

Endocyclic Ring-Opening of Fused Carbocyclic Cyclopropanes

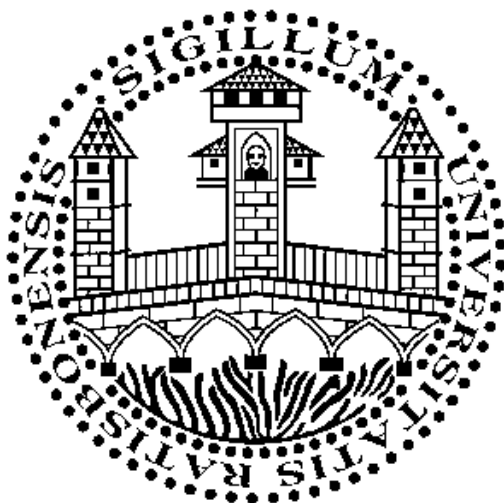
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Für meine Familie

*„Wenn wir wüssten, was wir tun, würde das
nicht Forschung heißen, oder?“ - (Albert
Einstein)*

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Abbreviations

Ac	acetyl	DEPT	distortionless enhancement by polarization transfer
Ac ₂ O	acetic anhydride		
AcOH	acetic acid	DFT	density functional theory
AIBN	azobisisobutyronitrile	DIBAL- <i>H</i>	diisobutylaluminium hydride
approx.	approximately		
aq.	Aqueous	DMF	dimethylformamide
BCB	bicyclobutane	DMSO	dimethylsulfoxide
Boc	<i>tert</i> -butoxycarbonyl	<i>dr</i>	diastereomeric ratio
brine	saturated NaCl-solution	EA	ethyl acetate
<i>brsm</i>	based on recovered starting material	EB	Erythrosin B
		EDG	electron donating group
Bu	butyl	<i>ee</i>	enantiomeric excess
^t Bu	<i>tert</i> -butyl	e.g.	for example
°C	degrees Celcius	equiv	equivalents
cal.	calculated	ESI	electrospray ionization
cm ⁻¹	wavenumbers	Et	ethyl
¹³ C NMR	carbon NMR	<i>et al.</i>	and others (co-authors)
CP	1,3-cyclopentadiene	Et ₂ O	diethyl ether
<i>c.r.m.</i>	complex reaction mixture	EtOH	ethanol
CTFR	cystic fibrosis transmembrane conductance regulator	EWG	electron withdrawing group
d	day (s)	<i>gem</i>	geminal
2D	2-dimensional	h	hour(s)
DBU	1,8-diazabicyclo- [5.4.0]undec-7-en	HFIP	hexafluoroisopropanol
		¹ H NMR	proton NMR
DCM	dichloromethane	HPLC	high-performance liquid chromatography

HRMS	high-resolution mass	PE	petroleum ether
ISC	intersystem crossing	Pg	protecting group
IR	infrared	Ph	phenyl
<i>J</i>	coupling constant	ppm	parts per million
LED	light-emitting diodes	R	arbitrary residue
λ_{max}	max. UV-VIS wavelength	<i>rac</i>	racemic
M	molar (moles per liter)	R_f	retention factor
<i>m</i> CPBA	<i>meta</i> -chlorperbenzoic acid	R_T	residence time
Me	methyl	SET	single-electron-transfer
MeCN	acetonitrile	<i>t</i>	time
MeOH	methanol	T	temperature
MHz	megahertz	TBAF	tetra- <i>n</i> -butylammonium fluoride
M.p.	melting point	TCE	trichloro ethyl
MS	mass spectrometry	TEA	triethylamine
Ms	mesyl	Tf	triflate
MW	microwave irradiation	TFA	trifluoroacetic acid
NBS	<i>N</i> -bromosuccinimide	THF	tetrahydrofuran
n.d.	not determined	TLC	thin-layer chromatography
nm	nanometer(s)	TON	turnover number
NMO	<i>N</i> -methyl morpholine <i>N</i> -oxide	t_r	retention time
NMR	nuclear magnetic resonance	Ts	<i>p</i> -toluenesulfonyl
Nu	nucleophile	TS	transition state
OAc	acetate	TTMSS	tris(trimethylsilyl)silane
PCC	pyridinium chlorochromate	VCP	vinyl cyclopropane
		X	hetero

A. Introduction

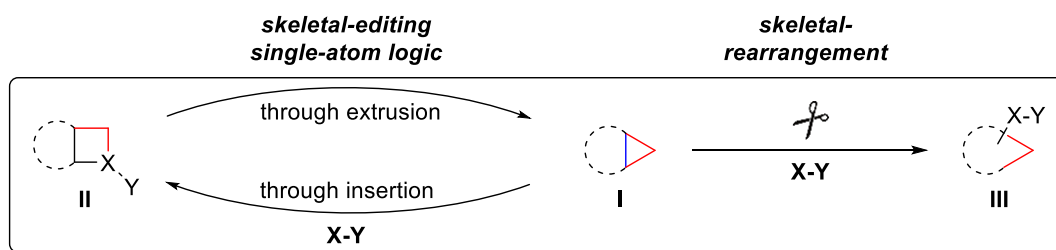
1. Endocyclic Ring-Opening of (*in-situ* generated) Fused Cyclopropanes

1.1. Introduction

The selective cleavage of bonds within a molecule is a recurring task for organic chemists, providing powerful tools to guide reactions with high precision in a particular direction. The ability to functionalize specific groups or bonds, while still tolerating other functional groups in a molecule, allows for the synthesis of complex structures from small molecules. A method to manipulate cyclic structures is “*skeletal editing*.” This term was defined by *Sarpong and Levin et al.* and describes the selective insertion or extrusion of atoms within a molecule, mainly in cyclic structures.^{1,2} In contrast, “*skeletal rearrangement*” represents a fundamental concept in organic synthesis, which involves reorganization of a cyclic core by relocating selective atoms, bonds, or functional groups within its structure.^{3,4} Especially for late-stage functionalization, these transformations are of great interest since the selective insertion, deletion or rearrangement of atoms speeds up the efficiency of discovering new drug candidates.^{2,3,5}

Regarding cyclopropanes, *skeletal editing*, as well as *skeletal-rearrangement* into larger ring systems are captivating tools since the high ring-strain (approx. 28-29 kcal/mol)⁶ provides a robust ring-opening driving force (Scheme 1).^{3,7–18} However, the polarization of the C–C bonds in cyclopropane and some of its derivatives is low.^{6,13,19,20}

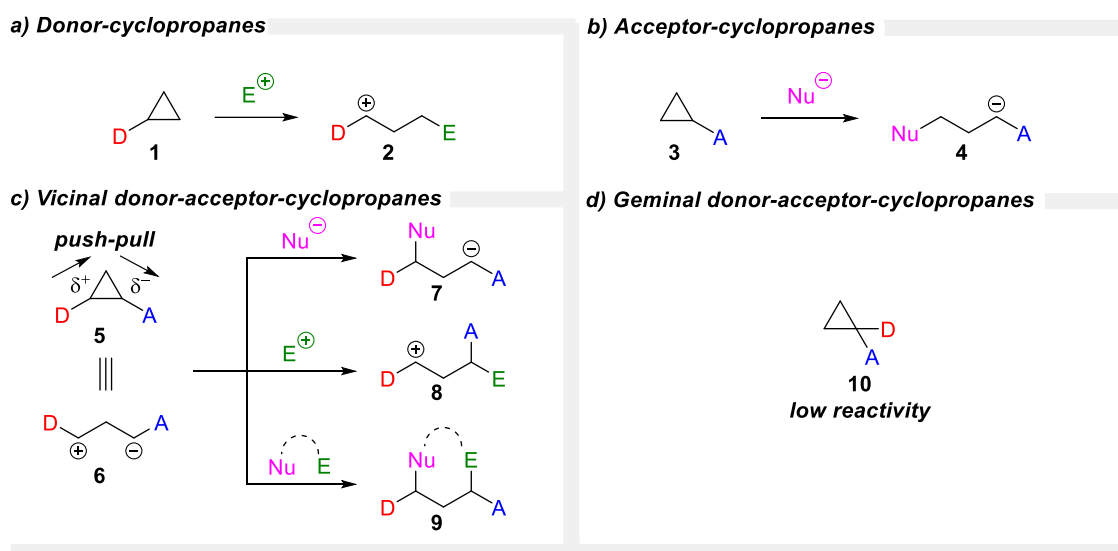
Scheme 1. *Skeletal-editing* vs. *skeletal-rearrangement* of fused cyclopropanes.



Therefore, heterolytic cleavage of cyclopropanes often requires additional groups that can activate the molecule for ring-opening. On the contrary, homolytic cleavage, which forms a diradical intermediate, generally occurs irrespective of the electronic nature of the substituents.^{7,13,21–23} The heterolytic cleavage is promoted *via* different types of

substitutions: On the one hand, donor groups allow for the electrophilic ring-opening by the polarization of the C-C bond within the cyclopropane **1** and stabilize the positive charge in an intermediate **2** (Scheme 2, a).¹³ On the other hand, acceptor groups enable the nucleophilic ring-opening of cyclopropane **3** in the opposite direction and stabilize the negative charge in **4** (Scheme 2, b).¹³

Scheme 2. General heterolytic C-C bond cleavage of DA-cyclopropanes.^{7,13,19}



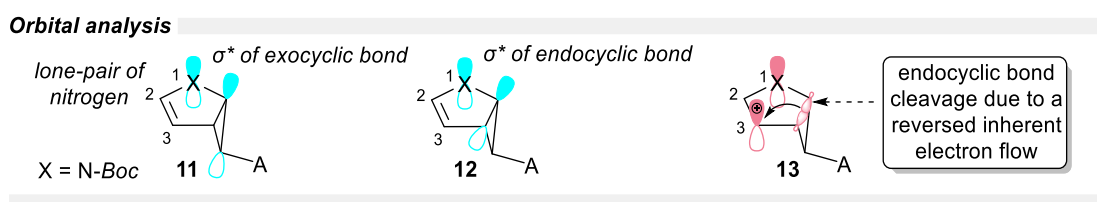
The combination of acceptor- and donor-effects in vicinal DA-cyclopropanes **5** enhances the polarization of the C–C bond between the two adjacent groups and facilitates the heterolytic cleavage. Under thermodynamically driven conditions, the formation of 1,3-dipoles **6** allows for a vast number of regio-, chemo-, and stereoselective reactions depending on their substitution pattern and reaction partners. One example is the [2+3]-cycloaddition reaction to **9** (Scheme 2, c). In *geminal*-DA-cyclopropanes, the electronic effects between acceptor and donor cancel each other out. Therefore, these compounds will not be discussed in the following review. (Scheme 2, d).^{7,13,14,23–36}

1.2. Endocyclic vs. Exocyclic Ring-Opening – An Overview

A unique scenario arises with bicyclic DA-cyclopropanes that are commonly synthesized from heterocycles using diazo acetates under transition-metal catalysis or blue-light photolysis.^{16,37–41} Hereby, a differentiation between an exocyclic and an endocyclic ring-opening can be made. The donor-acceptor substitution alongside the exocyclic C–C bond favors exocyclic ring-opening reactions and has become a powerful tool in organic

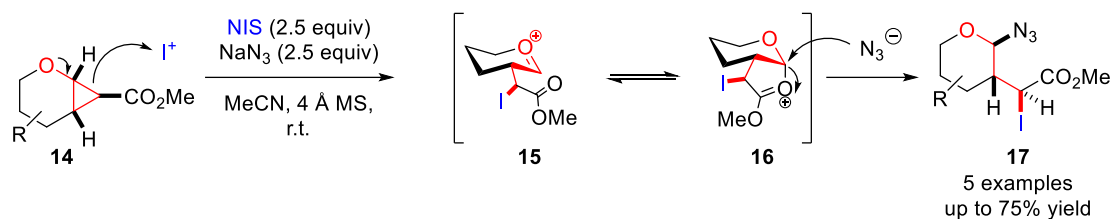
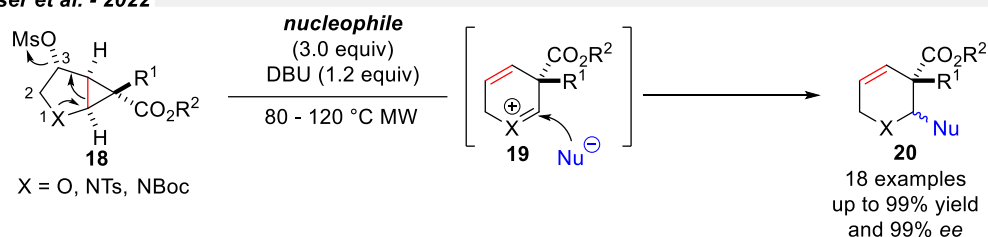
product synthesis.^{7,9,19,21,23,32,35,42–46} Besides, the selective endocyclic ring-opening reaction of bicyclic DA-cyclopropanes was demonstrated only for a few examples.^{17,42,44,47–60} This can be explained by the following reasons: The endocyclic bond is sterically more hindered and less accessible for a nucleophilic or electrophilic attack because it is surrounded by the neighboring rings. Moreover, due to the ideal alignment of donor- or acceptor substituents, the exocyclic bond is more polarized than the endocyclic bond and preferentially attacked by nucleophilic or electrophilic reagents.^{2,34,61,62} The lone pair in **11** is oriented parallel to the σ^* -C–C orbital of the exocyclic cyclopropane bond, which leads to a weakening of the bond strength. On the contrary, the endocyclic bond is not activated since the σ^* -orbital of the endocyclic C–C bond aligns perpendicularly to the lone pair (Figure 1). However, the inherent donor–acceptor electron flow can be reversed by introducing a strong electron-deficient center at C-3 that activates the endocyclic bond, as shown in **13**.^{29,61}

Figure 1. Orbital-analysis of bicyclic cyclopropane **11/12/13**.



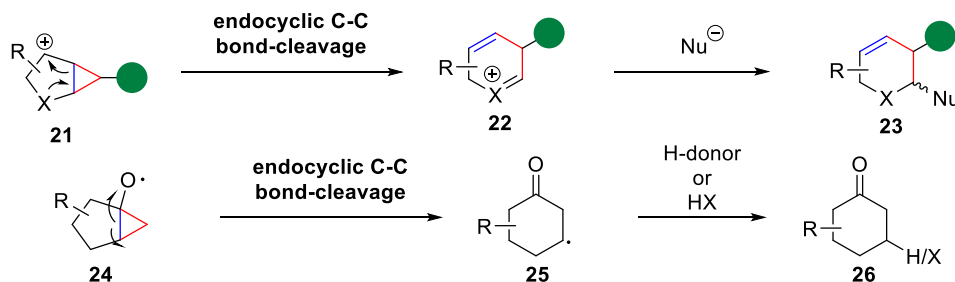
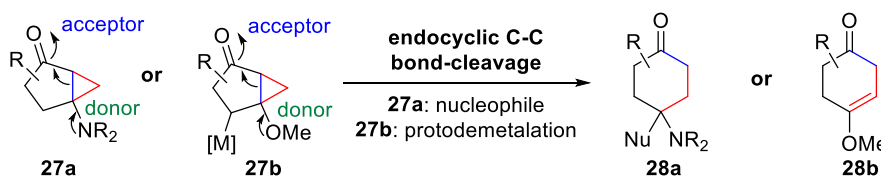
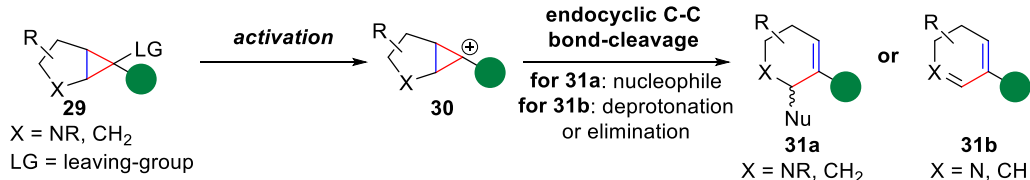
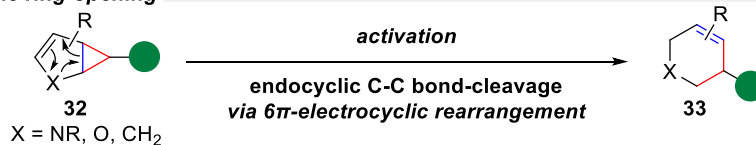
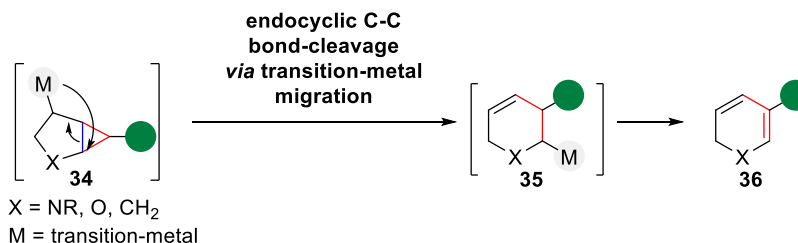
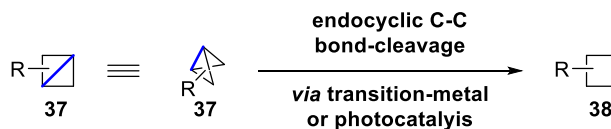
The different modes of ring-opening are outlined by comparing the following two reactions:

In 2013, *Chandrasekaran* and co-workers demonstrated the exocyclic ring-opening of DA-cyclopropane **14**. The donor-acceptor substitution and, thus, the +M-effect of the heteroatom and the -M-effect of the ester group activate the exocyclic bond *via* a “*push-pull-fashion*” for ring-opening mediated by NIS as an electrophile. Additionally, the methyl ester stabilizes the formed oxocarbenium ion **15** by neighboring group participation to afford **16**, which is then trapped by the nucleophile to obtain the ring-opening product **17** (Scheme 3, a).⁶³

Scheme 3. Exocyclic vs. endocyclic ring-opening due to substitution-pattern.**a) Chandrasekaran et al. 2013****b) Reiser et al. - 2022**

On the opposite, the electronic deficient center in **18** at C-3, generated by introducing a mesylate acting as a good leaving group, redirects the electronic flow and thus leads to an endocyclic C-C bond cleavage. After nucleophilic addition to **19**, the ring-expanded products **20** were obtained with excellent yields (Scheme 3, b).¹⁷

The above-mentioned reaction by *Reiser et al.* (Scheme 3b) can be understood by mesomeric stabilization: By generating a positive charge at C-3 next to the cyclopropane, ring-opening occurs to form the best stabilized cation, i.e., **21**. This ring-opening can also occur via a homolytic C-C bond cleavage: Driven by the formation of the stable C=O moiety, the O-centered radical **24** is transformed to the secondary C-centered radical **25** rather than to the corresponding primary radical that would have formed by exocyclic bond cleavage. (Scheme 4a). In DA-cyclopropanes **11**, the exocyclic bond is activated for ring-opening (see Figure 1). Conversely, a different donor-acceptor substitution in **27a/b** activates the endocyclic bond for ring-opening through a distinct electron flow, followed either by nucleophilic addition or protodemetalation, compounds **28a** or **28b** are obtained (Scheme 4, b). An endocyclic C-C bond cleavage via 2π-disrotatory ring-opening can be achieved by abstracting a leaving-group at the cyclopropane moiety **29**. Nucleophilic addition or deprotonation/elimination gives rise to the compounds **31a** or **31b** (Scheme 4, c). The effects and requirements of a 2π-disrotatory ring-opening are discussed in Chapter 1.6.

Scheme 4. Different reaction modes for endocyclic ring-opening.**a) Mesomeric stabilization****b) D-A substitution alongside the endocyclic-bond****c) 2 π -disrotary ring-opening****d) 6 π -electrocyclic ring-opening****e) Transition-metal migration****f) Ring-strain release**

Furthermore, 6 π -electrocyclic ring-openings within a bicycle are valuable transformations to change a molecule's core structure and trigger the endocyclic ring-opening of bicyclic cyclopropanes **32** (Scheme 4, d). Due to the ability to walk along the carbon chain, transition metals can catalyze the endocyclic C–C bond cleavage of bicyclic cyclopropanes **34** through migration (Scheme 4, e). Finally, examples will be shown that

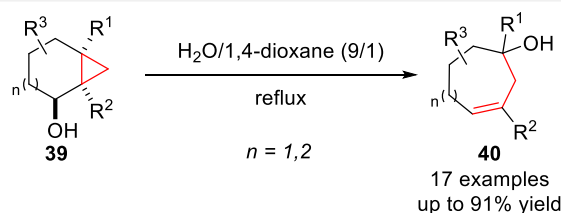
demonstrate endocyclic ring-opening of inactivated cyclic systems driven by the release of a high ring strain (Scheme 4, f).

1.3. Endocyclic Ring-Opening via Mesomeric Stabilization

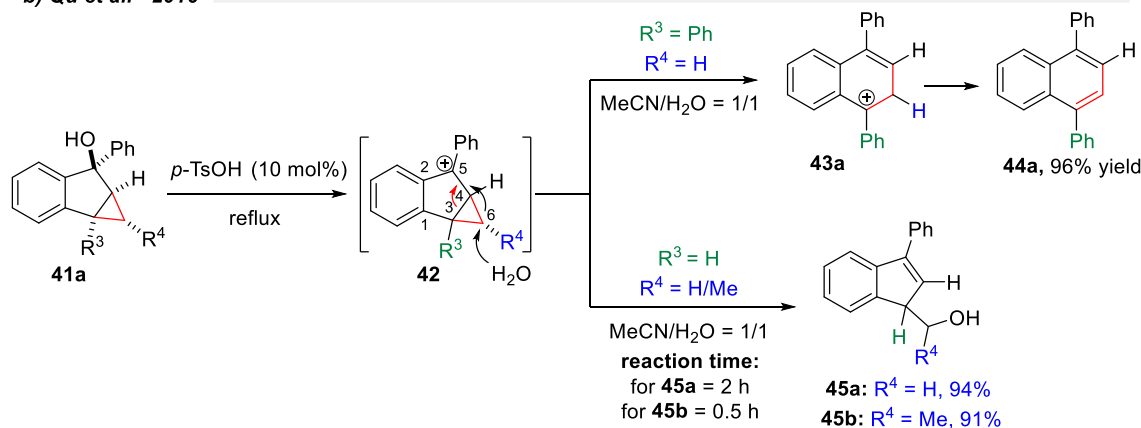
In 2015, the group of *Qu et al.* demonstrated a thermal endocyclic ring-opening process with a leaving group in α -position to the cyclopropane **39**, resulting in ring-enlarged products **40** with significant scope (Scheme 5, a).⁴⁸ Two mechanistic possibilities were assumed: a) the slightly acidic hot water protonates the alcohol, followed by H₂O-release upon thermal activation. Then, the driving force for ring-strain released combined with cation stabilization leads to the ring-enlarged product **40** after endocyclic C-C bond cleavage and nucleophilic addition (S_N1) of water. b) Alternatively, these steps can occur in concert, i.e. water acts as a nucleophile in an S_N2'-reaction.

Scheme 5. Endocyclic C-C bond cleavage via α -leaving group strategy.

a) *Qu et al.* - 2015



b) *Qu et al.* - 2016



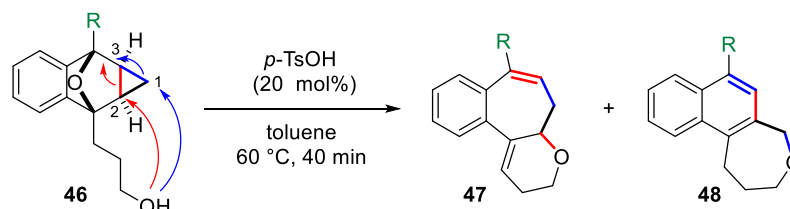
The same group published one year later (2016) an acid-catalyzed ring-opening approach of cyclopropyl methanol compound **41a**, in which the substitution pattern R³ directs the reaction outcome: Upon protonation of the alcohol group the endocyclic bond is cleaved with R³ = Ph as the donor, giving access to the naphthalene compound **44a** after ring-expansion and deprotonation (Scheme 5, b).⁶⁴ On the contrary, with R³ = H in compound

41a, exocyclic ring-opening to **45a/45b** occurs due to the lack of a substituent with a +M-effect at C-3 in **42**. Upon comparing $R^4 = \text{H}$ (**45a**) and $R^4 = \text{Me}$ (**45b**), it is evident that the +I-effect of the methyl group also activates the exocyclic bond, leading to a shortened reaction time (Scheme 5, b).^{64,65}

Similar observations were made by *Tam* and co-workers in 2019 (Table 1). The authors propose an initial protonation of the bridging oxygen in **46**. The alcohol tethered attacks either the C-1 or C-2 position to afford the ring-opening *via* an $\text{S}_{\text{N}}2'$ pathway to obtain the products **47** and **48**.⁶⁶ The +I-effect of $R = \text{Me}/\text{Et}$ directs the reaction towards $\text{S}_{\text{N}}1$ exocyclic ring-opening due to better carbon cation stabilization through $\sigma\text{-C}^1\text{-C}^3 \rightarrow \text{p-orbital}$ while weakening the $\text{C}^1\text{-C}^3$ bond. The attack of the alcohol mainly gives rise to the products **48** (Table 1, entries 2-3). Electron-withdrawing groups destabilize the molecule, and a nucleophile is required to assist in an $\text{S}_{\text{N}}2'$ -reaction. Without the appearance of charges the 6-exo-tet cyclization should be geometrically more favorable than the 7-exo-tet to selectively afford the kinetic product **47** with a moderate yield (Table 1, entries 4-5).

Table 1. Endocyclic vs. exocyclic ring-opening depending on the substitution pattern.

Tam et al. - 2019



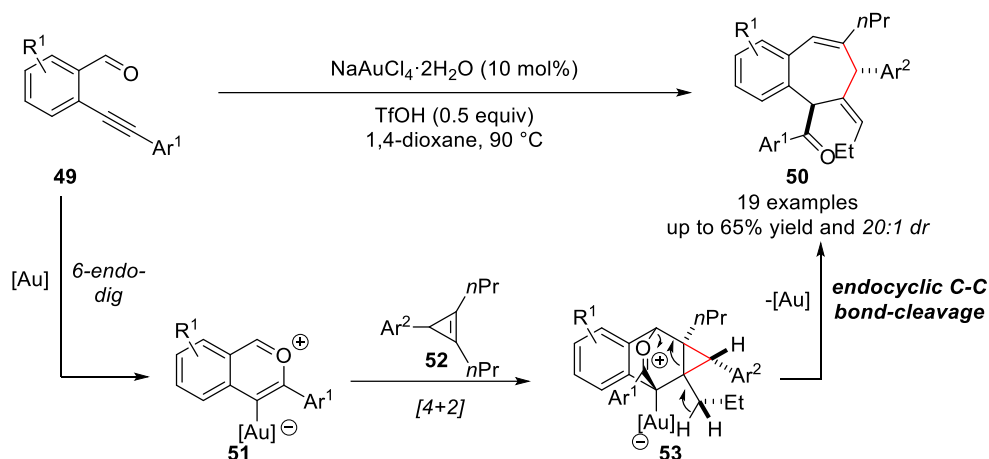
Entry	R	Yield 47 [%]	Yield 48 [%]
1	H	60	19
2	Me	29	57
3	Et	32	37
4	CO ₂ Me	28	0
5	COMe	40	0

In 2019, *Cao et al.* demonstrated an endocyclic ring-opening from a similar compound **53**, which was synthesized *via* a gold(III)-catalyzed 6-*endo*-dig cyclization reaction of **49**, forming the intermediate **51** that undergoes [4+2]-cycloaddition with cyclopropene **52**. In difference to the previous examples in which a nucleophile assisted the ring-opening, here

the availability of a proton that can initiate a concerted E2-type elimination/ring expansion resulting in the formation of 7-membered carbocycles **50** (Scheme 6) dictates the endocyclic bond cleavage of the cyclopropane.^{8,67}

Scheme 6. Gold-catalyzed cyclopropanation followed by endocyclic ring-opening.

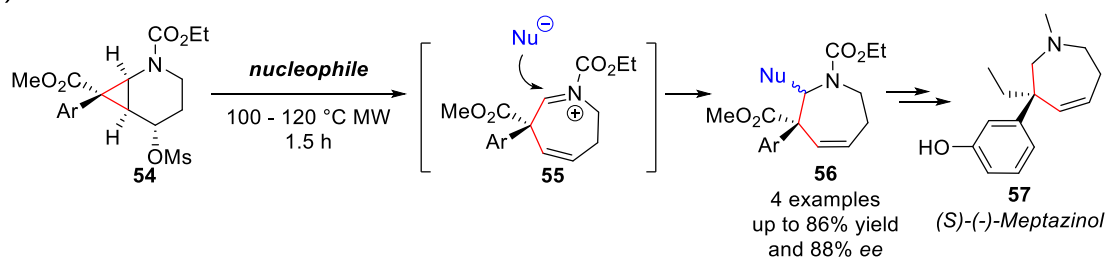
Cao et al. - 2019



Following the strategy presented in Scheme 3 for furans, in 2022 the synthesis of (*S*)-(-)-*meptazinol* (**57**, Scheme 7) was described, utilizing the endocyclic ring-opening of **54** to **55** as the key step.⁶⁸

Scheme 7. Endocyclic ring-opening of compound **54**.⁶⁸

a) Reiser et al. - 2022



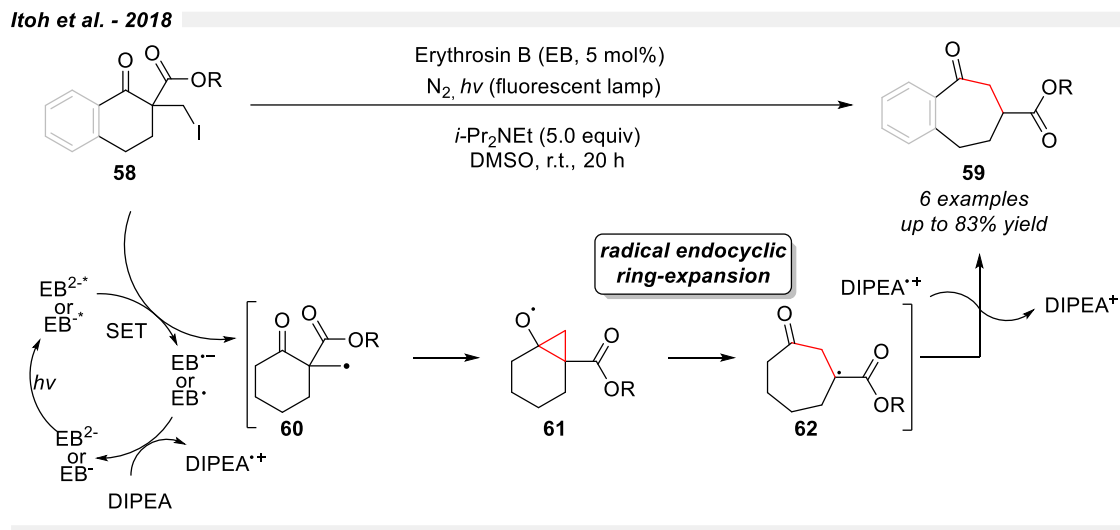
1.4. Cyclopropane Ring Enlargements via Radical Intermediates

Besides cationic activation processes, radical-initiated pathways for cyclopropane ring enlargements have been demonstrated in recent years.

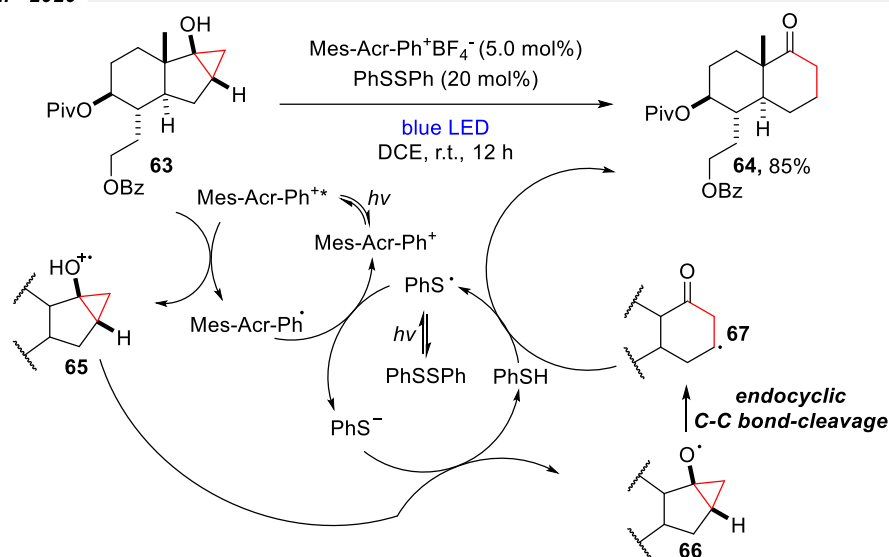
Itoh and co-workers improved the *Beckwith–Dowd*⁶⁹ ring-expansion by utilizing an organic dye for the photocatalyzed radical ring-enlargement of **58**.⁷⁰ Reduction of the C–I bond *via* photo-induced SET starts a radical cascade from primary radical **60** forming cyclopropane **61**, in which the donor-acceptor activated endocyclic cyclopropane bond is

cleaved to form the more stable tertiary radical **62**. To close the catalytic cycle hydrogen is abstracted from DIPEA^{•+} to give rise to **59** (Scheme 8).⁷⁰

Scheme 8. Photocatalyzed Beckwith–Dowd ring-expansion by Itoh and co-workers.



Cyclopropanols also, in the absence of a vicinal acceptor, undergo rapid ring-opening upon transforming the hydroxyl group to an O-centered radical driven by the release of ring-strain and the formation of a carbonyl moiety at the expense of a C-centered radical.^{71–74} This strategy was exploited by *Hurski et al.* with bicyclic cyclopropanol **63**, which was amenable to one-electron oxidation with concurrent deprotonation using acridinium catalyst ($\text{Mes-Acr-Ph}^+\text{BF}_4^-$) under blue-light excitation to form radical **66**. The endocyclic ring-opening to the secondary radical **67** is favored over the exocyclic ring-opening would result in a less stable primary radical (Scheme 9).⁷⁵

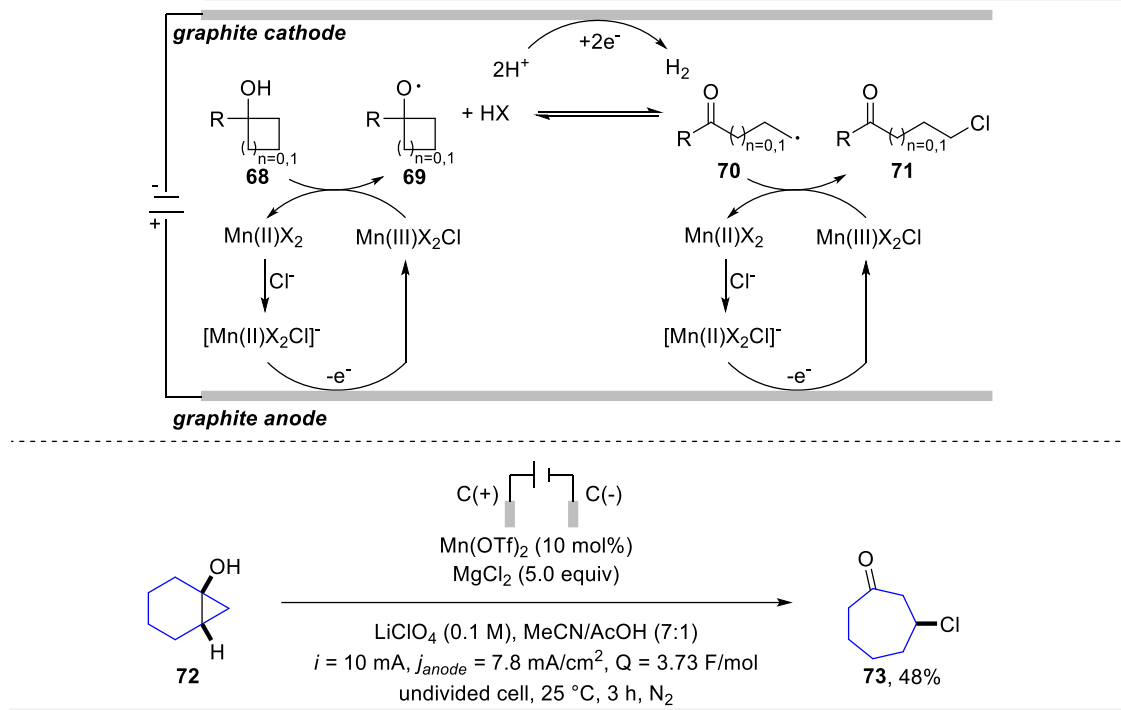
Scheme 9. Photocatalyzed ring-opening of cyclopropanols using acridinium catalyst.*Hurski et al. - 2020*

The field of organic electrochemistry is experiencing a renaissance steered by the demand for environmentally benign processes. Furthermore, the improvement and standardization of batch and flow electrochemical reactors have made them more attractive to the synthetic community.^{76–79} Not surprisingly, electrochemical strategies have also been applied to achieve ring-openings of cyclopropane moieties.

In 2019, *Morill* and co-workers described the electrochemically induced ring-opening of cycloalkanols **68**, producing chlorinated ketones **71** using a Mn(II) catalyst. From a mechanistic point of view, the radical endocyclic ring-opening can be compared to the previously demonstrated photocatalyzed reaction of cyclopropanol **63**, with the driving force of radical stabilization and C=O bond formation. Most examples of this study were shown for cyclobutanols, but the feasibility of a cyclopropanol **72** ring-expansion is illustrated as well, giving rise to **73** in 48% (Scheme 10).⁸⁰

Scheme 10. Electrochemical and radical-initiated ring-opening of cyclobutanols/cyclopropanol.

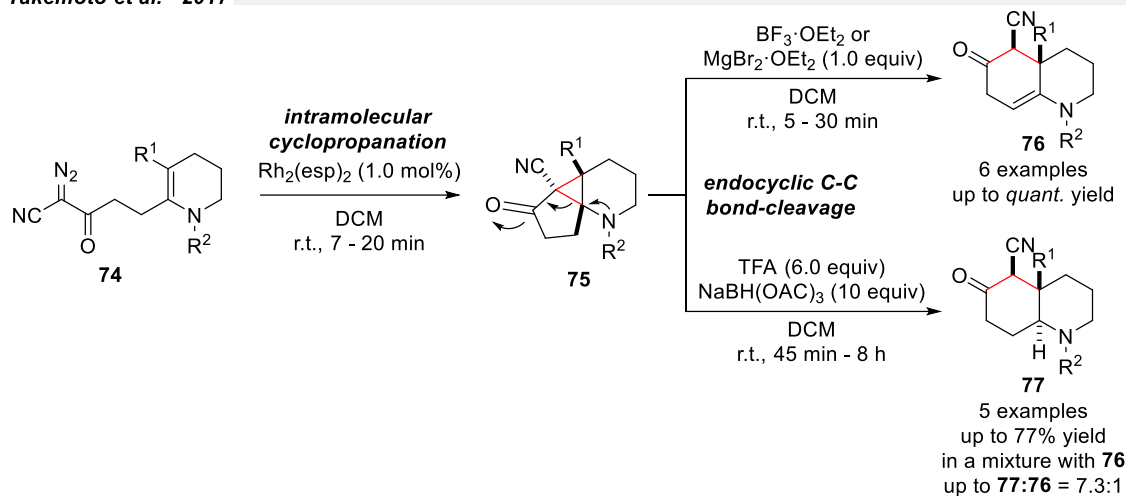
Morrill et al. - 2019



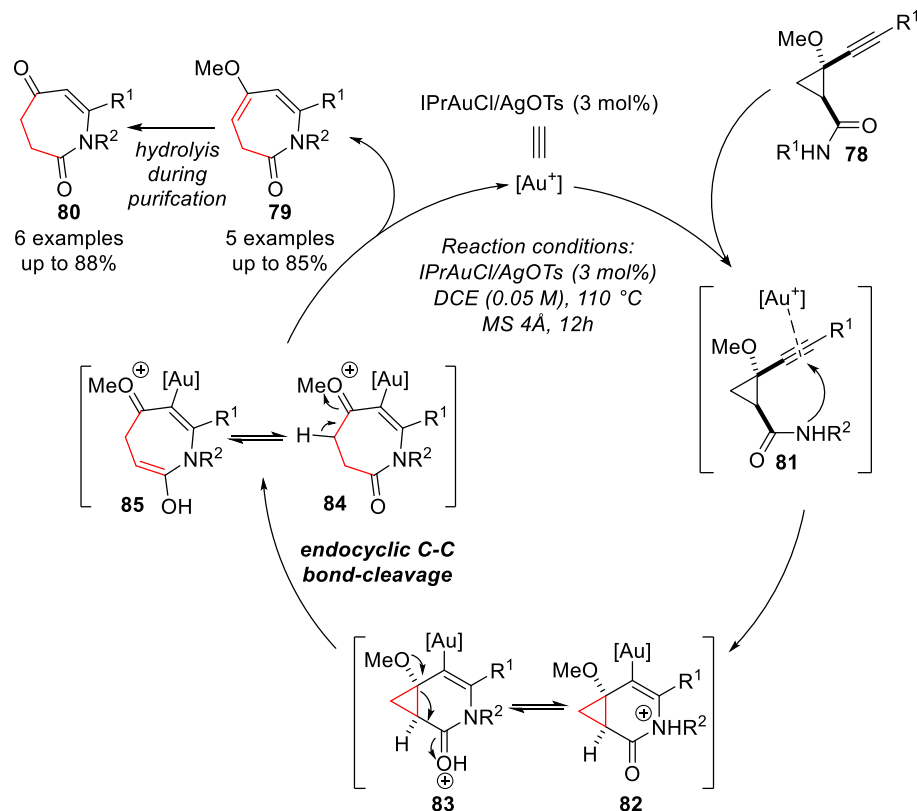
1.5. Donor-Acceptor Substitution Along the Endocyclic-Bond

Introducing donor and acceptor groups alongside the endocyclic bond results in a “push-pull-effect” between these groups and allows for an endocyclic C-C bond cleavage.

In their study, *Takemoto et al.* demonstrated a reaction cascade using diazo compound **74**, which undergoes intramolecular cyclopropanation with the help of a Rh(II) catalyst, resulting in the formation of cyclopropane **75**. Utilizing a Lewis acid increases the -M-effect of the carbonyl group in **75**. The lone-pair of the nitrogen as a donor and the -M-effect activate the endocyclic bond for ring-opening. While a proton transfer delivers the octahydroquinolines **76**, stereoselective reduction gives rise to the decahydroquinolines **77**. The endocyclic ring opening only occurs from the perspective of the cyclopentanone, while from the perspective of the piperidine structure, it is an exocyclic opening. Additionally, the authors showed that this process is accessible in a one-pot reaction starting from the diazo compound **74** (Scheme 11).⁸¹

Scheme 11. Lewis acid catalyzed one-pot ring-opening of **74**.Takemoto *et al.* - 2017

In 2017, *Aguilar et al.* illustrated a reaction that allows for the regioselective synthesis of azepinones **79/80** by gold-catalyzed cycloisomerization of functionalized cyclopropyl alkynes **78**.

Scheme 12. Gold-catalyzed cyclopropanation followed by endocyclic C-C bond cleavage.Aguilar *et al.* - 2017

The key step of this transformation is the *in-situ* formation of the bicyclic cyclopropanes **82/83** that are donor-acceptor substituted along the endocyclic bond. Noteworthy is that the gold catalyst does not participate in the endocyclic C-C bond cleavage. In a “*push-pull-fashion*”, the lone pair of the methoxy-group and the -M-effect of the carbonyl-group activate the endocyclic bond for ring-opening and give access to the 7-membered ring-systems **84** and **85**. After protodemetalation, azepinones **79** and **80** are obtained in good yields (Scheme 12).^{82,83}

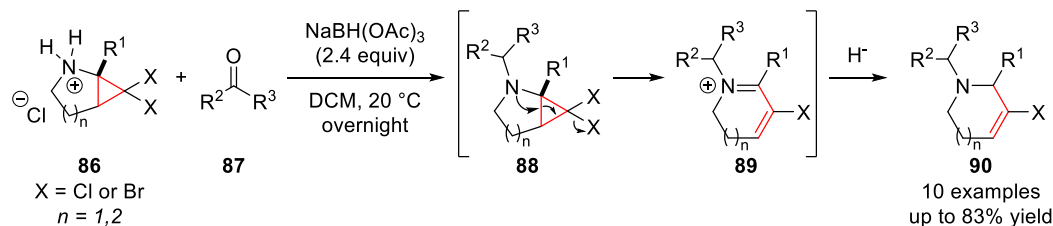
1.6. Leaving-Group on the Cyclopropane – 2π -Disrotatory Ring-Opening

Another approach that allows for a ring-expansion reaction is to generate a positive charge directly at the cyclopropane moiety through cleavage of a leaving group, followed by a 2π -disrotatory rearrangement.

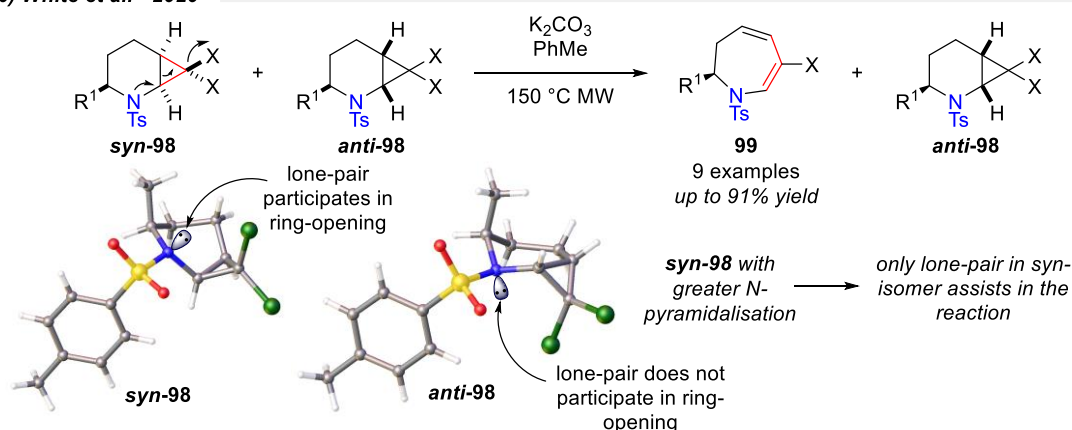
In 2017, *Six et al.* demonstrated a dehalogenative endocyclic ring-opening of the aminocyclopropane salts **86** under reductive amination conditions leading to functionalized azepanes ($n = 2$) and piperidines ($n = 1$) **90**.⁸⁴ The nitrogen lone-pair of aminocyclopropane **88** donates electrons into the ring system (“*push-effect*”) and supports the halogen-abstraction. Then, 2π -disrotatory rearrangement results in an endocyclic C-C bond cleavage from **88** (Scheme 13, a). The relative configuration of the leaving-group and the substituent on the cyclopropane are important for the reaction outcome. The authors discovered that the monochlorinated cyclopropane compounds **exo-91** and **endo-91** show different reactivities. While the *exo*-compound does not undergo the desired ring-opening reaction and instead forms the tertiary cyclopropylamine **92**, the *endo*-compound is converted into the ring-enlarged tetrahydroazepine **96**. This chemoselective transformation is in agreement with the *Woodward–Hoffmann–DePuy* rules: The authors postulate that the reaction proceeds through a 2π -electrocyclic cyclopropane-cleavage in a concerted way. Furthermore, the direction of the disrotatory ring-opening is determined by the relative configurations of the cyclopropane carbon atoms. The endocyclic bond breaks in the direction of the developing positive charge. Consequently, the substituents *trans* to the leaving group need to shift outward (see **94** to **95** in Scheme 13, a), resulting in the unacceptably strained E-isomer **93** from **exo-91**. However, **endo-91** is transformed into the Z-isomer **97** to afford the tetrahydroazepine **96** (Scheme 13, a).⁸⁴

Scheme 13. Ring-enlargement of halogenated aminocyclopropanes. The X-ray structures of **syn/anti-98** are taken from *ref. 85*.

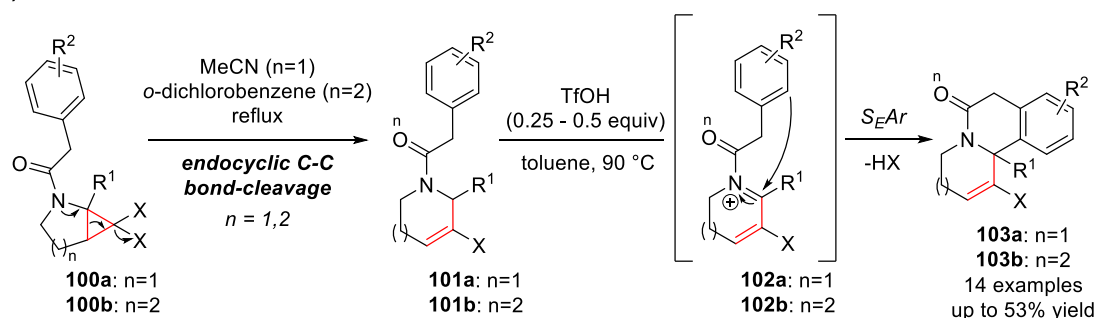
a) Six et al. - 2017



b) White et al. - 2020



c) Six et al. - 2023



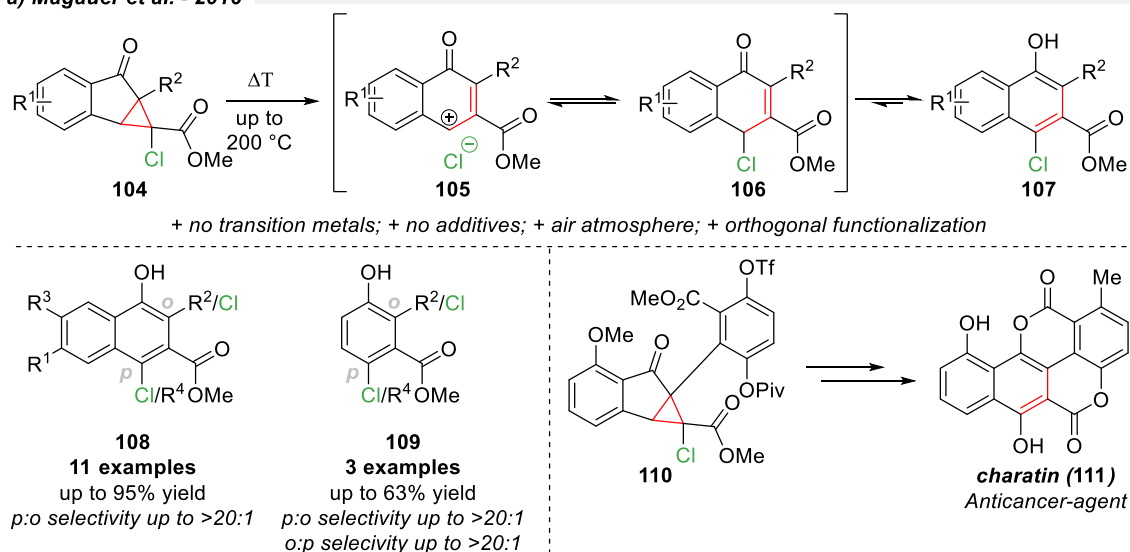
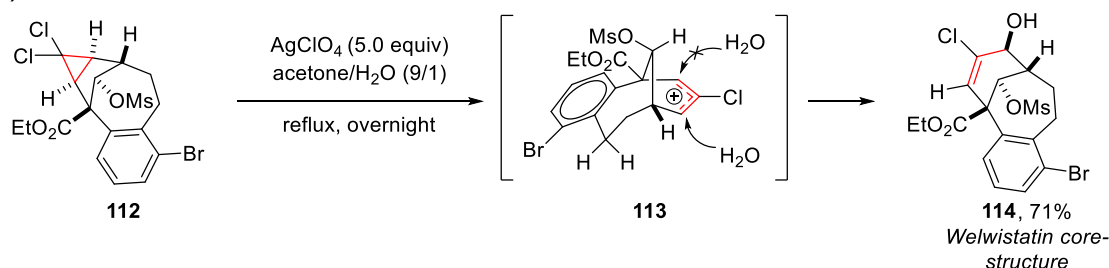
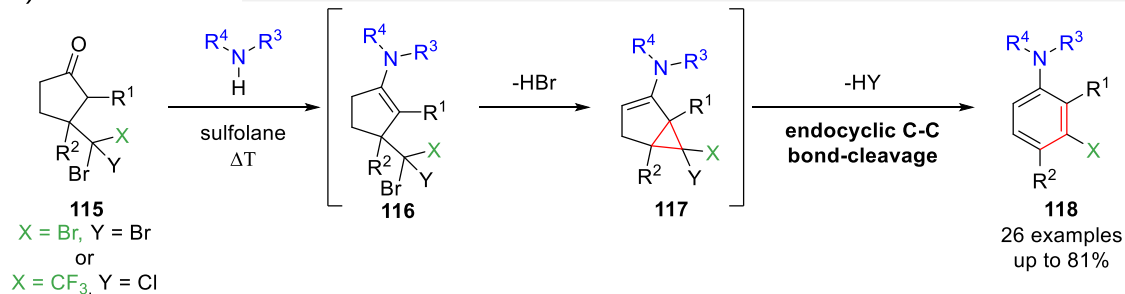
In 2020, *White* and co-workers discovered a similar chemoselective ring-opening reaction (Scheme 13, b).⁸⁵ When the **syn/anti-98** mixture is irradiated in the microwave at high temperatures and basic conditions, only the **syn**-isomer undergoes the desired ring-opening to **99**, while the **anti**-isomer does not react. The authors used X-ray structures of

syn-98 and **anti-98** to show that a higher degree of nitrogen pyramidalization in the *syn*-isomer occurs. Therefore, it was postulated that only the *syn*-isomer's nitrogen lone pair (see X-ray **syn/anti-98**, Scheme 13, b) can contribute to the ring-opening process.⁸⁵

Recently, *Six et al.* enhanced their study from 2017.⁸⁴ Via the described 2π -disrotatory rearrangement, cyclopropanated pyrrolidines **100a** are converted into stable pyridines **101a**. This method also allows for the synthesis of strained azepines **101b**. Additionally, after ring-enlargement, TfOH regenerates the cyclic iminium species **102** that can proceed in an intramolecular electrophilic aromatic substitution sequence to yield the polycyclic systems **103** (Scheme 13, c).⁸⁶

A study by *Magauer et al.* revealed that carbocyclic systems such as compound **104** require thermal activation of up to 200 °C to initiate a dehydrochlorination/endocyclic ring-opening process. In contrast to the heterocyclic compounds in Scheme 13, the lack of lone-pair and the -M-effect of the carbonyl group increase the activation barrier. The thermally activated disrotatory 2π -electrocyclic ring-opening of compound **104** leads to benzyl-cation **105**, followed by a regioselective attack of chloride-anion and aromatization to **107**. The substituted naphthols **108** and phenols **109** were obtained with good *para/ortho* selectivity. Moreover, the synthetic value was demonstrated by implementing this process into a synthetic route to the drug molecule *charatin* (**111**), an anticancer agent (Scheme 14, a).⁸⁷

In 2017, the *gem*-dichloro cyclopropane **112** was effectively converted into the ring-expanded system **114** via a dehydrochlorination/electrocyclic ring-opening process, followed by nucleophilic water addition (Scheme 14, b).^{51,55,88} In contrast to the reactions using aminocyclopropanes (see Scheme 13), the lack of donor-substituent results in a higher activation barrier for the halogen abstraction. Therefore, a silver catalyst and reflux conditions are required to initiate the chlorine cleavage followed by 2π -electrocyclic rearrangement. The subsequent nucleophilic attack of water to the cationic intermediate **113** takes place stereoselectively on the cyclic system's less hindered face. The molecule obtained (**114**, 71%) contains a core structure of *Welwistatin*, known as a cytotoxin (Scheme 14, b).^{88,89}

Scheme 14. Silver-promoted endocyclic C-C bond cleavage.**a) Magauer et al. - 2016****b) Chiu et al. - 2017****c) Bunch et al. - 2022**

Bunch and co-workers synthesized the highly functionalized aniline compounds **118** via a reaction cascade. The authors propose an imine formation from **115** followed by tautomerization to the enamine **116**, which then undergoes cyclization to the cyclopropane **117**. Then, the thermally allowed 2π -electrocyclic ring-opening takes place to form the aromatic aniline derivative **118** via dehydrohalogenation/endocyclic ring-opening (Scheme 14, c).⁹⁰

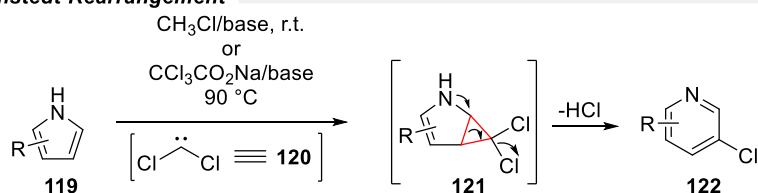
The *Ciamician-Dennstedt* rearrangement demonstrated that cyclopropanation of *N*-unprotected pyrroles **119** with dichlorocarbene **120**, generated under harsh conditions from $\text{CH}_3\text{Cl}/\text{NaOH}$, directly yields the 3-chloropyridines **122** by endocyclic ring-

expansion of the *in-situ* cyclopropane-adduct **121** (Scheme 15, a).⁹¹ However, yields are low due to the harsh reaction conditions and the *Reimer–Tiemann* formylation of pyrrole as a competing reaction.¹⁶

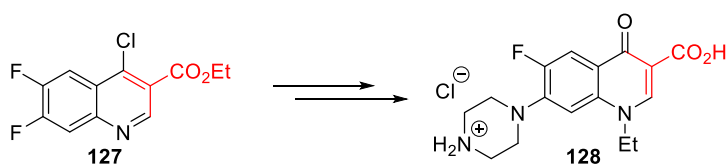
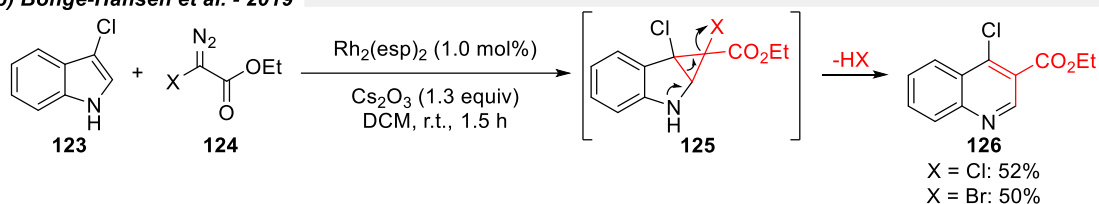
Bonge-Hansen and co-workers demonstrated a similar but more practicable way for this transformation.⁹² Rh(II)-catalyzed cyclopropanation of indole **123** with **124** delivers the *in-situ* DA-cyclopropane **125**, which rapidly undergoes endocyclic ring-opening to quinoline **126**. The fact that the *in-situ* synthesized cyclopropane **125** does not require further activation for dehydrohalogenation shows that the additional heteroatom and its “*push-effect*” significantly impact the reaction. Notably, the exocyclic cyclopropane bond in **125**, being in a donor–acceptor relationship between the ester group and the indole nitrogen, is not cleaved. With a halogen as a leaving group, 2 π -electrocyclic rearrangement occurs preferentially. This reaction was utilized to synthesize norfloxacin hydrochloride **128** from **127**, a potent quinoline antibiotic (Scheme 15, b).⁹²

Scheme 15. Endocyclic ring-opening via *Ciamician-Dennstedt* rearrangement.

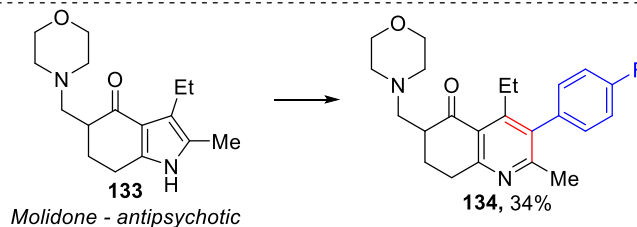
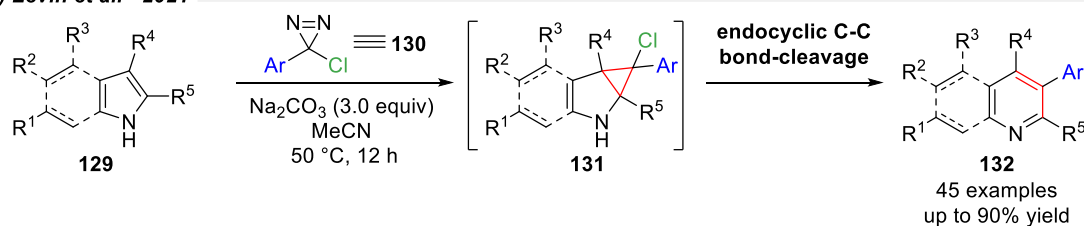
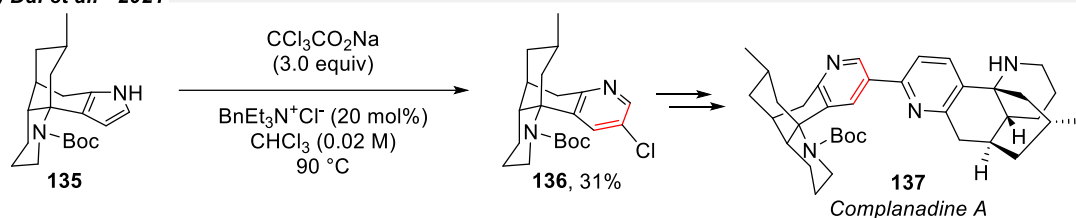
a) Ciamician-Dennstedt-Rearrangement



b) Bonge-Hansen et al. - 2019

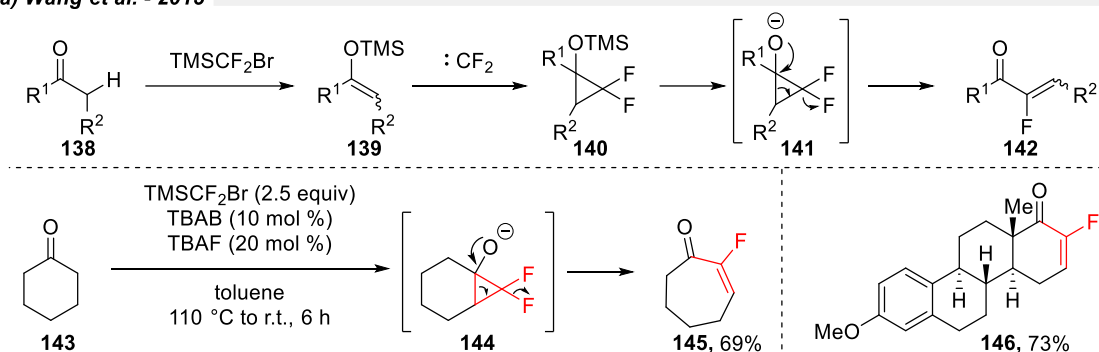
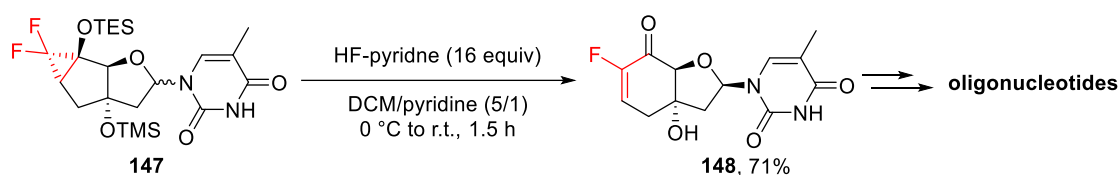


In 2021, the *Levin* group expanded the thermal dehydrochlorination/ring-opening method, taking inspiration from the *Ciamician-Dennstedt* rearrangement. The method was extended to pyrroles and indoles **129**, which are first cyclopropanated by the diazirine **130** to form cyclopropane **131**. Under mild conditions, thermally activated endocyclic C–C bond cleavage results in the formation of pyridines or quinolines **132** (Scheme 16, a).⁹³

Scheme 16. Variants of the *Ciamician-Dennstedt* rearrangement.**a) Levin et al. - 2021****b) Dai et al. - 2021**

Furthermore, the synthetic value was demonstrated by transforming complex structures such as the *Molidone* (**133**) into the corresponding pyridine **134**.⁹³ In contrast to the harsh reaction conditions of *Ciamician-Dennstedt*, a more elegant protocol was reported by using the sodium salt of trichloroacetic acid under phase-transfer-catalysis. By this approach, *Dai et al.* obtained pyridine **136** from unprotected pyrrole **135**, a key step in synthesizing *Complanadine A* (**137**, Scheme 16, b).⁹⁴

Wang et al. have reported a sophisticated method to perform cyclopropanation of ketone **138/143** or silyl enol ether **139** using difluorocarbene. This difluorocarbene is generated from TMSCF_2Br under phase-transfer-catalysis, followed by ring-expansion. The method provides a way to access α -fluor substituted enones **142** and **145** (Scheme 17, a).⁹⁵ Similar to the *Ciamician-Dennstedt* reaction, the heteroatom in **144** donates electrons to support the fluor abstraction that initiates the endocyclic ring opening. Notably, the -I-effect of the fluor-atoms and the +M-effect of the oxygen along the exocyclic bond do not lead to an exocyclic cyclopropane cleavage, suggesting that the -I effect is insufficient to activate this bond. The authors demonstrated the synthetic value by a late-stage functionalization to form compound **146** (Scheme 17, a).

Scheme 17. Ring-opening of *gem*-difluoro cyclopropanes.**a) Wang et al. - 2015****b) Leumann et al. - 2018**

In 2018, *Leumann et al.* utilized this method to synthesize the ring-enlarged tricyclic compound **148** via dehydrofluorination/ring-opening of cyclopropane **147**. The molecule was incorporated into an oligonucleotide to study the pairing properties with complementary DNA and RNA (Scheme 17, b).^{95,96}

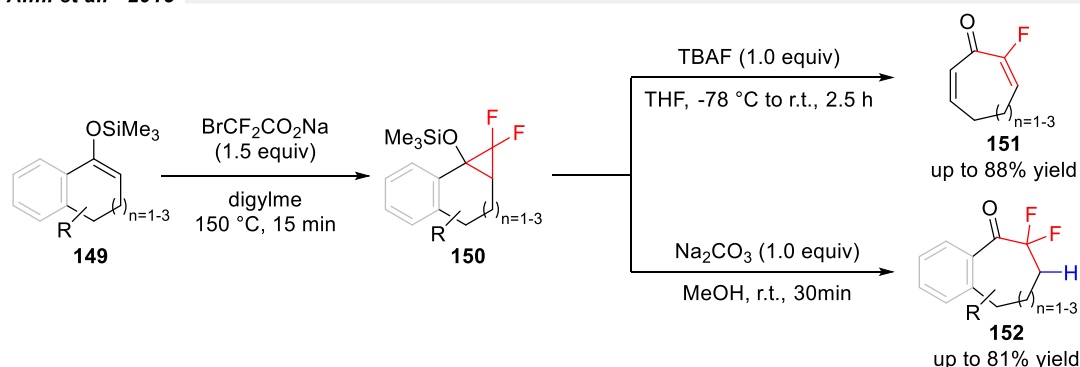
In 2015, *Amii et al.* used the sodium salt of bromodifluoroacetate to form the difluoro cyclopropane **150** from **149**. This cyclopropane undergoes the same endocyclic ring-opening process as shown in Scheme 17a. The addition of TBAF resulted in the formation of α -fluorine substituted enones **151** in good yields (Scheme 18, a). Using MeOH as a protic solvent under basic conditions, the availability of a proton changes the reaction course and gives rise to the *gem*-difluorinated cycloalkanone **152** as the product. In a “push-pull-fashion” alongside the endocyclic bond resulting from the donor (heteroatom) and the acceptor (electrophile), endocyclic C-C bond cleavage of **150** occurs, followed by electrophilic addition (Scheme 18, a).⁹⁷

Dilman et al. demonstrated that this reaction can also occur under acidic conditions. The provision of a proton facilitates the endocyclic bond cleavage of **153**. In contrast, under aprotic conditions, (DCM) ring-opening via dehydrofluorination from **155** predominantly result in the formation of the monofluorinated enones **157**. This illustrates the selective reactivity of these compounds (Scheme 18 b).⁹⁸ Utilizing NXS as the electrophile, the *gem*-difluoro cyclopropane **160** undergoes an endocyclic ring-expansion via halogenation

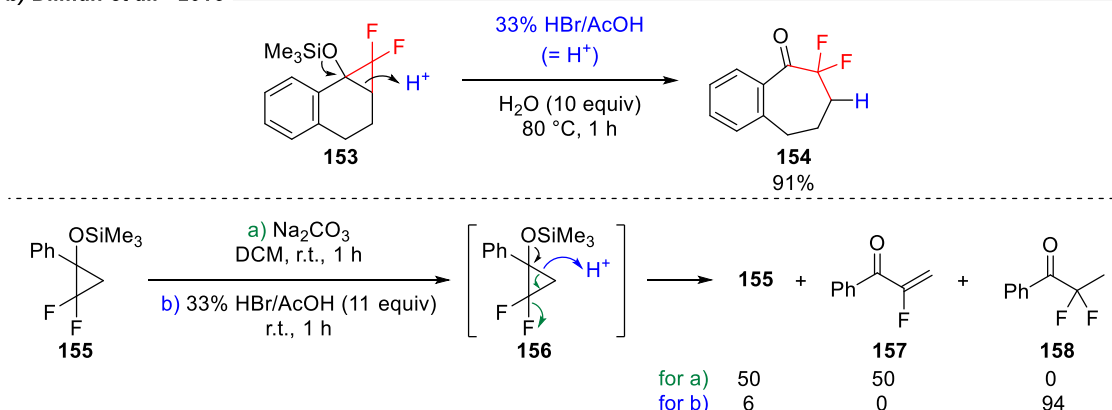
of the C-H bond to form **161** (Scheme 18, c).⁹⁹ The notable feature of this reaction is the capability to simultaneously introduce a *gem*-difluoromethyl group and an additional halogen substituent into a ketone.

Scheme 18. Expansion of the endocyclic ring-opening of *gem*-difluoro cyclopropanes.

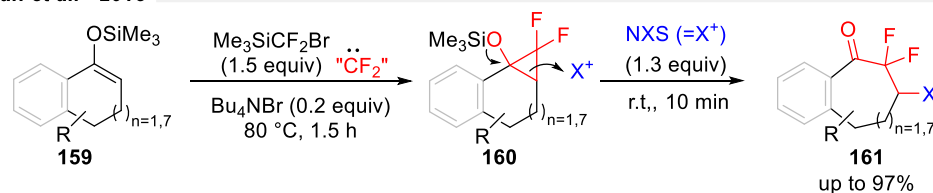
a) Amii et al. - 2015



b) Dilman et al. - 2015

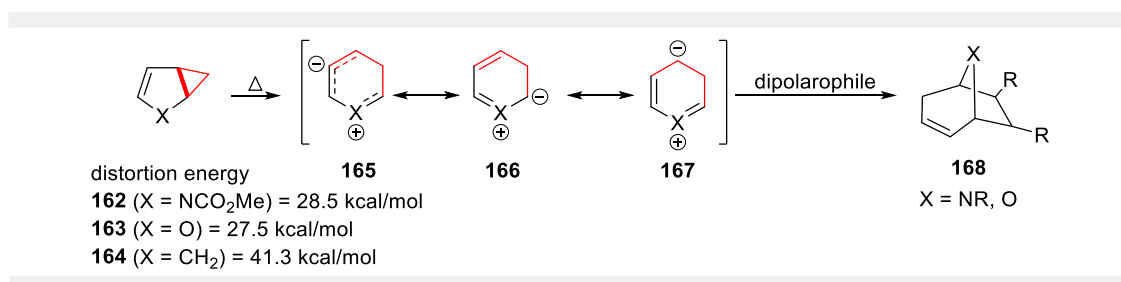


b) Dilman et al. - 2015



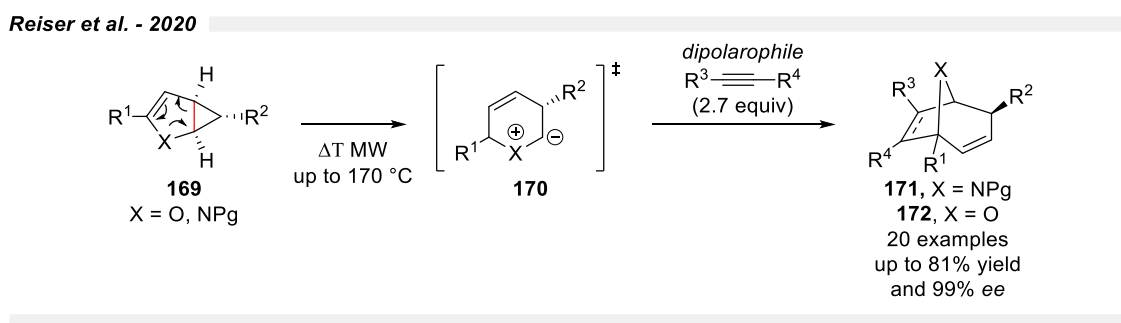
1.7. 6π-Electrocyclic Ring-Opening

Electrocyclic rearrangement can be used as a versatile tool in organic synthesis to rearrange the core structure of a molecule by activating a compound with light or thermal energy. In 2013, mechanistic studies by Yu and co-workers confirmed that low distortion energies allow the rearrangement of a molecule by thermal activation.¹⁰⁰

Scheme 19. 6 π -electrocyclic ring-opening of bicyclic cyclopropanes.¹⁰¹

While the distortion energies of homo-pyrrole **162** (28.5 kcal/mol) and homo-furan **163** (27.5 kcal/mol) are relatively low, due to the +M-effect of the heteroatom, the high distortion energy of bicyclo[3.1.0]hex-2-ene **164** of 41.3 kcal/mol does not allow the formation of a 1,3-dipole **165** under thermal activation. Therefore, heating of **162/163** results in a 6 π -electrocyclic ring-opening to ring-expanded dipoles **165**, **166**, and **167**. Adding a dipolarophile affords the bridged system **168** (Scheme 19).^{100,101}

In 2020, *Reiser et al.* took advantage of this reaction type and irradiated the cyclopropanated pyrroles/furans **169** at high temperatures using the microwave, which resulted in a 6 π -electrocyclic rearrangement. The *in-situ* formed transient 1,3-dipole **170** was then trapped by a dipolarophile, which affords the bridged molecules **171/172** via [3+2]-cycloaddition (Scheme 20).^{47,101}

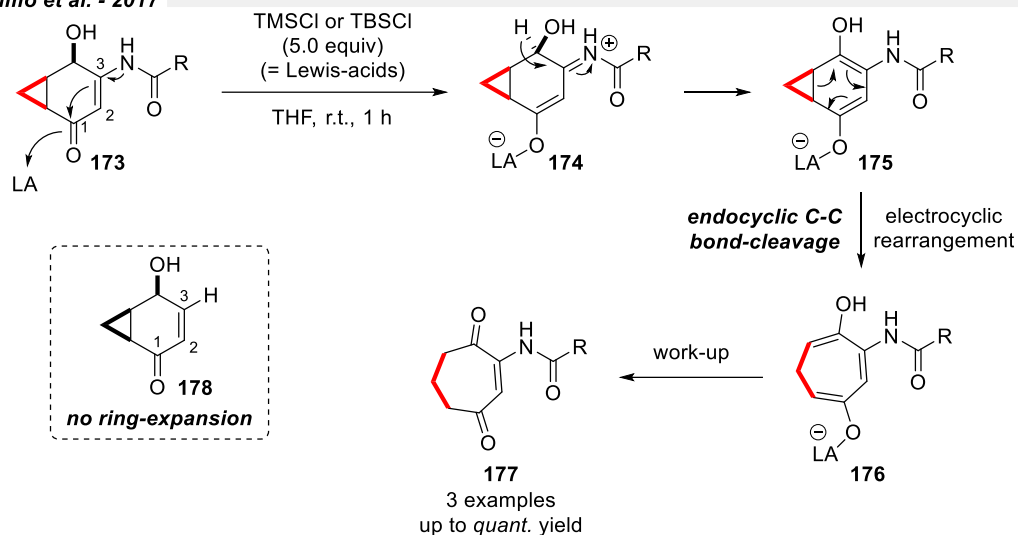
Scheme 20. Thermal-activated 6 π -electrocyclic endocyclic ring-opening.

As *Nagumo* and co-workers showed in 2017, this reaction is not limited to heterocyclic compounds. Starting from **173**, the authors observed the 7-membered carbocycles **177** with excellent yields. It was discovered that the substitution pattern at the C-3 position is crucial for the endocyclic ring-opening process since **178** did not lead to ring-enlarged products under the same conditions. Therefore, the authors postulated that the Lewis acid coordinates with the carbonyl to form an iminium-ion **174** facilitated by the +M-effect of

the nitrogen. Subsequent deprotonation results in norcaradiene motif **175**, which converts into **176** via 6 π -electrocyclic ring-opening (Scheme 21).¹⁰²

Scheme 21. Electrocyclic ring-opening of **173**.

Nagumo et al. - 2017



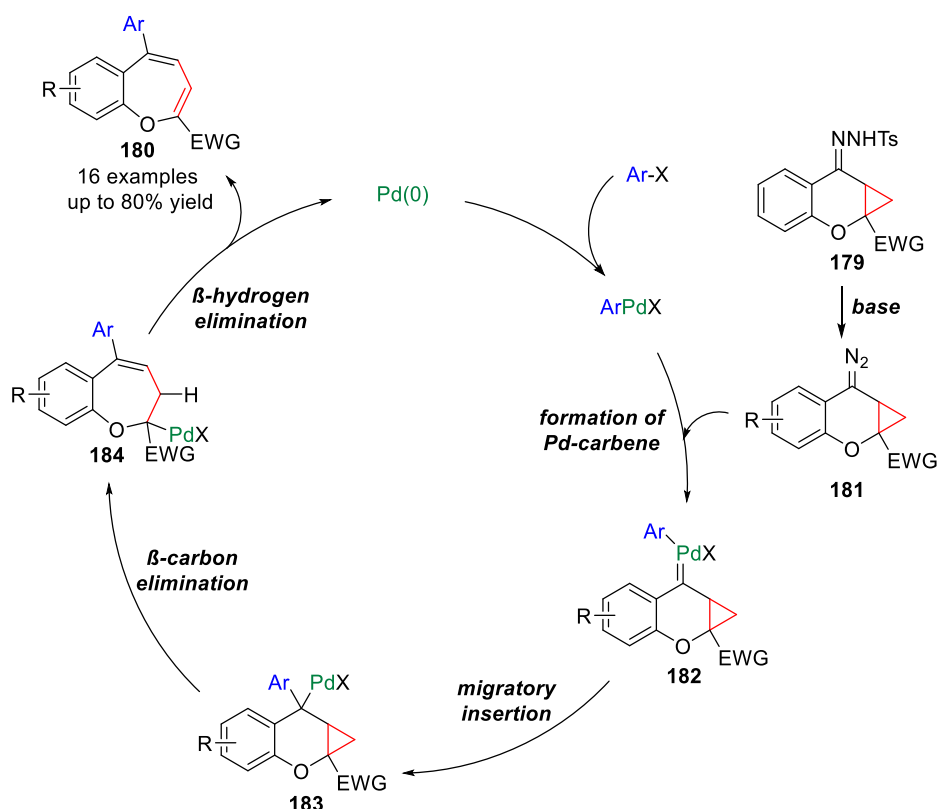
1.8. Transition-Metal Migration

As shown in the previous chapters, Lewis or Brønsted acids often facilitate ring-expansion reactions. In recent years, the selective cleavage of cyclopropane bonds *via* transition-metal catalysis has gained significant attention.

The *Bamford-Stevens reaction* shows that tosylhydrazones can form diazo-compounds upon treatment with strong bases.¹⁰³ Furthermore, Pd-catalyzed ring-opening reactions of cyclopropanes bearing a tosylhydrazone-group together with aryl halides were investigated in former literature reactions.¹⁰⁴ In 2016, *Zhou* and co-workers utilized this reaction type to synthesize the benzoxepines **180** *via* an endocyclic ring-enlargement reaction, starting from tosylhydrazone **179**. The key-step of this reaction involves the formation of the Pd-carbene species **182**, followed by migratory insertion, which shifts the palladium to the designated α -cyclopropyl-position (**183**). β -carbon-elimination leads to the desired ring-opening reaction to afford benzoxepines **180** in a vast number of examples (Scheme 22).¹⁰⁵

Scheme 22. Pd-catalyzed ring-enlargement of tosylhydrazones **179**.¹⁰⁵

Zhou et al. - 2016

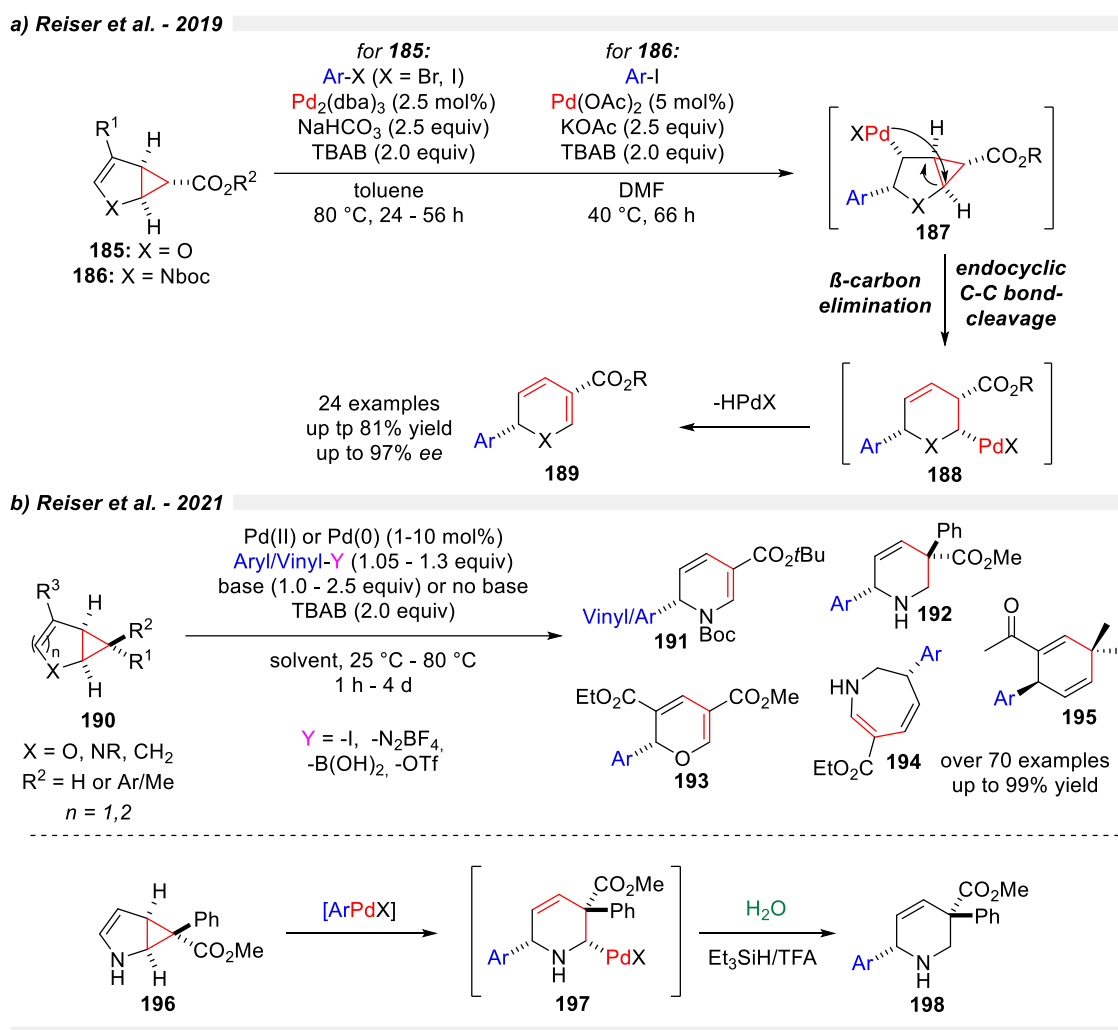


Similarly, *Reiser* and co-workers demonstrated an endocyclic ring-opening reaction via β -carbon-elimination of compound **187**, giving rise to six-membered heterocycles **189** with excellent yields and *ee*'s. In contrast to *Zhou*'s reaction, the desired alkyl-palladium intermediate **187** was accessible via a *Heck-type* reaction of heterocyclic vinyl cyclopropanes **185** or **186**. Notably, the initial electronic setting of the fused cyclopropanes (**185/186**) directs the palladium into the desired α -cyclopropyl-position (Scheme 23, a).⁶¹

In 2021, this reaction type was extended to various bicyclic cyclopropanes **190**. By this approach, the authors demonstrated access to larger ring systems **194** and 1,4-cyclohexadienes **195**. Furthermore, an assortment of coupling partners, such as aryl boronic acids, aryl diazonium salts (*Heck-Matsuda-type reaction*)²⁵, vinyl triflates, and aryl halides, gave rise to over 70 examples of ring-expansion products (**191** – **195**). Remarkably, the study was enhanced to *gem*-substituted cyclopropanes **196**. In this case, the organopalladium intermediate **197** cannot recover the catalyst through β -hydrogen-elimination. Therefore, water was employed as a nucleophile to displace the palladium

and to close the catalytic cycle. After a reduction with $\text{Et}_3\text{SiH/TFA}$, tetrahydropyridine **198** was obtained (Scheme 23, b).¹⁰⁶

Scheme 23. Pd-catalyzed ring-opening of vinyl cyclopropanes.

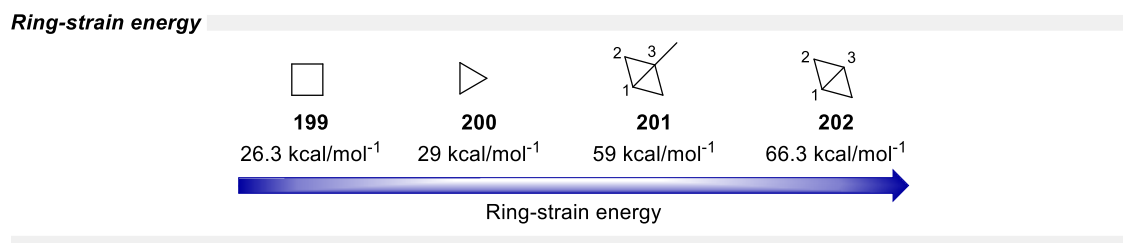


1.9. Release of Ring-Strain

Bicyclobutanes (BCB) are a fascinating class of compounds in organic chemistry that contains unique characteristics such as high reactivity, compact size, and electronic properties of both σ and π bonds of the $\text{C}^1\text{-C}^3$ bond (Scheme 24). The primary driving force behind reactions involving BCB is the significant reduction of ring-strain. While (substituted) BCB possesses a ring-strain energy (RSE) in the range of 59 – 66.3 kcal/mol^{-1} , an endocyclic C-C bond cleavage to cyclobutane means a loss of about 40 kcal/mol^{-1} (Scheme 24).¹⁰⁷ In synthetic chemistry, utilizing BCB in ring-strain release reactions has recently emerged as a powerful tool to synthesize bicyclo[1.1.0]pentanes,

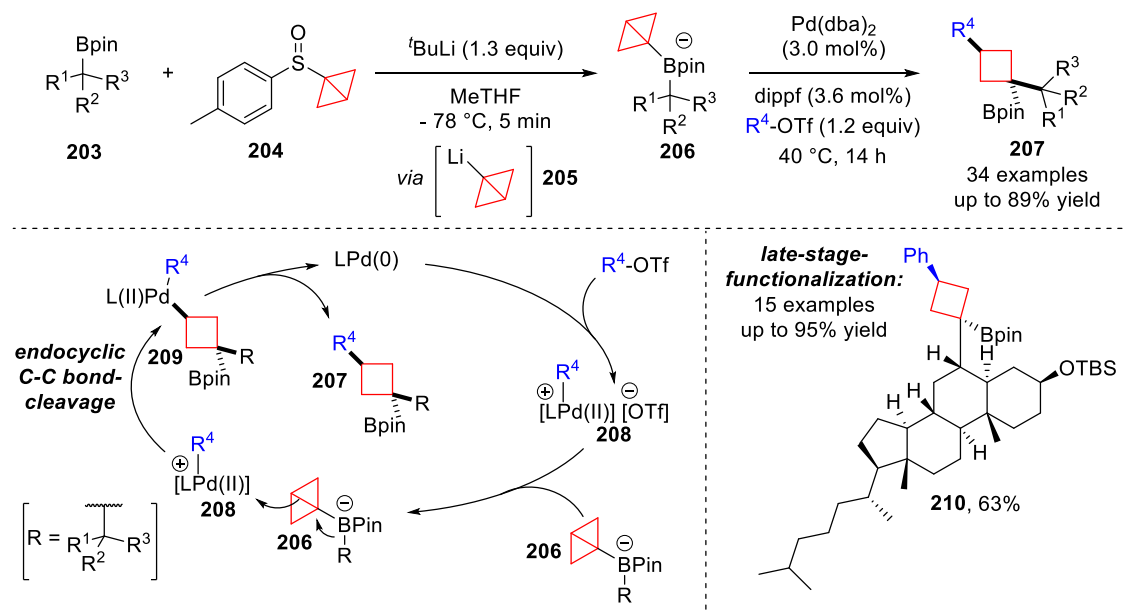
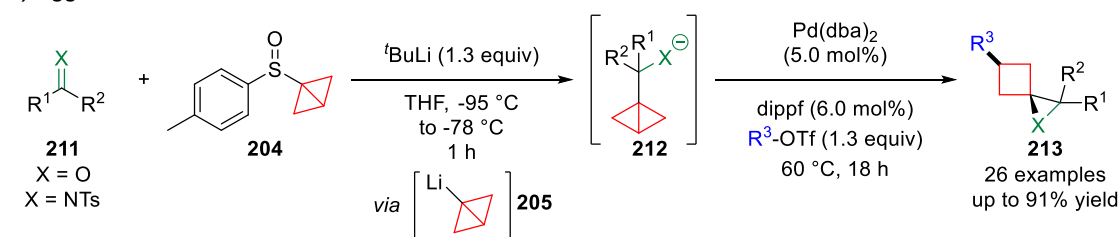
azetidines, and cyclobutanes, especially in combination with transition-metals.^{108,109} In contrast to cyclobutane **199**, the RSE of cyclopropane **200** is slightly higher, resulting in a preferential endocyclic rather than exocyclic ring-opening (Scheme 24).

Scheme 24. Ring-strain energy of cyclobutane **199**, cyclopropane **200** and BCB **201/202**.



An approach of Pd-catalyzed endocyclic C-C bond cleavage of bicyclobutanes, exploiting the ring-strain release as the driving force, was shown by *Aggarwal et al.*¹⁰⁹ The classical *Suzuki–Miyaura* reaction is a reaction sequence beginning with oxidative addition between an aryl halide and Pd(0), followed by transmetalation with an organoboron reagent, and reductive elimination.^{109–111} In 2019, *Aggarwal* and co-workers described a similar reaction type with a new fundamental reaction step: endocyclic C-C bond cleavage of a strained bicyclo[1.1.0]butyl boronate complex **206** via C–C σ bond carbopalladation to yield the highly substituted cyclobutanes **207** (Scheme 25, a).¹⁰⁹

The authors' mechanistic hypothesis begins with a classical oxidative addition between the Pd(0)-complex and the aryl/alkyl-triflate ($R^4\text{-OTf}$) to obtain the reactive aryl-Pd(II)-species **208**. This species **208** reacts then with the previously synthesized boronate-complex **206** from the sterically more accessible *exo*-face of the bicycle. The interaction of the two species **206** and **208** results in a 1,2-metallate rearrangement. This leads to simultaneous 1,2-migration of R to the α -carbon, cleavage of the central C–C σ bond, and formation of a C–Pd bond at the β -carbon (= C–C σ bond carbopalladation, **209**). Reductive elimination then affords the arylated cyclobutanes **207** in various examples. In addition to their importance as synthetic intermediates, cyclobutanes can be found in numerous natural products and drug molecules.^{112–114} Therefore, the utility of this method was demonstrated in variety of late-stage functionalization (e.g., compound **210**, Scheme 25, a).¹⁰⁹

Scheme 25. C-C σ bond carbopalladation demonstrated by *Aggarwal* and co-workers.**a) Aggarwal et al. - 2019****b) Aggarwal et al. - 2023**

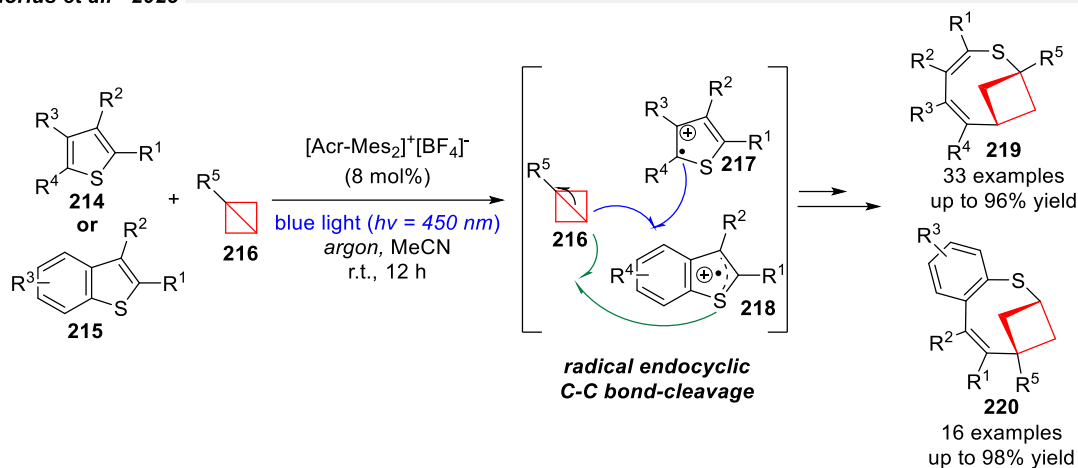
Recently, *Aggarwal* and co-workers expanded the study by using bicyclobutyl carbinolate compound **212** as the starting material, which was synthesized from carbonyl or imine **211** and bicyclobutane **204**. In a similar reaction, C-C σ bond alkoypalladation occurs with the simultaneous formation of a new C-O bond at the α -carbon. This is followed by endocyclic cleavage of the strained central C-C bond and palladation of the β -carbon. Finally, reductive elimination gives rise to the 1-oxaspiro-[2.3]hexane or 1-azaspiro[2.3]hexane products **213** in excellent yields (Scheme 25, b).¹¹⁵

Glorius et al. utilized the high ring-strain of BCB to afford the endocyclic ring-expansion of compound **216** under photocatalytic conditions. Mechanistic studies have shown that the blue-light excited-state photocatalyst $[\text{Acr-Mes}_2]^+[\text{BF}_4]^-$ is quenched by the (benzo)thiophenes **214** or **215**, resulting in the formation of the radicals **217** or **218**. DFT-calculations disclosed that the rate-determining step is the addition of the radicals **217/218** to BCB **216**, accompanied by endocyclic C-C bond cleavage. After a reaction cascade, cyclobutane is inserted into the thiophene ring, giving rise to bicyclic ring systems **219** or

220 (Scheme 26).¹¹⁶ This insertion of a carbocycle into a heterocycle follows a new concept called the “ring-in-a-heterocycle concept.”

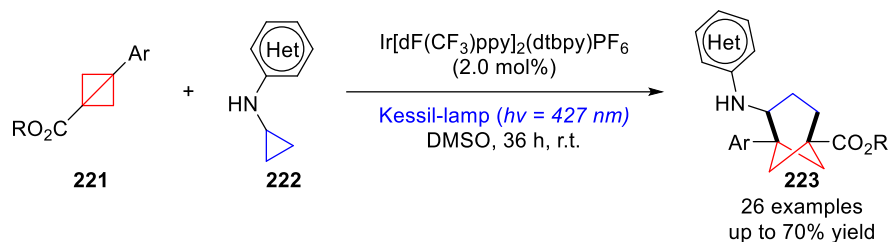
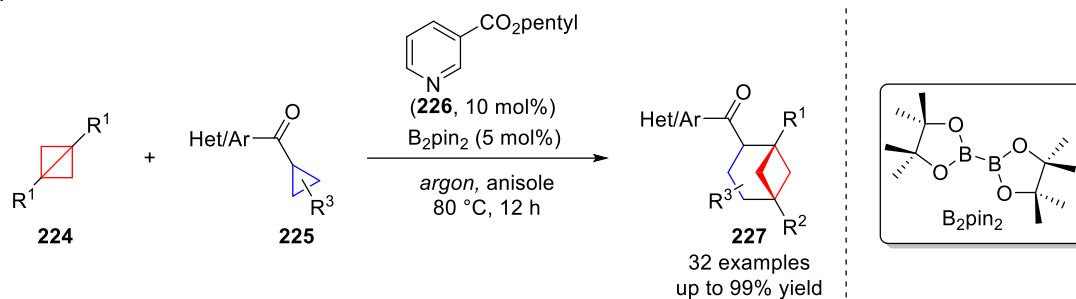
Scheme 26. The “ring-in-a-heterocycle concept” by Glorius *et al.*

Glorius et al. - 2023



In a comparable approach, *Molander et al.* illustrated the radical endocyclic C-C bond cleavage of BCB **221**. The authors reported a photochemical $[3\sigma + 2\sigma]$ annulation reaction between BCB-compound **221** and aminocyclopropane **222** under Ir(III) catalyst irradiation. The 4-aminobicyclo[3.1.1]heptanes **223** were obtained in good yields (Scheme 27, a).¹¹⁷ In contrast, *Li et al.* described a selective $[2\sigma + 2\sigma]$ radical cycloaddition reaction between BCB **224** and cyclopropyl ketones **225** via a pyridine-assisted boronyl radical catalysis. This method is modular, concise, and atom-economical, providing high yields of the desired bicyclo[3.1.1]heptanes **227** (Scheme 27, b).¹¹⁸

When comparing, it is evident that the *Molander* reaction has certain disadvantages. For instance, an expensive iridium catalyst is used, albeit furnishing lower yields. On the other hand, *Li's* method uses the inexpensive non-metallic boron-compound B₂pin₂ as the catalyst, resulting in almost quantitative yield.

Scheme 27. "Ring-in-a-ring concept" by Molander *et al.* and Li *et al.*^{117,118}**a) Molander *et al.* - 2022****b) Li *et al.* - 2023****1.10. Conclusion**

In this short literature review, the versatile reaction behavior of cyclopropanes has been demonstrated, allowing for the endocyclic C-C bond cleavage, a valuable synthetic concept for designing highly functionalized large ring systems with diverse chemical functionalities. During recent years, it was shown that small changes in the substitution pattern and the reaction conditions lead to selective cleavage of the cyclopropane bond with notable differences in the resulting products. Furthermore, the reactivity of the cyclopropanes is investigated in all essential areas of organic synthesis: From transition-metal catalysis and (Lewis-)acid catalysis to electrochemical- or photocatalyzed reactions and thermal activation. Continued research in this area of chemistry extends the possibility of the selective ring-opening strategy of cyclopropanes. Above all, synthesizing large ring systems and late-stage derivatization increases the efficiency of finding new drug related molecules.

2. References

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B. Main Part

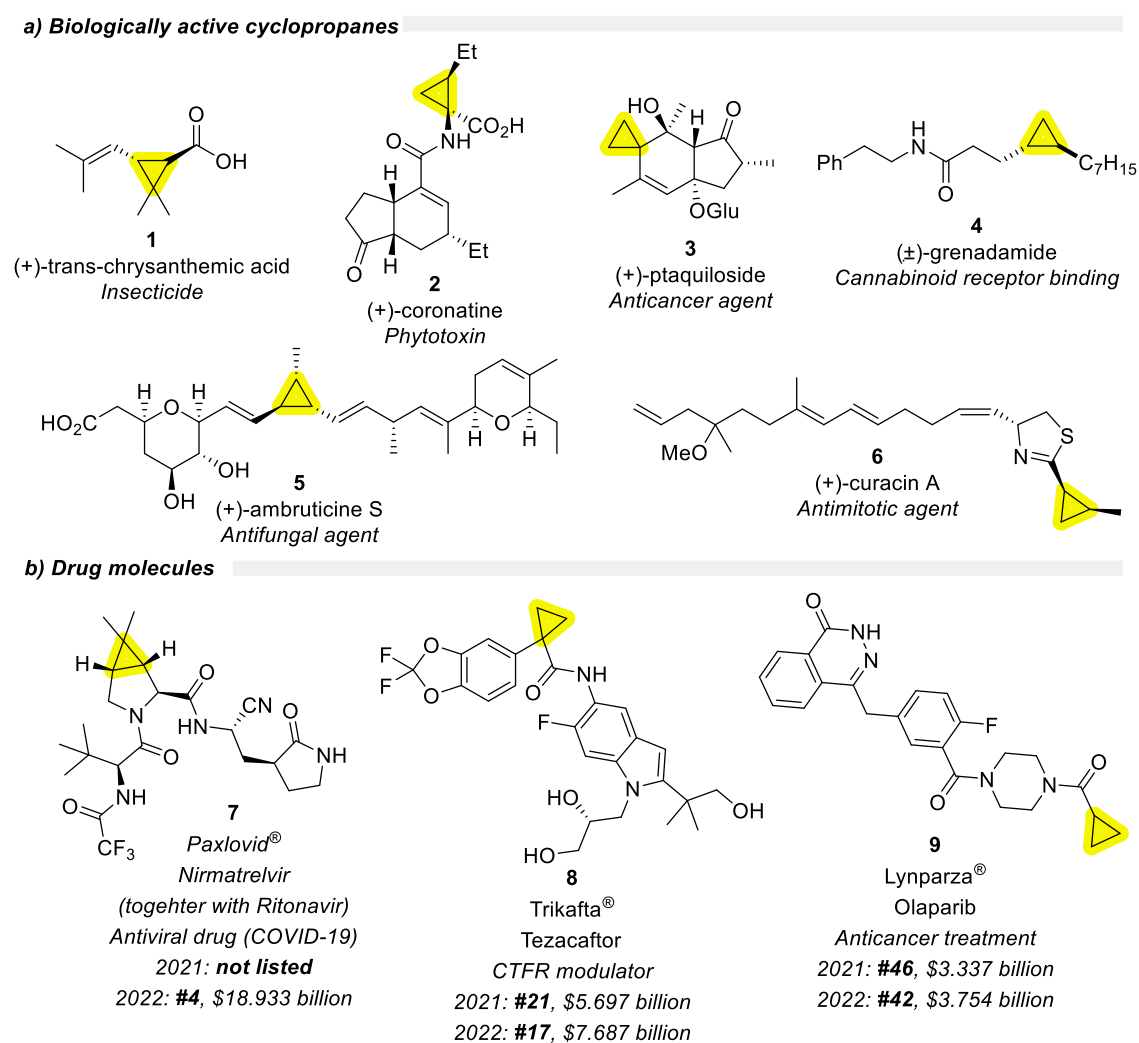
1. Direct Cyclopropanation of Cyclopentadiene

1.1. Introduction

1.1.1 Biologically Active Cyclopropanes

Cyclopropanes – first described by August Freund in 1882¹ – are of great interest in pharmaceutical and organic chemistry since the cyclopropane skeleton is widely distributed in various natural products with biological activity.^{2–8} Isolated from plants, fungi, and microorganisms, this structural motif can mostly be found in terpenoids, fatty acid metabolites, pheromones, and unusual amino acids.⁵

Figure 2. a) Biologically active cyclopropanes. b) Synthetically active cyclopropanes.



Some important biologically active cyclopropanes that occur in nature (a) and are seen as drug precursors include: (+)-trans- chrysanthemic acid (**1**), an early example of an insecticide isolated from the pyrethrum flowers.^{5,9,10} (+)-Coronatine (**2**), produced by *Pseudomonas syringae* strains, shows phytotoxin activity¹¹. (+)-ptaquiloside (**3**), a major toxin of *bracken*, and (+)-curacin A (**6**) isolated from the cyanobacterium *Lyngbya majuscula*. Both show antimitotic and anticancer properties and are considered potential drug lead candidates.^{5,12–14} Another natural cyclopropane from the bacterium *Lyngbya majuscula* is (±)-grenadamide (**4**) with cannabinoid receptor binding activity of $K_i = 4.7 \mu\text{M}$ and a modest brine shrimp toxicity of $\text{LD}_{50} = 5 \mu\text{g/mL}$.^{15,16} Lastly, (+)-ambruticin S (**5**) is an antifungal polyketide from the myxobacterium *Polyangium cellulorum* (Figure 2, a).¹⁷

A comparison of sales data for drug molecules on the market reveals a continuous increase in the significance of cyclopropane drug leads. Nirmatrelvir (**7**), for example, sold under the brand name Paxlovid[®] together with Ritonavir, is an antiviral drug used to treat of mild to moderate COVID-19 symptoms, especially for adults with high-risk progression.¹⁸ Not listed in 2021, it is among the top four selling drugs in retail sales with \$18.933 billion in 2022.¹⁹ Tezacaftor (**8**), known by the brand name Trikafta[®], improved its sales from \$5.697 billion in 2021 to \$7.687 billion in 2022, rising from the 21st to 17th best-selling pharmaceuticals in retail-sales and is used in combination with Ivacaftor and Elexacaftor for the treatment of cystic fibrosis.^{19,20} Olaparib (Lynparza[®], **9**), a PARP-inhibitor drug for the therapy of ovarian cancer, improved to 42nd place with sales of \$3.754 billion in 2022 (2021: 46th place, \$3.337 billion in sales, Figure 2, b).^{19,21–23}

In conclusion, developing new synthetic routes and designing novel potential biological active cyclopropanes as potent drug molecules for the pharmaceutical industry is a challenging task for organic chemists.

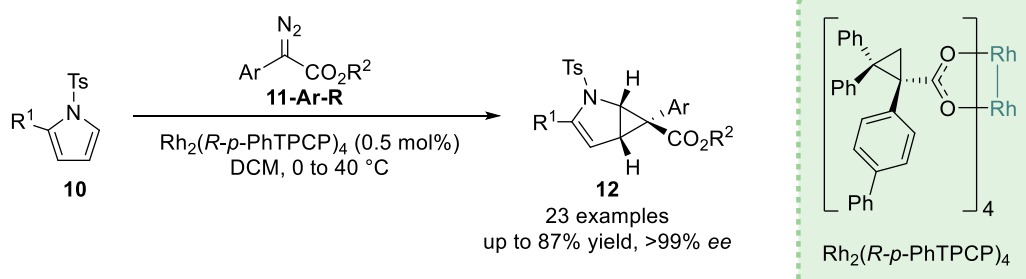
1.1.2 Rhodium and Blue-Light Cyclopropanation

Besides the classical approaches, such as the *Simmons-Smith cyclopropanation*²⁴, the *Johnson-Corey-Chaykovsky reaction*,^{25,26} or the *Kulinkovich reaction*²⁷ numerous amounts of various cyclopropanation reactions have been developed over the past few decades with significant impact in organic chemistry.^{28–34} Among all the methods in the literature, the cyclopropanation of olefins by diazo compounds under transition-metal

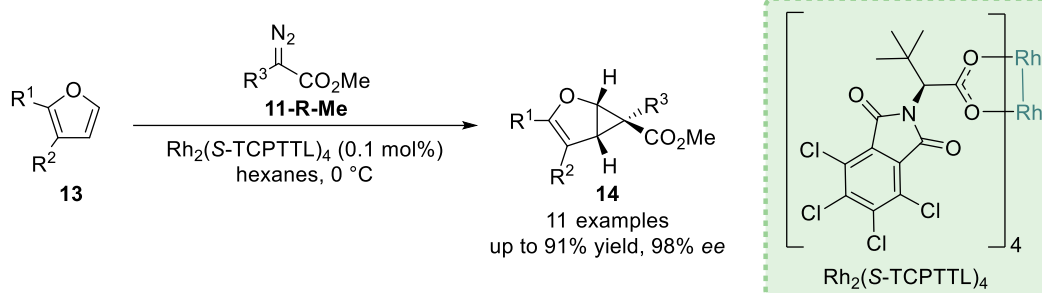
catalysis is one of the best-studied and efficient strategies, particularly with a view on the design of enantiopure compounds.^{35–42}

Scheme 28. Selected examples of Rh(II)- and Cu(I)-catalyzed cyclopropanation of furan and pyrrole.

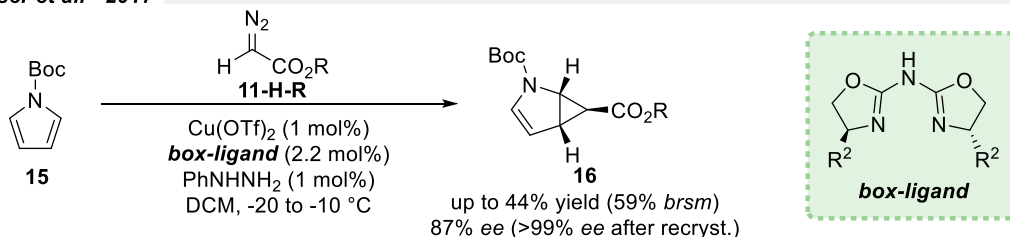
Reiser and Davies et al. - 2019



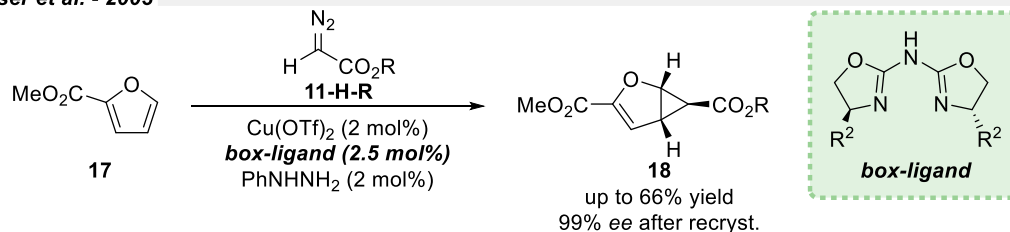
Davies and Reiser et al. - 2017



Reiser et al. - 2017



Reiser et al. - 2003

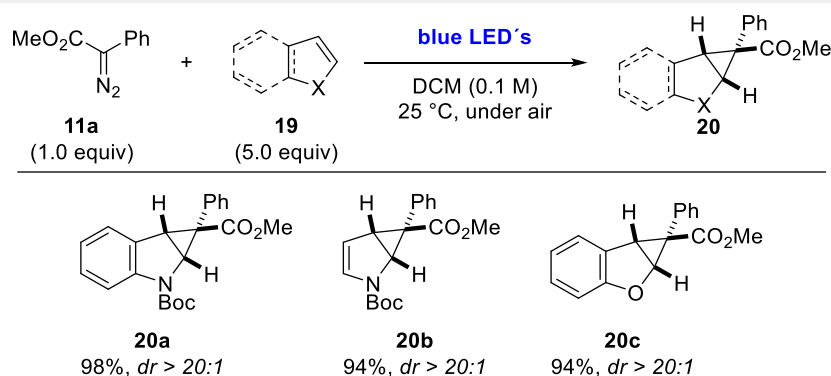


Used transition-metals are copper (Cu), gold (Au), palladium (Pd), rhodium (Rh), zinc (Zn), ruthenium (Ru), iron (Fe), nickel (Ni), cobalt (Co), titanium (Ti) and yttrium (Y) which all have different properties and catalytic effects leading to an immense cyclopropanation scope depending on the catalyst.²⁹ *Reiser et al.* and *Davies et al.* together extensively studied the (asymmetric) cyclopropanation of heterocycles, mostly furans **13** and **17** or pyrroles **10** and **15**, using diazoacetates under Rh(II)- or Cu(I)

catalysis.^{28,43–53} Interestingly, aryl diazoacetates **11-Ar-R** could be used under rhodium-catalysis, while non-aryl acetates **11-H-R** only succeeded with copper (Scheme 28).

Davies et al. introduced a new method for cyclopropanation reactions of styrene and some heterocycles/carbocycles **19** in 2018. Unlike the traditional transition-metal catalyzed cyclopropanation, this method does not require a catalyst. Instead, it utilizes blue-light photolysis to form a carbene from an aryl diazo-compound **11a**. The process is stereoselective and gave rise to compounds **20a–c** (Scheme 29).⁵⁴

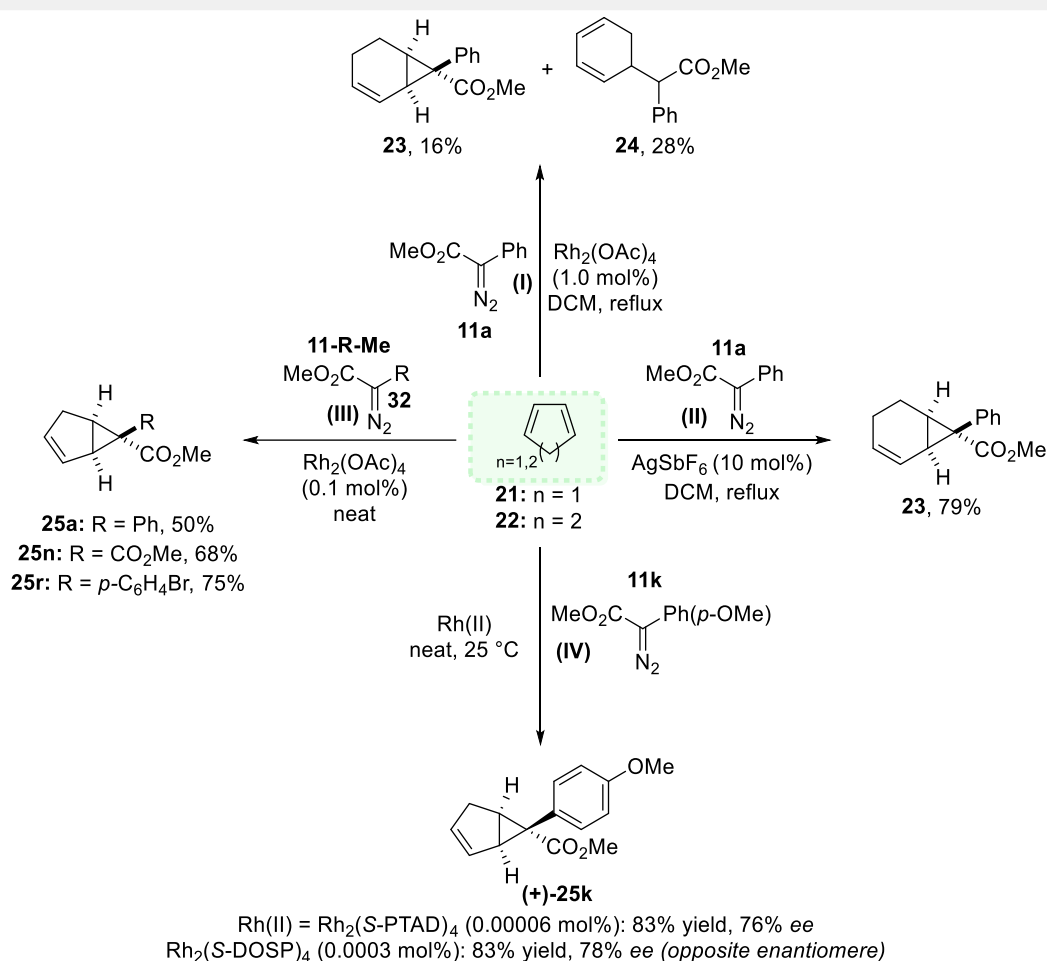
Scheme 29. Selected examples of photochemical cyclopropanation of heterocycles.



Since then, the photochemical cyclopropanation reaction with diazoacetates under visible-light has become a powerful method.^{54–61} When this project started in early 2020, the process of directly combining cyclopropanation of carbocyclic analogs, specifically cyclopentadiene **21** with diazo acetates, had not been thoroughly explored (Scheme 30).^{62–65}

In the case of the Rh(II)-catalyzed cyclopropanation of 1,3-cyclohexadiene **22**, the vinyl cyclopropane **23** (16%) was formed only as a side product. The C-H insertion as the predominant reaction (**24**, 28 %, Scheme 30, I) could be avoided by using a silver catalyst (**23**, 79%, Scheme 30, II).⁶³ Cyclopropanation of cyclopentadiene **21** was done by using Rh₂(OAc)₄ with good yields (**25a,n,r**, Scheme 30, III), while asymmetric cyclopropanation was done by using minimal amounts of Rh₂(S-PTAD)₄ or Rh₂(S-DOSP)₄. The desired enantiomer (+)/(-)-**25k** was obtained with high turnover numbers in a solvent-free reaction medium (Scheme 30, IV).^{64,65}

Scheme 30. Selected examples of direct cyclopropanation of cyclopentadiene **21** and 1,3-cyclohexadiene **22**.

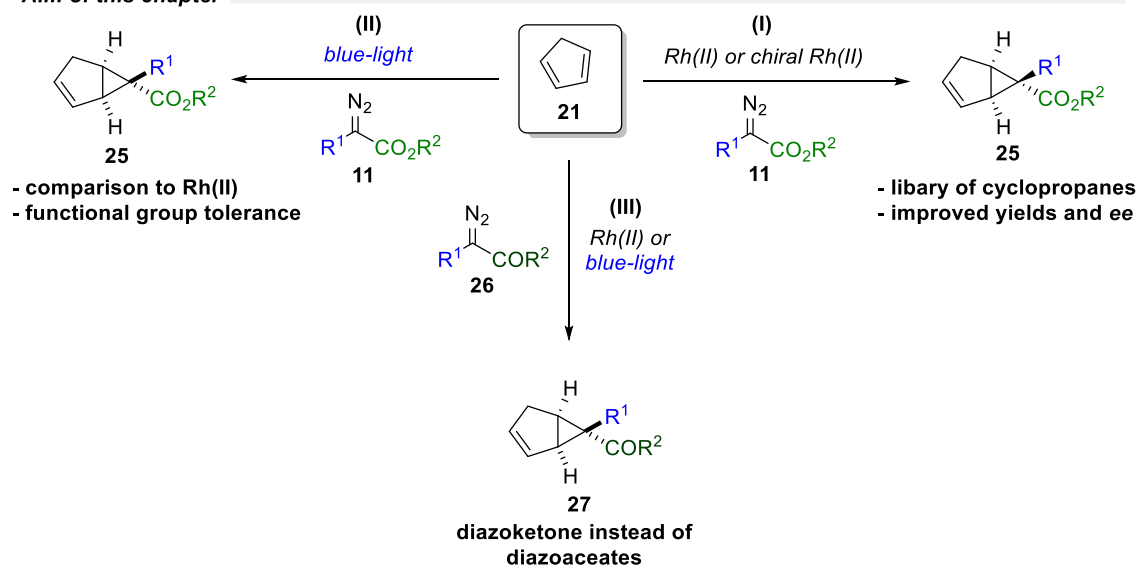


1.1.3 Aim of This Chapter

For this chapter, the aim was to expand the scope of the cyclopropanation of cyclopentadiene **21** using rhodium while improving the asymmetric reaction towards higher yields, greater reaction scope, and increased *enantiomeric excess* (Scheme 31, I).

In the second part, the blue-light mediated cyclopropanation of cyclopentadiene **21** using aryl diazoacetates **11** should be compared to established Rh(II)-cyclopropanation, and conclusions from the scope and yield should be gained towards functional group robustness (Scheme 31, II).

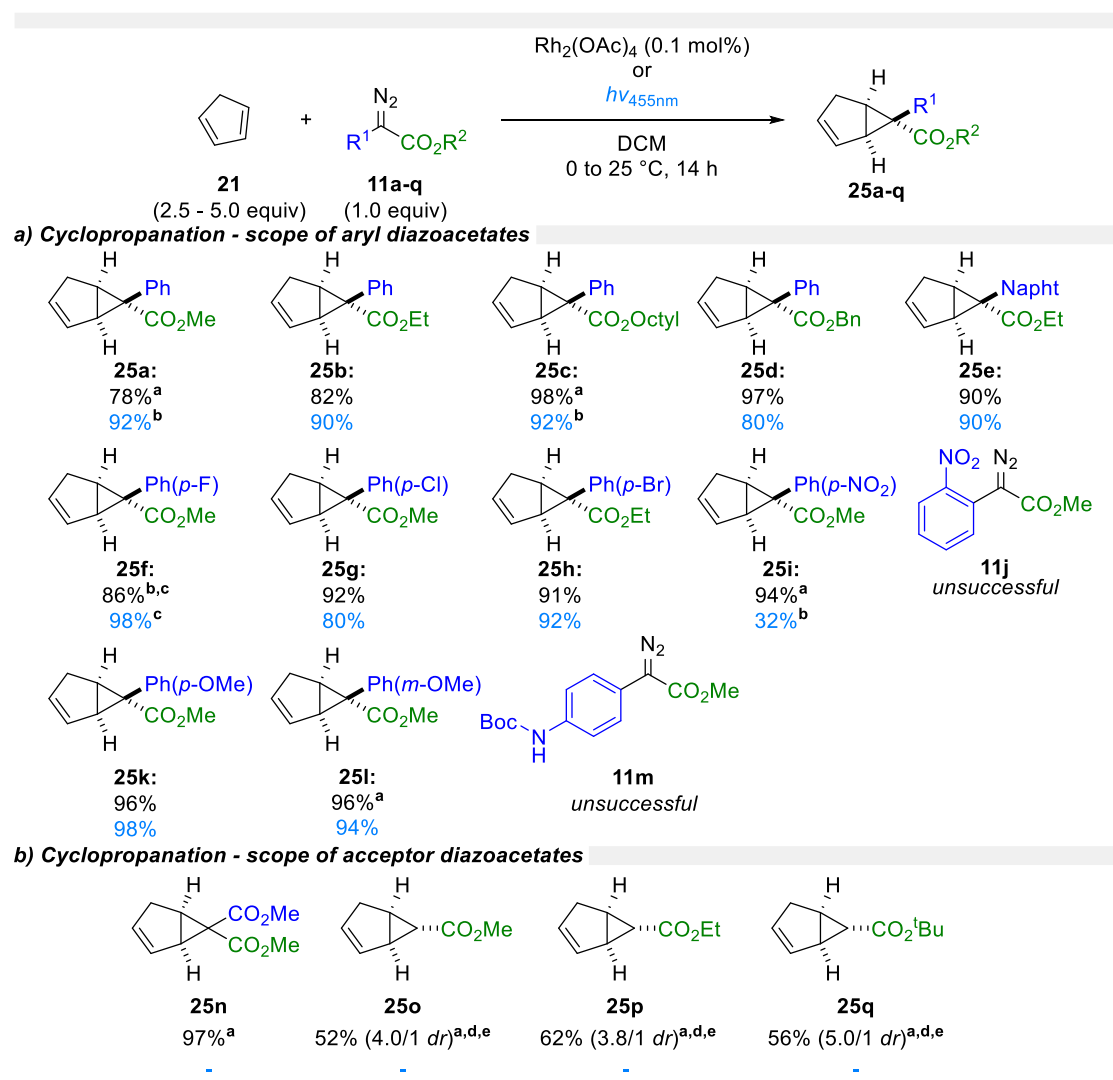
Finally, the best conditions from cyclopropanation of cyclopentadiene will be adapted for diazoketones **26** to investigate their behavior under Rh(II) catalysis and blue-light excitation (Scheme 31, III).

Scheme 31. Aim of this chapter.**Aim of this chapter**

1.2. Comparison of Rh(II)-Catalyzed and Blue-Light-Promoted Cyclopropanation of Cyclopentadiene

With a slightly modified literature procedure, the cyclopropane **25a** was obtained in good yield (78%) and could be synthesized on a gram-scale.⁶⁴

Scheme 32. Scope of the Rh(II)-catalyzed vs. blue-light promoted cyclopropanation of cyclopentadiene.⁶⁶



Reactions were performed on a 1.0 – 2.0 mmol scale. 2.5 – 5.0 equiv cyclopentadiene (**21**) were used. [a] Gram-scale synthesis: **11a** (59.0 mmol) to **25a** (9.90 g), **11c** (9.11 mmol) to **25c** (2.79 g), **11i** (9.09 mmol) to **25i** (2.22 g), **11l** (29.3 mmol) to **25l** (6.87 g), **11n** (15.6 mmol) to **25n** (2.96 g), **11o** (43.2 mmol) to **25o** (3.08 g), **11p** (23.8 mmol) to **25p** (2.24 g), **11q** (12.0 mmol) to **25q** (1.21 g) [b] Yield was determined using fumaronitrile as internal standard. [c] Reactions were performed on a 3.0 mmol scale. [d] Diastereomeric ratio was determined from crude ¹H-NMR. [e] Major diastereomer is shown.

With a practicable protocol, a library of different substituted vinyl cyclopropanes **25a-q** was synthesized with moderate to excellent yields. By increasing the steric of the ester moiety, compared to **25a**, a trend was observed, showing yields of up to 98%

(**25d**~**25c**>**25b**>**25a**), which is probably an outcome of better stability in solution of the used aryl diazoacetates (**11d**~**11c**>**11b**>**11a**). No significant tendency was seen by increasing the aryl group's steric or introducing electron-withdrawing or -donating groups at the phenyl-moiety. However, obtained yields are excellent, ranging from 86% to 96% (**25f** – **25l**), showing that this method is robust for many functional groups. Only aryl diazoacetates **11j** and **11m** could not be used with this method. The free amine functionality of **11m** probably is poisonous to the catalyst. Since *para*-NO₂ is tolerated, the *ortho*-position of the nitro group has to be the problem without any reasonable explanation (Scheme 32, a).

In the study, acceptor diazoacetates without an aryl group were used to synthesize compound **25n**, which had an excellent yield of 97%. Lacking the steric hindrance of the aryl group, acceptor-only diazoacetates **11o** – **11q** produced the cyclopropanes with diastereomeric ratios ranging from *dr* = 3.8/1 (**25p**) to *dr* = 4.0/1 (**25o**) and *dr* = 5.0/1 (**25q**). Compared to the aryl diazoacetates, the stability of **11o**-**11q** decreases in solution, which should explain the additional drop in yield (Scheme 32, b).⁶⁵

Proceeding with the blue-light mediated cyclopropanation of cyclopentadiene, a new reaction protocol following a publication by Davies *et al.* was developed.⁵⁴ 5.0 equivalents cyclopentadiene **21** and 1.0 equivalent of the corresponding aryl diazoacetate **11a-m**, both dissolved in DCM, are irradiated under blue-light ($h\nu = 455\text{nm}$), achieving excellent yields of **25** (Scheme 32, a).

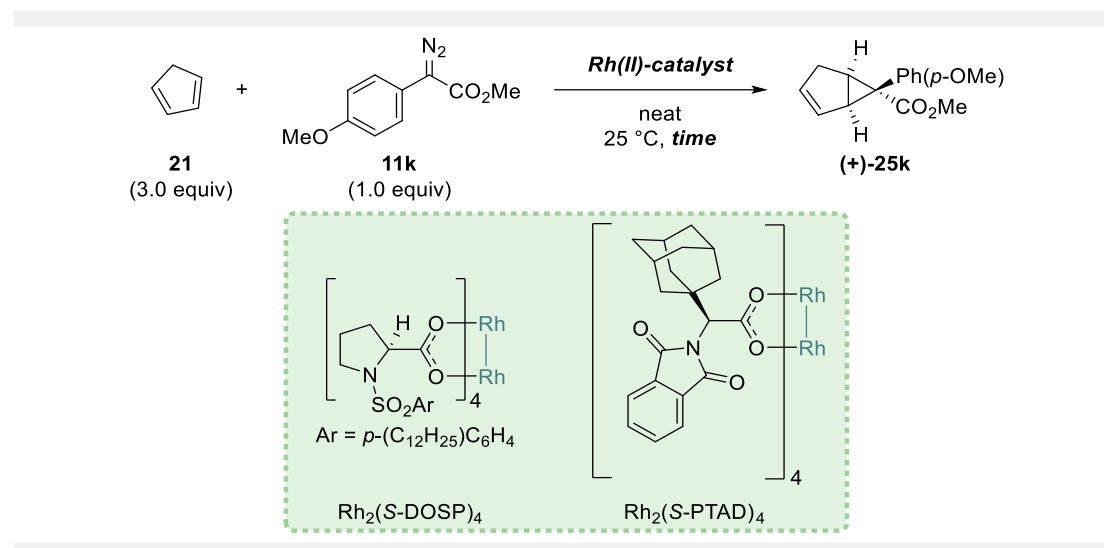
Compared to the Rh(II)-catalyzed reaction, the results are similar without following a particular trend. Yields are excellent from 80% (**25d**) to 98% (**25f/25k**), and again high diastereoselectivity (*dr* > 20:1) was achieved. In some cases (**11a** and **11f**), the yields could be improved, showing that the photochemical reaction is as robust as the transition-metal catalyzed cyclopropanation. Only the yield of **25i** (32%) dropped significantly, possibly, because the NO₂ group gets excited itself under blue-light and undergoes an ISC (intersystem crossing), forming a biradical. Diazoacetates lacking the aryl group are not tolerated in this method since they could not be excited, which is in agreement with the literature (Scheme 32, a) and b).⁶⁵

Summarized, the direct cyclopropanation of cyclopentadiene could be effectively achieved by two distinct methods with a good scope, excellent yields of up to 98%, high diastereoselectivity, and a straightforward reaction setup.

1.3. Asymmetric Cyclopropanation

Biological active cyclopropanes often have unique chiral characteristics, so novel or improved asymmetric cyclopropanation is particularly interesting for organic synthesis.²⁹ Besides the vast number of asymmetric reactions that have been shown in this field in recent years,^{5,29,36,42,67} the asymmetric cyclopropanation of cyclopentadiene **21** with diazoacetates remained underexplored. In 2010, *Davies et al.* conducted a study on the asymmetric Rh(II)-catalyzed cyclopropanation of cyclopentadiene **21** using diazoacetate **11k**. They reported good yields and a moderate enantiomeric excess (ee) in a solvent-free reaction with high turnover numbers (TONs) and low catalyst loading (Table 2).⁶⁵

Table 2. Asymmetric cyclopropanation of cyclopentadiene with **11k**.⁶⁵



Entry	Catalyst	Loading [mol%]	Time [h]	Yield (+)- 25k [%]	ee (+)- 25k [%]	TON
1	$\text{Rh}_2(\text{S-DOSP})_4$	0.0003	9	83	78	2.6×10^5
2	$\text{Rh}_2(\text{S-PTAD})_4$	0.0001	10	86	74 ^{a)}	6.7×10^5
3	$\text{Rh}_2(\text{S-PTAD})_4$	0.00006	72	83	76 ^{a)}	1.3×10^6

^a Opposite enantiomer of drawn product formed.

In cooperation with the *Davies* group, the aim was to enhance the *ee*'s and expand the scope of their previously shown study.^a

Starting with an *ee* screen of the cyclopropanation of cyclopentadiene (**21**, 2.0 equiv) with phenyl diazoacetate **11a** (1.0 equiv) as a model substrate in DCM, the influence of temperature together with different Rh(II) catalysts (Figure 3) were first investigated (Table 3).

Figure 3. Rh(II) catalysts for asymmetric cyclopropanation of cyclopentadiene.

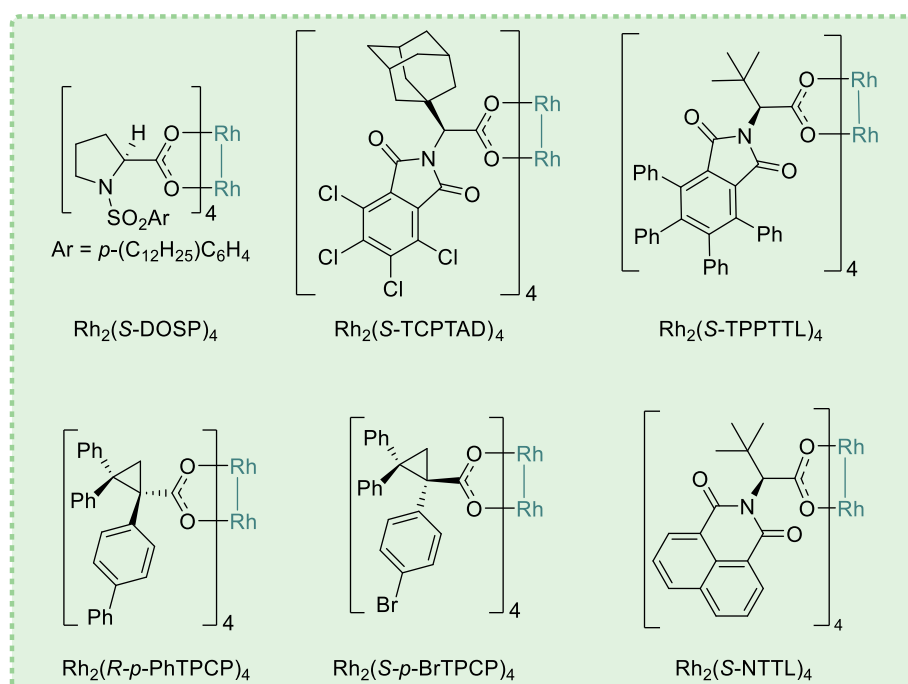


Table 3. Catalyst screening at different temperatures.⁶⁶

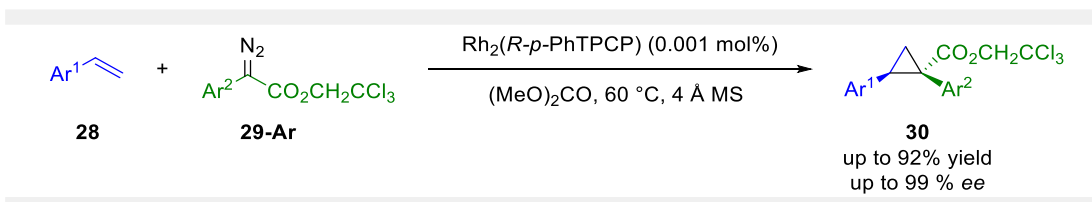
Entry	Catalyst	T [°C]	<i>ee</i> of (±)25a @ 210 nm
1	Rh ₂ (R-NTTL) ₄	25	18%

^a The following asymmetric cyclopropanation studies were performed by Terrence-Thang Huy Nguyen (*Davies* group) at Emory University and are part of his ongoing PhD-thesis. The results were published in Fischer, S.; Nguyen, T.-T. H.; Ratzenboeck, A.; Davies, H. M. L.; Reiser, O. *Org. Lett.* **2023**, *25*, 4411–4415.⁶⁶ For more detailed information, see the SI of *ref.* 66.

2	$\text{Rh}_2(R\text{-NTTL})_4$	0	-
3	$\text{Rh}_2(R\text{-NTTL})_4$	-78	83%
4	$\text{Rh}_2(S\text{-}p\text{-BrTPCP})_4$	25	60%
5	$\text{Rh}_2(S\text{-}p\text{-BrTPCP})_4$	0	74%
6	$\text{Rh}_2(S\text{-}p\text{-BrTPCP})_4$	-78	72%
7	$\text{Rh}_2(R\text{-TCPTAD})_4$	25	8%
8	$\text{Rh}_2(R\text{-TCPTAD})_4$	0	2%
9	$\text{Rh}_2(R\text{-TCPTAD})_4$	-78	2%
10	$\text{Rh}_2(S\text{-DOSP})_4$	25	70%
11	$\text{Rh}_2(S\text{-DOSP})_4$	0	72%
12	$\text{Rh}_2(S\text{-DOSP})_4$	-78	-
13	$\text{Rh}_2(S\text{-TPPTTL})_4$	25	40%
14	$\text{Rh}_2(S\text{-TPPTTL})_4$	0	34%
15	$\text{Rh}_2(S\text{-TPPTTL})_4$	-78	4%

No combination of the tested rhodium catalyst and different temperatures significantly improved the enantiomeric excess of the reaction. Hence, a different type of diazoacetates was used for this project, based on a recent study by *Davies et al.*: The cyclopropanation of styrene **28** with trichloroethyl-diazoacetates **29-Ar** (TCE-diazoacetates) was proven to afford high *ee*'s together with a low catalyst loading of $\text{Rh}_2(R\text{-}p\text{-PhTPCP})_4$ (Scheme 33).⁶⁸

Scheme 33. Cyclopropanation of styrene with TCE-diazoacetates.⁶⁸



A reaction screening was performed using 2,2-trichloroethyl 2-diazo-2-phenylacetate (**29a**) as the model substrate and 0.5 mol% $\text{Rh}_2(\text{S-}p\text{-PhTPCP})_4$ as the catalyst at different temperatures (Table 4).

Table 4. Temperature screening of cyclopropanation of cyclopentadiene with TCE-diazoacetate.⁶⁶

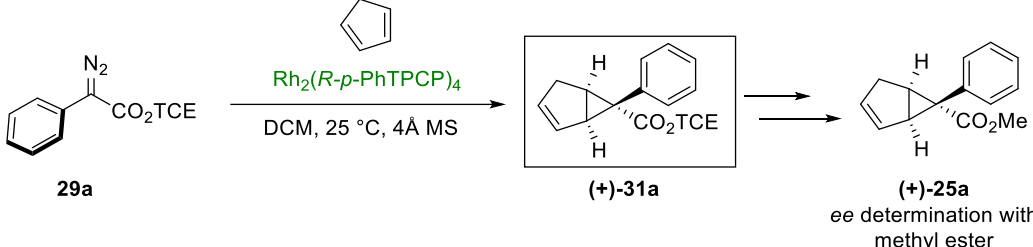
Reaction scheme: 29a + 21 (2.0 equiv) $\xrightarrow[\text{DCM, 18 h, T, 4\AA MS}]{\text{Rh}_2\text{L}_4 \text{ (0.5 mol\%)}}$ (-)-31a (Racemate via $\text{Rh}_2(\text{OAc})_4$, Unable to separate TCE product via HPLC) $\xrightarrow[\text{DMF, 24 h, 25 }^\circ\text{C}]{\text{1) Zn, AcOH, 24 h, 25 }^\circ\text{C}; \text{2) K}_2\text{CO}_3, \text{MeI}}$ (-)-25a (Racemate via $\text{Rh}_2(\text{OAc})_4$, e.r. - 50:50, e.e. - 0%)				
Entry	Catalyst	T [°C]	Yield of (-)-31a	ee of (-)-25a @ 210 nm
1	$\text{Rh}_2(\text{S-}p\text{-PhTPCP})_4$	25	75%	>90%
2	$\text{Rh}_2(\text{S-}p\text{-PhTPCP})_4$	-20	67%	98%
3	$\text{Rh}_2(\text{S-}p\text{-PhTPCP})_4$	-40	70%	n.d.
4	$\text{Rh}_2(\text{S-}p\text{-BrTPCP})_4$	-20	73%	86%
5	$\text{Rh}_2(\text{S-}p\text{-BrTPCP})_4$	-40	77%	86%

Issues occurred with the HPLC analysis of the TCE-compound **31a** since the racemate, formed by $\text{Rh}_2(\text{OAc})_4$, could not be separated. Therefore, the *ee* determination of the asymmetric reaction was difficult to analyze. In an additional step, the cyclopropane **31a** was converted into the desired product **25a** by transesterification, which was then possible to analyze *via* HPLC. The obtained *ee*'s of (-)-**25a** seemed to be very high (up to 98%). However, the results could be falsified due to the width of the peak of the other enantiomer in the HPLC chromatogram. For accurate *ee*-determination, $\text{Rh}_2(\text{S-}p\text{-PhTPCP})_4$ was switched to $\text{Rh}_2(\text{R-}p\text{-PhTPCP})_4$ (see *ref.* 66 for detailed information and chromatogram-analysis).⁶⁶

Furthermore, a *react-IR* study was done to determine the optimal catalyst concentration at 0.05 mol% of $\text{Rh}_2(\text{R-}p\text{-PhTPCP})_4$ (see *ref.* 66 for detailed information and *react-IR* study).⁶⁶ Since only moderate yields of (-)-**31a** were observed in the reaction (Table 4),

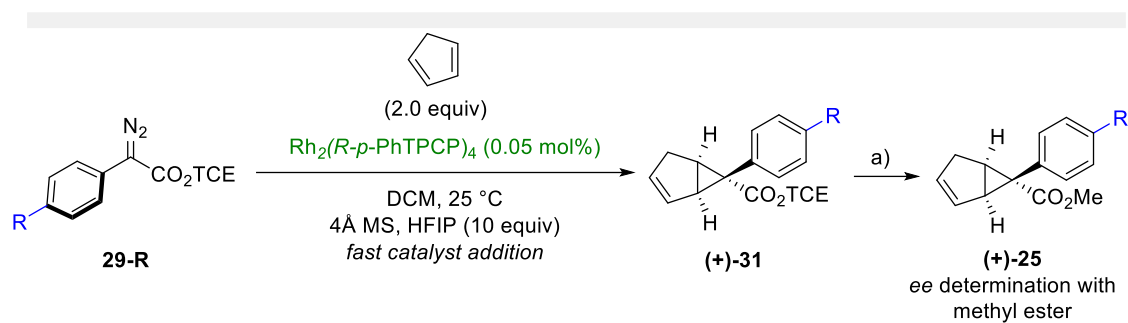
an optimization study of the asymmetric cyclopropanation was done based on the results of the *react-IR* study (Table 5).⁶⁶

Table 5. Optimization of the asymmetric reaction based on the *react-IR* study.⁶⁶

					
Entry	Cat. Loading [%]	CP [Equiv]	Deviations	Yield of (+)-31a [%]	ee of (+)-25a [%]
1	0.50	10	diazo addition >3 h	75	90
2	0.05	10	fast catalyst addition	71	90
3	0.05	2	fast catalyst addition	70	90
4 ^a	0.05	2	fast catalyst addition	95	90

[a] HFIP (10 equiv) was added to the reaction.

