THE DEVELOPMENT OF TRACELESS AND TRANSIENT DIRECTING GROUP STRATEGIES AND COMPLEMENTARY DIASTEREOSELECTIVE ALKYLATIONS OF IMIDAZOLIDINONES

by

BRIAN JOSEPH KNIGHT

(Under the Direction of Eric M. Ferreira)

ABSTRACT

The functionalization of unreactive bonds has been the focus of numerous new methodologies. Some major challenges lie in obtaining high levels of chemo- and regioselectivity in a minimal number of steps. To address these challenges, we aimed to develop a strategy where a temporarily group is installed to direct functionalization to a specific C–H bond. We focused our investigations toward developing that group for the functionalization of sp^2 C–H bonds of benzyl alcohols and ultimately developed a group that directs both alkenylations and arylations. It outcompetes other directing groups and functionalizes C–H bonds that are notably remote from this temporary group.

During the course of our investigations, we envisioned this new group's potential utility as a transient ligand capable of directing C–H functionalizations. This would entail the ligand covalently attaching temporarily to a substrate prior to functionalization. Additional strategies were explored to realize this ultimate goal.

Furthermore, our investigation into ligands for C–H functionalization led to the discovery of stereo-divergent outcomes in the alkylation of imidazolidinones. High levels of either cis or

trans configured products were obtained by substituting the attached temporary group. If this group is 1-naphthyl, high levels of trans products were observed. This contrasts the selectivity of the bulky isopropyl group and led us to investigate a potential electrostatic interaction as the rationale for diastereoselectivity.

INDEX WORDS: Catalysis, Palladium, C–H Functionalization, Traceless, Transient, Alkylation, Imidazolidinones

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DEDICATION

This manuscript is dedicated to my parents, Brian and Jayne Knight, for their loving support and endless encouragement for me to pursue my intellectual endeavors. Thank you both.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation at wavelength of sodium D line
ABNO	9-azabicyclo[3.3.1]nonane *N*-oxyl radical
Ac	acetyl
Am	amyl
app.	apparent
aq.	aqueous
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	bipyridyl
br	broad, broadened
Bu	butyl
Bz	benzoyl
C	Celsius
c	concentration for specific rotation measurement
cat.	catalytic
CDI	carbonyldiimidazole
cod	1,5-cyclooctadiene
comp.	complex
conv.	conversion

CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
DCE	1,2-dichloroethane
DIBAL	diisobutylaluminum hydride
DG	directing group
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMSO	dimethylsulfoxide
dr	diasteriomeric ratio
E	electrophile
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electrospray ionization
equiv	equivalents
Et	ethyl
FMOC	fluorenylmethyloxycarbonyl
func	functionalization
g	grams
h	hours
HFIP	hexafluoroisoproponal
KHMDS	potassium hexamethyldisilazide

HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	hertz
i	iso
imid.	imidazole
IR	infared
J	coupling constant
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
μ	micro
M	mega or molar
[M]	metal complex
m	milli or multiplet or meters
m/z	mass-to-charge ratio
Me	methyl
min	minutes
mol	moles
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n	normal
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NMI	1-methylimidazole
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
[O]	oxidation
o	ortho
p	pentet
p	para
PCC	pyridinium chlorochromate
pent	pentyl
Ph	phenyl
phen	phenanthroline
pH	hydrogen ion concentration in aqueous solution
pin	pinacolboranyl
Piv	pivaloyl (trimethylacetyl)
pK_a	acidity constant
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonic acid
Pr	propyl
py	pyridine
q	quartet
R_f	retention factor
s	singlet

sat.	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tertamethyl-1-piperidinyloxy radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid or trifluoroacetate
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	*p*-toluenesulfonyl or tosyl
UV	ultraviolet

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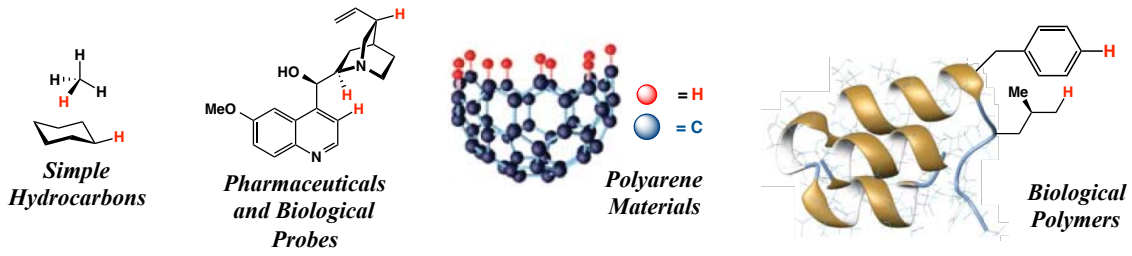
CHAPTER 1

TRACELESS AND TRANSIENT DIRECTING GROUP STRATEGIES

1.1. Research Objectives

Organic compounds consist of C–H and C–C bonds differentially connected and possibly adorned with heteroatoms (mainly oxygen, nitrogen, phosphorous, sulfur, or halogens). The array of bond connections allowed by carbon produces the extraordinary diversity of organic compounds found in nature. These compounds exist as small molecules such as methane (the simplest organic compound) and other simple hydrocarbons (such as petroleums) (Figure 1.1.1). Living organisms are the true wellspring of this diversity consisting of more complex small molecules as well as biologic polymers. Chemists have expanded this wealth of compounds by synthesizing pharmaceuticals, biological probes, functional materials, and plastics.

Figure 1.1.1. C–H Bonds in a Diversity of Organic Compounds

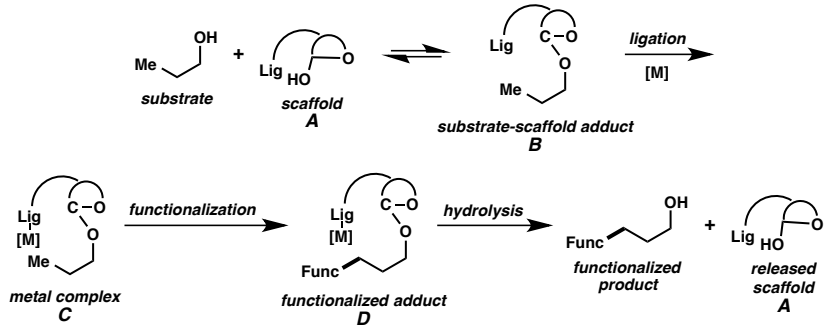


Organic chemists rely on an ever-expanding variety of transformations to circumvent the limitations in obtaining these compounds. Because C–H and C–C bonds are the most ubiquitous bonds in organic compounds, the selective functionalization of both remains of great interest in organometallic and synthetic chemistry.[1] The products of these transformations hold prodigious promise for expanding many scientific frontiers in areas such as natural products synthesis and

discovery[2], pharmaceuticals[2], proteomics[3], industrial manufacturing[4], and material science[5]. The primary challenge in this field is the development of highly selective transformations that functionalize particular C–H or C–C bonds in the presence of numerous other ubiquitous C–H and C–C bonds. Vast numbers of functionalization conditions that achieve the desired levels of selectivity require a directing group embedded in the molecule. This restriction limits the generality of these procedures. To circumvent this constraint, efforts have been taken to develop traceless directing groups that are temporarily installed prior to functionalization that can be subsequently removed.

Our research goal is to develop useful strategies that complement and enhance known methods of C–H and C–C functionalization (Figure 1.1.2). Our research methodology has focused on the development of a scaffold (**A**) that contains both a directing group and functionality capable of thermodynamic exchange. Covalent attachment of a substrate to this scaffold would produce a substrate/scaffold adduct (**B**). Isolation of this compound and subjection to metal catalyzed functionalization conditions would initially generate metal complex (**C**). The spatial location of the metal center positions it in proximity to certain C–H bonds over others. Site-directed functionalization would afford transformed substrate/adduct (**D**). Upon substrate extrusion, the functionalized product is released and the free ligand (**A**) is regenerated. If this series of events occurs in three discrete steps and requires stoichiometric quantities of ligand (**A**), it is a tracelessly directed functionalization. However, if all three steps occur in one-pot with catalytic amounts of ligand (**A**), this is a transiently directed functionalization. The focus of our research has been on the discovery of novel traceless directing groups that have the potential to eventually be expanded towards transiently directed C–H functionalization scaffolds.

Figure 1.1.2. The General Concept for Transiently Directed Functionalization



We plan on pursuing this strategy by developing a scaffold that utilizes an acetal and exchanges and functionalizes alcohols. To precede the discussion of these developments, it is important to discuss the advantages and limitations of directed functionalization by unprotected alcohols and the benefits of traceless directing group strategies with regards to alcohols. Additionally, a discussion on traceless directing group strategies utilized for other functional groups will provide context for our investigations and expose limitations for future studies. Finally, a discussion on the state of the art with regards to transiently directed functionalization as well as other transiently directed metal catalyzed reactions illustrates the challenges in this field and provides a benchmark for our inquiries.

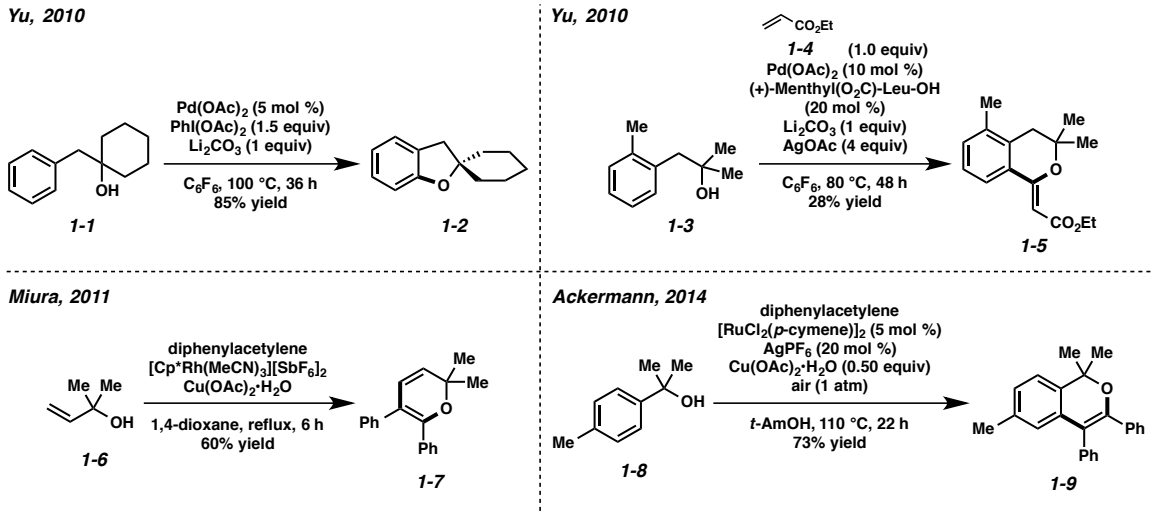
1.2. Direct Functionalizations and Traceless Directing Groups for Alcohols

Due to the ubiquity of alcohols and oxygen-containing compounds in natural products and pharmaceuticals, the direct functionalization of alcohols has been recently investigated. Many examples utilize the alcohol as a directing group, but subsequently incorporate into the transformations new bond connections to produce ethers (Scheme 1.2.1). Utilizing alcohols in this manner can produce unique bond disconnections and efficient syntheses; however, the desire to develop functionalizations without the ultimate loss of the alcohol group has led to the invention of clever strategies to mask it as a temporarily different functional group. This

simultaneously protects the alcohol from the reaction conditions and imparts diverse reactivity different from the parent alcohol.

Yu was the first to investigate the direct functionalization of arene sp^2 C–H bonds using unprotected alcohols (Scheme 1.2.1). His conditions utilize a Pd^{II}-Pd^{IV} cycle and a Pd^{0}-Pd^{II} cycle to afford benzofurans [6] (**1-2**) and benzopyrans [7] (**1-5**) products, respectively. Miura and Ackermann later published on the oxidative cyclization of allylic and benzyl alcohols with alkynes catalyzed by Ru[8] and Rh[9], respectively. Although highly efficient, alcohol directed C–H functionalization has generally utilized *tertiary* alcohols, limiting the strategy's overall scope. A few outliers use *primary* and *secondary* alcohols, but limited examples report diminished yields (Scheme 1.2.2). The general wisdom is that the alcohol functional group is prone to oxidation, fragmentation, and other decomposition pathways.

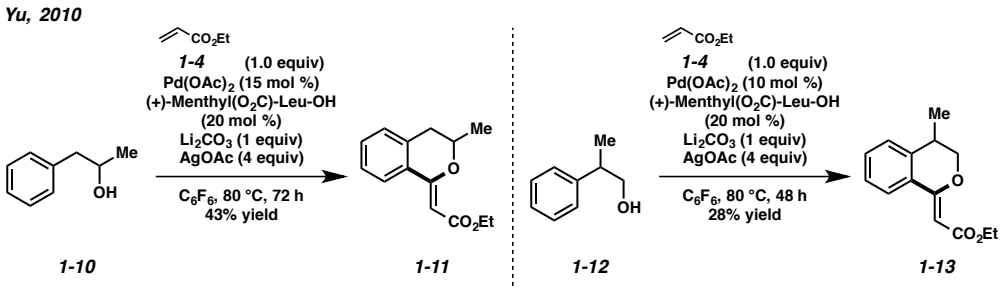
Scheme 1.2.1. Examples of Alcohol Directed Functionalizations



The alternative strategy of masking an alcohol temporarily with a protecting group/directing group and subsequently removing that group after functionalization has afforded solutions for numerous transformations. If cleavage of the temporary group affords a structure

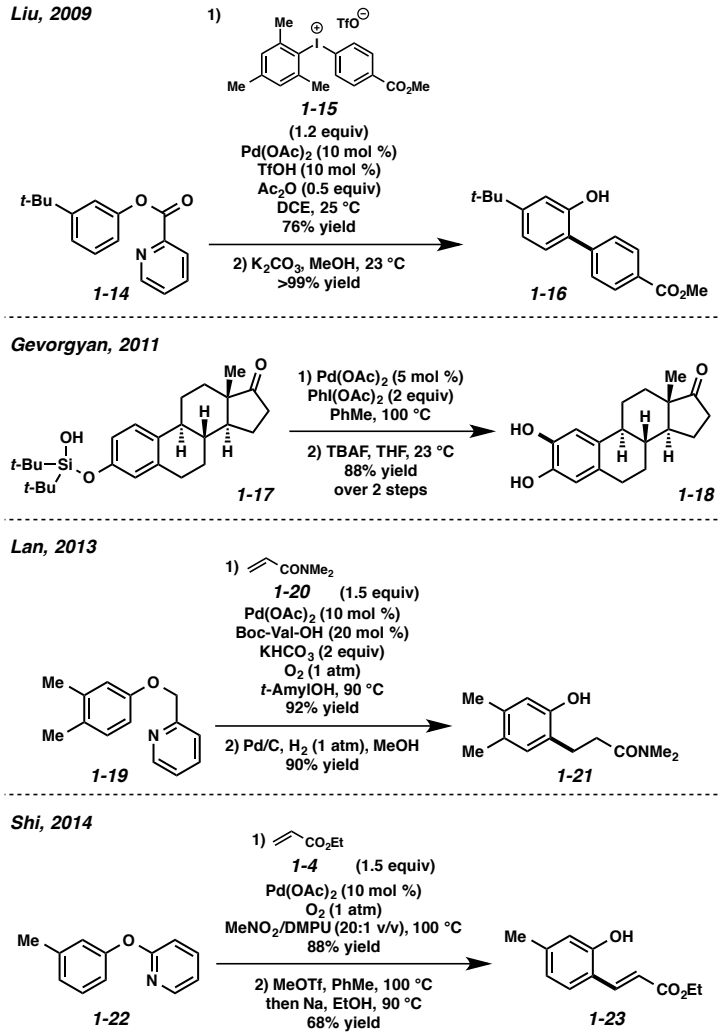
unchanged except for the site of functionalization, the process is referred to as a traceless directing group strategy.

Scheme 1.2.2. Primary and Secondary Alcohol Directed Functionalizations



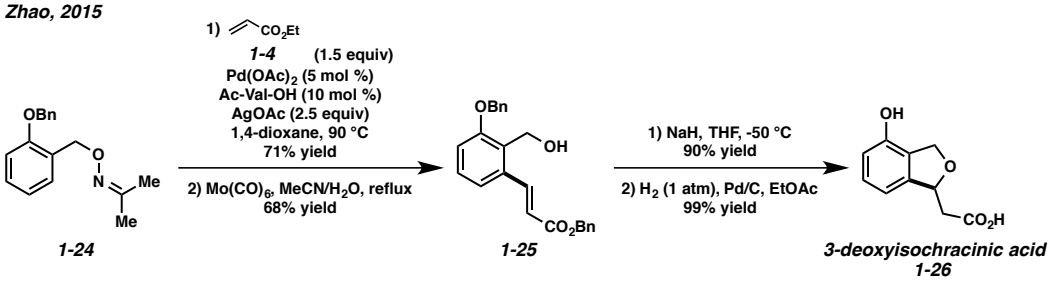
This approach has been employed in the functionalization of phenolic sp^2 C–H bonds. Numerous directing groups have been developed, and most commonly the transformations have been accomplished with palladium (Scheme 1.2.3). Liu reported the arylation of phenolic picolinates with aryl iodonium salts, and the directing group was removed by saponification with methanolic K_2CO_3 (**1-14**→**1-16**). Gevorgyan disclosed the *ortho*-hydroxylation of phenolic silanols to catechols (**1-17**→**1-18**). Lan utilized methylene-pyridyl ethers to direct alkenylation, and hydrogenolysis simultaneously reduced the alkene and removed the directing group (**1-19**→**1-21**). Shi developed a 2-pyridylether directing group which alkenylates phenol derivatives. Conversion of the pyridine to a methyl pyridinium and treatment with ethoxide removed the directing group in moderate yield over two steps (**1-22**→**1-23**). The commonality of all these methods is the attachment of the directing group and functionalization with subsequent cleavage resulting in the retention of the initial phenol.

Scheme 1.2.3. Tracelessly Directed Functionalization of Phenols



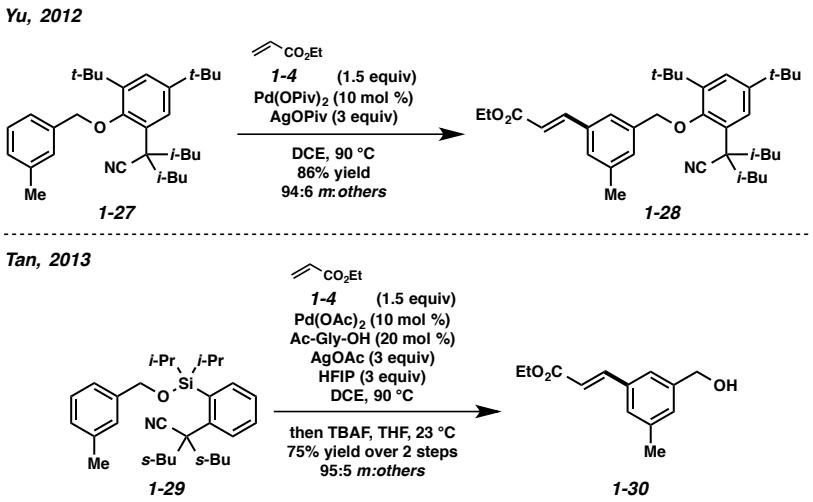
This strategy has been expanded to include the functionalization of sp^2 C–H bonds of benzyl alcohols. Zhao developed a simple temporary group capable of *ortho*-alkenylation by utilizing the *exo*-directing mode of oximes (Scheme 1.2.4), and this group was trivially installed in one-step and one-pot through Mitsunobu chemistry and removed by heating with stoichiometric $Mo(CO)_6$ or zinc dust. The alkenylated alcohol (**1-25**) was converted to 3-deoxyisoochracinic acid (**1-26**) in two steps, providing a convenient route to this simple antibiotic.

Scheme 1.2.4 Zhao's Oxime Directed Alkenylation of Benzyl Alcohols



Yu reported a *meta*-selective directing group capable of alkenylation[10], arylation[11], and acetoxylation[12] of benzyl ethers (Scheme 1.2.5). The directing group was detached from the substrate by hydrogenation resulting in *meta*-alkylated toluenes. To circumvent this limitation, Tan developed a temporary directing group for benzyl alcohols by modifying Yu's group into a silyl ether.[13] This adaptation still retained the high meta selectivity (>78:22 *m*:*others*), gave moderate selectivity for the *mono*-olefinated product (>2:1 mono/di), and afforded yields generally over 50%. The directing group was easily cleaved with TBAF to generate the *meta*-functionalized alcohol (**1-29**→**1-30**).

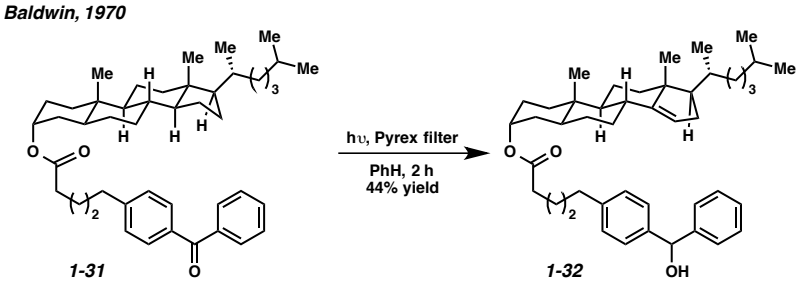
Scheme 1.2.5. meta-Selective Directing Groups for Benzyl Alcohols



Implementation of the temporary directing group strategy to include the functionalization of sp^3 C–H bonds would dramatically expand the utility of this chemistry. Aliphatic alcohols are ubiquitous in nature[14] and are frequent functional group handles in the synthesis of complex natural products. Due to their higher bond strengths, precise selectivity for functionalizing a single desired C–H bond is challenging. Conformational and electronic biases mediated through reagent and condition selection can afford the desired site- and chemoselectivity.

Arguably the first report of site-selective sp^3 functionalization mediated by a temporary directing group, Breslow investigated the remote dehydrogenation of *n*-alkyl alcohols facilitated through an ester-linked benzophenone (i.e., esters of *n*-$C_{14}H_{30}O$ through *n*-$C_{20}H_{42}O$).[15] This work was expanded by Baldwin to include the remote functionalization of steroids (**1-31**→**1-32**, Scheme 1.2.6).[16,17] Constrained by both the shape of the steroid and the tether length, upon irradiation, the ketyl radicals selectively abstract two hydrogens to afford the functionalized product. A simple saponification provides the dehydrogenated steroids.

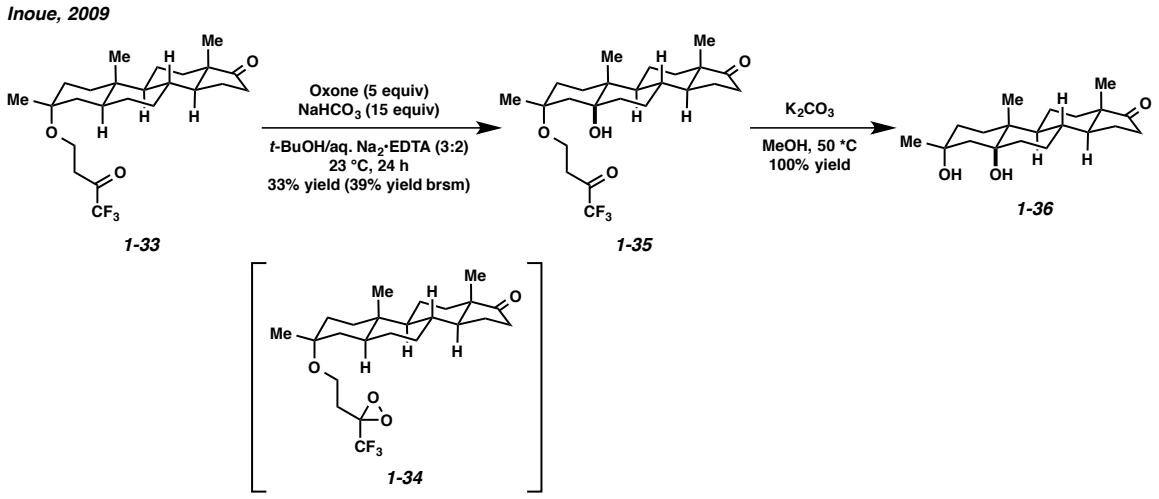
Scheme 1.2.6. Baldwin's Site-Selective sp^3 C–H Functionalization via Ketyl Radicals



By an analogous strategy, Inoue developed a site-selective hydroxylation of steroids by the intramolecular generation of a dioxirane (**1-34**) from a tethered trifluoromethylketone (Scheme 1.2.7).[18] Although the yield is low for the formation of steroid **1-35**, this transformation only hydroxylates the C-5 carbon. This selectivity is derived from both the tether length and the orientation of the axial C–H bonds. The directing group can be removed in methanolic K_2CO_3 to

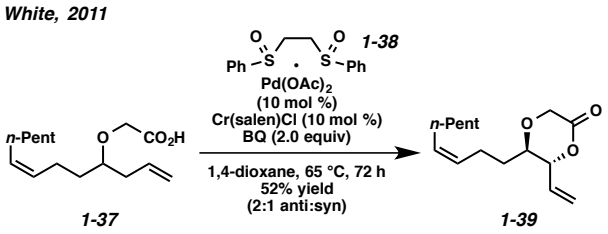
generate the functionalized steroid (**1-36**) in excellent yield. A disadvantage of this strategy is a three-step procedure to attach the directing group.

Scheme 1.2.7. Inoue's Site-Selective sp^3 C–H Functionalization via Dioxirane



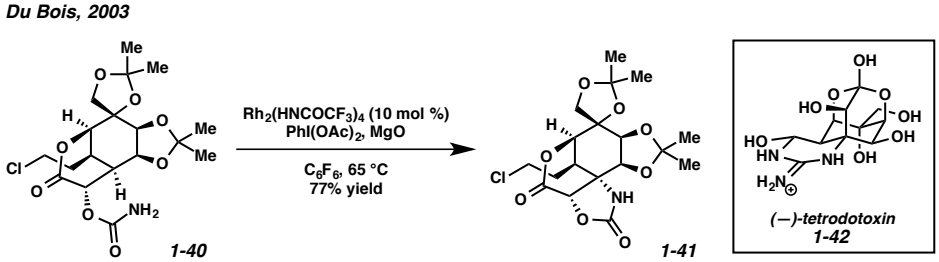
In contrast to the previous two examples, the vast majority of sp^3 functionalization strategies implemented with traceless directing groups have utilized metal mediated transformations. Activated sp^3 C–H bonds (e.g., allylic or benzylic) represent easier substrates for selective functionalizations due to the lower bond strengths of these bonds.[19] White disclosed a Pd^{II}-sulfoxide ligand catalyzed allylic amination in the preparation of *syn*-1,2- and 1,3-amino alcohols.[20] This work was later expanded to include Pd^{II}-sulfoxide intramolecular allylic C–H oxidation to form 1,4-dioxan-2-ones (**1-37**→**1-39**, Scheme 1.2.8).[21] The selectivity of this transformation is notable: the nucleophile adds in the allylic position resulting in a 1,2-diol relationship as opposed to the homoallylic position or the product resulting in a 1,3-diol relationship. The directing group was easily attached by a Williamson ether synthesis with α-bromoacetate, and the directing group could ultimately be removed with samarium diiodide.

Scheme 1.2.8. White's Allylic Oxidation



An efficient method for site-selective sp^3 C–H functionalization was reported by Du Bois utilizing rhodium-nitrenoid catalyzed insertions into aliphatic sp^3 C-H bonds directed by sulfamates.[22] Carbamates were also included in the directing groups that facilitate this transformation, generally in better yields affording oxazolidinones (**1-40**→**1-41**, Scheme 1.2.9).[23] This technology was successfully implemented in the total synthesis of (–)-tetrodotoxin (**1-42**) through a late-stage C–H amination generated by a rhodium nitrenoid.[24] This transformation leaves the synthetically useful carbamate protecting group.

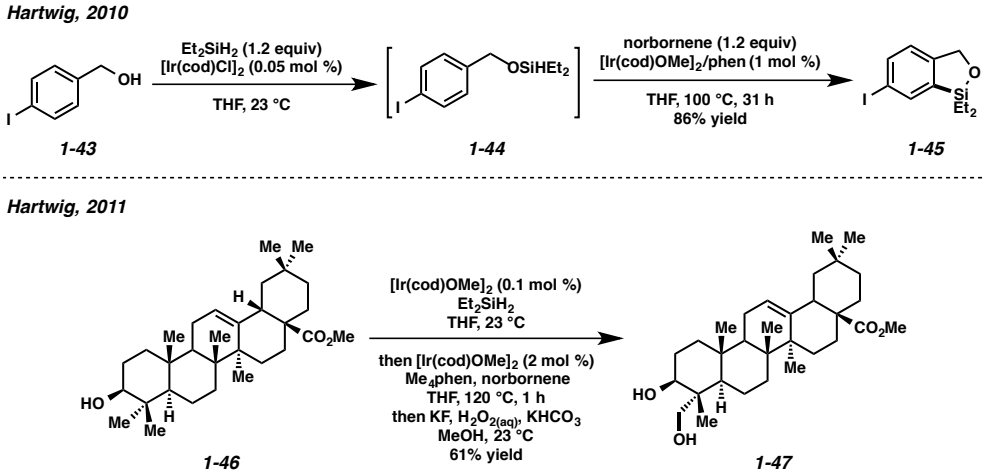
Scheme 1.2.9. Du Bois' Rhodium Nitrenoid Amination



Hartwig described a procedure for the *ortho*-silylation of benzyl alcohols or benzaldehydes initially proceeding through an iridium-catalyzed dehydrosilylation or a hydrosilylation, respectively (Scheme 1.2.10).[25] By adding an additional iridium catalyst to the same pot, the resulting silane undergoes a dehydrosilylation with the proximate arene (**1-43**→**1-45**). These conditions worked well in the presence of aryl halides which contrast them to many of the palladium catalyzed C–H functionalization conditions. The aryl silanes were shown to successfully cross-couple under Hiyama conditions to afford *ortho*-aryl benzyl alcohols. This

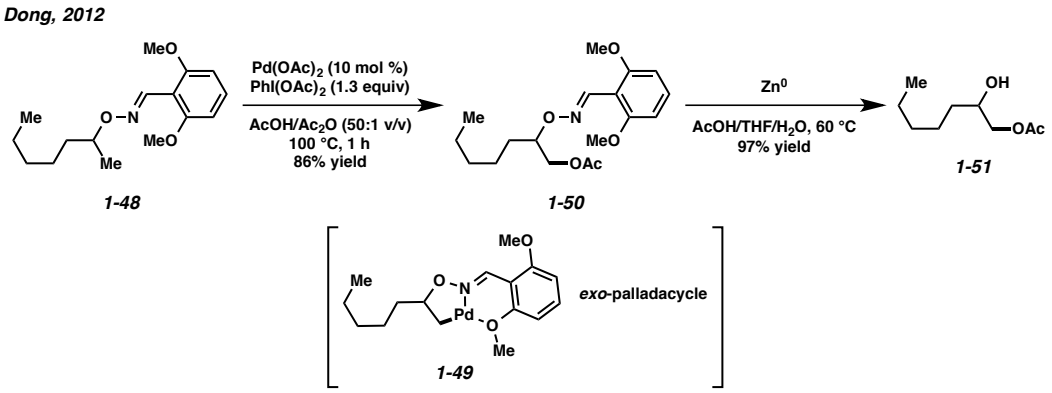
procedure worked remarkably well for the functionalization of steroids. Expanding on this work, Hartwig reported a truly exceptional one-pot procedure consisting of dehydrosilylation of a free alcohol (**1-46**), then dehydrosilyation of an sp^3 C–H bond, and finally cleavage of the silanol to afford the resulting diol (**1-47**).

Scheme 1.2.10. Hartwig's Dehydrosilylation/Oxidation



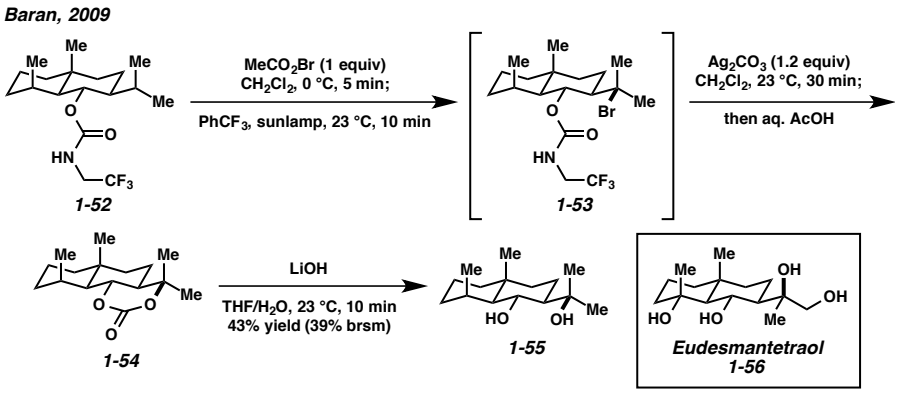
The Dong group disclosed an oxime directed acetoxylation of aliphatic alcohols (Scheme 1.2.11).[26] The transformation proceeds through an exo-palladacycle (**1-49**). Cleavage of the oximes could be performed with zinc dust in acid (**1-50**→**1-51**), while the ester could easily be removed by saponification. The products of this transformation represent differentially substituted diols.

Scheme 1.2.11. Dong's Vicinal Oxidation of Alcohols



The development of methods that utilize radical intermediates will likely generate transformations with unique selectivities compared to transition metal-catalyzed conditions. Baran has recently investigated a traceless directing group strategy based on the Hofmann-Löffler-Freytag reaction, which led to the synthesis of numerous natural products including eudesmantetraol (**1-56**, Scheme 1.2.12).[27] Trifluoroethyl carbamate (**1-52**), the product of an alcohol and an isocyanate, was treated with bromoacetate to generate the *N*-bromo carbamate. Photolysis homolytically cleaves the N–Br bond, and the resulting N• is conformationally biased to abstract a proximal equatorial hydrogen. Recombination affords the tertiary alkyl bromide (**1-53**), which can undergo silver-assisted nucleophilic substitution. Hydrolysis of carbonate **1-54** produces the original and newly formed hydroxyls of alcohol **1-55**. The selectivity of this transformation is quite amazing; a molecule with one functional group handle can deliver controlled reactivity at one methine in the presence of three other proximal methines.

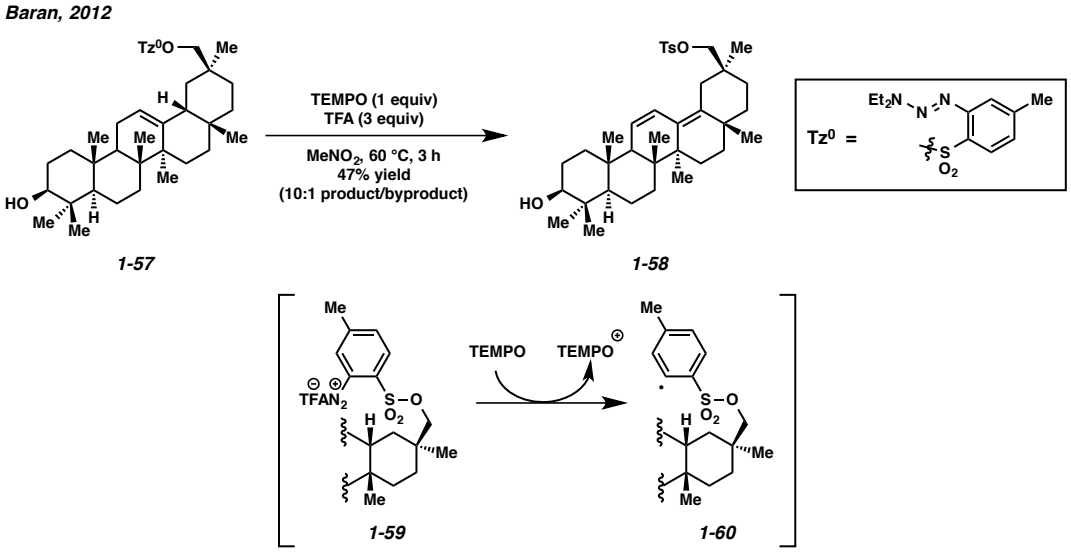
Scheme 1.2.12. Baran's Selective Oxidation of Proximal sp^3 C–H Bonds



In 2012, Baran disclosed another radical based C–H functionalization strategy for the dehydrogenation of alkanes (Scheme 1.2.13).[28] Described as a "portable desaturase", the Tz^0 moiety can abstract H_2 off a substrate when exposed to TFA and TEMPO (**1-57**→**1-58**. The conditions are believed to generate intermediate **1-59**, which upon SET with TEMPO produces aryl radical (**1-60**) primed to abstract hydrogen. A second SET between the substrate radical and

TEMPO$^+$ followed by an E_1-type elimination would afford the product. The conditions are quite spectacular; dehydrogenation of steroid-like **1-57** occurs in the presence of an unprotected alcohol and H-abstraction occurs at one site even though there is a proximal axial-hydrogen and methyl group. The transformation leaves behind the synthetically useful tosyl group, which can be cleaved by reductive methods or be used in substitution chemistry.

Scheme 1.2.13. Baran's Radical Dehydrogenation of Alkenes

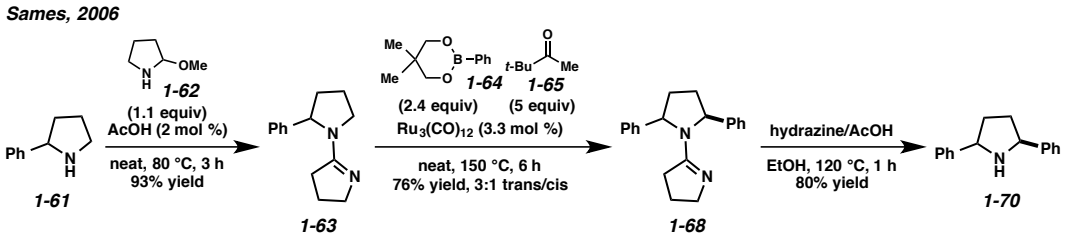


1.3. Traceless Directing Groups for Other Functional Groups

The examples above were all with respect to the direct or traceless functionalization of alcohols. Because our ultimate goal is to achieve synthetically useful and interesting transient functionalization strategies, the direction of the project is not limited to the exchange and functionalization of alcohols. We have entertained the idea of implementing other functional groups. To add context to the above discussion of traceless directing groups and influence the future directions of this project, it is prudent to briefly discuss traceless directed functionalization outside the framework of alcohols.

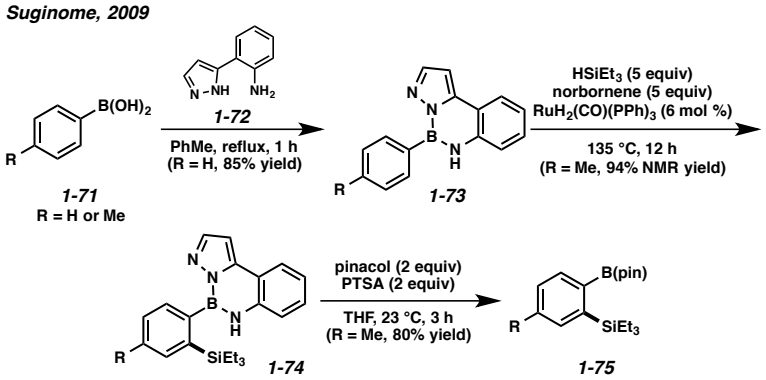
There have been very few reports of truly traceless directing group C–H functionalization strategies for non-alcohol functional groups. Sames developed a ruthenium-catalyzed method to arylate the least-hindered side of pyrrolidines through the generation of an amidate directing group (Scheme 1.3.1). [29] This was installed through an oxidative attachment of α-methoxypyrrolidine **1-62** with pyrrolidines (**1-61**) in good yield. The substrate undergoes cycloruthenation, and the subsequent hydride is sequestered by ketone **1-65**, which is the terminal oxidant. This resulting alkoxides can help facilitate transmetallation to afford the functionalized product (**1-68**). The amidate can be removed by heating with acidic hydrazine to afford the arylated pyrrolidine in good overall yield. This oxidative attachment is unique; however, it does require harsh conditions to remove the directing group.

Scheme 1.3.1. Sames' Arylation of Pyrrolidines



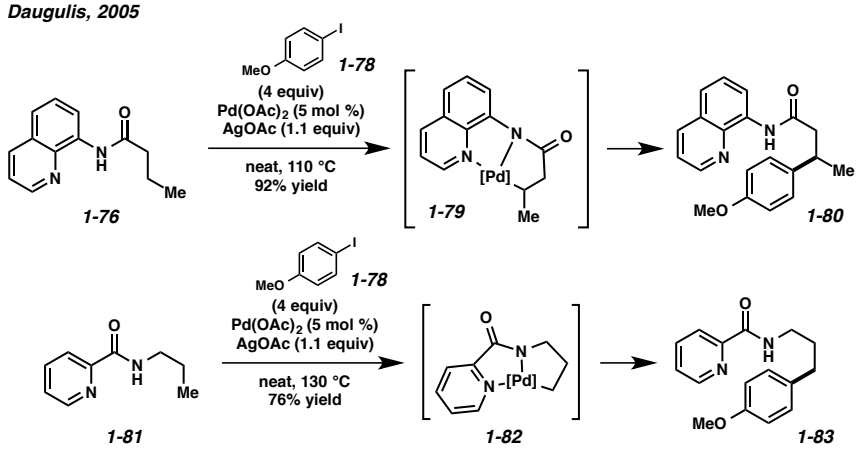
In 2009, Suginome developed a truly unique traceless directing group, aniline **1-72**, capable of condensing onto boronic acids and facilitating a ruthenium directed oxidative silylation of boronic amides (**1-71**→**1-74**) (Scheme 1.3.2).[30] The pyrazole is believed to direct this reaction[31], while norbornene is used as the oxidizing agent. Acidic treatment of the resulting boronic amides (**1-74**) with pinacol affords *ortho*-silyl boronic esters (**1-75**) in good overall yield under mild conditions.

Scheme 1.3.2. Suginome's Silylation of Boronic Acids



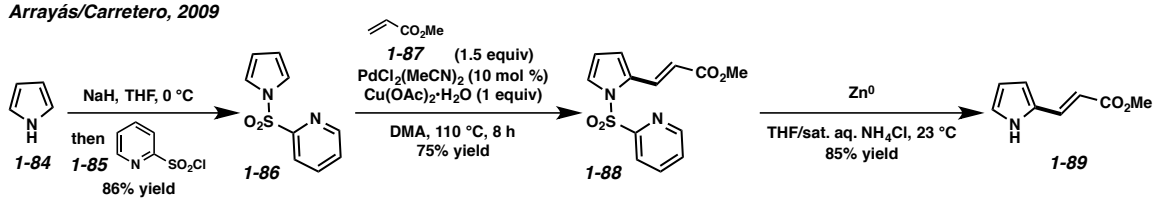
Sames' and Suginome's work relied on ruthenium catalyzed dehydrogenation. More commonly in directed functionalization, pyridine and oxime based systems are used in concert with palladium catalysis. One of the original and most important of these traceless directing group strategies was the arylation of carboxylic acids and amines initially reported by Daugulis (Scheme 1.3.3).[32] Simple amidation of these two functional groups with 8-aminoquinoline or picolinic acid, respectively, affords substrates capable of bidentate chelation and palladium mediated sp^3 functionalization with aryl iodides. The resulting products (amide **1-79** and amide **1-82**) can be saponified with LiOH to afford the arylated carboxylic acids or amines. Corey and Chen have expanded this work to include the β-functionalization of amino acids.[33]

Scheme 1.3.3. Daugulis' Arylation of sp^3 C–H Bonds



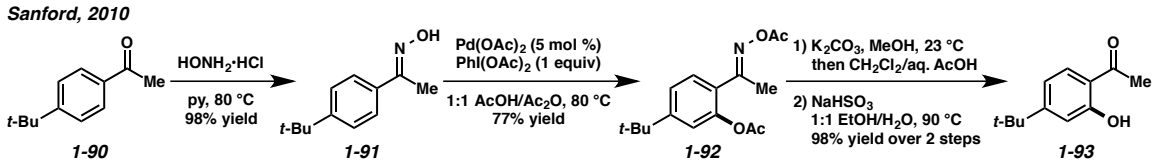
Arrayás and Carretero pursued an analogous strategy by using a 2-pyridyl sulfonamide instead of a picolinate (Scheme 1.3.4).[34] This directing group could facilitate the alkenylation of both pyrroles and indoles at the 2-position. The directing group could be removed under numerous conditions: sulfonamide **1-88** was treated with zinc dust in an acidic media at ambient temperature furnishing the alkenylated pyrrole in good yield without over-reduction.

Scheme 1.3.4. Arrayás and Carretero's Alkenylation of Pyrroles



Sanford was a pioneer in the area of Pd^{II}-Pd^{IV} directed C–H functionalization. She was the first to report Pd-mediated C–H acetoxylation directed by pyridines (Scheme 1.3.5).[35] She later showed that oximes could act as a suitable directing group.[36] This was developed into a traceless directing group strategy for the functionalization of aryl ketones. Conversion of the ketone (**1-90**) to the oxime occurs in excellent yield. The acetoxylation conditions simultaneously acetylate the oxime and then functionalize the arene. A two-step procedure removes the directing group: saponification with methanolic K_2CO_3 followed by reduction with $NaHSO_3$ and hydrolysis with adventitious water unmasks the ketone.

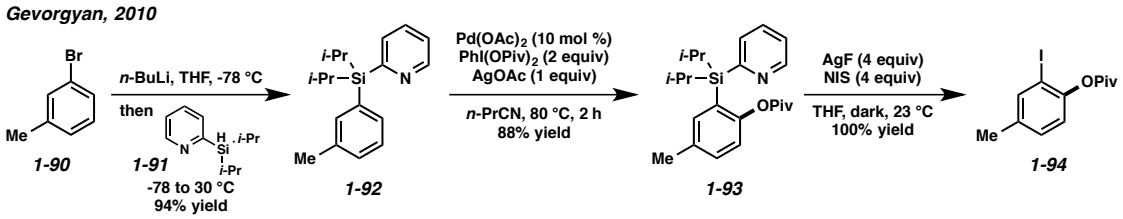
Scheme 1.3.5. Sanford's *ortho*-Acetoxylation via Oximes



Similar to the methods described above, Gevorgyan developed a traceless directing group for aryl halides (Scheme 1.3.6).[37] Lithium halogen exchange of aryl bromide **1-90** and addition

into 2-pyridyl diisopropylsilane **1-91** installs the directing group. The pyridine readily pivalates the arene in good yield. The removal of the directing group and reinstallation of the aryl halide is accomplished by treatment of AgF and NIS. As can be seen, attachment of a pyridyl-group is a reoccurring strategy in directed functionalization.

Scheme 1.3.6. Gevorgyan's *ortho*-Pivaloylation of Aryl Halides



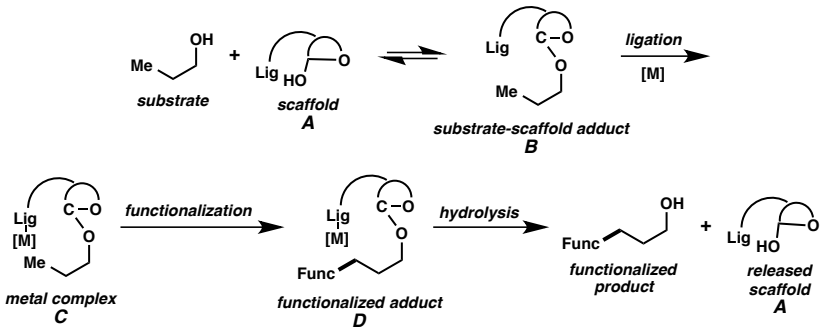
Achieving high selectivity between chemically undifferentiated C–H bonds during a transformation typically necessitates the use of a directing group. This constraint has led to the development of traceless directing group strategies that have obtained tremendous levels of selectivity and utility. Although not always the case, these methods often require three individual steps with discrete workups and purifications. Many have attempted to telescope steps or develop procedures of sequential addition to increase a method's overall efficiency (notably Hartwig, Scheme 1.2.10). The logical advancement of these strategies is to develop conditions and catalysts that can temporally act as directing groups by transiently exchanging under the reaction conditions.

1.4. Transient Directing Groups and Strategies

The ultimate goal for this project is the development of strategies that can be catalytic both in metal and in transiently exchanging scaffold (Figure 1.1.2). Although it is widely recognized that the achievement of a transient scaffold and complementary conditions has the potential to achieve unconventional selectivity and efficiency, relatively few examples have been reported in the literature. This is likely due to the constraint that the exchange conditions not

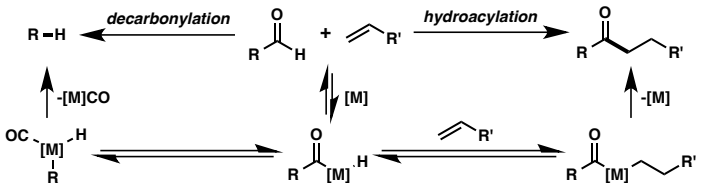
disturb C–H functionalization, and additionally, functionalization not disturb exchange. Furthermore, the substrate and scaffold should be stable to the reaction conditions in all circumstances (i.e., all possible intermediates of attachment and functionalization).

Figure 1.1.2 (recreated). The General Concept for Transiently Directed Functionalization



There have been only a few examples of transiently directed metal catalysis. The first report was to solve the problem of intermolecular hydroacylation. This is the reaction between an alkene and an aldehyde to afford a ketone.[38] It consists of a chemoselective C–H insertion of an aldehyde's sp^2 C–H bond followed by β-hydride insertion of an alkene and reductive elimination to afford the ketone product (Figure 1.4.1).[39] This is technically a selective C–H functionalization, but since the aldehyde C–H bond is relatively weak, it is often not included in other C–H functionalization discussions.[40] The major sidereaction observed in this transformation is decarbonylation of the aldehyde. The resulting rhodium carbonyl byproduct is often incapable of reentering the catalytic cycle; therefore strategies that suppress decarbonylation and encourage alkene insertion are crucial for obtaining high hydroacylation yields.

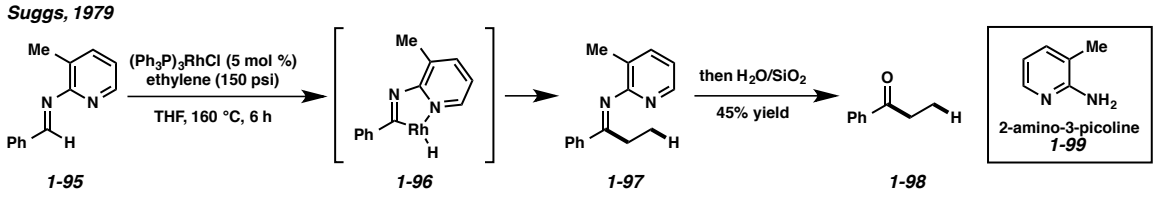
Figure 1.4.1. The Hydroacylation Reaction



Many functional groups have been shown to direct hydroacylations, and these groups geometrically constrain the resulting metallacycle, inhibiting decarbonylation. This strategy is useful when a substrate has the necessary directing functionality; however most substrates lack this requisite, which presents a major limitation in the broad implementation of this chemistry.

Suggs improved the intermolecular hydroacylation of aldehydes lacking directing groups by converting the aldehydes to imines (Scheme 1.4.1).[41] The hydroimination of aldimine **1-95** was accomplished with [$(Ph_3P)_3RhCl$] at 160 °C under 150 psi of ethylene affording ketimine **1-97**. Hydrolysis facilitated by SiO_2 afforded the corresponding ketone **1-98**. The use of 2-amino-3-picoline **1-99** as an easily attachable directing group dramatically affected the efficacy of this reaction, readily positioning rhodium to insert into the imine's C–H bond affording the 5-membered metallacycle **1-96** and circumventing decarbonylation.

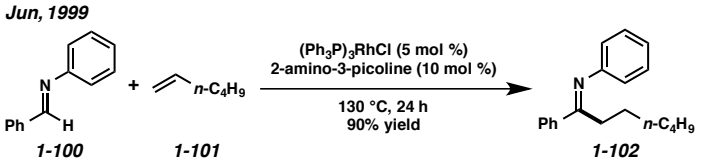
Scheme 1.4.1. Suggs' Hydroacylation with Pyridyl Imines



A surprising result was observed by Jun, where aldimine **1-100**, bearing no internal directing group, could afford ketimine **1-102** under the hydroacylation conditions in the presence of catalytic 2-amino-3-picoline **1-99** (Scheme 1.4.2).[42] In the absence of 2-amino-3-picoline (**1-99**), however, the formation of ketimine **1-102** was not observed. This is highly suggestive that a

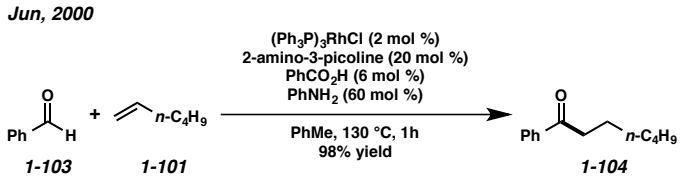
trans-imination occurs to afford aldimine **1-96** prior to hydroimination. This discovery illuminated the possibility that these aminopyridines and their derivatives along with a rhodium catalysts could be used to develop transient functionalization systems that afford otherwise unattainable selectivities and reactivity.

Scheme 1.4.2. Juns' Hydroacylation of Imines Through Transimination



It was later reported that preformation of an imine could be avoided completely in the hydroacylation of aldehydes (Scheme 1.4.3).[43] Jun illustrated the remarkable utility of this dual scaffold/rhodium catalysis by showing the direct hydroacylation of benzaldehyde **1-103** and hexene **1-101** to afford ketone **1-104** *in 98% yield!* This reaction did require substantial optimization to obtain transient exchange with the 2-aminopyridine scaffold (**1-99**). This was accomplished by adding benzoic acid, as a Brønsted acid source, and aniline, presumed to limit decarbonylation by generating the imine *in situ*.

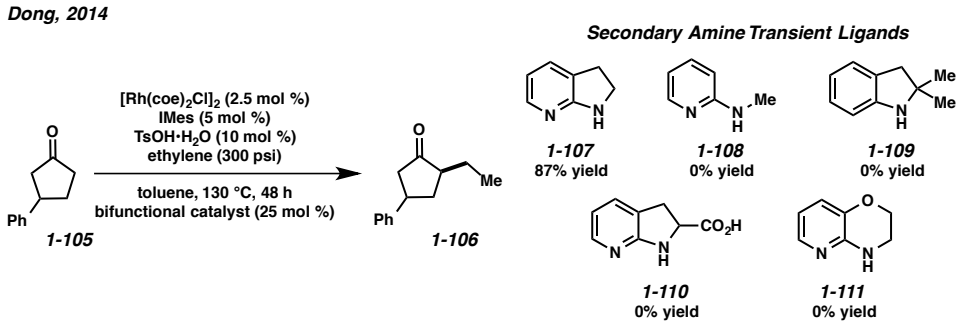
Scheme 1.4.3. Jun's Hydroacylation of Aldehydes Through Transimination



Dong developed a unique transiently functionalization scaffold for the α-alkylation of ketones.[44] Analogous to the efforts of Suggs and Jun, numerous secondary amine transient ligands (**1-107–1-111**) were investigated under the hypothesis that a secondary amine would more readily produce enamines and would be exchangeable under the reaction conditions (Scheme 1.4.4). The resulting enamine sp^2 C–H bonds would be more reactive and could

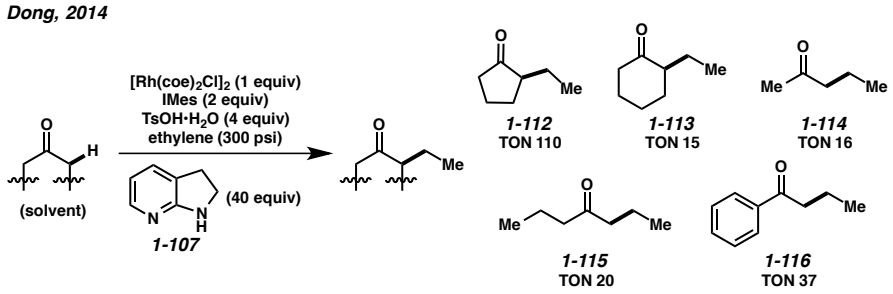
undergo activation. Somewhat surprisingly, most of the transient ligands investigated did not exhibit reactivity. Amine **1-107** was uniquely competent for the α-alkylation of cyclopentanone **1-105**, affording ketone **1-106** in 87%.

Scheme 1.4.4. Dong's α-Alkylation via Transimination (Ligand Evaluation)



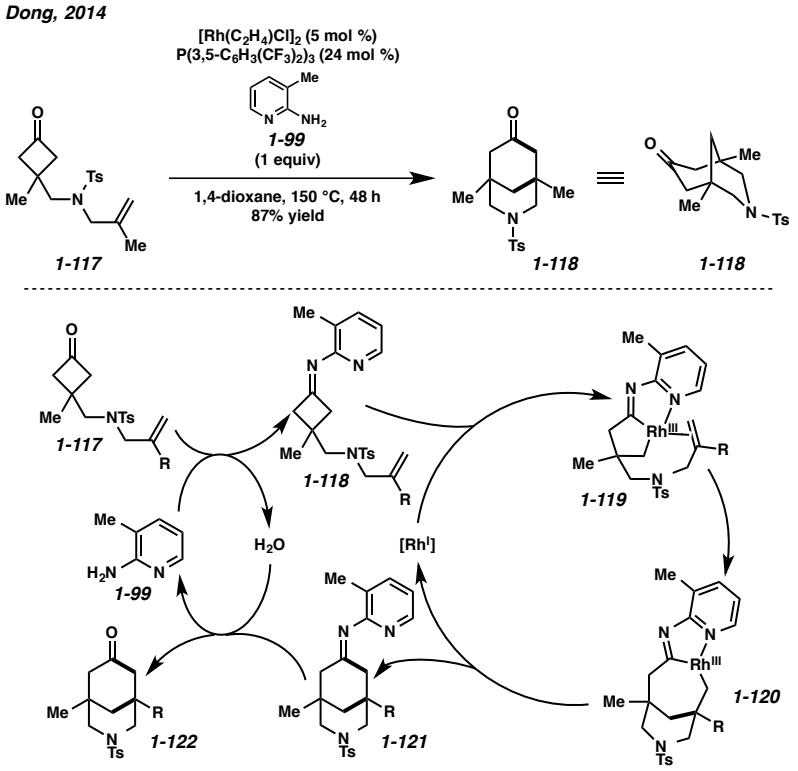
The scope of this reaction was investigated, and this procedure generally displayed high yields with numerous substituted cyclopentanones. Modest turnover numbers were observed when cyclopentanone was reacted with various alkenes and when various ketones were reacted with ethylene (Scheme 1.4.5). This is a mild alkylation procedure that exhibits wide functional group tolerance. This method should be delineated from harsher conditions such as the use of LDA to form lithium enolates or other sensitive conditions such as Stork-enamine alkylations[45] that require the pregeneration of the enamine. It also avoids the use of alkylating agents such as alkyl bromides and iodides for more stable and readily available alkenes. This chemistry is novel; however, until the turnover numbers are substantially increased, the use of rhodium may be the major economic inhibition of the wide expansion of this technology.

Scheme 1.4.5. Dong's α-Alkylation via Transimination (Substrate Evaluation)



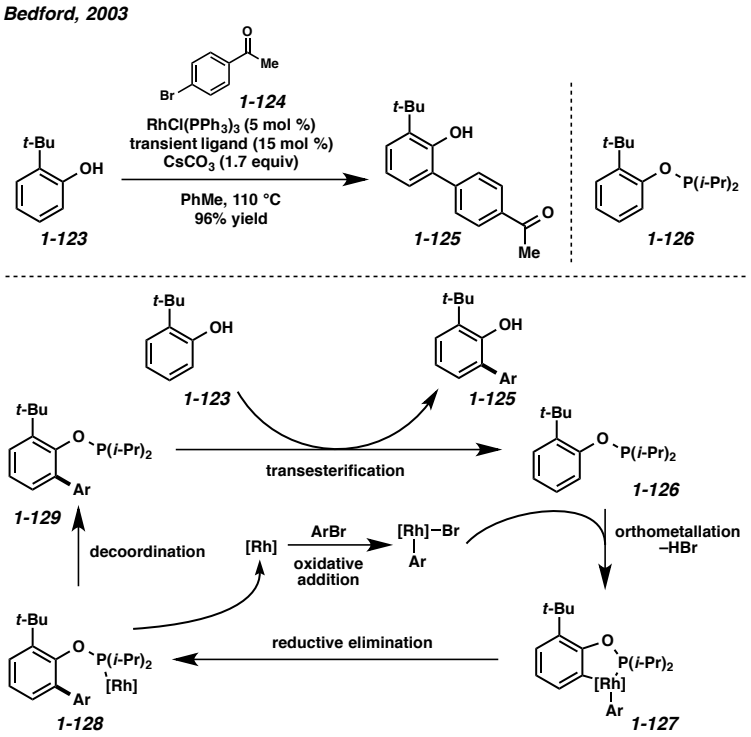
The expansion of this catalytic strategy to included C–C bond functionalization would generate very unique transformations. Dong explored the transient functionalization of cyclobutanones using the exchagable ligand 3-amino-2-picoline (**1-99**) to produce bridged bicycles resulting from a formal [4+2].[46] The *in situ* condensation of the amine followed by directed C–C insertion produces Rh^{III} metallacycle **1-119**. After alkene insertion on an internal olefin, reductive elimination affords the bicycle (**1-121**). *In situ* hydrolysis of the transient ligand generates product (**1-122**) and releases the transient ligand (Scheme 1.4.6). The optimized conditions of this procedure required 1 equivalent of this ligand, which requires improvement, but this ligand is transiently attaching to the substrate and being hydrolyzed from the product *in situ*. These products were transformed by ring-expansion and –contraction to additional bicycles, and the transformation was shown to give modest stereoselectivity (up to 37% ee) when a chiral ligand was used.

Scheme 1.4.6. Dong's C–C Bond Functionalization via Transimiantion Catalysis



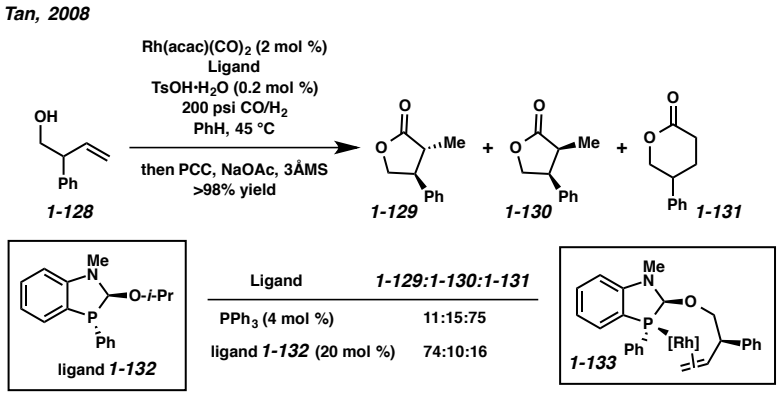
In a deviation away from transimination, Bedford disclosed a strategy predicated on the exchange of phenols with phosphinites (Scheme 1.4.7).[47] Treatment of phenol **1-123** and aryl bromide **1-124** in the presence of a rhodium catalyst and a phosphinite ligand generated *ortho*-arylated phenol in excellent yield. Mechanistically, once an unfunctionalized phenol is attached, the phosphinite can coordinate to an aryl-rhodium and the substrate can undergo *ortho*-metallation. Reductive elimination, decoordination, and phenol exchange affords the arylated product. This strategy was very elegant and was a great expansion past transimination with respect to transiently directed C–H functionalization.

Scheme 1.4.7. Bedford's Transient ortho-Arylation Through Phosphinite Exchange



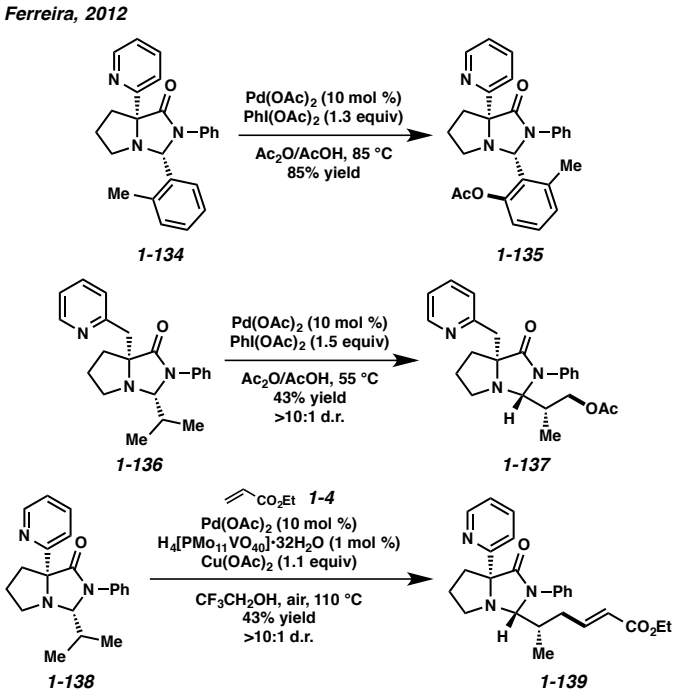
Another transient strategy was implemented in hydroformylation chemistry, a common method for making aldehydes from alkenes using a rhodium catalyst and syngas (H_2 and CO).[48] The reaction often suffers from poor branch selectivity and generally affords terminal aldehydes. An internal directing group can modify this selectivity and favor the branched products. Breit employed the above phosphinite exchange strategy in the hydroformylation of bis- and tris-homoallylic alcohols.[49] Expanding on this work, Tan creatively designed an aminal containing phosphine ligand that could transiently exchange an alcohol under acidic conditions (Scheme 1.4.8).[50] The use of ligand **1-132** in the hydroformylation of homoallylic alcohol **1-128** dramatically increases branched selectivity compared to the use of PPh_3. The intramolecularity of this reaction can be seen in rhodium complex **1-133**, and this tethering disfavors reaction pathways leading to the linear products.

Scheme 1.4.8. Tan's Hydroformylation Through Transient Catalysis



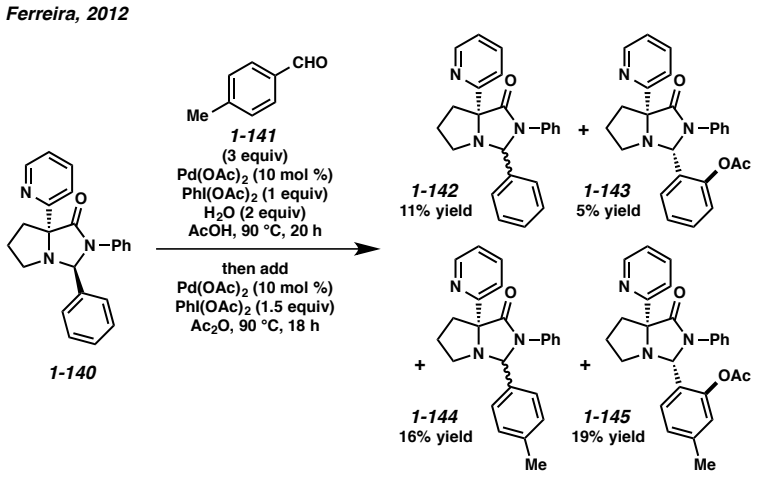
In an attempt to expand the strategies for transiently directed C–H functionalization, Ferreira and coworkers developed proline-derived scaffolds capable of sp^2 and sp^3 acetoxylations and alkenylations and ideally transient functionalization via aminal exchange (Scheme 1.4.9).[51] Their investigations were also an attempt to broaden transient functionalization to include unactivated sp^3 C–H bonds (i.e., not the α-C–H bonds of a ketone), which to this point has yet to be accomplished. The yields varied between poor and good, but the scaffold was capable of transformations with chemo-, regio-, and diastereoselectivity. Most notably, the sp^2-sp^3 oxidative coupling between the scaffold/isobutyraldehyde adduct (**1-138**) and ethyl acrylate (**1-4**) afforded the resulting enoate (**1-139**) as one diastereomer in good dr and in 43% yield. Unfortunately, cleavage of this scaffold was particularly difficult, excluding it as an effective traceless directing group.[52] Although the functionalization reactions and detachment were unable to be optimized to be more synthetically useful, the high levels of selectivity should continue to encourage the development of new traceless directing groups.

Scheme 1.4.9. Ferreira's Directed sp^2 and sp^3 Functionalization by an Amino Amide Scaffold



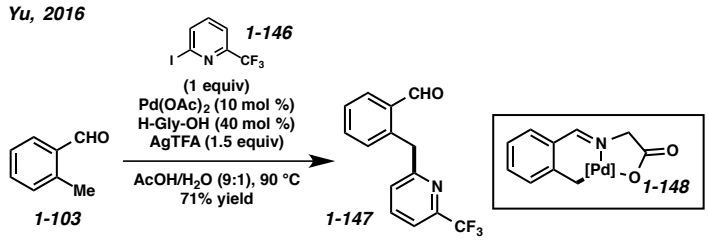
Despite the proline-based scaffold's non-optimal performance as traceless directing groups, Ferreira investigated their ability to act as transient directing groups (Scheme 1.4.10). They subjected *tran*s-aminal **1-140** to palladium-based acetoxylation conditions in AcOH with excess aldehyde **1-141**. This reaction was sub-stoichiometric in scaffold with respect to the exchanging aldehyde and was therefore an attempt towards catalytic conditions. It was known that the aminal would have to isomerize to the cis isomer before functionalization would occur. The reaction afforded numerous products: *cis*- and *trans*-oxazolidinones **1-142** and **1-144** as well as functionalized *cis*-oxazolidinones **1-143** and **1-145**. The isomerization and exchange of the aldehydes illustrates the desired trans-aminalization, and the arene-functionalization demonstrates the requisite synchronization. This experiment should be considered a proof-of-principle that aminals/acetals can be included in the exchange functionality used in transient directed C–H functionalization.

Scheme 1.4.10. Ferreira's Transient Acetoxylation of Aldehydes



During the development of this manuscript, Yu reported the first example of transiently directed sp^3 C–H functionalization (Scheme 1.4.11).[53] The use of glycine as both a transimination and bidentate catalyst cleverly positions the metal center near the o-methyl group affording metallacycle **1-148**. Subsequent reaction with aryl iodide **1-146** affords the functionalized product in good yield. The use of chiral amino acids produces high levels of enantioselectivity.

Scheme 1.4.11. Yu's Transient Arylation of Aldehydes



1.5. Research Objectives Revisited

The unique power and advantages associated with transiently directed C–H and C–C functionalization has been illustrated above. We aim to expand on those discoveries by identifying scaffolds and strategies that utilize a transient directing group in the pursuit of

methodologies that provide unique transformations or unprecedented levels of regio-, chemo-, and diastereoselectivity that are typically associated with internal directing groups. We envision designing a scaffold that contains an acetal as the exchanging functionality and alcohols as the exchanging substrate. This strategy slightly deviates from the developments of Ferreira in that it replaces aldehydes for alcohols as the exchangeable substrate. This modification was chosen due to the high reactivity of aldehydes and the predicted stability of alcohols under many functionalization conditions.

Due to our previous investigations toward our ultimate goal of transiently directed C–H and C–C functionalization, we became aware of the scale of the challenge undertaken. In pursuit of this ultimate goal, we focused our studies on the identification of a chemical space that could provide checkpoint advancements that would produce methodological utility along each step of development. We envision a scaffold that contains the requisite exchanging functionality for eventual transient C–H and C–C functionalization but also acts as a useful traceless directing group. With these ambitions and considerations in mind, we embarked on the journey towards traceless and transient directed C–H and C–C functionalization.

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CHAPTER 2

THE DEVELOPMENT OF A TRACELESS DIRECTING GROUP FOR C–H FUNCTIONALIZATION OF BENZYL ALCOHOLS

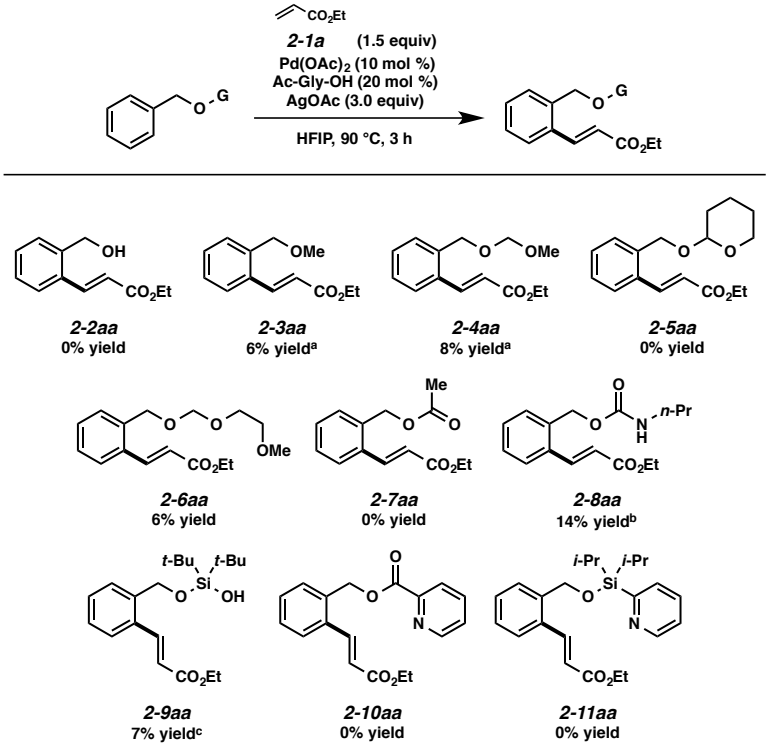
2.1. Analysis of Potential Directing Groups for Benzyl Alcohol Alkenylation

As mentioned in Chapter 1, we are pursuing the development of traceless directing group strategies and are ultimately interested in expanding these toward transient C–H functionalization. Reports of both traceless and transient strategies were covered in Chapter 1. To initiate our investigation, we first needed to identify a chemical space that would afford meaningful and interesting reactivity or products. To identify this chemical space, we investigated the known C–H functionalization transformations for a number of common functional group. Those groups with a dearth of reactions were then analyzed for their exchange properties. The investigations performed by Ferreira had increased our awareness of the challenges associated with transient functionalization utilizing aldehydes.[1] An alternative group was desired that could still utilize aminal or acetal exchange.

There were relatively few C–H functionalization transformations for benzyl alcohols when this study was initiated. We suspected that this would be an ideal functional group to pursue traceless and transient functionalization. We chose to refine the substrate class to primary benzyl alcohols due to the limited functionalizations of this group. We were curious if known protecting groups or directing groups could act as a traceless group and facilitate functionalization.

We envisioned numerous protecting groups on benzyl alcohol imparting this reactivity, and initiated this investigation using Yu's and coworkers' conditions for directed alkenylation (ethyl acrylate, 10 mol % $Pd(OAc)_2$, 20 mol % Ac-Gly-OH, 3 equiv AgOAc, HFIP, 90 °C).[2] These conditions have been used with numerous functional groups as well as have directed remote functionalizations. Ethers, acetals, esters, and carbamates were all uniformly ineffectual (Table 2.1.1). The di-*tert*-butyl-silanol group, which had previously been employed in phenol-based functionalizations, showed little reactivity. Pyridyl-incorporated esters (**2-10aa**) and ethers (**2-11aa**) failed to induce functionalization.

Table 2.1.1. Common Protecting and Directing Group Facilitated Alkenylation of Benzyl Alcohols[a]

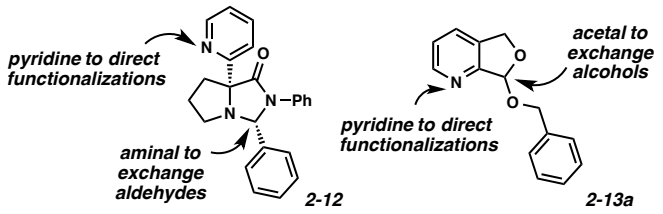


a) All values are NMR yields obtained using 1-octene as an internal standard. b) Increasing the reaction time from 3 to 6 h increased the yield to 16%. c) This value corresponds to the *ortho* contribution of a mixture of olefinated products.

We suspected that a unique directing group would need to be developed. Consequently, we were interested in developing a robust scaffold that includes both a pyridine for directing

functionalization and an acetal for easy attachment and removal as well as exchange. These structural features would need to be hybridized effectively to successfully produce a new traceless/transient scaffold. The proposed directing group shares similar structural features to the directing group reported by Ferreira and coworkers (Figure 2.1.1).[1]

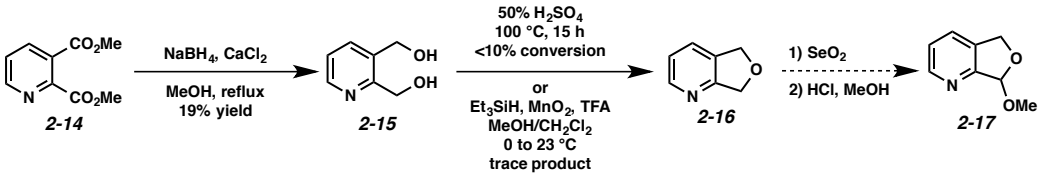
Figure 2.1.1. Structural Similarities Between our Functionalization Scaffolds



2.2. Scaffold Synthesis

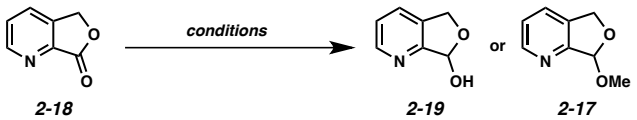
It was envisioned that scaffold **2-17** (precursor to **2-13a**) could be synthesized by readily available and commercial diester **2-14** (Scheme 2.2.1). We attempted a reduction of both esters but found that this transformation was problematic. The product is highly water-soluble and appears to chelate to the byproducts of the reducing agents (e.g., boron or aluminum salts). We were able to successfully isolate the diol once but found our procedure was not reproducible.[3] An acidic etherification produced <10% yield of ether **2-16**. A similar finding has been reported suggesting that the pyridine buffers the substrate from further protonation and etherification.[4] We attempted to produce the ether by oxidation to the hemiacetal through treatment with MnO_2 and subsequent *in situ* reduction by Et_3SiH and TFA; however, only trace product was observed. Site selective oxidation of this product followed by acetalization was envisioned to afford the desired scaffold.

Scheme 2.2.1. Attempted Synthesis of Acetal **2-17**



Alternatively, numerous conditions were explored to reduce lactone **2-18** to afford either hemiacetal **2-19** or methyl acetal **2-17**. Treatment of this lactone with DIBAL produced trace amounts of hemiacetal (Table 2.2.1, entry 1). We suspected at the time, and latter confirmed, that the product is very water-soluble. We investigated conditions to circumvent isolation of this hemiacetal by adding PTSA, 3Å molecular sieves, and MeOH, but we obtained trace product of acetal **2-17** (Table 2.2.1, entry 2). Hydroboration of the lactone with BH_3•DMS or BH_3•py followed by acidic MeOH either gave a complex mixture or no reaction, respectively (Table 2.2.1, entries 3 and 4). L-Selectride afforded a complex mixture (Table 2.2.1, entry 5). The isolation of these compounds may have been problematic due to chelation to the boron or aluminum salts. Finally, ruthenium catalyzed hydrosilylation was ineffectual (Table 2.2.1, entry 6). This may be due to the pyridine inhibiting catalysis for this reaction.

Table 2.2.1. Failed Conditions to Convert Lactone **2-18** to Hemiacetal **2-19** and Acetal **2-17**

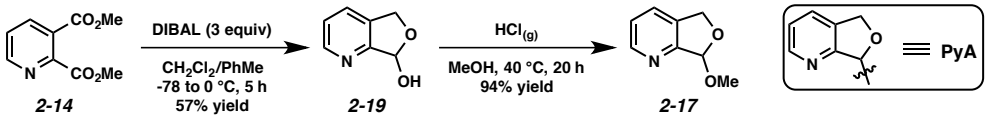


Entry	Conditions	Results
1	DIBAL (3 equiv), CH_2Cl_2/hexanes, -78 to 23 °C	<10% yield **2-19**
2	DIBAL (3 equiv), CH_2Cl_2/hexanes, -78 to 23 °C; PTSA (1.5 equiv), 3ÅMS, MeOH, 23 °C	<10% yield **2-17**
3	BH_3•DMS, THF, 0 °C; PTSA (10 mol %), MeOH, 23 °C	complex mixture
4	BH_3•py, THF, 0 °C; PTSA (10 mol %), MeOH, 23 °C	no reaction
5	L-Selectride (1.05 equiv), THF, -78 °C; PTSA (1.5 equiv), MeOH, 65 °C	complex mixture
6	Et_3SiH (1.5 equiv), [$Ru_3(CO)_{12}$] (1 mol %), PhMe, 100 °C; PTSA (1.5 equiv), MeOH, 65°C	no reaction

We once again tried to target hemiacetal **2-19** and methyl acetal **2-17** (Scheme 2.2.2). The isolation of hemiacetal **2-19** required the development of an appropriate isolation procedure

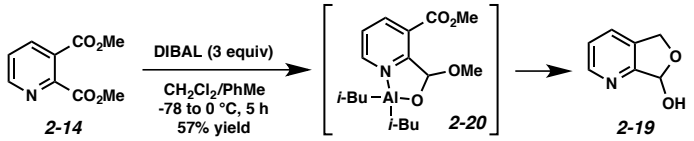
without an aqueous workup. To initiate our synthesis, diester **2-14** was reduced by 3 equivalents of DIBAL, and the resulting solution was subjected to a Fieser and Fieser workup. To this material was added $MgSO_4$ and celite. The mixture was then filtered and the product was purified by flash column chromatography. This isolation procedure both avoids water and dechelates the product from the aluminium salts, affording the hemiacetal **2-17** in 57% yield as the only constitutional isomer observed. Hemiacetal **2-19** can be converted to methyl acetal **2-17** in excellent yield by stirring in methanolic HCl. Both the hemiacetal and the methyl acetal contain the directing group, which we have named **Py**ridine **A**cetal (**PyA**).

Scheme 2.2.2. Synthesis of Methyl Acetal **2-17**



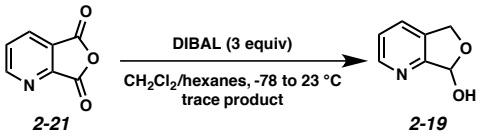
The selectivity of this reduction warrants a discussion. During the course of developing this procedure, the opposite constitutional isomer was never observed. This is surprising since the ester at the 2-position is more electrophilic, which would suggest that the first two equivalents would attack that position (Scheme 2.2.3). These inconsistent data can be explained by a chelation effect where the first equivalent of DIBAL is directed by the pyridine to reduce the ester at the 2-position. This results in aluminum alkoxide **2-20**, and if it does not collapse (like a Weinreb amide), the other two equivalents may reduce the ester at the 3-position. Upon work up, this complex breaks up to release hemiacetal **2-19**.

Scheme 2.2.3. Rationale for Regioselectivity of Hemiacetal **2-19**



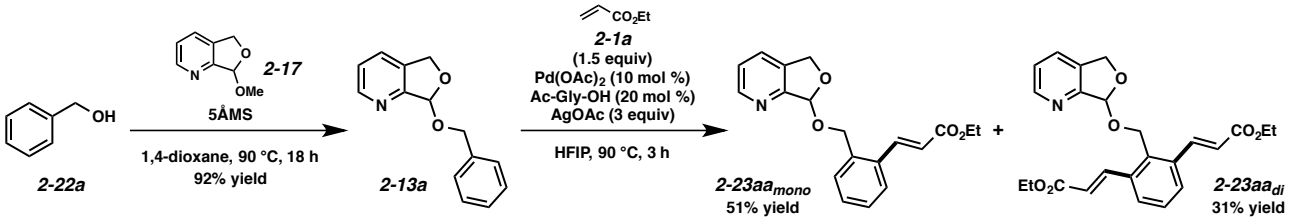
An alternative strategy toward hemiacetal **2-19** was also investigated. Reduction of anhydride **2-21** with 3 equivalents of DIBAL only produced trace amounts of hemiacetal **2-19** (Scheme 2.2.4). This convinced us that the synthesis of hemiacetal **2-19** is sufficient through the route described in Scheme 2.2.2.

Scheme 2.2.4. DIBAL Reduction of Anhydride **2-21**



We conveniently discovered that the simply heating methyl acetal **2-17** with benzyl alcohol (**2-22a**) in the presence of 5Å molecular sieves affords desired acetal **2-13a** (Scheme 2.2.5). This product was treated to the alkenylation conditions described by Yu, and fortunately olefinated acetal **23aa** was obtained in 82% yield (51:31 mono/di).[5]

Scheme 2.2.5. Attachment and Functionalization of PyA-Acetals

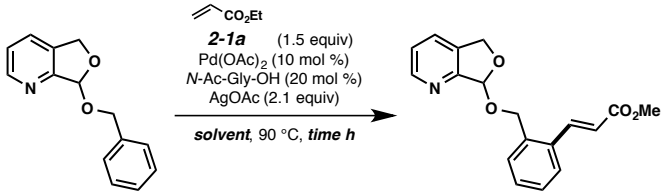


2.3. Alkenylation Optimization

Our optimized alkenylation conditions were obtained through meticulous and iterative screenings of reaction conditions. Optimization was approached by initially analyzing a single variable. The conditions that produced the best outcome were utilized in the next screen and another variable was then analyzed. This procedure eventually led to the conditions implemented in Scheme 2.2.5. We initially utilized conditions similar to Yu's and coworkers (methyl acrylate, 10 mol % $Pd(OA)_2$, 20 mol % Ac-Gly-OH, 2.1 equiv AgOAc, 90 °C), but analyzed the effect of

solvent on this reaction first. *t*-Amyl alcohol and *t*-butyl methyl ether were both ineffectual as solvents (Table 2.3.1, entries 1 and 2). HFIP, hexanes, and toluene all led to complete decomposition over 13 h (Table 2.3.1, entries 5, 6, and 9). HFIP afforded some product at 0.67 h. DCE, 1,4-dioxane, hexafluorobenzene, and α,α,α-trifluorotoluene imparted useful reactivity (Table 2.3.1, entries 3, 4, 8, and 10). Although 1,4-dioxane gave a better ratio of product to starting material, DCE afforded cleaner conversion to the product and was therefore used in further studies.

Table 2.3.1. Initial Screening of Solvents[a]



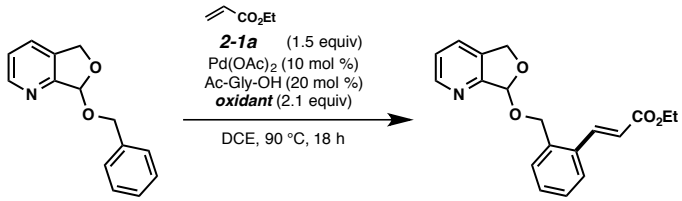
Entry	Solvent	2-13a:2-23ab		
		0.67 h	3 h	13 h
1	*t*-amyl alcohol	10.3:1	2.6:1	1.5:1
2	*t*-butyl methyl ether	>20:1	>20:1	17.5:1
3	1,2-dichloroethane	17.6:1	5.5:1	3.6:1
4	1,4-dioxane	18.9:1	7.5:1	2.9:1
5	hexafluoroisopropanol	1:>20	—	—
6	hexanes	>20:1	>20:1	—
7	hexadecafluoroheptane	—	—	>20:1
8	hexafluorobenzene	>20:1	>20:1	6.5:1
9	toluene	12.5:1[b]	4.3:1[b]	—
10	α,α,α–trifluorotoluene	>20:1	>20:1	7.5:1

a) The reaction conditions were as follows: acetal **2-13a** (0.100 mmol), methyl acrylate **2-1b** (1.0 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (2.1 equiv), and DCE (1.0 mL) were heated at 90 °C for ***X h***. b) This ratio represents **2-13a** and olefinated toluene and not the ratio of **2-13a** and **2-23ab**.

We continued to optimize this reaction through an iterative method, and decided to vary the oxidant. AgOAc worked the best of all the silver salts (Table 2.3.2, entries 2-7) and worked better at lower concentrations (Table 2.3.2, entry 2 compared to entry 3). An oxygen

environment produced very little product (Table 2.3.2, entry 8) and the addition of a heteropolyacid reoxidation catalyst further decreased the yield (Table 2.3.2, entry 9). Copper and benzoquinone were not effective oxidants (Table 2.3.2, entries 10 and 12), and the addition of catalytic silver did not further facilitate the reaction.[6] Oxidants capable of producing Pd^{IV} were ineffective and led to significant decomposition (Table 2.3.2, entries 14 and 15). We decided to pursue other variables while utilizing AgOAc as the oxidant (Table 2.3.2, entry 2).

Table 2.3.2. Screening of Oxidants[a]



2-13a *2-23aa*

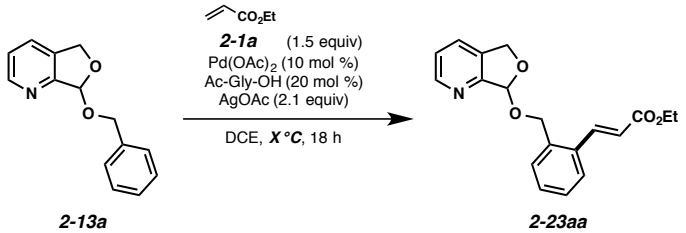
Entry	Oxidant	Conv. (%)[b]	Yield (%, mono/di)[b]
1	—	11	11/0
2	AgOAc	65	48/7
3	AgOAc[c]	49	25/trace
4	AgOPiv	51	10/0
5	AgOTfa	69	0/0
6	AgOTf	100	0/0
7	Ag_2CO_3[d]	43	32/trace
8	O_2 (1 atm)	47	19/0
9	O_2 (1 atm)/$H_4[pMo_{11}VO_{40}]\bullet 32H_2O$[e]	56	13/0
10	$Cu(OAc)_2$	75	26/0
11	$Cu(OAc)_2$/AgOAc[f]	62	16/0
12	Benzoquinone	22	9/0
13	Benzoquinone/AgOAc[f]	13	10/0
14	*t*-BuOOH (5 M in CH_2Cl_2)[g]	64	10/0
15	$K_2S_2O_8$[g]	100	0/0

a) Unless otherwise noted, the reaction conditions were as follows: acetal **2-13a** (0.100 mmol), ethyl acrylate **2-1a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), ***oxidant*** (2.1 equiv), and DCE (1.0 mL) were heated at 90 °C for 18 h. b) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard. c) 0.40 mL of DCE was used instead of 1.0 mL. d) 1.05 equiv of Ag_2CO_3 was used instead of 2.1 equiv. e) 1 mol % of $H_4[PMo_{11}VO_{40}]\bullet 32H_2O$ was used. f) 2.0 equiv of oxidant and 0.1 equiv of AgOAc was used g) 2.0 equiv of oxidant was used instead of 2.1 equiv.

Next, we varied the reaction temperature. The transformation performed best at 90 °C (Table 2.3.3, entry 3). Lower temperatures were sluggish, and there was substantial starting

material (Table 2.3.3, entries 1 and 2). Heating the reaction to 100 °C led to significant decomposition (Table 2.3.3, entry 4).

Table 2.3.3. Screening of Reaction Temperature[a]



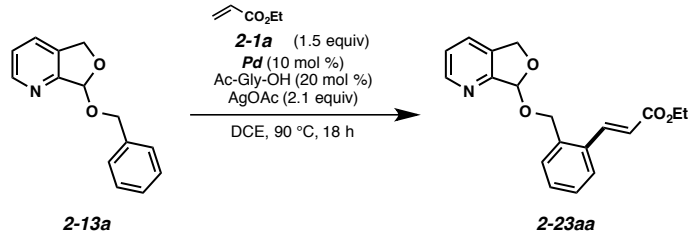
2-13a *2-23aa*

Entry	Temperature (°C)	rsm (%)[b]	Yield (mono) (%)[b]	Yield (di) (%)[b]
1	70	81	13	0
2	80	72	22	0
3	90	35	48	7
4	100	6	13	2

a) The reaction conditions were as follows: acetal **2-13a** (0.100 mmol), ethyl acrylate **2-1a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (2.1 equiv), and DCE (1.0 mL) were heated at ***X* °C** for 18 h. b) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

Modifications of the palladium catalysts all were equally ineffectual. The second best catalyst was $Pd(OTf)_2$, which was interesting since AgOTf led to complete decomposition (Table 2.3.4, entry 4). $Pd(OPiv)_2$ showed very poor reactivity, suggesting steric hindrance likely inhibits substrate coordination or carboxylate-facilitated C–H deprotonation (Table 2.3.4, entry 3). Phosphines inhibited the reaction (Table 2.3.4, entries 6 and 8).

Table 2.3.4. Screening of Palladium Catalysts[a]



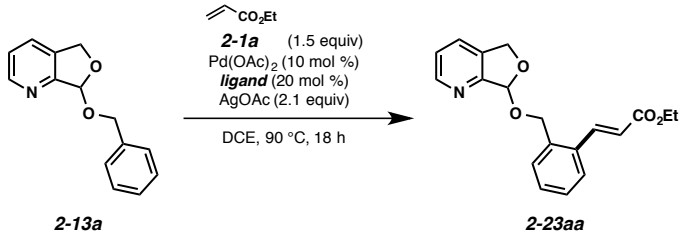
2-13a *2-23aa*

Entry	Pd	rsm (%)[b]	Yield (mono) (%)[b]	Yield (di) (%)[b]
1	—	100	0	0
2	$Pd(OAc)_2$	35	48	7
3	$Pd(OPiv)_2$	71	10	0
4	$Pd(OTf)_2$	47	35	7
5	$PdCl_2$	80	20	0
6	$PdCl_2(PPh_3)_2$	92	3	0
7	$PdCl_2(MeCN)_2$	72	27	trace
8	$Pd(PPh_3)_4$	85	0	0
9	$Pd_2(dba)_3$	80	20	0

a) The reaction conditions were as follows: acetal **2-13a** (0.1 mmol), ethyl acrylate **2-1a** (1.5 equiv), ***Pd*** (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (2.1 equiv), and DCE (1.0 mL) were heated at 90 °C for 18 h. b) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

We suspected that the most consequential way to enhance reactivity would be to vary the ligand on palladium. We decided to focus our investigations around mono-protected amino acids based on Yu's previous success.[7] Increasing the size of the R-group of the amino acid was inversely related to the yield, once again suggesting steric effects dramatically affect the reactivity (Table 2.3.5, entries 2 and 5-9). The sodium salt of acetyl glycine was less effective than the free acid (Table 2.3.5, entry 3). Varying the amide group dramatically decreased the yields (Table 2.3.5, entries 10-13). Other attempts to utilize ligands that were not α-amino acid derived did not improve the yield.

Table 2.3.5. Screening of Ligands[a]



2-13a *2-23aa*

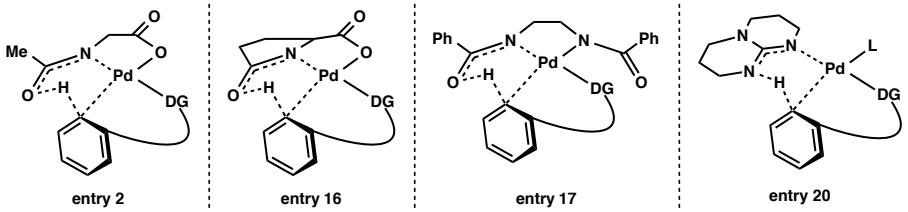
Entry	Ligand		Conv. (%)[b]	Yield (%, mono/di)[b]	Entry	Ligand		Conv. (%)[b]	Yield (%, mono/di)[b]
1	—		27	20/0	11	TfaHN CO_2H	*2-24i*	26	7/0
2	AcHN CO_2H	*2-24a*	65	48/7	12	BocHN CO_2H	*2-24j*	41	11/0
3[c]	AcHN CO_2H	*2-24a*	60	34/trace	13	FmocHN CO_2H	*2-24k*	35	8/0
4	AcHN CO_2Na	*2-24b*	52	21/trace	14	AcHN CO_2H	*2-24l*	41	16/0
5	AcHN CO_2H, Me	*2-24c*	53	38/5	15	BocHN CO_2H, Ph	*2-24m*	42	13/0
6	AcHN CO_2H, Me, Me	*2-24d*	31	21/trace	16	CO_2H, O, N H	*2-24n*	35	5/0
7	AcHN CO_2H, Me, Me	*2-24e*	35	29/trace	17	BzHN NHBz	*2-24o*	29	trace/0
8	AcHN CO_2H, Me, Me	*2-24f*	34	18/trace	18	NHAc, OH	*2-24p*	39	18/0
9	AcHN CO_2H, Me, Me, Me	*2-24g*	14	11/0	19[d]	N, NHAc	*2-24q*	6	trace/0
10	OHCHN CO_2H	*2-24h*	39	16/0	20[d]	N, N, N H	*2-24r*	14	8/0

a) Unless otherwise noted, the reaction conditions were as follows: acetal **2-13a** (0.1 mmol), ethyl acrylate **2-1a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), ***ligand*** (20 mol %), AgOAc (2.1 equiv), and DCE (1.0 mL) were heated at 90 °C for 18 h. b) Yield was determined by ^1H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard. c) 40 mol % of Ac-Gly-OH was used instead of 20 mol %. d) 10 mol % of the ligand was used instead of 20 mol %.

N-acetyl-glycine is believed to break the C–H bond through a concerted-metalation-deprotonation (CMD) facilitated by the amide carbonyl (Figure 2.3.1).[8] We hypothesized that pyroglutamic acid would situate the carbonyl in the requisite orientation for functionalization

(Table 2.3.5, entry 16); however, the reactivity substantially decreased. Dibenzoyl ethylenediamine was used to decrease the conformational requirements of the substrate to be positioned near a carbonyl (Table 2.3.5, entry 17). Triazabicyclodecene was hypothesized to be able to perform a similar CMD mechanism, but would be more basic than an amide carbonyl (Table 2.3.5, entry 20). Neither of these ligands improved the reaction.

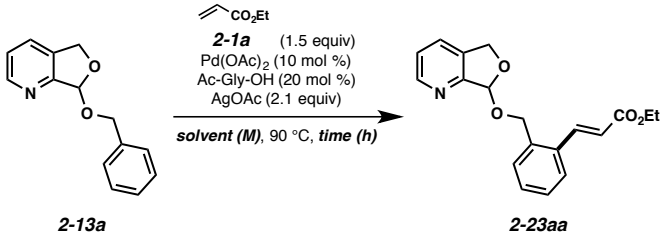
Figure 2.3.1. Rationale to Encourage Concerted Metalation-Deprotonation



Non-coordinating solvents worked best with this reaction. Our initial studies utilized DCE as the solvent, but the reaction was unable to achieve desirable yields. At 0.100 M in DCE, the reaction affords functionalized products in 55% yield (Table 2.3.6, entry 3). To increase the yield, we switched the solvent to HFIP. At 0.050 M, the yield was increased to 69% yield (Table 2.3.6, entry 6).

Bases are sometimes a crucial additive in facilitating C–H functionalization. The effect of a base was therefore investigated (Table 2.3.7); however, this did not improve the yield.

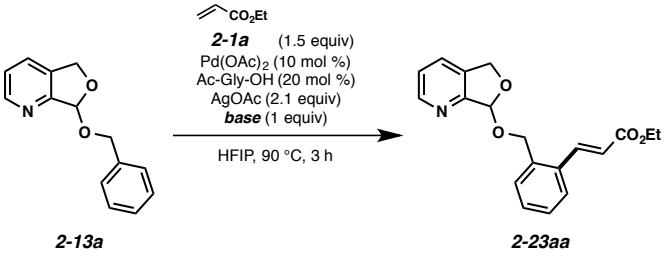
Table 2.3.6. Screening of Solvents and Concentration[a]



Entry	Solvent	Concentration (M)	Time (h)	rsm (%)[b]	Yield (mono/di) (%)[b]
1	DCE	0.025	18	29	41/8
2	DCE	0.050	18	25	38/8
3	DCE	0.100	18	35	48/7
4	DCE	0.250	18	51	25/1
5	HFIP	0.025	3	10	33/18
6	HFIP	0.050	3	10	53/16
7	HFIP	0.100	3	15	34/9
8	HFIP	0.250	3	18	30/4

a) The reaction conditions were as follows: acetal **2-13a** (0.100 mmol), ethyl acrylate **2-1a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (2.1 equiv), and ***DCE*** or ***HFIP*** (***X*** mL) were heated at 90 °C for either 18 or 3 h. b) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

Table 2.3.7. Screening of Bases[a]

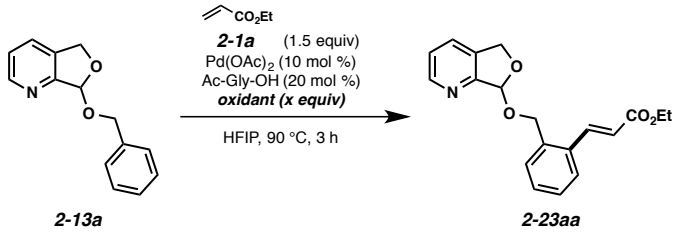


Entry	Base	rsm (%)[b]	Yield (mono) (%)[b]	Yield (di) (%)[b]
1	—	10	53	16
2	NaOAc	28	43	7
3	Na_2CO_3	24	46	12
4	NaOTs	15	40	14
5	4-Me-di-*t*-Bupyridine	30	41	12

a) The reaction conditions were as follows: acetal **2-13a** (0.100 mmol), ethyl acrylate **2-1a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (2.1 equiv), ***base*** (1 equiv), and HFIP (2.0 mL) were heated at 90 °C for 18 h. b) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

We found it prudent to reinvestigate the choice of oxidant relative to HFIP. AgOAc still performed better than Ag_2CO_3 under these conditions (Table 2.3.8). The yield peaked around 3 equivalents of AgOAc, and additional equivalents favored the production of the di-alkenylated product.

Table 2.3.8. Screening of Oxidant Loading[a]

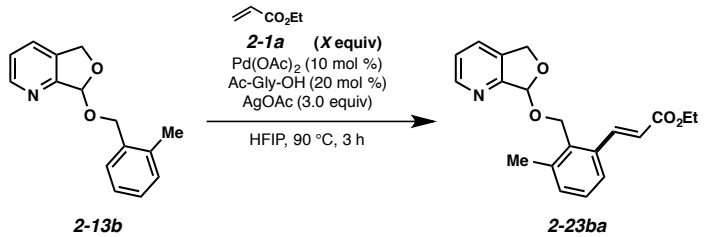


Entry	Oxidant, equiv	rsm (%)[b]	Yield (mono) (%)[b]	Yield (di) (%)[b]
1	—	31	5	0
2	AgOAc, 2.1	10	53	16
3	AgOAc, 3.0	10	55	24
4	AgOAc, 4.0	8	30	40
5	Ag_2CO_3, 1.05	53	15	0
6	Ag_2CO_3, 1.5	57	17	0
7	Ag_2CO_3, 2.0	64	22	0

a) The reaction conditions were as follows: acetal **2-13a** (0.100 mmol), ethyl acrylate **2-1a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), ***Ag*** (***X*** equiv), and HFIP (2.0 mL) were heated at 90 °C for 3 h. b) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

We decided to switch substrates to complete our optimization. The addition of an *ortho*-methyl group would exclude the formation of the diolefinated product, simplifying the optimization. We suspected that the olefins could be performing dual roles as both coupling partners and as electron-deficient ligands to facilitate catalysis. Acetal **2-13b** was subjected to the functionalization conditions varying the olefin concentration. The amount of ethyl acrylate that maximized the yield was 1.5 equivalents, which afforded the alkenylated product in 55% yield (Table 2.3.9, entry 2).

Table 2.3.9. Screening of Olefin Loading[a]

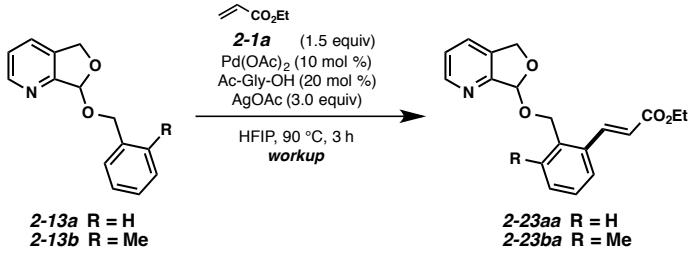


Entry	Olefin equiv	rsm (%)[b]	Yield (%)[b]
1	1.1	trace	50
2	1.5	5	55
3	2.0	trace	44
4	2.5	trace	43
5	3.0	trace	47

a) The reaction conditions were as follows: acetal **2-13b** (0.100 mmol), ethyl acrylate **2-1b** (***X*** equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (3.0 equiv), and HFIP (2.0 mL) were heated at 90 °C for 3 h. b) Yield was determined by ^1H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

During the optimization, the reaction yields had plateaued. Olefinated products were observed in 79% and 55% yield for acetals **2-23aa** and **2-23ba** respectively (Table 2.3.10, entries 1 and 3). We suspected that the products were chelating to either palladium or silver in the reaction mixture. The removal of residual palladium in intermediates toward active pharmaceuticals has been investigated.[9] The addition of both a chelation reagent (e.g., ethylenediamine) and a solid adsorbent (e.g., celite) removed significant quantities of residual palladium by simple filtration, and this procedure was implemented in the dechelation of metal impurities from our products. This increased the yield 4% and 19%, respectively (Table 2.3.10, entries 2 and 4).

Table 2.3.10. Reaction Workup Analysis[a]

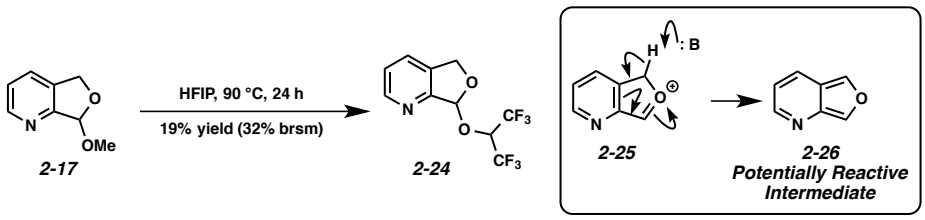


Entry	R	Workup	rsm (%)[b]	Yield (mono/di) (%)[b]
1	H	–	10	55/24
2[c]	H	w/ ethylenediamine and celite	7	51/31
3	Me	–	5	55/–
4[c]	Me	w/ ethylenediamine and celite	6	74/–

a) The reaction conditions were as follows: acetal **2-13a** or **2-13b** (0.100 mmol), ethyl acrylate **2-1a** (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (3.0 equiv), and HFIP (2.0 mL) were heated at 90 °C for 3 h. b) Yield was determined by ^1H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard. c) The reaction was cooled to ambient temperature, ethylenediamine (150 wt. % relative to acetal) and celite (300 wt. % relative to acetal) were added, and the mixture was stirred for 18 h.

HFIP acetal **2-24** was observed as a side product in some reactions during the optimization screen (Scheme 2.3.1). It is observed more prominently with longer reaction times and when acid additives are used. Interestingly, this side product could be generated by simply heating acetal **2-17** in HFIP at 90 °C; however, acetal **2-24** was obtained in a very low yield. It is suspected that this highly ionizing solvent encourages ionization, and decomposition may be occuring through deprotonation of oxocarbenium **2-25** to form the potentially reactive intermediate **2-26**.

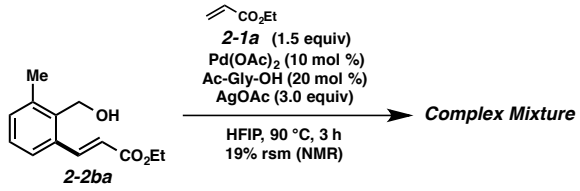
Scheme 2.3.1. HFIP Exchange with Acetal **2-17**



Since HFIP exchanges with an attached alcohol, the released alcohol becomes exposed to the reaction conditions. We knew that benzyl alcohol is not stable to these conditions (Table

2.1.1), but we were curious if functionalized alcohols would decompose under identical conditions. Alcohol **2-2ba** nearly completely decomposed after 3 h under the alkenylation conditions (Scheme 2.3.2)

Scheme 2.3.2. Decomposition of Alkenylated Alcohol **2-2ba**



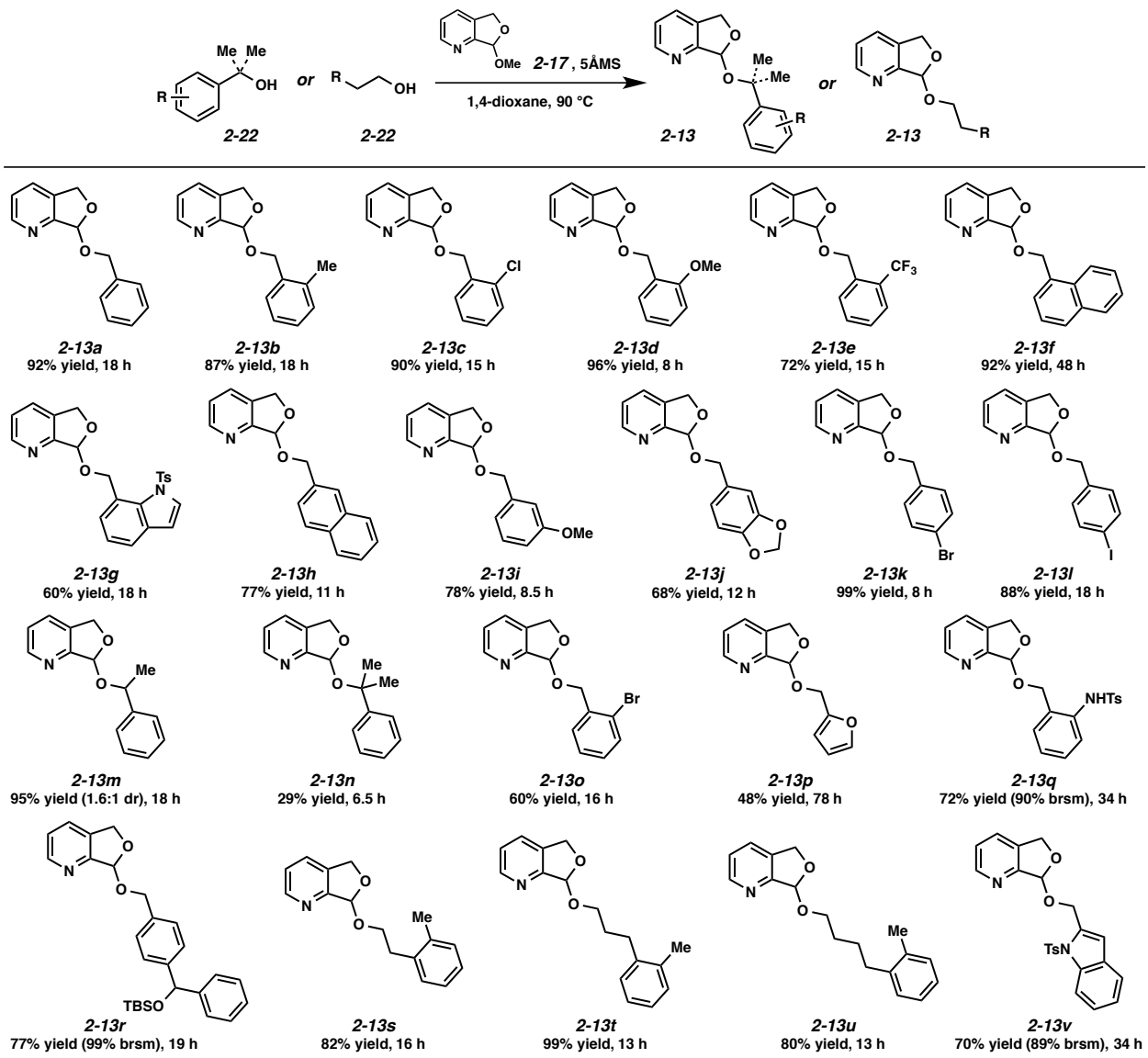
Although our ultimate conditions slowly decompose the substrate acetals and more quickly decompose the released alcohols, we were able to obtain sufficient yield. Our findings suggest there is an ideal reaction time for each substrate where the product yield is maximized and decomposition is minimized.

2.4. Attachment, Alkenylation, and Cleavage Scope

The attachment procedure implementing acetal **2-17** and 5Å molecular sieves proved to be generally useful and afforded benzyl acetals in good to excellent yields in most cases (Table 2.4.1). Acid-sensitive substrates (**2-13n** and **2-13p**) afforded products in lower yields (29% and 48%, respectively).

Over the course of our investigations, there were a few alcohols that did not attach at all (Table 2.4.2). Alcohols **2-22w-β** did not afford acetal products using acetal **2-17** and 5Å molecular sieves. Most of these alcohols have an electron-withdrawing group at the para position. This binary reactivity between very reactive alcohols and non-reactive alcohols is very intriguing, and unfortunately, we do not have any substantial insights into the mechanism of attachment due to the heterogeneity of the conditions. Additionally, under these conditions, both alcohols **2-22γ** and **2-22δ** afforded a complex mixture of attachment products.

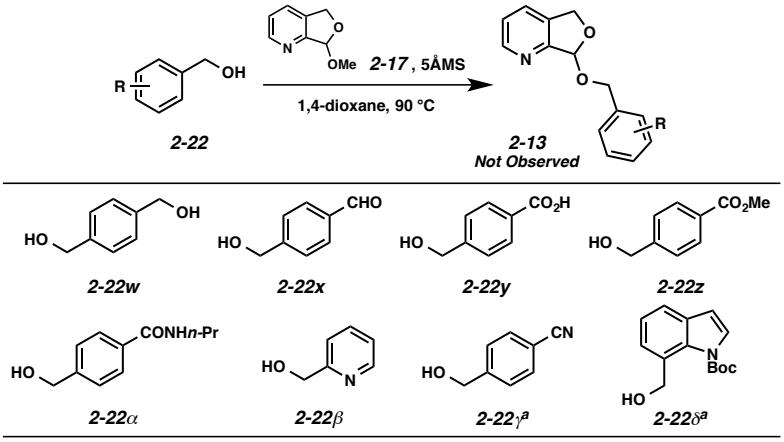
Table 2.4.1. The Attachment Scope to the PyA Scaffold



To circumvent this issue, we chose to pursue an alternative strategy and investigated other methods of exchange that avoid acetal **2-17**. We suspected hemiacetal **2-19** could be used instead and would attach under dehydrative conditions. The use of DCC or $ZnCl_2$ did not provide the attachment product (Table 2.4.3, entries 1 and 4). Inspired by the attachment with methyl acetal **2-17** and 5Å molecular sieves, hemiacetal **2-19** and 3Å molecular sieves was investigated (Table 2.4.3, entry 3), but no reaction was observed. The use of $(EtO)_2POCl$ and Et_3N as well as

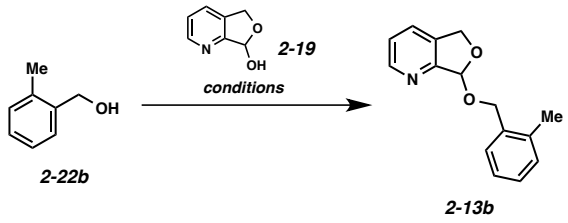
$MgSO_4$ and TsOH were successful at producing acetal **2-13b** (Table 2.4.3, entries 3 and 5), with the latter reaction cleanly affording the product.

Table 2.4.2. Alcohols That Do Not Attach to the PyA Scaffold through Acetal **2-17**



a) These reactions afforded a mixture of attachment products.

Table 2.4.3. Screen of Dehydrative Conditions for Alcohol Attachment to PyA Scaffold

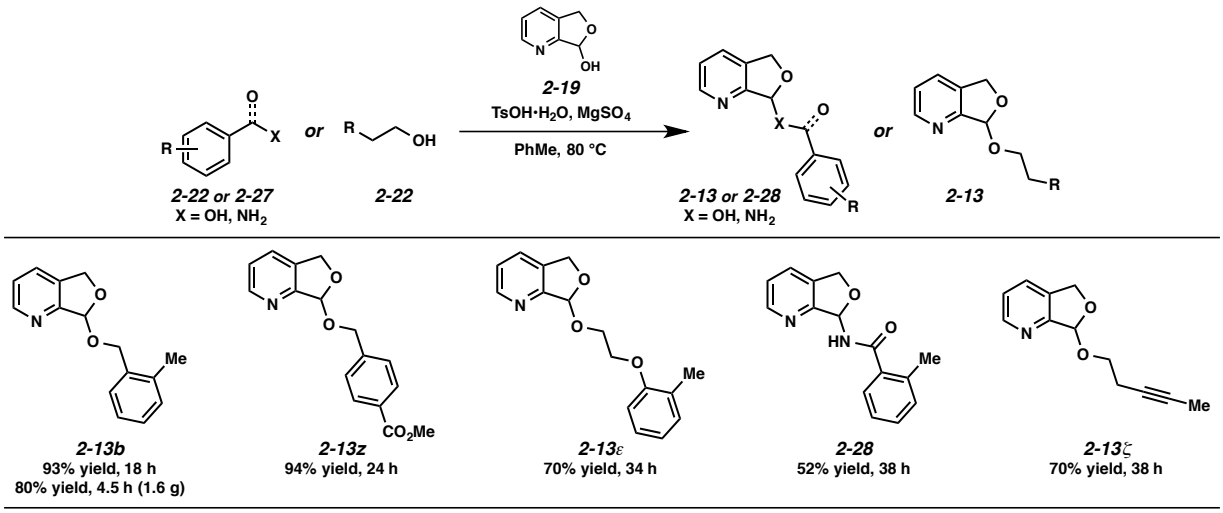


Entry	Conditions	Results
1	DCC, CH_2Cl_2, 0 to 23 °C	product not observed
2	3AMS, 1,4-dioxane, 80 °C	no reaction
3	$(EtO)_2POCl$, Et_3N, CH_2Cl_2, 0 to 23 °C	product observed
4	$ZnCl_2$, PhMe, 80 °C	product not observed
5	$MgSO_4$, TsOH·H_2O, PhMe, 80 °C	product observed (very clean)

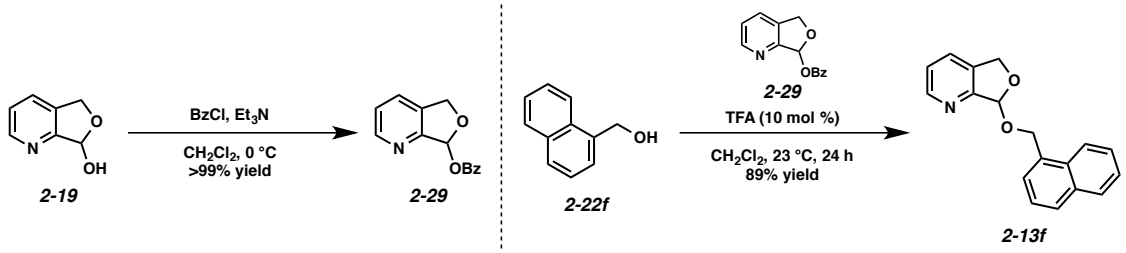
The dehydrative method using $MgSO_4$ and TsOH was general for the attachment of both alcohols and benzamides, affording products in 70-93% yield for the former and 52% yield for the latter (Table 2.4.4). The attachment conditions worked successfully on gram-scale to afford acetal **2-19** in 80% yield.

Additional methods were also investigated for the attachment of alcohols to the PyA scaffold (Scheme 2.4.1). Benzoylated scaffold **2-29** was obtained from hemiacetal **2-19** in quantitative yield, and this was used with catalytic TFA to afford acetal **2-13f** in 89% yield at 23 °C. This benzoylated scaffold readily exchanges and may be useful in transient functionalization.

Table 2.4.4. Dehydrative Method for the Attachment of Alcohols to Hemiacetal **2-19**



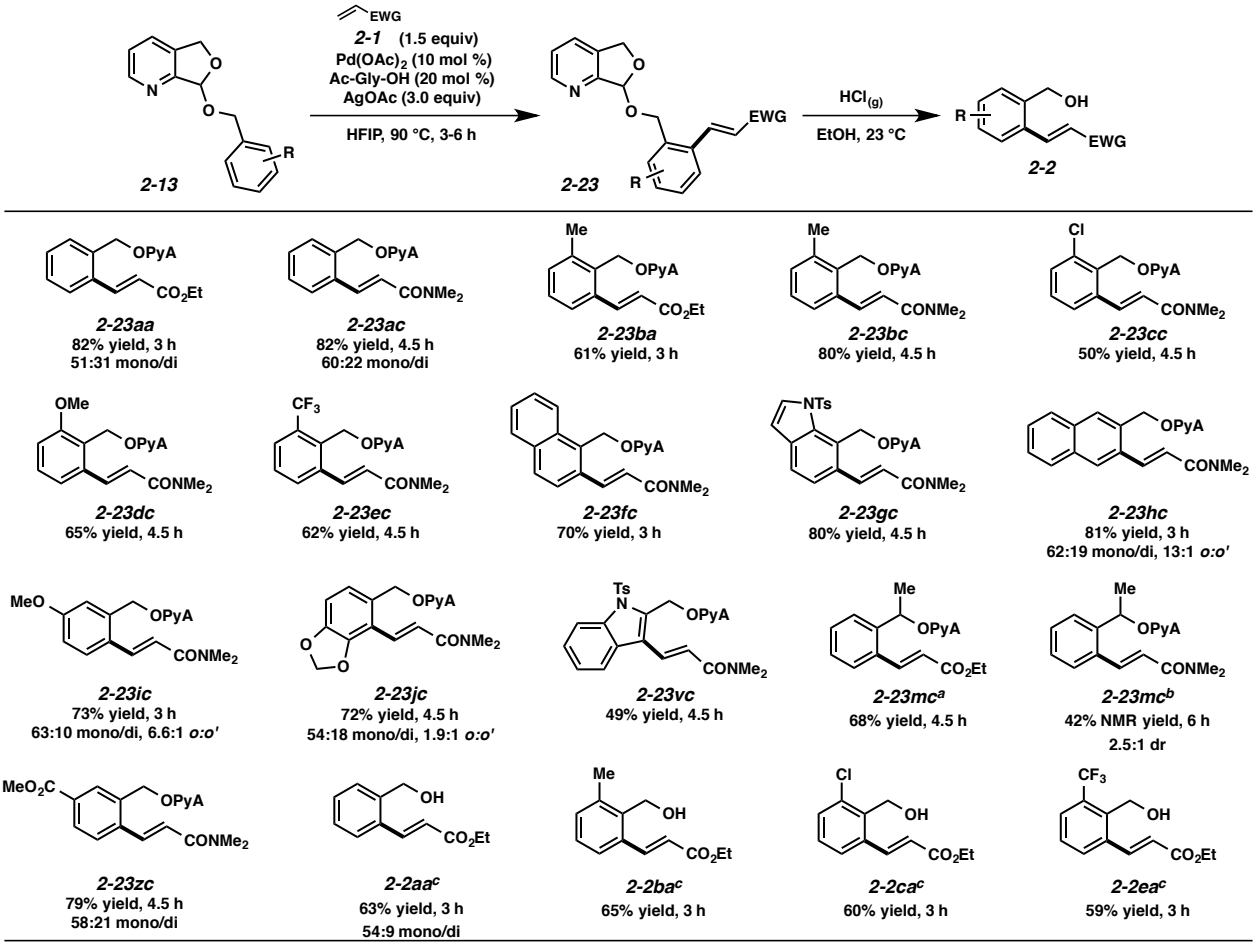
Scheme 2.4.1. Attachment Conditions Implementing PyA-Benzoate **2-29**



A series of attached benzyl alcohols were subjected to the oxidative olefiniation conditions with either ethyl acrylate or *N*,*N*-dimethylacrylamide (Table 2.4.5). In cases where only monoolefination can occur (i.e., *ortho*-substituted arenes), moderate to good yields were observed. Heterocycles could be obtained in good yield (**2-23gc**). When diolefination was possible, approximately 3:1 mixtures were produced. Of these monoolefinated products, products formed with a range of regioselectivities. The factors that influence this selectivity are unclear. The difference between **2-23ic** and **2-23jc**, for example, is notable, and this suggests that subtle influences are governing selectivity. There were no real differences between substrates containing electron-donating and electron-withdrawing groups. Some of the alkenylated products

were treated with ethanolic HCl to afford olefinated alcohols in 2 steps in overall useful yields (**2-2aa-ac** and **2-2ae**).

Table 2.4.5. The Alcohol Scope of PyA Directed Functionalization

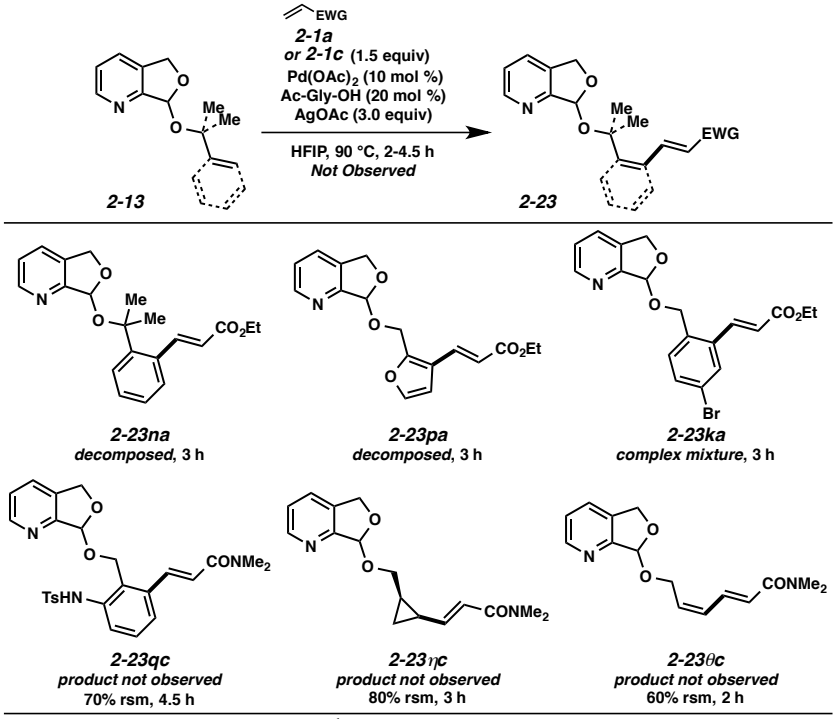


a) The starting material was a single diastereomer (the major diastereomer from the attachment step). b) The starting material was a 1.6:1 mixture of diastereomers. c) After the alkenylation conditions, the unpurified products were subjected to ethanolic $HCl_{(g)}$ at 23 °C.

A few substrates did not generate functionalized products (Table 2.4.6). Although substrates of secondary alcohols afforded alkenylated products, substrates of tertiary alcohols were labile (**2-23na**). Furfuryl acetal also decomposed under the reaction conditions (**2-23pa**). Aryl bromides were not compatible with these conditions (**2-23ka**). This was surprising since the aryl bromides are compatible with similar conditions when alternative directing groups are utilized. Substrate **2-23qc** containing *ortho*-tosylamide did not react. This may form a tridentate

chelate which inhibits functionalization (*vide infra*).[10] Cyclopropane **2-23ηc** and alkene **2-23θc** did not react under these conditions.

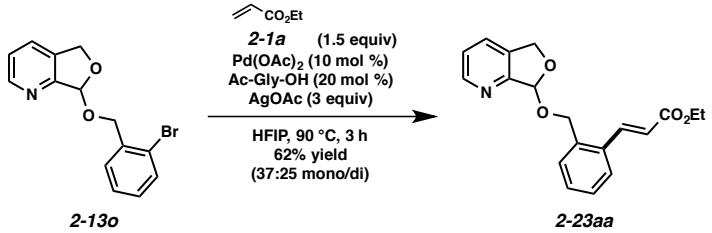
Table 2.4.6. Substrates That Do Not Functionalize Under the Reaction Conditions[a]



a) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

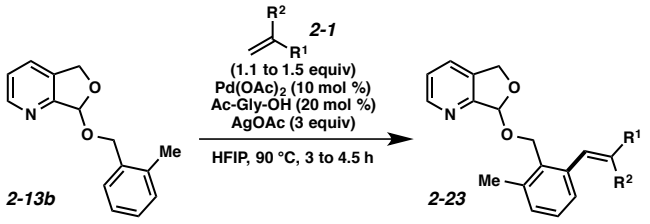
Acetal **2-13o** produced olefin **2-23aa** in 62% yield (37:25 mono/di) under the standard alkenylation conditions (Scheme 2.4.2). The result consists of both a standard and an oxidative Heck reaction. This was a surprise to us since other directed alkenylation reactions using these conditions but different directing groups are typically stable to aryl bromides. It represents an example of how this directing group is unique compared to others that facilitate similar chemistry.

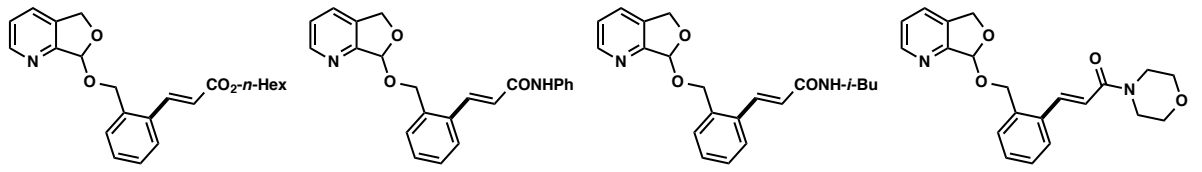
Scheme 2.4.2. Alkenylation of PyA-Containing Aryl Bromide



Alkene coupling partners were evaluated (Table 2.4.7). Other acrylates and acrylamides were effective reactants (**2-23bd-bh**). Electron-deficient styrenes were competent partners; however, more neutral styrenes produced products in diminished yields. Oxazolidinones and phosphine oxides were compatible, but acrylonitrile barely afforded product.

Table 2.4.7. The Olefin Scope of PyA Directed Functionalization



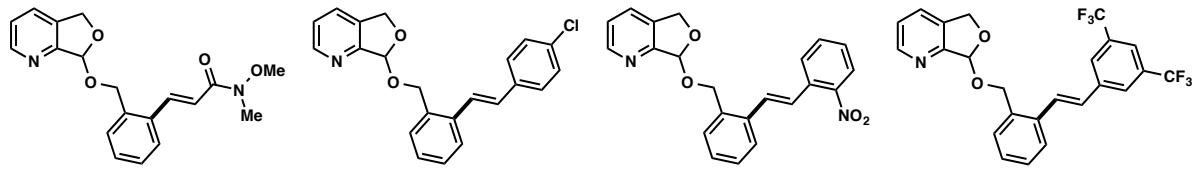


2-23bd
69% yield

2-23be
50% yield

2-23bf
61% yield

2-23bg
83% yield

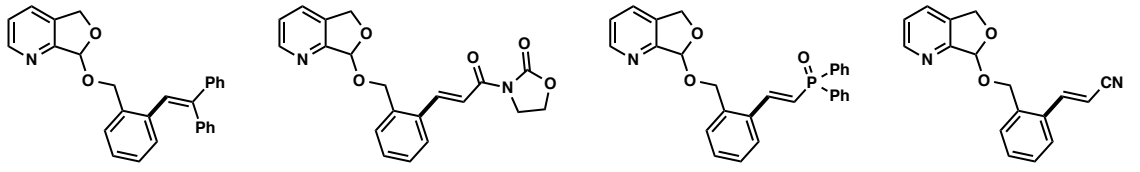


2-23bh
73% yield

2-23bi
40% yield

2-23bj
74% yield

2-23bk
79% yield



2-23bl
27% yield

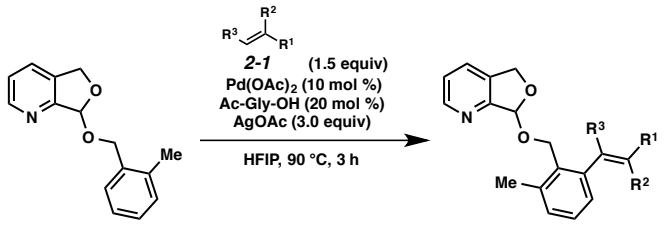
2-23bm
64% yield

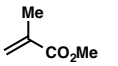
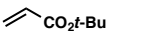
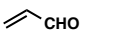
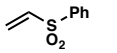
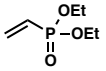
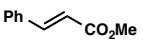
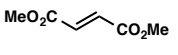
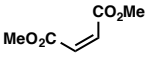
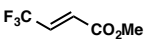
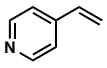
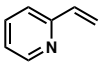
2-23bn
60% yield

2-23bo
10% yield

Unfortunately, many alkene partners did not successfully react (Table 2.4.8). These substrates can be separated into two classes, unclean reactions (i.e., reactions that produced substantial decomposition) and clean reactions (i.e., reactions where the crude NMR contains only acetal **2-13b** and the olefin partner). *t*-Butyl enoates showed diminished yields with substantial decomposition, and methyl methacrylate produced a complex mixture of products. Acroleins, methyl vinyl ketones, vinyl sulfoxides, and vinyl phosphonates did not afford observable products. In contrast, 1,2-disubstituted alkenes and vinyl pyridines were simply unreactive.

Table 2.4.8. Problematic Alkene Coupling Partners for the PyA Directed Functionalization[a]



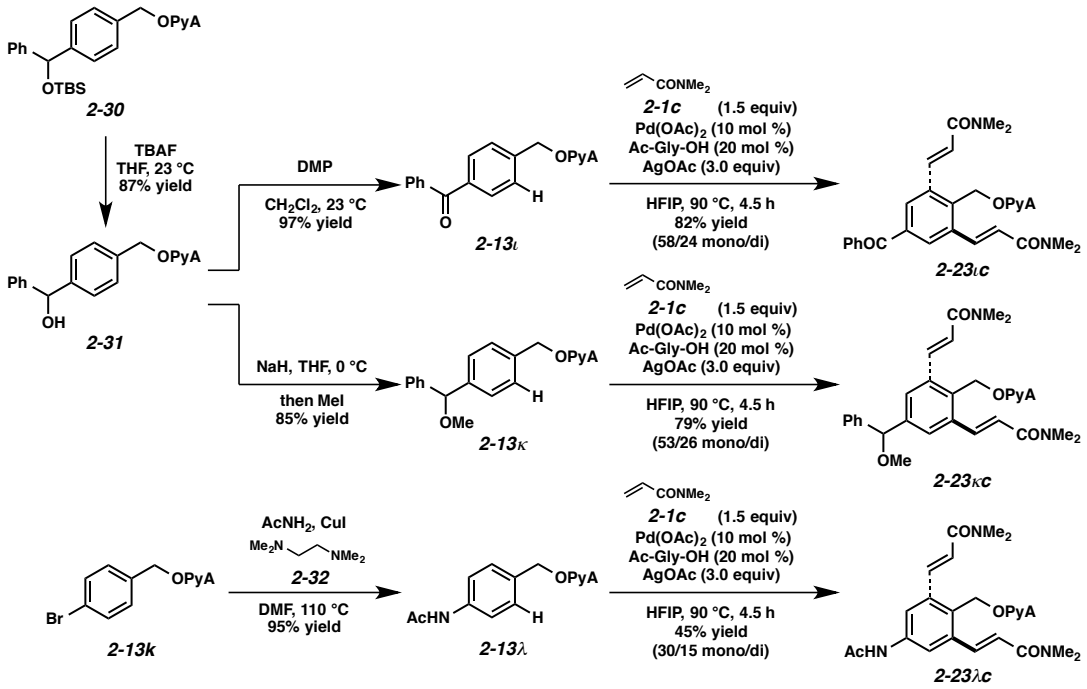
Unclean Reactions					
					
2-1p	***2-1q***	***2-1r***	***2-1s***	***2-1t***	***2-1u***
72% rsm complex mixture	*8% rsm 17% yield*	*51% rsm product not observed*	*0% rsm product not observed*	*63% rsm product not observed*	*93% rsm product not observed*
Clean Reactions					
					
2-1v	***2-1w***	***2-1x***	***2-1y***	***2-1z***	***2-1α***
85% rsm product not observed	*79% rsm product not observed*	*86% rsm product not observed*	*78% rsm product not observed*	*83% rsm product not observed*	*83% rsm product not observed*

a) Yield was determined by ^{1}H NMR analysis of the unpurified reaction mixture using 1-octene as an internal standard.

We were interested in further illustrating the utility of the PyA group. This scaffold can be implemented as a protecting group analogous to other acetal species. Scheme 2.4.3 is illustrative; desilylation, alcohol oxidation, etherification, and copper-catalyzed amidation[11] were effective transformations of PyA-containing substrates. These acetals (**2-13ι**, **2-13κ**, and **2-13λ**) all smoothly afforded olefinated products as one constitutional isomer, albeit in lower yield with

respect to **2-13λ**. Gratifyingly, the ketone, ether, and acetamide are outcompeted by the PyA group despite the former groups ability to direct functionalizations.[12]

Scheme 2.4.3. The Use of the PyA Group as a Protecting Group



In comparison, ketones **2-33** and **2-34** and acetamide **2-36** were subjected to the reaction conditions to illustrate the difference in reactivity when the PyA group was or wasn't present (Scheme 2.4.4). Ketone **2-33** produced a complex mixture of olefinated products; however, ketone **2-34** only functionalized in 22% yield producing a 2:1 mixture of mono/di alkenylated products. Acetamide **2-36** was more reactive, affording 8.6:1 mixture of mono/di alkenylated products in 67% yield. This is suggestive that these directing groups are substantially inhibited in the presence of the PyA group.

Other reactions were investigated to support the claim that the PyA scaffold may be used as a protecting group. Both the bromo and iodo arene substrates **2-13k** and **2-13i** were subjected to lithiation followed by quenching of this species with either electrophile **2-38** or **2-39** (Table 2.4.9). Low yields were obtained through this method, and in all cases, substantial deshalo- and

halo-arenes were isolated. We currently suspect that some degree of substrate deprotonation is a source of the low yields observed.

Scheme 2.4.4. Alkenylations Directed by Other Directing Groups

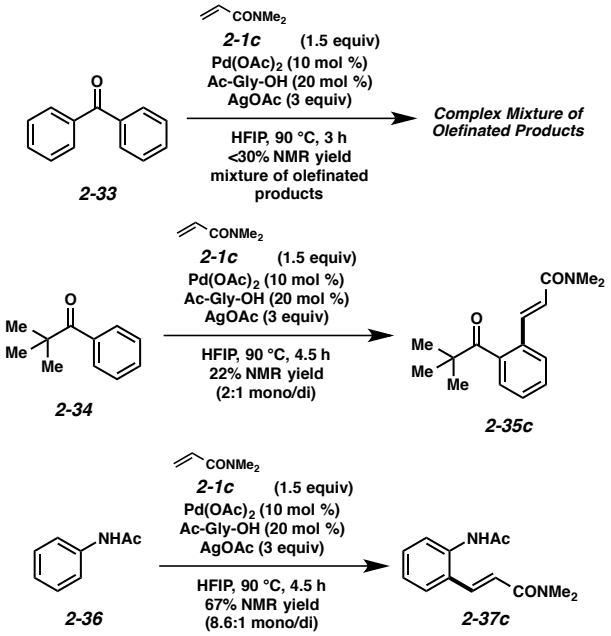
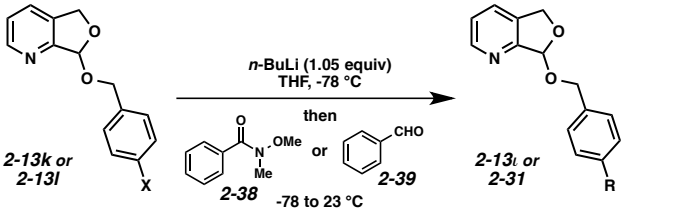
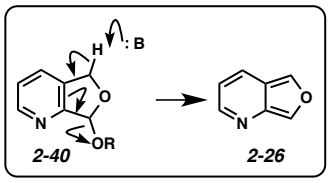


Table 2.4.9. Lithiation and Alkylation Attempts in the Presence of the PyA Group



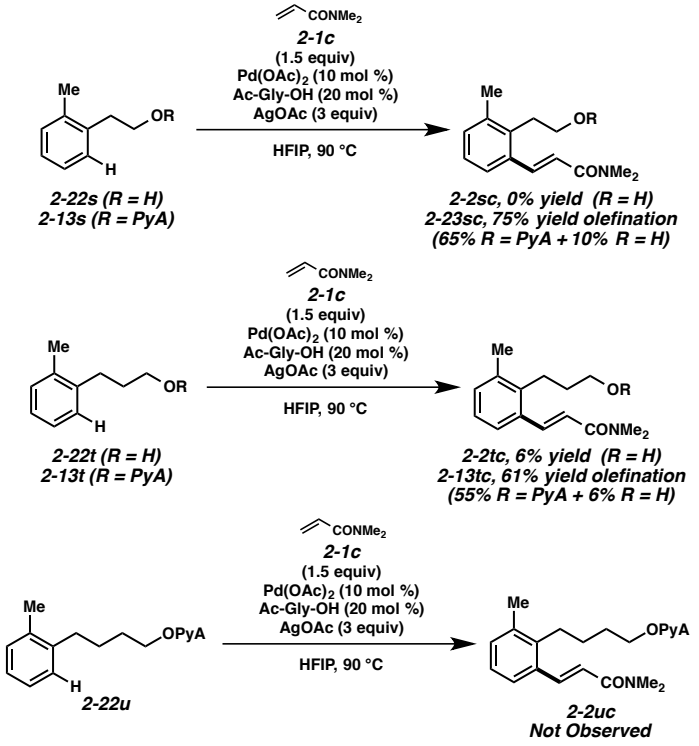
Entry	X	R	Yield
1	Br	CHOHPh *2-31*	37%
2	Br	COPh *2-13ℓ*	47%
3	I	CHOHPh *2-31*	trace



We were interested in increasing the breadth and utility of our alkenylation procedure. We sought to functionalize more remote alcohols (i.e., beyond benzylic alcohols), and these more remote bond-forming events are rare, presumable due to the difficulty in forming larger metallacycles. Both homobenzylic and bishomobenzylic substrates produced alkenylated

products in good yield (**2-23sc** and **2-23tc**, respectfully), although with slight cleavage of the PyA scaffold (Scheme 2.4.5). Unprotected alcohols produced little to no products, comparatively. Tris-homobenzylic alcohol substrate **2-22u** was unreactive showing a limit to the length required for functionalization.

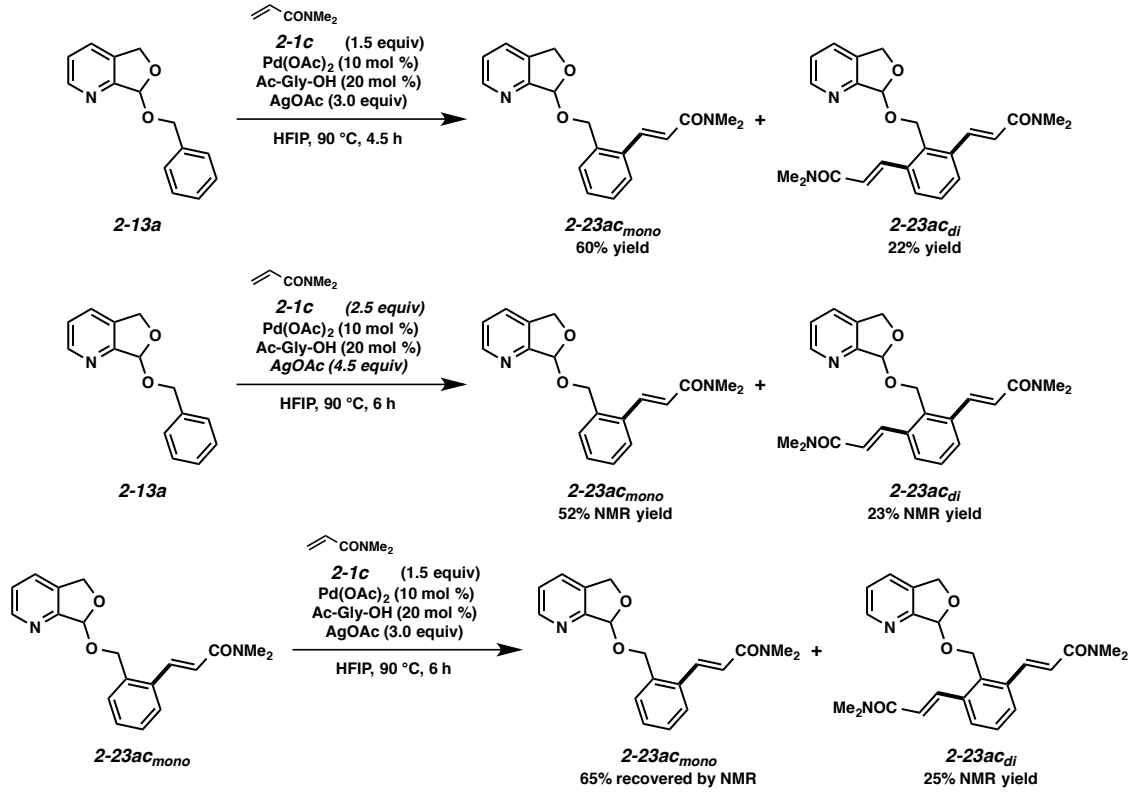
Scheme 2.4.5. Remote Functionalizations Using the PyA-Acetal



We became interested in encouraging the diolefinated products. The standard alkenylation of acetal **2-13a** produced the monoolefinated product in 60% yield and the diolefinated product in 22% yield (Scheme 2.4.6). Increasing the amount of alkene coupling partner (2.5 equiv) and the equivalents of AgOAc (4.5 equiv) produced a modest decrease in the monoolefinated acetal and a marginal increase in the diolefinated acetal. Subjecting the monoolefin **2-23ac** to the alkenylation conditions showed marginal decomposition and generated marginally more diolefinated product compared to the other two conditions. This is suggestive of

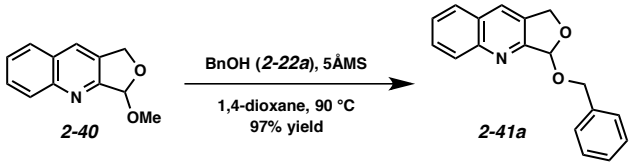
substrate inhibition, and may be due to the alkene acting as a ligand on palladium and plausibly forming a tridentate chelate (*vide infra*).[10]

Scheme 2.4.6. Conditions to Optimize the Diolefinated Product



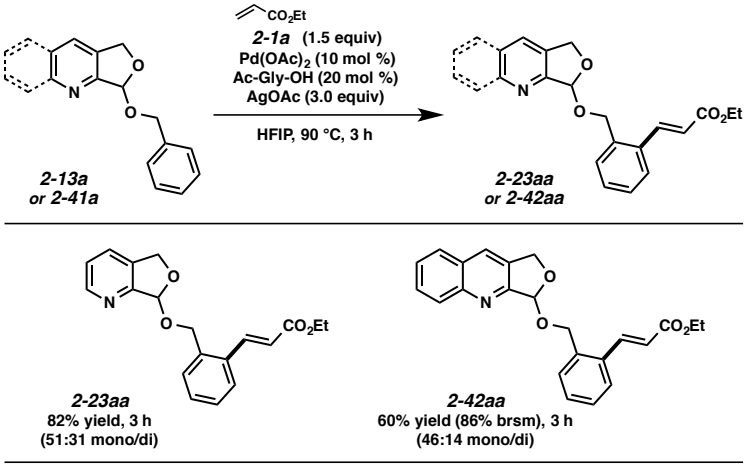
An alternative **Qu**inoline **A**cetal (**QuA**) scaffold was developed.[13] This was attached through the 5Å molecular sieves method to generate benzyl acetal **2-41a** in 97% yield (Scheme 2.4.7).

Scheme 2.4.7. Synthesis of Quinoline Acetal **2-41a**



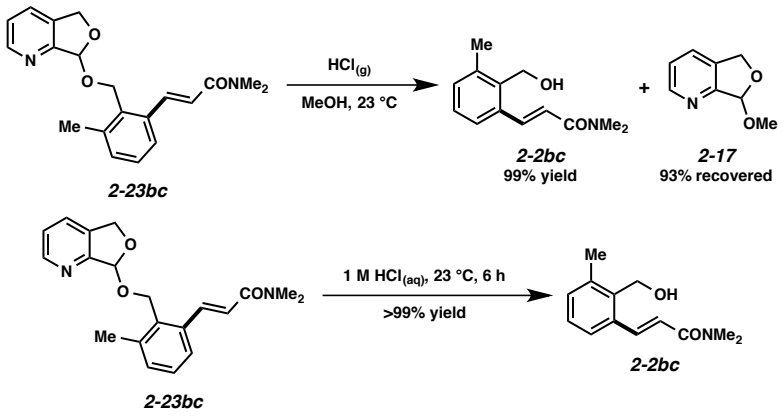
The PyA and the QuA scaffold were compared under the alkenylation conditions (Table 2.4.10). The functionalization using the QuA group was less reactive than the PyA group, although it afforded a higher mono/di ratio.

Table 2.4.10. Comparison of the PyA and QuA Group

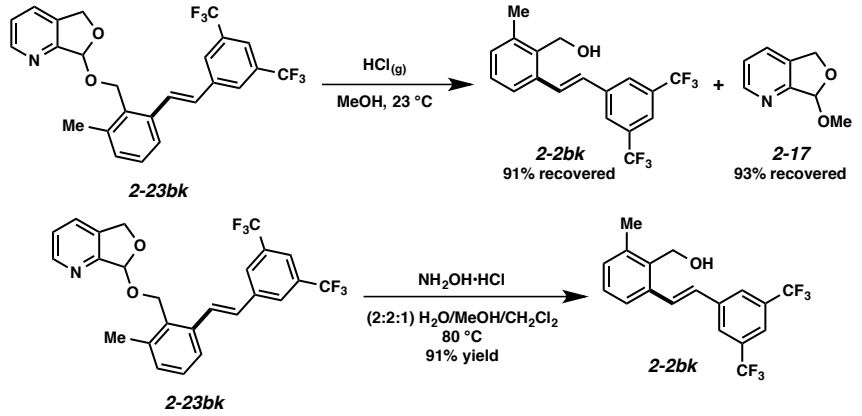


Both acrylamide **2-23bc** and styrene **2-23bk** could be cleaved with gaseous HCl in methanol to afford the cleaved products in excellent yields with high recovery of the PyA scaffold (Scheme 2.4.8 and Scheme 2.4.9). Alternatively, the scaffold could be removed with aqueous HCl in quantitative yield. The PyA group could also be cleaved from the styrene substrate with hydroxylamine hydrochloride in great yield. These latter two methods, however, do not allow for the recovery of the scaffold.

Scheme 2.4.8. Cleavage Conditions of the PyA-Scaffold from Olefin **2-23bc**



Scheme 2.4.9. Cleavage Conditions of the PyA-Scaffold from Olefin **2-23bk**

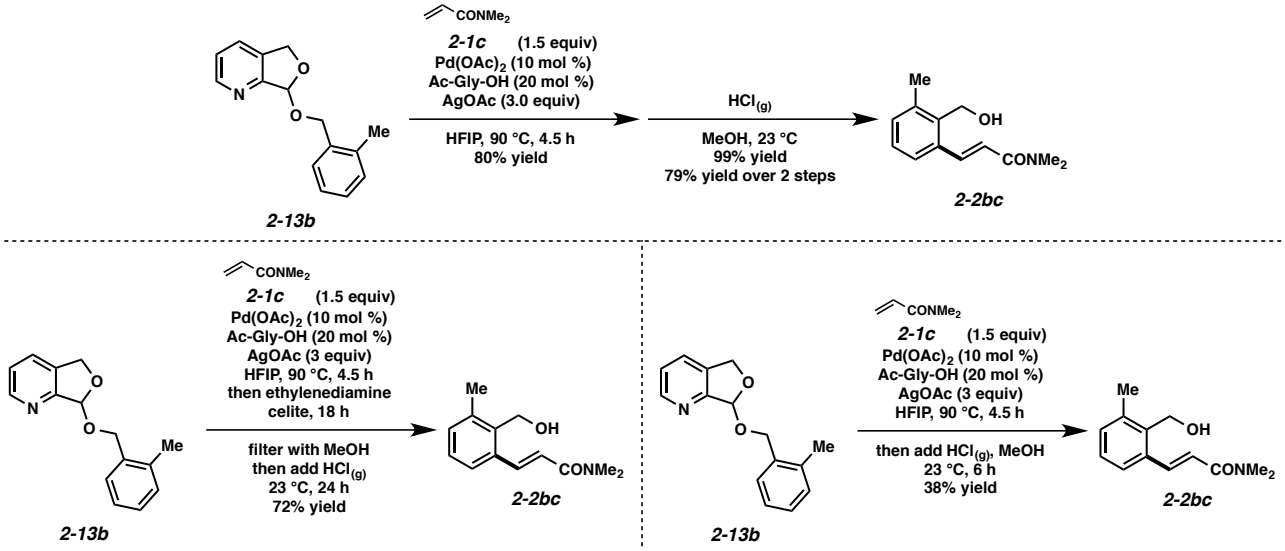


2.5. Telescoping and Transient Experiments

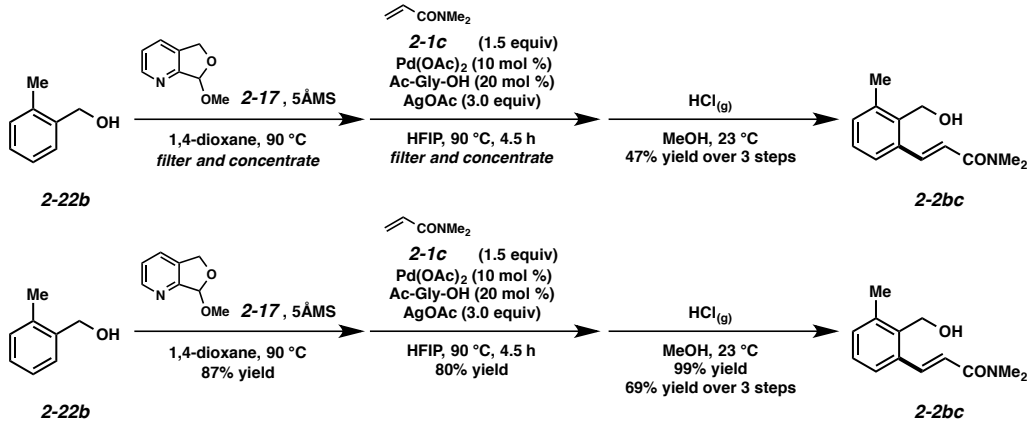
We were interested in converting this basic traceless directing group procedure toward a streamlined procedure for the alkenylation of benzyl alcohols (Scheme 2.5.1). Using the standard alkenylation conditions followed by intermediate purification and then cleavage affords the functionalized alcohol in 79% yield over 2 steps. If the alkenylation reaction is subjected to the standard work-up procedure, filtratered, and then subjected to methanolic HCl, then the yield is only moderately decreased (72% instead of 79% yield). Consequently, if methanolic HCl is added to the alkenylation reaction mixture upon completion, the yield of the functionalized alcohol drops to 38%.

With the knowledge that that the alkenylation step had to include a filtration between it and the cleavage step, we started to investigate a procedure that would consist of 3 steps and only 1 purification (Scheme 2.5.2). This telescoping procedure toward alcohol **2-2bc** included intermediate filtration and concentration between the first two steps prior to cleavage of the PyA group, and the overall yield of alcohol **2-2bc** was 47%. In comparison, the 3-step sequence produces this alcohol in 69% yield.

Scheme 2.5.1. Comparison of 2 Step Procedures from Acetal **2-13b** to Olefin **2-2bc**

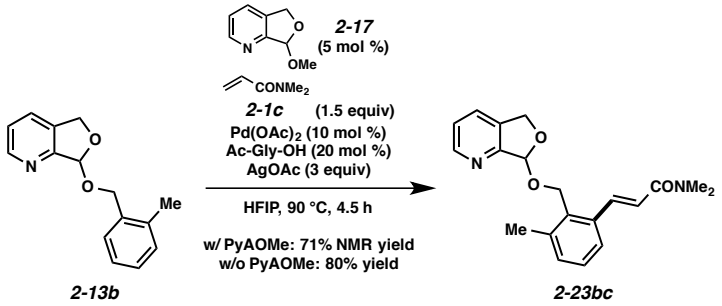


Scheme 2.5.2. Comparison of 3 Step Procedures to afford Olefin **2-2bc** Using Acetal **2-17**



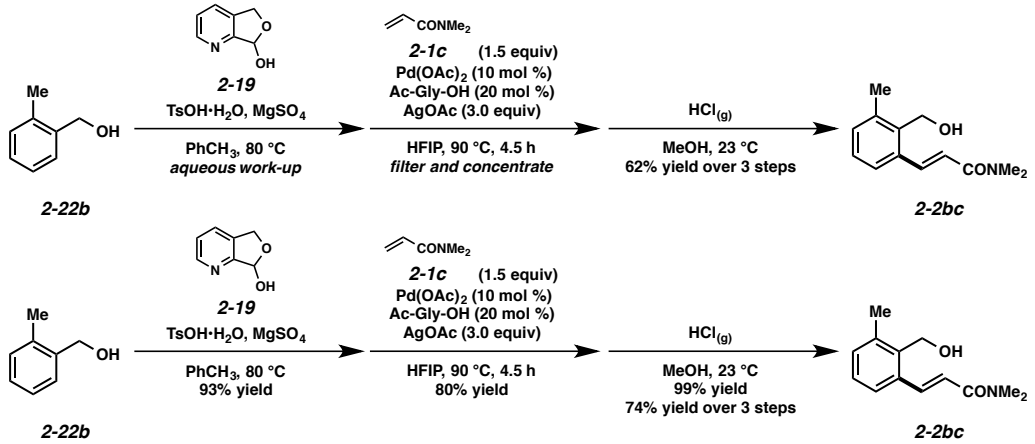
To address this discrepancy in yield, we compared the difference between functionalizing with pure acetal **2-13b** compared to a mixture of this acetal doped with 5% methyl acetal **2-17** (Scheme 2.5.3). The yield decreased when this additive was present in the functionalization. This was informative since the post-attachment mixture often contained <10% of both alcohol **2-22b** and acetal **2-17**. This convinced us that we should investigate a separate attachment strategy to successfully implement a telescoping procedure.

Scheme 2.5.3. Alkenylation of Acetal **2-13b** Containing Trace Amounts of Acetal **2-17**



Since hemiacetal **2-19** is water-soluble and therefore can be removed by a simple aqueous workup, the dehydrative conditions looked optimistic. We performed a telescoping procedure implementing the hemiacetal (Scheme 2.5.4). Attaching the PyA group to alcohol **2-22b** through hemiacetal **2-19** followed by an aqueous workup, functionalizing and filtering, and then methanolic HCl to detach the scaffold afforded alcohol **2-2bc** in 62% yield over 3-telescoped steps. The analogous 3-step procedure with 3 purifications afforded the product in 74% yield. Although the multiple purification procedure is overall better, this represents an attempt to streamline our traceless directed functionalization.

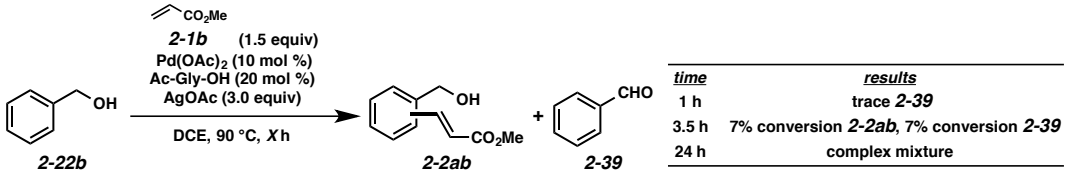
Scheme 2.5.4. Comparison of 3 Step Procedures to afford Olefin **2-2bc** Using Acetal **2-19**



We briefly investigated if this alkenylation could be expanded toward transient functionalization. We were curious if benzyl alcohol (**2-22b**) was stable to the functionalization

conditions long enough for alkenylation to occur (Scheme 2.5.5). The alcohol was stable under these conditions for 1 h with only trace formation of benzaldehyde (**2-39**). At 3.5 h, both olefinated alcohol **2-2ab** and benzaldehyde **2-39** were observed in 7% yield. At 24 h, a complex mixture was observed. We suspected that a sufficiently fast functionalization reaction could outpace decomposition, which would open the possibility for transient functionalization. This is predicated that functionalization does not generate intermediates that increase decomposition (e.g., generation of acetic acid).

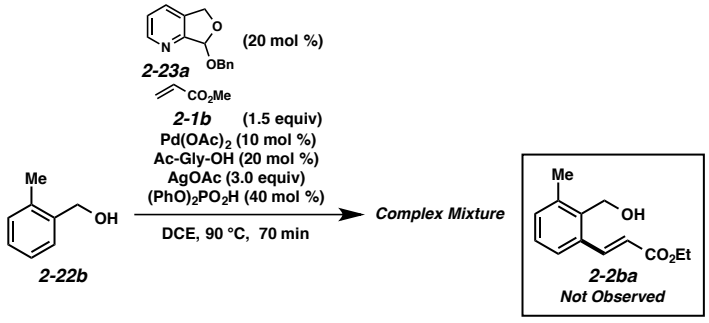
Scheme 2.5.5. Alkenylation of Benzyl Alcohol



time	results
1 h	trace *2-39*
3.5 h	7% conversion *2-2ab*, 7% conversion *2-39*
24 h	complex mixture

We performed one experiment to directly investigate transient functionalization (Scheme 2.5.6). Subjecting alcohol **2-22b** to the standard functionalization conditions in DCE with catalytic scaffold **2-23a** and diphenyl phosphoric acid did not generate alcohol **2-2ba** and instead produced a complex mixture. The alkenylation conditions we have evaluated thus far do not seem to be compatible with transient functionalization.

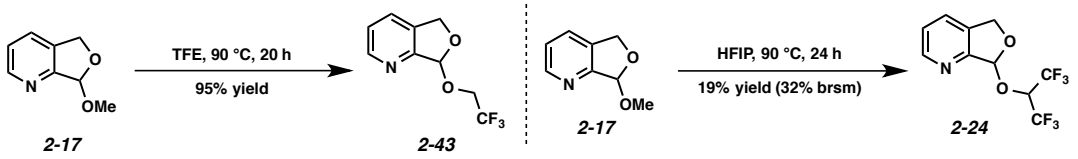
Scheme 2.5.6. Attempt to Implement the PyA-Scaffold in Transient Functionalization



Although these alkenylation conditions are likely incompatible with transient functionalization, we suspect that the discovery of new reactions may be more successful in

synchronizing these two ideas. Many functionalization reactions are uniquely facilitated by fluorinated solvents (*vide infra*), and much like in our alkenylation conditions, these solvents may be necessary for achieving reactivity. It is therefore plausible that conditions will be discovered that implement either TFE or HFIP. Advantageously, both of these solvents facilitate exchange without the use of additives (Scheme 2.5.7); however, TFE exchanges with high scaffold structural fidelity (**2-17**→**2-43**) while HFIP decomposes this scaffold over time (**2-17**→**2-24**).

Scheme 2.5.7. TFE and HFIP Exchange of Acetal **2-17**

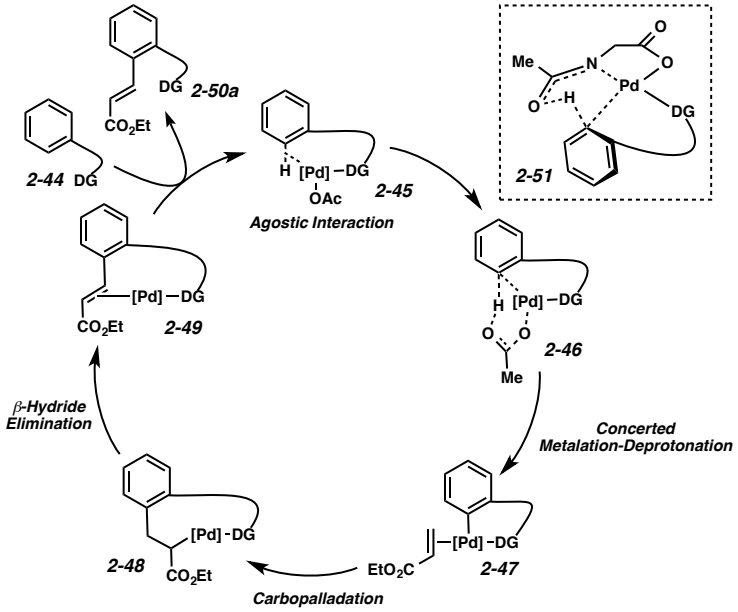


2.6. Alkenylation Mechanism

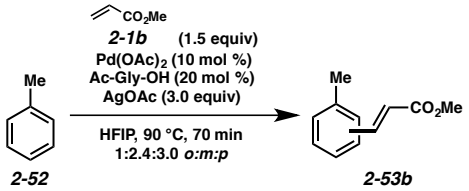
The generally accepted mechanism of directed alkenylation under these conditions is as follows (Figure 2.6.1). The directing group-containing substrate **2-44** coordinates palladium. An internal acetate facilitates a concerted metalation-deprotonation (**2-46**). Carbopalladation, β-hydride elimination, and substrate decomplexation releases the olefinated products. When mono-protected amino acids (e.g., Ac-Gly-OH) are utilized, it has been calculated that the ligand is both bidentate and facilitates a concerted metalation-deprotonation (**2-51**).[8]

Throughout our investigation in the PyA directed alkenylation, we observed only ortho functionalization. The reaction conditions, however, are not site-selective in the absence of a directing group. Toluene, instead of a PyA-containing substrate, was subjected to the conditions to afford a mixture of olefinated products (Scheme 2.6.1).

Figure 2.6.1. The Generally Accepted Alkenylation Mechanism Under Our Conditions



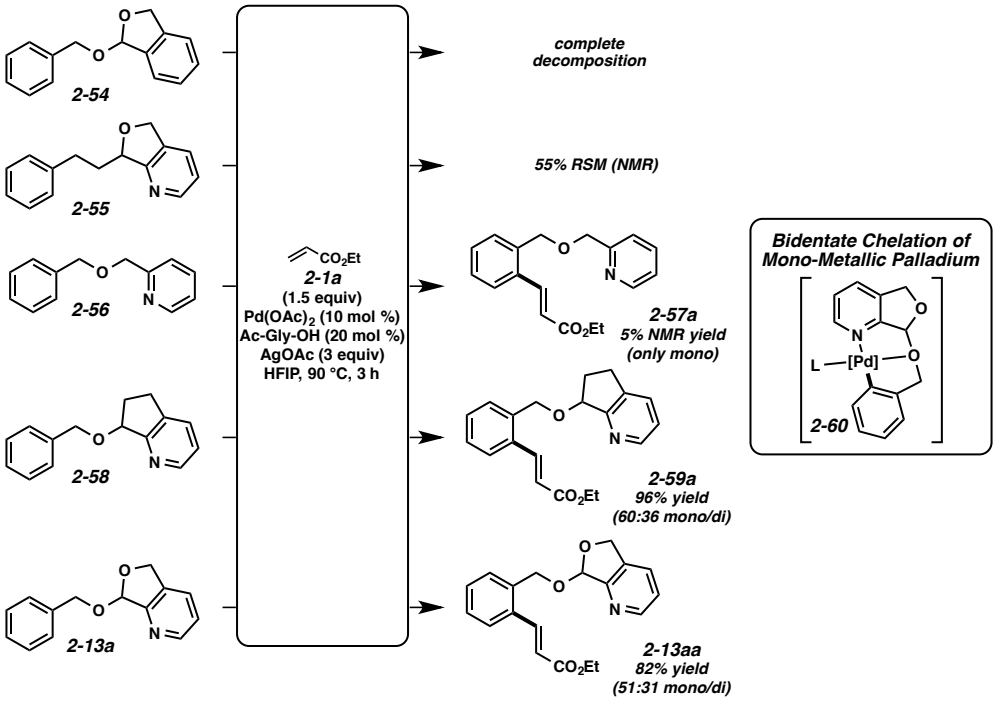
Scheme 2.6.1. Alkenylation of Toluene



The nature of the directing group merits further discussion. We were curious as to which structural components of the scaffold impart reactivity. Structural variants were revealing (Scheme 2.6.2). Acetal **2-54** completely decomposed under the reaction conditions. The sensitivity of this substrate is notably higher than the acetals in Table 2.1.1 (MOM and MEM acetals). Pyridine **2-55** was completely unreactive. Pyridyl ether **2-56**, which lacks the furan ring, afforded minimal product. Informatively, ether **2-58**, containing a cyclopentane ring, restored high reactivity. In fact, this substrate was the most reactive of any substrates subjected to the reaction conditions. The PyA-containing acetal (**2-13a**) afforded a lower yield, possible due to some exchange of alcohols on the acetal. A few conclusions can be drawn from these experiments. It is plausible that the pyridine buffers the substrate from the acidic conditions

inhibiting decomposition through acetal ionization. Bidentate chelation of the nitrogen and oxygen are likely important at some point in the overall reaction.[14] The fused ring system reduces the conformational degrees of freedom, presumably encouraging a proximal relationship between the metal and the C–H bond. Lastly, the acetal is not needed to impart reactivity and only facilitates attachment and cleavage. This data supports the probable cyclometalated species **2-60** that likely undergoes bidentate chelation.

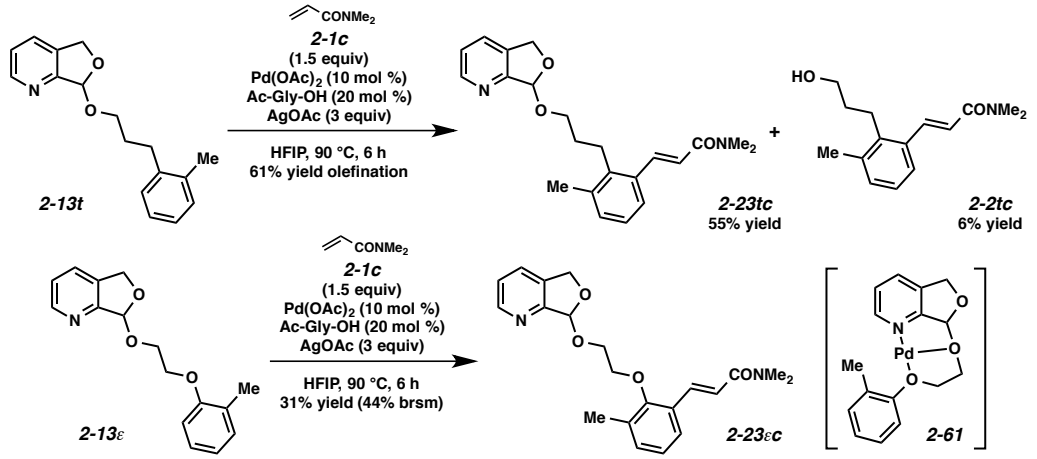
Scheme 2.6.2. Alkenylations of Structural Variants



To further investigate the plausibility of bidentate metallacycle **2-60**, we analyzed substrates capable of tridentate chelation (Scheme 2.6.3). We compared bis-homobenzylic acetal **2-13t** with analogous acetal **2-13ε**, and the latter was substantially less reactive. This could be inhibited by the formation of tridentate chelate **2-61**. This additional chelation may explain the lack of reactivity for the *ortho*-sulfonamide-containing acetal **2-13q** (Table 2.4.6) and the product inhibition observed by diolefinated products (Scheme 2.4.5).

There are some inconsistent data to the bidentate chelate (**2-60**) model. It's been calculated that mono-protected amino acids, such as Ac-Gly-OH, require two sites on palladium during C–H bond breaking. Additionally, the C–H bond and the directing group require two sites. Palladium would have too many points of coordination if the PyA group requires an additional site. This, however, could be explained if bimetallic species were operative. Houk has investigated C–H bond breaking facilitated through PdPd and PdAg bimetallic species, which may instead be operable.[6]

Scheme 2.6.3. Remote Alkenylation of Structural Variants

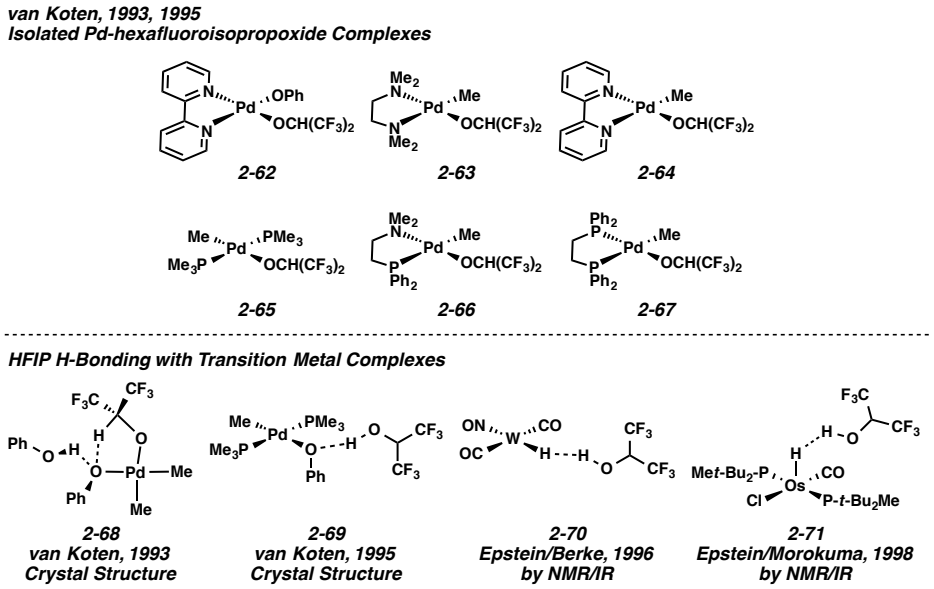


The dramatic increase in reactivity observed when the reaction is performed in HFIP is highly curious. This solvent is uniquely competent at facilitating C–H functionalization.[2,15] It is known that HFIP, TFE, and TFA as well as other perfluorinated solvents are highly ionizing and are poor nucleophiles.[16] HFIP has been shown to enhance the rate of numerous reactions such as hydrogenations of benzenes,[17] sulfoxide oxidation,[18] epoxide openings,[19] and imino [4+2] cycloadditions.[20] It facilitates hydrolysis of difficult substrates, such as those containing 1-adamantyl–, (9-methyl)-9-norbornyl–, and *tert*-butyl–substitution.[16, 21] Acidity and H-bond donation are the most common arguments for the reactivity enhancement and rate acceleration observed. Legros has attempted to delineate the individual contributions (i.e., acidity, H-bonding,

or some possible promoter effect) relative to HFIP and other fluorinated solvents.[22] Unsurprisingly, calculations suggest that HFIP is highly electron-deficient with relatively little charge on oxygen; however, this study did suggest that the oxygen of HFIP might be more electron-deficient than that of nonafluoro-*tert*-butanol.[23]

There have been a number of studies that may add insight into HFIP's enhancement of Pd catalyzed C–H functionalization. It is commonly used as the reaction solvent, and Tan reported its use as an additive for *meta*-directed alkenylations (Scheme 1.2.5). This is particularly curious and may suggest that, when used as an additive, it may encourage the reaction through a second coordination sphere stabilization mode compared to outer sphere bulk solvolysis stabilization. Numerous complexes have been isolated with a hexafluoroisopropoxide ligand (**2-62–2-67**) (Figure 2.6.1). Their exchange equilibrium with phenoxide ligands has been observed, and they are all stable to β-hydride elimination.[24] X-ray crystal structures[24] and spectroscopic data[25] have identified strong H-bonding effects (**2-68–2-71**). Most notably is the intramolecular H–bond observed in complex **2-68** where the electron-deficient C–H bond of the hexafluoroisopropoxide ligand bonds to an internal ligand. This is proposed by van Koten to represent the initial stage of base-assisted β-hydride elimination, but this second coordination sphere H-bonding could be relevant to HFIP's unique capacity to facilitate C–H functionalization reactions. It is currently unclear why HFIP dramatically accelerates the C–H functionalization in Pd^{0}-Pd^{II} systems, but these studies are likely informative of the relevant transition states.

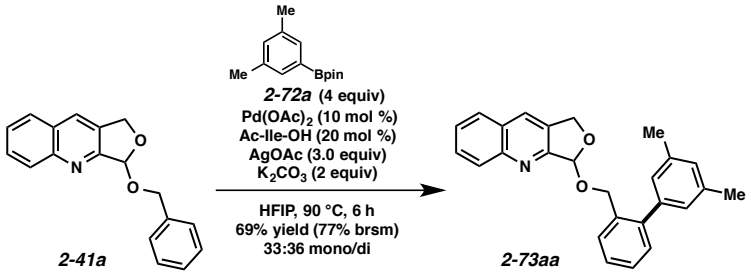
Figure 2.6.2. Complexes that Contain Hexafluoroisopropanol or Hexafluoroisopropoxide



2.7. Other Functionalization Attempts

We have investigated other functionalization reactions utilizing our PyA and QuA scaffolds. Yu reported the *meta*-selective arylation of benzyl ethers.[26] Utilizing similar conditions, Dr. Qiankun Li has explored arylations with our scaffolds. The PyA-substrates were not as active, but switching to QuA-acetal **2-41a** afforded the arylated product in good yield (Scheme 2.7.1).

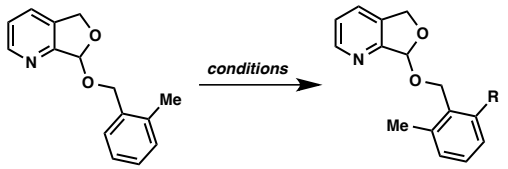
Scheme 2.7.1. QuA-Scaffold Directed Arylation



We have attempted to discover new reactivity with this PyA directing group, and have been interested in expanding from sp^2 to sp^3 C–H functionalization. The first step to obtaining

this reactivity with palladium is to observe reactivity through conditions that favor a Pd^{II}-Pd^{IV} cycle. We pursued the arylation conditions with acetal **2-13b** (Table 2.7.1). Conditions that implement $Pd(OAc)_2$ and either iodobenzene or iodonium salts failed to afford any product. Additionally, acetoxylation conditions were equally unsuccessful.

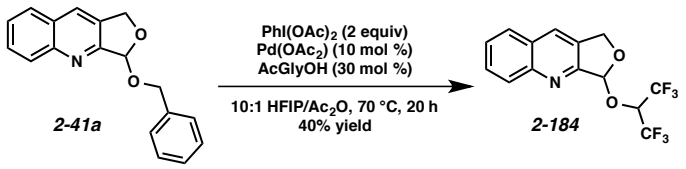
Table 2.7.1. Failed Arylation and Acetoxylation Attempts of Acetal **2-13b**



Entry	Conditions	Results
1	PhI (1.5 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (3 equiv), DCE, 90 °C	R = Ph, product not observed
2	Ph_2IBF_4 (1.5 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (3 equiv), DCE, 90 °C	R = Ph, product not observed
3	$PhI(OAc)_2$ (2 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (30 mol %), 10:1 DCE/Ac_2O	R = OAc, product not observed

The increase in reactivity we observed between the PyA and QuA groups in the oxidative Suzuki reaction (Scheme 2.7.1) compelled us to investigate the QuA group for other transformations. We subjected acetal **2-41a** to the same acetoxylation conditions that were implemented in Table 2.7.1. Instead of observing the desired functionalization, we isolated the HFIP-acetal **2-184** in 40% yield (Scheme 2.7.2).

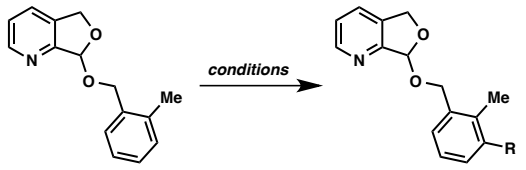
Scheme 2.7.2. Attempted QuA-Scaffold Directed Acetoxylation



Other pyridine-directed reactions were performed in the attempt to discover new reactivity. Utilizing conditions developed by Larrosa and Ackermann for the directed tosylation and alkylation of arenes,[27] we were unsuccessful in directing functionalization (Table 2.7.2). Our alkenylation and arylation conditions are the only ones that have produced reactivity, and

diverging from these conditions with different metal catalysts, oxidants, or coupling partners has not yet been fruitful.

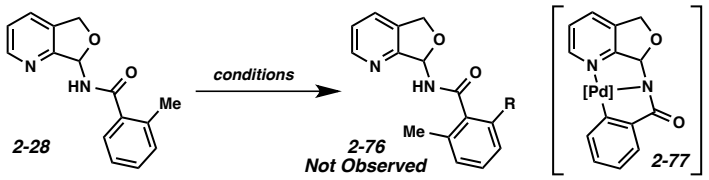
Table 2.7.2. Failed *meta*-Functionalization Attempts of Acetal **2-13b**



Entry	Conditions	Results
1	[Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), K_2CO_3, TsCl, MeCN, 100 °C	R = Ts, product not observed
2	[Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $MesCO_2H$ (30 mol %), K_2CO_3, *c*-HexI, HFIP, 100 °C	R = *c*-Hex, product not observed
3	[Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $MesCO_2H$ (30 mol %), K_2CO_3, *c*-HexI, 1,4-dioxane, 100 °C	R = *c*-Hex, product not observed

We suspected that modification of the substrate would impart new reactivity. By attaching benzamides to the scaffold, it was hypothesized that an L,X-type ligated species would be capable of functionalization similar to chemistry developed by Daugulis (Table 2.7.3, metallacycle **2-77**).[28] Unfortunately, this reactivity was not observed under a range of conditions.

Table 2.7.3. Failed Functionalizations of Benzamide **2-28**



Entry	Conditions	Results
1	PhI (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (1.0 equiv), *t*-BuOH, 90 °C, 20 h	R = Ph, *product not observed*
2	PhI (1.5 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (1.0 equiv), HFIP, 90 °C, 3 h	R = Ph, *product not observed*
3	benzoxazole (2 equiv), $Cu(OAc)_2$ (10 mol %), xylenes, 130 °C, 3 h	R = (2-benzoxazolyl), *decomposed*
4	PhBr (1.2 equiv), $RuCl_2$(*p*-cymene) (5 mol %), PPh_3 (40 mol %), Na_2CO_3 (2 equiv), PhMe, 130 °C, 3 h	R = Ph, *product not observed*
5	BuBr (2 equiv), $NiCl_2(PPh_3)_2$ (10 mol %), AgOTf (20 mol %), Na_2CO_3 (2 equiv), Ag_2CO_3, PhMe, 130 °C, 3 h	R = Bu, *product not observed*

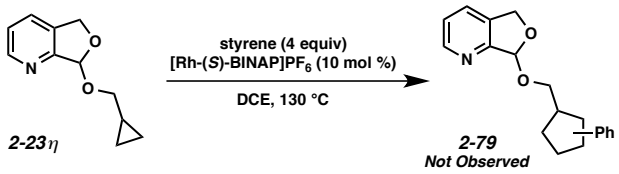
Expanding the available reactions directed by the PyA group to include sp^3 C–H bonds would dramatically enhance its utility. Acidifying the sp^3 C–H bond would assist in the concerted metalation-deprotonation event. Acetal **2-43**, containing an adjacent CF_3 group, would provide the necessary acidification; however, arylation with $Pd(OAc)_2$, AgOAc, and PhI did not produce the desired product (Scheme 2.7.3).

Scheme 2.7.3. Attempted PyA-Scaffold Directed Arylation



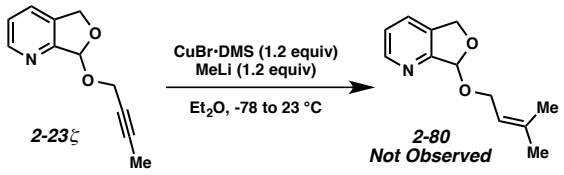
At this point, we were interested in moving toward C–C bond functionalization reactions. These conditions often use rhodium catalysts and are often unencumbered in the presence of acid catalysts. This would be compatible with our ultimate goal of transient functionalization. All of the transient functionalization conditions reported in Chapter 1 use rhodium, and the stability to acid could allow for acetal exchange. To initiate this investigation, cyclopropane **2-23η** was subjected to numerous rhodium catalysts, but the desired reactivity has yet to be observed (Scheme 2.7.4). We suspect that activating the cyclopropane or an analogous cyclobutane as cyclopropanones or cyclobutanones may foster this reactivity.

Scheme 2.7.4. Attempted PyA-Scaffold Directed C–C Functionalization



In an attempt to diverge from bond functionalization reactivity toward the directed activation of a functional group, we subjected acetal **2-23ζ** to a copper-mediated nucleophilic addition into alkynes (Scheme 2.7.5). Alkene **2-80** was not observed, but further investigation into this type of chemistry may produce interesting new transformations.

Scheme 2.7.5. Attempted PyA-Scaffold Directed Alkyne Functionalization



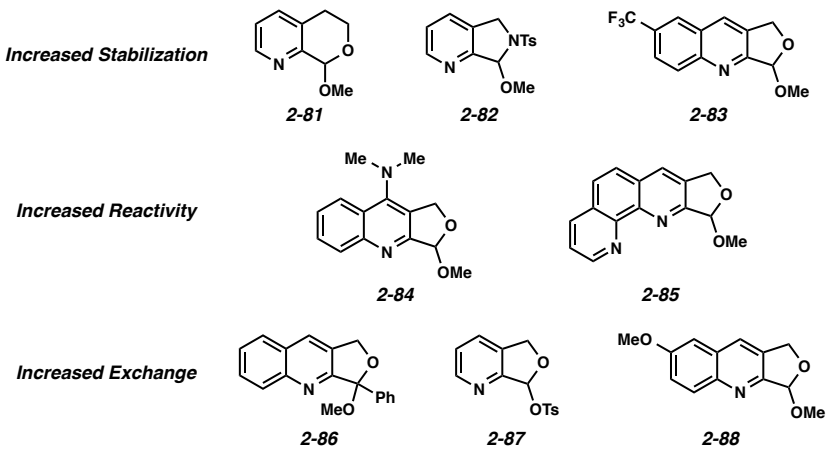
Unfortunately, this section does not illustrate many new reactions directed by the PyA group; however, further investigation into both substrate and condition modifications will likely produce additional examples.

2.8. Scaffold Diversification

The future direction of this project may stem from the development of new scaffold derivatives as much as new reaction conditions. Modification of both our PyA and QuA scaffolds will be crucial in the optimization of new reactions and in the development of a transient C–H functionalization catalyst/ligand. The purpose of this section is to discuss some of the routes and intermediates that could be useful in the development of these future scaffolds.

The three scaffold properties we are interested in encouraging are (1) stabilizing the scaffold from unwanted alcohol exchange and decomposition, (2) enhancing the functionalization reactivity, and (3) encouraging exchange of alcohols for transient catalysis (Figure 2.8.1). Scaffold **2-81** may be less likely to undergo decomposition upon ionization due to its decreased capacity to become aromatic. Aminal **2-82** and acetal **2-83** will likely discourage exchange by destabilizing the resulting carbocation. Increased and new reactivity may be discovered by making these scaffolds more electron-rich (**2-84**) or by converting these quinolines to phenanthrolines (**2-85**). Enhancing exchange can be encouraged by either stabilizing the oxocarbenium by making it both secondary and benzylic (**2-86**) or making the arene more electron-rich (**2-88**). Additionally, making the leaving group more active (**2-87**) could produce more actively exchanging scaffolds.

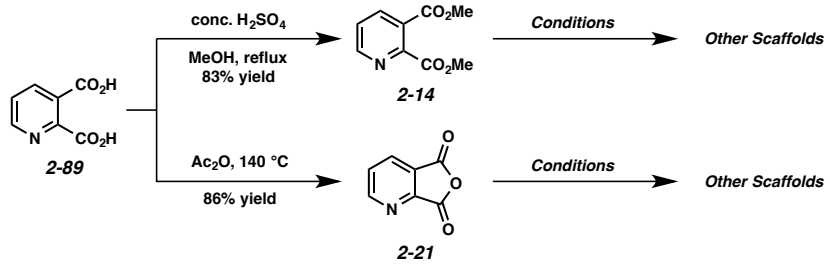
Figure 2.8.1. Potential Scaffolds for Future Functionalization Reactivity Studies



Any discussion on the derivatization of pyridine substrates would be incomplete without referencing Baran's book on the synthesis of heterocycles, The Portable Chemist.[29] This document clearly illustrates how to make bond disconnections or functional group installations on pyridines, and effectively ranks a method's likely success. In addition to this book, Nakao has written a useful review on the diversification of pyridine substrates.[30] Both of these two references should be consulted before any scaffold synthesis is attempted.

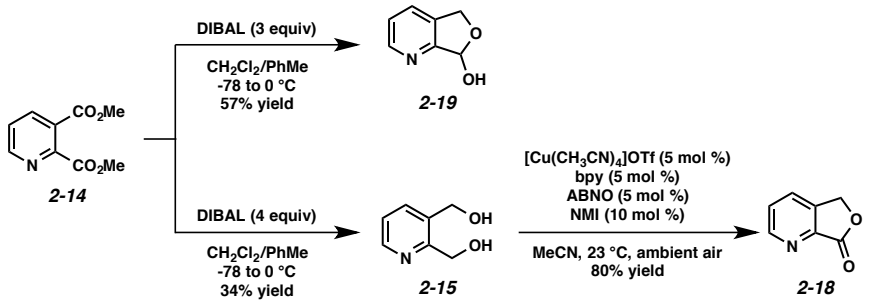
The PyA scaffold described above is ultimately generated from pyridine-2,3-dicarboxylic acid (**2-89**). This compound is commercially available and cheap ($0.74/g from Sigma-Aldrich). It can easily be converted to diester **2-14** in 83% yield through a Fischer esterification or dehydrated with acetic anhydride to afford anhydride **2-21** in 86% yield (Scheme 2.8.1). These two substrates can be converted to other 2,3-disubstituted pyridines, which could be useful as intermediates in the synthesis of future scaffolds.

Scheme 2.8.1. Diversification of Diacid **2-89**



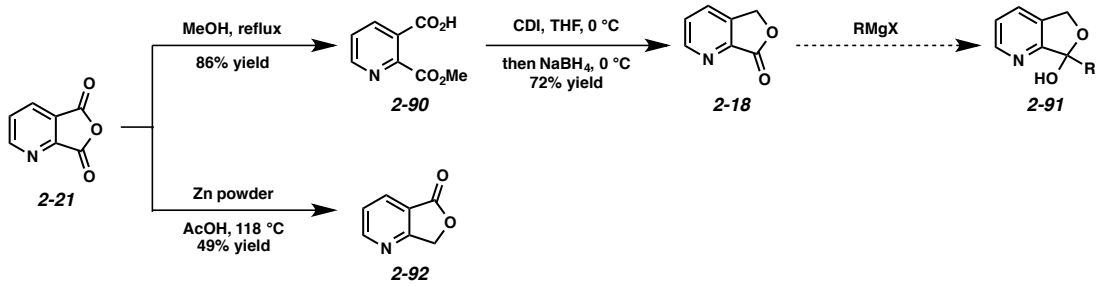
The addition of 3 equivalents of DIBAL to diester **2-14** affords hemiacetal **2-19** (Scheme 2.8.2). Alternatiely, the addition of 4 equivalents of DIBAL reproducibly affords diol **2-15** in 34% yield, and this diol has been shown by Stahl to selectively oxidize to lactone **2-18** in 80% yield through copper catalysis.[31]

Scheme 2.8.2. Diversification of Diester **2-14**



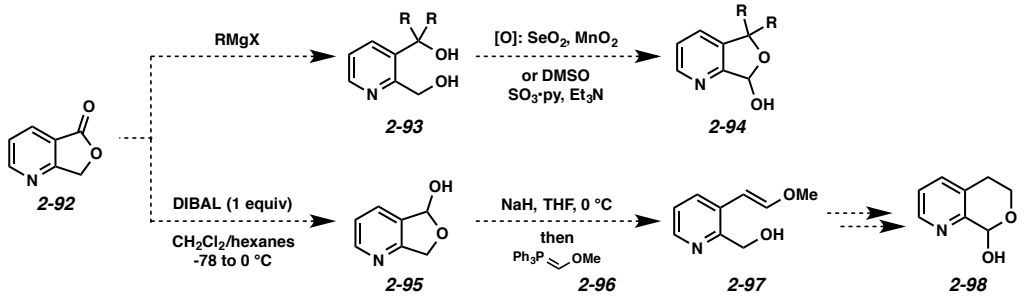
Anhydride **2-21** can also be useful as a precursor to future scaffolds (Scheme 2.8.3). Chen developed a sequence toward lactone **2-18** by first opening the anhydride with methanol.[32] The resulting acid was converted to the mixed-anhydride and reduced with $NaBH_4$ in 64% yield over 2 steps. This lactone could be useful in the synthesis of hemiketal **2-91**. Isomeric lactone **2-92** can be obtained by treating anhydride **2-21** with zinc powder in acetic anhydride. This procedure is reported in the literature; however, lactone **2-18** is incorrectly assigned as the product.[33]

Scheme 2.8.3. Diversification of Anhydride **2-21**



Lactone **2-92** could be utilized in the synthesis of hemiacetals **2-94** and **2-98** (Scheme 2.8.4). The addition of nucleophiles into this lactone would afford diol **2-93,** which could be oxidized to hemiacetal **2-94**. Alternatively, a one-carbon homologated hemiacetal **2-98** could have distinct advantages with respects to reactivity. The selective reduction of lactone **2-92** with one equivalent of DIBAL followed by treatment of the resulting hemiacetal (**2-95**) with Wittig reagent **2-96** should afford vinyl ether **2-97**. This product is positioned for the conversion to hemiacetal **2-98** in just a few steps.

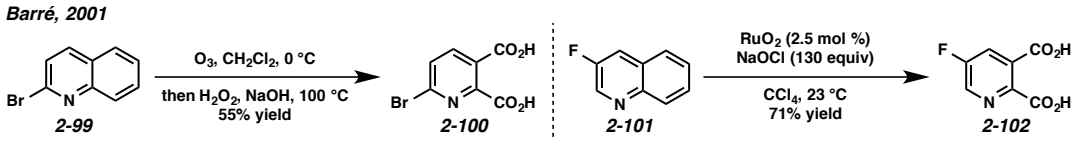
Scheme 2.8.4. Diversification of Lactone **2-92**



Pyridine-2,3-dicarboxylic acid (**2-89**) is shown above as the ultimate precursor for the synthesis of many di-substituted pyridine scaffold intermediates. Derivatives of this compound are not readily commercially available. If such derivatives are desired, they can be obtained through the oxidation of quinolines. Barré reported the conversion of substituted quinolines to substituted pyridine-2,3-dicarboxylic acids by the treatment of either ozone followed by an oxidative work-up (**2-99**→**2-100**) or catalytic RuO_2 and NaOCl (**2-101**→**2-102**) (Scheme

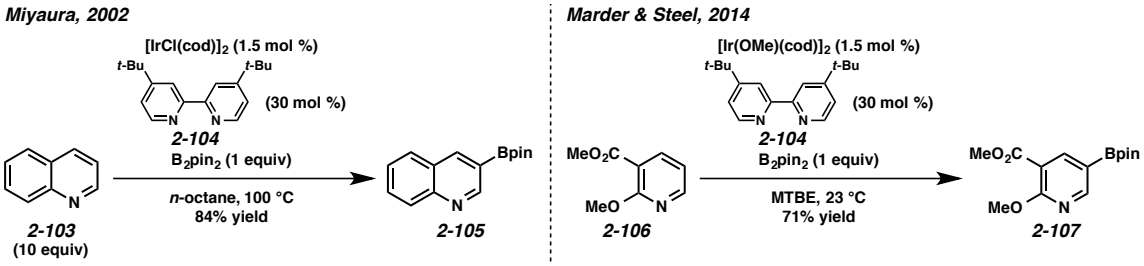
2.8.5).[34] These pyridine-2,3-dicarboxylic acids may be utilized under conditions described above to afford substituted scaffold analogs.

Scheme 2.8.5. Barré's Oxidation of Quinolines to Quinolinic Acids



Late-stage diversification of these pyridine scaffolds may be desired during scaffold development. The installation of either C–C or C–O bonds around the pyridine could greatly expand the scaffold's steric and electronic properties. These bonds could be installed through the addition of a boronate ester. Miyaura reported the iridium-catalyzed borylation of pyridines and quinolines; Marder and Steel then expanded on this work (Scheme 2.8.6).[35] They provided conditions for this reaction that are incredibly mild and thoroughly investigated the variables that control regioselectivity.

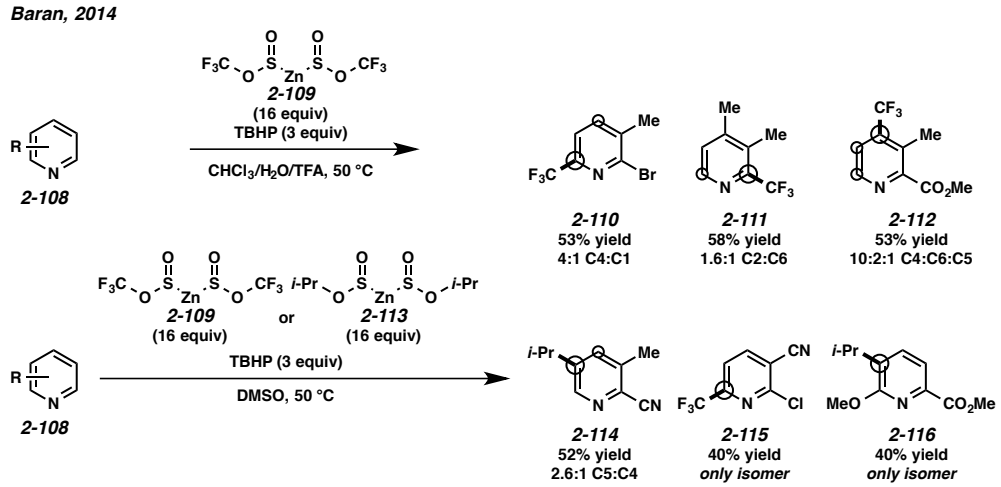
Scheme 2.8.6. Borylation of Pyridines and Quinolines



Alternatively, pyridines can be derivatized under radical conditions. Baran reported the functionalization of C–H bonds of pyridines with alkyl- or fluoroalkyl substituents (Scheme 2.8.7).[36] These reactions are facilitated by the chemical or electrochemical oxidation of zinc sulfinates (**2-109** or **2-113**). The conditions tolerated pyridine substrates containing electron-donating and electron-withdrawing groups as well as halides. Baran also thoroughly investigated

the factors governing regioselectivity, and provided a highly predictive model for both selectivity and reactivity.

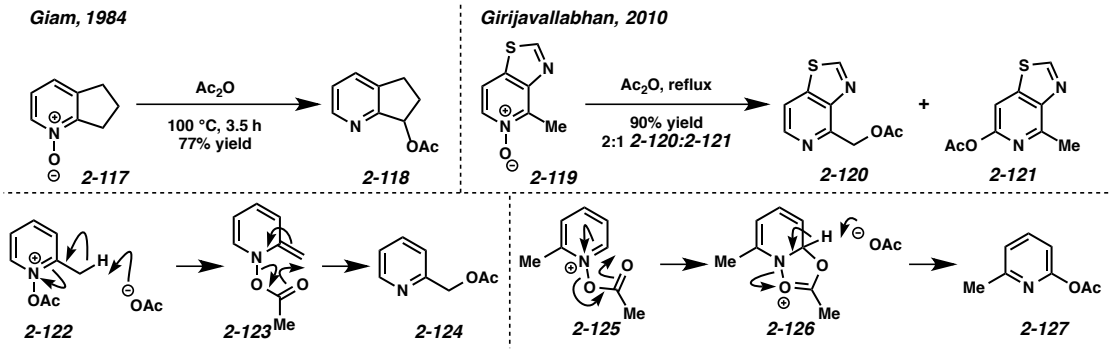
Scheme 2.8.7. Baran's Functionalization of Pyridines



A more traditional method for substituting pyridine derivatives is the Boekelheide reaction.[37] This is the initial conversion of a pyridine to its N-oxide followed by treatment with acetic anhydride. Alkyl substituents are typically preferred for acetoxylation over the arene. This is illustrated in Scheme 2.8.8, where *N*-oxide is transformed to acetate **2-118** in 77% yield.[38] An example by Girijavallabhan demonstrates the typical selectivity observed in these reactions (**2-119**→**2-120** and **2-121**).[39] Treatment with other anhydrides, such as trifluoroacetic anhydride, also facilitates this reaction; however and to my knowledge, no study has been performed comparing the selectivity and reactivity of different anhydride solvents (Ac_2O, TFAA, Piv_2O, etc.). Substitution at the α-position arises from α-deprotonation of pyridinium **2-122** followed by an electrocyclic cyclization of enamine **2-123** to afford acetate **2-124**. Comparatively, arene substitution occurs through a separate mechanism where the acetate of pyridinium **2-125** adds to the α-position. An E_2-type mechanism of this oxonium species affords acetate **2-127**. It is

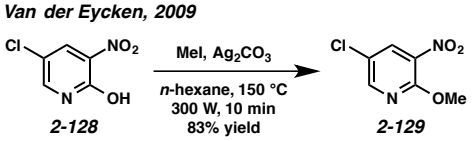
reasonable to suspect that the electronics and sterics of these acetate nucleophiles/bases could modulate between these two mechanisms.

Scheme 2.8.8. The Boekelheide Reaction



Shown above are two methods to install oxidation on a pyridine (Scheme 2.8.6 and Scheme 2.8.8). Both of these methods can be used to generate hydroxyl-substituted pyridines. O-alkylation of these substrates would provide electron-rich scaffolds that may be useful in encouraging both functionalization and exchange. Informatively, numerous reports suggested that these hydroxyl-substituted pyridines would be difficult to alkylate since they are more nucleophilic at nitrogen. To overcome this limitation, Van der Eycken disclosed a procedure for the selective O-alkylation of these substrates (Scheme 2.8.9).[40] Treatment of hydroxypyridine with Ag_2CO_3 and MeI under microwave irradiation affords the O-alkylated product in good yield.

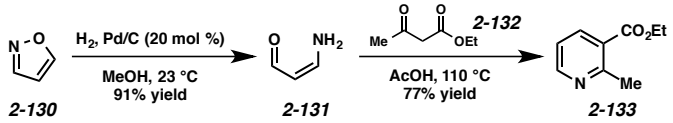
Scheme 2.8.9. Alkylation of 2-Hydroxypyridines



All of the methods shown above either generate pyridine-2,3-dicarboxylic acids or transform them toward scaffold precursors. Alternative routes toward 2,3-disubstituted pyridines could provide breadth in the options for scaffold diversification. Hydrogenation of the N–O bond

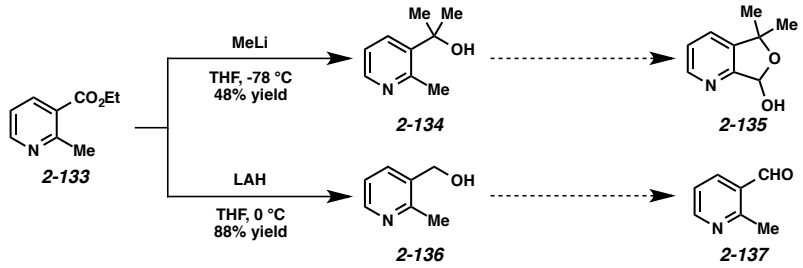
of isoxazole (**2-130**) affords β-aminoacrolein in 91% yield (Scheme 2.8.10). This intermediate can then be cyclized to generate 2,3-disubstituted pyridine **2-133** in 77% yield.

Scheme 2.8.10. Pyridine Synthesis from Isoxazole



This precursor can be reduced at the 3-position with nucleophiles or LAH (Scheme 2.8.11). SeO_2 or other oxidation procedures will likely convert alcohol **2-134** to hemiacetal **2-135**. Oxidation of alcohol **2-136** to aldehyde **2-137** could be useful in performing a one-carbon homologation of these precursors as seen in Scheme 2.8.4.

Scheme 2.8.11. Diversification of Pyridine **2-133**



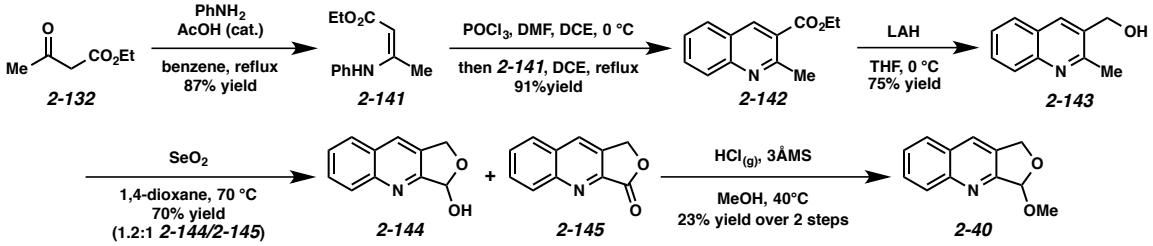
Another modification that could be interesting would be substitutions of the *endo*-oxygen of these scaffolds for a nitrogen. These *N,O*-aminals may be more stable to exchange, and therefore more robust under functionalization conditions. We attempted to synthesize hemiaminal **2-140** (Scheme 2.8.12). First we reduced diester **2-14** to the corresponding diol. This has been reported, but the irreproducibility of this procedure is commented on frequently in the literature.[3] We treated the resulting complex of this reduction with $SOCl_2$ to afford dichloride **2-138**. This compound is reported to cyclize in the presence of an amine and base to generate pyrrolidine **2-139**. Oxidation of these compounds could produce hemiaminal **2-140**.

Scheme 2.8.12. Proposed Synthesis of Structurally Similar *N,O*-Aminal Scaffold



Diversification of these scaffolds toward quinolines has already proved to be fruitful (*vide supra*). A general procedure for the methodical modification of these directing groups would greatly reduce the cost in time and resources in producing substrate analogs. We initially targeted and developed a straightforward route toward quinoline **2-40** (Scheme 2.8.13). Ethyl acetoacetate (**2-132**) was heated with aniline in benzene with catalytic acetic acid to afford β-aminoenoate **2-141** in 87% yield. This product was treated with Vilsmeier reagent followed by heated, which produced the quinoline core (**2-142**) in 91% yield. Reduction of the ester was uneventful to generated alcohol **2-143** in 75% yield. Oxidation with SeO_2 afforded a mixture of hemiacetal **2-144** and lactone **2-145** in 70% yield as a 1.2:1 mixture, respectfully. Treatment of this mixture with gaseous HCl in MeOH with 3Å molecular sieves produces methyl acetal **2-40** in 23% yield over 2 steps.

