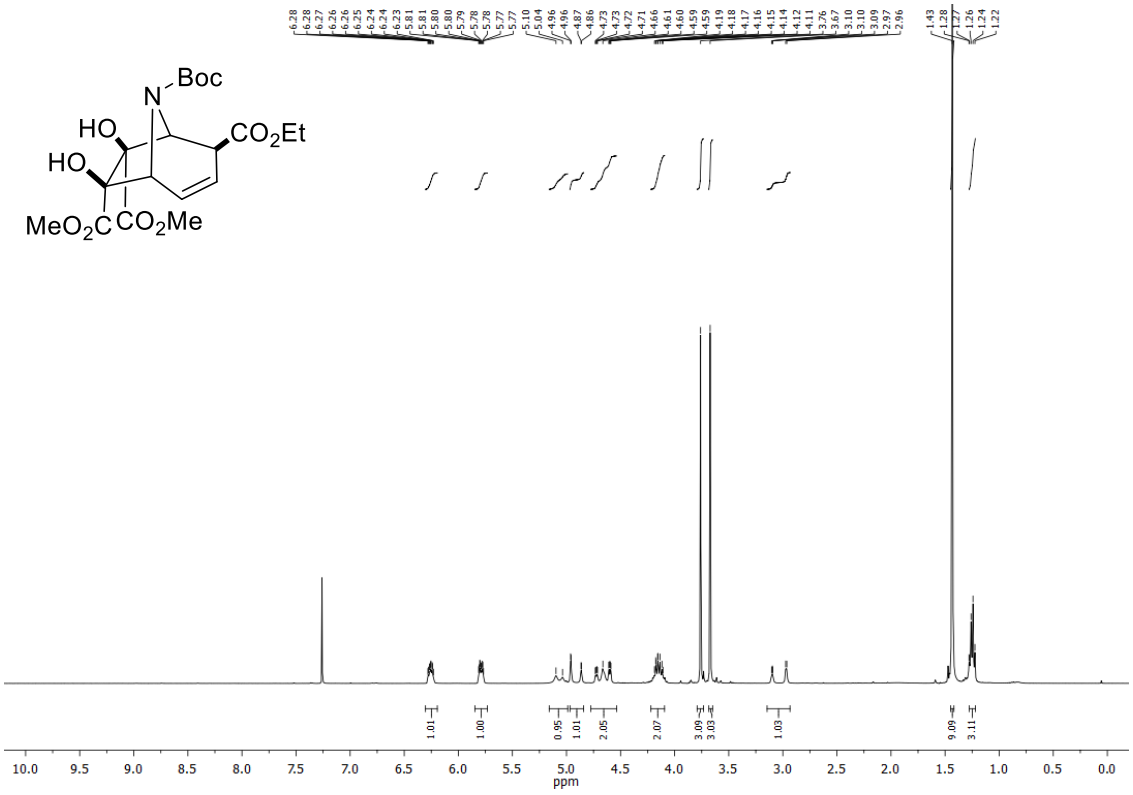


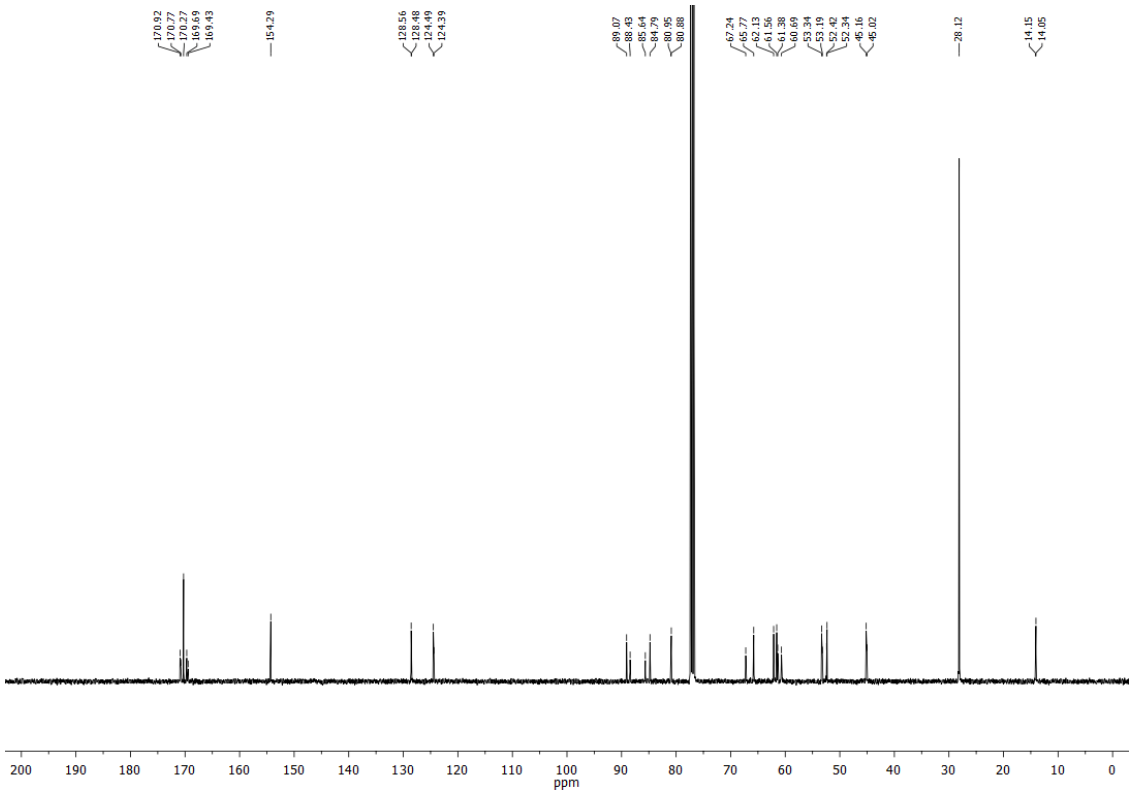
Compound **170**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



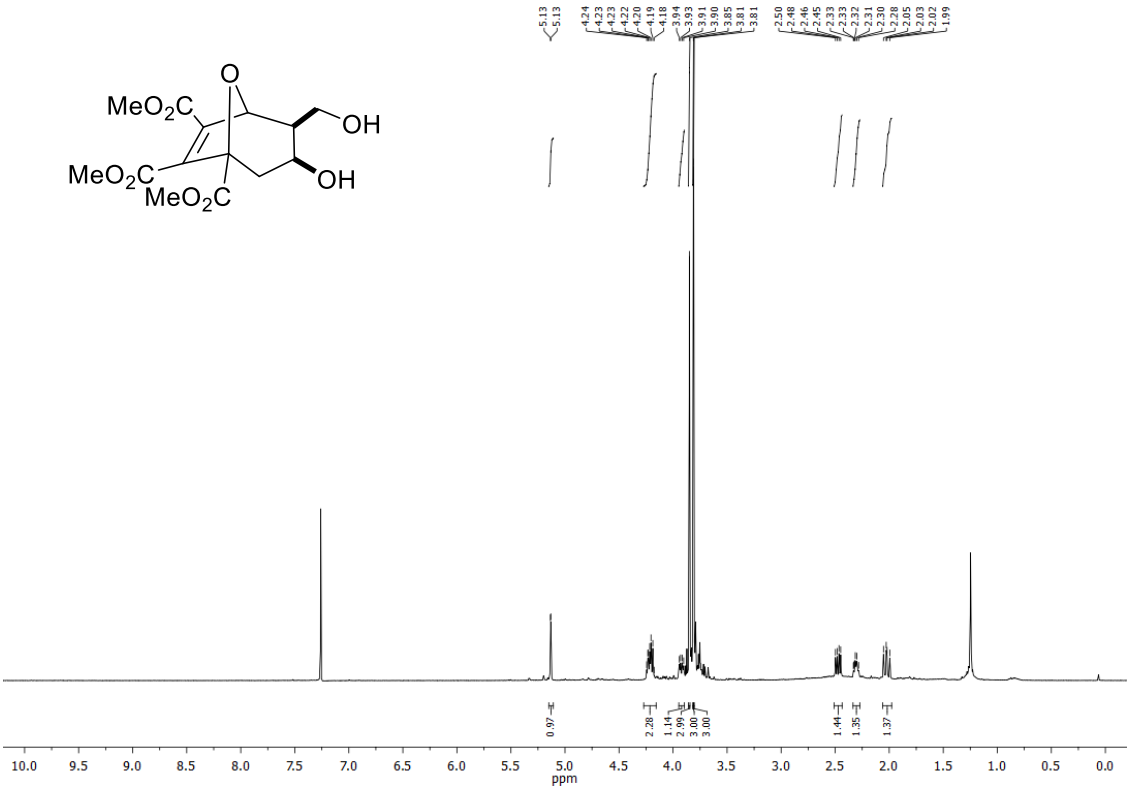


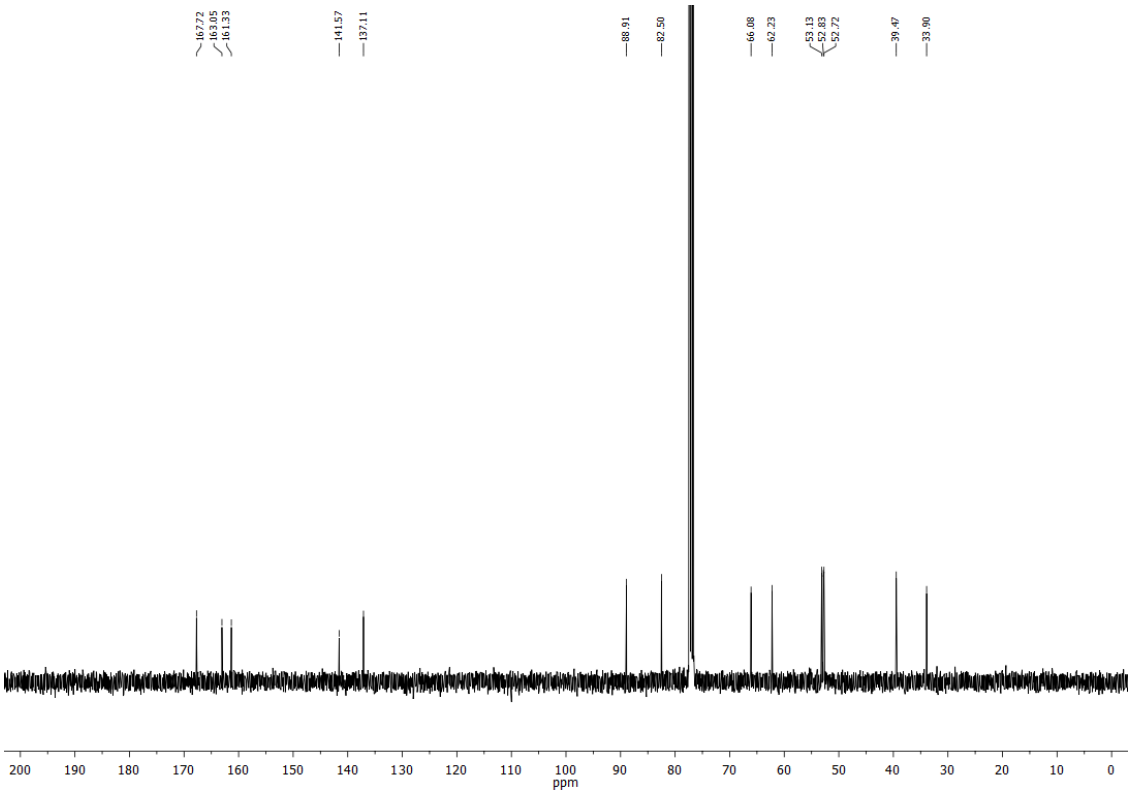
Compound **171**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



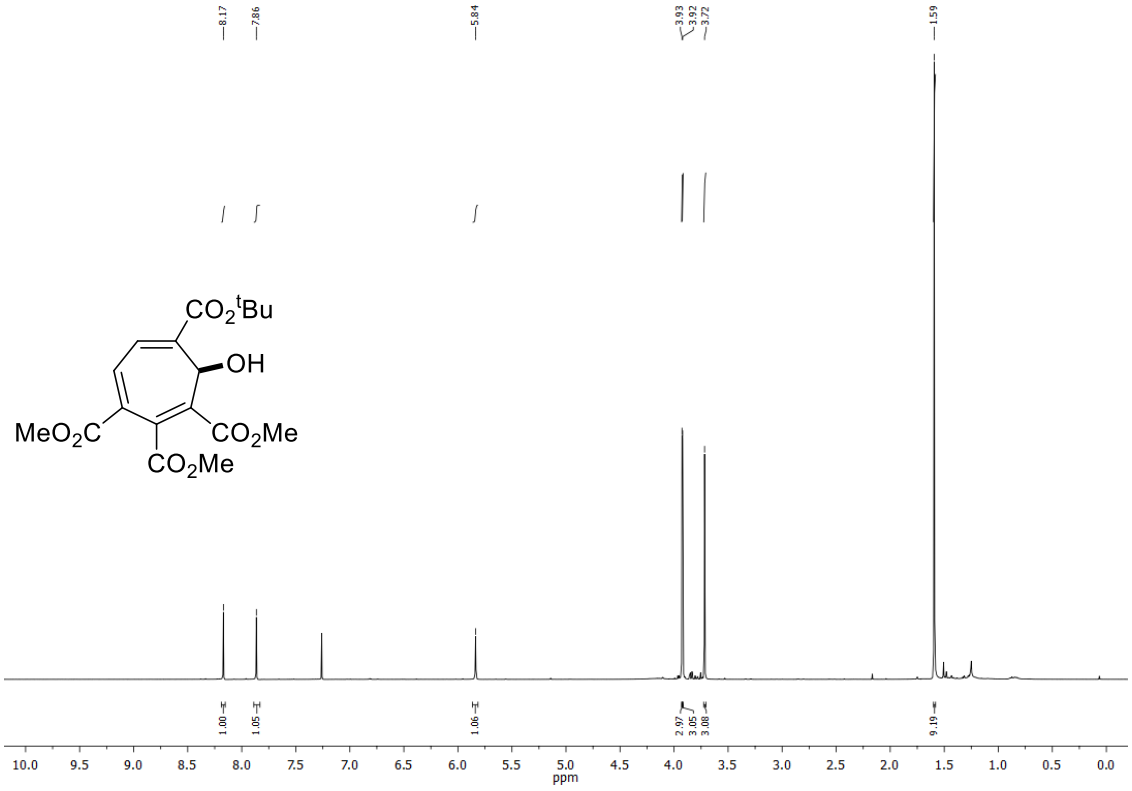


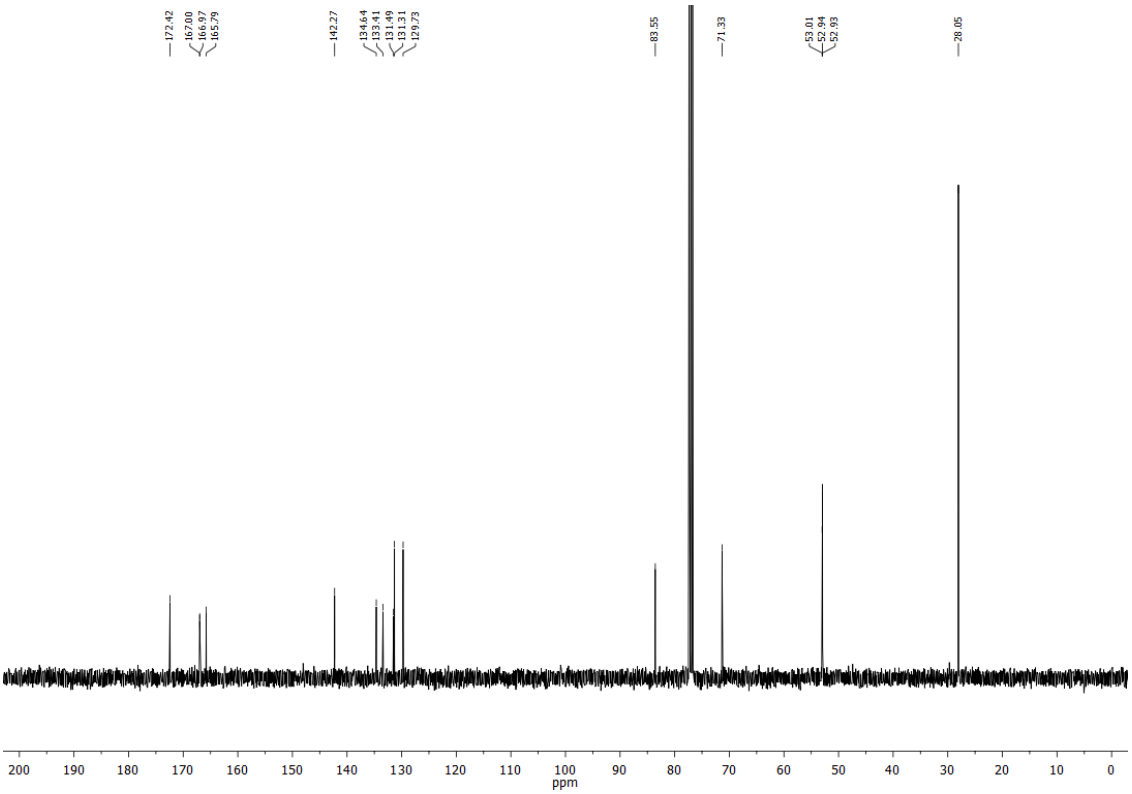
Compound **183**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



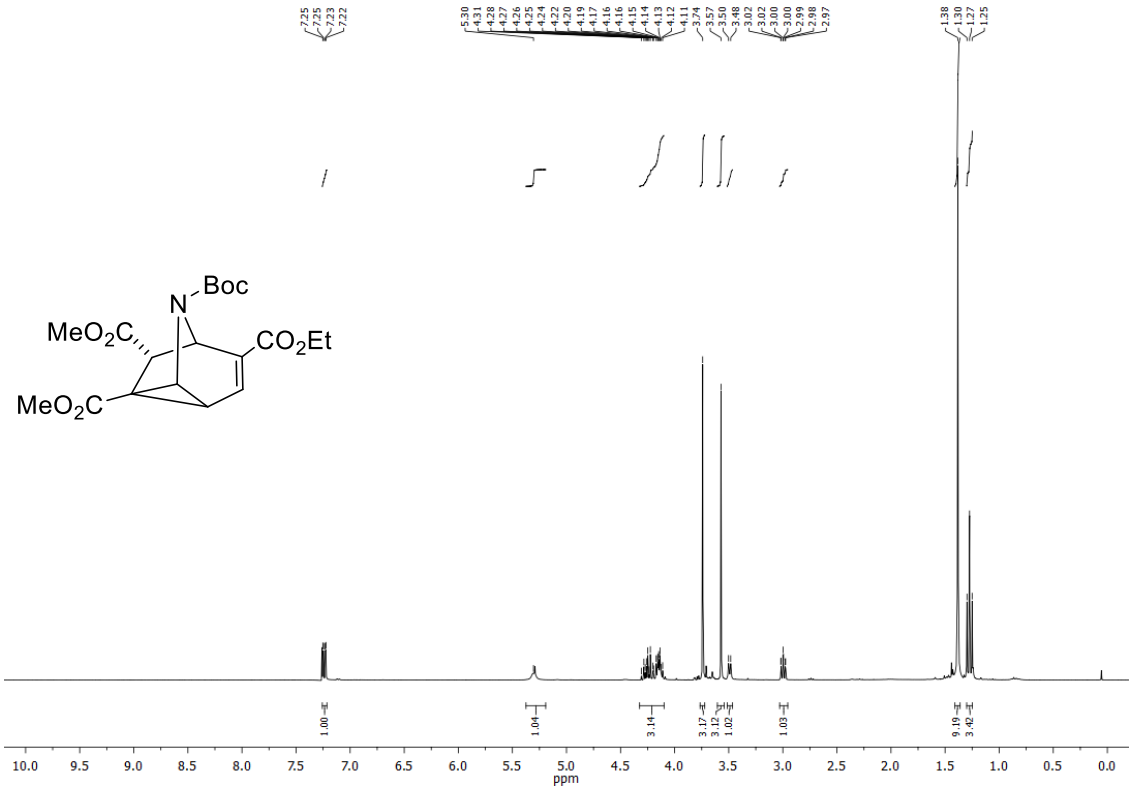


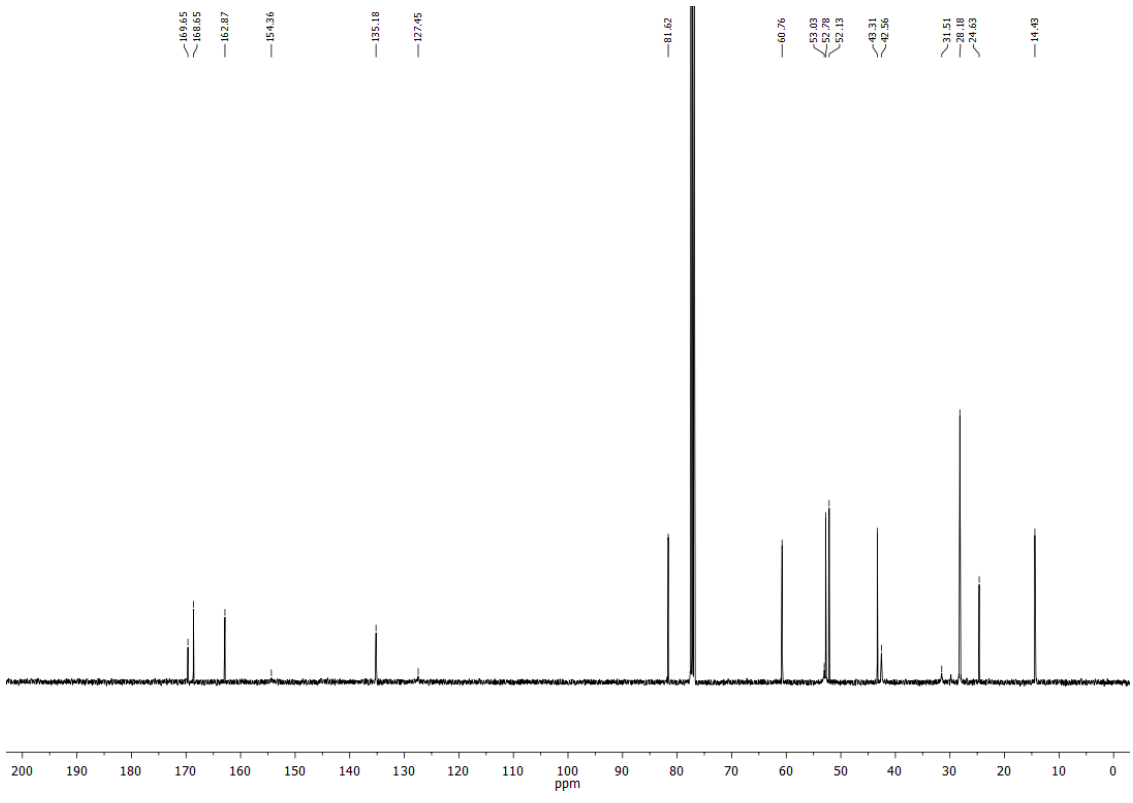
Compound **192**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



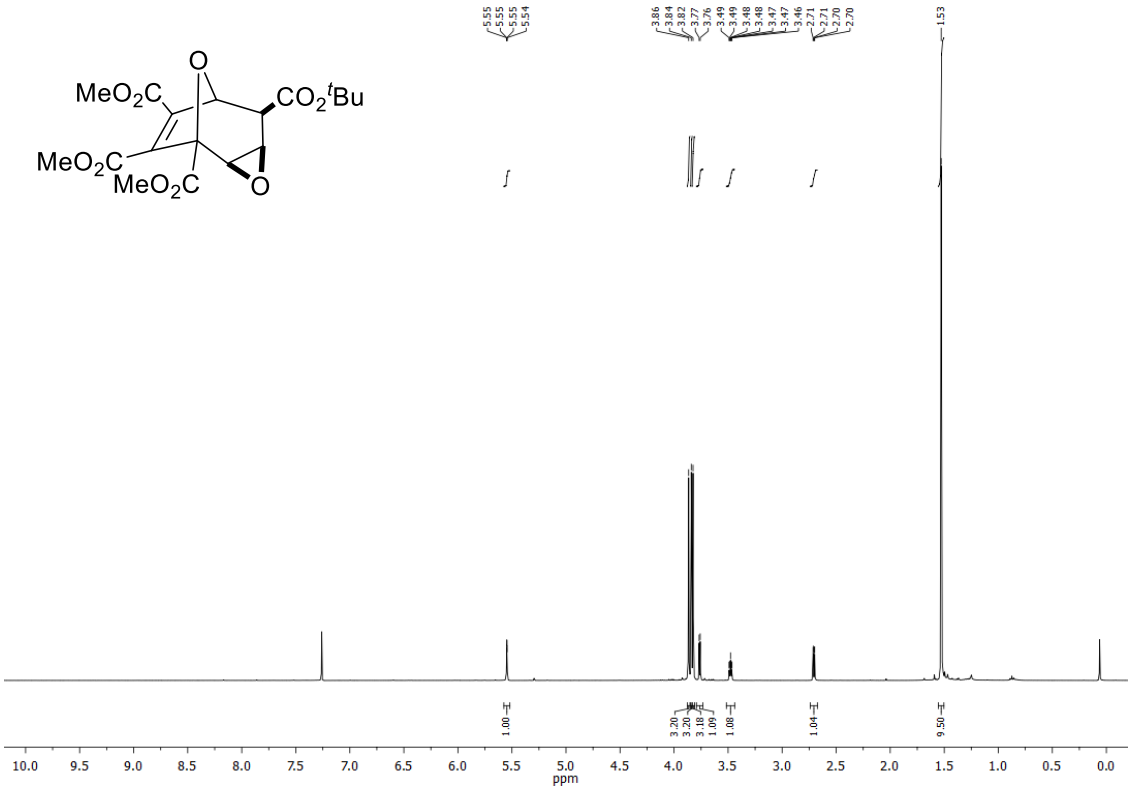


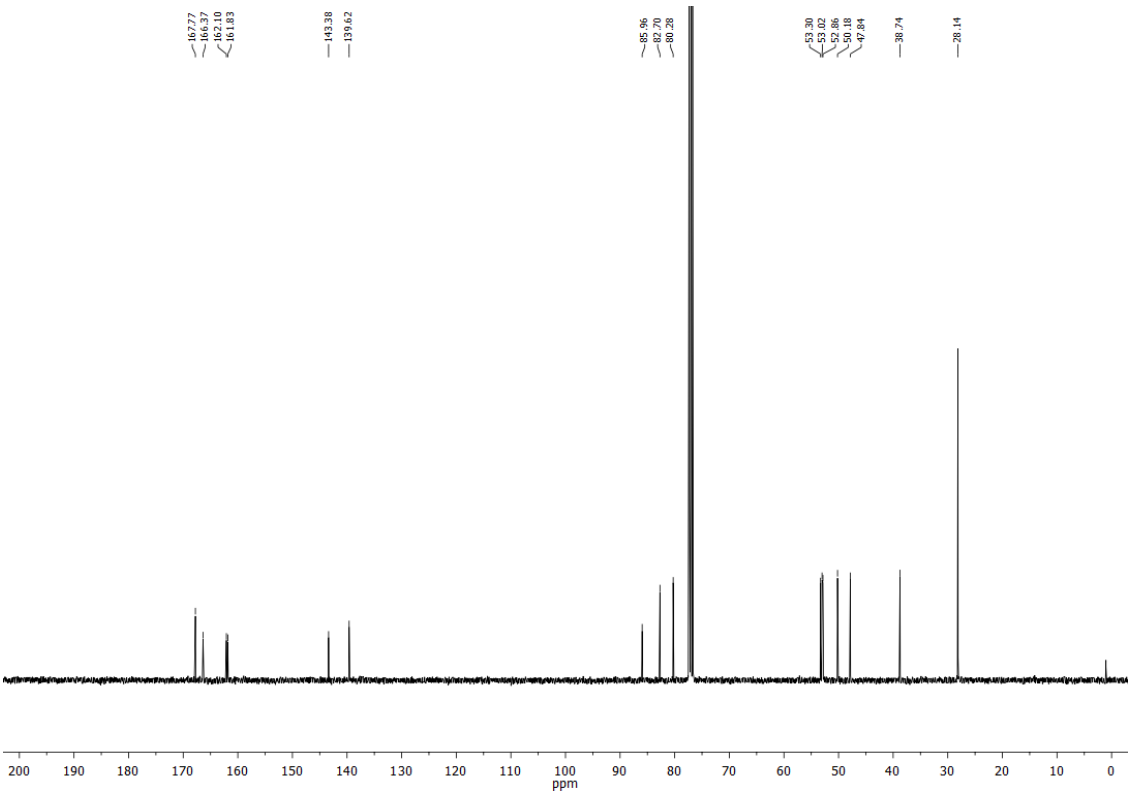
Compound **197**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



