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Synthesis of Functionalized Tetrahydropyridine Derivatives via SnCl4-Promoted [4+2] Cycloaddition of Donor-Acceptor Cyclobutanes and Nitriles

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Abstract

The formation of carbon-heteroatom bonds is pivotal in obtaining structural frameworks present in a variety of important natural products and bioactive molecules. In that regard, Lewis-acid promoted cycloadditions of strained carbocycles have proven to be powerful tools for the construction of heterocyclic frameworks. The Pagenkopf group was the first to discover the cycloaddition of donor-acceptor (DA) cyclopropanes with nitriles. Since the strain energy of cyclobutane is comparable to that of cyclopropane, our group has sought to extend to the comparatively unexplored homologous cyclobutane scaffold. Disclosed here is the first [4+2] cycloaddition of nitriles with DA cyclobutanes *via* Lewis-acid activation. This work describes the synthesis of tetrahydropyridine derivatives in moderate to good yields. A variety of electronically diverse cyclobutanes engaged in [4+2] cycloaddition with both aliphatic and aromatic nitriles. Reduction of the cycloadduct affords substituted piperidine exclusively as the *cis*-2,6-diastereomer in excellent yield, and the cycloadduct also undergoes clean dealkoxycarbonylation.

Summary for Lay Audience

The formation of chemical bonds is pivotal in obtaining key structural frameworks present in a variety of important natural products and bioactive molecules. Strain-activated carbon ring systems have proven to be powerful building blocks in the field of synthetic organic chemistry. These compounds are strain-activated because they possess chemical bond angles that deviate from the favorable 109.5° tetrahedron bond angle. In this thesis, we use small strain-activated carbocycles that are endowed with chemical groups, that is, donor and acceptor groups, to further enhance their chemical reactivity. The donor and acceptor groups are attached adjacent to one another, and they hence facilitate bond cleavage between them to give a ring opened intermediate. This ring-opened form can subsequently go through a plethora of interesting reactions. These small strained-activated molecules have received rising research interest because of their ability to easily react with various partners to give new compounds or structural frameworks not easily synthesized. The current work investigated new compounds obtained from the reaction of these strain-activated carbocycles. The chemistry disclosed herein is a flexible method for the synthesis of valuable nitrogen-containing structures, such as tetrahydropyridines. Mechanistic insights are provided, and the synthetic potential of products was demonstrated. We expect that this chemistry can prove to be a useful tool in applications such as target-oriented synthesis of natural products and pharmaceutically important molecules.

This thesis is dedicated to the only person that gave me the confidence to pursue chemistry, who continues to be my source of inspiration.

Acknowledgments

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List of Schemes

List of Abbreviations

A	electron-acceptor
Å	Angstrom
AACD	alkoxy-activated cyclobutane-1,1-dicarboxylate
Ac	acetyl
anhyd	anhydrous
app	apparent
aq	aqueous
Ar	aryl
Bn	benzyl
br	broad
Bu	butyl
bp	boiling point
Calcd	calculated
CAM	cerium ammonium molybdate
cat.	catalytic
D	electron-donor
d	doublet
DA	donor-acceptor
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets

DCE	1,2-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
dq	doublet of quartets
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
E^+	electrophile
Et	ethyl
eq	equation
equiv.	equivalent
g	gram (s)
h	hour (s)
HMBC	heteronuclear multiple-bond correlation spectroscopy
HRMS	high-resolution mass spectrometry
Hz	hertz
Imid	imidazole
*i*Pr	isopropyl
J	coupling constant
m	multiplet
MAD	methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)
mbar	millibar
Me	methyl

mg	milligram (s)
MHz	megahertz
min	minute (s)
mL	milliliter (s)
mol	mole (s)
MS	molecular sieves
Ms	methanesulfonyl
ms	millisecond (s)
m/z	mass to charge ratio
*n*Bu	*n*-butyl
Nu^-	nucleophile
NMR	nuclear magnetic resonance
NTf_2	*N,N-bis*(trifluoromethylsulfonyl)imide
nOe	nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect Spectroscopy
OTf	trifluoromethanesulfonate
Ph	phenyl
PMP	para-methoxyphenyl
ppm	parts per million
q	quartet
qd	quartet of doublets
quin	quintet
rac	racemic

RBF	round bottom flask
RM	reaction mixture
R_f	retention factor
rt	room temperature
s	singlet
Satd	saturated
t	triplet
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
*t*Bu	tert-butyl
td	triplet of doublets
temp	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TFA	trifluoroacetic acid
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
tt	triplet of triplets
μM	micromolar
μw	microwave irradiation

Chapter 1. The Chemistry of Cyclopropanes and Cyclobutanes

This chapter discusses the structural characteristics and reactivity of small strain-activated carbocycles. Their presence in natural products and in important synthetic molecules will be illustrated. The works on DA cyclopropanes will be mentioned. The preceding reports and the seminal works in DA cyclobutane cycloaddition chemistry will be discussed. Additionally, the reactions of DA cyclobutanes and the reactions of our alkoxy-activated DA cyclobutanes will be reviewed.

1.1 Introduction

1.1.1 Introduction to Cyclopropanes and Cyclobutanes

In the field of synthetic organic chemistry, there are several useful building blocks for achieving specific molecular frameworks or compounds. Small ring systems have established prominence in synthetic chemistry due to their ability to construct highly functionalized molecules. Three- and four-membered rings (cyclopropanes and cyclobutanes) are small rings that have significant angle strain resulting from the distortion of the sp^3 hybridized carbon bond, normally having a favorable tetrahedral bond angle of 109.5°. As a result of bond angle distortion, the chemical reactivity of such compounds is often enhanced, leading to ring cleavage products. In contrast, cyclopentanes and cyclohexanes have substantially less angle strain and do not undergo the same type of transformations of their more strained counterparts.

1.1.2 Small Carbocycles in Natural Products and Important Synthetic Molecules

Although cyclopropanes and cyclobutanes are the most strained carbocycles, they still occur in complex natural products including steroids, terpenoids, and alkaloids.[1] Naturally occurring or synthesized cyclopropanes and/or cyclobutanes with simple functionalities are endowed with a broad spectrum of biological properties.[2] Even the introduction of a cyclopropane and/or a cyclobutane moiety has demonstrated an improved overall biological potency, including antibiotic, antiviral, antitumor, and neurochemical activities.

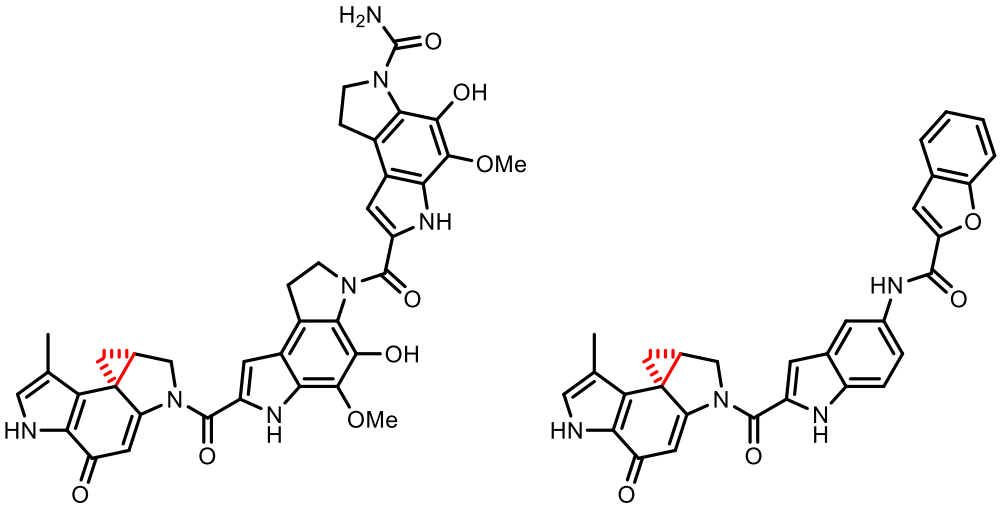


Figure 1: Cyclopropane antibiotic CC 1065 and its synthetic analog, adozelesin.

CC 1065 is a highly potent antibiotic isolated from *Streptomyces zelensis* that contains a reactive cyclopropane ring (Figure 1). This structural moiety is responsible for cleaving DNA by readily reacting with amino acids, nucleosides, and nucleotides under physiological conditions.[3] Thus, covalent adducts are formed with DNA to break DNA strands. The synthetic analog, adozelesin, is also a potent antitumor agent. Compounds containing cyclopropyl units were also shown to alkylate the N-3 atom of adenine in DNA.[4]

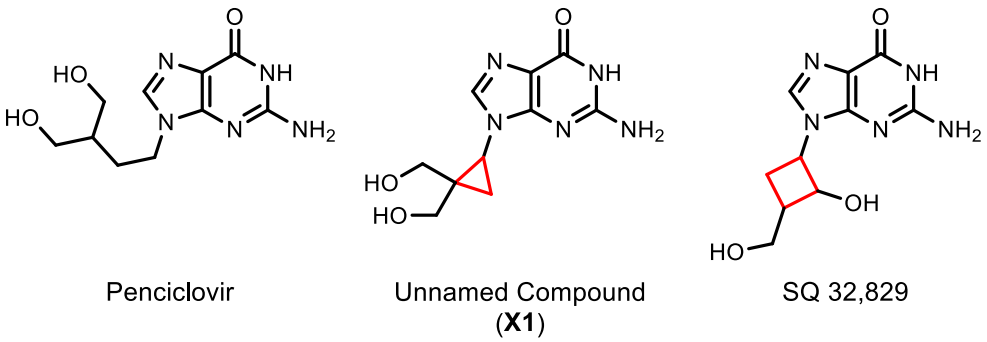
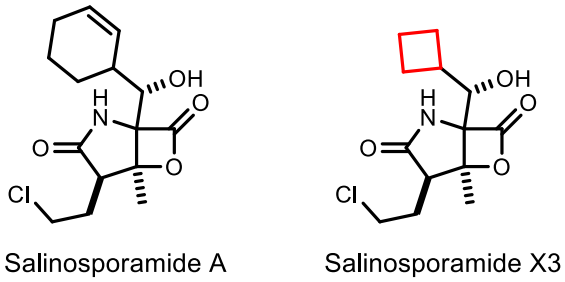


Figure 2: Synthetic antiviral agents containing cyclopropyl and cyclobutyl groups.

Synthetically modified nucleosides have been known to inhibit the replication of viruses. Penciclovir had emerged as a potent and selective anti-herpes virus agent.[5] The cyclopropyl analog

was synthesized with the expectation of improved anti-retroviral activity, but it was devoid of any activity (X1). Interestingly, the cyclobutyl analog, SQ 32,829, exhibited potent antiviral activity and thus received considerable attention (Figure 2).[6]



Salinosporamide A Salinosporamide X3

Figure 3: Anticancer natural product salinosporamide A and its synthetic analog, salinosporamide. X3.

Salinosporamide A is a natural proteasome inhibitor isolated from the marine bacteria, *Salinispora tropica* and *Salinispora arenicola*. It is currently in phase III clinical trials being studied as a potential anticancer agent (Marizomib).[7] The synthetic analog, salinosporamide X3, is a promising drug candidate for the treatment of multiple myeloma and mantle cell lymphoma (Figure 3).[8]

There is a rare class of structurally unique natural products that incorporates both cyclopropane and cyclobutane units (Figure 4). A small sesquiterpenoid (X2) isolated from the Formosan Soft Coral *Clavularia inflata var. luzoniana* represents the first example of natural products distinguished by a tightly fused skeleton between a cyclopropane and a cyclobutane.[9] In 2015, a new class of immunosuppressive agents also featuring an unprecedented carbon skeleton was isolated from *Phyllanthus hainanensis*. Amongst others in the family, phainanoid A exhibits exceptionally potent immunosuppressive activities.[10]

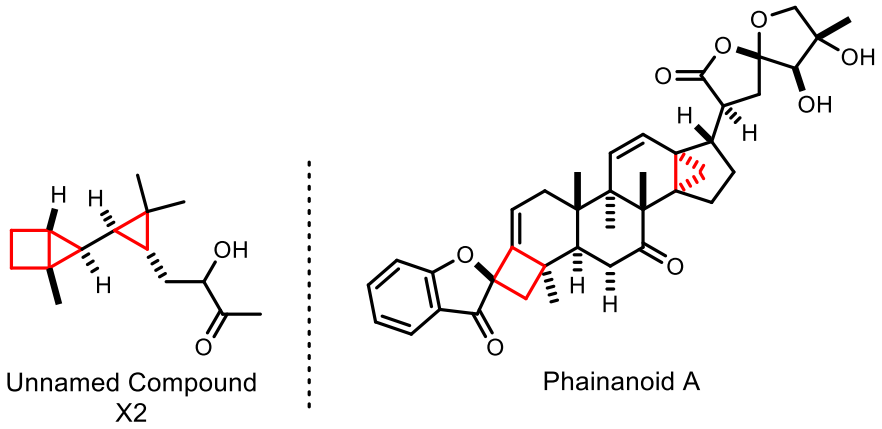


Figure 4: The structures of natural products with both cyclopropane and cyclobutane moieties.

1.2 The Chemistry of Cyclopropanes and Cyclobutanes

1.2.1 Structural Characteristics of Cyclopropanes and Cyclobutanes

The exploitation of strained ring systems as key building blocks for the construction of highly functionalized molecules has gained appreciable attention in organic synthesis.[11] The reactivity of cyclopropanes and cyclobutanes can be attributed to their bond angle and torsional strain. The strain of these ring systems is characterized by three types of individual strain: 1) transannular strain, that is, van der Waals interactions between atoms across the ring,[12] 2) torsional strain due to eclipsing conformations between neighboring atoms, and 3) angle strain owing to distorted bond angles from the ideal.[13] Because the strain energy of cyclobutane (26.3 kcal/mol) is comparable to that of cyclopropane (27.5 kcal/mol), it is plausible to expect similar reactivity profiles from them (Figure 5a).[14]

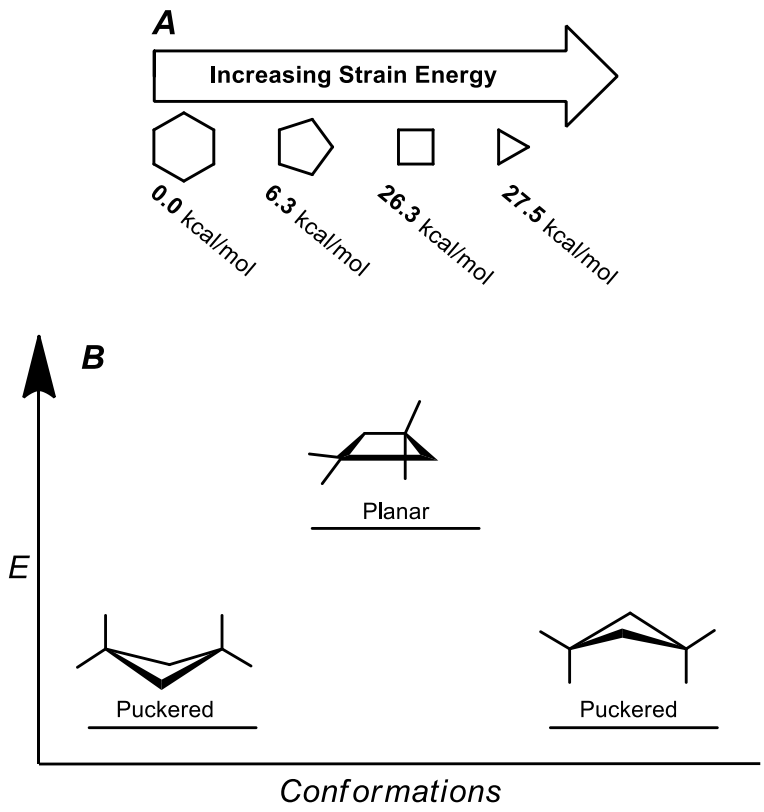


Figure 5: a) Ring strain energies of carbocycles, b) conformational distortions of cyclobutanes.

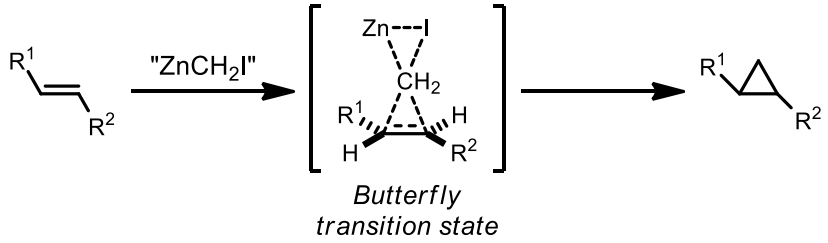
The ideal bond angle of 109.5° is distorted to 60° for cyclopropanes and cyclopropanes exist as a planar equatorial triangle. The cyclobutane ring system has bond angles that are less drastically smaller and less distorted from the stable 109.5° bond angle of the tetrahedral geometry. Cyclobutane adopts a puckered conformation with a C–C–C bond angle of 88°. This puckered conformation decreases torsional strain, but it also results in a smaller C–C–C bond angle, which in turn increases the angle strain. Nonetheless, this conformation is more favorable than the constrained planar cyclobutane, which has a bond angle of 90°. Cyclobutanes have bond angles of 88° because the planar cyclobutane would have the methylene groups in an eclipsed position, which results in highly unfavorable torsional strain, as indicated by the x-axis representing the strain energy (*E*) of the depicted conformation (Figure 5b). Sterics is not always an influential factor in torsional strain as demonstrated by an unsubstituted cyclobutane for example as the hydrogens play no steric role in torsional strain. All torsional strain includes a stereoelectronic component called hyperconjugation.[15] Staggered conformations are stabilized because a filled sigma bonding orbital donates into an unfilled antibonding orbital. However, eclipsed conformations lose this stabilization which results in torsional strain. As a result, these highly strained molecules are more easily cleaved compared with larger ring systems because cyclopropanes and cyclobutanes have significantly larger strain energy.

1.2.2 Classical Preparations of Cyclopropanes—Cyclopropanation

Cyclopropanes have played an important role as a versatile functional handle in synthetic chemistry. Since the first synthesis of the cyclopropane ring by August Freund in 1882,[16] much attention has been given to the cyclopropane subunit and many methods for the synthesis of cyclopropanes have been developed.

1.2.2.1 Simmons–Smith Reaction

The classical cyclopropanation reaction reported by Simmons and Smith treats simple alkenes with a mixture of methylene iodide and zinc–copper couple to give cyclopropanes.[17] Later, Furukawa developed a faster and stereospecific modification of the Simmons–Smith reaction by replacing the zinc–copper couple with diethyl zinc, Et_2Zn.[18] In the presence of allylic alcohols/ethers, the organozinc species stereoselectively adds to the double bond on the *syn* face of the alcohol group, due to the chelating effect of the oxygen atom to the organozinc reagent.[19] Interestingly, excess carbenoid can reverse the directing effect of alcohols.[20] The reaction is proposed to proceed through a "butterfly-type" transition state that delivers a methylene group from $IZnCH_2I$ to the double bond (Scheme 1).

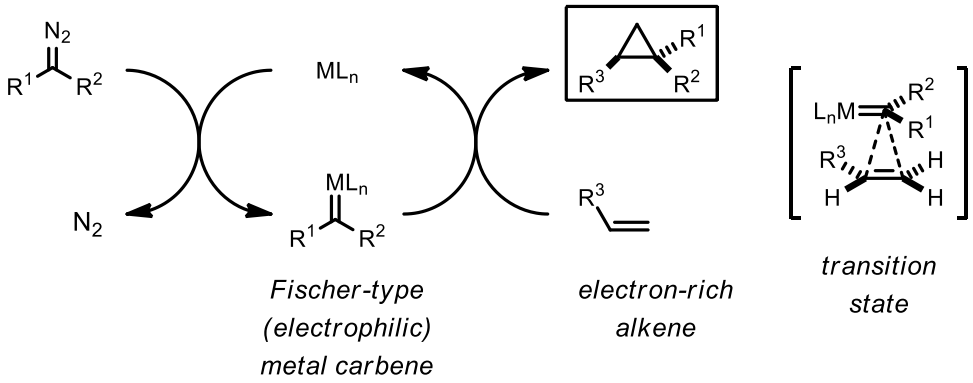


Scheme 1: Proposed scheme of Simmons–Smith cyclopropanation *via* a "butterfly" transition state.

1.2.2.2 Diazo Compounds

The lack of functionalities on cyclopropanes prepared through the Simmons–Smith constrains subsequent synthetic manipulations. Transition metal catalyzed cyclopropanation with α-diazoester can be adopted to retain functional handles on the resulting cyclopropane. The reaction involves the cyclopropanation of election-rich alkenes *via* carbenoids formed from electron-deficient diazo compounds.[21] The products formed from diazoesters include activated acceptor cyclopropanes and donor-acceptor cyclopropanes, the latter of which will be discussed

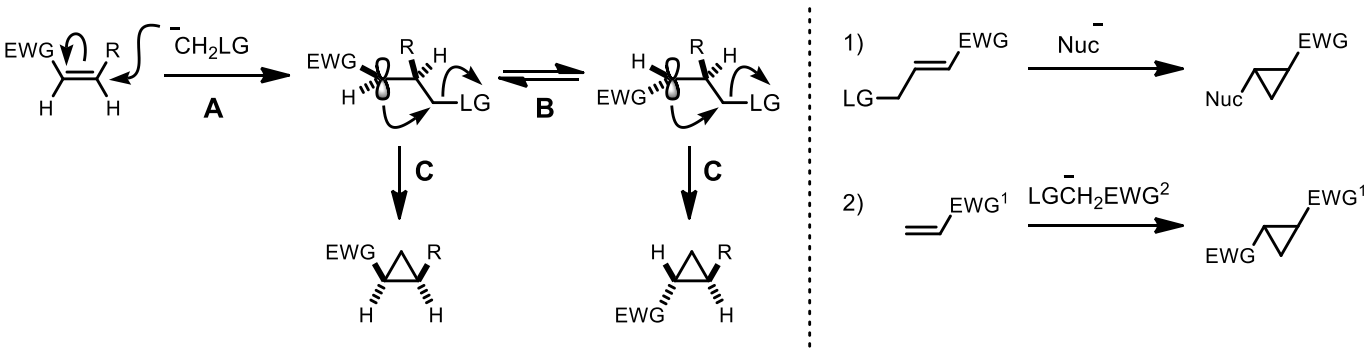
later in this thesis. The ester group provides an advantageous functional handle suitable for additional synthetic modifications. The catalytic cycle proceeds through a Fischer-type (electrophilic) metal carbene formed from diazo species (Scheme 2). The reactions are catalyzed typically by dirhodium tetraacetate, or by some more remarkable chiral derivatives.[22]



Scheme 2: Cyclopropanation using metal carbenes.

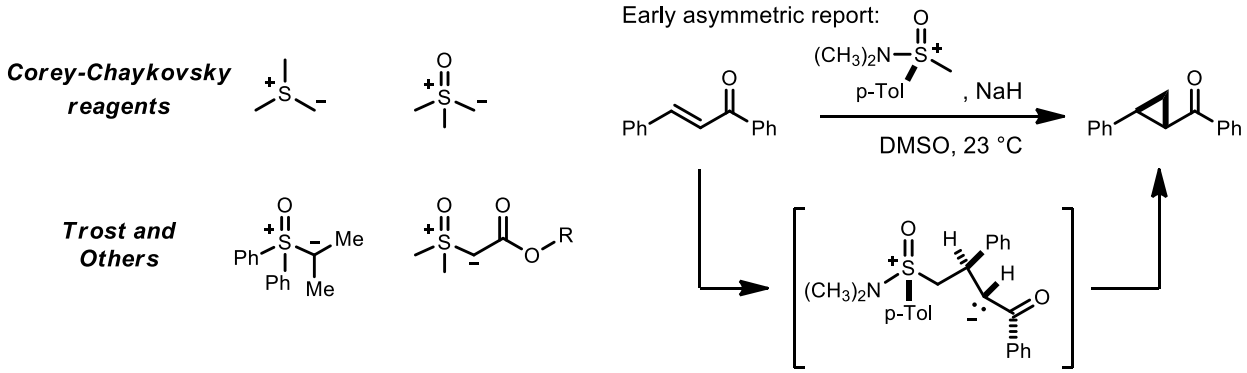
1.2.2.3 Michael-Initiated Ring Closure

Another strategy for generating cyclopropanes is through Michael-initiated ring closure (MIRC) reactions.[23] MIRC reactions involve a conjugate addition to an electrophilic alkene to produce an enolate that subsequently undergoes an intramolecular ring closure.[21] These reactions also can be stereoselective when the ring closure (**C**) occurs faster than the rotation about the single bond in the first intermediate (**B**) (Scheme 3a). Alternatively, generation of a configurationally stable tetrahedral intermediate after the first addition may also give a stereospecific product. The process of MIRC can originate from the reaction between two types of substrates/reactants. The formation of cyclopropanes involves: 1) the nucleophilic addition to electrophilic substrates containing a leaving group or 2) the addition of a nucleophile bearing a leaving group to electrophilic substrates (Scheme 3b).



Scheme 3: a) Stereospecific MIRC reaction and b) types of substrates and reagents for MIRC reactions.

The most effective reagents for methylene transfer are heteroatom-derived ylides. The synthetic potential of such reaction was realized by Corey when he reported the use of sulfur ylides, methylenedimethylsulfoxonium reagents, for cyclopropanations in the 1960s.[24] Later, an optically enriched oxosulfonium was developed by Johnson to stereoselectively cyclopropanate chalcones (Scheme 4).[25]



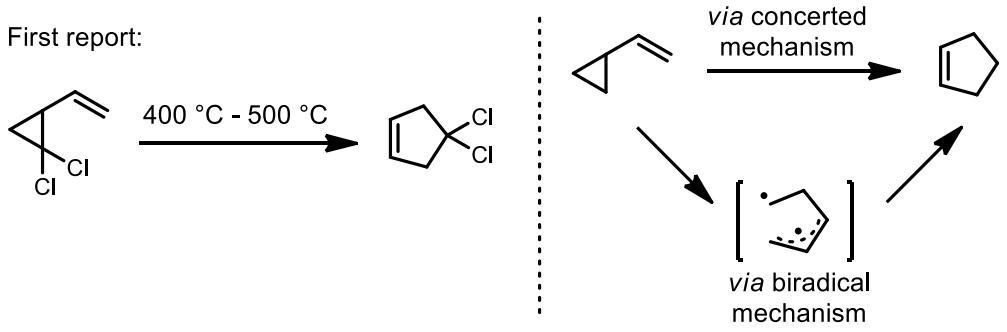
Scheme 4: Sulfur ylide reagents and the first asymmetric cyclopropanation through chiral ylides.

1.2.3 Reactions with Cyclopropanes

Cyclopropane derivatives can undergo various transformations under the influence of diverse chemical reagents, including electrophiles, nucleophiles, radicals, and/or physical forces such as heat and light. The cyclopropane ring has reactivity that resembles the C=C carbon double bond. As a result, the unique reactivity and properties of cyclopropanes has been exploited as a versatile tool in organic synthesis.

1.2.3.1 Vinylcyclopropane Rearrangements

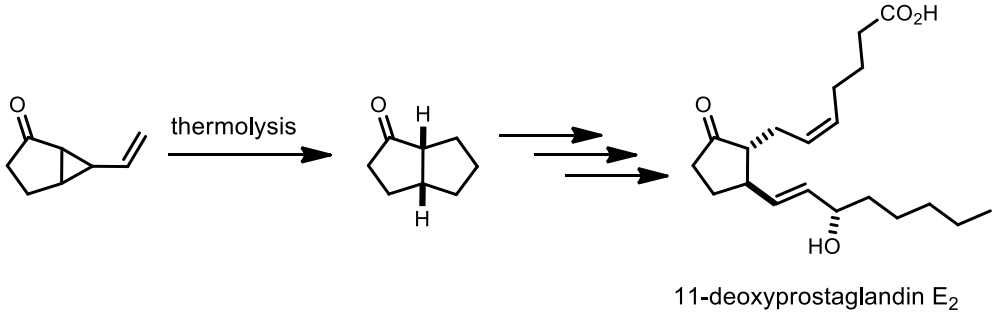
Implementation of an adjacent π-system can greatly alter the chemical properties of cyclopropanes. Vinylcyclopropanes undergo a unimolecular rearrangement into cyclopentene rings upon heating. In 1959, Neureiter reported the first thermo vinylcyclopropane–cyclopentene rearrangement (Scheme 5).[26] The ring expansion event has been suggested to have either an orbital symmetry-controlled pericyclic mechanism and/or a diradical two-step mechanism.



Scheme 5: Mechanism of vinylcyclopropane–cyclopentene rearrangement.

The vinylcyclopropane–cyclopentene rearrangement has been very useful because vinylcyclopropanes are readily available and the resulting cyclopentene products are abundant in natural products. In 1975, Corey employed vinylcyclopropanes in the total synthesis of 11-deoxyprostaglandin E_2 (Scheme 6).[27] The key bicyclic cyclopentane intermediate was formed from

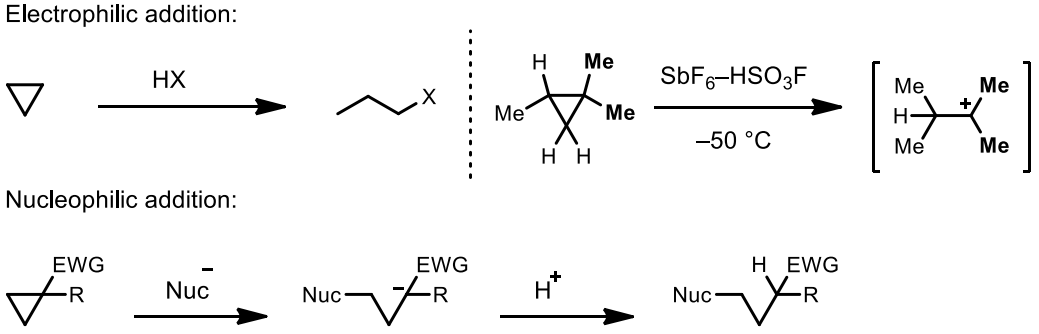
the thermolysis of vinylcyclopropane. The rearrangement and its heteroatom variants have flourished and continue to see usage in natural product synthesis to this day.[28]



Scheme 6: Total synthesis of 11-deoxyprostaglandin E2 via vinylcyclopropane rearrangement.

1.2.3.2 Electrophilic/Nucleophilic Additions

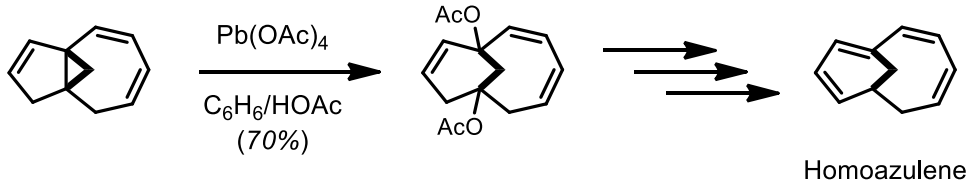
Since the cyclopropane ring behaves like a C=C double bond, treatment with an appropriate electrophile would result in the addition of the electrophile with simultaneous fission of the ring. Electrophilic addition typically follows Markovnikov's rule for substituted cyclopropanes, *i.e.*, the electrophile (H^+) adds to the carbon to generate the more stable carbocation. For example, the addition of SbF_6–HSO_3F to 1,1,2-trimethylcyclopropane gave the 2,3-dimethyl-2-butyl cation (Scheme 7). Conversely, nucleophilic cleavage of cyclopropane is only viable when the cyclopropane is bearing an electron-withdrawing substituent, which resembles the classical Michael addition.[29]



Scheme 7: Electrophilic addition and nucleophilic addition of cyclopropanes.

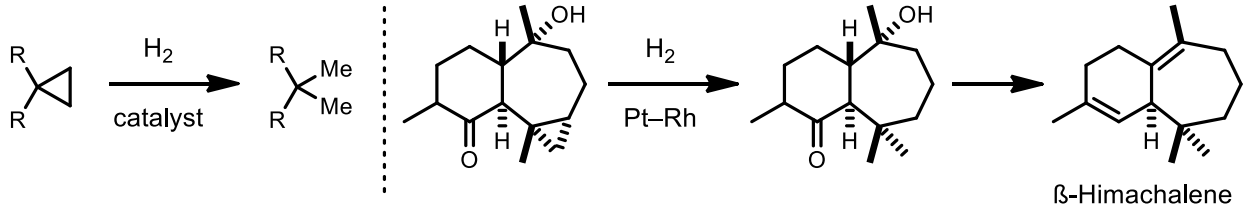
1.2.3.3 Oxidative/Reductive Ring Fissions

There are simple two methods for the cleavage of cyclopropane: 1) oxidative fission and 2) reductive fission. Both methods involve the breakage of a C–C bond of the cyclopropane, followed by the formation of two bonds of higher oxidation state for the former and lower oxidation state for the latter. Oxidative cleavage is influenced by steric and electronic effects of substitution on the ring. The properties of the oxidizing agents can also facilitate regio- and stereoselective opening of the cyclopropane. For example, Scott reported the oxidation of the cyclopropane in [5.3.1]propellane with lead tetraacetate to give the corresponding diacetate (Scheme 8).[30]



Scheme 8: Oxidative cleavage of cyclopropane.

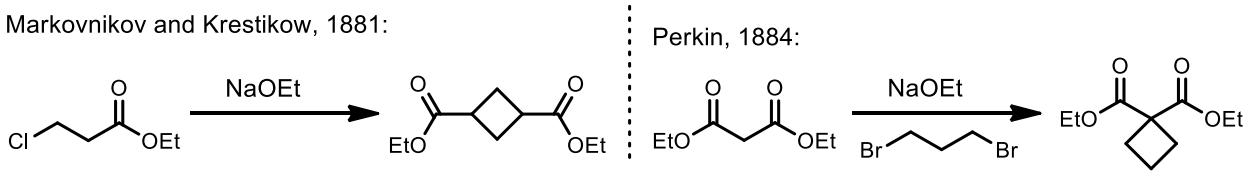
Reductive cleavage of cyclopropanes occurs at the least substituted bond *via* catalytic hydrogenation for the general synthesis of *gem*-dimethyl groups. For example, in a key step to synthesize β-himachalene, Pt–Rh catalyzed hydrogenation of the cyclopropane in the tricyclic molecule affords the *gem*-dimethyl groups (Scheme 9).[31]



Scheme 9: Reductive ring fission of cyclopropane via hydrogenation.

1.2.4 Synthetic Methods for the Construction of Cyclobutanes

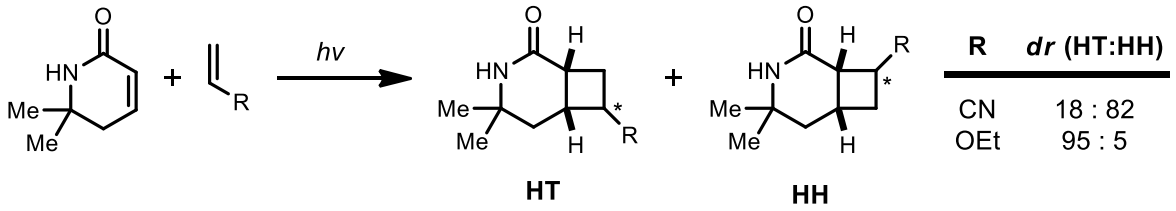
The earliest account of the synthesis of cyclobutanes dates back to 1880s when Perkin described the condensation of diethyl malonate with 1,3-dibromopropane, and when Markovnikov and Krestikow reported the homocondensation of ethyl 3-chloropropionate (Scheme 10).[32] Although nearly 140 years has elapsed, the synthesis of cyclobutanes has only emerged as versatile building blocks in synthetic chemistry within the last four decades.



Scheme 10: Early reports of the preparation of cyclobutanes.

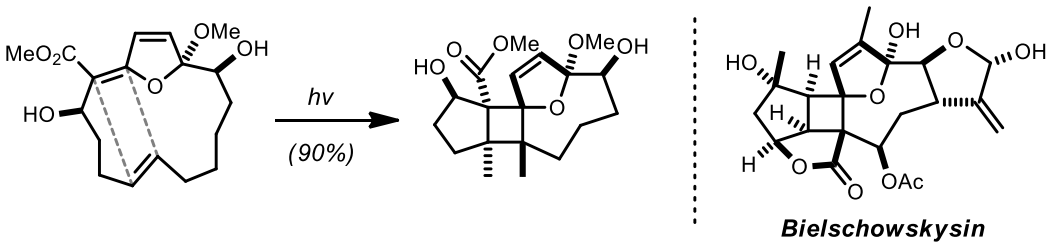
1.2.4.1 Photochemical [2+2] Cycloadditions

[2+2] Photocycloaddition reactions include both dimerization of alkene and reaction between two different alkenes, and the latter is surely more useful. Enones and alkenes have been the most prominent substrates for [2+2] cycloaddition and they have demonstrated incredible synthetic value for the construction of complex molecular frameworks. The regioselectivity of the cycloaddition depends on the substituents on the alkene and the conjugated α,β-unsaturated carbonyl, where at least two constitutional isomers (head-head or head-tail) may be formed (Scheme 11). The head-head (HH) isomer occurs when the enone carbonyl and alkene substitution of highest priority are proximal and the head-tail (HT) isomer occurs when the enone carbonyl and alkene substitution of highest priority are distal. The HH-isomer is favored when the alkene has an electron-withdrawing group. On the other hand, the HT-isomer becomes favored when the alkene has an electron donating group.[33] The mechanism involves a step-wise radical process, but stereoselective and variants have also emerged. Additionally, the use cyclic enones prevents competitive *cis-trans* isomerization.



Scheme 11: Effect of electronics on regioselectivity of [2+2] photocycloaddition.

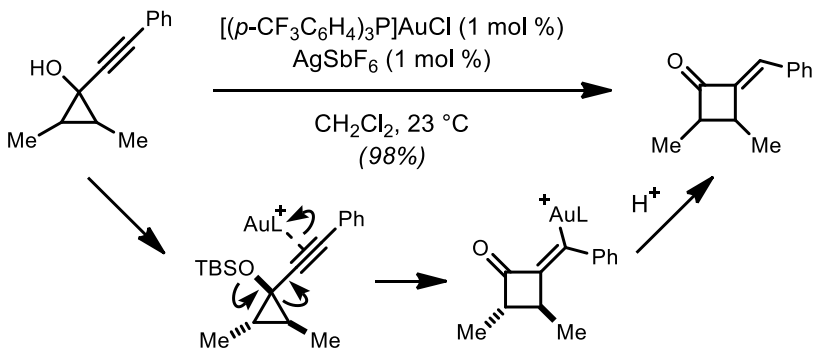
Photochemical [2+2] cycloaddition has been a valuable tool for the construction of multicyclic molecules. Nicolaou and co-workers reported an exquisite transannular [2+2] photocycloaddition of a macrocyclic intermediate towards the total synthesis of bielschowskysin **(**Scheme 12**)**.[34]



Scheme 12: Photocycloaddition of macrocyclic precursor to bielschowskysin.

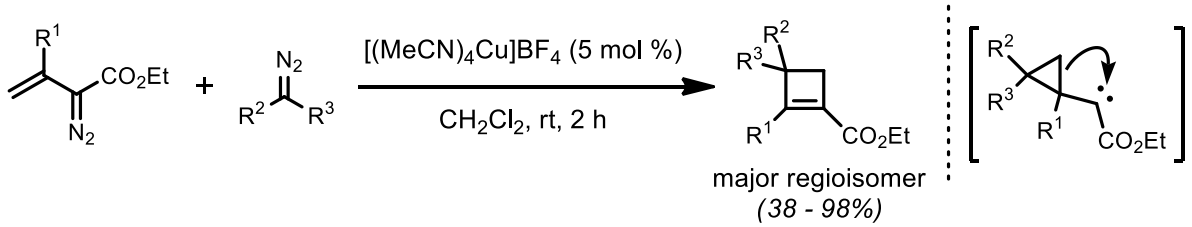
1.2.4.2 Cyclobutanes from Cyclopropanes

Cyclopropanes can also be useful intermediates to synthesize cyclobutanes. The placement of a donor group on the C-1 position of the cyclopropane ring increases its proclivity for cyclobutane formation. The rearrangement usually involves the migration of more substituted carbon. Recent advances in this rearrangement chemistry include the Au(I)-catalyzed ring-expansion of cyclopropanols (Scheme 13). Toste and co-workers showed that alkynyl cyclopropanols can undergo ring expansion upon treatment with catalytic Au(I).[35] The mechanism is proposed to involve a 1,2-alkyl shift.



Scheme 13: Au(I)-catalyzed ring expansion of cyclopropanes.

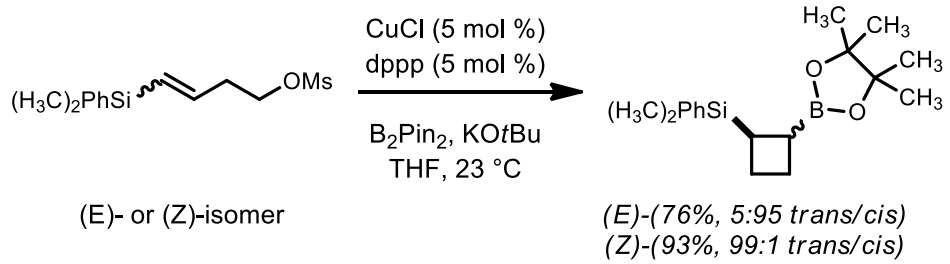
Barluenga and co-workers demonstrated that a Cu(I) catalyst was able to form carbenoid species through a cascade process between simple and vinyldiazo systems (Scheme 14). The substrates undergo a cyclopropanation of the activated alkene to form the cyclopropyl intermediate, which subsequently leads to the formation of the cyclobutene *via* ring enlargement.[36]



Scheme 14: Diazo compounds toward carbenoids for the synthesis of cyclobutanes.

1.2.4.3 1,4-Ring Closure

Another method to form cyclobutanes is through a ring closure event. Cyclobutylboronates are synthetically facile intermediates because a myriad of synthetic transformations can take advantage of the reactive C–B bond. A novel catalytic protocol was recently developed for stereoselectively accessing cyclobutylboronates. Ito and co-workers reported a Cu(I)-catalyzed reaction of (*Z*)- and (*E*)- homoallylic sulfonates to afford 1,2-disubstituted cyclobutanes (Scheme 15).[37] Only aryl- and silyl-substituted alkenes engage in borocupration.



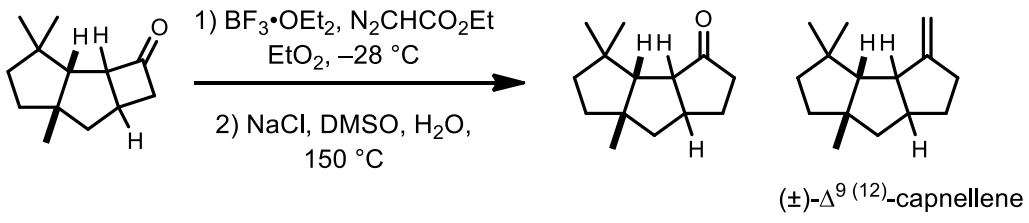
Scheme 15: Cu(I)-catalyzed 1,4-ring closure.

1.2.5 Reactions of Cyclobutanes

Cyclobutanes derivatives are excellent substrates used for the synthesis of both acyclic and cyclic systems, including carbocyclic and heterocyclic compounds. It is because of this wide range of applicability that cyclobutanes experienced rising development in the recent decades.

1.2.5.1 Cyclobutane Ring Expansion

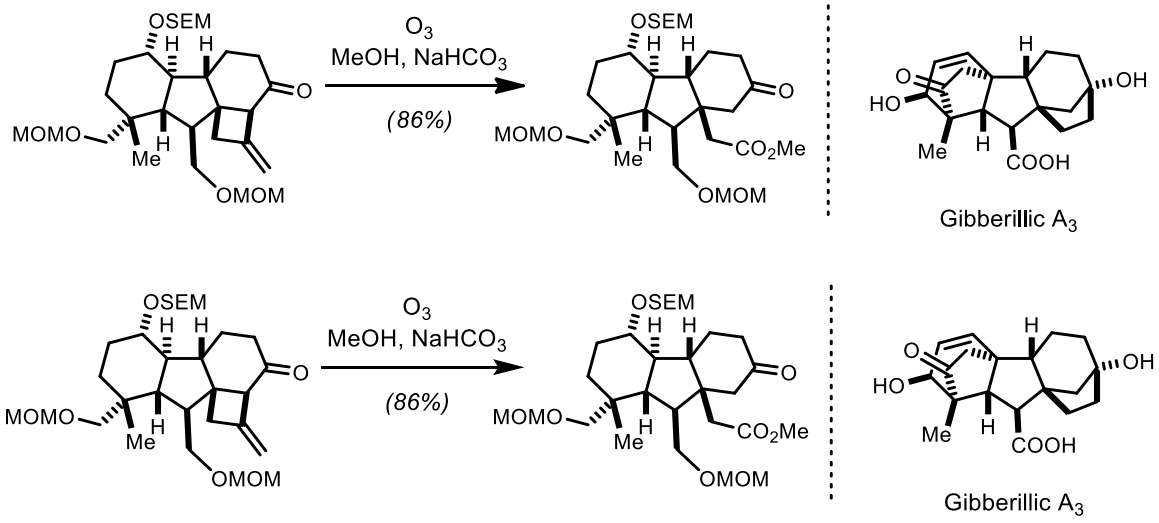
Ring expansion from 4-membered carbocycles to larger ring systems or heterocycles has proved to be an invaluable tool for synthetic chemistry. Among the various methods, the use of diazomethane was key in the total synthesis of important molecules. Ring expansions tend to favor to the electron-rich α-carbon and disfavor the α-carbon with electron-withdrawing groups. Furthermore, effects as a result steric hinderance and ring strain also influence the approach of the diazomethane. Stille and Grubbs realized a practical method to transform cyclobutane in the presence of ethyl diazoacetate and $BF_3 \cdot OEt_2$, en route to completing the synthesis of (±)-$\Delta^{9\,(12)}$-capnellene (Scheme 16).[38]



Scheme 16: Cyclobutane ring expansion towards capnellene.

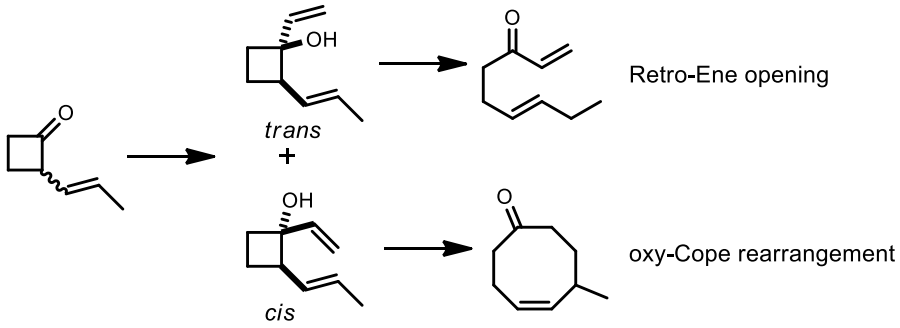
1.2.5.2 Ring Opening Reactions

Just like cyclopropanes, ring opening of cyclobutanes is also feasible. The substitutions on the ring are the major influences in facilitating ring fission and can sometimes contribute to maintaining the stereochemistry during nucleophilic addition. For example, in the total synthesis of gibberellic acid, Yamada and co-workers treated the tetracyclic precursor with ozone to convert the exocyclic alkene to the carbonyl. [39] The cyclobutanone subsequently underwent a nucleophilic opening, affording the tricyclic keto-ester (Scheme 17).



Scheme 17: Cyclobutane ring opening towards to total synthesis of gibberillic A3

Besides, cyclobutyl 1,5-diene can also undergo Cope rearrangement. This reaction becomes an oxy-Cope rearrangement when a hydroxyl- group is available at the C-3 position, which allows milder reaction condition. Barnier and co-workers reported that the *cis* relationships between the vinyl groups of the cyclobutane was essential to the oxy-Cope rearrangement. For the *trans*-isomer, a retro-ene opening afforded the ketone (Scheme 18).[40]



Scheme 18: Influence of stereochemistry on the behavior of 1,2-dialkenylcyclobutanols: oxy-Cope versus retro-ene rearrangements

1.3 Chemistry of Activated Cyclopropanes and Cyclobutanes

Donor-acceptor cyclopropanes (DACP) have been extensively studied and utilized as versatile building blocks for the construction of diverse heterocycles, carbocycles, and functionalized ring-opened compounds. This field continues to flourish to this day. [41]

1.3.1 Modes of Activation

As mentioned before, cyclopropanes are very high in energy because of their inherent ring strain (115 kJ/mol). Nonetheless, the C–C bonds of the cyclopropane ring can still remain intact in various situations. In order to facilitate bond cleavage, an activating group can be installed. An example is the use of an electron-donating group, such as an aryl or alkoxy group, to activate the cyclopropane and stabilize the incipient carbocation. Conversely, the addition of an electron-withdrawing group, such as a carbonyl or nitro group, increases the electrophilicity of the cyclopropane. Interestingly, with vicinally attached donor and acceptor groups, the reactivity of cyclopropane is further enhanced by polarizing the C–C bond between the donor and acceptor groups through a "push-pull" mechanism. The subsequent zwitterionic intermediate as a result of heterolytic cleavage is rationalized because the donor stabilizes the positive charge and the acceptor group stabilizes the negative charge (Figure 6). This zwitterionic structure is the basis of much of the research in DA cyclobutane chemistry since it provides the parent substrate with the proclivity to proceed through several fascinating reactions.

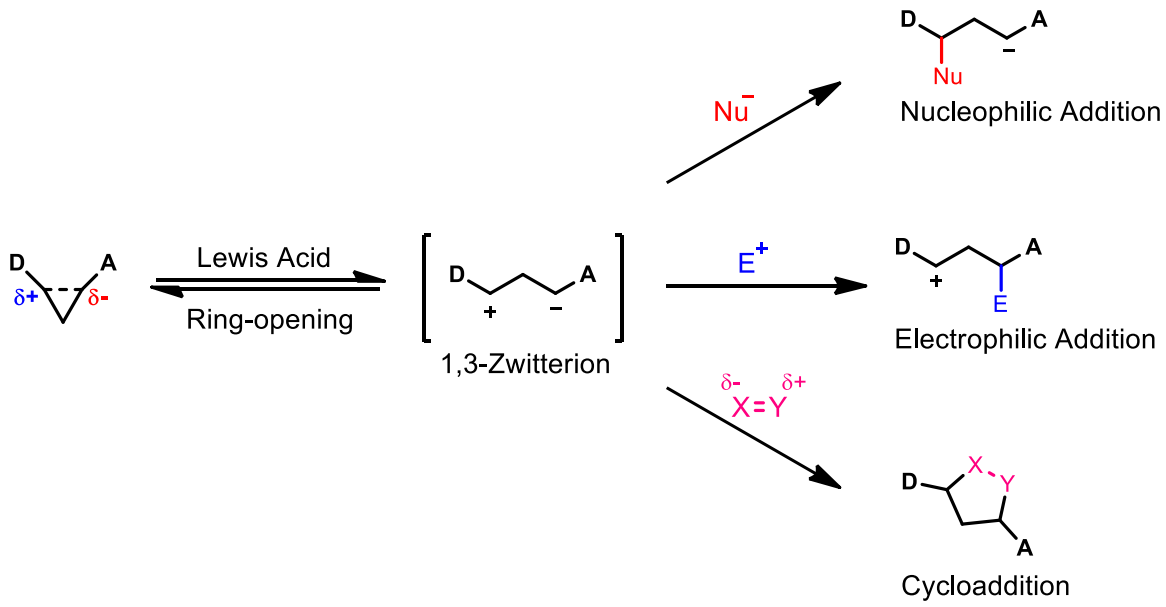
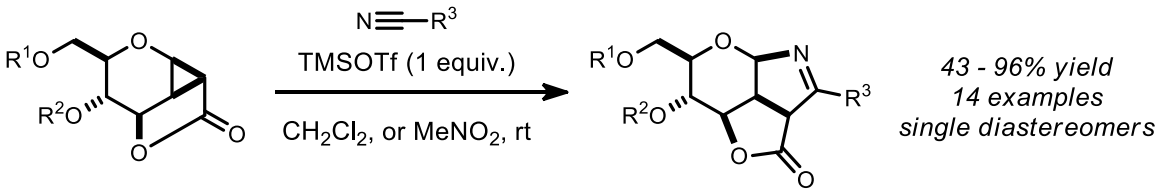


Figure 6: Modes of reactivity with DA cyclopropane.