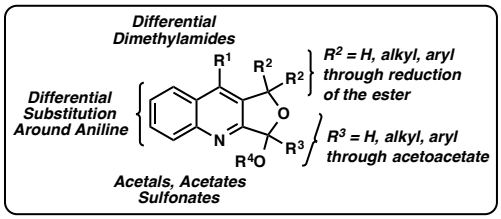
Scheme 2.8.13. Synthesis of QuA-Scaffold



This route appears to be highly versatile in diversifying these scaffolds (Figure 2.8.2). Modifications around the benzene ring of the scaffold will be derived from diverse anilines. The R^1 position is installed from the Vilsmeier reagent, and other dimethylamides will produce substitution at this position. Substitution at the R^2 position comes from reduction of the ester.

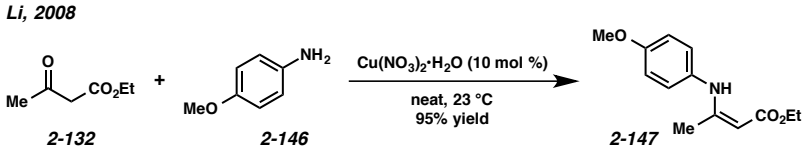
Reducing with LAH, alkyl or aryl lithiums, or Grignards can sterically and electronically modify this position. The R^3 substituent comes from the particular acetoacetate. Finally, the acetal can be substituted with different groups (R^4) and be converted to acetates or sulfonates.

Figure 2.8.2. Versatility of the Scaffold Diversification Route



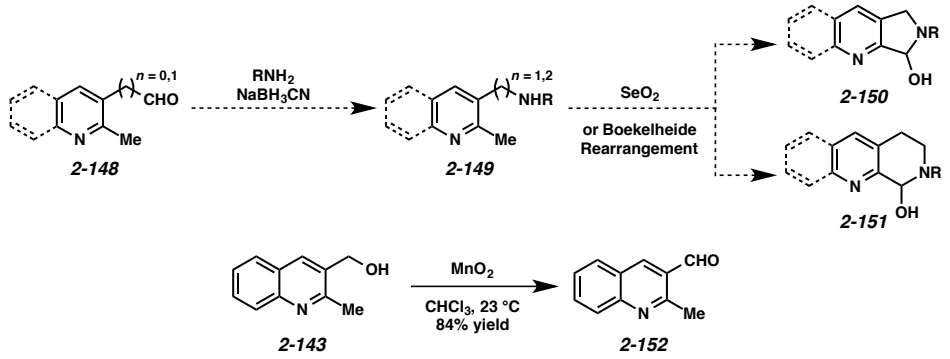
The first step in this scaffold modification has been previously investigated. Li reported the condensation of neutral and electron-rich anilines with acetoacetates uneventfully affords β-aminoenoates such as **2-147**, generally in high yield (Scheme 2.8.14).[41]

Scheme 2.8.14. Alternative Synthesis of β-Aminoacrylates



These quinoline and pyridine scaffolds may be converted to aminals **2-150** or **2-151** through reductive aminations of aldehydes at the 3-position (Scheme 2.8.15). Oxidation of the methyl group could produce the hemiaminal. Oxidation of quinoline **2-143** with MnO_2 cleanly affords aldehyde **2-152** in 84% yield, and this reaction would likely be successful to generate pyridine **2-137**.

Scheme 2.8.15. Alternative Synthesis of *N,O*-Aminal Scaffolds



These procedures and strategies should be useful in future diversification of these scaffolds. Modifications of these types may, hopefully, facilitate the discovery of new reactivity. Additionally, these changes should provide new scaffolds that are highly active toward exchange and may produce the desired entry into transient functionalization.

2.9. Experimental Section

2.9.1. Materials and Methods

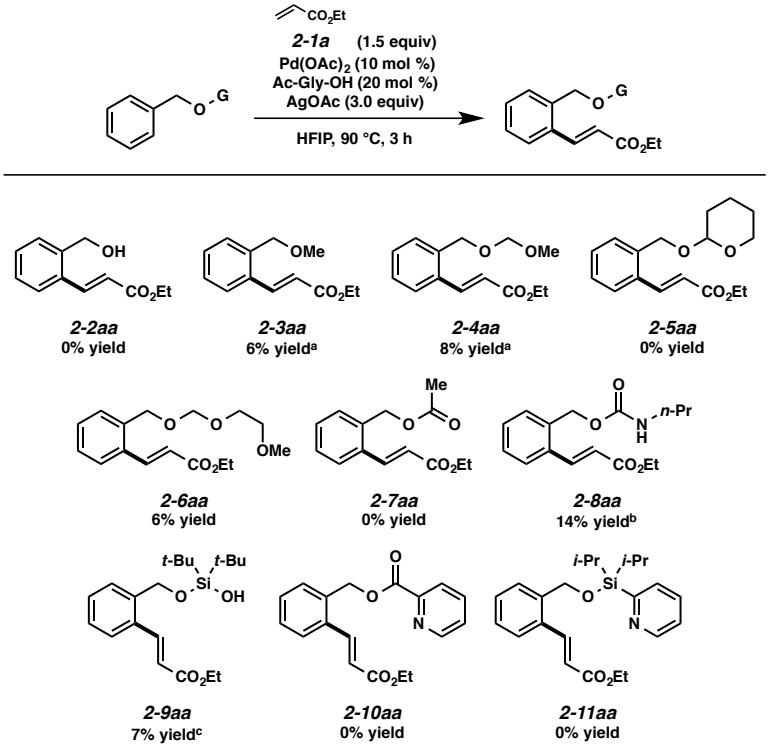
Reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, dichloromethane, diethyl ether, and toluene were purified by passing through activated alumina columns. 1,4-Dioxane was stored over activated 3ÅMS. Anhydrous HCl gas was regularly prepared by adding concentrated HCl to anhydrous $CaCl_2$. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, Ma), Sigma-Aldrich (St. Louis, MO), Oakwood Products (West Columbia, SC), Strem (Newport, MA), and TCI America (Portland, OR). Qualitative TLC and preparatory plate chromatography was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to $KMnO_4$, CAM, or Dragendorff stain solutions followed by heating. Flash column chromatography was performed using Silicycle silica gel (230-400 mesh). ^{1}H NMR spectra were

acquired on either a Varian Mercury 300 (at 300 MHz), a Varian 400 MR (at 400 MHz), Varian Mercury Plus (at 400 MHz), or a Varian Unity Inova (at 500 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz), Varian Mercury Plus (at 100 MHz), or a Varian Unity Inova (at 125 MHz) and are reported relative to $SiMe_4$ (δ 0.0). ^{19}F NMR spectra were acquired on a Varian 400 MR (at 376 MHz) and are reported relative to $PhCF_3$ (δ -63.7). All IR spectra were obtained as a film with a Nicolet iS50 FT-IR or an IRPrestige-21 Spectrophotometer. Low-resolution mass spectrometry data were acquired on an Agilent 1200 series HPLC equipped with an Agilent 6130 quadrupole LC/MS. High-resolution mass spectrometry data was acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS or by the University of Georgia Proteomics and Mass Spectrometry Core Facility on a Bruker Esquire 3000 Plus Ion Trap Spectrophotometer.

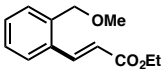
2.9.2. Experimental Procedures and Studies

Experimental Procedure and Studies from Section 2.1

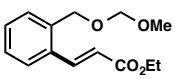
Table 2.1.1 (recreated). Common Protecting and Directing Group Facilitated Alkenylation of Benzyl Alcohols[a]



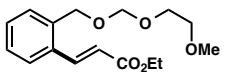
a) Reactions were preformed according to the general procedure. All values are NMR yields obtained using 1-octene as an internal standard. b) This value corresponds to the ortho contribution of a mixture of olefinated products. c) Increasing the reaction time from 3 to 6 h increased the yield to 16%.



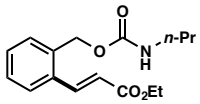
Olefin 2-3aa: Representative peaks in ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 15.9 Hz, 1H), 6.40 (d, J = 15.9 Hz, 1H).



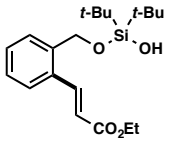
Olefin 2-4aa: Representative peaks in ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 15.9 Hz, 1H), 6.40 (d, J = 15.9 Hz, 1H).



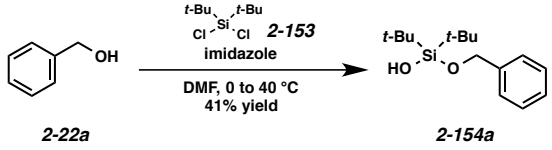
Olefin 2-6aa: Representative peak in ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 16.2 Hz, 1H).



Olefin 2-8aa: Representative peaks in ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 15.9 Hz, 1H), 6.38 (d, J = 15.9 Hz, 1H).



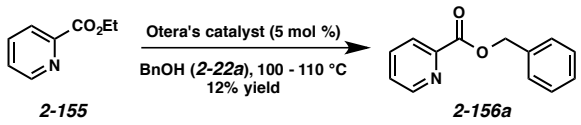
Olefin 2-9aa: Representative peak in ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 15.9 Hz, 1H).



To a stirring solution of benzyl alcohol (**2-22a**, 248 mg, 2.29 mmol) and imidazole (408 mg, 6.00 mmol) in DMF (10.0 mL) at 0 °C was added di-*t*-butyl dichlorosilane (**2-153**, 422 mg, 1.98 mmol). The solution was warmed to 40 °C and stirred for 12 h. Upon completion, the reaction mixture was cooled to 0 °C and sat. Aq. $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude silanol was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford silanol **2-154a** (214 mg,

41% yield, R_f = 0.33 in 9:1 hexanes/EtOAc) as a colorless oil.

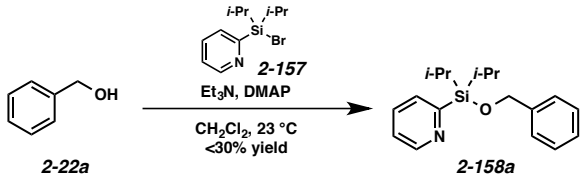
Silanol 2-154a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (comp. m, 4H), 7.28-7.22 (comp m, 1H), 4.94 (s, 2H), 1.95 (s, 1H), 1.06 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 128.4, 127.1, 126.3, 65.4, 27.6, 20.7; IR (film) 2965, 2933, 2890, 2858, 826 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{15}H_{26}O_2Si + Na]^+$: 289.1594, found 289.1593.



2-155 *2-156a*

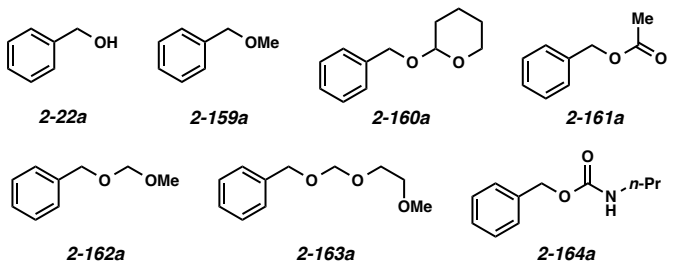
A solution of ethyl 2-picolinate (**2-155**, 398 mg, 2.63 mmol) and Otera's catalyst[42] (159 mg, 0.133 mmol) in benzyl alcohol (**2-22a**, 13.2 mL) was heated at 100-110 °C and stirred for 14 h. The mixture was cooled to ambient temperature and poured into EtOAc (100 mL). The solution was extracted with 1 M aq. HCl (3 x 20 mL), the organic layer was discarded, and the combined aqueous layers were neutralized with sat. Aq. Na_2CO_3 (100 mL). The aqueous mixture was extracted with EtOAc (20 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation. The resulting oil was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford benzyl 2-picolinate (**2-156a**, 67.6 mg, 12% yield, R_f = 0.25 in 7:3 hexanes/EtOAc) as a colorless oil.

Benzyl picolinate 2-156a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.8 Hz, 1H) 8.13 (d, *J* = 8.0 Hz, 1H), 7.82 (tt, *J* = 8.0, 1.6 Hz, 1H), 7.51-7.44 (comp. m, 3H), 7.41-7.30 (comp. m, 3H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 150.1, 148.2, 137.1, 135.8, 128.7, 128.5, 127.0, 125.4, 67.6; IR (film) 1737, 1717, 1584, 1455, 1302, 1290, 1243, 1122 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{11}NO_2 + H]^+$: 214.1, found 214.1.



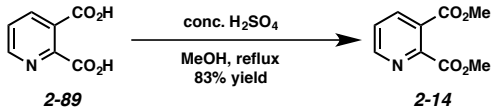
To a stirring solution of pyridyl silane **2-157**[43] (250 mg, 1.29 mmol) in CH_2Cl_2 (5.70 mL) in an ambient temperature bath was added *N*-bromosuccinimide (230 mg, 1.29 mmol) in 4 portions over 1 min. Upon completion of the reaction by TLC (within 30 min), the solution was transferred by cannula to a solution of benzyl alcohol (**2-22a**, 0.147 mL, 1.42 mmol), triethylamine (0.198 mL, 1.42 mmol), and DMAP (15.8 mg, 0.129 mmol) in CH_2Cl_2 (5.70 mL), and the mixture was stirred at room temperature for 2 h. Upon completion, water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford semi-pure silyl ether **2-158a** (117 mg, <30% yield, R_f = 0.22 in 9:1 hexanes/EtOAc) as a beige oil. Silyl ether **2-158a** decomposes on SiO_2 and was found to decompose in hexafluoroisopropanol when heated to 90 °C.

Silyl ether 2-158a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.8 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.21 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.98 (s, 2H), 1.46 (septet, *J* = 7.2 Hz, 2H), 1.12 (d, *J* = 7.2 Hz, 6H), 1.07 (d, *J* = 7.2 Hz, 6H); LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{25}NOSi + H]^+$: 300.2, found 300.2.



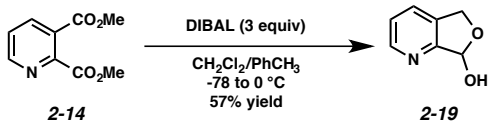
Benzyl alcohol (**2-22a)**, ether **2-159a**, acetal **2-160a**, and ester **2-161a** are all commercially available. Acetal **2-162a**[44], acetal **2-163a**[44], and carbamate **2-164a**[45] can be synthesized by known procedures.

Experimental Procedure and Studies from Section 2.2



To a suspension of pyridine-2,3-dicarboxylic acid (**2-89**, 30.0 g, 180 mmol) in MeOH (120 mL) at 0 °C was slowly added concentrated H_2SO_4 (12.0 mL), and then the suspension was stirred and heated at reflux for 20 h. The reaction solution was cooled to 0 °C and was slowly neutralized with sat. aq. Na_2CO_3 (200 mL). The MeOH was removed by rotary evaporation, and the organic materials were extracted with CH_2Cl_2 (6 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford analytically pure dimethyl ester **2-14** (29.3 g, 83% yield, R_f = 0.35 in 1:1 hexanes/EtOAc) as a beige solid.

Diester 2-14: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.17 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.49 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.9, 151.9, 150.8, 137.7, 126.6, 125.1, 53.3, 53.1; IR (film) 1726, 1426, 1284, 1131, 1077 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_9H_9NO_4 + H]^+$: 196.1, found 196.1.

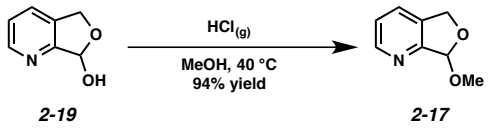


2-14 *2-19*

To a stirring suspension of diester **2-14** (7.29 g, 37.4 mmol) in CH_2Cl_2 (146 mL) cooled to -78 °C was added diisobutylaluminum hydride (85.0 mL, 1.32 M in $PhCH_3$, 112 mmol) dropwise over 10 min. The solution was stirred for 5 h at -78 °C, and was then warmed to 0 °C and stirred for 30 min. To the reaction was carefully added water (4.37 mL) dropwise, and then 3.8 M NaOH (4.37 mL) dropwise, and finally water (13.1 mL). The suspension was warmed to ambient temperature and was stirred for 20 min before $MgSO_4$ (~80 g) and celite (~40 g) were added. Stirring was stopped, and the mixture was allowed to sit overnight. The suspension was then filtered through a glass-fritted funnel, and the solids were washed with excess MeOH (100 mL). The filter cake was collected and heated in MeOH (~300 mL, approx. reflux) for ~5 min before refiltering and washing with excess hot MeOH (~150 mL) until the solution passing the filter was no longer UV active by TLC. This washing procedure was repeated 4-5 times to sufficiently remove the product material from the residual solids. (*Note:* Hemiacetal **2-19** is highly water soluble, and thus measures were taken to avoid aqueous treatments in workup procedures.) The combined filtrates were concentrated by rotary evaporation and purified by flash column chromatography (20:1 EtOAc/MeOH eluent) to afford hemiacetal **2-19** (2.92 g, 57% yield, R_f = 0.24 in EtOAc) as a beige solid.

Hemiacetal 2-19 (characterized as a 10:1 mixture of hemiacetal/aldehyde)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 0.10H), 8.71 (d, J = 4.4 Hz, 0.10H), 8.53 (d, J = 5.0 Hz, 1H), 7.99 (d, J = 7.6 Hz, 0.10H), 7.62 (d, J = 7.8 Hz, 1H), 7.50 (dd, J = 7.6, 4.4 Hz, 0.10H), 7.29 (dd, J = 7.8, 5.0 Hz, 1H), 6.57 (s, 1H), 6.12 (br. s, 1.1H), 5.30 (d, J = 13.2 Hz, 1H), 5.05 (d, J = 13.2 Hz, 1H), 4.94 (s, 0.20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 158.8, 149.7, 149.1, 148.8, 139.0, 136.9, 133.1,

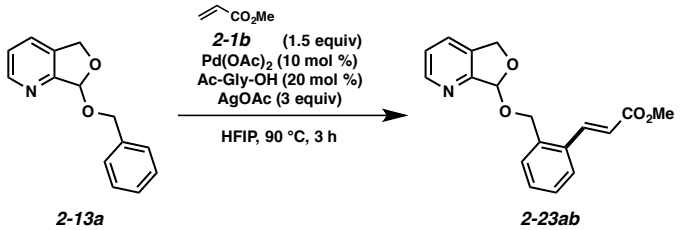
130.8, 127.6, 123.7, 98.7, 70.1, 61.9; IR (film) 3179, 1425, 1070, 1005, 911 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_7H_7NO_2 + H]^+$: 138.0550; found 138.0551.



2-19 *2-17*

A round-bottomed flask holding a solution of hemiacetal **2-19** (3.25 g, 23.7 mmol) in MeOH (240 mL) at 23 °C was bubbled anhydrous HCl for 1 min. The flask was capped (yellow plastic cap), and the mixture was heated and stirred at 40 °C for 20 h. Upon completion, the reaction was poured into a mixture of ~1:1 ice/sat. aq. Na_2CO_3 (400 mL), and it was then concentrated by rotary evaporation to remove MeOH. The mixture was extracted with EtOAc (3 x 200 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (EtOAc eluent) to afford methyl acetal **2-17** (3.35 g, 94% yield, R_f = 0.43 in EtOAc) as an amber oil.

Methyl acetal 2-17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.27 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.04 (d, *J* = 2.0 Hz, 1H) 5.23 (dd, *J* = 13.2, 2.0 Hz, 1H), 5.08 (d, *J* = 13.2 Hz, 1H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.0, 133.1, 129.9, 123.7, 105.9, 70.6, 55.9; IR (film) 1374, 1087, 1023, 1007, 962 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_8H_9NO_2 + H]^+$: 152.0706, found 152.0706.



2-13a *2-23ab*

Alkenylation reactions between acetal **2-13a** and methyl acrylate (**2-1b**) were performed according to the general alkenylation procedure in 2.7.3.

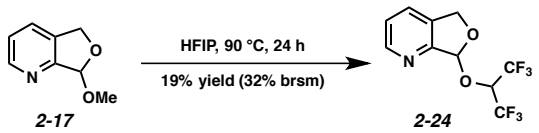
Monoolefin 2-23ab: Representative peaks in ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 4.5 Hz, 1H), 8.12 (d, J = 15.6 Hz, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.39-7.25 (comp. m, 3H), 6.39 (d, J = 15.6 Hz, 1H), 6.26 (s, 1H), 5.43 (d, J = 13.5 Hz, 1H), 5.15 (d, J = 13.5 Hz, 1H), 5.13 (d, J = 11.1 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 3.82 (s, 3H).

Diolefin 2-23ab: Representative peaks in ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 16.0 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 6.23 (d, J = 2.1 Hz, 1H).

Experimental Procedure and Studies from Section 2.3

The conditions used for optimization are described in each table in section 2.3. All ligands in Table 2.3.4 are known compounds and are commercially available.

The HFIP acetal (**2-24**) was observed as a side product in some reactions during the optimization screen. It is observed more prominently with longer reaction times and when acid additives are used.

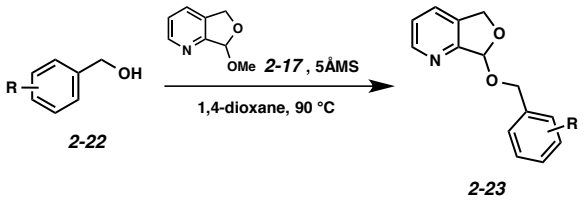


A solution of methyl acetal **2-17** (30.2 mg, 0.200 mmol) in hexafluoroisopropanol (2.00 mL) was heated at 90 °C and stirred for 24 h. The solution was cooled to ambient temperature and concentrated by rotary evaporation. The crude residue was purified by column chromatography (7:3 hexanes/EtOAc eluent) to afford hexafluoroisopropyl acetal **2-24** (10.8 mg, 19% yield (32% brsm), R_f = 0.34 in 7:3 hexanes/EtOAc) as a white solid.

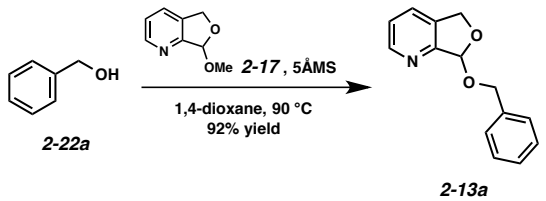
Hexafluoroisopropyl acetal 2-24: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.8 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.35 (dd, J = 7.6, 4.8 Hz, 1H), 6.30 (s, 1H), 5.27 (d, J = 13.2 Hz, 1H), 5.13 (d, J = 13.2 Hz, 1H), 4.77 (septet, $^{3}J_{H\text{-}F}$ = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 150.3, 133.1, 130.1, 124.4, 105.2, 71.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.4 (dq, $^{4}J_{F\text{-}F}$ = 8.6 Hz, $^{3}J_{H\text{-}F}$ = 6.0 Hz, 3F), -75.1 (dq, $^{4}J_{F\text{-}F}$ = 8.6, $^{3}J_{H\text{-}F}$ = 6.0 Hz, 3F); IR (film) 1287, 1218, 1187, 1100, 1050, 959 cm^{-1}; HRMS (DART+) *m/z* calc'd for $(M + H)^+$ $[C_{10}H_7F_6NO_2 + H]^+$: 288.0453, found 288.0454.

Experimental Procedure and Studies from Section 2.4

General Procedure for the Molecular Sieves Induced Attachment of Alcohols to the PyA Scaffold

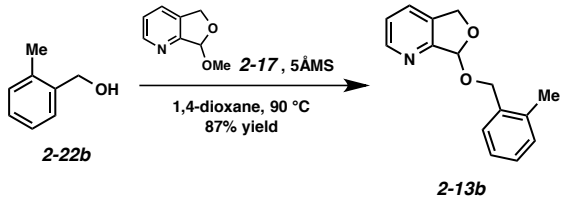


In either a 2-dram vial sealed with a PTFE-lined cap or a flask with a condenser attached, a suspension of alcohol **2-22** (1 equiv), methyl acetal **2-17** (1.05 equiv), and 5Å molecular sieves (1.25 g/mmol alcohol) in 1,4-dioxane (0.63 M) was heated at 90 °C (without stirring) for 18 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc and celite were added to the mixture. This suspension was filtered through a pad of celite with 9:1 EtOAc/MeOH, the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography to afford acetal **2-23**.



In a flask with a condenser attached, a suspension of benzyl alcohol (**2-22a**, 340 mg, 3.15 mmol), methyl acetal **2-17** (502 mg, 3.32 mmol), and 5Å molecular sieves (3.93 g) in 1,4-dioxane (5.00 mL) was heated at 90 °C (without stirring) for 18 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~30 mL) and celite (~3.0 g) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (300 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford acetal **2-13a** (661 mg, 92% yield, R_f = 0.39 in 1:1 hexanes/EtOAc) as a colorless oil.

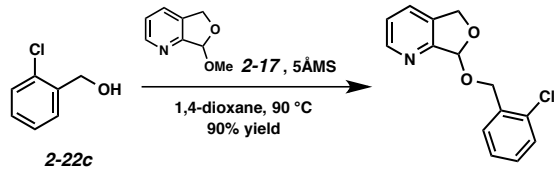
Acetal 2-13a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 4.8, 1.2 Hz, 1H) 7.63 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.46-7.41 (comp. m, 2H), 7.38-7.31 (comp. m, 2H), 7.30-7.25 (comp. m, 2H), 6.23 (d, *J* = 2.0 Hz, 1H), 5.27 (dd, *J* = 13.2, 2.0 Hz, 1H), 5.09 (d, *J* = 13.2 Hz, 1H), 4.85 (ABq, *J* = 11.6 Hz, Δν = 25.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 149.9, 137.7, 133.3, 129.9, 128.5, 128.3, 127.9, 123.6, 104.3, 70.5, 70.3; IR (film) 2870, 1589, 1364, 1073, 1006 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{13}NO_2 + H]^+$: 228.1019, found 228.1024.



In a flask with a condenser attached, a suspension of 2-methylbenzyl alcohol (**2-22b**, 778 mg, 6.37 mmol), methyl acetal **2-17** (1.01 g, 6.69 mmol), and 5Å molecular sieves (7.96 g) in 1,4-dioxane (10.1 mL) was heated at 90 °C (without stirring) for 18 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~60 mL) and celite (~6.0 g) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 20 mm) with 9:1 EtOAc/MeOH (400 mL), the filtrate concentrated by rotary evaporation, and the residue purified

by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13b** (1.34 g, 87% yield, R_f = 0.36 in 3:2 hexanes/EtOAc) as a colorless oil.

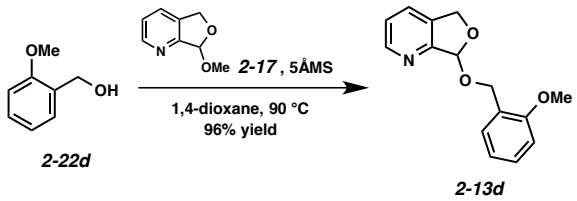
Acetal 2-13b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.43-7.39 (comp. m, 1H), 7.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.26-7.14 (comp. m, 3H), 6.22 (d, *J* = 2.0 Hz, 1H), 5.27 (dd, *J* = 13.2, 2.0 Hz, 1H), 5.09 (d, *J* = 13.2 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 149.9, 137.1, 135.6, 133.2, 130.4, 129.8, 129.3, 128.1, 126.0, 123.6, 104.3, 70.5, 68.8, 19.1; IR (film) 1588, 1363, 1075, 1000, 745 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{15}NO_2 + H]^+$: 242.1183, found 242.1176.



In a 2-dram vial with a PTFE-lined cap, a suspension of 2-chlorobenzyl alcohol (**2-22c**, 71.3 mg, 0.500 mmol), methyl acetal **2-17** (79.4 mg, 0.525 mmol), and 5Å molecular sieves (625 mg) in 1,4-dioxane (0.794 mL) was heated at 90 °C (without stirring) for 15 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (200 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13c** (118 mg, 90% yield, R_f = 0.34 in 7:3 hexanes/EtOAc) as a beige solid.

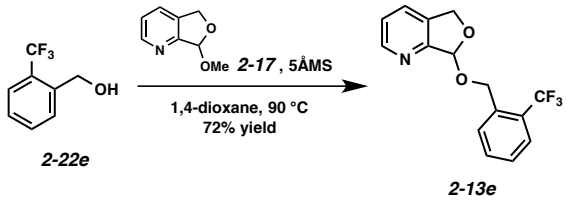
Acetal 2-13c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.4 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 4.4 Hz, 1H), 7.27-7.18 (comp. m, 2H), 6.27 (s, 1H), 5.29 (d, *J* =13.2 Hz, 1H), 5.11 (d, *J* = 13.2 Hz, 1H), 4.95 (ABq, *J*

=12.8 Hz, Δν = 33.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.0, 135.7, 133.3, 133.0, 130.0, 129.5, 129.3, 128.8, 126.9, 123.7, 104.7, 70.6, 67.3; IR (film) 1088, 1007, 914, 791, 752 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{12}ClNO_2 + H]^+$: 262.0629, found 262.0631.



In a 2-dram vial with a PTFE-lined cap, a suspension of 2-methoxybenzyl alcohol (**2-22d**, 69.4 mg, 0.500 mmol), methyl acetal **2-17** (79.4 mg, 0.525 mmol), and 5Å molecular sieves (625 mg) in 1,4-dioxane (0.794 mL) was heated at 90 °C (without stirring) for 8 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13d** (123 mg, 96% yield, R_f = 0.16 in 7:3 hexanes/EtOAc) as a white solid.

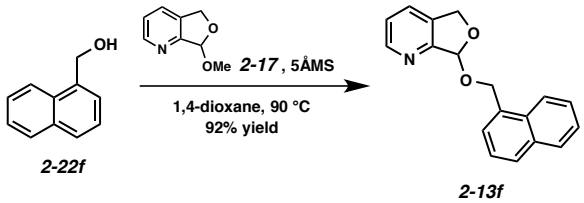
Acetal 2-13d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.8 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.30-7.23 (comp. m, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.27 (s, 1H), 5.28 (d, *J* = 13.2 Hz, 1H), 5.09 (d, *J* = 13.2 Hz, 1H), 4.91 (ABq, *J* = 12.4 Hz, Δν = 18.7 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.2, 149.8, 133.3, 129.8, 129.3, 128.8, 126.2, 123.5, 120.5, 110.3, 104.4, 70.4, 65.1, 55.5; IR (film) 1495, 1236, 1076, 999, 752 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{15}NO_3 + H]^+$: 258.1125, found 258.1129.



2-22e *2-13e*

In a 2-dram vial with a PTFE-lined cap, a suspension of 2-(trifluoromethyl)benzyl alcohol (**2-22e**, 88.6 mg, 0.500 mmol), methyl acetal **2-17** (79.4 mg, 0.525 mmol), and 5Å molecular sieves (625 mg) in 1,4-dioxane (0.794 mL) was heated at 90 °C (without stirring) for 15 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13e** (106 mg, 72% yield, R_f = 0.40 in 3:2 hexanes/EtOAc) as a colorless oil.

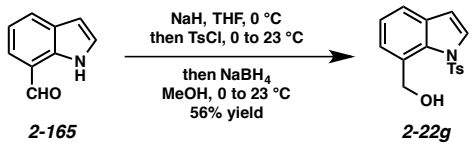
Acetal 2-13e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.26 (d, *J* = 2.0 Hz, 1H), 5.27 (dd, *J* = 13.6, 2.0 Hz, 1H), 5.10 (d, *J* = 13.6 Hz, 1H), 5.04 (ABq, *J* = 13.2 Hz, Δν = 36.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 150.0, 136.7, 133.3, 132.2, 130.0, 129.4, 127.5 (q, $^2J_{C\text{-}F}$ = 30.5 Hz), 127.4, 125.7 (q, $^3J_{C\text{-}F}$ = 5.7 Hz), 124.5 (q, $^1J_{C\text{-}F}$ = 272.0 Hz), 123.8, 104.7, 70.6, 66.1 (q, $^4J_{C\text{-}F}$ = 2.9 Hz); IR (film) 1314, 1119, 1007, 910, 731 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{12}F_3NO_2 + H]^+$: 296.0893, found 296.0892.



2-22f *2-13f*

In a 2-dram vial with a PTFE-lined cap, a suspension of 1-naphthalenemethanol (**2-22f**, 47.5 mg, 0.300 mmol), methyl acetal **2-17** (47.6 mg, 0.315 mmol), and 5Å molecular sieves (375 mg) in 1,4-dioxane (0.476 mL) was heated at 90 °C (without stirring) for 48 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford acetal **2-13f** (277 mg, 92% yield, R_f = 0.35 in 3:2 hexanes/EtOAc) as a white solid.

Acetal 2-13f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.4 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.26 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.35 (s, 1H), 5.41 (d, *J* = 11.4 Hz, 1H), 5.32 (d, *J* = 13.0 Hz, 1H), 5.21 (d, *J* = 11.4 Hz, 1H), 5.14 (d, *J* = 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.9, 133.9, 133.3, 133.2, 131.9, 129.9, 128.9, 128.6, 127.1, 126.4, 125.8, 125.4, 124.1, 123.7, 104.5, 70.7, 68.6; IR (film) 1088, 1003, 912, 793, 779 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{15}NO_2 + H]^+$: 278.1176, found 278.1177.

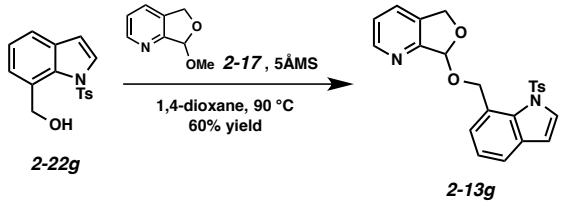


2-165 *2-22g*

To a stirring solution of 7-formylindole (**2-165**,[46] 400 mg, 2.76 mmol) in THF (7.08 mL) at 0 °C was added NaH (165 mg, 60% dispersion in mineral oil, 4.13 mmol) in 4 portions over 2 min, and the mixture was held at 0 °C for 10 min. Then TsCl (788 mg, 4.13 mmol) was added in a single portion, and the resulting mixture was warmed to 23 °C. After 1 h, the reaction mixture was cooled to 0 °C, MeOH (2.00 mL) was added, and then $NaBH_4$ (313 mg, 8.27 mmol) was

added in 4 portions over 2 min. The mixture was warmed to ambient temperature and stirred for 1 h. Upon completion, the reaction mixture was quenched with sat. aq. Na_2CO_3 (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude reaction mixture was purified by flash column chromatography (13:7 hexanes/EtOAc eluent) to afford alcohol **2-22g** (465 mg, 56% yield, R_f = 0.33 in 13:7 hexanes/EtOAc) as a colorless oil that slowly transformed to a white solid.

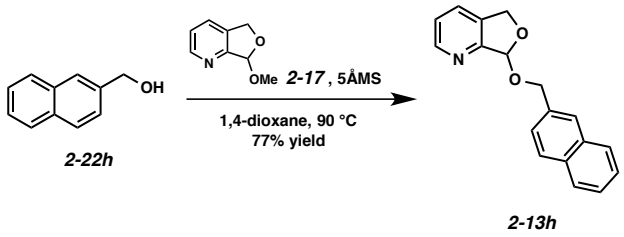
Alcohol 2-22g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 3.8 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 3.8 Hz, 1H), 4.88 (s, 2H), 3.31 (br. s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.7, 133.6, 133.5, 130.1, 130.0, 128.4, 127.9, 126.4, 124.5, 121.6, 110.3, 63.9, 21.7; IR (film) 3379, 1350, 1165, 1072, 980 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{16}H_{15}NO_3S + Na]^+$: 324.0665, found 324.0672.



In a 2-dram vial with a PTFE-lined cap, a suspension of alcohol **2-22g** (121 mg, 400 mmol), methyl acetal **2-17** (63.5 mg, 0.420 mmol), and 5Å molecular sieves (500 mg) in 1,4-dioxane (0.635 mL) was heated at 90 °C (without stirring) for 18 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified

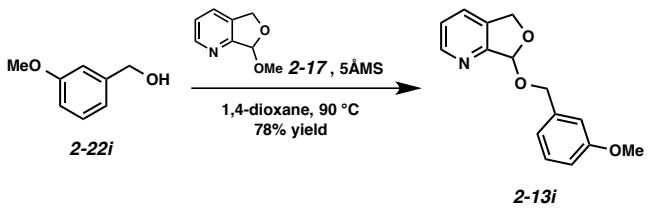
by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford acetal **2-13g** (101 mg, 60% yield, R_f = 0.27 in 3:2 hexanes/EtOAc) as a white foam.

Acetal 2-13g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.6 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 7.6, 4.6 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 3.6 Hz, 1H), 6.27 (s, 1H), 5.27 (s, 2H), 5.26 (d, *J* = 13.2 Hz, 1H), 5.08 (d, *J* = 13.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 149.8, 144.7, 135.8, 133.4, 133.3, 133.2, 130.2, 129.9, 129.8, 126.7, 126.1, 125.3, 124.3, 123.6, 120.7, 110.4, 104.5, 70.6, 67.2, 21.7; IR (film) 1363, 1173, 1089, 1005, 910 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{20}N_2O_4S + H]^+$: 421.1217, found 421.1211.



In a 2-dram vial with a PTFE-lined cap, a suspension of 2-naphthalenemethanol (**2-22h**, 47.5 mg, 0.300 mmol), methyl acetal **2-17** (47.6 mg, 0.315 mmol), and 5Å molecular sieves (375 mg) in 1,4-dioxane (0.476 mL) was heated at 90 °C (without stirring) for 11 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13h** (64.2 mg, 77% yield, R_f = 0.21 in 7:3 hexanes/EtOAc) as a white solid.

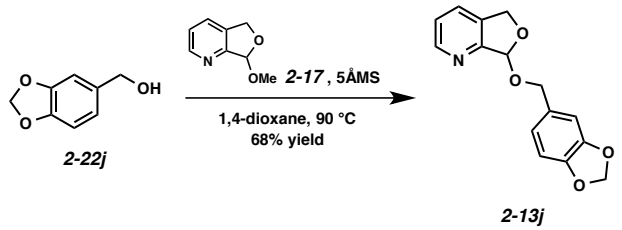
Acetal 2-13h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.6 Hz, 1H), 7.88 (s, 1H), 7.86-7.79 (comp. m, 3H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.49-7.44 (comp. m, 2H), 7.28 (dd, *J* = 7.6, 4.6 Hz, 1H), 6.29 (s, 1H), 5.29 (d, *J* = 13.2 Hz, 1H), 5.10 (d, *J* = 13.2 Hz, 1H), 5.01 (ABq, *J* = 11.8 Hz, Δν = 24.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.9, 135.2, 133.4, 133.3, 133.1, 129.9, 128.3, 128.1, 127.8, 127.1, 126.2, 126.1, 126.0, 123.7, 104.2, 70.6, 70.4; IR (film) 1367, 1078, 1005, 910, 729 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{15}NO_2 + H]^+$: 278.1176, found 278.1176.



In a 2-dram vial with a PTFE-lined cap, a suspension of 3-methoxybenzyl alcohol (**2-22i**, 55.3 mg, 0.400 mmol), methyl acetal **2-17** (63.5 mg, 0.420 mmol), and 5Å molecular sieves (500 mg) in 1,4-dioxane (0.635 mL) was heated at 90 °C (without stirring) for 8.5 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford acetal **2-13i** (80.5 mg, 78% yield, R_f = 0.14 in 3:2 hexanes/EtOAc) as a colorless oil.

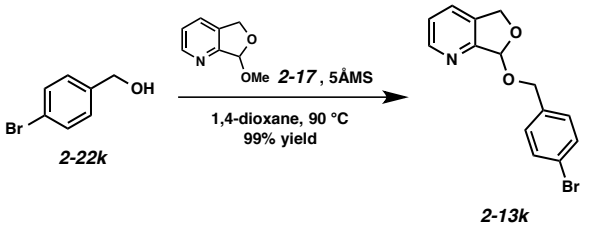
Acetal 2-13i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.26 (dd, *J* = 7.6, 4.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 5.25 (d, *J* = 13.2 Hz, 1H), 5.08 (d, *J* = 13.2 Hz, 1H), 4.81 (ABq, *J* = 11.6 Hz, Δν = 24.6 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.6, 149.8, 139.2, 133.2, 129.9, 129.5, 123.6, 120.5, 113.7, 113.4, 104.2, 70.5, 70.2, 55.3; IR (film)

1491, 1445, 1250, 1001, 727 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{15}NO_3 + H]^+$: 258.1125, found 258.1126.



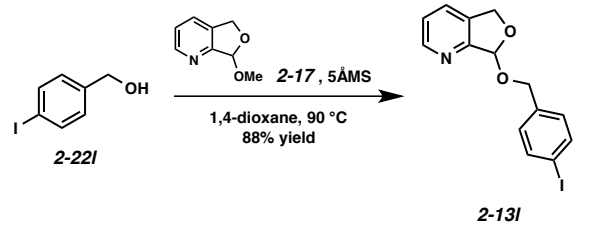
In a 2-dram vial with a PTFE-lined cap, a suspension of alcohol **2-22j** (55.3 mg, 0.400 mmol), methyl acetal **2-17** (63.5 mg, 0.420 mmol), and 5Å molecular sieves (500 mg) in 1,4-dioxane (0.635 mL) was heated at 90 °C (without stirring) for 12 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford acetal **2-13j** (73.9 mg, 68% yield, R_f = 0.32 in 1:1 hexanes/EtOAc) as a white solid.

Acetal 2-13j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.18 (d, *J* = 2.0 Hz, 1H), 5.91 (s, 2H), 5.24 (dd, *J* = 13.2, 2.0 Hz, 1H), 5.06 (d, *J* = 13.2 Hz, 1H), 4.72 (ABq, *J* = 11.2 Hz, Δν = 27.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.8, 147.8, 147.3, 133.1, 131.4, 129.8, 123.5, 121.9, 109.1, 108.1, 103.9, 101.0, 70.4, 70.2; IR (film) 1491, 1445, 1250, 1001, 727 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{13}NO_4 + H]^+$: 272.0917, found 272.0918.



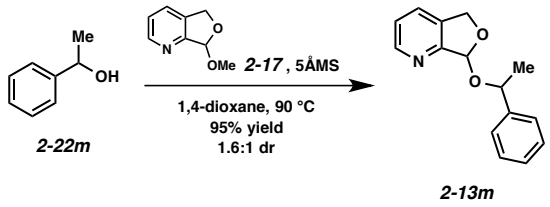
In a 2-dram vial with a PTFE-lined cap, a suspension of 4-bromobenzyl alcohol (**2-22k**, 56.1 mg, 0.300 mmol), methyl acetal **2-17** (47.6 mg, 0.315 mmol), and 5Å molecular sieves (375 mg) in 1,4-dioxane (0.476 mL) was heated at 90 °C (without stirring) for 4 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (3:2 EtOAc/hexanes eluent) to afford acetal **2-13k** (90.1 mg, 99% yield, R_f = 0.36 in 3:2 EtOAc/hexanes) as a white solid.

Acetal 2-13k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.8 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.28 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.20 (d, *J* = 1.6 Hz, 1H), 5.25 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.09 (d, *J* = 13.2 Hz, 1H), 4.78 (ABq, *J* = 12.0 Hz, Δν = 23.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.9, 136.8, 133.2, 131.6, 130.0, 129.8, 123.7, 121.7, 104.3, 70.6, 69.5; IR (film) 2922, 1489, 1070, 1007, 795 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{12}BrNO_2 + H]^+$: 306.0124, found 306.0130.



4-Iodobenzyl alcohol **2-22l** (454 mg, 1.94 mmol) was subjected to the general procedure for 18 h. The crude residue purified by flash column chromatography (13:7 hexanes/EtOAc eluent) to afford acetal **2-13l** (604 mg, 88% yield, R_f = 0.29 in 13:7 hexanes/EtOAc) as a white solid.

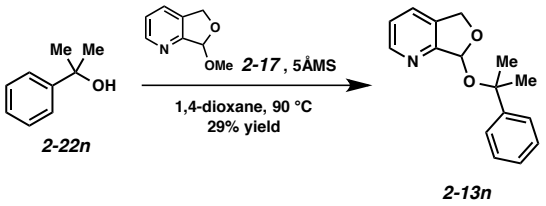
Acetal 2-13l: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.6 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.64 (d, 7.6 Hz, 1H), 7.28 (dd, *J* = 7.6, 4.6 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.20 (d, *J* = 2.0 Hz, 1H), 5.25 (dd, *J* = 13.2, 2.0 Hz, 1H), 5.09 (d, *J* = 13.2 Hz, 1H), 4.77 (ABq, *J* = 13.0 Hz, Δν = 23.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 150.0, 137.6, 137.5, 133.2, 130.1, 130.0, 123.7, 104.3, 93.4, 70.6, 69.6; IR (film) 1488, 1080, 1001, 913, 792 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{12}INO_2 + H]^+$: 354.0, found 354.0.



In a 2-dram vial with a PTFE-lined cap, a suspension of α-methylbenzyl alcohol (**2-22m**, 36.7 mg, 0.300 mmol), methyl acetal **2-17** (47.6 mg, 0.315 mmol), and 5Å molecular sieves (375 mg) in 1,4-dioxane (0.476 mL) was heated at 90 °C (without stirring) for 18 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford acetal **2-13m** (major diastereomer, 42.4 mg, 59% yield, R_f = 0.33 in 3:2 hexanes/EtOAc) as a colorless oil and acetal **2-13m** (minor diastereomer, 26.3 mg, 36% yield, R_f = 0.21 in 3:2 hexanes/EtOAc) as a colorless oil that slowly transformed to a white solid.

Acetal 2-13m (major diastereomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.6 Hz, 1H), 5.96 (d, *J* = 1.6 Hz, 1H), 5.25 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.06 (q, *J* = 6.4 Hz, 1H), 5.03 (d, *J* = 13.2 Hz, 1H), 1.52 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 149.9, 142.8, 133.3, 129.8, 128.7, 127.8, 126.8, 123.5, 102.0, 75.3, 70.2, 24.5; IR (film) 1082, 1001, 914, 764, 702 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{15}NO_2 + H]^+$: 242.1176, found 242.1177.

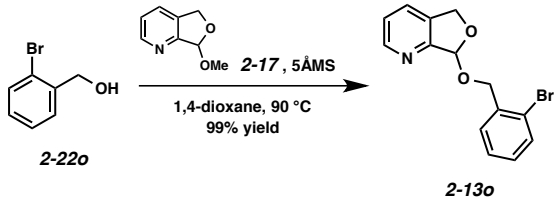
Acetal 2-13m (minor diastereomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.8 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.29-7.23 (comp. m, 2H), 6.27 (d, *J* = 1.6 Hz, 1H), 5.11 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.06 (q, *J* = 6.4 Hz, 1H), 4.95 (d, *J* = 13.2 Hz, 1H), 1.60 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 149.8, 144.3, 133.2, 129.9, 128.4, 127.4, 126.3, 123.5, 103.9, 103.8, 70.2, 23.3; IR (film) 1072, 1003, 912, 791, 700 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{15}NO_2 + H]^+$: 242.1176, found 242.1176



In a 2-dram vial with a PTFE-lined cap, a suspension of 2-phenyl-2-propanol (**2-22n**, 54.5 mg, 0.400 mmol), methyl acetal **2-17** (63.5 mg, 0.420 mmol), and 5Å molecular sieves (500 mg) in 1,4-dioxane (0.635 mL) was heated at 90 °C (without stirring) for 6.5 h. Upon completion, the reaction was cooled to ambient temperature and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), concentrated by rotary evaporation, and purified by flash column

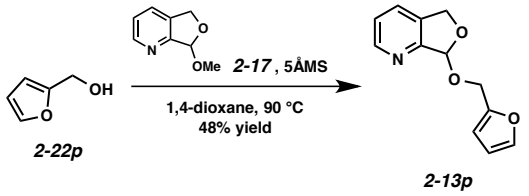
chromatography (4:1 hexanes/EtOAc eluent) to afford acetal **2-13n** (29.6 mg, 29% yield, R_f = 0.22 in 4:1 hexanes/EtOAc) as a white solid.

Acetal 2-13n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.24 (dd, *J* = 7.2, 4.8 Hz, 1H), 6.12 (s, 1H), 5.22 (d, *J* = 12.8 Hz, 1H), 4.94 (d, *J* = 12.8 Hz, 1H), 1.82 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 149.9, 146.4, 133.1, 129.7, 128.4, 127.2, 126.4, 123.2, 101.0, 79.2, 69.9, 31.6, 28.4; IR (film) 1368, 1065, 999, 911, 762 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{17}NO_2 + H]^+$: 256.1332, found 256.1334.



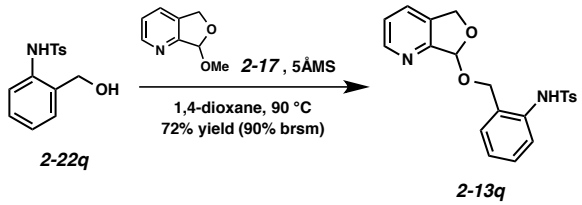
2-bromo alcohol **2-22o** (93.5 mg, 0.500 mmol) was subjected to the general procedure for 16 h. The crude residue purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford acetal **2-13o** (152 mg, 99% yield, R_f = 0.33 in 3:2 hexanes/EtOAc) as a white solid.

Acetal 2-13o: ^{1}H (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.33-7.27 (comp. m, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.27 (s, 1H), 5.29 (d, *J* = 13.2 Hz, 1H), 5.11 (d, *J* = 13.2 Hz, 1H), 4.92 (ABq, *J* = 13.2 Hz, Δν = 33.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.0, 137.3, 133.3, 132.5, 130.0, 129.5, 129.1, 127.5, 123.7, 122.8, 104.7, 70.7, 69.6; IR (film) 1086, 1007, 914, 752, 669 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{12}BrNO_2 + H]^+$: 306.0, found 306.0.



Alcohol **2-22p** (29.4 mg, 0.300 mmol) was subjected to the general procedure for 78 h. The crude residue purified by flash column chromatography (8:2 hexanes/EtOAc eluent) to afford acetal **2-13p** (31.0 mg, 48% yield, R_f = 0.28 in 6:4 hexanes/EtOAc) as a white solid.

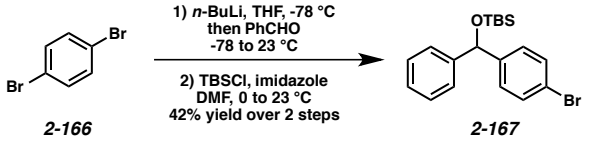
Acetal 2-13p: ^{1}H (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8, Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.40 (d, *J* = 2.8 Hz, 1H), 6.33 (d, *J* = 2.8 Hz, 1H), 6.20 (d, *J* = 1.6 Hz, 1H), 5.26 (dd, *J* = 13.0, 1.6 Hz, 1H), 5.08 (d, *J* = 13.0 Hz, 1H), 4.78 (ABq, *J* = 13.0, Δν = 16.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.2, 149.9, 143.1, 133.2, 129.9, 123.6, 110.4, 110.0, 103.8, 70.6, 62.2; IR (film) 1070, 1003, 924, 793, 745 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{11}NO_3 + Na]^+$: 240.1, found 240.1.



Alcohol **2-22q** (1.66 mg, 0.600 mmol) was subjected to the general procedure for 34 h. The crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford acetal **2-13q** (172 mg, 72% yield, 90% brsm, R_f = 0.32 in 1:1 hexanes/EtOAc) as a white film.

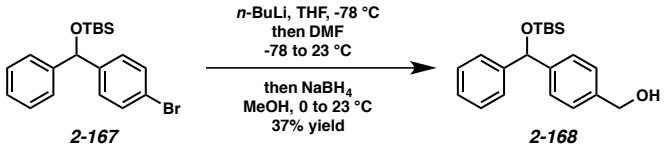
Acetal 2-13q: ^{1}H (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.8 Hz, 1H), 8.29 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.27 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.18 (s, 1H), 5.45 (d, *J* = 13.2 Hz, 1H), 5.21 (d, *J* = 13.2 Hz, 1H), 4.44 (s, 2H), 2.36 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 156.3, 150.3, 143.6, 137.3, 136.8, 132.9, 130.34, 130.32, 129.8, 129.6, 128.2, 127.1, 125.0, 124.2, 123.2, 104.6, 71.2, 68.8, 21.7; IR (film) 3274, 1336, 1157, 1005, 910 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{20}N_2O_4S + H]^+$: 397.1217, found 397.1216.



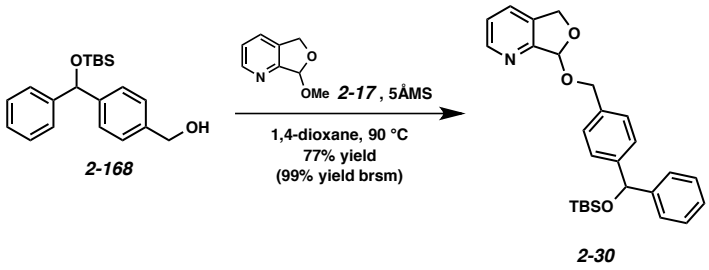
2-166 *2-167*

To a solution of 1,4-dibromobenzene (**2-166**, 2.00 g, 8.48 mmol) in THF (42.4 mL) at -78 °C was added *n*-BuLi (3.56 mL, 2.50 M in hexanes, 8.90 mmol) over 5 min, and the solution was stirred for 30 min. To this solution was added benzaldehyde (0.948 mL, 9.33 mmol) dropwise over 1 min, and the solution was left to stir for 30 min before the cooling bath was removed and the reaction was allowed to warm to 23 °C. The reaction mixture was diluted with water (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (4:1 hexanes/Et_2O) to afford the alcohol (2.04 g, R_f = 0.22 in 4:1 hexanes/Et_2O) that was sufficiently pure to be carried to the next step. This material was dissolved in DMF (14.5 mL) and cooled to 0 °C. TBSCl (2.33 g, 15.5 mmol) and then imidazole (1.58 g, 23.2 mmol) were added to the stirring solution, and it was maintained at 0 °C for 30 min before the solution was warmed to 23 °C. The solution was stirred at 23 °C for 24 h, and it was then diluted with water (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (hexanes eluent) to afford silyl ether **2-167** (1.89 g, 42% yield over 2 steps, R_f = 0.38 in hexanes) as a colorless oil.



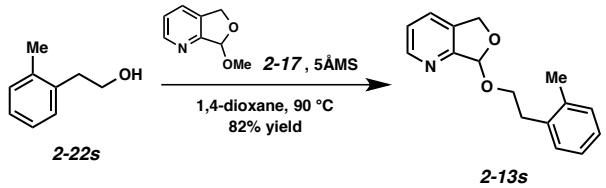
To a solution of silyl ether **2-167** (783 mg, 2.08 mmol) in THF (10.3 mL) at -78 °C was added *n*-BuLi (0.871 mL, 2.50 M in hexanes, 2.18 mmol) over 5 min, and the solution was stirred for 30 min. To this orange solution was added DMF (0.800 mL, 10.4 mmol) dropwise over 1 min, and the solution was stirred for 30 min before the cooling bath was removed, and the reaction was allowed to warm to 23 °C. The reaction mixture was cooled to 0 °C, and MeOH (5.20 mL) was added, followed by $NaBH_4$ (157 mg, 4.15 mmol) in 1 portion. The cooling bath was removed, and the suspension was stirred for 10 min at 23 °C. The reaction mixture was diluted with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude alcohol was purified by flash column chromatography (3:2 hexanes/Et_2O) to afford alcohol **2-168** (254 mg, 37% yield, R_f = 0.33 in 3:2 hexanes/Et_2O) as a colorless oil.

Alcohol 2-168: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.0 Hz, 1H), 5.77 (s, 1H), 4.64 (s, 2H), 1.79 (s, 1H), 0.94 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 144.9, 139.6, 128.3, 127.1, 126.6, 126.3, 76.5, 65.3, 26.0, 18.4, -4.68, -4.70; IR (film) 3113, 862, 835, 778, 699 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{28}O_2Si + Na]^+$: 351.1751, found 351.1751.



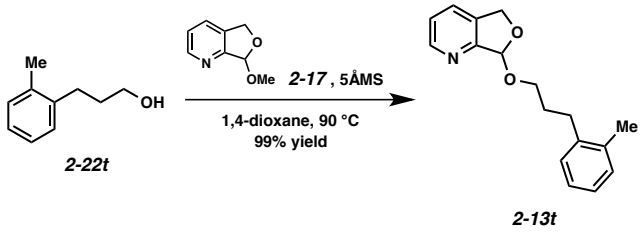
In a 2-dram vial with a PTFE-lined cap, a suspension of alcohol **2-168** (98.6 mg, 0.300 mmol), methyl acetal **2-17** (47.6 mg, 0.315 mmol), and 5Å molecular sieves (375 mg) in 1,4-dioxane (0.476 mL) was heated at 90 °C (without stirring) for 19 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-30** (104 mg, 77% yield (99% yield brsm), R_f = 0.34 in 7:3 hexanes/EtOAc) as a colorless oil.

Acetal 2-30: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.5 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.38-7.32 (comp. m, 6H), 7.29-7.23 (comp. m, 3H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 5.75 (s, 1H), 5.25 (dd, *J* = 13.0, 2.0 Hz, 1H), 5.08 (d, *J* = 13.0 Hz, 1H), 4.78 (ABq, *J* = 11.5 Hz, Δν = 36.6 Hz, 2H), 0.92 (s, 9H), -0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 149.8, 145.3, 144.9, 136.2, 133.2, 129.9, 128.24, 128.22, 127.0, 126.4, 126.3, 123.6, 104.2, 76.6, 70.5, 70.1, 25.6, 18.4, -4.69, -4.74; IR (film) 1066, 1009, 863, 837, 775 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{27}H_{33}NO_3Si + H]^+$: 448.2302, found 448.2302.



In a 2-dram vial with a PTFE-lined cap, a suspension of alcohol **2-22s** (68.1 mg, 0.500 mmol), methyl acetal **2-17** (79.4 mg, 0.525 mmol), and 5Å molecular sieves (625 mg) in 1,4-dioxane (0.794 mL) was heated at 90 °C (without stirring) for 16 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (13:7 hexanes/EtOAc eluent) to afford acetal **2-13s** (105 mg, 82% yield, R_f = 0.28 in 13:7 hexanes/EtOAc) as a beige oil.

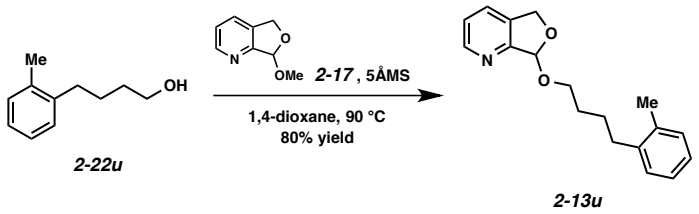
Acetal 2-13s: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.28 (dd, *J* = 7.2, 4.8 Hz, 1H), 7.22-7.08 (comp. m, 4H), 6.19 (s, 1H), 5.22 (d, *J* = 12.8 Hz, 1H), 5.07 (d, *J* = 12.8 Hz, 1H), 4.03-3.84 (comp. m, 2H), 3.10-2.93 (comp. m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.9, 136.53, 136.47, 133.1, 130.2, 129.9, 129.4, 126.5, 126.1, 123.6, 105.0, 70.4, 68.4, 33.8, 19.5; IR (film) 1098, 1003, 914, 793, 746 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{17}NO_2 + H]^+$: 256.1332, found 256.1334.



In a 2-dram vial with a PTFE-lined cap, a suspension of alcohol **2-22t** (15.0 mg, 0.100 mmol), methyl acetal **2-17** (15.9 mg, 0.105 mmol), and 5Å molecular sieves (125 mg) in 1,4-dioxane (0.159 mL) was heated at 90 °C (without stirring) for 13 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1

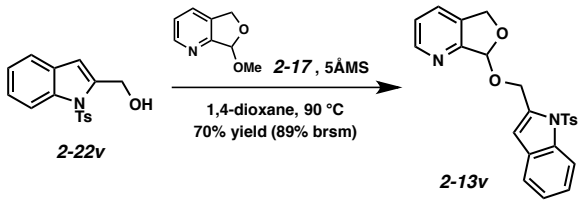
EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (4:1 hexanes/acetone eluent) to afford acetal **2-13t** (26.6 mg, 99% yield, R_f = 0.14 in 4:1 hexanes/acetone) as a beige oil.

Acetal 2-13t: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.28 (dd, *J* = 7.2, 4.8 Hz, 1H), 7.19-7.06 (comp. m, 4H), 6.15 (s, 1H), 5.25 (d, *J* = 12.8 Hz, 1H) 5.08 (d, *J* = 12.8 Hz, 1H), 3.93-3.83 (comp. m, 1H), 3.81-3.73 (comp. m, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.96 (app. quint, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.9, 140.1, 136.1, 133.1, 130.2, 129.9, 129.0, 126.00, 125.97, 123.6, 105.2, 70.4, 68.4, 30.2, 29.7, 19.4; IR (film) 1370, 1087, 1008, 793, 746 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{19}NO_2 + H]^+$: 270.1489, found 270.1490.



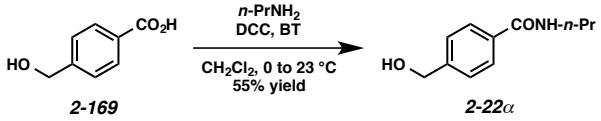
In a 2-dram vial with a PTFE-lined cap, a suspension of alcohol **2-22u**[47] (82.1 mg, 0.500 mmol), methyl acetal **2-17** (79.4 mg, 0.525 mmol), and 5Å molecular sieves (625 mg) in 1,4-dioxane (0.794 mL) was heated at 90 °C and stirred for 13 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (150 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13u** (113 mg, 80% yield, R_f = 0.33 in 7:3 hexanes/EtOAc) as a colorless oil.

Acetal 2-13u: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.0 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.27 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.13-7.05 (comp. m, 4H), 6.12 (d, *J* = 2.0 Hz, 1H), 5.22 (dd, *J* = 13.3, 2.0 Hz, 1H), 5.06 (d, *J* = 13.2 Hz, 1H), 3.87 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.76 (dt, *J* = 9.5, 6.5 Hz, 1H), 2.62 (dt, *J* = 8.3, 1.5 Hz, 2H), 2.29 (s, 3H), 1.80-1.72 (comp. m, 2H), 1.70-1.62 (comp. m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 150.0, 140.8, 136.1, 133.2, 130.3, 130.0, 129.1, 126.02, 125.99, 123.7, 105.1, 70.5, 69.0, 33.2, 29.9, 26.9, 19.5; IR (film) 1092, 1004, 909, 786, 744 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{21}NO_2 + H]^+$: 284.1648, found 284.1648.



Alcohol **2-22v** (226 mg, 0.750 mmol) was subjected to the general procedure 34 h. The crude residue purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13v** (222 mg, 70% yield (89% brsm), R_f = 0.13 in 7:3 hexanes/EtOAc) as a white foam.

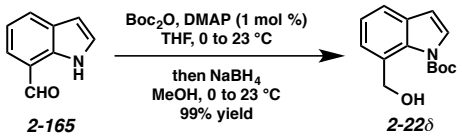
Acetal 2-13v: ^{1}H (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.4, Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.35-7.24 (comp. m, 2H), 7.19 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 6.34 (s, 1H), 5.34-5.26 (comp. m, 2H), 5.22 (d, *J* = 13.6 Hz, 1H), 5.12 (d, *J* = 13.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.8, 144.8, 137.2, 137.0, 135.7, 133.4, 130.0, 129.8, 129.4, 127.2, 124.6, 123.7, 123.5, 121.1, 114.5, 111.5, 104.4, 70.6, 63.6, 21.7; IR (film) 1368, 1173, 1005, 910, 726 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{20}N_2O_4S + H]^+$: 421.1217, found 421.1218.



2-169 *2-22α*

To a stirring suspension of acid **2-169** (100 mg, 0.657 mmol), *n*-$PrNH_2$ (119 μL, 1.45 mmol), and DCC (570 mg, 2.76 mmol) was added BT (195 mg, 1.45 mmol) at 0 °C, and then this suspension was warmed to 23 °C and stirred for 36 h. The reaction mixture was then added to 1 M HCl (50 mL) and extracted into EtOAc (50 mL). The organic layer was washed with sat. Na_2CO_3 (50 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (7:3 hexanes/EtOAc) to afford amide **2-22α** (70.0 mg, 55% yield, R_f = 0.19 in 7:3 hexanes/EtOAc) as a white solid.

Amide 2-22α: ^{1}H (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.2, Hz, 1H), 7.81 (d, *J* = 4.2 Hz, 1H), 6.24 (br. s, 1H), 3.94 (s, 1H), 3.43 (q, *J* = 7.2 Hz, 2H), 1.65 (sextet, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 132.7, 130.0, 127.0, 52.5, 42.0, 23.0, 11.6; IR (film) 1722, 1634, 1549, 1281, 1113 cm^{-1}.



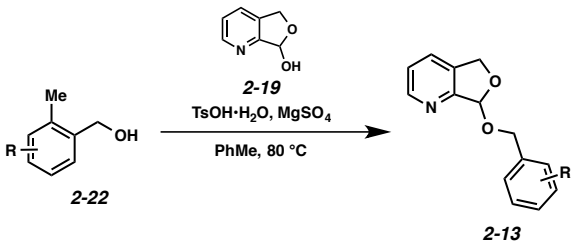
2-165 *2-22δ*

To a stirring solution of 7-formylindole (**2-165**[46], 100 mg, 0.679 mmol) in THF (4.00 mL) at 23 °C was added Boc_2O (222 mg, 1.02 mmol) and then DMAP (4.9 mg, 6.79 μmol). After 24 h, the reaction mixture was cooled to 0 °C, MeOH (3.40 mL) was added, and then $NaBH_4$ (77.1 mg, 2.04 mmol) was added in one portion. After 1 h, 1 M HCl (50 mL) was added carefully and the reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The

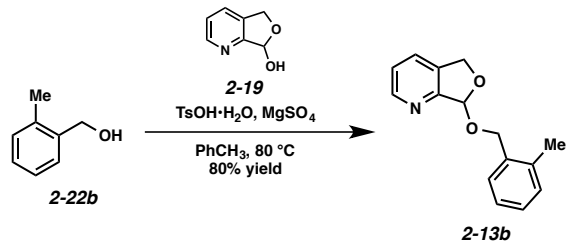
resulting residue was purified with flash column chromatography (9:1 hexanes/EtOAc) to afford alcohol **2-22δ** (167 mg, 99% yield, R_f = 0.18 in 9:1 hexanes/EtOAc) as a light yellow oil.

Alcohol 2-22δ: ^{1}H (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.8, Hz, 1H), 7.51 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.32 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 3.8 Hz, 1H), 4.89 (s, 2H), 3.95 (br. s, 1H), 1.66 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 133.6, 132.5, 128.33, 128.26, 127.8, 123.7, 121.2, 108.2, 84.5, 64.9, 28.2; IR (film) 3433, 1731, 1328, 1151, 1020 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{17}NO_3 + Na]^+$: 270.1, found 270.1.

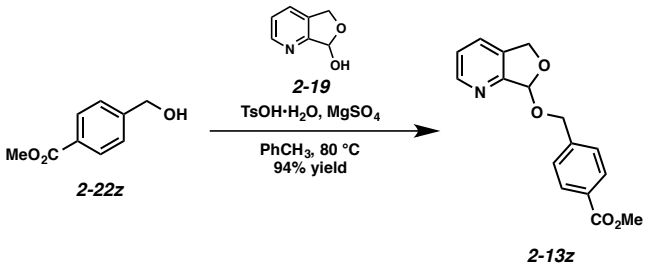
General Procedure for the Dehydrative Attachment of Substrates to the PyA Scaffold



A suspension of alcohol **2-22** (1 equiv), hemiacetal **2-19** (1.05 equiv), TsOH•H_2O (10 mol %), and $MgSO_4$ (3 equiv) in $PhCH_3$ (0.33 M) in either a sealed round-bottom flask (caped with a plastic yellow cap) or a vial sealed with a PTFE cap was heated to 80 °C and stirred until determined to be complete by TLC. Upon completion, water was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography to afford acetal **2-13**.



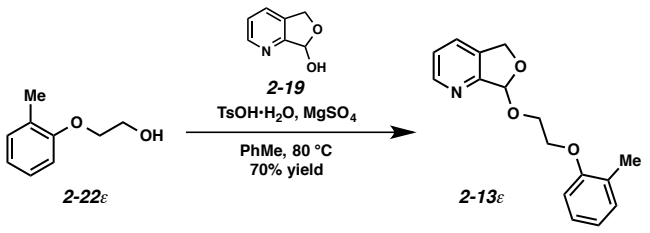
A suspension of alcohol **2-22b** (1.04 g, 8.47 mmol), hemiacetal **2-19** (1.22 g, 8.90 mmol), $TsOH•H_2O$ (161 mg, 0.847 mmol), and $MgSO_4$ (3.06 g, 25.4 mmol) in $PhCH_3$ (25.7 mL) was heated to 80 °C and stirred for 4.5 h. Upon completion, water (50 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford acetal **2-13b** (1.63 g, 80% yield, R_f = 0.36 in 3:2 hexanes/EtOAc) as a colorless oil.



A suspension of alcohol **2-22z** (28.7 mg, 0.173 mmol), hemiacetal **2-19** (25.0 mg, 0.182 mmol), $TsOH•H_2O$ (3.3 mg, 17.3 μmol), and $MgSO_4$ (62.5 mg, 0.519 mmol) in $PhCH_3$ (0.576 mL) in a 2-dram vial was heated to 80 °C and stirred for 24 h. Upon completion, water (15 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford acetal **2-13z** (46.2 mg, 94% yield, R_f = 0.30 in 3:2 hexanes/EtOAc) as a white solid.

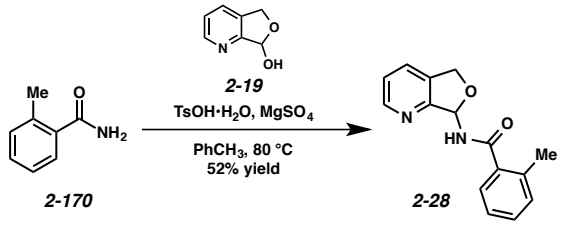
Acetal 2-13z: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.29 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.23 (s, 1H), 5.26 (d, *J* = 13.2 Hz, 1H), 5.09 (d, *J* = 13.2 Hz, 1H), 4.89 (ABq, *J* = 12.4 Hz, Δν = 22.3, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 157.4, 150.0, 143.1, 133.2, 130.0, 129.8,

129.5, 127.7, 123.8, 104.6, 70.6, 69.6, 52.2; IR (film) 1719, 1279, 1108, 1008, 755 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{15}NO_4 + H]^+$: 286.1074, found 286.1075.



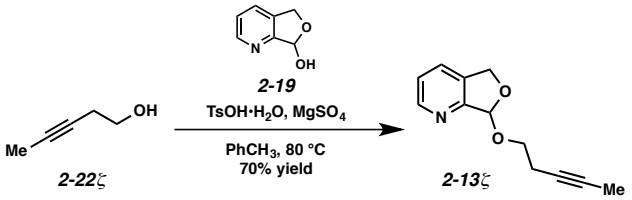
Alcohol **2-22ε** (152 mg, 1.00 mmol) was subjected to the general procedure for 38 h. The crude residue purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford acetal **2-13ε** (189 mg, 70% yield, R_f = 0.36 in 1:1 hexanes/EtOAc) as a colorless oil.

Acetal 2-22ε: ^{1}H (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.8, Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.29 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.16-7.09 (comp. m, 2H), 6.87-6.79 (comp. m, 2H), 6.26 (d, *J* = 2.0 Hz, 1H), 5.26 (dd, *J* = 13.2, 2.0 Hz, 1H), 5.09 (d, *J* = 13.2, 2H), 4.24-4.21 (comp. m, 4H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 157.0, 149.9, 130.8, 130.1, 126.8, 123.8, 120.6, 111.3, 105.2, 70.5, 67.4, 67.0, 16.4; IR (film) 1591, 1496, 1250, 1008, 751 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{17}NO_3 + H]^+$: 272.1, found 272.1.



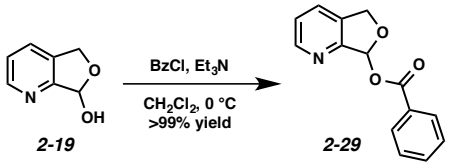
Alcohol **2-170** (135 mg, 1.00 mmol) was subjected to the general procedure for 38 h. The crude residue purified by flash column chromatography (EtOAc eluent) to afford benzamide **2-28** (172 mg, 55% yield, R_f = 0.30 /EtOAc) as a white solid.

Benzamide 2-28: ^{1}H (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.4, Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.33-7.27 (comp. m, 2H), 7.24-7.14 (comp. m, 2H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 5.19 (ABq, *J* = 13.2, Δν = 37.9 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 157.5, 150.1, 136.9, 135.4, 133.6, 131.3, 130.4, 130.0, 127.1, 125.8, 123.7, 83.5, 70.3, 20.1; IR (film) 3283, 1661, 1523, 1016, 745 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{14}N_2O_2 + H]^+$: 255.1, found 255.1.



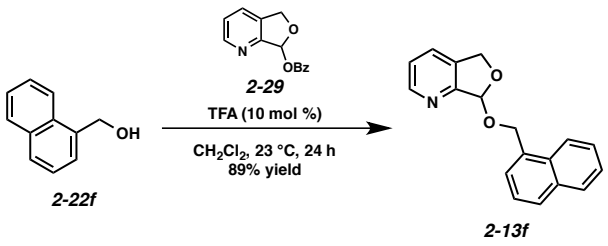
Alcohol **2-22ζ** (84.1 mg, 1.94 mmol) was subjected to the general procedure for 38 h. The crude residue purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford acetal **2-13ζ** (142 mg, 70% yield, R_f = 0.42 in 1:1 hexanes/EtOAc) as a colorless oil.

Acetal 2-13ζ: ^{1}H (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.8, Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.13 (d, *J* = 1.6 Hz, 1H), 5.22 (dd, *J* = 13.2 Hz, 1H), 5.06 (d, *J* = 13.2 Hz, 1H), 3.90-3.76 (comp. m, 2H), 2.59-2.42 (comp. m, 2H), 1.76 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.9, 133.2, 129.9, 123.7, 105.0, 77.0, 75.5, 70.5, 67.4, 20.5, 3.7; IR (film) 1090, 1024, 1003, 913, 789 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{13}NO_2 + Na]^+$: 226.11, found 226.1.



To a stirring solution of hemiacetal **2-19** (125.0 mg, 0.911 mmol) and Et_3N (140 µL, 1.00 mmol) in CH_2Cl_2 (3.00 mL) at 0 °C was added BzCl (116 µL, 1.00 mmol) over 1 min, and the reaction mixture was warmed to 23 °C and stirred for 2 h. Upon completion by TLC, CH_2Cl_2 (20 mL) and sat. Na_2CO_3 (20 mL) were added to the reaction mixture. The organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (6:4 hexanes/EtOAc eluent) to afford benzoate **2-29** (262 mg, >99% yield, R_f = 0.45 in 6:4 hexanes/EtOAc) as a white solid.

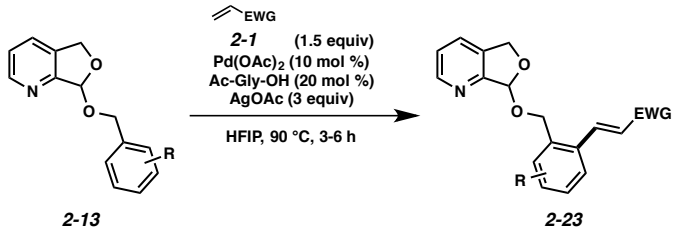
Benzoate 2-29: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.8, Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.43-7.35 (comp. m, 3H), 5.38 (d, *J* = 13.2 Hz, 1H), 5.22 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 156.1, 150.2, 133.4, 133.2, 130.0, 129.8, 129.7, 128.3, 124.0, 98.6, 71.7; IR (film) 1721, 1263, 1047, 931, 710 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{11}NO_3 + H]^+$: 242.0812, found 242.0810.



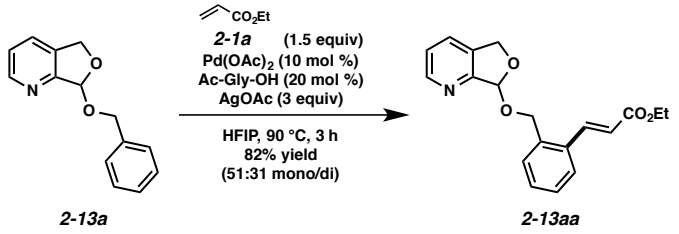
To a solution of alcohol **2-22f** (15.8 mg, 0.100 mmol) and benzoate **2-29** (36.2 mg, 0.150 mmol) in CH_2Cl_2 (0.330 mL) in a 2-dram vial was added TFA (2.2 µL, 10.0 µmol) and stirred for 24 h at 23 °C. Upon completion by TLC, water (15 mL) was added, and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash

column chromatography (3:2 hexanes/EtOAc eluent) to afford acetal **2-13f** (24.7 mg, 89% yield, R_f = 0.35 in 3:2 hexanes/EtOAc) as a white solid.

General Procedure for the Alkenylation of PyA Scaffold Acetals



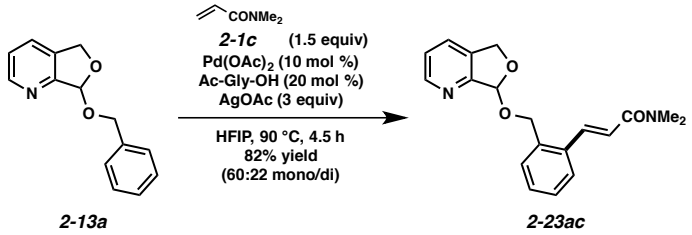
A suspension of acetal **2-13** (1 equiv), alkene (**2-1**, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 10 mol %), *N*-acetylglycine (20 mol %), and AgOAc (3 equiv) in hexafluoroisopropanol (0.05 M) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3-6 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (~150 wt % relative to **2-13**) and celite (~300 wt % relative to **2-13**) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2, the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2. The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography to afford olefin **2-23**.



A suspension of acetal **2-13a** (22.7 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap

was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford olefin **2-23aa** (29.7 mg, 82% yield, 1:0.61 mono/di, R_f = 0.21 in 3:2 hexanes/EtOAc) as a colorless oil.

Olefin 2-23aa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 8.55 (d, *J* = 4.8 Hz, 0.61H), 8.19 (d, *J* = 15.8 Hz, 1.22H), 8.10 (d, *J* = 15.8 Hz, 1H), 7.64 (app. d, *J* = 7.6 Hz, 1.61H), 7.57 (app. t, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.37-7.22 (comp. m, 4.44H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1.22H), 6.29 (s, 0.61H), 6.26 (s, 1H), 5.53 (d, *J* = 13.6 Hz, 0.61H), 5.42 (d, *J* = 13.2 Hz, 1H), 5.20-5.05 (comp. m, 3.22H), 4.91 (d, *J* = 10.8 Hz, 0.61H), 4.78 (d, *J* = 11.2 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2.44H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3.66H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.6, 157.3, 157.1, 149.73, 149.71, 142.0, 141.7, 136.3, 136.2, 134.3, 133.8, 133.32, 133.26, 130.2, 129.9, 129.81, 129.78, 128.9, 128.42, 128.36, 126.6, 123.5, 121.9, 120.2, 104.3, 104.2, 70.7, 70.5, 67.9, 62.6, 60.6, 60.4, 14.3; IR (film) 1710, 1637, 1312, 1165, 1003 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M_{mono} + H)^+$ $[C_{19}H_{19}NO_4 + H]^+$: 326.1387, found 326.1390; HRMS (ESI+) *m/z* calc'd for $(M_{di} + H)^+$ $[C_{24}H_{25}NO_6 + H]^+$: 424.1755, found 424.1756.

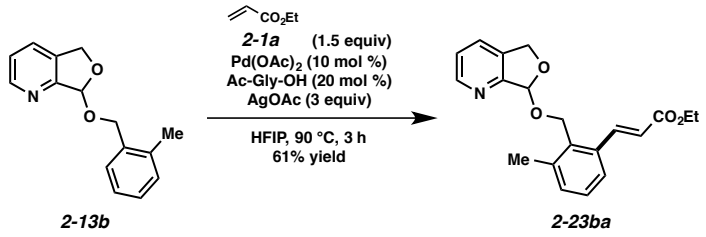


A suspension of acetal **2-13a** (22.7 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (19:1 EtOAc/hexanes eluent) to afford monoolefin **2-23ac** (19.6 mg, 60% yield, R_f = 0.31 in 19:1 EtOAc/hexanes) as a white solid. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory plate chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23ac** (9.3 mg, 22% yield, R_f = 0.22 in EtOAc/MeOH) as a white solid.

Monoolefin 2-23ac: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.8 Hz, 1H), 8.00 (d, *J* = 15.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.35-7.23 (comp. m, 3H), 6.83 (d, *J* = 15.2 Hz, 1H), 6.25 (s, 1H), 5.45 (d, *J* = 13.2 Hz, 1H), 5.14 (d, *J* = 13.2 Hz, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 3.16 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 157.6, 149.8, 139.5, 136.2, 135.1, 133.6, 130.2, 130.0, 129.4,

128.3, 126.8, 123.6, 120.2, 104.3, 70.7, 67.8, 37.7, 36.1; IR (film) 1768, 1652, 1605, 1389, 1005 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{20}N_2O_3 + H]^+$: 325.1547, found 325.1554.

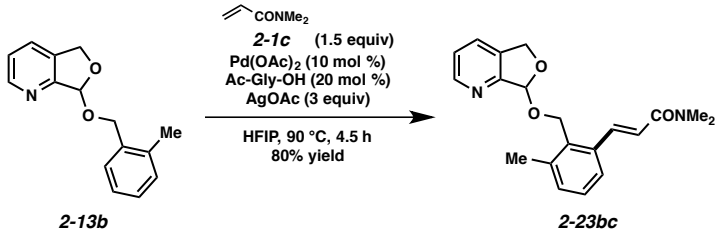
Diolefin 2-23ac: ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.8 Hz, 1H), 8.08 (d, *J* = 15.2 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.83 (d, *J* = 15.6 Hz, 2H), 6.27 (s, 1H), 5.57 (d, *J* = 13.6 Hz, 1H), 5.18 (d, *J* = 13.6 Hz, 1H), 5.08 (d, *J* = 10.4 Hz, 1H), 4.86 (d, *J* = 10.4 Hz, 1H), 3.18 (s, 6H), 3.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 157.4, 149.6, 140.1, 137.8, 133.71, 133.69, 130.0, 128.8, 128.1, 123.6, 121.9, 104.1, 70.9, 63.3, 37.7, 36.1; IR (film) 1645, 1600, 1391, 995, 727 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{27}N_3O_4 + H]^+$: 422.2074, found 422.2077.



A suspension of acetal **2-13b** (121 mg, 0.500 mmol), ethyl acrylate (**2-1a**, 79.8 μL, 0.750 mmol), $Pd(OAc)_2$ (11.2 mg, 50.0 μmol), *N*-acetylglycine (11.7 mg, 0.100 mmol), and AgOAc (250 mg, 1.50 mmol) in hexafluoroisopropanol (10.0 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation and the crude residue was

purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford olefin **2-23ba** (104 mg, 61% yield, R_f = 0.27 in 3:2 hexanes/EtOAc) as a beige oil.

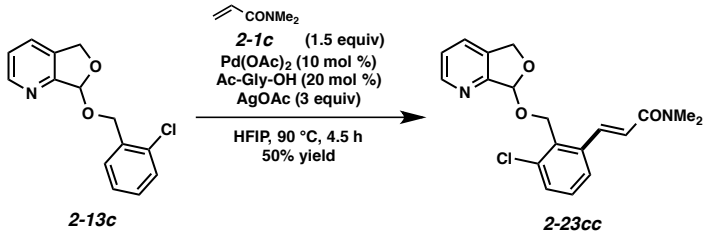
Olefin 2-23ba: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.21 (d, *J* = 16.0 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.39 (dd, *J* = 5.6, 4.2 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.20 (d, *J* = 5.6 Hz, 1H), 7.20 (d, *J* = 4.2 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.24 (d, *J* = 2.0 Hz, 1H), 5.42 (dd, *J* = 13.6, 2.0 Hz, 1H), 5.15 (d, *J* = 13.6 Hz, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 4.86 (d, *J* = 10.4 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 157.6, 149.9, 143.1, 139.1, 135.6, 134.2, 133.4, 132.2, 129.9, 128.7, 124.9, 123.6, 120.9, 104.4, 70.7, 63.6, 60.5, 19.8, 14.5; IR (film) 1707, 1312, 1178, 1165, 1001 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{21}NO_4 + H]^+$: 340.1543, found 340.1539.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was

concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (9:1 EtOAc/MeOH eluent) to afford olefin **2-23bc** (27.1 mg, 80% yield, R_f = 0.26 in 9:1 EtOAc/MeOH) as a white solid.

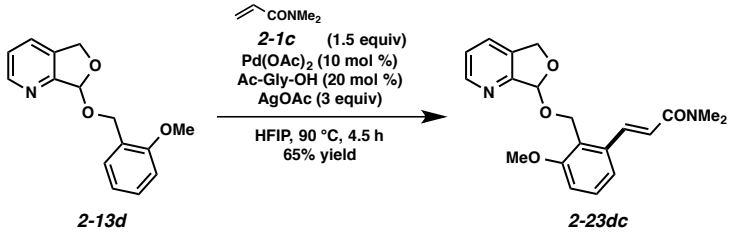
Olefin 2-23bc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.09 (d, *J* = 15.4 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.34 (app. d, *J* = 6.8 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.17 (app. s, 1H), 6.80 (d, *J* = 15.4 Hz, 1H), 6.23 (s, 1H), 5.44 (d, *J* = 13.2 Hz, 1H), 5.15 (d, *J* = 13.2 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 4.83 (d, *J* = 10.2 Hz, 1H), 3.16 (s, 3H), 3.08 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 157.6, 149.7, 140.7, 139.2, 137.0, 133.8, 133.5, 131.4, 129.9, 128.5, 125.2, 123.6, 121.0, 104.3, 70.7, 63.8, 37.7, 36.1, 19.8; IR (film) 1651, 1610, 1387, 1069, 1003 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{22}N_2O_3 + H]^+$: 339.1703, found 339.1706.



A suspension of acetal **2-13c** (25.7 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second

plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc eluent) to afford olefin **2-23cc** (27.5 mg, 50% yield, R_f = 0.32 in EtOAc) as a white solid.

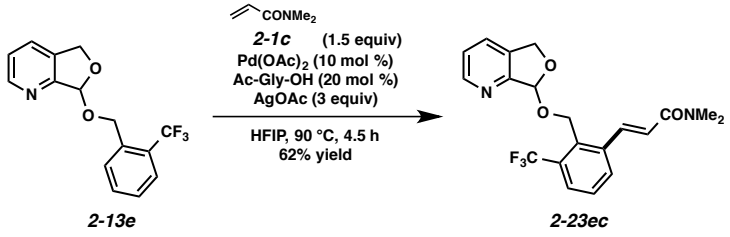
Olefin 2-23cc: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.5 Hz, 1H), 8.01 (d, *J* = 15.1 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.25-7.19 (comp. m, 2H), 6.81 (d, *J* = 15.1 Hz, 1H), 6.27 (d, *J* = 1.5 Hz, 1H), 5.45 (dd, *J* = 13.5, 1.5 Hz, 1H), 5.13 (d, *J* = 13.5 Hz, 1H), 5.11 (d, *J* = 10.5 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 3.13 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 157.6, 149.8, 139.6, 139.1, 133.6, 133.4, 130.30, 129.99, 129.6, 125.9, 123.7, 122.2, 104.5, 70.8, 64.0, 37.7, 36.1; IR (film) 1651, 1609, 1065, 998, 788 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{19}ClN_2O_3 + H]^+$: 359.1157, found 359.1158.



A suspension of acetal **2-13d** (24.2 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary

evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc eluent) to afford olefin **2-23dc** (23.0 mg, 65% yield, R_f = 0.29 in EtOAc) as a white solid.

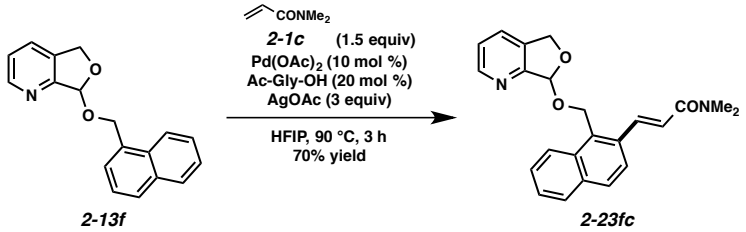
Olefin 2-23dc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.0 Hz, 1H), 8.04 (d, *J* = 15.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.24 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.21 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 15.4 Hz, 1H), 6.26 (s, 1H), 5.48 (d, *J* = 13.4 Hz, 1H), 5.13 (d, *J* = 13.4 Hz, 1H), 5.01 (ABq, *J* = 10.0 Hz, Δν = 18.6 Hz, 2H), 3.84 (s, 3H), 3.12 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 158.6, 157.8, 149.6, 140.1, 138.1, 133.7, 129.9, 129.4, 124.5, 123.4, 120.9, 119.2, 111.5, 104.4, 70.6, 60.5, 56.0, 37.6, 36.1; IR (film) 1646, 1392, 1252, 995, 788 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{22}N_2O_4 + H]^+$: 355.1652, found 355.1652.



A suspension of acetal **2-13e** (19.7 mg, 66.7 μmol), *N,N*-dimethylacrylamide (**2-1c**, 10.3 μL, 0.100 mmol), $Pd(OAc)_2$ (1.5 mg, 6.67 μmol), *N*-acetylglycine (1.6 mg, 13.3 μmol), and AgOAc (33.6 mg, 0.200 mmol) in hexafluoroisopropanol (1.33 mL) in a 2-dram vial with a PTFE-lined cap was heated 90 °C and stirred at for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm,

EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc eluent) to afford olefin **2-23ec** (16.3 mg, 62% yield, R_f = 0.29 in EtOAc) as a white solid.

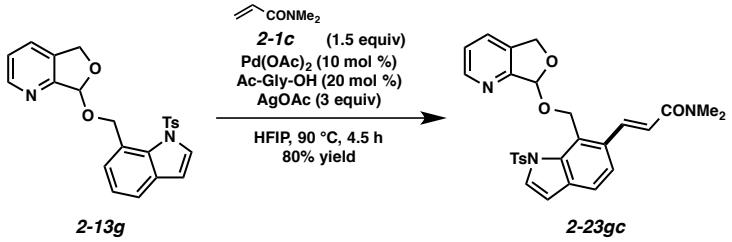
Olefin 2-23ec: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.0 Hz, 1H), 8.09 (d, *J* = 15.4 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 7.4, 5.0 Hz, 1H), 6.81 (d, *J* = 15.4 Hz, 1H), 6.25 (s, 1H), 5.52 (d, *J* = 13.6 Hz, 1H), 5.15 (d, *J* = 13.6 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 3.14 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 157.4, 149.8, 139.3 (q, $^5J_{C\text{-}F}$ = 2.1 Hz), 133.9, 133.6, 130.7 (q, $^2J_{C\text{-}F}$ = 29.8 Hz), 129.9, 128.6, 126.9 (q, $^1J_{C\text{-}F}$ = 272.7 Hz), 126.5 (q, $^3J_{C\text{-}F}$ = 5.8 Hz), 123.6, 122.3, 104.5, 70.8, 63.0 (q, $^4J_{C\text{-}F}$ = 2.1 Hz), 37.7, 36.1; IR (film) 1653, 1109, 1062, 1000, 805 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{19}F_3N_2O_3 + H]^+$: 393.1421, found 393.1421.



A suspension of acetal **2-13f** (24.1 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient

temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc → 9:1 EtOAc/MeOH eluent) to afford olefin **2-23fc** (26.2 mg, 70% yield, R_f = 0.51 in 9:1 EtOAc/MeOH) as a white solid.

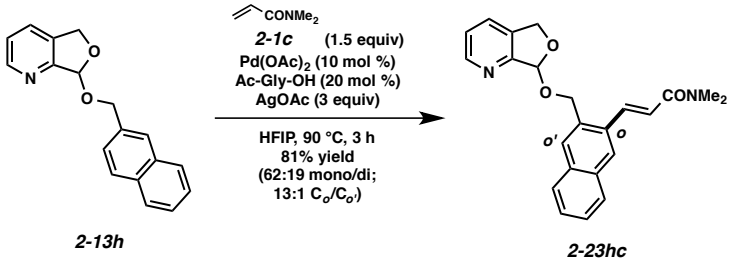
Olefin 2-23fc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.6 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 15.2 Hz, 1H), 7.78 (app. d, *J* = 9.2 Hz, 2H), 7.64-7.55 (comp. m, 3H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.6 Hz, 1H), 6.96 (d, *J* = 15.2 Hz, 1H), 6.38 (s, 1H), 5.46 (d, *J* = 13.6 Hz, 1H), 5.43 (d, *J* = 10.8 Hz, 1H), 5.31 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 13.6 Hz, 1H), 3.22 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 157.5, 149.8, 140.3, 133.99, 133.96, 133.5, 133.2, 131.6, 130.0, 129.3, 128.4, 127.2, 126.5, 125.2, 124.4, 123.6, 121.8, 104.3, 70.9, 62.5, 37.7, 36.2; IR (film) 1642, 1594, 1505, 1263, 1005 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{22}N_2O_3 + H]^+$: 375.1703, found 375.1708.



A suspension of acetal **2-13g** (42.0 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined

cap was heated at 90 °C and stirred for 6 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (3:2 hexanes/EtOAc → EtOAc eluent) to afford olefin **2-23gc** (41.4 mg, 80% yield, R_f = 0.26 in EtOAc) as a white powder.

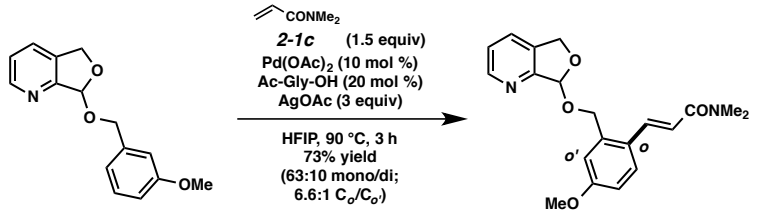
Olefin 2-23gc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.22 (d, *J* = 15.2 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 3.6 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 7.4, 4.8 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.75 (d, *J* = 15.6 Hz, 1H), 6.61 (d, *J* = 3.6 Hz, 1H), 6.32 (s, 1H), 5.73 (d, *J* = 13.6 Hz, 1H), 5.62 (d, *J* = 10.6 Hz, 1H), 5.30 (d, *J* = 10.6 Hz, 1H), 5.19 (d, *J* =13.6 Hz, 1H), 3.12 (s, 3H), 3.06 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 158.1, 149.4, 144.7, 140.9, 136.7, 134.84, 134.81, 134.5, 134.0, 132.7, 129.9, 129.6, 127.5, 125.2, 123.3, 123.2, 121.4, 119.7, 111.3, 104.3, 70.8, 64.0, 37.7, 36.2, 21.7; IR (film) 1643, 1599, 1366, 1172, 1004 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{28}H_{27}N_3O_5S+ H]^+$: 518.1744, found 518.1734.



A suspension of acetal **2-13h** (27.7 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (9:1 EtOAc/MeOH eluent) to afford monoolefin **2-23hc** (23.3 mg, 13:1 *o*/*o'*, 62% yield, R_f = 0.37 in 9:1 EtOAc/MeOH) as a beige solid. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory plate chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23hc** (8.8 mg, 19% yield, R_f = 0.56 in 9:1 EtOAc/MeOH) as a white solid.

Monoolefin 2-23hc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 8.11 (d, *J* = 15.4 Hz, 1H), 8.01 (s, 1H), 7.94 (s, 1H), 7.84-7.78 (comp. m, 2H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.49-7.43 (comp. m, 2H), 7.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.96 (d, *J* = 15.4 Hz, 1H), 6.32 (d, *J* = 1.2 Hz, 1H), 5.49 (dd, *J* = 13.2, 1.2 Hz, 1H), 5.24 (d, *J* = 11.4 Hz, 1H), 5.16 (d, *J* = 13.2 Hz, 1H), 4.95 (d, *J* = 11.4 Hz, 1H), 3.20 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 157.5, 149.8, 140.0, 133.63, 133.57, 133.4, 133.0, 130.0, 129.1, 128.0, 127.9, 126.8, 126.6, 126.4, 123.7, 120.5, 104.3, 70.8, 68.4, 37.7, 36.1; IR (film) 1652, 1584, 1389, 994, 910 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{22}N_2O_3 + H]^+$: 375.1703, found 375.1702.

Diolefin 2-23hc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.8 Hz, 1H), 8.29 (d, *J* = 15.2 Hz, 1H), 8.28 (d, *J* = 15.6 Hz, 1H), 8.04-7.99 (comp. m, 1H), 7.98 (s, 1H), 7.83-7.79 (comp. m, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.51-7.47 (comp. m, 2H), 7.22 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.02 (d, *J* = 15.6 Hz, 1H), 6.95 (d, *J* = 15.2 Hz, 1H), 6.28 (s, 1H), 5.60 (d, *J* = 13.6 Hz, 1H), 5.20 (d, *J* = 13.6 Hz, 1H), 5.13 (d, *J* = 9.8 Hz, 1H), 4.88 (d, *J* = 9.8 Hz, 1H), 3.29 (s, 3H), 3.22 (s, 3H), 3.16 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 166.1, 157.4, 149.5, 140.8, 138.6, 136.4, 135.0, 133.5, 132.8, 132.1, 130.3, 129.8, 128.4, 127.0, 126.9, 126.6, 126.5, 125.6, 123.5, 121.1, 104.1, 70.9, 65.0, 37.71, 37.67, 36.1; IR (film) 1649, 1607, 1008, 914, 730 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{28}H_{29}N_3O_4 + H]^+$: 472.2231, found 472.2232.



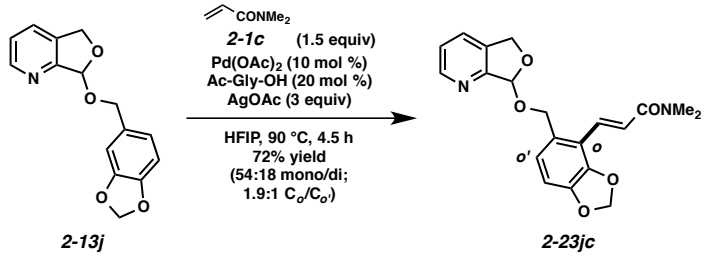
2-13i *2-23ic*

A suspension of acetal **2-13i** (25.5 mg, 92.7 μmol), *N,N*-dimethylacrylamide (**2-1c**, 14.3 μL, 0.139 mmol), $Pd(OAc)_2$ (2.1 mg, 9.27 μmol), *N*-acetylglycine (2.2 mg, 19.0 μmol), and AgOAc (46.4 mg, 0.278 mmol) in hexafluoroisopropanol (1.85 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc

eluent) to afford monoolefin **2-23ic** (20.6 mg, 6.6:1 *o*/*o'*, 63% yield, R_f = 0.33 in EtOAc) as a white film. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory plate chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23ic** (5.1 mg, 10% yield, R_f = 0.19 in 9:1 EtOAc/MeOH) as a white solid.

Monoolefin 2-23ic: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.8 Hz, 1H), 7.92 (d, *J* = 15.4 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.72 (d, *J* = 15.4 Hz, 1H), 6.25 (s, 1H), 5.43 (d, *J* = 13.2 Hz, 1H), 5.13 (d, *J* = 13.2 Hz, 1H), 5.07 (d, *J* = 11.4 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 3.82 (s, 3H), 3.14 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 160.6, 157.4, 149.7, 138.9, 138.2, 133.5, 130.0, 128.1, 127.1, 123.7, 117.6, 114.7, 114.3, 104.3, 70.7, 67.7, 55.5, 37.6, 36.1; IR (film) 1647, 1594, 1505, 1394, 1262 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{22}N_2O_4 + H]^+$: 355.1652, found 355.1651.

Diolefin 2-23ic: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.8 Hz, 1H), 8.12 (d, *J* = 15.6 Hz, 1H), 7.89 (d, *J* = 15.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.22 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.08 (d, *J* = 15.6 Hz, 1H), 6.85 (d, *J* = 8.8 Hz. 1H), 6.75 (d, *J* = 15.6 Hz, 1H), 6.25 (s, 1H), 5.58 (d, *J* = 13.6 Hz, 1H), 5.20 (d, *J* = 13.6 Hz, 1H), 5.02 (d, *J* = 9.6 Hz, 1H), 4.72 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 3.25 (s, 3H), 3.18 (s, 3H), 3.10 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 167.0, 158.9, 157.5, 149.6, 140.1, 136.0, 134.6, 133.7, 130.1, 129.9, 128.1, 127.8, 124.7, 123.6, 119.2, 110.8, 104.1, 71.0, 64.1, 55.9, 37.8, 37.7, 36.1; IR (film) 1649, 1601, 1397, 1266, 1008 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{25}H_{29}N_3O_5 + H]^+$: 452.2180, found 452.2179.

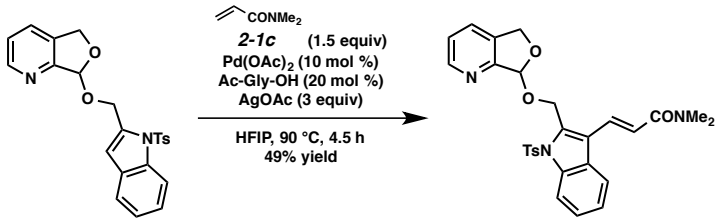


A suspension of acetal **2-13j** (27.1 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (9:1 EtOAc/MeOH eluent) to afford monoolefin **2-23jc** (20.0 mg, 1:0.53 *o*/*o'*, 54% yield, R_f = 0.33 in 9:1 EtOAc/MeOH) as a white solid. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory plate chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23jc** (8.2 mg, 18% yield, R_f = 0.12 in 9:1 EtOAc/MeOH) as a white solid.

Monoolefin 2-23jc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.8 Hz, 0.53H), 8.52 (d, *J* = 4.8 Hz, 1H), 7.93 (d, *J* = 15.2 Hz, 0.53H), 7.84 (d, *J* = 15.6 Hz, 1H), 7.63 (app. d, *J* = 7.6 Hz, 1.53H), 7.28-7.21 (comp. m, 2.53H), 7.03 (s, 0.53H), 6.98 (s, 0.53H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 15.2 Hz, 0.53H), 6.23 (app. s, 1.53H), 6.04 (s, 1H), 6.01 (s,

1H), 5.96 (s, 0.53H), 5.95 (s, 0.53H), 5.52 (d, *J* = 13.6 Hz, 1H), 5.42 (d, *J* = 13.2 Hz, 0.53H), 5.18-4.98 (comp. m, 3.06H), 4.76-4.67 (comp. m, 1.53H), 3.14 (s, 0.53H), 3.13 (s, 1H), 3.06 (app. s, 1.53H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.9, 157.6, 149.8, 149.7, 148.8, 147.85, 147.82, 146.7, 138.9, 133.9, 133.7, 133.6, 131.5, 130.1, 130.0, 128.8, 124.3, 123.64, 123.57, 122.9, 118.2, 118.1, 110.4, 108.4, 106.1, 104.2, 104.1, 101.5, 101.4, 70.8, 70.7, 68.1, 67.4, 37.6, 36.1, 36.0; IR (film) 1642, 1584, 1394, 1452, 999 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{20}N_2O_5 + H]^+$: 369.1445, found 369.1446.

Diolefin 2-23jc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 1H), 8.01 (d, *J* = 15.2 Hz, 1H), 7.90 (d, *J* = 15.2 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 15.2 Hz, 1H), 7.21 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.95 (s, 1H), 6.74 (d, *J* = 15.2 Hz, 1H), 6.26 (s, 1H), 6.06 (s, 1H), 6.02 (s, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 5.19 (d, *J* = 10.0 Hz, 1H), 5.06 (d, *J* = 10.6 Hz, 1H), 4.84 (d, *J* = 10.6 Hz, 1H), 3.19 (s, 3H), 3.16 (s, 3H), 3.08 (app. s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 166.7, 157.4, 149.6, 147.9, 147.3, 139.9, 133.81, 133.76, 131.6, 130.0, 128.8, 124.0, 123.5, 120.4, 123.5, 120.4, 119.5, 107.1, 104.0, 101.7, 70.9, 62.7, 37.71, 37.66, 36.12, 36.06; IR (film) 1649, 1607, 1391, 1003, 730 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{25}H_{27}N_3O_6 + H]^+$: 466.1973, found 466.1972.

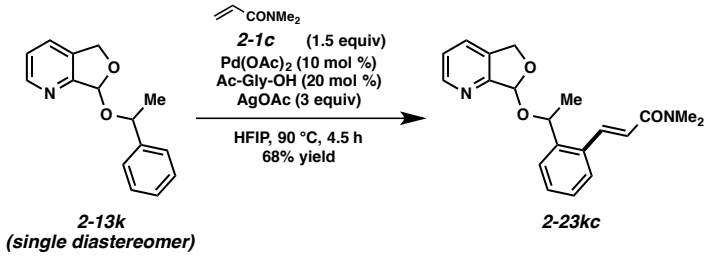


2-13v *2-23vc*

A suspension of acetal **2-13v** (42.0 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined

cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (I:1 EtOAc/hexanes → EtOAc eluent) to afford monoolefin **2-23vc** (25.6 mg, 49% yield, R_f = 0.52 in EtOAc) as a white solid.

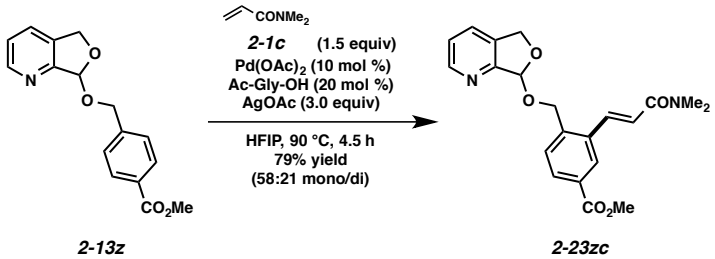
Olefin 2-23vc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 15.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz 1H), 7.32-724 (comp. m, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 15.6 Hz, 1H), 6.40 (s, 1H), 5.42-5.31 (comp. m, 3H), 5.15 (d, *J* = 13.2 Hz, 1H), 3.19 (s, 3H), 3.09 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 157.6, 149.7, 144.9, 136.4, 135.8, 135.4, 133.5, 132.4, 129.9, 129.7, 127.9, 127.7, 125.8, 124.0, 123.7, 121.2, 121.0, 120.3, 115.1, 104.3, 70.8, 59.2, 37.6, 36.1, 21.7; IR (film) 1654, 1612, 1370, 1176, 1003 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{28}H_{27}N_3O_5S + H]^+$: 518.17445, found 518.1753.



A suspension of acetal **2-13k** (24.1 mg, 0.100 mmol, the major diastereomer from the attachment), *N,N*-dimethylacrylamide (**2-1c**, 15.5 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0

μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 6 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc eluent) to afford olefin **2-23kc** (23.0 mg, 68% yield, R_f = 0.33 in EtOAc) as a white film.

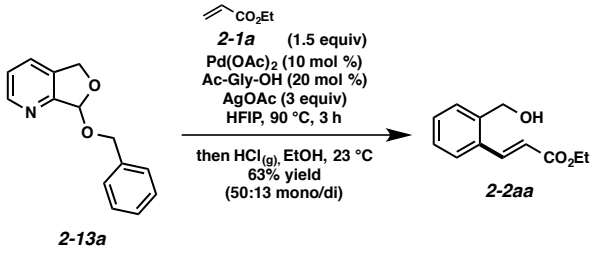
Olefin 2-23kc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.8 Hz, 1H), 8.06 (d, *J* = 15.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.26 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.79 (d, *J* = 15.2 Hz, 1H), 5.93 (s, 1H), 5.51 (q, *J* = 6.4 Hz, 1H), 5.24 (d, *J* = 13.2 Hz, 1H), 5.02 (d, *J* = 13.2 Hz, 1H), 3.18 (s, 3H), 3.08 (s, 3H), 1.45 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 158.0, 149.8, 142.2, 139.5, 134.0, 133.4, 130.1, 129.9, 127.6, 126.7, 126.6, 123.5, 120.4, 102.1, 70.9, 70.2, 37.6, 36.0; IR (film) 1642, 1589, 1389, 973, 910 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{22}N_2O_3 + H]^+$: 339.1703, found 339.1704.



A suspension of acetal **2-13z** (28.5 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated to 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc eluent) to afford monoolefin **2-23zc** (22.2 mg, 58% yield, R_f = 0.26 in EtOAc) as a white solid. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory thin-layer chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23zc** (10.1 mg, 21% yield, R_f = 0.18 in 9:1 EtOAc/MeOH) as a white solid.

Monoolefin 2-23zc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.94 (d, *J* = 15.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.90 (d, *J* = 15.6 Hz, 1H), 6.26 (d, *J* = 1.6 Hz, 1H), 5.41 (dd, *J* = 13.0, 1.6 Hz, 1H), 5.13 (d, *J* = 13.0 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 4.86 (d, *J* = 12.2 Hz, 1H), 3.92 (s, 3H), 3.18 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.4, 157.3, 149.9, 141.3, 138.2, 134.8, 133.5, 130.11, 130.07, 129.9, 129.5, 127.7, 123.8, 121.1, 104.5, 70.8, 67.3, 52.4, 37.7, 36.1; IR (film) 1721, 1651, 1605, 998, 727 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{22}N_2O_5 + H]^+$: 383.1601, found 383.1600.

Diolefin 2-23zc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 1H), 8.11 (s, 2H), 8.07 (d, *J* = 15.2 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.90 (d, *J* = 15.2 Hz, 2H), 6.26 (s, 1H), 5.60 (d, *J* = 13.8 Hz, 1H), 5.20 (d, *J* = 13.8 Hz, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 4.89 (d, *J* = 10.2 Hz, 1H), 3.93 (s, 3H), 3.20 (s, 6H), 3.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 166.3, 157.2, 149.7, 139.2, 138.1, 133.7, 130.4, 130.0, 128.7, 123.7, 122.8, 104.3, 71.0, 63.0, 52.6, 37.8, 36.1; IR (film) 1722, 1654, 1612, 1397, 1008 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{29}N_3O_6 + H]^+$: 480.2128, found 480.2131.

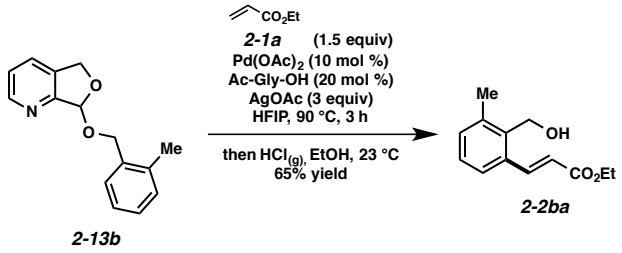


A suspension of acetal **2-13a** (22.7 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated to 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The solution was concentrated by rotary evaporation, EtOH (1.00 mL) was added to the residue, and anhydrous HCl was bubbled through the solution for 1 min. The solution was stirred at 23 °C for 20 h. Sat. aq. Na_2CO_3 (5 mL) was added to the reaction mixture, and it was extracted with EtOAc (3 x 10 mL), washed with brine (5 mL), and dried with $MgSO_4$.

The solution was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford alcohol **2-2aa** (10.7 mg, 12:1 mono/di, 54% yield, R_f = 0.33 in 7:3 hexanes/EtOAc) as a colorless oil. An additional portion of the diolefinated alcohol (2.5 mg, 9% yield) was isolated as the isobenzofuran.

Alcohol 2-2aa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.84 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.81 (br. s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 141.5, 139.6, 133.3, 130.3, 128.9, 128.5, 127.1, 120.6, 63.2, 60.9, 14.5; IR (film) 3455, 1701, 1318, 1182, 914 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M_{mono} + Na)^+$ $[C_{12}H_{14}O_3 + Na]^+$: 229.0835, found 229.0836.

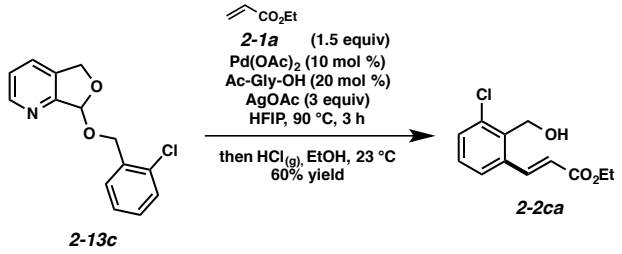
Diolefin 2-2aa: Representative peaks in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 16.0 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 2H); HRMS (ESI+) *m/z* calc'd for $(M_{di} + Na)^+$ $[C_{17}H_{20}O_5 + Na]^+$: 327.1203, found 327.1203.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc

eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The solution was concentrated by rotary evaporation, EtOH (1.00 mL) was added to the residue, and anhydrous HCl was bubbled through the solution for 1 min. The solution was stirred at 23 °C for 25 h. Sat. aq. Na_2CO_3 (5 mL) was added to the reaction mixture, and it was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried with $MgSO_4$. The solution was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford alcohol **2-2ba** (14.2 mg, 65% yield, R_f = 0.33 in 7:3 hexanes/EtOAc) as a colorless oil. Additionally, 2-methylbenzyl alcohol (**2-22b**, 2.1 mg, 17% yield) was isolated.

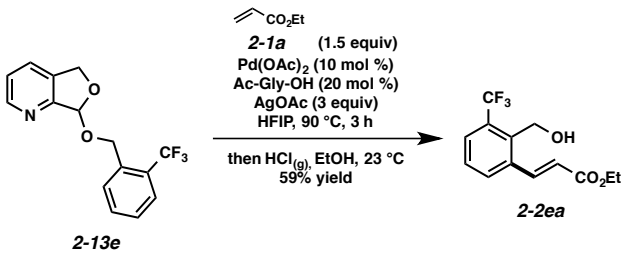
Alcohol 2-2ba: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 15.6 Hz, 1H), 7.43 (t, *J* = 4.8 Hz, 1H), 7.23 (app. d, *J* = 4.8 Hz, 2H), 6.37 (d, *J* = 15.6 Hz, 1H), 4.83 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 1.66 (br. s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 142.6, 138.2, 137.2, 134.8, 132.4, 128.6, 125.2, 121.2, 60.7, 58.7, 19.6, 14.5; IR (film) 3425, 2925, 1709, 1632, 1312, 1180, 1163, 1005 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{16}O_3 + H]^+$: 221.1172, found 221.1175.



A suspension of acetal **2-13c** (26.2 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap

was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The solution was concentrated by rotary evaporation, EtOH (1.00 mL) was added to the residue, and anhydrous HCl was bubbled through the solution for 1 min. The solution was stirred at 23 °C for 25 h. Sat. aq. Na_2CO_3 (5 mL) was added to the reaction mixture, and it was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried with $MgSO_4$. The solution was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford alcohol **2-2ca** (18.0 mg, 60% yield, R_f = 0.31 in 4:1 hexanes/EtOAc) as a colorless oil. Additionally, 2-chlorobenzyl alcohol (**2-22c**, 6.3 mg, 36% yield) was isolated.

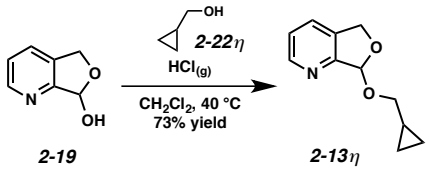
Alcohol 2-2ca: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 15.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 4.94 (s, 2H), 4.28 (q, *J* = 6.8 Hz, 2H), 1.96 (br. s, 1H), 1.34 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 141.5, 137.0, 136.5, 135.8, 131.1, 129.7, 126.2, 122.6, 61.0, 59.1, 14.5; IR (film) 3460, 1701, 1313, 1176, 1024 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{12}H_{13}ClO_3 + Na]^+$: 263.0445, found 263.0447.



A suspension of acetal **2-13e** (29.5 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The solution was concentrated by rotary evaporation, EtOH (1.00 mL) was added to the residue, and anhydrous HCl was bubbled through the solution for 1 min. The solution was stirred at 23 °C for 25 h. Sat aq. Na_2CO_3 (5 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried with $MgSO_4$. The solution was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford alcohol **2-2ea** (11.0 mg, 40% yield, R_f = 0.33 in 1:1 hexanes/EtOAc) as a white solid. An additional portion of the olefinated alcohol (5.2 mg, 19% yield) was isolated as the isobenzofuran. Additionally, 2-(trifluoromethyl)benzyl alcohol (**2-22e**, 4.3 mg, 24% recovered alcohol) was isolated.

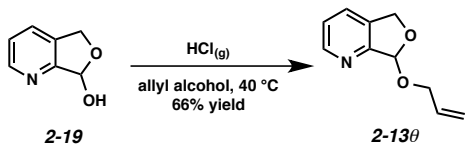
Alcohol 2-2ea: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 16.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.90 (d, *J* = 3.2 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.86 (br. s, 1H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 141.1, 137.5, 137.1, 131.1, 129.9 (q, $^2J_{C\text{-}F}$ = 30.0 Hz), 128.7, 127.2 (q, $^3J_{C\text{-}F}$ = 5.8 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 272.9 Hz), 122.8, 61.0, 58.1 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 14.5**;** IR (film) 1701,

1318, 1166, 1113, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{13}H_{13}F_3O_3 + Na]^+$: 297.0709, found 297.0710.



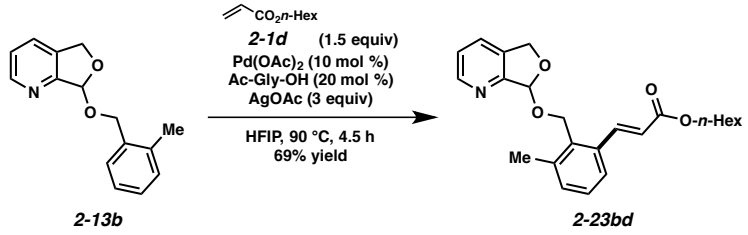
A round-bottomed flask holding a solution of hemiacetal **2-19** (1.00 g, 7.29 mmol) and cyclopropylcarbinol (**2-22η**, 2.37 mL, 29.2 mmol) in CH_2Cl_2 (12.2 mL) at 23 °C was bubbled anhydrous HCl for 1 min. The flask was capped (yellow plastic cap), and the mixture was heated and stirred at 40 °C for 24 h. Upon completion, the reaction was poured into a mixture of ~1:1 ice/sat. aq. Na_2CO_3 (50 mL), and it was then concentrated by rotary evaporation to remove MeOH. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (6:4 hexanes/EtOAc eluent) to afford acetal **2-13η** (1.01 g, 73% yield, R_f = 0.22 in 6:4 hexanes/EtOAc) as a colorless oil.

Acetal 2-13η: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.8, Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.15 (d, *J* = 2.0 Hz, 1H), 5.23 (dd, *J* = 13.2, 2.0 Hz, 1H), 5.04 (d, *J* = 13.2 Hz, 1H), 3.60 (d, *J* = 7.2 Hz, 2H), 1.24-1.10 (comp. m, 1H), 0.61-0.48 (comp. m, 2H), 0.34-0.16 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 149.9, 133.2, 129.9, 123.6, 104.6, 73.7, 70.4, 10.7, 3.5, 3.3; IR (film) 1373, 1080, 1004, 911, 790 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{13}NO_2 + Na]^+$: 214.1, found 241.1.



To a suspension of hemiacetal **2-19** (1.00 g, 7.29 mmol) in allyl alcohol (**2-22θ**, 72.9 mL) was bubbled anhydrous HCl for 1 min. The flask was capped (yellow plastic cap) and heated at 40 °C for 18 h. Upon completion, the reaction was cooled to 0 °C and it was added sat. Na_2CO_3 (100 mL). The product was extracted into EtOAc (3 x 100 mL), and the combined organic layers were washed with brine (100 mL), dried under $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (6:4 hexanes/EtOAc eluent) to afford acetal **2-13θ** (1.00 g, 66% yield, R_f = 0.23 in 6:4 hexanes/EtOAc) as a colorless oil.

Acetal 2-13θ: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.8, Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.15 (d, *J* = 2.0 Hz, 1H), 6.06-5.96 (comp. m, 1H), 5.35 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.26-5.18 (comp. m, 2H), 5.05 (d, *J* = 13.2 Hz, 1H), 4.35-4.24 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.9, 134.3, 133.1, 129.9, 123.6, 117.9, 104.3, 70.4, 69.7; IR (film) 1077, 1021, 1004, 914, 789 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{10}H_{11}NO_2 + Na]^+$: 200.1, found 200.1.

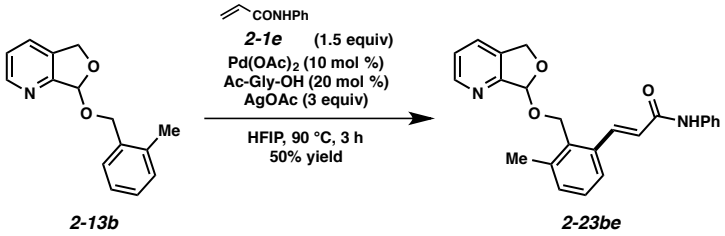


2-13b *2-23bd*

A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), *n*-hexyl acrylate (**2-1d**, 26.4 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc

eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (13:7 hexanes/EtOAc) to afford olefin **2-23bd** (27.2 mg, 69% yield, R_f = 0.37 in 13:7 hexanes/EtOAc) as a colorless oil.

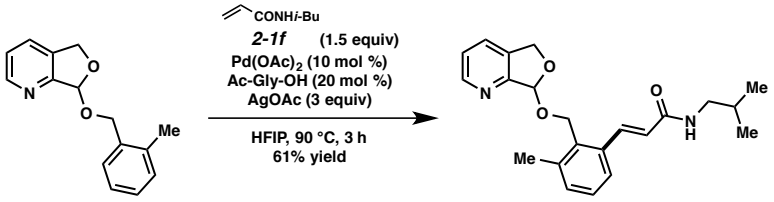
Olefin 2-23bd: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.8 Hz, 1H), 8.20 (d, *J* = 15.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 4.4 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.20 (d, *J* = 4.4 Hz, 2H), 6.36 (d, *J* = 15.6 Hz, 1H), 6.24 (s, 1H), 5.43 (d, *J* = 12.8 Hz, 1H), 5.15 (d, *J* = 12.8 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 12.8 Hz, 1H), 4.21 (t, *J* = 6.8 Hz, 2H), 2.49 (s, 3H), 1.71 (quint, *J* = 6.8 Hz, 2H), 1.46-1.36 (comp. m, 2H), 1.36-1.27 (comp. m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 157.5, 149.8, 143.1, 139.1, 135.6, 134.1, 133.4, 132.2, 129.9, 128.6, 124.9, 123.6, 120.8, 104.3, 70.7, 64.8, 63.6, 31.6, 28.8, 25.8, 22.7, 19.9, 14.2; IR (film) 1711, 1313, 1166, 1003, 793 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{29}NO_4 + H]^+$: 396.2169, found 396.2174.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), *N*-phenylacrylamide (**2-1e**, 22.1 mg, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture

was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford olefin **2-23be** (19.5 mg, 50% yield, R_f = 0.27 in 1:1 hexanes/EtOAc) as a light green oil.

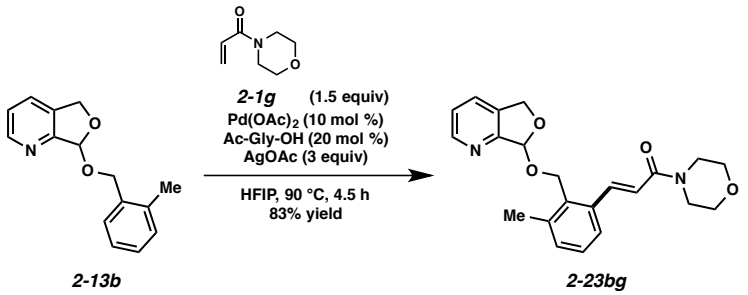
Olefin 2-23be: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (br. s, 1H), 8.60 (d, *J* = 5.2 Hz, 1H), 7.89 (d, *J* = 15.8 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 6.8 Hz, 1H), 7.14 (d, *J* = 15.8 Hz, 1H), 7.11 (dd, *J* = 8.0, 6.8 Hz, 1H), 6.37 (s, 1H), 5.38 (d, *J* = 13.4 Hz, 1H), 5.20 (d, *J* = 13.4 Hz, 1H), 5.12 (d, *J* = 9.2 Hz, 1H), 4.70 (d, *J* = 9.2 Hz, 1H), 2.51 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 164.9, 157.4, 149.3, 139.7, 139.4, 138.3, 133.9, 132.5, 130.9, 130.8, 129.1, 128.7, 127.7, 124.4, 124.0, 119.9, 104.9, 70.9, 66.7, 19.7; IR (film) 3263, 1596, 1533, 1444, 1003 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{22}N_2O_3 + H]^+$: 387.1703, found 387.1703.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), *N*-isobutylacrylamide[48] (**2-1f**, 19.1 mg, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined

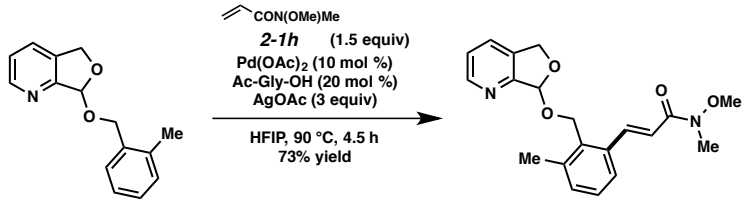
cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (9:1 EtOAc/hexanes eluent) to afford olefin **2-23bf** (22.3 mg, 61% yield, R_f = 0.29 in 9:1 EtOAc/hexanes) as a colorless oil.

Olefin 2-23bf: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 1H), 7.82 (d, *J* = 16.0 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.53 (br. s, 1H), 7.30 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 16.0 Hz, 1H), 6.25 (s, 1H), 5.37 (d, *J* = 13.6 Hz, 1H), 5.16 (d, *J* = 13.6 Hz, 1H), 5.09 (d, *J* = 9.6 Hz, 1H), 4.69 (d, *J* = 9.6 Hz, 1H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.48 (s, 3H), 1.96-1.84 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 157.4, 149.4, 139.2, 138.2, 138.1, 133.6, 132.7, 130.7, 130.4, 128.6, 126.9, 126.8, 124.0, 104.9, 70.8, 66.2, 47.3, 28.8, 20.49, 20.46, 19.7; IR (film) 3300, 1003, 1659, 1622, 1549 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{22}H_{26}N_2O_3 + Na]^+$: 389.1836, found 389.1838.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), acrylamide **2-1g**[48] (21.2 mg, 0.15 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (19:1 EtOAc/hexanes eluent) to afford olefin **2-23bg** (31.4 mg, 83% yield, R_f = 0.29 in 19:1 EtOAc/hexanes) as a white solid.

Olefin 2-23bg: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 1H), 8.07 (d, *J* = 15.4 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.32 (dd, *J* = 7.6 Hz, 1H), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 15.4 Hz, 1H), 6.22 (s, 1H), 5.39 (d, *J* = 13.2 Hz, 1H), 5.14 (d, *J* = 13.2 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 4.82 (d, *J* = 10.2 Hz, 1H), 3.80-3.62 (br. m, 8H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 157.5, 149.7, 141.6, 139.3, 136.9, 133.6, 133.4, 131.5, 129.9, 128.6, 125.5, 123.6, 120.3, 104.2, 70.7, 67.1, 63.9, 46.5, 42.6, 19.7; IR (film) 1643, 1606, 1428, 1229, 1003 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{24}N_2O_4 + H]^+$: 381.1809, found 381.1808.

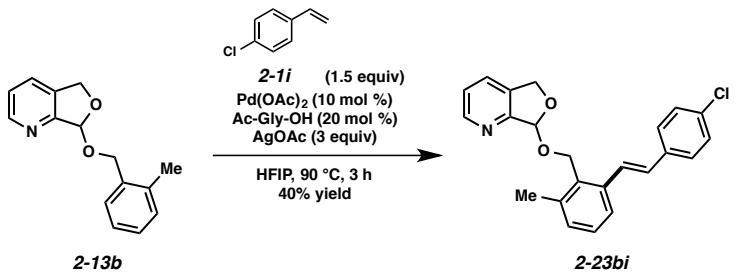


2-13b *2-23bh*

A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), acrylamide **2-1h**[49] (17.3 mg, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (9:1 EtOAc/hexanes eluent) to afford olefin **2-23bh** (25.9 mg, 73% yield, R_f = 0.21 in 9:1 EtOAc/hexanes) as a white foam.

Olefin 2-23bh: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.22 (d, *J* = 15.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 6.4, 2.6 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.20 (d, *J* = 6.4 Hz, 1H), 7.18 (d, *J* = 2.6 Hz, 1H), 6.93 (d, *J* = 15.6 Hz, 1H), 6.24 (s, 1H), 5.48 (d, *J* = 13.4 Hz, 1H), 5.15 (d, *J* = 13.4 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.85 (d, *J* = 10.4 Hz, 1H), 3.73 (s, 3H), 3.32 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 157.6, 149.7, 141.9, 139.1, 136.5, 134.2, 133.6, 131.8, 129.9, 128.5, 124.9, 123.6, 104.3, 70.7, 63.6, 62.0, 32.7,

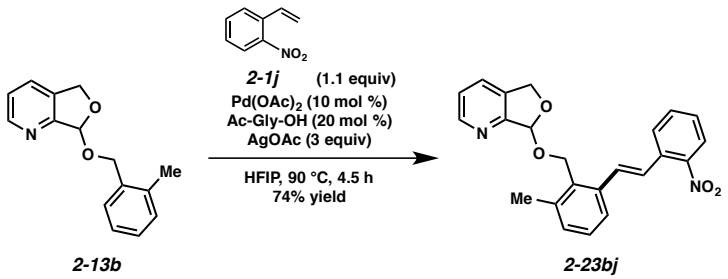
19.8; IR (film) 3438, 1651, 1613, 1382, 1003 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{22}N_2O_4 + H]^+$: 355.1652, found 355.1655.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), 4-chlorostyrene (**2-1i**, 20.8 mg, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by preparatory thin-layer chromatography (7:3 hexanes/EtOAc eluent) to afford olefin **2-23bi** (15.0 mg, 40% yield, R_f = 0.27 in 7:3 hexanes/EtOAc) as a colorless oil.

Olefin 2-23bi: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 16.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.26 (dd, *J* = 8.0, 4.4 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 16.0 Hz, 1H), 6.29 (d, *J* = 1.6 Hz, 1H), 5.26 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.13 (d, *J* = 13.2 Hz, 1H), 4.95 (ABq, *J* = 10.2 Hz, Δν = 35.4 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.0, 138.8, 138.3, 136.5, 133.20, 133.17, 132.7, 130.2, 130.0, 129.9, 128.9, 128.7,

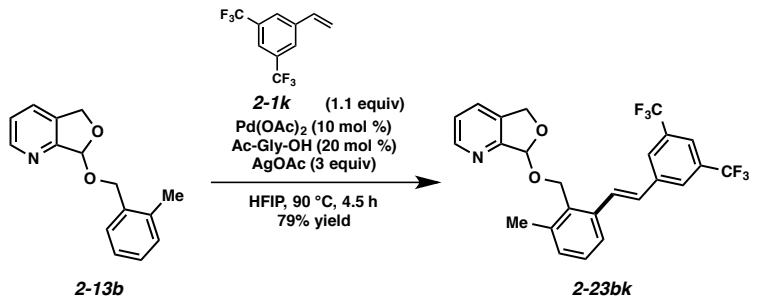
128.1, 127.8, 124.2, 123.7, 104.4, 70.7, 64.0, 19.9; IR (film) 2921, 1589, 1489, 1073, 1005 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{20}ClNO_2 + H]^+$: 378.1255, found 378.1261.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), 2-nitrostyrene[50] (**2-1j**, 16.4 mg, 0.110 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (3:2 EtOAc/hexanes eluent) to afford stilbene **2-23bj** (28.9 mg, 74% yield, R_f = 0.27 in 3:2 EtOAc/hexanes) as a yellow solid.

Stilbene 2-23bj: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.8 Hz, 1H), 8.97 (app. d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 16.2 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 16.2 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.27-7.21 (comp. m, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 5.25 (dd, *J* = 13.2, 1.2 Hz, 1H), 5.10 (d, *J* = 13.2 Hz, 1H), 4.96 (ABq, *J* = 10.6 Hz, Δν = 24.4 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 149.9, 148.1, 138.7, 137.8, 133.6, 133.18, 133.16, 132.9, 132.4, 130.8, 129.9, 129.0,

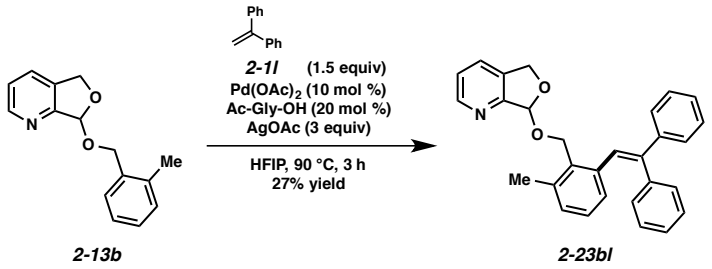
128.8, 128.0, 126.0, 124.8, 124.7, 123.7, 104.3, 70.7, 63.8, 19.8; IR (film) 1521, 1342, 994, 910, 725 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{20}N_2O_4 + H]^+$: 389.1496, found 389.1495.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), styrene **2-1k** (26.4 mg, 0.110 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford stilbene **2-23bk** (38.0 mg, 79% yield, R_f = 0.29 in 7:3 hexanes/EtOAc) as a white solid.

Stilbene 2-23bk: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.8 Hz, 1H), 8.07 (s, 2H), 7.91 (d, *J* = 16.2 Hz, 1H), 7.76 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 16.2 Hz, 1H), 6.40 (s, 1H), 5.22 (ABq, *J* = 12.8 Hz, Δν = 49.9 Hz, 2H), 4.96 (ABq, *J* = 10.4 Hz, Δν = 36.1 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 150.1, 140.2, 138.9, 137.6, 133.1, 133.0,

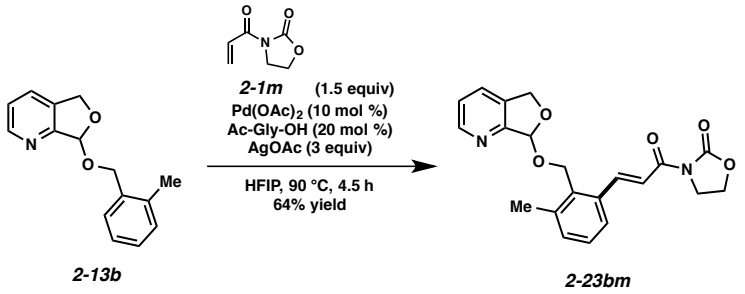
132.0 (q, $^{2}J_{C\text{-}F}$ = 33.1 Hz), 131.2, 130.9, 129.9, 128.8, 128.2, 126.7 (q, $^{3}J_{C\text{-}F}$ = 3.3 Hz), 125.0, 124.4, 123.8, 123.6 (q, $^{1}J_{C\text{-}F}$ = 271.1 Hz) 122.3, 120.8 (septet, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 104.5, 70.7, 64.0, 19.9; IR (film) 1381, 1281, 1182, 1134, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^{+}$ $[C_{25}H_{19}F_6NO_2 + H]^{+}$: 480.1393, found 480.1392.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), α,α-diphenylethene (**2-1l**, 26.5 mg, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (7:3 EtOAc/hexanes) to afford a mixture of olefin **2-23bl** and acetal **2-13b** (24.3 mg, 27% yield **2-23bl**, 54% rsm **2-13b**, R_f = 0.28 in 7:3 EtOAc/hexanes). An analytically pure sample of olefin **2-23bl** was obtained by preparatory plate chromatography (7:3 EtOAc/hexanes) to afford a white oil.

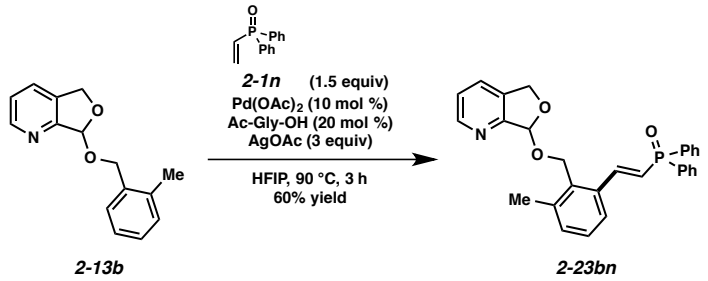
Olefin 2-23bl: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38-7.28 (comp. m, 6H), 7.23-7.15 (comp. m, 4H), 7.09-7.04 (comp. m, 2H), 6.95 (d, *J* = 7.6

Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.21 (s, 1H), 5.06 (ABq, *J* = 13.8 Hz, Δν = 47.1 Hz, 2H), 4.92 (ABq, *J* = 10.6 Hz, Δν = 34.8 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 149.8, 143.7, 143.6, 140.3, 138.9, 138.3, 133.9, 133.2, 131.0, 129.7, 129.2, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 127.1, 123.5, 104.2, 70.6, 64.7, 19.8; IR (film) 1073, 1005, 910, 731, 704 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{29}H_{25}NO_2 + H]^+$: 420.1958, found 420.1964.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), *N*-acryloyloxazolidinone **2-1m** (21.1 mg, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (4:1 EtOAc/hexanes eluent) to afford olefin **2-23bm** (24.4 mg, 64% yield, R_f = 0.38 in 4:1 EtOAc/hexanes) as a white solid.

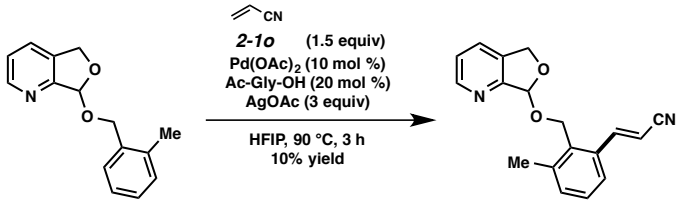
Olefin 2-23bm: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 8.42 (d, *J* = 15.6 Hz, 1H), 7.80 (d, *J* = 15.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 4.4 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.22 (app. d, *J* = 4.4 Hz, 2H), 6.25 (d, *J* = 1.6 Hz, 1H), 5.45 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.16 (d, *J* = 13.2 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.88 (d, *J* = 10.4 Hz, 1H), 4.46 (t, *J* = 8.0 Hz, 2H), 4.18-4.11 (comp. m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 157.5, 153.7, 149.8, 144.6, 139.0, 135.5, 134.6, 133.5, 132.7, 129.9, 128.8, 125.2, 123.6, 118.9, 104.3, 70.7, 63.4, 62.2, 43.0, 19.8; IR (film) 1768, 1684, 1352, 1221, 1005 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{20}N_2O_5 + H]^+$: 381.1445, found 381.1445.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), diphenylvinylphosphine oxide[51] (**2-1n**, 34.2 mg, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column

chromatography (19:1 EtOAc/MeOH eluent) to afford olefin **2-23bn** (28.2 mg, 60% yield, R_f = 0.26 in EtOAc) as a colorless oil.

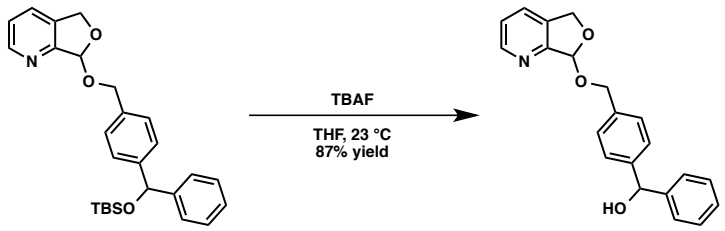
Olefin 2-23bn: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 4.8 Hz, 1H), 7.93 (dd, $^4J_{H\text{-}P}$ = 19.8 Hz, $^3J_{H\text{-}H}$ = 17.3 Hz, 1H), 7.84 (dd, $^3J_{H\text{-}P}$ = 12.0 Hz, $^3J_{H\text{-}H}$ = 7.4 Hz, 2H), 7.75 (dd, $^3J_{H\text{-}P}$ = 12.0 Hz, $^3J_{H\text{-}H}$ = 7.4 Hz, 2H), 7.55 (d, J = 7.6 Hz, 1H), 7.54-7.38 (comp. m, 7H), 7.24-7.17 (comp. m, 3H), 6.81 (dd, $^4J_{H\text{-}P}$ = 23.2 Hz, $^3J_{H\text{-}H}$ = 17.3 Hz, 1H), 6.12 (d, J = 1.2 Hz, 1H), 5.30 (d, J = 13.2, 1.2 Hz, 1H), 5.03 (d, J = 13.2 Hz, 1H), 5.02 (d, J = 10.4 Hz, 1H), 4.76 (d, J = 10.4 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 149.7, 146.3 (d, $^2J_{C\text{-}P}$ = 3.7 Hz), 139.1, 136.9, 136.7, 133.7, 133.45, 133.36 (d, $^1J_{C\text{-}P}$ = 104.5 Hz), 133.2 (d, $^1J_{C\text{-}P}$ = 105.4 Hz), 131.94, 131.87 (d, $^4J_{C\text{-}P}$ = 2.0 Hz), 131.8 (d, $^4J_{C\text{-}P}$ = 2.0 Hz), 131.7 (d, $^2J_{C\text{-}P}$ = 98.0 Hz), 131.6 (d, $^2J_{C\text{-}P}$ = 97.0 Hz), 129.9, 128.72 (d, $^3J_{C\text{-}P}$ = 11.6 Hz), 128.66 (d, $^3J_{C\text{-}P}$ = 12.0 Hz), 125.3, 123.6, 122.6 (d, $^2J_{C\text{-}P}$ = 3.7 Hz), 104.2, 70.7, 63.8, 19.8; IR (film) 1590, 1435, 1180, 1002, 725 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{29}H_{26}NO_3P + H]^+$: 468.1723, found 468.1733.



A suspension of acetal **2-13b** (24.1 mg, 0.100 mmol), acrylonitrile (**2-1o**, 9.8 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc

eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by preparatory plate chromatography (1:1 hexanes/EtOAc eluent) to afford acrylonitrile **2-23bo** (2.9 mg, 10% yield, R_f = 0.36 in 1:1 hexanes/EtOAc) as a colorless film.

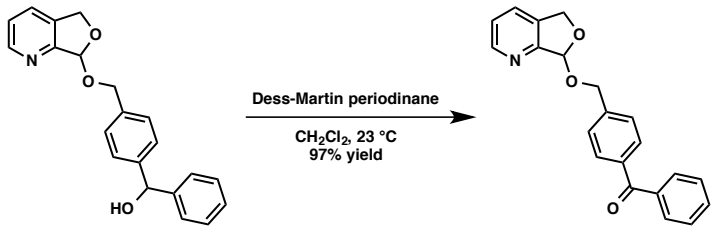
Acrylonitrile 2-23bo: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 16.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.33-7.19 (comp. m, 4H), 6.23 (s, 1H), 5.81 (d, *J* = 16.6 Hz, 1H), 5.34 (d, *J* = 13.2 Hz, 1H), 5.18 (d, *J* = 13.2 Hz, 1H), 4.89 (ABq, *J* = 10.8 Hz, Δν = 22.4 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 150.1, 149.7, 139.2, 134.8, 133.9, 133.2, 133.1, 130.1, 128.9, 124.2, 123.9, 118.6, 104.4, 98.5, 70.9, 63.2, 19.8; IR (film) 2215, 1003, 911, 788, 731 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{16}N_2O_2 + H]^+$: 293.1285, found 293.1285.



2-30 *2-31*

To a stirring solution of acetal **2-30** (60.4 mg, 0.135 mmol) in THF (0.450 mL) at 23 °C was added TBAF (0.270 mL, 1.0 M in THF, 0.270 mmol). After 3 h, water (10 mL) was added to the reaction mixture, and it was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude alcohol was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford alcohol **2-31** (39.1 mg, 87% yield, R_f = 0.20 in 1:1 hexanes/EtOAc) as a white foam.

Alcohol 2-31: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.0 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.35 (app. d, *J* = 8.0 Hz, 4H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.28-7.22 (comp. m, 2H), 6.20 (s, 1H), 5.83 (s, 1H), 5.25 (d, *J* = 13.3 Hz, 1H), 5.08 (d, *J* = 13.3 Hz, 1H), 4.81 (ABq, *J* = 11.8 Hz, Δν = 33.8 Hz, 2H), 2.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 149.9, 143.9, 143.5, 137.0, 133.2, 129.9, 128.6, 128.5, 127.7, 126.7, 126.6, 123.7, 104.2, 76.2, 70.5, 70.1; IR (film) 3269, 1082, 1008, 793, 704 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{19}NO_3 + H]^+$: 334.1438, found 334.1439.

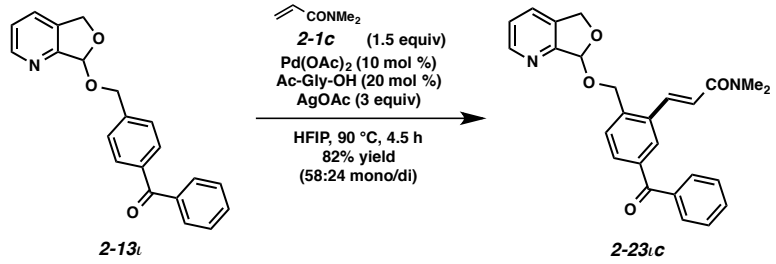


2-31 *2-13ι*

To a stirring solution of alcohol **2-31** (66.7 mg, 0.200 mmol) in CH_2Cl_2 (2.86 mL) at 23 °C was added Dess-Martin periodinane (89.1 mg, 0.210 mmol). After 1.5 h, water (20 mL) was added to the reaction mixture, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude oil was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford ketone **2-13ι** (64.1 mg, 97% yield, R_f = 0.36 in 1:1 hexanes/EtOAc) as a colorless oil that slowly transformed to a white solid.

Ketone 2-13ι: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.80-7.75 (comp. m, 4H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.60-7.51 (comp. m, 3H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.26 (d, *J* = 1.6 Hz, 1H), 5.27 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.11 (d, *J* = 13.2 Hz, 1H), 4.92 (ABq, *J* = 12.4 Hz, Δν = 22.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 157.4, 150.0, 142.6, 137.8, 136.9, 133.2, 132.5, 130.4, 130.1, 130.0, 128.4, 127.7, 123.8, 104.5, 70.6, 69.6; IR

(film) 1652, 1310, 1273, 2005, 704 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{17}NO_3+H]^+$: 332.1281, found 332.1282.

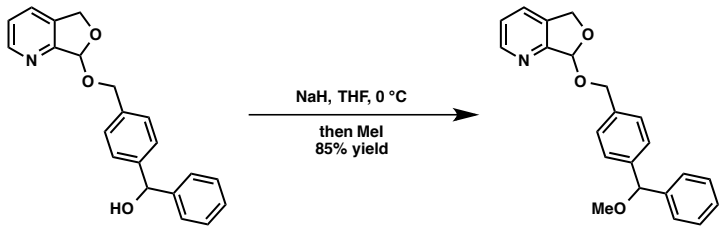


A suspension of acetal **2-13ι** (33.1 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (EtOAc eluent) to afford monoolefin **2-23ιc** (24.9 mg, 58% yield, R_f = 0.26 in EtOAc) as a white solid. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory plate chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23ιc** (12.8 mg, 24% yield, R_f = 0.15 in 9:1 EtOAc/MeOH) as a white film.

Monoolefin 2-23ιc: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.0 Hz, 1H), 8.00 (s, 1H), 7.97 (d, *J* = 15.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.70-7.56 (comp. m, 4H), 7.47 (t, *J* = 7.6 Hz, 2H),

7.28 (dd, *J* = 7.6, 5.0 Hz, 1H), 6.87 (d, *J* = 15.6 Hz, 1H), 6.28 (d, *J* = 1.2 Hz, 1H), 5.43 (dd, *J* = 13.2, 1.2 Hz, 1H), 5.15 (d, *J* = 13.2 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 4.89 (d, *J* = 12.4 Hz, 1H), 3.14 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 166.3, 157.3, 149.9, 140.7, 138.3, 137.5, 137.4, 135.0, 133.5, 132.8, 130.9, 130.2, 130.1, 129.2, 128.5, 128.0, 123.8, 121.4, 104.5, 70.8, 67.3, 37.7, 36.1; IR (film) 1652, 1594, 1394, 1005, 726 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{24}N_2O_4 + H]^+$: 429.1809, found 429.1818.

Diolefin 2-23ιc: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 1H), 8.10 (d, *J* = 15.2 Hz, 2H), 7.85 (s, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.27-7.22 (comp. m, 1H), 6.86 (d, *J* = 15.2 Hz, 2H), 6.29 (s, 1H), 5.62 (d, *J* = 14.0 Hz, 1H), 5.21 (d, *J* = 14.0 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 4.92 (d, *J* = 10.4 Hz, 1H), 3.17 (s, 6H), 3.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 166.3, 157.3, 149.8, 139.3, 138.1, 138.0, 137.5, 137.1, 133.8, 133.2, 130.3, 130.1, 129.2, 128.7, 123.8, 123.1, 104.4, 71.1, 63.1, 37.8, 36.2; IR (film) 1649, 1612, 1397, 1008, 730 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{31}H_{31}N_3O_5 + H]^+$: 526.2336, found 526.2337.

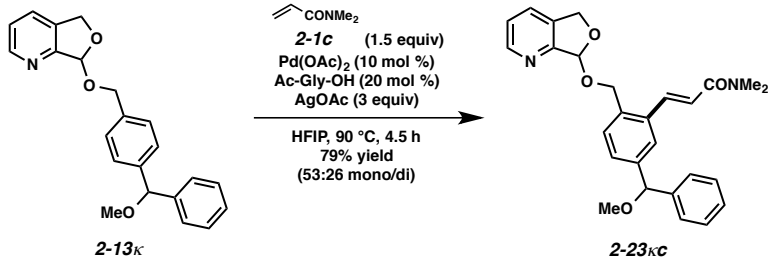


2-31 *2-13κ*

To a solution of alcohol **2-31** (39.1 mg, 0.117 mmol) in THF (1.17 mL) at 0 °C was added NaH (10.3 mg, 60% dispersion in mineral oil, 0.258 mmol), and the mixture was stirred at this temperature for 30 min. MeI (22 μL, 0.351 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred for 2 h. An additional portion of MeI (22 μL, 0.351 mmol) was then added to the reaction mixture at 0 °C, and the mixture was stirred for 2 h. Upon completion as

determined by TLC, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude ether was purified by flash column chromatography (7:3 hexanes/EtOAc) to afford methyl ether **2-13κ** (34.7 mg, 85% yield, R_f = 0.16 in 7:3 hexanes/EtOAc) as a colorless oil.

Methyl ether 2-13κ: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.5 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.35-7.27 (comp. m, 6H), 7.25 (dd, *J* = 7.5, 4.5 Hz, 1H), 7.22 (t, *J* = 6.5 Hz, 1H), 6.21 (d, *J* = 2.0 Hz, 1H), 5.25 (d, *J* = 13.0 Hz, 1H), 5.23 (s, 1H), 5.07 (d, *J* = 13.0 Hz, 1H), 4.82 (ABq, *J* = 11.5 Hz, Δν = 34.9 Hz, 2H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.8, 142.1, 141.7, 136.8, 133.2, 129.9, 128.4, 127.5, 127.1, 126.9, 123.6, 104.1, 85.3, 70.5, 70.0, 57.1; IR (film) 1086, 1075, 1005, 789, 700 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{21}NO_3 + H]^+$: 348.1594, found 348.1594.



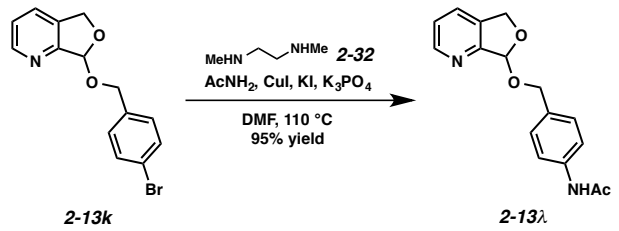
A suspension of acetal **2-13κ** (34.7 mg, 99.9 μmol), *N,N*-dimethylacrylamide (**2-1c**, 15.4 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 9.99 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.0 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary

evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 1:1 EtOAc/MeOH eluent, ~20 mL). The solution was concentrated by rotary evaporation and the crude reaction mixture was purified by flash column chromatography (EtOAc eluent) to afford monoolefin **2-23κc** (23.4 mg, 53% yield, R_f = 0.19 in EtOAc) as a white foam. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory plate chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23κc** (13.8 mg, 26% yield, R_f = 0.16 in 9:1 EtOAc/MeOH) as a white solid.

Monoolefin 2-23κc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 15.5 Hz, 1H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.53 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.31-7.26 (comp. m, 5H), 7.25-7.21 (comp. m, 2H), 6.80 (d, *J* = 15.5 Hz, 1H), 6.23 (d, *J* = 1.5 Hz, 1H), 5.43 (dd, *J* = 13.0, 1.5 Hz, 1H), 5.23 (s, 1H), 5.12 (d, *J* = 13.0 Hz, 1H), 5.06 (d, *J* = 11.3 Hz, 1H), 4.76 (d, *J* = 11.3 Hz, 1H), 3.37 (s, 3H), 3.14 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 157.5, 149.7, 142.2, 141.8, 139.3, 135.4, 135.2, 133.5, 130.4, 130.0, 128.5, 128.0, 127.9, 127.7, 127.0, 125.12, 125.08, 123.6, 120.4, 104.2, 85.1, 70.7, 67.6, 57.2, 37.7, 36.1; IR (film) 1648, 1600, 1072, 1003, 732 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{27}H_{28}N_2O_4 + H]^+$: 445.2122, found 445.2122.

Diolefin 2-23κc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.0 Hz, 1H), 8.03 (d, 15.5 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 2H), 7.33-7.22 (comp. m, 5H), 7.21 (dd, *J* = 8.0, 5.0, 1H), 6.81 (d, *J* = 15.5 Hz, 2H), 6.24 (s, 1H), 5.58 (d, *J* = 13.5 Hz, 1H), 5.22 (s, 1H), 5.17 (d, *J* = 13.5 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 4.82 (d, *J* = 10.8 Hz, 1H), 3.37 (s, 3H), 3.18 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 157.4, 149.6, 142.6, 141.4, 140.0, 138.0, 133.7, 132.8, 130.0, 128.6, 127.9, 127.11, 127.09, 126.6, 126.5, 123.6, 122.2, 104.1, 85.0, 84.9, 70.9, 63.28,

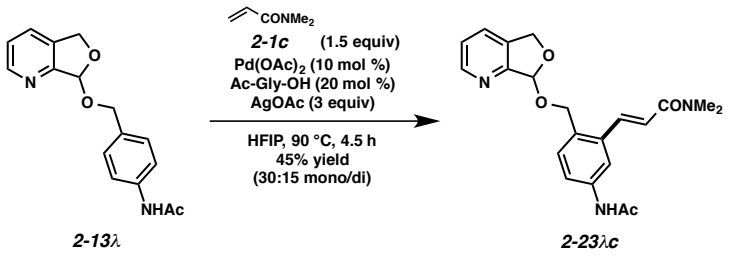
63.26, 57.29, 57.26, 37.8, 36.1; IR (film) 1649, 1607, 1397, 1003, 669 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{32}H_{35}N_3O_5 + H]^+$: 542.2649, found 542.2649.



2-13k *2-13λ*

In a 2-dram vial, a suspension of acetal **2-13κ** (91.8 mg, 0.300 mmol), K_3PO_4 (191 mg, 0.900 mmol), KI (49.8 mg, 0.300 mmol), *N,N'*-dimethylethylenediamine (**2-32**, 29.1 μL, 0.270 mmol), CuI (17.1 mg, 90.0 μmol), and acetamide (70.9 mg, 1.20 mmol) in DMF (0.690 mL) was stirred while Ar was bubbled through the mixture (10 min). The vial was flushed with Ar, sealed with a PTFE-lined cap, and heated to 110 °C and stirred for 15 h. Upon completion, the mixture was diluted with a 10% aq. LiCl solution (30 mL) and was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (30 mL), then brine (30 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude amide was purified by flash column chromatography (EtOAc eluent) to afford acetanilide **2-13λc** (81.0 mg, 95% yield, R_f = 0.12 in 40:1 EtOAc/MeOH) as a white solid.

Acetanilide 2-13λc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.89 (br. s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.27 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.20 (s, 1H), 5.25 (d, *J* = 13.2 Hz, 1H), 5.08 (d, *J* = 13.2 Hz, 1H), 4.76 (ABq, *J* = 11.2 Hz, Δν = 34.1 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 157.5, 149.7, 137.8, 133.3, 133.2, 130.1, 129.1, 123.7, 119.8, 104.0, 70.5, 69.9, 24.6; IR (film) 3306, 1668, 1537, 1315, 1007 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{16}H_{16}N_2O_3 + Na]^+$: 307.1053, found 307.1054.

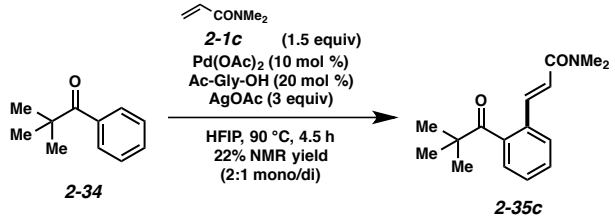


A suspension of acetal **2-13λ** (28.4 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (9:1 EtOAc/MeOH eluent) to afford monoolefin **2-23λc** (10.7 mg, 28% yield, R_f = 0.15 in 9:1 EtOAc/MeOH) as a white solid. The column was washed with MeOH, the filtrate concentrated by rotary evaporation, and the residue was purified by preparatory plate chromatography (9:1 EtOAc/MeOH eluent) to afford diolefin **2-23λc** (8.1 mg, 7.9:1 di/mono, 17% yield, R_f = 0.03 in 9:1 EtOAc/MeOH) as a beige solid.

Monoolefin 2-23λc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.14 (s, 1H), 7.92 (d, *J* = 15.2 Hz, 1H), 7.88 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.32-7.23 (comp. m, 3H), 6.80 (d, *J* = 15.2 Hz, 1H), 6.23 (s, 1H), 5.43 (d, *J* = 13.6 Hz, 1H), 5.11 (d, *J* = 13.6 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 3.10 (s, 3H), 3.03 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 166.8, 157.5, 149.6, 139.1, 138.5, 135.7, 133.7, 131.7, 131.1, 130.2, 123.8,

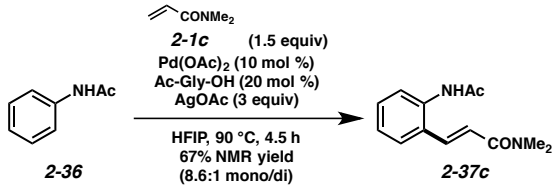
120.5, 120.4, 117.7, 104.1, 70.7, 67.6, 37.6, 36.1, 24.7; IR (film) 1642, 1589, 1394, 1005, 726 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{23}N_3O_4 + H]^+$: 382.1761, found 382.1761.

Diolefin 2-23λc: ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (br. s, 1H), 8.50 (d, *J* = 4.8 Hz, 1H), 7.92 (d, *J* = 15.2 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 2H), 7.30-7.24 (comp. m, 1H), 6.68 (d, *J* = 15.2, 2H), 6.33 (s, 1H), 5.56 (d, *J* = 13.8 Hz, 1H), 5.20 (d, *J* = 13.8 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.80 (d, *J* = 10.6 Hz, 1H), 3.07 (s, 6H), 3.02 (s, 6H), 2,14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 166.4, 157.5, 149.4, 139.2, 139.1, 137.5, 133.9, 130.3, 129.1, 123.9, 121.5, 118.6, 104.3, 70.9, 63.0, 37.6, 36.1, 24.6; IR (film) 1642, 1595, 1005, 910, 741 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{30}N_4O_5 + H]^+$: 479.2289, found 479.2290.



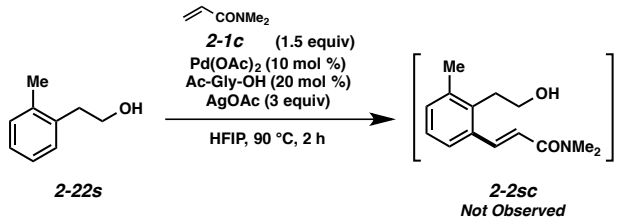
Ketone **2-34** was subjected to the reaction conditions, affording olefin **2-35c** (2:1 mono/di, 22% NMR yield).

Ketone 2-35c: Representative peaks of mono- and diolefinated products in ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 15.6 Hz), 7.64 (d, *J* = 15.6 Hz), 6.86 (d, *J* = 15.6 Hz), 6.84 (d, *J* = 15.9 Hz).

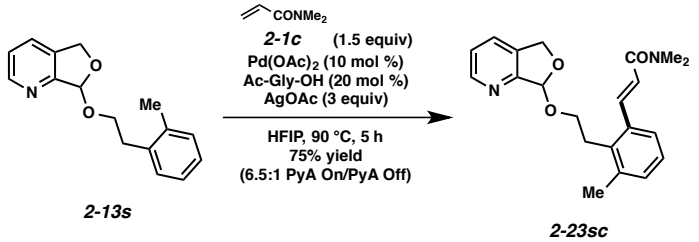


Acetanilide (**2-36**) was subjected to the reaction conditions, affording olefin **2-37c** (8.6:1 mono/di, 67% NMR yield).

Olefin 2-37c: This compound's spectroscopic data corresponds to previously reported data.[52]



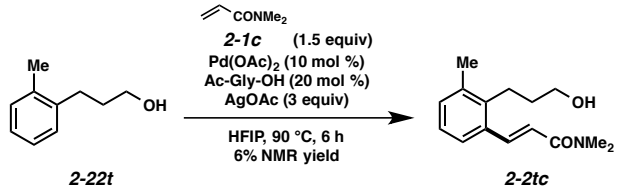
A suspension of alcohol **2-22s** (13.6 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 2 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and olefin **2-2sc** was not observed by NMR in the crude residue.



A suspension of acetal **2-13s** (25.5 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 5 h. Upon completion, the reaction was cooled to ambient

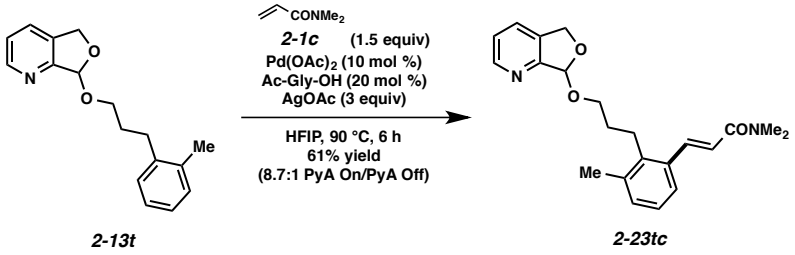
temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by preparatory thin-layer chromatography (39:1 EtOAc/MeOH eluent) to afford olefin **2-23sc** (25.1 mg, 75% yield (1:0.15 PyA group attached/PyA group detached), R_f = 0.44 in 39:1 EtOAc/MeOH) as a colorless oil.

Olefin 2-23sc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.8 Hz, 1H), 8.04 (d, *J* = 15.2 Hz, 0.15H), 7.99 (d, *J* = 15.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 0.15H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.18-7.08 (comp. m, 2.30H), 6.75 (d, *J* = 15.2 Hz, 0.15H), 6.72 (d, *J* = 15.0 Hz, 1H), 6.14 (d, *J* = 1.6 Hz, 1H), 5.23 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.04 (d, *J* = 13.2 Hz, 1H), 3.89-3.73 (comp. m, 2H), 3.72 (t, *J* = 7.6 Hz, 0.30H), 3.20-3.25 (comp. m, 2.30H), 3.14 (app. s, 1.45H), 3.05 (app. s, 1.45H), 2.37 (s, 0.45H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.6, 157.4, 149.7, 141.0, 140.4, 137.63, 137.59, 136.0, 135.6, 135.5, 135.2, 133.1, 131.5, 131.3, 129.8, 126.51, 126.48, 124.7, 124.5, 123.4, 120.3, 119.5, 104.8, 70.3, 67.4, 62.2, 37.5, 37.4, 35.92, 35.86, 32.8, 30.2, 20.1, 20.0; IR (film) 1642, 1595, 1005, 910, 741 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{24}N_2O_3 + H]^+$: 353.1860, found 353.1858.



A suspension of alcohol **2-22t** (15.0 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 6 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and olefin **2-2tc** was observed in small quantities (6% NMR yield) in the crude residue.

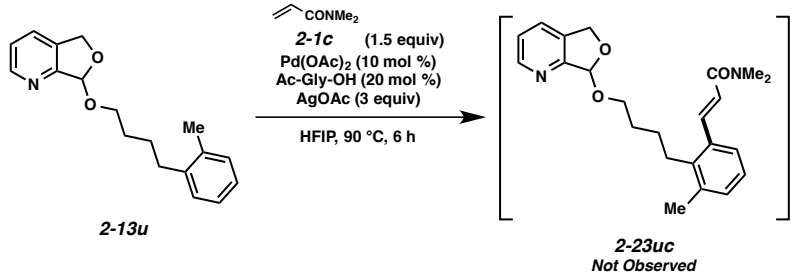
Olefin 2-2tc: Representative peaks in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 15.0 Hz, 1H), 6.75 (d, J = 15.0 Hz, 1H).



A suspension of acetal **2-13t** (26.9 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 6 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and

the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by preparatory thin-layer chromatography (39:1 EtOAc/MeOH eluent) to afford olefin **2-23tc** (21.6 mg, 61% yield (1:0.11 PyA group attached/PyA group detached), R_f = 0.52 in 39:1 EtOAc/MeOH) as a colorless oil.

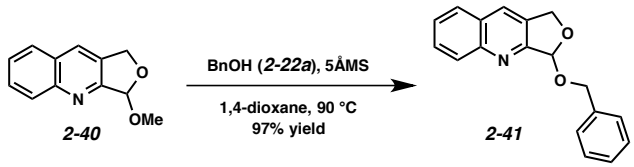
Olefin 2-23tc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.8 Hz, 1H), 8.06 (d, *J* = 15.0 Hz, 0.11H), 7.97 (d, *J* = 15.2 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 0.11H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.17-7.06 (comp. m, 2.22H), 6.74 (d, *J* = 15.0 Hz, 0.11), 6.72 (d, *J* = 15.2 Hz, 1H), 6.14 (s, 1H), 5.25 (d, *J* = 13.4 Hz, 1H), 5.07 (d, *J* = 13.4 Hz, 1H), 3.90-3.71 (comp. m, 2H), 3.68 (t, *J* = 6.0 Hz, 0.22H), 3.17 (s, 0.33H), 3.14 (s, 3H), 3.06 (s, 0.33H), 3.05 (s, 3H), 2.88 (t, *J* = 8.8 Hz, 0.22H), 2.84 (t, *J* = 8.0 Hz, 2H), 1.92-1.80 (comp. m, 2H), 1.79-1.70 (comp. m, 0.22H)**;** ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 157.6, 140.9, 139.9, 137.1, 134.9, 137.1, 134.9, 105.2, 70.5, 68.5, 37.6, 36.0, 30.6, 26.0, 20.0; IR (film) 2924, 1647, 1600, 1004, 727 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{26}N_2O_3 + H]^+$: 367.2016, found 367.2016.



2-13u *2-23uc* *Not Observed*

A suspension of acetal **2-13u** (28.4 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to

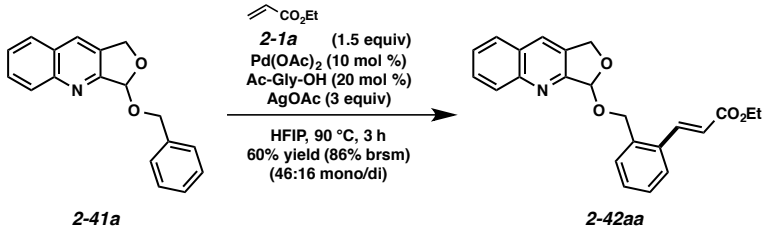
ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and olefin **2-23uc** was not observed by NMR in the crude residue.



In a 2-dram vial, a suspension of methyl acetal **2-40** (78.9 mg, 0.389 mmol), benzyl alcohol (**2-22a**, 40.1 mg, 0.371), and 5Å molecular sieves (463 mg) in 1,4-dioxane (0.590 mL) was heated at 90 °C for 25 h. Upon completion, the reaction was cooled to ambient temperature, and EtOAc (~5.0 mL) and celite (~500 mg) were added to the mixture. This suspension was filtered through a pad of celite (65 mm x 10 mm) with 9:1 EtOAc/MeOH (200 mL), the filtrate concentrated by rotary evaporation, and the residue purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford acetal **2-41a** (99.8 mg, 97% yield, R_f = 0.28 in 4:1 hexanes:EtOAc) as a colorless oil that slowly turned to a white solid.

Quinoline 2-41a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4, 1H), 8.05 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.2, 2H), 7.34 (t, *J* = 7.2, 2H), 7.30-7.25 (comp m, 1H), 6.32 (s, 1H), 5.40 (d, *J* = 13.2 Hz, 1H), 5.23 (d, *J* = 13.2 Hz, 1H), 4.91 (ABq, *J* = 11.6 Hz, Δν = 28.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 148.6, 137.7, 130.7, 129.9, 129.6, 129.0, 128.5, 128.4, 128.1, 128.0, 127.9, 127.2, 103.6, 70.5, 70.0; IR

(film) 2921, 2867, 1503, 1319, 1070, 1007, 911, 752 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{15}NO_2 + H]^+$: 278.1176, found 278.1177.

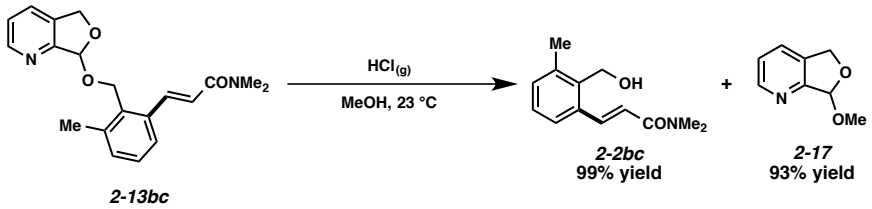


A suspension of acetal **2-41a** (27.7 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (4:1 → 7:3 → 11:9 hexanes/EtOAc eluent) to afford olefin **2-42aa** (23.1 mg, 60% yield (86% brsm), 46:16 mono/di, $R_{f(mono)}$ = 0.16 in 7:3 hexanes/EtOAc, $R_{f(di)}$ = 0.47 in 11:9 hexanes/EtOAc) as a colorless oil.

Monoolefin 2-42aa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 16.0 Hz, 1H), 8.08 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.60-7.54 (comp. m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.38-7.27 (comp. m, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.37 (s, 1H), 5.61 (d, *J* = 13.4 Hz, 1H), 5.30 (d, *J* = 13.4 Hz, 1H), 5.25 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6,

166.9, 159.0, 141.7, 136.2, 133.9, 130.8, 130.4, 129.9, 129.6, 129.5, 129.3, 128.5, 127.9, 127.8, 127.2, 126.6, 120.1, 103.6, 0.1, 68.2, 60.5, 14.4; IR (film) 1709, 1315, 1178, 1009, 910 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{21}NO_4 + H]^+$: 376.2, found 376.2.

Diolefin 2-42aa: ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* =15.8 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.58-7.54 (comp. m, 3H), 7.33 (t, *J* = 8.0 Hz, 1H), 6.39 (s, 1H), 6.37 (d, *J* = 15.8 Hz, 2H), 5.71 (d, *J* = 13.4 Hz, 1H), 5.34 (d, *J* = 13.4 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 4H), 1.37 (t, *J* = 7.2 Hz, 6H); LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{28}H_{27}NO_6 + H]^+$: 474.2, found 474.3.



2-13bc

2-2bc 99% yield

2-17 93% yield

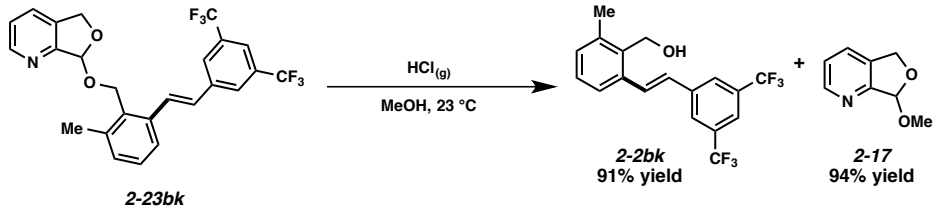
To a solution of acetal **2-13bc** (36.7 mg, 0.108 mmol) in MeOH (1.08 mL) was bubbled anhydrous HCl for 1 min. The reaction mixture was stirred at 23 °C in a sealed 2-dram vial for 36 h, and it was then concentrated by rotary evaporation and MeOH was azeotropically removed with Et_2O. The crude mixture was purified by flash column chromatography (EtOAc eluent) on basic SiO_2 (treated with 9:1 hexanes/triethylamine and dried by rotary evaporation) to afford alcohol **2-2bc** (23.6 mg, 99% yield, R_f = 0.20 in EtOAc) as a white solid and methyl acetal **2-17** (15.3 mg, 93% yield, R_f = 0.43 in EtOAc) as an amber oil.

Alcohol 2-2bc: ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 15.2 Hz, 1H), 7.38 (dd, *J* = 5.8, 3.0 Hz, 1H), 7.20 (d, *J* = 3.0 Hz, 1H), 7.20 (d, *J* = 5.8 Hz, 1H), 6.79 (d, *J* = 15.2 Hz, 1H), 4.81 (s, 2H), 3.15 (s, 3H), 3.04 (s, 3H), 2.71 (br. s, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 140.7, 138.3, 137.3, 135.8, 131.7, 128.2, 125.0, 120.4, 58.5, 37.6, 36.1, 19.6; IR (film)

3358, 1642, 1589, 1394, 1010 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{17}NO_2 + H]^+$; 220.1332, found 220.1333.



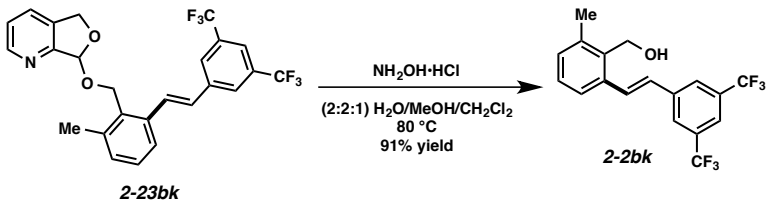
Acetal **2-13bc** (36.7 mg, 0.100 mmol) was dissolved in 1 M HCl (1.00 mL) and stirred at 23 °C for 6 h. As the reaction proceeded, the clear suspension slowly became opaque. Upon completion by TLC, the reaction mixture was poured into water (15 mL) and extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (EtOAc eluent) on basic SiO_2 (treated with 9:1 hexanes/triethylamine and dried by rotary evaporation) to afford alcohol **2-2bc** (21.9 mg, >99% yield, R_f = 0.20 in EtOAc) as a white solid.



To a solution of acetal **2-23bk** (15.9 mg, 0.0332 mmol) in MeOH (0.332 mL) at 23 °C was bubbled anhydrous HCl for 1 min. The reaction mixture was stirred at 23 °C in a sealed 2-dram vial for 28 h, and it was then concentrated by rotary evaporation and MeOH was azeotropically removed with Et_2O. The crude mixture was purified by flash column chromatography (9:1 hexanes/EtOAc → EtOAc eluent) to afford alcohol **2-2bk** (10.9 mg, 91% yield, R_f = 0.25 in 9:1

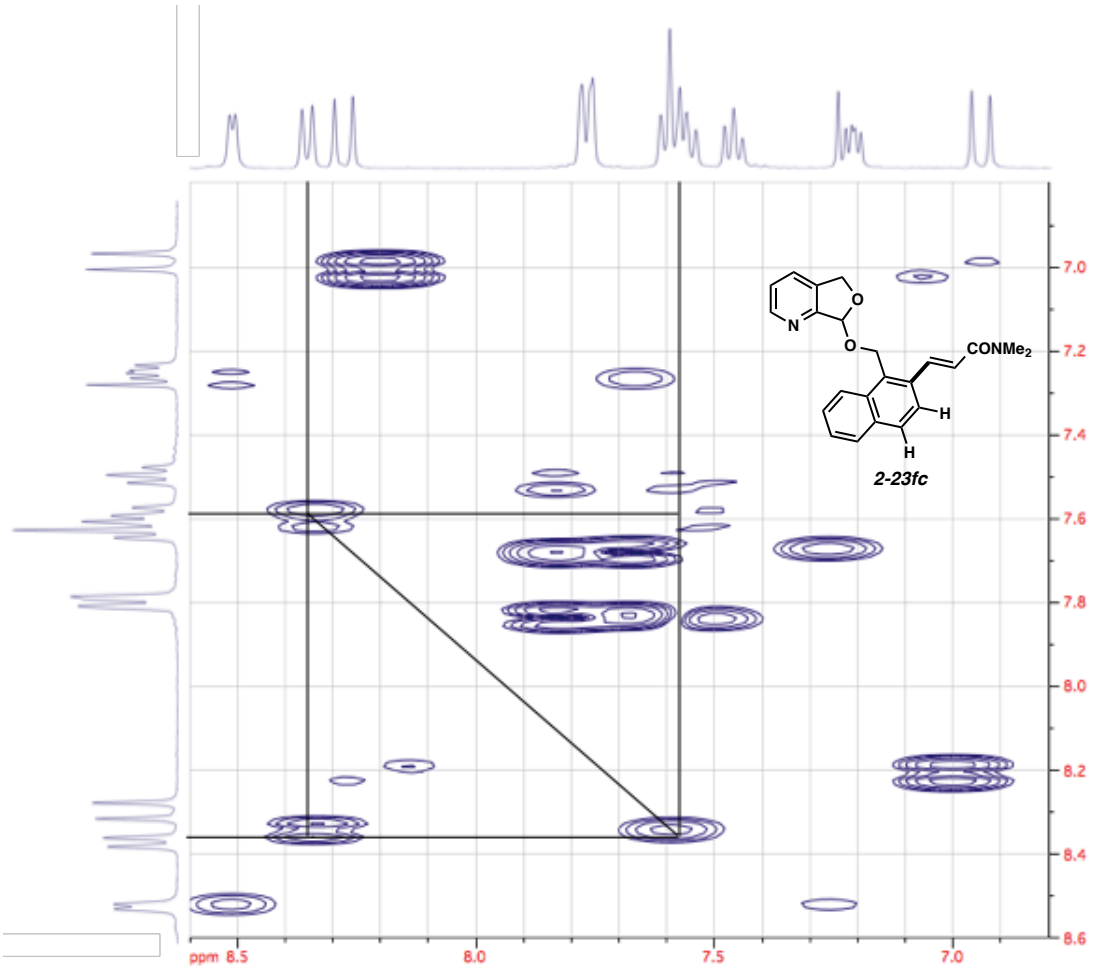
hexanes/EtOAc) as a white solid and methyl acetal **2-17** (4.7 mg, 94% yield, R_f = 0.43 in EtOAc) as an amber oil.

Alcohol 2-2bk: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.76 (s, 1H), 7.70 (d, *J* = 16.2 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 16.2 Hz, 1H), 4.88 (d, *J* = 4.8 Hz, 2H), 2.49 (s, 3H), 1.47 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.9, 136.8, 136.1, 132.2 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 131.2, 130.6, 128.8, 128.7, 126.5 (q, $^3J_{C\text{-}F}$ = 3.2 Hz), 124.8, 123.5 (q, $^1J_{C\text{-}F}$ = 271.0 Hz), 121.1 (septet, $^3J_{C\text{-}F}$ = 3.8 Hz), 59.2, 19.7; IR (film) 3374, 1379, 1278, 1163, 1126 cm^{-1}; HRMS (ESI-) *m/z* calc'd for $(M - H)^-$ $[C_{18}H_{14}F_6O - H]^-$: 359.0876, found 359.0877.

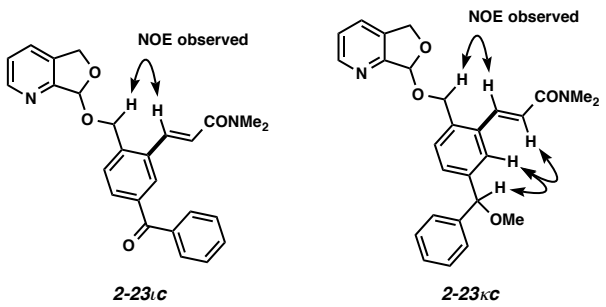


2-23bk *2-2bk*

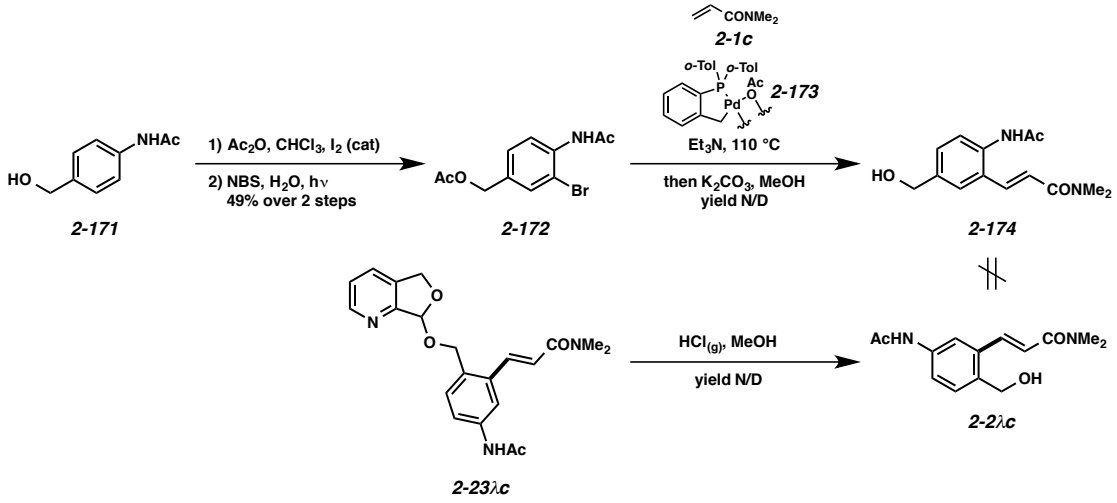
To a suspension of acetal **2-23bk** (19.0 mg, 39.6 μmol) and $NH_2OH{\bullet}H_2O$ (3.0 mg, 43.4 μmol) in a mixture of 2:2:1 H_2O/MeOH/CH_2Cl_2 (0.332 mL) was stirred at 80 °C in a sealed 2-dram vial for 24 h. Upon completion by TLC, the reaction mixture was then concentrated by rotary evaporation and solvent was azeotropically removed with Et_2O. The crude mixture was purified by flash column chromatography (9:1 hexanes/EtOAc → EtOAc eluent) to afford alcohol **2-2bk** (13.0 mg, 91% yield, R_f = 0.25 in 9:1 hexanes/EtOAc) as a white solid.



Acetal **2-13f** was olefinated at the C-2 position on the naphthyl ring. To unambiguously assign the structure of olefin **2-23fc**, a ^{1}H-^{1}H COSY was performed. Three arene spin systems were observed: the pyridine system containing 3 hydrogens, a system containing 4 hydrogens, and a third system that contains only 2 hydrogens. This evidence supports the assigned structure where olefination occurs at C-2.

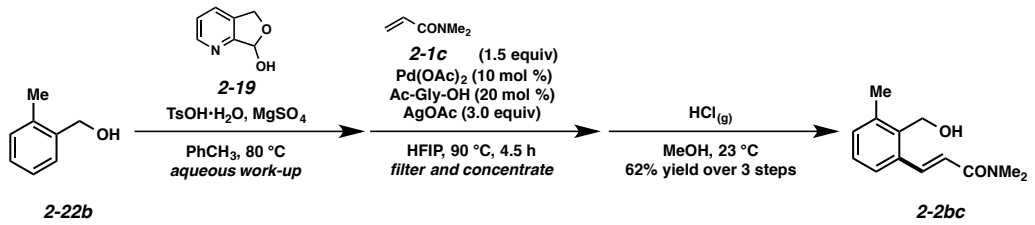


The structures of monoolefin **2-23ιc** and monoolefin **2-23κc** were determined by the observation of an NOE interaction.



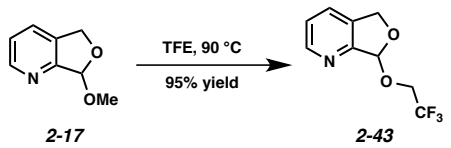
The structure of monoolefin **2-23λc** was determined by cleavage of the PyA scaffold with methanolic HCl to afford alcohol **2-2λc** and comparing the resulting product to independently synthesized alcohol **2-174**. Aryl bromide **2-172** was synthesized by acetylation of benzyl alcohol **2-171**[53] and bromination[54] of the resulting ester. Cross coupling between this aryl bromide and acrylamide **2-1c** followed by methanolic potassium carbonate afforded alcohol **2-174**. Alcohol **2-274** and alcohol **2-2λc** did not match by ^{1}H NMR.

Experimental Procedure and Studies from Section 2.5



A suspension of 2-methylbenzyl alcohol (**2-22b**, 12.2 mg, 0.100 mmol), hemiacetal **2-19** (13.7 mg, 0.105 mmol), TsOH•H_2O (1.9 mg, 10.0 μmol), and $MgSO_4$ (36.1 mg, 0.300 mmol) in $PhCH_3$ (0.330 mL) in a 2-dram vial was heated to 80 °C and stirred for 18 h. Upon completion, sat. aq. Na_2CO_3 (5 mL) was added to the reaction mixture, and the mixture was extracted into EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated by rotary evaporation to afford a crude mixture containing the product acetal (**2-13b**). This crude mixture was treated with $Pd(OAc)_2$ (2.0 mg, 9.00 μmol), *N*-acetylglycine (2.1 mg, 18.0 μmol), AgOAc (45.1 mg, 0.270 mmol), and *N,N*-dimethylacrylamide (**2-1c**, 13.9 μL, 0.135 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap, which was then heated to 90 °C and stirred for 4.5 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation to afford crude olefin **2-23bc**. This mixture was dissolved in MeOH (1.00 mL), and anhydrous HCl was bubbled into the solution for 1 min. The reaction mixture was stirred at 23 °C in a sealed 2-dram vial for 24 h, and it was then

concentrated by rotary evaporation, and MeOH was azeotropically removed with Et_2O. The crude mixture was purified by flash column chromatography (EtOAc eluent) on basic SiO_2 (treated with 9:1 hexanes/triethylamine and dried by rotary evaporation) to afford alcohol **2-2bc** (13.5 mg, 62% yield over 3 steps, R_f = 0.20 in EtOAc) as a white solid.

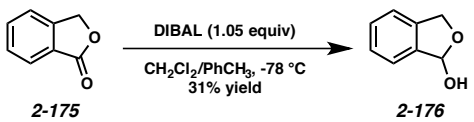


2-17 *2-43*

A solution of acetal **2-17** (15.1 mg, 0.100 mmol) in TFE (2.0 mL) was stirred and heated at 90 °C for 20 h. The solvent was then removed by rotary evaporation and purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford acetal **2-43** (20.8 mg, 95% yield, R_f = 0.44 in 1:1 hexanes/EtOAc) as a colorless oil.

Acetal 2-43: (400 MHz, $CDCl_3$) 8.61 (d, J = 5.0, Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.32 (dd, J = 8.0, 5.0 Hz, 1H), 6.18 (d, J = 2.0 Hz, 1H), 5.26 (dd, J = 13.2, 2.0 Hz, 1H), 5.10 (d, J = 13.2 Hz, 1H), 4.11 (q, $^2J_{H\text{-}F}$ = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 150.2, 133.2, 130.1, 124.1, 123.9 (q, $^1J_{C\text{-}F}$ = 276.7 Hz), 104.9, 71.0, 65.0 (q, $^2J_{C\text{-}F}$ = 34.8 Hz); IR (film) 2982, 1377, 1277, 1157, 1107 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_9H_8F_3NO_2 + H]^+$: 220.1, found 220.1.

Experimental Procedure and Studies from Section 2.6

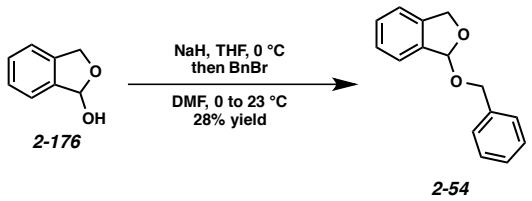


2-175 *2-176*

To a solution of phthalide **2-175** (1.00 g, 7.46 mmol) in CH_2Cl_2 (34 mL) at -78 °C was added a solution of diisobutylaluminum hydride (5.65 mL, 1.32 M in $PhCH_3$, 7.83 mmol) over 10 min.

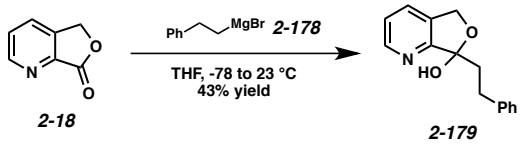
The reaction mixture was stirred for 1.5 h at -78 °C, and upon completion sat. aq. Na_2SO_4 (5 mL) was added, and the mixture was allowed to warm to ambient temperature. To this mixture was added anhydrous Na_2SO_4 (10 g), and the mixture was stirred overnight and then filtered through a Buchner funnel and washed with CH_2Cl_2 (50 mL). The filtrate was concentrated by rotary evaporation, and the resulting oil was purified by flash column chromatography (1:1 Et_2O/hexanes → 2:1 Et_2O/hexanes eluent) to afford hemiacetal **2-176** (314 mg, 31% yield, R_f = 0.21 in 2:1 hexanes/E_2O) as a colorless oil.

Hemiacetal 2-176: This compound's spectroscopic data corresponds to previously reported data.[55]



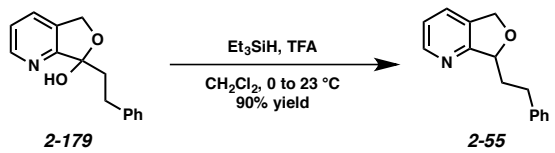
To a solution of hemiacetal **2-176** (101 mg, 0.742 mmol) in THF (3.7 mL) at 0 °C was added NaH (74.2 mg, 60% dispersion in mineral oil, 1.86 mmol) in one portion, and the mixture was stirred at 0 °C for 1 h. To the suspension was added dropwise a solution of BnBr (1.00 mL, 0.705 M in DMF, 0.705 mmol), and the mixture was warmed to 23 °C by removal of the cooling bath. The suspension was stirred for 20 h, and upon completion as determined by TLC, it was then quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by column chromatography (39:1 → 9:1 hexanes/Et_2O eluent) to afford acetal **2-54** (46.4 mg, 28% yield, R_f = 0.36 in 9:1 hexanes/Et_2O) as a colorless oil.

Acetal 2-54: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.26 (comp. m, 9H), 6.36 (s, 1H), 5.27 (d, J = 12.6 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.73 (ABq, J = 11.6 Hz, Δν = 22.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 138.2, 137.7, 129.3, 128.5, 128.1, 127.81, 127.76, 123.2, 121.2, 106.3, 72.5, 69.1; IR (film) 2359, 2340, 1005, 908, 729 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{14}O_2 + Na]^+$: 249.0886, found 249.0886.



2-18 *2-179*

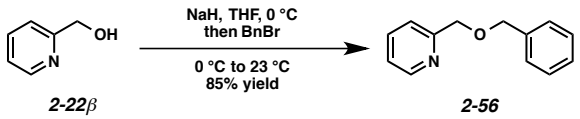
Magnesium turnings were ground in a mortar immediately before use. The metal (919 mg, 37.8 mmol) was suspended in THF (54 mL) and a few drops of iodine in methyl *tert*-butyl ether (10 M) were added. Then phenethyl bromide (5.00 g, 27.0 mmol) was added portionwise at 23 °C. The stirring solution was refluxed for 2 h to afford a solution of phenethylmagnesium bromide (0.035 M). In a separate flask, lactone **2-18**[32] (250 mg, 1.85 mmol) was suspended in THF (1.9 mL) cooled to -78 °C, and to this suspension was added Grignard solution **2-178** (52.9 mL, 0.035 M, 1.85 mmol) dropwise over 10 min. The resulting suspension was stirred for 2.5 h, and then it was warmed to ambient temperature by removal of the cooling bath. Sat. aq. $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The resulting oil was dissolved in CH_3CN (50 mL) and washed with pentane (3 x 50 mL), and the CH_3CN layer was removed by rotary evaporation. The crude oil was purified by flash column chromatography (3:1 EtOAc/hexanes eluent) to afford hemiacetal **2-179** (192 mg, 43% yield, R_f = 0.29 in 3:1 EtOAc/hexanes) as a white solid.



2-179 *2-55*

To a solution of hemiacetal **2-179** (136 mg, 0.565 mmol) and triethylsilane (0.451 mL, 2.82 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C was added trifluoroacetic acid (0.649 mL, 8.47 mmol) dropwise. The solution was stirred at 0 °C for 2 h, and then it was warmed to 23 °C by removal of the cooling bath, and it was stirred for 30 min. Upon completion as determined by TLC, water (5 mL) and CH_2Cl_2 (30 mL) were added to the reaction mixture, and the mixture was extracted with sat. aq. NH_4Cl (3 x 20 mL). The combined aqueous layers were brought to pH 12 by the addition of sat. aq. Na_2CO_3 (60 mL), and the mixture was extracted with EtOAc (4 x 30 mL). The combined EtOAc layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated by rotary evaporation to afford analytically pure ether **2-55** (115 mg, 90% yield, R_f = 0.37 in EtOAc) as a colorless oil.

Ether 2-55: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (app. s, 1H), 7.85 (d, J = 8.0 Hz, 1H) 7.32-7.25 (comp. m, 3H), 7.23-7.16 (comp. m, 3H), 4.92 (br. s, 1H), 4.57 (ABq, J = 12.8 Hz, Δν = 36.7 Hz, 2H), 2.89-2.76 (comp. m, 2H), 2.03-1.88 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 146.8, 141.7, 137.2, 132.9, 128.7, 128.5, 126.1, 123.0, 69.3, 60.6, 39.8, 31.9; IR (film) 2359, 1678, 1454, 1202, 1036 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{15}NO + H]^+$: 226.1226, found 226.1226.

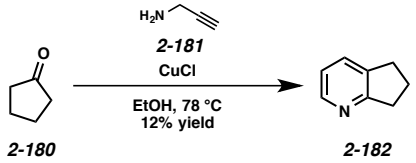


2-22β *2-56*

To a solution of alcohol **2-22β** (417 mg, 3.82 mmol) in THF (9.6 mL) at 0 °C was added NaH (229 mg, 60% dispersion in mineral oil, 5.73 mmol) in one portion. The suspension was stirred

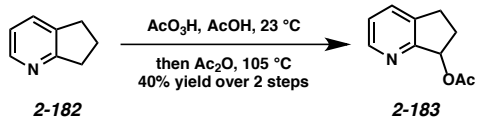
for 25 min at 0 °C, and then benzyl bromide (500 μL, 4.21 mmol) was added to the reaction in one portion at this temperature. The ice bath was removed, allowing the reaction to warm to 23 °C, and it was stirred for 2 h before being quenched with water (10 mL). Et_2O (30 mL) was added, and the mixture was extracted with 1 M aq. HCl (3 x 30 mL). The combined aqueous layers were neutralized with sat. aq. Na_2CO_3 (90 mL), and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated by rotary evaporation to afford ether **2-56** (643 mg, 85% yield, R_f = 0.27 in 4:1 hexanes/EtOAc) as a yellow oil, which was sufficiently pure to be evaluated in the functionalization.

Ether 2-56: This compound's spectroscopic data corresponds to previously reported data.[56]



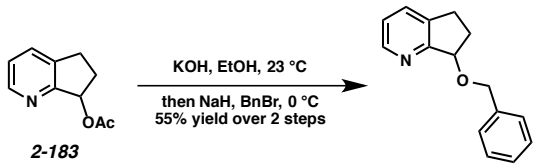
A suspension of cylcopentanone (**2-180**, 1.26 g, 15.0 mmol), propargylamine (**2-181**, 1.44 mL, 15.0 mmol), and anhydrous CuCl (50.4 mg, 0.375 mmol) in absolute EtOH (60 mL) was heated at reflux for 13 h. Upon completion as determined by TLC, EtOAc (50 mL) and 1 M aq. HCl (50 mL) were added. The layers were separated, and the organic layer was discarded. The pH of the aqueous layer was raised by the addition of sat. Na_2CO_3 (50 mL). The mixture was then extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford pyridine **2-182** (222 mg, 12% yield, R_f = 0.31 in EtOAc) as a light green oil, which was sufficiently pure to be carried to the next step.

Pyridine 2-182: This compound's spectroscopic data corresponds to previously reported data.[57]



2-182 *2-183*

To a solution of pyridine **2-182** (222 mg, 1.86 mmol) in CH_2Cl_2 (4.2 mL) at 23 °C was added peracetic acid (2.65 g, 32% w/w solution in dilute AcOH, 11.2 mmol), and the mixture was stirred at 23 °C for 8 h. Upon completion as determined by TLC, the mixture was extracted with water (5 mL), and residual peracetic acid was azeotropically removed by successive additions of water and concentration by rotary evaporation. (Peracetic acid removal was confirmed by starch paper test.) Ac_2O (3.2 mL) was added to the resulting crystalline solid (284 mg), and the mixture was heated to 105 °C and stirred for 10 min. The resulting dark brown mixture was concentrated by rotary evaporation, and Ac_2O was azeotropically removed with heptane. The residue was purified by flash column chromatography (1:1 EtOAc/hexanes eluent) to afford acetate **2-183** (131 mg, 40% yield over 2 steps, R_f = 0.16 in 1:1 EtOAc/hexanes) as a colorless oil.

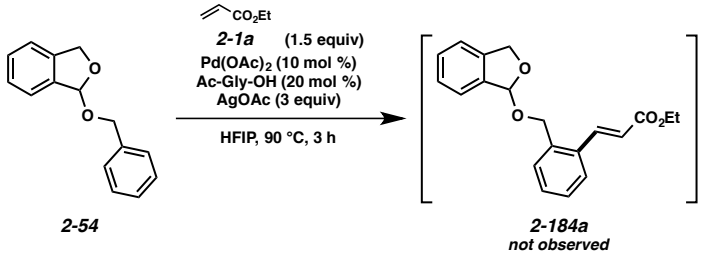


2-183 *2-58*

To a solution of acetate **2-183** (131 mg, 0.738 mmol) in EtOH (1.5 mL) at 23 °C was added powdered KOH (124 mg, 2.21 mmol), and the reaction was stirred for 10 min. Upon completion as determined by TLC, AcOH (125 μL) was added to the reaction mixture, and it was then concentrated by rotary evaporation to afford a mixture of clear crystals suspended in a purple oil. This mixture was dissolved in THF (6.0 mL), and it was then cooled to 0 °C. To this solution was added NaH (148 mg, 60% dispersion in mineral oil, 3.69 mmol), and the resulting mixture was stirred at 0 °C for 30 min. To the suspension was added benzyl bromide (439 μL, 3.69 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The ice bath was removed and the

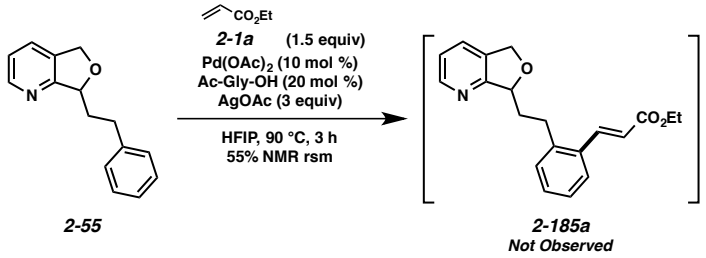
mixture was allowed to warm to 23 °C and stirred for 1 h. Upon completion as determined by TLC, the reaction mixture was poured into 1 M aq. HCl (30 mL) and washed with EtOAc (3 x 30 mL). The organic layers were discarded, and the pH of the aqueous layer was raised with sat. aq. Na_2CO_3 (30 mL). The aqueous mixture was extracted with EtOAc (3 x 30 mL), and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified with column chromatography (4:1 hexanes/EtOAc eluent) to afford ether **2-58** (91.2 mg, 55% yield over 2 steps, R_f = 0.25 in 4:1 hexanes/EtOAc) as a colorless oil.

Ether 2-58: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.8 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.15 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.95 (dd, *J* = 6.8, 3.6 Hz, 1H), 4.85 (ABq, *J* = 12.0 Hz, Δν = 44.0, 2H), 3.11 (ddd, *J* = 16.0, 8.0, 7.2 Hz, 1H), 2.81 (ddd, *J* = 16.0, 8.8, 4.8 Hz, 1H), 2.41-2.32 (comp. m, 1H), 2.25-2.15 (comp. m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 148.2, 138.7, 137.4, 133.1, 128.4, 128.0, 127.5, 123.1, 81.7, 71.4, 31.2, 28.1; IR (film) 1090, 1069, 791, 737, 698 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{15}NO + H]^+$: 226.1226, found 226.1227.

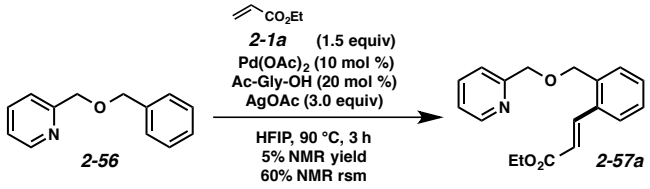


A suspension of acetal **2-54** (22.6 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient

temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and olefin **2-184a** was not observed by NMR in the crude residue.

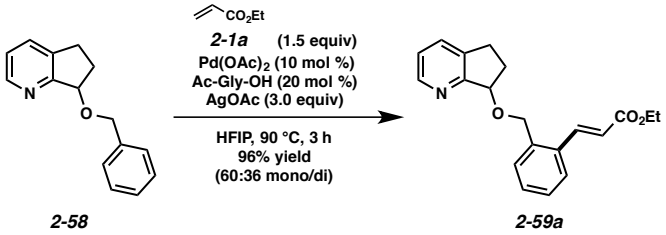


A suspension of pyridine **2-55** (22.5 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and olefin **2-185a** was not observed by NMR in the crude residue. Pyridine **2-185a** (55% recovered starting material) was observed by NMR in the crude residue.



A suspension of ether **2-56** (19.9 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated to 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 µL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent). The filtrate was concentrated by rotary evaporation, and olefin **2-57a** was observed in small quantities (5% NMR yield, 60% recovered starting material) in the crude residue.

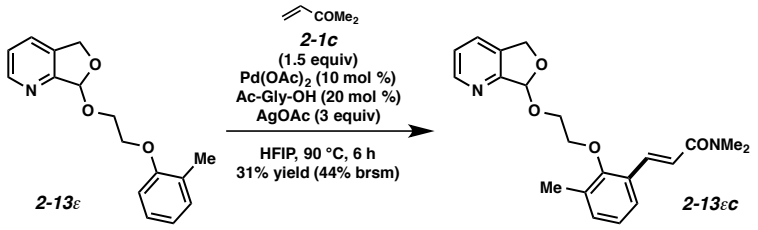
Olefin 2-57a: Representative peaks in ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 16.0 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H).



A suspension of pyridine **2-58** (22.6 mg, 0.100 mmol), ethyl acrylate (**2-1a**, 16.0 µL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 µmol), *N*-acetylglycine (2.3 mg, 20.0 µmol), and AgOAc (50.1 mg, 0.300 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap

was heated to 90 °C and stirred for 3 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford olefin **2-59a** (34.9 mg, 1.6:1 mono/di, 96% yield, $R_{f(mono)}$ = 0.31 and $R_{f(di)}$ = 0.20 in 1:1 hexanes/EtOAc) as a white solid.

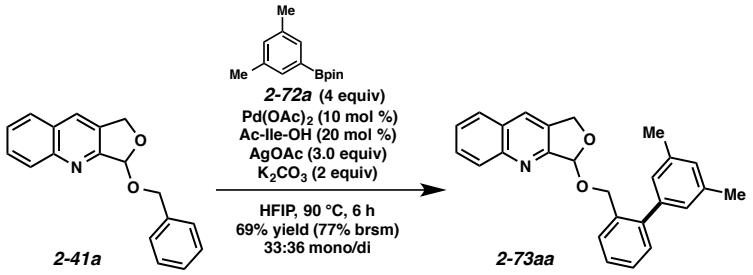
Olefin 2-59a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.8 Hz, 1H), 8.49 (d, *J* = 4.8 Hz, 1.6H), 8.15 (d, *J* = 15.6 Hz, 2H), 8.05 (d, *J* = 15.6 Hz, 1H), 7.61-7.56 (comp. m, 2.6H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1.6H), 7.43-7.26 (comp. m, 5.8H), 7.21-7.14 (comp. m, 2.6H), 6.36 (d, *J* = 15.6 Hz, 1.6H), 6.33 (d, *J* = 15.6 Hz, 2H), 5.20 (d, *J* = 11.2 Hz, 1H), 5.03-4.96 (comp. m, 4.2H), 4.90 (d, *J* = 11.6 Hz, 1.6H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 7.2H), 3.18-3.08 (comp m, 2.6H), 2.89-2.79 (comp m, 2.6H), 2.48-2.38 (comp m, 2.6H), 2.28-2.18 (comp m, 2.6H), 1.34 (t, *J* = 7.2 Hz, 10.8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.7, 163.1, 163.0, 148.3, 148.2, 142.6, 142.1, 137.6, 137.5, 137.4, 136.3, 135.5, 134.0, 133.2, 130.1, 130.0, 128.8, 128.5, 128.4, 128.3, 128.0, 126.8, 123.2, 121.7, 121.7, 120.1, 82.4, 82.3, 69.5, 64.6, 60.6, 60.5, 31.1, 28.2, 14.5; IR (film) 1711, 1166, 1045, 909, 730 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M_{mono} + H)^+$ $[C_{20}H_{21}NO_3 + H]^+$: 324.1594, found 324.1595; HRMS (ESI+) *m/z* calc'd for $(M_{di} + H)^+$ $[C_{25}H_{27}NO_5 + H]^+$: 422.1962, found 422.1964.