Lowering the equivalents of cyclopentadiene **21** from 10 to 2.0, together with a fast addition of the rhodium catalyst and an additional 10 equivalents of HFIP, improved the yield of the cyclopropanation to 95% and 90% *ee* of **(+)-25a** (Table 5, Entry 4). This suggests that the reaction is favored under water-free conditions. With these optimized conditions in hand, the scope was expanded to a small library of molecules (Table 6).

Table 6. Expanding the scope of the asymmetric cyclopropanation.⁶⁶

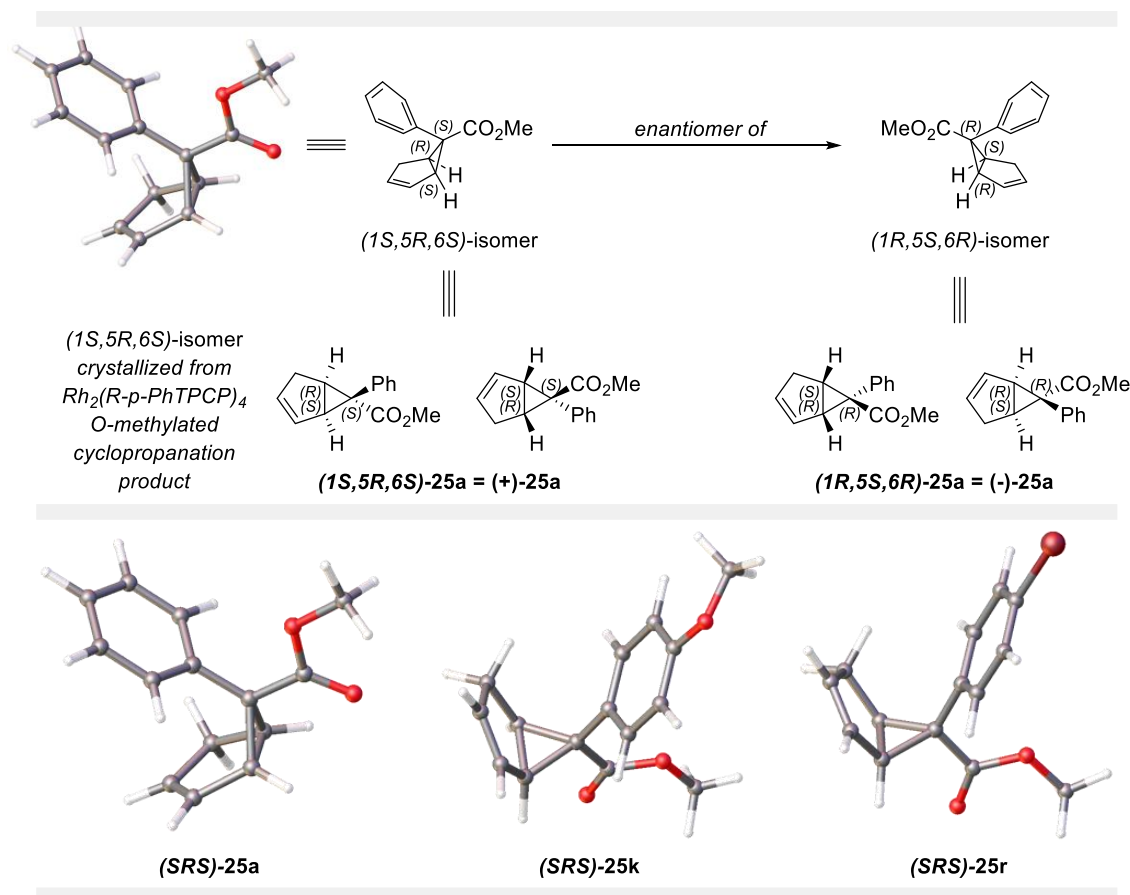
Entry	Substrate: -R	Yield of (SRS)-31 [%]	Yield of (+)-25 ^{b)} [%]	ee of (+)-25 [%]
1 ^{c)}	29a: -H	(+)-31a: 95	(+)-31a: 71	(+)-25a: 90
2	29k: -OMe	(+)-31k: 97	(+)-31k: 65	(+)-25k: 94
3	29r: -Br	(+)-31r: 85	(+)-31r: 56	(+)-25r: 90
4	29s: -CF ₃	(+)-31s: 84	(+)-31s: 56	(+)-25s: 90

Reactions were performed on a 0.7 – 1.0 mmol scale. [a] i. Zn-dust (<10 μm, 5.0 equiv), AcOH as solvent (0.1 M), 24 h, 25 °C; ii. K₂CO₃ (5.0 equiv), DMF, MeI (5.0 equiv), 24 h, 25 °C. [b] Overall yield is reported over 3 steps starting from compound **29**. [c] 10 equiv of Zn-dust (<10 μm), 1.5 equiv of potassium carbonate, and 1.5 equiv of iodomethane were used. The absolute configuration of **25a**, **25k**, and **25r** was determined by X-ray structure analysis. See the SI for details.

By introducing an electron-donating group, the yield (**31k**, 97%) and the *enantiomeric excess* (94%) were improved in contrast to the model substrate **25a** (Table 6, Entry 2). EWGs slightly decreased the yield but did not directly impact the reaction (Table 6, Entry 3 - 4). The reaction requires an additional transesterification step to obtain the desired compound **25**, which significantly reduces the overall yield.

The absolute configuration of the cyclopropanes synthesized with Rh₂(*R-p*-PhTPCP)₄ was investigated to complete this chapter (see Figure 4).

Figure 4. Analysis of the absolute configuration of **25a** and x-ray structures of **(1S,5R,6S)-25a**, **(1S,5R,6S)-25k** and **(1S,5R,6S)-25r**.⁶⁶



A final study investigated the direct asymmetric cyclopropanation with a small screening. While the solvent-free literature method⁶⁵ gave an *ee* of 78%, this study was performed with DCM as solvent.⁶⁶ Hence, we postulated that a potential issue is the catalyst/starting-material system's solubility. Therefore, relatively to DCM, the more non-polar pentane was used as a solvent. With the respective *R*- or *S*-DOSP catalyst, high yields of up to 88% and good *ee*'s were achieved (81 – 84%, Table 7). However, compared to the previous results, no significant improvement was observed.

Table 7. Direct asymmetric cyclopropanation using pentane as solvent.

Entry	n of 11a [mmol]	Catalyst	Yield of (+)-25a [%]	ee of (+)-25a [%]
1	7.0	Rh ₂ (R-DOSP) ₄	87	83
2 ^{a)}	7.0	Rh ₂ (S-DOSP) ₄	87	81
3 ^{a)}	24	Rh ₂ (S-DOSP) ₄	88	84

[a] The opposite enantiomer (**1R,5S,6R**)-**25a** is synthesized.

Summarized, the asymmetric cyclopropanation of cyclopentadiene was improved on a former study from *Davies et al.*,⁶⁵ obtaining excellent yields of up to 97% and excellent *ee* of up to 94%. Several examples proved the absolute configuration.⁶⁶ Compared to the literature method, the disadvantage is the additional transesterification step to (+)-**25a**, which reduces the yield.

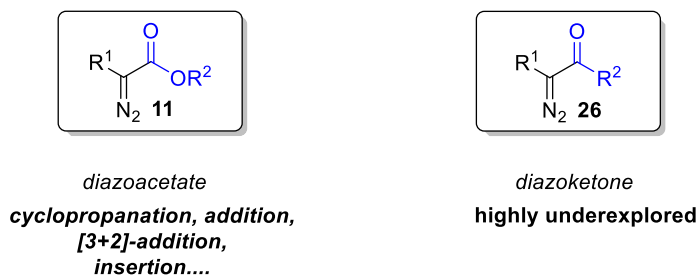
1.4. [2+2]-Cycloaddition vs. Cyclopropanation Using α -Diazoketones

As demonstrated in the previous chapter, while cyclopropanation reactions using diazoacetates and transition-metals have been extensively studied, cyclopropanation using diazoketones under transition-metal catalysis remains largely unexplored.⁶⁹ Furthermore, the few examples reported mostly include cyclopropanation of styrene and its derivatives or intramolecular cyclopropanation of α -diazoketones.^{70–76} To the best of our knowledge, no direct rhodium-catalyzed cyclopropanation of cyclopentadiene or furane derivatives with diazoketones **26** is reported.

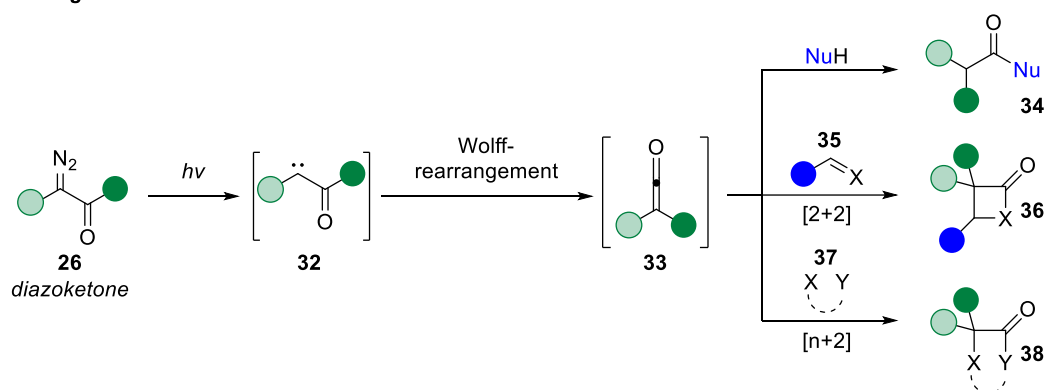
On the other hand, α -diazoketones **26** are known and commonly used as ketene precursors **33**, formed by a *Wolff*-rearrangement after carbene-formation (**32**) under UV- or visible-light irradiation (Figure 5, b).^{77–79}

Figure 5. (a) Transition-metal catalysis of diazoketones and (b) Wolff-rearrangement of diazoketones under visible-light irradiation.⁷⁸

a) Transition-metal catalysis



b) Blue-light

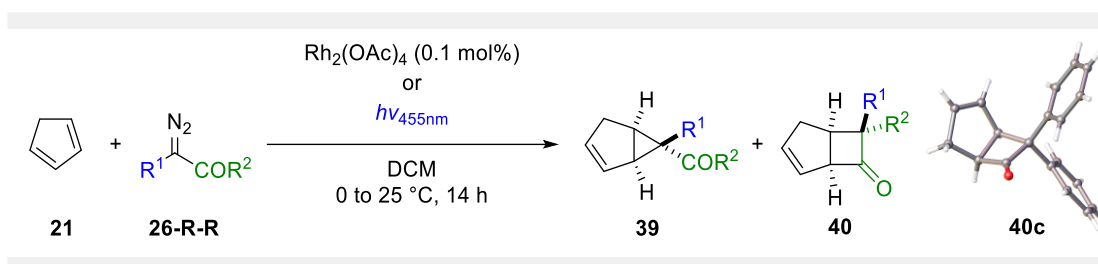


The objective was to compare the use of diazoketones **26** and cyclopentadiene **21** under rhodium catalysis or blue-light irradiation with diazoacetates **11**. The optimized conditions from Scheme 32 were applied using cyclopentadiene **21** and diazoketones **26** under Rh₂(OAc)₄ catalysis or blue-light irradiation (Table 8).

Commencing with 1-diazo-1-phenylpropan-2-one (**26a**) and rhodium(II) as the catalyst, the expected cyclopropane synthesis *via* carbene formation was observed. However, compared to the diazoacetates, the yield dropped to a moderate level (**39a**, 59%, Table 8, Entry 1), which might result from less carbene stability. When blue-light irradiation was utilized, cyclopropane **39a** was obtained in small amounts (6%). However, the formation of cyclobutanone **40a** (85%) is more interesting. The product must form *via* [2+2]-cycloaddition between cyclopentadiene **21** and a ketene, which is obtained *in-situ* after Wolff-rearrangement of diazoketone **26a** (Table 8, Entry 2). The same results were observed by using the more electron-rich 1-diazo-1-(4-methoxyphenyl)propan-2-one (**26b**, Table 8, Entry 3 - 4). The yield of the cyclobutanone **40b** decreased, compared to **40a**, probably due to a better stability of the *in-situ* formed carbene, which causes a slower

Wolff-rearrangement. When using the stable 2-diazo-1,2-diphenylethan-1-one **26c** under blue-light irradiation, a high yield of 97% of **40c** was achieved (Table 8, Entry 5).

Table 8. Reactivity of diazoketones **26-R-R** under Rh(II) catalysis and blue-light irradiation.



Entry	-R ¹	-R ²	Activation	Yield of 39 [%]	Yield of 40 [%]
1	Ph,	Me	Rh ₂ (OAc) ₄	39a , 59	-
2	Ph	Me	$h\nu_{455\text{nm}}$	39a , 6	40a , 85
3	Ph(<i>m</i> -OMe)	Me	Rh ₂ (OAc) ₄	39b , 50	-
4	Ph(<i>m</i> -OMe)	Me	$h\nu_{455\text{nm}}$	39b , 15	40b , 51
5	Ph	Ph	$h\nu_{455\text{nm}}$	-	40c , 97

Reactions were done on a 0.2 – 0.5 mmol scale.

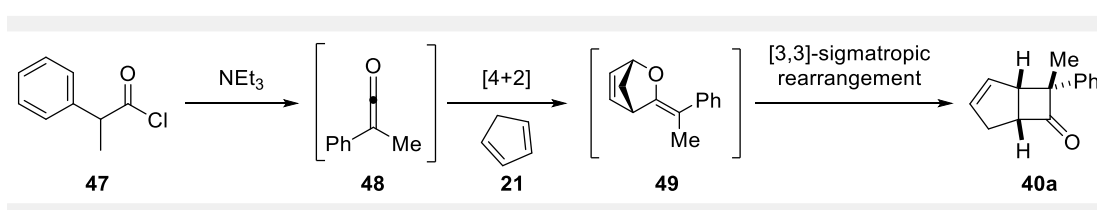
The heterocycles **41**, **42**, and **43** were tested in the reaction conditions for [2+2]-cycloaddition to expand the scope. However, no product could be isolated by utilizing the aromatic molecules furan **41** or N-Ts-pyrrole **42** (Table 9, Entry 1 - 2). On the other hand, the non-aromatic dihydrofuran **43** reacted well and produced the cyclobutanone **46** in moderate yield (Table 9, Entry 3). Hence, two different reaction paths are possible using the aromatics **41** and **42**: 1) The formed ketene undergoes photochemically allowed [2+2]-cycloaddition with **41** or **42**, but the product gets excited and decomposes. 2) The ketene does not break the aromaticity of **41** and **42** under photochemical conditions.

Table 9. Heterocycles and diazoketones under blue-light irradiation.

41: X = O 42: X = NTs 43 26a $h\nu_{455\text{nm}}$ DCM 0 to 25 °C, 14 h 44: X = O 45: X = NTs 46: X = O, no double-bond		
Entry	Starting material	Result
1	furan, 41	decomposition
2	pyrrole, 42	decomposition
3	2,3-dihydrofuran, 43	63% of 46

Reactions were done on a 0.5 mmol scale.

Typically, these type of cyclobutanones are synthesized *via* [2+2]-cycloaddition of phenyl(methyl)ketene **48**, generated *in-situ* *via* dehydrochlorination of 2-phenylpropanoyl chloride **47** with NEt₃ to cyclopentadiene **21** under thermal conditions.⁸⁰ Notably, there is strong evidence that under thermal conditions, the initial compound formed is the Diels-Alder product **49** ([4+2]-cycloaddition), which then undergoes a [3,3]-sigma tropic rearrangement (Scheme 34).⁸¹

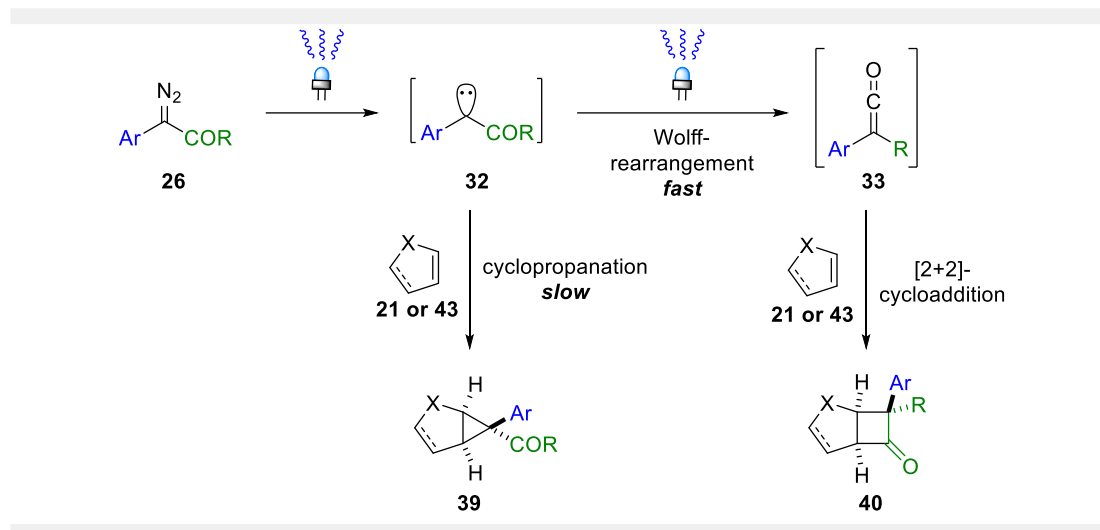
Scheme 34. Possible reaction pathway under thermal conditions.⁸¹

In the case of the visible-light mediated synthesis of the cyclobutanones from diazoketones, no evidence for an initial [4+2]-cycloaddition reaction was found. The formation of **46** supports this suggestion because the Diels-Alder reaction is impossible with the starting material **43**.

Therefore, we mechanistically propose an initial formation of carbene **32** from diazoketone **26** through blue-light photolysis, followed by slow cyclopropanation with the presented olefine or faster *Wolff*-rearrangement forming ketene **33**. The main product

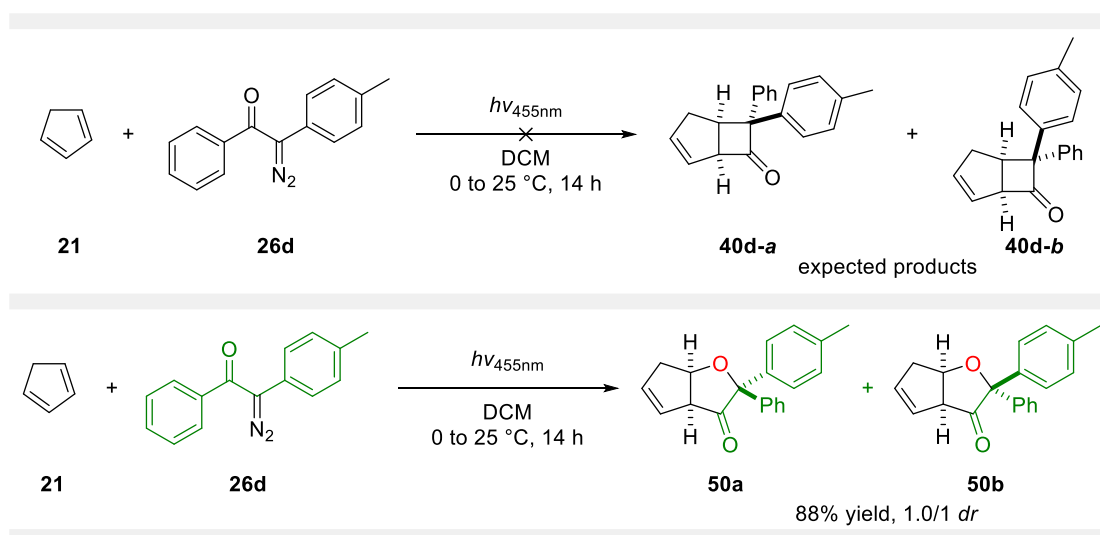
cyclobutanone **40** is then obtained *via* [2+2]-cycloaddition between the olefine and the ketene **33** (Scheme 35).

Scheme 35. Proposed mechanism for the cyclopropanation and [2+2]-cycloaddition of diazoketones.



Summarized, with the optimized conditions, an access to a new class of bicyclic vinyl cyclopropanes **39** bearing a ketone group instead of an ester was developed. Furthermore, cyclobutanones **40** are now accessible in high yields *via* a photochemical [2+2]-cycloaddition.

Scheme 36. Unusual reaction of diazoketone **26d**.



During blue-light irradiation, the combination of 2-diazo-1-phenyl-2-(p-tolyl)ethan-1-one (**26d**) and cyclopentadiene **21** resulted in an unusual reaction. Due to the previous results (Table 8), the cyclobutanones **40d-a** and **40d-b** were expected as the products.

However, in the case of diazoketone **26d**, additional oxygen was incorporated into the molecule. ^{13}C -NMR and 2D-NMR analysis (see the SI) showed a mixture of the diastereomers **50a** and **50b** (Scheme 36). For the moment, the formation of this mixture cannot be explained, but further studies on this reaction are ongoing.

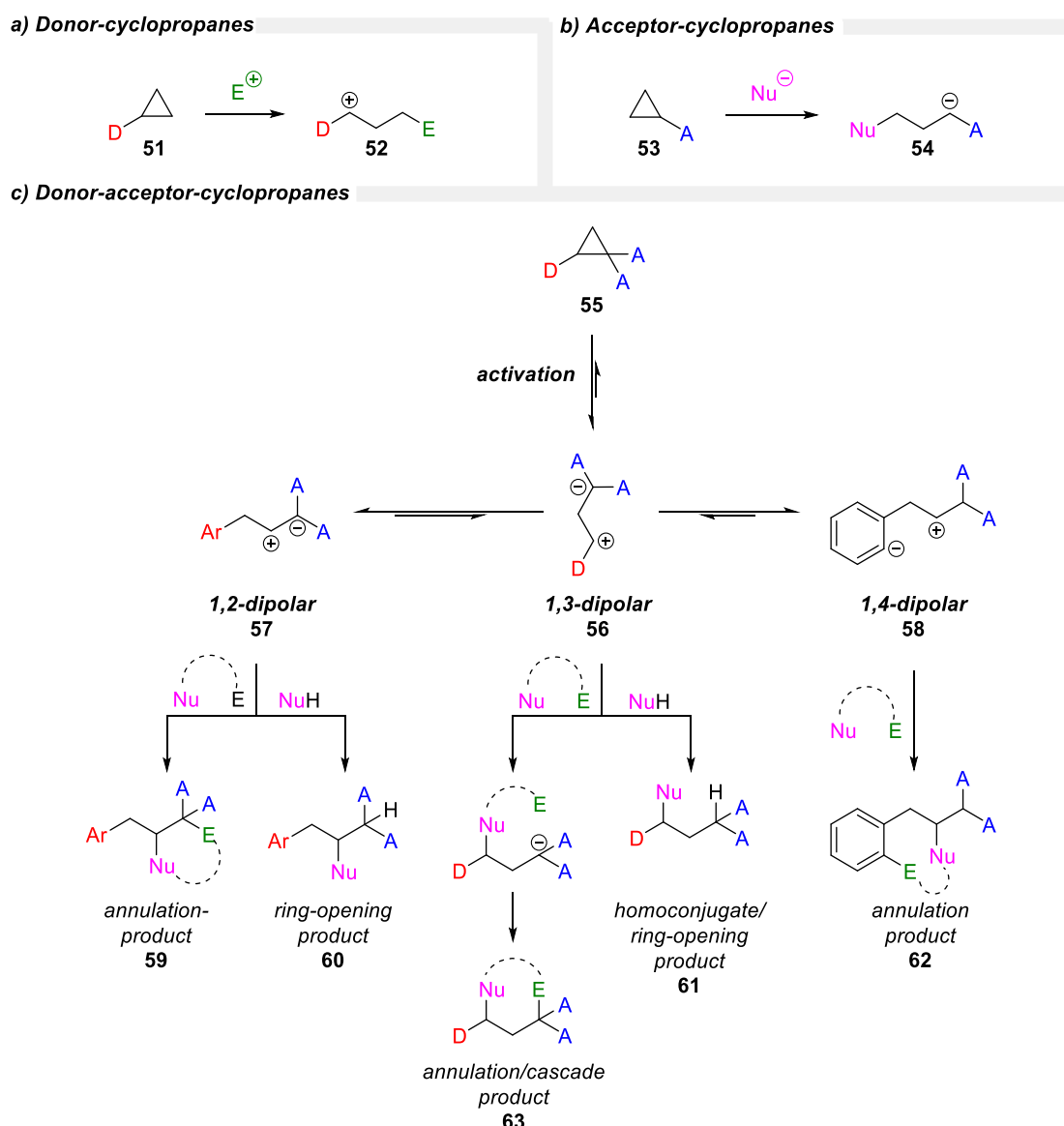
2. Endocyclic Ring-Opening of Cyclopropanated Cyclopentadiene

2.1. Introduction

2.1.1 High Reactivity of Cyclopropanes

Besides the interesting properties, the structural motif of cyclopropanes shows, represented in many biologically active compounds, the high reactivity due to their high ring strain (*approx.* 28 kcal/mol) has become a key player in organic synthesis to synthesize more complex molecules.⁸²

Scheme 37. Reactivity of cyclopropanes depending on substitution and reaction partners.



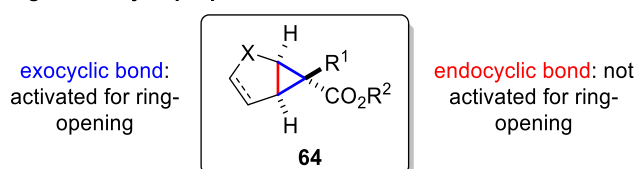
Depending on reaction conditions and reaction partners, cyclopropanes offer properties of saturated or unsaturated hydrocarbons.⁸³ Furthermore, versatile ring-opening reactions are possible through polarization of the cyclopropane ring, resulting from substitution with EWGs (acceptors) or EDGs (donors).⁸⁴ While donor substituents are introduced for easier electrophilic ring-opening (Scheme 37, a), acceptor groups facilitate the nucleophilic ring-opening reactions (Scheme 37, b). In this field of chemistry, vicinal donor-acceptor (DA) substituted cyclopropanes have a crucial role due to their selective and versatile ring-opening potential. *Via* (i) thermal activation, (ii) Lewis- or Brønsted-acid/base-mediated activation, or (iii) transition-metal catalysis, a 1,3-zwitterionic species can be formed, stabilized by the donor and acceptor groups. It can be trapped with either electrophiles or nucleophiles for ring-opening reactions or a linked nucleophile-electrophile species to undergo cycloaddition reactions. These reactions have been exploited in many instances, such as natural product synthesis and the construction of complex molecules (Scheme 37, c).^{28,83–95}

2.1.2 Selective C–C Bond Cleavage of Bicyclic Cyclopropanes

As mentioned in the introduction, DA-cyclopropanes can undergo a great number of selective ring-opening reactions depending on their substitution pattern and reaction partners. Mainly, exocyclic ring-opening reactions of cyclopropanated heterocycles or carbocycles were investigated in various examples,^{84,86,87,89,90,93,96–101} while the selective endocyclic ring-opening of DA-cyclopropanes remains unexploited.^{43,45,67,98,99,102–113} This lack of exploration can be attributed to the intrinsic electronic properties of type **64** compounds, where the exocyclic bond is activated for ring-openings (Figure 6).^{43,66}

Figure 6. Intrinsic electronic setting of **64**.

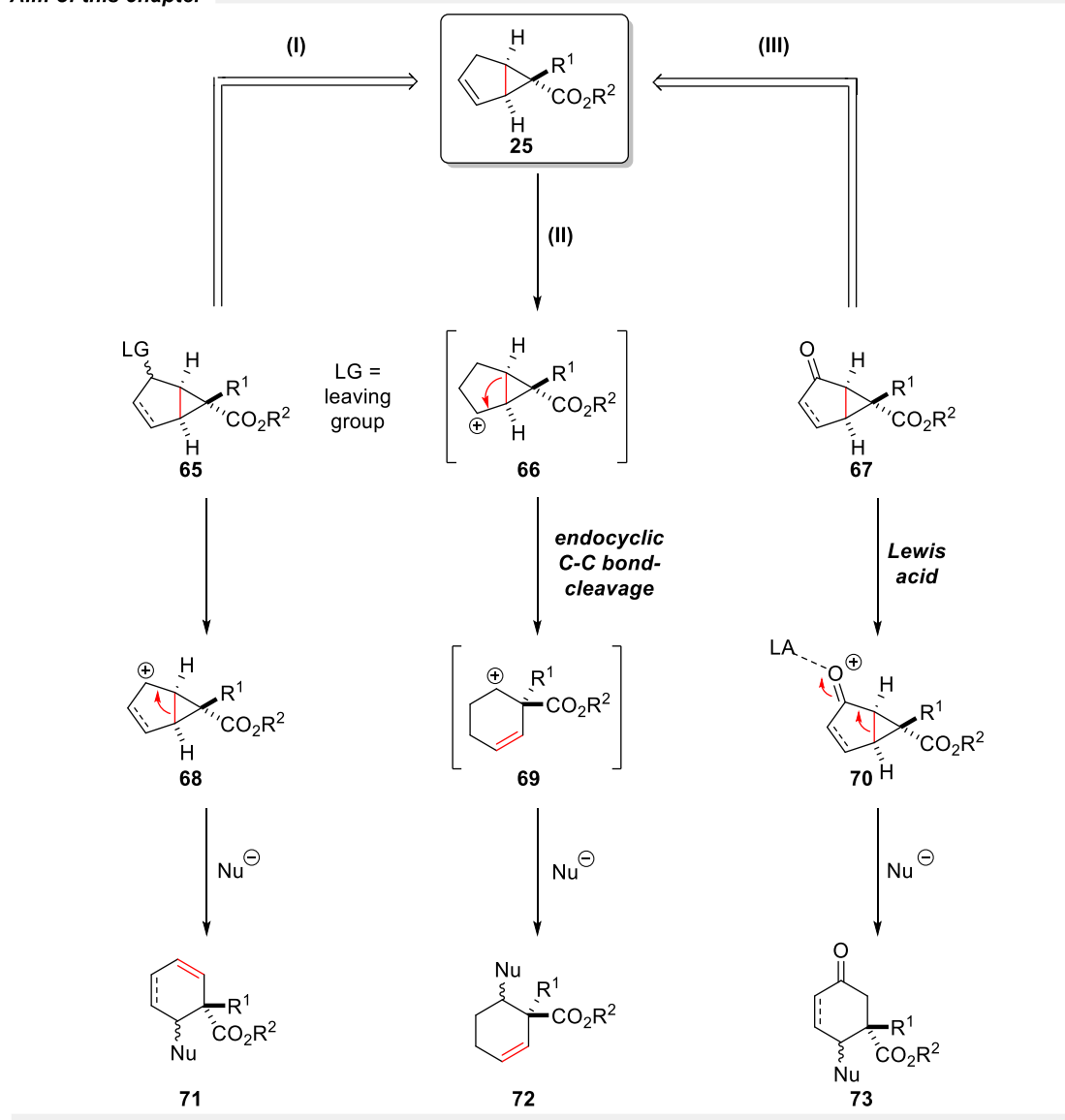
Intrinsic electronic setting of D-A cyclopropanes



2.1.3 Aim of This Chapter

Scheme 38. Aim of this chapter.

Aim of this chapter



In this chapter, the aim is to identify the conditions that facilitate the selective endocyclic ring-opening of the cyclopropanes **25** that were synthesized earlier. Our strategy primarily involves creating a positive charge adjacent to the cyclopropane moiety, which should trigger the selective cleavage of the C-C bond.

First, leaving groups should be introduced and removed under basic, acidic, or thermal activation, followed by the desired endocyclic ring-expansion. After nucleophilic trapping, access to cyclohexenes **71** should be realized (Scheme 38, I).

The second approach concentrates on the double bond of the vinyl cyclopropanes **25**, which should generate a carbocation under acidic conditions to afford cyclohexenes from type **72** (Scheme 38, II).

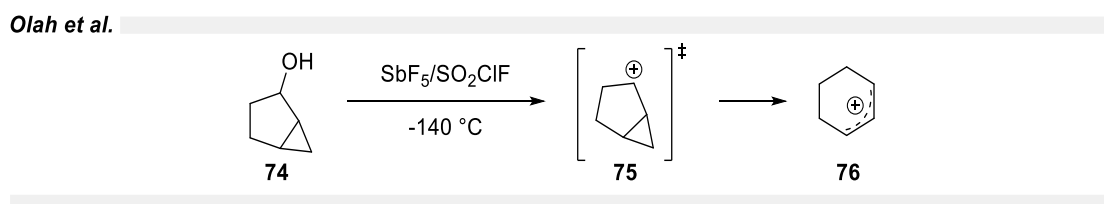
Finally, a carbonyl group that could be activated by Lewis acids and forms cyclohexanones **73** should be introduced (Scheme 38, III).

2.2. Endocyclic Ring-Opening Initiated via Positive Polarization

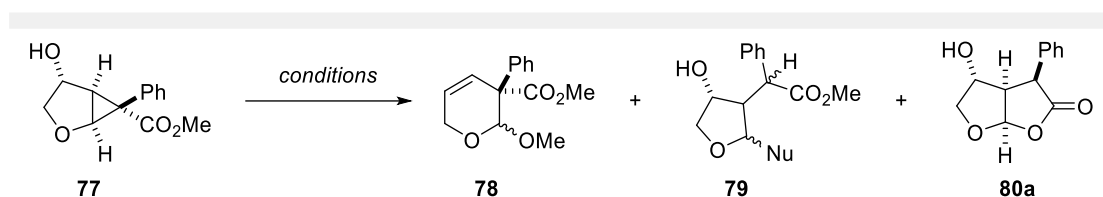
2.2.1 Previous Endocyclic Ring-Opening via α -Leaving Group Strategy

In the 1980s, *Olah et al.* illustrated the formation of a cyclopropyl carbinyl cation **75** via solvolysis of the hydroxy group of **74** using a super acidic system ($\text{SbF}_5/\text{SO}_2\text{ClF}$), which then rearranged under endocyclic C–C bond cleavage to form the cation **76**. The formation of **75** was directly demonstrated in an NMR tube and detected by NMR. However, the authors indicated that nucleophilic addition to this cation **75** is problematic.¹¹⁴ The driving force of releasing the ring strain of **75** and rearranging to the more stable cyclohexane structure **76** seems exceptionally high, since this reaction is observed at temperatures below $-140\text{ }^\circ\text{C}$ (Scheme 39).

Scheme 39. Solvolysis of compound **74**.

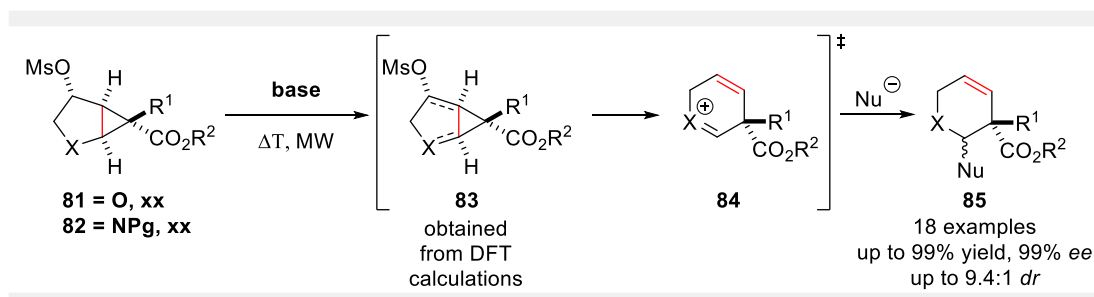


Based on these results, *Robert Eckl* started a study with heterocyclic cyclopropane **77**, bearing an alcohol next to the cyclopropane. The $-\text{OH}$ group was cleaved under acidic conditions in the presence of a nucleophile.¹¹⁵ However, the endocyclic C–C bond cleavage was not accessible with various acids. Instead, the exocyclic bond was activated and cleaved, forming tetrahydrofuran derivatives **79**. Further lactonization afforded compound **80a**, which is in accordance with the literature (Table 10).^{115,116}

Table 10. (Lewis) Acid-mediation ring-expansion of alcohol **77**.¹¹⁵

Entry	Reagent	Solvent	T [°C]	Time [h]	Results
1	10% HCl	THF/MeOH (2:1)	55	24	complex mixture, traces of 80a
2	TFA, Et ₃ SiH	DCM	0	24	complex mixture
3	H ₂ SO ₄	MeOH	25	24	32% 79a (Nu = OMe)
4	BF ₃ ·Et ₂ O, Et ₃ SiH	DCM	-78	20	83% 79b (Nu = H)

Since acidic conditions were not tolerated due to acid-catalyzed hydrolysis followed by lactonization, *Reiser* and co-workers switched to basic activation and -OMS as a terrific leaving group.^{43,115} A protocol was established, using various bases (NEt₃, K₂CO₃, or DBU) to support the -OMs cleavage under microwave (MW) irradiation and subsequent trapping by a nucleophile to synthesize the functionalized six-membered heterocycles from type **85**. The versatility of the utilized monocyclopropanated heterocycles (**81/82**, furane and pyrroles), bases, and nucleophiles demonstrates the robustness of the method (Scheme 40).^{43,115}

Scheme 40. Endocyclic ring-expansion of bicyclic heterocycles **81/82** via base- and MW-activation.

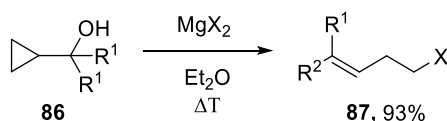
It was found through DFT-calculations that there is no formation of a cyclopropyl carbocation after the activation of compounds **81/82** by base/MW. Instead, polarization

occurs, leading to a simultaneous release of the leaving group and C–C bond cleavage from **83**. These results are not consistent with the solvolysis of **74**, where the cation **75** is formed prior to the ring-enlargement.^{43,114}

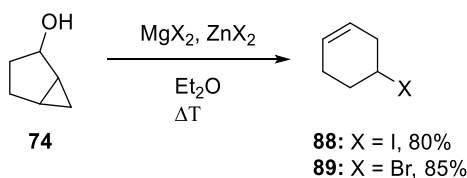
Other examples demonstrate the capability of metal halides and Brønsted acids to trigger a ring-opening reaction of cyclopropylmethanols and additionally tolerate carbocyclic bicyclic cyclopropanes (Scheme 41).^{112,113,117}

Scheme 41. Brønsted-acid and metal-halide ring-opening.

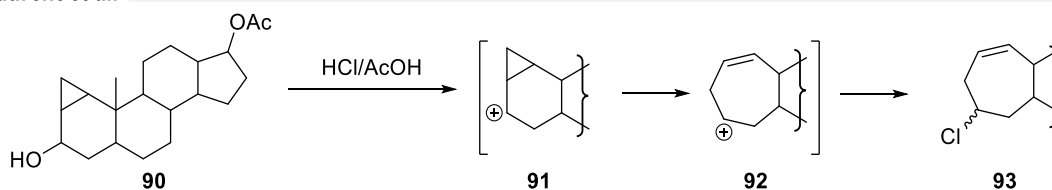
Argenti et al.



McCormick et al.

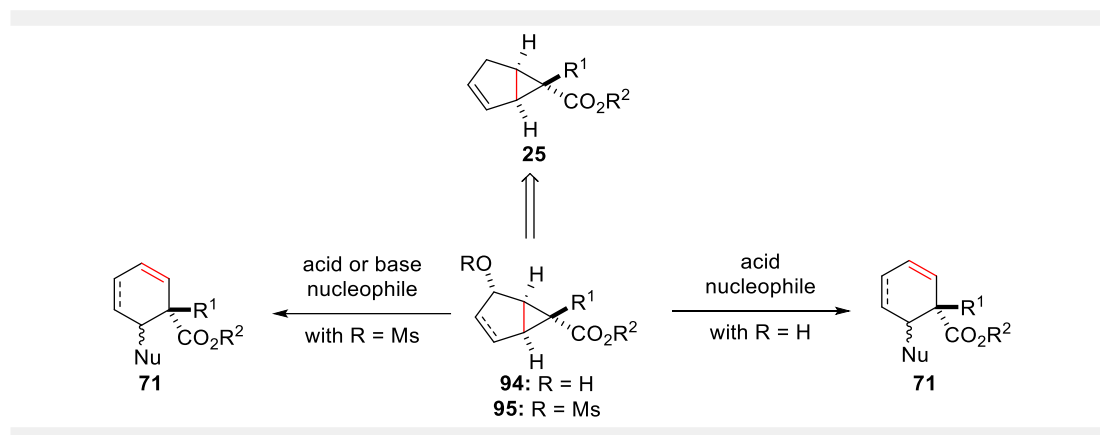


Laurent et al.

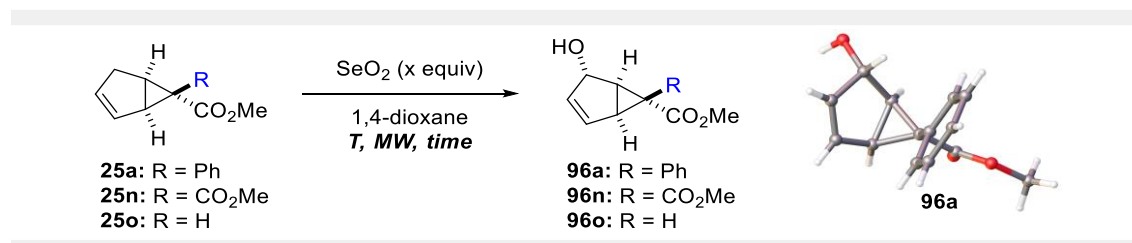


2.2.2 Synthesis of Starting Materials

Based on these results, the strategy was to introduce an alcohol group and a mesylate group to **25** next to the cyclopropane moiety and investigate their driving force for endocyclic C–C bond cleavage. Additionally, a positive polarization should be generated under basic or acidic conditions (Scheme 42).

Scheme 42. Strategy for endocyclic ring-expansion of oxygenated precursors **94/95**.

A classical Riley-oxidation¹¹⁸ using the model substrate **25a** (1.0 equiv) and SeO_2 (3.0 equiv) dissolved in 1,4-dioxane gave rise to the allylic alcohol **96a** in 85% yield (Table 11, Entry 1). After a screening, the yield could be increased to 99% on the gram-scale by the concentration of the reaction mixture and lowering the amounts of selenium dioxide (Table 11, Entry 9). Bearing a second acceptor group ($-CO_2Me$) instead of a donor ($-Ph$), the yield dropped slightly to 83% (**96n**, Table 11, Entry 10).

Table 11. Riley-oxidation of vinyl cyclopropanes **25a/n/o**.

Entry	n of 25 [mmol]	R	Equiv (SeO ₂)	Time [h]	T [°C]	Conc. Solvent [M]	Yield [%]
1	0.5	Ph	3.0	2	110	0.06	85, 96a
2	0.6	Ph	3.0	1	130	0.08	92, 96a
3	0.6	Ph	3.0	1	130	0.15	94, 96a
4	0.5	Ph	3.0	1	130	0.71	92, 96a
5	2.3	Ph	3.0	1	130	0.28	86, 96a

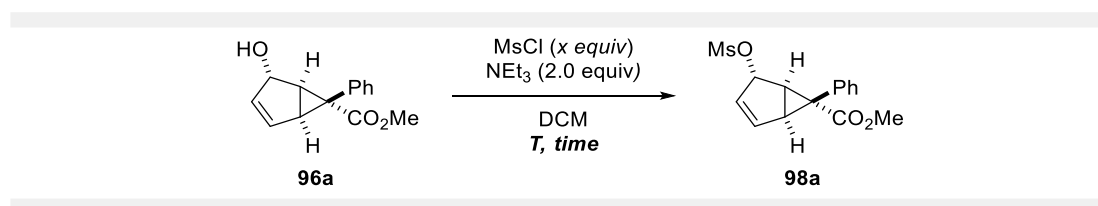
6	2.4	Ph	3.0	1	130	1.6	93, 96a
7	2.3	Ph	1.1	1	130	1.5	98, 96a
8	5.6	Ph	1.1	1	130	2.3	98, 96a
9	5.1	Ph	1.1	1	130	2.2	99, 96a
10	2.9	CO ₂ Me	1.1	1	130	2.2	83, 96n
11	0.9	H	1.1	0.5	130	2.2	decomposition
12	1.3	H	1.5	0.5	130	2.2	decomposition
13	1.7	H	1.1	0.5	100	2.2	25, 96o
14	1.3	H	3.0	0.5	100	2.2	21, 96o
15	1.5	H	1.1	1	80	2.2	<i>c.r.m.</i>

The acceptor cyclopropane **25o** was used as a diastereomeric mixture (4.0/1 *dr*). Under the previously optimized conditions at 130°C, only decomposition was observed, probably due to the instability of the starting material without the additional stabilizing phenyl group. A decrease in the reaction temperature gave rise to the desired compound **96o**, but only low yields were obtained (Table 11, Entry 13 - 14). Again, the instability of the starting material **25o** and product **96o** could be the problem.

When DMSO was used as a solvent, the allylic alcohol **25a** dimerized to compound **97** (87%, Scheme 43). This reaction is the first indication that the endocyclic ring-opening might be challenging since formation of **97** should occur *via* a carbocation next to the cyclopropane moiety.

Scheme 43. Dimerization of **25a**.

Further, the synthesized alcohol **96a** should be converted to the allylic mesylate **98a** to get an excellent leaving group next to the cyclopropane. Based on former results from our group, the first test reaction started with adding MsCl (1.3 equiv) and NEt₃ (2.0 equiv) dissolved in DCM to the alcohol **96a** at 0 °C.⁴³ TLC showed complete conversion of the starting material after 30 minutes, but after evaporation of the solvent, only decomposition was observed (Table 12, Entry 1).

Table 12. Mesylation of allylic alcohol **96a**.

Entry	MsCl [equiv]	T [°C]	Time [h]	Result
1 ^{a)}	1.3	0	0.5	decomposition
2 ^{b)}	1.1	0	1	not identified product
3 ^{b)}	1.1	-15	0.5	≈ 92% of 98a , no isolation or analysis possible

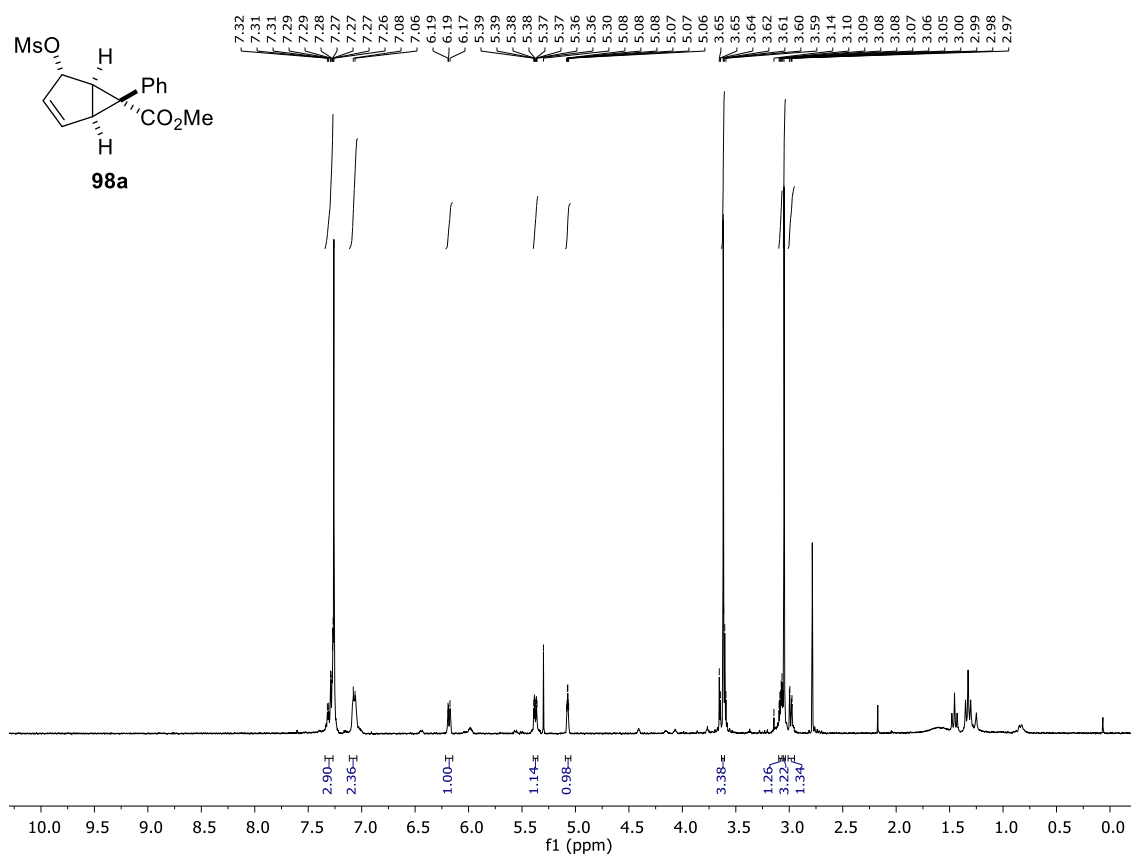
Reactions were performed on a 0.5 – 0.7 mmol scale. [a] Evaporation of the solvent at 60 °C water bath temperature. [b] Evaporation of solvent at 25 °C water bath temperature.

When the reaction was repeated, and the solvent was removed at 25 °C, the product could not be identified (Table 12, Entry 2). Running the reaction at -15 °C and reevaporating at 25 °C afforded the desired mesylate **98a** based on ¹H-NMR (Table 12, Entry 2 and Figure 7). However, no further analysis, isolation, or reaction was possible due to the immediate

decomposition of the compound. The allylic position of the mesylate group probably makes it an outstanding leaving group that undergoes cleavage with a low energy barrier.

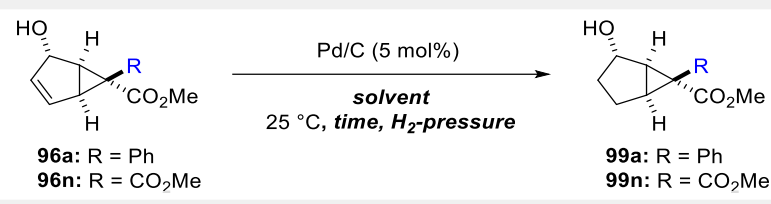
^1H -NMR of the reaction shows the relevant peaks with the proper integrals of **98a**, but further analysis was not possible (Figure 7).

Figure 7. Crude- ^1H NMR of **98a**.

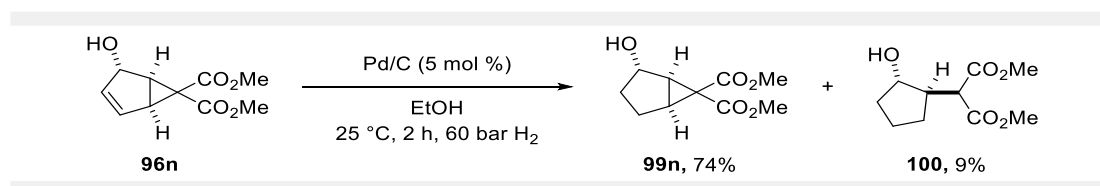


Determining that the allylic alcohol was the issue, the double bond of the alcohol **96a** was reduced, followed by a mesylation of the alcohol group. Hydrogenation was done in an autoclave at 60 bar H_2 -pressure using Pd/C as a heterogeneous catalyst. In EtOH or ethyl acetate, the desired product **99a** was obtained in quantitative yield on a gram-scale (Table 13). The optimized conditions were then applied to the alcohol **99a** bearing two acceptor groups, but again the yield slightly dropped to 74% (Table 13, Entry 6):

Table 13. Pd/C hydrogenation of allylic alcohol **96**.

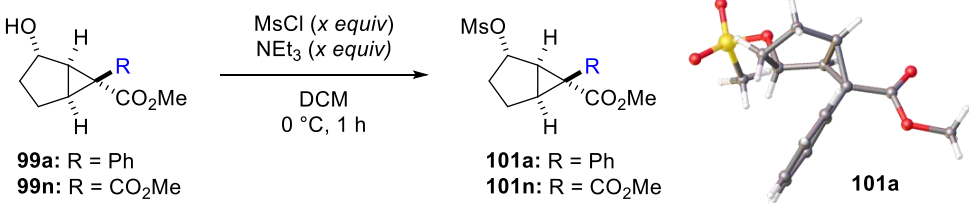
						
Entry	-R	n of 96 [mmol]	Solvent	Time [h]	H ₂ [bar]	Yield [%]
1	Ph	0.8	MeOH	12	20 to 60	0, 99a
2	Ph	1.1	EtOH	4	60	98, 99a
3	Ph	0.9	EA	4	60	quant., 99a
4	Ph	5.6	EA	4	60	98, 99a
5	Ph	2.8	EA	2	80	96, 99a
6	CO ₂ Me	1.9	EA	2	60	74, 99n

Interestingly, when the acceptor-acceptor cyclopropane **96n** was utilized, compound **100** formed as a side product (9%) *via* exocyclic ring-opening. This indicates that two electronic withdrawing groups activate the exocyclic bond, concluding that endocyclic ring-opening with acceptor-acceptor cyclopropanes might not be possible (Scheme 44).

Scheme 44. Exocyclic ring-opening as a side reaction.

With the reduced alcohols in hand, mesylation of the alcohol was repeated. Utilizing the compound **99a** afforded the desired mesylate **101a** in good yields after a screening (Table 14). The robustness of this mesylation was demonstrated on a gram-scale synthesis (Table 14, Entry 4). Notably, product **101n** decomposed within days in the fridge (7 °C), highlighting the reactivity of the compound and proving that the allylic position of the mesylate was the issue in the previous attempts of synthesizing **98a**.

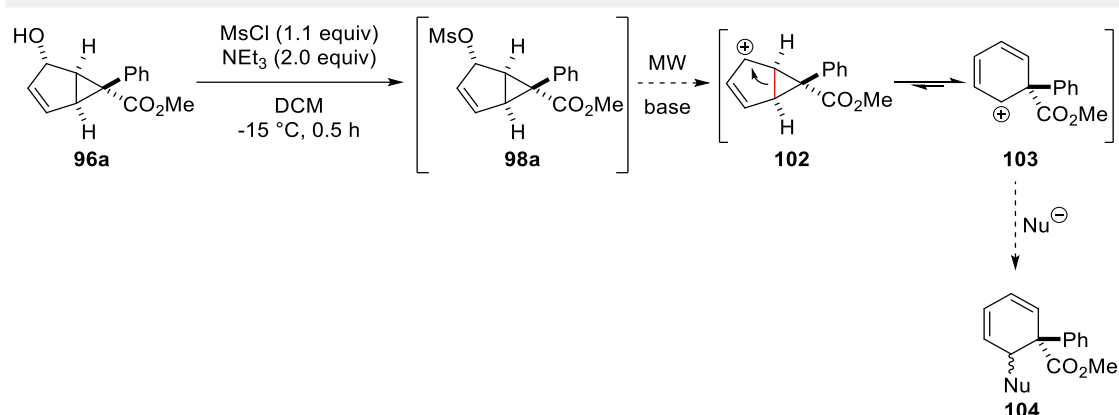
Table 14. Mesylation of reduced alcohol.

 99a: R = Ph 99n: R = CO₂Me 101a: R = Ph 101n: R = CO₂Me 101a				
Entry	-R	n of 99 [mmol]	MsCl [equiv]	Yield [%]
1	Ph	0.9	1.3	89, 101a
2	Ph	3.0	1.3	80, 101a
3	Ph	0.8	1.1	96, 101a
4	Ph	5.4	1.1	85, 101a
5	CO ₂ Me	0.9	1.1	87, 101n

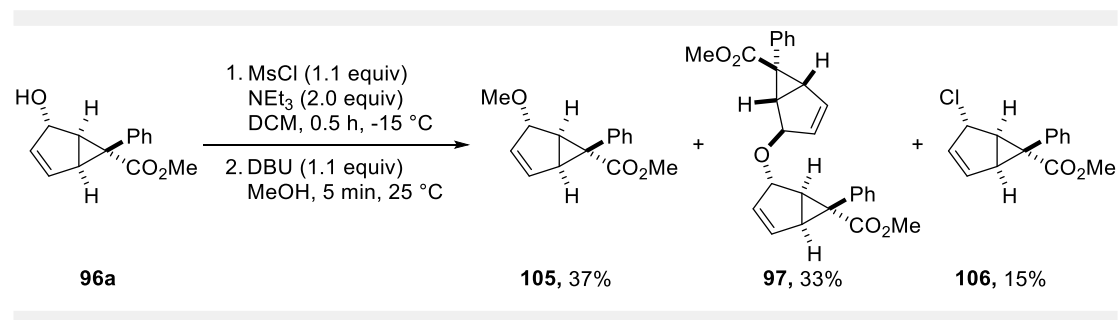
Furthermore, the acceptor-acceptor cyclopropane **96n** was converted to the mesylate **101n**, with the optimized conditions gaining similar high yields (Table 14, Entry 5). Noteworthy, **101n** decomposed within hours in the fridge, proving again the instability/high reactivity of the mesylated compounds.

2.2.3 Mesylated Compounds as Precursor for Endocyclic Ring-Opening

With the mesylated compound **101a** as a promising starting material for endocyclic ring-opening, studies of the behavior under different conditions were done based on former results with the heterocyclic cyclopropanes **81/82** (see Scheme 40).⁴³ Since it was not possible to isolate the allylic mesylate **98a**, the first strategy was to synthesize the mesylate **98a** *in-situ* from **96a**. Immediate base addition should form a cyclopropyl carbocation **102**, possibly undergoing the endocyclic ring-opening. Finally, nucleophilic trapping of the cation **103** should yield cyclohexenes **104** (Scheme 45).

Scheme 45. Strategy for endocyclic ring-opening of allylic mesylate **98a** under basic conditions.

The desired endocyclic C–C bond cleavage of mesylate **98a** was not observed under basic conditions. Instead, as the main product **105** was formed through $\text{S}_{\text{N}}1$ with retention of the $-\text{OMe}$ group, proving the formation of a carbocation of type **102**. However, allylic cation **102** is so stabilized that the actual driving force of release of the ring strain is insufficient to break the cyclopropane bond. As a second central product, **97** was obtained through dimerization, which agrees with the literature.¹¹⁹ The side product **106** was obtained *via* $\text{S}_{\text{N}}1$ and retention of the stereochemistry with chloride-anions from MsCl , highlighting the stability of the allylic carbocation **102** (Scheme 46).

Scheme 46. Mesylation followed by base/MW activation of allylic alcohol **96a**.

After this failed attempt and due to the instability of the actual starting material **98a**, the study was continued with the more stable mesylate **101a**. By adding DBU and microwave irradiation, the $-\text{OMs}$ group should be cleaved off. Simultaneously, MeOH is present as a nucleophilic solvent (Table 15).

Table 15. Screening of mesylate **101a** under various conditions.

Entry	Additive [equiv]	Nu	Solvent	Time [h]	T [°C]	25a [%]	107 ^{a)} [%]	108 [%]
1	DBU (2.5)	MeOH	MeOH	1	100	26	67 (3.7/1 <i>dr</i>)	—
2	DBU (2.5)	109^{b)}	MeCN	1	100	67	—	—
3	DBU (2.5)	MeOH	MeOH	24	25	17	70 (2.5/1 <i>dr</i>)	6
4	—	—	MeCN	1	100	43	—	3
5 ^{c)}	—	—	DMF	1	100	63	—	traces
6 ^{c)}	—	—	DMF	1	130	76	—	traces
7 ^{c)}	—	—	DMSO	0.5	100	60	—	—
8 ^{c)}	—	—	DMSO	0.5	130	65	—	—
9 ^{c)}	—	—	1,4-dioxane	0.5	130	84	—	traces
10 ^{c)}	—	—	toluene	1	100	59	—	16
11 ^{c)}	—	—	toluene	1	130	44	—	26
12	—	—	toluene	3	80	almost no conversion		
13 ^{c)}	—	—	toluene	0.5	150	39	—	30
14 ^{c)}	—	—	toluene	0.5	150	44	—	34
15	—	—	toluene	24	60	no conversion		

16^{c)}	—	—	toluene	24	80	45	—	25
17^{c)}	Amberlyst 15 [®] (20 wt%)	—	toluene	0.5	150	65	—	31
18^{c)}	DBU (2.5)	—	toluene	0.5	150	83	—	—

Reactions were performed on a 0.2 – 0.5 mmol scale. [a] Major diastereomer **107a** is shown. [b] Cyclohexanol **109** (3.0 equiv) was used as the nucleophile. [c] Yield was determined by ¹H-NMR with 1,3-dioxolan-2-one as the internal standard.

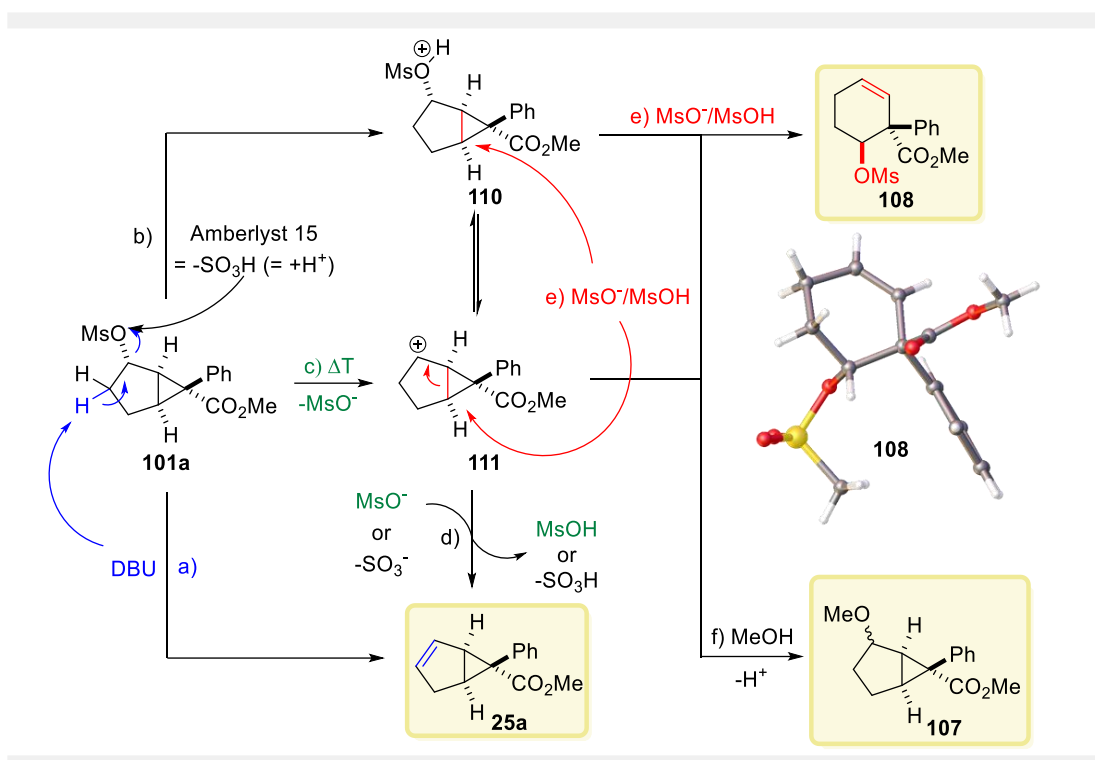
DBU (2.5 equiv) as the base and MeOH (excess) as the nucleophilic solvent did not give rise to the desired endocyclic ring-opening. Instead, the elimination reaction of -OMs mediated by DBU resulted in the starting material **25a** (26%) as a side product. As the main reaction, S_N1 with retention of the stereochemistry occurred, obtaining a diastereomeric mixture of **107a/b** (67%, 3.7/1 *dr*, Table 15, Entry 1). The S_N1 reaction consistently proves the formation of a carbocation that must be highly stabilized since it undergoes intermolecular substitution reactions rather than intramolecular rearrangement with ring strain relief. With this knowledge, the idea was to use a bulky nucleophile to slow down the substitution reaction and favor the cleavage of the intramolecular C–C bond. Nevertheless, this idea was quickly when using cyclohexanol **109** (3.0 equiv) as the nucleophile—only elimination afforded **25a** in high yield (67%, Table 15, Entry 2). Altering the approach from thermal activation to concentrating in a basic environment, elimination (**25a**, 17%) and substitution (**107**, 70%, 2.5/1 *dr*) was observed. However, an unexpected cyclohexene product bearing -OMs **108** (6%) formed as a minor product (Table 15, Entry 3). This compound **108** must form *via the* desired endocyclic C–C bond cleavage. Excess of nucleophilic MeOH does not add to the molecule, which indicates that postulated cyclohexene carbocation from type **69** is not formed. Thus, no additional nucleophile is required, which has the advantage of preventing the initial substitution reaction.

Additionally, the base should be omissible as this should hinder elimination reactions. Among the various polar and non-polar solvents examined (Table 15, Entry 4 – 11), toluene achieved the best results for the endocyclic C–C bond cleavage with 16% of **108**, but still with elimination as the main reaction. A temperature screening demonstrated that high energy is needed to favor endocyclic ring-expansion to overcome the energy barrier

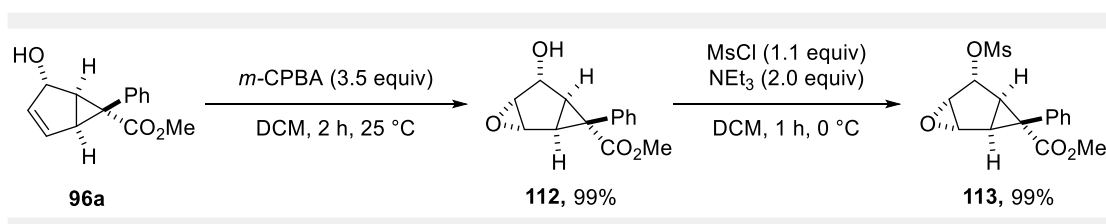
of the remarkably stabilized bicyclic cyclopropane core. At 150 °C without MW-activation, 34% of the cyclohexene **108** was obtained as the best result (Table 15, Entry 14). However, in all cases, the elimination reaction remained predominant, probably *via* an E₁-mechanism favored by the high temperatures. Control experiments under acidic conditions (Table 15, Entry 17) and basic conditions (Table 15, Entry 18) support these assumptions.

Compared to the heterocyclic analogues (Scheme 40), it was evident that the heteroatom within the ring system has a key role in this transformation. While the bicyclic carbocycles only show a “*pull-effect*” from the generated positive polarization next to the cyclopropane moiety, the heteroatom in **81/82** additionally lowers the energy barrier of the reaction by donating electrons (“*push-effect*”).⁴³ Furthermore, literature demonstrates a few examples that compounds of type **101a** with a good leaving group favor solvent-dependent S_N1- or S_N2 reaction,^{120–122} especially when the cyclopropane moiety is functionalized with electron-withdrawing groups.^{122,123} Nevertheless, other examples demonstrate the ability of cyclopropylmethanols to undergo endocyclic C–C bond cleavage under acidic conditions having EDG at the cyclopropane.^{115,124}

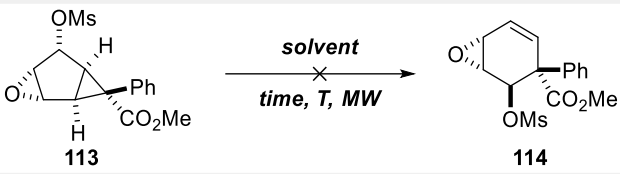
Mechanistically, we postulate that the elimination reaction to **25a** is supported by the base (Scheme 47, a) or high temperatures forming a carbocation **111** under MsO[−] release (Scheme 47, c) followed by E₁-elimination (Scheme 47, d). If a non-bulky nucleophile is present, the S_N1 reaction to **107** is favored over elimination (Scheme 47, f) and vice versa for a steric nucleophile. Under acidic conditions, initial protonation of the mesylate group to **110** and release of MsOH takes place, followed by E₁-elimination to obtain **25a** as the main product (Scheme 47, b). It was postulated that no cyclohexene carbocation from type **69** as an intermediate is formed. Therefore, it was proposed that **108** forms *via* an S_N2'-type reaction from **110** or **111** with MsO[−]/MsOH as the nucleophile (Scheme 47, e). This would also explain the high diastereoselectivity of the endocyclic ring-expansion product **108**, which was proved by X-ray analysis. The same considerations are done for path c) with the difference that the release of MsO[−] is mediated by high temperatures.

Scheme 47. Mechanistic considerations for the formation of **25a**, **107**, and **108**.

Further considerations led to a study to prevent the elimination reaction from **101a** by blocking the position with functional groups. For that purpose, epoxidation by adding *m*-CPBA (3.5 equiv) to the allylic alcohol **96a** dissolved in DCM afforded **112**. A further mesylation reaction resulted in the desired protected mesylate **113** with both steps in almost quantitative yield (Scheme 48).

Scheme 48. Synthesis of mesylate **113** with blocked elimination position.

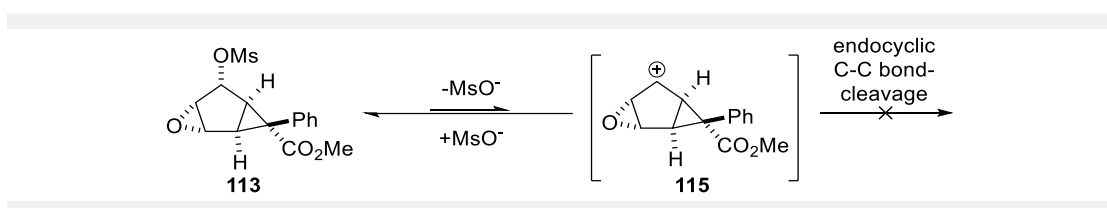
Surprisingly, with the best conditions for C–C bond cleavage from before (Table 16, Entry 1 -3) and even higher thermal activation of up to 200 °C in a microwave oven, the mesylate **113** did not react, that led to the following conclusion:

Table 16. Unsuccessful endocyclic C–C bond cleavage of mesylate **113**.


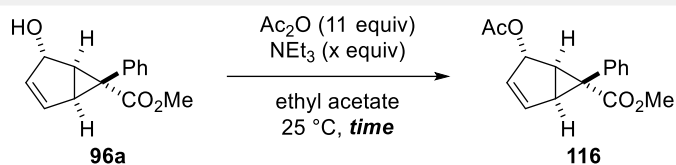
Entry	Solvent	Time [h]	Temperature [°C]	Result
1	toluene	1.5	130 - 150	no conversion
2	toluene	2	200	no conversion
3	MeCN	1.5	150	no conversion

Reactions were performed on a 0.20 – 0.25 mmol scale.

The introduced epoxide stabilizes the mesylate compound **113**. Notwithstanding, the formation of a carbocation **115** was assumed, but nucleophilic backreaction is overall preferred (Scheme 49). Presumably, due to the additional steric hindrance of the epoxide, S_N2' reaction, as postulated in Scheme 47, is unfavored or impossible. Further investigations should focus on different activation methods, such as using bases, acids, or Lewis acids. However, epoxide groups could cause problematic side reactions due to their ring-opening driving force under various conditions.

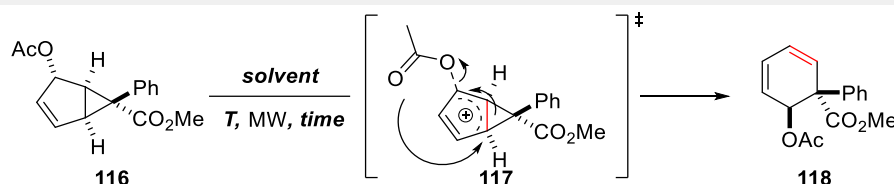
Scheme 49. Postulated equilibrium of **113** at high temperatures.

Continuing with the latter idea to prevent an elimination reaction, a similar approach focused on utilizing a compound of type **116** bearing a good leaving group in an allylic position. Starting from allylic alcohol **96a**, transformation into an -OAc group using an excess of Ac_2O and NEt_3 dissolved in ethyl acetate gave rise to **116**. Predicting that -OAc is a good leaving group, the idea was to synthesize cyclohexadienes from type **118** upon heating in an allylic position.

Table 17. Synthesis of allylic acetate **116** via acetylation from **98a**.

Entry	n of 96a [mmol]	Equiv of NEt ₃	Time [h]	Yield 116 [%]
1	0.64	38	3	86
2	1.76	38	3	67
3	4.69	20	4	87

However, merely thermal activation and different types of polar solvents did not lead to a reaction (Table 18). The -OAc group may require higher temperatures or additional Lewis acid activation to be cleaved off. (Lewis acid activation will be discussed later in Chapter 2.2.7).

Table 18. Behavior of allylic acetate **116** under thermal activation.

Entry	Solvent	T [°C]	Time [h]	Result
1	toluene	130	7	no conversion
2	toluene	150	7	no conversion
3	toluene	150 (no MW)	24	no conversion
4	MeCN	130	7	no conversion
5	DMSO	130	7	no conversion

Reactions were performed on a 0.2 mmol scale.

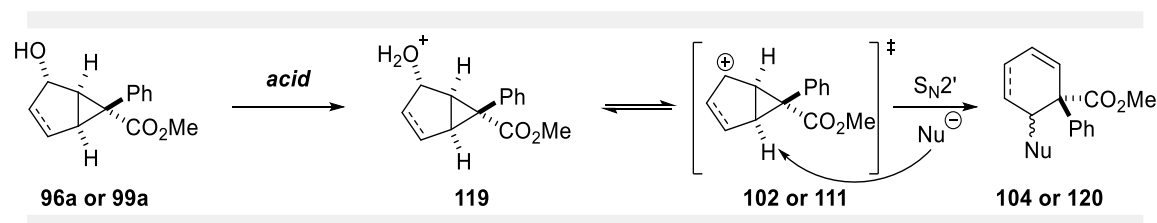
In conclusion, carbocyclic bicyclic cyclopropanes of type **101a** were capable of undergoing endocyclic C–C bond cleavage. In contrast to heterocyclic analogues **81/82**, no “*push-effect*” supports the reactions due to the lack of heteroatom within the ring system. Therefore, depending on the conditions, the main reaction **101a** remained as an elimination or substitution.

With these results in hand, the focus was set to external activation, such as a strongly acidic environment, to get a better understanding of the reaction driving forces of the cyclopropyl carbocation **111**.

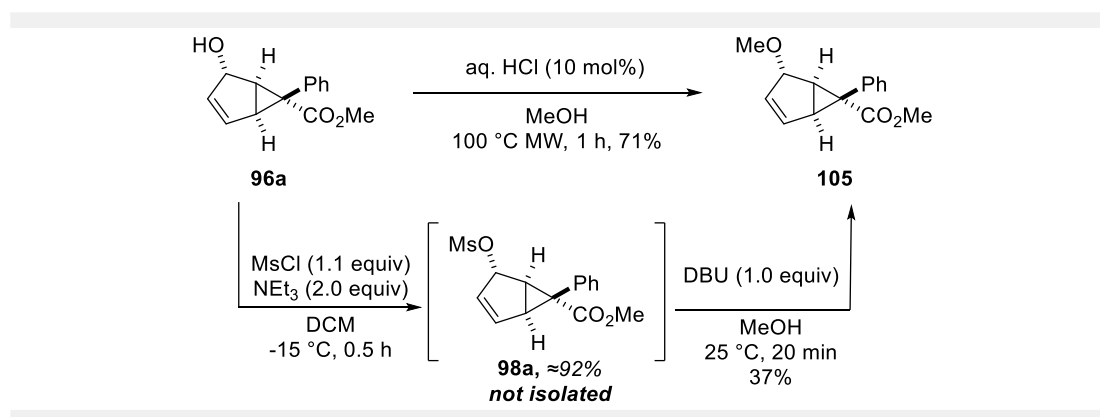
2.2.4 Acid-Mediated Endocyclic Ring-Opening of Cyclopropylmethanols

In the previous study, it was found that generating an allylic mesylate from **98a** was not possible due to instability issues. Therefore, it was decided to use the alcohol **96a** which had already been synthesized. This alcohol was expected to create the desired carbocation **111** under acidic conditions. While catalytic acids should generate H_2O^+ as a good leaving group, small nucleophiles should trigger the ring-expansion reaction *via* $\text{S}_{\text{N}}2'$ as postulated before (Scheme 47).

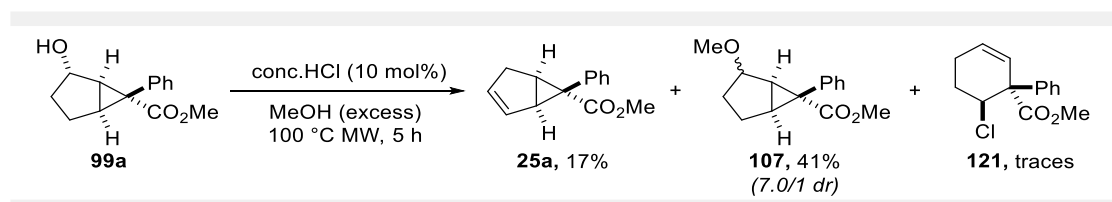
Scheme 50. Strategy for acid-catalyzed endocyclic ring-opening of **96a** and **99a**.



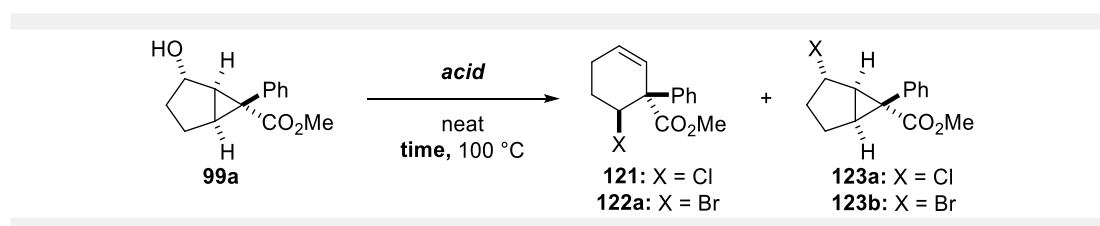
A first test reaction showed allylic alcohol **96a** with catalytic amounts of conc. HCl (10 mol%) dissolved in MeOH as nucleophilic solvent at 100 °C again resulted in $\text{S}_{\text{N}}1$ reaction providing **105** with retention of the stereochemistry (Scheme 51). It was concluded that an allylic carbocation **102** is too stable to undergo endocyclic ring-opening. Especially, when bearing a phenyl group at the cyclopropane moiety that consequently stabilizes the compound by steric hindrance and probably π -stacking.

Scheme 51. Formation of **105** via allylic carbocation.

During the use of reduced alcohol **99a**, an unexpected formation of cyclohexene **121** occurred as a side product alongside elimination (**25a**) and substitution (**107**, Scheme 52). Considering that excess nucleophilic MeOH is present, this result is surprising and a further hint for the postulated mechanism, in which no cyclohexene carbocation from type **69** is formed (see Scheme 47). Furthermore, to cause the S_N2' reaction and to cleave the C-C bond, a strong nucleophile such as the chloride-anion is required, while the nucleophilicity of MeOH is too weak.

Scheme 52. Alcohol **99a** under acidic conditions.

Based on these results, a reaction screening with an excess of conc. HCl or conc. HBr as Brønsted acids was carried out (Table 19). Concentrated hydrobromic acid was the best option due to its strength and the nucleophilicity of the bromide anion, resulting in 89% yield of cyclohexene **122a** (Table 19, Entry 4).

Table 19. Endocyclic C–C bond cleavage of **99a**.

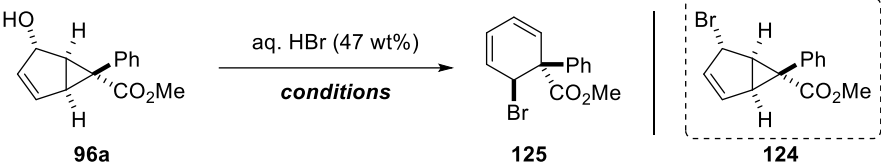
Entry	Acid (equiv)	X	Time [h]	Yield 121 [%]	Yield 123a [%]
1	HCl (15)	Cl	3	44	36
2	HBr (15)	Br	0.5	46, 122a	34, 123b
3	HBr (15)	Br	1.5	74, 122a	traces
4	HBr (10)	Br	1.5	89, 122a	—
5	HBr (50)	Br	1.5	89, 122a	—
6	HCl (50)	Cl	1.5	47	24

Reactions were performed on a 0.5 mmol scale.

1) Notably, the initial formation of cyclopropane **123b**, formed *via* S_N1 reaction after 0.5 h (Table 19, Entry 2), cannot be observed after prolonged reaction time (1.5 h, Table 19, Entry 4). This indicates the postulated endocyclic C-C bond cleavage of S_N2'-type. 2) The high diastereoselectivity of the ring-expansion (>20:1 *dr*) shows that the bromo-anion is part of the ring-opening process and cyclohexene cation **69** is not formed. 3) The elimination reaction leading to **25a** is not observed with a significant excess of the acid (Table 19, Entry 5 – 6), while it occurs under catalytic conditions (see Scheme 52). This is an indication that the vinyl cyclopropane **25a** also undergoes endocyclic C–C bond cleavage under harsh acidic conditions. This proposal will be discussed in Chapter 2.2.6.

In a further step, the allylic alcohol **96a** was applied to these ring-opening conditions using an excess of aq. HBr (Table 20). However, ring-expansion was not observed; and decomposition occurred relatively fast at 100 °C, showing less stability under an excess acid and high temperatures. Lowering the temperature and adding solvents for solubility issues led to the formation of the allylic bromide **124** in high yield *via* S_N1 reaction. This demonstrates a less driving force of ring strain release for the allylic carbocation **102** (Table 20, Entry 2 – 4).

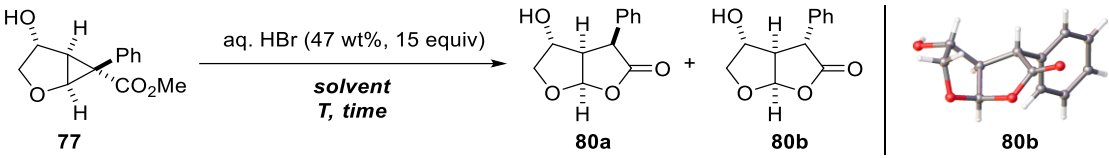
Table 20. Behavior of allylic alcohol **96a** under excess of aq. HBr.

					
Entry	HBr [equiv]	solvent	Time [h]	T [°C]	Result
1	15	neat	1	100	decomposition
2	15	neat	1	25	stirring not possible
3	15	DCM	1	25	88% of 124
4	15	DCM	72	25	96% of 124

Reactions were performed on a 0.3 mmol scale.

To complete the study, the heterocyclic analogue **77**, synthesized *via* a reaction cascade from the literature¹¹⁵, was tested under excess of aq. hydrobromic acid (Table 21).

Table 21. Exocyclic ring-opening of compound **77**.

					
Entry	Solvent	Time [min]	T [°C]	80a [%]	80b [%]
1	neat	10	100	decomposition	
2	neat	20	25	solubility issues	
3	MeCN	60	25	39 ^{a)}	42

Reactions were performed on a 0.2 – 0.3 mmol scale. [a] Compound **80a** could not be purified, and yield was determined *via* ratio to **80b** from crude ¹H-NMR.

At 100°C, the heterocycle decomposed due to the heteroatom's donor effect within the ring system, exhibiting higher reactivity. Lowering the temperature and adding a solvent gave the lactones **80a** and **80b** (81%, 0.93/1.0 *dr*) *via* exocyclic ring-opening, followed

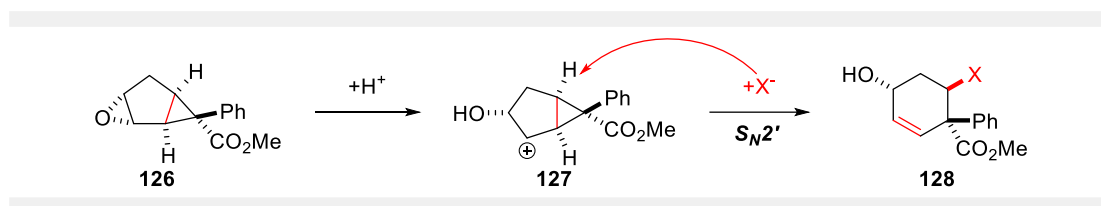
by hydrolysis and lactonization. This is in agreement former results from the literature.^{115,116} The diastereomer **80a** could not be separated and purified but was analyzed from crude ¹H-NMR.

Nevertheless, suitable conditions for the endocyclic ring-expansion for the alcohol **99a** were identified. In the next step, the scope should be expanded to oxygenated compounds that could form similar carbocations from type **111**.

2.2.5 Acid-Mediated Endocyclic Ring-Opening of Epoxides

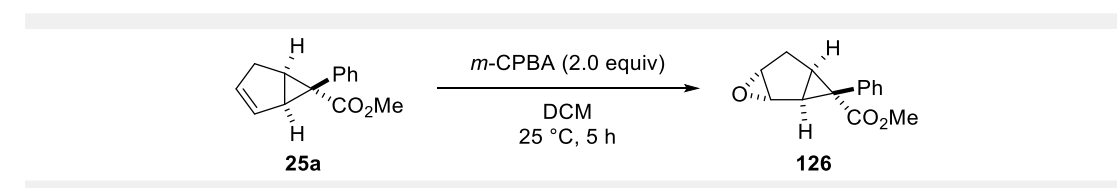
Under acidic conditions, epoxides are well known to open via S_N1 reaction forming a carbocation. The aim was to utilize carbocation **127** to induce C–C bond cleavage, producing highly functionalized cyclohexenes **128** from **126**(Scheme 53).

Scheme 53. Strategy for endocyclic ring-opening of epoxides.



It should be noted that epoxide **126** was expected to have side reactions as epoxide opening could occur from different sides. Epoxidation of **25a** was done with *m*-CPBA, obtaining **126** in quantitative yield on gram-scale (Table 22).

Table 22. Epoxidation of compound **25a**.



Entry	n of 25a [mmol]	Yield of 126 [%]
1	0.53	94
2	5.60	quantitative

Starting with optimized conditions and using an excess of aqueous HBr, cyclohexene **129** (19%, 3.0/1 *dr*) was formed *via* desired endocyclic ring-opening at 100 °C. Traces of substitution product **131** were also observed (Table 23, Entry 1), but the overall yield remained low. Therefore, the reaction temperature was lowered to ambient temperatures, which afforded the cyclohexene **129a** (7%), as well as **130** (14%), *via* desired ring-expansion reaction, and again S_N1-product **131** (25%, Table 23, Entry 2).

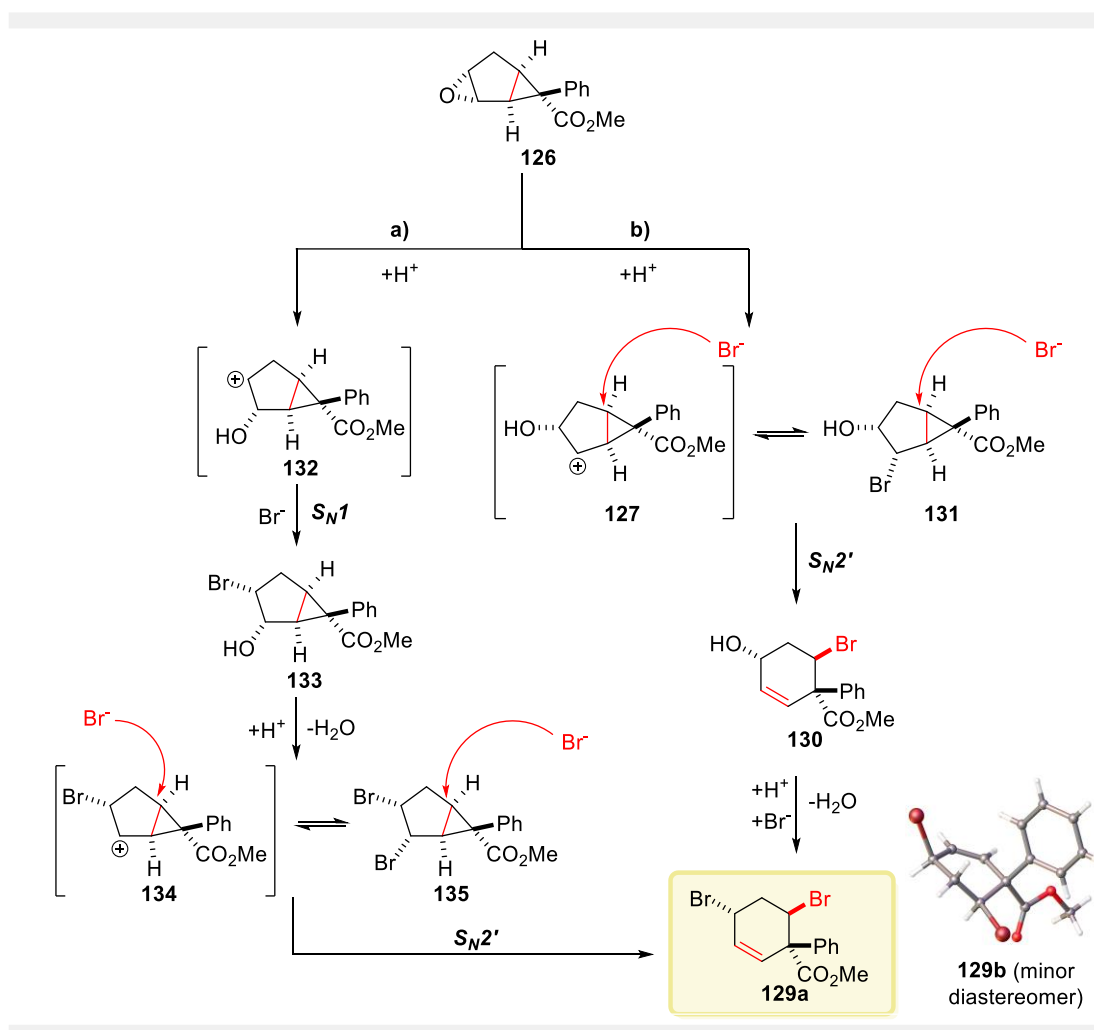
Table 23. Endocyclic ring-opening of epoxide **126**.⁶⁶

Entry	Solvent	Time [h]	T [°C]	129 ^a [%]	130 [%]	131 [%]
1	—	0.5	100	19 (3.0/1 <i>dr</i>)	—	5
2	—	1	25	7	14	25

Reactions were performed on a 0.2 – 0.4 mmol scale. [a] only major diastereomer **129a** is shown.

Mechanistically, we propose the same S_N1 reaction for the formation of **131** and S_N2' reaction for **129** and **130** as postulated before (Scheme 47). However, some differences have to be clarified:

The dibromo compound **129** could be formed *via* different pathways: Path **a**) first shows the epoxide ring-opening opposite to path **b**), followed by S_N1-addition of the bromide-anion leading to **133**. The second protonation generates carbocation **134** or dibromide **135** that can both undergo endocyclic ring-opening *via* S_N2'. More plausible is path **b**) in which first carbocation **127** is formed or/and respective S_N1-product **131**, followed by S_N2'-ring-opening yielding allylic alcohol **130**. After deoxygenative allylic bromination compound **129a** is obtained (Scheme 54).

Scheme 54. Formation of cyclohexene **129a**.

Compared to **111**, the carbocation from type **127** is more reactive due to the additional EDG group, making the epoxide **126** unsuitable for harsh acidic conditions. Therefore, it was claimed that epoxide **126** is more similar to the heterocyclic cyclopropanes **81/82**. Thus, milder conditions, such as the catalytic use of acids and weaker nucleophiles (MeOH or H_2O), could be more effective.

Indeed, the reactive epoxide **126** could undergo endocyclic ring-opening with catalytic amounts of Amberlyst 15® (20 mol%) as an acid and MeOH (excess) as a nucleophile. Due to the weak nucleophilicity of MeOH, high temperatures are required, and activation in a microwave oven supports the reaction. However, the ring-expansion remains a side reaction with a low yield of only 17% (**138**, Table 24, Entry 2), while $\text{S}_{\text{N}}1$ is the main reaction. In principle, stronger nucleophiles could support the C–C bond cleavage and favor the ring-expansion. The nucleophilic solvent was replaced with an

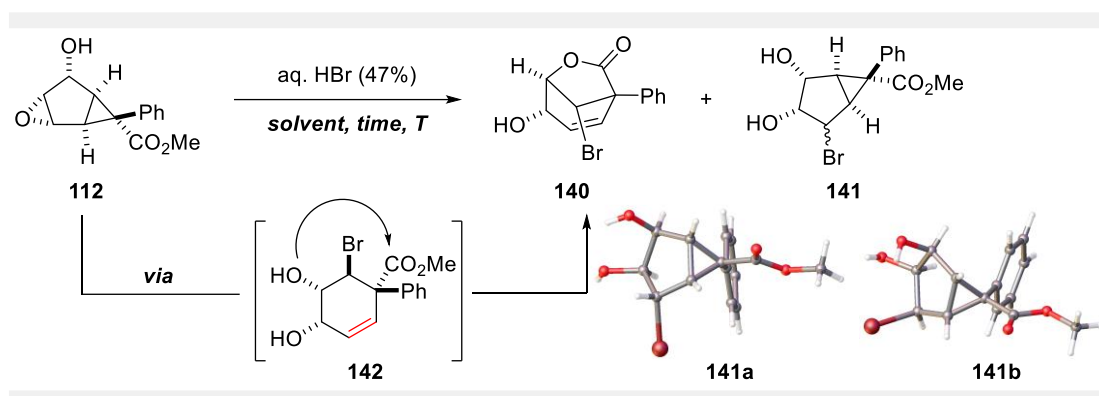
H₂O/1,4-dioxane mixture with water as the nucleophile. This gave a similar mass balance with small amounts of ring-expansion product **139** (12%), which supports the statement for the requirement of stronger nucleophiles (Table 24, Entry 5).

Table 24. Acid-catalyzed endocyclic ring-opening of epoxide **126**.

Entry	Additive	Solvent	T [°C]	Time [h]	136a [%]	136b ^{a)} [%]	138 ^{a)} [%]	
1	—	MeOH	reflux	4	17	30	15	
2	—	MeOH	100, MW	2	24	36	17	
3	—	MeOH	25	24	no conversion of 126			
4	MeOH (2.0 equiv)	toluene	100, MW	2	decomposition			
5	—	H ₂ O/1,4-dioxane (1/1)	100, MW	2	34, 137a	25, 137b^{a)}	12, 139^{a)}	

Reactions were performed on a 0.2 – 1.0 mmol scale. [a] Products **136b/138** and **137b/139** are not separable.

The previously synthesized alcohol **112** bearing an epoxide group was tested with the optimal ring-opening conditions using an excess of aq. HBr-solution. Surprisingly, the 7-membered lactone **140** was obtained as the main product, likely formed *via* lactonization after endocyclic ring-expansion. Nonetheless, yields were considerably low (22 – 27%) due to decomposition (Table 25, Entry 1 – 5). The reactivity of the epoxides was manifested by short reaction times, even at ambient temperatures (Table 25, Entry 6). However, at room temperature, the primary products remained as the substitution products **141a/b** (54%, 2.4/1 *dr*) from S_N1 reaction. Utilizing different solvents to see the behavior of the reaction in a non-polar to polar environment did not favor the endocyclic C–C bond cleavage and allowed no further conclusions (Table 25, Entry 8 – 15).

Table 25. Endocyclic C–C bond cleavage of **112** using an excess of aq. HBr.⁶⁶

Entry	HBr [equiv]	Solvent	Time	T [°C]	140 [%]	141a/b [%]
1	15	neat (H ₂ O)	10 min	100	24	-
2^a)	7.0	neat (H ₂ O)	10 min	100	22	-
3^a)	7.0	neat (H ₂ O)	1 h	100	26	-
4^a)	50	neat (H ₂ O)	10 min	100	25	-
5^a)	15	neat (H ₂ O)	5 min	150	27	-
6	15	neat (H ₂ O)	1 h	25	15	54 (<i>dr</i> = 2.4/1)
7	7.0	neat (H ₂ O)	1 h	25	almost no conversion	
8^a)	15	DMSO	10 min	100	14	28 (<i>dr</i> = 3.4/1)
9^a)	15	MeCN	10 min	100	16	38 (<i>dr</i> = 2.0/1)
10^a)	15	1,4-dioxane	10 min	100	20	30 (<i>dr</i> = 2.5/1)
11^a)	15	1,4-dioxane	1 h	100	21	-
12^a)	15	acetone	10 min	100	22	31 (<i>dr</i> = 1.4/1)

13^{a)}	15	toluene	10 min	100	30	18 (<i>dr</i> = 1.3/1)
14	10	toluene	10 min	100	26	18 (<i>dr</i> = 1.4/1)
15^{a)}	15	toluene	10 min	100, MW	25	-

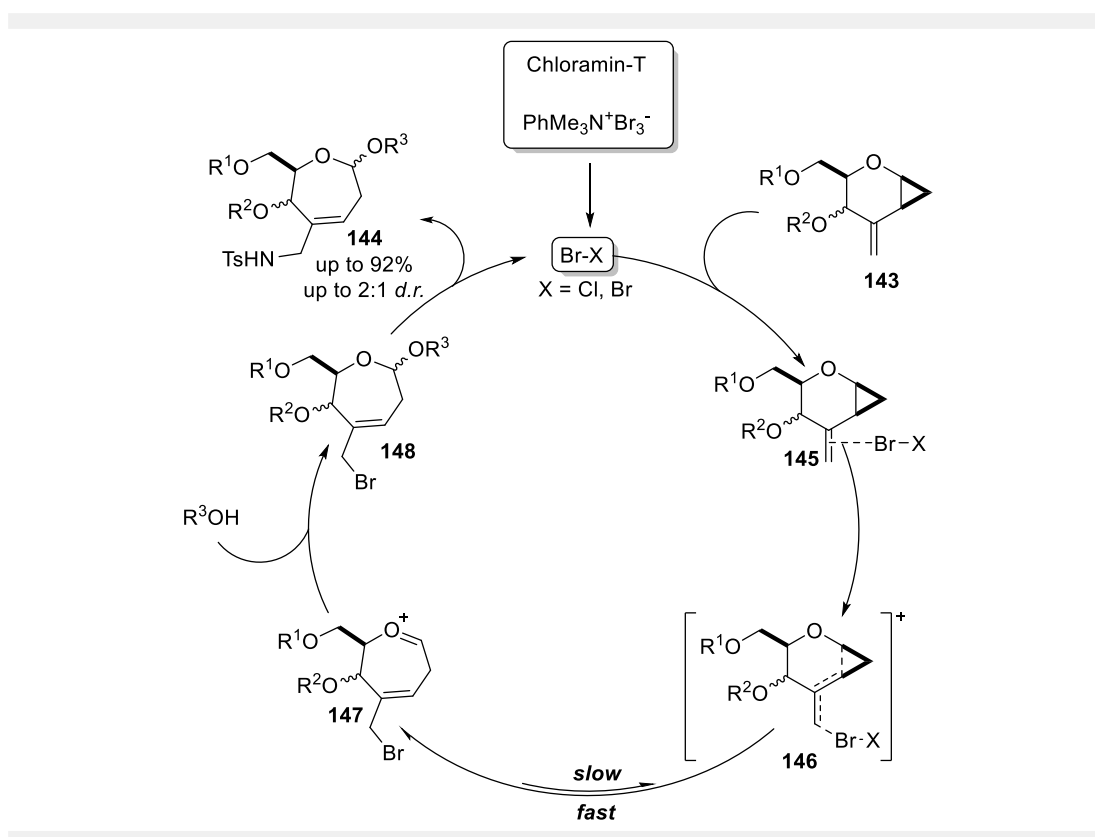
Reactions were performed on a 0.2 mmol scale. [a] Yield was determined from crude ¹H-NMR using fumaronitrile as an internal standard.

The combination of alcohol **101a**, strongly acidic aq. HBr, and the strong nucleophilicity of the bromide-anion is optimal for the endocyclic ring-opening of carbocyclic cyclopropanes. On the other hand, epoxides from type **126** or **112** are more reactive towards acids due to the additional -OH group. This group donates electrons in the ring system, making it behave like heterocyclic cyclopropanes from type **81/82**. This allows for ring-expansion even with weak nucleophiles under catalytic acidic conditions. However, yields are generally low due to the epoxides' higher reactivity, which leads to decomposition under excess of acid, making them unsuitable for these harsh conditions.

2.2.6 Brønsted-Acid or Electrophile Mediated Ring-Opening of Vinyl Cyclopropanes

In 2014 *Ganesh et al.* postulated that endocyclic ring-expansion should be possible by the introduction of an exocyclic methylene group, utilizing its electron-rich character by activating with an electrophile. Indeed, the interhalogen electrophiles Br-X assist in the endocyclic C–C bond cleavage of **143** to form 7-membered compounds **144**.

Scheme 55. Postulated mechanism of electrophile-activated endocyclic ring-opening.

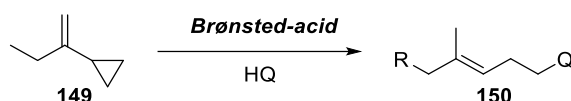


Mechanistically, they propose an initial *in-situ* formation of interhalogen compounds Br-X from the reaction between chloramine-T and PTAB. The electrophiles add to the vinyl cyclopropane bond forming transient cationic intermediate **146**, which undergoes spontaneous ring-expansion. This is triggered by the “pull-effect” of the carbocation, together with the donor-characteristic of the heteroatom within the ring system (“push-effect”). The planar oxonium intermediate **147** is then attacked by an external nucleophile and subsequent replacement of the bromo group by TsN[−] resulting in the desired oxepane **144** (Scheme 55).⁹⁸

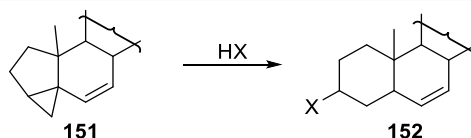
In 2018 *Schroeder et al.*¹²⁵ patented a ring-opening reaction of cyclopropylvinyl compounds **149** using Brønsted acids HQ (HQ = R'CO₂H and a hydrogen halide selected from HCl, HBr or HI) synthesizing homoallylic compounds **150** (Scheme 56). Additionally, a much older publication from *Riegel et al.*¹²⁶ demonstrates a similar reaction with Brønsted acids HX (X = Cl, Br, I), causing an endocyclic ring-expansion reaction of vinyl cyclopropanes **151** (Scheme 56).

Scheme 56. Brønsted-acid ring-opening of VCP.

Schroeder et al.

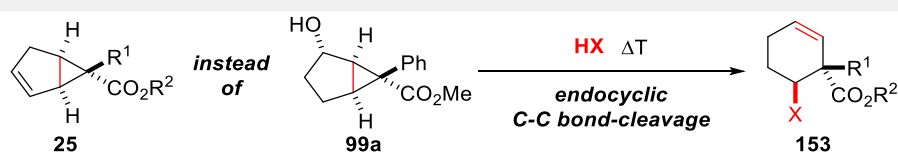


Riegel et al.



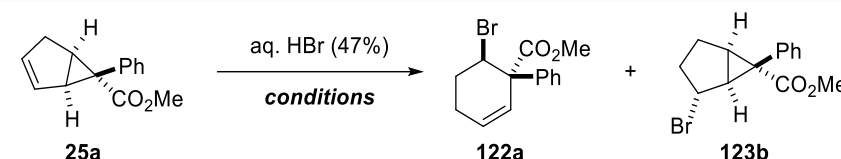
By combining these literature reactions with our previously demonstrated endocyclic ring-opening of alcohol **99a** (see Table 19), the necessity of an alcohol group was questioned. Consequently, it was postulated that the same ring-opening reaction should be possible with vinyl cyclopropanes **25** applying the same optimized conditions (Scheme 57).

Scheme 57. Strategy for endocyclic ring-opening of VCP **25**.



Indeed, cyclohexene **122a** was directly synthesized from **25a** on gram-scale with almost quantitative yield (Table 26, Entry 3). Initially, product **123b** was formed as the main product after 15 min and completely converted to the cyclohexene **122a** after 1.5 h (Table 26, Entry 2 and 3).

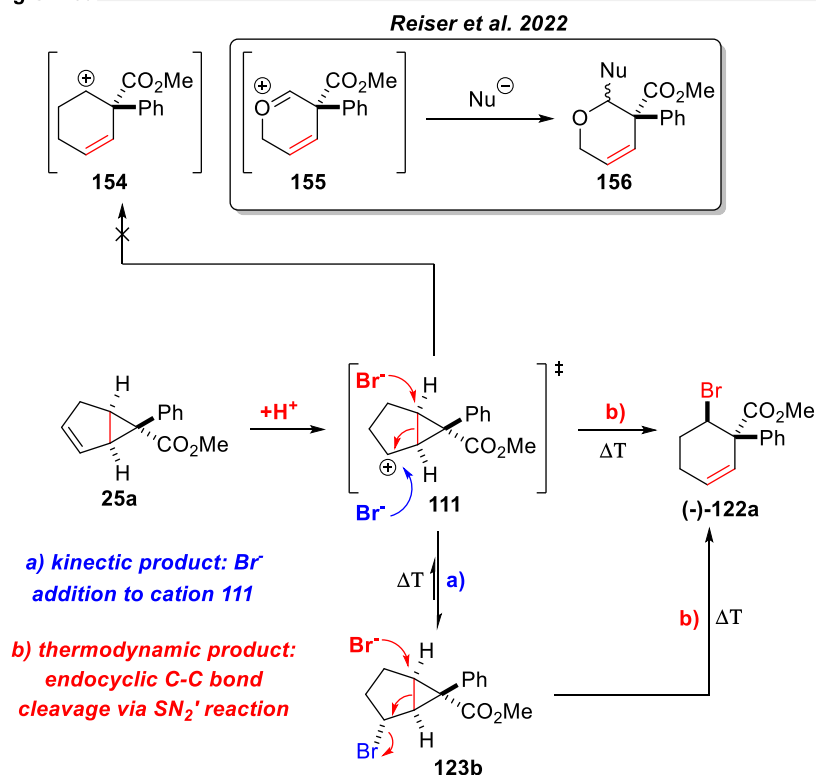
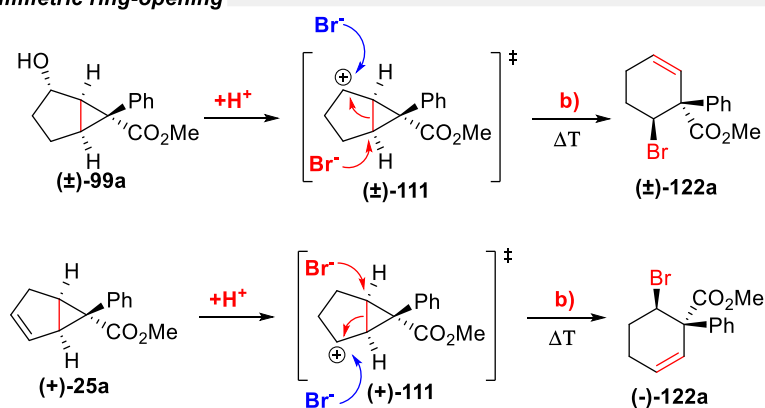
Table 26. Aq. HBr mediated ring-expansion of VCP **25a**.⁶⁶

						
Entry	SM [mmol]	HBr [equiv]	Time	T [°C]	122a [%]	123b [%]
1 ^{a)}	0.20	50	1 h	100	86	-
2 ^{a)}	0.58	10	15 min	100	43 (<i>brsm</i>)	55 (<i>brsm</i>)
3	7.75	10	1.5 h	100	99	-

[a] Yield was determined from crude ¹H-NMR with fumaronitrile as the internal standard.

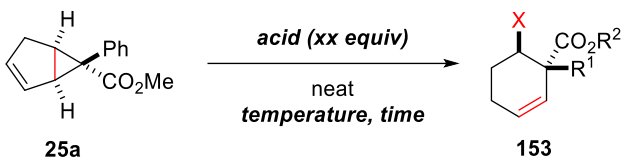
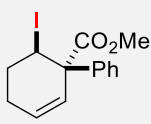
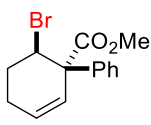
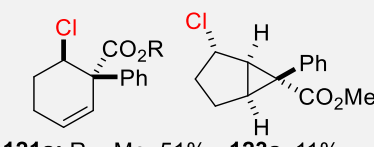
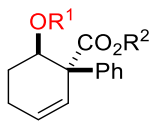
Based on the previously obtained results, the following mechanism was proposed (Scheme 58): After a short reaction time, kinetic product **123b** is formed *via* cation **111**, to which bromo-anion adds from the sterically less hindered convex face of the bicycle **123b**. Prolonging the reaction to 1.5 h resulted in the quantitative formation of **122a**. Considering the low diastereoselectivity of the demonstrated addition of nucleophiles to cation **155** from literature⁴³ and the high diastereoselectivity of the endocyclic ring-opening of VCP **25a** and alcohol **99a** led to the conclusion: the bromide must be introduced anti to the leaving group of **123b** *via* S_N2' reaction from the sterically hindered concave face of the bicycle and thus the formation of a carbocation from type **154** is disproved (Scheme 58, a).

Additionally, enantiopure starting materials could give access to the selective formation of the enantiomer (-)-**122a** from VCP (+)-**25a** and the enantiomer (±)-**122a** from alcohol (±)-**99a** due to the regioisomeric formation of the cation (±)-**111** and (+)-**111** (Scheme 58, b). The asymmetric reaction with chiral (+)-**25a** was later demonstrated in Scheme 59.

Scheme 58. Postulated endocyclic ring-expansion of VCP **25a** and alcohol **99a** assisted by aq. HBr.⁶⁶**a) Ring-opening of 25a****b) Potential asymmetric ring-opening**

With a robust and scalable method to afford cyclohexene **122a**, various acids were screened to see the influence of acids and limitations of the ring-opening (Table 27).

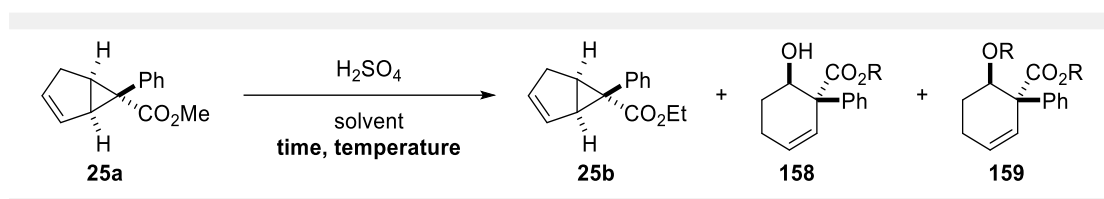
Table 27. Acid-scope of endocyclic ring-opening.⁶⁶

					
Entry	Acid [equiv]	<i>pK_a</i>	T [°C]	Time [h]	Result
1	aq. HI (57 wt%, 10)	-10	80	1	 157 , 55%
2	aq. HBr (47 wt%, 10)	-9	100	1.5	 122a , 99%
3	aq. HCl (37 wt%, 10)	-6	100	4	 121a : R = Me, 51% 123a , 11% 121b : R = H, 29%
4 ^a	conc. H ₂ SO ₄ (10)	-3	150	10	 158a : R ¹ =H, R ² =Et: 31% 159a : R ¹ =R ² =Et, 25%
5 ^a	conc. <i>p</i> -TsOH (10)	-2.8	100	3	no conversion
6	conc H ₃ PO ₄ (15)	2.1	100-150	1-16	no conversion
7	AcOH (20 equiv)	4.76	100	1-5	no conversion

Reaction conditions: Entry 1: **25a** (0.45 mmol); Entry 2: **25a** (7.75 mmol); Entry 3: **25a** (0.44 mmol); Entry 4: EtOH was added as a solvent, **25a** (0.5 mmol); Entry 5: **25a** (0.3 mmol); Entry 6: **25a** (0.2 – 0.5 mmol); Entry 7: **25a** (0.3 – 0.5 mmol). [a] For Entries 4 and 5, see additional screening Tables 28 and 29.

During the screening of these acids, certain trends with respect to the quantitative HBr-mediated ring-opening reaction can be observed (Table 27): A slightly stronger acid (HI, $pK_a = -10$) afforded cyclohexene **157** (55%) with reduced reaction temperature and time but also decreased yield. Probably, the desired S_N2' reaction is faster due to iodine as a better leaving group and nucleophile in contrast to bromine. The significant acidity of aq. HI, together with iodine as a good leaving group, caused the decomposition of the product **157** (Table 27, Entry 1). Consequently, weaker aq. HCl requires prolonged reaction time since chloride is a weaker nucleophile and leaving group. Decomposition does not occur, giving rise to 80% of endocyclic ring-opening products **121a** and **121b**. However, even after a 4 h reaction time, still the addition-product **123a** (11%) can be observed, while the extended reaction time leads to hydrolysis to **121b** (Table 27, Entry 3). H_2SO_4 required EtOH as solvent. EtOH and traces of water act as nucleophiles in this reaction, giving rise to endocyclic ring-opening products **158a** (31%) and **159b** (25%) after transesterification. Notably, high temperatures are required due to the weak nucleophiles and weaker acidity of H_2SO_4 (Table 27, Entry 4). A separate screening for H_2SO_4 can be seen in Table 28. Even at elevated temperatures, increased amounts of acid or/and prolonged reaction times *p*-TsOH, H_3PO_4 , and AcOH were too weak of acidity to protonate the double of **25a** and initiate any reaction (Table 27, Entry 5 -7), confirming their limitations in this reaction.

Reactions with H_2SO_4 were different from those with HI, HBr, or HCl. H_2SO_4 is strong enough to protonate the double bond of **25a** but the counterion HSO_4^- is a poor nucleophile and cannot trigger the S_N2' reaction needed for ring-opening. Therefore, a separate screening utilizing H_2SO_4 as the acid towards different nucleophilic solvents was carried out (Table 28). Water only afforded traces of the cyclohexene product **158b** (R=Me) and conversion of **25a** was slow. Unexpectedly, extending the reaction time led to a complex mixture (Table 28, Entry 1 – 2). Reducing the temperature resulted in a significantly slower conversion of the starting material (Table 28, Entry 3).

Table 28. Screening of H₂SO₄ as acid.

Entry	-R	H ₂ SO ₄ [equiv]	Solvent	Time [h]	T [°C]	25b [%]	158a [%]	159a [%]
1	Me	10	H ₂ O	1	100	almost no conversion, traces of 158b (R=Me)		
2	Me	10	H ₂ O	3	100	<i>c.r.m.</i>		
3	Me	10	H ₂ O	3	80	almost no conversion, traces of 158b (R=Me)		
4	Me	10	MeOH	1.5	100-120	<i>c.r.m.</i>		
5	Me	10	MeOH	0.5	120, MW	pressure too high in MW		
6	Me	10	MeOH	0.5	120	almost no conversion		
7	Me	2	MeOH	2	120	almost no conversion		
8	Me	2	MeOH	24	120	decomposition		
9	Me	Amberlyst 15®	MeOH	3	120	no conversion		
10	Et	10	EtOH	1.5	120	33	16	7
11	Et	10	EtOH	3.5	120	37	26	7
12	Et	10	EtOH	10	150	—	31	25

Reactions were performed on a 0.2 – 0.5 mmol scale.

Due to potential solubility issues, a nucleophilic solvent was used to facilitate the conversion of **25a**. The right combination of temperature, acid, equivalents, and reaction time could not be found for MeOH as a nucleophilic solvent (Table 28, Entry 4 – 9). However, EtOH was successful but required high temperatures from 120 to 150 °C and extended reaction times of up to 10 h due to its low nucleophilicity (Table 28, Entry 10 – 12). Transesterification product **25b** was the main product, with side products **158a** and **159a** observed due to decreased temperatures and short reaction times. 150 °C and 10 h of reaction time led to **158a** (31%) and **159a** (25%) as the main products, confirming the mechanistic proposal (Table 28, Entry 12). Water as the nucleophile likely arises from both the solvent and conc. H₂SO₄. Remarkably, H₂O is present in much smaller quantities than EtOH, but the slightly better nucleophilicity seems to have a big impact.

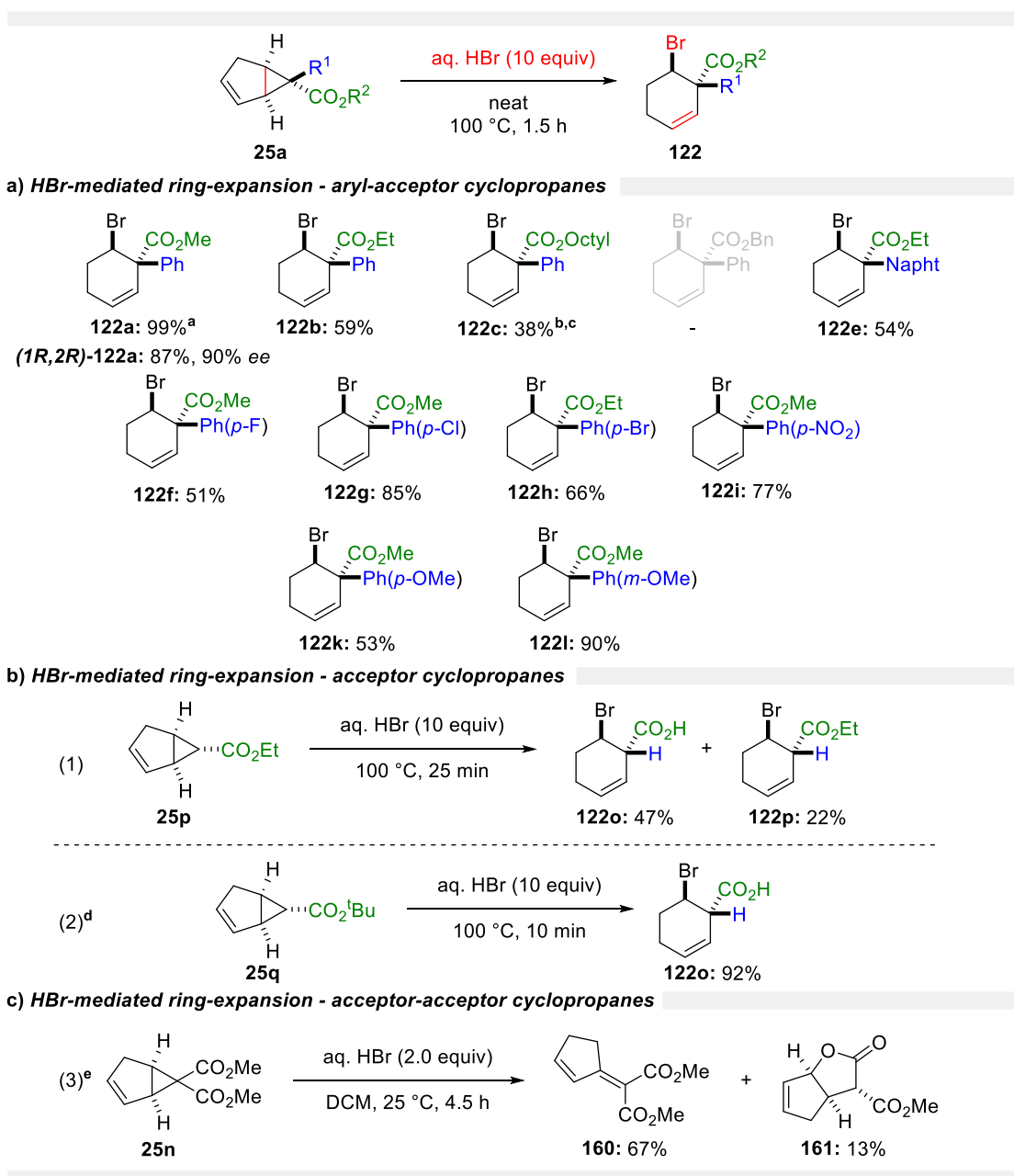
Also, *p*-toluenesulfonic acid (*pK*_a = -2.8) was investigated in a short study. In that case, a *pK*_a of -2.8 is insufficient for protonation of the double bond, even under temperatures of up to 120 °C. Only transesterification was observed quantitatively (Table 29).

Table 29. Screening of *p*-TsOH.⁶⁶

Entry	Solvent	<i>p</i> -TsOH [equiv]	Time [h]	T [°C]	Result
1	H ₂ O	10	0.5 - 3	100	no conversion
2	EtOH	7	15	120	91% of 25b
3	EtOH	10	1	120	99% of 25b

Reactions were performed on a 0.3 mmol scale. Solvent: 0.5 mL.

In the next step, the scope of the HBr-mediated reaction was expanded towards different functionalized vinyl cyclopropanes **25a-25q**, and their behavior and limitations in this transformation were studied (Scheme 59):

Scheme 59. Scope of the HBr-mediated ring-expansion of different VCPs.⁶⁶

Reactions were performed on a 0.2 – 0.3 mmol scale. [a] Gram-scale synthesis: **25a** (7.75 mmol) to **122a** (2.26 g) [b] Yield was determined by NMR using fumaronitrile as the internal standard. [c] MeCN was used as a solvent. [d] 1.2 mmol of **25q** was used. [e] 0.53 mmol of **25n** was used.

In agreement with the nucleophilic attack of the bromide in the neopentyl position, steric factors of the aryl-moiety play a role (**25d** > **25a** > **25q**). A naphthyl substituent hinders the addition of bromide and decreases the yield (**122e**, 54%). If the aryl substituent is missing (**25p**, **25q**), the less steric hindrance leads to fast reaction times and high yields alongside hydrolysis to form carboxylic acid **122o** (92%) from **25q**. It is assumed that the *tert*-butyl ester of **25q** undergoes initial and rapid hydrolysis under acidic conditions, which reduces the steric hindrance. On the other hand, the hydrolysis of the ethyl ester

from **25p** is slow, resulting in the formation of both carboxylic acid **122o** (47%) and cyclohexene **122p** (22%) (Scheme 59).

An increased steric barrier of the ester group (**25d** > **25c** > **25b** > **25a**) results in a noticeable drop in yield up to the termination of the reaction. Probably, bulkier esters prevent the formation of the addition product from type **123b** or at least slow down the addition. This indicates that the addition reaction must occur before desired S_N2'. EWGs, as well as EDGs, were tolerated without recognizing a particular trend. Notably, the enantioselectivity from (*SRS*)-**25a** (90% *ee*) was maintained ((*1R,2R*)-**122a**), 87%, 90% *ee*), demonstrating that this reaction is suitable for asymmetric synthesis. Acceptor-acceptor cyclopropane **25n** competes with the protonation of an ester group, which results in exocyclic ring-opening and a conjugated diester **160** (67%), followed by lactonization in **161** (13%) (Scheme 59).

In the next step, the ester group of **25a** was reduced by LiAlH₄ (1.5 equiv) to obtain the alcohol **25t**. This was done to investigate the reaction's tolerance towards functional groups other than esters (Table 30).

The change from external acceptor- to donor group results in a higher reactivity. Endocyclic ring-opening works, but only low yields were obtained at 100 °C (**122t**, 12%) since the external –OH group is probably protonated. Consequently, the molecule breaks down to decomposition under these harsh acidic conditions (Table 30, Entry 1). Lower temperatures and DCM as a solvent to overcome solubility issues resulted in 23% **122t**. The decomposition proves the high reactivity of the compound (Table 30, Entry 3).

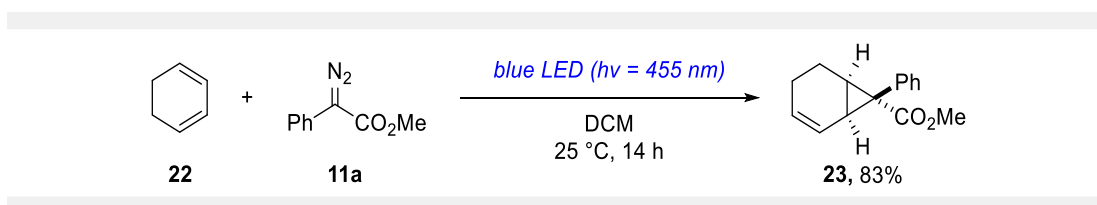
Table 30. Synthesis of **25t** and its behavior under excess of aq. HBr.⁶⁶

Entry	HBr [equiv]	Solvent	Time	T [°C]	122t [%]
1	15	neat (H ₂ O)	45 min	100	12
2	15	neat (H ₂ O)	1 h	25	no conversion
3 ^{a)}	15	DCM	4 h	25	23

Reactions were performed on a 0.2 mmol scale. [a] Yield was determined by ¹H-NMR with fumaric acid dinitrile as the internal standard.

The driving force of the endocyclic ring-expansion of **25** is, on the one hand, the release of ring strain of the bicycle and, on the other hand, the formation of the extremely stabilized cyclohexane core. It was questioned whether larger ring systems would be able to undergo the desired ring-expansion reaction. Cyclopropanated cyclohexadiene **23**, for example, would form the seven-membered ring system **162**, which is challenging to synthesize otherwise.

For that purpose, the cyclopropanated carbocycle **23** was synthesized *via* a slightly modified literature procedure (Scheme 60)⁵⁴, while **163** was readily available in our group from a different project.

Scheme 60. Synthesis of cyclopropane **23**.

As expected, larger ring systems did not undergo endocyclic ring-opening (Table 31). Bicyclic cyclohexadiene decomposed under the optimized conditions, while shorter reaction times gave an inseparable complex mixture (Table 31, Entry 1 – 2). Since the driving force of forming a highly stable product, as seen in cyclohexenes **122**, is absent,

these conditions are no longer suitable for larger ring systems. Consequently, cyclooctadiene is unreactive at 100 °C and does not undergo endocyclic ring-opening at elevated temperatures (Table 31, Entry 3 – 6).

Table 31. Behavior of larger ring system under excess of aq. HBr.

$n = 1,3$ $n = 1: \mathbf{23}$
 $n = 3: \mathbf{163}$

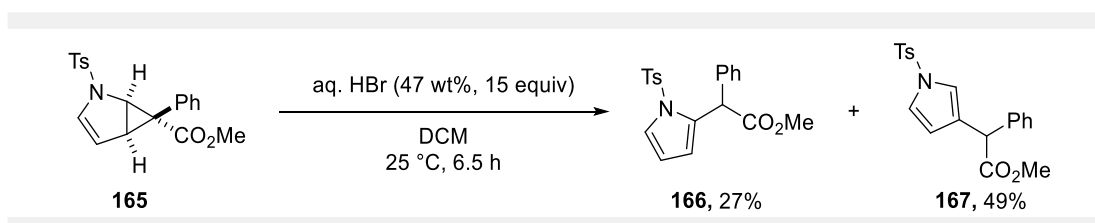
$n = 1,3$ $n = 1: \mathbf{162}$
 $n = 3: \mathbf{164}$

Entry	SM	HBr [equiv]	Solvent	Time [h]	T [°C]	Result
1	23	10	neat (H ₂ O)	1.5	100	decomposition
2	23	10	neat (H ₂ O)	10 min	100	<i>c.r.m.</i>
3	163	15	neat (H ₂ O)	1	100	no conversion
5	163	15	MeCN	2	120	no conversion
6	163	15	neat (H ₂ O)	1	150	<i>c.r.m.</i>

Reactions were performed on a 0.2 mmol scale.

Heterocyclic VCP analogue pyrrole **165** was tested for completing the study. In accordance with the previous results exocyclic ring-opening occurred, followed by re-aromatization to **166** (27%) and **167** (49%) (Scheme 61).

Scheme 61. Exocyclic ring-opening of pyrrole **165**.



Summarized, a high-yielding, metal-free and stereoselective method for endocyclic C–C bond cleavage with a good scope of bicyclic vinyl cyclopropanes was demonstrated. Various strong acids to form highly functionalized cyclohexenes from type **122**. Limitations were observed with weak nucleophiles and weak acids or too reactive

compounds that undergo side reactions or decomposition under the harsh acidic conditions. Additionally, heterocycles were not allowed due to their exocyclic ring-opening driving force under acidic conditions.

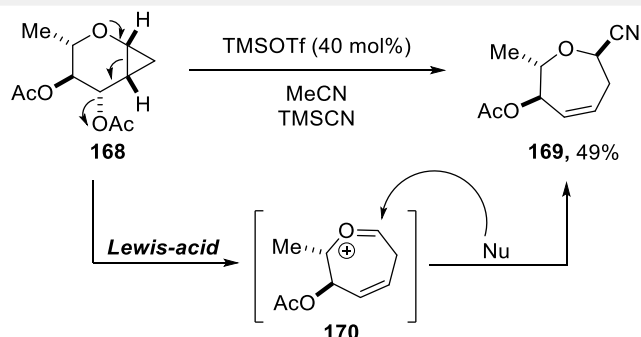
However, a few examples can be found in the literature of heterocyclic and carbocyclic cyclopropanes exhibiting endocyclic ring-opening under the same activation methods.

2.2.7 Lewis Acid Mediated Endocyclic Ring-Opening

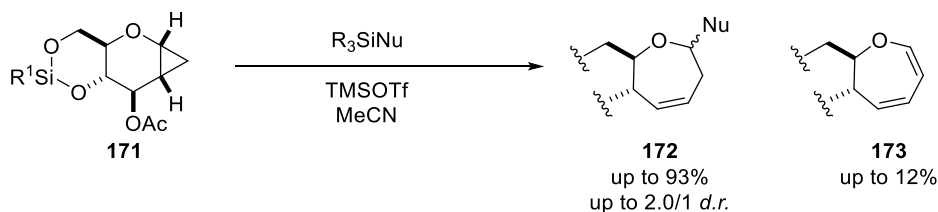
In the mid-90s, *Hoberg et al.* demonstrated a ring-expansion mediated by a Lewis acid (TMSOTf). In this case, the Lewis acid activates the –OAc group next to the cyclopropane ring of **168**. The positive polarization and the donor effect of the oxygen result in the endocyclic ring-opening. A nucleophile then traps the intermediate cation **170** to form the desired expanded compound **169** (Scheme 62).¹²⁷ Introducing a protecting group increased the yields to 93% of **172**. However, the diastereoselectivity decreased, and formation of the side product **173** was observed (Scheme 62).^{107,128}

Scheme 62. Lewis acid mediated ring-expansion of cyclopropanated carbohydrates.

Hoberg et al. - 1995



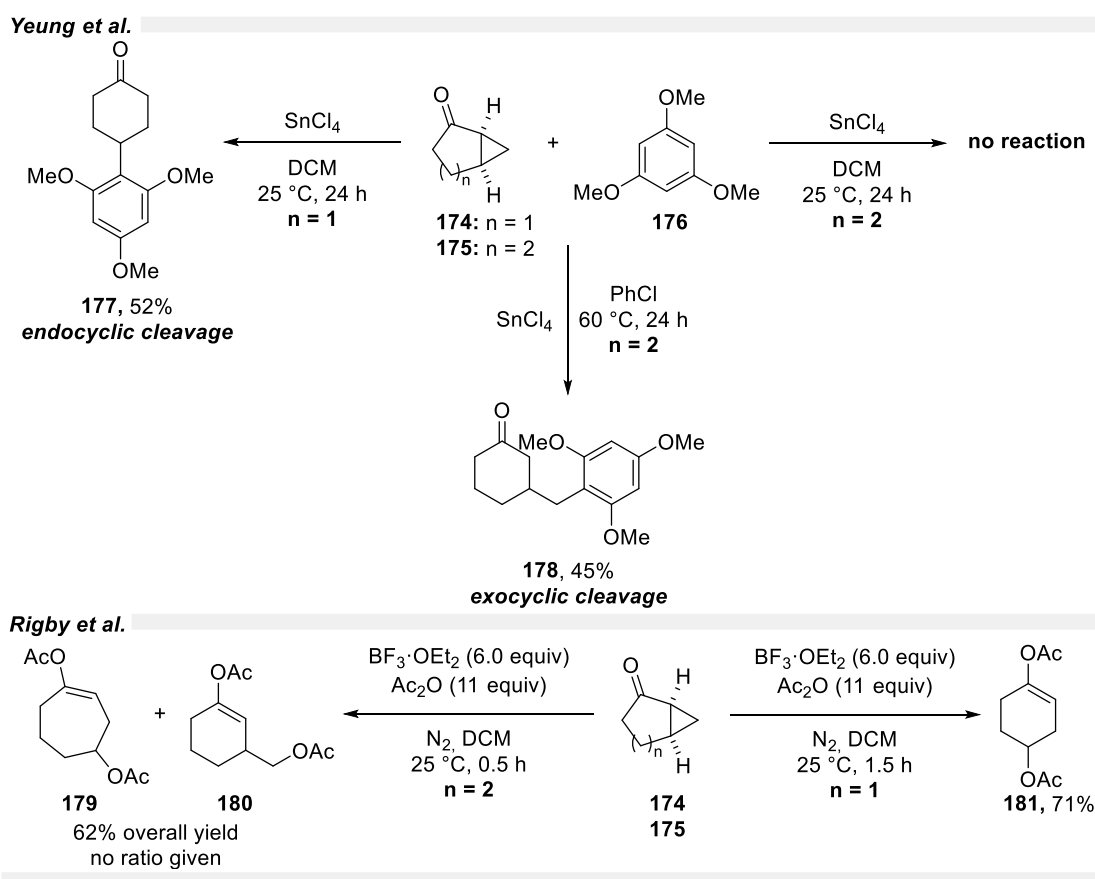
Hoberg et al. - 1997



Sridhar et al. came up with a similar method, but instead of using a leaving group for Lewis acid activation, a carbonyl group next to the cyclopropane ring was introduced. TMSOTf produces a positive charge and thus an acceptor effect (“pull-effect”), achieving endocyclic ring-expansion of carbohydrates.¹⁰³

In 2013 *Yeung et al.* expanded the Lewis acid activated ring-expansion reaction to carbocyclic cyclopropanes **174/175**.⁹⁹ Noteworthy, the desired reaction only works with cyclopropanated cyclopentanone **174**. The exocyclic bond is cleaved in larger ring systems, such as the bicyclic cyclohexanone **175**. Consequently, this led to the conclusion that the increased ring strain of **174** favors an endocyclic ring-opening. Additionally, a significant difference in the ring-expansion of the heterocyclic analogues is the lack of donor (“*push-effect*”) of the heteroatom. Therefore, it is postulated that a nucleophile is required to donate electrons into the molecule and thus is part of the ring-expansion process (Scheme 63).⁹⁹

Scheme 63. Lewis acid activated ring-opening of carbocyclic cyclopropanes.

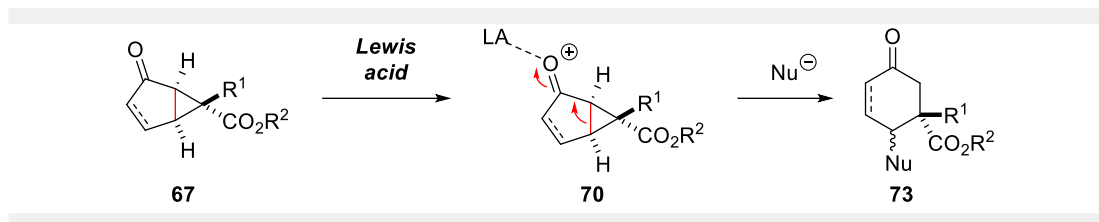


Similar results were obtained by *Rigby et al.*¹¹¹ using a different Lewis acid ($\text{BF}_3 \cdot \text{OEt}_2$), and nucleophile (Scheme 63) and further examples also show the capability of $\text{Sn}(\text{OTf})_2$ ¹²⁹ and TMSOTf ¹⁰⁴ to initiate endocyclic ring-opening.

Our strategy focused on Lewis acid-activation of an introduced carbonyl group next to the cyclopropane generating a positive charge. With a nucleophile that donates electrons

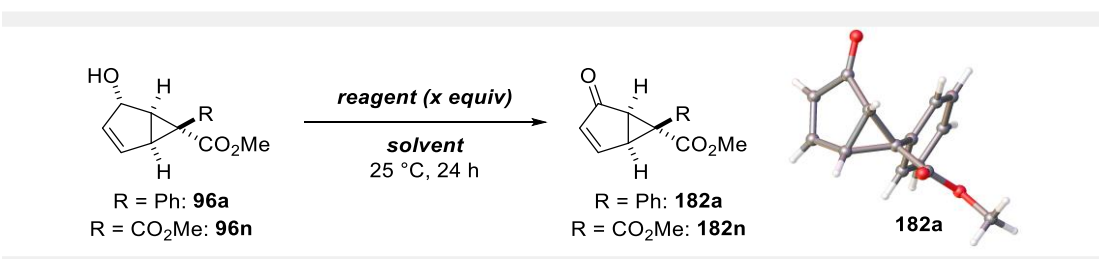
into the molecule, endocyclic ring-opening should be accessible from compound **67**, resulting in highly functionalized cyclohexanones **73** (Scheme 64).

Scheme 64. Strategy for Lewis acid mediated ring-opening.



Taking advantage of the allylic alcohol **96a/n**, α,β -unsaturated ketone **182a/n** was synthesized in high yields *via* allylic oxidation using MnO_2 , while other oxidation reagents were unsuccessful (Table 32).

Table 32. Allylic oxidation of alcohol **96**.



Entry	-R	n of 96 [mmol]	Solvent	Reagents (equiv)	182a [%]
1	Ph	0.5	MeCN	^t BuOOH (5.0), CuBr (0.05)	no conversion
2 ^{a)}	Ph	0.5	DCM	oxalyl chloride (2.0), NEt ₃ (3.0), DMSO (3.0)	8% of 182a
3	Ph	1.6	DCM	MnO ₂ (15)	83
4	Ph	5.1	DCM	MnO ₂ (15)	83
5	Ph	5.4	DCM	MnO ₂ (10)	81
6	Ph	4.9	DCM	MnO ₂ (2.5)	27
7 ^{b)}	CO ₂ Me	3.2	DCM	MnO ₂ (10)	54, 182n

[a] Reaction was stirred at -65 °C for 2 h. [b] Yield was calculated over 2 steps starting from compound **25n**.

Secondly, the reduced form **183a/n** was obtained *via* hydrogenation using Pd/C (Table 33).

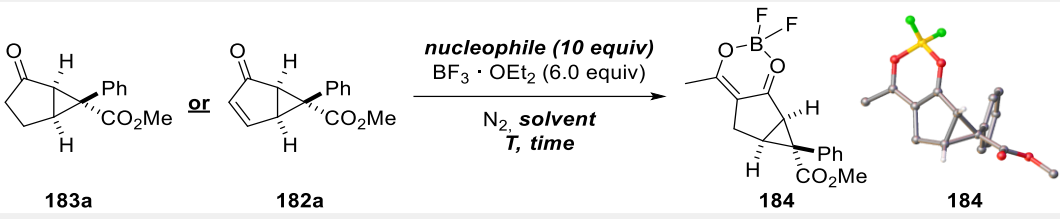
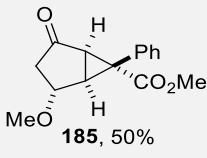
Table 33. Hydrogenation of α,β -unsaturated ketone **182a/n**.

Entry	-R	n of SM [mmol]	H ₂ [bar]	Time [h]	Yield [%]
1	Ph	1.4	40	4	183a , 99
2	CO ₂ Me	0.7	60	2	183n , 92

With these compounds in hand, the relatively easily applicable conditions from *Rigby et al.*¹¹¹ using BF₃·OEt₂ as the Lewis acid and Ac₂O as the nucleophile were utilized (Table 34).

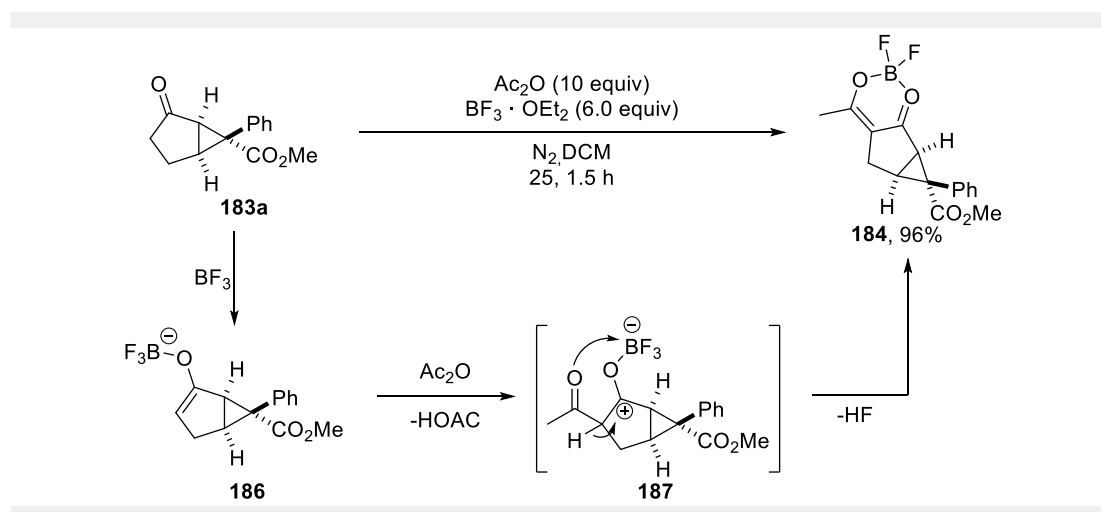
Surprisingly, compound **183a** was converted to the 1,3-diketoneboron difluoride compound **184** in high yield, even under reflux conditions (Table 34, Entry 1 – 2). Due to the steric hindrance of phenyl and ester group from **183a**, the nucleophile (AcO⁻) cannot assist in the ring-opening. Instead, **183a** undergoes electrophilic acylation *via* enol **186** to form a 1,3-diketone **187**, followed by protection of BF₃ (**184**, Scheme 65) which is in agreement with the literature.¹³⁰ This structure motive has synthetic value in organic chemistry to synthesize enamines and substituted pyrazoles from diketones.¹³¹

Table 34. BF₃·OEt₂-mediated reaction of **182a** and **183a**.