1.3.2 Chemistry of DA Cyclopropanes

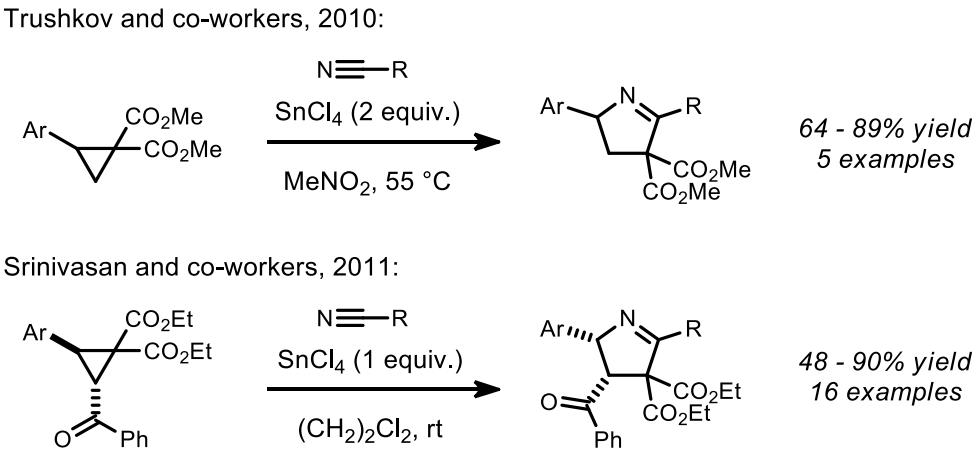
In 2003, Pagenkopf and co-workers for the first time reported a successful formal [3+2] cycloaddition of glucal-derived DA cyclopropanes with nitriles. Through TMSOTf activation, various nitriles participated in the cycloaddition to afford 1-pyrrolines in good to excellent yields (Scheme 19).[42] All the cycloadducts were obtained exclusively as one diastereomeric product.



Scheme 19: TMSOTf-promoted [3+2] cycloaddition of DA cyclopropanes and nitriles.

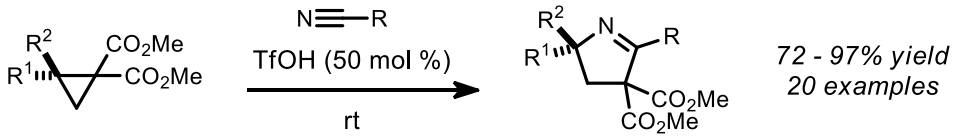
In 2010, Trushkov and co-workers reported a similar [3+2] cycloaddition reaction utilizing less electron-rich aryl donors but with geminally attached methyl ester groups. They found that using super-stoichiometric $SnCl_4$ promoted efficient cyclizations in good to excellent yield. However, only alkyl nitriles were investigated for this cycloaddition reaction (Scheme 20).[43] Under

the same conditions, Trushkov explored the details of the reaction pathway using enantiopure DA cyclopropanes.[44] They found that the reaction with acetonitrile resulted in a racemic mixture of 1-pyrroline cycloadduct, suggesting that the reaction pathway proceeds through an achiral zwitterionic intermediate. Later in 2011, Srinivasan and co-workers extended this methodology to more reactive DA cyclopropanes (Scheme 20).[45] Stoichiometric $SnCl_4$ promoted the [3+2] cycloaddition to give 1-pyrrolines as single *cis*-diastereomers in good yields. The cycloaddition demonstrated a broad substitution scope, including alkyl and aryl nitriles.



Scheme 20: $SnCl_4$-promoted [3+2] cycloaddition of DA cyclopropanes and nitriles.

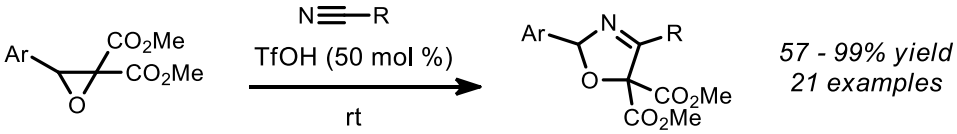
More recently, Wang and co-workers reported an expeditious TfOH-catalyzed [3+2] cycloaddition between DA cyclopropanes and nitriles (Scheme 21).[46] They demonstrated that the scope of tolerated substituents in both cyclopropanes and nitriles was broad. Reactions were complete within 5 minutes and the cycloadducts were obtained in excellent yields.



Scheme 21: TfOH-catalyzed [3+2] cycloaddition of DA cyclopropanes with nitriles.

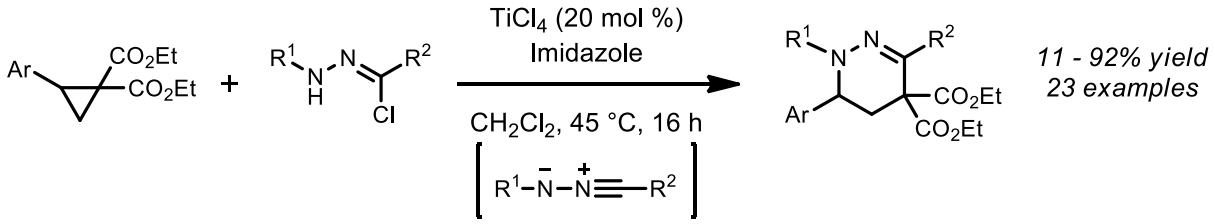
1.3.3 Similar Cycloaddition Reactions to Afford Heterocyclic Frameworks

Related cycloadditions of nitriles with strain-activated carbocycles have been recently developed as well. In 2015, an efficient chemoselective [3+2] cycloaddition of nitriles and donor-acceptor oxiranes, derived from the epoxidation of alkylidene malonates, was reported by Zhong and co-workers.[47] Structurally diverse 2,5-dihydrooxazoles were prepared under mild conditions in the presence of TfOH with up to excellent yields (Scheme 22).



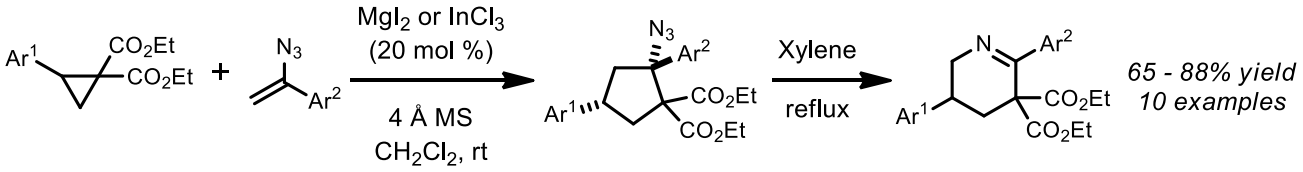
Scheme 22: TfOH-catalyzed [3+2] cycloaddition donor-acceptor oxiranes and nitriles.

In 2016, Werz and co-workers reported an elegant $TiCl_4$ catalyzed [3+3] cycloaddition between donor-acceptor cyclopropanes and *in situ* generated nitrile imines. Activated by a catalytic amount of $TiCl_4$, tetrahydropyridazine derivatives were obtained in good to excellent yields (Scheme 23).[48]



Scheme 23: $TiCl_4$-catalyzed [3+3] cycloaddition of DA cyclopropanes and nitrile imines.

The Banerjee group was the first to report a DA cyclopropane-based preparation of tetrahydropyridines from the ring-expansion of azidocyclopentanes (Scheme 24).[49] The azidocyclopentane precursor was derived from a diastereoselective [3+2] cycloaddition between DA cyclopropanes and vinyl azides. Subsequent thermal chemoselective ring-expansion in xylene afforded the formal [3+3] cycloadduct in good to excellent yield.



Scheme 24: Lewis acid catalyzed [3+2] cycloaddition/thermal ring expansion of DA cyclopropanes and vinyl azides.

1.3.4 Seminal Works in DA Cyclobutane Chemistry

The reactivity of cyclobutanes, complemented by their inherent ring strain, can be further enhanced by incorporating activating substituents. Analogously to the DA cyclopropanes, vicinally substituted electron-donating and electron-accepting groups polarizes the C–C bond through a push-pull mechanism to result in a 1,4-zwitterionic intermediate (Figure 7). As we have seen, this mode of activation has been studied and developed extensively for donor-acceptor (DA) cyclopropanes.[41,50] DA cyclobutanes have only recently been applied in ring-opening and cycloaddition manipulations, both of which have been useful in natural product synthesis.[51,52,53]

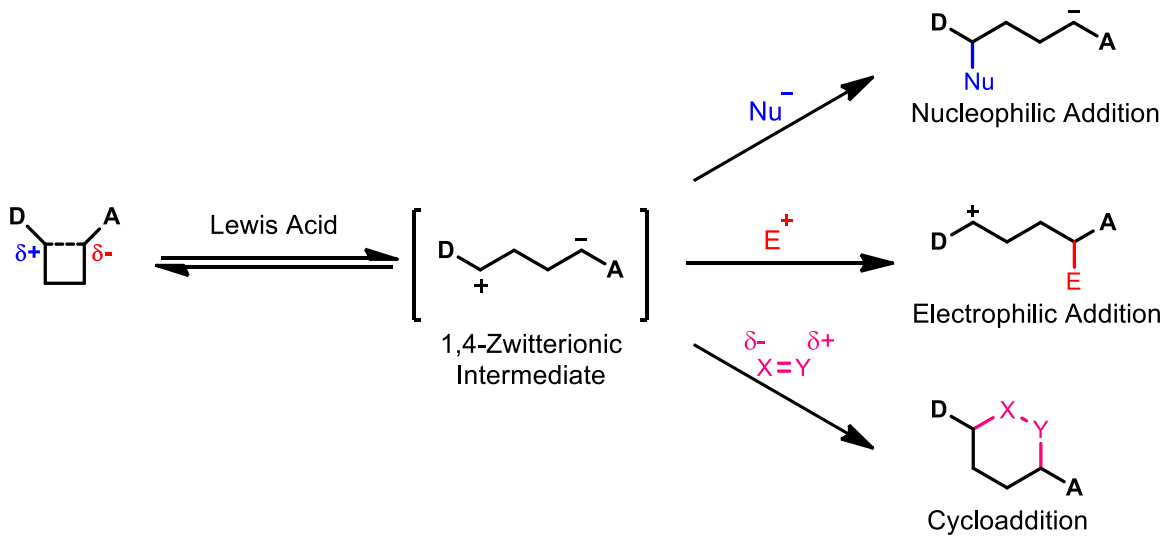
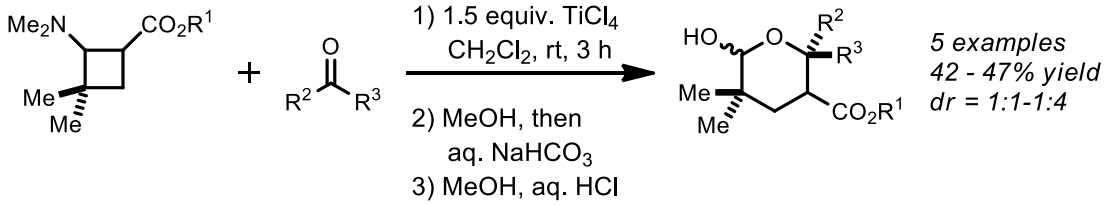


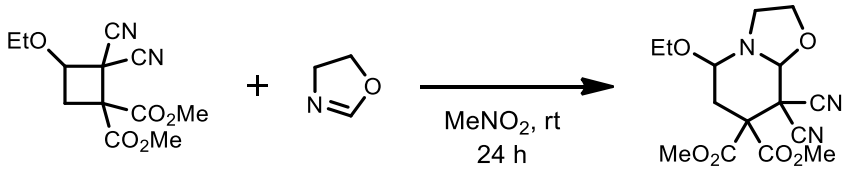
Figure 7: Possible reaction routes of DA cyclobutanes.

Although the use of DA cyclobutanes have been reported in the literature for several decades, it was only until 1991 that Saigo reported their application in cycloaddition reactions.[54] Saigo proposed that, similar to their cyclopropane counterparts, an amino-activated cyclobutane ester can undergo a Lewis acid-mediated ring-opening reaction to form a 1,4-zwitterionic intermediate. These intermediates can subsequently undergo annulations with various dipolarophiles. Saigo reported that the synthesis of tetrahydropyrans occurred *via* the annulation of the amino-activated cyclobutane esters with aldehydes or ketones when treated with stoichiometric $TiCl_4$ (Scheme 25). The reaction displayed modest yields and low diastereoselectivity to afford a mixture of hemiacetals.



Scheme 25: [4+2] Cycloaddition of amino-activated DA cyclobutane esters with carbonyls.

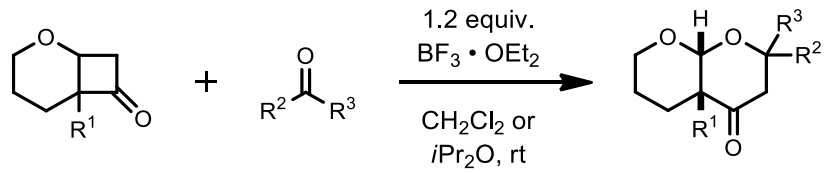
Annulations of such kind remained unreported until 1997 when Suzuki disclosed a related cycloaddition with alkoxy-based donor cyclobutanes.[55] Suzuki and co-workers disclosed a [4+2] cycloaddition reaction between highly reactive DA cyclobutanes and 2-oxazoline without the need for a Lewis acid (Scheme 26).



Scheme 26: [4+2] Cycloaddition of highly activated DA cyclobutanes with 2-oxazolines.

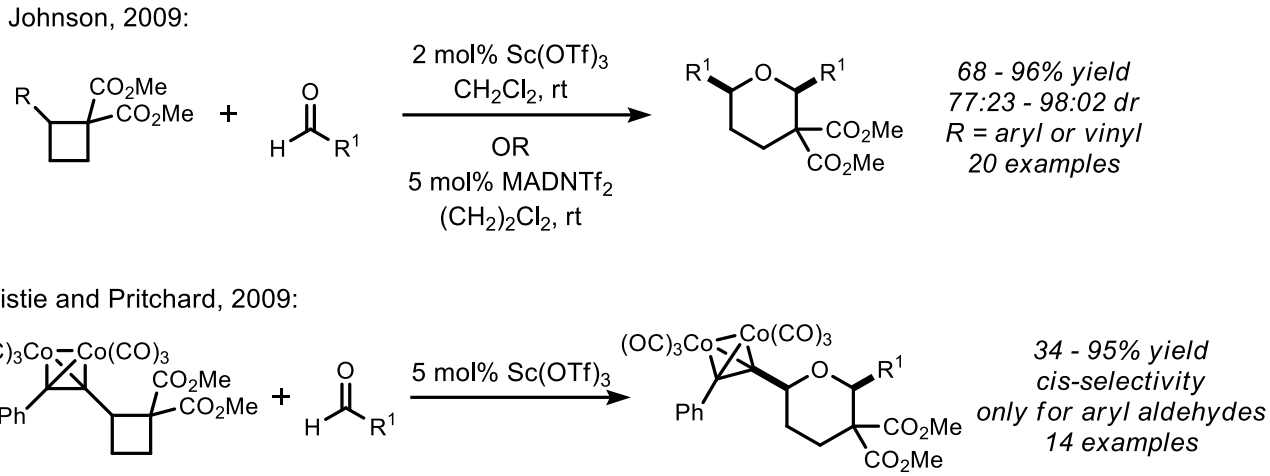
This kind of reactivity remained largely neglected until 2008 when contributions were kick-started by Matsuo *et al*. who developed a Lewis acid-promoted [4+2] cycloaddition of

alkoxycyclobutones and carbonyl compounds.[56] Matsuo's reaction was the first example of cyclobutanones undergoing intermolecular annulation with dipolarophiles (Scheme 27).



Scheme 27: The [4+2] cycloaddition of 3-alkoxycyclobutanones with carbonyl compounds.

Thereafter, a handful of contributions were made independently by the research groups of Johnson, and of Christie and Pritchard.[57] Johnson and co-workers disclosed a Lewis acid-catalyzed [4+2] cycloaddition of cyclobutanes and aldehydes to provide disubstituted tetrahydropyrans (Scheme 28).[58] This cycloaddition was highly diastereoselective for the *cis*-2,6-diastereomer with aryl aldehydes, however the diastereoselectivity dropped to 77:23 in the case of cinnamaldehyde. The more reactive and bulky Lewis acid $MADNTf_2$ was able to extend the reaction scope to aliphatic aldehydes.



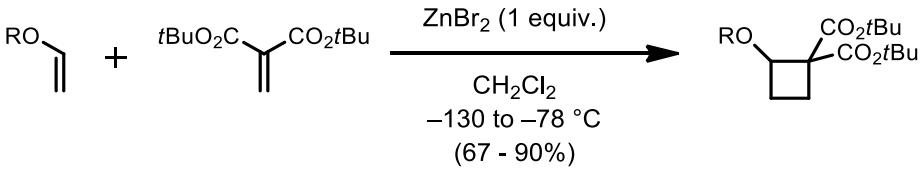
Scheme 28: The [4+2] cycloaddition of carbon-activated cyclobutanes with aldehydes.

Christie and Pritchard reported a similar $Sc(OTf)_3$ catalyzed cycloaddition reaction with a cobalt-alkyne complex as the electron-donor that readily proceeds *via* a Nicholas-type reaction (Scheme 28).[59] Aryl aldehydes provided tetrahydropyran products as single diastereomers in good

to excellent yields. However, the diastereoselectivity drops to only 20%–23% *dr* when aliphatic aldehydes were used.

1.3.5 Preparation of DA Cyclobutanes

Work in the preparation of alkoxy-activated cyclobutanes has been limited in the literature. In 1986, Roberts reported the preparation of alkoxy-activated cyclobutanes from enol ethers and methylidene malonates in good yields *via* a [2+2] annulation using stoichiometric amounts of $ZnBr_2$ (Scheme 29).[60]

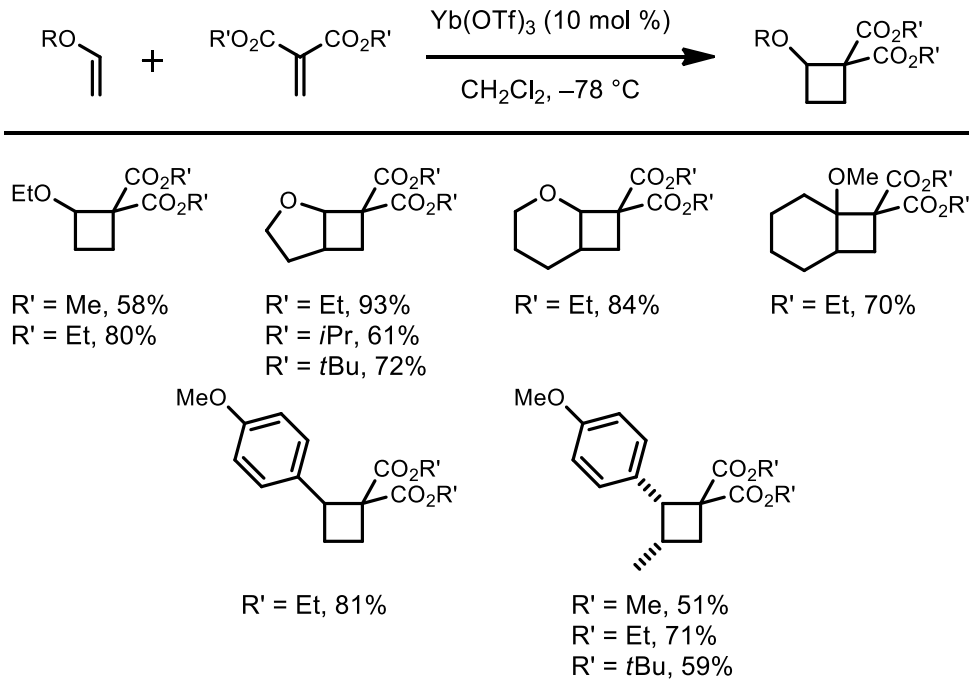


Scheme 29: Robert's synthesis of alkoxy-activated DA-cyclobutanes.

Although this procedure makes use of readily available enol ethers, it could not be extended beyond utilizing *tert*-butyl methylidene malonates. In 2009, Pagenkopf and co-workers reported a modified preparation of alkoxy-activated cyclobutanes, which gave access to the more reactive methyl- or ethyl-substituted AACDs.[61] This was accomplished by using weaker Lewis acids such as $Yb(OTf)_3$ in catalytic amounts (10 mol %). Roberts' use of stoichiometric $ZnBr_2$ was found to be too harsh for the more reactive diester examples. It was later realized that $Zn(OTf)_2$ more effectively catalyzed the [2+2] cycloaddition to provide the DA cyclobutane in higher yields.

Under the optimized reaction conditions, various cyclic and acyclic enol ethers underwent cycloadditions with a variety of reactive alkylidene malonates. The AACDs were generated in good to excellent yields as single diastereomers (Table 1). From the results of seminal reports on DA cyclobutanes alongside our experience with alkoxy-activated cyclopropanes, we sought to explore the reactivity of alkoxy-activated cyclobutane 1,1-dicarboxylates (AACDs).

Table 1: The modified synthesis of AACDs.

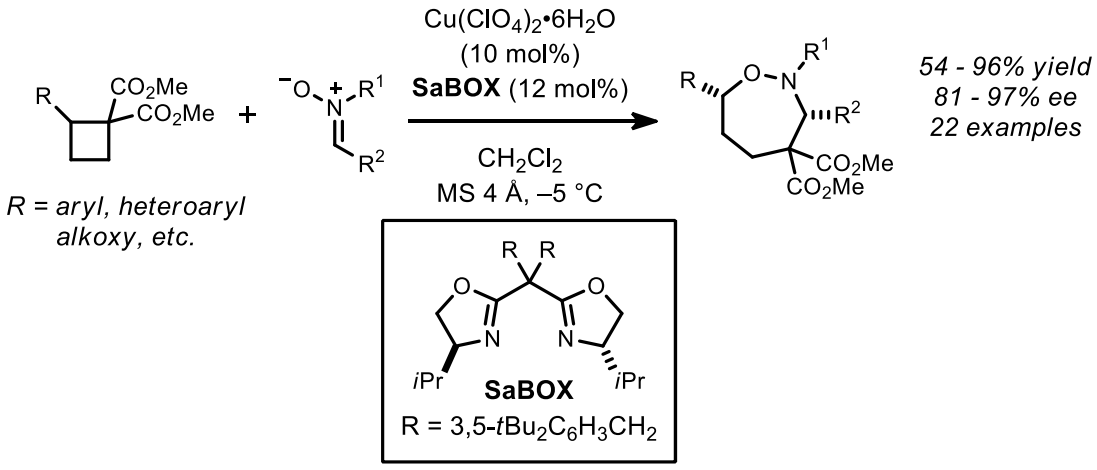


1.4 The Chemistry of Cyclobutanes

Ever since the seminal reports by Johnson, and Christie and Pritchard, the literature has flourished with a multitude of interesting works exploring several variants of DA cyclobutanes undergoing cycloaddition reactions with various dipolarophiles. There have been many advances in reaction tuning for stereoselectivity and regioselectivity, and for maximizing yields. Moreover, application of such reactions has been seen in the total synthesis of natural products.[52,53]

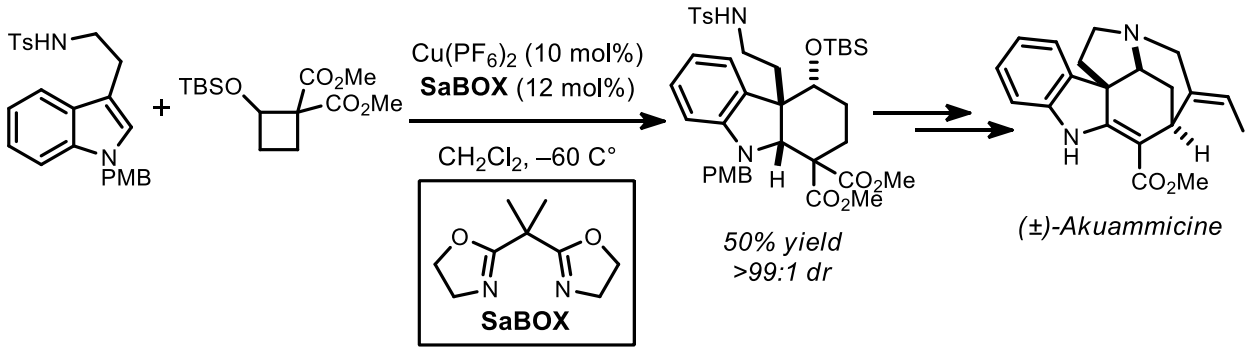
1.4.1 Cycloadditions of DA Cyclobutanes

Tang and co-workers reported the first enantioselective variant of the [4+3] cycloaddition reaction between DA cyclobutanes and nitrones.[62] They developed a series of side arm modified bisoxazolines (SaBOX) that improved both the reactivity and the enantioselectivity of formal [3+2] cycloaddition of DA cyclopropanes.[63] A sterically hindered chiral SaBOX/Cu(II) complex catalyzed the cycloaddition to give a broad range of multifunctionalized 1,2-oxazepanes (Scheme 30).



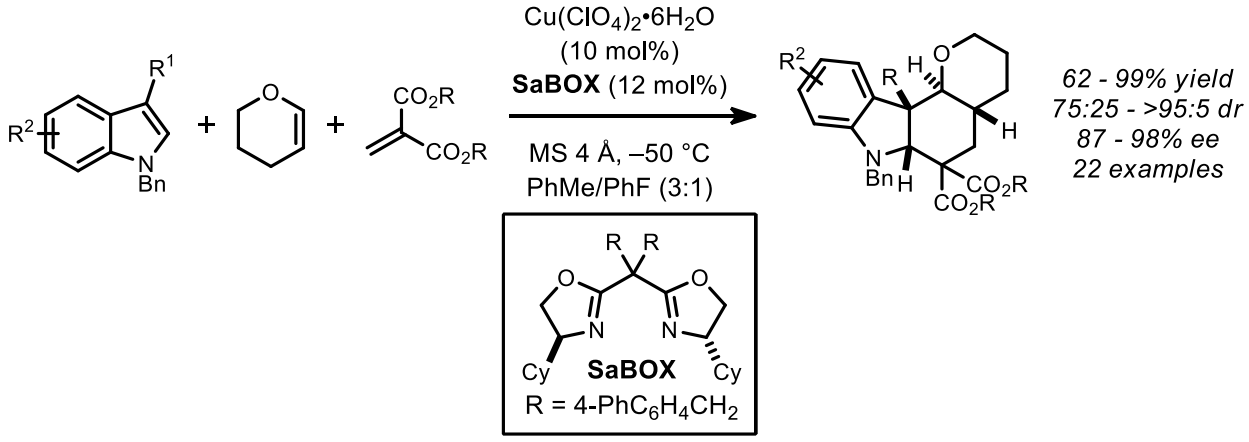
Scheme 30: Enantioselective [4+3] cycloaddition of DA cyclobutanes with nitrones.

Tang and co-workers adapted their sterically hindered chiral Cu(II)/SaBOX catalysis protocol for the construction of cyclohexa-fused indolines (Scheme 31). The synthetic method achieved excellent enantioselectivity with broad substrate scope and enabled the formal total synthesis of (±)-akuammicine.[52]



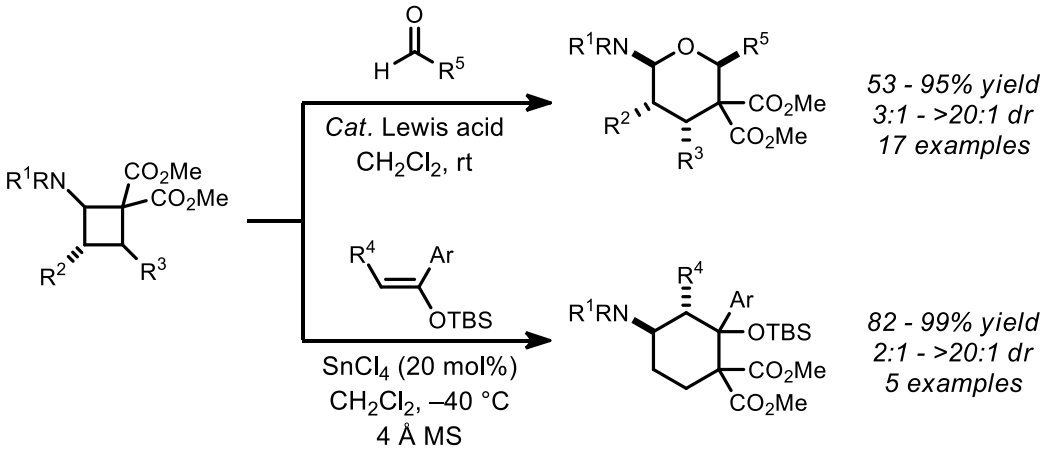
Scheme 31: Synthesis of (±)-akuammicine via [4+2] cycloaddition of DA cyclobutane.

Recently, the Tang group developed a highly regio-, diastereo- and diastereoselective Cu(II)/BOX-catalyzed multicomponent reaction between indoles, 2,3-dihydropyran and methylene malonates (Scheme 32).[64] Highly enantioenriched tetracyclic indolines were obtained using a modified protocol stemming from our seminal work on the preparation of AACDs. The AACDs are generated *in situ* and subsequently undergo [4+2] cycloaddition with the indole.



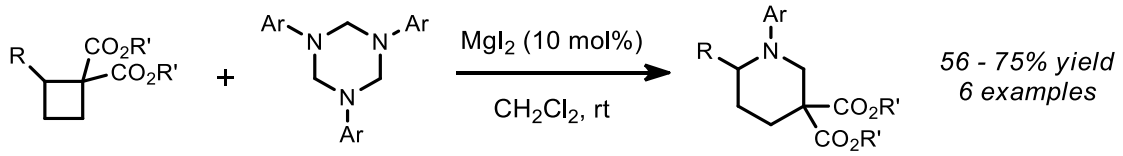
Scheme 32: The three-component formal [2+2+2] cycloaddition reaction between indoles, 2,3-dihydropyran, and methylene malonates *via in situ* generated DA cyclobutane.

A facile preparation of amino-activated DA cyclobutane has been realized by Waser and co-workers *via* an Fe(III)-catalyzed [2+2] cycloaddition of enimides and alkylidene malonates.[65] Waser and co-workers have also shown that these amino-activated DA cyclobutanes were viable substrates for [4+2] cycloaddition chemistry.[66] Cycloaddition reactions were catalyzed by $Sc(OTf)_3$ or $FeCl_3 \cdot Al_2O_3$ between aldehydes and amino-activated cyclobutanes (Scheme 33). When thymine- or fluorouracil-substituted cyclobutanes were employed as donor groups, $Hf(OTf)_4$ was required to the afford the cycloadduct. They also disclosed that the [4+2] cycloaddition proceeded between silyl enol ethers and less substituted cyclobutanes in the presence of $SnCl_4$ as a catalyst.



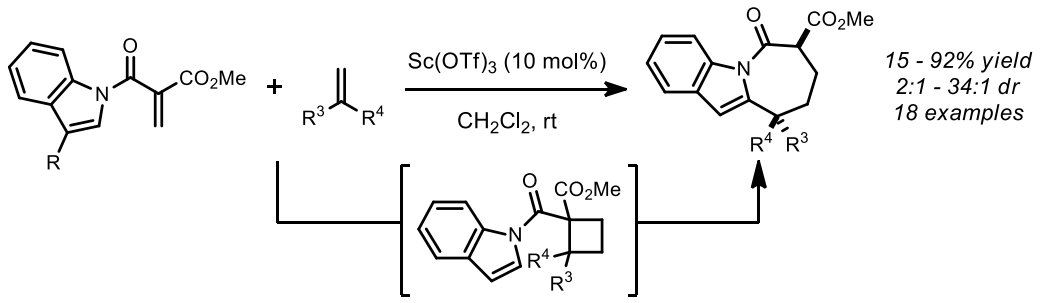
Scheme 33: The [4+2] cycloaddition of amino-activated cyclobutane 1,1-dicarboxylates.

The Werz group reported that in the presence of catalytic MgI_2, DA cyclopropanes and DA cyclobutanes undergo [3+2] and [4+2] cycloadditions, respectively, with formaldimines generated from triazinanes (Scheme 34).[67] The influence of MgI_2 was important for the decomposition of the triazinane. The protocol allowed for the preparation of a variety of pyrrolidines and piperdines with tolerance of a broad range of functional groups.



Scheme 34: The formal [4+2] cycloaddition of DA cyclobutanes with formylimine surrogates.

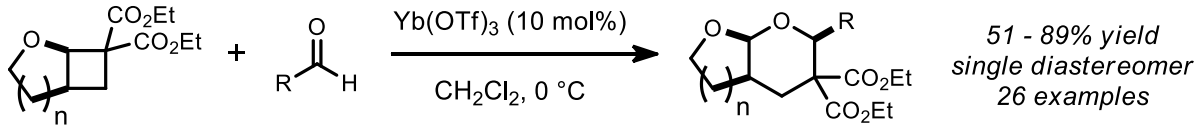
The first intramolecular variant of the cycloaddition of DA cyclobutanes was disclosed by France and co-workers (Scheme 35).[68] They developed a diastereoselective $Sc(OTf)_3$ catalyzed approach to azepino[1,2-*a*]indole in high yield and high diastereoselectivities. The reaction presumably proceeded through a Lewis acid-catalyzed [2+2] cycloaddition between alkenes and *N*-indolyl alkylidene β-amide esters to form a putative DA cyclobutane intermediate, which subsequently underwent an intramolecular ring-opening cyclization.



Scheme 35: Synthesis of azepino[1,2-α]indoles *via* $Sc(OTf)_3$-catalyzed [5+2] cycloaddition of DA cyclobutane intermediates.

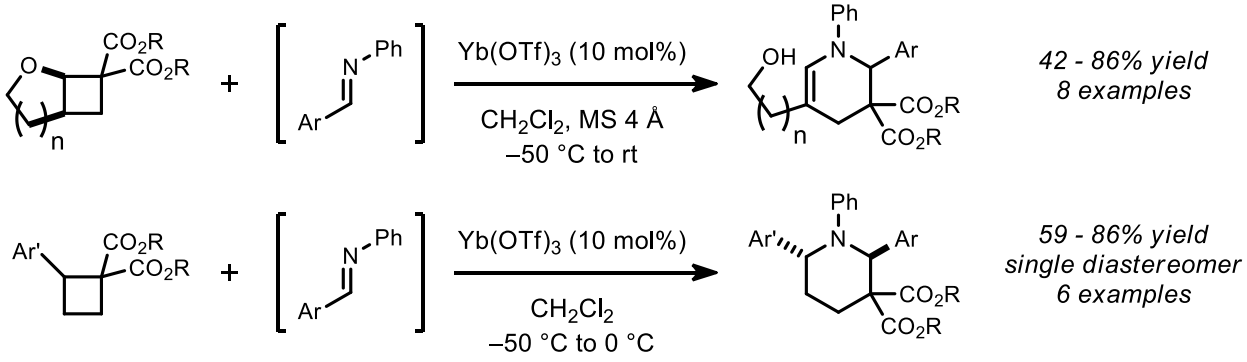
1.4.2 Cycloadditions of Alkoxy-Activated Cyclobutanes

Fortuitously, the $Yb(OTf)_3$ Lewis acid used for the catalytic preparation of AACDs (Table 1) was found to also catalyze their subsequent [4+2] cycloaddition with aldehydes.[61] A broad reaction scope was demonstrated with various aldehydes, including aryl, heteroaryl, vinyl, and alkynyl substitutions (Scheme 36). Tetrahydropyrans were obtained in good to excellent yields as single diastereomers. However, aliphatic aldehydes only modestly engaged in the cycloaddition.



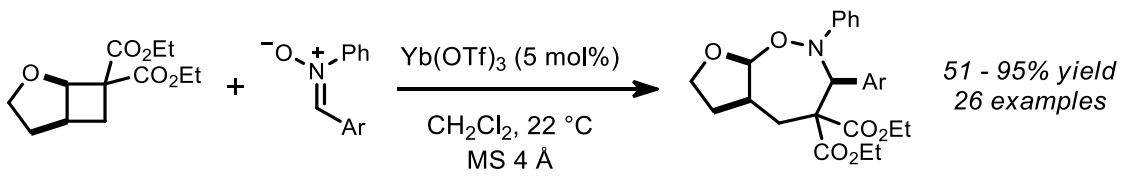
Scheme 36: The [4+2] cycloaddition of AACDs with aldehydes.

Upon confirming the usefulness of the cycloaddition chemistry with AACDs, the Pagenkopf group became interested in exploring their versatility with other possible dipolarophiles. We sought to investigate the reactivity of imines after having seen their successful utilization in cycloadditions with DA cyclopropanes.[50] $Yb(OTf)_3$ catalyzed the reaction of AACDs in the presence of imines generated *in situ* to afford piperidine products (Scheme 37).[61] Aryl ether activated cyclobutanes also underwent cycloadditions under similar conditions to exclusively afford *trans*-2,6-piperidines.



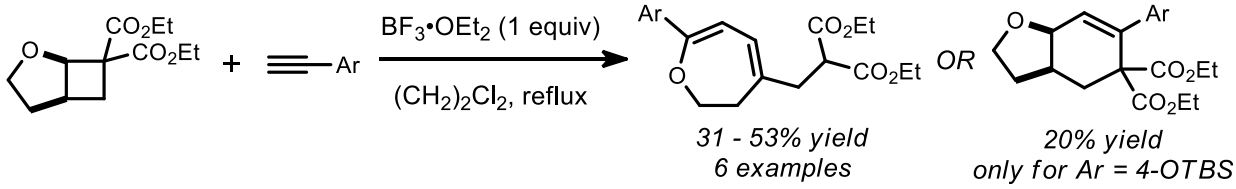
Scheme 37: The [4+2] cycloaddition of AACDs with imines.

Nitrones, acting as 1,3-dipoles, have shown success as excellent dipolarophiles in the cycloaddition of DA cyclopropanes.[69] We quickly found that nitrones also underwent a cycloaddition with DA cyclobutanes in the presence of $Yb(OTf)_3$ (Scheme 38).[70] At lower temperatures, diastereomeric mixtures were obtained containing the kinetically preferred *trans*-diastereomer. Interestingly, when the reaction was performed at room temperature, the *cis*-diastereomer was formed exclusively as the thermodynamic product.



Scheme 38: The [4+3] cycloaddition of AACDs with nitrones.

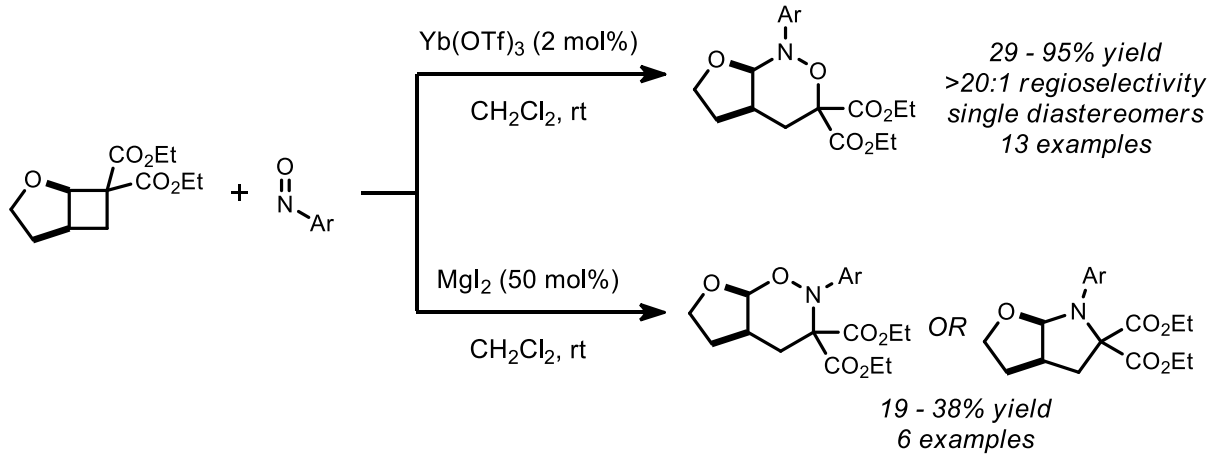
Our group also became interested in studying terminal alkynes as reactive cycloaddition partners, since efficient [3+2] cycloadditions between terminal alkynes and DA cyclopropanes have been reported.[71] We disclosed a stoichiometric $BF_3 \cdot OEt_2$-promoted reaction between AACDs and terminal alkynes, but the expected [4+2] cycloadduct was obtained only when 4-silyloxy phenylacetylene was used and the yield was also low (Scheme 39).[72] Instead of the desired cycloadduct, 2,3-dihydrooxepines were obtained *via* an addition/rearrangement sequence when electron-neutral or electron-rich phenylacetylenes were used.



Scheme 39: $BF_3 \cdot OEt_2$-promoted reactions of AACDs with terminal alkynes.

Another dipolarophile we sought to explore were nitroso compounds. The nitroso group have demonstrated versatility in several synthetic transformations.[73] We were the first to report the application of nitrosoarenes in cycloaddition chemistry with DA cyclobutanes. $Yb(OTf)_3$ effectively catalyzed the [4+2] cycloaddition of AACDs with nitrosoarenes with the regioselectivity favoring the aminal over the acetal (Scheme 40),[74] in which the overall success depended on the use of electron-poor to electron-neutral nitrosoarenes. MgI_2 emerged as the best catalyst to extend the scope to encompass electron-rich nitrosoarenes, albeit giving the acetal only in low yields.[75] Interestingly, when the reaction was treated with more MgI_2 or left to stir for longer

periods of time, the pyrrolidine was formed *via* a MgI_2 promoted deoxygenation of the acetal.

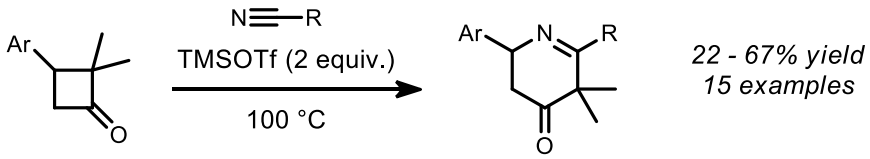


Scheme 40: The $Yb(OTf)_3$-catalyzed [4+2] cycloaddition and MgI_2 promoted cycloaddition of AACDs with nitrosoarenes.

1.5 Project Rationale

Inspired by the successful cycloaddition reactions of DA cyclobutanes and a diverse array of dipolarophiles, between DA cyclopropanes and nitriles, and related cycloaddition reactions, we became interested in evaluating the reactivity of DA cyclobutanes with nitriles. Successfully obtaining diverse heterocyclic scaffolds would allow access to a library of biologically important structural frameworks. If we can establish efficient methodologies, we can then apply them in the total synthesis of complex natural products and pharmaceutically relevant compounds.

With respect to cyclobutanes, Matsuo and co-workers recently employed aryl-substituted cyclobutanones, structurally distinct from the DA cyclopropanes and DA cyclobutanes, with exocyclic electron-withdrawing functionalities in a cycloaddition reaction (Scheme 41).[76] In this report, they disclosed a TMSOTf-promoted formal [4+2] cycloaddition between 3-phenylcyclobutanones and nitriles. Various nitriles including alkyl and aromatic nitriles reacted to afford dihydropyridones, albeit in moderate yields.



Scheme 41: TMSOTf-promoted [4+2] cycloaddition of cyclobutanones and nitriles.

It is worth noting that the initial focus of this project aims to investigate the reactivity of a particular class of DA cyclobutanes, that is, the aryl-activated DA cyclobutanes. We wanted to at this stage explore the less activated variant of DA cyclobutanes and their ability to engage in cycloaddition. The focus on aryl-activated DA cyclobutanes was rationalized not only by their amenability to undergo ring-opening but to also have the ability to persist as reactive intermediates in the reaction media. In addition, aryl groups are more tunable because of the capability to vary electronics by adjusting substitutions on the arene. Indeed, alkoxy-activated cyclobutanes are of

higher reactivity, but interception by the desired nucleophile before decomposition and/or side-reactions poses some difficulty in method development. Moreover, there is less versatility in varying electronics of an alkoxy group. Nonetheless, having already shown so much promise in cycloaddition chemistry, the more activated, alkoxy-substituted cyclobutane will also be explored in detail in the future. As such, we sought to commence the study by investigate the reactivity profiles of aryl-activated DA cyclobutanes with nitriles under Lewis acid treatment.

Chapter 2. The Cycloaddition Between Donor-Acceptor Cyclobutanes and Nitriles

In the recent decade, several contributions have been disclosed to explore the utility of DA cyclobutanes as reactive partners in cycloaddition. This thesis seeks to expand contributions further by utilizing aryl-activated DA cyclobutanes and nitriles as reactive partners. Investigation between these two partners will be discussed.

2.1 Introduction

2.1.1 Nitriles as Reactive Cycloaddition Partners

Although nitriles have been utilized in a variety of transformations, their application as reactive partners in cycloaddition reactions has been limited. Owing to their chemical stability as reflected by their bond energy (854 kJ/mol), they are typically less reactive than alkynes (835 kJ/mol).[77] In fact, a previous study from 1950 reported that thermal [4+2] cycloaddition between dienes and unactivated nitriles gave miniscule amounts of pyridine derivative after reaction at an extraordinarily high temperature of 600 °C.[78] Nevertheless, a handful of works have been disclosed to demonstrate an enhanced practicality for various nitrile cycloaddition reactions at relatively milder conditions.

2.1.2 Access to Tetrahydropyridines

Nitrogen-containing heterocycles are significant structural motifs of various important natural products and pharmaceutically active compounds.[79] The tetrahydropyridine ring is of synthetic interest as these motifs are present in many bioactive natural products. Alkaloids possessing the tetrahydropyridine ring include solacongestidine and 2-methyl-6-pentadecyl-2,3,4,5-tetrahydropyridine, which exhibit antifungal properties,[80] ealaenis C and pyracyclumine H, which display antileukemic activities,[81] and daphnezomine N, which displays antilymphoma properties (Figure 8).[82] Novel and efficient development of the tetrahydropyridine scaffold is motivated by the promising bioactivities of these natural products.

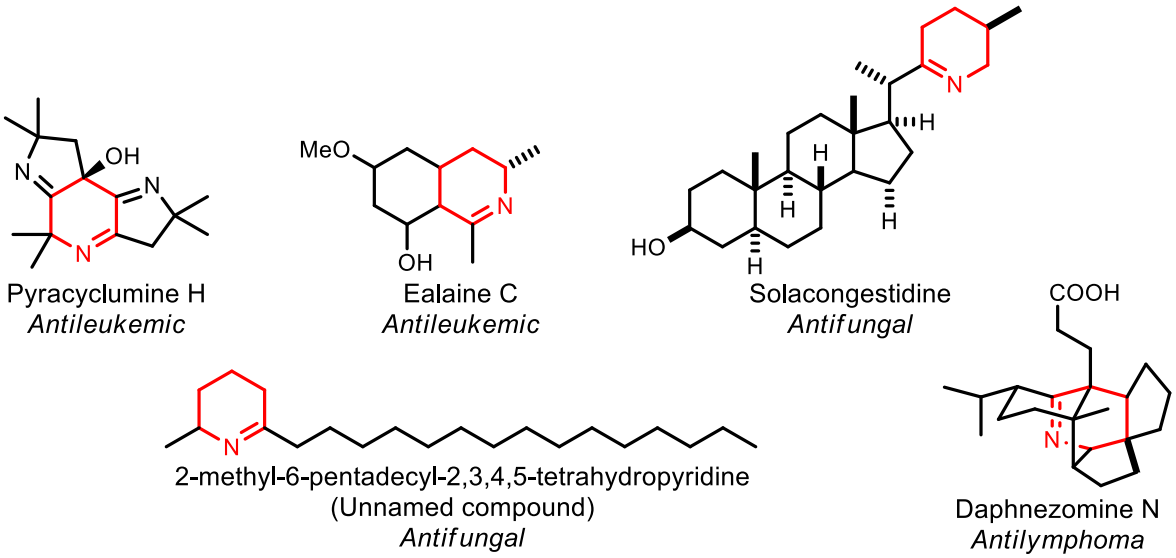


Figure 8: Tetrahydropyridine natural products.

2.2 Results and Discussion

Nitriles have been demonstrated to be effective reaction partners in a variety of transformations. The nitrile as a functional group has received considerable attention in the cycloadditions of DA cyclopropane. However, they have not yet seen comparable involvement in [4+2] cycloadditions with aryl-activated DA cyclobutanes.

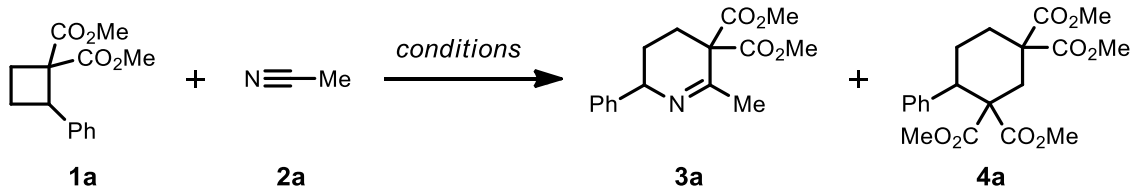
2.2.1 The [4+2] Cycloaddition between DA Cyclobutanes and Nitriles

In order to explore the [4+2] cycloaddition reaction of DA cyclobutanes and nitriles, the reaction between cyclobutane **1a** and acetonitrile was chosen as a model reaction to screen the Lewis acids and to optimize the reaction conditions for the cycloaddition to give the tetrahydropyridine **3a**. To start, the reaction was conducted with 1 equiv of cyclobutane **1a** and 5 equiv of acetonitrile **2a** in DCM at room temperature. Neither $Sc(OTf)_3$ nor $Yb(OTf)_3$ was an effective catalyst, despite their excellent success in catalyzing cycloadditions between DA cyclobutanes and aldehydes.[58,83] Several other Lewis acids such as $Pr(OTf)_3$, $Mg(OTf)_2$, MgI_2, $BF_3{\cdot}OEt_2$, were all ineffective (entry 21–24), even at elevated temperatures. TMSOTf and TfOH were also ineffective, despite success in promoting a similar nitrile cycloaddition with DA cyclopropanes.[42,46] After all these initial experiments, we eventually found that super-stoichiometric $SnCl_4$ best promoted the [4+2] cycloaddition reaction between the aryl-activated cyclobutane dicarboxylate and acetonitrile to give the tetrahydropyridine cycloadduct **3a** at room temperature in 39% yield (entry 25) (Table 2).

Lowering the amount of $SnCl_4$ from 2.1 to 1.5 equiv did not show an adverse effect (entry 25–27). However, further lowering the loading to 0.5 equiv led to unsatisfactory yields (entry 28). The yields varied only slightly when studying the effect of solvent polarity of aprotic solvents

(entry 29–31). In all, DCE was the best solvent that gave 44% yield when used along with 1.5 equiv $SnCl_4$ at room temperature (entry 31). Lower temperatures decreased the yield (entry 32), whereas elevated temperatures to 55 °C improved the yield modestly to 52% (entry 33). Further increasing the temperature above 55 °C led to inferior yields (entry 34–35), and it was found that the carbocyclic side-product (**4a**) became favored. The yield increased significantly to 78% when acetonitrile was used as a solvent (entry 36). This entry demonstrated that sufficient $SnCl_4$ remained to promote the cycloaddition regardless of the formation of the known $SnCl_4$ adduct with acetonitrile, *i.e.*, $SnCl_4 \cdot (MeCN)_2$.[84] Therefore, the optimal reaction conditions for the [4+2] cycloaddition were identified as 1.5 equiv of $SnCl_4$ in DCE at 55 °C.

Table 2: Catalyst screening for the [4+2] cycloaddition of DA cyclobutanes and nitriles.



1a **2a** **3a** **4a**

Entry	Lewis acid (equiv)	Solvent	Temp.	Time (h)	Yield (%)[a]
1	$Pr(OTf)_3$ (5 mol%)	DCM	rt	48	nr[b]
2	$Pr(OTf)_3$ (5 mol%)	DCM	55 °C	24	nr
3	$Yb(OTf)_3$ (5 mol%)	DCM	rt	17	nr
4	$Yb(OTf)_3$ (5 mol%)	DCM	55 °C	15	trace
5	$Sc(OTf)_3$ (5 mol%)	DCM	rt	24	nr
6	$Sc(OTf)_3$ (5 mol%)	DCM	55 °C	28	16%
7	$Mg(OTf)_2$ (10 mol%)	DCM	rt	2	nr
8	$Mg(OTf)_2$ (10 mol%)	DCM	55 °C	12	nr
9	$Mg(ClO_4)_2$ (10 mol%)	DCM	rt	2	nr
10	$Mg(ClO_4)_2$ (10 mol%)	DCM	55 °C	12	nr
11	$MgBr_2$ (50 mol%)	DCM	rt	2	nr
12	$MgBr_2$ (50 mol%)	DCM	55 °C	12	nr

13	MgI_2 (50 mol%)	DCM	rt	2	nr
14	MgI_2 (50 mol%)	DCM	55 °C	12	dec[c]
15	$Sn(Oct)_2$ (5 mol%)	DCM	rt	6	nr
16	$Sn(Oct)_2$ (5 mol%)	DCM	55 °C	4	nr
17	$Sn(Oct)_2$ (1.5 equiv)	DCM	rt	6	nr
18	$Sn(Oct)_2$ (1.5 equiv)	DCM	55 °C	4	nr
19	$BF_3{\cdot}OEt_2$ (10 mol%)	DCM	rt	3	nr
20	$BF_3{\cdot}OEt_2$ (10 mol%)	DCM	55 °C	16	nr
21	TfOH (10 mol%)	DCM	rt	2	nr
22	TfOH (10 mol%)	DCM	55 °C	2	nr
23	TMSOTf (10 mol%)	DCM	0 °C → rt	18	trace[d]
24	TMSOTf (1.1 equiv)	DCM	0 °C → rt	18	18%
25	$SnCl_4$ (2.1 equiv)	DCM	rt	3	44%
26	$SnCl_4$ (1.5 equiv)	DCM	rt	3	43%
27	$SnCl_4$ (1.1 equiv)	DCM	rt	24	39%
28	$SnCl_4$ (0.5 equiv)	DCM	rt	3	26%
29	$SnCl_4$ (1.5 equiv)	$MeNO_2$	rt	3	36%
30	$SnCl_4$ (1.5 equiv)	Toluene	rt	3	37%
31	$SnCl_4$ (1.5 equiv)	DCE	rt	3	44%
32	$SnCl_4$ (1.5 equiv)	DCE	0 °C	3	33%
33	$SnCl_4$ (1.5 equiv)	DCE	55 °C	3	52%
34	$SnCl_4$ (1.5 equiv)	DCE	70 °C	3	37%
35	$SnCl_4$ (1.5 equiv)	DCE	85 °C	3	38%
36	$SnCl_4$ (1.5 equiv)	MeCN	55 °C	2	78% [a]

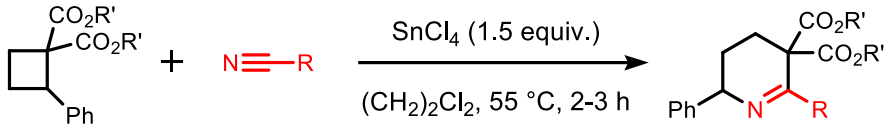
Typical reaction conditions: The reaction was conducted with **1a** (0.4 mmol), **2a** (2.0 mmol), Lewis acid (*x* equiv), and solvent (3 mL). [a] Isolated yield of **3a**. [b] No reaction. [c] Decomposition. [d] Trace amounts of 3a formed. [e] Acetontrile as solvent (0.1 M cyclobutane, 192 equiv of acetonitrile).