A suspension of acetal **2-13ε** (27.1 mg, 0.100 mmol), *N,N*-dimethylacrylamide (**2-1c**, 15.5 μL, 0.150 mmol), $Pd(OAc)_2$ (2.2 mg, 10.0 μmol), *N*-acetylglycine (2.3 mg, 20.0 μmol), and AgOAc (50.1 mg, 0.150 mmol) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 6 h. Upon completion, the reaction was cooled to ambient temperature, ethylenediamine (40 μL) and celite (70 mg) were added, and the resulting mixture was stirred overnight. The mixture was filtered through a plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL), the filtrate was concentrated by rotary evaporation, and the resulting residue was dissolved in EtOAc and then filtered through a second plug of SiO_2 (5 mm x 20 mm, EtOAc → 9:1 EtOAc/MeOH eluent, ~20 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by preparatory thin-layer chromatography (19:1 EtOAc/MeOH eluent) to afford olefin **2-23εc** (11.4 mg, 31% yield (44% brsm), R_f = 0.27 in 19:1 EtOAc/MeOH) as a white solid.

Olefin 2-23εc: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.0 Hz, 1H), 7.81 (d, *J* = 15.8 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.35-7.28 (comp. m, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.18 (d, *J* = 15.8 Hz, 1H), 6.23 (d, *J* = 1.6 Hz, 1H), 5.28 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.09 d, *J* = 13.2 Hz, 1H), 4.12-4.02 (comp. m, 2H), 3.08 (s, 3H), 3.03 (s, 3H), 2.30 (s, 3H); LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{24}N_2O_2 + H]^+$: 369.2, found 369.2.

Experimental Procedures and Studies from Section 2.7

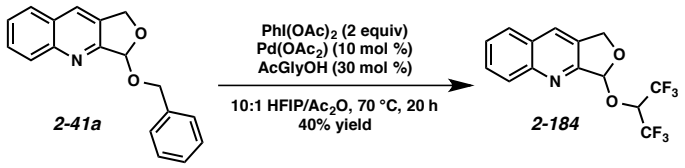


A suspension of acetal **2-41a** (27.8 mg, 0.100 mmol), boronic ester **2-72a** (93.0 mg, 0.400 mmol), $Pd(OAc)_2$ (2.3 mg, 10.3 μmol), *N*-acetylisoleucine (3.4 mg, 20.0 μmol), $AgCO_3$ (55.9 mg, 0.203 mmol), and K_2CO_3 (27.8 mg, 0.201) in hexafluoroisopropanol (2.00 mL) in a 2-dram vial with a PTFE-lined cap was heated at 90 °C and stirred for 6 h. Upon completion by TLC, the crude reaction mixture was filtered through a plug of SiO_2 (30 mm x 10 mm) with Et_2O (50 mL). The filtrate was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (20:1→10:1 hexanes/EtOAc eluent) to afford monoarylated acetal **2-73aa** (12.5 mg, 33% yield, R_f = 0.26 in 5:1 hexanes/EtOAc) as a yellow oil and diarylated acetal **2-73aa** (17.6 mg, 36% yield, R_f = 0.52 in 5:1 hexanes/EtOAc) as a yellow oil.

Monoarylated acetal 2-73aa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.36-7.28 (comp. m, 2H), 7.26-7.23 (comp. m, 1H), 7.05 (s, 2H), 7.01 (s, 1H), 6.23 (s, 1H), 5.32 (d, *J* = 13.2 Hz, 1H), 5.18 (d, *J* = 13.2 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 148.6, 142.3, 140.8, 137.6, 134.9, 130.7, 129.98, 129.93, 129.7, 129.5, 128.88, 128.83, 128.0, 127.9, 127.7, 127.38, 127.35, 127.1, 103.9, 69.9, 68.7, 21.5.

Diarylated acetal 2-73aa: ^{1}H (400 MHz, $CDCl_3$) δ 8.17 (d, v 8.4 Hz, 1H), 8.02 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.71 (dt, *J* = 8.4, 6.5 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 8.4, 6.4 Hz,

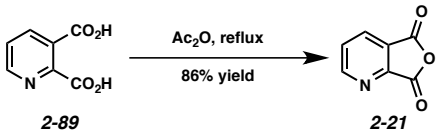
1H), 7.27 (d, J = 8.0 Hz, 2H), 7.23 (s, 4H), 7.03 (s, 2H), 5.89 (s, 1H), 5.10 (q, J = 16.0 Hz, 2H), 4.71 (d, J = 13.2 Hz, 1H), 4.36 (d, J = 13.2 Hz, 1H), 2.42 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 148.7, 145.0, 141.5, 137.4, 132.1, 130.6, 130.2, 129.4, 129.2, 128.9, 128.4, 127.92, 127.86, 127.81, 127.0, 103.8, 69.6, 66.8, 21.5.



A solution of quinoline **2-41a** (16.3 mg, 58.8 μmol), $PhI(OAc)_2$ (37.9 mg, 118 μmol), $Pd(OAc)_2$ (1.3 mg, 5.88 μmol), and Ac-Gly-OH (2.1 mg, 17.6 μmol) in 10:1 HFIP/Ac_2O (0.646 mL) was stirred and heated at 70 °C for 20 h. Upon completion, the solvent was azeotropically removed by addition of heptane and rotary evaporation. The crude residue was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford quinoline **2-184** (8.0 mg, 40% yield, R_f = 0.38 in 4:1 hexanes/EtOAc) to afford a white solid.

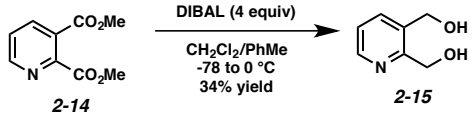
Quinoline 2-184: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.0, Hz, 1H), 8.12 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0, 7.6 Hz, 1H), 7.62 (dd, J = 8.0, 7.6 Hz, 1H), 6.39 (s, 1H), 5.34 (ABq, J = 13.2 Hz, Δν = 52.0 Hz, 1H), 4.88 (heptet, $^2J_{C\text{-}F}$ = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 148.5, 130.1, 130.0, 129.9, 129.5, 128.2, 128.1, 127.8, 104.2, 71.2 (heptet, $^2J_{C\text{-}F}$ = 32.5 Hz), 70.9; IR (film) 1288, 1219, 1194, 1101, 966 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{14}H_9F_6NO_2 + H]^+$: 338.1, found 338.1.

Experimental Procedures and Studies from Section 2.8



Diacid **2-89** (9.00 g, 53.9 mmol) was dissolved in acetic anhydride (108 mL) and was heated and stirred at reflux for 3 h. Upon completion, the solvent was distilled away from the product while at reflux and at atmospheric pressure until the mixture reached a volume of ~20 mL. The mixture was cooled to 23 °C, added hexanes (50 mL), and then cooled to 0 °C. The mixture was triturated to afford anhydride **2-21** (6.93 mg, 86% yield, R_f = 0.16 in EtOAc) as sufficiently pure beige solid.

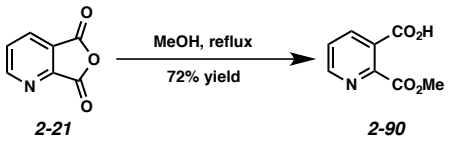
Anhydride 2-21: ^{1}H NMR (300 MHz, D_6-acteone) δ 9.19 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.54 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.01 (dd, *J* = 7.8, 4.8 Hz, 1H). This compound's spectroscopic data corresponds to previously reported data.[58]



To a stirring suspension of diester **2-14** (1.00 g, 5.12 mmol) in CH_2Cl_2 (20.0 mL) cooled to -78 °C was added diisobutylaluminum hydride (15.5 mL, 1.32 M in PhMe, 20.5 mmol) dropwise over 10 min. The solution was stirred for 5 h at -78 °C, and was then warmed to 0 °C and stirred for 30 min. To the reaction was carefully added water (0.798 mL) dropwise, and then 3.8 M NaOH (0.798 mL) dropwise, and finally water (2.39 mL). The suspension was warmed to ambient temperature and was stirred for 20 min before $MgSO_4$ (~11 g) and celite (~5 g) were added. Stirring was stopped, and the mixture was allowed to sit overnight. The suspension was then filtered through a glass-fritted funnel, and the solids were washed with excess MeOH (14 mL). The filter cake was collected and heated in MeOH (~50 mL, approx. reflux) for ~5 min before refiltering and washing with excess hot MeOH (~20 mL) until the solution passing the filter was no longer UV active by TLC. This washing procedure was repeated 4-5 times to sufficiently remove the product material from the residual solids. (*Note:* Diol **2-15** is highly

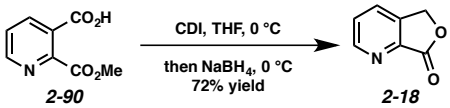
water soluble, and thus measures were taken to avoid aqueous treatments in workup procedures.) The combined filtrates were concentrated by rotary evaporation and purified by flash column chromatography (8:2 EtOAc/MeOH eluent) to afford diol **2-15** (242 mg, 34% yield, R_f = 0.0.26 in 8:2 EtOAc/MeOH) as a beige solid.

Diol 2-15: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.0 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.86 (s, 2H, OH) 4.77 (s, 2H), 4.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 146.4, 136.1, 135.5, 122.9, 62.5, 59.8; IR (film) 3283, 2874, 2467, 1635, 1582, 1437, 1038, 797 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_7H_9NO_2 + H]^+$: 140.1, found 140.1.



Anhydride **2-21** (5.85 g, 39.3 mmol) was dissolved and refluxed and stirred in methanol for 2 h. The reaction mixture was then concentrated by rotary evaporation. The crude solid was dissolved in EtOAc (30 mL) at reflux and filtered to remove insoluble solids. The filtrate was concentrated by rotary evaporation and the crude solid was recrystallized from EtOAc to afford ester **2-90** (6.11 g, 86% yield, R_f = 0.29 in 7:3 hexanes/EtOAc) as a white powder solid.

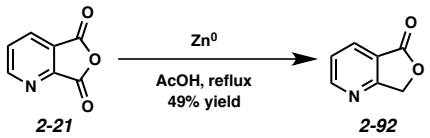
Ester 2-90: ^{1}H NMR (300 MHz, CD_3OD) δ 8.72 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.54 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.01 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.94 (s, 3H). This compound's spectroscopic data corresponds to previously reported data.[32]



A solution of ester **2-90** (6.11 g, 33.7 mmol) in THF (1535 mL) was treated with CDI (7.27 g,

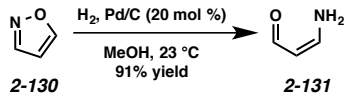
44.9 mmol) at 0 °C. After stirring for 1 hour, $NaBH_4$ (2.12 g, 56.0 mmol) was added in four equal portions. The reaction mixture was stirred for 2 h at 0 °C and then was added MeOH (2.0 mL) carefully. Water (30 mL) was then added to the reaction mixture, and the product was extracted into EtOAc (3 x 30 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (EtOAc eluent) to afford lactone **2-18** (3.28 g, 72% yield, R_f = 0.33 in EtOAc) as a white solid.

Lactone 2-18: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 4.5 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 7.8, 4.5 Hz, 1H), 5.41 (s, 2H). This compound's spectroscopic data corresponds to previously reported data.[32]



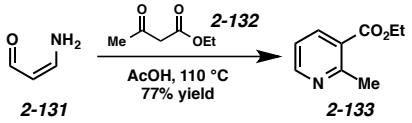
Anhydride **2-21** (100 mg, 0.671 mmol) and zinc powder (110 mg, 1.68 mmol) in acetic acid (2.0 mL) was heated at reflux for 1 h. The suspension was then filtered through a plug of glass wool and washed with boiling AcOH (2.0 mL). The reaction mixture was concentrated by rotary evaporation and was then passed through a plug of SiO_2 (30 cm x 10 cm) with MeOH (10 mL). The solvent was removed by rotary evaporation and the crude material was purified by column chromatography (EtOAc eluent) to afford lactone **2-92** (44.0 mg, 49% yield, R_f = 0.43 in EtOAc) as a yellow solid.

Lactone 2-92: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (dd, J = 5.0, 1.5 Hz, 1H), 8.23 (dd, J = 7.8, 1.5 Hz, 1H), 7.51 (dd, J = 7.8, 5.0 Hz, 1H), 5.36 (s, 2H). This compound's spectroscopic data corresponds to previously reported data.[58]



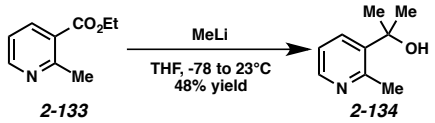
A suspension of isoxazole (**2-130**, 1.03 g, 14.9 mmol) and palladium on carbon (206 mg, 10 mol %) in EtOH (12.0 mL) was stirred under H_2 (~1.4 atm) at 23 °C for 32 h. The reaction mixture was filtered through celite (60 cm x 30 cm) with MeOH (150 mL), and the filtrate was concentrated by rotary evaporation and residual solvent was azeotropically removed with Et_2O to afford sufficiently pure enoate **2-131** (960 mg, 91% yield) as a white solid.

Enoate 2-131: ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (d, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 12.4 Hz, 1H), 5.38 (dd, *J* = 12.4, 9.2 Hz, 1H). This compound's spectroscopic data corresponds to previously reported data.[59]



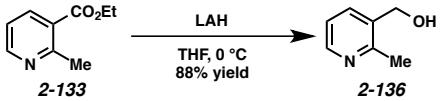
A suspension of β-aminoacrolein **2-131** (941 mg, 13.2 mmol), ethyl acetoacetate (**2-132**, 1.86 mL, 14.6 mmol), and NH_4OAc (3.06 g, 39.7 mmol) in AcOH (46.0 mL) was heated and stirred at 110 °C for 90 min. Upon completion by TLC, the solvent was azeotropically removed with heptane, and the reaction mixture was added sat. $NaHCO_3$ (30 mL). The product was extracted into EtOAc (3 x 30 mL), and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (EtOAc eluent) to afford pyridine **2-133** (1.67 g, 77% yield, R_f = 0.19 in EtOAc) as an amber oil.

Pyridine 2-133: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.8 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.85 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H). This compound's spectroscopic data corresponds to previously reported data.[60]



To a stirring solution of pyridine **2-133** (543 mg, 3.29 mmol) in THF (16.5 mL) was added MeLi (4.76 mL, 1.45 M, 6.91 mmol) over 5 min at -78 °C. After 1 h, the reaction mixture was removed from the cooling bath and warmed to ambient temperature and was then quenched with sat. $NaHCO_3$ (30 mL). The reaction mixture was extracted with EtOAc (3 x 30 mL), and the combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (17:3 Et_2O/hexanes eluent) to afford alcohol **2-134** (237 mg, 48% yield, R_f = 0.13 in 17:3 Et_2O/hexanes) as a white powder.

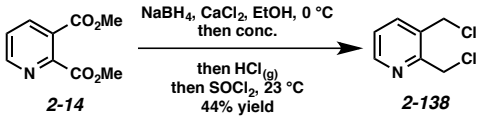
Alcohol 2-134: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 4.6 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.25 (br. s, 1H), 2.66 (s, 3H), 1.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 146.5, 141.9, 133.4, 120.8, 71.7, 30.5, 24.9; IR (film) 3208, 1574, 1427, 909, 729 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{13}NO + H]^+$: 152.1, found 152.2.



To a solution of pyridine **2-133** (41.2 mg, 0.249 mmol) dissolved in THF (0.500 mL) was added LAH (18.9 mg, 0.498 mmol) in one portions at 0 °C. The reaction mixture stirred for 2 h at 0 °C and was then quenched with EtOAc (30 mL) at 0 °C. Brine (15 mL) was added to the suspension

and the product was extracted into EtOAc (8 x 30 mL). The combined organic layers was dried with $MgSO_4$ and concentrated by rotary evaporation. The resulting material was sufficiently pure pyridine **2-136** (27.0 mg, 88% yield, R_f = 0.17 in EtOAc) as an amber oil.

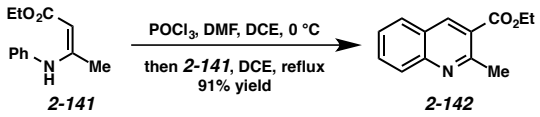
Pyridine 2-136: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.0 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.70 (s, 2H), 2.49 (s, 3H). This compound's spectroscopic data corresponds to previously reported data.[61]



2-14 *2-138*

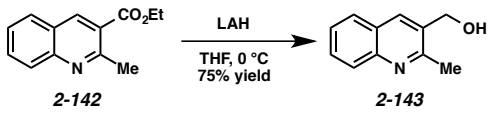
To a stirring suspension of diester **2-14** (3.02 g, 15.4 mmol) and $NaBH_4$ (2.91 g, 76.9 mmol) in EtOH (22.0 mL) at 0 °C was added a suspension of $CaCl_2$ (1.51 g, 13.6 mmol) in EtOH (9.28 mL) over the course of 30 min keeping the reaction mixtures temperature below 5 °C, and then the ice bath was removed and the suspension was allowed to stir at 23 °C for 2 h. Upon completion by TLC, a solution of 1:1 EtOH/1 M $HCl_{(aq)}$ (12.0 mL) was added to the reaction mixture and the suspension was stirred at ambient temperature for 30 min. The solvent was then removed by rotary evaporation followed by high-vacuum distillation (<1 mmHg) to produce a white solid. The crude product was ground to a powder and refluxed in EtOH (54 mL) for 1 hour. Once the suspension cooled to ambient temperature, the suspension was treated with anhydrous HCl until the solution was pH <1. The solvent was removed by rotary evaporation, and the residual solids were washed added saturated Na_2CO_3 (15 mL). The product was extracted into Et_2O (3 x 15 mL), and the combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated by rotary evaporation to afford dichloride **2-138** (1.20 g, 44% yield). The resulting colorless oil was sufficiently pure; however, upon concentration, it rapidly turned dark red.

Dichloride 2-138: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.0 Hz, 1H), 7.76 (d, *J* = 6.0 Hz, 1H), 7.31 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.83 (s, 2H), 4.75 (s, 2H). This compound's spectroscopic data corresponds to previously reported data.[62]



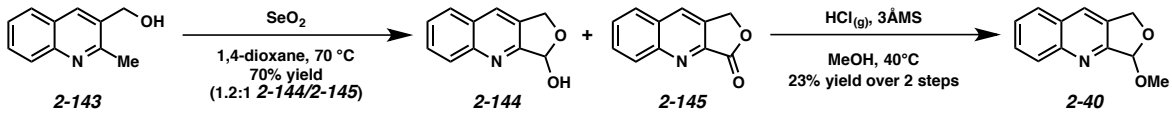
To a solution of DCE (49 mL) and DMF (3.56 g, 48.7 mmol) cooled to 0 °C was added $POCl_3$ (7.47 g, 48.7 mmol) dropwise over 1 min and then was stirred at 20 °C for 2 h. To this suspension was added a solution of ester **2-141**[63] (10.0 g, 48.7 mmol) in DCE (49 mL) over 1 min at 0 °C. The reaction mixture was heated to reflux over 30 min and was maintained at reflux for 3 h. The reaction mixture was cooled to 0 °C and then added sat. $NaHCO_3$ (400 mL). The mixture was extracted with CH_2Cl_2 (3 x 200 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude quinolone was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford quinolone **2-142** (9.58 g, 91% yield, R_f = 0.26 in 4:1 hexanes/EtOAc) as a beige solid.

Quinoline 2-142: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.98 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.6, 148.7, 139.9, 131.7, 128.7, 128.6, 126.6, 125.9, 124.1, 61.5, 25.8, 14.4; IR (film) 2970, 2928, 1711, 1492, 1423, 1276, 1199, 1063 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{13}NO_2 + H]^+$: 216.1, found 216.1.



To a solution of quinoline **2-142** (9.58 g, 44.5 mmol) dissolved in THF (89 mL) was added LAH (1.69 g, 44.5 mmol) in four portions at 0 °C. The reaction mixture stirred for 2 h at 0 °C and was then quenched with EtOAc (150 mL) at 0 °C. The suspension was added H_2O (300 mL) and was extracted into EtOAc (3 x 300 mL) (note: isopropyl alcohol was required to break the resulting emulsions). The combined organic layers were washed with brine (300 mL), dried with Na_2SO_4, and concentrated by rotary evaporation. The crude quinolone was hot slurried in refluxing Et_2O (100 mL) and was filtered to afford quinolone **2-143** (5.03 g, 65% yield, R_f = 0.19 in EtOAc) as a yellow powder. The filtrate was concentrated and slowly recrystallized from CH_2Cl_2 to afford quinolone **2-143** (0.752 mg, 10% yield, R_f = 0.19 in EtOAc) as colorless crystals.

Quinoline 2-143: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 4.87 (s, 2H), 2.71 (s, 3H), 2.35 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 147.0, 133.7, 132.5, 129.2, 128.2, 127.4, 127.0, 125.9, 62.6, 22.5; IR (film) 3165, 2870, 1721, 1622, 1494, 1422, 1242, 1049 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{11}NO + H]^+$: 174.1, found 174.1.



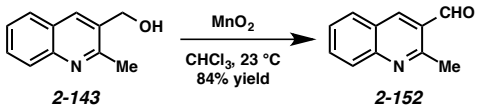
Alcohol **2-143** (1.00 g, 5.77 mmol) and SeO_2 (384 mg, 3.46 mmol) suspended in 1,4-dioxane (58 mL) was heated and stirred at 70 °C for 50 h. The suspension was then added a second charge of SeO_2 (182 mg, 1.73 mmol) and heated and stirred at 70 °C for 44 h. The reaction mixture filtered through a pad of SiO_2 and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (7:3 EtOAc/hexanes eluent) to afford a mixture of hemiacetal **2-144** (R_f = 0.35 in 7:3 EtOAc/hexanes) and lactone **2-145** (R_f = 0.46 in 7:3 EtOAc/hexanes) as a red solid (451 mg, 1.2:1 mixture).

Hemiacetal 2-144 (major product): Representative peaks in the ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, *J* = 1.2 Hz 1H), 5.46 (d, *J* = 13.2 Hz, 1H), 5.21 (dd, *J* = 13.2, 1.2 Hz, 1H).

Lactone 2-145 (minor product): Representative peak in the ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (s, *J* = 1.2 Hz 1H).

The mixture of hemiacetal **2-144** and lactone **2-145** (451 mg, 1.2:1 mixture) in MeOH (60 mL) was added 3Å molecular sieves (1.00 g) and then was bubbled anhydrous HCl for 1 min. The reaction mixture was heated and stirred for 25.5 h at 40 °C. The suspension was cooled to 23 °C and then was poured into sat. Na_2CO_3 (200 mL). To this mixture was added celite (5 g), and the suspension was filtered through a glass frit. The filtrate was then was concentrated to ~200 mL by rotary evaporation. The crude mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford quinoline **2-40** (263 mg, 23% yield over 2 steps, R_f = 0.32 in 7:3 hexanes/EtOAc) as a colorless oil.

Quinoline 2-40: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4, 1H), 8.05 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.56 (dd, *J* = 7.2, 1.2 Hz, 1H), 5.38 (d, *J* = 13.2, 1H), 5.23 (d, *J* = 13.2, 1H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.5, 130.3, 129.8, 129.5, 128.9, 127.9, 127.8, 127.1, 105.0, 69.9, 55.9; IR (film) 2928, 2828, 1503, 1319, 1079, 1025, 1010, 756 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{11}NO_2 + H]^+$: 202.1, found 202.1.

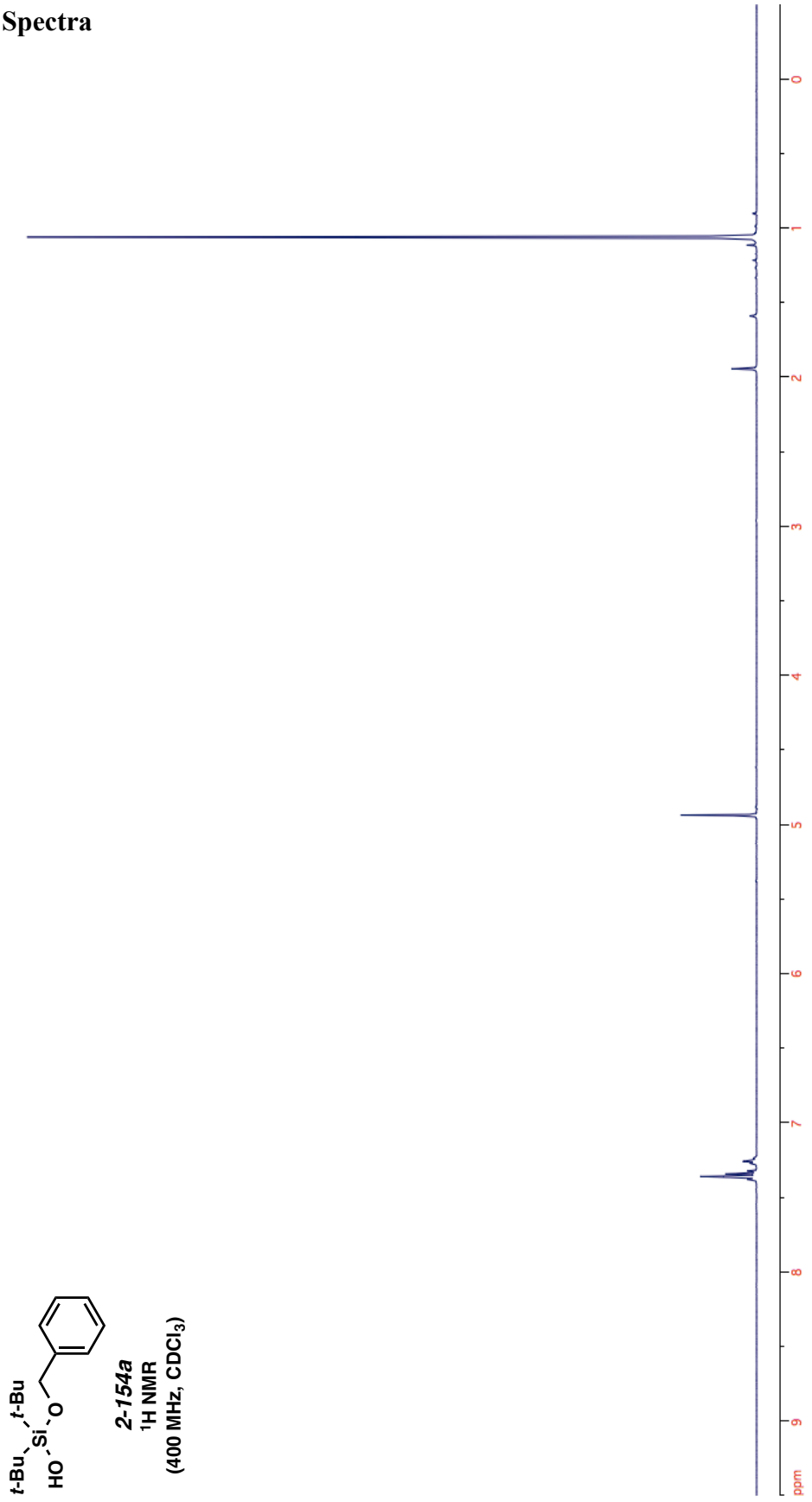


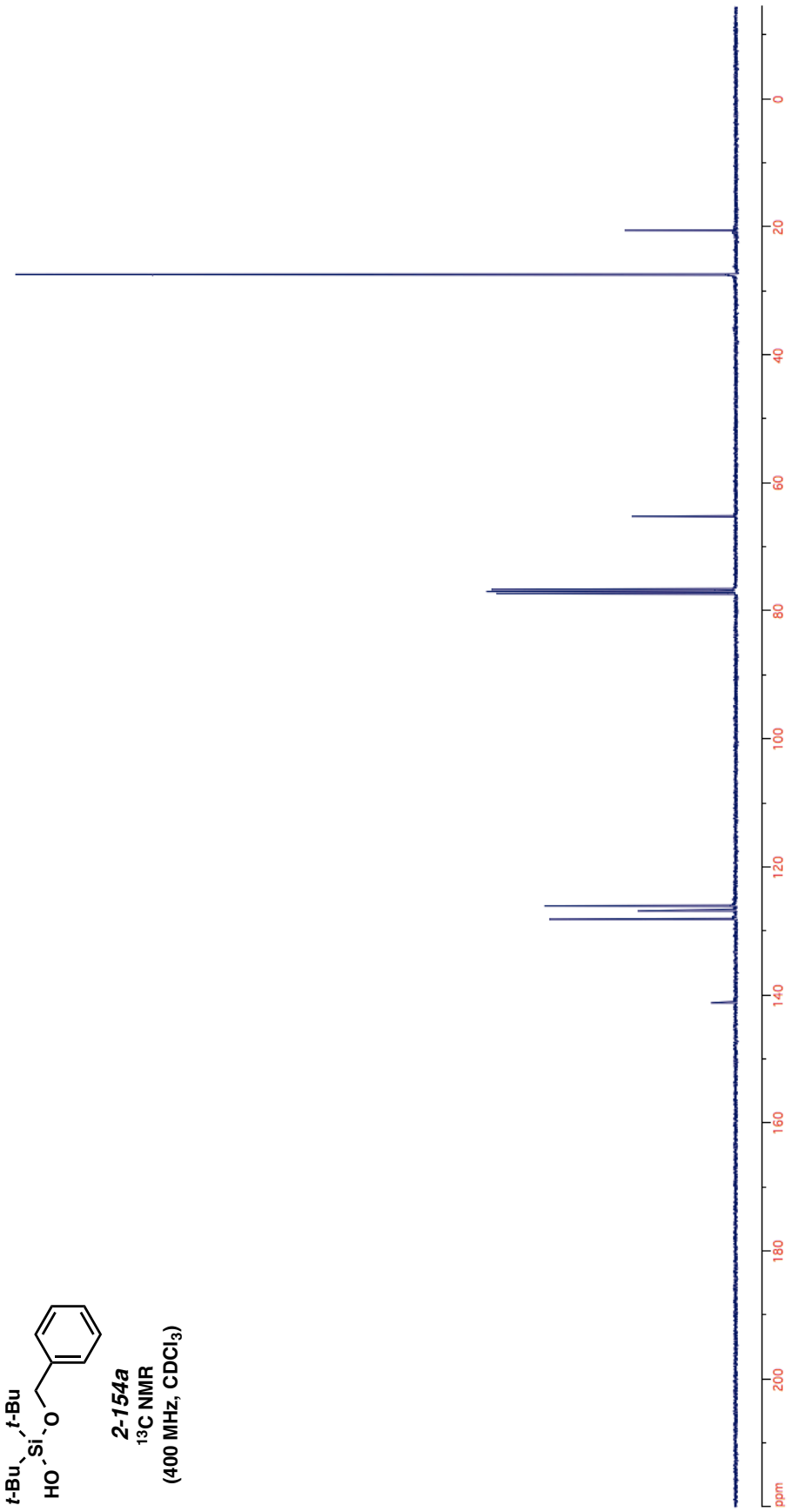
2-143 *2-152*

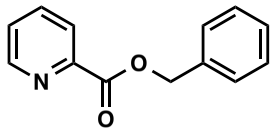
To a stirring solution of alcohol **2-143** (500 mg, 2.89 mmol) in $CHCl_3$ (9.63 mL) was added MnO_2 (4.52 g, 52.0 mmol) and stirred at 23 °C. After 12 h, the reaction mixture was filtered through Celite (10 cm x 70 cm) and the cake was washed with CH_2Cl_2 (150 mL). The filtrate was concentrated by rotary evaporation and the crude residue was purified by flash column chromatography to afford aldehyde **2-152** (416 mg, 84% yield, R_f = 0.40 in 7:3 hexanes/EtOAc) as a white crystalline solid.

Aldehyde 2-152: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.4 (s, 1H), 8.59 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 8.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 158.5, 142.6, 132.9, 129.2, 128.9, 128.2, 127.1, 126.2, 24.1; IR (film) 1707, 1618, 1561, 1420, 761 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{10}H_9NO + H]^+$: 172.1, found 172.1.

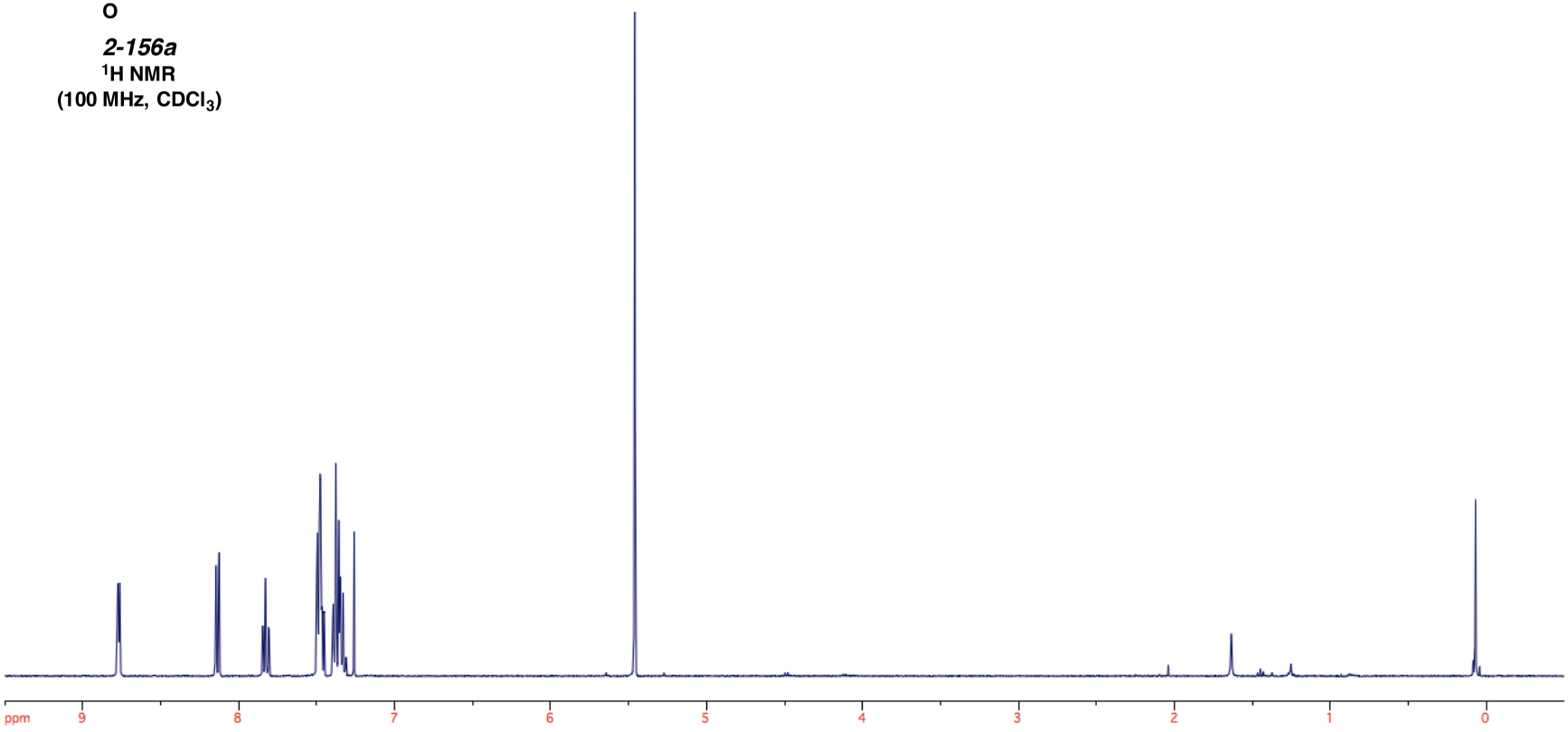
2.7.3. NMR Spectra

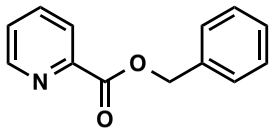



t-Bu
t-Bu
Si
HO
O
2-154a
13C NMR
(400 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm



2-156a
^{1}H NMR
(100 MHz, $CDCl_3$)

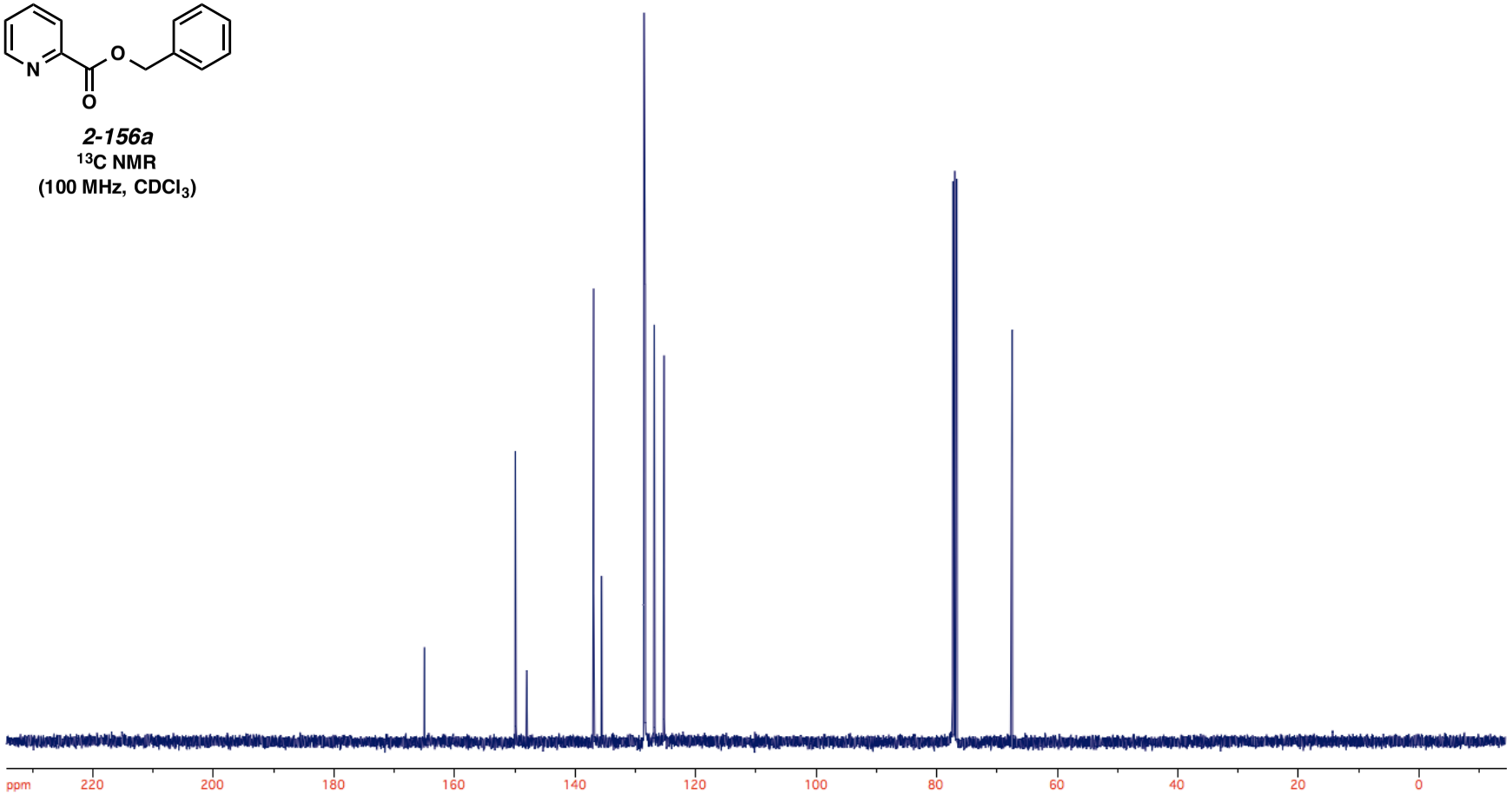


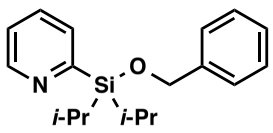


2-156a

^{13}C NMR

(100 MHz, $CDCl_3$)

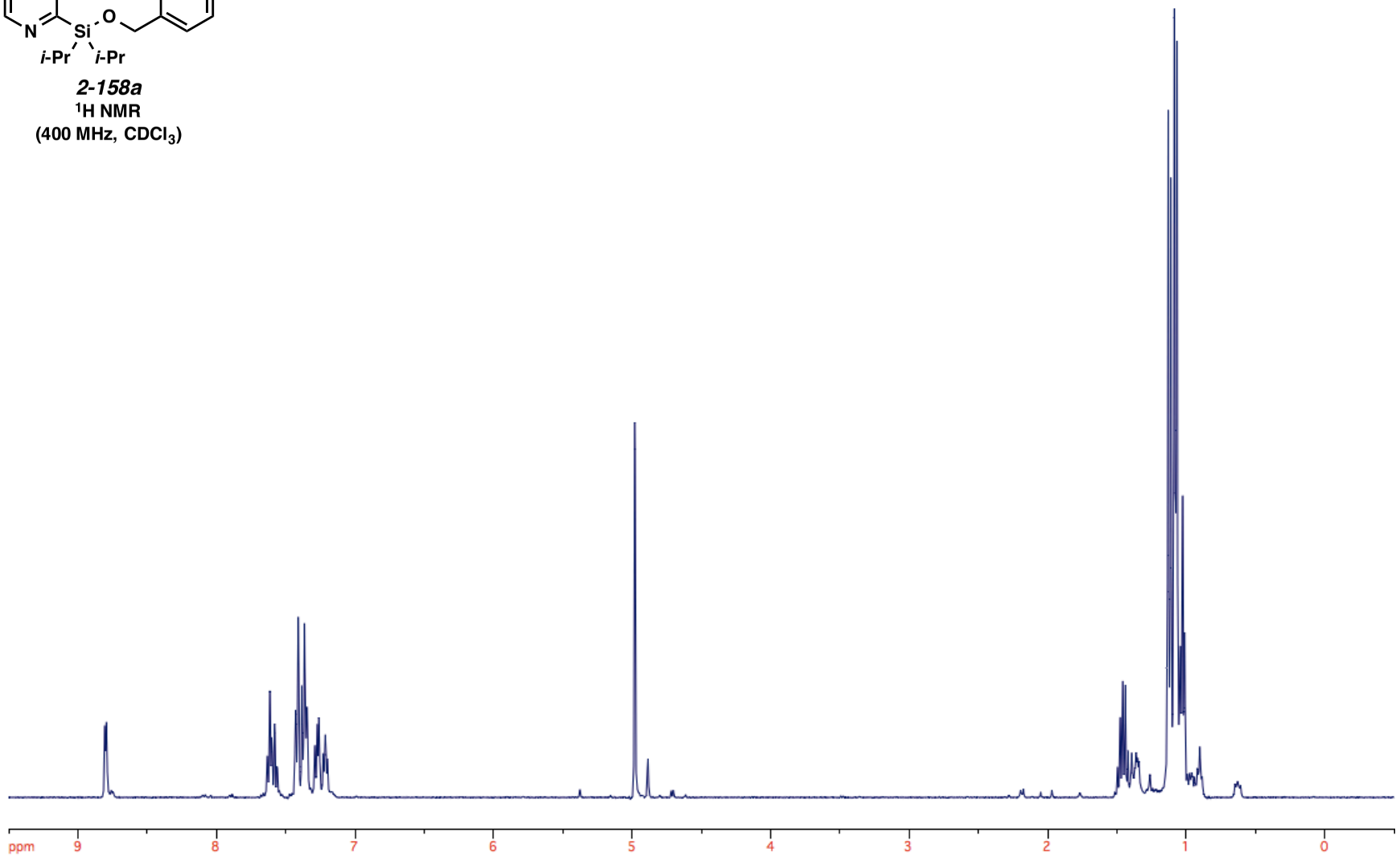




2-158a

^{1}H NMR

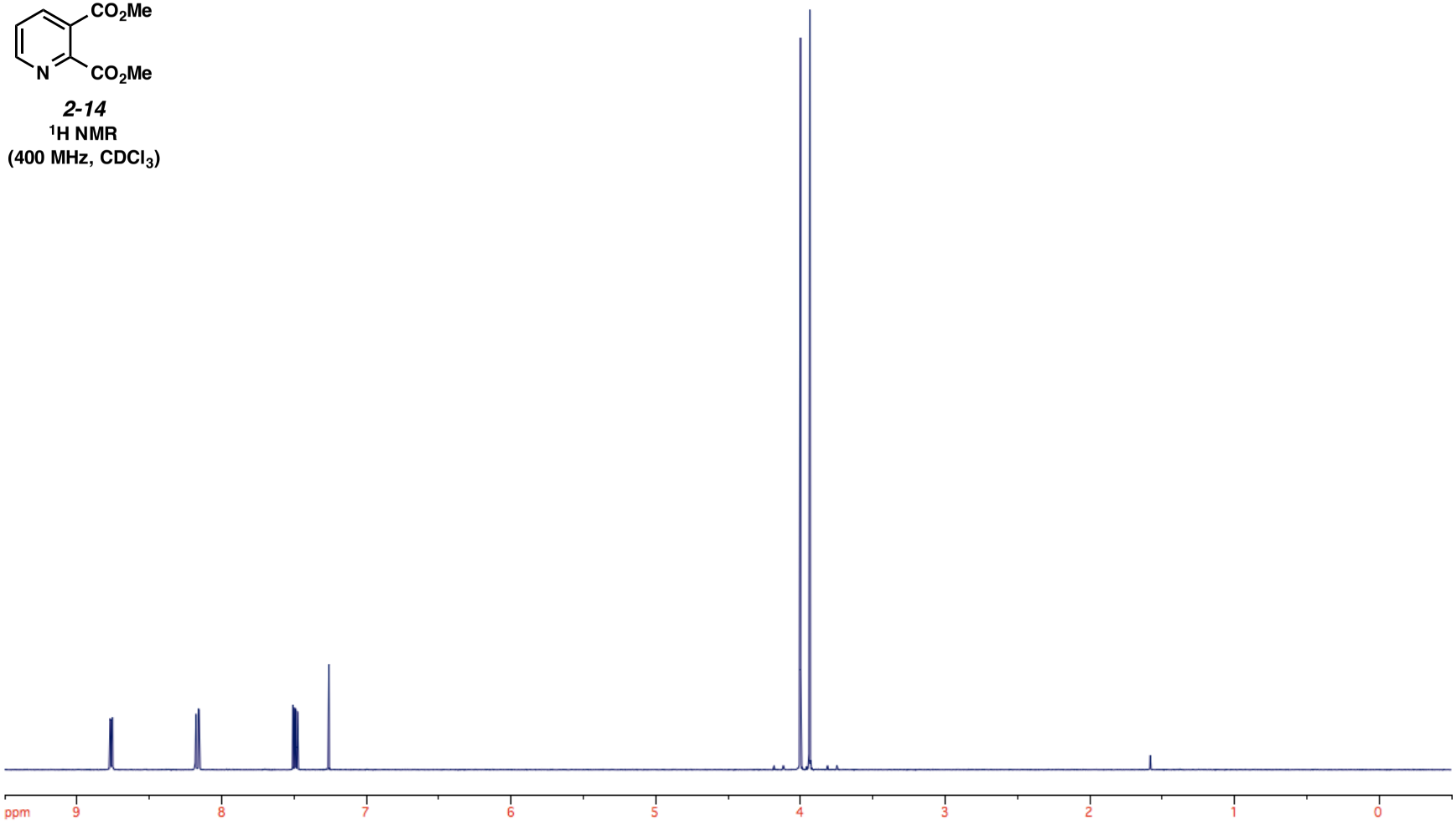
(400 MHz, $CDCl_3$)

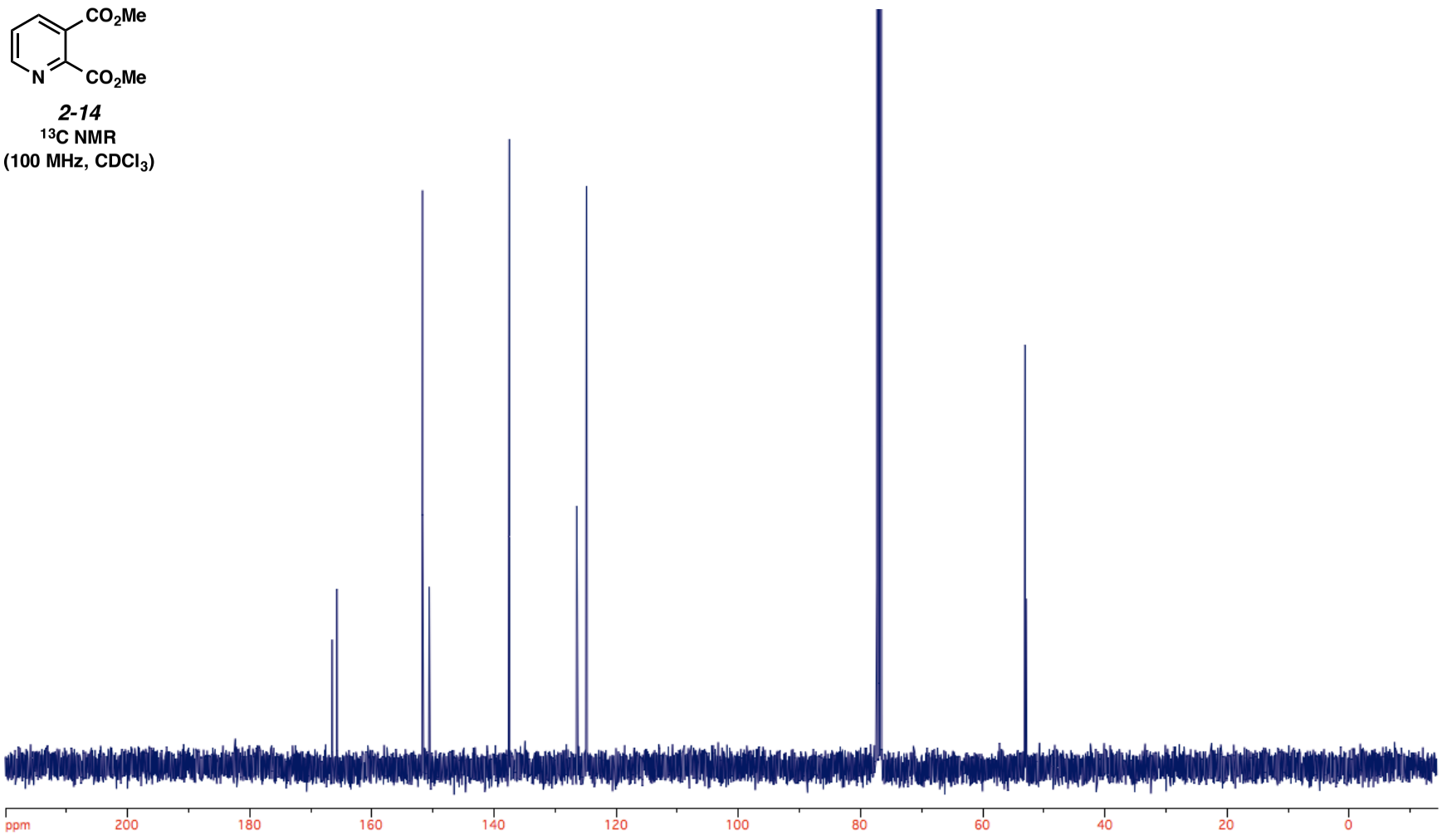


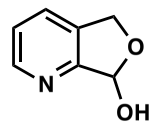
2-14

^{1}H NMR

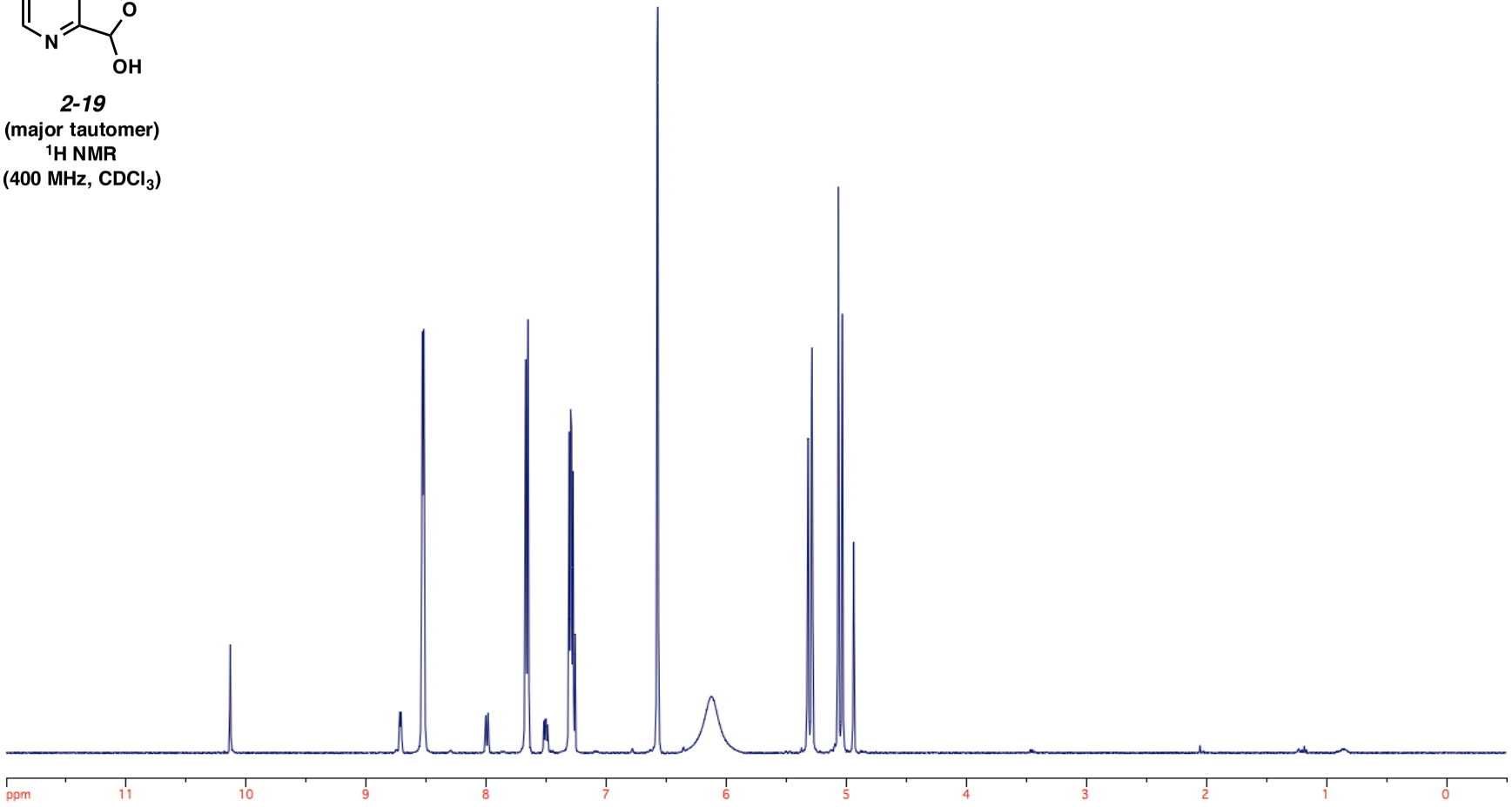
(400 MHz, $CDCl_3$)

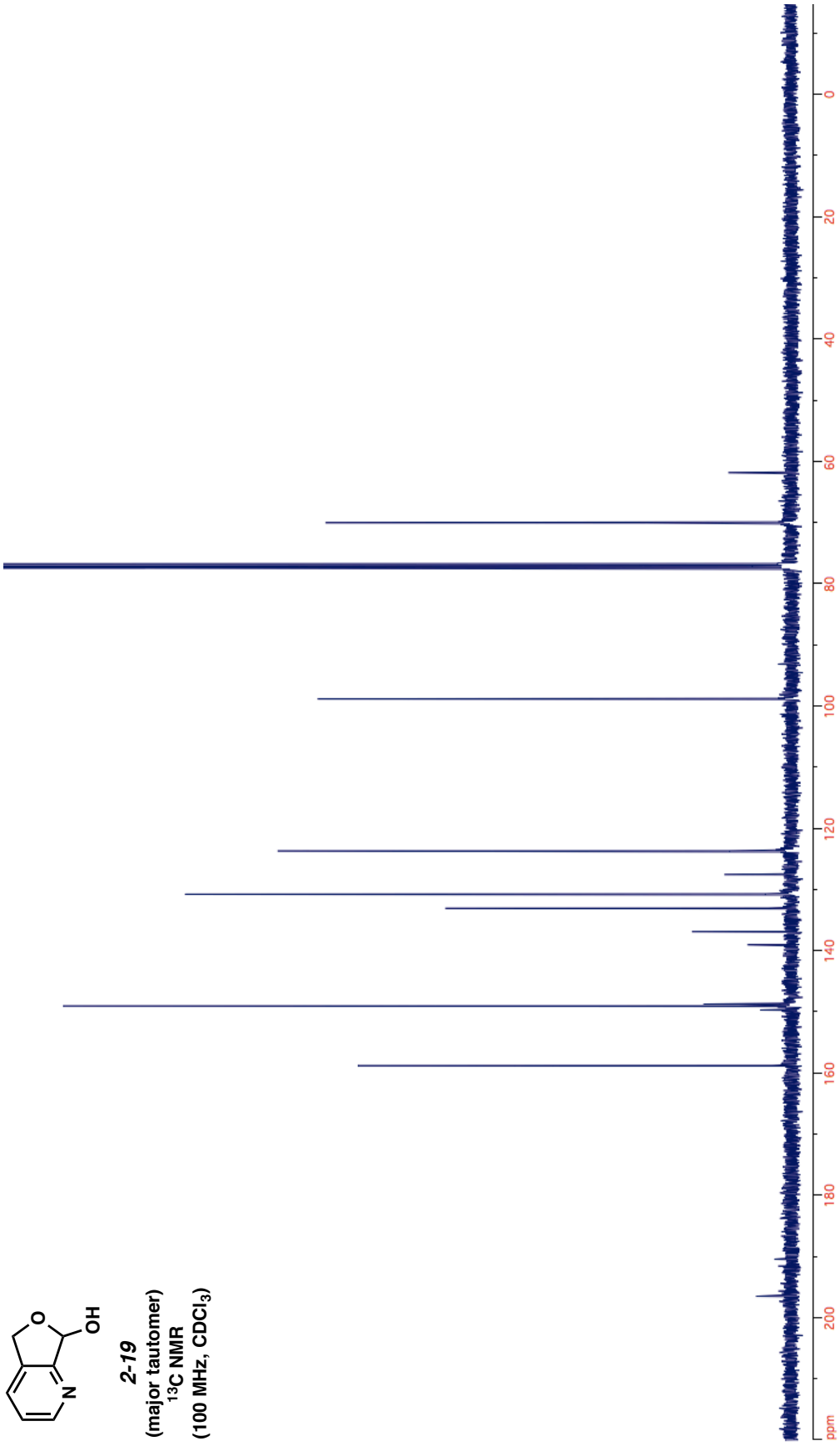



CO2Me
N
CO2Me
2-14
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0



2-19
(major tautomer)
^{1}H NMR
(400 MHz, $CDCl_3$)



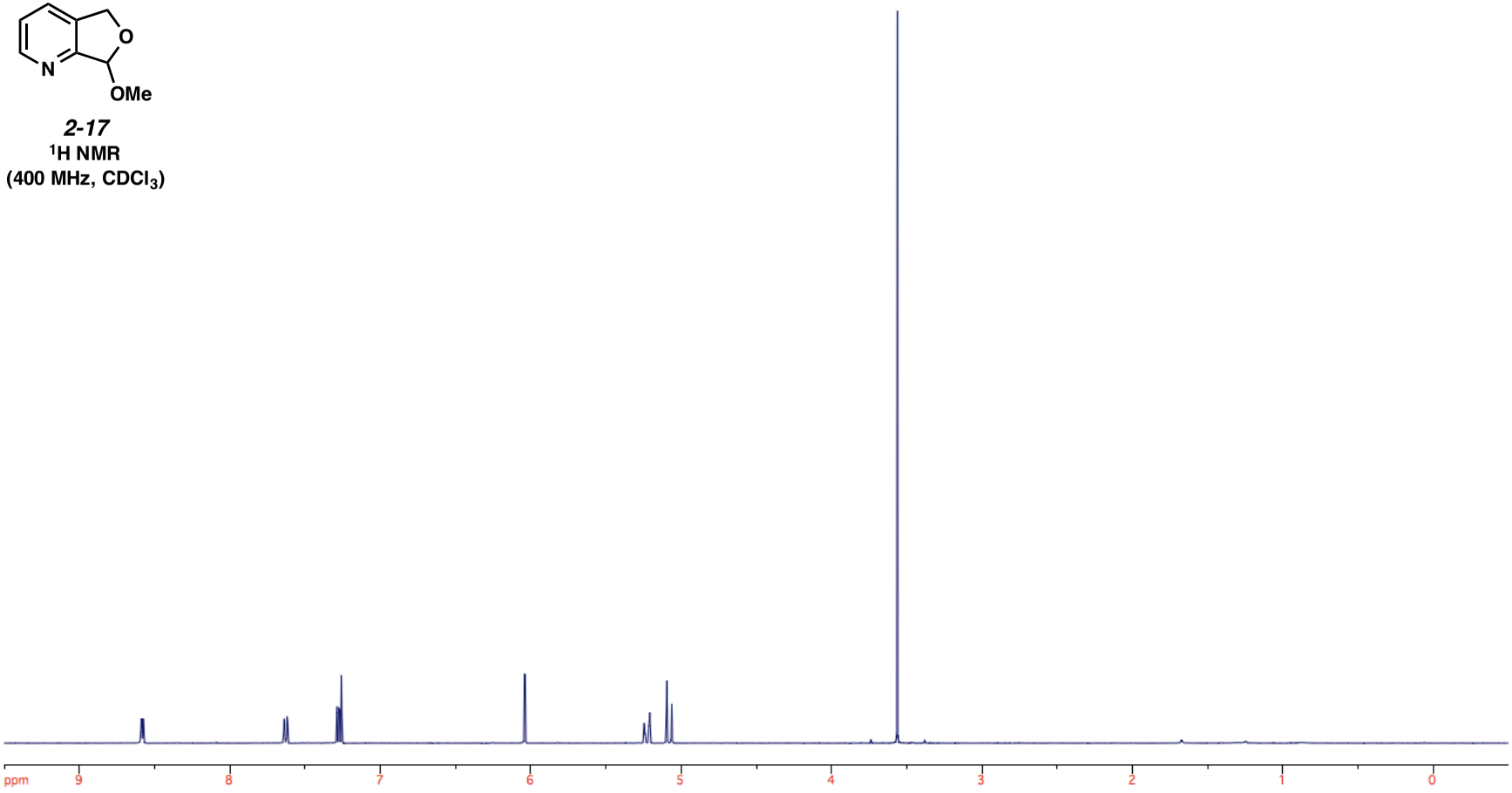


2-19
(major tautomer)
^{13}C NMR
(100 MHz, $CDCl_3$)

2-17

^{1}H NMR

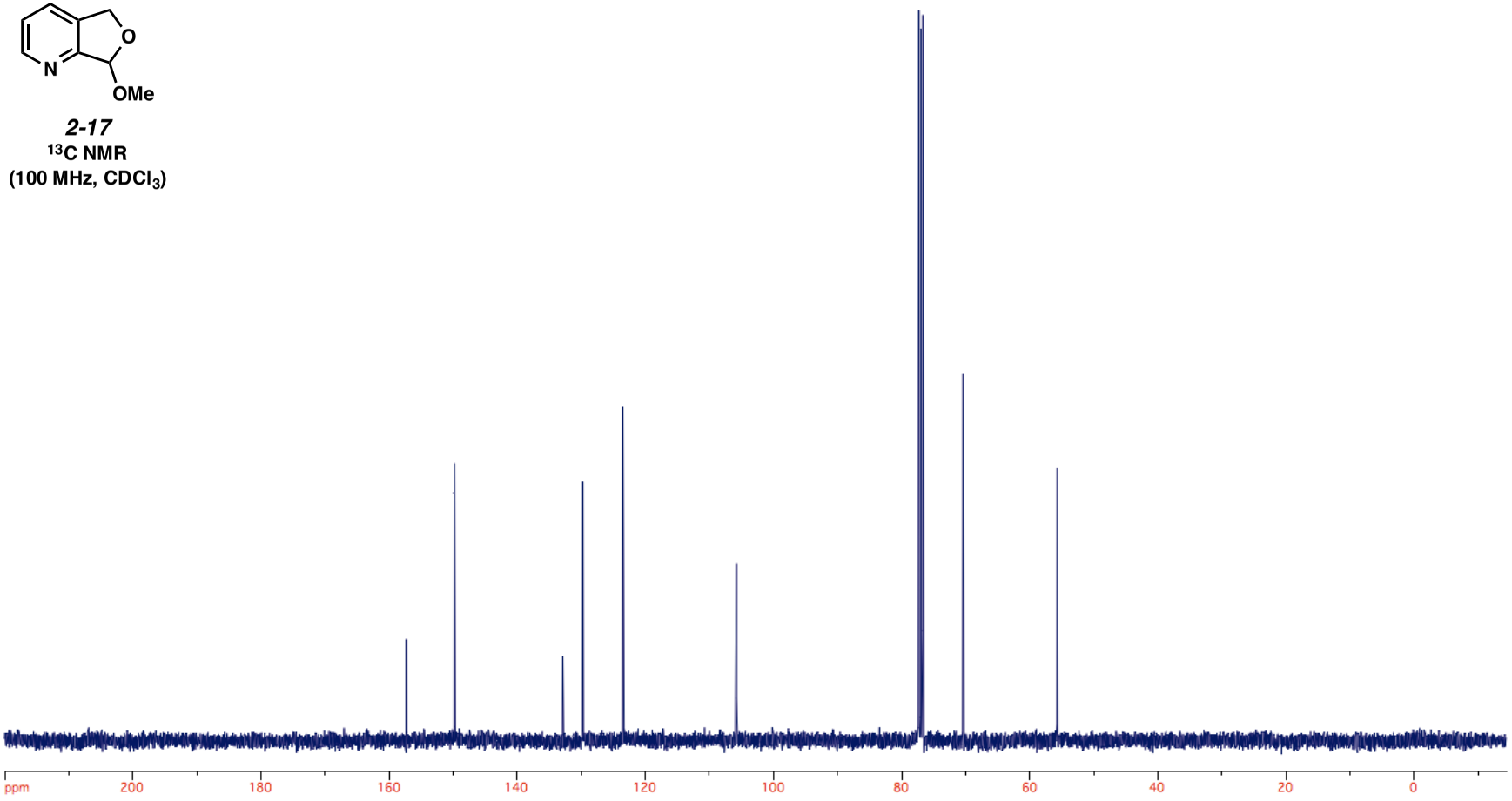
(400 MHz, $CDCl_3$)

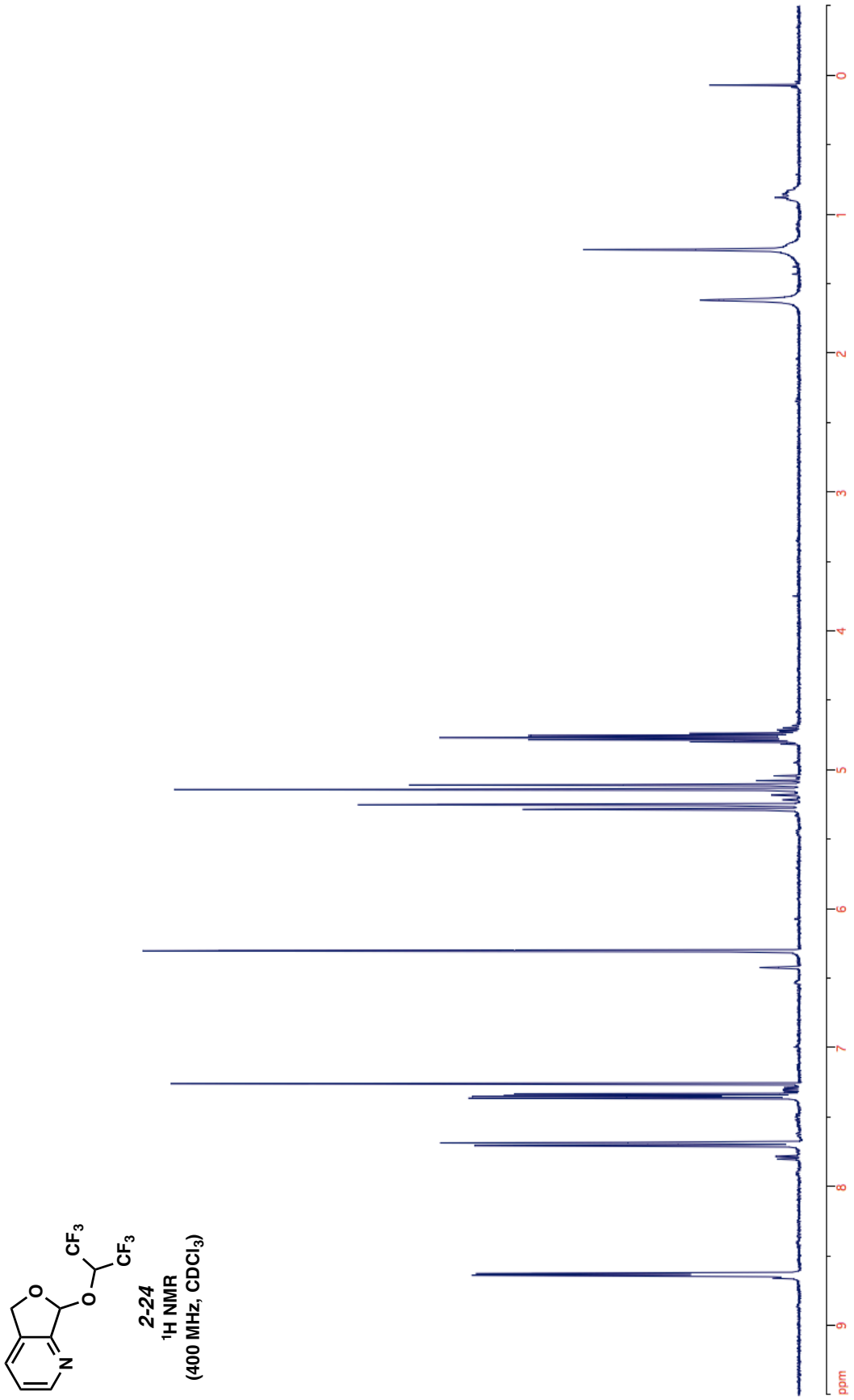


2-17

^{13}C NMR

(100 MHz, $CDCl_3$)

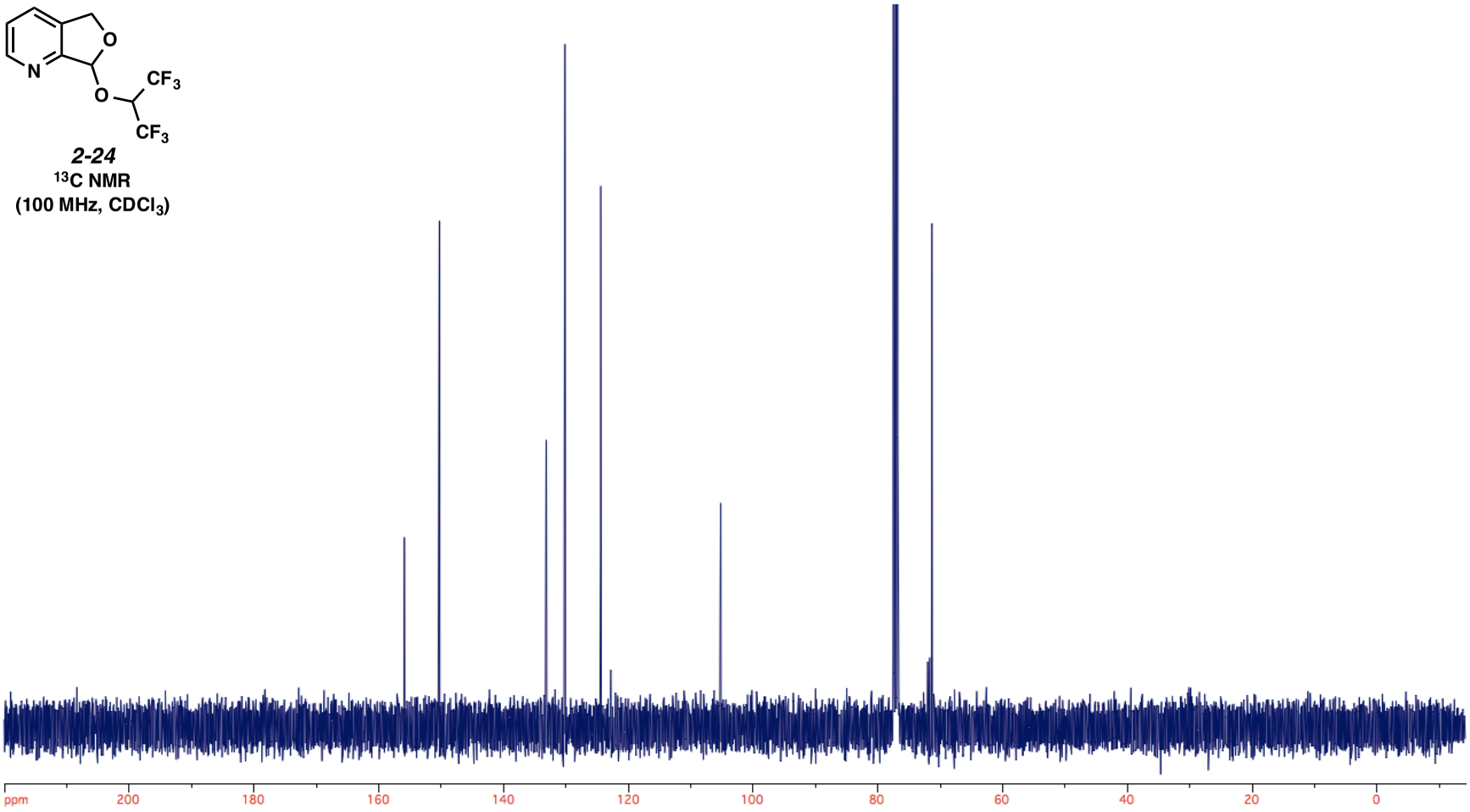



CF3
CF3
O
O
N
2-24
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

2-24

^{13}C NMR

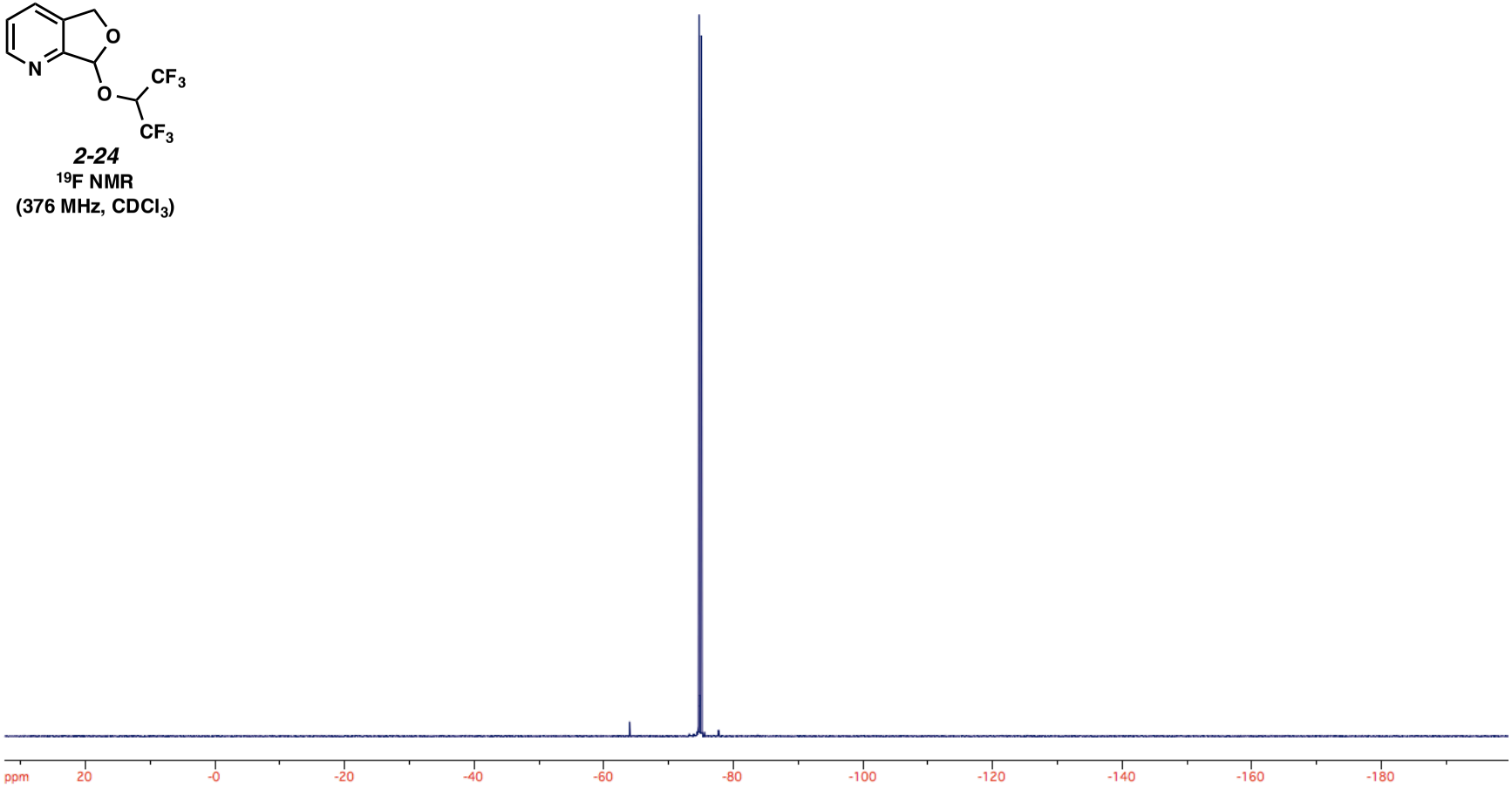
(100 MHz, $CDCl_3$)

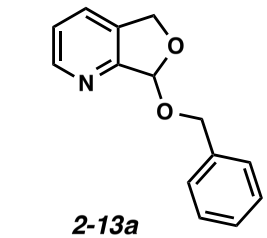


2-24

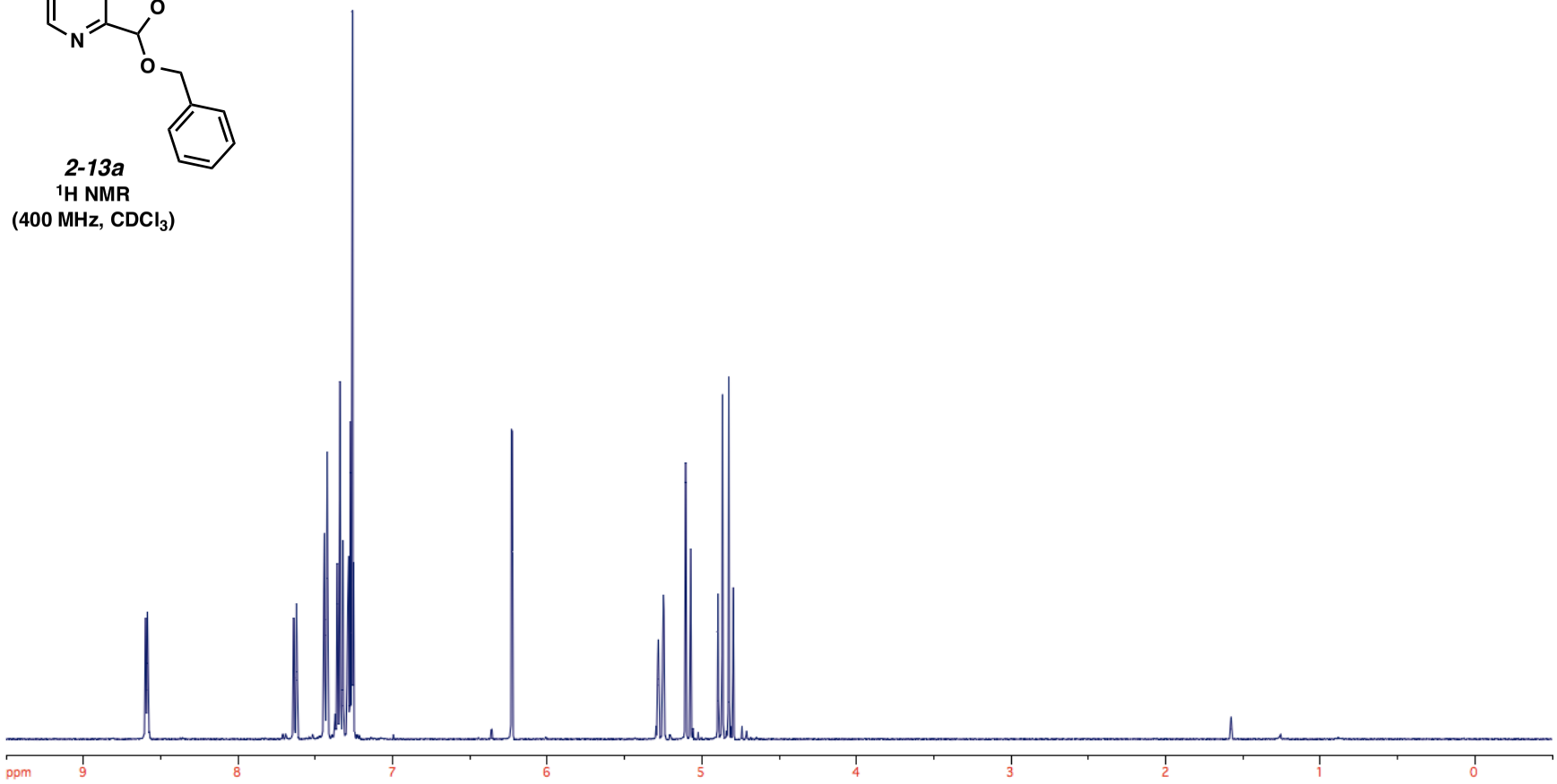
^{19}F NMR

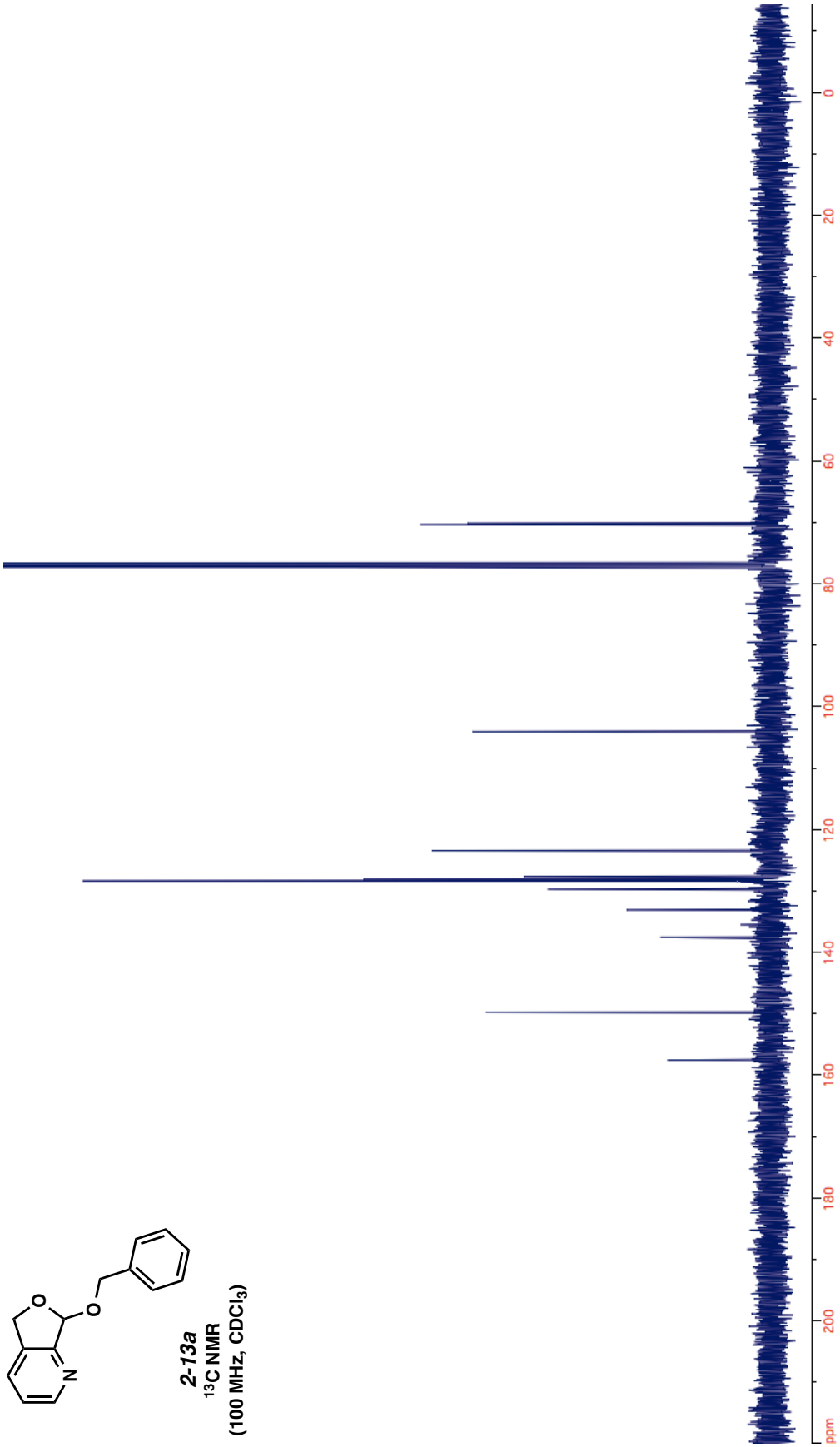
(376 MHz, $CDCl_3$)

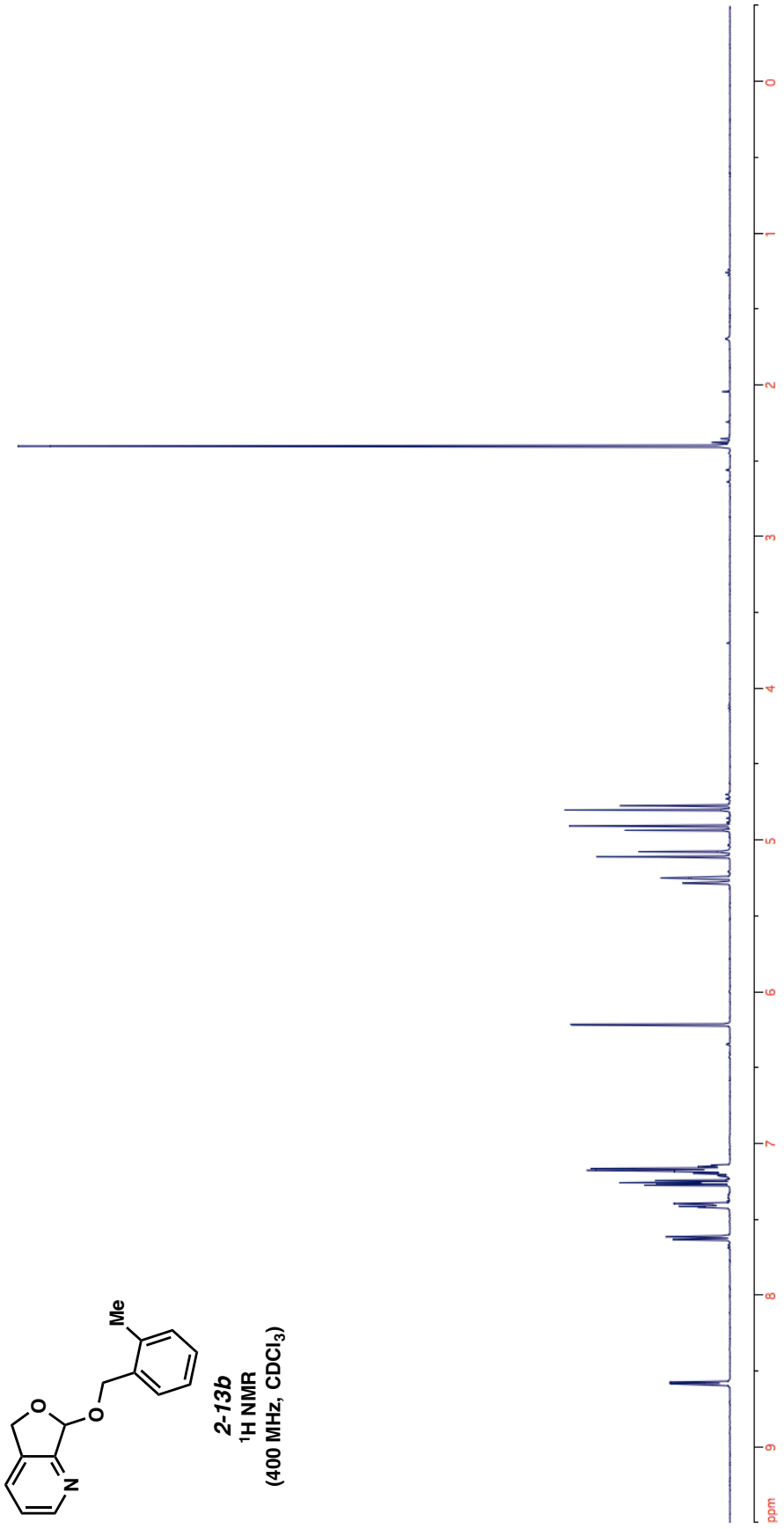




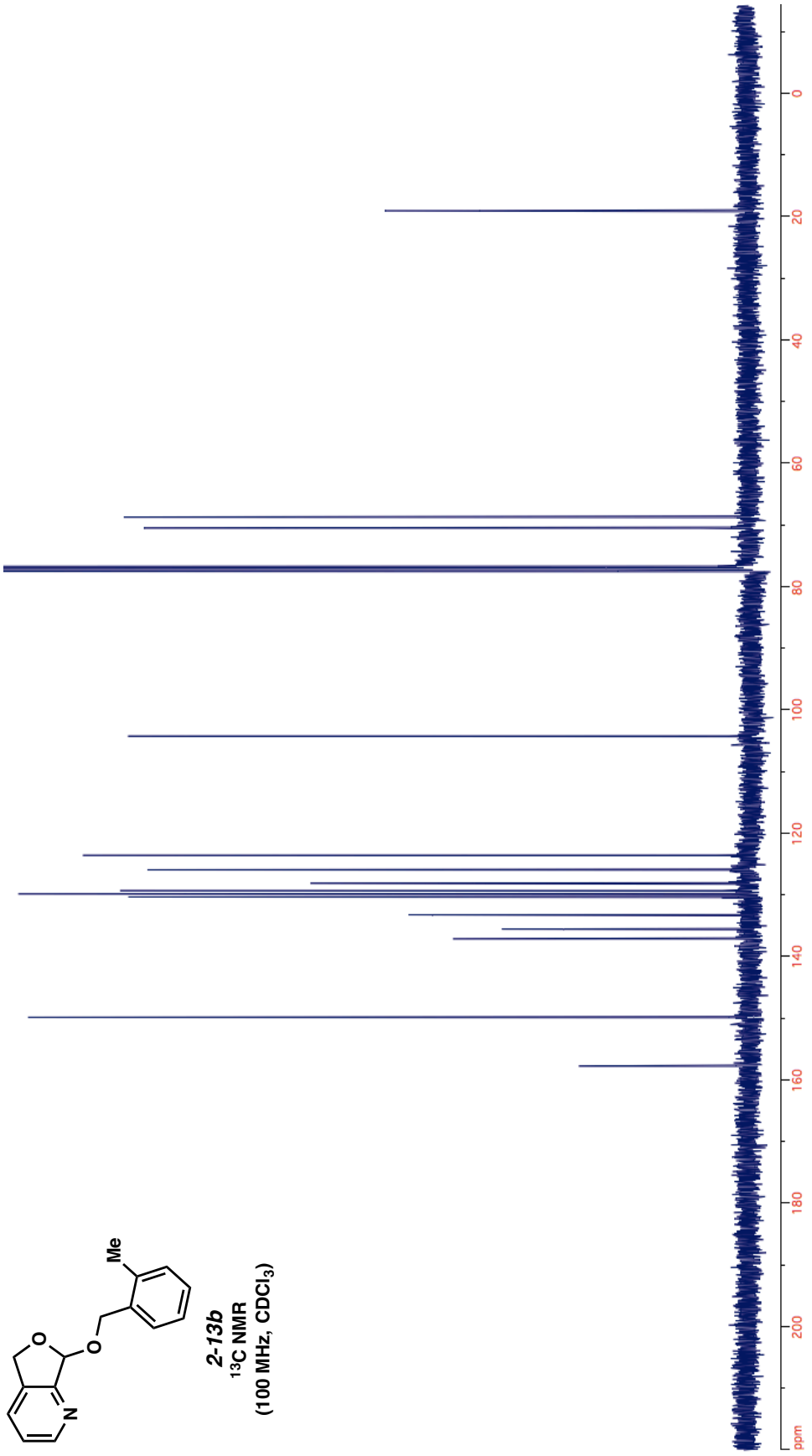
2-13a
^{1}H NMR
(400 MHz, $CDCl_3$)

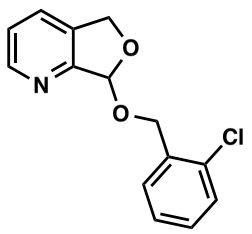



O
O
N
2-13a
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

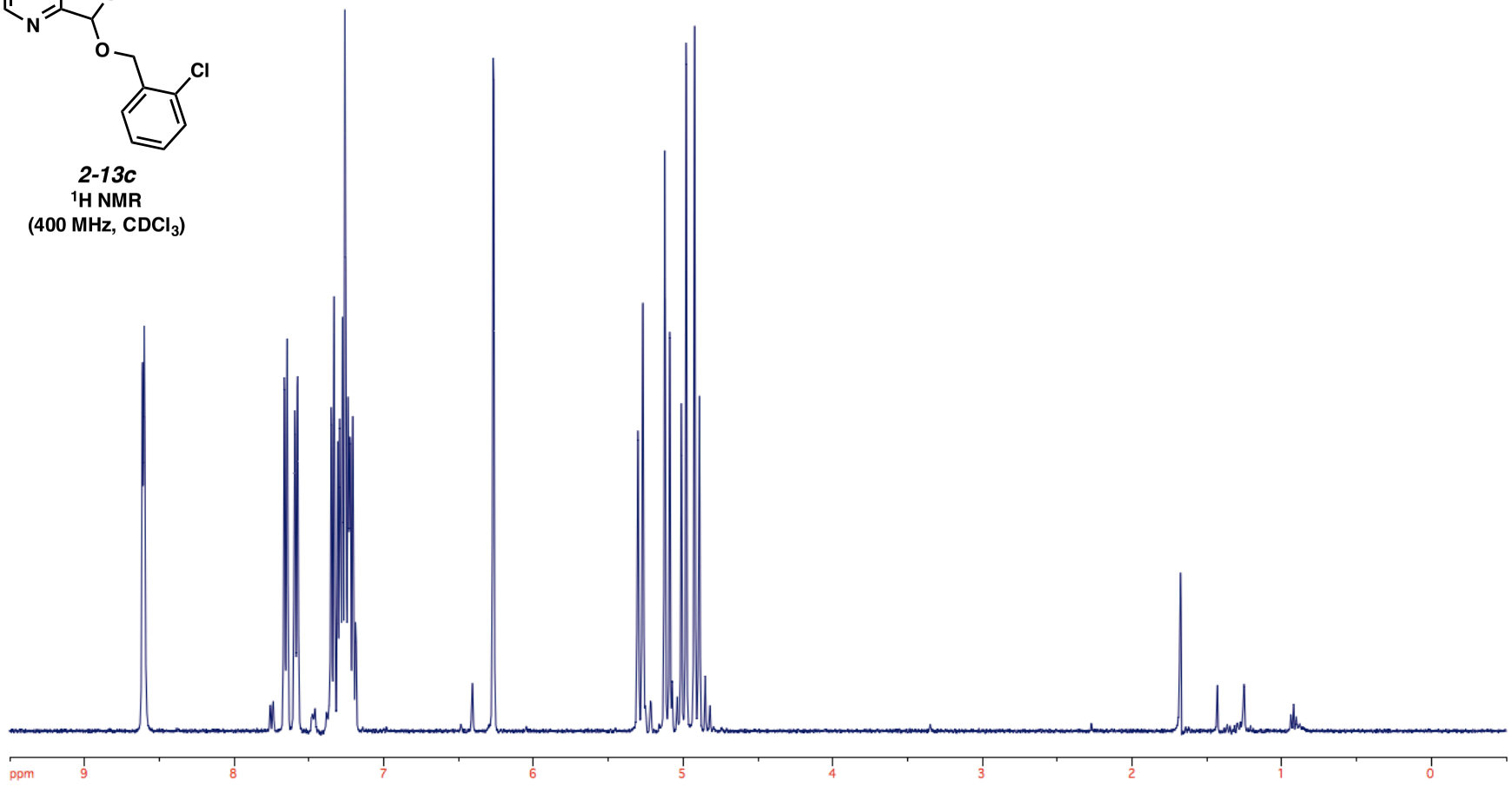


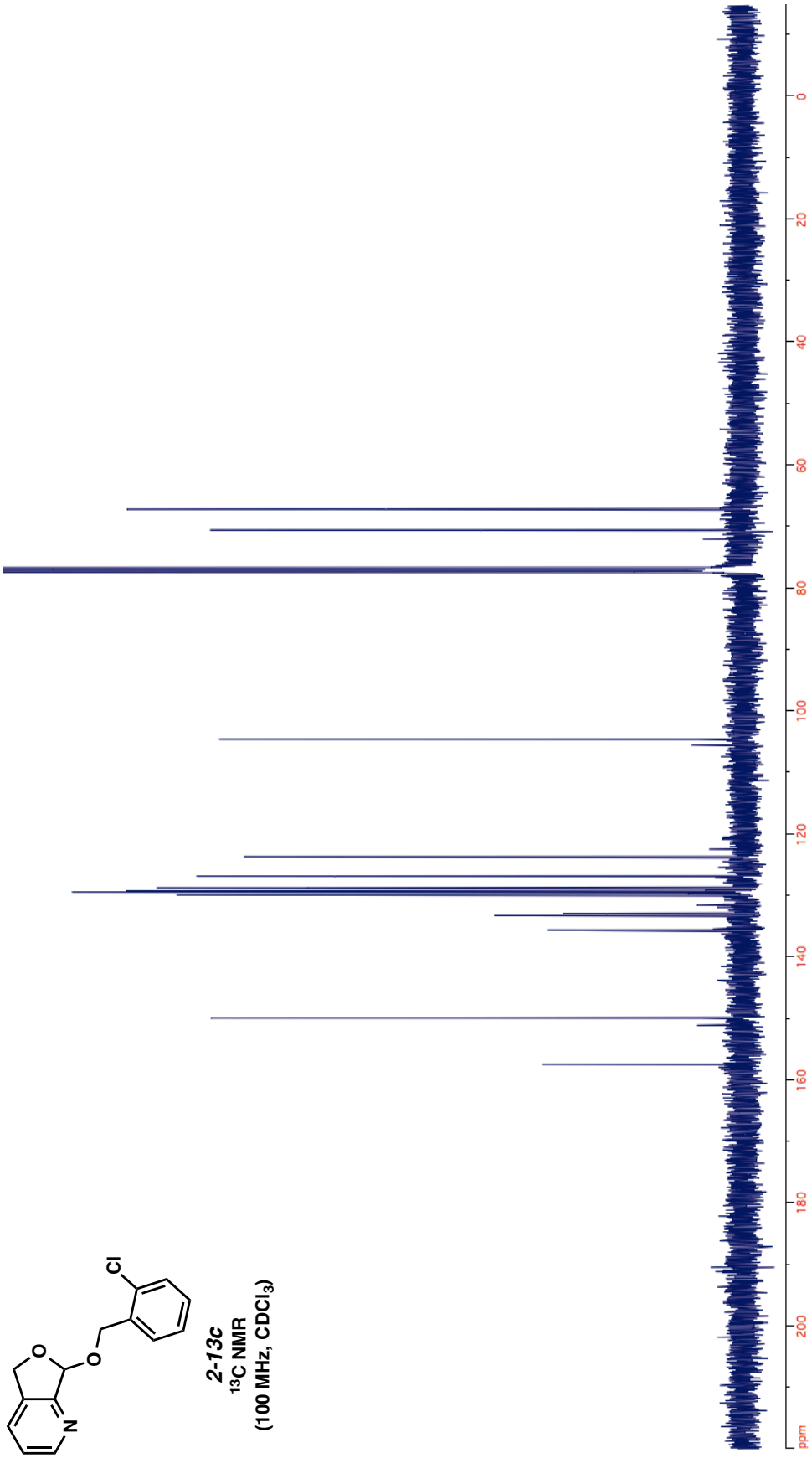
2-13b
^{1}H NMR
(400 MHz, $CDCl_3$)


Me
O
O
N
2-13b
^{13}C NMR
(100 MHz, $CDCl_3$)
ppm
0
20
40
60
80
100
120
140
160
180
200

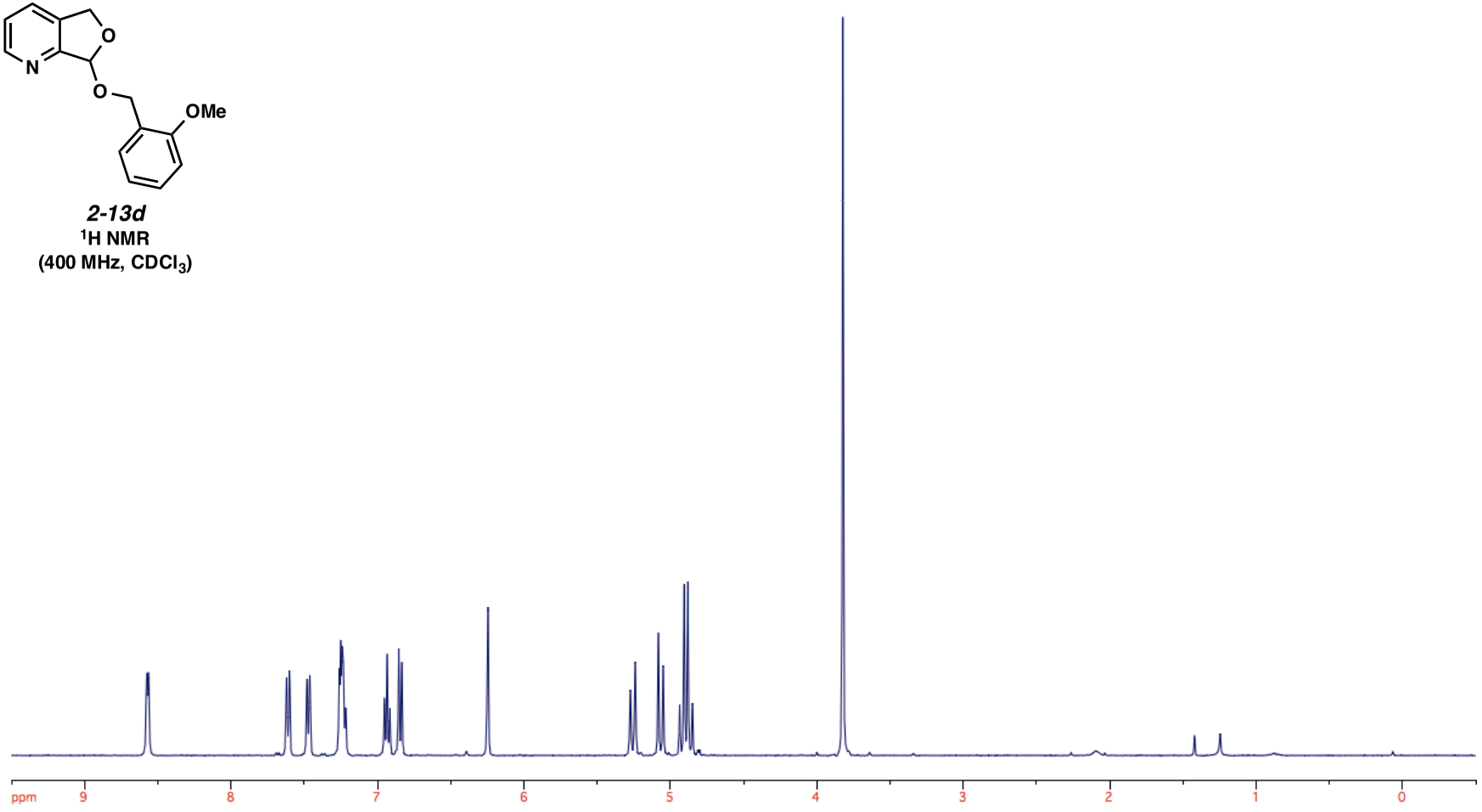


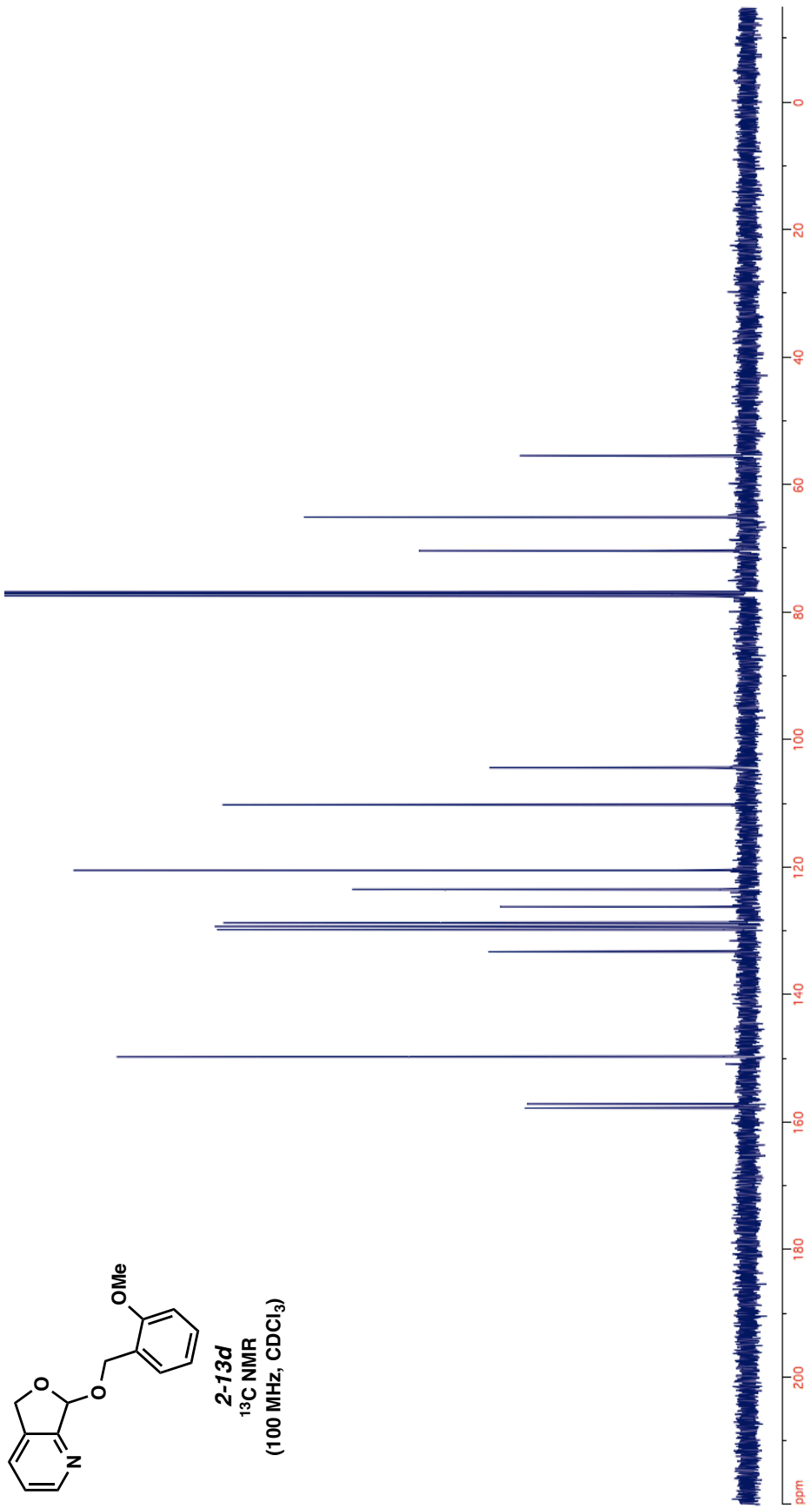
2-13c
^{1}H NMR
(400 MHz, $CDCl_3$)

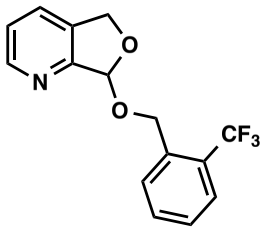



Cl
O
O
N
2-13c
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

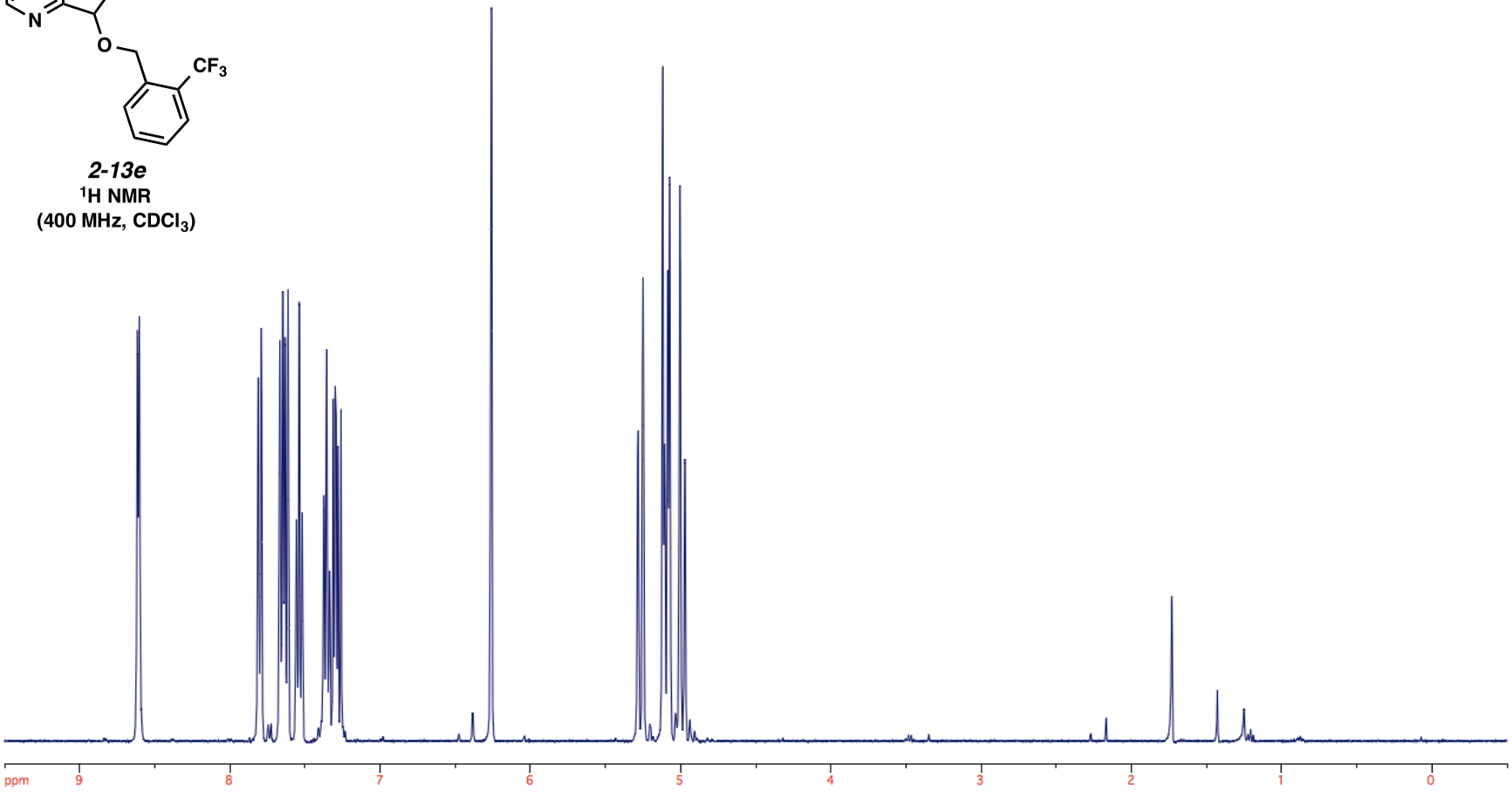
2-13d
^{1}H NMR
(400 MHz, $CDCl_3$)



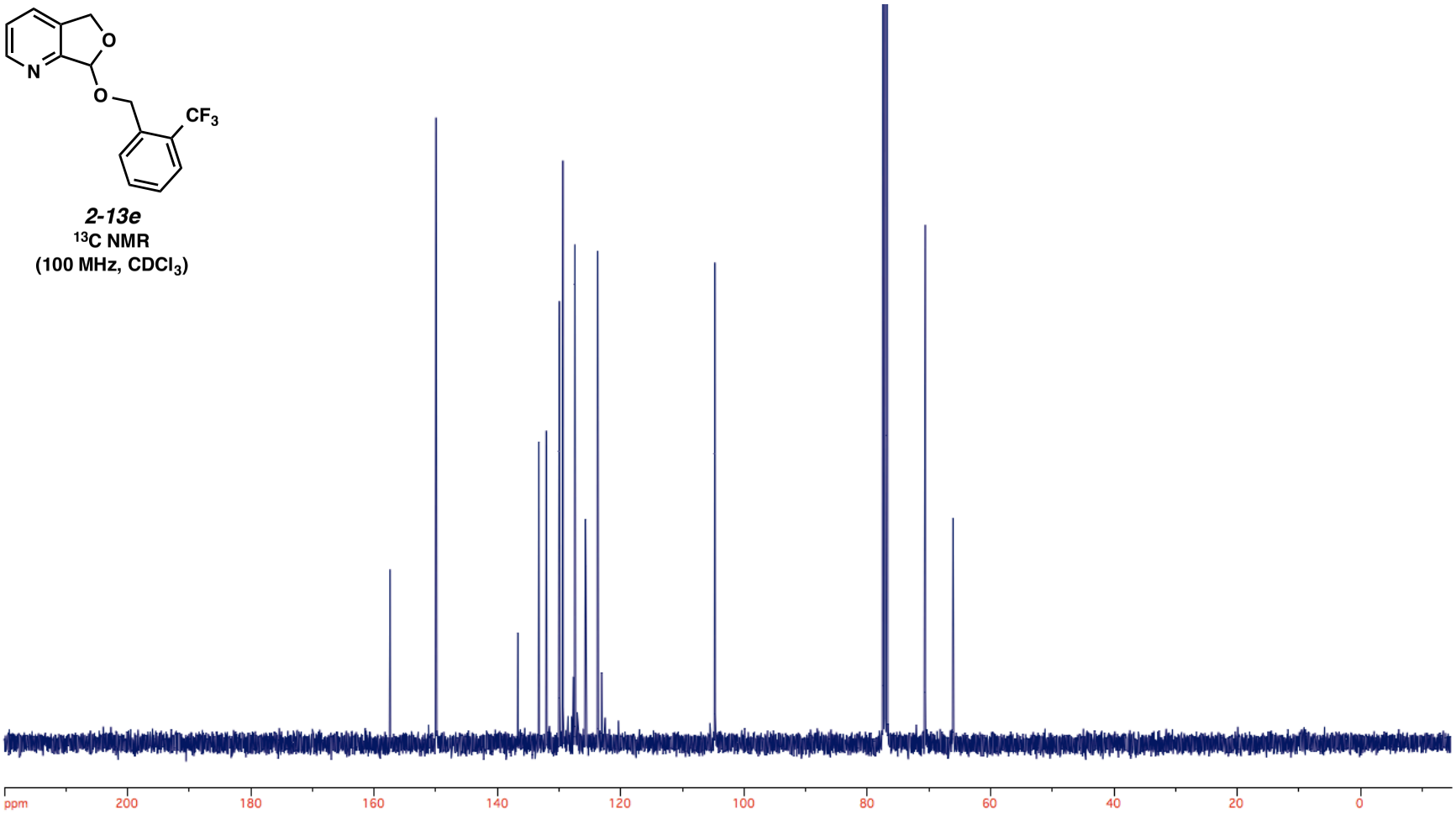

OMe
O
O
N
2-13d
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

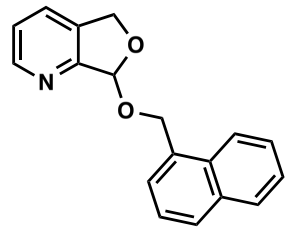


2-13e
^{1}H NMR
(400 MHz, $CDCl_3$)



2-13e
^{13}C NMR
(100 MHz, $CDCl_3$)

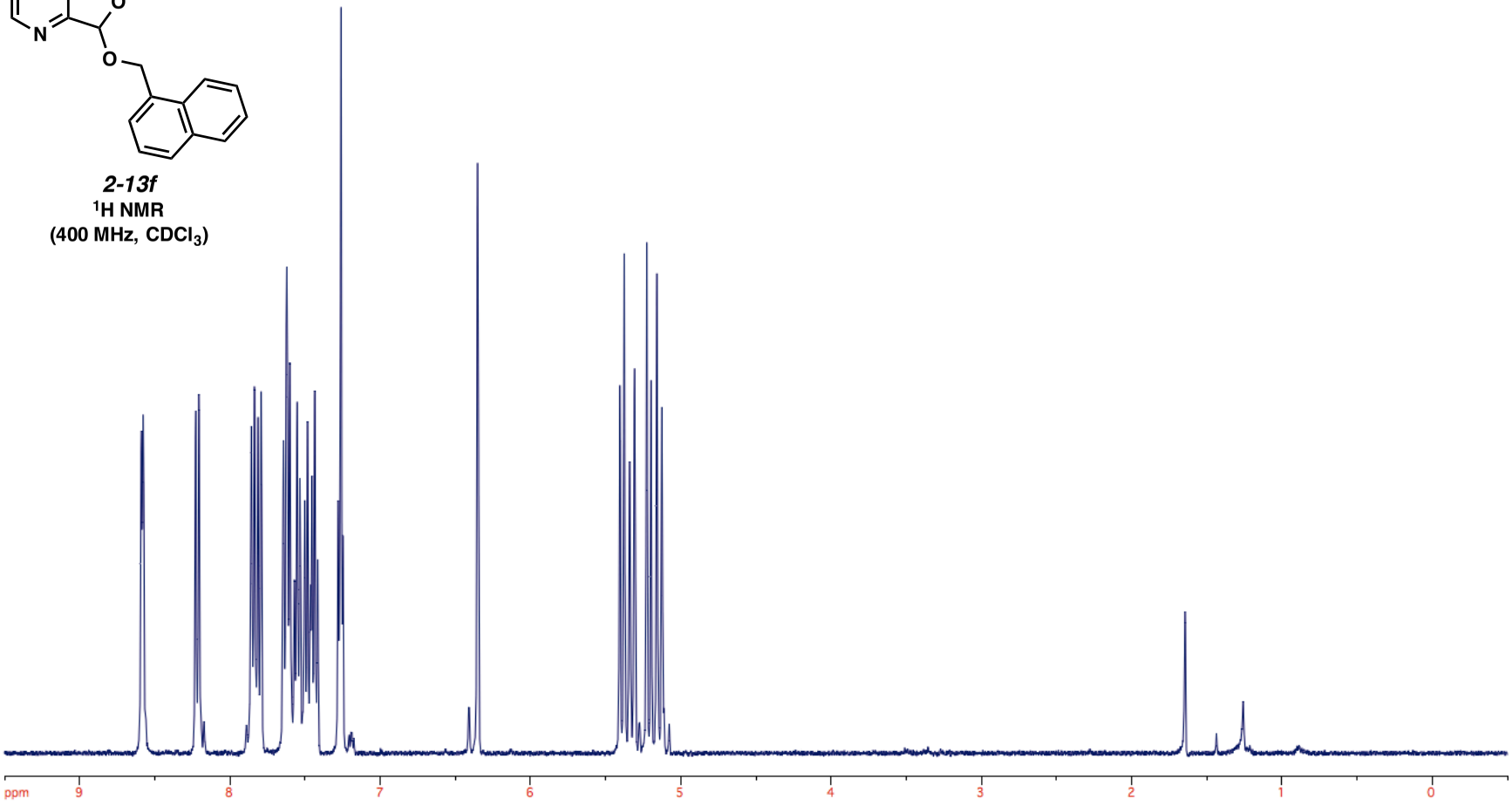


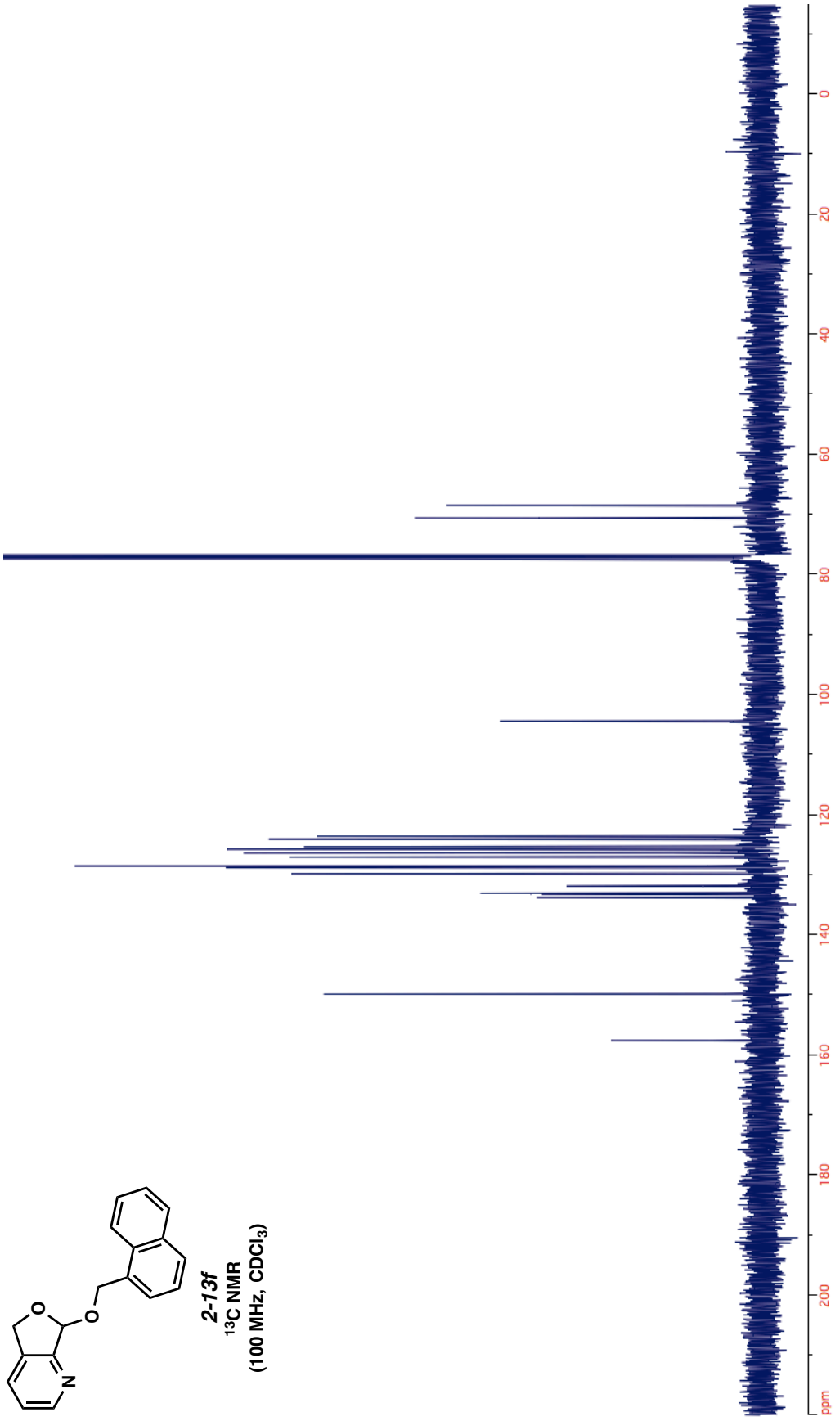


2-13f

^{1}H NMR

(400 MHz, $CDCl_3$)

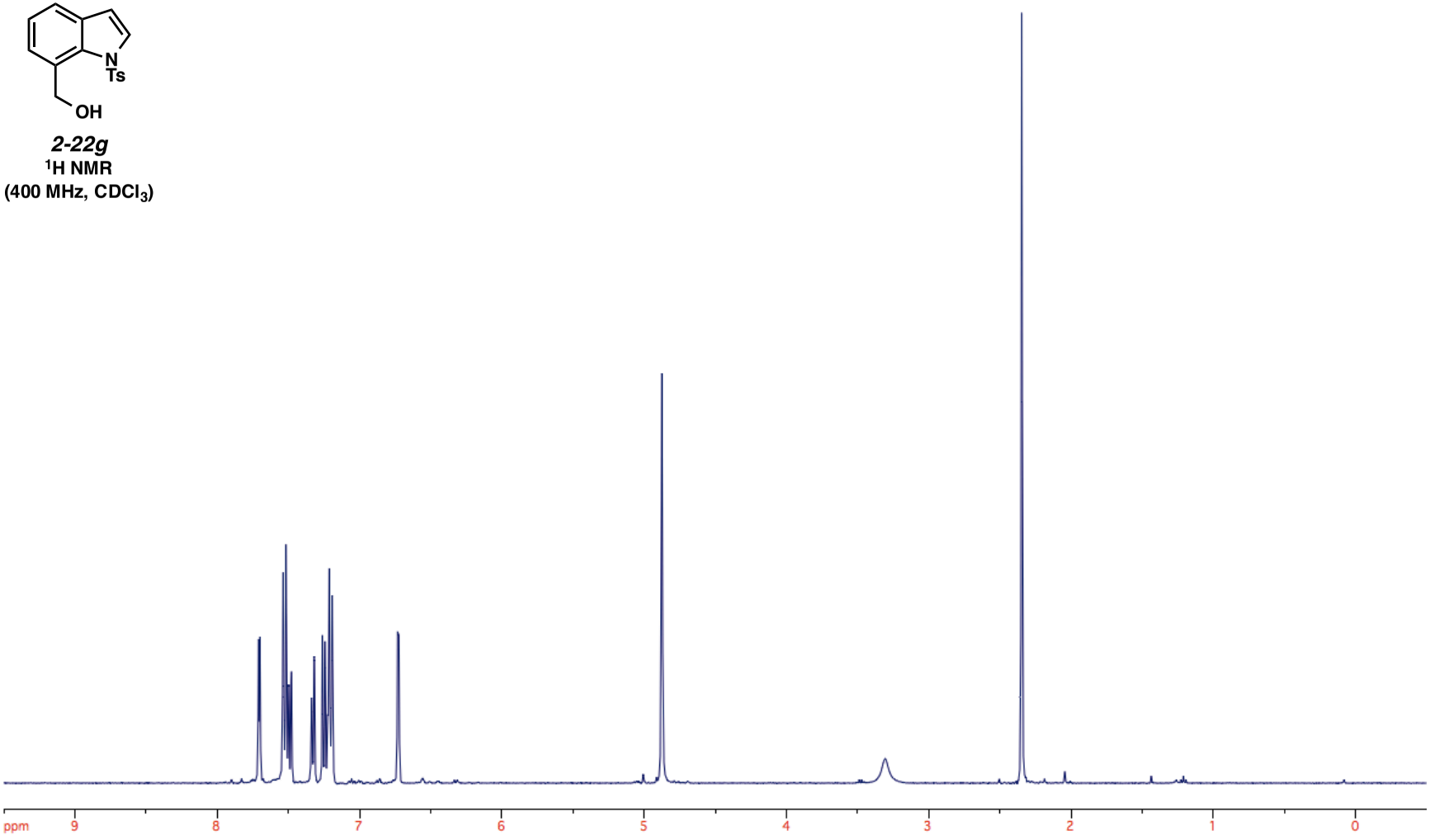


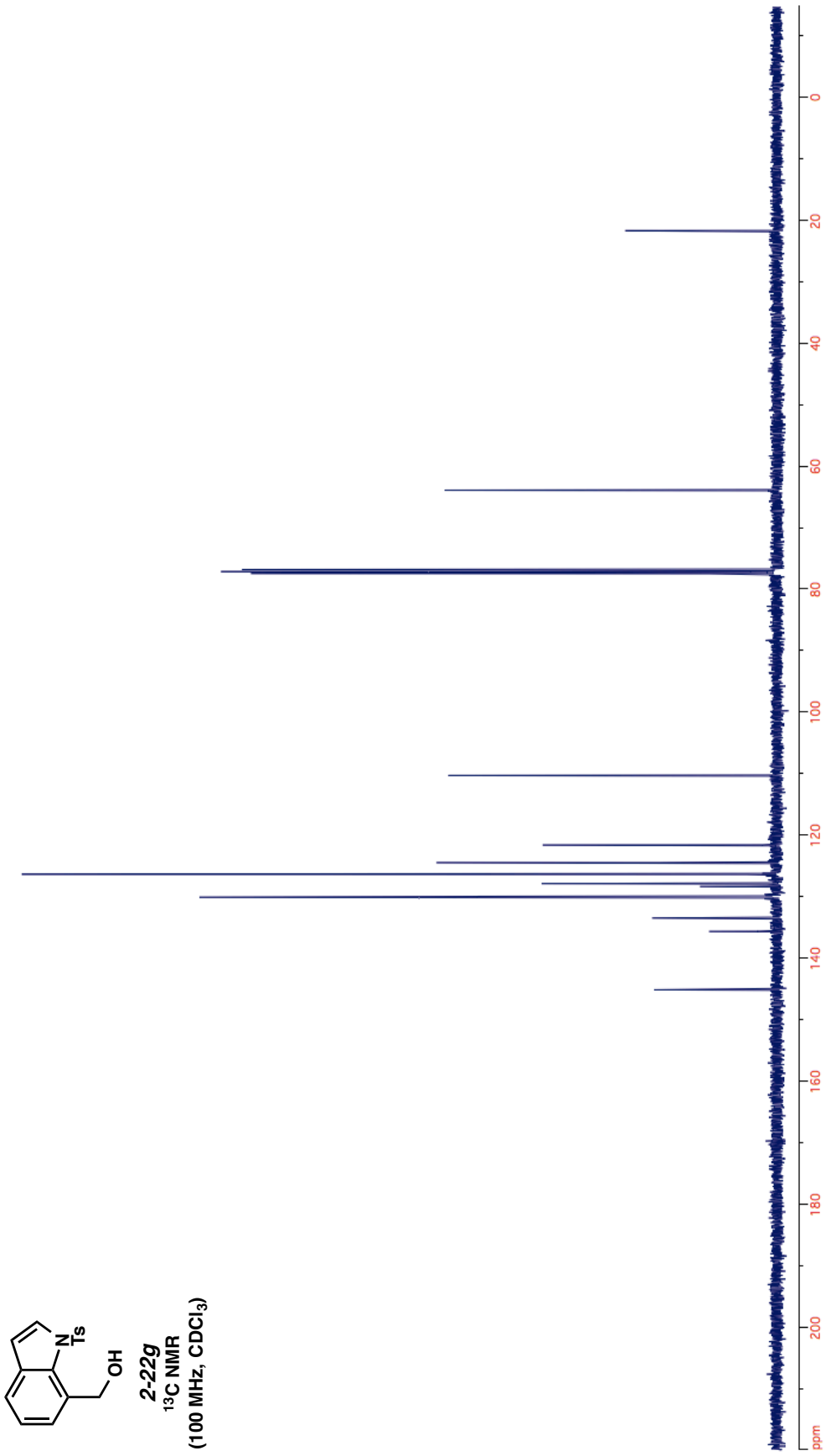

O
O
N
2-13f
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

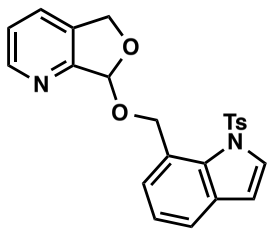
2-22g

^{1}H NMR

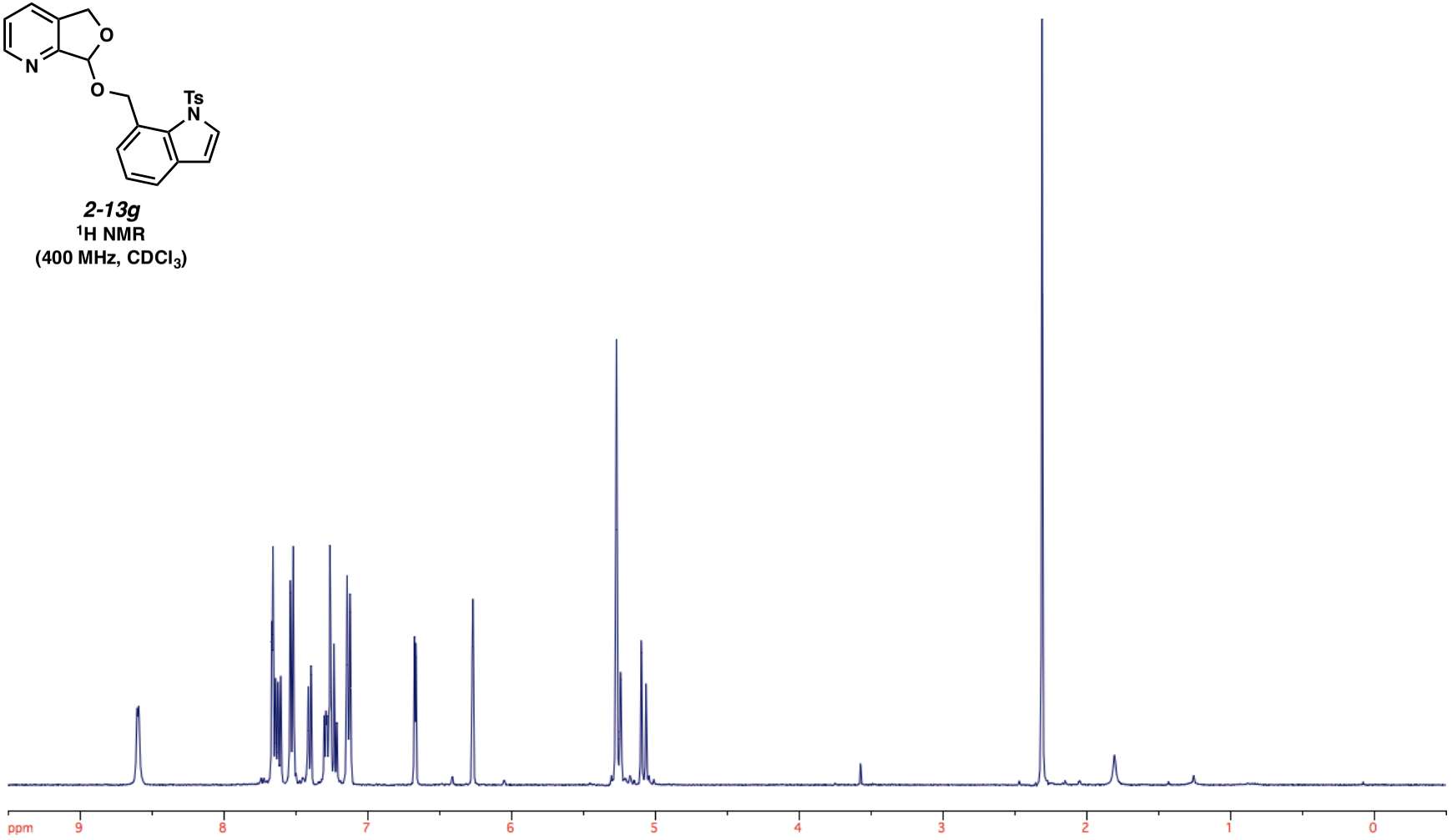
(400 MHz, $CDCl_3$)

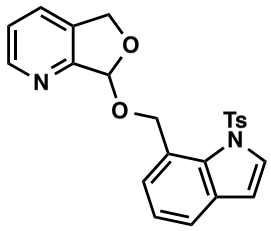



N
Ts
OH
2-22g
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200



2-13g
^{1}H NMR
(400 MHz, $CDCl_3$)

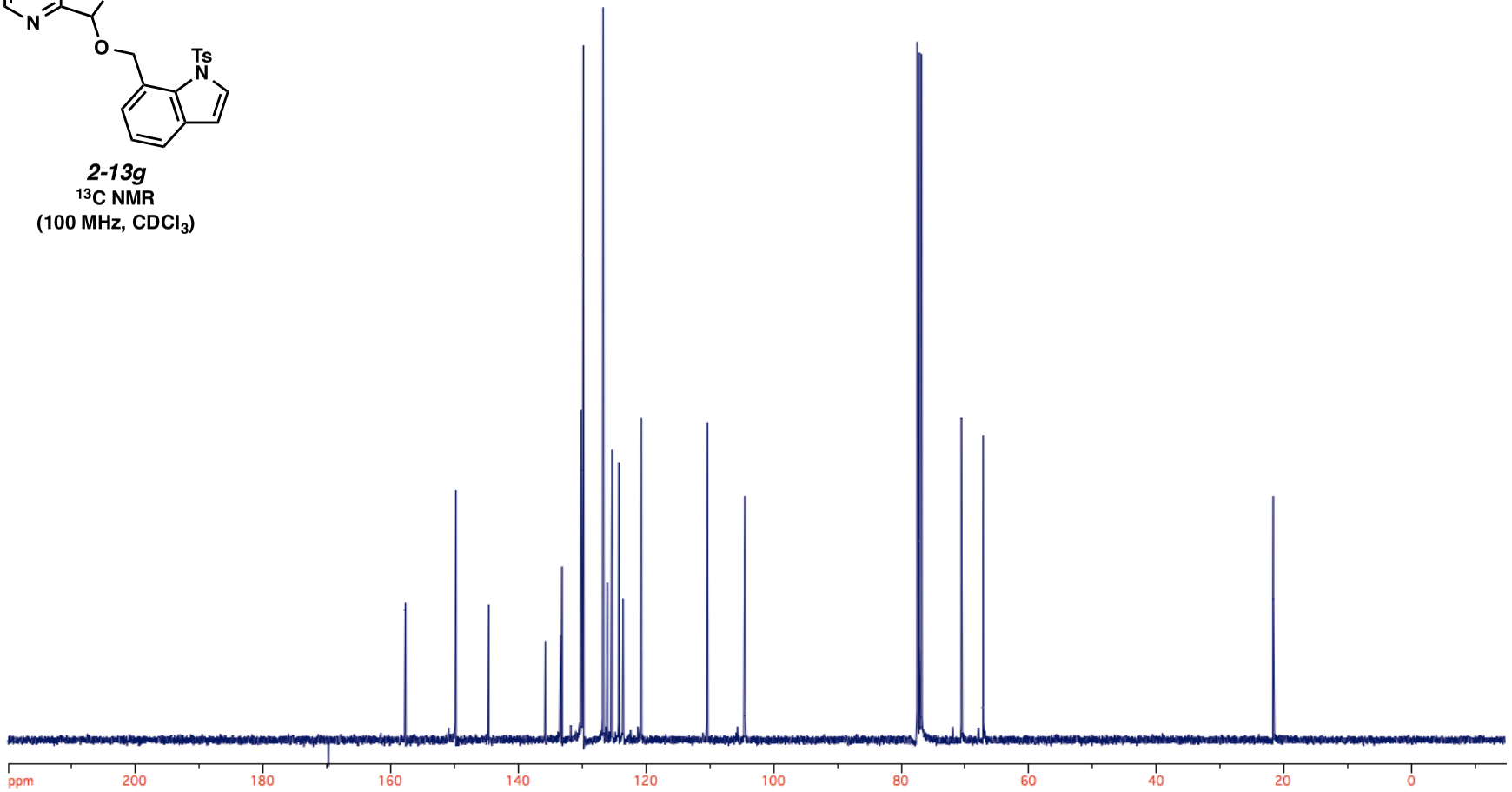


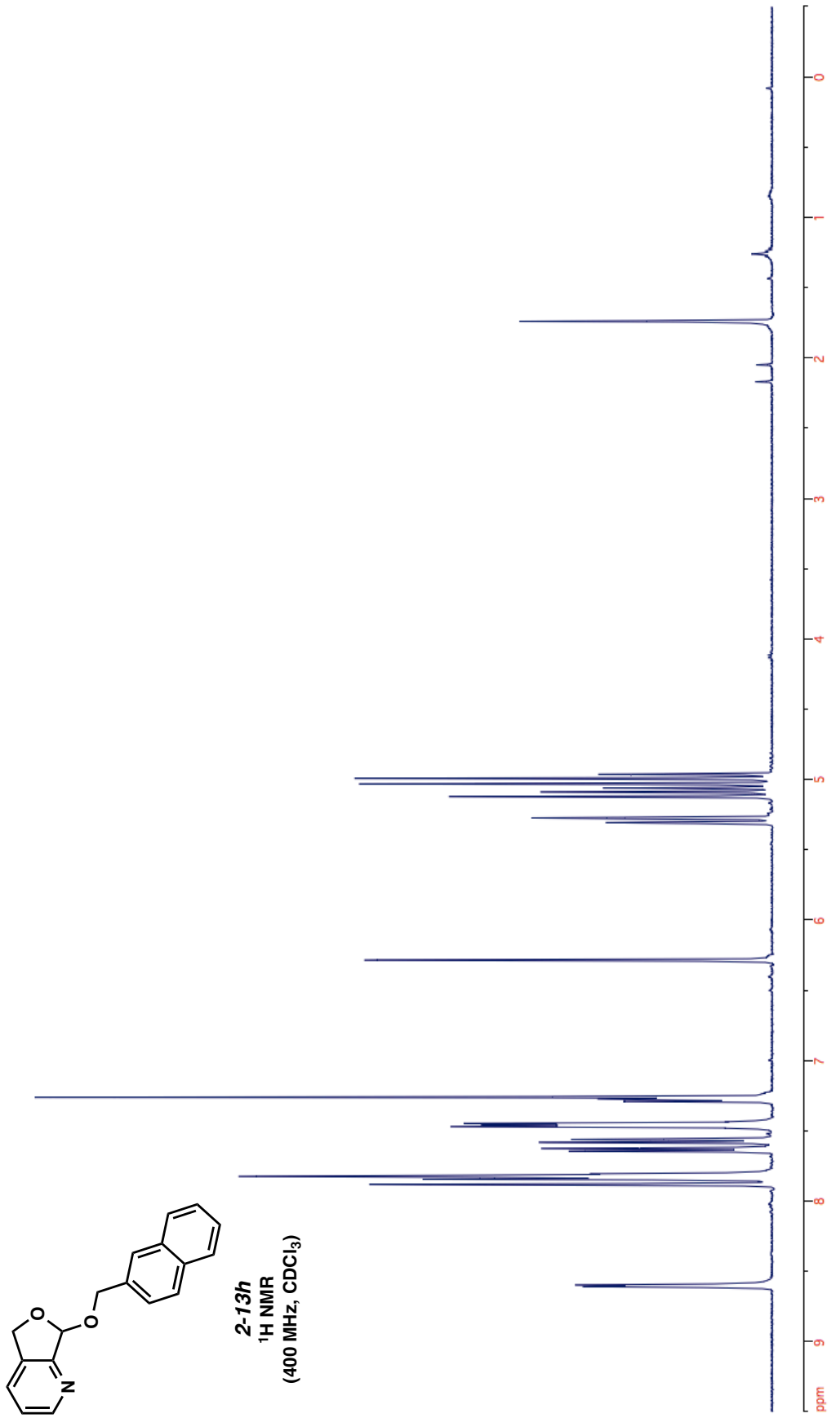


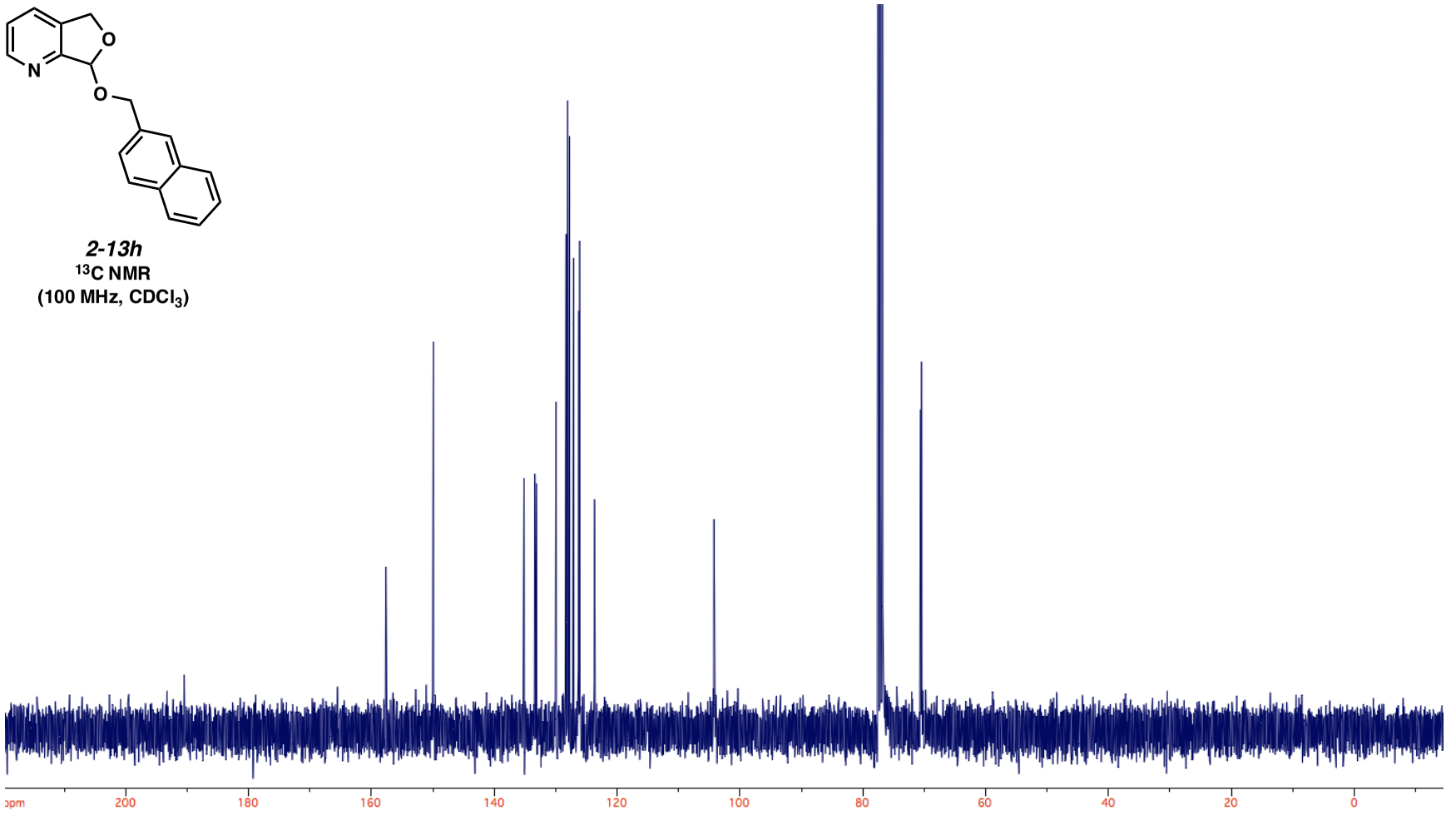
2-13g

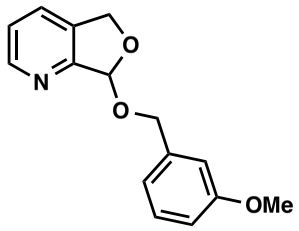
^{13}C NMR

(100 MHz, $CDCl_3$)

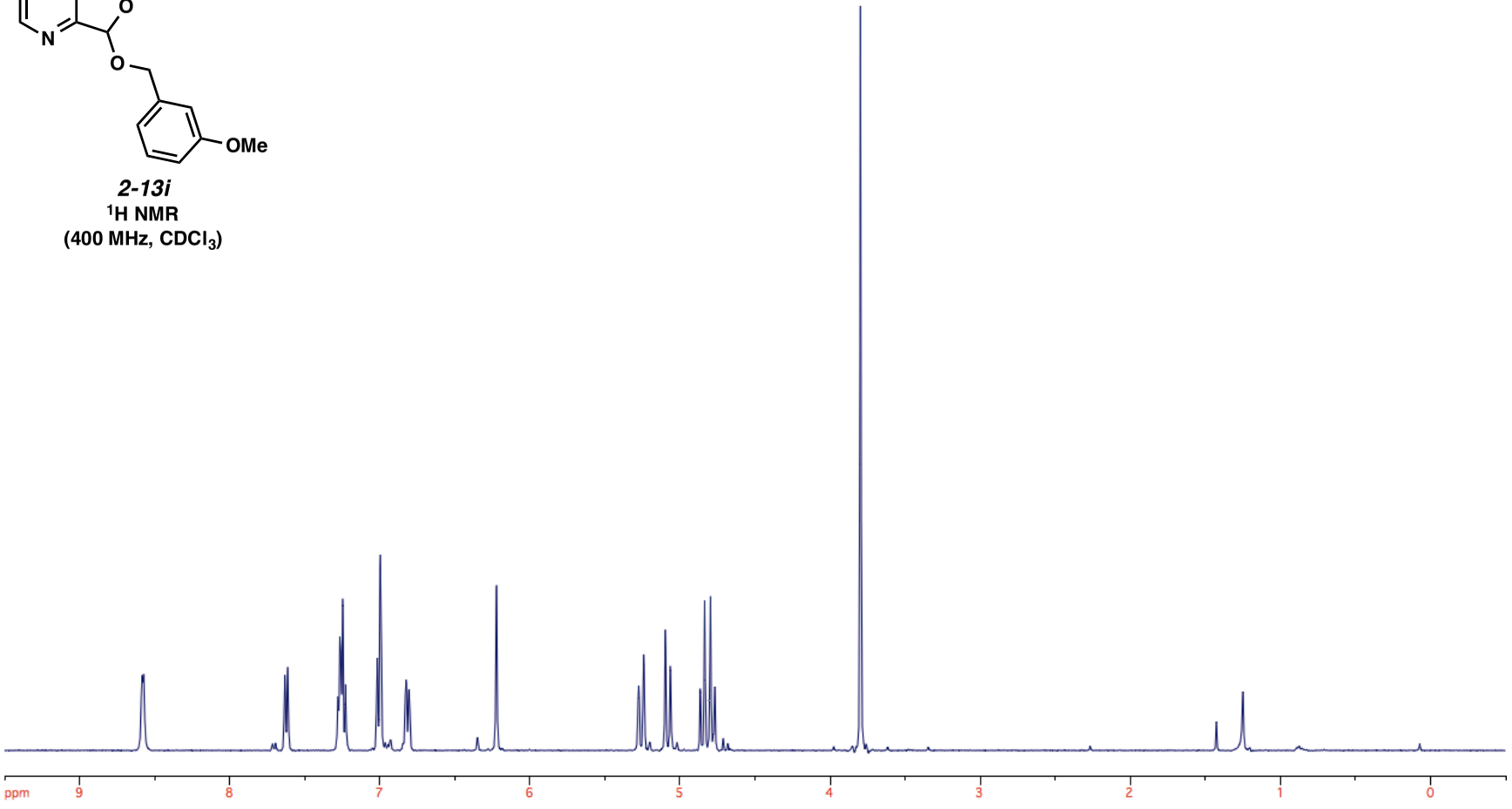


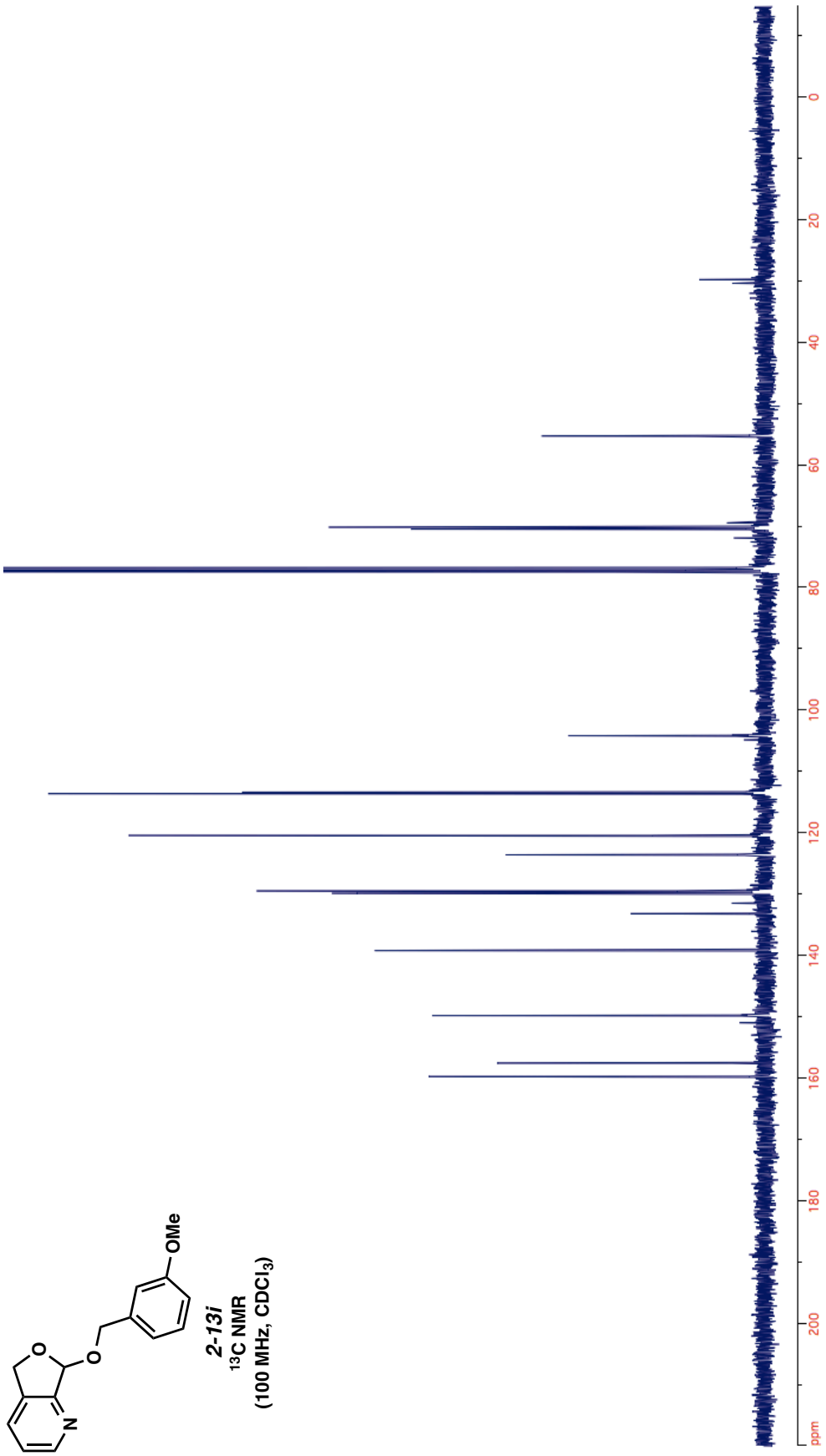

2-13h
^{1}H NMR
(400 MHz, $CDCl_3$)
ppm
9
8
7
6
5
4
3
2
1
0
O
O
N

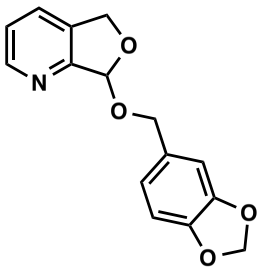

O
N
O
2-13h
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0



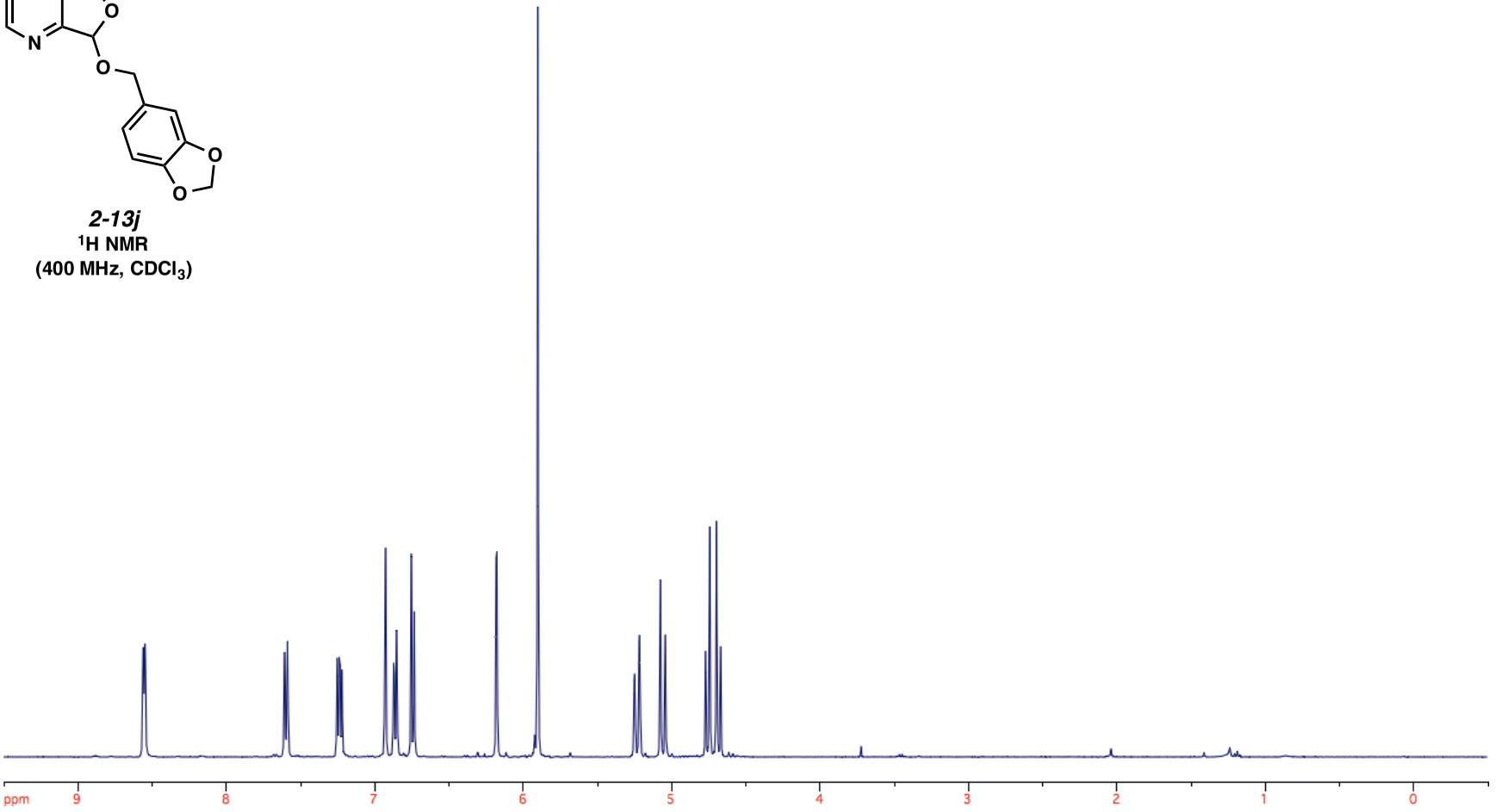
2-13i
^{1}H NMR
(400 MHz, $CDCl_3$)

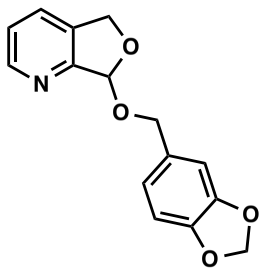



OMe
O
O
N
2-13i
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

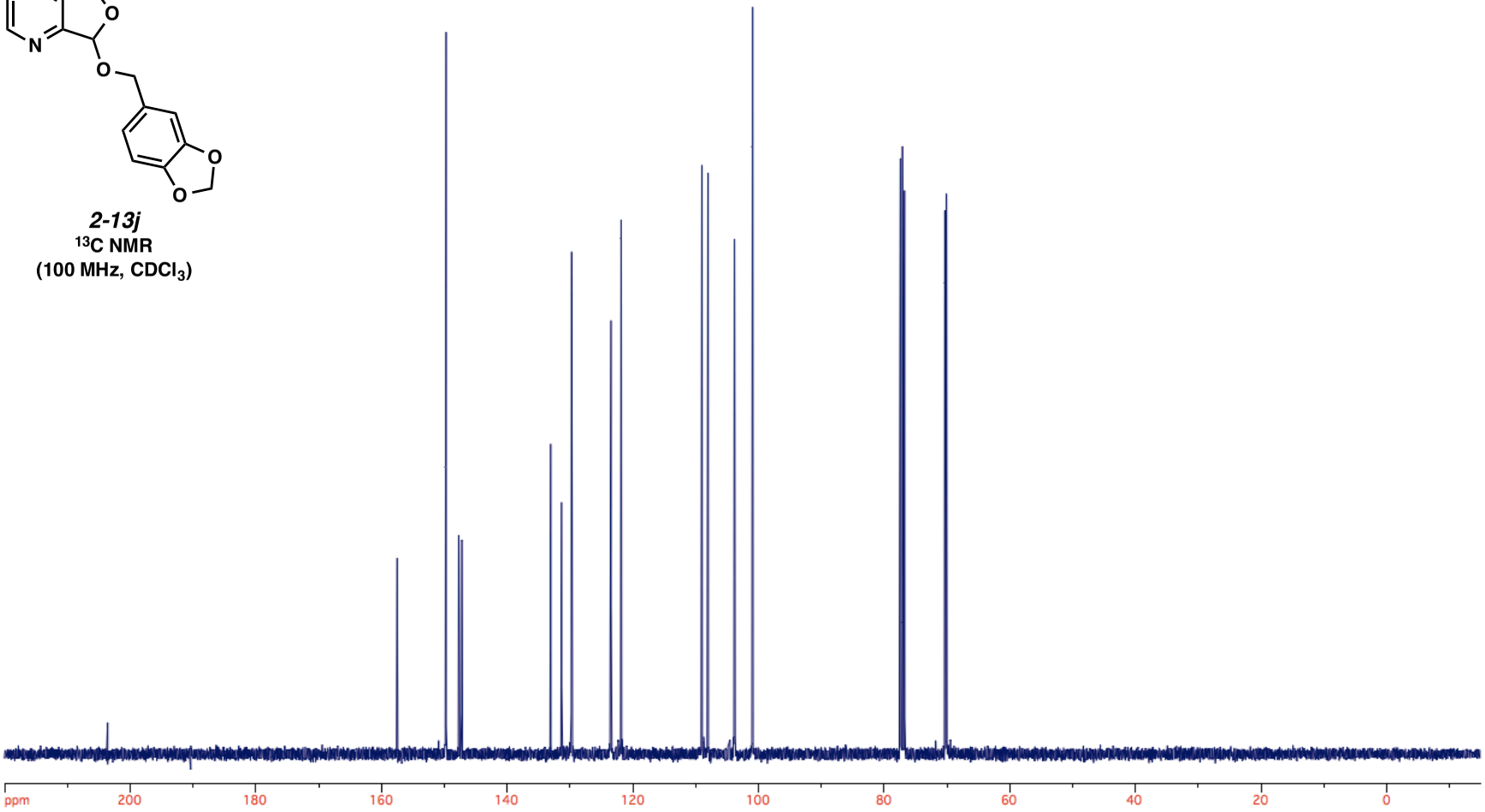


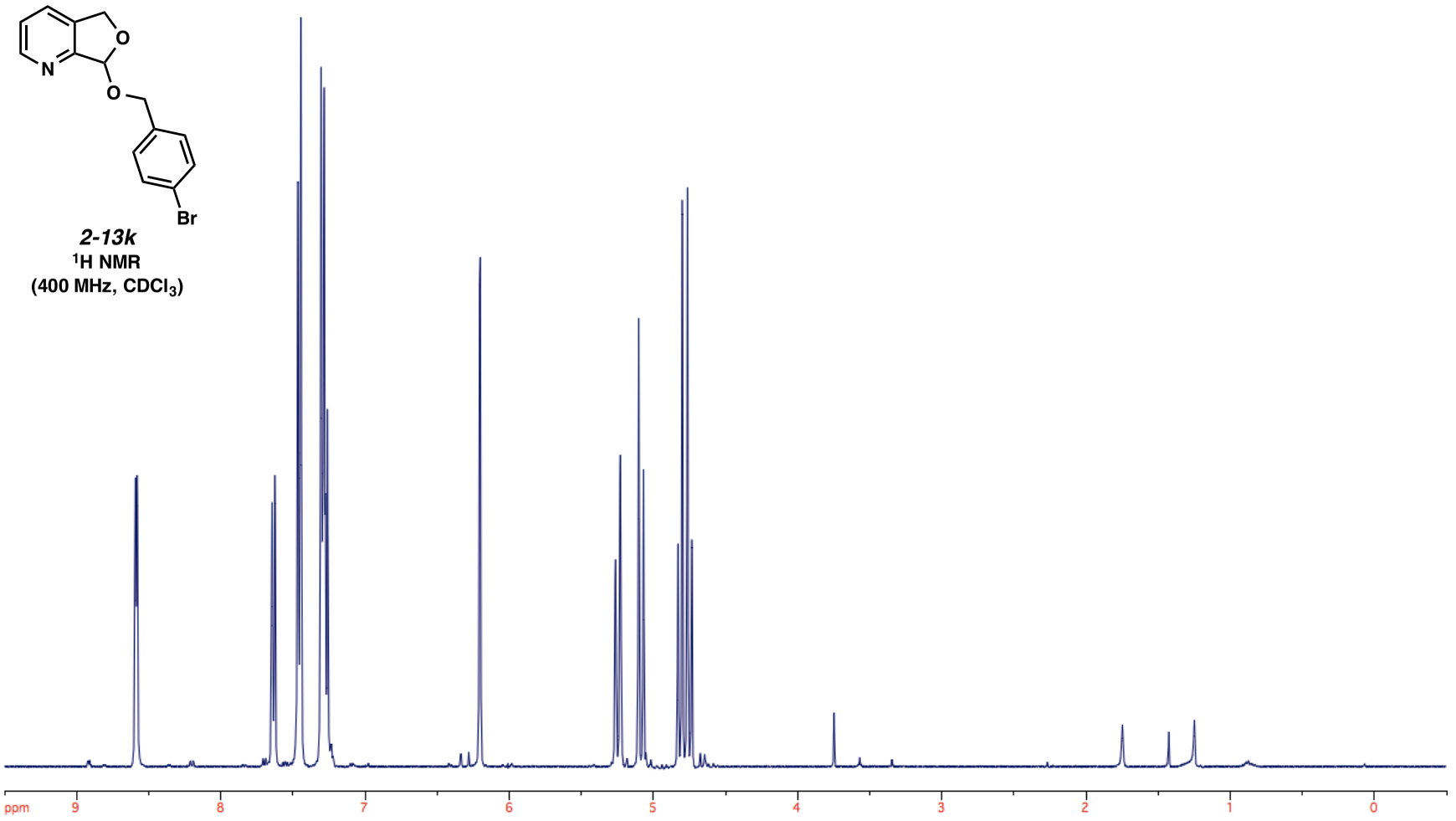
2-13j
^{1}H NMR
(400 MHz, $CDCl_3$)

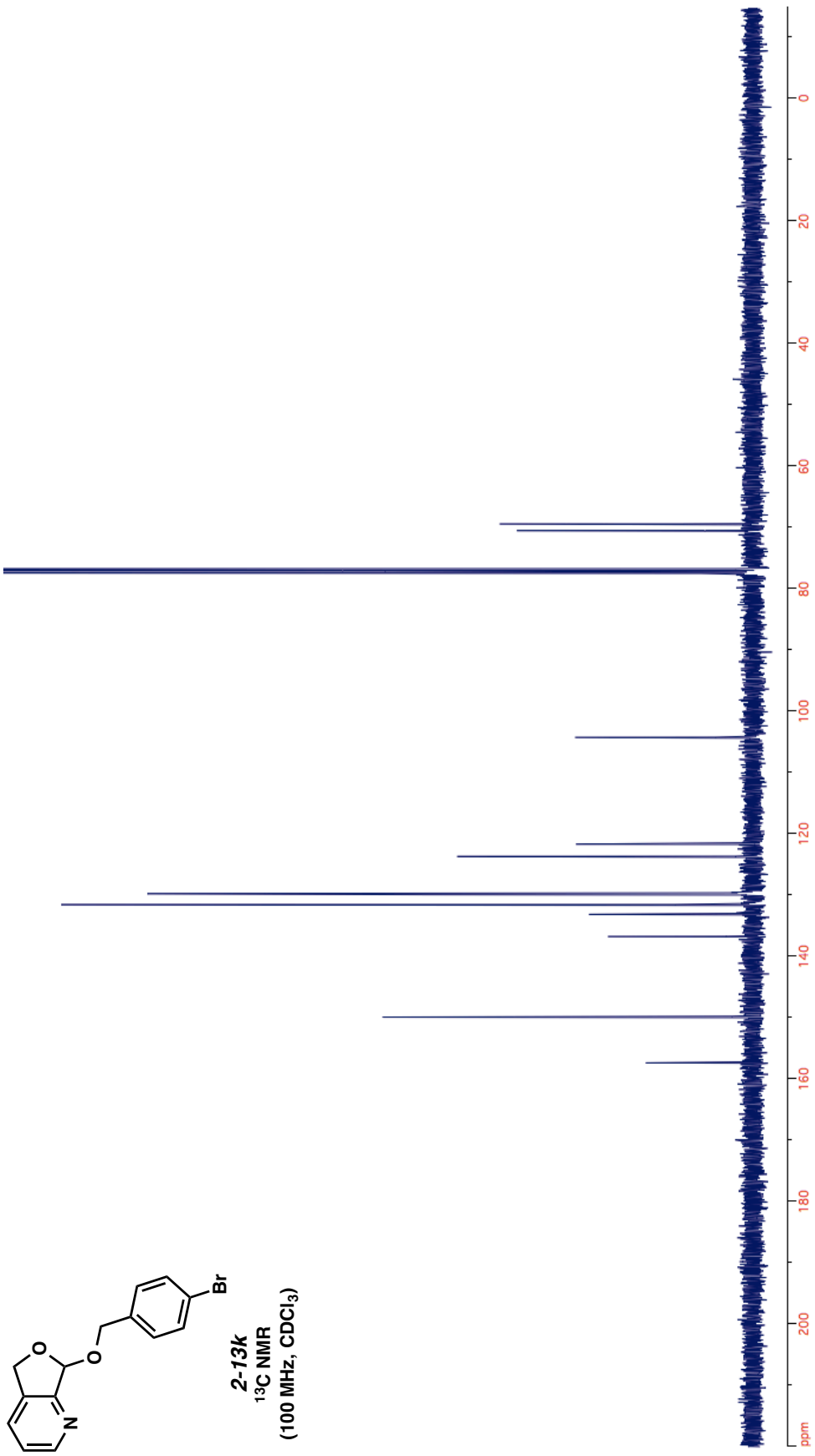


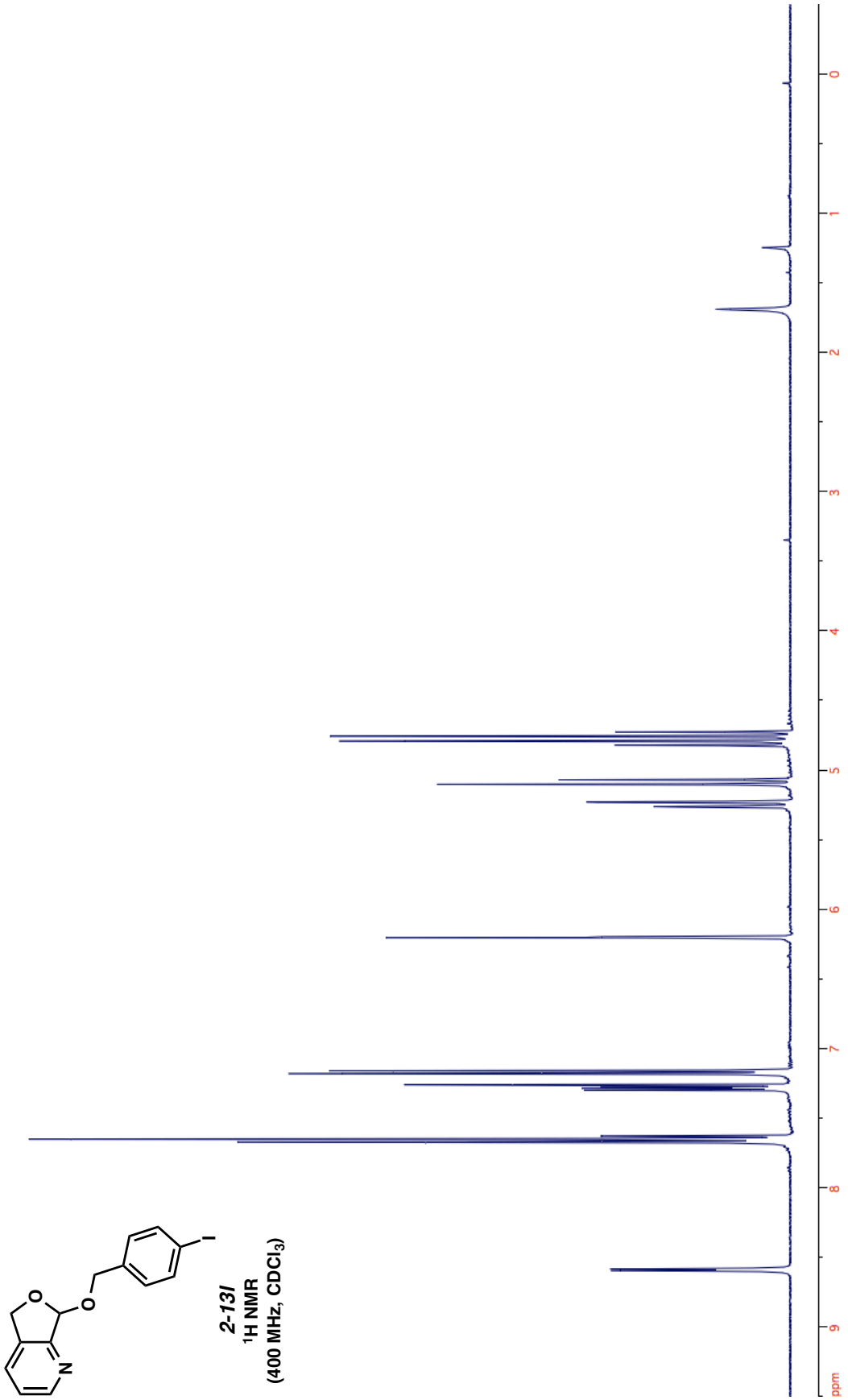


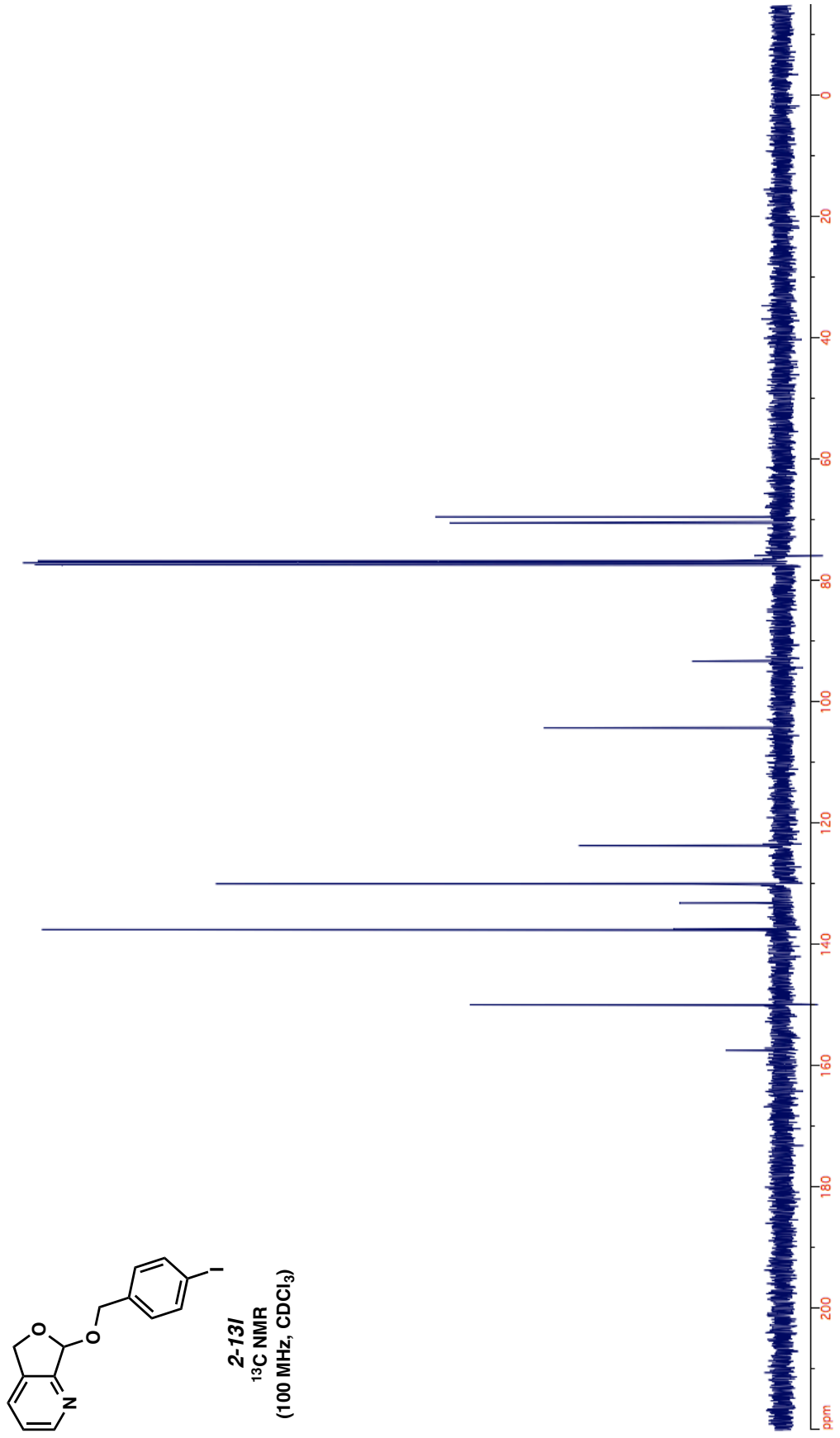
2-13j
^{13}C NMR
(100 MHz, $CDCl_3$)

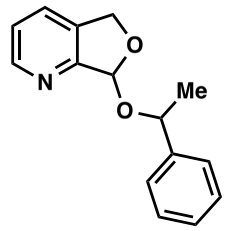



N
O
O
Br
2-13k
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0

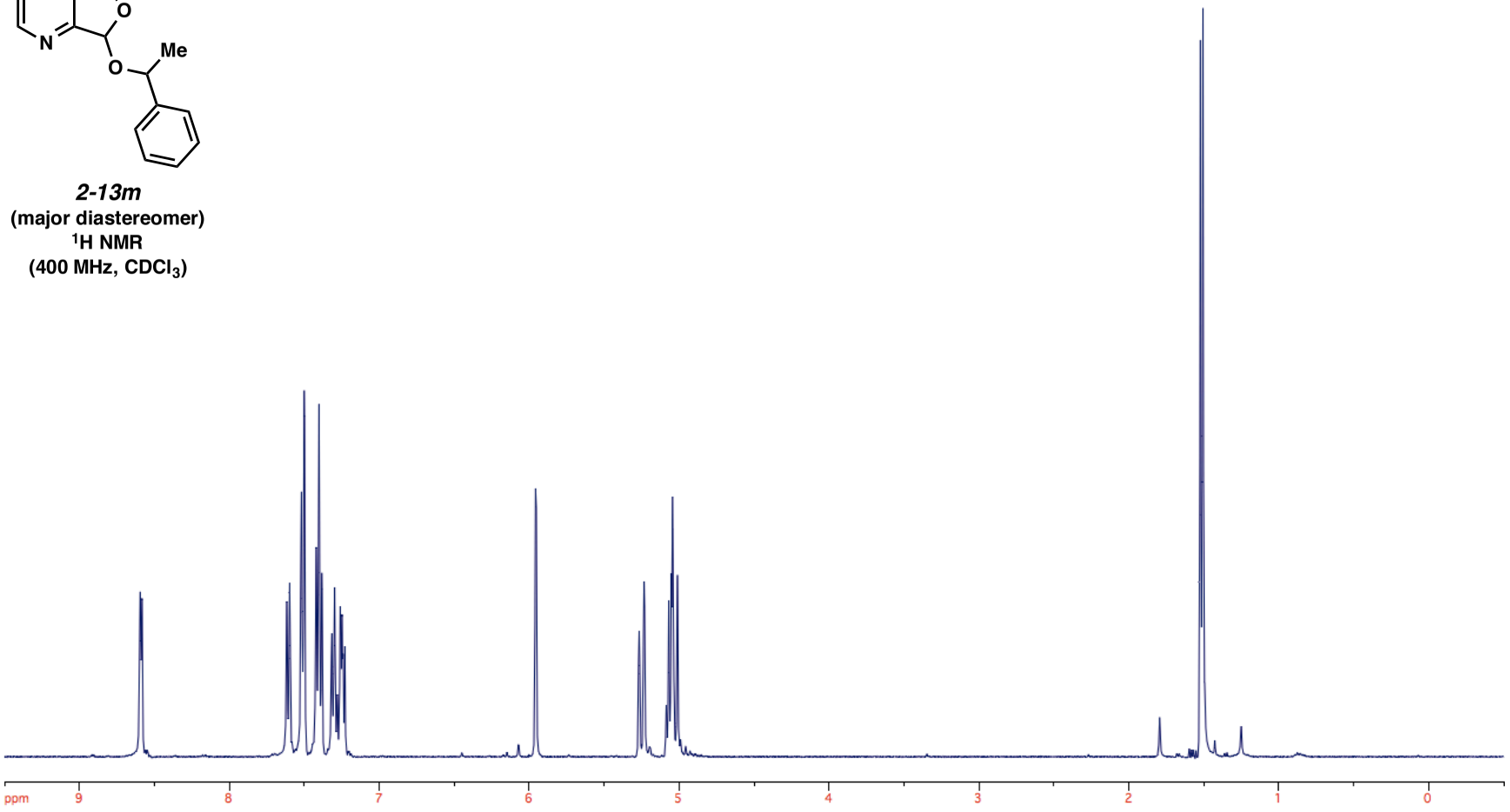

Br
O
O
N
2-13k
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


I
O
O
N
2-13l
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

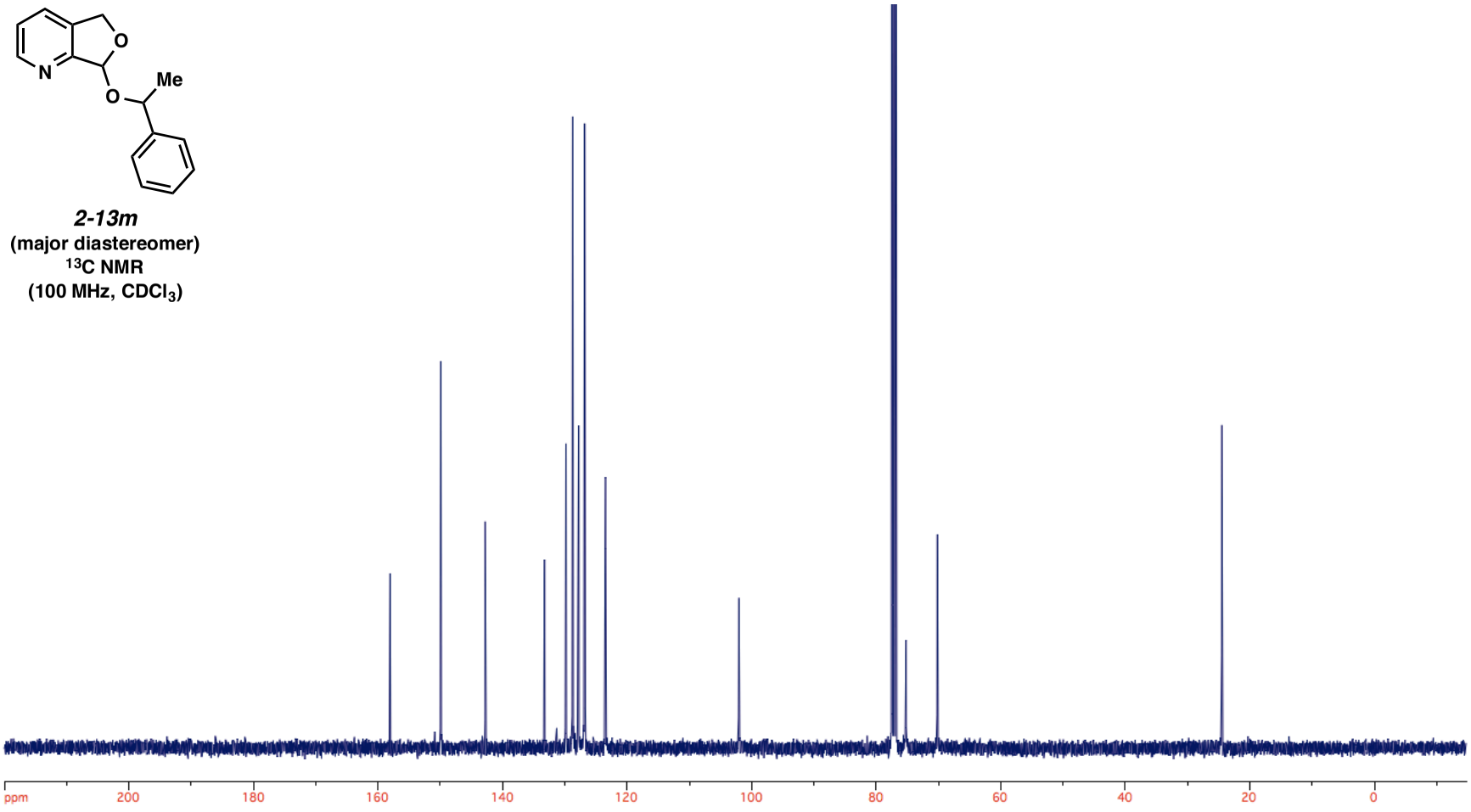

I
O
O
N
2-13l
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

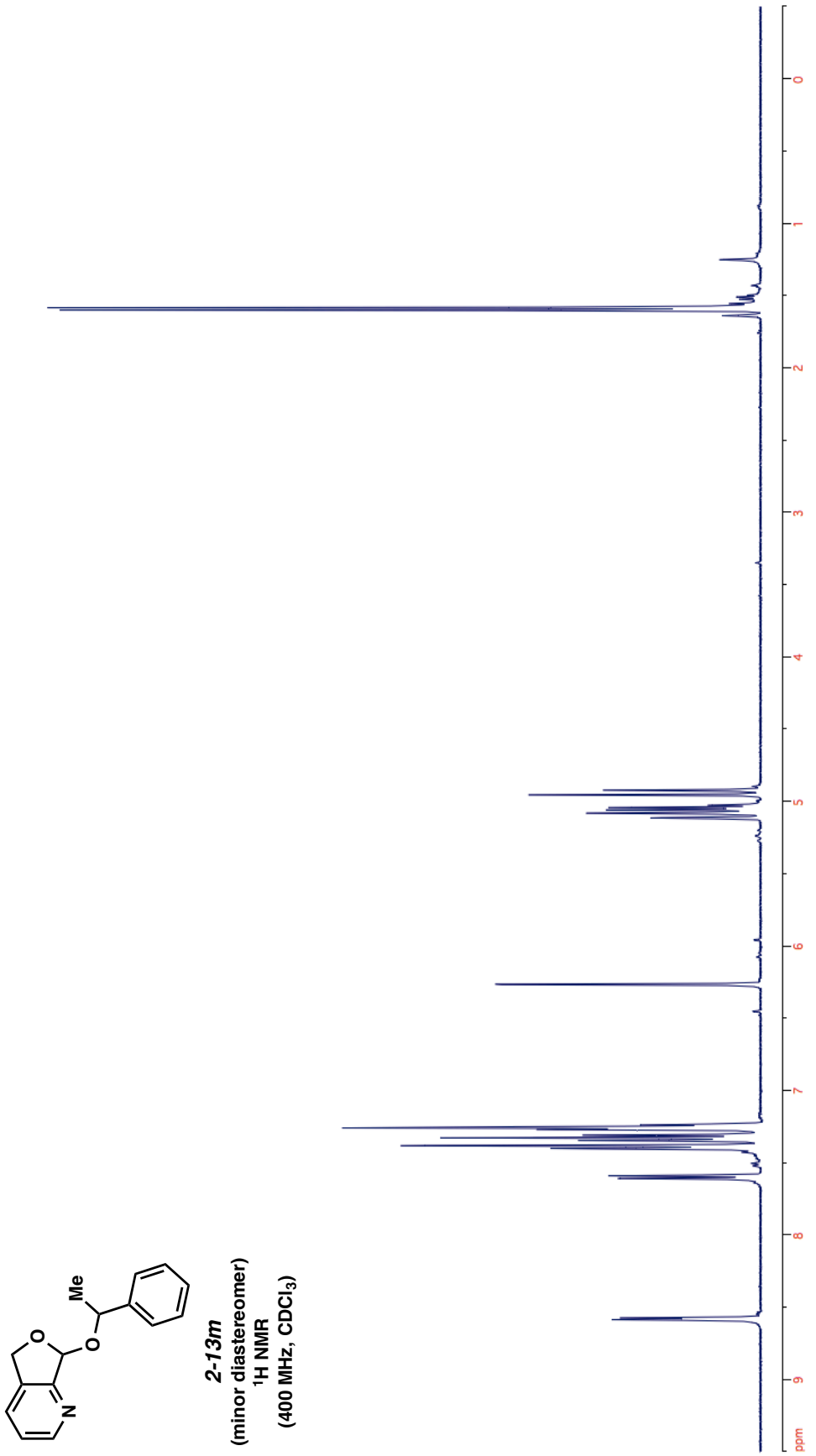


2-13m
(major diastereomer)
^{1}H NMR
(400 MHz, $CDCl_3$)

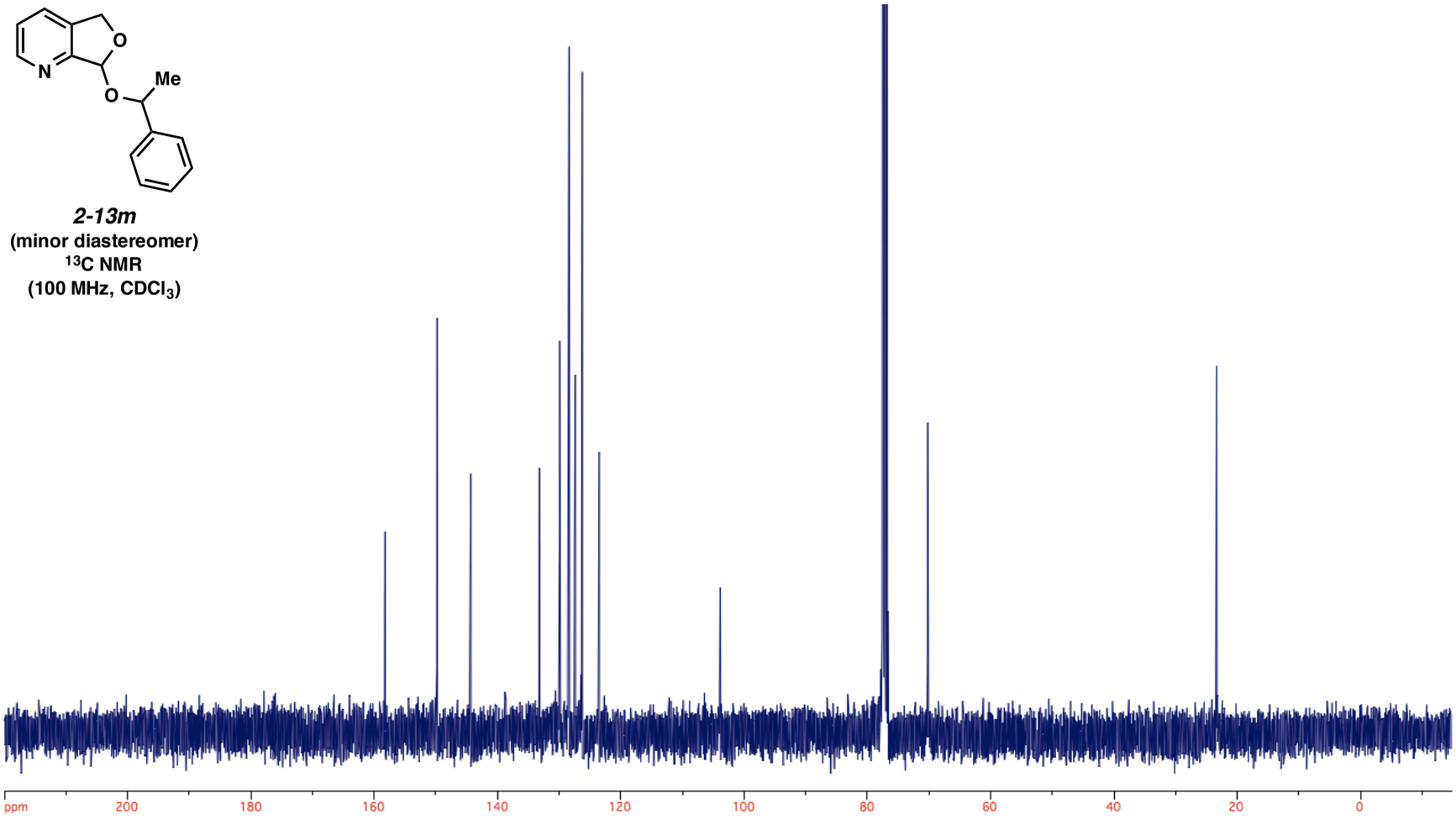


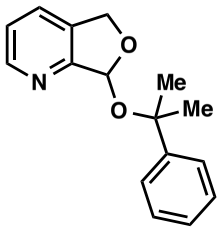
2-13m
(major diastereomer)
^{13}C NMR
(100 MHz, $CDCl_3$)



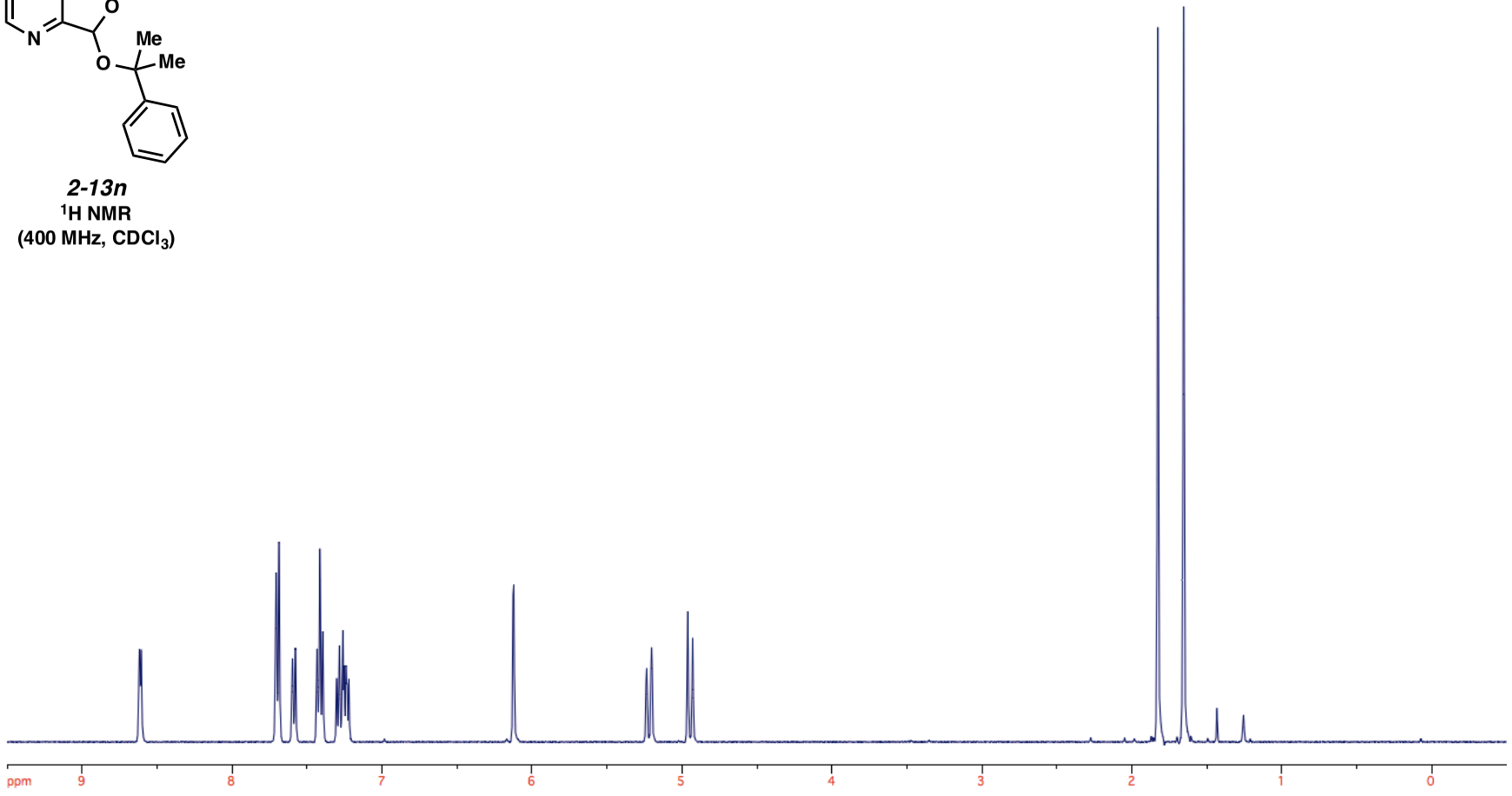

Me
O
O
N
2-13m
(minor diastereomer)
^{1}H NMR
(400 MHz, $CDCl_3$)
ppm
0
1
2
3
4
5
6
7
8
9

2-13m
(minor diastereomer)
^{13}C NMR
(100 MHz, $CDCl_3$)

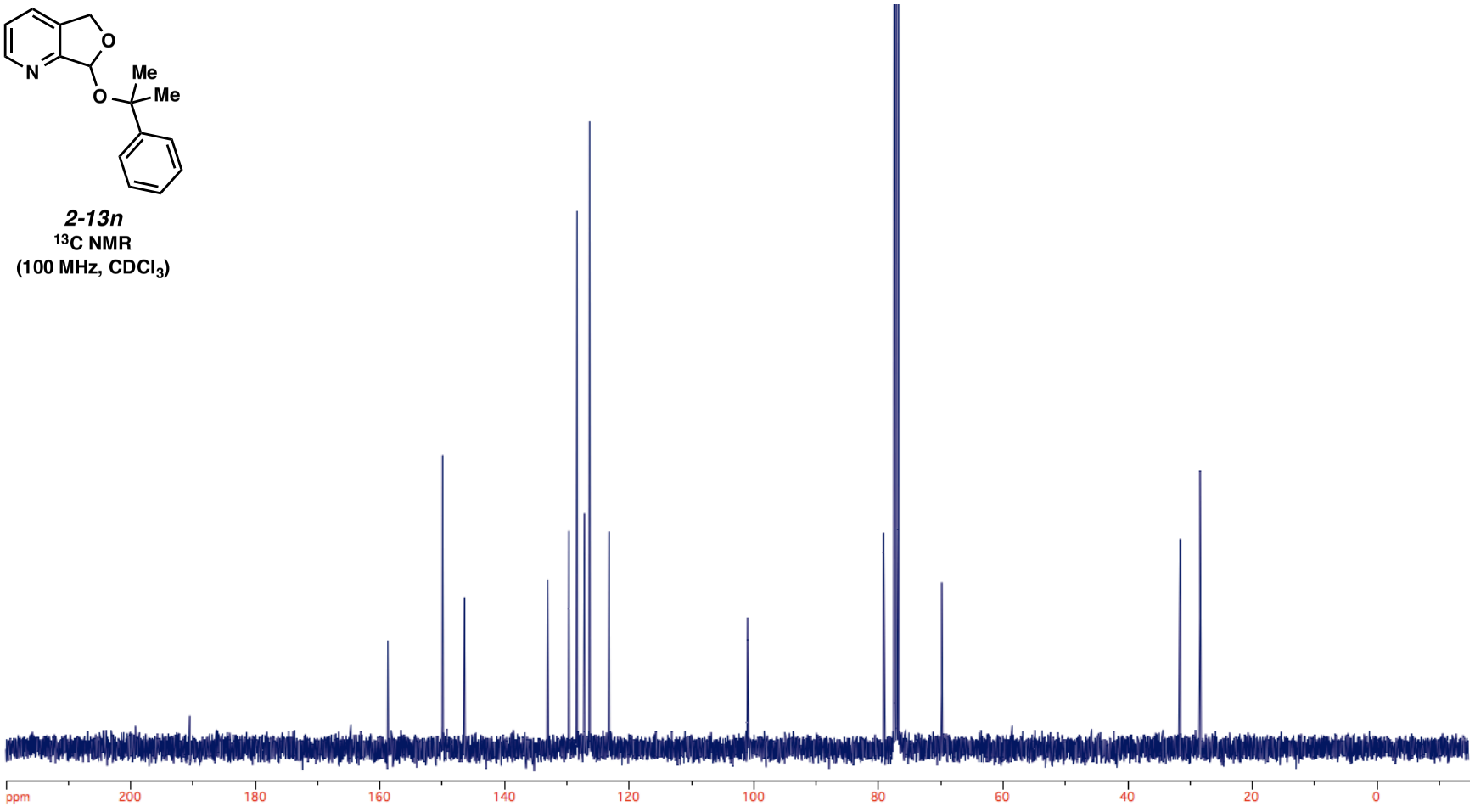


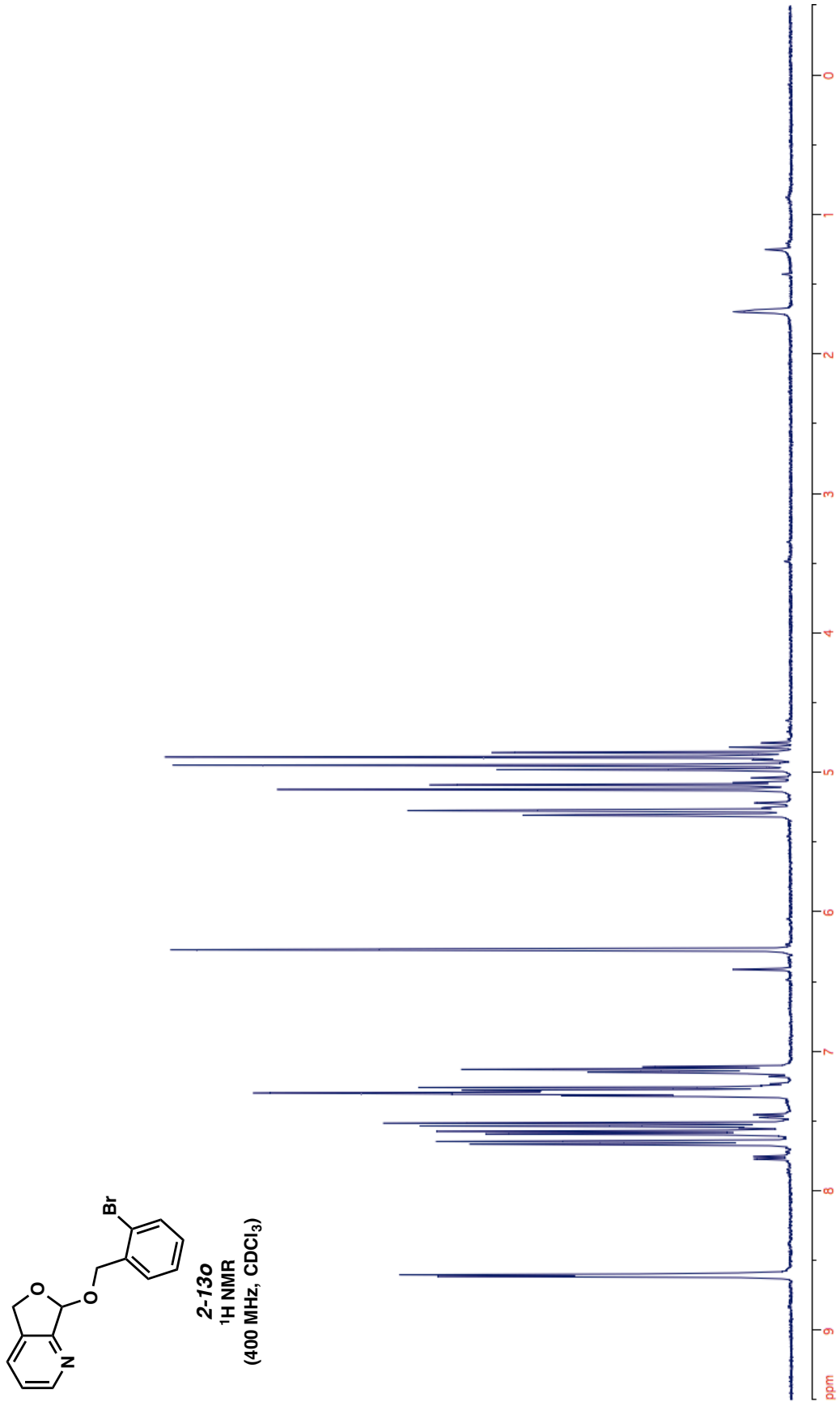


2-13n
^{1}H NMR
(400 MHz, $CDCl_3$)