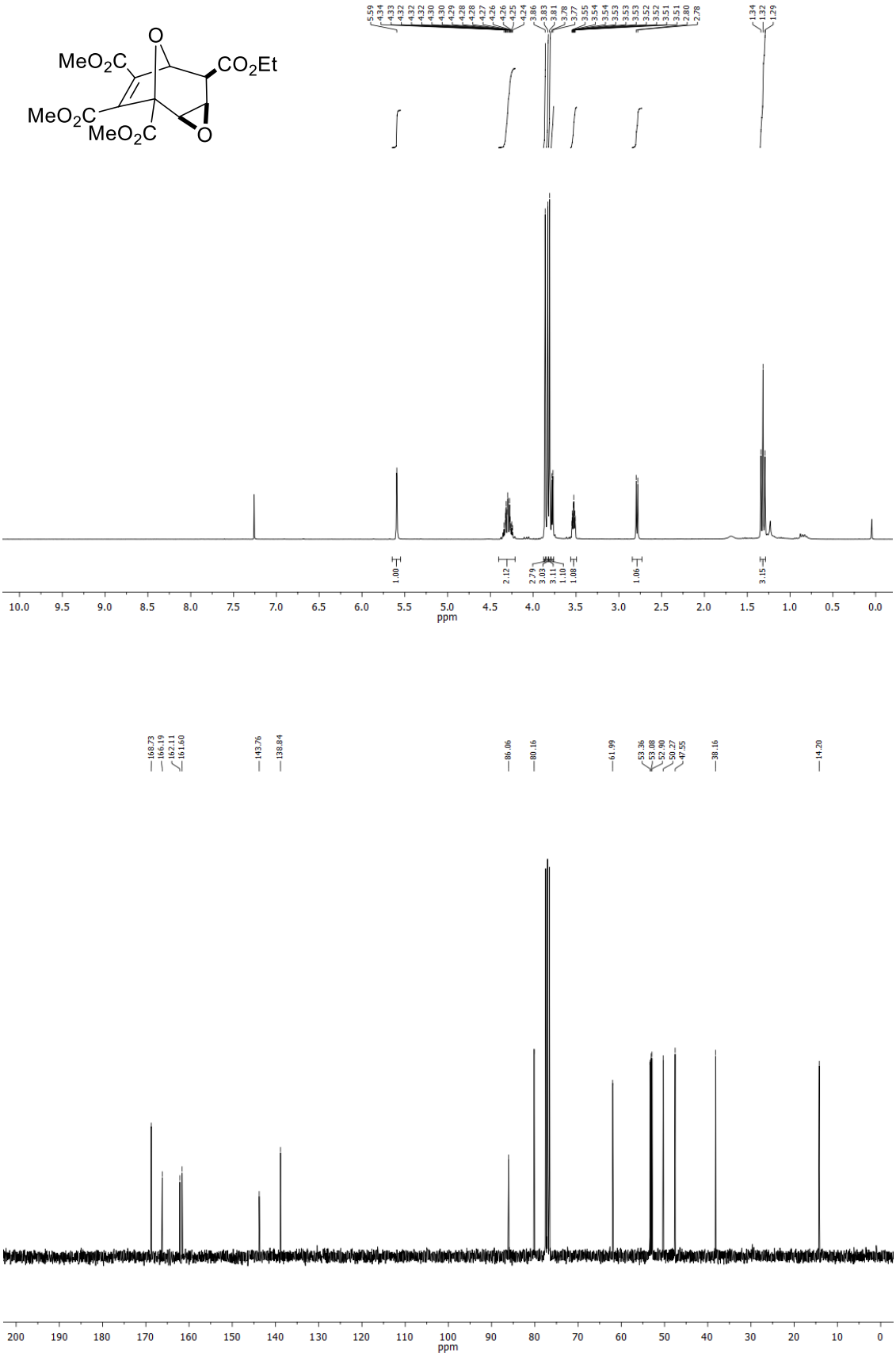


Compound **198b**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

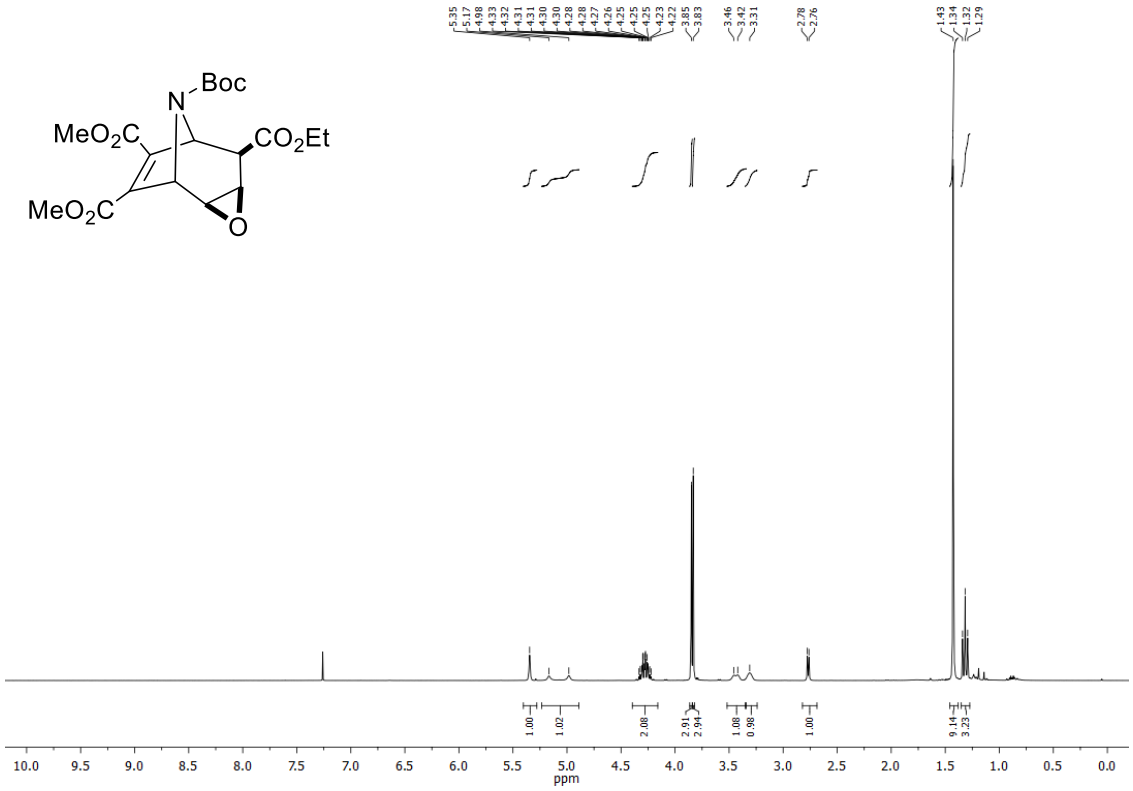


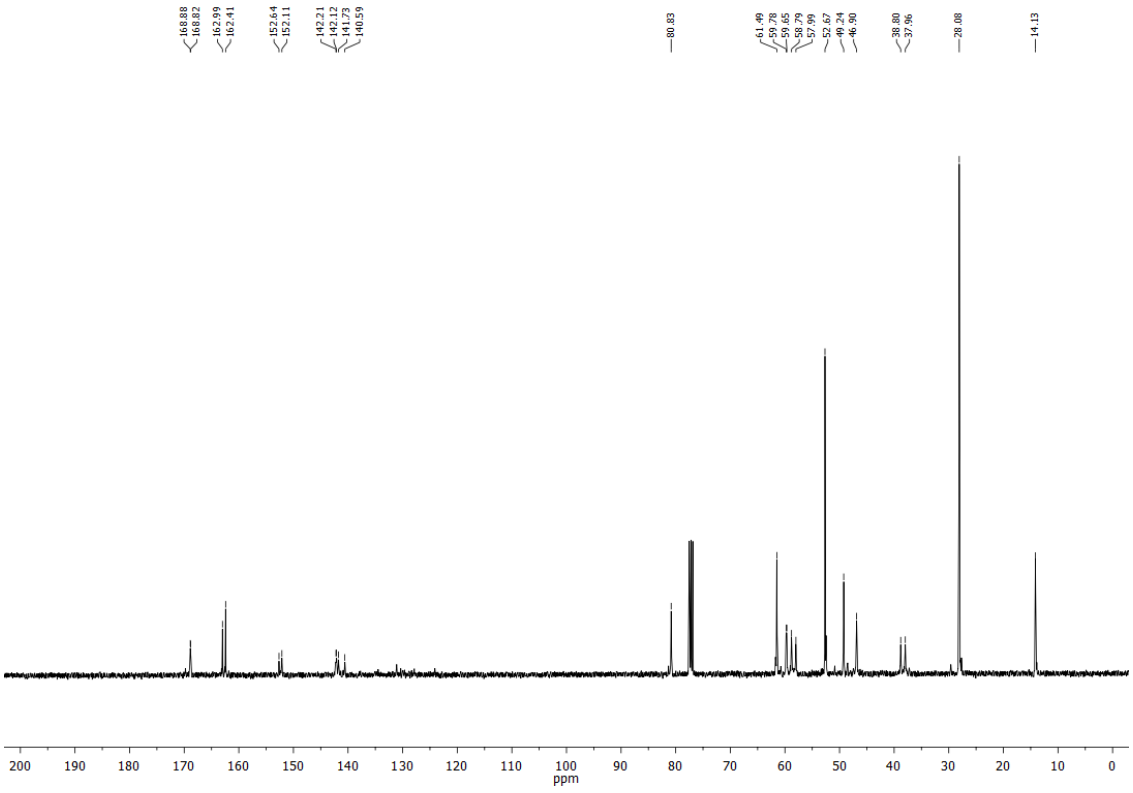


Compound **198a**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):

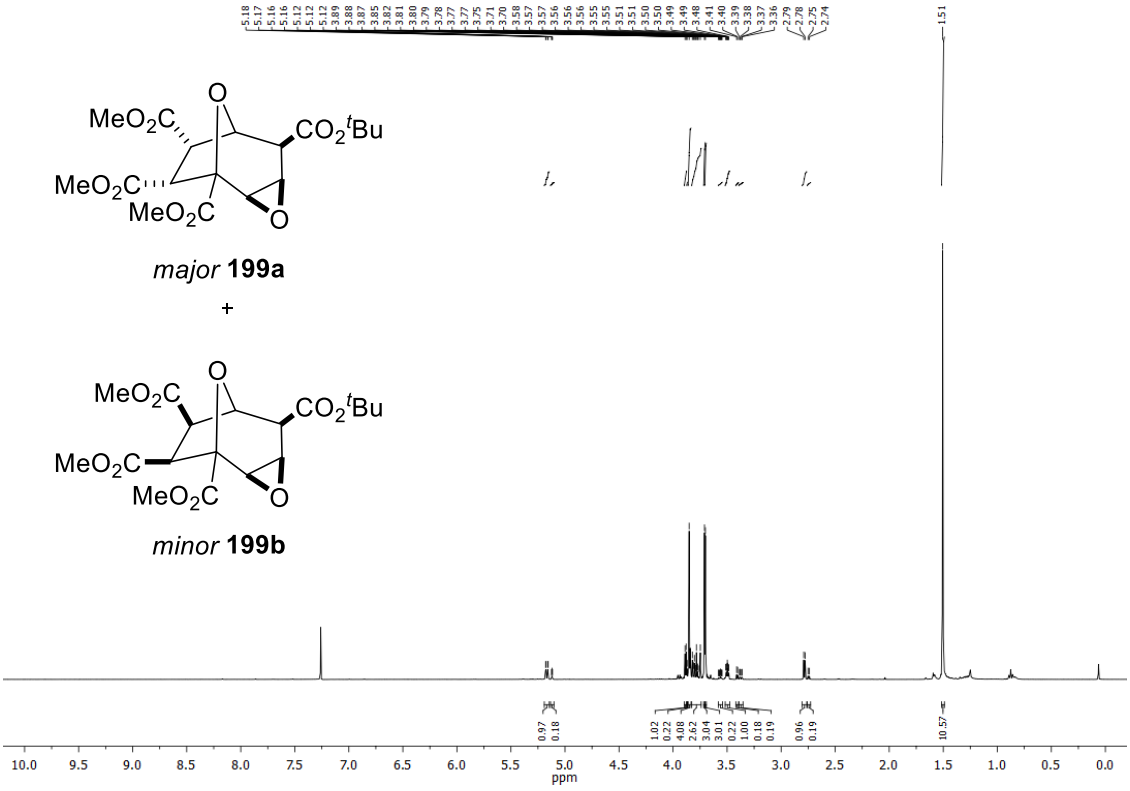


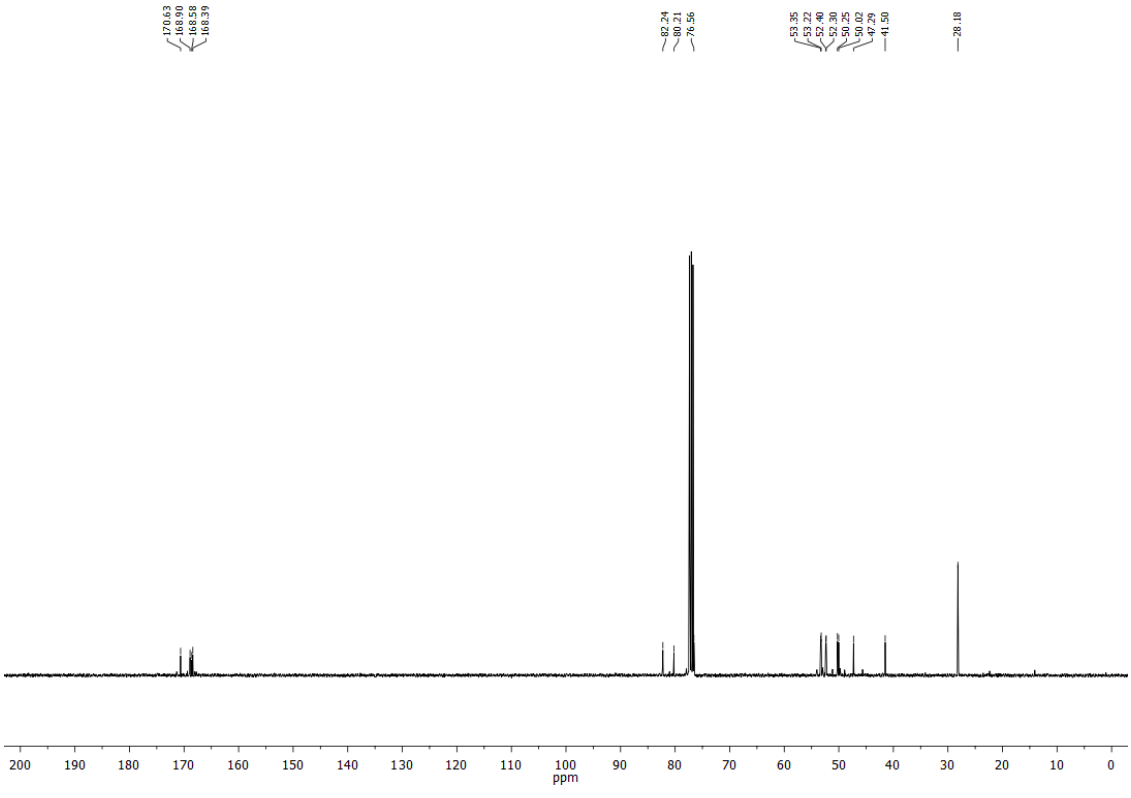
Compound **187**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



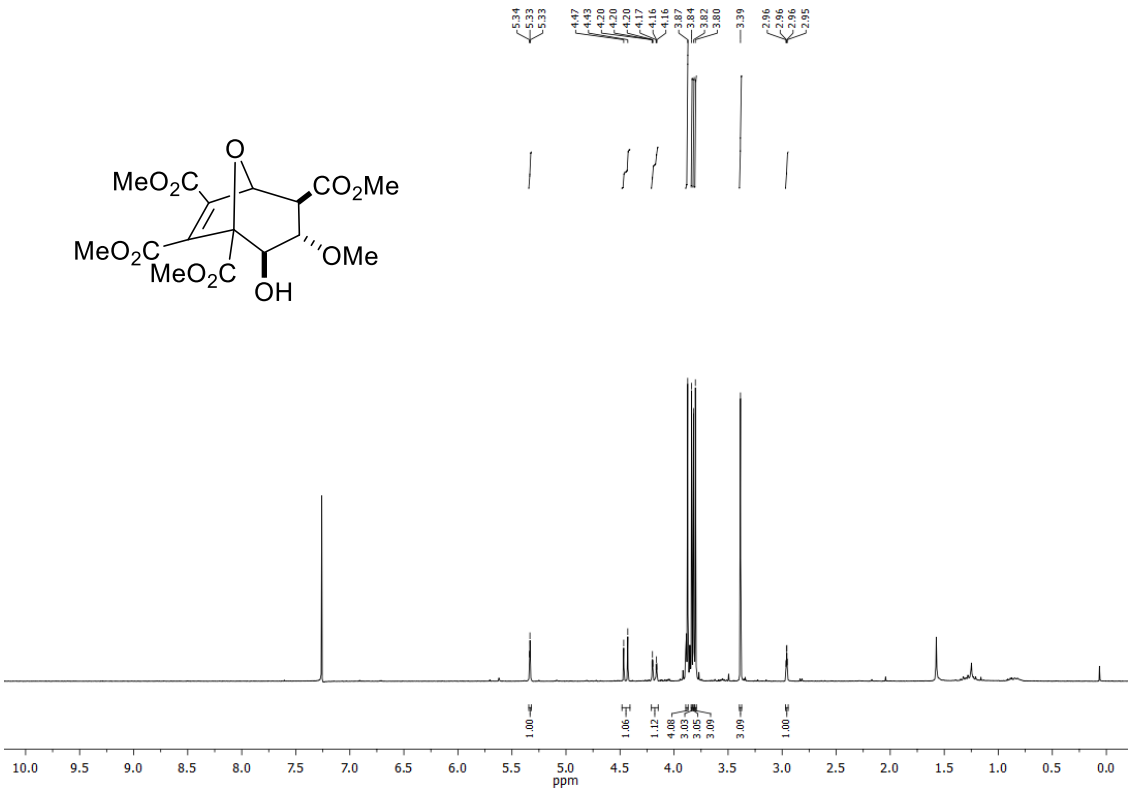


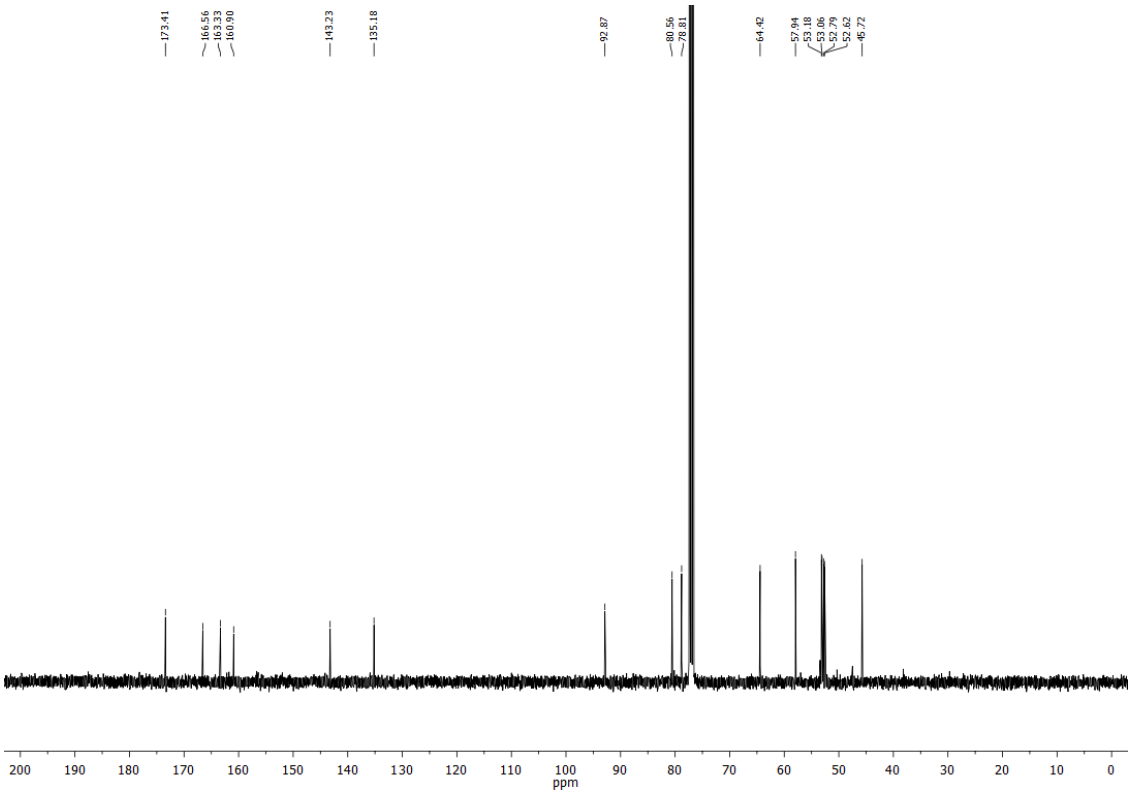
Compound **199**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



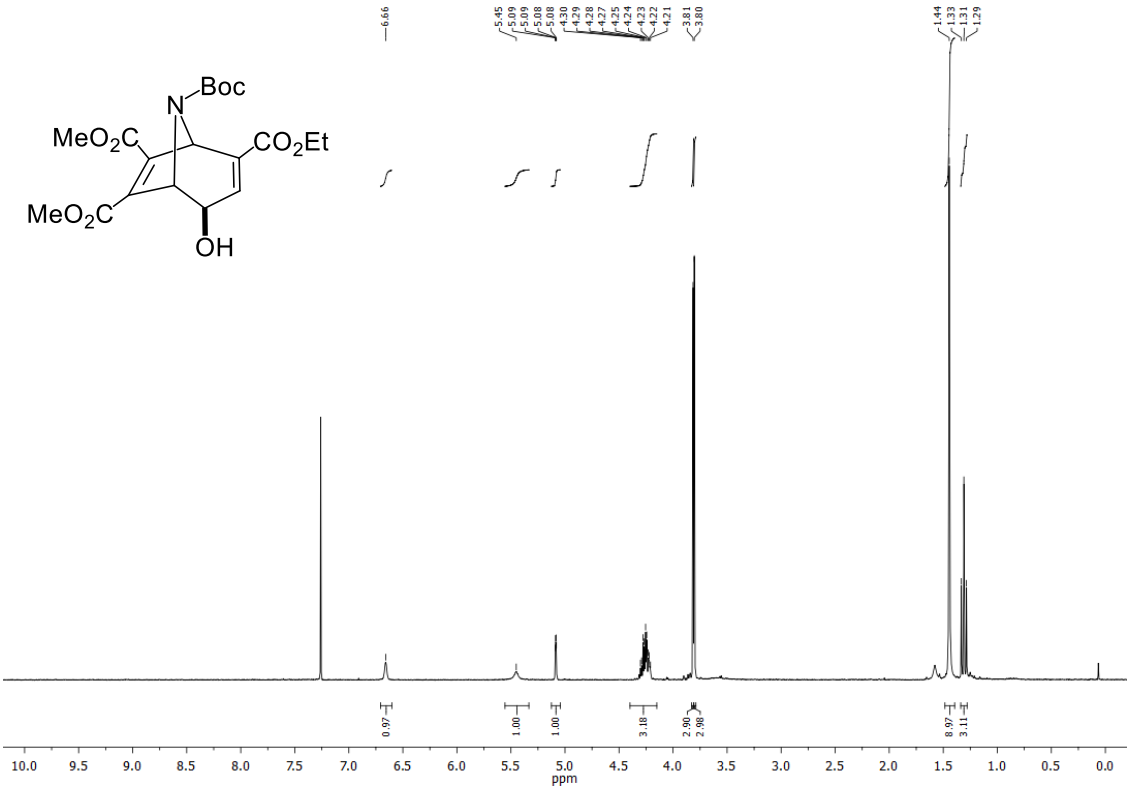


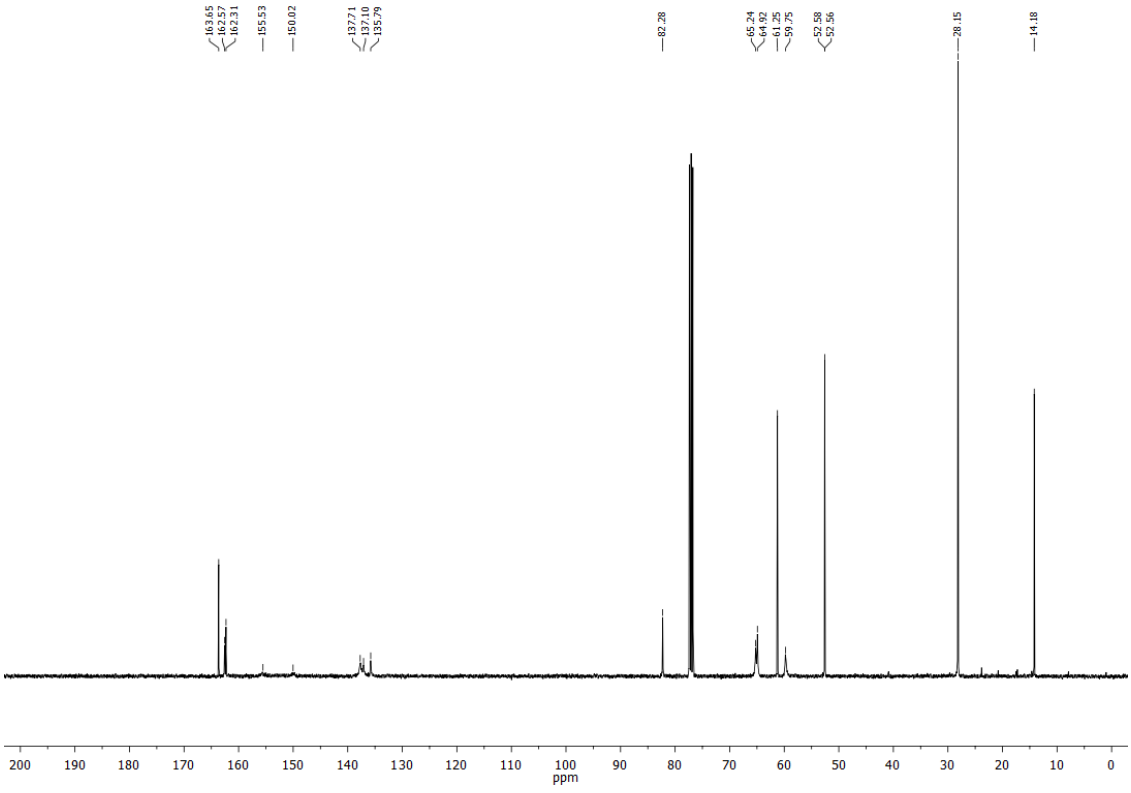
Compound **201**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