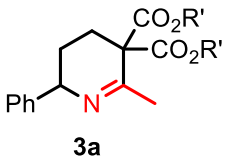
Under the optimal conditions, the substitution scope of the nitriles was investigated and the results are summarized in Table 3. The [4+2] cycloaddition was successful with a broad scope of nitriles. For all the subsequent nitriles, 3 equivalents were used. Various saturated and branched alkyl nitriles engaged to give cycloadducts in moderate to good yield (**3a–e**). It is known that increasing the size of the esters from methyl to ethyl on the cyclobutane decreases reactivity and helps reduce the decomposition of the cyclobutane.[61,83] The effect of varying the ester groups was previously investigated and substantiated by our work on the [4+2] cycloaddition of aldehydes and imines with DA cyclobutanes. Indeed, it was also observed that the size of ester groups plays a considerable role in managing reactivity and in reducing decomposition of the DA cyclobutane. The cycloaddition of acetonitrile with the diethyl ester **1a-Et** allowed the reaction to proceed more smoothly to give **3a-Et** in 70% yield whereas **1a-Me** only allowed 52% yield. Furthermore, by running the reaction in acetonitrile as the solvent, the yield improved to 91% (**3a-Et**). Substrates bearing diethyl esters generally showed higher yields when compared with dimethyl esters because of an attenuated coordination effect on $SnCl_4$ Lewis acid. In conjunction to the hard activation strength of $SnCl_4$, reducing the reactivity away from the more reactive dimethyl esters mitigated side reactions. It seems the intricate nature of this reaction requires a delicate balance between the electronics of the donor and acceptor groups, in addition to the coordination strength with the diester chain as a function of ester chain length.

Intriguingly, unprotected hydroxypropionitrile successfully proceeded through the cycloaddition reaction even though the hydroxy group has a propensity to coordinate Sn (**3f**). Another fascinating result was observed when the reaction was performed in the presence of 3-methoxyacrylonitrile where an aldehyde functional group was installed on the cycloadduct. The resulting vinylogous formamide (**3g**), a rather rare functional group, was formed exclusively as the

(*Z*)-isomer. Instead of isolating the [4+2] cycloadduct, a hydrolysis of the cycloadduct occurred during work-up where the oxonium ion was formed as an intermediate similar to that of the hydrolysis of acetals. The formation of a vinylogous formamide was also observed under similar conditions in our previous analogous work on the cycloaddition of DA cyclopropanes and nitriles.[42] Moreover, the isolation of the (*Z*)-isomer was likely avoiding the allylic strain from the neighboring ester groups and perhaps some favorable hydrogen bonding between the amine and the aldehyde as well. The interaction, as evident by nOe studies, demonstrated a close through-space relationship between the aldehydic and vinylic hydrogens which confirms the (*Z*) stereochemistry of the vinylogous formamide. An additional result to mention is the ^{1}H NMR peak comparisons of the vinylogous formamide to that of the parent compound, *N*-methyl formamide for example. The N-H peak for *N*-methyl formamide resides around 7.4 ppm whereas the N-H peak of the vinylogous analog in this example (**3g**) is observed at 11.6 ppm. More than 4 ppm difference between the compounds can be explained by the enhanced deshielding effect provided by vinylogous group to the formamide nitrogen.

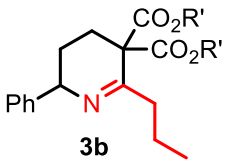
Table 3: The substituent scope of nitriles and their reaction with DA cyclobutanes.





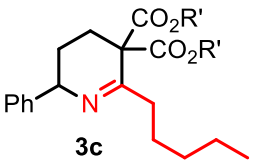
3a

R' = Me (52%, 78%[a])
R' = Et (70%, 91%[a])



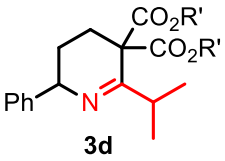
3b

R' = Me (44%)



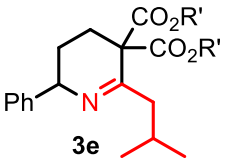
3c

R' = Me (39%)



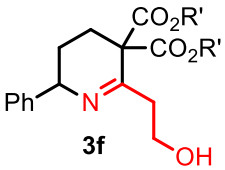
3d

R' = Me (48%)
R' = Et (58%)



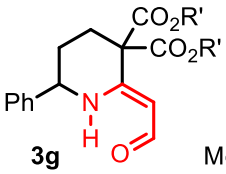
3e

R' = Me (58%)
R' = Et (74%)



3f

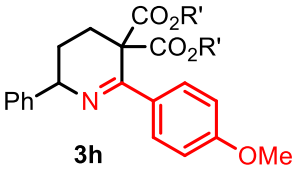
R' = Me (34%)



3g

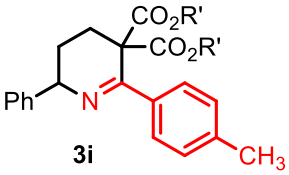
R' = Me (35%)

from



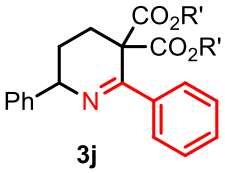
3h

R' = Me (63%)
R' = Et (78%)



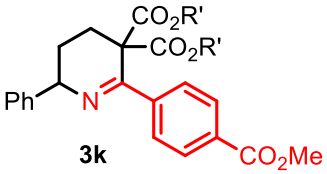
3i

R' = Me (57%)



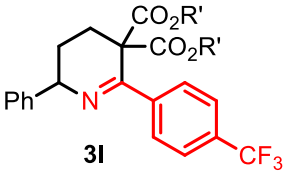
3j

R' = Me (49%)
R' = Et (75%)



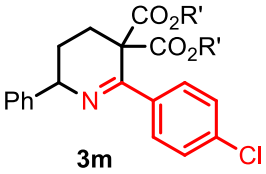
3k

R' = Me (38%)



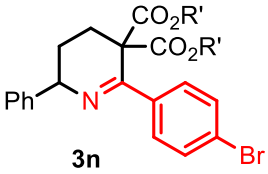
3l

R' = Me (18%)



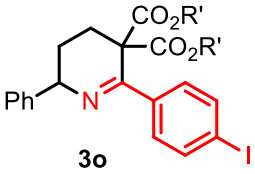
3m

R' = Me (31%)



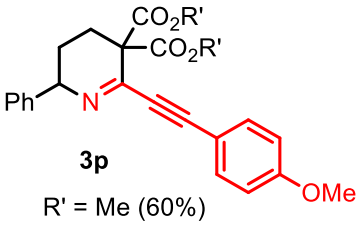
3n

R' = Me (43%)
R' = Et (65%)



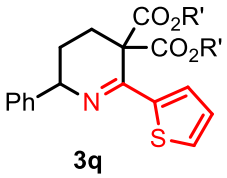
3o

R' = Me (55%)



3p

R' = Me (60%)



3q

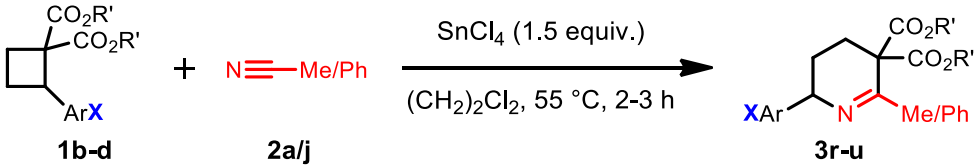
R' = Me (60%)
R' = Et (83%)

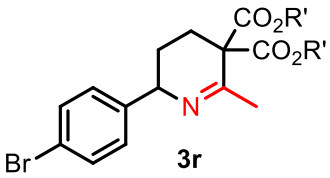
Cycloaddition of model cyclobutanes **1a-Me** and **1a-Et** with nitriles. [a]Acetonitrile used as solvent (0.1 M). General procedure: To a solution of cyclobutane (1.0 equiv, 0.4 mmol) and nitrile (3.0 equiv, 1.2 mmol) in dichloroethane (DCE) at 55 °C was added dropwise $SnCl_4$ (1.5 equiv, 0.6 mmol) in 2 mL DCE.

Electronically diverse aromatic nitriles (**3h–q**) were well tolerated, providing the cycloadduct in moderate to good yields. More strongly electron-donating groups such as *para*-methoxy (**3h**) are the most efficient reactive partners. On the other hand, a decline in yield was observed as more electron-withdrawing nitriles were evaluated, such as *para*-trifluoromethyl (**3l**). In addition, the cycloaddition reaction with aryl halides (**3m–o)** were successful in moderate yields. Alkynyl nitriles also underwent effective cycloaddition when supported with sufficient electronic donation, such as an anisole group (**3p**). 2-Thienyl nitriles also effectively engaged in the cycloaddition reaction (**3q**). The electronic trends observed with these aryl nitriles were consistent with a Ritter-type reaction mechanism.[85]

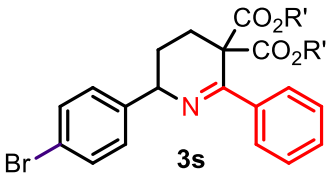
Next, the structural versatility of the cyclobutane was investigated (Table 4). To further evaluate the generality of the reaction, we selected acetonitrile (**2a**) and benzonitrile (**2j**) as the model alkyl and aryl nitriles, respectively, to explore various cyclobutanes (**1b–d**). Contrary to the electronic trend in the scope of the aryl nitrile, an inverse effect was observed when the aryl group of the cyclobutane was varied. The more electron-poor groups provided greater yields than the more electron-rich groups. Particularly, the *para*-bromo group afforded the cycloadducts with acetonitrile and benzonitrile in 71% and 82% yield, respectively (**3r-Et, 3s-Et**). These adducts, alongside the aryl halide adducts **3m–o**, would prove to be useful for a plethora of synthetic transformations, such as the many cross-coupling reactions that utilizes aryl halide substrates.

Table 4: Scope of cycloaddition with cyclobutanes with acetonitrile and benzonitrile.

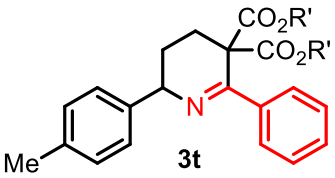




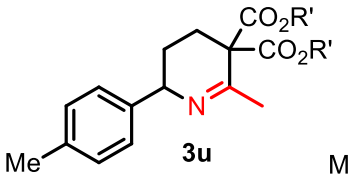
R' = Me (64%)
R' = Et (71%)



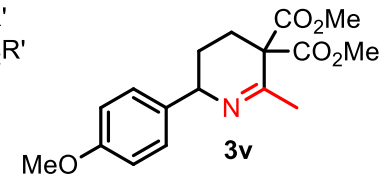
R' = Me (68%)
R' = Et (82%)



R' = Me (43%)
R' = Et (45%)



R' = Me (44%)
R' = Et (37%)



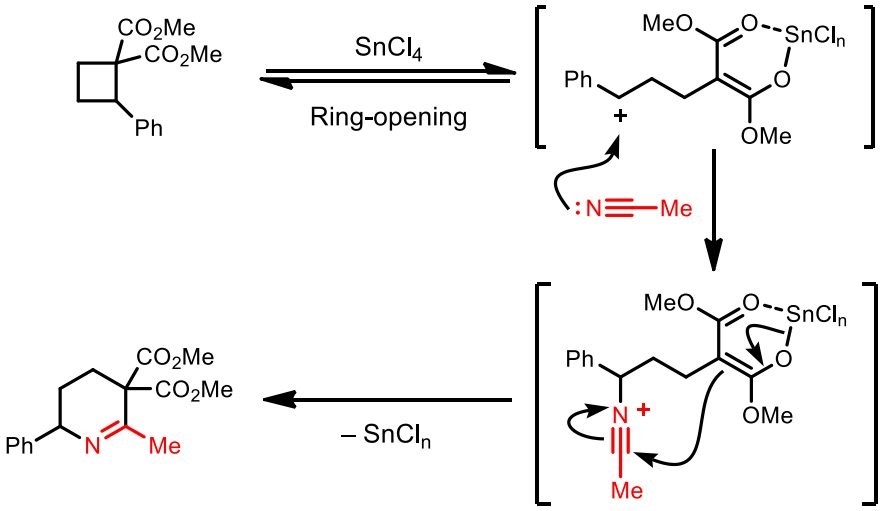
R' = Me (21%)
R' = Et (27%)

The cycloaddition seems to be hampered when the arene group of the cyclobutane carries electron-rich substituents. Particularly, increasing the donating strength on the arene group of the cyclobutane led to poor yields with acetonitrile and resulted in decomposition in the reaction with benzonitrile, and a considerable amount of the carbocyclic side product (**4a**) was formed. It appears that the side reaction pathway becomes significantly more competitive when the arene can strongly stabilize the benzylic carbocation, for instance when it carries a *para*-methoxy group (**3v**). As a result, application of donor-substituted aryl cyclobutanes for this work's [4+2] cycloaddition reaction is limited in this regard.

It is unclear whether the nitrile attack occurs *via* an S_N2 mechanism or *via* a putative zwitterionic intermediate, although the latter seems more likely. The postulated mechanism outlined in Scheme 42 illustrates the assumption that the cyclobutane exists as the zwitterionic

intermediate. Upon ring-opening to afford the zwitterionic intermediate, like a Ritter reaction, the nucleophilic nitrile attacks the benzylic carbocation to form a Ritter-type nitrilium intermediate. The rationale for the involvement of the nucleophilic component of this mechanism is substantiated by the mechanistic studies provided by our similar work on the [4+2] cycloaddition of DA cyclobutanes and aldehydes.[83] Our report showed that the pathway had a complete preference for electron-rich aldehyde, ruling out any involvement of an electrophilic component. Thus, the resulting nitrilium ion is subsequently intercepted by an intramolecular attack of the enolate to afford the tetrahydropyridine cycloadduct. This pathway is similar to the one proposed by Matsuo for the reaction between cyclobutanones and aldehydes or ketones where the cyclobutanone undergoes ring-opening to form a zwitterionic intermediate, followed by annulation to afford tetrahydropyrans.[56] Trushkov also proposed a similar mechanism for the analogous DA cyclopropane cycloaddition with nitriles.[44]

Unlike the proposed achiral zwitterionic intermediate pathways, an S_N2-like mechanism through a tight ion-pair was suggested for the [3+2] cycloaddition reaction between cyclopropane 1,1-diesters with aldehydes by Johnson and co-workers.[86] Through this tight-ion pair interaction, the stereochemical information is retained to make the cycloaddition stereoselective. It thought of as a form of a pseudo-S_N2 reaction where there is a continuum between the S_N2 and the S_N1 reaction mechanisms. However, when a complete ring-opening event occurs, all stereochemical information of the cycloalkane is lost as the achiral cationic intermediate proceeds through the cycloaddition.



Scheme 42: Proposed mechanism of the [4+2] cycloaddition of DA cyclobutanes and nitriles.

It worth noting that the studied [4+2] cycloaddition was found to be unfeasible with some nitrile partners for various reasons. A list of the failed nitriles and their results are summarized in Table 5. The reaction of acrylonitrile provided an inseparable complex mixture (entry 1). The presumed [4+2] cycloadduct formed *in situ* might have behaved as a potent Michael acceptor resulting in various side-reactions, isomerizations, and/or decomposition during reaction work-up or purification. The bulky pivalonitrile was unsuccessful (entry 2). Pivalonitrile has shown success in Ritter reactions,[87] but in the present work, it is believed that the nitrilium intermediate from the preceding nucleophilic attack is "stuck" and is unable to undergo the subsequent cyclization event as a result of steric hinderance. As demonstrated from the reaction scope, the cycloaddition became inefficient with electron-withdrawing groups on the nitrile. The cycloaddition was completely suppressed in the presence of strongly electron-deficient nitriles (entry 4–5), such as *para*-nitrobenzonitrile, and increasing temperature and/or reaction time only pushed the reaction to completion for solely the side product. It can be thus inferred that the stabilization of the nitrilium intermediate is key to the success of the cycloaddition reaction. The reaction of bromopropionitrile, cinnamonitrile, furonitrile, trimethylsilyl cyanide only resulted in decomposition (entry 3, 6–8).

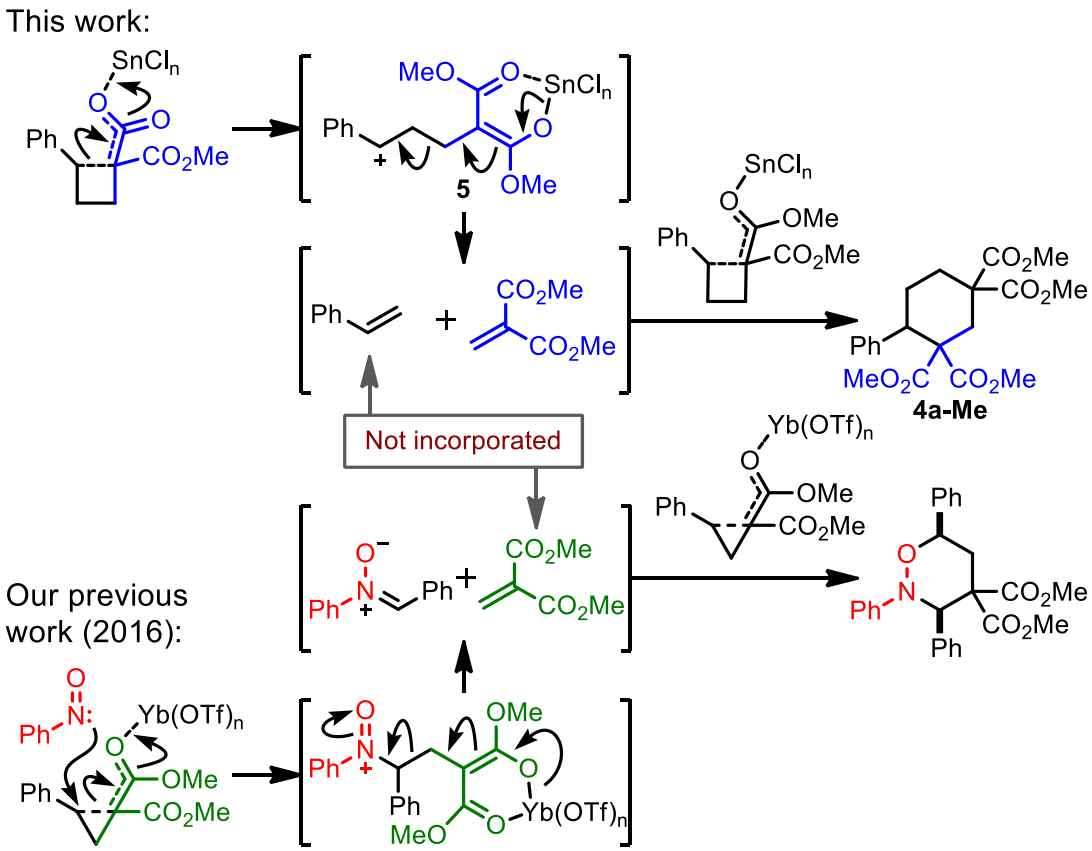
Aminobenzonitrile, cyanoacetanilide, and cyanopyridines were incompatible reactive partners presumably because $SnCl_4$ has a stronger preference to coordinate to the existing basic nitrogen lone pairs (entry 9–13). As a result, Lewis acid activation of the geminal diesters was terminated and only starting material was recovered. The $SnCl_4$ equivalents were increased to 4.5 to see if the reaction would still occur whilst the nitriles were tin-coordinated but the results were unfruitful. Interestingly, the reaction of 2-cyanopyridine led to a dark brown tar (entry 10). The effect of an adjacent nitrile group and lone pair coordination of 2-cyanopyridine might have caused some form of C–H bond activation for the nitrile to undergo several subsequent reactions, leading to the overall decomposition of the reaction mixture.

Table 5: Failed nitrile examples.

Entry	Nitrile	Result
1	Acrylonitrile	Complex mixture
2	Pivalonitrile	Complex mixture
3	3-Bromopropionitrile	Decomposition
4	4-Nitrobenzonitrile	Side-product
5	1,4-Dicyanobenzene	Side-product
6	Cinnamonitrile	Decomposition
7	2-Furonitrile	Decomposition
8	Trimethylsilyl cyanide	Decomposition
9	4-Aminobenzonitrile	No reaction
10	4'-Cyanoacetanilide	No reaction
11	2-Cyanopyridine	Decomposition
12	3-Cyanopyridine	No reaction
13	4-Cyanopyridine	No reaction

2.2.2 Investigating the Side Reaction of DA Cyclobutanes

Due to the presence of several electrophilic and nucleophilic centres, isomerizations and/or recombinations can occur with one another. These events have been well documented with several DA cyclopropanes.[88] It has been reported that $SnCl_4$ and other strongly activating Lewis acids were able to induce the lactonization of DA cyclopropanes.[89] In the presented work, we report a different phenomenon occurring for the low yielding and failed reactions. Scheme 43 depicts the rationale for the formation of the observed carbocyclic side-product where the DA cyclobutane was the sole reactant. The formation of the carbocycle starts with the zwitterionic intermediate whereby it subsequently undergoes E1cB fragmentation into styrene and methylene malonate. The methylene malonate can then undergo the [4+2] cycloaddition with another zwitterionic molecule to form the 6-membered carbocyclic framework. For the intended reactions that had moderate to good yields, little to trace amounts of this side-product was formed. However, for the examples with low yields, the side-product was obtained in greater amounts or exclusively. Therefore, the ability of the dipolarophiles to quickly trap the zwitterionic intermediate is important in preventing the cyclobutane fragmentation event and the subsequent formation of the undesired side-product (**4a**).

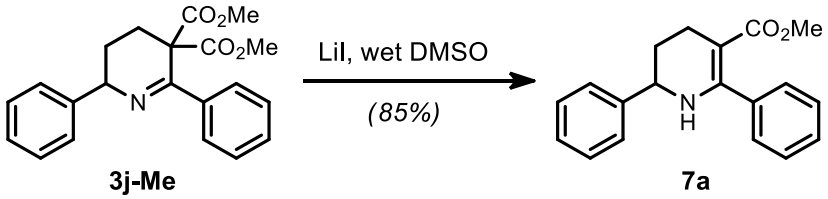


Scheme 43: Proposed mechanism for the formation of the carbocycle side-product.

Analogously, we previously investigated this tandem fragmentation/recombination phenomenon extensively with cross-over experiments using DA cyclopropanes in the presence of $Yb(OTf)_3$ catalyst.[90] The report discloses a tandem ring-opening, elimination, and cycloaddition of DA cyclopropanes with nitrosoarenes. In this report, the nitrone, rather than the methylidene malonate, reacts with another equivalent of activated cyclopropane to give tetrahydro-1,2-oxazine products instead of the expected isoxazolidine cycloadducts. What is happening here is different from the isomerization and cyclodimerization products reported by Tomilov's group,[88] and others,[91] and our 6-membered carbocycle can prove to be a useful intermediate in target-oriented synthesis.

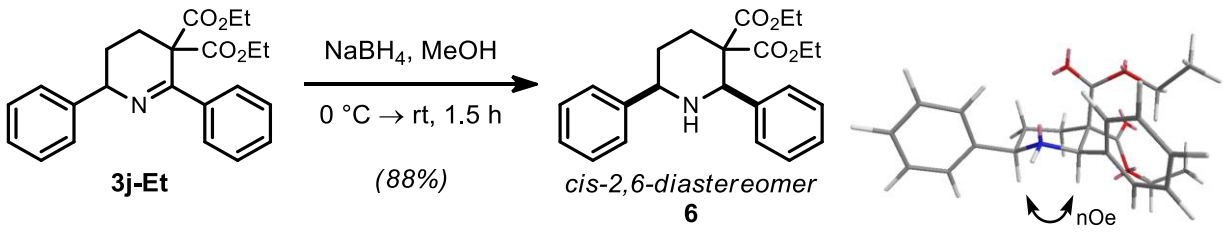
2.2.3 The Synthetic Potential of the Tetrahydropyridine Cycloadduct

To expand the synthetic potential of the [4+2] cycloadducts, we sought to examine the amenability of the tetrahydropyridine core through classic transformations. We found that the cycloadduct was cleanly transformed to the vinylogous carbamate in excellent yield *via* a Krapcho dealkoxycarbonylation (Scheme 44) using LiI in wet DMSO.[92] However, this synthetic route is limited to only dimethyl esters and the reaction failed to proceed for the cycloadducts from diethyl esters. Nonetheless, the product of these transformations has functional appendages that can be subjected to additional synthetic manipulations.



Scheme 44: Krapcho dealkoxycarbonylation of the tetrahydropyridine cycloadduct.

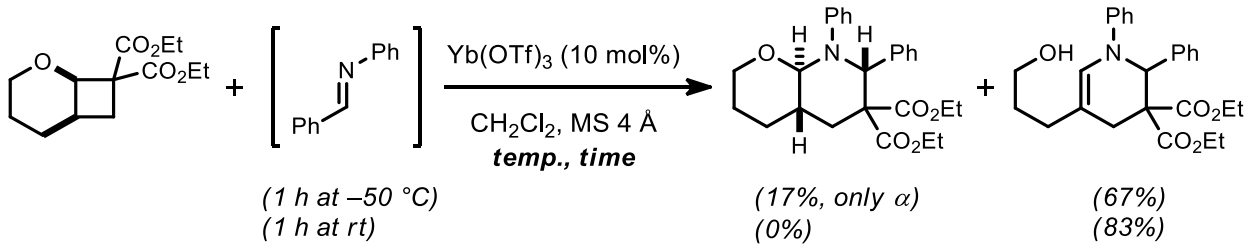
Furthermore, a substituted piperidine derivative was readily accessed in excellent yield by reduction with $NaBH_4$ in MeOH (Scheme 45). The transformation generated a new stereogenic centre, and the product was obtained in a diastereoselective manner. The *cis*-2,6-diastereomer was formed exclusively as the geometry was elucidated using 2D-NMR nOe studies. This stereochemical outcome aligns with the work by Johnson and co-workers where they report the diastereoselective formation of the *cis*-2,6-diastereomer of tetrahydropyrans *via* [4+2] cycloaddition between DA cyclobutanes and aryl aldehydes.[58]



Scheme 45: Diastereoselective reduction of the tetrahydropyridine cycloadduct.

2.2.4 Preliminary Studies of the Nitrile Cycloaddition of Alkoxy-Activated DA Cyclobutanes

Having demonstrated that the DA cyclobutanes bearing aryl-based carbon donors effectively undergo a formal [4+2] cycloaddition reaction with nitriles, we wanted to explore the nitrile cycloaddition chemistry with our AACDs. In the past, we have shown that imines undergo cycloaddition chemistry with AACDs to afford piperidines (Scheme 37). The formation of the bicyclic piperidine was observed only when the reaction was conducted at low temperatures, but the yield was low. The formation and isolation of hemi-aminal groups brings some difficulty due to their inherent instability, and as a result, conversion to the elimination product was favored when warmed to room temperature (Scheme 46**)**.



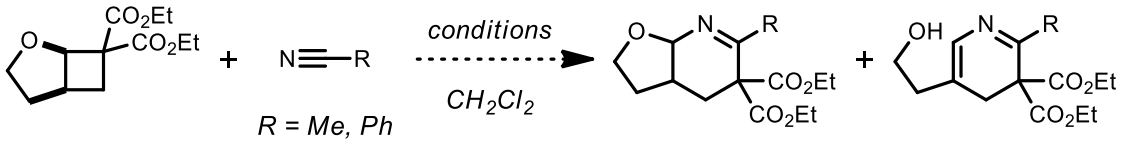
Scheme 46: The [4+2] cycloaddition and elimination between DA cyclobutanes and imines.

The analogous hemi-iminal may be obtained from AACDs and nitriles using similar reaction conditions, although the stability of the desired cycloadduct may prove to be problematic. The elimination product is expected to be isolated at least, which seems to also be the favorable product due to the extension of conjugation.

Preliminary experiments were conducted to investigate to propensity of the nitrile group to undergo cycloaddition with AACDs using alkyl- (MeCN) and phenyl-substituted (PhCN). Results are summarized in Table 6. Several Lewis acid screening experiments were conducted at -78 °C; however, no change in TLC was observed. Upon slowly warming the reaction mixtures, only decomposition of the cyclobutane was observed (entry 1–14). It appears that the nitrile lacks sufficient nucleophilicity in order to proceed through the cycloaddition manifold. Any

incorporation of the nitrile was absent. A change in procedure was then devised as was inspired from our work on $BF_3{\cdot}OEt_2$-promoted reaction between AACDs and alkynes (Scheme 12). The previous protocol by the Pagenkopf group involved the addition of all reaction components together and immediately placing the flask into a pre-heated oil bath and heating to DCE reflux temperature (entry 15–17). However, this was not helpful for the current reaction.

Table 6: Preliminary reaction condition screening for the reaction between AACDs and nitriles.



Entry	Lewis acid (equiv)	R	Solvent.	Temp.	Result
1	$Yb(OTf)_3$ (10 mol%)	Me	MeCN	rt	dec
2	$Yb(OTf)_3$ (10 mol%)	Me	MeCN	-40 °C	dec
3	$Yb(OTf)_3$ (10 mol%)	Me	DCM	-78 °C → rt	dec
4	$La(OTf)_3$ (10 mol%)	Me	DCM	-78 °C	dec
5	$Zn(OTf)_2$ (10 mol%)	Me	DCM	-78 °C → rt	dec
6	$ZnBr_2$ (10 mol%)	Me	DCM	-78 °C → rt	nr
7	$Yb(OTf)_3$ (10 mol%)	Ph	DCM/$MeNO_2$	-78 °C	dec
8	$La(OTf)_3$ (10 mol%)	Ph	DCM/$MeNO_2$	-78 °C	dec
9	$Zn(OTf)_2$ (10 mol%)	Ph	DCM	-78 → 0 °C	dec
10	$ZnBr_2$ (10 mol%)	Ph	DCM	-78 °C → rt	dec
11	AgOTf (10 mol%)	Ph	DCM	0 °C → rt	dec
12	$Cu(OTf)_2$	Ph	DCM	0 °C	dec
13	$[Cu(OTf)]_2{\cdot}C_6H_6$	Ph	DCM	0 °C	dec

14	TMSOTf (1.1 equiv.)	Ph	DCM	0 °C	dec
15	$Yb(OTf)_3$ (10 mol%)	Ph	DCE	reflux	dec
16	$BF_3 \cdot OEt_2$ (10 mol%)	Ph	DCE	reflux	dec
17	$BF_3 \cdot OEt_2$ (1.1 equiv.)	Ph	DCE	reflux	dec

Typical reaction conditions: Reactions were run in the indicated solvent at 0.4 mmol scale with MeCN or PhCN (10 equiv.). DCM = dichloromethane. DCE = dichloroethane. MeNO2 = nitromethane. MeCN = acetonitrile. PhCN = benzonitrile. dec = decomposition. nr = no reaction.

Chapter 3. Conclusion

In conclusion, we have disclosed the first [4+2] cycloaddition between DA cyclobutanes and nitriles *via* a $SnCl_4$-promoted strategy for the synthesis of structurally diverse tetrahydropyridines. The reaction tolerates a variety of electronically diverse cyclobutanes and both aliphatic and aromatic nitriles. However, the reaction falls short when strongly electron-donating groups are on the cyclobutane, or when the nitriles carry basic nitrogen substitutions, inherently incompatible with $SnCl_4$. We have also further demonstrated the synthetic amenability of the cycloadduct to additional synthetic transformations. For example, reduction with $NaBH_4$ gave exclusively *cis*-2,6-piperidine and the Krapcho dealkoxycarbonylation gave the vinylogous carbamate, both in excellent yields.

Chapter 4. Future Work

The formal [4+2] cycloaddition reaction is postulated to proceed through an achiral zwitterionic intermediate. As a result, the products are obtained as a racemic mixture. Previously, a work studied enantio-pure DA cyclopropanes in the presence of Lewis acid which revealed the degradation of enantiopurity towards a racemic mixture over time.[86] Studies on an asymmetric variant of the cycloaddition reaction by controlling the achiral environment to achieve an enantiomerically pure product would be an intriguing venture for this reaction and for others to follow.

With regard to the cycloaddition reaction occurring with other types of DA cyclobutanes, the work on investigating the reactivity of AACDs with nitriles is an ongoing effort. Although the preliminary results were unfruitful, more judicious method development to tune nitrile nucleophilicity while maintaining the integrity of the reactive AACDs is crucial for the success of the cycloaddition event. Additional experiments are underway, particularly investigating the use of *para*-methoxybenzonitrile as an activated nitrile reactive partner.

Moreover, we sought to investigate other dipolarophiles. Allyl silanes have been brought to light as an excellent dipolarophile for a formal [4+2] cycloaddition, as well as an effective reagent for the allylic alkylation of cyclobutanes. Work on the chemoselective reaction between cycloaddition and allylation of the cyclobutane is underway.

Chapter 5. Experimental Section

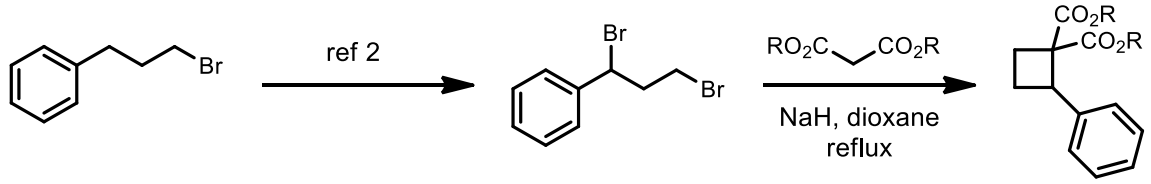
5.1 General Experimental Details

All reactions were performed under argon atmosphere unless otherwise indicated. Flasks were oven- or flame-dried and cooled in a desiccator prior to use. Solvents and reagents were purified by standard methods.[93] All chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions was monitored by thin layer chromatography (TLC) using SilicaPlate Aluminum Backed TLC 200 μm. The plates were visualized by UV light (254 nm) and by staining with ceric ammonium molybdate (CAM). Flash column chromatography was performed with Silica Flash P60 60Å silica gel from *SiliCycle*® according to the Still method.[94]

^{1}H NMR and ^{13}C NMR spectroscopic data were obtained on either 400 or 600 MHz spectrometers (Bruker 400, Inova 400, and Inova 600). All spectra were obtained in deuterated chloroform and were referenced to the residual chloroform at δ = 7.26 ppm for the ^{1}H spectra and the centre peak of the triplet at δ = 77.0 ppm for the ^{13}C spectra. The coupling constant '*J*' is in Hz. The peak multiplicities are given in the following abbreviations: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplet, m = multiplet. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS spectrometer at an ionizing voltage of 70 eV. Infrared Spectra (IR) were acquired using a Bruker FTIR spectrometer ALPHA II.

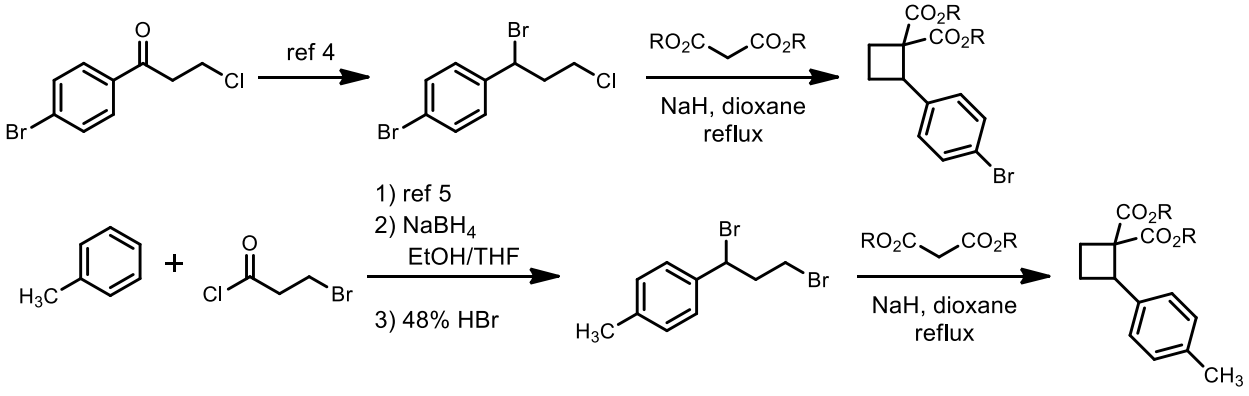
5.2 Preparation and Characterization of Compounds

Preparation of aryl-activated cyclobutane−1,1-dicarboxylates

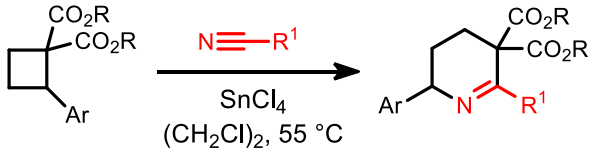


A 2-neck round bottom flask was affixed with a reflux condenser and was equipped with a magnetic stir bar. To a solution of (1,3-dibromopropyl)benzene[95] (1.0 equiv), malonate (1.0 equiv), and anhydrous dioxane was added sodium hydride (1.1 equiv) in 3 portions over approximately 10 min at rt. The reaction was heated at reflux for 1 h, cooled to rt, and additional sodium hydride (1.1 equiv) was added. The reaction was then heated at reflux for an addition 12 h before being cooled to rt. The resulting heterogeneous mixture was filtered through celite, and the filter cake was washed with Et_2O. The organic solution was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The crude cyclobutane was purified by flash column chromatography (2.5%–5.0% EtOAc/hexanes).

The *p*-bromo[96] and tolyl[97] cyclobutanes (shown below) were prepared according to the general procedure, and the precursors were made according literature procedures.

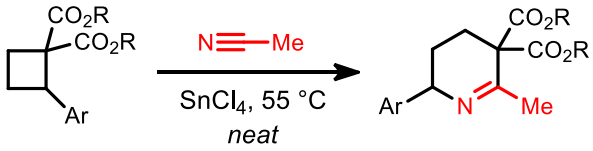


General $SnCl_4$-Promoted Cycloaddition Procedure:



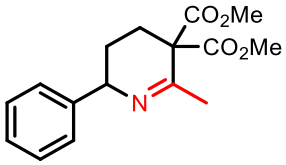
To a solution of cyclobutane (1.0 equiv, 0.4 mmol) and nitrile (3.0 equiv, 1.2 mmol) in 1,2-dichloroethane (DCE) at 55 °C was added dropwise a solution of $SnCl_4$ (1.5 equiv, 0.6 mmol, 156 mg) in DCE (2 mL). After 3 h or full consumption of cyclobutane (monitored by TLC), the reaction mixture was poured into an aqueous saturated $NaHCO_3$ solution, and extracted with DCM (3×15 mL). The combined organic layers were washed with water, dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexanes) to give the corresponding product.

General $SnCl_4$-Promoted Cycloaddition Procedure with MeCN Solvent:



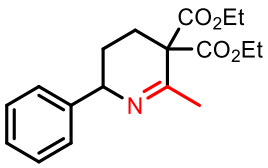
To an acetonitrile solution of the cyclobutane (1.0 equiv, 0.4 mmol, 0.1 mmol/mL) at 55 °C was added neat $SnCl_4$ (1.5 equiv, 0.6 mmol, 70 µL) dropwise. After 2 h (monitored by TLC) the reaction was cooled to room temperature and acetonitrile was removed under reduced pressure. The crude reaction mixture was dissolved in dichloromethane (DCM), poured into a saturated aqueous $NaHCO_3$ solution, and extracted with DCM (3×15 mL). The combined organic layers were washed with water, dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexanes) to give the corresponding product.

Characterization Data Summaries for New Compounds:



Dimethyl 2-methyl-6-phenyl-5,6-dihydropyridine-3,3(4*H*)-dicarboxylate (3a-Me).

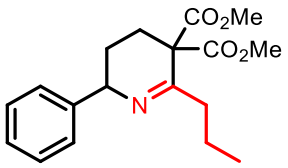
The title compound was prepared according to the general procedure to afford a pale-yellow oil (60 mg, 52%). **R_f** = 0.29 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.37–7.28 (m, 2H), 7.26–7.16 (m, 3H), 4.68 (ddq, *J* = 9.8, 4.4, 2.1 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.44 (ddd, *J* = 13.4, 6.3, 3.3 Hz, 1H), 2.31 (ddd, *J* = 13.4, 11.7, 3.3 Hz, 1H), 2.23 (d, *J* = 2.2 Hz, 3H), 2.03 (dddd, *J* = 14.1, 6.4, 5.5, 3.3 Hz, 1H), 1.45 (dddd, *J* = 14.0, 11.7, 9.1, 3.4 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.05, 169.67, 160.11, 143.84, 128.46, 126.83, 126.68, 61.76, 59.43, 53.07, 53.05, 27.50, 27.35, 25.81. **IR**, *v* (cm^{-1}): 3027, 2953, 2861, 1727, 1657, 1602, 1434, 1251, 1166. **HRMS** *m/z* 289.1321 (calcd. for $C_{16}H_{19}NO_4$, 289.1314).



Diethyl 2-methyl-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3a-Et).

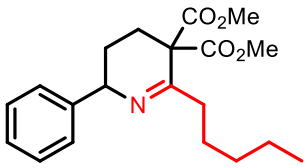
The title compound was prepared according to the general procedure to afford a pale-yellow oil (88 mg, 70%). **R_f** = 0.35 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.36–7.29 (m, 2H), 7.26–7.17 (m, 3H), 4.68 (m, 1H), 4.33–4.24 (m, 4H), 2.43 (dddd, *J* = 13.3, 6.4, 3.4, 1.0 Hz, 1H), 2.31 (dddd, *J* = 13.1, 11.5, 3.2, 1.1 Hz, 1H), 2.25 (m, 3H), 2.07–1.98 (m, 1H), 1.51–1.40 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.53, 169.17, 160.48, 143.96, 128.40, 126.76, 126.69, 62.11, 61.98, 61.76,

59.57, 41.90, 27.42, 27.37, 25.84, 13.99, 13.96. **IR**, *v* (cm^{-1}): 2938, 1723, 1656, 1448, 1250. **HRMS** *m/z* 317.1628 (calcd. for $C_{18}H_{23}NO_4$, 317.1627).



Dimethyl 6-phenyl-2-propyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3b-Me).

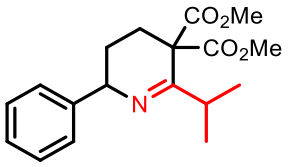
The title compound was prepared according to the general procedure to afford a pale-yellow oil (56 mg, 44%). **R_f** = 0.55 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.35–7.29 (m, 2H), 7.26–7.18 (m, 3H), 4.72 (ddt, *J* = 7.6, 5.1, 2.2 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.52–2.27 (m, 4H), 2.04 (dddd, *J* = 14.0, 6.4, 5.6, 3.3 Hz, 1H), 1.79–1.64 (m, 2H), 1.40 (dddd, *J* = 14.0, 11.6, 9.0, 3.4 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.20, 169.87, 162.68, 144.18, 128.35, 126.65, 126.58, 61.24, 59.66, 53.00, 52.93, 39.79, 27.68, 20.01, 13.94. **IR**, *v* (cm^{-1}): 2954, 1727, 1657, 1434, 1250, 1165. **HRMS** *m/z* 317.1624 (calcd. for $C_{18}H_{23}NO_4$, 317.1627).



Dimethyl 2-pentyl-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3c-Me).

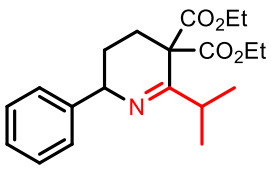
The title compound was prepared according to the general procedure to afford a pale-yellow oil (53 mg, 39%). **R_f** = 0.50 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.34–7.31 (m, 2H), 7.25–7.20 (m, 3H), 4.72 (ddd, *J* = 10.8, 5.3, 2.1 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.50 (dddd, *J* = 15.9, 10.1, 5.9, 1.7 Hz, 1H), 2.44–2.33 (m, 2H), 2.31 (ddd, *J* = 13.2, 11.6, 3.2 Hz,

1H), 2.04 (dddd, *J* = 13.9, 6.4, 5.6, 3.2 Hz, 1H), 1.75–1.63 (m, 2H), 1.41 (dddd, *J* = 14.0, 12.0, 8.9, 3.3 Hz, 1H), 1.36–1.27 (m, 4H), 0.92–0.86 (m, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.16, 169.85, 162.90, 144.14, 128.31, 126.61, 126.57, 61.19, 59.65, 52.97, 52.91, 37.82, 31.71, 27.67, 27.62, 26.42, 22.53, 14.08. **IR**, *v* (cm^{-1}): 2953, 1728, 1657, 1433, 1248, 1166. **HRMS** *m/z* 345.1932 (calcd. for $C_{20}H_{27}NO_4$, 345.1940).



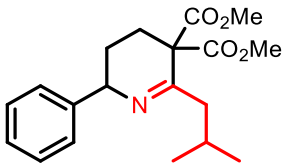
Dimethyl 2-isopropyl-6-phenyl-5,6-dihydropyridine-3,3(4*H*)-dicarboxylate (3d-Me).

The title compound was prepared according to the general procedure to afford a pale-yellow oil (61 mg, 48%). **R_f** = 0.57 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.35–7.30 (m, 2H), 7.24–7.19 (m, 3H), 4.74 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.78 (h, *J* = 6.7 Hz, 1H), 2.40 (ddd, *J* = 13.3, 6.7, 3.2 Hz, 1H), 2.31 (ddd, *J* = 13.4, 11.4, 3.2 Hz, 1H), 2.04 (dddd, *J* = 13.8, 6.7, 5.5, 3.2 Hz, 1H), 1.40 (dddd, *J* = 14.3, 11.7, 8.7, 3.3 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 170.11, 169.94, 168.26, 144.29, 128.34, 126.60, 126.57, 60.89, 59.90, 52.96, 52.87, 35.88, 27.93, 27.81, 22.42, 22.36. **IR**, *v* (cm^{-1}): 2953, 1727, 1656, 1434, 1250. **HRMS** *m/z* 317.1625 (calcd. for $C_{18}H_{23}NO_4$, 317.1627).



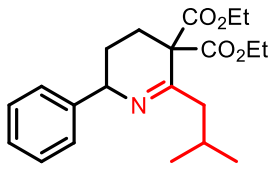
Diethyl 2-isopropyl-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3d-Et).

The title compound was prepared according to the general procedure to afford a pale-yellow oil (78 mg, 57%). **R_f** = 0.64 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.34–7.19 (m, 5H), 4.76 (dd, *J* = 8.6, 5.4 Hz, 1H), 4.33–4.22 (m, 4H), 2.84 (hept, *J* = 6.7 Hz, 1H), 2.40 (ddd, *J* = 13.4, 6.7, 3.5 Hz, 1H), 2.31 (ddd, *J* = 13.4, 11.1, 3.2 Hz, 1H), 2.05 (dddd, *J* = 13.9, 6.7, 5.5, 3.2 Hz, 1H), 1.46–1.37 (m, 1H), 1.36–1.24 (m, 12H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.61, 169.46, 168.59, 144.34, 128.25, 126.55, 126.51, 62.05, 61.87, 60.87, 59.99, 35.69, 27.98, 27.68, 22.45, 22.42, 13.96, 13.94. **IR**, *v* (cm^{-1}): 2978, 2934, 2871, 1725, 1656, 1448, 1367, 1241, 1175, 1022, 753, 699. **HRMS** *m/z* 345.1936 (calcd. for $C_{20}H_{27}NO_4$, 345.1940).



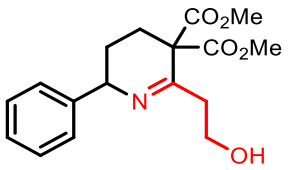
Dimethyl 2-isobutyl-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3e-Me).

The title compound was prepared according to the general procedure to afford a pale-yellow oil (77 mg, 58%). **R_f** = 0.60 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.35–7.30 (m, 2H), 7.25–7.21 (m, 3H), 4.71 (ddt, *J* = 8.6, 5.6, 3.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.44 (ddd, *J* = 13.4, 6.2, 3.3 Hz, 1H), 2.40–2.25 (m, 4H), 2.05 (dtd, *J* = 14.6, 5.9, 3.3 Hz, 1H), 1.43 (dddd, *J* = 15.1, 12.3, 9.2, 3.3 Hz, 1H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 170.22, 169.85, 161.41, 144.35, 128.36, 126.65, 61.44, 59.81, 52.92, 52.81, 46.25, 27.98, 27.67, 25.01, 22.84, 22.23. **IR**, *v* (cm^{-1}): 2954, 1727, 1657, 1434, 1250, 1165. **HRMS** *m/z* 331.1778 (calcd. for $C_{19}H_{25}NO_4$, 331.1784).



Diethyl 2-isobutyl-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3e-Et).

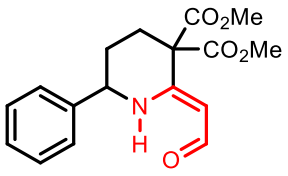
The title compound was prepared according to the general procedure to afford a pale-yellow oil (106 mg, 74%). **R_f** = 0.68 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.35–7.21 (m, 5H), 4.72 (app ddd, *J* = 9.4, 5.4, 2.6 Hz, 1H), 4.32–4.22 (m, 4H), 2.47–2.37 (m, 2H), 2.36–2.28 (m, 3H), 2.05 (dddd, *J* = 13.9, 5.9, 5.9, 3.3 Hz, 1H), 1.49–1.39 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 13.4 Hz, 3H) 0.95 (d, *J* = 13.4 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.76, 169.43, 161.74, 144.46, 128.32, 126.68, 126.61, 62.00, 61.87, 61.50, 59.89, 46.27, 27.89, 27.77, 24.89, 22.90, 22.31, 14.02, 13.98. **IR**, *v* (cm^{-1}): 2985, 2867, 1725, 1657, 1449, 1366, 1257, 1162, 1094, 1023, 751, 699. **HRMS** *m/z* 359.2093 (calcd. for $C_{21}H_{29}NO_4$, 359.2097).



Dimethyl 2-(2-hydroxyethyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3f-Me).

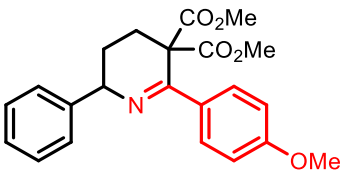
The title compound was prepared according to the general procedure to afford a yellow oil (43 mg, 34%). **R_f** = 0.27 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.34 (app t, *J* = 7.3 Hz, 2H), 7.30–7.25 (m, 3H), 4.25 (dd, *J* = 7.7, 5.2 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.51–3.43 (m, 2H), 3.37 (t, *J* = 7.4 Hz, 1H), 2.57–2.48 (m, 2H), 2.07 (dddd, *J* = 11.8, 9.2, 6.7, 3.9 Hz, 1H), 1.91–1.80 (m, 2H), 1.70–1.64 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.65, 169.64, 140.90, 128.69, 128.12, 126.49, 117.77, 82.51, 63.22, 52.52, 52.48, 51.34, 35.59,

25.24, 18.95. **IR**, *v* (cm^{-1}): 2954, 2251, 1729, 1435, 1097. **HRMS** *m/z* 319.1420 (calcd. for $C_{17}H_{21}NO_5$, 319.1415).



(*Z*)-Dimethyl 2-(2-oxoethylidene)-6-phenylpiperidine-3,3-dicarboxylate (3g-Me).