						
Entry	SM	Nu	Solvent	T [°C]	Time [h]	Result
1	183a	Ac ₂ O	DCM	25	1.5	96% of 184
2	183a	Ac ₂ O	DCM	reflux	1.5	90% of 184
3	183a	Ac ₂ O	DCM	-78	6	traces of 184
4	183a	Ac ₂ O	THF	reflux	1.5	decomposition
5	183a	MeOH	MeOH	25	1.5	no conversion
6	182a	Ac ₂ O	DCM	25	4	no conversion
7	182a	MeOH	MeOH	25	1.5	 185 , 50%
8	183n	Ac ₂ O	DCM	25	1.5	<i>c.r.m.</i>

Reactions were performed on a 0.3 mmol scale.

With **182a** as the starting material, no conversion using Ac₂O was observed, but 1,4-*Michael*-addition occurred with MeOH as the nucleophile giving rise to **185** (50%, Table 34, Entry 7). The steric hindrance of the cyclopropane and the nucleophile (AcO⁻), the weak nucleophilicity (MeOH), and the possibility of side reactions (acylation, 1,4-*Michael*-addition) make the ketone **182n** unsuitable for endocyclic C–C bond cleavage with BF₃·OEt₂. The acceptor-acceptor ketone **183n** gave an unidentified reaction mixture (Table 34, Entry 8).

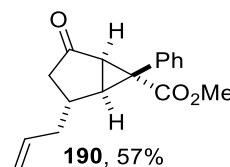
Scheme 65. Formation of BF₂-protected diketone **184**.

BF₃·OEt₂ was replaced with TMSOTf as the Lewis acid and strong nucleophiles were utilized in a further step: Starting off with the α,β -unsaturated ketone **182a**, and hydride (Et₃SiH = H⁻) as a small and effective nucleophile, the endocyclic C–C bond cleavage was not successful. **182a** rather undergoes reduction of the double bond forming **183a**, followed by 1,4-*Michael*-addition with unreacted α,β -unsaturated ketone as electrophile **183a**, leading to dimer **189** in high yields (Table 35, Entry 1). Consequently, allyltrimethylsilane as the nucleophile created the 1,4-*Michael*-addition product **190** (Table 35, Entry 2).

Table 35. TMSOTf-mediated reaction of α,β -unsaturated ketone **182a**.

Entry	Nu	Time [h]	Result
1	H ⁻ (Et ₃ SiH)	2	

2 allyltrimethylsilane 5



Reactions were performed on a 0.3 – 0.5 mmol scale.

It was assumed that endocyclic ring-opening could also occur with functionalized ketones **185** and **190**. Unfortunately, the concave face, as well as the convex face, of the bicycle are too sterically hindered to allow the attack of a nucleophile. Therefore, the reduced ketone **183a** was a promising starting material since side reactions such as 1,4-*Michael*-addition or hydrogenation are impossible. Furthermore, the steric hindrance should be moderate. However, when **183a** was utilized, the results were quite challenging to analyze (Table 36).

Table 36. TMSOTf-mediated reaction of ketone **183a**.

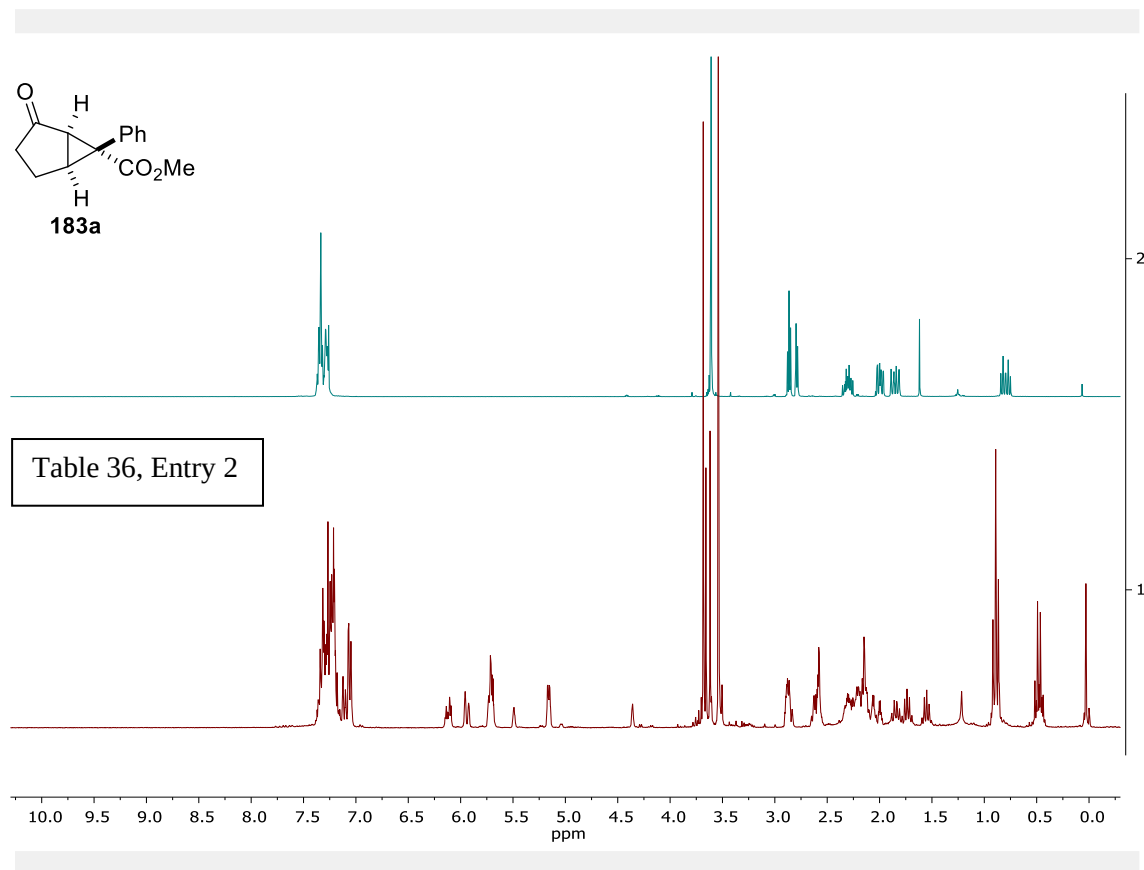
Entry	Nu	T [°C]	Time [h]	Result
1	H ⁺ (Et ₃ SiH)	-78 to 25	14	unidentified cyclohexene product, side reactions
2	H ⁺ (Et ₃ SiH)	25	2	unidentified cyclohexene product, side reactions
3	H ⁺ (Et ₃ SiH)	-78	2	unidentified cyclohexene product, side reactions
4	allyltrimethylsilane	-78 to 25	5	no conversion
5 ^{a)}	H ⁺ (Et ₃ SiH)	100	0.5	<i>c.r.m.</i>

[a] MeCN was used as a solvent. Reactions were performed on a 0.2 – 0.5 mmol scale.

Product separation from the crude mixture was unsuccessful. However, crude ¹H-NMR (Figure 8) showed a signal pattern of a cyclohexene compound that is lost after

purification by column-chromatography, hinting that slightly acidic conditions lead to the decomposition of the unidentified products (Table 36, Entry 1 – 3). Neither basic nor acidic workups were successful. Furthermore, at least four signals for a $-\text{CO}_2\text{Me}$ group show that more products are formed but could not be identified (Figure 8). Reduction and oxidation reactions did not convert the unidentified molecules into unreactive and separable compounds. Importantly, allyltrimethylsilane as the nucleophile does not lead to any conversion of the ketone **183a** (Table 36, Entry 4). This proves that the nucleophilicity of the hydride (Et_3SiH) initiates the reaction, probably by an initial reduction of the carbonyl group.

Figure 8. ^1H -NMR of ketone **183** and crude ^1H -NMR of reaction with TMSOTf and Et_3SiH .

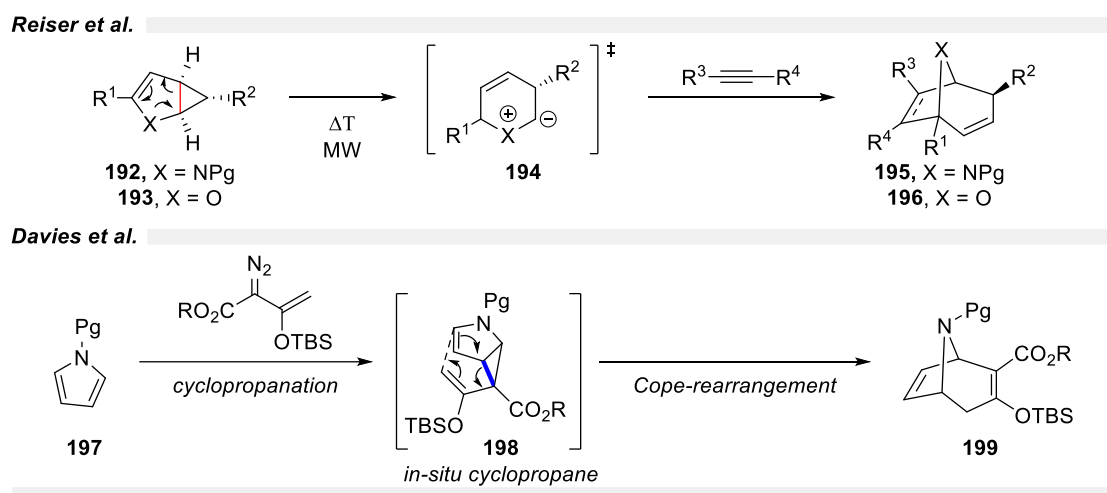


In conclusion, finding suitable conditions for the Lewis acid-mediated ring-expansion of ketones **182a** and **183a** was impossible. While α,β -unsaturated ketone **183a** rather undergoes 1,4-*Michael*-addition, ketone **182a** gave rise to unusual BF_3 -protected acylation product **184**, that could have synthetic value in organic chemistry. A promising reaction with TMSOTf and ketone **182a** showed signals of a ring-expansion product, but instability, side reactions, and purification issues made the identification impossible.

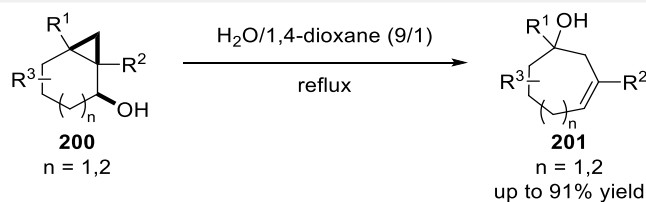
2.2.8 Endocyclic Ring-Expansion via Rearrangement Reactions

Besides the intermolecular activation methods, a few examples in the literature show an endocyclic ring-opening *via* an intramolecular rearrangement reaction. Based on the former work of *Herges and Ugi et al.*¹³², *Klärner et al.*¹³³ and *Yu et al.*,¹³⁴ our group developed a 6π -retro-electrocyclic ring-opening of monocyclopropanated furans and pyrroles **192/193** activated under microwave irradiation (Scheme 66).⁴⁵ After endocyclic C–C bond cleavage, the transition state **194** is trapped by a dipolarophile to synthesize tropanes **195/196** with good yields and *ee* *via* [3+2]-cycloaddition. Again, the main driving force is the “*push-effect*” of the heteroatom within the ring system and thermal activation (Scheme 66). In contrast, *Davies et al.* took advantage of a Cope-rearrangement to synthesize similar tropanes **199** starting from pyrrole **197**. However, the *in situ* formed cyclopropane intermediate **198** undergoes an exocyclic C–C bond cleavage to form the product (Scheme 66).^{135,136}

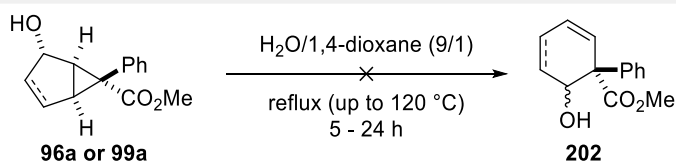
Scheme 66. Tropane synthesis *via* rearrangement of bicyclic frameworks.



A study from *Qu et al.* shows the endocyclic ring-expansion of bicyclic cyclopropyl carbinols **200** in a refluxing mixture of water and 1,4-dioxane (9/1). The –OH group is cleaved under thermal activation to produce a positive charge next to the cyclopropane, which triggers the endocyclic ring-opening. No addition of an external catalyst is necessary, and water is used as a catalyst and as a reaction medium simultaneously (Scheme 67).^{102,124,137,138}

Scheme 67. Hot-water promoted endocyclic C–C bond cleavage.*Qu et al.*

When applied to these conditions, neither the allylic alcohol **96a** nor the reduced compound **99a** gave any reaction. It was concluded that the additional steric hindrance from $-\text{Ph}$ and $-\text{CO}_2\text{Me}$ prevents the nucleophilic attack of H_2O , which is essential for the ring-opening process. Together with the weak nucleophilicity of water, endocyclic ring-expansion is not accessible, even under high thermal activation. This underlines that the assistance of the nucleophile *via* $\text{S}_{\text{N}}2'$ is crucial for endocyclic C–C bond cleavage (Scheme 68). Further attempts should concentrate on small and extremely strong nucleophiles.

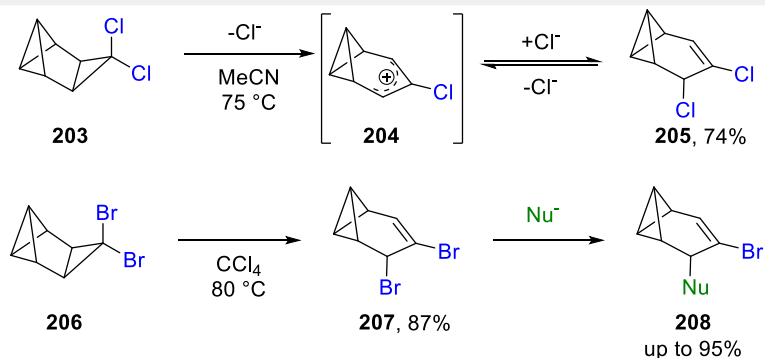
Scheme 68. Failed conversion of **96a** and **99a** in hot-water.

A different rearrangement approach was demonstrated by *Christl et al.*, who utilized *geminal* substituted dihalogen-cyclopropanes **203/206**. Upon thermal activation, the exo-halogen group is cleaved off and the endocyclic C–C bond rearranges to the carbocation **204**. Nucleophilic addition by the halogen-anion affords **205**. A nucleophile can chemoselectively substitute these compounds to produce **208** (Scheme 69).^{139,140} *Wessjohann et al.* and *Bentley et al.* further improved this study with a one-pot synthesis of compounds **212/213** from **209/210** (Scheme 69).^{108,109} In 2006, *Banwell et al.* used AgBF_4 as a catalyst in this reaction to cleave the halogen from **209** at lower temperatures (18 °C), followed by nucleophilic trapping with **214**, which gave the compounds **215a/b** in moderate yields (Scheme 69).¹⁰⁵ All these reactions are based on forming a positive charge next to the cyclopropane moiety. However, these reactions demonstrated that

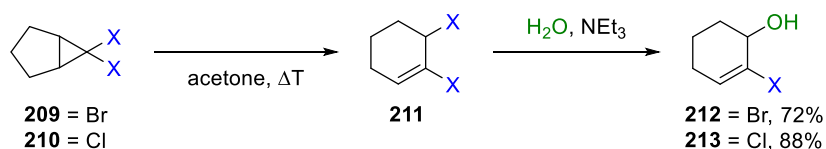
inactivated carbocyclic cyclopropanes are possible for the endocyclic C–C bond cleavage.

Scheme 69. Rearrangement of different *gem*-dihalogen cyclopropanes.

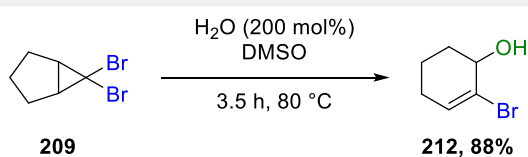
Christl et al.



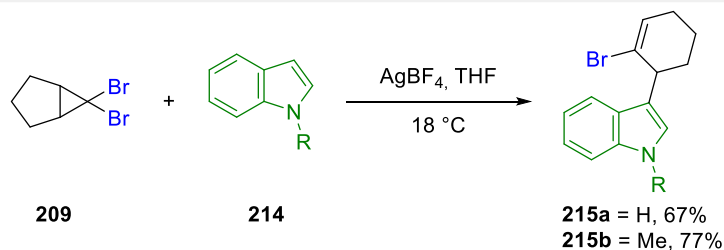
Bentley et al.



Wessjohann et al.

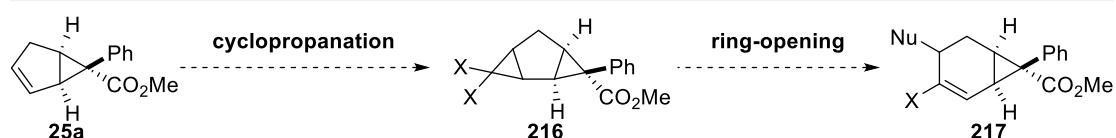


Banwell et al.



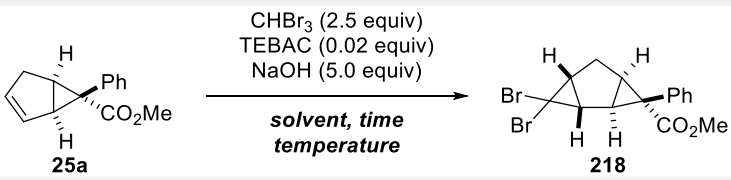
It was questioned about whether it is possible to perform a second cyclopropanation on the vinyl cyclopropane **25a** to create a tricycle from type **216**. An endocyclic ring-opening on **216** would provide conclusions about the influence of –Ph and –CO₂Me on the stability of the cyclopropane ring (Scheme 70).

Scheme 70. Strategy for endocyclic ring-opening of dihalogen-cyclopropanes **216**.



For that purpose, the dihalogen-cyclopropane compound **218** was synthesized after a slightly modified literature procedure (Table 37).¹⁰⁵

Table 37. Synthesis of dicyclopropane compound **218**.

						
Entry	n of SM [mmol]	Solvent	Time [h]	T [°C]	Activation	Yield 218 [%]
1	0.9	DCM	11	60	sonication	72
2	0.7	DCM	1.5	60	MW	62
3	7.0	DCM	—	60	MW	upscaling not possible
4	0.7	DCE	12	100	pressure tube	95
5	1.6	DCE	12	100	pressure tube	82

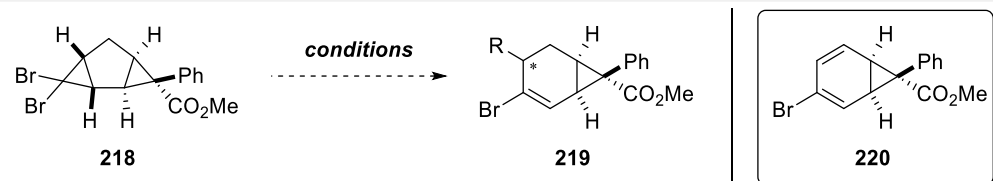
Reactions were performed with V(solvent) = 1 mL = 0.5 mmol of SM.

While sonication was used as the method of choice in the literature, standard heating in an oil bath and a pressure tube with a higher boiling solvent (DCE instead of DCM) gave rise to the desired compound **218** with 95% yield (Table 37, Entry 4).

A study was carried out utilizing the previously shown conditions from Scheme 69. Starting off with the conditions from *Bentley et al.*,¹⁰⁹ no reaction was observed under a basic environment and heating, which made clear that the tricyclic compound **218** is much more stable than the bicyclic **209** (Table 38, Entry 1). Since acetone with a low boiling point (56 °C) could only be heated further to a limited extent, conditions from *Wessjohann et al.*¹⁰⁸ were applied. Using DMSO as a high boiling solvent with temperatures gave rise to the cyclohexadiene compound **220** (35%, 44% *brsm*). In contrast to the literature, the nucleophilic substitution with H₂O is not observed. Instead, elimination occurs at high temperatures (Table 38, Entry 2). Through multiple attempts of heating with sea sand, observation suggested that the heat did not fully reach the Schleck tube. Consequently,

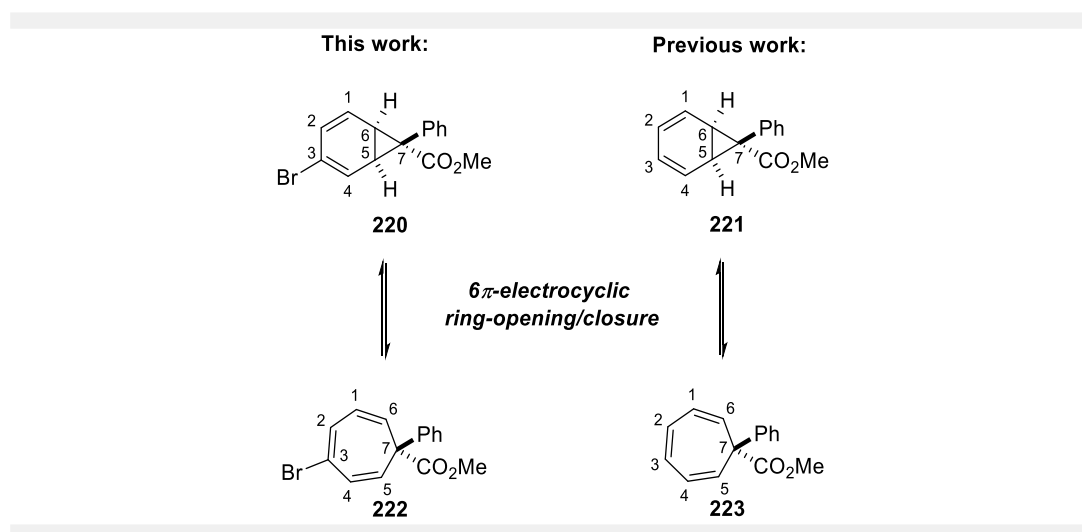
heating was switched to an oil-bath. Indeed, the conversion of starting material **218** was completed but also led to the decomposition of product **220**, which was only obtained in 20% yield (Table 38, Entry 3). Decreased temperatures and shorter reaction times afforded 50% of compound **220** (Table 38, Entry 4). Trying to lower the temperature and additional MW-activation was not successful (Table 38, Entry 5). Reaction conditions from *Banwell et al.* using a silver catalyst to lower the activation barrier were not suitable for **218** as the starting material, showing once more the increased stability of the molecule influenced by $-\text{Ph}$ and $-\text{CO}_2\text{Me}$ (Table 38, Entry 6).

Table 38. Endocyclic ring-opening of dihalogen-cyclopropane **218**.

							
Entry	Nu [equiv]	-R	Additive	Solvent	Time [h]	T [°C]	Results
1	H ₂ O	OH	NEt ₃	acetone	24	80 – 130	no conversion
2 ^{a)}	H ₂ O	OH	—	DMSO	12	200	35% of 220 , 44% <i>brsm</i>
3	H ₂ O	OH	—	DMSO	12	200	20% of 220
4	H ₂ O	OH	—	DMSO	2.5	150	50% of 220
5	H ₂ O	OH	—	DMSO	1	110, MW	<i>c.r.m.</i> , traces of 220
6	MeOH	OMe	AgNO ₃	THF	18	25 – 100	no conversion

[a] Reaction-flask was heated in sea sand. Reactions were performed on a 0.2 – 0.5 mmol scale.

Notably, the cyclohexadiene **221** rapidly undergoes endocyclic ring-expansion *via* a 6π -electrocyclic rearrangement reaction, forming a 1:1 equilibrium between **221** and **223** (Scheme 71) even until temperatures of $-60\text{ }^{\circ}\text{C}$.^{141,142} This rapid equilibration is proved by the position of the ppm-signals of the 5,6-protons in the ^1H -NMR at 4.31, an intermediate position of those expected for the 5,6-hydrogens of **221** and **223**.

Scheme 71. Equilibration of cyclohexadiene **221** and cycloheptatriene **223**.

A publication from *Koenigs et al.* demonstrated a visible-light-mediated synthesis of compound **221**.⁶⁰ However, they claim to not see the formation of the equilibrium but show identical spectroscopic data with no explanation given. Since the signals of the 5,6-protons of **220** are shifted more downfield than expected, the existence of the equilibrium, as shown in Scheme 71, is postulated. No studies have been conducted so far to provide evidence.

In conclusion, cyclopropylmethanol **96a/99a** rearrangement does not occur under thermal activation due to the steric hindrance of $-\text{Ph}$ and $-\text{CO}_2\text{Me}$ that prevent $\text{S}_{\text{N}}2'$ reaction of water as a weak nucleophile. Further rearrangement attempts of dihalogen-compound **218** gave rise to cyclopropanated cyclohexadiene **220**. An equilibrium between **220** and **222** by endocyclic ring-opening via electrocyclic 6π -rearrangement is established with high probability.

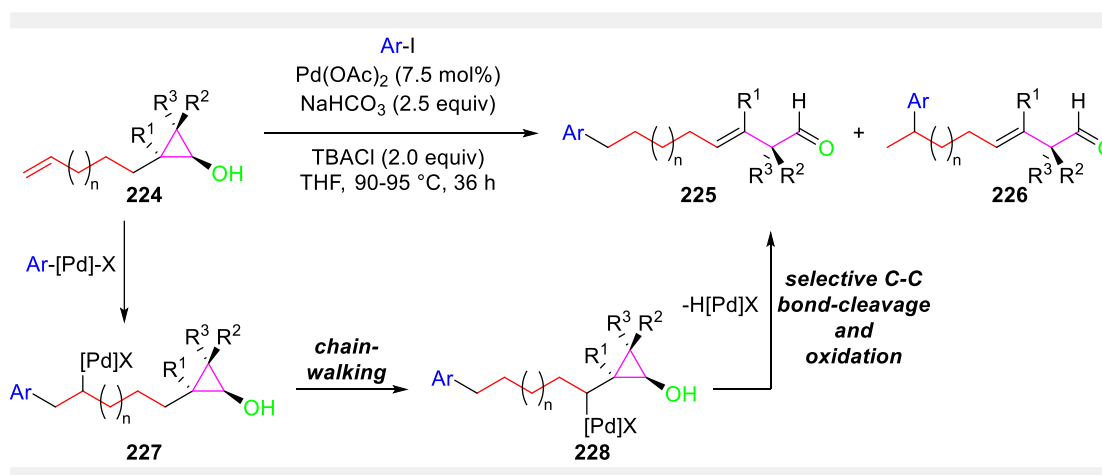
2.3. Endocyclic Ring-Opening via Negative Polarization

2.3.1 Introduction

In addition to previously mentioned methods that utilize Brønsted or Lewis acids to target an electron-deficient center next to the cyclopropane, other methods use transition-metal catalysis to induce ring-opening by generating an electron-rich center. Typical utilized transition-metals are nickel, iridium, rhodium, ruthenium, iron, zirconium, or palladium. Especially, *Heck*-type or *Heck-Matsuda*-type reactions using Pd catalysts are of great interest to cleave inactivated cyclopropane bonds selectively.^{143–149}

In recent years, *Marek et al.* have shown that vinyl cyclopropanes can undergo ring-opening with the introduction of palladium at the α -cyclopropyl position. This transformation involves β -carbon elimination as a key step, which leads to the formation of ring-opening products **225** and **226** after alcohol oxidation. As a result of the chain-walking of the Pd species alongside the carbon chain, the transformations are not limited to VCP but are also suitable for cyclopropanes bearing a remote double bond (Scheme 72, only formation of **225** is shown).^{146,150–152}

Scheme 72. *Heck*-type ring-opening of (vinyl) cyclopropanes **224**.



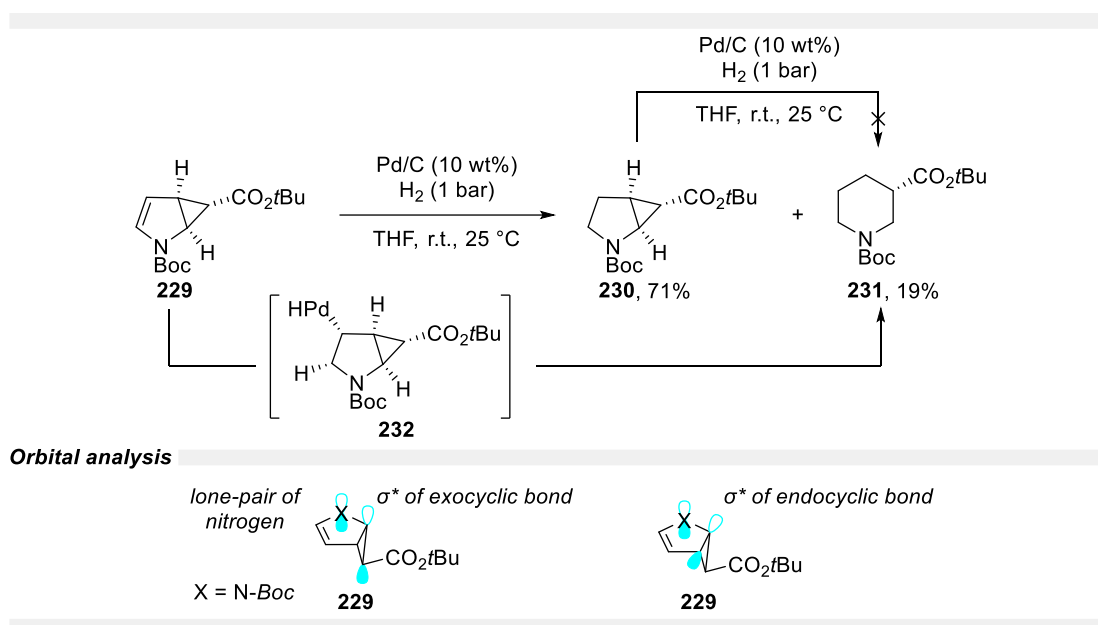
This study focused on C–C bond cleavage of endocyclic bonds in a bicyclic system and, thus, ring-expansion reactions.

2.3.2 Previous Endocyclic Ring-Opening of Bicyclic Cyclopropanes

In 2017, *Reiser* and co-workers discovered a similar reaction type. While the initial idea was to hydrogenate the double bond of cyclopropanated pyrrole **229**, unexpected six-membered piperidine compound **231** was obtained as a side product that must form *via* endocyclic ring-expansion. When pyrrolidine **230** was placed under hydrogenation conditions again, there was no conversion. This indicates that **231** is formed directly from **229**, possibly *via* reaction intermediate **232** (Figure 9)^{46,147}

This reaction is even more surprising, looking closer into an orbital analysis: Since the lone pair of the heteroatom is aligned in parallel to the σ^* -C–C orbital of the exocyclic cyclopropane bond, consequently, this bond can be activated easily for exocyclic ring-opening by Lewis- or Brønsted acids. However, endocyclic ring-opening should not be allowed directly from **229** since the σ^* -orbital of the endocyclic C–C bond lies perpendicularly to the nitrogen lone pair and thus is not activated (Figure 9), confirming the formation of the hydropalladium-species **232** as reaction intermediate.^{46,147}

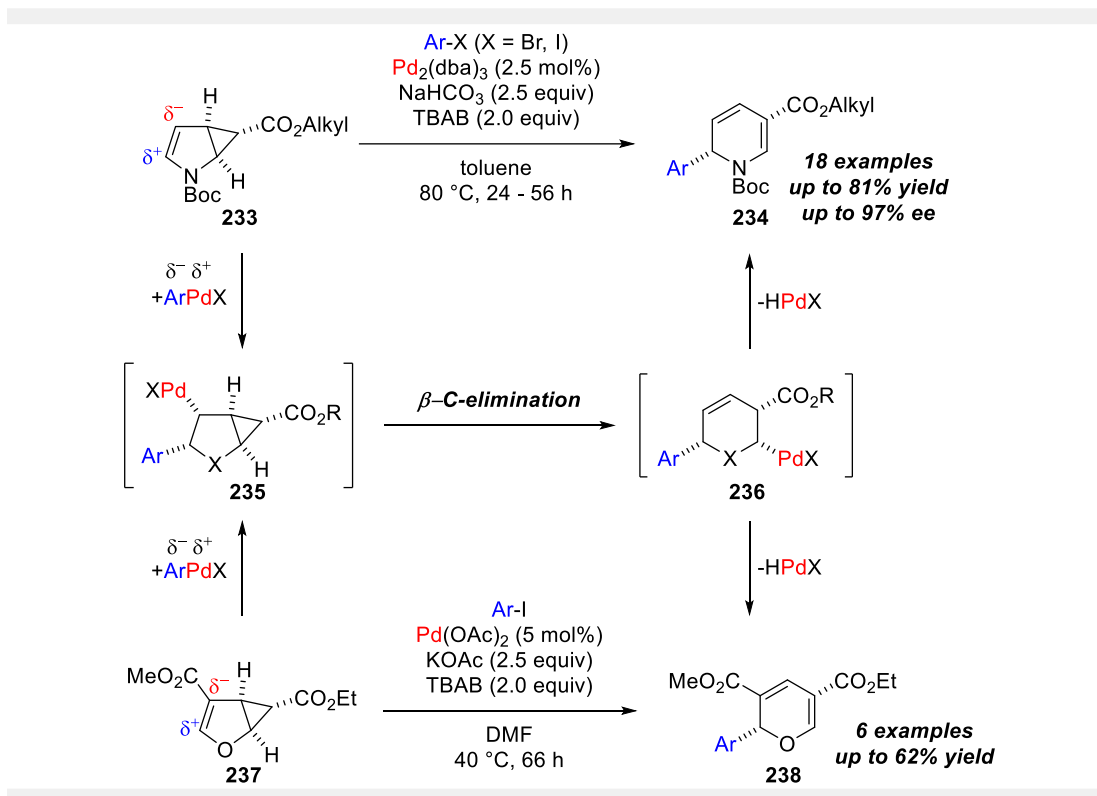
Figure 9. Unexpected ring-expansion of **229**.



This ring-expansion catalyzed by palladium in a *Heck*-type or *Heck*-Matsuda-type reaction was extensively studied by *Reiser et al.*^{46,48,147} In 2019, the authors demonstrated this reaction using cyclopropanated pyrroles **233** and furans **237** that can be coupled with a variety of aryl/heterocyclic halides, leading to the formation of dihydropyridines,

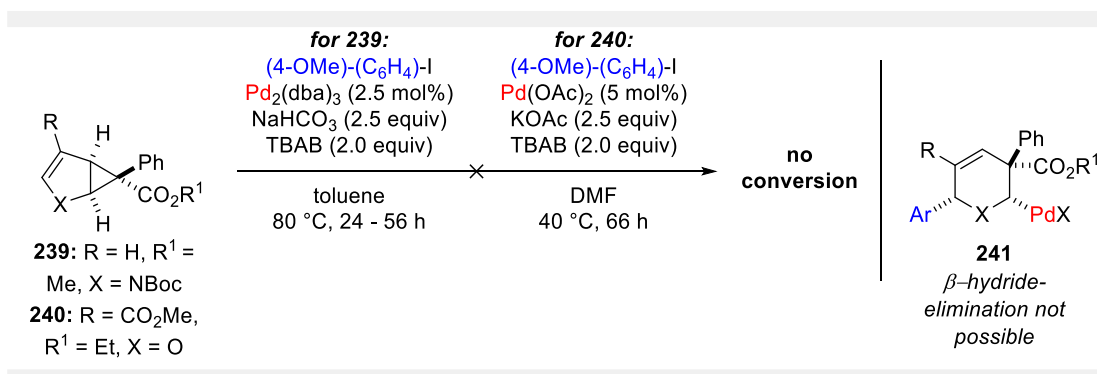
pyridines, and 2H-pyrans. The reaction was catalyzed by either $\text{Pd}_2(\text{dba})_2$ or $\text{Pd}(\text{OAc})_2$ and showed a great scope. (Scheme 73).

Scheme 73. Ring-expansion of cyclopropanated pyrroles **233** and furans **237** via Heck-type reaction.⁴⁶



The position of the heteroatom within the ring system determines the attack of the active organopalladium-species (ArPdX) from the convex face of the bicycle in a regioselective manner. This leads to the placement of palladium (PdX) in the required α -cyclopropyl position (**235**), creating a negative polarization. This allows for β -C-elimination and subsequent ring-expansion to occur (Scheme 73). After β -hydride-elimination six-membered heterocycles from type **234/238** are accessible.⁴⁶

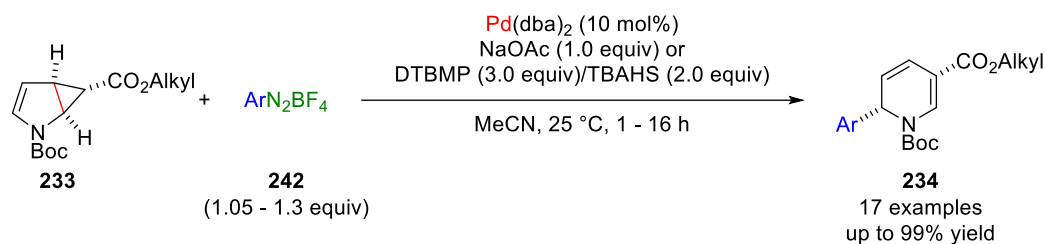
Scheme 74. Failed conversion of *gem*-cyclopropanes **239/240**.



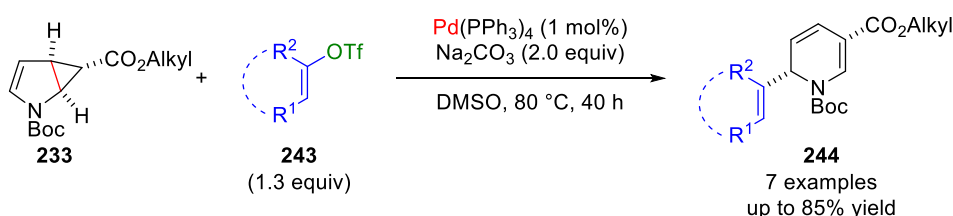
In 2019, it was observed that the use of *gem*-substituted cyclopropanes of type **239/240** was limited as the potentially formed intermediate **241** had no accessible hydrogen for *trans*- β -hydride elimination, which made catalytic cycle closure impossible. (Scheme 74).⁴⁶

Scheme 75. Developments on the Pd-catalyzed ring-opening of monocyclopropanated heterocycles.⁴⁸

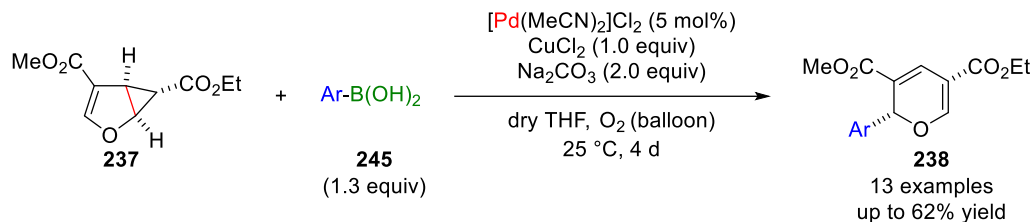
a) Coupling partner: aryl diazonium salts



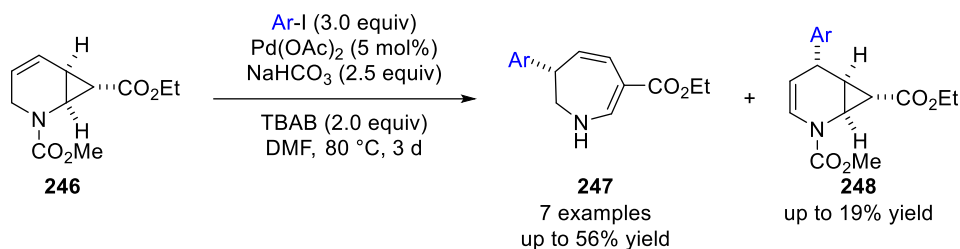
b) Coupling partner: vinyl triflates



c) Coupling partner: aryl boronic acids



d) Enhanced ring-system: azepines

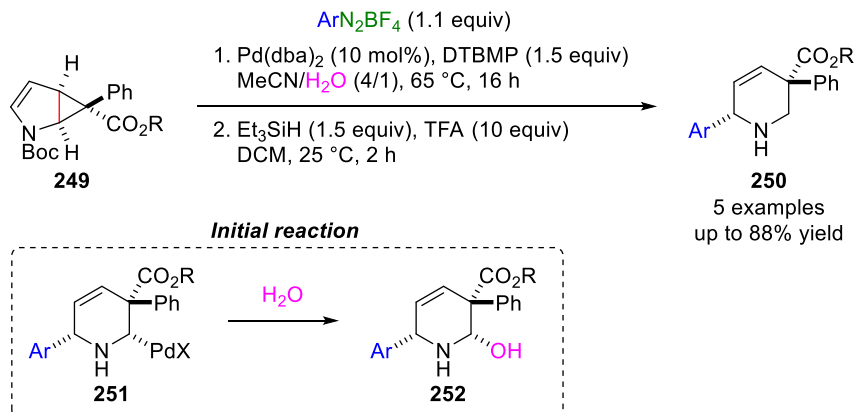


In 2021, this strategy was improved with some interesting developments: For pyrroles of type **233**, the highly reactive aryl diazonium salts provided higher yields with greater functional group tolerance compared to aryl halides (Scheme 75). Furthermore, vinyl triflates **243** were also demonstrated as suitable coupling partners for pyrroles as well as aryl boronic acids **245** for corresponding furans **237** (Scheme 75). Moreover, the larger ring system **247** was accessible from six-membered compound **246**, but noteworthy with

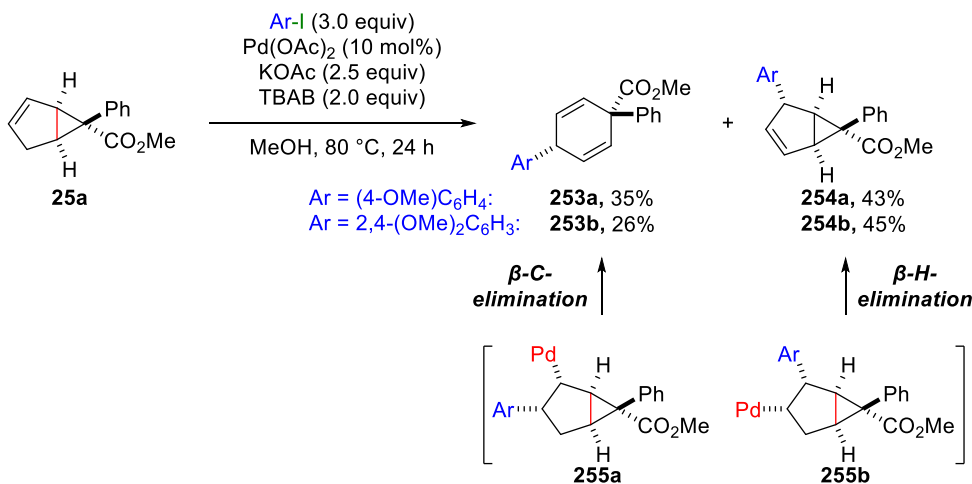
the formation of side product **248** due to a contrary regioselective attack of the palladium Scheme 75).^{48,147}

Scheme 76. Ring-expansion of gem-disubstituted cyclopropanes.⁴⁸

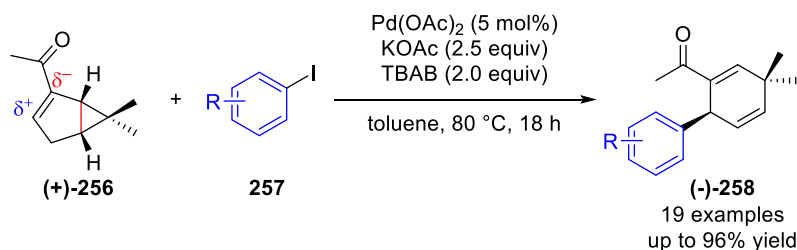
a) gem-disubstituted pyrroles



b) gem-disubstituted carbocycles



c) gem-disubstituted carbocycles



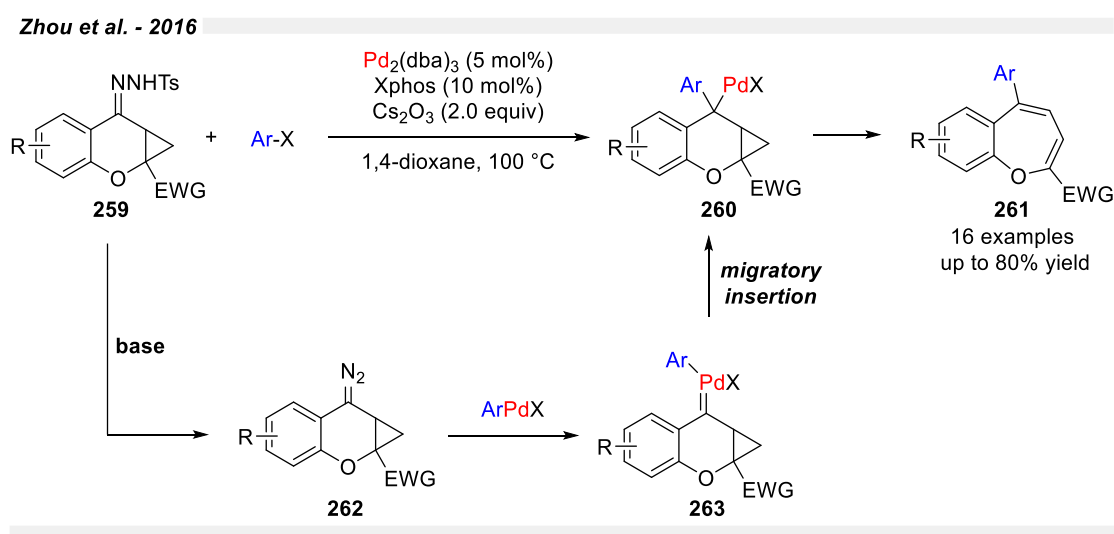
To overcome the issues of *gem*-disubstituted cyclopropanes **239/240** (see Scheme 75), two distinct strategies were employed: 1) Substitution of palladium in **251** was done by adding a nucleophile to the reaction. Initially, H_2O replaces the palladium, which was then reduced by Et_3SiH /TFA to get access to compound **250** (Scheme 76).⁴⁸ 2) The second idea concentrated on using *gem*-disubstituted carbocyclic analogues **25a** because, theoretically, this would allow β -dehydropalladation without using additional

nucleophiles. Indeed, *Reiser* and co-workers demonstrated the capability of these compounds to undergo ring-opening under *Heck*-type conditions. However, the ring-expansion to 1,4-cyclohexadienes **253a/b** was observed as the side reaction because the inverse attack of the aryl palladium species (ArPdX) occurs since the initial electronic setting of **25a** does not direct regioselective attack (Scheme 76).^{48,b}

The regioselectivity issue from **25a** could be overcome by using the cyclopropanated carbocycle **(+)-256** that leads to 1,4-cyclohexadienes **(-)-258** in excellent yields and a broad functional group tolerance (Scheme 76).^{48,147}

A different ring-expansion reaction, catalyzed by palladium, was demonstrated by *Zhou* and co-workers. Upon treatment of hydrazone **259** with a base, a diazo compound **262** is formed, *in-situ* followed by Pd-carbene (**263**) formation, which undergoes migratory insertion to afford the α -cyclopropyl palladium compound **260**. With palladium in this position, β -C-elimination occurs to yield the benzoxepines **261** after β -dehydropalladation (Scheme 77).¹⁵³

Scheme 77. Pd-catalyzed ring-expansion via *in-situ* formed diazo compounds **262**.¹⁵³

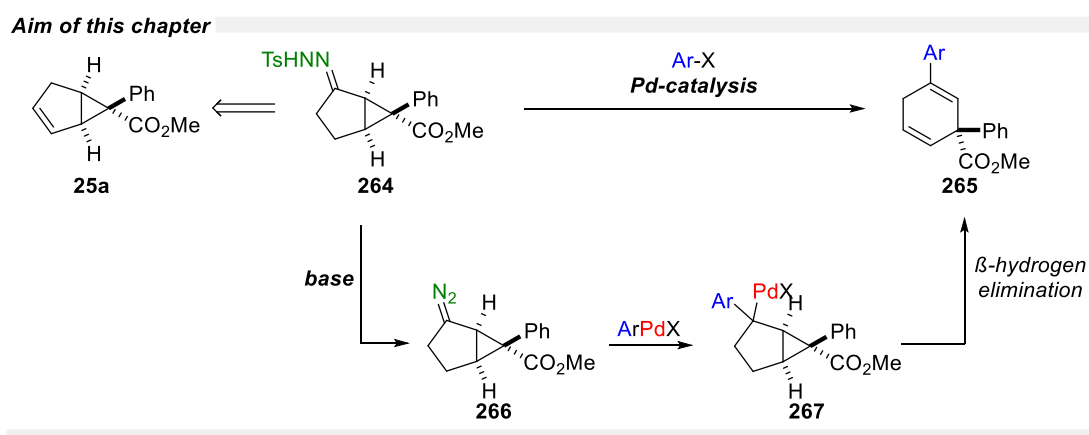


^b The investigation of the *Heck*-type reaction of compounds **253** and **254** was carried out as part of Sebastian Fischer's master's thesis in the working group of Prof. Dr. Reiser, created in 2019.

2.3.3 Aim of This Chapter

Combining the latter method¹⁵³ and the results from *Reiser et al.*,^{46,48,147} the strategy focused on introducing a hydrazone-moiety next to the cyclopropane group of carbocyclic VCP **25a**. Under basic conditions **264** should form *in-situ* diazo compound **266**. After Pd-carbene formation and migratory insertion, α -cyclopropyl palladium compound **267** should be afforded. This way, regioselectivity issues, as shown with VCP **25a** (Scheme 76), could be avoided, and 1,4-cyclohexadienes **265** would become accessible as the main product (Scheme 78).

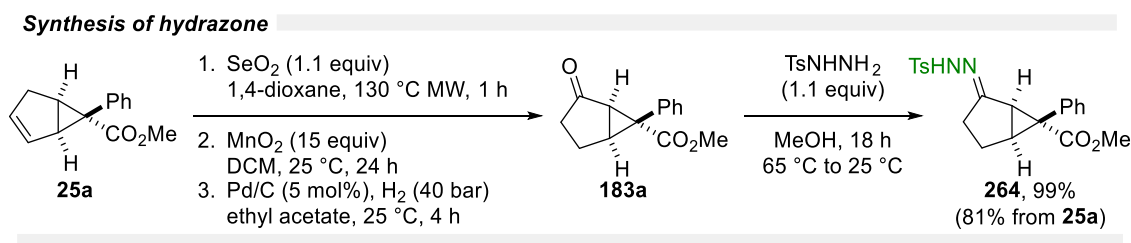
Scheme 78. Aim of this chapter.



2.3.4 Pd-Catalyzed Ring-Opening via *in-situ* Diazomethyl Cyclopropane

To synthesize the desired hydrazone **264**, tosyl hydrazine was added to the previously synthesized ketone **183a**, resulting in a quantitative yield. Regarding vinyl cyclopropane **25a**, the overall yield is 81% (Scheme 79).

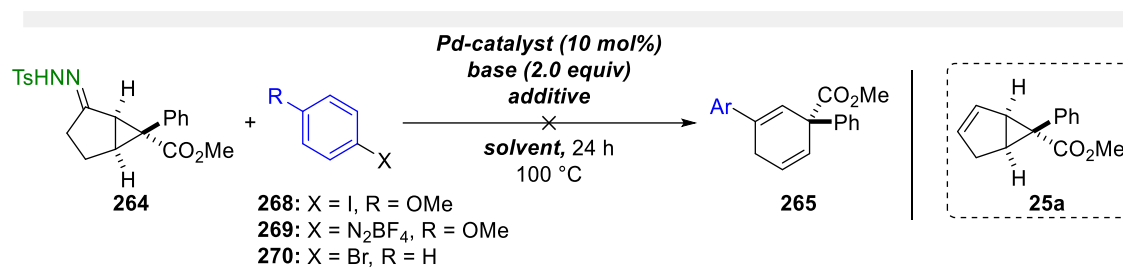
Scheme 79. Synthesis of hydrazone **264**.



With this compound in hand, several palladium-catalyzed screening reactions towards coupling partner were carried out. With $\text{Pd}(\text{OAc})_2$, Cs_2CO_3 as the base and **268** as the

coupling partner dissolved in MeOH at 100 °C for 24 h, no reaction was observed (Table 39, Entry 1). It was reasoned that the base cannot deprotonate the hydrazone group, and the formation of the required diazo compound is not possible. Using K_2CO_3 as the base did not improve the outcome (Table 39, Entry 2). It was determined that issues with solubility prevented the desired reaction. However, changing the solvent from MeOH to MeCN did not lead to any improvement (Table 39, Entry 3). In contrast, adding TBAB as a phase transfer catalyst (PTC) led to decomposition but at least gave complete conversion of the starting material **264** (Table 39, Entry 4). In different solvents (MeCN and toluene) and with TBAB as PTC, only **25a** could be observed as a product that forms via a *Bamford-Steven reaction*.¹⁵⁴ This process the *in-situ* formation of the required diazo compound **266** (Table 39, Entry 5-6). However, the release of N_2 and alkene synthesis is faster than Pd-carbene (**267**) formation. Therefore, aryl diazonium salt **269** was used as a more reactive coupling partner but led to decomposition (Table 39, Entry 7). Applying the optimized conditions from Zhou and co-workers¹⁵³ was not possible since the starting material **264** was not soluble in 1,4-dioxane. Switching to MeCN as the solvent gave again **25a** as the product (Table 39, Entry 8 – 9).

Table 39. Hydrazone **265** reactivity under Pd catalysis and basic conditions.

 268: X = I, R = OMe 269: X = N_2BF_4, R = OMe 270: X = Br, R = H						
Entry	Catalyst	Base	Solvent	Ar-X	Additive	Result
1	$Pd(OAc)_2$	Cs_2CO_3	MeOH	268	—	no conversion
2	$Pd(OAc)_2$	K_2CO_3	MeOH	268	—	no conversion
3	$Pd(OAc)_2$	Cs_2CO_3	MeCN	268	—	no conversion
4	$Pd(OAc)_2$	Cs_2CO_3	MeOH	268	TBAB (2.0 equiv)	decomposition
5	$Pd(OAc)_2$	Cs_2CO_3	MeCN	268	TBAB (2.0 equiv)	formation of 25a

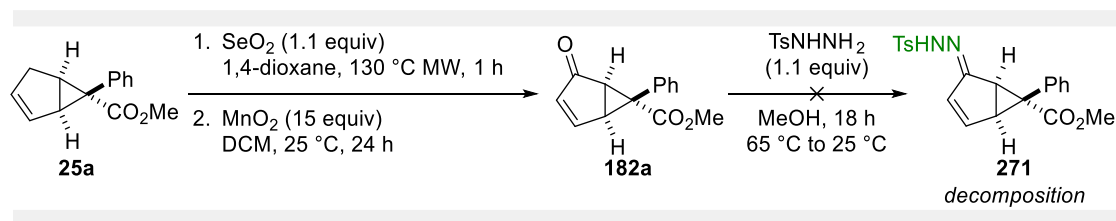
6	Pd(OAc) ₂	Cs ₂ CO ₃	toluene	268	TBAB (2.0 equiv)	formation of 25a
7^a	Pd(OAc) ₂	Cs ₂ CO ₃	toluene	269	TBAB (2.0 equiv)	decomposition
8^b	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1,4-dioxane	270	Xphos (2.0 equiv)	stirring not possible
9^b	Pd ₂ (dba) ₃	Cs ₂ CO ₃	MeCN	270	TBAB (2.0 equiv) Xphos (2.0 equiv)	formation of 25a

Reactions were performed on a 0.2 mmol scale. Reaction conditions: Ar-X (2.0 equiv), [a] reaction temperature was set to 60 °C due to reactive aryl diazonium salt **269**. [b] 5 mol% of catalyst was used.

Summarized, suitable conditions for the ring-expansion of **264** via Pd-catalyzed carbene migratory insertion were not found. Intramolecular *Bamford-Stevens reaction* leading to alkene **25a** occurs faster than intermolecular addition of the active palladium species (ArPdX) to the formed *in-situ* carbene **266**. This explains why *Zhou et al.* could only apply benzylic hydrazones **259**, in which a *Bamford-Stevens reaction* is impossible. Further investigations should concentrate on blocking the α -position to the hydrazone of **264** to prevent alkene-synthesis and tolerate the desired Pd-carbene formation.

The attempt to prevent alkene synthesis using an allylic hydrazone failed as we were unable to synthesize **271** from **182** (Scheme 80).

Scheme 80. Failed synthesis of allylic hydrazone **271**.



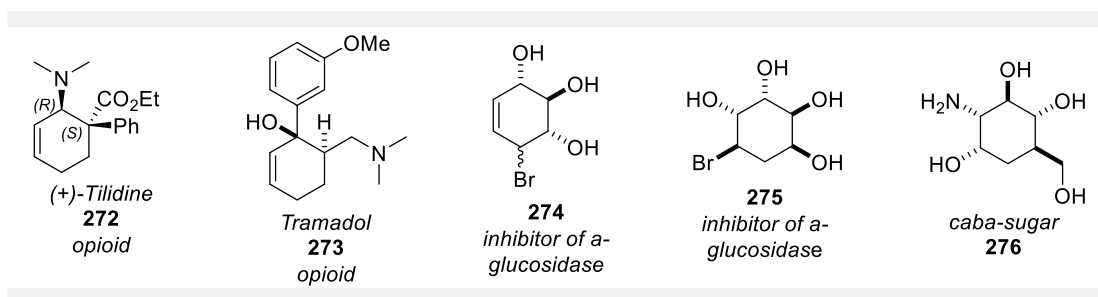
3. Functionalization of Six-Membered Carbocycles

3.1. Biologically Active Six-Membered Carbocycles

One principal aim of synthetic organic chemistry is the development of new or advantageous routes to complex chemical structures such as biologically active molecules or drugs. Focusing on simple six-membered carbocycles, a variety of active compounds can be listed.

Tilidine (**272**), known under its brand name *Valoron*, is considered as low-to-medium-potency synthetic opioid and pain killer with approx. 1/5 of the analgesic effect of morphine.¹⁵⁵ It is metabolized in the liver, acts as μ -agonist and is usually combined with *Naloxone* (an opioid antagonist) as an antidote for drug abuse.^{156,157} Notably, the (1*S*,2*R*)-form is twenty-three times more active than its (1*R*,2*S*)-enantiomer.¹⁵⁸ *Tramadol* (**273**, brand name: *Ultram* and more) is also used as an opioid pain medication to treat moderate to moderately severe pain.¹⁵⁹ Like *Tilidine*, it is further metabolized in the liver and possesses the following properties: agonist of the μ -, δ -, and κ -opioid receptor ($\mu > \delta > \kappa$), serotonin reuptake inhibitor, norepinephrine reuptake inhibitor, and serotonin 5-HT_{2C} receptor antagonist, and many more.^{160,161} Both brominated conduritol compound **274** and brominated quercitol **275** are known as inhibitors for α -glucosidase,^{162,163} while carba-sugars such as **276** are lead structures for the development of new antibiotics (Scheme 81).¹⁶⁴

Scheme 81. Selected examples of small six-membered molecules with therapeutic value.



3.2. Aim of This Chapter

After obtaining cyclohexene **122a**, which has a double bond, a bromide, and an ester group, the final study aimed to showcase the molecule's synthetic potential by:

- 1) Introducing additional functionalities.
- 2) Replacing or derivatizing the current groups.
- 3) Build up more complex molecules.

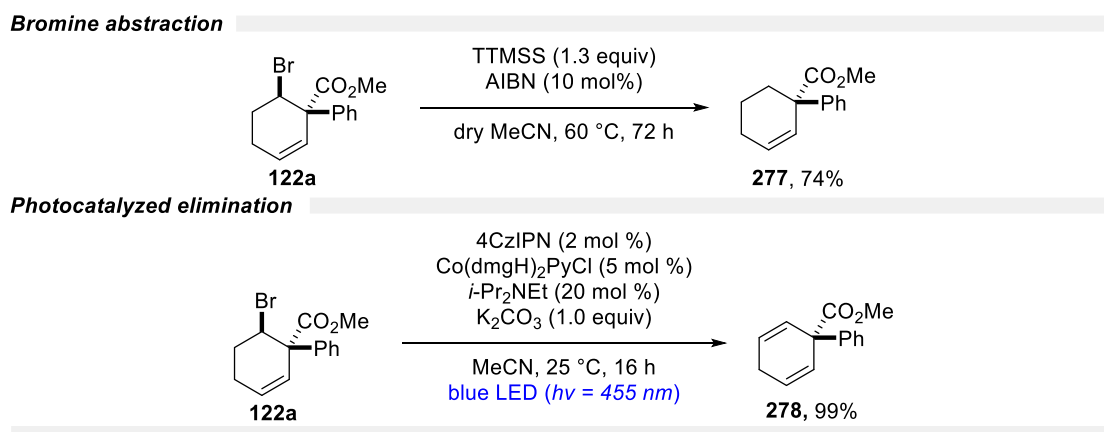
3.3. Functionalization of Methyl 2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (**122a**)

3.3.1 Bromine in Neopentyl-Position

Alkyl halide reactions can be found in an enormous variety in the literature. The task was to investigate the behavior of the bromine in neopentyl-position under different reaction conditions while focusing on the abstraction, elimination, and substitution of the halide.

Under modified literature conditions, the bromine group was abstracted *via* a radical pathway using TTMS and AIBN to produce compound **277** (Scheme 82).¹⁶⁵

Scheme 82. Bromine abstraction and elimination of **122a**.



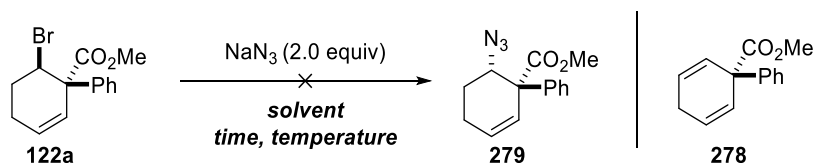
Cyclohexadiene **278** was not accessible *via* base-promoted E₂-elimination since the bromine is most likely located in an equatorial position in the half-chair conformation of the cyclohexene. Thus, the p-orbitals cannot overlap in the transition state to form the double bond. However, the elimination was successful under conditions from *Leonori et al.*¹⁶⁶ An E₂-type reaction on alkyl halides by an interplay of α -aminoalkyl radical-mediated halogen-atom transfer (XAT) with desaturative cobalt catalysis and blue-light irradiation obtained the 1,4-cyclohexadiene **278** (Scheme 82, see *ref. 166* for mechanism).

Nucleophilic substitution on a secondary alkyl halogen allows S_N1- and S_N2-type reactivity depending on the reaction conditions. However, S_N2 reaction of neopentyl-bromides, as it is present in compound **122a**, is nearly impossible or extremely slow, with neopentyl-bromide reacting approx. 10⁵-times slower than primary alkyl halides.^{167,168} The bulky neighboring groups and the potential leaving group do not allow attack by the nucleophile.¹⁶⁹ Additionally, the equatorial position of the bromine group in **122a** is unfavorable for S_N2. For S_N1, resulting carbocation intermediates rather undergo intramolecular rearrangements followed by elimination and substitution reactions.^{167,169}

Based on this knowledge, it was doubted that nucleophilic substitution of the bromine is possible under classical S_N2-type reaction conditions. Nevertheless, an S_N2-approach using NaN₃ as the nucleophile according to literature conditions was tested (Table 40). NaN₃ was chosen as the nucleophile because the incorporation of nitrogen would approximate a *Tilidine* analogue.^{170,171}

Table 40. S_N2 reaction approach using NaN₃.

S_N2-approach



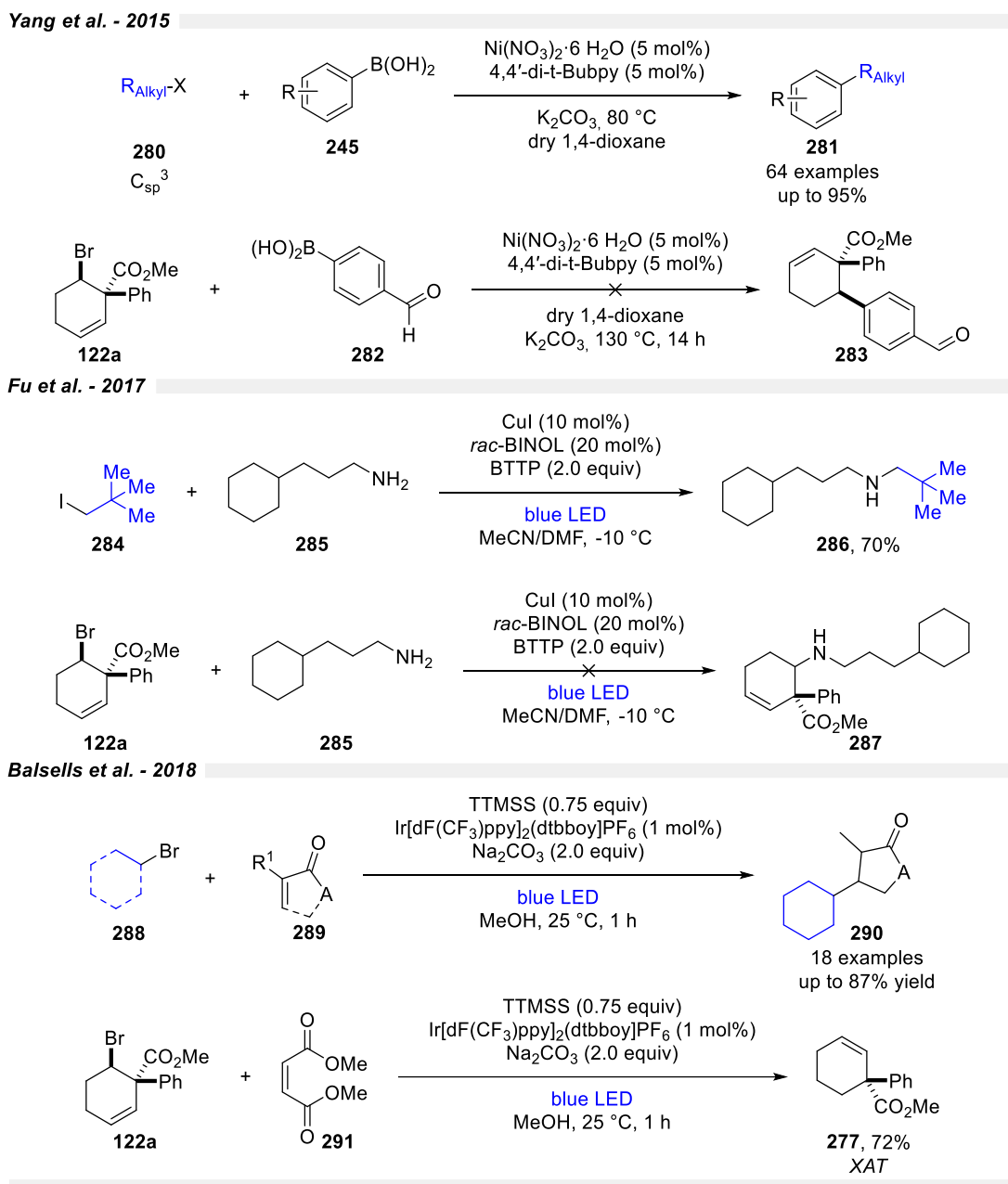
Entry	Solvent	T [°C]	Time [h]	Result
1	DMF	80	16	no conversion
2	DMF	80	72	no conversion
3	DMF	125	16	33% of 278
4	DMSO	80	16	almost no conversion, traces of 278
5 ^{a)}	H ₂ O (+TBAB)	100	2.5	no conversion

Reactions were performed on a 0.5 mmol scale. [a] TBAB (0.1 equiv) was added.

As expected, the S_N2 reaction was unsuccessful under classical conditions, but elimination was observed at higher temperatures yielding **278** in 33% (Table 40, Entry 3). Dealing with a C_{sp3}-Br group in compound **280**, the literature shows a tremendous

amount of formal substitution reactions: *Yang et al.* demonstrated in 2015 a nickel-catalyzed C_{sp^3} - C_{sp^2} Suzuki-type coupling using functionalized alkyl halides **280** and boronic acids with a mild base.¹⁷² Since the authors showed a broad functional group tolerance, these conditions were applied to C_{sp^3} -Br compound **122a**. However, no starting material conversion was observed even at 130 °C, highlighting the robustness and steric hindrance towards the bromine group (Scheme 83).

Scheme 83. Non-classical substitution attempts of **122a**.

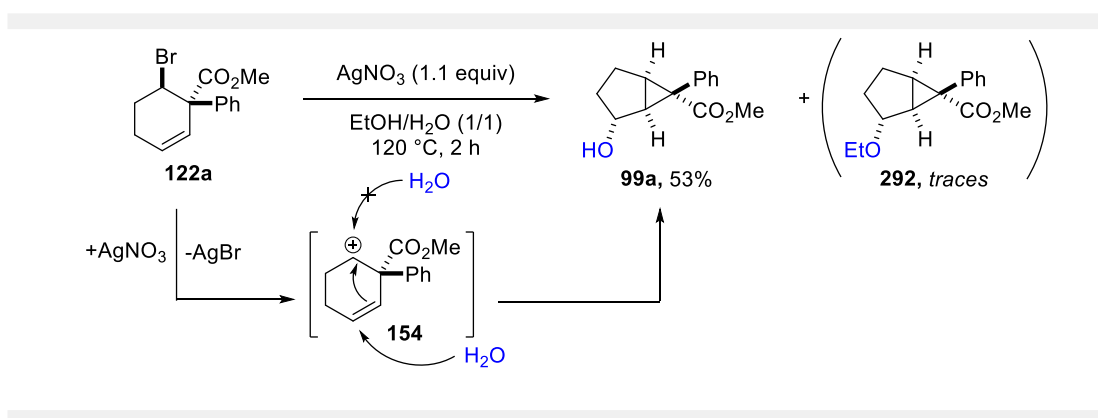


Fu et al. achieved the substitution of the neopentyl-iodide **284** using a copper-catalyzed alkylation of aliphatic amines **285** induced by visible-light, which was considered as a

promising reaction type for compound **122a**.¹⁷³ However, it turned out that the steric hindrance of the $-\text{CO}_2\text{Me}$ and $-\text{Ph}$ groups must be higher than the *tert*-butyl group since no reaction occurred (Scheme 83). Another proof for the extreme robustness of the bromine group was shown with reaction conditions from *Balsells et al.*, who used a silyl-mediated photoredox-catalyzed *Giese*-type reaction to add non-activated alkyl bromides **288** to *Michael*-acceptors **289**.¹⁷⁴ In case of compound **122a**, XAT followed by a HAT reaction afforded compound **277** (72% yield). From this product, the formation of an alkyl-radical can be concluded, which does not add to the *Michael*-acceptor due to its high steric hindrance (Scheme 83).

Since a secondary alkyl halide **122a** is present, substituting the bromine with a small nucleophile could occur under $\text{S}_{\text{N}}1$ reaction conditions. Typically, $\text{S}_{\text{N}}1$ is in polar protic solvents since the hydrogen bonds stabilize the intermediary carbocation. In addition, high temperatures and a good leaving group favor $\text{S}_{\text{N}}1$ over $\text{S}_{\text{N}}2$. Lewis acids, such as silver nitrate, can also facilitate the abstraction of halides removing the free halide anion. Surprisingly, when using AgNO_3 (1.1 equiv), the bromine abstraction of compound **122a** under a high temperature of $120\text{ }^\circ\text{C}$ dissolved in $\text{H}_2\text{O}/\text{EtOH}$ (1/1) was not observed. Instead, intramolecular re-cyclopropanation *via* $\text{S}_{\text{N}}1$ followed by nucleophilic addition of H_2O afford the cyclopropane **99a**. In the crude mixture, traces of compound **292** derived from nucleophilic addition with EtOH could be detected, although purification was not possible (Scheme 84).

Scheme 84. Intramolecular $\text{S}_{\text{N}}1$ -substitution of **122a**.



Summarized, classical $\text{S}_{\text{N}}2$ -conditions, $\text{C}_{\text{sp}3}\text{-C}_{\text{sp}2}$ Suzuki-type coupling, and radical pathways *via* photoredox-catalyzed *Giese* reaction failed to give any substitution reaction, showing the robustness of an alkyl-bromine in neopentyl-position. Furthermore, the steric

hindrance by $-\text{CO}_2\text{Me}$ and $-\text{Ph}$ is manifested since neopentyl-suitable conditions are not tolerated, and even the formed alkyl-radical from **122a** instead undergoes a HAT reaction than coupling with an external acceptor. $\text{S}_{\text{N}}1$ -conditions can be titled partly successful, showing intramolecular substitution, while intermolecular substitution is not possible due to the steric hindrance.

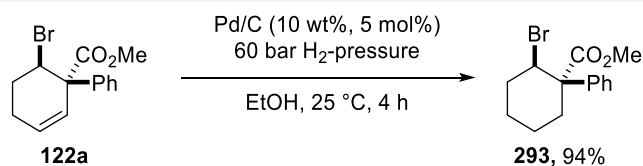
3.3.2 Double Bond Derivatization

The next aim of this study was to take advantage of the double bond's reactivity and access its allylic position to synthesize highly functionalized bromides with at least three stereocenters.

A simple reduction of the double bond was achieved by hydrogenation using Pd/C (5 mol%) system dissolved in EtOH at 60 bar H_2 -pressure, yielding **293** (94%, Scheme 85).

Scheme 85. Reduction of **122a**.

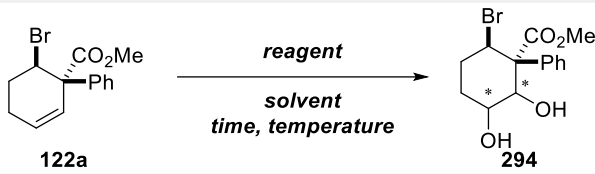
hydrogenation



The direct introduction of a diol is of great synthetic value since two new stereocenters will be formed, and the alcohol groups lead to a new molecule reactivity. Hence, dihydroxylation of **122a** was performed with $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (0.05 equiv) and NMO (2.0 equiv) as co-oxidant or a $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (0.07 equiv) and NaIO_4 (1.5 equiv) system (Table 41).¹⁷⁵

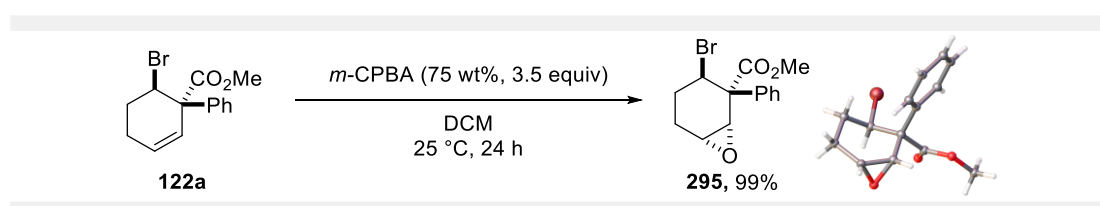
Surprisingly, the *syn*-diol synthesis was unsuccessful with either ruthenium or osmium, with no logical explanation. The literature shows a variety of dihydroxylation using exactly these conditions with a broad tolerance of functionality groups and sterically hindered double bonds.^{175–178} Reports only indicate that highly substituted olefins are not very reactive towards dihydroxylation reagents, which should not be accurate for **122a**.¹⁷⁸ Electronic and steric reasons that prevent the reaction are not apparent.

Table 41. Failed direct dihydroxylation of **122a** using OsO₄/NMO or RuCl₃/NaIO₄.

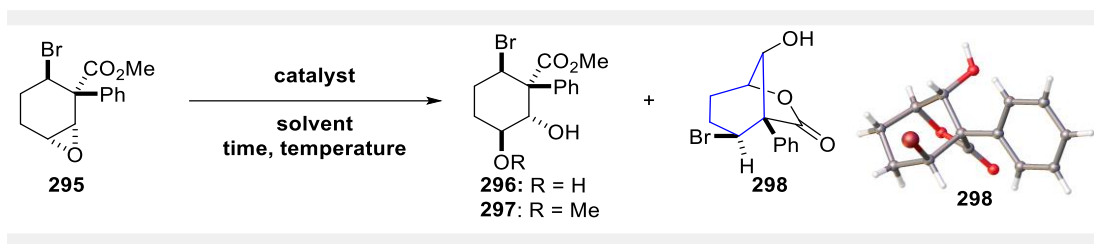
					
Entry	Reagent [equiv]	Solvent	T [°C]	Time	Result
1	K ₂ OsO ₄ ·2H ₂ O (0.05 equiv), NMO (2.0 equiv)	acetone	25	24 h	no conversion
2	K ₂ OsO ₄ ·2H ₂ O (0.05 equiv), NMO (2.0 equiv)	acetone	25 to 50	6 d	no conversion
3	RuCl ₃ ·3H ₂ O (0.07 equiv), NaIO ₄ (1.5 equiv)	MeCN	25	3 d	no conversion

Reactions were performed on a 0.2 – 0.4 mmol scale.

These results are even more surprising when compared to an epoxidation reaction applying *m*-CPBA (3.5 equiv), which occurs at room temperature under mild conditions giving rise to **295** with high diastereoselectivity in quantitative yield. This demonstrates the accessibility for electrophiles to add from the ester side (Scheme 86).

Scheme 86. Epoxidation of **122a**.

Having epoxide **295** in hand, the next step was to access the diol from the epoxide ring-opening. Under acidic conditions, *trans* compound **297** and *trans*-diol **296** were synthesized *via* S_N1 in good yields (Table 42, Entry 3 and 5). Surprisingly, side product **298** was formed *via* intramolecular lactonization. It was obtained at high temperatures and selectively synthesized in toluene without a nucleophile (Table 42, Entry 11).

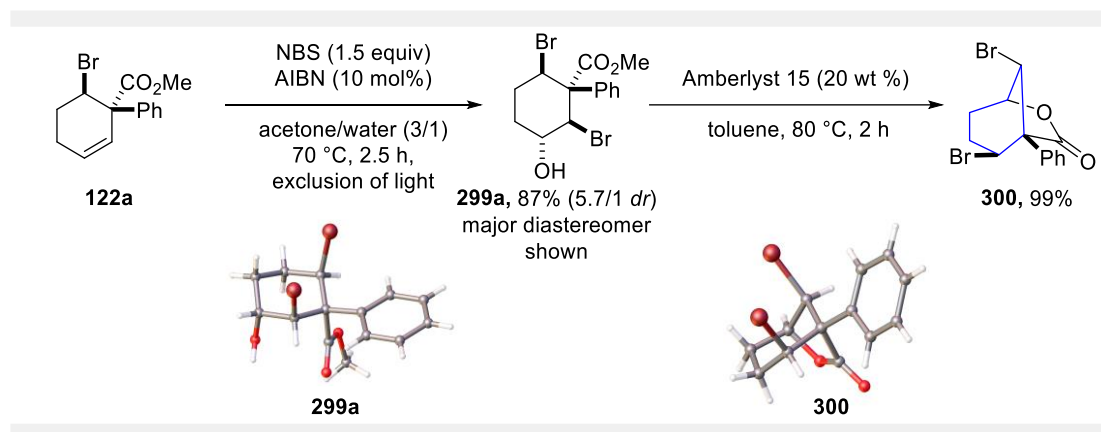
Table 42. Epoxide ring-opening.

Entry	-R	Catalyst [equiv]	Solvent	Time [h]	T [°C]	296 or 297 [%]	298 [%]
1^a	Me	Amberlyst 15 (20 wt%)	MeOH (excess)	2.5	100, MW	53	38
2^a	Me	H ₂ SO ₄ (1.0)	MeOH (excess)	2.5	100, MW	70	19
3	Me	H ₂ SO ₄ (1.0)	MeOH (excess)	6	50	71	-
4	Me	H ₂ SO ₄ (3.0)	MeOH (excess)	6	50	67	-
5	H	H ₂ SO ₄ (1.0)	H ₂ O/MeCN (1/1)	6	50	64 (86 <i>brsm</i>)	-
6	Me	H ₂ SO ₄ (10)	MeCN	0.5	120, MW	decomposition	
7	Me	H ₂ SO ₄ (10)	MeCN	0.5	100, MW	decomposition	
8	Me	H ₂ SO ₄ (3.0)	MeCN	0.5	100, MW	decomposition	
9	Me	H ₂ SO ₄ (3.0)	MeCN	0.5	80, MW	decomposition	
10	Me	H ₂ SO ₄ (1.5)	MeCN	0.5	80, MW	decomposition	
11^a	Me	H ₂ SO ₄ (1.5)	toluene	0.5	80, MW	-	61
12	Me	H ₂ SO ₄ (1.5)	toluene	15 min	80	-	40
13	Me	H ₂ SO ₄ (1.5)	toluene	5 min	120	decomposition	

Reactions were performed on a 0.2 – 0.5 mmol scale. [a] Yield was determined by ¹H-NMR with fumaric acid dinitrile as the internal standard.

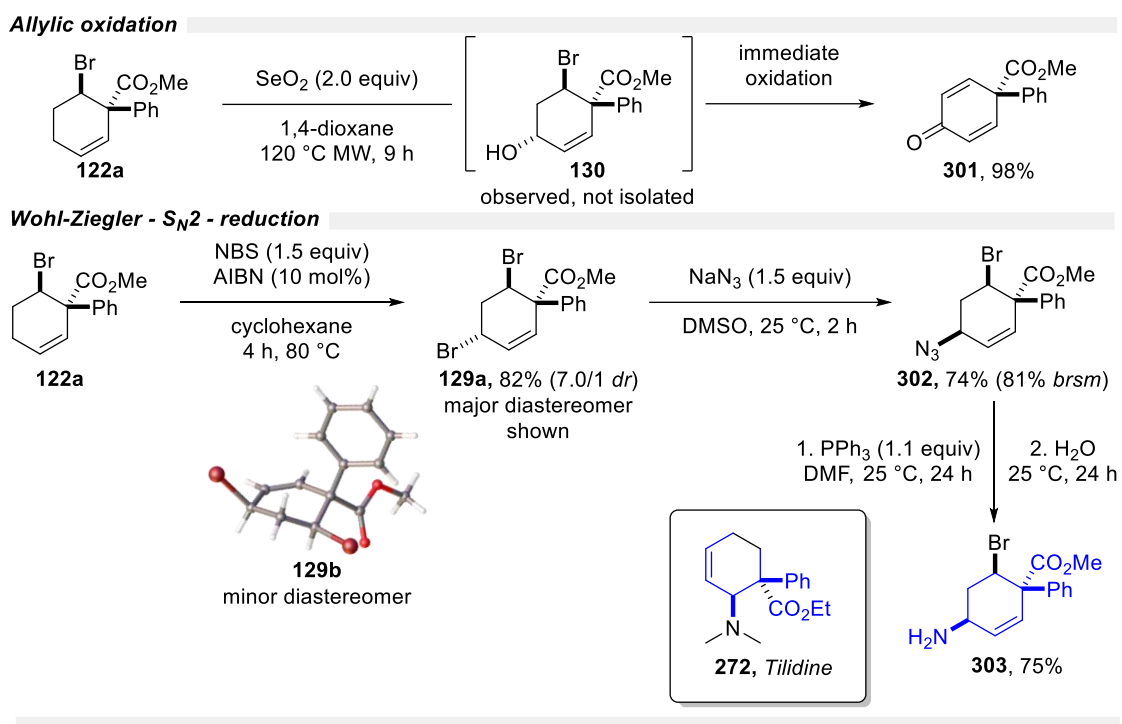
A similar lactonization process gave access to dibrominated lactone **300** under acidic conditions from compound **299**, which was synthesized *via* halohydrin reaction. (Scheme 87).

Scheme 87. Halohydrin formation followed by lactonization.



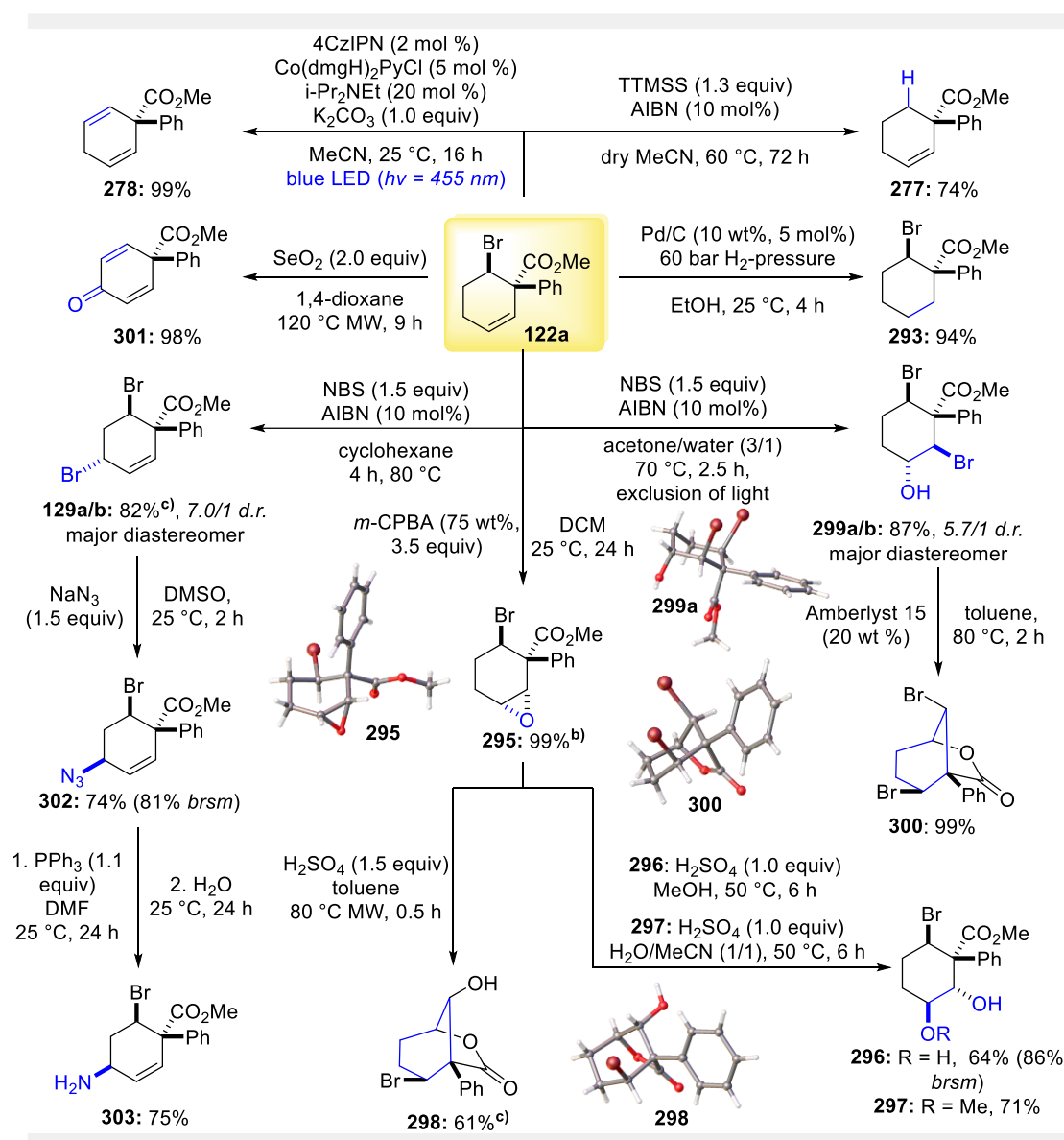
Taking advantage of the allylic position, the allylic oxidation with congruent HBr-elimination gave rise to ketone **301**. While desired compound **130** was observed during the reaction, SeO₂ immediately initiates a second oxidation process leading to compound **301** (Scheme 88).

To insert amino groups, a reaction cascade consisting of *Wohl-Ziegler* bromination¹⁷⁹, S_N2-substitution by azide, and reduction to the amine was performed. Interestingly, the radical allylic bromination process initiated by AIBN and NBS still delivered a passable diastereoselective ratio (7.0/1 *d.r.*) due to the steric influence of the *para*-Ph group and the *meta*-Br group. Chemoselective substitution of the new bromine group afford azide **302** could be done *via* classical S_N2-conditions, exploiting the inactivity of the neopentyl-bromine. Reduction gave rise to the amine **303**, which can be seen as a brominated *Tilidine* analogue with potential biological activity (Scheme 88).

Scheme 88. Functionalization in allylic position.

Summarized, functionalization of **122a** with a broad variety of groups ($-\text{NH}_2$, $-\text{Br}$, $-\text{N}_3$, $-\text{OH}$) was possible, leading to highly functionalized cyclohexenes/cyclohexanes containing four stereocenters and good to high diastereoselectivity. Furthermore, a brominated *Tilidine* analogue **303** with potential biological activity was accessible *via* a reaction cascade. Synthetic value for more complex molecules was already observed from the high lactonization potential of **299a** and **295**. Oxidation and reductions were made easily with mild and classical reaction conditions (Scheme 89).

3.3.3 Overview - Functionalization

Scheme 89. Functionalization of **122a** – An overview.

C. Summary

This dissertation deals with the endocyclic ring-opening of cyclopropanated cyclopentadiene compounds for synthesizing highly functionalized carbocyclic six-membered rings.

The first chapter shows that cyclopropanation of cyclopentadiene with diazo acetates with rhodium as the catalyst or with blue-light excitation is a high-yielding and robust method with a wide range of functional group tolerance. In contrast, diazo ketones provide the desired cyclopropanes only with rhodium catalysis, while blue-light excitation leads to cyclobutanones through a *Wolff-rearrangement* followed by a [2+2] cycloaddition. In cooperation with the *Davies* group, their study of the asymmetric cyclopropanation of cyclopentadiene, published in 2010,⁶⁵ is improved in terms of enantiomeric excess.

The second chapter then deals with the selective endocyclic ring-opening of the previously synthesized carbocyclic vinyl cyclopropanes. Similar to *Reiser et al.*^{43,115} (2022), who demonstrated the ring-expansion of cyclopropanated heterocycles, the carbocyclic analogues should undergo endocyclic ring-opening. A positive charge should be generated next to the cyclopropane skeleton by introducing functional groups and various activation methods, which should lead to endocyclic ring-opening. However, due to the missing “*push-effect*” of the heteroatom, the endocyclic bond cannot be sufficiently activated to trigger the desired reaction. Therefore, ring-expansion is only observed as a side reaction with mostly substitution/elimination or Lewis acid-catalyzed addition reactions predominating. Only the addition of large amounts of Brønsted acids enables the selective ring-expansion of vinyl cyclopropanes, and cyclopropylmethanols, with hydrobromic acid proving to be the suitable combination in terms of acid strength and nucleophilicity of the anion. It can be concluded that the nucleophile plays a crucial role in the ring-opening process of cyclopropanated carbocycles. The HBr-assisted ring-expansion is successfully demonstrated on a variety of differently functionalized vinyl cyclopropanes. Highly functionalized six-membered carbocycles are obtained in high yield.

Furthermore, in Chapter 2, a palladium-catalyzed endocyclic ring-opening should be achieved by introducing a hydrazone group next to the cyclopropane. Combining the conditions of the demonstrated *Heck-type* ring-expansion of vinyl cyclopropanes (*Reiser et al.* in 2021)⁴⁸ and the palladium-catalyzed ring-opening of N-tosylhydrazone

cyclopropanes (*Zhou et al.* in 2016)¹⁵³ is unsuccessful. Instead, *Bamford–Stevens* reaction takes place as the predominant reaction.

Finally, chapter 3 demonstrates the ability of the functionalized six-membered rings as building blocks for the synthesis of more complex molecules. Oxidations, reductions, substitutions, eliminations, and the introduction of various functional groups are successfully achieved with good stereoselectivity and yields. Only the chemoselective substitution of the bromine in neopentyl-position cannot be realized with external nucleophiles.

D. Zusammenfassung

Die vorliegende Arbeit ist eine Weiterführung der Dissertation von Robert Eckl¹¹⁵ (Arbeitskreis Prof. Dr. Reiser) und befasst sich mit der endozyklischen Ringöffnung von cyclopropanierten Cyclopentadienverbindungen zur Synthese hochfunktionalisierter carbozyklischer Sechsringe.

Im ersten Kapitel wird gezeigt, dass die Cyclopropanierung von Cyclopentadien mit Diazoestern sowohl mit Rhodium als Katalysator, als auch unter Anregung mit blauem Licht sehr tolerant gegenüber den verschiedensten funktionellen Gruppen ist und beide Methoden eine ähnlich hohe Ausbeute erzielen können. Diazoketone hingegen liefern die gewünschten Cyclopropane nur mit Rhodiumkatalyse. Unter Anregung mit blauem Licht führen sie zu Cyclobutanonen durch eine Wolff-Umlagerung gefolgt von einer [2+2]-Cycloaddition. In Kooperation mit der Davies-Gruppe wird ihre 2010 veröffentlichte Studie⁶⁵ der asymmetrischen Cyclopropanierung von Cyclopentadien durch Nutzung von TCE-Diazoestern hinsichtlich enantiomerem Überschuss verbessert.

Das zweite Kapitel beschäftigt sich dann mit der selektiven endozyklischen Ringöffnung der dargestellten carbozyklischen Vinylcyclopropane. Ähnlich wie es Reiser *et al.*⁴³ (2022) mit cyclopropanierten Heterozyklen zeigten, soll durch Einführung von funktionellen Gruppen und verschiedener Aktivierungsmethoden eine positive Ladung neben dem Cyclopropangerüst erzeugt werden, welches zu einer endozyklischen Ringöffnung führen soll. Durch den fehlenden „Push-Effekt“ des Heteroatoms kann die endozyklische Bindung aber nicht hinreichend aktiviert werden, wodurch die gewünschte Ringöffnung nur als Nebenreaktion beobachtet wird und meist Substitutions-/Eliminierungsreaktionen bzw. Lewis-Säure katalysierte Additionsreaktionen vorherrschen. Erst die Zugabe von großen Mengen an Brønsted-Säure ermöglicht die Ringerweiterung von Vinylcyclopropanen und Cyclopropylmethanolen, wobei sich Bromwasserstoffsäure als geeignete Kombination hinsichtlich Säurestärke und Nukleophile des Anions erweist. Es kann darauf geschlossen werden, dass das Nukleophil eine entscheidende Rolle im Ringöffnungsprozess spielt. Die HBr-assistierte Ringerweiterung wird an einer Vielzahl verschieden-funktionalisierter Vinylcyclopropane erfolgreich gezeigt und somit können hochfunktionalisierte Sechsringe mit hoher Ausbeute synthetisiert werden.

Außerdem soll in Kapitel 2 die palladiumkatalysierte endozyklische Ringöffnung durch Einführung einer Hydrazongruppe neben dem Cyclopropan erreicht werden. Die Kombination der Bedingungen der zuvor gezeigten Heck-typ Ringerweiterung von Vinylcyclopropanen (*Reiser et al* in 2021)⁴⁸ und der palladiumkatalysierten Ringöffnung von N-Tosylhydrazoncyclopropanen (*Zhou et al.* in 2016)¹⁵³ führt lediglich zu einer Bamford-Stevens-Reaktion, jedoch nicht zur gewünschten Ringöffnungsreaktion.

Kapitel 3 demonstriert abschließend die Fähigkeit der aus Kapitel 2 synthetisierten funktionalisierten Sechsringe als Bausteine zur Synthese komplexerer Moleküle. Oxidationen, Reduktionen, Substitutionen, Eliminierungen und die Einführung verschiedenster funktioneller Gruppen mit guter Stereoselektivität werden erfolgreich erreicht. Lediglich die selektive Substitution des Bromids in Neopentylstellung kann mit externen Nukleophilen nicht erzielt werden.

E. Experimental Part

1. General Information

Moisture sensitive reactions were performed in flame-dried glassware and under nitrogen atmosphere. Asymmetric reactions were done in collaboration with the *Davies* group and were carried out in oven-dried glassware under argon atmosphere unless otherwise stated. Commercially available chemicals were used without further purification and anhydrous solvents were prepared according to established procedures.^c Used H₂O is deionized H₂O, unless otherwise stated. Photochemical reactions were carried out in oven-dried glassware. EtOAc and hexanes for chromatography were distilled prior to use. The reported yields are isolated compounds unless otherwise stated.

Chromatography

Thin layer chromatography (TLC) was performed with precoated aluminum sheets (ALUGRAM[®] Xtra SIL G/UV₂₅₄ from MACHEREY-NAGEL GmbH & Co. KG, thickness 0.2 mm). Visualization was done by UV light ($\lambda = 254$ nm) and/or staining with vanillin (6.0 g vanillin, 100 mL ethanol (95%), 1 mL conc. sulfuric acid) or potassium permanganate (2.0 g Na₂CO₃, 1.0 g KMnO₄, 100 mL DI H₂O (deionized H₂O) or/and followed by heating. Column chromatography was performed with silica gel (Merck Geduran Si 60, 0.063-0.200 mm particle size) and flash silica gel 60 (Merck Geduran Si 60, 0.040-0.063 mm particle size).

Microwave reactions

Microwave-assisted experiments were carried out on an Anton Paar Monowave 300 reactor in a sealed vessel.

NMR-Spectroscopy

¹H NMR- and ¹³C NMR-spectra were recorded on Bruker Avance 300 (300 MHz for ¹H, 75 MHz for ¹³C) NMR spectrometer, or on Bruker Avance III 400 (400 MHz for ¹H, 101 MHz for ¹³C) NMR spectrometer, or Varian/Bruker 400 (400 MHz for ¹H, 101 MHz for ¹³C) NMR spectrometer, or on INOVA/Bruker 500 (500 MHz for ¹H) NMR spectrometer,

^c a) Armarego, W. L. F.; Chai, C. L. L., *Purification of Laboratory Chemicals*. 6 ed.; Butterworth-Heinemann Oxford, 2009.

b) Hünig, S.; Felderhoff, M.; Kemmerer, M.; Kreitmeier, P.; Märkl, G.; Sauer, J.; Seifert, M.; Sustmann, R.; Troll, *Integriertes Organisch-Chemisches Praktikum (I.O.C.-Praktikum)*; 1. ed.; Lehmanns, 2007.

or on INOVA/Bruker 600 (600 MHz for ^1H , 151 MHz for ^{13}C) NMR spectrometer. The spectra were recorded in CDCl_3 (δ 7.26 ppm) and chemical shifts for ^1H NMR were reported as δ , parts per million (ppm), relative to the signal of CHCl_3 . Spectra were evaluated in 1st order and the coupling constants J are reported in Hertz (Hz). Spin multiplicities were reported in abbreviations as: s = singlet, bs = broad-singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, dp = doublet of pentet, qd = quartet of doublet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, ddq = doublets of doublet of quartet, dtd = doublet of triplet of doublet, dtt = doublet of triplet of triplet, tdd = triplet of doublet of doublet, ttq = triplet of triplet of quartet, dddd = doublet of doublet of doublet of doublet, dddd = doublet of doublet of triplet of doublet, dtdd = doublet of triplet of doublet of doublet and m = multiplet. Chemical shifts for ^{13}C -NMR were reported as δ , parts per million (ppm), relative to the signal of CHCl_3 (δ 77.16 ppm). NMR yields were determined using fumaronitrile or ethylene carbonate as internal standard.

Mass Spectrometry

High resolution mass spectra (HRMS) were obtained on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000 or Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS and are reported in m/z . High-resolution mass spectra were measured using atmospheric pressure chemical ionization (APCI), electron ionization (EI), electrospray ionization (ESI) with a quadrupole time-of-flight (Q-TOF) detector. The analysis was done by the Central Analytical Laboratory (University Regensburg). For asymmetric reactions: mass spectra were taken on a Thermo Finnigan LTQ-FTMS spectrometer with APCI, ESI or NSI.

IR-Spectroscopy

Infrared spectra (IR) were measured on a Biorad Excalibur FTS 3000 spectrophotometer and are reported in unit of cm^{-1} . For asymmetric reactions: IR spectra were measured on a Nicolet iS10 FT-IR spectrometer from Thermo Scientific and reported in unit of cm^{-1} .

X-Ray Analysis

X-ray crystallographic analysis was performed by the Central Analytic Department of the University of Regensburg using an Agilent Technologies SuperNova, Agilent Technologies Gemini R Ultra, Agilent GV 50 or Rigaku GV 50.

Crystallization was done by dissolving small amounts of the desired solid in DCM or diethyl ether or hexanes (if diethyl ether was used, the solution was warmed up to 50 °C in a water bath) and slowly evaporated within 48 h at ambient temperatures/pressure.

Melting Points

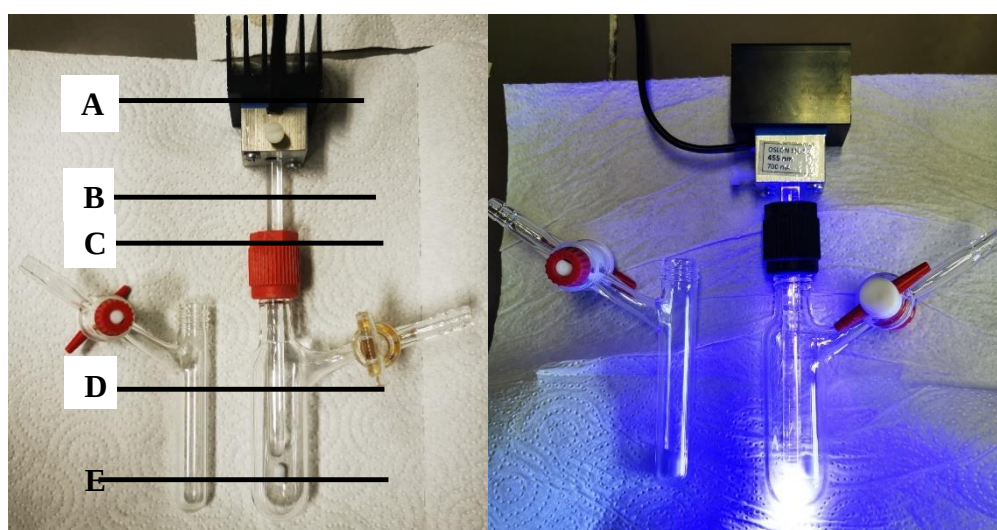
The measurement of melting points was carried out on an SRS MPA100 - Automated melting point system by OptiMelt. For asymmetric reactions: Melting points were measured in open capillary tubes with a Mel-Temp Electrothermal melting point apparatus and are uncorrected.

Photochemical Reactions

For all photochemical reactions monochromatic light emitting diodes (LED) were used as irradiation source. All relevant data are taken from the official data sheets provided by Osram, which are available free of charge *via* the internet at the Osram web page:

Blue-light-promoted reactions were performed using a LED-stick OSOLON® SSL 80 deep blue (3 W, 700 mA, dominant wavelength $\lambda_{\text{dom}} = 455 \text{ nm}$, spectral bandwidth at 50% $I_{\text{max}} = 20 \text{ nm}$, radiant power at 25 °C and 700 mA $\sim 900 \text{ mW}$) as irradiation source. The LED is placed on a glass rod (8 mm diameter; borosilicate glass; Schott Borofloat® 33) as fiber optics, which directly immerses in the reaction mixture. For the detailed reaction setup see Figure S1.

Photochemical Setup^d



^d Fischer, S.; Nguyen, T.-T. H.; Ratzenboeck, A.; Davies, H. M. L.; Reiser, O. *Org. Lett.* 2023, 25, 24, 4411–4415.

Figure S 1. Photochemical setup for cyclopropanation reactions. (A) LED, (B) glass rod, (C) Teflon adapter, (D) Schlenk tube (left: 10 mL, right: 20 mL), (E) Teflon-coated stir-bar.

Optical Rotation

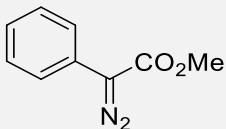
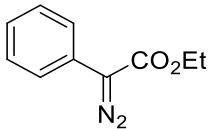
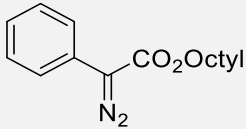
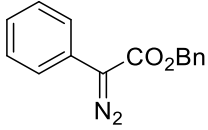
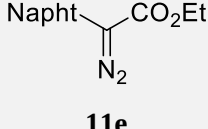
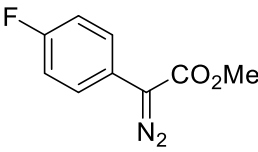
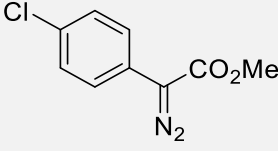
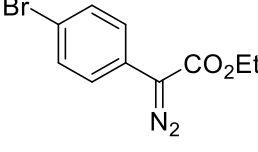
Optical rotations were measured at Emory university using a Rudolph Research Analytical - Autopol IV Automatic Polarimeter.

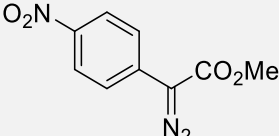
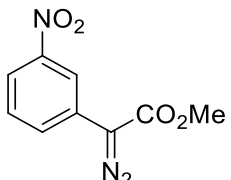
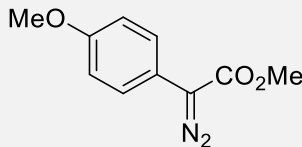
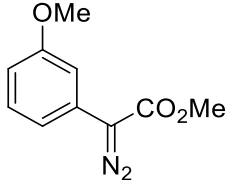
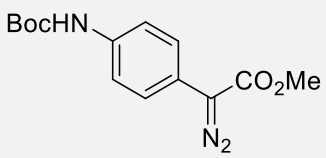
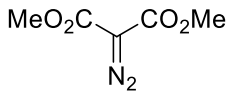
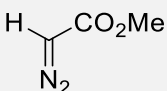
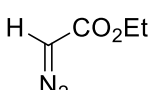
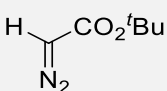
Enantiomeric Excess (*ee*) and Racemic Mixture:

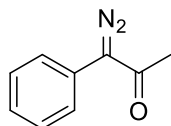
Racemic standards were generated by performing reactions with $\text{Rh}_2(R/S\text{-Ligand})_4$ which was generated by dissolving an equimolar mixture of the *R* and *S* catalyst in a minimal amount of DCM and concentrating *in vacuo*. Additionally, racemic standards can be generated by performing reactions with achiral $\text{Rh}_2(\text{OAc})_4$. The enantiomeric excess (*ee*) was determined by High performance liquid chromatography (HPLC) analysis and was performed on either Varian Prostar model 410 HPLC, Agilent 1100 Technologies HPLC or Agilent Technologies 1290 Infinity UHPLC instruments, and the data outlined below varies in presentation based on the software used for each system. The HPLC instruments used *iso*-propanol/hexane gradient and commercial ChiralPak/ChiralCel columns from Daicel Chemical Industries, notably ChiralPak AD-H (5 μm particle size, 4.6 mm vs. 250 mm), ChiralCel OZ-H (5 μm particle size, 4.6 mm vs. 250 mm), and ChiralCel OD-H (5 μm particle size, 4.6 mm vs. 250 mm), ChiralCel AS-H (5 μm particle size, 4.6 mm vs. 250 mm), and ChiralCel OJ-H (5 μm particle size, 4.6 mm vs. 250 mm).

2. Literature Known Starting Materials

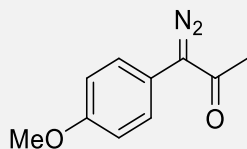
Table S 1. Literature known starting materials.

Chemical structure	Chemical name	Synthesis according to reference
 11a	methyl 2-diazo-2-phenylacetate	Davies, H. M. L.; Hansen, T.; Churchill, M. R., <i>J. Am. Chem. Soc.</i> 2000 , 122, 3063–3070.
 11b	ethyl 2-diazo-2-phenylacetate	Zhang, Y.; Yao, Y.; He, L.; Liu, Y.; Shi, L. <i>Adv. Synth. Catal.</i> 2017 , 359, 2754–2761
 11c	octyl 2-diazo-2-phenylacetate	Khade, V. V.; Thube, A. S.; Warghude, P. K., Bhat, R. G.; <i>Tetrahedron Lett.</i> , 2021, 77, 153258.
 11d	octyl 2-diazo-2-phenylacetate	Zhang, Y.; Yao, Y.; He, L.; Liu, Y.; Shi, L.; <i>Adv. Synth. Catal.</i> 2017 , 359, 2754.
 11e	ethyl 2-diazo-2-(naphthalen-2-yl)acetate	Chen, G.; Song, J.; Yu, Y.; Luo, X.; Li, C.; Huang, X.; <i>Chem. Sci.</i> , 2016 , 7, 1786–1790.
 11f	methyl 2-diazo-2-(4-fluorophenyl)acetate	Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A.S.C; Yu, W.-Y.; <i>Org. Lett.</i> 2010 , 3, 604–607.
 11g	methyl 2-(4-chlorophenyl)-2-diazoacetate	Davies, H. M. L.; Hansen, T.; Churchill, M. R., <i>J. Am. Chem. Soc.</i> 2000 , 122, 3063–3070.
 11h	ethyl 2-(4-bromophenyl)-2-diazoacetate	Bess, E. N D.; Guptill, M.; Davies, H. M. L.; Sigman, M. S.; <i>Chem. Sci.</i> 2015 , 6, 3057–3062.

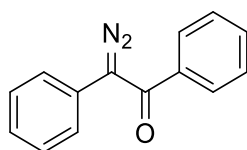
 11i	methyl 2-diazo-2-(4-nitrophenyl)acetate	Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A.S.C; Yu, W.-Y.; <i>Org. Lett.</i> 2010 , 3, 604–607.
 11j	methyl 2-diazo-2-(2-nitrophenyl)acetate	Munaretto, L. S.; Santos, C. Y. d.; Gallo, R. D. C.; Okada, Jr. C. Y.; Deflon, V. M.; Jurberg, I. D., <i>Org. Lett.</i> 2021 , 23, 9292–9296.
 11k	methyl 2-diazo-2-(4-methoxyphenyl)acetate	Davies, H. M. L.; Hansen, T.; Churchill, M. R., <i>J. Am. Chem. Soc.</i> 2000 , 122, 3063–3070.
 11l	methyl 2-diazo-2-(3-methoxyphenyl)acetate	Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A.S.C; Yu, W.-Y.; <i>Org. Lett.</i> 2010 , 3, 604–607.
 11m	methyl 2-(4-((tert-butoxycarbonyl)amino)phenyl)-2-diazoacetate	Xu, G.; Tang, S.; Shao, Y.; Sun, J., <i>Chem. Commun.</i> 2019 , 55, 9096-9099.
 11n	dimethyl 2-diazomalonate	Zhang, P.; Zeng, J.; Pan, P.; Zhang, X.-j.; Yan, M. <i>Org. Lett.</i> 2022 , 24, 2, 536–541.
 11o	methyl 2-diazoacetate	Searle, N. E. Ethyl Diazoacetate. <i>Org. Synth.</i> 1956 , 36, 25.
 11p	ethyl 2-diazoacetate	Searle, N. E. Ethyl Diazoacetate. <i>Org. Synth.</i> 1956 , 36, 25.
 11q	tert-butyl 2-diazoacetate	Nicewicz, D. A.; Breteche, G.; Johnson, J. S. <i>Org. Synth.</i> 2008 , 85, 278.

**26a**

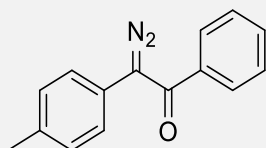
1-diazo-1-phenylpropan-2-one

Denton, J. R.; Davies, H. M. L., *Org. Lett.* **2009**, *11*, 4, 787–790.**26b**

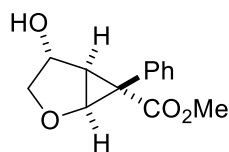
1-diazo-1-(4-methoxyphenyl)propan-2-one

Zeller, K.-P.; *Chem. Ber.* **1979**, *112*, 678-688.**26c**

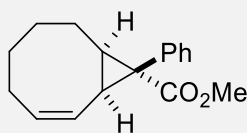
2-diazo-1,2-diphenylethan-1-one

Denton, J. R.; Davies, H. M. L., *Org. Lett.* **2009**, *11*, 4, 787–790.**26d**

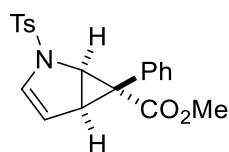
2-diazo-1-phenyl-2-(p-tolyl)ethan-1-one

Song, W.; Guo, J.; Stephan, D. W., *Org. Chem. Front.* **2023**, *10*, 1754-1758.**77**

methyl-4-hydroxy-6-phenyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate

Eckl, R. **2022**, *Dissertation*, University of Regensburg.**163**

methyl-9-phenylbicyclo[6.1.0]non-2-ene-9-carboxylate

Wurzer, N.; Klimczak, U.; Babl, T.; Fischer, S.; Angnes, R. A.; Kreutzer, D.; Pattanaik, A.; Rehbein, J.; Reiser, O. *ACS Catal.* **2021**, *11*, 12019-12028.**165**

methyl-6-phenyl-2-tosyl-2-azabicyclo[3.1.0]hex-3-ene-6-carboxylate

Eckl, R. **2022**, *Dissertation*, University of Regensburg.

3. Experimental Procedures

3.1. Synthesis of Cyclopropanes^e

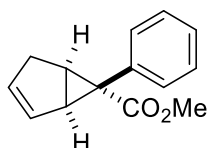
General Procedure GP-I:

After a modified literature procedure,^f freshly distilled cyclopentadiene (**21**, 5.0 equiv) and diazo compound (1.0 equiv) were dissolved in DCM (0.5 M) in an oven-dried Schlenk-flask equipped with a glass rod (see general information for further experimental details) at 0 °C. The reaction mixture was irradiated with blue-light ($h\nu = 455\text{nm}$) for 14 h and allowed to warm of up to room temperature. Then, the solvent was evaporated under reduced pressure and the crude product was purified by recrystallization, flash column chromatography or a washing step with pentane.

General Procedure GP-II:

After a modified literature procedure,^g a flame-dried two-neck round-bottom flask was charged with freshly distilled cyclopentadiene (**21**, 2.5 equiv) and $\text{Rh}_2(\text{OAc})_4$ (0.1 mol%) dissolved in dry DCM under nitrogen atmosphere. Within 2 h a solution of diazo compound (1.0 equiv) dissolved in dry DCM (0.2 – 0.5 M) was added dropwise *via* a syringe pump at 0 °C. After addition, the reaction mixture was stirred for another 12 h and allowed to warm of up to room temperature. The reaction mixture was filtered through basic Al_2O_3 , the solvent was evaporated under reduced pressure and the crude product was purified by recrystallization, flash column chromatography or a washing step with pentane.

methyl (1S*,5R*,6S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (25a**):**



Following the general procedure **GP-I** using cyclopentadiene (**21**, 1.24 g, 18.7 mmol, 5.0 equiv) and methyl 2-diazo-2-phenylacetate (**11a**, 660 mg, 3.75 mmol, 1.0 equiv)

^e Fischer, S.; Nguyen, T.-T. H.; Ratzenboeck, A.; Davies, H. M. L.; Reiser, O. *Org. Lett.* 2023, 25, 24, 4411–4415.

^f Jurberg, I. D.; Davies, H. M. L. *Chem. Sci.* **2018**, 9, 5112–5118.

^g Gratia, S.; Mosesohn, K.; Diver, S. T. *Org. Lett.* 2016, 18, 5320–5323.

dissolved in DCM (0.5 M) gave the title compound **25a** (680 mg, 3.43 mmol, 92%) as a colorless solid after recrystallization from ethanol. The yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 9.76 g, 148 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (20.0 mg, 59.0 μmol , 0.1 mol%) and methyl 2-diazo-2-phenylacetate (**11a**, 10.4 g, 59.0 mmol, 1.0 equiv) dissolved in dry DCM (0.5 M) under nitrogen atmosphere gave the title compound **25a** (9.90 g, 46.2 mmol, 78%) as a colorless solid after recrystallization from ethanol.

R_f = 0.57 (hexanes/ethyl acetate = 9/1, stained in vanillin)

M.p.: 109 – 110 °C.

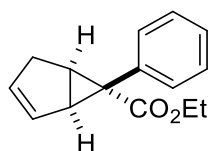
^1H NMR (400 MHz, CDCl_3): δ 7.35 – 7.18 (m, 3H), 7.16 – 7.03 (m, 2H), 5.75 (dq, J = 6.0, 1.9 Hz, 1H), 5.28 – 5.04 (m, 1H), 3.59 (s, 3H), 3.04 – 2.83 (m, 1H), 2.77 – 2.51 (m, 2H), 2.16 – 1.94 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.4, 133.1, 132.9, 132.8, 129.7, 127.6, 126.7, 52.4, 40.8, 37.8, 34.1, 32.4.

IR: $\nu[\text{cm}^{-1}]$ = 3042, 2952, 2907, 1700, 1599, 1498, 1431, 1361, 1320, 1245, 1057, 1021, 977, 936, 783, 753, 708.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_2$ [M^+]: 214.0988, found 214.0993.

ethyl (1S*,5R*,6S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (25b):



Following the general procedure **GP-I** using cyclopentadiene (**21**, 827 mg, 12.5 mmol, 5.0 equiv) and ethyl 2-diazo-2-phenylacetate (**11b**, 476 mg, 2.50 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25b** (517 mg, 2.26 mmol, 90%) as a yellow oil after washing with pentane.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 300 mg, 4.53 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (0.62 mg, 1.81 μmol , 0.1 mol%) and ethyl 2-diazo-2-phenylacetate

(**11b**, 345 mg, 1.81 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen atmosphere gave the title compound **25b** (340 mg, 1.49 mmol, 82%) as a yellow oil after a washing with pentane.

Method 3: A pressure-tube charged with a magnetic stir-bar was loaded with vinyl cyclopropane **25a** (72.0 mg, 0.34 mmol, 1.0 equiv) dissolved in EtOH (0.25 M) and *p*-toluenesulfonic acid monohydrate (639 mg, 3.36 mmol, 10 equiv). The reaction mixture was stirred for 1 h at 120 °C. Then, DCM (10 mL) and H₂O (10 mL) were added, and the phases were separated. The organic phase was washed with H₂O (2x10 mL), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1) to obtain the product **25b** (75.6 mg, 0.33 mmol, 99%) as yellow oil.

R_f = 0.62 (hexanes/ethyl acetate = 9/1, stained in vanillin).

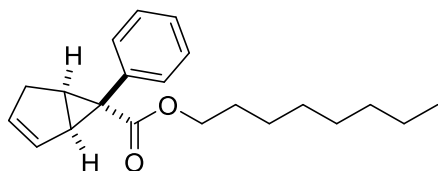
¹H NMR (400 MHz, CDCl₃): δ 7.31 – 7.18 (m, 3H), 7.15 – 7.03 (m, 2H), 5.80 – 5.70 (m, 1H), 5.20 (ddd, *J* = 5.6, 2.8, 1.5 Hz, 1H), 4.05 (qd, *J* = 7.1, 3.2 Hz, 2H), 2.92 (ddd, *J* = 6.7, 3.7, 1.6 Hz, 1H), 2.72 – 2.54 (m, 2H), 2.19 – 1.97 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 173.8, 133.2, 132.8, 132.7, 129.8, 127.5, 126.6, 60.9, 40.4, 38.0, 34.1, 32.1, 14.2.

IR: ν[cm⁻¹] = 3060, 3030, 2982, 2907, 1715, 1446, 1320, 1282, 1238, 1163, 1129, 1029, 749.

HRMS: (EI-MS) *m/z* calculated for C₁₅H₁₆O₂ [*M*⁺]: 228.1145, found 228.1148.

octyl (1*S**,5*R**,6*S**)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (**25c**)



Following the general procedure **GP-I** using cyclopentadiene (**21**, 367 mg, 5.56 mmol, 5.0 equiv) and octyl 2-diazo-2-phenylacetate (**11v**, 305 mg, 1.11 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25c** (320 mg, 1.02 mmol, 92%) as a

yellow oil after washing the crude product with pentane. The yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 1.51 g, 22.8 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (3.09 mg, 9.11 μmol , 0.1 mol%) and octyl 2-diazo-2-phenylacetate (**11c**, 2.50 g, 9.11 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen atmosphere gave the title compound **25c** (2.79 g, 8.93 mmol, 98%) as a yellow oil after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1).

R_f = 0.81 (hexanes/ethyl acetate = 5/1, stained in vanillin).

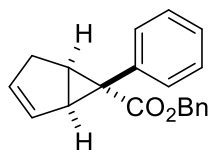
^1H NMR (400 MHz, CDCl_3): δ 7.26 – 7.15 (m, 3H), 7.14 – 7.04 (m, 2H), 5.75 (dq, J = 5.8, 2.0 Hz, 1H), 5.21 (dq, J = 5.6, 2.0 Hz, 1H), 4.02 – 3.92 (m, 2H), 2.91 (dp, J = 6.7, 2.3 Hz, 1H), 2.62 (dd, J = 4.4, 1.5 Hz, 2H), 2.09 (dq, J = 16.9, 2.3 Hz, 1H), 1.56 – 1.42 (m, 2H), 1.26 – 1.08 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.9, 133.3, 132.8, 132.7, 129.7, 127.5, 126.6, 65.0, 40.4, 38.1, 34.1, 32.0, 31.7, 29.2, 29.0, 28.5, 25.7, 22.7, 14.1.

IR: $\nu[\text{cm}^{-1}]$ = 3064, 3030, 2962, 2855, 1714, 1603, 1498, 1446, 1379, 1323, 1282, 1163, 1133, 1074, 1006, 983, 928, 857, 783, 746.

HRMS: (EI-MS) m/z calculated for $\text{C}_{21}\text{H}_{28}\text{O}_2$ [M^+]: 312.2084, found 312.2086.

Benzyl (1S*,5R*,6S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (25d):



Following the general procedure **GP-I** using cyclopentadiene (**21**, 445 mg, 6.74 mmol, 5.0 equiv) and benzyl 2-diazo-2-phenylacetate (**11d**, 340 mg, 1.35 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25d** (311 mg, 1.07 mmol, 80%) as yellow oil after washing the crude product with pentane.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 396 mg, 5.13 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (1.0 mg, 2.3 μmol , 0.1 mol%) and benzyl 2-diazo-2-phenylacetate (**11d**, 518 mg, 2.05 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen

atmosphere gave the title compound **25d** (579 mg, 2.00 mmol, 97%) as a yellow oil after washing the crude product with pentane.

R_f = 0.71 (hexanes/ethyl acetate = 3/1, stained in vanillin).

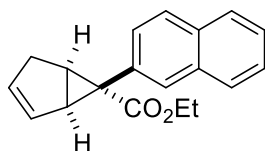
¹H NMR (400 MHz, CDCl₃): δ 7.33 – 7.20 (m, 6H), 7.13 (ddd, *J* = 7.4, 3.1, 1.6 Hz, 4H), 5.76 (dq, *J* = 5.5, 1.8 Hz, 1H), 5.21 (dq, *J* = 5.5, 2.0 Hz, 1H), 5.13 – 4.98 (m, 2H), 2.96 (dq, *J* = 5.6, 2.0 Hz, 1H), 2.72 – 2.52 (m, 2H), 2.10 (dq, *J* = 18.1, 2.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 173.6, 136.4, 133.0, 132.9, 132.8, 129.7, 128.4, 127.7, 127.6, 127.1, 126.7, 66.2, 40.7, 38.1, 34.1, 32.2.

IR: ν[cm⁻¹] = 3060, 3030, 2900, 1707, 1498, 1446, 1375, 1320, 1282, 1223, 1163, 1059, 1014, 973, 790, 734, 697.

HRMS: (EI-MS) *m/z* calculated for C₂₀H₁₈O₂ [*M*⁺]: 290.1301, found 290.1305.

ethyl (1*S,5*R**,6*S**)-6-(naphthalen-2-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25e):**



Following the general procedure **GP-I** using cyclopentadiene (**21**, 365 mg, 5.51 mmol, 5.0 equiv) and ethyl 2-diazo-2-(naphthalen-2-yl)acetate (**11e**, 265 mg, 1.10 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25e** (277 mg, 1.00 mmol, 90%) as colorless oil after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1).

Following the general procedure **GP-II** using cyclopentadiene (**21**, 168 mg, 2.55 mmol, 2.5 equiv), Rh₂(OAc)₄ (1.0 mg, 2.3 μmol, 0.2 mol%) and ethyl 2-diazo-2-(naphthalen-2-yl)acetate (**11e**, 245 mg, 1.02 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen atmosphere gave the title compound **25e** (257 mg, 0.92 mmol, 90%) as a colorless oil after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1).

R_f = 0.62 (hexanes/ethyl acetate = 9/1, stained in vanillin).

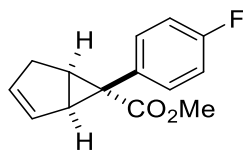
^1H NMR (400 MHz, CDCl_3): δ 7.93 – 7.73 (m, 3H), 7.70 – 7.60 (m, 1H), 7.55 – 7.38 (m, 2H), 7.30 (dd, J = 8.4, 1.8 Hz, 1H), 5.86 (dq, J = 5.6, 2.1 Hz, 1H), 5.18 (dtd, J = 5.5, 2.2, 1.3 Hz, 1H), 4.11 (qd, J = 7.1, 0.6 Hz, 2H), 3.11 – 3.01 (m, 1H), 2.83 – 2.61 (m, 2H), 2.20 (dq, J = 18.0, 2.3 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.9, 133.1, 132.9, 132.4, 131.9, 131.0, 130.9, 129.7, 127.8, 127.7, 127.1, 125.7, 125.6, 61.0, 40.8, 38.1, 34.2, 32.3, 14.3.

IR: $\nu[\text{cm}^{-1}]$ = 3056, 2982, 2904, 2251, 1703, 1603, 1506, 1368, 1282, 1241, 1163, 1115, 1059, 992, 906, 828, 727.

HRMS: (EI-MS) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{O}_2$ [M^+]: 278.1301, found 278.1295.

methyl (1S*,5R*,6S*)-6-(4-fluorophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25f):



Following the general procedure **GP-I** using cyclopentadiene (**21**, 1.02 g, 15.5 mmol, 5.0 equiv) and methyl 2-diazo-2-(4-fluorophenyl)acetate (**11f**, 602 mg, 3.10 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25f** (711 mg, 3.06 mmol, 98%) as yellow oil after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1).

Following the general procedure **GP-II** using cyclopentadiene (**21**, 624 mg, 9.44 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (1.28 mg, 3.78 μmol , 0.1 mol%) and methyl 2-diazo-2-(4-fluorophenyl)acetate (**11f**, 733 mg, 3.78 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen atmosphere gave the title compound **25f** (756 mg, 3.26 mmol, 86%) as a slightly yellow oil. The yield was determined from ^1H -NMR using fumaronitrile as internal standard.

Due to relaxation time, ^1H -NMR shows broadened signals and in the ^{13}C -NMR signals are missing. Structure was verified by the subsequent reaction (see compound 122f).

R_f = 0.76 (hexanes/ethyl acetate = 9/1, stained in vanillin).

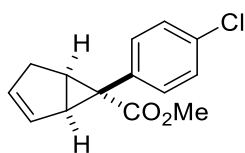
^1H NMR (400 MHz, CDCl_3): δ 7.25 – 7.16 (m, 1H), 7.12 – 6.79 (m, 3H), 5.77 (dp, J = 5.9, 2.0 Hz, 1H), 5.24 (s, 1H), 3.60 (s, 3H), 2.98 (d, J = 11.0 Hz, 1H), 2.77 – 2.59 (m, 2H), 2.37 – 1.84 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.6, 129.0, 128.9, 123.2, 123.2, 115.5, 115.3, 52.5, 34.2.

IR: $\nu[\text{cm}^{-1}]$ = 3064, 2952, 2907, 2840, 1718, 1495, 1454, 1327, 1282, 1241, 1163, 1103, 977, 924, 816, 760, 716.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{F}$ [M^+]: 232.0894, found 232.0899.

methyl (1S*,5R*,6S*)-6-(4-chlorophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25g):



Following the general procedure **GP-I** using cyclopentadiene (**21**, 596 mg, 9.02 mmol, 5.0 equiv) and methyl 2-(4-chlorophenyl)-2-diazoacetate (**11g**, 380 mg, 1.80 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25g** (360 mg, 1.45 mmol, 80%) as yellow solid after washing the crude product with pentane.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 332 mg, 5.02 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (0.70 mg, 2.01 μmol , 0.1 mol%) and ethyl methyl 2-(4-chlorophenyl)-2-diazoacetate (**11g**, 423 mg, 2.01 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen atmosphere gave the title compound **25g** (462 mg, 1.86 mmol, 92%) as a colorless solid after washing the crude product with pentane.

R_f = 0.59 (hexanes/ethyl acetate = 9/1, stained in vanillin).

M.p.: 110 – 114 $^\circ\text{C}$.

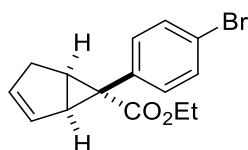
^1H NMR (400 MHz, CDCl_3): δ 7.25 – 7.20 (m, 2H), 7.14 – 6.96 (m, 2H), 5.73 (dt, J = 5.8, 2.0 Hz, 1H), 5.32 – 5.16 (m, 1H), 3.59 (s, 3H), 3.01 – 2.85 (m, 1H), 2.75 – 2.54 (m, 2H), 2.01 (dt, J = 18.0, 2.3 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.0, 134.2, 133.0, 132.6, 131.6, 129.5, 127.9, 52.4, 40.8, 37.2, 34.1, 32.4.

IR: $\nu[\text{cm}^{-1}]$ = 3060, 2952, 2907, 1715, 1495, 1435, 1323, 1282, 1163, 1088, 1059, 1014.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{Cl}$ [M^+]: 248.0599, found 248.0602.

ethyl (1S*,5R*,6S*)-6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25h)



Following the general procedure **GP-I** using cyclopentadiene (**21**, 268 mg, 4.05 mmol, 5.0 equiv) and ethyl 2-(4-bromophenyl)-2-diazoacetate (**11h**, 218 mg, 0.81 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25h** (208 mg, 0.74 mmol, 92%) as yellow oil after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 10/1).

Following the general procedure **GP-II** using cyclopentadiene (**21**, 123 mg, 1.86 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (0.40 mg, 7.3 μmol , 0.1 mol%) and ethyl 2-(4-bromophenyl)-2-diazoacetate (**11h**, 200 mg, 0.74 mmol, 1.0 equiv) dissolved in dry DCM (0.5 M) under nitrogen atmosphere gave the title compound **25h** (208 mg, 0.68 mmol, 91%) as a slightly yellow oil after washing the crude product with pentane.

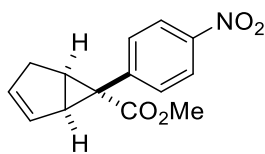
R_f = 0.51 (hexanes/ethyl acetate = 9/1, stained in vanillin).

^1H NMR (400 MHz, CDCl_3): δ 7.44 – 7.31 (m, 2H), 7.05 – 6.91 (m, 2H), 5.72 (dt, J = 5.9, 2.1 Hz, 1H), 5.22 (dtd, J = 5.6, 2.2, 1.3 Hz, 1H), 4.05 (qd, J = 7.1, 2.7 Hz, 2H), 2.91 (dt, J = 6.5, 1.7 Hz, 1H), 2.71 – 2.56 (m, 2H), 2.01 (dq, J = 18.3, 2.3 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.3, 134.5, 133.0, 132.4, 130.8, 129.5, 120.7, 61.1, 40.4, 37.5, 34.1, 32.1, 14.2.

IR: $\nu[\text{cm}^{-1}]$ = 3060, 2982, 2904, 1717, 1595, 1491, 1394, 1368, 1320, 1234, 1129, 1100, 1070, 1010, 924, 850, 749.

HRMS: (EI-MS) m/z calculated for $\text{C}_{15}\text{H}_{15}\text{O}_2\text{Br}$ [M^+]: 306.0250, found 306.0251.

methyl (1S*,5R*,6S*)-6-(4-nitrophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25i):

Following the general procedure **GP-I** using cyclopentadiene (**21**, 217 mg, 3.28 mmol, 5.0 equiv) and methyl 2-diazo-2-(4-nitrophenyl)acetate (**11i**, 145 mg, 0.66 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25i** (55.0 mg, 0.21 mmol, 32%) as an orange solid after washing the crude product with pentane. The yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 1.50 g, 22.7 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (3.08 mg, 9.09 μmol , 0.1 mol%) and methyl 2-diazo-2-(4-nitrophenyl)acetate (**11i**, 2.01 g, 9.09 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen atmosphere gave the title compound **25i** (2.22 g, 8.56 mmol, 94%) as an orange solid after washing the crude product with pentane.

R_f = 0.42 (hexanes/ethyl acetate = 9/1, stained in vanillin).

M.p.: 118 – 122 °C.

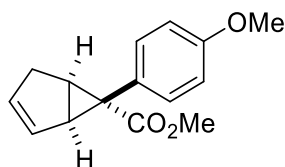
^1H NMR (400 MHz, CDCl_3): δ 8.33 – 7.95 (m, 2H), 7.39 – 7.15 (m, 2H), 5.77 (dq, J = 5.9, 1.9 Hz, 1H), 5.21 (dq, J = 5.5, 2.0 Hz, 1H), 3.59 (s, 3H), 3.00 (dt, J = 5.6, 2.0 Hz, 1H), 2.79 – 2.62 (m, 2H), 2.12 – 1.89 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.9, 146.8, 141.1, 133.8, 133.1, 129.5, 122.9, 52.6, 40.8, 37.5, 34.1, 32.6.

IR: $\nu[\text{cm}^{-1}]$ = 3064, 2952, 2907, 2844, 1718, 1603, 1521, 1435, 1349, 1282, 1241, 1163, 1059, 1014, 932, 857, 794, 749

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 260.0920, found 260.0917.

methyl (1S*,5R*,6S*)-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25k)



Following the general procedure **GP-I** using cyclopentadiene (**21**, 409 mg, 6.18 mmol, 5.0 equiv) and methyl 2-diazo-2-(4-methoxyphenyl)acetate (**11k**, 255 mg, 1.24 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25k** (269 mg, 1.21 mmol, 98%) as a yellow solid after washing the crude product with pentane.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 187 mg, 2.82 mmol, 2.5 equiv), Rh₂(OAc)₄ (0.40 mg, 11.3 μmol, 0.1 mol%) and methyl 2-diazo-2-(4-methoxyphenyl)acetate (**11k**, 233 mg, 1.13 mmol, 1.0 equiv) dissolved in dry DCM (0.2 M) under nitrogen atmosphere gave the title compound **25k** (264 mg, 1.13 mmol, 96%) as a yellow solid after washing the crude product with pentane.

Experimental data matched with those previous reported.^h

R_f = 0.44 (hexanes/ethyl acetate = 9/1, stained in vanillin).

¹H NMR (400 MHz, CDCl₃): δ 7.06 – 6.97 (m, 2H), 6.84 – 6.75 (m, 2H), 5.74 (dq, J = 5.8, 2.0 Hz, 1H), 5.27 – 5.17 (m, 1H), 3.77 (s, 3H), 3.58 (s, 3H), 2.90 (ddt, J = 6.8, 2.6, 1.5 Hz, 1H), 2.68 – 2.57 (m, 2H), 2.14 – 1.98 (m, 1H).

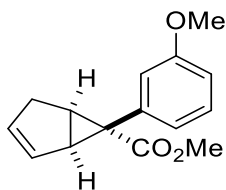
¹³C NMR (101 MHz, CDCl₃): δ 174.7, 158.3, 133.8, 132.9, 129.6, 125.0, 113.1, 55.1, 52.4, 40.9, 37.1, 34.1, 32.4.

IR: ν[cm⁻¹] = 3060, 2996, 2952, 2836, 1711, 1610, 1513, 1461, 1431, 1282, 1234, 1163, 1129, 1033, 977, 854, 731, 708

HRMS: (EI-MS) m/z calculated for C₁₅H₁₆O₃ [M⁺]: 244.1094, found 244.1089.

^h Pelphey, P.; Hansen, J.; Davies, H. M. L. *Chem. Sci.* **2010**, *1*, 254.

methyl (1S*,5R*,6S*)-6-(3-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25l):



Following the general procedure **GP-I** using cyclopentadiene (**21**, 519 mg, 7.86 mmol, 5.0 equiv) and methyl 2-diazo-2-(3-methoxyphenyl)acetate (**11l**, 324 mg, 1.57 mmol, 1.0 equiv) dissolved in DCM (0.5 M) gave the title compound **25l** (362 mg, 1.48 mmol, 94%) as yellow solid after washing the crude product with pentane.

Following the general procedure **GP-II** using cyclopentadiene (**21**, 4.85 g, 73.4 mmol, 2.5 equiv), Rh₂(OAc)₄ (9.95 mg, 29.3 μmol, 0.1 mol%) and methyl 2-diazo-2-(3-methoxyphenyl)acetate (**11l**, 6.05 g, 29.3 mmol, 1.0 equiv) dissolved in dry DCM (0.5 M) under nitrogen atmosphere gave the title compound **25l** (6.87 g, 28.1 mmol, 96%) as a slightly yellow solid after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1).

R_f = 0.53 (hexanes/ethyl acetate = 5/1, stained in vanillin).

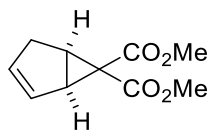
M.p.: 106 – 108 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.21 – 7.14 (m, 1H), 6.77 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.72 – 6.61 (m, 2H), 5.73 (dq, J = 5.6, 1.8 Hz, 1H), 5.24 (dq, J = 4.4, 1.5, 1.0 Hz, 1H), 3.78 (s, 3H), 3.59 (s, 3H), 2.99 – 2.84 (m, 1H), 2.70 – 2.57 (m, 2H), 2.25 – 2.07 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 174.3, 158.9, 134.6, 132.8, 129.6, 128.4, 125.4, 119.0, 111.9, 55.1, 52.4, 40.9, 37.8, 34.1, 32.4.

IR: ν[cm⁻¹] = 3060, 3001, 2952, 2907, 2837, 1715, 1610, 1491, 1431, 1327, 1286, 1241, 1163, 1126, 1044, 977, 932, 861, 828, 790, 760, 701

HRMS: (EI-MS) m/z calculated for C₁₅H₁₆O₃ [M⁺]: 244.1094, found 244.1097.

dimethyl (1S*,5R*)-bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylate (25n):

Following the general procedure **GP-II** using cyclopentadiene (**21**, 2.58 g, 39.0 mmol, 2.5 equiv), $\text{Rh}_2(\text{OAc})_4$ (5.92 mg, 15.6 μmol , 0.1 mol%) and dimethyl 2-diazomalonate (**11n**, 2.57 g, 15.6 mmol, 1.0 equiv) dissolved in dry DCM (0.5 M) under nitrogen atmosphere gave the title compound **25n** (2.96 g, 15.1 mmol, 97%) as a slightly yellow oil after purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

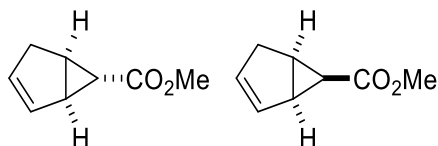
R_f = 0.68 (hexanes/ethyl acetate = 3/1, stained in vanillin).

^1H NMR (400 MHz, CDCl_3): δ 5.73 (dq, J = 5.9, 2.1 Hz, 1H), 5.60 – 5.52 (m, 1H), 3.65 (s, 3H), 3.57 (s, 3H), 2.78 – 2.71 (m, 1H), 2.70 – 2.58 (m, 2H), 2.38 (tt, J = 6.3, 1.2 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 170.3, 166.5, 132.2, 129.5, 52.7, 52.2, 39.4, 38.7, 34.4, 31.6.

IR: $\nu[\text{cm}^{-1}]$ = 3064, 3001, 2952, 2907, 2844, 1722, 1435, 1316, 1249, 1199, 1156, 1081, 1029, 992, 924, 857, 820, 787, 712.

HRMS: (EI-MS) m/z calculated for $\text{C}_{10}\text{H}_{12}\text{O}_4$ [M^+]: 196.0730, found 196.0734.

methyl (1S*,5R*,6S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (25o) and methyl (1S*,5R*,6R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (25o-a):

Following the general procedure **GP-II** using cyclopentadiene (**21**, 5.71 g, 86.4 mmol, 2.0 equiv), $\text{Rh}_2(\text{OAc})_4$ (14.5 mg, 42.6 μmol , 0.1 mol%) and methyl 2-diazoacetate (**11o**, 45.5 g, 9.5 wt% in DCM, 43.2 mmol, 1.0 equiv) dissolved in dry DCM (0.5 M) under nitrogen atmosphere gave a mixture of the title compounds **25o** and **25o-a** (3.08 g, 22.4 mmol, 52%, dr = 4.0/1) as a colorless oil after purification by flash column

chromatography (hexanes/ethyl acetate = 100/1 to 10/1). When the solvent was evaporated under reduced pressure, the H₂O bath temperature must not exceed 30 °C.