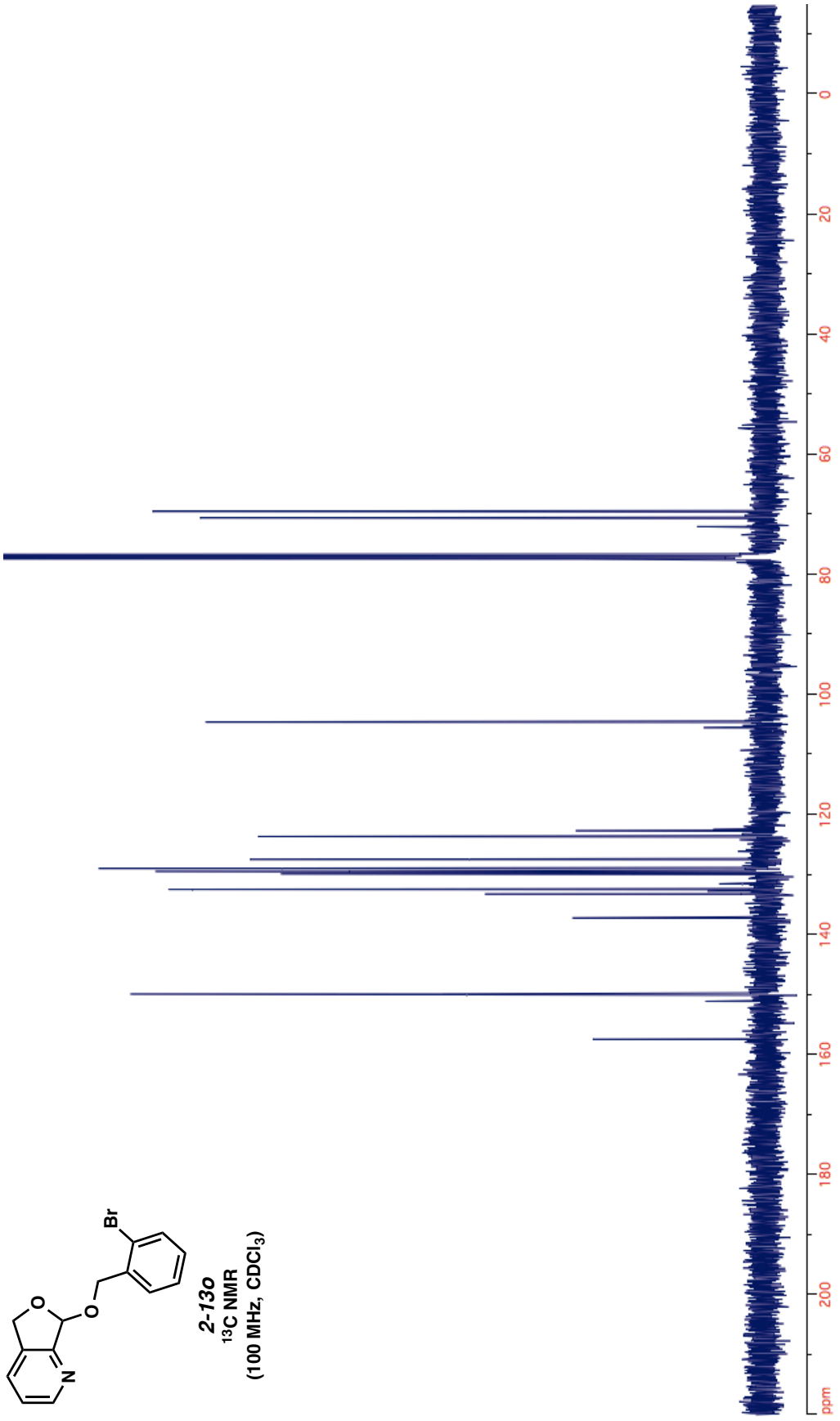


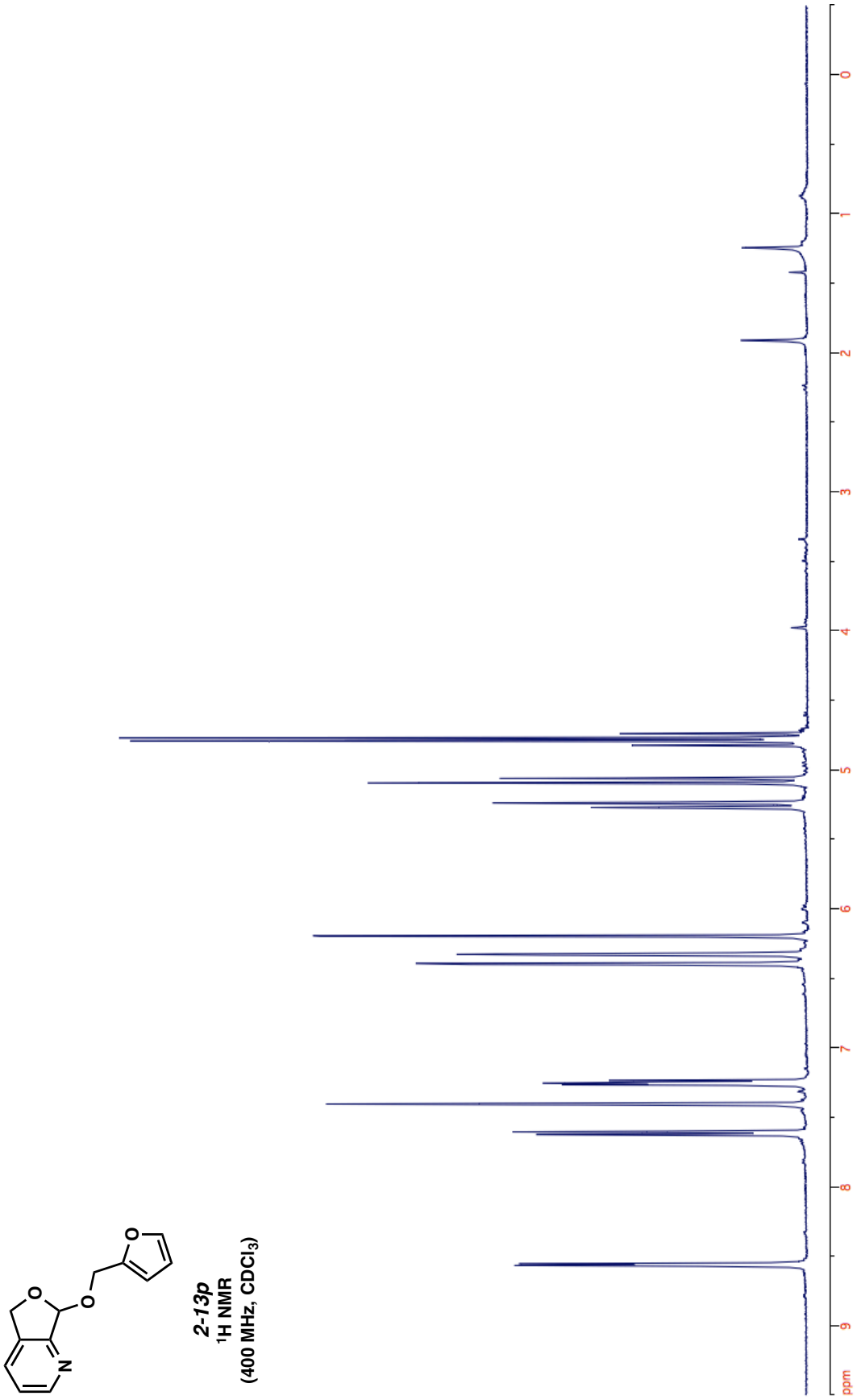
2-13n
^{13}C NMR
(100 MHz, $CDCl_3$)

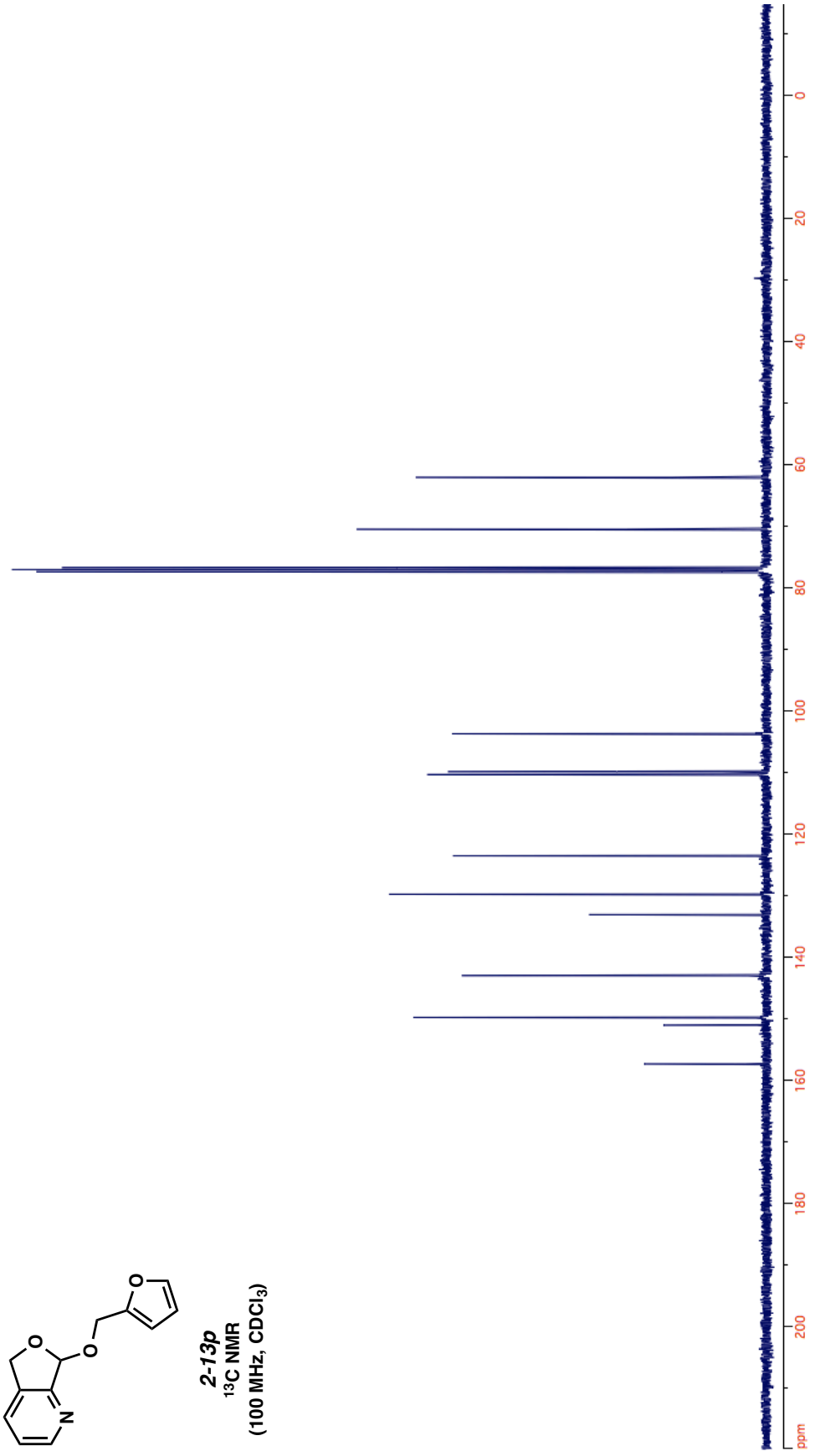


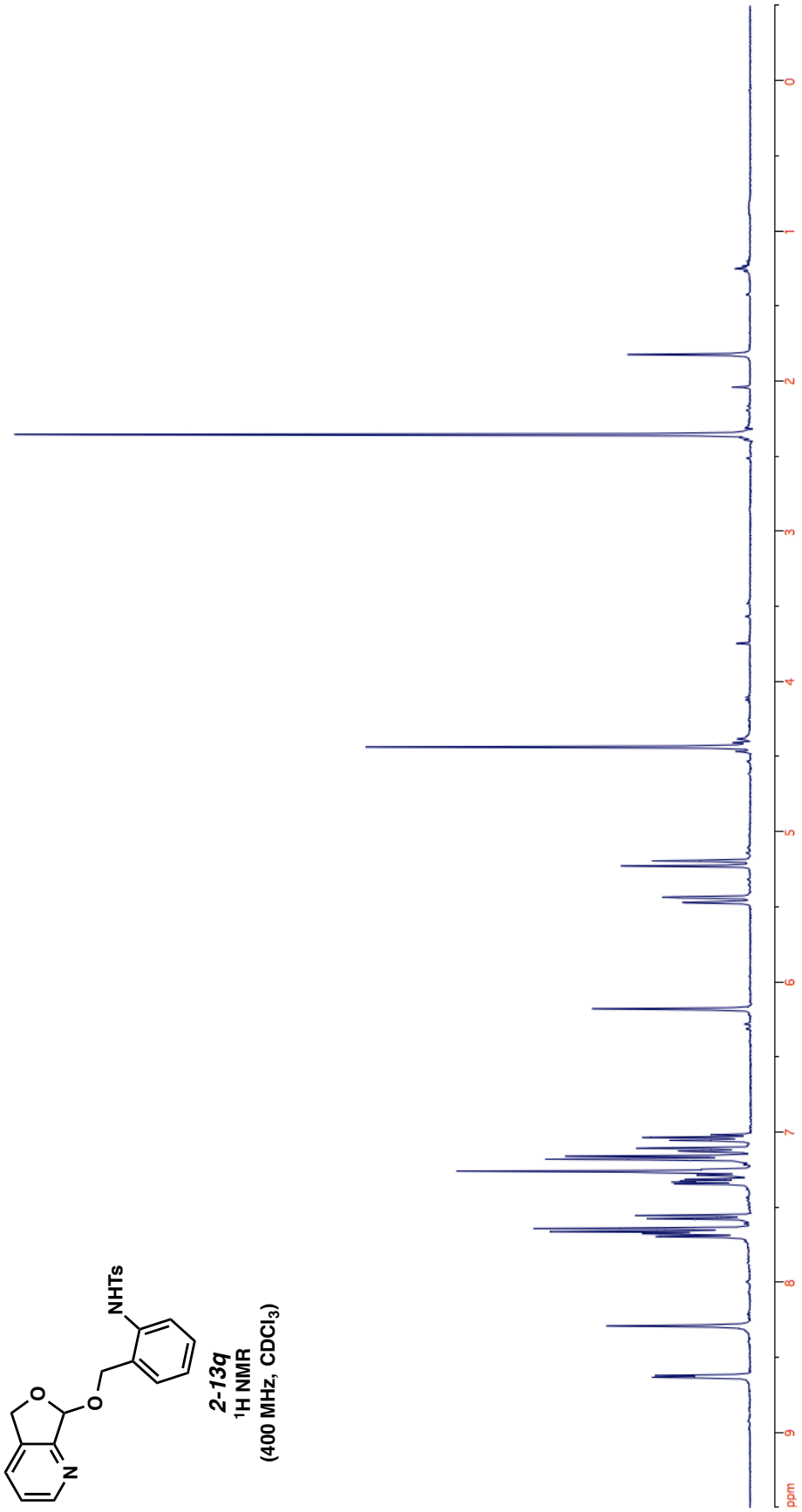


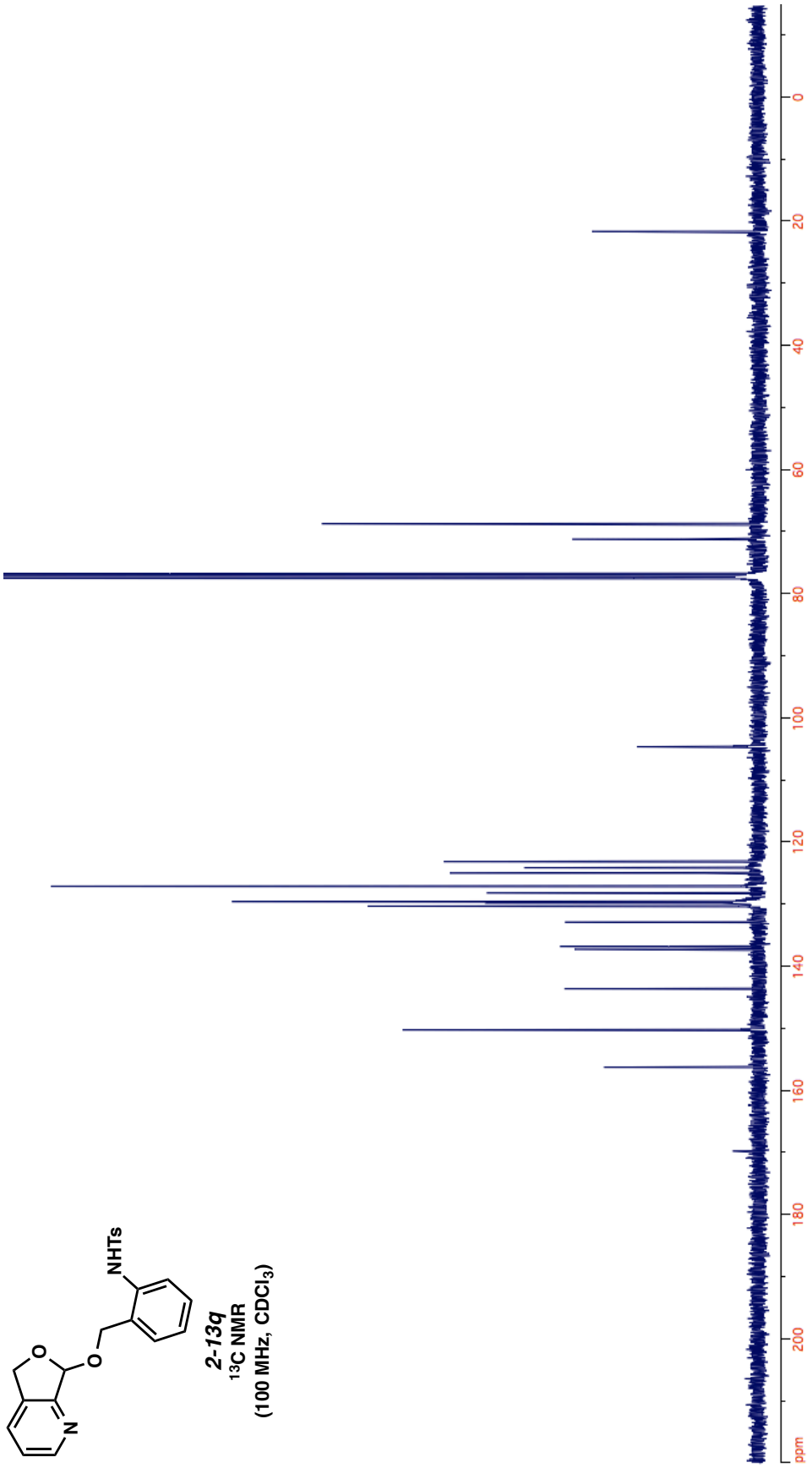
2-13o
^{1}H NMR
(400 MHz, $CDCl_3$)


Br
O
O
N
2-13o
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

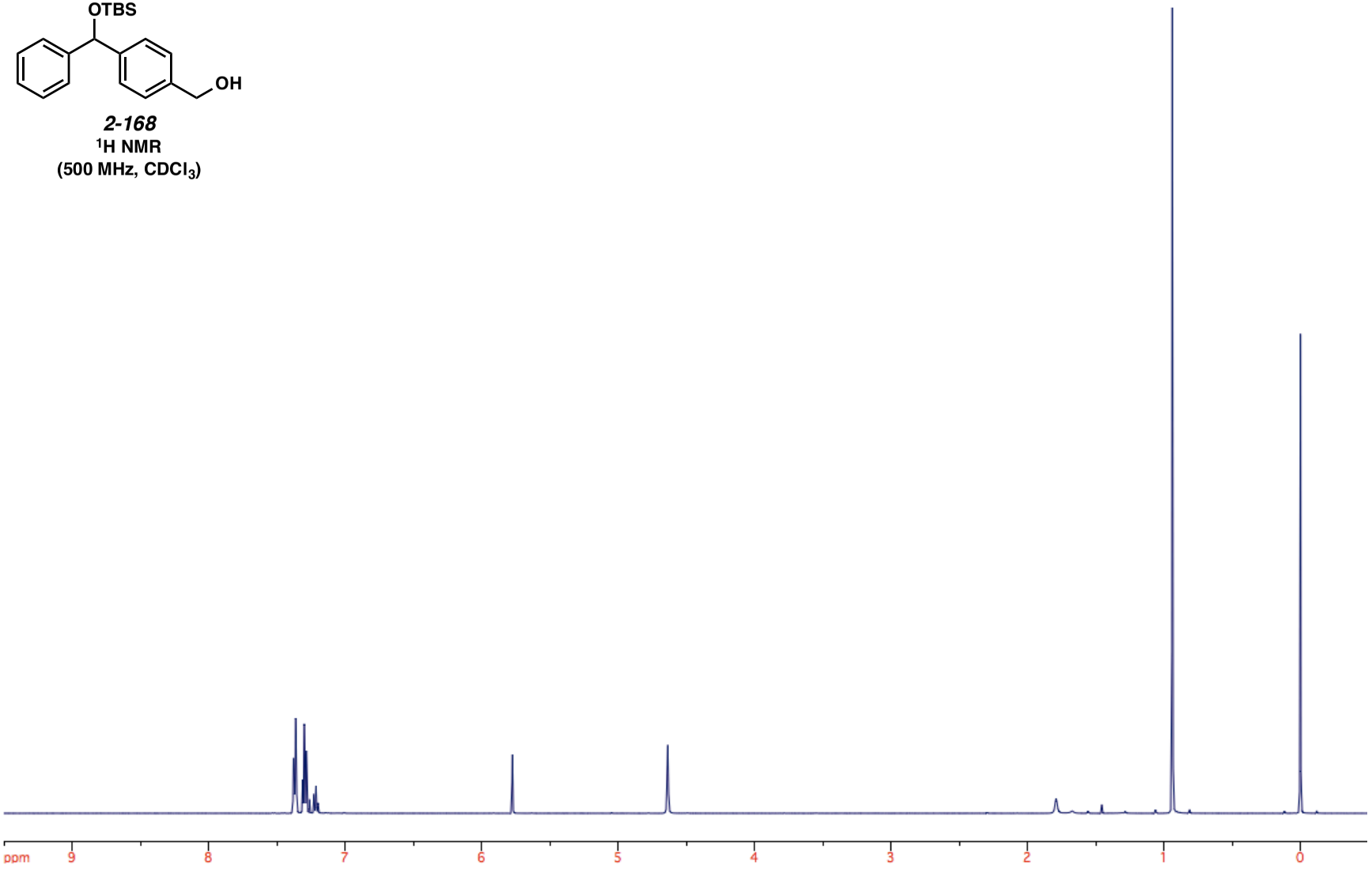

O
O
O
N
2-13p
¹H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

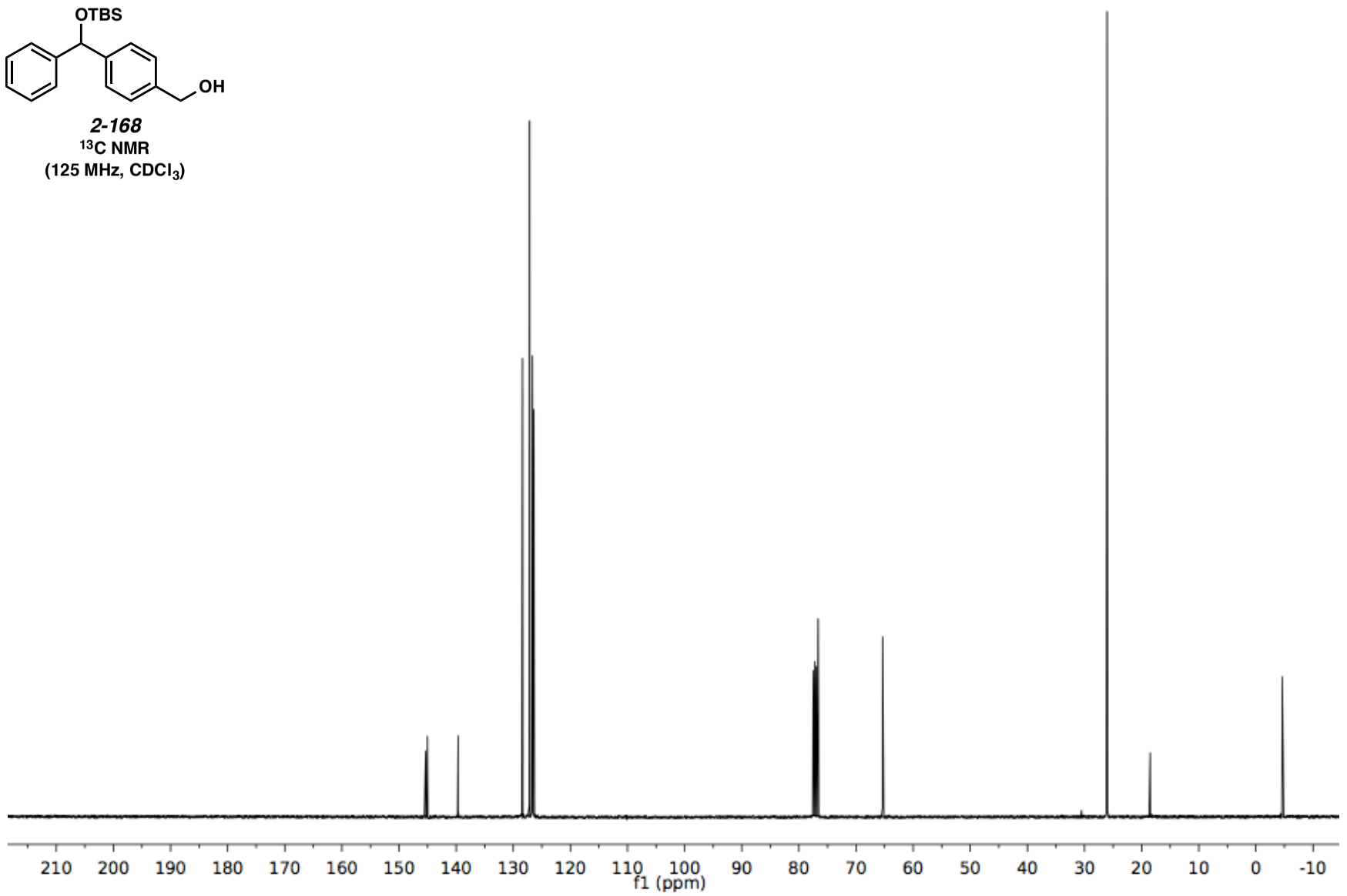

O
O
N
O
2-13p
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


NHTs
O
O
N
2-13q
^{1}H NMR
(400 MHz, $CDCl_3$)
ppm
0
1
2
3
4
5
6
7
8
9

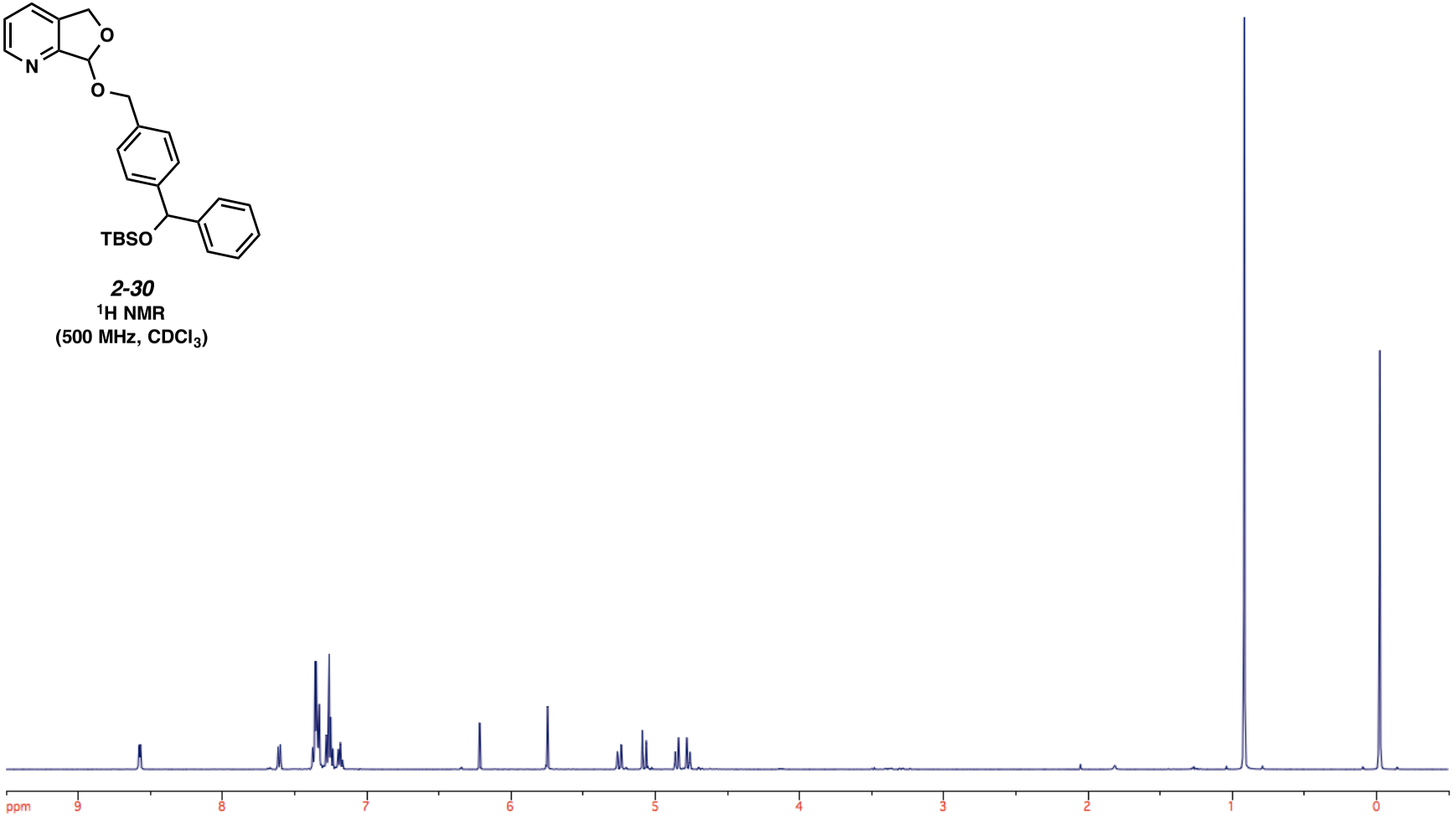

NHTs
O
O
N
2-13q
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

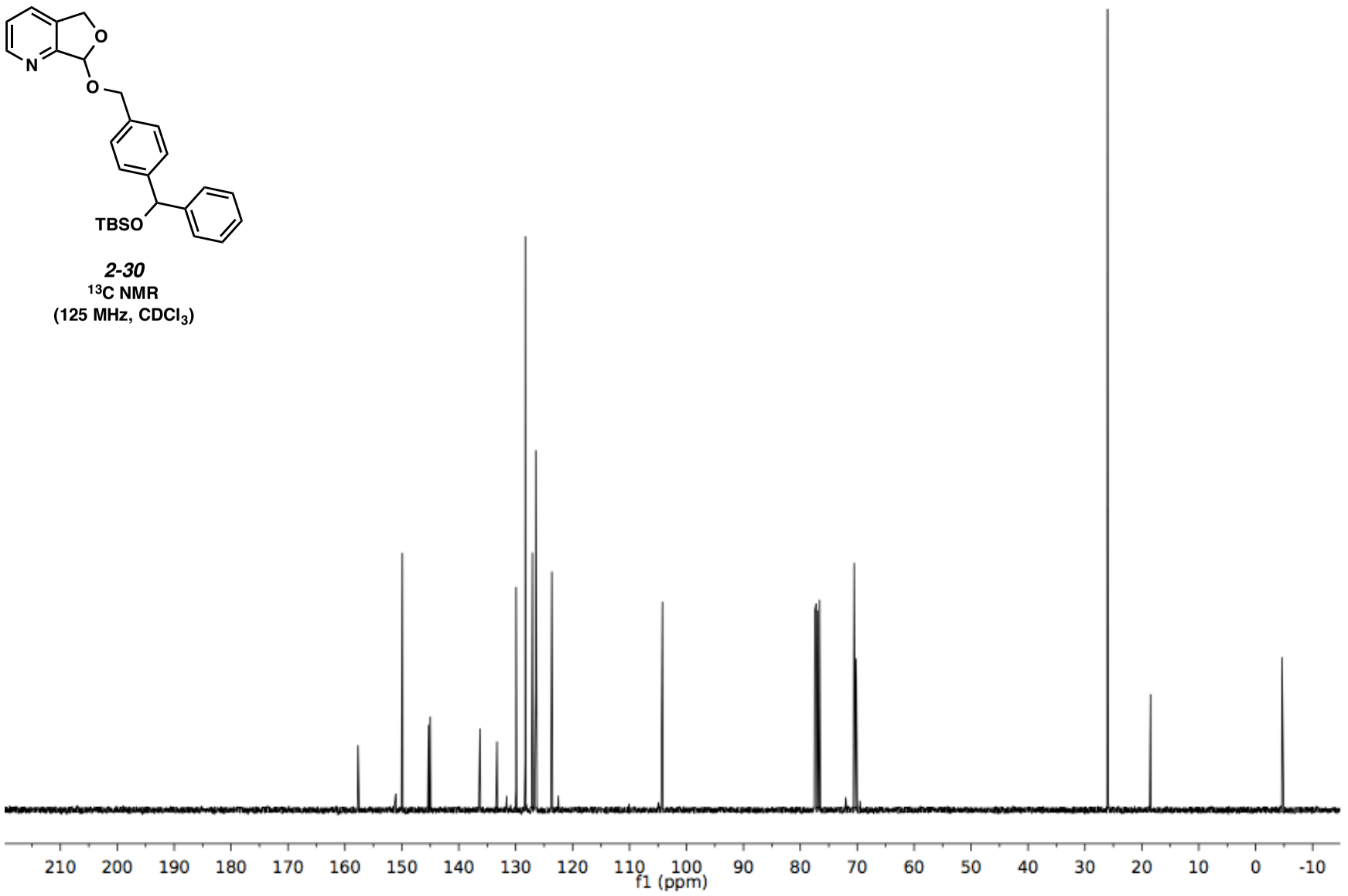
2-168
^{1}H NMR
(500 MHz, $CDCl_3$)

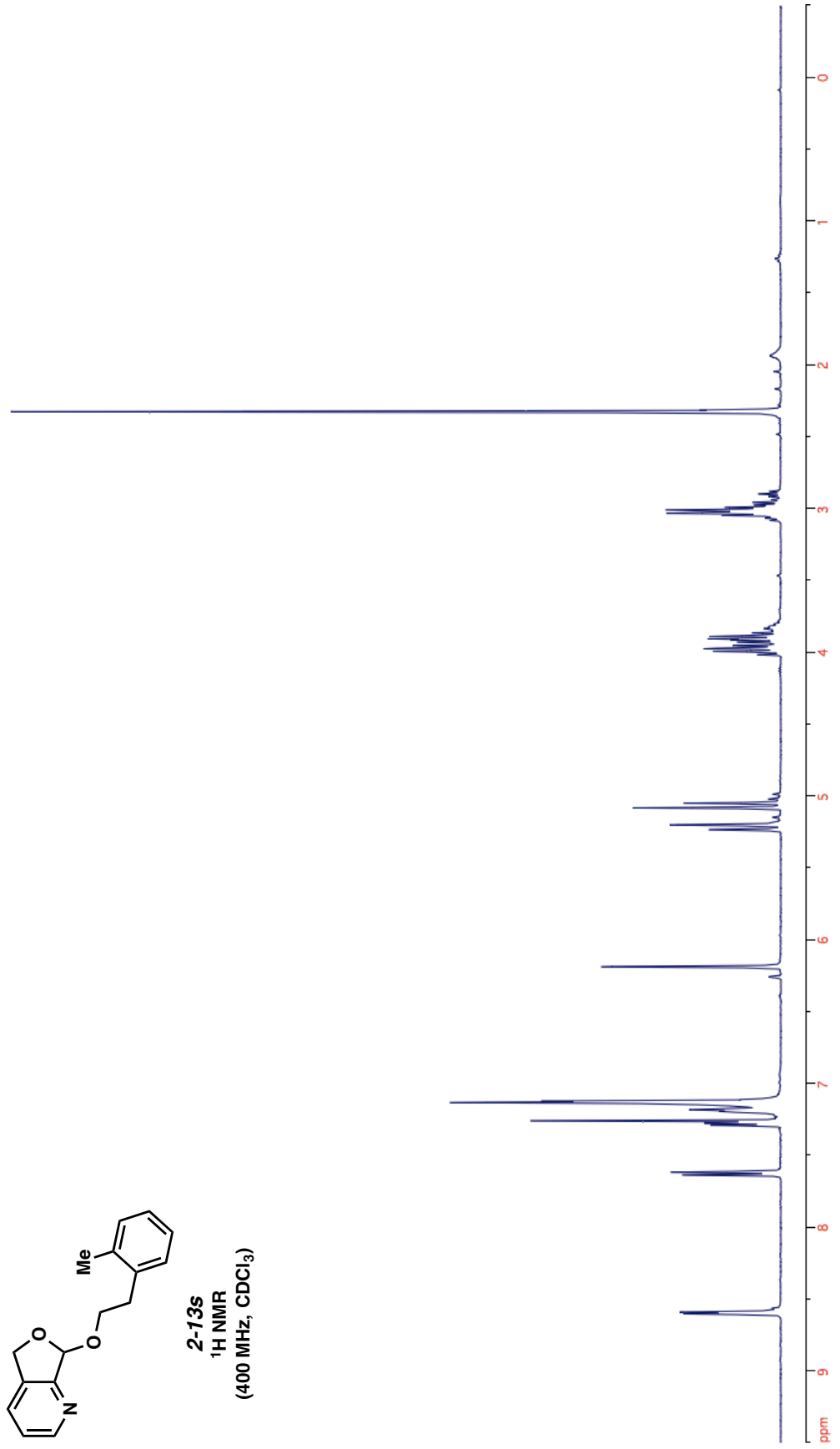


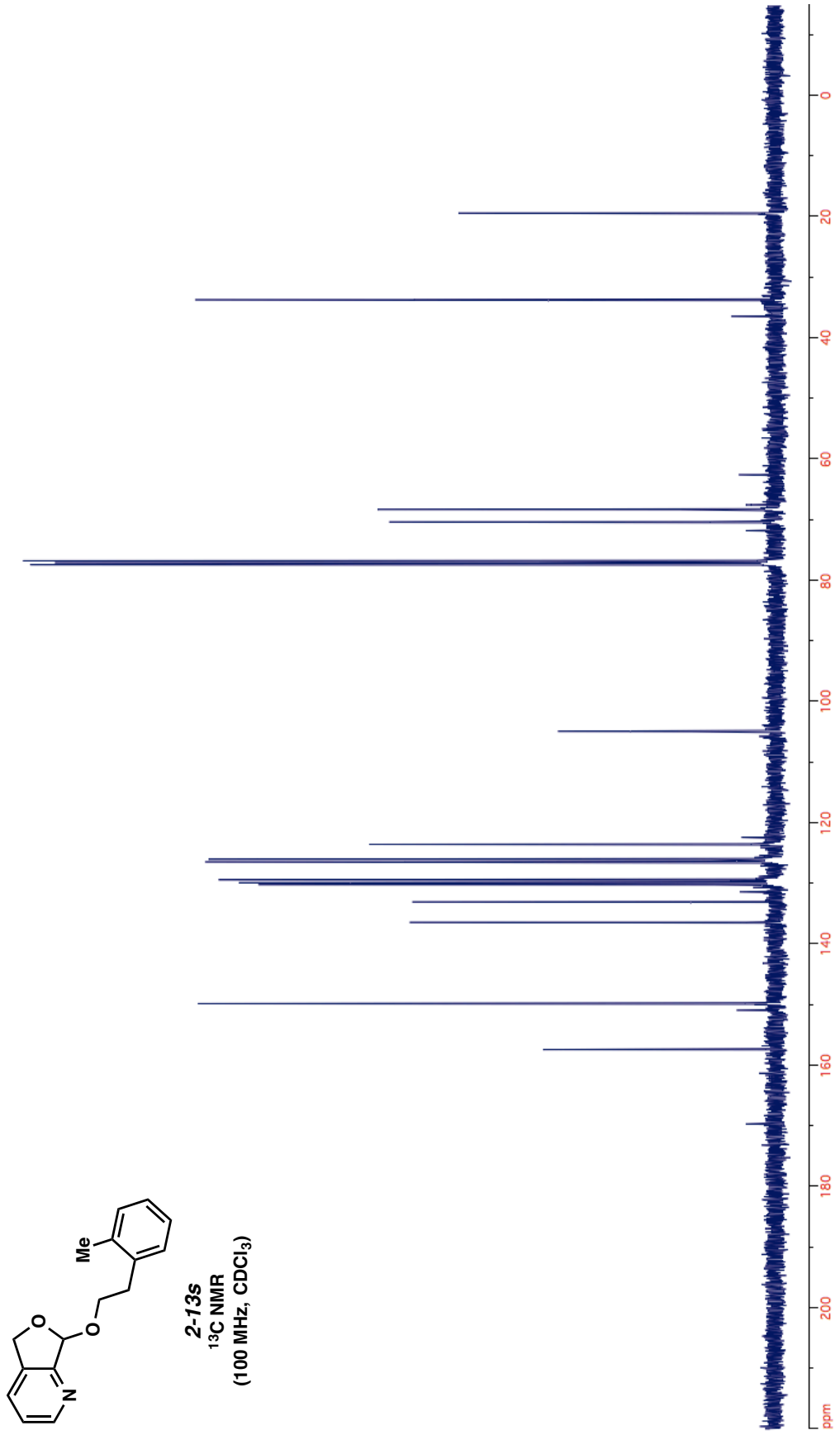

OTBS
OH
2-168
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

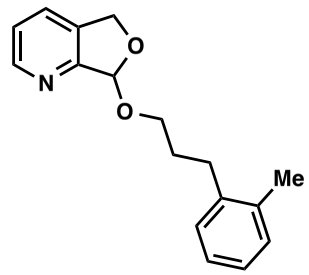
2-30
^{1}H NMR
(500 MHz, $CDCl_3$)



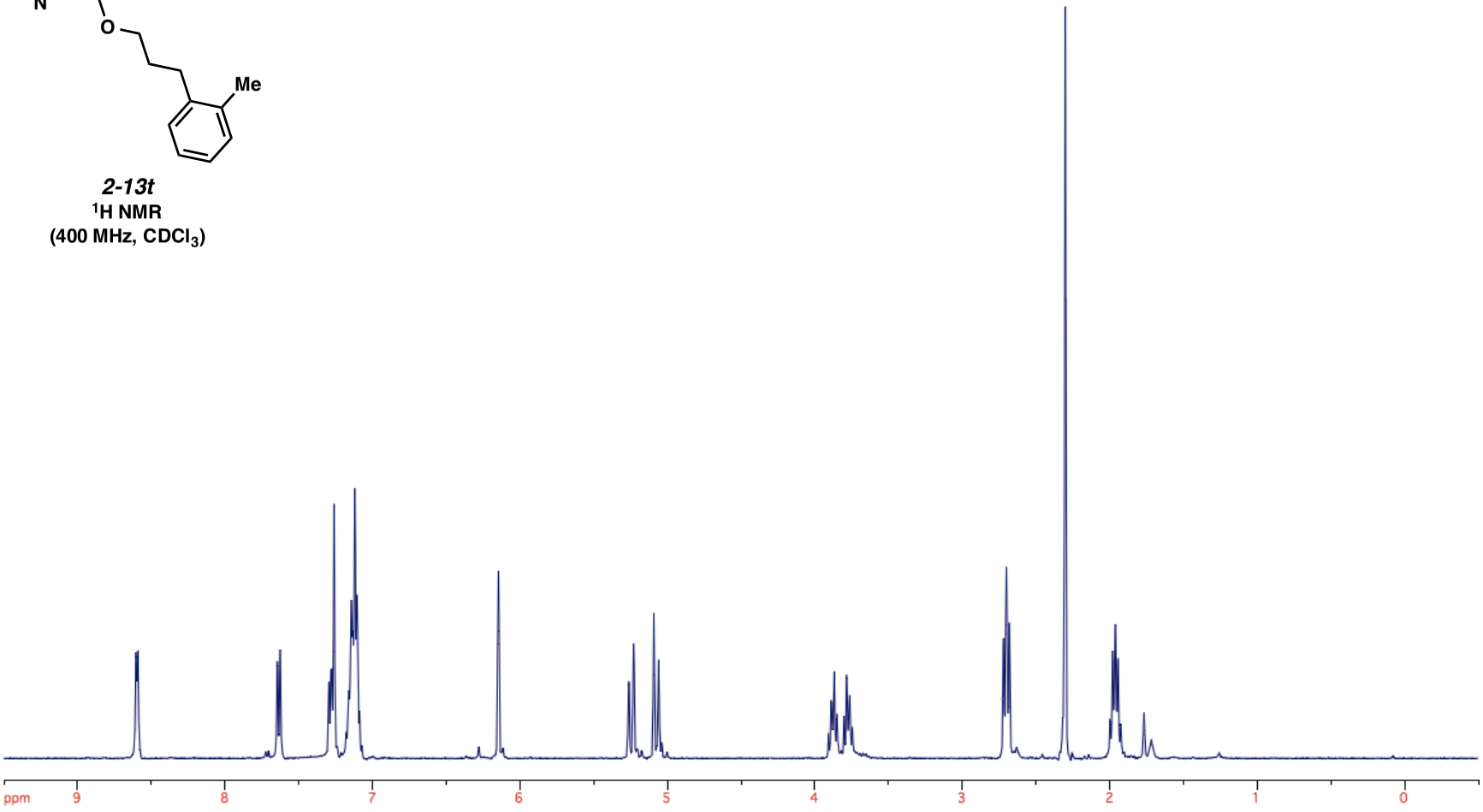

O
N
O
TBSO
2-30
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

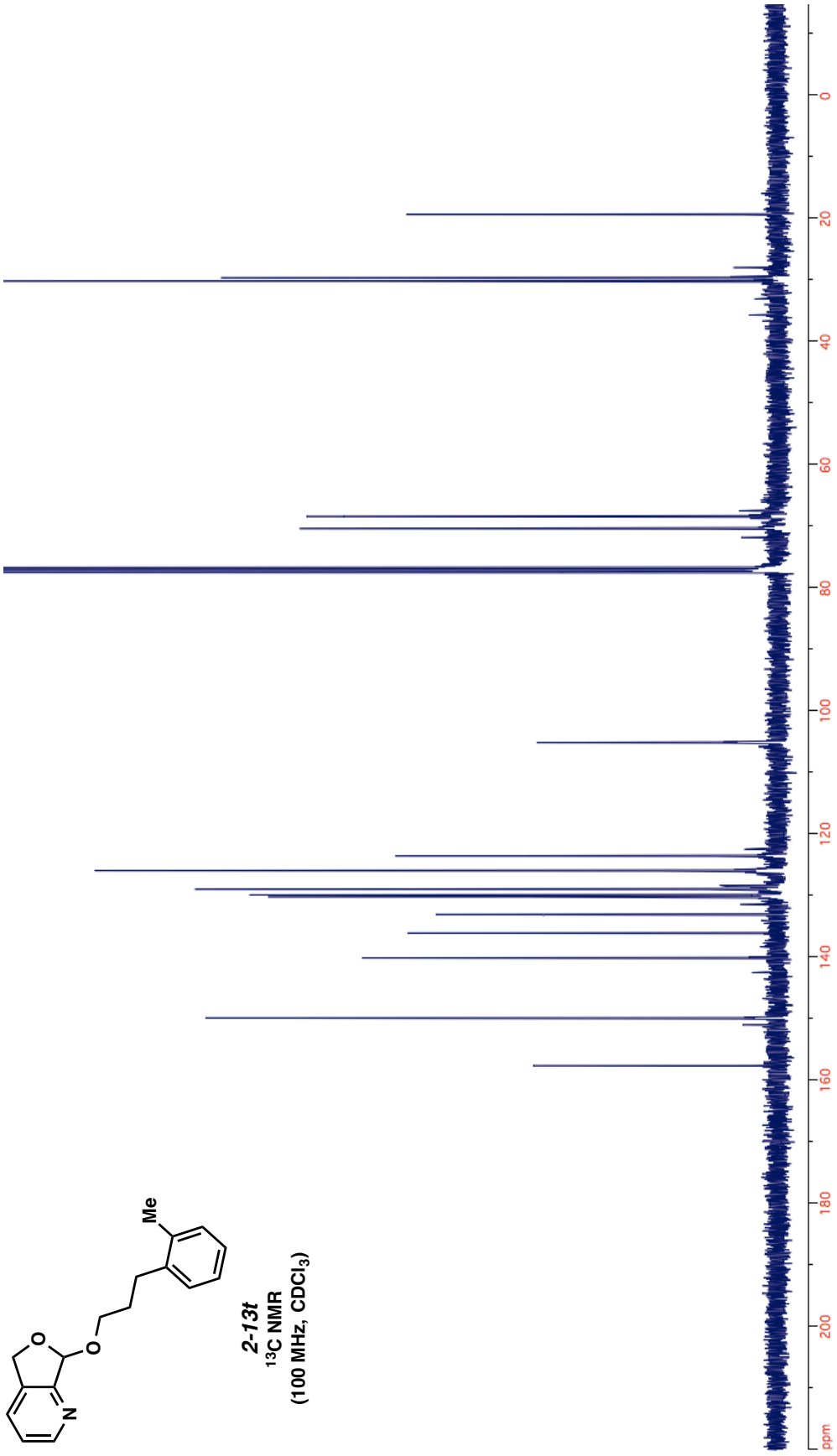

Me
O
O
N
2-13s
¹H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9


Me
O
O
N
2-13s
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

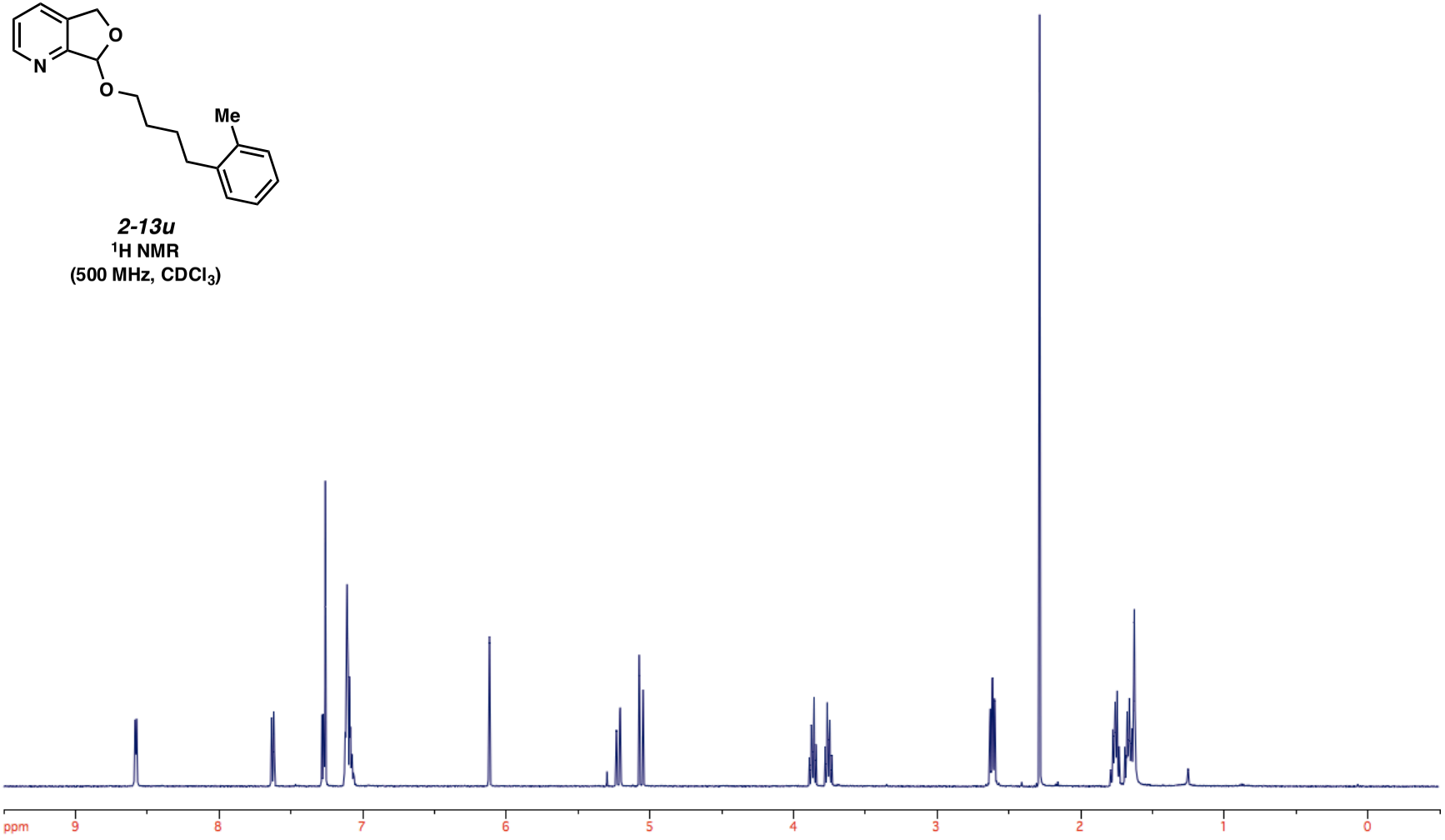


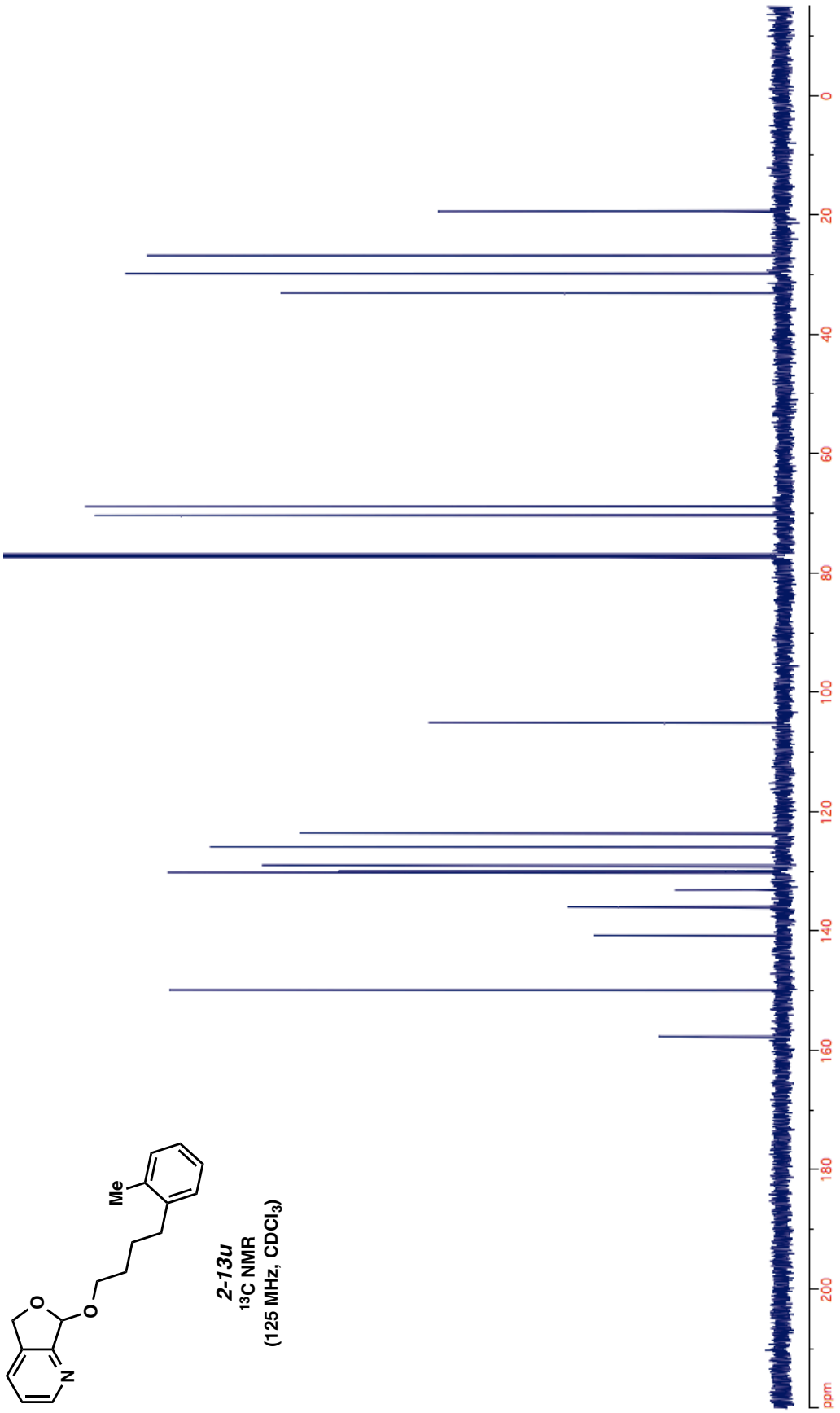
2-13t
^{1}H NMR
(400 MHz, $CDCl_3$)



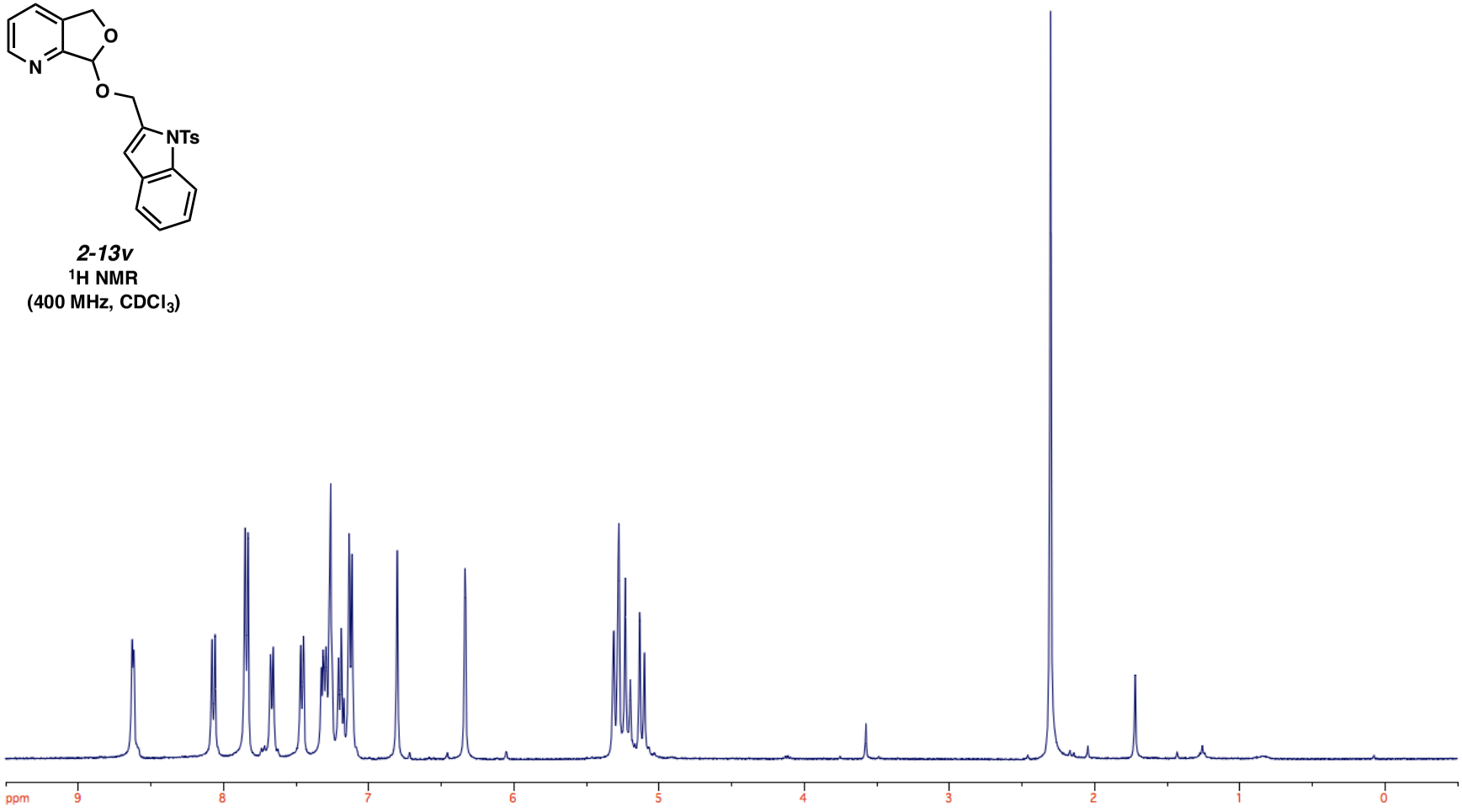

Me
O
O
N
2-13t
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

2-13u
^{1}H NMR
(500 MHz, $CDCl_3$)

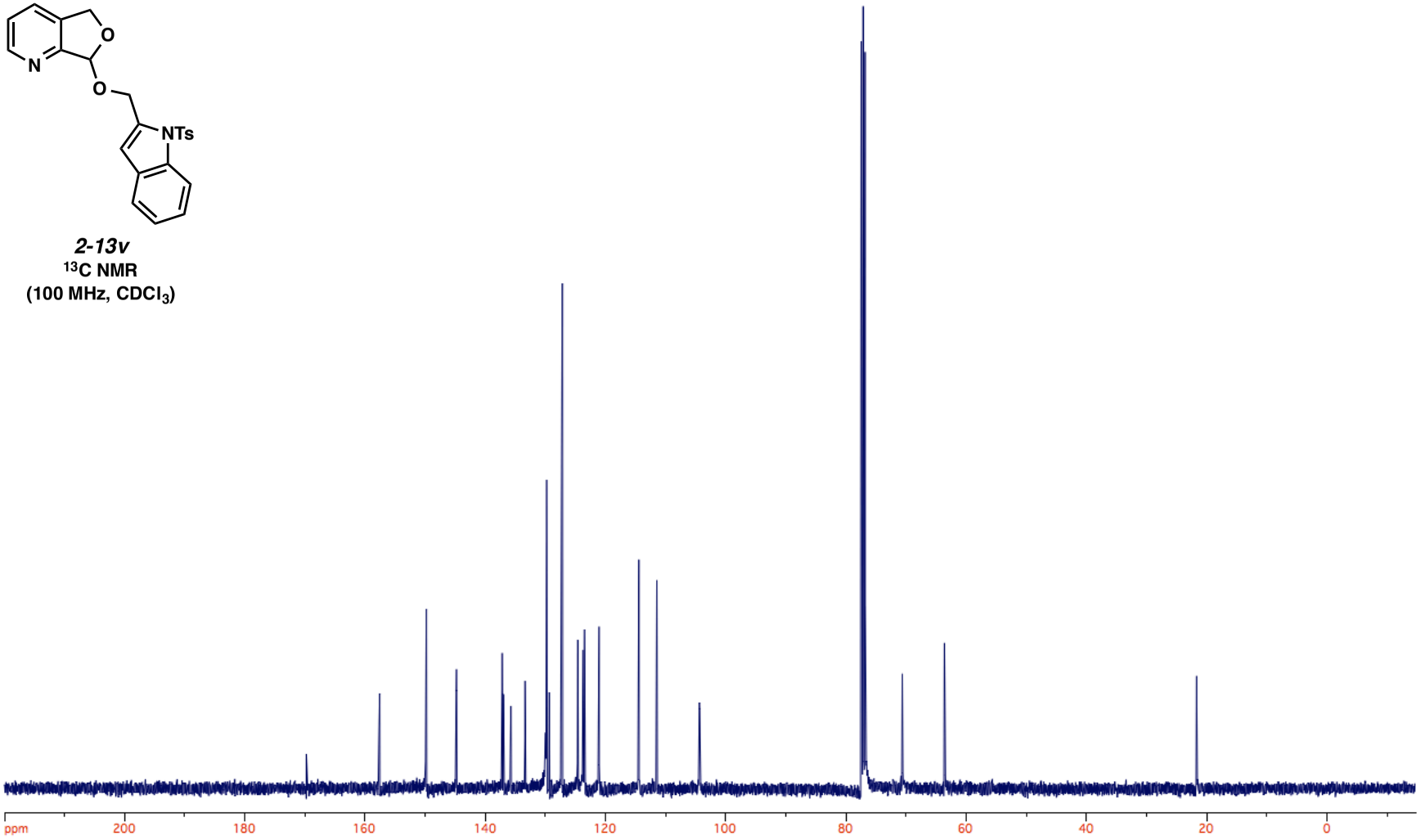


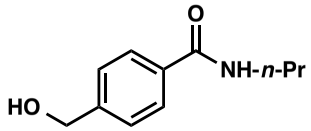

Me
O
O
N
2-13u
13C NMR
(125 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

2-13v
^{1}H NMR
(400 MHz, $CDCl_3$)

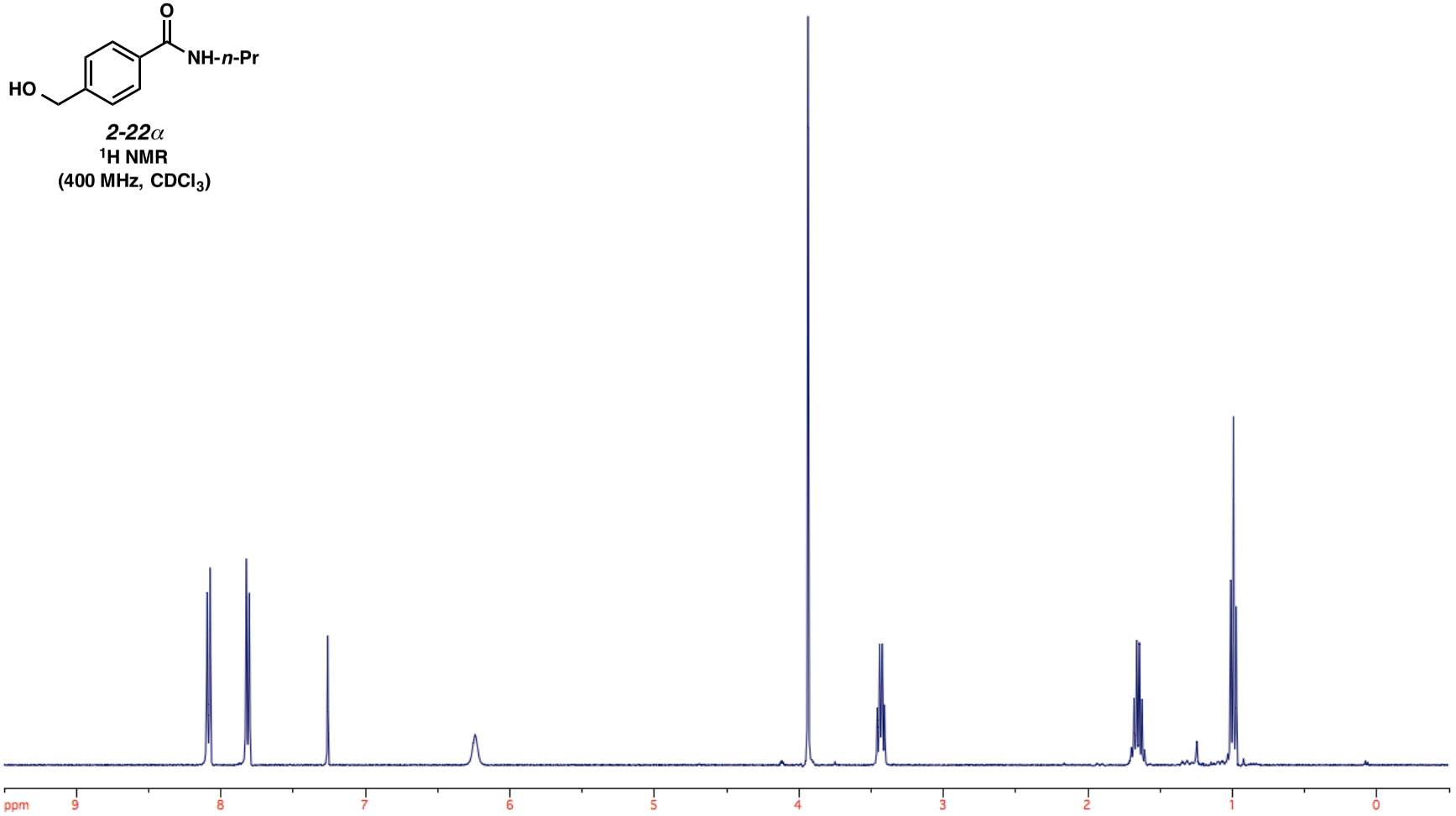


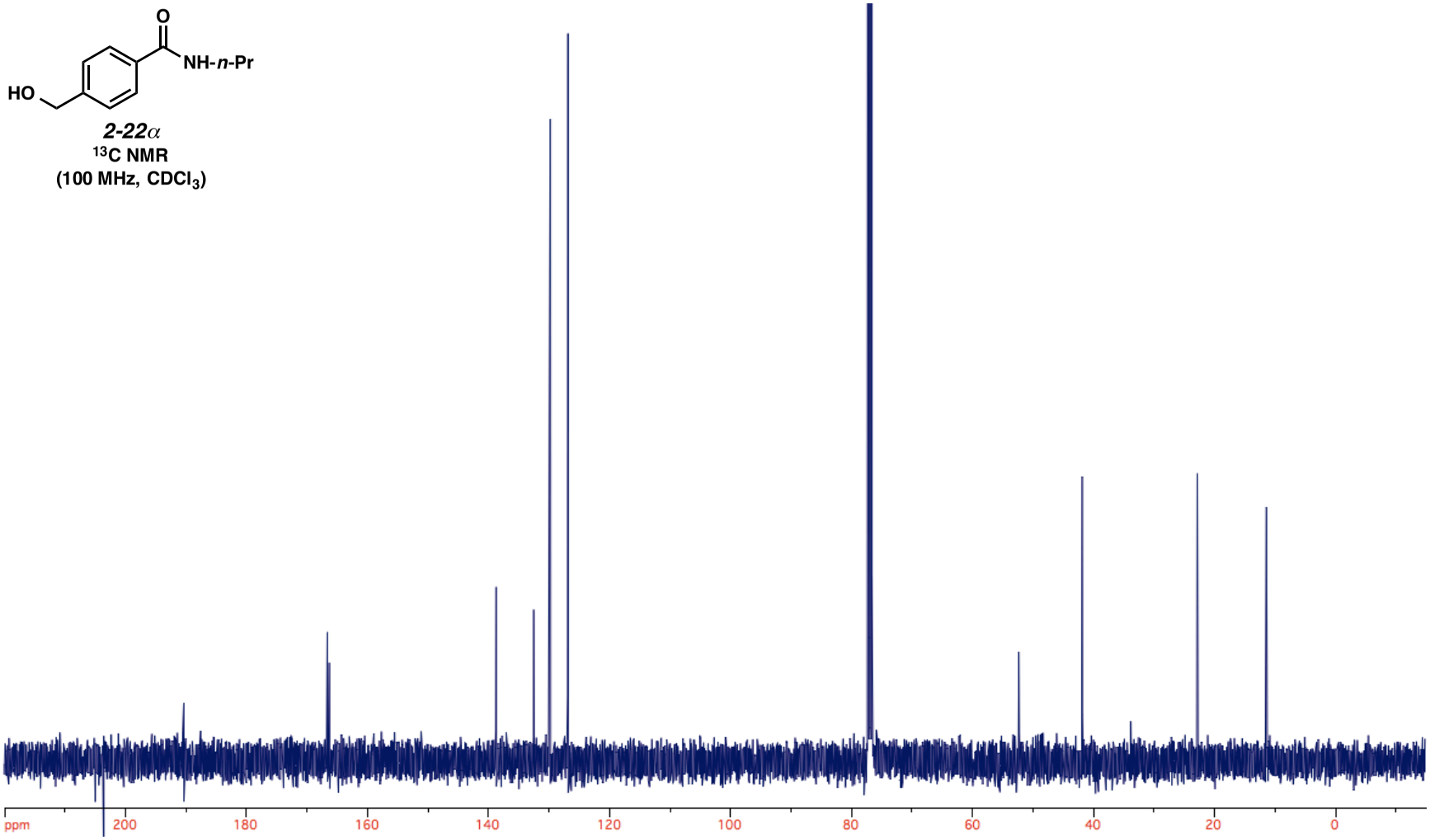
2-13v
^{13}C NMR
(100 MHz, $CDCl_3$)



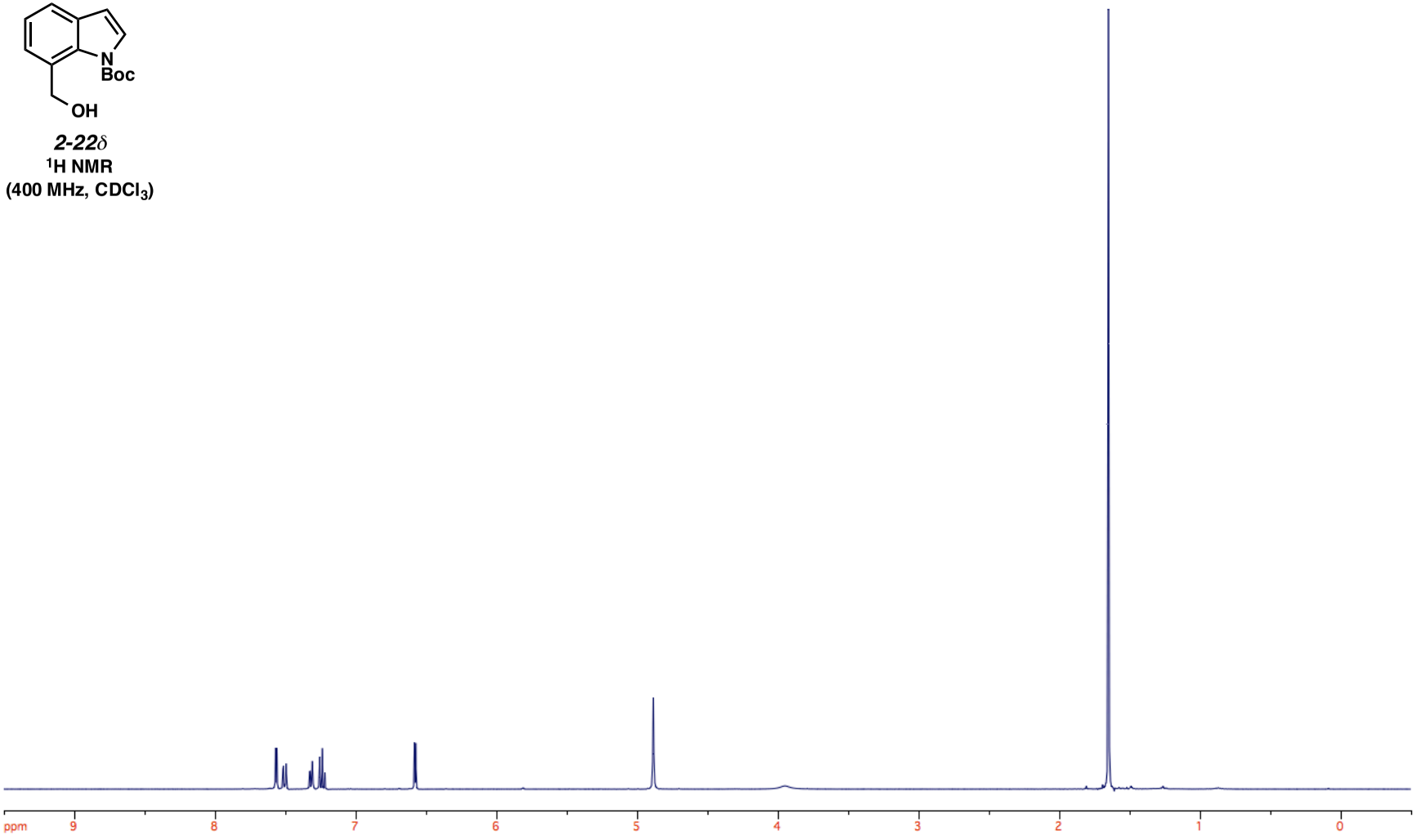


2-22α
^{1}H NMR
(400 MHz, $CDCl_3$)

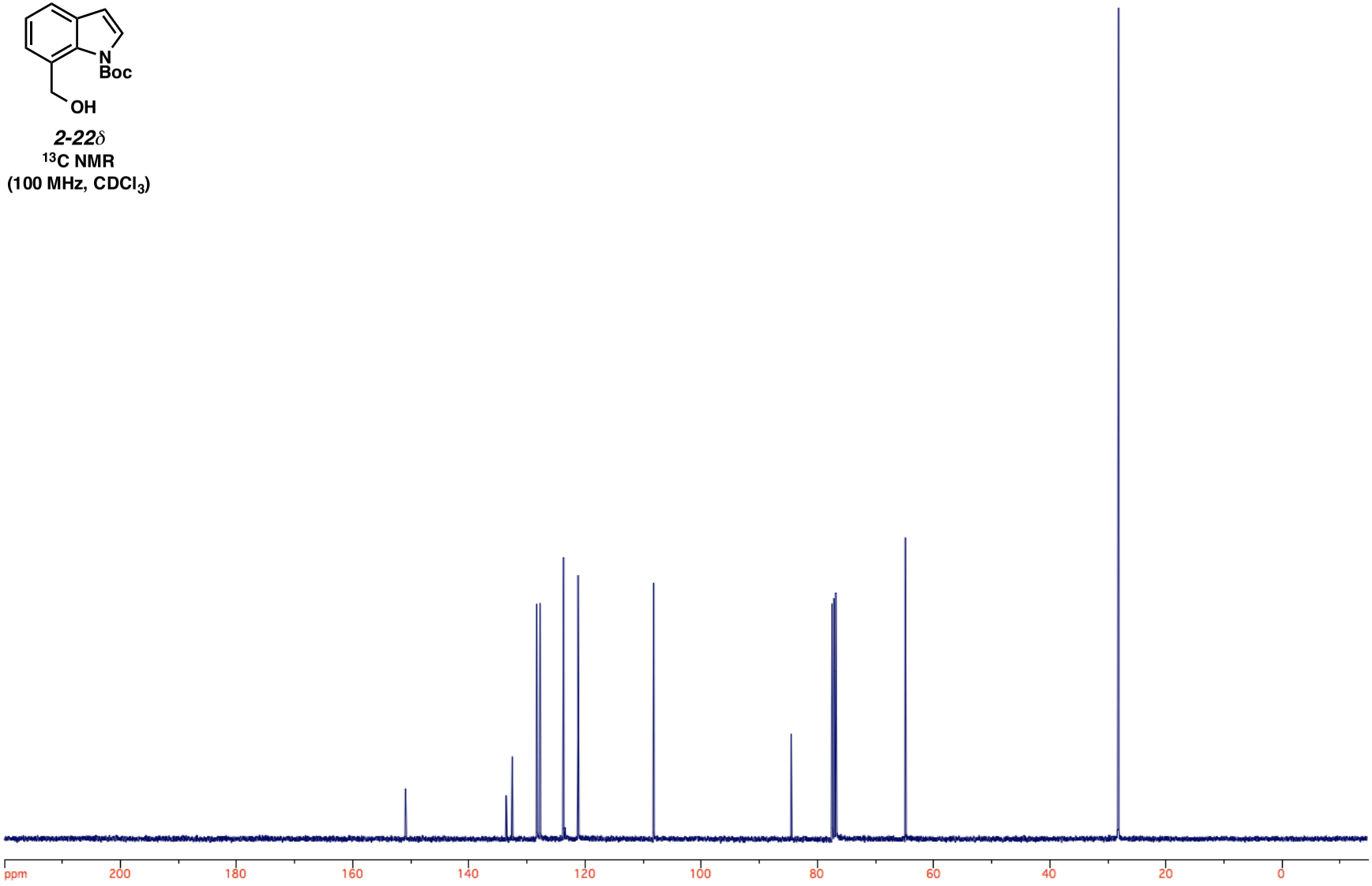


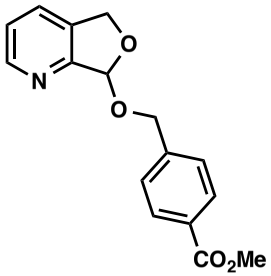

O
NH-n-Pr
HO
2-22α
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

2-22δ
^{1}H NMR
(400 MHz, $CDCl_3$)

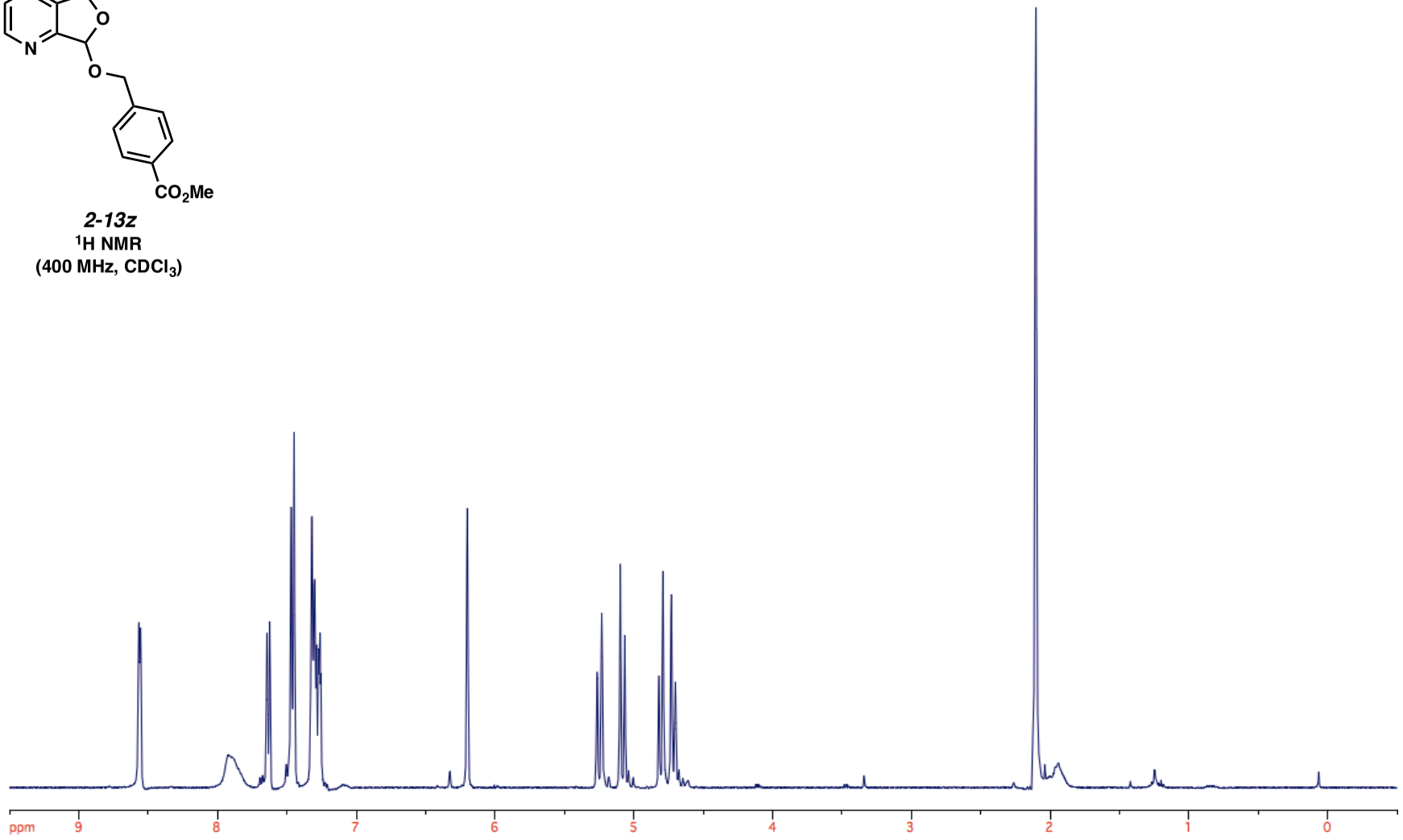


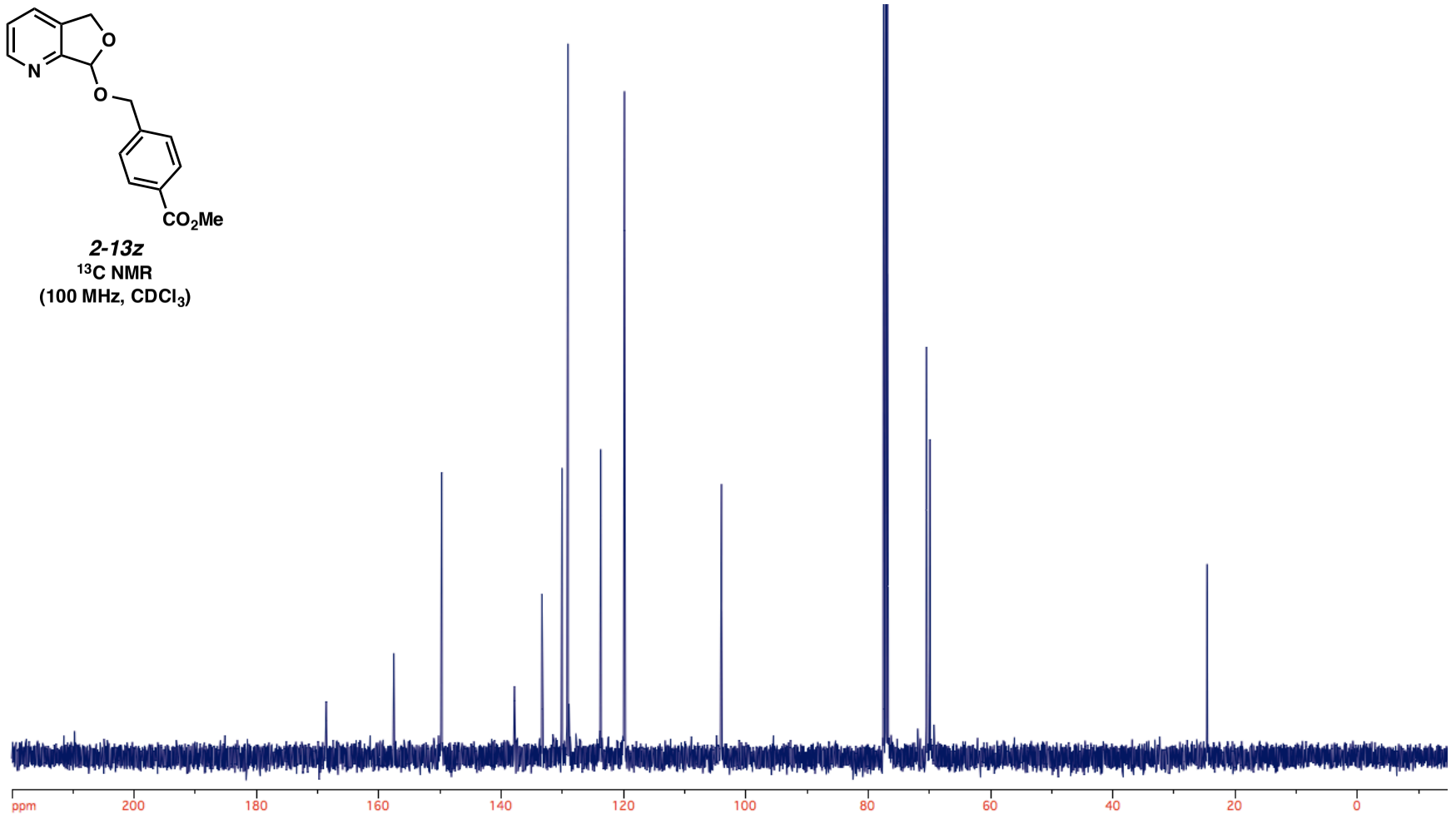
2-22δ
^{13}C NMR
(100 MHz, $CDCl_3$)





2-13z
^{1}H NMR
(400 MHz, $CDCl_3$)

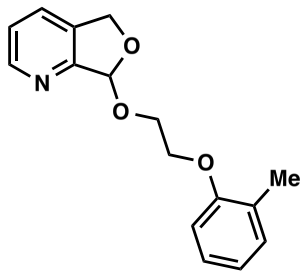




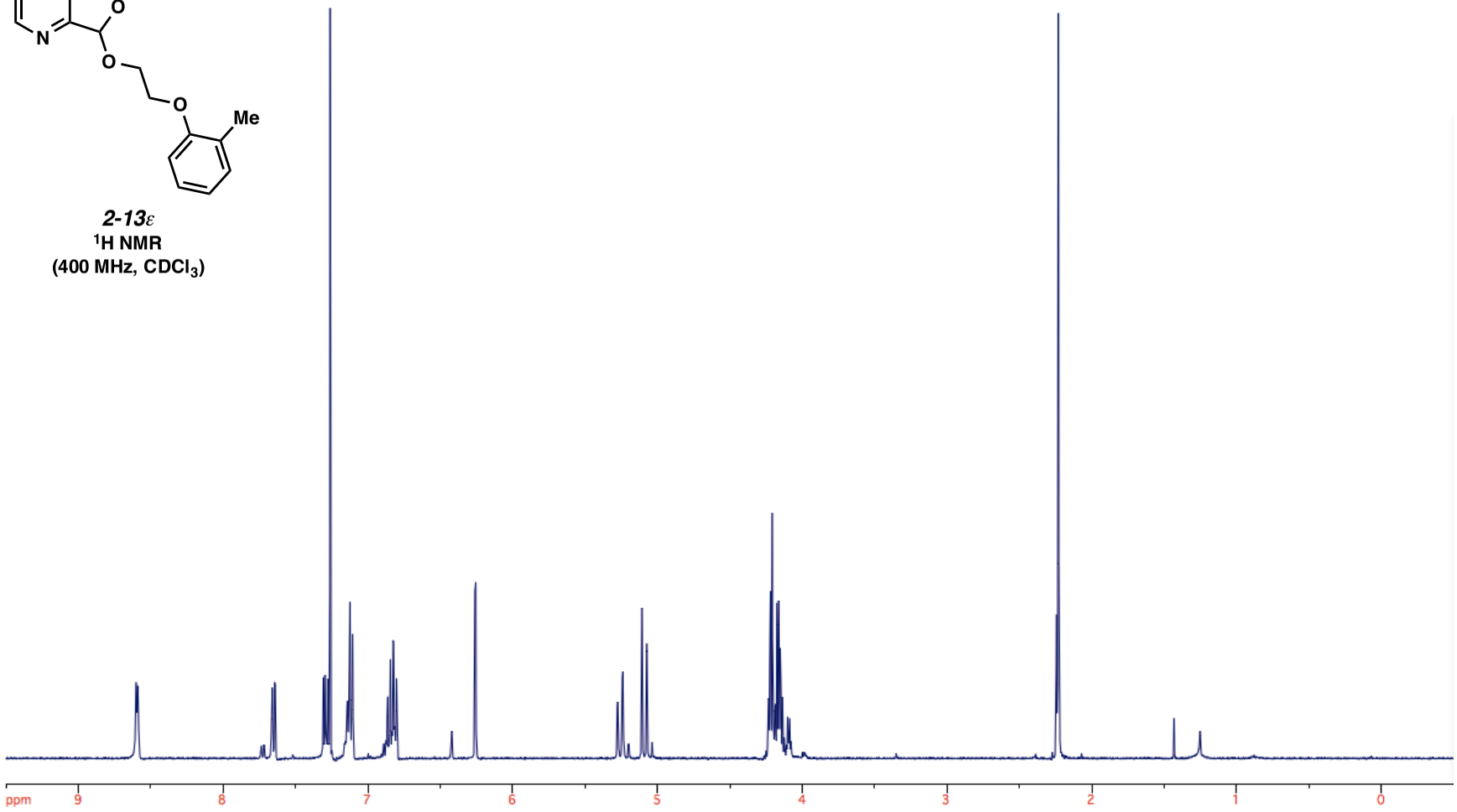
2-13z

^{13}C NMR

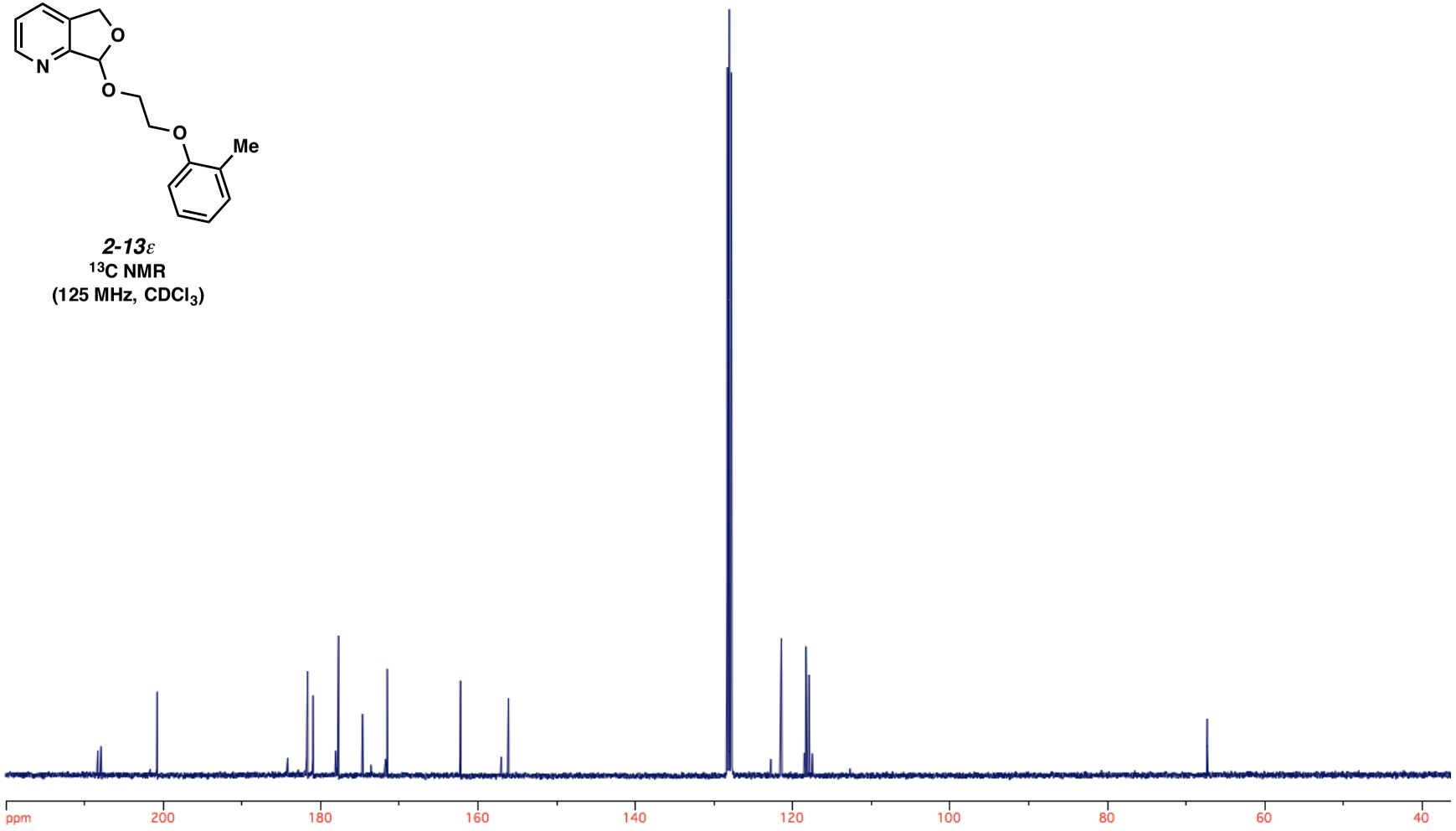
(100 MHz, $CDCl_3$)

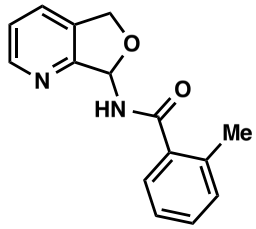


2-13ε
^{1}H NMR
(400 MHz, $CDCl_3$)



2-13ε
^{13}C NMR
(125 MHz, $CDCl_3$)

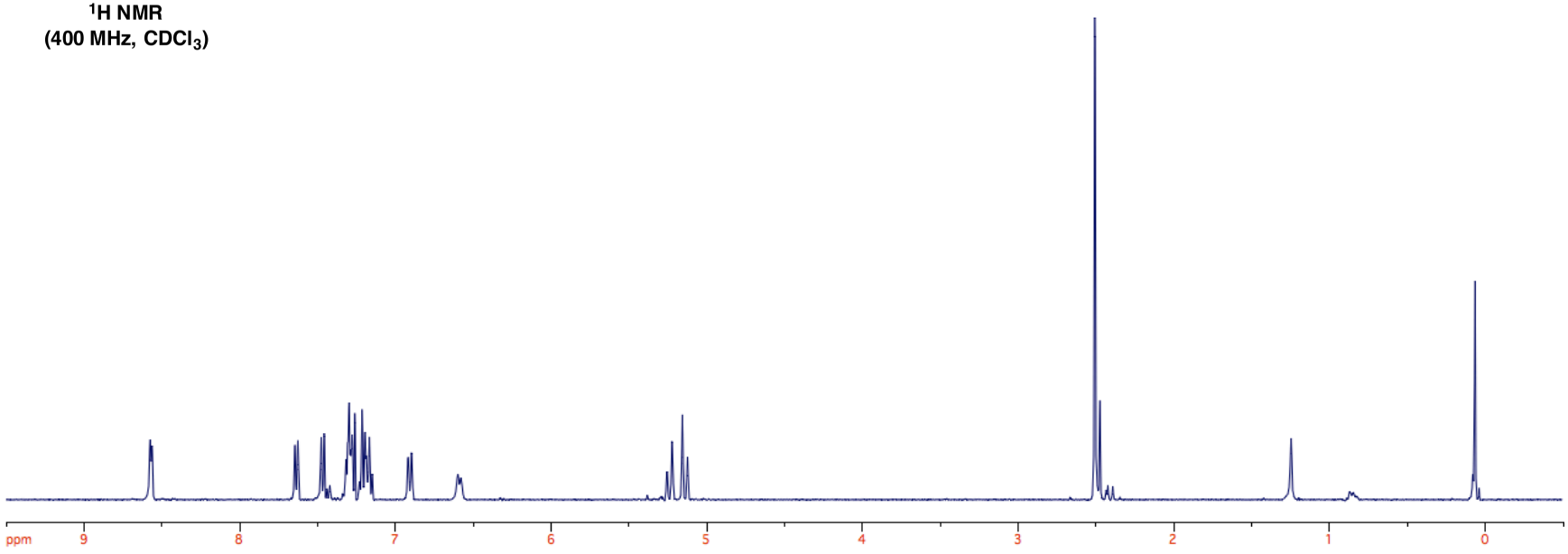


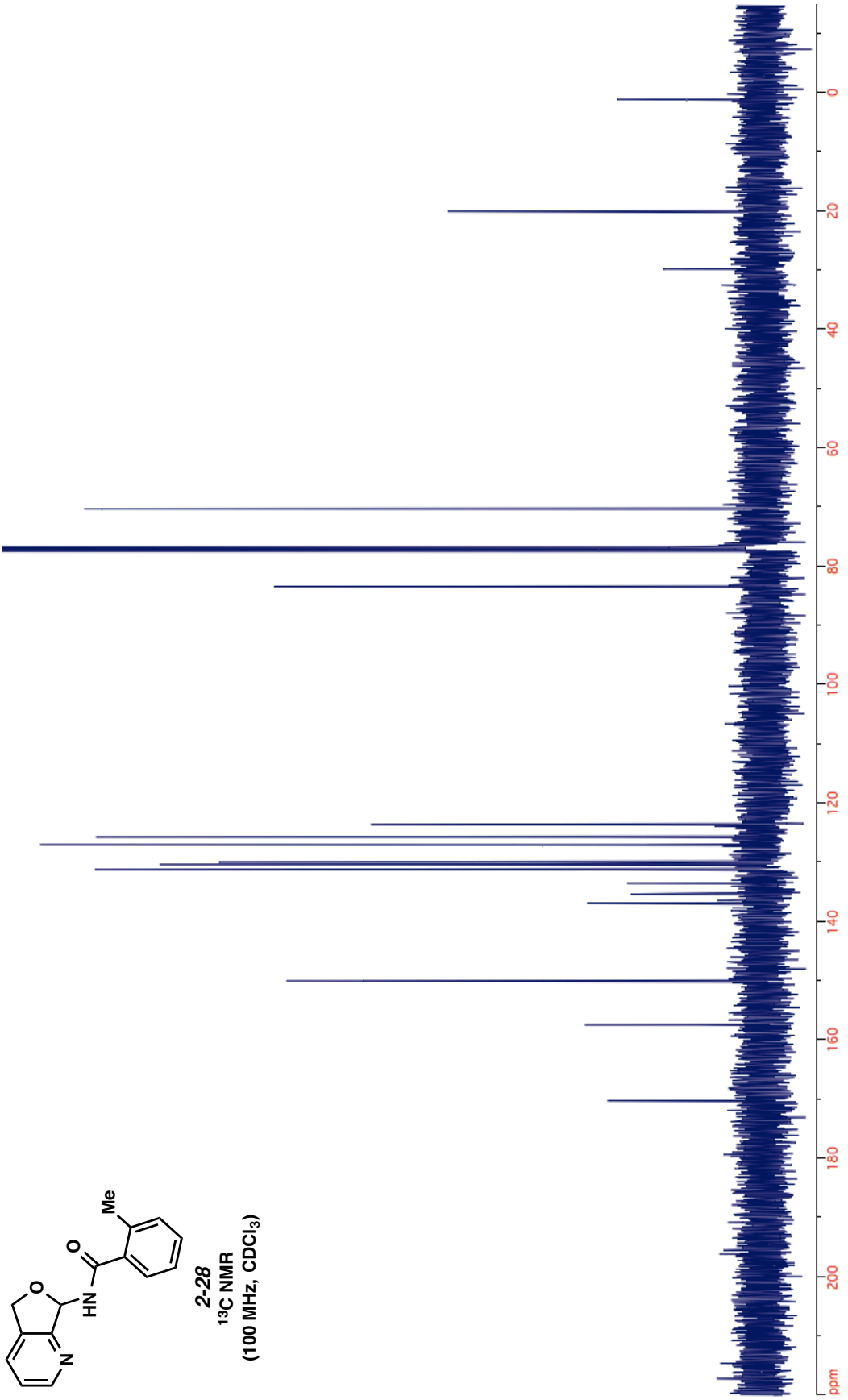


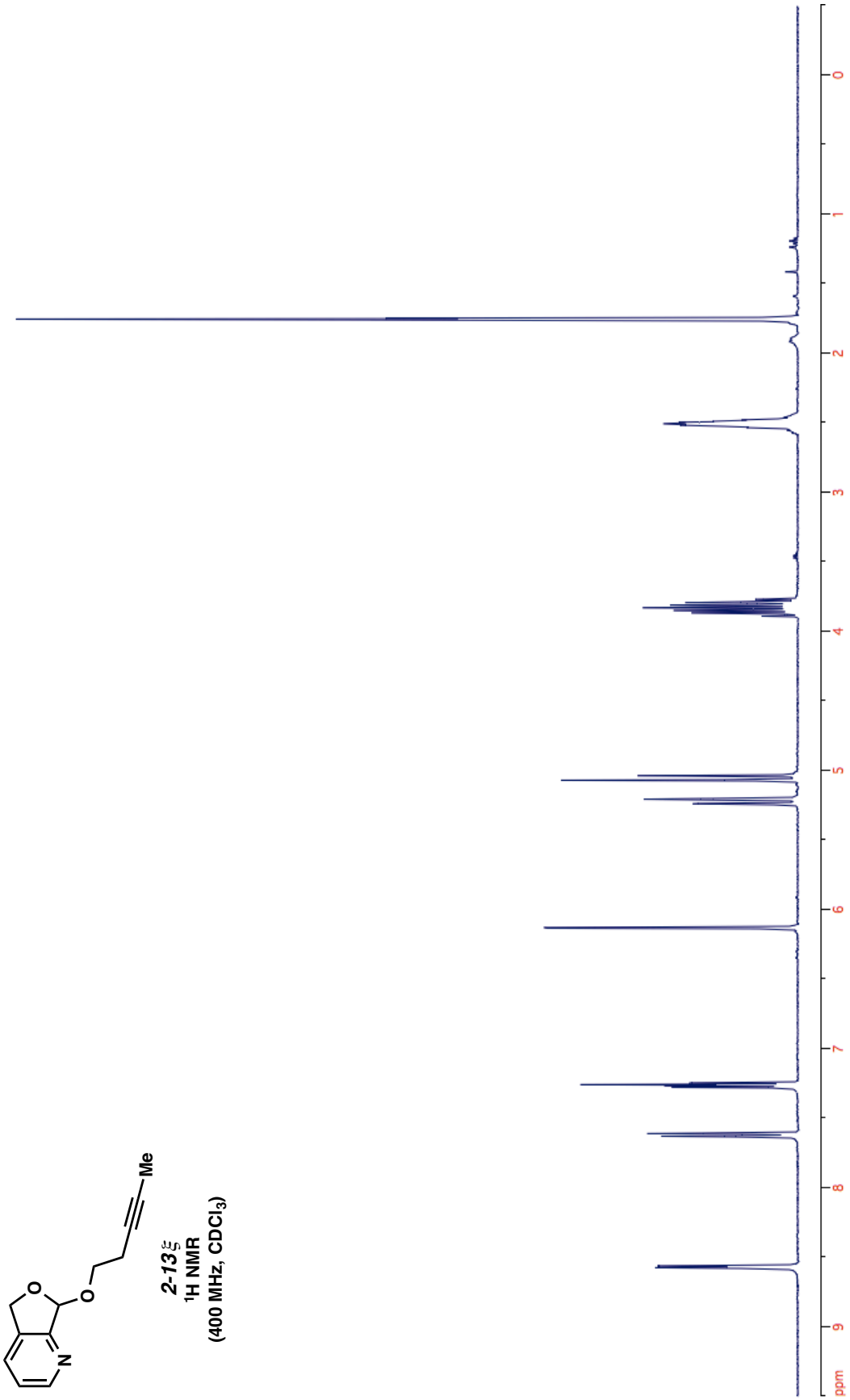
2-28

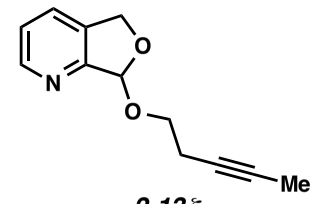
^{1}H NMR

(400 MHz, $CDCl_3$)

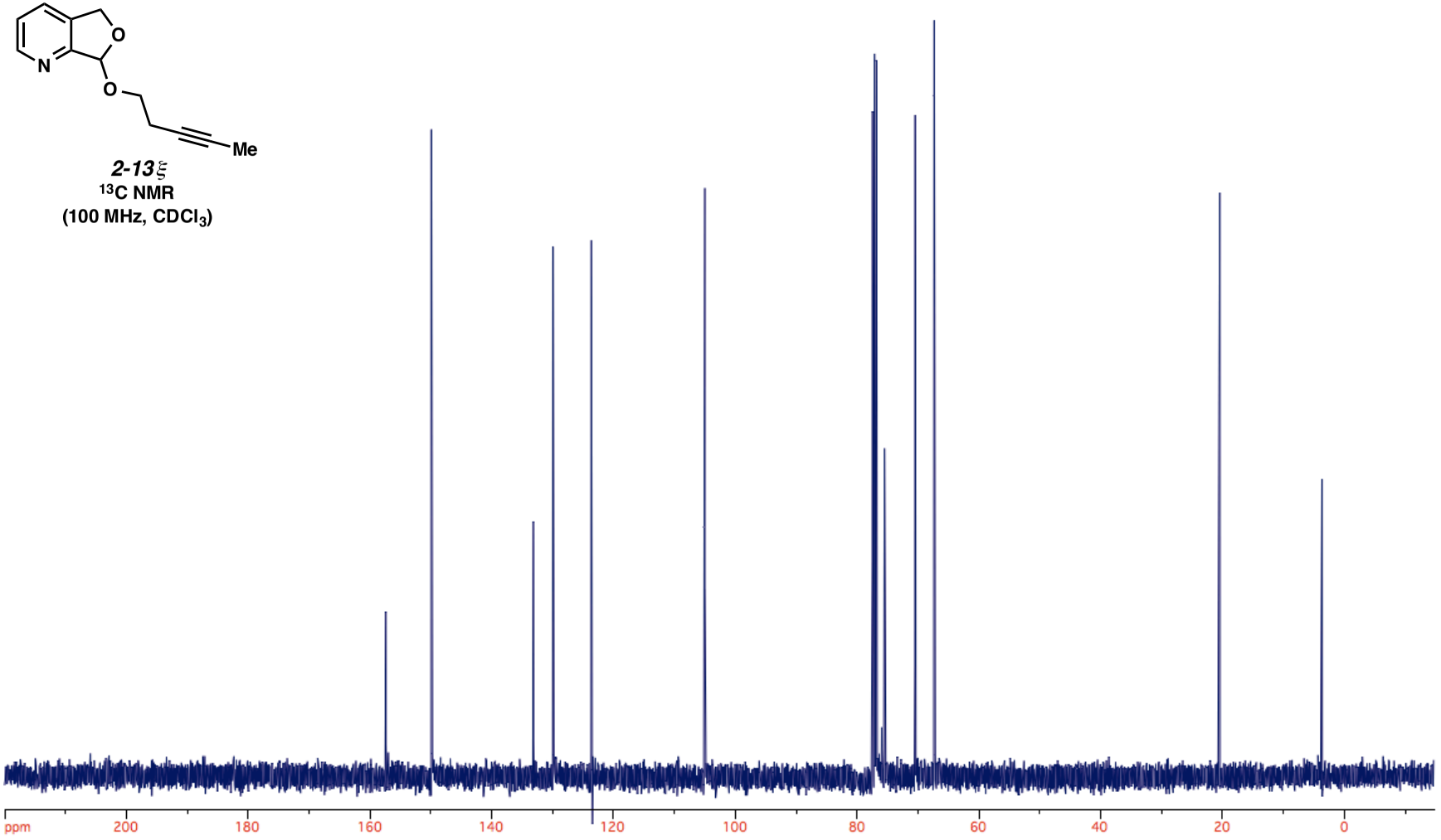



Me
O
HN
O
N
2-28
^{13}C NMR
(100 MHz, $CDCl_3$)
0
20
40
60
80
100
120
140
160
180
200
ppm


Me
O
O
N
2-13ξ
¹H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0



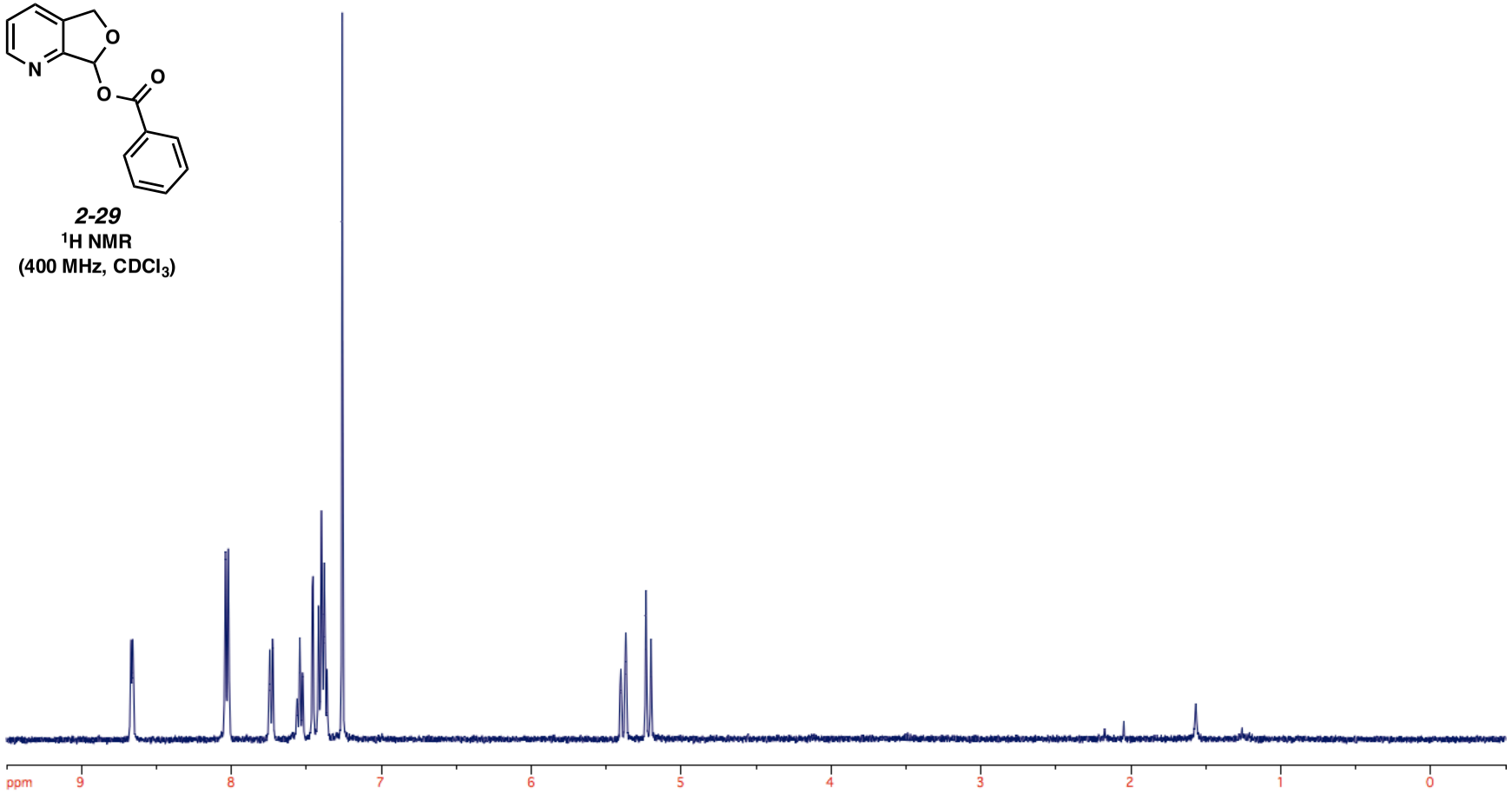
2-13ξ
^{13}C NMR
(100 MHz, $CDCl_3$)



2-29

^{1}H NMR

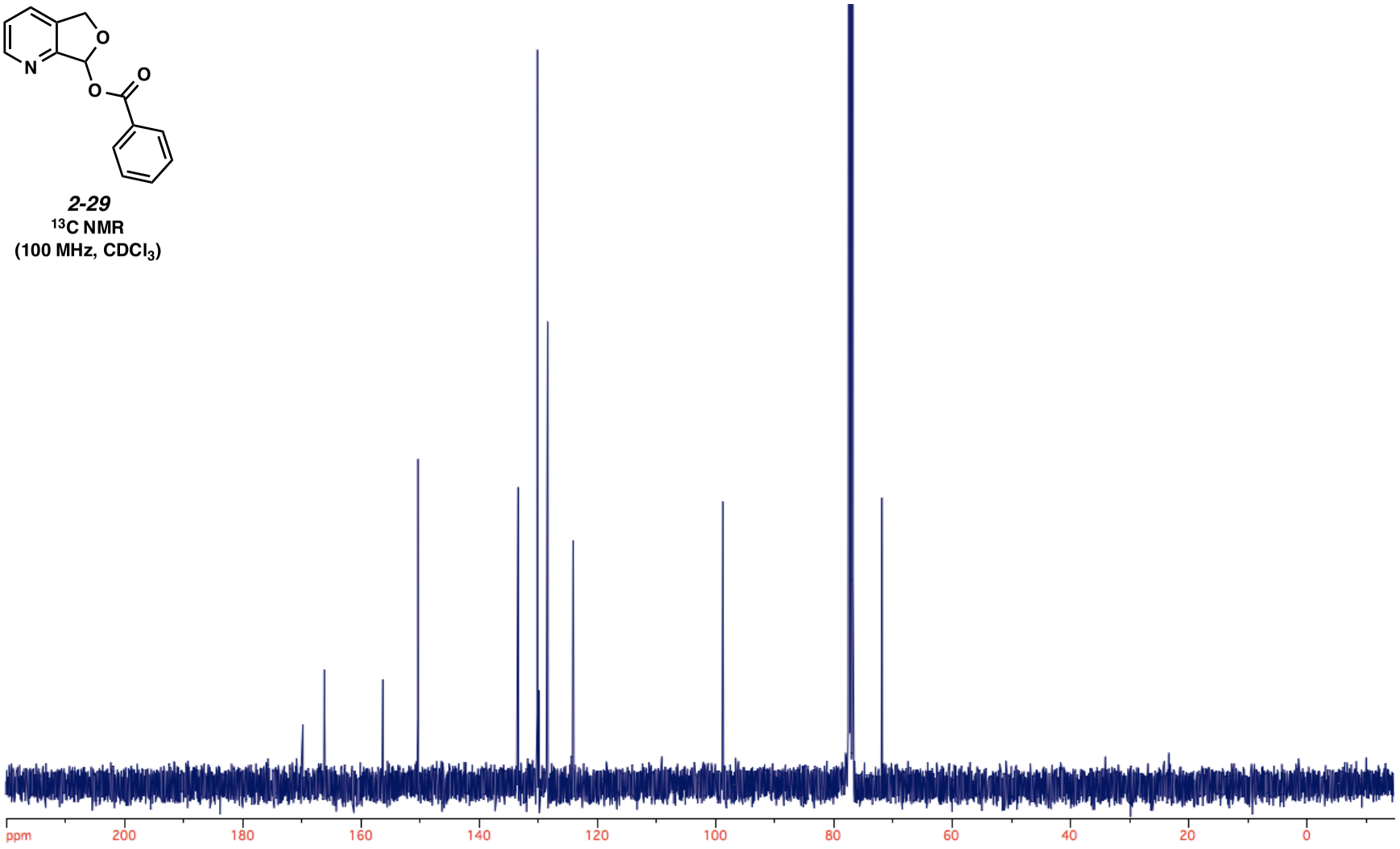
(400 MHz, $CDCl_3$)



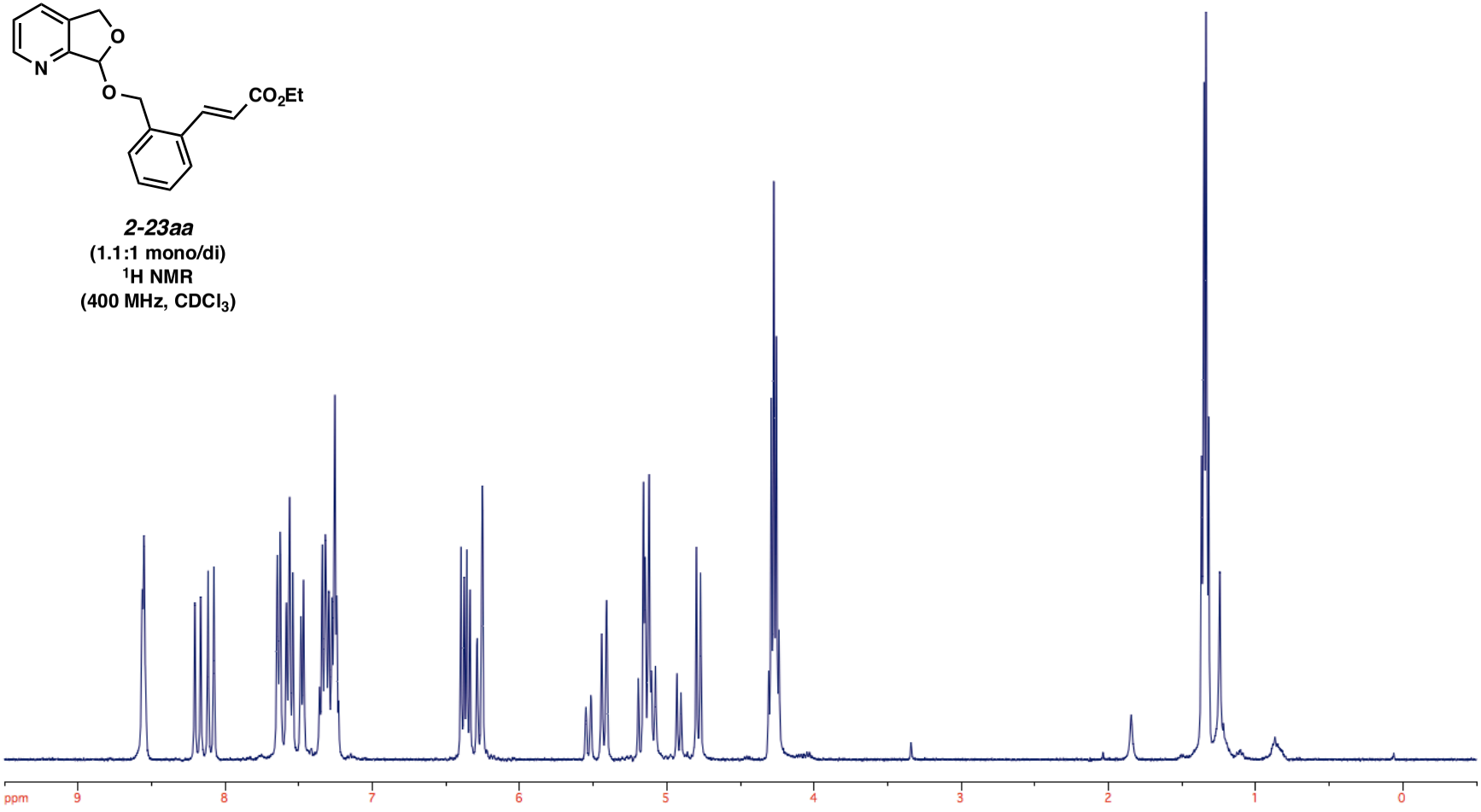
2-29

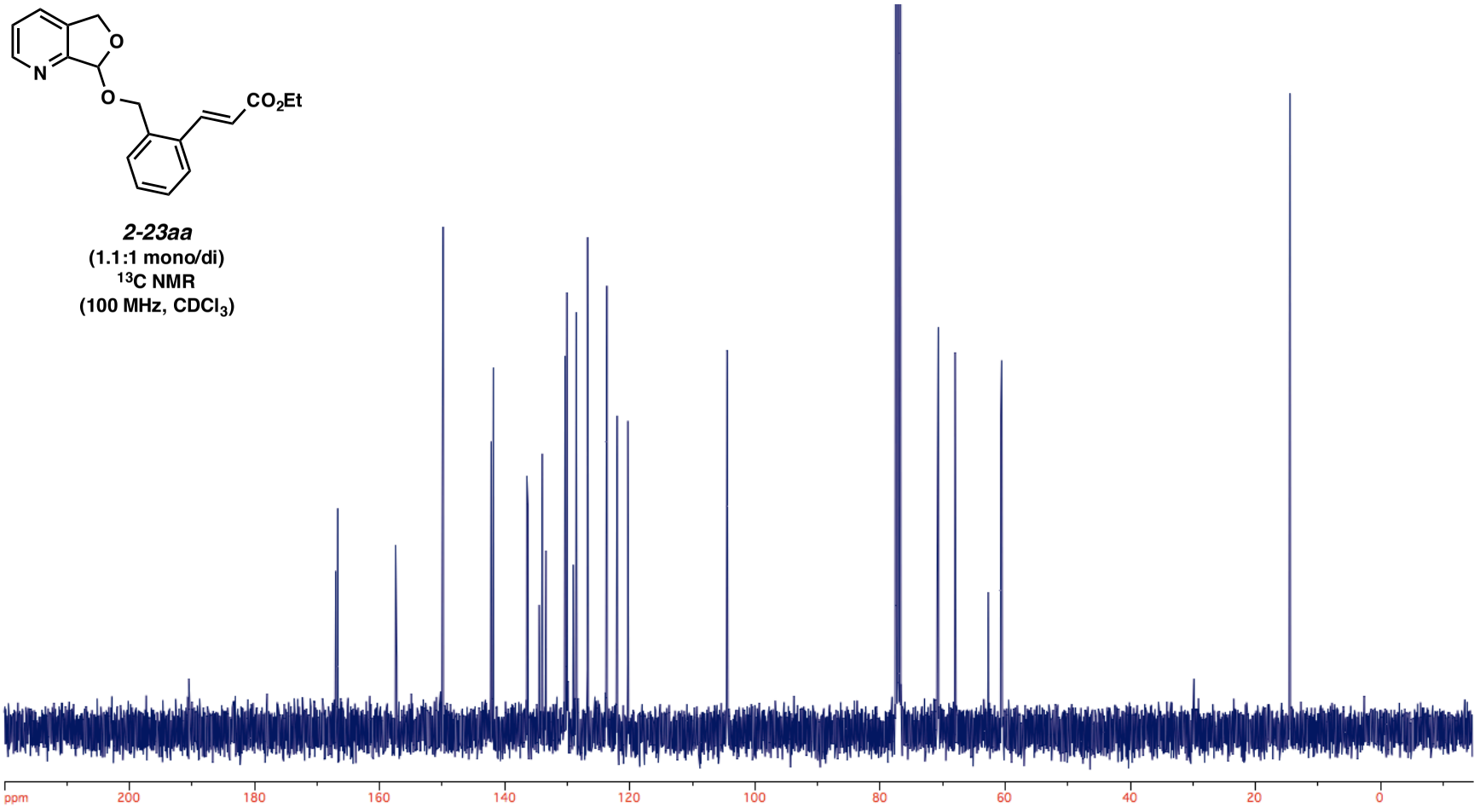
^{13}C NMR

(100 MHz, $CDCl_3$)

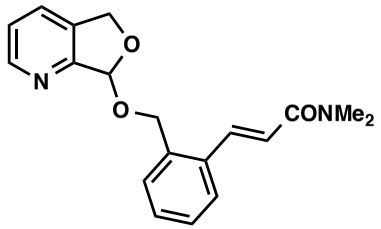


2-23aa
(1.1:1 mono/di)
^{1}H NMR
(400 MHz, $CDCl_3$)

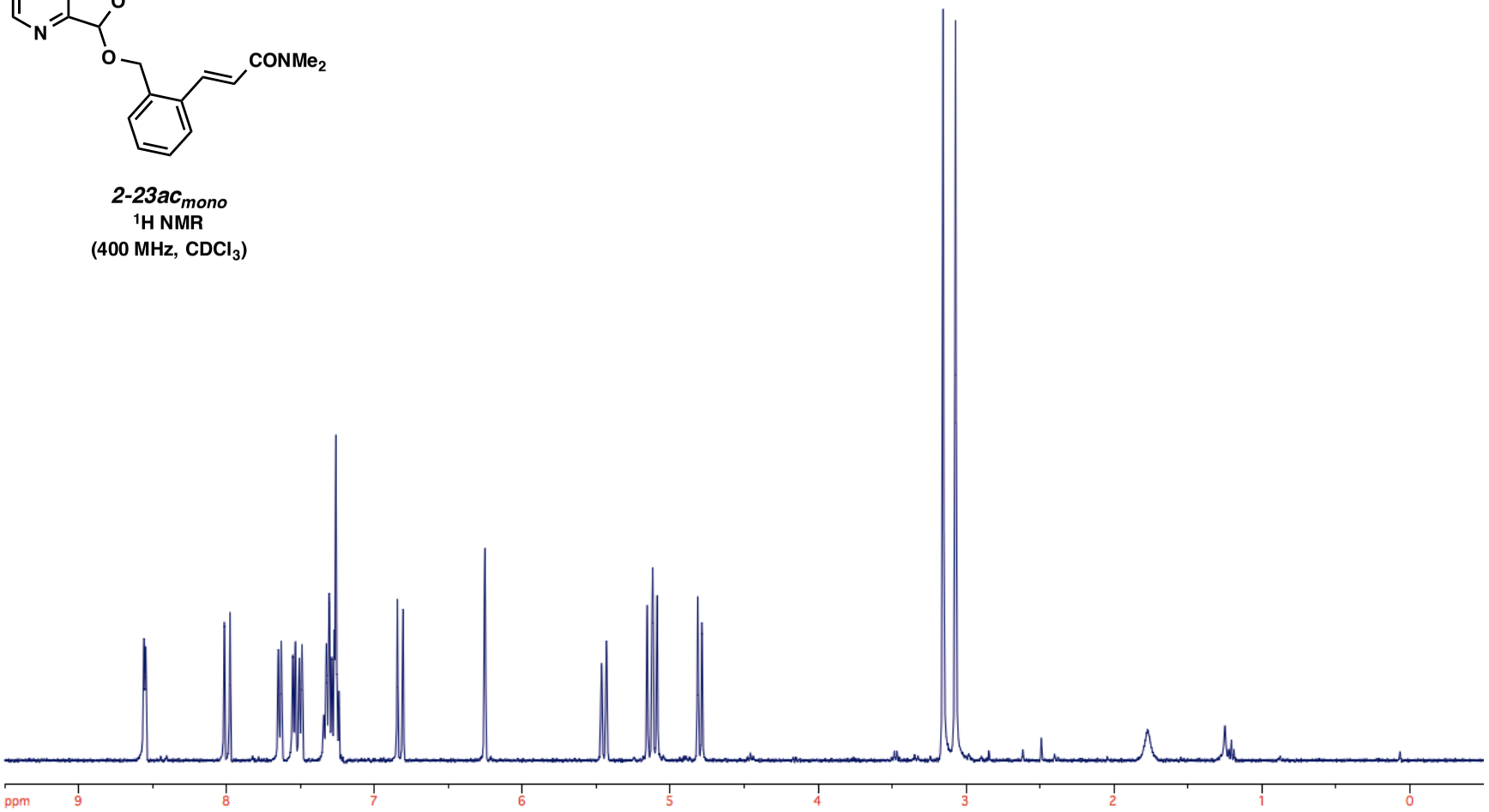


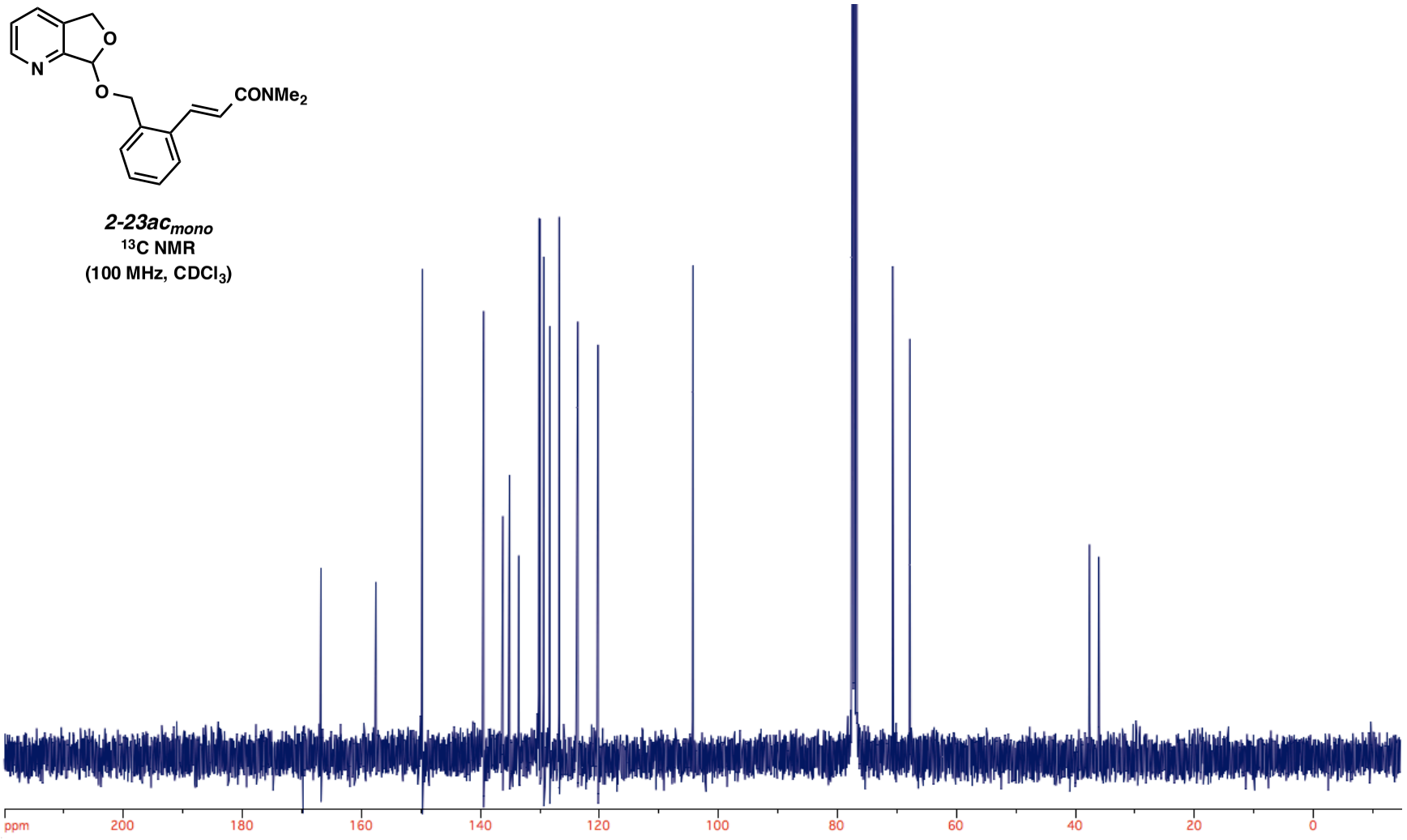


2-23aa
(1.1:1 mono/di)
^{13}C NMR
(100 MHz, $CDCl_3$)

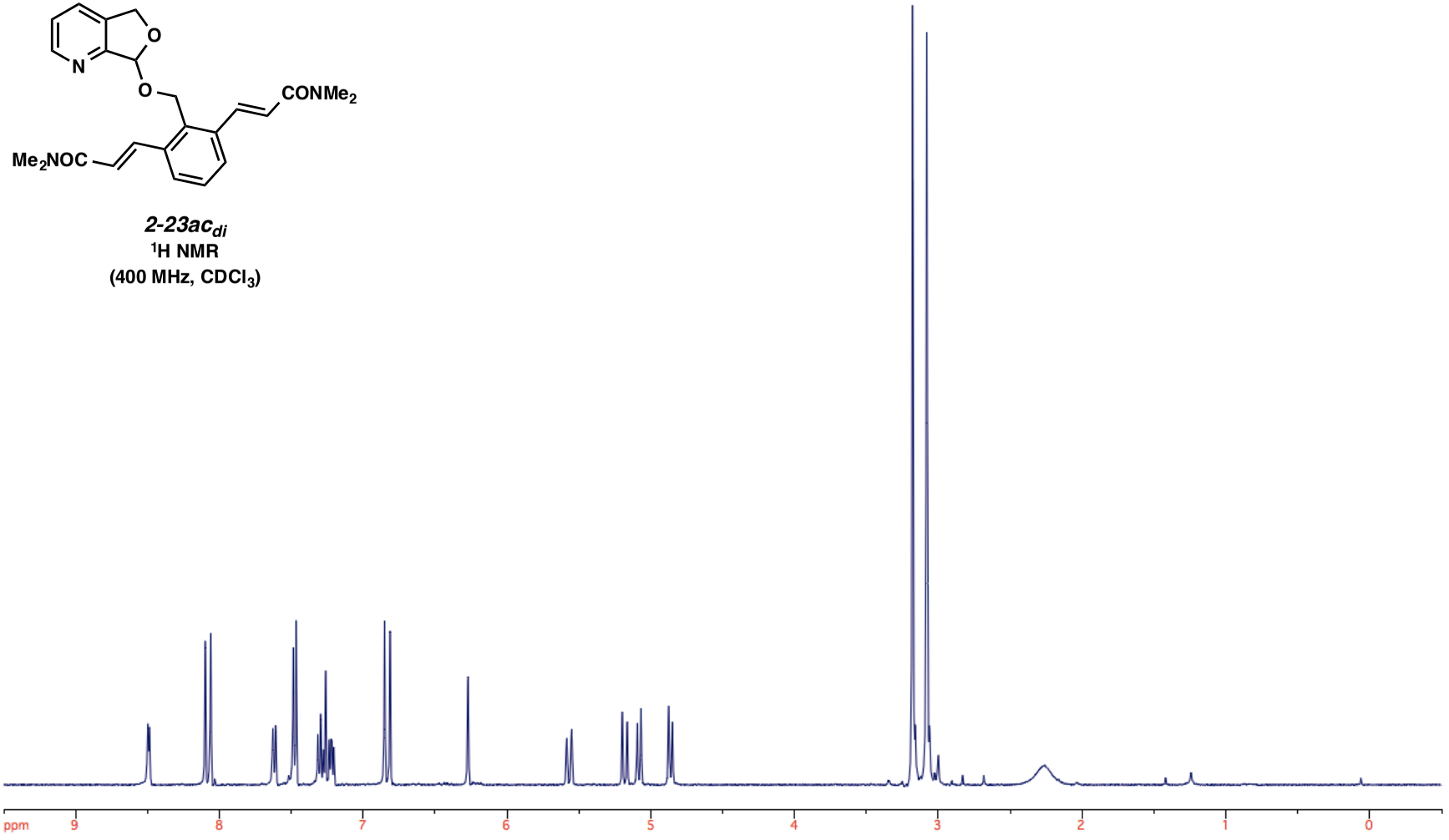


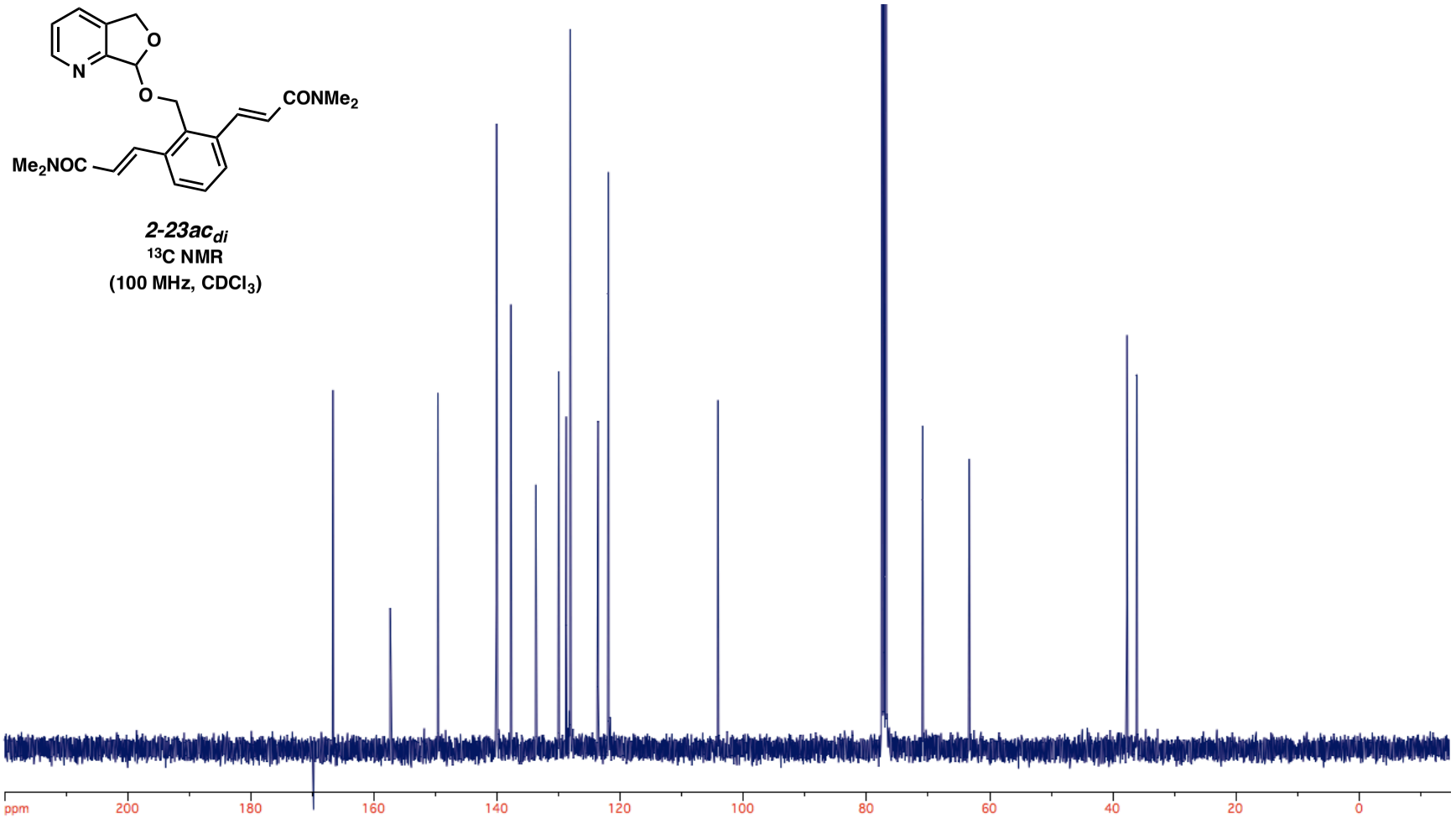
***2-23ac*$_{mono}$**
^{1}H NMR
(400 MHz, $CDCl_3$)



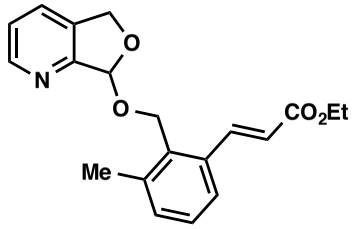

O
N
O
CONMe2
2-23ac mono
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

***2-23ac*$_{di}$**
^{1}H NMR
(400 MHz, $CDCl_3$)

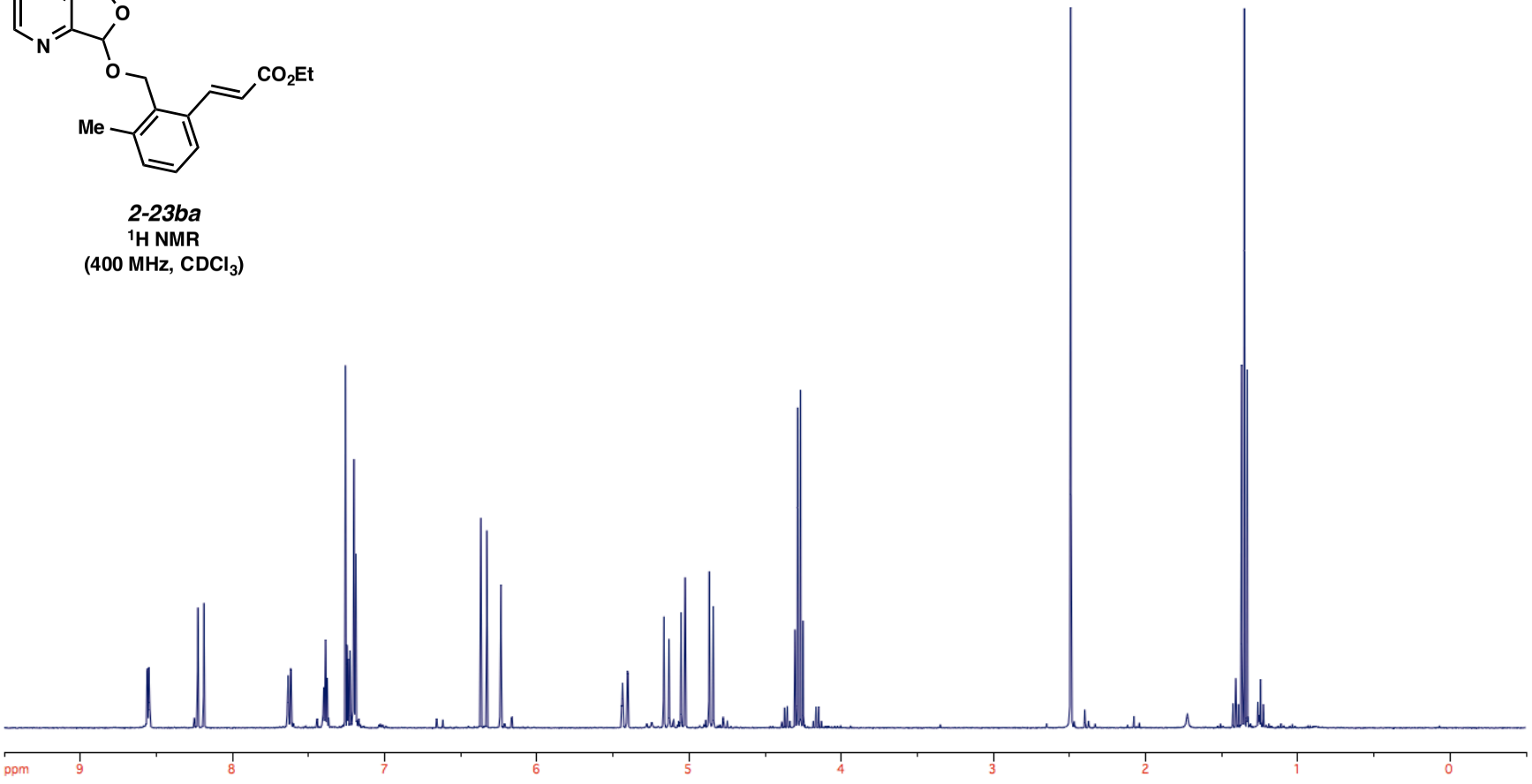


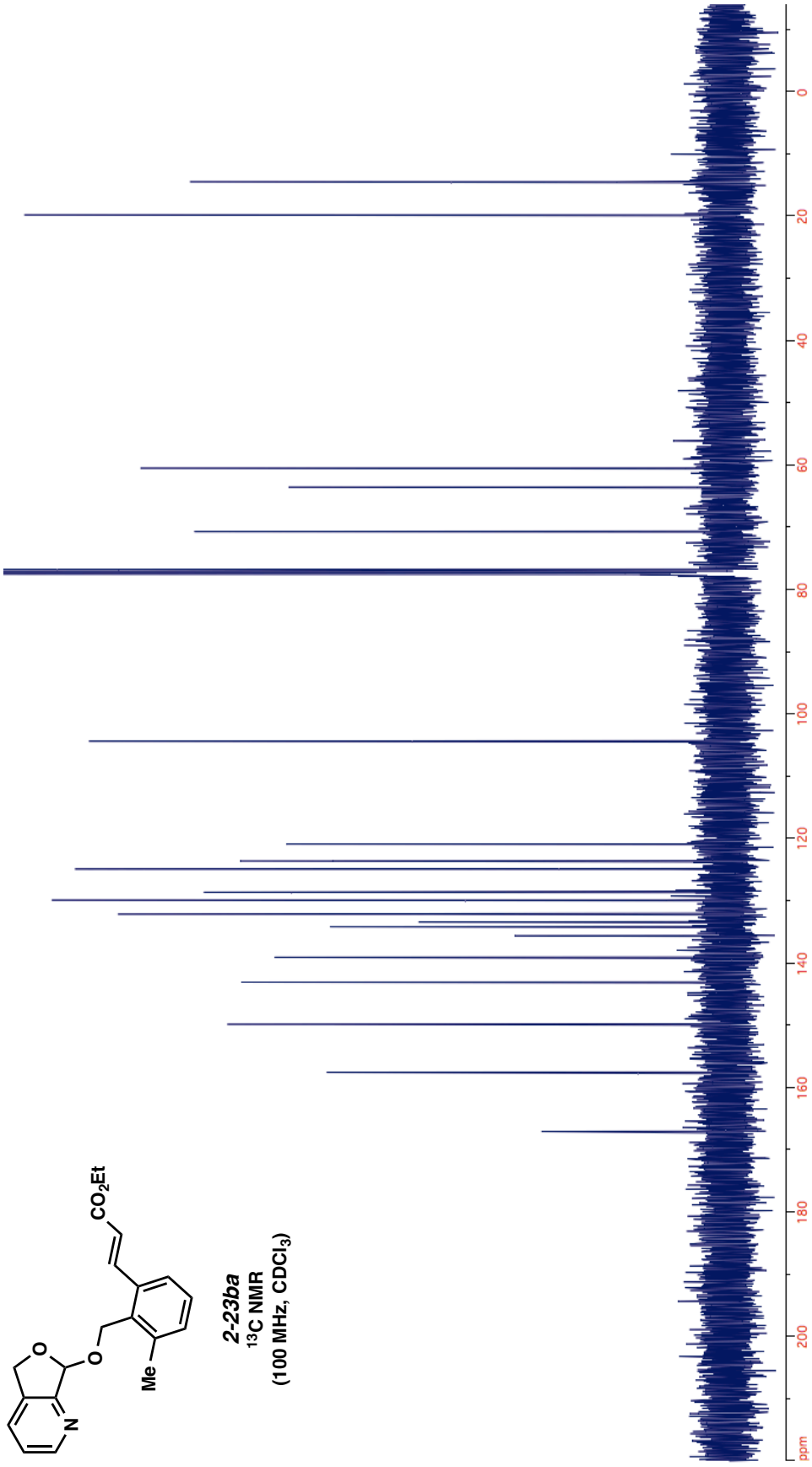


2-23ac$_{di}$
^{13}C NMR
(100 MHz, $CDCl_3$)

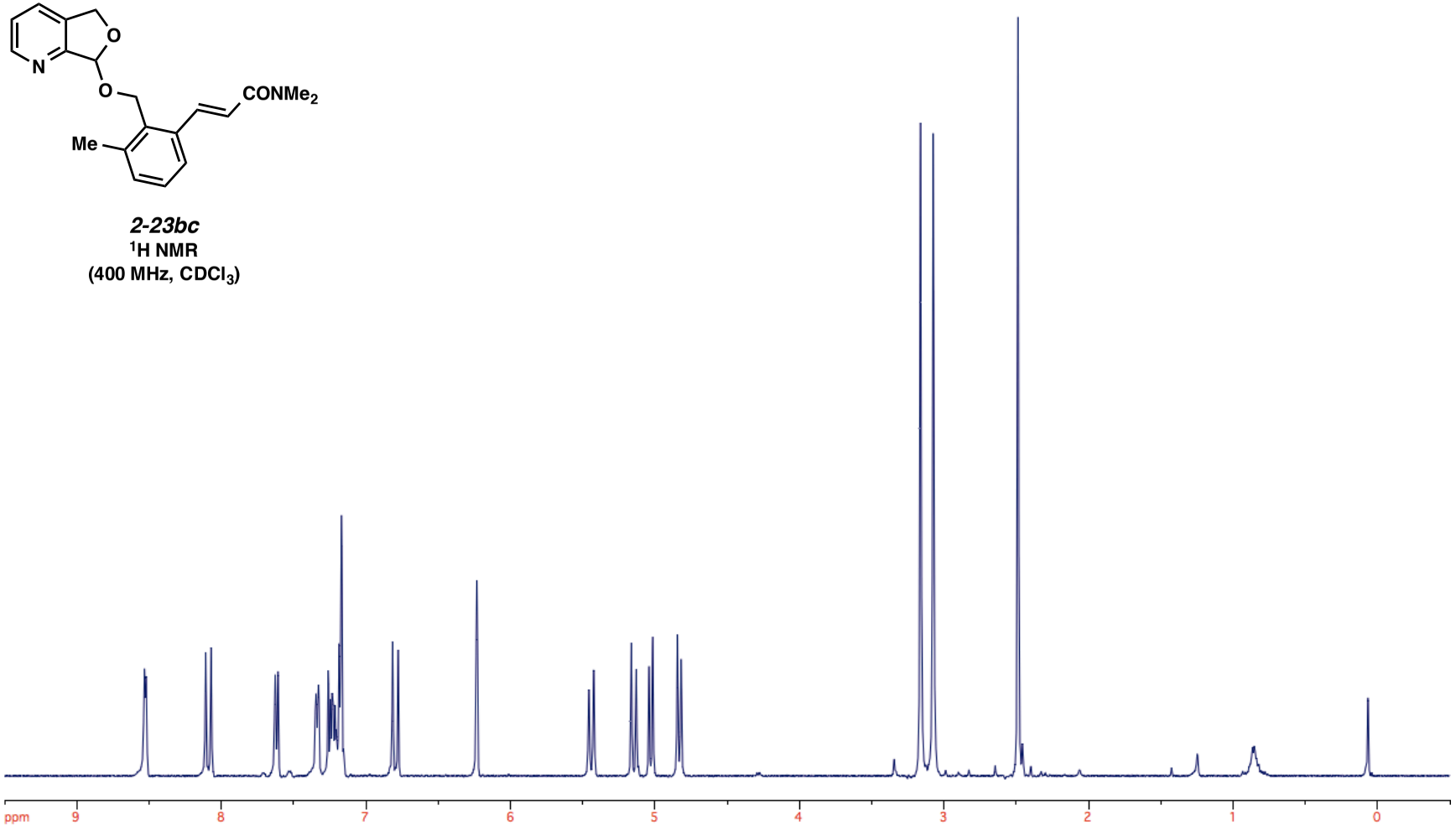


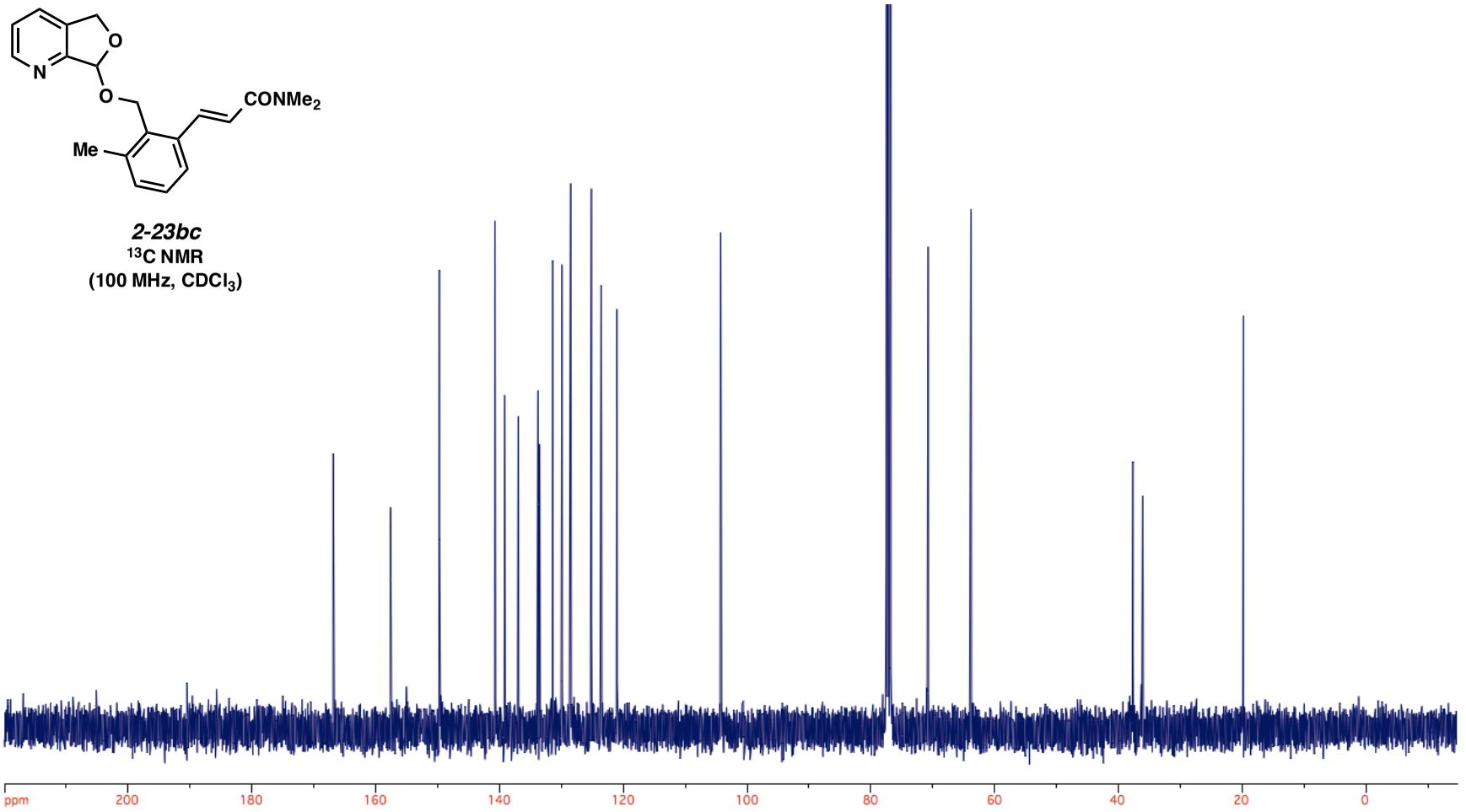
2-23ba
^{1}H NMR
(400 MHz, $CDCl_3$)




CO2Et
Me
O
O
N
2-23ba
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

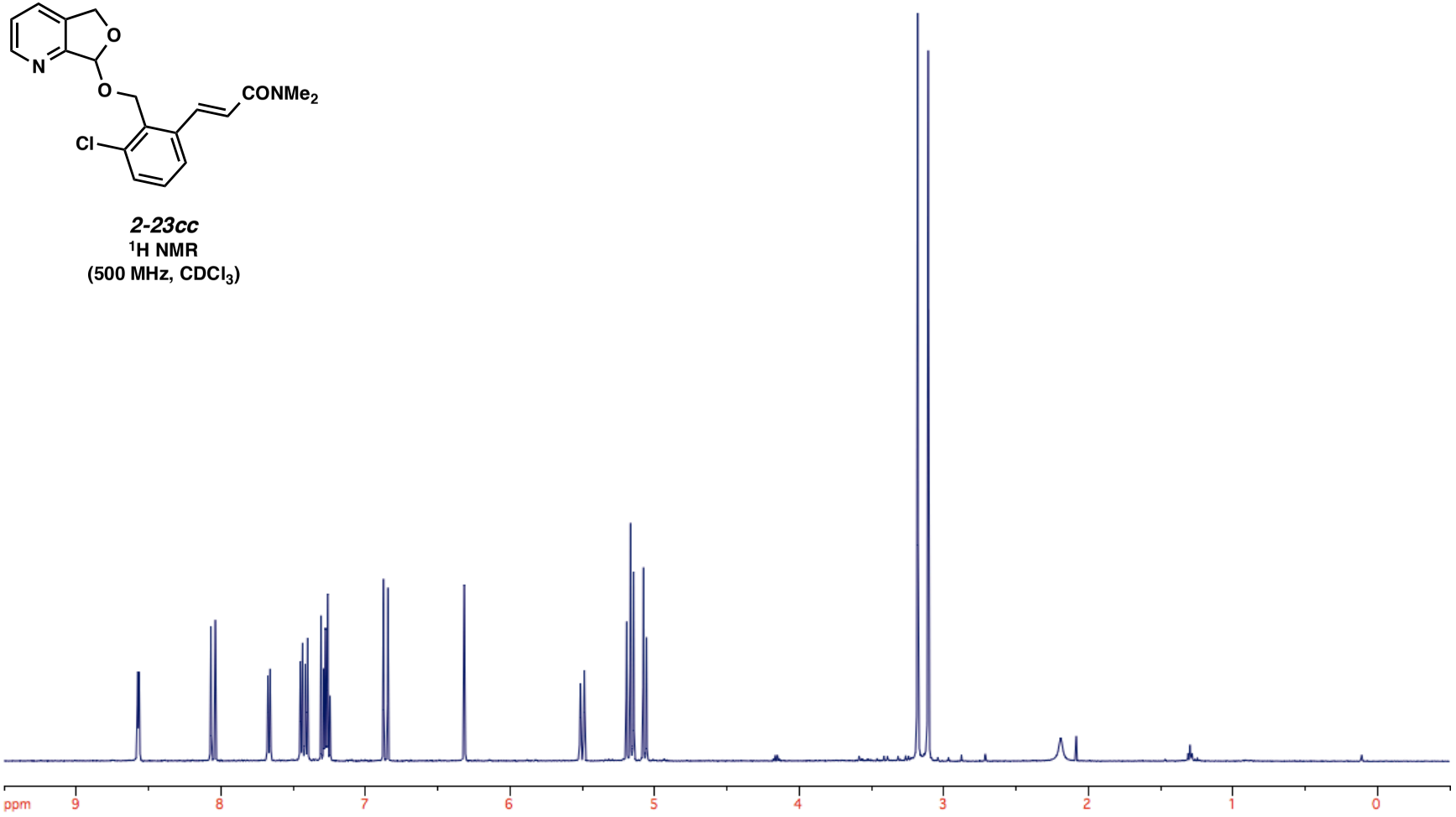
2-23bc
^{1}H NMR
(400 MHz, $CDCl_3$)

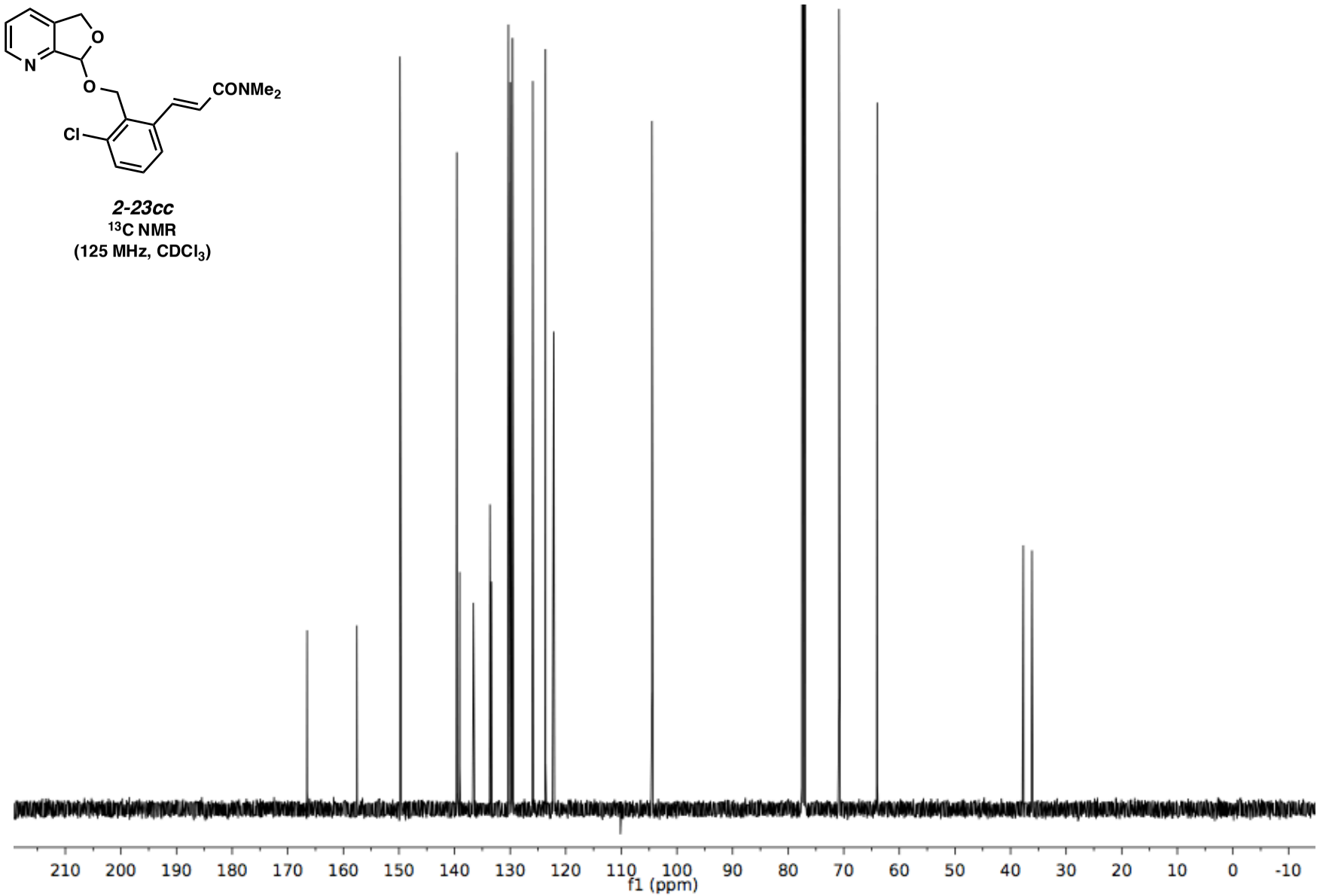




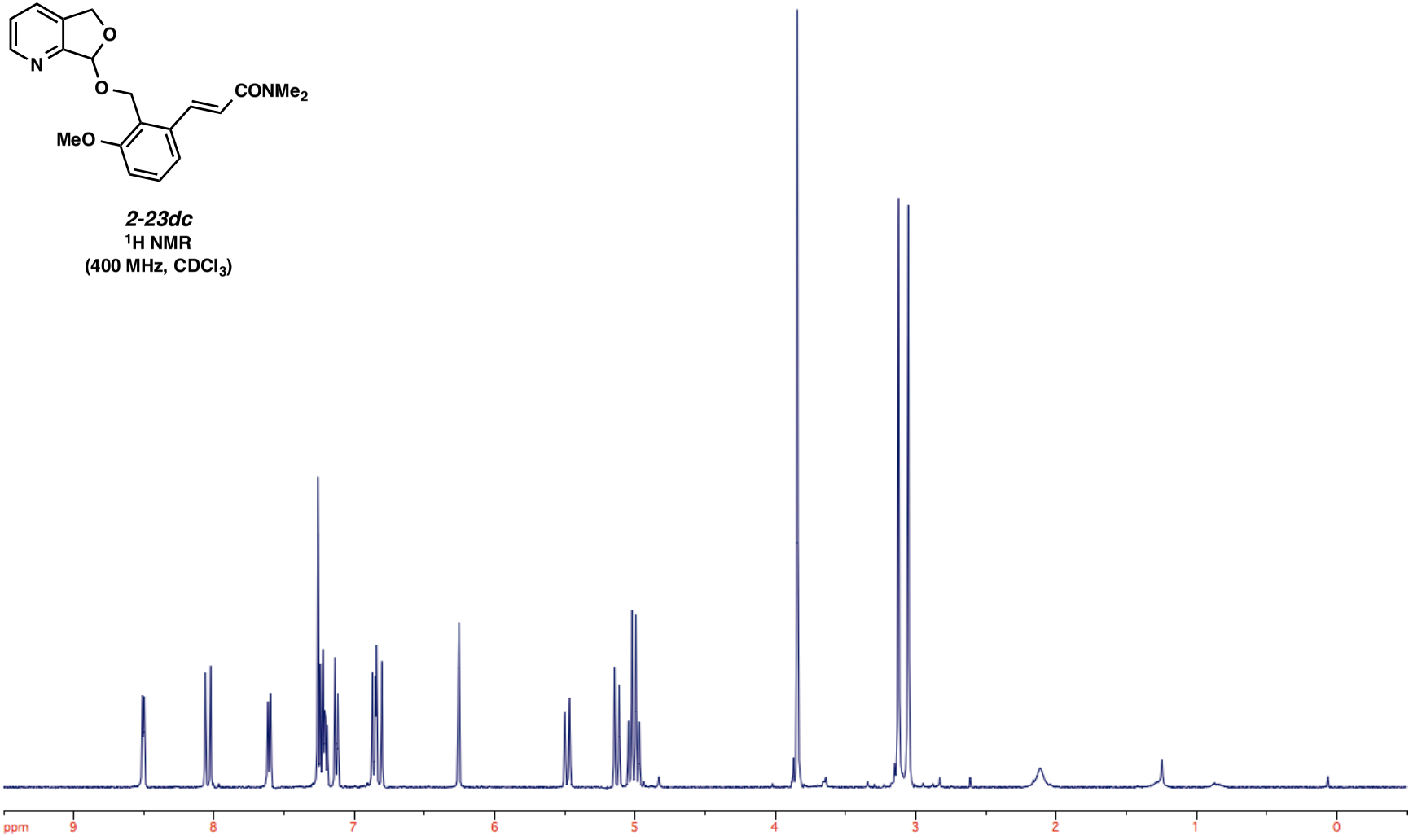
2-23bc
^{13}C NMR
(100 MHz, $CDCl_3$)

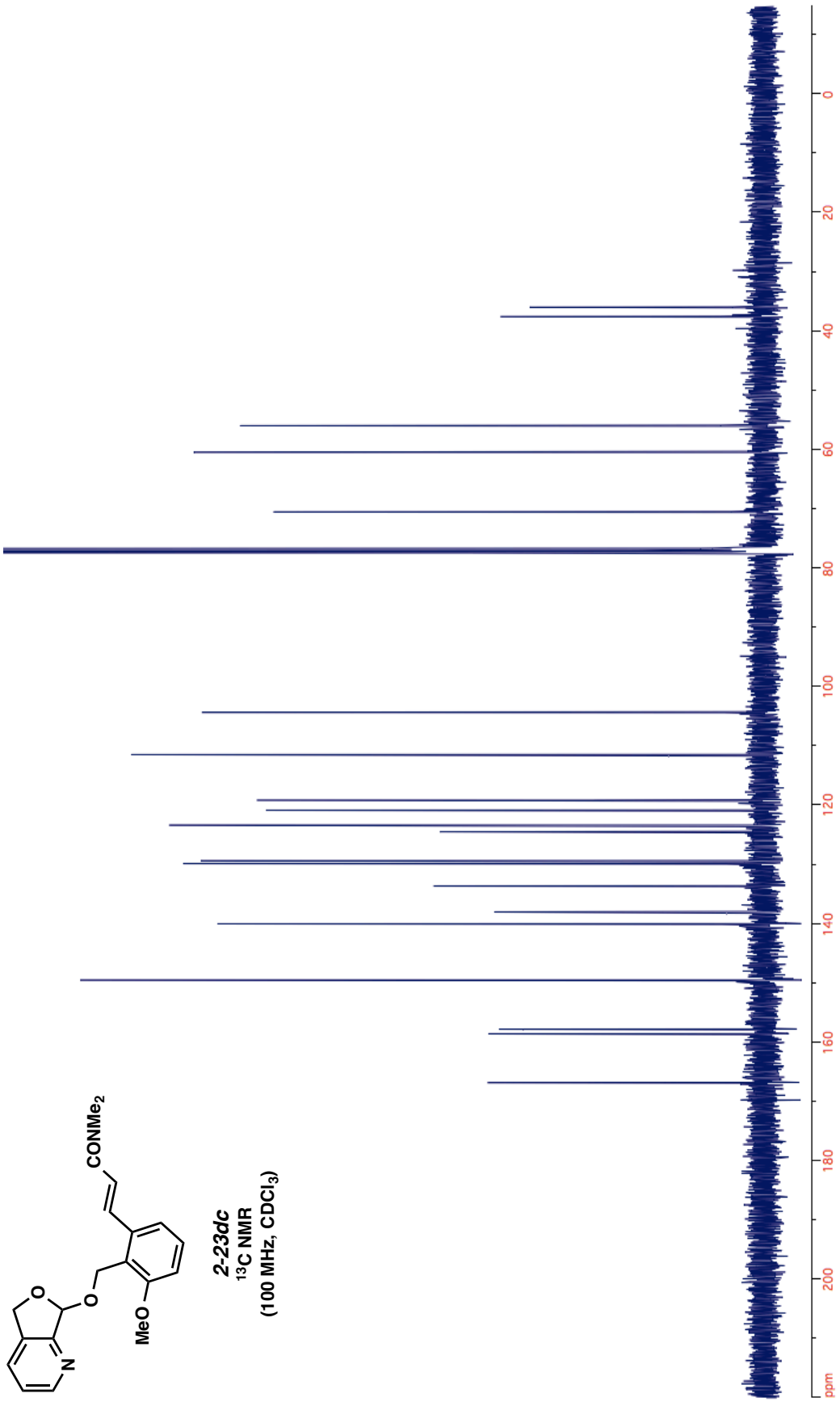
2-23cc
^{1}H NMR
(500 MHz, $CDCl_3$)



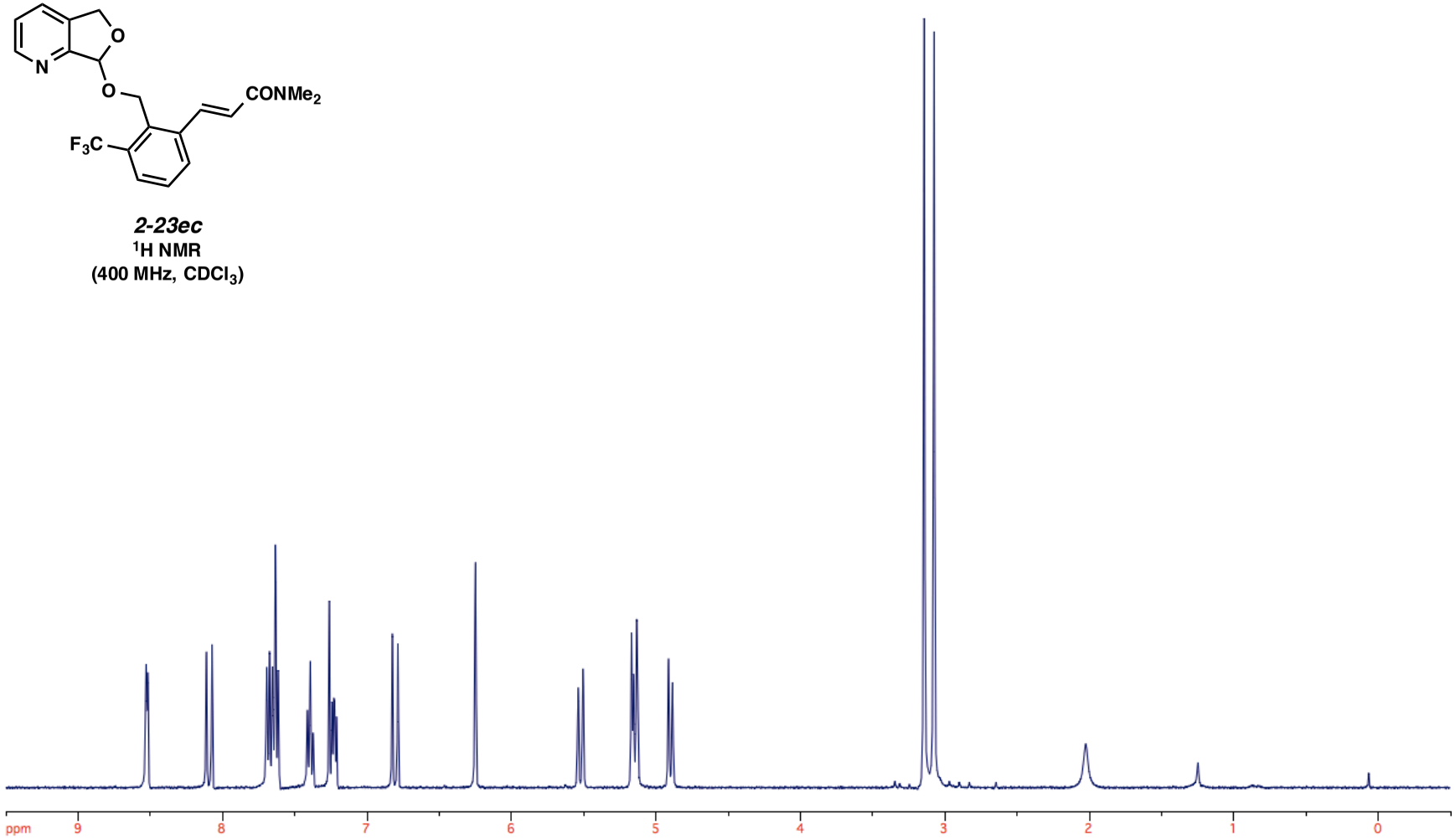

O
N
O
CONMe2
Cl
2-23cc
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2-23dc
^{1}H NMR
(400 MHz, $CDCl_3$)

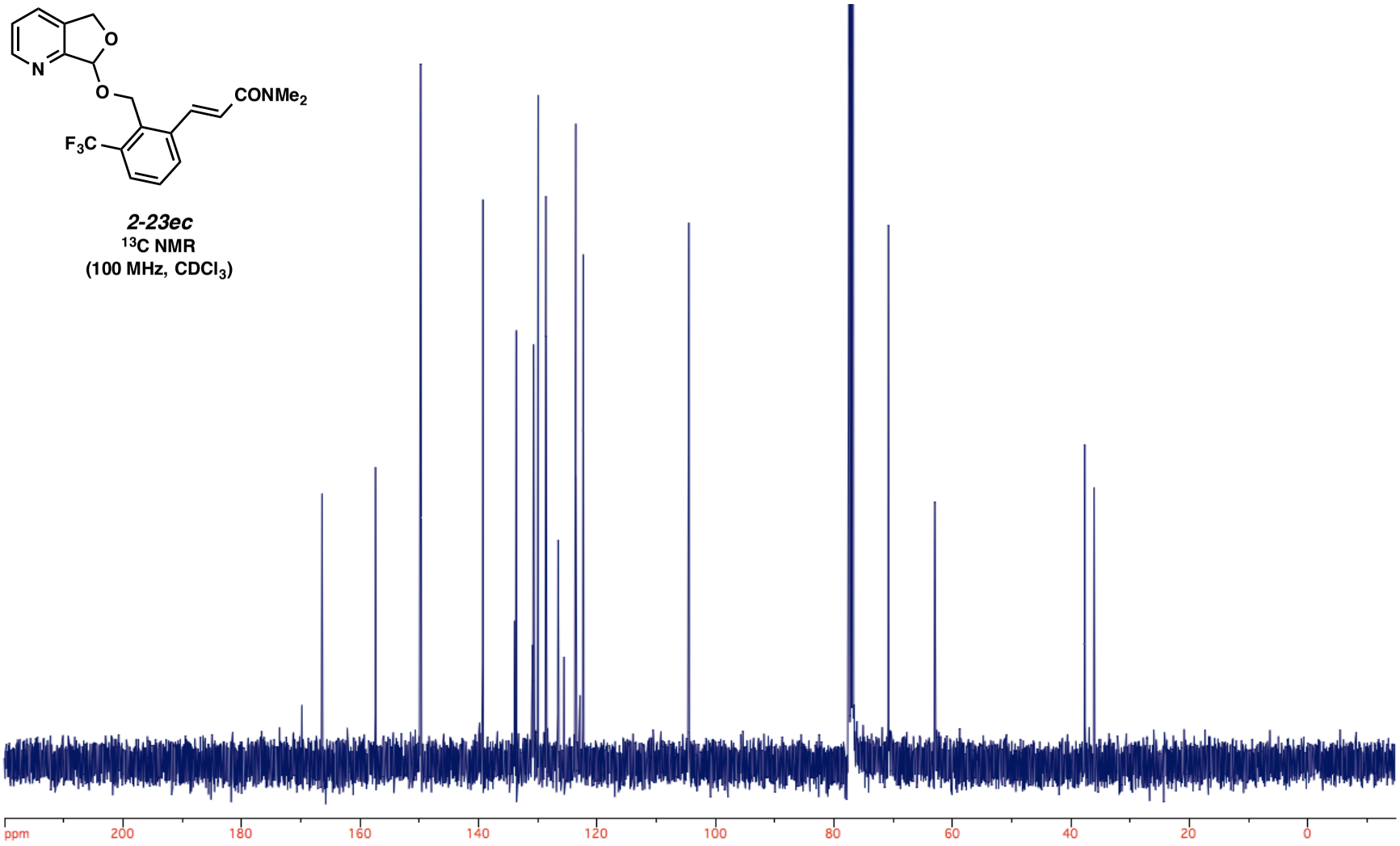


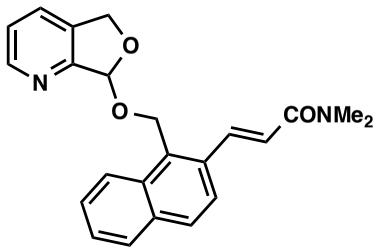

CONMe2
MeO
O
O
N
2-23dc
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

2-23ec
^{1}H NMR
(400 MHz, $CDCl_3$)

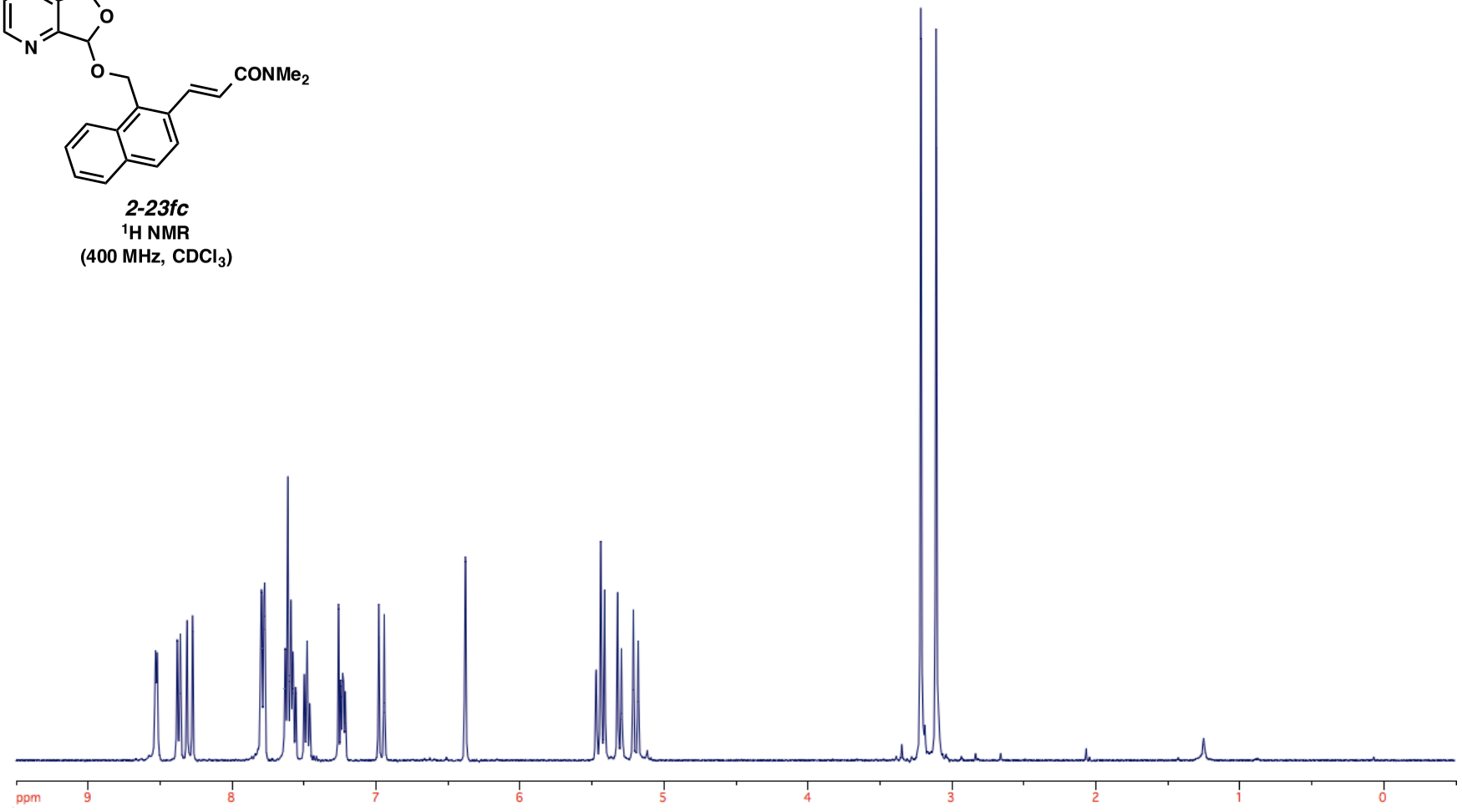


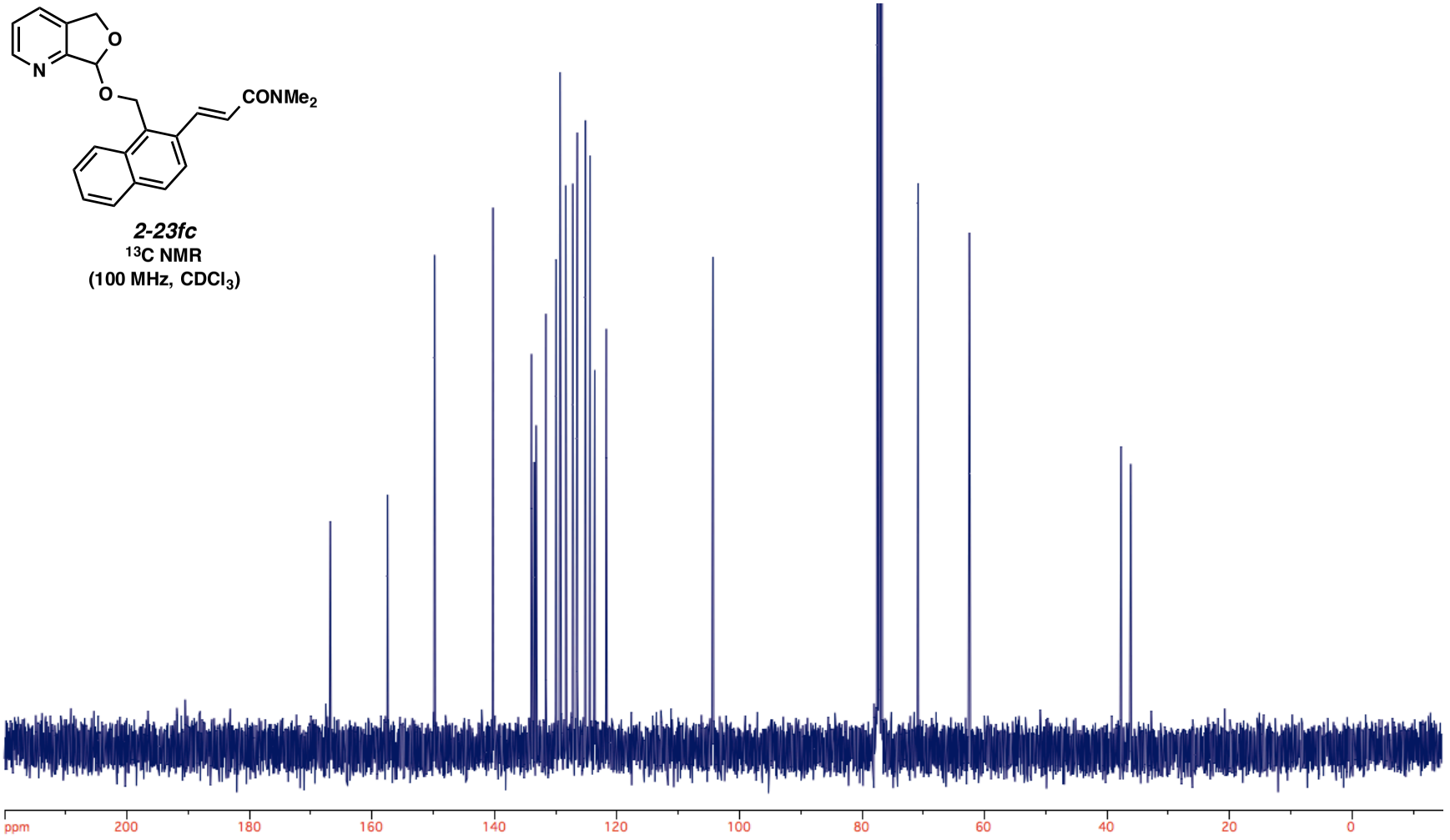
2-23ec
^{13}C NMR
(100 MHz, $CDCl_3$)

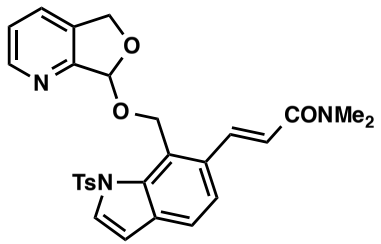




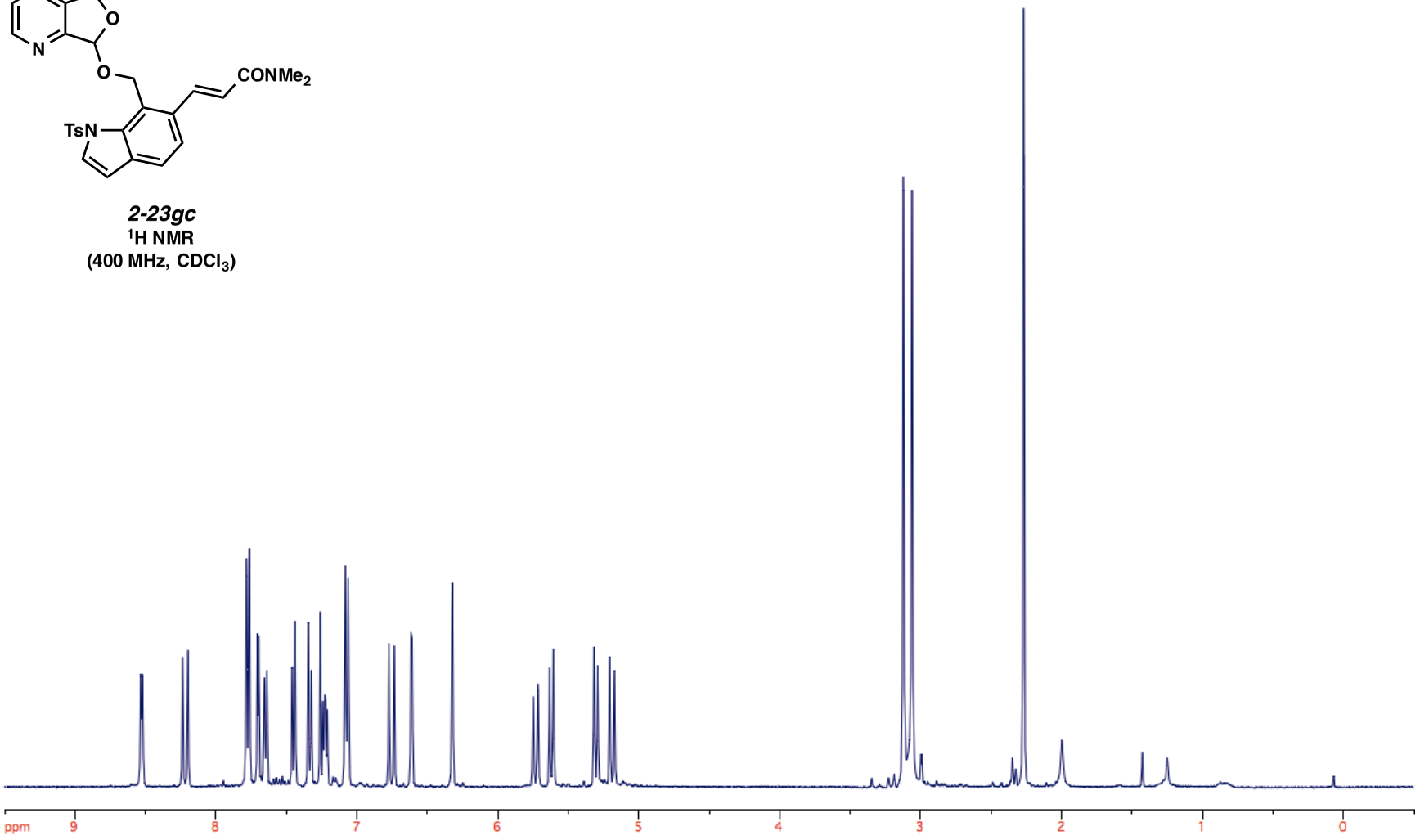
2-23fc
^{1}H NMR
(400 MHz, $CDCl_3$)

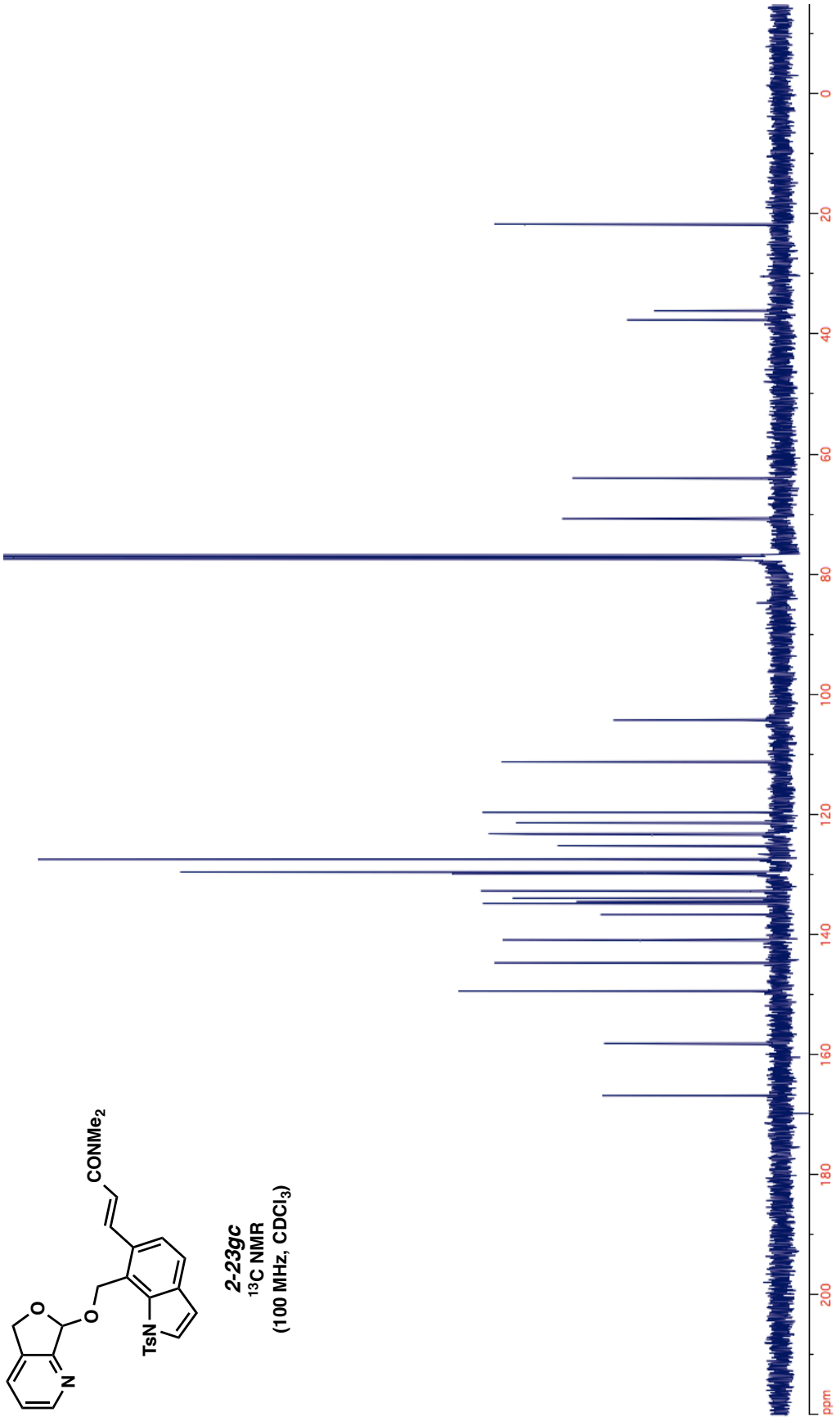


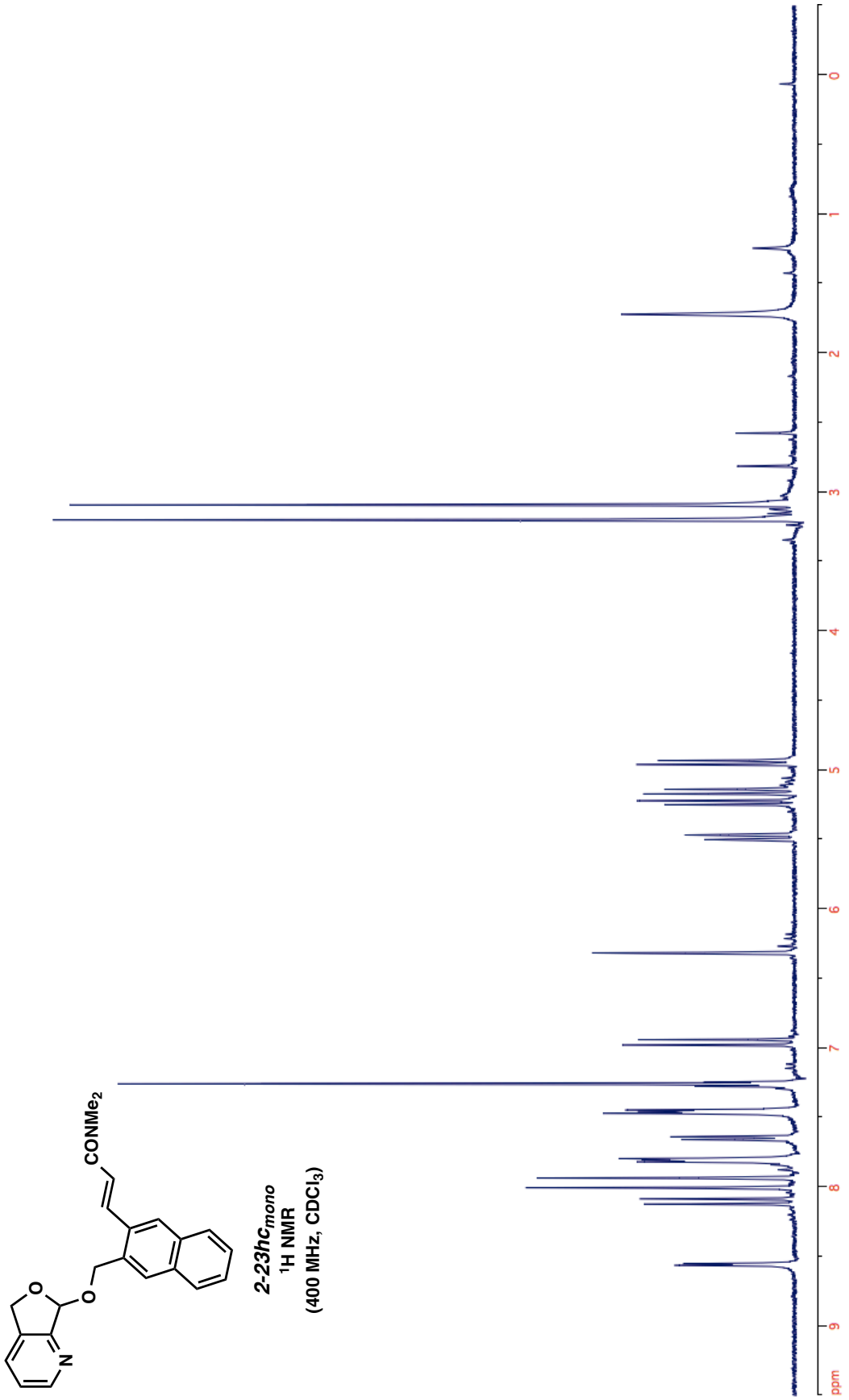

O
N
O
CONMe2
2-23fc
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

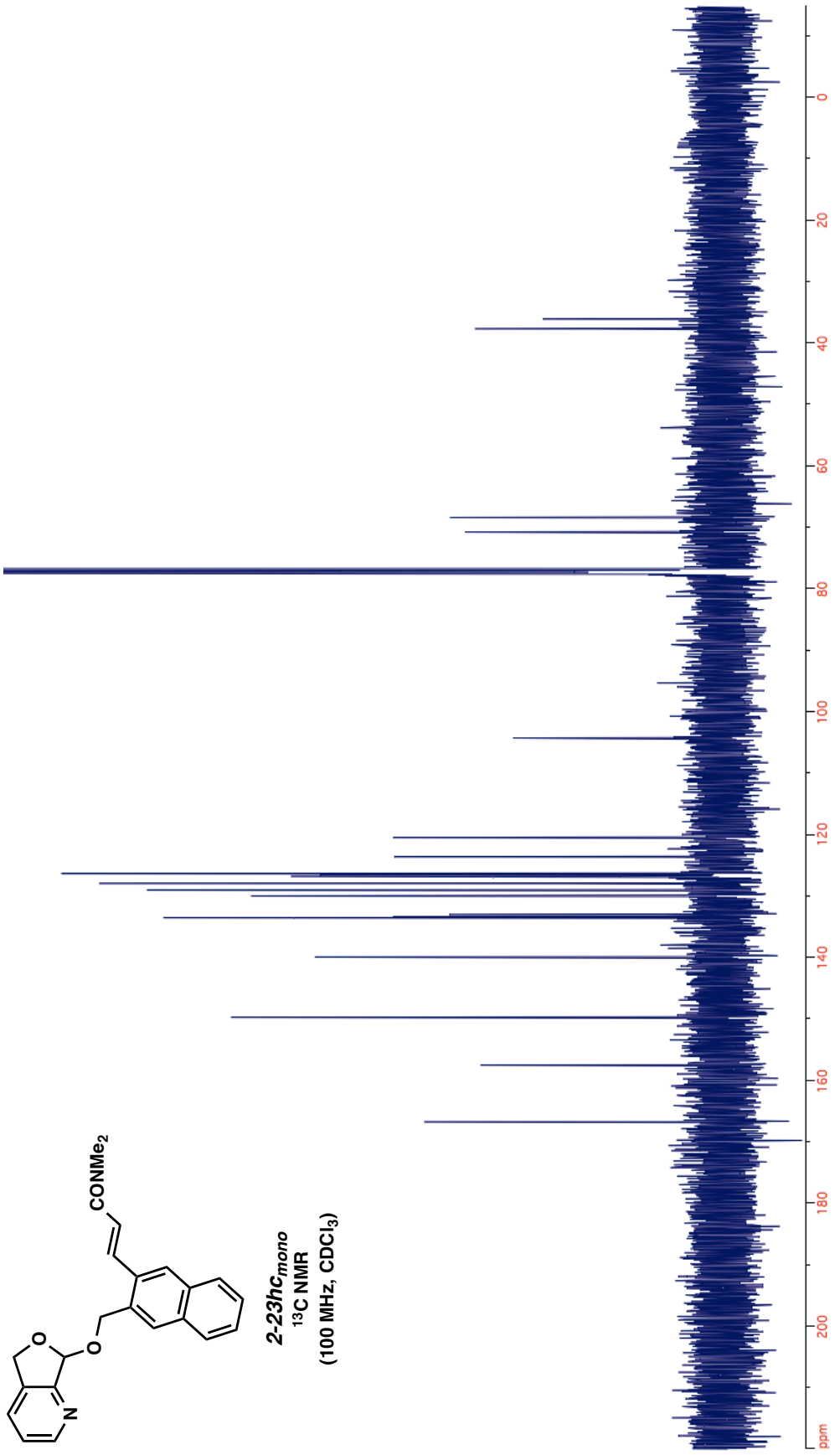


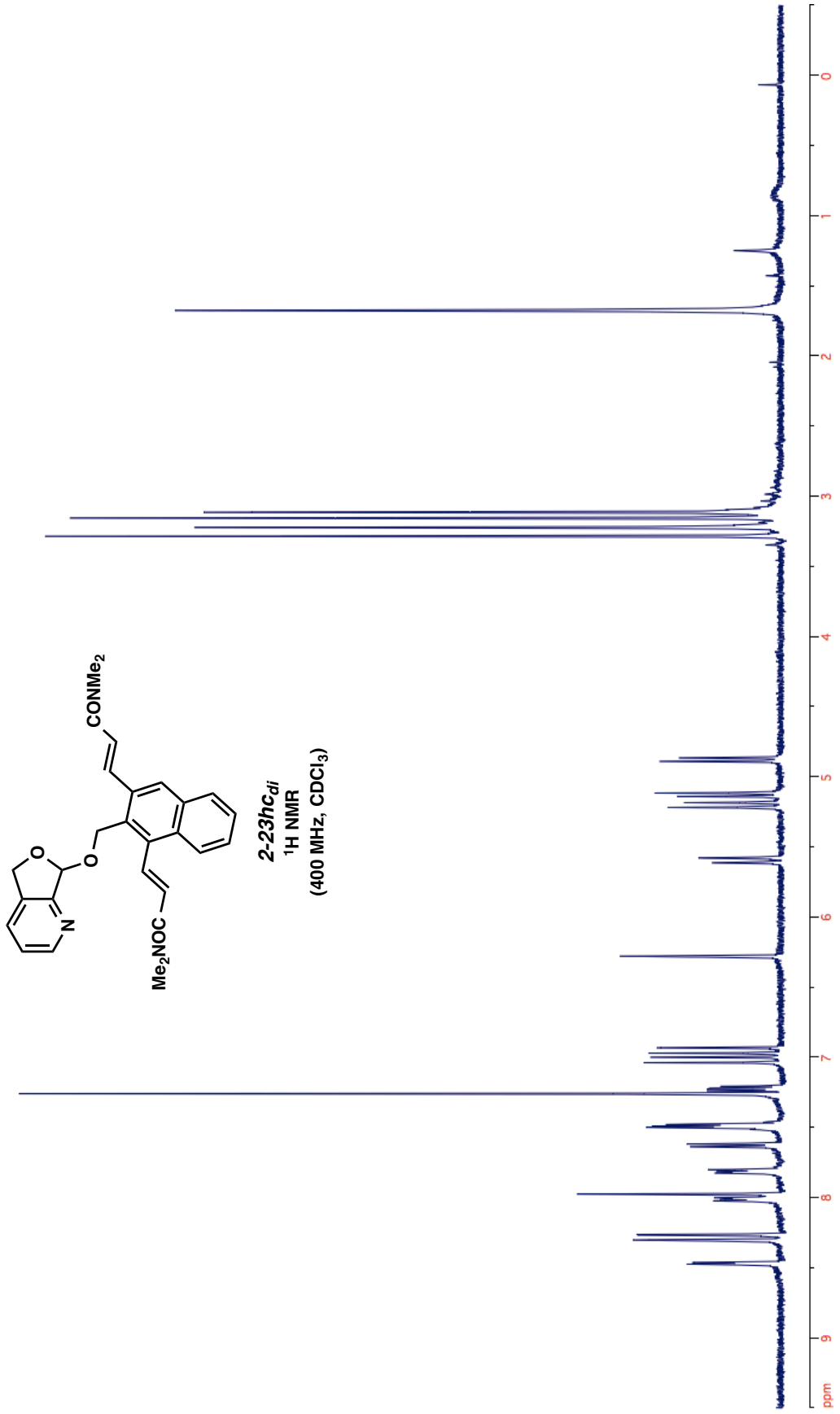
2-23gc
^{1}H NMR
(400 MHz, $CDCl_3$)