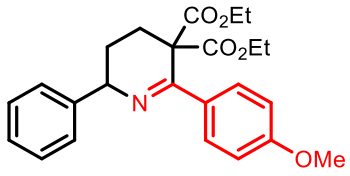
The title compound was prepared according to the general procedure to afford a yellow solid (45 mg, 35%), mp 134–135 °C. **R_f** = 0.19 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 11.56 (s, 1H), 9.08 (d, *J* = 2.6 Hz, 1H), 7.41–7.27 (m, 5H), 5.16 (d, *J* = 2.6 Hz, 1H), 4.61 (ddd, *J* = 9.1, 5.6, 1.7 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.51 (ddd, *J* = 13.8, 6.7, 3.3 Hz, 1H), 2.43 (ddd, *J* = 13.9, 11.1, 3.2 Hz, 1H), 2.21–2.12 (m, 1H), 1.67 (dddd, *J* = 14.4, 11.8, 8.9, 3.4 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 186.77, 169.15, 169.00, 158.22, 142.01, 128.92, 128.04, 126.08, 96.10, 58.78, 56.11, 53.49, 28.35, 26.97. **IR**, *v* (cm^{-1}): 2952, 2850, 2200, 1729, 1619, 1573, 1257. **HRMS** *m/z* 317.1263 (calcd. for $C_{17}H_{19}NO_5$, 317.1263).



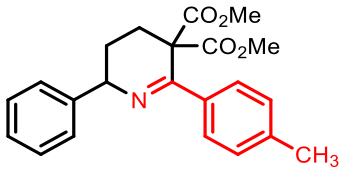
Dimethyl 2-(4-methoxyphenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3h-Me).

The title compound was prepared according to the general procedure to afford an off-white syrup (96 mg, 63%). **R_f** = 0.30 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.75–7.67 (m, 2H), 7.39–7.34 (m, 2H), 7.33–7.29 (m, 2H), 7.28–7.24 (m, 1H), 6.91–6.84 (m, 2H),

4.97 (dd, *J* = 8.7, 5.9 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H), 2.57 (ddd, *J* = 13.2, 6.5, 3.8 Hz, 1H), 2.47 (ddd, *J* = 13.2, 11.2, 3.5 Hz, 1H), 2.21–2.13 (m, 1H), 1.60–1.53 (m, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.41, 170.31, 160.42, 160.30, 144.18, 132.09, 129.24, 128.47, 126.77, 126.74, 113.15, 61.92, 59.02, 55.23, 52.98, 52.92, 29.49, 27.55. **IR**, *v* (cm^{-1}): 2953, 1728, 1604, 1433, 1250. **HRMS** *m/z* 381.1576 (calcd. for $C_{22}H_{23}NO_5$, 381.1576).

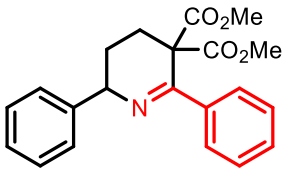


Diethyl 2-(4-methoxyphenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3h-Et). The title compound was prepared according to the general procedure to afford a pale-yellow oil (106 mg, 74%). **R_f** = 0.59 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.74–7.65 (m, 2H), 7.35–7.22 (m, 5H), 6.86–6.81 (m, 2H), 4.94 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.22 (app qd, *J* = 7.1, 2.4 Hz, 2H), 4.16–4.04 (m, 2H), 3.81 (s, 3H), 2.54 (ddd, *J* = 13.2, 6.5, 3.8 Hz, 1H), 2.44 (ddd, *J* = 13.1, 11.1, 3.5 Hz, 1H), 2.15 (dddd, *J* = 14.0, 6.3, 6.3, 3.6 Hz, 1H), 1.56 (dddd, *J* = 14.3, 11.2, 8.7, 3.8 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.85, 169.79, 160.82, 160.39, 144.29, 132.33, 129.45, 128.41, 126.77, 126.71, 113.01, 61.99, 61.97, 61.94, 59.15, 55.24, 29.37, 27.62, 13.88, 13.68. **IR**, *v* (cm^{-1}): 2980, 2937, 2906, 1726, 1605, 1512, 1246, 1174, 1028, 837, 730, 699. **HRMS** *m/z* 409.1887 (calcd. for $C_{24}H_{27}NO_5$, 409.1889).



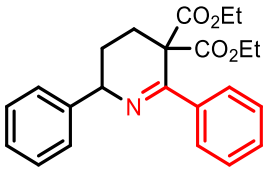
Dimethyl 6-phenyl-2-(p-tolyl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3i-Me).

The title compound was prepared according to the general procedure to afford a white solid (83 mg, 57%), mp 85–88 °C. **R_f** = 0.38 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.63–7.57 (m, 2H), 7.36–7.31 (m, 2H), 7.29–7.21 (m, 3H), 7.17–7.08 (m, 2H), 4.94 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 2.58–2.41 (m, 2H), 2.34 (s, 3H), 2.15 (dddd, *J* = 14.1, 6.2, 6.2, 3.6 Hz, 1H), 1.60–1.50 (m, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.34, 170.28, 160.99, 144.12, 139.26, 136.65, 128.57, 128.48, 127.60, 126.78, 126.75, 62.01, 59.07, 52.97, 52.90, 29.50, 27.57, 21.25. **IR**, *v* (cm^{-1}): 2953, 2921, 1740, 1631, 1428, 1242. **HRMS** *m/z* 365.1619 (calcd. for $C_{22}H_{23}NO_4$, 365.1627).



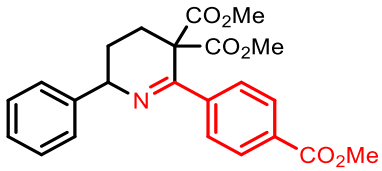
Dimethyl 2,6-diphenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3j-Me).

The title compound was prepared according to the general procedure to afford a white solid (68 mg, 49%), mp 79–81 °C. **R_f** = 0.53 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.72–7.66 (m, 2H), 7.36–7.31 (m, 5H), 7.29–7.26 (m, 2H), 7.26–7.23 (m, 1H), 4.95 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 2.55 (ddd, *J* = 13.3, 6.4, 3.9 Hz, 1H), 2.48 (ddd, *J* = 13.2, 11.3, 3.7 Hz, 1H), 2.16 (dddd, *J* = 14.2, 6.3, 6.3, 3.6 Hz, 1H), 1.60–1.55 (m, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.22, 170.19, 161.38, 143.97, 139.42, 129.23, 128.52, 127.88, 127.68, 126.84, 126.75, 62.15, 59.29, 53.00, 52.90, 29.33, 27.55. **IR**, *v* (cm^{-1}): 2955, 1747, 1625, 1435, 1250. **HRMS** *m/z* 351.1461 (calcd. for $C_{21}H_{21}NO_4$, 351.1471).



Diethyl 2,6-diphenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3j-Et).

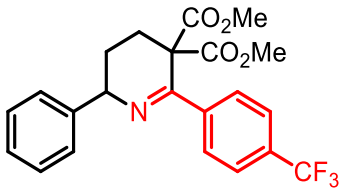
The title compound was prepared according to the general procedure to afford a white solid (114 mg, 75%). mp 98–100 °C. $\mathbf{R_f}$ = 0.37 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77–7.67 (m, 2H), 7.36–7.21 (m, 8H), 4.95 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.21 (qd, *J* = 7.2, 1.5 Hz, 2H), 4.15–3.99 (m, 2H), 2.60–2.41 (m, 2H), 2.17 (dddd, *J* = 12.4, 6.2, 6.2, 3.7 Hz, 1H), 1.63–1.54 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.71, 169.63, 144.08, 139.61, 129.16, 128.48, 127.93, 127.78, 127.77, 126.81, 126.78, 62.19, 62.07, 61.99, 59.40, 29.24, 27.64, 13.85, 13.58. **IR**, *v* (cm^{-1}): 2980, 1724, 1632, 1452, 1242. **HRMS** *m/z* 379.1779 (calcd. for $C_{23}H_{25}NO_4$, 379.1784).



Dimethyl 2-(4-(methoxycarbonyl)phenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3k-Me).

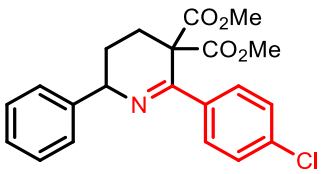
The title compound was prepared according to the general procedure to afford a pale-yellow syrup (62 mg, 38%). $\mathbf{R_f}$ = 0.42 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.04–7.97 (m, 2H), 7.81–7.73 (m, 2H), 7.40–7.26 (m, 5H), 4.97 (dd, *J* = 8.9, 6.0 Hz, 1H), 3.92 (s, 3H), 3.75 (s, 3H), 3.60 (s, 3H), 2.57 (ddd, *J* = 13.3, 6.3, 3.9 Hz, 1H), 2.48 (ddd, *J* = 13.3, 11.3, 3.6 Hz, 1H), 2.18 (dddd, *J* = 14.2, 6.2, 6.2, 3.6 Hz, 1H), 1.65–1.56 (m, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.96, 169.90, 166.76, 160.82, 143.58, 143.50, 130.57, 129.17, 128.60,

127.80, 127.00, 126.69, 62.44, 59.25, 53.13, 53.02, 52.17, 29.27, 27.48. **IR**, *v* (cm^{-1}): 2952, 2921, 2852, 1722, 1454, 1435, 1274, 1107. **HRMS** *m/z* 409.1527 (calcd. for $C_{23}H_{23}NO_6$, 409.1525).



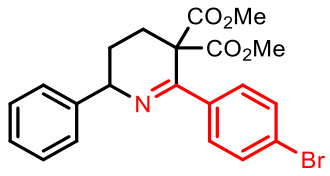
Dimethyl 6-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3l-Me).

The title compound was prepared according to the general procedure to afford a pale-yellow oil (30 mg, 18%). $\mathbf{R_f}$ = 0.50 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.38–7.33 (m, 2H), 7.27–7.25 (m, 3H), 4.97 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 2.58 (ddd, *J* = 13.2, 6.2, 3.6 Hz, 1H), 2.48 (ddd, *J* = 13.2, 11.6, 3.4 Hz, 1H), 2.19 (dddd, *J* = 14.3, 6.2, 6.2, 3.2 Hz, 1H), 1.61–1.57 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.91, 169.89, 160.31, 143.51, 142.65, 128.62, 128.20, 127.03, 126.67, 124.85, 124.82, 120.68, 62.47, 59.24, 53.17, 53.05, 29.31, 27.46. **IR**, *v* (cm^{-1}): 2953, 2926, 2856, 1729, 1633, 1451, 1326, 1245, 1165, 1122, 1067. **HRMS** *m/z* 419.1340 (calcd. for $C_{22}H_{20}F_3NO_4$, 419.1344).

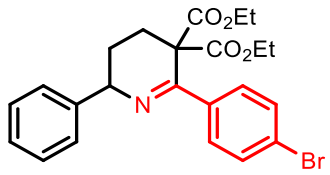


Dimethyl 2-(4-chlorophenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3m-Me).

The title compound was prepared according to the general procedure to afford a clear colorless syrup (48 mg, 31%). **R_f** = 0.44 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.71–7.66 (m, 2H), 7.38–7.30 (m, 4H), 7.28–7.24 (m, , 3H), 4.95 (dd, *J* = 8.9, 6.0 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 2.57 (ddd, *J* = 13.2, 6.4, 3.6 Hz, 1H), 2.47 (ddd, *J* = 13.2, 11.5, 3.5 Hz, 1H), 2.17 (dddd, *J* = 14.1, 6.2, 6.2, 3.5 Hz, 1H), 1.57 (dddd, *J* = 14.7, 11.5, 8.9, 3.6 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 170.03, 170.00, 160.17, 143.68, 137.76, 135.35, 129.16, 128.54, 128.03, 126.92, 126.65, 62.23, 59.11, 53.09, 53.00, 29.31, 27.44. **IR**, *v* (cm^{-1}): 2952, 2871, 1727, 1631, 1433, 1241. **HRMS** *m/z* 385.1074 (calcd. for $C_{21}H_{20}ClNO_4$, 385.1081).

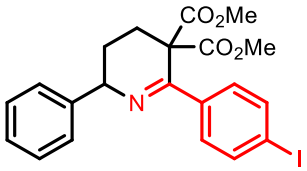


Dimethyl 2-(4-bromophenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3n-Me). The title compound was prepared according to the general procedure to afford a pale-yellow syrup (74 mg, 43%). **R_f** = 0.39 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.61–7.56 (m, 2H), 7.47–7.43 (m, 2H), 7.35–7.31 (m, 2H), 7.27–7.23 (m, 3H), 4.92 (dd, *J* = 8.9, 6.0 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 2.54 (ddd, *J* = 13.2, 6.3, 3.6 Hz, 1H), 2.44 (ddd, *J* = 13.2, 11.5, 3.5 Hz, 1H), 2.15–2.12 (m, 1H), 1.57–1.50 (m, 2H). **^{13}C NMR** (151 MHz, Chloroform-*d*) 170.05, 170.02, 160.27, 143.69, 138.25, 131.04, 129.45, 128.58, 126.95, 126.68, 123.83, 62.28, 59.09, 53.12, 53.04, 29.36, 27.47. **IR**, *v* (cm^{-1}): 2952, 1727, 1630, 1433, 1250. **HRMS** *m/z* 429.0580 (calcd. for $C_{21}H_{20}BrNO_4$, 429.0576).



Diethyl 2-(4-bromophenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3n-Et).

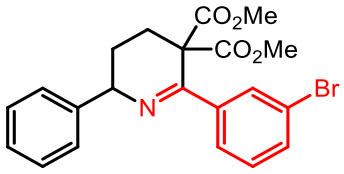
The title compound was prepared according to the general procedure to afford a pale-yellow oil (118 mg, 65%). **R_f** = 0.40 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.34 (app t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 3.5 Hz, 2H), 4.94 (dd, *J* = 8.9, 6.0 Hz, 1H), 4.30–4.17 (m, 2H), 4.16–4.02 (m, 2H), 2.55 (ddd, *J* = 13.4, 6.4, 4.0 Hz, 1H), 2.44 (ddd, *J* = 13.0, 11.4, 3.5 Hz, 1H), 2.16 (dddd, *J* = 12.9, 6.1, 6.1, 3.6 Hz, 1H), 1.57 (dddd, *J* = 15.2, 13.1, 8.9, 3.7 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.49, 143.75, 138.38, 130.91, 129.68, 128.53, 126.92, 126.70, 123.74, 62.31, 62.21, 62.15, 59.22, 41.94, 29.26, 27.54, 13.88, 13.66. **IR**, *v* (cm^{-1}): 2981, 2936, 2872, 1725, 1631, 1449, 1225, 1174, 1084, 1023, 700. **HRMS** *m/z* 457.0876 (calcd. for $C_{23}H_{24}BrNO_4$, 457.0889).



Dimethyl 2-(4-iodophenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3o-Me).

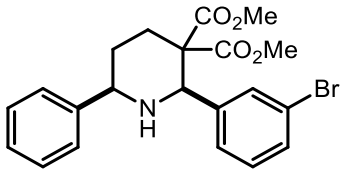
The title compound was prepared according to the general procedure to afford a pale-yellow syrup (105 mg, 55%). **R_f** = 0.67 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72–7.63 (m, 2H), 7.49–7.44 (m, 2H), 7.37–7.31 (m, 2H), 7.28–7.26 (m, 1H), 7.25 (d, *J* = 6.2 Hz, 2H), 4.94 (dd, *J* = 8.9, 5.9 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 2.56 (ddd, *J* = 13.2, 6.3, 3.7 Hz, 1H), 2.46 (ddd, *J* = 13.2, 11.4, 3.5 Hz, 1H), 2.16 (dtd, *J* = 14.1, 6.2, 3.6 Hz, 1H), 1.55 (dddd,

J = 14.1, 11.4, 8.9, 3.7 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.00, 169.96, 160.40, 143.64, 138.79, 136.98, 129.50, 128.54, 126.92, 126.65, 95.92, 62.24, 59.00, 53.10, 53.03, 29.34, 27.44. **IR**, *v* (cm^{-1}): 3027, 2951, 2868, 1727, 1433, 1244, 1167. **HRMS** *m/z* 477.0435 (calcd. for $C_{21}H_{20}INO_4$, 477.0437).



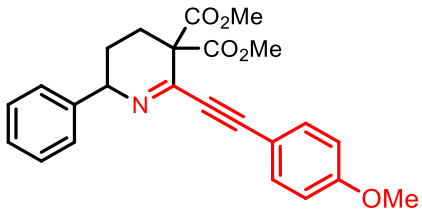
Dimethyl 2-(3-bromophenyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3*).

The title compound was prepared according to the general procedure to afford an inseparable mixture with the tetraester side-product. **HRMS** *m/z* 429.0571 (calcd. for $C_{21}H_{20}BrNO_4$, 429.0576).



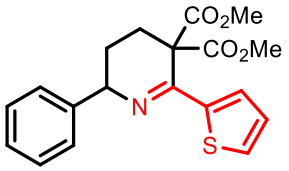
(2*R*,6*R*)-Dimethyl 2-(3-bromophenyl)-6-phenylpiperidine-3,3-dicarboxylate (3).**

The title compound was prepared following the literature protocol,[98] to afford a clear colorless oil. **R_f** = 0.71 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.46–7.39 (m, 4H), 7.29–7.19 (m, 5H), 4.38 (s, 1H), 3.87 (dd, *J* = 9.0, 5.7 Hz, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 2.58 (dt, *J* = 13.5, 3.5 Hz, 1H), 2.24–2.14 (m, 1H), 2.05 (s, 1H), 1.91–1.80 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.60, 169.93, 143.19, 140.53, 131.49, 128.45, 128.44, 127.60, 127.44, 121.03, 114.28, 66.28, 61.51, 58.96, 52.83, 52.24, 51.59, 41.92, 33.78, 30.63. **IR**, *v* (cm^{-1}): 3345, 3030, 2950, 2854, 1723, 1457, 1434, 1258, 1236, 1010, 729, 700. **HRMS** *m/z* 431.0744 (calcd. for $C_{21}H_{22}BrNO_4$, 431.0732).



Dimethyl 2-((4-methoxyphenyl)ethynyl)-6-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3p-Me).

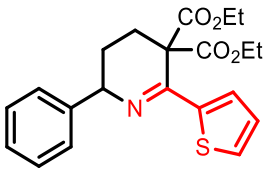
The title compound was prepared according to the general procedure to afford a yellow oil (97 mg, 60%). **R_f** = 0.27 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.48–7.43 (m, 2H), 7.34 (app t, *J* = 7.7 Hz, 2H), 7.26–7.23 (m, 3H), 6.87–6.83 (m, 2H), 4.90–4.84 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 2.52 (ddd, *J* = 9.8, 5.2, 2.4 Hz, 1H), 2.44–2.38 (m, 1H), 2.14–2.06 (m, 1H), 1.59–1.51 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.30, 169.09, 160.53, 147.99, 143.15, 133.97, 128.51, 127.02, 126.81, 114.05, 113.65, 90.06, 86.40, 62.81, 60.52, 55.31, 53.30, 53.26, 27.22, 27.01. **IR**, *v* (cm^{-1}): 3027, 2953, 2842, 2212, 1731, 1599, 1509, 1434, 1249, 1170, 732, 700. **HRMS** *m/z* 405.1566 (calcd. for $C_{24}H_{23}NO_5$, 405.1576).



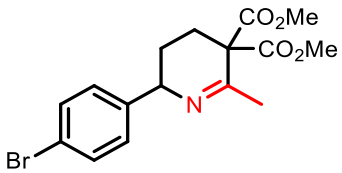
Dimethyl 6-phenyl-2-(thiophen-2-yl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3q-Me).

The title compound was prepared according to the general procedure to afford a lime-yellow oil (85 mg, 60%). **R_f** = 0.47 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.36–7.33 (m, 2H), 7.31–7.24 (m, 5H), 7.00 (dd, *J* = 5.1, 3.8 Hz, 1H), 5.01 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.58 (ddd, *J* = 13.2, 7.1, 3.1 Hz, 1H), 2.42 (ddd, *J* = 13.2, 11.1, 3.1 Hz,

1H), 2.15 (dddd, *J* = 14.0, 7.0, 5.6, 3.1 Hz, 1H), 1.56 (dddd, *J* = 14.2, 11.2, 8.2, 3.1 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 170.16, 169.54, 154.80, 145.47, 143.65, 128.41, 128.28, 127.29, 127.08, 126.76, 126.70, 61.36, 58.43, 53.12, 29.16, 27.39. **IR**, *v* (cm^{-1}): 2953, 1728, 1614, 1431. **HRMS** *m/z* 357.1032 (calcd. for $C_{19}H_{19}NO_4S$, 357.1035).

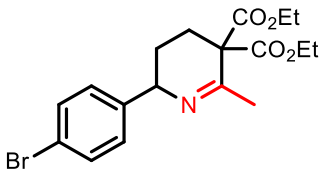


Diethyl 6-phenyl-2-(thiophen-2-yl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3q-Et). The title compound was prepared according to the general procedure to afford a pale-yellow oil (128 mg, 83%). **R_f** = 0.67 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.38–7.24 (m, 7H), 6.99 (app dd, *J* = 5.1, 3.8 Hz, 1H), 5.01 (dd, *J* = 8.0, 5.6 Hz, 1H), 4.30–4.12 (m, 4H), 2.56 (ddd, *J* = 13.2, 7.3, 3.1 Hz, 1H), 2.41 (ddd, *J* = 13.4, 10.9, 3.1 Hz, 1H), 2.14 (dddd, *J* = 13.8, 7.1, 5.6, 3.0 Hz, 1H), 1.60 (dddd, *J* = 8.0, 6.6, 2.6 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.58, 169.03, 155.45, 143.70, 128.38, 128.12, 127.51, 127.10, 126.77, 126.75, 62.20, 62.15, 61.41, 58.68, 29.69, 28.92, 27.47, 13.86, 13.76. **IR**, *v* (cm^{-1}): 2979, 2958, 2906, 1726, 1614, 1448, 1240, 1173, 1094, 1021, 857, 700. **HRMS** *m/z* 385.1344 (calcd. for $C_{21}H_{23}NO_4S$, 385.1348).

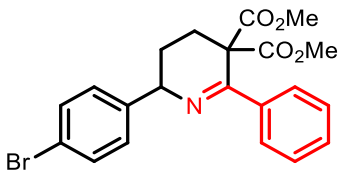


Dimethyl 6-(4-bromophenyl)-2-methyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3r-Me). The title compound was prepared according to the general procedure to afford a yellow solid (94 mg, 64%), mp 88–91 °C. **R_f** = 0.22 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*)

δ 7.48–7.42 (m, 2H), 7.11–7.04 (m, 2H), 4.66–4.60 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.42 (ddd, *J* = 13.4, 6.2, 3.3 Hz, 1H), 2.31 (ddd, *J* = 13.4, 11.8, 3.3 Hz, 1H), 2.22 (d, *J* = 2.2 Hz, 3H), 2.01 (dddd, *J* = 14.0, 6.2, 5.5, 3.3 Hz, 1H), 1.38 (dddd, *J* = 14.0, 11.8, 9.2, 3.3 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.88, 169.55, 160.67, 142.91, 131.52, 128.44, 120.66, 61.09, 59.36, 53.11, 53.09, 27.44, 27.23, 25.81. **IR**, *v* (cm^{-1}): 2960, 2925, 1724, 1645, 1436, 1249. **HRMS** *m/z* 367.0423 (calcd. for $C_{16}H_{18}BrNO_4$, 367.0419).

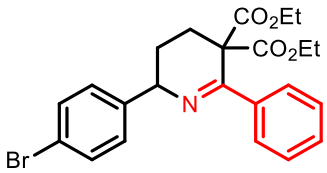


Diethyl 6-(4-bromophenyl)-2-methyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3r-Et). The title compound was prepared according to the general procedure to afford a yellow oil (112 mg, 71%). **R_f** = 0.43 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.48–7.36 (m, 2H), 7.09–7.04 (m, 2H), 4.64–4.58 (m, 1H), 4.29–4.22 (m, 4H), 2.38 (ddd, *J* = 13.4, 6.2, 3.3 Hz, 1H), 2.30–2.25 (m, 1H), 2.21 (d, *J* = 2.1 Hz, 3H), 1.99 (dddd, *J* = 14.7, 6.0, 6.0, 3.3 Hz, 1H), 1.40 (dddd, *J* = 13.8, 12.0, 8.9, 3.2 Hz, 1H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.31 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.39, 169.06, 161.10, 143.04, 131.50, 128.47, 120.62, 62.20, 62.08, 61.12, 59.53, 27.33, 27.32, 25.87, 14.01, 13.97. **IR**, *v* (cm^{-1}): 2980, 1723, 1656, 1247, 1175. **HRMS** *m/z* 395.0730 (calcd. for $C_{18}H_{22}BrNO_4$, 395.0732).

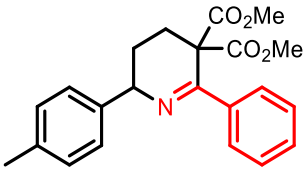


Dimethyl 6-(4-bromophenyl)-2-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3s-Me).

The title compound was prepared according to the general procedure to afford a white solid (117 mg, 68%), mp 111–112 °C. **R_f** = 0.35 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) 7.70–7.65 (m, 2H), 7.50–7.44 (m, 2H), 7.39–7.31 (m, 3H), 7.19–7.14 (m, 2H), 4.89 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.74 (s, 3H), 3.59 (s, 3H), 2.53 (ddd, *J* = 13.2, 6.1, 4.1 Hz, 1H), 2.48 (ddd, *J* = 13.2, 11.3, 3.7 Hz, 1H), 2.18–2.13 (m, 1H), 1.53–1.45 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 170.11, 170.02, 161.89, 143.02, 139.24, 131.60, 129.37, 128.50, 127.93, 127.64, 120.70, 61.52, 59.23, 53.05, 52.93, 29.31, 27.41. **IR**, *v* (cm^{-1}): 2955, 1754, 1720, 1618, 1445, 1250. **HRMS** *m/z* 429.0579 (calcd. for $C_{21}H_{20}BrNO_4$, 429.0576).

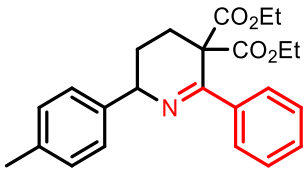


Diethyl 6-(4-bromophenyl)-2-phenyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3s-Et). The title compound was prepared according to the general procedure to afford a yellow oil (150 mg, 82%). **R_f** = 0.48 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.72–7.67 (m, 2H), 7.48–7.43 (m, 2H), 7.36–7.29 (m, 3H), 7.19–7.15 (m, 2H), 4.89 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.25–4.16 (m, 2H), 4.13–3.99 (m, 2H), 2.53 (ddd, *J* = 13.2, 6.1, 4.1 Hz, 1H), 2.47 (ddd, *J* = 13.2, 11.3, 3.7 Hz, 1H), 2.15 (dddd, *J* = 14.1, 6.1, 6.1, 3.7 Hz, 1H), 1.51 (dddd, *J* = 14.1, 11.3, 9.1, 4.1 Hz, 1H), 1.30–1.21 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.60, 169.47, 162.40, 143.15, 139.45, 131.54, 129.27, 128.52, 127.87, 127.81, 120.64, 62.12, 62.03, 61.56, 59.34, 29.23, 27.50, 13.85, 13.55. **IR**, *v* (cm^{-1}): 2980, 1723, 1632, 1474, 1239, 1174. **HRMS** *m/z* 457.0879 (calcd. for $C_{23}H_{24}BrNO_4$, 457.0889).



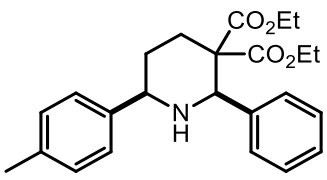
Dimethyl 2-phenyl-6-(p-tolyl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3t-Me).

The title compound was prepared according to the general procedure to afford a white solid (55 mg, 43%), mp 131–134 °C. **R_f** = 0.49 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.72–7.67 (m, 2H), 7.36–7.30 (m, 3H), 7.19–7.13 (m, 4H), 4.92 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 2.54 (ddd, *J* = 13.2, 6.6, 3.8 Hz, 1H), 2.47 (ddd, *J* = 13.2, 11.1, 3.6 Hz, 1H), 2.33 (s, 3H), 2.14 (dddd, *J* = 14.1, 6.3, 6.3, 3.6 Hz, 1H), 1.59–1.52 (m, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 170.23, 170.22, 161.06, 141.02, 139.45, 136.38, 129.16, 127.84, 127.69, 126.64, 61.85, 59.24, 52.94, 52.86, 29.29, 27.53, 21.06. **IR**, *v* (cm^{-1}): 2951, 2922, 1730, 1434, 1250. **HRMS** *m/z* 365.1626 (calcd. for $C_{22}H_{23}NO_4$, 365.1627).



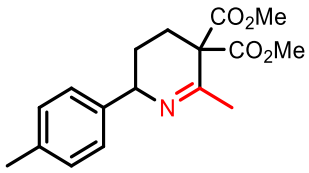
Diethyl 2-phenyl-6-(p-tolyl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3t-Et).

The title compound was prepared according to the general procedure to afford an inseparable mixture with the tetraester side-product. **HRMS** *m/z* 393.1952 (calcd. for $C_{24}H_{27}NO_4$, 393.1940).



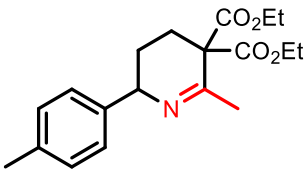
(2*R*,6*R*)-diethyl 2-phenyl-6-(*p*-tolyl)piperidine-3,3-dicarboxylate (3t-Et*).

The title compound was prepared following a literature protocol,[98] to afford a clear colorless oil. **R_f** = 0.78 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 6.7 Hz, 2H), 7.32–7.20 (m, 5H), 7.14 (d, *J* = 7.5 Hz, 2H), 4.40 (s, 1H), 4.19–3.98 (m, 4H), 3.90 (dd, *J* = 10.8, 4.1 Hz, 1H), 2.64–2.56 (m, 1H), 2.33 (s, 3H), 2.23 (ddd, *J* = 13.0, 13.0, 5.3 Hz, 2H), 1.94–1.84 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 171.42, 169.70, 141.31, 140.84, 136.88, 129.05, 128.62, 127.29, 126.59, 66.35, 61.80, 61.03, 60.44, 58.89, 33.92, 30.57, 21.07, 13.83, 13.77. **IR**, *v* (cm^{-1}): 2980, 2936, 1723, 1446, 1253, 1226. **HRMS** *m/z* 395.2104 (calcd. for $C_{24}H_{29}NO_4$, 395.2097).



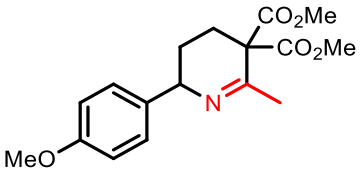
Dimethyl 2-methyl-6-(p-tolyl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3u-Me).

The title compound was prepared according to the general procedure to afford a white solid (47 mg, 44%), mp 84–87 °C. **R_f** = 0.36 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.14 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.65 (app ddd, *J* = 8.2, 5.5, 2.1 Hz, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 2.43 (ddd, *J* = 13.3, 6.4, 3.3 Hz, 1H), 2.33–2.27 (m, 4H), 2.21 (d, *J* = 2.2 Hz, 3H), 2.00 (dddd, *J* = 14.6, 5.9, 5.9, 3.1 Hz, 1H), 1.44 (dddd, *J* = 14.7, 12.0, 8.9, 3.3 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 170.08, 169.71, 159.79, 140.89, 136.35, 129.11, 126.57, 61.47, 59.43, 53.04, 53.01, 27.47, 27.32, 25.79, 21.05. **IR**, *v* (cm^{-1}): 2923, 1721, 1649, 1439, 1252. **HRMS** *m/z* 303.1475 (calcd. for $C_{17}H_{21}NO_4$, 303.1471).



Diethyl 2-methyl-6-(p-tolyl)-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3u-Et).

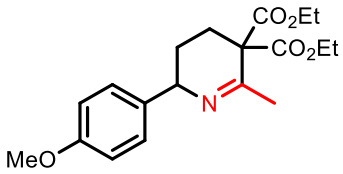
The title compound was prepared according to the general procedure to afford an off-white solid (49 mg, 37%), mp 60 °C. $\mathbf{R_f}$ = 0.37 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.13 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 4.63 (app ddd, *J* = 8.2, 5.5, 2.3 Hz, 1H), 4.30–4.22 (m, 4H), 2.39 (ddd, *J* = 13.3, 6.5, 3.3 Hz, 1H), 2.30 (s, 3H), 2.27 (ddd, *J* = 13.3, 11.6, 3.3 Hz, 1H), 2.21 (d, *J* = 2.1 Hz, 3H), 1.98 (dddd, *J* = 14.1, 6.5, 5.6, 3.3 Hz, 1H), 1.43 (dddd, *J* = 13.9, 11.7, 8.9, 3.3 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.57, 169.22, 160.24, 140.99, 136.31, 129.07, 126.60, 62.09, 61.97, 61.49, 59.59, 27.40, 27.34, 25.83, 21.05, 14.00, 13.97. **IR**, *v* (cm^{-1}): 2935, 1741, 1716, 1659, 1241. **HRMS** *m/z* 331.1794 (calcd. for $C_{19}H_{25}NO_4$, 331.1784).



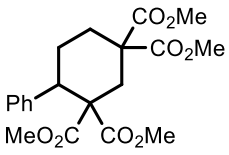
Dimethyl 6-(4-methoxyphenyl)-2-methyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3v-Me).

The title compound was prepared according to the general procedure to afford a clear yellow oil (27 mg, 21%). $\mathbf{R_f}$ = 0.18 (30% EtOAc/hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.63 (ddq, *J* = 9.0, 3.4, 2.0 Hz, 1H), 3.82 (s, 6H), 3.79 (s, 3H), 2.42 (ddd, *J* = 13.4, 6.4, 3.4 Hz, 1H), 2.30 (ddd, *J* = 13.3, 11.5, 3.2 Hz, 1H), 2.21 (d, *J* = 2.0 Hz, 3H), 1.99 (dddd, *J* = 14.8, 5.9, 5.9, 3.2 Hz, 1H), 1.43 (dddd, *J* = 14.5, 11.9, 8.9, 3.4 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.95, 169.67, 158.56, 127.77, 113.89, 61.09, 59.45, 55.28, 53.11, 53.08, 29.69, 27.37, 27.32, 25.71. **IR**, *v* (cm^{-1}): 3000, 2953, 2838, 1727, 1656, 1610, 1511, 1435, 1242, 1173, 1033, 811. **HRMS** *m/z* 319.1418 (calcd. for $C_{17}H_{21}NO_5$, 319.1420).

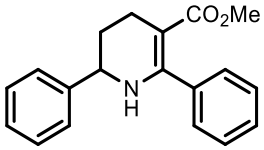


Diethyl 6-(4-methoxyphenyl)-2-methyl-5,6-dihydropyridine-3,3(4H)-dicarboxylate (3v-Et). The title compound was prepared according to the general procedure to afford a clear yellow oil (37 mg, 27%). **R_f** = 0.30 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.14–7.10 (m, 2H), 6.88–6.85 (m, 2H), 4.64 (app ddq, *J* = 9.9, 4.4, 2.2 Hz, 1H), 4.32–4.25 (m, 4H), 3.79 (s, 3H), 2.41 (ddd, *J* = 13.3, 6.5, 3.3 Hz, 1H), 2.29 (ddd, *J* = 13.3, 11.6, 3.3 Hz, 1H), 2.23 (d, *J* = 2.0 Hz, 3H), 1.99 (dddd, *J* = 14.0, 6.4, 5.5, 3.2 Hz, 1H), 1.44 (dddd, *J* = 14.5, 11.9, 8.9, 3.3 Hz, 1H), 1.32 (app td, *J* = 7.1, 2.6 Hz, 6H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 169.53, 169.21, 158.50, 127.77, 113.84, 62.11, 61.99, 61.16, 59.58, 55.27, 27.44, 27.32, 25.81, 14.01, 13.97. **IR**, *v* (cm^{-1}): 2980, 2936, 2837, 1723, 1656, 1611, 1511, 1445, 1367, 1242, 1174, 1033. **HRMS** *m/z* 347.1730 (calcd. for $C_{19}H_{25}NO_5$, 347.1733).



Tetramethyl 4-phenylcyclohexane-1,1,3,3-tetracarboxylate (4a-Me).

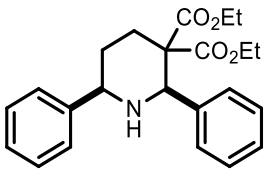
The title compound was prepared according to the general procedure without the nitrile to afford a white solid. mp 99–101 °C. **R_f** = 0.34 (30% EtOAc/hexanes). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.30–7.23 (m, 3H), 7.21–7.17 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.62 (s, 3H), 3.41 (s, 3H), 3.36 (dd, *J* = 8.8, 4.3 Hz, 1H), 2.99 (d, *J* = 15.1 Hz, 1H), 2.86 (d, *J* = 15.1 Hz, 1H), 2.38 (ddd, *J* = 13.7, 7.6, 3.8 Hz, 1H), 2.33–2.26 (m, 1H), 2.06 (dddd, *J* = 14.0, 8.0, 4.2, 4.2 Hz, 1H), 1.93 (ddd, *J* = 13.6, 9.2, 4.0 Hz, 1H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 171.73, 171.69, 171.56, 170.22, 141.50, 129.13, 127.84, 126.86, 57.12, 52.95, 52.85, 52.77, 52.46, 51.93, 45.90, 34.47, 28.60, 25.87. **HRMS** *m/z* 392.1508 (calcd. for $C_{20}H_{24}O_8$, 392.1471).



Methyl 2,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5).

The title compound was prepared as follows: LiI (0.32 mmol was added to a solution of the tetrahydropyridine **3h** (0.15 mmol) in DMSO. The reaction was brought to reflux for 2 h and then cooled to rt. At the end of the reaction, as judged by NMR aliquots, the mixture was diluted in diethyl ether and hexanes, washed with brine, water, then brine again. The organic layer was dried with $MgSO_4$ and then concentrated under reduced pressure to afford the vinylogous carbamate (**7a**) as a white solid, (85%, 49 mg). mp 149–152 °C. **R_f** = 0.43 (30% EtOAc/Hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.38–7.27 (m, 10H), 4.49 (ddd, *J* = 8.4, 3.6, 2.5 Hz, 1H), 4.29 (s, 1H), 3.45 (s, 3H), 2.59–2.55 (m, 2H), 2.17–2.11 (m, 1H), 1.95 (dddd, *J* = 12.9, 8.0, 8.0, 6.6 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 168.64, 154.31, 143.08, 139.70, 128.73, 128.37, 128.02, 127.80, 127.71, 126.35, 94.20, 56.14, 50.38, 30.01, 22.00. **IR**, *v*

(cm^{-1}): 3311, 2923, 2852, 1732, 1628, 1510, 1433, 1356, 1174. **HRMS** *m/z* 293.1412 (calcd. for $C_{19}H_{19}NO_2$, 293.1416).



(2*R*,6*R*)-Diethyl 2,6-diphenylpiperidine-3,3-dicarboxylate (6).

The title compound was prepared following the literature protocol as follows:[98] $NaBH_4$ (0.32 mmol) was added to a solution of the tetrahydropyridine (**3h**) (0.15 mmol) in methanol (2 mL) at 0 °C. The reaction was allowed to stir at rt for 1.5 h. At the end of the reaction as judged by TLC analysis, the solvent was evaporated and the residue was taken up in diethyl ether and saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3× 15 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford the piperidine (**6a**) as a white solid (88%, 50 mg), mp 90–91 °C. $\mathbf{R_f}$ = 0.62 (30% EtOAc/Hexanes). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.50–7.46 (m, 2H), 7.44–7.40 (m, 2H), 7.35–7.30 (m, 2H), 7.28–7.18 (m, 4H), 4.41 (s, 1H), 4.22–3.96 (m, 4H), 3.94 (dd, *J* = 10.4, 4.4 Hz, 1H), 2.61 (ddd, *J* = 13.4, 3.4, 3.4 Hz, 1H), 2.24 (ddd, *J* = 13.4, 11.5, 5.4 Hz, 1H), 2.17 (s, 1H), 1.98–1.84 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 171.38, 169.69, 144.25, 140.81, 128.64, 128.40, 127.33, 127.31, 126.68, 66.34, 62.11, 61.05, 60.46, 58.87, 33.90, 30.89, 30.60, 13.83, 13.77. **IR**, *v* (cm^{-1}): 2980, 2936, 1723, 1446, 1253, 1226. **HRMS** *m/z* 381.1925 (calcd. for $C_{23}H_{27}NO_4$, 381.1940).

5.3 Notes and References

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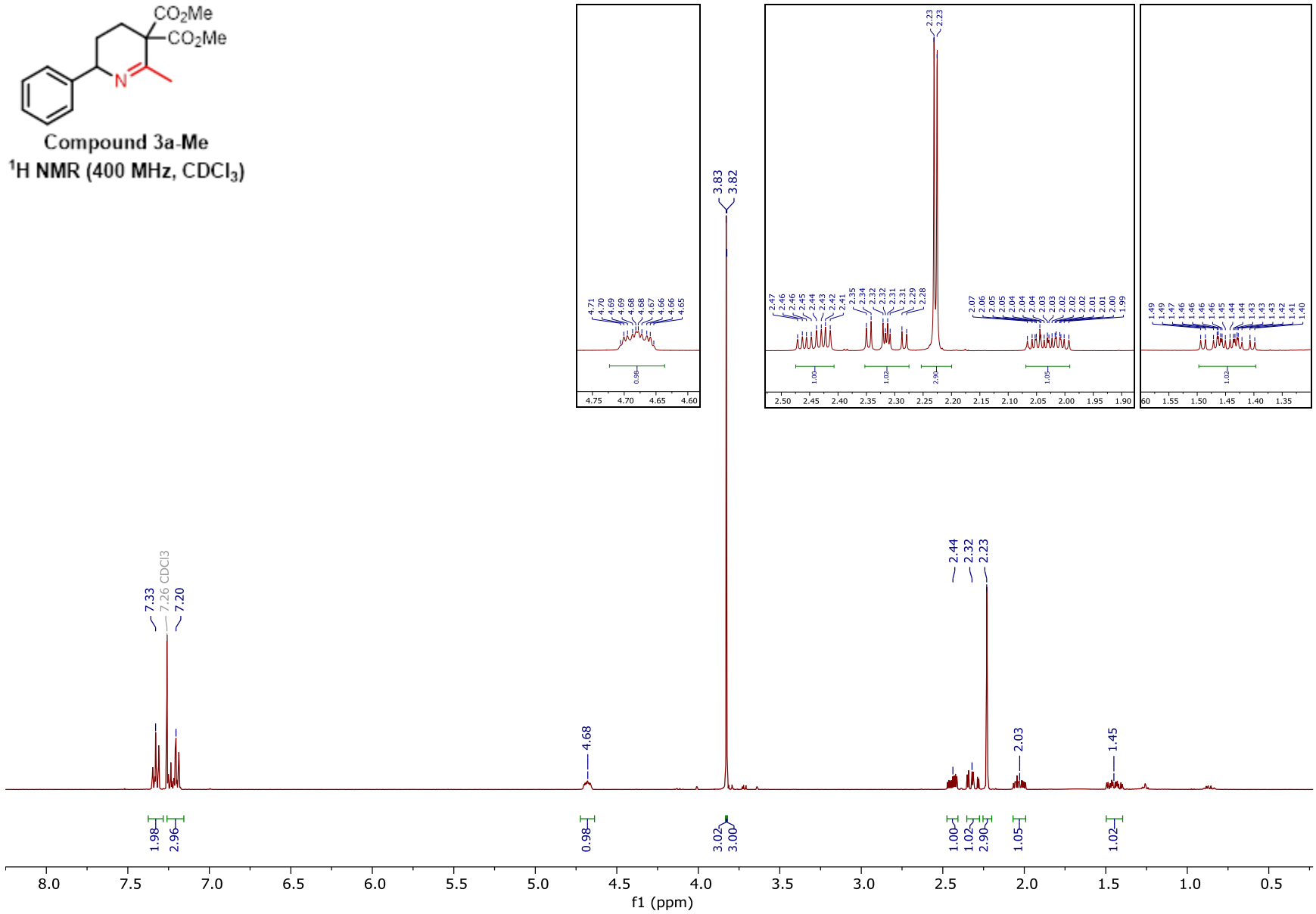
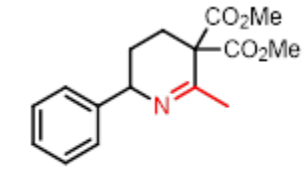
[98] Blackburn, L., Taylor, R. J. K. In Situ Oxidation−Imine Formation−Reduction Routes from Alcohols to Amines. *Org. Lett.* **2001**, *3*, 1637–1639.

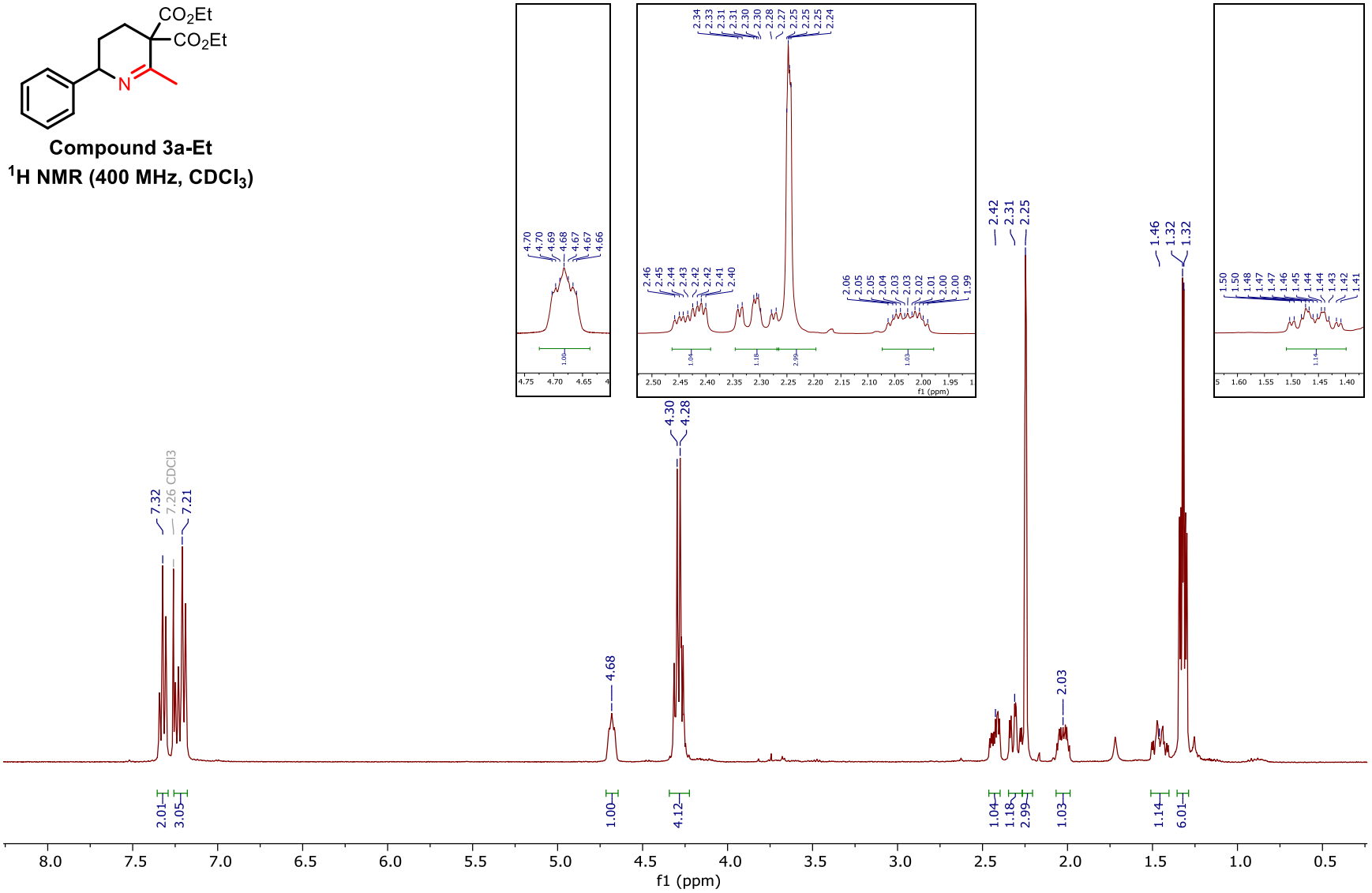
Appendix I. NMR Spectral Data for New Compounds for Chapter 2

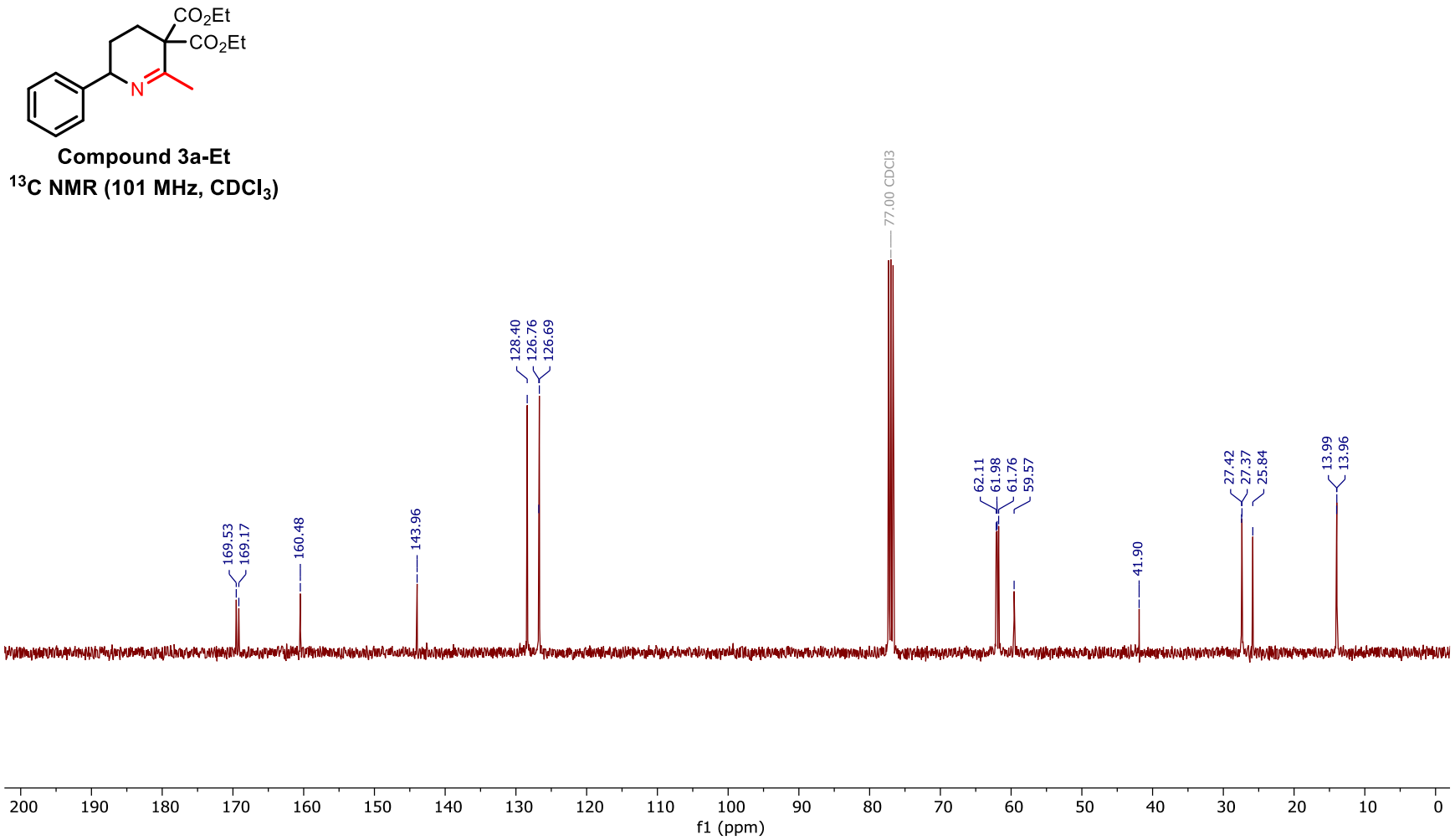

CO2Me
CO2Me
N
Compound 3a-Me
1H NMR (400 MHz, CDCl3)
7.33
7.26 CDCl3
7.20
4.68
3.83
3.82
2.44
2.32
2.23
2.03
1.45
1.98
2.96
0.98
3.02
3.00
1.00
1.02
2.90
1.05
1.02
f1 (ppm)