R_f (**25o**) = 0.67 (hexanes/ethyl acetate = 9/1, stained in vanillin) and **R_f** (**25o-a**) = 0.64 (hexanes/ethyl acetate = 9/1, stained in vanillin).

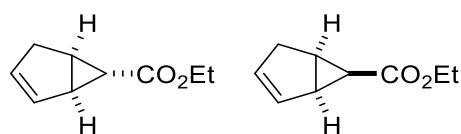
¹H NMR (400 MHz, CDCl₃): δ 5.92 (dq, J = 5.9, 2.0 Hz, 1H), 5.70^{minor} (ddq, J = 5.1, 1.8, 1.0 Hz, 0.26H), 5.64^{minor} (dt, J = 5.5, 2.0 Hz, 0.26H), 5.57 – 5.51 (m, 1H), 3.66 (s, 3H), 3.58^{minor} (s, 0.78H), 2.84 – 2.75^{minor} (m, 0.27H), 2.75 – 2.64 (m, 1H), 2.62 – 2.50^{minor} (m, 0.26H), 2.49 – 2.38 (*signals are overlapping*, m, 2.27H), 2.21 (dt, J = 6.4, 5.2, 1.7 Hz, 1H), 2.04 – 1.95^{minor} (m, 0.26H), 1.80^{minor} (tt, J = 8.3, 0.7 Hz, 0.26H), 1.03 – 0.94 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 173.9, 170.0, 132.8, 132.1, 130.5, 126.8, 51.6, 51.2, 36.2, 34.5, 33.0, 31.6, 30.2, 26.2, 23.0, 22.2.

IR: ν[cm⁻¹] = 3064, 2952, 2907, 2840, 1722, 1595, 1387, 1439, 1353, 1301, 1267, 1162, 1043, 969, 920, 883, 838, 775, 723, 693.

HRMS: (EI-MS) acquisition time (minor product): 4.0023-4.0356 min; m/z calculated for C₈H₁₀O₂ [M⁺]: 138.0675, found 138.0673; acquisition time (major product): 4.1355-4.1721 min; m/z calculated for C₈H₁₀O₂ [M⁺]: 138.0675, found 138.0674.

ethyl (1S*,5R*,6S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (25p) and ethyl (1S*,5R*,6R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (25p-a):



Following the general procedure **GP-II** using cyclopentadiene (**21**, 3.93 g, 59.4 mmol, 2.5 equiv), Rh₂(OAc)₄ (10.5 mg, 23.8 μmol, 0.1 mol%) and ethyl 2-diazoacetate (**11p**, 29.0 g, 9.35 wt% in DCM, 23.8 mmol, 1.0 equiv) dissolved in dry DCM (0.5 M) under nitrogen atmosphere gave a mixture of the title compounds **25p** and **25p-a** as a yellow oil. After purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 10/1) two fractions with different product mixture ratios were obtained. When the solvent was evaporated under reduced pressure, the H₂O bath temperature must not exceed 30 °C. Compound decomposes after few days.

Fraction 1: 1.80 g, 11.8 mmol, 50%, *dr*: (25p /25p-a) = 8.0/1.

Fraction 2: 0.44 mg, 2.90 mmol, 12%, *dr*: (25p /25p-a) = 0.67/1.

Overall yield: 2.24 g, 14.7 mmol, 62%, *dr*: (25p /25p-a) = 3.8/1.

R_f (1o) = 0.70 (hexanes/ethyl acetate = 5/1, stained in vanillin) and **R_f (25p-a)** = 0.67 (hexanes/ethyl acetate = 5/1, stained in vanillin).

Fraction 1: ¹H NMR (400 MHz, CDCl₃): δ 5.92 (dq, *J* = 6.0, 1.9 Hz, 1H), 5.73 – 5.60^{minor} (m, 0.23H), 5.59 – 5.47 (m, 1H), 4.14 – 4.01 (*signals are overlapping*, m, 2.28H), 2.85 – 2.75^{minor} (m, 0.13H), 2.77 – 2.62 (m, 1H), 2.61 – 2.51^{minor} (m, 0.13H), 2.52 – 2.39 (m, 2H), 2.26 – 2.15 (m, 1H), 1.97^{minor} (td, *J* = 7.4, 6.1 Hz, 0.13H), 1.79^{minor} (ddd, *J* = 8.4, 7.7, 0.8 Hz, 0.12H), 1.30 – 1.18 (*signals are overlapping*, m, 3.52H), 0.97 (dd, *J* = 3.2, 2.1 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 173.4, 132.6, 132.1, 130.4, 127.0, 60.3, 59.9, 36.2, 34.4, 33.0, 31.3, 30.4, 26.1, 23.2, 22.0, 14.3.

IR: ν[cm⁻¹] = 3064, 2982, 2907, 2840, 1718, 1446, 1383, 1301, 1260, 1156, 1044, 988, 921, 865, 831, 779.

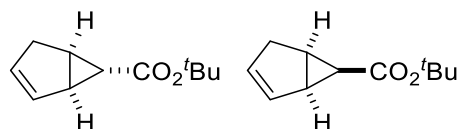
Fraction 2: ¹H NMR (400 MHz, CDCl₃): 5.93 (dq, *J* = 6.1, 2.0 Hz, 0.67H), 5.73 – 5.62 (m, 2H), 5.54 (dq, *J* = 5.4, 2.1 Hz, 0.66H), 4.15 – 3.97 (*signals are overlapping*, m, 3.36H), 2.80 (dq, *J* = 18.2, 2.0, 1.0 Hz, 1H), 2.73 – 2.65 (m, 0.68H), 2.56 (ddtd, *J* = 18.3, 7.3, 1.9, 0.9 Hz, 1H), 2.48 – 2.39 (*signals are overlapping*, m, 2.33H), 2.20 (dtd, *J* = 6.8, 5.3, 4.4, 2.5 Hz, 0.66H), 2.02 – 1.93 (m, 1H), 1.79 (ddd, *J* = 8.4, 7.7, 0.8 Hz, 1H), 1.29 – 1.16 (*signals are overlapping*, m, 5.13H), 0.97 (dd, *J* = 3.2, 2.1 Hz, 0.66H).

¹³C NMR (101 MHz, CDCl₃): δ 173.4, 169.6, 132.6, 132.1, 130.4, 127.0, 60.3, 59.9, 36.2, 34.4, 33.0, 31.4, 30.4, 26.1, 23.3, 22.0, 14.3.

IR: ν[cm⁻¹] = 3064, 2982, 2907, 2840, 1722, 1406, 135, 1264, 1178, 1137, 1036, 992, 924, 865, 775, 697.

HRMS: (EI-MS) acquisition time (major product): 4.5046 – 4.5279 min; *m/z* calculated for C₉H₁₂O₂ [M⁺]: 152.0832, found 152.0835; acquisition time (minor product): 4.6377 – 4.6610 min; *m/z* calculated for C₉H₁₂O₂ [M⁺]: 152.0832, found 152.0834.

tert-butyl (1S*,5R*,6S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (25q) and tert-butyl (1S*,5R*,6R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (25q-a):



Following the general procedure **GP-II** using cyclopentadiene (**21**, 1.98 g, 30.0 mmol, 2.5 equiv), Rh₂(OAc)₄ (5.30 mg, 12.0 μmol, 0.1 mol%) and *tert*-butyl 2-diazoacetate (**11q**, 16.5 g, 10.4 wt% in DCM, 12.0 mmol, 1.0 equiv) dissolved in dry DCM (0.5 M) under nitrogen atmosphere gave a mixture of the title compounds **25q** and **25q-a** (1.21 g, 6.71 mmol, 56%, *dr* = 5.0/1) as a colorless oil after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 20/1). The diastereomeric ratio was determined from the crude ¹H-NMR. After purification by flash column chromatography the ratio changed to *dr* = 2.0/1. After two more purification steps by flash column chromatography, we were able to obtain a fraction with 86% purity of compound **25q** (determined from ¹H-NMR using fumaronitrile as internal standard), which was further used for the endocyclic ring-opening reaction to obtain **122o**.

R_f (**25q**) = 0.71 (hexanes/ethyl acetate = 9/1, stained in KMnO₄) and **R_f** (**25q-a**) = 0.69 (hexanes/ethyl acetate = 9/1, stained in KMnO₄).

¹H NMR (400 MHz, CDCl₃): δ 5.92 – 5.87 (m, 1H), 5.68 – 5.60^{minor} (m, 0.87H), 5.53 – 5.46 (m, 1H), 2.80 – 2.71^{minor} (m, 0.45H), 2.70 – 2.61 (m, 1H), 2.56 – 2.49^{minor} (m, 0.45H), 2.45 – 2.30 (*signals are overlapping*, m, 2.47H), 2.11 (td, *J* = 6.6, 3.1 Hz, 1H), 1.88^{minor} (q, *J* = 7.0 Hz, 0.44H), 1.73^{minor} (q, *J* = 8.3 Hz, 0.48H), 1.42 (s, 9H), 1.37^{minor} (s, 4.09H), 0.87 (t, *J* = 2.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 172.7, 169.0, 132.2, 132.0, 130.2, 127.6, 80.1, 79.9, 36.1, 34.1, 32.9, 31.4, 30.8, 28.2, 28.2, 25.7, 24.6, 21.6.

IR: ν[cm⁻¹] = 3064, 2978, 2907, 2840, 1715, 1390, 1305, 1275, 1144, 1074, 1040, 921, 831, 768, 727, 697.

HRMS: (EI-MS) acquisition time (minor product): 4.4518-4.4618 min; *m/z* calculated for C₁₁H₁₆O₂ [*M*⁺]: 180.1145, found 180.1149; acquisition time (major product): 4.5551-4.5717 min; *m/z* calculated for C₁₁H₁₆O₂ [*M*⁺]: 180.1145, found 180.1146.

3.2. Asymmetric Cyclopropanationⁱ

General Procedure GP-III: Synthesis of diazoacetates:

To a flame dried round-bottom flask charged with a magnetic stir-bar, was added corresponding trichloroethyl-phenyl acetate compound (1.0 equiv), *o*-NBSA (1.5 equiv) and anhydrous MeCN (0.3 M). The mixture was purged with N₂ for 10 min, sealed topped with a N₂-balloon and cooled to 0 °C via an ice/H₂O bath. Then, DBU (4.0 equiv) was added slowly to the stirred reaction mixture at 0 °C and stirred for another 1 h at 0 °C. The solvent was then removed under reduced pressure and the crude product was purified by flash column chromatography.

General Procedure GP-IV: Asymmetric Cyclopropanation of Cyclopentadiene (21):

Caution: All diazoacetates were used carefully due to their potentially explosive behavior. It is recommended to avoid heating when using these compounds and to run the reactions behind a protective shield.^j

Prior to the reaction, 4Å MS was activated by heating a flame-dried round-bottom flask containing

4Å MS *in vacuo* for over 3 hours. The activated 4Å MS was placed and stored into a >150 °C oven. When activated 4Å MS is required, the stored activated 4Å MS is transferred into a vessel and flame-dried *in vacuo*. The activated 4Å MS is cooled *in vacuo* and ready to use.

Prior to the reaction, activated 4Å MS was placed into a flame-dried vial containing stock solution of HFIP. The vial was capped with a rubber septum and sparged with N₂ gas for over 15 minutes. After the vial was topped with a N₂ balloon, it was ready to use.

Prior to the reaction, SPS-grade DCM was distilled over CaH using a short-path distillation apparatus into a flame-dried collecting round-bottom flask containing activated 4Å MS. The dry distilled SPS-grade DCM was sparged with N₂ gas for over 15 minutes. After the flask was topped with a N₂ balloon, it was ready to use.

ⁱ The “Asymmetric Cyclopropanation of Cyclopentadiene” chapter is part of the dissertation of Terrence-Thang H. Nguyen from Emory University and co-published in Fischer, S.; Nguyen, T.-T. H.; Ratzenboeck, A.; Davies, H. M. L.; Reiser, O. *Org. Lett.* **2023**, 25, 4411–4415.

^j Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. *Organic process research & development* **2020**, 24, 67–84.

Prior to the reaction, a flame-dried 10 mL volumetric flask containing 4.0 mg of $\text{Rh}_2(\text{R-}p\text{-PhTPCP})_4$ was capped with a septum and backed with N_2 three times. The flask was topped with an N_2 balloon. The dirhodium catalyst was dissolved with 10 mL N_2 -sparged, dry distilled SPS-grade DCM. 2.0 mL of this stock solution is transferred into the reaction (1.00 mmol scale) to equate to 0.05 mol% catalyst loading.

When running the reaction, to a flame-dried 20 mL vial containing activated 4Å MS (2.0 g activated 4Å MS per 1.0 mmol of diazo) was added: donor-acceptor diazo compound (1.0 mmol, 1.0 equiv). The vessel was then backfilled with N_2 three times and then topped with an N_2 balloon. Subsequently, neat, N_2 -sparged, dry distilled SPS-grade DCM (0.06 M), distilled cyclopenta-1,3-diene (**21**, 2.0 mmol, 2.0 equiv) and N_2 -sparged 1,1,1,3,3,3-hexafluoropropan-2-ol (10 mmol, 10 equiv) was added to the mixture and allowed to stir at 25 °C for 10 minutes. Stock solution of $\text{Rh}_2(\text{R-}p\text{-PhTPCP})_4$ (2.0 mL, 0.5 μmol , 0.05 mol% loading) was added to the reaction vessel in one portion. The reaction mixture was stirred for 18 h at 25 °C and then filtered through a packed-celite frit *in vacuo* with DCM. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/diethyl ether, Biotage Isolera Four Flash Chromatography System was used; 0% for 5 CV to 0 - 100% for 5 CV to 100% for 5 CV; 25 g Sfär DLV columns; 100 mL/min flowrate; detector set to 210 nm & 254 nm absorbance; SNAP KP-Sil 100 g setting) unless other conditions are stated otherwise. The collected fractions were concentrated *in vacuo* to afford desired cyclopropanated compound.

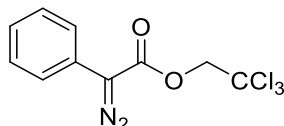
General Procedure GP-V: Transesterification

To a vial was added TCE-cyclopropane compound (1.0 equiv), zinc dust (<10 μm particle size, 5.0 equiv to 10 equiv), acetic acid (0.1 M, 1.0 equiv) open to air *via* a vent-needle. The mixture was stirred vigorously overnight with a vent-needle. The suspension was then diluted with H_2O (150 mL) and EtOAc (150 mL). The bilayer was then extracted with EtOAc (3x150 mL), organic layers combined & dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure to obtain carboxylic acid cyclopropane, which was subjected to *O*-alkylation without further purification.

To a flame-dried 20 mL vial was added carboxylic acid cyclopropane (1.0 equiv), potassium carbonate (1.5 to 5.0 equiv), DMF (1.0 equiv, 0.25 to 1.00 M), and iodomethane (1.5 to 5.0 equiv). The mixture was stirred overnight at ambient temperature.

The solution was then diluted with H₂O (150 mL) and EtOAc (150 mL), extracted with EtOAc (3x 150 mL), the organic layers were combined, dried over MgSO₄, filtered and the crude product was purified by flash column chromatography.

2,2,2-trichloroethyl 2-diazo-2-phenylacetate (29a):



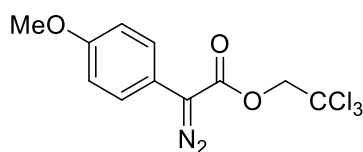
Following general procedure **GP-III** using 2,2,2-trichloroethyl 2-phenylacetate (2.11 g, 7.9 mmol, 1.0 equiv), *o*-NBSA (2.70 g, 11.8 mmol, 1.5 equiv), anhydrous MeCN (0.3 M) and DBU (4.81 g, 31.6 mmol, 4.0 equiv) gave the title compound **29a** (2.30 g, 7.8 mmol, 99%) as orange solid after purification by flash column chromatography (gradient 0 - 100% diethyl ether; 100 g Biotage Sfär DLV column; flow rate 100 mL/min; product elutes at 0% ether).

¹H-NMR and IR analysis is in good agreement with literature precedent.^k

¹H NMR (600 MHz, CDCl₃) δ 7.52 – 7.49 (m, 2H), 7.45 – 7.38 (m, 2H), 7.25 – 7.21 (m, 1H), 4.92 (s, 2H).

IR: ν[cm⁻¹] = 2953, 2090, 1709, 1598, 1498, 1448, 1374, 1334, 1285, 1239, 1137, 1084, 1048, 1029, 925, 821, 783, 752, 715, 689, 668, 577, 506, 494, 471, 445, 435, 421, 404.

2,2,2-trichloroethyl 2-diazo-2-(4-methoxyphenyl)acetate (29k)



Following general procedure **GP-III** using 2,2,2-trichloroethyl 2-(4-methoxyphenyl)acetate (3.00 g, 10 mmol, 1.0 equiv), *o*-NBSA (3.40 g, 15 mmol, 1.5 equiv), anhydrous MeCN (0.3 M) and DBU (6.10 g, 40 mmol, 4.0 equiv) gave the title compound **6i** (2.50 g, 7.7 mmol, 77%) as orange solid after purification by flash column

^k Fu, L.; Mighion, J. D.; Voight, E. A.; Davies, H. M. L. *Chem. Eur. J.* **2017**, 23, 3272–3275.

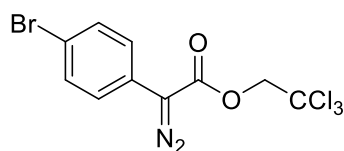
chromatography (gradient 0 - 100% diethyl ether; 100 g Biotage Sfär DLV column; flow rate 100 mL/min; product elutes at 0% ether).

^1H -NMR and IR analysis is in good agreement with literature precedent.¹

^1H NMR (600 MHz, CDCl_3) δ 7.43 – 7.39 (m, 2H), 6.99 – 6.95 (m, 2H), 4.90 (s, 2H), 3.82 (s, 3H).

IR: $\nu[\text{cm}^{-1}]$ = 3004, 2935, 2094, 1694, 1608, 1512, 1459, 1443, 1380, 1342, 1296, 1255, 1237, 1187, 1138, 1086, 1032, 924, 834, 796, 772, 729, 714, 639, 614, 580, 529, 512, 450, 442, 434, 419, 402.

2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**29r**)



Following general procedure **GP-III** using 2,2,2-trichloroethyl 2-(4-bromophenyl)acetate (3.50 g, 10 mmol, 1.0 equiv), *o*-NBSA (3.40 g, 15 mmol, 1.5 equiv), anhydrous MeCN (0.3 M) and DBU (6.10 g, 40 mmol, 4.0 equiv) gave the title compound **29r** (3.00 g, 8.0 mmol, 80%) as orange solid after purification by flash column chromatography (gradient 0 - 100% diethyl ether; 100 g Biotage Sfär DLV column; flow rate 100 mL/min; product elutes at 0% ether).

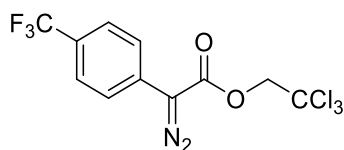
^1H -NMR and IR analysis is in good agreement with literature precedent.^m

^1H NMR (600 MHz, CDCl_3) δ 7.55 – 7.51 (m, 2H), 7.40 – 7.37 (m, 2H), 4.92 – 4.91 (m, 2H).

IR: $\nu[\text{cm}^{-1}]$ = 2954, 2093, 1715, 1490, 1374, 1341, 1276, 1239, 1141, 1084, 1044, 1007, 926, 823, 785, 730, 717, 578, 522, 492, 433, 411, 401.

¹ Bess, E. N.; Guptill, D. M.; Davies, H. M. L.; Sigman, M. S. *Chem. Sci.* **2015**, 6, 3057–3062.

^m Bess, E. N.; Guptill, D. M.; Davies, H. M. L.; Sigman, M. S. *Chem. Sci.* **2015**, 6, 3057–3062.

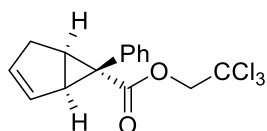
2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (29s)

Following general procedure **GP-III** using 2,2,2-trichloroethyl 2-(4-(trifluoromethyl)phenyl)acetate (3.40 g, 10 mmol, 1.0 equiv), *o*-NBSA (3.40 g, 15 mmol, 1.5 equiv), anhydrous MeCN (0.3 M) and DBU (6.10 g, 40 mmol, 4.0 equiv) gave the title compound **6r** (3.00 g, 8.2 mmol, 82%) as orange solid after purification by flash column chromatography (gradient 0 - 100% diethyl ether; 100 g Biotage Sfär DLV column; flow rate 100 mL/min; product elutes at 0% ether).

$^1\text{H-NMR}$ and IR analysis is in good agreement with literature precedent.ⁿ

$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.64 (q, J = 8.5 Hz, 4H), 4.93 (s, 2H).

IR: $\nu[\text{cm}^{-1}]$ = 2097, 1716, 1617, 1577, 1520, 1420, 1386, 1323, 1238, 1200, 1122, 1084, 1069, 1044, 1016, 928, 840, 824, 790, 767, 738, 716, 594, 578, 522, 500, 473, 467, 451, 441, 434, 430, 424, 418, 413, 408, 403.

2,2,2-trichloroethyl (1*S*,5*R*,6*S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-31a):

Following the general procedure **GP-IV** using cyclopenta-1,3-diene (**21**, 132 mg, 2.00 mmol, 2.0 equiv), 2,2,2-trichloroethyl 2-diazo-2-phenylacetate (**29a**, 294 mg, 1.00 mmol, 1.0 equiv), N_2 -sparged, dry distilled SPS-grade DCM (0.06 M), N_2 -sparged 1,1,1,3,3,3-hexafluoropropan-2-ol (1.68 g, 10 mmol, 10 equiv) and stock solution of $\text{Rh}_2(R\text{-}p\text{-PhTPCP})_4$ (882 μg , 2.0 mL, 0.5 μmol , 0.05 mol%) gave the title compound **(1*S*,5*R*,6*S*)-31a** (315 mg, 0.95 mmol, 95%) as colorless oil after purification by flash column chromatography (hexanes/diethyl ether, Biotage Isolera Four Flash Chromatography System was used; 0% for 5 CV to 0 - 100% for 5 CV to 100% for 5 CV; 25 g Sfär DLV

ⁿ Bess, E. N.; Guptill, D. M.; Davies, H. M. L.; Sigman, M. S. *Chem. Sci.* **2015**, 6, 3057–3062.

columns; 100 mL/min flowrate; detector set to 210 nm & 254 nm absorbance, the product eluted out at 40% ether).

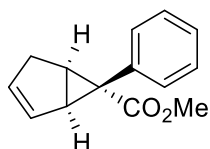
^1H NMR: (400 MHz, CDCl_3): δ 7.31 – 7.20 (m, 3H), 7.16 – 7.10 (m, 2H), 5.78 (dt, J = 5.9, 2.2 Hz, 1H), 5.28 – 5.24 (m, 1H), 4.72 – 4.58 (m, 2H), 3.07 (dt, J = 6.6, 2.3 Hz, 1H), 2.80 – 2.63 (m, 2H), 2.20 – 2.10 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 133.1, 132.9, 132.1, 129.4, 127.6, 127.0, 95.1, 74.2, 41.1, 37.7, 34.2, 32.7.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{O}_2\text{Cl}_3$ $[\text{M}+\text{H}]^+$: 331.0054, found 331.0049.

$[\alpha]_{\text{D}}^{20}$: + 83.11 $^\circ$ (c = 0.59 g/100 mL, EtOAc).

methyl (1*S*,5*R*,6*S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-25a):



Following general procedure **GP-V** using 2,2,2-trichloroethyl 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((**1*S*,5*R*,6*S*)-31a**, 235 mg, 710 μmol , 1.0 equiv), zinc dust (<10 μm , 464 mg, 7.10 mmol, 10 equiv) and acetic acid (0.1 M) gave the corresponding 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylic acid (119 mg, 594 μmol , 84%) which was further subjected to *O*-alkylation using 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylic acid (142 mg, 709 μmol , 1.0 equiv), potassium carbonate (147 mg, 1.06 mmol, 1.5 equiv), DMF (1.0 M) and iodomethane (151 mg, 66.5 μL , 1.06 mmol, 1.5 equiv), which gave the title compound methyl 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((**1*S*,5*R*,6*S*)-25a**, 135 mg, 630 μmol , 89%, 90% *ee*) as a colorless solid after purification by flash column chromatography (hexanes/ethyl acetate, gradient elution 0 - 100% ethyl acetate).

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from hexanes.

M.p.: 103 – 105 $^\circ\text{C}$.

^1H NMR: (400 MHz, CDCl_3): δ 7.32 – 7.18 (m, 3H), 7.13 – 7.08 (m, 2H), 5.75 (dt, J = 5.6, 2.1 Hz, 1H), 5.23 – 5.18 (m, 1H), 3.58 (s, 3H), 2.94 – 2.90 (m, 1H), 2.70 – 2.59 (m, 2H), 2.11 – 2.02 (m, 1H).

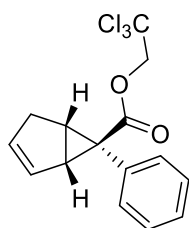
^{13}C NMR (101 MHz, CDCl_3): δ 174.5, 133.0, 132.9, 132.8, 129.7, 127.6, 126.7, 52.4, 40.8, 37.8, 34.1, 32.4

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$: 215.1067, found 215.1064.

$[\alpha]_{\text{D}}^{20}$: + 162.62 ° (c = 0.47 g/100 mL, EtOAc).

HPLC: (OD-H column, 0.1% *iso*-propanol in hexane, 0.5 mL/min, 0.5 mg/mL, 90 min, UV 210 nm) retention times of 40.4 min (minor) and 42.0 min (major) 90% *ee* with $\text{Rh}_2(\text{R-}p\text{-PhTPCP})_4$.

2,2,2-trichloroethyl (1*R*,5*S*,6*R*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*R*,5*S*,6*R*)-31a):

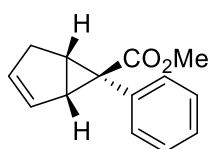


Procedure similar as **GP-IV**. To a flame-dried 20 mL vial was added $\text{Rh}_2(\text{S-}p\text{-PhTPCP})_4$ (4.41 mg, 2.50 μmol , 0.5 mol%), DCM (0.06 M), and 4Å MS (activated MS was cooled *in vacuo*). The mixture was back-filled with nitrogen three times. Neat, N_2 -sparged, distilled cyclopenta-1,3-diene (**21**, 330 mg, 420 μL , 5.0 mmol, 10 equiv) was added to the mixture and allowed to stir at 25 °C for 10 minutes. The red liquid 2,2,2-trichloroethyl 2-diazo-2-phenylacetate (**29a**, 147 mg, 0.50 mmol, 1.0 equiv) was added to the reaction vessel *via* a multi-syringe pump (syringe-tared Air-Tite 22Gx4" long hypodermic needle was used, multi-syringe pump settings -- 1 mL syringe, 0.002 mL/min, diameter 4.71 mm, vol 0.200 mL). After slow-addition, the tail-end residue within the syringe was manually syringed into the reaction. The reaction mixture was stirred at 25 °C for 24 h, then filtered through a packed-celite pipette, and the filtrate was concentrated *in vacuo* at 25 °C. The crude product was subjected to flash column chromatography with purification conditions the same as **(1*S*,5*R*,6*S*)-31a**. The collected fractions were concentrated *in vacuo* to afford the title compound **(1*R*,5*S*,6*R*)-31a** (124 mg, 375 μmol , 75%) as a yellow clear oil.

¹H NMR: (600 MHz, CDCl₃): δ 7.31 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 7.15 – 7.11 (m, 2H), 5.79 (dq, *J* = 6.0, 2.2 Hz, 1H), 5.30 – 5.22 (m, 1H), 4.69 (dd, *J* = 12.0, 0.5 Hz, 1H), 4.61 (dd, *J* = 12.0, 0.5 Hz, 1H), 3.07 (dt, *J* = 6.8, 2.3 Hz, 1H), 2.76 (t, *J* = 6.9 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.24 – 2.09 (m, 1H).

¹³C NMR (151 MHz, CDCl₃): δ 172.2, 133.2, 132.9, 132.1, 129.4, 127.6, 127.0, 95.1, 74.2, 41.1, 37.7, 34.2, 32.7.

methyl (1*R*,5*S*,6*R*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*R*,5*S*,6*R*)-25a):



Following general procedure **GP-V** using 2,2,2-trichloroethyl 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate **(1*R*,5*S*,6*R*)-31a** (115 mg, 348 μmol, 1.0 equiv), zinc dust (<10 μm, 114 mg, 1.74 mmol, 5.0 equiv) and acetic acid (0.1 M) gave the corresponding 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylic acid (66.0 mg, 330 μmol, 95%) which was further subjected to *O*-alkylation: To a flame-dried vial charged with a stir-bar was added 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylic acid (69.6 mg, 348 μmol, 1.0 equiv), methanol (0.5 mL) and DCM (2.0 mL). To the stirring solution at 25 °C was added (trimethylsilyl)diazomethane solution in ether (59.6 mg, 261 μL, 2.0 M, 522 μmol, 1.5 equiv) drop-wise open to air. After complete addition of (trimethylsilyl)diazomethane, the reaction was allowed to stir for an additional 1 hour at 25 °C. The crude product was purified via flash column chromatography to afford the title compound **(1*R*,5*S*,6*R*)-25a** (42.2 mg, 197 μmol, 57%) as a colorless solid.

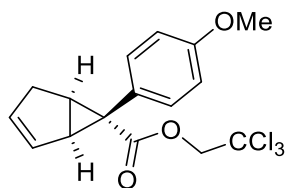
M.p.: 103 – 104 °C.

¹H NMR: (400 MHz, CDCl₃): δ 7.34 – 7.17 (m, 2H), 7.13 – 7.07 (m, 1H), 5.79 – 5.71 (m, 1H), 5.20 (ddt, *J* = 4.5, 3.7, 1.6 Hz, 0H), 3.58 (s, 2H), 2.95 – 2.88 (m, 0H), 2.70 – 2.58 (m, 1H), 2.12 – 2.01 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 174.5, 133.0, 132.9, 132.8, 129.7, 127.6, 126.7, 52.4, 40.8, 37.8, 34.1, 32.4.

[α]_D²⁰: - 174.73 ° (*c* = 0.18 g/100 mL, EtOAc).

2,2,2-trichloroethyl (1*S*,5*R*,6*S*)-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-31k)



Following the general procedure **GP-IV** using cyclopenta-1,3-diene (**21**, 132 mg, 2.00 mmol, 2.0 equiv), 2,2,2-trichloroethyl 2-diazo-2-(4-methoxyphenyl)acetate (**29k**, 324 mg, 1.00 mmol, 1.0 equiv), N₂-sparged, dry distilled SPS-grade DCM (0.06 M), N₂-sparged 1,1,1,3,3,3-hexafluoropropan-2-ol (1.68 g, 10 mmol, 10 equiv) and stock solution of Rh₂(*R-p*-PhTPCP)₄ (882 µg, 2.0 mL, 0.50 µmol, 0.05 mol%) gave the title compound **(1*S*,5*R*,6*S*)-31k** (351 mg, 0.97 mmol, 97%) as pale yellow oil after purification by flash column chromatography (hexanes/diethyl ether, Biotage Isolera Four Flash Chromatography System was used; 0% for 5 CV to 0 - 100% for 5 CV to 100% for 5 CV; 25 g Sfär DLV columns; 100 mL/min flowrate; detector set to 210 nm & 254 nm absorbance, the product eluted out at 40% ether).

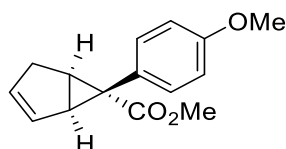
¹H NMR: (400 MHz, CDCl₃): δ 7.04 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.77 (dq, *J* = 6.2, 2.1 Hz, 1H), 5.29 – 5.26 (m, 1H), 4.72 – 4.58 (m, 2H), 3.78 (s, 3H), 3.04 (dq, *J* = 6.2, 1.8 Hz, 1H), 2.77 – 2.63 (m, 2H), 2.17 – 2.08 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 172.5, 158.5, 133.9, 133.3, 129.3, 124.0, 113.2, 95.2, 74.2, 55.1, 41.2, 37.0, 34.2, 32.7.

HRMS: (APCI-MS) *m/z* calculated for C₁₆H₁₆O₃Cl₃ [M+H]⁺: 361.0160, found 361.0152.

[α]_D²⁰: + 91.55 ° (*c* = 0.90 g/100 mL, EtOAc).

methyl (1*S*,5*R*,6*S*)-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-25k):



Following general procedure **GP-V** using 2,2,2-trichloroethyl 6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (**(1S,5R,6S)-31k**, 274 mg, 758 μmol , 1.0 equiv), zinc dust ($<10\ \mu\text{m}$, 248 mg, 3.79 mmol, 5.0 equiv) and acetic acid (0.1 M) gave the corresponding 6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (142 mg, 617 μmol , 81%) which was further subjected to *O*-alkylation using 6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (142 mg, 617 μmol , 1.0 equiv), potassium carbonate (426 mg, 3.08 mmol, 5.0 equiv), DMF (0.25 M) and iodomethane (438 mg, 193 μL , 3.08 mmol, 5.0 equiv), which gave the title compound 6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (**(1S,5R,6S)-25k**, 120 mg, 491 μmol , 80%, 94% *ee*) as a colorless solid after purification by flash column chromatography (hexanes/ethyl acetate, gradient elution 0 - 100% ethyl acetate).

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from hexanes.

M.p.: 124 – 125 °C.

^1H NMR: (600 MHz, CDCl_3): δ 7.01 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.77 – 5.70 (m, 1H), 5.24 – 5.21 (m, 1H), 3.78 (s, 3H), 3.59 (s, 3H), 2.89 (dd, J = 6.5, 2.6 Hz, 1H), 2.67 – 2.58 (m, 2H), 2.08 – 2.02 (m, 1H).

^{13}C NMR (151 MHz, CDCl_3): δ 174.7, 158.2, 133.8, 132.9, 129.6, 125.0, 113.1, 55.1, 52.4, 40.9, 37.0, 34.0, 32.4

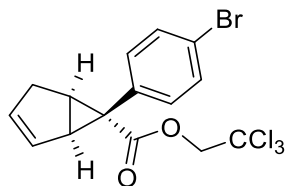
HRMS: (APCI-MS) m/z calculated for $\text{C}_{15}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 245.1172, found 245.1168.

$[\alpha]_{\text{D}}^{20}$: + 162.68 ° (c = 0.23 g/100 mL, EtOAc).^o

HPLC: (OJ column, 3% *iso*-propanol in hexane, 2.0 mL/min, 0.5 mg/mL, 35 min, UV 230 nm) retention times of 14.5 min (major) and 21.4 min (minor) 94% *ee* with $\text{Rh}_2(\text{R-}p\text{-PhTPCP})_4$.

^o Absolute configuration is confirmed by X-ray crystallography and the result is indicative that the sign of the previously reported optical rotation is incorrect: Pelphrey, P.; Hansen, J.; Davies, H. M. L. *Chem. Sci.* **2010**, *1*, 254.

2,2,2-trichloroethyl (1*S*,5*R*,6*S*)-6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-31r):



Following the general procedure **GP-IV** using cyclopenta-1,3-diene (**21**, 132 mg, 2.00 mmol, 2.0 equiv), 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**29r**, 372 mg, 1.00 mmol, 1.0 equiv), N₂-sparged, dry distilled SPS-grade DCM (0.06 M), N₂-sparged 1,1,1,3,3,3-hexafluoropropan-2-ol (1.68 g, 10.0 mmol, 10 equiv) and stock solution of Rh₂(*R-p*-PhTPCP)₄ (882 µg, 2.0 mL, 0.50 µmol, 0.05 mol%) gave the title compound **(1*S*,5*R*,6*S*)-31r** (350 mg, 0.85 mmol, 85%) as pale yellow oil after purification by flash column chromatography (hexanes/diethyl ether, Biotage Isolera Four Flash Chromatography System was used; 0% for 5 CV to 0 - 100% for 5 CV to 100% for 5 CV; 25 g Sfär DLV columns; 100 mL/min flowrate; detector set to 210 nm & 254 nm absorbance, the product eluted out at 30% ether.).

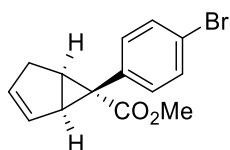
¹H NMR: (500 MHz, CDCl₃): δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 5.77 (dq, *J* = 5.5, 2.1 Hz, 1H), 5.28 (dtd, *J* = 5.6, 2.2, 1.2 Hz, 1H), 4.75 – 4.57 (m, 2H), 3.06 (ddd, *J* = 6.4, 3.5, 1.6 Hz, 1H), 2.77 – 2.67 (m, 2H), 2.12 – 2.05 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 171.7, 134.6, 133.5, 131.2, 130.9, 129.2, 121.2, 95.0, 74.2, 41.1, 37.2, 34.2, 32.8.

HRMS: (APCI-MS) *m/z* calculated for C₁₅H₁₃O₂BrCl₃ [M+H]⁺: 408.9159 found 408.9155.

[α]_D²⁰: + 32.92 ° (*c* = 0.18 g/100 mL, EtOAc).

methyl (1*S*,5*R*,6*S*)-6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-25r)



Following general procedure **GP-V** 2,2,2-trichloroethyl 6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (**(1S,5R,6S)-31r**, 333 mg, 811 μ mol, 1.0 equiv), zinc dust (<10 μ m, 265 mg, 4.06 mmol, 5.0 equiv) and acetic acid (0.1 M) gave the corresponding 6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (185 mg, 663 μ mol, 82%) as a colorless solid which was further subjected to *O*-alkylation using 6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (185 mg, 663 μ mol, 1.0 equiv), potassium carbonate (458 mg, 3.31 mmol, 5.0 equiv), DMF (0.25 M) and iodomethane (470 mg, 207 μ L, 3.31 mmol, 5.0 equiv), which gave the title compound (**(1S,5R,6S)-25r** (155 mg, 529 μ mol, 80%, 90% *ee*) as a colorless solid after purification by flash column chromatography (hexanes/ethyl acetate, gradient elution 0 - 100% ethyl acetate).

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from hexanes.

M.p.: 133 – 134 °C.

¹H NMR: (600 MHz, CDCl₃): δ 7.39 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 5.72 (dq, *J* = 6.0, 2.1 Hz, 1H), 5.25 – 5.21 (m, 1H), 3.59 (s, 3H), 2.92 (dt, *J* = 6.4, 2.3 Hz, 1H), 2.70 – 2.59 (m, 2H), 2.05 – 1.97 (m, 1H).

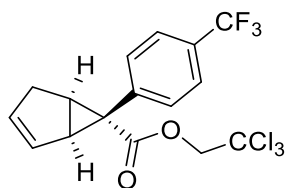
¹³C NMR (151 MHz, CDCl₃): δ 173.9, 134.6, 133.1, 132.2, 130.9, 129.4, 120.9, 52.4, 40.7, 37.2, 34.0, 32.3.

HRMS: (APCI-MS) *m/z* calculated for C₁₄H₁₄O₂Br [M+H]⁺: 293.0172, found 293.0167.

[α]_D²⁰: + 141.29 ° (*c* = 0.17 g/100 mL, EtOAc).

HPLC: (OD column, 0.1% *iso*-propanol in hexane, 0.5 mL/min, 0.5 mg/mL, 90 min, UV 210 nm) retention times of 34.8 min (minor) and 38.8 min (major) 90% *ee* with Rh₂(*R-p*-PhTPCP)₄.

2,2,2-trichloroethyl (1*S*,5*R*,6*S*)-6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-31*s*):



Following the general procedure **GP-IV** using cyclopenta-1,3-diene (**21**, 132 mg, 2.00 mmol, 2.0 equiv), 2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (**29s**, 362 mg, 1.00 mmol, 1.0 equiv), N₂-sparged, dry distilled SPS-grade DCM (0.06 M), N₂-sparged 1,1,1,3,3,3-hexafluoropropan-2-ol (1.68 g, 10 mmol, 10 equiv) and stock solution of Rh₂(*R-p*-PhTPCP)₄ (882 µg, 2.0 mL, 0.50 µmol, 0.05 mol%) gave the title compound (**(1*S*,5*R*,6*S*)-31*s***) (350 mg, 0.85 mmol, 85%) as a clear pale yellow oil after purification by flash column chromatography (hexanes/diethyl ether, Biotage Isolera Four Flash Chromatography System was used; 0% for 5 CV to 0 - 100% for 5 CV to 100% for 5 CV; 25 g Sfär DLV columns; 100 mL/min flowrate; detector set to 210 nm & 254 nm absorbance, the product eluted out at 40% ether.).

Due to relaxation time, ¹H-NMR shows broadened signals and in the ¹³C-NMR signals are missing.

¹H NMR: (500 MHz, CDCl₃): δ 7.54 (dd, *J* = 8.6, 0.8 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 5.79 (dq, *J* = 5.5, 2.1 Hz, 1H), 5.27 (dtd, *J* = 5.6, 2.2, 1.2 Hz, 1H), 4.72 – 4.58 (m, 2H), 3.11 (dt, *J* = 6.6, 2.1 Hz, 1H), 2.83 – 2.69 (m, 2H), 2.13 – 2.06 (m, 1H).

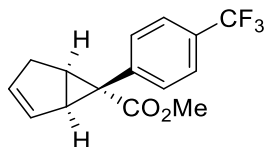
¹³C NMR (101 MHz, CDCl₃): δ 171.4, 136.3, 133.5, 133.2, 129.2, 124.7, 124.6, 94.9, 74.2, 41.1, 37.4, 34.2, 32.8.

¹⁹F NMR: (376 MHz, CDCl₃) δ: -62.5.

HRMS: (APCI-MS) *m/z* calculated for C₁₆H₁₃Cl₃F₃O₂ [M+H]⁺: 398.9928, found 398.9922.

[α]_D²⁰: + 10.56 ° (*c* = 0.28 g/100 mL, EtOAc).

methyl (1*S*,5*R*,6*S*)-6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-25s):



Following general procedure **GP-V** 2,2,2-trichloroethyl 6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((**1*S*,5*R*,6*S*)-31s**, 299 mg, 748 μ mol, 1.0 equiv), zinc dust (<10 μ m, 245 mg, 3.74 mmol, 5.0 equiv) and acetic acid (1.0 M) gave the corresponding 6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (189 mg, 705 μ mol, 94%) as colorless solid, which was further subjected to *O*-alkylation using 6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (189 mg, 705 μ mol, 1.0 equiv), potassium carbonate (487 mg, 3.52 mmol, 5.0 equiv), DMF (0.25 M) and iodomethane (500 mg, 220 μ L, 3.52 mmol, 5.0 equiv), which gave the title compound (**1*S*,5*R*,6*S*)-25s** (140 mg, 496 μ mol, 70%) as a colorless solid after purification by flash column chromatography (hexanes/ethyl acetate, gradient elution 0 - 100% ethyl acetate).

Due to long relaxation time, ^1H -NMR shows broadened signals and in the ^{13}C -NMR signals are missing.

M.p.: 84 – 85 $^{\circ}\text{C}$.

^1H NMR: (500 MHz, CDCl_3): δ 7.52 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 5.75 (dd, J = 5.6, 2.5 Hz, 1H), 5.23 – 5.18 (m, 1H), 3.59 (s, 3H), 2.99 – 2.94 (m, 1H), 2.73 – 2.64 (m, 2H), 2.06 – 1.98 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.6, 137.3, 133.2, 133.0, 129.5, 124.59, 124.57, 52.5, 40.7, 37.5, 34.1, 32.4.

^{19}F NMR: (376 MHz, CDCl_3) δ : -62.4.

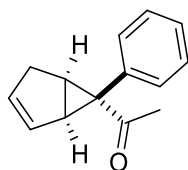
HRMS: (APCI-MS) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{F}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 283.0940, found 283.0935.

$[\alpha]_{\text{D}}^{20}$: + 129.14 $^{\circ}$ (c = 0.51 g/100 mL, EtOAc).

HPLC: (OD column, 0.1% *iso*-propanol in hexane, 0.5 mL/min, 0.5 mg/mL, 90 min, UV 210 nm) retention times of 27.9 min (minor) and 32.0 min (major) 90% *ee* with Rh₂(*R-p*-PhTPCP)₄.

3.3. Cyclopropanation Using α -Diazoketones

1-((1S*,5R*,6S*)-6-phenylbicyclo[3.1.0]hex-2-en-6-yl)ethan-1-one (39a):



Following general procedure **GP-I** using 1-diazo-1-phenylpropan-2-one (**26a**, 470 mg, 2.93 mmol, 1.0 equiv), freshly distilled cyclopentadiene (**21**, 485 mg, 7.34 mmol, 2.5 equiv) and $\text{Rh}_2(\text{OAc})_4$ (12.9 mg, 29.3 μmol , 1 mol %) dissolved in DCM (0.2 M) and stirring 14 h at 25 °C gave the title compound **39a** (342 mg, 1.72 mmol, 59%) as colorless oil after purification by flash column chromatography (hexanes/ethyl acetate = 99/1 to 10/1)

R_f = 0.53 (hexanes/ethyl acetate = 9/1 stained in vanillin).

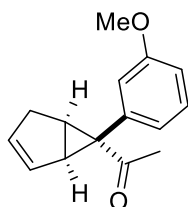
^1H NMR: (400 MHz, CDCl_3): δ 7.35 – 7.23 (m, 3H), 7.16 – 7.08 (m, 2H), 5.75 (dq, J = 6.0, 2.1 Hz, 1H), 5.22 (dtd, J = 5.5, 2.2, 1.3 Hz, 1H), 2.89 – 2.76 (m, 1H), 2.73 – 2.57 (m, 2H), 2.04 (dq, J = 18.5, 2.3 Hz, 1H), 1.90 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 208.2, 134.9, 133.2, 133.0, 130.0, 128.1, 127.0, 46.5, 44.0, 34.4, 34.4, 30.6.

IR: $\nu[\text{cm}^{-1}]$ = 3060, 3026, 2903, 1685, 1495, 1446, 1420, 1357, 1279, 1223, 1163, 1006, 757, 708.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_2$ $[\text{M}]^+$: 198.10392, found 198.10334.

1-((1S,5R,6S)-6-(3-methoxyphenyl)bicyclo[3.1.0]hex-2-en-6-yl)ethan-1-one (39b):



Following general procedure **GP-I** using 1-diazo-1-(3-methoxyphenyl)propan-2-one (**26b**, 70.0 mg, 369 μmol , 1.0 equiv), freshly distilled cyclopentadiene (**21**, 60.8 mg, 0.92

mmol, 2.5 equiv) and $\text{Rh}_2(\text{OAc})_4$ (1.6 mg, 3.7 μmol , 1 mol %) dissolved in DCM (0.2 M) and stirring 14 h at 25 °C gave the title compound **39b** (42.0 mg, 184 μmol , 50%) as colorless oil after purification by flash column chromatography (hexanes/ethyl acetate = 99/1 to 10/1).

R_f = 0.42 (hexanes/ethyl acetate = 9/1 stained in vanillin).

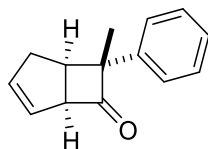
^1H NMR: (400 MHz, CDCl_3): δ 7.23 (t, J = 7.9 Hz, 1H), 6.81 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.76 – 6.62 (m, 2H), 5.75 (dq, J = 5.7, 1.9 Hz, 1H), 5.28 (dq, J = 5.6, 2.1 Hz, 1H), 3.80 (s, 3H), 2.82 (ddd, J = 7.3, 3.4, 2.0 Hz, 1H), 2.71 – 2.59 (m, 2H), 2.18 – 2.04 (m, 1H), 1.94 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 208.1, 159.3, 136.5, 133.2, 130.0, 129.1, 112.1, 55.2, 44.0, 34.5, 30.4.

IR: $\nu[\text{cm}^{-1}]$ = 3060, 3004, 2915, 2837, 1685, 1607, 1487, 1357, 1282, 1223, 1163, 1081, 1036, 1003, 932, 880, 816, 783.

HRMS: (EI-MS) m/z calculated for $\text{C}_{15}\text{H}_{16}\text{O}_2$ $[\text{M}]^+$: 228.11448, found 228.11478.

(1R*,5S*,7R*)-7-methyl-7-phenylbicyclo[3.2.0]hept-3-en-6-one (40a):



Following general procedure **GP-II** using 1-diazo-1-phenylpropan-2-one (**26a**, 210 mg, 1.31 mmol, 1.0 equiv) and freshly distilled cyclopentadiene (**21**, 433 mg, 6.56 mmol, 5.0 equiv) dissolved in DCM (0.5 M) and stirring 14 h at 25 °C gave the title compound **40a** (220 mg, 1.11 mmol, 85%) as yellow oil after purification by flash column chromatography (hexanes/ethyl acetate = 99/1 to 10/1).

R_f = 0.58 (hexanes/ethyl acetate = 9/1 stained in vanillin).

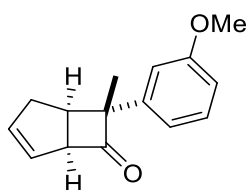
^1H NMR: (400 MHz, CDCl_3): δ 7.37 – 7.23 (m, 4H), 7.23 – 7.15 (m, 1H), 5.69 (dq, J = 5.9, 1.9 Hz, 1H), 5.50 (dq, J = 5.8, 2.3 Hz, 1H), 4.03 (ddd, J = 9.1, 7.2, 1.5 Hz, 1H), 3.58 (ddt, J = 7.1, 3.7, 1.9 Hz, 1H), 2.78 – 2.61 (m, 1H), 2.49 (ddq, J = 17.2, 9.5, 2.1 Hz, 1H), 1.68 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 215.9, 140.7, 133.4, 131.3, 128.2, 126.4, 126.2, 71.5, 57.2, 51.6, 34.3, 27.2.

IR: $\nu[\text{cm}^{-1}]$ = 3056, 2960, 2922, 2855, 1771, 1603, 1495, 1446, 1297, 1241, 1170, 1133, 1058, 973, 924, 753, 701.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}$ $[\text{M}]^+$: 198.10392, found 198.10372.

(1R*,5S*,7R*)-7-(3-methoxyphenyl)-7-methylbicyclo[3.2.0]hept-3-en-6-one (40b):



Following general procedure **GP-II** using 1-diazo-1-(3-methoxyphenyl)propan-2-one (**26b**, 200 mg, 1.05 mmol, 1.0 equiv) and freshly distilled cyclopentadiene (**21**, 348 mg, 5.26 mmol, 5.0 equiv) dissolved in DCM (0.5 M) and stirring 14 h at 25 °C gave the title compound **40b** (122 mg, 0.53 mmol, 51%) as yellow oil after purification by flash column chromatography (hexanes/ethyl acetate = 99/1 to 10/1).

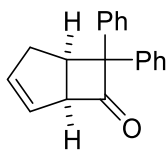
R_f = 0.49 (hexanes/ethyl acetate = 9/1 stained in vanillin).

^1H NMR: (400 MHz, CDCl_3): δ 7.21 (t, J = 7.9 Hz, 1H), 6.98 – 6.84 (m, 2H), 6.74 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 5.69 (dq, J = 5.9, 1.9 Hz, 1H), 5.60 – 5.44 (m, 1H), 4.01 (ddd, J = 9.1, 7.2, 1.4 Hz, 1H), 3.79 (s, 3H), 3.56 (ddq, J = 7.1, 3.6, 1.9 Hz, 1H), 2.78 – 2.59 (m, 1H), 2.48 (ddq, J = 17.1, 9.4, 2.1 Hz, 1H), 1.67 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 215.6, 159.4, 142.4, 133.3, 131.3, 129.2, 118.6, 112.1, 111.7, 71.5, 57.1, 55.1, 51.6, 34.3, 27.2.

IR: $\nu[\text{cm}^{-1}]$ = 3056, 3001, 2960, 2922, 2855, 1767, 1580, 1487, 1431, 1349, 1290, 1226, 1174, 1036, 932, 876, 824, 738, 701.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{16}\text{O}_2$ $[\text{M}]^+$: 228.11448, found 228.11482.

(1R*,5S*)-7,7-diphenylbicyclo[3.2.0]hept-3-en-6-one (40c):

Following general procedure **GP-II** using 2-diazo-1,2-diphenylethan-1-one (**26c**, 104 mg, 0.47 mmol, 1.0 equiv) and freshly distilled cyclopentadiene (**21**, 155 mg, 2.34 mmol, 5.0 equiv) dissolved in DCM (0.5 M) and stirring 14 h at 25 °C gave the title compound **40c** (118 mg, 0.45 mmol, 97%) as slightly yellow solid after washing the crude product with pentane.

Structure was confirmed by X-ray crystallography.

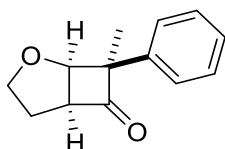
R_f = 0.64 (hexanes/ethyl acetate = 9/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.50 – 7.46 (m, 2H), 7.37 – 7.27 (m, 4H), 7.26 – 7.22 (m, 2H), 7.19 – 7.14 (m, 1H), 5.80 (dq, J = 5.9, 2.0 Hz, 1H), 5.54 (dt, J = 6.0, 2.3 Hz, 1H), 4.38 (ddt, J = 7.2, 3.9, 2.0 Hz, 1H), 3.95 (ddd, J = 8.9, 7.4, 1.3 Hz, 1H), 2.80 (ddtd, J = 17.2, 3.5, 2.3, 1.3 Hz, 1H), 2.51 (ddq, J = 17.2, 9.1, 2.1 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 212.3, 141.0, 140.7, 134.1, 131.1, 128.9, 128.2, 127.1, 127.1, 127.0, 126.5, 79.9, 58.6, 49.5, 34.6.

IR: ν[cm⁻¹] = 3056, 2952, 2919, 2851, 1771, 1722, 1599, 1491, 1446, 1275, 1241, 1107, 1029, 865, 738, 701.

HRMS: (APCI-MS) m/z calculated for C₁₉H₁₆O [M+H]⁺: 261.1274, found 261.1273.

(1R*,5S*,7R*)-7-methyl-7-phenyl-2-oxabicyclo[3.2.0]heptan-6-one (46):

Following general procedure **GP-II** using 1-diazo-1-phenylpropan-2-one (**26a**, 170 mg, 1.06 mmol, 1.0 equiv) and 2,3-dihydrofuran (**43**, 372 mg, 5.31 mmol, 5.0 equiv) dissolved in DCM (0.5 M) and stirring 14 h at 25 °C gave the title compound **46** (137 mg, 0.68

mmol, 63%) as colorless oil after purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 3/1).

R_f = 0.45 (hexanes/ethyl acetate = 4/1 stained in vanillin).

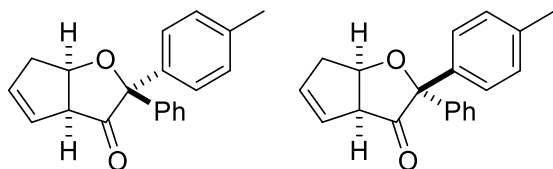
¹H NMR: (400 MHz, CDCl₃): δ 7.39 – 7.34 (m, 2H), 7.29 – 7.23 (m, 2H), 7.22 – 7.12 (m, 1H), 4.72 (d, J = 5.6 Hz, 1H), 4.01 – 3.87 (m, 1H), 3.80 (ddd, J = 9.5, 7.8, 1.9 Hz, 1H), 3.18 (ddd, J = 11.0, 9.2, 5.8 Hz, 1H), 2.09 (dddd, J = 12.6, 5.8, 2.3, 1.0 Hz, 1H), 1.87 (dddd, J = 12.6, 11.1, 9.6, 7.8 Hz, 1H), 1.45 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 214.8, 138.4, 128.4, 126.8, 126.3, 80.4, 68.6, 68.5, 60.8, 28.8, 26.0.

IR: ν[cm⁻¹] = 2960, 2863, 1771, 1603, 1495, 1446, 1372, 1238, 1126, 1081, 992, 951, 861, 760, 701.

HRMS: (EI-MS) m/z calculated for C₁₃H₁₄O₂ [M]⁺: 202.09883, found 202.09843.

(2R*,3aS*,6aR*)-2-phenyl-2-(p-tolyl)-6,6a-dihydro-2H-cyclopenta[b]furan-3(3aH)-one (50a) and (2S*,3aS*,6aR*)-2-phenyl-2-(p-tolyl)-6,6a-dihydro-2H-cyclopenta[b]furan-3(3aH)-one (50b):



Following general procedure **GP-II** using 2-diazo-1-phenyl-2-(p-tolyl)ethan-1-one (**26d**, 80.0 mg, 0.39 mmol, 1.0 equiv) and cyclopentadiene (**21**, 112 mg, 1.69 mmol, 5.0 equiv) dissolved in DCM (0.5 M) and stirring 14 h at 25 °C gave a 1:1 product mixture of the title compounds **50a/b** (87.0 mg, 0.39 mmol, 88%) as colorless oil after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 10/1)

R_f = 0.58 (hexanes/ethyl acetate = 9/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.98 – 7.87 (m, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.44 – 7.38 (m, 3H), 7.31 (dt, J = 8.2, 7.0 Hz, 6H), 7.25 – 7.20 (m, 1H), 7.13 (dd, J = 8.0, 4.5 Hz, 4H), 5.90 (ttt, J = 5.8, 2.3, 1.2 Hz, 2H), 5.32 (dt, J = 5.8, 4.6 Hz, 2H), 5.24 (ddd, J =

10.9, 5.4, 2.4 Hz, 2H), 4.59 (dddq, $J = 8.6, 4.8, 2.3, 1.2$ Hz, 2H), 2.74 (dq, $J = 18.2, 2.3$ Hz, 2H), 2.66 – 2.51 (m, 2H), 2.31 (d, $J = 3.4$ Hz, 6H).

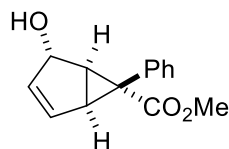
^{13}C NMR (101 MHz, CDCl_3): δ 199.7, 199.1, 143.7, 138.4, 137.3, 135.2, 133.8, 133.3, 132.8, 132.2, 131.2, 130.5, 130.4, 130.3, 130.0, 129.1, 129.0, 128.9, 128.6, 128.6, 128.3, 128.2, 128.1, 127.5, 124.8, 124.8, 97.2, 97.2, 80.9, 80.9, 54.9, 41.1, 21.7, 21.2.

IR: $\nu[\text{cm}^{-1}] = 3060, 3030, 2940, 1674, 1607, 1580, 1510, 1446, 1260, 1182, 984, 939, 902, 816, 775, 727$.

HRMS: (APCI-MS) acquisition time (**50a** or **50b**): 11.366-11.461min; m/z calculated for $\text{C}_{20}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$: 291.1380, found 291.1377; acquisition time (**50a** or **50b**): 11.461-11.589 min; m/z calculated for $\text{C}_{20}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$: 291.1380, found 291.1379.

3.4. Functionalization of Cyclopropanes and Ring-Opening Reactions

methyl (1S*,4S*,5R*,6R*)-4-hydroxy-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (96a):



Vinyl cyclopropane **25a** (1.10 g, 5.10 mmol, 1.0 equiv) and SeO_2 (0.63 g, 5.70 mmol, 1.1 equiv) were dissolved in 1,4-dioxane ($c = 2.2 \text{ M}$) in a sealed vessel (20 psi) and heated to 130°C for 1 h in a microwave oven. The reaction mixture was filtered through a pad of celite with DCM (20 mL). The filtrate was washed with sat. NaHCO_3 -solution (20 mL), H_2O (20 mL) and brine (20 mL). The aq. phase was extracted with an addition portion of DCM (15 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 9/1 to 3/1) to yield the desired product **96a** (1.17 g, 5.10 mmol, 99%) as yellow solid.^p

Structure was confirmed by X-ray-crystallography.

$R_f = 0.24$ (hexanes/ethyl acetate = 2/1 stained in vanillin).

M.p.: 109 - 110 $^\circ\text{C}$

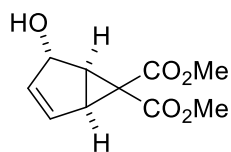
^1H NMR: (400 MHz, CDCl_3): δ 7.38 – 7.19 (m, 3H), 7.19 – 6.94 (m, 2H), 5.99 (dt, $J = 5.6, 1.7 \text{ Hz}$, 1H), 5.40 (ddd, $J = 5.5, 2.2, 1.4 \text{ Hz}$, 1H), 4.15 (s, 1H), 3.60 (s, 3H), 2.97 (dt, $J = 6.1, 2.3 \text{ Hz}$, 1H), 2.75 (dd, $J = 6.1, 1.4 \text{ Hz}$, 1H), 1.54 (bs, –OH).

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 134.3, 133.7, 132.6, 132.3, 127.7, 127.1, 75.9, 52.6, 44.6, 39.7, 37.6.

IR: $\nu[\text{cm}^{-1}] = 3481, 3056, 3004, 2952, 2926, 1962, 1435, 1397, 1249, 1264, 1234, 1133, 1029, 995, 962, 932, 869, 801, 738, 701$.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 231.1016, found 231.1020.

^p Eckl, R.; Fischer, S.; Sonnleitner, C. M.; Schmidhuber, D.; Rehbein, J.; Reiser, O. *ACS Org. Inorg. Au* **2022**, 2, 169–174.

dimethyl (1S*,4S*,5R*)-4-hydroxybicyclo[3.1.0]hex-2-ene-6,6-dicarboxylate (96n)

Vinyl cyclopropane **25n** (576 mg, 2.94 mmol, 1.0 equiv) and SeO₂ (359 mg, 3.23 mmol, 1.1 equiv) were dissolved in 1,4-dioxane (*c* = 2.2 M) in a sealed vessel (20 psi) and heated to 130 °C for 1 h in a microwave oven. The reaction mixture was filtered through a pad of celite with DCM (20 mL). The filtrate was washed with sat. NaHCO₃-solution (20 mL), H₂O (20 mL) and brine (20 mL). The aq. phase was extracted with an additional portion of DCM (15 mL). The combined organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 9/1 to 3/1) to yield the desired product **96n** (520 mg, 2.45 mmol, 83%) as yellow oil.

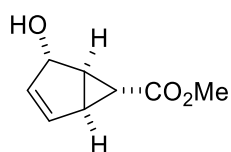
R_f = 0.16 (hexanes/ethyl acetate = 3/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 6.04 (ddd, *J* = 5.5, 2.0, 0.9 Hz, 1H), 5.78 (ddt, *J* = 5.5, 2.2, 1.0 Hz, 1H), 4.79 (td, *J* = 2.3, 1.0 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 2.88 (dt, *J* = 5.7, 2.2 Hz, 1H), 2.56 – 2.44 (m, 1H), 1.70 (bs, –OH).

¹³C NMR (101 MHz, CDCl₃): δ 168.4, 165.9, 134.0, 133.2, 75.2, 52.9, 52.5, 44.8, 38.6, 36.4.

IR: *v*[cm⁻¹] = 3380, 2956, 2848, 1722, 1439, 1312, 1241, 1159, 1092, 1029, 992, 913, 790.

HRMS: (APCI-MS) *m/z* calculated for C₁₀H₁₃O₅ [M+H]⁺: 213.0757, found 213.0760.

methyl (1S*,4S*,5R*,6R*)-4-hydroxybicyclo[3.1.0]hex-2-ene-6-carboxylate (96o):

Vinyl cyclopropane **25o** (229 mg, 1.66 mmol, 1.0 equiv, 4.0/1 *dr*) and SeO₂ (202 mg, 1.82 mmol, 1.1 equiv) were dissolved in 1,4-dioxane (*c* = 2.2 M) in a sealed vessel (20

psi) and heated to 100 °C for 0.5 h in a microwave oven. The reaction mixture was filtered through a pad of celite with DCM (20 mL). The filtrate was washed with sat. NaHCO₃-solution (20 mL), H₂O (20 mL) and brine (20 mL). The aq. phase was extracted with an addition portion of DCM (15 mL). The combined organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 50/1 to 3/1) to yield the desired product **96o** (64.5 mg, 0.42 mmol, 25%) as yellow oil.

R_f = 0.1 (hexanes/ethyl acetate = 9/1 stained in vanillin).

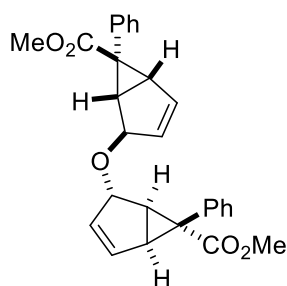
¹H NMR: (400 MHz, CDCl₃): δ 6.15 (ddt, J = 5.5, 1.9, 0.8 Hz, 1H), 5.65 (dt, J = 5.5, 1.8 Hz, 1H), 4.50 (td, J = 2.4, 1.0 Hz, 1H), 3.64 (s, 3H), 2.47 (dq, J = 4.7, 2.3 Hz, 1H), 2.33 (ddd, J = 5.5, 3.5, 1.1 Hz, 1H), 2.27 b(s, –OH), 1.07 (dd, J = 3.4, 2.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 171.4, 136.1, 132.6, 76.6, 51.8, 34.3, 34.2, 31.7.

IR: ν[cm⁻¹] = 3377, 3064, 2956, 2251, 1715, 1439, 1394, 1349, 1282, 1170, 1107, 1029, 962, 910, 790, 723.

HRMS: (EI-MS) m/z calculated for C₈H₁₀O₃ [M]⁺: 154.06245, found 154.06230.

methyl (1R*,4R*,5S*,6S*)-4-(((1R*,2S*,5S*,6R*)-6-(methoxycarbonyl)-6-phenylbicyclo[3.1.0]hex-3-en-2-yl)oxy)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (97):



A sealed vessel was charged with viny cyclopropane **25a** (1.11 g, 5.20 mmol, 1.0 equiv) and SeO₂ (635 mg, 5.72 mmol, 1.1 equiv) dissolved in DMSO (2.5 mL). The reaction mixture was stirred for 1 h at 100 °C in a microwave oven. Then, the solution was filtered through a pad of celite with DCM. The filtrate was washed with sat. NaHCO₃ solution (10 mL), water (10 mL) and brine (10 mL). The combined aq. layer was extracted with DCM (2 x 15 mL) and the combined organic layer was dried over Na₂SO₄. The solvent

was removed under reduced pressure and the crude product was purified by flash column chromatography to yield the title compound **97** (1.00 g, 2.26 mmol, 87%) as yellow oil.

$R_f = 0.44$ (hexanes/ethyl acetate = 3/1 stained in vanillin).

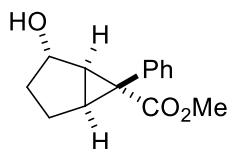
^1H NMR: (400 MHz, CDCl_3): δ 7.31 – 7.24 (m, 6H), 7.14 – 6.99 (m, 4H), 6.02 (ddt, $J = 13.4, 5.6, 1.6$ Hz, 2H), 5.38 (ddt, $J = 9.1, 5.5, 1.7$ Hz, 2H), 4.08 (dq, $J = 4.9, 1.8$ Hz, 2H), 3.60 (d, $J = 4.4$ Hz, 6H), 2.97 (ddt, $J = 9.7, 6.2, 2.3$ Hz, 2H), 2.75 (ddd, $J = 26.0, 6.2, 1.3$ Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.4, 134.1, 132.7, 132.6, 132.5, 132.5, 132.4, 127.8, 127.8, 127.1, 81.2, 80.3, 52.6, 44.2, 44.1, 38.2, 38.0, 38.0.

IR: $\nu[\text{cm}^{-1}] = 3060, 3027, 2952, 1715, 1435, 1361, 1230, 1133, 1047, 999, 936, 865, 734, 701, 671$.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{28}\text{H}_{27}\text{O}_5$ $[\text{M}+\text{H}]^+$: 443.1853, found 443.1854.

methyl (1R*,2S*,5S*,6R*)-2-hydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (99a):



An autoclave vial was charged with allylic alcohol **96a** (197 mg, 0.86 mmol, 1.0 equiv) and Pd/C (21.1 mg, 10w/w%, 10 mol%) dissolved in ethyl acetate (0.9 M). Then, the vial was placed in an autoclave, sealed and pressurized to 60 bars with H_2 at 25 °C for 4 h. The reaction mixture was then filtered through a pad of silica and washed with ethyl acetate. The solvent was removed under reduced pressure to obtain the desired alcohol **99a** (201 mg, 0.86 mmol, quant.) without further purification as white solid.^q

$R_f = 0.26$ (hexanes/ethyl acetate = 3/1 stained in vanillin).

M.p.: 64 – 67 °C

^q Eckl, R.; Fischer, S.; Sonnleitner, C. M.; Schmidhuber, D.; Rehbein, J.; Reiser, O. *ACS Org. Inorg. Au* **2022**, 2, 169–174.

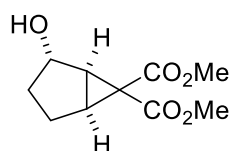
^1H NMR: (400 MHz, CDCl_3): δ 7.37 – 7.26 (m, 3H), 7.20 – 7.14 (m, 2H), 4.22 (d, J = 5.6 Hz, 1H), 3.57 (s, 3H), 2.55 – 2.33 (m, 2H), 2.29 – 2.04 (m, 1H), 1.73 (ddd, J = 13.8, 8.9, 1.1 Hz, 1H), 1.64 (s, –OH), 1.36 – 1.21 (m, 1H), 0.40 – 0.09 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.9, 134.3, 130.3, 128.4, 127.3, 74.2, 52.6, 40.7, 35.9, 33.7, 32.9, 24.4.

IR: $\nu[\text{cm}^{-1}]$ = 3519, 3407, 3034, 2952, 2907, 1700, 1495, 1431, 1372, 1323, 1230, 1170, 1137, 984, 868, 734.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 233.1172, found 233.1173.

dimethyl (1R*,2S*,5S*)-2-hydroxybicyclo[3.1.0]hexane-6,6-dicarboxylate (99n**):**



An autoclave vial was charged with allylic alcohol **96n** (392 mg, 1.85 mmol, 1.0 equiv) and Pd/C (98.3 mg, 92.4 μmol , 10 w/w%, 5 mol %) dissolved in ethanol (0.9 M). Then, the vial was placed in an autoclave, sealed and pressurized to 60 bar with H_2 at 25 $^\circ\text{C}$ for 2 h. The reaction mixture was then filtered over silica and washed with DCM. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 5/1 to 1/1) to yield the desired alcohol **99n** (292 mg, 1.36 mmol, 74%) as colorless oil.

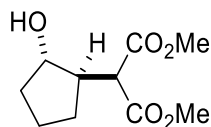
R_f = 0.38 (hexanes/ethyl acetate = 1/1 stained in vanillin).

^1H NMR: (400 MHz, CDCl_3): δ 4.34 (d, J = 5.4 Hz, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 2.82 (s, 1H), 2.24 – 2.05 (m, 3H), 1.92 (ddd, J = 13.5, 8.7, 1.0 Hz, 1H), 1.63 (dd, J = 15.5, 9.3 Hz, 1H), 1.07 (dddd, J = 15.7, 10.3, 8.6, 5.4 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 170.1, 167.6, 73.2, 52.9, 52.7, 40.0, 36.2, 33.8, 32.0, 24.2.

IR: $\nu[\text{cm}^{-1}]$ = 3399, 2956, 1722, 1439, 1375, 1316, 1245, 1197, 1163, 1110, 1051, 977, 869, 820, 734, 701, 678.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{10}\text{H}_{15}\text{O}_5$ $[\text{M}+\text{H}]^+$: 215.0914, found 215.0914.

dimethyl 2-((1R*,2S*)-2-hydroxycyclopentyl)malonate (100):

An autoclave vial was charged with allylic alcohol **96n** (392 mg, 1.85 mmol, 1.0 equiv) and Pd/C (98.3 mg, 92.4 μ mol, 10 w/w%, 5 mol %) dissolved in ethanol (1.0 mL). Then, the vial was placed in an autoclave, sealed and pressurized to 60 bar with H₂ at 25 °C for 2 h. The reaction mixture was then filtered over silica and washed with DCM. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 5/1 to 1/1) to yield the title compound **100** (35.3 mg, 163 μ mol, 9%) as colorless oil.

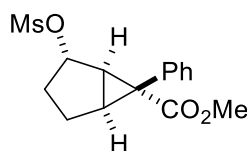
R_f = 0.44 (hexanes/ethyl acetate = 1/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 3.98 (dt, *J* = 7.0, 5.4 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.36 (d, *J* = 9.7 Hz, 1H), 2.61 (bs, –OH), 2.36 (tdd, *J* = 9.6, 8.2, 5.9 Hz, 1H), 1.98 – 1.85 (m, 2H), 1.78 – 1.52 (m, 3H), 1.41 – 1.18 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 170.3, 169.4, 76.9, 55.4, 52.7, 52.5, 47.9, 34.6, 29.6, 22.4.

IR: ν [cm⁻¹] = 2440, 2956, 2878, 1730, 1439, 1320, 1249, 1200, 1152, 1096, 1021, 854, 798.

HRMS: (APCI-MS) *m/z* calculated for C₁₀H₁₇O₅ [M+H]⁺: 217.1071, found 217.1070.

methyl (1R*,2S*,5S*,6R*)-2-((methylsulfonyl)oxy)-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (101a):

A round-bottom flask was charged with alcohol **99a** (191 mg, 0.82 mmol, 1.0 equiv) and NEt₃ (166 mg, 1.64 mmol, 2.0 equiv) dissolved in DCM and cooled to 0 °C. MsCl (103 mg, 0.90 mmol, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with 1 M HCl (10 mL), the organic layer

was separated and washed with 1 M HCl (10 mL), 2 M NaOH (10 mL), water (10 mL) and brine (10 mL). The combined aq. phases were extracted with an additional portion of DCM (2 x 10 mL) and the combined organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure to yield the product **101a** (245 mg, 0.79 mmol, 96%) without further purification as yellow solid.

R_f = 0.33 (hexanes/ethyl acetate = 3/1 stained in vanillin).

M.p.: 73- 77 °C

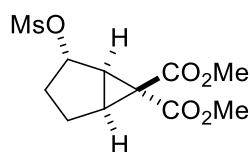
¹H NMR: (400 MHz, CDCl₃): δ 7.38 – 7.28 (m, 3H), 7.22 – 7.16 (m, 2H), 5.06 (d, J = 5.6 Hz, 1H), 3.57 (s, 3H), 3.03 (s, 3H), 2.65 (dd, J = 6.4, 1.5 Hz, 1H), 2.50 (dd, J = 6.4, 5.1 Hz, 1H), 2.21 (dddd, J = 13.9, 10.7, 9.6, 5.2 Hz, 1H), 1.78 (ddd, J = 13.8, 8.6, 1.0 Hz, 1H), 1.66 – 1.57 (m, 1H), 0.39 (dddd, J = 16.0, 10.5, 8.6, 5.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 173.0, 133.4, 130.0, 128.8, 127.7, 84.6, 52.8, 38.8, 37.8, 35.9, 33.8, 31.4, 24.5.

IR: ν[cm⁻¹] = 3030, 2952, 2870, 1718, 1498, 1357, 1245, 1182, 1074, 1044, 973, 887, 742, 708.

HRMS: (APCI-MS) m/z calculated for C₁₅H₁₉O₅S [M+H]⁺: 311.0948, found 311.0947.

dimethyl (1R,2S,5S)-2-((methylsulfonyl)oxy)bicyclo[3.1.0]hexane-6,6-dicarboxylate (101n)



A round-bottom flask was charged with alcohol **99n** (198 mg, 0.92 mmol, 1.0 equiv) and NEt₃ (187 mg, 1.85 mmol, 2.0 equiv) dissolved in DCM and cooled to 0 °C. MsCl (116 mg, 1.02 mmol, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with 1 M HCl (10 mL), the organic layer was separated and washed with 1 M HCl (10 mL), 2 M NaOH (10 mL), water (10 mL) and brine (10 mL). The combined aq. phases were extracted with an additional portion of DCM (2 x 10 mL) and the combined organic layer was dried over Na₂SO₄. The solvent

was removed under reduced pressure to yield the product **101n** (235 mg, 0.80 mmol, 87%) without further purification as yellow oil.

No mass was measured, since the mesylate 101n decomposed within hours in the freezer ($< 0\text{ }^{\circ}\text{C}$).

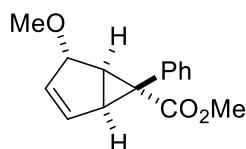
$R_f = 0.47$ (hexanes/ethyl acetate = 2/1 stained in vanillin).

^1H NMR: (400 MHz, CDCl_3): δ 5.23 (d, $J = 5.4$ Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.03 (s, 3H), 2.42 (dd, $J = 6.1, 1.3$ Hz, 1H), 2.35 (dd, $J = 6.1, 4.7$ Hz, 1H), 2.29 – 2.14 (m, 1H), 2.08 – 1.97 (m, 2H), 1.43 – 1.20 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 169.1, 166.8, 83.4, 53.2, 53.0, 38.5, 37.1, 36.2, 33.8, 30.8, 24.2.

IR: $\nu[\text{cm}^{-1}] = 3027, 2960, 1722, 1439, 1331, 1252, 1159, 1096, 1051, 962, 924, 872, 783$.

methyl (1S,4S,5R,6R)-4-methoxy-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (105):



A sealed microwave vial was charged with allylic alcohol **96a** (138 mg, 0.60 mmol, 1.0 equiv) dissolved in MeOH (2.0 mL) and aq. HCl solution (5.91 mg, 0.06 mol, 37 wt%, 10 mol%). The reaction mixture was stirred for 1 h at $100\text{ }^{\circ}\text{C}$ in a microwave oven, then washed with water (2 x 10 mL) and extracted with MeOH (15 mL). The aq. layer was additionally extracted with MeOH (2 x 10 mL) and the combined organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 9/1 to 3/1) to yield the product **105** (104 mg, 0.43 mmol, 71%) as slightly yellow solid.

$R_f = 0.56$ (hexanes/ethyl acetate = 3/1 stained in vanillin).

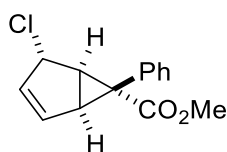
^1H NMR: (400 MHz, CDCl_3): δ 7.34 – 7.19 (m, 3H), 7.14 – 7.02 (m, 2H), 6.05 (dt, $J = 5.7, 1.6$ Hz, 1H), 5.39 (dt, $J = 5.7, 1.8$ Hz, 1H), 3.88 (q, $J = 2.0$ Hz, 1H), 3.62 (s, 3H), 3.38 (s, 3H), 2.98 (dt, $J = 6.3, 2.4$ Hz, 1H), 2.80 (dd, $J = 6.3, 1.5$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 134.4, 132.6, 132.5, 131.8, 127.7, 127.1, 83.8, 55.2, 52.6, 43.9, 37.9, 36.7.

IR: $\nu[\text{cm}^{-1}]$ = 3027, 2986, 2952, 2822, 1715, 1435, 1368, 1230, 1193, 1096, 969, 939, 738, 705, 664.

HRMS: (EI-MS) m/z calculated for $\text{C}_{15}\text{H}_{16}\text{O}_3$ $[\text{M}]^+$: 244.10940, found 244.10955.

methyl (1S*,4S*,5R*,6R*)-4-chloro-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (106):



Alcohol **96a** (161 mg, 0.70 mmol, 1.0 equiv) was dissolved in DCM at $-15\text{ }^{\circ}\text{C}$ and NEt_3 (142 mg, 1.4 mmol, 2.0 equiv) was added to the solution. MsCl (88.1 mg, 0.77 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 0.5 h at $-15\text{ }^{\circ}\text{C}$. Then, the reaction was quenched with 1 M HCl (1x10 mL), the organic layer was separated and washed with 1 M HCl (1x10 mL), 2 M NaOH (1x10 mL) and brine. The aqueous layer was extracted with an additional portion of DCM (20 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to yield the crude product **98a** (172 mg, 0.58 mmol, 92%).

The crude product **98a** was immediately converted without further purification, because of its instability: The crude product **98a** (172 mg 0.58 mmol, 1.0 equiv) was dissolved in MeOH and DBU (93.4 mg, 0.61 mmol, 1.1 equiv) was added to the solution, which immediately turned dark brown. After 20 min of stirring at ambient temperatures, the reaction mixture was extracted with DCM (3x10 mL). The organic layer was washed with 1 M HCl (1x10 mL), water (1x20 mL) and brine. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (hexanes/ethyl acetate = 9/1 to 3/1) to yield the title compound **106** (20.1 mg, 0.08 mmol, 15%) as slightly yellow solid.

R_f = 0.73 (hexanes/ethyl acetate = 3/1 stained in vanillin).

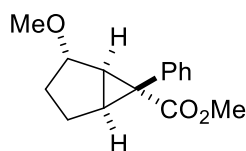
^1H NMR: (400 MHz, CDCl_3): δ 7.34 – 7.19 (m, 3H), 7.06 (dd, J = 7.4, 2.1 Hz, 2H), 5.98 (dt, J = 5.5, 1.7 Hz, 1H), 5.35 (ddd, J = 5.4, 2.2, 1.3 Hz, 1H), 4.41 (td, J = 2.4, 1.2 Hz, 1H), 3.61 (s, 3H), 3.12 (dt, J = 6.1, 2.3 Hz, 1H), 3.08 – 2.98 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.0, 132.3, 132.0, 131.4, 130.6, 127.0, 126.3, 60.3, 51.7, 43.6, 38.6, 37.4.

IR: $\nu[\text{cm}^{-1}]$ = 3027, 2952, 2922, 2851, 2363, 1718, 1498, 1435, 1353, 1320, 1238, 1129, 1059, 1028, 969, 939, 891, 805, 738, 701.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{Cl}$ $[\text{M}]^+$: 248.0599, found 248.0602.

methyl (1R*,2S*,5S*,6R*)-2-methoxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (107a):



Method A: A Schlenk-flask was charged with mesylate **101a** (120 mg, 388 μmol , 1.0 equiv) and DBU (148 mg, 969 μmol , 2.5 equiv) dissolved in MeOH (2.0 mL) and stirred for 24 h at ambient temperatures. Ethyl acetate (10 mL) was added and washed with H_2O (2 x 15 mL) and brine (15 mL). The combined aq. layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude reaction mixture was analyzed by ^1H -NMR using 1,4-dicyanobenzene as internal standard, to obtain the title compound **107a** (47.8 mg, 194 μmol , 50%).

Method B: A sealed microwave vessel was charged with alcohol **99a** (135 mg, 582 μmol , 1.0 equiv) and conc. HCl (5.7 mg, 37 wt%, 58.1 μmol , 10 mol%) dissolved in MeOH (2.0 mL), placed in a microwave oven and stirred for 5 h at 100 $^\circ\text{C}$. MeOH (10 mL) and H_2O (10 mL) were added, the phases were separated and the organic phase was washed with H_2O (2 x 10 mL) and brine (20 mL). The combined aq. phase was extracted with an additional portion of MeOH (10 mL) and the combined organic phase was dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was

purified by flash column chromatography to obtain the title compound **107a** (39.0 mg, 158 μmol , 27%, 36% *brsm*) as colorless solid.

R_f = 0.53 (hexanes/ethyl acetate = 3/1 stained in vanillin).

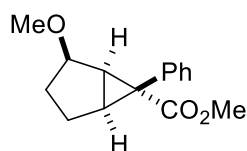
^1H NMR: (400 MHz, CDCl_3): δ 7.31 – 7.21 (m, 3H), 7.17 – 7.10 (m, 2H), 3.66 (d, J = 5.8 Hz, 1H), 3.52 (s, 3H), 3.29 (s, 3H), 2.48 (dd, J = 6.7, 1.4 Hz, 1H), 2.33 (dd, J = 6.6, 5.1 Hz, 1H), 2.16 – 1.96 (m, 1H), 1.66 (ddd, J = 13.7, 8.8, 1.1 Hz, 1H), 1.34 (ddt, J = 15.1, 9.7, 1.3 Hz, 1H), 0.07 (dddd, J = 14.8, 10.4, 8.8, 5.8 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.0, 134.5, 130.3, 128.4, 127.2, 83.3, 56.4, 52.5, 37.8, 35.4, 33.9, 29.5, 24.8.

IR: $\nu[\text{cm}^{-1}]$ = 3030, 2948, 2881, 2822, 1715, 1495, 1435, 1357, 1327, 1167, 1137, 1096, 969, 928, 887.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{15}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 247.1329, found 247.1334.

methyl (1R*,2R*,5S*,6R*)-2-methoxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (107b):



Method A: A Schlenk-flask was charged with mesylate **101a** (120 mg, 388 μmol , 1.0 equiv) and DBU (148 mg, 969 μmol , 2.5 equiv) dissolved in MeOH (2.0 mL) and stirred for 24 h at ambient temperatures. Ethyl acetate (10 mL) was added and washed with H_2O (2 x 15 mL) and brine (15 mL). The combined aq. layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude reaction mixture was analyzed by ^1H -NMR using 1,4-dicyanobenzene as internal standard, to obtain the title compound **107b** (19.2 mg, 78.0 μmol , 20%).

Method B: A sealed microwave vessel was charged with alcohol **99a** (135 mg, 582 μmol , 1.0 equiv) and conc. HCl (5.7 mg, 37 wt%, 58.1 μmol , 10 mol%) dissolved in MeOH (2.0 mL), placed in a microwave oven and stirred for 5 h at 100 $^\circ\text{C}$. MeOH (10 mL) and H_2O (10 mL) were added, the phases were separated and the organic phase was washed with

H₂O (2 x 10 mL) and brine (20 mL). The combined aq. phase was extracted with an additional portion of MeOH (10 mL) and the combined organic phase was dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to obtain the title compound **107b** (5.0 mg, 20.3 μ mol, 3%, 5% *brsm*) as colorless solid.

R_f = 0.56 (hexanes/ethyl acetate = 3/1 stained in vanillin).

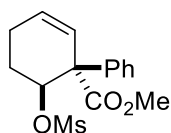
¹H NMR: (400 MHz, CDCl₃): δ 7.49 – 7.26 (m, 5H), 4.27 (ddd, *J* = 9.6, 8.4, 4.6 Hz, 1H), 3.55 (s, 3H), 3.41 (s, 3H), 2.51 (dd, *J* = 7.2, 4.6 Hz, 1H), 2.22 (dd, *J* = 7.2, 5.0 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.82 (dd, *J* = 13.8, 8.6 Hz, 1H), 1.62 – 1.51 (m, 1H), 0.31 – 0.11 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 174.5, 134.2, 127.7, 127.1, 84.0, 57.4, 52.5, 37.0, 35.8, 31.7, 27.0, 23.8.

IR: ν [cm⁻¹] = 3030, 2952, 2822, 1715, 1602, 1498, 1435, 1364, 1323, 1200, 1141, 1070, 1033, 962, 872, 790.

HRMS: (APCI-MS) *m/z* calculated for C₁₅H₁₉O₃ [M+H]⁺: 247.1329, found 247.1329.

methyl (1R*,2S*)-2-((methylsulfonyl)oxy)-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (108):



A Schlenk-flask was charged with mesylate **101a** (63.0 mg, 0.20 mmol, 1.0 equiv) dissolved in toluene (1.0 mL) and stirred for 0.5 h at 150 °C. DCM (15 mL) was added and the reaction mixture was washed with water (2 x 10 mL), brine (10 mL) and dried over Na₂SO₄ to yield the desired product **108** (21.5 mg, 0.07 mmol, 34%) in a mixture with **25a** (19.1 mg, 0.09 mmol, 34%). The yield was determined by ¹H-NMR using ethylene carbonate. A crystal for X-Ray could be obtained by evaporating from DCM.

R_f = 0.44 (hexanes/ethyl acetate = 3/1 stained in vanillin).

M.p.: 110 – 112 °C

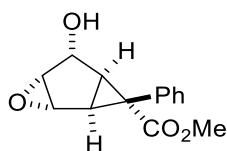
¹H NMR: (400 MHz, CDCl₃): δ 7.42 – 7.28 (m, 5H), 6.22 – 6.08 (m, 1H), 5.96 (ddt, *J* = 10.3, 2.6, 1.4 Hz, 1H), 5.43 (dt, *J* = 5.4, 1.5 Hz, 1H), 3.71 (s, 3H), 2.45 – 2.30 (m, 1H), 2.18 (s, 3H), 2.17 – 2.03 (m, 2H), 0.89 (ddd, *J* = 15.8, 12.8, 7.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 172.9, 139.1, 131.0, 128.5, 127.9, 127.6, 124.8, 80.8, 55.4, 52.7, 37.0, 26.3, 20.6.

IR: ν[cm⁻¹] = 2952, 1718, 1439, 1357, 1327, 1305, 1238, 1167, 1141, 1097, 969, 738, 708.

HRMS: (EI-MS) *m/z* calculated for C₁₅H₁₈O₅S [M]⁺: 310.08695, found 310.08704.

methyl (1S*,2S*,4R*,5R*,6R*,7S*)-5-hydroxy-7-phenyl-3-oxatricyclo[4.1.0.0^{2,4}]heptane-7-carboxylate (112):



A round-bottom flask was charged with allylic alcohol **96a** (361 mg, 1.57 mmol, 1.0 equiv) and *m*-CPBA (1.26 g, 75 wt%, 5.49 mmol, 3.5 equiv) dissolved in DCM (0.2 M) and stirred for 2 h at 25 °C. Then, the reaction was quenched with sat. aq. Na₂S₂O₃-solution and the phases were separated. The aq. phase was extracted with DCM (3x10 mL) and the combined organic phases were washed with sat. NaHCO₃-solution (2x20 mL), brine (20 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure to obtain the desired epoxide **112** (383 mg, 1.55 mmol, 99%) without further purification as slightly yellow solid.

R_f = 0.20 (hexanes/ethyl acetate = 3/1 stained in vanillin).

M.p.: 122 – 125 °C

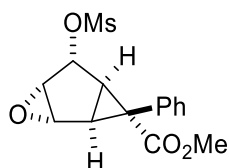
¹H NMR: (400 MHz, CDCl₃): δ 7.39 – 7.29 (m, 3H), 7.24 – 7.16 (m, 2H), 4.12 (d, *J* = 2.6 Hz, 1H), 3.59 (s, 3H), 3.54 (dd, *J* = 2.6, 1.7 Hz, 1H), 2.93 (dt, *J* = 6.0, 0.7 Hz, 1H), 2.83 (tt, *J* = 2.5, 1.1 Hz, 1H), 2.32 (bs, –OH), 2.01 (dt, *J* = 6.0, 1.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 172.2, 132.0, 131.5, 128.5, 127.9, 71.2, 60.5, 56.7, 52.8, 39.2, 35.3, 33.0.

IR: $\nu[\text{cm}^{-1}]$ = 3474, 3030, 2952, 1718, 1602, 1498, 1435, 1401, 1327, 1238, 1133, 1062, 969, 909, 811, 813, 745, 708.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_4$ [M^+]: 246.0887, found 246.0886.

methyl (1S*,2S*,4S*,5R*,6R*,7R*)-5-((methylsulfonyl)oxy)-7-phenyl-3-oxatricyclo[4.1.0.0^{2,4}]heptane-7-carboxylate (113):



A round-bottom flask was charged with alcohol **112** (159 mg, 0.64 mmol, 1.0 equiv) and NEt_3 (130 mg, 1.29 mmol, 2.0 equiv) dissolved in DCM and cooled to 0 °C. MsCl (92.3 mg, 0.81 mmol, 1.25 equiv) was added dropwise and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with 1 M HCl (10 mL), the organic layer was separated and washed with 1 M HCl (10 mL), 2 M NaOH (10 mL), water (10 mL) and brine (10 mL). The combined aq. phases were extracted with an additional portion of DCM (2 x 10 mL) and the combined organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure to yield the product **113** (209 mg, 0.64 mmol, *quant.*) without further purification as yellow solid.

R_f = 0.62 (hexanes/ethyl acetate = 1/1 stained in vanillin).

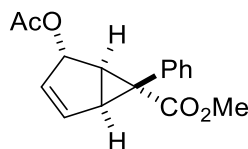
^1H NMR: (400 MHz, CDCl_3): δ 7.43 – 7.31 (m, 3H), 7.25 – 7.20 (m, 2H), 4.96 (d, J = 2.4 Hz, 1H), 3.61 (s, 3H), 3.55 (t, J = 2.2 Hz, 1H), 3.11 (s, 3H), 3.05 – 2.93 (m, 2H), 2.26 (dt, J = 6.1, 1.6 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.4, 131.4, 130.9, 128.9, 128.3, 78.4, 59.2, 54.4, 53.0, 39.8, 38.9, 35.3, 30.1.

IR: $\nu[\text{cm}^{-1}]$ = 3030, 2956, 2851, 1722, 1603, 1498, 1357, 1293, 1245, 1174, 1137, 1066, 1029, 962, 917, 846, 812, 738.

HRMS: (EI-MS) m/z calculated for $\text{C}_{15}\text{H}_{16}\text{O}_6\text{S}$ [M^+]: 324.06621, found 324.06606.

methyl (1S*,4S*,5R*,6R*)-4-acetoxy-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (116):



Alcohol **96a** (1.08 g, 4.69 mmol, 1.0 equiv) was dissolved in EA (15 mL) and NEt₃ (9.49 g, 93.8 mmol, 20 equiv) followed by addition of acetic anhydride (5.27 g, 51.6 mmol, 11 equiv). After 4 h, the reaction was quenched with H₂O (10 mL) and extracted with DCM (4 x 40 mL) and the combined organic layer was washed with 1 M HCl (3 x 20 mL) and sat. NaHCO₃ (2 x 20 mL). The organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure and the crude product was which was purified by column chromatography (hexanes/ethyl acetate = 5/1) to obtain the product **116** (1.12 g, 4.12 mmol, 87%) as slightly yellow oil.

R_f = 0.66(hexanes/ethyl acetate = 3/1 stained in vanillin).

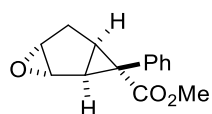
¹H NMR: (400 MHz, CDCl₃): δ 7.31 – 7.22 (m, 3H), 7.11 (d, J = 6.9 Hz, 2H), 6.19 – 5.91 (m, 1H), 5.33 (ddd, J = 5.5, 2.2, 1.4 Hz, 1H), 5.14 (dt, J = 3.7, 1.8 Hz, 1H), 3.60 (s, 3H), 3.07 – 2.94 (m, 1H), 2.75 (dd, J = 6.1, 1.3 Hz, 1H), 2.07 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 172.2, 170.4, 135.7, 132.5, 131.9, 130.7, 128.0, 127.3, 52.7, 44.5, 37.9, 36.7, 21.2.

IR: ν[cm⁻¹] = 2956, 1711, 1454, 1428, 1320, 1238, 1178, 1074, 1029, 962, 880, 835, 790, 749, 708.

HRMS: (ESI-MS) m/z calculated for C₁₆H₁₇O₄ [M+H⁺]: 273.1121, found 273.1122.

methyl (1S*,2S*,4R*,6R*,7S*)-7-phenyl-3-oxatricyclo[4.1.0.0^{2,4}]heptane-7-carboxylate (126):



A round-bottom flask was charged with vinyl cyclopropane **25a** (1.20 g, 5.60 mmol, 1.0 equiv) and *m*-CPBA (2.58 g, 75 wt%, 11.2 mmol, 2.0 equiv) dissolved in DCM (0.2 M)

and stirred for 5 h at 25 °C. Then, the reaction was quenched with sat. aq. Na₂S₂O₃-solution and the phases were separated. The aq. phase was extracted with DCM (3x10 mL) and the combined organic phases were washed with sat. NaHCO₃-solution (2x20 mL), brine (20 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure to obtain the desired epoxide **126** (1.29 g, 5.60 mmol, quant.) without further purification as colorless solid.

R_f = 0.4 (hexanes/ethyl acetate = 5/1 stained in vanillin).

M.p.: 81 - 84 °C

¹H NMR: (400 MHz, CDCl₃): δ 7.38 – 7.32 (m, 2H), 7.31 – 7.25 (m, 1H), 7.22 – 7.16 (m, 2H), 3.56 (s, 3H), 3.43 (dt, J = 2.6, 1.2 Hz, 1H), 2.81 (d, J = 6.6 Hz, 1H), 2.59 (tt, J = 2.5, 1.0 Hz, 1H), 2.21 (ddd, J = 15.1, 5.8, 1.4 Hz, 1H), 2.01 (tt, J = 5.8, 1.2 Hz, 1H), 1.81 (dd, J = 15.2, 2.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 173.2, 132.4, 132.0, 128.4, 127.5, 60.2, 54.5, 52.6, 39.6, 36.6, 29.1, 28.4.

IR: ν[cm⁻¹] = 3023, 2952, 2844, 1710, 1603, 1495, 1431, 1390, 1327, 1290, 1245, 1133, 1066, 1010, 932, 876, 839, 708.

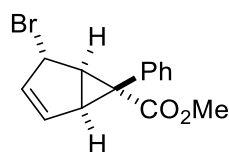
HRMS: (APCI-MS) m/z calculated for C₁₄H₁₅O₃ [M+H]⁺: 231.1016, found 231.1019.

3.5. Acid-Mediated Ring-Opening of Oxygenated Precursors

General Procedure GP-VI:

An oven dried Schlenk-flask was charged with a magnetic stir-bar, vinyl cyclopropane (1.0 equiv) or epoxide (1.0 equiv) or alcohol (1.0 equiv) and respective strong aq. acid (excess). The Schlenk-flask was placed in an aluminum heating block and stirred for 15 min – 10 h at 80 – 150 °C until TLC showed complete conversion of starting material. Then, H₂O (10 mL) and DCM (10 mL) were added, the phases were separated and the organic phase was washed with H₂O (2x10 mL). The combined aq. phases were extracted with an additional portion of DCM (15 mL) and the combined organic phases were dried over Na₂SO₄. The solvent was evaporated and the crude product was purified by flash column chromatography.

methyl (1R*,4R*,5S*,6S*)-4-bromo-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (124):



Following the general procedure **GP-VI** using vinyl cyclopropane **96a** (72.0 mg, 0.31 mmol, 1.0 equiv) and aq. hydrobromic acid solution (161 mg, 47 wt%, 0.94 mmol, 3.0 equiv) dissolved in DCM (0.3 M) gave the title compound **124** (87.8 mg, 0.30 mmol, 96%) as a yellow oil after stirring 72 h at 25 °C without further purification.

R_f = 0.73 (hexanes/ethyl acetate = 3/1 stained in vanillin).

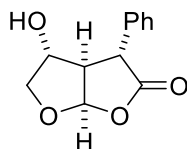
¹H NMR: (400 MHz, CDCl₃): δ 7.36 – 7.17 (m, 3H), 7.13 – 6.99 (m, 2H), 5.92 (ddt, J = 5.4, 1.9, 0.9 Hz, 1H), 5.41 (ddd, J = 5.4, 2.2, 1.2 Hz, 1H), 4.55 (td, J = 2.1, 0.9 Hz, 1H), 3.61 (s, 3H), 3.31 – 3.09 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 172.0, 133.8, 132.7, 132.4, 131.6, 128.1, 127.4, 52.7, 51.8, 44.8, 40.1, 38.9.

IR: ν[cm⁻¹] = 3060, 2952, 1718, 1498, 1435, 1320, 1238, 1156, 1126, 1062, 969, 936, 787, 738, 701.

HRMS: (EI-MS) m/z calculated for C₁₄H₁₃BrO₂ [M⁺]: 292.0093, found 292.0087.

(3R*,3aR*,4R*,6aR*)-4-hydroxy-3-phenyltetrahydrofuro[2,3-b]furan-2(3H)-one (80b):



Following general procedure **GP-VI** using alcohol **77** (63.0 mg, 269 μ mol, 1.0 equiv) and aq. HBr-solution (694 mg, 47 wt%, 4.03 mmol, 15 equiv) dissolved in MeCN (0.25 M) gave the title compound **80b** (25.0 mg, 114 μ mol, 42%) after stirring 1 h at 25 °C. (total yield is 80%, see Table 21)

Structure was confirmed by X-Ray crystallography.

R_f = 0.27 (hexanes/ethyl acetate = 1/1 stained in vanillin).

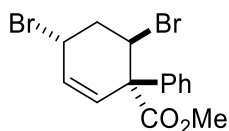
¹H NMR: (400 MHz, CDCl₃): δ 7.44 – 7.31 (m, 3H), 7.25 – 7.21 (m, 2H), 6.34 (d, J = 5.6 Hz, 1H), 4.45 (d, J = 2.8 Hz, 1H), 4.20 – 4.00 (m, 2H), 3.62 (d, J = 5.9 Hz, 1H), 3.21 (tt, J = 5.7, 1.0 Hz, 1H), 2.04 (bs, –OH).

¹³C NMR (101 MHz, CDCl₃): δ 175.2, 136.6, 129.4, 128.2, 127.5, 106.3, 76.6, 74.3, 57.2, 49.6.

IR: ν [cm⁻¹] = 3452, 3064, 3030, 2989, 2889, 1774, 1603, 1498, 1454, 1357, 1316, 1230, 1178, 1103, 973, 857, 824, 753, 701.

HRMS: (APCI-MS) m/z calculated for C₁₂H₁₂O₄ [M+H]⁺: 221.0808, found 221.0811

methyl (1R*,2R*,4R*)-2,4-dibromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (129a):



Method 1: Following the general procedure **GP-VI** using epoxide **126** (144 mg, 0.63 mmol, 1.0 equiv) and aq. hydrobromic acid solution (1.08 g, 47 wt%, 6.25 mmol, 10 equiv) gave the title compound **129a** (33.4 mg, 89.3 μ mol, 14%) as a slightly yellow oil

after stirring 30 min at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 3/1).

Method 2: A Schlenk-flask was charged with cyclohexene compound **122a** (112 mg, 0.38 mmol, 1.0 equiv), AIBN (6.23 mg, 37.9 μ mol, 0.1 equiv) and NBS (101 mg, 0.57 mmol, 1.5 equiv) dissolved in cyclohexane (1.5 mL). The Schlenk-flask was placed in an aluminum heating block and stirred for 2.5 h at 70 °C. Then DCM (10 mL) and H₂O (10 mL) were added, the phases were separated and the aq. phase was extracted with an additional portion of DCM (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 100/1 to 3/1) to obtain the desired product **129a** as slightly yellow oil (100 mg, 0.27 mmol, 70%). The yield was determined from crude ¹H-NMR using ethylene carbonate as internal standard.

R_f = 0.51 (hexanes/ethyl acetate = 9/1 stained in vanillin).

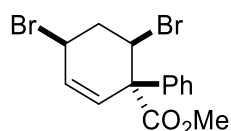
¹H NMR: (400 MHz, CDCl₃): δ 7.34 – 7.21 (m, 3H), 7.21 – 7.08 (m, 2H), 6.22 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.99 (dt, *J* = 10.2, 1.3 Hz, 1H), 5.08 (td, *J* = 5.3, 1.0 Hz, 1H), 4.84 (tdd, *J* = 6.1, 3.3, 1.4 Hz, 1H), 3.65 (s, 3H), 2.61 (dd, *J* = 6.1, 5.2 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 172.2, 138.6, 131.4, 128.3, 128.2, 128.1, 127.6, 56.6, 53.1, 52.2, 43.8, 40.0.

IR: ν [cm⁻¹] = 3030, 2952, 2844, 2356, 1730, 1295, 1435, 1245, 1088, 1040, 947, 895, 801, 738, 701.

HRMS: (EI-MS) *m/z* calculated for C₁₄H₁₄O₂Br₂ [*M*⁺]: 371.9355, found 371.9344.

methyl (1*S,2*S**,4*R**)-2,4-dibromo-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-carboxylate (129b):**



Method 1: Following the general procedure **GP-VI** using epoxide **126** (144 mg, 0.63 mmol, 1.0 equiv) and aq. hydrobromic acid solution (1.08 g, 47 wt%, 6.25 mmol, 10 equiv) gave the title compound **129b** (10.0 mg, 26.7 μ mol, 5%) as a slightly yellow oil

after stirring 0.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 3/1).

Method 2: A Schlenk-flask was charged with cyclohexene compound **122a** (112 mg, 0.38 mmol, 1.0 equiv), AIBN (6.23 mg, 37.9 μ mol, 0.1 equiv) and NBS (101 mg, 0.57 mmol, 1.5 equiv) dissolved in cyclohexane (1.5 mL). The Schlenk-flask was placed in an aluminum heating block and stirred for 2.5 h at 70 °C. Then DCM (10 mL) and H₂O (10 mL) were added, the phases were separated and the aq. phase was extracted with an additional portion of DCM (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 100/1 to 3/1) to obtain the desired product **129b** as slightly yellow solid (16.0 mg, 44.8 μ mol, 11%). The yield was determined from crude ¹H-NMR using ethylene carbonate as internal standard.

Structure was confirmed by X-ray-crystallography. Crystals were obtained by crystallization from DCM.

M.p.: 156 – 160 °C

R_f = 0.44 (hexanes/ethyl acetate = 9/1 stained in vanillin).

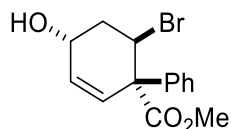
¹H NMR: (400 MHz, CDCl₃): δ 7.44 – 7.28 (m, 5H), 6.29 (ddd, *J* = 10.0, 2.5, 1.0 Hz, 1H), 5.97 (dd, *J* = 10.0, 1.8 Hz, 1H), 4.92 (dd, *J* = 12.9, 3.2 Hz, 1H), 4.79 (ddt, *J* = 9.2, 6.8, 2.2 Hz, 1H), 3.77 (s, 3H), 2.81 – 2.67 (m, 1H), 2.57 – 2.35 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 172.7, 136.0, 131.9, 129.9, 129.4, 128.2, 127.6, 58.4, 53.0, 49.4, 42.8, 39.0.

IR: ν [cm⁻¹] = 3030, 3001, 2952, 1737, 1494, 1435, 1338, 1297, 1245, 1223, 1118, 1029, 947, 913, 798, 738, 701.

HRMS: (EI-MS) *m/z* calculated for C₁₄H₁₄O₂Br₂ [*M*⁺]: 371.9355, found 371.9346.

methyl (1R*,2R*,4R*)-2-bromo-4-hydroxy-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (130):



Following general procedure **GP-VI** using epoxide **126** (109 mg, 473 μmol , 1.0 equiv) and aq. HBr solution (1.14 g, 47 wt%, 6.63 mmol, 14 equiv) and stirring for 1 h at 25 $^{\circ}\text{C}$ gave the title compound **130** (20.0 mg, 64.4 μmol , 14%) after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 10/1).

R_f = 0.2 (hexanes/ethyl acetate = 3/1 stained in vanillin).

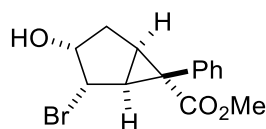
$^1\text{H NMR}$: (400 MHz, CDCl_3): δ 7.40 – 7.31 (m, 3H), 7.29 – 7.24 (m, 2H), 6.15 (d, J = 1.7 Hz, 2H), 5.16 (dd, J = 6.3, 2.4 Hz, 1H), 4.62 (ddd, J = 7.8, 5.6, 1.1 Hz, 1H), 3.69 (s, 3H), 2.57 (dt, J = 13.9, 5.8 Hz, 1H), 2.25 (ddd, J = 14.0, 7.9, 2.5 Hz, 1H), 1.70 (bs, –OH).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 172.4, 139.9, 132.8, 128.3, 127.9, 127.5, 127.0, 65.0, 56.5, 53.7, 53.0, 39.1.

IR : $\nu[\text{cm}^{-1}]$ = 3404, 3034, 2952, 2855, 1726, 1602, 1495, 1435, 1327, 1241, 1111, 1059, 1021, 909, 865, 805, 779, 701.

HRMS : (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{16}\text{BrO}_3$ $[\text{M}+\text{H}]^+$: 311.0277, found 311.0279.

methyl (1S*,2S*,3R*,5R*,6S*)-2-bromo-3-hydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (131):



Following general procedure **GP-VI** using epoxide **126** (109 mg, 473 μmol , 1.0 equiv) and aq. HBr solution (1.14 g, 47 wt%, 6.63 mmol, 14 equiv) and stirring for 1 h at 25 $^{\circ}\text{C}$ gave the title compound **131** (37.5 mg, 121 μmol , 25%) after purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 10/1).

R_f = 0.24 (hexanes/ethyl acetate = 3/1 stained in vanillin).

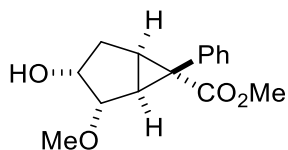
^1H NMR: (400 MHz, CDCl_3): δ 7.68 (s, 1H), 7.35 – 7.05 (m, 4H), 4.38 (dd, J = 7.9, 5.0 Hz, 1H), 3.48 (s, 3H), 2.81 (q, J = 7.9 Hz, 1H), 2.58 (dd, J = 7.4, 4.9 Hz, 1H), 2.25 (dd, J = 7.4, 5.5 Hz, 1H), 2.16 (dd, J = 13.8, 7.5 Hz, 1H), 1.95 (ddd, J = 13.9, 8.5, 5.5 Hz, 1H), 1.80 (bs, –OH).

^{13}C NMR (101 MHz, CDCl_3): δ 173.4, 132.4, 128.1, 127.9, 75.0, 58.2, 52.9, 38.2, 36.7, 32.5, 30.5.

IR: $\nu[\text{cm}^{-1}]$ = 3489, 3056, 3030, 2952, 1718, 1602, 1498, 1435, 1327, 1267, 1238, 1167, 1081, 984, 936, 872, 794, 727, 667.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{15}\text{BrO}_3$ $[\text{M}]^+$: 310.01991, found 310.01939.

methyl (1S*,2S*,3R*,5R*,6S*)-3-hydroxy-2-methoxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (136a)



A sealed vessel was charged with epoxide **126** (232 mg, 1.01 mmol, 1.0 equiv) dissolved in MeOH (2.0 mL) and catalytic amounts of Amberlyst® 15 (46.4 mg, 20 wt%) and placed in a microwave oven. The reaction mixture was stirred for 2 h at 100 °C, filtered through a pad of celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 6/1 to 1/1) to yield the title compound **136a** (64 mg, 244 μmol , 24%) as colorless solid.

R_f = 0.18 (hexanes/ethyl acetate = 3/1 stained in vanillin).

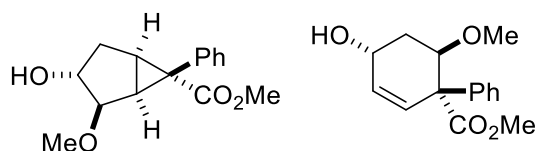
^1H NMR: (400 MHz, CDCl_3): δ 7.37 – 7.27 (m, 3H), 7.19 – 7.14 (m, 2H), 3.57 (s, 3H), 3.54 (s, 3H), 3.52 (d, J = 5.4 Hz, 1H), 2.60 (q, J = 7.3 Hz, 1H), 2.50 (d, J = 7.2 Hz, 1H), 2.33 (dd, J = 7.2, 5.3 Hz, 1H), 2.15 (dd, J = 13.9, 7.2 Hz, 1H), 1.82 (ddd, J = 13.7, 8.1, 5.4 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.8, 133.9, 130.5, 128.7, 127.7, 81.1, 71.5, 58.3, 52.7, 36.3, 34.3, 33.9, 32.0.

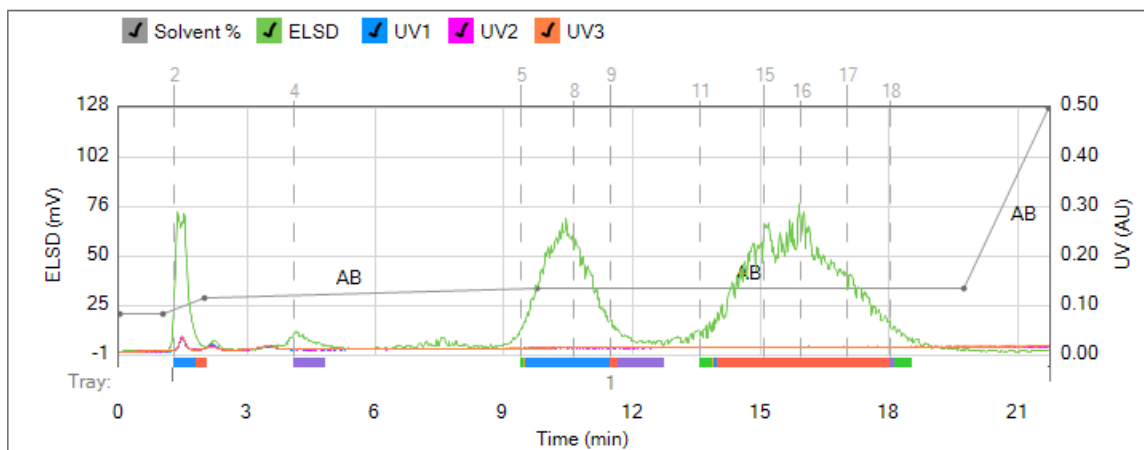
IR: $\nu[\text{cm}^{-1}]$ = 3519, 2952, 1718, 1498, 1435, 1327, 1238, 1096, 958, 746, 708.

HRMS: (APCI-MS) m/z calculated for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1278, found 263.1281.

methyl (1S*,2R*,3R*,5R*,6S*)-3-hydroxy-2-methoxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (136b) and methyl (1S*,2R*,4R*)-4-hydroxy-2-methoxy-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (138):



A sealed vessel was charged with epoxide **126** (232 mg, 1.01 mmol, 1.0 equiv) dissolved in MeOH (2.0 mL) and catalytic amounts of Amberlyst® 15 (46.4 mg, 20 wt%) and placed in a microwave oven. The reaction mixture was stirred for 2 h at 100 °C, filtered through a pad of celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 6/1 to 1/1) to yield the title compounds **136b** (94.2 mg, 359 μ mol, 36%) and **138** (44.8 mg, 171 μ mol, 17%) as an inseparable mixture of products.



R_f = 0.11 (hexanes/ethyl acetate = 3/1 stained in vanillin).

1H NMR: (400 MHz, $CDCl_3$): δ 7.40 – 7.17 (signals are overlapping, m, 7.49H), 6.11 (**138**, ddd, J = 10.2, 2.8, 0.8 Hz, 0.48H), 6.02 (**138**, dt, J = 10.2, 1.3 Hz, 0.48H), 4.42 (**138**, ddt, J = 7.6, 4.8, 2.3 Hz, 0.48H), 4.20 (**138**, dt, J = 7.0, 1.7 Hz, 0.49H), 4.03 (dd, J = 6.8, 4.9 Hz, 1H), 3.68 (**138**, s, 1.44H), 3.55 (s, 3H), 3.51 (s, 3H), 3.05 (**138**, s, 1.44H), 2.70 (td, J = 8.0, 6.9 Hz, 1H), 2.52 (dd, J = 7.7, 4.9 Hz, 1H), 2.27 – 2.12 (signals are

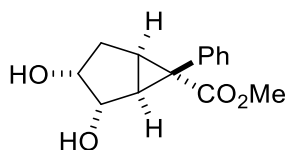
overlapping, m, 2.48H), 1.94 (ddd, $J = 13.9, 8.3, 5.5$ Hz, 1H), 1.81 (signals are overlapping, m, 1.98H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.2, 173.6, 138.8, 133.9, 133.2, 128.3, 128.1, 128.0, 127.6, 127.5, 127.3, 90.1, 78.8, 73.2, 64.5, 57.9, 57.8, 56.9, 52.7, 52.5, 37.3, 33.7, 32.6, 32.0, 28.3.

IR: $\nu[\text{cm}^{-1}] = 3414, 3030, 2933, 2825, 1715, 1498, 1435, 1327, 1238, 1107, 969, 932, 798, 701$.

HRMS: (APCI-MS) acquisition time (**136b**): 1.753 – 1.824 min; m/z calculated for $\text{C}_{15}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 263.1278, found 263.1282; acquisition time (**138**, minor product): 1.915 – 2.168 min; m/z calculated for $\text{C}_{15}\text{H}_{19}\text{O}_4$ $[\text{M}^+]$: 263.1278, found 263.1274.

methyl (1S*,2S*,3R*,5R*,6S*)-2,3-dihydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (137a)



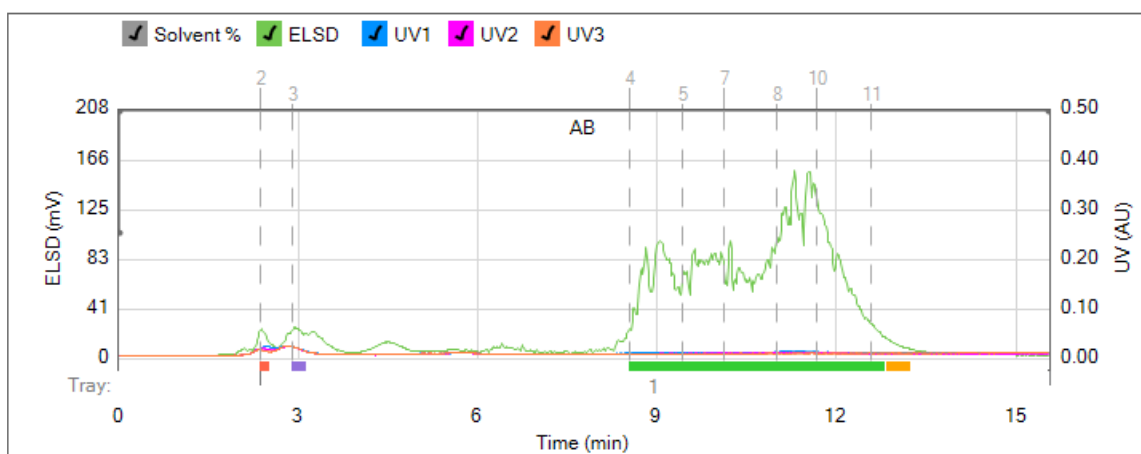
A sealed microwave vessel was charged with epoxide **126** (71.0 mg, 308 μmol , 1.0 equiv) dissolved in a mixture of H_2O /1,4-dioxane (1/1, 2.0 mL), placed in a microwave oven and stirred for 2 h at 100 $^\circ\text{C}$. DCM (10 mL) was added and the reaction mixture was washed with H_2O (2 x 10 mL) and brine (10 mL). The phases were separated and the aq. phase was extracted with an additional portion of DCM (10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by automated flash column chromatography (hexanes/ethyl acetate = 1/1 to 0/1) to yield the title compound **137a** (25.8 mg, 104 μmol , 34%) as colorless solid.

Column: Generic Silica 24g
Flow Rate: 28 mL/min
Equilibration: 5.0 min
Run Length: 15.6 min
Mode: Flash Dry

Solvent A: Petroleum Ether
Solvent B: Ethyl acetate
Solvent C: Empty
Solvent D: Empty
Slope Detection: Off

UV Threshold: 0.05 AU
UV Sensitivity: Low
UV1 Wavelength: 254 nm
UV2 Wavelength: 265 nm
UV3 Wavelength: 280 nm

ELSD Threshold: 20 mV
ELSD Sensitivity: Low
Collection: Collect Peaks
Per-Vial Volume: 25 mL
Non-Peak Volume: 25 mL



$R_f = 0.2$ (hexanes/ethyl acetate = 1/1 stained in vanillin).

M.p.: 134 – 136 °C

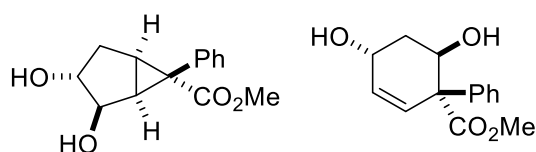
^1H NMR: (400 MHz, CDCl_3): δ 7.60 – 7.14 (m, 5H), 4.26 (dd, $J = 6.9, 5.2$ Hz, 1H), 3.48 (s, 3H), 2.50 (q, $J = 7.6$ Hz, 1H), 2.36 (dd, $J = 7.5, 5.2$ Hz, 1H), 2.19 – 2.03 (m, 4H), 1.83 (ddd, $J = 13.8, 8.3, 5.5$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.1, 134.6, 128.4, 127.6, 81.5, 74.6, 52.7, 37.1, 35.9, 32.2, 28.0.

IR: $\nu[\text{cm}^{-1}] = 3396, 2952, 2855, 1715, 1435, 1327, 1238, 1074, 932, 731, 705$.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$: 249.1121, found 249.1122.

methyl (1S*,2R*,3R*,5R*,6S*)-2,3-dihydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (137b), methyl (1S*,2R*,4R*)-2,4-dihydroxy-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (139):



A sealed microwave vessel was charged with epoxide **126** (71.0 mg, 308 μmol , 1.0 equiv) dissolved in a mixture of H_2O /1,4-dioxane (1/1, 2.0 mL), placed in a microwave oven and

stirred for 2 h at 100 °C. DCM (10 mL) was added and the reaction mixture was washed with H₂O (2 x 10 mL) and brine (10 mL). The phases were separated and the aq. phase was extracted with an additional portion of DCM (10 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by automated flash column chromatography (hexanes/ethyl acetate = 1/1 to 0/1) to yield an inseparable mixture of the title compounds **137b** (13.9 mg, 56.0 μmol, 18%) and **139** (2.6 mg, 10.5 μmol, 3%). The yield of **137b** (25%) and **139** (12%) was determined from the ratios to **137a** in the crude ¹H-NMR.

No signals of 139 can be found in the ¹³C-NMR, since only very small amounts could be isolated.

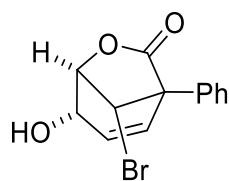
R_f = 0.18 (hexanes/ethyl acetate = 1/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.40 – 7.27 (*signals are overlapping*, m, 3.64H), 7.26 – 7.23 (**139**, m, 0.41H), 7.20 – 7.14 (m, 2H), 6.16 (**139**, dd, J = 10.1, 3.5 Hz, 0.20H), 6.10 – 6.02 (**139**, m, 0.20H), 4.65 (**139**, dd, J = 9.3, 2.9 Hz, 0.20H), 4.50 – 4.40 (**139**, m, 0.20H), 3.96 (d, J = 5.2 Hz, 1H), 3.72 (**139**, s, 0.61H), 3.56 (s, 3H), 2.58 (td, J = 7.8, 5.2 Hz, 1H), 2.47 (d, J = 7.1 Hz, 1H), 2.36 (*signals are overlapping*, dd, J = 7.1, 5.2 Hz, 1.20H), 2.25 (bs, 2H), 2.15 (*signals are overlapping*, dd, J = 13.9, 7.5 Hz, 1.23H), 1.98 – 1.79 (*signals are overlapping*, m, 1.42H).

¹³C NMR (101 MHz, CDCl₃): δ 173.5, 134.1, 130.5, 128.7, 127.7, 71.8, 71.5, 52.7, 37.0, 36.4, 33.3, 31.7.

IR: ν[cm⁻¹] = 3403, 2952, 1718, 1498, 1435, 1241, 1074, 1029, 746, 705.

HRMS: (APCI-MS) acquisition time (**137b**): 5.636-5.663 min; m/z calculated for C₁₄H₁₇O₄ [M+H]⁺: 249.1121, found 249.1116; acquisition time (**139**): 5.823-5.856 min; m/z calculated for C₁₄H₁₇O₄ [M⁺]: 249.1121, found 249.1121.

(4S*,5R*)-8-bromo-4-hydroxy-1-phenyl-6-oxabicyclo[3.2.1]oct-2-en-7-one (140):

Following the general procedure **GP-VI** using alcohol **112** (58.8 mg, 0.24 mmol, 1.0 equiv) and aq. hydrobromic acid solution (616 mg, 47 wt%, 3.58 mmol, 15 equiv) gave the title compound **140** (21.3 mg, 72.1 μ mol, 30%) as a slightly yellow solid after stirring 10 min at 100 °C in toluene. The yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

R_f = 0.53 (hexanes/ethyl acetate = 1/1 stained in vanillin).

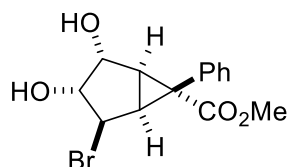
M.p.: 112 – 115 °C

^1H NMR: (400 MHz, CDCl_3): δ 7.57 – 7.35 (m, 5H), 6.23 – 5.97 (m, 2H), 4.95 (ddd, J = 5.8, 2.8, 1.9 Hz, 1H), 4.74 (ddd, J = 13.6, 5.2, 2.2 Hz, 2H), 2.06 (bs, –OH).

^{13}C NMR (101 MHz, CDCl_3): δ 171.6, 133.8, 131.8, 129.7, 128.9, 128.6, 127.6, 78.7, 66.3, 53.5, 53.2.

IR: $\nu[\text{cm}^{-1}]$ = 3414, 3064, 2926, 2855, 1785, 1502, 1450, 1450, 1401, 1345, 1290, 1238, 1126, 1079, 999, 969, 747, 701.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{13}\text{H}_{12}\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$: 294.9964, found 294.9965.

methyl (1R*,2S*,3S*,4S*,5S*,6R*)-2-bromo-3,4-dihydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (141a):

Following the general procedure **GP-VI** using alcohol **112** (69.0 mg, 0.28 mmol, 1.0 equiv) and aq. hydrobromic acid solution (732 mg, 47 wt%, 4.20 mmol, 15 equiv) gave the title compound **141a** (35.0 mg, 0.11 mmol, 38%) as a slightly yellow solid after

stirring 1 h at 25 °C. The yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from diethyl ether.

R_f = 0.29 (hexanes/ethyl acetate = 1/1 stained in vanillin).

M.p.: 147 – 151 °C

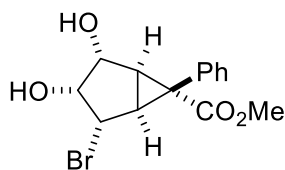
^1H NMR: (400 MHz, CDCl_3): δ 7.80 (d, J = 6.7 Hz, 1H), 7.42 – 7.28 (m, 3H), 7.17 (s, 1H), 4.53 (dd, J = 8.5, 4.9 Hz, 1H), 4.08 (d, J = 5.0 Hz, 1H), 3.59 (s, 3H), 2.94 (dd, J = 8.5, 4.9 Hz, 1H), 2.70 (dd, J = 7.3, 4.9 Hz, 1H), 2.60 – 2.35 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.7, 133.9, 132.1, 129.9, 128.2, 75.9, 70.6, 54.9, 53.1, 39.1, 36.2, 36.0.

IR: $\nu[\text{cm}^{-1}]$ = 3391, 3030, 2952, 2926, 2855, 1718, 1494, 1435, 1323, 1267, 1234, 1077, 954, 907, 872, 790, 734, 705.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{Br}$ $[\text{M}+\text{H}]^+$: 327.0226, found 327.0228.

methyl (1R*,2R*,3S*,4S*,5S*,6R*)-2-bromo-3,4-dihydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (141b):



Following the general procedure **GP-VI** using alcohol **112** (69.0 mg, 0.28 mmol, 1.0 equiv) and aq. hydrobromic acid solution (723 mg, 47 wt%, 4.20 mmol, 15 equiv) gave the title compound **141b** (15.0 mg, 0.05 mmol, 16%) as a slightly yellow solid after stirring 1 h at 25 °C. The yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from diethyl ether.

R_f = 0.40 (hexanes/ethyl acetate = 1/1 stained in vanillin).

M.p.: 133 – 137 °C

¹H NMR: (400 MHz, CDCl₃): δ 7.43 – 7.32 (m, 3H), 7.21 – 7.11 (m, 2H), 4.48 (d, J = 5.5 Hz, 1H), 4.04 (d, J = 4.8 Hz, 1H), 3.60 (s, 3H), 2.96 (d, J = 6.9 Hz, 1H), 2.73 (d, J = 6.9 Hz, 1H), 2.58 (s, 1H), 2.03 (bs, –OH).

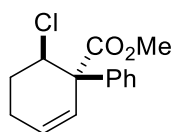
¹³C NMR (101 MHz, CDCl₃): δ 171.8, 133.0, 129.9, 129.2, 128.4, 72.1, 71.5, 56.1, 53.1, 38.9, 38.7, 36.6.

IR: ν[cm⁻¹] = 3440, 2952, 2926, 2855, 1718, 1498, 1327, 1241, 1115, 1021, 965, 917, 872, 790, 734.

HRMS: (APCI-MS) m/z calculated for C₁₄H₁₆O₄Br [M+H]⁺: 327.0226, found 327.0232.

3.6. Cyclohexenes *via* Acid-Mediated Ring-Opening of Vinylcyclopropanes

methyl (1R*,2R*)-2-chloro-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (121a):



Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (94.0 mg, 0.44 mmol, 1.0 equiv) and aq. hydrochloric acid solution (648 mg, 37 wt%, 6.58 mmol, 15 equiv) gave the title compound **121a** (56.3 mg, 0.23 mmol, 51%) as a slightly yellow oil after stirring 4 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate/AcOH = 20/1/0.1 to 5/1/0.1). Yield was determined from crude ¹H-NMR using fumaronitrile as internal standard.

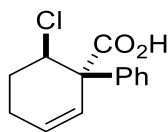
R_f = 0.80 (hexanes/ethyl acetate/AcOH = 3/1/0.1, stained in KMnO₄).

¹H NMR: (400 MHz, CDCl₃): δ 7.33 – 7.22 (m, 5H), 6.10 – 6.00 (m, 1H), 5.98 – 5.88 (m, 1H), 4.93 (ddd, J = 6.3, 2.3, 1.2 Hz, 1H), 3.62 (s, 3H), 2.44 – 2.30 (m, 1H), 2.19 – 1.95 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 173.5, 139.5, 130.0, 128.1, 127.60, 127.57, 125.3, 61.3, 56.6, 52.7, 28.4, 21.7.

IR: ν[cm⁻¹] = 3034, 3001, 2952, 1730, 1495, 1431, 1230, 1081, 1025, 980, 805, 768, 701.

HRMS: (APCI-MS) m/z calculated for C₁₄H₁₆O₂Cl [M+H]⁺: 251.0833, found 251.0835.

(1R*,2R*)-2-chloro-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylic acid (121b):

Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (94.0 mg, 0.44 mmol, 1.0 equiv) and aq. hydrochloric acid solution (648 mg, 37 wt%, 6.58 mmol, 15 equiv) gave the title compound **121b** (29.9 mg, 0.13 mmol, 29%) as a slightly yellow oil after stirring 4 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate/AcOH = 20/1/0.1 to 5/1/0.1). Yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

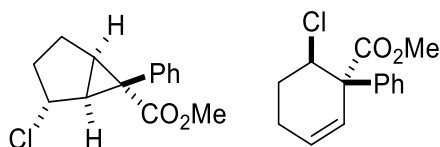
R_f = 0.56 (hexanes/ethyl acetate/AcOH = 3/1/0.1, stained in KMnO_4).

^1H NMR: (400 MHz, CDCl_3): δ 7.45 – 7.28 (m, 5H), 6.17 (dt, J = 10.1, 3.4 Hz, 1H), 6.11 – 6.00 (m, 1H), 4.99 – 4.91 (m, 1H), 2.54 – 2.33 (m, 1H), 2.20 (ttd, J = 12.3, 6.0, 3.3 Hz, 2H), 2.12 – 1.95 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 178.9, 138.7, 130.6, 128.1, 127.9, 127.8, 124.9, 60.8, 56.5, 28.3, 21.9.

IR: $\nu[\text{cm}^{-1}]$ = 3034, 2937, 2632, 1700, 1495, 1405, 1271, 768, 701.

HRMS: (EI-MS) m/z calculated for $\text{C}_{13}\text{H}_{13}\text{O}_2\text{Cl}$ [M^+]: 236.0599, found 236.0600.

methyl (1S*,2R*,5R*,6S*)-2-chloro-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (123a) and methyl (1R*,2R*)-2-chloro-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (121a):

Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (94.0 mg, 0.44 mmol, 1.0 equiv) and aq. hydrochloric acid solution (648 mg, 37 wt%, 6.58 mmol, 15 equiv) gave the title compound **123a** (11.0 mg, 0.04 mmol, 11%) in a mixture with compound **121a** as a slightly yellow oil after stirring 4 h at 100 °C and purification by

flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1). Yield was determined from crude ^1H -NMR using fumaronitrile as internal standard.

R_f = 0.81 (hexanes/ethyl acetate/AcOH = 3/1/0.1, stained in KMnO_4).

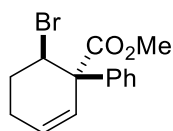
^1H NMR: (400 MHz, CDCl_3): δ 7.35 – 7.23 (*signals are overlapping*, m, 6.3H), 7.14 (**123a**, d, J = 7.0 Hz, 0.67H), 6.06 (dddd, J = 10.3, 4.2, 2.9, 0.7 Hz, 1H), 5.98 – 5.91 (m, 1H), 4.95 (ddd, J = 6.3, 2.4, 1.2 Hz, 1H), 4.32 (**123a**, d, J = 6.0 Hz, 0.34H), 3.64 (s, 3H), 3.53 (**123a**, s, 0.93H), 2.63 (**123a**, dd, J = 6.6, 1.2 Hz, 0.33H), 2.49 (**123a**, dd, J = 6.6, 5.0 Hz, 0.34H), 2.42 – 2.29 (m, 1H), 2.31 – 2.21 (**123a**, m, 0.33H), 2.22 – 1.96 (m, 3H), 1.80 – 1.70 (**123a**, m, 0.36H), 1.60 – 1.54 (**123a**, m, 0.32H), 0.44 (**123a**, dddd, J = 15.6, 10.9, 8.2, 6.0 Hz, 0.36H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.6, 139.5, 133.9, 130.0, 128.7, 128.1, 127.6, 127.6, 127.6, 125.4, 61.8, 61.3, 56.6, 52.7, 41.3, 37.3, 34.2, 33.9, 28.4, 24.4, 21.7.

IR: $\nu[\text{cm}^{-1}]$ = 3034, 2952, 2363, 1730, 1495, 1435, 1305, 1234, 1077, 1025, 701.

HRMS: (EI-MS) acquisition time (minor product): 7.1284-7.1318 min; m/z calculated for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{Cl}$ [M^+]: 250.0755, found 250.0758; acquisition time (major product): 7.1451-7.1551 min; m/z calculated for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{Cl}$ [M^+]: 250.0755, found 250.0761.

methyl (1R*,2R*)-2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122a):



Method 1: Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (1.66 g, 7.75 mmol, 1.0 equiv) and aq. hydrobromic acid solution (13.3 g, 47 wt%, 77.7 mmol, 10 equiv) gave the title compound **122a** (2.26 g, 7.66 mmol, 99%) as a slightly yellow oil after stirring 1.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

Method 2: Following the general procedure **GP-VI** using alcohol **99a** (81.4 mg, 0.35 mmol, 1.0 equiv) and aq. hydrobromic acid solution (603 mg, 47 wt%, 3.50 mmol, 10 equiv) gave the title compound **122a** (91.7 mg, 0.31 mmol, 89%) as a slightly yellow oil

after stirring 1.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

R_f = 0.78 (hexanes/ethyl acetate = 3/1, stained in KMnO₄).

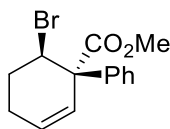
¹H NMR: (400 MHz, CDCl₃): δ 7.37 – 7.17 (m, 5H), 6.15 – 5.85 (m, 2H), 5.07 (ddd, J = 6.3, 2.7, 1.3 Hz, 1H), 3.61 (s, 3H), 2.43 – 2.33 (m, 1H), 2.31 – 2.19 (m, 1H), 2.14 – 2.01 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 173.2, 140.7, 129.8, 128.1, 127.6, 127.2, 125.4, 56.1, 55.9, 52.7, 29.3, 22.5.

IR: ν[cm⁻¹] = 3034, 3001, 2952, 2840, 1730, 1495, 1431, 1223, 1021, 977, 857, 801, 775, 738, 697.

HRMS: (EI-MS) m/z calculated for C₁₄H₁₅O₂Br [M⁺]: 294.0250, found 294.0248.

methyl (1*R*,2*R*)-2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-carboxylate ((1*R*,2*R*)-122a)



Racemic standard was made from performing the oxidative endocyclic ring-opening with racemic methyl 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate **25a**. Chiral standard was made from performing the oxidative endocyclic ring-opening with enantiopure methyl (1*S*,5*R*,6*S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((**1*S*,5*R*,6*S*)-25a**, 90% *ee*).

To a 2-dram vial was added methyl (1*R*,5*S*,6*R*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((**1*S*,5*R*,6*S*)-25a**, 16.8 mg, 78.4 μmol, 1.0 equiv, 90% *ee*) and HBr (135 mg, 90.6 μL, 784 μmol, 47% wt, 10 equiv). The reaction vessel was sealed with electric tape and heated to 100 °C for 1.5 hour. The brown reaction was cooled, diluted with DCM/H₂O, the bilayer stirred for several minutes, the water aspirated out of the solution, and the organic layer washed several times with H₂O. The organic layer was then dried over MgSO₄, filtered through celite, and concentrated *in vacuo* to afford a brown oil (crude mass recovery was 25.5 mg). The crude material was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 1/1). The collected fractions were

concentrated *in vacuo* to afford the product as a brown oil. The brown oil was resuspended in pure hexanes, sonicated which precipitated the impurities, and then the filtrate was filtered through a 2-micron syringe filter. The yellow filtrate concentrated *in vacuo* to afford the title compound **(1R,2R)-122a** (20.2 mg, 68.4 μ mol, 87%, 90% *ee*) as a yellow oil.

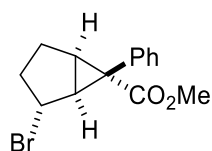
Spectroscopic data matched with those previously reported.

¹H NMR: (600 MHz, CDCl₃): δ 7.39 – 7.34 (m, 2H), 7.33 – 7.29 (m, 3H), 6.15 – 6.08 (m, 1H), 6.03 (ddd, *J* = 10.1, 2.4, 1.4 Hz, 1H), 5.12 (ddd, *J* = 6.4, 2.5, 1.2 Hz, 1H), 3.68 (s, 3H), 2.50 – 2.40 (m, 1H), 2.34 – 2.24 (m, 1H), 2.23 – 2.12 (m, 2H).

HPLC: (AS-H column, 0.1% *iso*-propanol in hexane, 1.0 ml/min, 0.5 mg/mL, 30 min, UV 210 nm) retention times of 8.2 min (major) and 11.9 min (minor) 90% *ee* from Rh₂(*R*-*p*-PhTPCP)₄ cyclopropanation product.

$[\alpha]_D^{20}$: - 32.84 ° (*c* = 0.52 g/100 mL, EtOAc).

methyl (1S*,2R*,5R*,6S*)-2-bromo-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (123b):



Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (125 mg, 0.58 mmol, 1.0 equiv) and aq. hydrobromic acid solution (1.00 g, 47 wt%, 5.80 mmol, 10 equiv) gave the title compound **123b** (71.0 mg, 0.24 mmol, 43%, *brsm*: 55%) as a colorless oil after stirring 15 min at 100 °C. The yield was determined from crude ¹H-NMR using fumaronitrile as internal standard.

R_f = 0.64 (hexanes/ethyl acetate = 5/1 stained in KMnO₄).

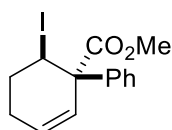
¹H NMR: (400 MHz, CDCl₃): δ 7.40 – 7.27 (m, 3H), 7.18 (d, *J* = 7.0 Hz, 2H), 4.41 (d, *J* = 5.9 Hz, 1H), 3.57 (s, 3H), 2.87 – 2.73 (m, 1H), 2.57 (dd, *J* = 6.6, 5.0 Hz, 1H), 2.32 (dddd, *J* = 14.0, 10.8, 9.0, 5.0 Hz, 1H), 1.75 (ddd, *J* = 21.5, 14.9, 8.5 Hz, 2H), 0.56 (dddd, *J* = 16.4, 10.8, 8.0, 6.0 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.8, 133.8, 129.9, 128.8, 127.6, 52.9, 52.7, 42.1, 38.1, 34.6, 34.3, 24.4.

IR: $\nu[\text{cm}^{-1}]$ = 2952, 2863, 1718, 1495, 1435, 1327, 1301, 1238, 1193, 1156, 1066, 1025, 965, 834, 705.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{Br}$ [M^+]: 294.0250, found 294.0245.

methyl (1R*,2R*)-2-iodo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (157)



Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (96.0 mg, 0.45 mmol, 1.0 equiv) and aq. hydroiodic acid solution (1.01 g, 57 wt%, 4.50 mmol, 10 equiv) gave the title compound **157** (84.5 mg, 0.25 mmol, 55%) as a slightly brown oil after stirring 1 h at 80 °C and purification by flash column chromatography (hexanes/ethyl acetate = 50/1 to 5/1).

R_f = 0.64 (hexanes/ethyl acetate = 15/1, stained in KMnO_4).

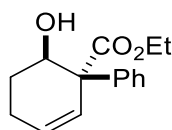
^1H NMR: (400 MHz, CDCl_3): δ 7.40 – 7.27 (m, 5H), 6.16 – 5.96 (m, 2H), 5.29 (ddd, J = 4.4, 2.7, 1.1 Hz, 1H), 3.66 (s, 3H), 2.63 – 2.34 (m, 1H), 2.26 – 2.11 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.1, 142.9, 129.6, 128.2, 127.8, 126.6, 125.5, 55.7, 52.8, 38.9, 31.2, 24.3.