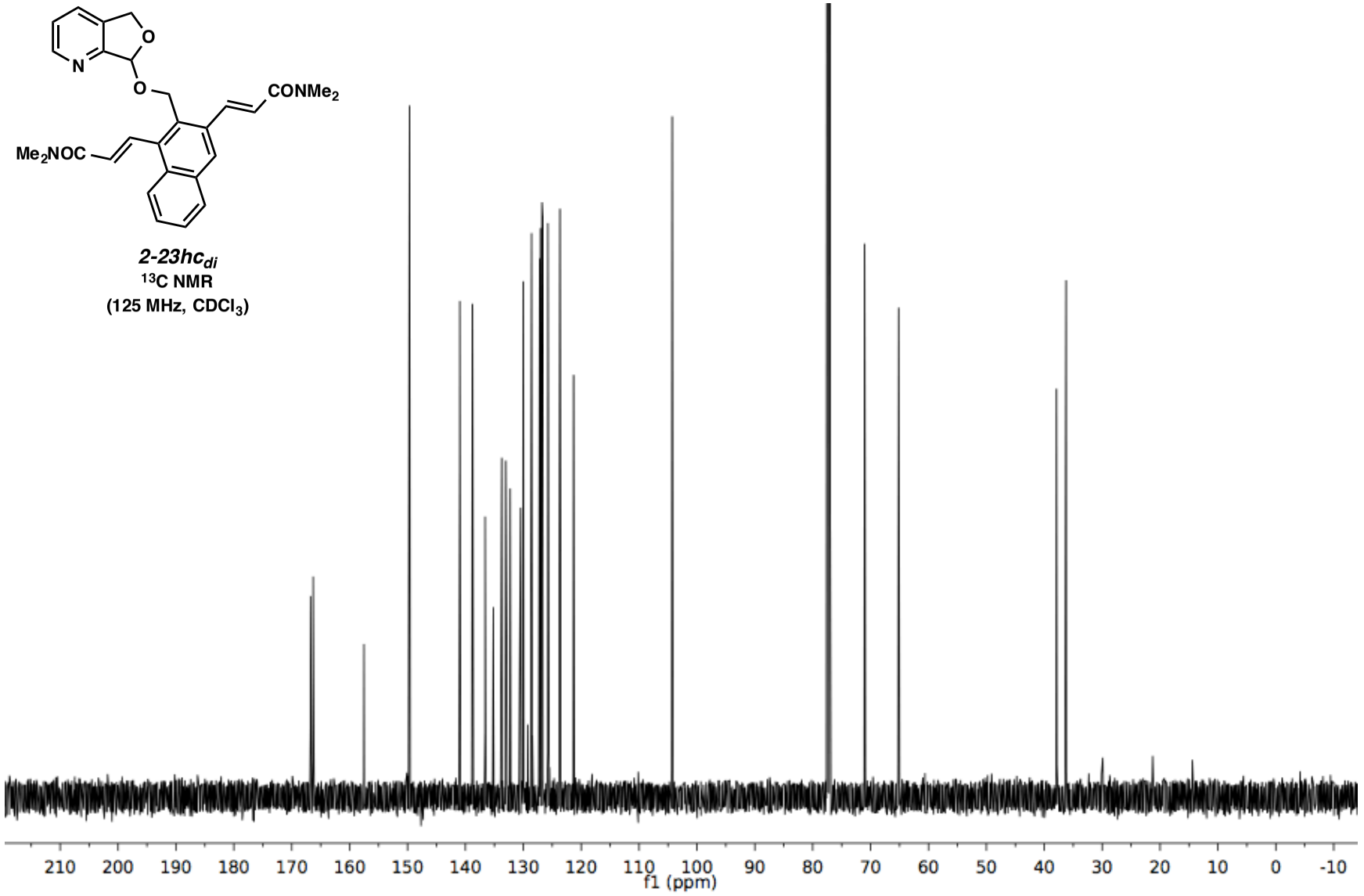


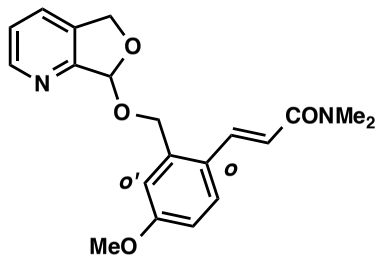

CONMe2
TsN
O
O
N
2-23gc
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200


CONMe2
O
O
N
2-23hc_mono
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

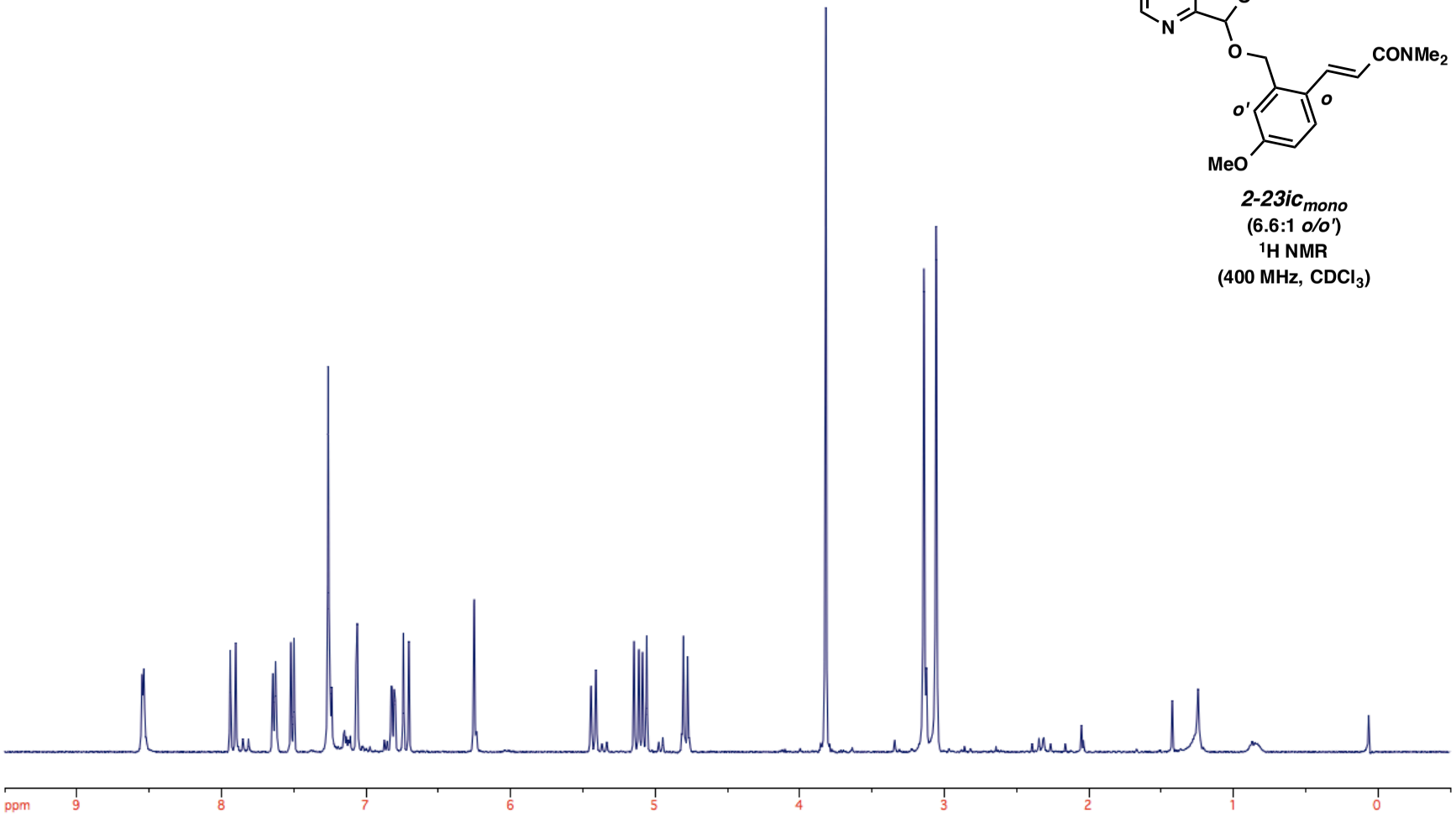

CONMe2
O
O
N
2-23hc_mono
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

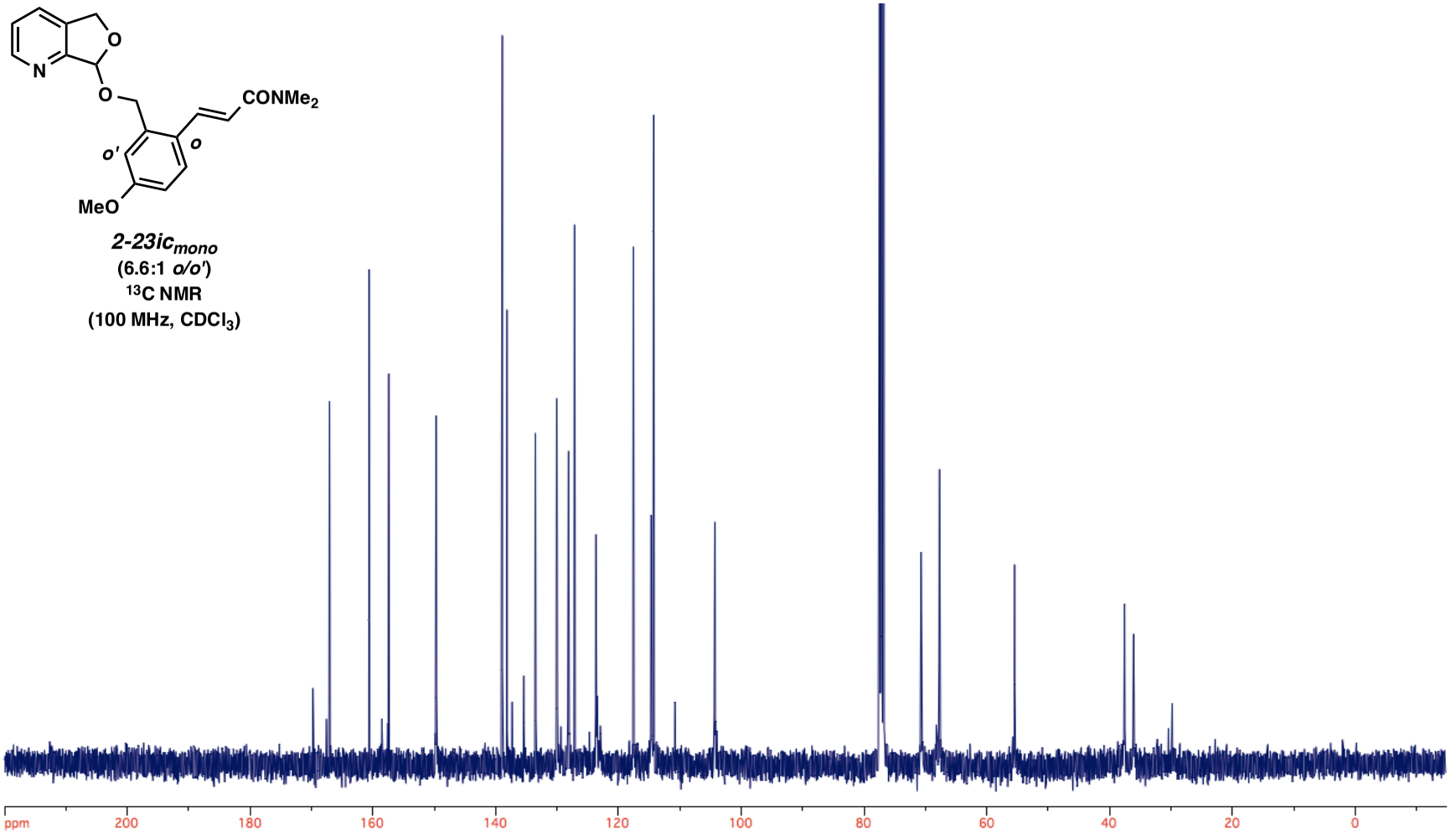

CONMe2
Me2NOC
O
O
N
2-23hcdi
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0


N
O
O
CONMe2
Me2NOC
2-23hcdi
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



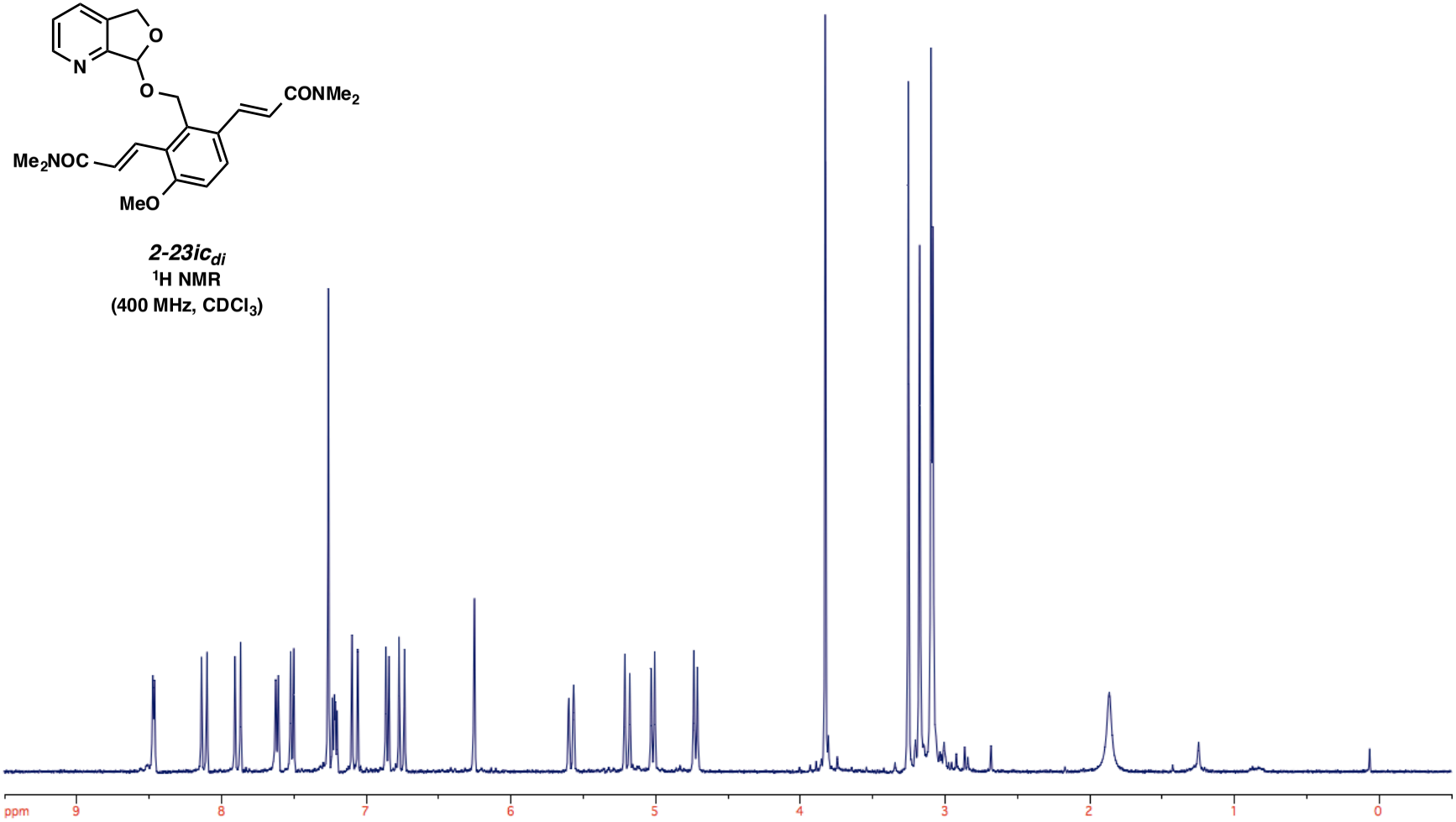
***2-23ic*$_{mono}$**
(6.6:1 *o*/*o'*)
^{1}H NMR
(400 MHz, $CDCl_3$)

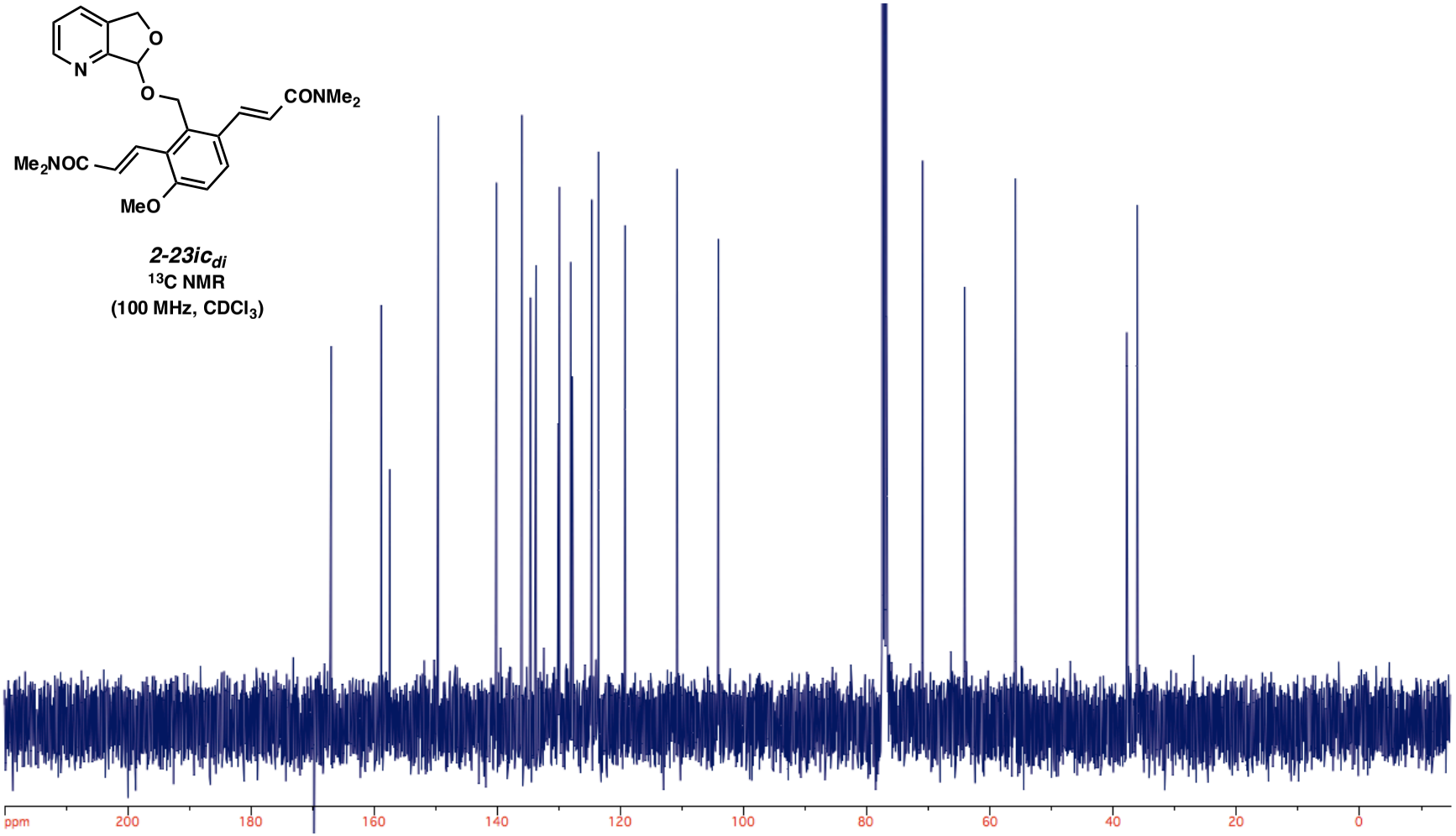




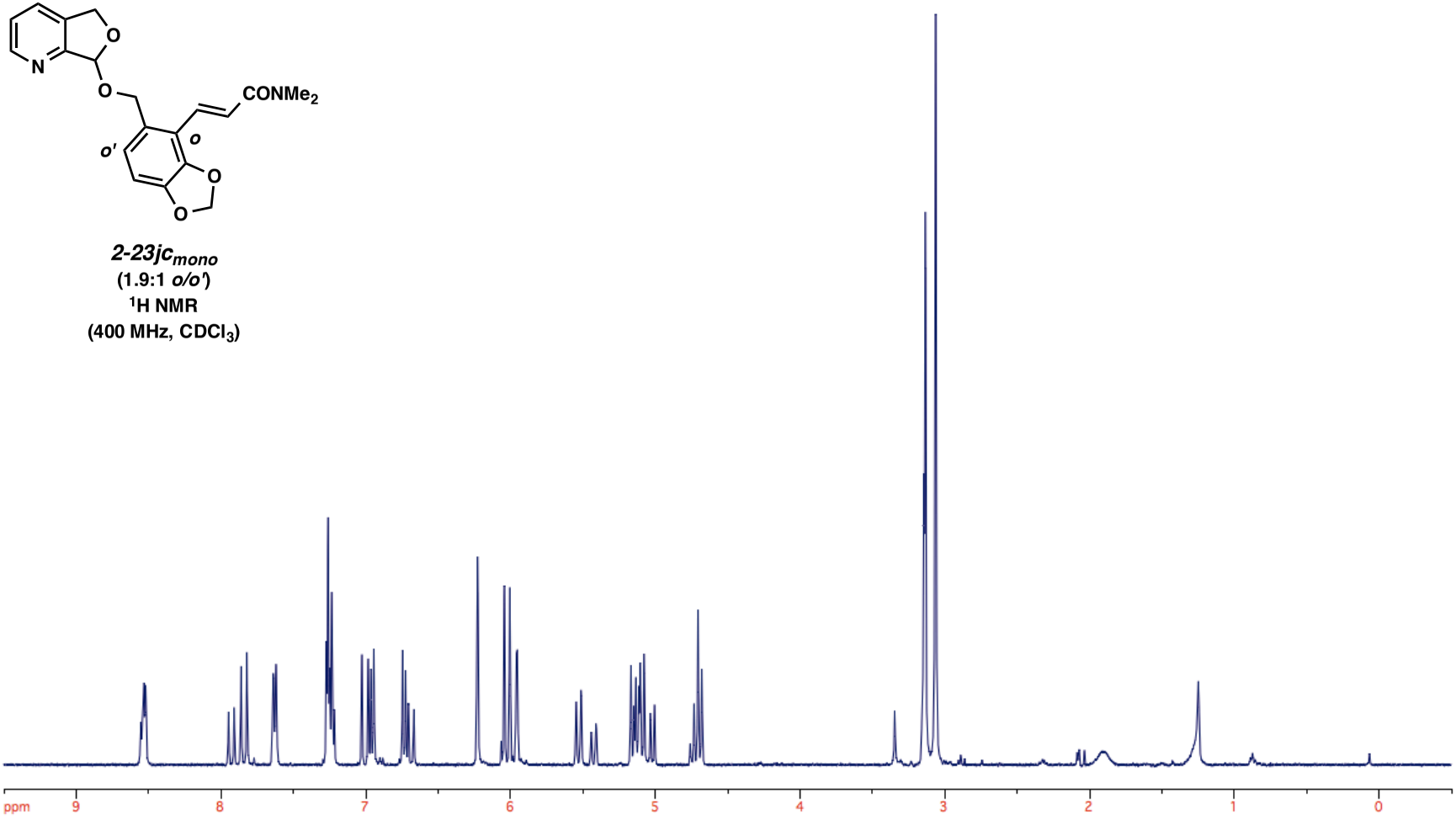
***2-23ic*$_{mono}$**
(6.6:1 *o/o'*)
^{13}C NMR
(100 MHz, $CDCl_3$)

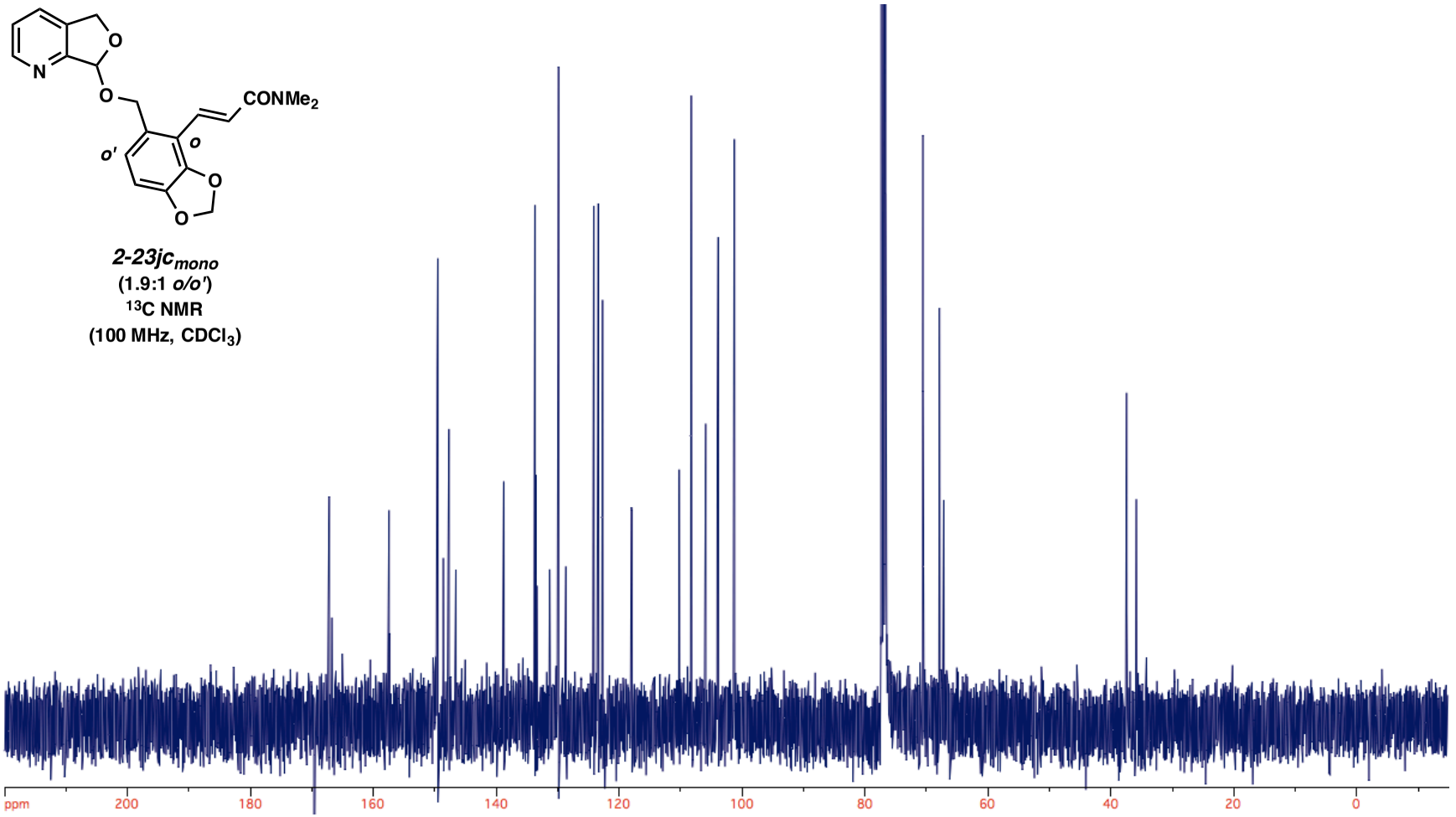
***2-23ic*$_{di}$**
^{1}H NMR
(400 MHz, $CDCl_3$)



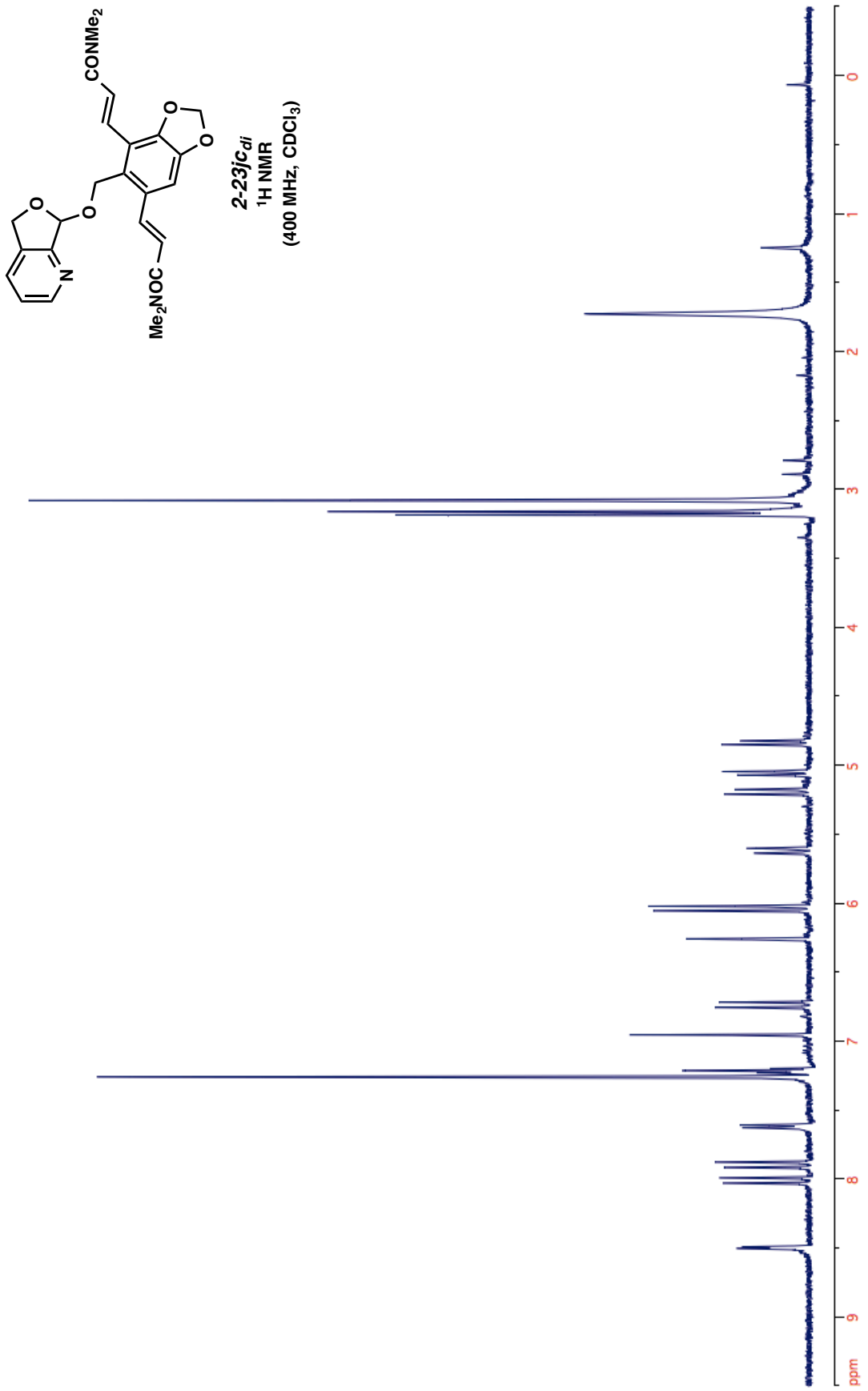

O
N
O
CONMe2
Me2NOC
MeO
2-23ic_di
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

***2-23jc*$_{mono}$**
(1.9:1 *o*/*o'*)
^{1}H NMR
(400 MHz, $CDCl_3$)

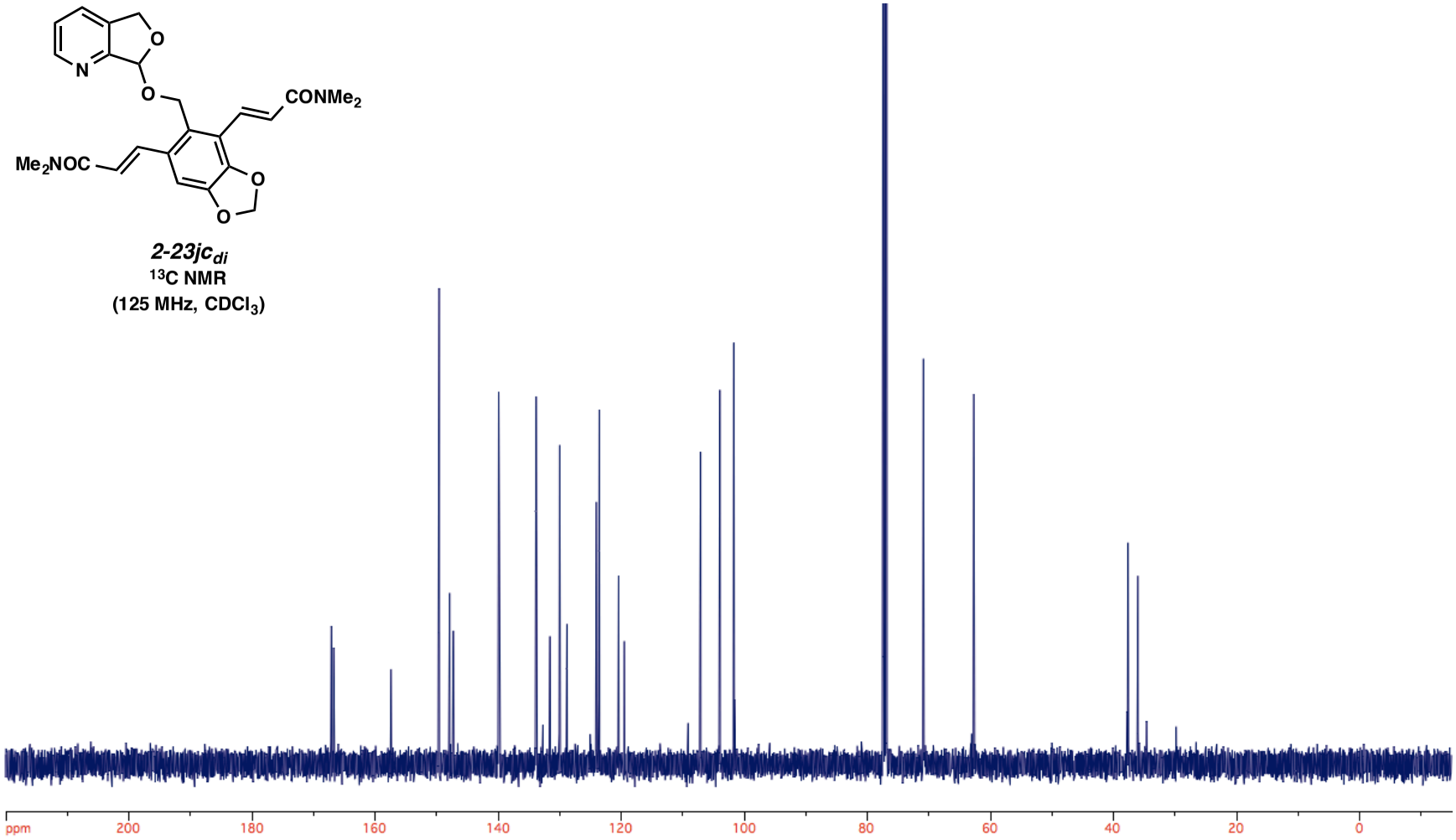




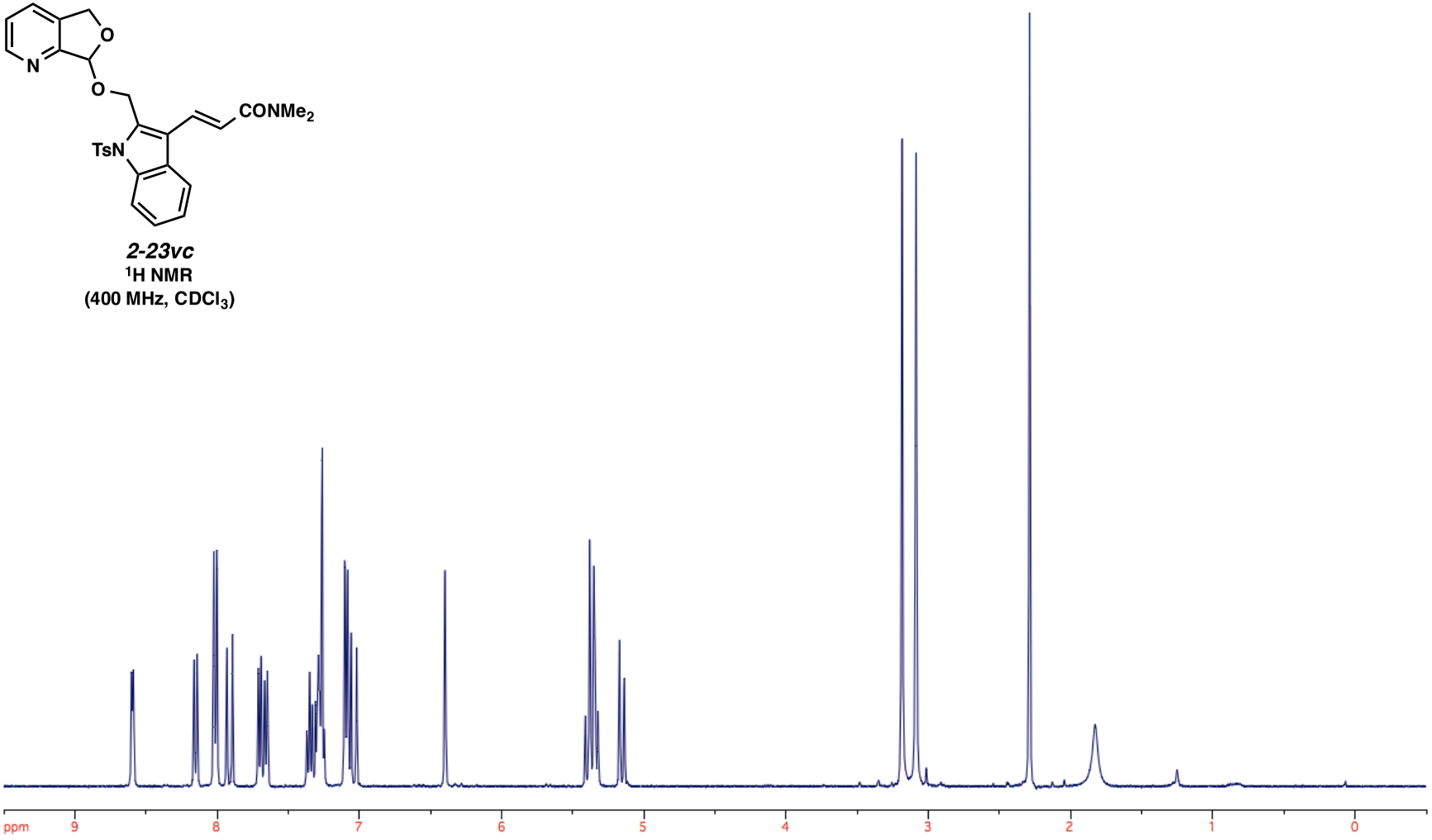
***2-23jc*$_{mono}$**
(1.9:1 *o*/*o'*)
^{13}C NMR
(100 MHz, $CDCl_3$)

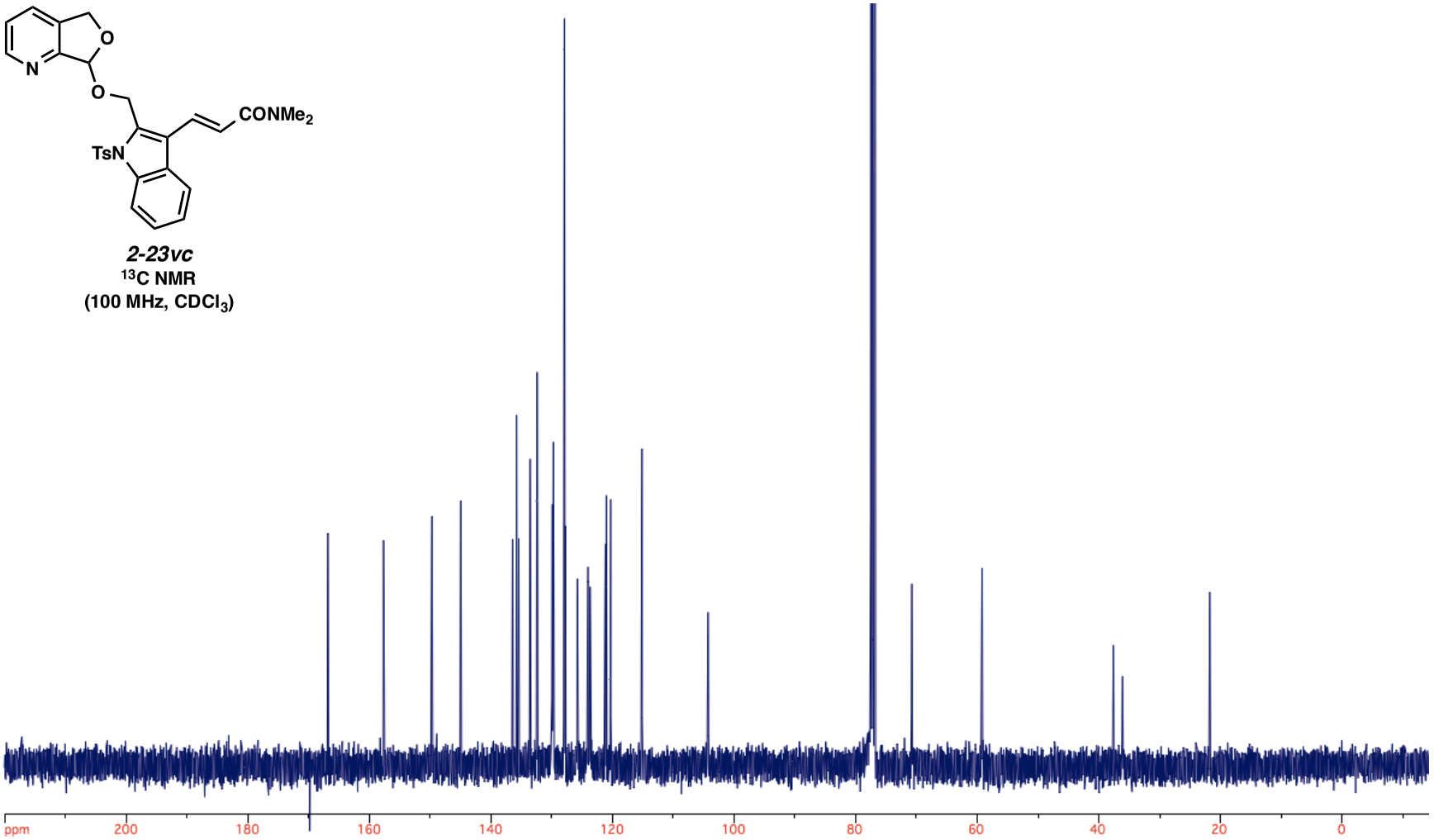

CONMe2
Me2NOC
2-23jcdi
1H NMR
(400 MHz, CDCl3)
ppm

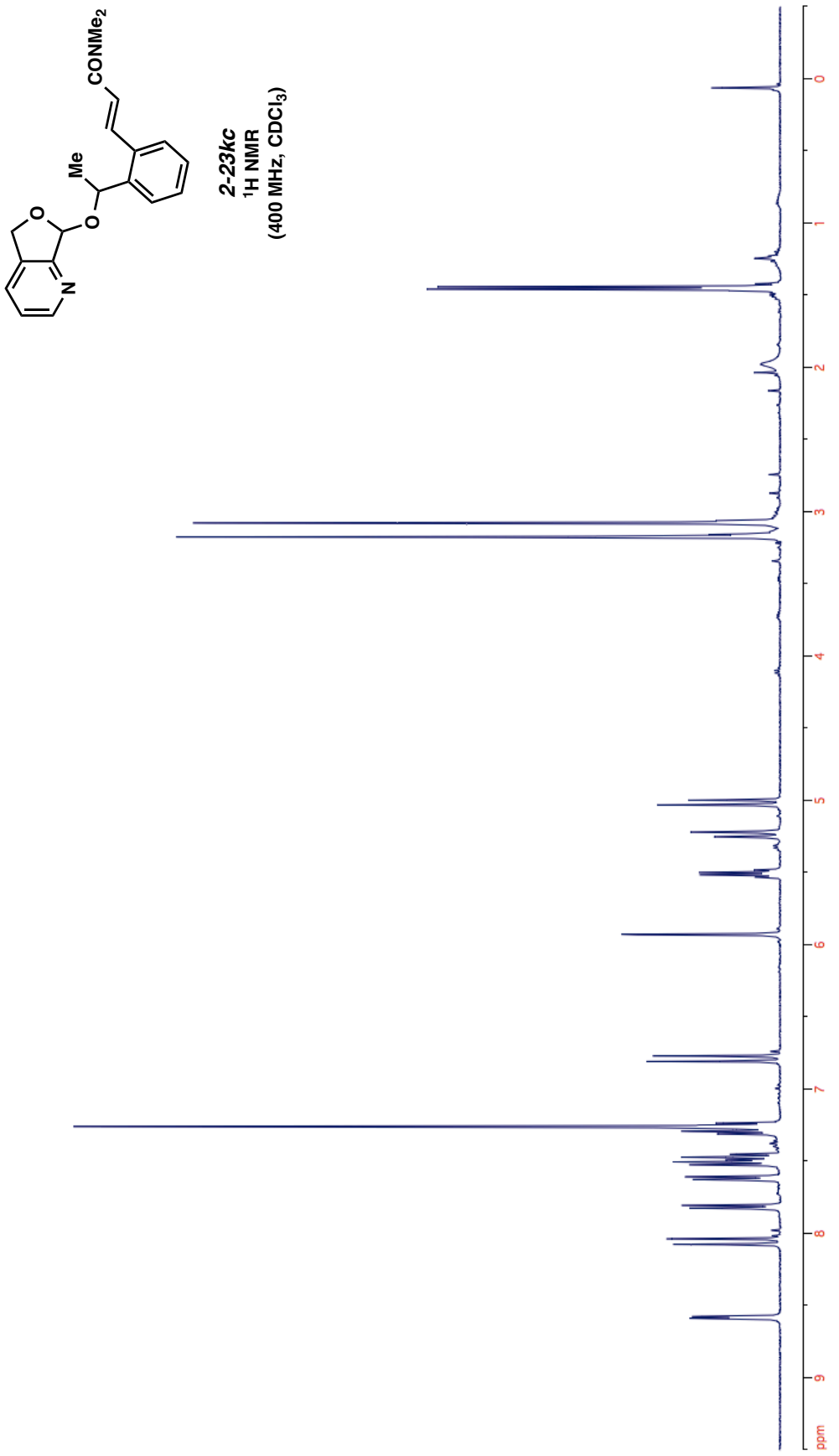
***2-23jc*$_{di}$**
^{13}C NMR
(125 MHz, $CDCl_3$)

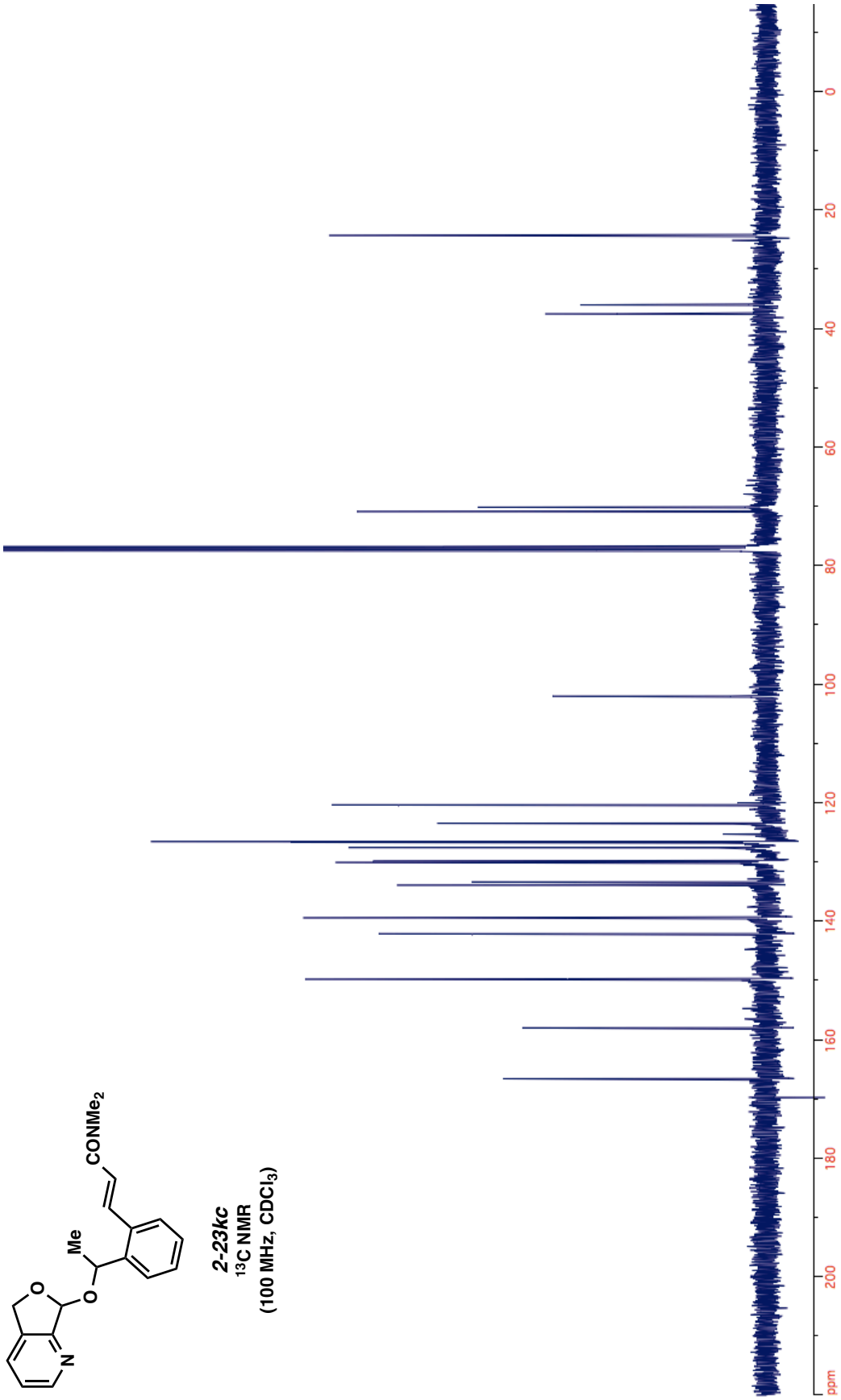


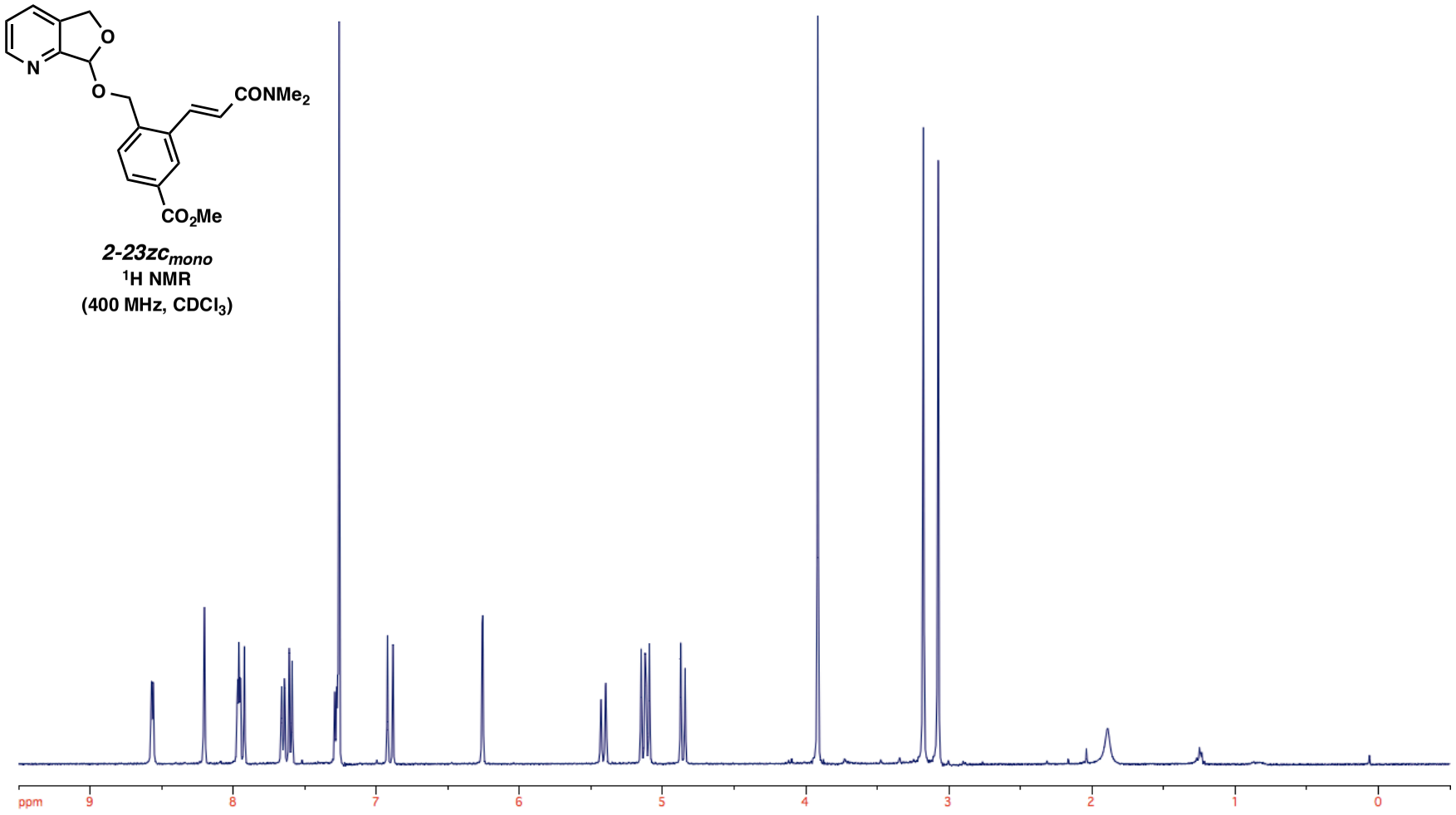
2-23vc
^{1}H NMR
(400 MHz, $CDCl_3$)

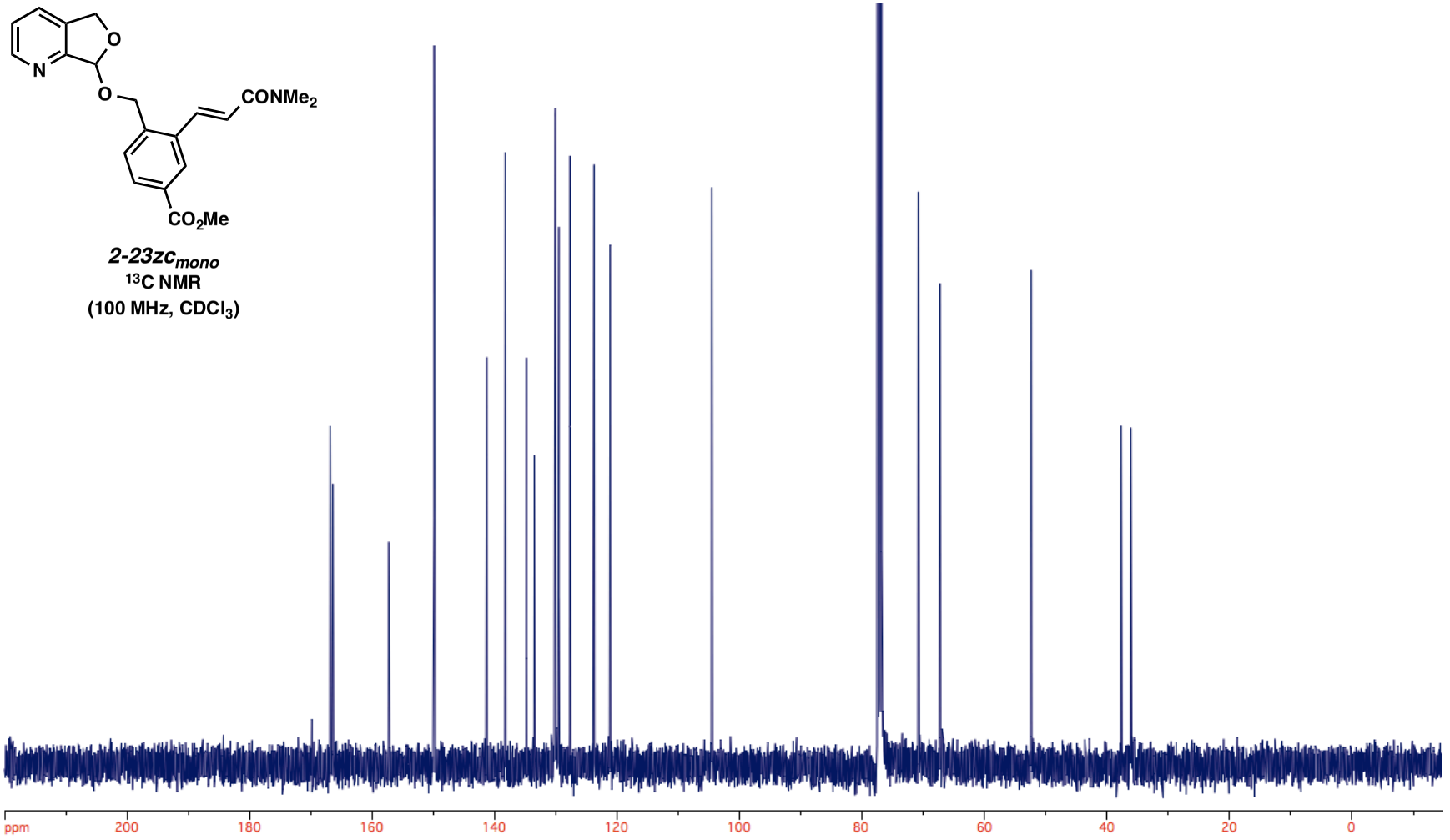



O
N
O
CONMe2
TsN
2-23vc
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

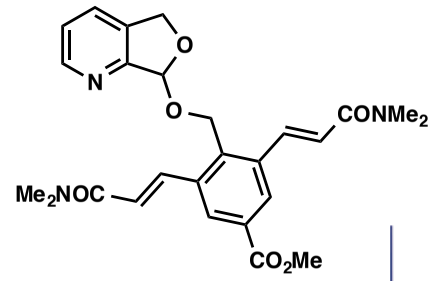

CONMe2
Me
O
O
N
2-23kc
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0


CONMe2
Me
O
O
N
2-23kc
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

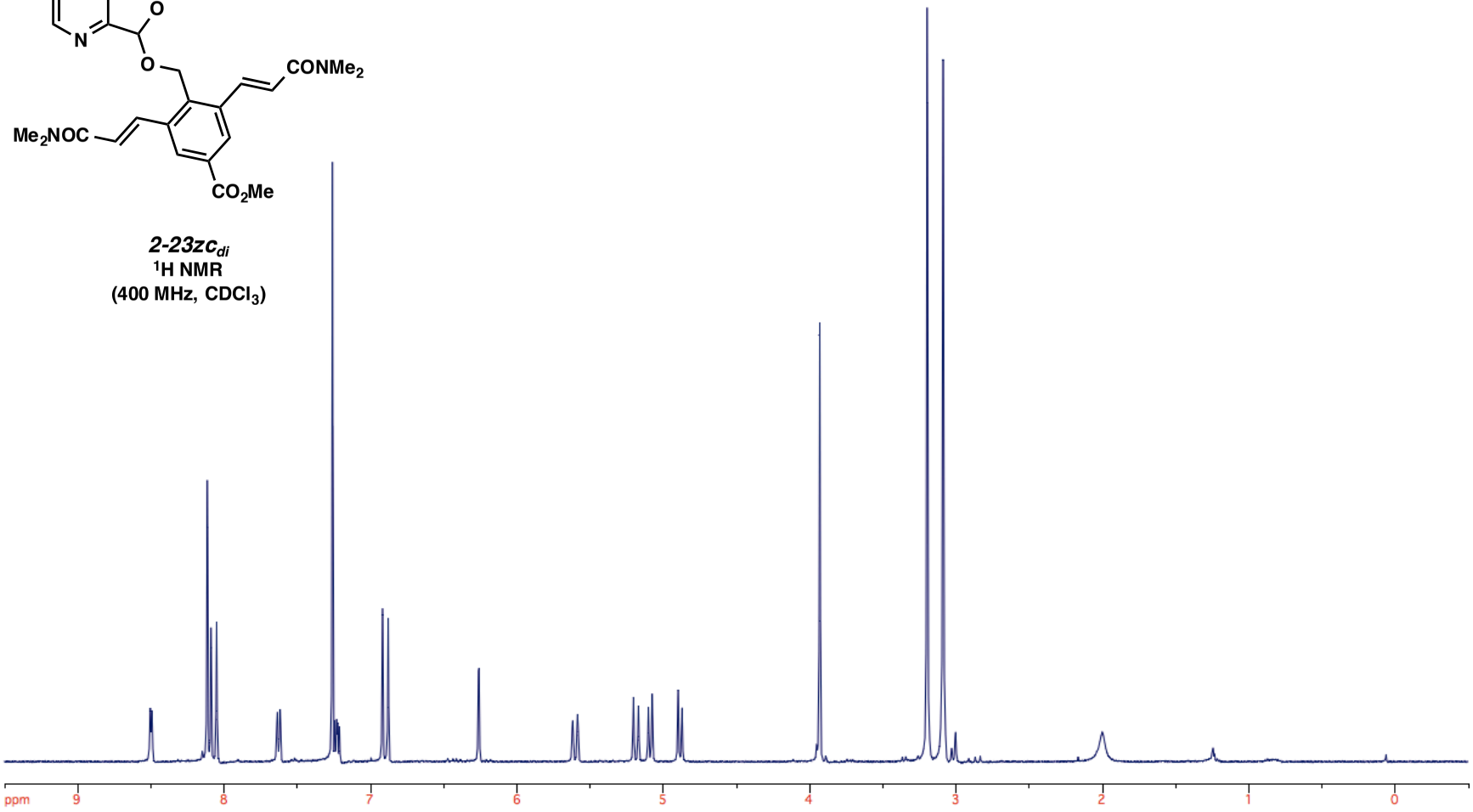

O
N
O
CONMe2
CO2Me
2-23zcmono
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0

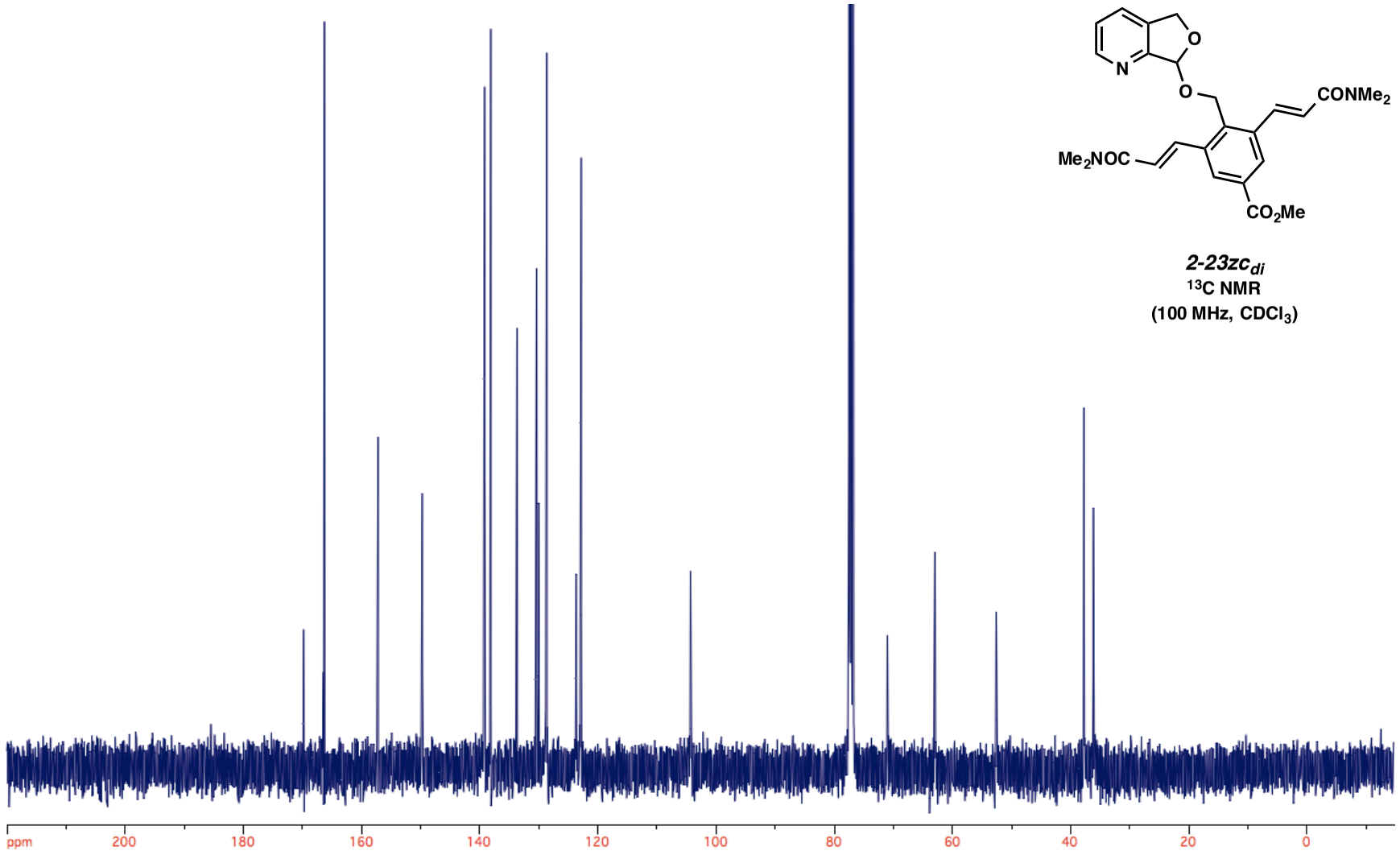


***2-23zc*$_{mono}$**
^{13}C NMR
(100 MHz, $CDCl_3$)

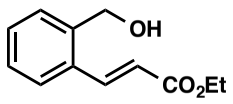


2-23zc$_{di}$
^{1}H NMR
(400 MHz, $CDCl_3$)

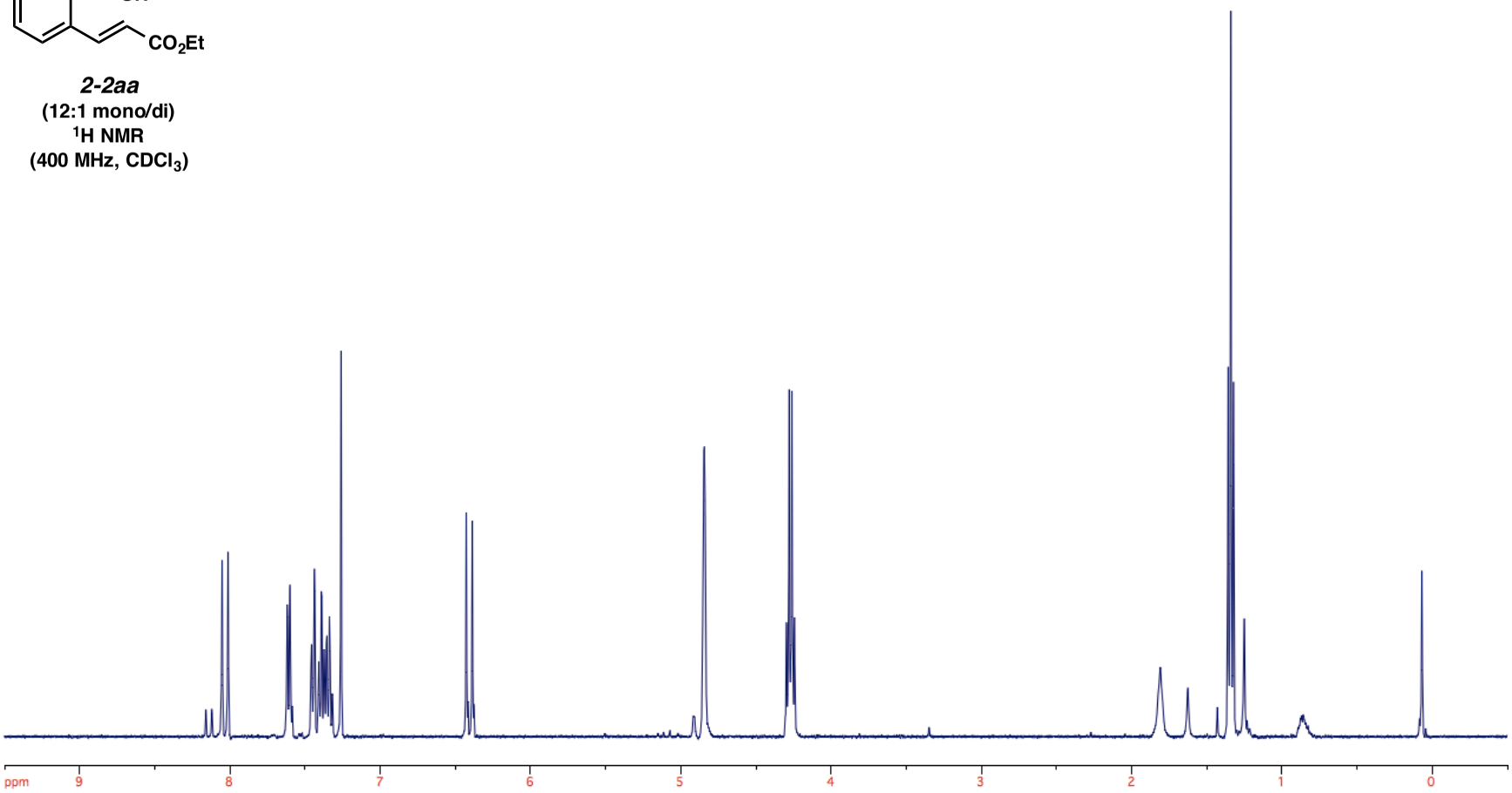


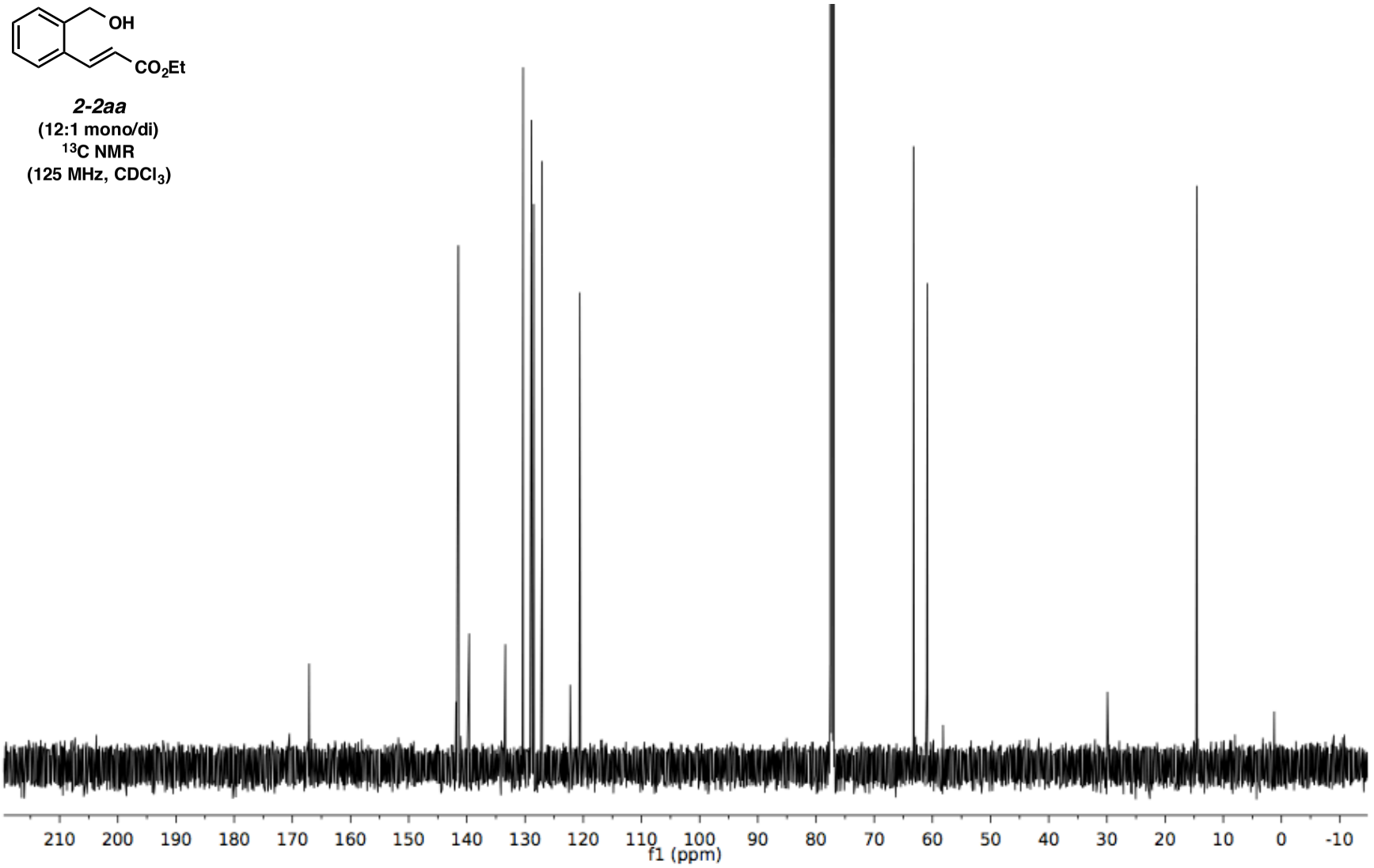


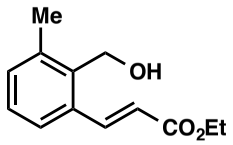
2-23zc$_{di}$
^{13}C NMR
(100 MHz, $CDCl_3$)



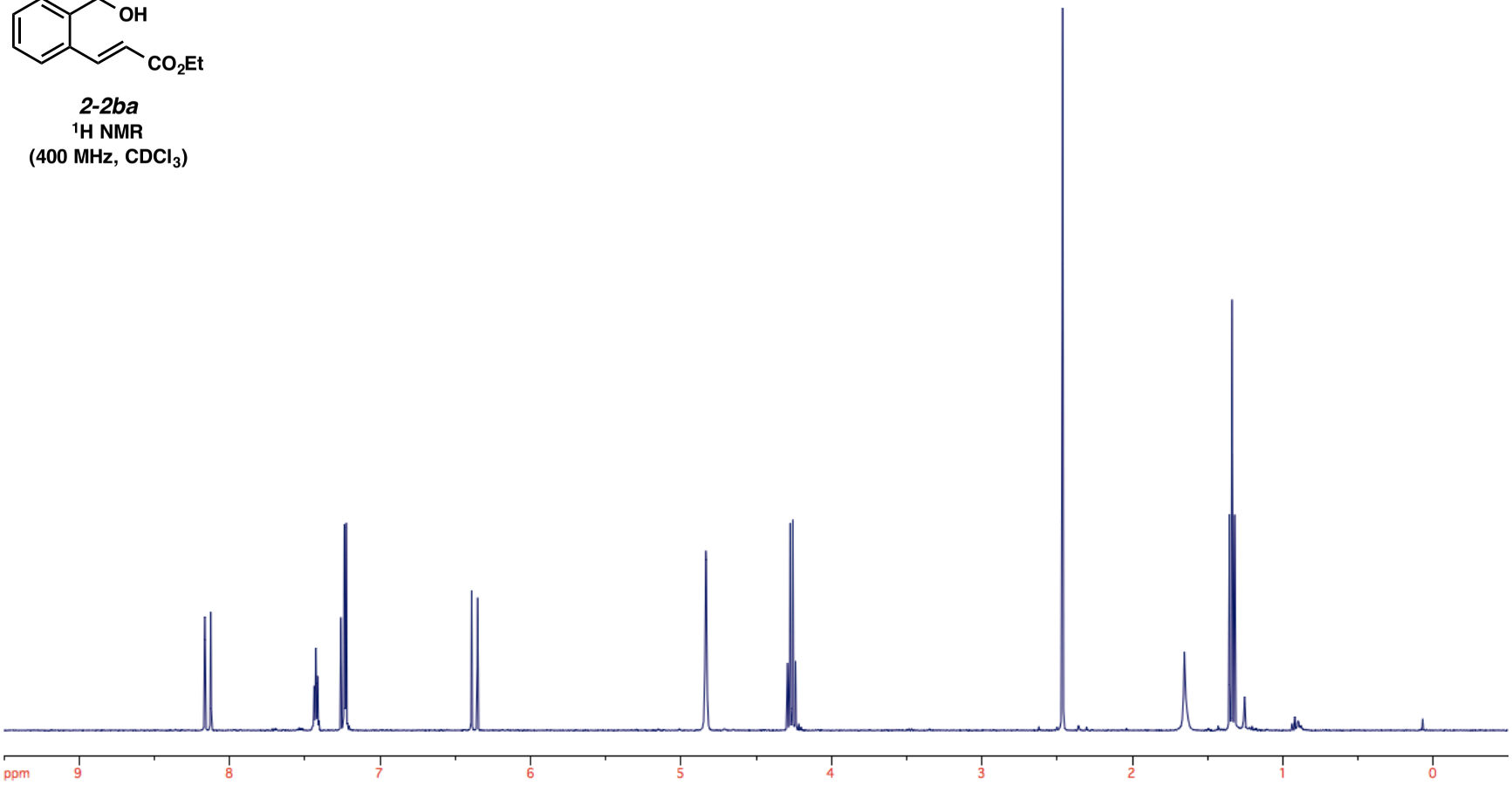
2-2aa
(12:1 mono/di)
^{1}H NMR
(400 MHz, $CDCl_3$)

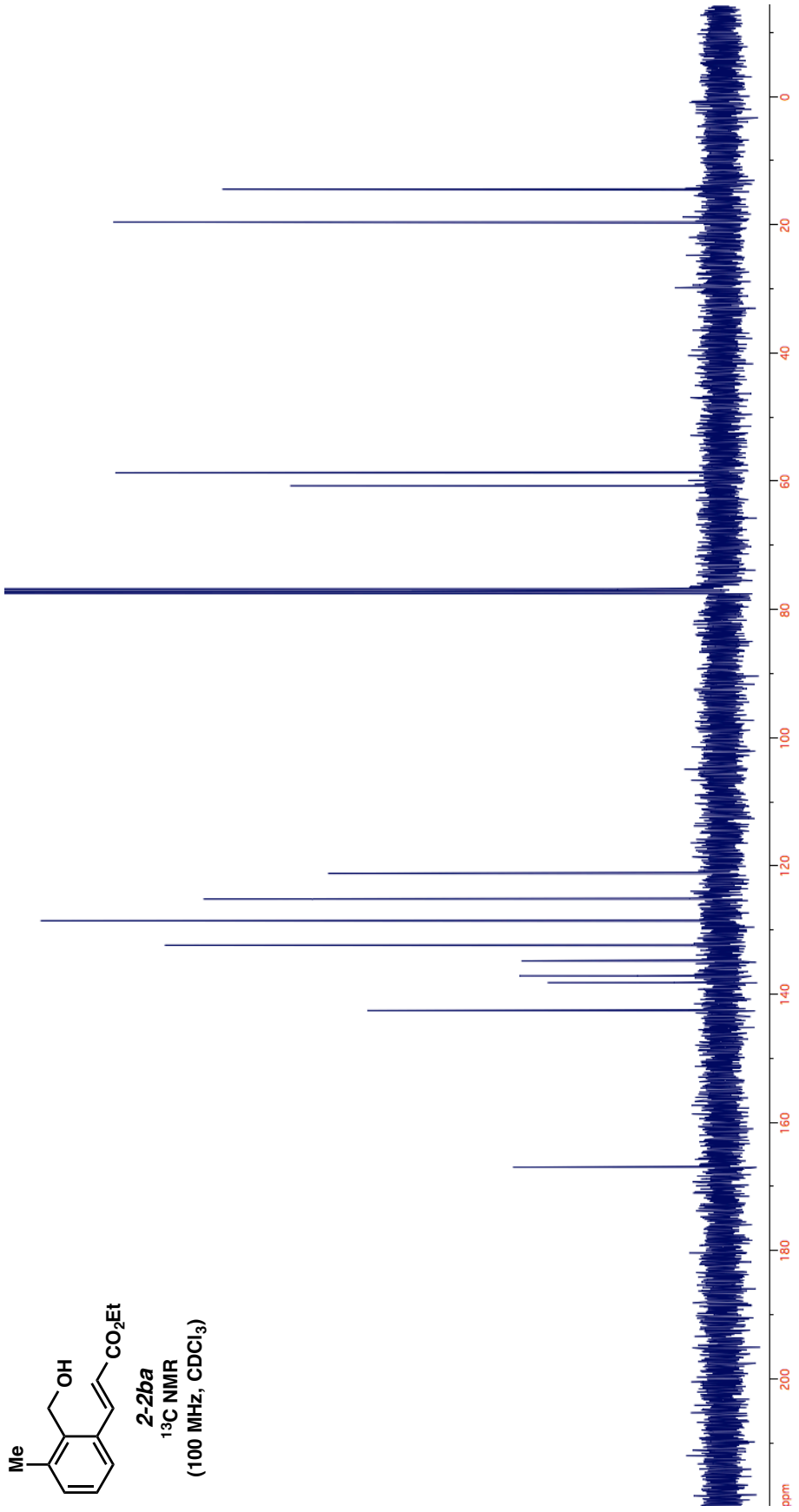


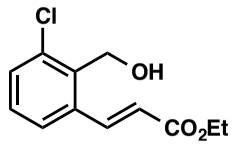

OH
CO2Et
2-2aa
(12:1 mono/di)
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



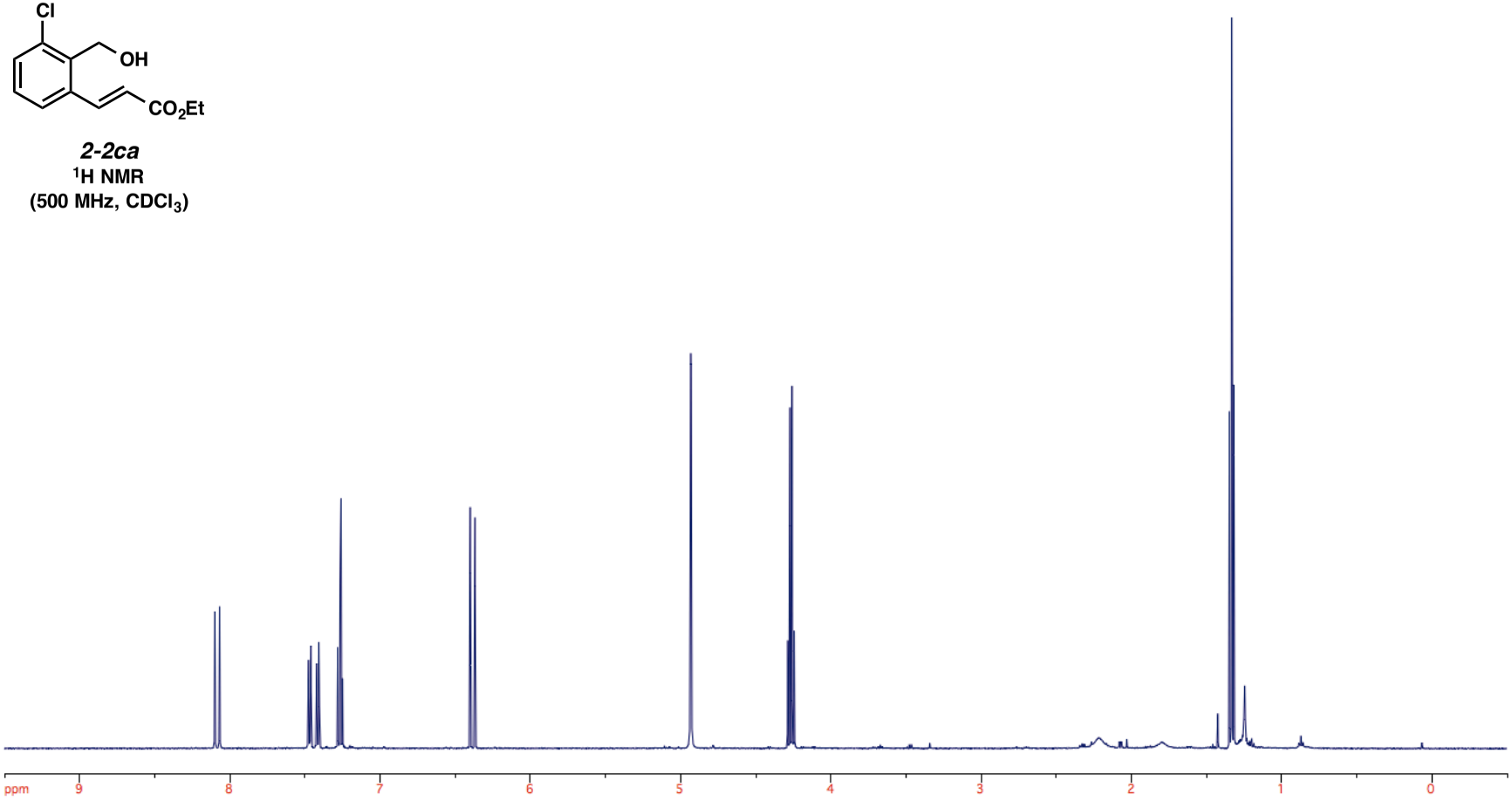
2-2ba
^{1}H NMR
(400 MHz, $CDCl_3$)

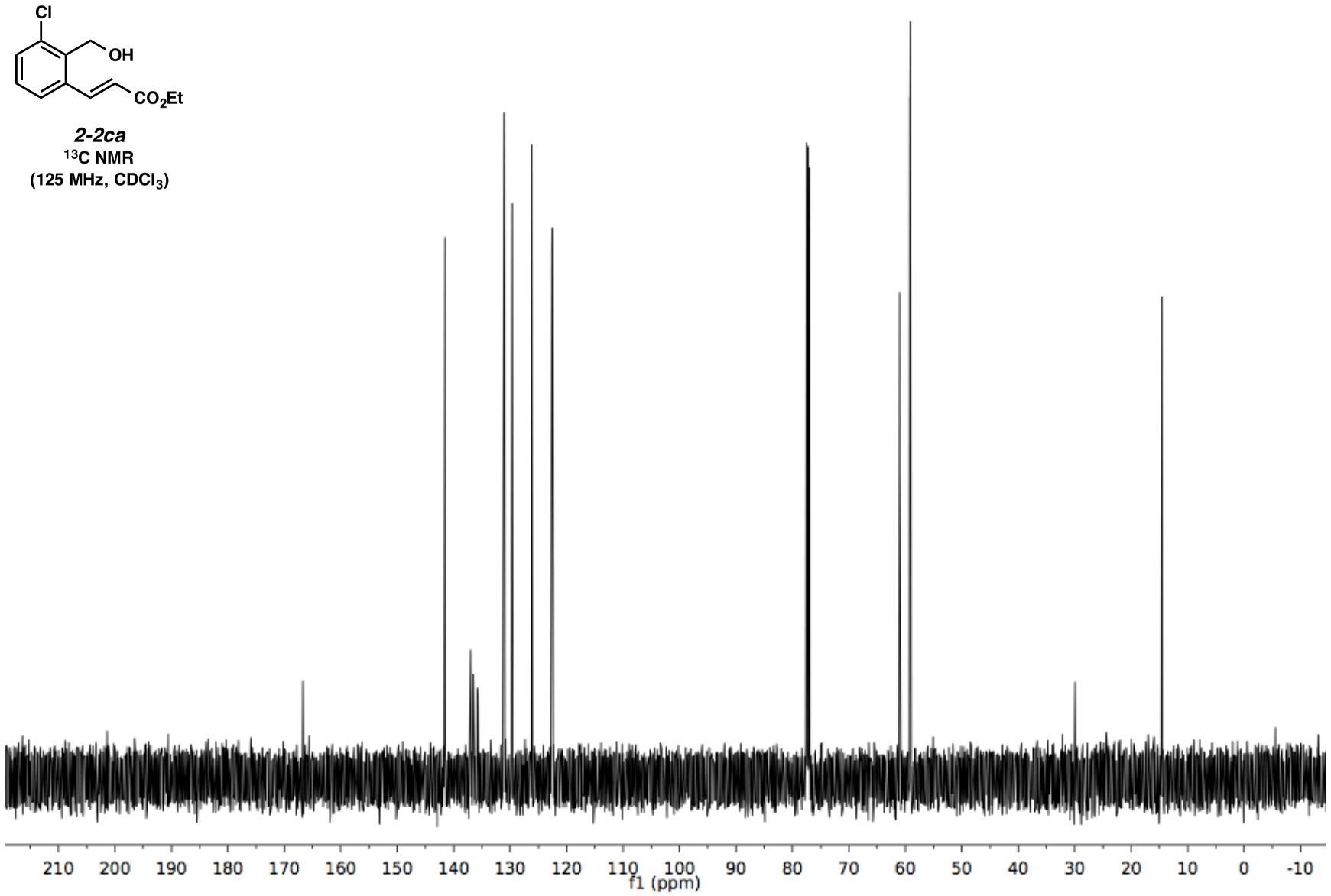


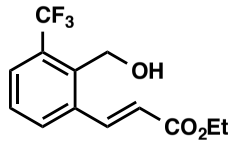

Me
OH
CO2Et
2-2ba
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm



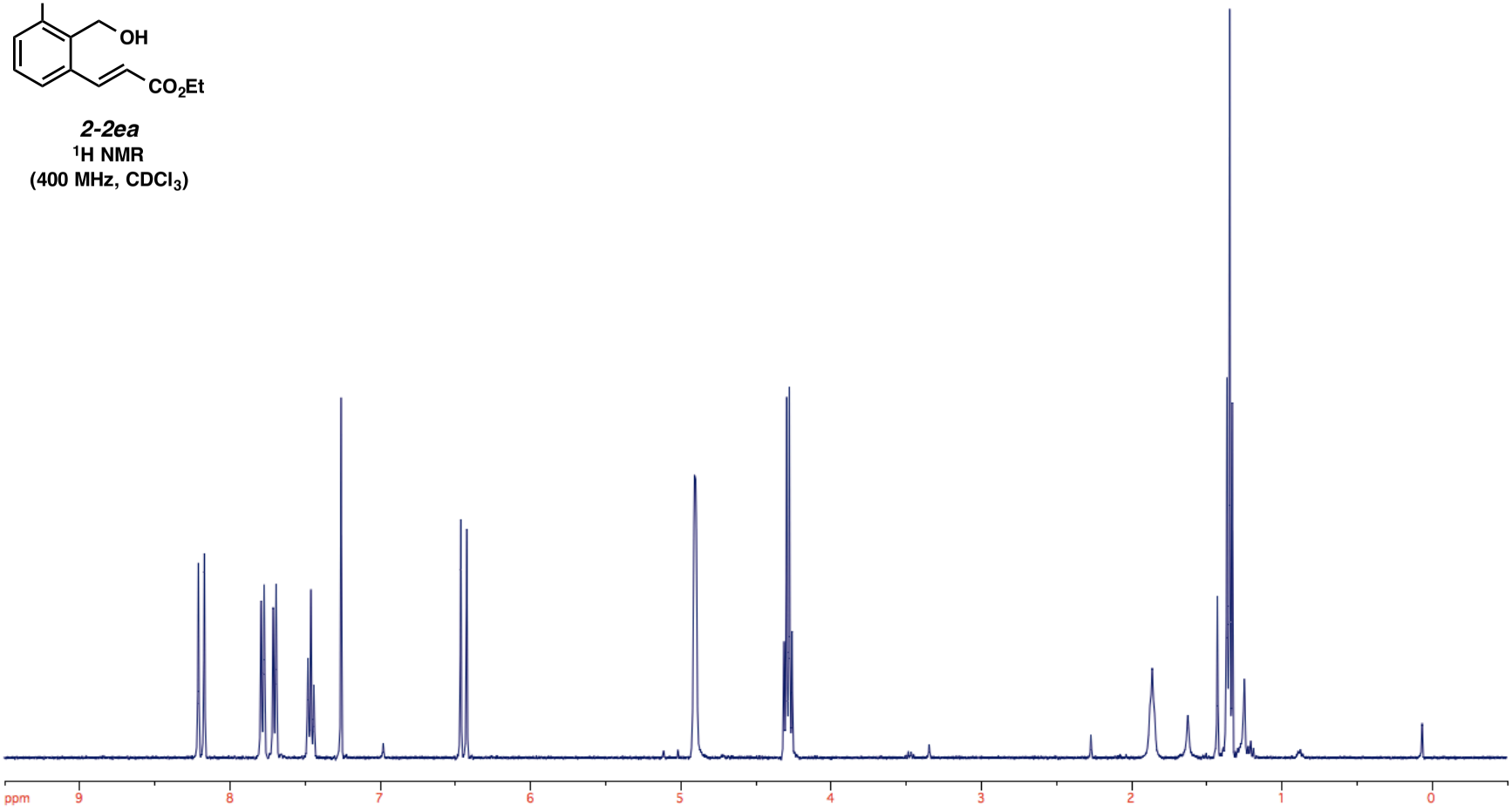
2-2ca
^{1}H NMR
(500 MHz, $CDCl_3$)

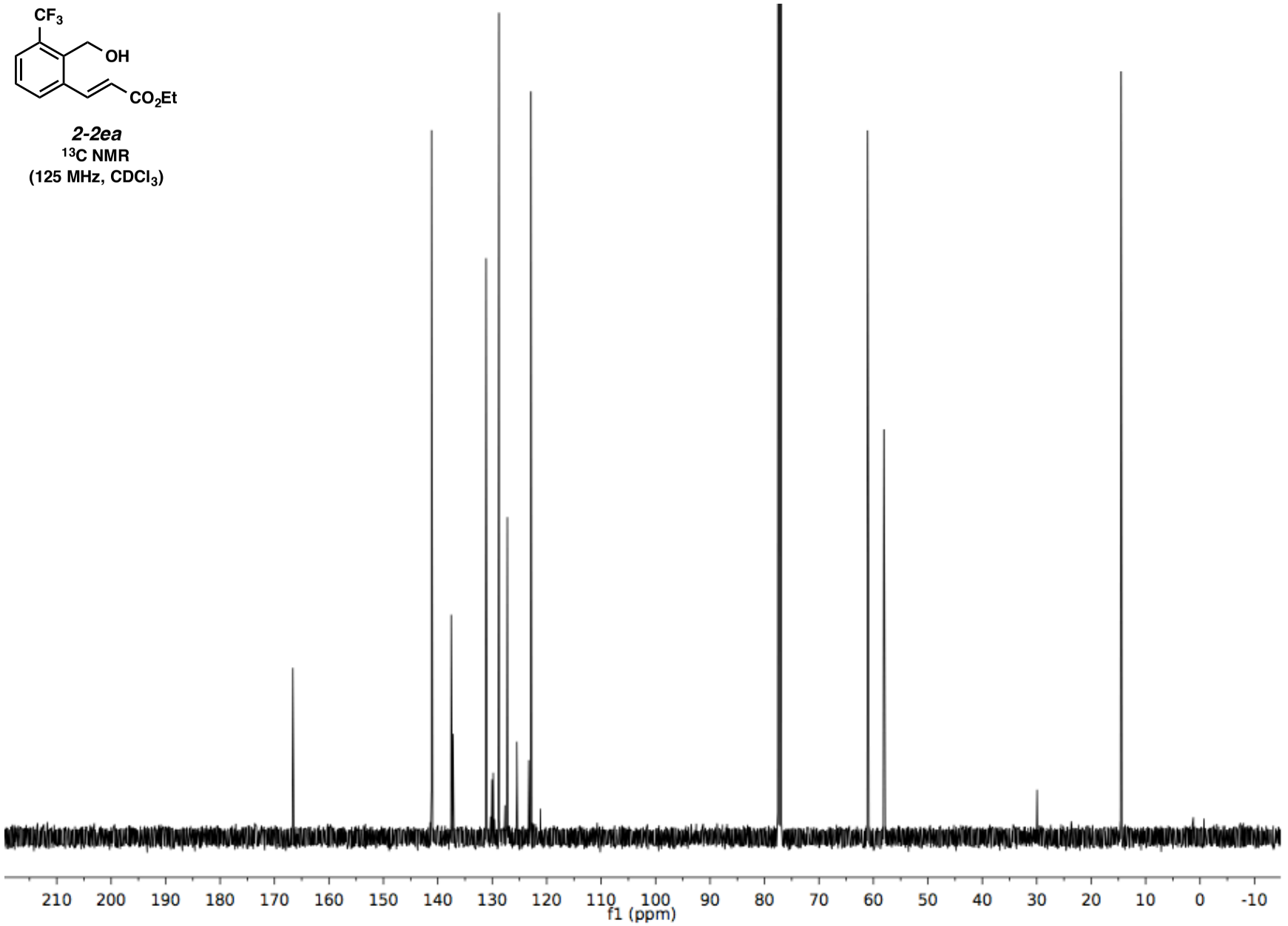


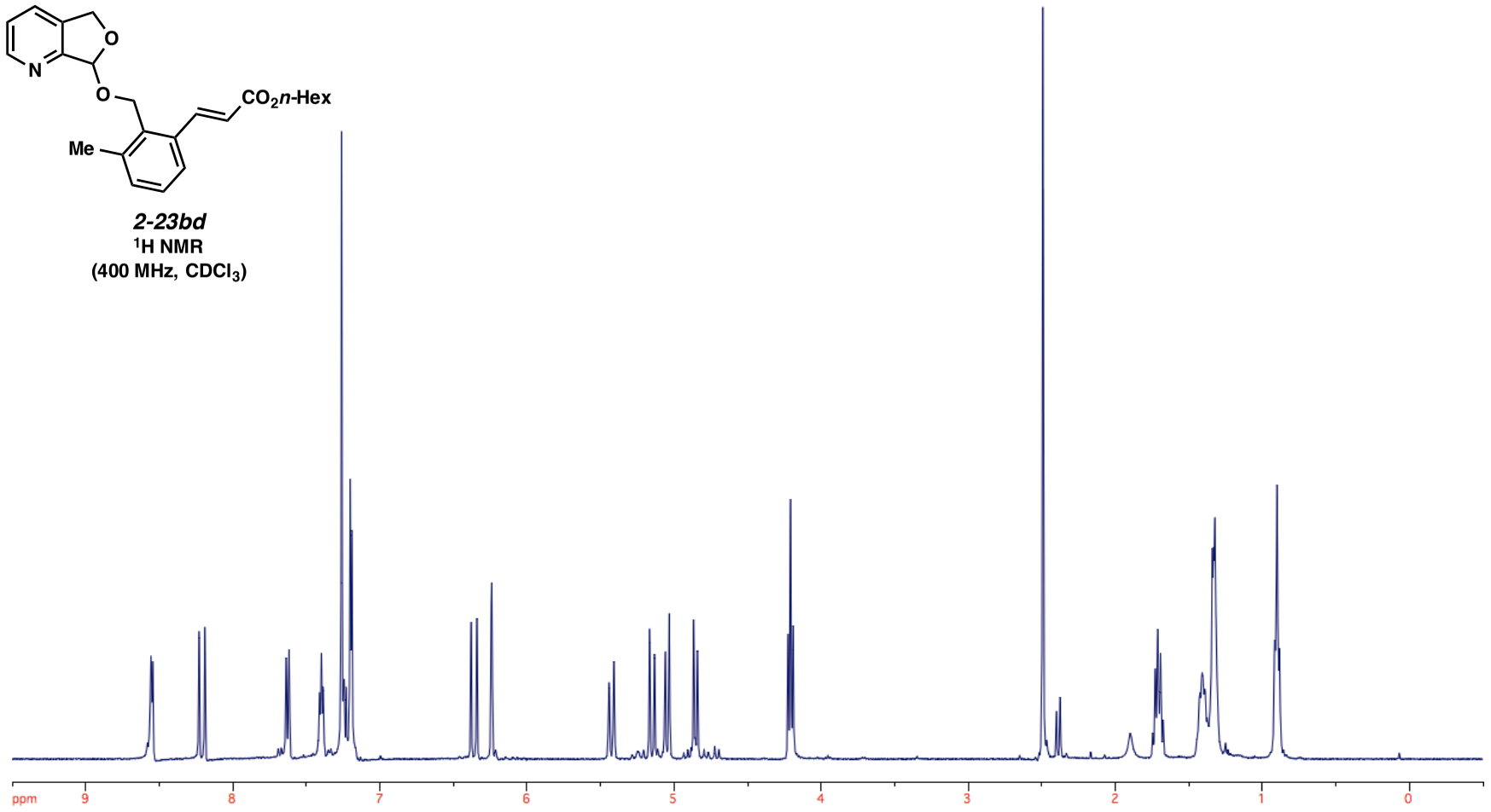

Cl
OH
CO2Et
2-2ca
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



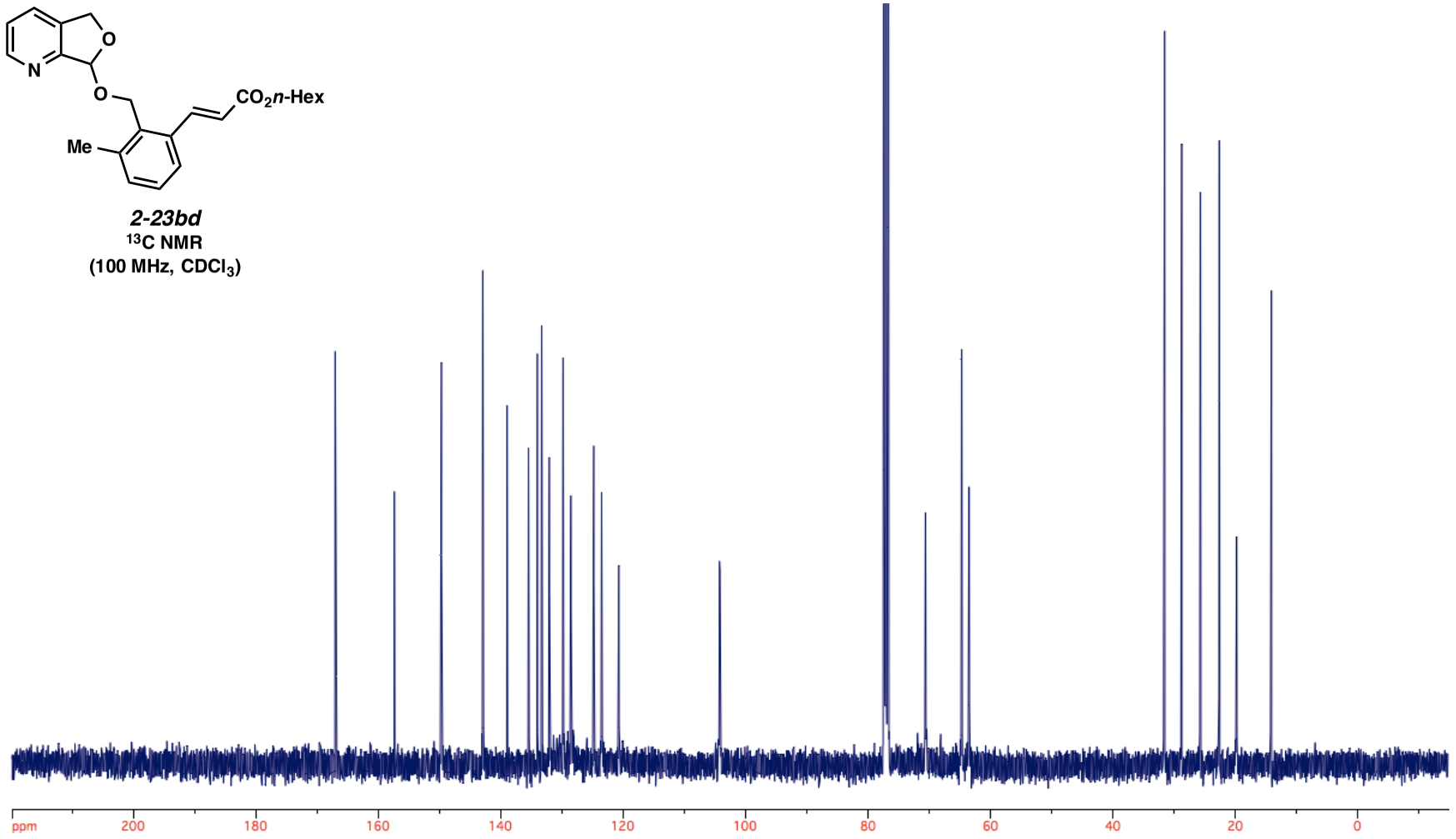
2-2ea
^{1}H NMR
(400 MHz, $CDCl_3$)

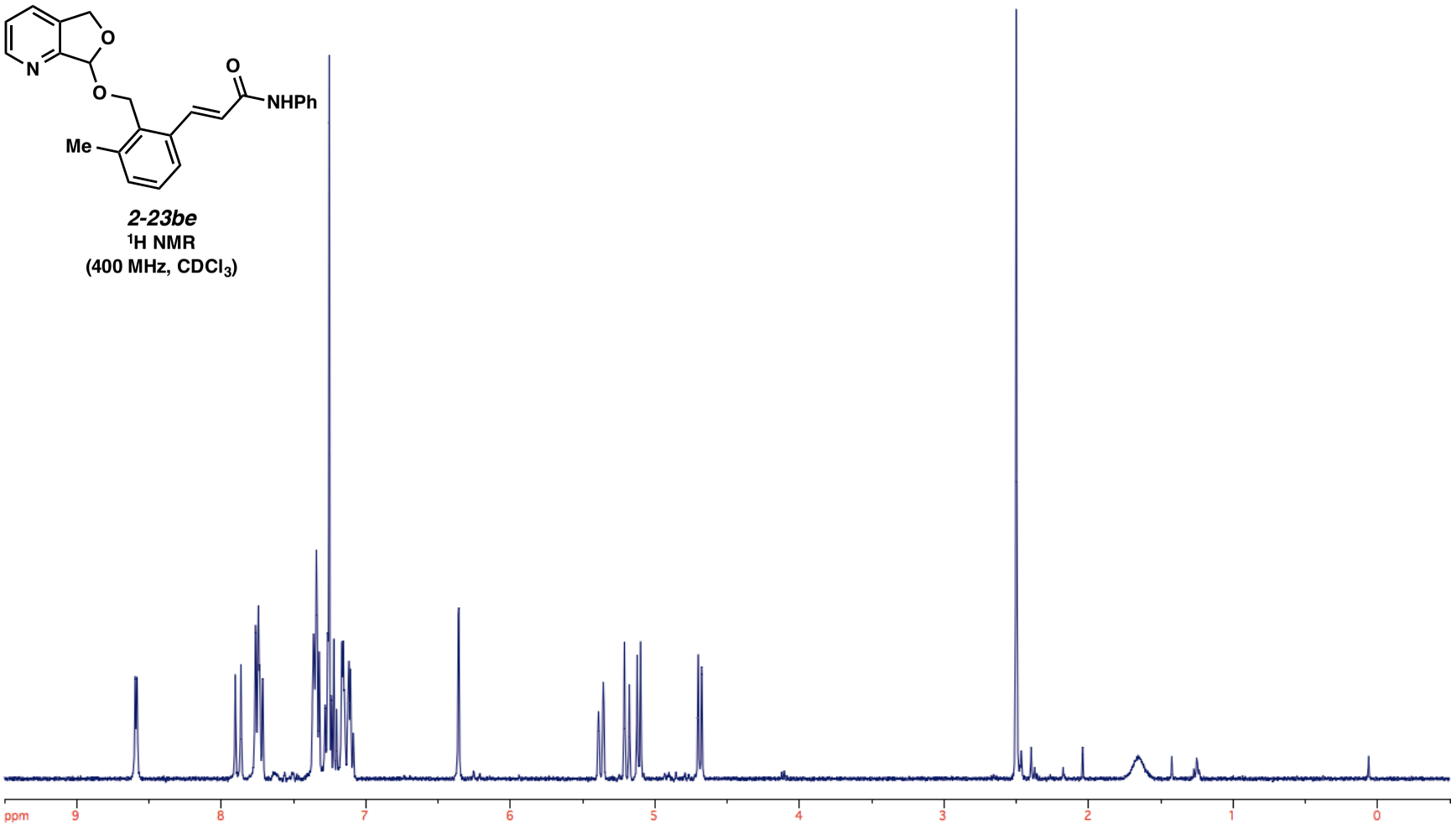



CF3
OH
CO2Et
2-2ea
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



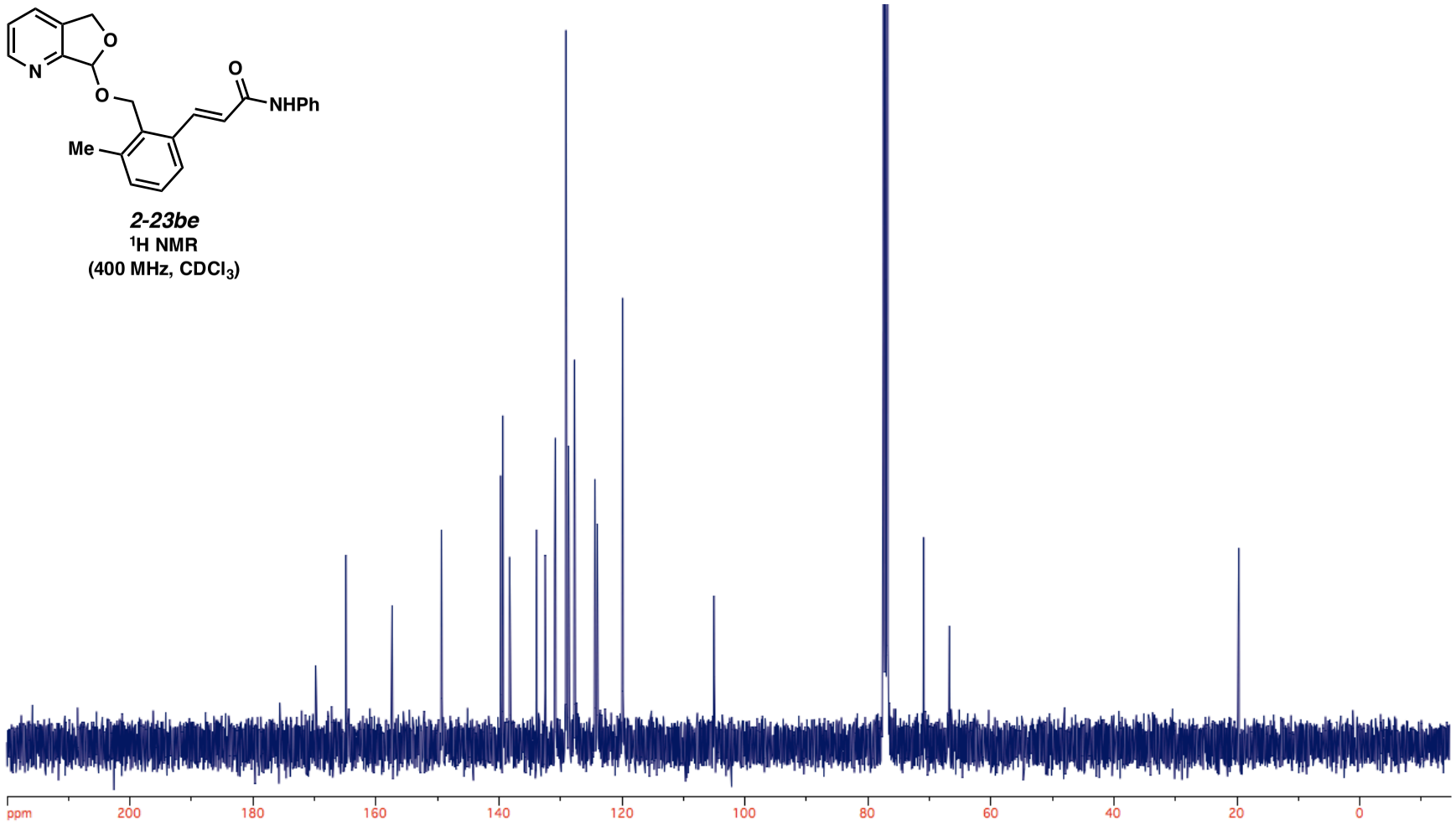
2-23bd
^{1}H NMR
(400 MHz, $CDCl_3$)

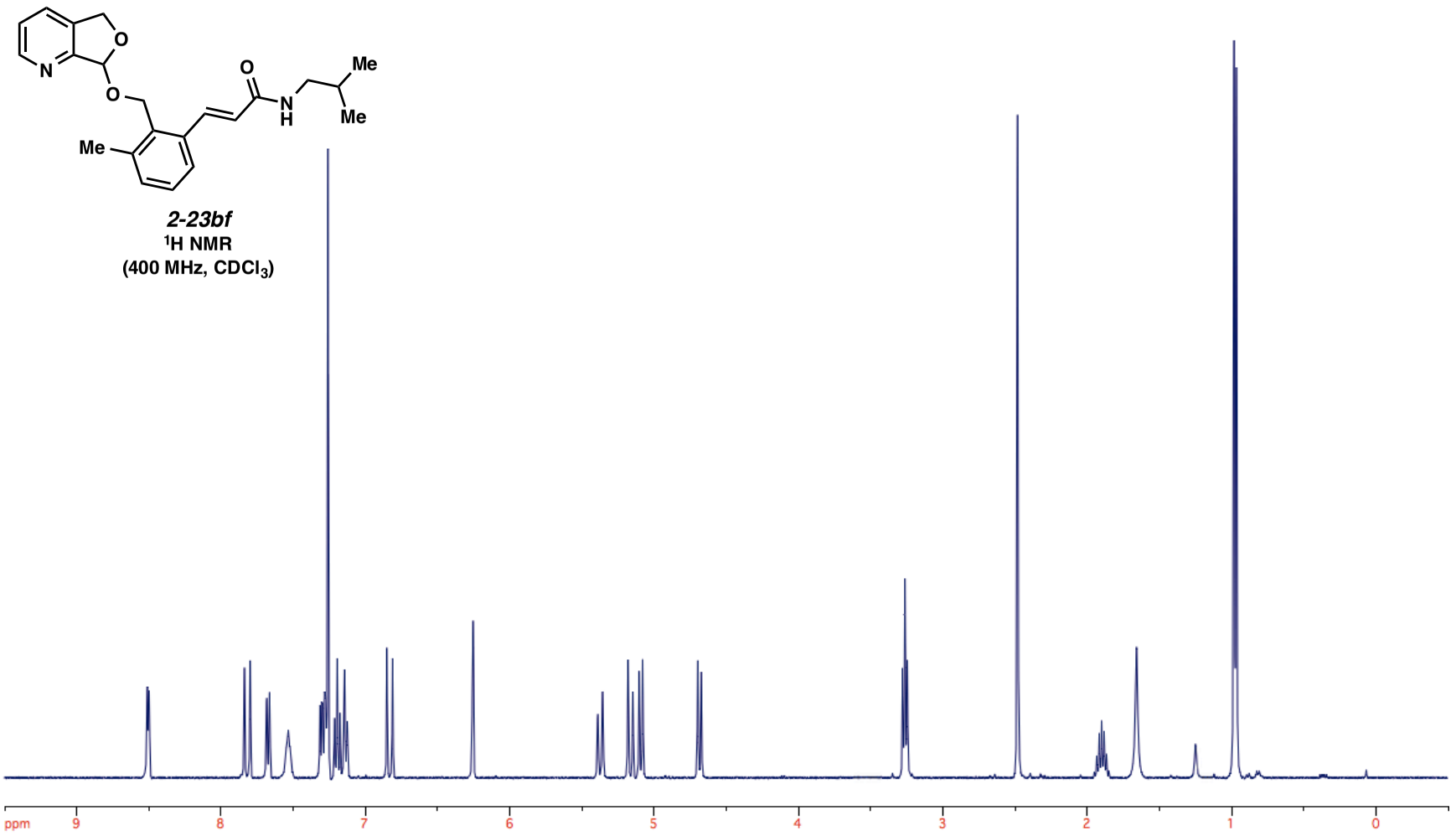

N
O
O
CO2n-Hex
Me
2-23bd
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0



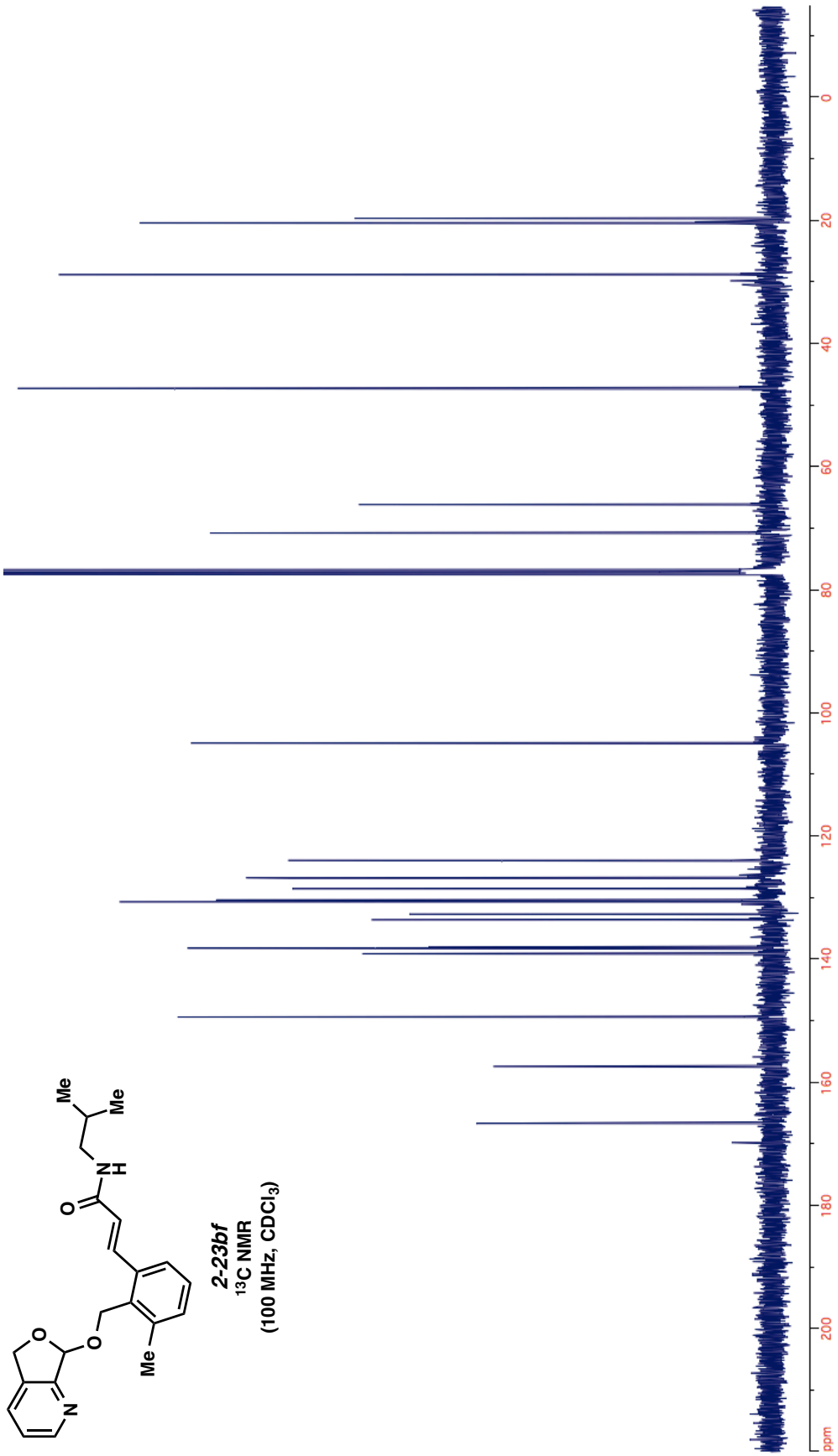
2-23be
^{1}H NMR
(400 MHz, $CDCl_3$)

2-23be
^{1}H NMR
(400 MHz, $CDCl_3$)

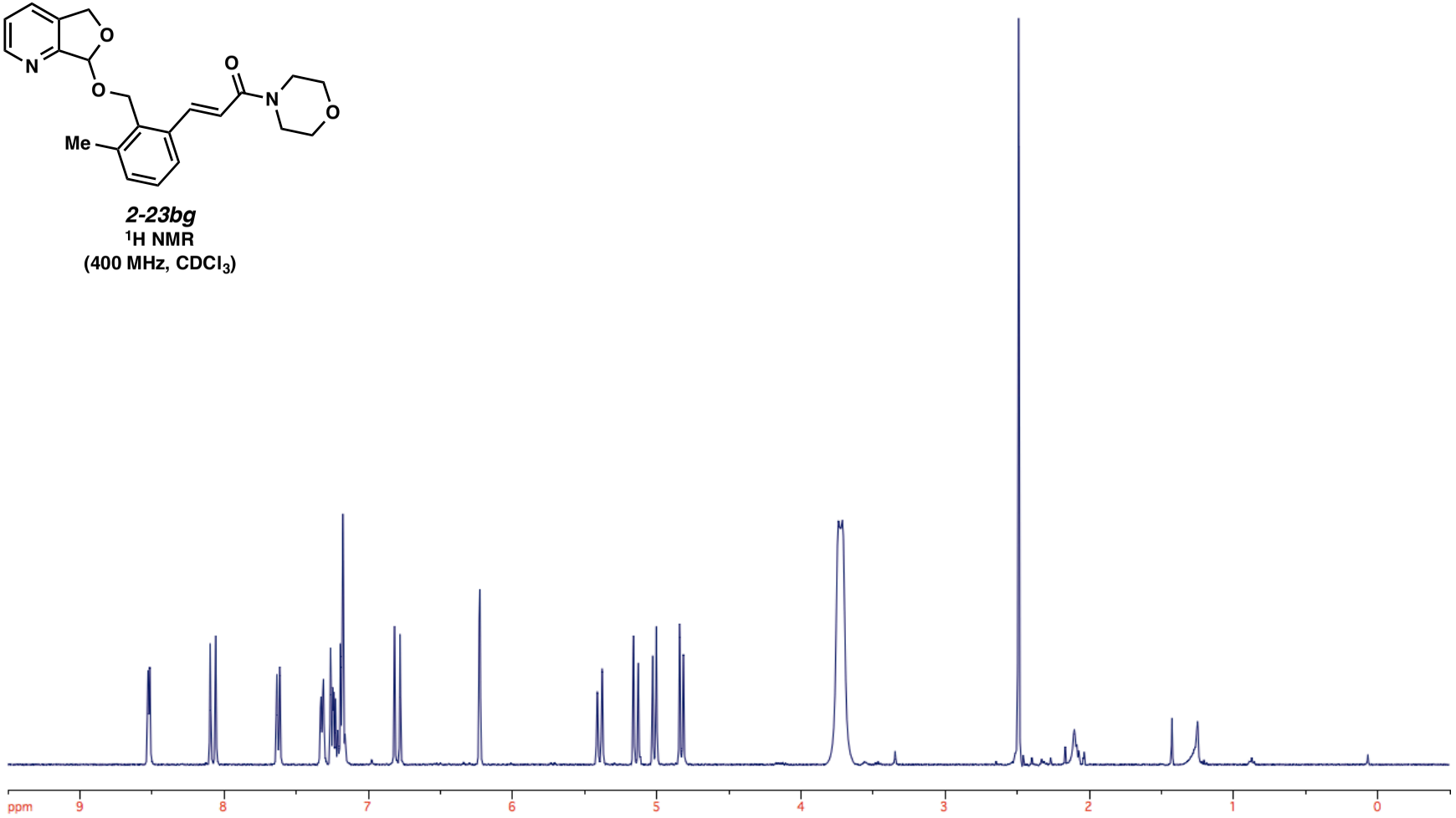


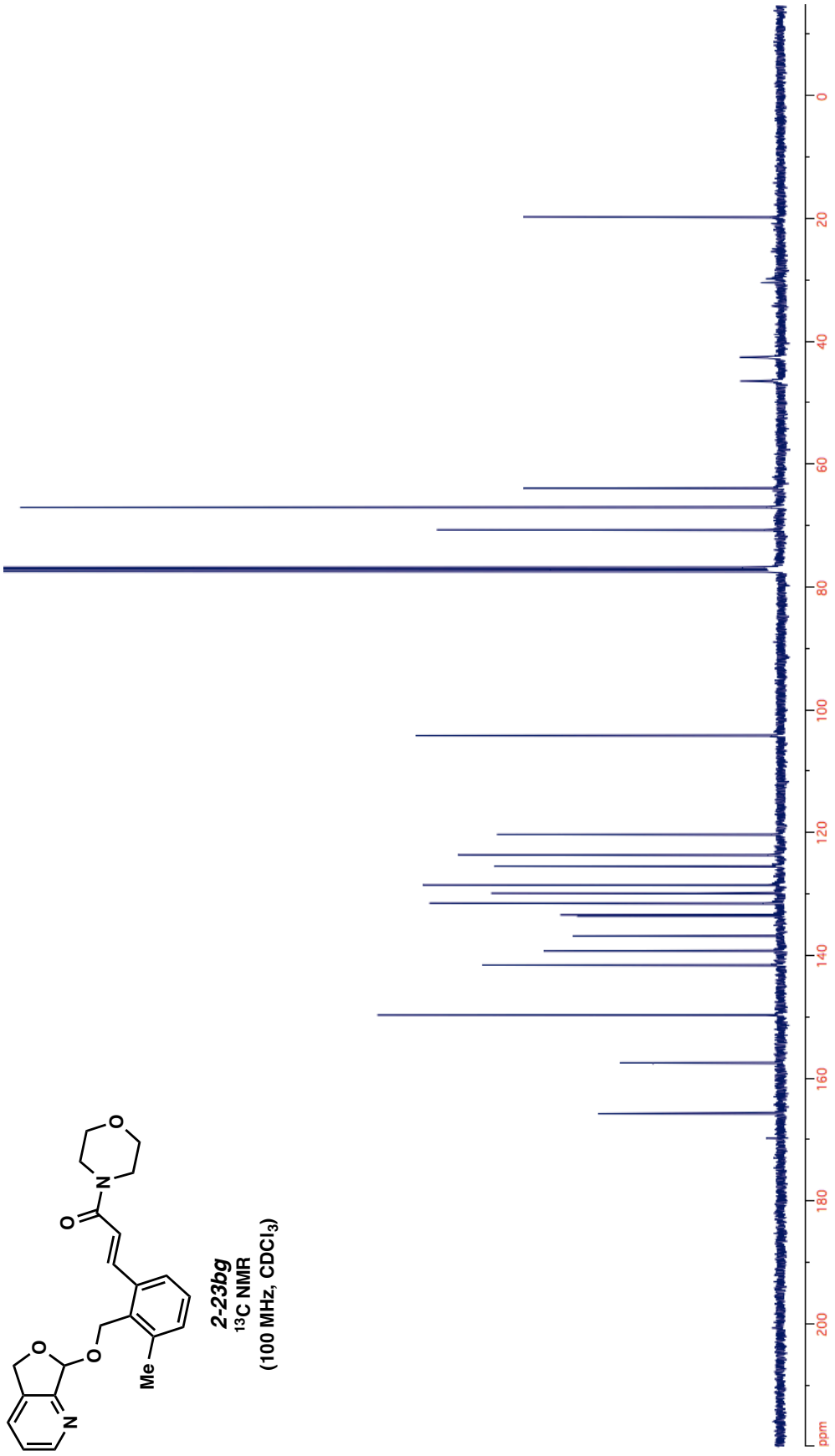


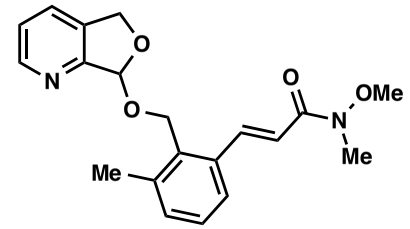
2-23bf
^{1}H NMR
(400 MHz, $CDCl_3$)


Me
Me
N
H
O
O
O
O
Me
N
2-23bf
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

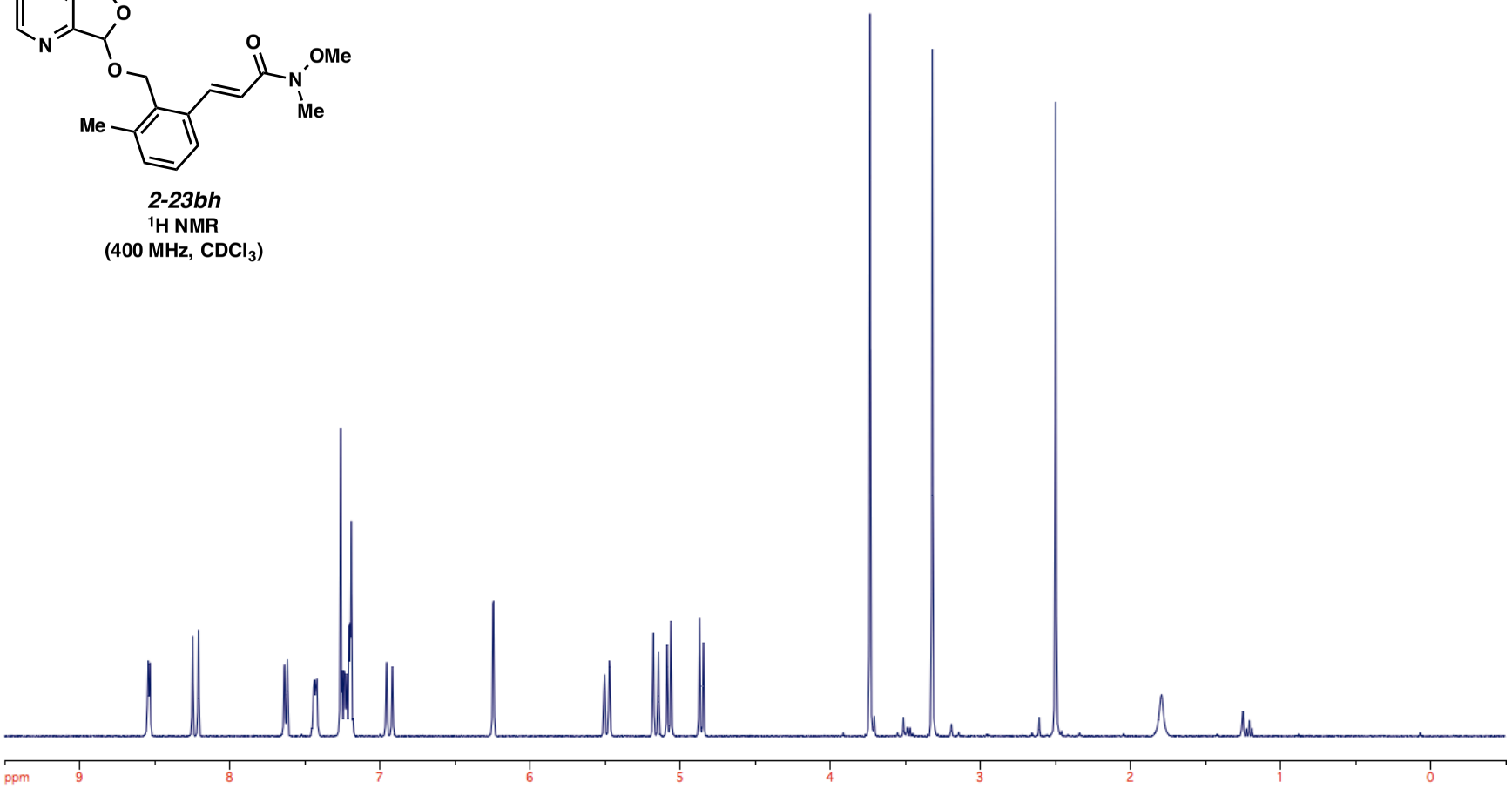
2-23bg
^{1}H NMR
(400 MHz, $CDCl_3$)

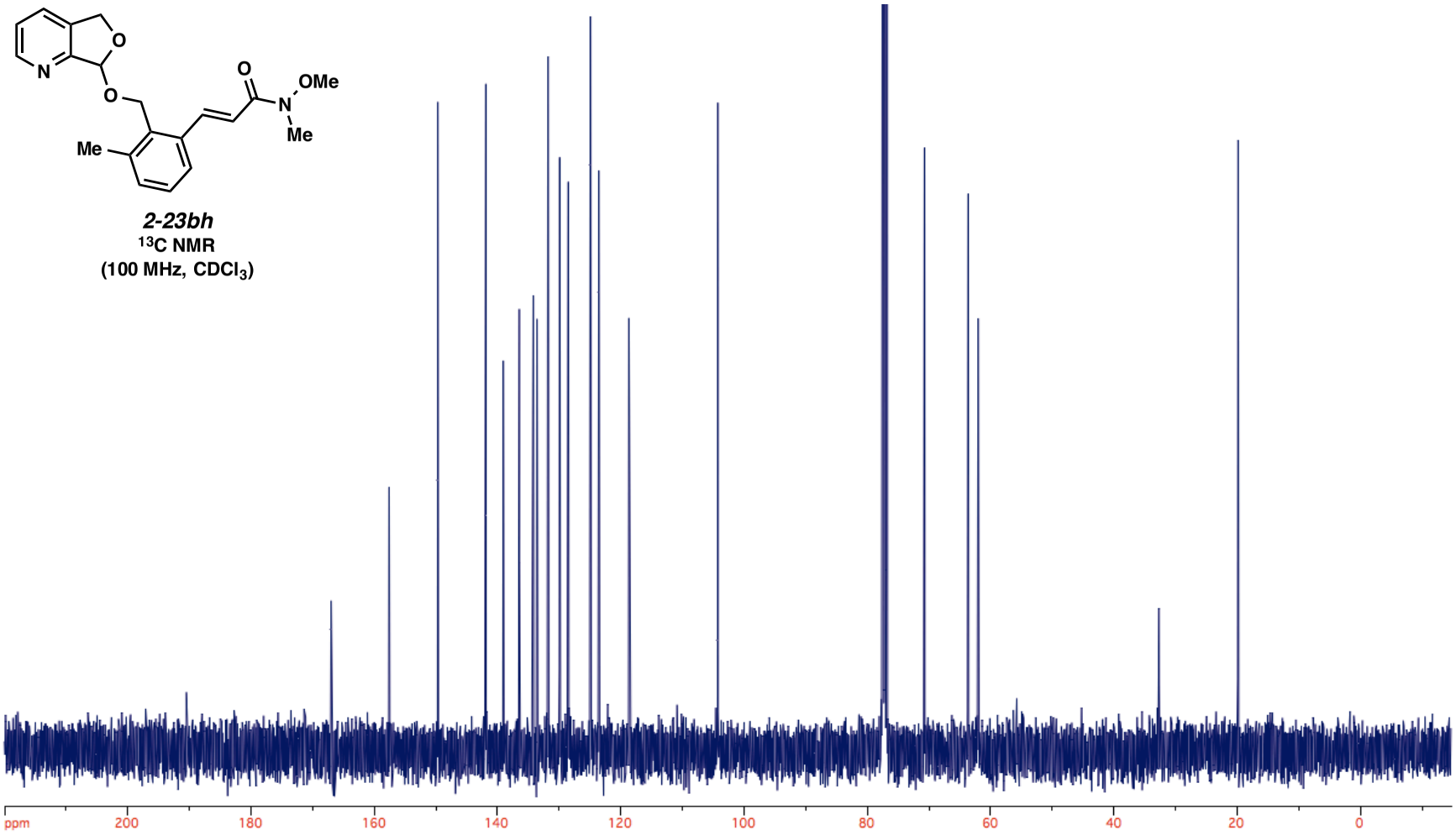



O
N
O
O
O
O
N
Me
2-23bg
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

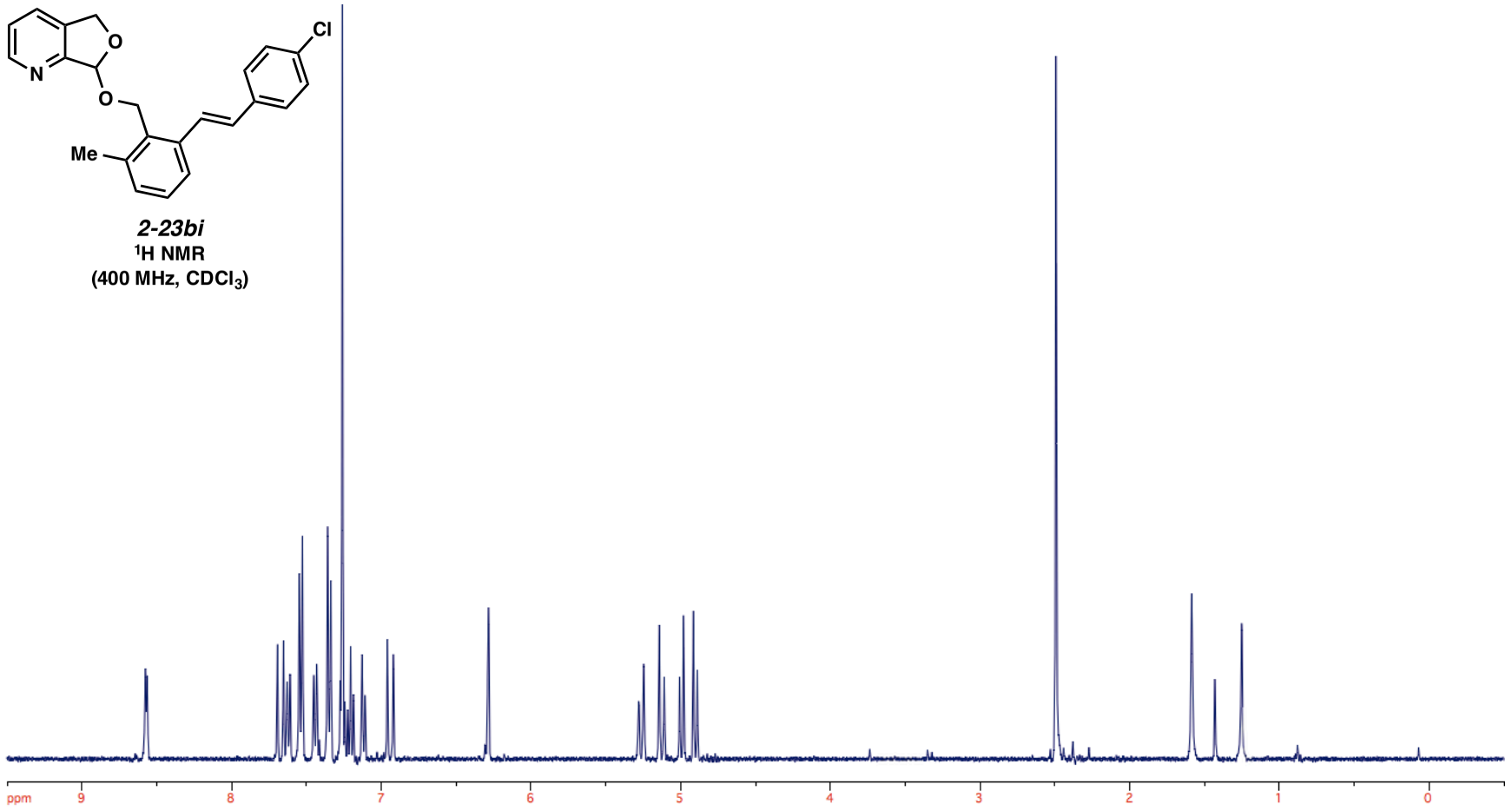


2-23bh
^{1}H NMR
(400 MHz, $CDCl_3$)

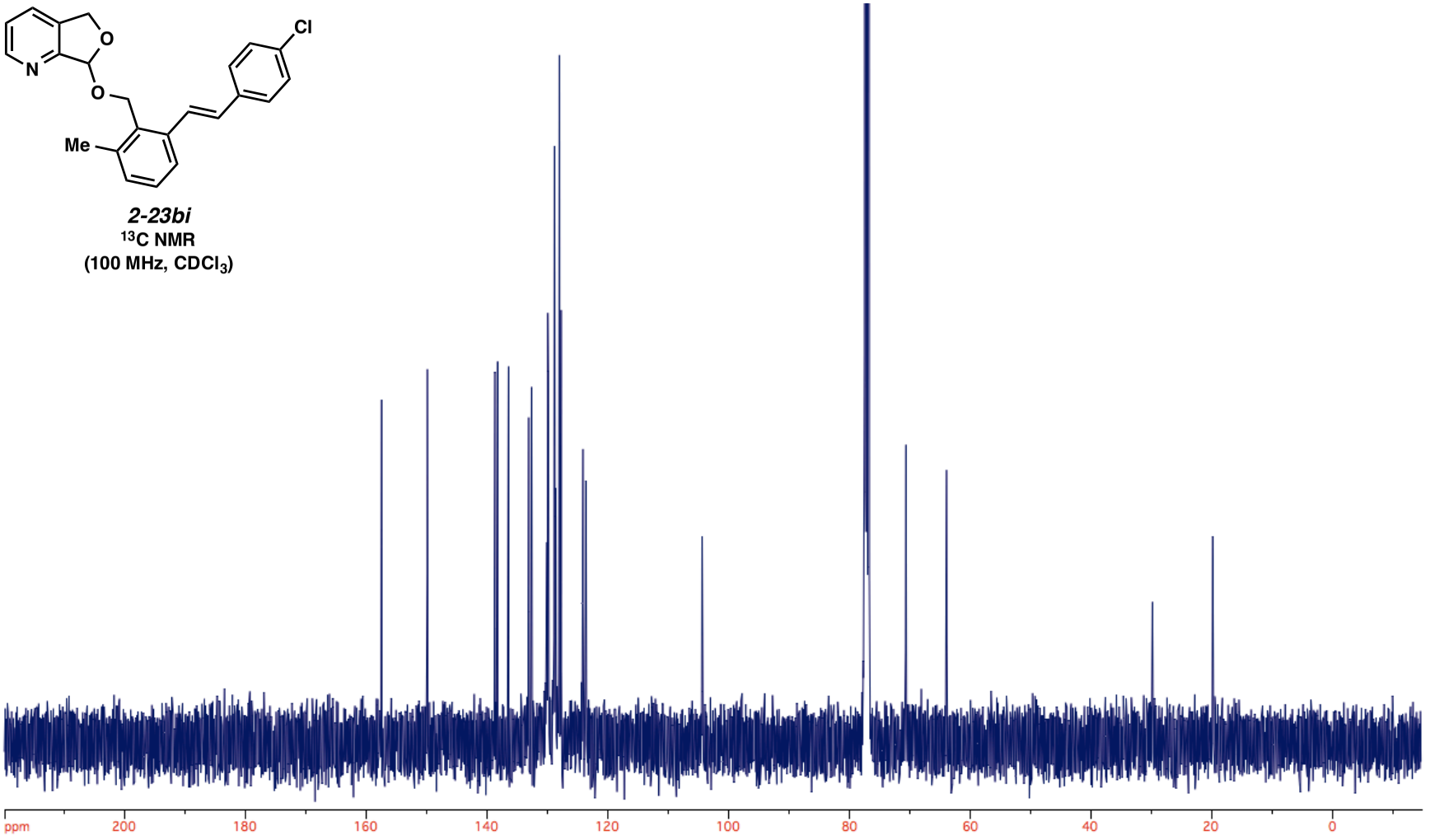




2-23bh
^{13}C NMR
(100 MHz, $CDCl_3$)



2-23bi
^{1}H NMR
(400 MHz, $CDCl_3$)

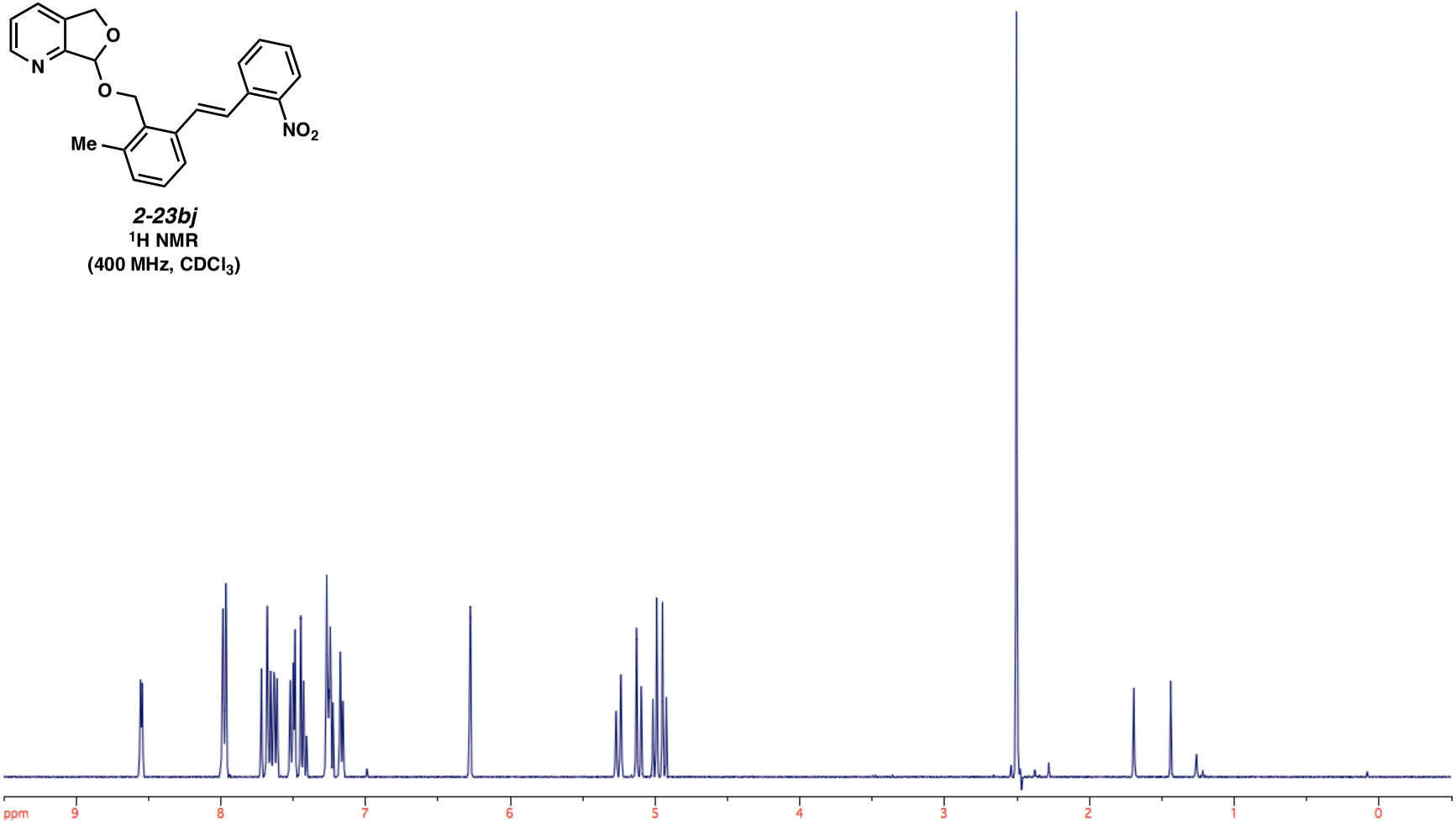


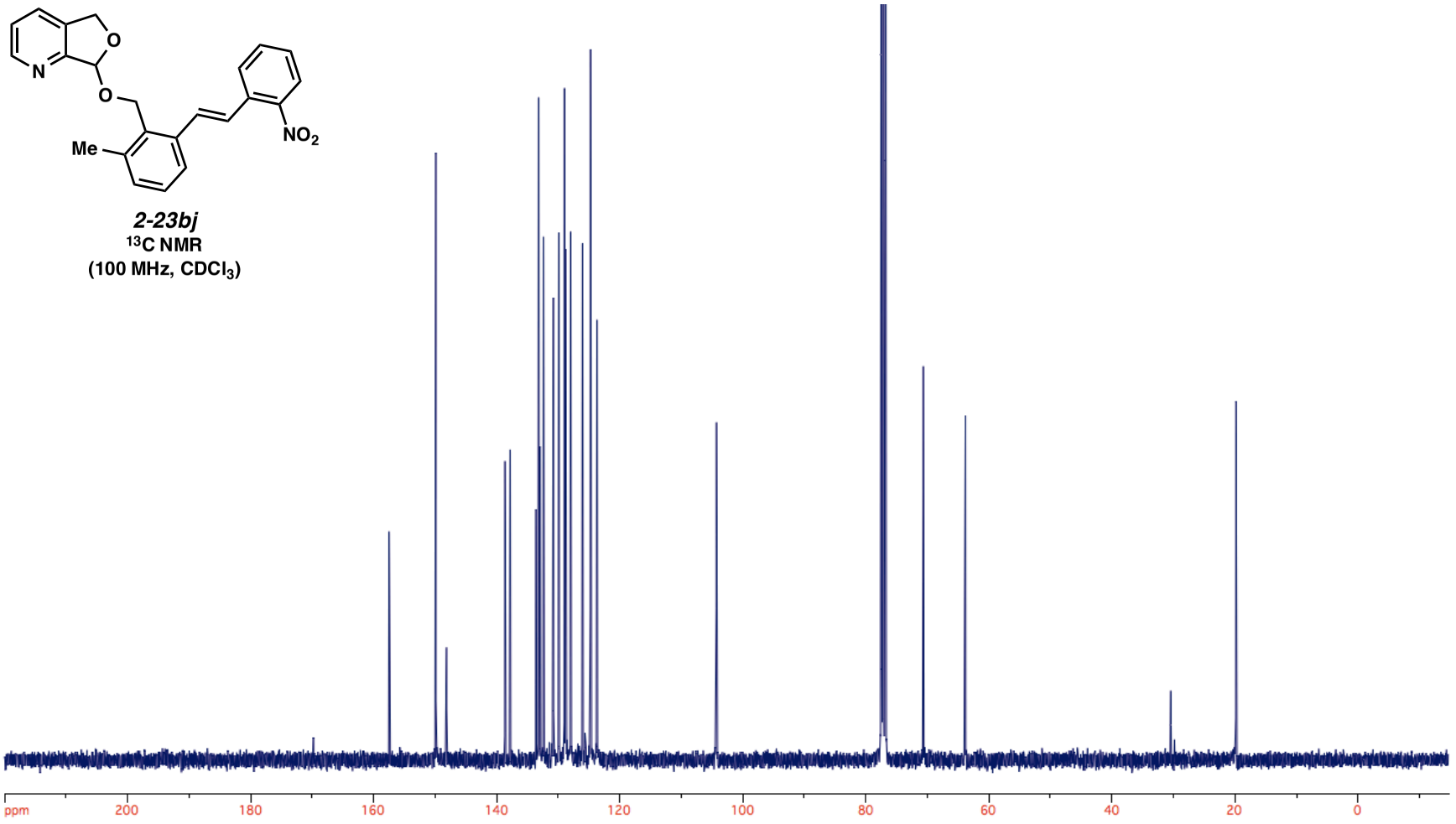
2-23bi

^{13}C NMR

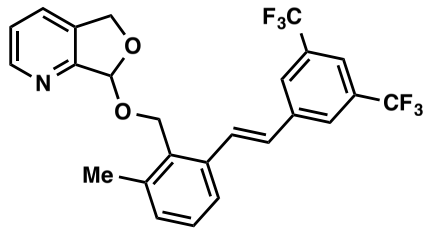
(100 MHz, $CDCl_3$)

2-23bj
^{1}H NMR
(400 MHz, $CDCl_3$)

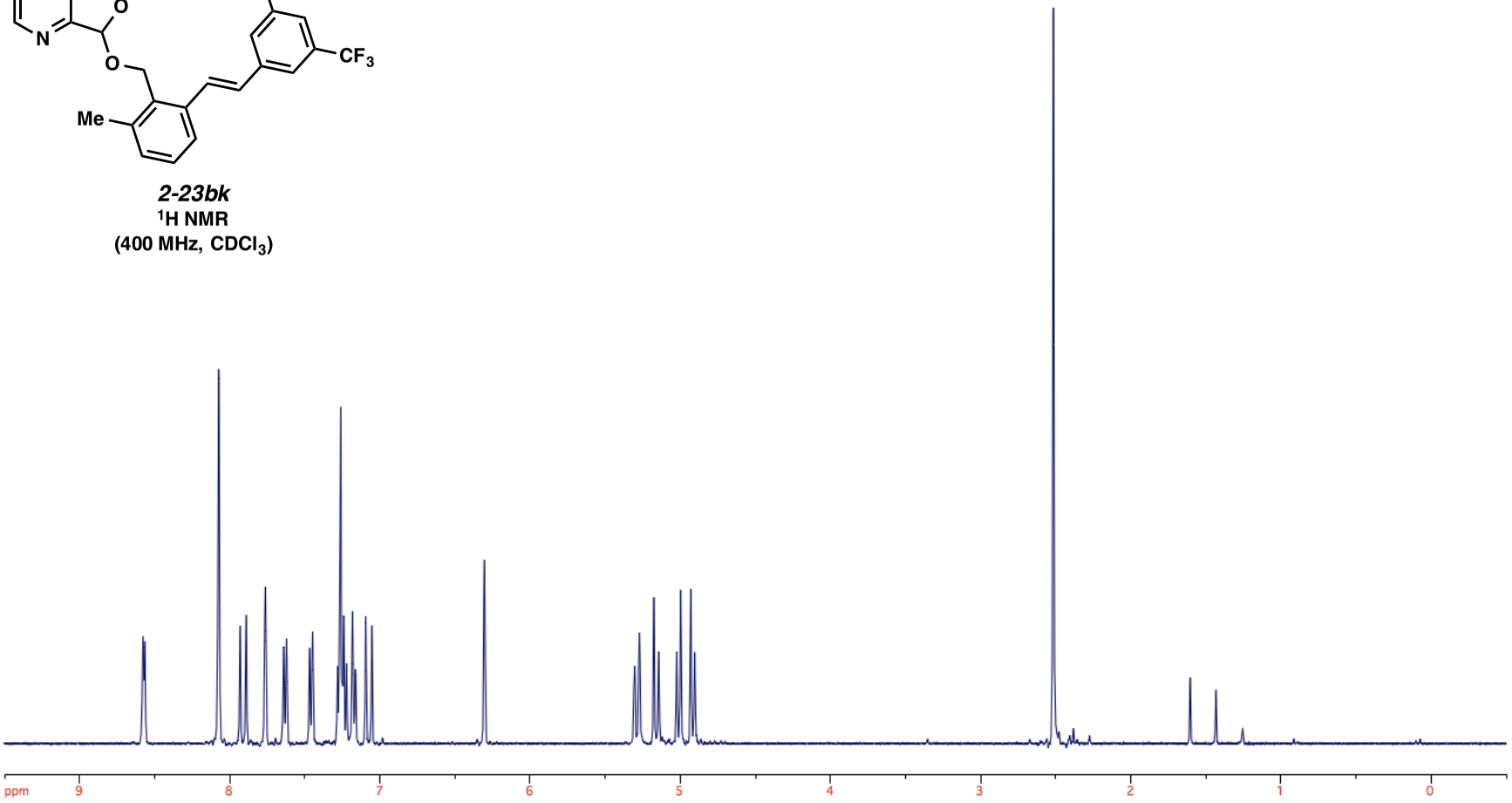


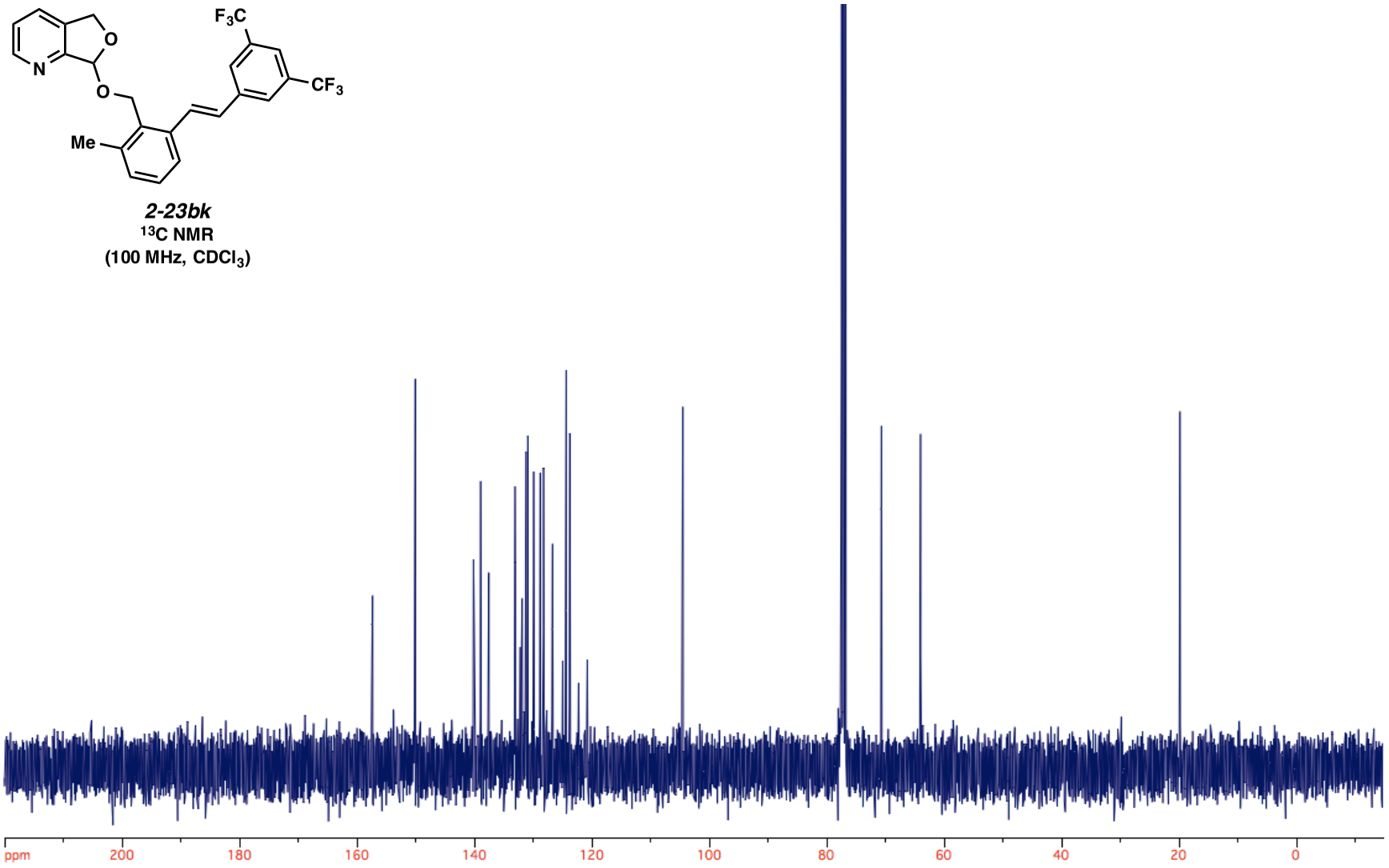


2-23bj
^{13}C NMR
(100 MHz, $CDCl_3$)

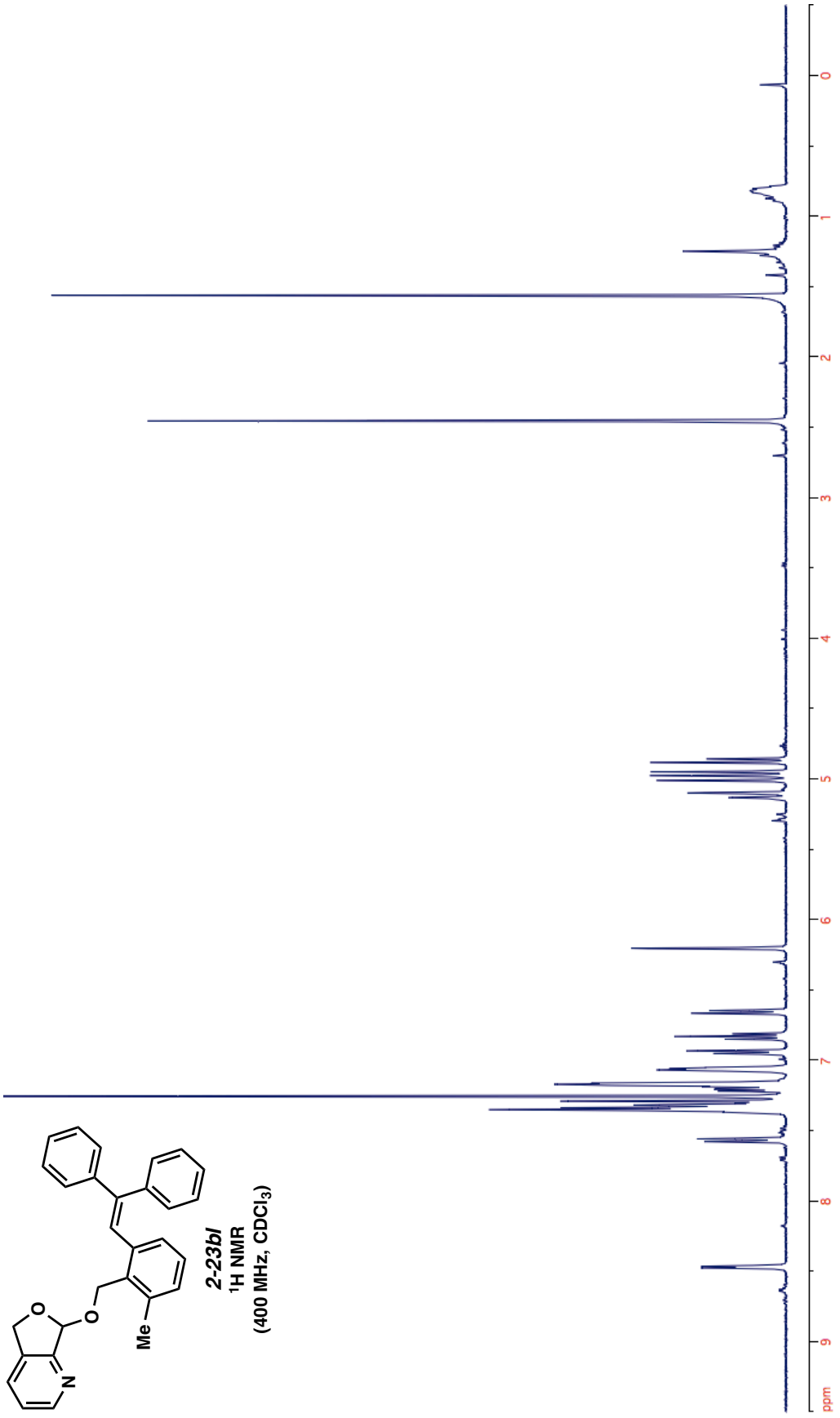


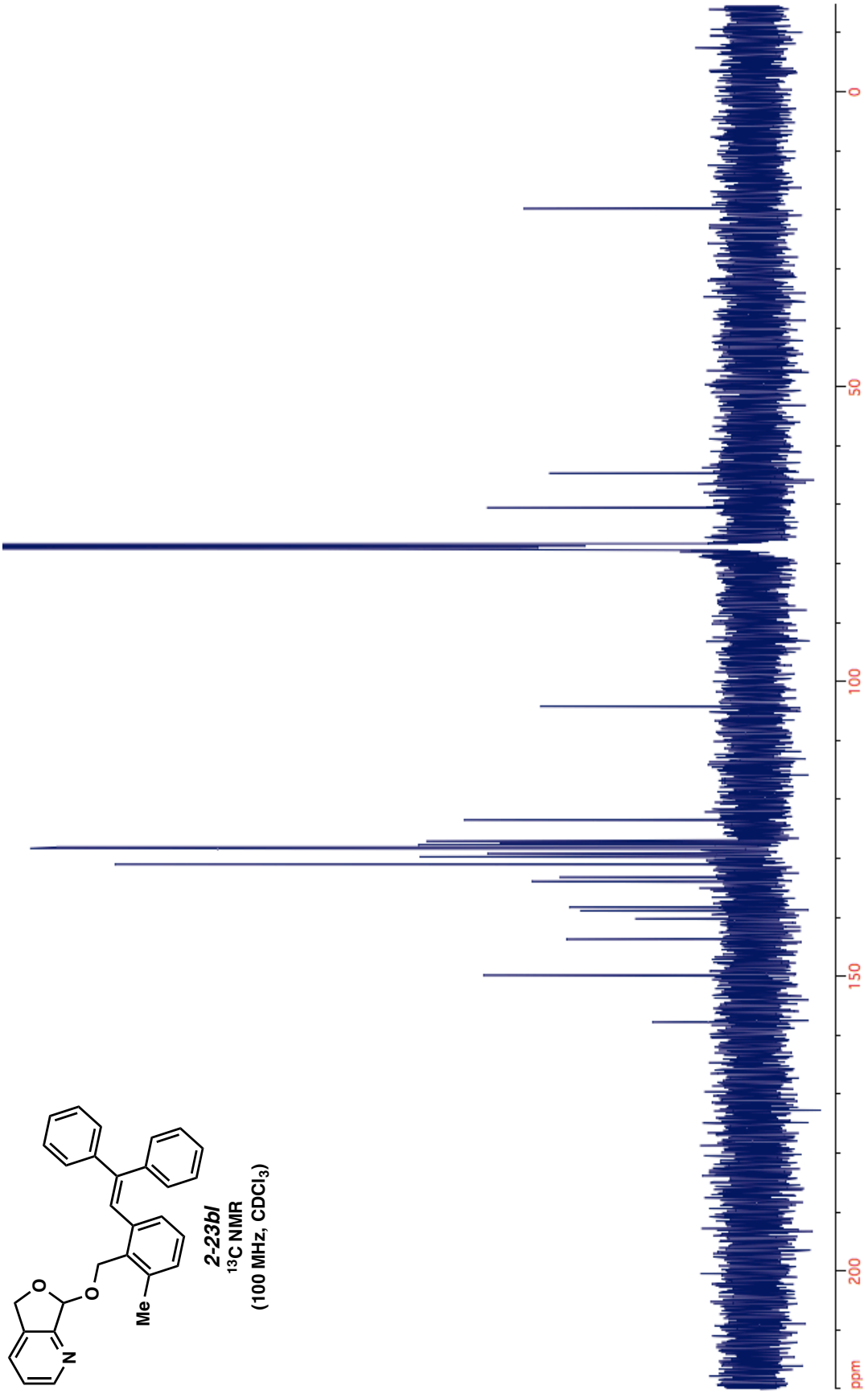
2-23bk
^{1}H NMR
(400 MHz, $CDCl_3$)



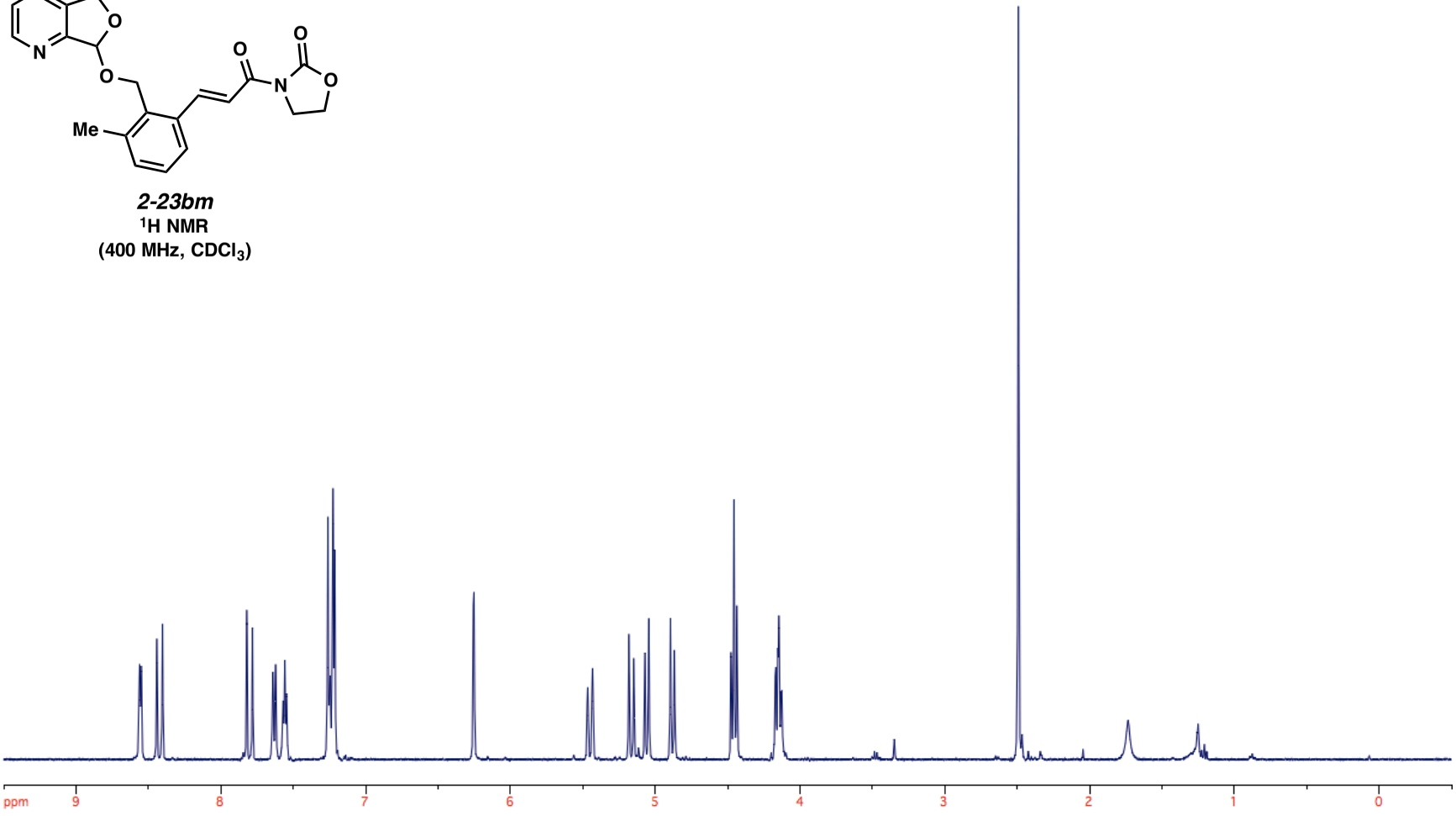


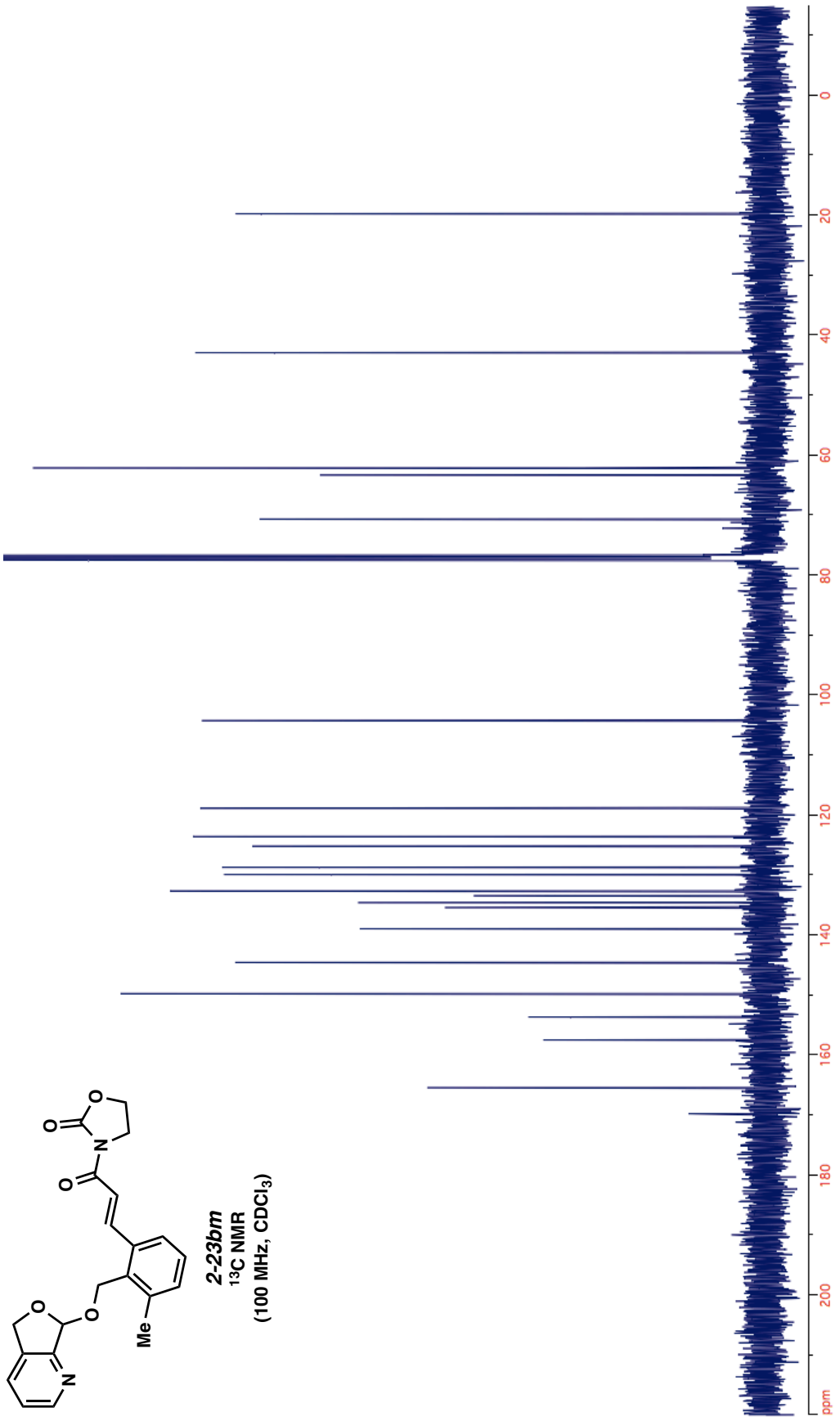
2-23bk
^{13}C NMR
(100 MHz, $CDCl_3$)

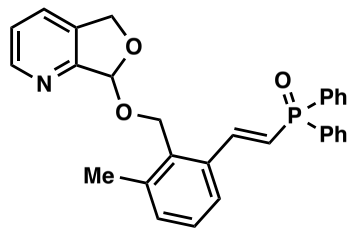

O
O
Me
N
2-23bl
^{1}H NMR
(400 MHz, $CDCl_3$)
ppm
0
1
2
3
4
5
6
7
8
9


O
O
Me
N
2-23bl
13C NMR
(100 MHz, CDCl3)
0
50
100
150
200
ppm

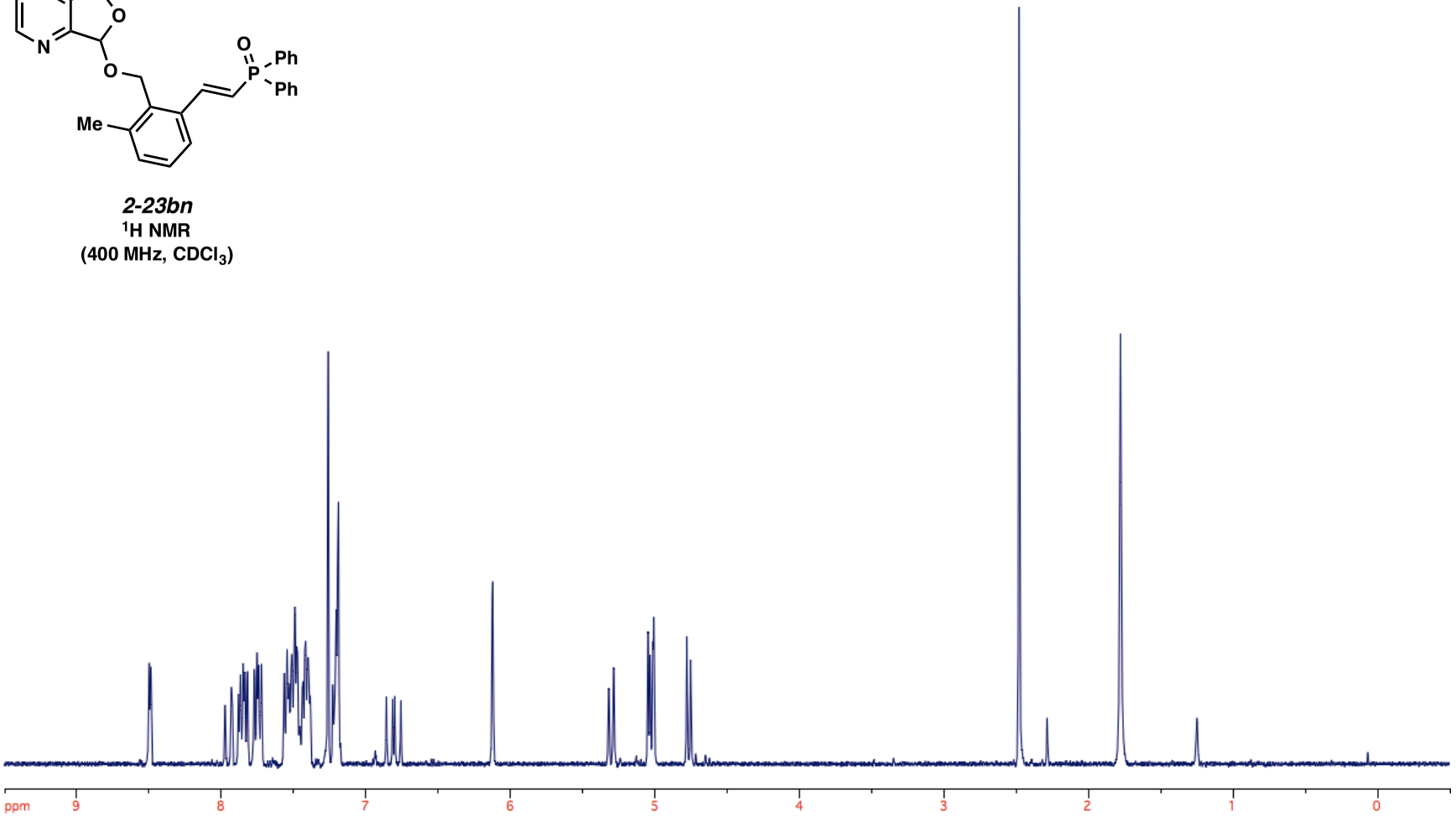
2-23bm
^{1}H NMR
(400 MHz, $CDCl_3$)



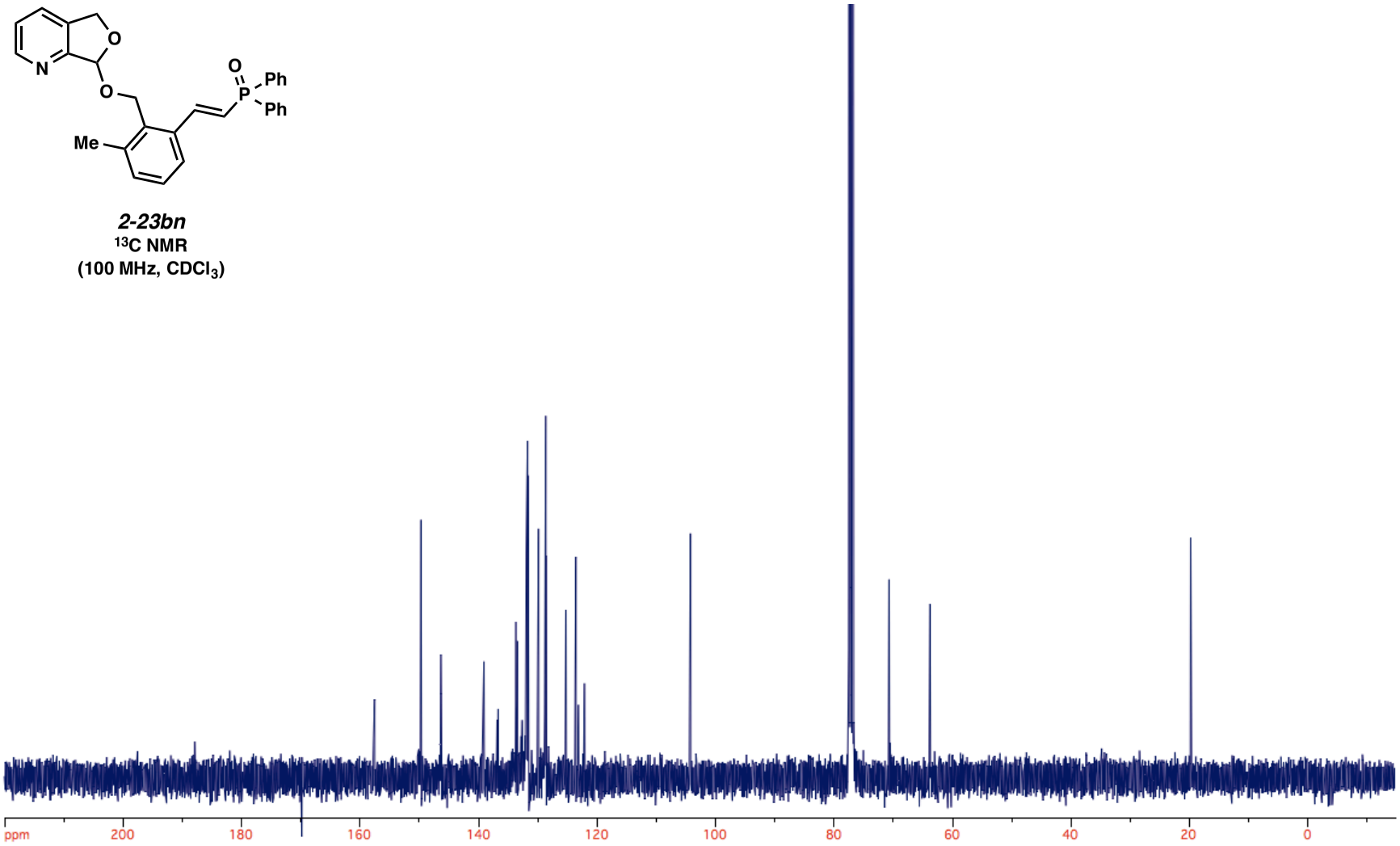

O
O
N
O
O
O
N
Me
2-23bm
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

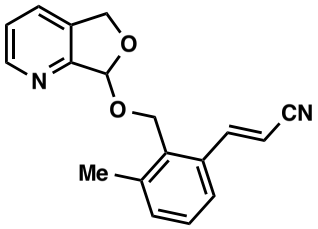


2-23bn
^{1}H NMR
(400 MHz, $CDCl_3$)

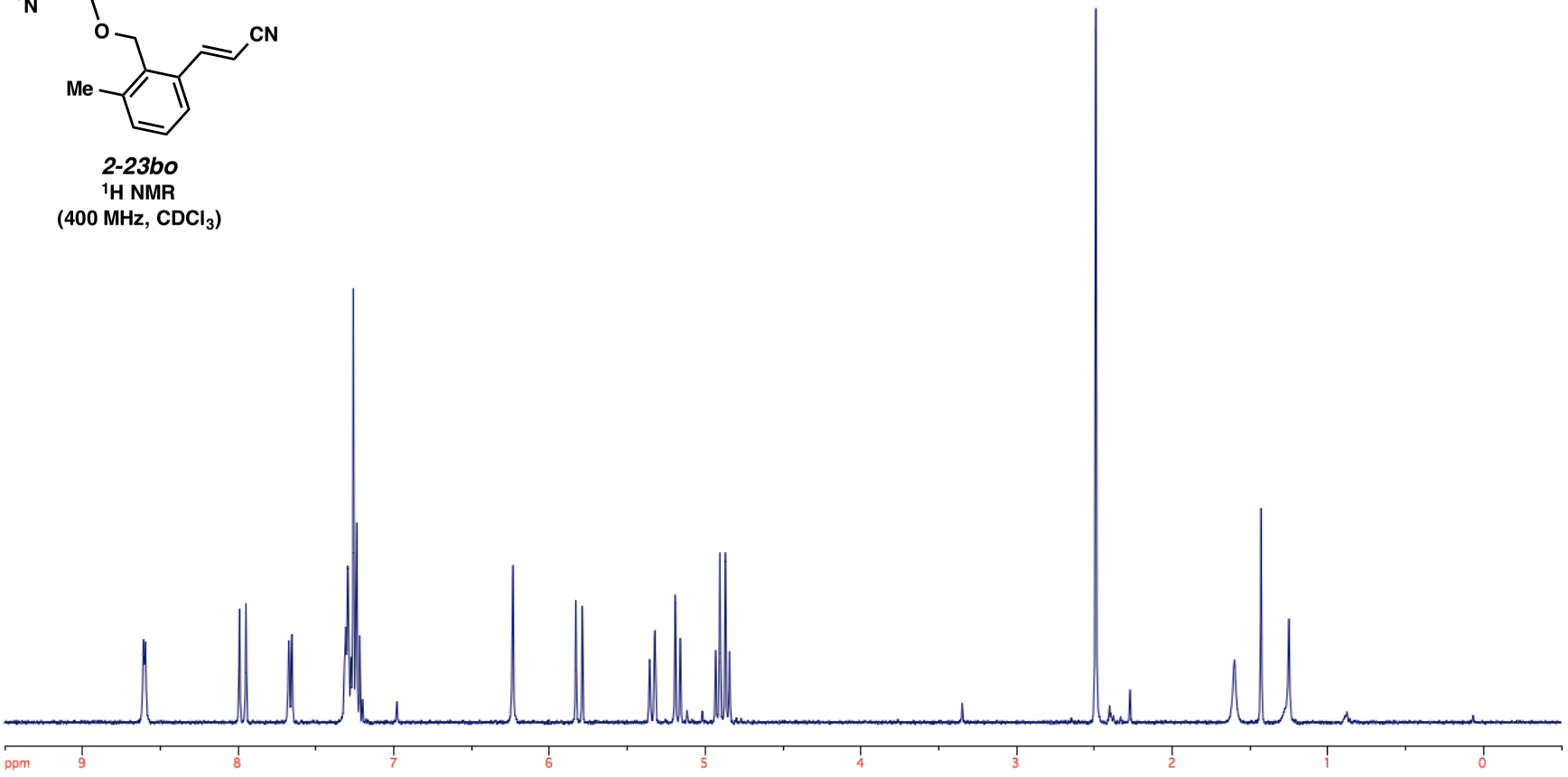


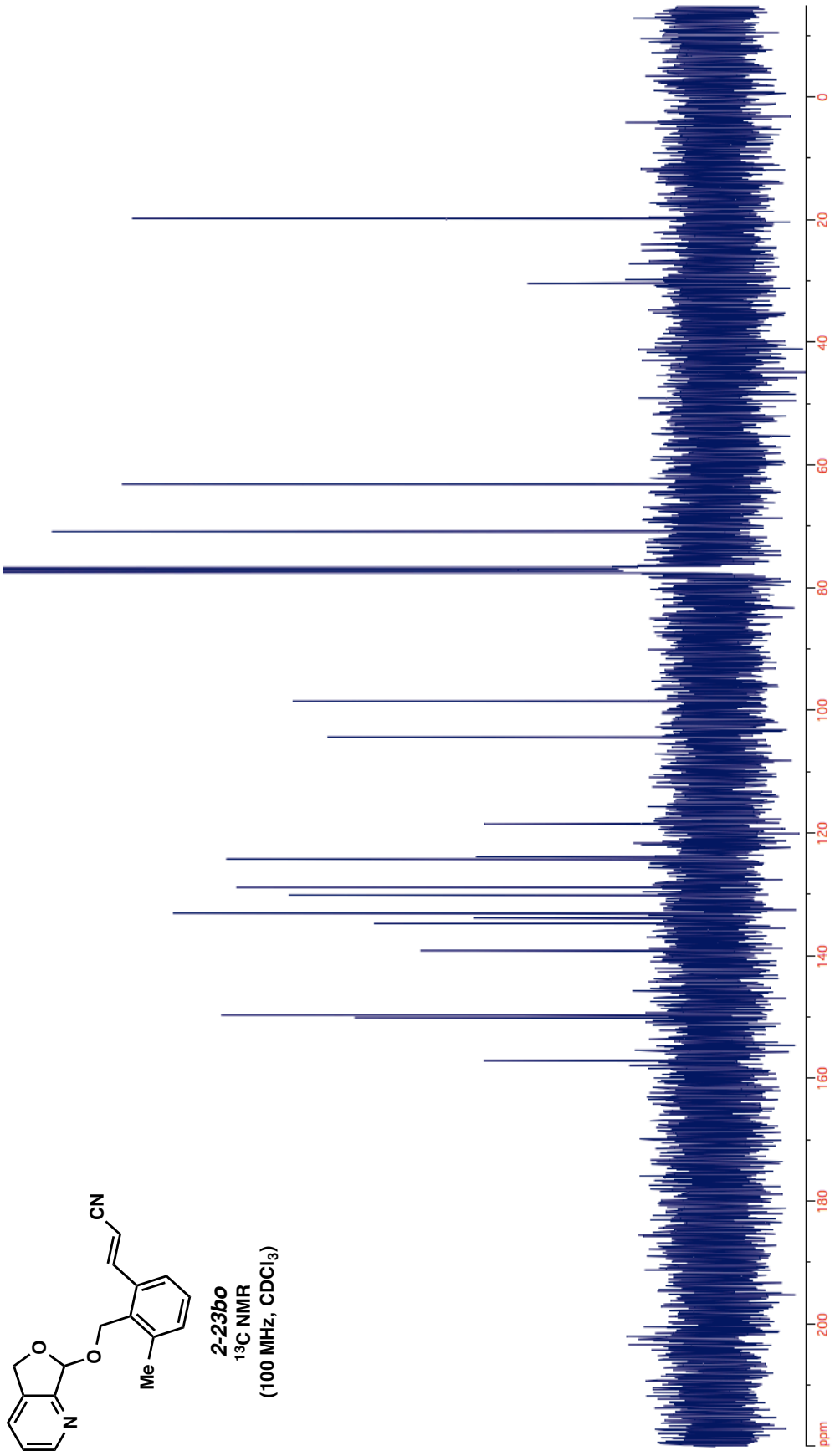
2-23bn
^{13}C NMR
(100 MHz, $CDCl_3$)

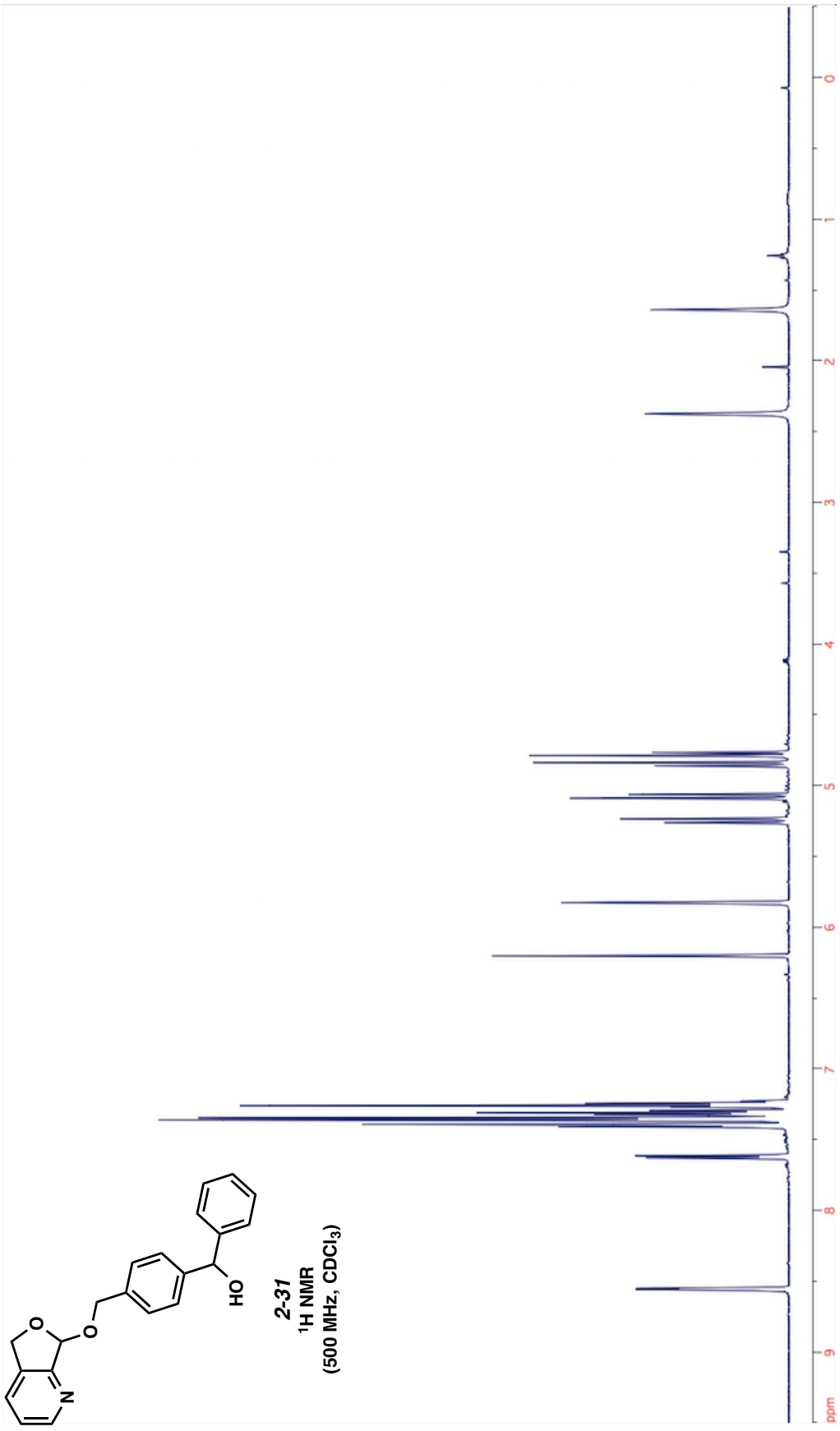




2-23bo
^{1}H NMR
(400 MHz, $CDCl_3$)



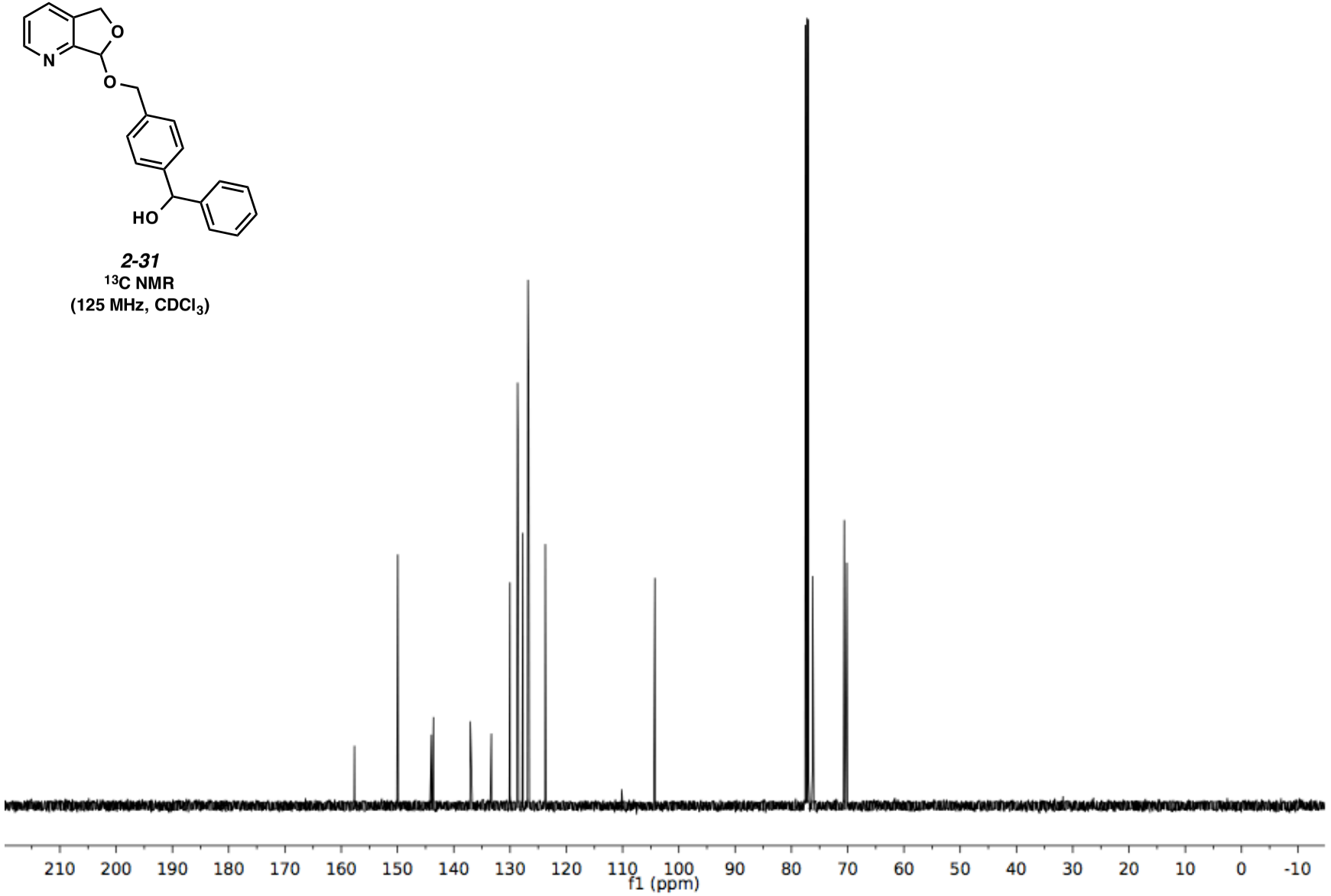

CN
O
O
Me
N
2-23bo
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

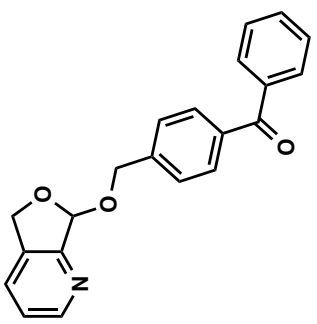

HO
O
O
N
2-31
1H NMR
(500 MHz, CDCl3)
0
1
2
3
4
5
6
7
8
9
ppm

2-31

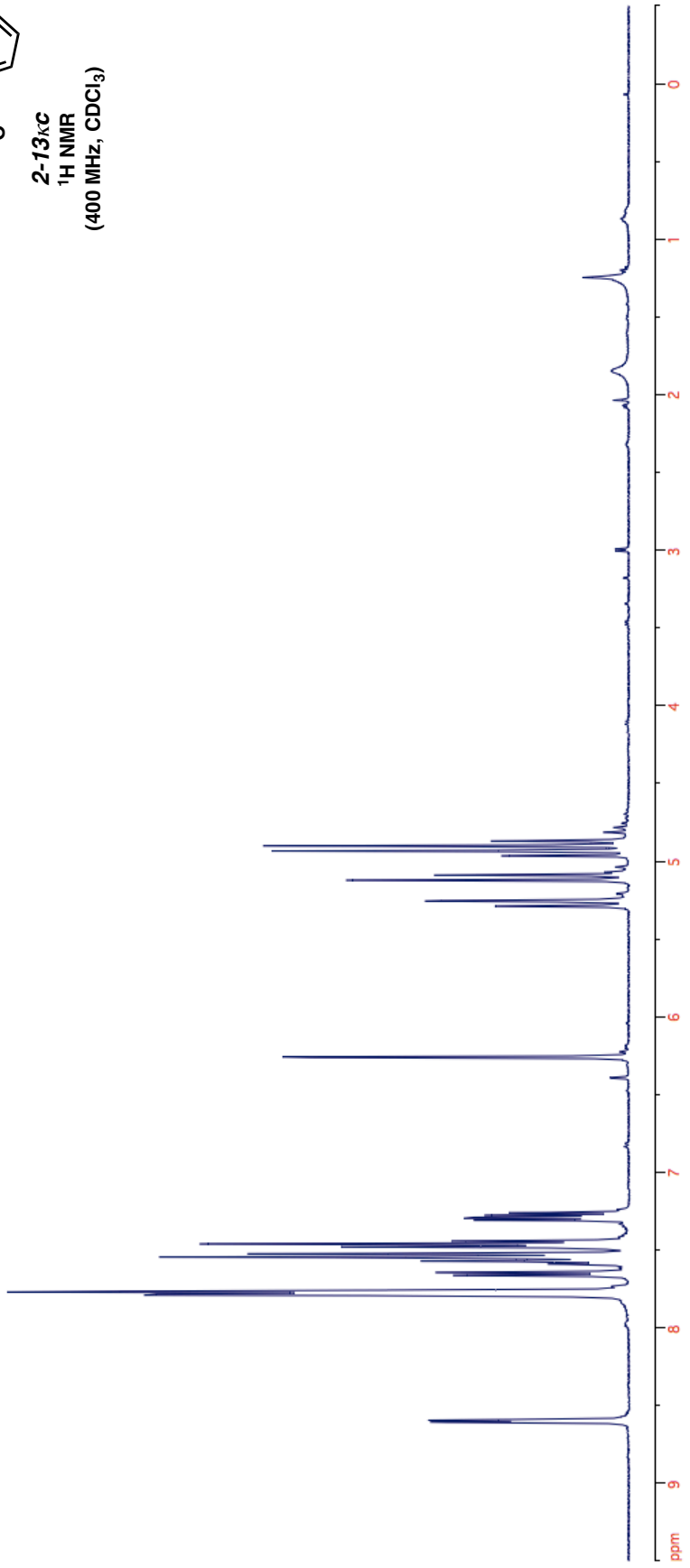
^{13}C NMR

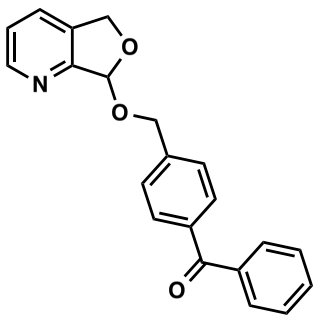
(125 MHz, $CDCl_3$)



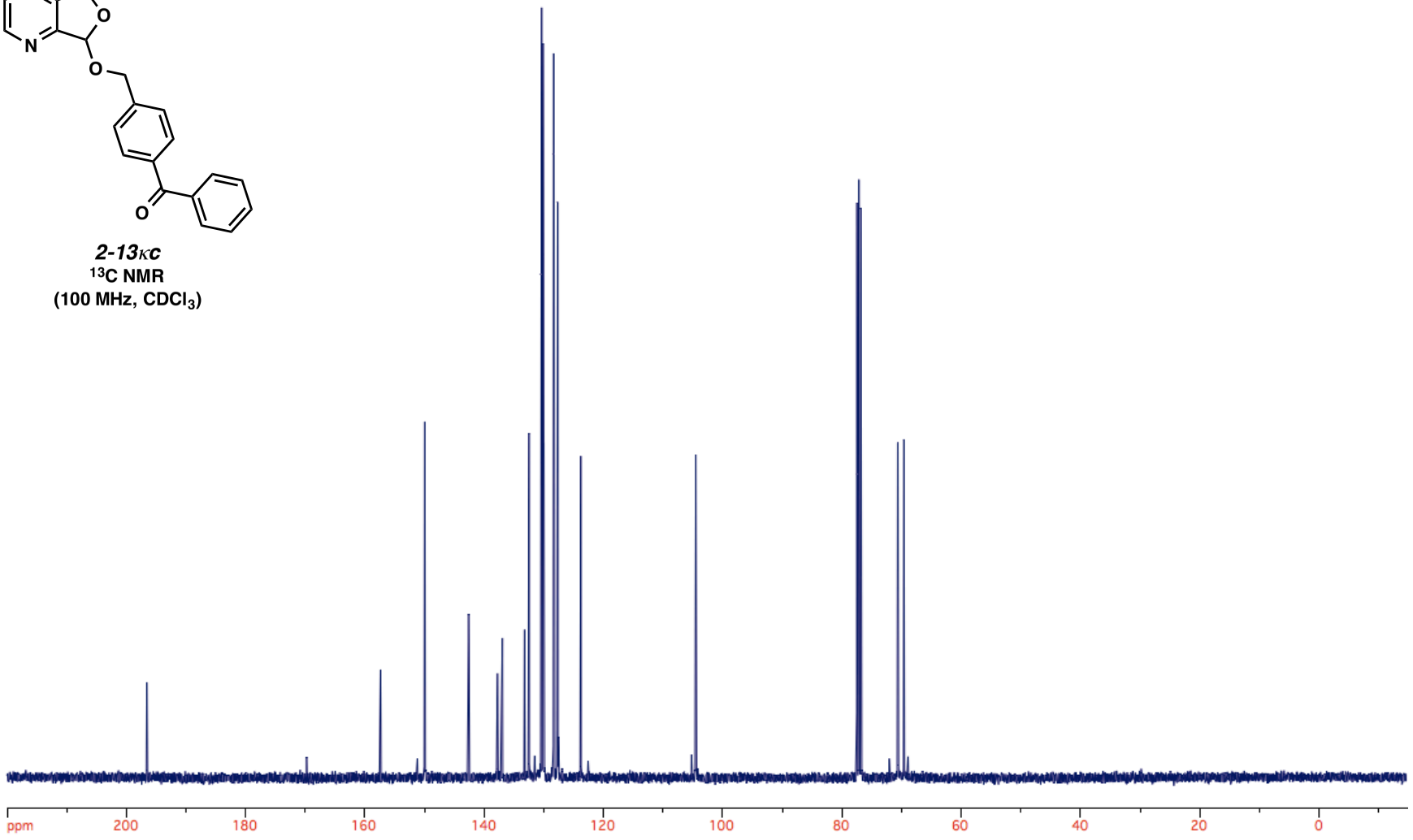


2-13*kc*
^{1}H NMR
(400 MHz, $CDCl_3$)