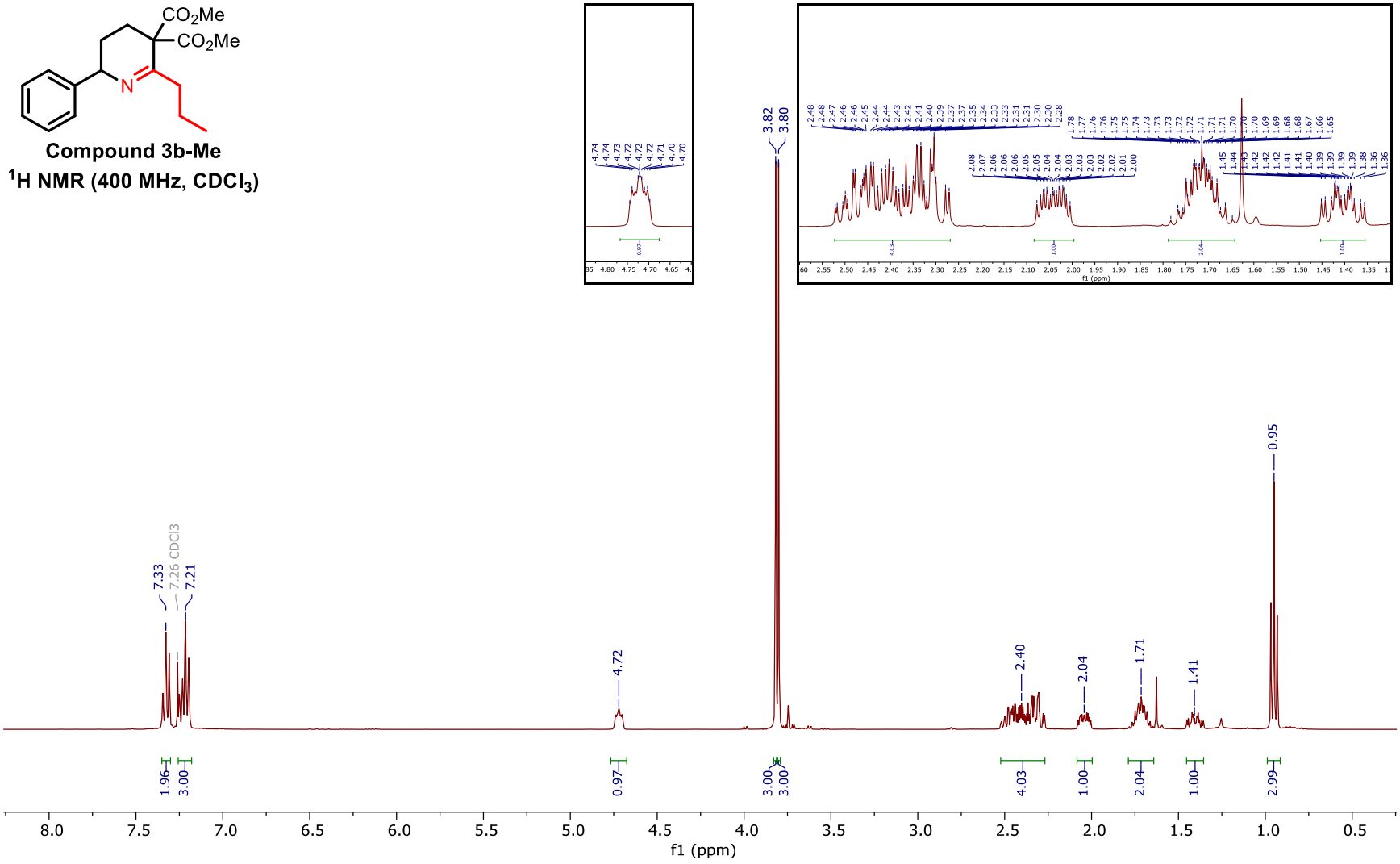


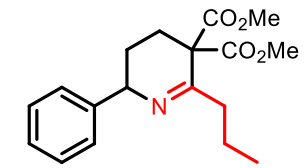
Compound 3a-Me

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


CO2Et
CO2Et
N
Compound 3a-Et
1H NMR (400 MHz, CDCl3)
7.32
7.26 CDCl3
7.21
4.68
4.30
4.28
2.42
2.31
2.25
2.03
1.46
1.32
1.32
2.01
3.05
1.00
4.12
1.04
1.18
2.99
1.03
1.14
6.01
f1 (ppm)

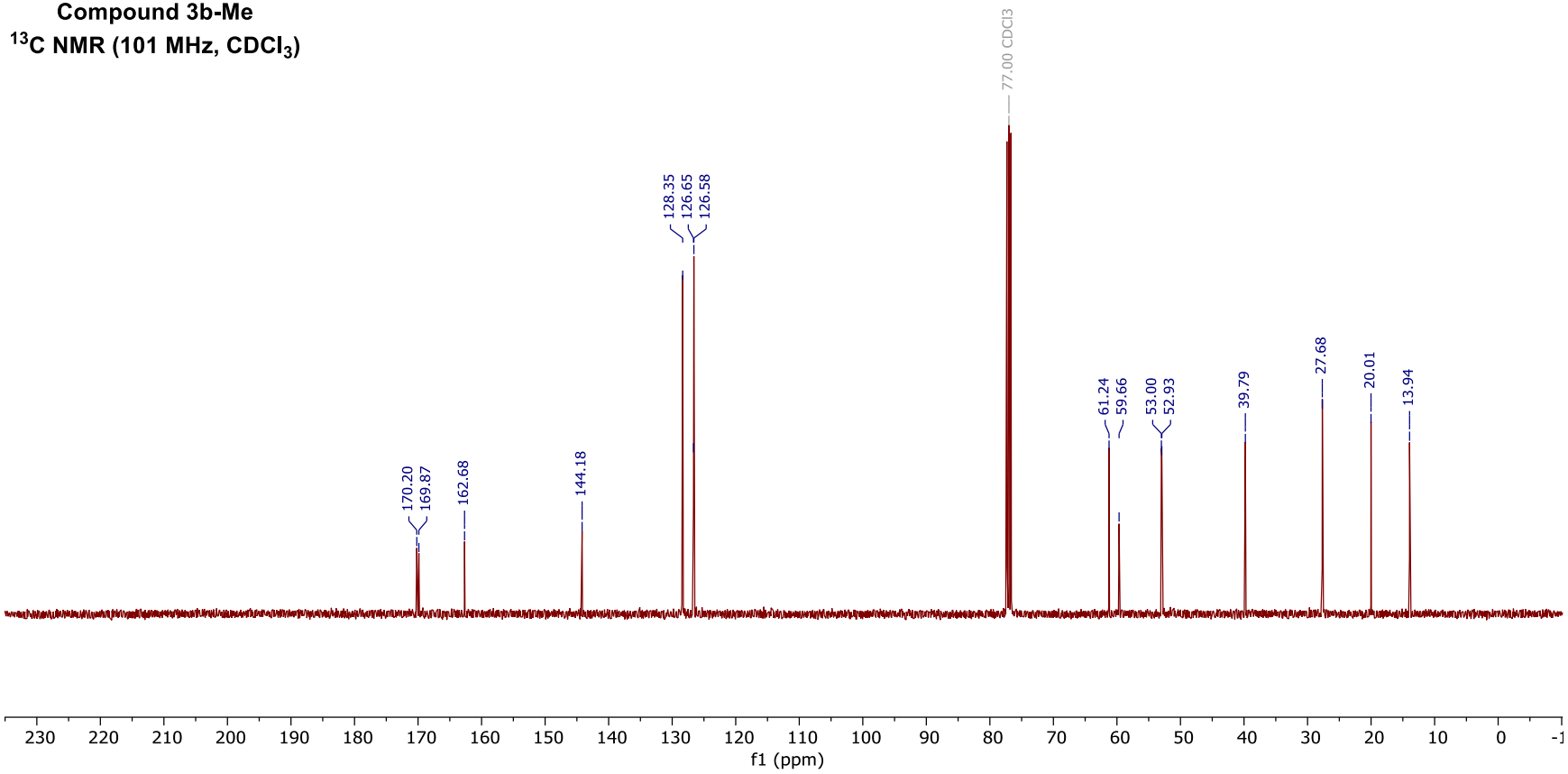

CO2Et
CO2Et
N
Compound 3a-Et
13C NMR (101 MHz, CDCl3)
77.00 CDCl3
169.53
169.17
160.48
143.96
128.40
126.76
126.69
62.11
61.98
61.76
59.57
41.90
27.42
27.37
25.84
13.99
13.96
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

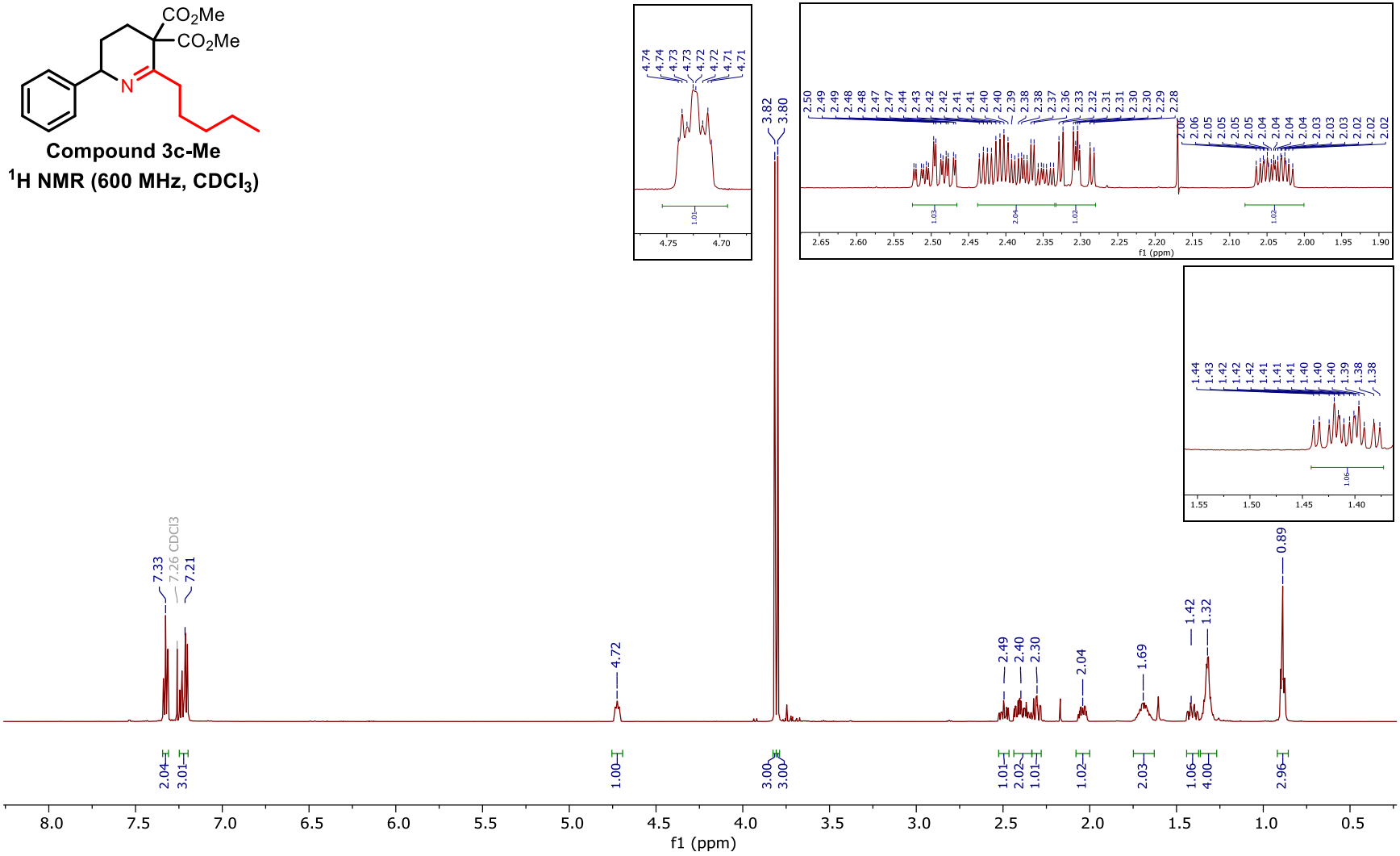

CO2Me
CO2Me
N
Compound 3b-Me
1H NMR (400 MHz, CDCl3)
7.33
7.26 CDCl3
7.21
4.72
3.82
3.80
2.40
2.04
1.71
1.41
0.95
1.96
3.00
0.97
3.00
3.00
4.03
1.00
2.04
1.00
2.99
f1 (ppm)

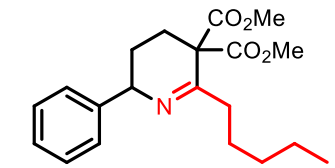


Compound 3b-Me

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

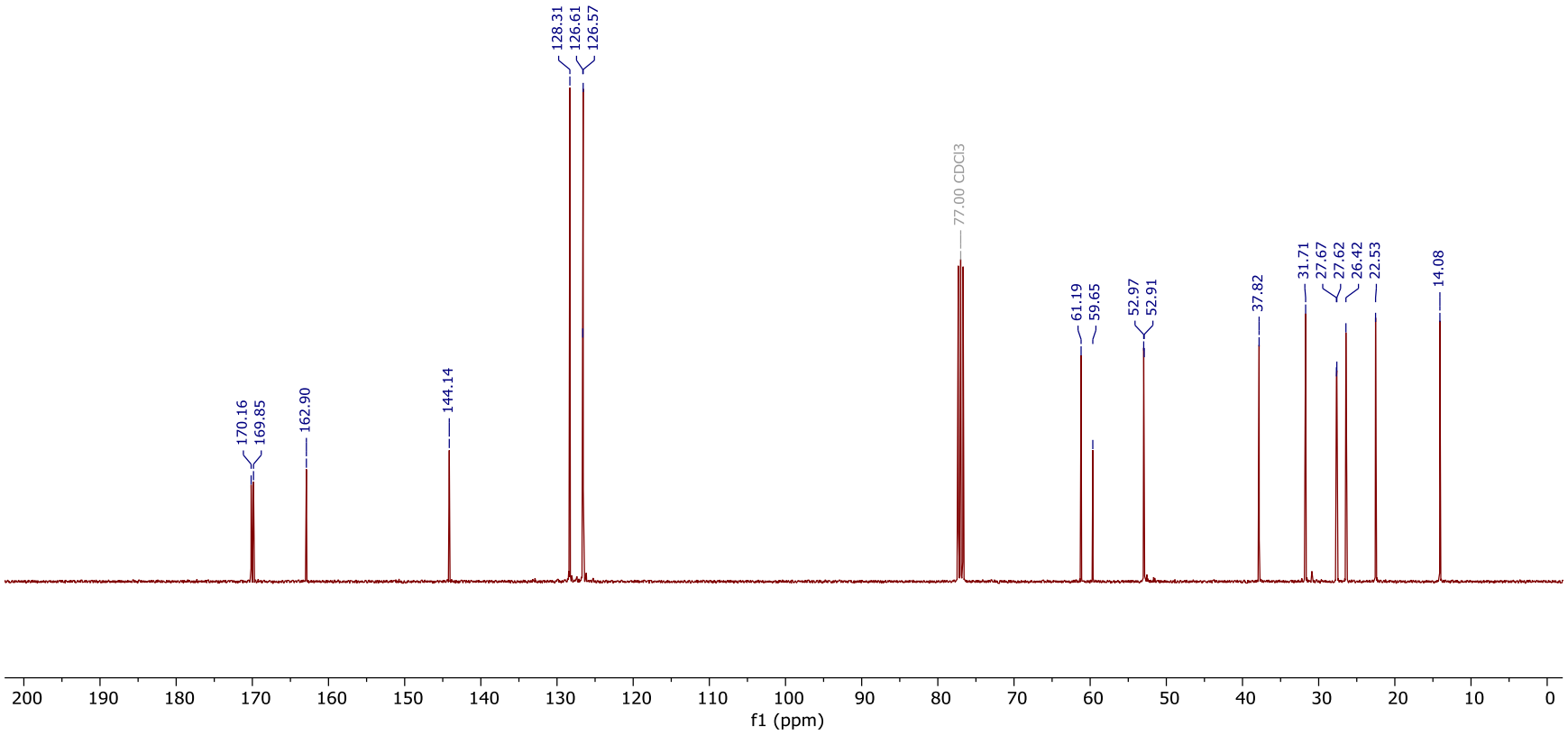


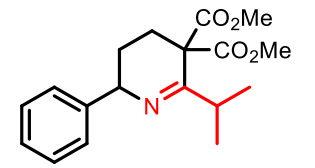

CO2Me
CO2Me
N
Compound 3c-Me
1H NMR (600 MHz, CDCl3)
7.33
7.26 CDCl3
7.21
4.72
3.82
3.80
2.49
2.40
2.30
2.04
1.69
1.42
1.32
0.89
2.04
3.01
1.00
3.00
3.00
1.01
2.02
1.01
1.02
2.03
1.06
4.00
2.96
f1 (ppm)



Compound 3c-Me

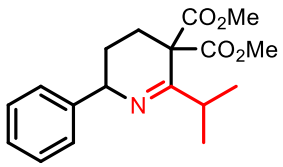
^{13}C NMR (101 MHz, $CDCl_3$)





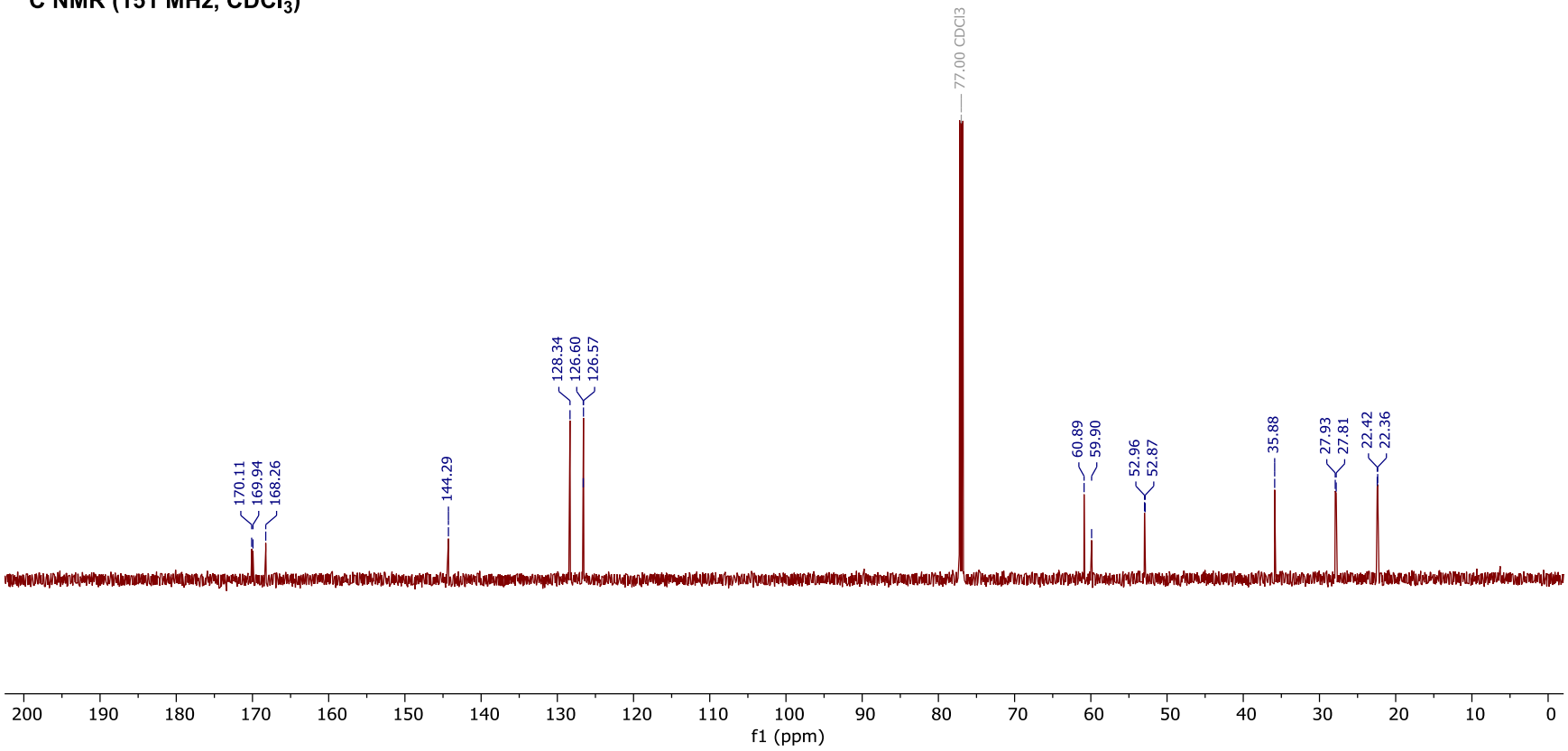
Compound 3d-Me

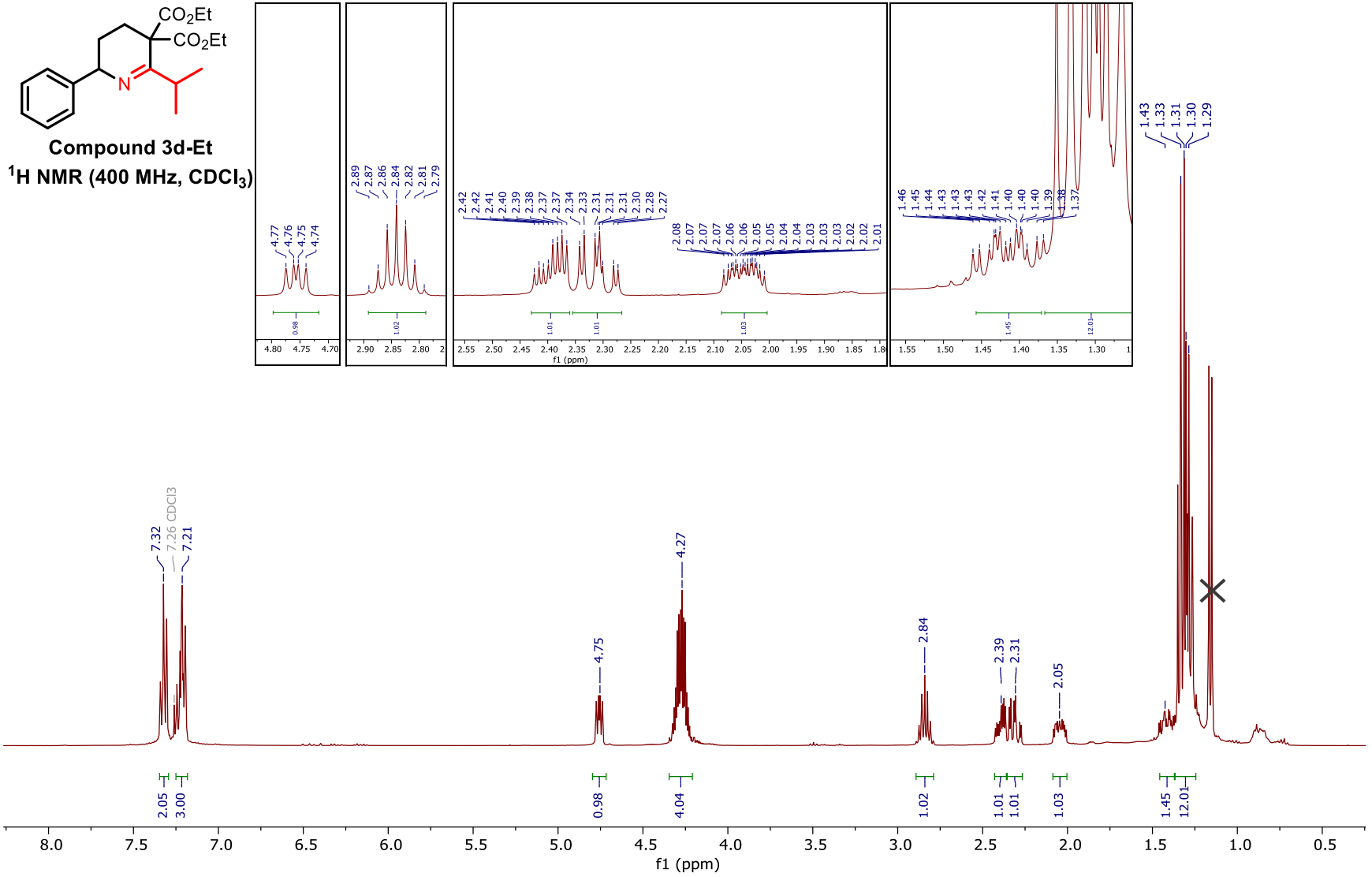
^{1}H NMR (600 MHz, $CDCl_3$)

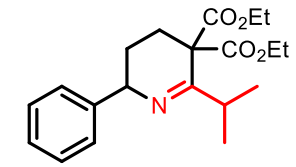


Compound 3d-Me

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

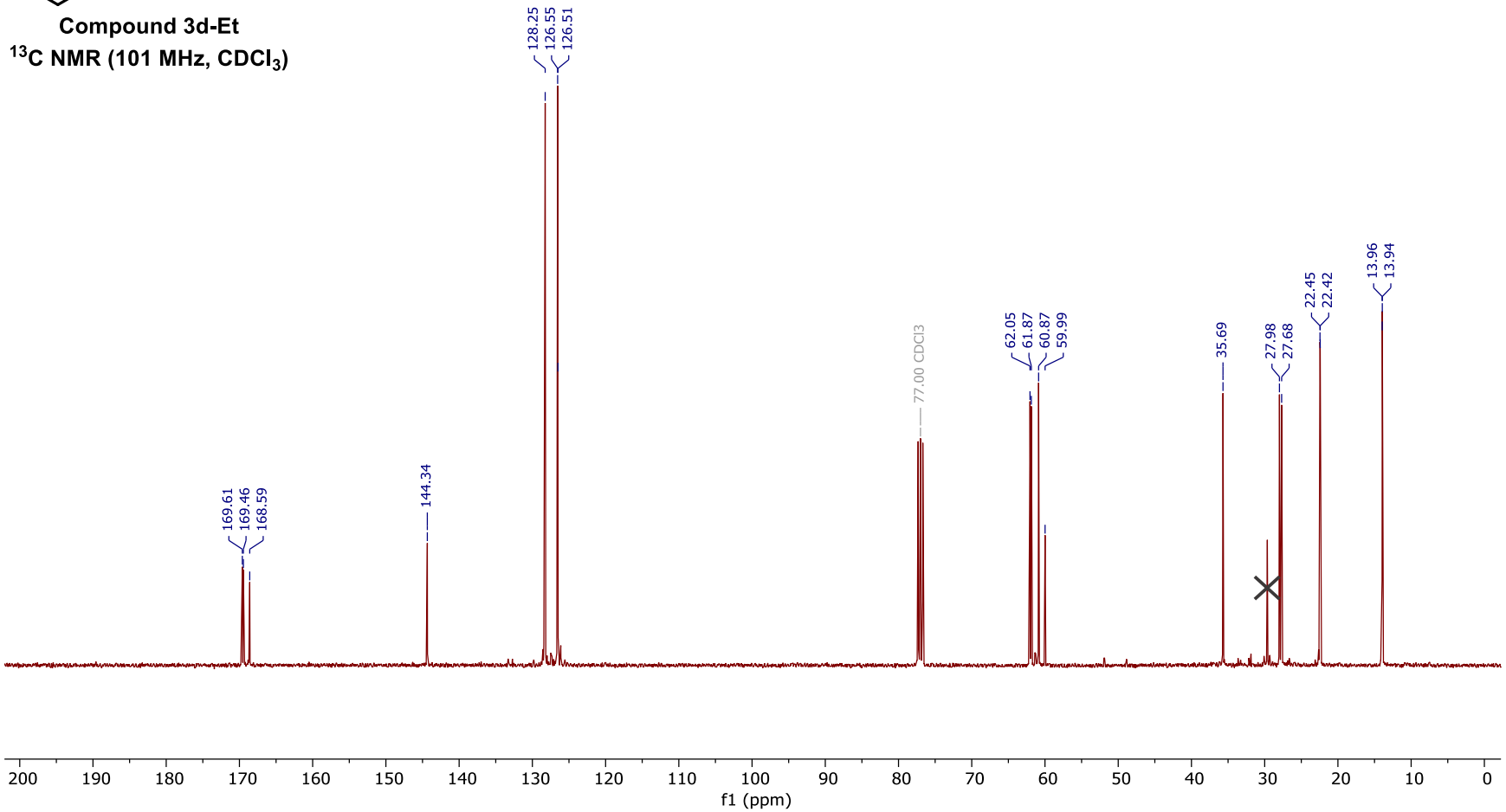


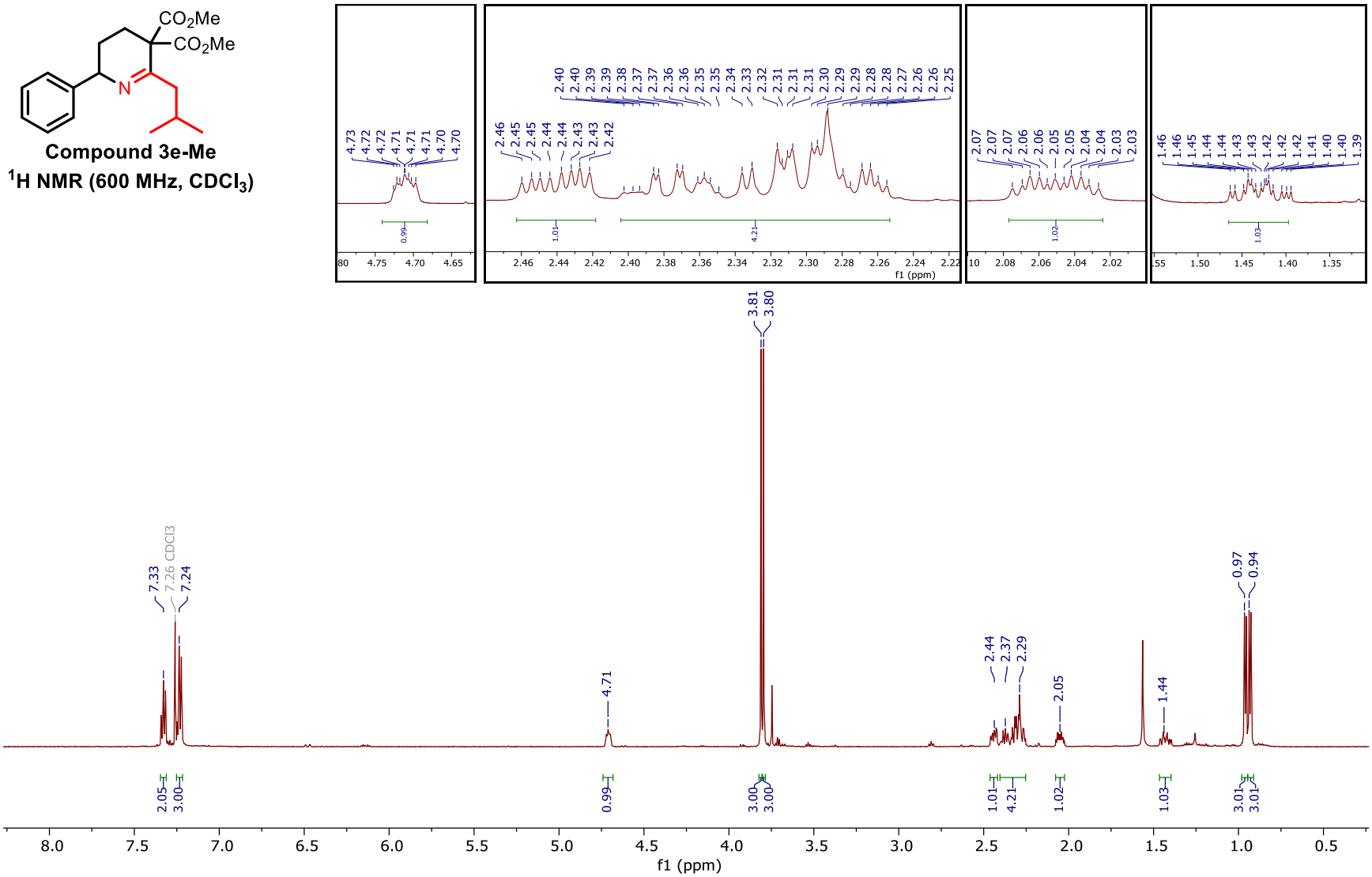

CO2Et
CO2Et
N
Compound 3d-Et
1H NMR (400 MHz, CDCl3)
7.32
7.26 CDCl3
7.21
4.75
4.27
2.84
2.39
2.31
2.05
1.43
1.33
1.31
1.30
1.29
2.05
3.00
0.98
4.04
1.02
1.01
1.01
1.03
1.45
12.01
f1 (ppm)

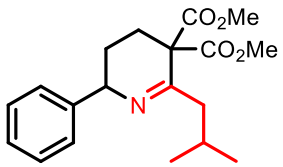


Compound 3d-Et

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

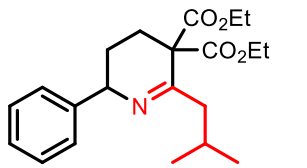



CO2Me
CO2Me
N
Compound 3e-Me
1H NMR (600 MHz, CDCl3)
7.33
7.26 CDCl3
7.24
4.71
3.81
3.80
2.44
2.37
2.29
2.05
1.44
0.97
0.94
f1 (ppm)



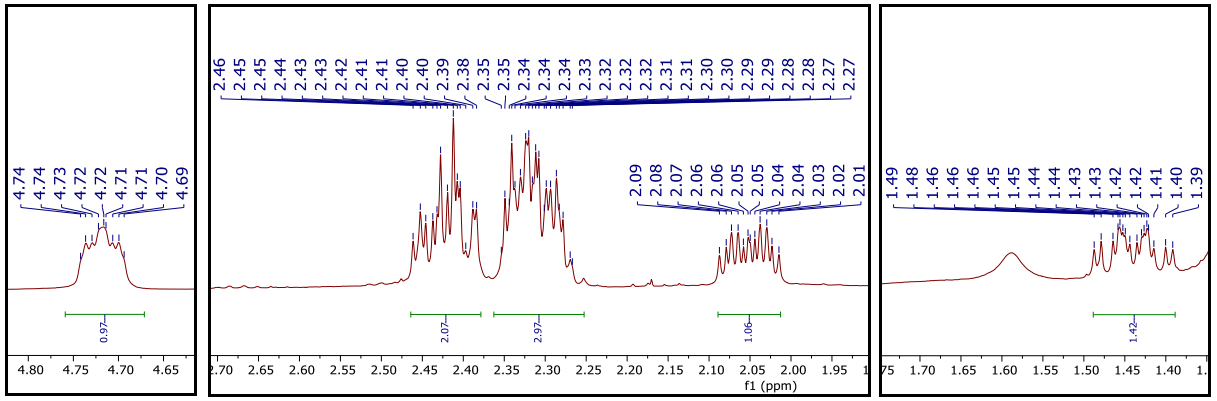
Compound 3e-Me

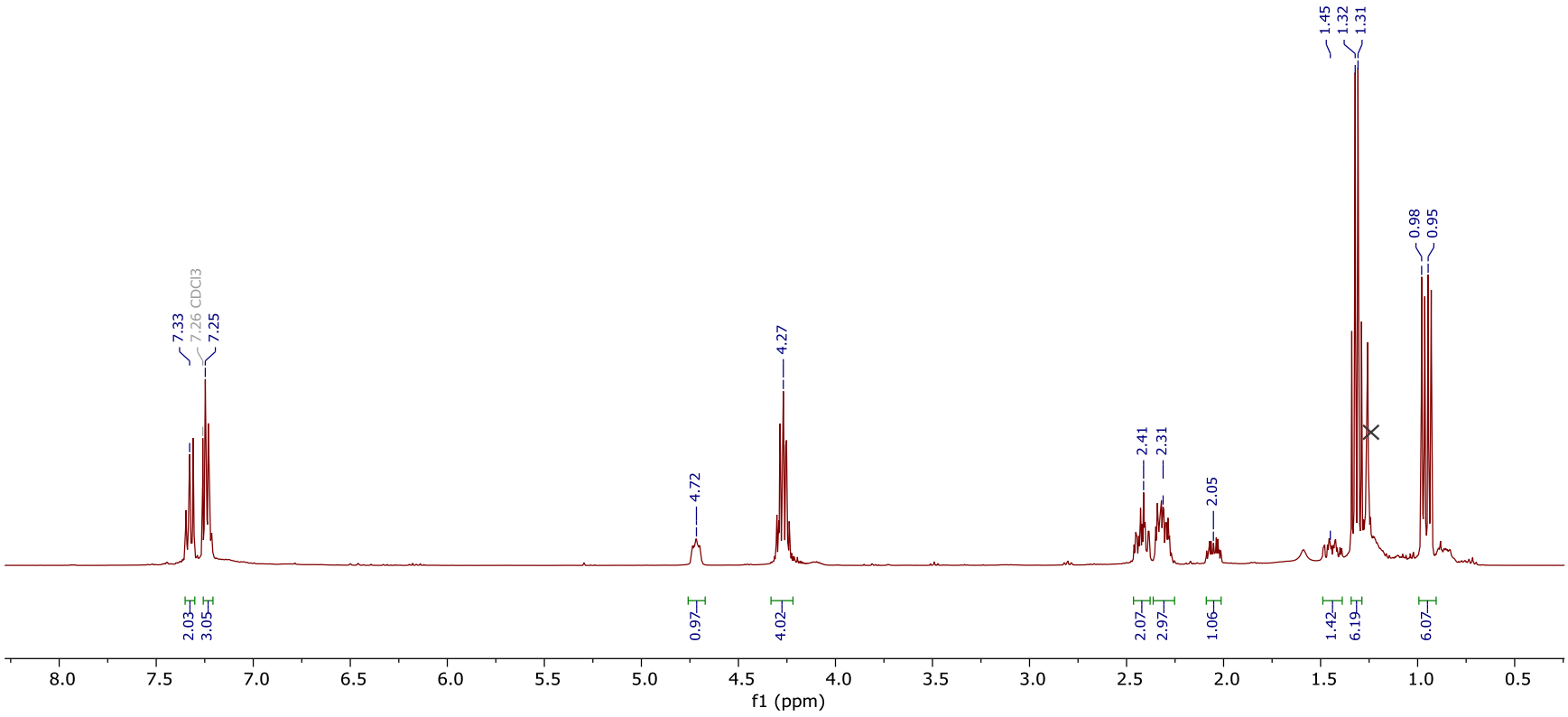
^{13}C NMR (151 MHz, $CDCl_3$)

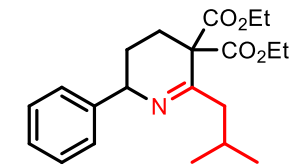


Compound 3e-Et

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

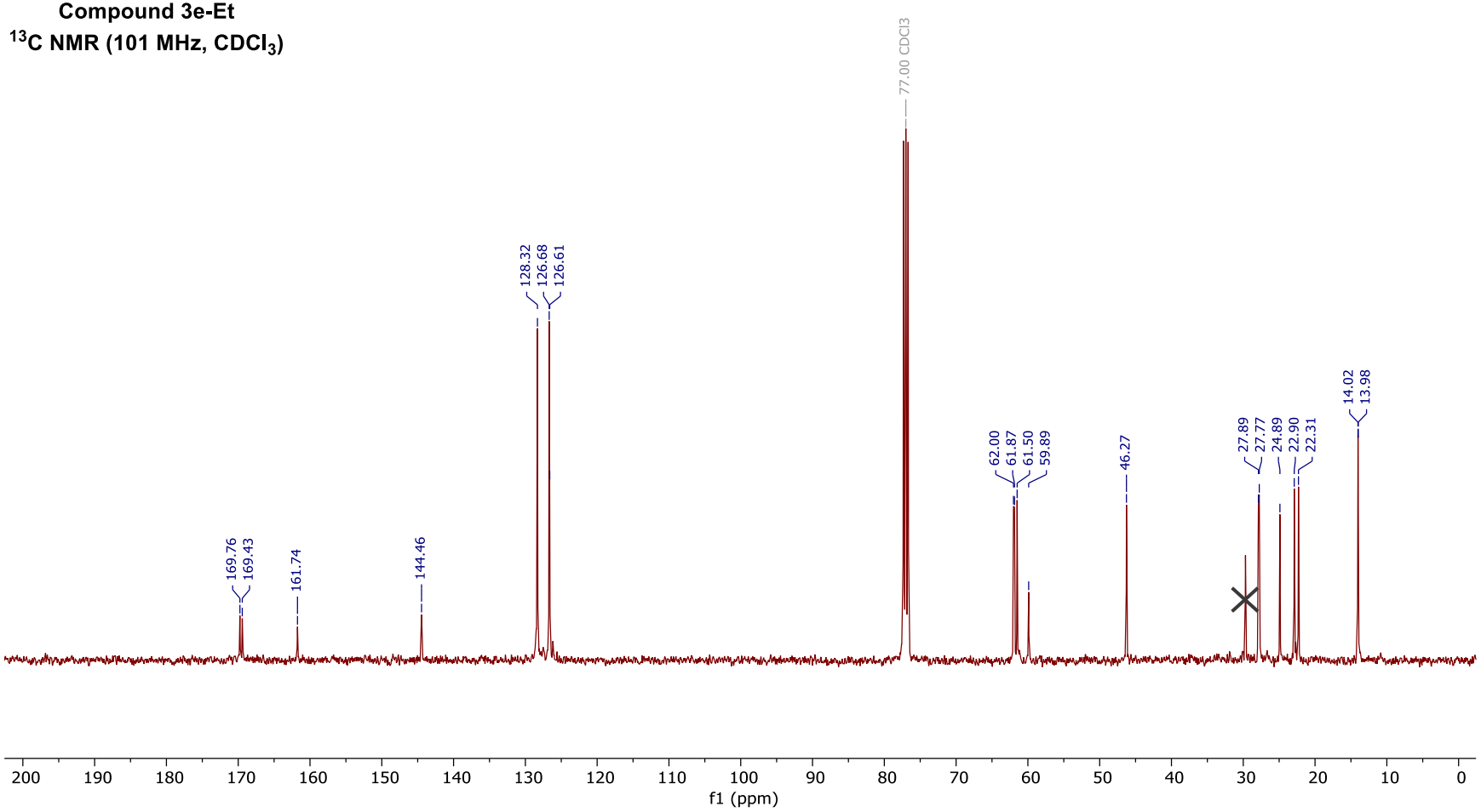


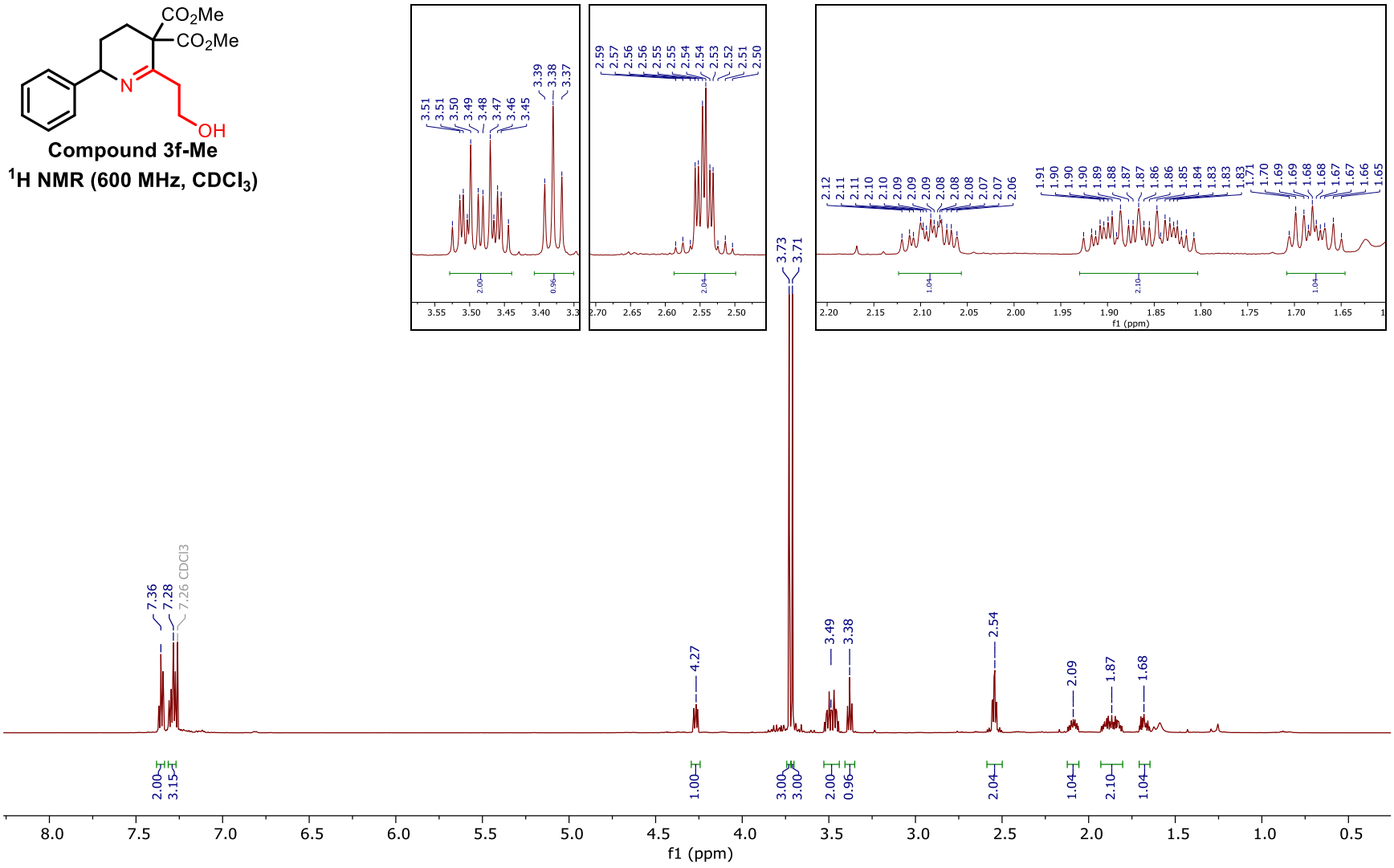


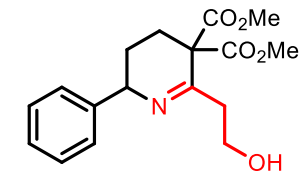


Compound 3e-Et

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

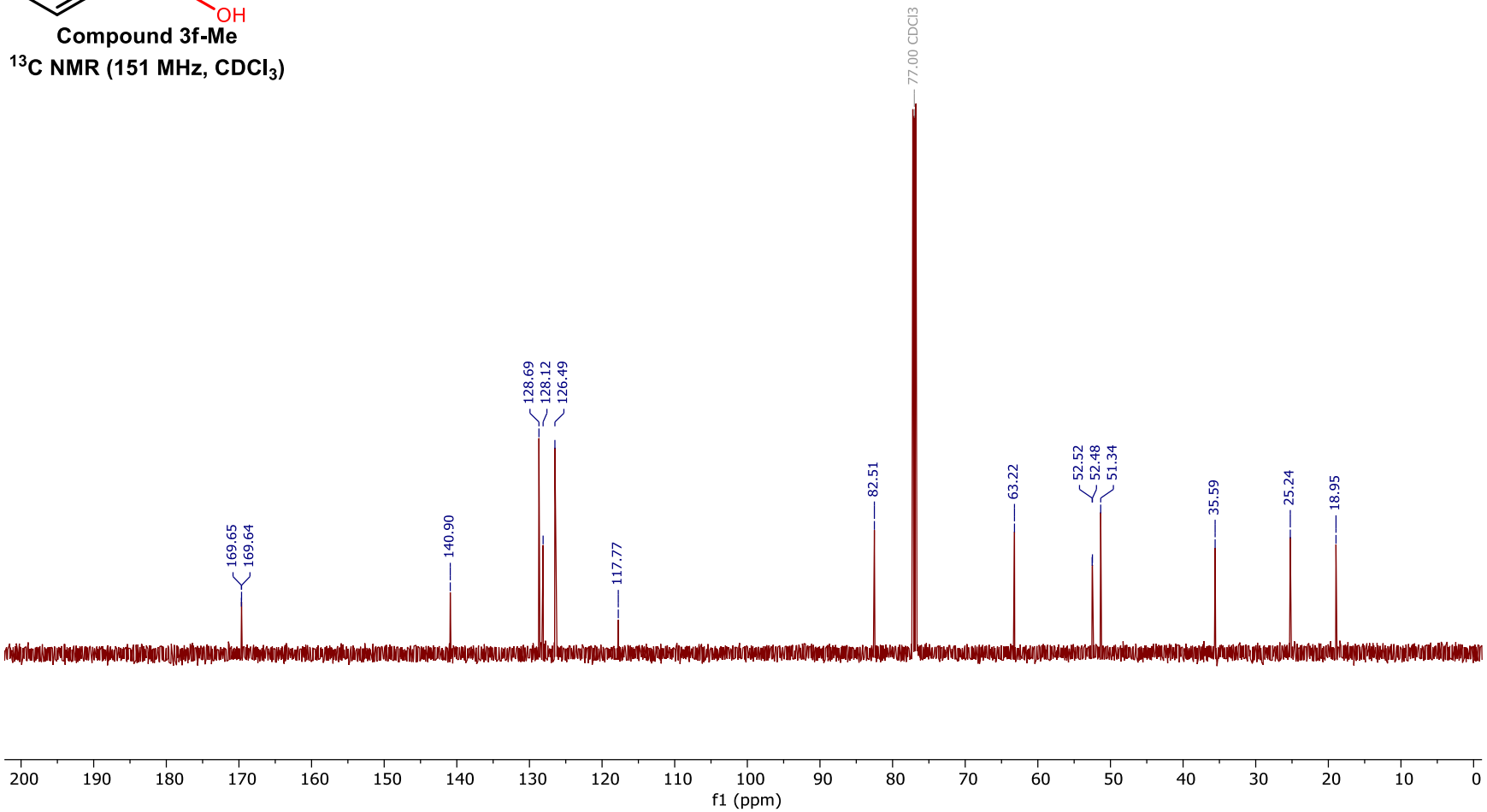


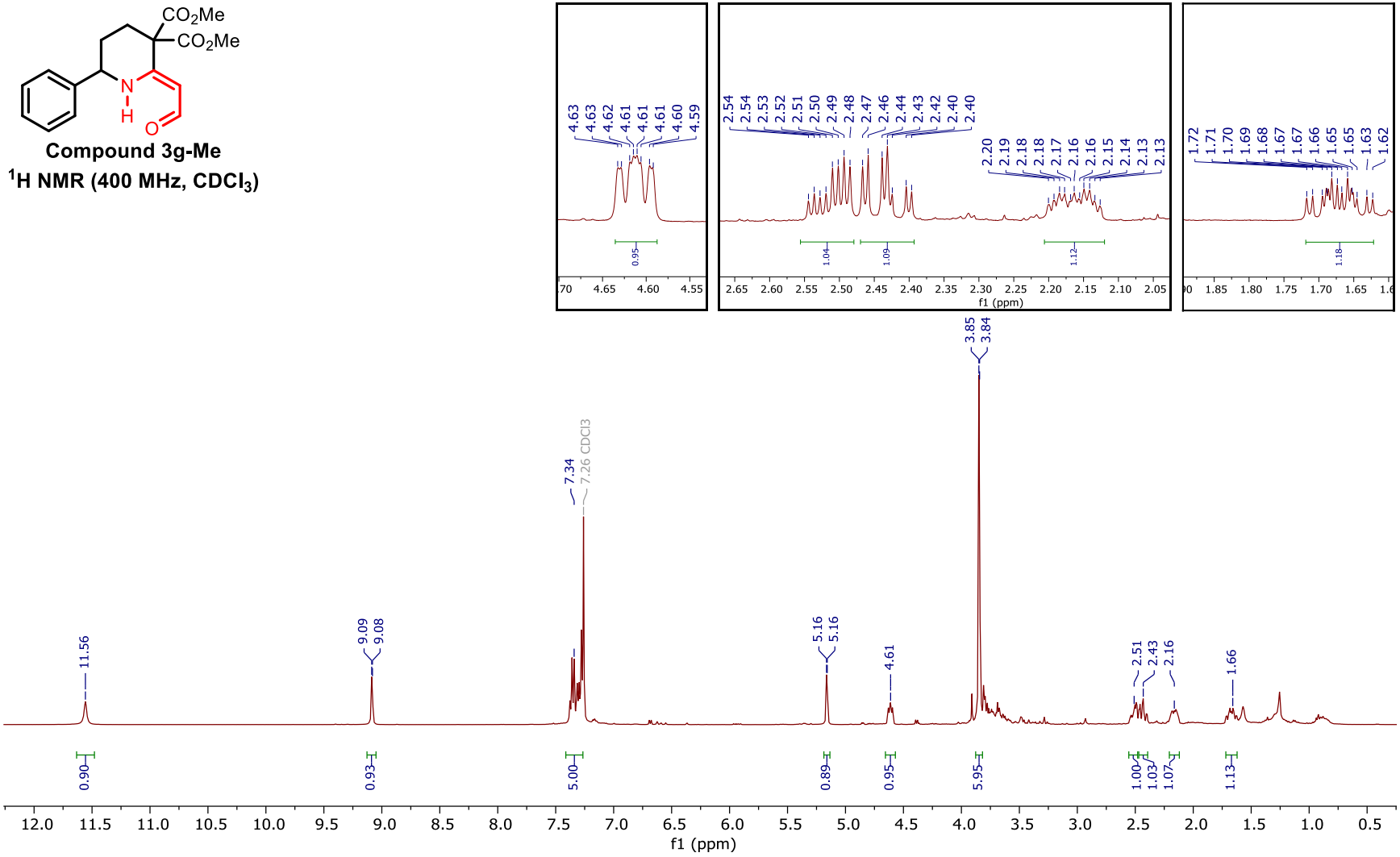

CO2Me
CO2Me
N
OH
Compound 3f-Me
1H NMR (600 MHz, CDCl3)
7.36
7.28
7.26 CDCl3
4.27
3.73
3.71
3.49
3.38
2.54
2.09
1.87
1.68
f1 (ppm)