IR: $\nu[\text{cm}^{-1}]$ = 3030, 2948, 2919, 2837, 1722, 1491, 1431, 1293, 1215, 1137, 1103, 1021, 977, 928, 801, 772, 834, 693.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{I}$ [M^+]: 342.0111, found 342.0102.

ethyl (1S*,2R*)-2-hydroxy-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (158a)



Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (108 mg, 0.50 mmol, 1.0 equiv) and conc. H₂SO₄ solution (510 mg, 97 wt%, 5.04 mmol, 10 equiv) dissolved in EtOH (0.25 M) gave the title compound **158a** (38.7 mg, 0.16 mmol, 31%) as yellow oil after stirring 10 h at 150 °C and purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 10/1).

R_f = 0.2 (hexanes/ethyl acetate = 9/1, stained in KMnO₄).

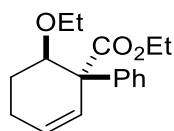
¹H NMR: (400 MHz, CDCl₃): δ 7.43 – 7.16 (m, 5H), 6.07 (dt, *J* = 10.1, 3.6 Hz, 1H), 5.92 (dt, *J* = 10.0, 2.1 Hz, 1H), 4.45 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.20 (qd, *J* = 7.1, 2.9 Hz, 2H), 2.44 (d, *J* = 3.8 Hz, 1H), 2.35 – 2.10 (m, 2H), 1.77 (dddd, *J* = 13.8, 6.3, 4.7, 3.0 Hz, 1H), 1.68 – 1.48 (m, 1H, *H*₂O-peak is overlapping), 1.21 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 174.9, 137.7, 130.5, 128.5, 128.1, 127.5, 126.1, 70.3, 61.3, 57.9, 25.2, 23.6, 14.0.

IR: ν[cm⁻¹] = 3552, 3034, 2982, 2937, 1722, 1651, 1599, 1495, 1446, 1387, 1249, 1081, 1040, 977, 934.

HRMS: (EI-MS) *m/z* calculated for C₁₅H₁₈O₃ [*M*⁺]: 246.1251, found 246.1244.

ethyl (1*S,2*R**)-2-ethoxy-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-carboxylate (159a):**



Following the general procedure **GP-VI** using vinyl cyclopropane **25a** (108 mg, 0.50 mmol, 1.0 equiv) and conc. H₂SO₄ solution (510 mg, 97 wt%, 5.04 mmol, 10 equiv) dissolved in EtOH (0.25 M) gave the title compound **159a** (34.0 mg, 0.12 mmol, 25%) as yellow oil after stirring 10 h at 150 °C and purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 10/1).

R_f = 0.51 (hexanes/ethyl acetate = 9/1, stained in KMnO₄).

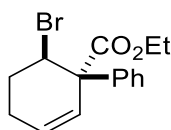
¹H NMR: (400 MHz, CDCl₃): δ 7.33 – 7.21 (m, 5H), 6.06 (dt, *J* = 10.1, 3.6 Hz, 1H), 5.96 – 5.76 (m, 1H), 4.16 (qd, *J* = 7.1, 2.6 Hz, 3H), 3.40 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.12 (dq, *J* = 9.4, 7.1 Hz, 1H), 2.33 – 2.20 (m, 1H), 2.07 (dtdd, *J* = 18.1, 6.0, 4.0, 2.0 Hz, 1H), 1.88 – 1.66 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 174.2, 140.0, 130.3, 128.4, 127.5, 126.8, 65.5, 61.0, 57.0, 24.3, 22.4, 15.3, 14.0.

IR: $\nu[\text{cm}^{-1}]$ = 3060, 3030, 2974, 2930, 2874, 1726, 1603, 1495, 1446, 1368, 1218, 1111, 1070, 1036, 984, 857.

HRMS: (EI-MS) m/z calculated for $\text{C}_{17}\text{H}_{22}\text{O}_3$ [M^+]: 274.1564, found 274.1565.

ethyl (1R*,2R*)-2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122b):



Following the general procedure **GP-VI** using vinyl cyclopropane **25b** (70.0 mg, 0.31 mmol, 1.0 equiv) and aq. hydrobromic acid solution (528 mg, 47 wt%, 3.10 mmol, 10 equiv) gave the title compound **122b** (56.0 mg, 0.18 mmol, 59%) as a slightly yellow oil after stirring 1.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

R_f = 0.56 (hexanes/ethyl acetate = 9/1, stained in KMnO_4).

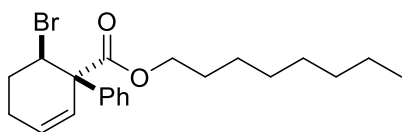
^1H NMR: (400 MHz, CDCl_3): δ 7.33 – 7.25 (m, 5H), 6.10 – 5.96 (m, 2H), 5.08 (ddd, J = 5.9, 2.9, 1.3 Hz, 1H), 4.11 (qd, J = 7.1, 3.0 Hz, 2H), 2.45 – 2.34 (m, 1H), 2.30 – 2.19 (m, 1H), 2.17 – 2.05 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.7, 140.8, 129.5, 128.0, 127.5, 127.2, 125.6, 61.6, 56.1, 56.0, 29.3, 22.5, 13.9.

IR: $\nu[\text{cm}^{-1}]$ = 2982, 2930, 1722, 1495, 1446, 1215, 1096, 1036, 861, 768, 697.

HRMS: (EI-MS) m/z calculated for $\text{C}_{15}\text{H}_{17}\text{O}_2\text{Br}$ [M^+]: 308.0406, found 308.0404.

octyl (1R*,2R*)-2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122c):



Following the general procedure **GP-VI** using vinyl cyclopropane **25c** (67.0 mg, 0.21 mmol, 1.0 equiv) and aq. hydrobromic acid solution (554 mg, 47 wt%, 3.22 mmol, 15 equiv) dissolved in MeCN (0.25 M) gave the title compound **122c** (26.5 mg, 0.07 mmol, 31%, 38% *brsm*) as a slightly yellow oil after stirring 3.5 h at 150 °C and purification by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1). Yield was determined from crude $^1\text{H-NMR}$ using fumaronitrile as internal standard.

R_f = 0.78 (hexanes/ethyl acetate = 19/1, stained in KMnO_4).

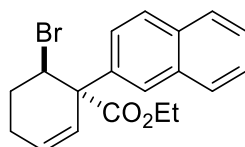
$^1\text{H NMR}$: (400 MHz, CDCl_3): δ 7.38 – 7.07 (m, 5H), 6.13 – 5.86 (m, 2H), 5.17 – 4.95 (m, 1H), 4.01 (t, J = 6.6 Hz, 2H), 2.46 – 2.32 (m, 1H), 2.29 – 2.18 (m, 1H), 2.17 – 2.03 (m, 2H), 1.56 – 1.38 (m, 2H), 1.25 – 1.04 (m, 10H), 0.81 (t, J = 7.1 Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 171.7, 139.8, 128.4, 126.9, 126.5, 126.1, 124.5, 64.6, 55.05, 54.95, 30.7, 28.2, 28.1, 28.0, 27.3, 24.6, 21.6, 21.4, 13.1.

IR: $\nu[\text{cm}^{-1}]$ = 3034, 2926, 2855, 1722, 1491, 1450, 1208, 1018, 805, 772, 734, 697.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{21}\text{H}_{30}\text{O}_2\text{Br}$ $[\text{M}+\text{H}]^+$: 393.1424, found 393.1424.

ethyl (1R*,6R*)-6-bromo-1-(naphthalen-2-yl)cyclohex-2-ene-1-carboxylate (122e):



Following the general procedure **GP-VI** using vinyl cyclopropane **25e** (73.0 mg, 0.26 mmol, 1.0 equiv) and aq. hydrobromic acid solution (451 mg, 47 wt%, 2.60 mmol, 10 equiv) gave the title compound **122e** (51.0 mg, 0.14 mmol, 54%) as a slightly yellow oil after stirring 1.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 3/1).

R_f = 0.64 (hexanes/ethyl acetate = 9/1, stained in KMnO_4).

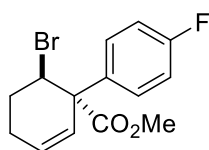
$^1\text{H NMR}$: (400 MHz, CDCl_3): δ 7.96 – 7.74 (m, 4H), 7.56 – 7.38 (m, 3H), 6.18 (s, 2H), 5.24 (dd, J = 6.3, 2.6 Hz, 1H), 4.17 (qd, J = 7.1, 3.9 Hz, 2H), 2.49 (ddd, J = 17.4, 8.9, 5.9 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.27 – 2.16 (m, 2H), 1.15 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.7, 138.2, 132.9, 132.7, 129.8, 128.3, 127.58, 127.55, 126.3, 126.1, 126.1, 125.6, 125.2, 61.7, 56.2, 55.8, 29.3, 22.6, 13.9.

IR: $\nu[\text{cm}^{-1}]$ = 3056, 2978, 2930, 1722, 1599, 1505, 1446, 1215, 1163, 1025, 947, 910, 861, 816, 779, 749, 697.

HRMS: (EI-MS) m/z calculated for $\text{C}_{19}\text{H}_{19}\text{O}_2\text{Br}$ [M^+]: 358.0563, found 358.0556.

methyl (1R*,2R*)-2-bromo-4'-fluoro-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122f):



Following the general procedure **GP-VI** using vinyl cyclopropane **25f** (80.0 mg, 0.34 mmol, 1.0 equiv) and aq. hydrobromic acid solution (593 mg, 47 wt%, 3.40 mmol, 10 equiv) gave the title compound **122f** (55.4 mg, 0.18 mmol, 51%) as a slightly yellow oil after stirring 1.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 15/1 to 3/1).

In the **^{13}C -NMR and ^1H -NMR** signal doubling and broadening due to rotamers is observed.

R_f = 0.57 (hexanes/ethyl acetate = 9/1, stained in vanillin).

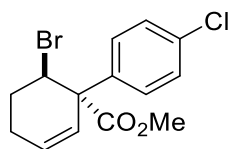
^1H NMR: (400 MHz, CDCl_3): δ 7.33 – 7.23 (m, 2H), 7.10 (td, J = 7.6, 1.3 Hz, 1H), 6.98 (ddd, J = 11.5, 8.1, 1.3 Hz, 1H), 6.20 – 6.04 (m, 1H), 5.79 (ddt, J = 10.2, 2.7, 1.5 Hz, 1H), 5.25 – 5.07 (m, 1H), 3.64 (s, 3H), 2.69 – 2.51 (m, 1H), 2.47 – 2.31 (m, 1H), 2.11 (dddd, J = 14.2, 9.8, 5.9, 2.8 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.3, 131.4, 130.0, 129.9, 129.5, 129.4, 125.0, 123.49, 123.46, 115.6, 115.3, 53.5, 53.20, 53.18, 52.8, 29.0, 22.3.

IR: $\nu[\text{cm}^{-1}]$ = 3038, 3001, 2952, 2840, 1737, 1491, 1454, 1230, 1159, 1025, 816, 757, 693.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{FBr}$ [M^+]: 312.0156, found 312.0155.

methyl (1R*,2R*)-2-bromo-4'-chloro-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122g):



Following the general procedure **GP-VI** using vinyl cyclopropane **25g** (80.0 mg, 0.32 mmol, 1.0 equiv) and aq. hydrobromic acid solution (554 mg, 47 wt%, 3.20 mmol, 10 equiv) gave the title compound **122g** (90.0 mg, 0.27 mmol, 85%) as a colorless oil after stirring 2.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

R_f = 0.55 (hexanes/ethyl acetate = 9/1, stained in vanillin).

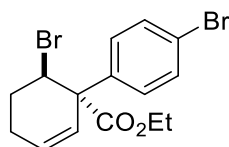
^1H NMR: (400 MHz, CDCl_3): δ 7.35 – 7.29 (m, 2H), 7.25 – 7.22 (m, 2H), 6.11 (dddd, J = 10.2, 4.2, 3.0, 0.8 Hz, 1H), 5.96 (ddt, J = 10.3, 2.9, 1.6 Hz, 1H), 5.18 – 5.00 (m, 1H), 3.68 (s, 3H), 2.43 (dddd, J = 21.5, 9.9, 5.3, 2.7 Hz, 1H), 2.32 – 2.22 (m, 1H), 2.16 (dddd, J = 17.5, 10.2, 5.8, 3.0 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.9, 139.1, 133.6, 130.2, 128.7, 128.2, 125.0, 55.8, 55.3, 52.8, 29.1, 22.6.

IR: $\nu[\text{cm}^{-1}]$ = 2952, 1729, 1491, 1431, 1405, 1301, 1219, 1096, 1021, 910, 824, 760.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{ClBr}$ [M^+]: 327.9860, found 327.9856.

ethyl (1R*,2R*)-2,4'-dibromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122h):



Following the general procedure **GP-VI** using vinyl cyclopropane **25h** (70.0 mg, 0.23 mmol, 1.0 equiv) and aq. hydrobromic acid solution (392 mg, 47 wt%, 2.30 mmol, 10 equiv) gave the title compound **122h** (58.5 mg, 0.15 mmol, 66%) as a slightly yellow oil

after stirring 1.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

R_f = 0.64 (hexanes/ethyl acetate = 9/1, stained in vanillin).

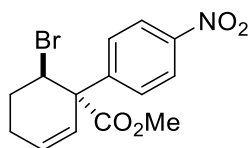
¹H NMR: (400 MHz, CDCl₃): δ 7.51 – 7.42 (m, 2H), 7.22 – 7.15 (m, 2H), 6.10 (dddd, J = 10.3, 4.3, 3.1, 0.8 Hz, 1H), 5.96 (ddt, J = 10.3, 2.8, 1.5 Hz, 1H), 5.17 – 4.99 (m, 1H), 4.15 (qd, J = 7.1, 2.1 Hz, 2H), 2.42 (dddd, J = 21.6, 9.8, 5.1, 2.6 Hz, 1H), 2.33 – 2.20 (m, 1H), 2.23 – 2.07 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 172.3, 139.7, 131.1, 130.0, 129.2, 125.2, 121.7, 61.8, 55.9, 55.3, 29.2, 22.6, 13.9.

IR: ν[cm⁻¹] = 2978, 2930, 1722, 1487, 1446, 1297, 1208, 1150, 1077, 1010, 857, 812, 701.

HRMS: (EI-MS) m/z calculated for C₁₅H₁₆O₂Br₂ [M⁺]: 385.9512, found 385.9505.

methyl (1R*,2R*)-2-bromo-4'-nitro-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122i):



Following the general procedure **GP-VI** using vinyl cyclopropane **25i** (90.0 mg, 0.35 mmol, 1.0 equiv) and aq. hydrobromic acid solution (598 mg, 47 wt%, 3.50 mmol, 10 equiv) gave the title compound **122i** (91.0 mg, 0.27 mmol, 77%) as a yellow oil after stirring 1 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

R_f = 0.36 (hexanes/ethyl acetate = 7/1, stained in KMnO₄).

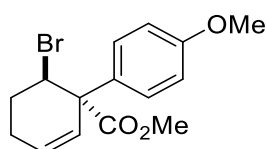
¹H NMR: (400 MHz, CDCl₃): δ 8.27 – 8.08 (m, 2H), 7.53 – 7.43 (m, 2H), 6.23 – 6.12 (m, 1H), 5.98 (ddt, J = 10.2, 2.8, 1.4 Hz, 1H), 5.14 – 5.05 (m, 1H), 3.70 (s, 3H), 2.52 – 2.38 (m, 1H), 2.36 – 2.26 (m, 1H), 2.24 – 2.10 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 172.2, 147.8, 147.3, 131.0, 128.4, 124.2, 123.2, 56.3, 54.3, 53.1, 29.1, 22.4.

IR: $\nu[\text{cm}^{-1}]$ = 2952, 1730, 1603, 1521, 1431, 1349, 1219, 111, 1021, 980, 951, 913, 854, 801, 741, 705.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4\text{Br}$ $[\text{M}+\text{NH}_4]^+$: 357.0444, found 357.0447.

methyl (1R*,2R*)-2-bromo-4'-methoxy-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122k):



Following the general procedure **GP-VI** using vinyl cyclopropane **25k** (54.0 mg, 0.22 mmol, 1.0 equiv) and aq. hydrobromic acid solution (381 mg, 47 wt%, 2.21 mmol, 10 equiv) gave the title compound **122k** (38.0 mg, 0.12 mmol, 53%) as a slightly yellow oil after stirring 1.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

R_f = 0.71 (hexanes/ethyl acetate = 3/1, stained in KMnO_4).

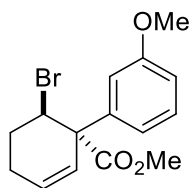
^1H NMR: (400 MHz, CDCl_3): δ 7.36 – 7.19 (m, 2H), 7.05 – 6.84 (m, 2H), 6.17 – 6.08 (m, 1H), 6.04 (ddt, J = 10.1, 2.5, 1.4 Hz, 1H), 5.16 (dq, J = 6.1, 1.2 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 2.47 (dtq, J = 18.2, 7.7, 2.3 Hz, 1H), 2.37 – 2.11 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.4, 158.9, 132.6, 129.5, 128.5, 125.7, 113.3, 56.3, 55.6, 55.2, 52.7, 29.2, 22.7.

IR: $\nu[\text{cm}^{-1}]$ = 3001, 2952, 2840, 1726, 1610, 1513, 1461, 1297, 1252, 1185, 1107, 1036, 910, 828, 805, 749.

HRMS: (EI-MS) m/z calculated for $\text{C}_{15}\text{H}_{17}\text{O}_3\text{Br}$ $[\text{M}^+]$: 324.0356, found 324.0357.

methyl (1R*,2R*)-2-bromo-3'-methoxy-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122l):



Following the general procedure **GP-VI** using vinyl cyclopropane **25l** (67.3 mg, 0.28 mmol, 1.0 equiv) and aq. hydrobromic acid solution (474 mg, 47 wt%, 2.80 mmol, 10 equiv) gave the title compound **122l** (73.3 mg, 0.25 mmol, 90%) as a slightly yellow oil after stirring 0.5 h at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1).

R_f = 0.71 (hexanes/ethyl acetate = 3/1, stained in KMnO₄).

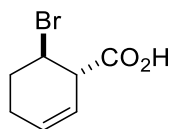
¹H NMR: (400 MHz, CDCl₃): δ 7.26 (t, J = 7.9 Hz, 1H), 6.93 – 6.78 (m, 3H), 6.11 – 6.05 (m, 1H), 6.01 (ddt, J = 10.3, 2.8, 1.5 Hz, 1H), 5.10 (ddd, J = 5.8, 2.6, 1.2 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.49 – 2.38 (m, 1H), 2.33 – 2.23 (m, 1H), 2.22 – 2.09 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 173.1, 159.4, 142.3, 129.8, 129.0, 125.2, 119.5, 113.6, 112.5, 55.9, 55.7, 55.2, 52.7, 29.3, 22.4.

IR: ν[cm⁻¹] = 3034, 3001, 2952, 2837, 1722, 1602, 1491, 1431, 1293, 1219, 1159, 1051, 1025, 999, 861, 835, 738, 693.

HRMS: (EI-MS) m/z calculated for C₁₅H₁₇O₃Br [M⁺]: 324.0356, found 324.0352.

(1S*,6R*)-6-bromocyclohex-2-ene-1-carboxylic acid (122o):



Following the general procedure **GP-VI** using vinyl cyclopropane **25q** (258 mg, 86 wt% 1.23 mmol, 1.0 equiv) and aq. hydrobromic acid solution (2.12 g, 47 wt%, 12.3 mmol, 10 equiv) gave the title compound **122o** (233 mg, 1.14 mmol, 92%) as a colorless oil after stirring 15 min at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate/AcOH = 20/1/0.1 to 3/1/0.1).

R_f = 0.33 (hexanes/ethyl acetate/AcOH = 19/1/0.1, stained in KMnO₄).

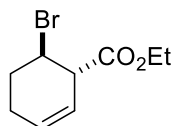
¹H NMR: (400 MHz, CDCl₃): δ 9.00 (bs, –OH), 5.94 (ddt, J = 10.0, 4.2, 3.1 Hz, 1H), 5.63 (ddt, J = 10.0, 3.7, 1.9 Hz, 1H), 4.57 (ddd, J = 9.6, 6.8, 2.8 Hz, 1H), 3.69 – 3.44 (m, 1H), 2.39 – 2.15 (m, 3H), 2.13 – 1.96 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 177.8, 129.5, 121.6, 51.4, 46.9, 30.6, 24.2.

IR: ν[cm⁻¹] = 3034, 2956, 2936, 2643, 1707, 1416, 1297, 1234, 1163, 1018, 913, 887, 775, 686.

HRMS: (APCI-MS) m/z calculated for C₇H₁₀O₂Br [M+H]⁺: 204.9859, found 204.9858.

ethyl (1S*,6R*)-6-bromocyclohex-2-ene-1-carboxylate (122p):



Following the general procedure **GP-VI** using vinyl cyclopropane **25p** (54.8 mg, 89 wt%, 0.32 mmol, 1.0 equiv) and aq. hydrobromic acid solution (552 mg, 47 wt%, 3.20 mmol, 10 equiv) gave the title compound **122p** (16.1 mg, 0.07 mmol, 22%) as a slightly yellow oil after stirring 25 min at 100 °C and purification by flash column chromatography (hexanes/ethyl acetate = 20/1 to 3/1).

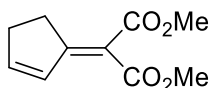
R_f = 0.53 (hexanes/ethyl acetate/AcOH = 19/1/0.1, stained in KMnO₄).

¹H NMR: (400 MHz, CDCl₃): δ 5.89 (dtd, J = 9.9, 3.7, 2.7 Hz, 1H), 5.58 (ddt, J = 9.9, 3.3, 2.0 Hz, 1H), 4.59 (ddd, J = 9.8, 6.9, 3.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.51 (dt, J = 7.0, 2.9 Hz, 1H), 2.35 – 2.13 (m, 3H), 2.12 – 1.98 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 171.9, 128.8, 122.3, 61.2, 51.7, 47.9, 30.8, 24.3, 14.2.

IR: ν[cm⁻¹] = 2960, 1737, 1651, 1446, 1372, 1252, 1215, 1193, 1096, 1033, 913, 857, 798, 734, 664.

HRMS: (APCI-MS) m/z calculated for C₉H₁₄O₂Br [M+H]⁺: 233.0172, found 233.0172.

dimethyl 2-(cyclopent-2-en-1-ylidene)malonate (160):

Following the general procedure **GP-VI** using vinyl cyclopropane **25n** (104 mg, 0.53 mmol, 1.0 equiv) and aq. hydrobromic acid solution (183 mg, 47 wt%, 1.06 mmol, 2 equiv) dissolved in DCM (0.5 M) gave the title compound **160** (70.0 mg, 357 μ mol, 67%) as a colorless oil after stirring 4.5 h at 25 °C and purification by flash column chromatography (hexanes/ethyl acetate = 9/1 to 3/1)

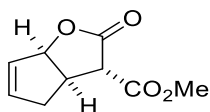
R_f = 0.53 (hexanes/ethyl acetate = 3/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 6.85 – 6.77 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.14 – 2.84 (m, 2H), 2.68 – 2.51 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 168.3, 166.5, 166.2, 152.4, 132.4, 115.4, 52.0, 51.8, 32.9, 31.0.

IR: ν [cm⁻¹] = 2997, 2952, 2844, 1701, 1603, 1435, 1320, 1256, 1223, 1200, 1062, 1029, 924, 760, 793.

HRMS: (EI-MS) m/z calculated for C₁₀H₁₂O₄ [M⁺]: 196.0730, found 196.0734.

methyl (3S*,3aR*,6aR*)-2-oxo-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-3-carboxylate (161):

Following the general procedure **GP-VI** using vinyl cyclopropane **25n** (104 mg, 0.53 mmol, 1.0 equiv) and aq. hydrobromic acid solution (183 mg, 47 wt%, 1.06 mmol, 2 equiv) dissolved in DCM (0.5 M) gave the title compound **161** (12.3 mg, 67.0 μ mol, 13%) as a colorless oil after stirring 4.5 h at 25 °C and purification by flash column chromatography (hexanes/ethyl acetate = 9/1 to 3/1)

R_f = 0.24 (hexanes/ethyl acetate = 3/1 stained in vanillin).

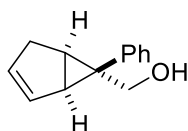
^1H NMR: (400 MHz, CDCl_3): δ 6.10 (ddq, $J = 4.6, 2.3, 1.2$ Hz, 1H), 5.95 – 5.84 (m, 1H), 5.59 (dtt, $J = 7.5, 2.3, 1.2$ Hz, 1H), 3.82 (s, 3H), 3.50 (dddd, $J = 8.2, 7.5, 6.5, 2.6$ Hz, 1H), 3.37 (d, $J = 6.5$ Hz, 1H), 2.89 – 2.74 (m, 1H), 2.39 (dp, $J = 17.6, 2.4$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.7, 168.3, 136.8, 129.0, 88.6, 53.9, 53.2, 40.2, 38.5.

IR: $\nu[\text{cm}^{-1}] = 2956, 2855, 1774, 1737, 1439, 1364, 1275, 1245, 1148, 1025, 962, 828, 749$.

HRMS: (APCI-MS) m/z calculated for $\text{C}_9\text{H}_{11}\text{O}_4$ $[\text{M}+\text{H}]^+$: 183.0652, found 183.0650.

((1S*,5R*,6S*)-6-phenylbicyclo[3.1.0]hex-2-en-6-yl)methanol (25t):



A flame-dried two-neck round-bottom flask was charged under nitrogen atmosphere with LiAlH_4 (284 mg, 7.5 mmol, 1.5 equiv) suspended in dry THF (15 mL/1.8 mmol LiAlH_4) at 0 °C. Ester **25a** (1.07 g, 5.0 mmol, 1.0 equiv) dissolved in THF (0.25 M) was added dropwise *via* an additional funnel and the reaction mixture was stirred for 1 h at 0 °C, then 24 h at ambient temperatures. The mixture was cooled down to 0 °C, EtOAc (20 mL) was added, and the reaction mixture was quenched by dropwise addition of sat. NH_4Cl solution, till no gas evolution was observed anymore. The phases were separated, and the aq. phase was washed with EtOAc (3x20 mL). The combined organic phases were dried over Na_2SO_4 , and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 10/1 to 1/1) to obtain the desired alcohol **25t** (907 mg, 4.87 mmol, 97%) as slightly yellow solid.

R_f = 0.49 (hexanes/ethyl acetate = 2/1, stained in vanillin).

M.p.: 77 – 82 °C

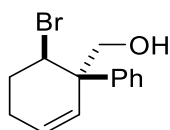
^1H NMR: (400 MHz, CDCl_3): δ 7.34 – 7.25 (m, 2H), 7.24 – 7.14 (m, 3H), 5.73 (dq, $J = 5.6, 2.2$ Hz, 1H), 5.12 (dtd, $J = 5.6, 2.2, 1.1$ Hz, 1H), 3.62 (d, $J = 11.2$ Hz, 1H), 3.41 (d, $J = 11.2$ Hz, 1H), 2.65 – 2.45 (m, 1H), 2.31 (dddd, $J = 6.3, 3.0, 2.1, 0.8$ Hz, 1H), 2.08 – 2.00 (m, 1H), 1.93 (ddt, $J = 7.6, 6.4, 1.2$ Hz, 1H), 1.59 (s, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 136.6, 132.1, 130.9, 130.7, 128.0, 126.5, 71.3, 39.0, 35.1, 33.1, 26.5.

IR: $\nu[\text{cm}^{-1}]$ = 3317, 3056, 3027, 2900, 2833, 1602, 1498, 1446, 1353, 1282, 1230, 1144, 1092, 1012, 962, 865, 820, 734, 701.

HRMS: (EI-MS) m/z calculated for $\text{C}_{13}\text{H}_{14}\text{O}$ [M^+]: 186.1039, found 186.1042.

((1R*,2R*)-2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-yl)methanol (122t):



Following the general procedure **GP-VI** using vinyl cyclopropane **25t** (60.2 mg, 0.32 mmol, 1.0 equiv) and aq. hydrobromic acid solution (835 mg, 47 wt%, 4.60 mmol, 15 equiv) gave the title compound **122t** (20.0 mg, 74.5 μmol , 23%) as a slightly yellow oil after stirring 4 h at 25 °C in DCM (0.25 M). The yield was determined from crude ^1H -NMR using ethylene carbonate as internal standard.

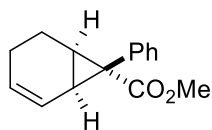
R_f = 0.49 (hexanes/ethyl acetate = 3/1, stained in vanillin).

^1H NMR: (400 MHz, CDCl_3): δ 7.44 – 7.29 (m, 5H), 6.28 – 6.08 (m, 1H), 5.75 (dt, J = 10.0, 2.1 Hz, 1H), 4.69 (dd, J = 11.6, 3.7 Hz, 1H), 4.12 (d, J = 10.6, 8.3 Hz, 1H), 3.97 (d, J = 10.7 Hz, 1H), 2.33 (ddt, J = 9.5, 7.0, 3.7 Hz, 2H), 2.21 – 2.03 (m, 2H), 1.59 (s, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 138.8, 130.0, 129.44, 129.38, 127.7, 127.4, 67.5, 56.1, 50.9, 29.3, 26.5.

IR: $\nu[\text{cm}^{-1}]$ = 3392, 3023, 2945, 2885, 2837, 1496, 1446, 1238, 1051, 1006, 921, 779, 701.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{13}\text{H}_{19}\text{NOBr}$ [$\text{M}+\text{NH}_4$] $^+$: 284.0645, found 284.0643.

methyl (1S*,6R*,7S*)-7-phenylbicyclo[4.1.0]hept-2-ene-7-carboxylate (23):

After a slightly modified literature procedure,^r cyclohexa-1,3-diene **22** (848 mg, 10.6 mmol, 5.0 equiv) and methyl 2-diazo-2-phenylacetate (**11a**, 373 mg, 2.12 mmol, 1.0 equiv) were dissolved in DCM (0.2 M) in a Schlenk-flask and irradiated with one blue LED-module ($h\nu = 450\text{ nm}$, see Figure S1 for photosetup) for 14 h at 25 °C. The solvent was removed under reduced pressure and the crude product was recrystallized from EtOH to yield the desired product **23** (400 mg, 1.75 mmol, 83%) as colorless solid.

Experimental data matched with those reported. (1)

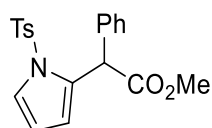
R_f = 0.56 (hexanes/ethyl acetate = 9/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.31 – 7.25 (m, 3H), 7.24 – 7.19 (m, 2H), 6.00 (ddd, $J = 9.1, 4.9, 3.2\text{ Hz}$, 1H), 5.41 (ddd, $J = 10.0, 5.9, 2.6\text{ Hz}$, 1H), 3.57 (s, 3H), 2.45 – 2.21 (m, 2H), 1.97 (ddt, $J = 14.7, 8.9, 2.0\text{ Hz}$, 1H), 1.81 (dddd, $J = 14.6, 10.8, 7.8, 5.0\text{ Hz}$, 1H), 1.66 – 1.45 (signals are overlapping with H₂O, m, 1H), 0.43 (dt, $J = 17.4, 8.8, 2.9\text{ Hz}$, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 174.0, 134.7, 131.7, 128.5, 127.8, 126.9, 122.7, 52.5, 40.4, 27.7, 25.6, 21.0, 16.8.

IR: $\nu[\text{cm}^{-1}] = 3034, 2930, 2840, 1703, 1495, 1431, 1238, 1059, 943, 913, 869, 816, 779, 693$.

HRMS: (EI-MS) m/z calculated for C₁₅H₁₆O₂ [M]⁺: 228.11448, found 228.11478.

methyl 2-phenyl-2-(1-tosyl-1H-pyrrol-2-yl)acetate (166):

^r Guo, Y.; Empel, C.; Pei, C.; Atodiressei, I.; Fallon, T.; Koenigs, R. M. *Org. Lett.* **2020**, 22, 13, 5126–5130.

Following general procedure **GP-VI** using vinyl cyclopropane **165** (51.0 mg, 138 μmol , 1.0 equiv) and aq. HBr-solution (356 mg, 47 wt%, 2.07 mmol, 15 equiv) dissolved in DCM (0.5 mL) gave the title compound **166** (13.9 mg, 37.6 μmol , 27%) after stirring 6.5 h at 25 °C.

R_f = 0.44 (hexanes/ethyl acetate = 3/1 stained in vanillin).

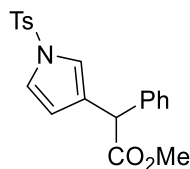
¹H NMR: (400 MHz, CDCl₃): δ 7.52 – 7.48 (m, 2H), 7.30 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.24 (ddd, *J* = 4.9, 2.6, 1.6 Hz, 3H), 7.21 – 7.15 (m, 2H), 7.15 – 7.10 (m, 2H), 6.23 (t, *J* = 3.4 Hz, 1H), 6.12 – 6.04 (m, 1H), 5.50 (s, 1H), 3.67 (s, 3H), 2.38 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 171.7, 144.8, 136.7, 136.1, 131.8, 129.8, 128.6, 128.6, 127.5, 126.8, 123.5, 115.8, 111.6, 52.5, 49.4, 21.6.

IR: $\nu[\text{cm}^{-1}]$ = 3034, 2926, 2952, 1740, 1685, 1595, 1495, 1454, 1368, 1234, 1174, 1118, 1018, 813, 730, 671.

HRMS: (APCI-MS) *m/z* calculated for C₂₀H₂₀NO₄S [M+H]⁺: 370.1108, found 370.1110.

methyl 2-phenyl-2-(1-tosyl-1H-pyrrol-3-yl)acetate (167):



Following general procedure **GP-VI** using vinyl cyclopropane **165** (51.0 mg, 138 μmol , 1.0 equiv) and aq. HBr-solution (356 mg, 47 wt%, 2.07 mmol, 15 equiv) dissolved in DCM (0.5 mL) gave the title compound **167** (25.3 mg, 68.5 μmol , 49%) after stirring 6.5 h at 25 °C.

R_f = 0.41 (hexanes/ethyl acetate = 3/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.73 – 7.65 (m, 2H), 7.31 – 7.17 (m, 7H), 7.09 – 6.99 (m, 2H), 6.19 (dd, *J* = 3.2, 1.7 Hz, 1H), 4.76 (s, 1H), 3.66 (s, 3H), 2.37 (s, 3H).

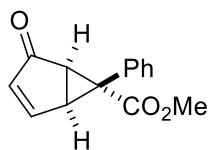
¹³C NMR (101 MHz, CDCl₃): δ 172.5, 145.0, 138.1, 136.0, 130.0, 129.8, 128.7, 128.6, 128.3, 127.5, 126.9, 126.3, 121.1, 118.9, 114.2, 52.4, 49.9, 21.6.

IR: $\nu[\text{cm}^{-1}]$ = 3138, 3030, 2952, 2926, 1737, 1595, 1454, 1368, 1271, 1170, 1100, 1062, 1018, 812, 723, 671.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{20}\text{H}_{20}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 370.1108, found 370.1110.

3.7. Lewis Acid Mediated Endocyclic Ring-Opening

methyl (1S*,5R*,6R*)-4-oxo-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (**182a**):



A round-bottom flask was charged with allylic alcohol **96a** (360 mg, 1.56 mmol, 1.0 equiv) dissolved in DCM (30 mL) and activated MnO_2 (2.04 g, 23.5 mmol, 15 equiv). The reaction mixture was stirred for 24 h at 25 °C. Then an additional portion of MnO_2 was added (300 mg, 3.45 mmol, 2.2 equiv) to the reaction mixture and stirred for 1 h, because **96a** was still detected *via* TLC. The crude reaction mixture was filtered over celite using DCM. The solvent was removed under reduced pressure and the product **182a** (297 mg, 1.30 mmol, 83%) was obtained as yellow solid without further purification.

R_f = 0.4 (hexanes/ethyl acetate = 3/1 stained in vanillin).

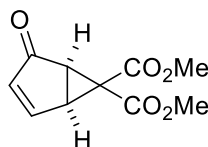
^1H NMR: (300 MHz, CDCl_3): δ 7.33 – 7.24 (m, 4H), 7.21 – 7.14 (m, 2H), 5.50 (dd, J = 5.6, 1.0 Hz, 1H), 3.64 (s, 3H), 3.40 (dd, J = 5.0, 2.6 Hz, 1H), 2.99 (dt, J = 5.1, 0.9 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 202.2, 170.2, 156.6, 132.5, 132.4, 131.5, 128.2, 127.9, 57.3, 53.0, 35.0, 34.7.

IR: $\nu[\text{cm}^{-1}]$ = 3481, 3086, 3060, 3008, 1700, 1495, 1431, 1342, 1308, 1238, 1170, 1115, 869, 820, 738, 705.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{12}\text{O}_3$ $[\text{M}]^+$: 228.07827, found 228.07810.

dimethyl (1S*,5R*)-4-oxobicyclo[3.1.0]hex-2-ene-6,6-dicarboxylate (**182n**)



Step 1: Vinyl cyclopropane **25n** (623 mg, 3.18 mmol, 1.0 equiv) and SeO_2 (388 mg, 3.49 mmol, 1.1 equiv) were dissolved in 1,4-dioxane (c = 2.2 M) in a sealed vessel (20 psi) and heated to 130 °C for 1.5 h in a microwave oven. The reaction mixture was filtered

through a pad of celite with DCM (20 mL). The filtrate was washed with sat. NaHCO_3 -solution (20 mL), H_2O (20 mL) and brine (20 mL). The aq. phase was extracted with an additional portion of DCM (15 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure, to yield the crude product **96n**, which was further used for allylic oxidation without purification.

Step 2: The crude product was dissolved in DCM and MnO_2 (2.76 g, 31.8 mmol, 10 equiv, calc. on compound **25n**) was added. The reaction mixture was stirred for 24 h at 25 °C, filtered through a pad of celite using DCM, washed with sat. NaHCO_3 -solution (2 x 20 mL), H_2O (2 x 20 mL), brine (20 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure to yield the product **182n** (362 mg, 1.70 mmol, 54%, calc. on compound **25n**) as yellow oil without further purification.

R_f = 0.20 (hexanes/ethyl acetate = 3/1 stained in vanillin).

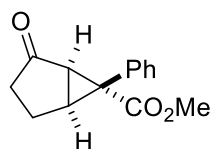
^1H NMR: (400 MHz, CDCl_3): δ 7.43 (dd, J = 5.7, 2.6 Hz, 1H), 5.82 (d, J = 5.6 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.25 (dd, J = 5.1, 2.6 Hz, 1H), 2.70 (dd, J = 5.1, 1.0 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 200.0, 166.3, 164.9, 155.3, 131.0, 55.7, 53.3, 53.1, 33.5, 33.4.

IR: $\nu[\text{cm}^{-1}]$ = 3079, 2960, 2926, 2855, 1733, 1573, 1439, 1305, 1249, 1200, 1081, 1014, 936, 898, 820, 734.

HRMS: (EI-MS) m/z calculated for $\text{C}_{10}\text{H}_{10}\text{O}_5$ $[\text{M}]^+$: 210.05227, found 210.05206.

methyl (1R*,5S*,6R*)-2-oxo-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (183a):



An autoclave vial was charged with allylic ketone **182a** (313 mg, 1.37 mmol, 1.0 equiv) Pd/C (72.9 mg, 10w/w%, 5 mol %) dissolved in ethyl acetate (1 mL). Then, the vial was placed in an autoclave, sealed and pressurized to 40 bar with H_2 at 25 °C for 4 h. The reaction mixture was then filtered over silica and washed with ethyl acetate. The solvent was removed under reduced pressure to yield the desired ketone **183a** (315 mg, 1.37 mmol, quant.) without further purification as white solid.

R_f = 0.47 (hexanes/ethyl acetate = 3/1 stained in vanillin).

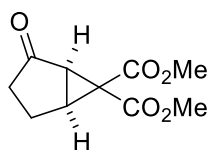
¹H NMR: (400 MHz, CDCl₃): δ 7.40 – 7.23 (m, 5H), 3.61 (s, 3H), 2.86 (t, J = 5.9 Hz, 1H), 2.79 (dt, J = 5.9, 1.1 Hz, 1H), 2.30 (dddd, J = 14.0, 10.9, 8.1, 5.9 Hz, 1H), 1.99 (ddd, J = 14.1, 9.1, 2.1 Hz, 1H), 1.85 (ddt, J = 19.6, 10.9, 1.8 Hz, 1H), 0.80 (dddd, J = 19.5, 9.0, 8.1, 0.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 212.8, 171.8, 132.5, 130.7, 128.8, 128.1, 53.1, 42.2, 39.2, 35.6, 34.9, 21.0.

IR: ν[cm⁻¹] = 2956, 1711, 1454, 1428, 1320, 1238, 1152, 1074, 1029, 961, 880, 835, 790, 749, 708.

HRMS: (APCI-MS) m/z calculated for C₁₄H₁₅O₃ [M+H]⁺: 231.1016, found 231.1015.

dimethyl (1R*,5S*)-2-oxobicyclo[3.1.0]hexane-6,6-dicarboxylate (183n):



An autoclave vial was charged with allylic ketone **182n** (148 mg, 704 μmol, 1.0 equiv) Pd/C (37.5 mg, 35.2 μmol, 10w/w%, 5 mol %) dissolved in ethyl acetate (1 mL). Then, the vial was placed in an autoclave, sealed and pressurized to 60 bar with H₂ at 25 °C for 2 h. The reaction mixture was then filtered over silica and washed with ethyl acetate. The solvent was removed under reduced pressure to yield the desired ketone **183n** (137 mg, 645 μmol, 92%) without further purification as slightly yellow oil.

R_f = 0.33 (hexanes/ethyl acetate = 1/1 stained in vanillin).

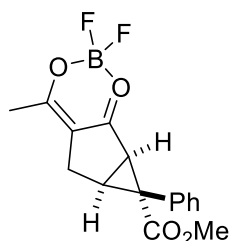
¹H NMR: (400 MHz, CDCl₃): δ 3.72 (s, 3H), 3.69 (s, 3H), 2.69 (t, J = 5.7 Hz, 1H), 2.47 (d, J = 5.7 Hz, 1H), 2.30 (dddd, J = 14.0, 11.3, 8.0, 5.7 Hz, 1H), 2.22 – 2.08 (m, 2H), 1.72 (dt, J = 19.5, 8.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 209.4, 167.9, 166.0, 53.3, 53.2, 40.8, 39.6, 35.2, 33.8, 20.7.

IR: ν[cm⁻¹] = 2960, 1733, 1439, 1357, 1316, 1260, 1178, 1092, 1040, 999, 921, 895, 831, 779, 734.

HRMS: (APCI-MS) m/z calculated for $C_{10}H_{13}O_5$ $[M+H]^+$: 213.0757, found 213.0757.

methyl (5aS*,6R*,6aR*)-2,2-difluoro-4-methyl-6-phenyl-5,5a,6,6a-tetrahydro-2H-113,214-cyclopropa[3,4]cyclopenta[1,2-e][1,3,2]dioxaborinine-6-carboxylate (184):



An oven-dried Schlenk-flask was charged with ketone **183a** (62.4 mg, 271 μ mol, 1.0 equiv) dissolved in dry DCM under nitrogen atmosphere. Acetic anhydride (277 mg, 2.71 mmol, 10 equiv) and $BF_3 \cdot O(C_2H_5)_2$ (231 mg, 1.63 mmol, 6.0 equiv) were added to the solution and the reaction mixture was stirred for 1.5 h at ambient temperatures under nitrogen atmosphere. Sat. $NaHCO_3$ -solution (10 mL) and DCM (10 mL) were added and the phases were separated. The aq. phase was extracted with DCM (2 x 10 mL) and the combined organic layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 2/1) to yield the title compound **184** (83.1 mg, 260 μ mol, 96%) as yellow oil. A crystal for X-Ray was obtained *via* slowly evaporating from DCM.

R_f = 0.38 (hexanes/ethyl acetate = 5/1 stained in vanillin).

M.p.: 130 – 133 °C.

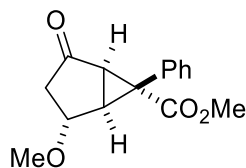
¹H NMR: (400 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 3H), 7.25 – 7.15 (m, 2H), 3.66 (s, 3H), 3.24 – 3.15 (m, 1H), 3.02 – 2.87 (m, 2H), 2.49 (dd, J = 14.8, 1.7 Hz, 1H), 1.76 (s, 3H).

¹³C NMR (101 MHz, $CDCl_3$): δ 192.8, 185.7, 171.4, 130.5, 130.1, 128.7, 128.4, 53.4, 40.8, 38.9, 31.1, 26.3, 21.6, 1.0.

IR: $\nu[cm^{-1}]$ = 3030, 2967, 2933, 2855, 1722, 1603, 1532, 1435, 1387, 1338, 1245, 1189, 1081, 1044, 872, 850, 705.

HRMS: (EI-MS) m/z calculated for $C_{16}H_{15}BF_2O_4$ $[M]^+$: 321.1104, found 321.1107.

methyl (1S*,2R*,5R*,6R*)-2-methoxy-4-oxo-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (185):



An oven-dried Schlenk-flask was charged with ketone **182a** (60.8 mg, 266 μmol , 1.0 equiv) dissolved in dry MeOH under nitrogen atmosphere. $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$ (226 mg, 1.60 mmol, 6.0 equiv) was added to the solution and the reaction mixture was stirred for 1.5 h at ambient temperatures under nitrogen atmosphere. Sat. NaHCO_3 -solution (10 mL) and DCM (10 mL) were added and the phases were separated. The aq. phase was extracted with DCM (2 x 10 mL) and the combined organic layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 2/1) to yield the title compound **185** (34.4 mg, 132 μmol , 50%) as yellow oil.

$R_f = 0.49$ (hexanes/ethyl acetate = 3/1 stained in vanillin).

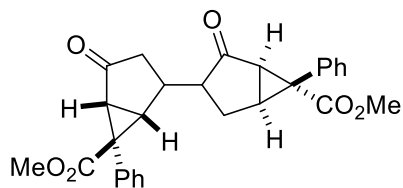
^1H NMR: (400 MHz, CDCl_3): δ 7.31 – 7.07 (m, 5H), 3.82 (d, $J = 5.8$ Hz, 1H), 3.56 (s, 3H), 3.29 (s, 3H), 3.01 (d, $J = 5.7$ Hz, 1H), 2.77 (d, $J = 5.6$ Hz, 1H), 1.85 (d, $J = 19.6$ Hz, 1H), 1.05 (dd, $J = 19.7, 5.8$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 209.7, 171.1, 132.2, 130.6, 128.9, 128.3, 76.8, 56.4, 53.2, 42.9, 40.6, 39.3, 38.4.

IR: $\nu[\text{cm}^{-1}] = 3030, 2989, 2952, 2900, 2829, 1722, 1498, 1439, 1394, 1312, 1282, 1230, 1182, 1096, 924, 872, 824, 742, 705$.

HRMS: (EI-MS) m/z calculated for $\text{C}_{16}\text{H}_{16}\text{O}_4$ $[\text{M}]^+$: 260.10431, found 260.10393.

dimethyl (1S*,1'R*,5R*,5'S*,6R*,6'R*)-2',4-dioxo-6,6'-diphenyl-[2,3'-bi(bicyclo[3.1.0]hexane)]-6,6'-dicarboxylate (189):



To a magnetically stirred solution of the ketone **182a** (60.0 mg, 263 μmol , 1.0 equiv) and triethylsilane (115 mg, 986 μmol , 3.75 equiv) dissolved in DCM (6 mL) at $-78\text{ }^{\circ}\text{C}$ was added TMSOTf (129 mg, 578 μmol , 2.2 equiv) and stirred for 2 h. The reaction mixture was quenched with saturated NaHCO_3 (6 mL) and extracted with DCM ($3 \times 20\text{ mL}$) and the combined organic layer was washed with brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 3/1) to obtain the title compound **189** (54.2 mmol, 118 μmol , 90%) as colorless solid.

R_f = 0.2 (hexanes/ethyl acetate = 3/1 stained in vanillin).

M.p.: 110 – 113 $^{\circ}\text{C}$

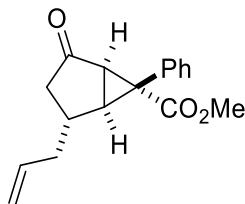
^1H NMR: (400 MHz, CDCl_3): δ 7.43 – 7.11 (m, 10H), 3.60 (s, 3H), 3.55 (s, 3H), 2.85 – 2.78 (m, 2H), 2.73 (dt, $J = 5.8, 1.0\text{ Hz}$, 1H), 2.44 – 2.39 (m, 2H), 2.24 (dd, $J = 14.2, 8.5\text{ Hz}$, 1H), 2.05 – 1.95 (m, 1H), 1.13 – 1.06 (m, 1H), 0.97 – 0.82 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 211.8, 211.1, 171.6, 171.4, 132.5, 132.1, 130.6, 130.5, 129.0, 128.9, 128.3, 128.2, 53.2, 53.1, 49.0, 42.5, 42.1, 39.8, 39.6, 38.7, 38.5, 33.9, 33.7, 24.7.

IR: $\nu[\text{cm}^{-1}] = 3030, 3060, 2952, 1718, 1435, 1316, 1234, 1178, 1074, 943, 880, 790, 731, 701$.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{28}\text{H}_{27}\text{O}_6$ $[\text{M}+\text{H}]^+$: 459.1802, found 459.1806.

methyl (1S*,2R*,5R*,6R*)-2-allyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (190)



A Schlenk-flask was charged with ketone **182a** (108 mg, 0.47 mmol, 1.0 equiv) and allyl trimethylsilane (108 mg, 0.94 mmol, 2.0 equiv) dissolved in DCM at -78 °C. TMSOTf (231 mg, 1.04 mmol, 2.2 equiv) was added and the resulting mixture was stirred for 5 h and allowed to warm of up to room temperature, quenched with sat. NaHCO₃ solution (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 3/1) to yield the title compound **190** (73.4 mg, 0.27 mmol, 57%) as colorless oil.

R_f = 0.73 (hexanes/ethyl acetate = 3/1 stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.32 – 7.24 (m, 3H), 7.23 – 7.19 (m, 2H), 5.68 (ddt, *J* = 17.3, 9.6, 6.6 Hz, 1H), 5.10 – 4.89 (m, 2H), 3.54 (s, 3H), 2.85 – 2.58 (m, 2H), 2.30 – 2.21 (m, 2H), 2.13 (dddd, *J* = 9.3, 8.0, 6.7, 5.3 Hz, 1H), 1.64 – 1.43 (m, 1H), 0.98 – 0.84 (m, 1H).

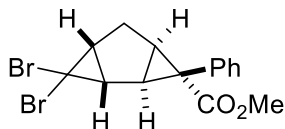
¹³C NMR (101 MHz, CDCl₃): 211.9, 171.7, 134.8, 132.8, 130.6, 128.8, 128.1, 117.9, 53.1, 41.9, 41.5, 40.6, 40.3, 39.5, 33.5.

IR: ν[cm⁻¹] = 3030, 2952, 2922, 1726, 1640, 1498, 1439, 1316, 1237, 1185, 1074, 973, 921, 865, 787, 742, 705.

HRMS: (EI-MS) *m/z* calculated for C₁₇H₁₈O₃ [M]⁺: 271.1329, found 271.1330.

3.8. Endocyclic Ring-Expansion via Rearrangement Reactions

methyl (1S,2R,3S,4R,6R)-7,7-dibromo-3-phenyltricyclo[4.1.0.0^{2,4}]heptane-3-carboxylate (218):



A pressure tube was charged with vinyl cyclopropane **25a** (150 mg, 700 μmol , 1.0 equiv), TEBAC (3.2 mg, 14 μmol , 2 mol%) and CHBr_3 (442 mg, 1.75 mmol, 2.5 equiv) dissolved in DCE. Powdered NaOH (140 mg, 3.50 mmol, 5.0 equiv) was added slowly to the solution and the reaction mixture was stirred at 100 $^\circ\text{C}$ for 11 h in a heating block. The mixture was filtered over celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 9/1) to yield the title compound **218** (257 mg, 666 μmol , 95%) as a yellow solid.

R_f = 0.60 (hexanes/ethyl acetate = 9/1 stained in vanillin).

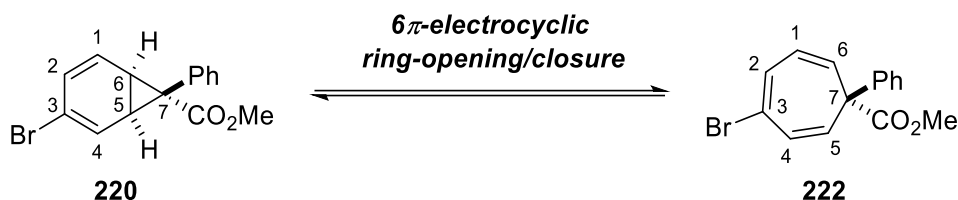
^1H NMR: (400 MHz, CDCl_3): δ 7.42 – 7.28 (m, 3H), 7.25 – 7.19 (m, 2H), 3.57 (s, 3H), 2.68 – 2.41 (m, 1H), 2.27 – 2.10 (m, 3H), 2.15 – 2.04 (m, 1H), 1.20 – 1.08 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.3, 133.1, 131.6, 128.4, 127.4, 52.6, 40.7, 39.4, 39.1, 37.8, 34.9, 33.5, 30.5.

IR: $\nu[\text{cm}^{-1}]$ = 3030, 2952, 2862, 1714, 1603, 1498, 1435, 1327, 1290, 1238, 1197, 1137, 1066, 1025, 913, 872, 790, 731.

HRMS: (EI-MS) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{O}_2\text{Br}_2$ $[\text{M}]^+$: 383.93551, found 383.93478.

methyl (1R*,6R*,7S*)-3-bromo-7-phenylbicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (220), methyl (S*)-4-bromo-1-phenylcyclohepta-2,4,6-triene-1-carboxylate (222):



A pressure tube was charged with compound **218** (240 mg, 622 μmol , 1.0 equiv) dissolved in DMSO (6.2 mL) and H_2O (44.8 μL , 44.8 mg, 2.49 mmol, 4.0 equiv) was added. The reaction was stirred for 2.5 h at 150 $^\circ\text{C}$ and allowed to cool down to ambient temperatures. H_2O (10 mL) was added and the reaction mixture was extracted with diethyl ether (2 x 10 mL), again washed with H_2O (2 x 10 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 3/1) to yield the title compounds **220** and **222** in an equilibrium (94.0 mg 308 μmol , 50%) as yellow solid.

R_f = 0.49 (hexanes/ethyl acetate = 3/1 stained in vanillin).

^1H NMR: (400 MHz, CDCl_3): δ 7.31 – 7.18 (m, 5H), 6.52 (dt, J = 7.8, 1.1 Hz, 1H), 6.31 – 6.20 (m, 2H), 4.58 (ddd, J = 6.6, 5.3, 1.0 Hz, 1H), 4.50 (dd, J = 7.8, 5.2 Hz, 1H), 3.71 (s, 3H).

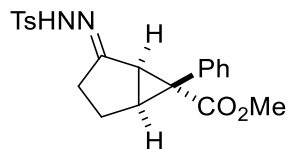
^{13}C NMR (101 MHz, CDCl_3): δ 175.0, 135.1, 131.0, 130.6, 127.4, 127.3, 126.8, 126.3, 121.4, 78.8, 77.3, 53.1, 39.9.

IR: $\nu[\text{cm}^{-1}]$ = 3030, 2952, 1715, 1603, 1495, 1435, 1334, 1245, 1152, 1070, 1006, 969, 924, 891, 805, 768, 731, 701.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{O}_2\text{Br}$ $[\text{M}+\text{H}]^+$: 305.0172, found 305.1076.

3.9. Pd-Catalyzed Ring-Expansion via *in-situ* Diazomethyl Cyclopropane

methyl(1R*,5S*,6R*, E)-6-phenyl-2-(2-tosylhydrazineylidene)bicyclo[3.1.0]hexane-6-carboxylate (264):



4-methylbenzenesulfonohydrazide (141 mg, 0.76 mmol, 1.1 equiv) was stirred and heated up to 65 °C in methanol (1.0 mL), until 4-methylbenzenesulfonohydrazide was completely dissolved. Then the ketone **183a** (159 mg, 0.69 mmol, 1.0 equiv) was added to the solution. After completion of the reaction as monitored by TLC (18 h), the crude product was obtained as a precipitate, which was washed with petroleum ether and then dried in vacuo and used without further purification: **264** (282 mg, 0.71 mmol, >100%)

$R_f = 0.49$ (PE/EA = 3/1).

^1H NMR (300 MHz, Chloroform- d): δ 7.95 – 7.77 (m, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.20 (tt, $J = 7.3, 1.4$ Hz, 1H), 6.95 (d, $J = 21.8$ Hz, 4H), 6.76 (s, 1H), 3.57 (s, 3H), 3.06 (d, $J = 6.4$ Hz, 1H), 2.66 (t, $J = 6.1$ Hz, 1H), 2.50 (s, 3H), 2.31 – 2.10 (m, 1H), 2.07 – 1.79 (m, 2H), 0.37 (dt, $J = 17.1, 8.2$ Hz, 1H).

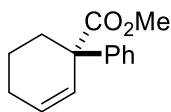
^{13}C NMR (101 MHz, CDCl_3): δ 172.1, 163.8, 144.2, 135.6, 132.6, 130.9, 129.7, 128.3, 128.1, 128.0, 127.6, 52.8, 39.6, 37.5, 34.5, 26.0, 23.8, 21.7.

IR: $\nu[\text{cm}^{-1}] = 3191, 3060, 2952, 1715, 1599, 1435, 1402, 1346, 1241, 1163, 1074, 1036, 965, 928, 846, 746, 693$.

HRMS: (APCI-MS) calc. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$ $[\text{M}-\text{H}]^+$: 399.1373, found 399.1380.

3.10. Post-Functionalization of Cyclohexenes

methyl (S*)-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (277):



An oven-dried Schlenk-flask was equipped with a stir-bar, charged with cyclohexene **122a** (89.0 mg, 0.30 mmol, 1.0 equiv), 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane (TTMSS) (97.5 mg, 392 μ mol, 1.3 equiv) and AIBN (4.95 mg, 30.2 μ mol, 10 mol%) dissolved in dry MeCN (0.3 M) and placed in an aluminum heating block. After three “freeze-pump-thaw” cycles, the reaction mixture was stirred for 72 h at 60 °C under nitrogen atmosphere. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 99/1 to 9/1) to obtain the desired product **277** (48.0 mg, 0.22 mmol, 74%) as colorless oil.

R_f = 0.58 (hexanes/ethyl acetate = 9/1, stained in KMnO_4).

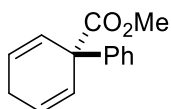
^1H NMR: (400 MHz, CDCl_3): δ 7.31 – 7.10 (m, 5H), 6.06 – 5.94 (m, 2H), 3.63 (s, 3H), 2.42 (ddd, J = 13.3, 8.4, 2.8 Hz, 1H), 2.10 – 1.90 (m, 2H), 1.75 (ddd, J = 13.2, 9.3, 3.0 Hz, 1H), 1.69 – 1.36 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 175.8, 144.9, 131.2, 129.0, 128.9, 127.3, 126.9, 52.8, 52.7, 35.2, 25.5, 20.0.

IR: $\nu[\text{cm}^{-1}]$ = 3030, 2945, 2837, 1730, 1491, 1435, 1245, 1208, 1167, 1111, 1085, 1051, 924, 839, 790, 731, 701.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{16}\text{O}_2$ [M^+]: 216.1145, found 216.1147.

methyl [1,1'-biphenyl]-1(4H)-carboxylate (278):



An oven-dried Schlenk-flask was equipped with a stir-bar and charged with cyclohexene **122a** (136 mg, 0.46 mmol, 1.0 equiv), 4CzIPN (7.27 mg, 9.21 μ mol, 2 mol%), $\text{Co}(\text{dmgH})_2\text{PyCl}$ (9.30 mg, 23.0 μ mol, 5 mol%), $i\text{-Pr}_2\text{Net}$ (11.9 mg, 92.2 μ mol, 20 mol%)

and K_2CO_3 (63.7 mg, 461 μmol , 1.0 equiv) dissolved in dry MeCN (0.3 M). After three “freeze-pump-thaw” cycles the reaction mixture was irradiated with a blue LED ($h\nu = 455\text{nm}$, for photochemical setup see Figure S1) for 16 h at 25 °C. The reaction mixture was washed with H_2O (2x10 mL), the aq. layer was extracted with DCM (2x10 mL) and the combined organic phase was dried over Na_2SO_4 and filtered through a pad of celite. The solvent was removed under reduced pressure to obtain the product **277** (97.8 mg, 0.46 mmol, 99%) as yellow oil without further purification. Reaction setup/conditions were adopted from *Leonori et al.*^s

$R_f = 0.78$ (hexanes/ethyl acetate = 3/1, stained in KMnO_4).

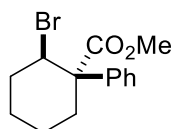
$^1\text{H NMR}$: (400 MHz, CDCl_3): δ 7.39 – 7.17 (m, 5H), 6.08 (dt, $J = 10.5, 1.9$ Hz, 2H), 6.02 – 5.91 (m, 2H), 3.74 (s, 3H), 2.75 – 2.65 (m, 2H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 174.2, 143.8, 128.7, 127.6, 127.5, 126.9, 126.3, 125.0, 52.4, 25.8.

IR : $\nu[\text{cm}^{-1}] = 3038, 2952, 2881, 2102, 1730, 1595, 1491, 1435, 1223, 1036, 943, 768, 738, 697$.

HRMS : (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{14}\text{O}_2$ [M^+]: 214.0988, found 214.0990.

methyl (1R*,2R*)-2-bromo-1-phenylcyclohexane-1-carboxylate (**293**):



An autoclave vial was charged with cyclohexene compound **122a** (118 mg, 0.40 mmol, 1.0 equiv) and Pd/C (21.3 mg, 10 wt%, 5 mol%) dissolved in ethanol (0.8 M). Then, the vial was placed in an autoclave, sealed and pressurized to 60 bars with H_2 at 25 °C for 4 h. The reaction mixture was filtered through a pad of silica and washed with ethyl acetate. The solvent was removed under reduced pressure to obtain the desired cyclohexane **293** (112 mg, 0.38 mmol, 94%) without further purification as colorless solid.

$R_f = 0.78$ (hexanes/ethyl acetate = 3/1, stained in KMnO_4).

^s Zhao, H.; McMillan, A. J.; Constantin, T.; Mykura, R. C.; Julia, F.; Leonori, D. *J. Am. Chem. Soc.* **2021**, *143*, 14806–14813.

M.p.: 46 – 49 °C

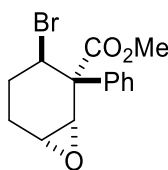
¹H NMR: (400 MHz, CDCl₃): δ 7.43 – 7.26 (m, 5H), 5.26 (q, J = 2.8 Hz, 1H), 3.65 (s, 3H), 2.55 (ddt, J = 13.1, 3.4, 1.7 Hz, 1H), 2.34 – 2.14 (m, 3H), 1.95 – 1.78 (m, 2H), 1.67 – 1.51 (m, 1H), 1.44 – 1.22 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 173.0, 142.3, 128.5, 127.5, 125.6, 60.1, 55.2, 52.6, 32.9, 26.8, 23.4, 19.8.

IR: ν[cm⁻¹] = 2937, 2859, 1718, 1580, 1491, 1446, 1290, 1230, 1141, 1085, 1036, 921, 820, 783, 730, 701.

HRMS: (EI-MS) m/z calculated for C₁₄H₁₇O₂Br [M⁺]: 296.0406, found 296.0411.

methyl (1S*,2S*,3R*,6R*)-3-bromo-2-phenyl-7-oxabicyclo[4.1.0]heptane-2-carboxylate (295):



Cyclohexene compound **122a** (1.54 g, 5.23 mmol, 1.0 equiv) was dissolved in DCM (0.2 M) and *m*-CPBA (4.21 g, 75 wt%, 18.3 mmol, 3.5 equiv) was added. The reaction mixture was stirred for 24 h at 25 °C, quenched with sat. aq. sodium thiosulfate solution and the phases were separated. The aq. layer was extracted with DCM (3x10 mL) and the combined organic phases were washed with sat. NaHCO₃-solution (2x20 mL), brine (2x20 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 10/1 to 1/1) to obtain the desired product **295** (1.62 g, 5.21 mmol, quant.) as slightly yellow solid.

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from DCM.

M.p.: 88 – 91 °C

R_f = 0.51 (hexanes/ethyl acetate = 5/1, stained in vanillin).

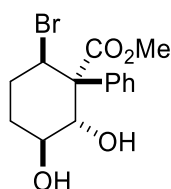
^1H NMR: (400 MHz, CDCl_3): δ 7.41 – 7.30 (m, 3H), 7.28 – 7.23 (m, 2H), 4.95 – 4.82 (m, 1H), 3.82 (d, J = 3.6 Hz, 1H), 3.75 (s, 3H), 3.53 (td, J = 3.2, 1.3 Hz, 1H), 2.33 – 2.23 (m, 1H), 2.19 – 2.03 (m, 2H), 1.93 – 1.77 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.9, 139.3, 128.1, 127.9, 55.8, 55.5, 53.7, 53.4, 52.8, 25.6, 21.6.

IR: $\nu[\text{cm}^{-1}]$ = 2952, 2863, 1718, 1495, 1435, 1327, 13001, 1238, 1193, 1156, 1025, 1066, 965, 824, 738, 705.

HRMS: (EI-MS) m/z calculated for $\text{C}_{14}\text{H}_{15}\text{O}_3\text{Br}$ [M^+]: 310.0199, found 310.0193.

methyl (1S*,2S*,3S*,6R*)-6-bromo-2,3-dihydroxy-1-phenylcyclohexane-1-carboxylate (296):



A round-bottom flask was charged with epoxide **295** (77.4 mg, 0.25 mmol, 1.0 equiv) dissolved in $\text{H}_2\text{O}/\text{MeCN}$ (0.13 M, 1/1), conc. H_2SO_4 (73.2 mg, 0.75 mmol, 3.0 equiv) was added and the reaction mixture was stirred for 6 h at 50 °C in an oil bath. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 5/1 to 1/3) to obtain the desired product **296** (52.3 mg, 0.16 mmol, 64%, 86% *brsm*) as colorless oil.

R_f = 0.06 (hexanes/ethyl acetate = 3/1, stained in vanillin).

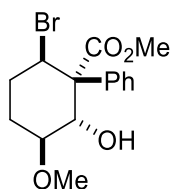
^1H NMR: (400 MHz, CDCl_3): δ 7.59 – 7.46 (m, 2H), 7.45 – 7.28 (m, 3H), 5.00 (dt, J = 3.5, 1.8 Hz, 1H), 4.44 (d, J = 9.7 Hz, 1H), 4.06 (bs, OH), 3.86 (s, 3H), 3.62 (td, J = 9.7, 6.4 Hz, 1H), 2.32 – 2.14 (m, 2H), 2.12 – 1.96 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.8, 138.8, 128.6, 128.2, 127.2, 73.7, 72.6, 59.4, 59.2, 53.2, 30.6, 27.0.

IR: $\nu[\text{cm}^{-1}]$ = 3463, 3008, 2952, 2878, 1711, 1498, 1435, 1297, 1223, 1051, 876, 842, 753, 697.

HRMS: (APCI-MS) m/z calculated for $C_{14}H_{18}O_4Br$ $[M+H]^+$: 329.0383, found 329.0387.

methyl (1S*,2S*,3S*,6R*)-6-bromo-2-hydroxy-3-methoxy-1-phenylcyclohexane-1-carboxylate (297):



A round-bottom flask was charged with epoxide **295** (102 mg, 0.33 mmol, 1.0 equiv) dissolved in MeOH (0.15 M). Then, H_2SO_4 (32.2 mg, 328 μ mol, 1.0 equiv) was added and the reaction mixture was stirred for 6 h at 50 °C in an oil bath. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 10/1 to 1/2) to obtain the desired product **297** (80.1 mg, 0.23 mmol, 71%) as slightly yellow oil.

R_f = 0.11 (hexanes/ethyl acetate = 5/1, stained in vanillin).

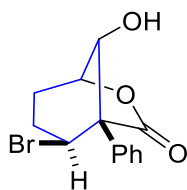
1H NMR: (400 MHz, $CDCl_3$): δ 7.56 – 7.49 (m, 2H), 7.39 – 7.28 (m, 3H), 4.96 (td, J = 3.0, 1.2 Hz, 1H), 4.59 (d, J = 9.7 Hz, 1H), 3.84 (s, 3H), 3.55 (s, 3H), 3.27 (ddd, J = 11.3, 9.6, 4.9 Hz, 1H), 2.29 – 2.16 (m, 2H), 2.14 – 2.05 (m, 1H), 2.00 – 1.86 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 139.1, 128.5, 127.9, 127.4, 81.5, 72.4, 60.1, 59.6, 57.7, 53.1, 30.6, 25.3.

IR: $\nu[cm^{-1}]$ = 3493, 2948, 2833, 1701, 1498, 1435, 1353, 1297, 1223, 1200, 1115, 1051, 924, 872, 842, 734, 697.

HRMS: (APCI-MS) m/z calculated for $C_{15}H_{20}O_4Br$ $[M+H]^+$: 343.0539, found 343.0545.

(1R*,2S*,5S*,8R*)-2-bromo-8-hydroxy-1-phenyl-6-oxabicyclo[3.2.1]octan-7-one (298):



Epoxide **295** (73.2 mg, 235 μ mol, 1.0 equiv) and H_2SO_4 (34.6 mg, 0.35 mmol, 1.5 equiv) were dissolved in toluene (0.1 M) in a sealed vessel (20 psi) and heated to 80 $^\circ\text{C}$ for 0.5 h in a microwave oven. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 5/1 to 1/1) to obtain the desired product **298** (42.5 mg, 0.14 mmol, 61%) as colorless crystals.

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from DCM.

M.p.: 181 – 185 $^\circ\text{C}$

R_f = 0.56 (hexanes/ethyl acetate = 1/1, stained in vanillin).

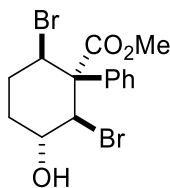
^1H NMR: (400 MHz, CDCl_3): δ 7.85 – 7.73 (m, 2H), 7.47 – 7.34 (m, 3H), 5.04 (d, J = 3.3 Hz, 1H), 4.83 (dd, J = 3.8, 2.5 Hz, 1H), 4.51 – 4.37 (m, 1H), 2.62 – 2.43 (m, 1H), 2.36 – 2.22 (m, 1H), 2.23 – 2.11 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 172.9, 133.9, 128.6, 128.4, 128.3, 80.6, 76.1, 60.7, 57.1, 29.9, 24.1.

IR: $\nu[\text{cm}^{-1}]$ = 3288, 2960, 2863, 1774, 1498, 1446, 1338, 1297, 1219, 141, 1096, 984, 906, 835, 760, 731.

HRMS: (EI-MS) m/z calculated for $\text{C}_{13}\text{H}_{13}\text{O}_3\text{Br}$ [M^+]: 296.0043, found 296.0043.

methyl (1S*,2R*,3R*,6R*)-2,6-dibromo-3-hydroxy-1-phenylcyclohexane-1-carboxylate (299a):



A round-bottom flask was charged with cyclohexene **122a** (151 mg, 0.51 mmol, 1.0 equiv) and NBS (182 mg, 1.02 mmol, 2.0 equiv) dissolved in an acetone/H₂O (0.21 M, 3/1) mixture. The reaction mixture was stirred for 6 h at 25 °C in an oil bath, quenched with sat. sodium thiosulfate solution until the initial yellow color had faded. The phases were separated, the aq. phase was extracted with DCM (3x10 mL) and the combined organic phases were washed with H₂O (2x20 mL), brine (2x20 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1) to obtain the desired product **299a** (149 mg, 0.38 mmol, 74%) as colorless crystals.

In ¹H-NMR and ¹³C-NMR signals are missing or signal broadening is observed due to long relaxation time. However, structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from DCM.

M.p.: 155 – 158 °C

R_f = 0.27 (hexanes/ethyl acetate = 3/1, stained in vanillin).

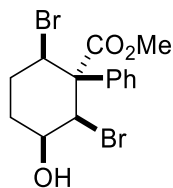
¹H NMR: (400 MHz, CDCl₃): δ 7.70 – 7.57 (m, 2H), 7.41 – 7.29 (m, 3H), 5.39 (s, 1H), 5.20 (s, 1H), 4.53 (td, J = 5.4, 2.7 Hz, 1H), 3.65 (s, 3H), 2.62 (d, J = 8.9 Hz, 2H), 2.29 – 2.07 (m, 1H), 1.88 – 1.71 (m, 1H), 1.54 (d, J = 25.6 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 171.0, 129.0, 127.8, 127.5, 70.8, 53.3, 50.7, 28.3.

IR: ν[cm⁻¹] = 3511, 2952, 2859, 1730, 1502, 1446, 1323, 1226, 1066, 988, 962, 753, 693, 667.

HRMS: (APCI-MS) m/z calculated for C₁₄H₁₆O₃Br₂Na [M+Na]⁺: 412.9358, found 412.9356.

methyl (1S*,2R*,3S*,6R*)-2,6-dibromo-3-hydroxy-1-phenylcyclohexane-1-carboxylate (299b):



A round-bottom flask was charged with cyclohexene **122a** (151 mg, 0.51 mmol, 1.0 equiv) and NBS (182 mg, 1.02 mmol, 2.0 equiv) dissolved in an acetone/H₂O (0.21 M, 3/1) mixture. The reaction mixture was stirred for 6 h at 25 °C in an oil bath, quenched with sat. sodium thiosulfate solution until the initial yellow color had faded. The phases were separated, the aq. phase was extracted with DCM (3x10 mL) and the combined organic phases were washed with H₂O (2x20 mL), brine (2x20 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 100/1 to 5/1) to obtain the desired product **299b** (25.3 mg, 0.07 mmol, 13%) as colorless oil.

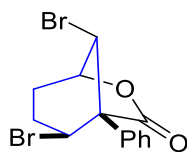
R_f = 0.36 (hexanes/ethyl acetate = 3/1, stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.34 – 7.20 (m, 5H), 4.83 (d, J = 10.2 Hz, 1H), 4.77 (td, J = 3.0, 1.1 Hz, 1H), 3.89 (td, J = 10.3, 5.6 Hz, 1H), 3.71 (s, 3H), 2.76 (s, 1H), 2.54 (dddd, J = 15.6, 13.0, 5.2, 3.2 Hz, 1H), 2.16 – 1.94 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 170.4, 138.8, 128.02, 127.98, 127.4, 71.3, 61.3, 61.0, 60.0, 52.7, 30.7, 28.4.

IR: ν[cm⁻¹] = 3522, 2952, 2870, 1718, 1498, 1446, 1364, 1331, 1297, 1267, 1200, 1152, 1070, 932, 768, 738, 697

HRMS: (APCI-MS) m/z calculated for C₁₄H₁₇O₃Br₂ [M+H]⁺: 390.9539, found 390.9538.

(1R*,2S*,8S*)-2,8-dibromo-1-phenyl-6-oxabicyclo[3.2.1]octan-7-one (300):

A round-bottom flask was charged with compound **299a** (83.0 mg, 0.21 mmol, 1.0 equiv) dissolved in toluene (0.1 M) and Amberlyst®15 (16.0 mg, 20 wt%) was added to the solution and stirred for 2 h at 80 °C in an oil bath. Amberlyst®15 was filtered off and the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 10/1 to 1/1) to obtain the desired product **300** (75.6 mg, 0.21 mmol, 99%) as colorless crystals.

Structure was confirmed by X-ray crystallography. Crystals were obtained by crystallization from DCM.

M.p.: 117 – 120 °C

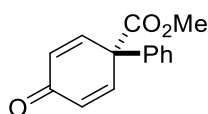
R_f = 0.29 (hexanes/ethyl acetate = 3/1, stained in vanillin).

¹H NMR: (400 MHz, CDCl₃): δ 7.70 – 7.62 (m, 2H), 7.51 – 7.38 (m, 3H), 5.01 (d, J = 3.3 Hz, 2H), 4.77 (dt, J = 6.1, 1.2 Hz, 1H), 2.82 – 2.62 (m, 2H), 2.50 (dd, J = 15.6, 5.4 Hz, 1H), 2.11 – 2.02 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 170.5, 135.1, 128.7, 126.7, 78.0, 53.9, 47.7, 45.9, 28.9, 19.4.

IR: ν[cm⁻¹] = 3522, 2952, 2870, 1718, 1498, 1446, 1364, 1331, 1297, 1267, 1200, 1152, 1070, 932, 768, 738, 697

HRMS: (EI-MS) m/z calculated for C₁₃H₁₂O₂Br₂ [M⁺]: 357.9197, found 357.9207.

methyl 4-oxo-[1,1'-biphenyl]-1(4H)-carboxylate (301):

Cyclohexene **122a** (112 mg, 0.38 mmol, 1.0 equiv) and SeO₂ (88.0 mg, 0.79 mmol, 2.1 equiv) were dissolved in 1,4-dioxane (0.4 M) in a sealed vessel (20 psi) and heated to 120

°C for 7 h in a microwave oven. The reaction mixture was filtered through a pad of celite with DCM (20 mL). The filtrate was washed with sat. NaHCO₃-solution (20 mL), H₂O (20 mL) and brine (20 mL). The aq. phase was extracted with an additional portion of DCM (15 mL). The combined organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 3/1) to obtain the desired product **301** (85.0 mg, 0.37 mmol, 98%) as yellow oil.

R_f = 0.4 (hexanes/ethyl acetate = 5/1, stained in KMnO₄).

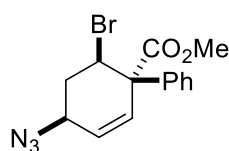
¹H NMR: (400 MHz, CDCl₃): δ 7.46 – 7.17 (m, 7H), 6.46 – 6.32 (m, 2H), 3.84 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 184.8, 169.8, 147.9, 137.1, 129.5, 128.7, 128.5, 126.3, 56.3, 53.4.

IR: ν[cm⁻¹] = 3060, 2956, 1737, 1670, 1633, 1491, 1435, 1398, 1244, 1178, 1074, 1036, 1003, 961, 924, 857, 798, 753, 7001.

HRMS: (EI-MS) m/z calculated for C₁₄H₁₂O₃ [M⁺]: 228.0781, found 228.0777.

methyl (1R*,2R*,4S*)-4-azido-2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (302):



A round-bottom flask was charged with allylic bromide compound **129a** (126 mg, 0.34 mmol, 1.0 equiv), sodium azide (32.9 mg, 0.51 mmol, 1.5 equiv) dissolved in DMSO (0.15 M) and stirred for 2 h at 25 °C. Then H₂O (20 mL) and hexanes/Et₂O (4/1, 20 mL) were added and the mixture was stirred for another 15 min. The phases were separated and the organic phase was washed with H₂O (3x10 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/ethyl acetate = 20/1 to 5/1) to obtain the desired product **302** (84 mg, 0.25 mmol, 74%, *brsm*: 81%) as yellow oil.

R_f = 0.43 (hexanes/ethyl acetate = 9/1, stained in KMnO₄).

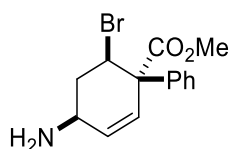
¹H NMR: (400 MHz, CDCl₃): δ 7.42 – 7.34 (m, 3H), 7.32 – 7.27 (m, 2H), 6.18 – 6.05 (m, 2H), 4.97 (dd, J = 12.1, 3.0 Hz, 1H), 4.14 (ddt, J = 9.2, 6.8, 1.4 Hz, 1H), 3.77 (s, 3H), 2.55 (dddd, J = 13.5, 6.6, 3.1, 0.8 Hz, 1H), 2.11 (ddd, J = 13.5, 12.1, 9.1 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 172.6, 136.5, 130.7, 129.6, 128.5, 128.2, 127.6, 58.4, 56.3, 53.0, 48.2, 34.5.

IR: ν[cm⁻¹] = 3030, 2922, 2866, 2102, 1736, 1670, 1495, 1435, 1245, 1036, 801, 701.

HRMS: (APCI-MS) m/z calculated for C₁₄H₁₅O₂N₃Br [M+H]⁺: 336.0342, found 336.0339.

methyl (1R*,2R*,4S*)-4-amino-2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (303):



A flame dried Schlenk-flask was charged with azide **302** (62.0 mg, 0.18 mmol, 1.0 equiv) and triphenylphosphine (58.1 mg, 221 μmol, 1.2 equiv) dissolved in dry THF (0.1 M) and the mixture was stirred for 24 h at 25 °C. Then, H₂O (166 mg, 9.20 mmol, 50 equiv) was added and the reaction mixture was stirred for another 24 h at ambient temperatures. The phases were separated, the organic phase was washed with H₂O (3x10 mL) and the aq. phase was extracted with DCM (3x10 mL). Then, the combined organic phases were extracted with 1M HCl-solution (3x10 mL). The combined aq. phase was then made basic with 2M NaOH-solution and again extracted with DCM (3x10 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was removed under reduced pressure to obtain the product **303** (43.0, 0.14 mmol, 75%) as yellow oil, without further purification.

R_f = 0.40 (hexanes/ethyl acetate = 5/1, stained in KMnO₄).

¹H NMR: (400 MHz, CDCl₃): δ 7.39 – 7.29 (m, 5H), 6.06 (ddd, J = 10.1, 2.5, 0.9 Hz, 1H), 5.91 (dd, J = 10.0, 2.2 Hz, 1H), 5.02 (dd, J = 11.7, 3.0 Hz, 1H), 3.74 (s, 3H), 3.60 (ddt, J = 8.6, 6.3, 2.3 Hz, 1H), 2.48 (dddd, J = 13.5, 6.3, 3.0, 0.9 Hz, 1H), 2.00 – 1.76 (m, 1H), 1.64 (bs, -NH₂).

^{13}C NMR (101 MHz, CDCl_3): δ 172.9, 137.6, 133.9, 129.4, 127.9, 127.6, 127.4, 58.2, 52.8, 50.6, 48.1, 38.7.

IR: $\nu[\text{cm}^{-1}]$ = 3030, 2952, 2926, 2855, 1733, 1648, 1491, 1435, 1390, 1241, 1118, 1092, 1029, 947, 910, 775, 731.

HRMS: (APCI-MS) m/z calculated for $\text{C}_{14}\text{H}_{17}\text{O}_2\text{NBr}$ $[\text{M}+\text{H}]^+$: 310.0437, found 310.0438.

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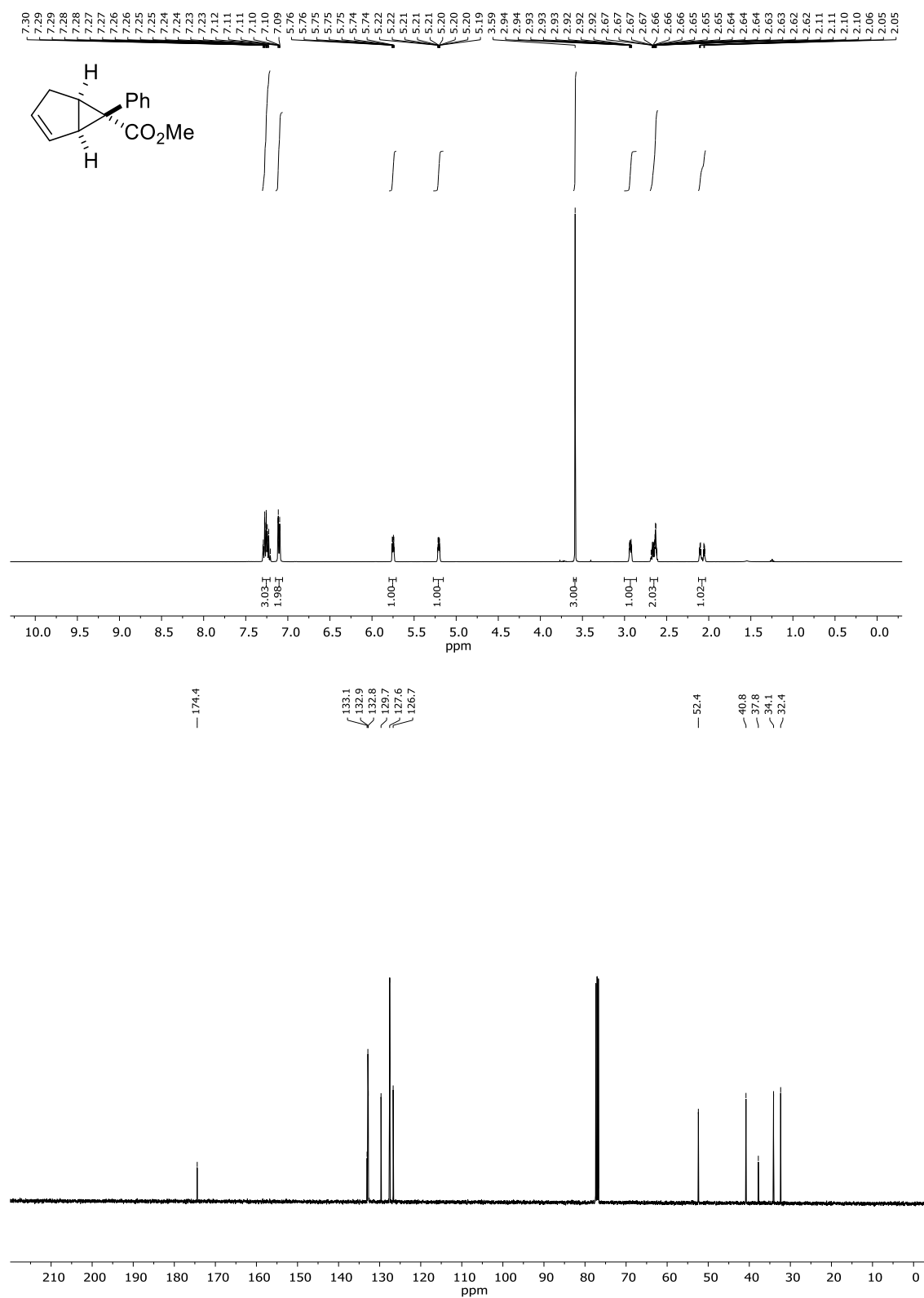
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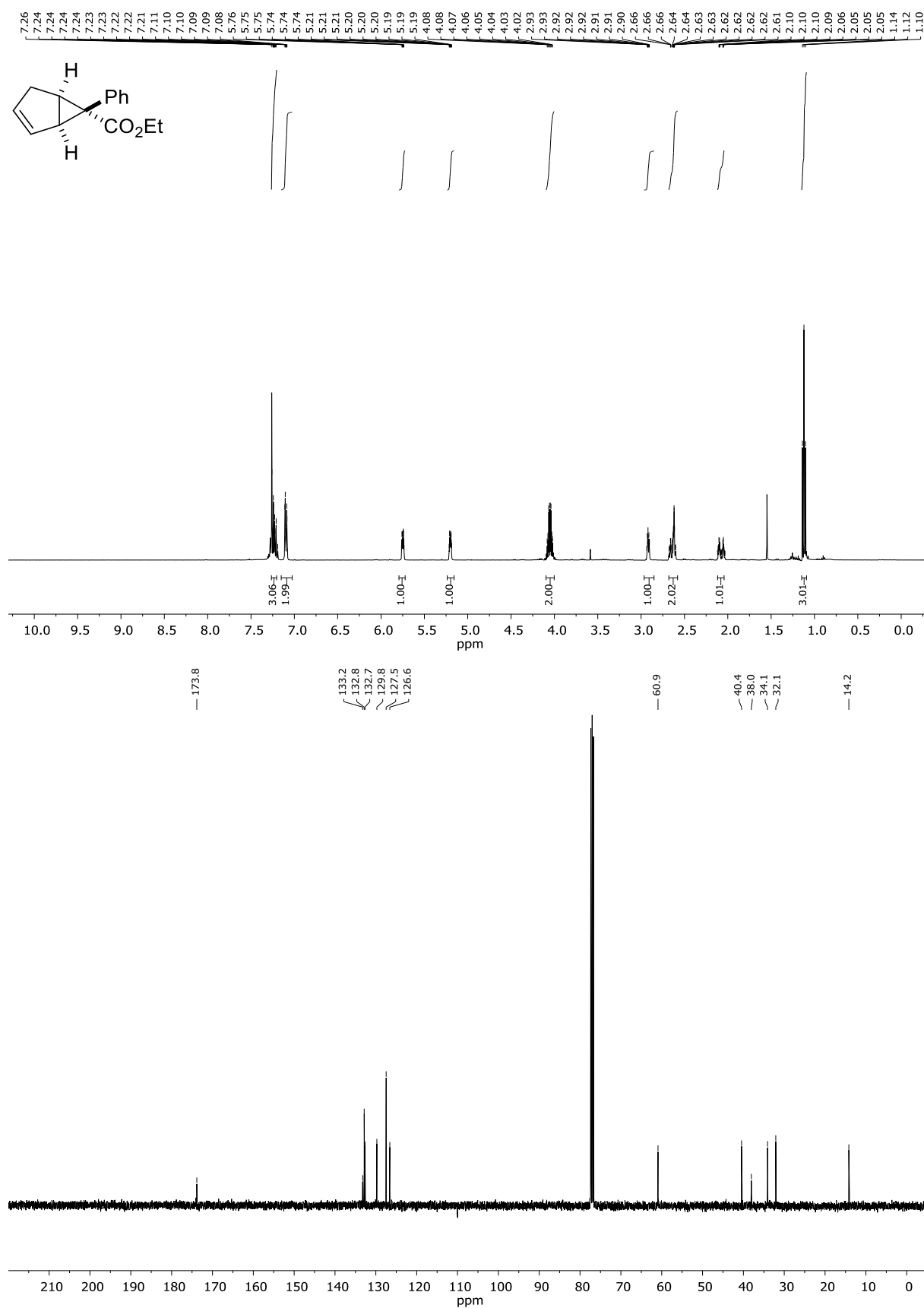
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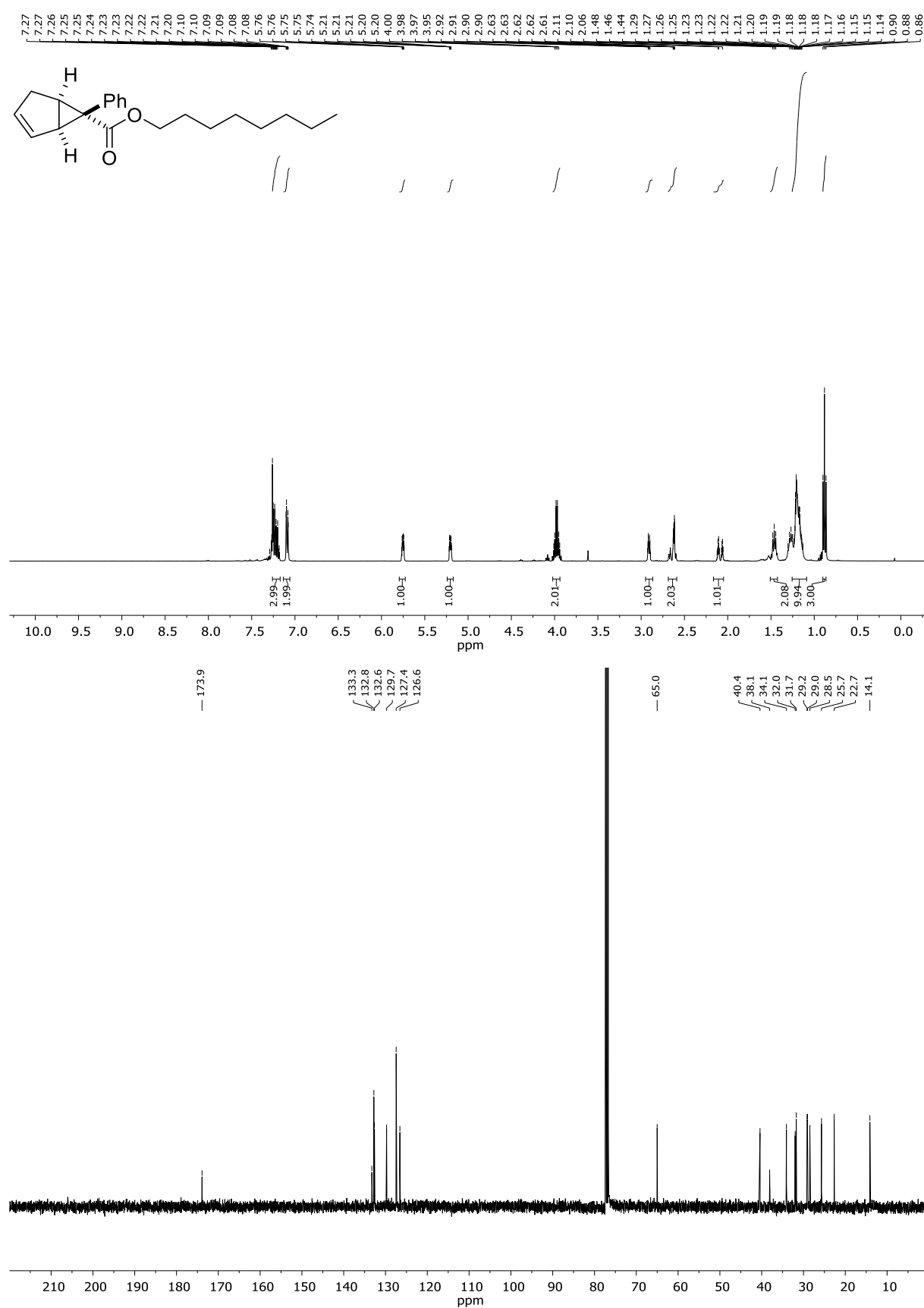
F. Appendix

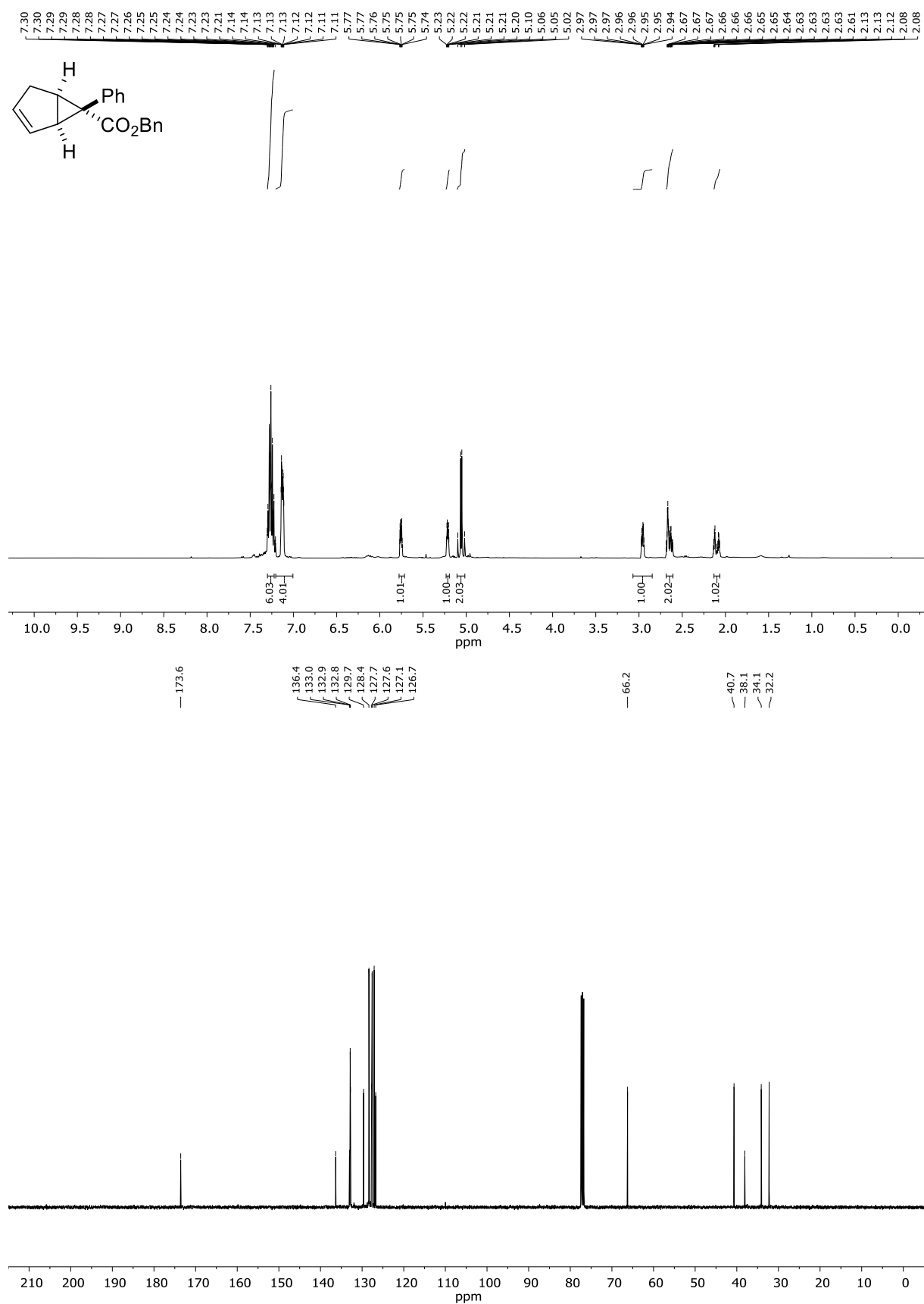
1. NMR-Spectra

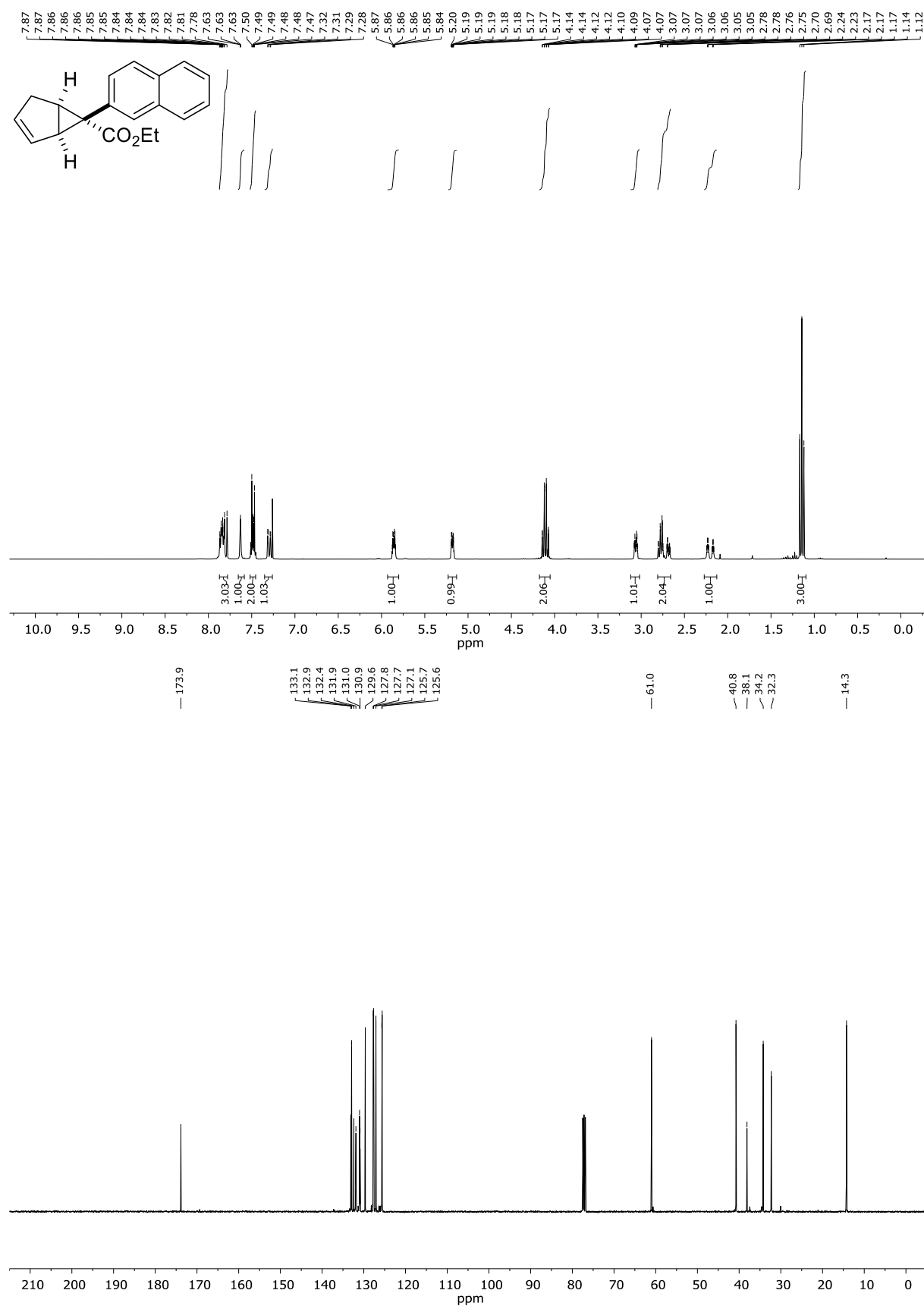
Compound 25a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

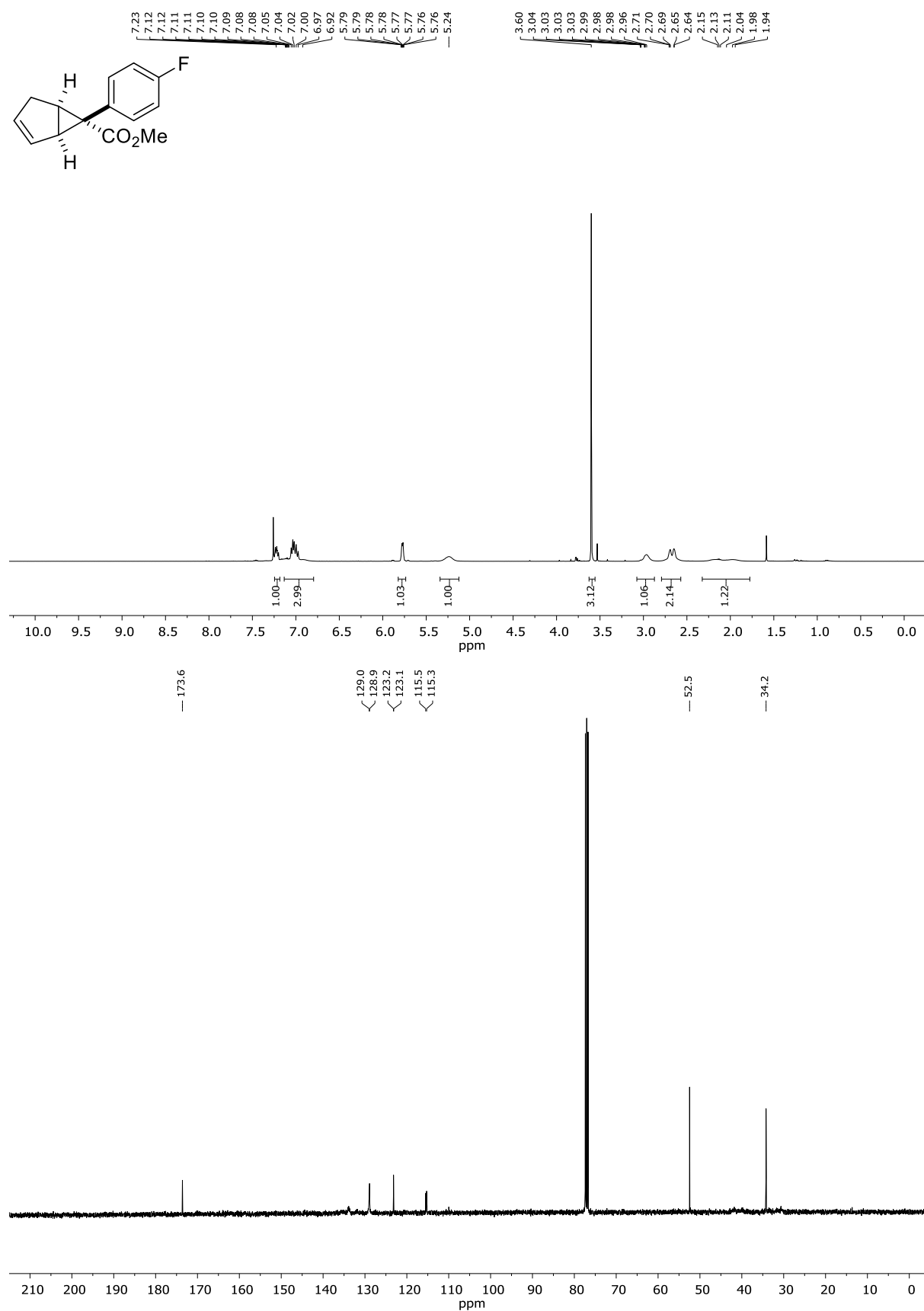


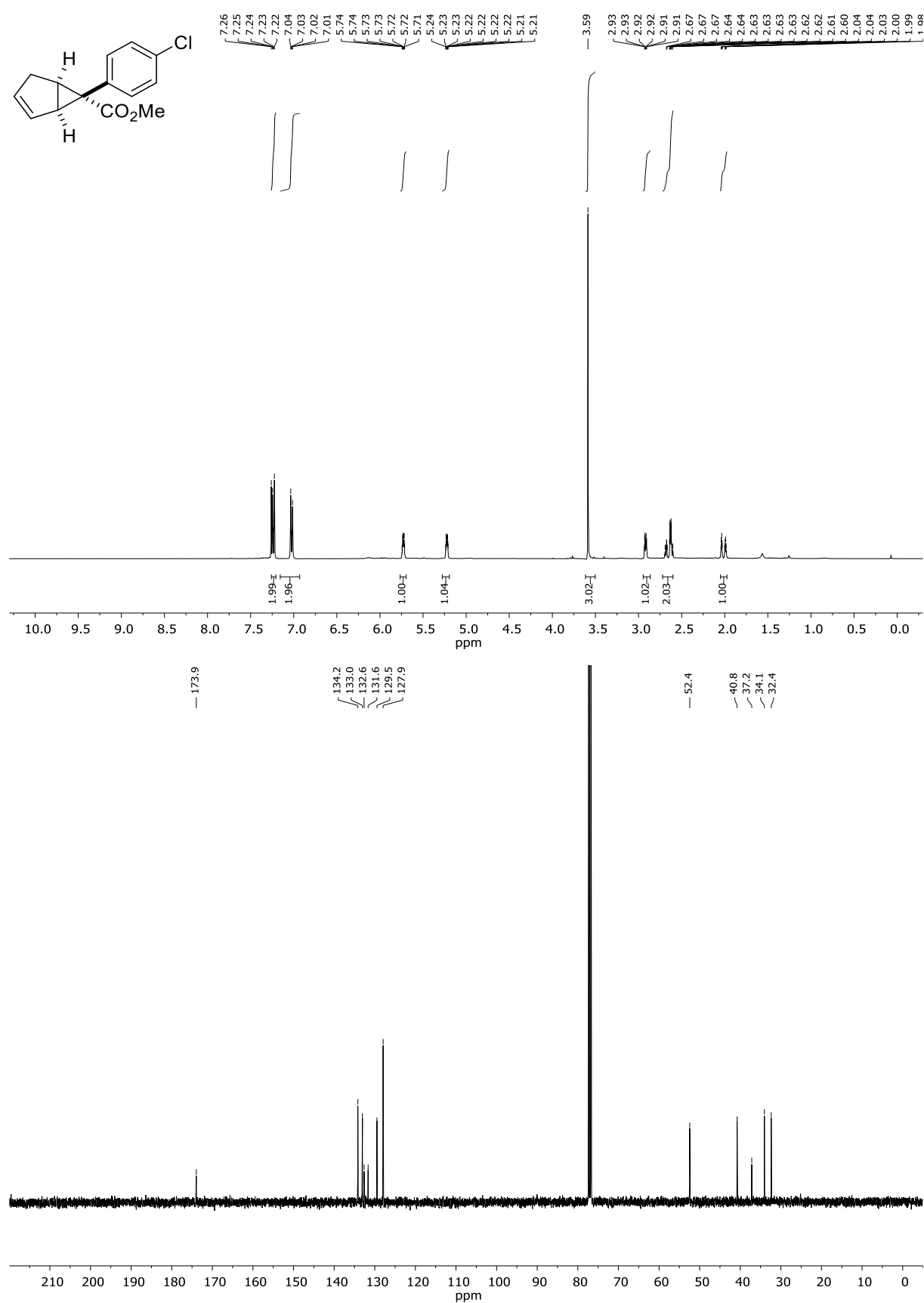
Compound 25b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

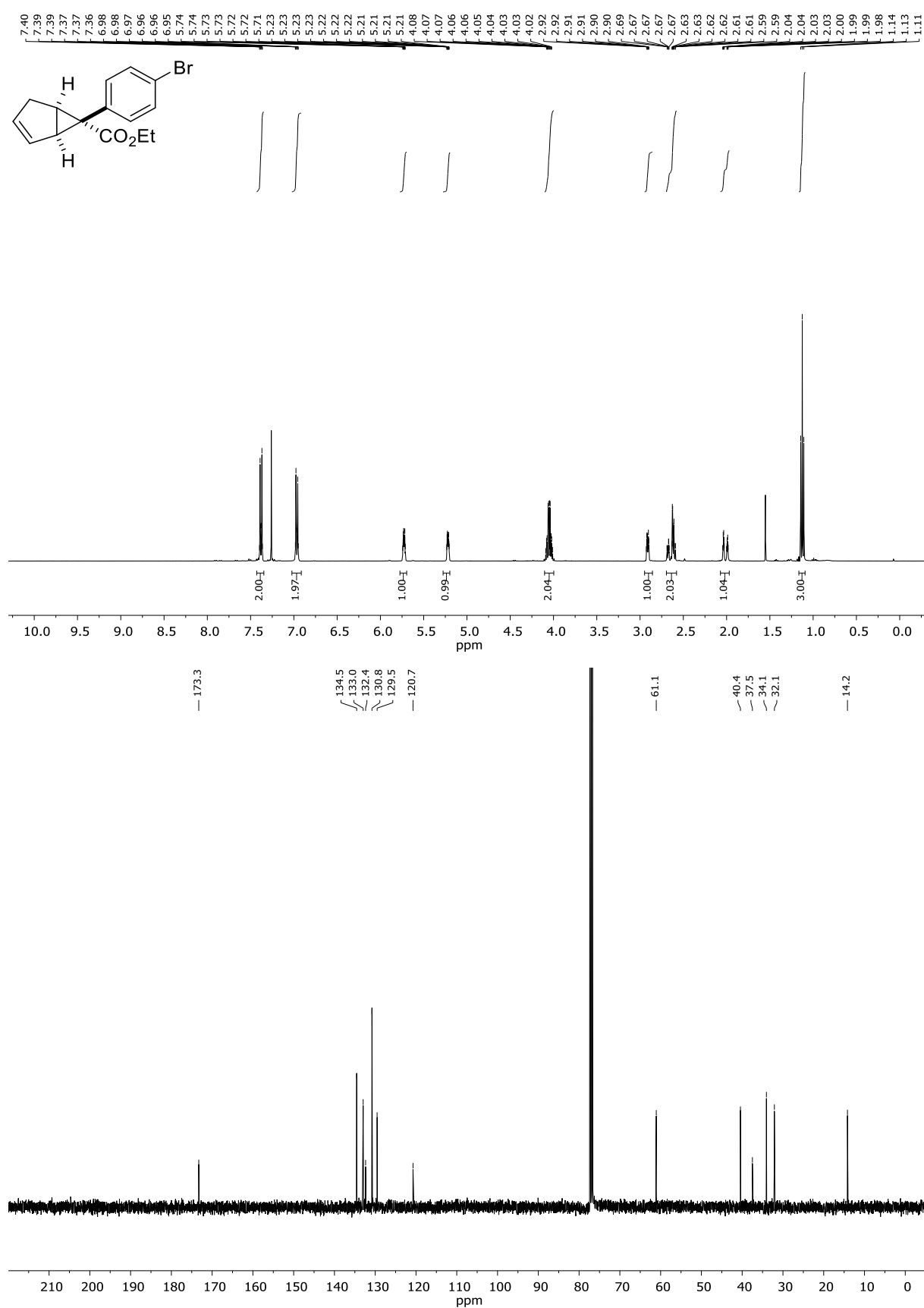
Compound 25c: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

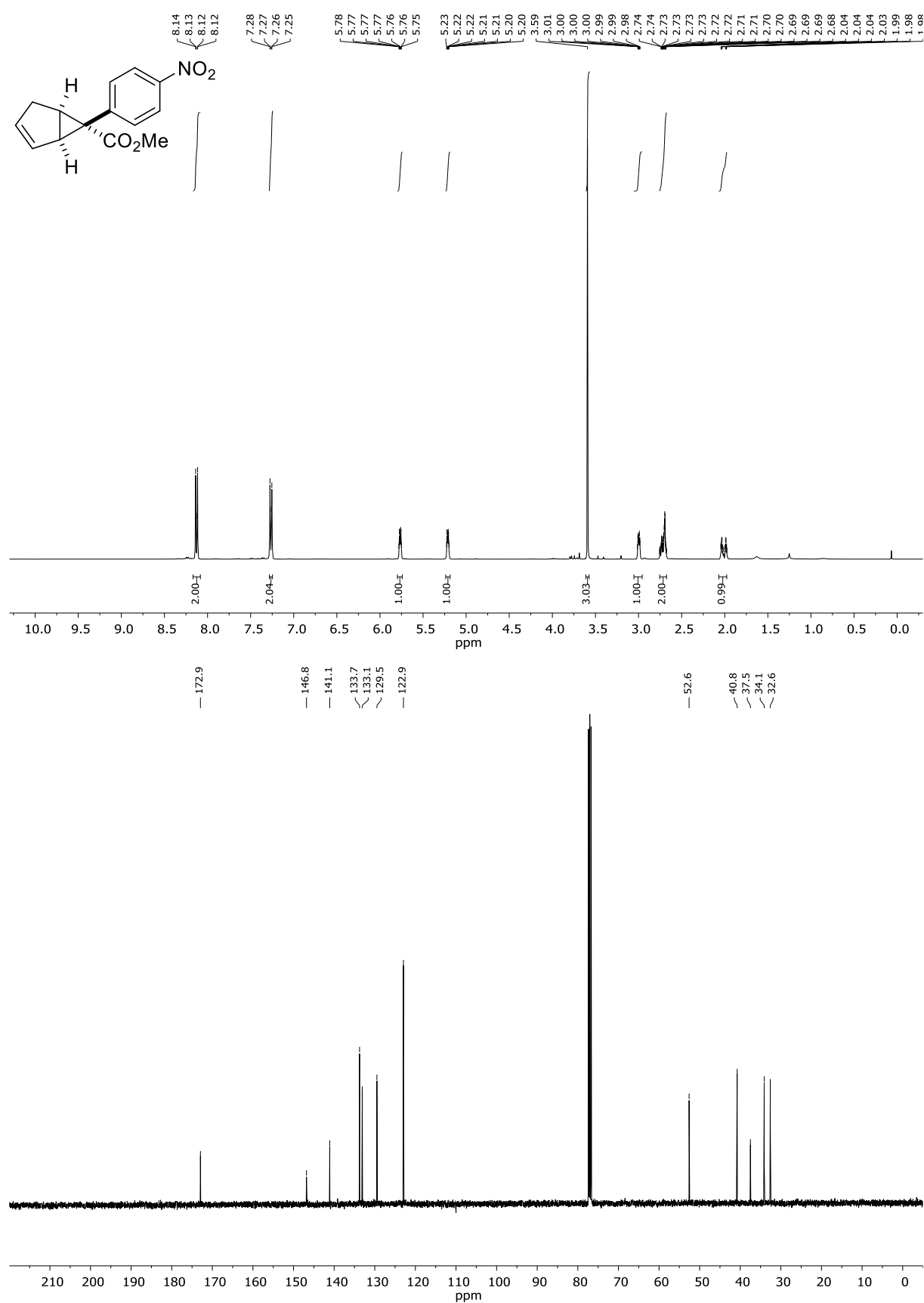
Compound 25d: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

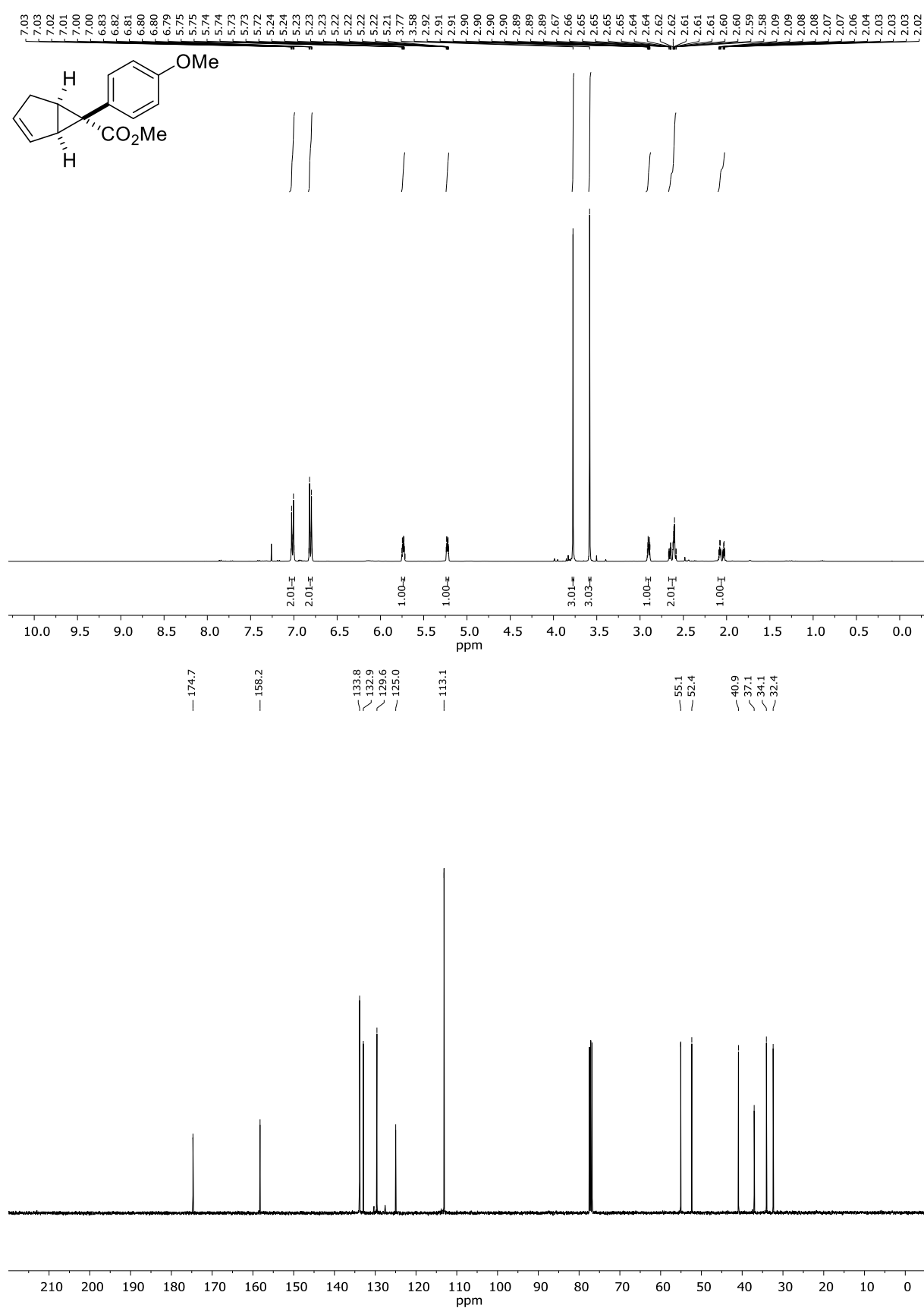
Compound 25e: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

Compound 25f: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

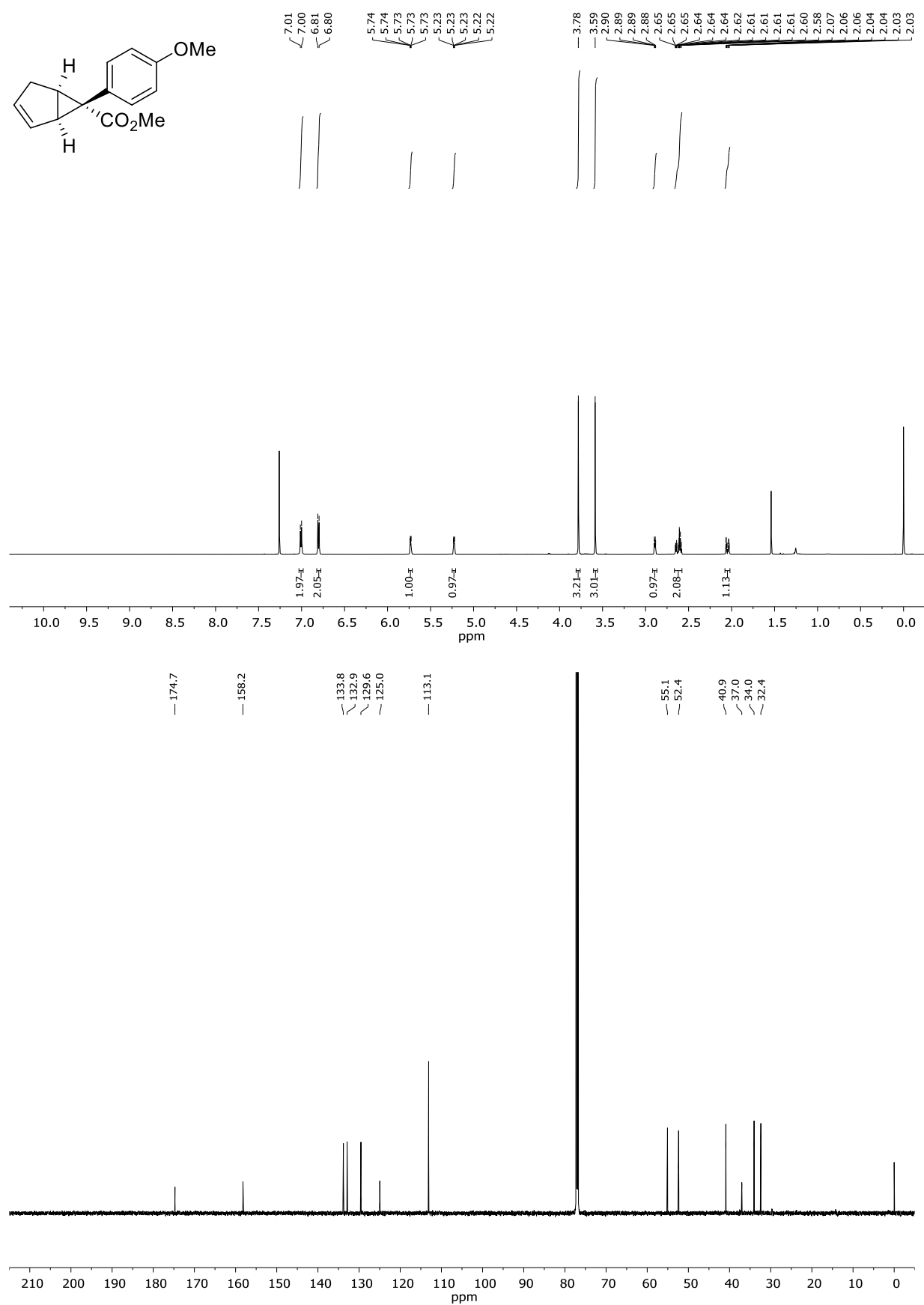
Compound 25g: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

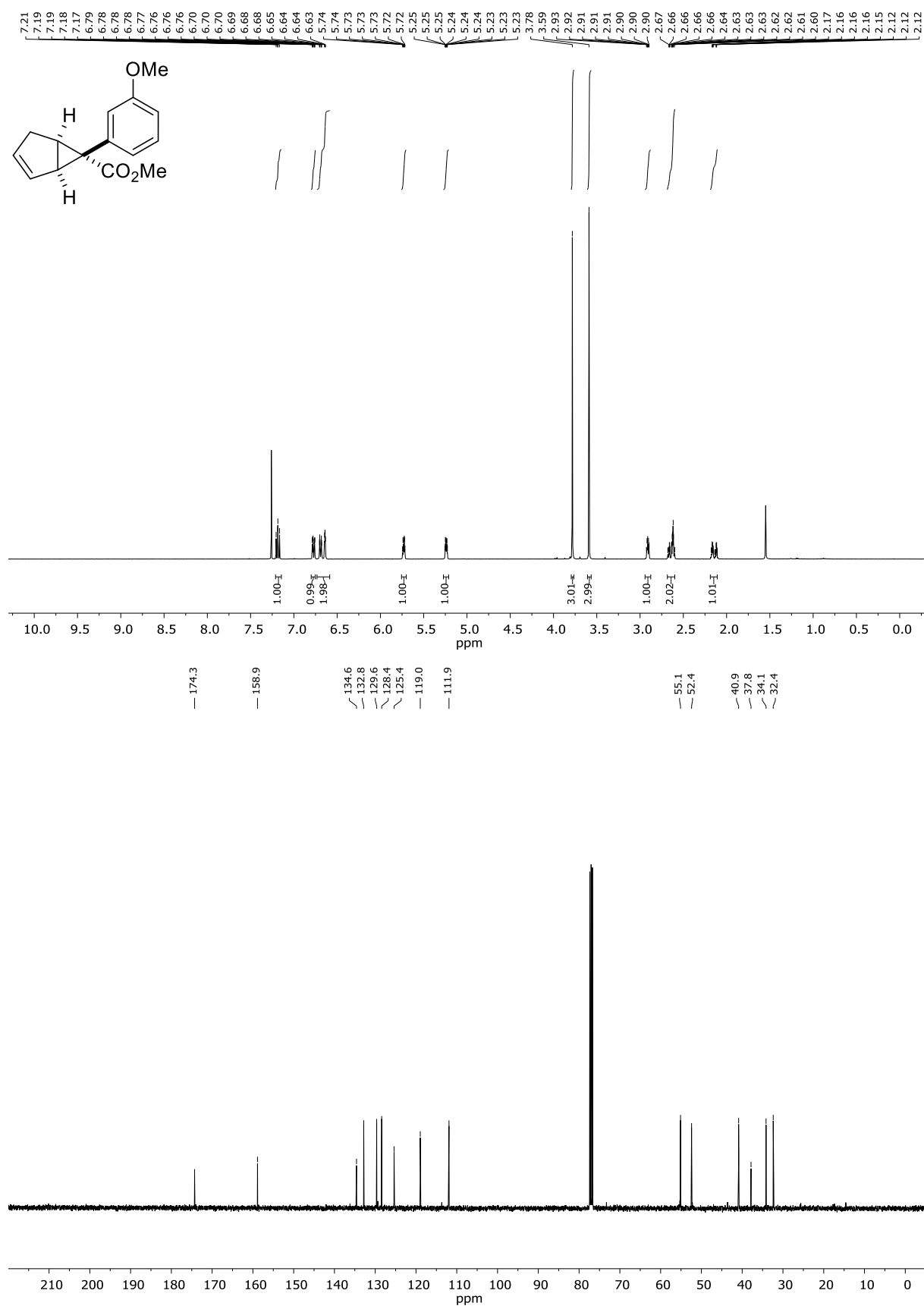
Compound 25h: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

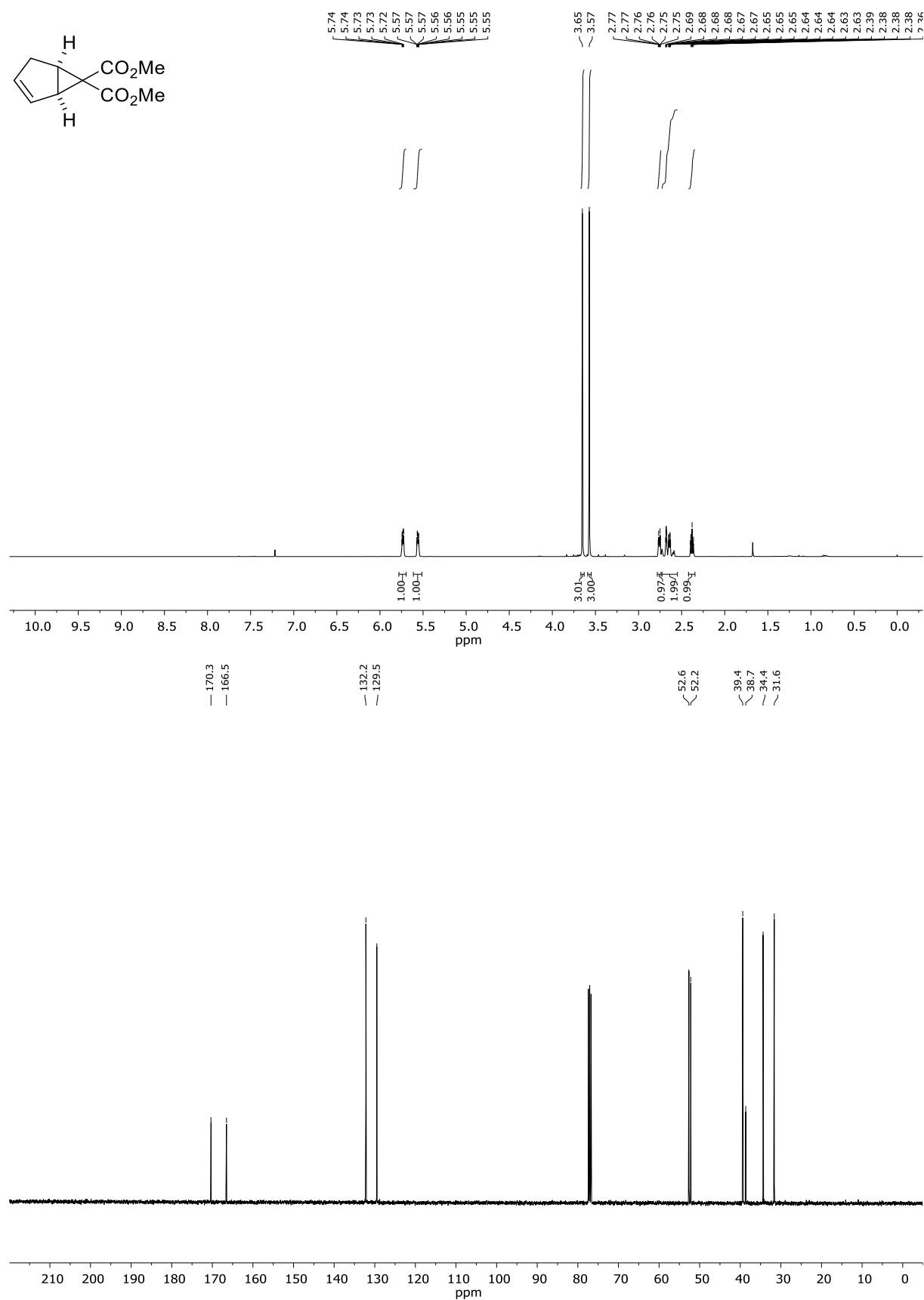
Compound 25i: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

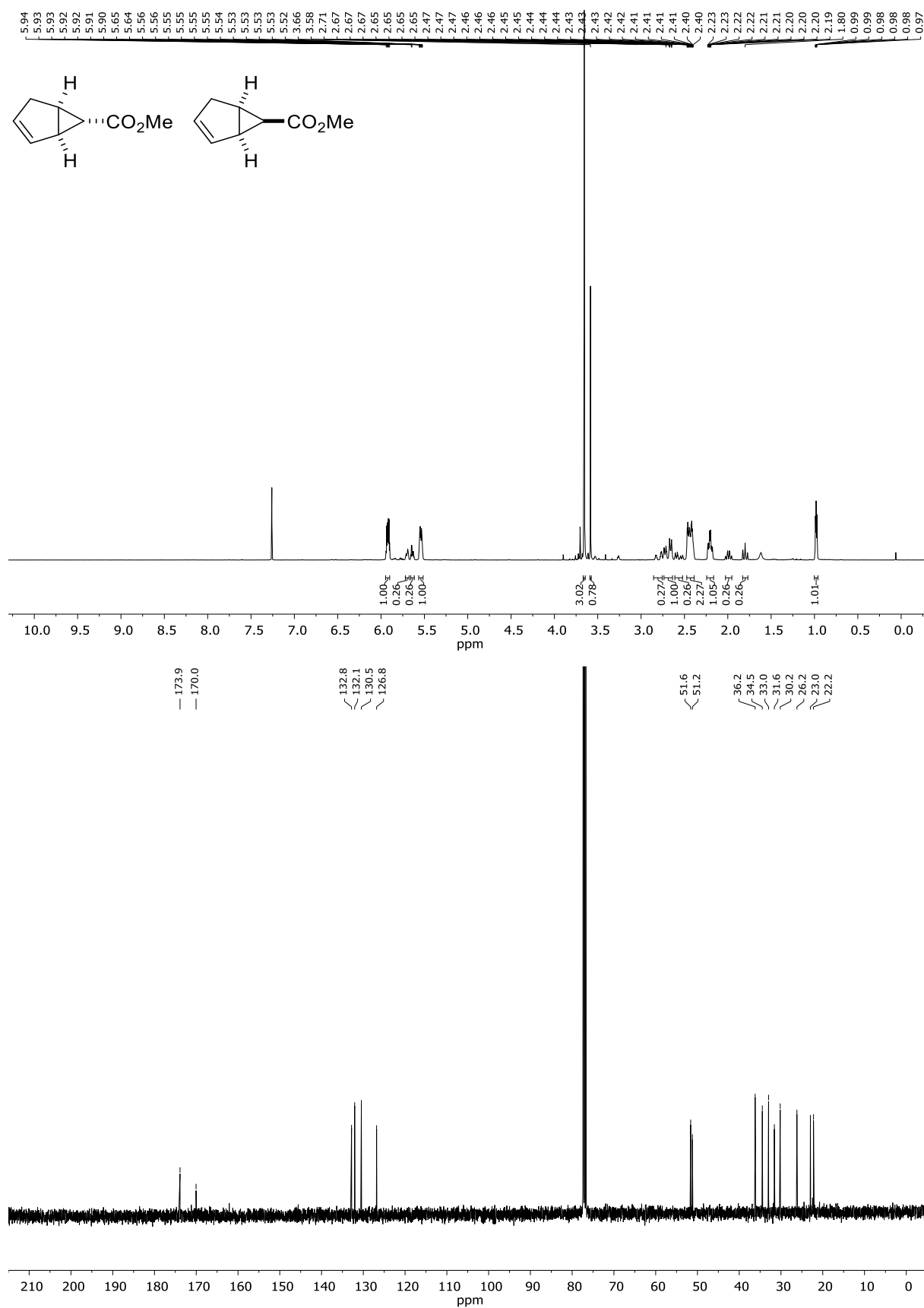
Compound 25k: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

Compound (1*S*,5*R*,6*S*)-25k: ^1H NMR (600 MHz, CDCl_3) and ^{13}C NMR (151 MHz, CDCl_3)

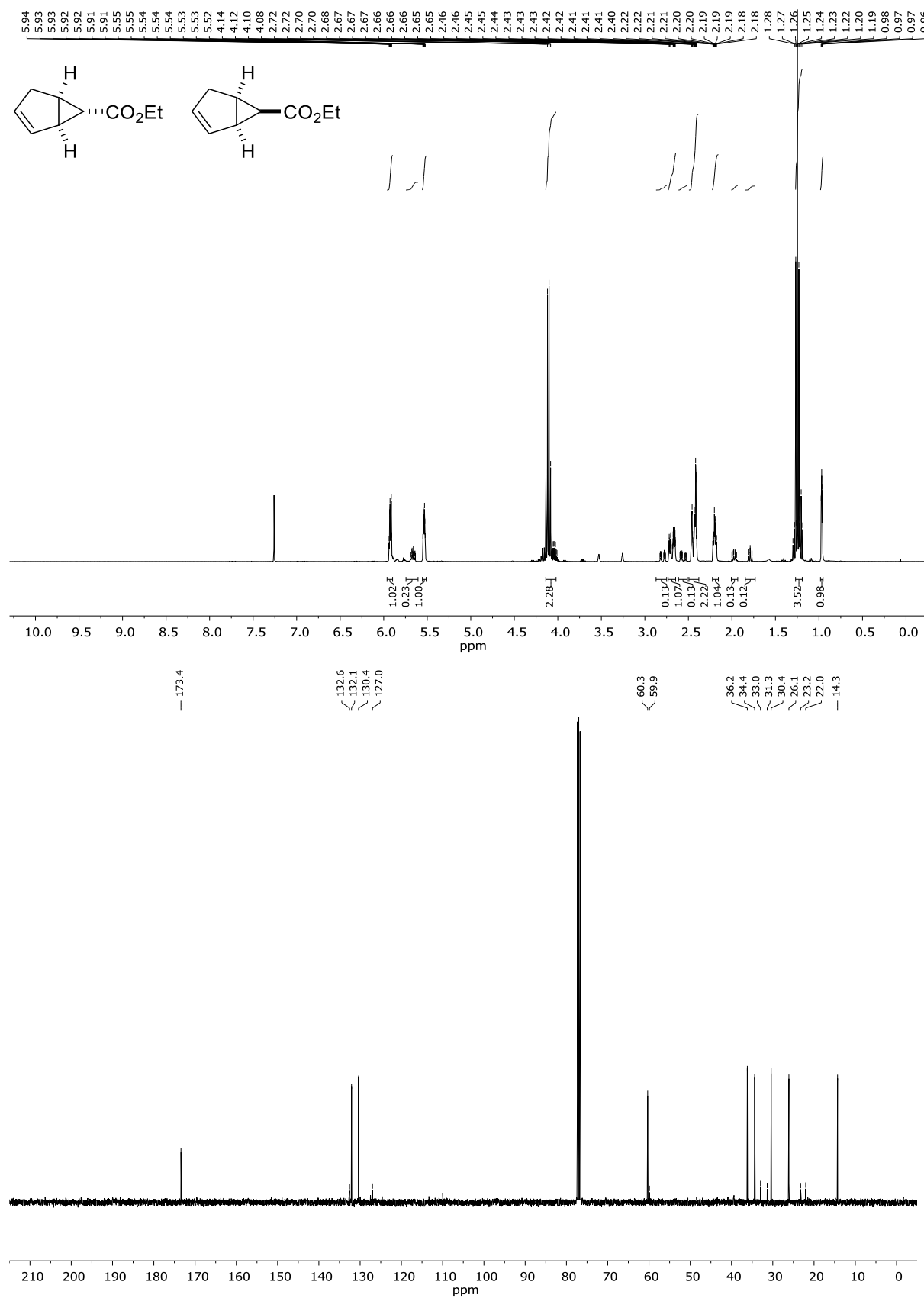


Compound 25I: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

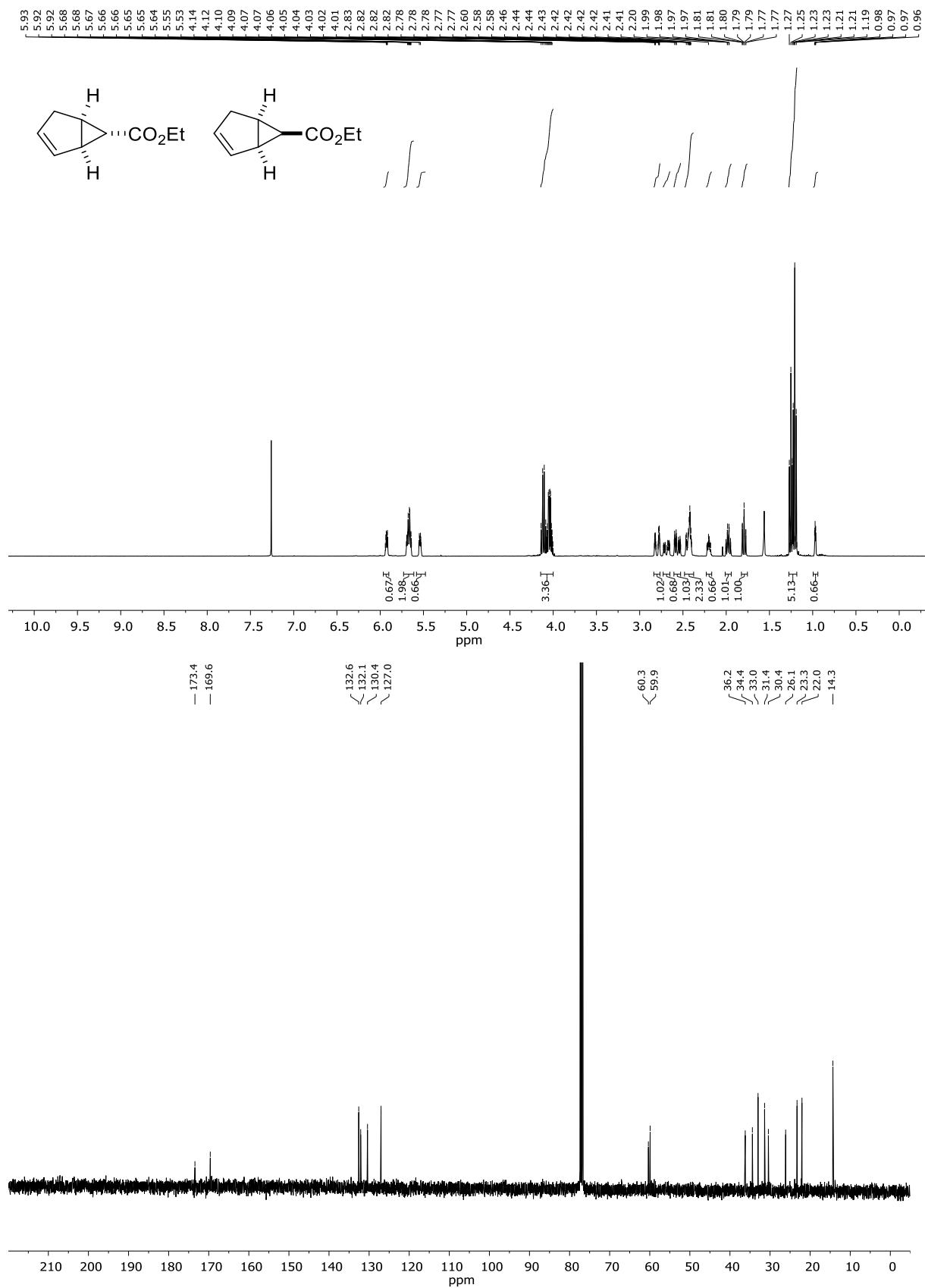
Compound 25n: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