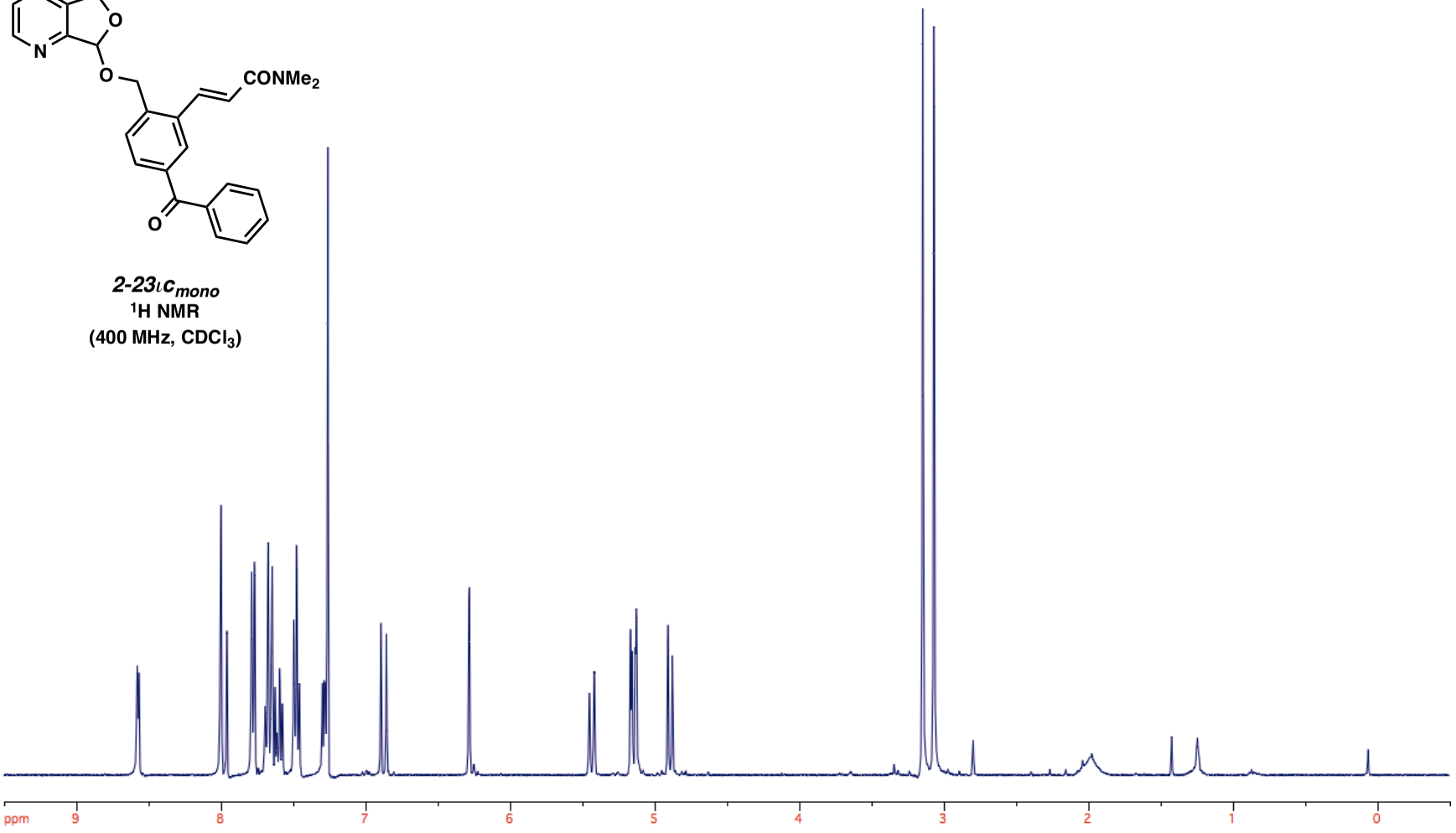




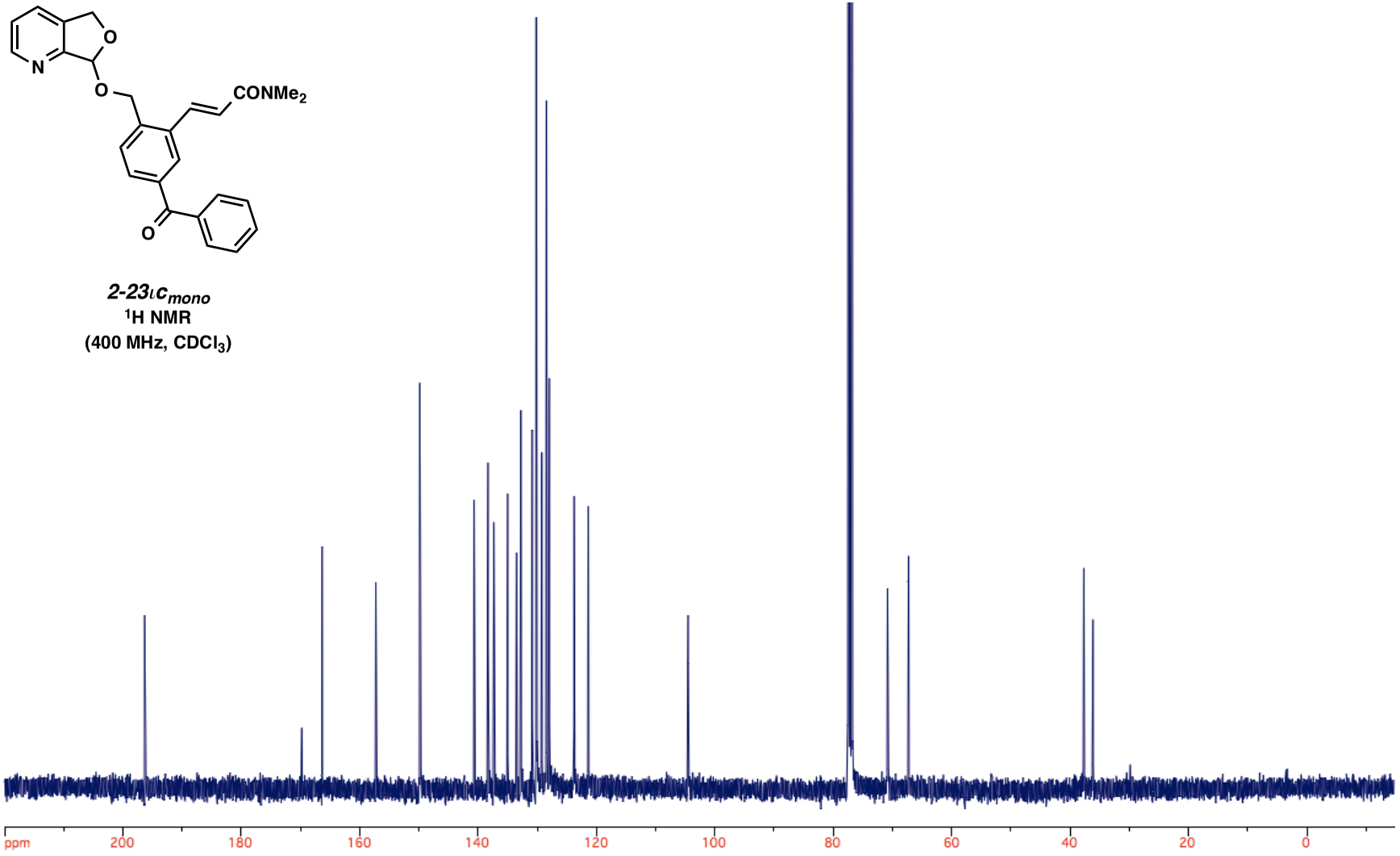
2-13κc
^{13}C NMR
(100 MHz, $CDCl_3$)

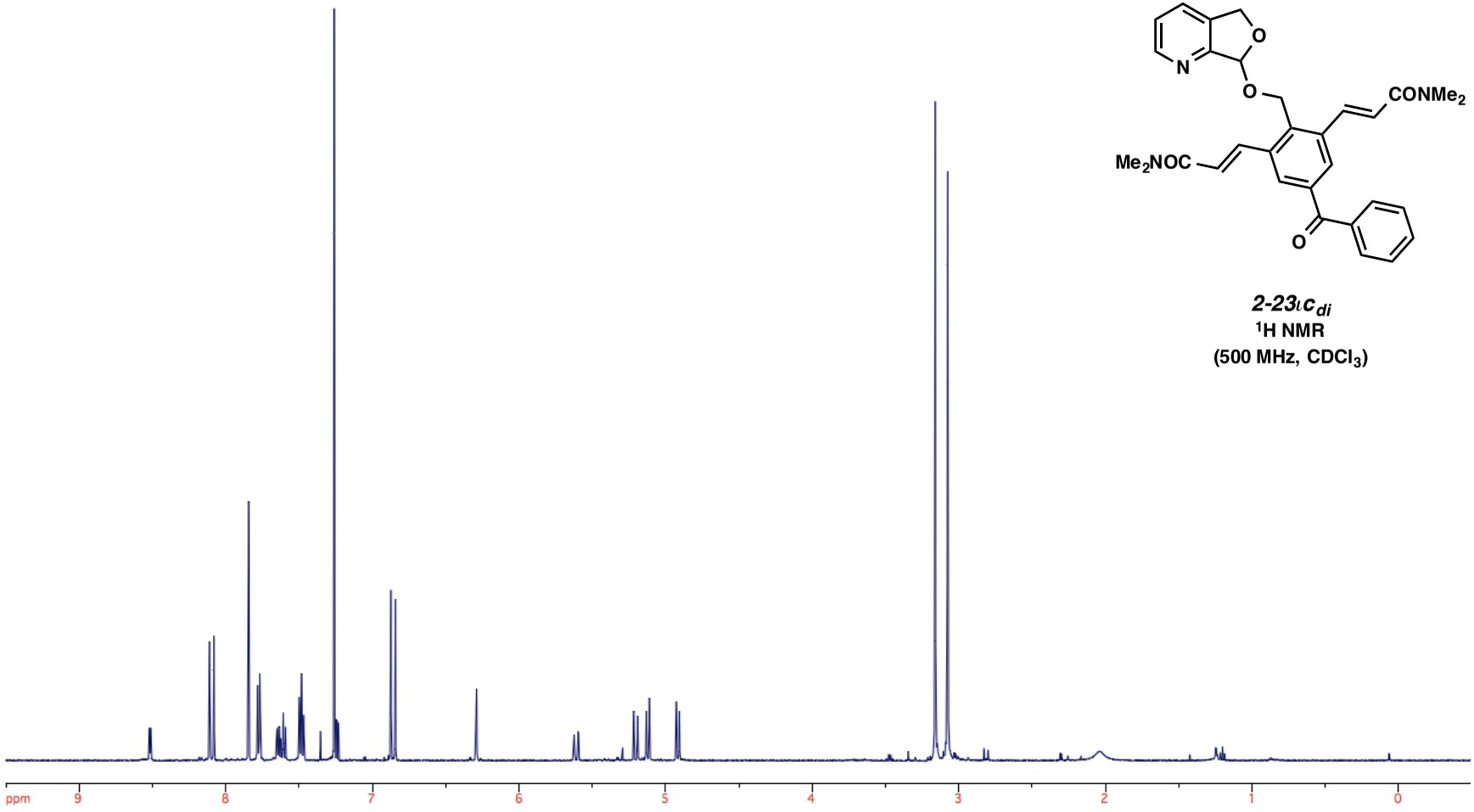


2-23ιc_{mono}
^{1}H NMR
(400 MHz, $CDCl_3$)

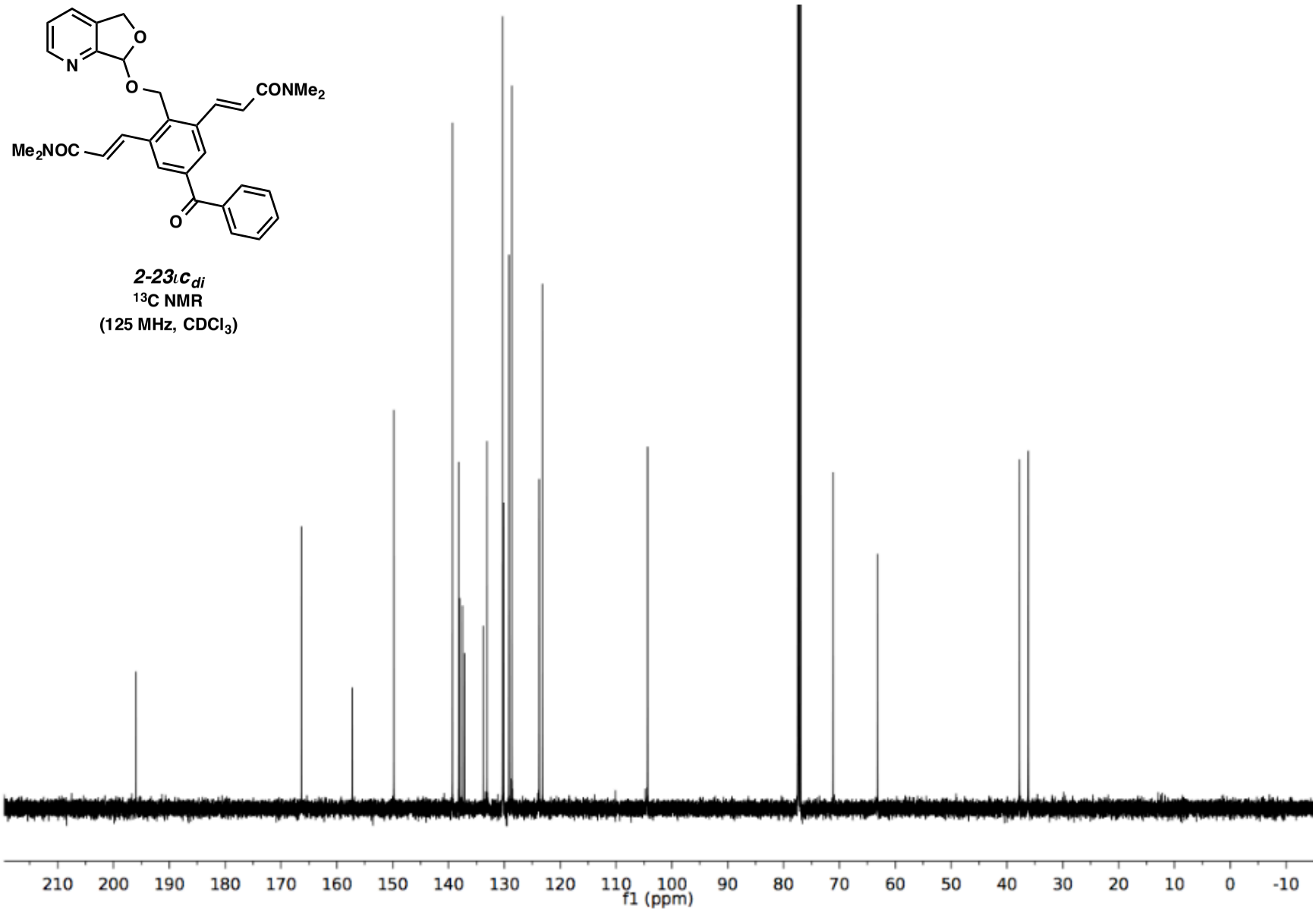


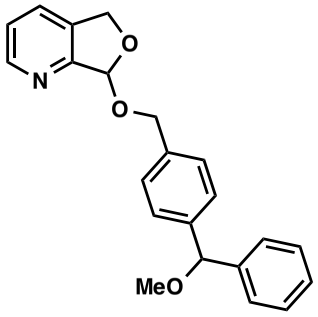
***2-23ιc*$_{mono}$**
^{1}H NMR
(400 MHz, $CDCl_3$)



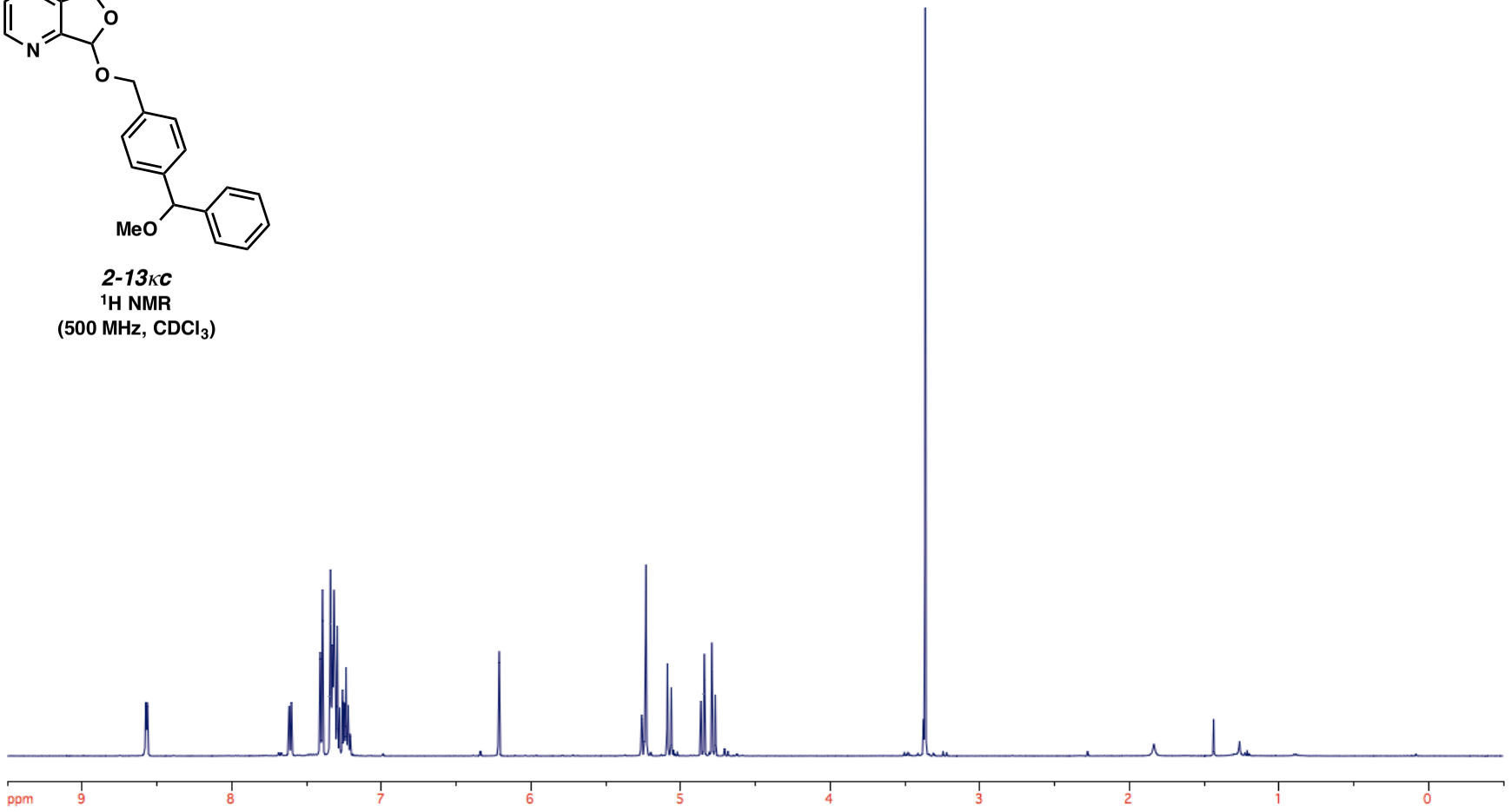


***2-23ιc*$_{di}$**
^{1}H NMR
(500 MHz, $CDCl_3$)

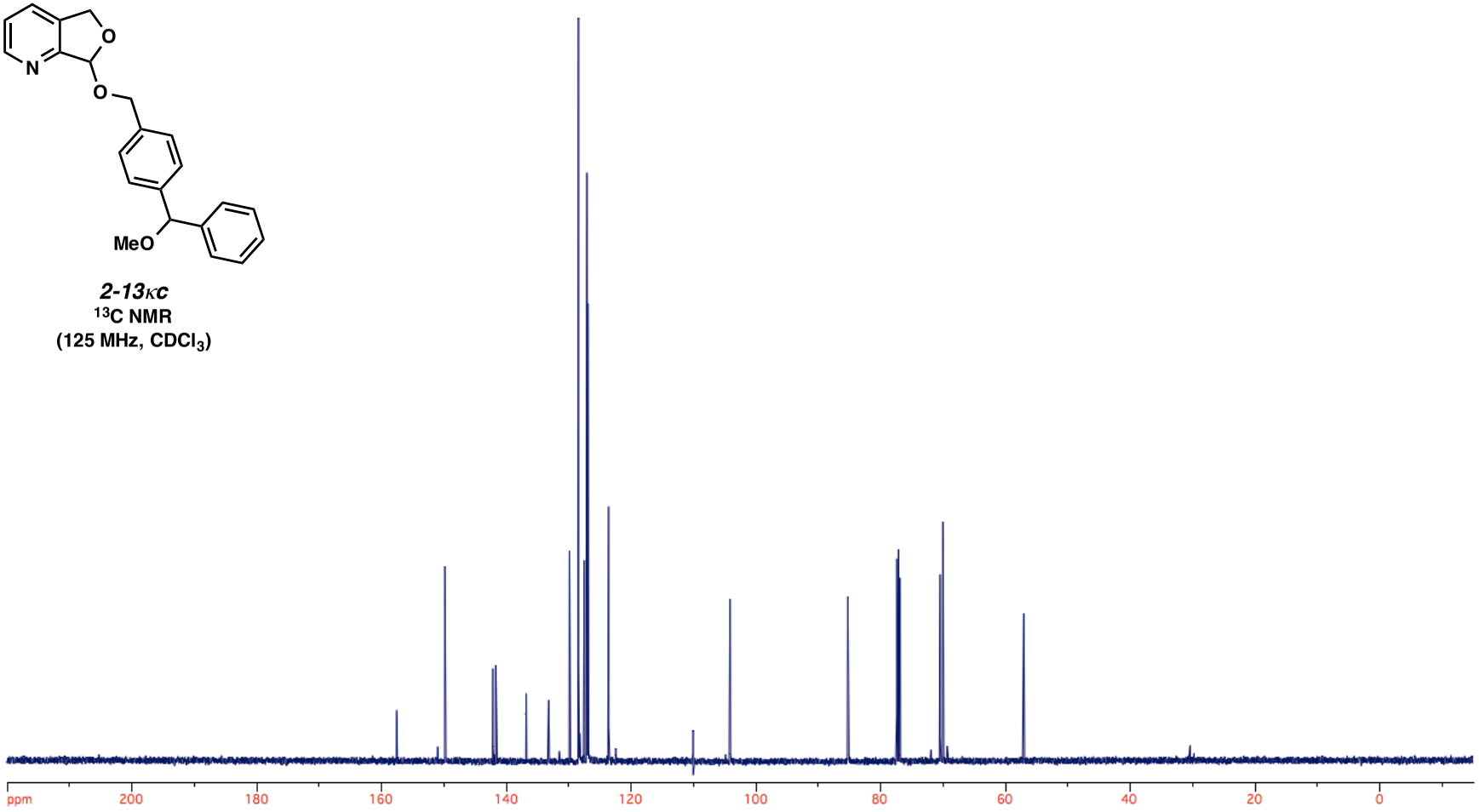

O
N
O
CONMe2
Me2NOC
O
2-23ιcdi
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

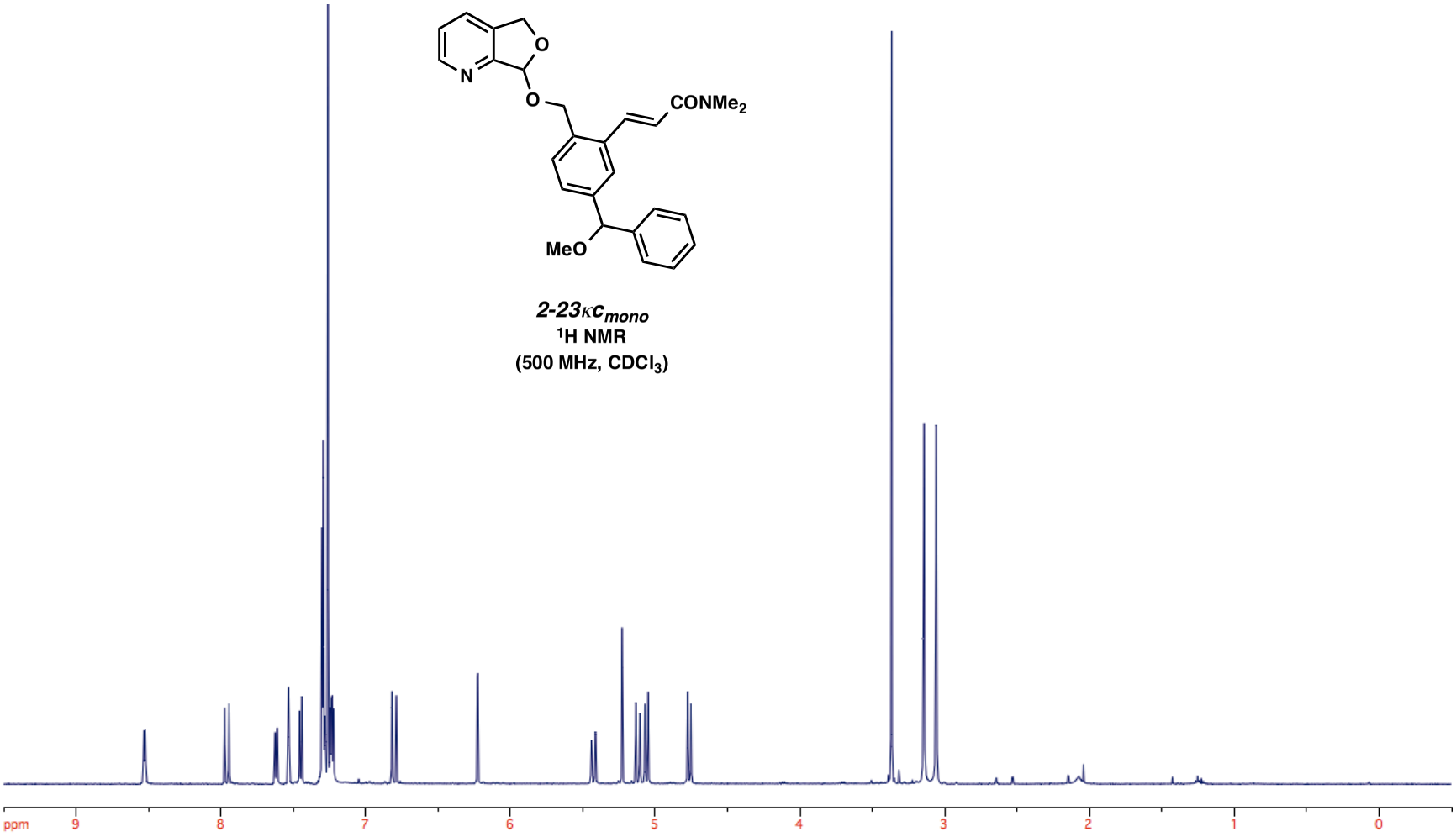


2-13κc
^{1}H NMR
(500 MHz, $CDCl_3$)



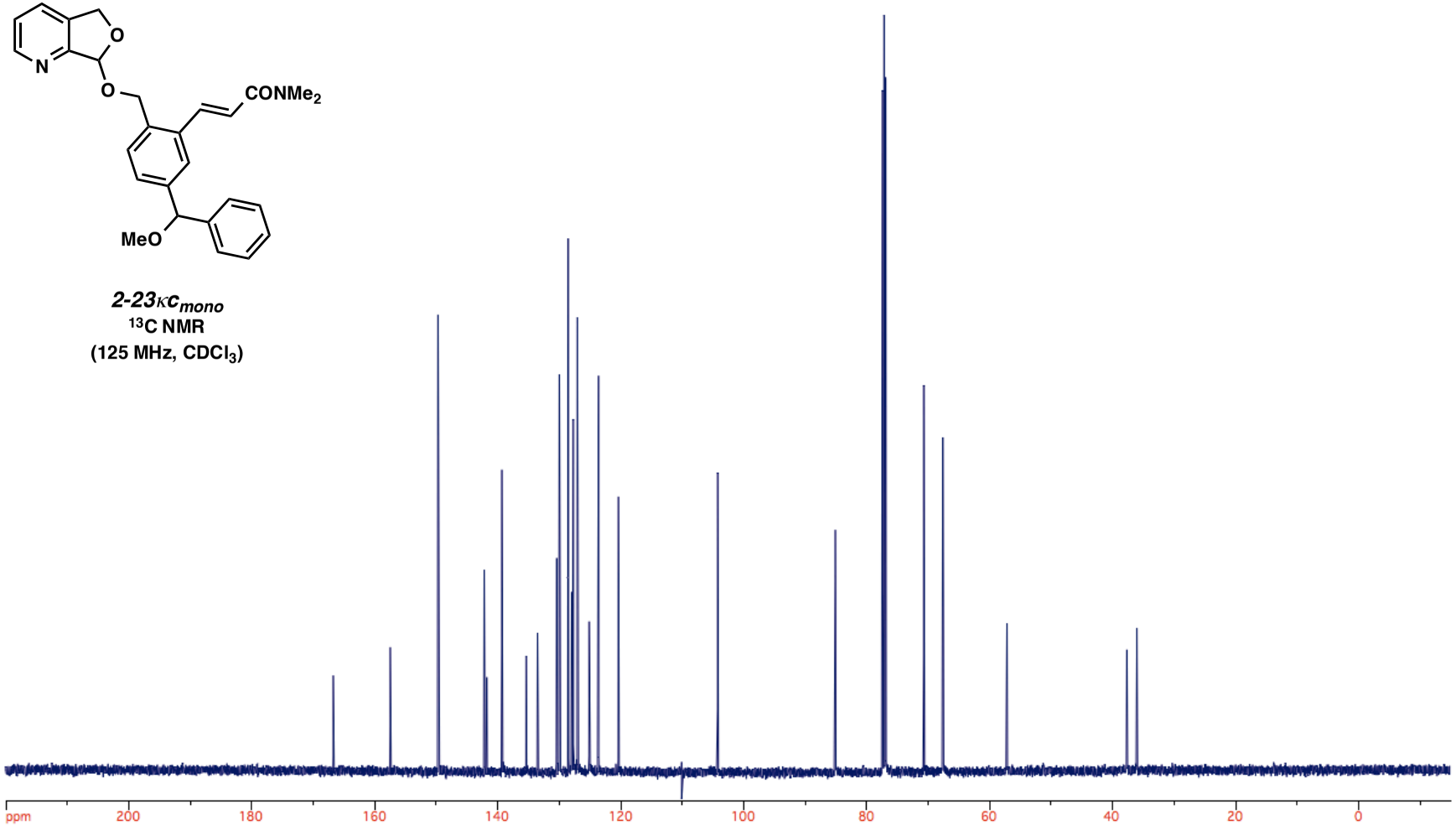
2-13κc
^{13}C NMR
(125 MHz, $CDCl_3$)

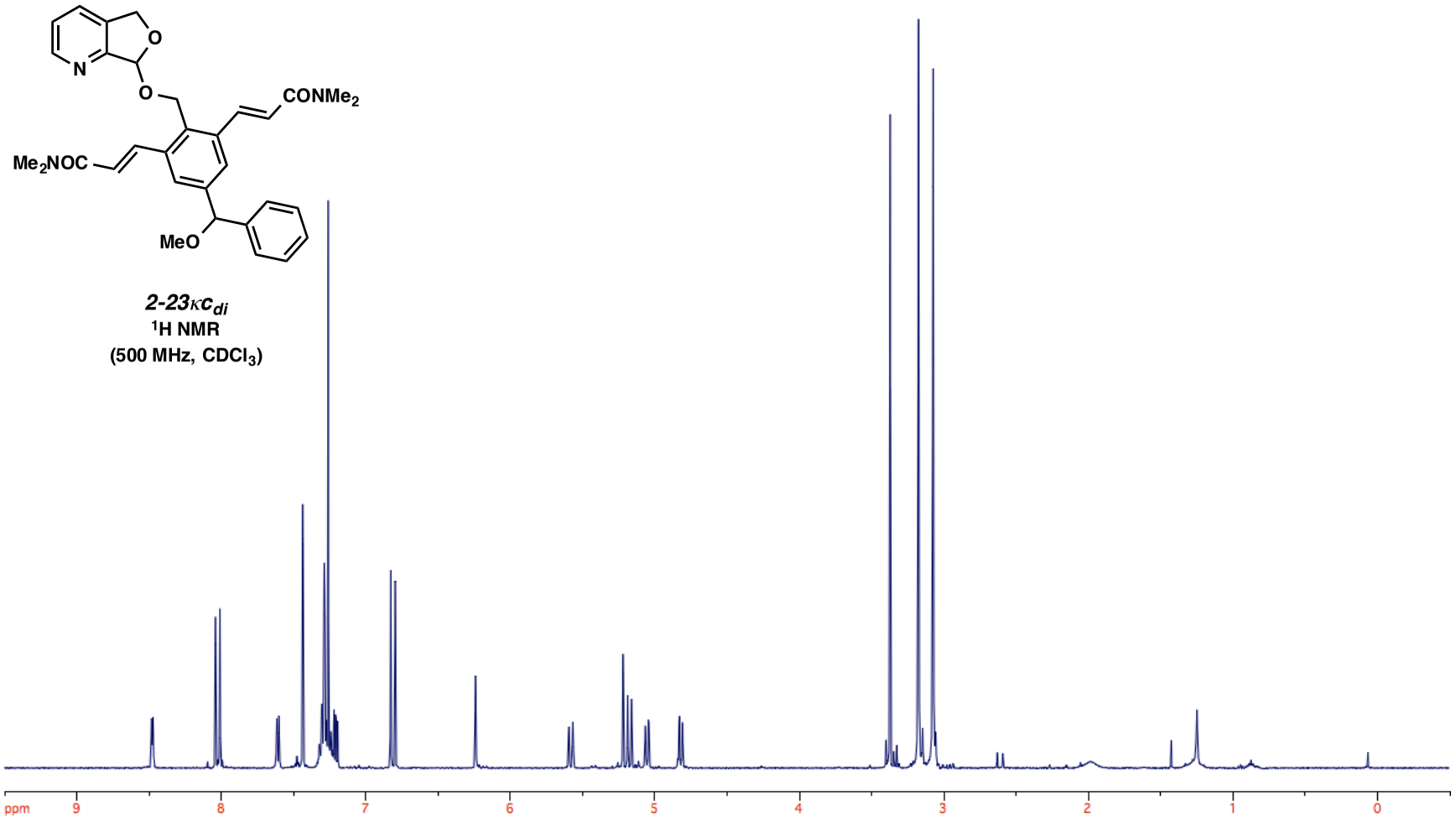




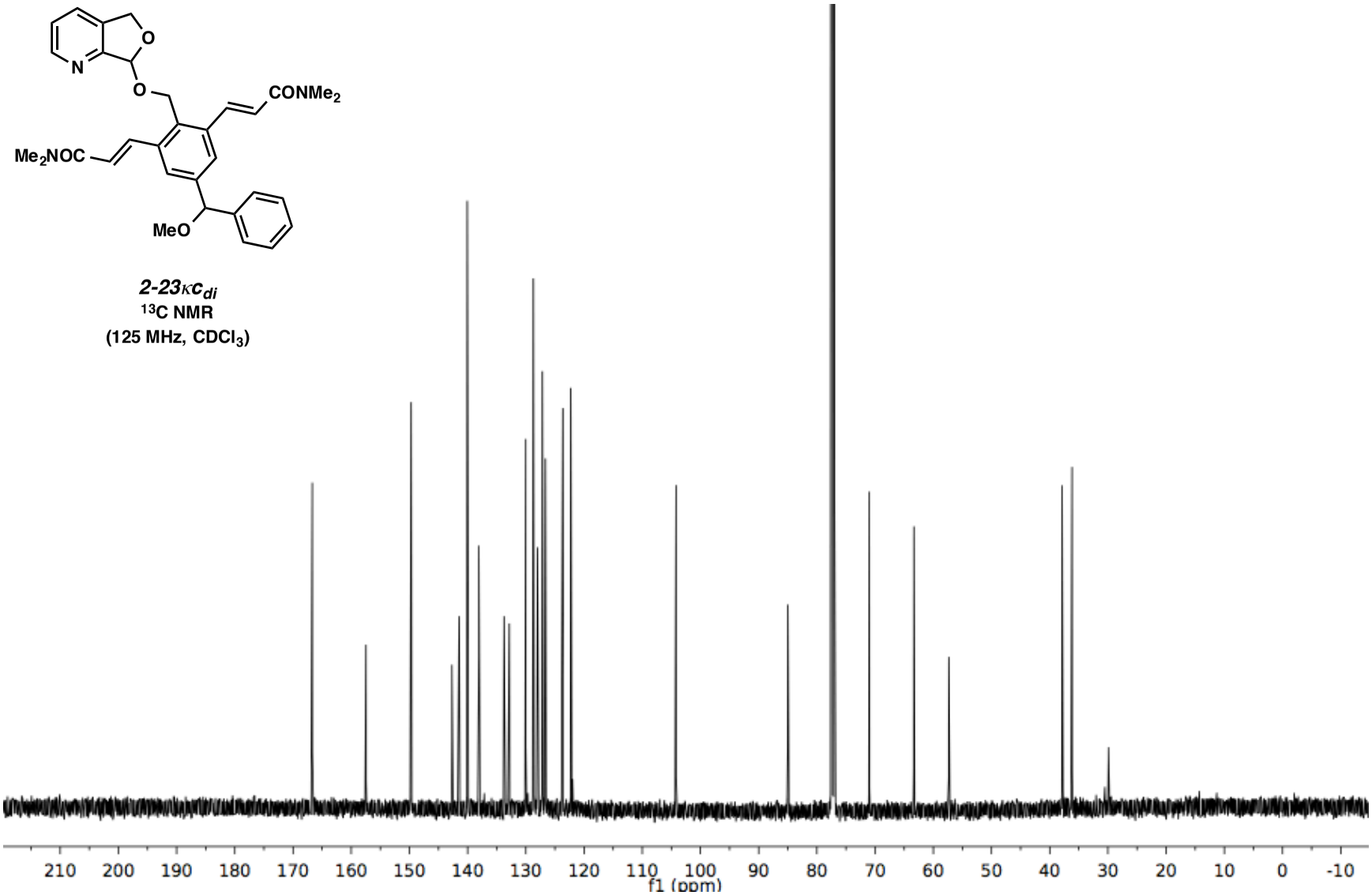
***2-23κc*$_{mono}$**
^{1}H NMR
(500 MHz, $CDCl_3$)

***2-23κc*$_{mono}$**
^{13}C NMR
(125 MHz, $CDCl_3$)





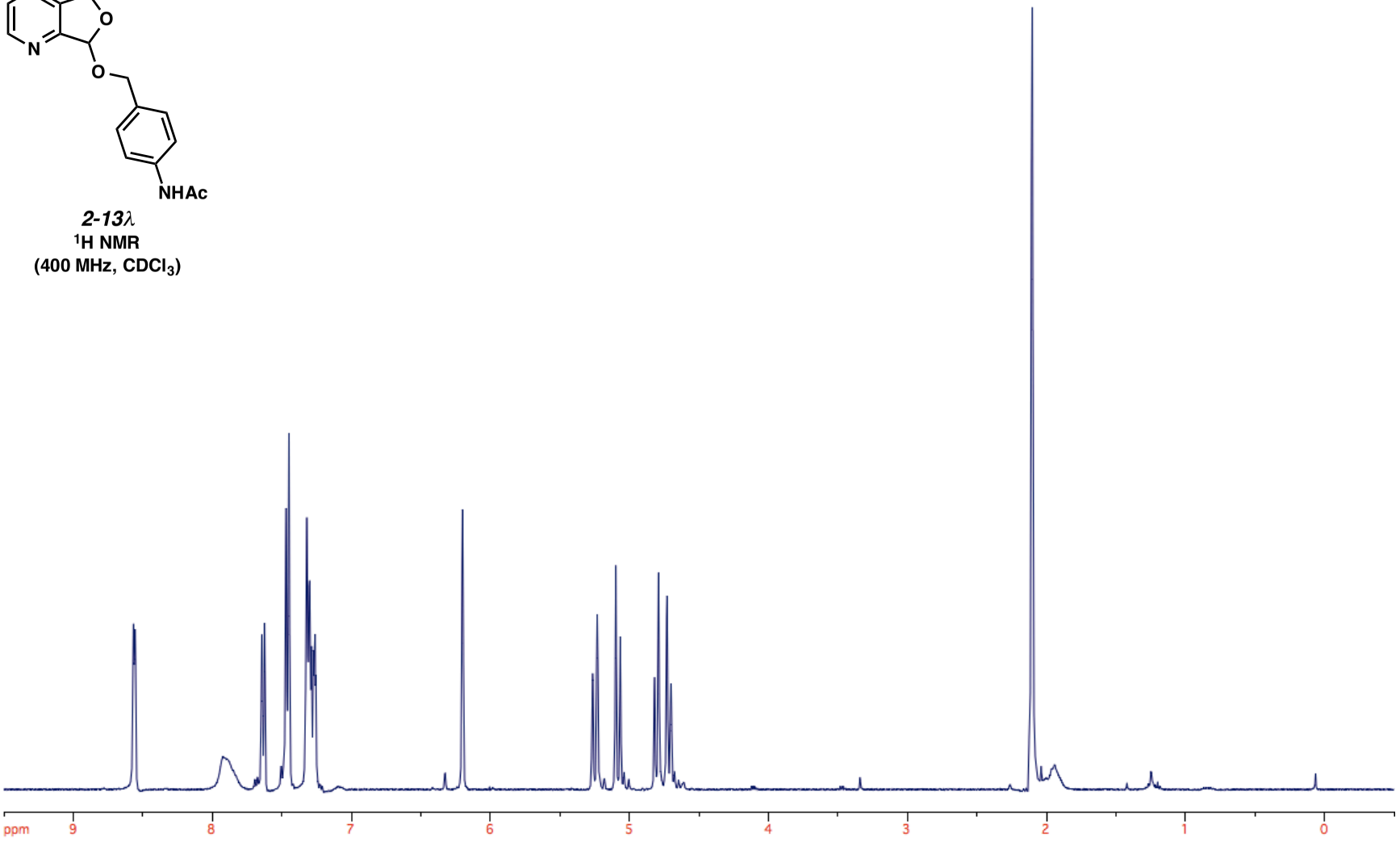
2-23κc ***di***
^{1}H NMR
(500 MHz, $CDCl_3$)

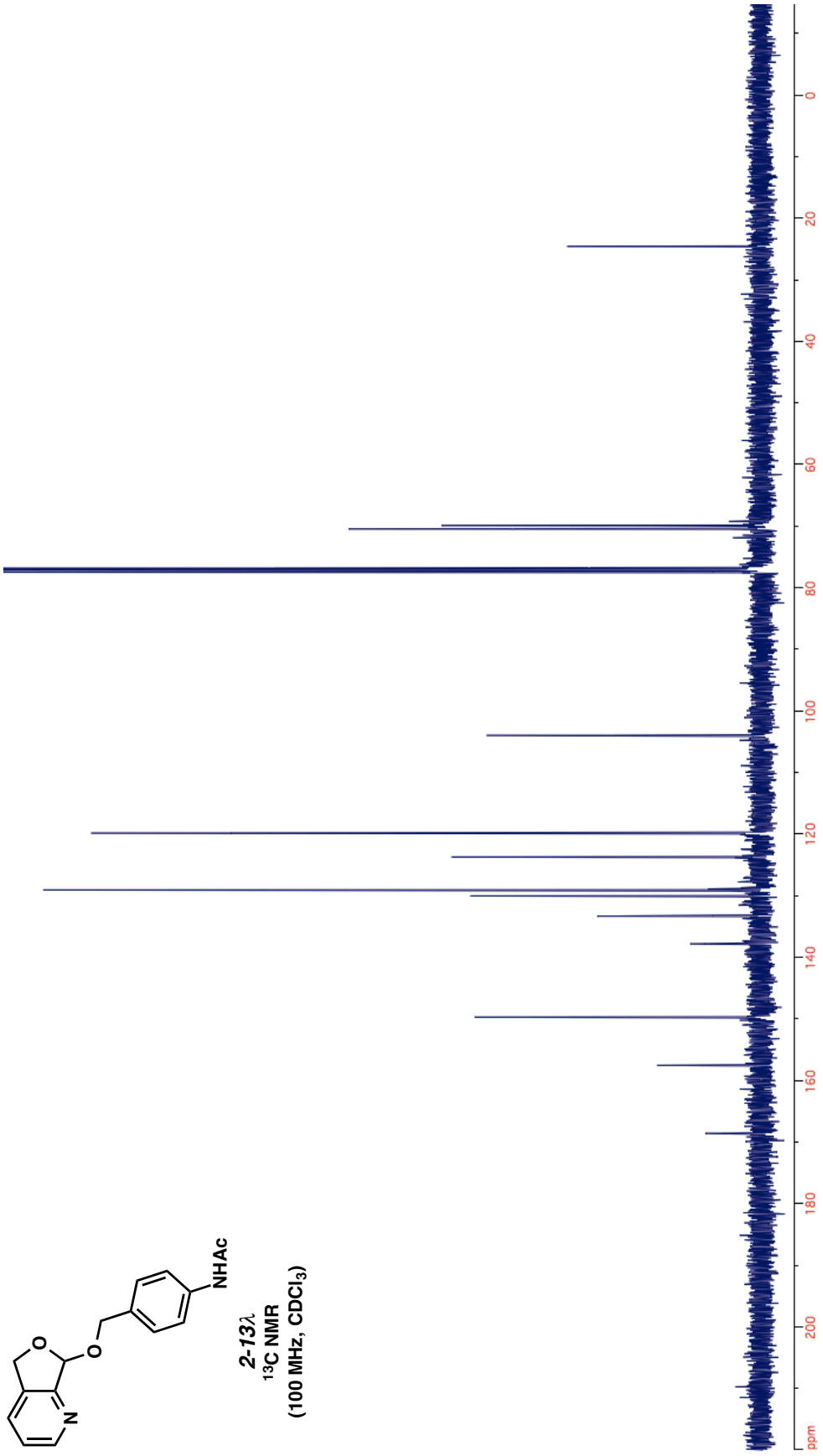

N
O
O
CONMe2
Me2NOC
MeO
2-23κcdi
13C NMR
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

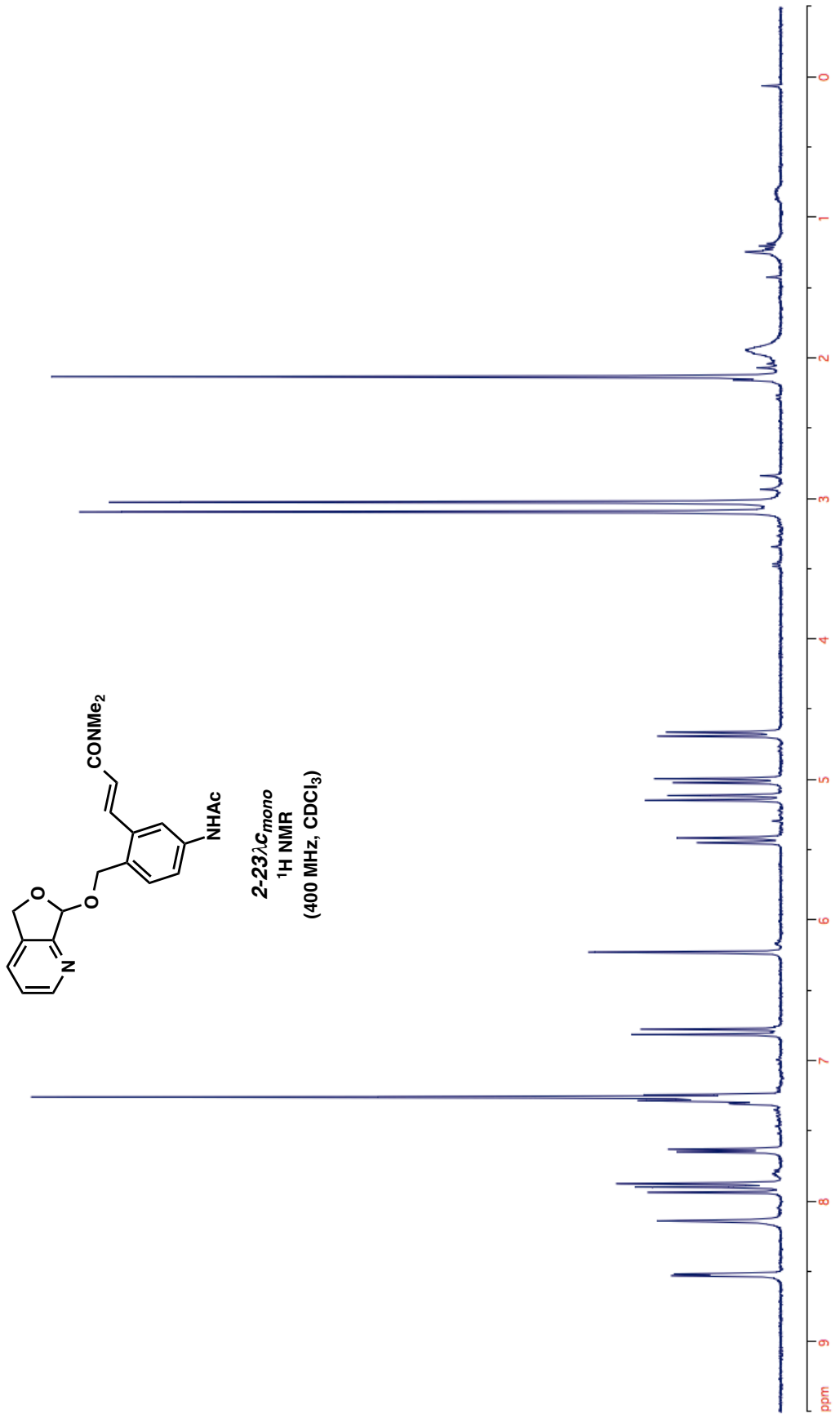
2-13λ

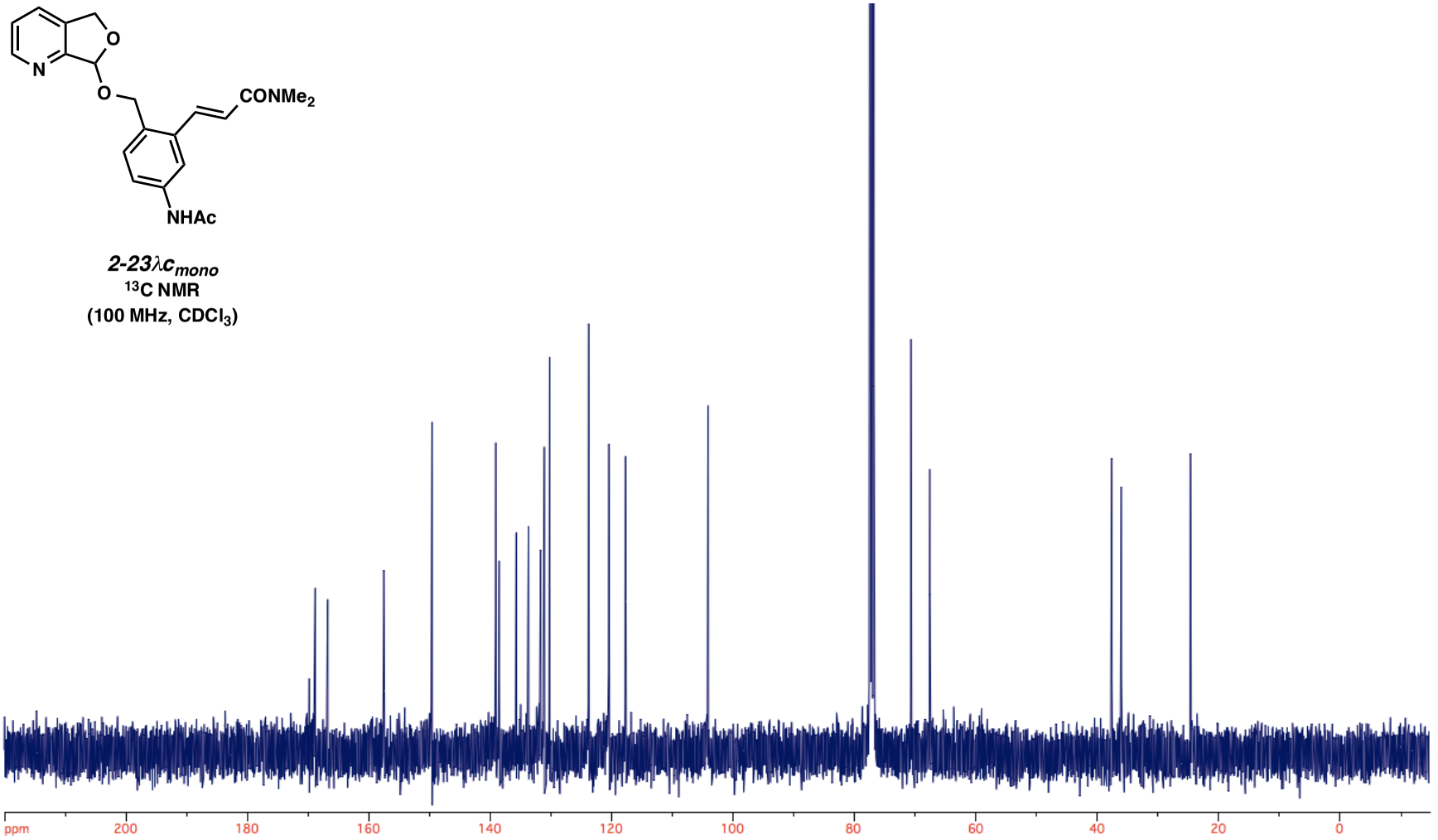
^{1}H NMR

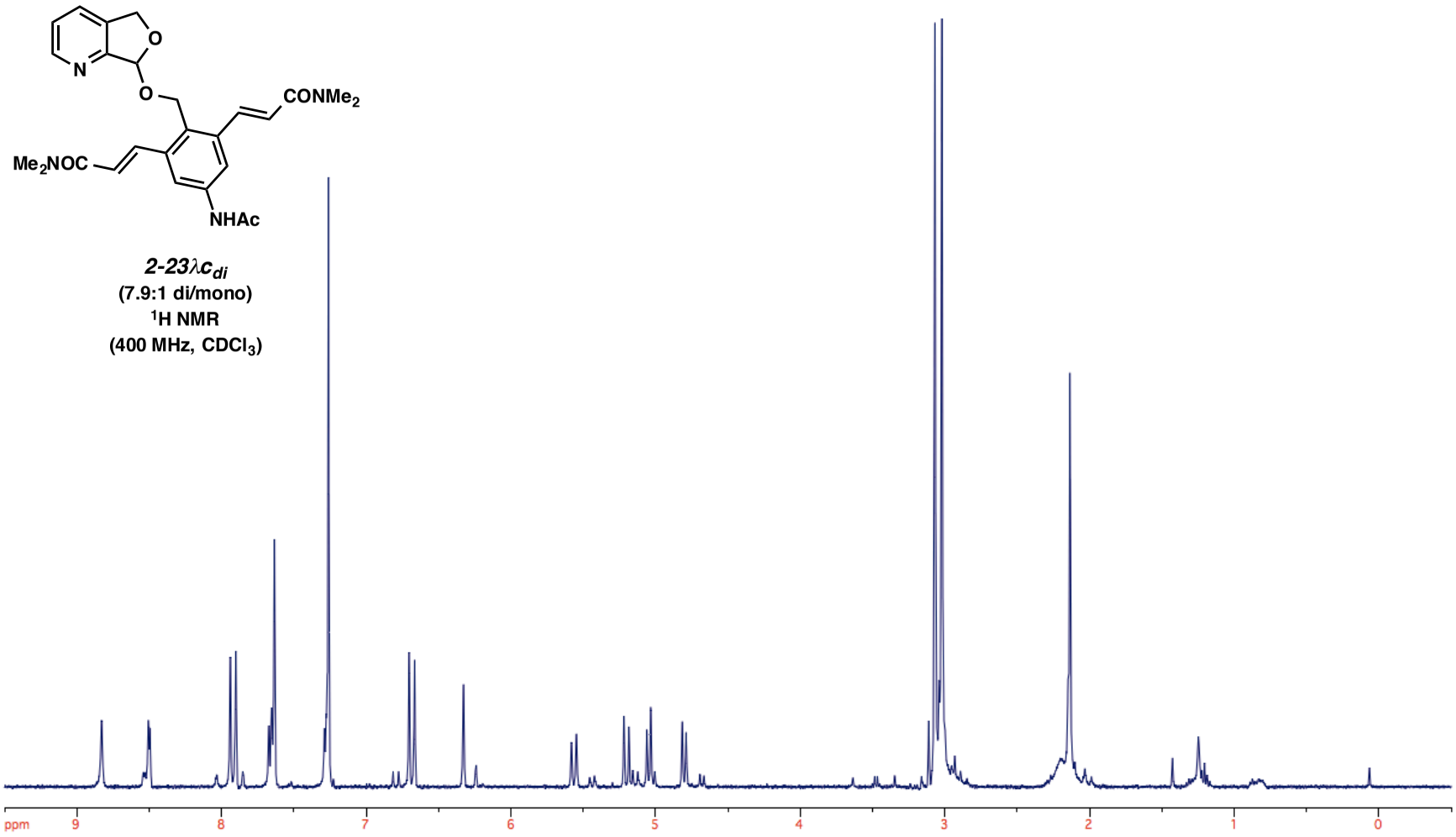
(400 MHz, $CDCl_3$)



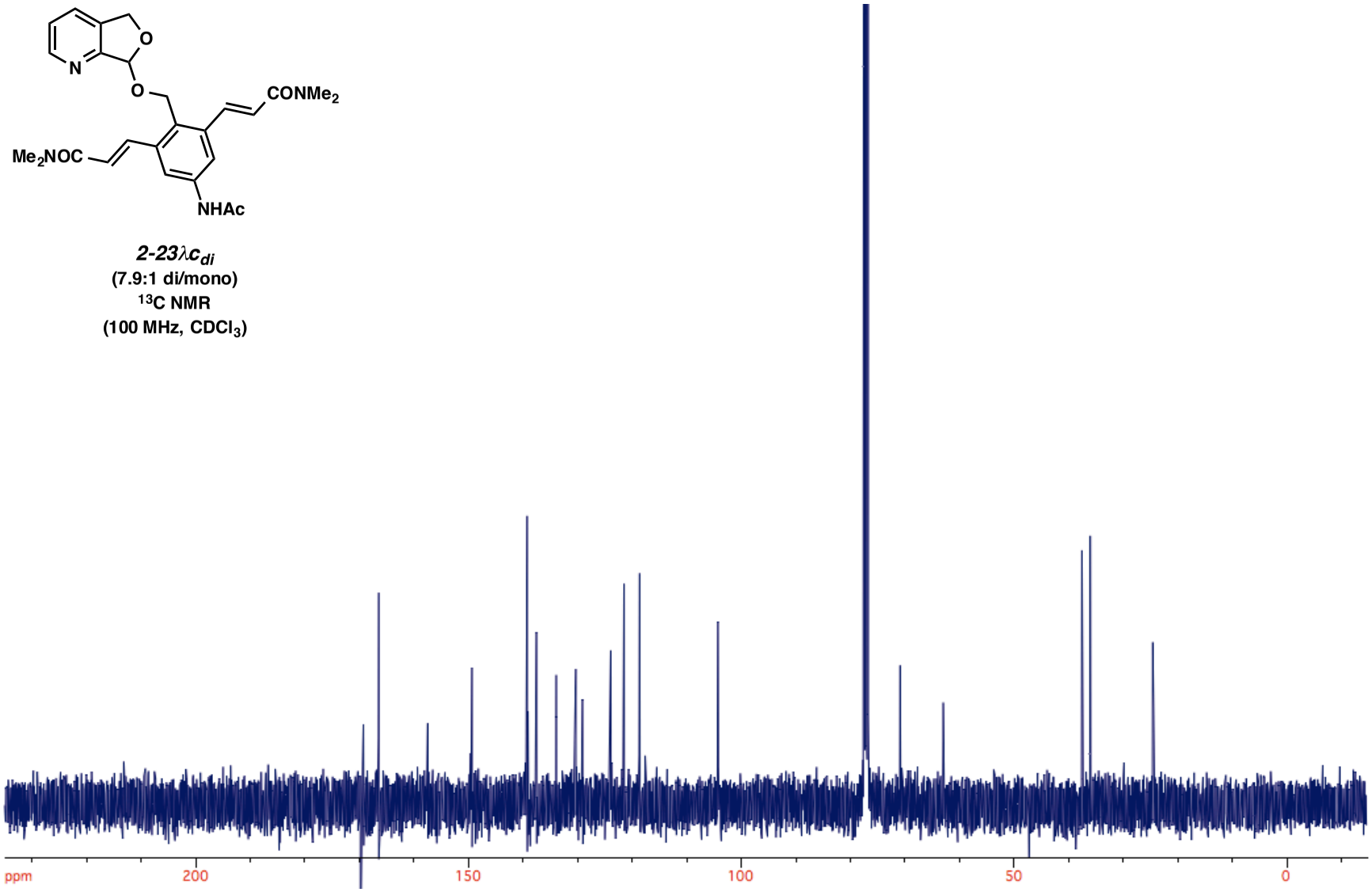

NHAc
O
O
N
2-13λ
^{13}C NMR
(100 MHz, $CDCl_3$)
ppm
0
20
40
60
80
100
120
140
160
180
200

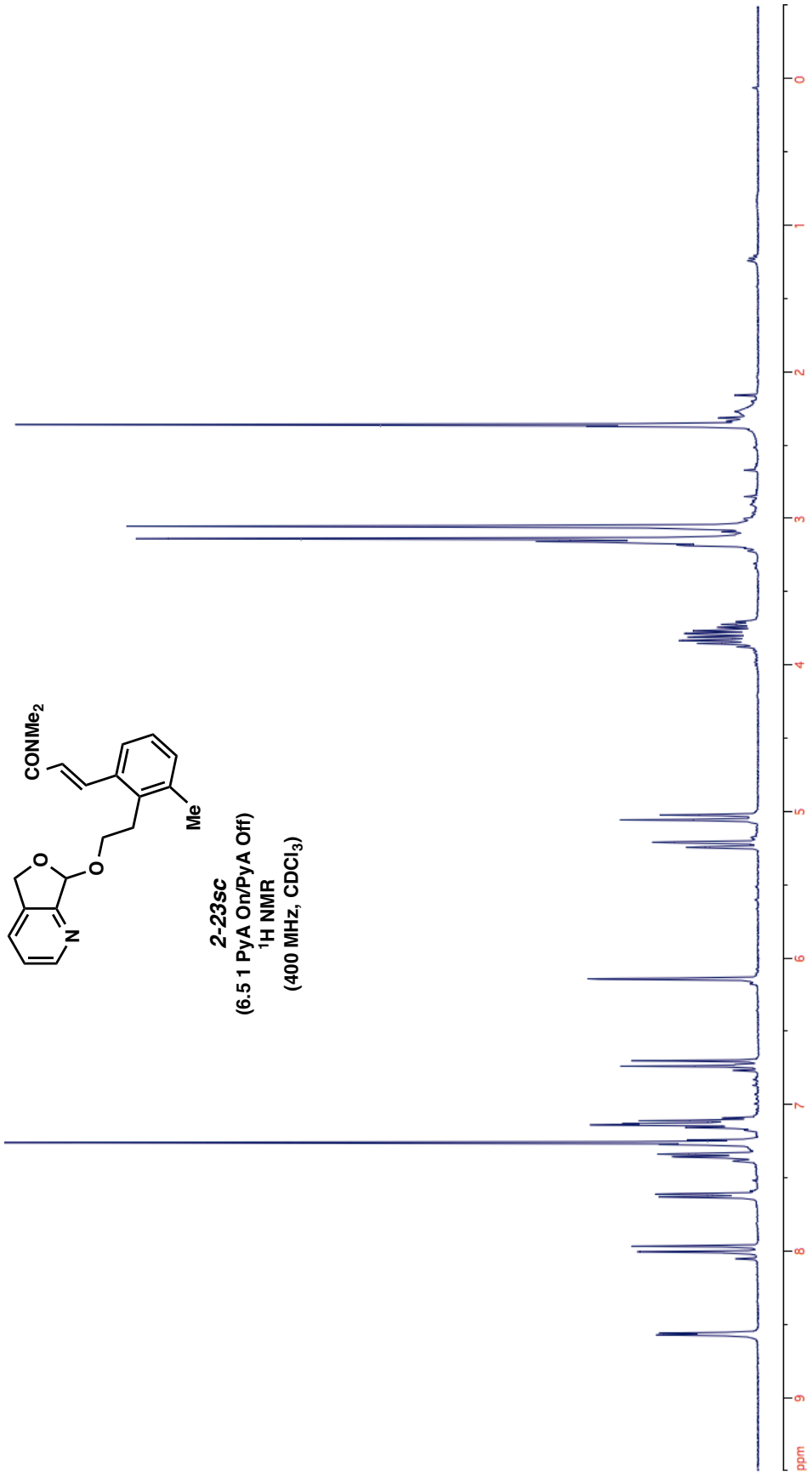

CONMe2
NHAc
O
O
N
2-23λc_mono
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

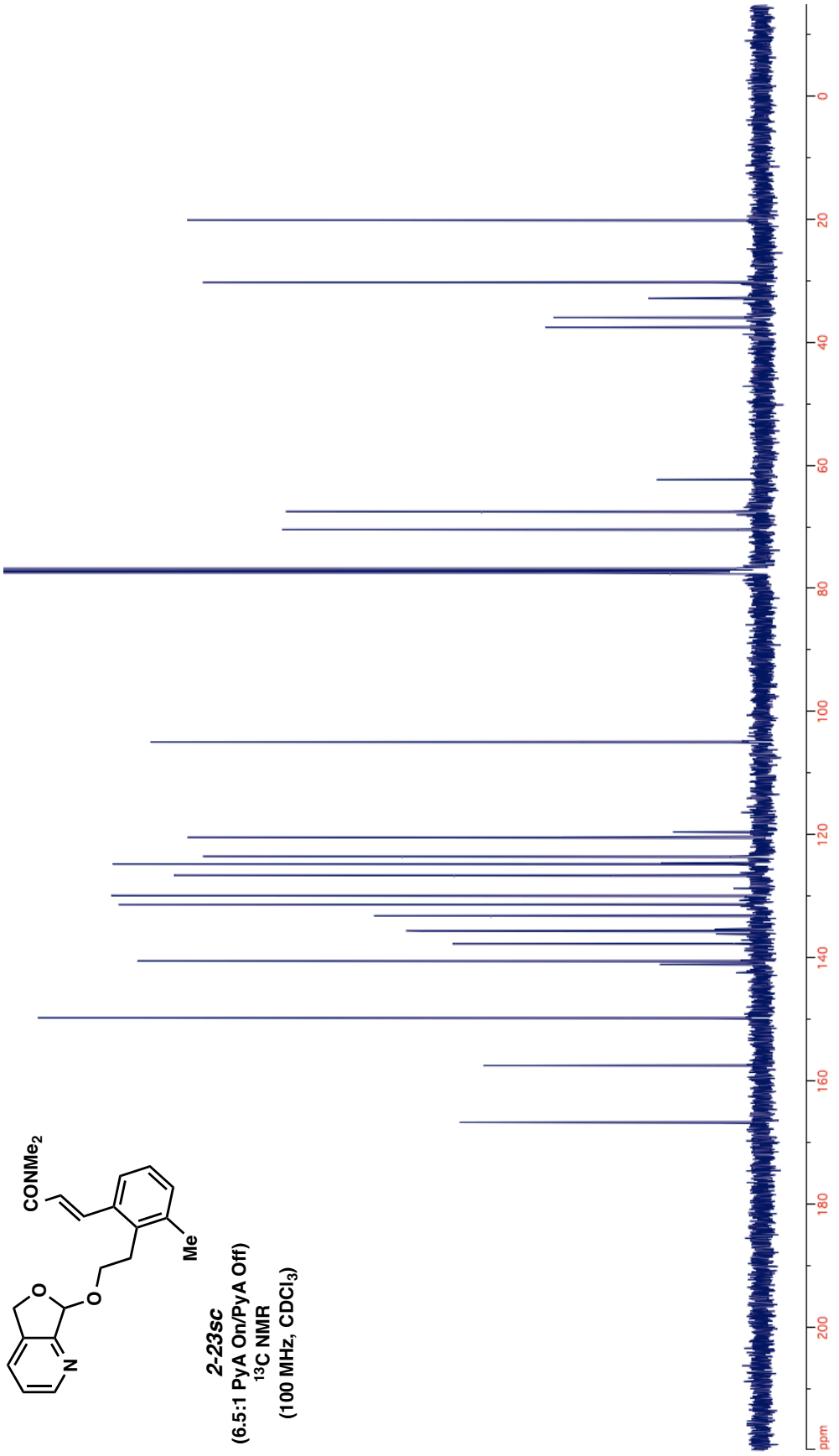

O
N
O
CONMe2
NHAc
2-23λcmono
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

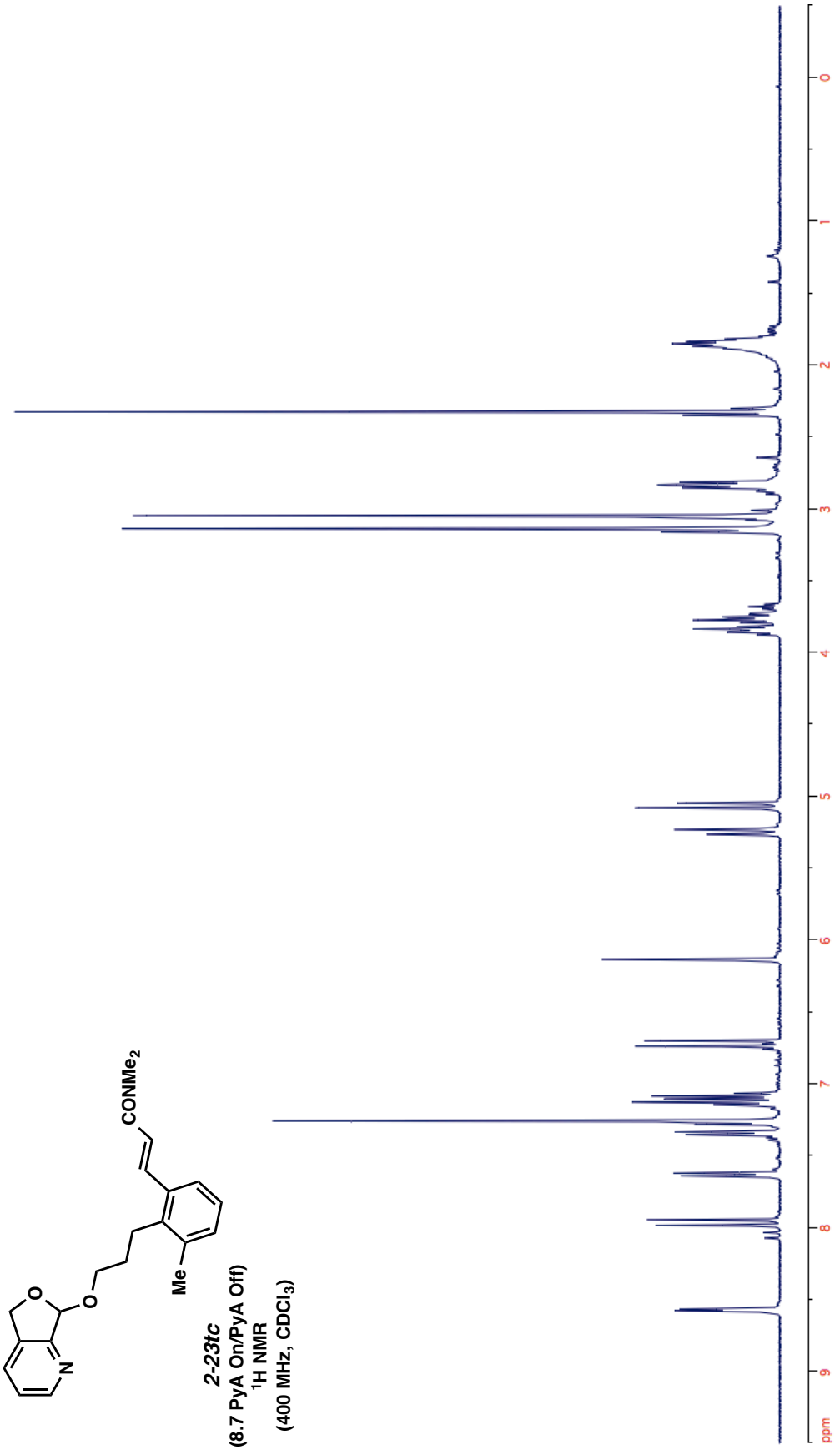

O
N
O
CONMe2
Me2NOC
NHAc
2-23λcdi
(7.9:1 di/mono)
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0

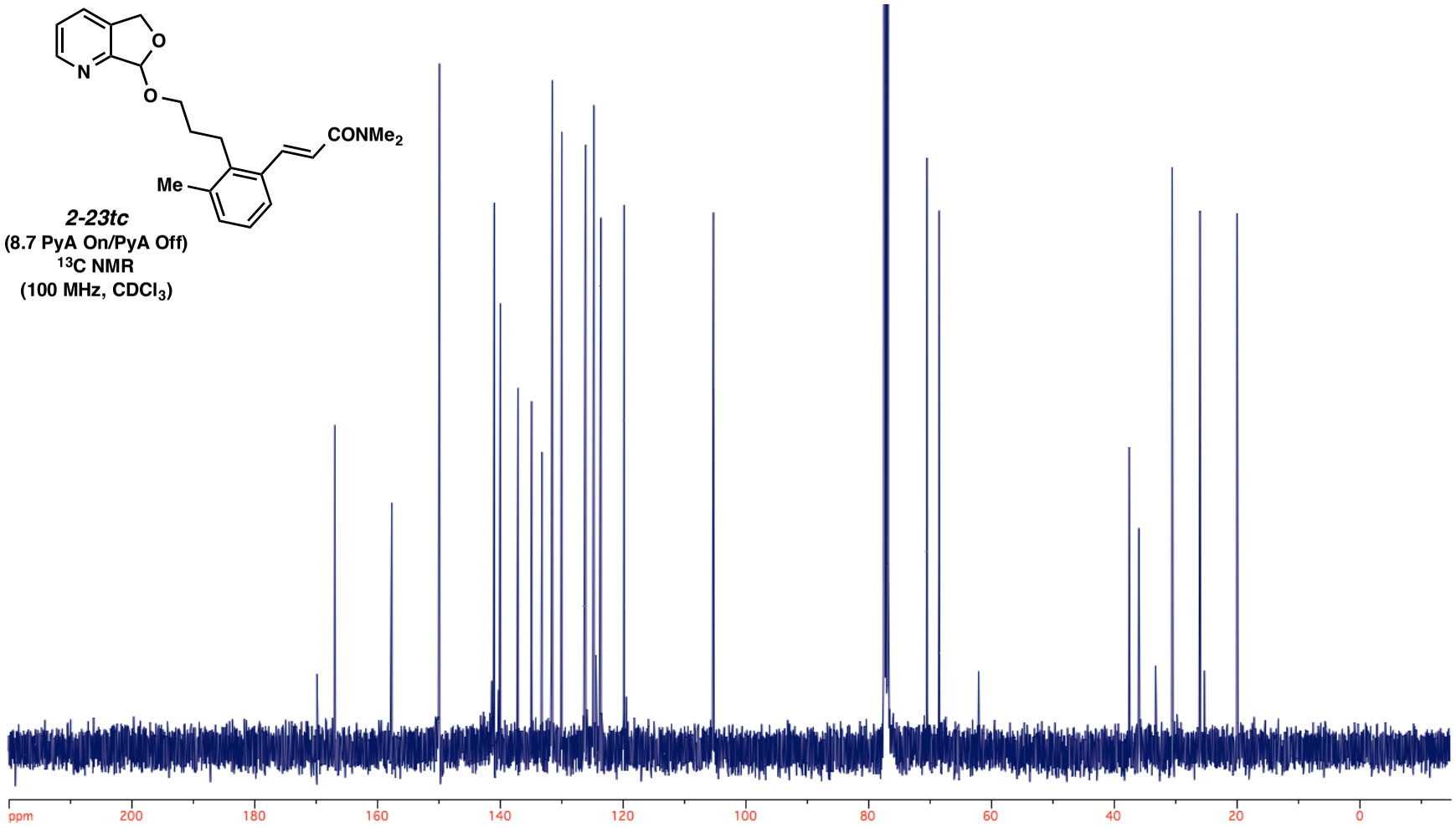
***2-23λc*$_{di}$**
(7.9:1 di/mono)
^{13}C NMR
(100 MHz, $CDCl_3$)

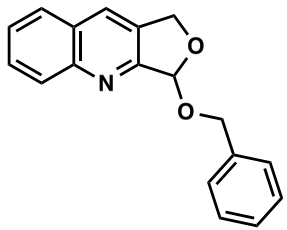



CONMe2
Me
O
O
N
2-23sc
(6.5 1 PyA On/PyA Off)
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

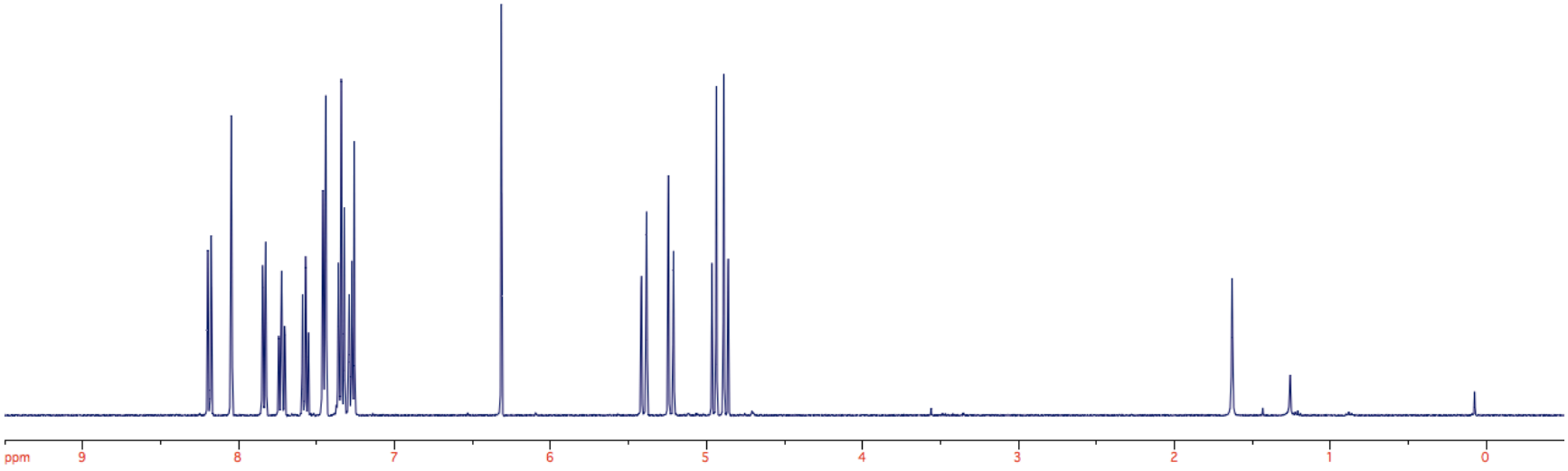

CONMe2
Me
O
O
N
2-23sc
(6.5:1 PyA On/PyA Off)
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

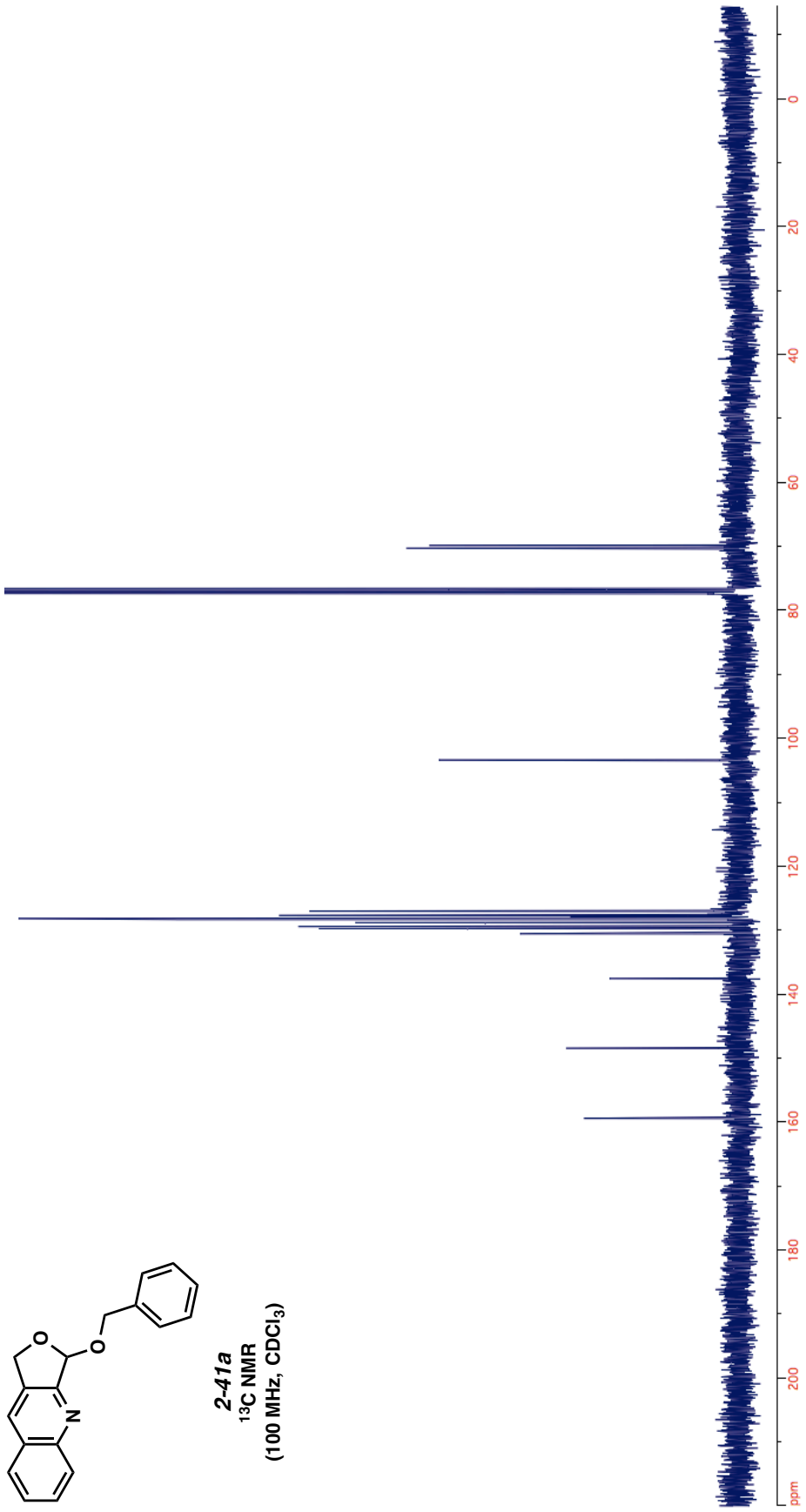

CONMe2
Me
O
O
N
2-23tc
(8.7 PyA On/PyA Off)
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

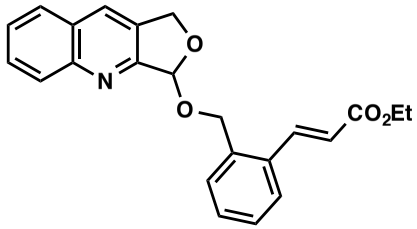

O
N
O
CONMe2
Me
2-23tc
(8.7 PyA On/PyA Off)
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0



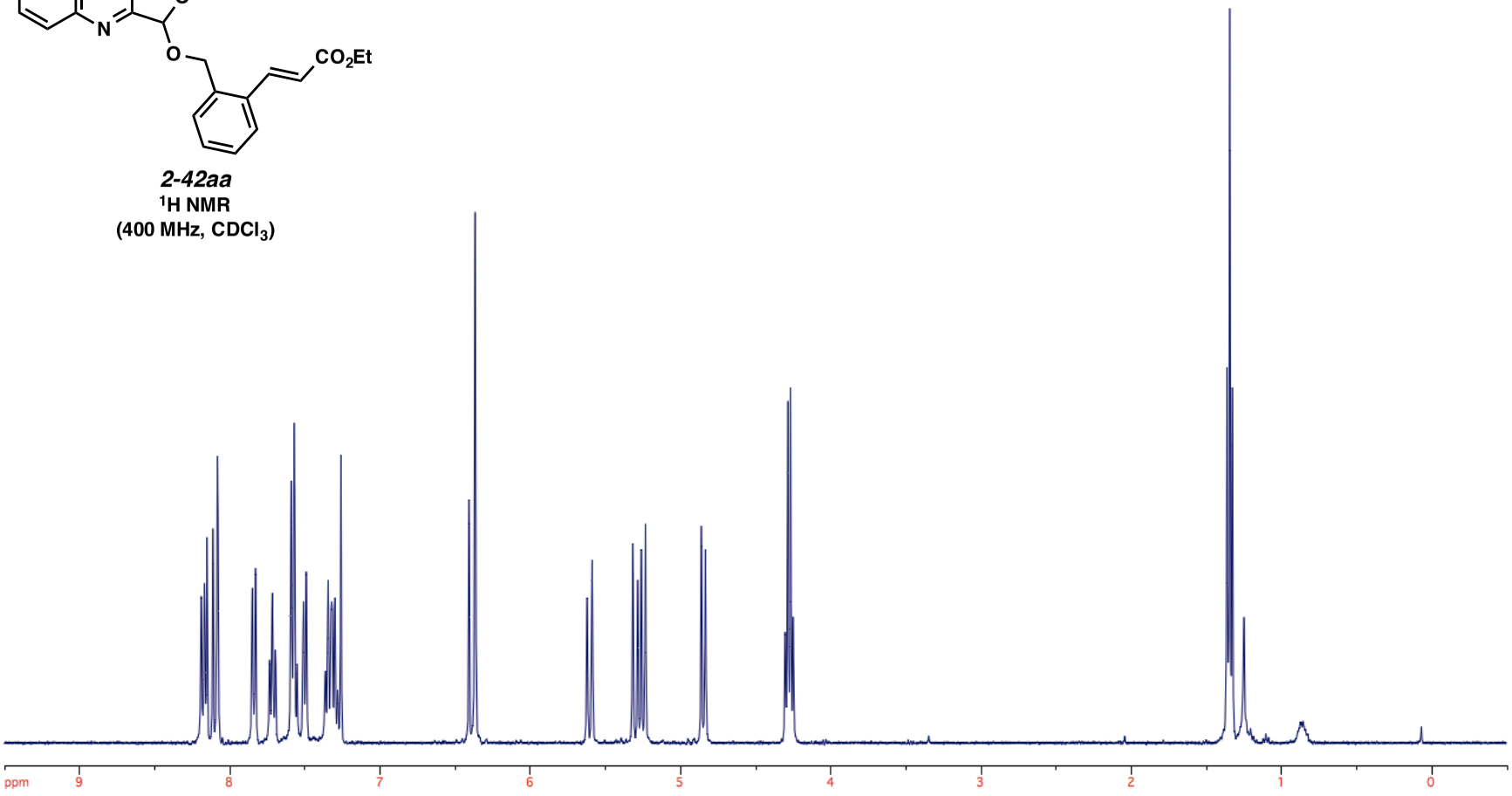
2-41a
^{1}H NMR
(400 MHz, $CDCl_3$)

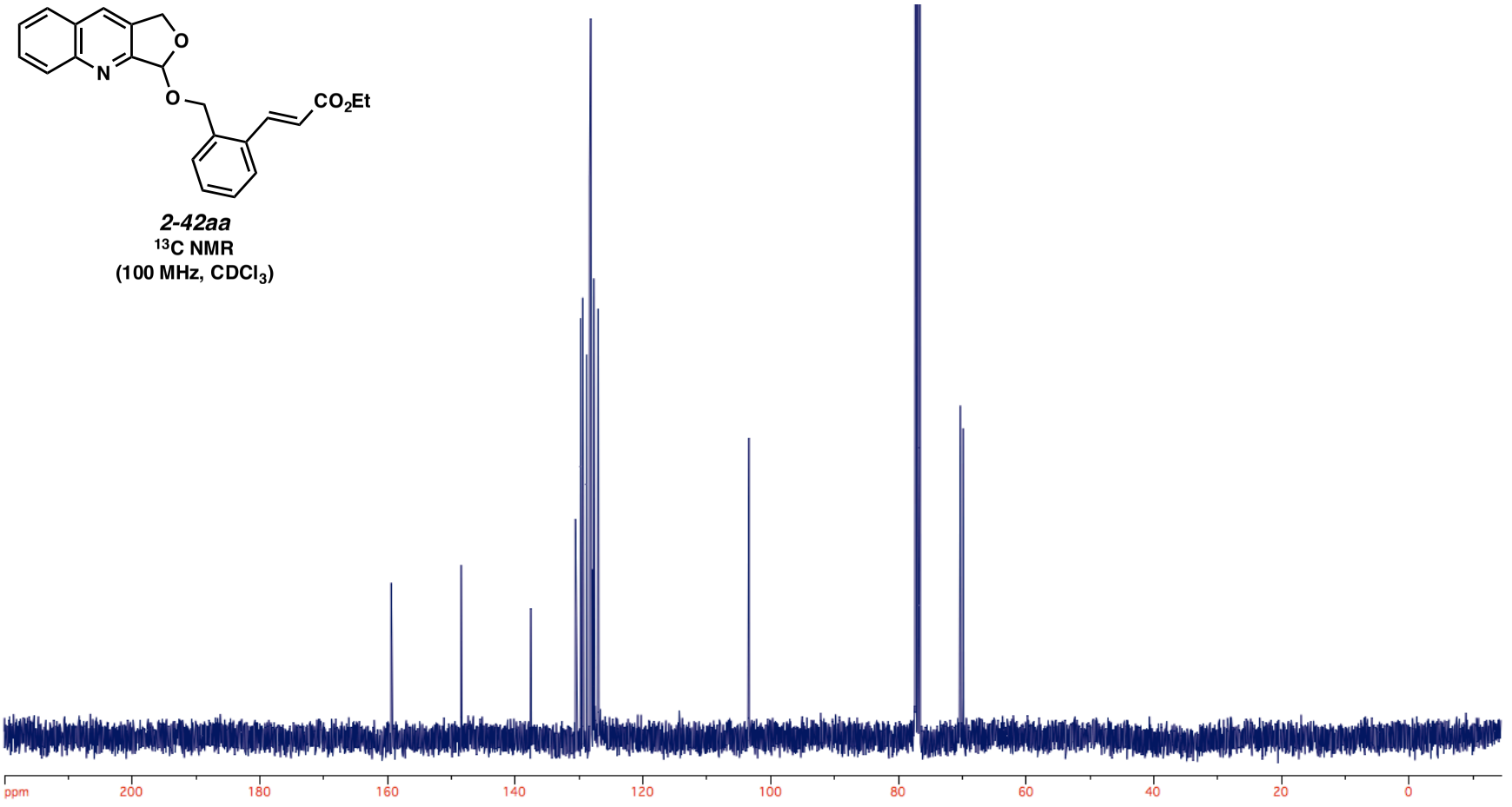



O
O
N
2-41a
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

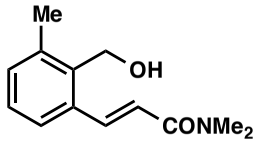


2-42aa
^{1}H NMR
(400 MHz, $CDCl_3$)

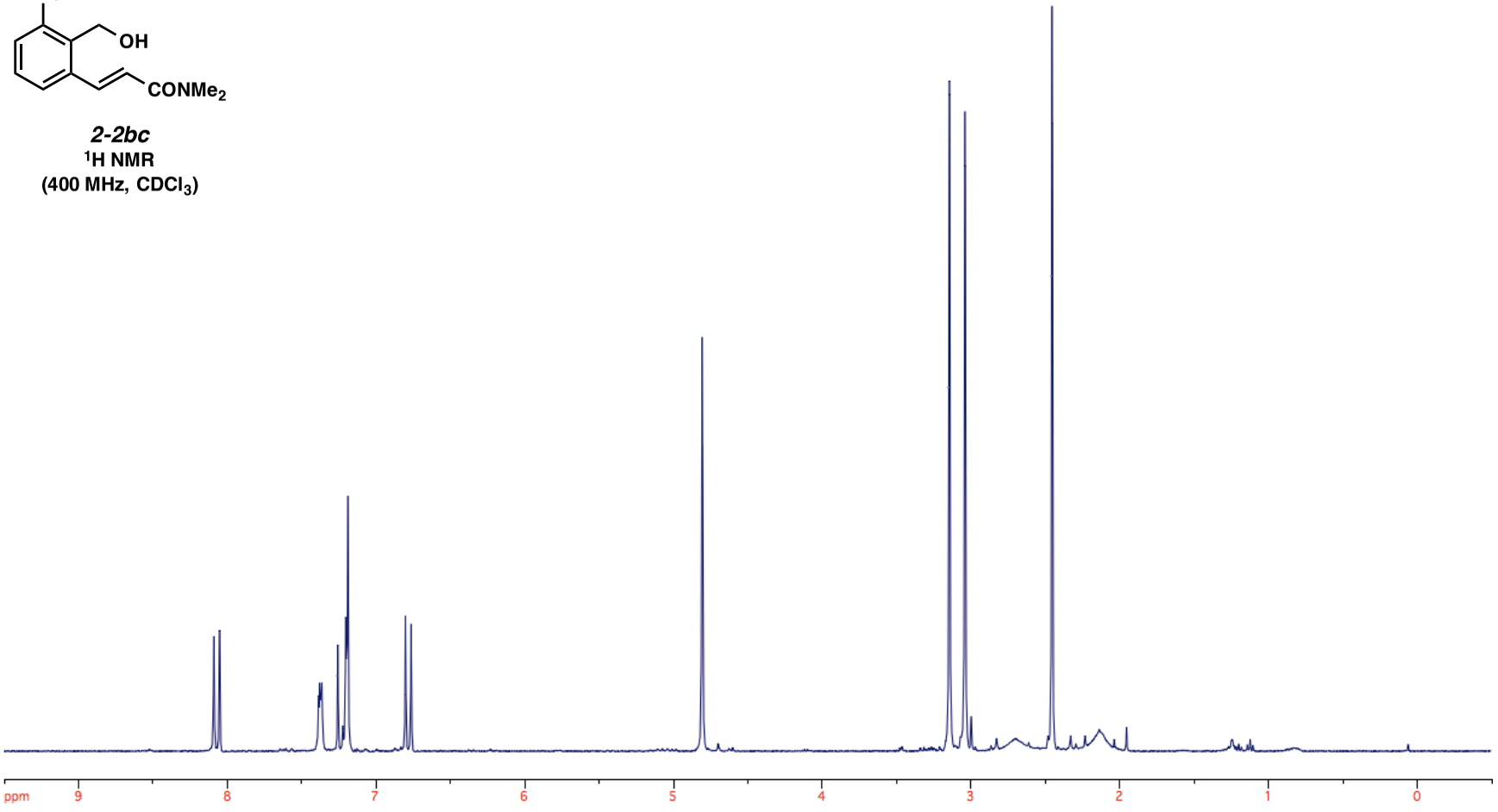


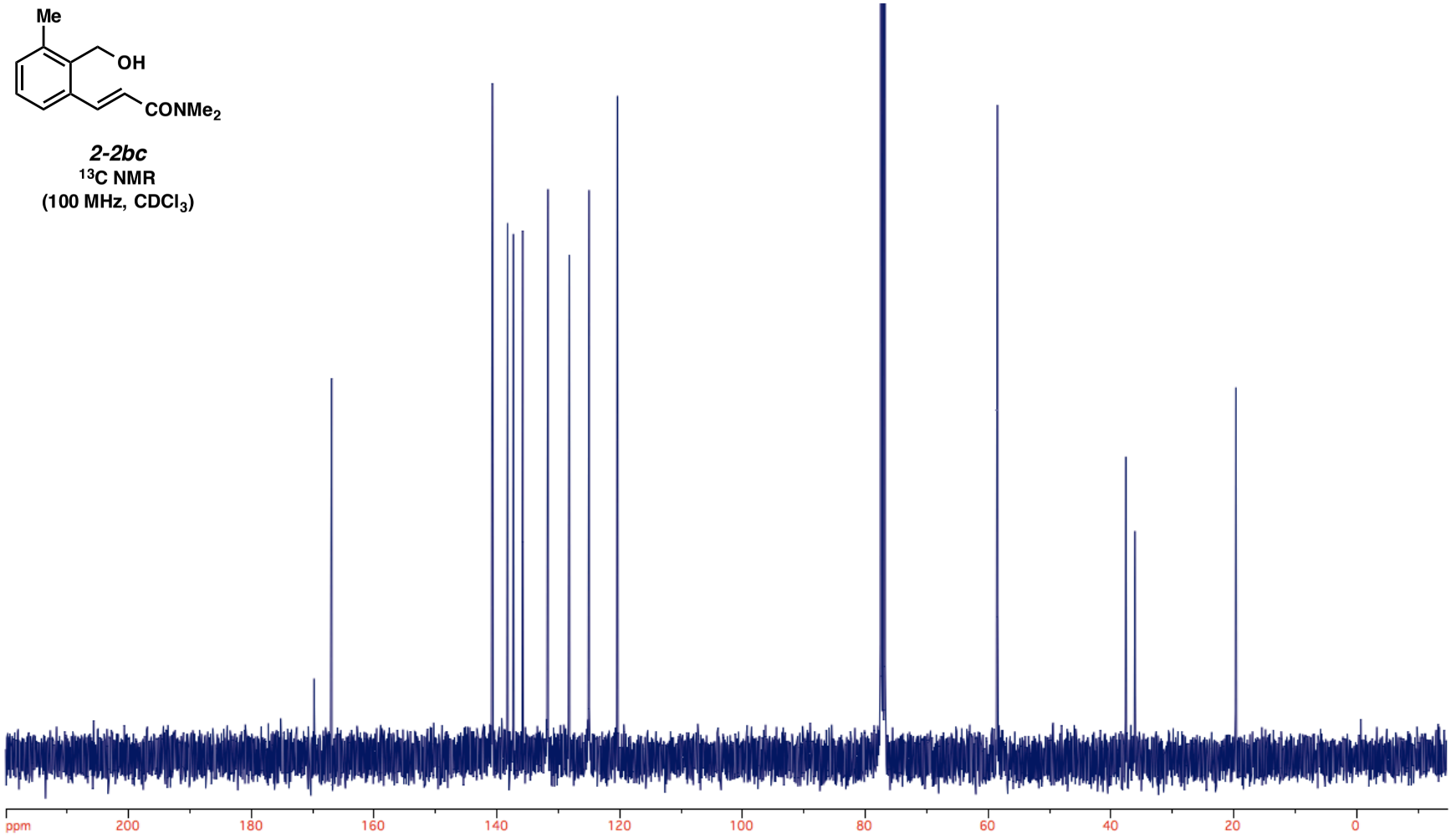


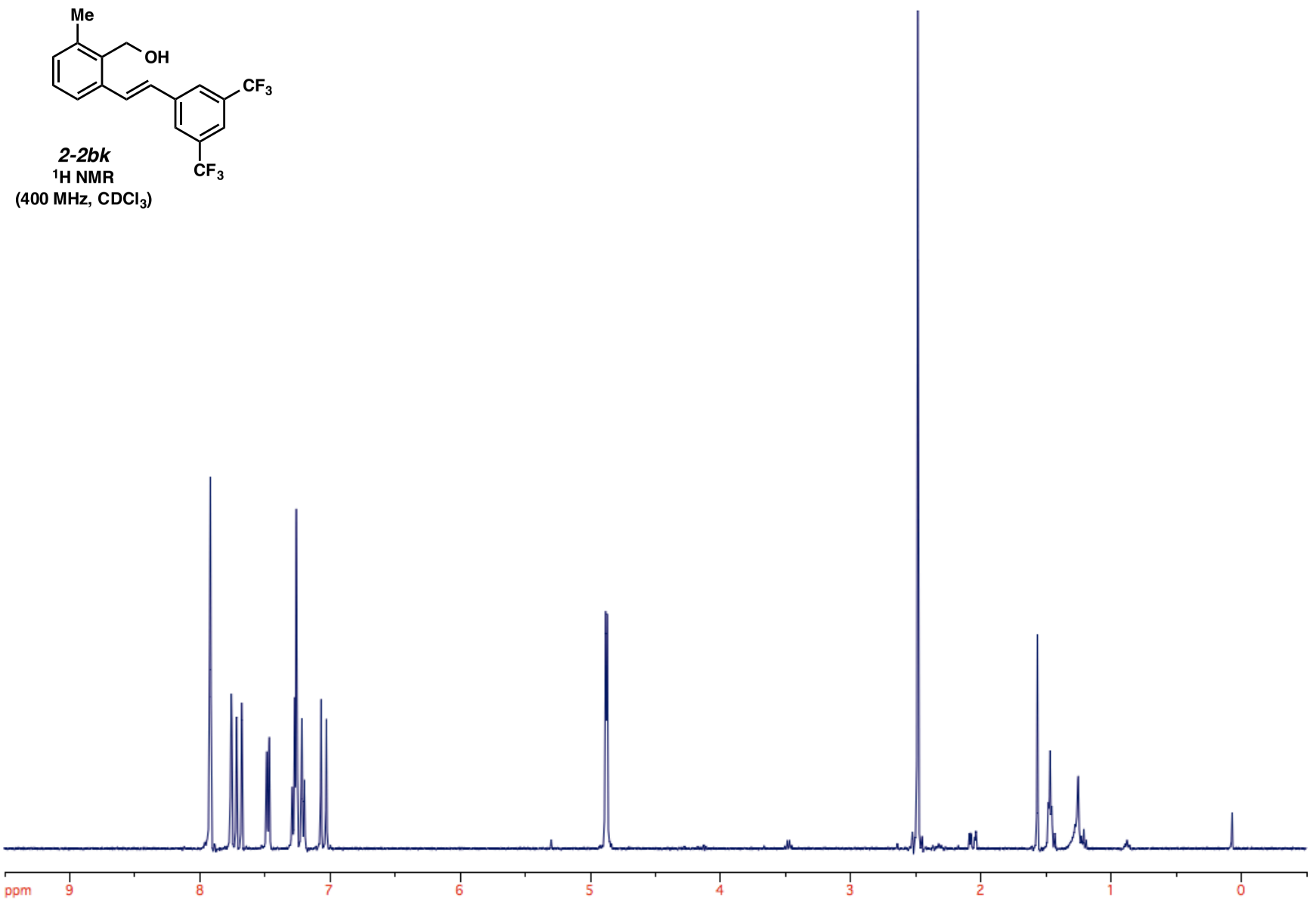
2-42aa
^{13}C NMR
(100 MHz, $CDCl_3$)

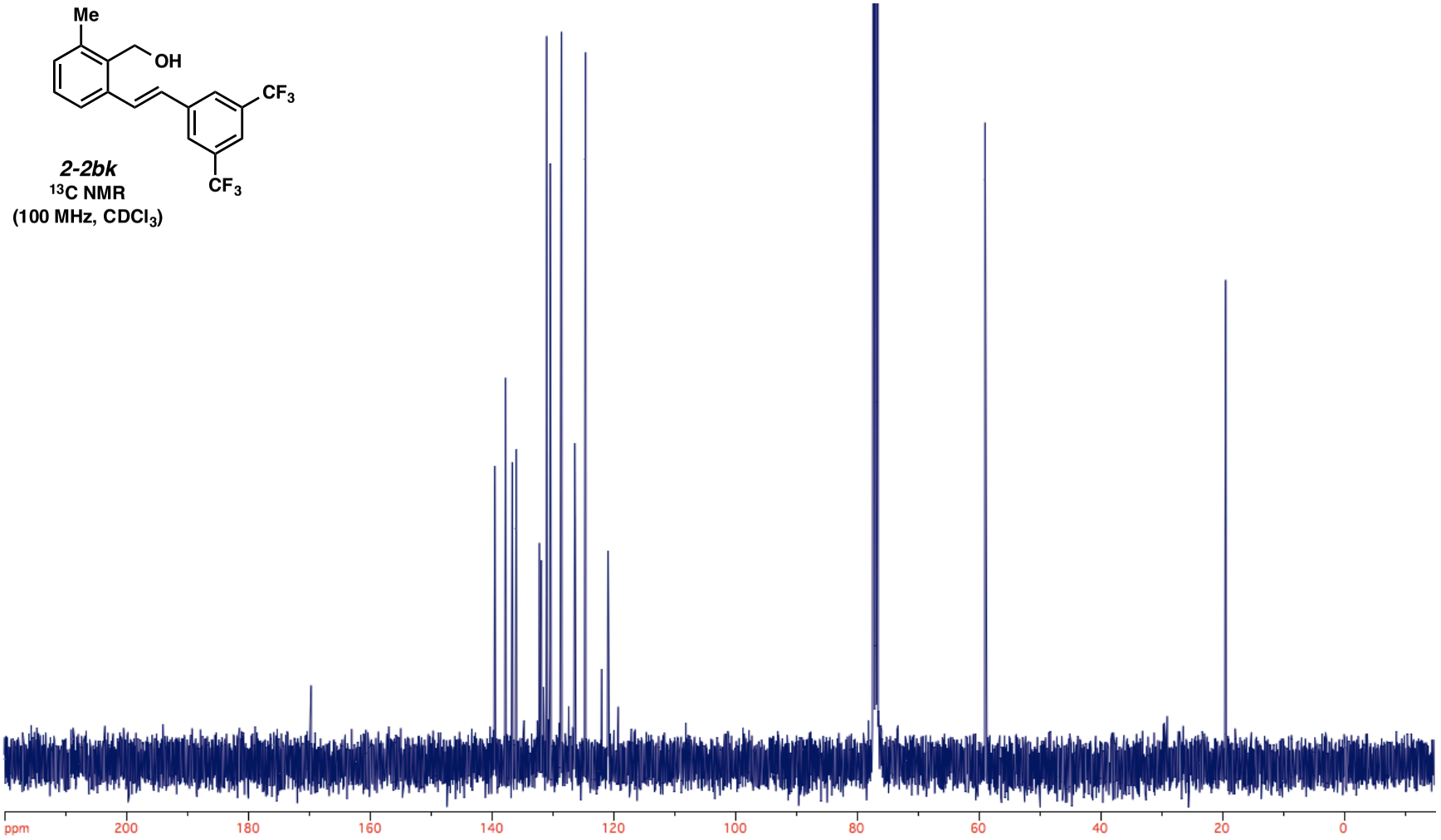


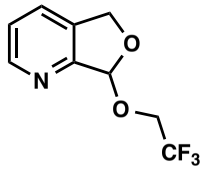
2-2bc
^{1}H NMR
(400 MHz, $CDCl_3$)




Me
OH
CONMe2
2-2bc
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0


Me
OH
CF3
CF3
2-2bk
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0

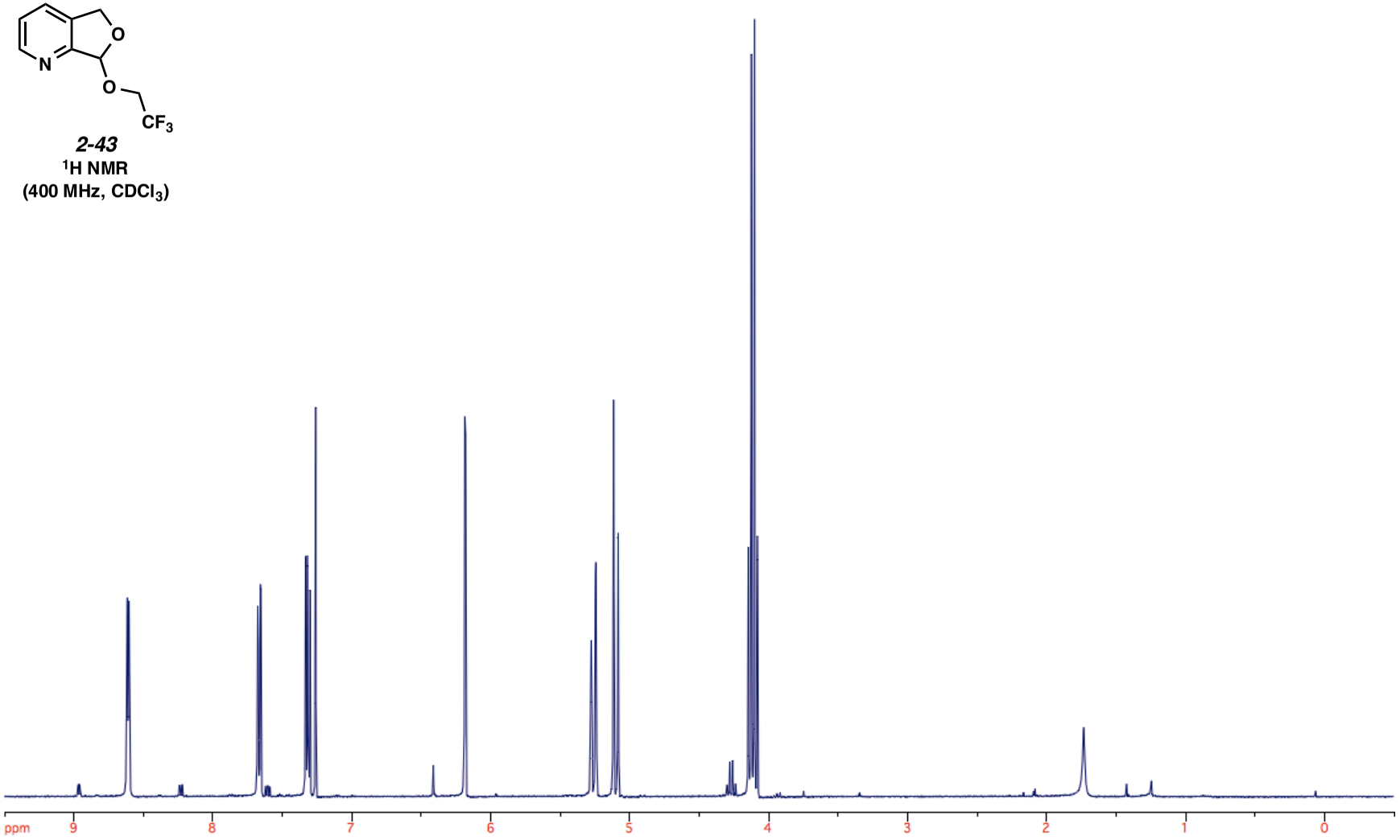

Me
OH
CF3
CF3
2-2bk
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0



2-43

^{1}H NMR

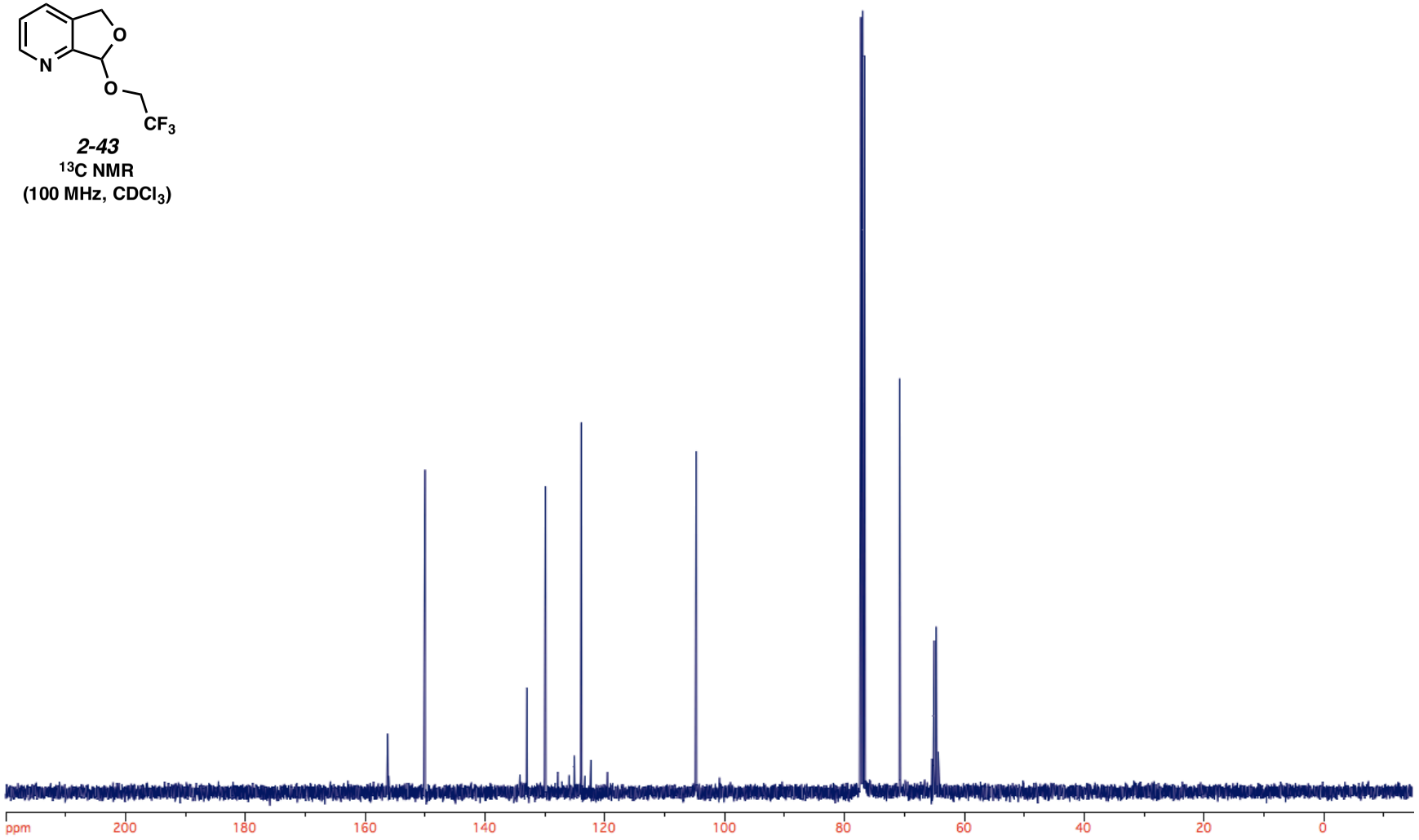
(400 MHz, $CDCl_3$)

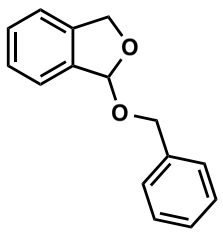


2-43

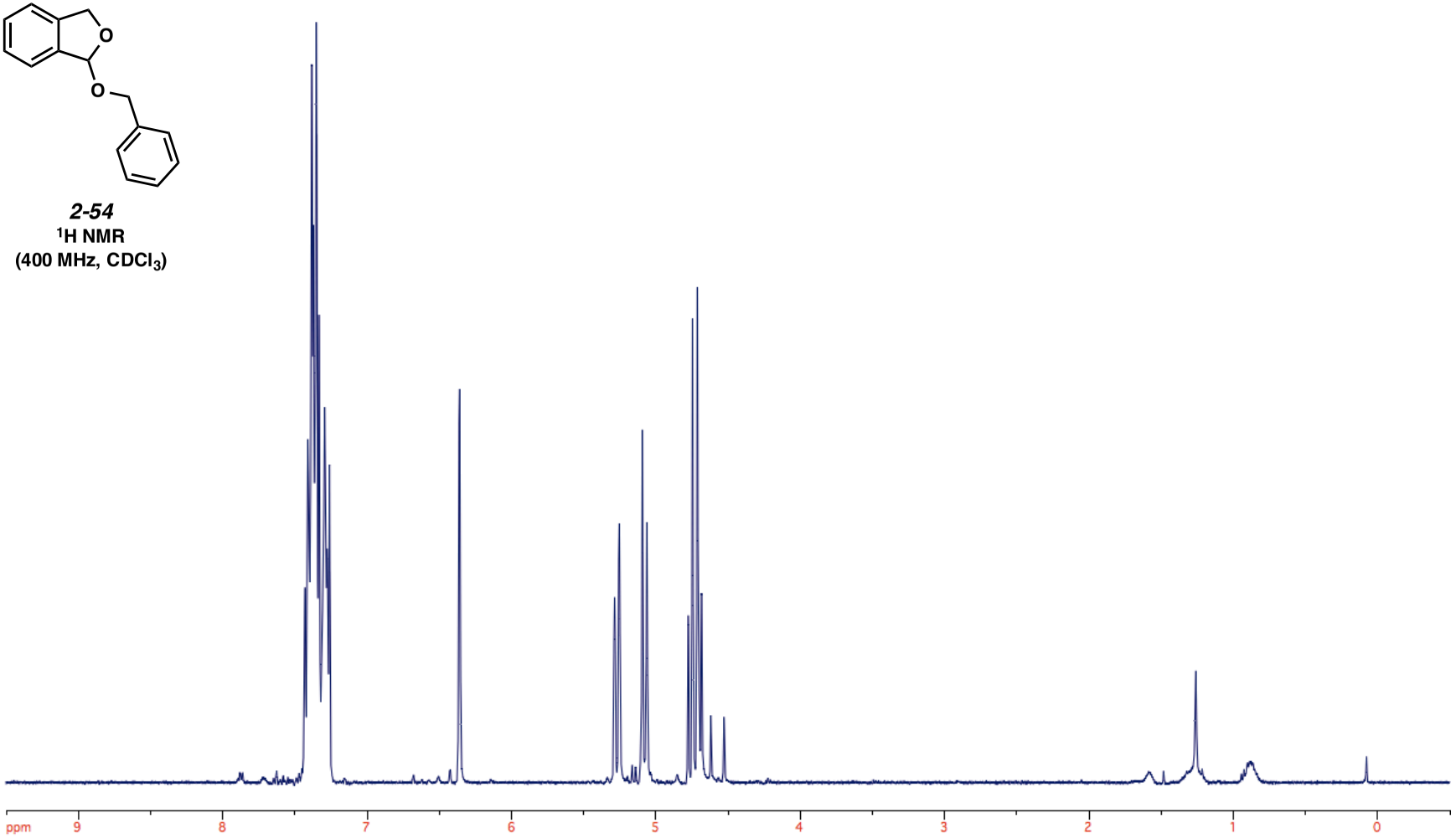
^{13}C NMR

(100 MHz, $CDCl_3$)

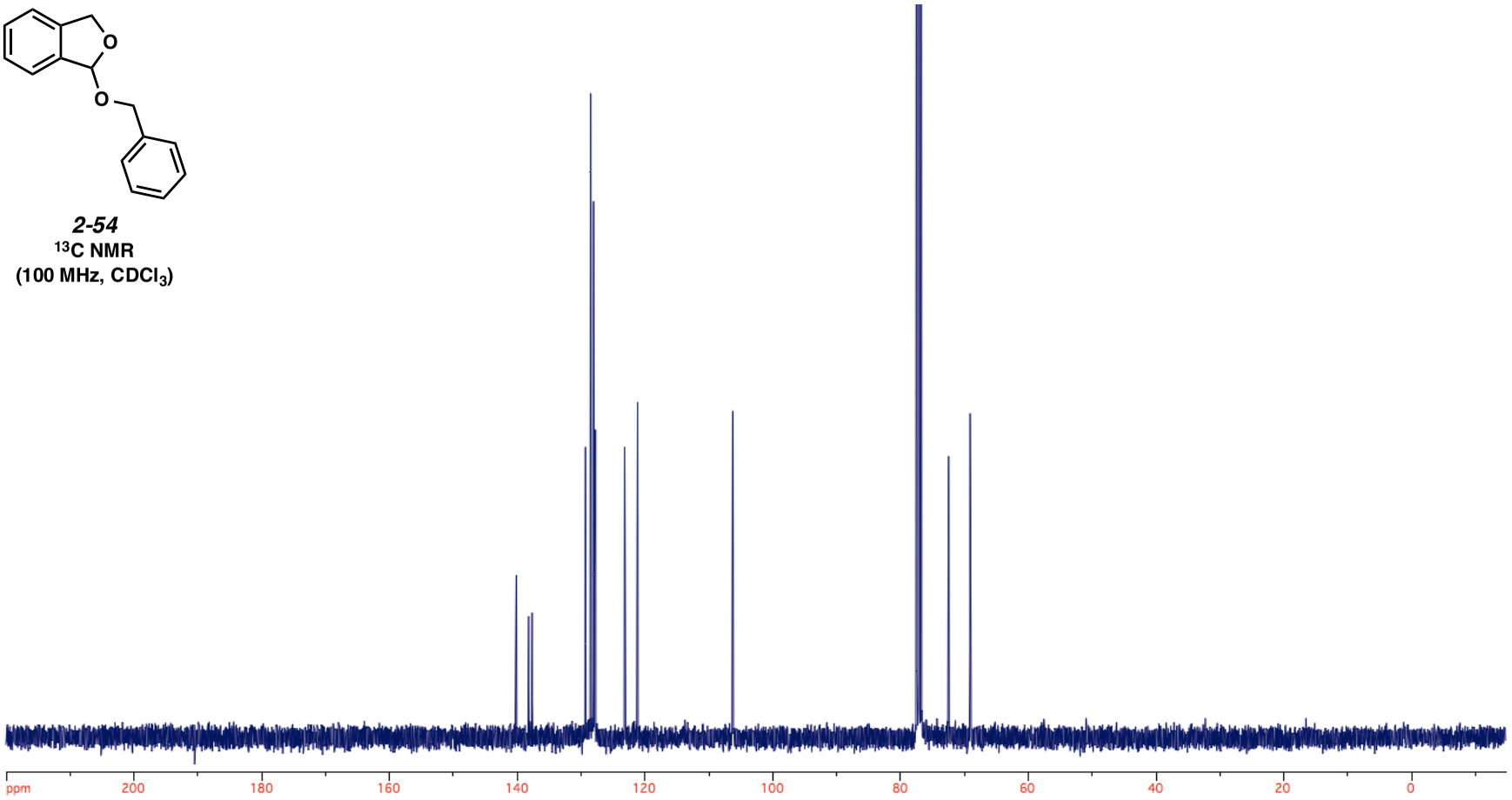


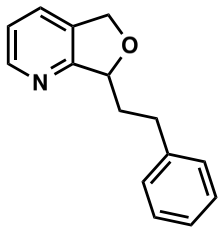


2-54
^{1}H NMR
(400 MHz, $CDCl_3$)

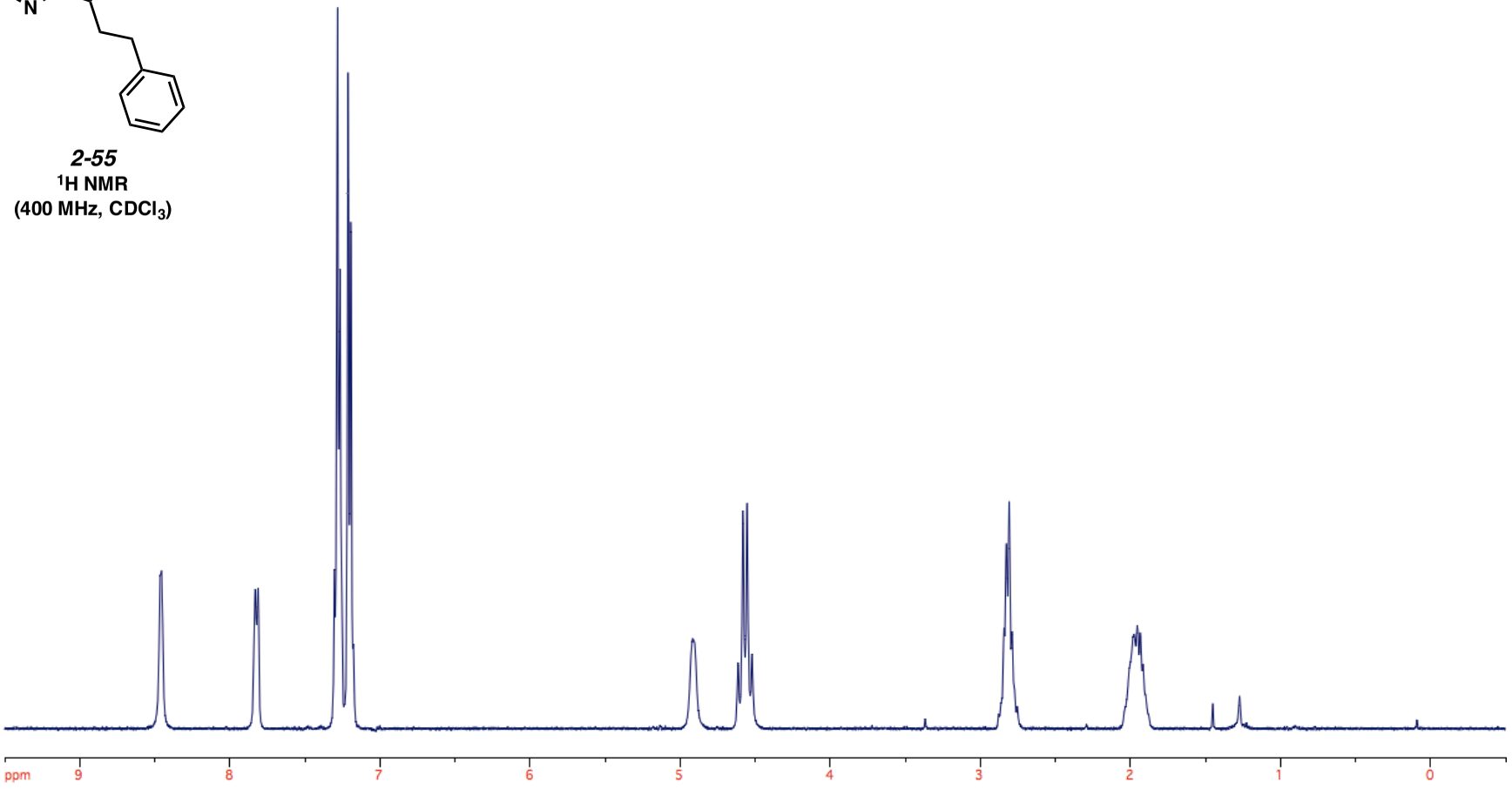


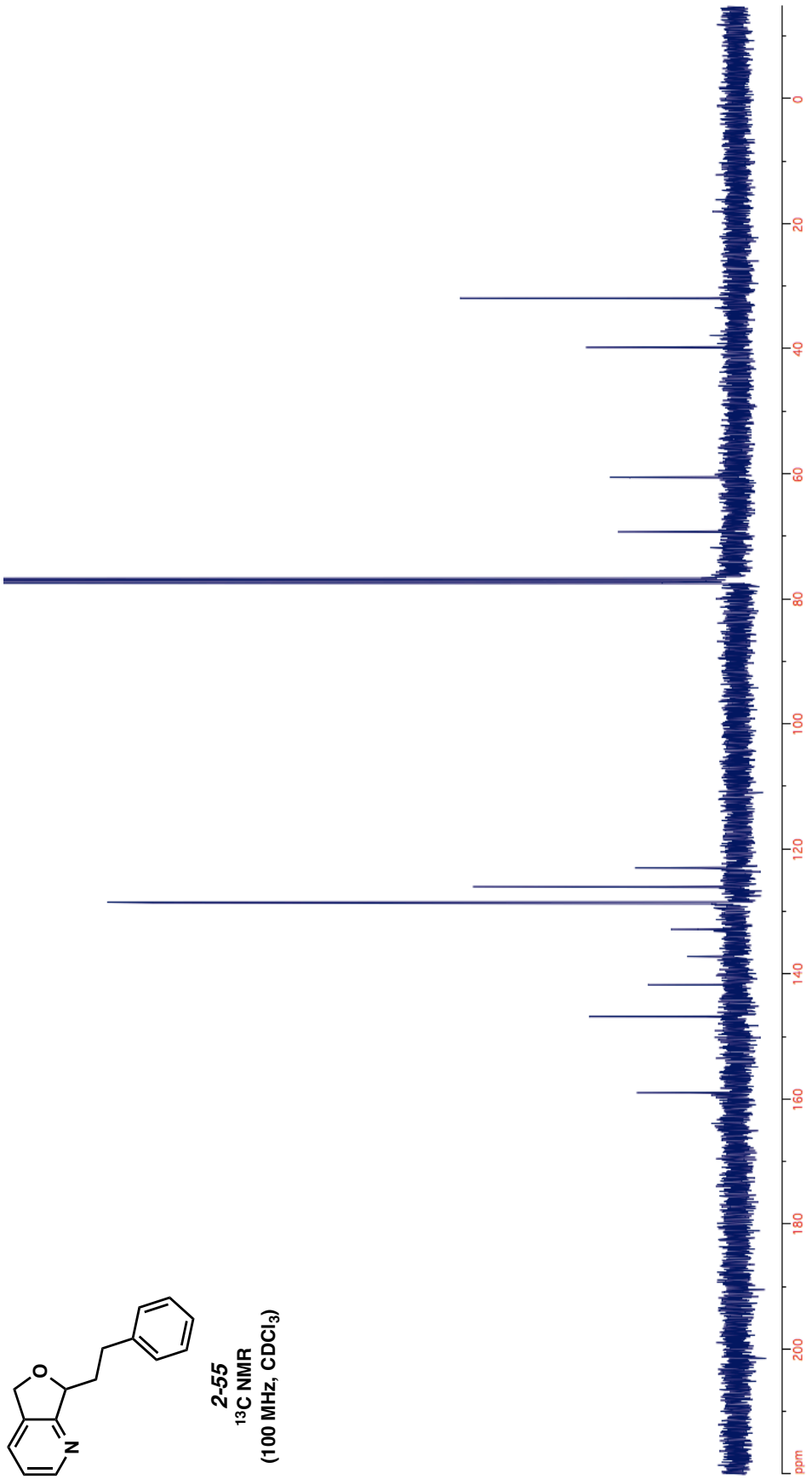
2-54
^{13}C NMR
(100 MHz, $CDCl_3$)

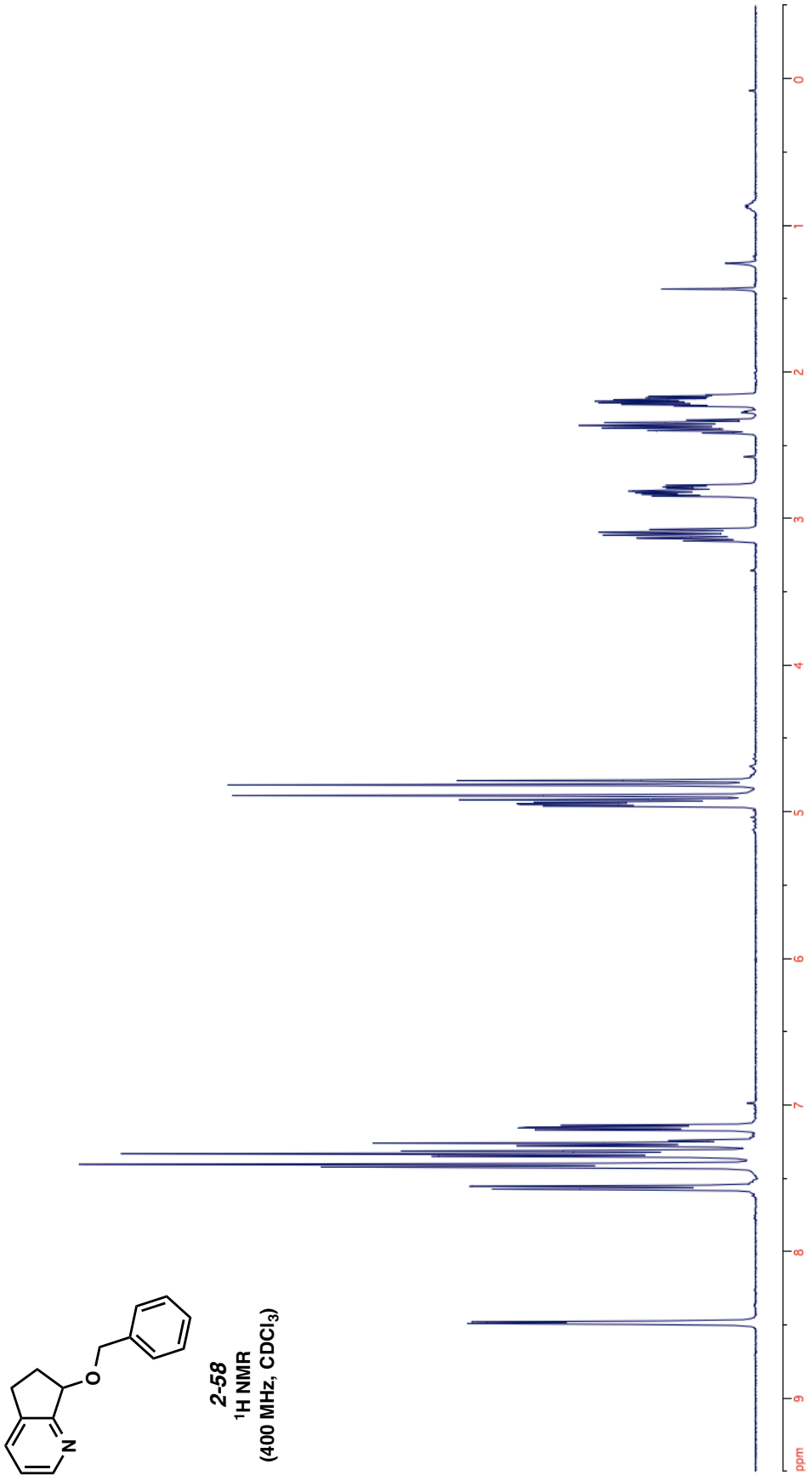


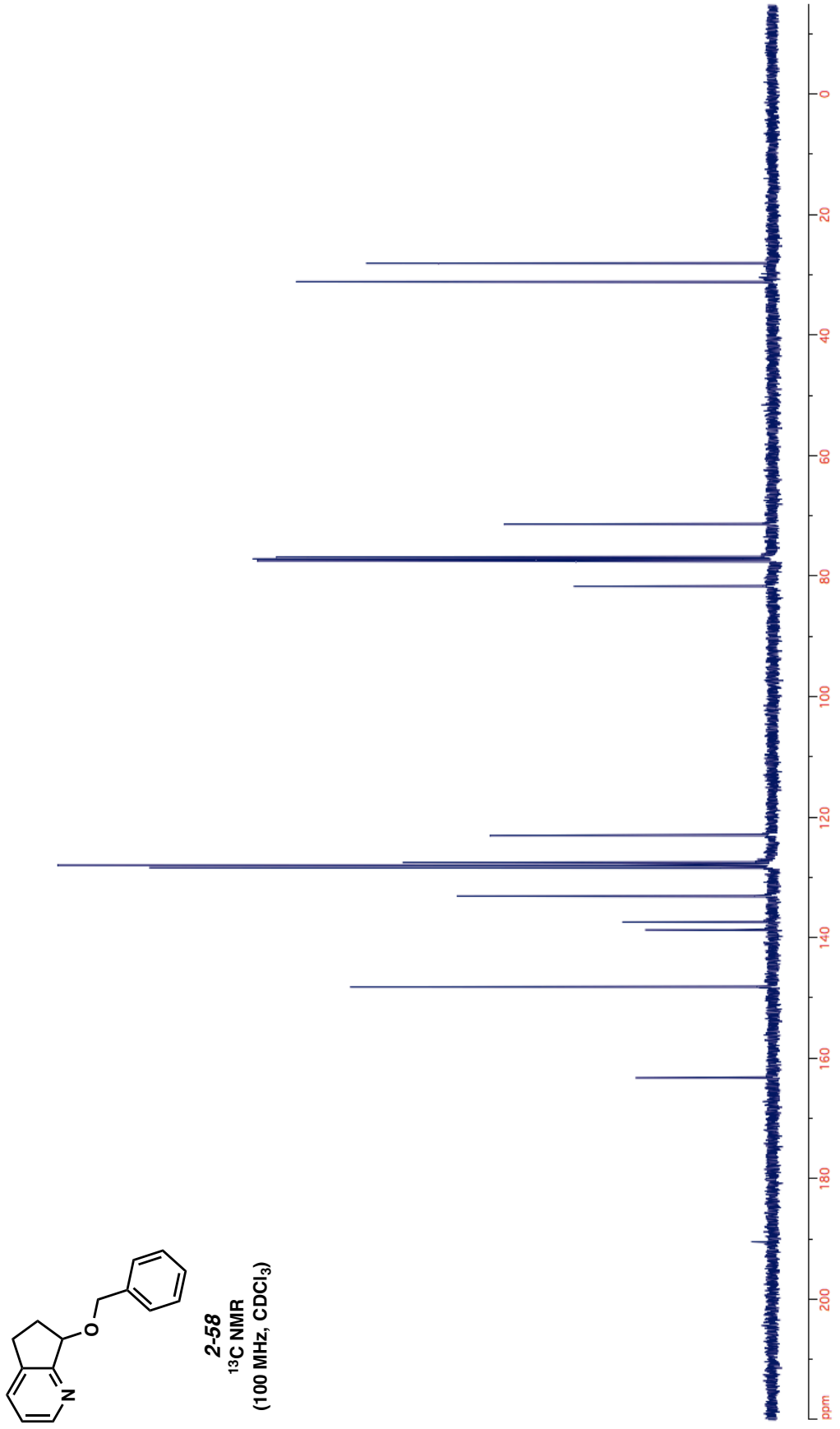


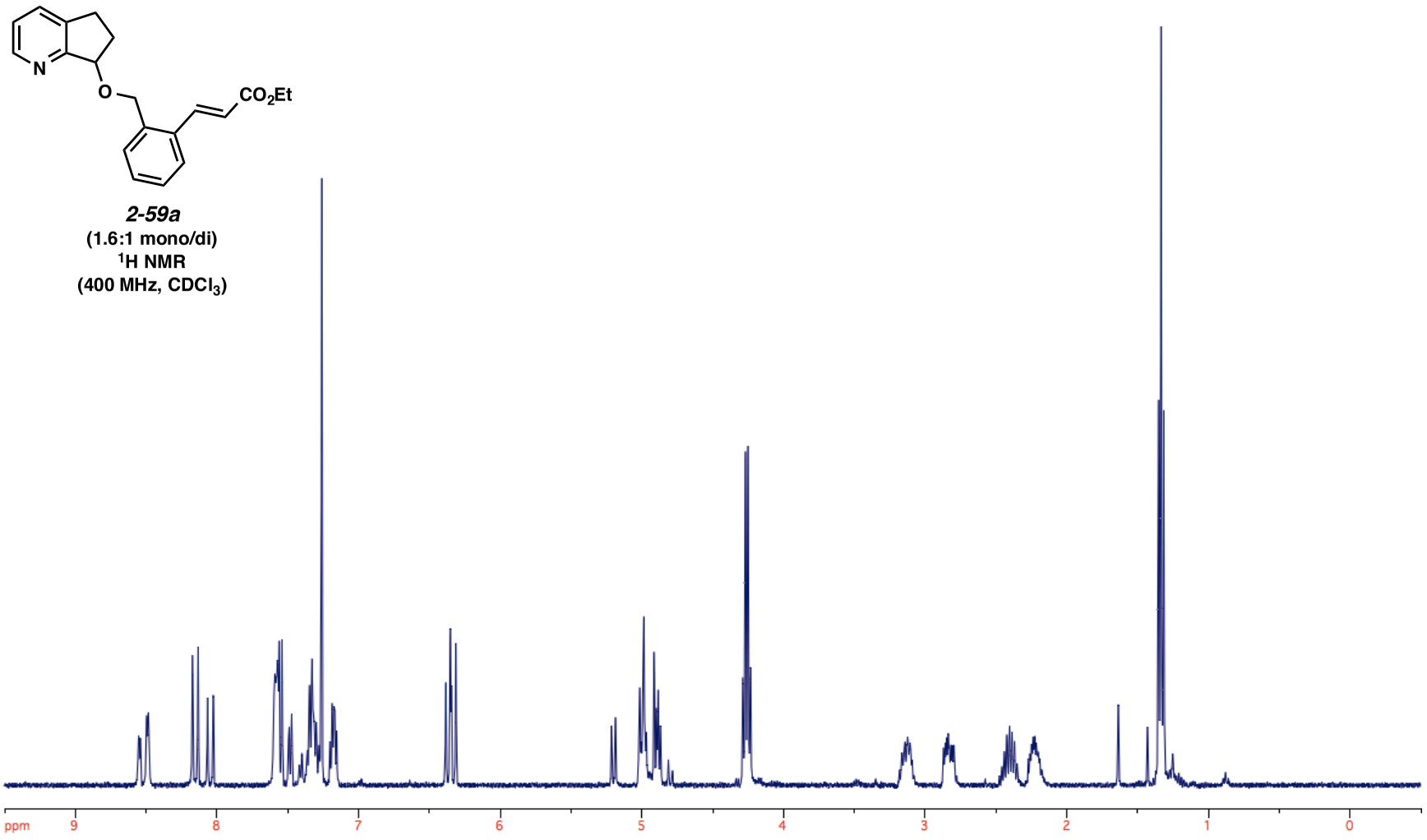
2-55
^{1}H NMR
(400 MHz, $CDCl_3$)



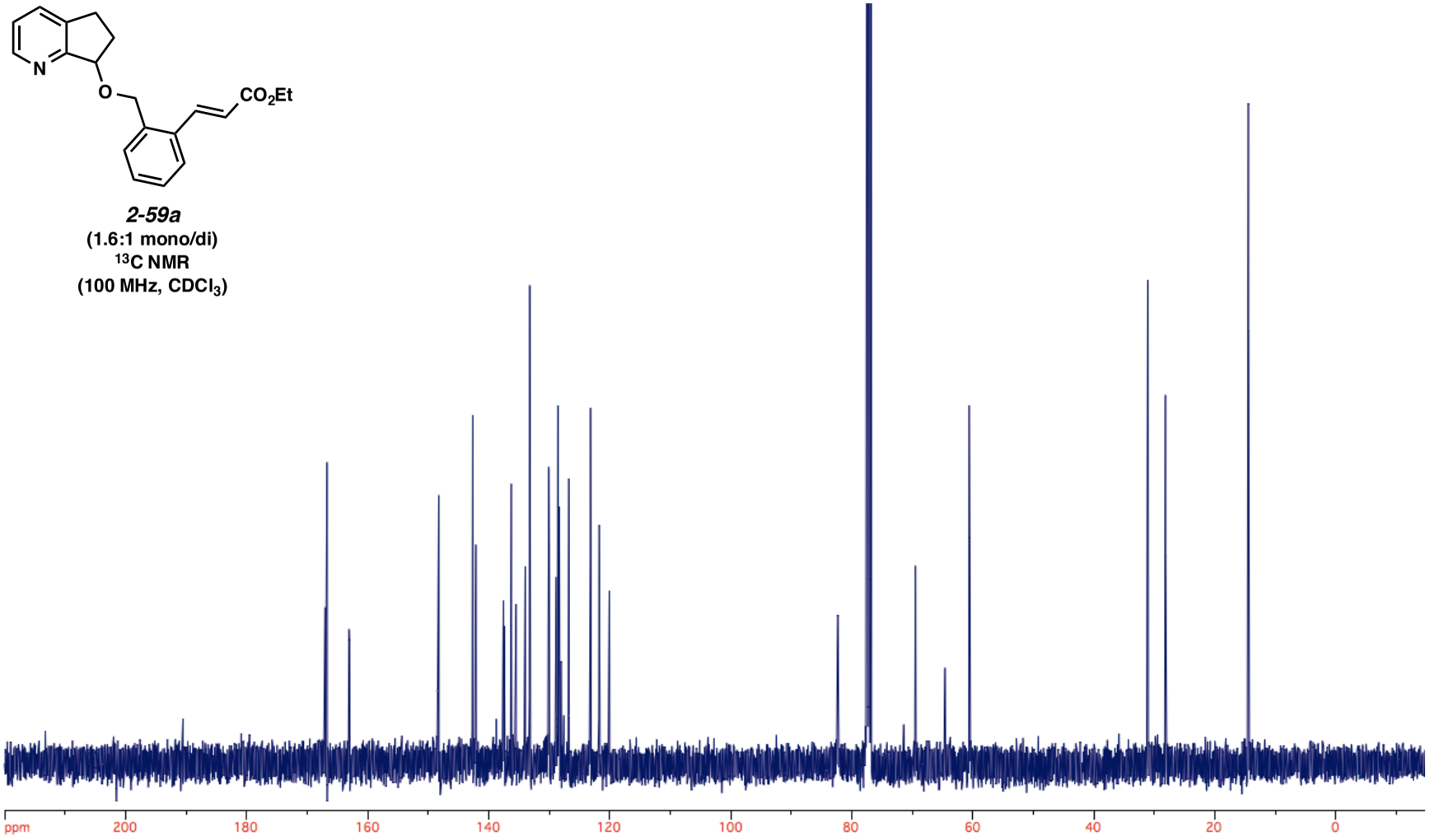

O
N
2-55
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200


O
N
2-58
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9


O
N
2-58
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

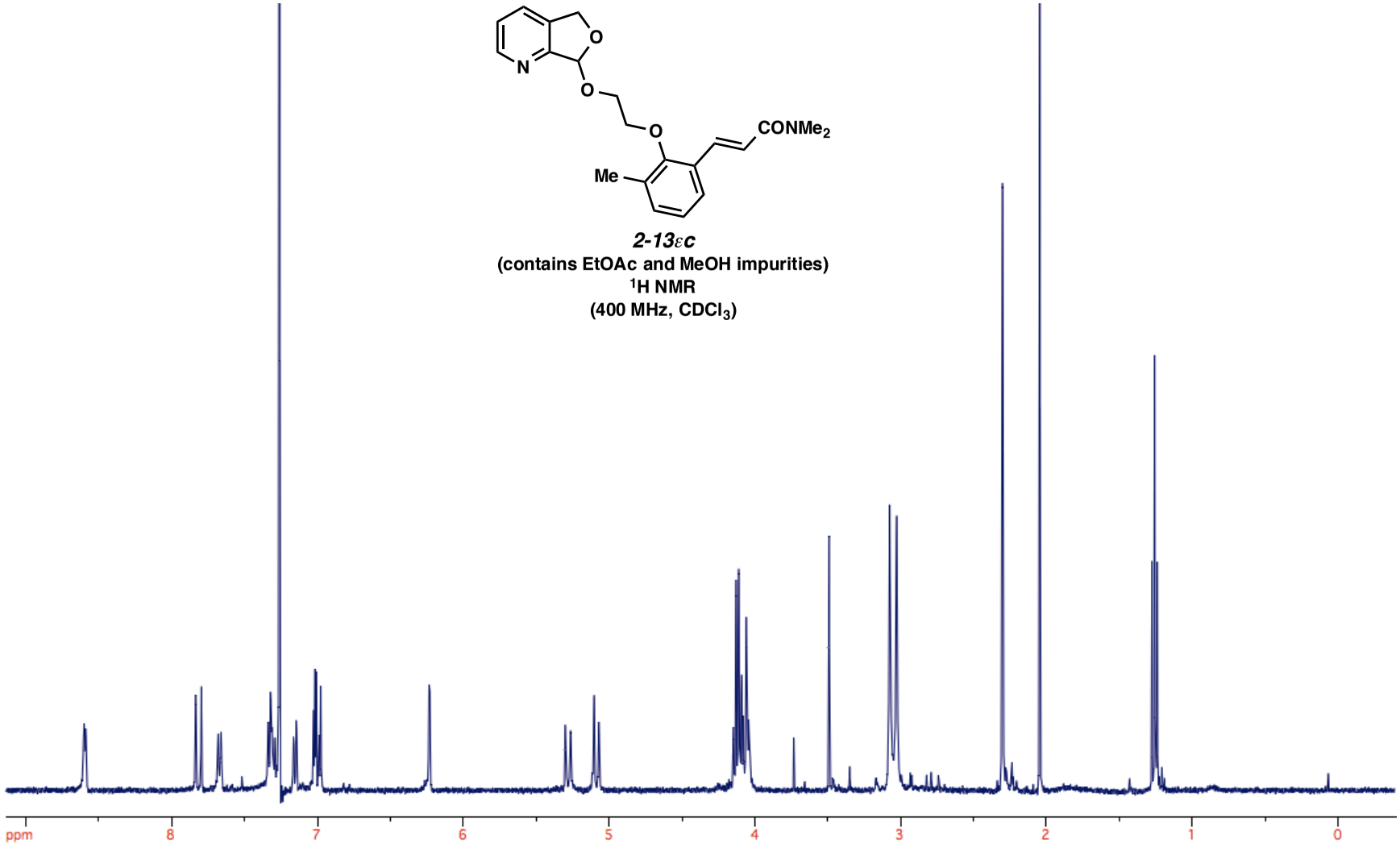


2-59a
(1.6:1 mono/di)
^{1}H NMR
(400 MHz, $CDCl_3$)

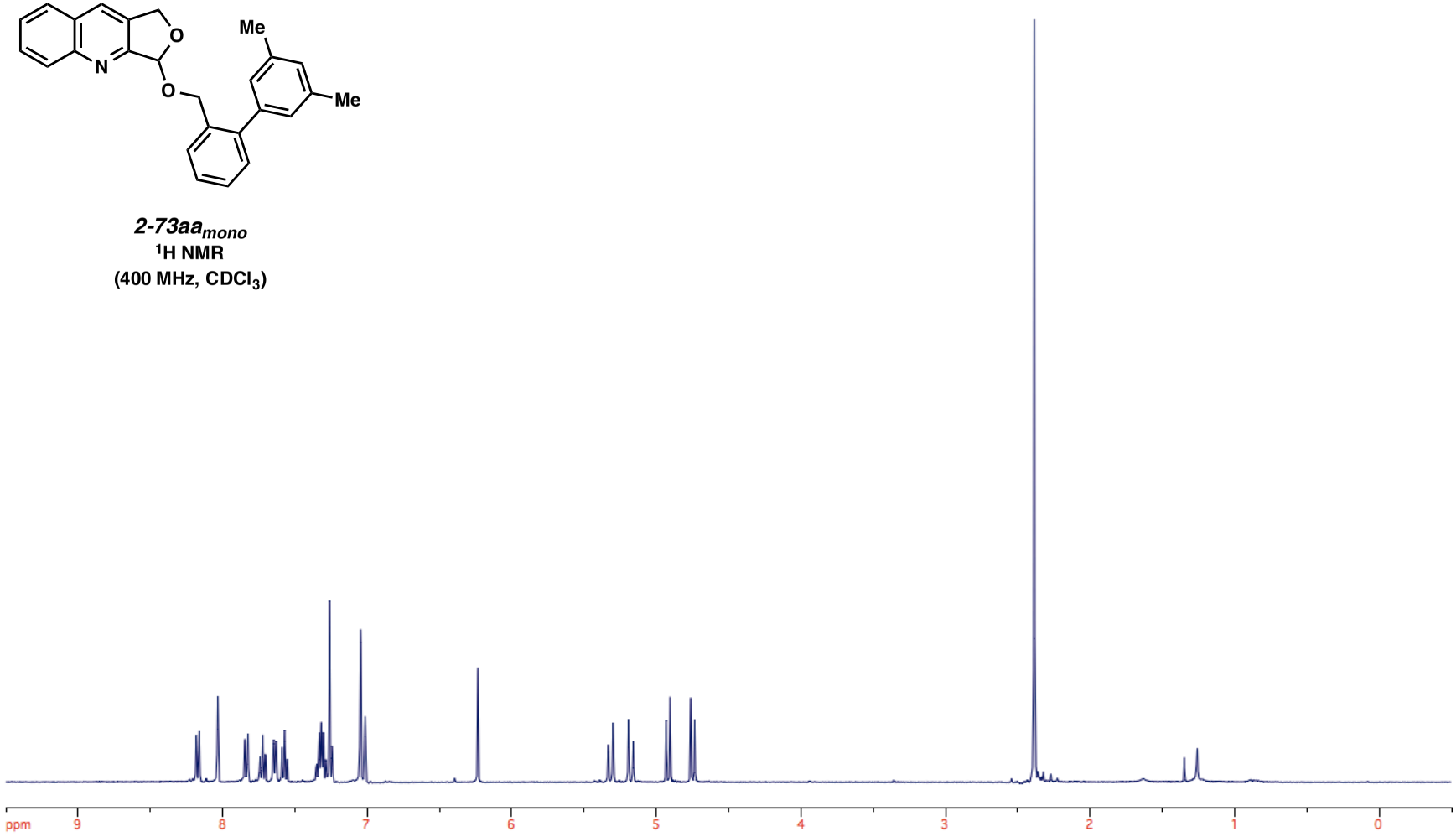


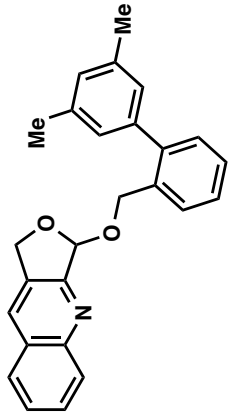
2-59a
(1.6:1 mono/di)
^{13}C NMR
(100 MHz, $CDCl_3$)

2-13εc
(contains EtOAc and MeOH impurities)
^{1}H NMR
(400 MHz, $CDCl_3$)

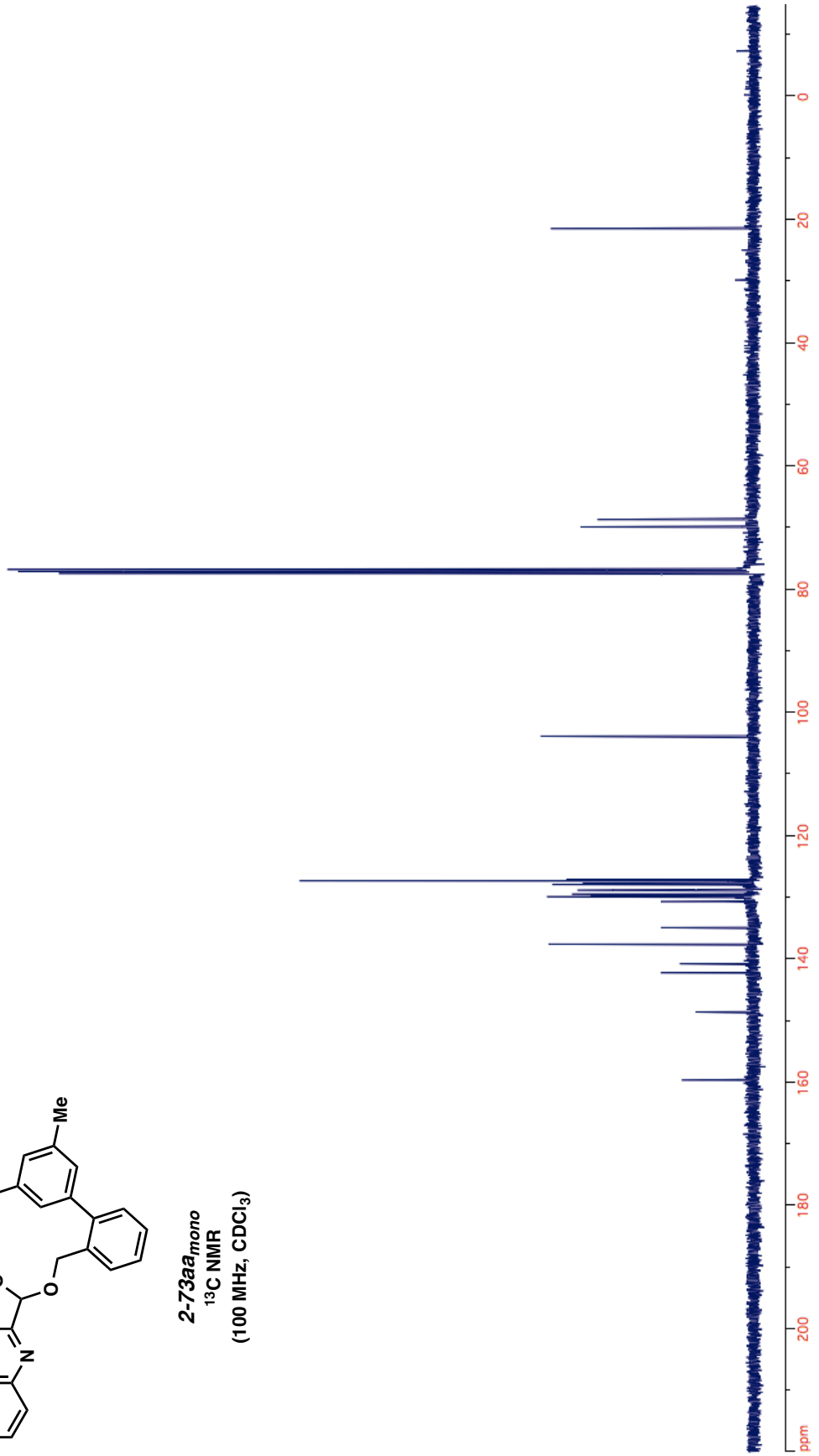


***2-73aa*$_{mono}$**
^{1}H NMR
(400 MHz, $CDCl_3$)

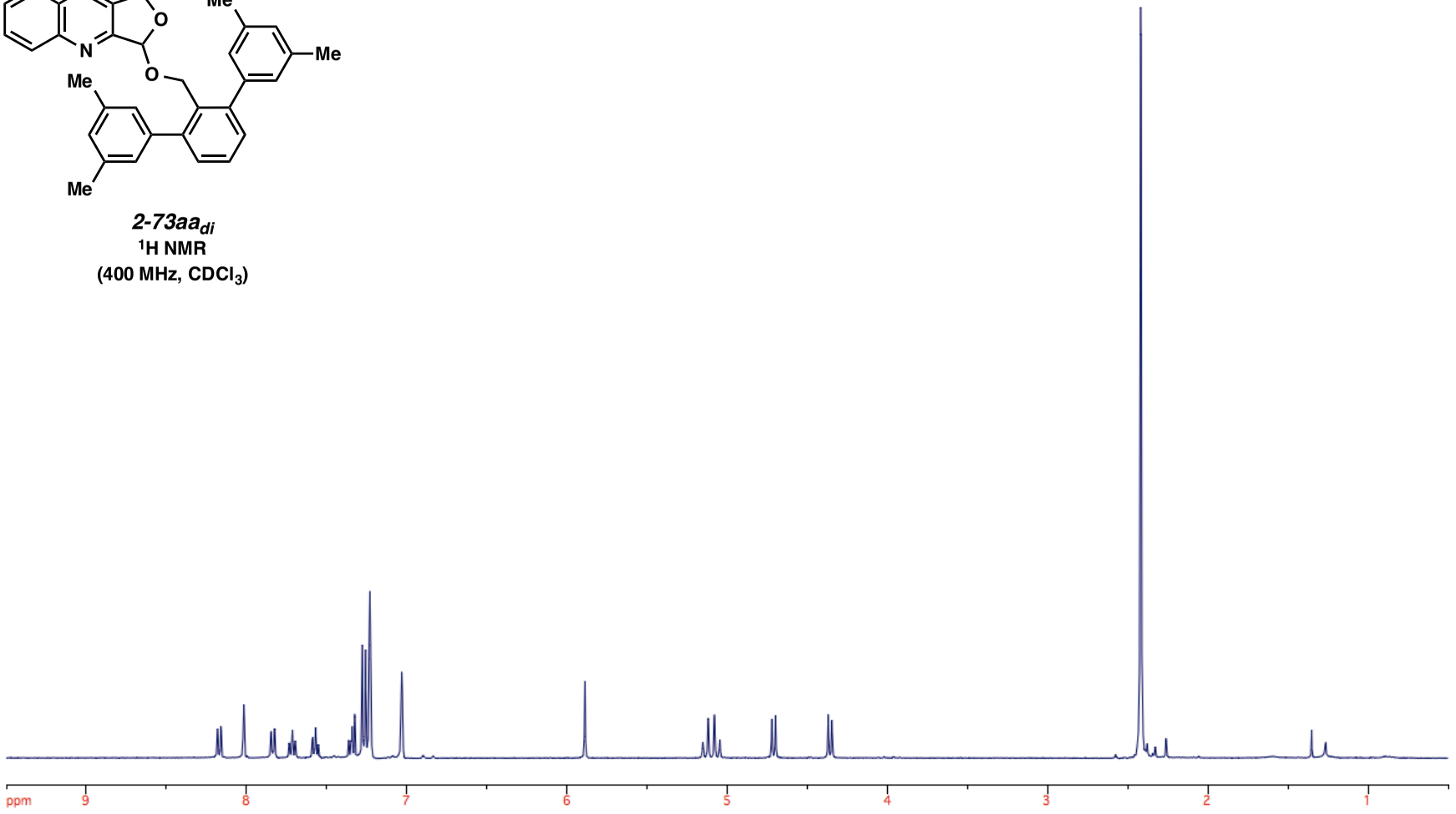


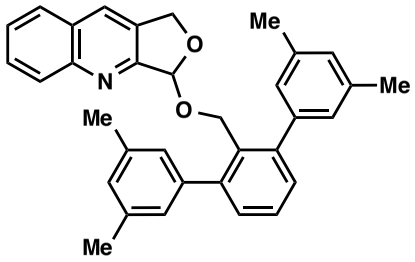


***2-73aa*$_{mono}$**
^{13}C NMR
(100 MHz, $CDCl_3$)

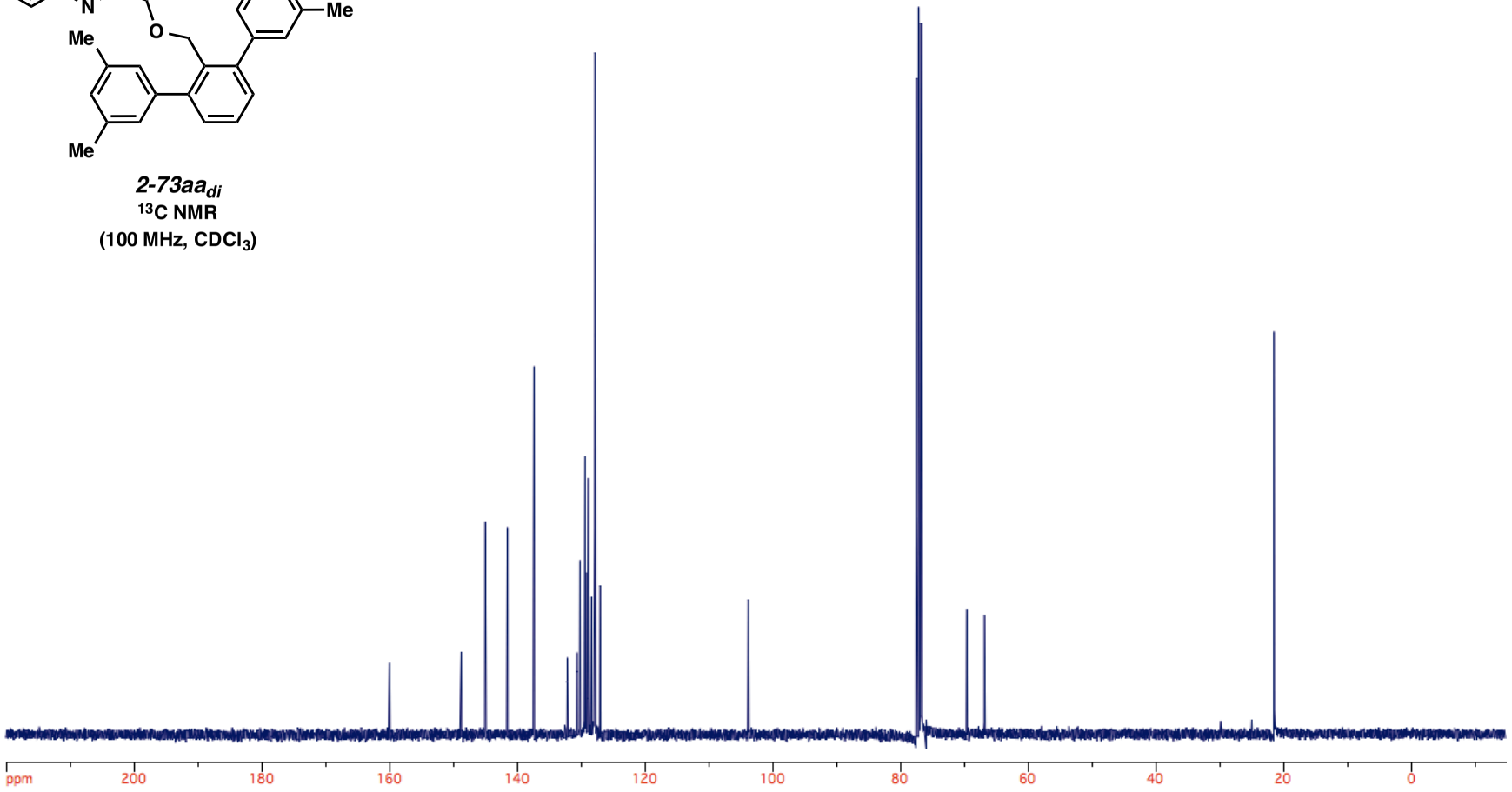


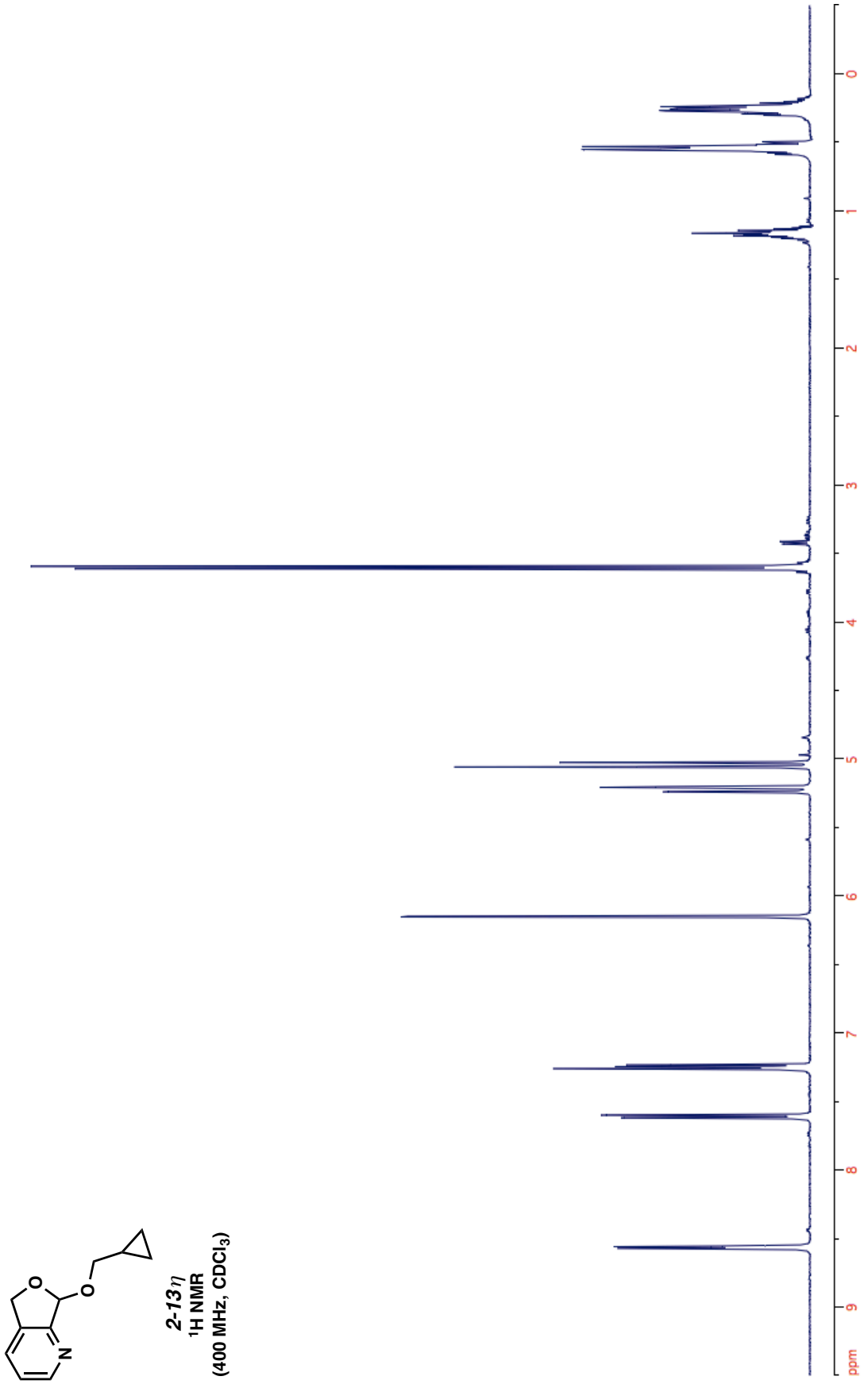
2-73aa$_{di}$
^{1}H NMR
(400 MHz, $CDCl_3$)



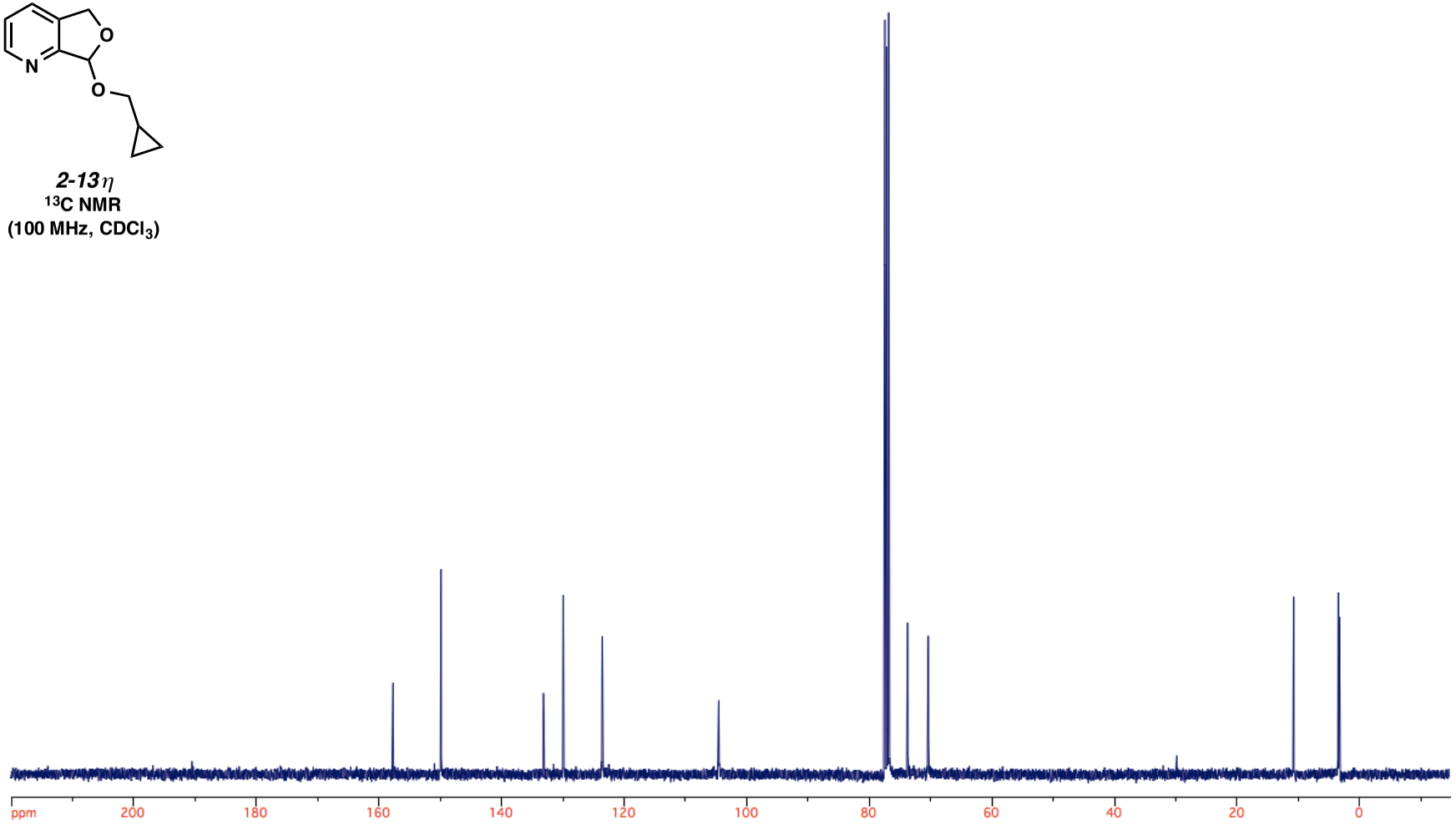


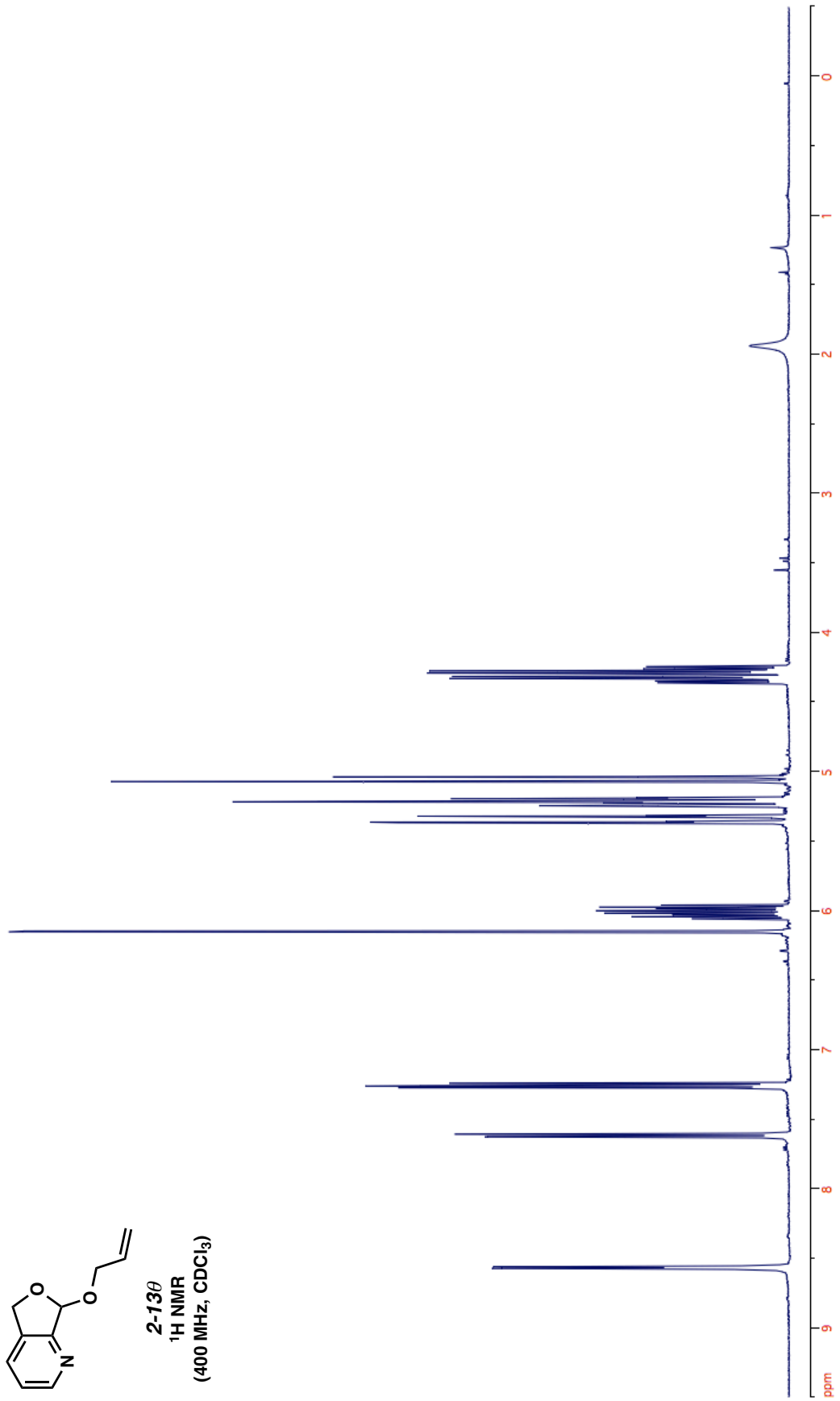
***2-73aa*$_{di}$**
^{13}C NMR
(100 MHz, $CDCl_3$)

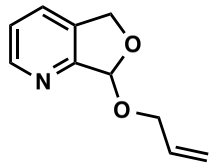



O
O
N
2-13η
¹H NMR
(400 MHz, CDCl3)
0
1
2
3
4
5
6
7
8
9
ppm

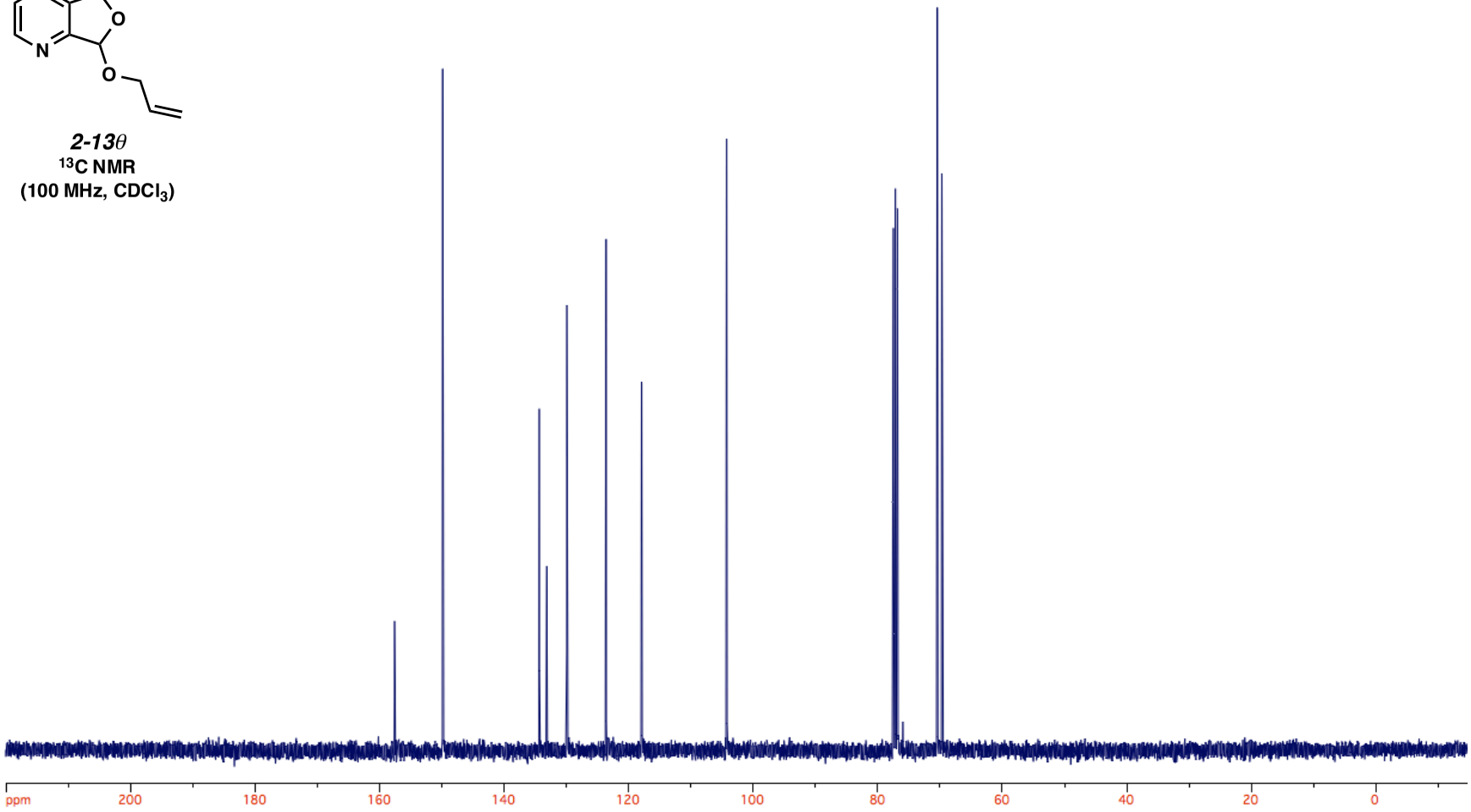
2-13η
^{13}C NMR
(100 MHz, $CDCl_3$)

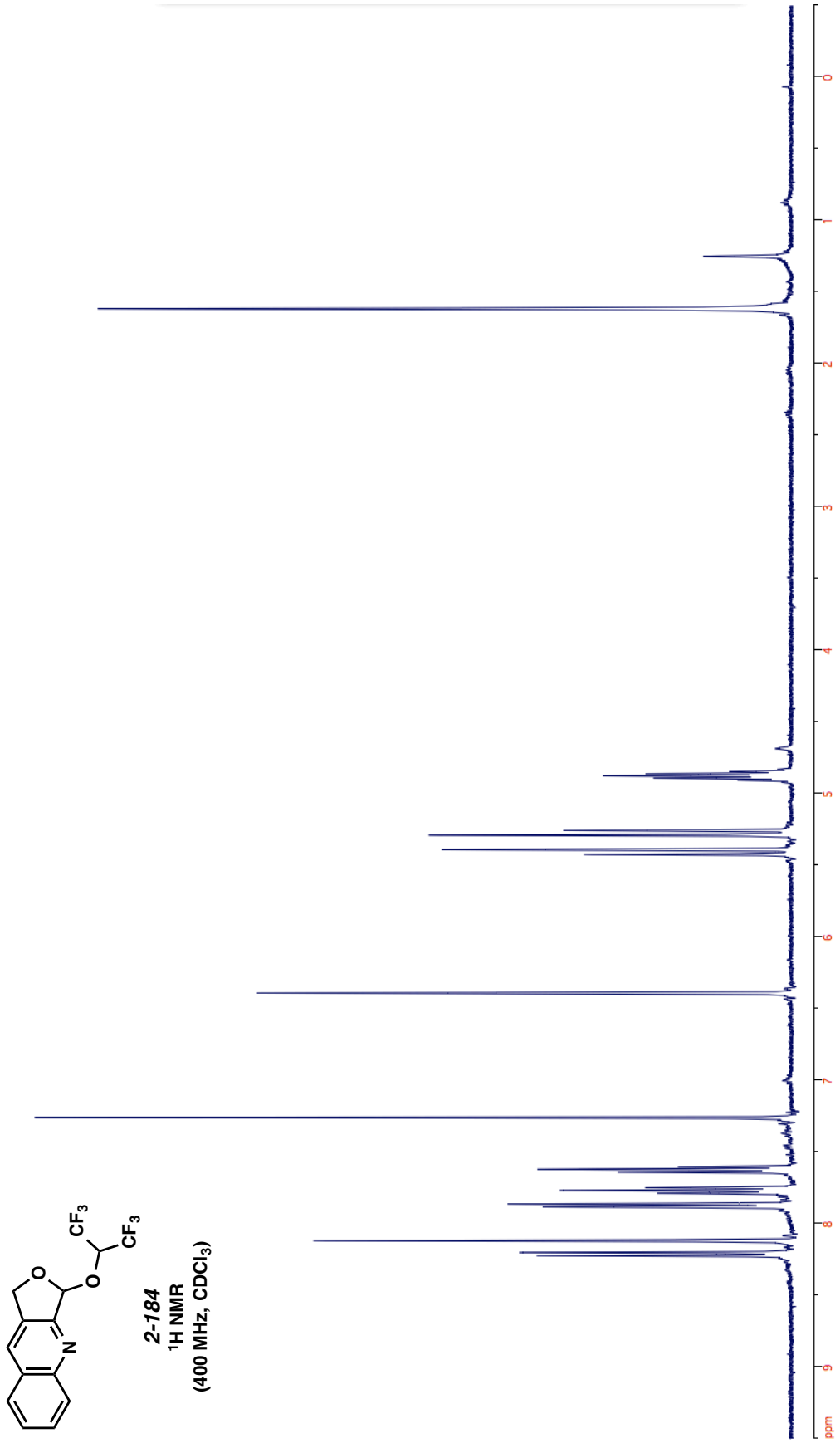


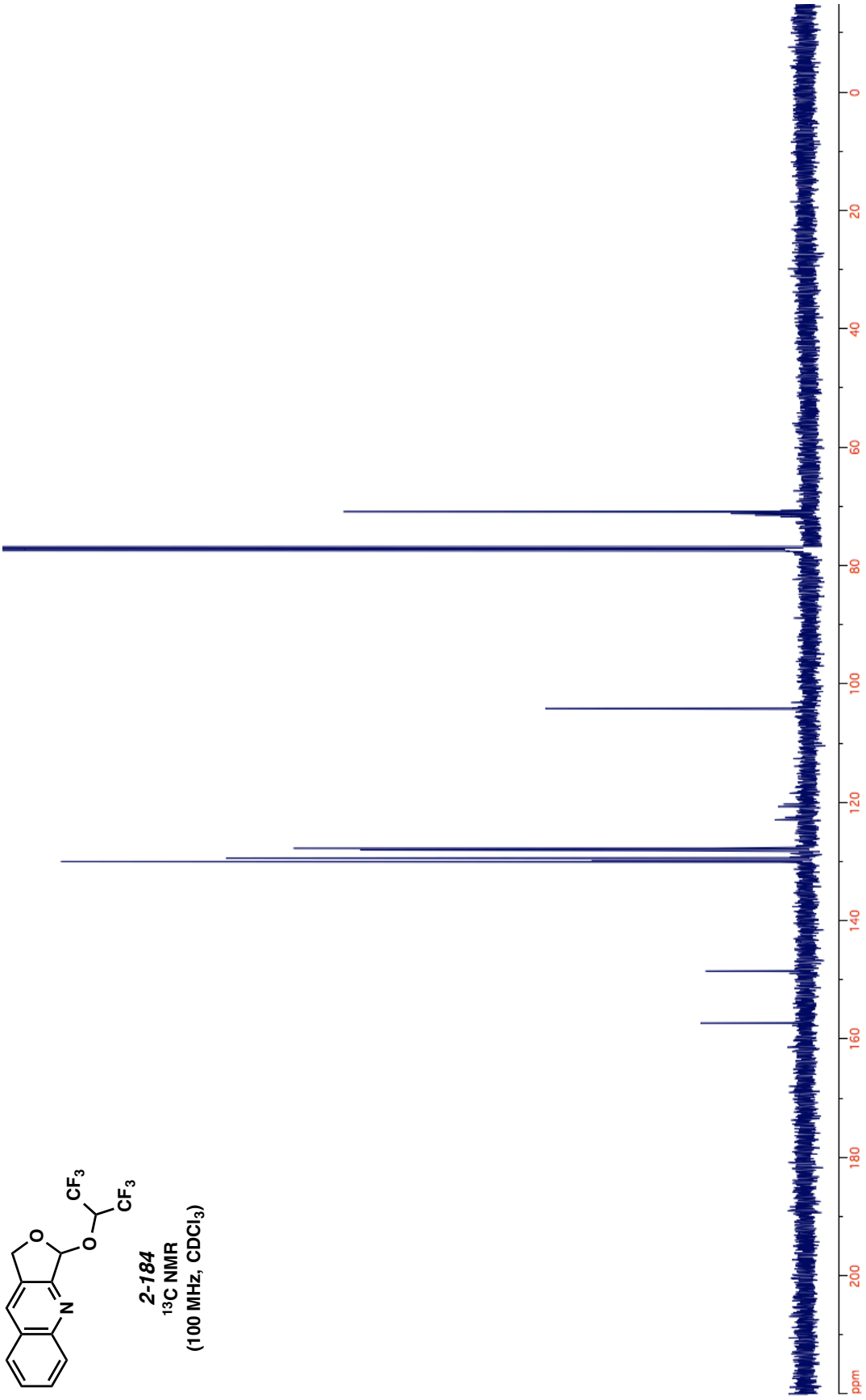

O
O
N
2-13θ
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

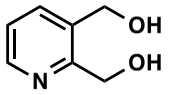


2-13θ
^{13}C NMR
(100 MHz, $CDCl_3$)

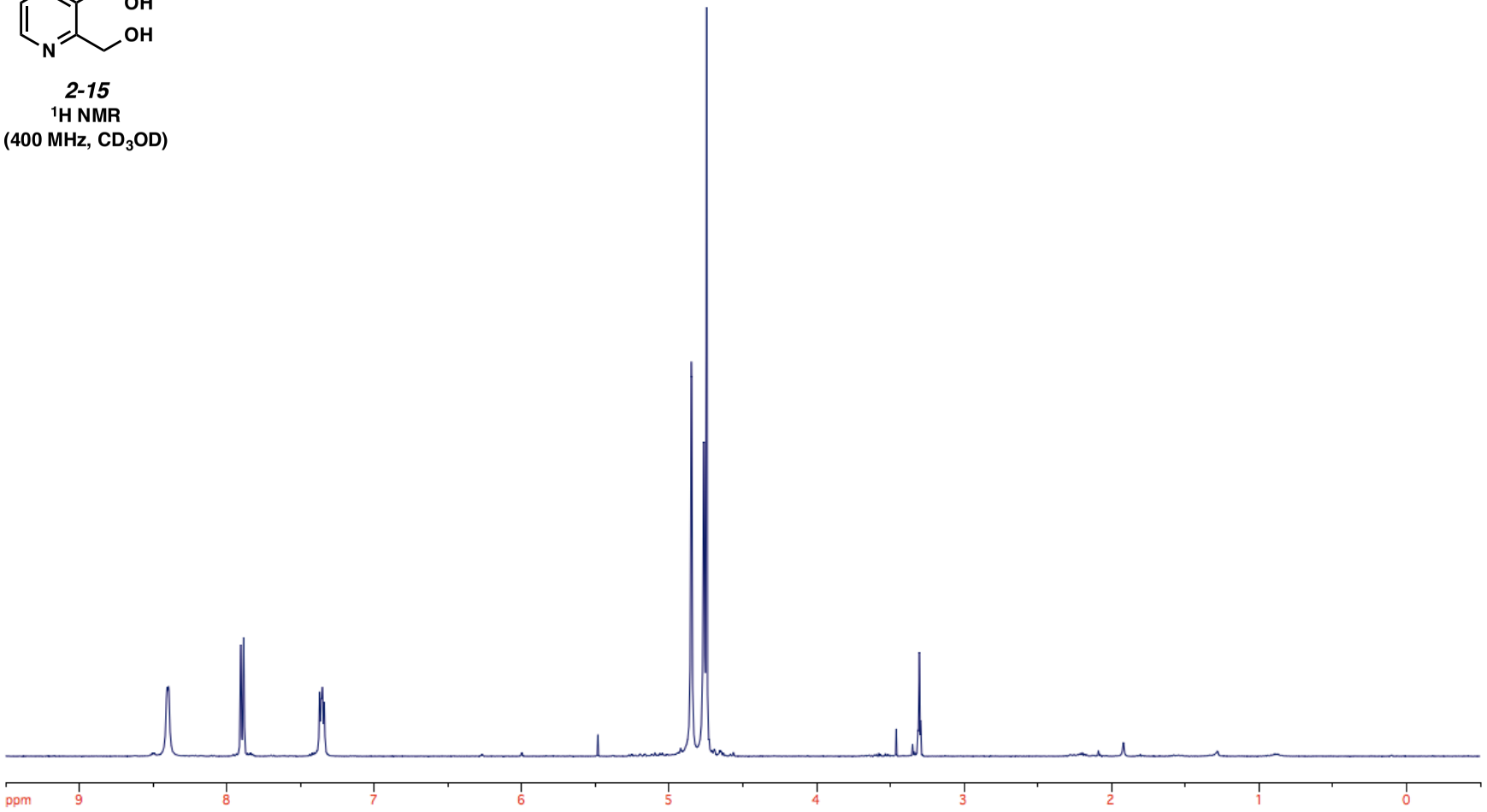



CF3
CF3
O
O
N
2-184
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

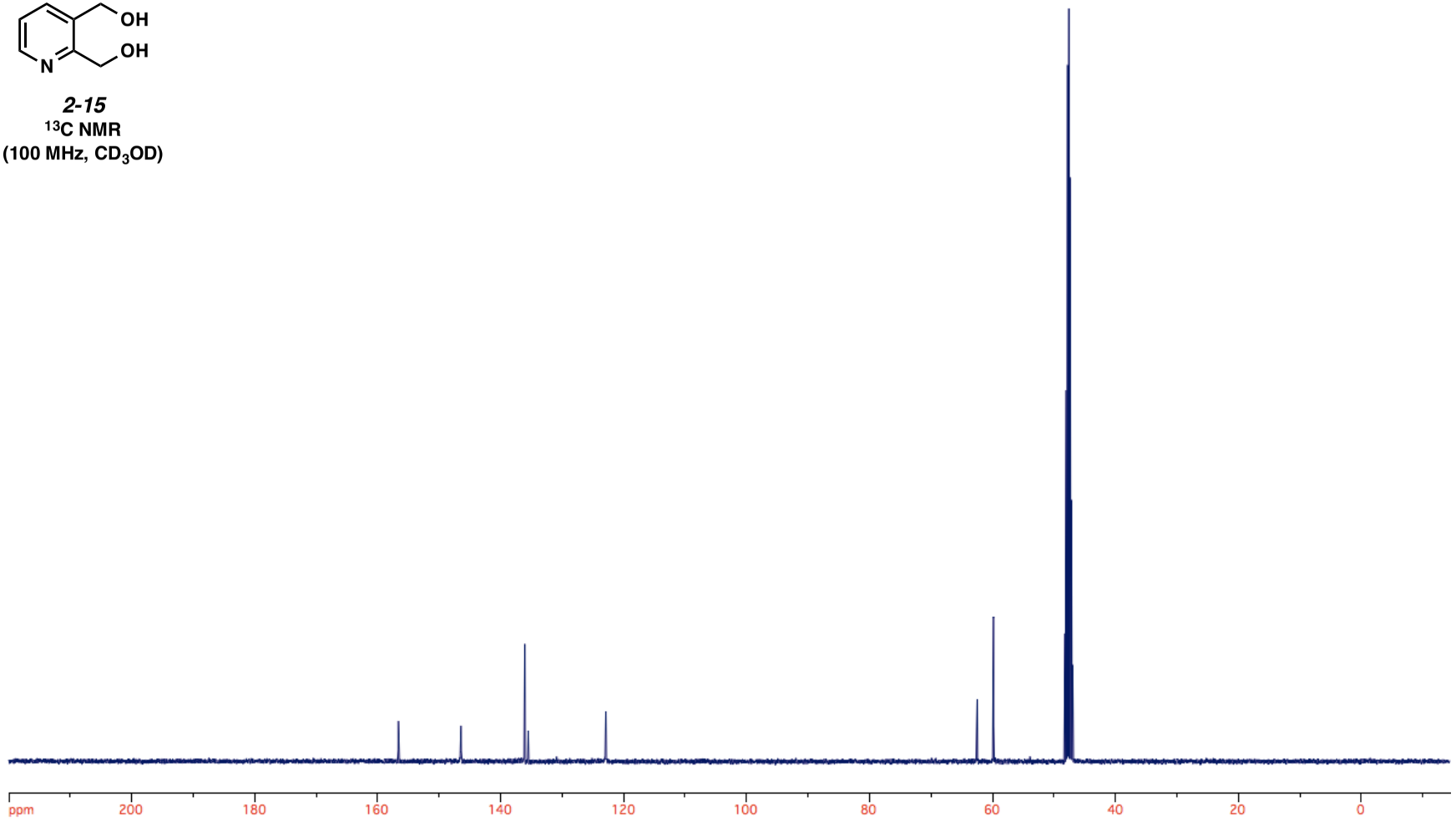

CF3
CF3
O
O
N
2-184
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm



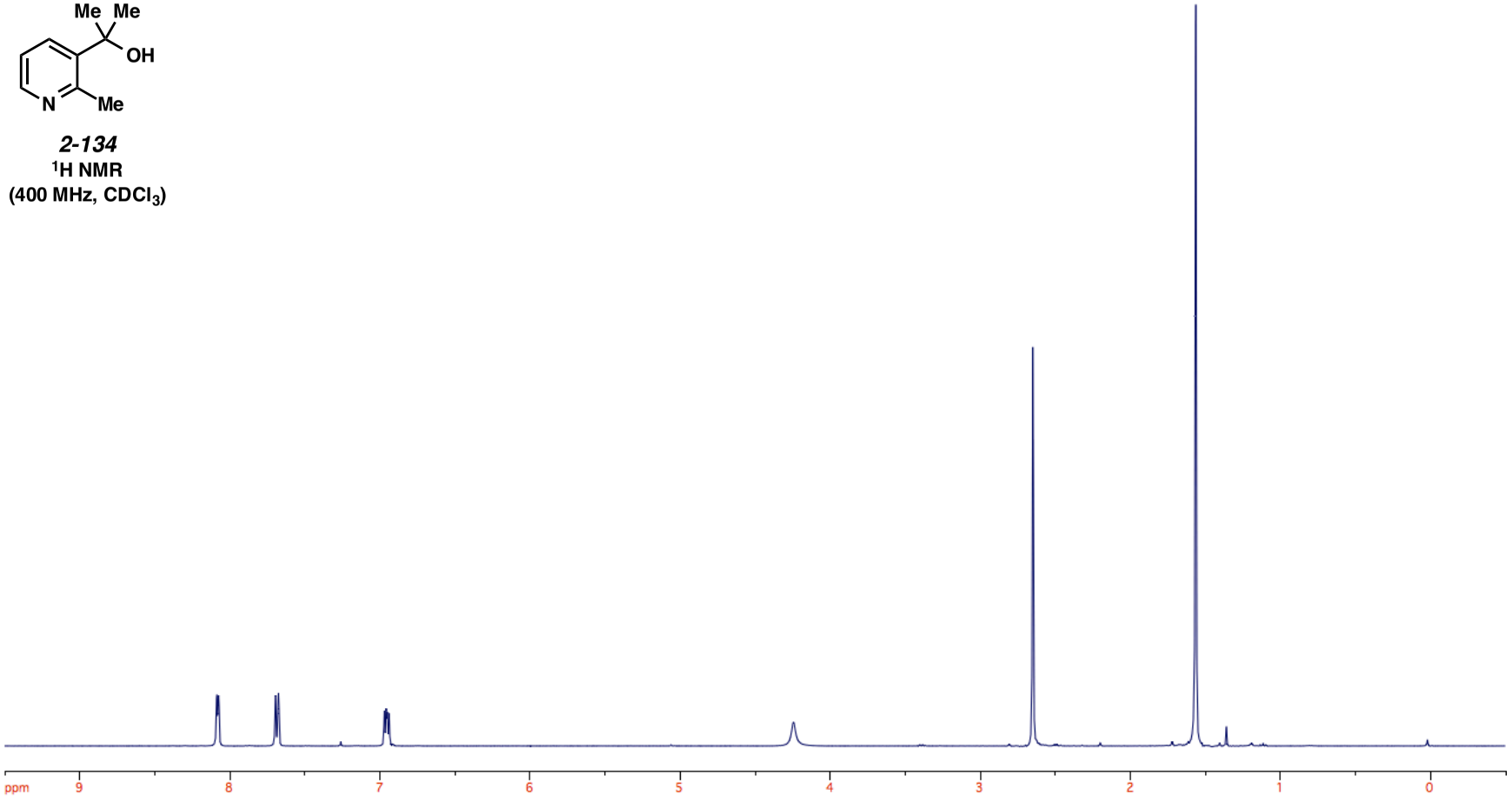
2-15
^{1}H NMR
(400 MHz, CD_3OD)



2-15
^{13}C NMR
(100 MHz, CD_3OD)



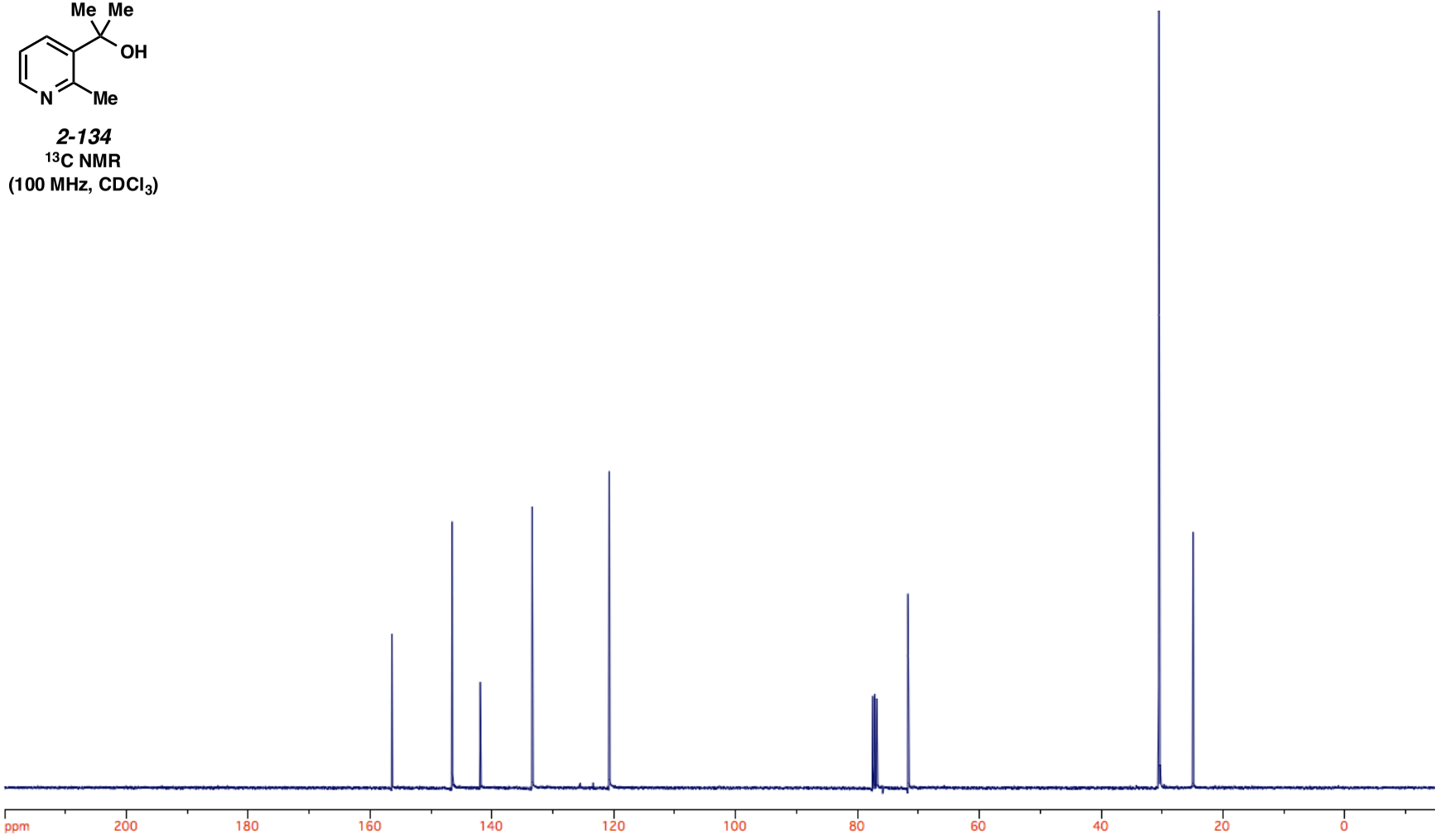
2-134
^{1}H NMR
(400 MHz, $CDCl_3$)

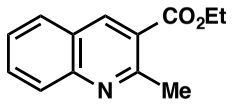


2-134

^{13}C NMR

(100 MHz, $CDCl_3$)

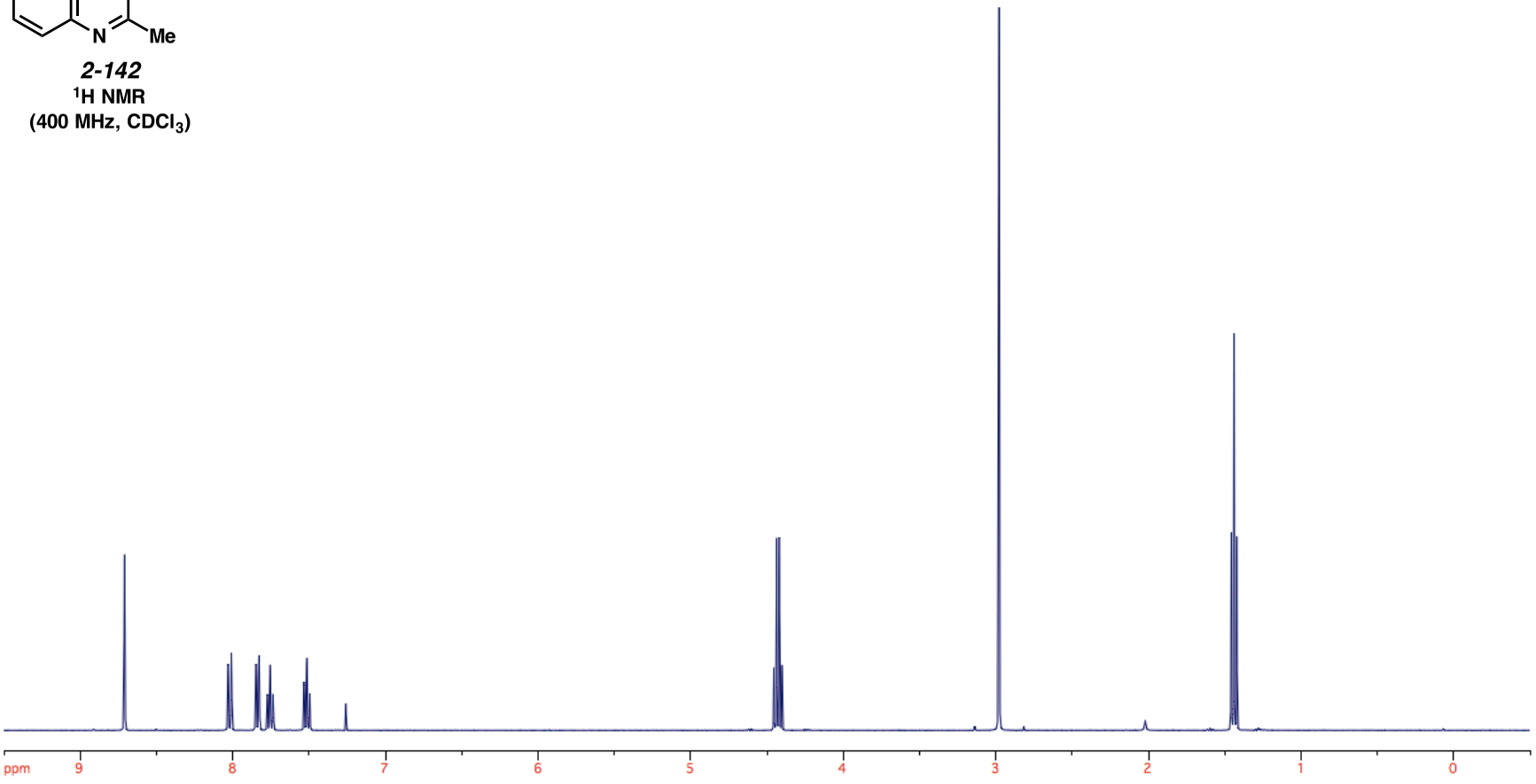


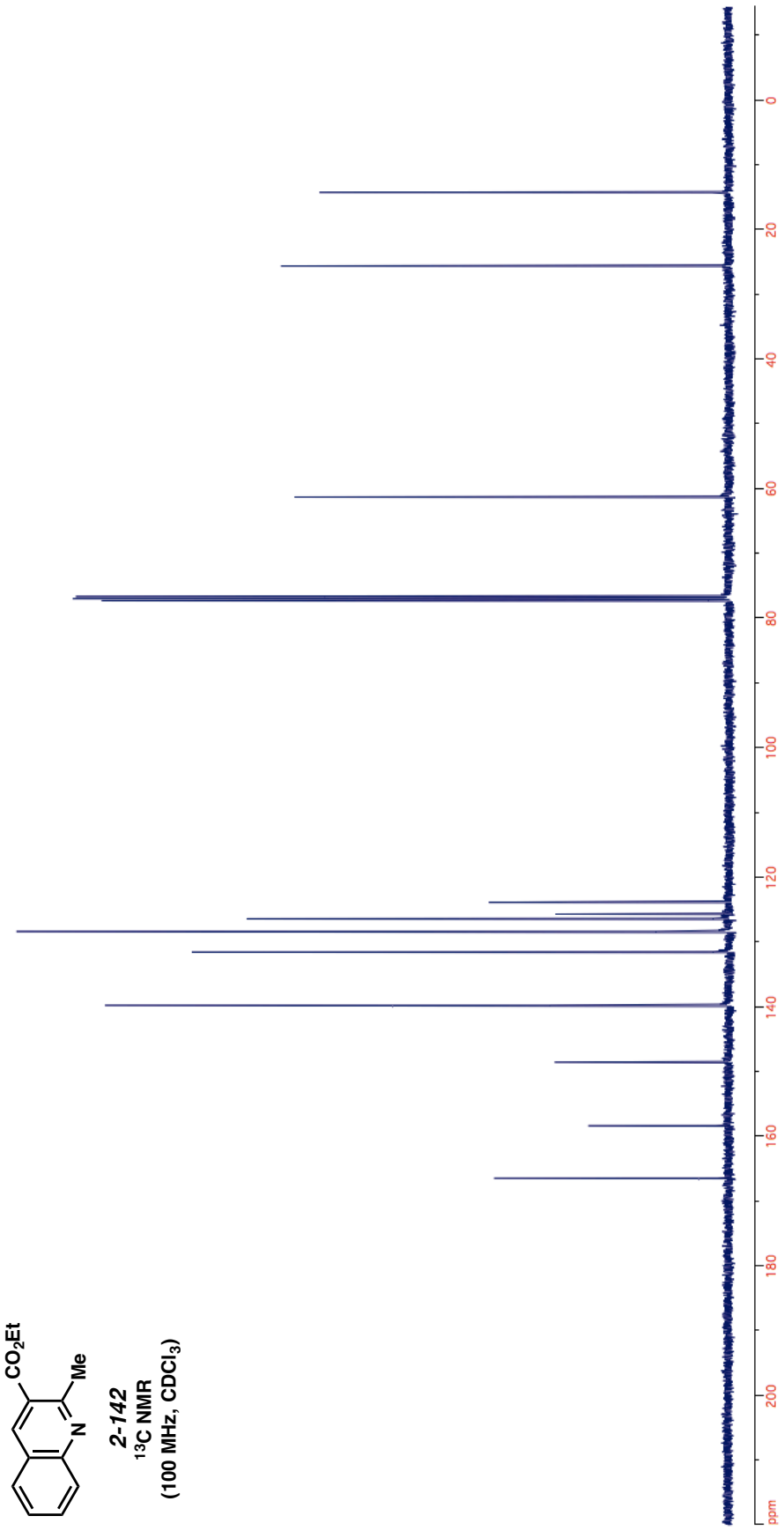


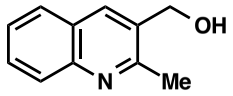
2-142

^{1}H NMR

(400 MHz, $CDCl_3$)



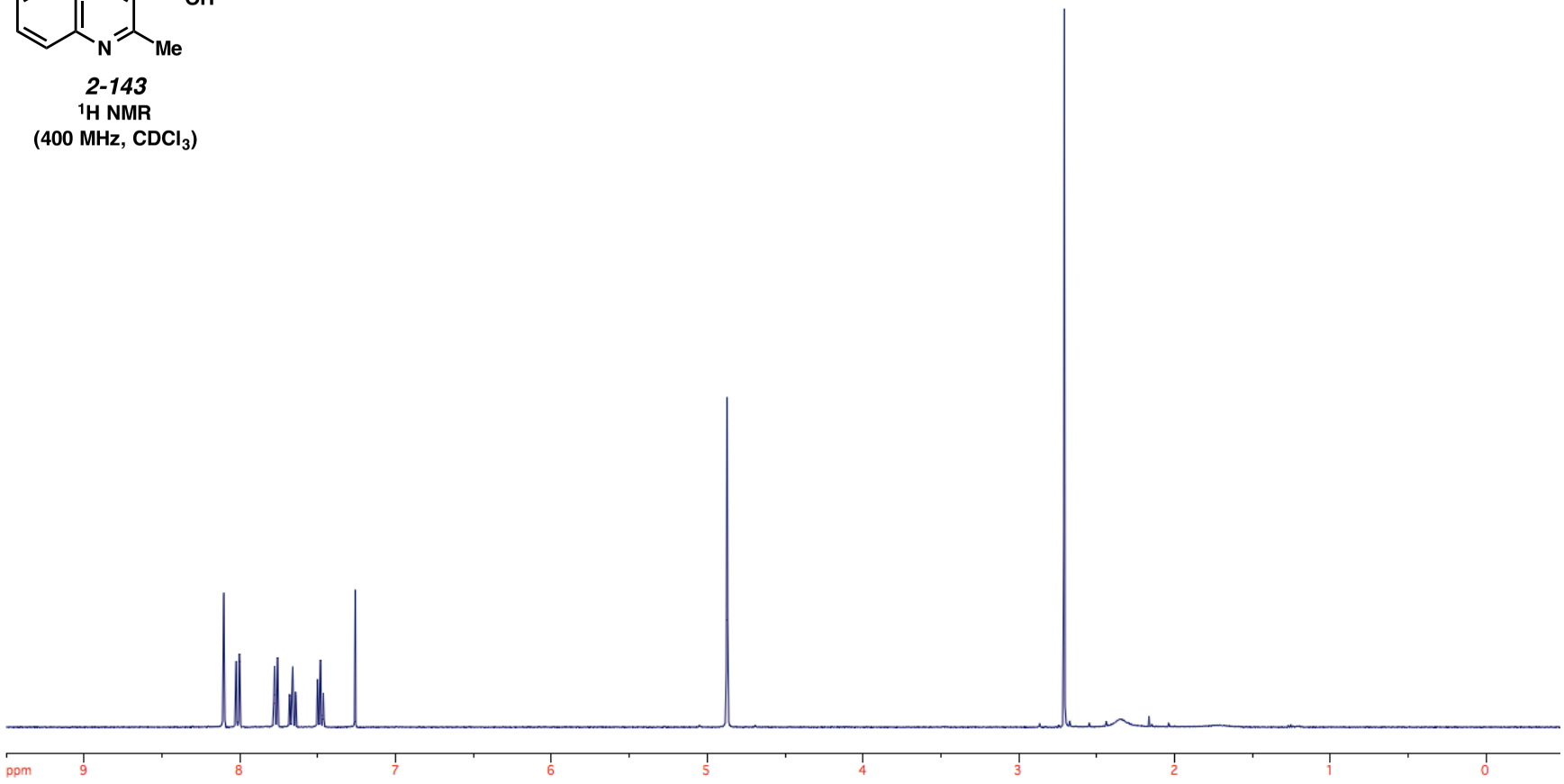

CO2Et
Me
N
2-142
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

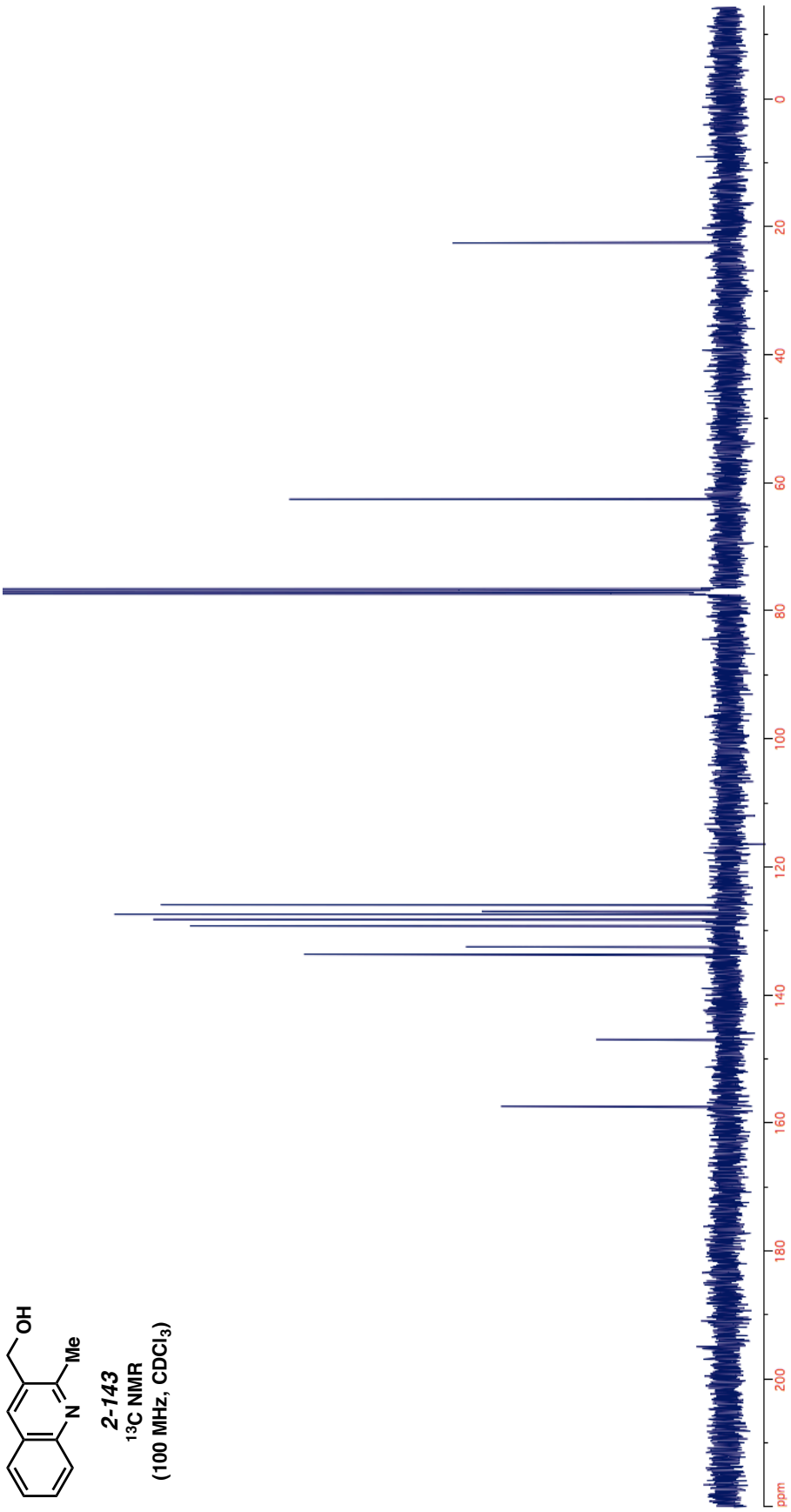


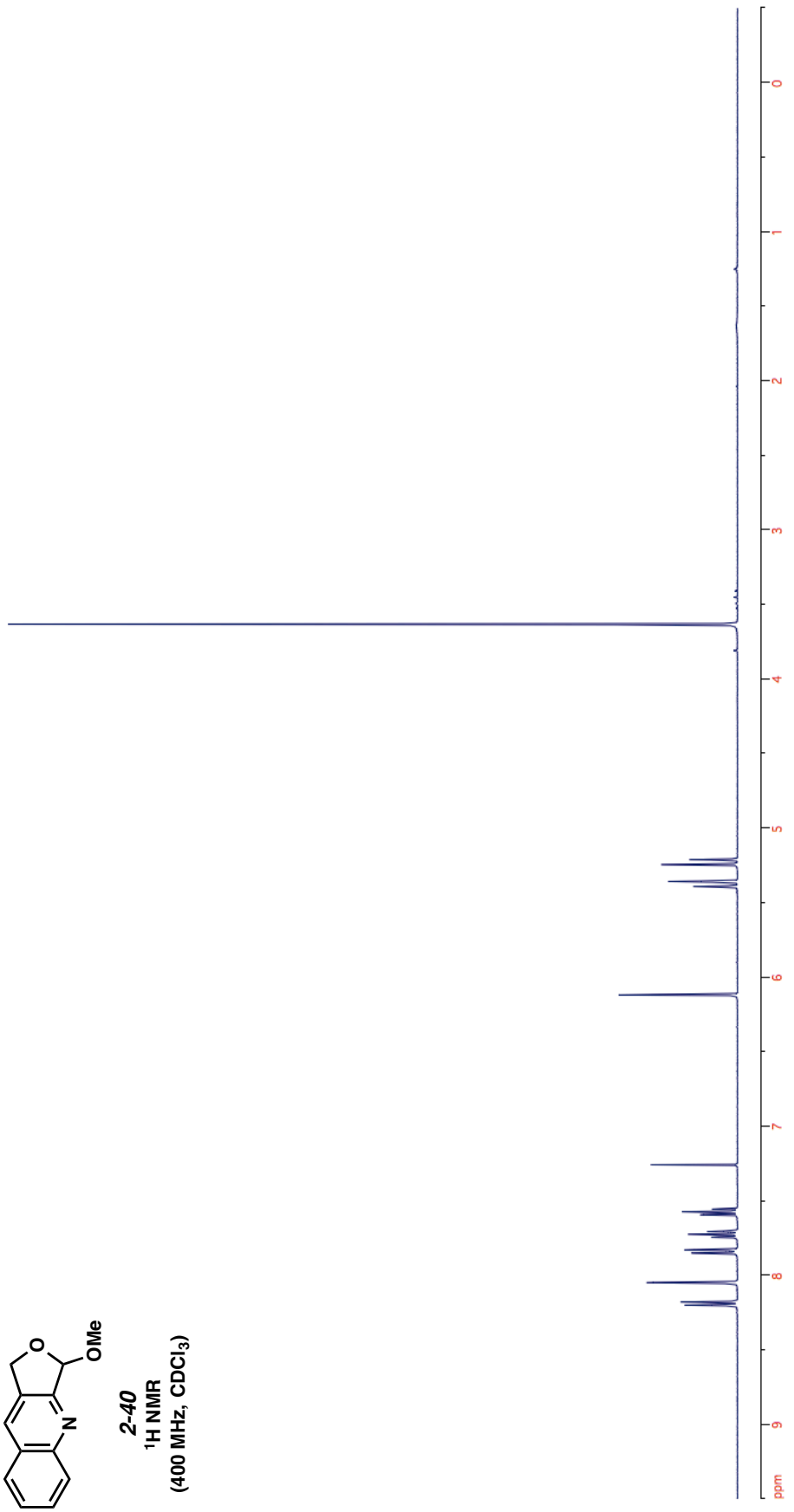
2-143

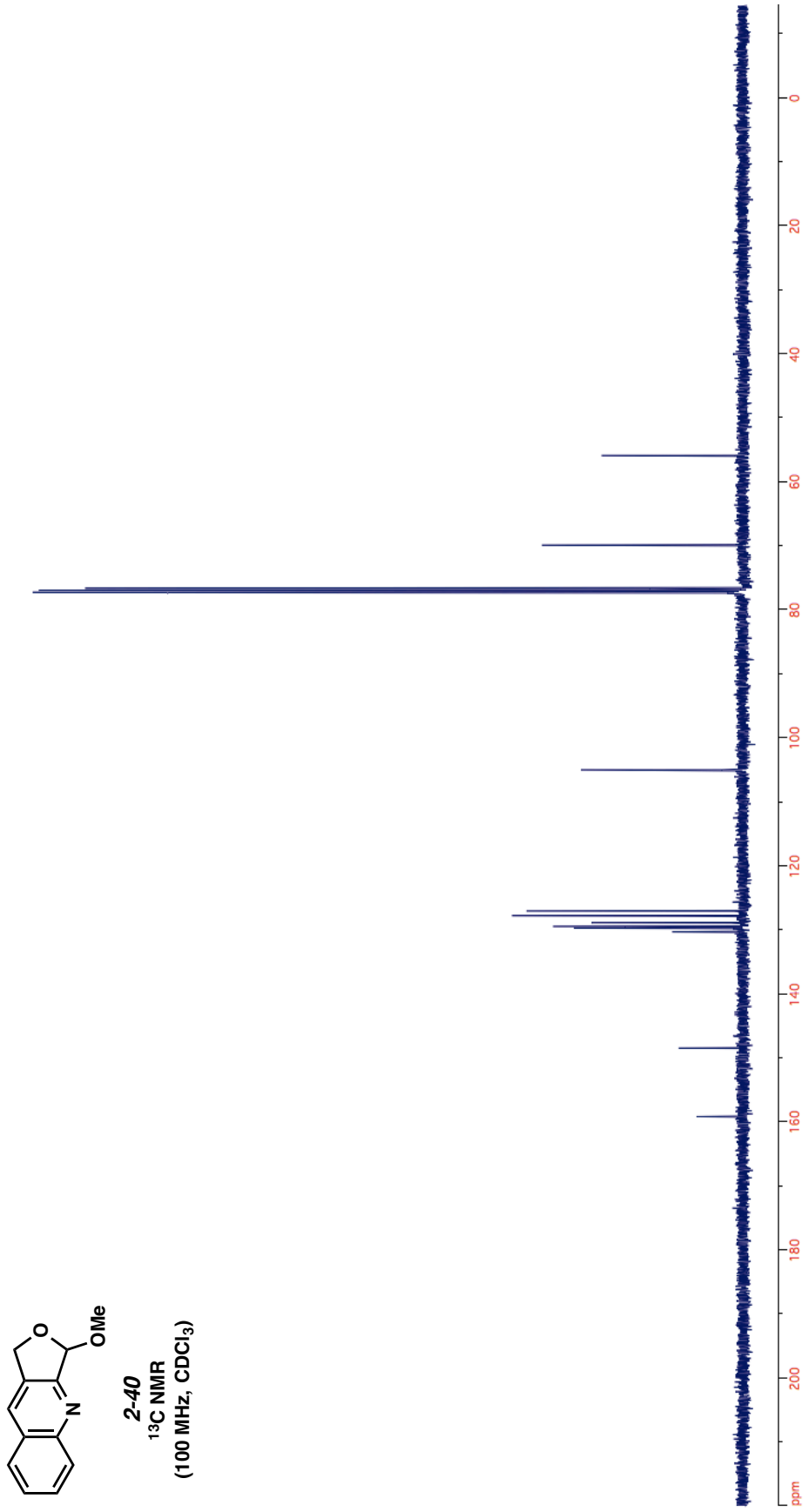
^{1}H NMR

(400 MHz, $CDCl_3$)

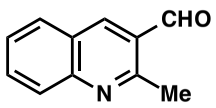



OH
Me
N
2-143
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


OMe
O
N
2-40
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0



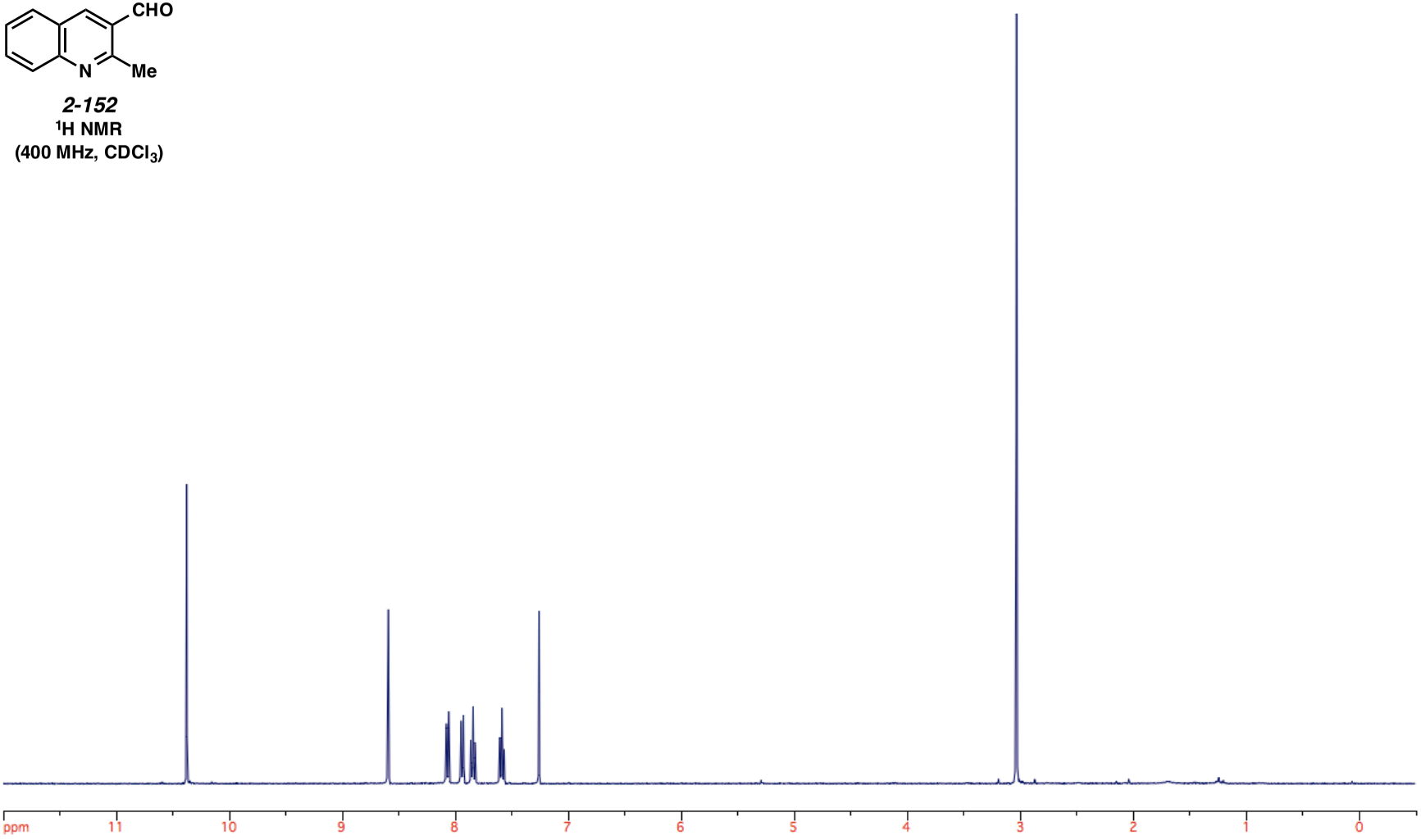
2-40
^{13}C NMR
(100 MHz, $CDCl_3$)

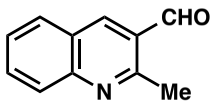


2-152

^{1}H NMR

(400 MHz, $CDCl_3$)

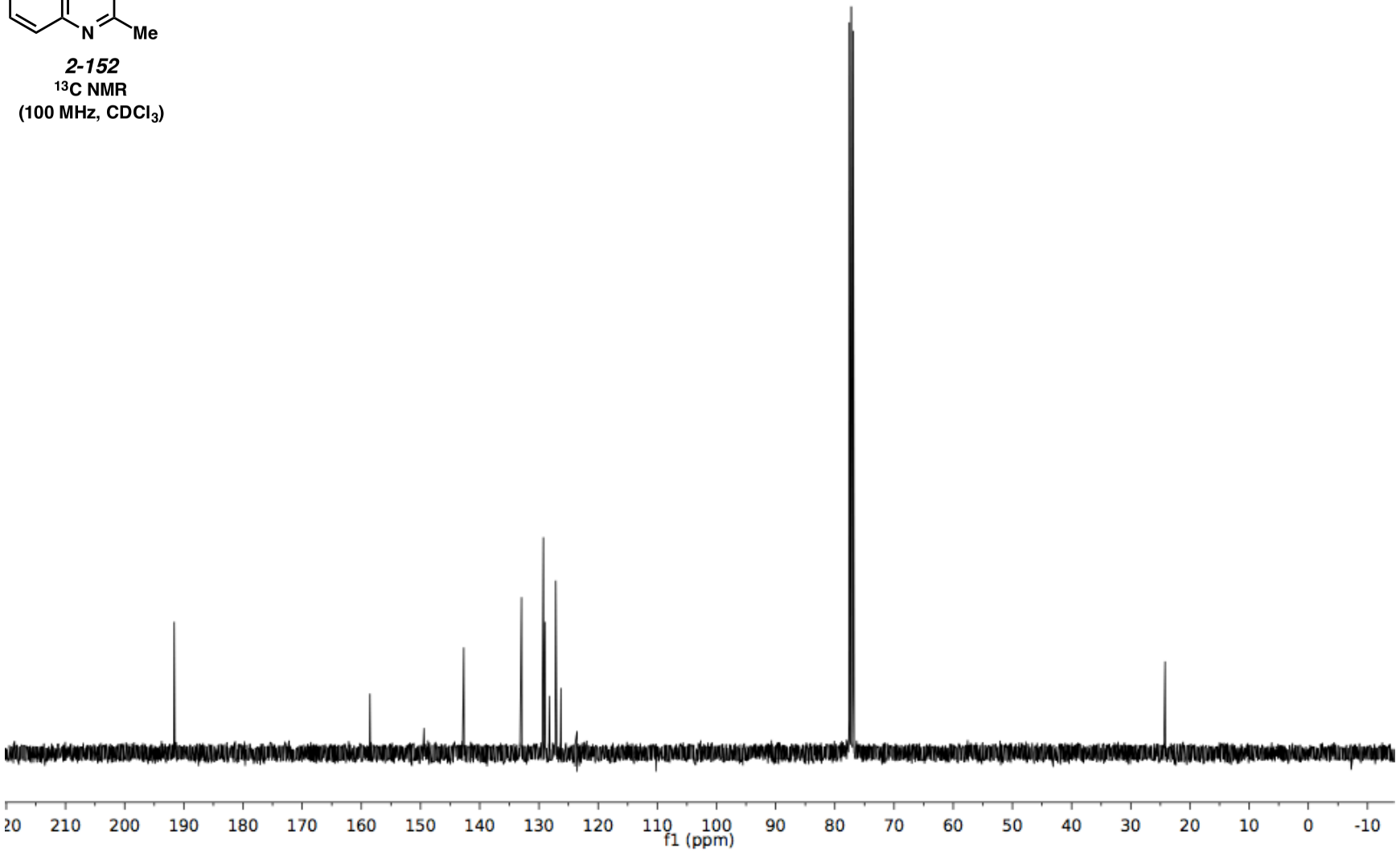




2-152

^{13}C NMR

(100 MHz, $CDCl_3$)



2.10. References and Notes

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(3) This is a common observation in the literature, see: (a) Grimm, J. S.; Maryanoff, C. A.; Patel, D. C.; Palmer, D. C.; Sorgi, K. L.; Stefanick, S. S.; Webster, R. R. H.; Zhang, X. *Org. Proc. Res. Dev.* **2002**, *6*, 938-942. (b) Sakya, S. M.; Van Der Berg, M.; Pouwer, K.; Humphrey, J. M.; Helal, C. J.; O'Donnell, C. J. *Tetrahedron Lett.* **2010**, *51*, 5859-5860. (c) Sperry, J. B.; Farr, R. M.; Levent, M.; Ghosh, M.; Hoagland, S. M.; Varsolona, R. J.; Sutherland, K. *Org. Proc. Res. Dev.* **2012**, *16*, 1854-1860.