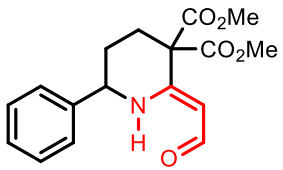


Compound 3f-Me

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

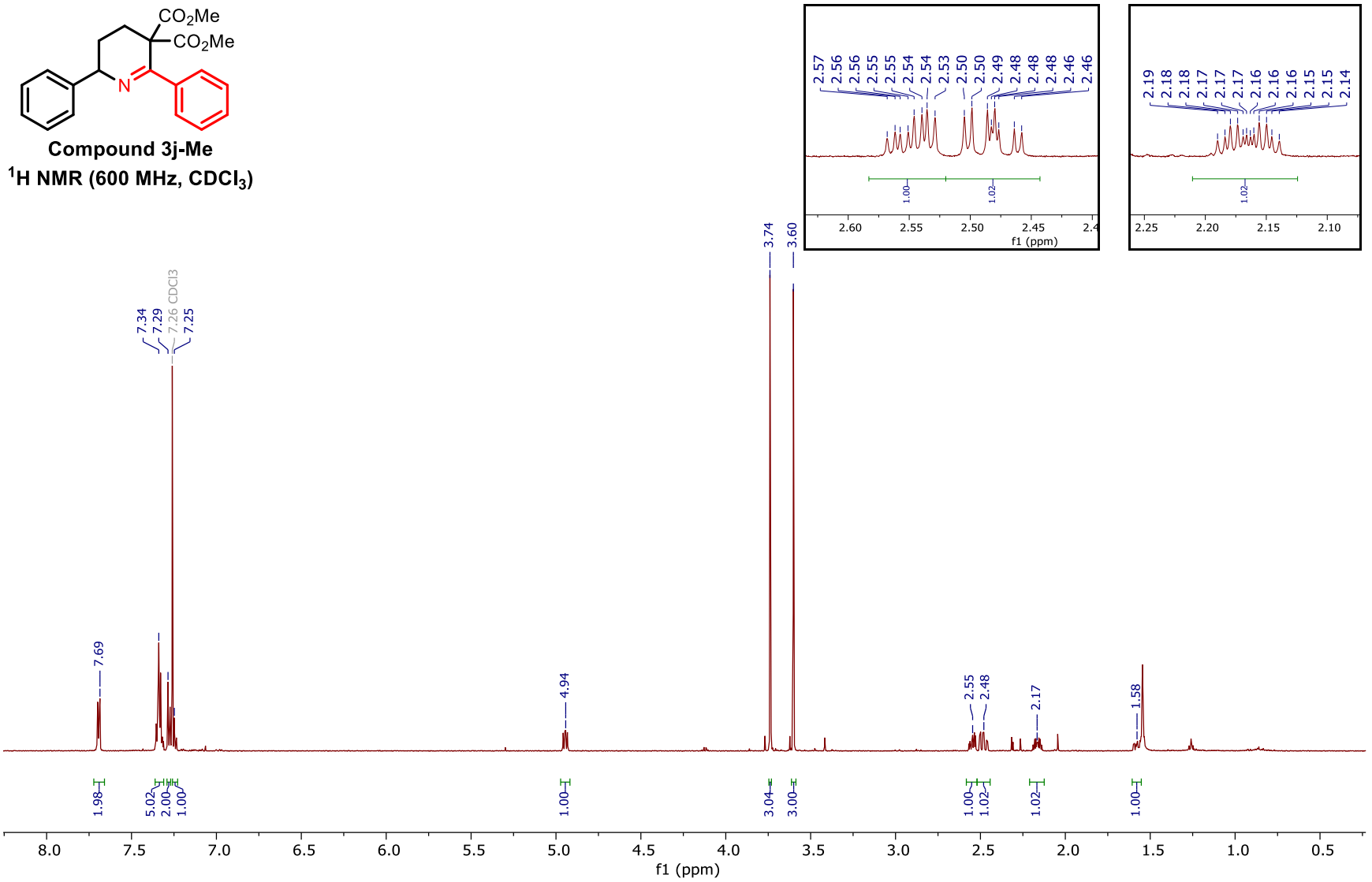


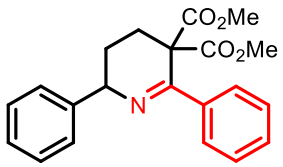

CO2Me
CO2Me
N
H
O
Compound 3g-Me
1H NMR (400 MHz, CDCl3)
11.56
9.09
9.08
7.34
7.26 CDCl3
5.16
5.16
4.61
3.85
3.84
2.51
2.43
2.16
1.66
0.90
0.93
5.00
0.89
0.95
5.95
1.00
1.03
1.07
1.13
f1 (ppm)



Compound 3g-Me

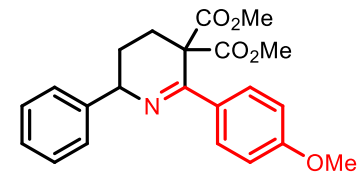
^{13}C NMR (151 MHz, $CDCl_3$)


CO2Me
CO2Me
N
Compound 3j-Me
1H NMR (600 MHz, CDCl3)
7.69
7.34
7.29
7.26 CDCl3
7.25
4.94
3.74
3.60
2.55
2.48
2.17
1.58
f1 (ppm)



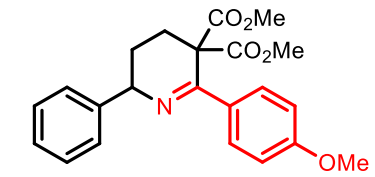
Compound 3j-Me

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



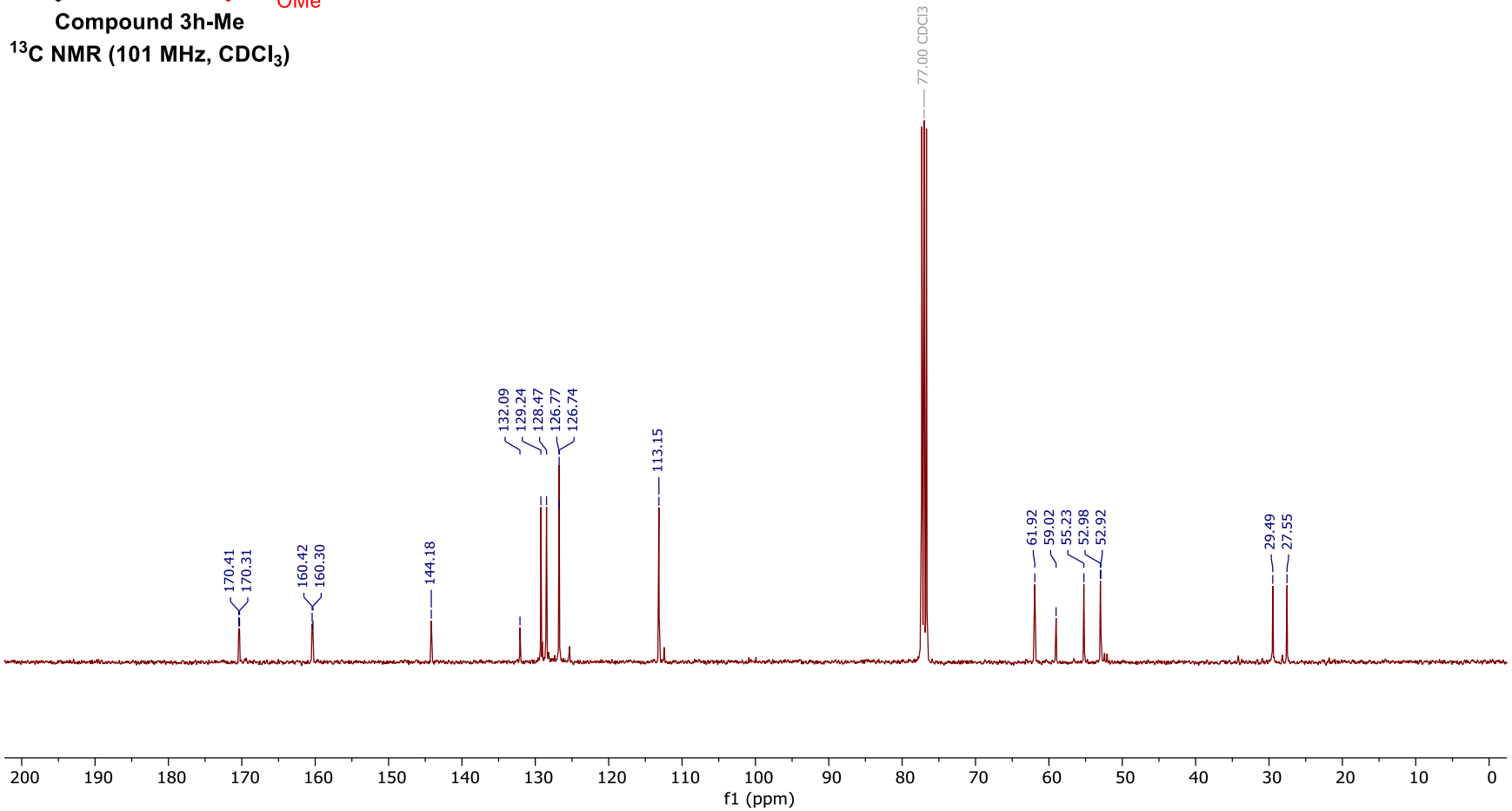
Compound 3h-Me

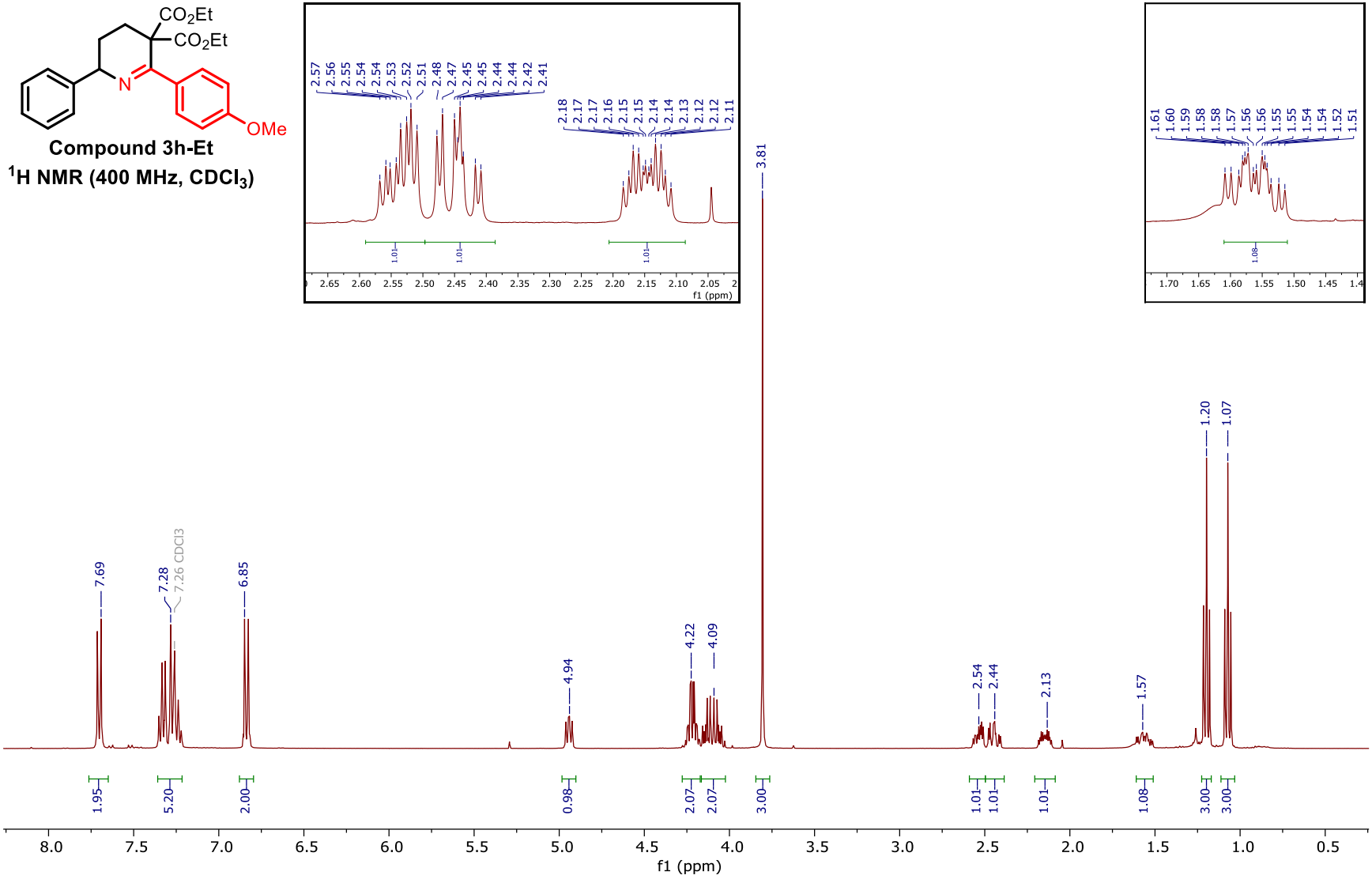
^{1}H NMR (400 MHz, $CDCl_3$)

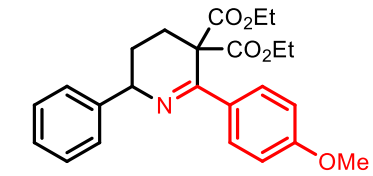


Compound 3h-Me

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

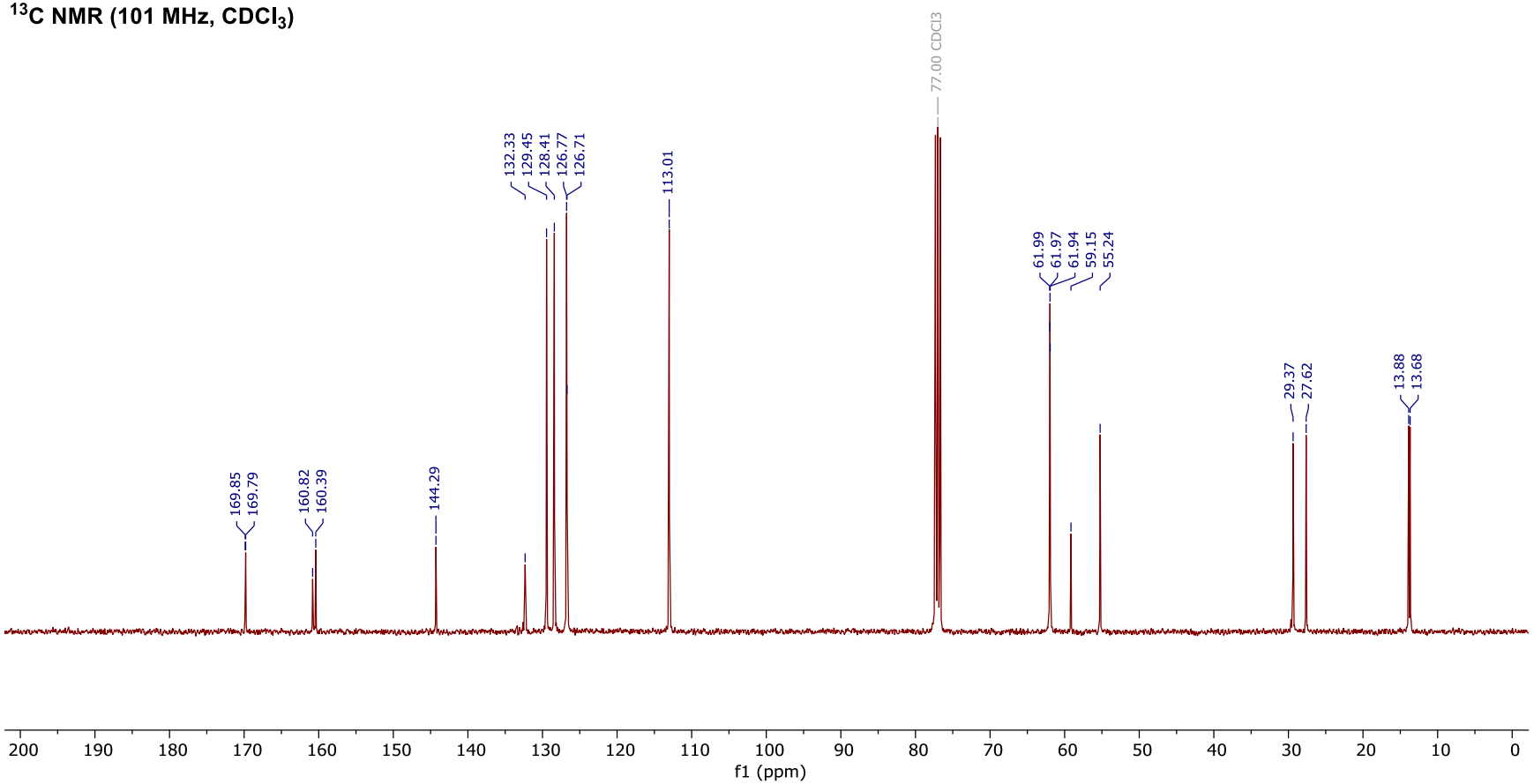


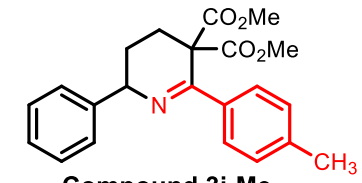

CO2Et
CO2Et
N
OMe
Compound 3h-Et
1H NMR (400 MHz, CDCl3)
7.69
7.28
7.26 CDCl3
6.85
4.94
4.22
4.09
3.81
2.54
2.44
2.13
1.57
1.20
1.07
f1 (ppm)



Compound 3h-Et

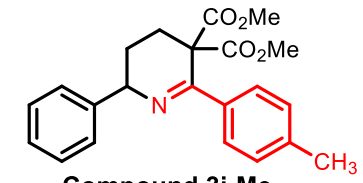
^{13}C NMR (101 MHz, $CDCl_3$)





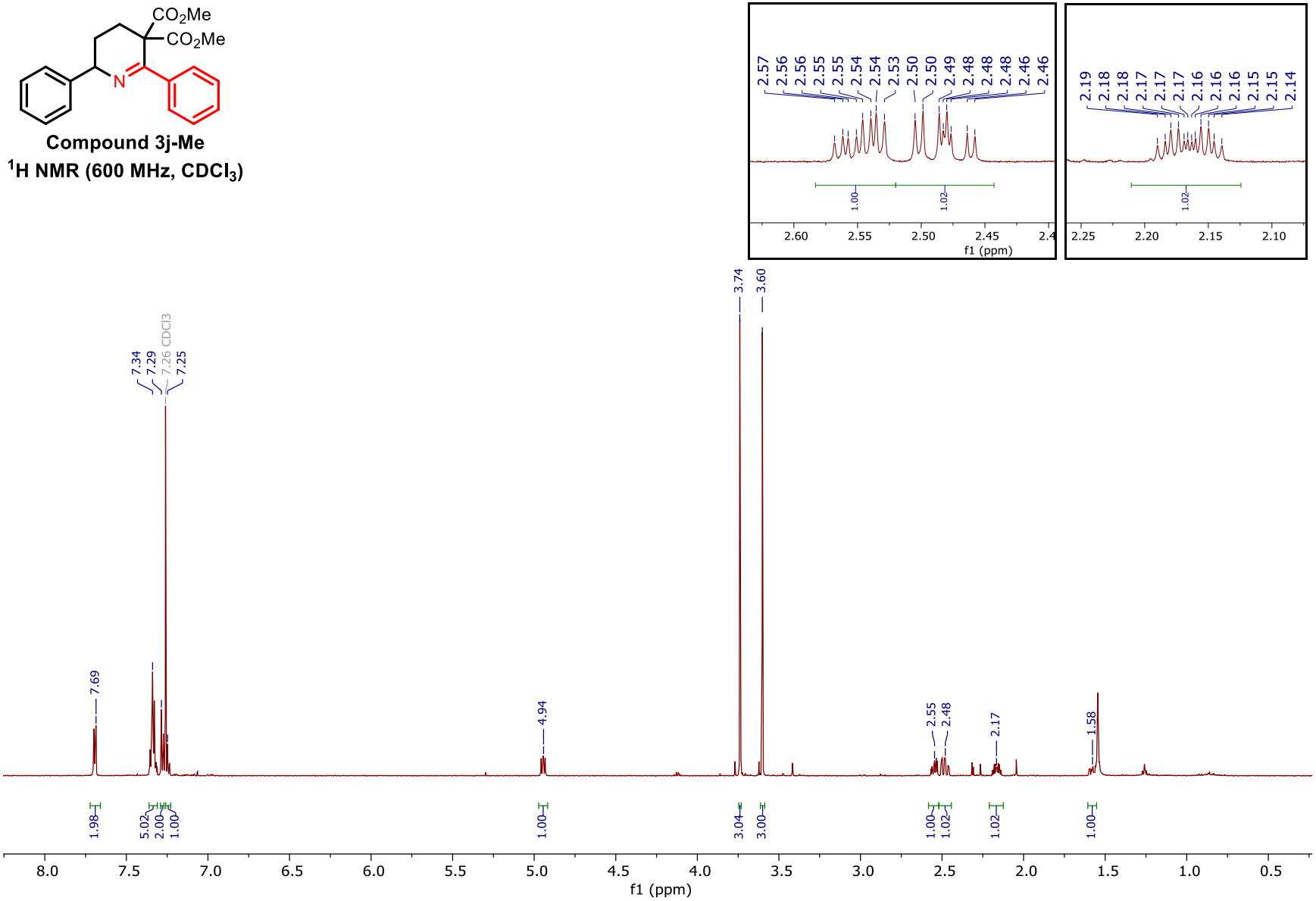
Compound 3i-Me

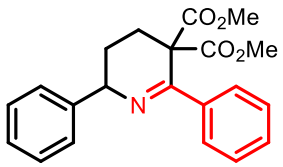
^{1}H NMR (400 MHz, $CDCl_3$)



Compound 3i-Me

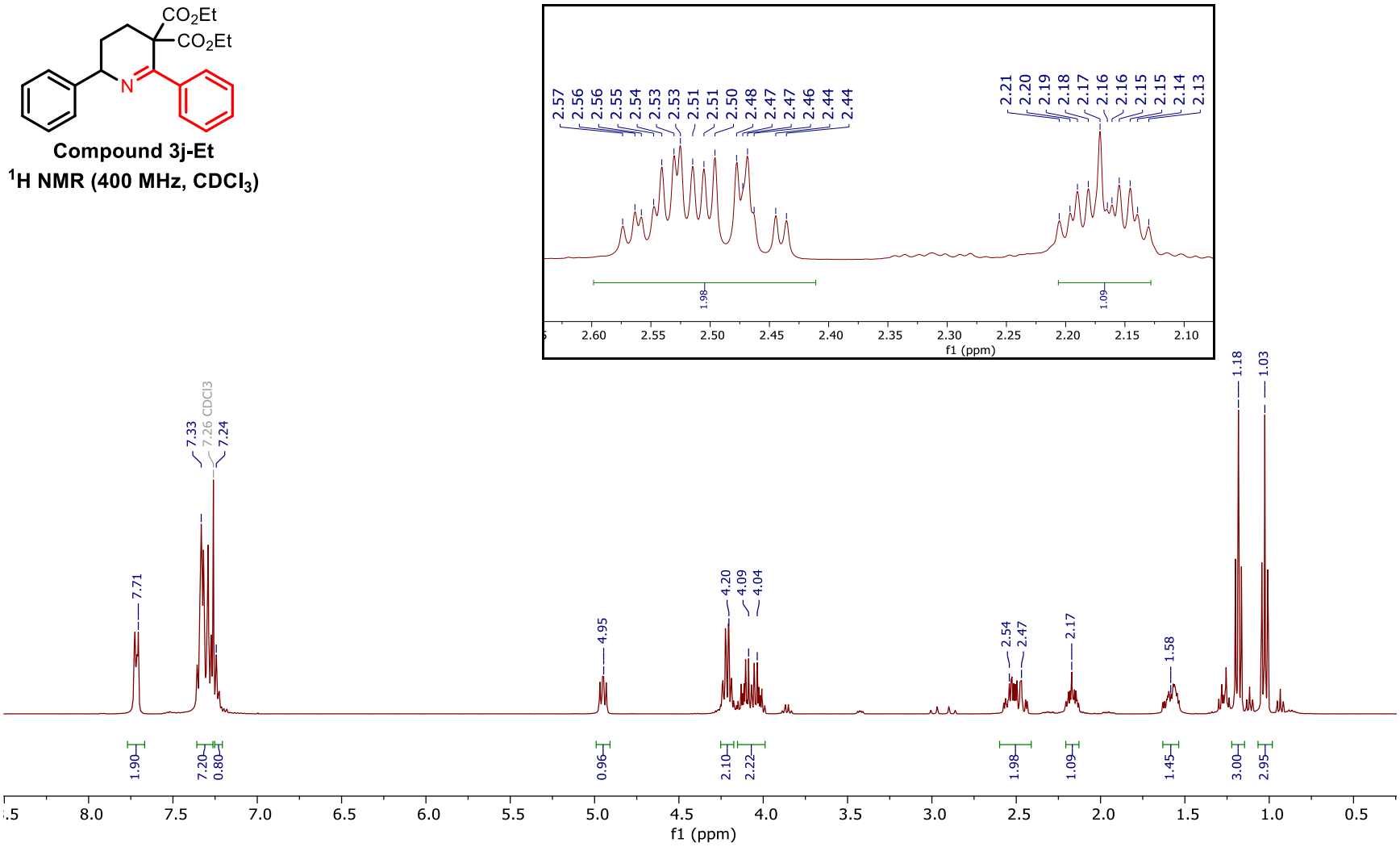
^{13}C NMR (101 MHz, $CDCl_3$)

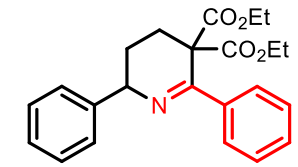

CO2Me
CO2Me
N
Compound 3j-Me
1H NMR (600 MHz, CDCl3)
2.57 2.56 2.56 2.55 2.55 2.54 2.54 2.53 2.50 2.50 2.49 2.48 2.48 2.46 2.46
1.00 1.02
2.60 2.55 2.50 2.45
f1 (ppm)
2.19 2.18 2.18 2.17 2.17 2.17 2.16 2.16 2.15 2.15 2.14
1.02
2.25 2.20 2.15 2.10
7.34 7.29 7.26 CDCl3 7.25
3.74 3.60
7.69
4.94
2.55 2.48
2.17
1.58
1.98 5.02 2.00 1.00 1.00 3.04 3.00 1.00 1.02 1.02 1.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)



Compound 3j-Me

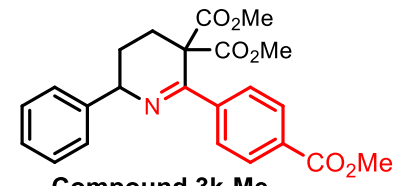
^{13}C NMR (101 MHz, $CDCl_3$)


CO2Et
CO2Et
N
Compound 3j-Et
1H NMR (400 MHz, CDCl3)
2.57
2.56
2.56
2.55
2.54
2.53
2.53
2.51
2.51
2.50
2.48
2.47
2.47
2.46
2.44
2.44
2.21
2.20
2.19
2.18
2.17
2.16
2.16
2.15
2.15
2.14
2.13
1.98
1.09
2.60
2.55
2.50
2.45
2.40
2.35
2.30
2.25
2.20
2.15
2.10
f1 (ppm)
7.33
7.26 CDCl3
7.24
7.71
4.95
4.20
4.09
4.04
2.54
2.47
2.17
1.58
1.18
1.03
1.90
7.20
0.80
0.96
2.10
2.22
1.98
1.09
1.45
3.00
2.95
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



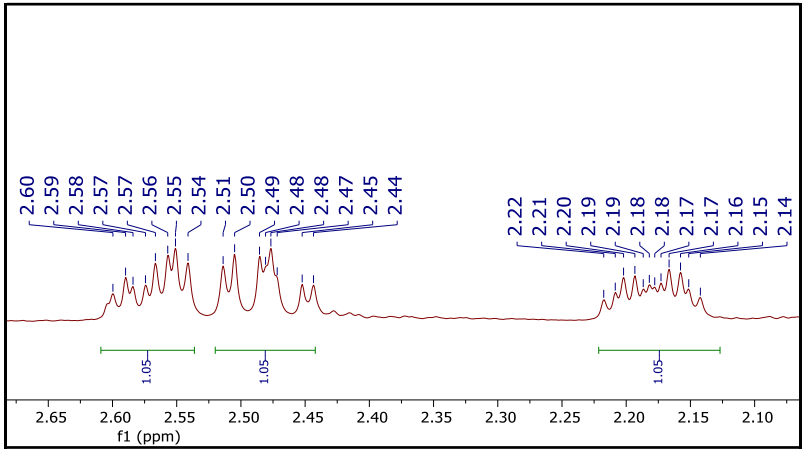
Compound 3j-Et

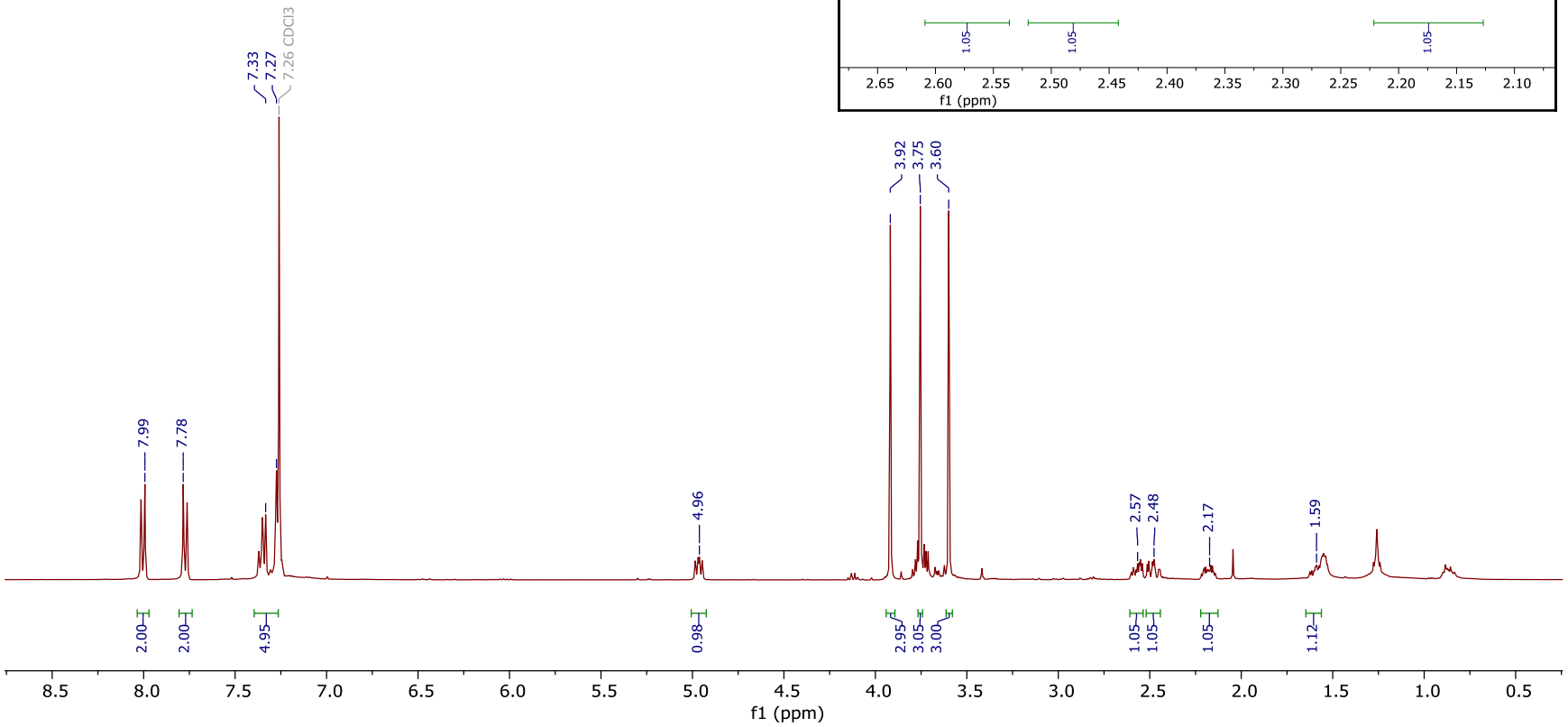
^{13}C NMR (101 MHz, $CDCl_3$)

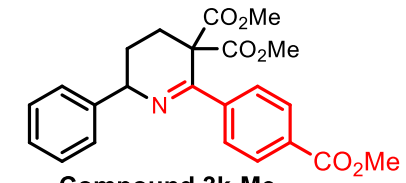


Compound 3k-Me

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

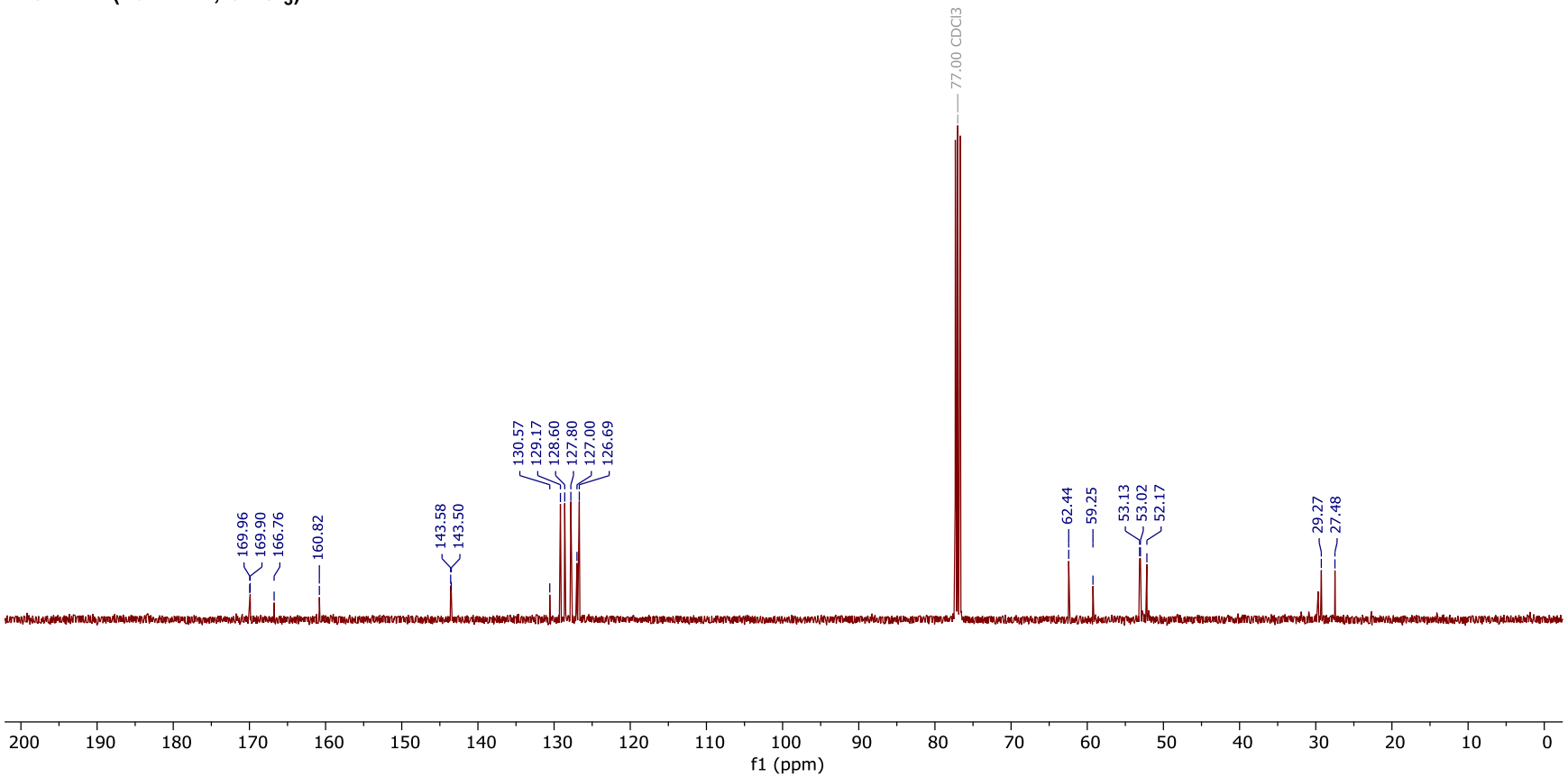


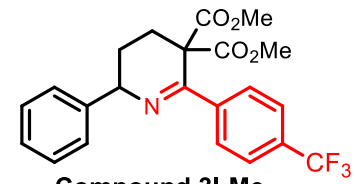




Compound 3k-Me

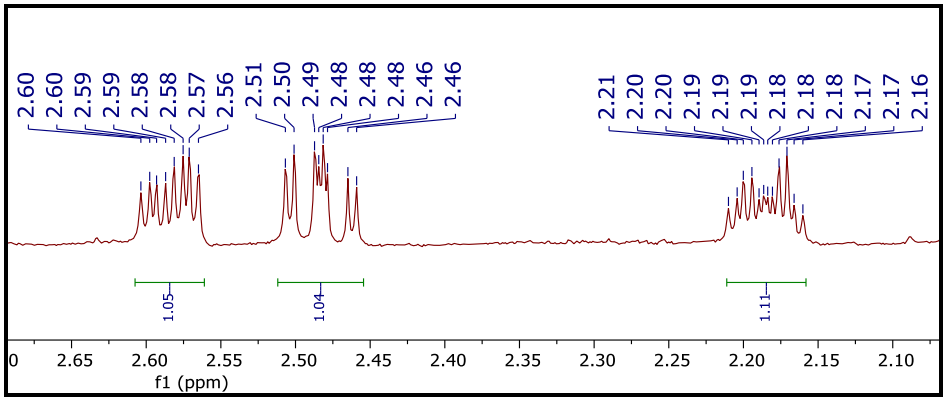
^{13}C NMR (101 MHz, $CDCl_3$)

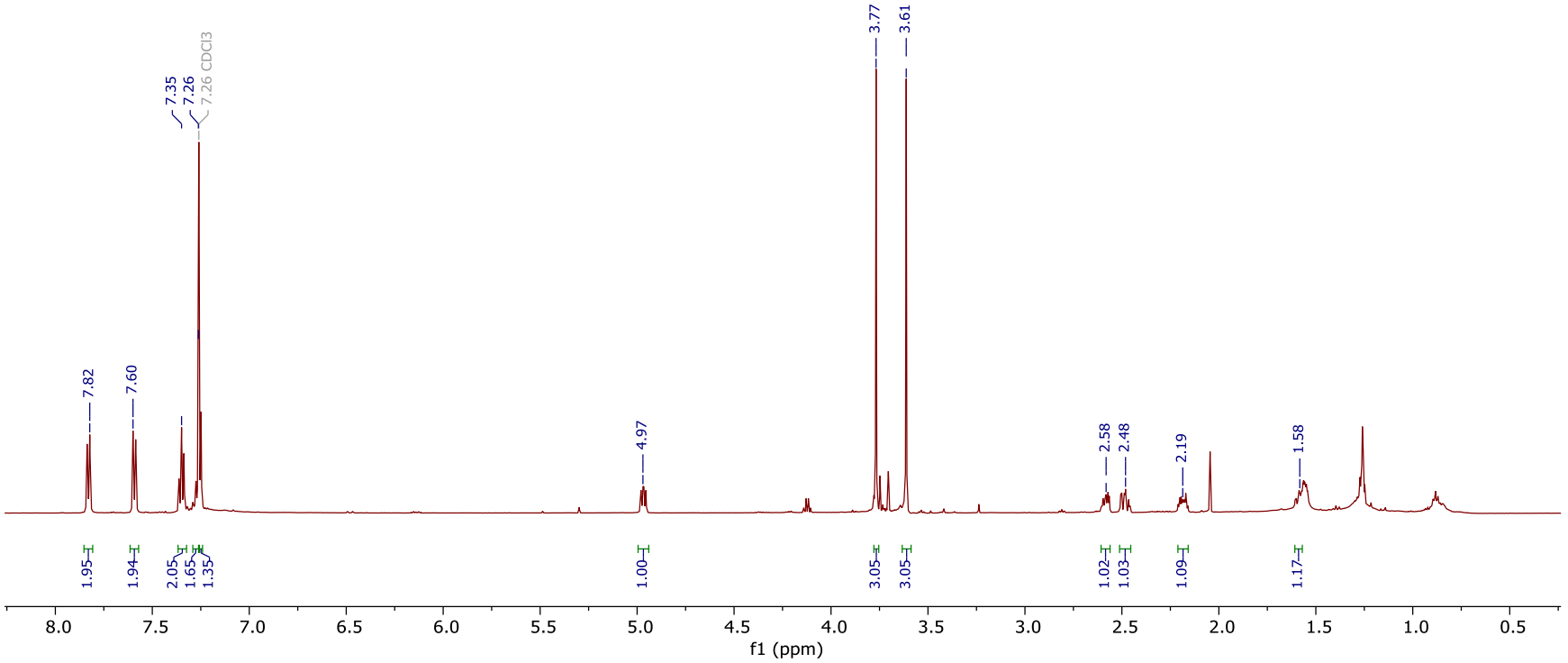


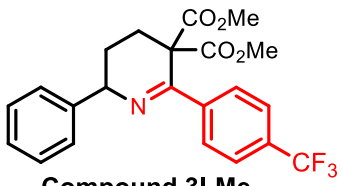


Compound 3l-Me

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

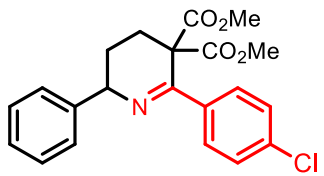






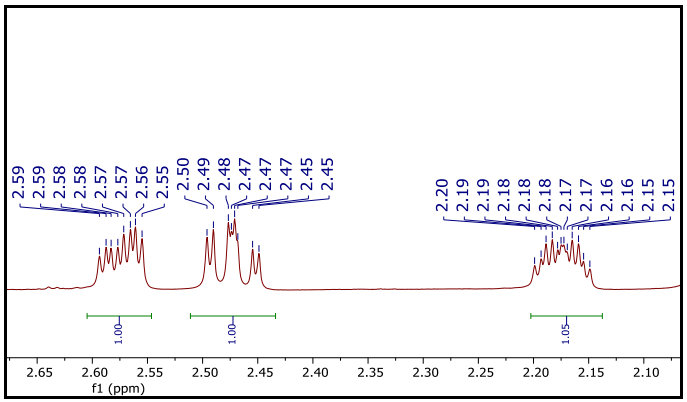
Compound 3l-Me

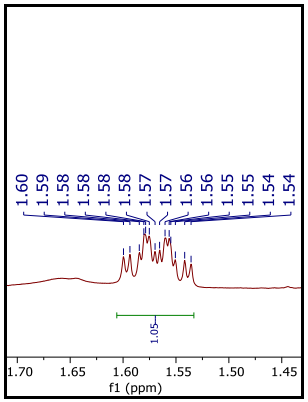
^{13}C NMR (151 MHz, $CDCl_3$)

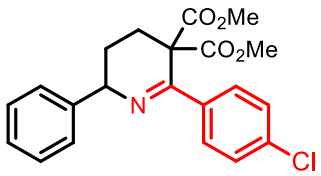


Compound 3m-Me

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

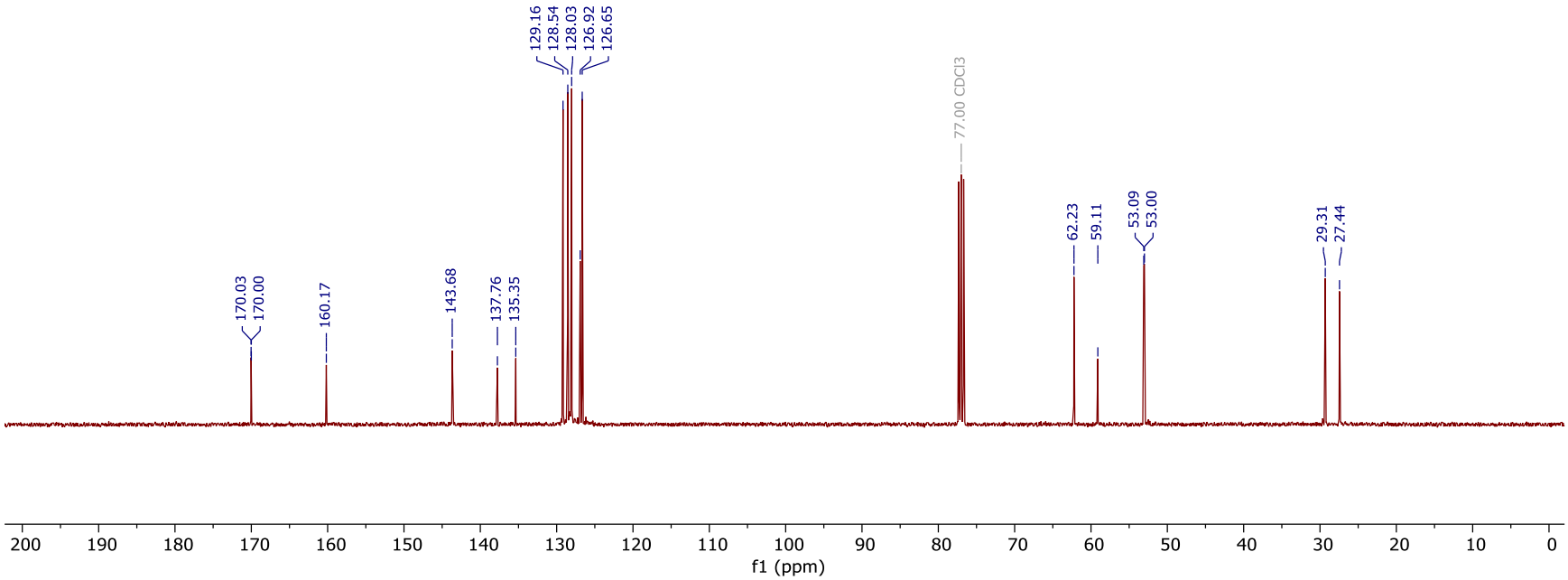


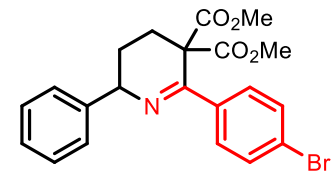




Compound 3m-Me

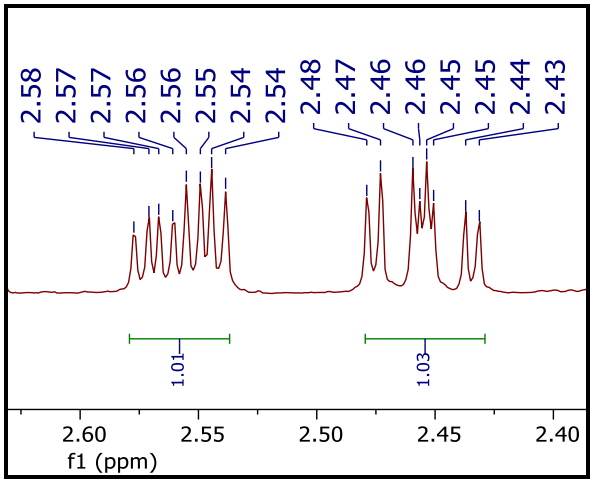
^{13}C NMR (151 MHz, $CDCl_3$)

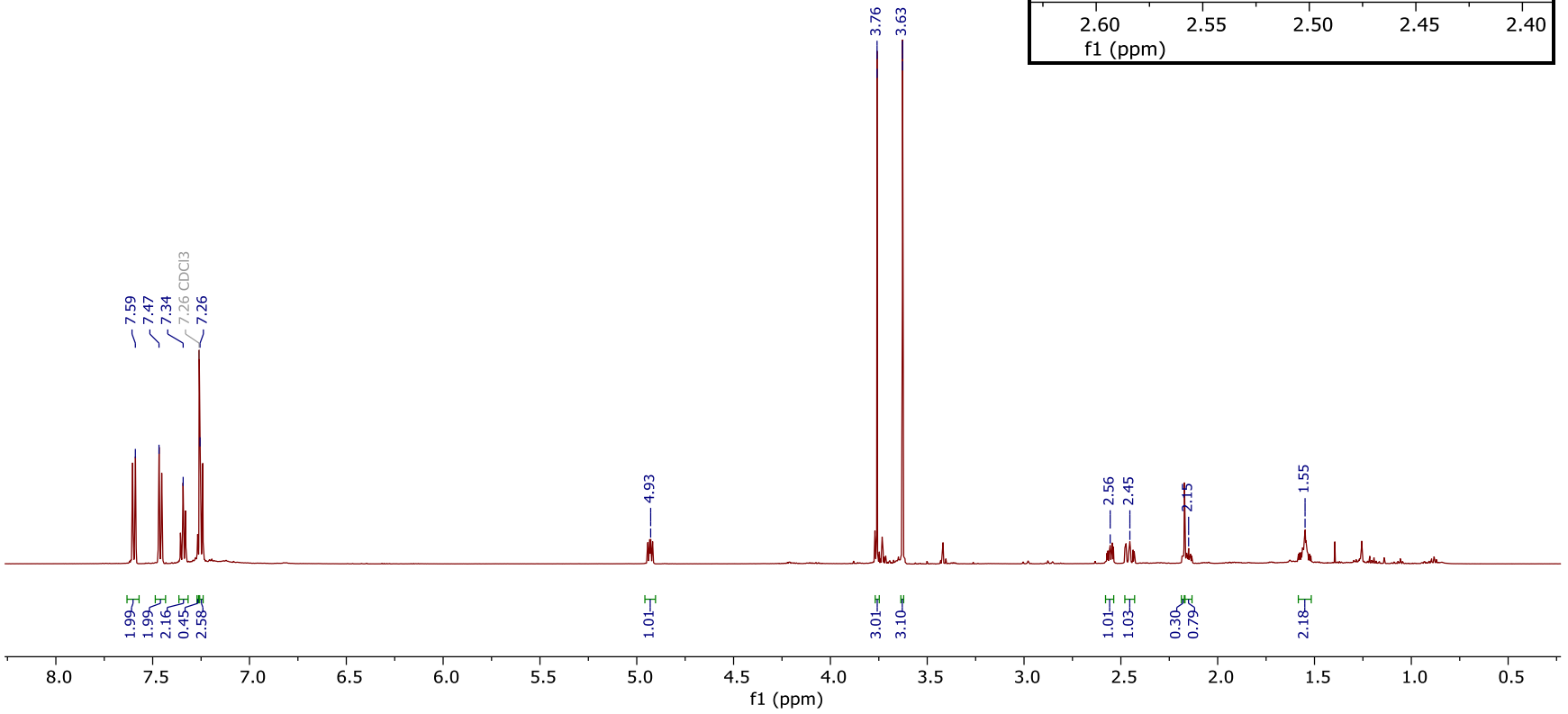


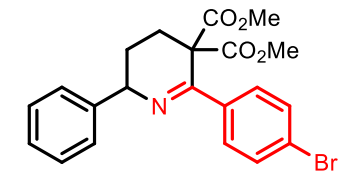


Compound 3n-Me

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

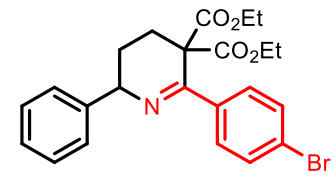






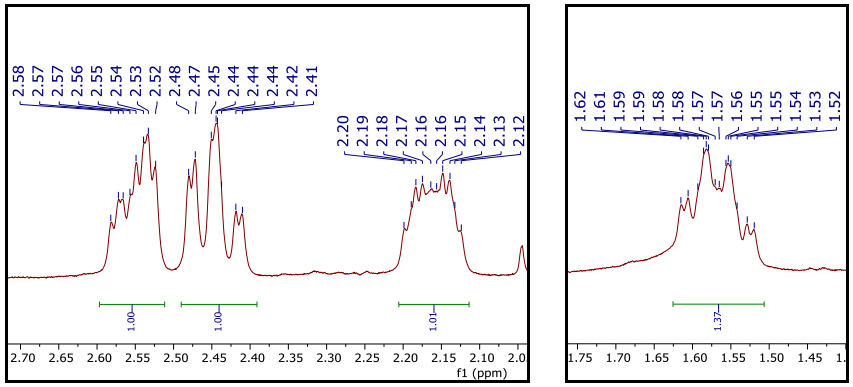
Compound 3n-Me

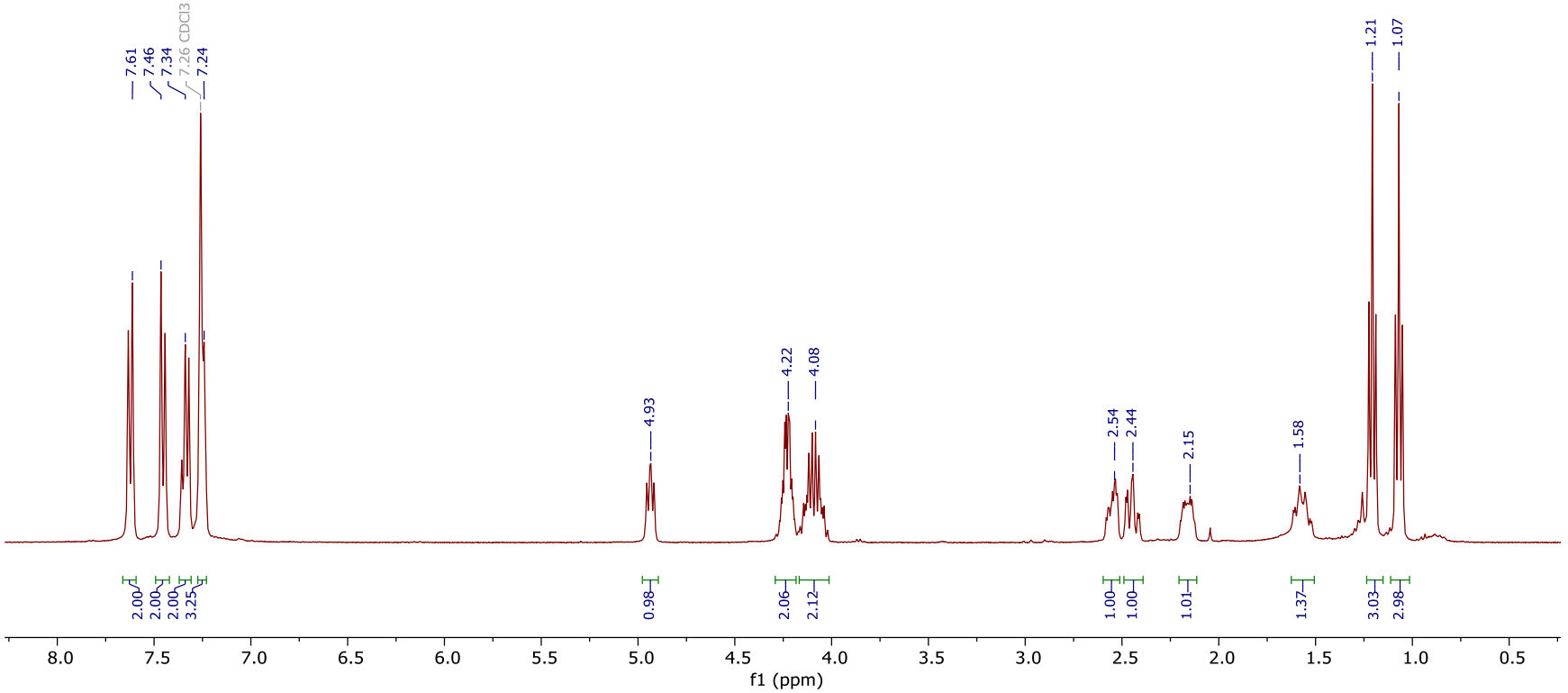
^{13}C NMR (151 MHz, $CDCl_3$)