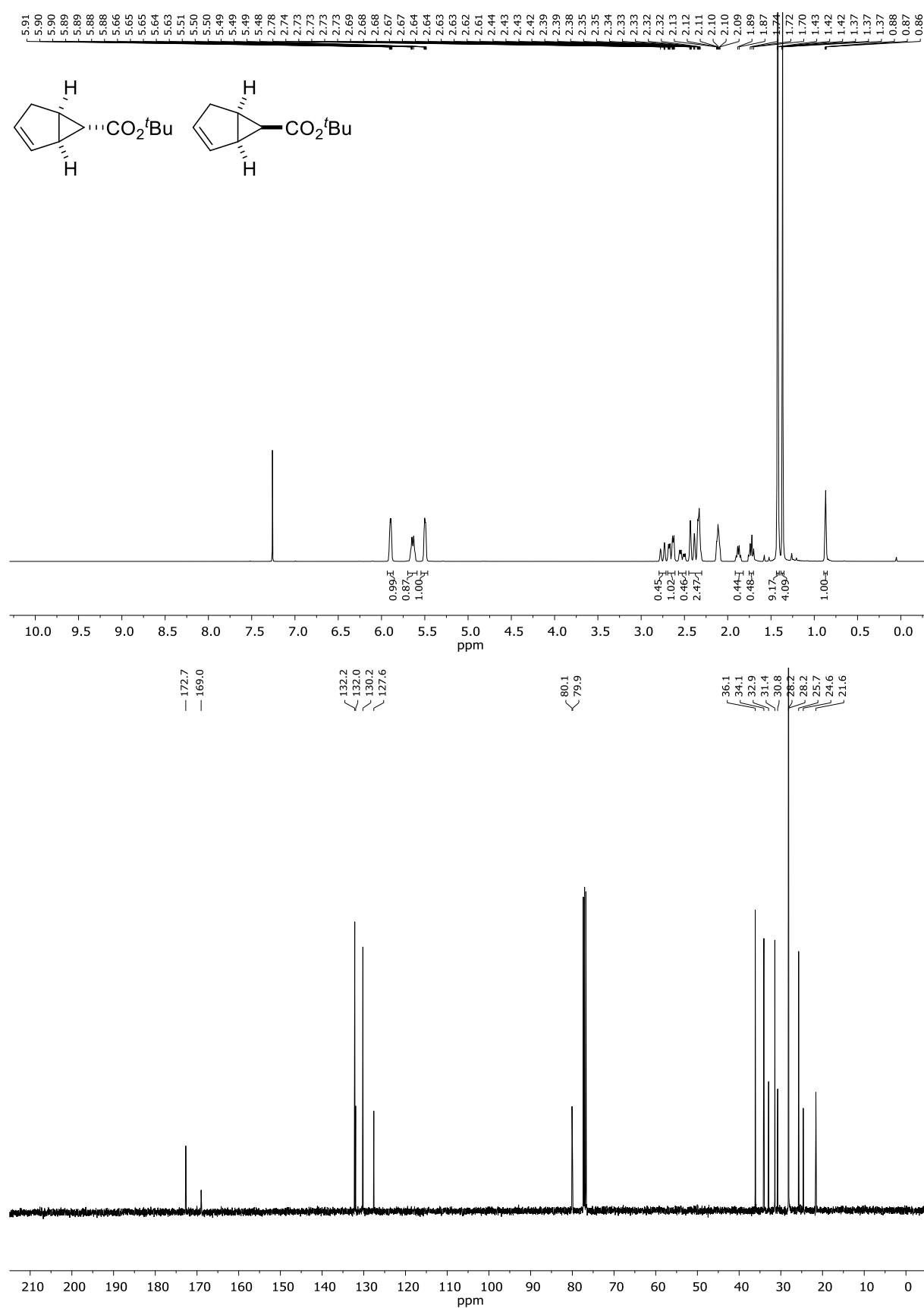
Compound 25o: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

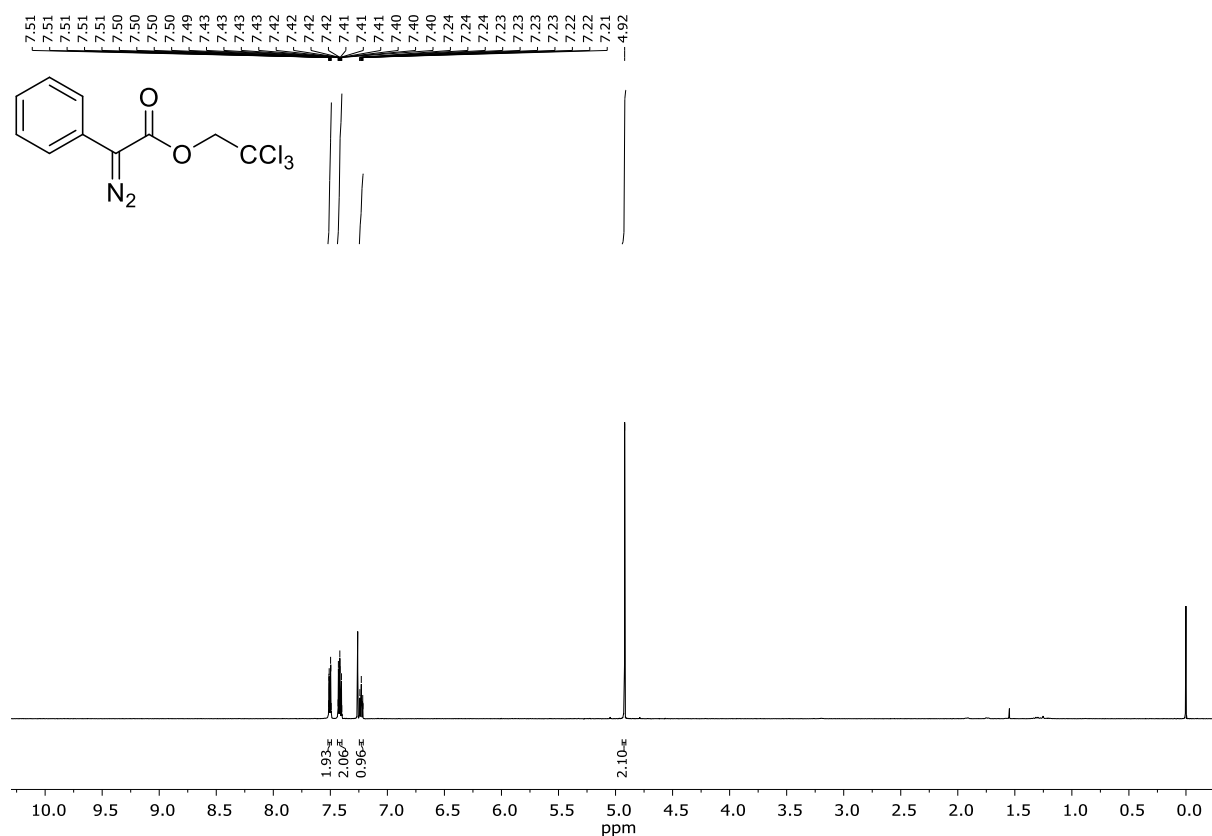
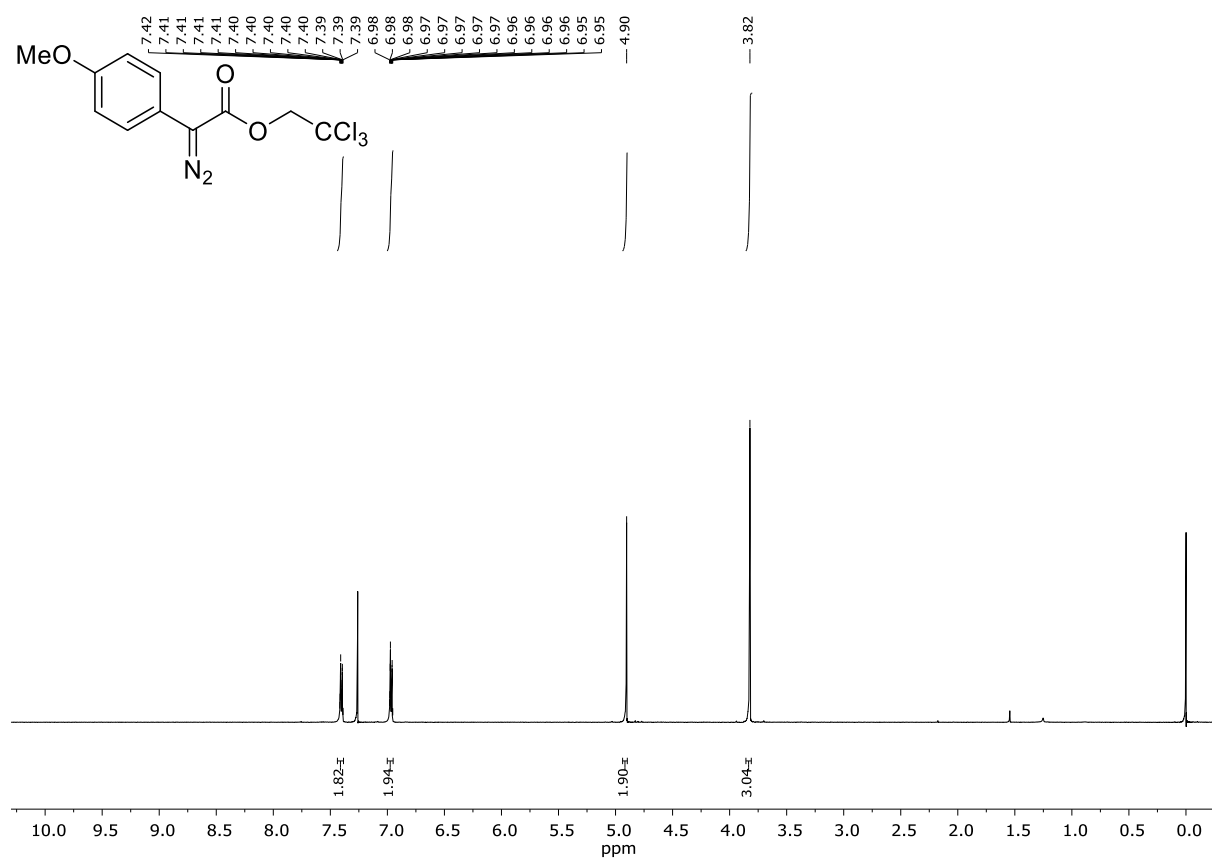
Compound **25p**, fraction **1**: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

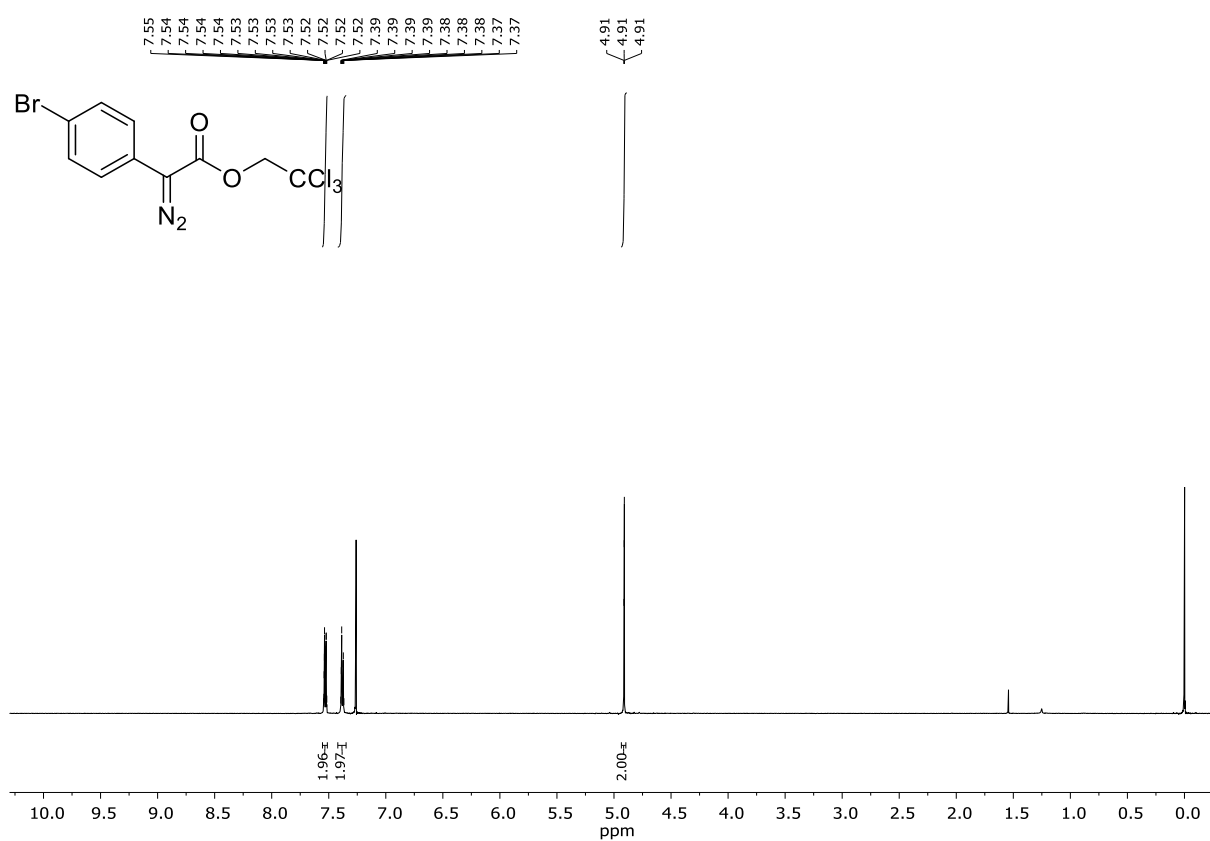
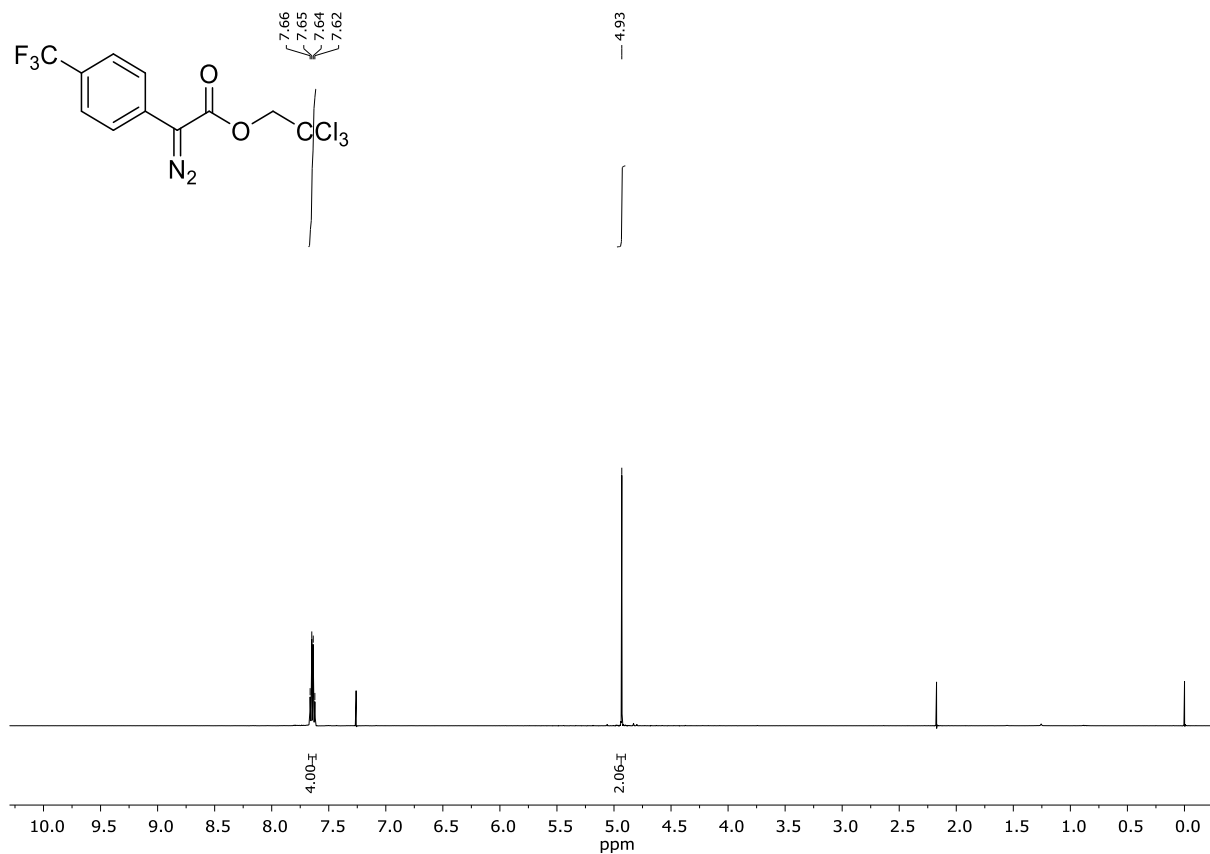


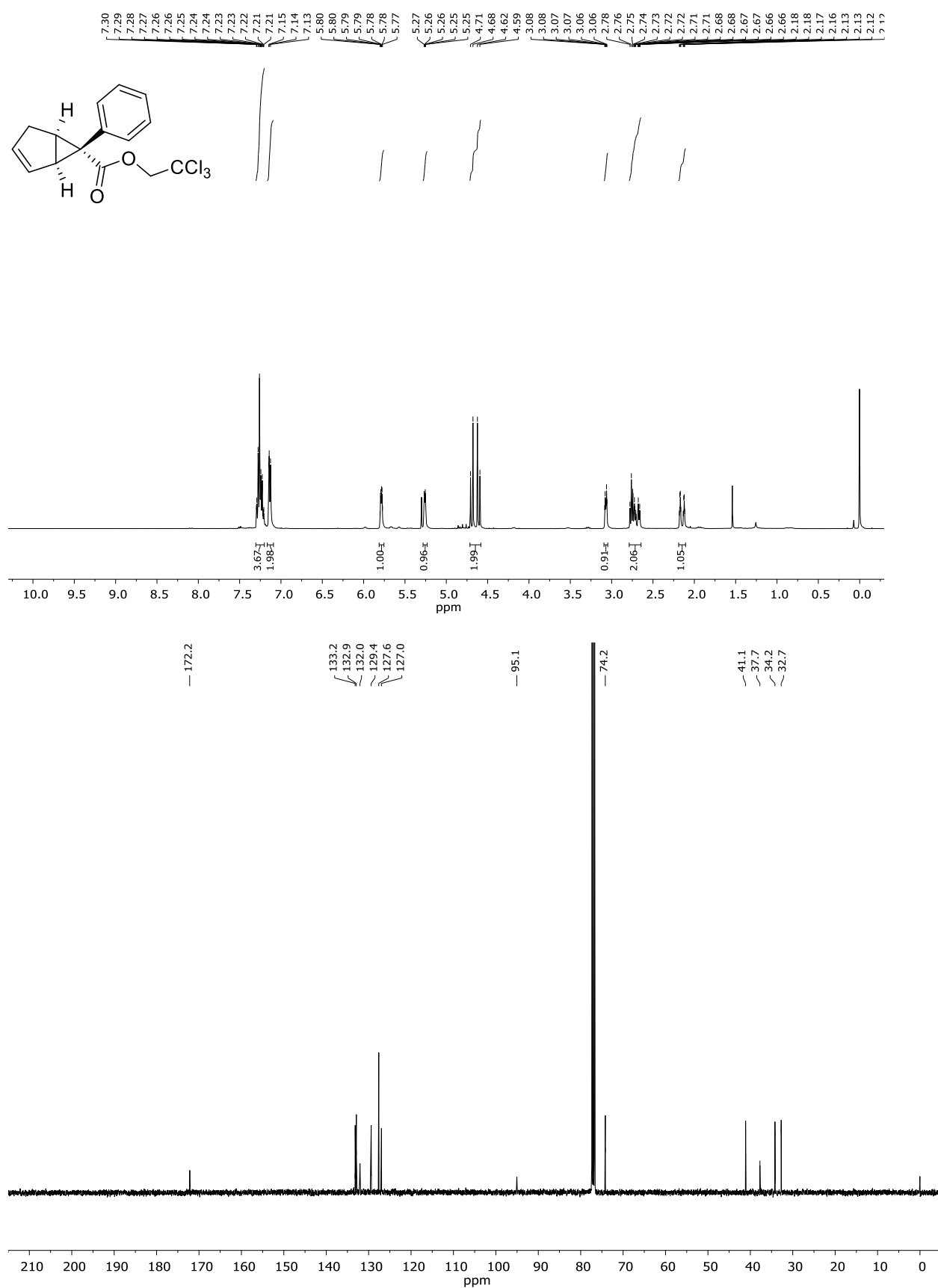
Compound 25p, fraction 2: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)



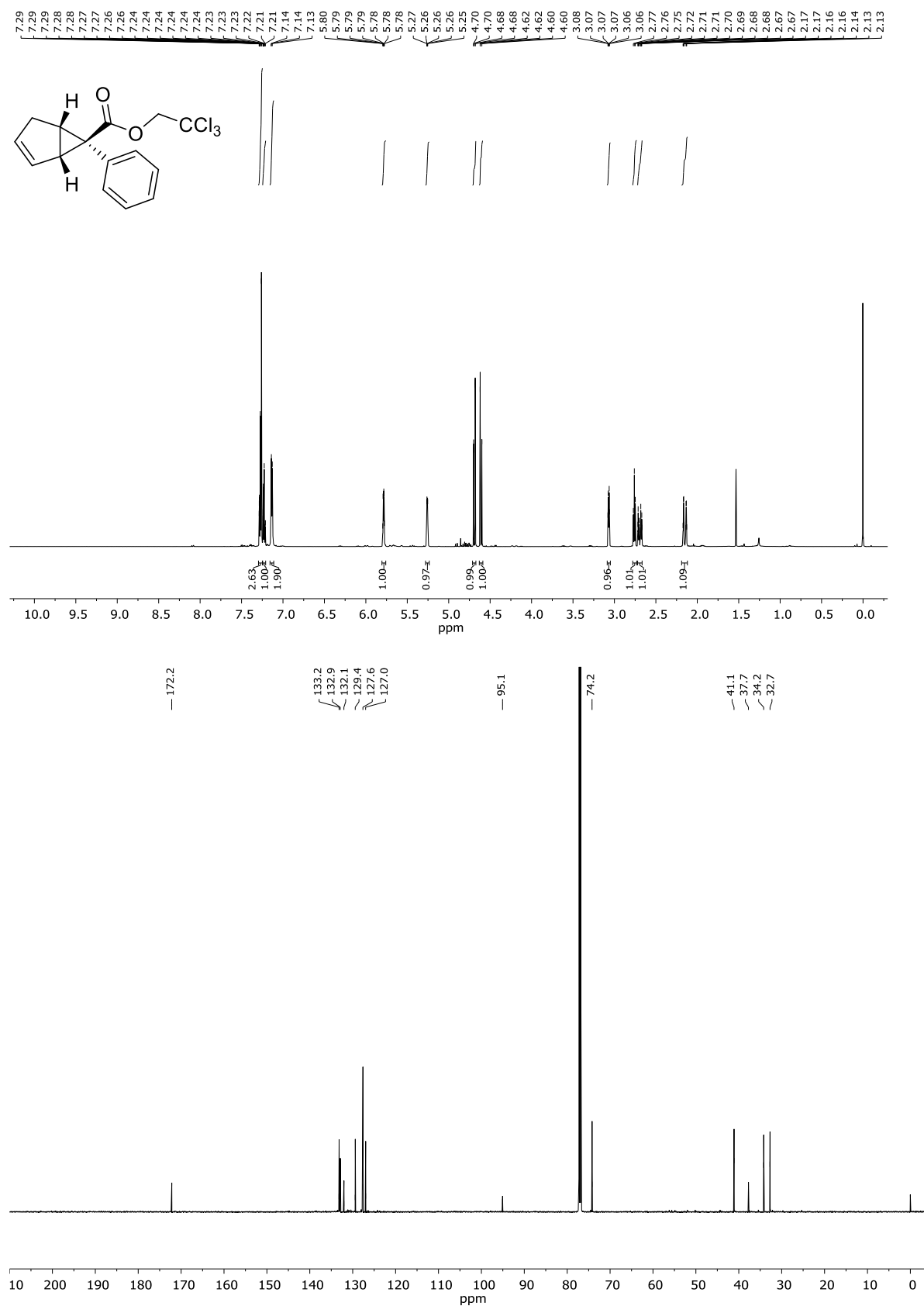
Compound 25q: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

Compound 29a: ^1H NMR (600 MHz, CDCl_3)**Compound 29k:** ^1H NMR (600 MHz, CDCl_3)

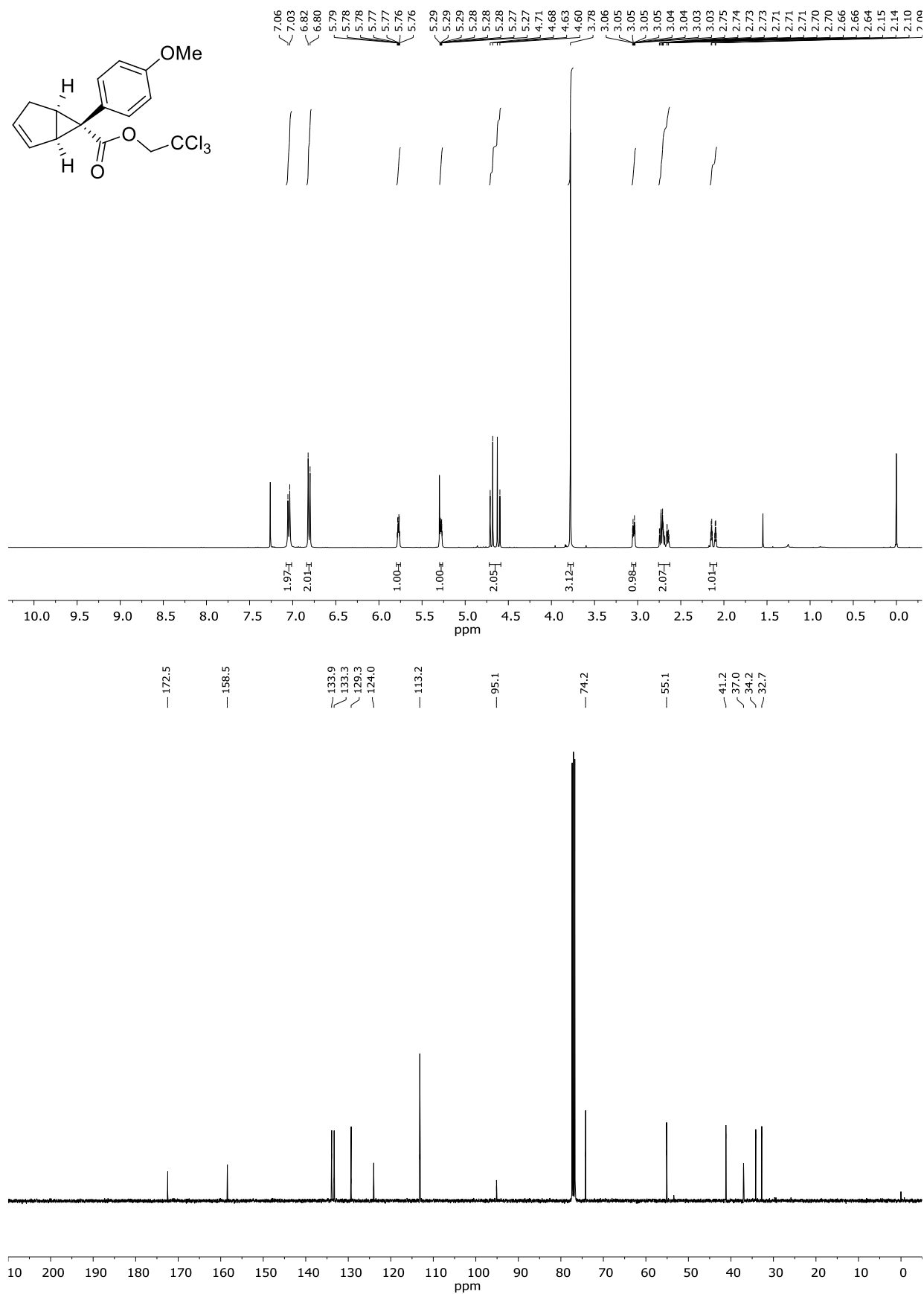
Compound 29r: ^1H NMR (600 MHz, CDCl_3)Compound 29s: ^1H NMR (600 MHz, CDCl_3)

Compound (1*S*,5*R*,6*S*)-31: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

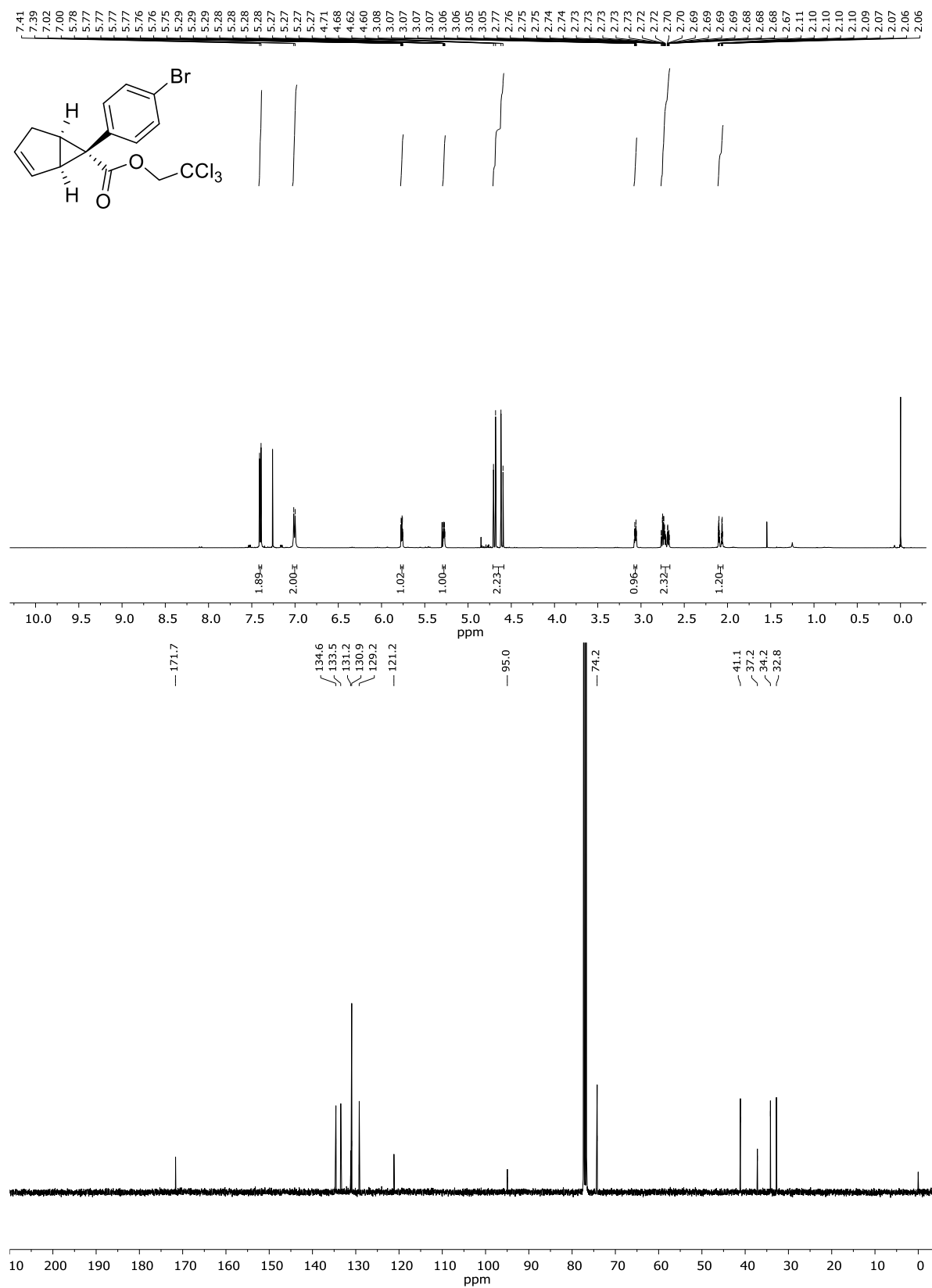
Compound (1*R*,5*S*,6*R*)-31a: ^1H NMR (600 MHz, CDCl_3) and ^{13}C NMR (151 MHz, CDCl_3)



Compound (1*S*,5*R*,6*S*)-31k: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)



Compound (1*S*,5*R*,6*S*)-31r: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)



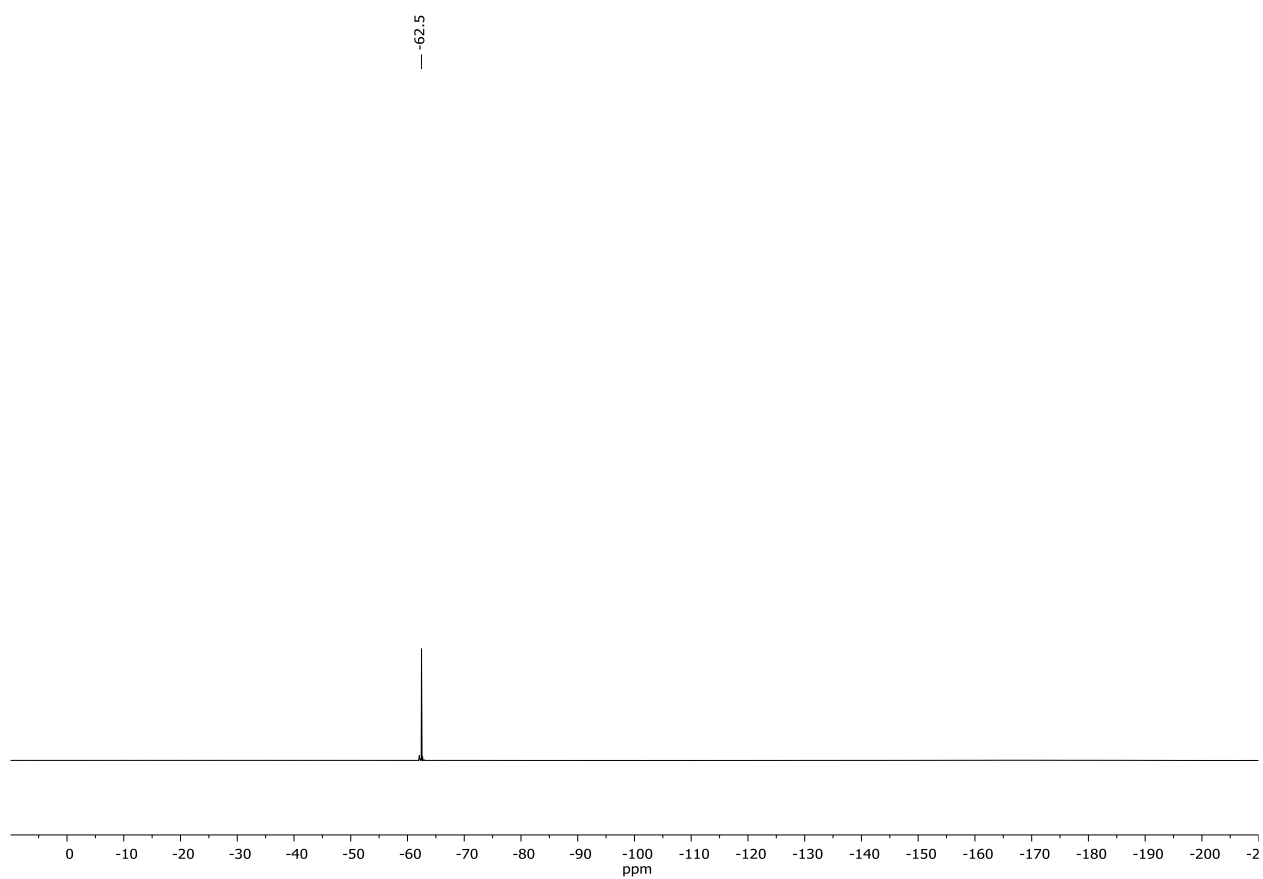
Chemical structure: CC1(C(=O)OCC1)c2cc(C(F)(F)F)ccc2

¹H NMR spectrum (top):

- Chemical shift range: 0.0 to 7.55 ppm.
- Integration values: 1.99, 2.27, 1.04, 1.00, 2.16, 0.96, 2.27, 1.20.

¹³C NMR spectrum (bottom):

- Chemical shift range: 0 to 200 ppm.
- Peak labels: 171.4, 136.3, 133.5, 133.2, 129.2, 124.7, 124.6, 94.9, 74.2, 41.1, 37.4, 34.2, 32.8.



Chemical structure: COC(=O)[C@H]1C=C[C@@H]1c2ccccc2

¹H NMR spectrum (top):

- Chemical shift range: 0.0 to 7.29 ppm.
- Integration values: 4.27, 1.95, 1.00, 0.98, 3.04, 0.98, 2.05, 1.03.

¹³C NMR spectrum (bottom):

- Chemical shift range: 0.0 to 174.5 ppm.

Chemical structure: COC(=O)[C@H]1C=CC[C@@H]1c2ccccc2

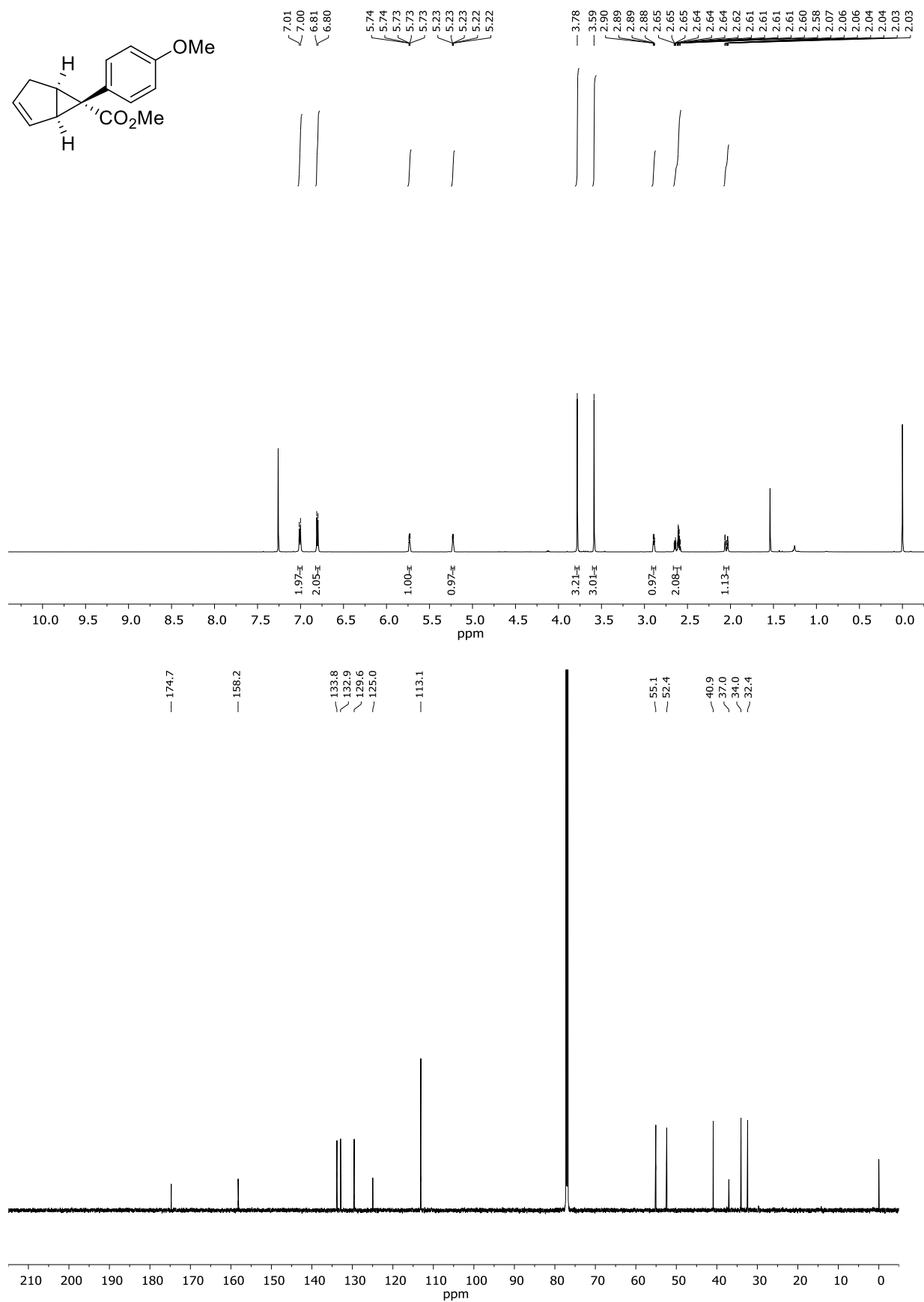
¹H NMR spectrum (top):

- Chemical shift range: 0.0 to 7.29 ppm.
- Integration values: 4.27, 1.96, 1.00, 0.99, 2.96, 0.98, 2.03, 1.03.

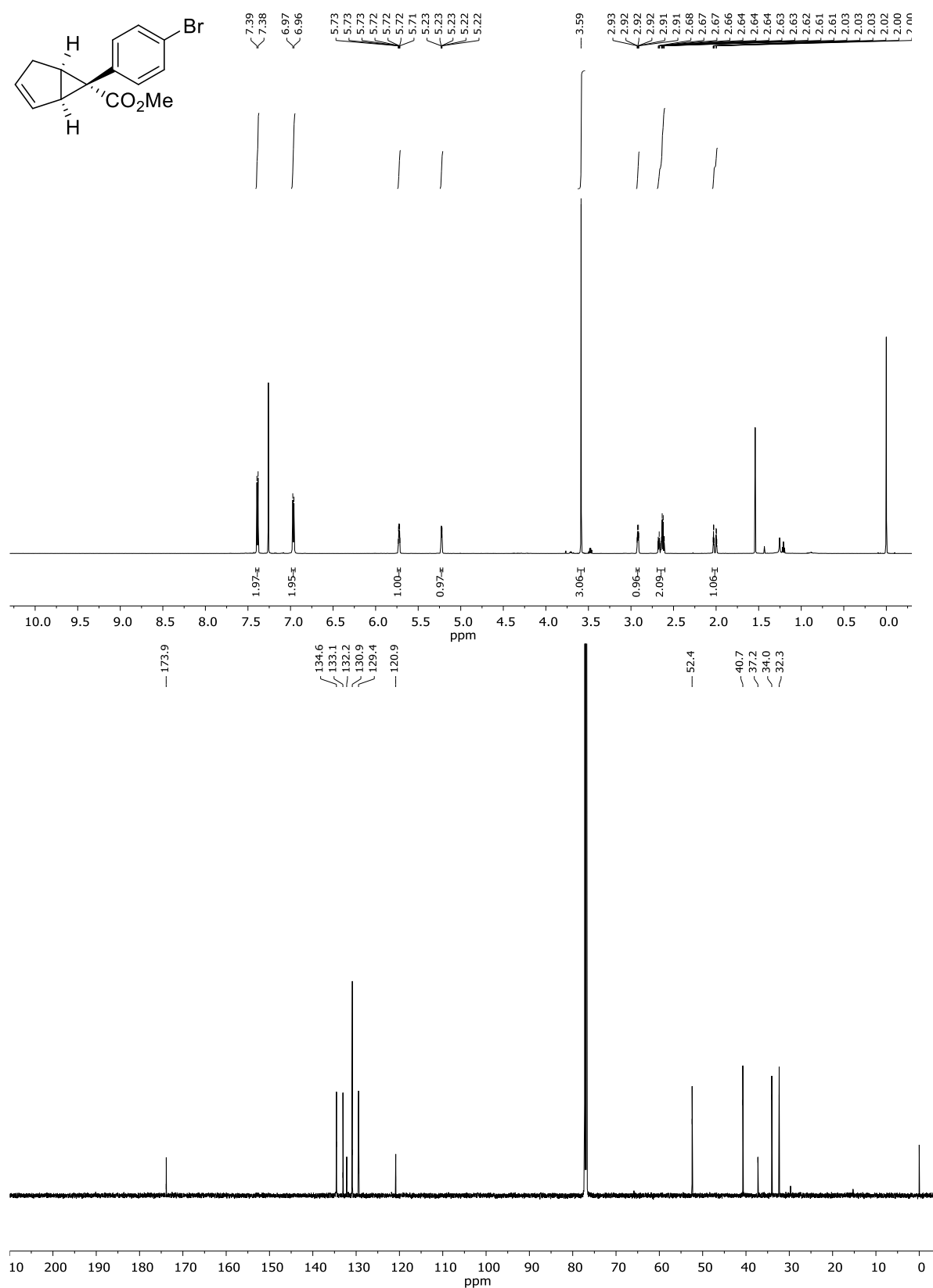
¹³C NMR spectrum (bottom):

- Chemical shift range: 32.4 to 174.5 ppm.

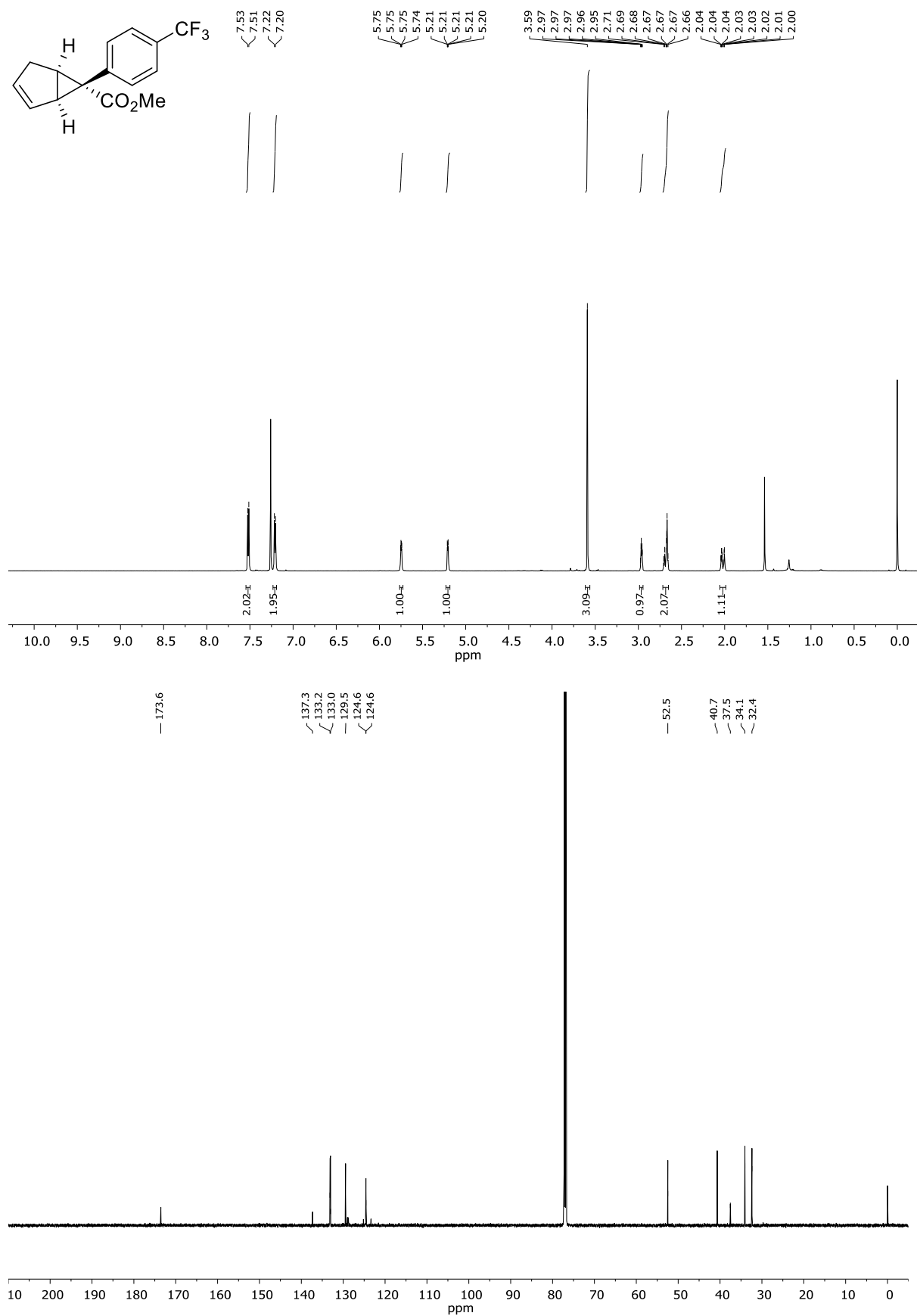
Compound (1*S*,5*R*,6*S*)-25k: ^1H NMR (600 MHz, CDCl_3) and ^{13}C NMR (151 MHz, CDCl_3)

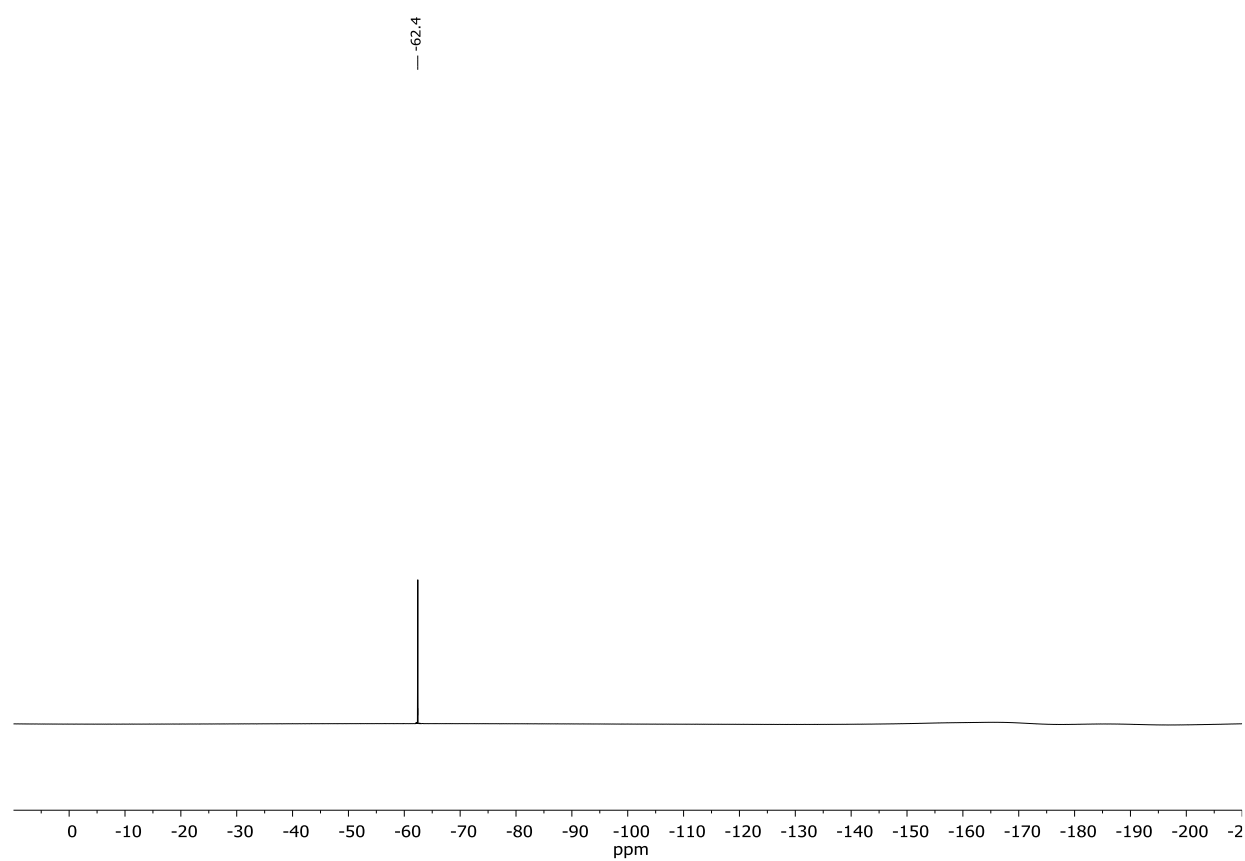


Compound (1*S*,5*R*,6*S*)-25r: ^1H NMR (600 MHz, CDCl_3) and ^{13}C NMR (151 MHz, CDCl_3)

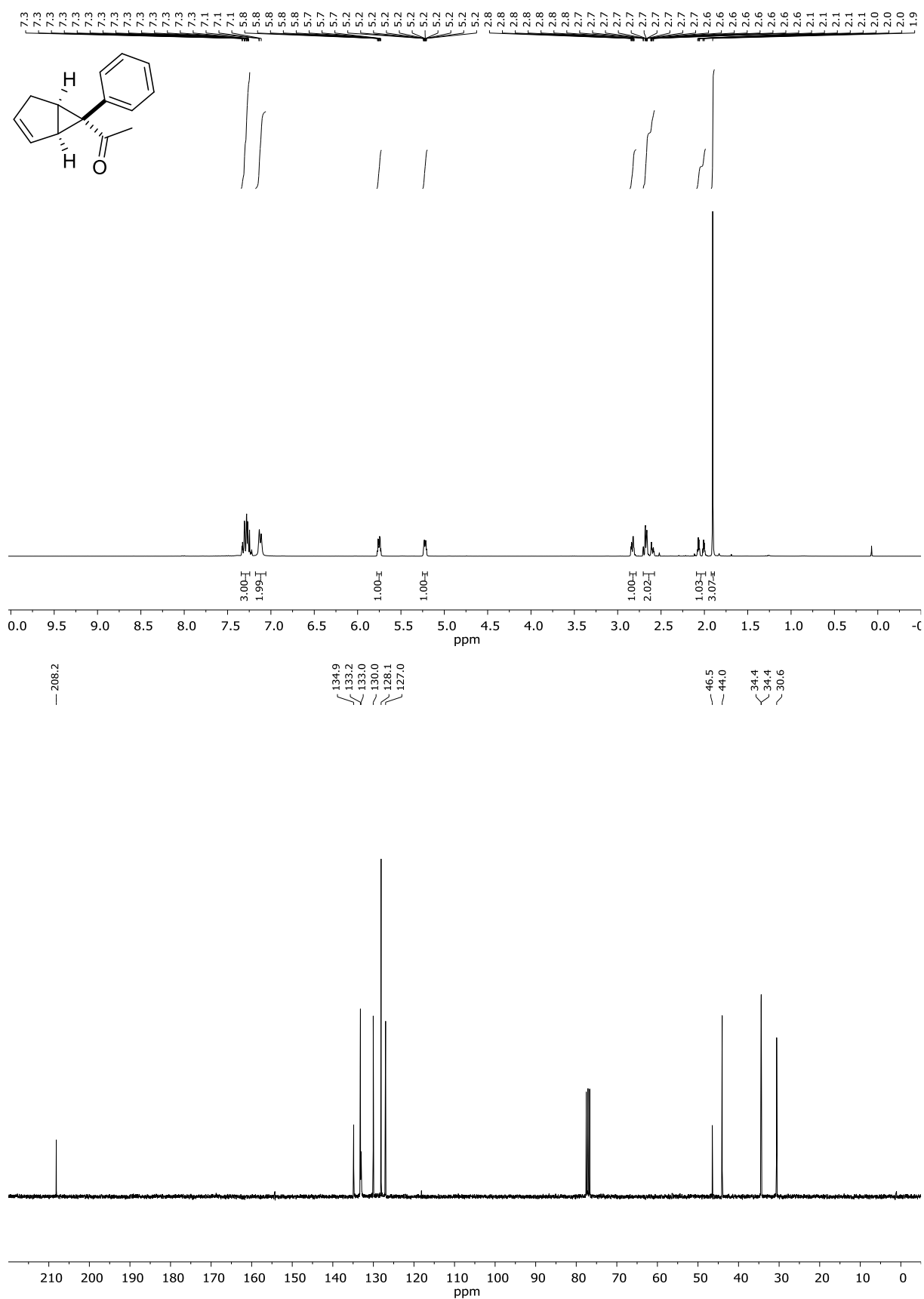


Compound (1*S*,5*R*,6*S*)-25s: ^1H NMR (600 MHz, CDCl_3), ^{13}C NMR (151 MHz, CDCl_3) and ^{19}F -NMR (565 MHz, CDCl_3):





Compound 39a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



Chemical structure: 1-(4-methoxyphenyl)-2-methyl-2-oxobicyclo[2.2.1]heptane

¹H NMR spectrum (top):

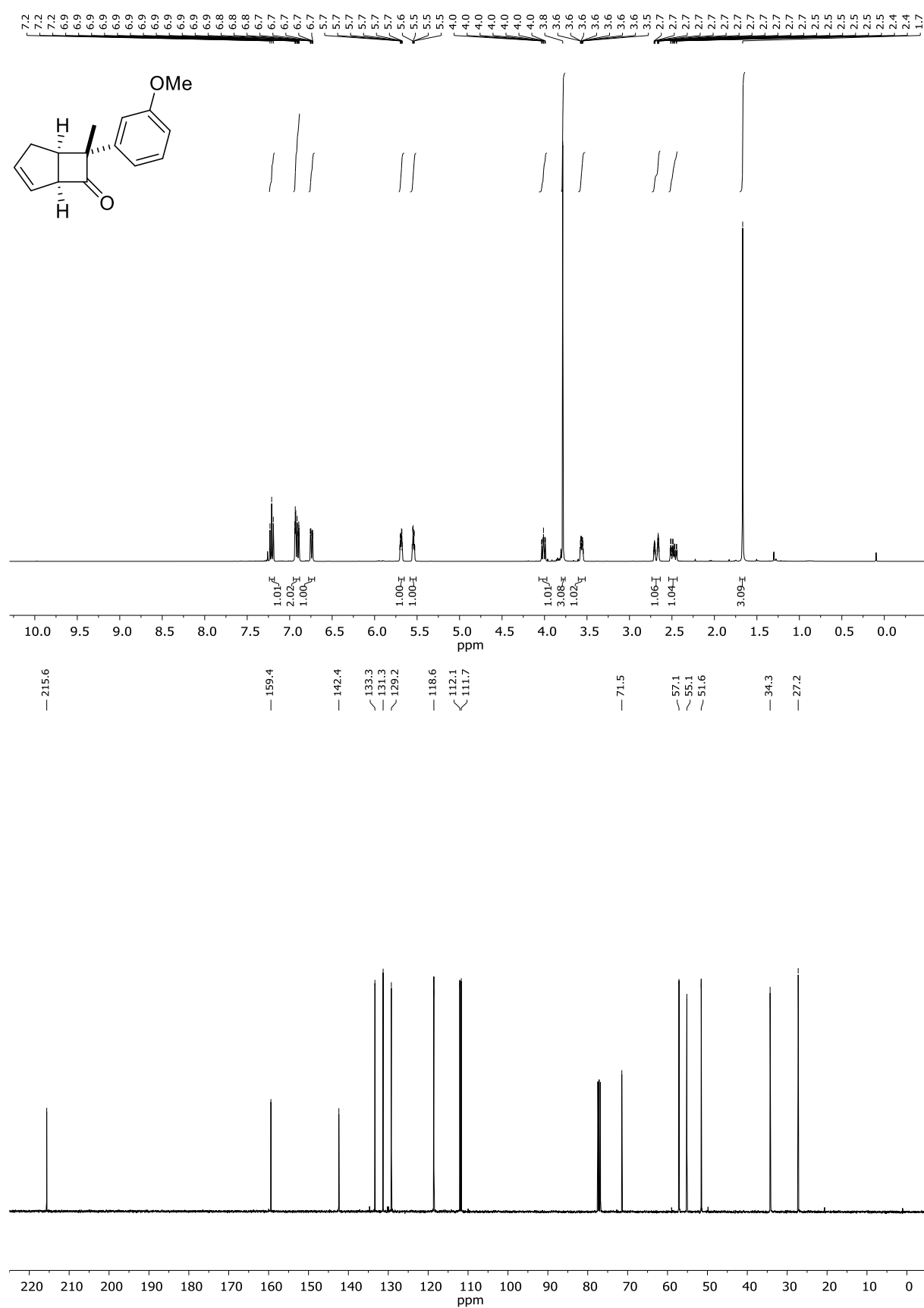
- Chemical shift range: 0.9 to 7.3 ppm
- Integration values: 1.06, 1.01, 1.92, 0.97, 0.98, 3.09, 0.98, 2.00, 0.98, 2.98

¹³C NMR spectrum (bottom):

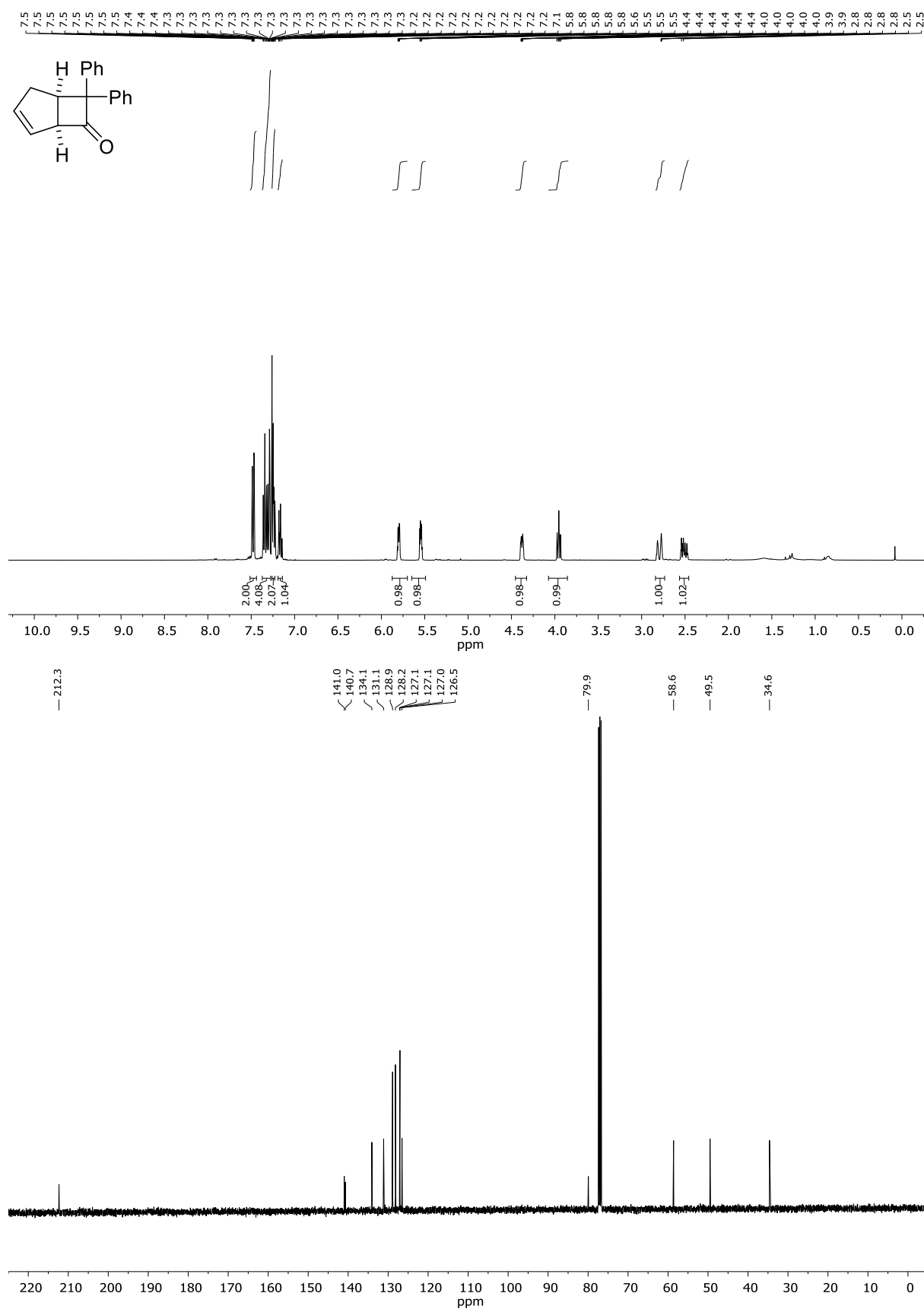
- Chemical shift range: 30 to 208 ppm
- Peak labels: 208.1, 159.3, 136.5, 133.2, 130.0, 129.1, 112.1, 55.2, 44.0, 34.5, 30.4

[illegible]

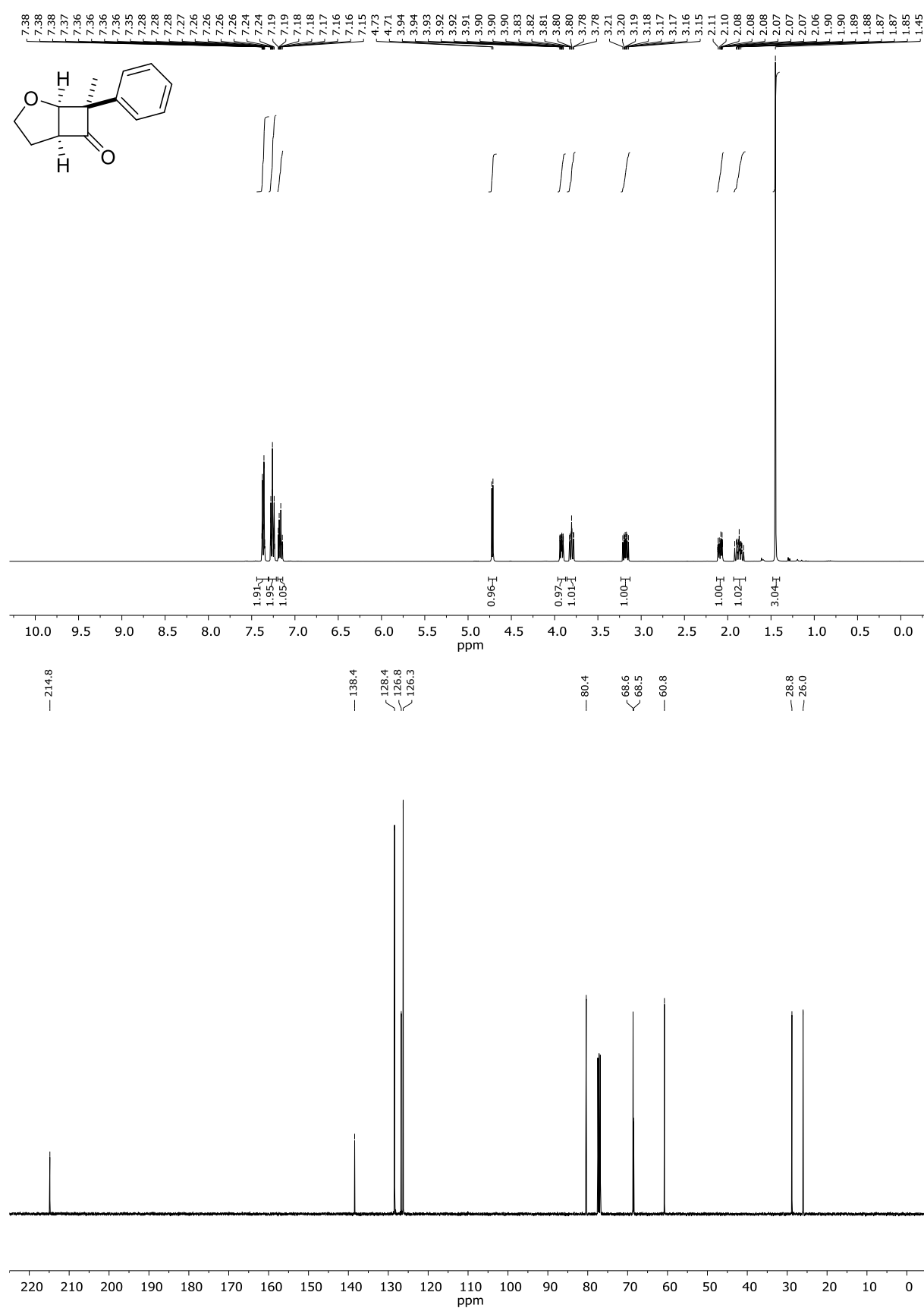
Compound 40b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



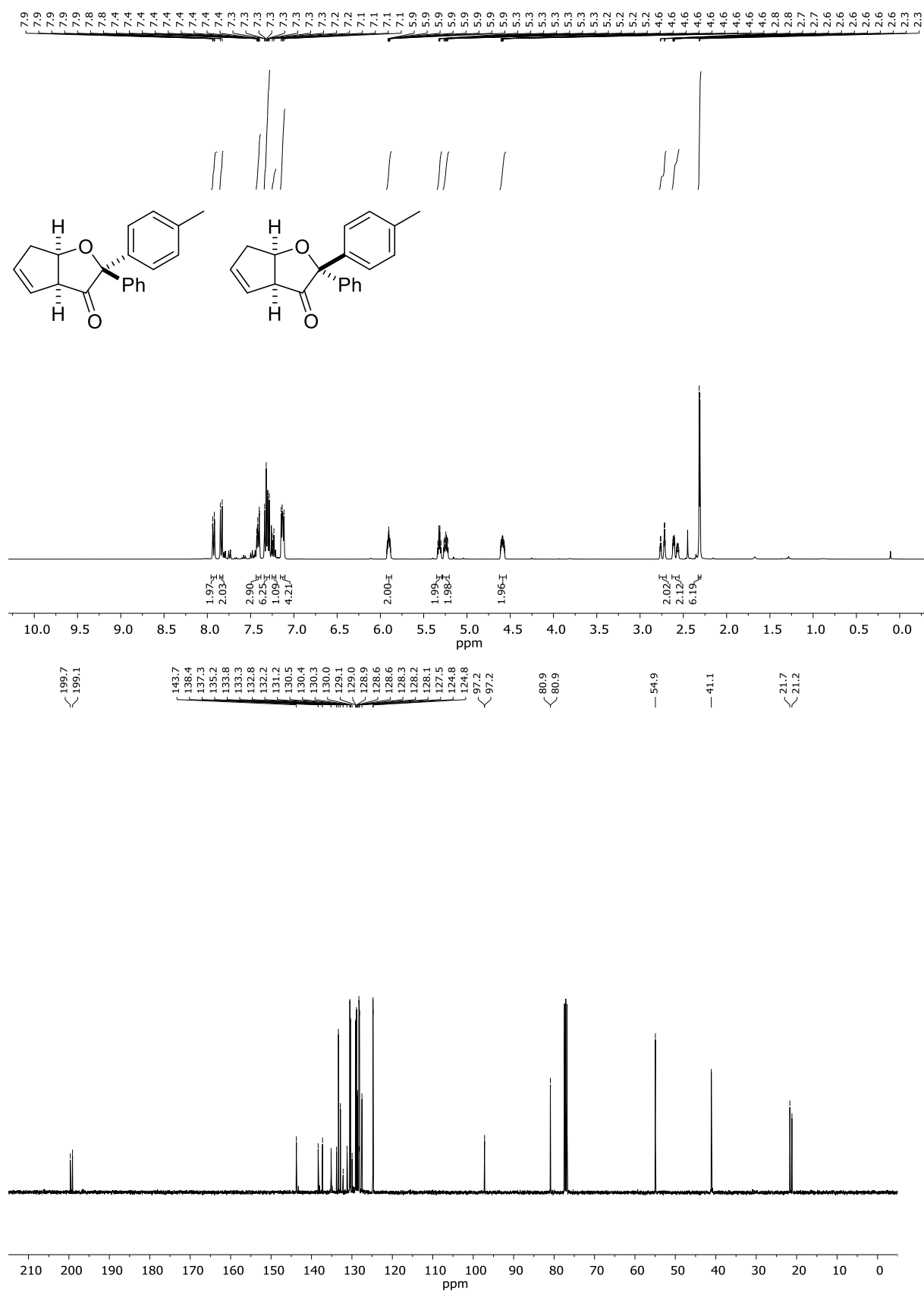
Compound 40c: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



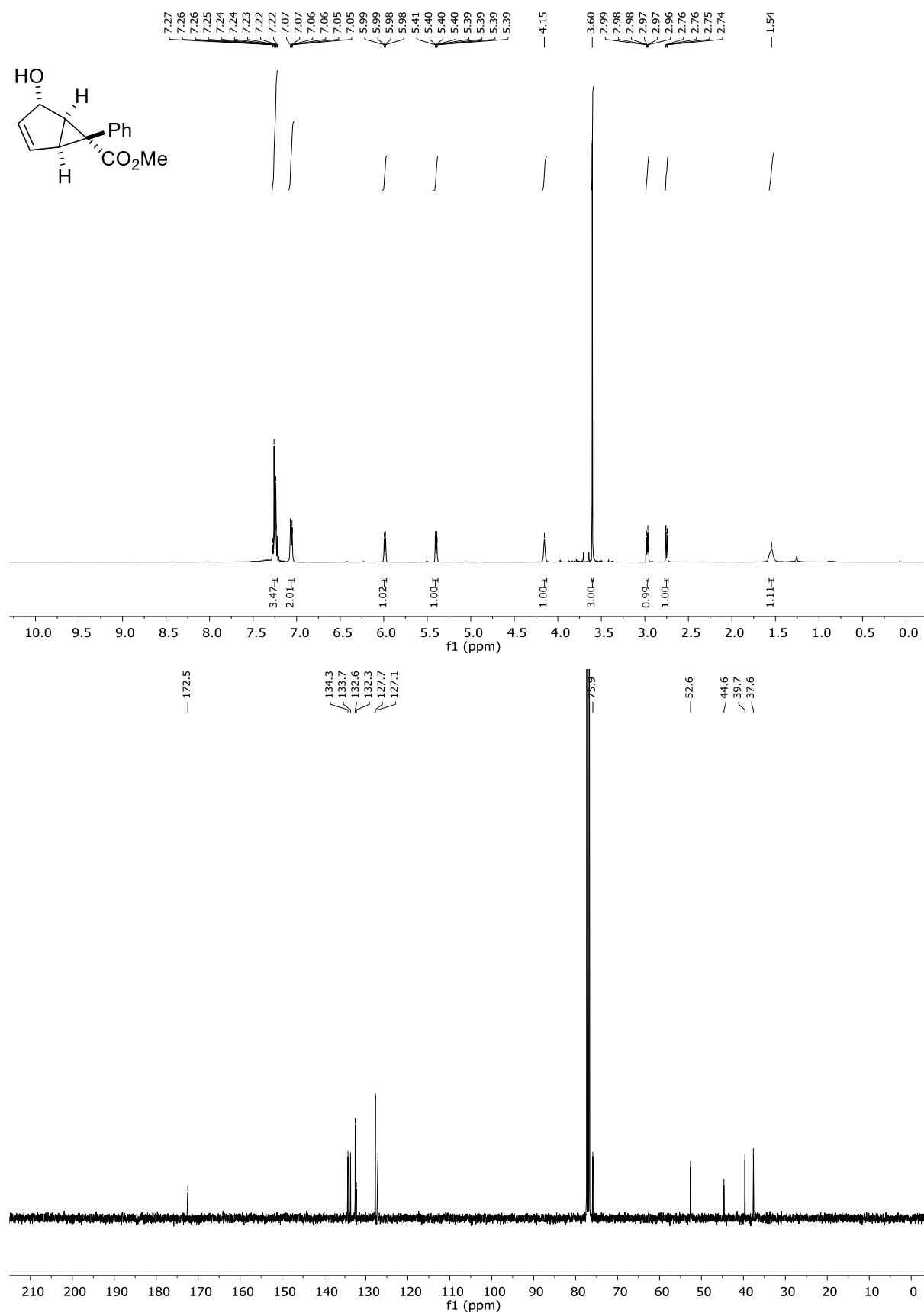
Compound 46: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



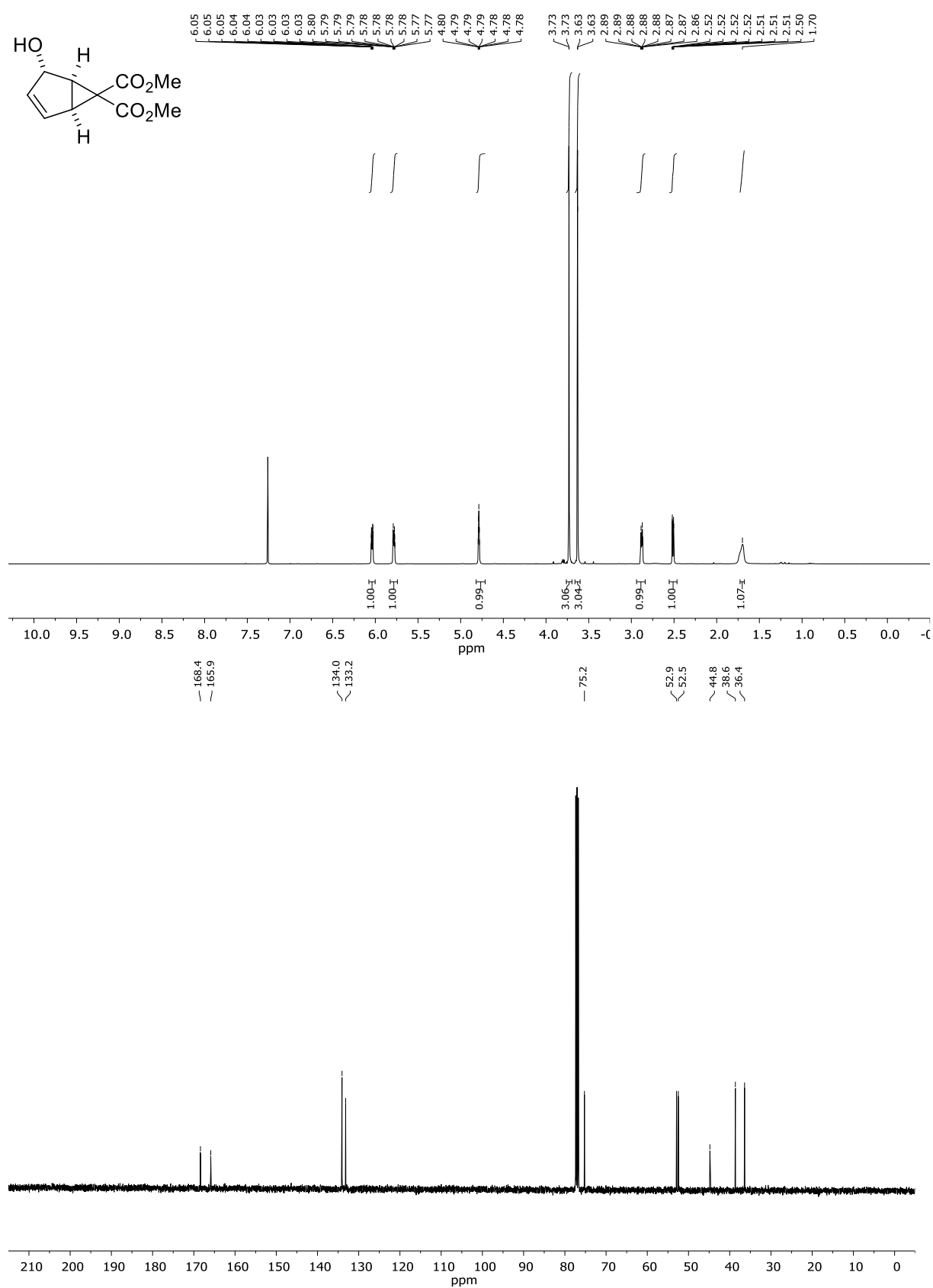
Compound 50a/b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



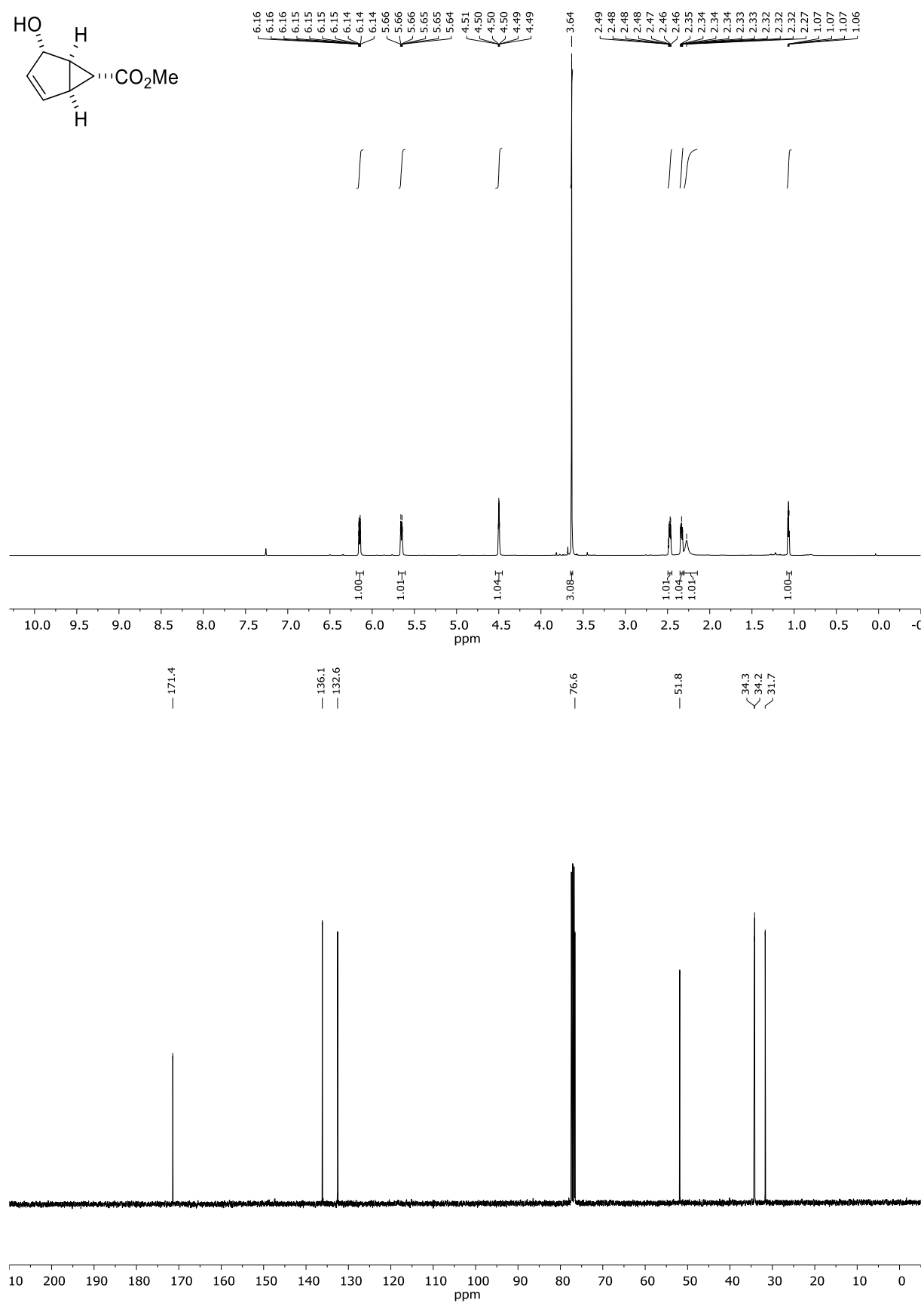
Compound 96a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



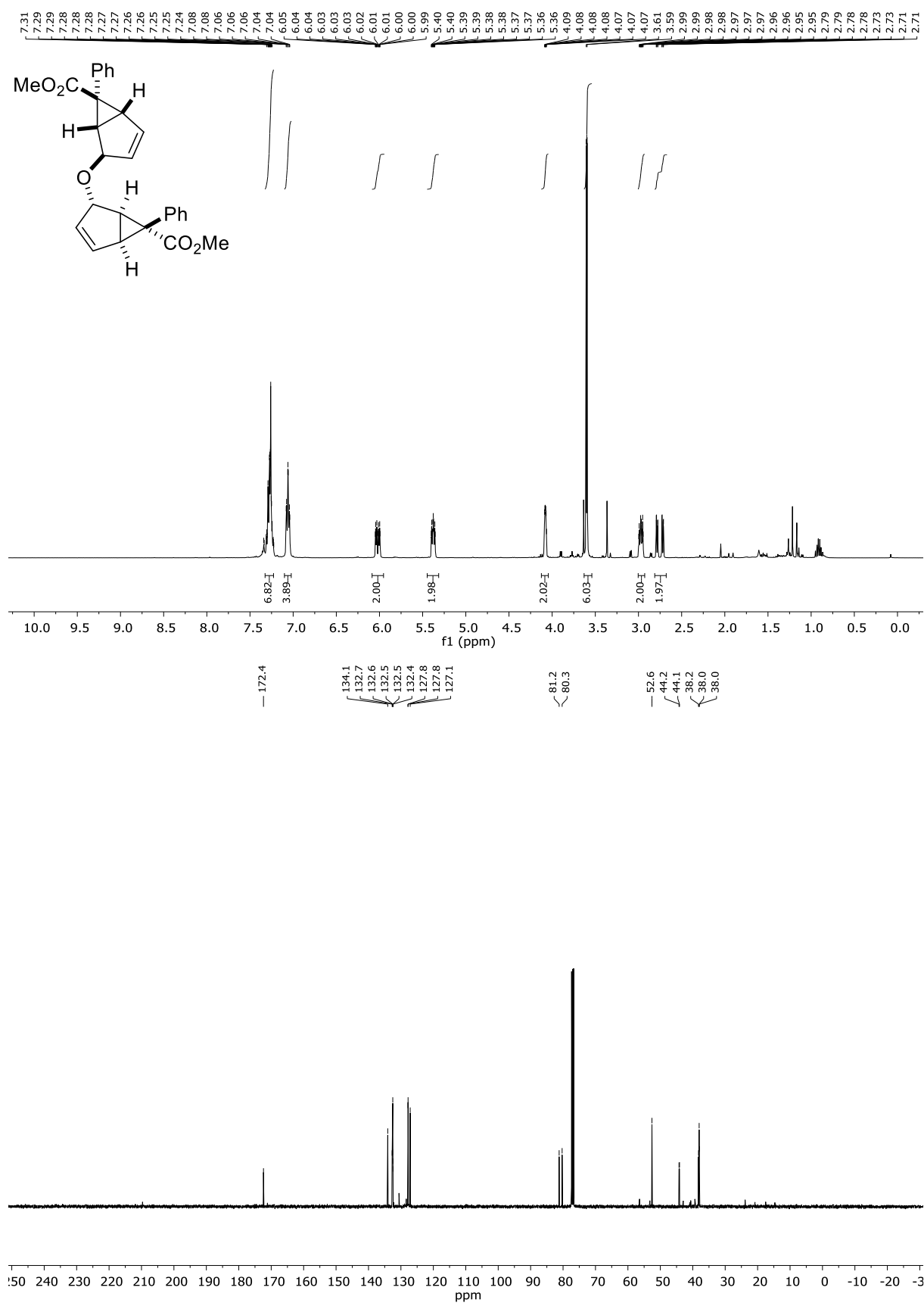
Compound 96n: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



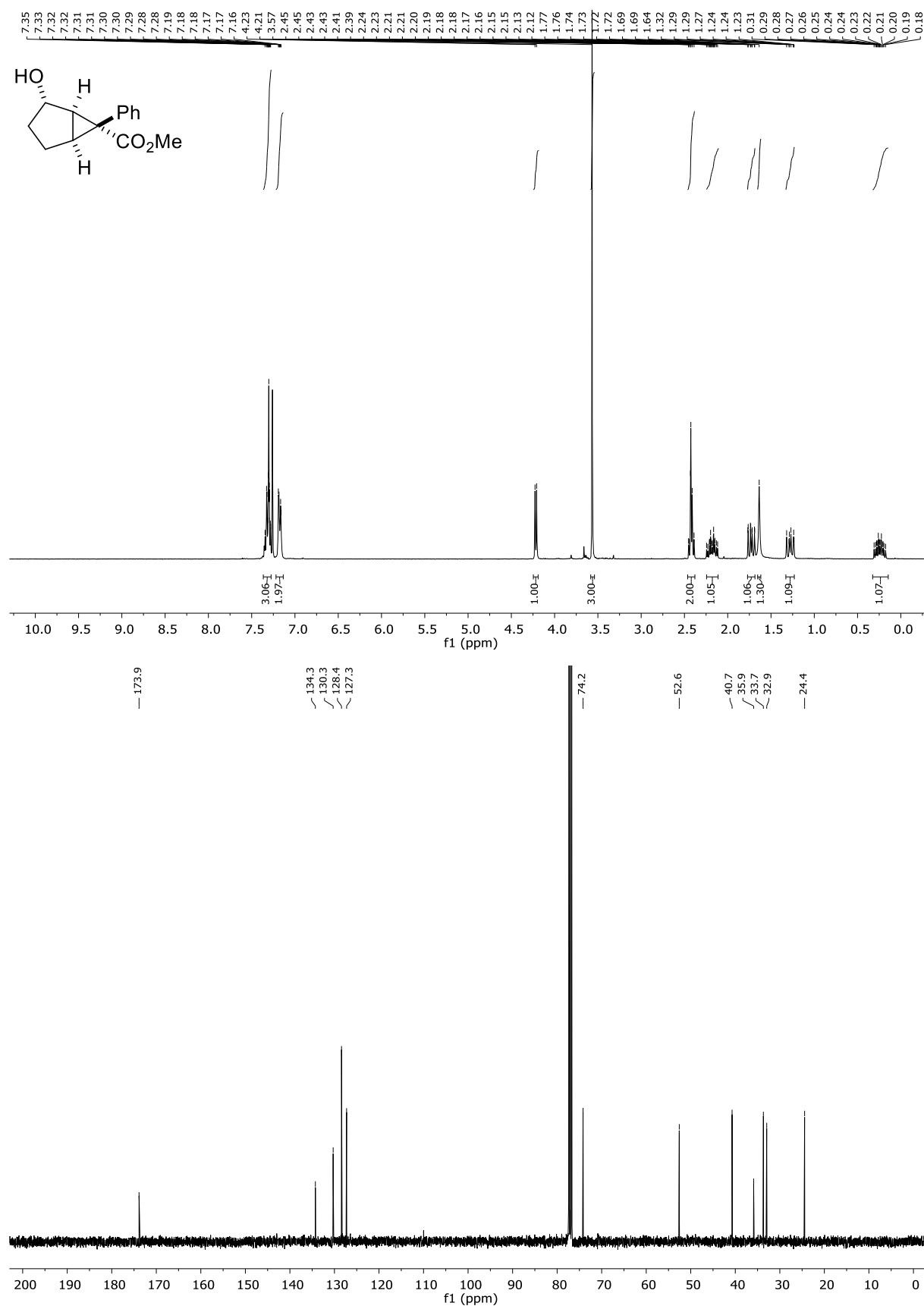
Compound 96o: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



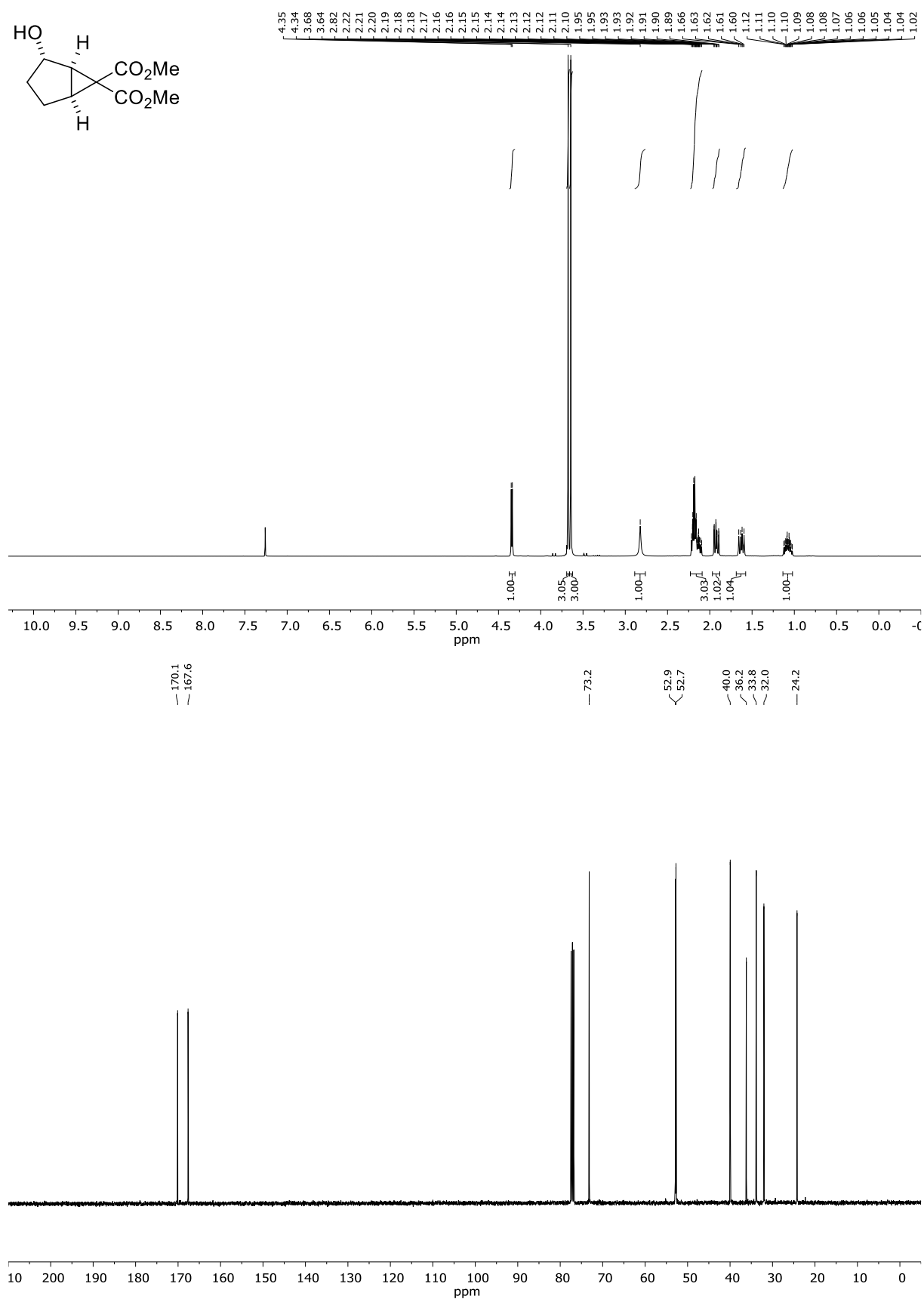
Compound 97: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



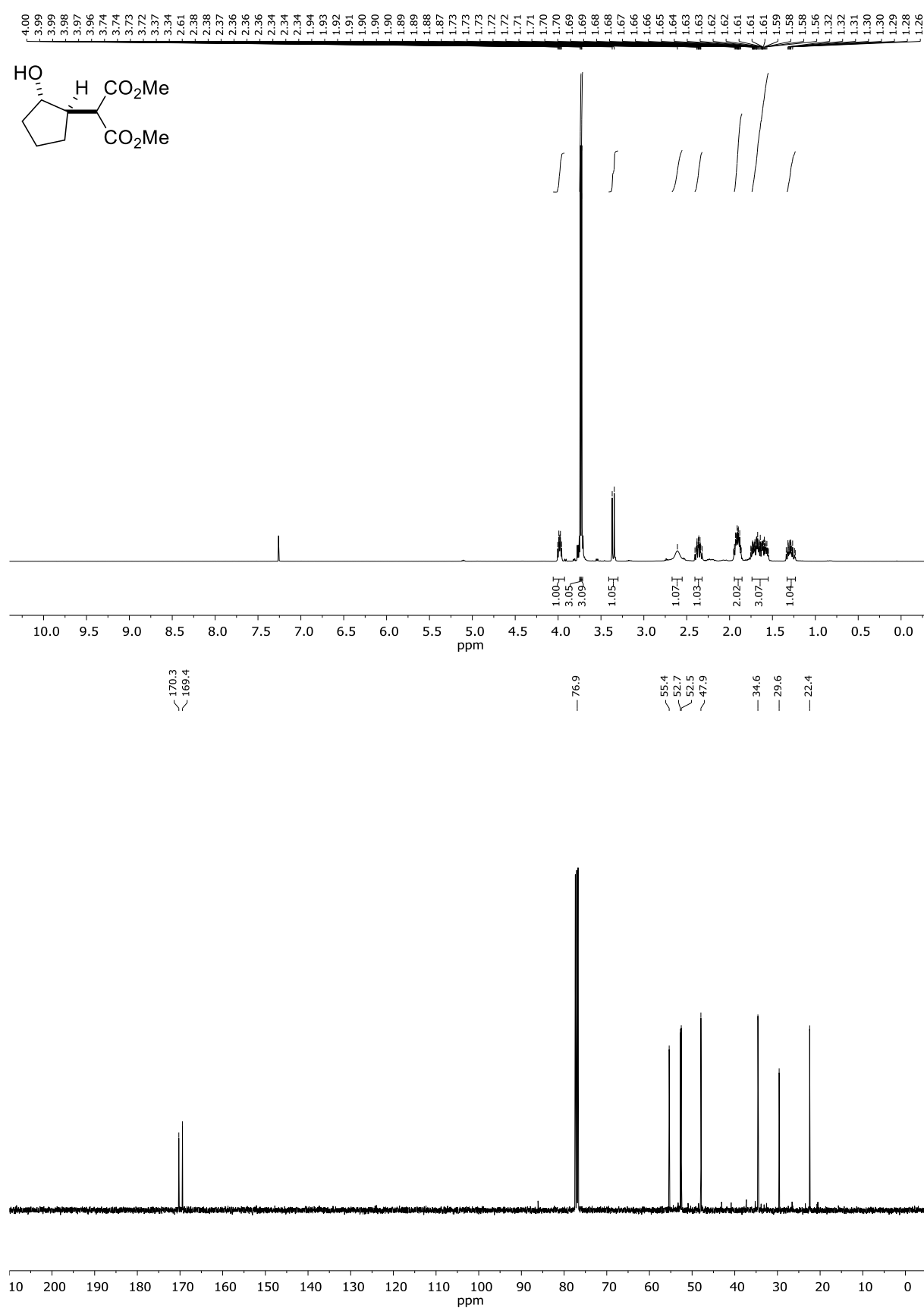
Compound 99a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



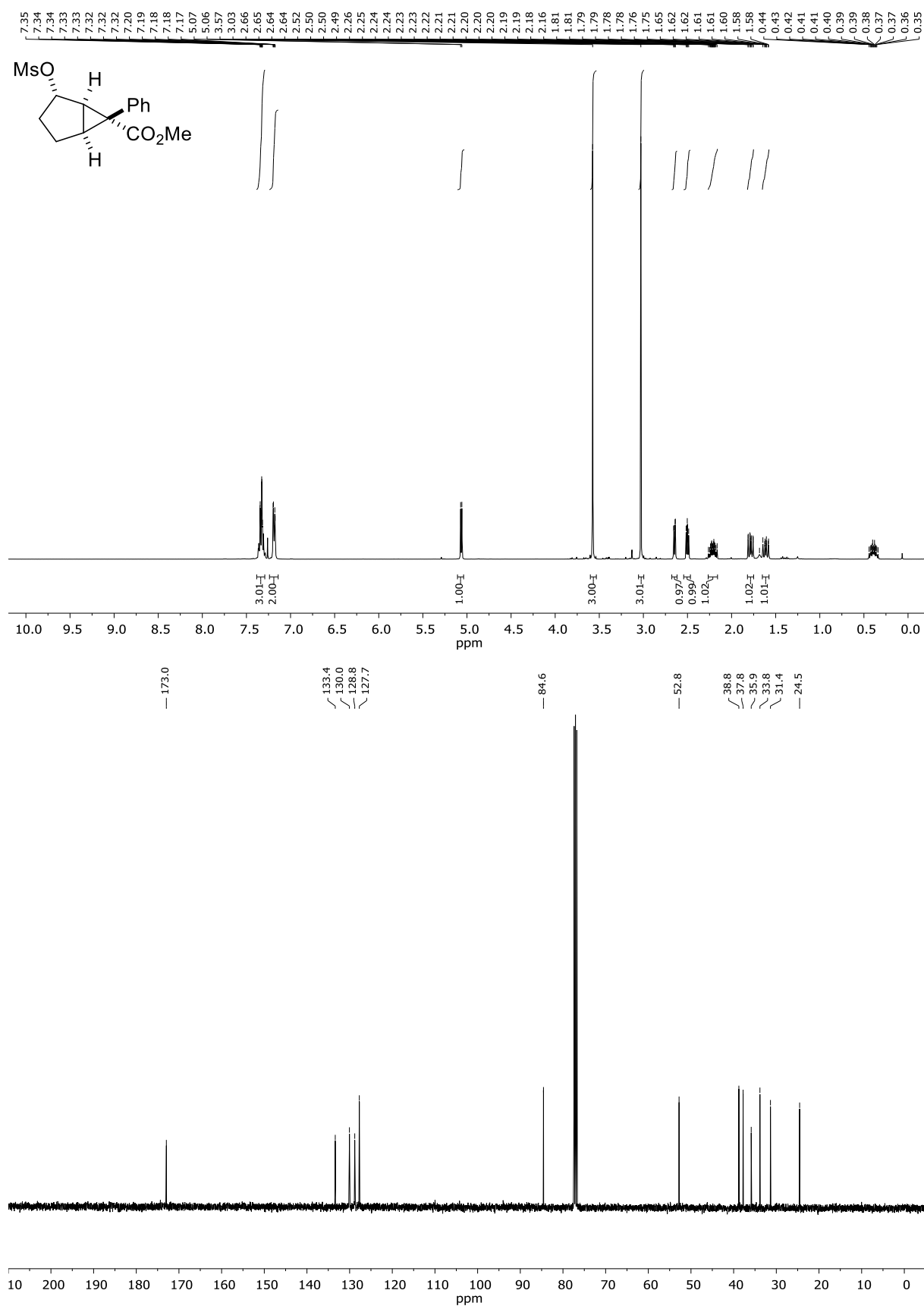
Compound 99n: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



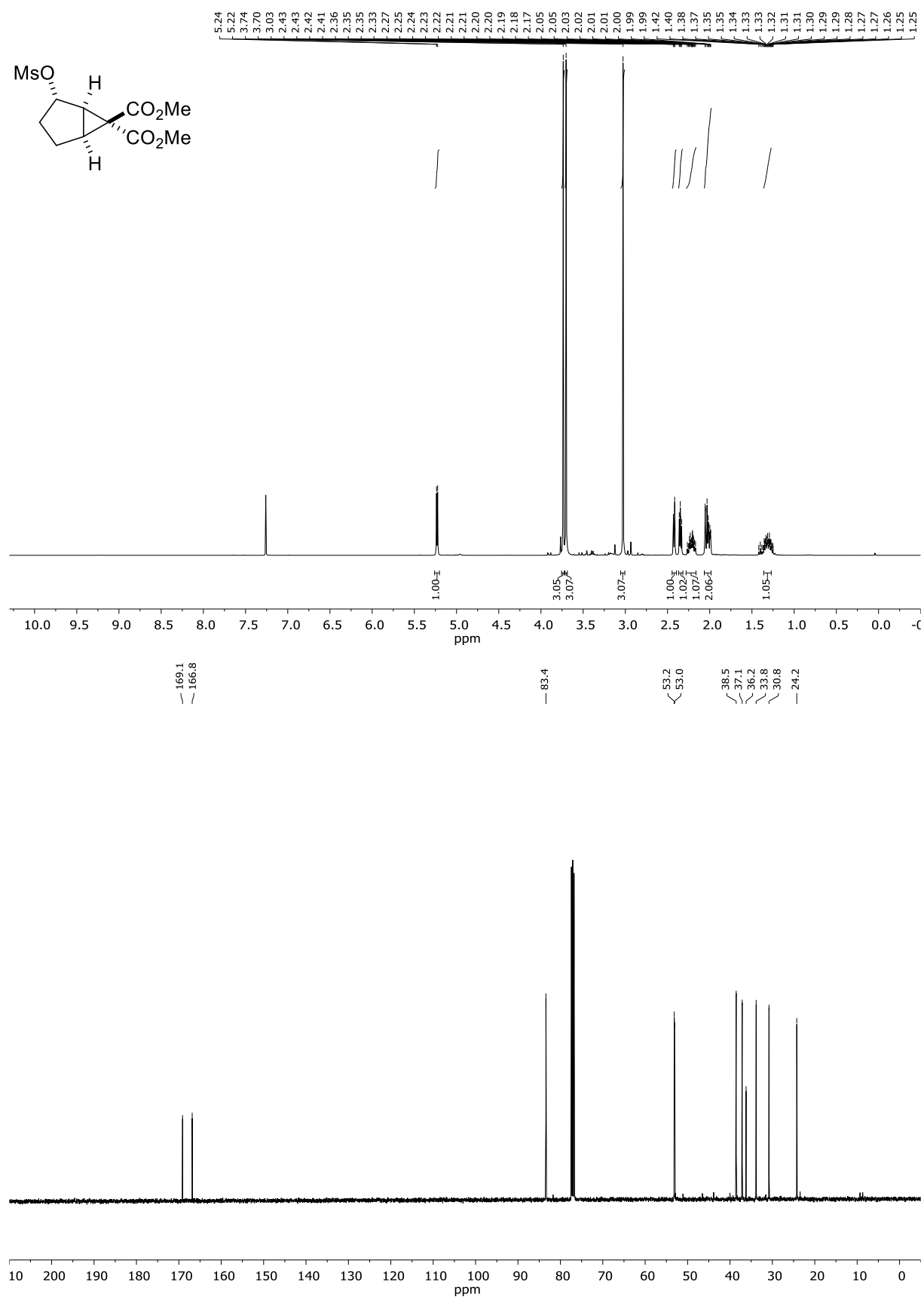
Compound 100: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



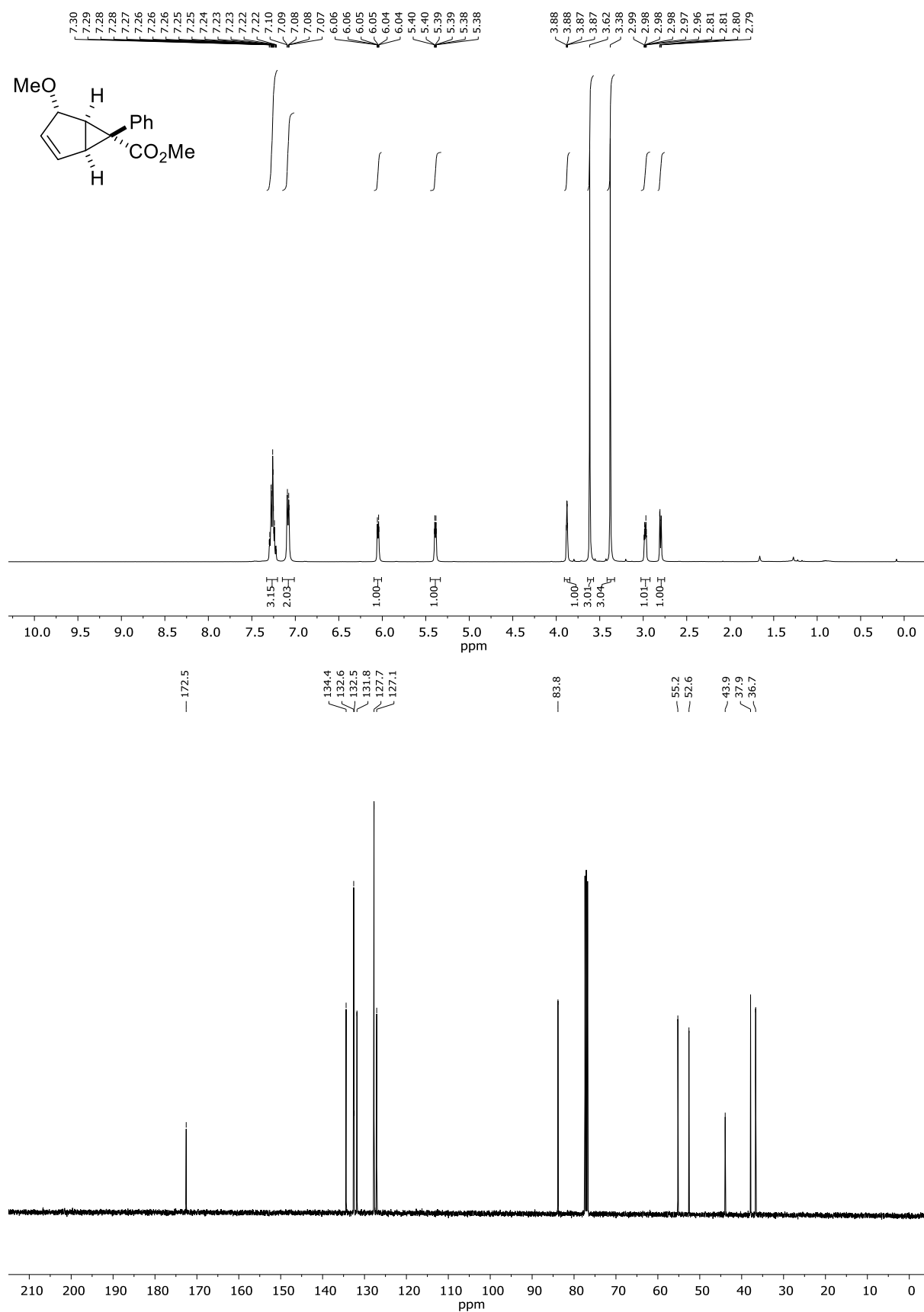
Compound 101a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



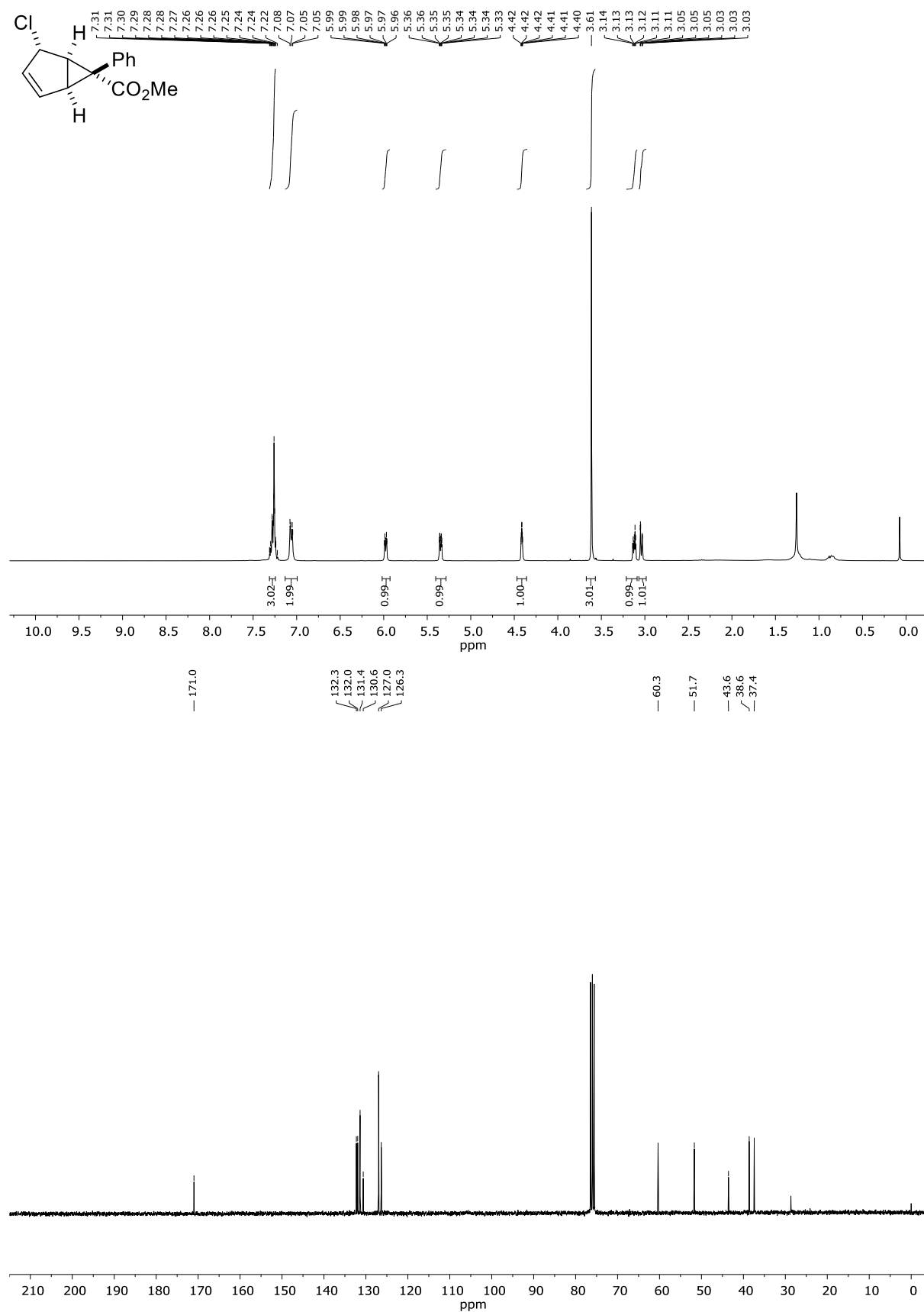
Compound 101n: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



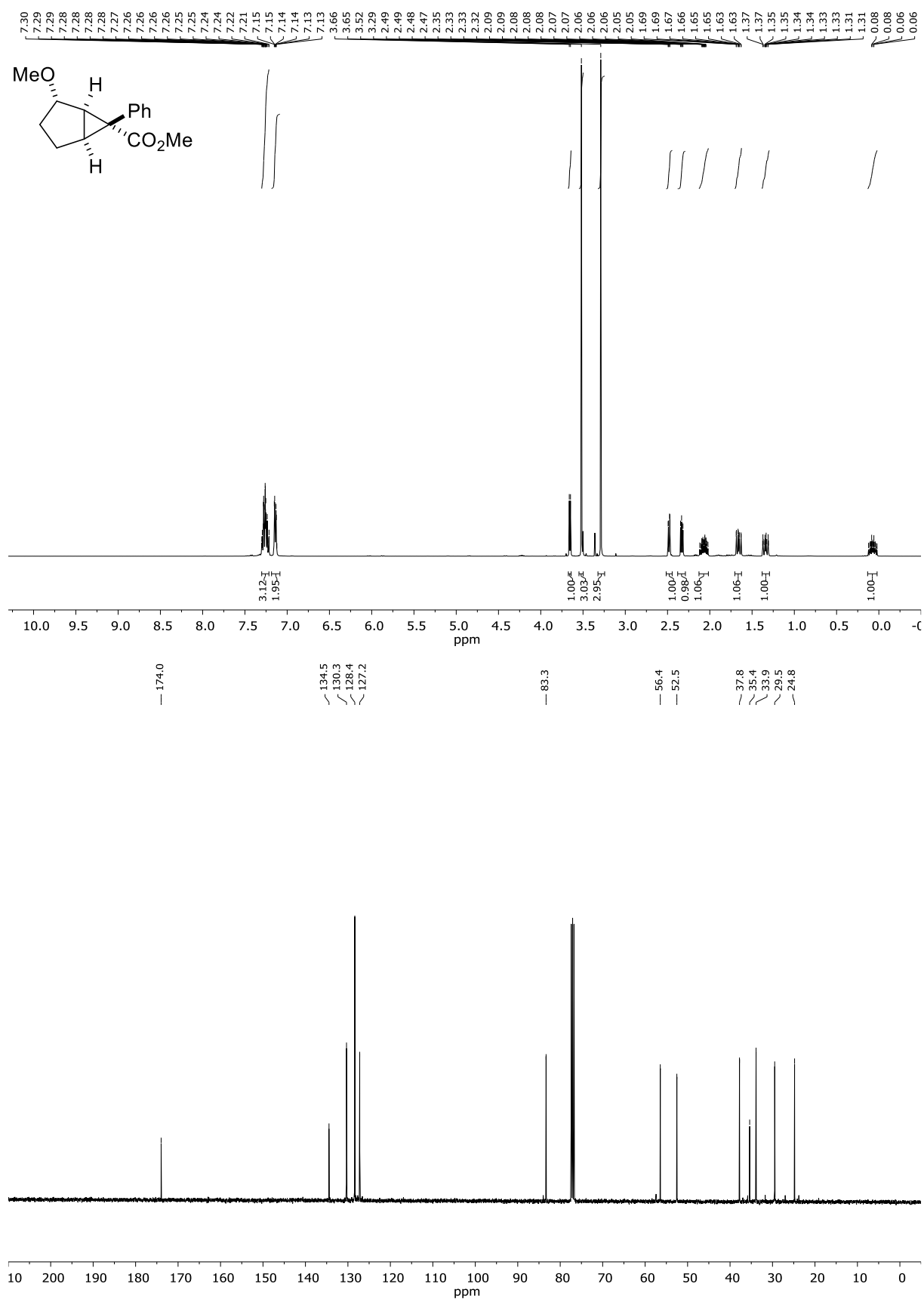
Compound 105: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



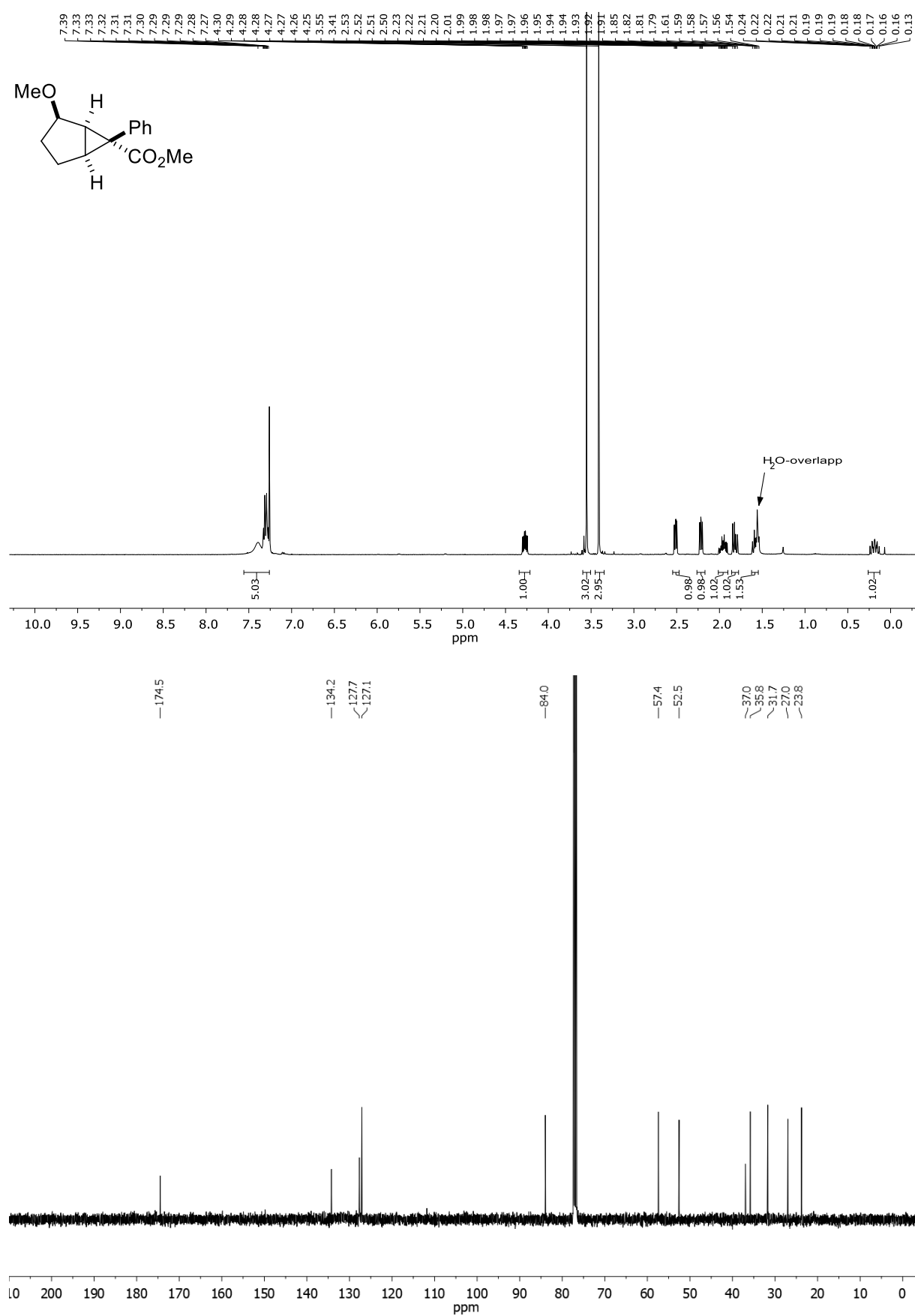
Compound 106: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



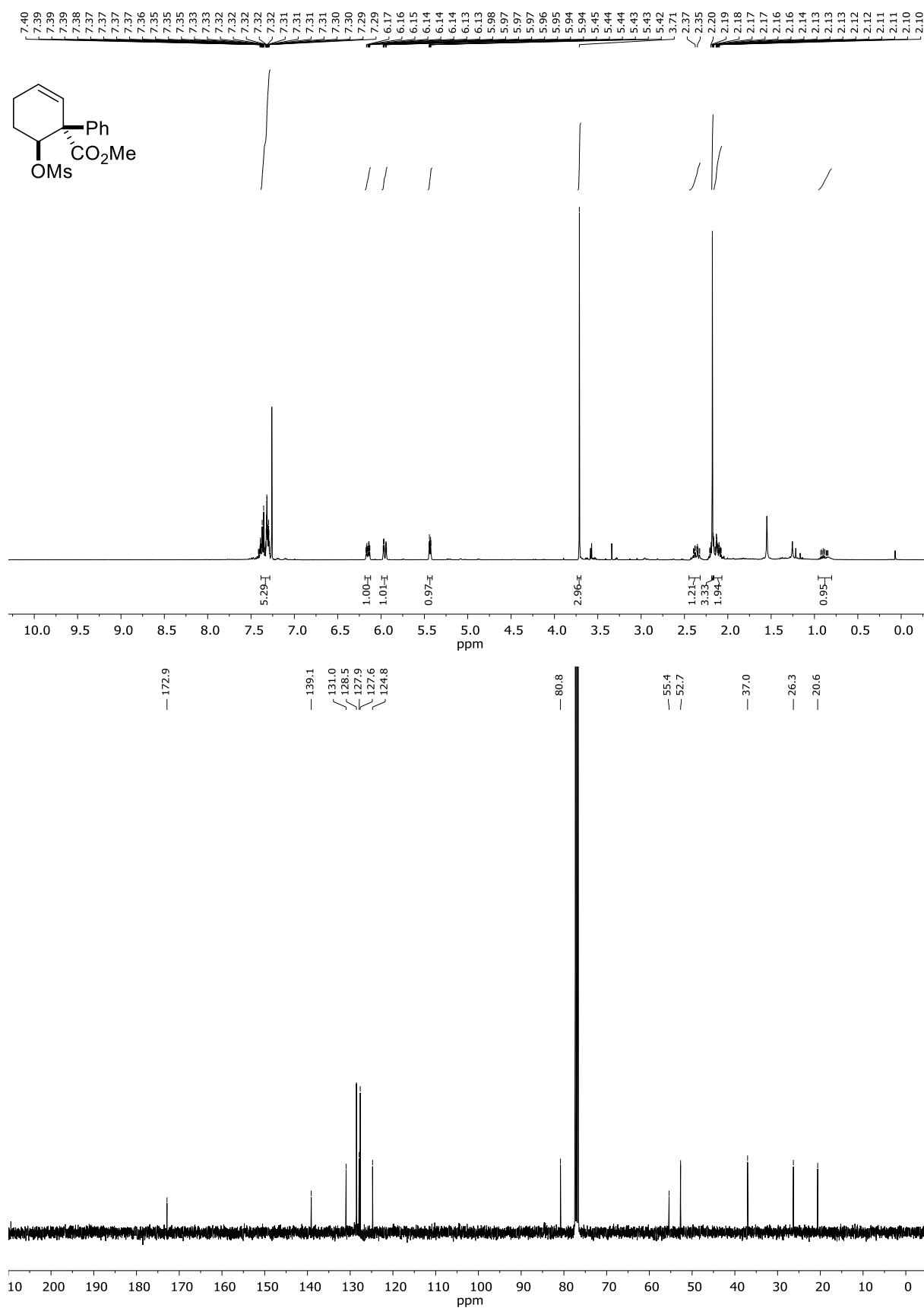
Compound 107a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



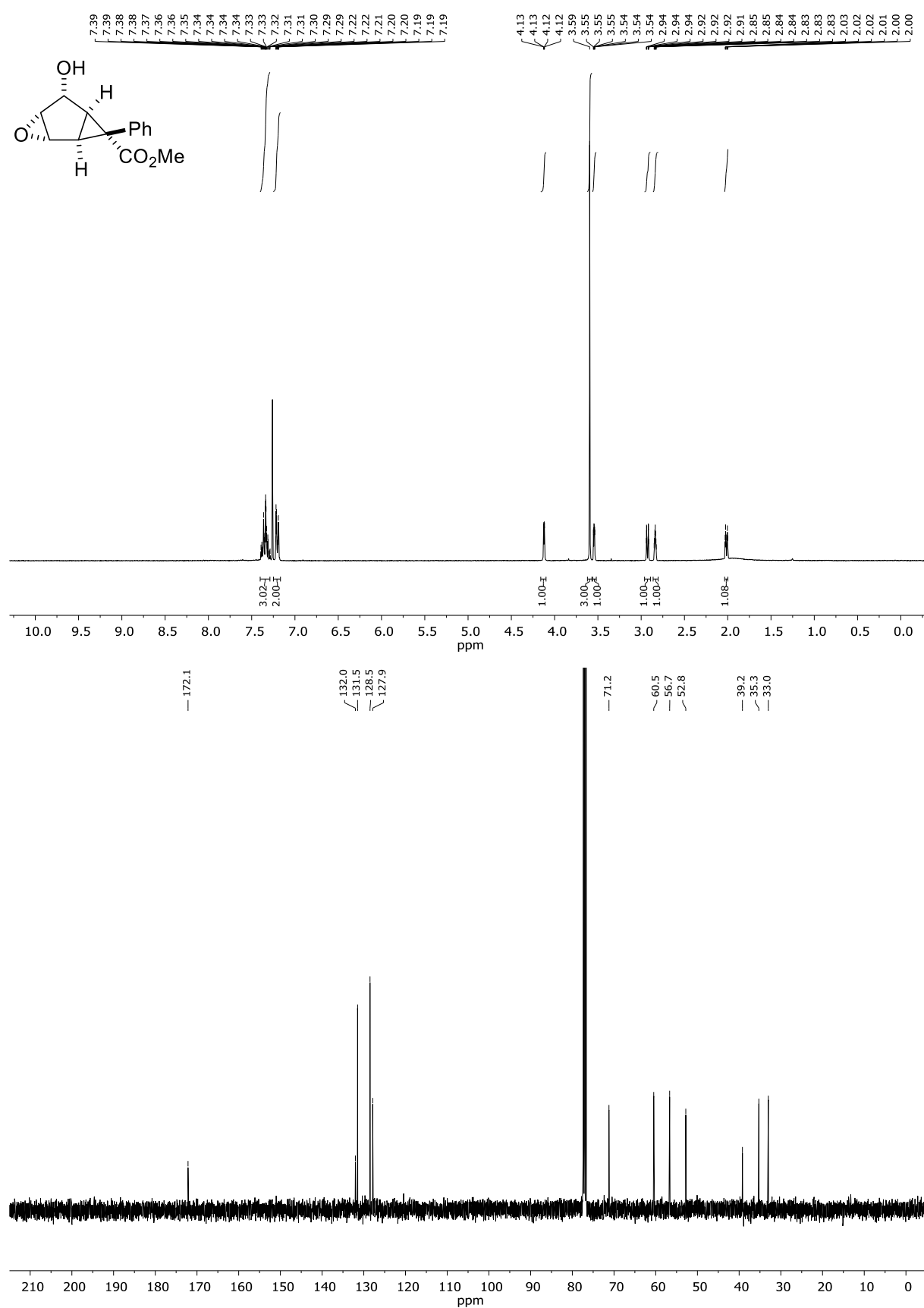
Compound 107b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



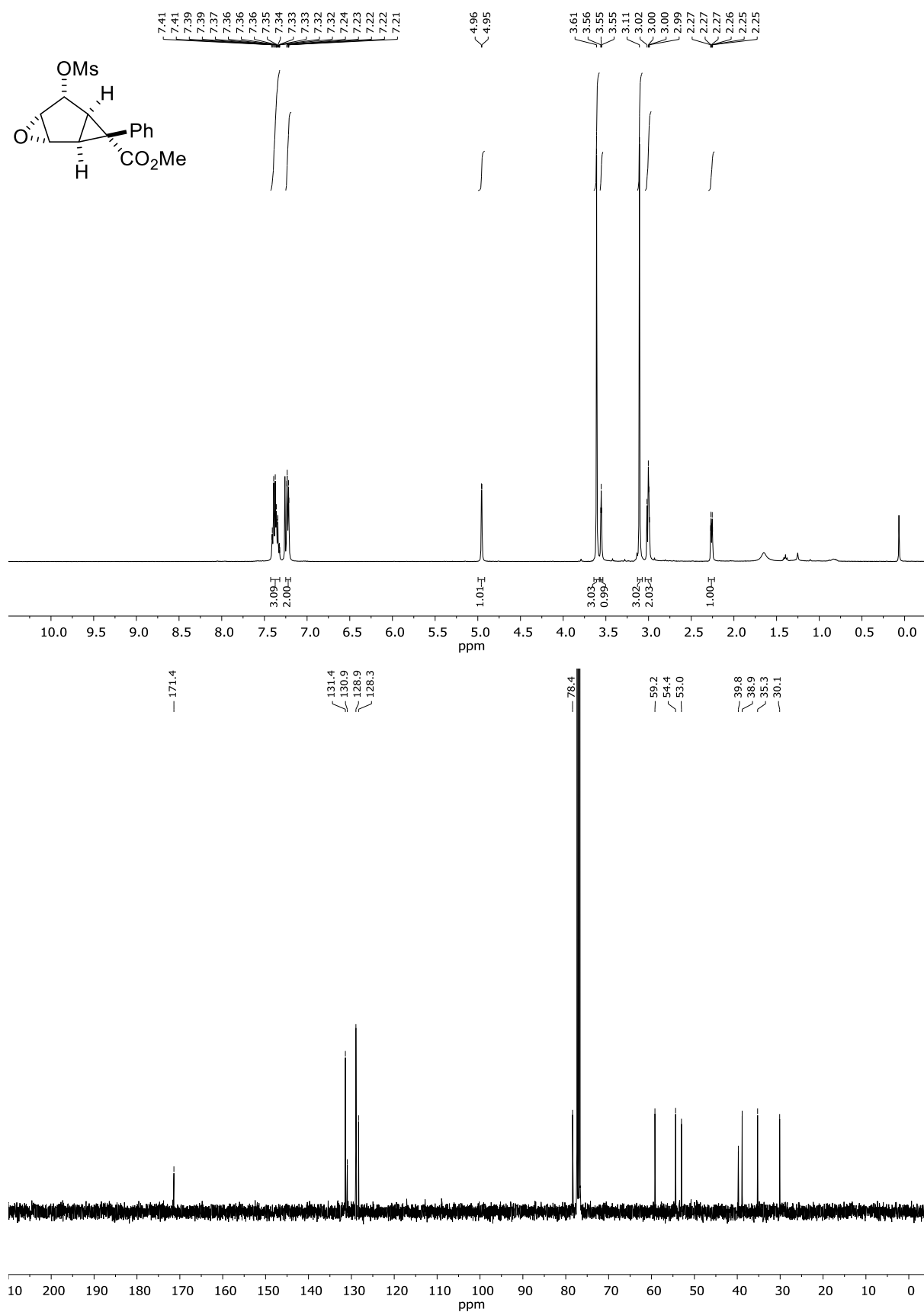
Compound 108: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



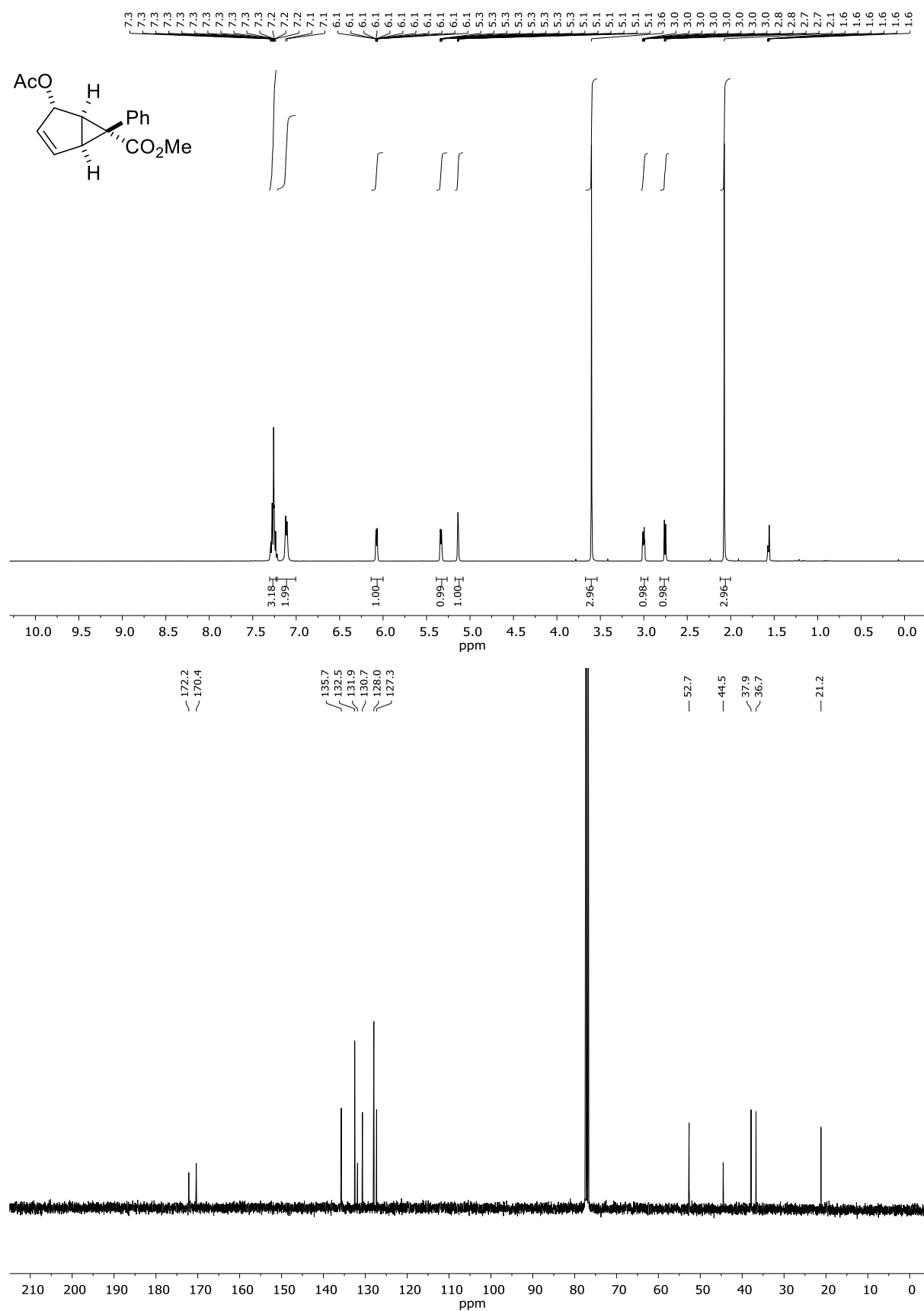
Compound 112: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



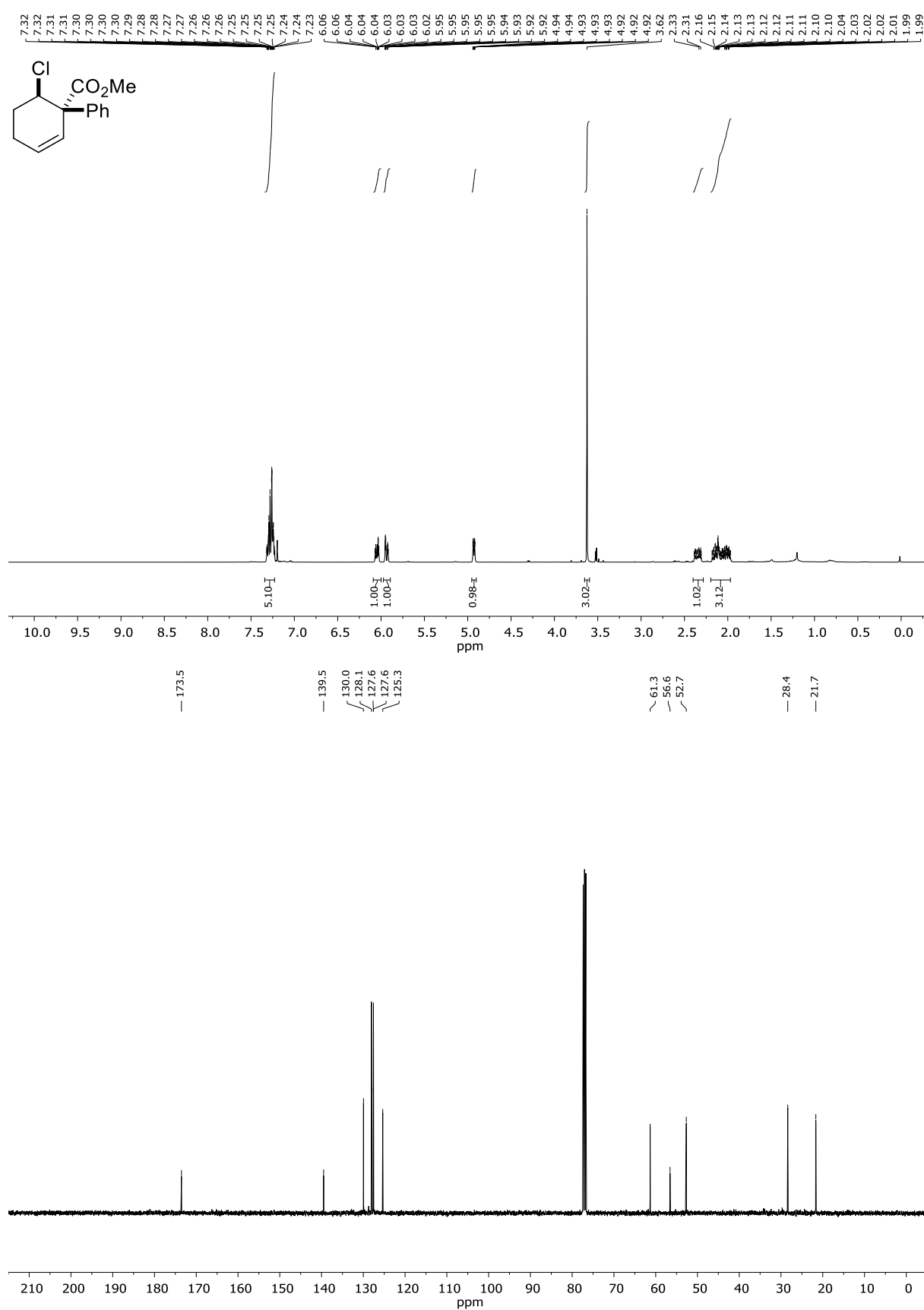
Compound 113: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