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(6) Computations suggest that silver may play a role in a heterodimeric PdAg species: see, Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T. S.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D., Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344-355.

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(8) For a general review of the concerted metalation-deprotonation mechanism: see, Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010,** *39*, 1118-1126. For an example more similar to these conditions: see, Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. *J. Am. Chem. Soc.* **2014**, *136*, 894-897.

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(10) See section 2.6.

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(12) (a) For ketones, see: Li, G.; Wan, L.; Zhang G.; Leow, D.; Spangler, J.; Yu, J.-Q. *J. Am. Chem. Soc*. **2015**, *137*, 4391–4397, and references therein; (b) For ethers, see: Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem., Int. Ed.,* **2012**, *52*, 1245–1247; (c) For acetamides, see: Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; and van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.

(13) The synthesis and development of this scaffold is covered in section 2.8.

(14) For select reviews on bidentate coordination in C–H functionalizations, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726–11743. (b) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res*. **2015**, *48*, 1053–1064.

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(16) (a) Sunko, D. E.; Szele, I. *Tetrahedron Lett.* **1972**, 3617-3620. (b) Schadt, F. L; Schleyer, P. v. R. *Tetrahedron Lett.* **1974**, 2335-2338.

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CHAPTER 3

THE PURSUIT TOWARD A TRANSIENT DIRECTING GROUP FOR sp^2 C–H FUNCTIONALIZATION OF BENZYL ALCOHOLS

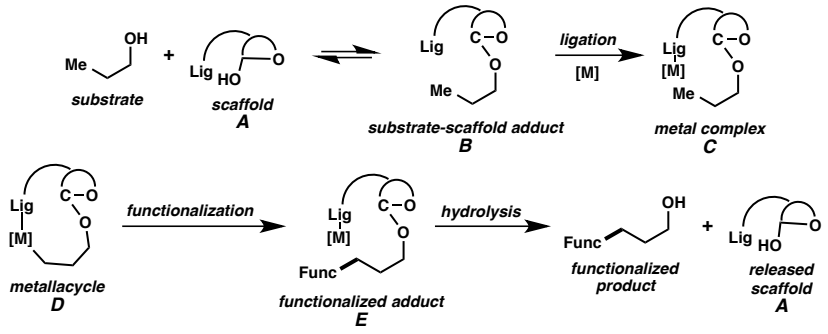
3.1. Introduction

Our investigations into developing transiently directing C–H and C–C functionalization strategies have afforded many insights into the requisite features to accomplish this objective. These findings have culminated in the discovery of the PyA directing group. We feel optimistic that this scaffold and its analogs provide a robust platform to explore transient functionalization chemistry. Many other strategies have been investigated; however, these pursuits have been either temporarily or permanently abandoned. The discoveries and insights obtained through these inquiries are worth a thorough discussion.

Upon proposal of a strategy and before the development of a new scaffold, we addressed four questions. 1) What is the locational relationship between the directing group and the attached substrate? In Figure 3.1.1, we ask if there are conformational issues likely to discourage a proximal relationship between the metal and the C–H bond to be functionalized in metal complex C or is metallacycle D reasonably sized. 2) What is the compatibility between the exchange and the functionalization conditions? In some situations, the conditions required for one may inhibit the other. 3) Do the necessary conditions of either exchange or functionalization require a substrate or scaffold that is likely to decompose under the integrated conditions? This question is related to question 2. In some cases, the conditions required to encourage both decompose the scaffold or the substrates. 4) Are the proposed scaffolds trivial or challenging to

obtain, and are there any synthetic obstacles requiring the development of novel methods? Scaffolds, such as A, often take non-trivial time, effort, and other resources to develop. By limiting our investigations to strategies and the development of scaffolds that provided favorable answers to these four questions, we could prioritize our time and resources to more prudently explore transiently directing functionalization.

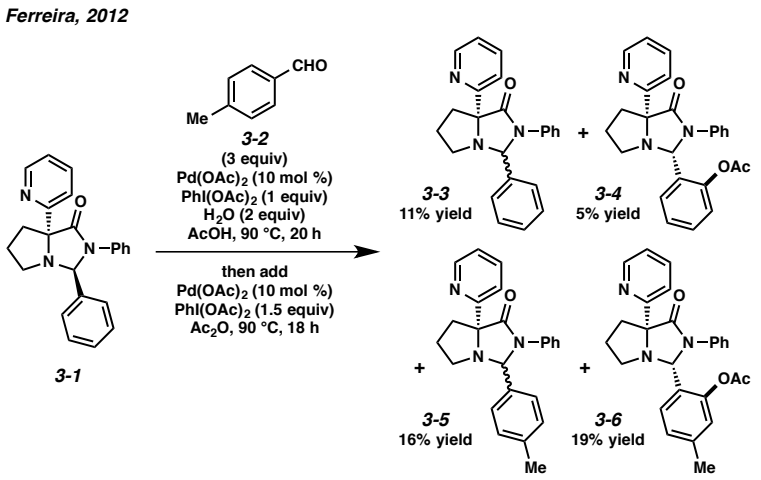
Figure 3.1.1. The General Concept for Transiently Directed Functionalization



3.2. Utilizing Vinylogy to Achieve Transiently Directing Scaffolds

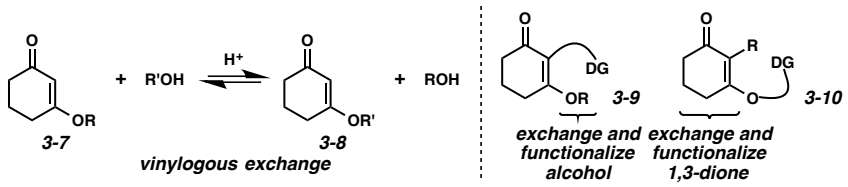
Erin Stache, my predecessor on this project, focused her investigations toward developing transiently directed C–H functionalization scaffolds.[1] She examined the exchange and functionalization properties of a series of amino acid derived directing groups, all of which contained either an acetal or aminal. By taking advantage of these functional groups' well-precedented properties of thermodynamic exchange, she identified a scaffold that could transiently functionalize aldehydes; however, the isolated imidazolidinones were obtained in low yields (Scheme 3.2.1). These products could be hydrolyzed to afford the functionalized aldehydes. We suspected that aldehydes were too sensitive to withstand most functionalization conditions if unprotected and freely exchanging.

Scheme 3.2.1. Transient Functionalization of Scaffold-Attached Imidazolidinone **3-1**



To circumvent this problem, we suspected that alcohols would be a more stable substrate class than aldehydes under the majority of functionalization conditions. In addition to investigating acetal- and aminal-containing scaffolds capable of covalently attaching alcohols (*vide supra*), we sought to find other compatible exchanging functional groups. The thermodynamic exchange of vinylogous esters is well precedented (Figure 3.2.1),[2] and the syntheses of these compounds are usually performed under identical conditions to those that generate acetals (e.g., acid and a Dean-Stark apparatus). This analogy was suggestive of a common thermodynamic exchange property that could be advantageous towards the development of a transient directing group. In this example, exchange would occur between alcohols or vinylogous esters, and either could be functionalized.

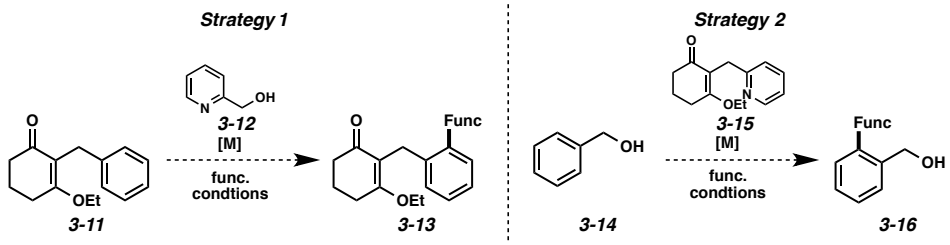
Figure 3.2.1. General Concept for Vinylogous Exchange Scaffold



We envisioned that two separate strategies could be simultaneously investigated using vinylogous esters (Figure 3.2.2). *Strategy 1* entails installing a directing group on the vinylogous

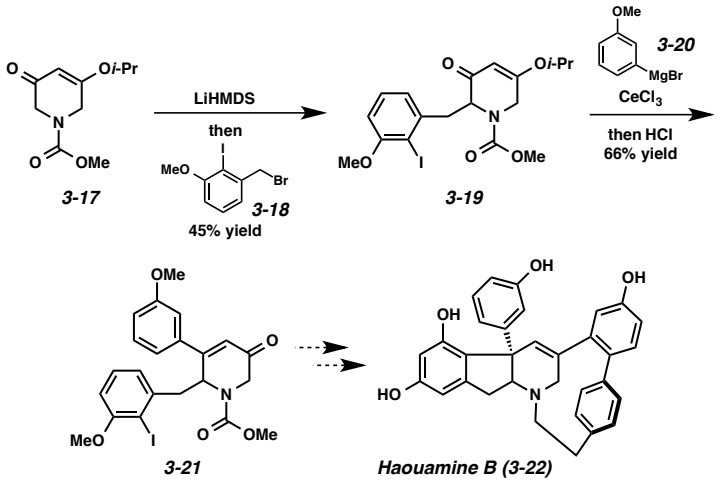
ester and transiently exchanging and functionalizing an alcohol (e.g., benzyl alcohol). Alternatively, *Strategy 2* would consist of exchanging an alcohol containing a directing group and functionalizing the vinylogous ester. Both strategies could lead to synthetically useful methods and would allow for breadth in the investigation of both the exchange and functionalization properties of this system.

Figure 3.2.2. Initial Vinylogy Strategies to Achieve Transiently Directed C–H Functionalization



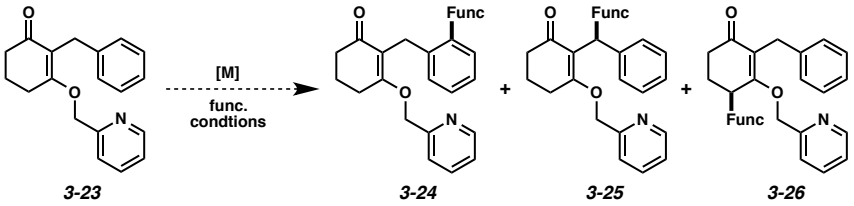
The various methods that afford diversely functionalized alcohols have been described above; however it is worth mentioning the utility of functionalizing vinylogous esters. This class of compounds is common in synthesis and is conventionally utilized in the generation of highly substituted 5- and 6-membered ring structures through Stork-Danheiser chemistry.[3] The utility of this method has been illustrated numerous times by generating early intermediates toward the synthesis of many natural products, as illustrated in Figure 3.2.3 toward haouamine B (**3-22**). C–H functionalization strategies may add complementarity in diversifying these Stork-Danheiser products and could utilize specific features of transition metal catalysis (e.g., the installation of stereocenters) to produce intermediates that are otherwise difficult to access.

Figure 3.2.3. An Example of Stork-Danheiser Chemistry in Total Synthesis



We chose to initially focus our investigation on *Strategy 1* since the scaffold development associated with *Strategy 2* had previously proven to be costly in both time and resources. The attached directing group in vinylogous ester **3-23** could plausibly direct functionalization to a few select positions (Figure 3.2.4). Under most functionalization conditions, the arene C–H bond is believed to be most likely to react (vinylogous ester **3-24**). Other activated positions include the dual benzylic/allylic position (vinylogous ester **3-25**) and the γ-allylic position (vinylogous ester **3-26**).

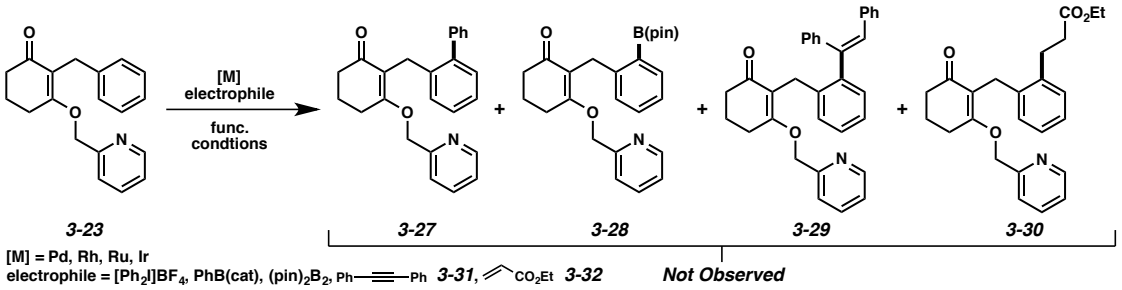
Figure 3.2.4. Potential Sites of Functionalization on Vinylogous Ester **3-23**



We extensively investigated conditions in pursuit of functionalizing vinylogous ester **3-23**, and conditions varied in metal complexes (Pd, Rh, Ru, Ir, etc.), additives, and electrophiles (e.g., iodonium salts, catechol boranes, diboranes, acetylenes, acrylates, etc.)[4] (Scheme 3.2.2). Functionalized products were not observed under the reaction conditions, and in general, the

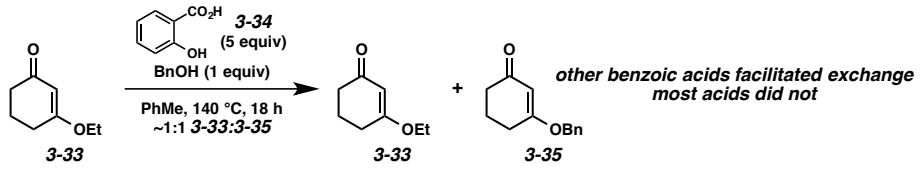
substrate was either stable to the conditions or generated a complex mixture. We were unable to determine if any of these mixtures contained products corresponding to vinylogous esters **3-27**, **3-28**, **3-29**, or **3-30**. At the time, this lack of reactivity persuaded us to pursue a different strategy.

Scheme 3.2.2. Functionalization Attempts of Vinylogous Ester **3-23**



While investigating if vinylogous ester **3-23** could direct functionalization, we simultaneously pursued the exchange properties of this substrate class. An exhaustive screen of acids and bases rarely facilitated any reaction, but it was observed that most benzoic acids enable exchange toward an equilibrium mixture. Treating vinylogous ester **3-33** with salicylic acid (**3-34**), discovered to be superior for accelerating this exchange, afforded a 1:1 mixture of vinylogous ester **3-33** and **3-35** within 18 h (Scheme 3.2.3). We were surprised at the lack of generality in acid-mediated exchange of vinylogous esters as well as the slow speed with which it took to arrive at equilibrium.

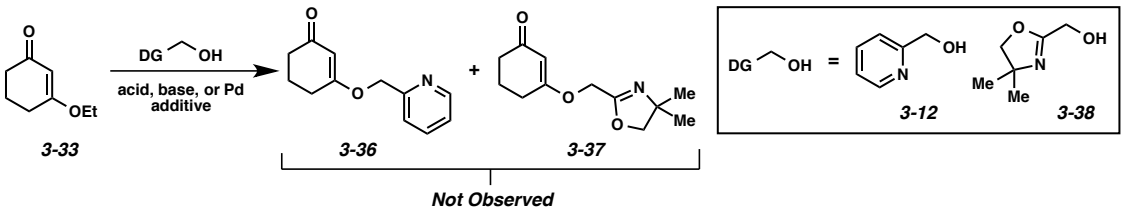
Scheme 3.2.3. Vinylogous Exchange of Vinylogous Ester **3-33**



In pursuit of achieving working conditions motivated by *Strategy 1*, we investigated the exchange of alcohols that contain directing groups. Based on previous work in our group, we were aware that these alcohols' behavior was not always analogous to more generic alcohols

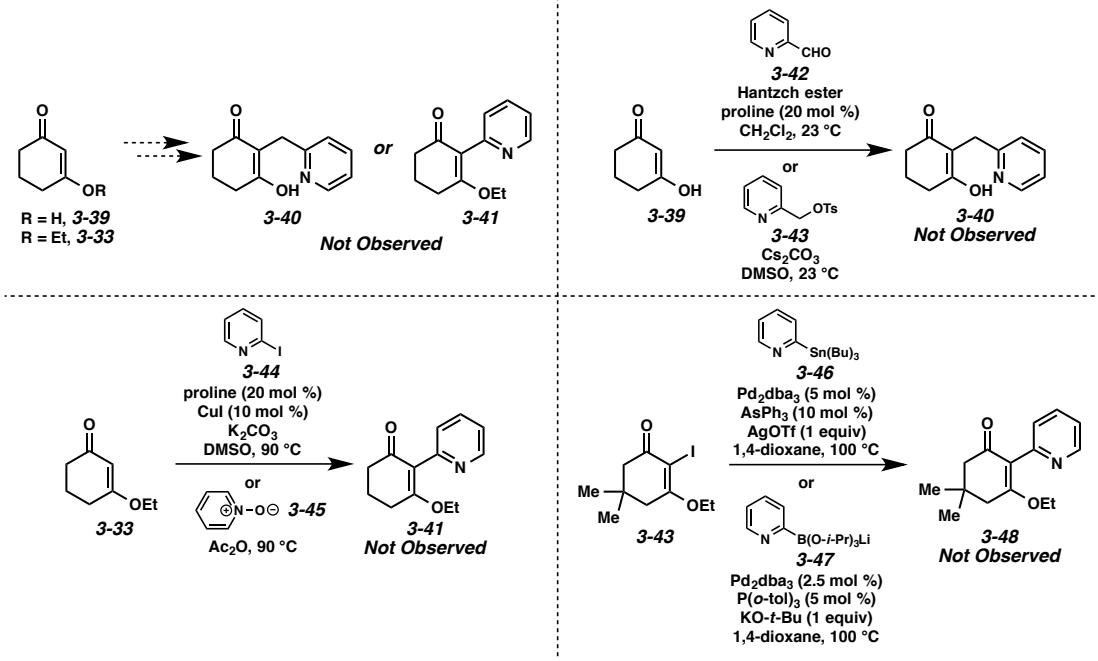
(e.g., EtOH, BnOH, etc.). Alcohols **3-12** and **3-38** were chosen due to the numerous transformations directed by both pyridines and oxazolines.[4] Acids and bases failed to catalyze exchange (Scheme 3.2.4), and surprisingly, benzoic acids completely lost their activity. It is plausible that the protonated species of these alcohols buffer the reaction as well as make the hydroxyl group less nucleophilic. Palladium catalysts were also attempted since these compounds can act as Lewis acids and could potentially initiate exchange. Additionally, these catalysts and resulting intermediates would be available to enable exchange under some functionalization conditions. To our disappointment, palladium catalysts were no better at facilitating exchange than traditional acids. The failure to achieve transient conditions or the desired functionalization led us to abandon *Strategy 2*.

Scheme 3.2.4. Vinylogous Exchange with Directing Group-Containing Alcohols



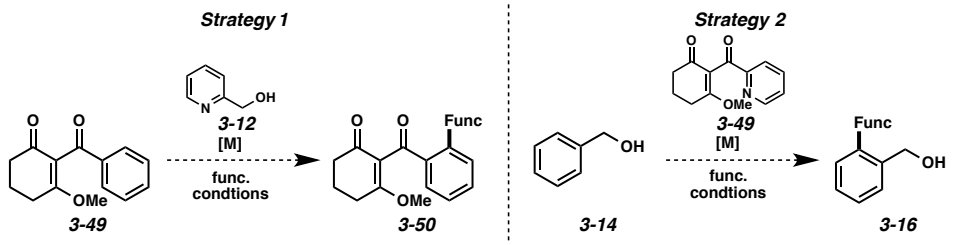
Over the course of the above investigations, we concurrently attempted to install directing groups on vinylogous acid **3-40** or vinylogous ester **3-41**. The installations of these groups were challenging (Figure 3.2.5). Vinylogous acid **3-40** was not observed either from reductive or standard alkylations conditions (**3-39**→**3-40**). Additionally, cross-coupling methods to attach a 2-pyridyl group were equally ineffectual (**3-31**→**3-41** or **3-43**→**3-48**). This difficulty suggested to us that a new scaffold motif would be more profitable; however, we were not ready to reject a strategy based on vinylogy and were interested in modifications that could encourage exchange and possibly ease installation of the directing group.[5]

Figure 3.2.5. Unsuccessful Installation of Directing Groups to Vinylogous Scaffold



We envisioned the addition of an acyl group at the 2-position of a vinylogous ester would make the β-position more electrophilic and would therefore facilitate exchange. This adjustment could be applied to both *Strategies 1* and *2* (Figure 3.2.6), but due to the ubiquity of alcohols in the literature and the rareness of 2-acyl-vinylogous esters, *Strategy 2* was afforded more attention.

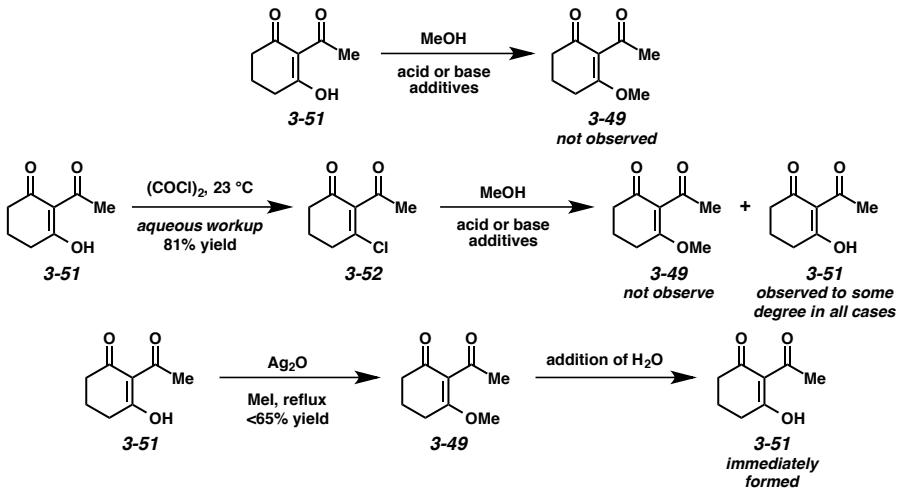
Figure 3.2.6. Modified Vinylogy Strategies to Achieve Transiently Directed C–H Functionalization



We were interested in investigating the exchange properties of these 2-acyl-vinylogous esters. In our initial attempt to synthesize these compounds, 2-acyl-vinylogous acid **3-51** was subjected to a series of acids and bases in MeOH in the attempt to generate vinylogous ester **3-**

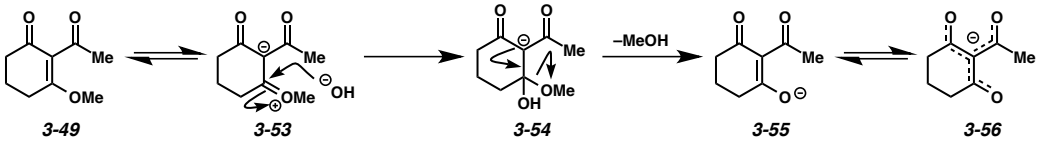
49; however, no reaction was observed (Scheme 3.2.5). A series of basic conditions with methyl iodide were also unsuccessful. Utilizing 2-acyl-vinylogous acid chloride **3-52** was envisioned as an alternative method for obtaining these compounds, but subjecting this water stable compound to either acidic or basic conditions in the presence of methanol did not afford vinylogous ester **3-49**. Instead, it produced, to some degree, 2-acyl-vinylogous acid **3-51** in all cases.[6] Vinylogous ester **3-49** could be formed by treating vinylogous acid **3-51** with silver oxide in refluxing methyl iodide under strictly anhydrous conditions. The addition of water or exposure to ambient moisture would convert vinylogous ester **3-49** to vinylogous acid **3-51**.[7]

Scheme 3.2.5. Syntheses of 2-Acyl Vinylogous Esters



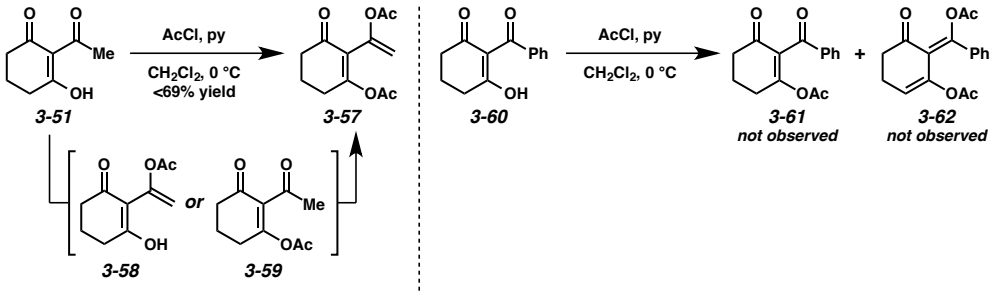
We had suspected that the addition of the 2-acyl group to vinylogous esters would make vinylogous exchange more facile. This definitely appears to be true with regards to vinylogous acid chlorides.[8] What was unexpected was the instability to water of 2-acyl vinylogous esters. It is currently unclear if hydration occurs through an S_N2 or $E1_{CB}$ mechanism, but the latter mechanism is currently favored. This rapid saponification of vinylogous ester **3-49** at the β-postion results in the enolate **3-54** (Figure 3.2.7). Extrusion of methoxide and deprotonation affords highly stabilized enolate **3-55**.

Figure 3.2.7. Saponification Mechanism of Vinylogous Ester **3-49**



At this point, we had sufficient evidence to suspect that these 2-acyl-vinylogous esters had the desired electrophilicity needed to rapidly exchange alcohols under anhydrous conditions. Unfortunately, it was very difficult to obtain these vinylogous methyl esters in high purity. In an attempt to better understand and potentially moderate these 2-acyl-vinylogous esters, we attempted to acetylate the hydroxyl group shown in vinylogous acid **3-51** (Scheme 3.2.6). We were unsure if this modification would temper this reactivity or enhance it; however, upon treatment of vinylogous acid **3-51** to acetyl chloride and pyridine, only diacetate **3-57** was observed. In contrast, under identical conditions, vinylogous acid **3-60** did not generate any observable product. This difference in reactivity is reasonably explained: vinylogous acid **3-51** could acetylate the 2-acyl oxygen or one of the vinylogous oxygens to afford *in situ* intermediate acetates **3-58** or **3-59**, respectively. By removing conjugation of one of the carbonyls, a subsequent acylation can occur to afford diacetate **3-57** as a stable product. Vinylogous acid **3-60** cannot form analogous vinyl acetate, and interestingly vinyl acetate **3-62** was not observed.

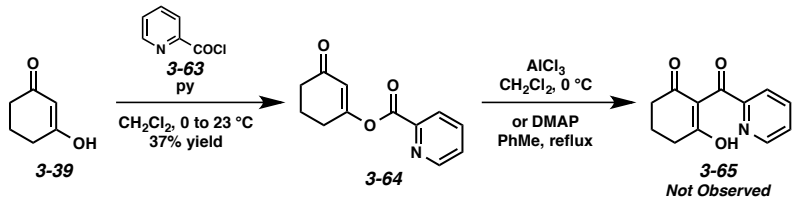
Scheme 3.2.6. Acylation Attempts of 2-Acyl Vinylogous Esters



In a final attempt to implement vinylogy in our investigations towards transiently directing C–H functionalization scaffolds, we attempted to develop a 2-picolinoyl-vinylogous

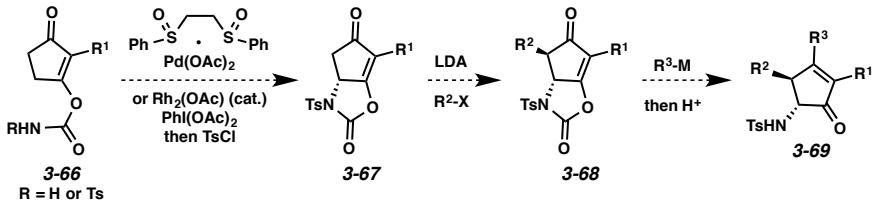
acid (Scheme 3.2.7). Despite the complications involved with the analogous vinylogous ester and acetate in our previous studies, we still suspected that the β-position of these acids were highly electrophilic, and *in situ* generation of a vinylogous ester could be all that is required to facilitate directed C–H functionalization. Synthesis of vinylogous ester **3-64** was achieved by addition of vinylogous acid **3-39** with picolinoyl chloride **3-63**; however, this product was highly sensitive to SiO_2 and acidic conditions. Subjecting this vinylogous ester to $AlCl_3$ did not appear to afford 2-picolinoyl-vinylogous acid **3-65**. It is most likely that this vinylogous ester **3-64** decomposed to the reaction conditions.[9]

Scheme 3.2.7. Synthetic Attempt Toward 2-Picolinoyl Vinylogous Esters



Since the vinylogous ester strategy has been abandoned, there have been reports in the literature suggesting a reinvestigation of this idea could possibly lead to a traceless directing group approach towards functionalizing these vinylogous esters. White's allylic oxidation procedure[10] and rhodium nitrenoids procedures[11] were never explored in our vinylogy studies, and implementing them in concert with Stork-Danheiser chemistry could afford highly substituted amino cyclopentanones (Figure 3.2.8).

Figure 3.2.8. Merging C–H Allylic Oxidation or Rhodium Nitrenoids with Stork-Danheiser Chemistry

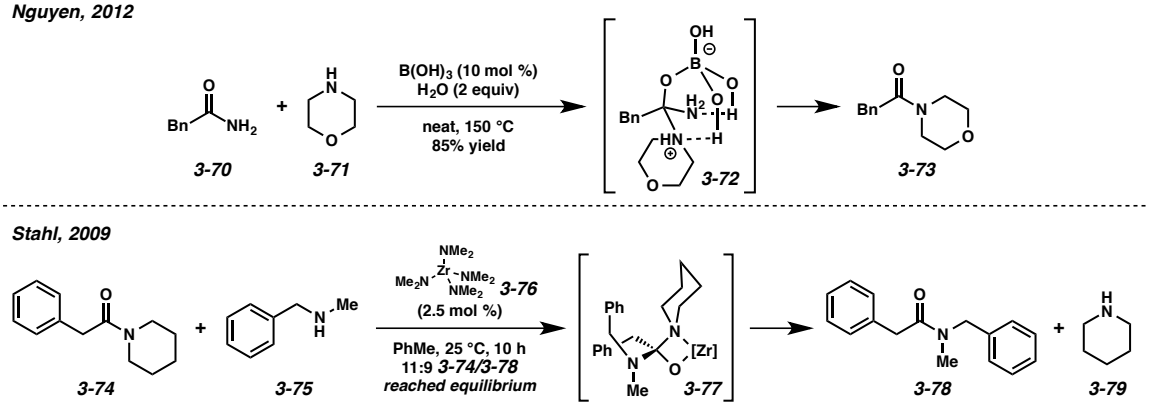


3.3. Utilizing Transamidation and Transesterification as a Strategy

In an attempt to expand the transient strategies in pursuit of our ultimate research objective, we found it prudent to investigate methods that diverge from the thermodynamic exchange of acetals/aminals and vinylogous esters. This divergence would require a judicious choice of functional group well precedented for thermodynamic exchange. Additionally, the directing group would ideally mediate numerous functionalizations, allowing for sufficient breadth compatible with the exchange conditions.

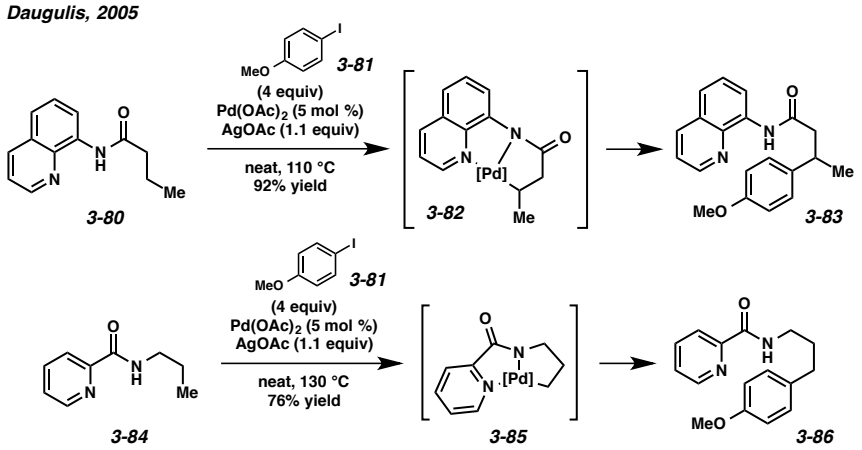
Although amides are thought to be quite thermodynamically stable, recently, a few reports have disclosed catalysts that achieve some degree of transamidation. Among these catalysts are $H_2NOH•HCl$[12] and L-proline[13]; however, they are limited to exchange with primary amides. Boric acid is a highly efficient catalyst that is moderately successful at exchanging secondary amides (Scheme 3.3.1).[14] Most impressively, Stahl has disclosed a series of highly efficient transamidation catalysts; among these are $Zr(NMe_2)_4$, $Hf(NMe_2)_4$, and $Sm(NTMS_2)_4$. This group of catalysts is capable of achieving thermodynamic mixtures between secondary amines and tertiary amides at ambient temperatures within hours.[15]

Scheme 3.3.1. Examples of Transamidation



To successfully merge transamidation with C–H functionalization, an exchangeable directing group would need to be either an amine or amide. Daugulis reported a procedure for the functionalization of sp^2 and sp^3 C–H bonds utilizing either picolinamides (**3-80**→**3-83**) or amides derived from 8-aminoquinoline (**3-84**→**3-86**) (Scheme 3.3.2).[16] This procedure afforded products in good to high yield and bond-disconnections that were previously unattainable.

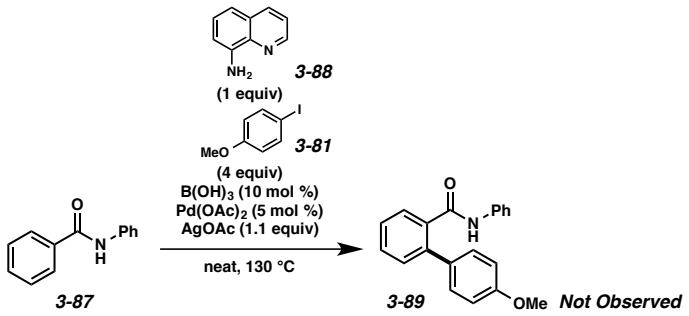
Scheme 3.3.2. Daugulis' Directed sp^3 C–H Arylation



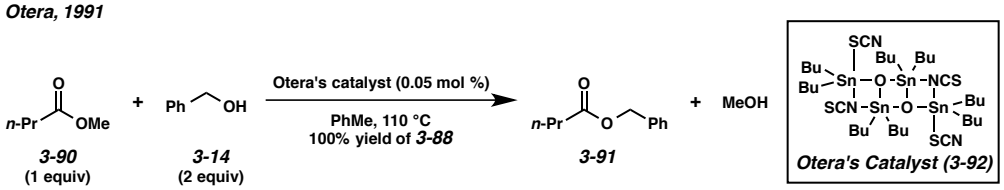
We attempted to merge Daugulis' C–H functionalization procedure with transamidation catalysis implementing boric acid (Scheme 3.3.3). We observed the exchange of benzamides using boric acid. The addition of C–H functionalization reagents stopped exchange completely and functionalization was not observed (**3-87**→**3-89**). We did not attempt to merge Stahl's catalyst with C–H functionalization due to the sensitivity of the transamidation catalyst. Due to the stability of the amide bond, transesterification was believed to be a more profitable venture.

Transesterification is the exchange of one alcohol for another on an ester. There have been numerous catalysts developed to facilitate this exchange, but arguable the most impressive is Otera's catalyst (**3-92**).[17] This distannoxane catalyst is capable of producing thermodynamic mixtures of alcohols and esters (Scheme 3.3.4) and can even exchange sterically hindered alcohols (e.g., neopentyl alcohol).

Scheme 3.3.3. Transient Functionalization Attempt Utilizing Daugulis' C–H Arylation and Transamidation

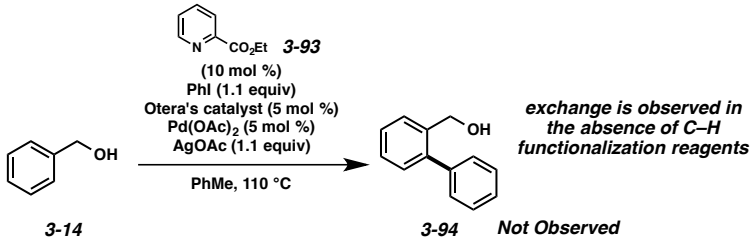


Scheme 3.3.4. Transesterification Utilizing Otera's Catalyst



Attempts were made to couple C–H functionalization with transesterification (Scheme 3.3.5). Conditions that utilize palladium were implemented, but functionalized products were not observed. Additionally, transesterification was not observed. We speculate that the issue is an incompatibility of the isocyanate ligands on Otera's catalyst with the C–H functionalization conditions.

Scheme 3.3.5. Transient Functionalization Attempt Utilizing Daugulis' C–H Arylation and Transesterification

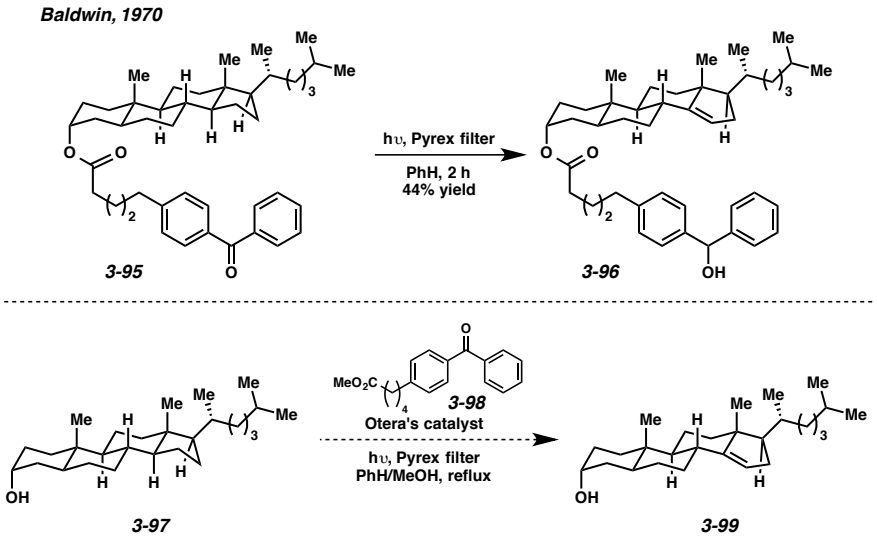


This phenomenal transesterification catalyst may not be attuned with transition metal catalysis, but it may still be useful in transient C–H functionalization catalysis. There are examples of non-transition metal C–H functionalization, and the most apparent application

would be with photo-initiated ketyl-based conditions such as those reported by Baldwin (Figure 3.3.1). Exchange of a benzophenone-linked alcohol (**3-98**) with a sterol (**3-97**) facilitated by Otera's catalyst under photolytic conditions could produce desaturated steroids (**3-99**). The intermediates of this reaction are likely to be compatible with Otera's catalyst. Electronic modification of the benzophenone might produce a more stable or active ketyl that could further facilitate this reaction.

Although we have yet to successfully couple either transamidation or transesterification with C–H functionalization, we contend that this strategy holds promise once the necessary conditions are met. The development of more generic or robust C–H functionalization catalysts and conditions may be sufficiently compatible to combine with the known exchange methods. Inversely, progressively more mild and robust exchange catalysts may allow for this unique synthesis. Due to the cornucopia of functionalization protocols in the literature and the relative dearth of transamidation or transesterification catalysts and methods that produce equilibrium mixtures in high yields, this strategy must be deferred until the necessary progress is made.

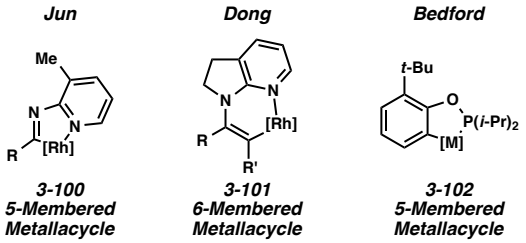
Figure 3.3.1. Merger of Transesterification and Photo-Induced C–H Functionalization



3.4. Utilizing Sulfinate Esters to Achieve Transiently Directing Scaffolds

The challenges described above lead us to critically analyze the components that are needed in a transient scaffold. The legitimate examples of transient directed C–H functionalization, reported by Jun, Dong, and Bedford and described in Chapter 1, share a few similarities. In all cases, the exchangeable groups (the amine or phenol) are contained within the metallacycle, which is either in a 5- or 6-membered ring (Figure 3.4.1). This is important since the common metallacycle sizes for functionalization reactions are a 5-membered ring and 6-membered rings. Larger metallacycles exists, but will be excluded from this discussion for the sake of simplicity.

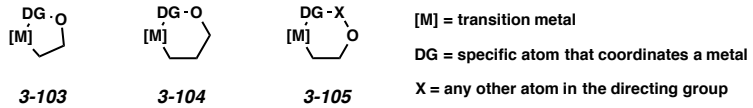
Figure 3.4.1. Metallacycles in Transiently Directing Scaffolds



A major difference between the pyridine directed scaffolds of Jun and Dong compared to the phosphinite scaffold of Bedford is the location in the ring between the directing group's chelating atom (i.e., the nitrogens of the pyridines and phosphorus of the phosphinite) and the exchanging atom (i.e., the nitrogens of the amines and oxygen of the phenol). In the Jun/Dong examples, the exchangeable atoms are two atoms from the directing group's atom (**3-100** and **3-101**); however, in the Bedford example, the exchangeable atom is directly attached to the directing group's atom (**3-102**). This latter strategy, the use of a transition metal-directing atom (i.e., the phosphinite phosphorous) that also exchanges a functional group reduces the overall amount of atoms contributed by that directing group to the metallacycle size (i.e., 1 atom in the phosphinite example). If constrained to 5- or 6-membered metallacycle sizes, this strategy could

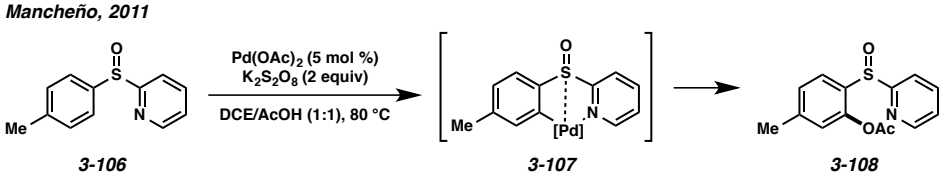
potentially functionalize the β or γ positions, respectively. Any additional atoms in the directing group reduce the distance away from the exchangeable atom that can be functionalized (i.e., 1 additional atom/β-functionalization or 2 additional atoms/α-functionalization). With respect to alcohols, the products of α-functionalization can be obtained through the addition of nucleophiles into aldehydes or ketones, therefore, scaffolds that afford α-functionalization may not be ideal. This leaves scaffolds that produce metallacycles such as **3-103–3-105** (Figure 3.4.2). A functional group that both exchanges alcohols and directs C–H functionalization would be ideal for achieving these metallacycle goals.

Figure 3.4.2. Ideal Metallacycle Structures for Transient Scaffolds



Sulfinate esters are an example of a functional group that may provide the necessary features for exchange and functionalization. Examples of sulfinate transesterification have been reported under thermal conditions as well as catalyzed by acids,[18] bases,[18] and even NBS.[19] Sulfinate esters have not been reported to direct C–H functionalization, however, sulfinyls have been utilized to form C–O[20] and C–C[21] bonds. Antonchick reported the acetoxylation of arenes directed by sulfinyl-2-pyridines (**3-106**→**3-108**, Scheme 3.4.1).[22]

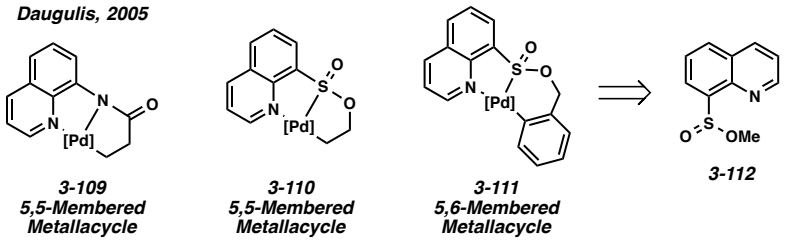
Scheme 3.4.1. Pyridyl-Sulfoxide Facilitated C–H Acetoxylation



By conceptually merging the C–H functionalization properties of 8-aminoquinoline based amides with sulfinate esters, we proposed scaffold **3-112** (Figure 3.4.3). It contains the quinoline

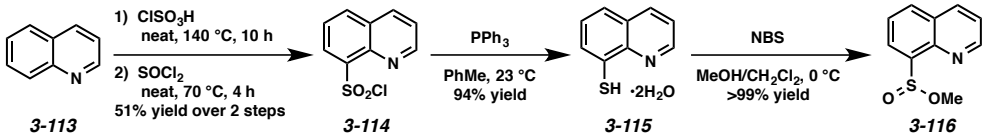
and the sulfinyl group at the 8-position that may undergo bidentate chelation; additionally, the sulfinate ester can exchange alcohols.

Figure 3.4.3. The Use of Sulfinate Esters as a Directing Group



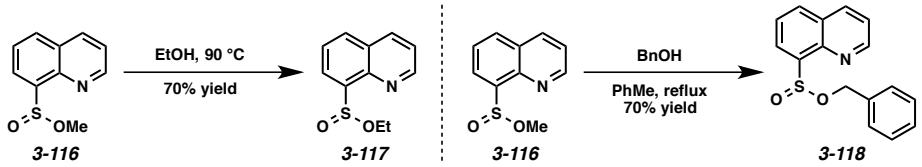
The synthesis of sulfinate scaffold **3-116** was uneventful (Scheme 3.4.2). Quinoline (**3-113**) was converted to the sulfuric acid selectively at the 8-position. The acid was then transformed to sulfonyl chloride **3-114** in 51% yield over 2 steps. Full reduction of the sulfur to 8-thioquinoline (**3-115**) was achieved in excellent yield by the addition of triphenylphosphine in PhMe at 23 °C. The thiol was selectively oxidized to sulfinate ester **3-109** in quantitative yield by *N*-bromosuccinimide.

Scheme 3.4.2. Synthesis of Sulfinate Ester **3-116**



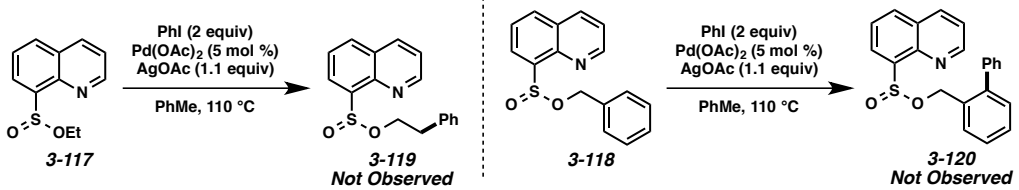
Sulfinate ester **3-116** was converted to both the ethyl sulfinate ester **3-117** and the benzyl sulfinate ester **3-118** in 70% yield (Scheme 3.4.3). These transformations were performed in the absence of additional reagents and were thermally induced. This sulfinate transesterification could be performed in either an alcoholic solvent or with stochiometric amounts of the exchanging alcohol. Although the yields of these two reactions were not excellent, these examples illustrate the simplicity of exchange. Acid or base catalysts might help further facilitate alcohol substitution.

Scheme 3.4.3. Alcohol Exchange with Sulfinate Ester **3-116**



Sulfinate esters **3-117** and **3-118** were subjected to Daugulis' functionalization conditions; however, arylated products were not observed (Scheme 3.4.4). When these functionalization conditions were utilized with stoichiometric amounts of palladium, a precipitate was isolated which was insoluble in all solvents. These results were identical when iridium and rhodium conditions were implemented. These insoluble complexes were subjected to acidic work-ups, but functionalized alcohols were not observed.

Scheme 3.4.4. Functionalization Attempts with Sulfinate Esters **3-117** and **3-118**



Other Pd, Rh, and Ir conditions did not produce functionalized products.

This scaffold platform was unproductive in the development of a novel C–H functionalization strategy. The unique properties of these quinoline sulfinate esters as it relates to late-transition metal complexes were unexpected. Unfortunately, this chemistry was not thoroughly explored, and these compounds might facilitate functionalization under the right conditions. The purpose for this discussion was to expand on the requisite features needed for a transient scaffold. These sulfinate esters contained sufficient overlap between the essential features of transient scaffolds and a common motif now found in C–H functionalization. This type of analysis is likely needed in the future development of new scaffold concepts and strategies.

3.5. Combined Insights

We have investigated three separate exchange strategies that have yet to be successfully integrated with C–H or C–C functionalization. Each of these pursuits has either led to insights or made us aware of precautions for future investigations. Our studies of vinylogous scaffolds illustrate a couple of obstacles that were recurrent during our investigations on this project. The locality and rigidity of the directing group is vitally important for the successful C–H functionalization. This can be seen in Chapter 2 where the PyA scaffold only functionalizes a remote arene and is limited to two very unique and similar conditions. Attempts to deviate from these conditions have yet to produce any additional functionalizations.

Our studies into transamidation/transesterification or sulfinate ester exchange coupled with C–H functionalization are unexhausted. The purpose of including these two sections is to expand the conceptual approaches that have been attempted toward transient C–H functionalization. A major limitation of this project has been the development of new scaffolds that exhibit thermodynamic exchange under some conditions. Due to the ubiquity of amides and esters, transamidation and transesterification removes scaffold synthesis from the list of challenges, and instead requires the discovery of compatible catalysts and conditions.

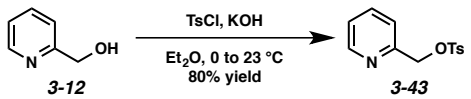
Our investigations into sulfinate ester scaffolds were unproductive toward developing a scaffold or conditions for transient C–H functionalization. Analyses of the features requisite for transient scaffolds were discussed. The general concepts behind the development of the sulfinate ester scaffold are ones we contend should be at the forefront of every new transient directing group's design.

3.6. Experimental Section

3.6.1. Materials and Methods

Reactions were performed under an argon atmosphere unless otherwise noted. Dichloromethane, diethyl ether, and toluene were purified by passing through activated alumina columns. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, Ma), Sigma-Aldrich (St. Louis, MO), Oakwood Products (West Columbia, SC), Strem (Newport, MA), and TCI America (Portland, OR). Qualitative TLC was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to $KMnO_4$, CAM, or Dragendorff stain solutions followed by heating. Flash column chromatography was performed using Silicylce silica gel (230-400 mesh). ^1H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz), a Varian 400 MR (at 400 MHz), or Varian Mercury Plus (at 400 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) or Varian Mercury Plus (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained as a film with a Nicolet iS50 FT-IR or an IRPrestige-21 Spectrophotometer. Low-resolution mass spectrometry data were acquired on an Agilent 1200 series HPLC equipped with an Agilent 6130 quadrupole LC/MS or at the Mass Spectrometry Core Facility on a Bruker Esquire 3000 Plus Ion Trap Spectrophotometer.

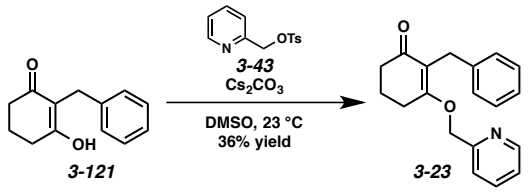
3.6.2. Preparative Procedures



To a stirring solution of alcohol **3-12** (1.70 g, 15.6 mmol) and TsCl (3.01 g, 15.8 mmol) in Et_2O at 0 °C was added freshly powdered KOH (4.65 g, 83.4 g) and then water (10 drops). The

reaction mixture was removed from the cooling bath and warmed to 23 °C and stirred for 1 h. The reaction mixture was filtered through a fritted glass filter to remove the KOH. The resulting filtrate was then concentrated by rotary evaporation without the use of a warming bath allowing the container to cool below 0 °C. The flask contained an upper band of an orange residue and below this a white crystalline powder. The white powder was removed without removing this upper band to afford sufficiently pure tosylate **3-43** (3.27 g, 80% yield, R_f = 0.34 in 1:1 hexanes/EtOAc).

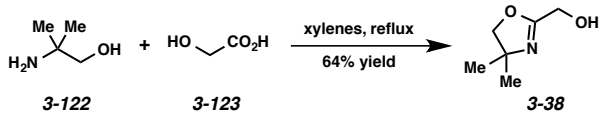
Tosylate 3-43: (300 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.70 (td, *J* = 7.8, 1.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.23 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.14 (s, 2H), 2.44 (s, 3H). This compound's spectroscopic data corresponds to previously reported data.[23]



To a suspension of tosylate **3-43** (3.74 g, 14.2 mmol) and Cs_2CO_3 (4.84 g, 14.9 mmol) in DMSO (15.4 mL) at 23 °C was added vinylogous acid **3-121**[24] (2.73 g, 13.5 mmol) and the resulting mixture was stirred for 18.5 h. Upon completion by TLC, EtOAc (100 mL) and 1:1 water/sat. Na_2CO_3 (100 mL) was added to the reaction mixture. The organic layer was washed with water (50 mL), and then brine (50 mL), dried with Na_2SO_4, and then concentrated by rotary evaporation. The crude residue was purified by flash column chromatography to afford ether **3-23** (1.45 g, 36% yield, R_f = 0.50 in EtOAc) as a colorless oil.

Ether 3-23: (400 MHz, $CDCl_3$) 8.55 (d, *J* = 4.0 Hz, 1H), 7.62 (dt, *J* = 8.0, 4.0 Hz, 1H), 7.26-7.18 (comp. m, 5H), 7.15-7.10 (comp. m, 2H), 5.21 (s, 2H), 3.72 (s, 2H), 2.61 (t, *J* = 2.4 Hz, 2H),

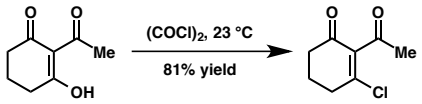
2.39 (t, J = 2.4 Hz, 2H), 1.98 (quintet, J = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 171.4, 149.3, 141.7, 137.3, 128.9, 128.2, 125.6, 123.1, 121.3, 120.1, 70.2, 36.5, 28.2, 25.7, 21.0; IR (film) 2984, 1613, 1379, 1176, 1082 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{19}NO_2 + H]^+$: 294.1, found 294.2.



3-122 *3-123* *3-38*

A stirring solution of amino alcohol **3-122** (4.78 g, 53.7 mmol) and carboxylic acid **3-123** (4.78 g, 53.7 mmol) was heated in xylenes (100 mL) at reflux for 3 h. Upon completion by TLC, the reaction mixture was cooled to ambient temperature and concentrated by rotary evaporation to a yellow oil, which was then distilled (81 °C, 0.16 mmHg) to afford alcohol **3-28** (4.42 g, 64% yield, R_f = 0.19 in 9:1 CH_2Cl_2/MeOH) as a colorless oil.

Alcohol 3-28: This compound's spectroscopic data corresponds to previously reported data.[25]



3-51 *3-52*

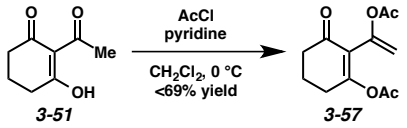
To vinylogous acid **3-51**[26] (1.03 g, 6.65 mmol) was added oxalyl chloride (6.65 mL), and the resulting solution was stirred at 23 °C for 30 min. Saturated $NaHCO_3$ (150 mL) was then added to the reaction mixture and the product was extracted into EtOAc (2 x 150 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to afford vinylogous acid chloride **3-52** (935 mg, 81% yield, R_f = 0.71 in 2:1 EtOAc/hexanes) as an orange solid.

Vinylogous acid chloride 3-52: This compound's spectroscopic data corresponds to previously reported data.[27]



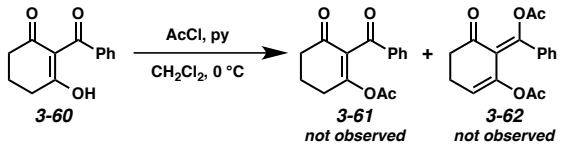
In a flame-dried round-bottom flask with a condenser attached, a suspension of vinylogous acid **3-51**[26] (100 mg, 0.649 mmol) and Ag_2O (107 mg, 0.461 mmol) in MeI (5.20 mL) was heated and stirred at reflux for 2.5 h. This reaction was determined to be complete by TLC using oven-dried TLC plates (dried for 5 min at ~180 °C). The reaction mixture was filtered through oven-dried Celite (heated for 12 h at ~180 °C, 20 cm x 30 cm) with dried Et_2O (10 mL). The filtrate was concentrated by rotary evaporation, and the crude material was purified flash column chromatography (dried Et_2O) using oven dried SiO_2 (heated for 12 h at ~180 °C) to afford partially pure vinylogous ester **3-49** (71.1 mg, <65% yield, R_f = 0.10 in Et_2O) as an orange oil.

Vinylogous acid 3-49: (300 MHz, $CDCl_3$) 3.83 (s, 3H), 2.63-2.52 (comp. m, 2H), 2.40-2.33 (comp. m, 2H), 2.34 (s, 3H), 2.07-1.96 (comp. m, 2H).

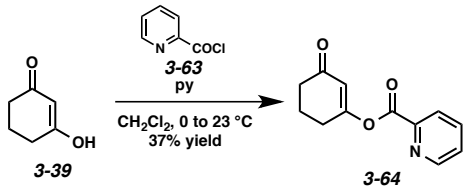


A stirring solution of vinylogous acid **3-51**[26] (1.05 g, 6.81 mmol), AcCl (1.07 mL, 15.0 mmol), and pyridine (1.10 mL, 13.6 mmol) in CH_2Cl_2 (17.0 mL) was heated at reflux for 18.5 h. Upon completion by TLC, the reaction mixture was concentrated by rotary evaoporation, and the crude residue was purified by flash column chromatography (2:1 Et_2O/hexanes) to afford partially pure diacetate **3-57** (1.13 g, <69% yield, R_f = 0.31 in 2:1 Et_2O/hexanes) as an amber oil.

Diacetate 3-57: This compound's spectroscopic data corresponds to previously reported data.[28]

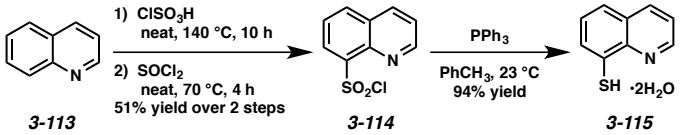


A stirring solution of vinylogous acid **3-60**[26] (55.6 mg, 0.257 mmol), AcCl (20 µL, 0.283 mmol), and pyridine (20.1 µL, 0.257 mmol) in CH_2Cl_2 (600 µL) was heated at reflux for 3 d. The reaction mixture was concentrated by rotary evaporation, and no product was observed in the crude NMR.



To a stirring suspension of picolinic acid (2.00 g, 16.2 mmol) in CH_2Cl_2 (16.0 mL) at 0 °C was added $SOCl_2$ (1.18 mL, 16.2 mmol) in one portion, and the reaction was warmed to 23 °C. After 3 h, to the reaction mixture was concentrated by rotary evaporation, and CH_2Cl_2 (80.0 mL) was added to the crude residue, vinylogous acid **3-39** (1.82 g, 16.2 mmol), and then pyridine (1.32 mL, 16.3 mmol) at 23 °C and stirred for 1 h. Saturated Na_2CO_3 (50 mL) was then added to the reaction mixture and it was then extracted with CH_2Cl_2 (100 mL). The organic layer was washed with water (50 mL) and then brine (50 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (EtOAc eluent) to afford vinylogous ester **3-64** (1.30 g, 37% yield, R_f = 0.28 in EtOAc) as a colorless oil. (*Note:* Picolinate **3-64** is unstable to prolonged expose to SiO_2).

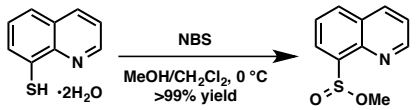
Picolinate 3-64: (300 MHz, $CDCl_3$) 8.82 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.20 (d, *J* = 7.7 Hz, 1H), 7.92 (td, *J* = 7.7, 1.5 Hz, 1H), 7.57 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.07 (s, 1H), 2.72 (t, *J* = 3.3 Hz, 2H), 2.51-2.44 (comp. m, 2H), 2.20-2.09 (comp. m, 2H).



3-113 *3-114* *3-115*

Sulfonyl chloride 3-114: This compound can be prepared through known procedures and its spectroscopic data corresponds to previously reported data.[29]

Thiol 3-115: This compound can be prepared through known procedures and its spectroscopic data corresponds to previously reported data.[30]

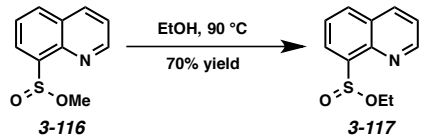


3-115 *3-116*

The controlled oxidation of thiol **3-115** to sulfinate ester **3-116** was achieved according to the procedure of Trost et al.[31] To a dark-red solution of thiol **3-115** (630 mg, 3.91 mmol) in 1:1 CH_2Cl_2/MeOH (20.0 mL) at 0 °C was added NBS (1.39 g, 7.82 mmol) in one portion. Immediately the solution turned yellow. After 15 min, the reaction mixture was poured into sat. $NaHCO_3$ (50 mL), and the product was extracted into CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (4:1→2:1 hexanes/EtOAc) to afford sulfinate ester **3-116** (810 mg, >99% yield, R_f = 0.37 in 7:3 hexanes/EtOAc) as a colorless oil.

Sulfinate ester 3-116: (400 MHz, $CDCl_3$) δ 9.02 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.35 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.26 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.74 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.53 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 145.3,

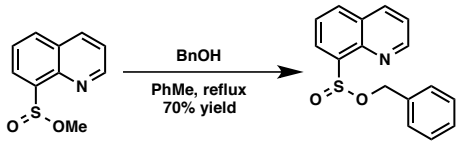
141.0, 136.4, 132.4, 128.6, 127.2, 126.1, 122.3, 51.4; IR (film) 3566, 1492, 1118, 969, 790 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{10}H_9NO_2S + H]^+$: 208.0, found 208.0.



3-116 *3-117*

A stirring solution of sulfinate ester **3-116** (50.0 mg, 0.241 mmol) in EtOH (2.40 mL) was heated to 90 °C in a sealed vial for 3 h. Upon completion, the reaction mixture was concentrated by rotary evaporation, and the crude residue was purified by flash column chromatography (7:3 hexanes/EtOAc) to afford sulfinate ester **3-117** (37.2 mg, 70% yield, R_f = 0.29 7:3 hexanes/EtOAc) as a colorless oil.

Sulfinate ester 3-117: (400 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.4, 1.8 Hz, 1H), 8.36 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.24 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.01 (dd, 8.0, 1.2 Hz, 1H), 7.72 (*J* = 8.0, 7.2 Hz, 1H), 7.51 (*J* = 8.4, 4.4 Hz, 1H), 4.28 (dq, *J* = 10.0, 7.2 Hz, 1H), 3.89 (dq, *J* = 10.0, 7.2 Hz, 1H), 1.26 (t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 145.1, 141.9, 136.3, 132.1, 128.5, 126.7, 126.2, 122.2, 62.9, 15.8; IR (film) 3566, 1492, 1120, 882, 830 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{11}NO_2S + H]^+$: 222.1, found 222.0.



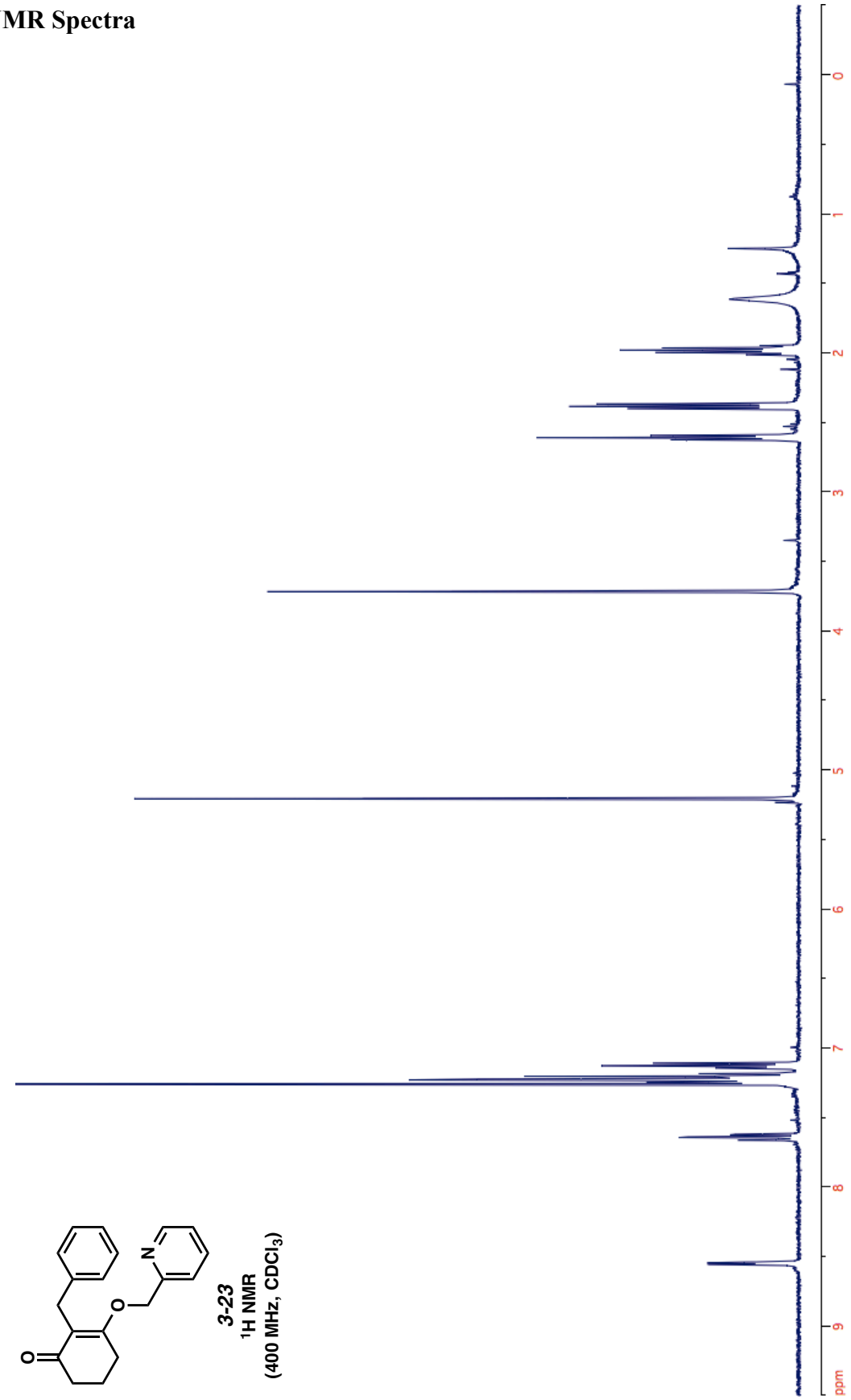
3-116 *3-118*

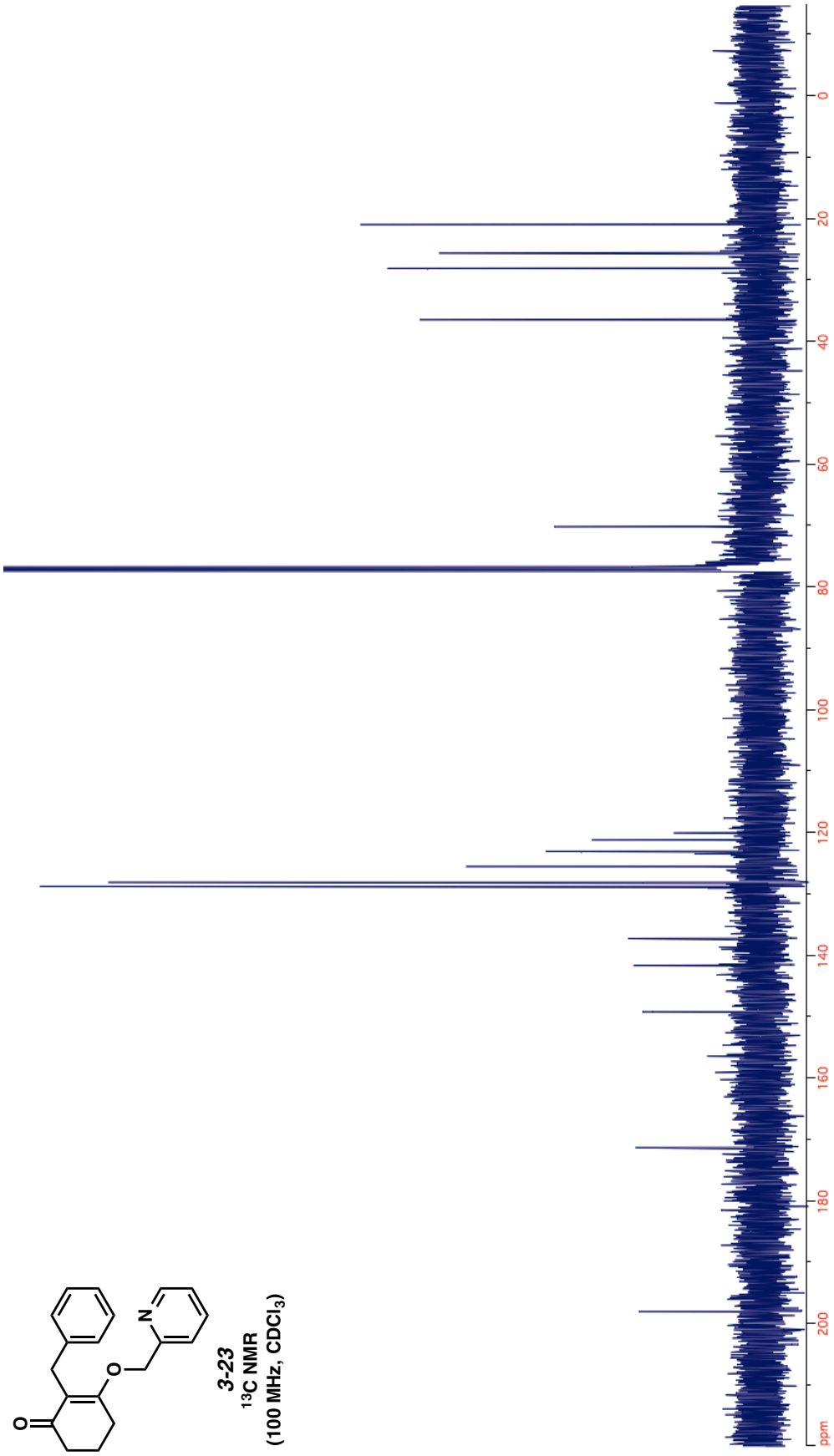
A stirring solution of sulfinate ester **3-116** (522 mg, 2.52 mmol) and BnOH (289 mL, 2.78 mmol) in PhMe (5.00 mL) was heated to reflux and stirred for 72 h. An additional portion of BnOH (1.00 mL, 9.62 mmol) was added to the reaction mixture, and it was heated at reflux for an additional 36 h. The reaction mixture was concentrated by rotary evaporation, and the residue

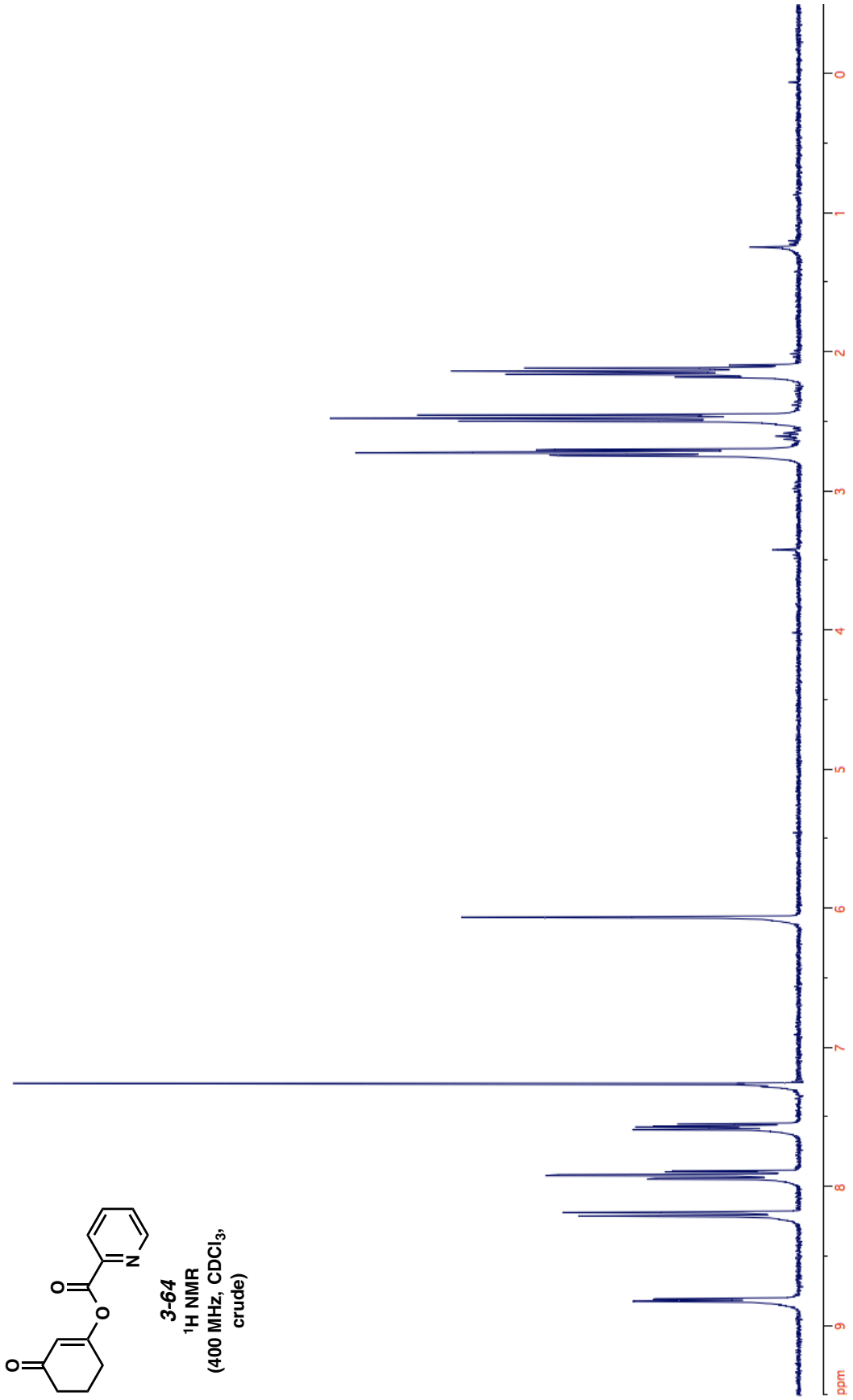
was purified by flash column chromatography (4:1→3:1→2:1 hexanes/EtOAc) to afford sulfinate ester **3-118** (420 mg, 70% yield, R_f = 0.37 in 7:3 hexanes/EtOAc) as a pale yellow oil.

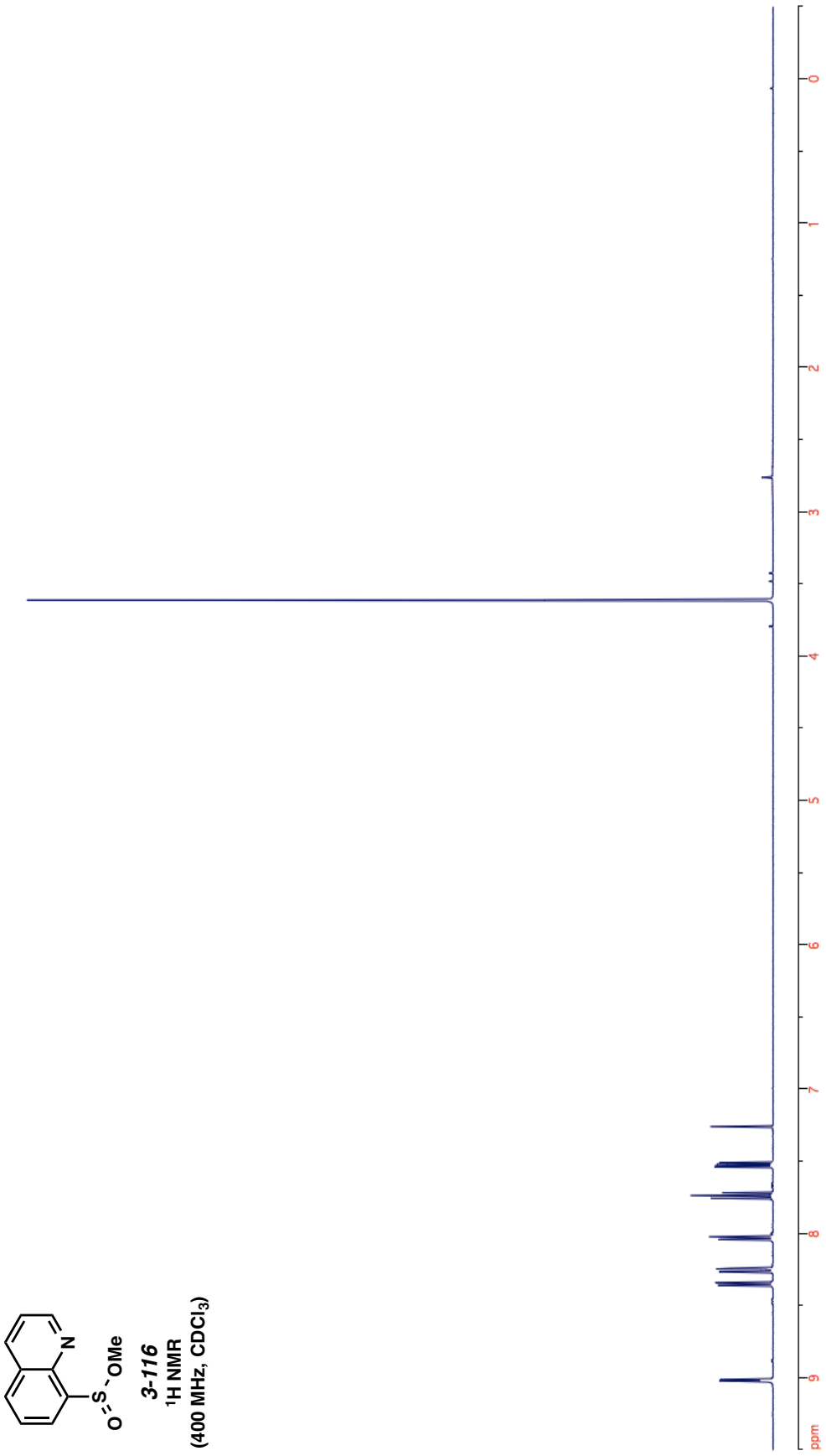
Sulfinate ester 3-118: (400 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.41 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.74 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.51 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.25-7.20 (comp. m, 5H), 5.11 (d, *J* = 11.6 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 145.1, 141.7, 136.2, 135.9, 132.3, 128.43, 128.39, 128.3, 128.2, 126.9, 126.1, 122.2, 67.9; IR (film) 3494, 1118, 828, 788, 693 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{13}NO_2S + H]^+$: 284.0, found 284.1.

3.6.3. NMR Spectra




O
O
N
3-23
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

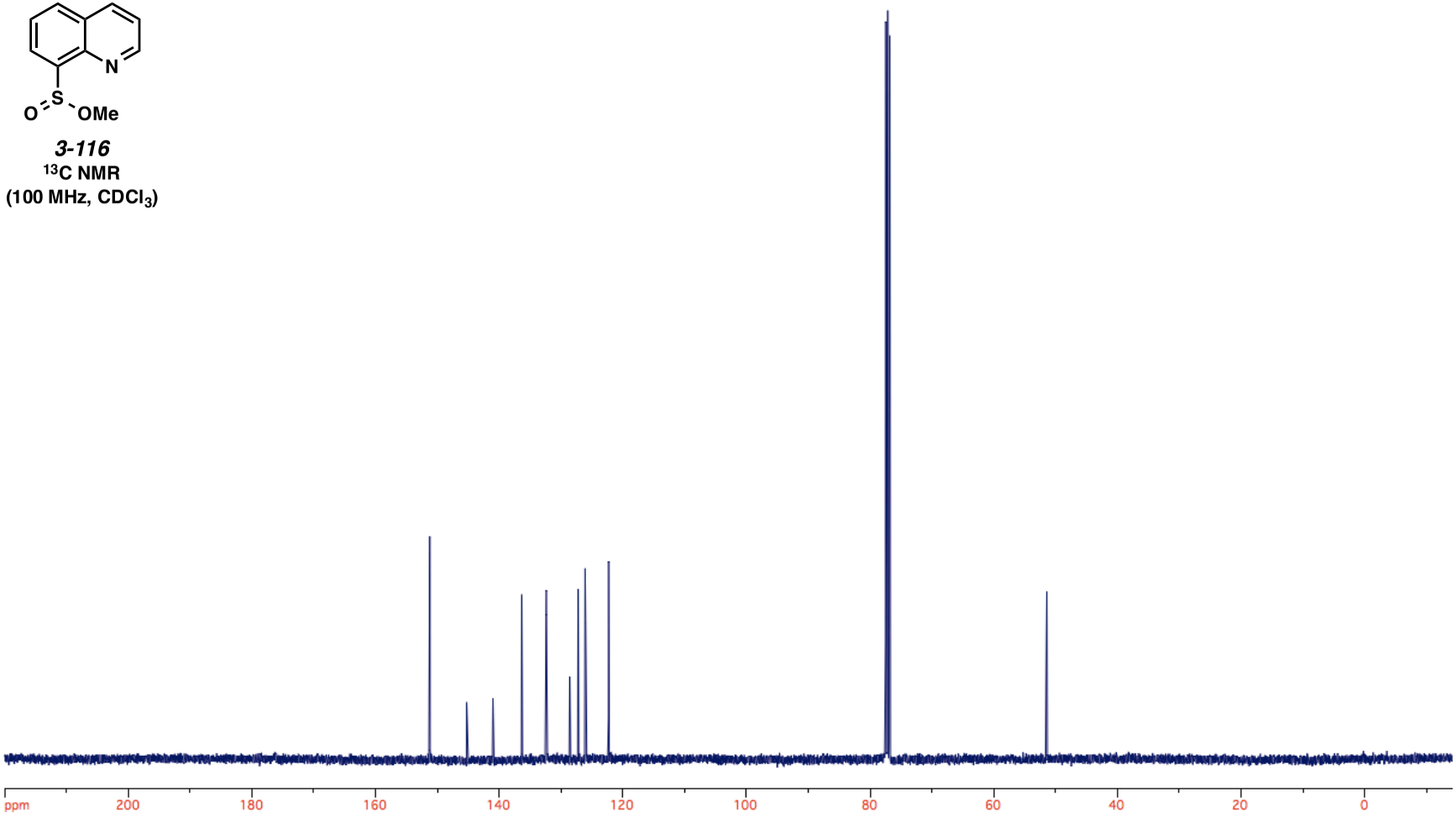

O
O
O
N
3-64
^{1}H NMR
(400 MHz, $CDCl_3$,
crude)
ppm
0
1
2
3
4
5
6
7
8
9

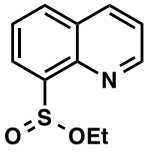

N
O
S
OMe
3-116
1H NMR
(400 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm

3-116

^{13}C NMR

(100 MHz, $CDCl_3$)

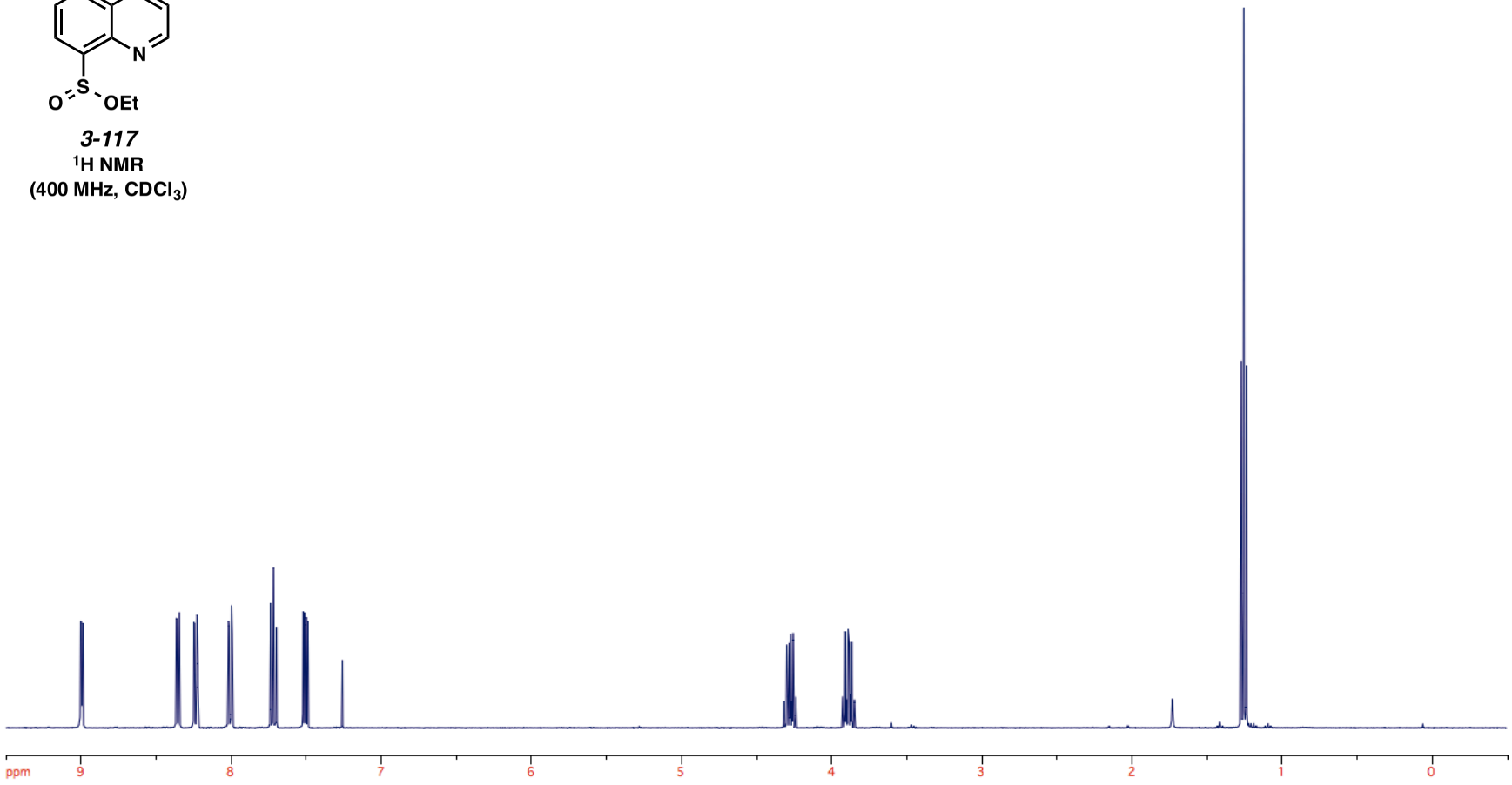


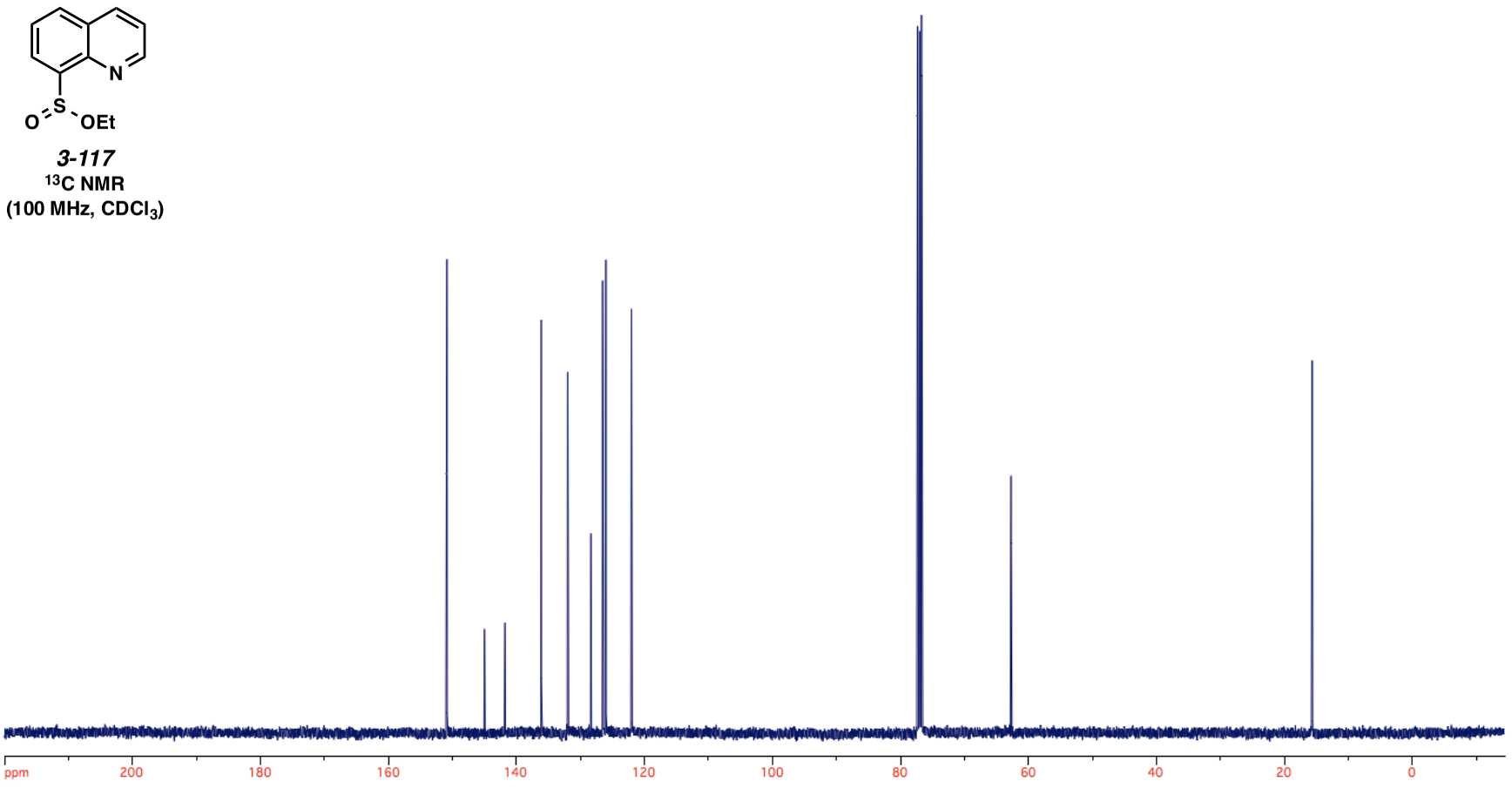


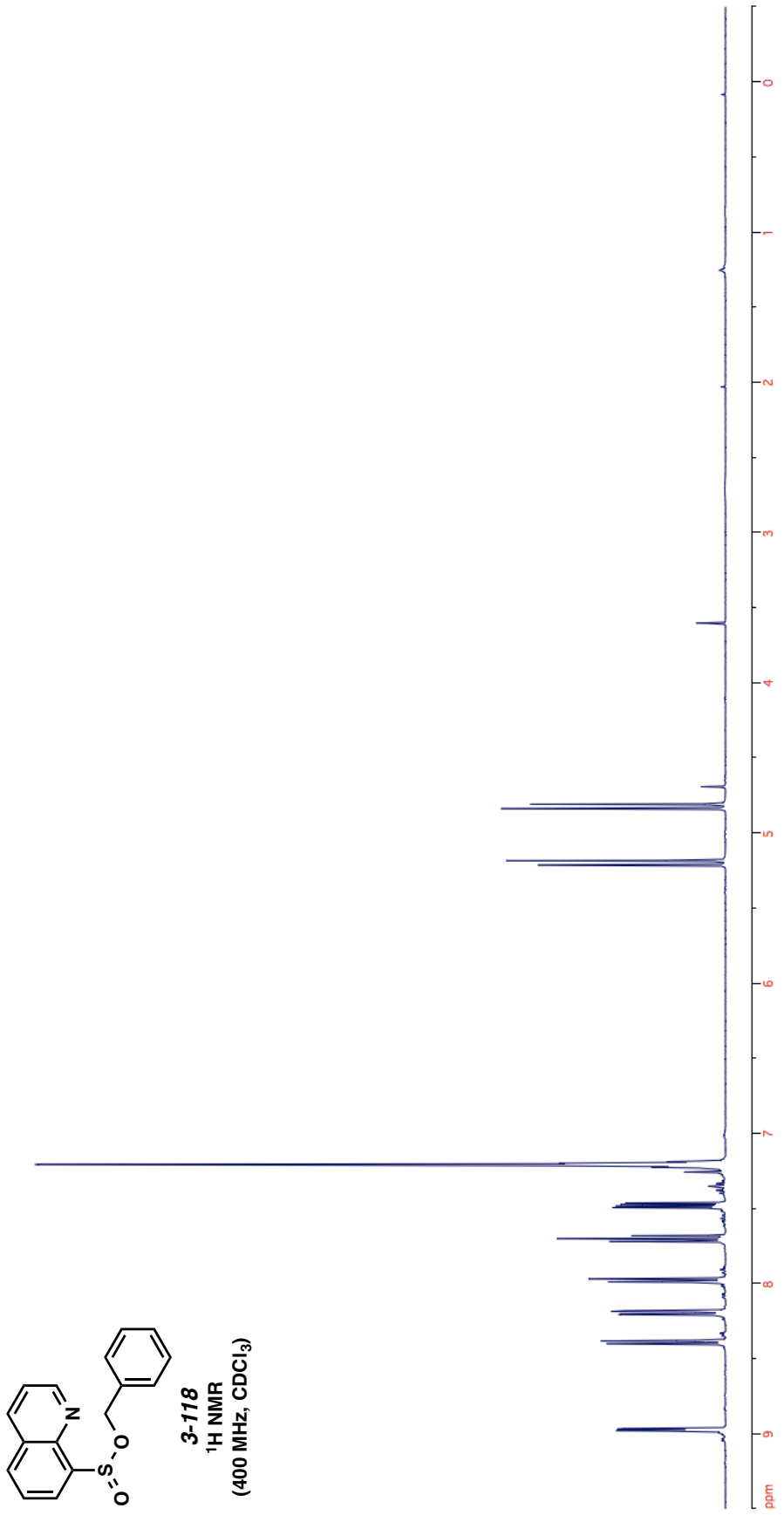
3-117

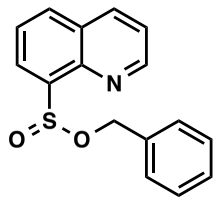
^{1}H NMR

(400 MHz, $CDCl_3$)




N
S
O
OEt
3-117
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

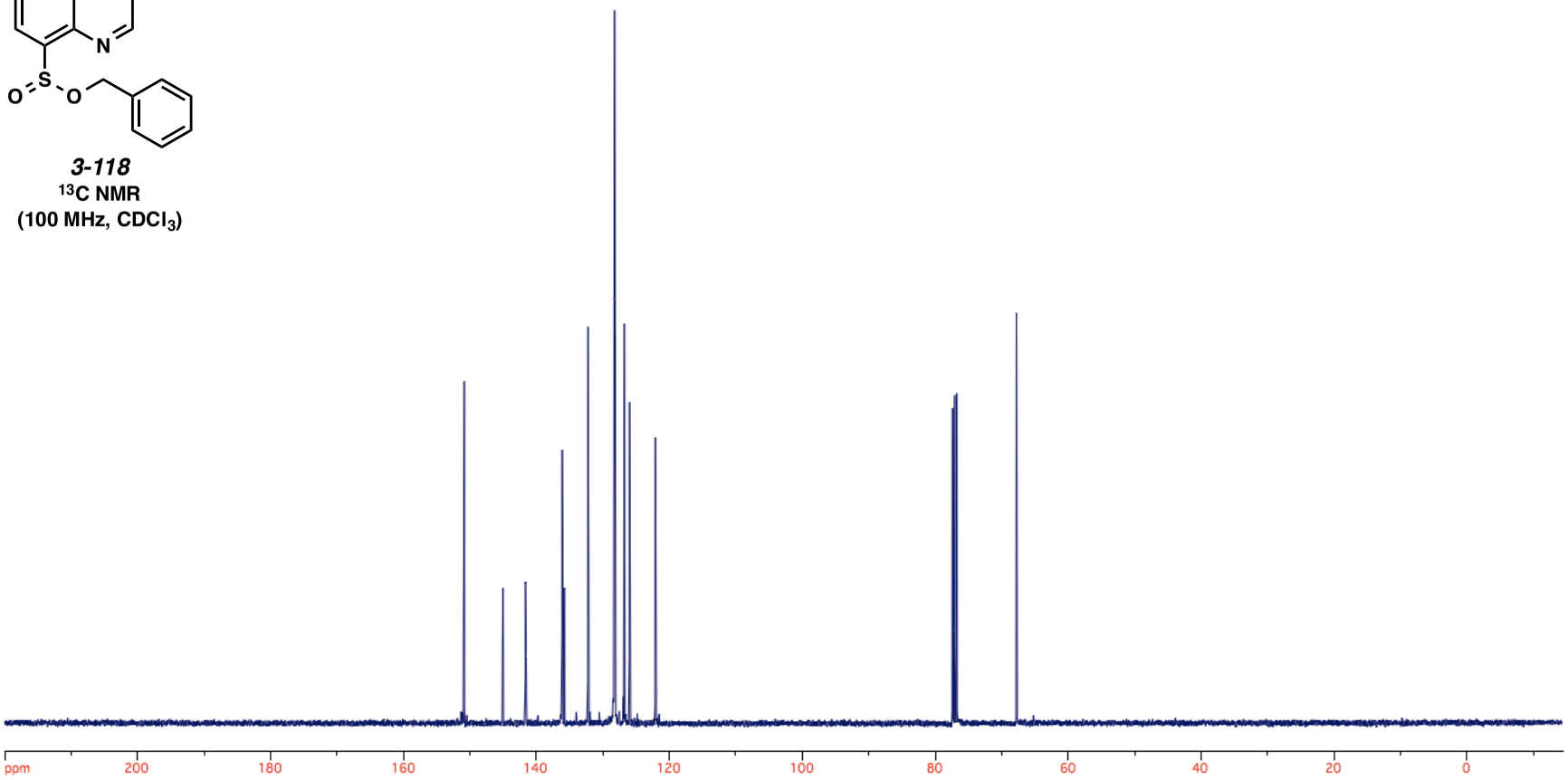

N
O
S
O
3-118
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9



3-118

^{13}C NMR

(100 MHz, $CDCl_3$)



3.7 References and Notes

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(5) Most literature procedures lack pyridines in their substrate scope. The methods that were investigated often failed if the procedure was developed for carbonaceous substrates. The substitution of a benzene on a model synthesis for a pyridine on a final scaffold often required a reanalysis of our synthetic scheme and approach. For a critique of substrate scopes in synthetic organic journals as they relate to pharmaceutical lead-like molecules (i.e., those that contain nitrogen), see: Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114-1122.

(6) The corresponding 2-hydro vinylogous acid chlorides did not undergo exchange when heated with acids or bases in MeOH.

(7) An aqueous work-up would result in complete conversion to vinylogous acid **3-51**.

(8) Treatment of a vinylogous acid chlorides with acids or bases in alcoholic solvents always produced some amount of exchange product.

(9) Throughout the course of our investigations, additional attention was required for the work-ups and isolations of pyridine containing compounds, especially when transition metals were used and when substrates contained acidic functional groups. This caveat was increasingly important when the substrate in question contained an acid labile group and the reaction produced a pyridine–metal complex that required an acidic work-up.

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CHAPTER 4

COMPLEMENTARY DIASTEREOSELECTIVE ALKYLATIONS OF IMIDAZOLIDINONES

4.1 Introduction

During the course of our investigations into transiently directed C–H and C–C functionalizations, scaffold design and synthesis has been a primary concern. The judicious choice of structure and route increases the odds that the desired scaffold will both be synthesized and direct functionalization. Throughout our investigations, synthetic insights and innovations have been achieved to successfully engineer novel scaffolds. One of these findings was discovered by Erin Stache during her inquires into α-quaternary prolines toward transiently directing scaffolds for the functionalization of both sp^2 and sp^3 C–H bonds.[1] The synthesis of these α-quaternary prolines proved to be superior to other known methods. Fortunately, this provided a platform to investigate the origin of selectivity that results in an interesting complementary bifurcation of the stereochemical outcomes of these alkylations.

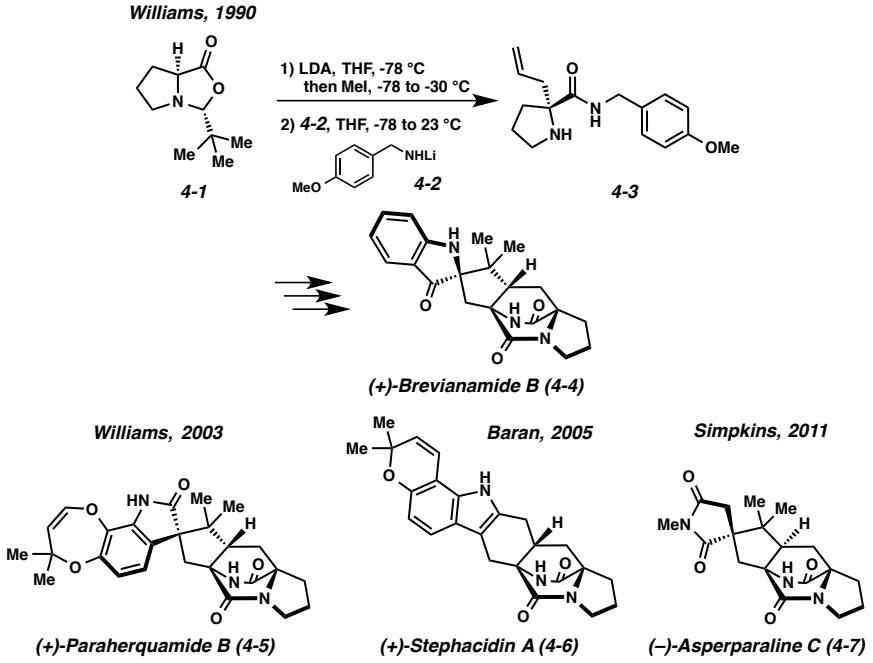
4.2 Applications of α-Quaternary Prolines

α-Quaternary proline-based amino acids and their derivatives are important compounds due to their application as catalysts and synthetic building blocks as well as in peptodimetic studies.[2] One of the most reliable methods for accessing this structural motif in enantioenriched form is the self-regeneration of stereocenters (SRS).[3,4] This strategy entails the attachment of a

temporary group that is used to govern the diastereoselectivity of a subsequent transformation. The removal of that group produces a single enantiomer.

The SRS strategy has been used to produce enantiopure starting materials in numerous total syntheses. Williams utilized this method to generate α-quaternary prolinamide **4-1** as the single source of chirality in his asymmetric synthesis of (+)-brevianamide B (**4-4**) (Scheme 4.2.1),[5] and it was later implemented again in his synthesis of paraherquamide B (**4-5**).[6] Baran and Simpkins also used identical alkylation approaches to install the necessary stereochemistry in their similar syntheses of (+)-stephacidin A (**4-6**)[7] and the core of (–)-asperparaline C (**4-7**)[8], respectively.

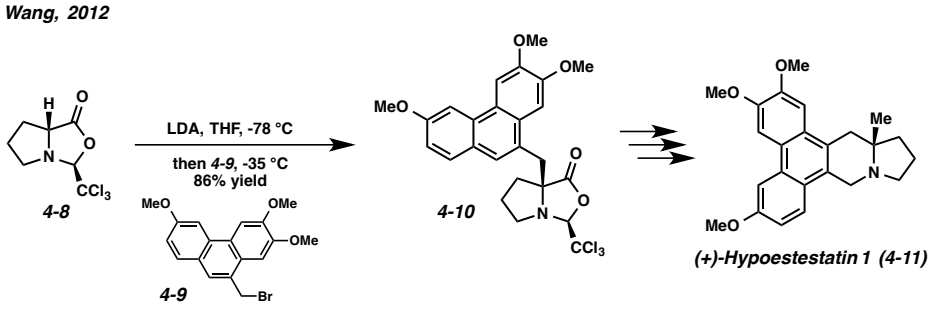
Scheme 4.2.1. Use of SRS Chemistry Toward Complex Alkaloids



Significant developments in this methodological approach have been reported with respect to the alkylation of prolines. Germanas replaced the *tert*-butyl group for a trichloromethyl group, which imparted oxidative stability of these oxazolidinones.[9] These could be alkylated with identical diastereoselective fidelity. Wang implemented this methodological advance in the

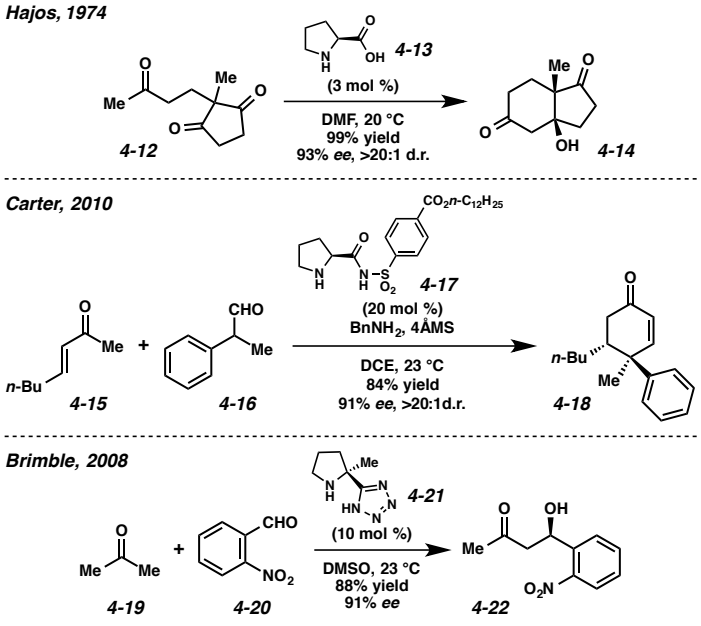
synthesis of the cytotoxic natural product hypoestestatin (**4-11**) (Scheme 4.2.2).[10] Brimble has also utilized this strategy in the synthesis of neuroprotective tripeptide GPE and its analogs.[11]

Scheme 4.2.2. Use of SRS Chemistry Toward Hypoestestatin 1 (**4-11**)



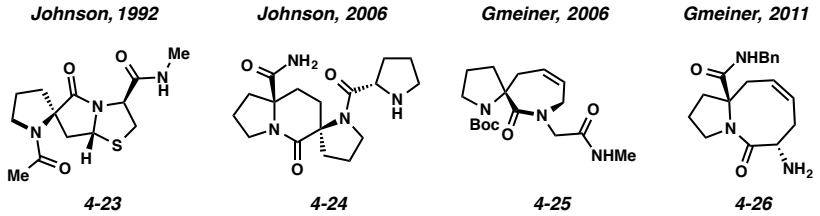
The use of α-quaternary alkylated proline analogs as catalysts is relatively rare; however, proline[12] and prolinamides[13] have been used to develop stereoselective transformations of spectacular utility (Scheme 4.2.3). To address the issue of catalyst decomposition in proline catalysis, Brimble designed a proline-based α-methyl aldol catalyst with a tetrazole H-bonding unit (**4-21**), which, to my knowledge, is the only α-alkylated proline-catalyst yet reported.[14]

Scheme 4.2.3. Proline-Derived Enantioselective Organocatalysis



This method has been used to produce structural mimics of type II β-turns (**4-23–4-26**) found in many bioactive peptides (Figure 4.2.1).[15] The structural rigidity imparted by constraining these alkylated units restricts rotation around numerous torsional angles. These tripeptide analogs have been used in conformational structure activity relationships.

Figure 4.2.1. Structural Mimics of Type II β-Turns for Peptodimetic Studies



4.3 *Syn*-Selective Alkylations of Prolinamide Derived Imidazolidinones

As mentioned above, our group previously explored the development of proline-derived scaffolds capable of directed C–H functionalization. Imidazolidinones **4-28** and **4-31** were capable of directed C–H acetoxylations and alkenylations (Scheme 4.3.1).[1] These stereochemical transformations may be controlled by enantiopure scaffolds, and the stereoselective generation of these scaffolds is predicated on the stereochemical fidelity of L-proline. The implementation of SRS with respect to these scaffolds generates imidazolidinones in phenomenal diastereoselectivity.

We viewed this alkylation strategy as a general approach to accessing compounds of the α-alkylated amino amide motif. The scope of this procedure was investigated with numerous different alkylating agents (Table 4.3.1). In all cases, only the 1,3-*cis* diastereomers were observed, and most were afforded in good yield. Both *N*-phenyl and *N*-*n*-butyl amides were investigated, and although the phenyl amides generally afforded better yields, the nature of this group was inconsequential to diastereoselectivity.

Scheme 4.3.1. Alkylation and Functionalization of Imidazolidinones

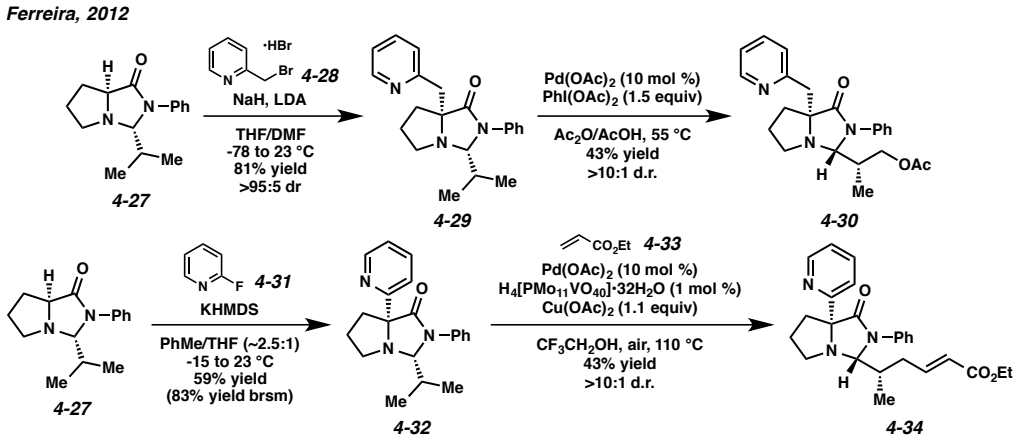
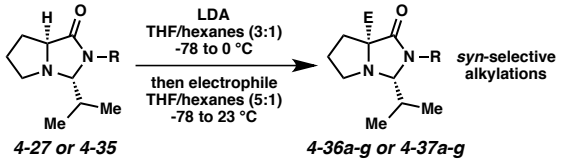
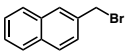


Table 4.3.1. The Scope of the *syn*-Selective Alkylations



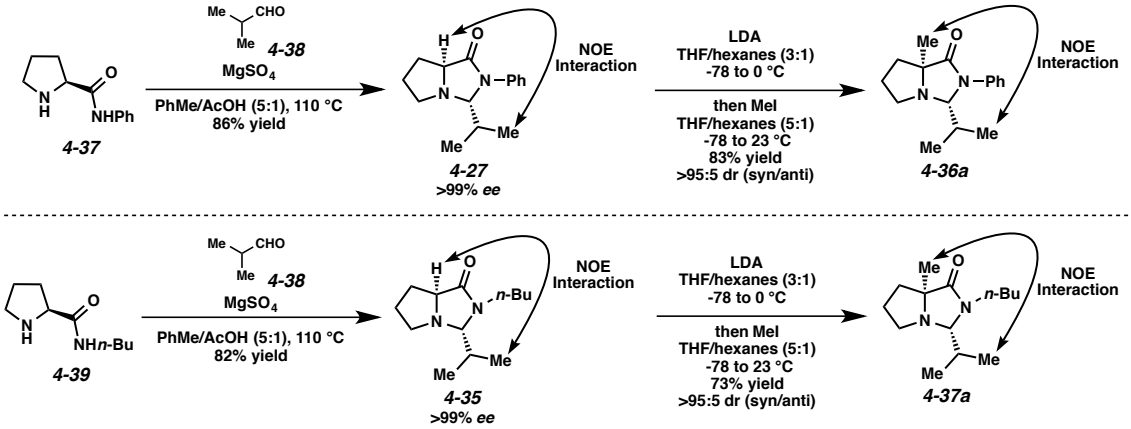
Entry	R	Electrophile	Product	Alkylation dr (syn/anti)[a]	% yield[b]
1	Ph	MeI	*4-36a*	>95:5	83
2	*n*-Bu	MeI	*4-37a*	>95:5	73
3	Ph	BnBr	*4-36b*	>95:5	91
4	*n*-Bu	BnBr	*4-37b*	>95:5	85
5	Ph	*n*-BuBr	*4-36c*	>95:5	77
6	*n*-Bu	*n*-BuBr	*4-37c*	>95:5	83
7	Ph		*4-36d*	>95:5	82
8	*n*-Bu		*4-37d*	>95:5	74
9	Ph		*4-36e*	>95:5	95
10	*n*-Bu		*4-37e*	>95:5	62
11	Ph		*4-36f*	>95:5	76
12	*n*-Bu		*4-37f*	>95:5	31
13[c]	Ph		*4-36g*	>95:5	92
14[c]	*n*-Bu		*4-37g*	>95:5	64

a) Diastereomeric ratio measured by ^{1}H NMR. b) Isolated yield of the cis diastereomer. c) LiCl (1.1 equiv) added.

The assignment of the reactions' diastereoselectivity needed to be determined. Imidazolidinones **4-27** and **4-35** were synthesized under acidic conditions; no epimerization was

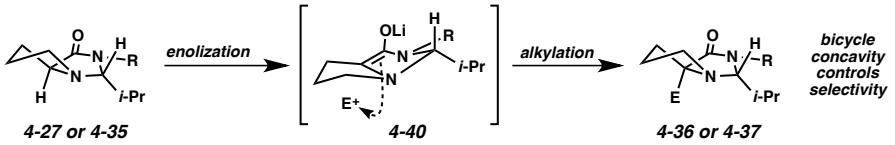
observed at the α-center (i.e., enantiopure products were isolated) (Scheme 4.3.2). An NOE interaction was observed between the highlighted protons of these imidazolidinones, identifying these products as the exo diastereomers. The corresponding endo diastereomers were never observed. These *syn*-alkylated products also showed NOE interactions between the α-methyl groups and the isopropyl groups.

Scheme 4.3.2. SRS Chemistry of Isopropyl Imidazolidinones



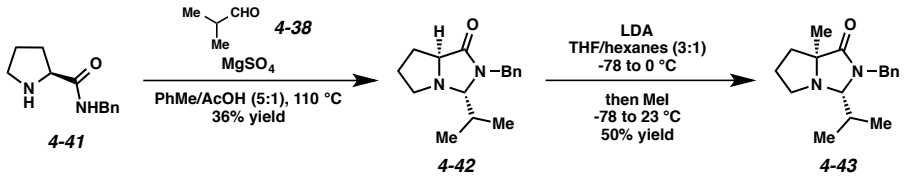
This alkylation is aligned with transformations of proline derived *N,O*-acetals and the origin of the stereochemical outcome can be understood through a similar rationale. The diastereoselectivity is derived from the steric influence of the isopropyl group (Figure 4.3.1). The enolate **4-40**, in its all-staggered orientation of the substituents across the N–C–N bonds position the pyrrolidine above the enolate plane.[16] Pyramidalization of both nitrogens of the imidazolidinone should occur upon enolization.[17] As the alkylating agent approaches the sp^2-hybridized enolate, the carbon begins to pyramidalize toward forming a *cis*-fused bicycle.[18] The isopropyl moves toward being situated on the convex face. This avoids steric congestion on the concave side of the bicycle.

Figure 4.3.1. Rationale of the *syn*-Selective Alkylation



To expand the scope of this reaction, we investigated the alkylation of *N*-benzyl imidazolidinones, with the expectation that the benzyl group could be removed by hydrogenolysis to access primary amides. We subjected bicycle **4-42** to the alkylation conditions, but the reaction showed substantial decomposition and afforded product in only 50% yield (Scheme 4.3.3).

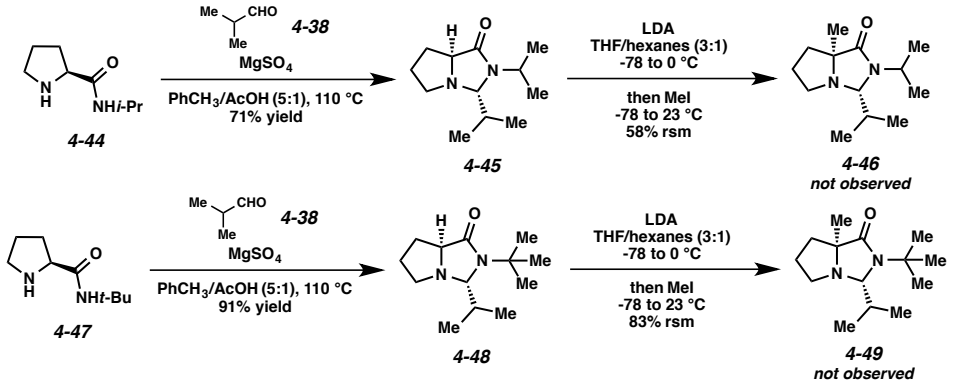
Scheme 4.3.3. Attachment and Alkylation of Benzyl Amides



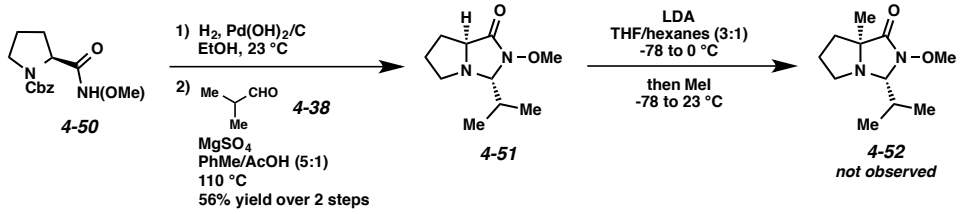
We also investigated imidazolidinones with α-branching off the amide (Scheme 4.3.4). Generations of these bicycles were performed in good yields. However, alkylations were not observed in when isopropyl or *tert*-butyl imidazolidinones (**4-45** or **4-48,** respectfully) or group were used. This branching likely inhibits the approach of the LDA to α-deprotonate the substrate; alternatively, it may discourage the enolate from undergoing alkylation.

Weinreb amide-like imidazolidinone **4-51** was envisioned to both alkylate and except nucleophiles to produce α-alkylated proline-ketones. It was obtained from Cbz-prolinamide **4-50** by hydrogenation and subsequent condensation (Scheme 4.3.5). This compound was subjected to the alkylation conditions, but imidazolidinone **4-52** was not observed and instead there was complete decomposition.

Scheme 4.3.4. Attachment and Alkylation of Isopropyl and *t*-Butyl Amides

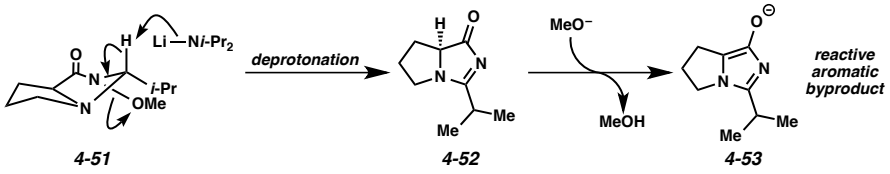


Scheme 4.3.5. Attachment and Alkylation Attempt of Methoxy Amides



This deleterious pathway possible proceeds through an E_2 elimination (Figure 4.3.2). Methoxide deprotonation of the resulting intermediate **4-52** would afford aromatic enolate **4-53**, which could be nucleophilic and therefore alkylate at a number of sites.

Figure 4.3.2. Potential Mechanism of Decomposition for Imidazolidinone **4-51**

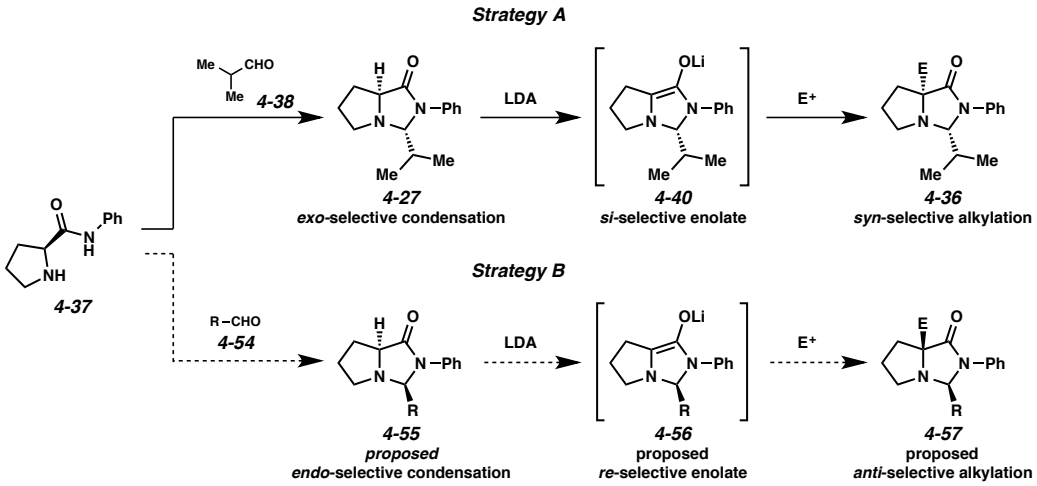


4.4. *Anti*-Selective Alkylations of Prolinamide Derived Imidazolidinones

During the course of our investigation into the *syn*-selective alkylation of imidazolidinones, we questioned the potential to access the opposite enantiomeric series through an alternative SRS strategy. Although the simplest approach would be to apply the same sequence described above to D-proline, this enantiomer is appreciably more expensive.

Additionally, a stereodivergent strategy has the potential to access enantioenriched diastereomers of quaternary-alkylated proline analogs (e.g., 4-hydoxy-L-proline, etc.) whose enantiomers are non-natural or are not readily available. As described above, the standard proline-SRS strategy, *Strategy A*, proceeds through an *exo*-selective condensation followed by a *syn*-selective alkylation (**4-27**→**4-36**, Figure 4.4.1). An alternative sequence, *Strategy B*, was envisaged where an *endo*-selective condensation would be followed by a *syn*-selective alkylation (**4-55**→**4-57**) affording imidazolidinones that could be converted to the enantiomeric amino amides of *Strategy A*.

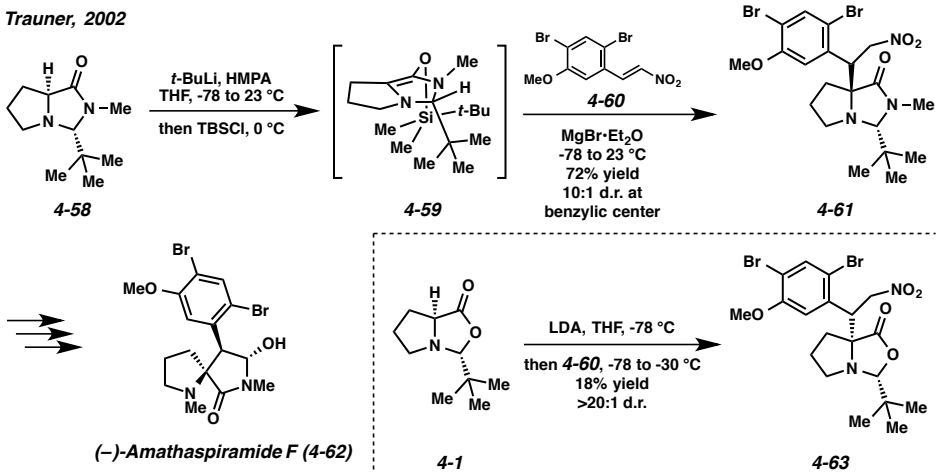
Figure 4.4.1. Proposed Sterevodivergent Strategies for Accessing Enantiomeric Series of α-Quaternary Amino Amides via SRS



Once again, Seebach's SRS with proline based *N,O*-acetals affords *cis*-alkylated products. We became aware of an interesting reversal in this selectivity with prolinamides observed by Trauner during his synthesis of (–)-amathaspiramide F (**4-62**).[19] They generated silyl enol ether **4-59** and treated it with nitroolefin **4-60** to afford the alkylated product **4-61** with inversion at the α-center (Scheme 4.4.1).[20] It was proposed that the *tert*-butyl group forces the methyl group up and therefore the bulky silyl group down. This orientation blocks the bottom face of the bicycle and forces alkylation from above. They produced the *syn*-product in low yield

through a conjugate addition of the lithium enolate (**4-1**→**4-63**). This study made us aware that we would have to be careful in our stereochemical analysis of these amide enolates while attempting to successfully implement *Strategy B*.

Scheme 4.4.1. Trauner's Example of an *anti*-Selective Alkylation with Imidazolidinone **4-58**

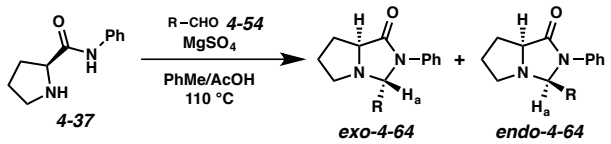


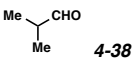
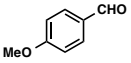
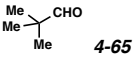
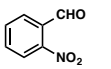
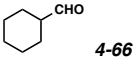
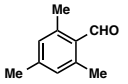
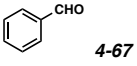
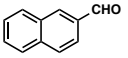
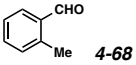
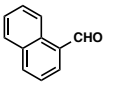
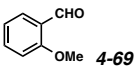
The success of *Strategy B* is predicated on both the potential to obtain *endo*-imidazolidinones and for these to dictate the diastereoselectivity of subsequent alkylations. It was assumed that endo imidazolidinones could be obtained by modifying either the temporary group (i.e., different aldehydes may favor the endo imidazolidinones) or the reaction conditions. Given both of those viable options, we decided to initially screen amide **4-37** with several aldehydes to produce a series of different imidazolidinones (Table 4.4.1). The imidazolidinones obtained from isobutyraldehyde (entry 1) and benzaldehyde (entry 4) through the described conditions are known to be both exo isomers. We suspected that imidazolidinones with alkyl or aryl temporary groups whose aminal hydrogen's ^{1}H NMR signal significantly deviates from 4.63 ppm (entry 1) and 5.68 ppm (entry 4), respectively, would indicate the endo diastereomer.

The products derived from the alkyl aldehydes all had signals that were similar to that of entry 1 and were therefore the process was determined to be *exo*-selective. This was not unexpected since pivaloyl and cyclohexyl are groups bulkier than the isopropyl group.

Attachment of aryl aldehydes afforded products with signals slightly more upfield (between 5.68-6.11 ppm). However, the condensation of amide **4-37** with naphthaldehyde (**4-74**) (entry 11) produced imidazolidinone **4-64** with an aminal signal at 6.49 ppm, which is 0.38 ppm more downfield than the next most downfield signal and 0.50 ppm more downfield than the average signal for aryl-temporary groups of 5.99 ppm (entry 4-6, 10, 11). This dramatic difference in the aminal hydrogen's chemical shift led us to tentatively assign it as the *endo*-imidazolidinone.

Table 4.4.1. Differential Aldehyde Condensation Toward the *endo*-Diastereomer

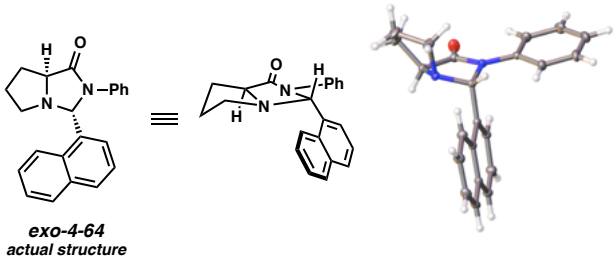


Entry	Aldehydes	H_a ^{1}H NMR δ	Entry	Aldehydes	H_a ^{1}H NMR δ
1	 4-38	4.63	7	 4-70	no aminal observed
2	 4-65	4.47	8	 4-71	significant decomposition
3	 4-66	4.58	9	 4-72	no aminal observed
4	 4-67	5.68	10	 4-73	5.82
5	 4-68	5.87	11	 4-74	6.49
6	 4-69	6.11			

We subjected imidazolidinone **4-64** to the alkylation conditions and ultimately determined that the alkylation of this imidazolidinone proceeded with inversion at the α-carbon compared to *N,O*-aminal alkylations (*vide infra*). This was suggestive that we had achieved our desired *endo*-selective condensation/*cis*-selective alkylation process. To confirm this sequence of events, we characterized imidazolidinone **4-64** by X-ray diffraction and were surprised that this imidazolidinone was actually in the exo confirmation (Figure 4.4.2). Therefore, our above NMR

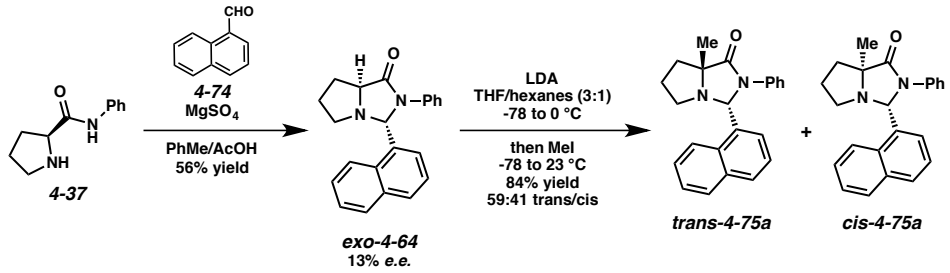
prediction for determining the endo imidazolidinones was incorrect, but it was successful in identifying a useful imidazolidinone to achieve a divergent alkylation process.

Figure 4.4.2. X-Ray Characterization of Imidazolidinone ***exo*-4-64**



Amide **4-37** and 1-naphthaldehyde (**4-74**) were condensed to afford *exo*-imidazolidinone **4-64** in 13% e.e. (Scheme 4.4.2). The subsequent alkylation afforded imidazolidinone **4-64** in 59:41 d.r. favoring the trans product. Despite the initial success in encouraging a divergent alkylation, the fidelity of the α-center needed to be conserved during imidazolidinone condensation and the diastereoselectivity of the alkylation had to be enhanced.

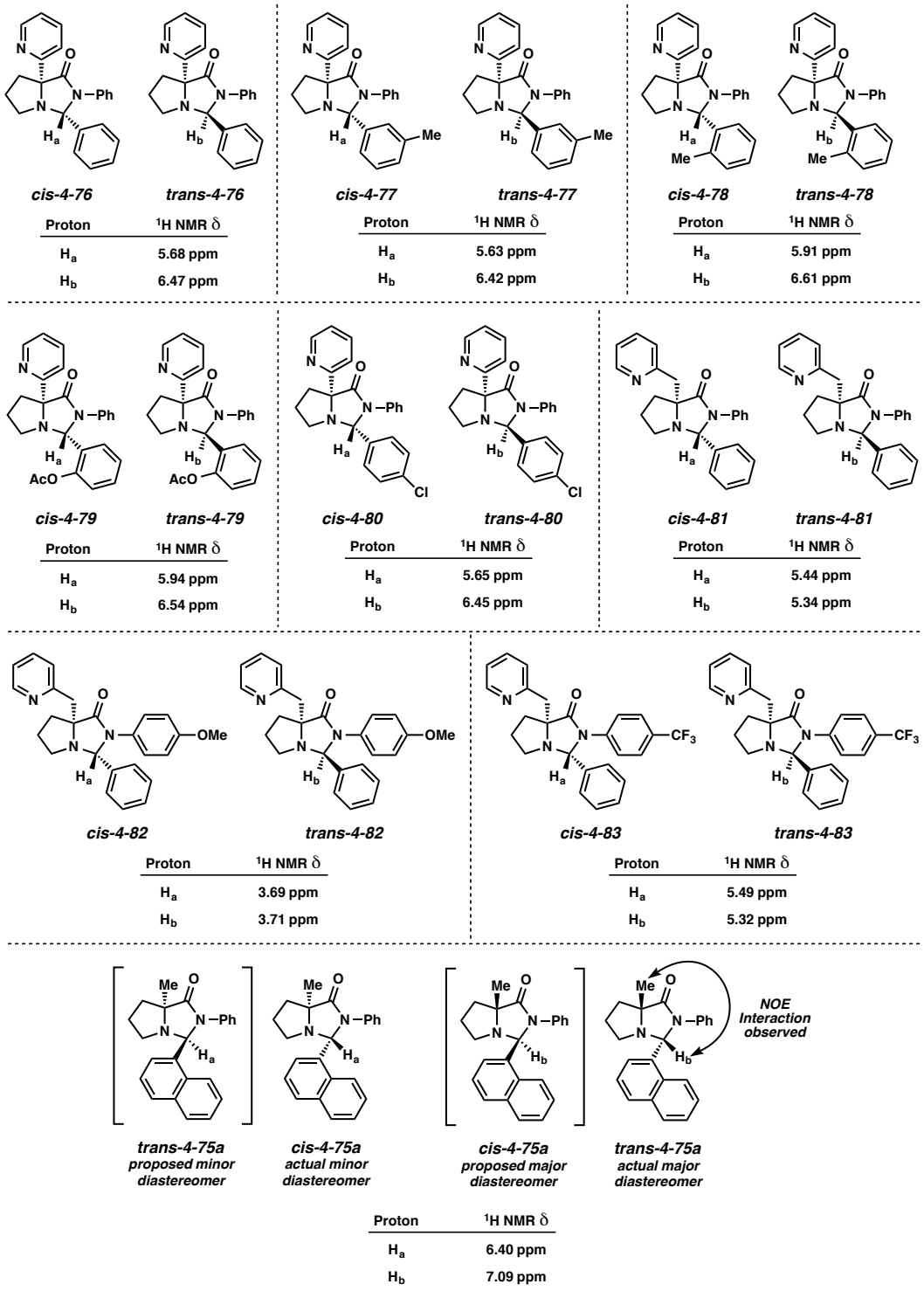
Scheme 4.4.2. Initial Alkylation of *exo*-Imidazolidinone **4-37**



To simplify our initial identification of the cis and trans diastereomers, we compared diagnostic aminal signals of numerous α-quaternary imidazolidinones synthesized previously in our laboratory (Figure 4.4.3).[1] In general, trans imidazolidinones' average aminal ^{1}H NMR signal was 6.06 ppm (0.43 ppm more downfield than trans imidazolidinones average aminal ^{1}H NMR signal of 5.63 ppm). There are two examples where the cis diastereomers' signal is more downfield (imidazolidinones **4-81** and **4-83**); however, the difference between the cis and trans

diastereomer's signals of these two imidazolidinones are relatively small (0.10 ppm and 0.17 ppm) respectively. Using this diagnostic method to analyze the alkylation of Scheme 4.4.2 was useful in assigning the major product as the trans imidazolidinone. Additionally, an NOE interaction was observed for imidazolidinone ***trans*-4-75a** but not imidazolidinone ***cis*-4-75a**.

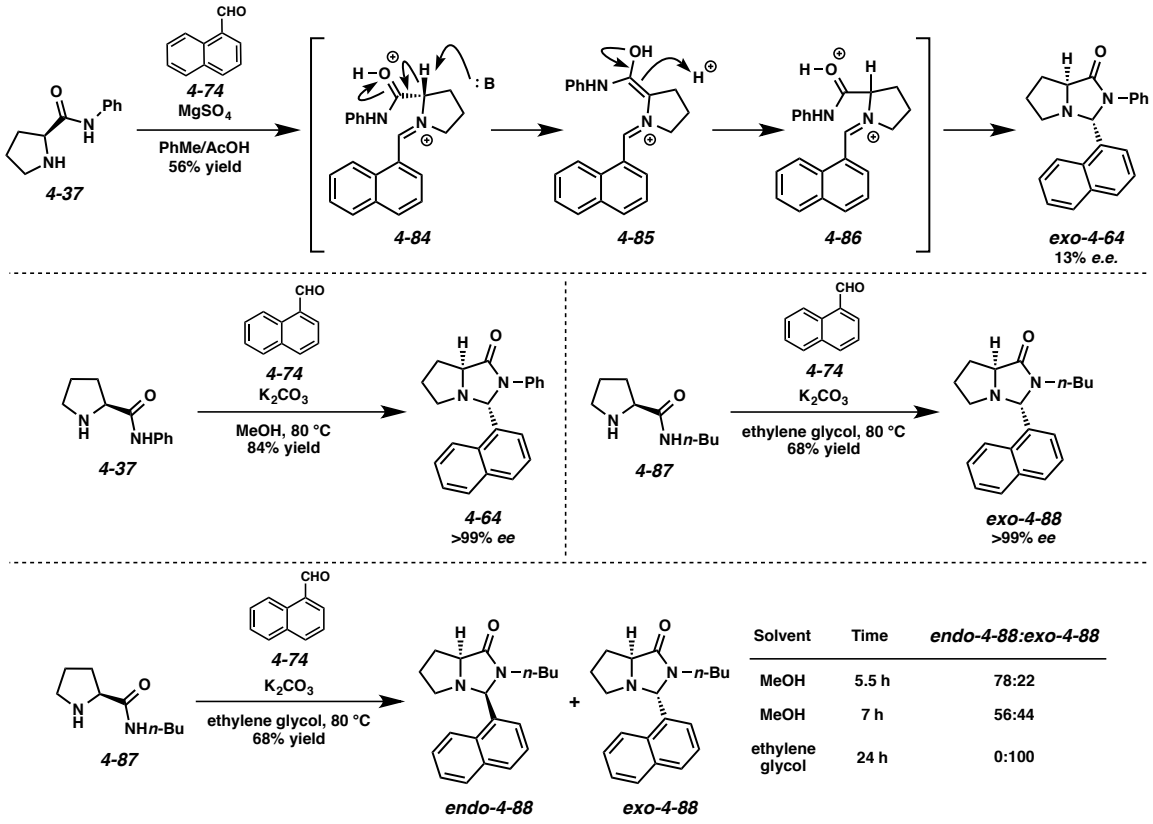
Figure 4.4.3. α-Quaternary Imidazolidinone Diagnostic Signals for Diastereomeric Analysis



To produce a desirable SRS strategy, we needed to fix the stereochemical erosion of naphthyl attachment. We observed epimerization under acidic attachment conditions (Scheme

4.4.3). Likely, this occurs through the formation of an iminium (**4-85**) acidifying the α-proton and leading to racemization. We suspected basic conditions would circumvent this problem. Methanolic K_2CO_3 achieved condensation without any epimerization. Interestingly, in the case of the *N*-*n*-Bu amide, the condensation is initially selective for the *endo*-product. Upon further heating, the reaction mixture can be fully converted to *exo*-imidazolidinone **4-88** as the thermodynamic product.[21] Further attempts were unfruitful in obtaining a highly *endo*-selective condensation.

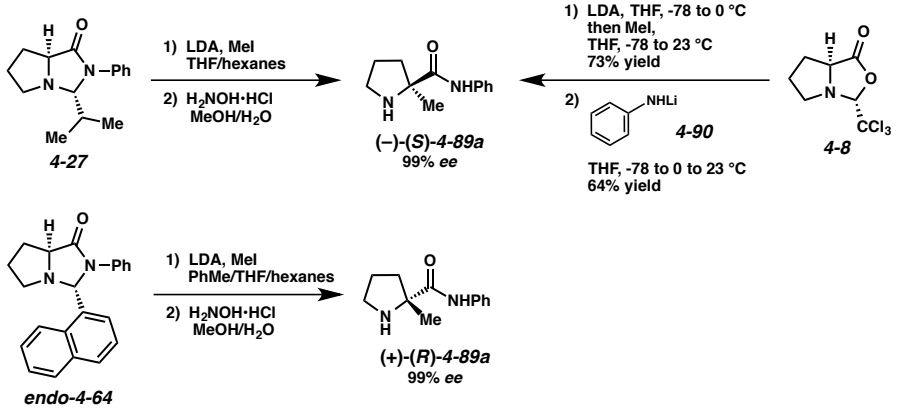
Scheme 4.4.3. Basic Attachment of 1-Naphthaldehyde with Prolinamides



In pursuit toward conclusive evidence of the stereochemical outcome obtained through our procedure, we compare the differences between these *syn*- and *anti*-selective alkylations (Scheme 4.4.4). The configuration of isopropyl-imidazolidinone products were determined to be cis when compared to a known method of alkylating *N*,*O*-oxazolidinone **4-8**, and both methods

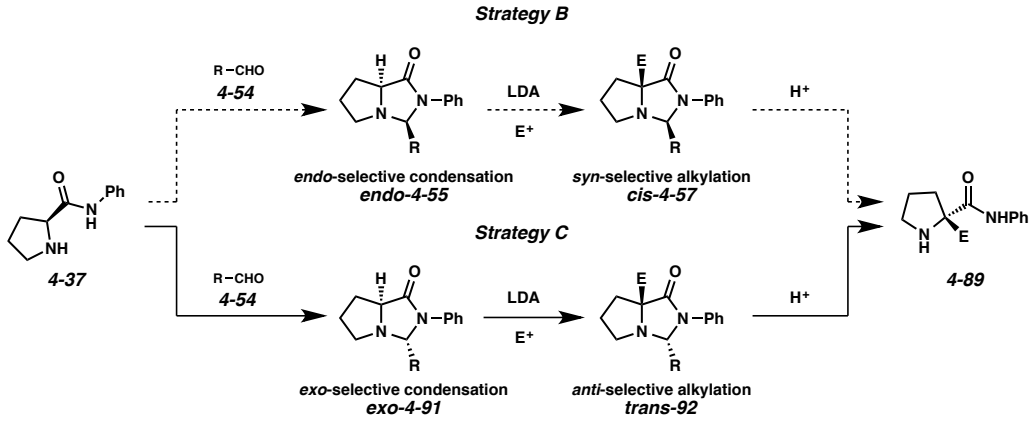
generate α-quaternary amino amide **(–)-(*S*)-4-89a** with identical rotations. The configuration of 1-naphthyl-imidazolidinone products produced amino amides with the opposite rotation. Due to these observations, we were confidant that the naphthyl-imidazolidinone alkylations were preceding through an *anti*-selective alkylation.

Scheme 4.4.4. Determination of Absolute Stereochemistry of α-Alkylated Prolinamides



At this point, we had all the necessary information to reevaluate our method and produce a useful SRS strategy. *Strategy B* has been shown not to be operable (Figure 4.4.4). Although we initially pursued an *endo*-selective condensation and this product would then favor a *syn*-selective alkylation, our discovered method went through a different sequence. Instead, we had identified an *exo*-selective condensation, and the temporary group actually encourages an *anti*-selective alkylation (*Strategy C*).

Figure 4.4.4. Reevaluation of Our Stereo-Reversal Strategy



We were hopeful that we could improve this modestly *anti*-selective alkylation. As we were determining the stereochemical consequences of the condensation and alkylation, we were simultaneously optimizing the diastereoselectivity (Table 4.4.2). Decreasing the deprotonation time (entry 2) compared to the standard conditions (entry 1) showed a modest decrease in conversion. However, keeping the deprotonation step at -78 °C dramatically affected conversion (entry 3). Holding the deprotonation step at 0 °C for 8 h enhanced diastereoselctivity modestly (entry 4), but significant starting material was observed. This might suggest a gradual change in the reactive enolate. The addition of the electrophile at temperatures lower than -98 °C significantly increased the dr of the reaction (entries 5 and 6, 70:30 and 65:35 anti/syn dr, respectively) compared to the standard conditions (entry 1, 54:46 anti/syn). The addition of LiBr or solvent additives to encourage solvent monomers (e.g., HMPA and DMPU) (entries 7, 8, and 9) did not dramatically affect dr. Surprisingly, LHMDS and KHMDS bases did not afford any products (entries 11 and 12). It may be that these bases are slightly too bulky to produce enolization. Suspiciously, the addition of dimethyl sulfate reversed the selectivity of the reaction and generated the alkylated product in 24:76 anti/syn ratio (entry 13). When water was used as the electrophile, pure imidazolidinone ***exo*-4-64** was converted to a mixture in 66:34 dr favoring

the exo diastereomer. Curiously, this *syn*-selective protonation affords selectivity similar to that obtained when dimethyl sulfate is used. The use of larger alkyl halide electrophiles increased the selectivity for the trans product (entries 15, 16, 17), and when BnBr was used, only the trans diastereomer was observed (entry 18). In the context of alkylations with MeI, the addition of either Et_2O or toluene increased the dr (entries 19 and 20). The use of toluene could afford methylated imidazolidinone ***trans*-4-75a** in 53% isolated yield, an improvement compared to the standard conditions, in which it was produced in 44% isolated yield (Scheme 4.4.5).

Scheme 4.4.5. Improvement in Diastereoselectivity with *exo*-Imidazolidinone Alkylations

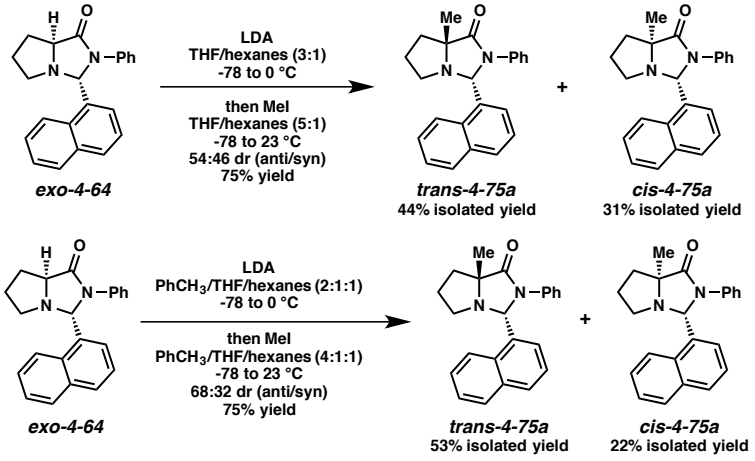
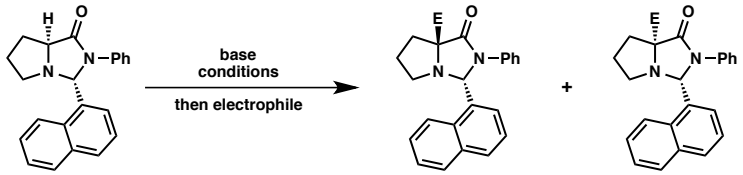


Table 4.4.2. Condition Screen to Optimize the *anti*-Selective Alkylation



endo-4-64

trans-4-75a-d or *endo-4-64* E = Me, Bu, allyl, Bn, H

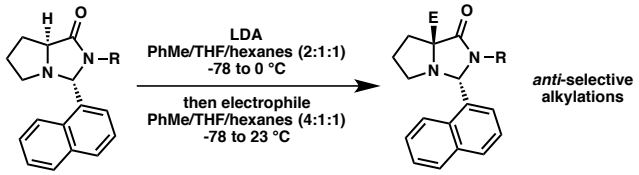
cis-4-75a-d or *exo-4-64* E = Me, Bu, allyl, Bn, H

Entry	Conditions	Product	Product/SM[a]	anti/syn[a]
1	LDA (1.1 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), THF/hexanes (5:1), -78 to 23 °C	*4-75a*	100/0	54:46
2	LDA (1.05 equiv), THF/hexanes (3:1), -78 to 0 °C, *20 min*; then MeI (1.05 equiv), -78 to 23 °C	*4-75a*	92/8	61:39
3	LDA (1.05 equiv), THF/hexanes (3:1), -78 °C, *140 min*; then MeI (1.05 equiv), -78 to 23 °C	*4-75a*	59/40	61:39
4	LDA (1.05 equiv), THF/hexanes (3:1), -78 to 0 °C, *8 h*; then MeI (1.05 equiv), -78 to 23 °C	*4-75a*	50/50	68:32
5	LDA (1.00 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), *-98 to 23 °C*	*4-75a*	93/7	70:30
6	LDA (1.05 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), THF/hexanes (5:1), *-100 to 23 °C*	*4-75a*	91/9	65:35
7	LDA (1.00 equiv), *LiBr* (1.00 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), -78 to 23 °C	*4-75a*	66/34	59:41
8	LDA (1.05 equiv), *HMPA* (4.2 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), THF/hexanes (5:1), -78 to 23 °C	*4-75a*	84/16	56:44
9	LDA (1.05 equiv), *DMPU* (4.2 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), THF/hexanes (5:1), -78 to 23 °C	*4-75a*	93/7	51:49
10	LDA (1.05 equiv), THF/hexanes (3:1), *-78 to 23 °C*, 70 min; then MeI (1.05 equiv), THF/hexanes (5:1), -78 to 23 °C	*4-75a*	95/5	60:40
11	*LHMDS* (1.1 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), -78 to 23 °C	*4-75a*	0/100	—
12	*KHMDS* (1.05 equiv), THF/PhMe (~1:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), -78 to 23 °C	*4-75a*	0/100	—
13	LDA (1.1 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then *Me_2SO_4* (1.05 equiv), -78 to 23 °C	*4-75a*	100/0	24:76
14	LDA (1.1 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then *H_2O* (1.05 equiv), -78 to 23 °C	*4-64*	—	34:66[b]
15	LDA (1.00 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then *n-BuBr* (1.05 equiv), -78 to 23 °C	*4-75c*	93/7	80:20
16	LDA (1.1 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then *n-BuI* (1.05 equiv), THF/hexanes (5:1), -78 to 23 °C	*4-75c*	100/0	76:24
17	LDA (1.05 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then *allyl iodide* (1.05 equiv), -78 to 23 °C	*4-75d*	100/0	70/30
18	LDA (1.05 equiv), THF/hexanes (3:1), -78 to 0 °C, 70 min; then *BnBr* (1.05 equiv), THF/hexanes (5:1), -78 to 23 °C	*4-75b*	91/9	100:0
19	LDA (1.05 equiv), *Et_2O/THF/hexanes* (2:1:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), *Et_2O/THF/hexanes* (4:1:1), -78 to 23 °C	*4-75a*	100/0	69:31
20	LDA (1.05 equiv), *PhMe/THF/hexanes* (2:1:1), -78 to 0 °C, 70 min; then MeI (1.05 equiv), *PhMe/THF/hexanes* (2:1:1), -78 to 23 °C	*4-75a*	100/0	72:28

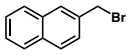
a) The product/starting material ratio and anti/syn ratio were determined by ^{1}H NMR analysis of the unpurified reaction mixture without the use of an internal standard. b) This number relates to the endo/exo ratio instead of the anti/syn ratio.

We investigated the scope of the *anti*-selective alkylation (Table 4.4.3). Only in the case of MeI with the *N*-phenylamide imidazolidinone (***trans*-4-75a**, entry 1) did we observe significant erosion in diastereoselectivity. Generally, diastereoselectivity was enhanced with greater electrophile size. In all cases, the diastereomers were chromatographically separable, and the trans products were obtained in good yields.

Table 4.4.3. The Scope of the *anti*-Selective Alkylations



endo-4-64 *trans-4-75a-g or trans-4-93a-g*

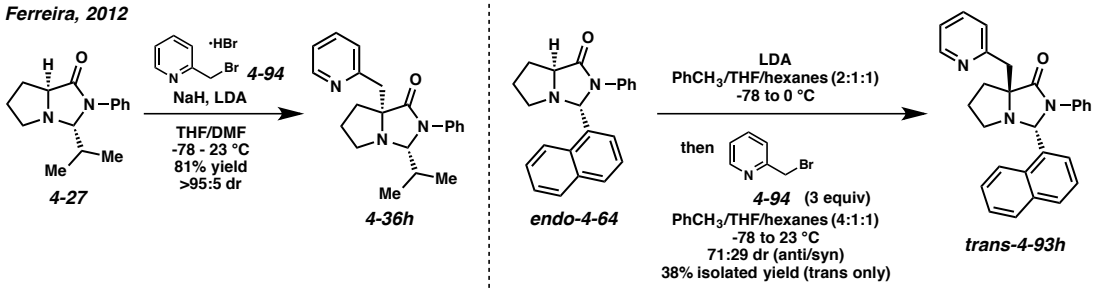
Entry	R	Electrophile	Product	Alkylation dr (anti/syn)[a]	% yield[b]
1	Ph	MeI	*trans-4-75a*	68:32	53
2	*n*-Bu	MeI	*trans-4-93a*	91:9	91
3	Ph	BnBr	*trans-4-75b*	92:8	66
4	*n*-Bu	BnBr	*trans-4-93b*	>95:5	90
5	Ph	BuBr	*trans-4-75c*	78:22	60
6	*n*-Bu	BuBr	*trans-4-93c*	>95:5	99
7	Ph		*trans-4-75d*	84:16	84
8	*n*-Bu		*trans-4-93d*	94:6	63
9	Ph		*trans-4-75e*	74:26	64
10	*n*-Bu		*trans-4-93e*	>95:5	93
11	Ph		*trans-4-75f*	91:9	77
12	*n*-Bu		*trans-4-93f*	92:8	69
13[c]	Ph		*trans-4-75g*	86:14	77
14[c]	*n*-Bu		*trans-4-93g*	>95:5	96

a) Diastereomeric ratio measured by ^{1}H NMR. b) Isolated yield of the trans diastereomer. [c] LiCl (1.1 equiv) added.

Imidazolidinones ***trans*-4-75g** and ***trans*-4-93g** are produced in good and excellent yield, respectively (Table 4.4.3) and have the opposite α-configuration compared to C–H

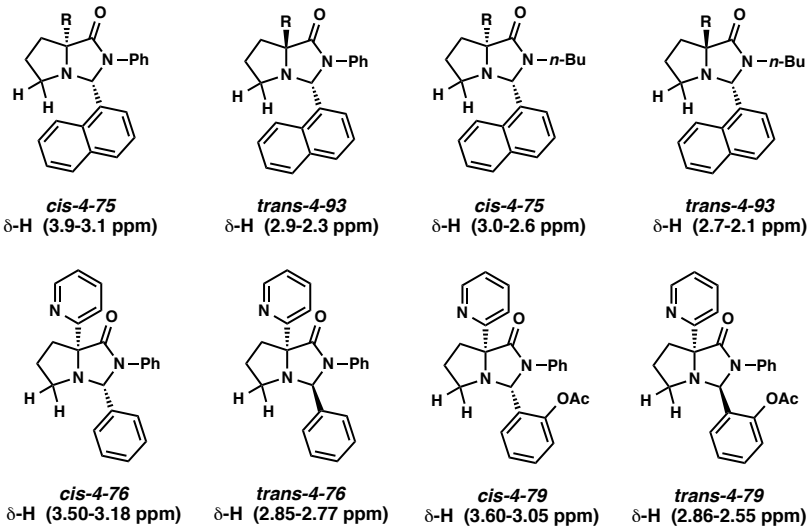
functionalization scaffold **4-36g**. The one-carbon homologated scaffold C–H functionalization scaffold **4-36h** can be produced in good yield by a modification of the *syn*-selective conditions (i.e., the addition of DMF and NaH) (Scheme 4.4.6). An attempt to generate the trans product was not as successful, and imidazolidinone ***trans*-4-93h** was generated in modest dr and in 38% yield.

Scheme 4.4.6. Imidazolidinone Alkylations with 2-(Bromomethyl)pyridine



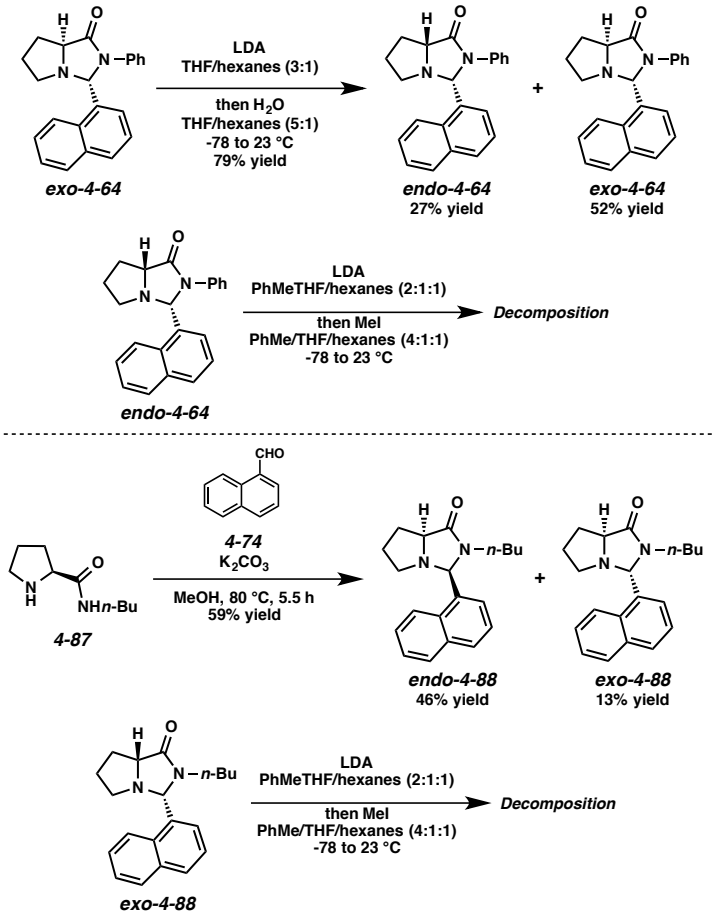
The proline δ-hydrogens of α-alkylated naphthyl imidazolidinone products were found to be highly diagnostic for identifying the cis and trans imidazolidinones as well as determining the diastereomeric ratio of crude alkylation mixtures (Figure 4.4.5). The cis imidazolidinone δ-hydrogens were consistently downfield compared to the corresponding trans imidazolidinone products. Our past work conforms to this analysis,[1] indicating that the δ-hydrogens of α-alkylated aryl imidazolidinones may be generally used to determine cis and trans configuration.

Figure 4.4.5. Diagnostic ^{1}H NMR Signals for Diastereomeric α-Alkylated Aryl Imidazolidinones



We were curious as to how the endo imidazolidinones would react under the alkylation conditions. Although we no longer needed to develop a SRS strategy with them since we had solved this question with our method, we still wanted to see if they would produce a *syn*-selective alkylation (i.e., *Strategy B*, Figure 4.4.4). The imidazolidinones ***endo*-4-64** and ***endo*-4-88** could be obtained from quenching the enolate of imidazolidinone ***exo*-4-64** and a kinetic condensation of amino amide **4-87** and 1-naphthaldehyde (**4-74**), respectively (Scheme 4.4.7). Both were subjected to the alkylation conditions, but instead completely decomposed. This is indicative of a general reactivity profile for these imidazolidinones. The exo products favor *anti*-alkylations and the endo products are unstable to those reaction conditions.

Scheme 4.4.7. Alkylation Attempts with *endo*-Imidazolidinones



Subsequent cleavage of the temporary group from these α-alkylated imidazolidinones would result in a convenient route to α-alkylated amino amides. An acid mediated aminolysis utilizing aniline (**4-95**) was previously developed by Erin Stache to cleave the temporary group from the proline-based functionalization scaffold affording α-alkylated amino amide **4-96d** in 70% yield (97% yield brsm) (Scheme 4.4.8).[1] Imidazolidinones ***cis*-4-36a-c** were subjected to the same conditions, and although effective in all cases, increased steric hindrance rendered the process difficult and resulted in diminished yields (Table 4.4.4). *Anti*-alkylated imidazolidinones ***trans*-4-75a-c** all unanimously reacted poorly under these conditions. These results were in stark contrast to the high stability observed for amino amide **4-96d**; this is probably due to a buffering

effect by the pyridine. It became obvious that a new cleavage method would be needed to - develop a general strategy for accessing enantiomeric pairs of α-alkylated amino amides.

Scheme 4.4.8. Temporary Group Cleavage of Pyridyl Imidazolidinone **4-36g**

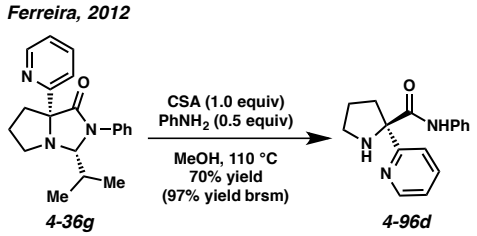
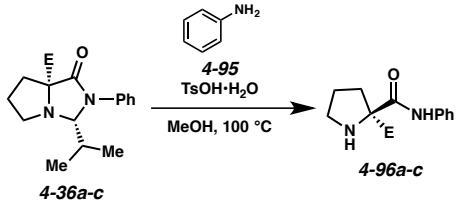
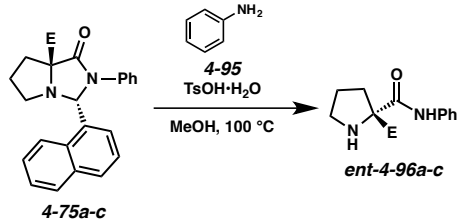


Table 4.4.4. Temporary Group Cleavage of *syn*- and *anti*-Alkylated Imidazolidinones





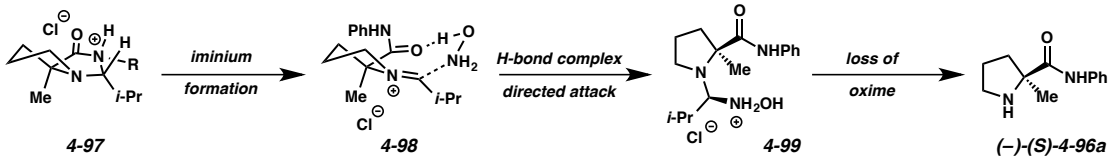
R	Substrate	E	Product	Yield (%)[a]	ee (%)[b]
1	*cis-4-36a*	Me	*(–)-(S)-4-96a*	83	99
2	*cis-4-36b*	Bn	*(+)-(R)-4-96b*	57 (73 brsm)	99
3	*cis-4-36c*	Bu	*(–)-(S)-4-96c*	55 (63 brsm)	99

R	Substrate	E	Product	Yield (%)[a]	ee (%)[b]
4	*trans-4-75a*	Me	*ent-(+)-(R)-4-96a*	62	99
5	*trans-4-75b*	Bn	*ent-(–)-(S)-4-96b*	69	99
6	*trans-4-75c*	Bu	*ent-(+)-(R)-4-96c*	55	99

a) Isolated Yields. b) Enantiomeric excess were determined by chiral HPLC.

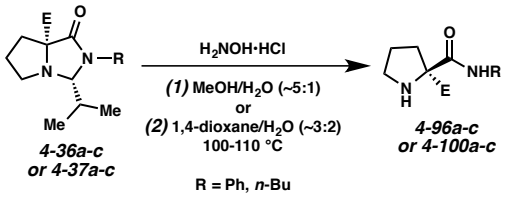
We hypothesized that using hydroxylamine would be more successful in accomplishing this cleavage. It is known to be highly nucleophilic, due to a significant α-effect, exhibiting substantially higher reactivity than amines of similar pK_a.[22] Interception of the presumed iminium (**4-98**) by hydroxylamine would result in the formation of labile aminal (**4-99**) further transforming to amino amide **(–)-(S)-4-96a**.[23, 24] Additionally, hydroxylamine has been implicated in the formation of H-bonding complexes to activate carbonyls.[25] This property is derived from the many H-bond donor and acceptor sites on the molecule, as well as unique H-bond geometries in relation to more common H-bonding reagents (e.g., water and ammonia). We envisioned an H-bond complex directed hydroxylamine attack (Figure 4.4.6).

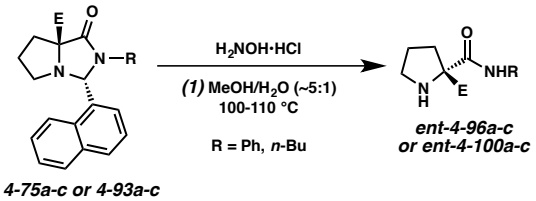
Figure 4.4.6. H-Bonding Rationale for Hydroxylamine Facilitated Aminal Cleavage



To our delight, hydroxylamine cleaved both *syn*- and *anti*- alkylated imidazolidinones in good to excellent yield (Table 4.4.5). Generally, *N*-phenyl and *N*-*n*-butyl amides reacted similarly, and aminolysis of trans imidazolidinones were moderately higher yielding than cis imidazolidinones. Benzyl alkylated products (entries 2, 5, 8, and 11) were afforded in slightly lower yields.

Table 4.4.5. Scope of Temporary Group Cleavage of *syn*- and *anti*-Alkylated Imidazolidinones





R	Substrate	Conditions	Product	Yield (%)[a]	R	Substrate	Conditions	Product	Yield (%)[a]
1	*cis-4-36a*	*(1)*, 100 °C	(–)-(*S*)-*4-96a*	>99	7	*trans-4-75a*	*(1)*, 100 °C	*ent*-(+)-(*R*)-*4-96a*	>99
2	*cis-4-36b*	*(1)*, 110 °C	(+)-(*R*)-*4-96b*	80	8	*trans-4-75b*	*(1)*, 110 °C	*ent*-(–)-(*S*)-*4-96b*	92
3	*cis-4-36c*	*(1)*, 110 °C	(–)-(*S*)-*4-96c*	>99	9	*trans-4-75c*	*(1)*, 110 °C	*ent*-(+)-(*R*)-*4-96c*	>99
4	*cis-4-37a*	*(1)*, 110 °C	(–)-(*S*)-*4-100a*	>99	10	*trans-4-93a*	*(1)*, 100 °C	*ent*-(+)-(*R*)-*4-100a*	98
5	*cis-4-37b*	*(2)*, 110 °C	(+)-(*R*)-*4-100b*	70	11	*trans-4-93b*	*(1)*, 100 °C	*ent*-(–)-(*S*)-*4-100b*	90
6	*cis-37c*	*(2)*, 110 °C	(–)-(*S*)-*4-100c*	88	12	*trans-4-93c*	*(1)*, 100 °C	*ent*-(+)-(*R*)-*4-100c*	99

a) Isolated yields.

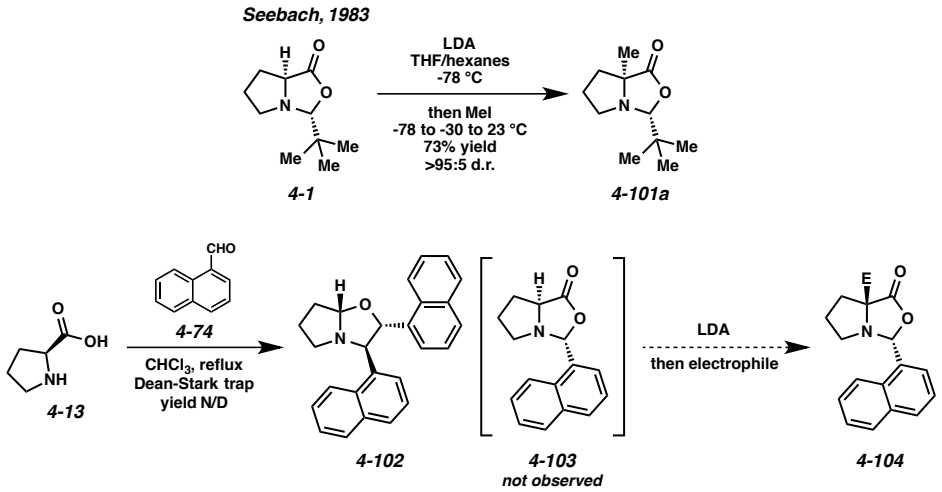
4.5. Investigations into the Origin of Diastereoselection

We were highly curious about the origin of diastereoselection. More specifically, we wanted to identify the contributing factors that produce this divergent stereochemical outcome during alkylations of imidazolidinones containing the 1-naphthyl group. The magnitude and direction of stereoselectivity for the *anti*-alkylations of *N*-phenyl or *N*-*n*-butyl amides were relatively consistent (Table 4.4.3), suggesting that arene-arene π interactions between the amide substituent and the temporary group are not primary contributors of selection.[26] The dramatic difference between the bulky isopropyl-group (*syn*-selective) and the less-sterically congested 1-naphthyl-group (*anti*-selective) led us to suspect that the 1-naphthyl group may be participating in an electrostatic interaction.

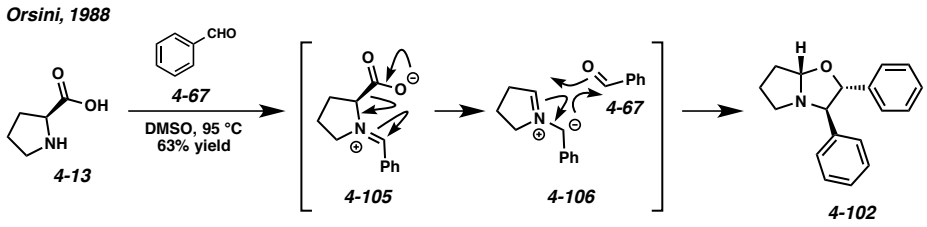
We questioned if this divergent behavior was operative during the alkylations of oxazolidinones. A more specific interest related to the effect the amide nitrogen substituent had on the overall alkylation. Notably in the Trauner example (Scheme 4.4.1), the addition of the methyl substitution on the amide nitrogen was suggested to have a subtle but substantial conformational effect, resulting in different enolate properties. We wanted to compare the alkylation of oxazolidinone **4-103** to the Seebach's highly *syn*-selective alkylation of oxazolidinone **4-1** (Scheme 4.5.1). Unfortunately, this experiment was unable to be performed due to the difficulty in isolating aryl oxazolidinones. Instead of generating oxazolidinone **4-103,** only aminal **4-102** was observed under the condensation conditions.

Orsini first observed this decarboxylative transformation, which is the result of a 1,3-dipolar cycloaddition between azomethine (**4-106**) and an aldehyde (**4-67**) (Scheme 4.5.2). Blackmond later reported on the conditions that facilitate this deleterious pathway in proline catalyzed aldol reactions.[27]

Scheme 4.5.1. Attempt to Investigate the *anti*-Alkylations of 1-Naphthyl Oxazlidinone **4-103**

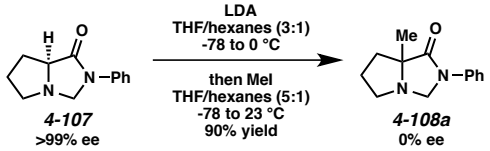


Scheme 4.5.2. Mechanistic Explanation of *N,O*-Aminal **4-102** Formation



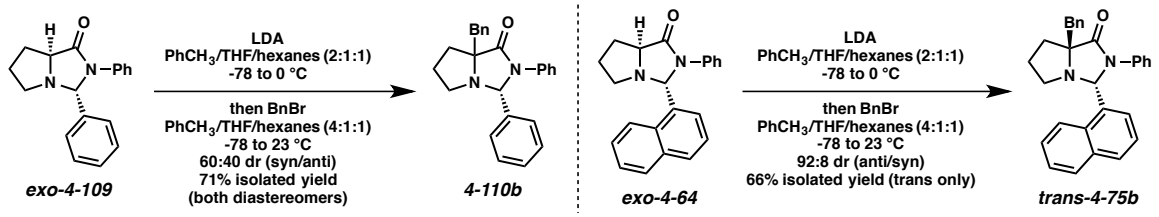
We questioned if a memory effect was operable in this stereochemical divergency.[28] We predicted this was an unlikely factor, but were unsure as to the degree the nitrogens could planarize as opposed to maintaining pyramidalization. To examine this hypothesis, we tested enantioenriched imidazolidinone **4-107**, lacking a governing group at the aminal position (Scheme 4.5.3). This substrate was alkylated with MeI affording a completely racemic product. Though this does not eliminate the possibility of a 'memory effect,' but this observation highly implicates planarization of the α-carbon prior to the addition of the electrophile.

Scheme 4.5.3. Alkylation of Imidazolidinone **4-107** Lacking a Stereocenter on the Temporary Group



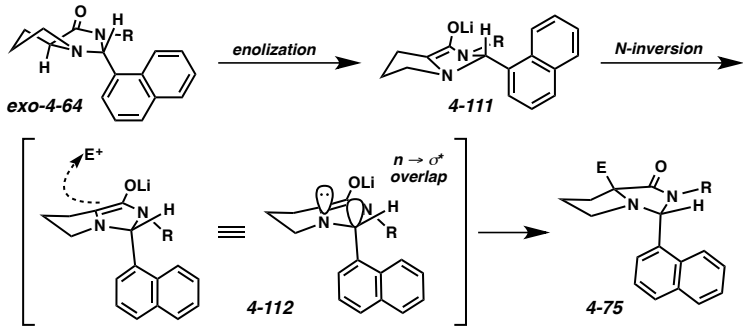
The nature of the aryl governing group would likely shed insight as to the origin of diastereoselectivity. We compared the alkylation of phenyl and 1-naphthyl imidazolidinones (***exo*-4-109** and ***exo*-4-64**, respectively) with benzyl bromide (Scheme 4.5.4). Phenyl imidazolidinone ***exo*-4-109** favored the syn product with a 60:40 dr. Dramatically, when the 1-naphthyl group was used, the dr was increased to 92:8 favoring the anti product.

Scheme 4.5.4. anti-Alkylation of Phenyl and 1-Naphthyl Imidazolidinones



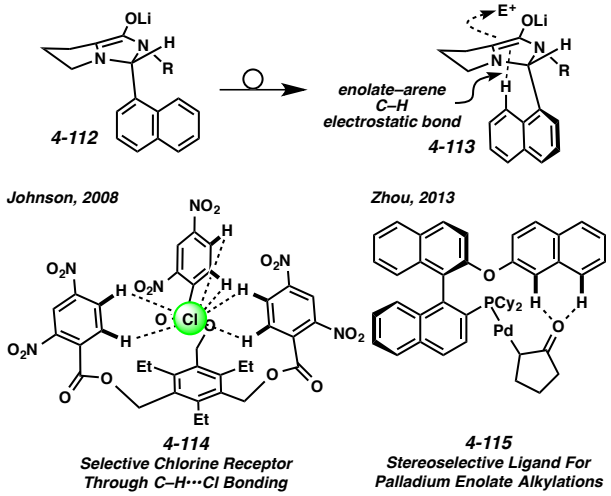
We have developed two models to explain the *anti*-selective alkylation of 1-naphthyl imidazolidinones. The first of these hypothesized that enolization would planarize the enolate carbon; this would be followed by inversion of the nitrogens (Figure 4.5.1). Delocalization of the nitrogen's lone pairs into the aminal C–C σ* orbital would produce conformation **4-112**. The 1-naphthyl-group would block an electrophile's approach from the bottom face, leading to an *anti*-selective alkylation. The alkylation of the phenyl imidazolidinone (***exo*-4-109→4-110b**) compared to the 1-naphthyl imidazolidinone (***exo*-4-64→*trans*-4-75b**) supports this analysis. The phenyl group should be less electron-withdrawing than the 1-naphthyl group.

Figure 4.5.1. Hyperconjugative Model to Explain the *anti*-Selectivity



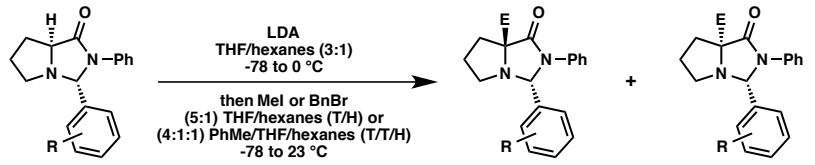
We have also considered an electrostatic interaction as the dictator of stereoselectivity. Specifically, if the 1-naphthyl ring was to rotate underneath the bicycle, then the modestly acidic naphthyl C-8 hydrogen could engage in a favorable interaction with the electron-rich enolate (**4-113**, Figure 4.5.2). The implementation of $arene_{edge}$–anion and $arene_{edge}$–Lewis base interactions have recently been studied, such as in the context of novel ion sensors (**4-114**) and ligand systems (**4-115**).[29,30] These reports were highly suggestive of the plausibility of this interaction, and the increase in *anti*-selectivity when toluene is replaced with THF supports this hypothesis.

Figure 4.5.2. Electrostatic Model to Explain the *anti*-Selectivity

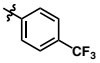
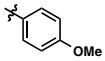


To test these two hypotheses, we evaluated a series of imidazolidinones derived from electronically differentiated benzaldehydes and naphthaldehydes. We tested either MeI or BnBr to interrogate the effect of the electrophile size, and we used either a 5:1 THF/hexanes or a 3:2:1 toluene/THF/hexane as the reaction media. The results can be seen in Table 4.5.1. The vast majority of these alkylations were *syn*-selective. Notably, the *p*-trifluoromethylphenyl and the *p*-cyanophenyl examples (entries 4-7 and 8-9) showed a greater preference for *syn*-alkylation than the parent phenyl case (entries 1-3). This seemed to refute our hypothesis of a hyperconjugative effect dictating selectivity (Figure 4.5.1).

Table 4.5.1. Alkylations of Modified-Phenyl Imidazolidinones



***exo*-4-109 or *exo*-4-116–*exo*-4-121** | ***trans*-4-110 or *trans*-4-122–*trans*-4-27** | ***cis*-4-110 or *cis*-4-122–*cis*-4-127**

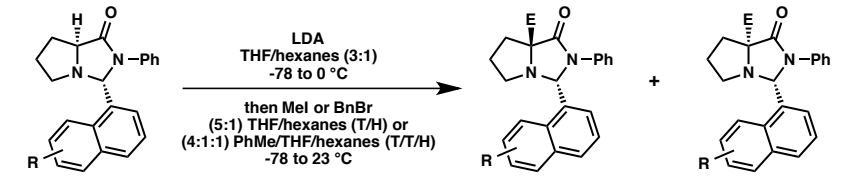
Entry	Phenyl Derivative	Electrophile	Solvent	Alkylation dr (anti/syn)[a]
1		MeI	T/H	45:55
2		MeI	T/T/H	46:54
3	***exo*-4-109**	BnBr	T/T/H	40:60
4		MeI	T/H	35:65
5		MeI	T/T/H	50:50
6	***exo*-4-116**	BnBr	T/H	24:76
7		BnBr	T/T/H	20:80
8		BnBr	T/H	26:74
9	 ***exo*-4-117**	BnBr	T/T/H	29:71
10		MeI	T/T/H	55:45
11	 ***exo*-4-118**	BnBr	T/T/H	36:64
12		MeI	T/H	14:86
13		MeI	T/T/H	10:90
14	***exo*-4-119**	BnBr	T/H	16:84
15		BnBr	T/T/H	19:81
16		MeI	T/H	39:61
17	 ***exo*-4-120**	MeI	T/T/H	67:33
18	 ***exo*-4-121**	MeI	T/H	9:91

a) Diastereomeric ratio measured by ^{1}H NMR.

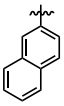
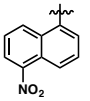
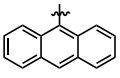
Derivatives of the naphthyl imidazolidinones were not much more informative (Table 4.5.2). The 5-fluoro-1-naphthyl case (entries 5-8), with a more acidic C-8 hydrogen, was modestly more *trans*-selective than the parent case (entries 1-4). The β-naphthyl example was less selective overall (entries 9-11), maybe behaving more like phenyl. The 8-methyl-1-naphthyl group boosted selectivity for the *anti*-product when MeI was used (entries 12 and 13) but for the *syn*-product when BnBr was used (entries 14 and 15). The 8-fluoro-1-naphthyl group gave a reversal in selectivity (7:93 anti/syn, entry 16) with MeI in THF, but under other conditions, the

substrate decomposed (entries 17 and 18). The 5-nitro (entry 19) and 9-anthracenyl (entry 20) imidazolidinones decomposed; they were predicted to improve the *trans*-selectivity by our electrostatic hypothesis.