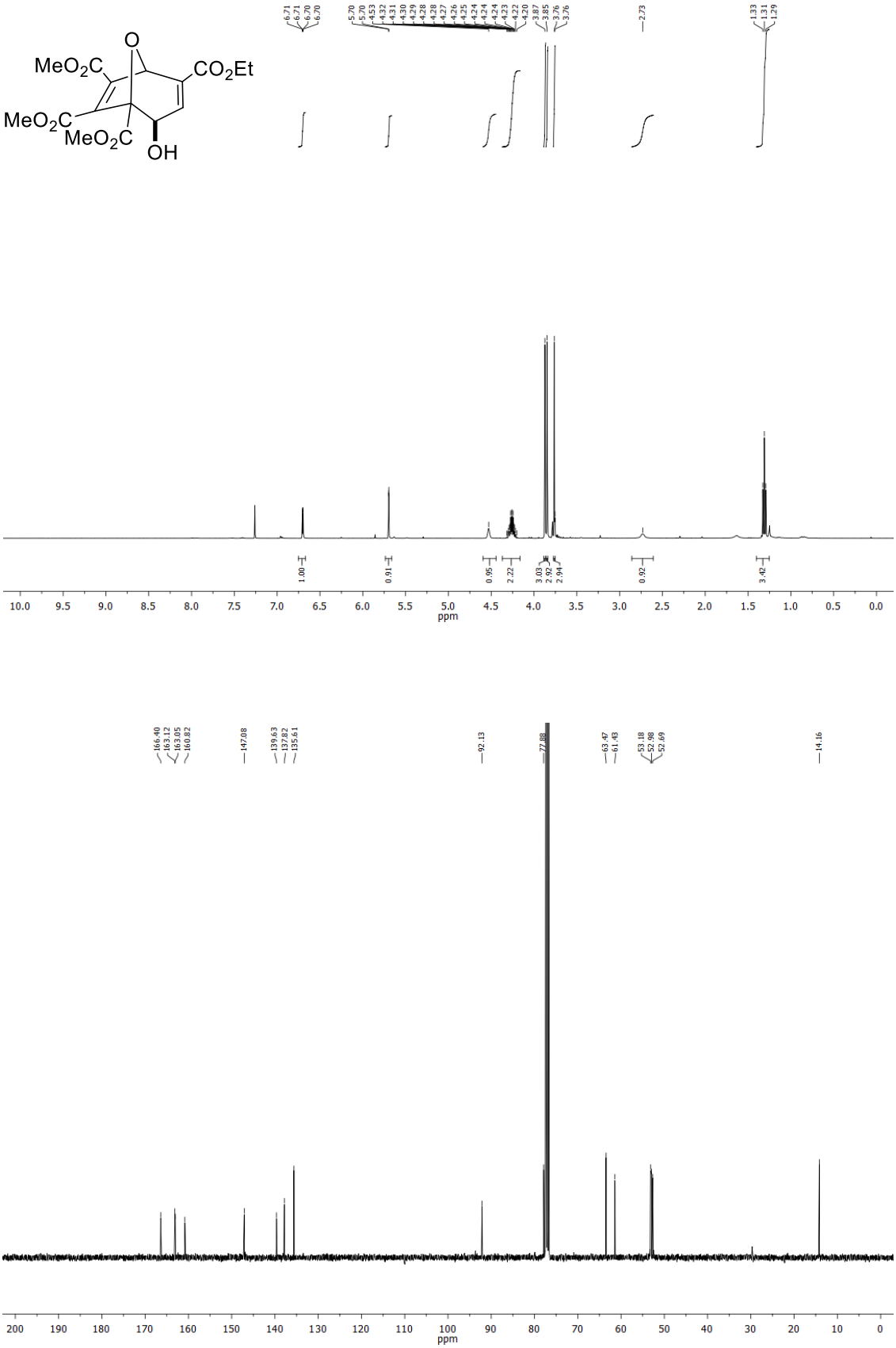


Compound **205**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

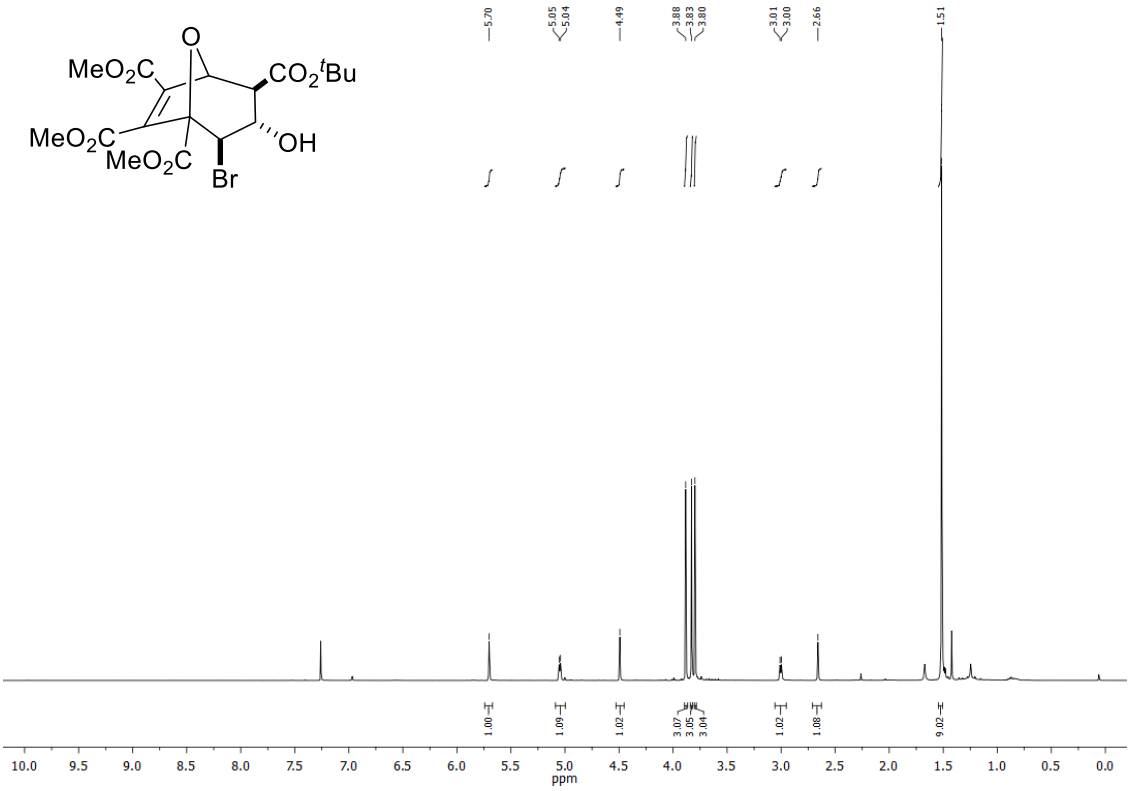


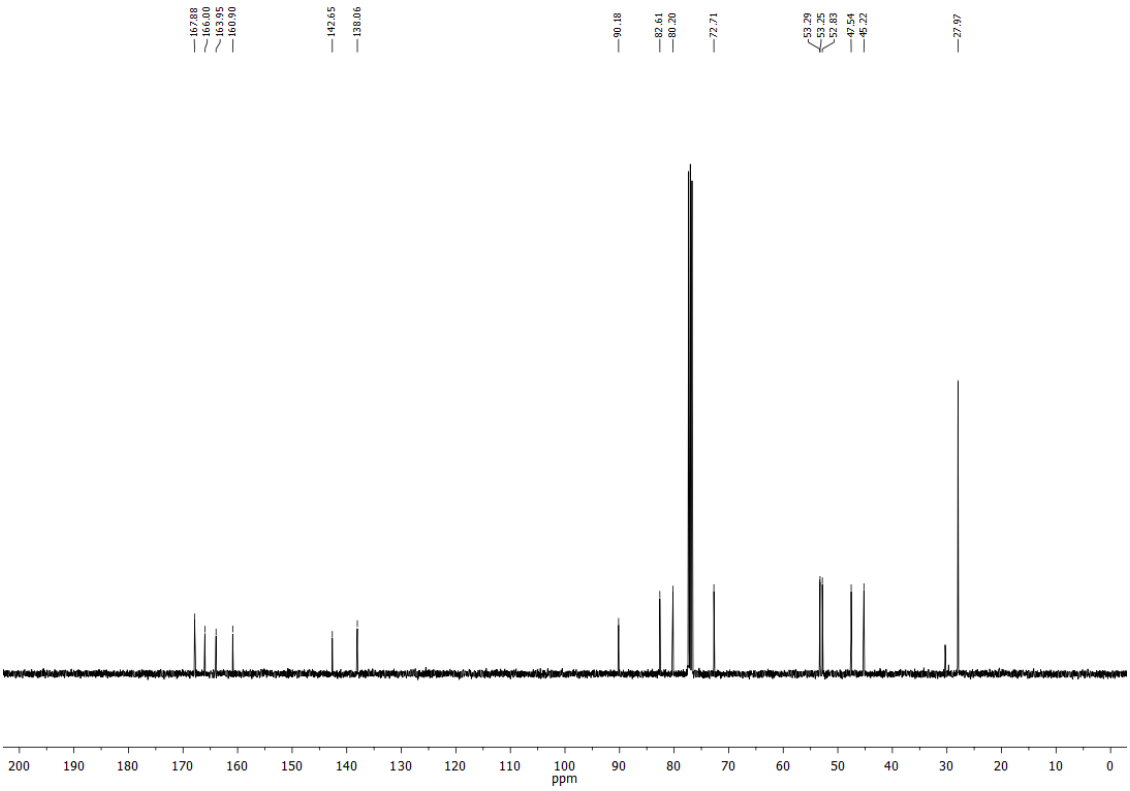


Compound **206**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):

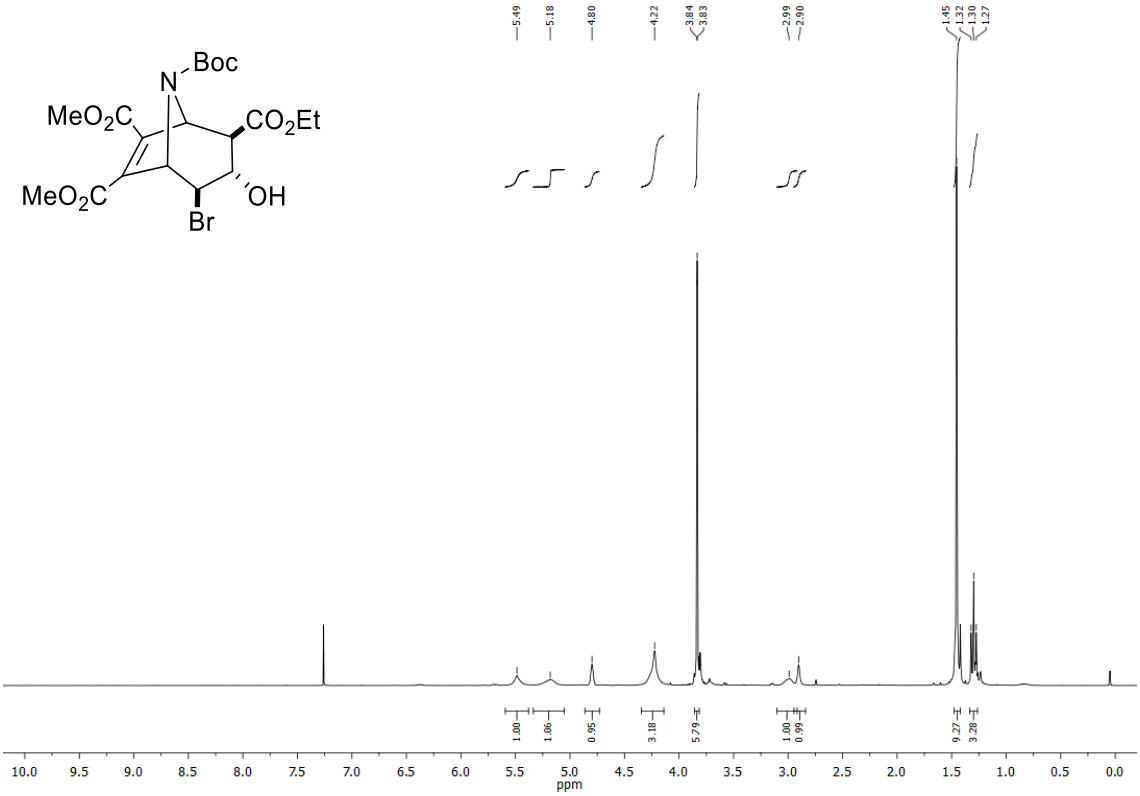


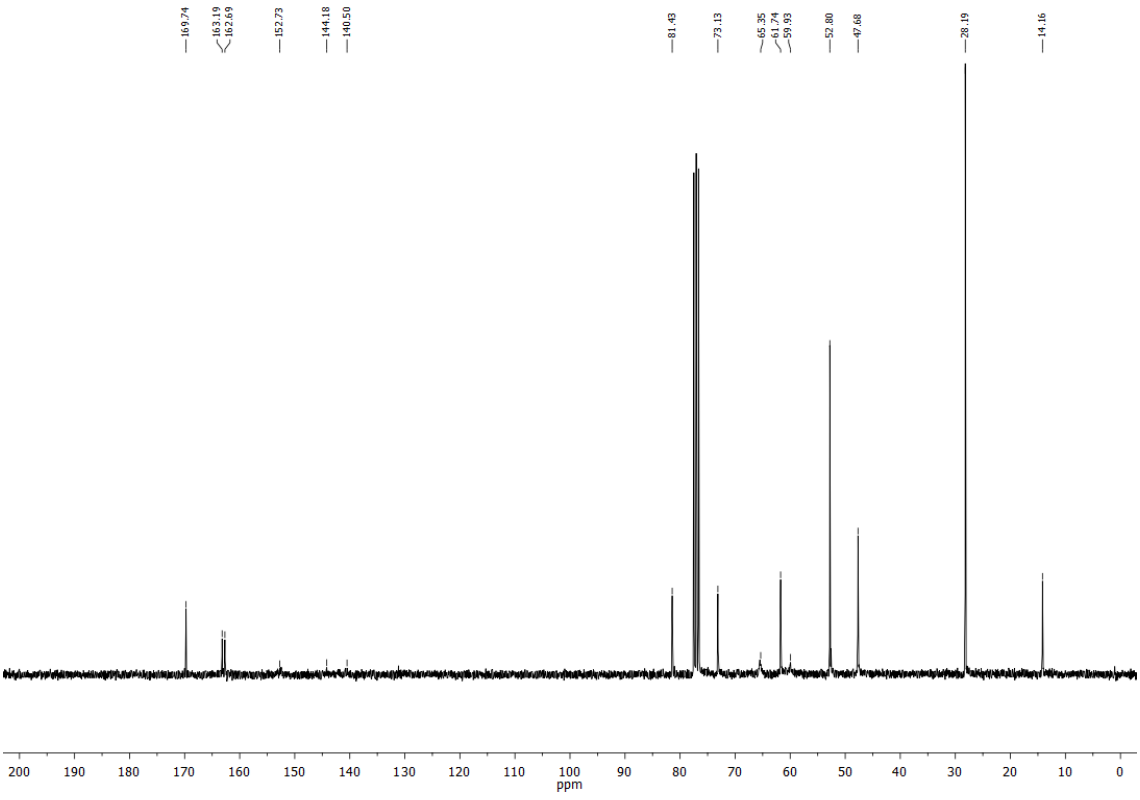
Compound **211**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



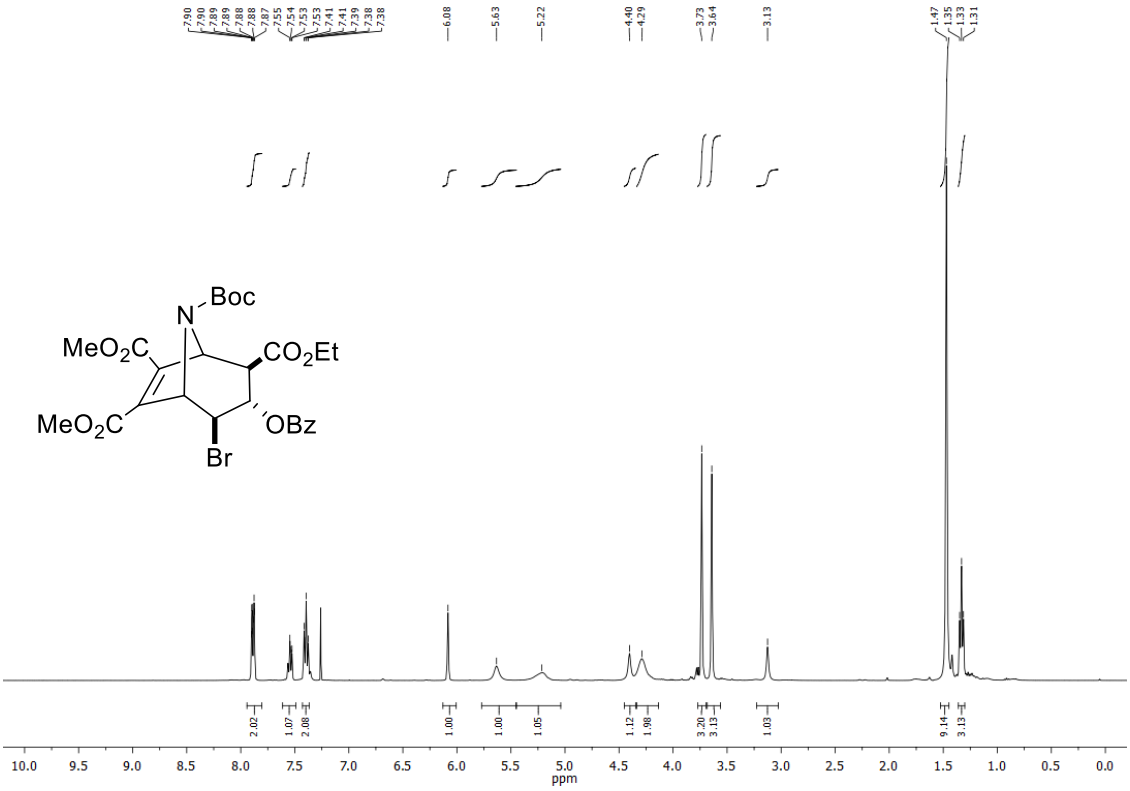


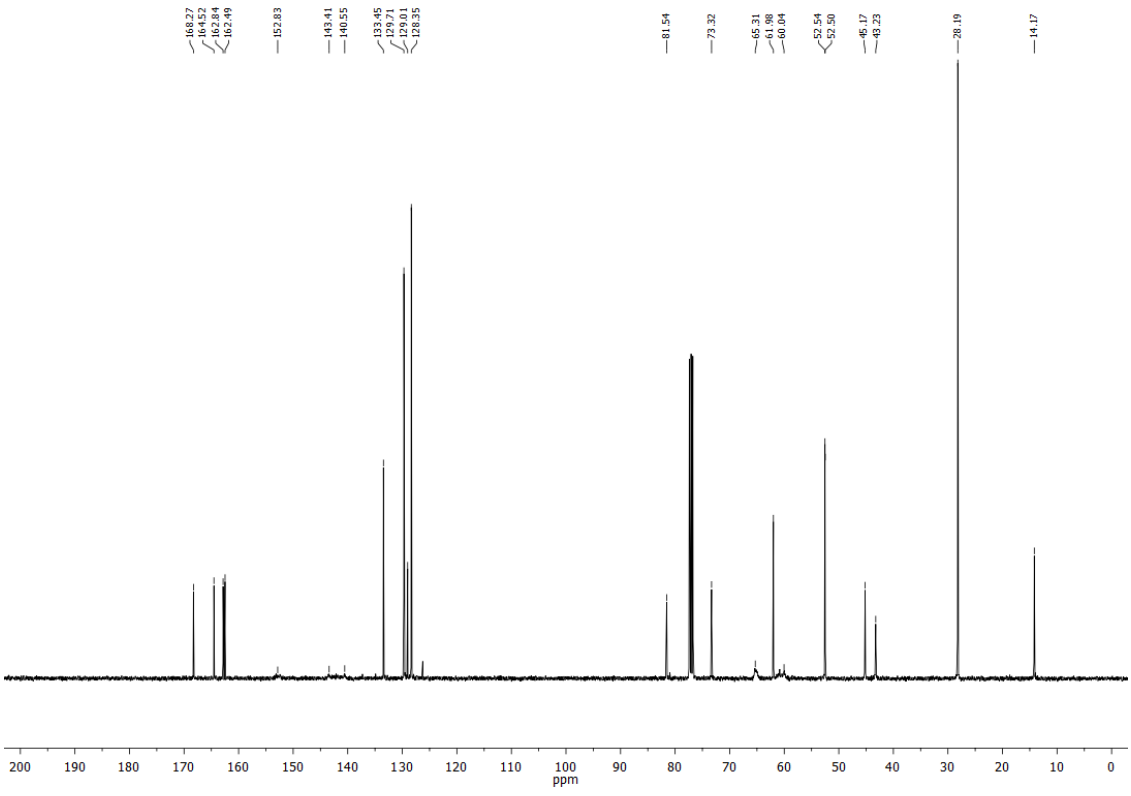
Compound **213**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



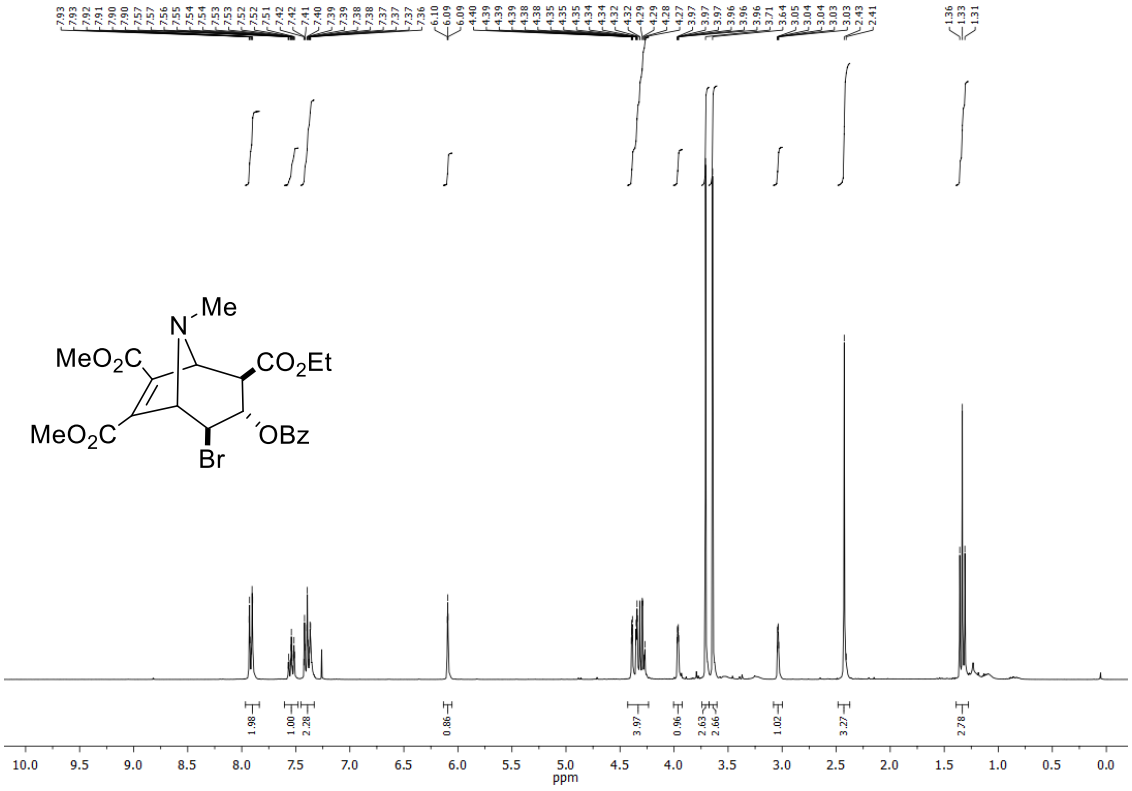


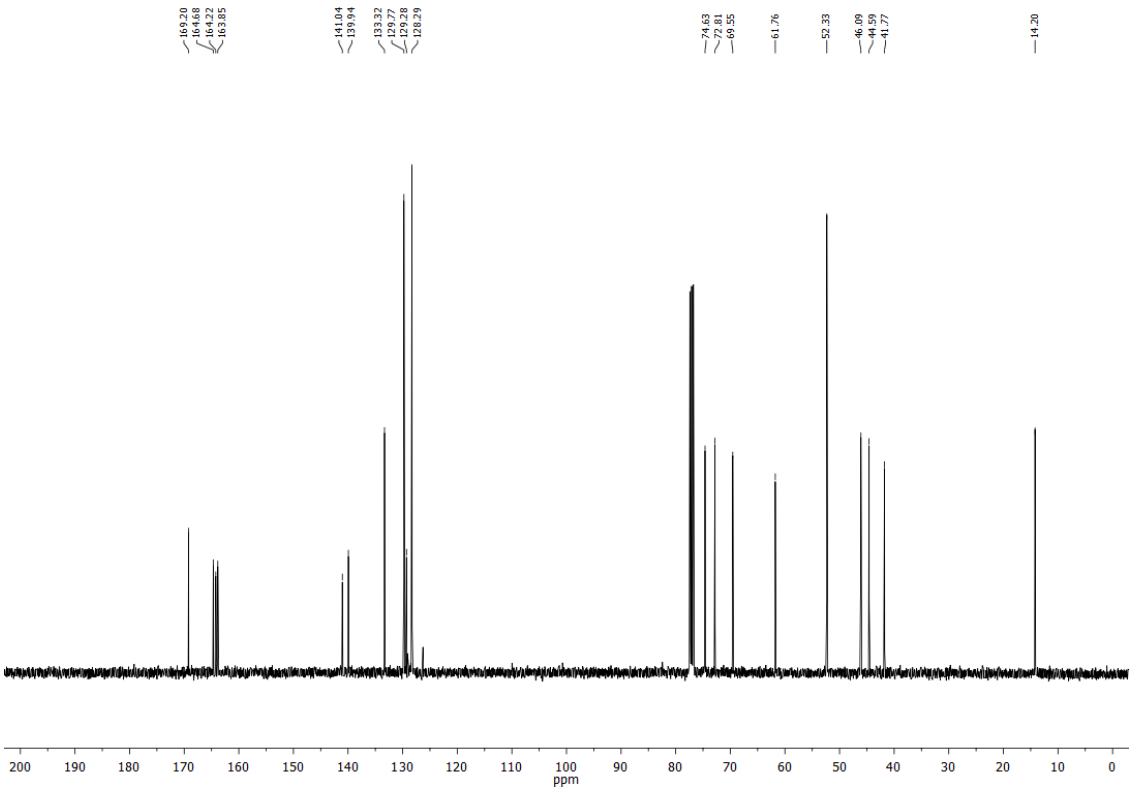
Compound **220**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