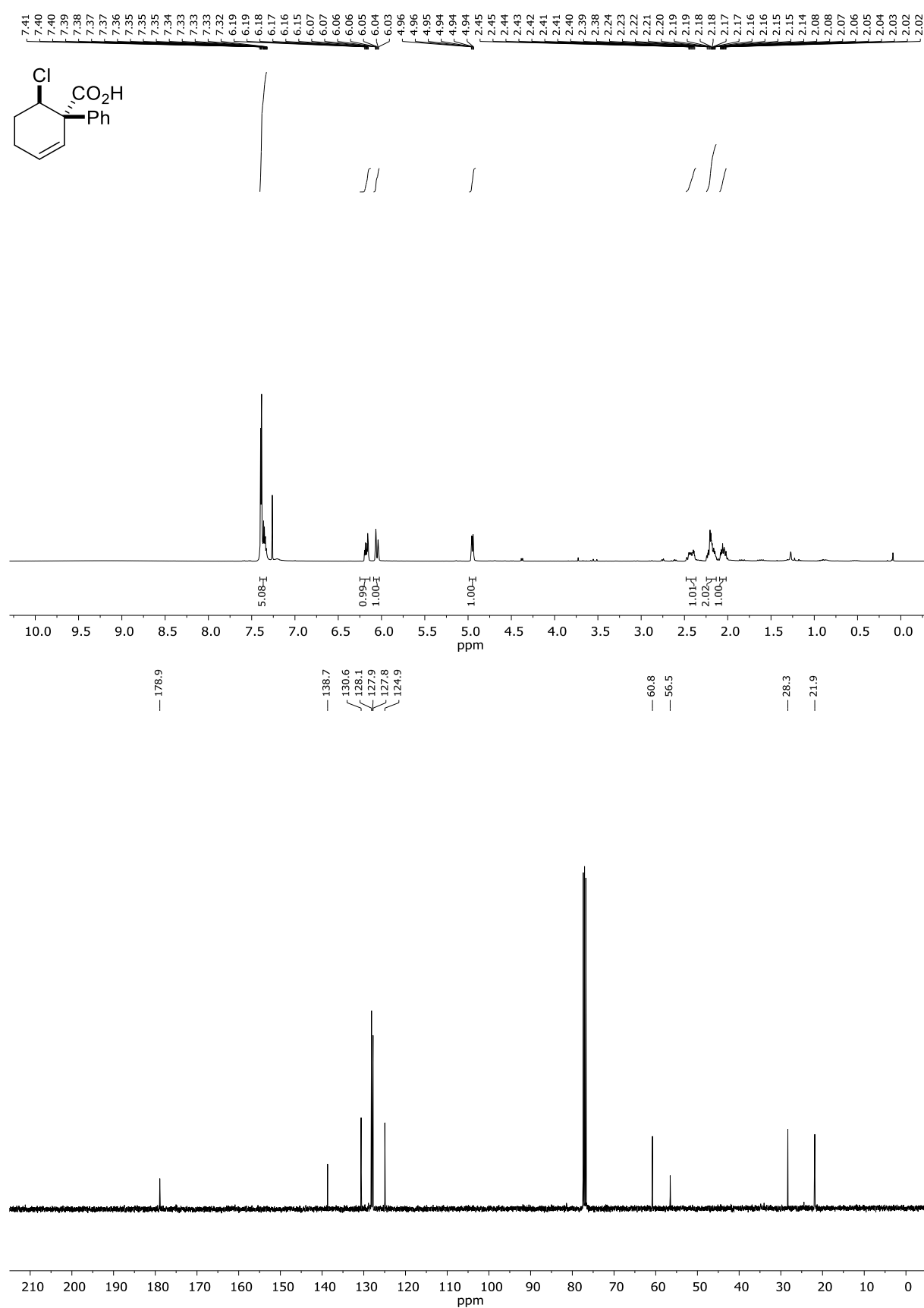
Compound 116: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



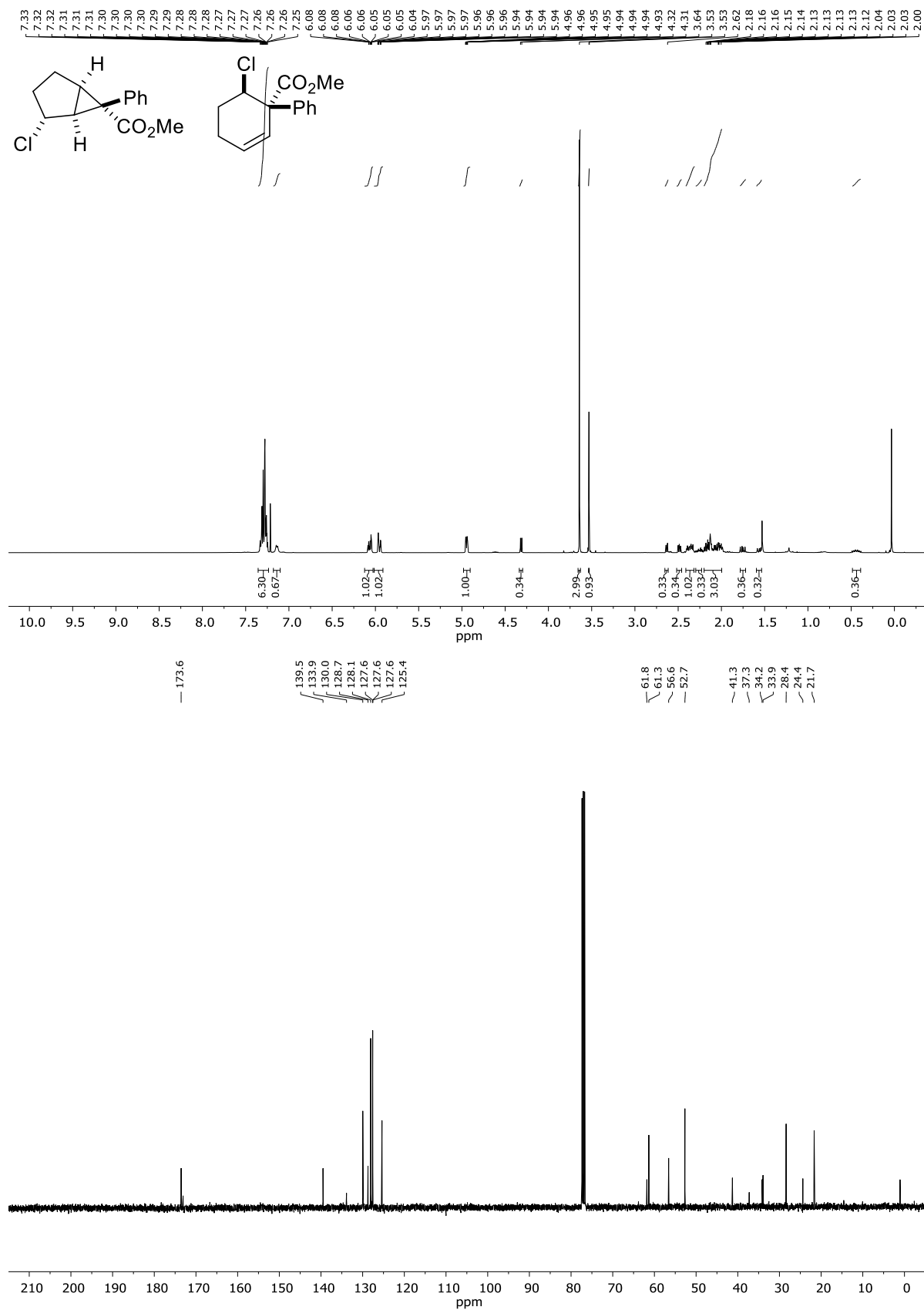
Compound 121a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



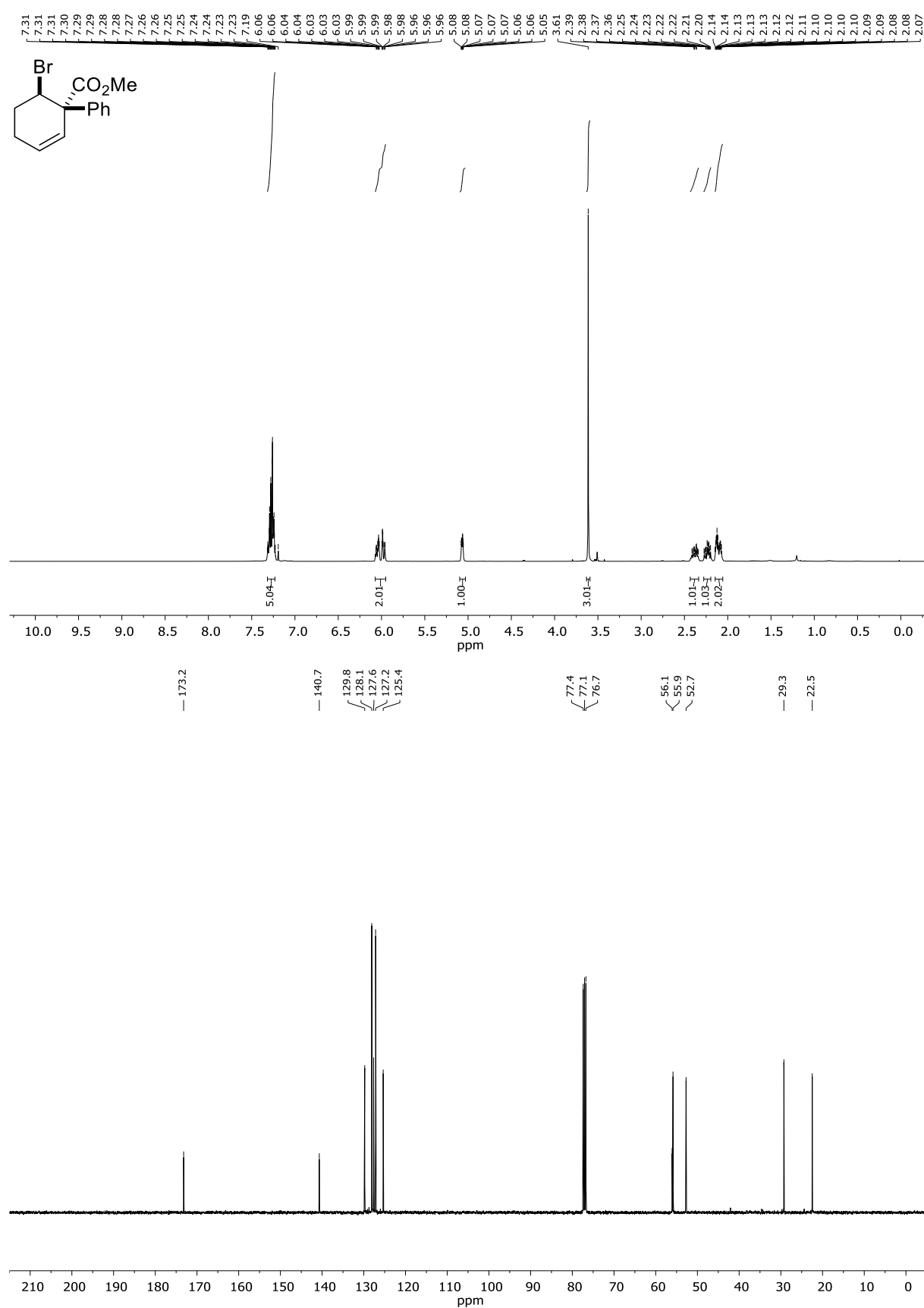
Compound 121b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



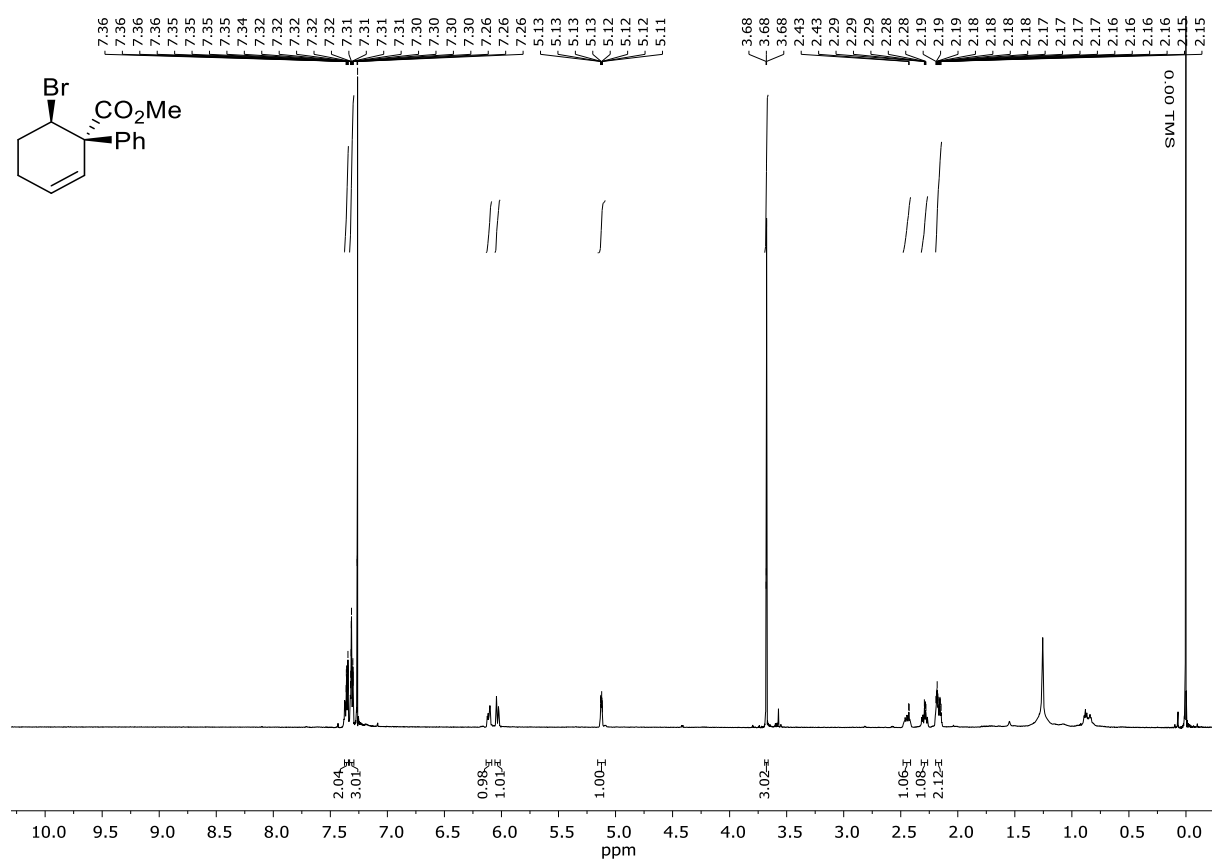
Compound 121a and 123a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



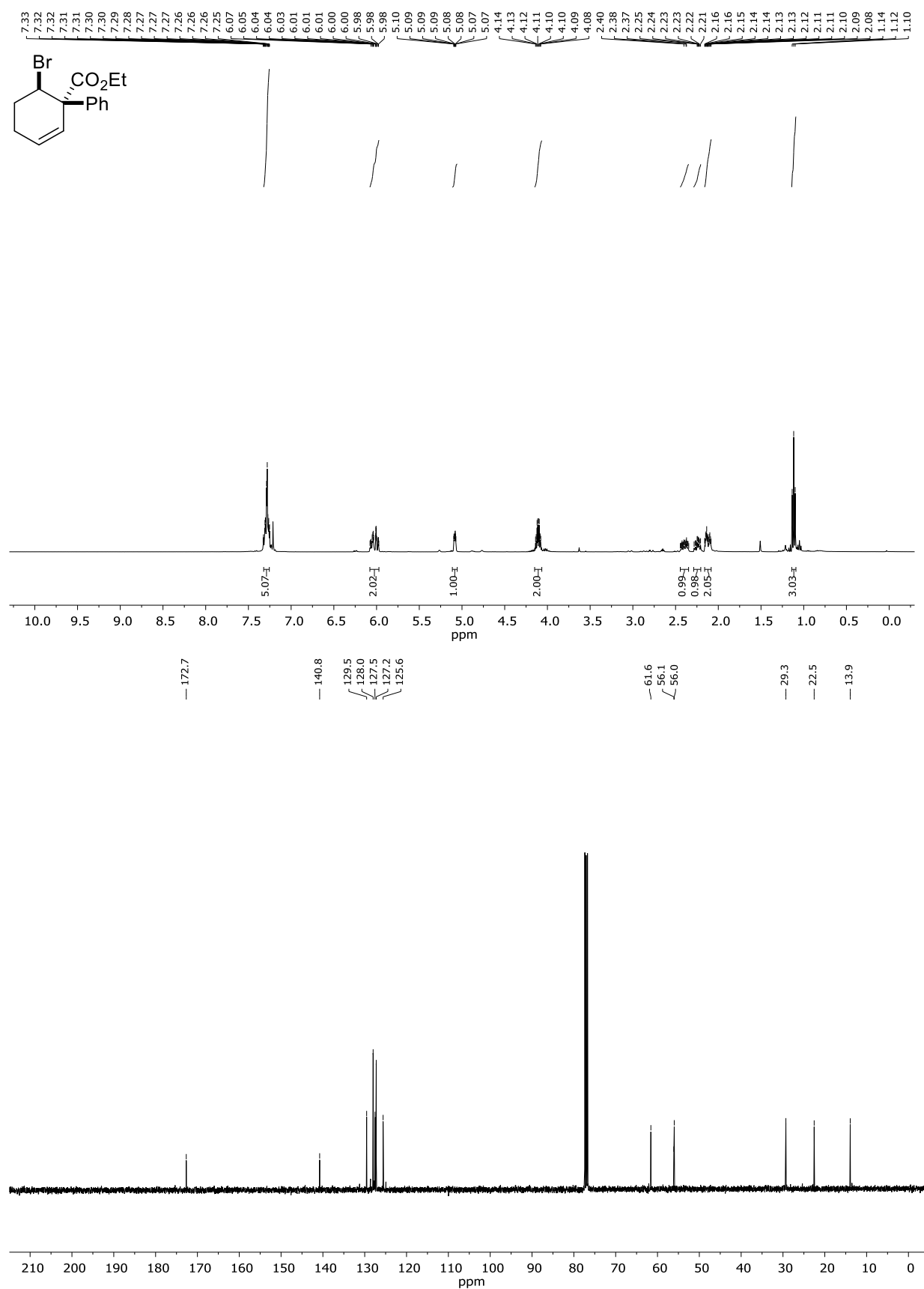
Compound 122a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



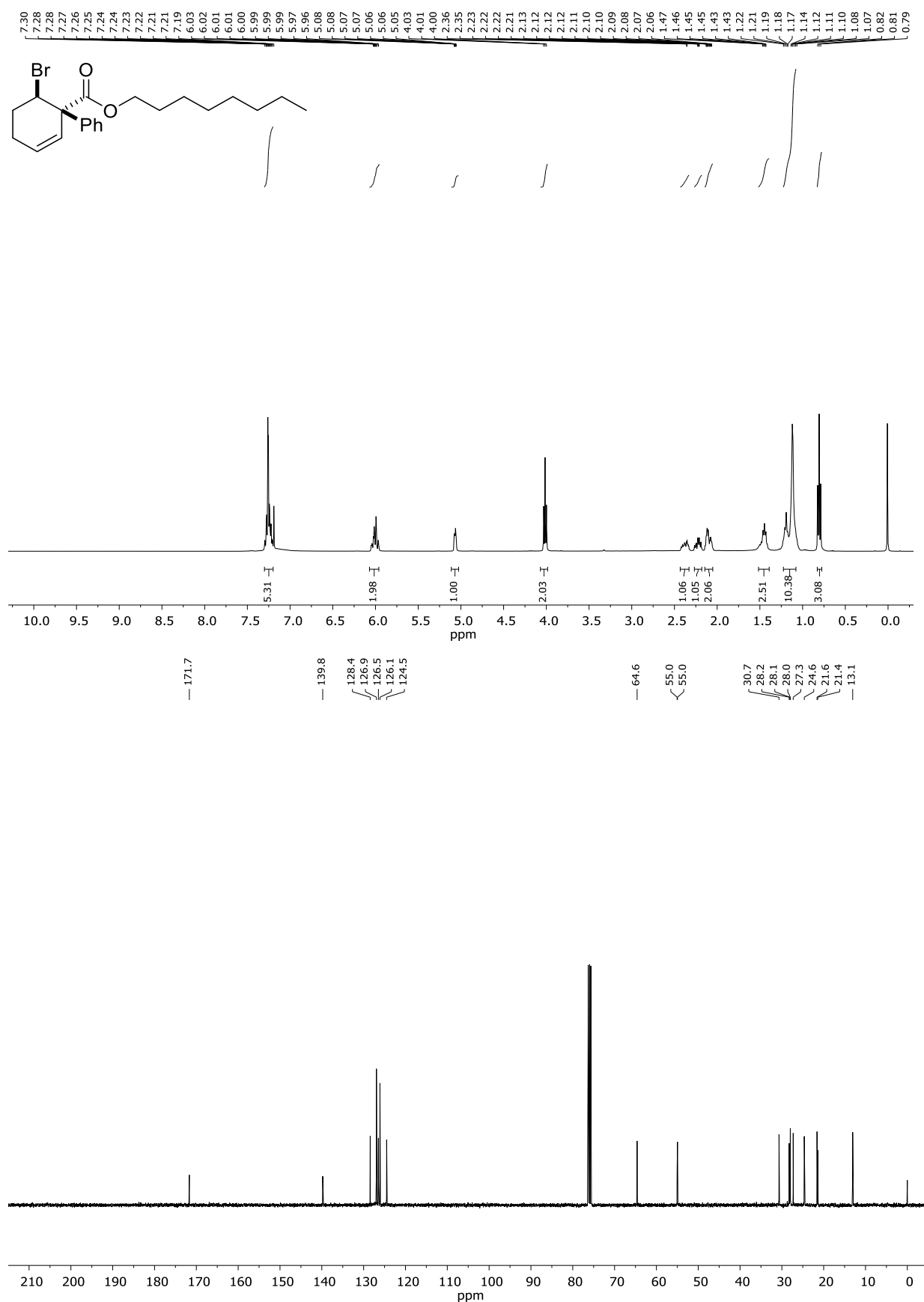
Compound (-)-122a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



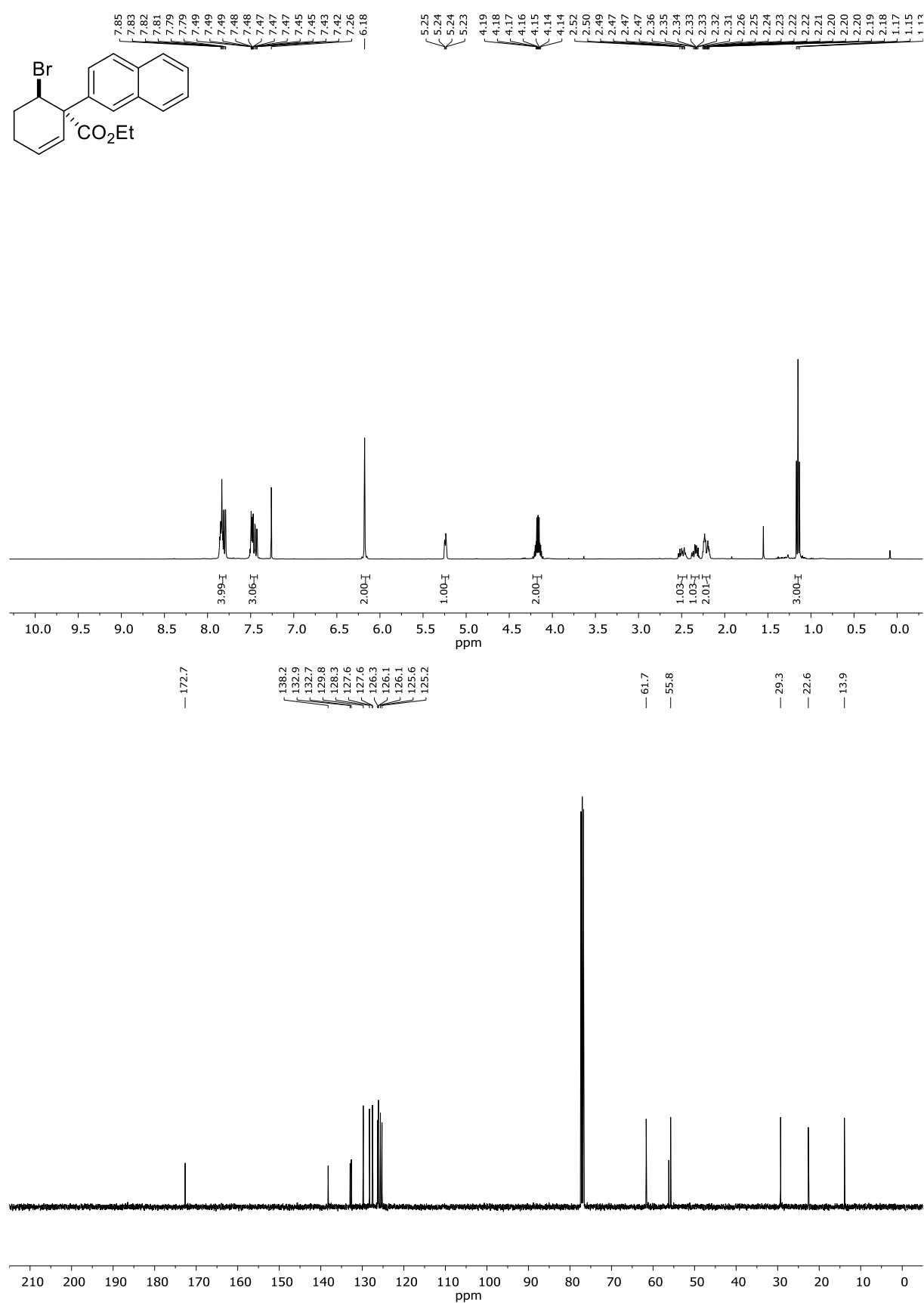
Compound 122b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



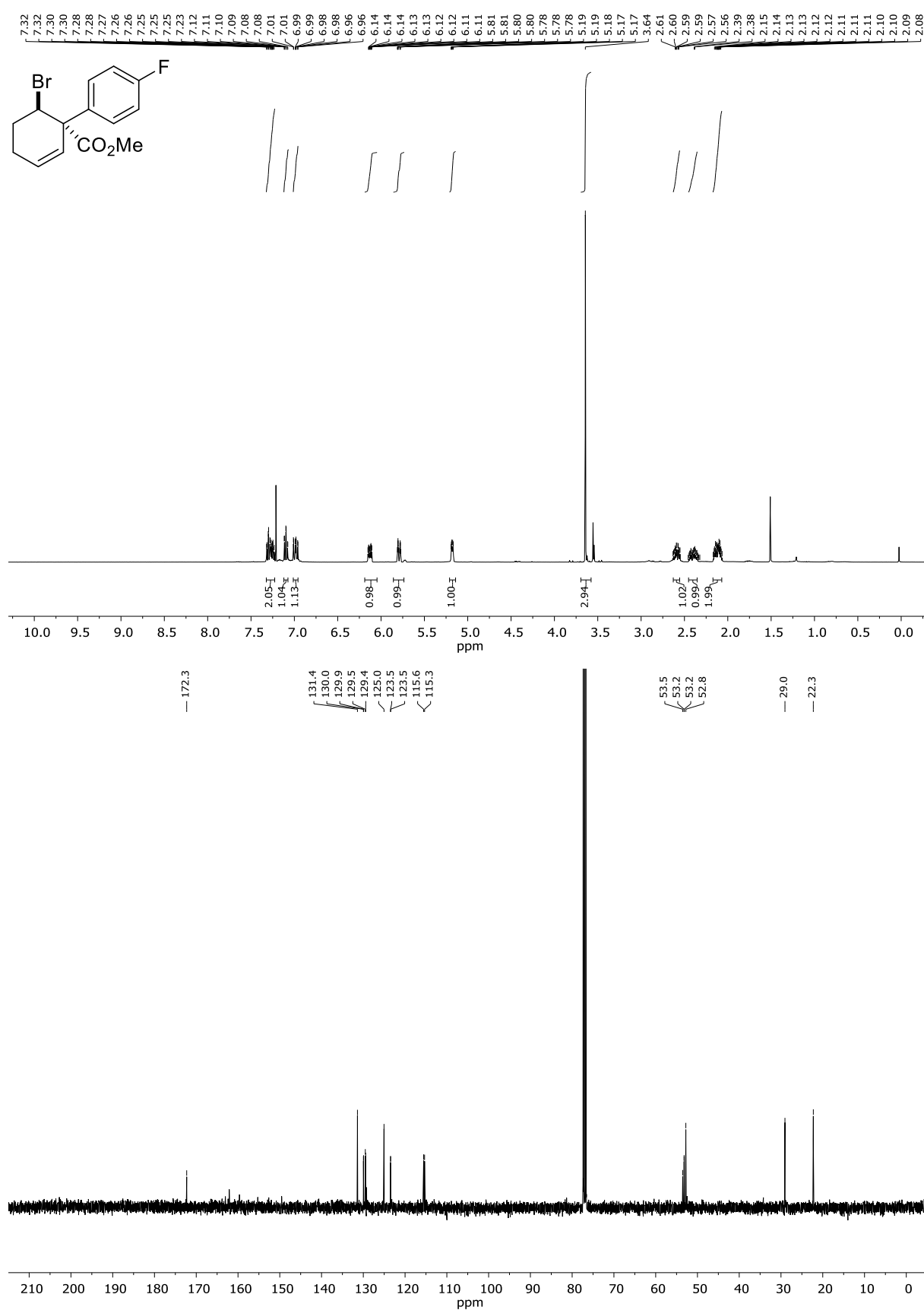
Compound 122c: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



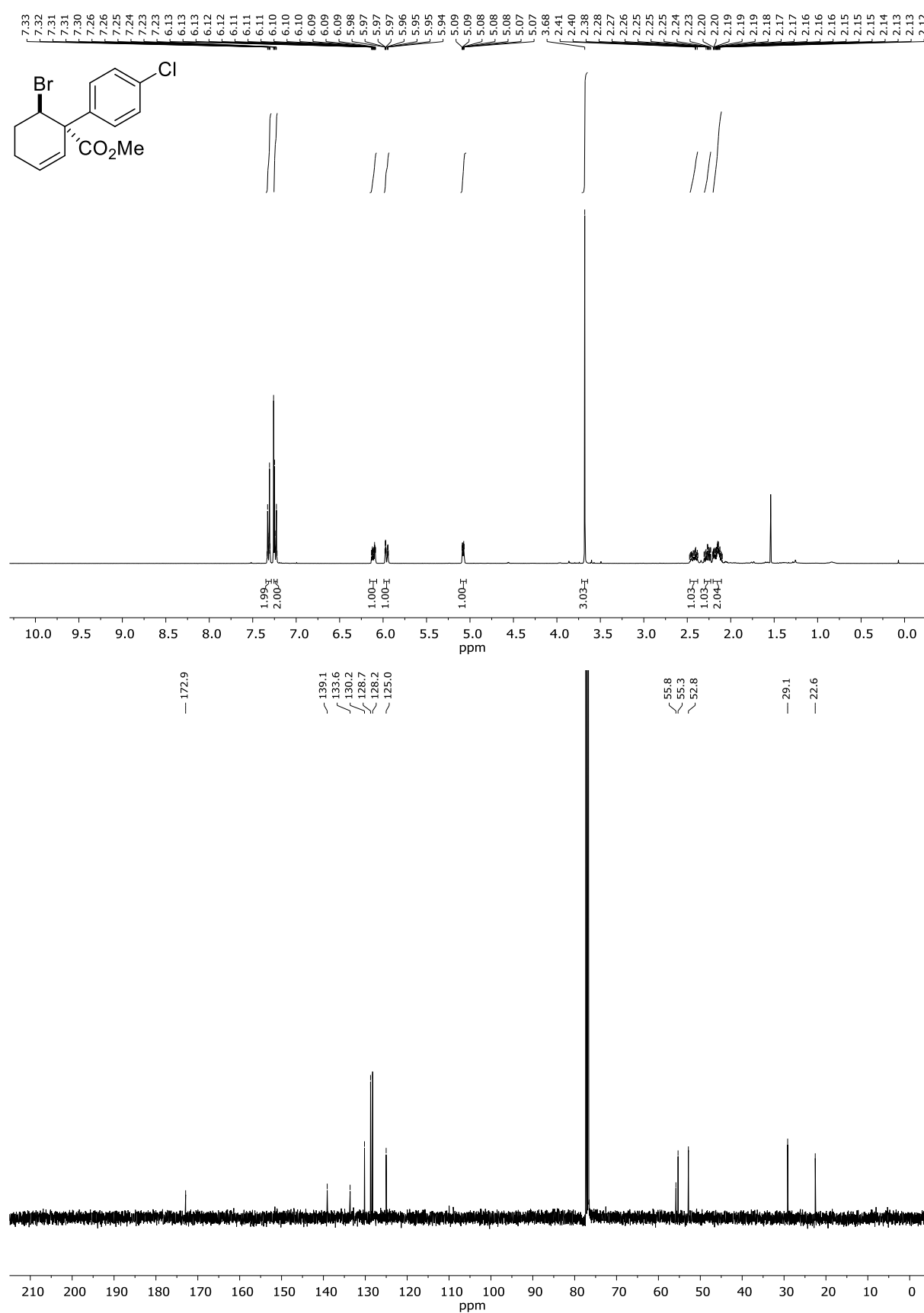
Compound 122e: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



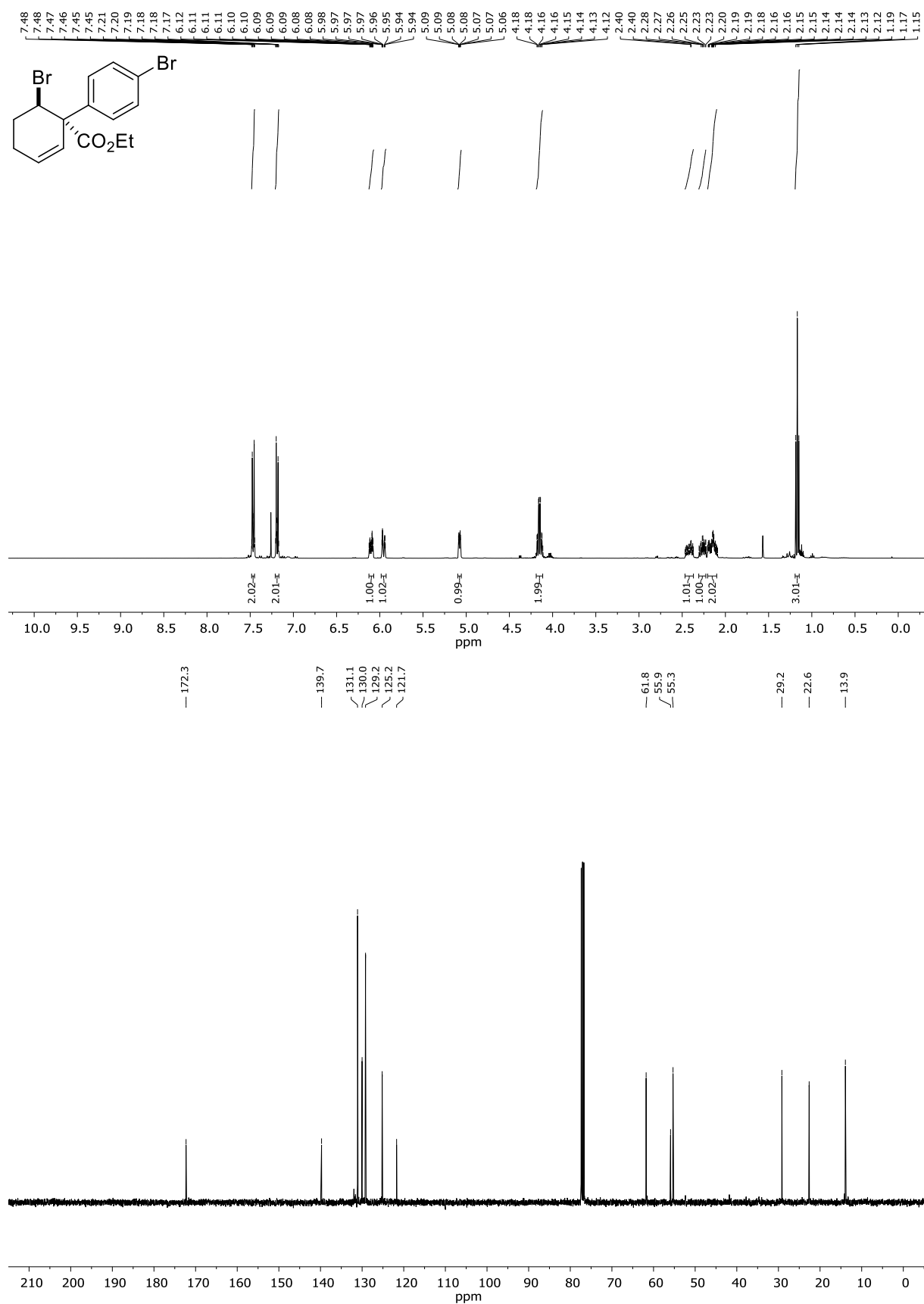
Compound 122f: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



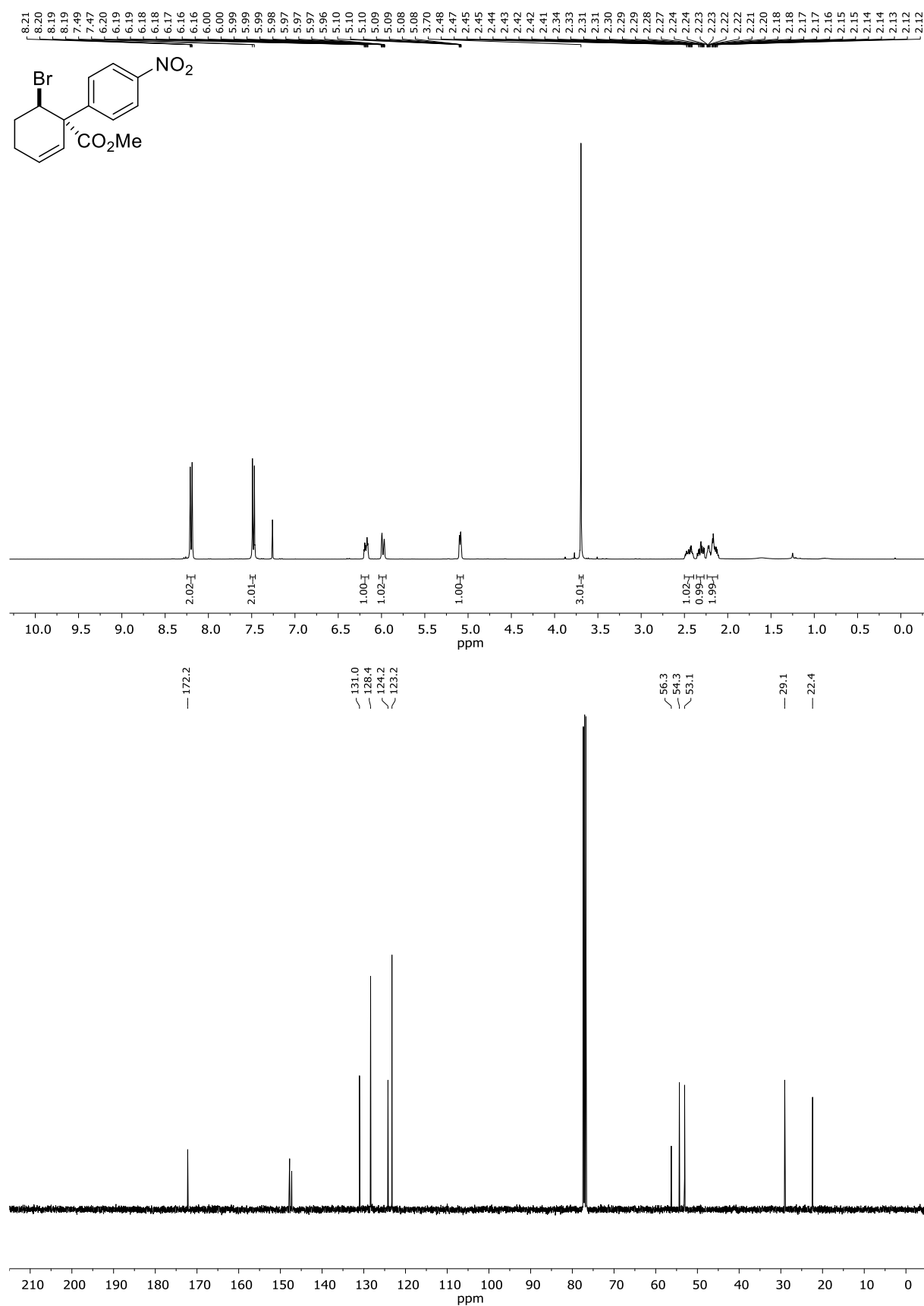
Compound 122g: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



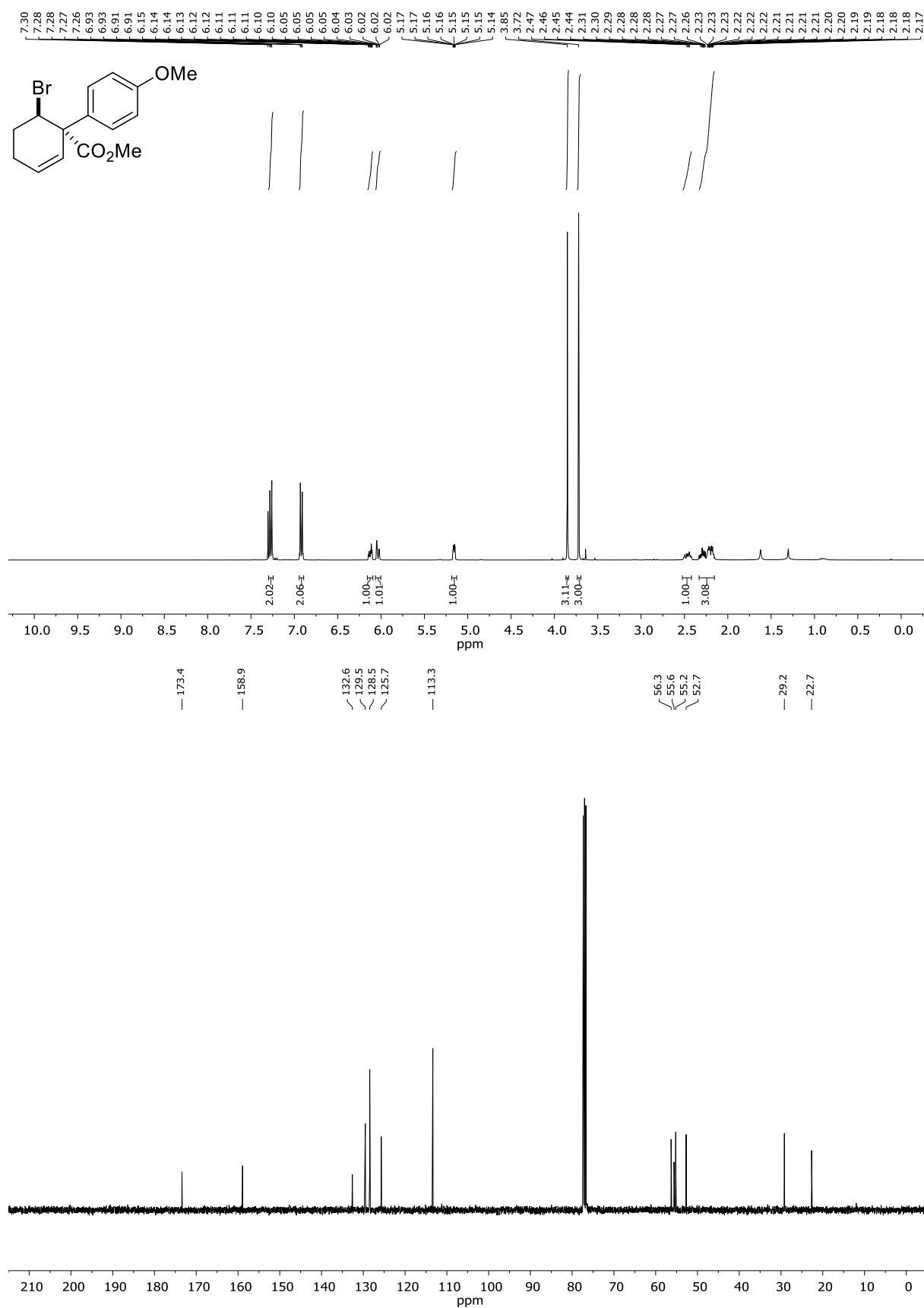
Compound 122h: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



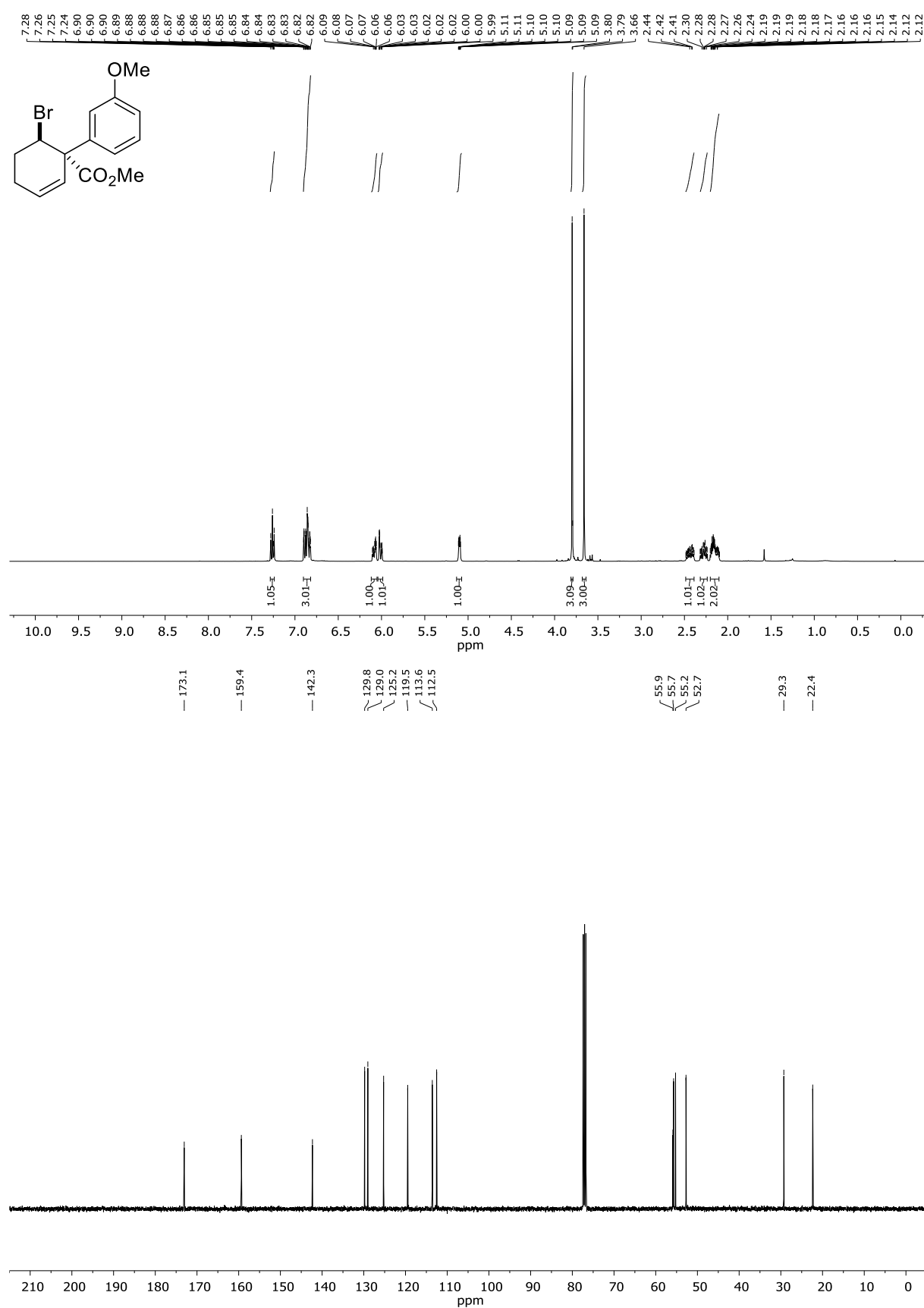
Compound 122i: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



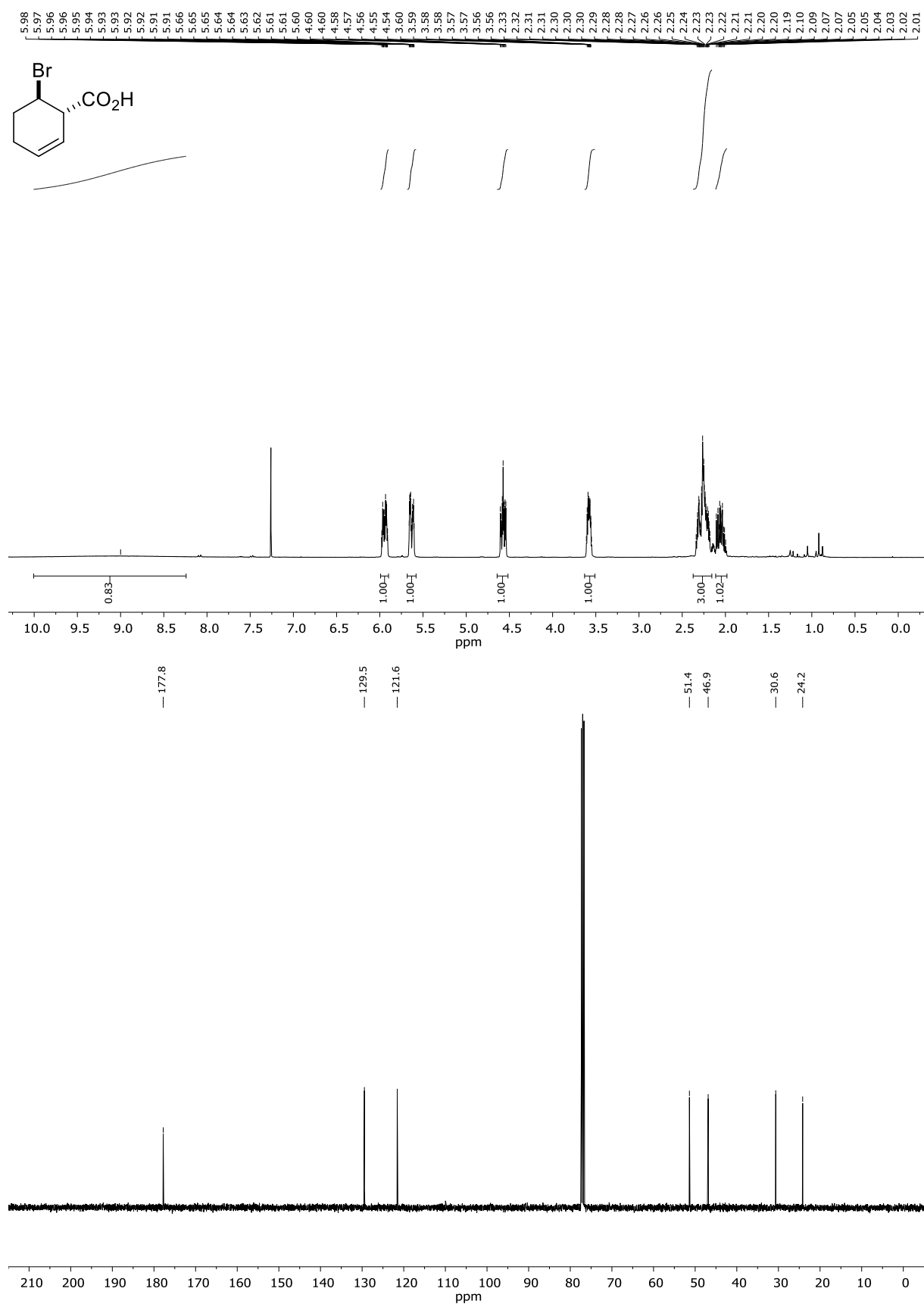
Compound 122k: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



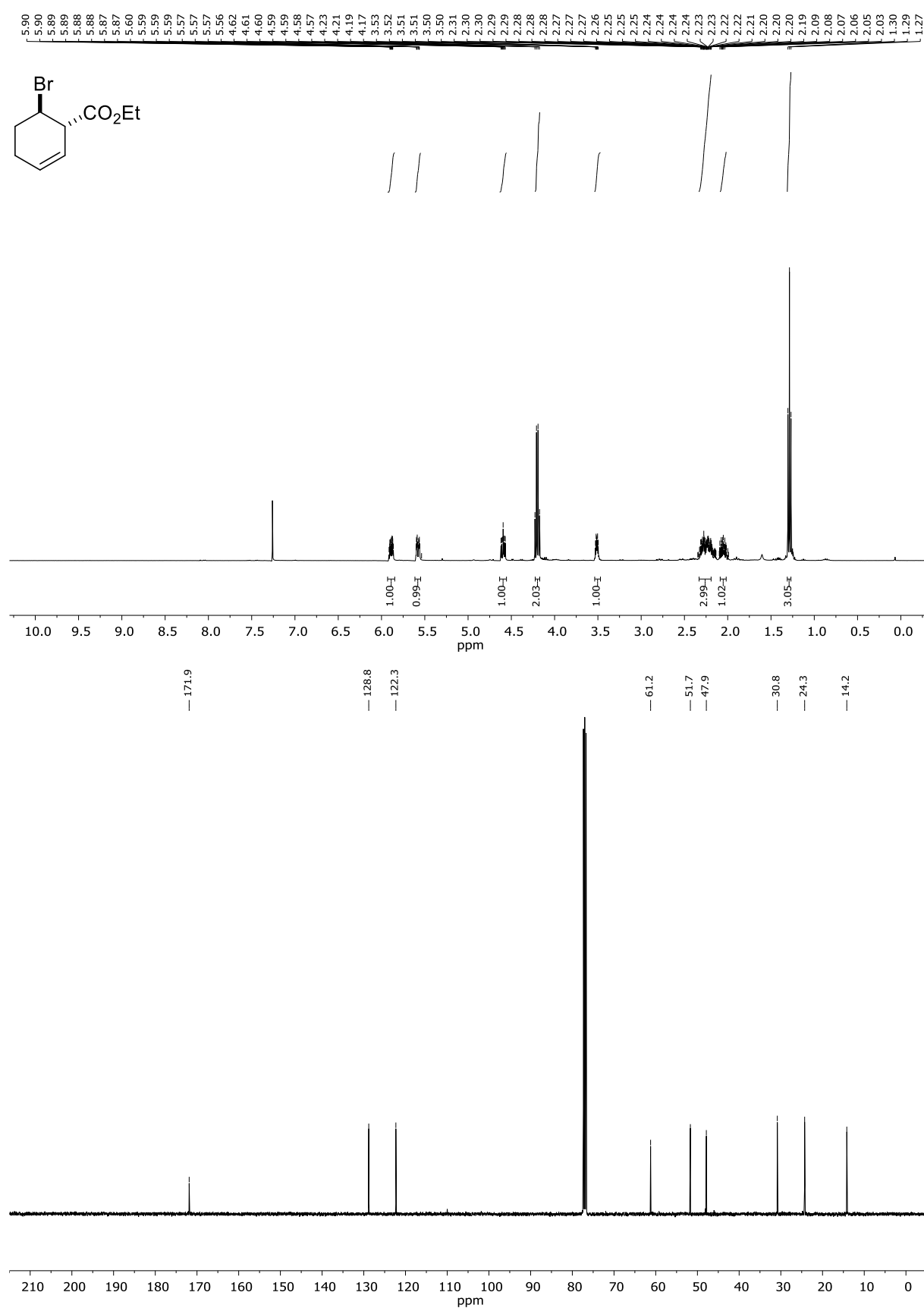
Compound 122i: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



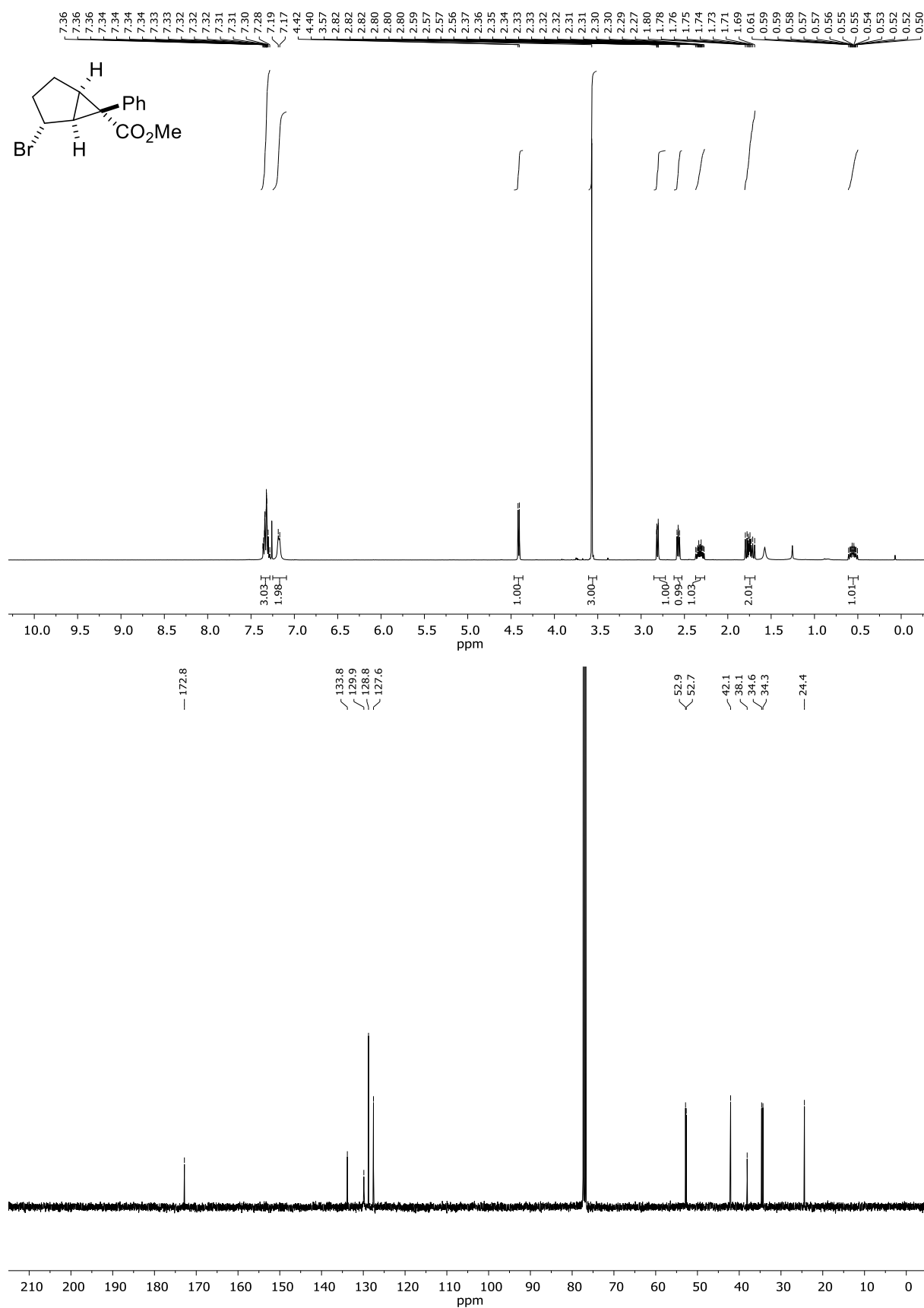
Compound 122o: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



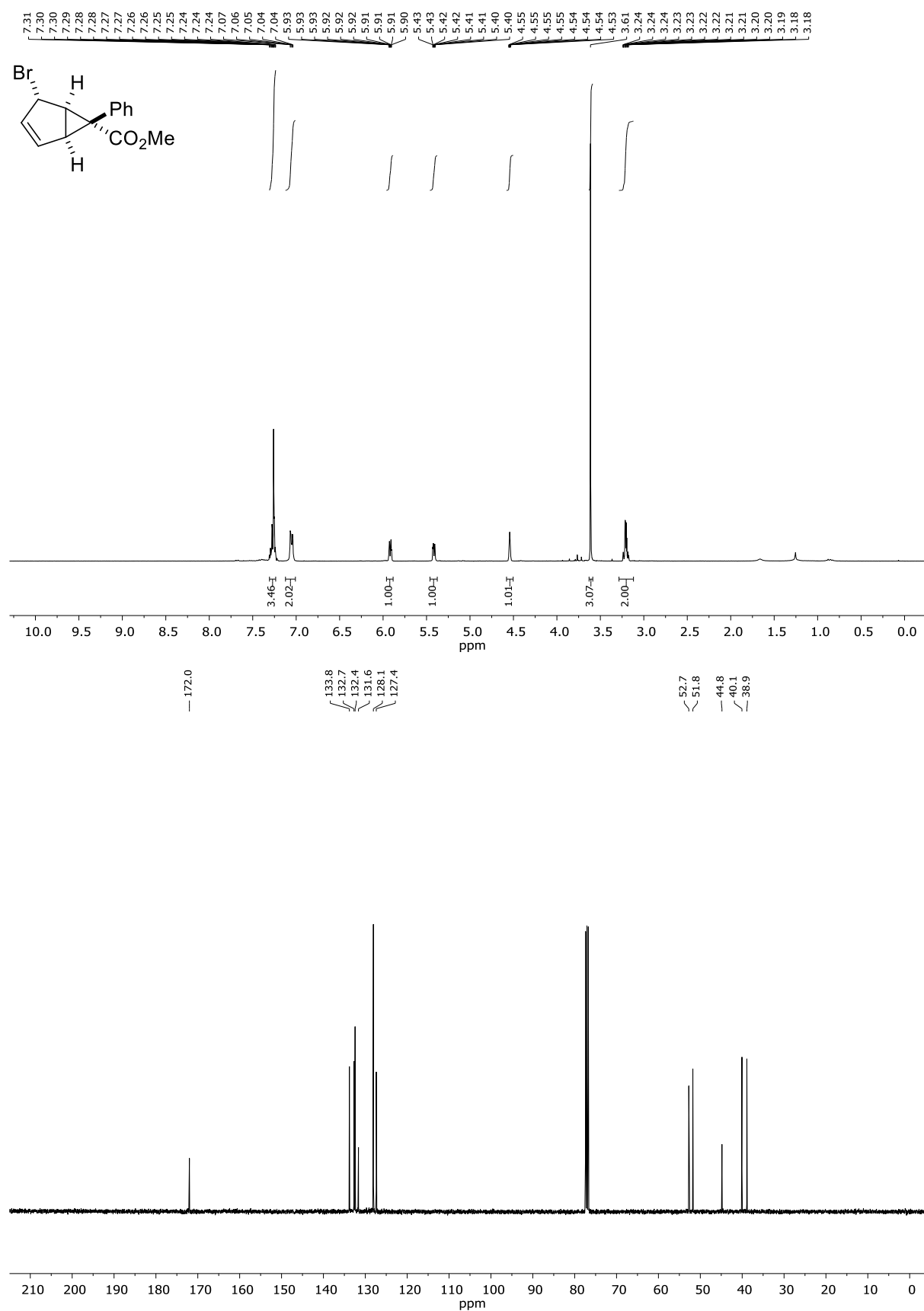
Compound 122p: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



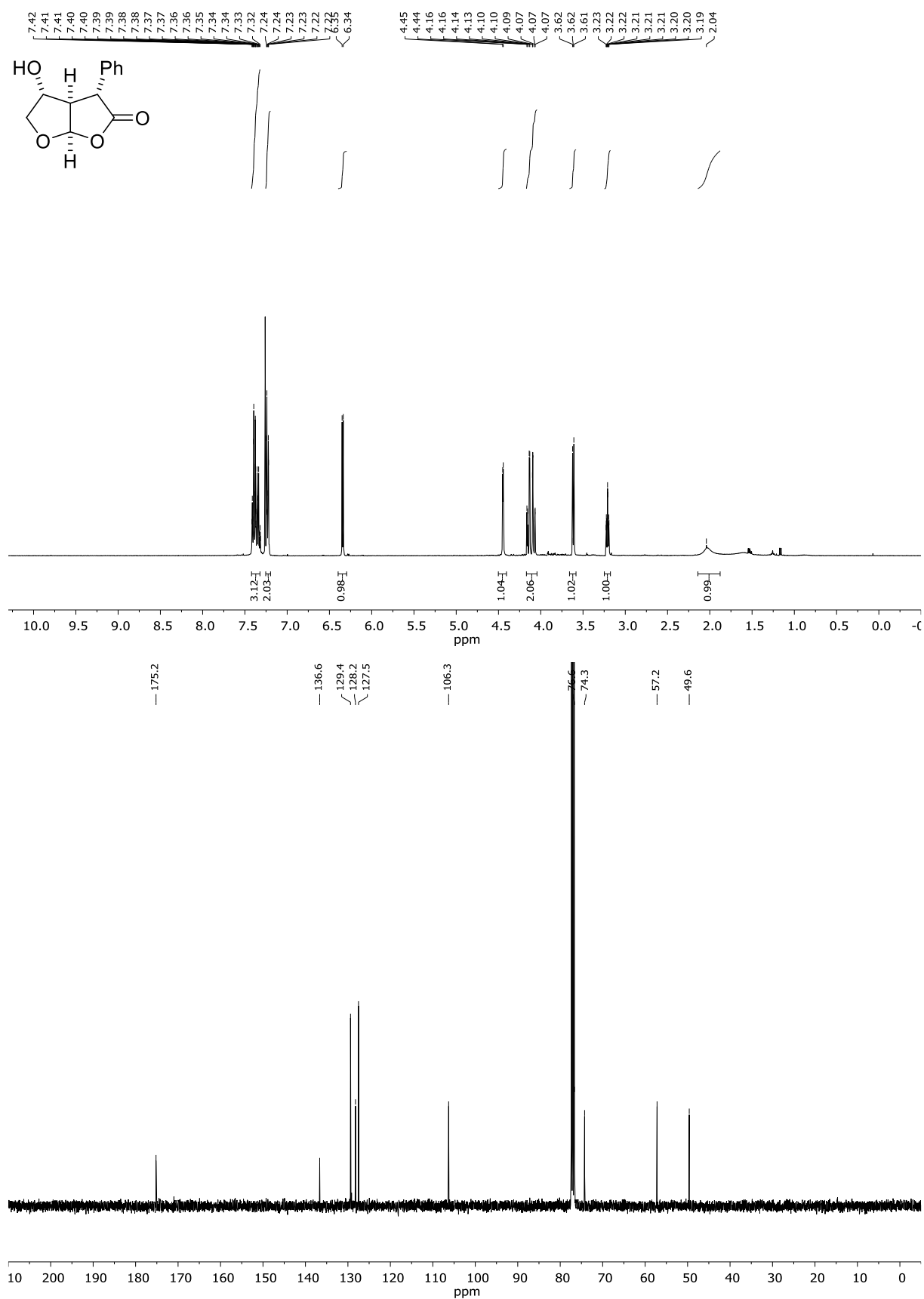
Compound 123b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):

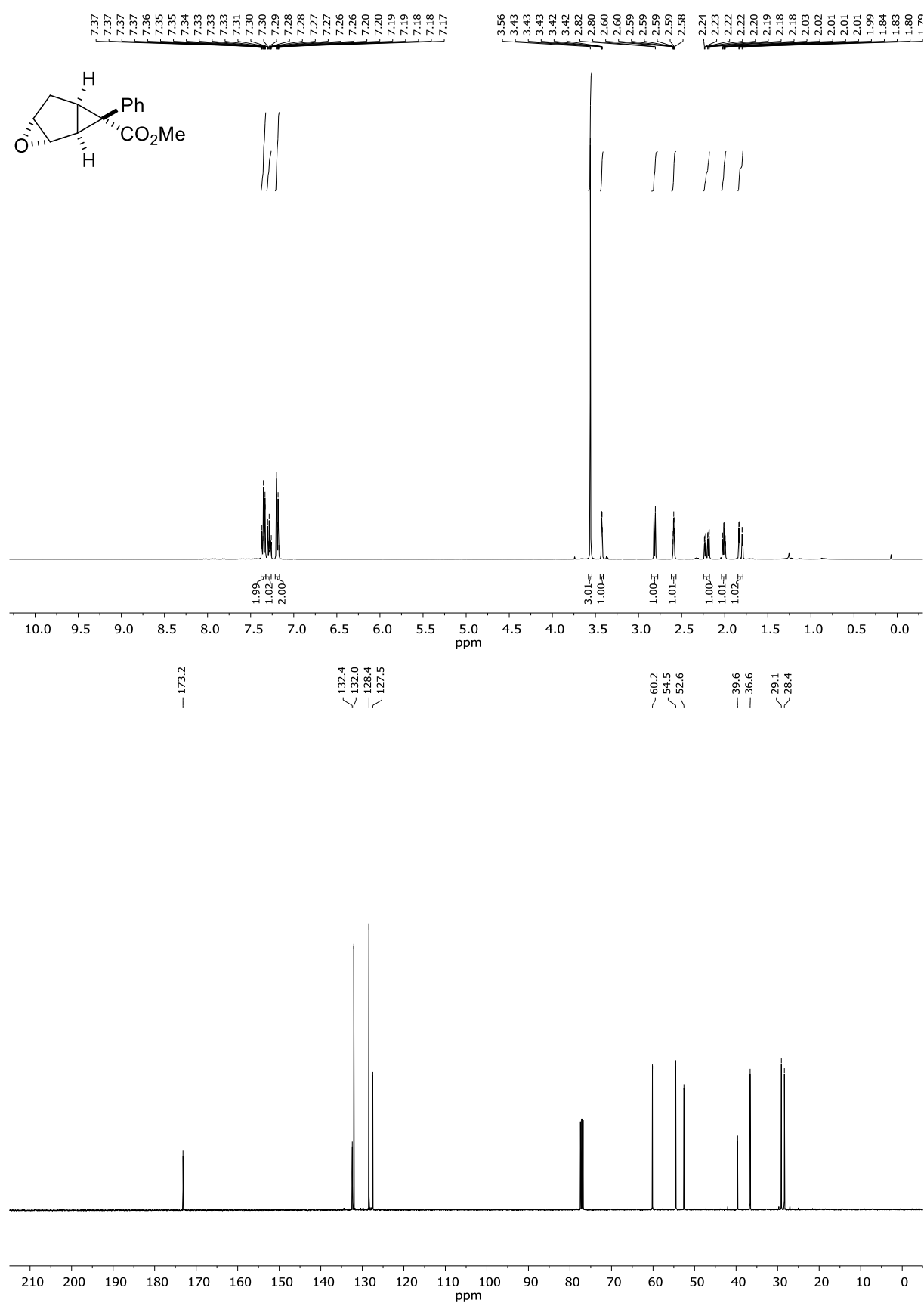


Compound 124: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):

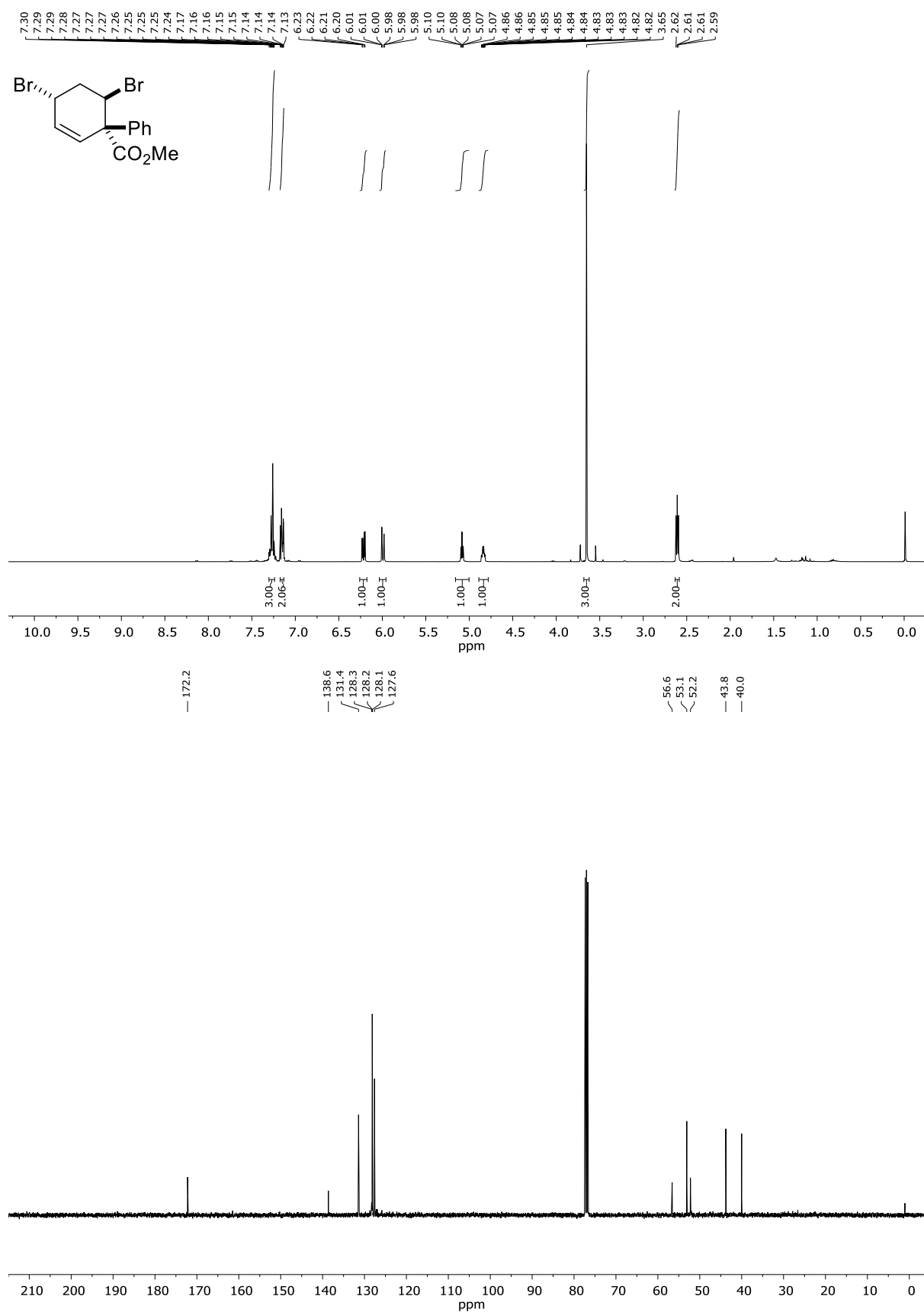


Compound 80b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):

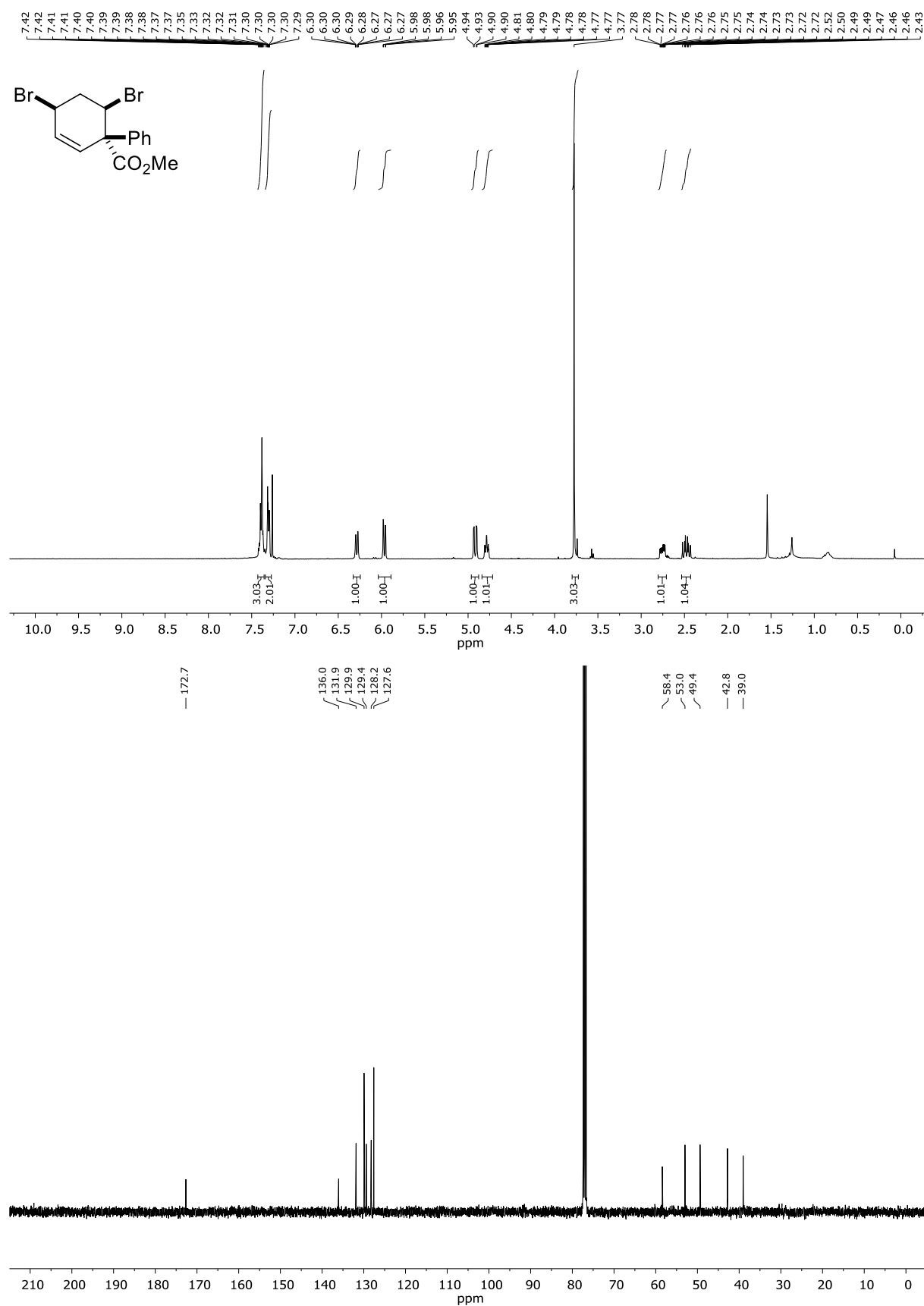


Compound 126: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

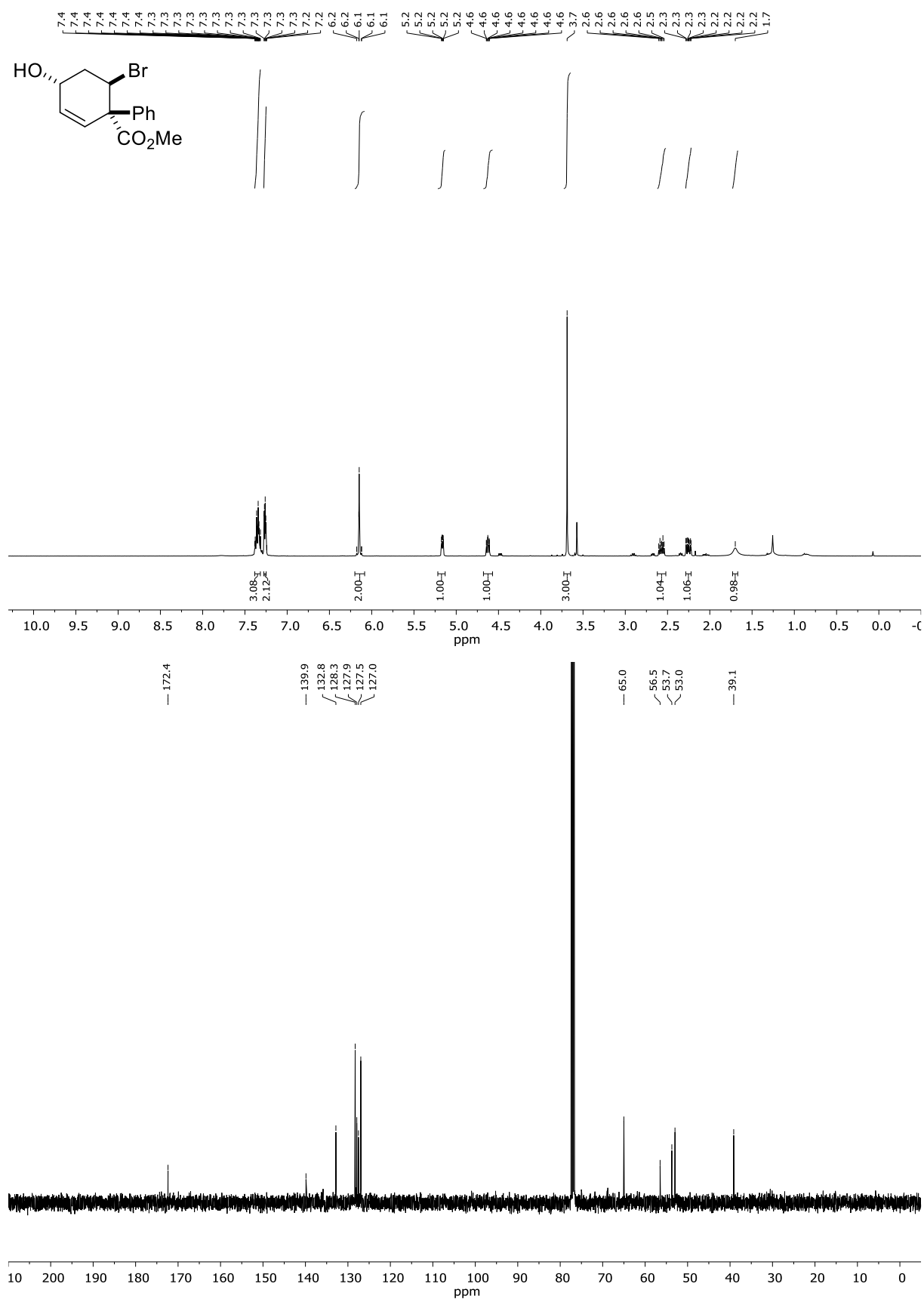
Compound 129a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



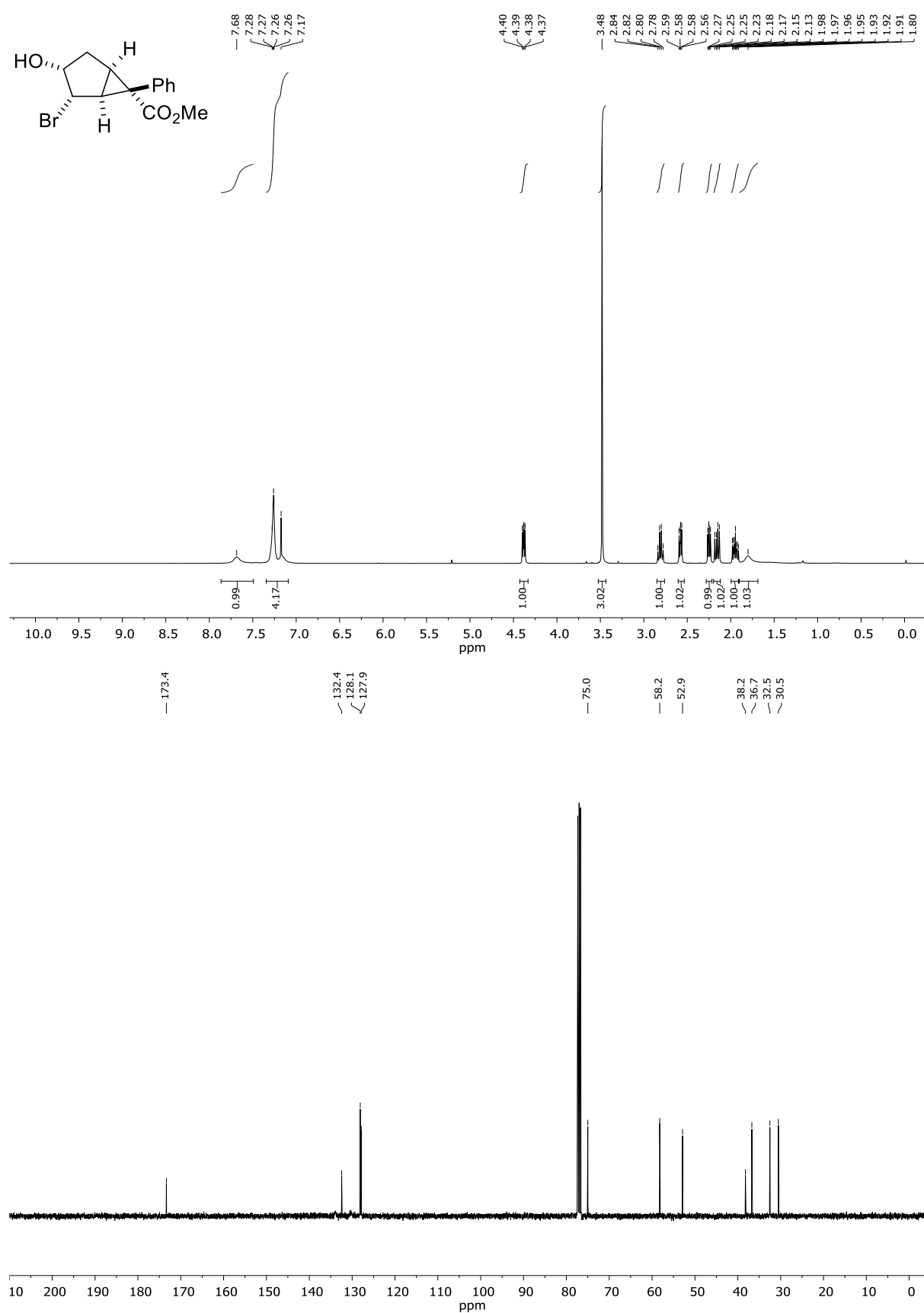
Compound 129b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



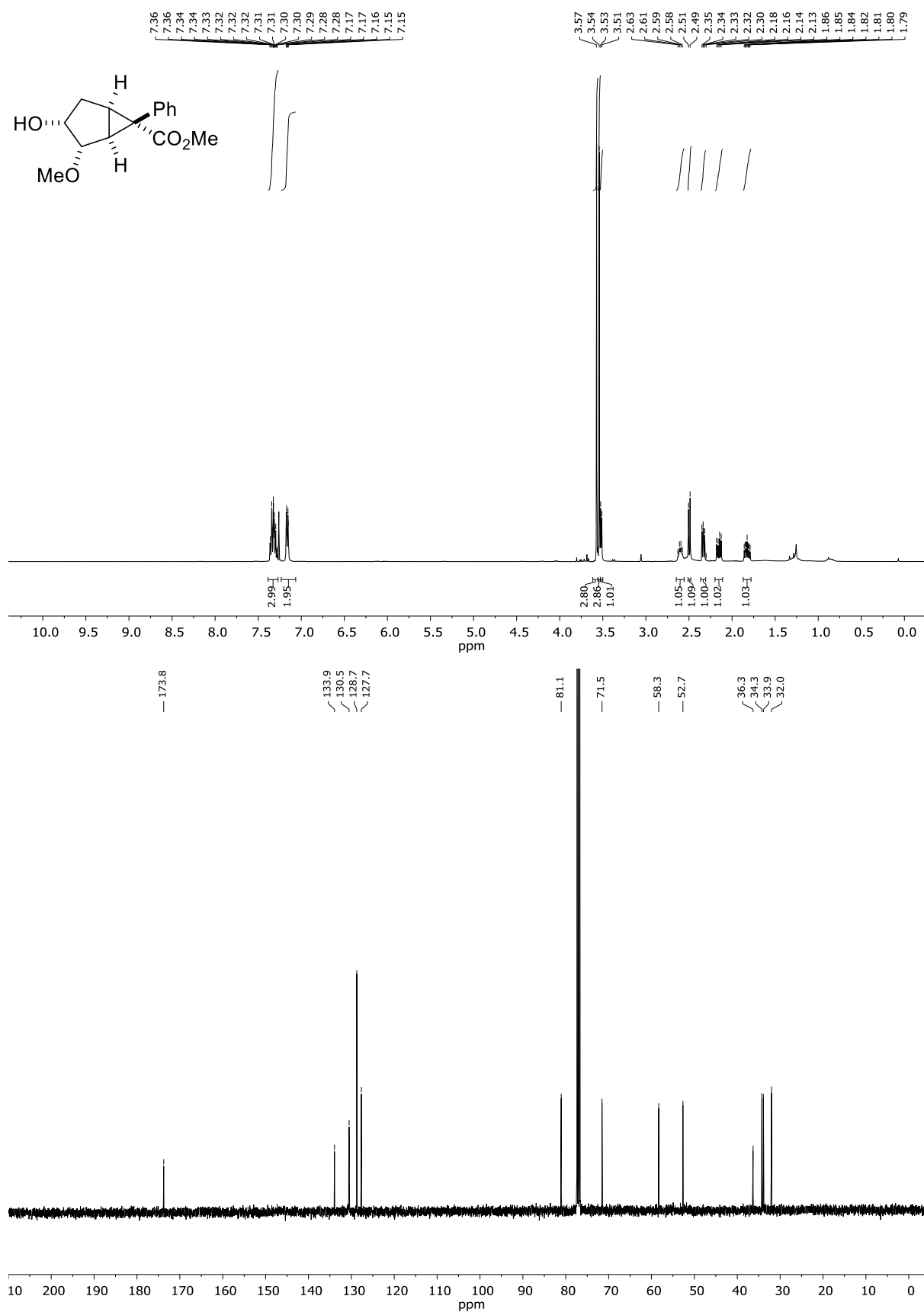
Compound 130: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



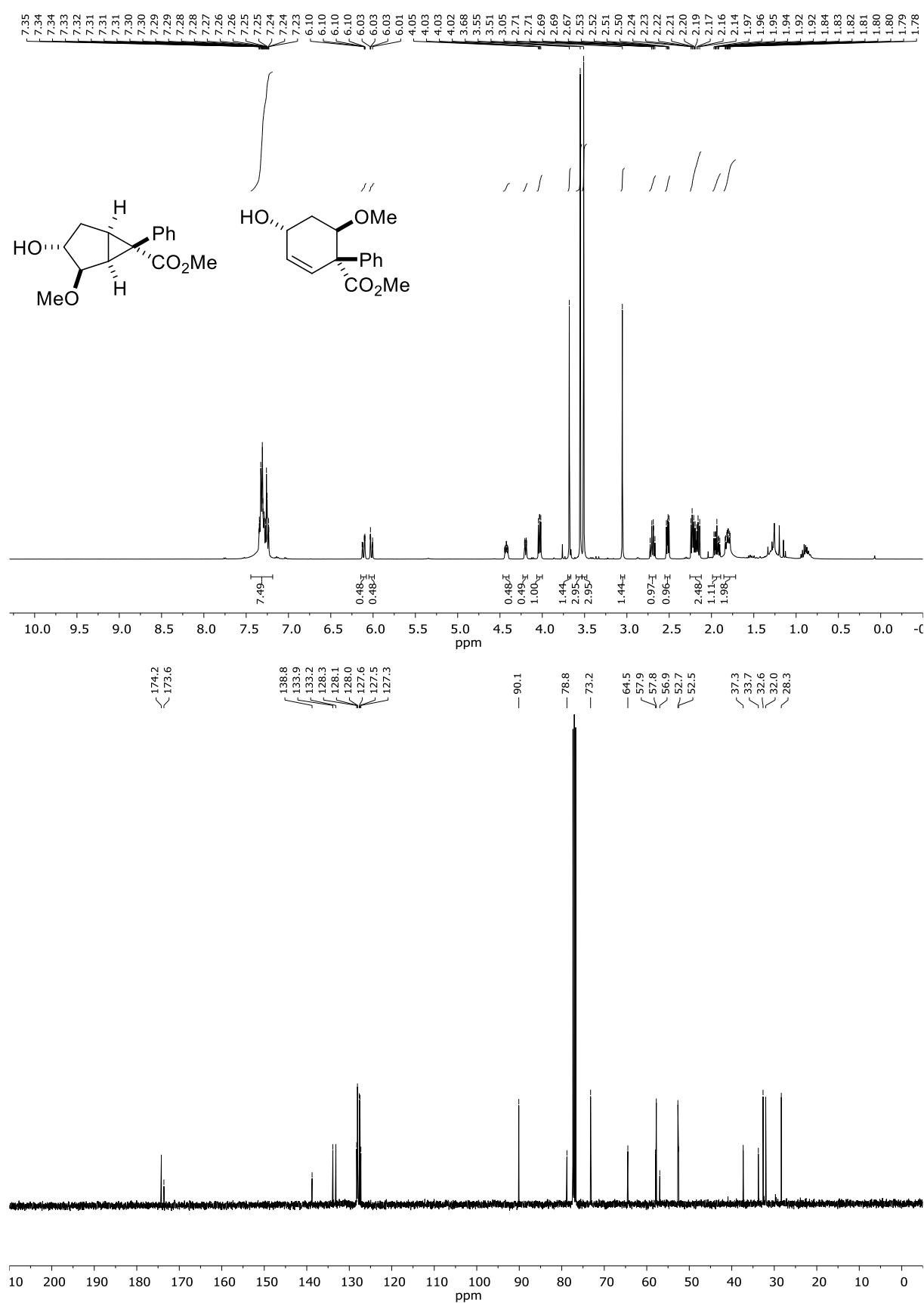
Compound 131: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



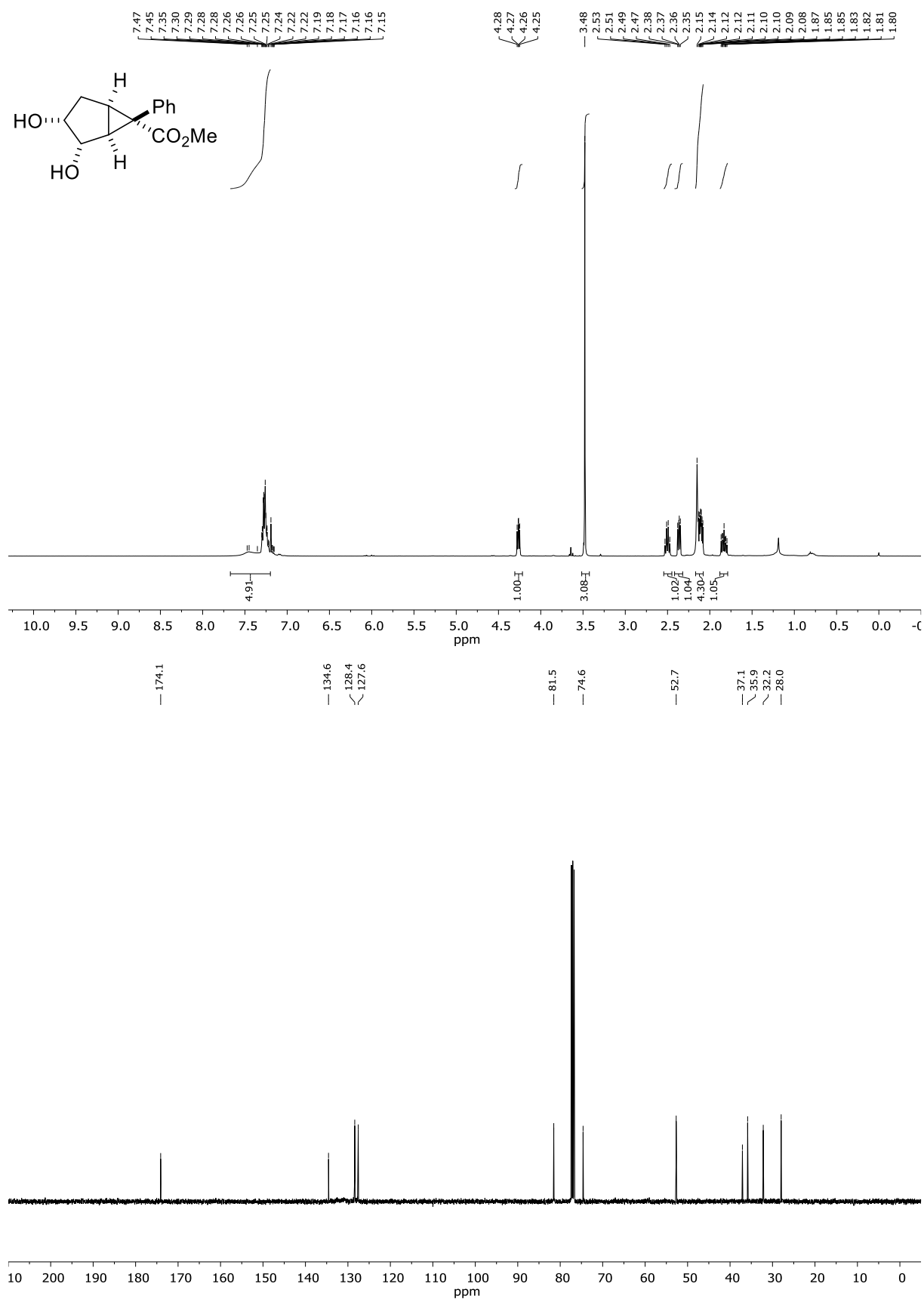
Compound 136a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



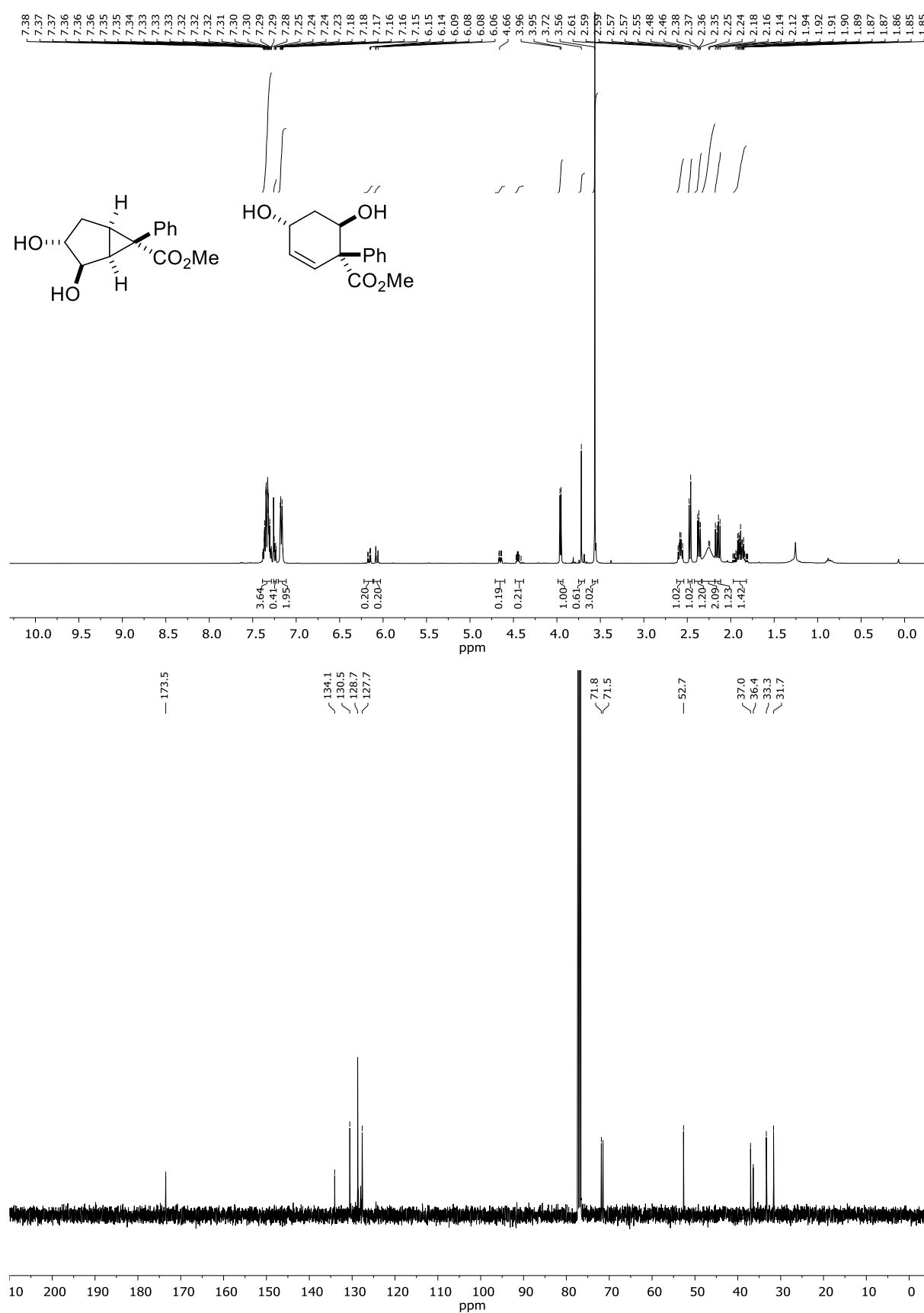
Compound 136b and 138: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



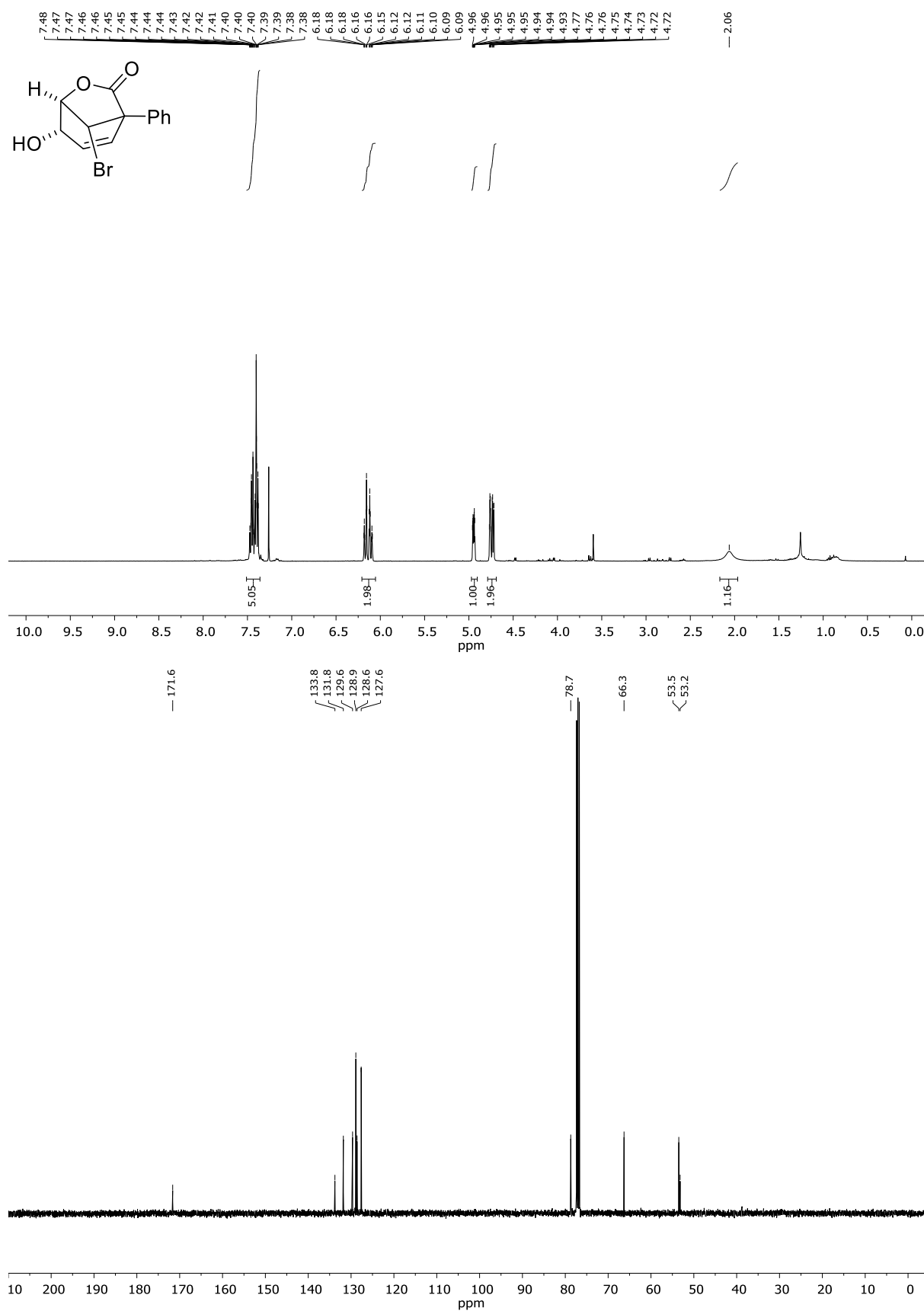
Compound 137a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



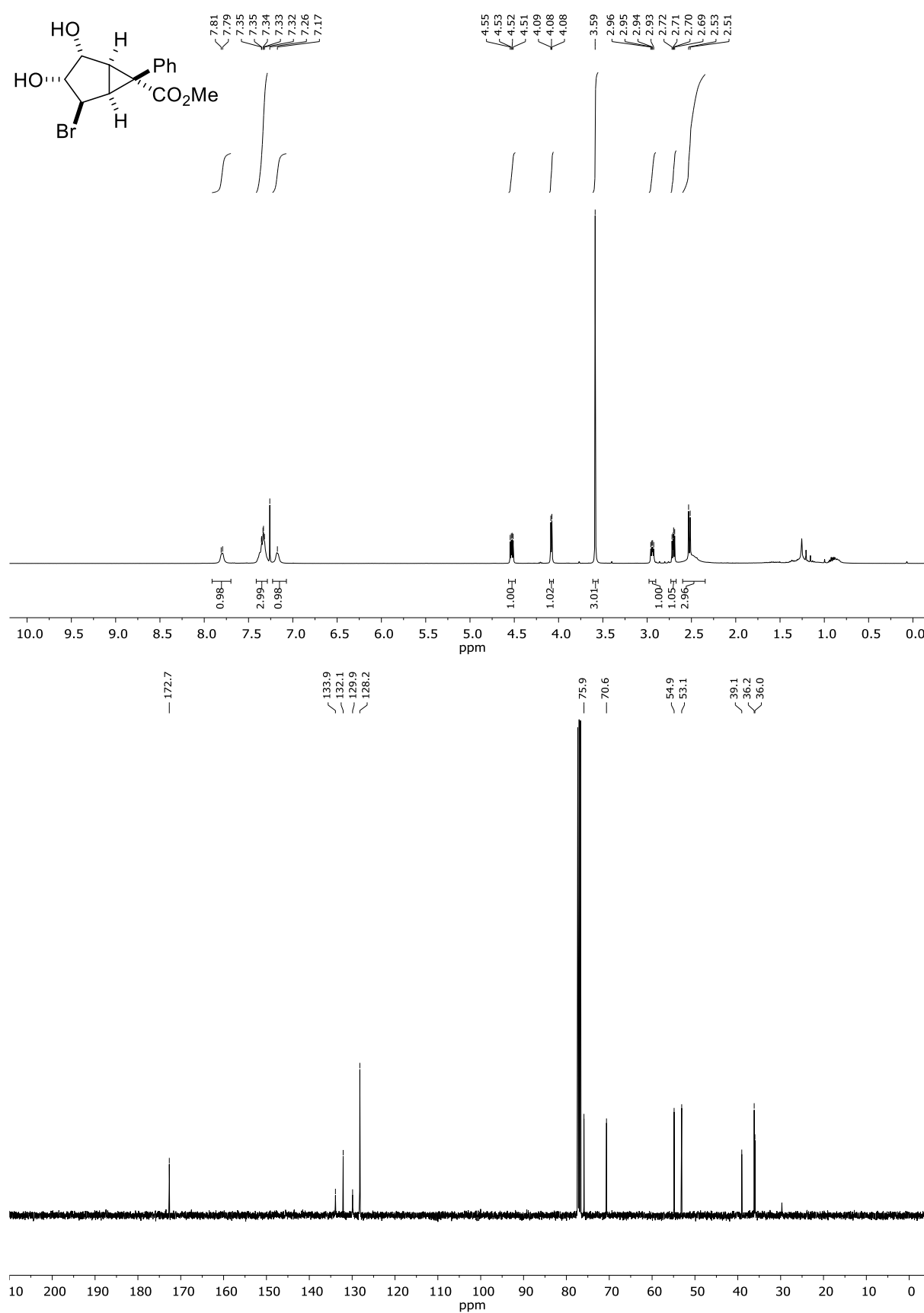
Compound 137b and 139: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



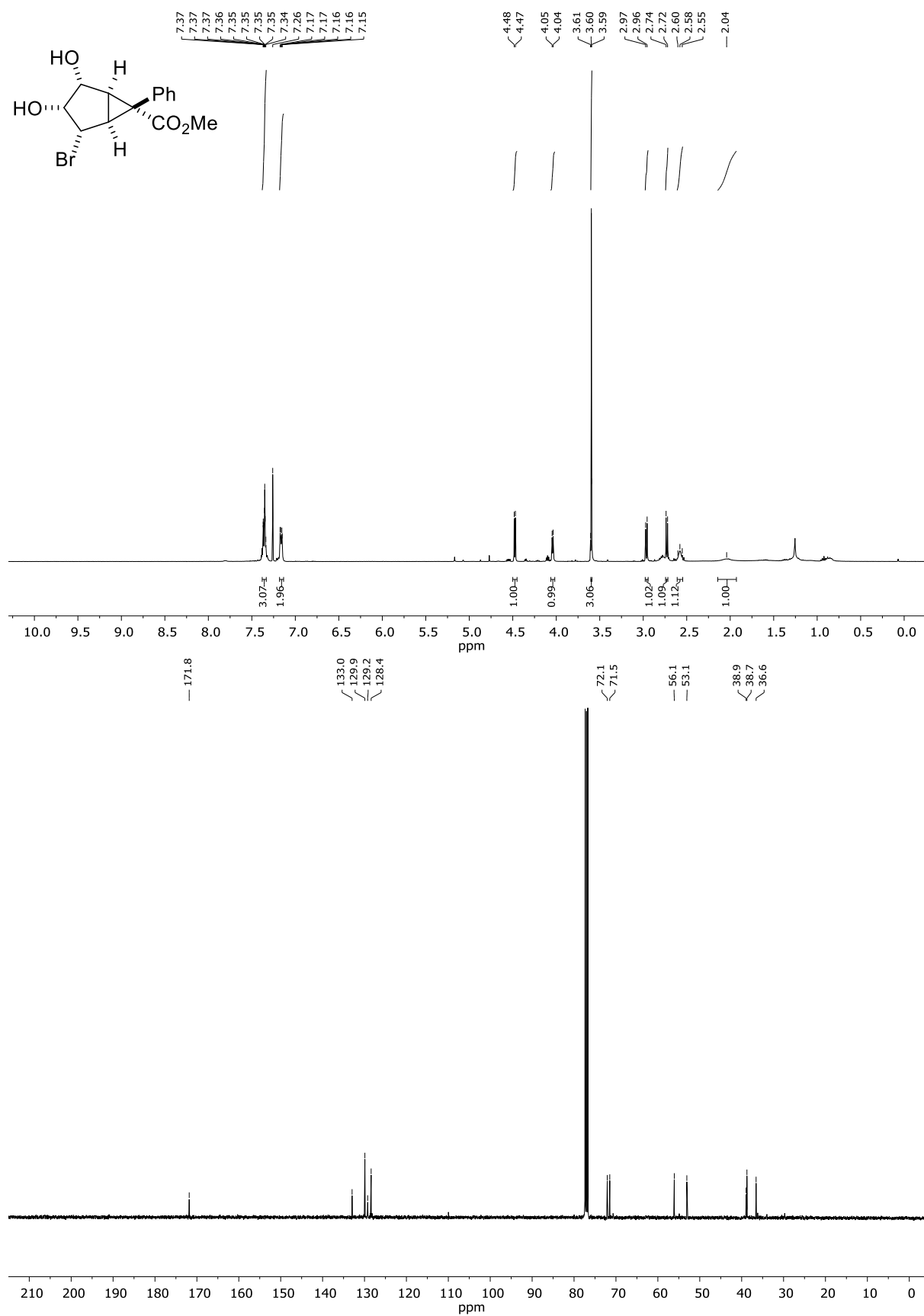
Compound 140: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



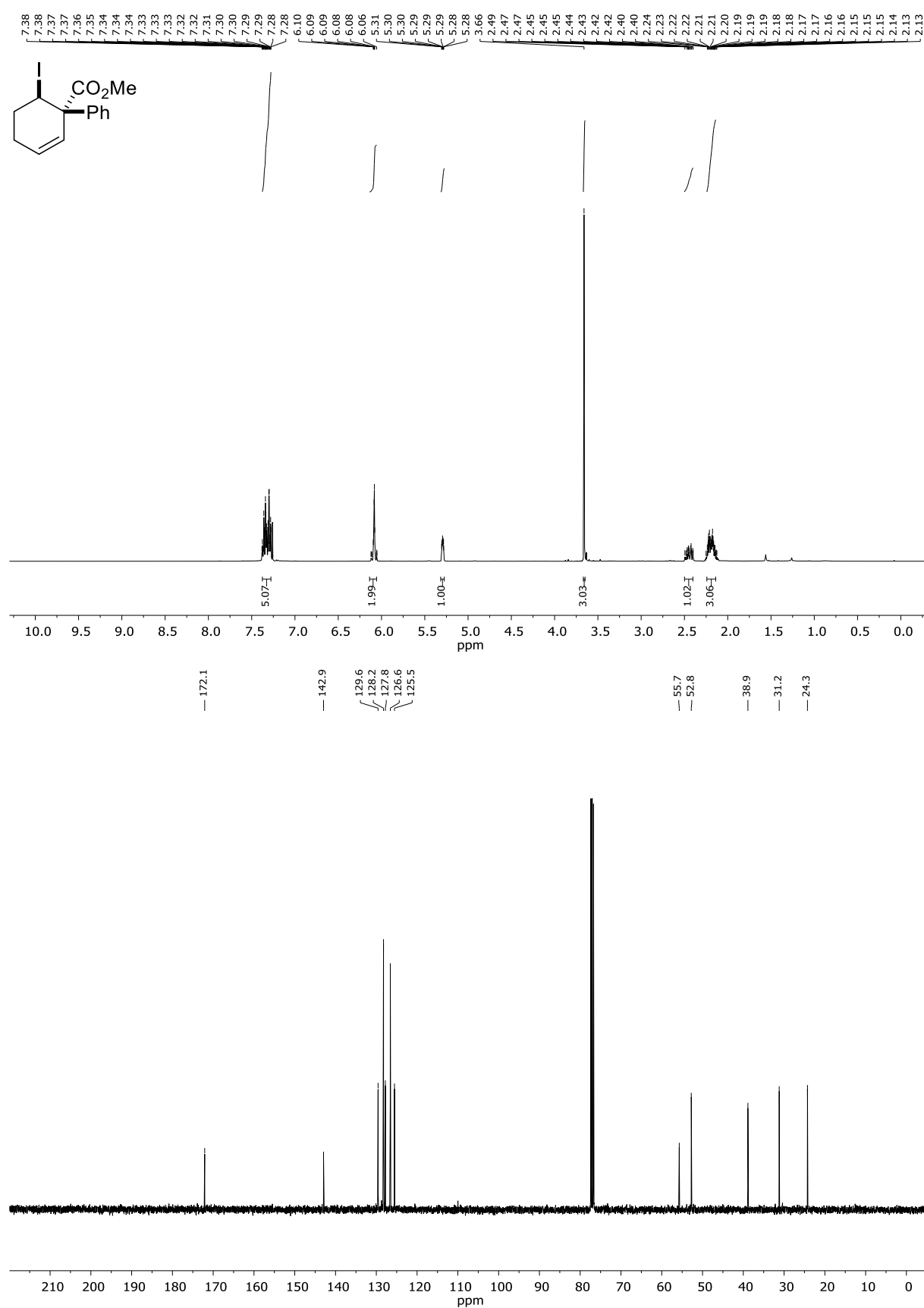
Compound 141a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



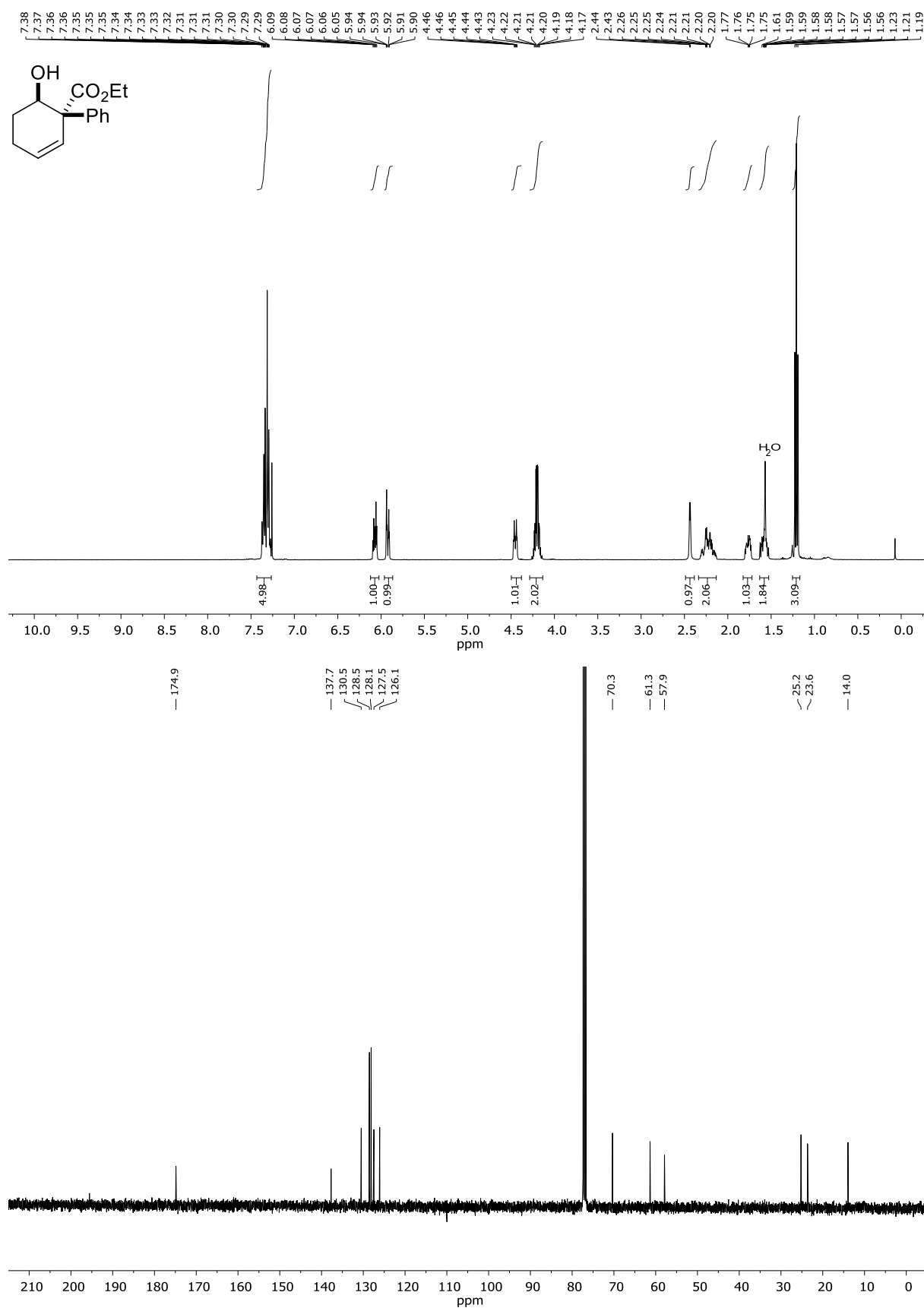
Compound 141b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



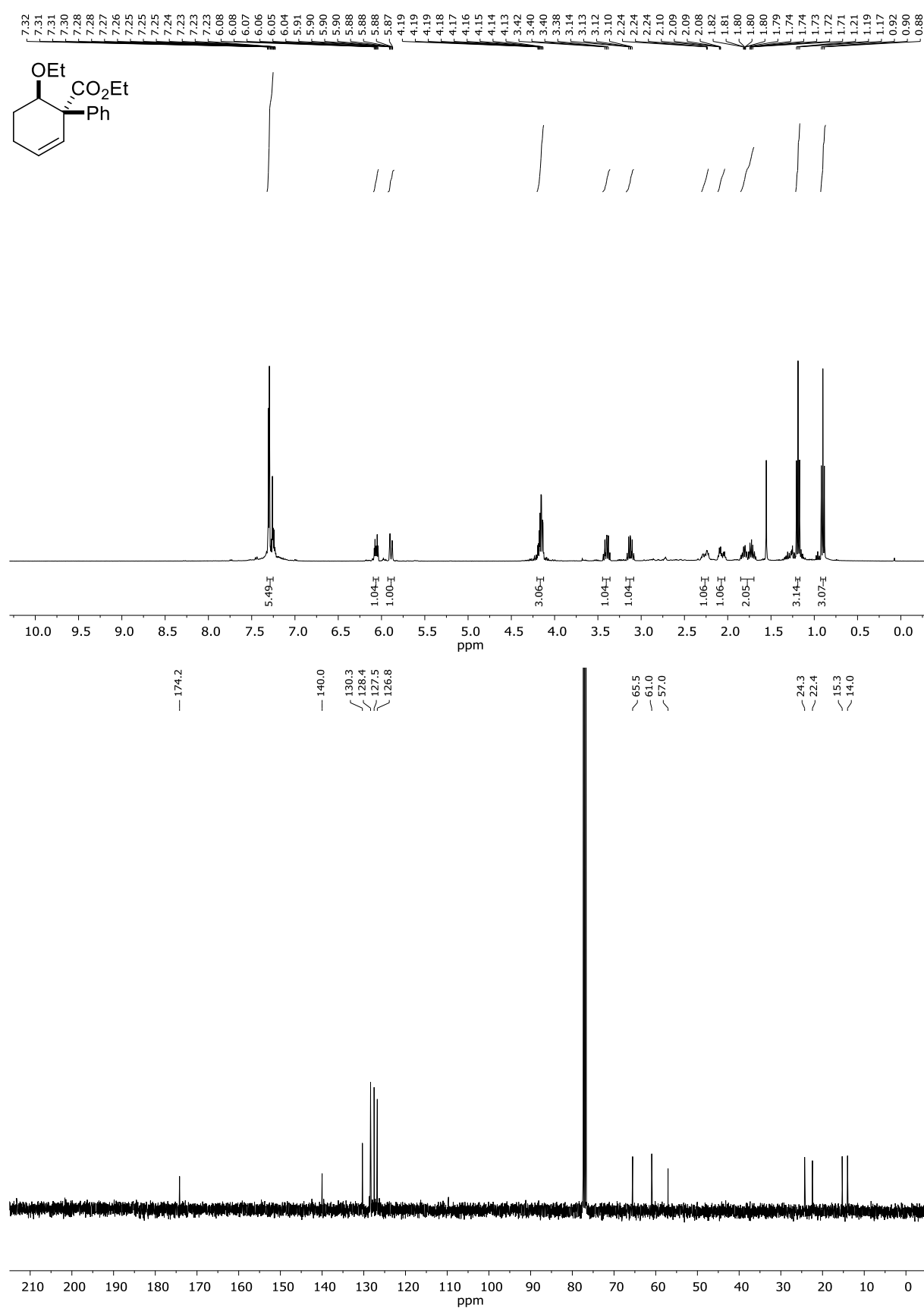
Compound 157: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



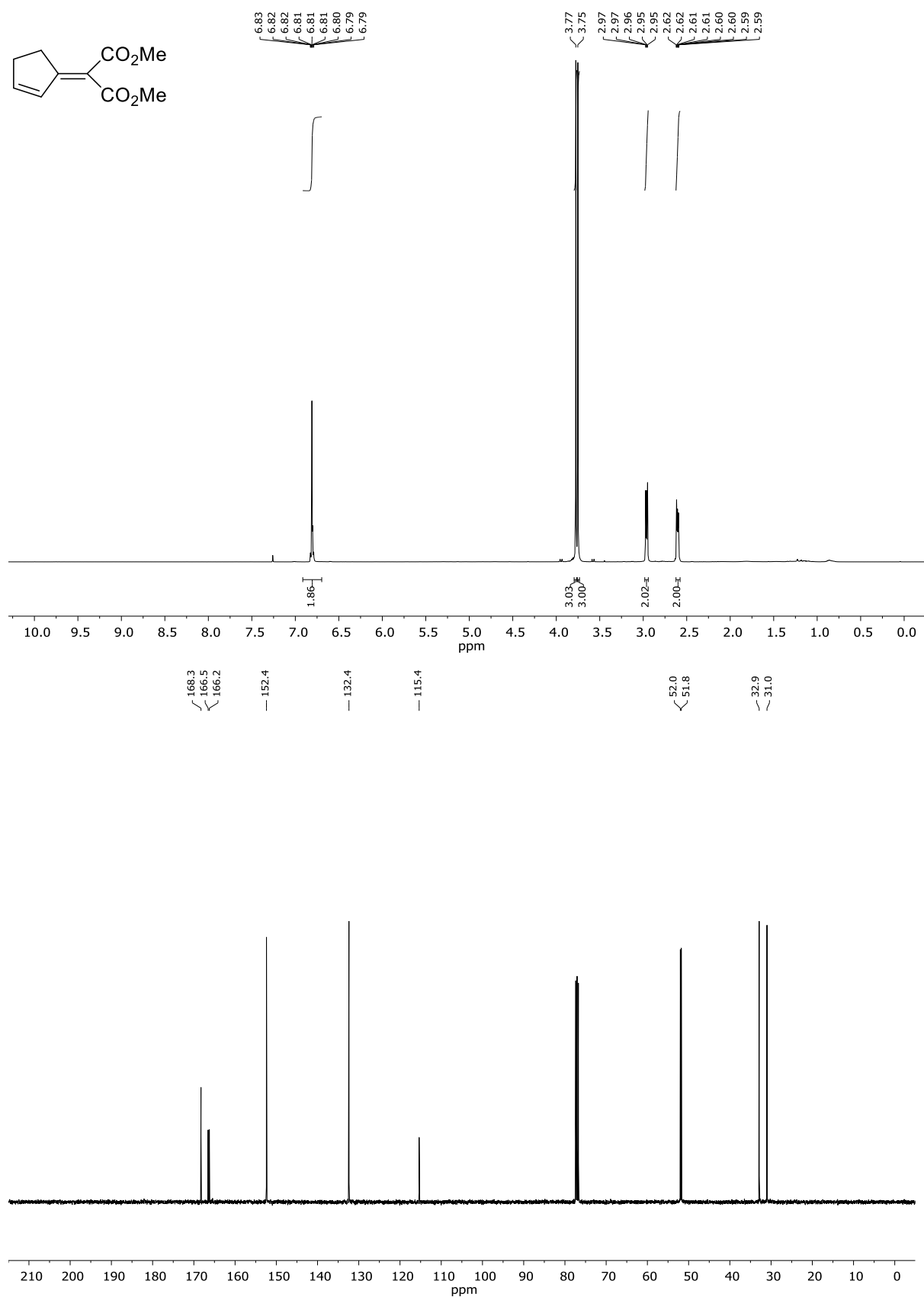
Compound 158a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



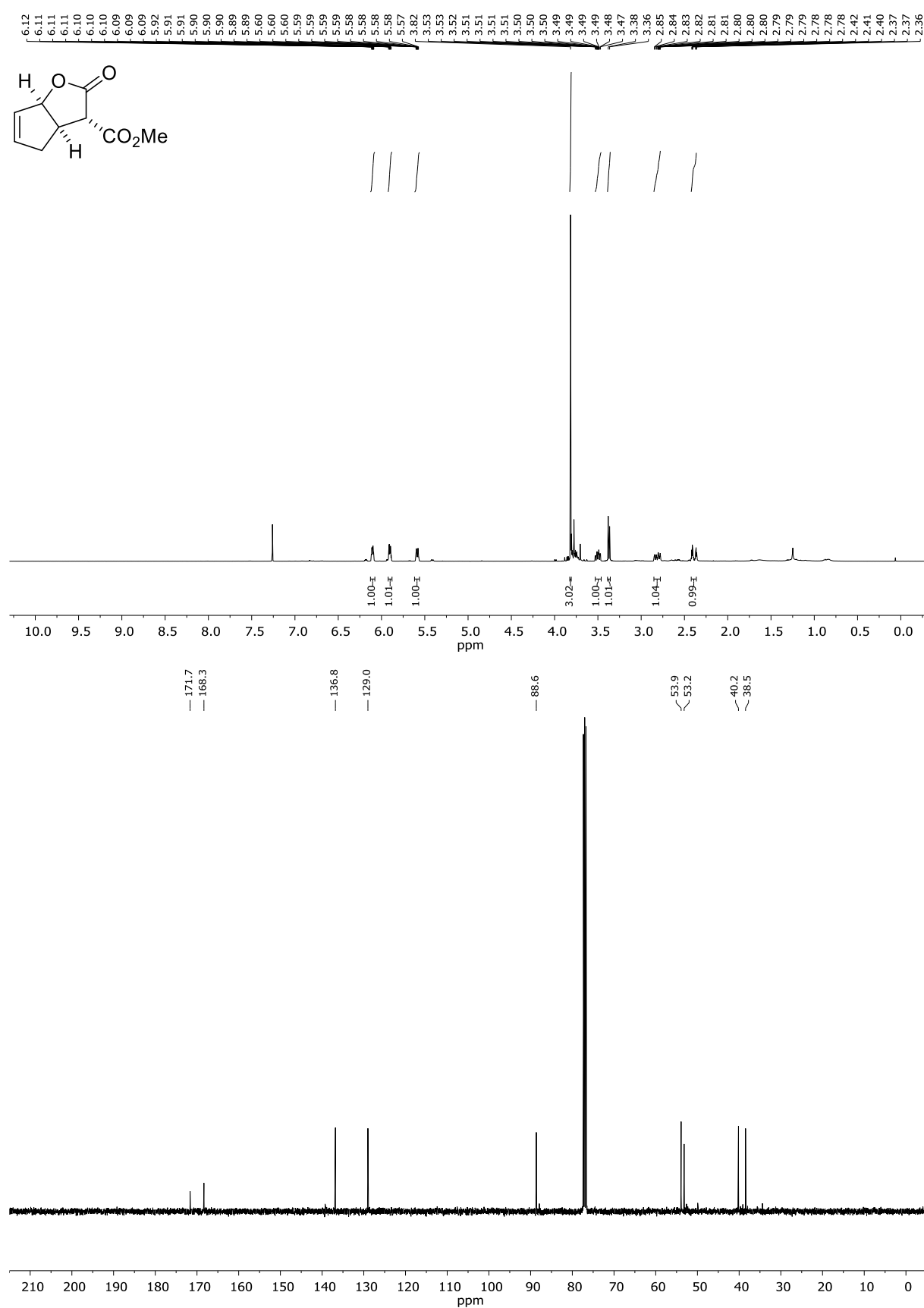
Compound 159a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



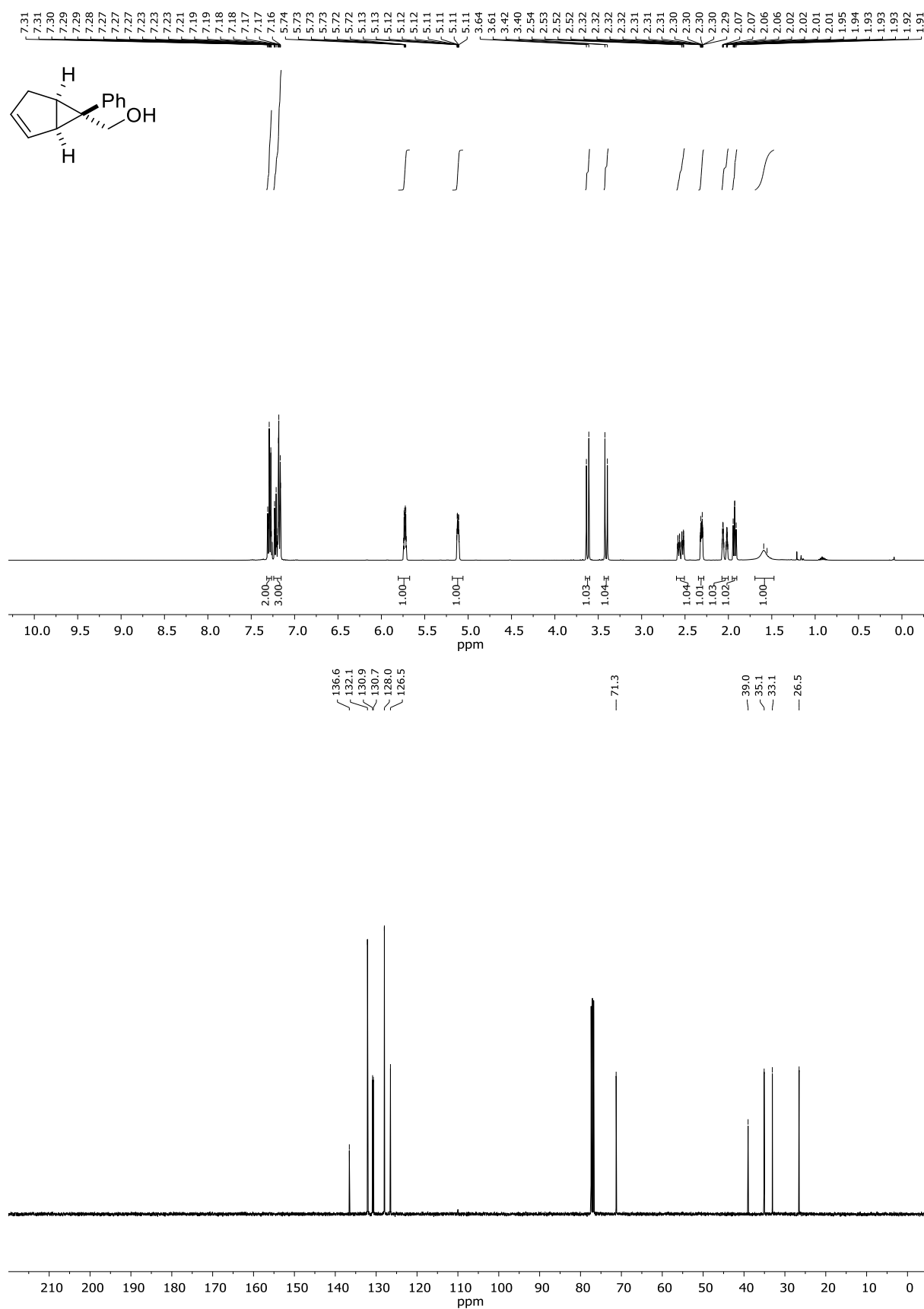
Compound 160: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



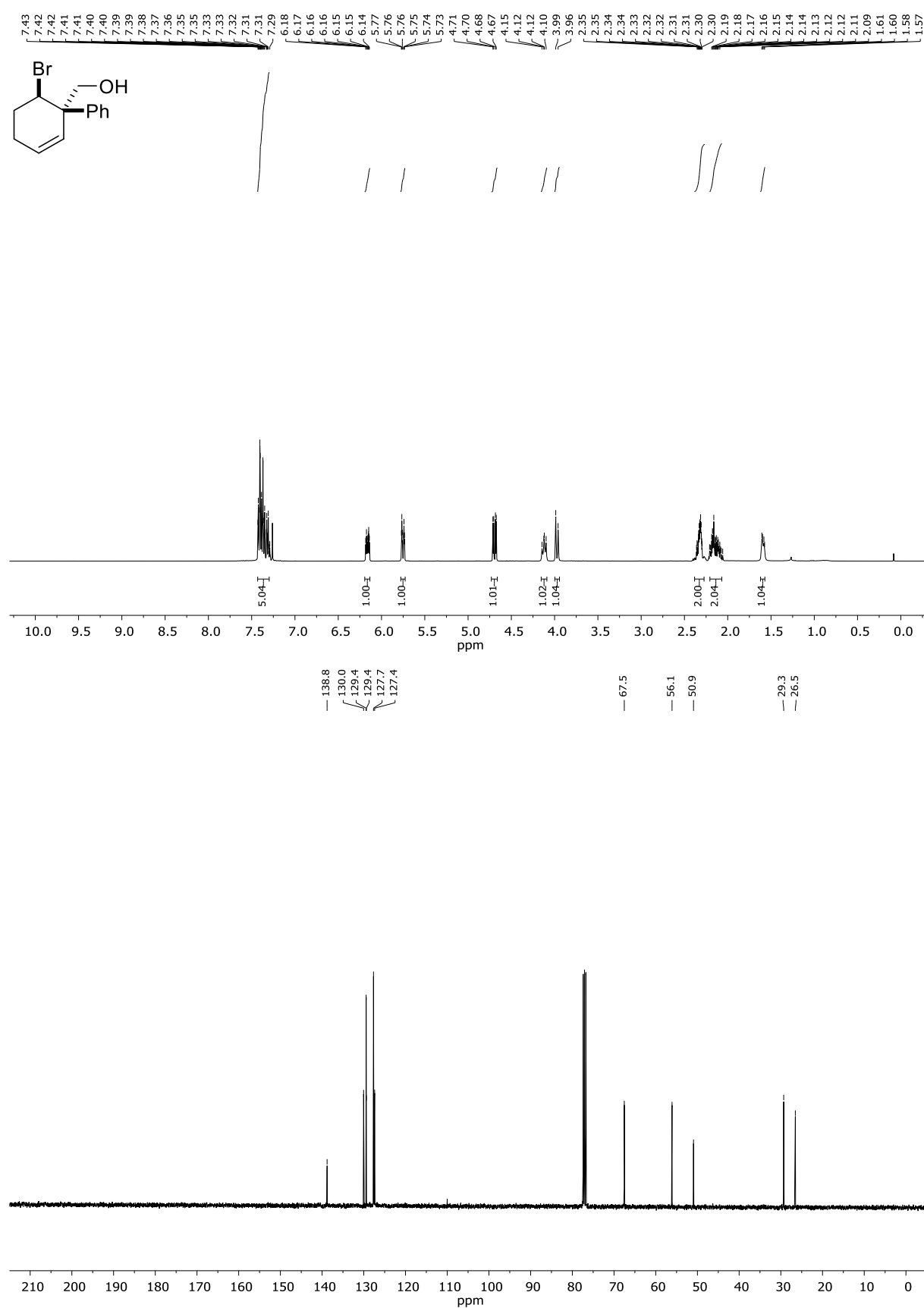
Compound 161: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



Compound 25t: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



Compound 122t: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



Chemical structure: (1R,2R)-1-phenyl-2-methoxycarbonylbicyclo[2.2.1]heptane

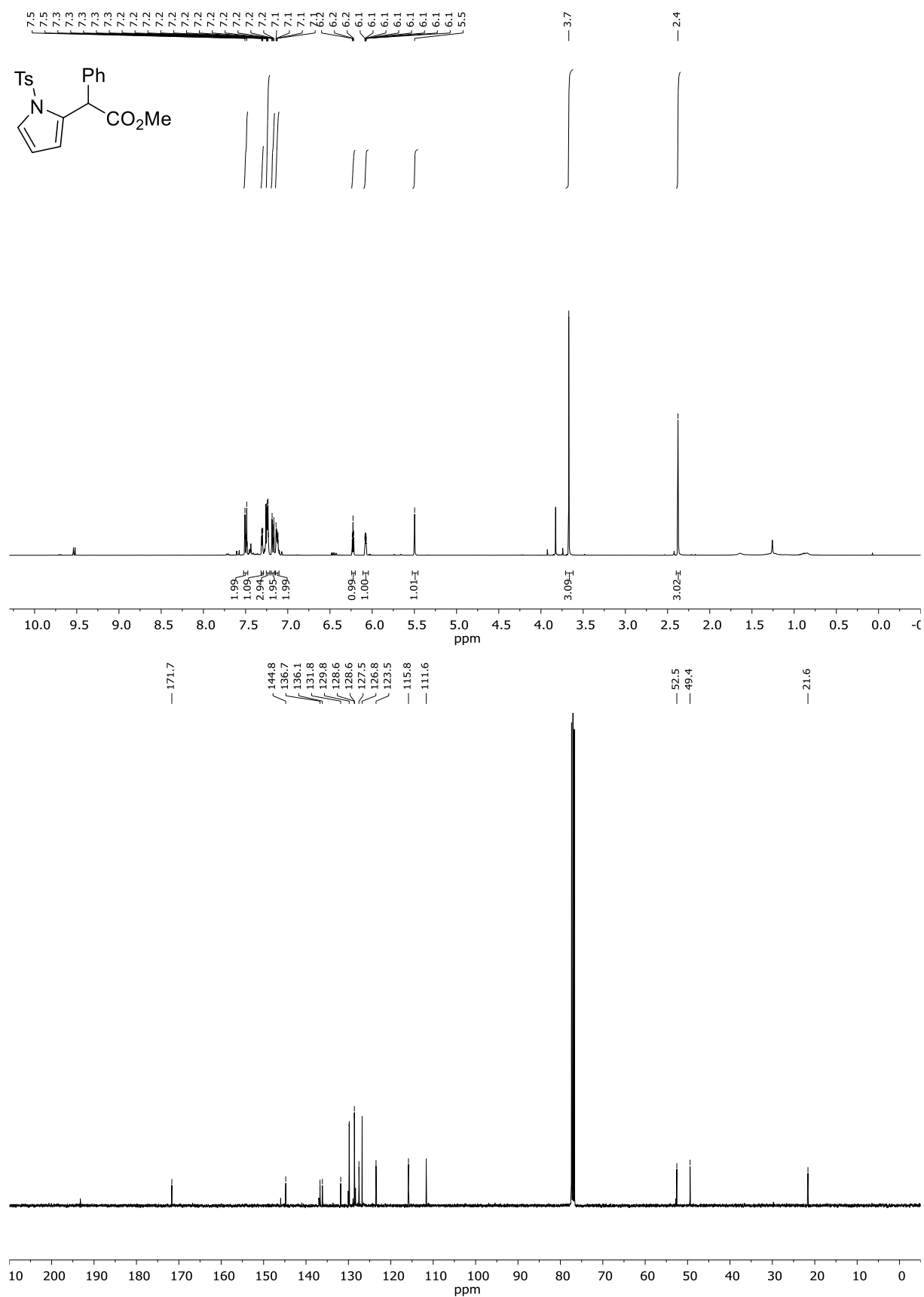
¹H NMR spectrum (top):

- Chemical shift range: 0.4 to 7.3 ppm
- Integration values: 3.05, 1.90, 1.02, 1.00, 2.99, 2.00, 1.06, 1.04, 1.58, 1.03
- Peak assignments: Aromatic protons (7.2-7.3 ppm), methoxy singlet (3.7 ppm), bicyclic protons (1.5-2.5 ppm), and a small peak at 0.4 ppm.