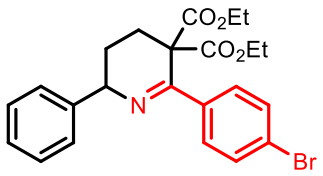


Compound 3n-Et

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

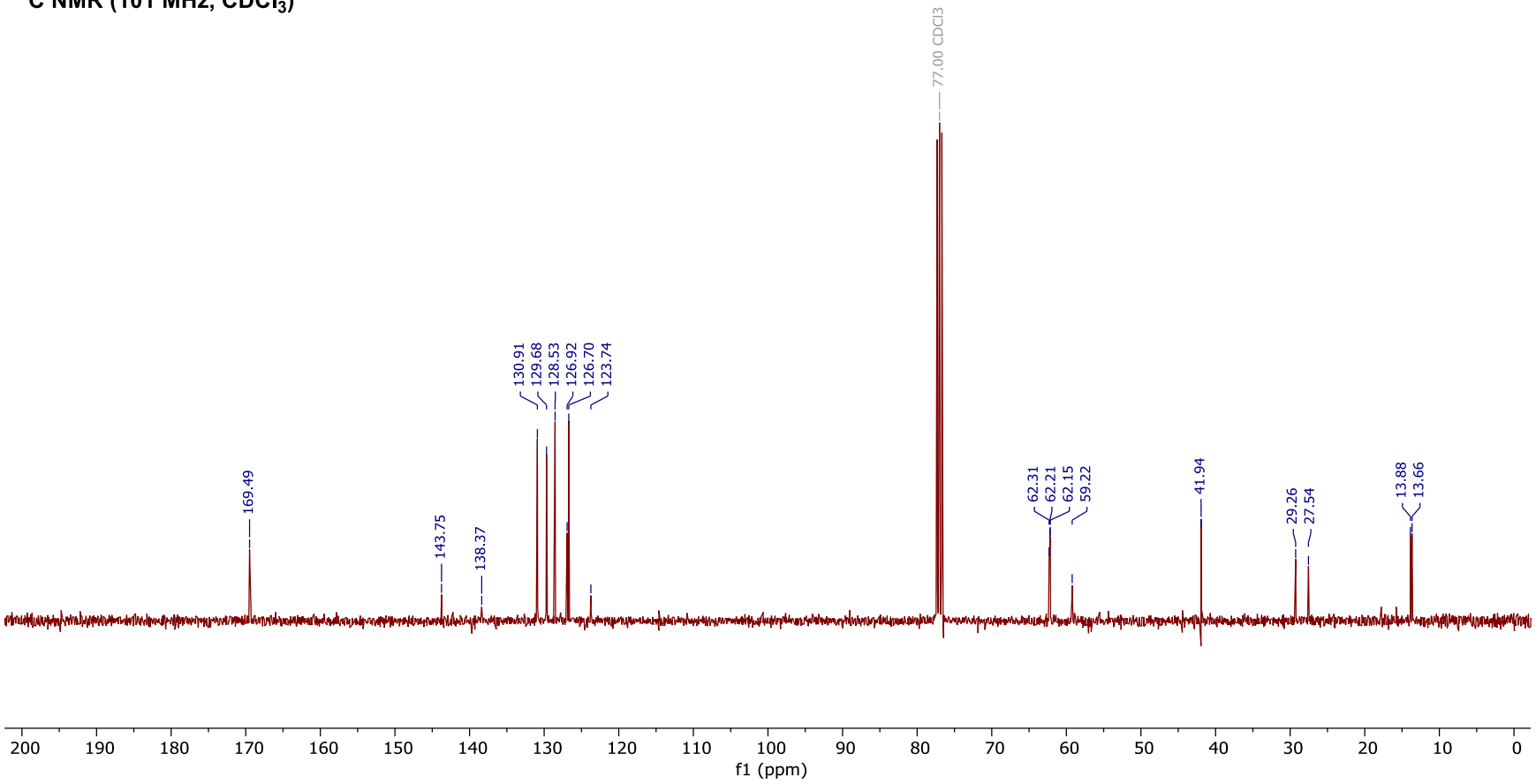


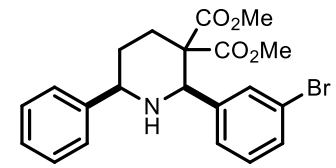




Compound 3n-Et

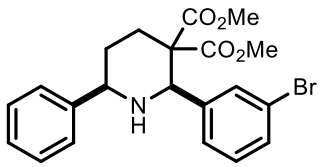
^{13}C NMR (101 MHz, $CDCl_3$)





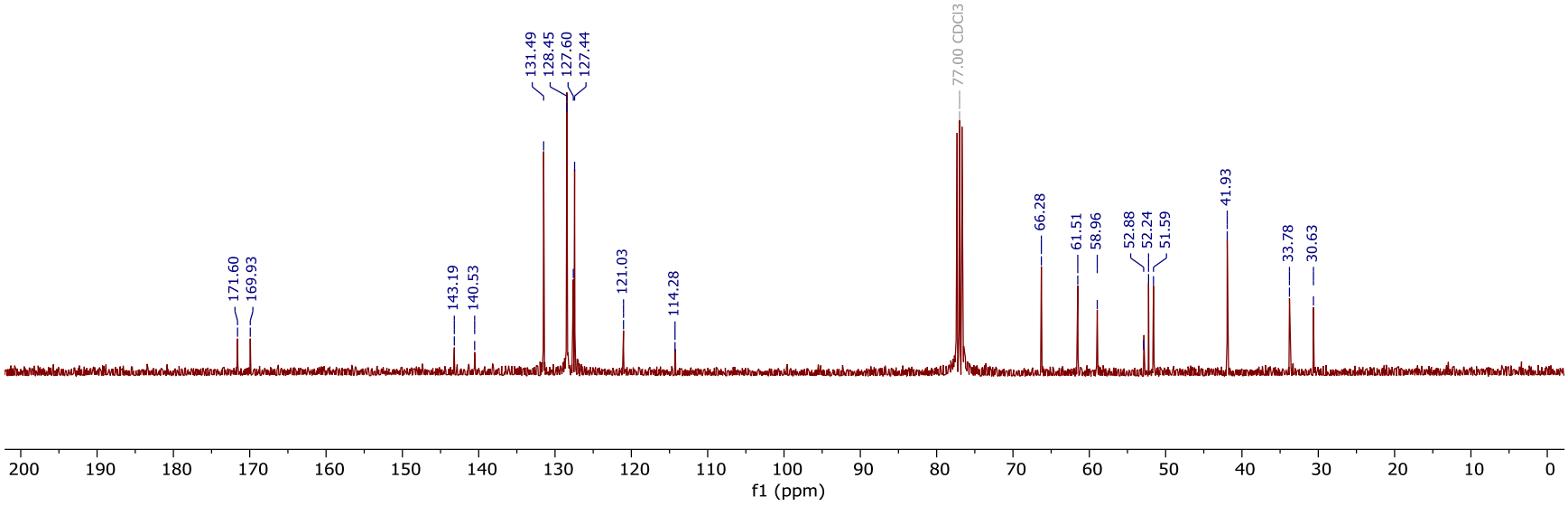
Compound 3n*-Me

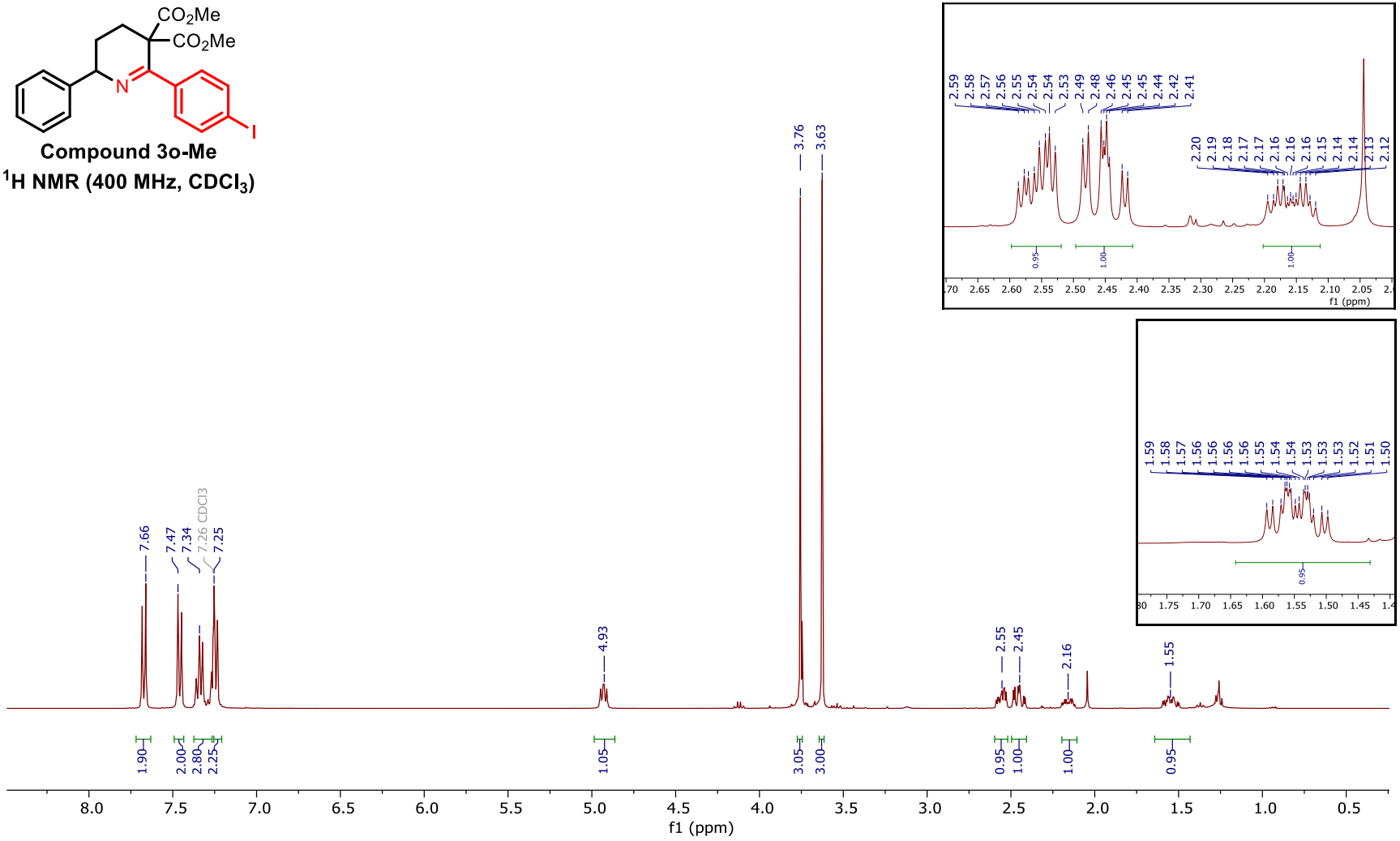
^{1}H NMR (400 MHz, $CDCl_3$)

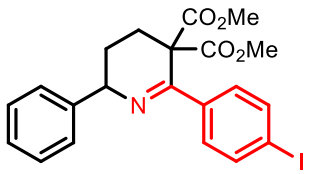


Compound 3n*-Me

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

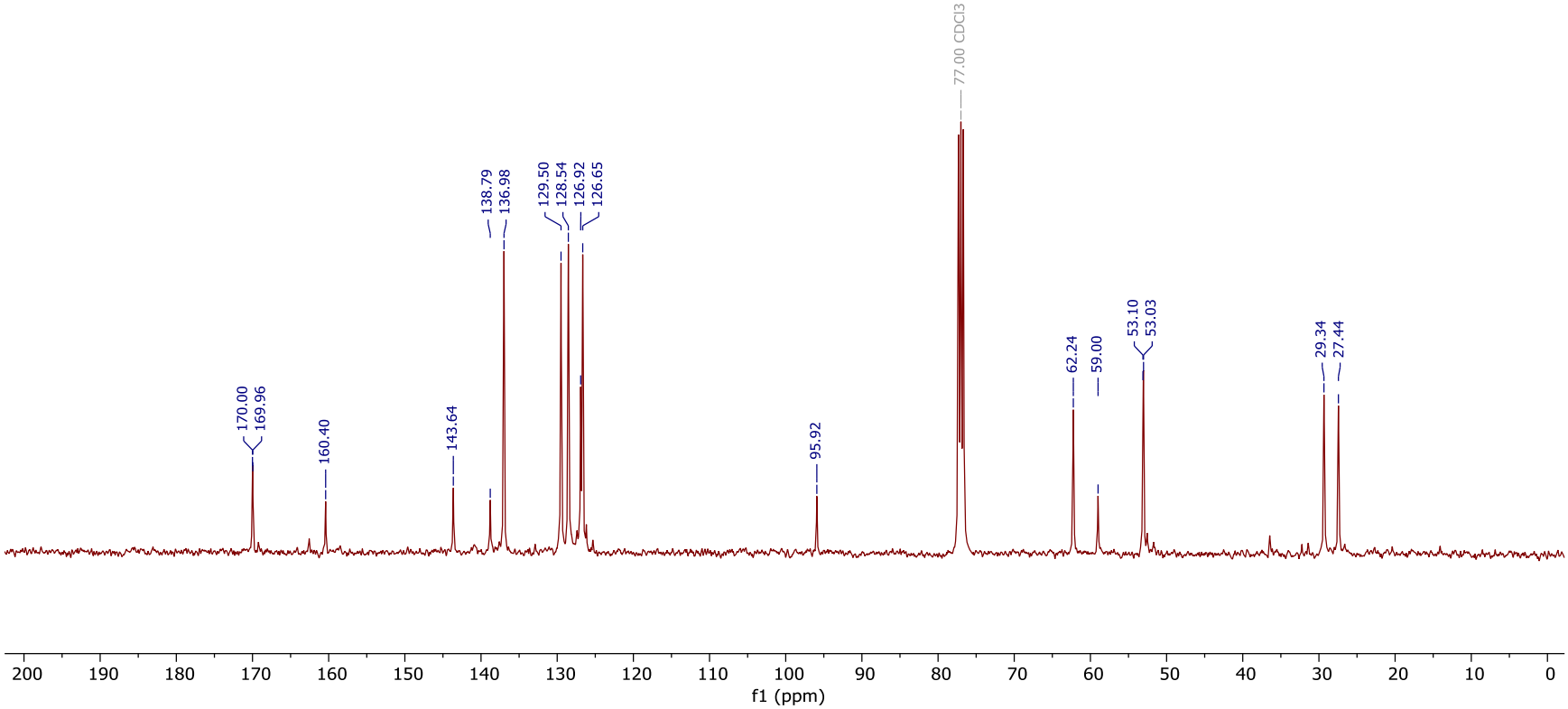


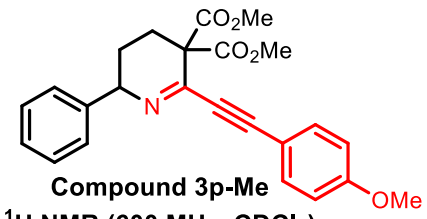

CO2Me
CO2Me
N
I
Compound 3o-Me
1H NMR (400 MHz, CDCl3)
7.66
7.47
7.34
7.26 CDCl3
7.25
4.93
3.76
3.63
2.55
2.45
2.16
1.55
1.90
2.00
2.80
2.25
1.05
3.05
3.00
0.95
1.00
1.00
0.95
f1 (ppm)



Compound 3o-Me

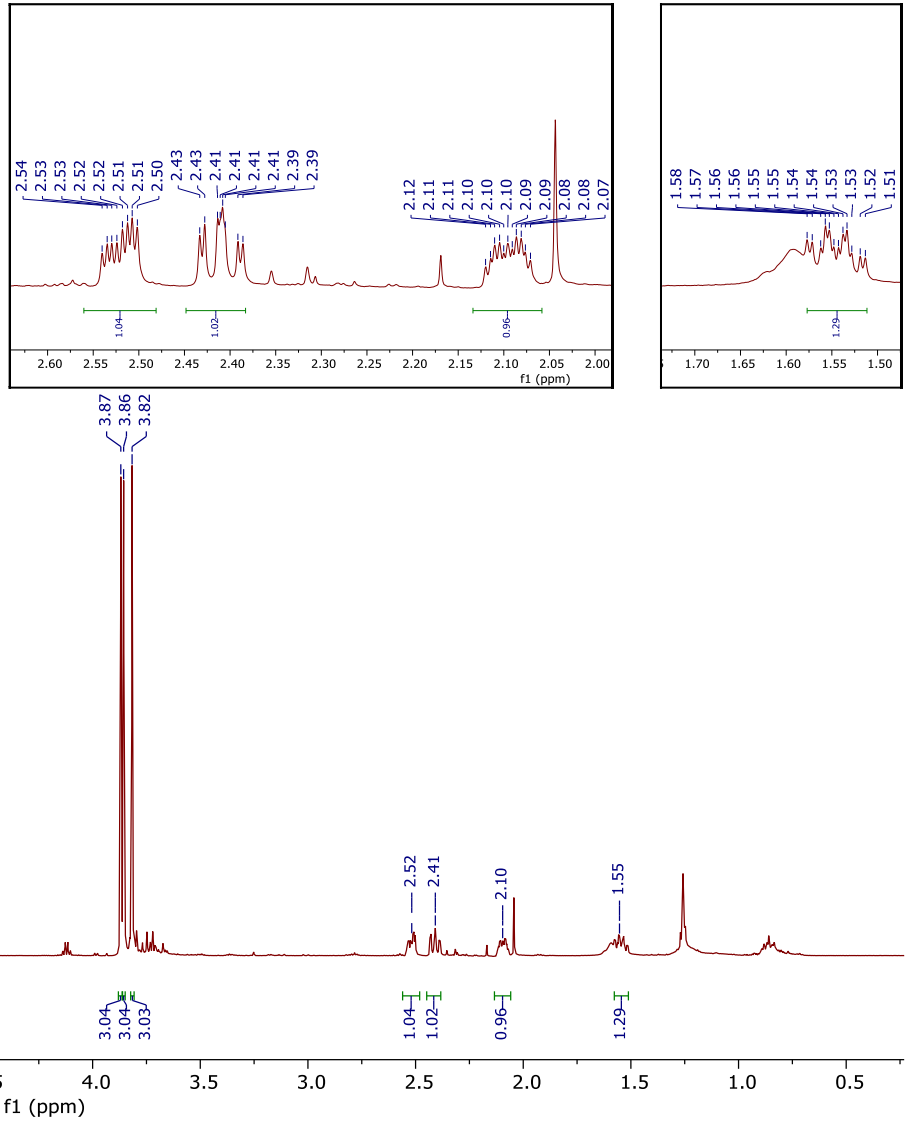
^{13}C NMR (101 MHz, $CDCl_3$)

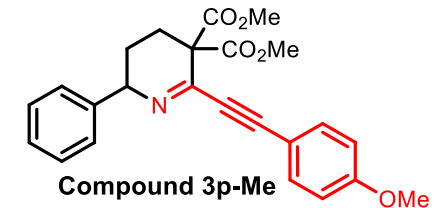




Compound 3p-Me

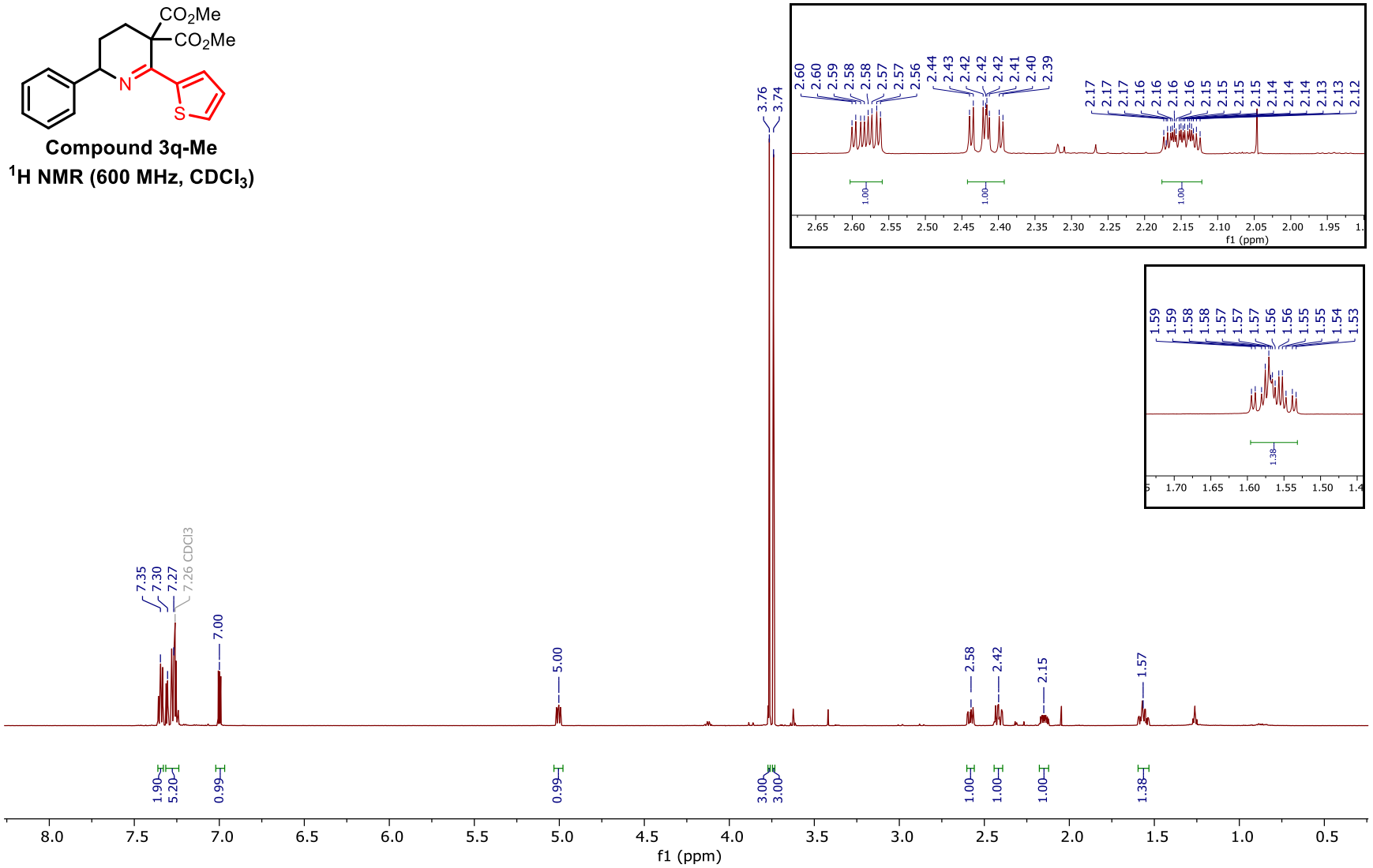
^{1}H NMR (600 MHz, $CDCl_3$)

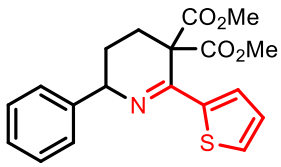




Compound 3p-Me

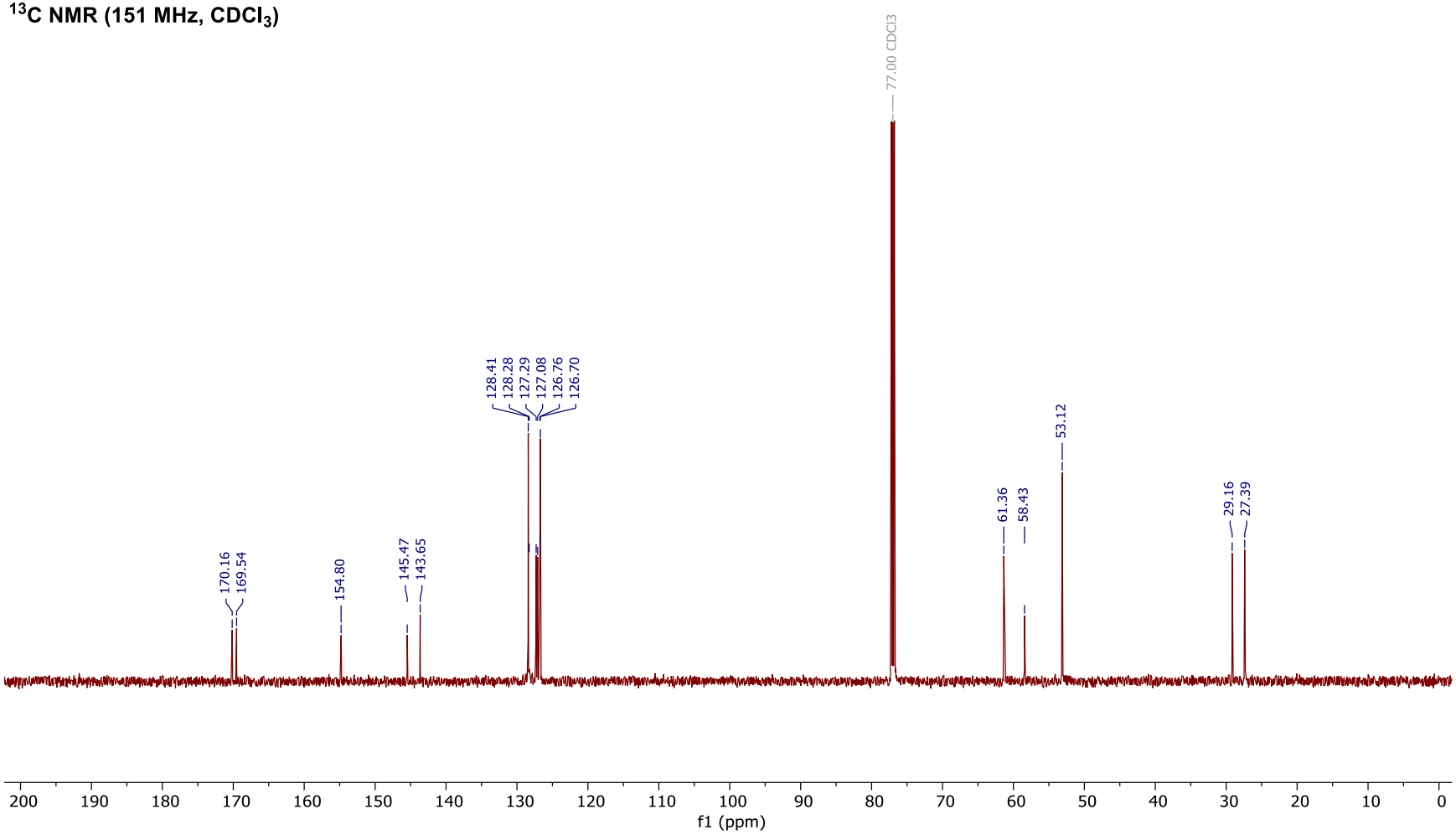
^{13}C NMR (151 MHz, $CDCl_3$)

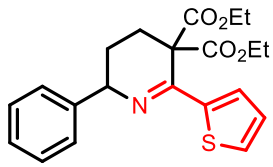

CO2Me
CO2Me
N
S
Compound 3q-Me
1H NMR (600 MHz, CDCl3)
7.35
7.30
7.27
7.26 CDCl3
7.00
5.00
3.76
3.74
2.58
2.42
2.15
1.57
1.90
5.20
0.99
0.99
3.00
3.00
1.00
1.00
1.00
1.38
f1 (ppm)



Compound 3q-Me

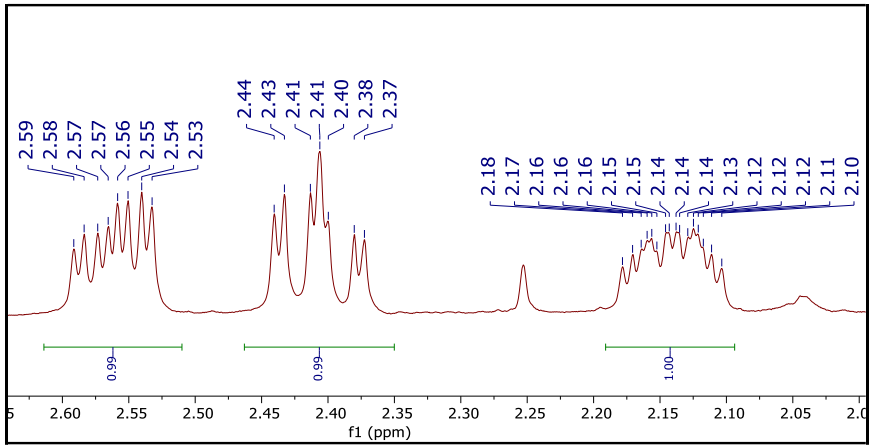
^{13}C NMR (151 MHz, $CDCl_3$)

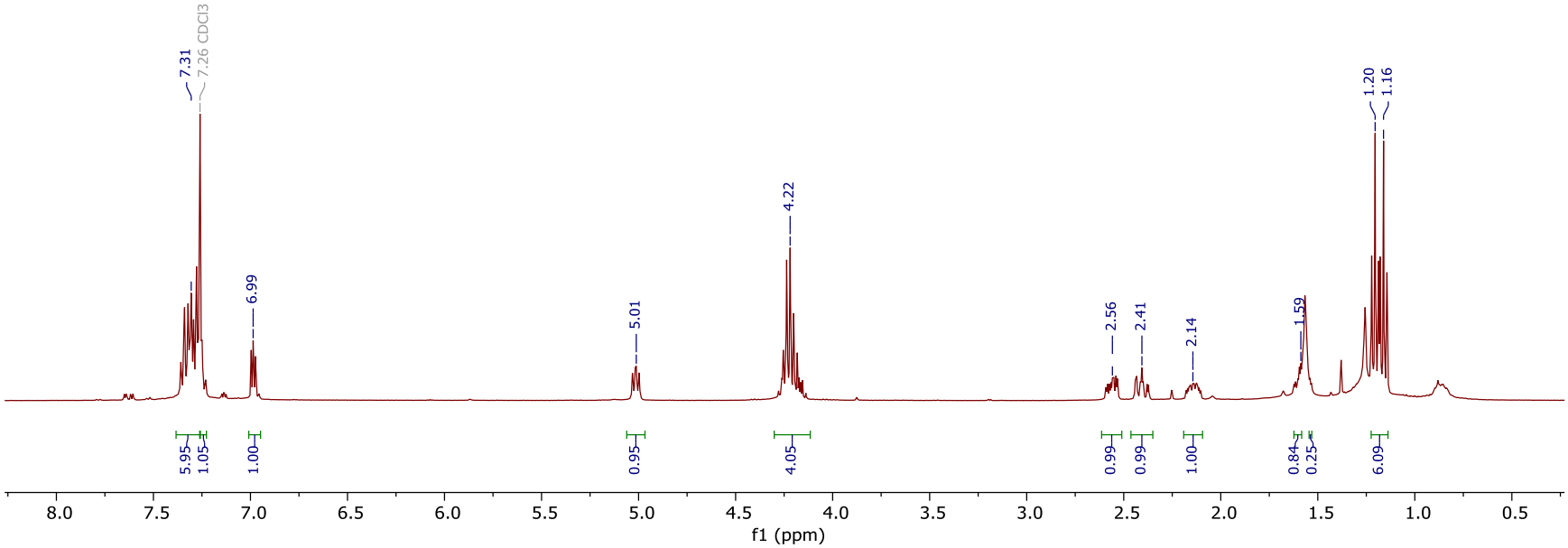


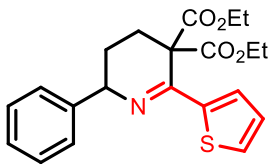


Compound 3q-Et

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

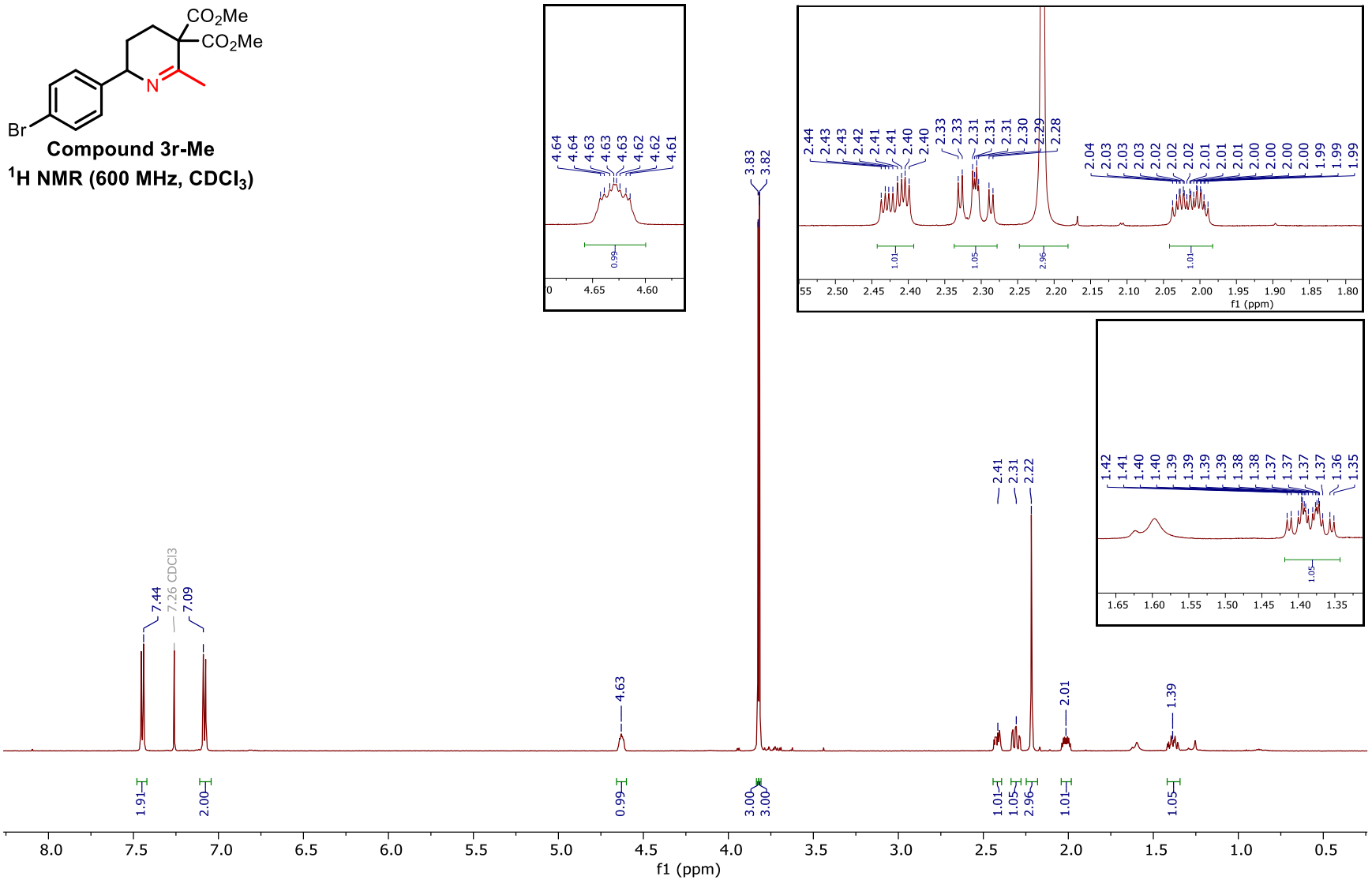


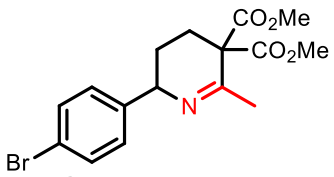




Compound 3q-Et

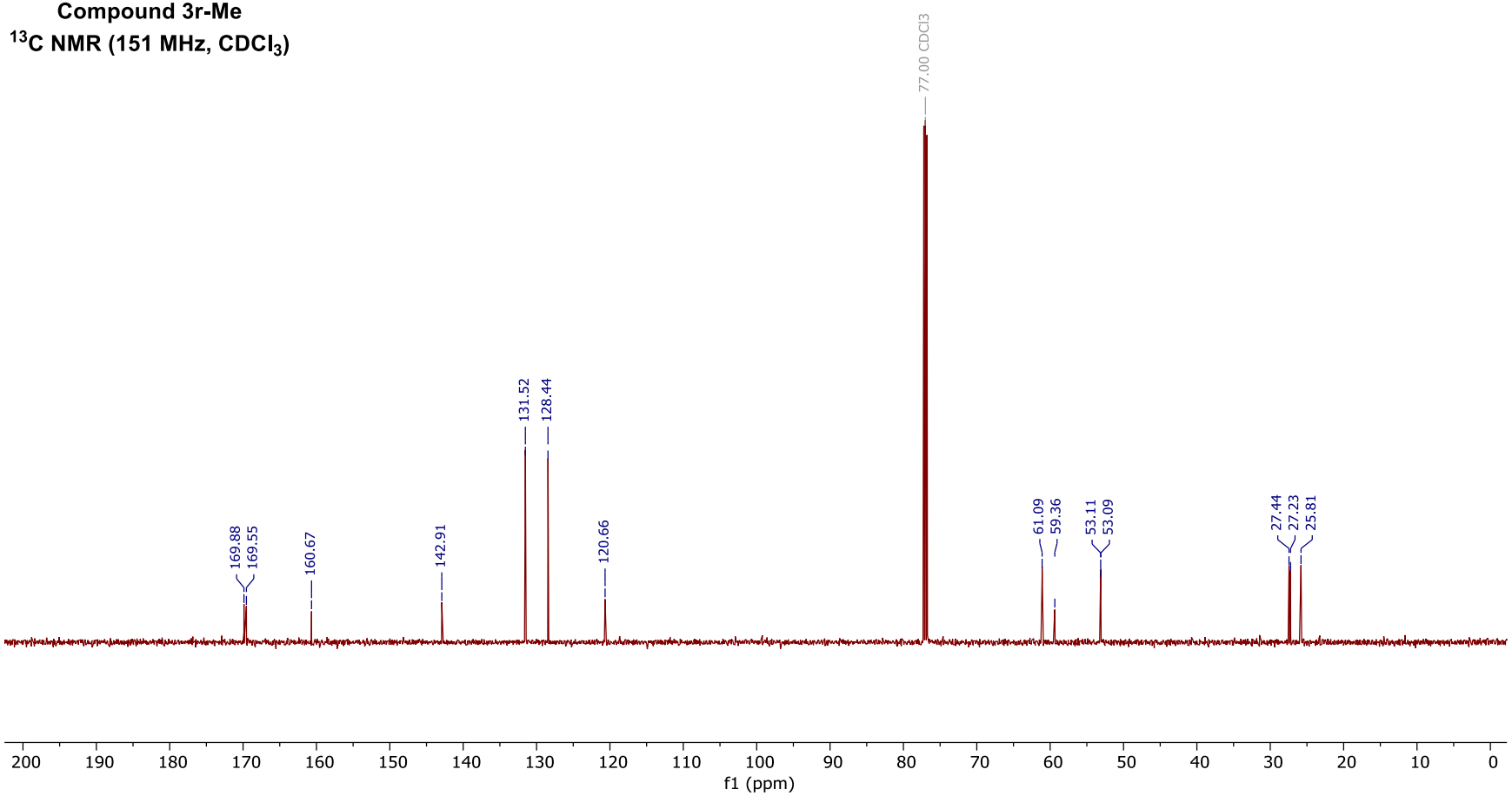
^{13}C NMR (101 MHz, $CDCl_3$)

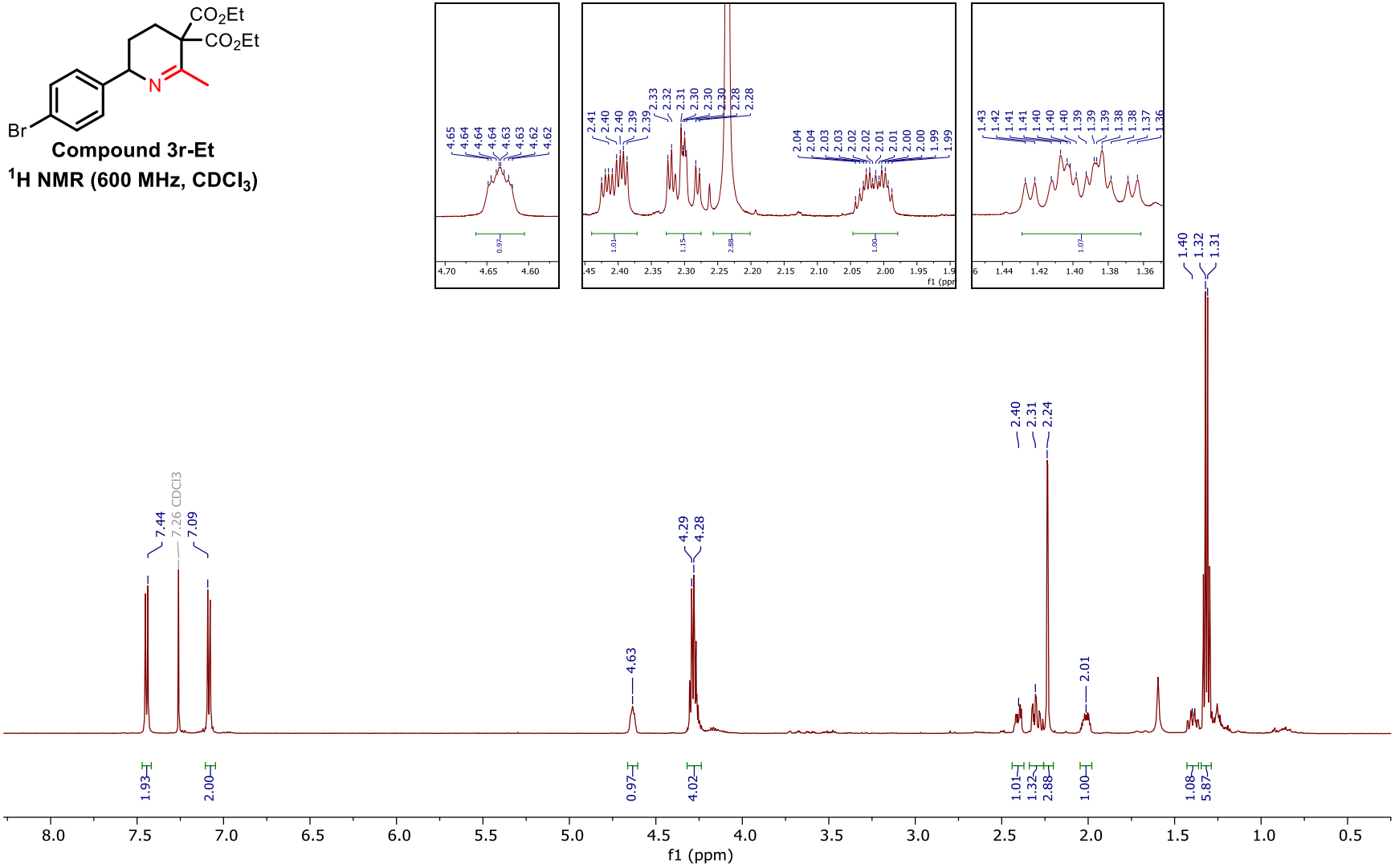

CO2Me
CO2Me
N
Br
Compound 3r-Me
1H NMR (600 MHz, CDCl3)
7.44
7.26 CDCl3
7.09
4.63
3.83
3.82
2.41
2.31
2.22
2.01
1.39
1.91
2.00
0.99
3.00
3.00
1.01
1.05
2.96
1.01
1.05
f1 (ppm)

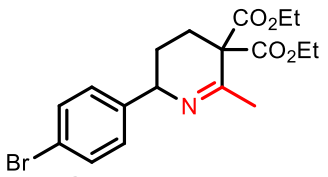


Compound 3r-Me

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

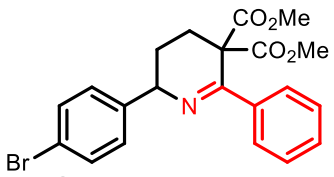



CO2Et
CO2Et
N
Br
Compound 3r-Et
1H NMR (600 MHz, CDCl3)
7.44
7.26 CDCl3
7.09
4.63
4.29
4.28
2.40
2.31
2.24
2.01
1.40
1.32
1.31
1.93
2.00
0.97
4.02
1.01
1.32
2.88
1.00
1.08
5.87
f1 (ppm)



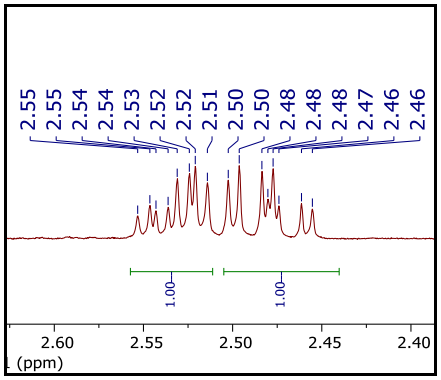
Compound 3r-Et

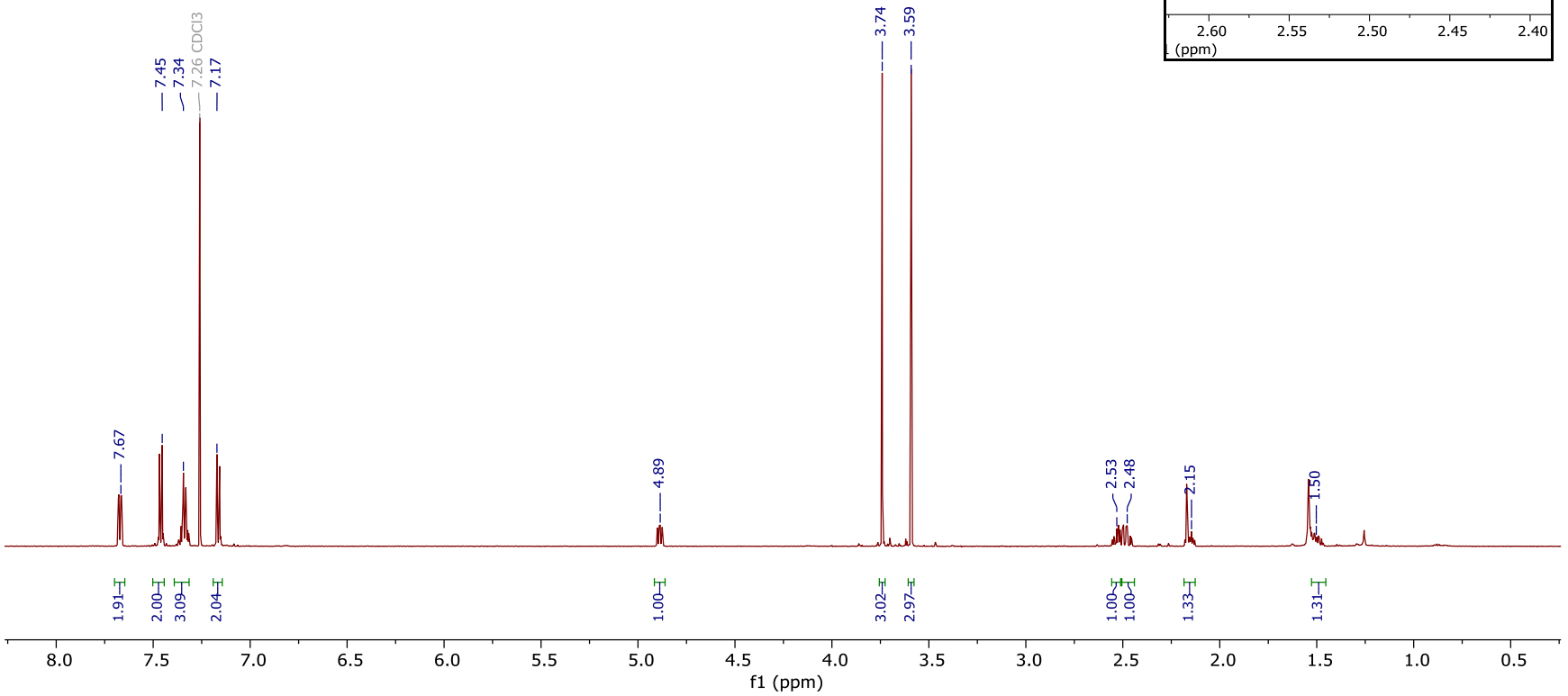
^{13}C NMR (151 MHz, $CDCl_3$)