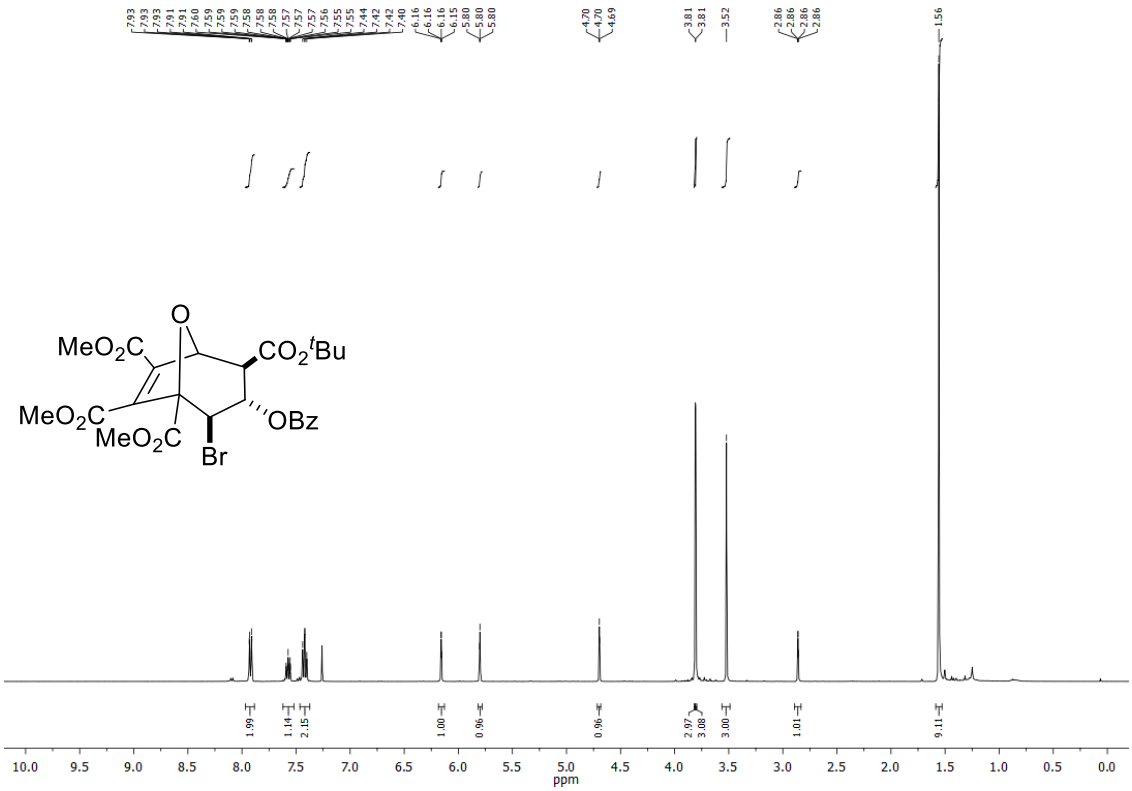


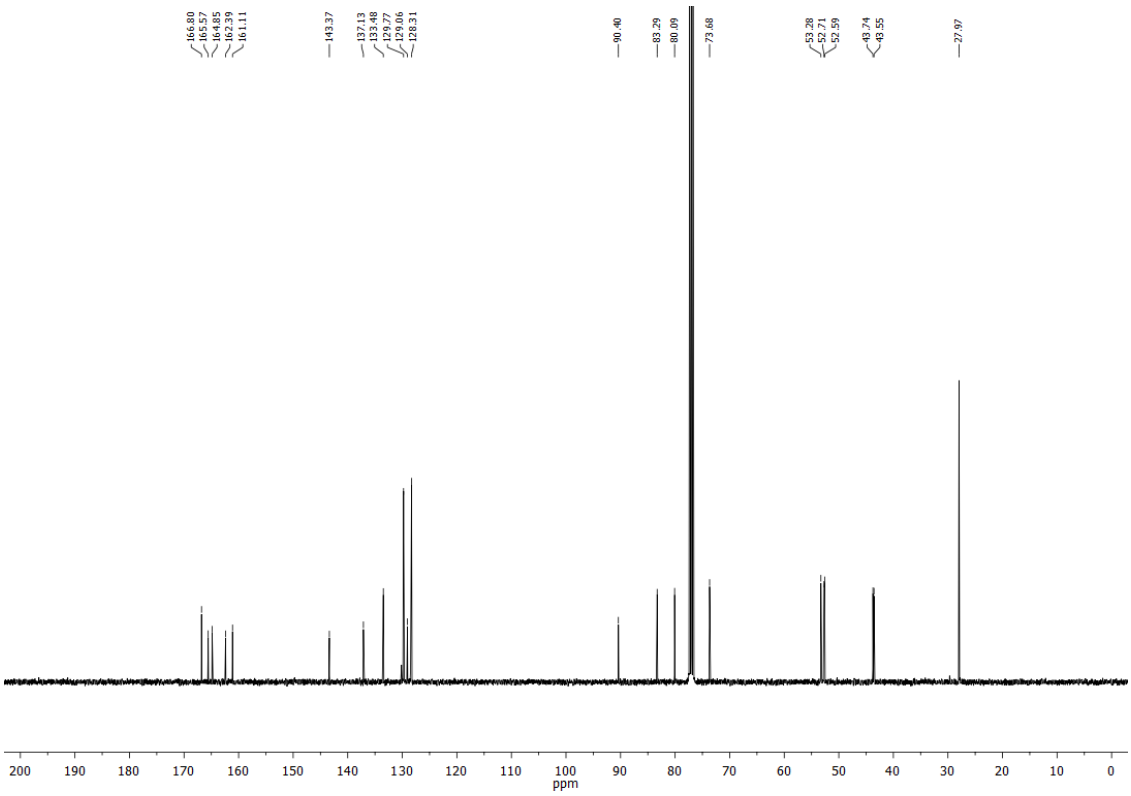
Compound **221**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



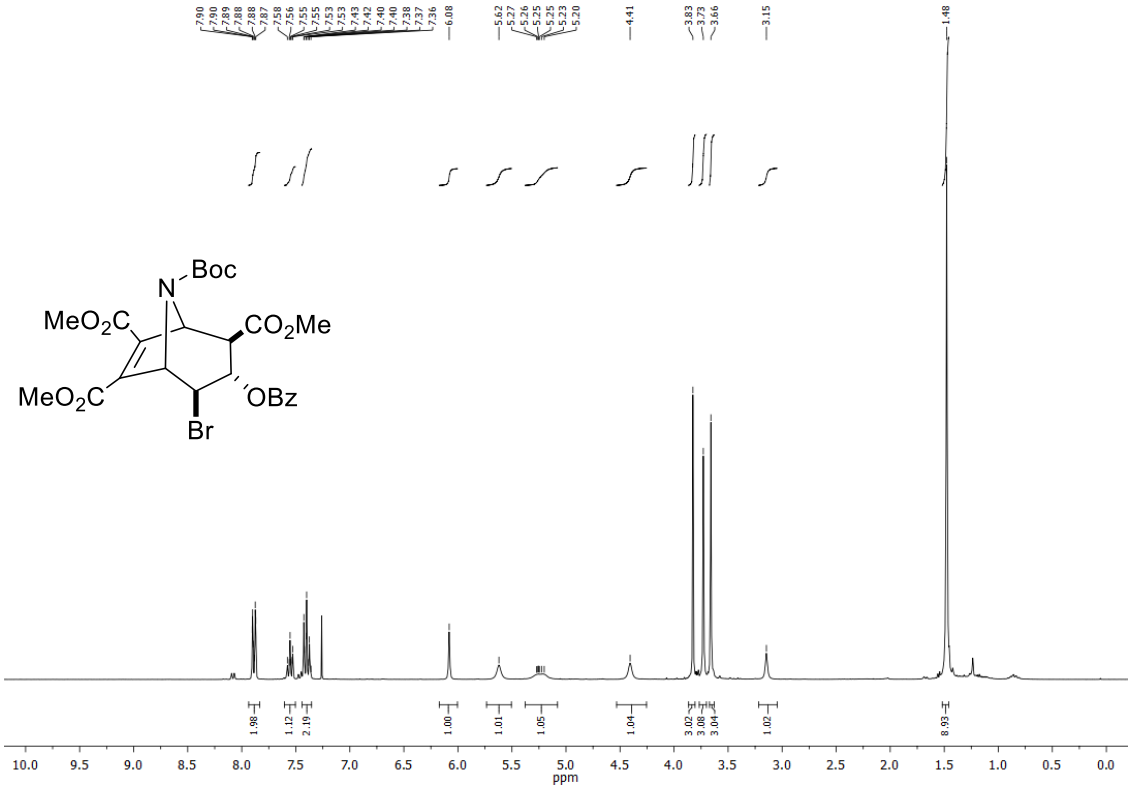


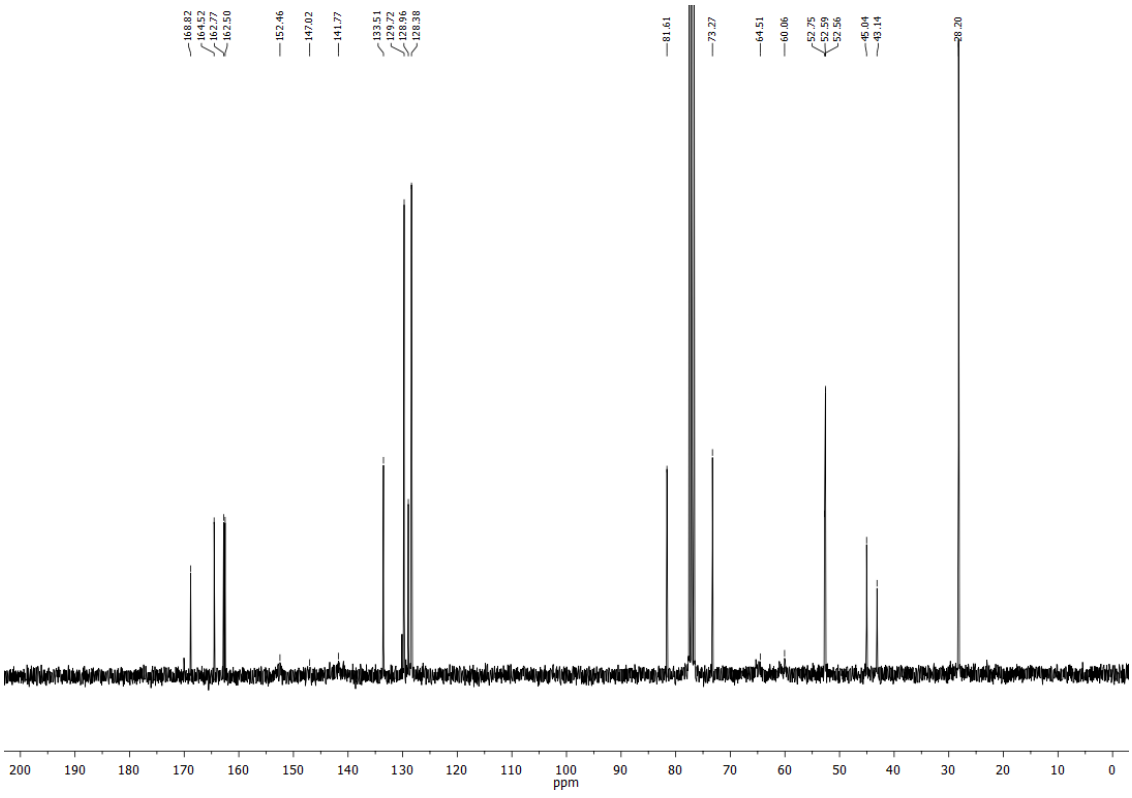
Compound **222**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



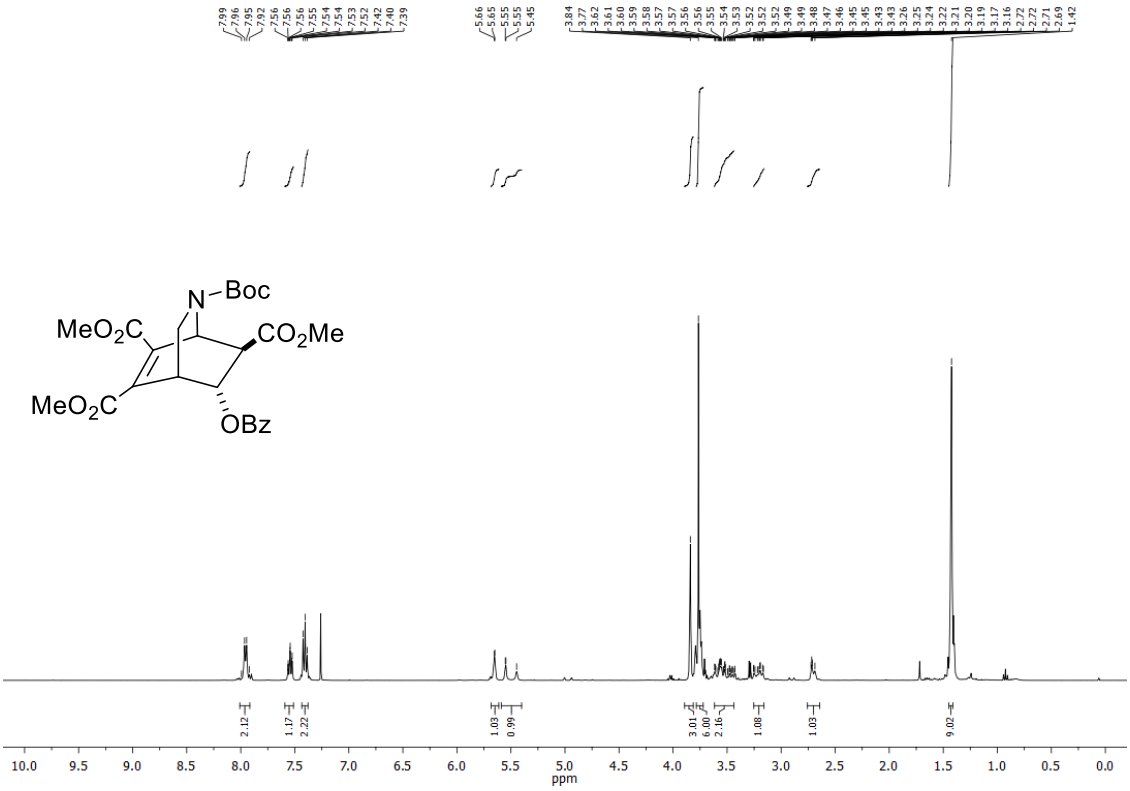


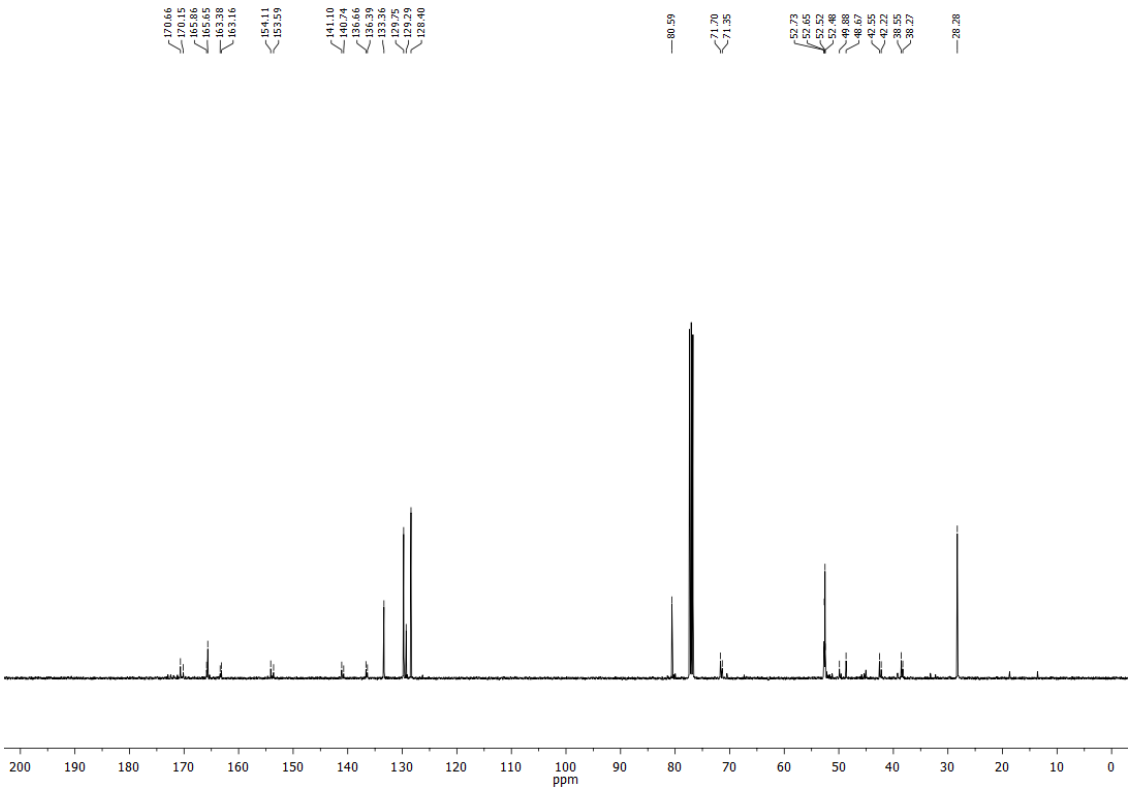
Compound **227**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$):



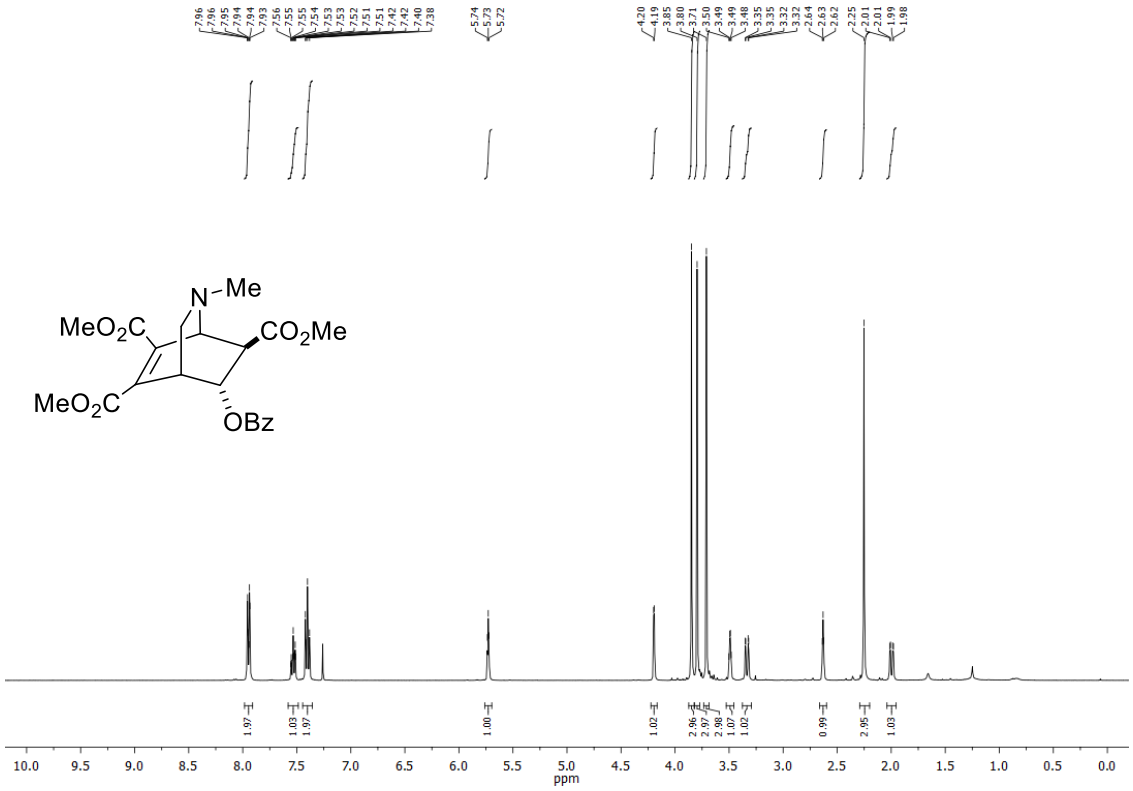


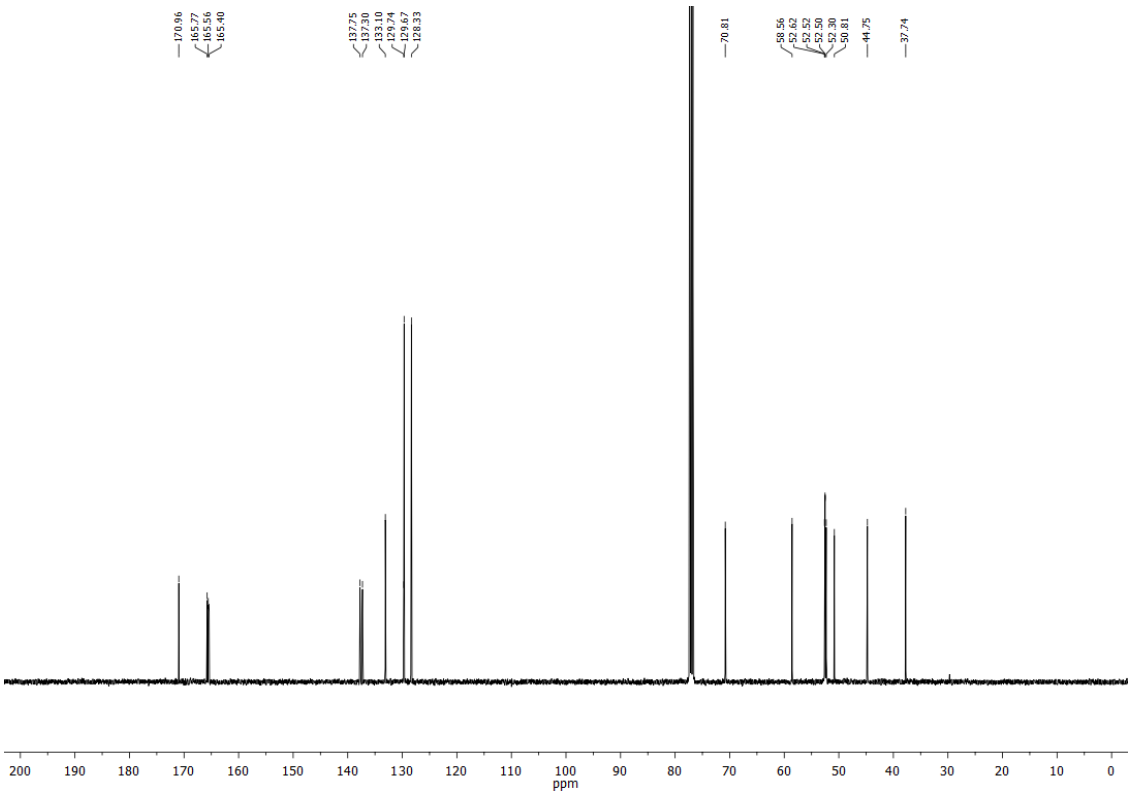
Compound **228**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