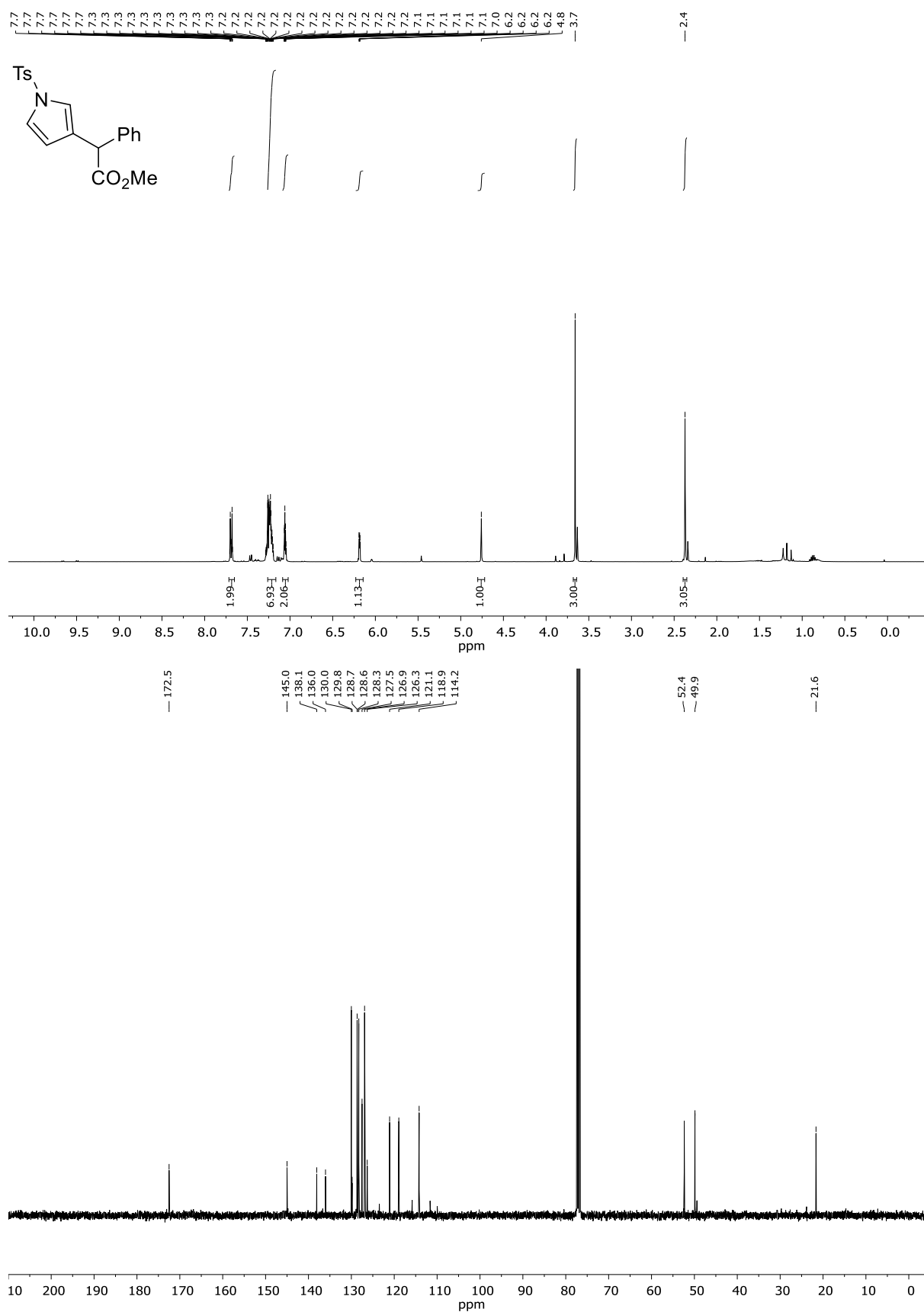
¹³C NMR spectrum (bottom):

- Chemical shift range: 16.8 to 174.0 ppm
- Peak assignments: Carbonyl carbon (174.0 ppm), aromatic carbons (122.7-134.7 ppm), methoxy carbon (52.5 ppm), and aliphatic carbons (16.8-27.7 ppm).

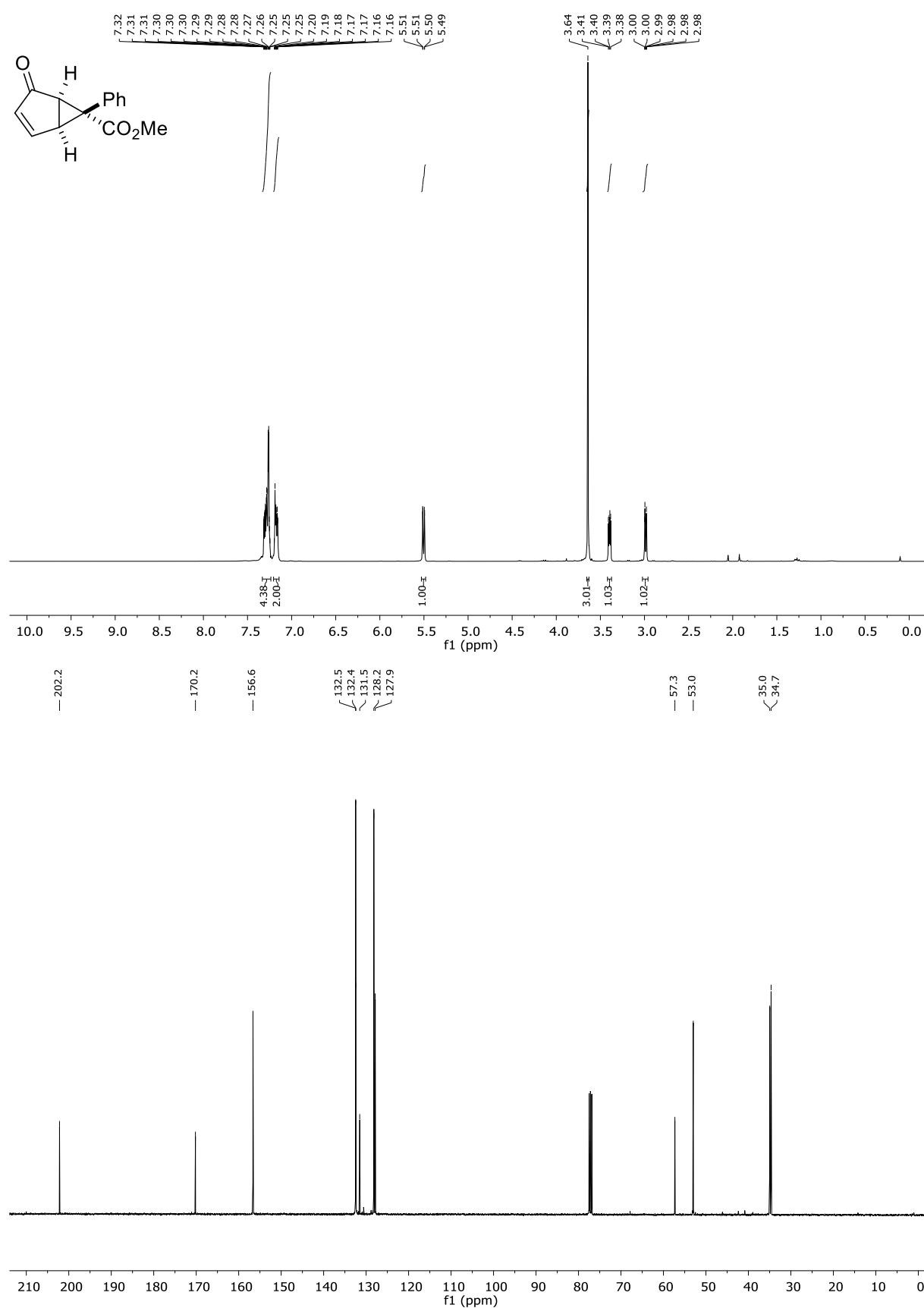
Compound 166: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



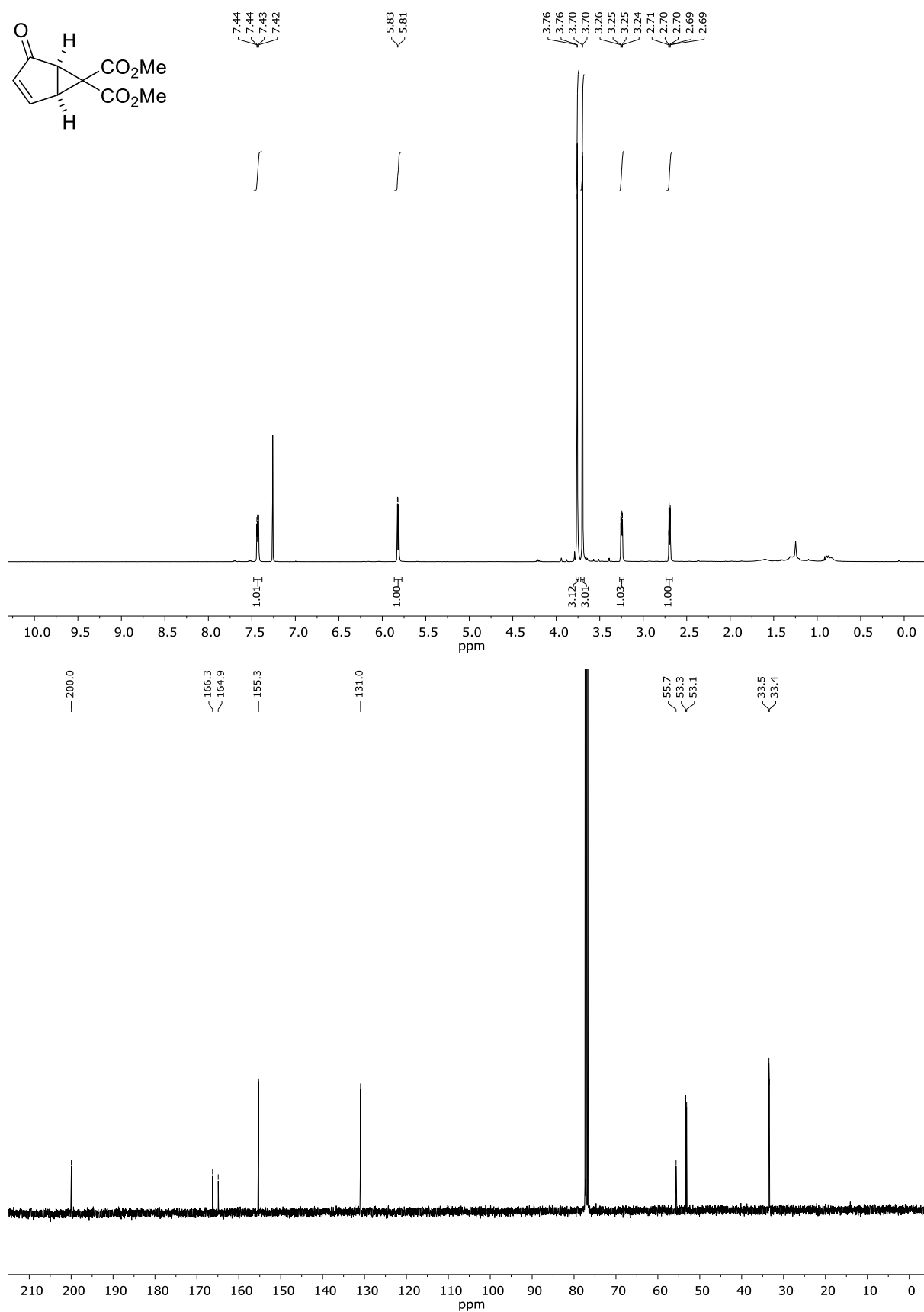
Compound 167: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



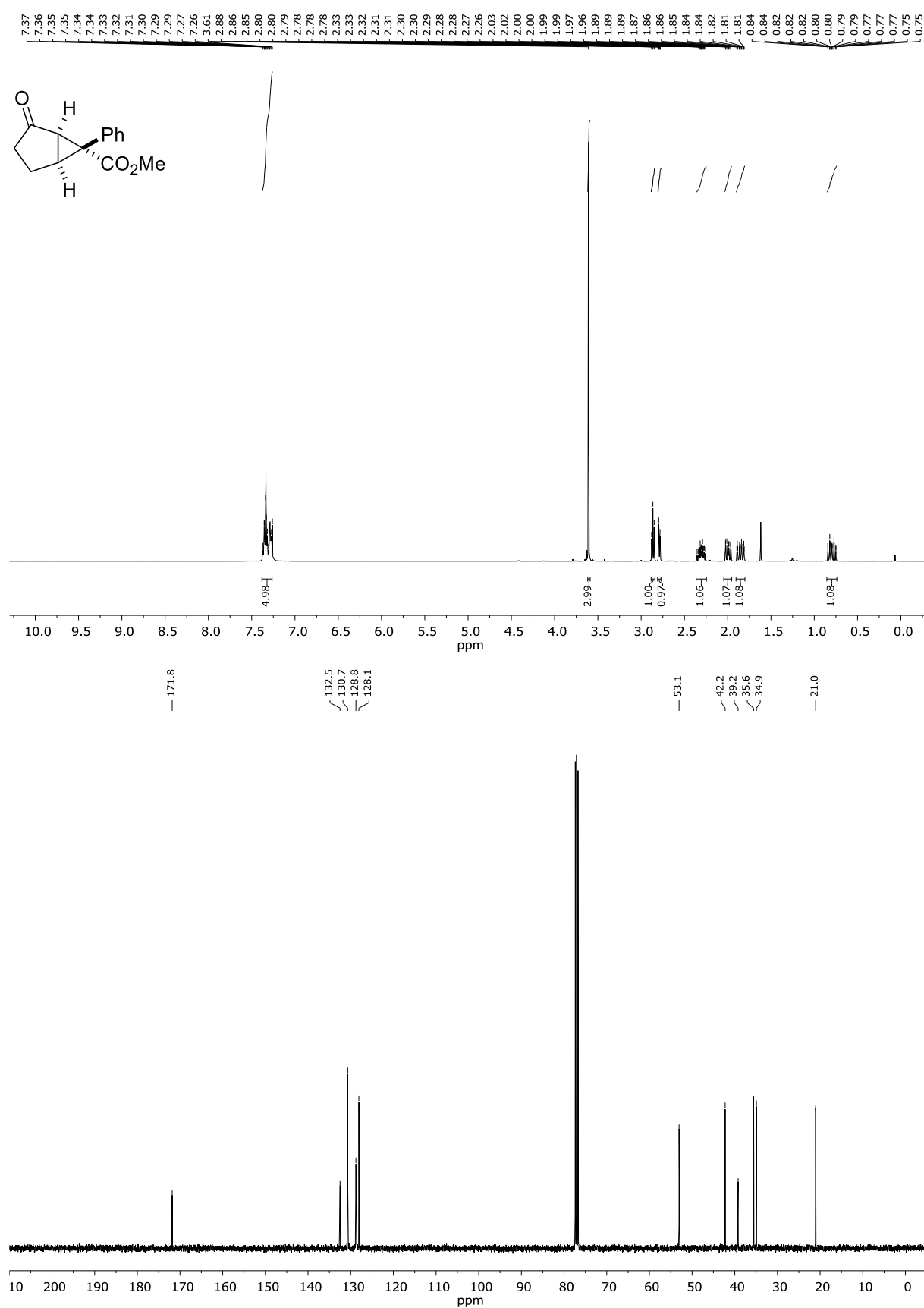
Compound 182a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



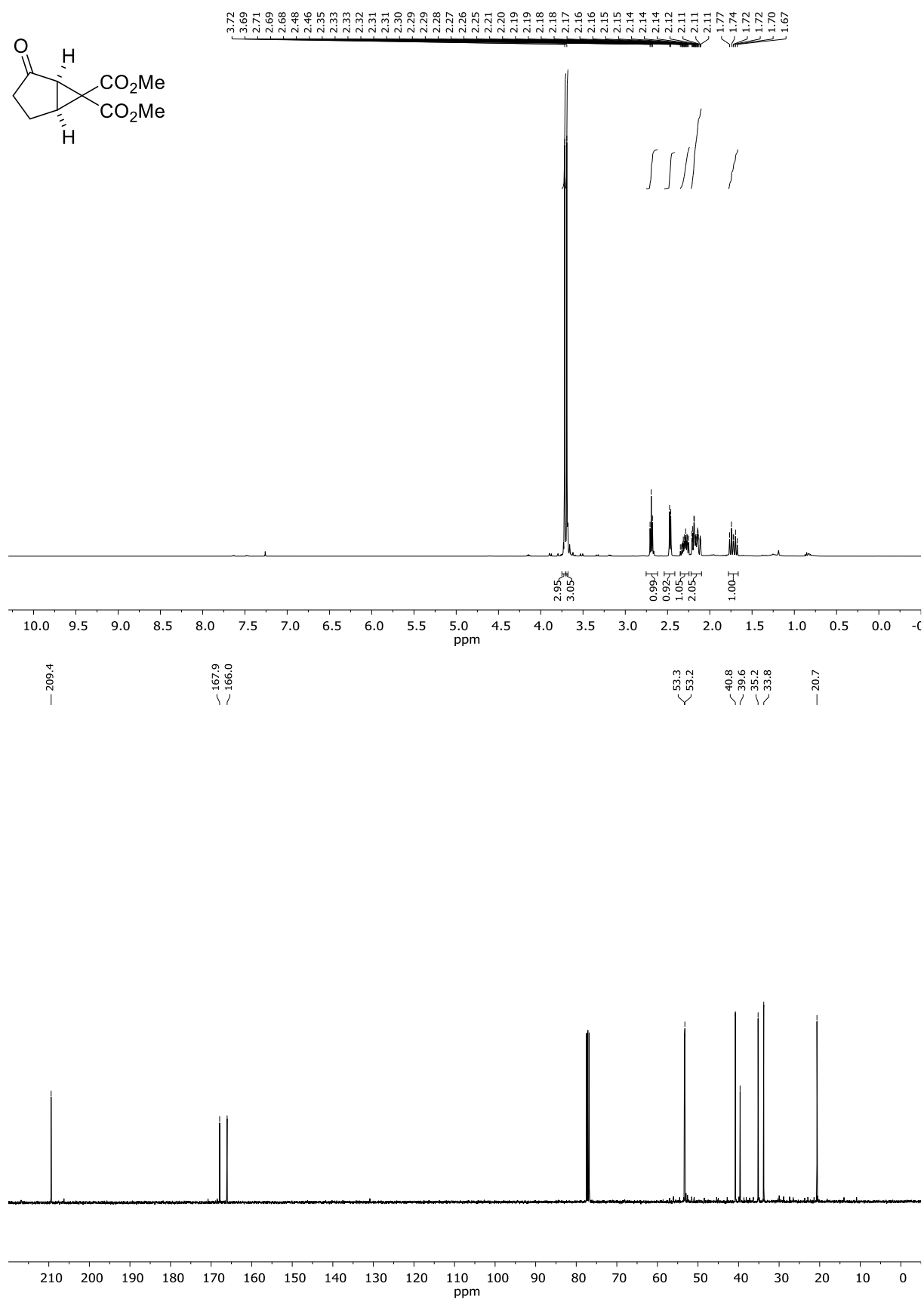
Compound 182n: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



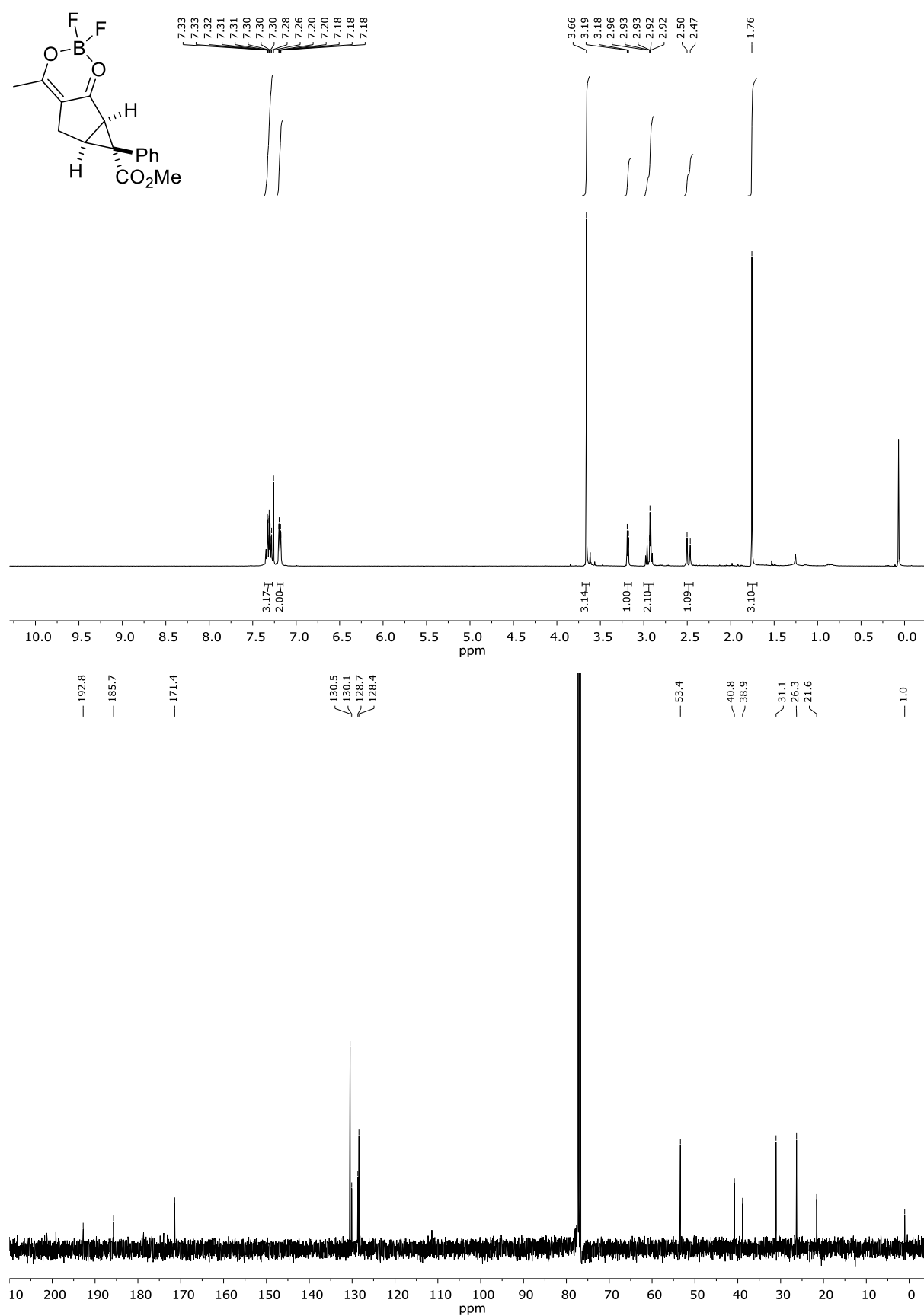
Compound 183a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



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



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



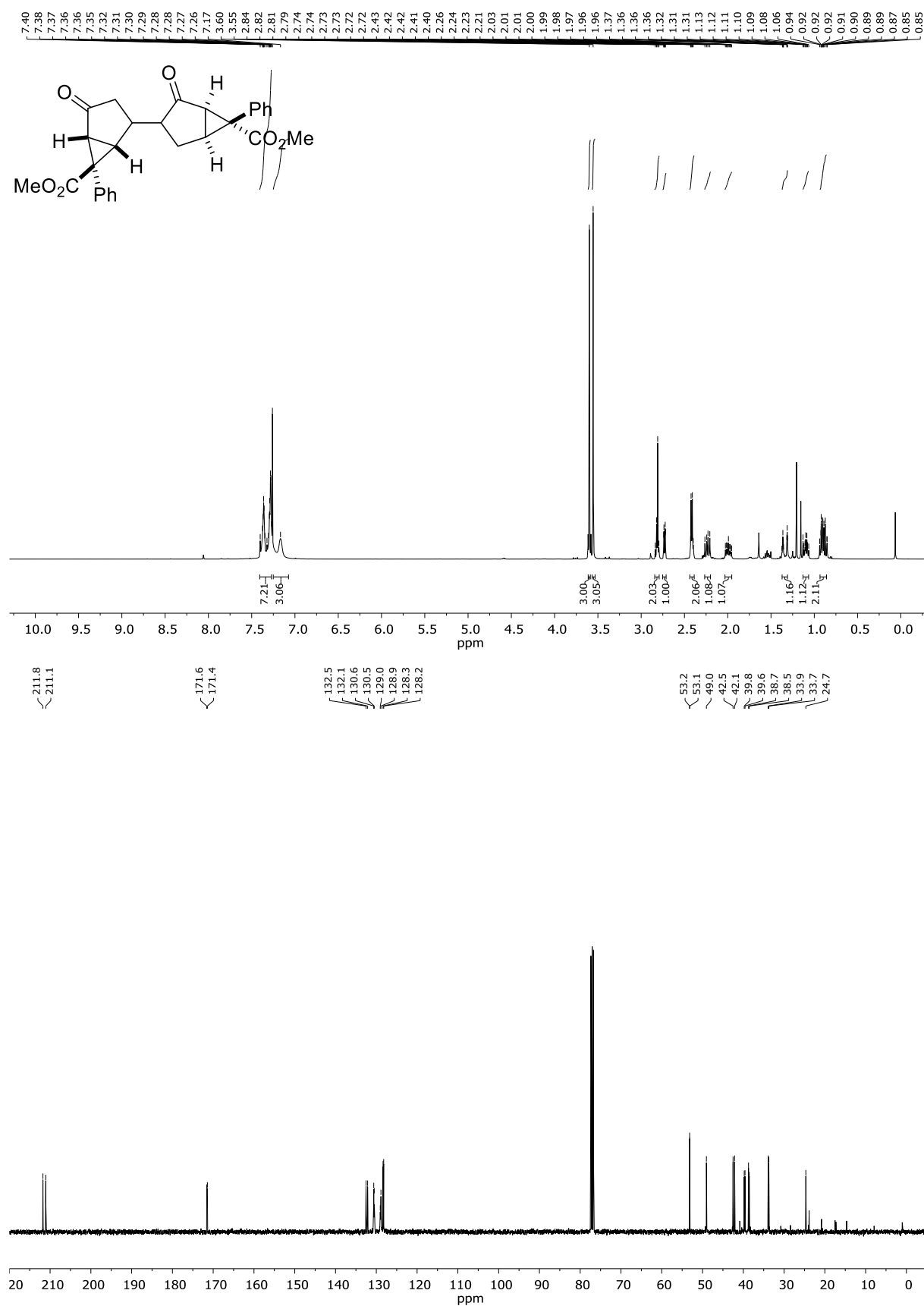
The figure displays the chemical structure of (1R,2R)-1-methoxy-2-phenyl-2-(methoxycarbonyl)bicyclo[2.2.1]heptan-5-one and its corresponding ¹H and ¹³C NMR spectra.

Chemical Structure: The structure shows a bicyclo[2.2.1]heptan-5-one core. At position 1, there is a methoxy group (MeO) and a hydrogen atom (H). At position 2, there is a phenyl group (Ph) and a methoxycarbonyl group (CO₂Me). The stereochemistry is (1R,2R).

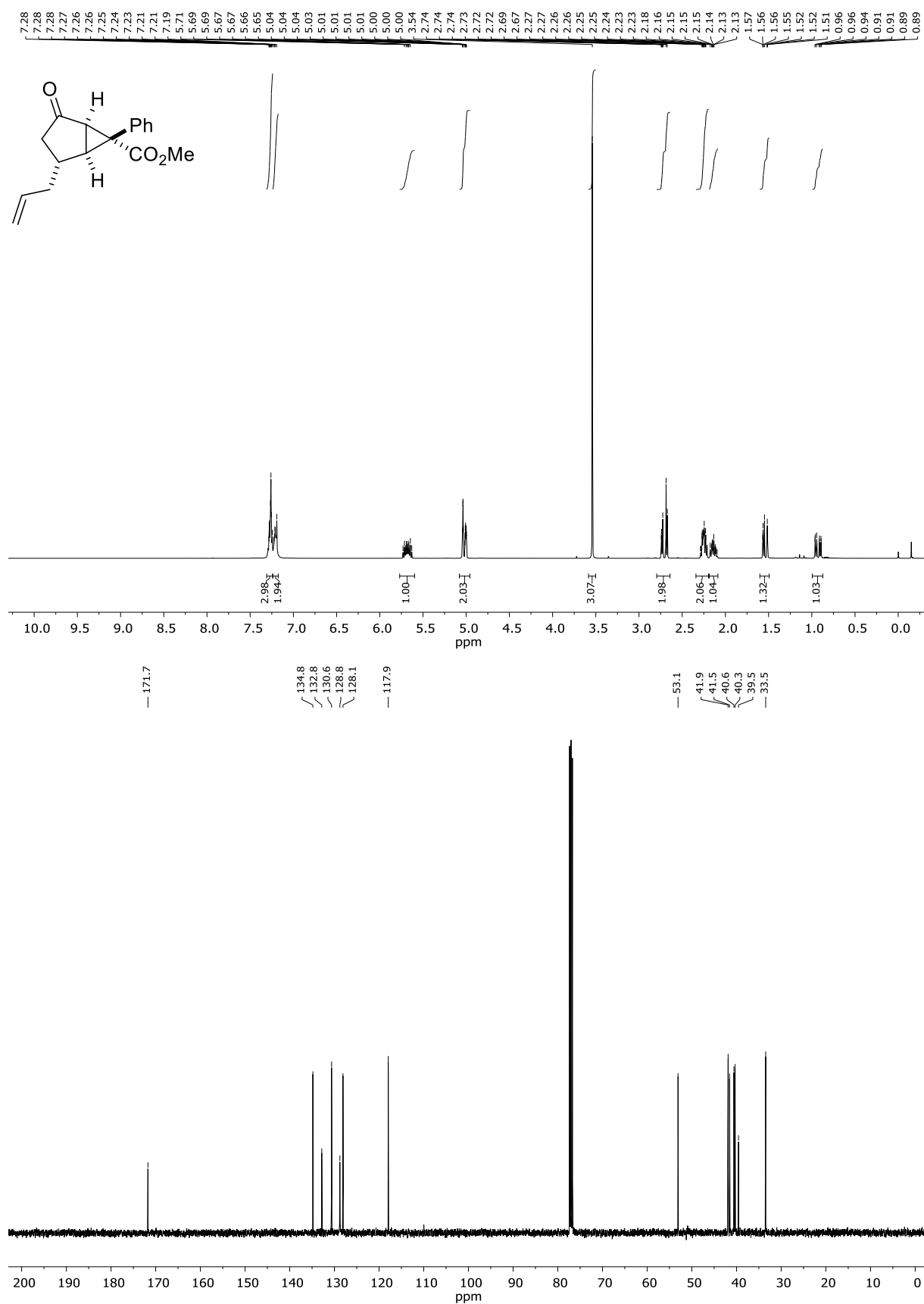
¹H NMR Spectrum (400 MHz, CDCl₃): The spectrum shows peaks in the aromatic region (7.2-7.4 ppm), a methoxy singlet (3.8 ppm), a methine multiplet (3.5 ppm), a methoxy singlet (3.3 ppm), a methoxy singlet (3.0 ppm), a methoxy singlet (2.8 ppm), a methoxy singlet (2.8 ppm), a methoxy singlet (1.9 ppm), a methoxy singlet (1.8 ppm), a methoxy singlet (1.1 ppm), a methoxy singlet (1.0 ppm), and a methoxy singlet (1.0 ppm). Integration values are provided for several peaks: 5.32, 1.00, 3.24, 3.02, 0.98, 1.03, 1.03, 1.03, 1.06.

¹³C NMR Spectrum (100 MHz, CDCl₃): The spectrum shows peaks at 209.7, 171.1, 132.2, 130.6, 128.9, 128.3, 76.8, 56.4, 53.2, 42.9, 40.6, 39.3, and 38.4 ppm.

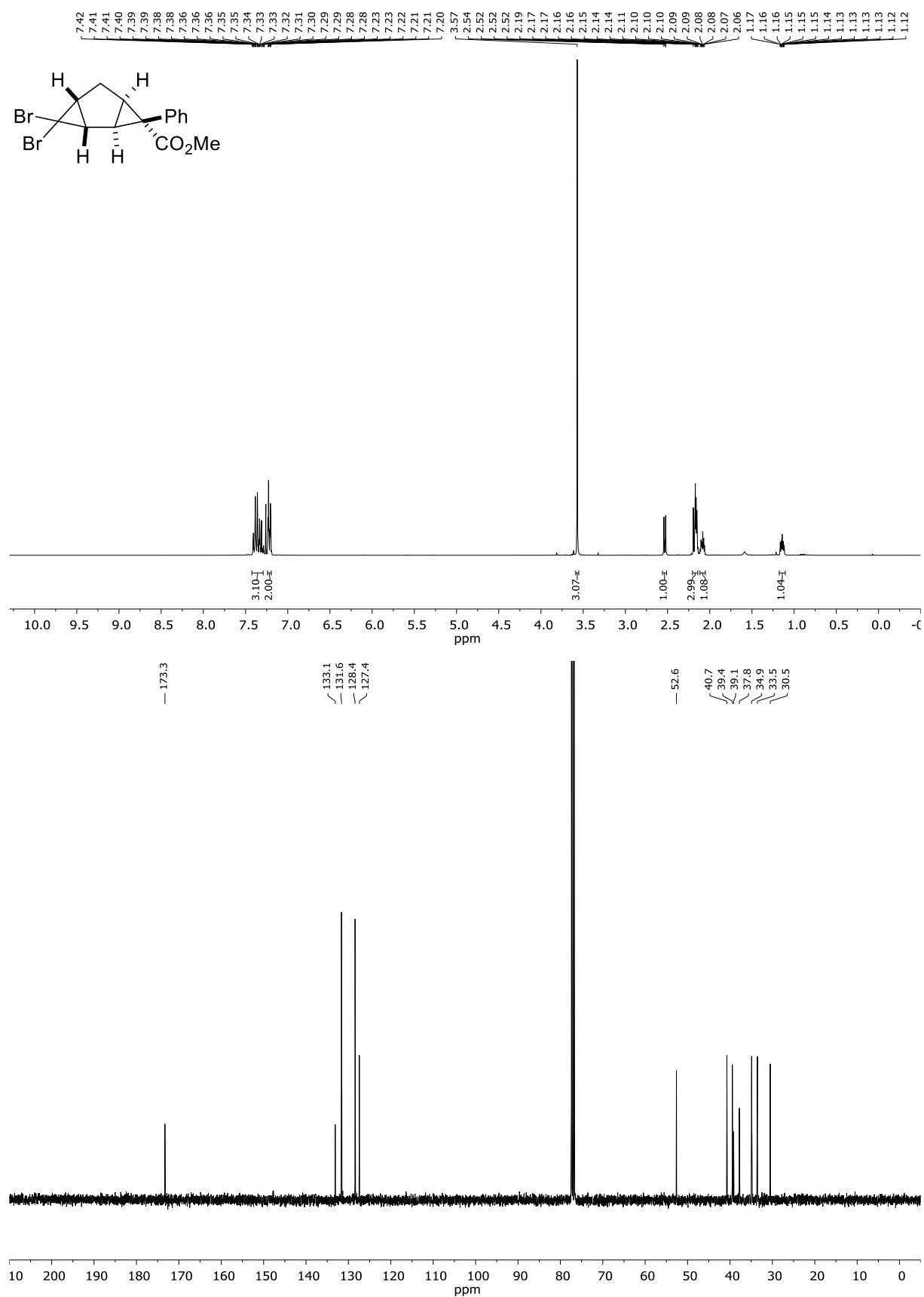
Compound 189: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



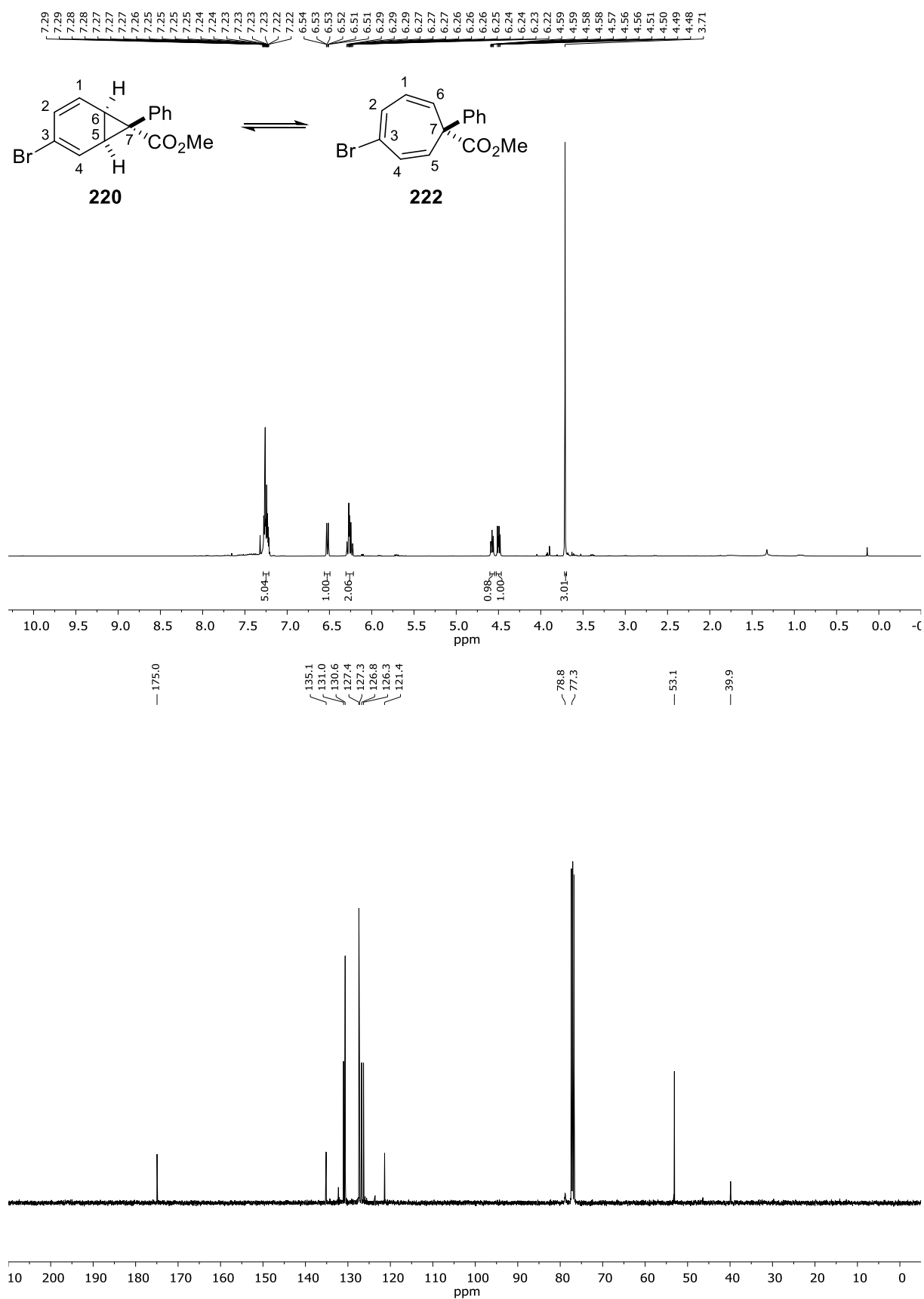
Compound 190: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):



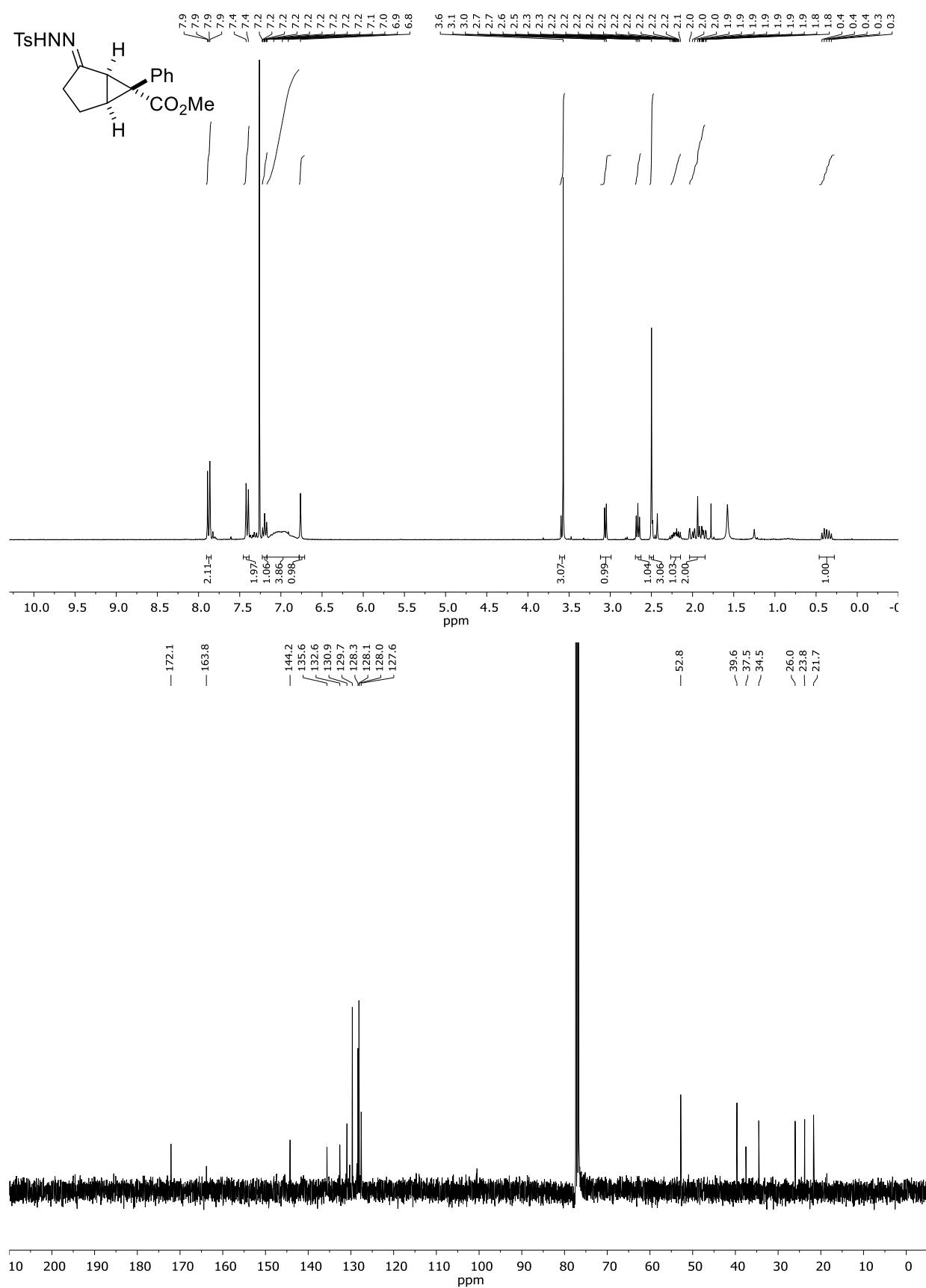
Compound 218: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):

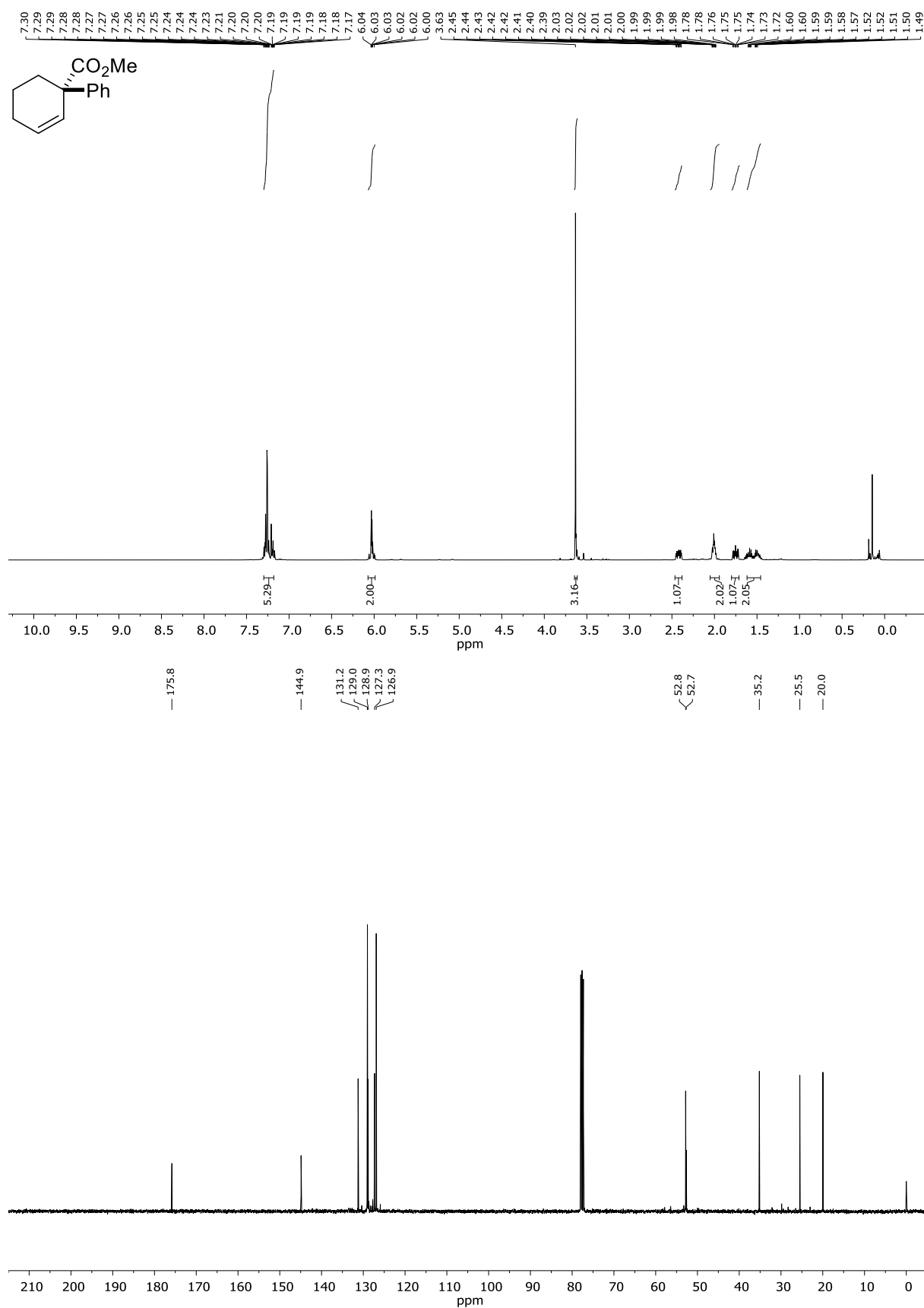


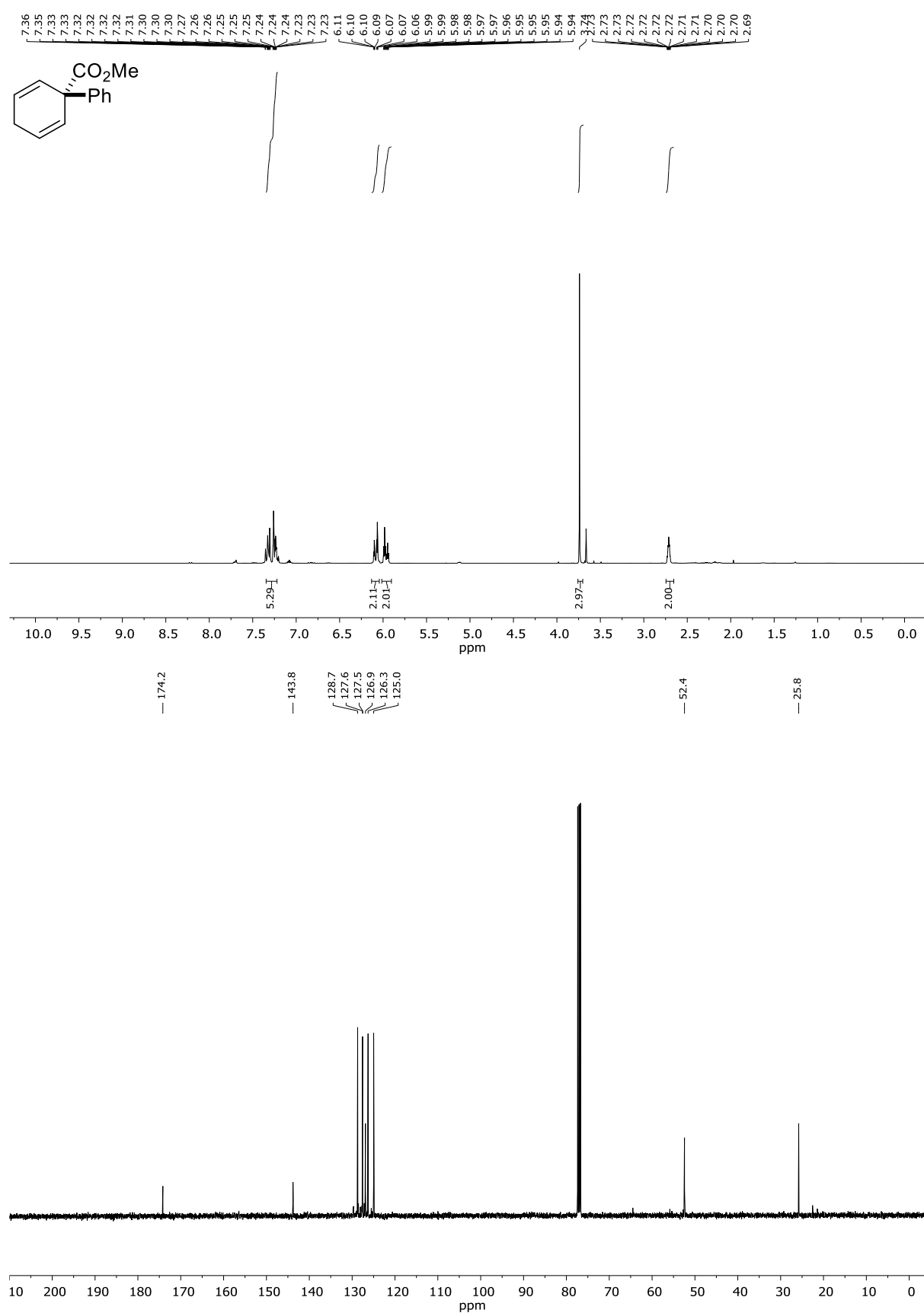
Compound 220 and 222: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):

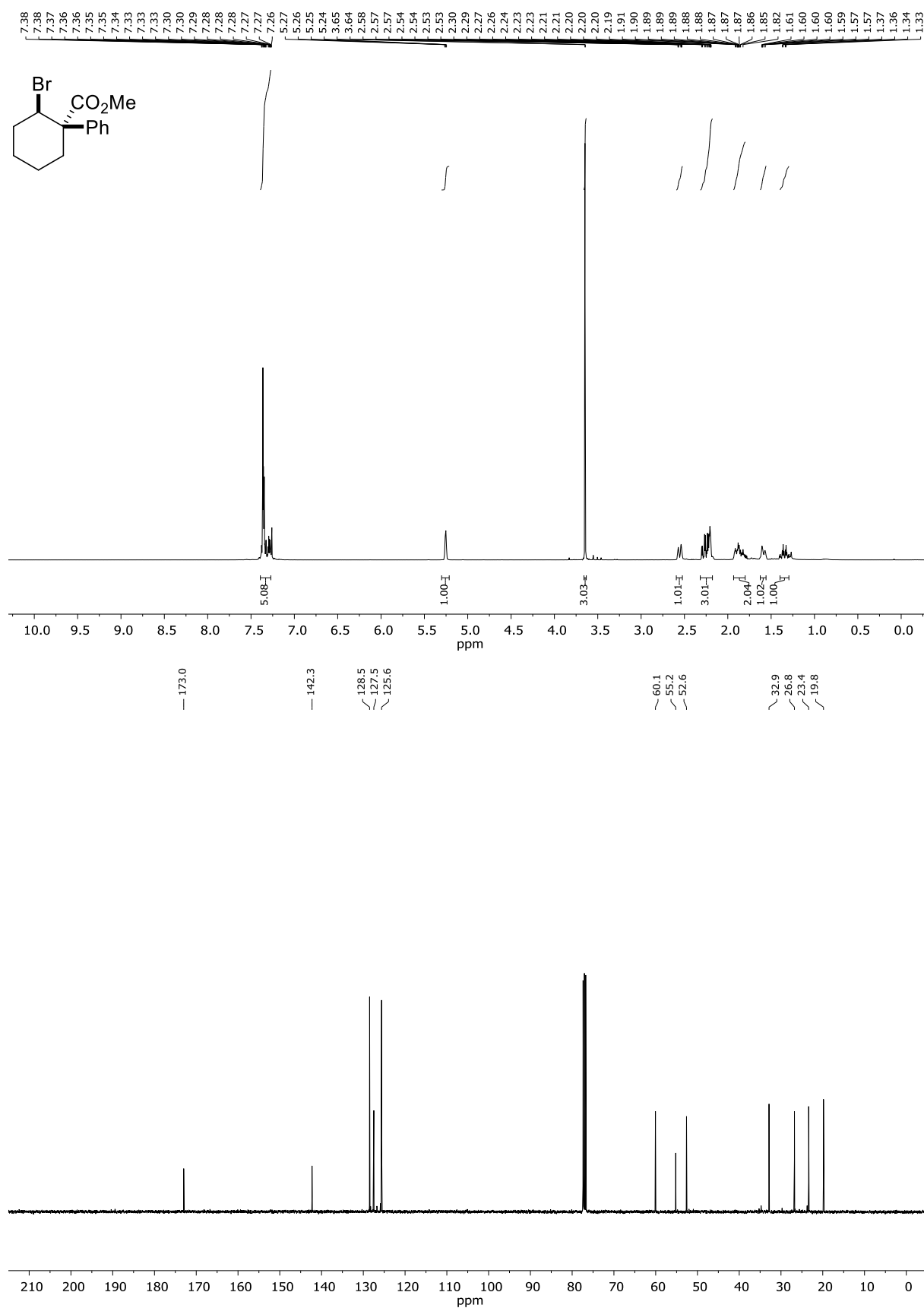


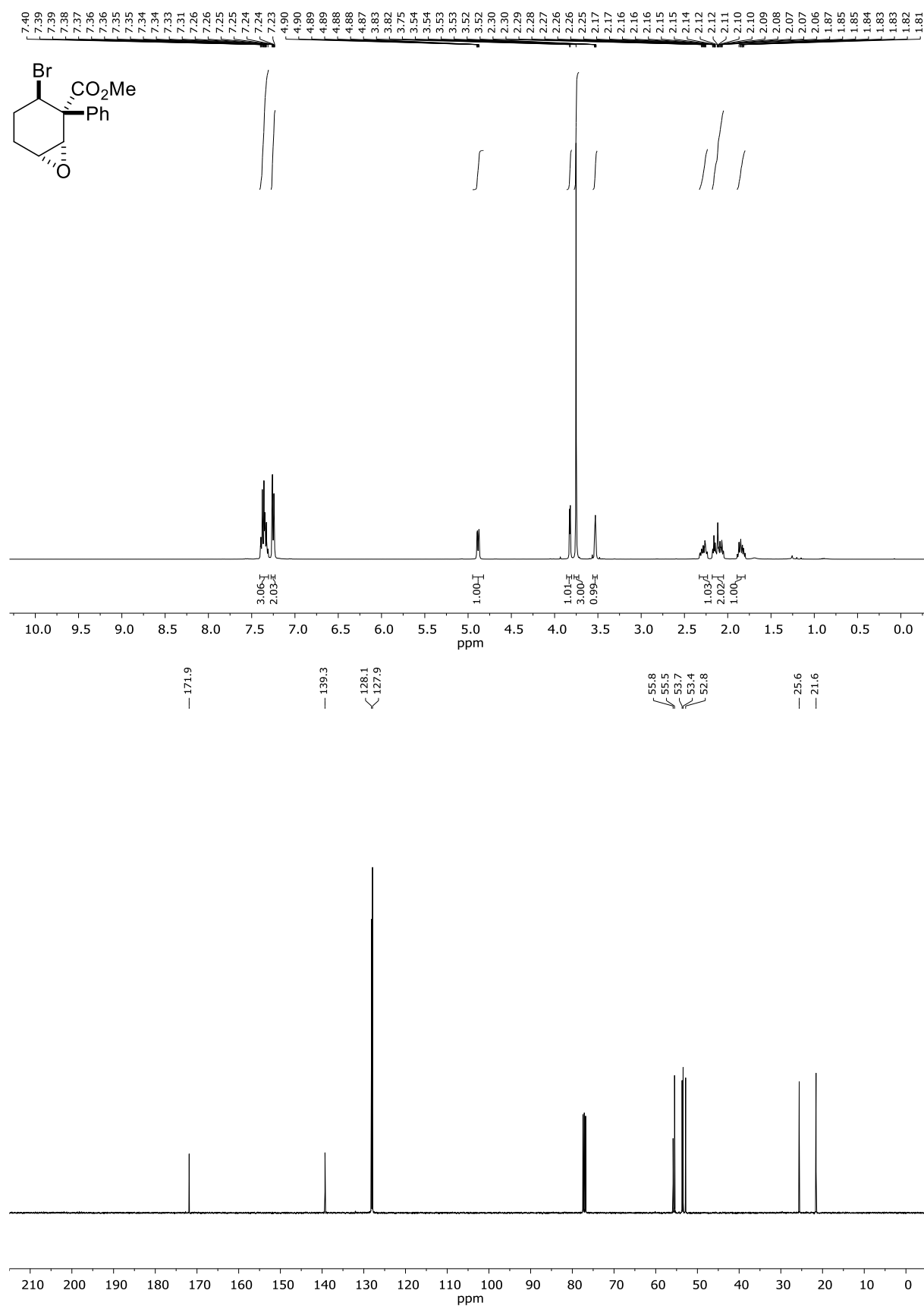
Compound 264: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3):

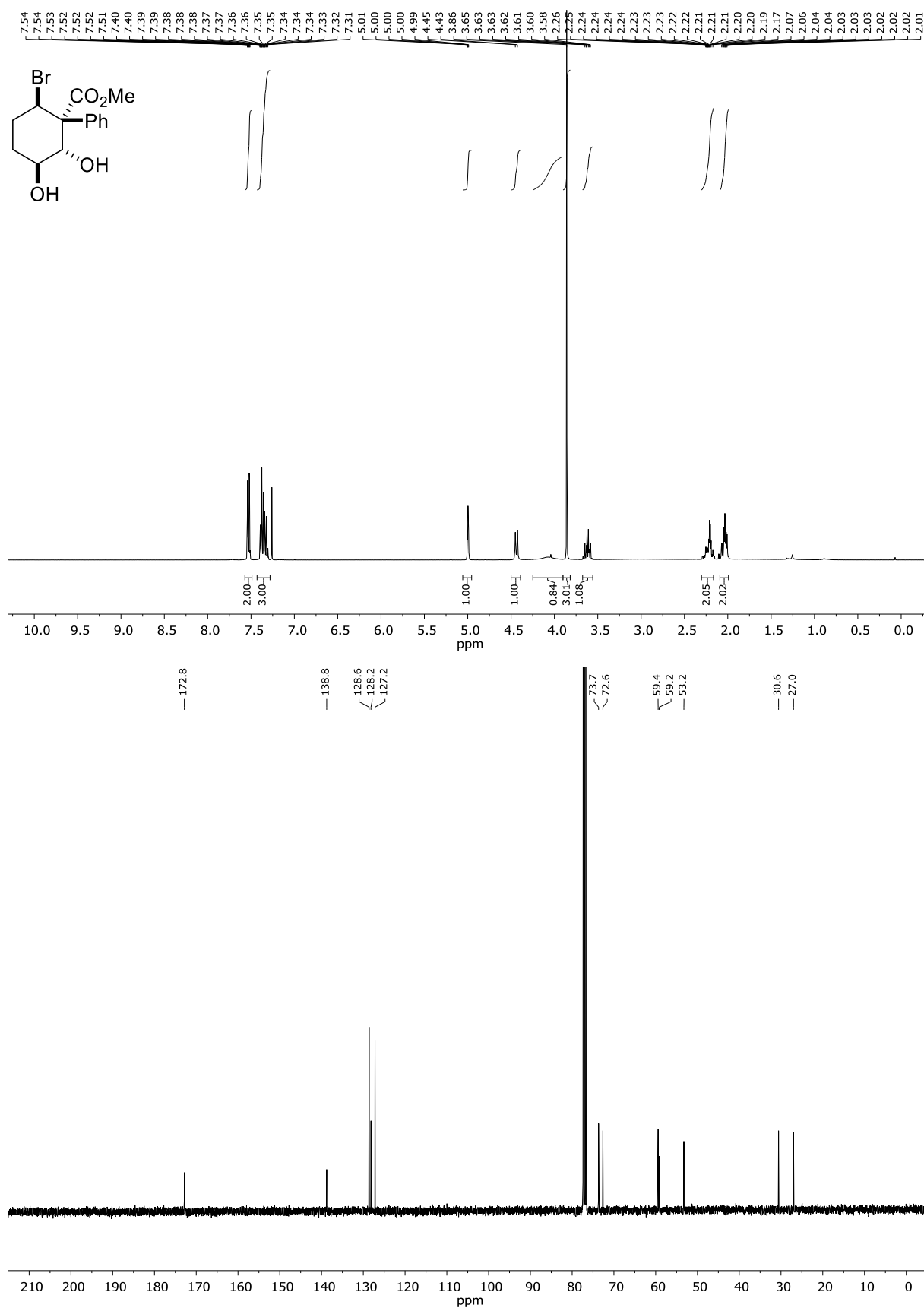


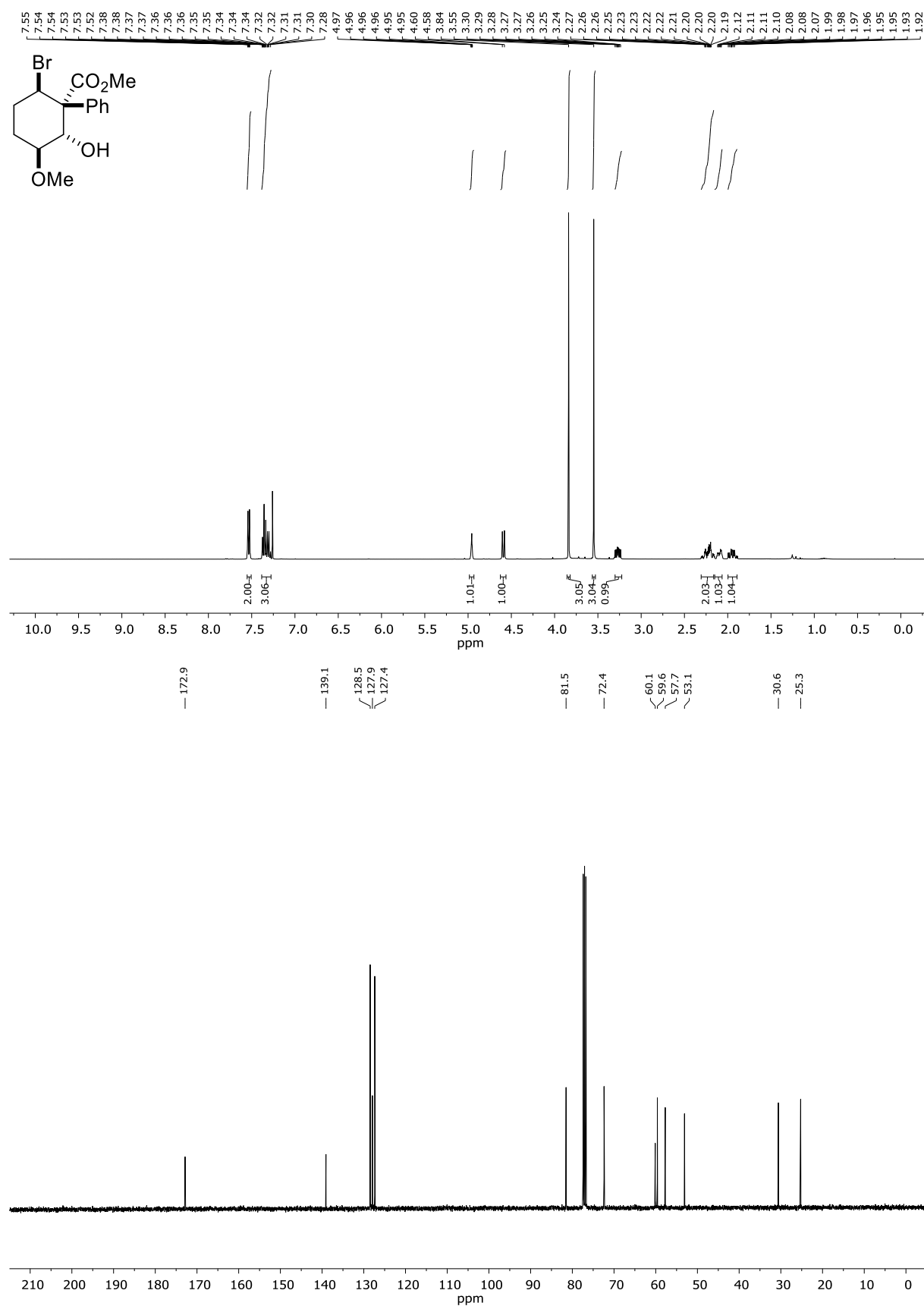
Compound 277: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

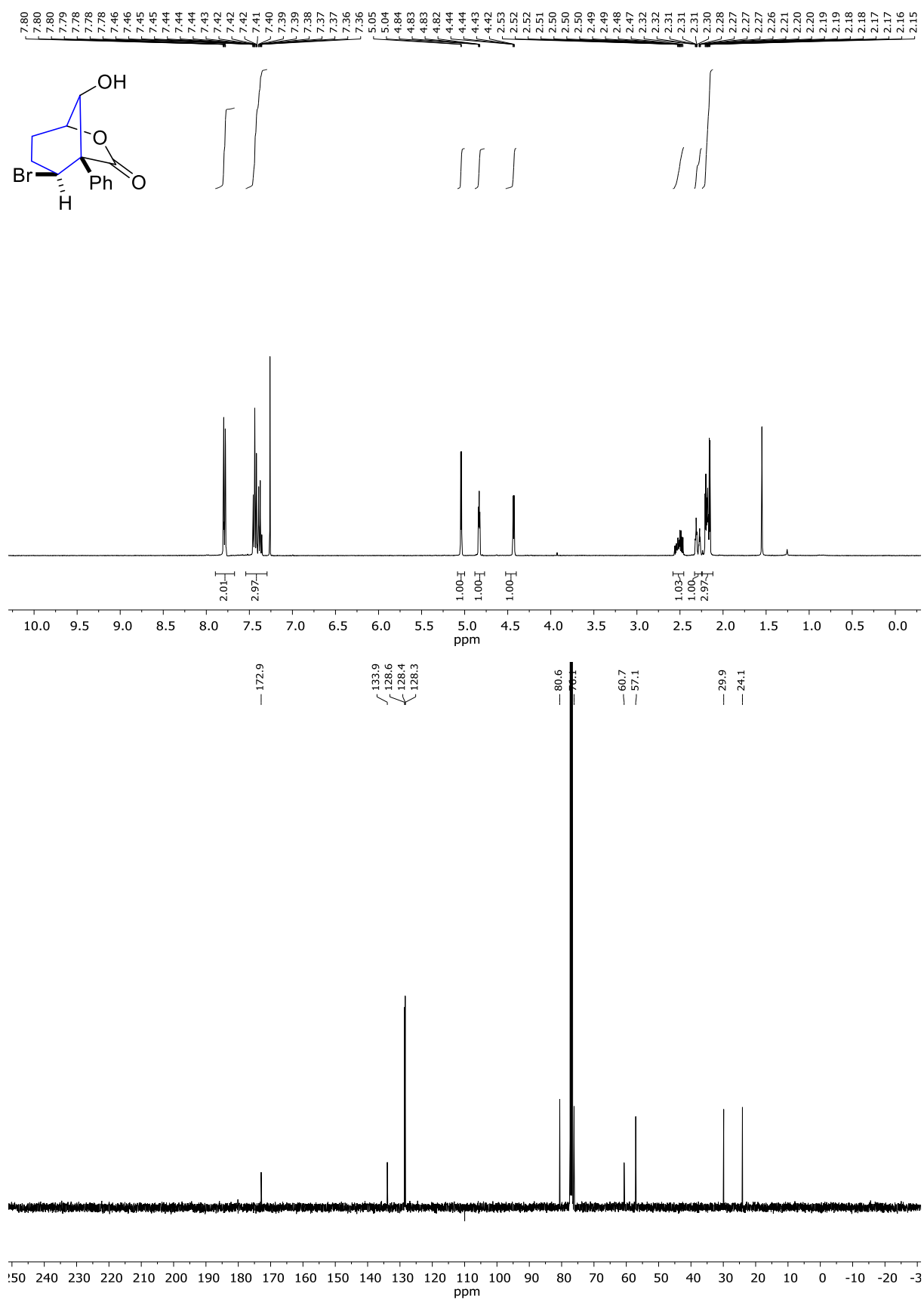
Compound 278: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

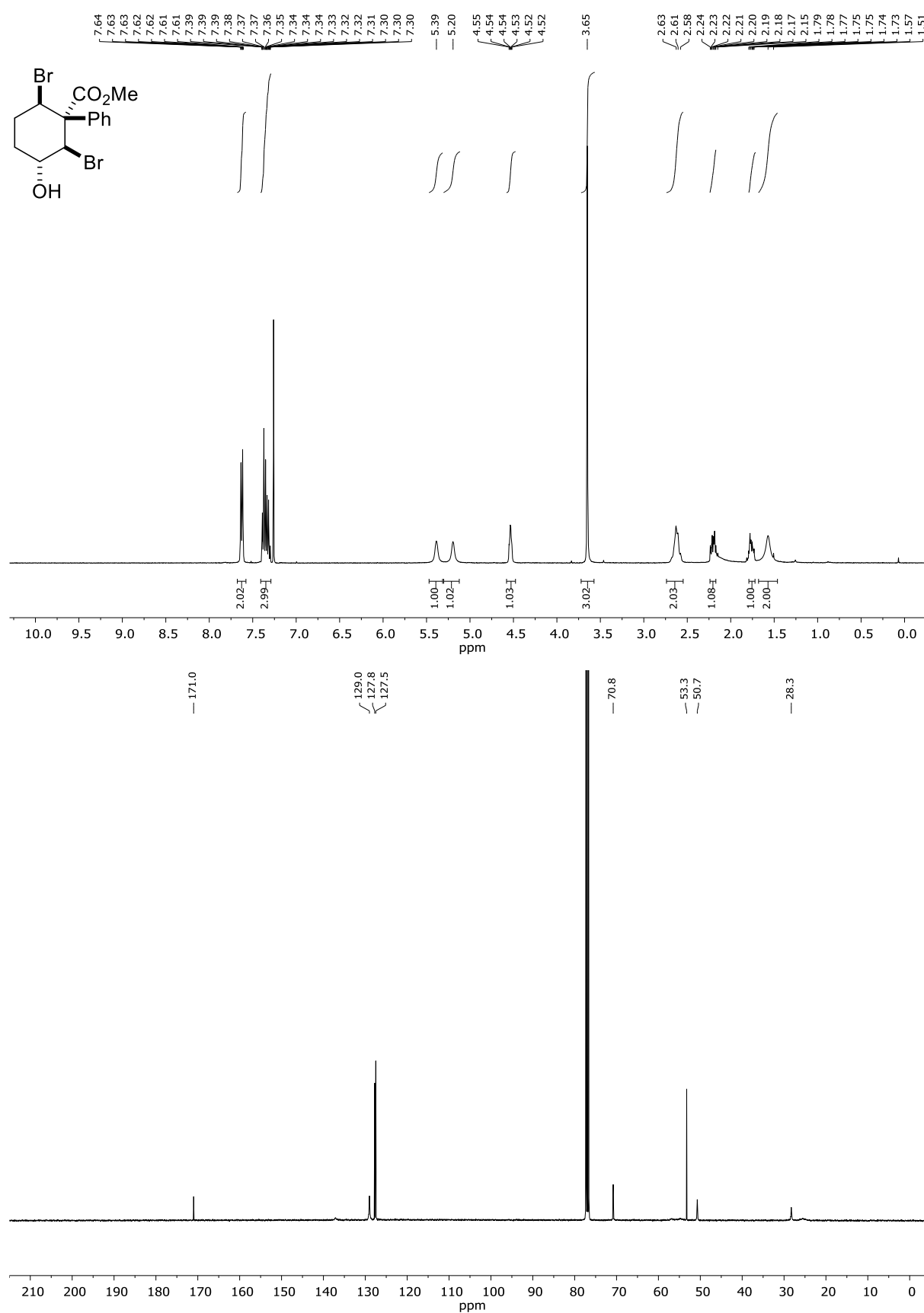
Compound 293: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

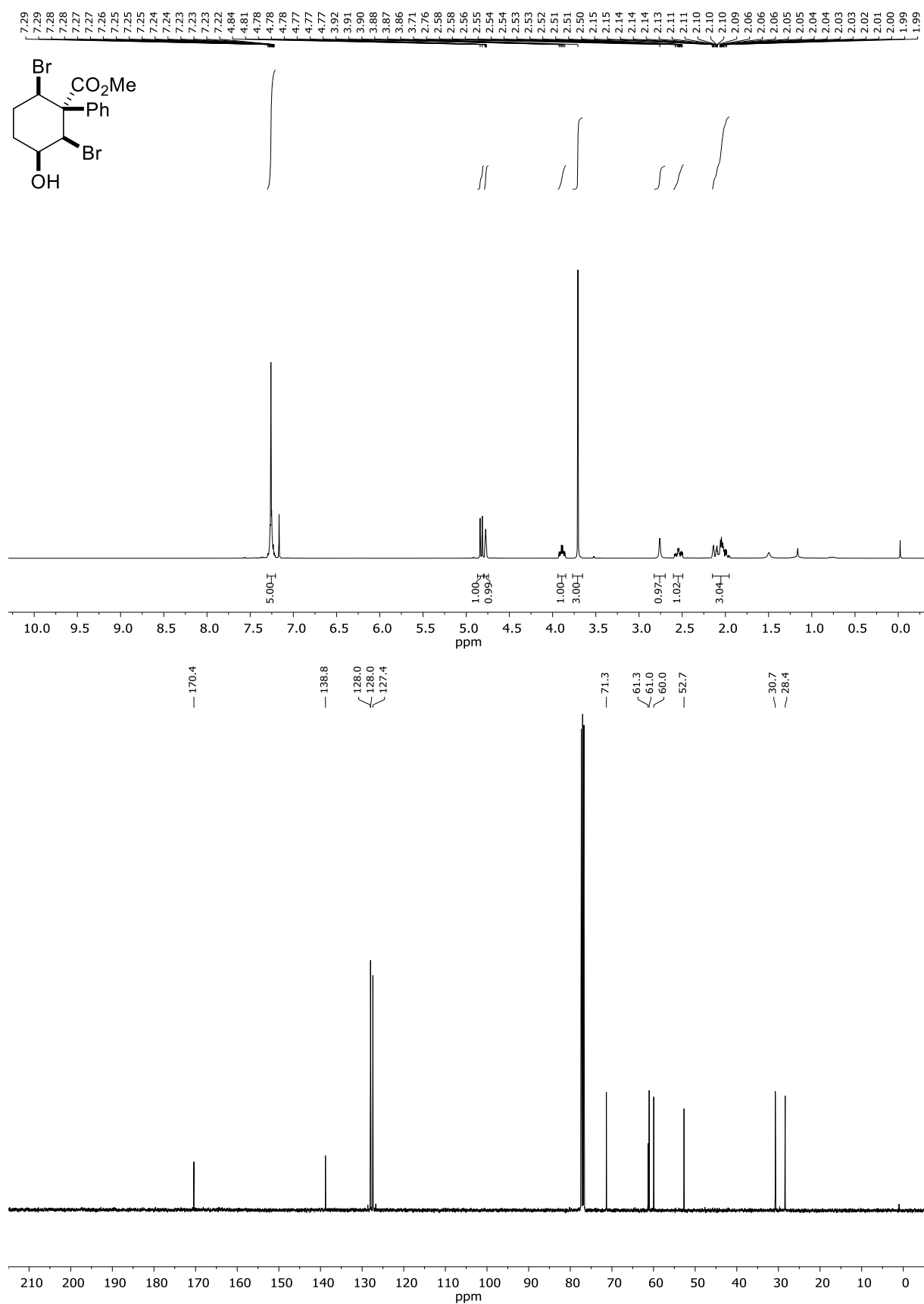
Compound 295: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

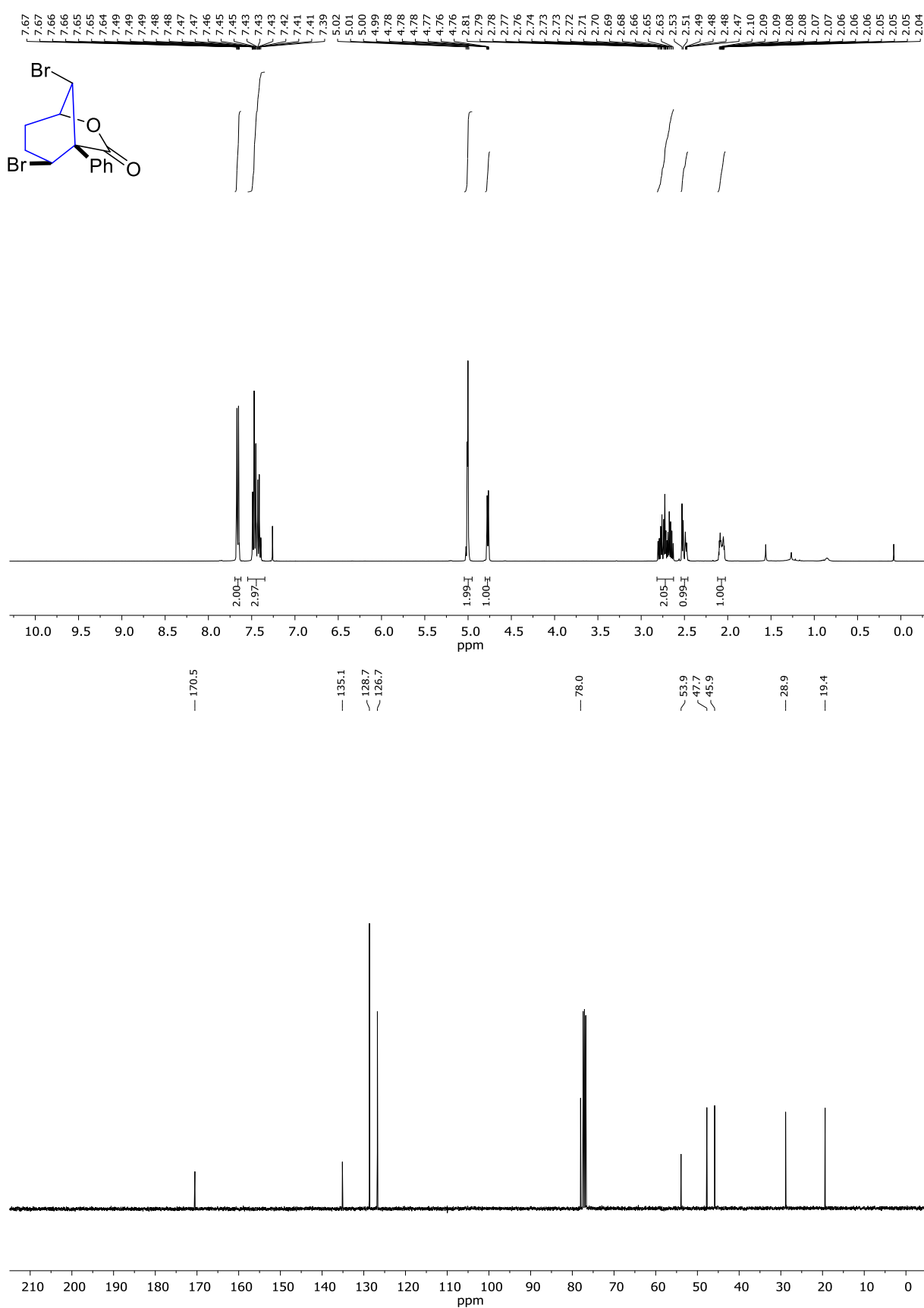
Compound 296: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

Compound 297: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

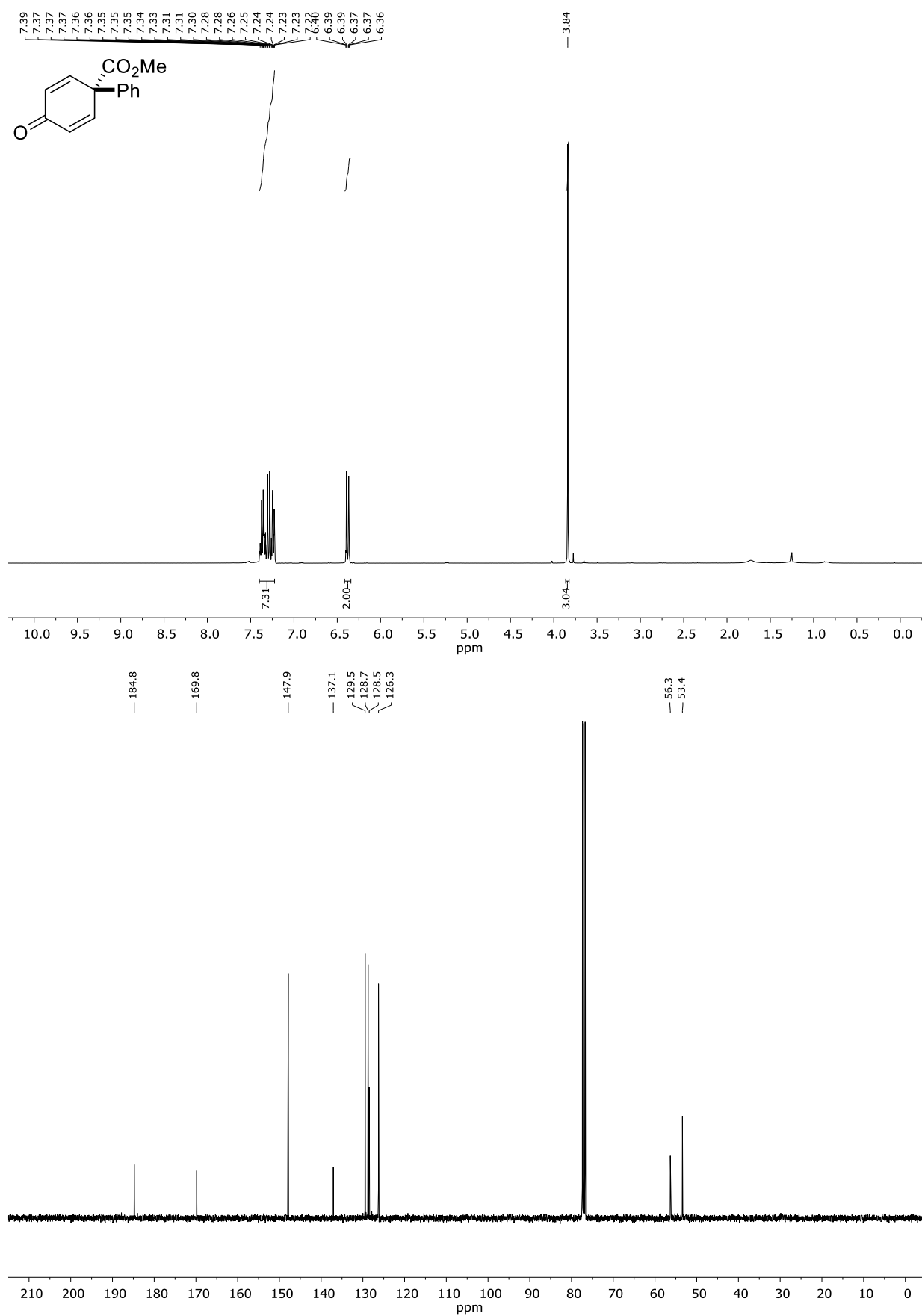
Compound 298: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

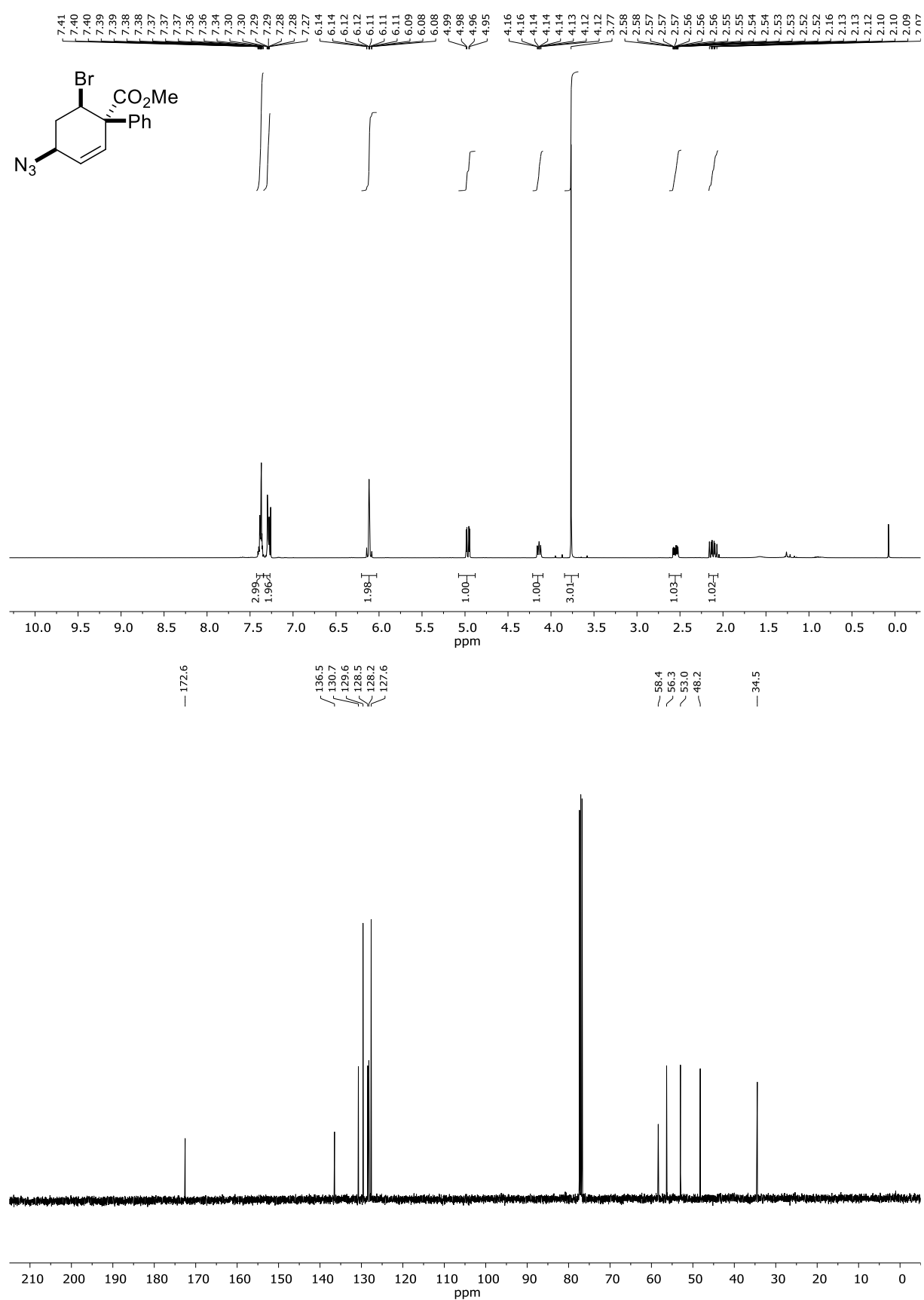
Compound 299a: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

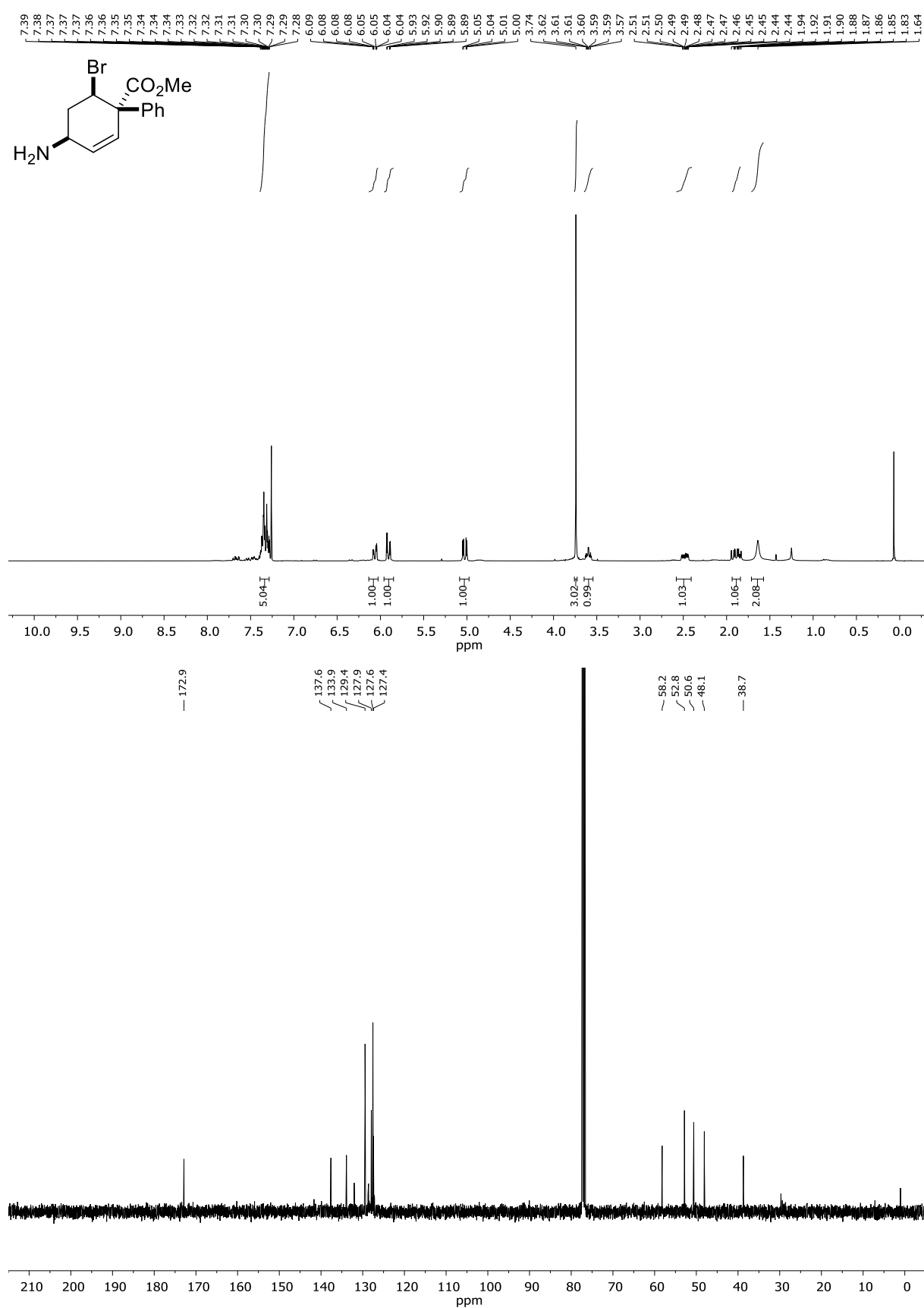
Compound 299b: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

Compound 300: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

Compound 301: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)



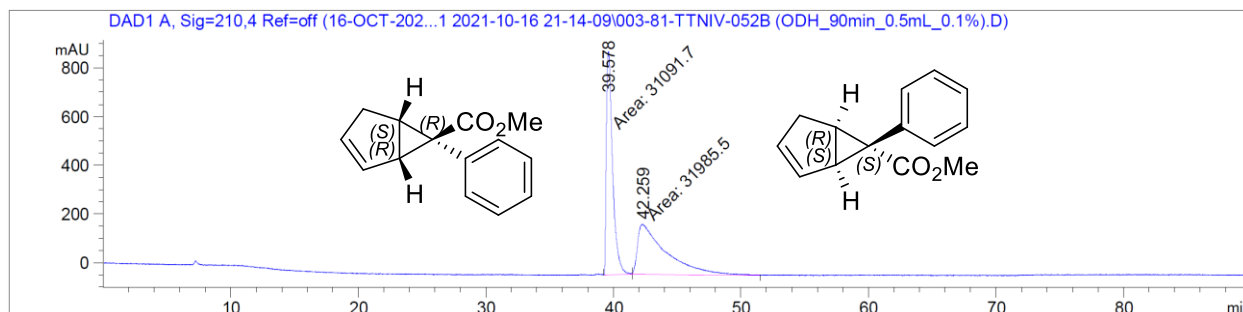
Compound 302: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

Compound 303: ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (101 MHz, CDCl_3)

2. HPLC–Chromatograms

Methyl 6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (25a):

Racemic mixture (25a):



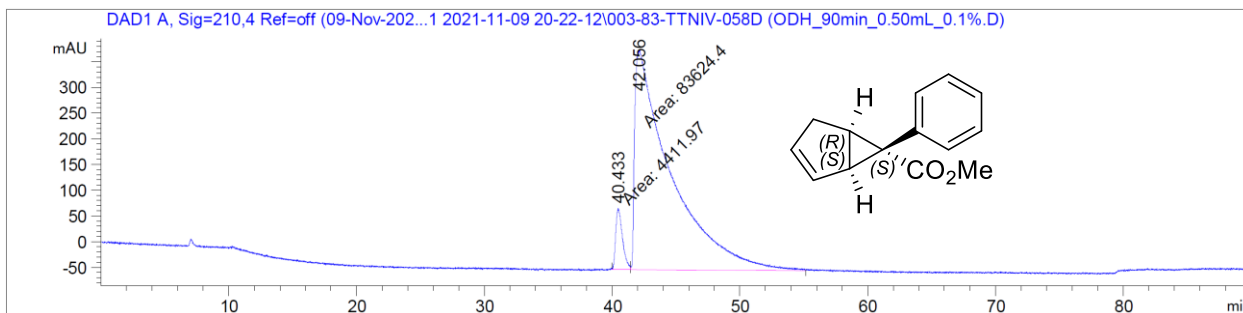
Signal 1: DAD1 A, Sig=210,4 Ref=off

HPLC (Chiralcel ODH column,
0.1% *iso*-propanol in hexane, 0.5
mL/min, 0.5 mg/mL, 90 min, UV
210 nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.578	MM	0.5653	3.10917e4	916.65179	49.2915
2	42.259	MM	2.5705	3.19855e4	207.38815	50.7085

Totals : 6.30772e4 1124.03995

Data for (1*S*,5*R*,6*S*)-25a:

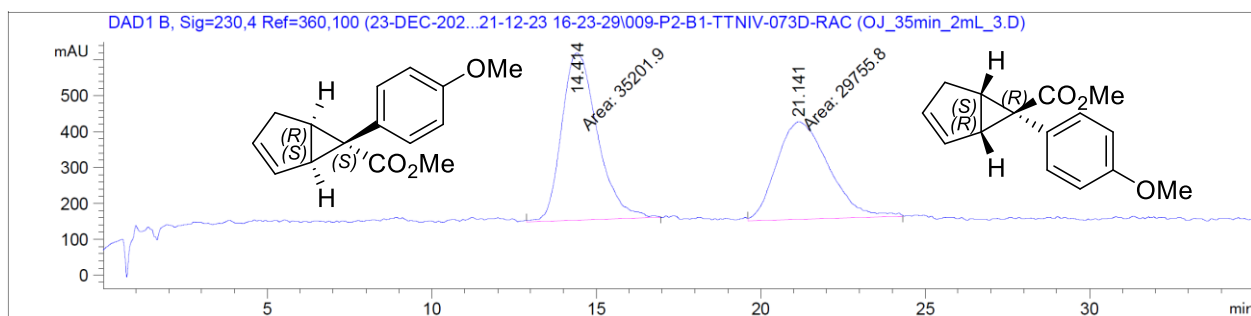


Signal 1: DAD1 A, Sig=210,4 Ref=off

HPLC (Chiralcel ODH column,
0.1% *iso*-propanol in hexane,
0.5 mL/min, 0.5 mg/mL, 90
min, UV 210 nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.433	MF	0.6124	4411.97119	120.07571	5.0115
2	42.056	FM	3.2574	8.36244e4	427.87100	94.9885

Totals : 8.80363e4 547.94671

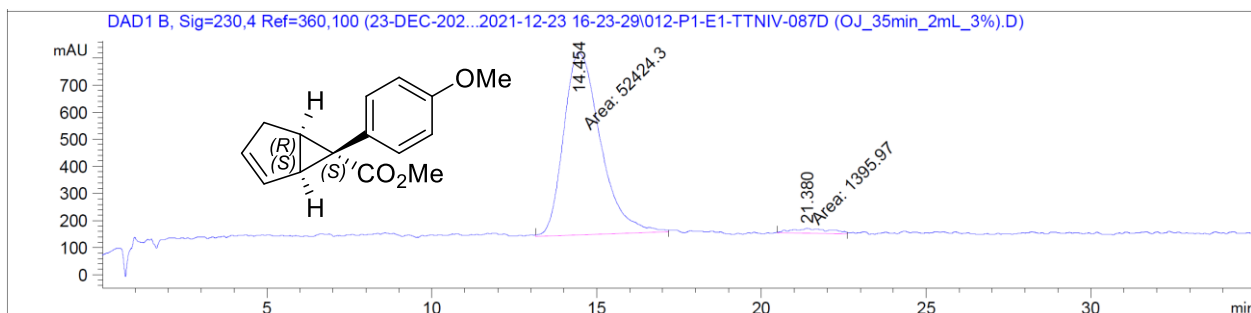
Methyl 6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25k):
Racemic mixture (25k):


Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.414	MM	1.2589	3.52019e4	466.03726	54.1920
2	21.141	MM	1.8253	2.97558e4	271.69766	45.8080

HPLC (Chiralcel OJ column,
3% *iso*-propanol in hexane, 2.0
mL/min, 0.5 mg/mL, 35 min,
UV 230 nm)

Totals : 6.49578e4 737.73492

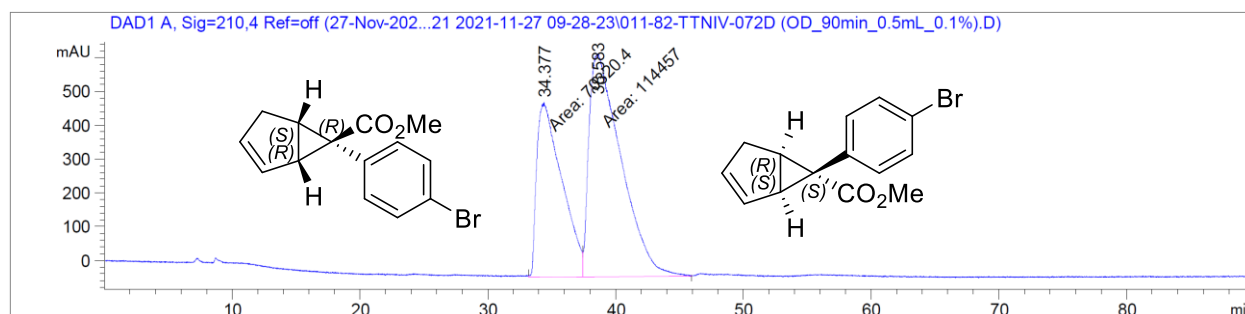
Data for (1*S*,5*R*,6*S*)-25k:


Signal 2: DAD1 B, Sig=230,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.454	MM	1.2918	5.24243e4	676.37341	97.4062
2	21.380	MM	1.3009	1395.97241	17.88470	2.5938

HPLC (Chiralcel OJ column,
3% *iso*-propanol in hexane, 2.0
mL/min, 0.5 mg/mL, 35 min,
UV 230 nm)

Totals : 5.38203e4 694.25811

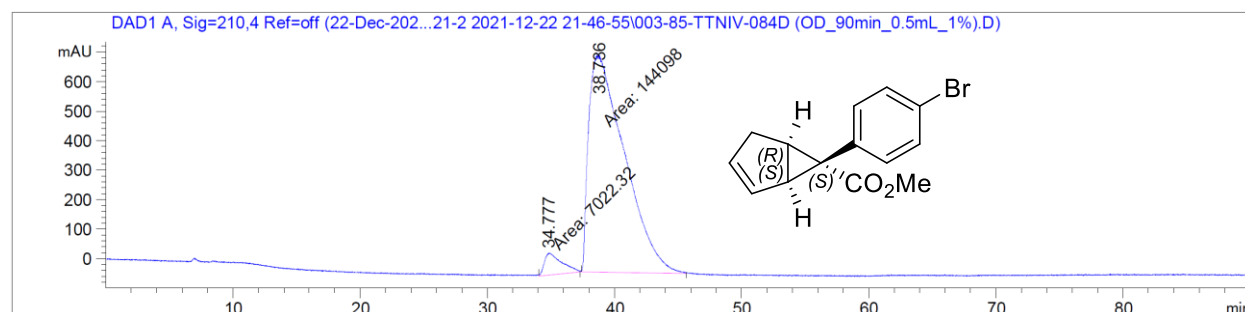
methyl 6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25r):**Data for racemic mixture (25r):**

Signal 1: DAD1 A, Sig=210,4 Ref=off

HPLC (Chiralcel OD column,
0.1% *iso*-propanol in hexane,
0.5 mL/min, 0.5 mg/mL, 90
min, UV 210 nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.377	MF	2.2654	7.03204e4	517.34271	38.0569
2	38.583	FM	2.8849	1.14457e5	661.23212	61.9431

Totals : 1.84777e5 1178.57483

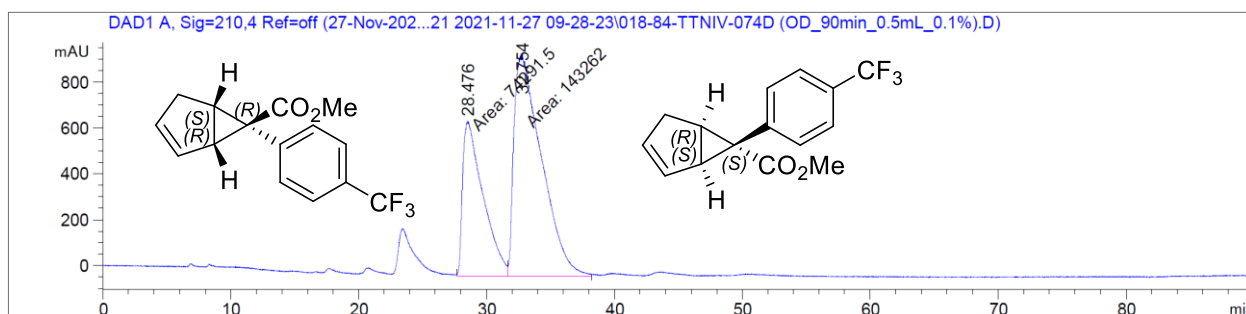
Data for (1S,5R,6S)-25r:

Signal 1: DAD1 A, Sig=210,4 Ref=off

HPLC (Chiralcel OD column,
0.1% *iso*-propanol in hexane,
0.5 mL/min, 0.5 mg/mL, 90
min, UV 210 nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.777	MM	1.5618	7022.31885	74.93700	4.6469
2	38.736	MM	3.2364	1.44098e5	742.06622	95.3531

Totals : 1.51120e5 817.00322

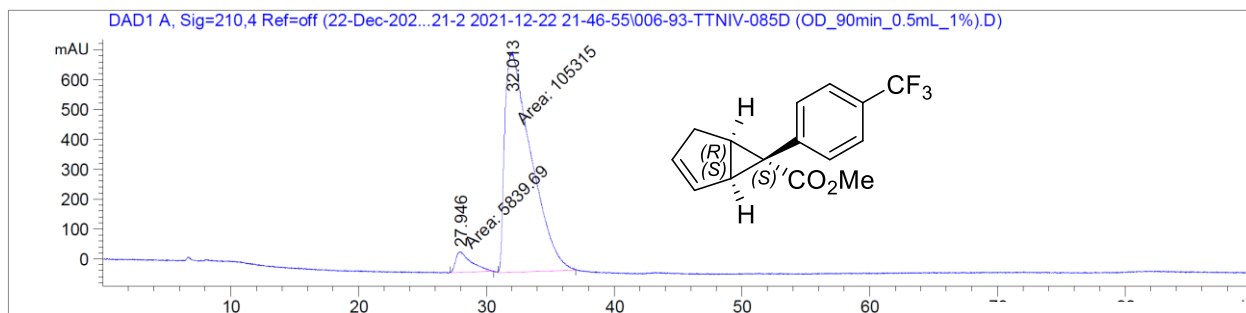
methyl 6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate (25s):
Data for racemic mixture (25s):


Signal 1: DAD1 A, Sig=210,4 Ref=off

 HPLC (Chiralcel OD column,
0.1% iso-propanol in hexane,
0.5 mL/min, 0.5 mg/mL, 90
min, UV 210 nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.476	MF	1.8323	7.42915e4	675.74866	34.1486
2	32.754	FM	2.4610	1.43262e5	970.20782	65.8514

Totals : 2.17553e5 1645.95648

Data for (1S,5R,6S)-25s:


Signal 1: DAD1 A, Sig=210,4 Ref=off

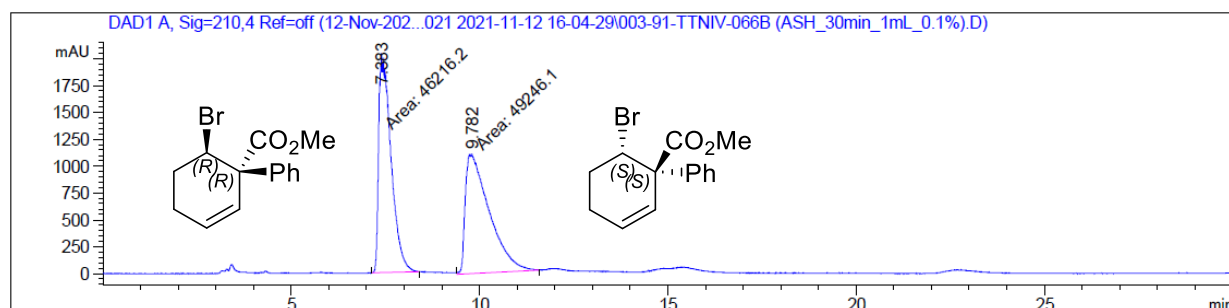
 HPLC (Chiralcel OD column,
0.1% iso-propanol in hexane,
0.5 mL/min, 0.5 mg/mL, 90
min, UV 210 nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.946	MM	1.3863	5839.68750	70.20698	5.2537
2	32.013	MM	2.3671	1.05315e5	741.51666	94.7463

Totals : 1.11154e5 811.72364

Methyl 2-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (122a)

Data for racemic mixture (122a):



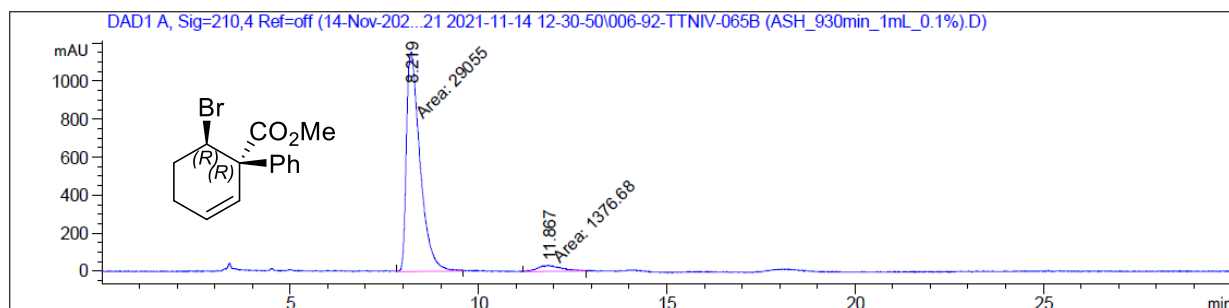
Signal 1: DAD1 A, Sig=210,4 Ref=off

HPLC (AS-H column,
0.1% iso-propanol in
hexane, 1.0 mL/min, 0.5
mg/mL, 30 min, UV 210
nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.383	MM	0.3764	4.62162e4	2046.25476	48.4131
2	9.782	MM	0.7331	4.92461e4	1119.57751	51.5869

Totals : 9.54623e4 3165.83228

Data for (1R,2R)-122a:



Signal 1: DAD1 A, Sig=210,4 Ref=off

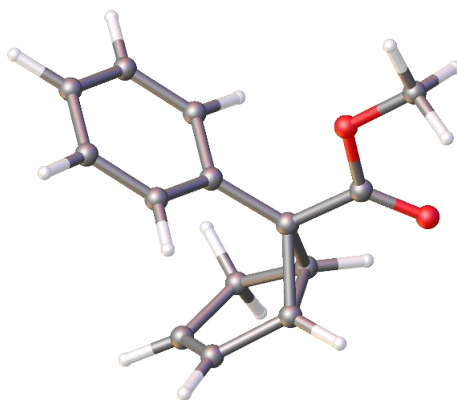
HPLC (AS-H column,
0.1% iso-propanol in
hexane, 1.0 mL/min, 0.5
mg/mL, 30 min, UV 210
nm)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.219	MM	0.4193	2.90550e4	1155.01904	95.4762
2	11.867	MM	0.7537	1376.68164	30.44363	4.5238

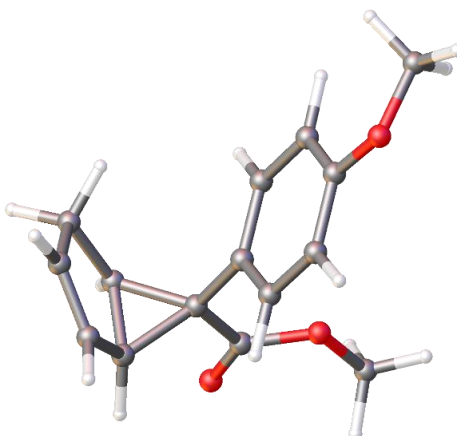
Totals : 3.04317e4 1185.46267

3. X-Ray Structures

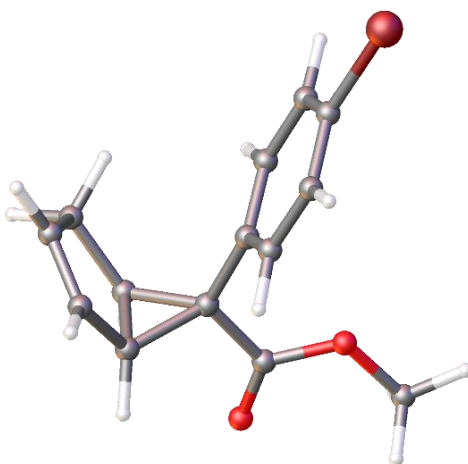
methyl (1*S*,5*R*,6*S*)-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-25a):



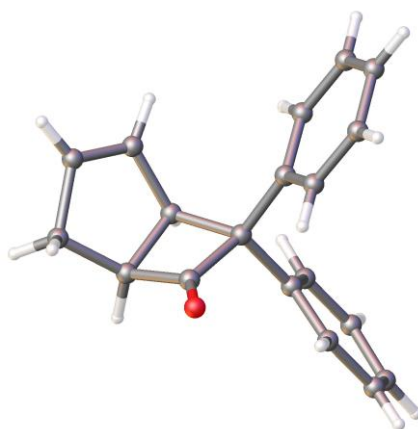
methyl (1*S*,5*R*,6*S*)-6-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-25k):



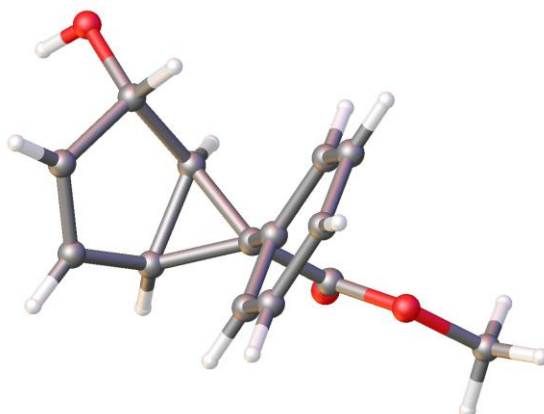
methyl (1*S*,5*R*,6*S*)-6-(4-bromophenyl)bicyclo[3.1.0]hex-2-ene-6-carboxylate ((1*S*,5*R*,6*S*)-25r):



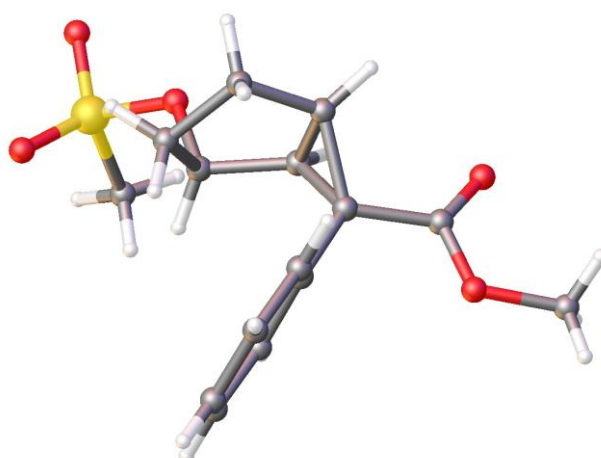
(1R*,5S*)-7,7-diphenylbicyclo[3.2.0]hept-3-en-6-one (40c):



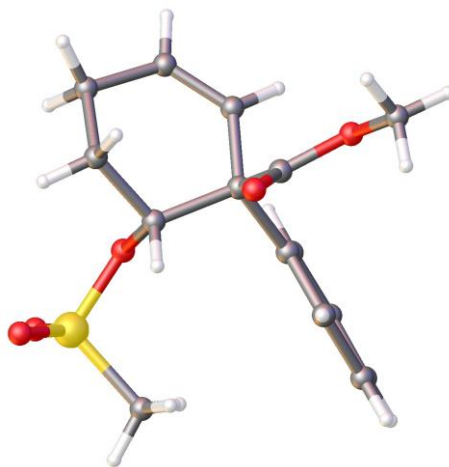
methyl (1S*,4S*,5R*,6R*)-4-hydroxy-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (96a):



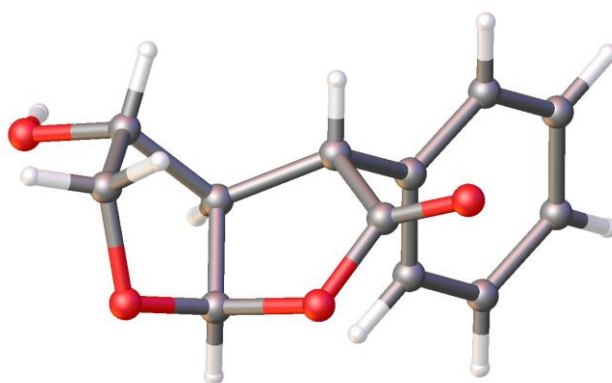
methyl (1R*,2S*,5S*,6R*)-2-((methylsulfonyl)oxy)-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (101a):



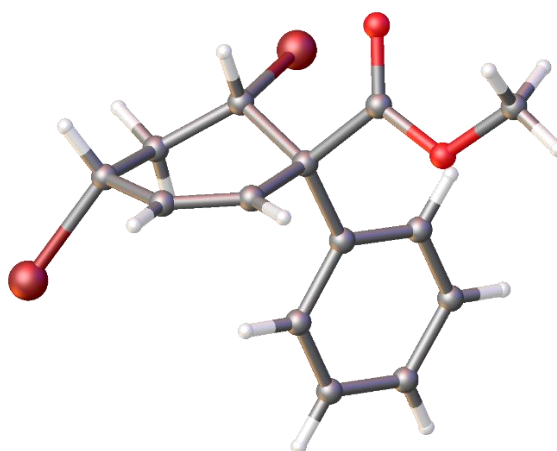
methyl (1R*,2S*)-2-((methylsulfonyl)oxy)-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (108):



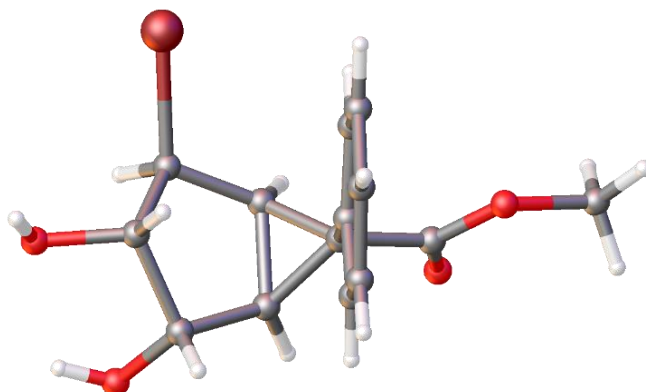
(3R,3aR,4R,6aR)-4-hydroxy-3-phenyltetrahydrofuro[2,3-b]furan-2(3H)-one (80b):



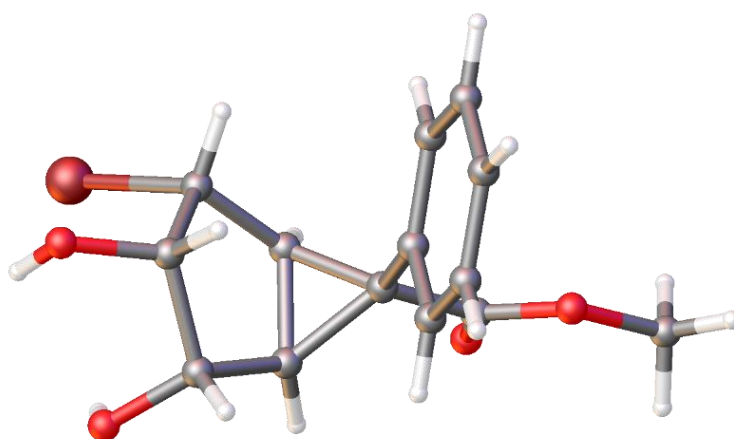
methyl (1S*,2S*,4R*)-2,4-dibromo-3,4-dihydro-[1,1'-biphenyl]-1(2H)-carboxylate (129b):



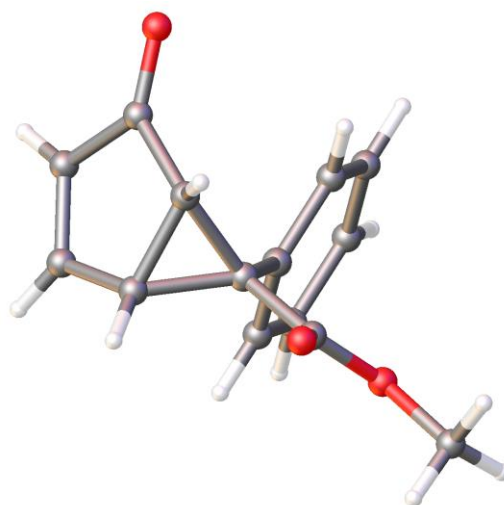
methyl (1R*,2S*,3S*,4S*,5S*,6R*)-2-bromo-3,4-dihydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (141a):



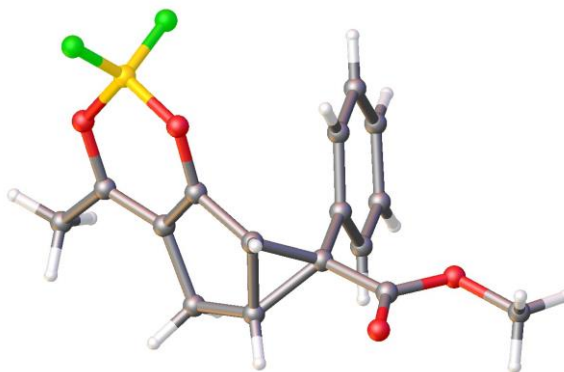
methyl (1R*,2R*,3S*,4S*,5S*,6R*)-2-bromo-3,4-dihydroxy-6-phenylbicyclo[3.1.0]hexane-6-carboxylate (141b):



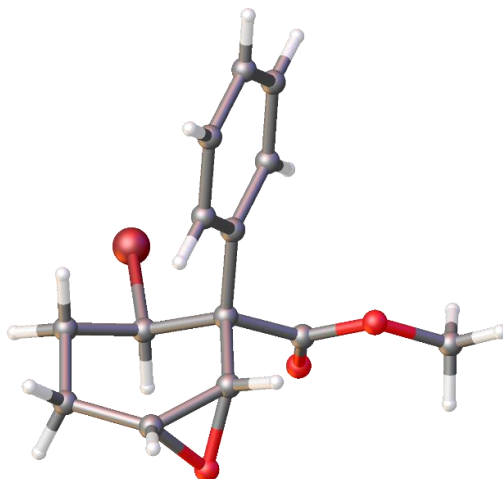
methyl (1S*,5R*,6R)-4-oxo-6-phenylbicyclo[3.1.0]hex-2-ene-6-carboxylate (182a):



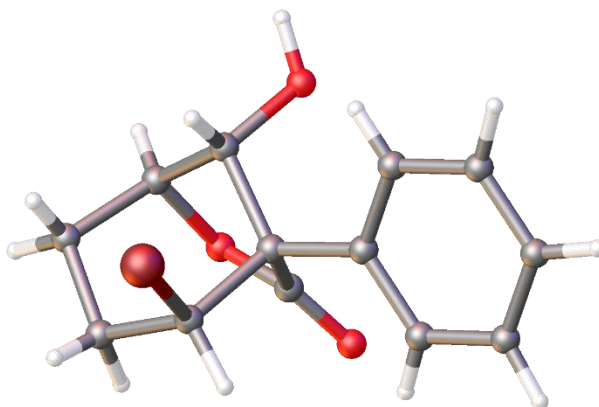
methyl (5a*S,6*R**,6a*R**)-2,2-difluoro-4-methyl-6-phenyl-5,5a,6,6a-tetrahydro-2*H*-1*H*,2*H*-cyclopropa[3,4]cyclopenta[1,2-*e*][1,3,2]dioxaborinine-6-carboxylate (184):**



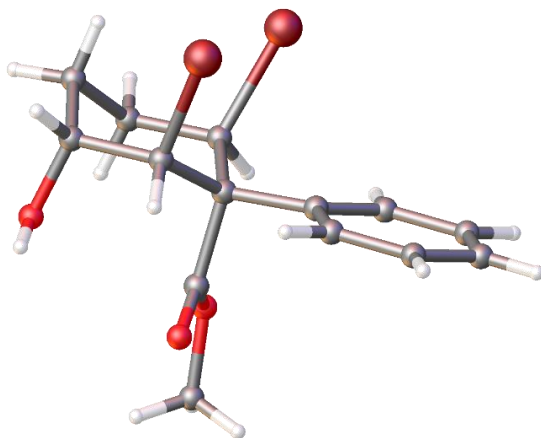
methyl (1*S,2*S**,3*R**,6*R**)-3-bromo-2-phenyl-7-oxabicyclo[4.1.0]heptane-2-carboxylate (295):**



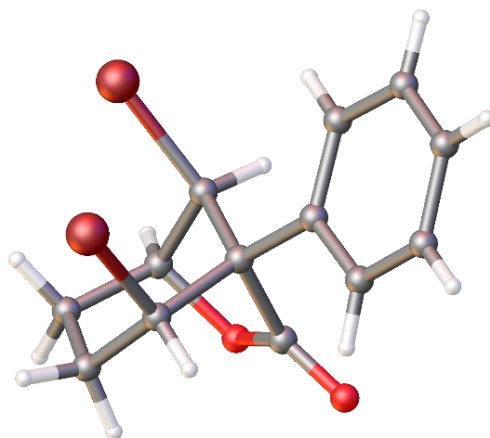
(1*R,2*S**,5*S**,8*R**)-2-bromo-8-hydroxy-1-phenyl-6-oxabicyclo[3.2.1]octan-7-one (298):**



methyl (1S*,2R*,3R*,6R*)-2,6-dibromo-3-hydroxy-1-phenylcyclohexane-1-carboxylate (299a):



(1S*,2R*,8R*)-2,8-dibromo-1-phenyl-6-oxabicyclo[3.2.1]octan-7-one (300):



Compound	(1 <i>S</i> ,5 <i>R</i> ,6 <i>S</i>)-25a	(1 <i>S</i> ,5 <i>R</i> ,6 <i>S</i>)-25k	(1 <i>S</i> ,5 <i>R</i> ,6 <i>S</i>)-25r	40c
CCDC	2250219	2250221	2250223	—
Formula	C ₁₄ H ₁₄ O ₂	C ₁₅ H ₁₆ O ₃	C ₁₄ H ₁₃ BrO ₂	C ₁₉ H ₁₆ O
<i>D</i> _{calc.} / g cm ⁻³	1.286	1.319	1.613	1.245
μ /mm ⁻¹	0.678	0.738	4.532	0.583
Formula Weight	214.266	244.292	293.162	260.338
Colour	colorless	colorless	colorless	clear colourless
Shape	needle-shaped	prism-shaped	block-shaped	plate-shaped
Size/mm ³	0.33×0.17×0.11	0.40×0.26×0.22	0.30×0.14×0.13	0.11×0.08×0.04
<i>T</i> /K	100.00(10)	100.01(12)	99.9(3)	123.00(10)
Crystal System	monoclinic	orthorhombic	orthorhombic	monoclinic
Flack Parameter	0.07(9)	0.10(10)	-0.011(15)	—
Hooft Parameter	0.07(9)	0.10(10)	-0.011(15)	—
Space Group	<i>P</i> 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> /Å	8.3151(1)	8.2714(1)	8.3219(1)	13.8374(4)
<i>b</i> /Å	16.6346(3)	9.2744(2)	9.1851(1)	6.45881(15)
<i>c</i> /Å	15.9965(3)	16.0411(3)	15.7909(1)	15.9077(4)
α /°	90	90	90	90
β /°	90.505(2)	90	90	102.339(3)
γ /°	90	90	90	90
<i>V</i> /Å ³	2212.52(6)	1230.55(4)	1207.02(2)	1388.87(6)
<i>Z</i>	8	4	4	4
<i>Z</i> '	4	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α	Cu K α
θ_{min} /°	2.76	5.51	5.57	3.27
θ_{max} /°	77.26	77.18	77.46	76.11
Measured Refl's.	36263	14262	19105	32874
Independent Refl.	8297	2438	2518	2841
Reflections with <i>I</i> > 2(<i>I</i>)	7755	2360	2458	2210
<i>R</i> _{int}	0.0523	0.0474	0.0503	0.0552
Parameters	1082	308	267	181
Restraints	1065	294	420	0
Largest Peak	0.1314	0.1469	0.2899	0.2346
Deepest Hole	-0.1166	-0.1199	-0.2485	-0.3089
GooF	1.0796	1.1016	1.0707	1.0133
<i>wR</i> ₂ (all data)	0.0543	0.0450	0.0404	0.1547
<i>wR</i> ₂	0.0530	0.0438	0.0393	0.1423
<i>R</i> ₁ (all data)	0.0294	0.0236	0.0190	0.0698
<i>R</i> ₁	0.0263	0.0207	0.0174	0.0552

Compound	96a	101a	108	80b
CCDC	—			
Formula	C ₁₄ H ₁₄ O ₃	C ₁₅ H ₁₈ O ₅ S	C ₁₅ H ₁₈ O ₅ S	C ₁₂ H ₁₂ O ₄
<i>D</i> _{calc.} / g cm ⁻³	1.320	1.382	1.389	1.426
μ /mm ⁻¹	0.753	2.105	2.116	0.898
Formula Weight	230.25	310.35	310.35	220.22
Colour	clear colourless	clear colourless	clear colourless	clear colourless
Shape	block	prism	block	prism
Size/mm ³	0.25×0.17×0.14	0.36×0.34×0.16	0.18×0.16×0.12	0.24×0.20×0.14
<i>T</i> /K	122.97(10)	123.01(10)	123.01(10)	123.01(10)
Crystal System	monoclinic	monoclinic	monoclinic	orthorhombic
Flack Parameter	—			0.10(19)
Hooft Parameter	—			0.21(3)
Space Group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	8.60580(10)	11.8079(3)	8.64930(7)	5.69600(10)
<i>b</i> /Å	8.41250(10)	5.97724(14)	15.02822(14)	10.33310(10)
<i>c</i> /Å	16.1596(3)	21.2272(5)	11.42465(10)	17.4265(2)
α /°	90.00	90	90	90
β /°	97.945(2)	95.233(2)	91.9214(8)	90
γ /°	90.00	90	90	90
<i>V</i> /Å ³	1158.67(3)	1491.94(6)	1484.18(2)	1025.68(2)
<i>Z</i>	4	4	4	4
<i>Z</i> '	1	1	1	1
Wavelength/Å	1.54184	1.54184	1.54184	1.54184
Radiation type	Cu K α	Cu K α	Cu K α	Cu K α
θ_{min} /°	5.53	3.759	4.864	4.976
θ_{max} /°	74.03	72.821	74.083	74.418
Measured Refl's.	12820	13977	19397	21002
Independent Refl.	2310	2930	3007	2074
Reflections with <i>I</i> > 2(<i>I</i>)	2130	2659	2933	2049
<i>R</i> _{int}	0.0296	0.0559	0.0295	0.0228
Parameters	156	193	193	194
Restraints	0	0	0	0
Largest Peak	0.265	0.383	0.381	0.138
Deepest Hole	-0.228	-0.407	-0.425	-0.194
GooF	1.065	1.038	1.041	1.053
<i>wR</i> ₂ (all data)	0.0929	0.0954	0.0721	0.0648
<i>wR</i> ₂	0.0906	0.0920	0.0717	0.0645
<i>R</i> ₁ (all data)	0.0380	0.0386	0.0273	0.0259
<i>R</i> ₁	0.0354	0.0349	0.0269	0.0256

Compound	129b	141a	141b	182a
CCDC				
Formula	C ₁₄ H ₁₄ Br ₂ O ₂	C ₁₄ H ₁₅ BrO ₄	C ₁₄ H ₁₅ BrO ₄	C ₁₄ H ₁₂ O ₃
<i>D</i> _{calc.} / g cm ⁻³	1.784	1.623	1.659	1.325
μ /mm ⁻¹	7.318	4.267	4.363	0.553
Formula Weight	374.07	327.17	327.17	228.24
Colour	clear colourless	clear colourless	clear colourless	clear colourless
Shape	plate-shaped	needle-shaped	prism-shaped	irregular
Size/mm ³	0.09×0.09×0.09	0.25×0.04×0.01	0.10×0.10×0.07	0.46×0.35×0.26
<i>T</i> /K	100.00(10)	123.00(10)	122.99(10)	123.01(10)
Crystal System	monoclinic	orthorhombic	monoclinic	monoclinic
Flack Parameter		0.11(3)		-0.13(8)
Hooft Parameter		-0.016(7)		-0.19(8)
Space Group	<i>P</i> 2 ₁ / <i>n</i>	<i>Pca</i> 2 ₁	<i>P</i> 2 ₁ / <i>c</i>	<i>Cc</i>
<i>a</i> /Å	9.90642(16)	8.49050(10)	6.78896(5)	11.8540(2)
<i>b</i> /Å	7.84454(12)	13.8434(2)	19.31074(11)	11.5374(2)
<i>c</i> /Å	18.5315(3)	22.7846(4)	9.99566(6)	16.8432(2)
α /°	90	90	90	90
β /°	104.7817(16)	90	92.0616(6)	96.7870(10)
γ /°	90	90	90	90
<i>V</i> /Å ³	1392.44(4)	2678.04(7)	1309.581(14)	2287.41(6)
<i>Z</i>	4	8	4	8
<i>Z</i> '	1	2	1	2
Wavelength/Å	1.54184	1.54184	1.54184	1.39222
Radiation type	Cu K α	Cu K α	Cu K α	Cu K
θ_{min} /°	4.646	3.192	4.580	4.775
θ_{max} /°	75.134	73.414	75.190	66.075
Measured Refl's.	27383	26506	5374	14058
Independent Refl.	2833	4837	5374	5168
Reflections with <i>I</i> > 2(<i>I</i>)	2687	4384	4882	5050
<i>R</i> _{int}	0.0397	0.0371	.	0.0252
Parameters	164	350	176	309
Restraints	0	1	0	2
Largest Peak	1.318	1.001	1.023	0.290
Deepest Hole	-0.921	-0.710	-0.858	-0.157
GooF	1.048	1.024	1.067	1.044
<i>wR</i> ₂ (all data)	0.0876	0.1151	0.1290	0.0830
<i>wR</i> ₂	0.0866	0.1114	0.1264	0.0822
<i>R</i> ₁ (all data)	0.0354	0.0473	0.0461	0.0325
<i>R</i> ₁	0.0339	0.0421	0.0434	0.0316

Compound	184	295	298	299a
CCDC				
Formula	C ₁₆ H ₁₅ BF ₂ O ₄	C ₁₄ H ₁₅ BrO ₃	C ₁₃ H ₁₃ BrO ₃	C ₁₄ H ₁₆ Br ₂ O ₃
<i>D</i> _{calc.} / g cm ⁻³	1.472	1.586	1.700	1.820
<i>μ</i> /mm ⁻¹	1.025	4.290	4.785	7.208
Formula Weight	320.09	311.17	297.14	392.09
Colour	clear light yellow	clear colourless	clear colourless	clear colourless
Shape	irregular	prism-shaped	needle-shaped	prism-shaped
Size/mm ³	0.26×0.20×0.15	0.17×0.12×0.05	0.25×0.07×0.05	0.20×0.12×0.09
<i>T</i> /K	123	123.01(10)	122.99(10)	123.01(10)
Crystal System	orthorhombic	monoclinic	trigonal	monoclinic
Flack Parameter	0.34(14)		-0.04(3)	<i>P</i> ₂ /c
Hooft Parameter	0.33(6)		-0.022(10)	7.96580(10)
Space Group	<i>P</i> ₂ ₁ ₂ ₁	<i>P</i> ₂ /c	<i>P</i> ₃ ₂	15.79130(10)
<i>a</i> /Å	7.6004(2)	7.01770(10)	12.48720(10)	11.42700(10)
<i>b</i> /Å	11.4778(2)	7.00160(10)	12.48720(10)	90
<i>c</i> /Å	16.5592(3)	26.5413(3)	6.44900(10)	95.5280(10)
<i>α</i> /°	90	90	90	90
<i>β</i> /°	90	91.7850(10)	90	1430.72(2)
<i>γ</i> /°	90	90	120	4
<i>V</i> /Å ³	1444.56(5)	1303.48(3)	870.869(19)	1
<i>Z</i>	4	4	3	1.54184
<i>Z</i> '	1	1	1	Cu K _α
Wavelength/Å	1.54184	1.54184	1.54184	4.792
Radiation type	Cu K _α	Cu K _α	Cu K _α	74.519
<i>Θ</i> _{min} /°	4.688	3.332	4.088	29617
<i>Θ</i> _{max} /°	72.760	73.259	66.397	2897
Measured Refl's.	8205	13929	15842	2885
Independent Refl.	2799	2546	2034	0.0197
Reflections with <i>I</i> > 2(<i>I</i>)	2647	2439	2007	174
<i>R</i> _{int}	0.0266	0.0210	0.0648	0
Parameters	212	164	206	1.204
Restraints	0	0	1	-0.526
Largest Peak	0.177	0.403	0.852	1.140
Deepest Hole	-0.139	-0.632	-0.744	0.0574
GooF	1.053	1.061	1.104	0.0573
<i>wR</i> ₂ (all data)	0.0649	0.0561	0.0891	0.0225
<i>wR</i> ₂	0.0634	0.0557	0.0884	0.0224
<i>R</i> ₁ (all data)	0.0285	0.0224	0.0352	
<i>R</i> ₁	0.0258	0.0215	0.0348	

Compound	300
CCDC	
Formula	C ₁₃ H ₁₂ Br ₂ O ₂
<i>D</i>_{calc.}/ g cm⁻³	1.897
<i>μ</i>/mm⁻¹	8.055
Formula Weight	360.05
Colour	clear colourless
Shape	prism-shaped
Size/mm³	0.13×0.08×0.05
<i>T</i>/K	123.00(10)
Crystal System	orthorhombic
Flack Parameter	
Hooft Parameter	
Space Group	<i>Pbca</i>
<i>a</i>/Å	10.01520(10)
<i>b</i>/Å	8.66780(10)
<i>c</i>/Å	29.0425(3)
<i>α</i>°	90
<i>β</i>°	90
<i>γ</i>°	90
<i>V</i>/Å³	2521.17(5)
<i>Z</i>	8
<i>Z</i>'	1
Wavelength/Å	1.54184
Radiation type	Cu K _α
<i>θ</i>_{min}/°	3.043
<i>θ</i>_{max}/°	75.156
Measured Refl's.	24670
Independent Refl.	2596
Reflections with <i>I</i> > 2(<i>I</i>)	2367
<i>R</i>_{int}	0.0395
Parameters	174
Restraints	14
Largest Peak	1.002
Deepest Hole	-0.684
GooF	1.063
<i>wR</i>₂ (all data)	0.0852
<i>wR</i>₂	0.0832
<i>R</i>₁ (all data)	0.0378
<i>R</i>₁	0.0342

4. Curriculum Vitae

PERSONAL DATA

Name:	Sebastian Fischer
Date of birth:	30.04.1996
Place of birth:	Prien am Chiemsee
Nationality:	German
Marital status:	not married

Education

Since 09/2023	Engineer for exhaust air purification for semiconductor processes - <i>Infineon</i>
Since 01/2020	PhD , Institute of Organic Chemistry, University of Regensburg, Prof. Dr. Oliver Reiser. “ <i>Endocyclic Ring-opening of Fused Carbocyclic Cyclopropanes</i> ”.
01/2019 – 09/2019	Master Thesis , University of Regensburg “ <i>Studies towards the synthesis of functionalized six-membered carbocycles via Heck arylation reaction starting from monocyclopropanated cyclopentadiene</i> ”. Institute of Organic Chemistry, Prof. Dr. Oliver Reiser.
11/2017-11/2019	Research-Assistant , University of Regensburg, Center of Analytics, Department of Mass Spectrometry, Prof. Dr. Matysik.
10/2017 – 09/2019	Studies in Chemistry (M. Sc.) , University of Regensburg.
05/2017 – 07/2017	Bachelor Thesis , University of Regensburg “ <i>Studien zur Synthese von Dermatolacton</i> ”, Institute of Organic Chemistry, Prof. Dr. Oliver Reiser.
10/2014 – 09/2017	Studies in Chemistry (B. Sc.) , University of Regensburg.
09/2006 – 07/2014	Abitur (A-levels) , Ludwig-Thoma-Gymnasium, Prien am Chiemsee.

Conferences & Presentations

08 – 09/2022	8th EuChemS Chemistry Congress , Lisbon, Portugal
09/2006 – 07/2014	23rd Christmas Colloquium , University of Regensburg

List of Publications

- **Fischer, S.**; Nguyen, T.-T. H.; Ratzenboeck, A.; Davies, H. M. L.; Reiser, O. *Stereoselective Synthesis of Highly Functionalized Cyclohexenes via Strong-Acid-Mediated Endocyclic C–C Bond Cleavage of Monocyclopropanated Cyclopentadienes*, *Org. Lett.* **2023**, 25, 24, 4411–4415.
- Eckl, R.; **Fischer, S.**; Sonnleitner, C. M.; Schmidhuber, D.; Rehbein, J.; Reiser, O. *Stereoselective Synthesis of Biologically Relevant Tetrahydropyridines and Dihydro-2H-pyrans via Ring-expansion of Monocyclopropanated Heterocycles*, *ACS Org. Inorg. Au* **2022**, 2, 169–174.
- Wurzer, N.; Klimczak, U.; Babl, T.; Fischer, S.; Angnes, R. A.; Kreutzer, D.; Pattanaik, A.; Rehbein, J.; Reiser, O. *Heck-Type Coupling of Fused Bicyclic Vinylcyclopropanes: Synthesis of 1,2-Dihydropyridines, 2,3-Dihydro-1H-azepines, 1,4-Cyclohexadienes, and 2H-Pyrans*, *ACS Catal.* **2021**, 11, 12019–12028.

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H. Declaration

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

Regensburg, March 2024

Sebastian Fischer