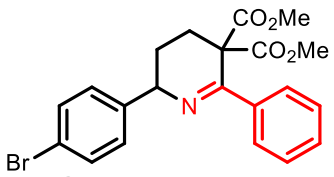


Compound 3s-Me

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

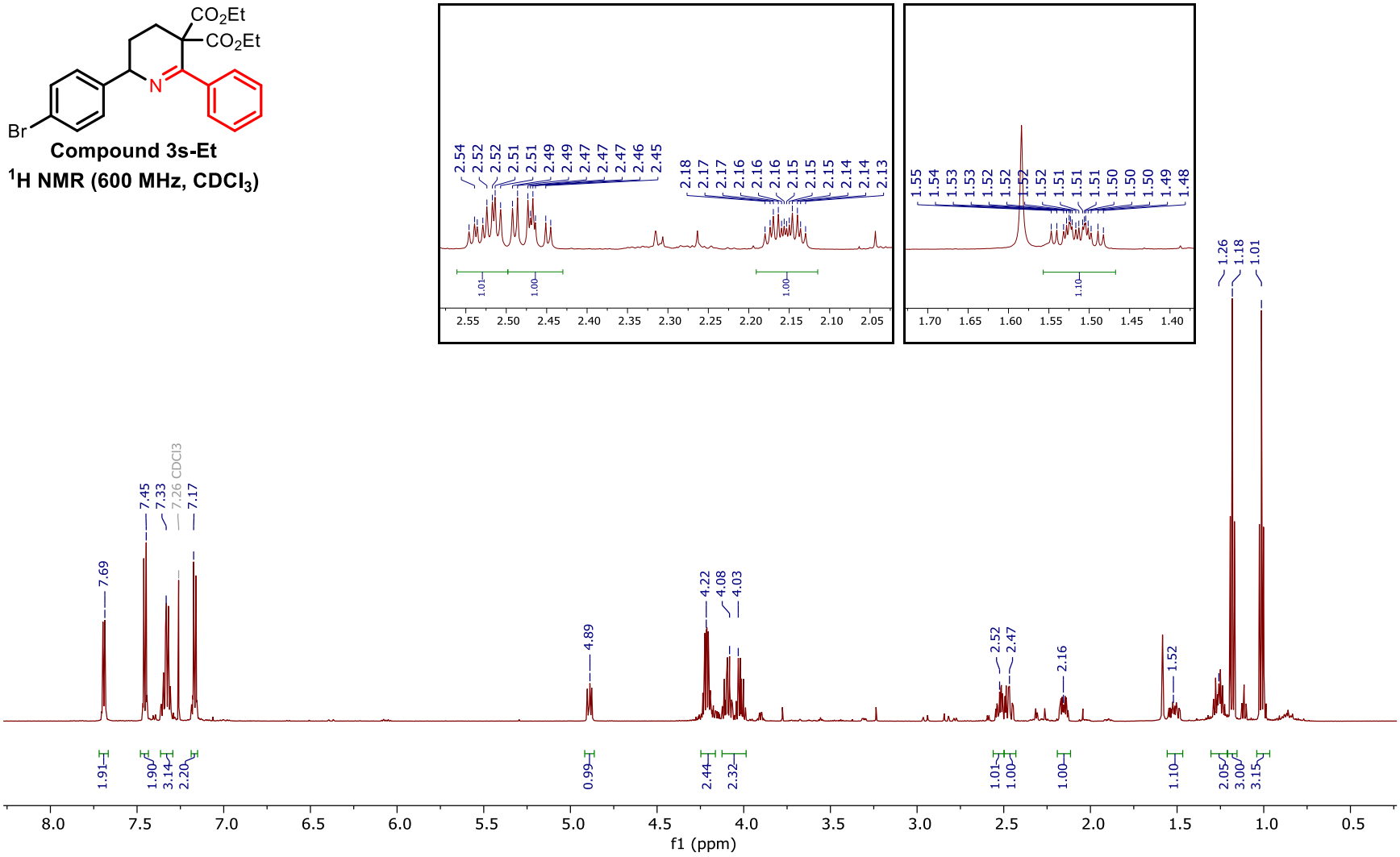


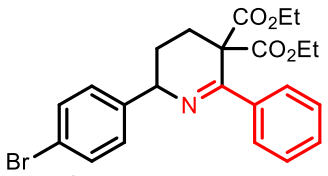




Compound 3s-Me

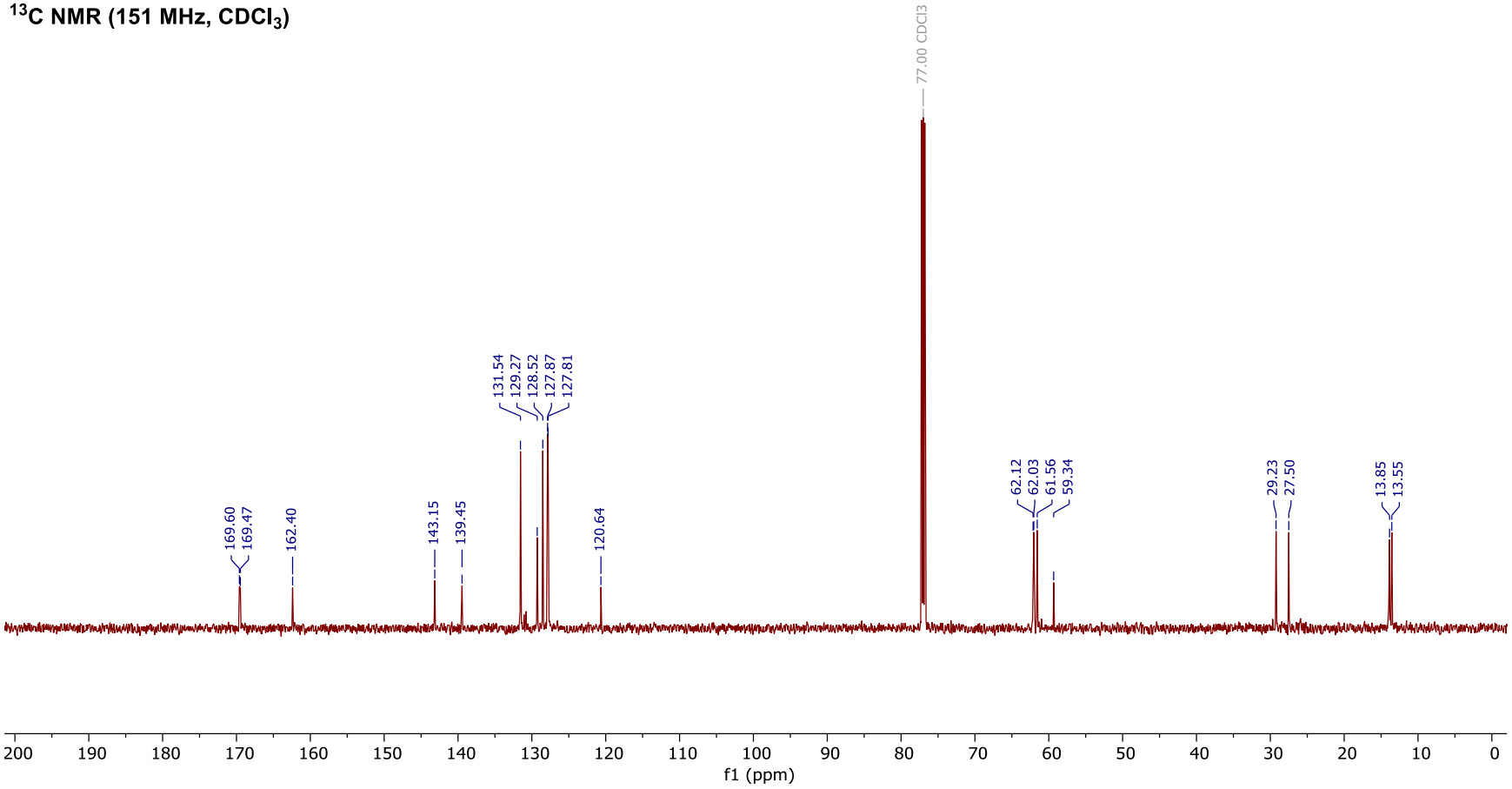
^{13}C NMR (151 MHz, $CDCl_3$)

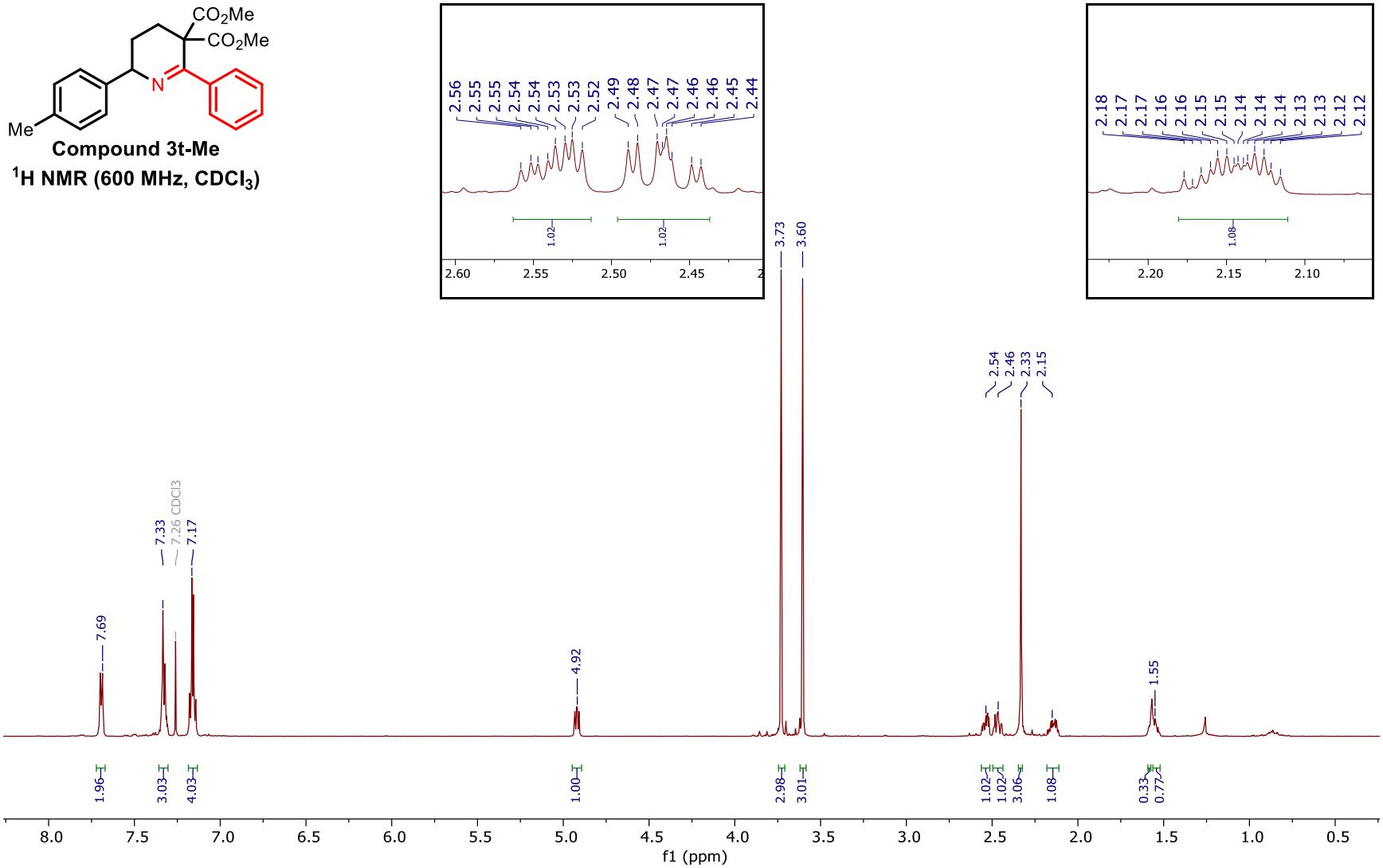

CO2Et
CO2Et
N
Br
Compound 3s-Et
1H NMR (600 MHz, CDCl3)
f1 (ppm)

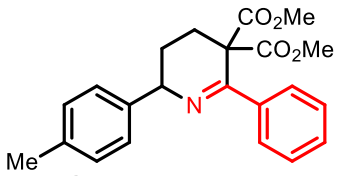


Compound 3s-Et

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

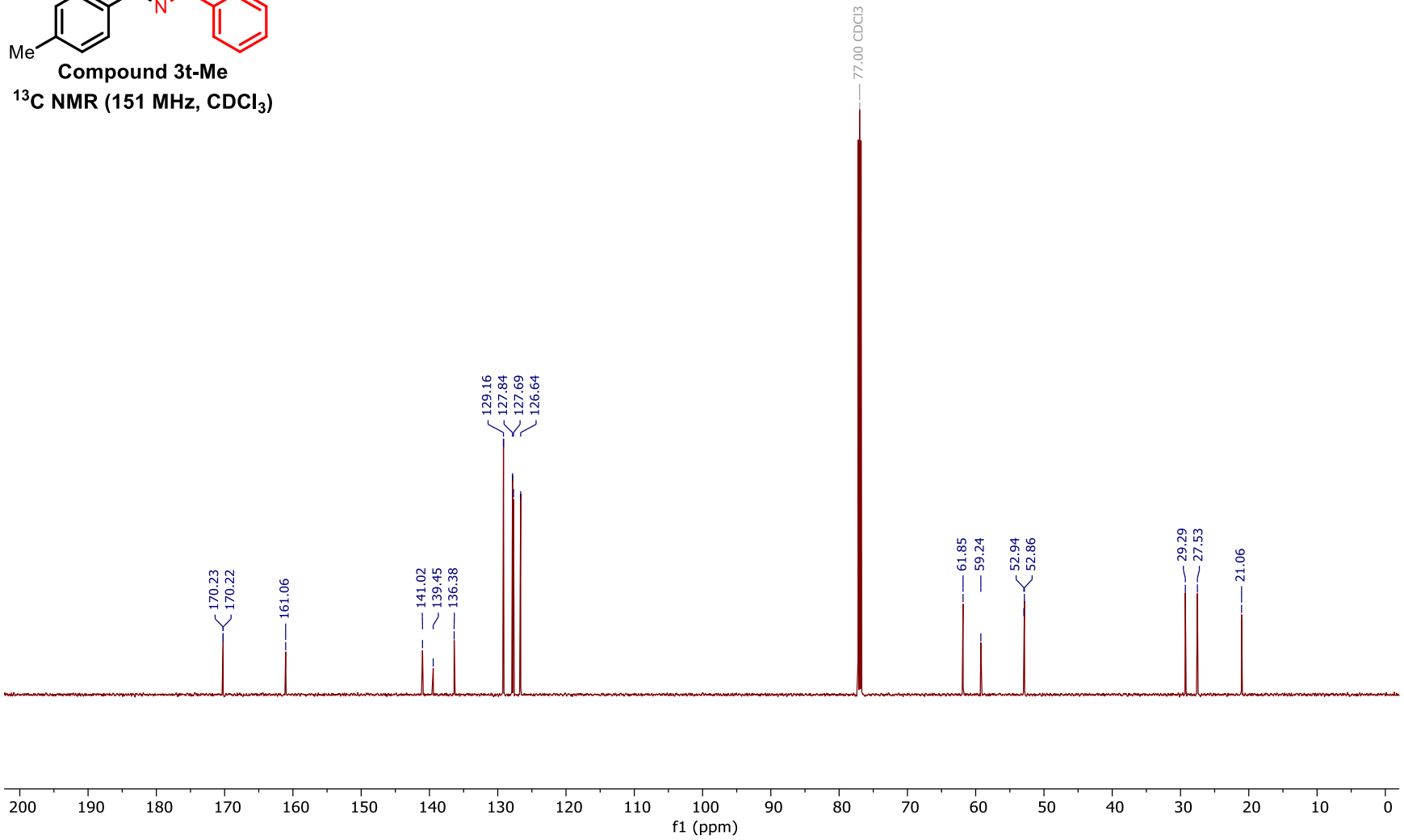


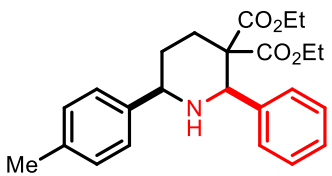

CO2Me
CO2Me
N
Me
Compound 3t-Me
1H NMR (600 MHz, CDCl3)
2.56 2.55 2.55 2.54 2.54 2.53 2.53 2.52 2.49 2.48 2.47 2.47 2.46 2.46 2.45 2.44
1.02 1.02
2.60 2.55 2.50 2.45
2.18 2.17 2.17 2.16 2.16 2.15 2.15 2.14 2.14 2.14 2.13 2.13 2.12 2.12
1.08
2.20 2.15 2.10
3.73 3.60
2.54 2.46 2.33 2.15
7.33 7.26 CDCl3 7.17
7.69
4.92
1.55
1.96 3.03 4.03 1.00 2.98 3.01 1.02 1.02 3.06 1.08 0.33 0.77
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)



Compound 3t-Me

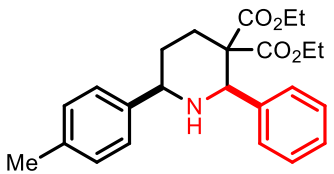
^{13}C NMR (151 MHz, $CDCl_3$)





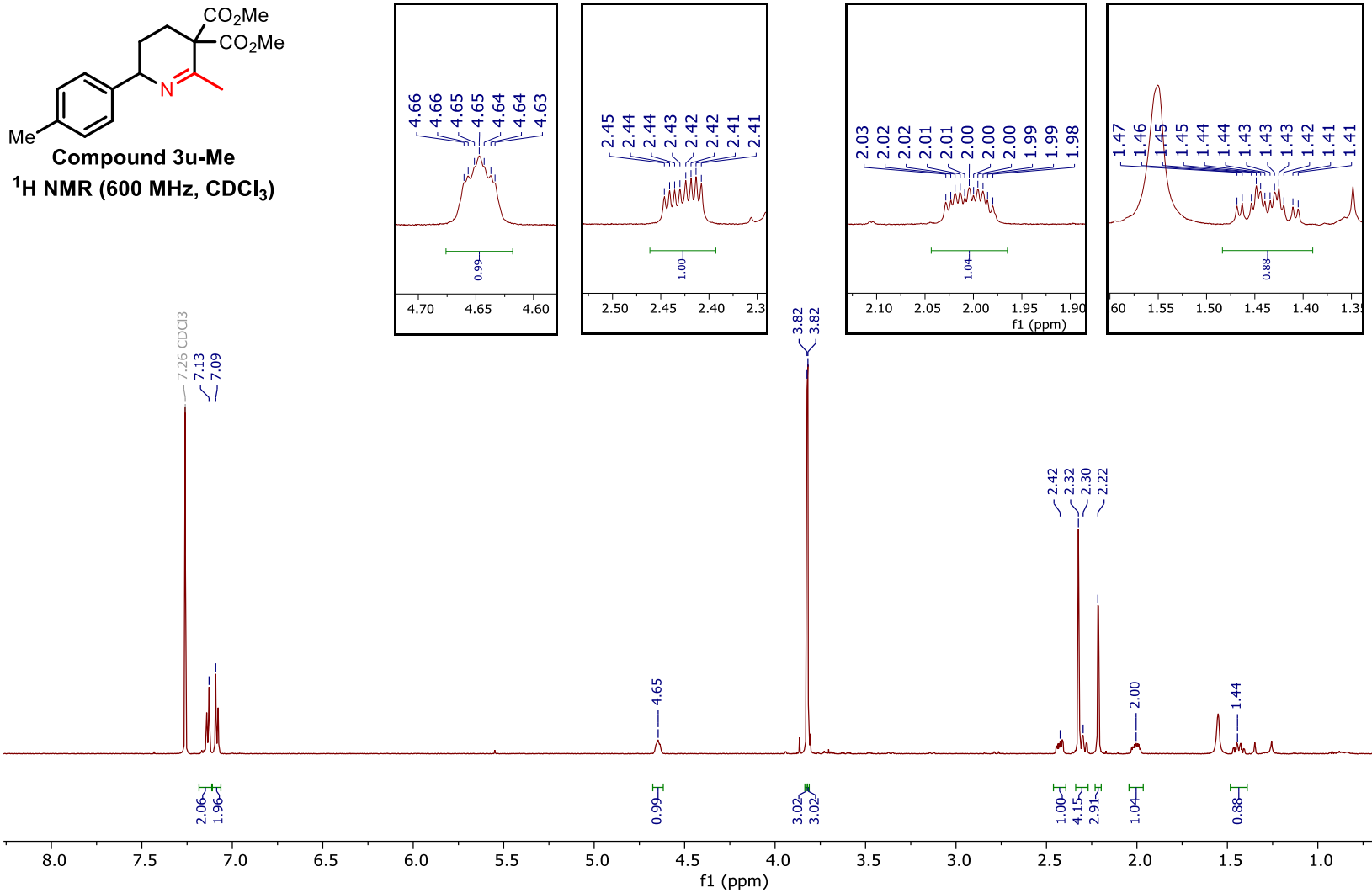
Compound 3t-Et*

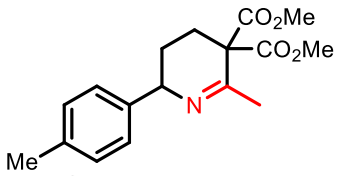
^{1}H NMR (400 MHz, $CDCl_3$)



Compound 3t-Et*

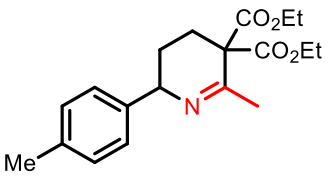
^{13}C NMR (101 MHz, $CDCl_3$)


CO2Me
CO2Me
N
Me
Compound 3u-Me
1H NMR (600 MHz, CDCl3)
7.26 CDCl3
7.13
7.09
4.65
3.82
3.82
2.42
2.32
2.30
2.22
2.00
1.44
f1 (ppm)



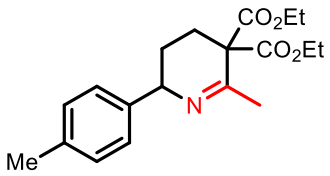
Compound 3u-Me

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



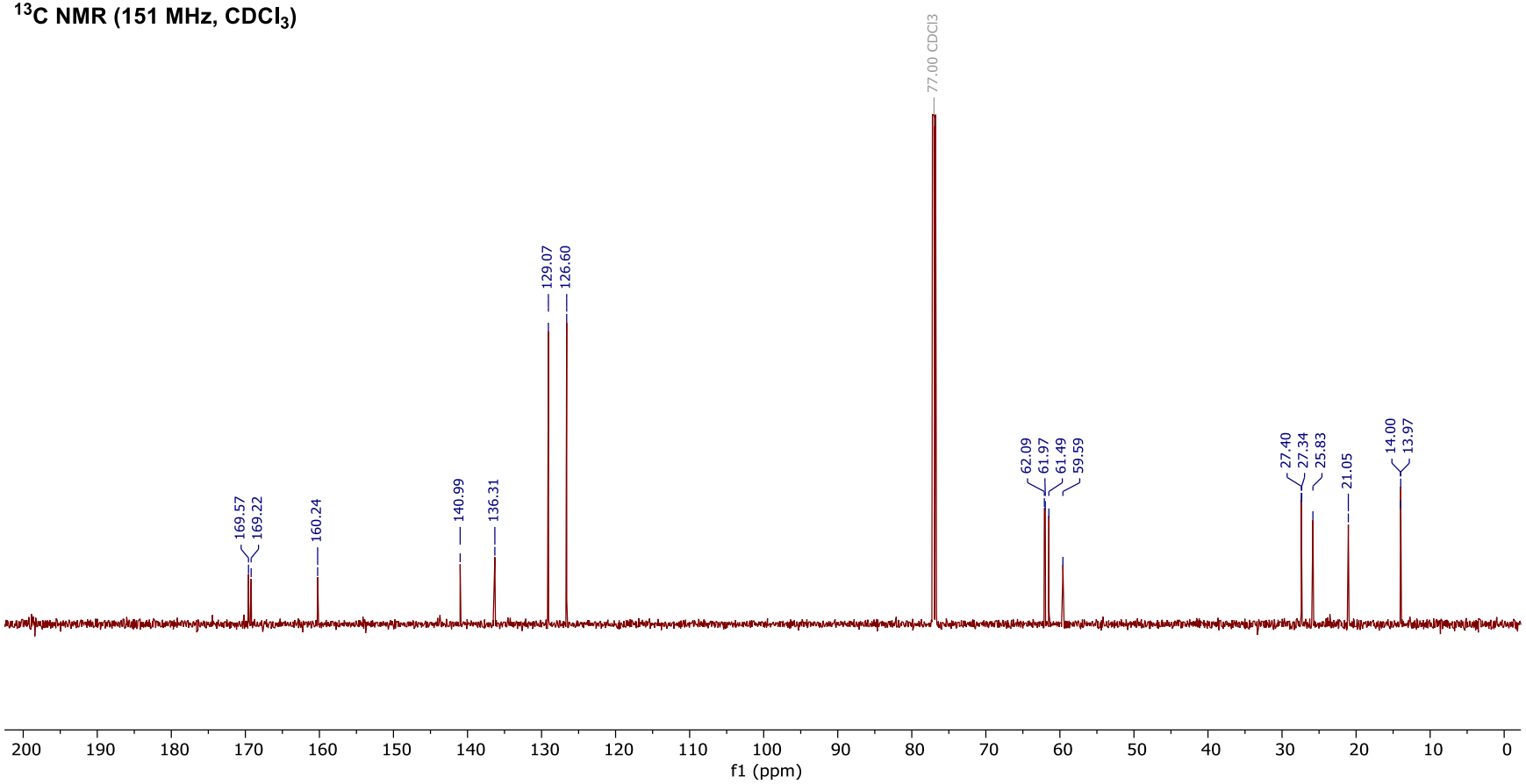
Compound 3u-Et

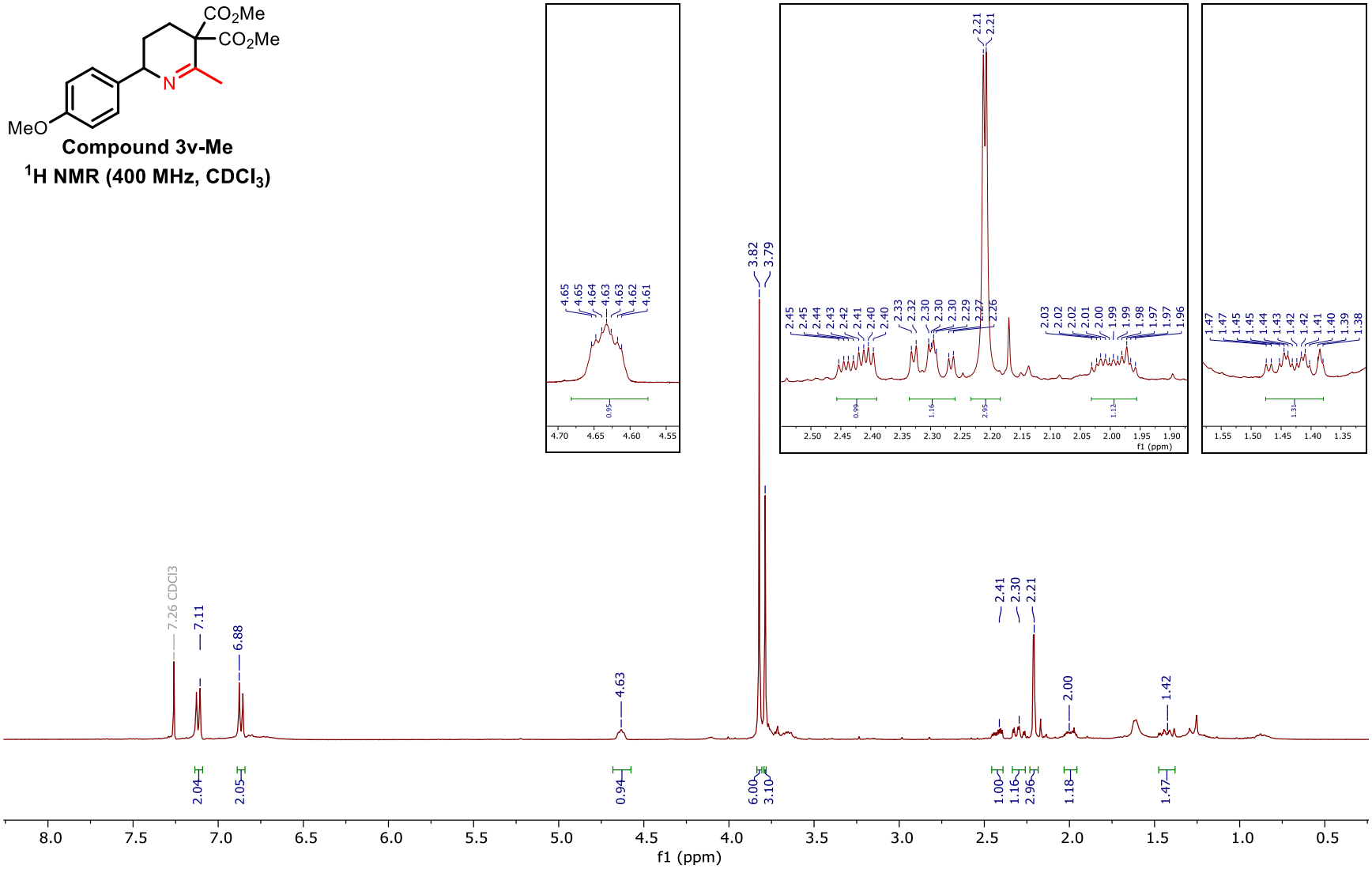
^{1}H NMR (600 MHz, $CDCl_3$)

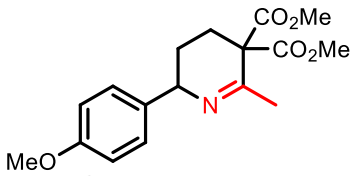


Compound 3u-Et

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

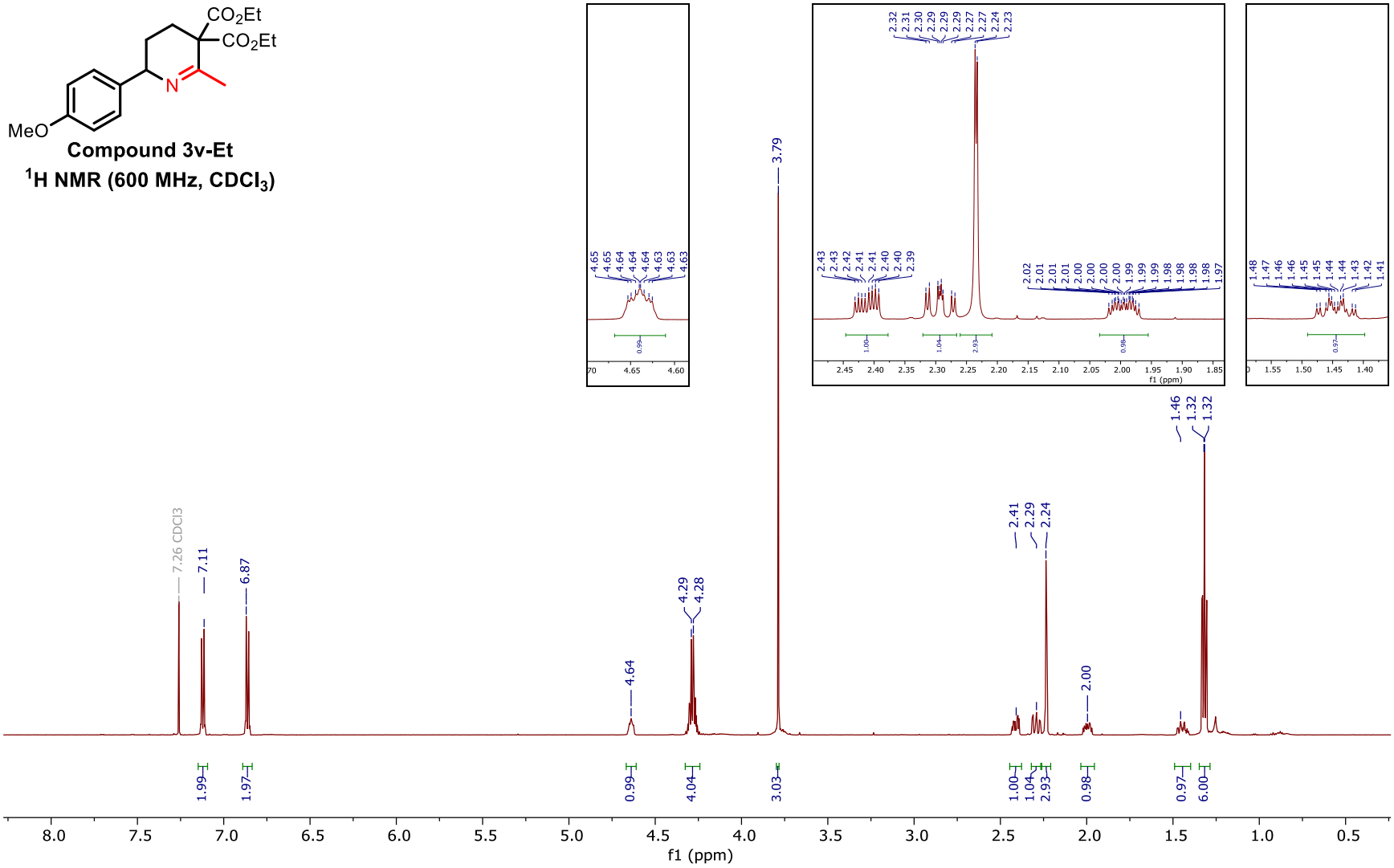


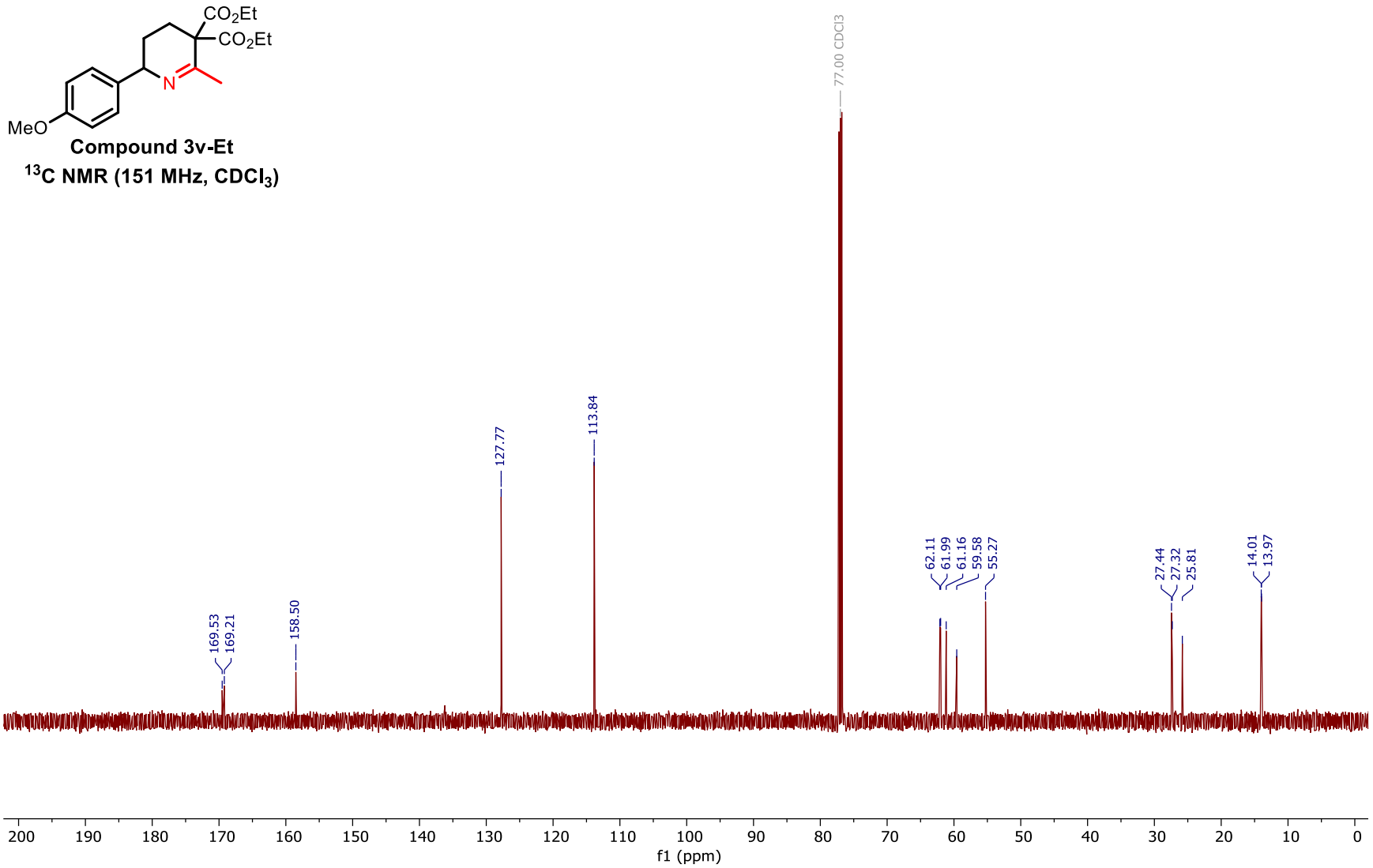

CO2Me
CO2Me
N
MeO
Compound 3v-Me
1H NMR (400 MHz, CDCl3)
7.26 CDCl3
7.11
6.88
4.63
3.82
3.79
2.41
2.30
2.21
2.00
1.42
2.04
2.05
0.94
6.00
3.10
1.00
1.16
2.96
1.18
1.47
f1 (ppm)



Compound 3v-Me

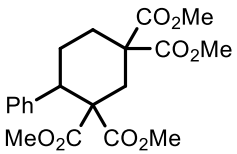
^{13}C NMR (101 MHz, $CDCl_3$)


CO2Et
CO2Et
N
MeO
Compound 3v-Et
1H NMR (600 MHz, CDCl3)
7.26 CDCl3
7.11
6.87
4.64
4.29
4.28
3.79
2.41
2.29
2.24
2.00
1.46
1.32
1.32
1.99
1.97
0.99
4.04
3.03
1.00
1.04
2.93
0.98
0.97
6.00
f1 (ppm)



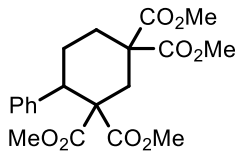
Compound 3v-Et

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



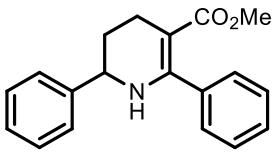
Compound 4a-Me

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



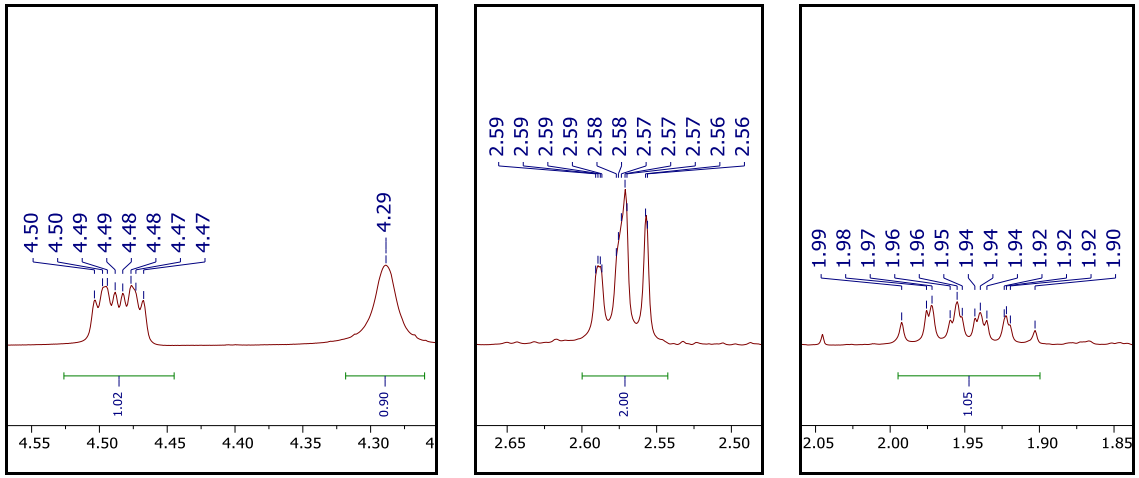
Compound 4a-Me

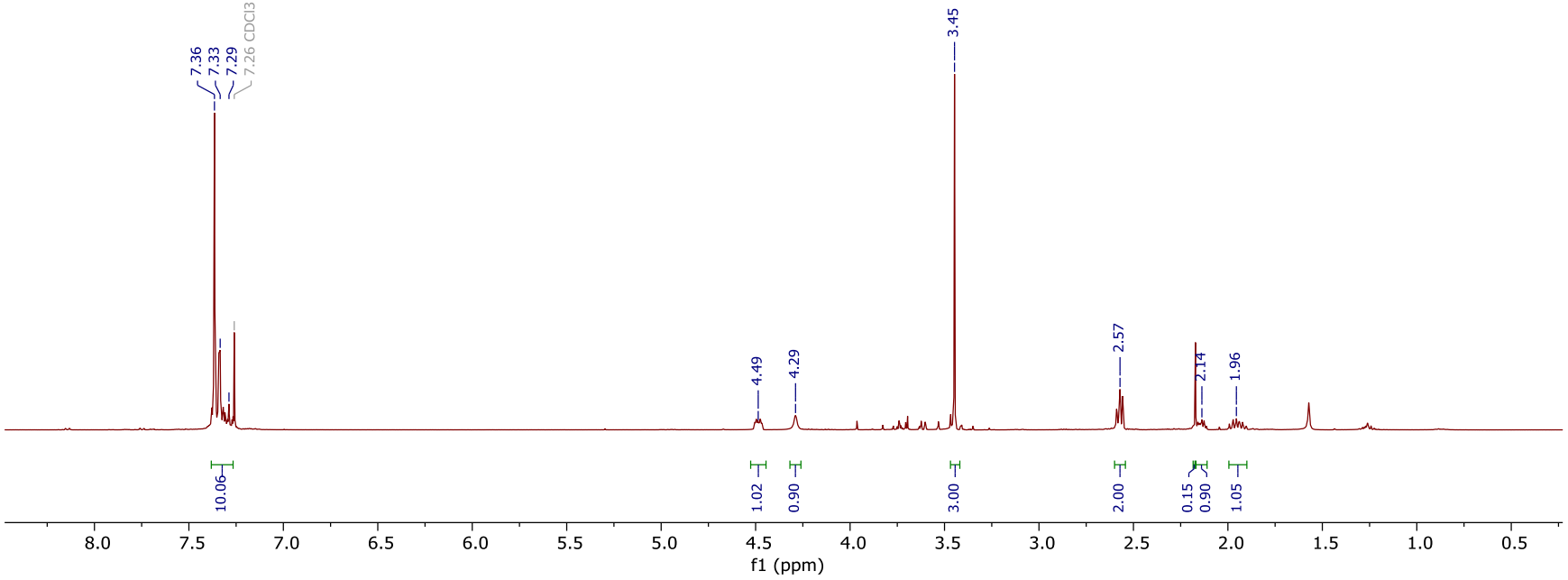
^{13}C NMR (151 MHz, $CDCl_3$)

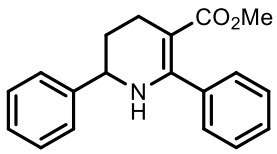


Compound 5

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

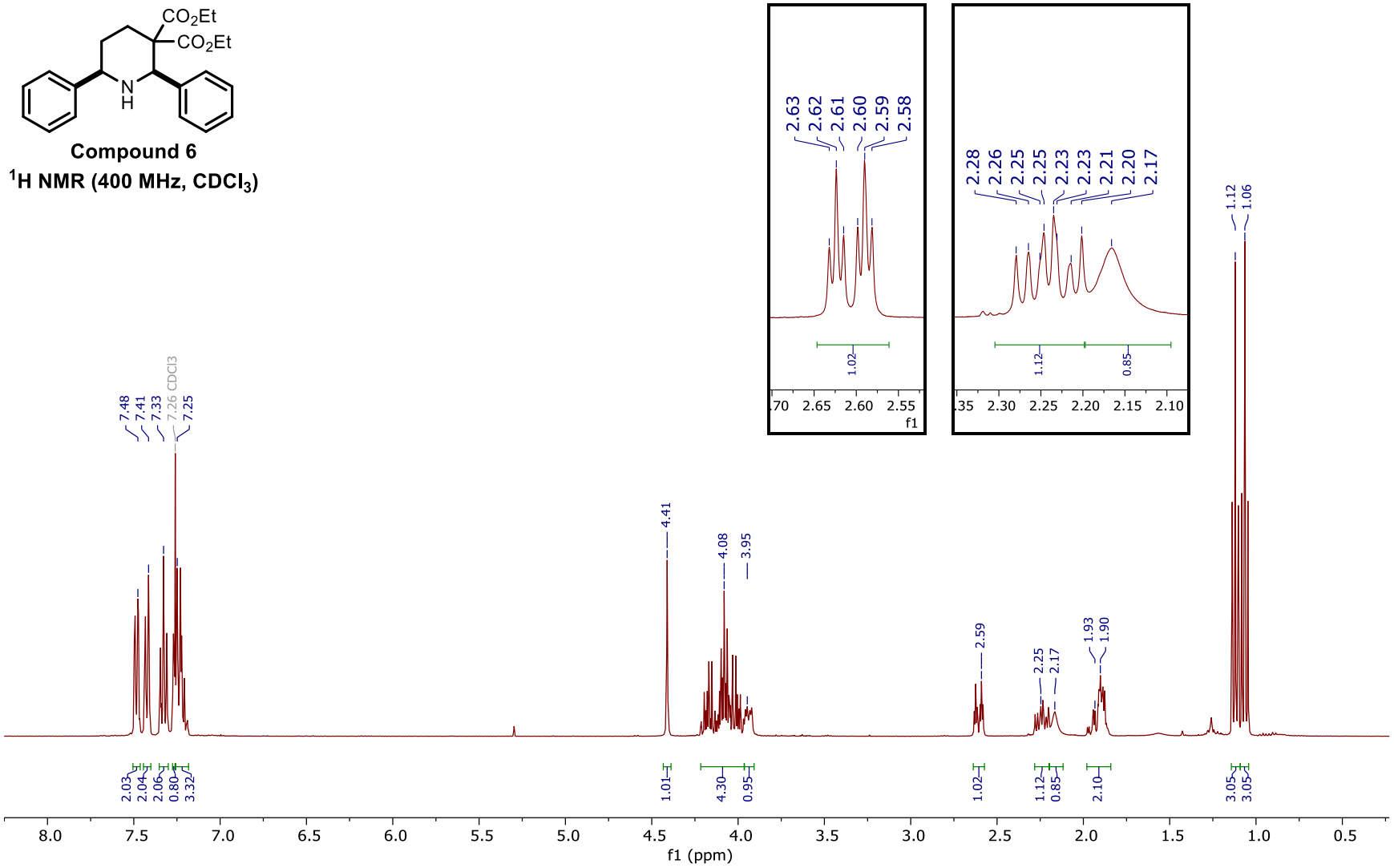


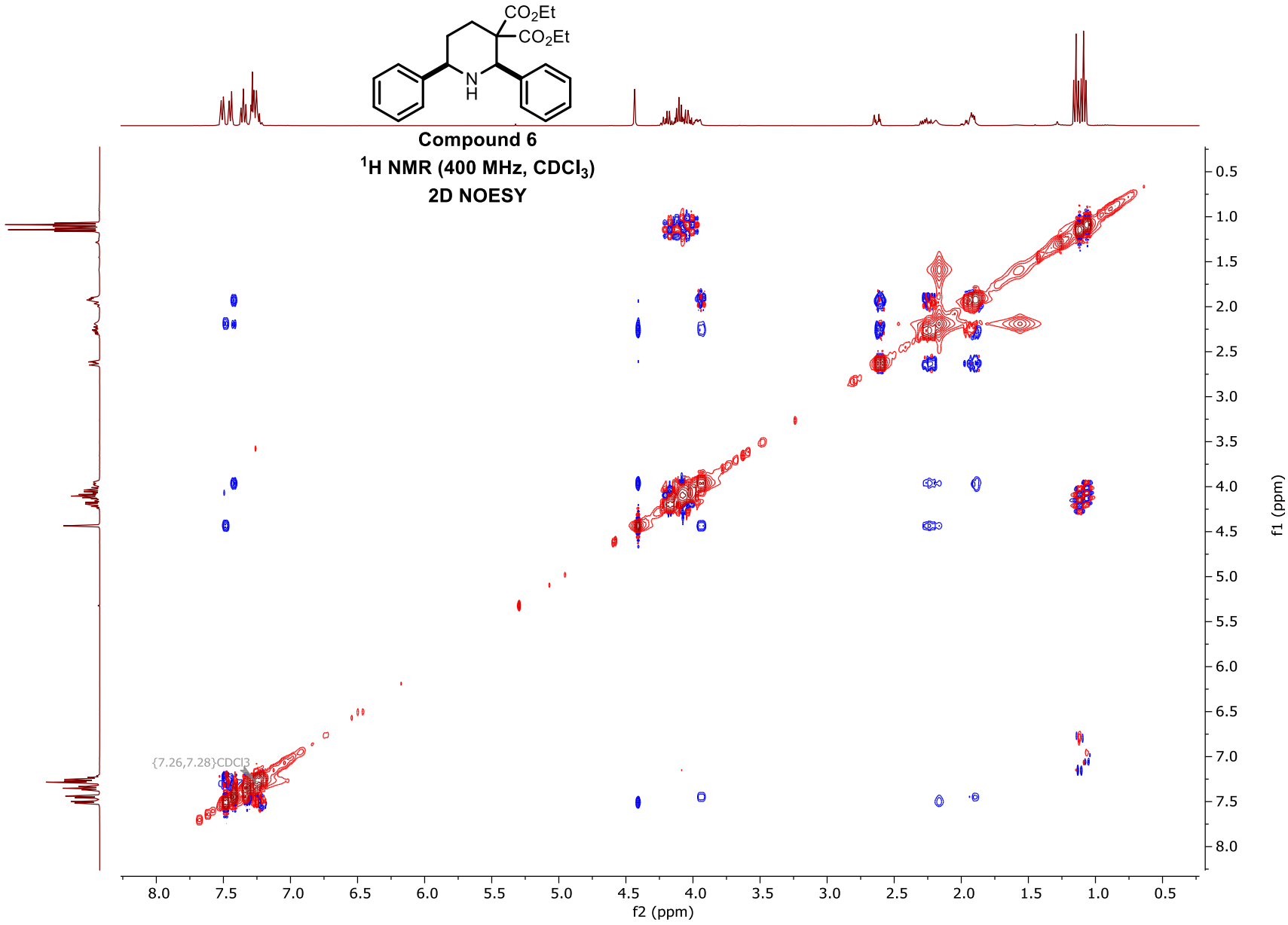


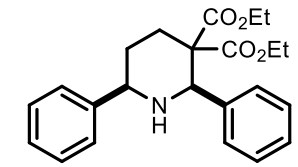


Compound 5

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


CO2Et
CO2Et
N
H
Compound 6
1H NMR (400 MHz, CDCl3)
7.48
7.41
7.33
7.26 CDCl3
7.25
4.41
4.08
3.95
2.59
2.25
2.17
1.93
1.90
1.12
1.06
2.63
2.62
2.61
2.60
2.59
2.58
2.28
2.26
2.25
2.25
2.23
2.23
2.21
2.20
2.17
2.03
2.04
2.06
0.80
3.32
1.01
4.30
0.95
1.02
1.12
0.85
2.10
3.05
3.05
f1 (ppm)


CO2Et
CO2Et
N
H
Compound 6
1H NMR (400 MHz, CDCl3)
2D NOESY
{7.26,7.28}CDCl3
f2 (ppm)
f1 (ppm)



Compound 6

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

Curriculum Vitae

Education

Aug 2019	**M.Sc.** in Organic Chemistry *The* University *of* Western Ontario, London, ON Canada Supervisor: Prof. Brian L. Pagenkopf
2017	**B.Sc. Honours** in Biochemistry and Molecular Biology Trent University, Peterborough, ON Canada Supervisor: Prof. David A. Ellis

Employment History

Sep 2017–Aug 2019	**Graduate Research/Teaching Assistant** Department of Chemistry *The* University *of* Western Ontario, London, ON Canada Supervisor: Prof. Brian L. Pagenkopf
Jan 2017–Apr 2017	**Chemistry Tutor** Chemistry Undergraduate Society Trent University, Peterborough, ON Canada
Sep 2016–Dec 2016	**Academic Assistant** Department of Chemistry Trent University, Peterborough, ON Canada
Jan 2013–Aug 2017	**Property Manager** Peterborough, ON Canada

Publications

1) **Tong, D.**; Wu, J.; Koo, D.; Bazinski, N.; Vemula, N.; Pagenkopf, B. L. Synthesis of Functionalized Tetrahydropyridines by $SnCl_4$-mediated [4+2] Cycloaddition between Donor–Acceptor Cyclobutanes and Nitriles. *Chem. Eur. J.* **2019**. *Manuscript accepted.*

Conference Presentations

1) **Tong, D.**; Wu, J.; Bazinski, N.; Koo, D.; Vemula, N.; Pagenkopf, B. L. *"Synthesis of functionalized tetrahydropyridine derivatives via Lewis acid-promoted [4+2] cycloaddition of donor–acceptor cyclobutanes and nitriles"*, **Oral Presentation**, 102nd Canadian Chemistry Conference and Exhibition (CCCE), Quebec City, QC, Canada, June 1-7, **2019**.

2) **Tong, D.**; Wu, J.; Koo, D.; Bazinski, N.; Vemula, N.; Pagenkopf, B. L. *"Lewis acid promoted [4+2] cycloaddition reactions of donor- acceptor cyclobutanes and nitriles towards functionalized tetrahydropyridine derivatives"*, **Poster Presentation**, 29th Quebec-Ontario Mini-Symposium on Synthetic and Bioorganic Chemistry (QOMSBOC) Conference, Toronto, ON, Canada, November 16-18, **2018**.

Awards & Affiliations

Sep 2017–Sep 2019	Member of Western Society of Graduate Students
Sep 2017–Sep 2019	Member of Chemistry Graduate Student Association
Sep 2017–Aug 2019	Western Graduate Research Scholarship
Sep 2016–Apr 2017	Chemistry Undergraduate Society
Sep 2015–Apr 2017	Dean’s Honour Roll