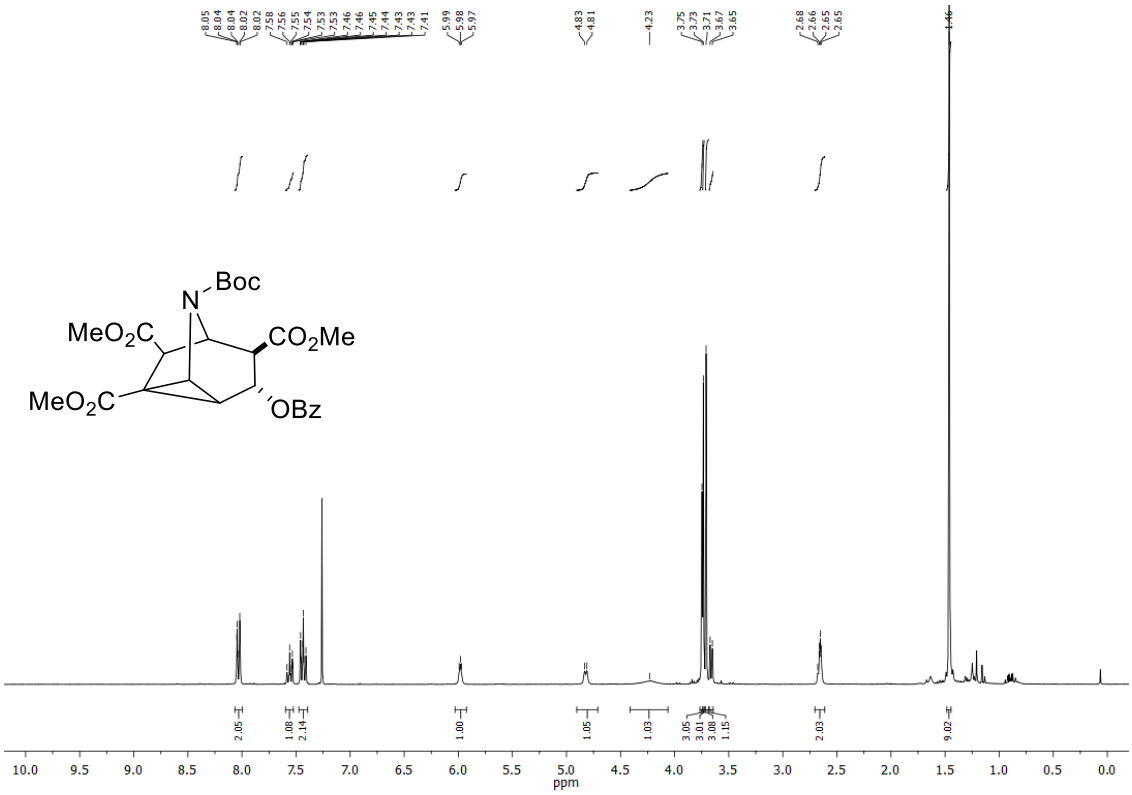


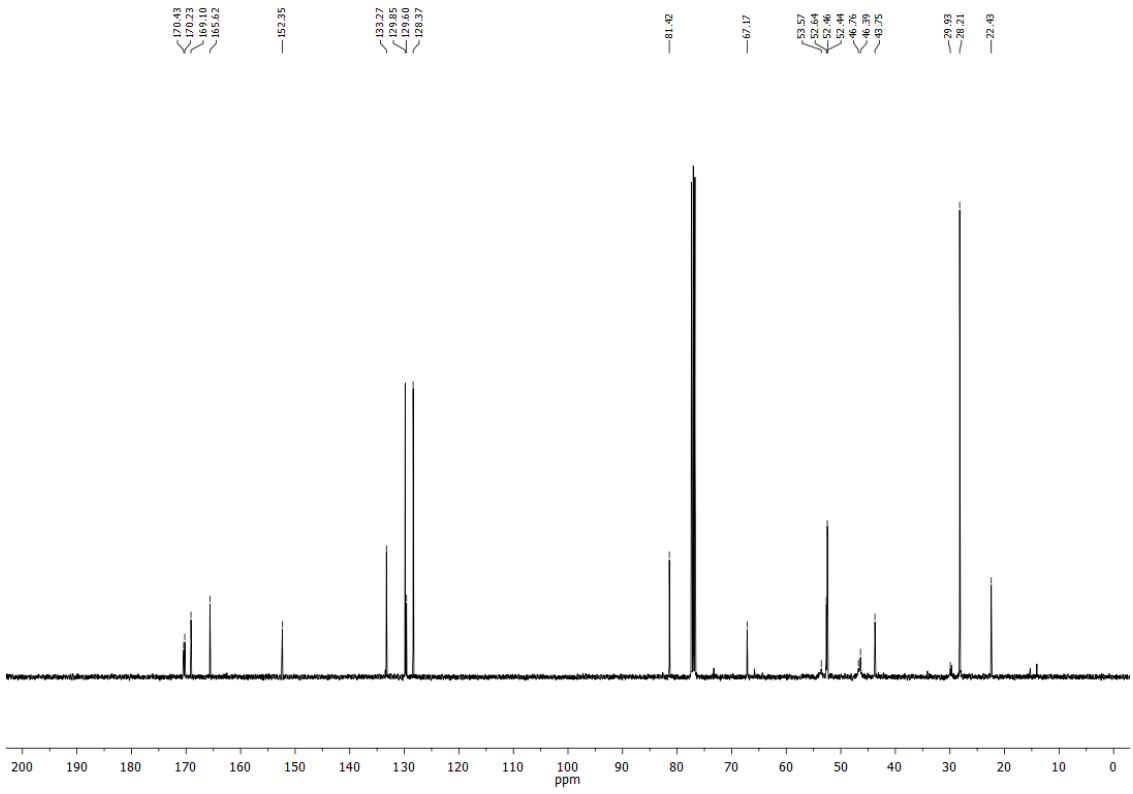
Compound **229**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



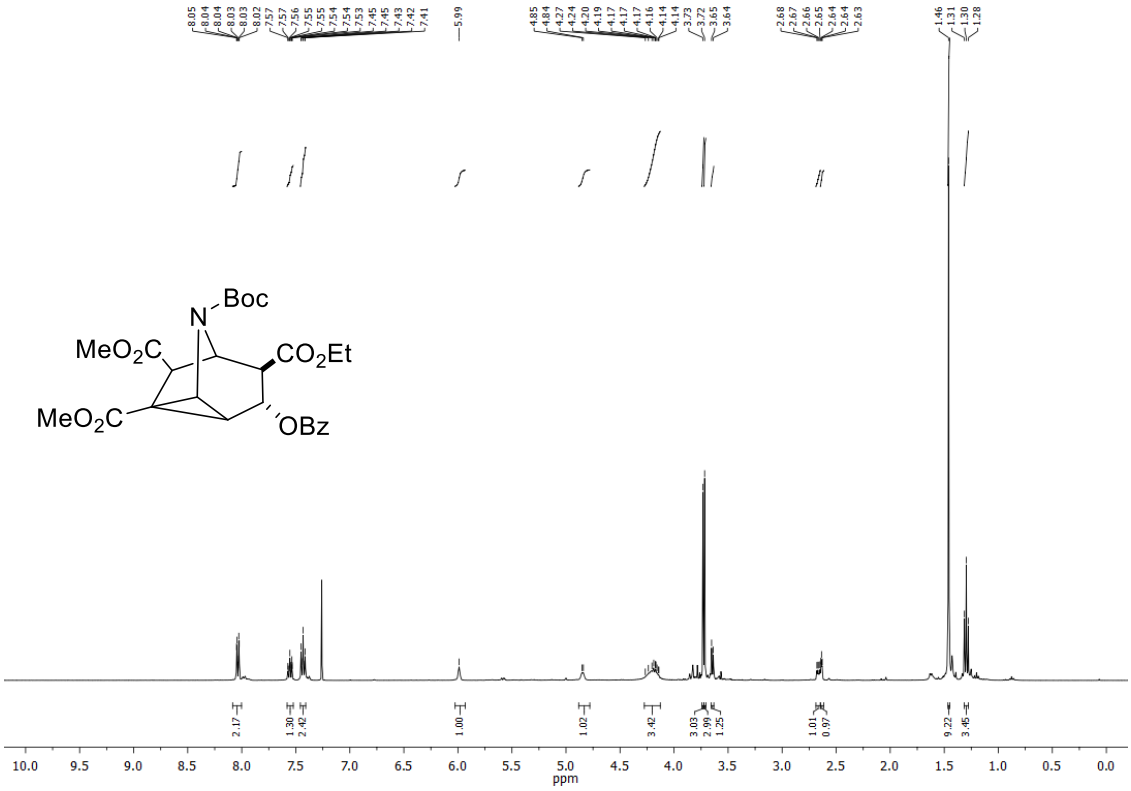


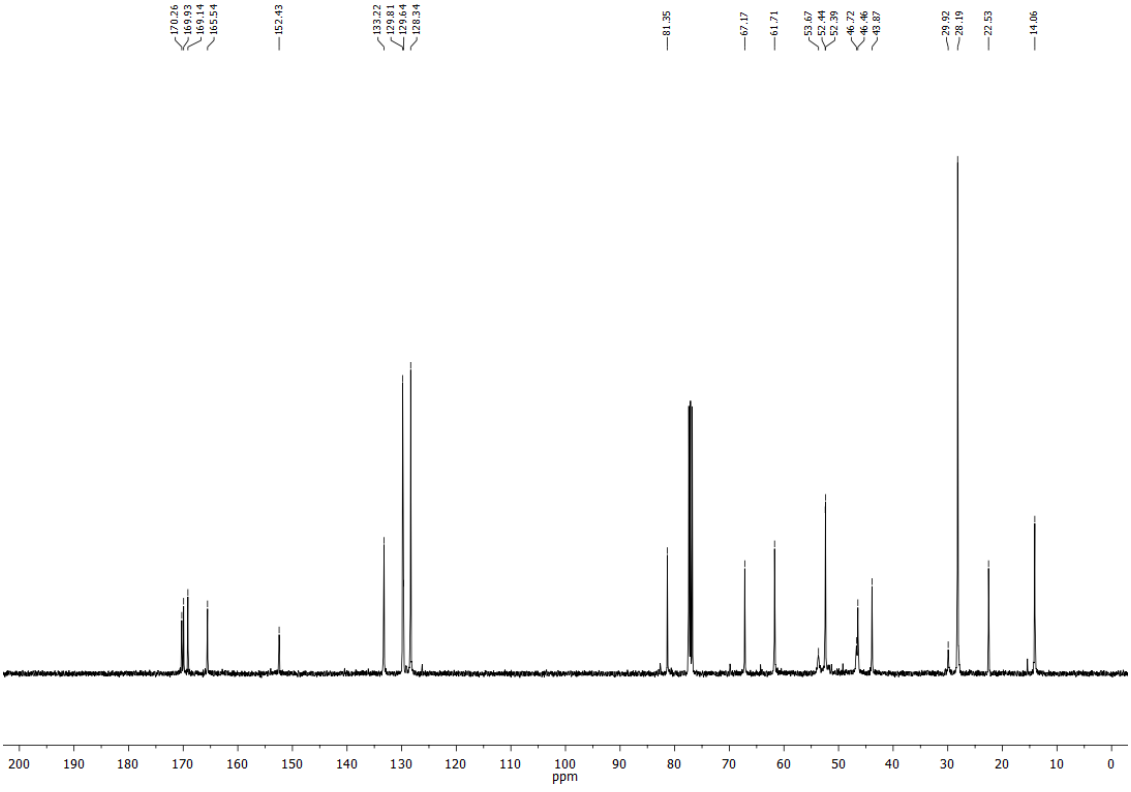
Compound **235a**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



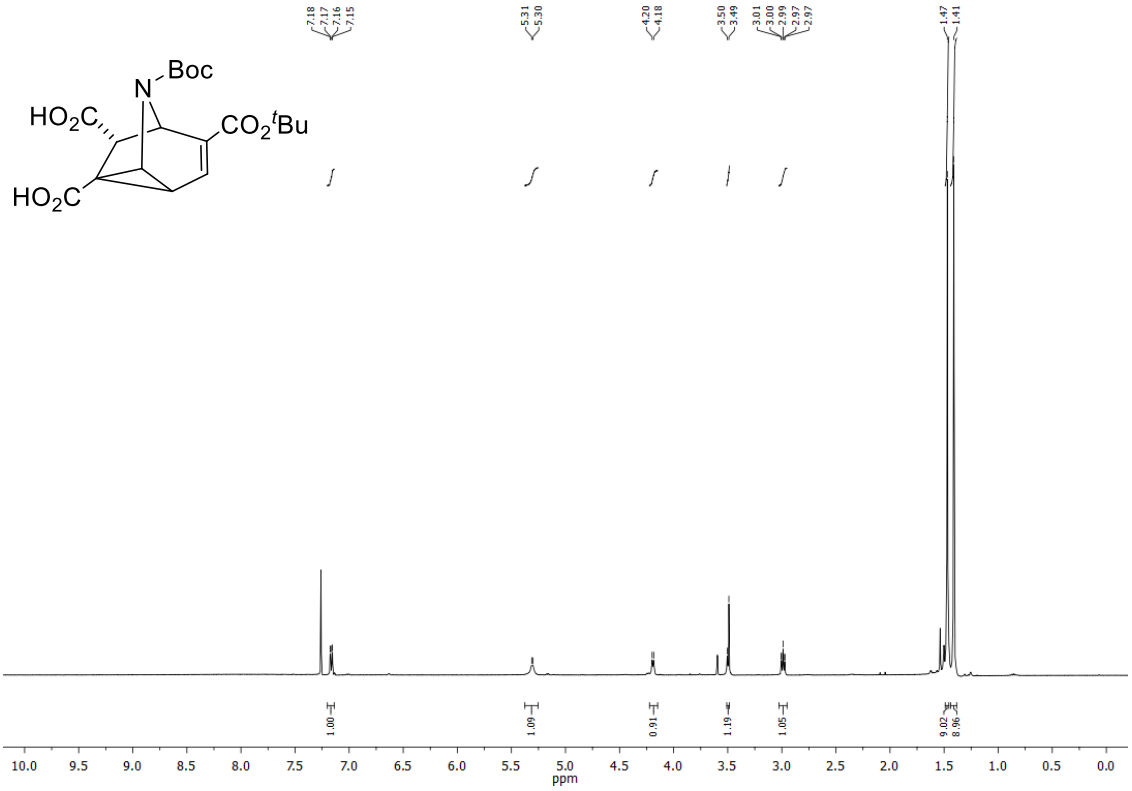


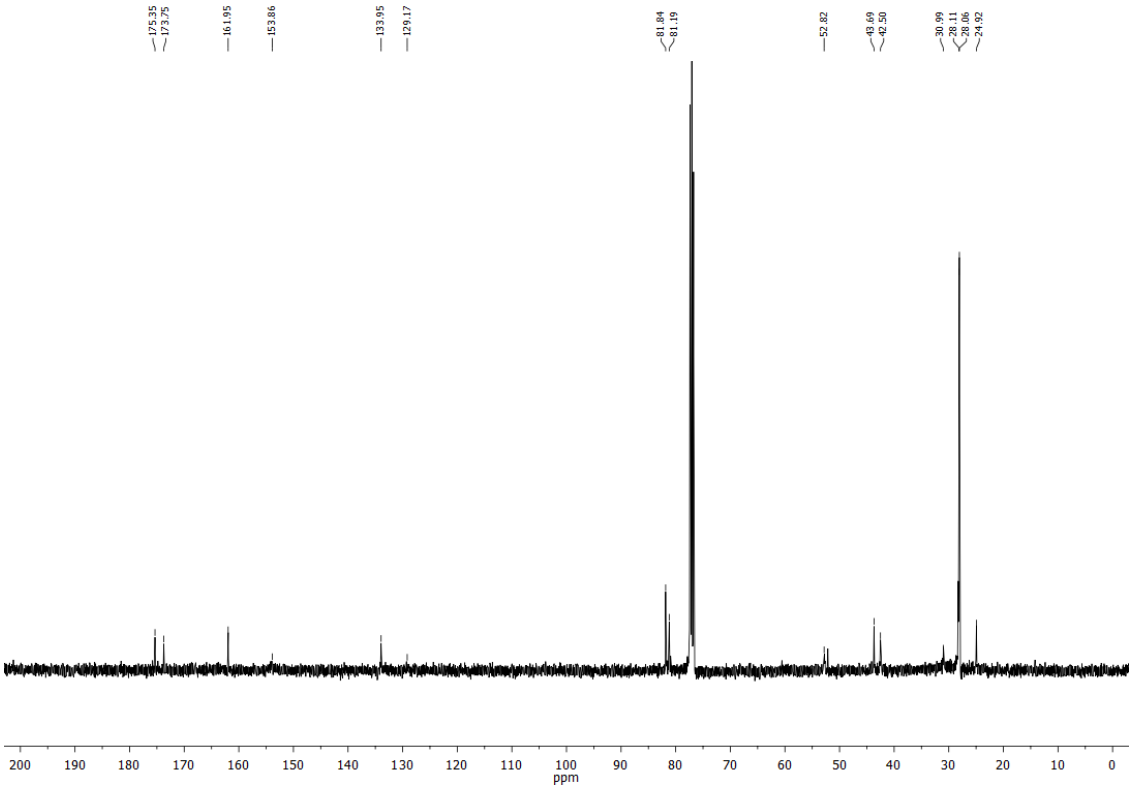
Compound **235b**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



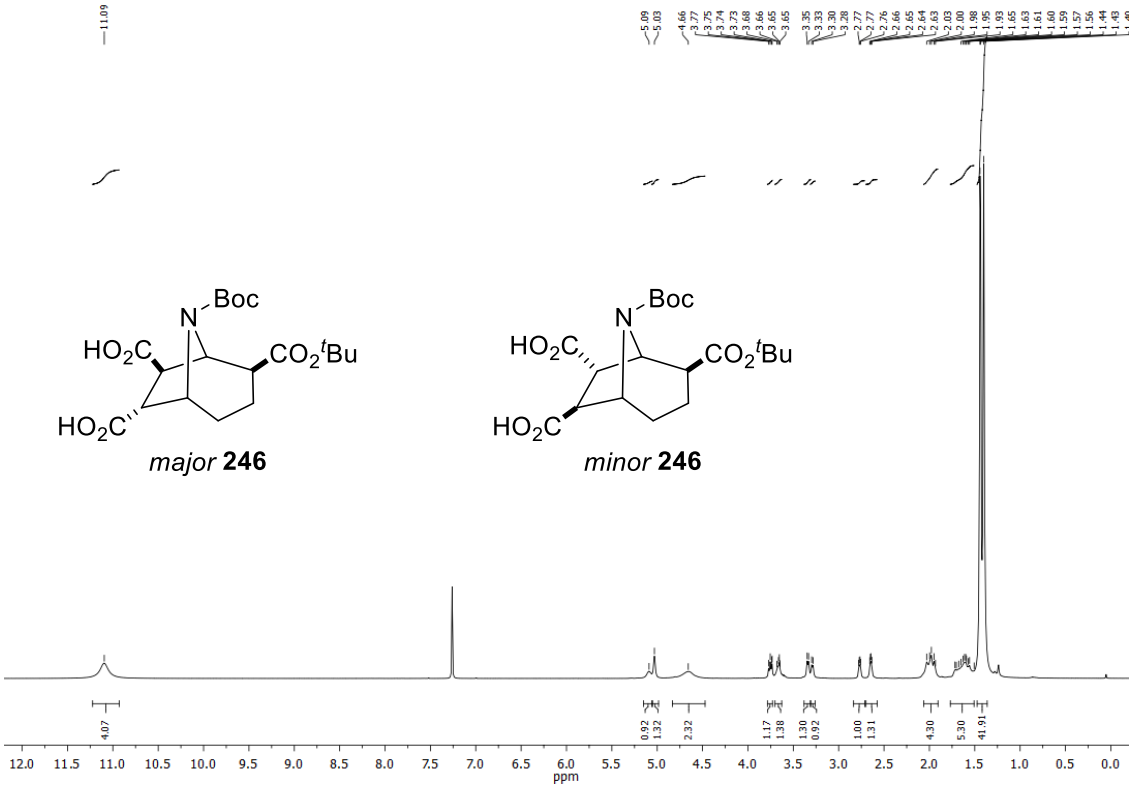


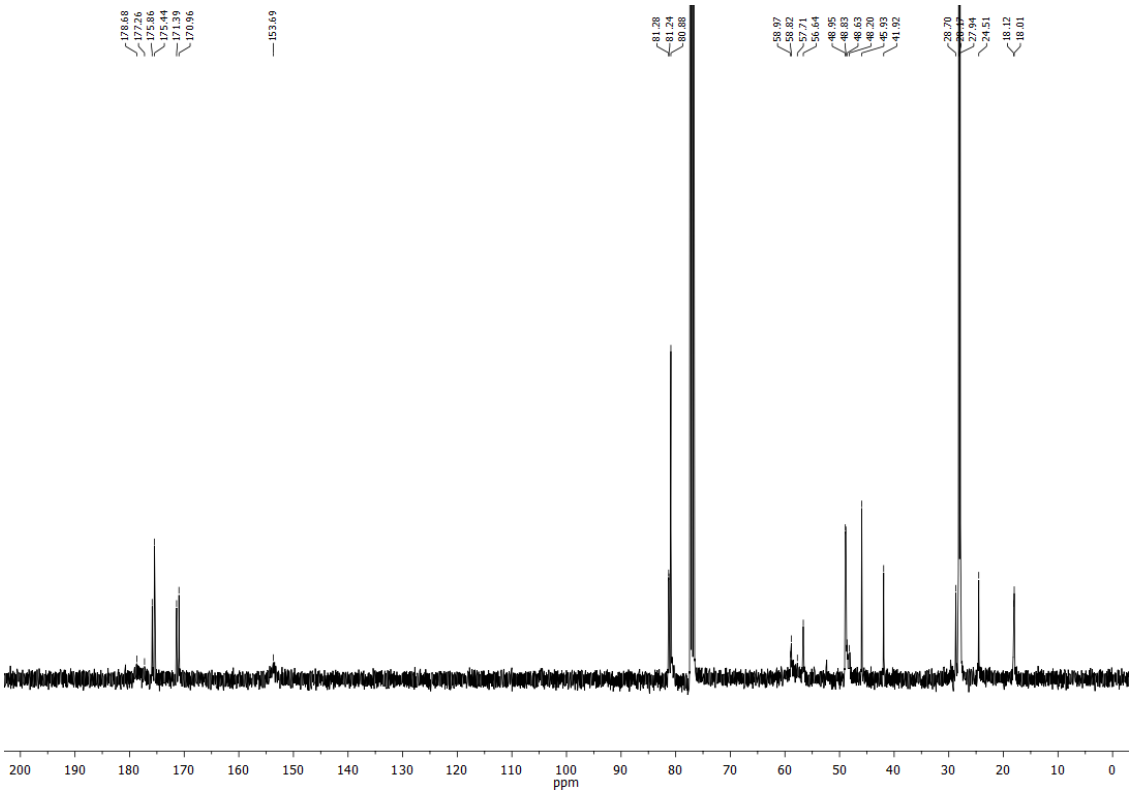
Compound **245**, ^{1}H NMR (400 MHz, MeOD) and ^{13}C NMR (101 MHz, MeOD):



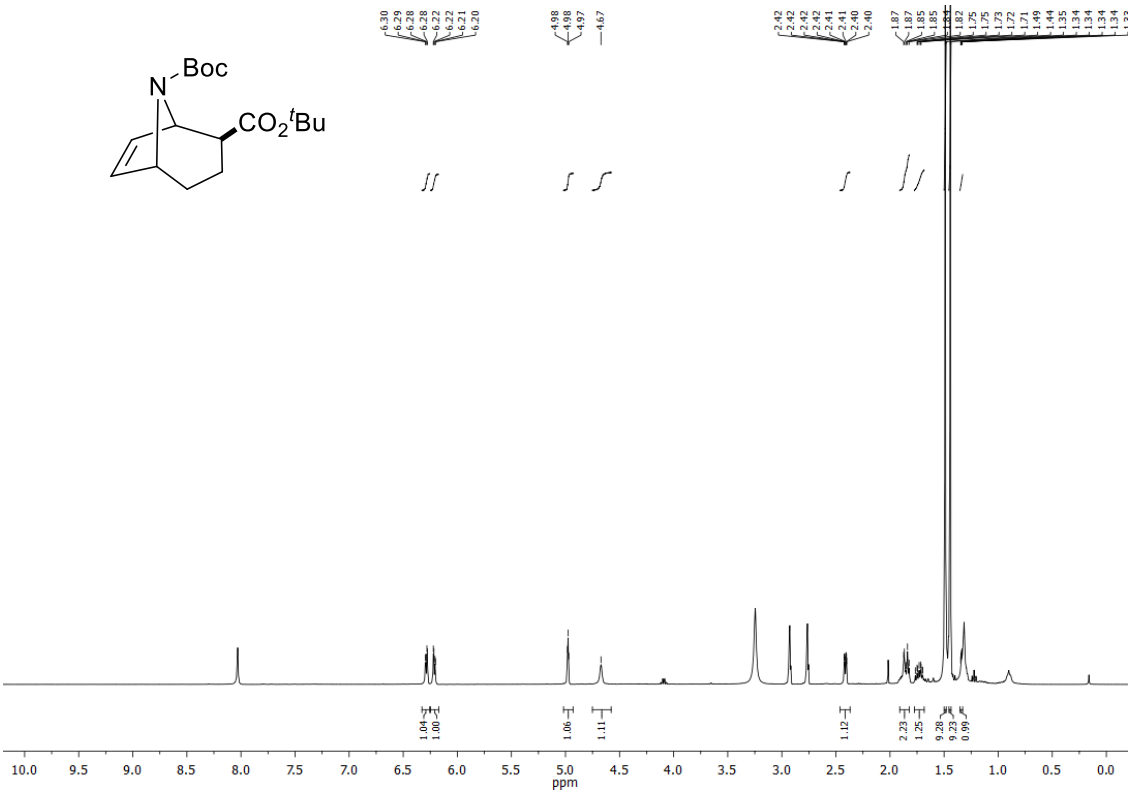


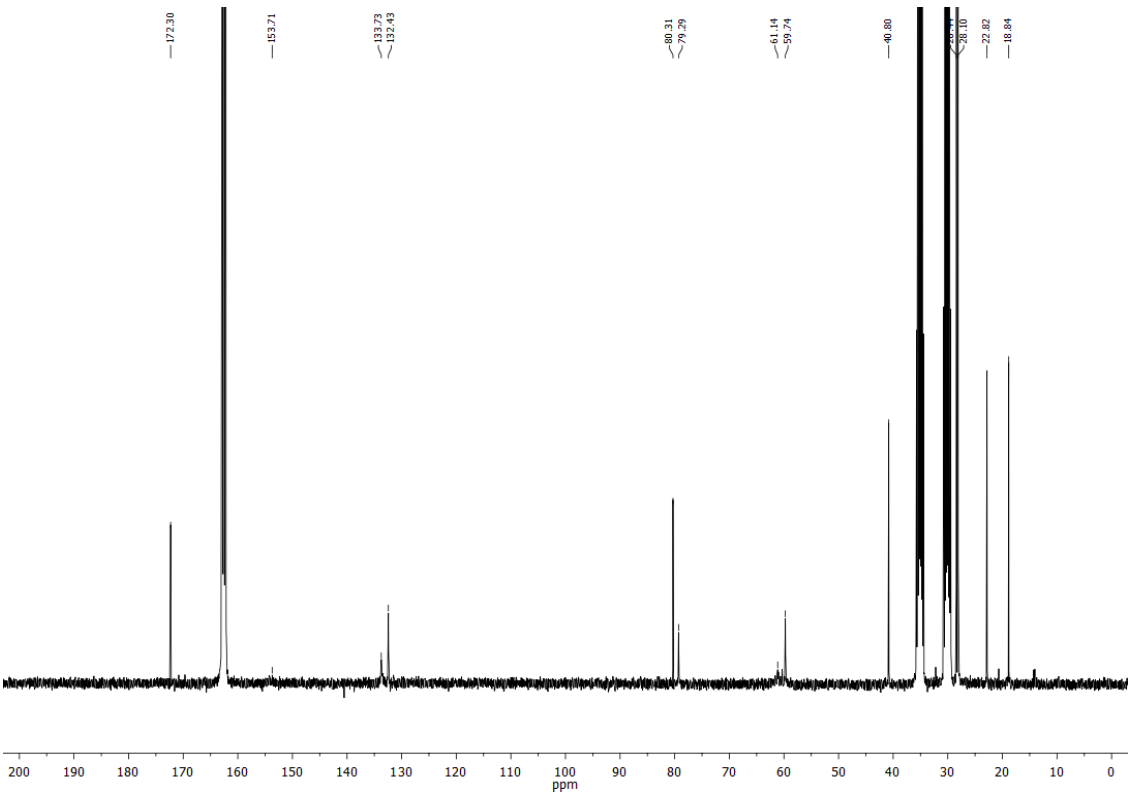
Compound **246**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



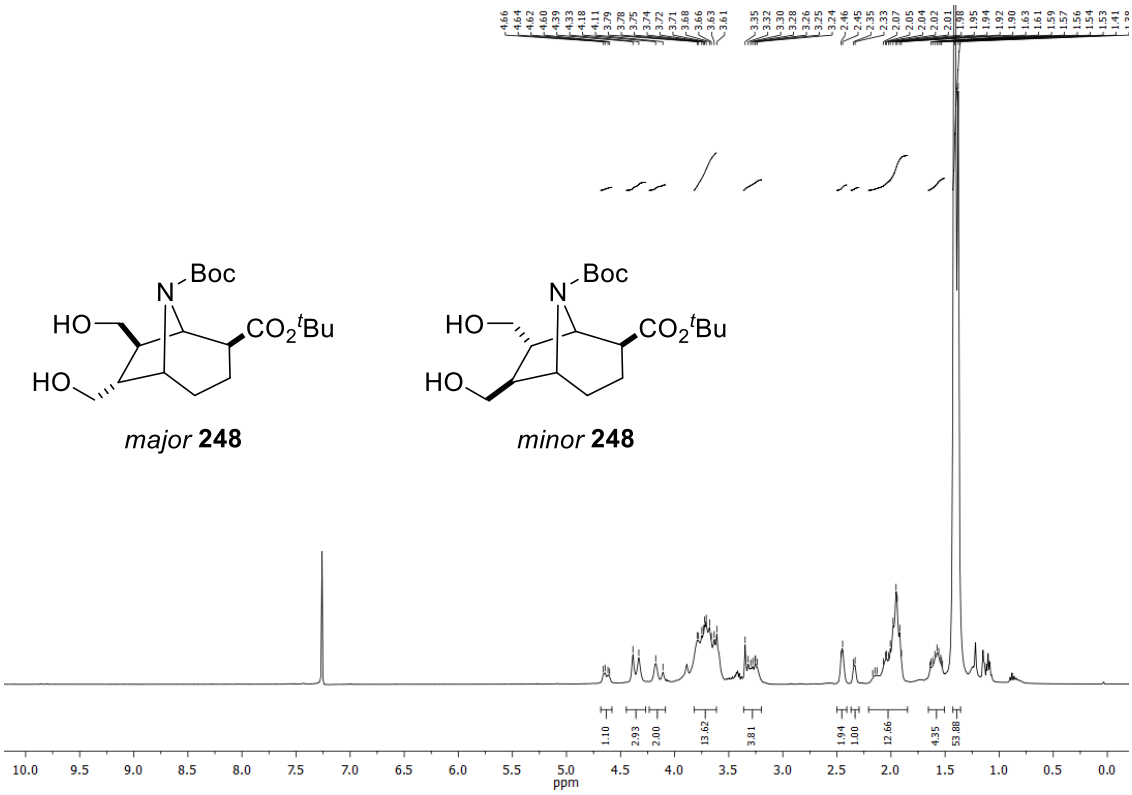


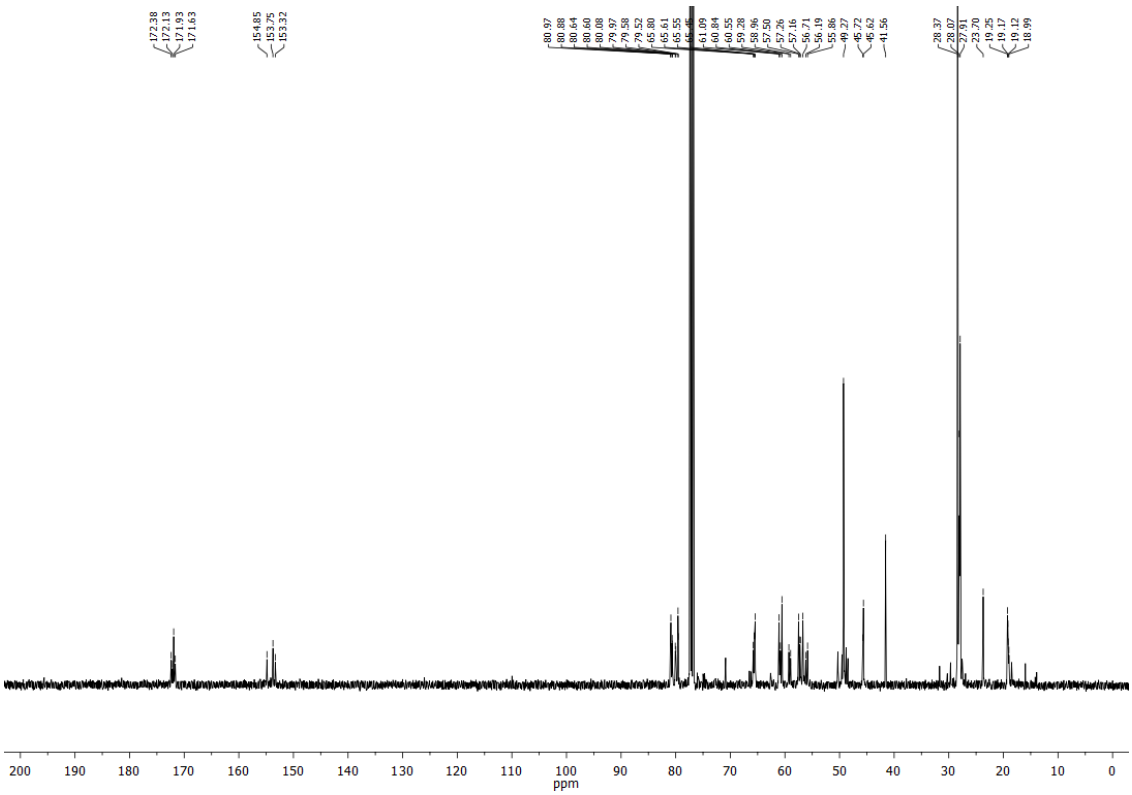
Compound **247**, ^{1}H NMR (400 MHz, DMF-d_7, 333 K) and ^{13}C NMR (101 MHz, DMF-d_7, 333 K):



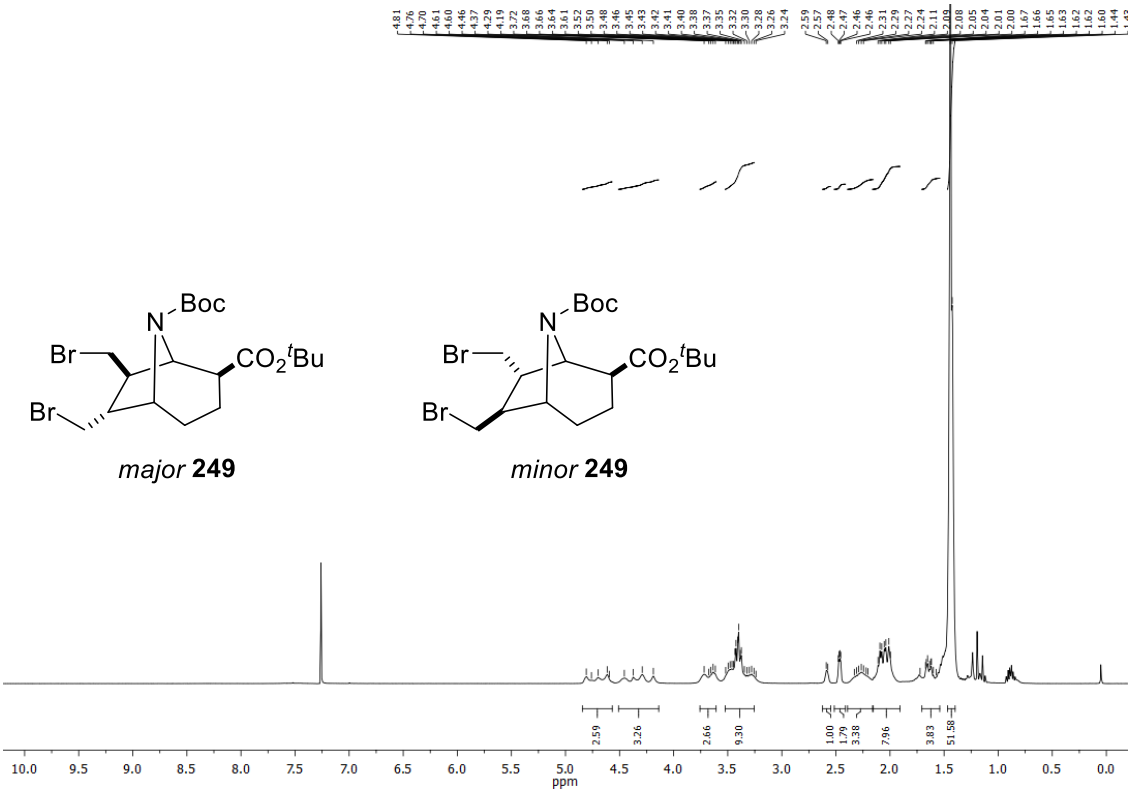


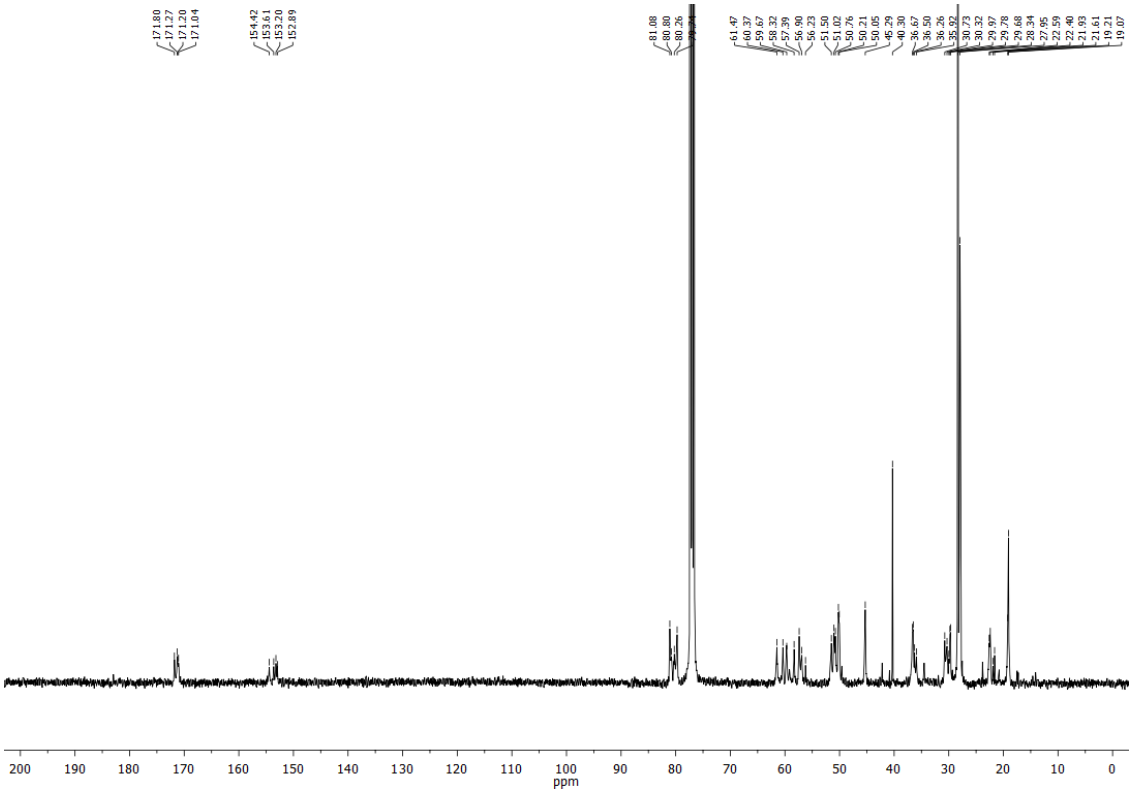
Compound **248**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



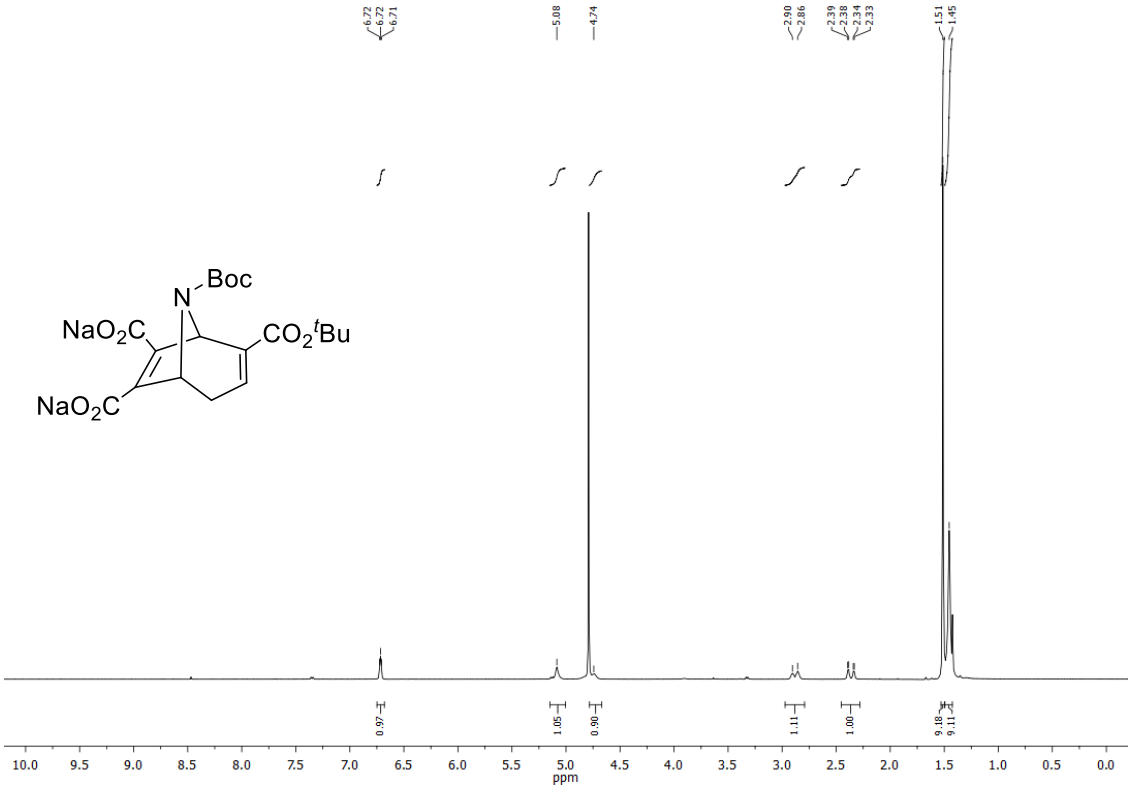


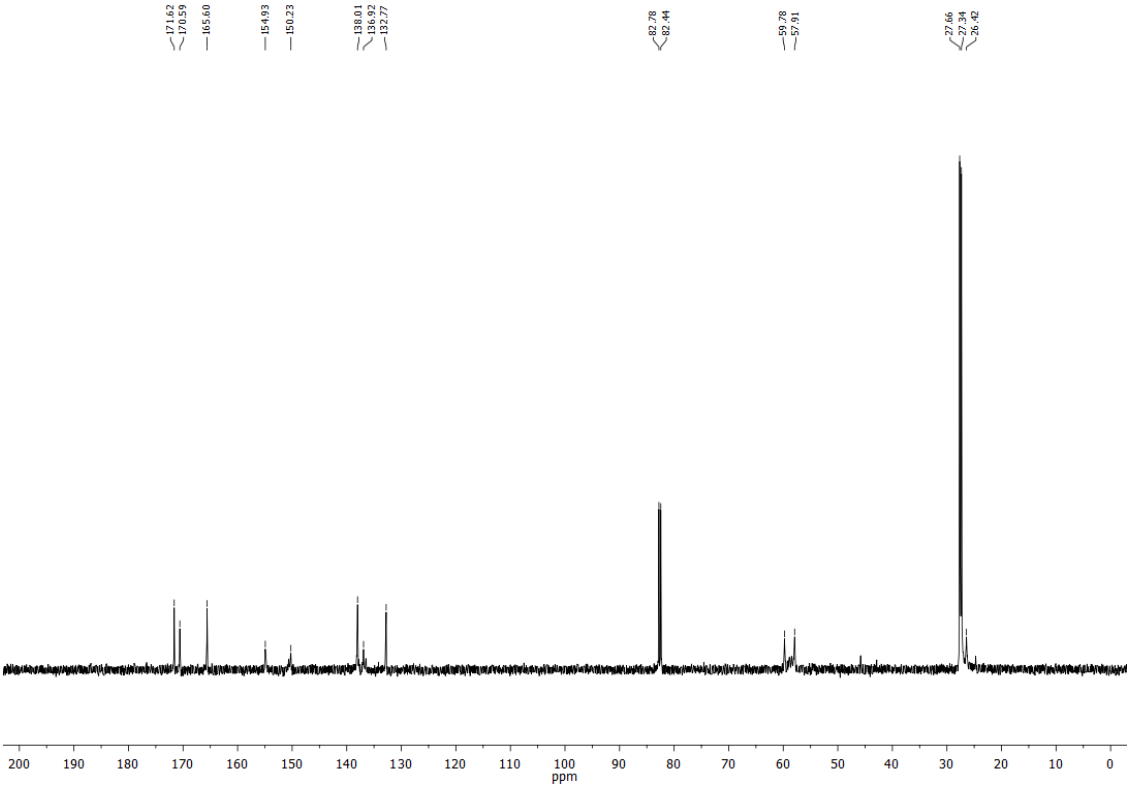
Compound **249**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



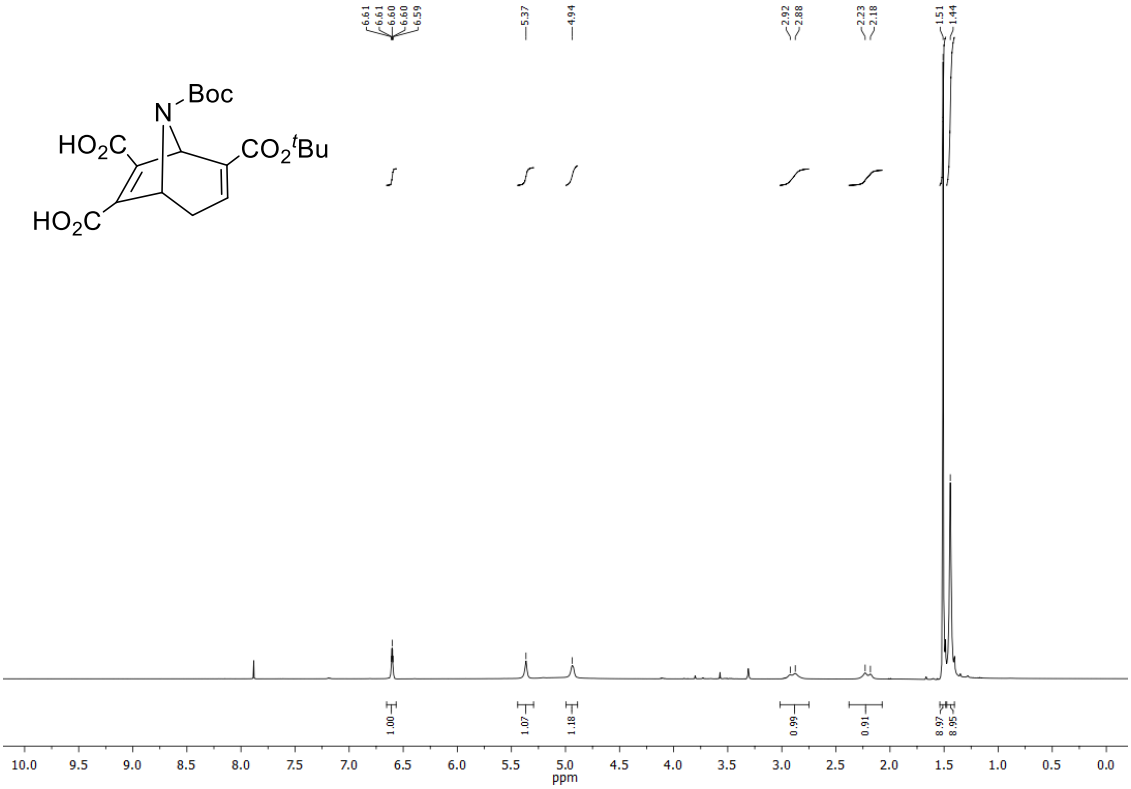


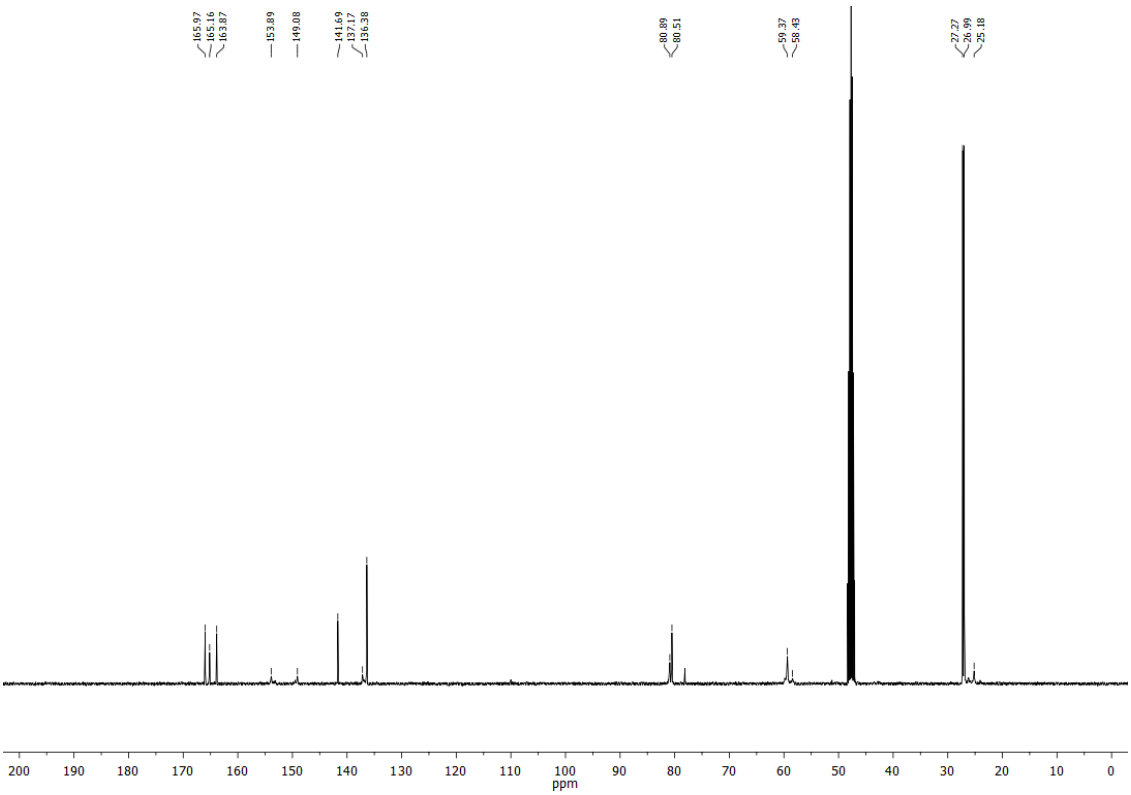
Compound **251**, ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (101 MHz, D_2O):



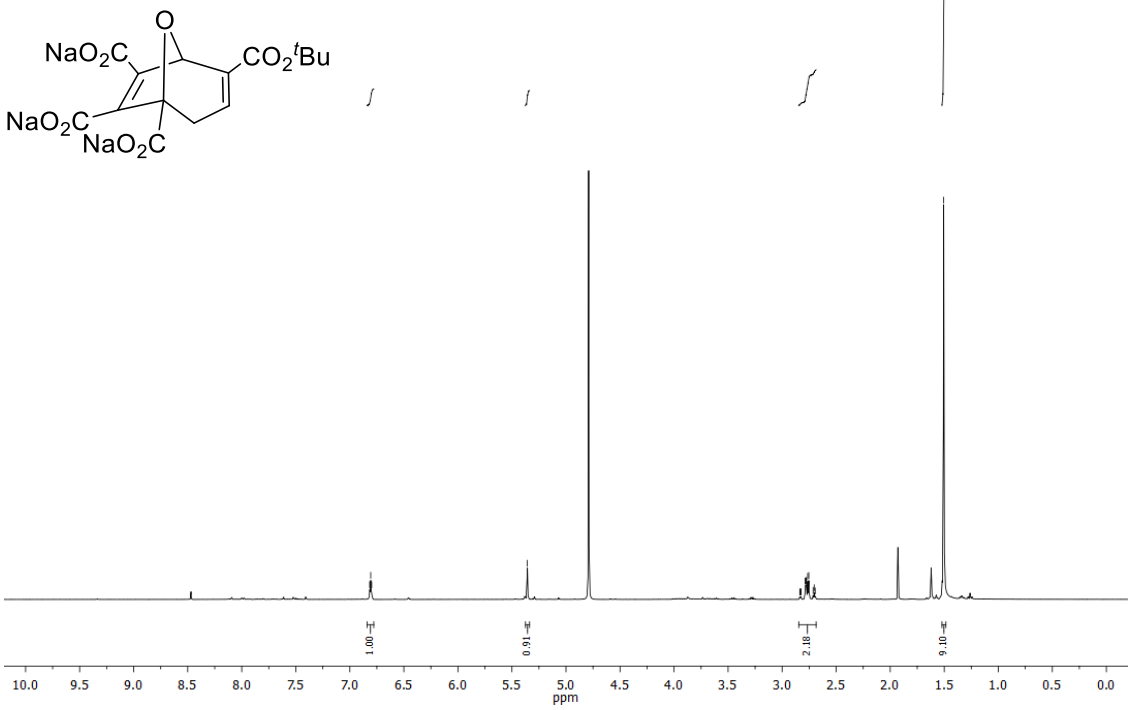


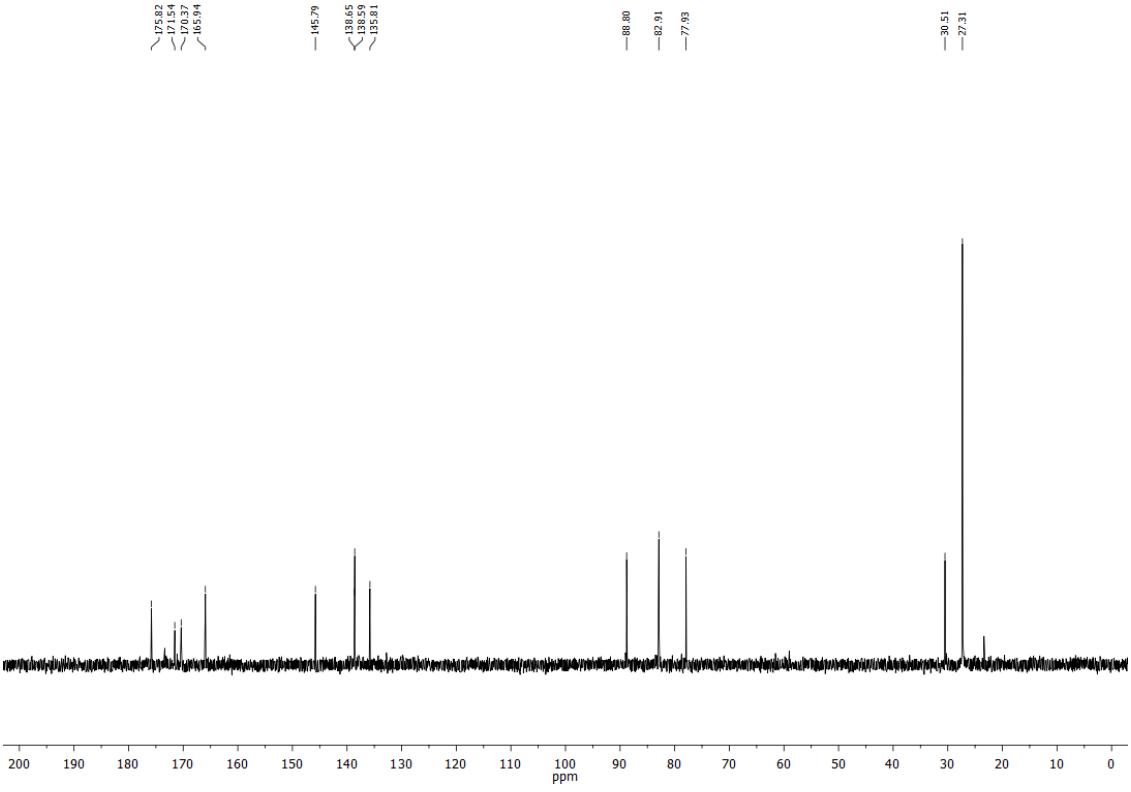
Compound **252**, ^{1}H NMR (400 MHz, MeOD) and ^{13}C NMR (101 MHz, MeOD):



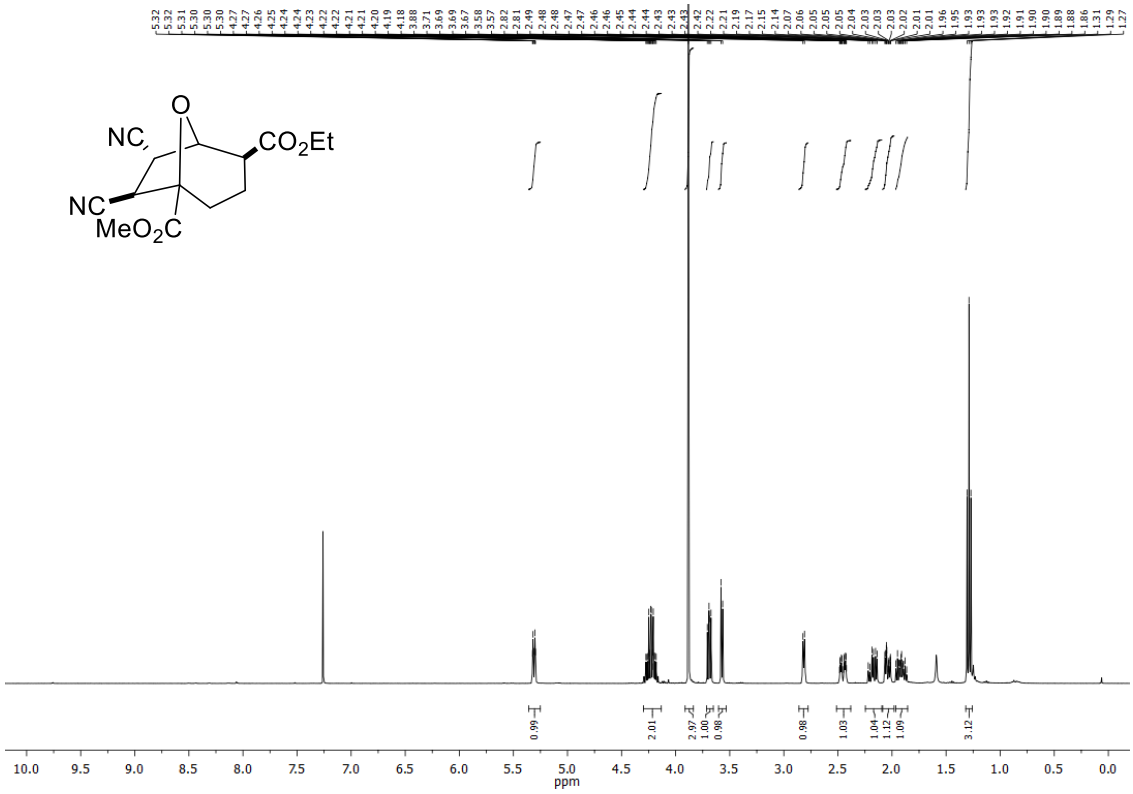


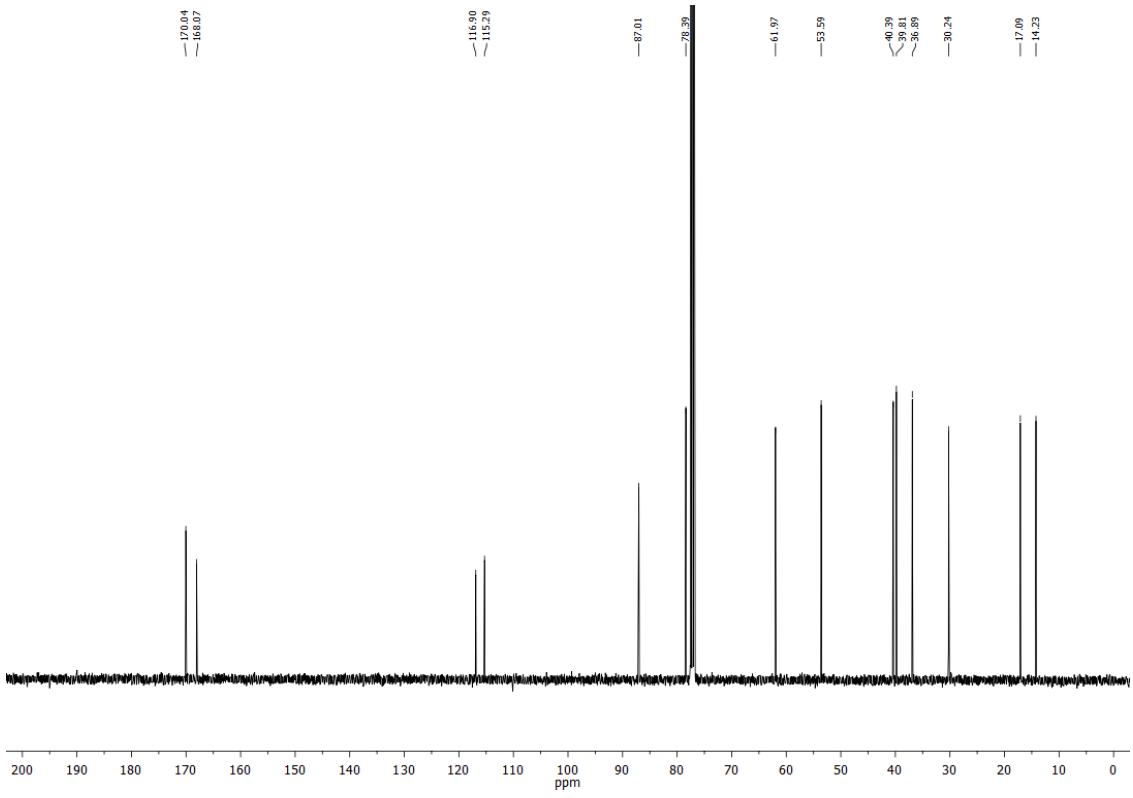
Compound **253**, ^{1}H NMR and ^{13}C NMR (D_2O):



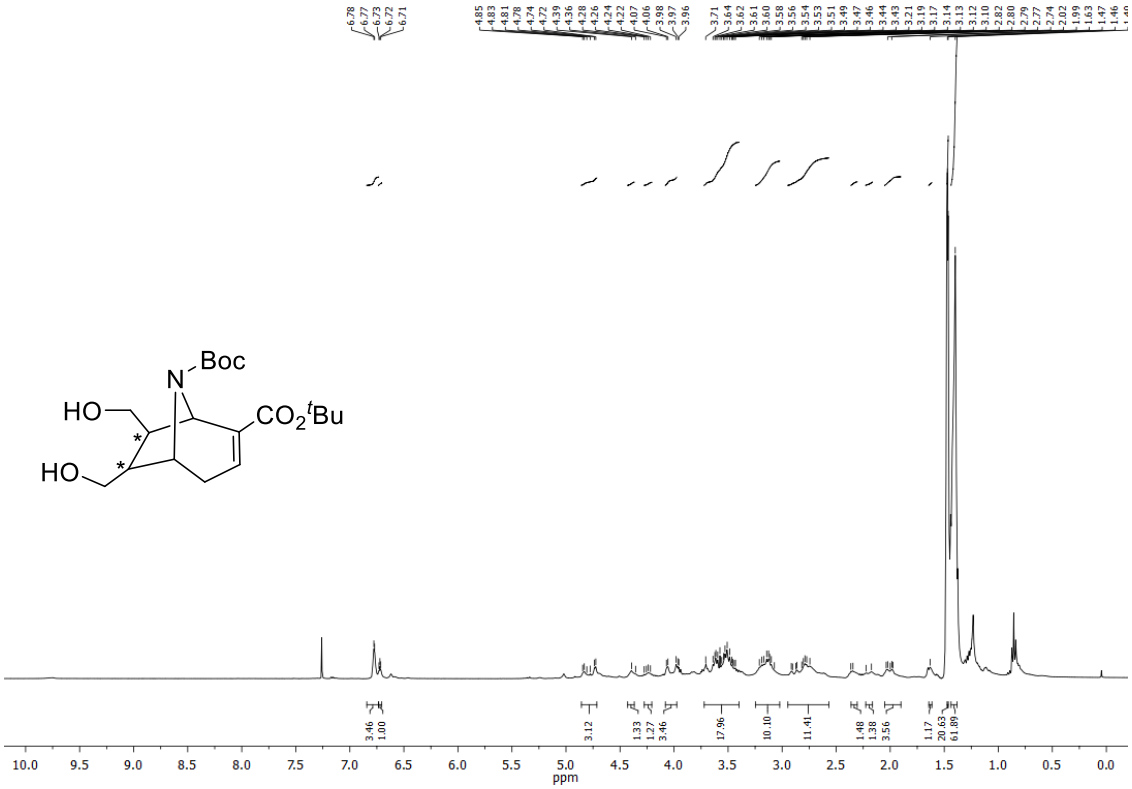


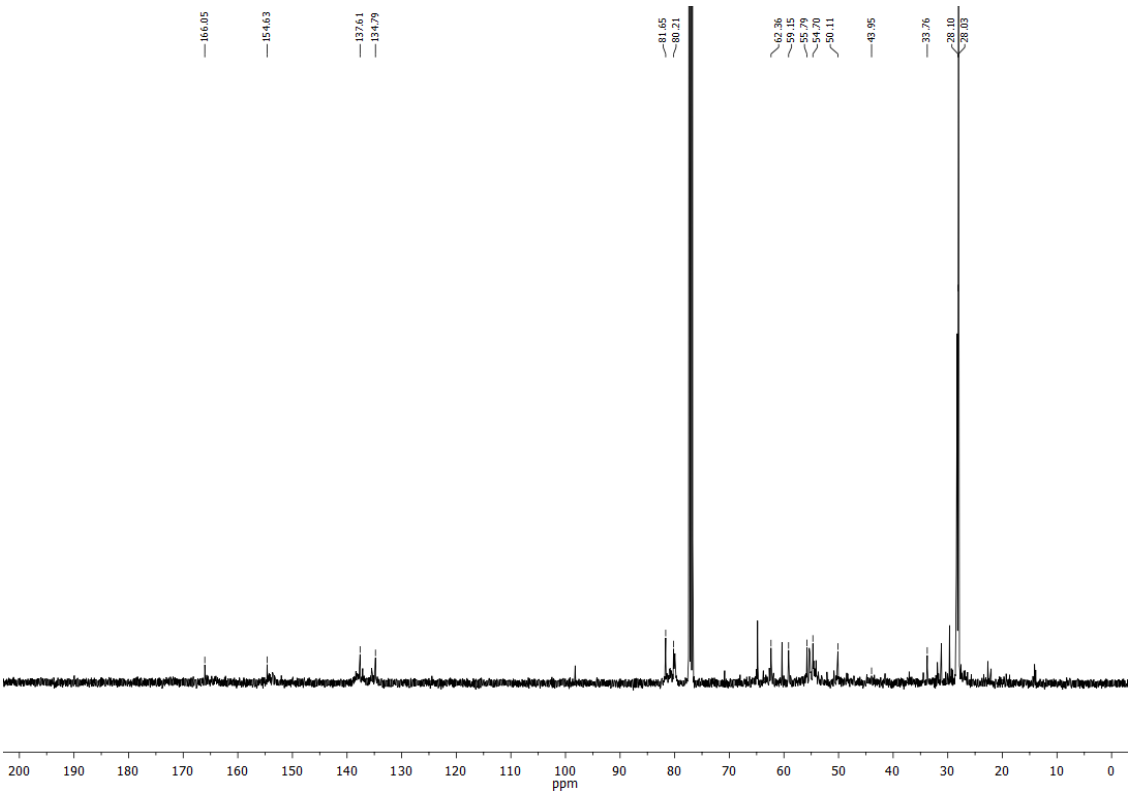
Compound **267**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



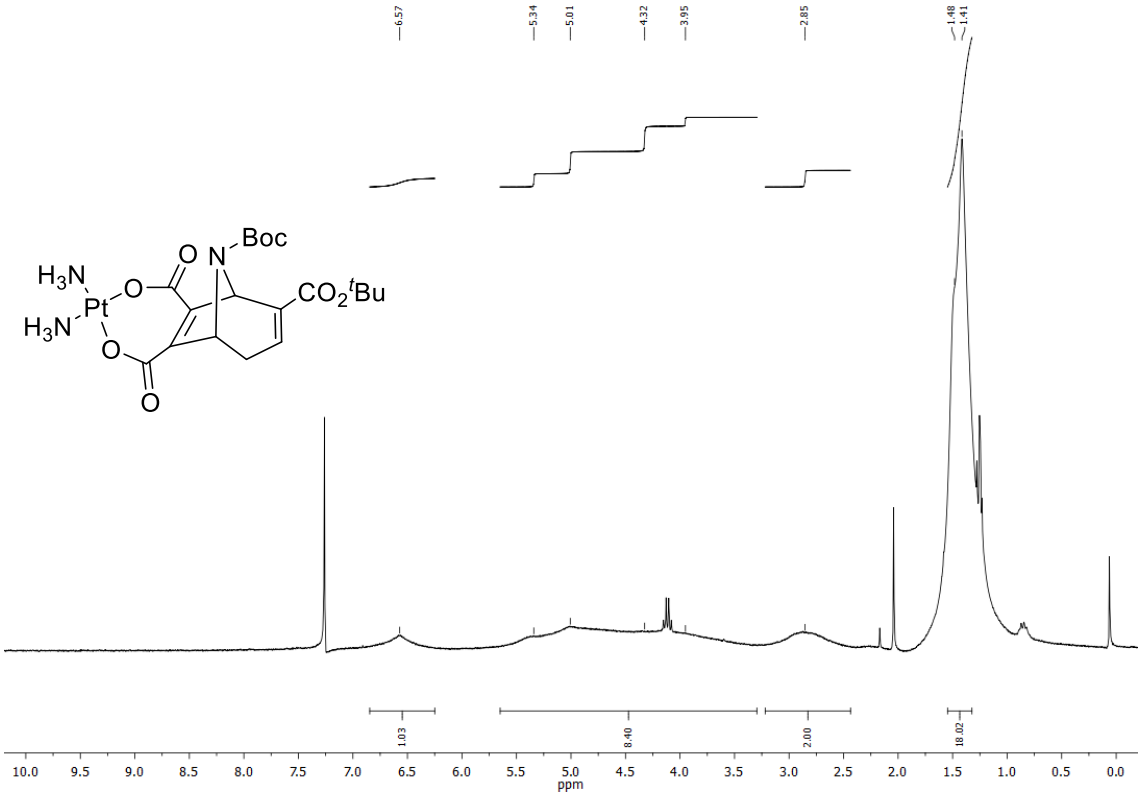


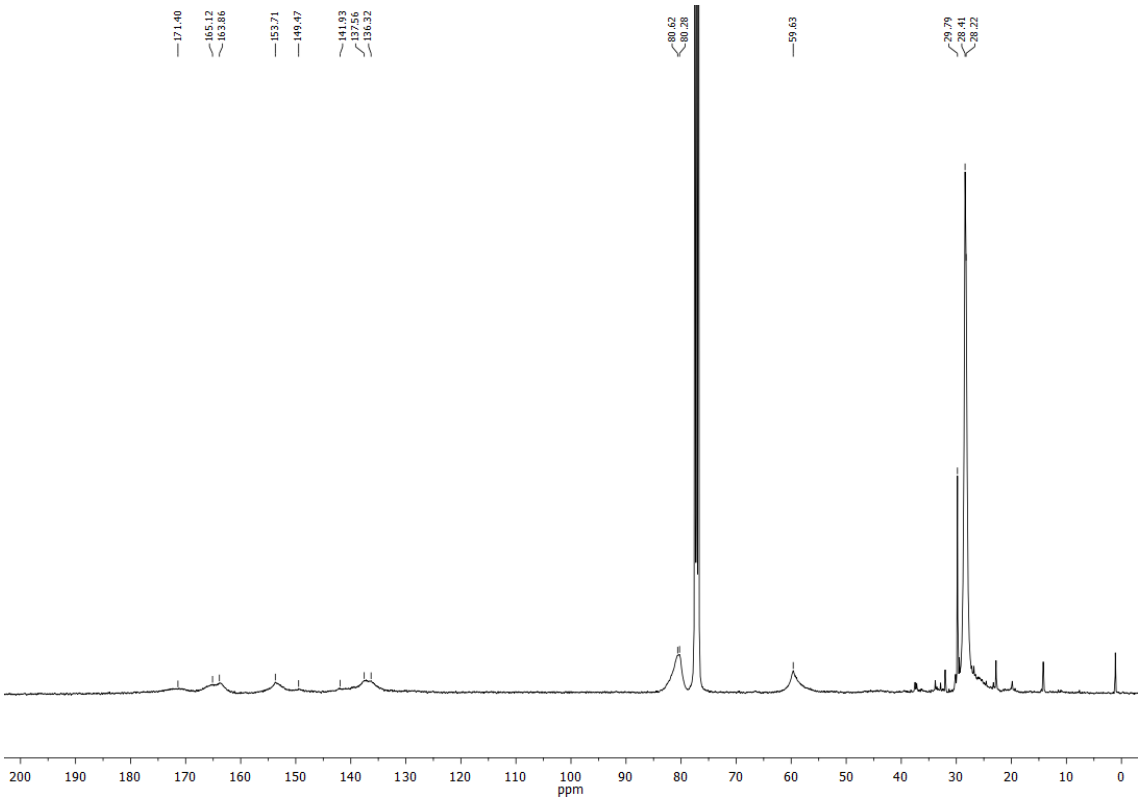
Compound **274**, ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



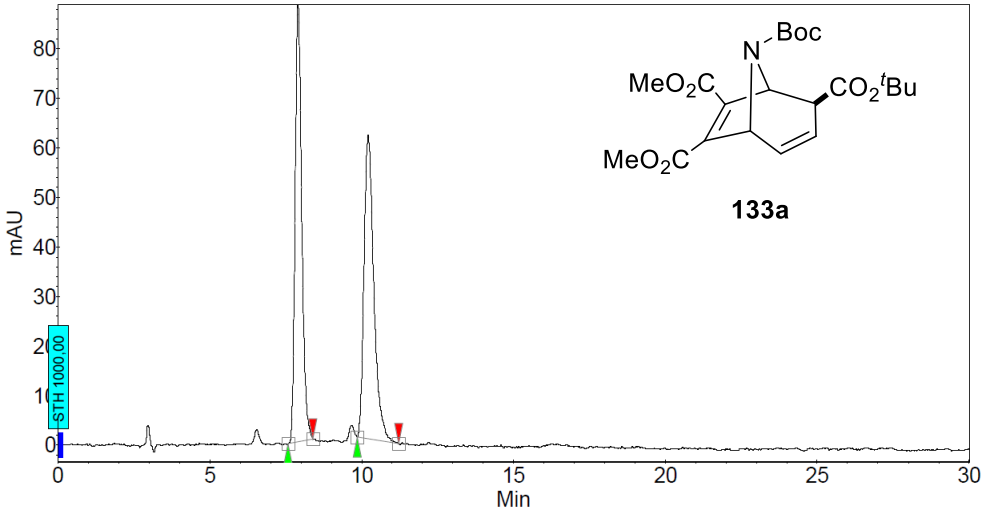


Compound **283**, ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (101 MHz, $CDCl_3$):



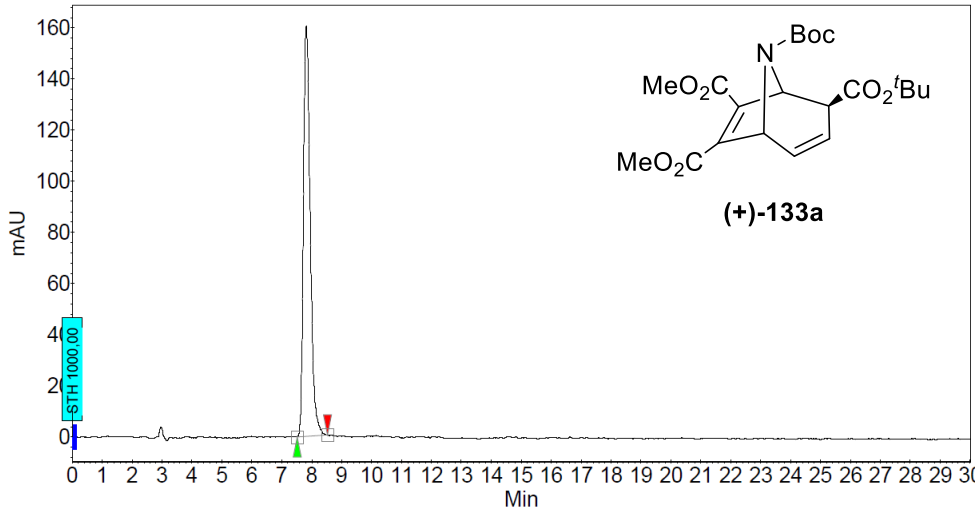


2 HPLC chromatograms



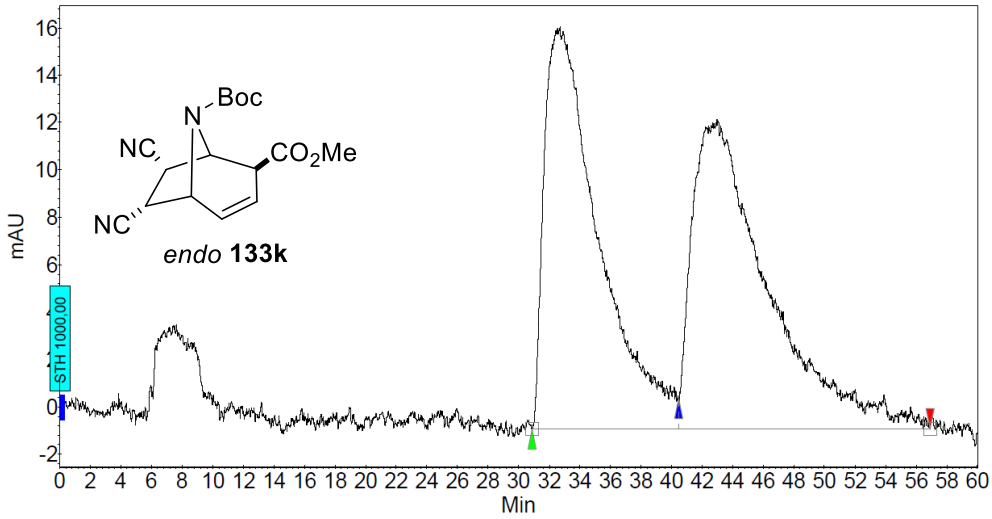
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	7.90	22.5	49.565
2	10.21	22.9	50.435
Total		45.5	100.00



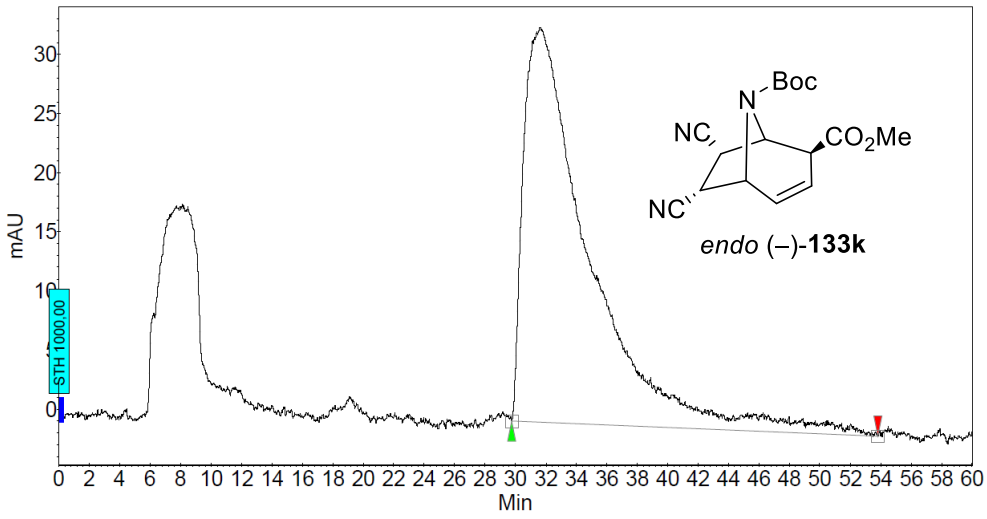
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	7.82	42.2	100



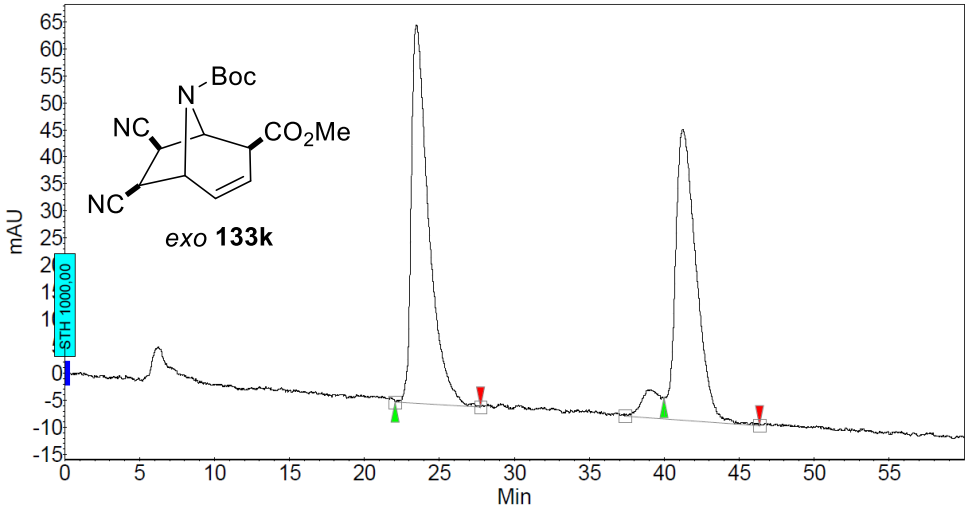
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	32.72	69.8	48.302
2	42.98	74.7	51.698
Total		144.4	100.00



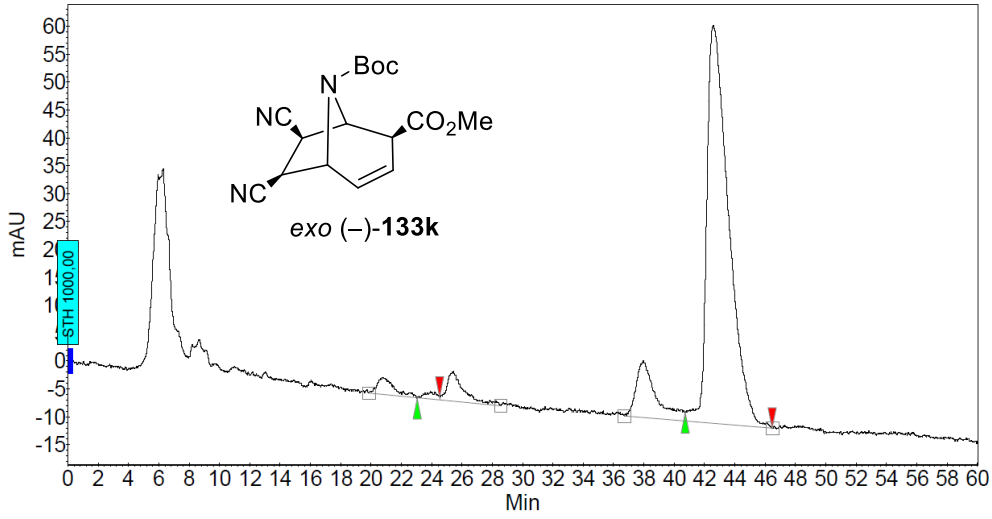
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	31.61	167.2	100.000



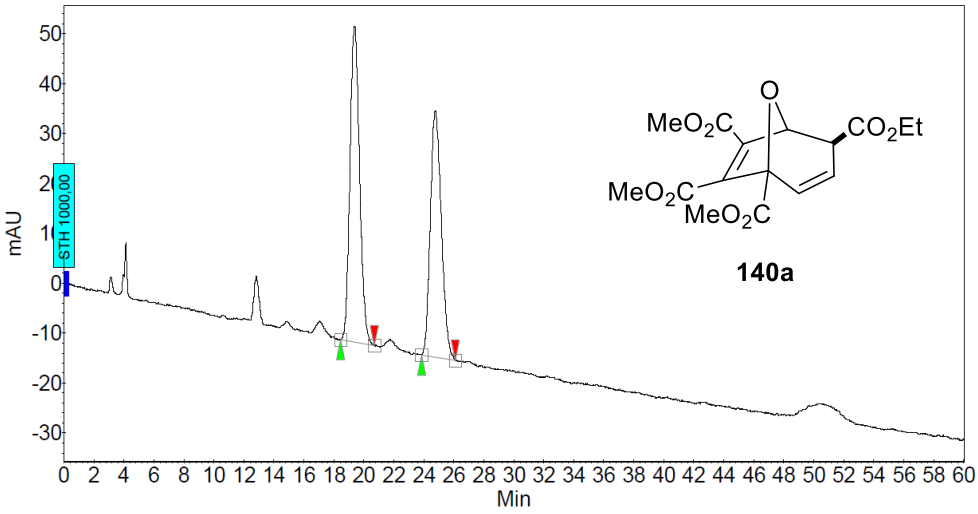
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	23.45	94.0	52.213
2	41.24	86.1	47.787
Total		180.1	100.00



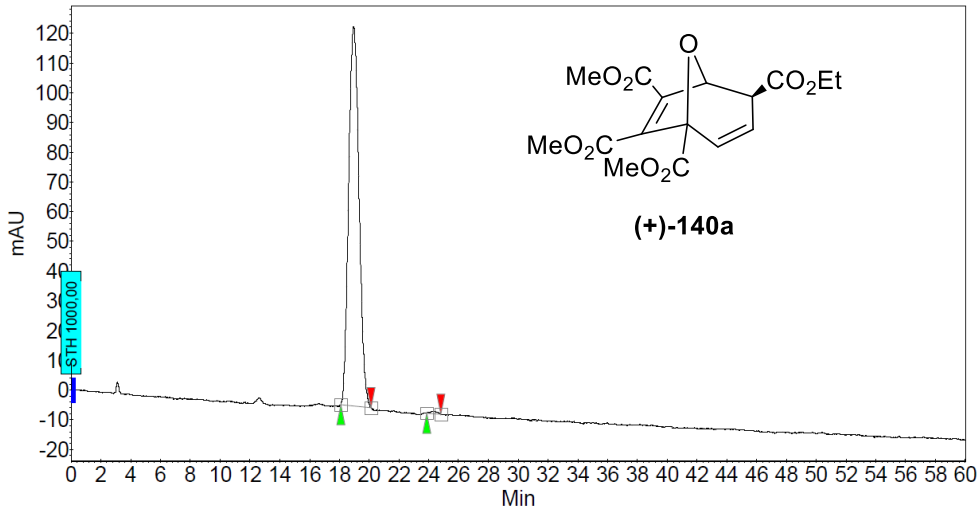
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	24.21	1.1	0.943
2	42.56	119.0	99.057
Total		120.1	100.00



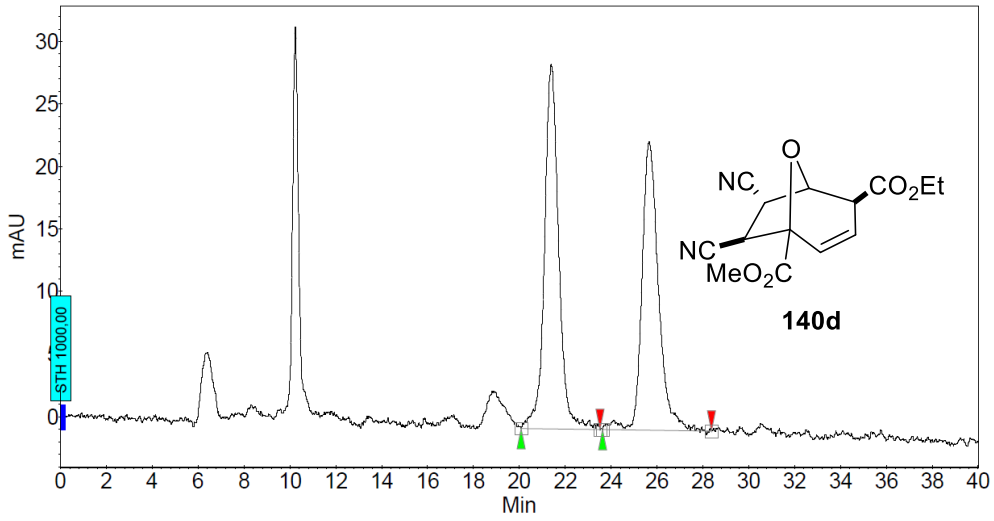
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	19.38	47.2	52.911
2	24.77	42.0	47.089
Total		89.1	100.00



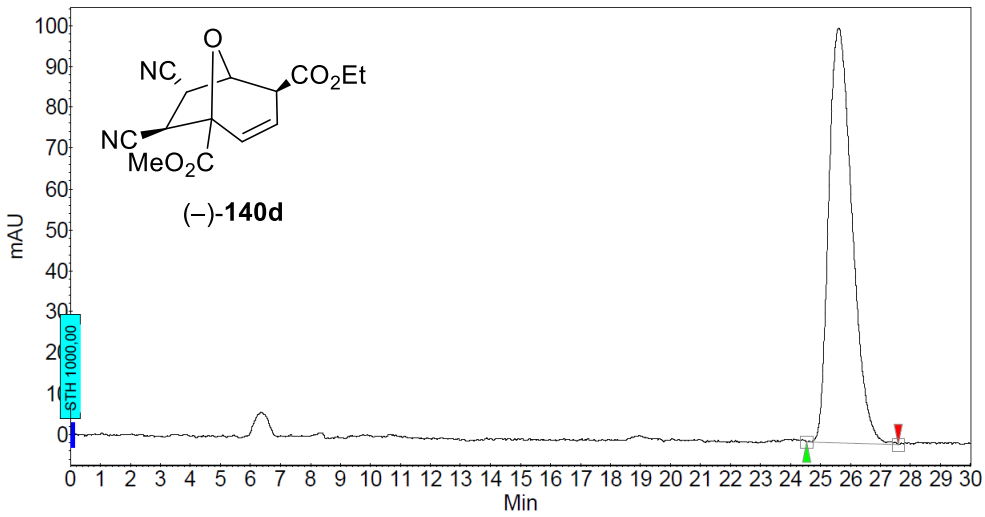
Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	18.96	103.2	99.544
2	24.37	0.5	0.456
Total		103.7	100.00



Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	21.39	21.0	51.997
2	25.66	19.4	48.003
Total		40.4	100.00



Peak Results:

Index	Time (min)	Area (mAU min)	Area (%)
1	25.61	91.4	100.000

3 X-ray crystallography data

ethyl (3*aS*,4*S*,5*S*,8*R*,8*aR*)-1,3-dioxo-9-tosyl-3,3a,4,5,8,8a-hexahydro-1*H*-4,8-epiminocyclohepta[c]furan-5-carboxylate (133h)

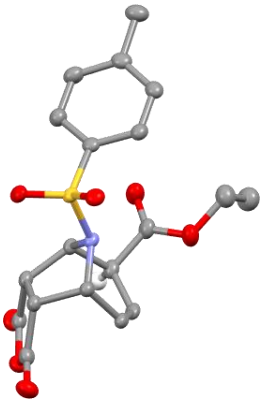


Table 1. Crystal Data and structure refinement for **133h**.

CCDC	1999261
Formula	$C_{19}H_{19}NO_7S$
$D_{calc.}$/ g cm^{-3}	1.458
μ/mm^{-1}	1.947
Formula Weight	405.41
Color	clear colorless
Shape	plate
Size/mm^3	0.24×0.14×0.07
T/K	297.77(10)
Crystal System	triclinic
Space Group	P-1
a/Å	10.9204(3)
b/Å	12.1622(4)
c/Å	14.6939(4)
α/°	94.115(2)
β/°	90.637(2)
γ/°	108.297(3)
V/Å^3	1846.97(10)
Z	4
Z'	2
Wavelength/Å	1.54184
Radiation type	CuK_α
Θ_{min}/°	3.840
Θ_{max}/°	73.737

Measured Refl.	48338
Independent Refl.	7407
Reflections Used	6246
R_{int}	0.0885
Parameters	509
Restraints	0
Largest Peak	0.875
Deepest Hole	-0.414
GooF	1.032
wR_2 (all data)	0.1128
wR_2	0.1064
R_1 (all data)	0.0490
R_1	0.0400

4-ethyl 1,6,7-trimethyl (1*R*,4*S*,5*S*)-8-oxabicyclo[3.2.1]octa-2,6-diene-1,4,6,7-tetracarboxylate ((+)-140a)

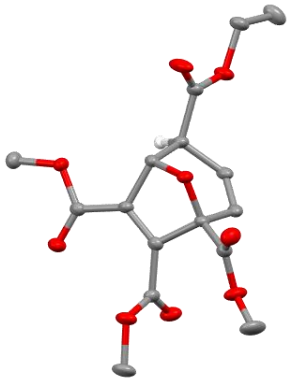


Table 2. Crystal Data and structure refinement for **((+)-140a)**.

CCDC	1999262
Formula	$C_{16}H_{18}O_9$
$D_{calc.}$/ g cm^{-3}	1.417
μ/mm^{-1}	1.008
Formula Weight	354.30
Color	clear colorless
Shape	prism
Size/mm^3	0.32×0.16×0.10
T/K	123.00(10)
Crystal System	monoclinic
Flack Parameter	-0.27(10)

Hooft Parameter	-0.23(8)
Space Group	$P2_1$
a/Å	11.4633(2)
b/Å	10.4467(2)
c/Å	13.8700(2)
α/°	90
β/°	90.5520(10)
γ/°	90
V/Å^3	1660.91(5)
Z	4
Z'	2
Wavelength/Å	1.54184
Radiation type	CuK_α
Θ_{min}/°	3.186
Θ_{max}/°	74.008
Measured Refl.	9844
Independent Refl.	5075
Reflections with I > 2(I)	4841
R_{int}	0.0258
Parameters	584
Restraints	1
Largest Peak	0.235
Deepest Hole	-0.190
GooF	1.039
wR_2 (all data)	0.0836
wR_2	0.0820
R_1 (all data)	0.0342
R_1	0.0319
Creation Method	
Solution	Olex2 1.2-alpha
Refinement	(compiled 2018.07.26 svn.r3523 for OlexSys, GUI svn.r5532)

4-ethyl 1-methyl (1*R*,4*S*,5*R*,6*R*,7*R*)-6,7-dicyano-8-oxabicyclo[3.2.1]oct-2-ene-1,4-dicarboxylate (*major* (–)-140d)

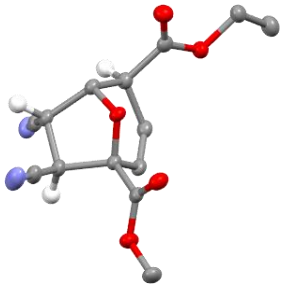


Table 3. Crystal Data and structure refinement for *major* **(–)-140d**.

CCDC	1999263
Formula	$C_{14}H_{14}N_2O_5$
$D_{calc.}$/ g cm^{-3}	1.398
μ/mm^{-1}	0.659
Formula Weight	290.27
Color	clear colorless
Shape	prism
Size/mm^3	0.19×0.13×0.10
T/K	123.00(10)
Crystal System	monoclinic
Flack Parameter	0.03(9)
Hooft Parameter	0.03(8)
Space Group	$P2_1$
a/Å	5.65010(10)
b/Å	10.67929(18)
c/Å	11.4284(2)
α/°	90
β/°	90.9031(16)
γ/°	90
V/Å^3	689.50(2)
Z	2
Z'	1
Wavelength/Å	1.39222
Radiation type	CuK_α
Θ_{min}/°	3.493
Θ_{max}/°	74.308
Measured Refl's.	13708
Ind't Refl's	3776
Refl's with I > 2(I)	3653

R_{int}	0.0351
Parameters	192
Restraints	1
Largest Peak	0.311
Deepest Hole	-0.132
GooF	1.061
wR_2 (all data)	0.0813
wR_2	0.0805
R_1 (all data)	0.0314
R_1	0.0302

2,8-di-*tert*-butyl 6,7-dimethyl (1*S*,5*R*)-8-azabicyclo[3.2.1]octa-2,6-diene-2,6,7,8-tetracarboxylate (152a)

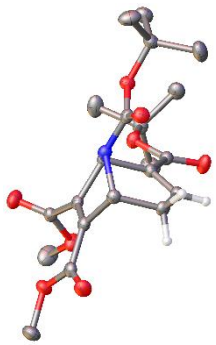


Table 4. Crystal Data and structure refinement for **152a**.

Formula	$C_{21}H_{29}NO_8$
$D_{calc.}$/ g cm^{-3}	1.268
μ/mm^{-1}	0.814
Formula Weight	423.45
Colour	clear colourless
Shape	prism
Size/mm^3	0.23×0.19×0.14
T/K	100.00(10)
Crystal System	triclinic
Space Group	*P*-1
a/Å	9.6424(2)
b/Å	9.66360(10)

c/Å	13.3060(2)
α/°	72.7660(10)
β/°	83.2980(10)
γ/°	69.489(2)
V/Å^3	1109.00(3)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu Kα
Θ_{min}/°	3.478
Θ_{max}/°	73.624
Measured Refl's.	34594
Indep't Refl's	4288
Refl's I≥2 σ(I)	3943
R_{int}	0.0304
Parameters	279
Restraints	0
Largest Peak	0.251
Deepest Hole	-0.216
GooF	1.047
wR_2 (all data)	0.0824
wR_2	0.0809
R_1 (all data)	0.0348
R_1	0.0322

8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,2*S*,5*R*,6*R*,7*S*)-6,7-dihydroxy-8-azabicyclo-[3.2.1]oct-3-ene-2,6,7,8-tetracarboxylate (171)

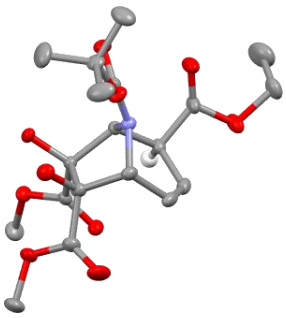


Table 5. Crystal Data and structure refinement for **171**.

CCDC	1999268
Formula	$C_{19}H_{27}NO_{10}$

$D_{calc.}$/ g cm^{-3}	1.358
μ/mm^{-1}	0.940
Formula Weight	429.41
Color	clear colorless
Shape	prism
Size/mm^3	0.25×0.15×0.08
T/K	123.01(10)
Crystal System	monoclinic
Space Group	$P2_1/n$
a/Å	10.16720(10)
b/Å	21.6652(2)
c/Å	19.1977(2)
α/°	90
β/°	96.5370(10)
γ/°	90
V/Å^3	4201.27(7)
Z	8
Z'	2
Wavelength/Å	1.54184
Radiation type	CuK$_\alpha$
Θ_{min}/°	4.081
Θ_{max}/°	74.212
Measured Refl.	43126
Independent Refl.	8419
Reflections with I > 2(I)	7647
R_{int}	0.0295
Parameters	777
Restraints	42
Largest Peak	0.501
Deepest Hole	-0.329
GooF	1.019
wR_2 (all data)	0.1112
wR_2	0.1073
R_1 (all data)	0.0437
R_1	0.0400

5-ethyl 1,7,8-trimethyl (1*S*,2*R*,4*R*,5*R*,6*S*)-3,9-dioxatricyclo[4.2.1.$0^{2,4}$]non-7-ene-1,5,7,8-tetracarboxylate (198a)

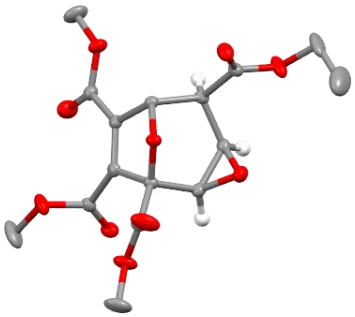


Table 6. Crystal Data and structure refinement for **198a**.

CCDC	1999265
Formula	$C_{16}H_{18}O_{10}$
$D_{calc.}$/ g cm^{-3}	1.397
μ/mm^{-1}	1.020
Formula Weight	370.30
Color	clear colorless
Shape	prism
Size/mm^3	0.27×0.12×0.08
T/K	123.00(10)
Crystal System	hexagonal
Flack Parameter	0.01(3)
Hooft Parameter	0.02(3)
Space Group	$P6_5$
a/Å	10.00860(10)
b/Å	10.00860(10)
c/Å	30.4389(3)
α/°	90
β/°	90
γ/°	120
V/Å^3	2640.62(6)
Z	6
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK_α
Θ_{min}/°	5.103
Θ_{max}/°	73.574
Measured Refl.	31431

Independent Refl.	3549
Reflections with I > 2(I)	3501
R_{int}	0.0267
Parameters	239
Restraints	1
Largest Peak	0.343
Deepest Hole	-0.182
GooF	1.039
wR_2 (all data)	0.0684
wR_2	0.0680
R_1 (all data)	0.0264
R_1	0.0260
Creation Method	
Solution	Olex2 1.2-alpha
Refinement	(compiled 2018.07.26 svn.r3523 for OlexSys, GUI svn.r5532)

9-(*tert*-butyl) 5-ethyl 7,8-dimethyl (1*S*,2*S*,4*R*,5*R*,6*S*)-3-oxa-9-azatricyclo[4.2.1.0^{2,4}]non-7-ene-5,7,8,9-tetracarboxylate (187)

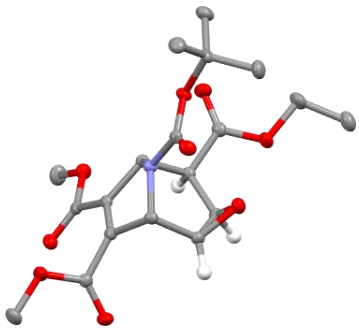


Table 7. Crystal Data and structure refinement for **187**.

CCDC	1999266
Formula	$C_{19}H_{25}NO_9$
$D_{calc.}$/ g cm^{-3}	1.387
μ/mm^{-1}	0.941
Formula Weight	411.40
Color	clear colorless
Shape	prism
Size/mm^3	0.34×0.27×0.20
T/K	123.01(10)

Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	8.45516(11)
b/Å	24.5268(3)
c/Å	9.65894(13)
α/°	90
β/°	100.4790(13)
γ/°	90
V/Å^3	1969.65(5)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK_α
Θ_{min}/°	4.993
Θ_{max}/°	74.260
Measured Refl.	21717
Independent Refl.	3965
Reflections with I > 2(I)	3735
R_{int}	0.0210
Parameters	268
Restraints	0
Largest Peak	0.251
Deepest Hole	-0.294
GooF	1.057
wR_2 (all data)	0.0822
wR_2	0.0805
R_1 (all data)	0.0340
R_1	0.0322
Creation Method	
Solution	Olex2 1.2-alpha
Refinement	(compiled 2018.07.26 svn.r3523 for OlexSys, GUI svn.r5532)

8-(*tert*-butyl) 2-ethyl 6,7-dimethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-bromo-3-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-2,6,7,8-tetracarboxylate (213)

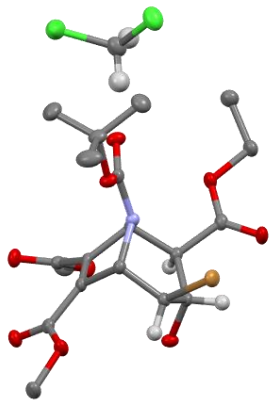


Table 8. Crystal Data and structure refinement for **213.**

CCDC	1999267
Formula	$C_{20}H_{28}BrCl_2NO_9$
$D_{calc.}$/ g cm^{-3}	1.598
μ/mm^{-1}	4.837
Formula Weight	577.24
Color	dull colorless
Shape	block
Size/mm^3	0.21×0.13×0.10
T/K	123.01(10)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	20.4103(4)
b/Å	9.77236(17)
c/Å	12.09234(16)
α/°	90
β/°	95.9969(14)
γ/°	90
V/Å^3	2398.70(7)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK_α
Θ_{min}/°	4.356
Θ_{max}/°	74.175
Measured Refl.	26622
Independent Refl.	4800

Reflections with I > 2(I)	4469
R_{int}	0.0316
Parameters	305
Restraints	0
Largest Peak	0.751
Deepest Hole	-0.570
GooF	1.088
wR_2 (all data)	0.0873
wR_2	0.0857
R_1 (all data)	0.0347
R_1	0.0324
Creation Method	
Solution	Olex2 1.2-alpha
Refinement	(compiled 2018.07.26 svn.r3523 for OlexSys, GUI svn.r5532)

trimethyl (1*S*,4*R*,7*R*,8*R*)-8-(benzoyloxy)-2-methyl-2-azabicyclo[2.2.2]oct-5-ene-5,6,7-tricarboxylate (228)

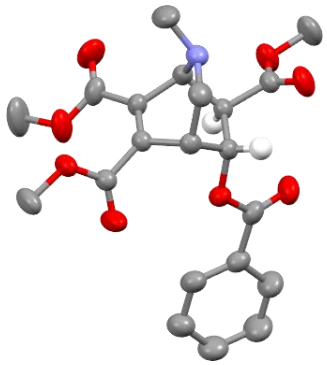


Table 9. Crystal Data and structure refinement for **228**.

CCDC	1999270
Formula	$C_{21}H_{23}NO_8$
$D_{calc.}$/ g cm^{-3}	1.338
μ/mm^{-1}	0.870
Formula Weight	417.40
Color	clear colorless
Shape	prism
Size/mm^3	0.20×0.11×0.06
T/K	293(2)
Crystal System	monoclinic
Space Group	$P2_1/c$

a/Å	19.5386(3)
b/Å	9.90775(17)
c/Å	10.74109(19)
α/°	90
β/°	94.6462(16)
γ/°	90
V/Å^3	2072.46(6)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK$_\alpha$
Θ_{min}/°	4.541
Θ_{max}/°	72.581
Measured Refl's.	22284
Ind't Refl's	4069
Refl's with I > 2(I)	3538
R_{int}	0.0208
Parameters	287
Restraints	151
Largest Peak	0.405
Deepest Hole	-0.241
GooF	1.028
wR_2 (all data)	0.1340
wR_2	0.1269
R_1 (all data)	0.0521
R_1	0.0461

4 Curriculum vitae

Personal data

Name	Carina Maria Sonnleitner
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Education

01/2018 – today/2021	**PhD Thesis** under supervision of Prof. Dr. O. Reiser University of Regensburg, Germany Thesis: *"The Synthesis of 8-Aza- and 8-Oxabicyclo-[3.2.1]octanes via [3+2]-Cycloadditions of cyclopropanated Furan and Pyrrole Derivatives"*
10/2015 – 09/2017	**Master of Science (M. Sc.), Chemistry** University of Regensburg, Germany Master Thesis under supervision of Prof. Dr. O. Reiser: *"Synthesis of Oxa-Heterocycles via Cyclopropanation of Furan and Derivatives"* (Note 1.0) Degree: 1.0
10/2012 – 09/2015	**Bachelor of Science (B.Sc.), Chemistry** University of Regensburg, Germany Bachelor Thesis under supervision of Prof. Dr. B. König: "Synthesis of Photochromic Azobenzodiazepines (1.0) Degree: 2.3
10/2011 – 09/2012	Studies in Pharmacy, University of Regensburg
09/2003 – 07/2011	**Allgemeine Hochschulreife** (A-levels) Gymnasium Pfarrkirchen, Germany Degree: 1.5

Professional references

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Conference and publication

„Stereoselective Synthesis of Tropanes via a 6π-Electrocyclic Ring-Opening / Huisgen [3+2]-Cycloaddition Cascade of Monocyclopropanated Heterocycles“
C. M. Sonnleitner, S. Park, R. Eckl, T. Ertl, O. Reiser, *Angew. Chem. Int. Ed.*, **2020,** *59*, 18110-18115.

Presentation in virtual XVI J-NOST (National Organic Symposium Trust) conference 10/2020

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I Declaration/Erklärung

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

Regensburg, den

Carina Sonnleitner