Table 4.5.2. Alkylations of Modified-Naphthyl Imidazolidinones



***exo*-4-64 or *exo*-4-128–*exo*-4-133** | ***trans*-4-75 or *trans*-4-128–*trans*-4-133** | ***cis*-4-75 or *trans*-4-128–*trans*-4-133**

Entry	Naphthyl Derivative	Electrophile	Solvent	Alkylation dr (anti/syn)[a]
1	 ***exo*-4-64**	MeI	T/H	54:46
2		MeI	T/T/H	68:32
3		BnBr	T/T/H	91:9
4		BnBr	T/H	92:8
5	 ***exo*-4-128**	MeI	T/H	64:36
6		MeI	T/T/H	68:32
7		BnBr	T/H	91:9
8		BnBr	T/T/H	94:6
9	 ***exo*-4-129**	MeI	T/H	53:47
10		MeI	T/T/H	50:50
11		BnBr	T/H	27:73
12	 ***exo*-4-130**	MeI	T/H	>95:5
13		MeI	T/T/H	>95:5
14		BnBr	T/H	<5:95
15		BnBr	T/T/H	<5:95
16	 ***exo*-4-131**	MeI	T/H	7:93
17		MeI	T/T/H	—[b]
18		BnBr	T/H	—[b]
19	 ***exo*-4-132**	MeI	T/H	—[c]
20	 ***exo*-4-133**	MeI	T/H	—[c]

a) Diastereomeric ratio measured by ^{1}H NMR. b) Only starting material and slight decomposition were observed. c) Complete decomposition was observed.

This is where our experimental investigations currently stand; however, alternative inquiries may provide further insights. Computational studies have been performed to identify the origin of diastereoselection, but the evidence remains unclear. To our knowledge, this is the first example of contrasting stereoselectivities in the family of SRS reactions where the stereochemical course is dictated solely by the temporary group. Our investigations into the origin of this stereochemical bifurcation seem to suggest that subtle influences are at play during the course of imidazolidinone alkylations.

4.6. Experimental Section

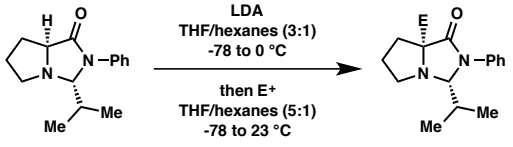
4.6.1. Materials and Methods

Reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, dichloromethane, and toluene were purified by passing through activated alumina columns. Diisopropylamine was distilled over CaH_2. 2-Fluoropyridine was freshly distilled before use. LiCl was dried at 150 °C for 12 h under high vacuum (<0.1 torr) before use. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, Ma), Sigma-Aldrich (St. Louis, MO), Oakwood Products (West Columbia, SC), Strem (Newport, MA), TCI America (Portland, OR), and Bachem (Torrance, CA). Qualitative TLC was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to ninhydrin, *p*-anisaldehyde, or $KMnO_4$ stain solutions followed by heating. Qualitative TLC of amino amide products required pretreatment of TLC plates with 9:1 hexanes/triethylamine followed by evaporation under reduced pressure (basic plates). Visualization of amino amide products required pretreatment of the plate with 19:1 1.0 N $HCl_{(aq)}$/isobutyraldehyde and heating to dryness before using ninhydrin stain solution. Flash

column chromatography was performed using Silicylce silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz) or a Varian 400 MR (at 400 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained on NaCl plates (film) with a Bruker Tensor 27 FT-IR or as a film with a Nicolet iS50 FT-IR. All high performance liquid chromatography was performed on an Agilent 1100 series HPLC with a Diacel OD-H column (5 μm, 25 cm x 4,6 mm, UV detection at 254 nm). Low-resolution mass spectrometry data were acquired on an Agilent 1200 series HPLC equipped with an Agilent 6130 quadrupole LC/MS. High-resolution mass spectrometry data was acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS or by the University of Georgia Proteomics and Mass Spectrometry Core Facility on a Bruker Esquire 3000 Plus Ion Trap Spectrophotometer. Optical rotations were obtained with a Rudolph Research Analytical Autopol III Polarimeter. Crystallographic data was obtained with a Bruker Kappa APEX II CCD diffractometer.

4.6.2. Preparative Procedures

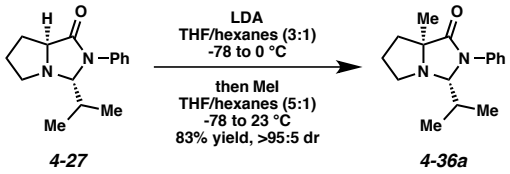
General Procedure for the syn-Selective Alkylation of Proline Imidazolidinones



4-27/4-35 ***4-36/4-37***

In a flame-dried flask, to a suspension of proline imidazolidinones **4-27/4-35** (1 equiv) in THF (1.0 M) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.1 equiv, 0.9 to 1.1 M in ~1:1 hexane/THF, -4 °C). The solution was then allowed to warm to 0 °C and stirred for 20 min, generally turning yellow. The solution was recooled to -78 °C, and to the solution

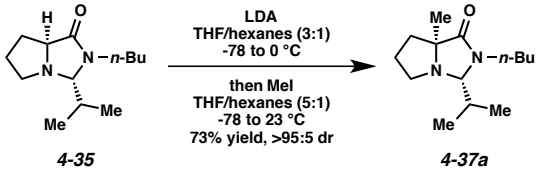
was added an equal volume of THF (bringing the reaction concentration to ~0.3 M; the additional THF improves stirring upon addition of the electrophile). The electrophile (1.1 equiv) was added at -78 °C, and the reaction mixture stirred at -78 °C for 1.5 h before the ice bath was removed and the suspension was allowed to warm gradually to ambient temperature. Upon completion, as determined by TLC, the reaction was quenched with water, and the mixture was extracted into EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinones **4-36**/**4-37** was purified by flash column chromatography.



4-27 *4-36a*

According to the general procedure, to a suspension of proline imidazolidinone **4-27** (1.08 g, 4.42 mmol) in THF (4.4 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (4.86 mL, 1.0 M, 4.86 mmol, -4°C). The solution was warmed to 0 °C and held for 20 min. The reaction solution was recooled to -78 °C, and to the solution was added THF (4.4 mL) and then methyl iodide (303 μL, 4.86 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (3:1 EtOAc/hexanes eluent) to afford *cis*-proline imidazolidinone **4-36a** (949 mg, 83% yield, R_f = 0.62 in 1:1 hexanes/EtOAc) as a yellow-orange solid.

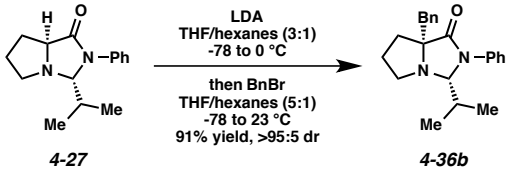
***cis*-Proline imidazolidinone 4-36a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (comp m, 4H), 7.24-7.16 (m, 1H), 4.50 (d, *J* = 2.4 Hz, 1H), 3.31-3.18 (m, 1H), 2.89-2.81 (m, 1H), 2.18-2.09 (m, 1H), 1.90-1.67 (comp m, 4H), 1.43 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 136.7, 129.2, 126.1, 124.4, 87.1, 71.3, 59.2, 38.2, 30.4, 26.3, 25.6, 18.4, 14.5; IR (film) 2967, 1701, 1598, 1499, 1410, 1384, 1216, 1074, 755, 697 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{22}N_2O + H]^+$: 259.1805, found 259.1809; $[\alpha]_D^{29}$ = -101.4 (*c* = 1.0, $CHCl_3$).



4-35 *4-37a*

According to the general procedure, to a suspension of proline imidazolidinone **4-35** (163 mg, 0.726 mmol) in THF (0.73 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.799 mL, 1.0 M, 0.799 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.73 mL) and then methyl iodide (49.7 μL, 0.799 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (3:2 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-37a** (126 mg, 73% yield, R_f = 0.47 in 3:2 hexanes/EtOAc) as a colorless oil.

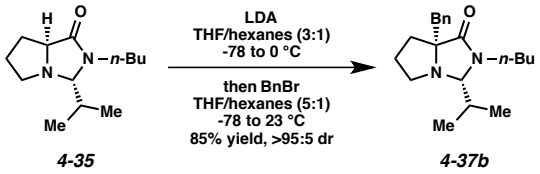
***cis*-Proline imidazolidinone 4-37a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (d, *J* = 2.0 Hz, 1H), 3.69 (dt, *J* = 13.6, 8.4 Hz, 1H), 3.13-3.07 (m, 1H), 2.75-2.64 (comp m, 2H), 2.03-1.94 (m, 1H), 1.92-1.80 (m, 1H), 1.79-1.70 (m, 1H), 1.67-1.53 (comp m, 2H), 1.52-1.37 (comp m, 2H), 1.33-1.21 (comp m, 2H), 1.25 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.71 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz) δ 176.0, 84.9, 70.6, 58.7, 39.5, 37.8, 29.9, 29.2, 25.8, 25.6, 20.2, 13.3, 14.2, 13.8; IR (film) 2960, 2931, 2871, 1690, 1442, 1386, 1306, 1098, 1073, 994 cm^{-1}; LRMS (ESI^{+}) *m/z* calc'd for $(M + H)^{+}$ $[C_{14}H_{26}N_2O + H]^{+}$: 239.2, found 239.0; $[\alpha]_D^{32}$ = -20.2 (*c* = 1.0, $CHCl_3$).



4-27 *4-36b*

According to the general procedure, to a suspension of proline imidazolidinone **4-27** (200 mg, 0.819 mmol) in THF (0.82 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.901 mL, 1.0 M, 0.901 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.82 mL) and then benzyl bromide (107 μL, 0.900 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-36b** (249 mg, 91% yield, R_f = 0.74 in 4:1 hexanes/EtOAc) as a white amorphous solid.

***cis*-Proline imidazolidinone 4-36b:** The characterization data matched the previously reported data for this compound.[1]

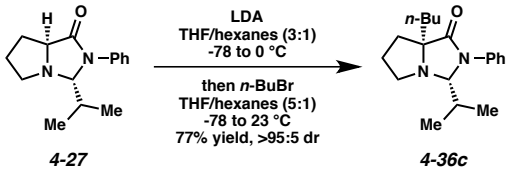


4-35 *4-37b*

According to the general procedure, to a suspension of proline imidazolidinone **4-35** (152 mg, 0.678 mmol) in THF (0.68 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.746 mL, 1.0 M, 0.746 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.68 mL) and then benzyl bromide (88.6 μL, 0.746 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-37b** (181 mg, 85% yield, R_f = 0.31 in 4:1 hexanes/EtOAc) as a beige oil.

***cis*-Proline imidazolidinone 4-37b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (comp m, 2H), 7.26-7.16 (comp m, 3H), 3.85 (d, J = 2.4 Hz, 1H), 3.75 (dt, J = 14.0, 8.0 Hz, 1H), 2.89 (ABq, J = 13.6 Hz, Δν = 26.7 Hz, 2H), 2.74 (ddd, J = 13.6, 8.0, 4.8 Hz, 1H), 2.55 (dd, J = 8.0, 4.8 Hz, 1H), 1.96-1.85 (comp m, 2H), 1.80-1.70 (m, 1H), 1.56-1.16 (comp m, 7H), 1.01 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.73 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 137.9, 131.1, 127.9, 126.4, 84.9, 74.4, 58.6, 42.5, 39.7, 34.0, 30.4, 29.2, 24.9, 20.2, 18.6, 14.7, 13.9; IR

(film) 2960, 2873, 1691, 1437, 1386, 1307, 1286, 1071, 765, 700 cm^{-1}; LRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{20}H_{30}N_2O + Na]^+$: 337.2, found 337.0; $[\alpha]_D^{32}$ = +3.4 (*c* = 1.0, $CHCl_3$).

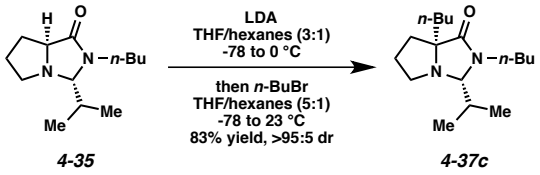


4-27 *4-36c*

According to the general procedure, to a suspension of proline imidazolidinone **4-27** (201 mg, 0.823 mmol) in THF (0.82 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.973 mL, 0.93 M, 0.905 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.82 mL) and then *n*-butyl bromide (97.8 μL, 0.905 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-36c** (212 mg, 77% yield, R_f = 0.22 in 9:1 hexanes/EtOAc) as a clear colorless oil.

***cis*-Proline imidazolidinone 4-36c**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (comp m, 4H), 7.20 (t, *J* = 6.8 Hz, 1H), 4.47 (app s, 1H) 3.15-3.01 (m, 1H), 2.94-2.81 (m, 1H), 2.14-2.06 (m, 1H), 1.90-1.73 (comp m, 4H), 1.73-1.60 (comp m, 2H), 1.53-1.42 (comp m, 2H), 1.41-1.30 (comp m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.74 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 136.7, 129.1, 126.1, 124.6, 86.4, 74.0, 58.9, 38.3, 35.2, 30.8, 26.0, 25.2, 23.3, 18.6, 14.8, 14.3; IR (film) 2960, 1698, 1598, 1500, 1410, 1313, 1148, 1075,

756, 698 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{28}N_2O + H]^+$: 301.2274, found 301.2277; $[\alpha]_D^{31} = +1.9$ (*c* = 1.0, CH_2Cl_2).

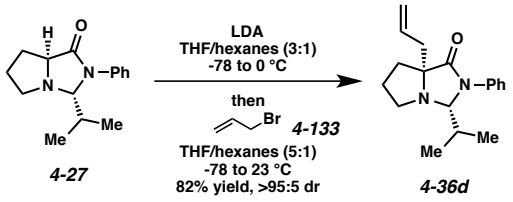


4-35 *4-37c*

According to the general procedure, to a suspension of proline imidazolidinone **4-35** (476 mg, 2.12 mmol) in THF (2.1 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (2.12 mL, 1.1 M, 2.33 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (2.1 mL) and then *n*-butyl bromide (251 μL, 2.33 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-37c** (494 mg, 83% yield, R_f = 0.40 in 4:1 hexanes/EtOAc) as a clear colorless oil.

***cis*-Proline imidazolidinone 4-37c:** ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (d, *J* = 2.0 Hz, 1H), 3.68 (dt, *J* = 14.0, 7.6 Hz, 1H), 2.96-2.90 (m, 1H), 2.75-2.66 (comp m, 2H), 1.98-1.90 (m, 1H), 1.91-1.79 (m, 1H), 1.75-1.58 (comp m, 3H), 1.53-1.19 (comp m, 10H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.6, 3H), 0.85 (t, *J* = 7.2, 3H), 0.71 (d, *J* = 6.8, 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 84.1, 73.4, 58.3, 39.5, 37.9, 34.9, 30.3, 29.2, 26.0, 25.1, 23.2, 20.2, 18.5, 14.5, 14.2, 13.8; IR (film) 2960, 2934, 2873, 1696, 1438, 1386, 1306, 1198, 1101, 1077 cm^{-1}; HRMS

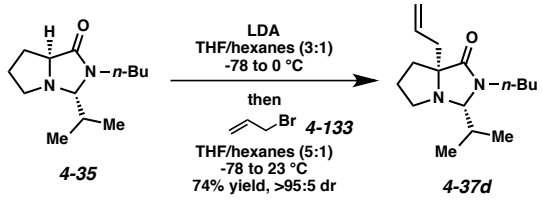
(ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{32}N_2O + H]^+$: 281.2587, found 281.2592; $[\alpha]_D^{30}$ = -9.4 (*c* = 1.0, CH_2Cl_2).



According to the general procedure, to a suspension of proline imidazolidinone **4-27** (200 mg, 0.819 mmol) in THF (0.82 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.901 mL, 1.0 M, 0.901 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 C, and to the solution was added THF (0.82 mL) and then allyl bromide (**4-133**, 77.9 μL, 0.901 mmol); it was held at -78 °C for 1.5 h before being allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (17:3 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-36d** (181 mg, 82% yield, R_f = 0.48 in 3:1 hexanes/EtOAc) as a white solid.

***cis*-Proline imidazolidinone 4-36d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.33 (comp m, 4H), 7.21 (tt, *J* = 6.8, 2.0 Hz, 1H), 6.05-5.94 (m, 1H), 5.21-5.12 (comp m, 2H), 4.49 (d, *J* = 2.8 Hz, 1H), 3.08 (ddd, *J* = 15.2, 9.6, 5.6 Hz, 1H), 2.86 (ddd, *J* = 15.2, 6.8, 3.6 Hz, 1H), 2.57-2.45 (comp m, 2H), 2.08 (ddd, *J* = 12.8, 8.0, 4.0 Hz, 1H), 1.93-1.82 (comp m, 2H), 1.81-1.72 (m, 1H), 1.70-1.59 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 136.7, 134.2, 129.2, 126.2, 124.6, 118.5, 86.9, 73.8, 59.3, 42.8, 34.7, 30.7, 25.3, 18.6, 14.9; IR (film) 2963, 1700, 1598, 1499, 1408, 1384, 1003, 915, 755, 692 cm^{-1}; HRMS (ESI$^+$) *m/z*

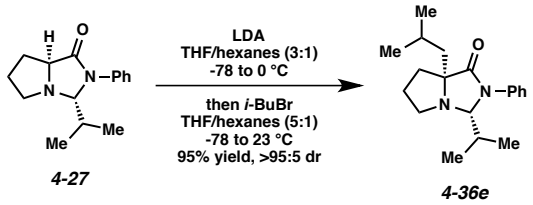
calc'd for $(M + H)^+$ $[C_{18}H_{24}N_2O + H]^+$: 285.1961, found 285.1963; $[\alpha]_D^{31}$ = +2.34 (*c* = 1.0, CH_2Cl_2).



According to the general procedure, to a suspension of proline imidazolidinone **4-35** (182 mg, 0.812 mmol) in THF (0.81 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.893 mL, 1.0 M, 0.893 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.81 mL) and then allyl bromide (**4-133**, 77.2 μl, 0.893 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-37d** (158 mg, 74% yield, R_f = 0.34 in 4:1 hexanes/EtOAc) as a colorless oil.

***cis*-Proline imidazolidinone 4-37d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97-5.85 (m, 1H), 5.11-5.06 (comp m, 2H), 3.83 (d, *J* = 2.4 Hz, 1H), 3.71 (dt, *J* = 14.0, 8.0 Hz, 1H), 2.93 (ddd, *J* = 15.4, 10.0, 5.2 Hz, 1H), 2.77-2.67 (comp m, 2H), 2.41-2.26 (comp m, 2H), 1.98-1.83 (comp m, 2H), 1.82-1.73 (m, 1H), 1.72-1.64 (comp m, 1H), 1.54-1.36 (comp m, 3H), 1.33-1.21 (comp m, 2H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 134.4, 118.1, 84.7, 73.1, 58.8, 42.5, 39.6, 34.3, 30.2, 29.2, 25.3, 20.2, 18.5, 14.6,

13.8; IR (film) 2959, 2873, 1689, 1436, 1386, 1307, 1067, 1004, 912 cm^{-1}; LRMS (ESI^+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{28}N_2O + H]^+$: 265.2, found 265.0; $[\alpha]_D^{32}$ = -9.4 (*c* = 1.0, $CHCl_3$).

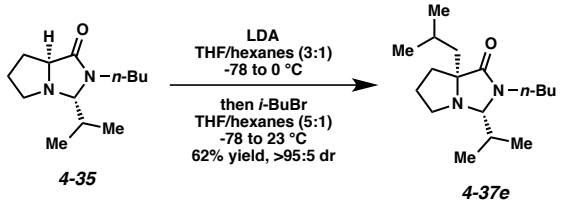


4-27 *4-36e*

According to the general procedure, to a suspension of proline imidazolidinone **4-27** (100 mg, 0.819 mmol) in THF (0.82 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.901 mL, 1.0 M, 0.901 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 C, and to the solution was added THF (0.82 mL) and then isobutyl bromide (98.0 μL, 0.901 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (17:3 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-36e** (235 mg, 95% yield, R_f = 0.46 in 17:3 hexanes/EtOAc) as a colorless oil.

***cis*-Proline imidazolidinone 4-36e:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (comp m, 4 H), 7.20 (tt, *J* = 7.2, 1.6 Hz, 1H), 4.47 (d, *J* = 2.8 Hz, 1H), 3.13 (ddd, *J* = 11.6, 9.2, 6.0 Hz, 1H), 2.92-2.84 (m, 1H), 2.05 (ddd, *J* = 13.2, 8.8, 5.2 Hz, 1H), 2.01-1.76 (comp m, 4H), 1.75-1.63 (comp m, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 136.8, 129.1, 126.1, 124.5, 86.2, 74.4,

58.4, 46.0, 35.8, 31.0, 25.5, 25.0, 24.5, 23.9, 18.6, 15.0; IR (film) 2958, 2871, 1670, 1599, 1500, 1460, 1148, 1072, 755, 696 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{28}N_2O+ H]^+$: 301.2273, found 301.2273; $[\alpha]_D^{30} = +0.4$ (*c* = 1.0, CH_2Cl_2).

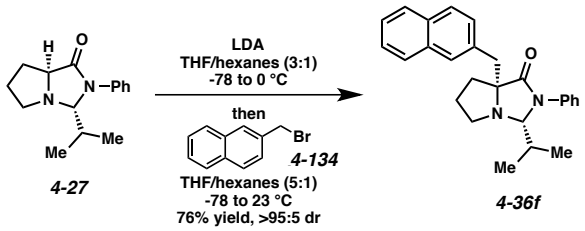


4-35 *4-37e*

According to the general procedure, to a suspension of proline imidazolidinone **4-35** (172 mg, 0.766 mmol) in THF (0.77 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.843 mL, 1.0 M, 0.843 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.77 mL) and then isobutyl bromide (91.6 μL, 0.843 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-37e** (172 mg, 62% yield, R_f = 0.39 in 4:1 hexanes/EtOAc) as a clear colorless oil.

***cis*-Proline imidazolidinone 4-37e:** ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (d, *J* = 2.4 Hz, 1H), 3.71 (dt, *J* = 14.0, 8.0 Hz, 1H), 3.00 (ddd, *J* = 11.6, 9.6, 6.8 Hz, 1H), 2.77-2.69 (comp m, 2H), 1.95-1.69 (comp m, 5H), 1.59-1.40 (comp m, 5H), 1.33-1.23 (comp m, 2H), 0.98 (d, *J* = 2.8 Hz, 3H), 0.96 (d, *J* = 2.4 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.917 (t, *J* = 7.6 Hz, 3H), 0.76 (d, *J* = 6.4

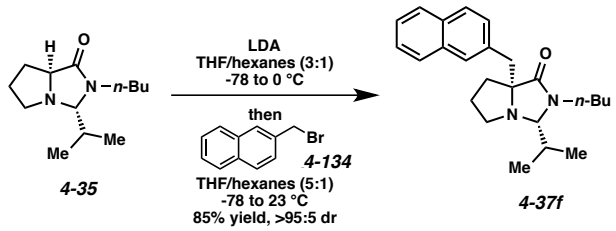
Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 84.2, 73.9, 58.0, 45.7, 39.6, 35.5, 30.5, 29.2, 25.5, 25.0, 24.4, 23.9, 20.2, 18.5, 14.7, 13.9; IR (film) 2956, 2931, 2870, 1691, 1435, 1386, 1376, 1305, 1101, 1074 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{32}N_2O + H]^+$: 281.2587, found 281.2584; $[\alpha]_D^{32}$ = -14.4 (*c* = 1.0, $CHCl_3$).



According to the general procedure, to a suspension of proline imidazolidinone **4-27** (100 mg, 0.410 mmol) in THF (0.41 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.451 mL, 1.0 M, 0.451 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 C, and to the solution was added THF (0.41 mL) and then bromide **4-134** (99.5 mg, 0.450 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (17:3 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-36f** (119 mg, 76% yield, R_f = 0.33 in 17:3 hexanes/EtOAc) as a white solid.

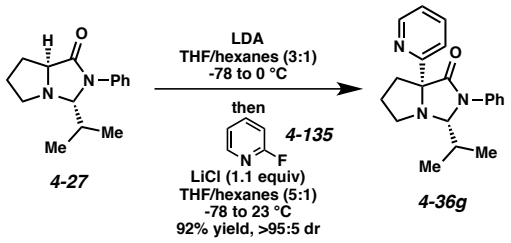
***cis*-Proline imidazolidinone 4-36f:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.81 (comp m, 3H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.51-7.37 (comp m, 6H), 7.26-7.21 (comp m, 1H), 4.53 (d, *J* = 2.8 Hz, 1H), 3.34 (d, *J* = 13.3 Hz, 1H), 3.18 (d, *J* = 13.3 Hz, 1H), 2.79-2.61

(comp m, 2H), 2.11 (ddd, J = 12.0, 8.0, 4.4 Hz, 1H), 1.98-1.89 (m, 1H), 1.88-1.78 (m, 1H), 1.59-1.44 (m, 1H), 1.39-1.26 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 136.6, 135.4, 133.4, 132.4, 129.8, 129.5, 129.2, 127.8, 127.7, 127.4, 126.3, 125.9, 125.5, 124.6, 87.1, 75.2, 59.0, 43.0, 34.5, 30.9, 24.9, 18.7, 15.0; IR (film) 1701, 1598, 1498, 1409, 1313, 1216, 1146, 1068, 908, 788 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{28}N_2O+ H]^+$: 385.2274, found 385.2279; $[\alpha]_D^{30}$ = +12.3 (c = 1.0, CH_2Cl_2).



According to the general procedure, to a suspension of proline imidazolidinone **4-35** (108 mg, 0.482 mmol) in THF (0.48 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.530 mL, 1.0 M, 0.530 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.48 mL) and then bromide **4-134** (117 mg, 0.531 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-37f** (181 mg, 85% yield, R_f = 0.26 in 4:1 hexanes/EtOAc) as a white amorphous solid.

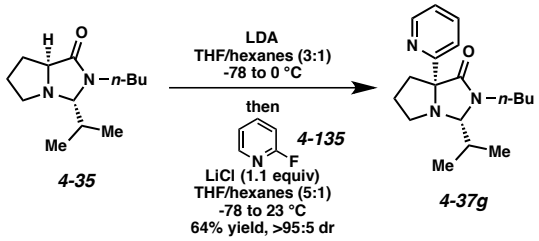
***cis*-Proline imidazolidinone 4-37f:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.77 (comp m, 3H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.47-7.41 (comp m, 2 H), 3.89 (d, *J* = 2.8 Hz, 1H), 3.79 (dt, *J* = 14.0, 8.0 Hz, 1H), 3.09 (ABq, *J* = 13.6 Hz, Δν = 15.4 Hz, 2H), 2.79 (ddd, *J* = 13.2, 8.0, 4.8 Hz, 1H), 2.62-2.47 (comp m, 2H), 2.02-1.88 (comp m, 2H), 1.87-1.77 (comp m, 1H), 1.60-1.42 (comp m, 2H), 1.41-1.28 (comp m, 3H), 1.27-1.14 (comp m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 135.7, 133.4, 132.4, 129.6, 129.5, 127.8, 127.6, 127.3, 125.8, 125.4, 85.0, 74.6, 58.6, 42.6, 39.8, 34.0, 30.5, 29.2, 24.9, 20.2, 18.6, 14.8, 13.9; IR (film) 2960, 2931, 2872, 1691, 1445, 1307, 1272, 1065, 820, 750 cm^{-1}; LRMS (ESI^{+}) *m/z* calc'd for $(M + H)^{+}$ $[C_{24}H_{32}N_2O + H]^{+}$: 365.3, found 365.0; $[\alpha]_D^{32}$ = +17.4 (*c* = 1.0, $CHCl_3$).



To a suspension of proline imidazolidinone **4-27** (296 mg, 1.21 mmol) and oven-dried LiCl (56.4 mg, 1.33 mmol) in THF (1.2 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.33 mL, 1.0 M, 1.33 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (1.2 mL) and then freshly distilled 2-fluoropyridine **4-135** (125 μL, 1.45 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and

the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-36g** (340 mg, 92% yield, R_f = 0.05 in 1:1 hexanes/EtOAc) as a beige solid.

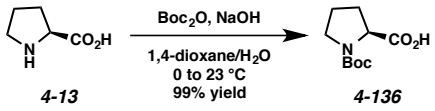
***cis*-Proline imidazolidinone 4-36g:** The characterization data matches the previously reported data.[1]



To a suspension of proline imidazolidinone **4-35** (226 mg, 1.01 mmol) and oven-dried LiCl (47.1 mg, 1.11 mmol) in THF (1.0 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.11 mL, 1.0 M, 1.11 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 C, and to the solution was added THF (1.0 mL) and then freshly distilled 2-fluoropyridine **4-135** (104 μL, 1.21 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash chromatography (3:2 → 2:3 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-37g** (249 mg, 64% yield, R_f = 0.23 in 3:2 EtOAC/hexanes) as a yellow oil.

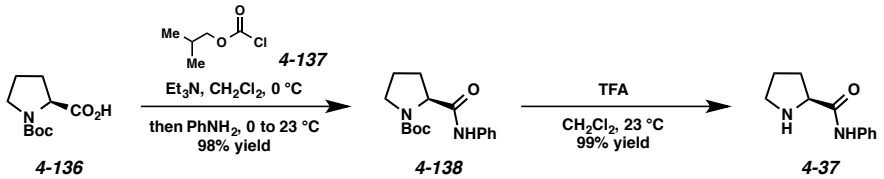
***cis*-Proline imidazolidinone 4-37g:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (comp m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.58 (td, *J* = 8.0, 2.0 Hz, 1H), 7.09 (comp m, 1H), 3.98 (d, *J* = 2.8 Hz, 1H), 3.77

(dt, *J* = 14.0, 8.0 Hz, 1H), 3.30 (ddd, *J* = 11.2, 8.0, 6.4 Hz, 1H), 2.87 (dt, *J* = 11.2, 6.0 Hz, 1H), 2.77 (ddd, *J* = 13.6, 8.0, 5.2 Hz, 1H), 2.44 (comp m, 1H), 2.33 (comp m, 1H), 1.92-1.66 (comp m, 3H), 1.55-1.46 (comp m, 2H), 1.37-1.27 (comp m, 2H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 6.8 Hz, 3H), 0.55 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 162.2, 149.3, 136.1, 121.8, 120.9, 84.4, 77.4, 58.8, 40.0, 38.4, 30.7, 29.2, 25.7, 20.2, 18.5, 14.8, 13.8; IR (film) 2959, 2931, 2872, 1687, 1586, 1429, 1305, 1088, 780, 749 cm^{-1}; LRMS (ESI$^+$) *m/z* calc'd for (M + Na)$^+$ [$C_{18}H_{27}N_3O$ + Na]$^+$: 324.2, found 323.9; $[\alpha]_D^{32}$ = -24.7 (*c* = 1.0, $CHCl_3$).



4-13 *4-136*

To a solution of (*S*)-proline **4-13** (15.0 g, 130 mmol) in aq. NaOH (1M, 261 mL) and dioxane (65.2 mL) at 0 °C was added Boc_2O (33.1 g, 154 mmol) portionwise over 20 min. The resulting mixture was stirred at 0 °C for 30 min, then allowed to warm to 23 °C and stirred overnight. The organic solvent was removed under reduced pressure. The remaining aqueous solution was acidified to pH ~2 with aq. $KHSO_4$ (1 M). The aqueous solution was extracted with $CHCl_3$ (3 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to afford carbamate **4-136** (28.0 g, 99% yield, R_f = 0.57 in EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.



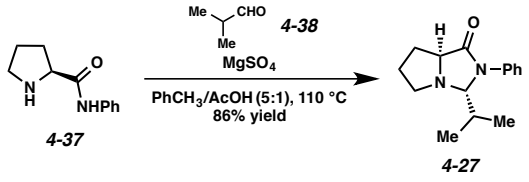
4-136 *4-138* *4-37*

To a solution of (*S*)-*N*-Boc proline **4-136** (2.50 g, 11.6 mmol) in CH_2Cl_2 (38.7 mL) at 0 °C was added isobutyl chloroformate **4-137** (1.67 mL, 12.8 mmol) and triethylamine (1.80 mL, 12.8

mmol). After stirring for 20 min at 0 °C, aniline (1.16 mL, 12.8 mmol) was added, and the reaction was warmed to 23 °C and stirred overnight. The reaction mixture was washed sequentially with aq. $KHSO_4$ (1 M, 50 mL), sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporation to afford a pale brown solid. The crude solid was suspended in hexanes (15 mL), cooled to 0 °C, and filtered to afford amide **4-138** (3.32 g, 98% yield, R_f = 0.52 in 1:1 hexanes/EtOAc) as a light brown solid, which was sufficiently pure to be taken on to the next step.

To a solution of amide **4-138** (3.32 g, 11.4 mmol) in CH_2Cl_2 (22.8 mL) at 23 °C was added TFA (17.6 mL, 228 mmol). The solution was stirred at 23 °C for 1 h, and upon completion the solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (20 mL) and water (10 mL) was added. The mixture was neutralized with solid Na_2CO_3 until pH ~9, and then it was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amino amide **4-37** (2.20 g, 99% yield, R_f = 0.03 in 7:3 EtOH/H_2O) as a white amorphous solid, which was sufficiently pure to be taken on to the next step.

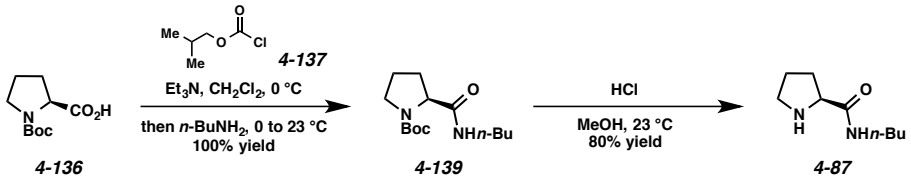
Amino amide 4-37: The spectroscopic data corresponds to previously reported data.[1]



A suspension of amino amide **4-37** (5.00 g, 26.3 mmol), isobutyraldehyde (**4-38**, 3.12 mL, 34.2 mmol), and $MgSO_4$ (4.75 g, 39.5 mmol) in PhMe (263 mL) and glacial acetic acid (53 mL) was heated to reflux and stirred overnight. Upon cooling, to the solution was added sat. aq. $NaHCO_3$ (800 mL), and the mixture was extracted with EtOAc (3 x 500 mL). The combined organic

layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude imidazolidinone was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford imidazolidinone **4-27** (5.54 g, 86% yield, R_f = 0.48 in 1:1 hexanes/EtOAc) as a white solid.

Proline imidazolidinone 4-27: The spectroscopic data corresponds to previously reported data.[1]

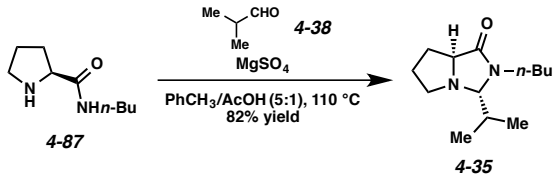


To a solution of (*S*)-*N*-Boc proline **4-136** (10.0 g, 46.5 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added isobutyl chloroformate (**4-137**, 6.36 mL, 51.1 mmol) and triethylamine (7.13 mL, 51.1 mmol). After stirring for 30 min at 0 °C, *n*-butylamine (5.07 ml, 51.1 mmol) was added and the ice bath was removed, allowing the reaction to warm to 23 °C and stir for 12 h. The reaction mixture was washed sequentially with aq. $KHSO_4$ (1 M, 200 mL), sat. aq. $NaHCO_3$ (200 mL), and brine (200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford carbamate **4-139** (12.6 g, >99% yield, R_f = 0.46 in EtOAc) as a clear colorless oil that slowly solidified, which was sufficiently pure to be taken on to the next step.

To a solution of carbamate **4-139** (10.9 g, 37.8 mmol) in MeOH (76 mL) at 23 °C was bubbled anhydrous HCl (produced by $CaCl_2$ and conc. HCl) for 1 min. The solution was stirred in a sealed vessel at 23 °C for 1 h, and then the solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (50 mL), and it was washed with sat. aq. Na_2CO_3 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amino amide **4-87** (5.15 g, 80%

yield, R_f = 0.48 in 7:3 EtOH/H_2O) as a yellow oil, which was sufficiently pure to be taken on to the next step.

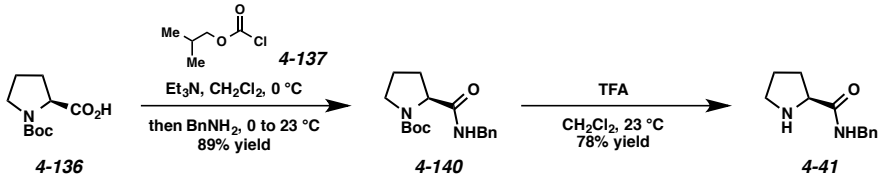
Amino amide 4-87: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 3.69 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.19 (q, *J* = 6.8 Hz, 2H), 3.02-2.94 (comp m, 1H), 2.90-2.82 (comp m, 1H), 2.23-2.18 (comp m, 1H), 2.15-2.05 (comp m, 1H), 1.91-1.83 (comp m, 1H), 1.73-1.61 (comp m, 2H), 1.50-1.40 (comp m, 2H), 1.37-1.26 (comp m, 2H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 60.7, 47.3, 38.7, 31.8, 30.9, 26.3, 20.2, 13.9; IR (film) 3307, 2959, 2933, 2873, 1654, 1529, 1460, 1379, 1250, 1104 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ [$C_9H_{18}N_2O$ + H]$^+$: 171.1492, found 171.1494; $[\alpha]_D^{33}$ = -70.4 (*c* = 1.0, CH_2Cl_2).



A suspension of amino amide **4-87** (5.74 g, 33.7 mmol), isobutyraldehyde (**4-38**, 4.00 mL, 43.8 mmol), and $MgSO_4$ (6.09 g, 50.6 mmol) in PhMe (337 mL) and AcOH (67 mL) was heated to reflux and stirred for 24 h. Upon cooling, the solution was quenched with sat. aq. $NaHCO_3$ (400 mL), and the mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford imidazolidinone **4-35** (16.8 g, 82% yield, R_f = 0.41 in EtOAc) as a yellow oil, which was sufficiently pure to be taken on to the next step.

Proline imidazolidinone 4-35: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 1H), 3.72-3.62 (comp m, 2H), 3.15 (dt, *J* = 9.2, 5.2 Hz, 1H), 2.73 (ddd, *J* = 13.6, 8.4, 4.8 Hz, 1H), 2.57 (dt, *J* = 10.0, 6.8 Hz, 1H), 2.12-2.01 (m, 1H), 1.95-1.83 (comp m, 2H), 1.80-1.68 (comp m, 1H), 1.68-1.58 (comp m, 1H), 1.53-1.38 (comp m, 2H), 1.33-1.22 (comp m, 2H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* =

7.4 Hz, 3H), 0.73 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 85.8, 65.8, 58.7, 39.6, 30.8, 29.3, 29.1, 25.3, 20.2, 18.4, 14.3, 13.8; IR (film) 2961, 2873, 1694, 1436, 1386, 1338, 1271, 1195, 1076 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{24}N_2O + H]^+$: 225.1961, found 225.1965; $[\alpha]_D^{31}$ = -27.0 (c = 1.0, CH_2Cl_2).

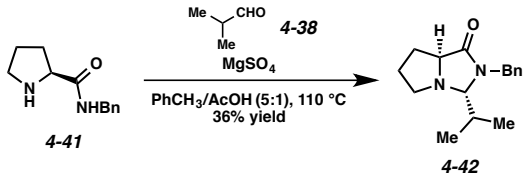


To a solution of (*S*)-*N*-Boc proline **4-136** (1.00 g, 4.65 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C was added isobutyl chloroformate (**4-137**, 636 µL, 5.11 mmol) and triethylamine (713 µL, 5.11 mmol). After stirring for 30 min at 0 °C, *n*-benzylamine (558 µl, 5.11 mmol) was added and the ice bath was removed, allowing the reaction to warm to 23 °C and stir for 25 h. The reaction mixture was washed sequentially with aq. $KHSO_4$ (1 M, 20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amide **4-140** (1.26 g, 89% yield, R_f = 0.23 in 9:1 CH_2Cl_2/MeOH) as a white powder.

To a solution of amide **4-140** (1.26 g, 4.13 mmol) in CH_2Cl_2 (8.30 mL) at 23 °C was added TFA (6.40 mL, 37.7 mmol). The solution was stirred at 23 °C for 1 h, and upon completion the solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (20 mL) and water (10 mL) was added. The mixture was neutralized with solid Na_2CO_3 until pH ~9, and then it was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amino amide **4-41** (657 mg, 78% yield, R_f = 0.23 in 9:1 CH_2Cl_2/MeOH) as a beige oil, which was sufficiently pure to be taken on to the next

step.

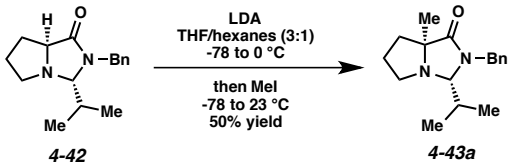
Amino amide 4-41: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br. s, 1H), 7.29-7.23 (comp. m, 2H), 7.22-7.17 (comp. m, 3H), 4.36 (d, *J* = 6.0 Hz, 2H), 3.72 (dd, *J* = 9.0, 5.4 Hz, 1H), 2.97-2.89 (comp. m, 1H), 2.84-2.77 (comp.m, 1H), 2.14 (br. s, 1H), 2.13-2.03 (comp. m, 1H), 1.93-1.84 (comp. m), 1.70-1.58 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 138.7, 128.7, 127.6, 127.3, 60.7, 47.3, 43.0, 30.9, 26.3, IR (film) 3314, 1656, 1521, 1248, 1104 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{16}N_2O + H]^+$: 205.1335, found 205.1333; $[\alpha]_D^{33}$ = -39.6 (*c* = 1.0, CH_2Cl_2).



A suspension of amino amide **4-41** (527 mg, 2.58 mmol), isobutyraldehyde (**4-38**, 306 μL, 3.35 mmol), and $MgSO_4$ (466 mg, 3.87 mmol) in PhMe (25.8 mL) and glacial acetic acid (5.16 mL) was heated to reflux and stirred for 9 h. Upon cooling, to the solution was added sat. aq. $NaHCO_3$ (100 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude imidazolidinone was purified by flash column chromatography (EtOAc eluent) to afford imidazolidinone **4-42** (239 mg, 36% yield, R_f = 0.35 in 1:1 hexanes/EtOAc) as a colorless oil.

Imidazolidinone 4-42: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.20 (comp. m, 3H), 7.16-7.12 (comp. m, comp. m, 2H), 5.03 (d, *J* = 14.8 Hz, 1H), 3.74 (comp. m, 1H), 3.70 (d, *J* =14.8 Hz, 1H), 3.68-3.66 (comp. m, 1H), 3.02 (dt, *J* = 9.6, 5.6 Hz, 1H), 2.42-2.34 (comp. m, 1H), 2.13-2.03 (comp. m, 1H), 1.98-1.82 (comp. m, 2H), 1.75-1.63 (comp. m, 1H), 1.63-1.52 (comp. m, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ; 174.9, 136.3,

128.9, 128.1, 127.8, 85.0, 65.7, 58.3, 43.9, 30.5, 29.2, 25.3, 18.3, 14.3; IR (film) 2965, 1696, 1436, 1258, 736 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{22}N_2O + H]^+$: 259.18055, found 259.1814; $[\alpha]_D^{33} = +62.6$ (*c* = 1.0, $CHCl_3$).

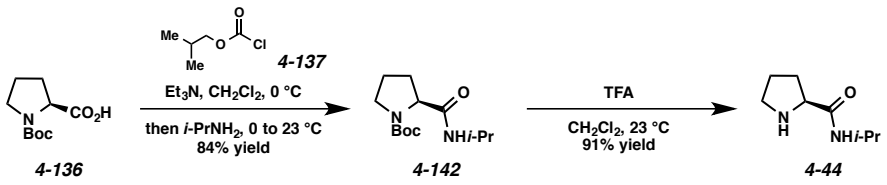


4-42 *4-43a*

To a suspension of proline imidazolidinone **4-42** (191 mg, 0.740 mmol) in THF (0.740 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (787 μL, 0.94 M, 0.740 mmol, -4°C). The solution was warmed to 0 °C and held for 20 min. The reaction solution was recooled to -78 °C, and to the solution was added methyl iodide (46 μL, 0.740 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *cis/trans*) was purified by flash column chromatography (4:1→1:1 hexanes/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-43a** (100 mg, 50% yield, R_f = 0.34 in 1:1 hexanes/EtOAc) as a colorless oil.

Imidazolidinone 4-43a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.19 (comp. m, 3H), 7.15-7.11 (comp. m, 2H), 5.07 (d, *J* = 14.6 Hz, 1H), 3.64 (d, *J* = 14.6 Hz, 1H), 3.55 (d, *J* = 2.4 Hz, 1H), 3.04-2.96 (comp. m, 1H), 2.54-2.46 (comp. m, 1H), 2.07-2.00 (comp. m, 1H), 1.83 (dp, *J* = 6.8, 2.4, 1H), 1.74-1.61 (comp. m, 2H), 1.51-1.41 (comp. m, 1H), 1.28 (s, 3H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.69 (d, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 136.4, 128.8, 128.1, 127.7, 84.1, 70.6, 58.6, 43.9, 38.1, 29.7, 25.8, 25.7, 18.2, 14.1, IR (film) 1693, 1434, 1072, 749, 701;

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{24}N_2O + H]^+$: 273.1961, found 273.1967.

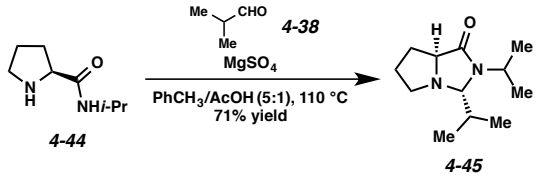


To a solution of (*S*)-*N*-Boc proline **4-136** (1.00 g, 4.65 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C was added isobutyl chloroformate (**4-137**, 636 µL, 5.11 mmol) and triethylamine (713 µL, 5.11 mmol). After stirring for 30 min at 0 °C, *i*-propylamine (435 µl, 5.11 mmol) was added and the ice bath was removed, allowing the reaction to warm to 23 °C and stir for 24 h. The reaction mixture was washed sequentially with aq. $KHSO_4$ (1 M, 20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amide **4-142** (1.00 g, 84% yield) as a white powder.

To a solution of amide **4-142** (0.999 g, 3.90 mmol) in CH_2Cl_2 (7.80 mL) at 23 °C was added TFA (6.60 mL, 38.9 mmol). The solution was stirred at 23 °C for 1 h, and upon completion the solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (20 mL) and water (10 mL) was added. The mixture was neutralized with solid Na_2CO_3 until pH ~9, and then it was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amino amide **4-44** (593 mg, 97% yield, R_f = 0.13 in 9:1 CH_2Cl_2/MeOH) as a yellow solid, which was sufficiently pure to be taken on to the next step.

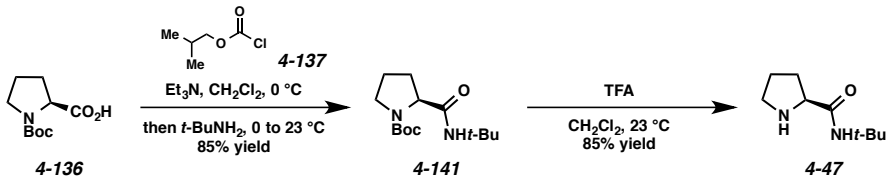
Amino amide 4-44: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (br. s, 1H), 4.06-3.92 (comp. m, 1H), 3.72-3.59 (comp. m, 1H), 3.04-2.92 (comp. m, 1H), 2.91-2.79 (comp. m, 1H), 2.27-2.02 (comp. m, 2H), 1.93-1.79 (comp. m, 1H), 1.74-1.59 (comp. m, 2H), 1.16-1.05 (comp. m, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 174.2, 60.7, 47.3, 40.6, 30.9, 26.7, 23.0, 22.9; IR (film) 3307, 2970, 1653, 1524, 1173 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_8H_{16}N_2O + H]^+$: 157.1335, found 157.1337; $[\alpha]_D^{32}$ = -79.8 (*c* = 1.0, CH_2Cl_2).



A suspension of amino amide **4-44** (245 mg, 1.57 mmol), isobutyraldehyde (**4-38**, 186 μL, 2.04 mmol), and $MgSO_4$ (283 mg, 2.36 mmol) in PhMe (15.7 mL) and glacial acetic acid (3.14 mL) was heated to reflux and stirred for 31 h. Upon cooling, to the solution was added sat. aq. $NaHCO_3$ (100 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude imidazolidinone was purified by flash column chromatography (EtOAc eluent) to afford imidazolidinone **4-45** (234 mg, 71% yield, R_f = 0.45 in EtOAc) as a yellow oil.

***exo*-Imidazolidinone 4-45:** ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (br. s, 1H), 3.94 (septet, *J* = 6.8, 1H), 3.70 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.16 (dt, *J* = 9.2, 5.6 Hz, 1H), 2.50 (dt, *J* = 9.0, 6.4 Hz, 1H), 2.11-2.01 (comp. m, 1H), 1.93-1.82 (comp. m, 2H), 1.79-1.61 (comp. m, 2H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.9, 65.9, 58.5, 44.4, 33.5, 28.5,25.2, 21.0, 19.4, 18.6, 14.6 IR (film) 2968, 1687, 1424, 1332, 1217 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{22}N_2O + H]^+$: 211.1805, found 211.1812; $[\alpha]_D^{33}$ = -28.5 (*c* = 1.0, $CHCl_3$).

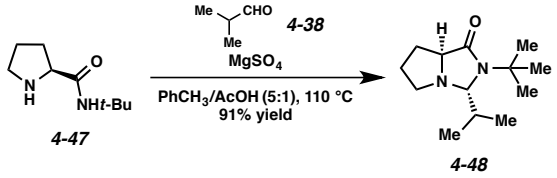


To a solution of (*S*)-*N*-Boc proline **4-136** (1.00 g, 4.65 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C was added isobutyl chloroformate (**4-137**, 636 µL, 5.11 mmol) and triethylamine (713 µL, 5.11 mmol). After stirring for 30 min at 0 °C, *t*-butylamine (539 µl, 5.11 mmol) was added and the ice bath was removed, allowing the reaction to warm to 23 °C and stir for 27 h. The reaction mixture was washed sequentially with aq. $KHSO_4$ (1 M, 20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amide **4-141** (1.06 g, 85% yield) as a white powder.

To a solution of amide **4-141** (1.06 g, 4.95 mmol) in CH_2Cl_2 (9.90 mL) at 23 °C was added TFA (7.60 mL, 44.8 mmol). The solution was stirred at 23 °C for 1 h, and upon completion the solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (20 mL) and water (10 mL) was added. The mixture was neutralized with solid Na_2CO_3 until pH ~9, and then it was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation to afford amino amide **4-47** (485 mg, 85% yield, R_f = 0.09 in 9:1 CH_2Cl_2/MeOH) as a beige oil, which was sufficiently pure to be taken on to the next step.

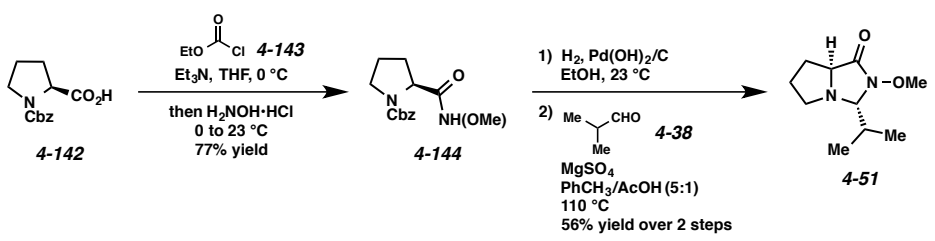
Amino amide 4-47: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br. s, 1H), 3.58 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.01-2.92 (comp. m, 1H), 2.89-2.80 (comp. m, 1H), 2.20 (br. s, 1H), 2.12-2.01 (comp. m, 1H), 1.89-1.79 (comp. m, 1H), 1.74-1.58 (comp. m, 2H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 61.3, 50.2, 47.3, 30.8, 28.8, 26.3; IR (film) 3308, 2967, 1660, 1521, 1229 cm^{-1};

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_9H_{18}N_2O + H]^+$: 171.1492, found 171.1492; $[\alpha]_D^{32}$ = -81.3 (*c* = 1.0, CH_2Cl_2).



A suspension of amino amide **4-47** (339 mg, 2.94 mmol), isobutyraldehyde (**4-38**, 349 μL, 3.83 mmol), and $MgSO_4$ (532 mg, 4.42 mmol) in PhMe (29.4 mL) and glacial acetic acid (5.89 mL) was heated to reflux and stirred for 28 h. Upon cooling, to the solution was added sat. aq. $NaHCO_3$ (100 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude imidazolidinone was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford imidazolidinone **4-48** (60.0 mg, 91% yield, R_f = 0.42 in 1:1 hexanes/EtOAc) as a yellow solid.

***exo*-Imidazolidinone 4-48:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (br. s, 1H), 3.62 (br. s, 1H), 3.17 (br. s, 1H), 2.50 (q, *J* = 8.0 Hz, 1H), 2.13-2.02 (comp. m, 1H), 1.98-1.89 (comp. m, 1H), 1.88-1.77 (comp. m, 1H), 1.75-1.63 (comp. M, 2H),1.39 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.2, 66.4, 58.4, 35.0, 29.2, 28.5, 28.0, 25.1, 18.8, 14.9; IR (film) 2967, 1687, 1403, 1366, 1275 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{24}N_2O + H]^+$: 225.1961, found 225.1966; $[\alpha]_D^{32}$ = -28,1 (*c* = 1.0, $CHCl_3$).

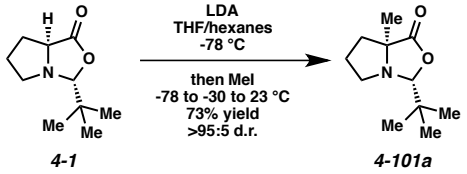


To a solution of (*S*)-*N*-Cbz proline **4-142** (1.00 g, 4.01 mmol) in THF (13.8 mL) at 0 °C was added ethyl chloroformate (**4-143**, 0.382 mL, 4.01 mmol) and triethylamine (1.07 mL, 8.02 mmol). After stirring for 40 min at 0 °C, H_2NOMe•HCl (402 mg, 4.81 mmol) was added, and after 2 h the reaction was warmed to 23 °C and stirred overnight. After 2 h, the reaction mixture was added sat. NH_4Cl (30 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude residued was purified by flash column chromatography (4:1 EtOAc/hexanes eluent) to afford amide **4-144** (864 mg, 77% yield, R_f = 0.24 in 4:1 EtOAc/hexanes) as a colorless oil.

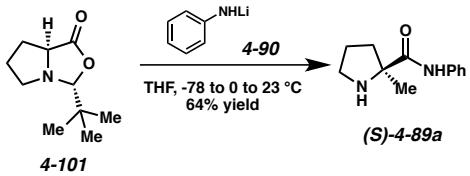
To a solution of amide **4-144** (864 g, 3.11 mmol) in EtOH (18.7 mL) at 23 °C was added $Pd(OH)_2/C$ (40.6 mg, 5 wt. %) and stirred under H_2 for 6 h. Upon completion by TLC, the reaction was filtered through celite (30 mm x 10 mm) with EtOH (100 mL) and concentrated by rotary evaporation to afford a viscous colorless oil. The residue was suspended with isobutyraldehyde (**4-38**, 0.369 mL, 4.04 mmol) and $MgSO_4$ (562 mg, 4.67 mmol) in PhMe (31 mL) and glacial acetic acid (6.2 mL) and was heated to reflux and stirred for 18 h. Upon cooling, to the solution was added sat. aq. $NaHCO_3$ (150 mL), and the mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4 and concentrated by rotary evaporation. The crude imidazolidinone was purified by flash column chromatography (4:1 EtOAc/hexanes eluent) to afford imidazolidinone **4-51** (344 mg, 56% yield over 2 steps, R_f = 0.33 in 4:1 EtOAc/hexanes) as a crystalline film.

Imidazolidinone 4-51: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (dd, *J* = 2.4, 1.6 Hz, 1H), 3.75 (s, 3H), 3.64 (dd, *J* = 7.6, 5.6 Hz, 1H), 3.19 (dt, *J* = 9.6, 5.6 Hz, 1H), 2.63 (dt, *J* = 9.6, 7.2 Hz, 1H), 2.15-2.00 (comp. m, 2H), 1.91-1.81 (comp. m, 1H), 1.79-1.70 (comp. m, 2H), 0.96 (d, *J* = 7.2

Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 84.1, 62.5, 62.1, 58.1, 31.2, 28.8, 25.2, 17.7, 15.2; IR (film) 2963, 1711, 1100, 1034, 985 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{10}H_{18}N_2O_2 + H]^+$: 199.1441, found 199.1443.

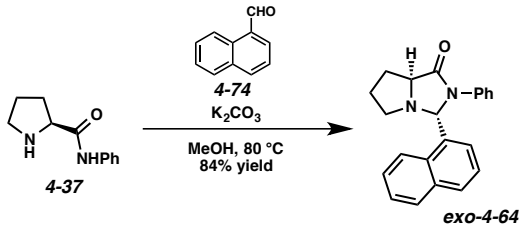


To a stirring suspension of proline imidazolidinone **4-1** (200 mg, 0.818 mmol) in THF (4.1 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.900 mL, 1.0 M, 0.900 mmol, -4 °C). After 1 h, methyl iodide (56.0 μL, 0.900 mmol) was added to the solution and the reaction mixture was stirred at -78 °C for 1 h before the ice bath was removed and the reaction mixture was warmed to 23 °C and allowed to stir overnight. Upon completion, the reaction was quenched with water (5 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation and the crude imidazolidinone was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford proline imidazolidinone **4-101a** (153 mg, 73% yield, R_f = 0.34 in 7:3 hexanes/EtOAc) as a clear colorless oil. The characterization data for imidazolidinone **4-101a** matched those previously report.[31]



To a stirring solution of aniline (0.478 mL, 5.25 mmol) in THF (2.42 mL) cooled to -78 °C was added *n*-butyllithium (2.13 mL, 2.35 M in hexanes, 5.00 mmol), and then it was warmed to 0 °C and stirred for 2 h. The lithium phenylamide solution **4-90** (2.20 mL, 1.0 M, 2.20 mmol) was

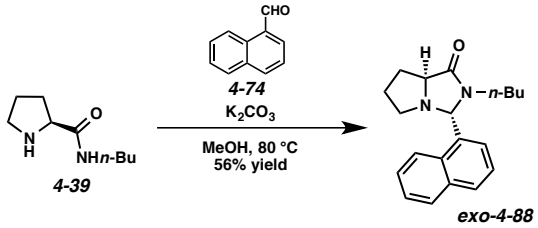
added to a stirred solution of imidazolidinone **4-101** (113 mg, 0.440 mmol) in THF (0.44 mL) at -78 °C. The solution was warmed to 0 °C over 2 h, and then the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature overnight. To the solution was added sat. aq. $NaHCO_3$ (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude aminal was purified by flash column chromatography with basic SiO_2 (3:2 Et_2O/hexanes eluent, silica was pretreated with 9:1 hexanes/triethylamine and then dried prior to use) to afford amino amide **(*S*)-4-89a** (57.9 mg, 64% yield, R_F = 0.24 in 7:3 hexanes/EtOAc on basic plates) as a white solid. The characterization data for this product matched those from the product synthesized above.



A solution of amino amide **4-37** (10.5 g, 55.1 mmol), 1-naphthaldehyde (**4-74**, 9.73 mL, 71.6 mmol), K_2CO_3 (15.2 g, 110 mmol) in methanol (167 mL) was heated to 80 °C and stirred for 5 h. Upon cooling, to the solution was added H_2O (300 mL), and the mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford imidazolidinone ***exo*-4-64** (15.2 g, 84% yield, R_f = 0.38 in 7:3 hexane/EtOAc) as a white solid.

Proline imidazolidinone *exo*-4-64: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.60-7.53 (comp m, 3H),

7.37 (t, J = 7.2 Hz, 1H), 7.30-7.22 (comp m, 3H), 7.09 (t, J = 7.2 Hz, 1H), 6.51 (s, 1H), 4.00 (d, J = 6.0 Hz, 1H), 3.74-3.65 (comp m, 1H), 3.03 (q, J = 9.2 Hz, 1H), 2.36-2.26 (comp m, 1H), 2.25-2.15 (comp m, 1H), 2.03-1.92 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 138.3, 134.6, 132.9, 130.8, 129.6, 129.4, 129.1, 127.1, 126.2, 125.4, 124.8, 122.8, 122.7, 119.8, 79.8, 64.5, 55.4, 27.0, 25.0; IR (film) 3063, 2968, 2822, 1701, 1598, 1499, 1390, 1346, 1311, 909 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{20}N_2O + H]^+$: 329.1658, found 329.1656; $[\alpha]_D^{29}$ = +7.7 (c = 1.0, CH_2Cl_2).

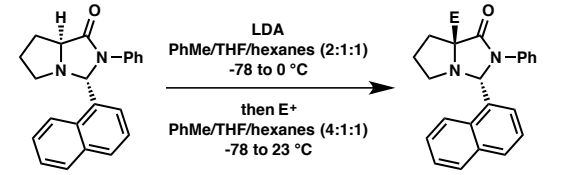


A suspension of amino amide **4-39** (4.17 g, 24.5 mmol), 1-naphthaldehyde (**4-74**, 4.32 g, 31.9 mmol), and K_2CO_3 (6.77 g, 49.0 mmol) in ethylene glycol (74 mL) was heated to 80 °C and stirred for 24 h. Upon cooling, to the suspension was added H_2O (600 mL), and the mixture was extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to produce a solid. This was filtered and washed with ice cold hexanes (30 mL) to afford imidazolidinone ***exo*-4-88** (3.93 g, 52% yield, R_f = 0.31 in 1:1 hexanes/EtOAc) as white crystals. The filtrate was concentrated and the residue was purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford an additional amount of imidazolidinone ***exo*-4-88** (0.313 mg, 4% yield).

Proline imidazolidinone *exo*-4-88: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.10 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.61 (ddd, J = 8.4, 7.2, 1.6 Hz, 1H), 7.54 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 5.89 (s, 1H), 3.91 (br

s, 1H), 3.86 (dt, *J* = 14.0, 8.0 Hz, 1H), 3.57-3.46 (comp m, 1H), 2.93 (q, *J* = 7.6 Hz, 1H), 2.68 (dt, *J* = 14.0, 6.8 Hz, 1H), 2.16 (q, *J* = 7.2 Hz, 2H), 1.96-1.86 (comp m, 2H), 1.52-1.43 (comp m, 2H), 1.37-1.23 (comp m, 2H), 0.89 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 134.6, 133.4, 131.2, 129.6, 129.3, 127.0, 126.1, 125.3, 123.0, 122.6, 79.3, 63.8, 55.9, 40.9, 29.7, 27.3, 25.1, 20.2, 13.9; IR (film) 2959, 2872, 1696, 1511, 1424, 1380, 1308, 1192, 1107, 780 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{24}N_2O + H]^+$: 309.1961, found 309.1965; $[\alpha]_D^{30}$ = +26.8 (*c* = 1.0, CH_2Cl_2).

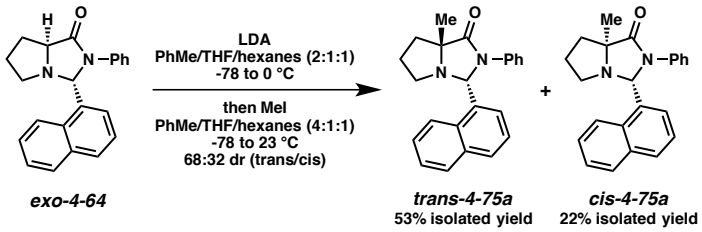
General Procedure for the anti-Selective Alkylation of Proline Imidazolidinone



***exo*-4-64/*exo*-4-88** *trans*-4-75/*trans*-4-93

In a flame-dried flask, to a suspension of proline imidazolidinone ***exo*-4-64/*exo*-4-88** (1 equiv) in PhMe (1.0 M) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.1 equiv, 0.9 to 1.1 M in ~1:1 hexane/THF, -4 °C). The solution was then allowed to warm to 0 °C and stirred for 70 min, generally turning deep red. The solution was recooled to -78 °C; and to the solution was added an equal volume of PhMe (bringing the reaction to ~0.3 M; the additional PhMe improves stirring upon addition of the electrophile). The electrophile (1.1 equiv) was added at -78 °C, and the reaction mixture stirred at -78 °C for 1.5 h before the cooling bath was removed, and the suspension was allowed to gradually warm to ambient temperature. Upon completion, as determined by TLC, the reaction was quenched with water, and the mixture was extracted into EtOAc. The combined organic layers were washed with brine and dried over

Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinone ***trans*-4-75/*trans*-4-93** was purified by flash column chromatography.

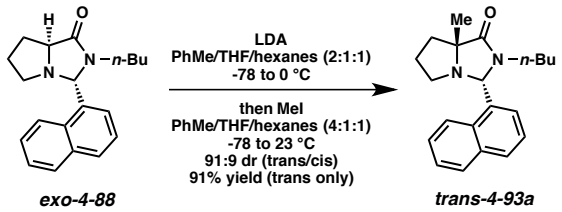


According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-64** (500 mg, 1.52 mmol) in PhMe (1.5 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.39 mL, 1.2 M, 1.67 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.5 mL) and then methyl iodide (238 μL, 1.68 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 68:32 *trans/cis*) was purified by flash column chromatography (24:1 CH_2Cl_2/EtOAc eluent) to afford *cis*-proline imidazolidinone **4-75a** (114 mg, 22% yield, R_f = 0.31 in 24:1 CH_2Cl_2/EtOAc) as a beige solid and *trans*-proline imidazolidinone **4-75a** (278 mg, 53% yield, R_f = 0.30 in 19:1 CH_2Cl_2/EtOAc) as a white foam.

***trans*-Proline imidazolidinone 4-75a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.31 (dd, *J* = 8.8, 1.2 Hz, 2H), 7.27-7.19 (comp m, 3H), 7.15 (d, *J* = 6.8 Hz, 1H), 7.09-7.02 (comp m, 2H), 2.60-2.51 (m, 1H), 2.51-2.41 (m, 1H), 2.18-2.07 (m, 1H), 1.98-1.89 (m, 1H),

1.77-1.61 (comp m, 2H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 133.8, 131.5, 129.5, 129.0, 128.9, 128.7, 127.0, 126.22, 126.16, 124.82, 124.75, 123.4, 121.8, 74.2, 71.1, 50.4, 35.6, 24.2, 22.9; IR (film) 3062, 2968, 2869, 1712, 1598, 1500, 1457, 1376, 1301, 1188 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{22}N_2O + H]^+$: 343.1811, found 343.1811; $[\alpha]_D^{29}$ = +70.6 (*c* = 1.0, CH_2Cl_2).

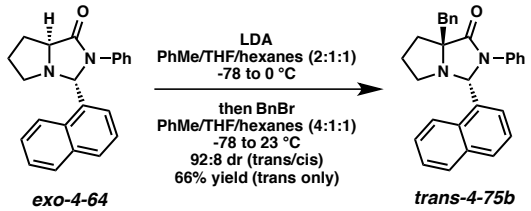
***cis*-Proline imidazolidinone 4-75a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.80 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.65 (ddd, *J* = 8.0, 6.8, 1.6 Hz, 1H), 7.61-7.54 (comp m, 3H), 7.36-7.30 (comp m, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.40 (s, 1H), 3.81-3.72 (quintet, *J* = 4.7 Hz, 1H), 3.24-3.14 (m, 1H), 2.45-2.38 (m, 1H), 1.96-1.85 (comp m, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 138.2, 135.0, 134.5, 131.1, 129.3, 129.2, 129.0, 126.8, 126.0, 125.1, 124.7, 123.7, 123.0, 120.3, 80.3, 71.8, 58.3, 38.0, 25.5, 24.9; IR (film) 2970, 1700, 1598, 1497, 1390, 1304, 909, 785, 758, 731 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{22}N_2O + H]^+$: 343.1805, found 343.1810; $[\alpha]_D^{29}$ = +115.1 (*c* = 1.0, CH_2Cl_2).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-88** (400 mg, 1.30 mmol) in (1.3 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.30 mL, 1.1 M, 1.43 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 minutes. The solution was recooled to -78 °C, and to the solution was added PhMe (1.3 mL) and then methyl iodide (89.0 μL, 1.43 mmol); it was held at -78 °C for 1.5 h before the

cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 91:9 *trans/cis*) was purified by flash column chromatography (9:1 CH_2Cl_2/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-93a** (408 mg, 91% yield, R_f = 0.16 in 9:1 CH_2Cl_2/EtOAc) as a beige oil.

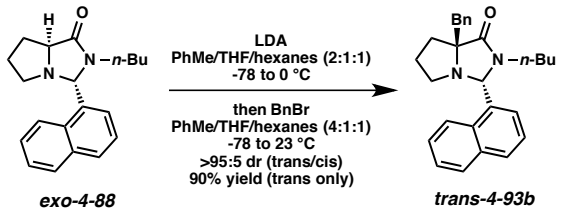
***trans*-Proline imidazolidinone 4-93a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.64-7.59 (comp m, 1H), 7.55 (td, *J* = 7.6, 1.0 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 6.43 (s, 1H), 3.85 (ddd, *J* = 14.0, 9.6, 6.8 Hz, 1H), 2.85 (ddd, *J* = 14.0, 9.2, 4.2 Hz, 1H), 2.42 (td, *J* = 9.6, 6.0 Hz, 1H), 2.25 (dt, *J* = 12.8, 8.8 Hz, 1H), 2.20-2.02 (m, 1H), 1.79 (ddd, *J* = 12.4, 8.0, 4.0 Hz, 1H), 1.69-1.56 (m, 1H), 1.54-1.30 (comp m, 3H), 1.49 (s, 3H), 1.29-1.10 (comp m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 134.0, 131.8, 129.4, 128.8, 127.1, 126.3, 125.2, 124.8, 123.3, 73.2, 70.6, 50.2, 42.1, 35.2, 28.6, 24.8, 23.7, 20.3, 13.8; IR (film) 2961, 2871, 1700, 1511, 1456, 1411, 1385, 1256, 1150, 792 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{26}N_2O + H]^+$: 323.2126, found 323.2126; $[\alpha]_D^{31}$ = -147.8 (*c* = 1.0, CH_2Cl_2).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-64** (400 mg, 1.22 mmol) in PhMe (1.2 mL) cooled to -78 °C was added a cooled solution of lithium

diisopropylamide (1.12 mL, 1.2 M, 1.34 mmol, -4 °C). The reaction solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.2 mL) and then benzyl bromide (159 μL, 1.34 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 92:8 *trans/cis*) was purified by flash column chromatography (99:1 CH_2Cl_2/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-75b** (338 mg, 66% yield, R_f = 0.35 in 99:1 CH_2Cl_2/EtOAc) as a white foam.

***trans*-Proline imidazolidinone 4-75b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 2H), 7.33-7.25 (comp m, 3H), 7.15 (t, *J* = 8.0 Hz, 3H), 7.02 (dd, *J* = 13.1, 7.1 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.67 (s, 1H), 3.48 (d, *J* = 13.2 Hz, 1H), 2.90 (d, *J* = 13.2 Hz, 1H), 2.56-2.46 (m, 1H), 2.46-2.35 (m, 1H), 2.24-2.13 (m, 1H), 2.09-2.04 (comp m, 1H), 1.72-1.64 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.44, 178.43, 138.0, 137.6, 133.7, 131.6, 130.4, 129.9, 128.75, 128.72, 128.52, 128.45, 127.1, 126.7, 126.02, 125.89, 125.0, 124.7, 123.9, 122.5, 75.9, 75.6, 51.2, 45.1, 36.4, 24.7; IR (film) 3062, 2967, 2246, 1705, 1598, 1499, 1455, 1376, 1303, 1241 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{29}H_{26}N_2O + H]^+$: 419.2118, found 419.2123; $[\alpha]_D^{30}$ = +203.2 (*c* = 1.0, CH_2Cl_2).

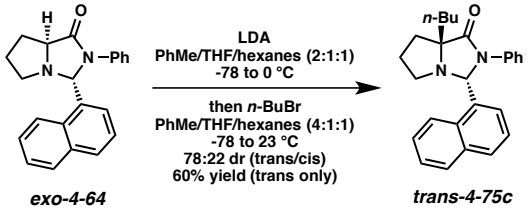


exo-4-88 *trans-4-93b*

According to the general procedure, to a suspension of proline *exo*-imidazolidinone **4-88** (400 mg, 1.30 mmol) in PhMe (1.3 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.30 mL, 1.1 M, 1.43 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.3 mL) and then benzyl bromide (170 μL, 1.43 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *trans/cis*) was purified by flash column chromatography (93:7 CH_2Cl_2/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-93b** (421 mg, 90% yield, R_f = 0.34 in 93:7 CH_2Cl_2/EtOAc) as a yellow oil.

***trans*-Proline imidazolidinone 4-93b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.61-7.52 (comp m, 3H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.27-7.19 (comp m, 2H), 5.58 (s, 1H), 3.58 (ddd, *J* = 13.6, 11.6, 4.8 Hz, 1H), 3.29 (d, *J* = 13.2 Hz, 1H), 2.84 (d, *J* = 13.2 Hz, 1H), 2.67-2.56 (comp m, 1H), 2.43-2.34 (comp m, 1H), 2.29-2.19 (comp m, 2H), 1.89 (dt, *J* = 12.4, 6.0 Hz, 1H), 1.60-1.39 (comp m, 2H), 1.02-0.83 (comp m, 3H), 0.83-0.72 (comp m, 1H), 0.63 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 137.8, 133.9, 131.9, 130.9, 130.5, 129.2, 128.8, 128.2, 126.9, 126.8, 126.1, 124.8, 123.6, 75.3, 74.9, 50.9, 44.5, 42.4, 36.2, 28.3, 25.3, 20.4, 13.7;

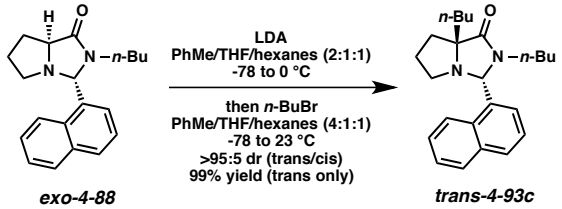
IR (film) 2960, 2870, 1697, 1511, 1494, 1454, 1387, 1334, 792, 701 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{27}H_{30}N_2O + H]^+$: 399.2441, found 399.2441; $[\alpha]_D^{31}$ = +1.3 (*c* = 1.0, CH_2Cl_2).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-64** (400 mg, 1.22 mmol) in PhMe (1.2 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.12 mL, 1.2 M, 1.34 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.2 mL) and then *n*-butyl bromide (144 μl, 1.34 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the crude imidazolidinone (dr = 78:22 *trans/cis*) was purified by flash column chromatography (400:1 CH_2Cl_2/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-75c** (281 mg, 60% yield, R_f = 0.16 in 400:1 CH_2Cl_2/EtOAc) as a colorless oil.

***trans*-Proline imidazolidinone 4-75c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 6.8 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.27-7.19 (comp m, 3H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 7.03 (s, 1H), 2.53 (td, *J* = 9.2, 6.4 Hz, 1H), 2.34 (dt, *J* = 12.8, 9.2 Hz, 1H), 2.19 (dt, *J* =

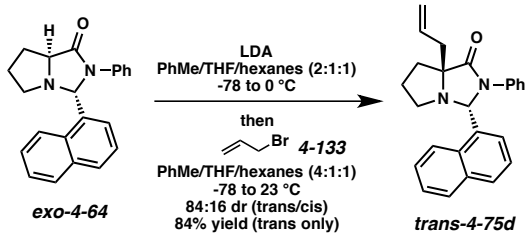
9.2, 4.8 Hz, 1H), 2.03-1.92 (comp m, 2H), 1.84 (td, *J* = 8.0, 4.4 Hz, 1H), 1.72-1.54 (comp m, 4H), 1.45 (q, *J* = 7.3 Hz, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 138.3, 133.8, 131.6, 129.8, 128.94, 128.88, 128.7, 127.0, 126.2, 126.0, 124.8, 123.5, 121.9, 75.3, 74.3, 50.8, 37.2, 34.6, 26.8, 24.8, 23.3, 14.2; IR (film) 1702, 1598, 1500, 1458, 1371, 1300, 1240, 1138, 909, 788, 759 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{28}N_2O + H]^+$: 385.2274, found 385.2281; $[\alpha]_D^{31}$ = +56.8 (*c* = 1.0, CH_2Cl_2).



exo-4-88 *trans-4-93c*

According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-88** (400 mg, 1.30 mmol) in PhMe (1.3 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.43 mL, 1.0 M, 1.43 mmol, -4 °C). The reaction solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.3 mL) and then *n*-butyl bromide (115 μL, 1.07 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *trans/cis*) was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-93c** (367 mg, 99% yield, R_f = 0.48 in 7:3 hexanes/EtOAc) as a beige oil.

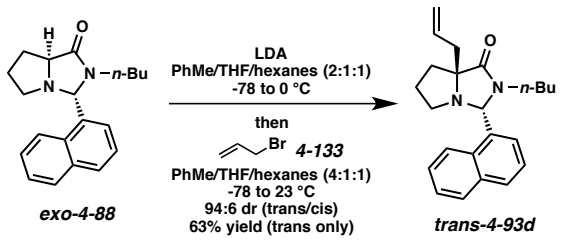
***trans*-Proline imidazolidinone 4-93c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.62 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.56 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 6.8 Hz, 1H), 6.39 (s, 1H), 3.85 (ddd, *J* = 14.0, 10.0, 6.0 Hz, 1H), 2.82 (ddd, *J* = 14.0, 10.0, 6.0 Hz, 1H), 2.43-2.34 (comp m, 1H), 2.20-2.10 (comp m, 2H), 1.91-1.76 (comp m, 2H), 1.72-1.32 (comp m, 9H), 1.29-1.12 (comp m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 134.0, 132.0, 130.5, 129.3, 128.9, 127.1, 126.2, 124.8, 124.7, 123.5, 74.7, 73.9, 50.6, 42.3, 38.2, 34.7, 28.8, 27.0, 25.4, 23.4, 20.5, 14.3, 13.8; IR (film) 2957, 2931, 2870, 1696, 1511, 1455, 1384, 1333, 791, 771 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{32}N_2O + H]^+$: 365.2587, found 365.2590; $[\alpha]_D^{35}$ = -84.0 (*c* = 1.0, $CHCl_3$).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-64** (400 mg, 1.22 mmol) in PhMe (1.2 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.22 mL, 1.1 M, 1.34 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.2 mL) and then allyl bromide (**4-133**, 116 μL, 1.34 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude

imidazolidinone (dr = 84:16 *trans/cis*) was purified by flash column chromatography (9:1 hexanes/Et_2O eluent) to afford *trans*-proline imidazolidinone **4-75d** (380 mg, 84% yield, R_f = 0.36 in 9:1 hexanes/Et_2O) as a white foam.

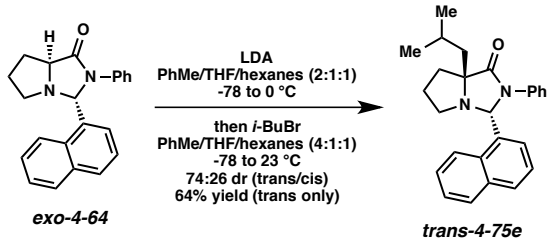
***trans*-Proline imidazolidinone 4-75d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.57 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.31-7.28 (comp m, 2H), 7.25-7.21 (comp m, 3H), 7.14 (d, *J* = 6.8 Hz, 1H), 7.05 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.03 (s, 1H), 6.19-6.05 (comp m, 1H), 5.34 (d, *J* = 16.8 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 2.77 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.56-2.47 (comp m, 2H), 2.33 (dt, *J* = 13.2, 8.8 Hz, 1H), 2.18-2.13 (comp m, 1H), 2.05-1.95 (comp m, 1H), 1.66-1.57 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 138.2, 133.8, 133.7, 131.6, 129.7, 129.0, 128.9, 128.7, 127.0, 126.2, 126.1, 125.0, 124.8, 123.6, 122.1, 119.1, 75.3, 74.4, 50.8, 41.5, 34.2, 24.6; IR (film) 1707, 1598, 1500, 1371, 1336, 1301, 1187, 1135, 788, 759 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{25}H_{24}N_2O + H]^+$: 369.2, found 368.9; $[\alpha]_D^{32}$ = +100.4 (*c* = 1.0, $CHCl_3$).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-88** (300 mg, 0.973 mmol) in PhMe (0.98 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.18 mL, 0.91 M, 1.07 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C; and to the solution was added PhMe (0.98 mL) and then allyl bromide (**4-133**, 92.5 μL, 1.07 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and

stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried with Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 94:6 *trans/cis*) was purified by flash column chromatography (25:1 CH_2Cl_2/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-93d** (212 mg, 63% yield, R_f = 0.14 in 25:1 CH_2Cl_2/EtOAc) as a colorless oil.

***trans*-Proline imidazolidinone 4-93d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 6.39 (s, 1H), 6.14-6.02 (comp m, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 3.84 (ddd, *J* = 13.6, 10.0, 6.0 Hz, 1H), 2.84 (ddd, *J* = 14.0, 10.0, 5.2 Hz, 1H), 2.65 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.48-2.34 (comp m, 2H), 2.18-2.07 (comp m, 2H), 1.88-1.79 (comp m, 1H), 1.59-1.08 (comp m, 6H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 134.1, 134.0, 132.0, 130.4, 129.3, 128.9, 127.1, 126.3, 125.0, 124.9, 123.5, 118.8, 74.5, 73.8, 50.6, 42.5, 42.3, 34.1, 29.0, 25.2, 20.5, 13.78; IR (film) 2960, 2932, 2871, 1696, 1416, 1385, 1191, 1104, 916, 792 cm^{-1}; LRMS (ESI+) *m/z* calc'd for (M + H)$^+$ $[C_{23}H_{28}N_2O + H]^+$: 349.2, found 348.9; $[\alpha]_D^{32}$ = -258.7 (*c* = 1.0, $CHCl_3$).

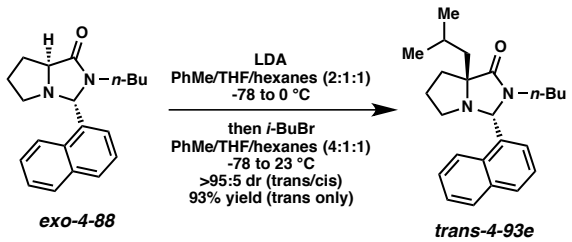


exo-4-64 *trans-4-75e*

According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-64** (400 mg, 1.22 mmol) in PhMe (1.2 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.22 mL, 1.1 M, 1.34 mmol, -4 °C). The solution was warmed to 0 °C and

held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.2 mL) and then isobutyl bromide (146 μL, 1.34 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 74:26 *trans/cis*) was purified by flash column chromatography (400:1 CH_2Cl_2/hexanes eluent) to afford *trans*-proline imidazolidinone **4-75e** (300 mg, 64% yield, R_f = 0.30 in 400:1 CH_2Cl_2/hexanes) as a white foam.

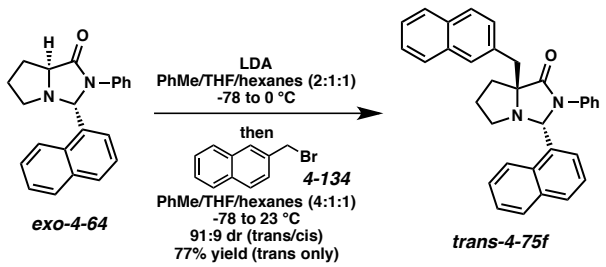
***trans*-Proline imidazolidinone 4-75e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.31 (dd, *J* = 8.8, 1.0 Hz, 2H), 7.26-7.20 (comp m, 3H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 2.57-2.46 (comp m, 1H), 2.33 (dt, *J* = 12.8, 8.8 Hz, 1H), 2.19-2.14 (comp m, 1H), 2.13-1.96 (comp m, 2H), 1.86-1.75 (comp m, 2H), 1.66-1.55 (comp m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 138.6, 133.9, 131.7, 129.9, 129.0, 128.9, 128.7, 127.0, 126.2, 124.8, 123.5, 121.8, 75.1, 74.4, 50.6, 45.1, 35.3, 25.3, 25.1, 24.8, 24.0; IR (film) 1706, 1598, 1500, 1369, 1300, 801, 786, 759, 732, 702 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{28}N_2O + H]^+$: 385.3, found 385.0; $[\alpha]_D^{32}$ = +46.4 (*c* = 1.0, $CHCl_3$).



exo-4-88 *trans-4-93e*

According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-88** (300 mg, 0.973 mmol) in PhMe (0.98 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.18 mL, 0.91 M, 1.07 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (0.98 mL) and then isobutyl bromide (116 μL, 1.07 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *trans/cis*) was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-93e** (331 mg, 93% yield, R_f = 0.40 in 4:1 hexanes/EtOAc) as a colorless oil.

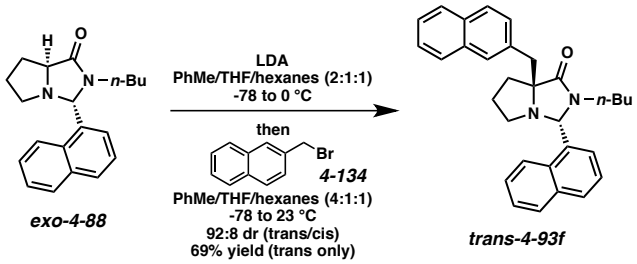
***trans*-Proline imidazolidinone 4-93e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.63-7.52 (comp m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 6.37 (s, 1H), 3.83 (ddd, *J* = 13.6, 10.0, 6.0 Hz, 1H), 2.86 (ddd, *J* = 15.2, 10.0, 5.2 Hz, 1H), 2.42-2.34 (comp m, 1H), 2.19-2.12 (comp m, 2H), 1.98-1.90 (comp m, 1H), 1.84 (ddd, *J* = 12.8, 7.6, 4.8 Hz, 1H), 1.73-1.64 (comp m, 2H), 1.56-1.33 (comp m, 4H), 1.28-1.17 (comp m, 2H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 134.0, 132.0, 130.5, 129.3, 128.9, 127.0, 126.2, 125.0, 124.9, 123.4, 74.0, 73.9, 50.1, 45.0, 42.3, 34.5, 28.7, 25.2, 25.1, 25.0, 24.5, 20.4, 13.8; IR (film) 2955, 2867, 1695, 1452, 1383, 1280, 1193, 1145, 791, 772 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{32}N_2O + H]^+$: 365.2587, found 365.2598; $[\alpha]_D^{35}$ = -98.3 (*c* = 1.0, $CHCl_3$).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-64** (400 mg, 1.22 mmol) in PhMe (1.2 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.22 mL, 1.1 M, 1.34 mmol, -4 °C). The reaction solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.2 mL) and then bromide **4-134** (296 mg, 1.34 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 91:9 *trans/cis*) was purified by flash column chromatography (CH_2Cl_2 → 3:2 hexanes/Et_2O eluent) to afford *trans*-proline imidazolidinone **4-75f** (440 mg, 77% yield, R_f = 0.34 in 6:4 hexanes/Et_2O) as a white foam.

***trans*-Proline imidazolidinone 4-75f:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.96 (comp m, 2H), 7.79 (t, *J* = 8.2 Hz, 4H), 7.66-7.54 (comp m, 3H), 7.52-7.40 (comp m, 3H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.07-7.03 (comp m, 2H), 7.01-6.98 (comp m, 2H), 6.71 (d, *J* = 7.6 Hz, 2H), 5.56 (s, 1H), 3.66 (d, *J* = 13.2 Hz, 1H), 3.07 (d, *J* = 13.2 Hz, 1H), 2.56-2.42 (comp m, 2H), 2.19-2.11 (comp m, 2H), 1.75-1.68 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 137.8, 135.1, 133.64, 133.59, 132.6, 131.4, 129.7, 128.9, 128.7, 128.6, 128.5, 127.9, 127.8, 127.7, 126.7, 126.1, 126.0, 125.8, 125.7, 125.0, 124.6, 123.8, 122.5, 75.8, 75.5, 51.2, 45.2, 36.4, 24.7; IR (film) 1704, 1598,

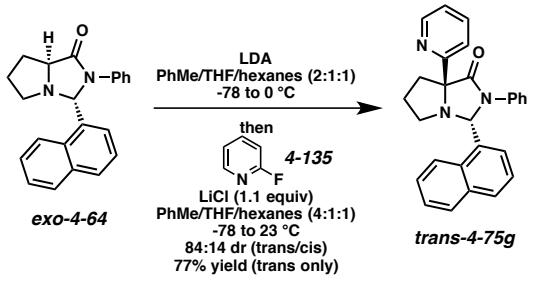
1500, 1375, 1302, 1241, 1135, 908, 788, 730 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{33}H_{28}N_2O + H]^+$: 469.2292, found 469.2292; $[\alpha]_D^{31}$ = +207.2 (*c* = 1.0, CH_2Cl_2).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-88** (300 mg, 0.973 mmol) in PhMe (0.97 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.07 mL, 1.0 M, 1.07 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (0.97 mL) and then bromide **4-134** (237 mg, 1.07 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 92:8 *trans/cis*) was purified by flash column chromatography (97:3 CH_2Cl_2/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-93f** (301 mg, 69% yield, R_f = 0.14 in 97:3 CH_2Cl_2/EtOAc) as a white foam.

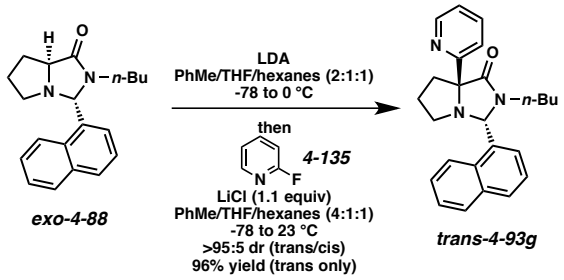
***trans*-Proline imidazolidinone 4-93f:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H), 7.90-7.78 (comp m, 6H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.47 (td, *J* = 6.8 Hz, 1H), 7.44-7.39 (comp m, 2H), 7.19 (d, *J* = 7.2 Hz, 1H), 5.48 (s, 1H), 3.59-3.49 (m, 1H), 3.47 (d, *J* = 13.2 Hz, 1H), 3.02 (d, *J* = 13.2 Hz, 1H), 2.55-2.45 (m, 1H), 2.45-2.37 (m, 1H), 2.32-2.23 (comp m, 2H), 1.95 (dt, *J* = 8.0, 4.8 Hz, 1H), 1.69-1.54 (m, 1H), 1.53-1.42 (m, 1H),

0.82-0.70 (m, 1H), 0.70-0.57 (comp m, 2H), 0.44-0.39 (m, 1H), 0.36 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 135.3, 133.9, 133.6, 132.6, 131.9, 130.4, 129.4, 129.3, 129.1, 128.8, 127.8, 127.7, 127.5, 126.9, 126.1, 126.0, 125.5, 124.77, 124.75, 123.6, 75.5, 74.9, 51.0, 44.8, 42.4, 36.4, 28.2, 25.3, 20.2, 13.4; IR (film) 2960, 2870, 1697, 1511, 1494, 1454, 1387, 1334, 792, 701 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{31}H_{32}N_2O + H]^+$: 449.2587, found 449.2591; $[\alpha]_D^{30}$ = +109.6 (*c* = 1.0, CH_2Cl_2).



To a suspension of *exo*-proline imidazolidinone **4-64** (264 mg, 0.804 mmol) and oven-dried LiCl (37.5 mg, 0.884 mmol) in PhMe (0.80 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.884 mL, 1.0 M, 0.884 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 C, and to the solution was added PhMe (0.80 mL) and then freshly distilled 2-fluoropyridine **4-135** (83.0 μL, 0.965 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 86:14 *trans/cis*) was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-75g** (250 mg, 77% yield, R_f = 0.23 in 3:2 hexanes/EtOAc) as a white foam.

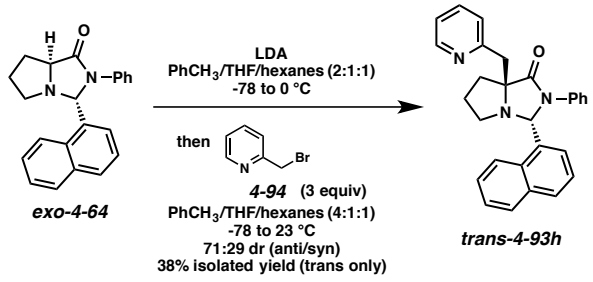
***trans*-Proline imidazolidinone 4-75g:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 7.6 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.79-7.73 (comp m, 1H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.34-7.22 (comp m, 5H), 7.18 (t, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 2.89 (dt, *J* = 13.2, 8.8 Hz, 1H), 2.77 (dt, *J* = 9.2, 7.2 Hz, 1H), 2.49 (ddd, *J* = 12.4, 7.2, 4.8 Hz, 1H), 2.43-2.33 (comp m, 1H), 1.86-1.75 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 160.4, 149.7, 138.5, 136.9, 133.8, 131.6, 129.7, 129.1, 128.8, 128.6, 127.2, 126.2, 126.1, 124.8, 124.7, 123.7, 122.7, 121.8, 121.4, 78.3, 75.3, 50.5, 36.3, 24.8; IR (film) 3062, 2971, 2870, 2245, 1712, 1598, 1500, 1370, 1302, 909 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{27}H_{23}N_3O + H]^+$: 406.1914, found 406.1917; $[\alpha]_D^{31}$ = +107.0 (*c* = 1.0, CH_2Cl_2).



To a suspension of *ex*o-proline imidazolidinone **4-88** (353 mg, 1.15 mmol) and oven-dried LiCl (53.6 mg, 1.27 mmol) in PhMe (1.15 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.27 mL, 1.0 M, 1.27 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (1.15 mL) and then freshly distilled 2-fluoropyridine **4-135** (119 μL, 1.38 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted into EtOAc (3 x 15 mL). The combined organic layers were washed

with brine (15 mL) and dried over Na_2SO_4. The solvent was then removed by rotary evaporation, and the crude imidazolidinone (dr = >95:5 *trans/cis*) was purified by flash column chromatography (7:3 EtOAc/hexanes eluent) to afford *trans*-proline imidazolidinone **4-93g** (446 mg, 96% yield, R_f = 0.27 in 7:3 EtOAc/hexanes) as a white foam.

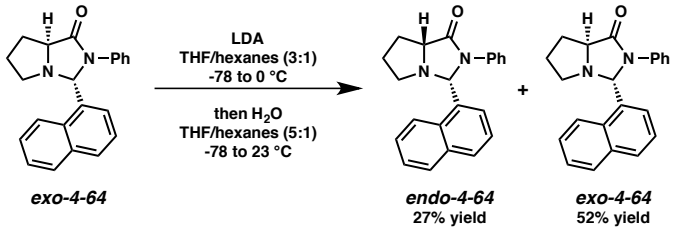
***trans*-Proline imidazolidinone 4-93g:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.8 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 7.91 (t, *J* = 6.8 Hz, 2H), 7.78-7.71 (comp m, 2H), 7.65 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.60-7.49 (comp m, 2H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.26-7.20 (comp m, 1H), 6.70 (s, 1H), 3.92-3.84 (comp m, 1H), 2.88 (ddd, *J* = 14.0, 8.4, 6.0 Hz, 1H), 2.72-2.57 (comp m, 2H), 2.45-2.31 (comp m, 2H), 1.75-1.58 (comp m, 2H), 1.34-1.22 (comp m, 2H), 1.08-0.94 (comp m, 2H), 0.67 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 161.2, 149.4, 136.6, 133.9, 131.9, 130.1, 129.3, 128.7, 127.1, 126.2, 124.9, 124.7, 123.5, 122.3, 121.0, 77.6, 74.3, 50.3, 42.3, 35.4, 28.5, 25.2, 19.8, 13.5; IR (film) 2959, 2871, 1696, 1586, 1429, 1383, 1281, 912, 791, 729 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{25}H_{27}N_3O + H]^+$: 386.2227, found 386.2237; $[\alpha]_D^{35}$ = -15.3 (*c* = 1.0, $CHCl_3$).



According to the general procedure, to a suspension of *exo*-proline imidazolidinone **4-64** (300 mg, 0.913 mmol) in PhMe (0.910 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.03 mL, 1.0 M, 1.05 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. While aminal ***exo*-4-64** was deprotonating, to a flask was added 2-(bromomethyl)pyridine hydrobromide (**4-94**, 0.693 mg, 2.74 mmol), and was free-based with sat.

aq. $NaHCO_3$ (10 mL). After 1 minute, the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), dried with Na_2SO_4, and concentrated at 0 °C to produce a pink oil which was added $PhCH_3$ (0.91 mL) and was stored for ~30 minutes at -78 °C to avoid decomposition. The solution was recooled to -78 °C, and to the solution was added the bromide solution (**4-94**, ~0.910 mL, ~3.01 M); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 71/29 *trans/cis*) was purified by flash column chromatography (7:3 CH_2Cl_2/EtOAc eluent) to afford *trans*-proline imidazolidinone **4-93h** (145 mg, 38% yield, R_f = 0.31 in 7:3 CH_2Cl_2/EtOAc) as a beige foam.

***trans*-Imidazolidinone 4-93h:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* =8.4 Hz, 1H), 7.67 (t, *J* = 8.4 Hz, 1H), 7.64 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.55-7.49 (comp. m, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.21-7.11 (comp. m, 4H), 7.05-6.99 (comp. m, 2H), 6.96-6.92 (comp. m, 2H) 5.71 (s, 1H), 3.62 (d, *J* = 12.8 Hz, 1H), 3.21 (d, *J* = 12.8 Hz, 1H), 2.55-2.40 (comp. m, 2H), 2.25-2.19 (comp. m, 1H), 2.19-2.11 (comp. m, 1H), 1.77-1.57 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 157.9, 149.4, 138.1, 136.5, 133.6, 131.5, 129.6, 128.8, 128.6, 128.5, 127.0, 126.1, 125.9, 124.9, 124.6, 123.8, 122.2, 122.0, 75.4, 75.3, 51.1, 46.8, 36.3, 24.5; IR (film) 1708, 1597, 1500, 1374, 1302 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_9H_{18}N_2O + H]^+$: 420.2070, found 420.2083; $[\alpha]_D^{31}$ = 141.1 (*c* = 1.0, CH_2Cl_2).

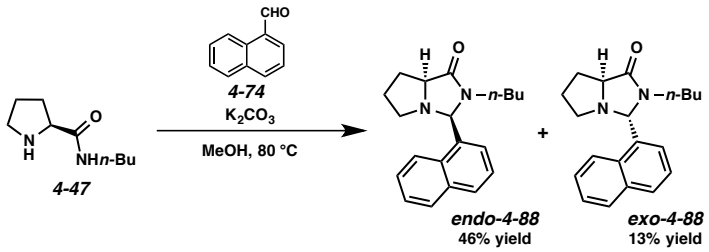


To a stirring suspension of *exo*-proline imidazolidinone **4-64** (500 mg, 1.22 mmol) in THF (1.5 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (1.68 mL, 1.0 M, 1.67 mmol, -4 °C). The reaction solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the mixture was added THF (1.5 mL) and water (2.00 mL, 111 mmol); it was held at -78 °C for 5 min before being allowed to warm to ambient temperature over 20 min. To the mixture was added water (30 mL), and it was then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The solution was concentrated in vacuo (crude DR 54:46 *syn/anti*) and the residue was purified by flash column chromatography (7:3 → 1:1 hexanes/EtOAc eluent) to afford *endo*-proline imidazolidinone **4-64** (134 mg, 27% yield, R_F = 0.44 in 7:3 hexanes/EtOAc) as a beige oil that slowly crystallized and *exo*-proline imidazolidinone **4-64** (262 mg, 52% yield, R_F = 0.38 in 7:3 hexanes/EtOAc) as a white solid.

***endo*-Imidazolidinone 4-64:** ^{1}H NMR (400 MHz, C_6D_6) δ 8.44 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.46-7.40 (comp m, 4 H), 7.29 (dd, *J* = 8.0, 6.8 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.01-6.96 (comp m, 2 H), 6.88 (dd, *J* = 8.0, 7.2 Hz, 1H), 6.82 (tt, *J* = 7.2, 1.2 Hz, 1H), 6.74 (s, 1H), 3.83 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.29-2.16 (comp m, 2H), 2.03-1.94 (comp m, 1H), 1.84-1.80 (comp m, 1H), 1.31-1.21 (comp m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 176.2, 139.2, 134.3, 131.9, 130.4, 129.1, 129.0, 128.7, 126.9, 126.33, 126.27, 125.0, 124.4, 124.2, 121.7, 75.7, 65.8, 49.1, 27.6, 25.0; IR (film) 3063, 2966, 1701, 1598, 1499, 1390, 1310, 908, 779, 730 cm^{-1};

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{20}N_2O + H]^+$: 329.1658, found 329.1658; $[\alpha]_D^{30}$ = +40.1 (*c* = 0.5, CH_2Cl_2).

Note: *endo*-Imidazolidinone **4-64** is unstable to silica and slowly converts to amino amide **4-37** and 1-naphthaldehyde.

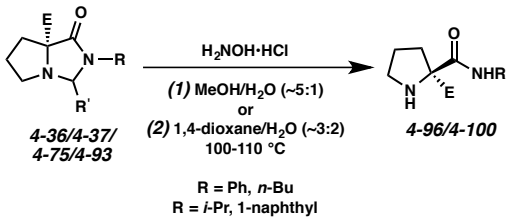


A suspension of amino amide **4-47** (1.41 g, 8.28 mmol), 1-naphthaldehyde (**4-74**, 1.68 g, 10.8 mmol), and K_2CO_3 (2.29 g, 16.6 mmol) in anhydrous MeOH (25 mL) was heated at 80 °C and stirred for 5.5 h. Upon cooling, to the solution was added sat. $NaHCO_3$ (200 mL), and the mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (1:1 → 3:2 EtOAc/hexanes) to afford *exo*-imidazolidinone **4-88** (0.33 g, 13% yield, R_f = 0.31 in 1:1 hexanes/EtOAc) as a white crystalline solid and *endo*-imidazolidinone **4-88** (1.18 g, 46% yield, R_f = 0.20 in 3:2 EtOAc/hexanes) as an orange oil.

***endo*-Imidazolidinone 4-88:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.4 Hz, 1H), 7.91 (t, *J* = 9.4 Hz, 2H), 7.65-7.54 (comp m, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 6.51 (s, 1H), 4.04-3.96 (comp m, 1H), 3.86 (ddd, 14.0, 9.6, 6.8 Hz, 1H), 2.87 (ddd, *J* = 14.0, 9.2, 5.2 Hz, 1H), 2.37 (td, *J* = 9.6, 6.4 Hz, 1H), 2.24-2.02 (comp m, 3H), 1.61-1.52 (comp m, 2H), 1.50-1.31 (comp m, 2H), 1.26-1.12 (comp m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 134.0, 131.8, 129.7, 128.9, 127.3, 126.4, 125.1, 124.8, 123.1, 74.9, 65.5, 49.3, 42.2, 28.7,

27.6, 25.3, 20.3, 13.7; IR (film) 2961, 2872, 1700, 1511, 1385, 1333, 1285, 1191, 1124, 791 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{24}N_2O + H]^+$: 309.1961, found 309.1966; $[\alpha]_D^{29}$ = +145.7 (*c* = 1.0, CH_2Cl_2).

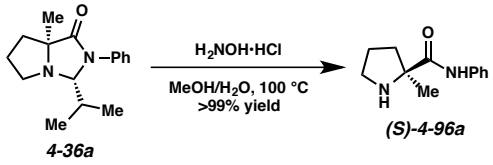
General Procedure for Imidazolidinone Aminolysis



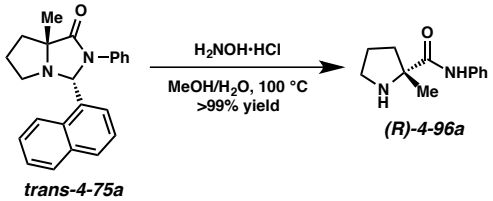
In a sealed ½ dram vial, a suspension of imidazolidinone **4-36/4-37/4-75/4-93** (1 equiv) and H_2NOH•HCl (3 equiv) in either 5:1 MeOH/H_2O (0.17 M) or 3:2 1,4-dioxane/H_2O (0.20 M) was heated at 100-110 °C. Upon cooling, the solution was added to 1 M $KHSO_4$ and was washed with EtOAc. To the aqueous layer was added sat. Na_2CO_3 until it reached pH ~12. The aqueous solution was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **4-96/4-100**.

Note: Amino amide products could be purified on basic SiO_2 (pretreated with 9:1 hexane/triethylamine) with a minimal decrease in the isolated yields.

Technical note: Minimization of reaction headspace in the sealed vials was important, presumably to keep the potentially volatile H_2NOH in the reaction mixture.



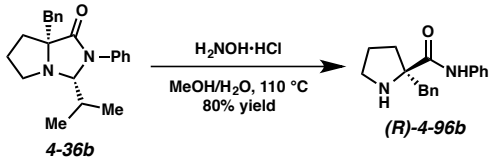
In a sealed ½ dram vial, a suspension of imidazolidinone **4-36a** (58.0 mg, 0.224 mmol) and H_2NOH•HCl (35.9 mg, 0.673 mmol) in MeOH (0.22 mL) and H_2O (1.1 mL) was heated at 100 °C and stirred for 4 h. Imidazolidinone **4-36a** slowly dissolved over the course of the reaction. Upon cooling, the solution was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (7 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*S*)-4-96a** (45.9 mg, >99% yield, R_f = 0.24 in 7:3 hexanes/EtOAc on basic plates) as a colorless oil. The amino amide was analytically pure without need for further purification.



In a sealed ½ dram vial, a suspension of *trans*-imidazolidinone **4-75a** (59.0 mg, 0.172 mmol) and H_2NOH•HCl (35.9 mg, 0.517 mmol) in MeOH (0.17 mL) and H_2O (0.86 mL) was heated at 100 °C and stirred for 21.5 h. *trans*-Imidazolidinone **4-75a** slowly dissolved over the course of the reaction. Upon cooling, the solution was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (7 x 5 mL), and the combined organic

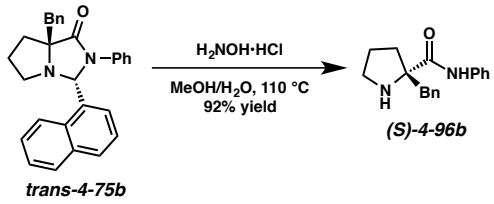
layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*R*)-4-96a** (35.1 mg, >99% yield, R_f = 0.24 in 7:3 hexanes/EtOAc on basic plates) as a colorless oil. The amino amide was analytically pure without need for further purification.

Amino amide 4-96a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (br s, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.32 (app. t, *J* = 8.0 Hz, 2H), 7.08 (tt, *J* = 8.0, 1.2 Hz, 1H), 3.14 (dt, *J* = 10.4, 6.8 Hz, 1H), 2.93 (dt, *J* = 10.4, 6.4 Hz, 1H), 2.40-2.32 (comp m, 1H), 1.81-1.65 (comp m, 3H), 1.64 (br s, 1H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 138.3, 129.0, 123.9, 119.2, 67.2, 47.4, 37.9, 26.8, 26.2; IR (film) 3263, 2966, 1678, 1601, 1518, 1440, 1312, 1135, 757, 692 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{16}N_2O + H]^+$: 205.1335, found 205.1340; (*S*): $[\alpha]_D^{31}$ = -40.8 (*c* = 1.0, CH_2Cl_2), (*R*): $[\alpha]_D^{30}$ = +40.0 (*c* = 1.0, CH_2Cl_2).



In a sealed ½ dram vial, a suspension of imidazolidinone **4-36b** (22.2 mg, 0.0664 mmol) and H_2NOH•HCl (13.8 mg, 0.199 mmol) in MeOH (0.066 mL) and H_2O (0.33 mL) was heated at 110 °C and stirred for 8 h. Imidazolidinone **4-36b** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any

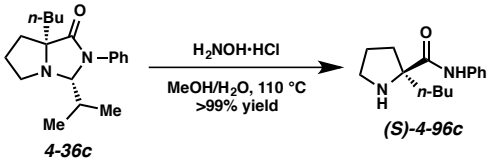
insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*R*)-4-96b** (14.9 mg, 80% yield, R_f = 0.57 in 7:3 hexanes/EtOAc on basic plates) as a beige crystalline solid. The amino amide was analytically pure without need for further purification.



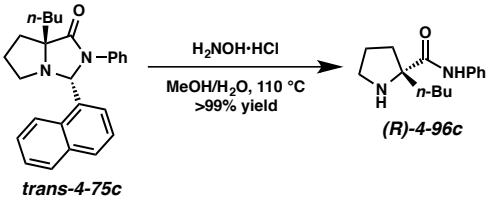
In a sealed ½ dram vial, a suspension of *trans*-imidazolidinone **4-75b** (41.3 mg, 0.099 mmol) and H_2NOH•HCl (20.6 mg, 0.296 mmol) in MeOH (0.10 mL) and H_2O (0.49 mL) was heated at 110 °C and stirred for 14 h. *trans*-Imidazolidinone **4-75b** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*S*)-4-96b** (25.4 mg, 92% yield, R_f = 0.57 in 7:3 hexanes/EtOAc on basic plates) as a beige crystalline solid. The amino amide was analytically pure without need for further purification.

Amino amide 4-96b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.33-7.21 (comp m, 5H), 7.17-7.13 (comp m, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 3.60 (d, *J* = 13.6 Hz, 1H), 3.08-2.99 (comp m, 1H), 3.00-2.89 (comp m, 1H), 2.75 (d, *J* = 13.6 Hz, 1H), 2.32 (quintet, *J* = 6.5 Hz, 1H), 1.94-1.86 (comp m, 1H), 1.87 (br s, 1H), 1.83-1.65 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 138.1, 137.0, 130.0, 129.0, 128.7, 127.1, 124.0, 119.6, 70.7, 46.9, 43.7, 37.1, 26.0; IR (film) 3261, 1680, 1601, 1515, 1441, 1310, 1174, 1102, 755, 702 cm^{-1}; HRMS

(ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{20}N_2O + H]^+$: 281.1648, found 281.1655; (*S*): $[\alpha]_D^{32}$ = -132.6 (*c* = 1.0, $CHCl_3$), (*R*): $[\alpha]_D^{32}$ = +131.0 (*c* = 1.0, $CHCl_3$).



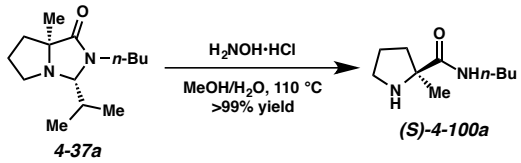
In a sealed ½ dram vial, a suspension of imidazolidinone **4-36c** (43.9 mg, 0.146 mmol) and H_2NOH•HCl (30.5 mg, 0.438 mmol) in MeOH (0.15 mL) and H_2O (0.73 mL) was heated at 110 °C and stirred for 8 h. Imidazolidinone **4-36c** slowly dissolved over the course of the reaction. Upon cooling, the solution was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (6 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*S*)-4-96c** (45.9 mg, >99% yield, R_f = 0.53 in 7:3 hexanes/EtOAc on basic plates) as a yellow oil. The amino amide was analytically pure without need for further purification.



In a sealed ½ dram vial, a suspension of *trans*-imidazolidinone **4-75c** (28.8 mg, 0.0749 mmol) and H_2NOH•HCl (15.6 mg, 0.225 mmol) in MeOH (0.075 mL) and H_2O (0.38 mL) was heated at 110 °C and stirred for 14 h. *trans*-Imidazolidinone **4-75c** slowly dissolved over the course of the

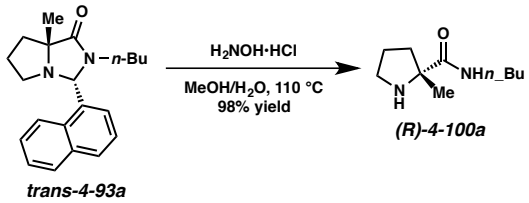
reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (6 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*R*)-4-96c** (18.4 mg, >99% yield, R_f = 0.53 in 7:3 hexanes/EtOAc on basic plates) as a yellow oil. The amino amide was analytically pure without need for further purification.

Amino amide 4-96c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 3.15-3.07 (m, 1H), 2.97-2.89 (m, 1H), 2.38-2.26 (m, 1H), 2.13-2.03 (m, 1H), 1.78-1.66 (comp m, 3H), 1.60-1.51 (m, 1H), 1.35-1.20 (comp m, 5H), 0.87 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 138.2, 129.0, 123.9, 119.3, 70.6, 47.4, 39.3, 37.1, 27.3, 26.4, 23.2, 14.1; IR (film) 3250, 2957, 2871, 2360, 1680, 1600, 1515, 1441, 1309, 754 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{22}N_2O + H]^+$: 247.2, found 246.9; (*S*): $[\alpha]_D^{31}$ = -8.9 (*c* = 1.0, $CHCl_3$), (*R*): $[\alpha]_D^{30}$ = +8.4 (*c* = 1.0, $CHCl_3$).



In a sealed ½ dram vial, a suspension of imidazolidinone **4-37a** (50.5 mg, 0.212 mmol) and H_2NOH•HCl (44.2 mg, 0.636 mmol) in MeOH (0.21 mL) and H_2O (1.1 mL) was heated at 110 °C and stirred for 21 h. Imidazolidinone **4-37a** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The

aqueous solution was extracted with EtOAc (10 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*S*)-4-100a** (39.2 mg, >99% yield, R_f = 0.10 in 7:3 hexanes/EtOAc on basic plates) as a yellow oil. The amino amide was analytically pure without need for further purification.

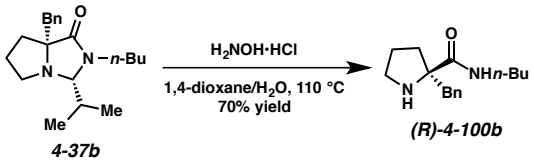


trans-4-93a *(R)-4-100a*

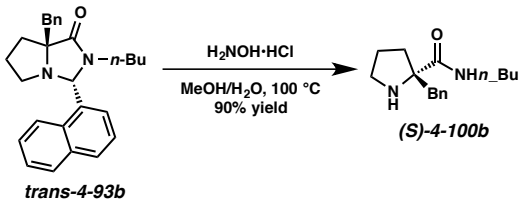
In a sealed ½ dram vial, a suspension of *trans*-imidazolidinone **4-93a** (50.4 mg, 0.156 mmol) and H_2NOH•HCl (32.6 mg, 0.469 mmol) in MeOH (0.16 mL) and H_2O (0.78 mL) was heated at 100 °C and stirred for 3 h. *trans*-Imidazolidinone **4-93a** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*R*)-4-100a** (28.2 mg, 98% yield, R_f = 0.10 in 7:3 hexanes/EtOAc on basic plates) as a yellow oil. The amino amide was analytically pure without need for further purification.

Amino amide 4-100a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 3.25-3.10 (comp m, 2H), 3.05 (dt, *J* = 10.4, 6.8 Hz, 1H), 2.79 (dt, *J* = 10.8, 6.4 Hz, 1H), 2.22 (quintet, *J* = 6.3 Hz, 1H), 1.88 (br s, 1H), 1.75-1.63 (comp m, 2H), 1.62-1.51 (comp m, 1H), 1.50-1.40 (comp m, 2H), 1.37

(s, 3H), 1.31 (comp m, 2H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 66.7, 47.2, 38.9, 37.7, 31.9, 26.7, 26.1, 20.2, 13.9; IR (film) 3315, 2958, 2930, 2871, 1651, 1515, 1458, 1367, 1229, 1138 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{10}H_{20}N_2O + H]^+$: 185.1655, found 185.1655; (*S*): $[\alpha]_D^{32}$ = -39.5 (*c* = 1.0, $CHCl_3$), (*R*): $[\alpha]_D^{31}$ = +40.9 (*c* = 1.0, $CHCl_3$).

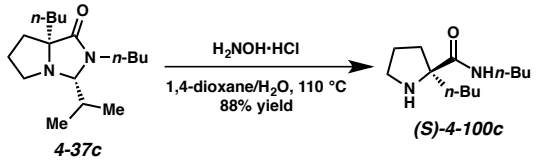


In a sealed ½ dram vial, a suspension of imidazolidinone **4-37b** (45.5 mg, 0.145 mmol) and H_2NOH•HCl (60.5 mg, 0.870 mmol) in dioxane (0.29 mL) and H_2O (0.44 mL) was heated at 110 °C and stirred for 70 h. Imidazolidinone **4-37b** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (5 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*R*)-4-100b** (32.6 mg, 88% yield, R_f = 0.50 in 7:3 hexanes/EtOAc on basic plates) as a yellow oil. The amino amide was analytically pure without need for further purification.

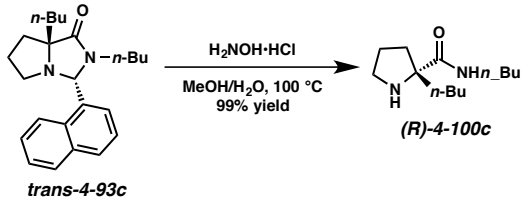


In a sealed ½ dram vial, a suspension of *trans*-imidazolidinone **4-93b** (57.4 mg, 0.144 mmol) and H_2NOH•HCl (30.0 mg, 0.432 mmol) in MeOH (0.14 mL) and H_2O (0.72 mL) was heated at 100 °C and stirred for 18 h. *trans*-Imidazolidinone **4-93b** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). The aqueous layer was added sat. Na_2CO_3 (10 mL) until pH ~12. The aqueous solution was extracted with EtOAc (5 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*S*)-4-100b** (36.6 mg, 90% yield, R_f = 0.50 in 7:3 hexanes/EtOAc on basic plates) as a colorless oil. The amino amide was analytically pure without need of further purification.

Amino amide 4-100b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.29-7.18 (comp m, 3H), 7.13 (d, *J* = 6.8 Hz, 2H), 3.49 (d, *J* = 13.6 Hz, 1H), 3.42-3.10 (comp m, 2H), 2.99 (dt, *J* = 10.2, 6.8 Hz, 1H), 2.83 (dt, *J* = 10.2, 6.4 Hz, 1H), 2.64 (d, *J* = 13.6 Hz, 1H), 2.20 (dt, *J* = 8.8, 6.8 Hz, 1H), 1.88 (br s, 1H), 1.85-1.76 (comp m, 1H), 1.73-1.61 (comp m, 2H), 1.40-1.32 (comp m, 2 H), 1.27-1.15 (comp m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 137.4, 129.9, 128.5, 126.8, 70.1, 46.8, 43.7, 38.9, 37.1, 37.1, 25.8, 20.1, 13.8; IR (film) 3330, 2956, 2929, 2871, 1653, 1515, 1454, 1105, 1030, 702 cm^{-1}; HRMS (ESI+) *m/z* calc'd for (M + H)$^+$ $[C_{16}H_{24}N_2O + H]^+$: 261.1961, found 261.1972; (*S*): $[\alpha]_D^{32}$ = -4.3 (*c* = 1.0, $CHCl_3$), (*R*): $[\alpha]_D^{32}$ = +4.0 (*c* = 1.0, $CHCl_3$).



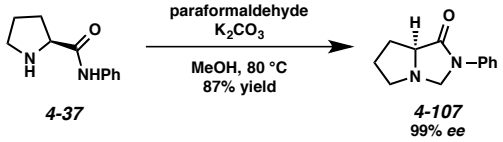
In a sealed ½ dram vial, a suspension of imidazolidinone **4-37c** (46.1 mg, 0.164 mmol) and H_2NOH•HCl (68.4 mg, 0.984 mmol) in dioxane (0.33 mL) and H_2O (0.49 mL) was heated at 110 °C and stirred for 70 h. Imidazolidinone **4-37c** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (5 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide **(*S*)-4-100c** (32.6 mg, 88% yield, R_f = 0.48 in 7:3 hexanes/EtOAc on basic plates) as a yellow oil. The amino amide was analytically pure without need for further purification.



In a sealed ½ dram vial, a suspension of *trans*-imidazolidinone **4-93c** (48.0 mg, 0.132 mmol) and H_2NOH•HCl (27.5 mg, 0.395 mmol) in MeOH (0.13 mL) and H_2O (0.66 mL) was heated at 110 °C and stirred for 33 h. *trans*-Imidazolidinone **4-93c** slowly dissolved over the course of the reaction. Upon cooling, the reaction was added to 1 M $KHSO_4$ (5 mL) and was washed with EtOAc (2 x 5 mL). To the aqueous layer was added sat. Na_2CO_3 (10 mL) until it reached pH ~12. The aqueous solution was extracted with EtOAc (5 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude film was dissolved in $CHCl_3$, and the solution was transferred to another container to remove any insoluble materials. This solution was concentrated by rotary evaporation to afford amino amide

(*R*)-4-100c (29.5 mg, 99% yield, R_f = 0.48 in 7:3 hexanes/EtOAc on basic plates) as a yellow oil. The amino amide was analytically pure without need for further purification.

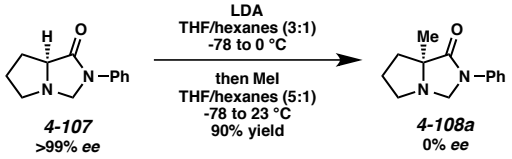
Amino amide 4-100c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 3.26-3.12 (comp m, 2H), 3.06-3.98 (comp m, 1H), 2.84-2.76 (comp m, 1H), 2.24-2.15 (comp m, 1H), 2.03-1.92 (comp m, 1H), 1.72-1.54 (comp m, 4H), 1.51-1.39 (comp m, 3H), 1.38-1.10 (comp m, 6H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.86 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 70.1, 47.2, 39.2, 38.9, 37.0, 31.9, 27.2, 26.2, 23.2, 20.2, 14.1, 13.9; IR (film) 3319, 2956, 2931, 2871, 1656, 1514, 1465, 1378, 1230, 1064 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{26}N_2O + H]^+$: 227.2118, found 227.2120; (*S*): $[\alpha]_D^{32}$ = -29.8 (*c* = 1.0, $CHCl_3$), (*R*): $[\alpha]_D^{33}$ = +31.3 (*c* = 1.0, $CHCl_3$).



A suspension of amino amide **4-37** (830 mg, 4.36 mmol), paraformaldehyde (170 mg, 5.67 mmol), and K_2CO_3 (1.21 g, 8.72 mmol) in anhydrous MeOH (13.2 mL) was heated at 80 °C and stirred for 3 h. Upon cooling, to the solution was added H_2O (100 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude solid was purified by flash column chromatography (49:1 EtOAc/MeOH eluent) to afford imidazolidinone **4-107** (763 mg, 87% yield, >99% ee, R_f = 0.25 in 49:1 EtOAc/MeOH) as a white solid.

Proline imidazolidinone 4-107: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (comp m, 2H), 7.40-7.35 (comp m, 2H), 7.16 (tt, *J* = 7.6, 1.2 Hz, 1H), 5.00 (d, *J* = 8.4 Hz, 1H), 4.57 (d, *J* = 8.4 Hz, 1H), 3.94 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.30 (dt, *J* = 9.6, 5.2 Hz, 1H), 2.70 (dt, *J* = 9.2, 8.0 1H), 2.24-

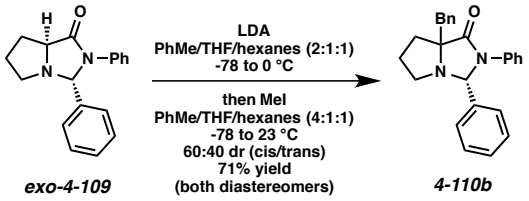
2.18 (comp m, 2 H), 1.90-1.83 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 138.1, 129.2, 124.9, 119.2, 70.6, 66.7, 56.0, 28.0, 25.3; IR (film) 1697, 1598, 1500, 1460, 1406, 1321, 1196, 1132, 759, 692 cm^{-1}; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{14}N_2O + H]^+$: 203.1, found 202.9; $[\alpha]_D^{32}$ = +8.3 (*c* = 1.0, $CHCl_3$).



To a suspension of proline imidazolidinone **4-107** (100 mg, 0.496 mmol) in THF (0.50 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.606 mL, 0.90 M, 0.546 mmol, -4 °C). The solution was warmed to 0 °C and held for 20 min. The solution was recooled to -78 °C, and to the solution was added THF (0.50 mL) and then methyl iodide (34.0 μL, 0.546 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone was purified by flash column chromatography (3:2 EtOAc/hexanes eluent) to afford proline imidazolidinone **4-108a** (96.6 mg, 90% yield, R_f = 0.24 in 98:2 CH_2Cl_2/MeOH, 0% *ee*) as a yellow solid.

Proline imidazolidinone 4-108a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (comp m, 2H), 7.38-7.33 (comp m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.92 (d, *J* = 8.4 Hz, 1H), 4.48 (d, *J* = 8.4 Hz, 1H), 3.34-3.29 (comp m, 1H), 2.77-2.71 (comp m, 1H), 2.39-2.30 (comp m, 1H), 1.89-1.77 (comp m, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 138.3, 129.2, 124.8, 119.1, 72.2, 68.9, 56.9, 35.7, 24.7, 22.6; IR (film) 1696, 1598, 1494, 1406, 1347, 1320, 1179, 1141, 1096, 760 cm^{-}

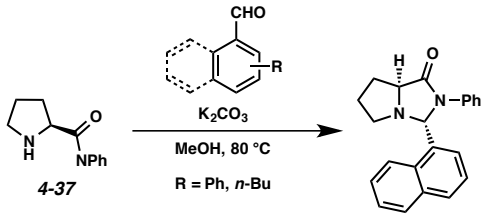
[1]; LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{16}N_2O + H]^+$: 217.1, found 216.9; $[\alpha]_D^{31}$ = -4.5 (*c* = 1.0, $CHCl_3$).



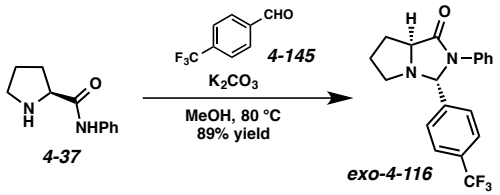
To suspension of *exo*-proline imidazolidinone **4-109** (105 mg, 0.371 mmol) in PhMe (0.37 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.453 mL, 0.90 M, 0.408 mmol, -4 °C). The reaction solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added PhMe (0.50 mL) and then benzyl bromide (48.5 μL, 0.408 mmol); it was held at -78 °C for 1.5 h before being allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude imidazolidinone (dr = 60:40 *cis/trans*) was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford an inseperable mixture of *cis*- and *trans*-proline imidazolidinone **4-110b** (98.6 mg, 71% yield, R_f = 0.26 in 4:1 hexanes/EtOAc) as a white foam.

Proline imidazolidinone 4-110b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (comp m, 1H), 7.25-7.08 (comp m, 9H), 7.05-7.00 (comp m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.5 Hz, 2H), 5.35 (s, 1H), 3.21 (d, *J* = 13.4 Hz, 1H), 3.10-2.96 (comp m, 2H), 2.75 (d, *J* = 13.4 Hz, 1H), 2.28 (ddd, *J* = 13.6, 8.4, 5.2 Hz, 1H), 1.93 (dt, *J* = 13.2, 8.0 Hz, 1H), 1.84-1.73 (comp m, 1H), 1.67-1.58 (comp m, 1H); LRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{25}H_{24}N_2O + H]^+$: 369.2, found 369.2.

General Procedure for the Basic Attachment of Aldehydes Toward Imidazolidinones



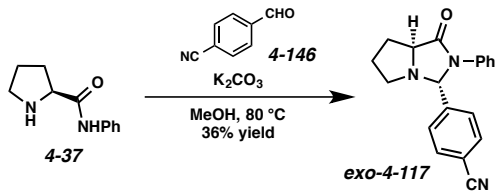
A solution of amino amide **4-37** (1 equiv), aryl aldehyde (1.3 equiv), K_2CO_3 (2 equiv) in methanol (0.33 M) was heated to 80 °C and stirred until complete by TLC. Upon cooling, to the solution was added H_2O, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography to afford imidazolidinone.



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-116** was afforded as a beige solid (R_f = 0.21 in 39:1 $CHCl_3/Et_2O$) isolated in 89% yield.

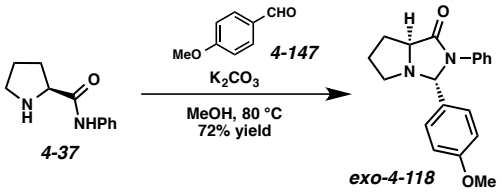
***exo*-Imidazolidinone 4-116:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 8.0, 7.2 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 5.74 (s, 1H), 4.00 (t, *J* = 7.0 Hz, 1H), 3.45 (dt, *J* = 10.0, 4.5 Hz, 1H), 2.90 (q, *J* = 4.5 Hz, 1H), 2.22 (q, *J* = 7.0, 2H), 1.95-1.85 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 143.6, 137.4, 130.9 (q, *J* = 32.4 Hz), 129.3, 126.7, 126.2 (q, *J* = 13.9 Hz), 125.5, 124.0 (q, *J* = 270.6 Hz), 121.2, 83.0, 64.5, 56.3, 27.7, 25.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.9; IR (film) 1697,

1496, 1379, 1329, 1111 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{17}F_3N_2O + H]^+$: 347.1366, found 347.1366.



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, imidazolidinone **4-117** was afforded as a beige solid (R_f = 0.30 in 7:3 EtOAc/hexanes) isolated in 36% yield.

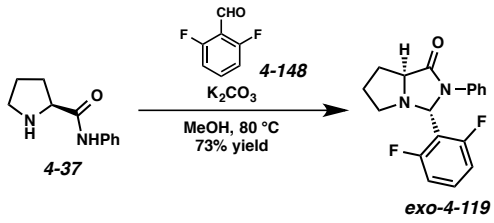
***exo*-Imidazolidinone 4-117:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0, 4H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 5.72 (s, 1H), 3.97 (t, *J* = 6.4 Hz, 1H), 3.43 (dt, *J* = 10.0, 4.8 Hz, 1H), 2.90 (q, *J* = 4.8 Hz, 1H), 2.25-2.17 (comp. m, 2H), 1.96-1.86 (comp. m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 144.8, 137.2, 132.9, 129.5, 127.2, 125.7, 121.2, 118.5, 112.6, 82.9, 64.5, 56.3, 27.8, 25.0; IR (film) 2232, 1700, 1494, 1379, 730 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{17}N_3O + H]^+$: 304.1444, found 304.1445.



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-118** was afforded as a white solid (R_f = 0.18 in 6:4 EtOAc/hexanes) isolated in 72% yield.

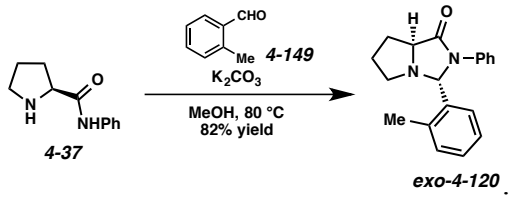
***exo*-Imidazolidinone 4-118:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.28 (dd, *J* = 8.0, 7.6 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2 H),

5.63 (s, 1H), 4.03 (t, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 3.41 (dt, *J* = 9.4, 5.2 Hz, 1H), 2.85 (dt, *J* = 9.4, 8.4 Hz, 1H), 2.20 (q, *J* = 7.2 Hz, 2H), 1.93-1.84 (comp. m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 159.8, 137.8, 131.7, 129.1, 127.4, 125.2, 121.3, 114.5, 83.4, 64.5, 56.0, 55.4, 27.6, 24.9; IR (film) 1700, 1379, 1252, 910, 731 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{20}N_2O_2 + H]^+$: 309.1598, found 309.1599.



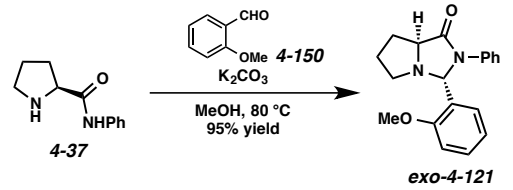
According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-119** was afforded as a white solid (R_f = 0.21 in 7:3 hexanes/EtOAc) isolated in 73% yield.

***exo*-Imidazolidinone 4-119:** A white solid (R_f = 0.21 in 7:3 hexanes/EtOAc) isolated in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 2H), 7.23-7.14 (comp. m, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.82 (dd, *J* = 8.0, 7.2 Hz, 2H), 6.14 (s, 1H), 4.24 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.41 (dt, *J* = 1.0, 6.4 Hz, 1H), 2.97 (dt, *J* = 10.0, 6.4 Hz, 1H), 2.31-2.11 (comp. m, 2H), 1.87 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 160.9 (dd, *J* = 248.1, 7.5 Hz), 136.7, 130.5 (t, *J* = 11.0 Hz), 129.2, 125.8, 121.9, 116.1 (t, *J* = 14.7 Hz), 112.2 (dd, *J* = 22.3, 3.6 Hz), 76.3 (t, *J* = 3.3 Hz), 65.9, 57.7, 28.9, 25.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -118.2; IR (film) 1700, 1468, 1379, 1120, 1005 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{16}F_2N_2O + H]^+$: 315.1303, found 315.1304



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-120** was afforded as a white solid (R_f = 0.33 in 7:3 hexanes/EtOAc) isolated in 82% yield.

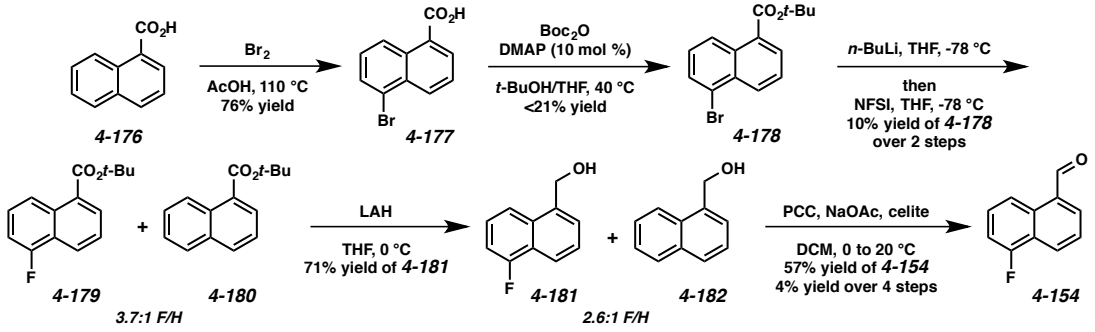
***exo*-Imidazolidinone 4-120:** A white solid (R_f = 0.33 in 7:3 hexanes/EtOAc) isolated in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.32-7.25 (comp. m, 3H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.15-7.04 (comp. m, 3H), 5.87 (s, 3H), 3.92 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.49-3.42 (comp. m, 1H), 2.86 (dt, *J* = 9.2, 7.2 Hz, 1H), 2.54 (s, 3H), 2.31-2.13 (comp. m, 2H), 1.97-1.84 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 138.2, 136.5, 135.8, 131.6, 129.1, 128.5, 126.6, 124.8, 124.3, 120.1, 80.3, 64.1, 55.8, 27.1, 25.0, 19.3; IR (film) 1700, 1594, 1500, 1379, 757 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{20}N_2O + H]^+$: 293.1648, found 293.1649.



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-121** was afforded as a white solid (R_f = 0.17 in 6:4 hexanes/EtOAc) isolated in 95% yield.

***exo*-Imidazolidinone 4-121:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.30-7.23 (comp. m, 3H), 7.10-7.04 (comp. m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.11 (s, 1H), 4.03 (t, *J* = 6.8 Hz, 1H), 3.93 (s, 3H), 3.47 (dt, *J* = 9.0, 5.2 Hz, 1H), 2.87 (dt, *J* = 9.0, 8.4

Hz, 1H), 2.21 (q, J = 6.8 Hz, 2H), 1.93-1.84 (comp. m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 156.9, 137.9, 129.7, 129.0, 127.0, 125.8, 124.8, 120.8, 120.5, 111.3, 78.5, 64.5, 56.3, 55.7, 27.6, 25.0; IR (film) 1700, 1594, 1500, 1379, 757 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{20}N_2O_2 + H]^+$: 309.1598, found 309.1598.



To a suspension of naphthoic acid **4-176** (6.00 g, 34.9 mmol) in glacial AcOH (40 mL) was slowly added bromine (2.00 mL, 39.0 mmol) dropwise. The reaction mixture was heated and stirred at 110 °C for 48 h. Upon completion, the reaction was slowly cooled to 0 °C and was filtered and washed with hexanes (20 mL, -10 °C) to afford 5-bromonaphthoic acid (**4-177**, 6.67 g, 76% yield, R_f = 0.19 in 7:3 hexanes/EtOAc) as a beige powder. The characterization data for alcohol **4-177** matched those previously reported.[32]

A suspension of naphthoic acid **4-177** (2.78 g, 11.1 mmol), Boc_2O (4.85 g, 22.2 mmol), and DMAP (135 mg, 1.11 mmol) in 2:1 mixture of *t*-BuOH/THF (44 mL) was heated and stirred at 40 °C for 18 h. Upon completion, the reaction mixture was concentrated by rotary evaporation and purified by column chromatography (9:1 hexanes/Et_2O eluent) to afford ester **4-178** (713 mg, <21% yield R_f = 0.66 in PhMe) as a semi-pure white solid. Ester **4-178** was sufficiently pure to use in the next step.

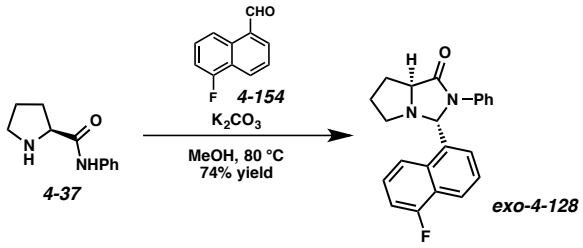
To a suspension of semi-pure ester **4-178** (686 mg, <2.23 mmol) in THF (11.1 mL) was added *n*-BuLi (1.61 mL, 2.5 M, 4.03 mmol) over 10 s and stirred at -78 °C, and the solution was left at -78 °C for 90 s before the addition of a solution of NFSI (1.69 g, 5.36 mmol) dissolved in THF (11.1 mL). The reaction mixture was left stirring at -78 °C for 25 min before the reaction was quenched with sat. $NaHCO_3$ (10 mL) and the mixture was warmed to 20 °C. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with brine (25 mL), dried under $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by column chromatography (PhMe → 9:1 hexanes/EtOAc) to afford an inseparable mixture of ester **4-179** and ester **4-180** (332 mg, 10% yield over 2 steps of **4-179**, 3.7:1 **4-179**/**4-180**, R_f = 0.79 in PhMe) as a white foam.

To a solution of ester **4-179** and ester **4-180** (332 mg, 1.08 mmol of **4-179**, 3.7:1 **4-179**/**4-180**) dissolved in THF (2.0 mL) cooled to 0 °C was added LAH (43.3 mg, 1.14 mmol) in one portion and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched at 0 °C with H_2O (40 μL), then 5 M NaOH (40 μL), and then H_2O (150 μL) and was then stirred at 20 °C for 15 min. The mixture was added $MgSO_4$ and was filtered through celite with EtOAc to afford an inseparable mixture of alcohol **4-181** and alcohol **4-182** (181 mg, 71% yield of **4-181**, 2.6:1 **4-181**/**4-182**, R_f = 0.03 in 9:1 hexanes/EtOAc) as a beige oil.

To a stirring suspension of pyridinium chlorochromate (196 mg, 0.909 mmol), sodium acetate (174 mg, 2.12 mmol), and celite (19 mg) in CH_2Cl_2 (2.2 mL) cooled to 0 °C was added a solution of alcohol **4-181** and alcohol **4-182** (181 mg, 0.773 mmol of **4-181**, 2.6:1 **4-181**/**4-182**) in CH_2Cl_2 (0.95 mL). The reaction mixture was warmed to 23 °C over 20 min and maintained at 23 °C for 14 h. The reaction mixture was filtered through florisil with CH_2Cl_2 (50 mL) and then

EtOAc (50 mL) as eluents to provide a crude mixture of naphthaldehyde **4-154** and 1-naphthaldehyde (**4-74**) (2.0:1 **4-154**/**4-74**, respectively). The mixture was purified by column chromatography (1:1 PhMe/pentane eluent) to afford naphthaldehyde **4-174** (75.7 mg, 57% yield, 4% yield over 4 steps, R_f = 0.40 in 1:1 PhMe/pentane) as a white solid.

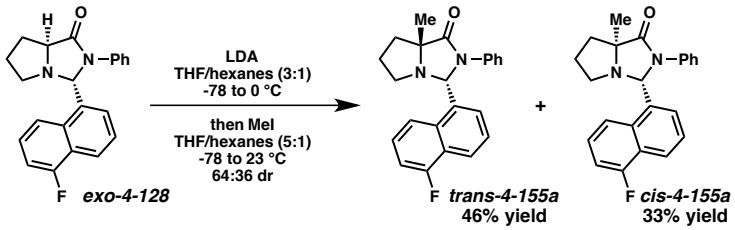
Naphthaldehyde 4-174: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.02 (d, *J* = 8.7 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.05 (dd, *J* = 7.0, 0.9 Hz, 1H), 7.70 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.62 (td, *J* = 8.2, 5.9 Hz, 1H), 7.27 (dd, *J* = 10.4, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.06, 157.54, 137.31, 131.83, 131.80, 131.27, 131.25, 129.30, 129.22, 127.74, 127.68, 125.37, 125.35, 124.37, 124.22, 121.00, 120.96, 111.02, 110.83; ^{19}F NMR (272 MHz, $CDCl_3$) δ -120.96; IR (film) 1695, 1681, 1595, 1577, 1466, 1403, 1216, 1174, 1152, 785 cm^{-1}; HRMS (DART+) *m/z* calc'd for $(M + NH_4)^+$ $[C_{11}H_7FO + NH_4]^+$: 192.0825, found 192.0815.



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-128** was afforded as a beige solid (R_f = 0.61 in 7:3 hexane/EtOAc) isolated in 74% yield.

***exo*-Imidazolidinone 4-128:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.60 (dt, *J* = 8.0, 5.6 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.43 (app. t, *J* = 7.8 Hz, 1H), 7.33 (app. d, *J* = 7.1 Hz, 1H), 7.29-7.22 (comp m, 3H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.44 (s, 1H), 3.94 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.68-3.61 (m, 1H), 3.00 (td, *J* = 9.4, 7.0 Hz, 1H), 2.36-2.25 (m, 1H), 2.25-2.14 (m, 1H), 2.03-1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 159.6 (d, *J*

= 251.3 Hz), 138.4, 133.4 (d, J = 2.4 Hz), 132.4 (d, J = 4.4 Hz), 129.2, 127.0 (d, J = 8.5 Hz), 125.8 (d, J = 1.8 Hz), 125.0 (d, J = 16.2 Hz), 124.8, 123.6, 121.8 (d, J = 6.1 Hz), 119.8, 118.7 (d, J = 4.0 Hz), 110.0 (d, J = 20.0 Hz), 80.0, 64.5, 55.4, 27.1, 25.1; ^{19}F NMR (272 MHz, $CDCl_3$) δ -120.8; IR (film) 1701, 1599, 1499, 1388, 1229 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{19}FN_2O + H]^+$: 347.1554, found 347.1548.

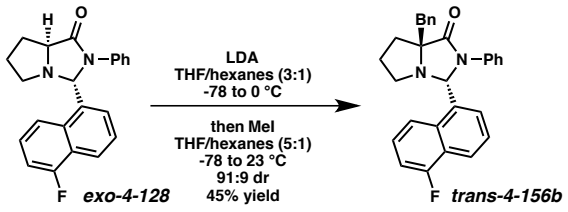


To a suspension of *exo*-proline aminal **4-128** (43.7 mg, 0.126 mmol) in THF (0.13 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.139 mL, 1.0 M, 1.39 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added THF (0.13 mL) and then methyl iodide (8.6 μl, 0.139 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude aminal (dr = 64:36 *anti/syn*; dr determined by ^{19}F NMR) was purified by flash column chromatography (39:1 CH_2Cl_2/Et_2O eluent) to afford *trans*-proline aminal **4-155a** (20.8 mg, 46% yield, R_f = 0.21 in 39:1 CH_2Cl_2/Et_2O) as a yellow oil and *cis*-proline aminal **4-155a** (15.1 mg, 33% yield, R_f = 0.10 in 39:1 CH_2Cl_2/Et_2O) as a white foam.

***trans*-Proline aminal 4-155a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.59 (dt, J = 8.0, 5.6 Hz, 1H), 7.34-7.20 (comp m, 7H), 7.09 (dt, J = 7.2, 1.2 Hz,

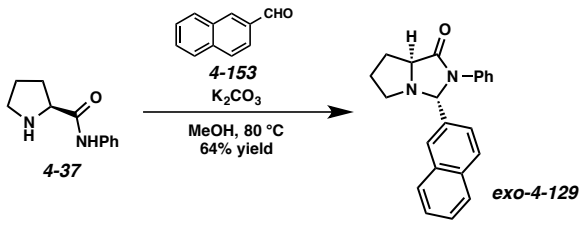
1H), 7.01 (s, 1H), 2.54 (dt, *J* = 9.6, 6.0 Hz, 1H), 2.46 (dt, *J* = 14.0, 9.6 Hz, 1H), 2.17-2.10 (m, 1H), 1.99-1.89 (m, 1H), 1.75-1.63 (comp m, 2H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 159.3 (d, *J* = 251.0 Hz), 138.4, 133.0 (d, *J* = 4.1 Hz), 129.7 (d, *J* = 2.6 Hz), 128.8, 127.1, 126.9 (d, *J* = 8.7 Hz), 125.1 (d, *J* = 1.6 Hz), 125.0, 124.3 (d, *J* = 16.0 Hz), 121.8, 121.5 (d, *J* = 6.1 Hz), 119.4 (d, *J* = 4.3 Hz), 110.0 (d, *J* = 19.8 Hz), 74.3, 71.2, 50.4, 35.6, 24.2, 22.9; ^{19}F NMR (272 MHz, $CDCl_3$) δ -121.33; IR (film) 1709, 1599, 1500, 1375, 1361, 1301, 1233, 1188, 787, 731 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{21}FN_2O + H]^+$: 361.1711, found 361.1719; $[\alpha]_D^{33}$ = +29.6 (*c* = 1.0, $CHCl_3$).

***cis*-Proline aminal 4-155a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.60-7.51 (comp m, 3H), 7.43-7.33 (comp m, 2H), 7.28-7.19 (comp m, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.33 (s, 1H), 3.76 (dt, *J* = 9.6, 5.2 Hz, 1H), 3.17 (dt, *J* = 9.2, 7.2 Hz, 1H), 2.47-2.33 (m, 1H), 1.96-1.79 (comp m, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 159.6 (d, *J* = 251.0 Hz), 138.2, 135.2 (d, *J* = 2.3 Hz), 132.7 (d, *J* = 4.4 Hz), 129.1, 126.7 (d, *J* = 8.5 Hz), 125.6 (d, *J* = 1.9 Hz), 124.9 (d, *J* = 15.8 Hz), 124.8 (d, *J* = 16.6 Hz), 121.6 (d, *J* = 6.2 Hz), 120.3, 119.1 (d, *J* = 4.2 Hz), 109.8 (d, *J* = 19.9 Hz), 80.4, 71.8, 58.3, 38.1, 25.5, 24.9; ^{19}F NMR (272 MHz, $CDCl_3$) δ -120.61; IR (film) 1700, 1600, 1497, 1389, 1303, 1228, 1183, 785, 758, 731 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{21}FN_2O + H]^+$: 361.1711, found 361.1723; $[\alpha]_D^{32}$ = +61.9 (*c* = 1.0, $CHCl_3$).



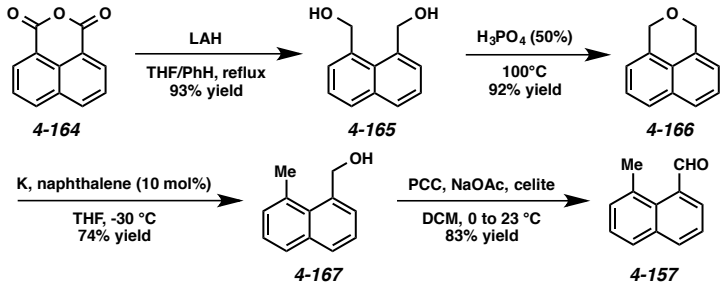
To a suspension of *exo*-proline aminal **4-128** (38.4 mg, 0.111 mmol) in THF (0.111 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.111 mL, 1.1 M, 1.22 mmol, -4 °C). The solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added THF (0.111 mL) and then benzyl bromide (14.5µl, 0.122 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude aminal (dr = 91;9 *anti/syn*; dr determined by ^{19}F NMR) was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford *trans*-proline aminal **4-156b** (21.7 mg, 45% yield, R_f = 0.30 in 4:1 hexanes/EtOAc) as a white foam.

***trans*-Proline aminal 4-156b:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.59-7.50 (comp. m, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.32-7.26 (comp. m, 3H), 7.24-7.12 (comp. m, 4H), 7.05-7.01 (comp. m, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.60 (s, 1H), 3.46 (d, *J* = 13.2 Hz, 1H), 2.88 (d, *J* = 13.2 Hz, 1H), 2.52-2.43 (comp. m, 1H), 2.42-2.35 (comp. m, 1H), 2.20-2.14 (comp. m, 1H), 2.10-2.02 (comp. m, 1H), 1.75-1.60 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 159.1 (d, *J* = 250.9 Hz), 137.9, 137.6, 133.1 (d, *J* = 4.3 Hz), 130.4, 130.0 (d, *J* = 2.6 Hz), 128.6, 128.5, 127.1, 126.8, 126.5 (d, *J* = 8.7 Hz), 125.2, 125.0 (d, *J* = 1.6 Hz), 124.8 (d, *J* = 16.0 Hz), 122.5, 121.2 (d, *J* = 6.0 Hz), 119.9 (d, *J* = 4.2 Hz), 109.8 (d, *J* = 19.7 Hz), 76.0, 75.7, 51.2, 45.1, 36.5, 24.7; ^{19}F NMR (272 MHz, $CDCl_3$) δ -121.65; IR (film) 1708, 1599, 1500, 1372, 1234 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{25}H_{29}FN_2O + H]^+$: 437.2020, found 437.2021; $[\alpha]_D^{26}$ = +10.9 (*c* = 1.0, $CHCl_3$).



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-129** was afforded as a beige solid (R_f = 0.11 in 7:3 hexane/EtOAc) isolated in 64% yield.

***exo*-Imidazolidinone 4-129:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.85-7.75 (comp m, 2H), 7.70 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.51-7.44 (comp. m, 3H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 5.83 (s, 1H), 4.10 (dd, *J* = 7.6, 6.0 Hz, 1H), 3.51-3.44 (comp. m, 1H), 3.94 (q, *J* = 4.4, Hz, 1H), 2.28-2.20 (comp. m, 2H), 1.98-1.88 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 137.8, 136.9, 133.4, 133.3, 129.4, 129.1, 128.3, 127.8, 126.6, 126.5, 125.2, 125.1, 124.0, 121.2, 83.9, 64.6, 56.1, 27.7, 25.0; IR (film) 1684, 1594, 1494, 1405, 820 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{20}N_2O + H]^+$: 329.1648, found 329.1649.



To THF (140 mL) cooled to 0 °C was added LAH (1.59 g, 42.0 mmol) and stirred at 0 °C for 3 h before the bath was removed and the suspension was warmed to 23 °C. To a suspension of naphthoic anhydride **4-164** in benzene (400 mL) was added via cannula to the LAH solution. After the addition was completed, the suspension was refluxed for 2.5 h. Upon cooling, the

residual LAH was quenched with a slow addition of water (50 mL) at 0 °C and then the suspension was added Rochelle salt (300 mL) and allowed to warm to 23 °C and left overnight. The suspension was filtered and then extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation to afford diol **4-165** (1.76 g, 93% yield, R_f = 0.65 in EtOAc) as beige needles. The diol was analytically pure without need for further purification. The characterization data for diol **4-165** matched those previously reported.[33]

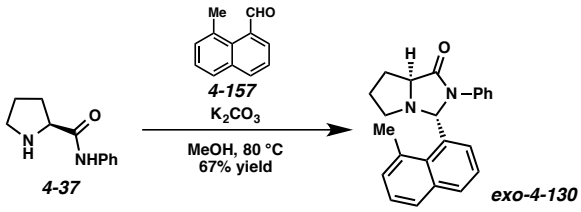
In a sealed 2 dram vial, a suspension of diol **4-165** (1.52 g, 8.06 mmol) in 50% H_3PO_4 (12 mL) was heated and stirred at 100 °C for 2 h. Upon cooling, the reaction was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with sat. $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL) and then dried over $MgSO_4$. The combined organic layers were concentrated by rotary evaporation to afford ether **4-166** (1.26 g, 92% yield, R_f = 0.72 in 7:3 hexanes/EtOAc) as a beige solid. The ether was analytically pure without need for further purification. The characterization data for ether **4-166** matched those previously reported.[34]

Potassium metal (1.26 g, 32.3 mmol, stored in mineral oil) was placed under Ar, washed with THF (2 x 4 mL), suspended in THF (38 mL) and added naphthylene (82.8 mg, 0.646 mmol).[35] This solution was refluxed and stirred for 15 min to produce a dark green solution. The mixture was cooled to -30 °C. A solution of ether **4-166** dissolved in THF (12 mL) was added to the potassium naphthalenide mixture dropwise over 10 min. An additional portion of THF (12 mL) was added to help facilitate transfer of ether **4-166**. The reaction was maintained at -30 °C and stirred for 2 h. Upon completion, water (12 mL) was added over 5 min at -30 °C, and then the reaction was warmed to ambient temperature. The reaction was extracted with EtOAc (3 x 30

mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude alcohol was purified by flash column chromatography (8:2 hexanes/EtOAc eluent) to afford alcohol **4-167** (825 mg, 74% yield, R_f = 0.20 in 8:2 hexanes/EtOAc) as a white solid. The characterization data for alcohol **4-167** matched those previously reported.[36]

To a stirring suspension of pyridinium chlorochromate (1.20 g, 5.57 mmol), sodium acetate (1.07 g, 13.0 mmol), and celite (116 mg) in CH_2Cl_2 (14 mL) cooled to 0 °C was added a solution of alcohol **4-167** (800 mg, 4.64 mmol) in CH_2Cl_2 (5.8 mL). The reaction mixture was warmed to 23 °C over 20 min and maintained at 23 °C for 17 h. The reaction mixture was filtered through florisil with CH_2Cl_2 (50 mL) and then EtOAc (50 mL) as eluents, and was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford aldehyde **4-157** (657 mg, 83% yield, R_f = 0.38 in 9:1 hexanes/EtOAc) as a white solid.

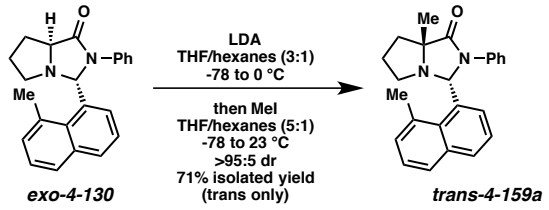
Aldehyde 4-157: The characterization data for aldehyde **4-157** matched those previously reported.[37]



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-130** was afforded as a white solid (R_f = 0.28 in 7:3 hexanes/EtOAc) isolated in 67% yield.

***exo*-Imidazolidinone 4-130:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.6, 1.6 Hz, 1H), 7.75 (dd, J = 7.2, 2.4 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.42-7.21 (comp. m, 6H), 7.05 (t, J = 7.6 Hz,

1H), 6.90 (s, 1H), 3.94 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.60 (ddd, 9.6, 6.8, 3.2 Hz, 1H), 3.14 (s, 3H), 2.84 (dt, *J* = 9.6, 2.0 Hz, 1H), 2.36-2.27 (m, 1H), 2.15-2.04 (m, 1H), 1.98-1.82 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 138.6, 136.7, 134.2, 133.4, 131.4, 131.30, 131.25, 129.2, 128.8, 125.7, 125.0, 124.6, 124.5, 119.9, 81.2, 63.9, 54.3, 26.5, 26.1, 24.5; IR (film) 1699, 1598, 1498, 1390, 1296 cm^{-1}; HRMS (ESI+) m/z calc'd for $(M+H)^+$ $[C_{23}H_{22}N_2O+H]^+$: 343.1805, found 343.1812.

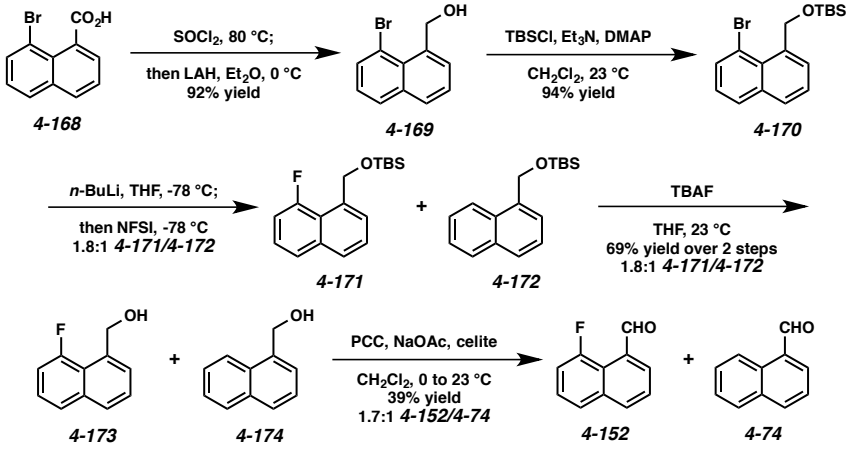


exo-4-130 *trans-4-159a*

To a suspension of *exo*-proline imidazolidinone **4-130** (30.6 mg, 0.0859 mmol) in THF (0.086 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.087 mL, 1.1 M, 0.0944 mmol, -4 °C). The reaction solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added THF (0.086 mL) and then methyl iodide (5.9 μl, 0.0944 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4. The solvent was removed by rotary evaporation, and the crude aminal (dr = >95:5 *trans/cis*) was purified by flash column chromatography (8:2 hexanes/EtOAc eluent) to afford *trans*-proline aminal **4-159a** (21.8 mg, 71% yield, R_f = 0.57 in 7:3 hexanes/EtOAc) as an opaque oil.

***trans*-Proline imidazolidinone 4-159a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, 8.4 *J* = 8.4 Hz, 2H), 7.46-7.30 (comp m, 6H), 7.24-7.16 (comp m, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 3.36 (s, 3H),

2.65 (dt, J = 9.6, 6.4 Hz, 1H), 2.42 (dt, J = 13.2, 8.8 Hz, 1H), 2.27-2.17 (comp m, 1H), 1.95-1.86 (comp m, 1H), 1.76-1.59 (comp m, 2H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 138.3, 135.7, 134.5, 131.9, 131.1, 130.7, 128.5, 128.3, 128.0, 125.4, 124.5, 124.0, 121.7, 75.1, 70.9, 50.2, 35.6, 24.7, 24.4, 22.8; IR (film) 1706, 1598, 1499, 1375, 1359, 1300, 1230, 1153, 909, 731 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{25}N_2O + H]^+$: 357.1967, found 357.1963; $[\alpha]_D^{32}$ = +44.3 (c = 1.0, $CHCl_3$).



A suspension of acid **4-168**[38] (973 mg, 3.88 mmol) in $SOCl_2$ (4.2 mL) was heated and stirred at 80 °C for 50 min. The reaction mixture was cooled to ambient temperature and $SOCl_2$ was azeotropically removed by successive additions of PhMe to provide a red solid. Et_2O (3.9 mL) was added to the cruse residue and it was cooled to 0 °C, then the mixture was added LAH (147 mg, 3.88 mmol) in one portion and was stirred at 0 °C for 50 min. The reaction was quenched with H_2O (147 μL), 5 M NaOH (147 μL), and then H_2O (450 μL) and was then stirred for 23 °C for 15 min. The reaction mixture was dried with $MgSO_4$ and then filtered through celite with EtOAc to afford alcohol **4-169** (844 mg, 92% yield, R_f = 0.48 in 7:3 hexanes/EtOAc) as a beige solid.

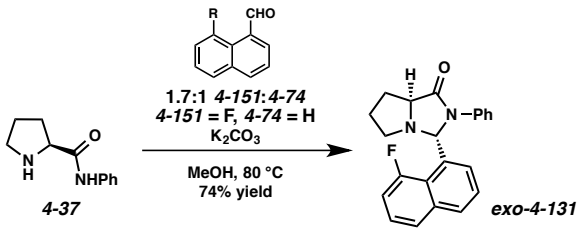
To a solution of TBSCl (616 mg, 4.09 mmol), Et_3N (700 μL, 5.03 mmol), and DMAP (42.3 mg, 0.347 mmol) in CH_2Cl_2 (8 mL) was added a solution of alcohol **4-169** (822 mg, 3.47 mmol) in CH_2Cl_2 (16 mL) and was stirred at 23 °C for 2 h. The reaction mixture was added sat. $NaHCO_3$ (50 mL) and was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried under Na_2SO_4, and concentrated by rotary evaporation. The crude mixture was purified by column chromatography (19:1 hexanes/EtOAc eluent) to afford silyl ether **4-170** (1.15 g, 94% yield, R_f = 0.47 in 19:1 hexanes/EtOAc) as a colorless oil.

To a solution of silyl ether **4-170** (1.10 g, 3.14 mmol) in THF (15.0 mL) was added *n*-BuLi (2.26 mL, 2.5 M, 5.66 mmol) over 10 s at -78 °C and the solution was left stirring at -78 °C for 90 s before the addition of a solution of NFSI (2.38 g, 7.55 mmol) dissolved in THF (15.0 mL). The reaction mixture was stirred at -78 °C for 25 min before the reaction mixture was added sat. $NaHCO_3$ (10 mL) and the mixture was warmed to 20 °C. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with brine, dried under $MgSO_4$, and concentrated by rotary evaporation.

To the crude mixture of silyl ethers (1.8:1 **4-173**/**4-174**) dissolved in THF (20. 0 mL) was added a solution of TBAF (3.14 mL, 1 M in THF, 3.14 mmol) at 23 °C and stirred for 6 h. Upon completion determined by TLC, water (20 mL) was added to the reaction mixture and then it was concentrated by rotary evaporation to remove residual THF. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with brine (20 mL), dried under $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (3:2 hexanes/EtOAc) to afford a mixture of alcohols **4-173** and **4-174** (490 mg, 1.8:1 **4-173**/**4-174**, 69% yield, R_f = 0.56 in 3:2 hexanes/EtOAc) as a white solid.

To a stirring suspension of pyridinium chlorochromate (560 mg, 2.60 mmol), sodium acetate (498 mg, 6.07 mmol), and celite (54 mg) in CH_2Cl_2 (6.4 mL) cooled to 0 °C was added a solution of naphthanol **4-173** and naphthanol **4-174** (488 mg, 1.8:1 **4-173**/**4-174**, 1.85 mmol of **4-173**) in CH_2Cl_2 (2.7 mL). The reaction mixture was warmed to 23 °C over 20 min and maintained at 23 °C for 12 h. The reaction mixture was filtered through florisil with CH_2Cl_2 (50 mL) and then EtOAc (50 mL) as eluents, and was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford aldehyde **4-152** (225 mg, 39% yield, 1.7:1 **4-152**/**4-74**, R_f = 0.40 in 1:1 PhMe/pentane) as a clear oil.

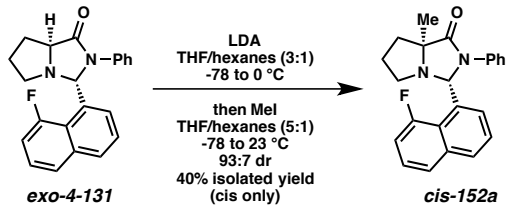
Aldehyde 4-152: The characterization data for aldehyde **4-152** matched those previously reported.[39]



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-131** was afforded as a colorless oil (R_f = 0.61 in 7:3 hexanes/EtOAc) isolated in 74% yield.

***exo*-Imidazolidinone 4-131:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J⁄48.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.47 (dt, J = 7.6, 4.8 Hz, 1H), 7.40-7.25 (comp. m, 5H), 7.09 (t, J = 7.2 Hz, 1H), 6.82 (s, 1H), 3.89 (dd, J = 9.2, 3.2 Hz, 1H), 3.66-3.64 (m, 1H), 2.97-2.87 (m, 1H), 2.33-2.23 (m, 1H), 2.21-2.10 (m, 1H), 1.98-1.81 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 159.5 (d, *J* = 249.8 Hz), 138.4, 137.2 (d, J = 5.9 Hz), 132.7 (d, J = 7.3 Hz), 129.2 (d, J = 2.7 Hz), 129.1, 126.3 (d, J = 4.8 Hz), 126.2 (d, J = 3.0 Hz), 125.5 (d, J = 3.7 Hz),

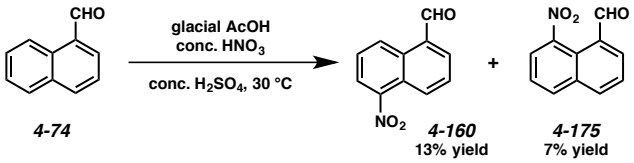
124.6, 123.5, 121.1 (d, J = 13.1 Hz), 119.8, 112.6 (d, J = 24.1 Hz), 80.8 (d, J = 14.3 Hz), 63.7, 55.3, 26.8, 24.8; ^{19}F NMR (272 MHz, $CDCl_3$) δ -107.9; IR (film) 1699, 1597, 1498, 1388, 1308 cm^{-1}; HRMS (ESI+) m/z calc'd for $(M+H)^+$ $[C_{22}H_{19}FN_2O+H]^+$: 347.1554, found 347.1557.



To a suspension of *exo*-proline imidazolidinone **4-131** (37.7 mg, 0.109 mmol) in THF (0.11 mL) cooled to -78 °C was added a cooled solution of lithium diisopropylamide (0.109 mL, 1.1 M, 0.120 mmol, -4 °C). The reaction solution was warmed to 0 °C and held for 70 min. The solution was recooled to -78 °C, and to the solution was added THF (0.11 mL) and then methyl iodide (7.5 μl, 0.120 mmol); it was held at -78 °C for 1.5 h before the cooling bath was removed, and it was allowed to gradually warm to ambient temperature and stirred overnight. The reaction was quenched with water (5 mL), and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4. The solvent was removed by rotary evaporation, and the crude aminal (dr = 93:7 *syn/anti*; dr determined by ^{19}F NMR) was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford *cis*-proline aminal **152a** (15.6 mg, 40% yield, R_f = 0.39 in hexanes/EtOAc) as a beige amorphous solid.

***cis*-Proline imidazolidinone 152a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dt, *J* = 7.6, 2.0 Hz, 1H), 7.70-7.65 (comp m, 2H), 7.46 (td, *J* = 7.6, 5.2 Hz, 1H), 7.38-7.24 (comp m, 7H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.76 (s, 1H), 3.78-3.73 (m, 1H), 3.17-3.06 (m, 1H), 2.44-2.30 (m, 1H), 1.88-1.80 (comp m, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 159.4 (d, *J* = 249.7 Hz), 138.4, 137.0

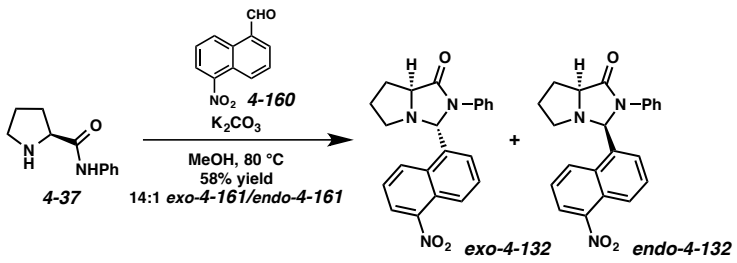
(d, J = 5.7 Hz), 134.8 (d, J = 7.5 Hz), 129.09, 129.06 (d, J = 3.1 Hz), 126.1 (d, J = 7.6 Hz), 126.0, 125.4 (d, J = 3.8 Hz), 124.6, 121.3 (d, J = 13.7 Hz), 120.2, 112.5 (d, J = 24.2 Hz), 81.0 (d, J = 13.4 Hz), 71.7, 58.9, 38.6, 25.5, 24.8; ^{19}F NMR (272 MHz, $CDCl_3$) δ -110.2; IR (film) 1700, 1598, 1496, 1461, 1389, 1303, 1223, 835, 817, 758 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{21}FN_2O + H]^+$: 361.1711, found 361.1711; $[\alpha]_D^{30}$ = +148.1 (*c* = 1.0, $CHCl_3$).



A suspension of naphthaldehyde **4-74** (20.0 g, 128 mmol) in a mixture of glacial AcOH (400 mL), conc. HNO_3 (278 mL), and conc. H_2SO_4 (14 mL) was heated and stirred at 30 °C for 72 h. The reaction mixture was poured into ice (600 mL) and was then added H_2O (100 mL) and was neutralized with Na_2CO_3 to pH 12. The organic layer was dried with $MgSO_4$ and was concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (8:2 hexanes/EtOAc eluent) to afford naphthaldehyde **4-160** (3.39 g, 13% yield, R_f = 0.26 in 8:2 hexanes/EtOAc) as an orange powder and naphthaldehyde **4-175** (1.76 g, 7% yield, R_f = 0.11 in 8:2 hexanes/EtOAc) as an orange powder.

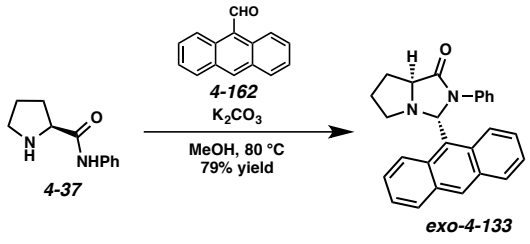
Aldehyde 4-160: The characterization data for aldehyde **4-160** matched those previously reported.[40]

Aldehyde 4-175: The characterization data for aldehyde **4-175** matched those previously reported. [40]



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinones **4-132** were afforded as a red foam (14:1 **exo-4-132**/**endo-4-132**, R_f = 0.38 in 6:4 hexanes/EtOAc) isolated in 58% yield.

Imidazolidinone 4-132: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.4 Hz, 1H), 8.41, (d, *J* = 8.8 Hz, 1H), 8.19 (dd, *J* = 8.8, 7.2 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.26 (dd, *J* = 8.0, 7.6 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.45 (s, 1H), 3.89 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.67-3.60 (comp. m, 1H), 3.00 (dt, *J* = 7.2, 2.4 Hz, 1H), 2.34-2.23 (comp. m, 1H), 2.23-2.12 (comp. m, 1H), 2.05-1.86 (comp. m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 148.1, 138.1, 134.1, 132.0, 129.3, 128.9, 128.7, 126.3, 125.3, 125.1, 124.4, 124.1, 123.5, 119.8, 79.9, 64.4, 55.3, 27.0, 25.0; IR (film) 1701, 1522, 1498, 1388, 1341 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{19}N_3O_3 + H]^+$: 374.1499, found 374.1498.



According to the general procedure for basic attachment of aldehydes towards imidazolidinones, *exo*-imidazolidinone **4-133** was afforded as an orange powder (R_f = 0.33 in 1:1 hexanes/EtOAc) isolated in 79% yield.

***exo*-Imidazolidinone 4-133:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (app br. s, 2H), 8.39 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.11 (s, 1H), 6.97 (t, *J* = 7.6 Hz, 2H), 6.85 (t, *J* = 7.6 Hz, 1H), 4.50 (t, *J* = 7.2 Hz, 1H), 3.26-3.05 (comp. m, 2H), 2.42-2.32 (comp. m, 2H), 2.21-2.07 (comp. m, 1H), 2.06-1.95 (comp. m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 139.5, 130.4, 129.9, 128.6, 127.1, 125.9, 124.8, 123.3, 79.2, 66.7, 55.2, 30.0, 24.9; IR (film) 1693, 1598, 1499, 1395, 1312 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{22}N_2O + H]^+$: 379.1805, found 379.1813.

4.6.3. Crystallographic Data

Table 1. Crystal Data and Structure Refinement for *exo*-imidazolidinone **4-64**

Identification code	ef11
Empirical formula	$C_{22}H_{20}N_2O$
Formula weight	328.40
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.3233(2)
b/Å	9.6627(4)
c/Å	14.0935(5)
α/°	90
β/°	100.794(2)
γ/°	90
Volume/Å^3	845.88(5)
Z	2
ρ_{calc}mg/mm^3	1.289
m/mm^{-1}	0.080
F(000)	348.0
Crystal size/mm^3	0.333 × 0.18 × 0.091
2Θ range for data collection	5.142 to 66.832°
Index ranges	$-8 \leq h \leq 9$, $-14 \leq k \leq 14$, $-21 \leq l \leq 21$
Reflections collected	23576
Independent reflections	6418[R(int) = 0.0394]
Data/restraints/parameters	6418/1/236
Goodness-of-fit on F^2	0.899
Final R indexes [I>=2σ (I)]	$R_1 = 0.0429$, $wR_2 = 0.1180$
Final R indexes [all data]	$R_1 = 0.0518$, $wR_2 = 0.1262$
Largest diff. peak/hole / e Å^{-3}	0.32/-0.23
Flack parameter	-0.4(5)

Table 2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for *exo*-4-64; U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor *exo*-imidazolidinone **4-64**

Atom	***x***	***y***	***z***	**U(eq)**
C1	4662(3)	4194(2)	9260.5(12)	23.9(4)
C2	6410(5)	5076(3)	9854.3(19)	25.9(8)
C3	8445(3)	4608(2)	9528.5(13)	24.5(4)
C4	7676(2)	4063.1(16)	8497.2(11)	14.4(3)
C5	8161(3)	2528.3(17)	8399.8(11)	14.8(3)
C6	5870(3)	448.8(16)	7892.4(11)	13.9(3)
C7	7513(3)	-521.1(18)	8176.6(13)	20.6(3)
C8	7047(4)	-1927.8(19)	8067.1(14)	26.7(4)
C9	4980(4)	-2390.5(19)	7670.6(14)	26.0(4)
C10	3384(3)	-1420.4(18)	7369.3(13)	22.1(4)
C11	3811(3)	-6.4(17)	7474.9(12)	17.4(3)
C12	4564(2)	2943.4(15)	7719.9(11)	11.9(3)
C13	4355(2)	3243.6(16)	6643.9(11)	11.7(3)
C14	5790(2)	2700.6(16)	6115.4(11)	13.6(3)
C15	5603(3)	2978.4(17)	5118.3(12)	16.9(3)
C16	3948(3)	3774.7(17)	4648.4(11)	16.2(3)
C17	2421(2)	4343.6(16)	5157.6(11)	13.8(3)
C18	2632(2)	4106.2(16)	6169.1(11)	12.4(3)
C19	1118(3)	4737.4(17)	6661.2(12)	16.2(3)
C20	-545(3)	5528.1(19)	6171.6(13)	19.3(3)
C21	-779(3)	5729.5(18)	5164.1(14)	20.2(3)
C22	674(3)	5154.5(17)	4674.0(12)	17.0(3)
N1	6242(2)	1884.2(14)	8046.3(9)	13.3(2)
N2	5308(2)	4169.7(14)	8299.3(9)	13.7(2)
O1	9947(2)	2000.2(15)	8611.2(10)	23.3(3)
C2A	6566(10)	4026(8)	10024(4)	27.4(17)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for *exo*-4-64; The Anisotropic Displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$ of *exo*-imidazolidinone **4-64**

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	24.3(8)	31.8(9)	17.8(7)	-8.2(7)	9.2(6)	-6.4(7)
C2	32.9(15)	31.1(16)	14.8(11)	-9.8(10)	7(1)	-5.7(11)
C3	24.0(8)	27.6(9)	19.3(8)	-8.3(7)	-2.4(6)	-3.2(7)
C4	14.7(6)	15.0(7)	13.4(6)	-1.0(5)	1.9(5)	-2.7(5)
C5	13.8(7)	16.4(7)	13.6(7)	0.9(5)	1.5(5)	-0.6(5)
C6	18.7(7)	12.3(6)	10.7(6)	1.1(5)	2.7(5)	-0.1(5)
C7	24.5(8)	15.3(7)	19.5(8)	1.0(6)	-2.5(6)	3.6(6)
C8	38.7(11)	14.1(8)	24.6(9)	2.8(6)	-1.0(7)	6.5(7)
C9	41.8(11)	12.2(7)	23.8(9)	1.3(6)	5.4(8)	-3.4(7)
C10	27.7(9)	15.9(7)	23.0(8)	-1.8(6)	5.8(7)	-7.0(7)
C11	18.4(7)	14.1(7)	19.4(7)	-0.1(6)	2.6(6)	-2.6(6)
C12	11.3(6)	11.9(6)	12.1(6)	0.6(5)	1.2(5)	0.4(5)
C13	11.2(6)	12.0(6)	11.5(6)	-0.1(5)	0.8(5)	0.0(5)
C14	13.9(6)	13.7(6)	13.3(7)	1.2(5)	3.0(5)	1.3(5)
C15	18.1(7)	18.4(7)	15.2(7)	0.2(6)	5.6(5)	1.8(6)
C16	18.4(7)	17.3(7)	13.0(6)	1.3(5)	3.1(5)	-0.8(6)
C17	14.6(6)	12.1(6)	14.1(6)	1.2(5)	0.7(5)	-1.4(5)
C18	11.9(6)	12.0(6)	12.9(6)	0.3(5)	1.5(5)	-0.4(5)
C19	15.7(7)	17.2(7)	15.5(7)	0.2(5)	2.6(5)	3.7(6)
C20	15.7(7)	19.3(7)	22.8(8)	1.7(6)	3.5(6)	4.8(6)
C21	16.7(7)	18.1(7)	24.4(8)	4.9(6)	0.1(6)	3.2(6)
C22	16.5(7)	15.9(7)	17.0(7)	4.7(5)	-1.2(6)	-0.5(5)
N1	13.2(6)	12.2(5)	13.3(6)	0.7(5)	0.0(4)	-0.1(5)
N2	15.3(6)	13.1(6)	12.7(5)	-2.6(4)	3.1(4)	-0.3(5)
O1	13.2(6)	21.9(6)	32.7(7)	0.7(5)	-0.6(5)	2.5(5)
C2A	34(3)	36(4)	13(2)	-3(2)	9(2)	-1(3)

Table 4. Bond Lengths for *exo*-imidazolidinone **4-64**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.517(3)	C10	C11	1.395(2)
C1	N2	1.486(2)	C12	C13	1.525(2)
C1	C2A	1.466(7)	C12	N1	1.484(2)
C2	C3	1.514(4)	C12	N2	1.466(2)
C3	C4	1.537(2)	C13	C14	1.381(2)
C3	C2A	1.589(7)	C13	C18	1.434(2)
C4	C5	1.526(2)	C14	C15	1.414(2)
C4	N2	1.475(2)	C15	C16	1.366(2)
C5	N1	1.372(2)	C16	C17	1.417(2)
C5	O1	1.224(2)	C17	C18	1.425(2)
C6	C7	1.401(2)	C17	C22	1.420(2)
C6	C11	1.396(2)	C18	C19	1.421(2)
C6	N1	1.417(2)	C19	C20	1.376(2)
C7	C8	1.393(3)	C20	C21	1.413(3)
C8	C9	1.395(3)	C21	C22	1.366(2)
C9	C10	1.385(3)			

Table 5. Bond Angles for *exo*-imidazolidinone **4-64**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
N2	C1	C2	102.45(16)	C14	C13	C18	119.20(13)
C2A	C1	N2	109.8(3)	C18	C13	C12	119.43(13)
C1	C2	C3	103.74(18)	C13	C14	C15	121.52(14)
C2	C3	C4	104.66(16)	C16	C15	C14	120.18(14)
C4	C3	C2A	99.4(2)	C15	C16	C17	120.38(14)
C5	C4	C3	112.64(14)	C16	C17	C18	119.93(13)
N2	C4	C3	106.56(13)	C16	C17	C22	120.89(14)
N2	C4	C5	105.37(12)	C22	C17	C18	119.18(14)
N1	C5	C4	107.13(13)	C17	C18	C13	118.74(13)
O1	C5	C4	125.12(15)	C19	C18	C13	122.98(13)
O1	C5	N1	127.75(16)	C19	C18	C17	118.28(13)
C7	C6	N1	121.24(14)	C20	C19	C18	121.01(14)
C11	C6	C7	119.53(15)	C19	C20	C21	120.42(16)
C11	C6	N1	119.21(14)	C22	C21	C20	119.89(15)
C8	C7	C6	119.41(17)	C21	C22	C17	121.19(15)
C7	C8	C9	121.32(18)	C5	N1	C6	127.58(13)
C10	C9	C8	118.70(17)	C5	N1	C12	109.40(13)
C9	C10	C11	120.98(17)	C6	N1	C12	122.64(13)
C10	C11	C6	120.02(16)	C4	N2	C1	105.74(12)
N1	C12	C13	111.30(12)	C12	N2	C1	113.98(13)
N2	C12	C13	111.05(12)	C12	N2	C4	104.91(12)
N2	C12	N1	104.40(11)	C1	C2A	C3	102.5(4)
C14	C13	C12	121.37(13)				

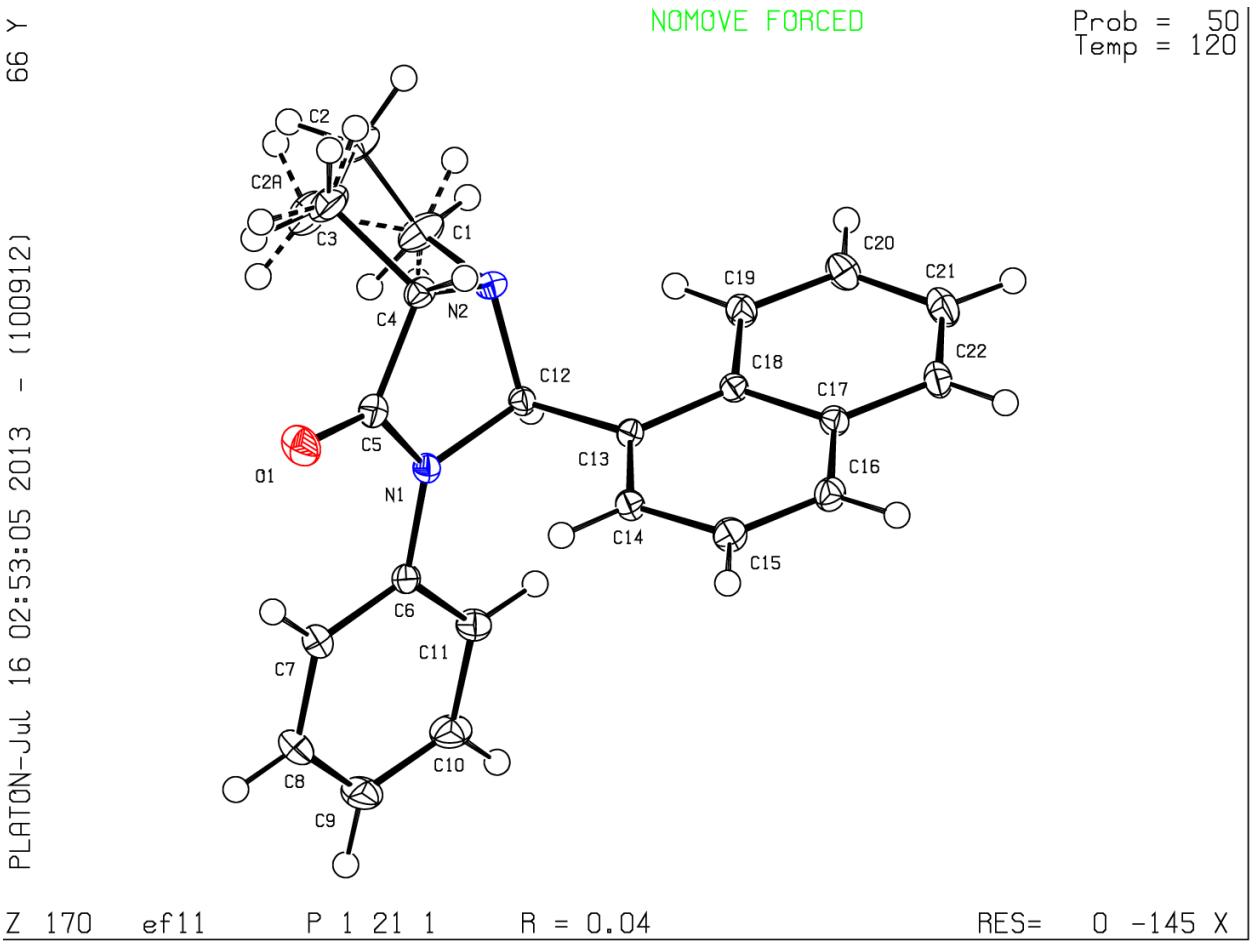
Table 6. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for *exo*-imidazolidinone **4-64**

Atom	*x*	*y*	*z*	U(eq)
H1A	4647	3251	9533	29
H1B	3225	4620	9222	29
H1BC	3946	5084	9348	29
H1BD	3628	3437	9300	29
H2A	6502	4909	10554	31
H2B	6139	6073	9719	31
H3A	9171	3869	9955	29
H3B	9456	5391	9531	29
H3BC	8511	5632	9548	29
H3BD	9864	4222	9826	29
H4	8306	4623	8022	17
H7	8932	-223	8442	25
H8	8158	-2585	8266	32
H9	4674	-3352	7609	31
H10	1977	-1722	7086	26
H11	2701	647	7263	21
H12	3149	2627	7861	14
H14	6930	2127	6429	16
H15	6631	2610	4774	20
H16	3820	3948	3977	19
H19	1256	4612	7339	19
H20	-1543	5941	6513	23
H21	-1943	6264	4828	24
H22	512	5300	3998	20
H2AA	6808	3041	10206	33
H2AB	6432	4569	10605	33

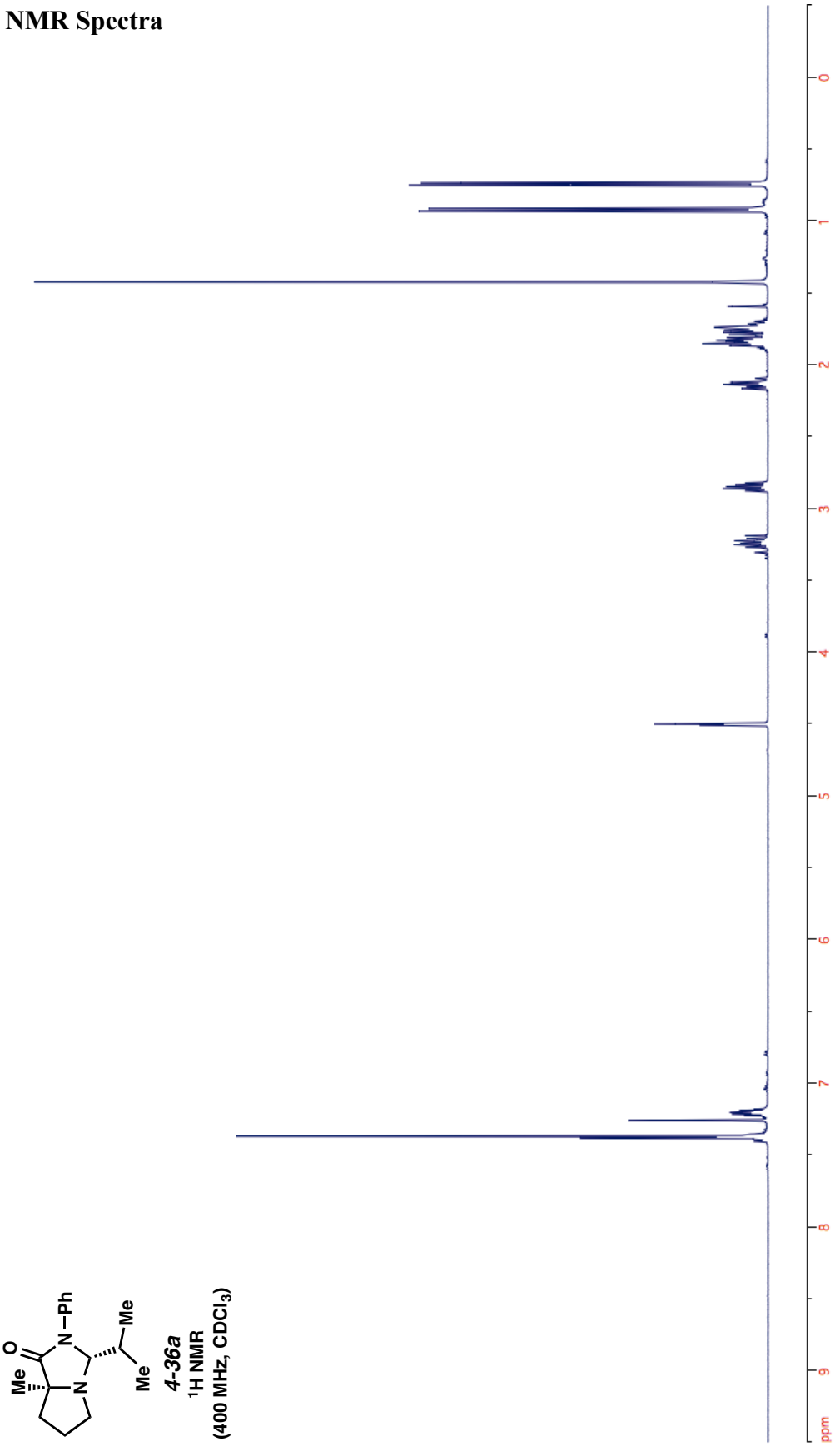
Crystal Structure Determination of *exo*-imidazolidinone **4-64**

Crystal Data for $C_{22}H_{20}N_2O$ (M =328.40): monoclinic, space group $P2_1$ (no. 4), a = 6.3233(2) Å, b = 9.6627(4) Å, c = 14.0935(5) Å, β = 100.794(2)°, V = 845.88(5) Å^3, Z = 2, T = 120(2) K, μ(MoKα) = 0.080 mm^{-1}, *Dcalc* = 1.289 g/mm^3, 23576 reflections measured (5.142 ≤ 2Θ ≤ 66.832), 6418 unique (R_{int} = 0.0394) which were used in all calculations. The final R_1 was 0.0429 (I > 2σ(I)) and wR_2 was 0.1262 (all data).

Figure 1. Crystal Structure of *exo*-Imidazolidnone **4-64**



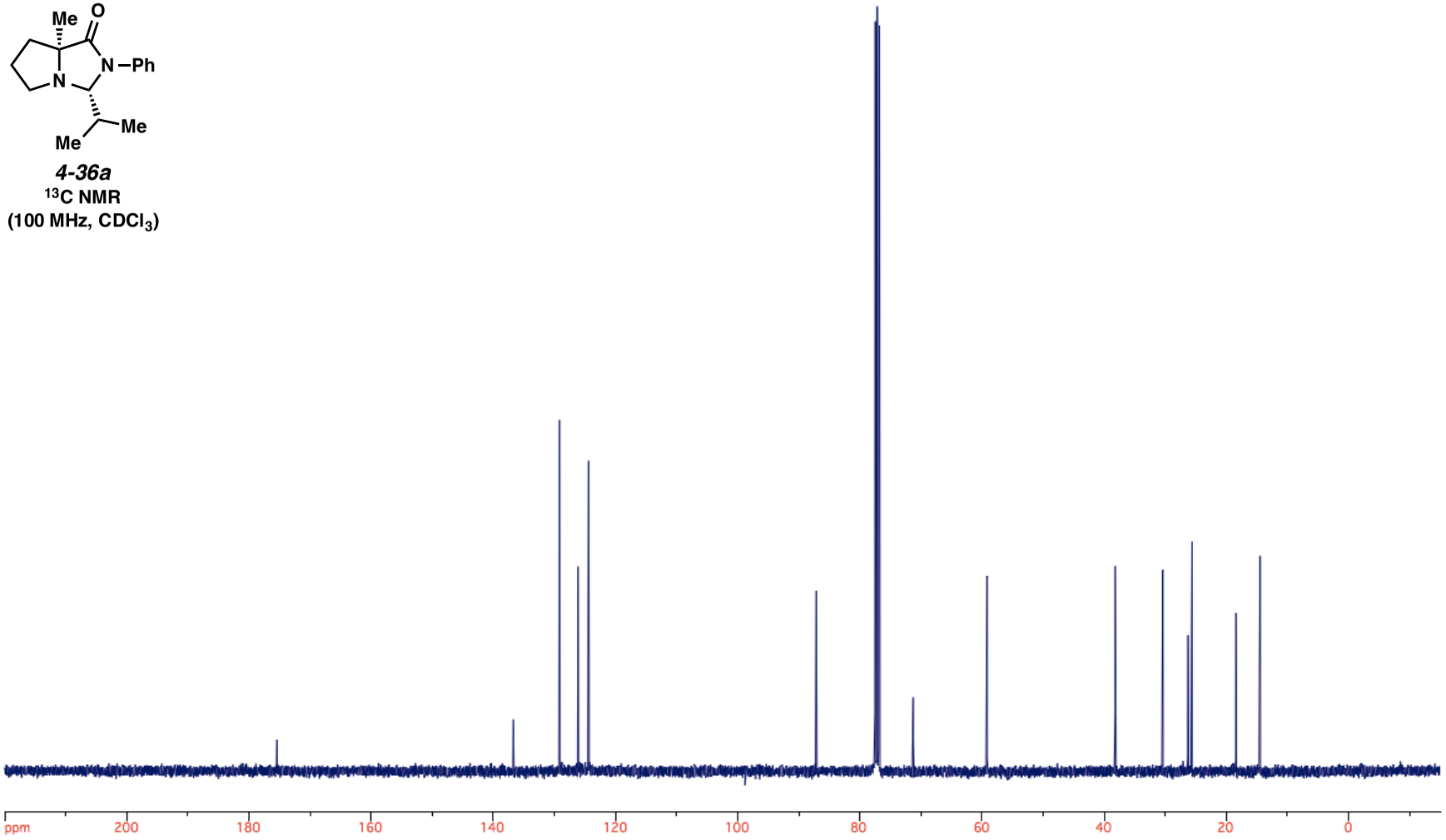
4.6.4. NMR Spectra



4-36a

^{13}C NMR

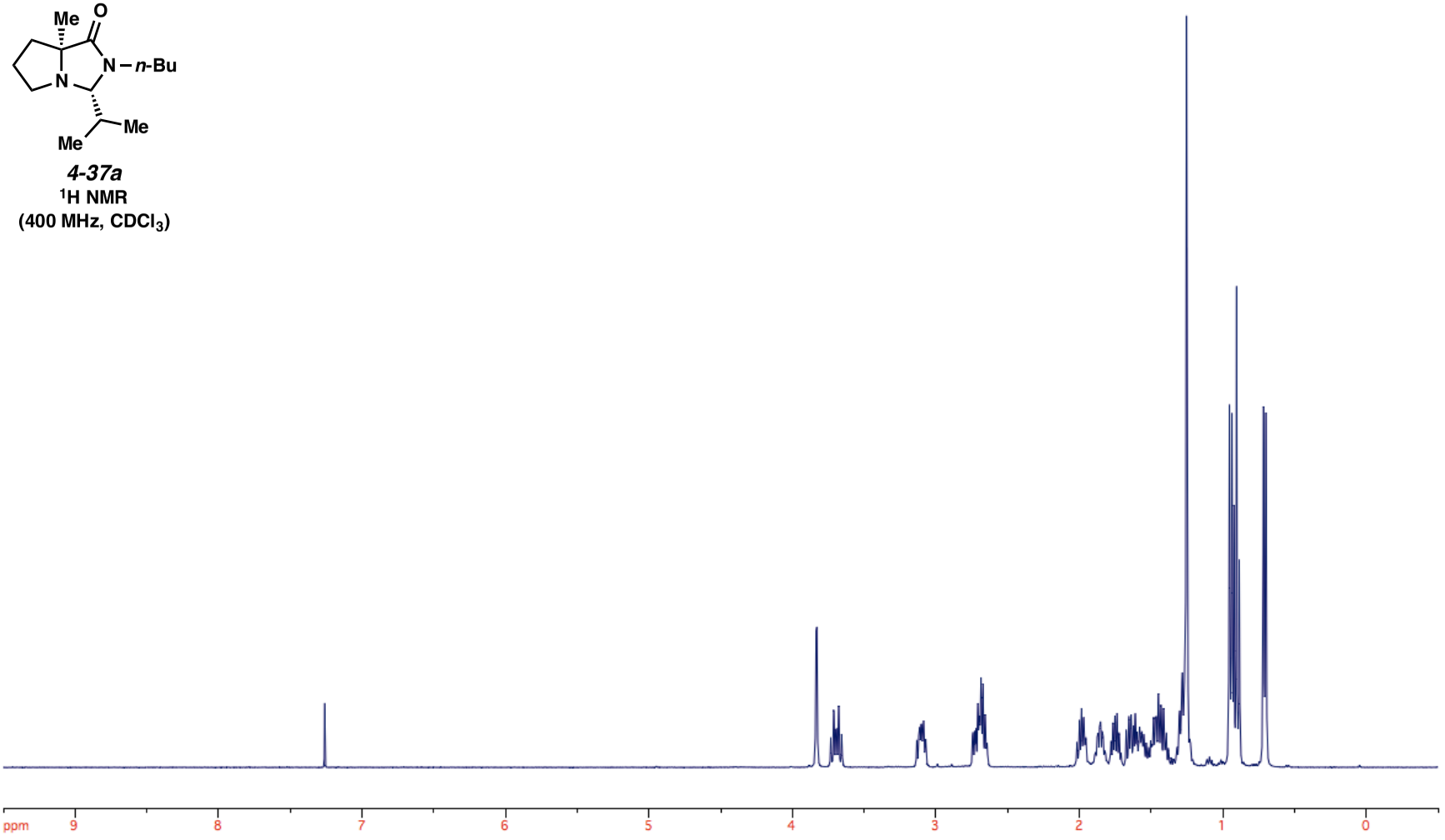
(100 MHz, $CDCl_3$)



4-37a

^{1}H NMR

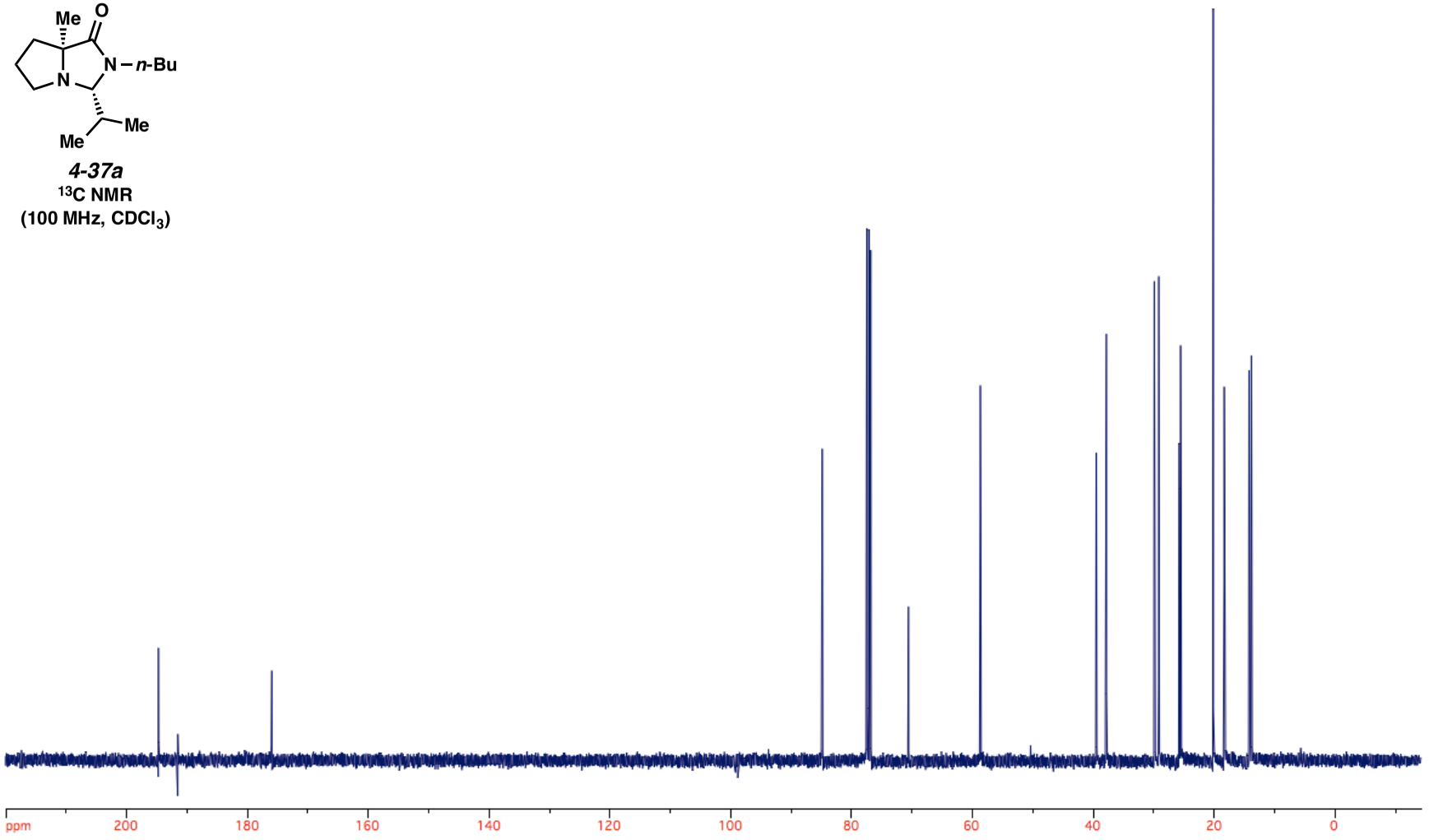
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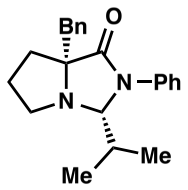


4-37a

^{13}C NMR

(100 MHz, $CDCl_3$)

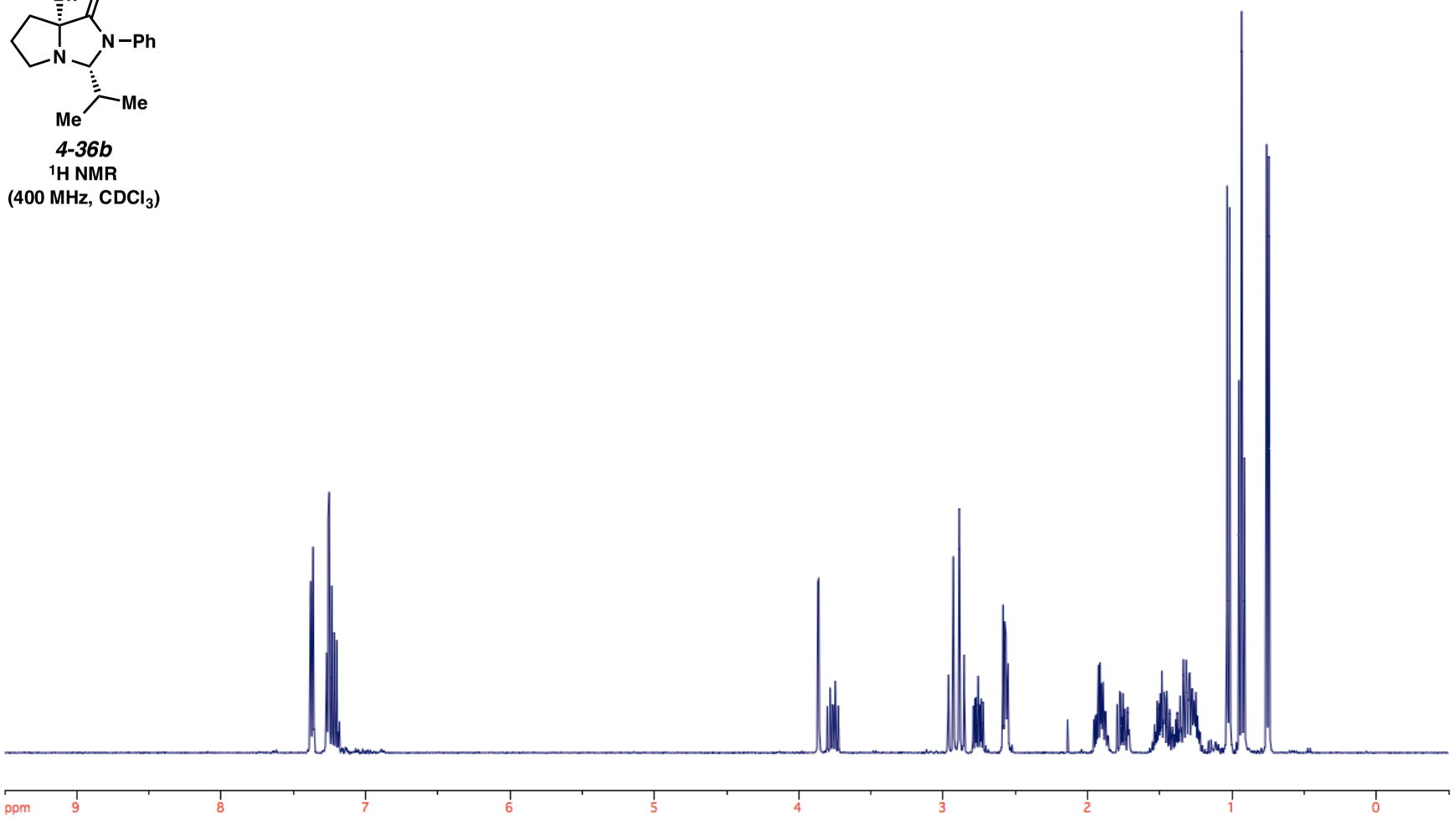


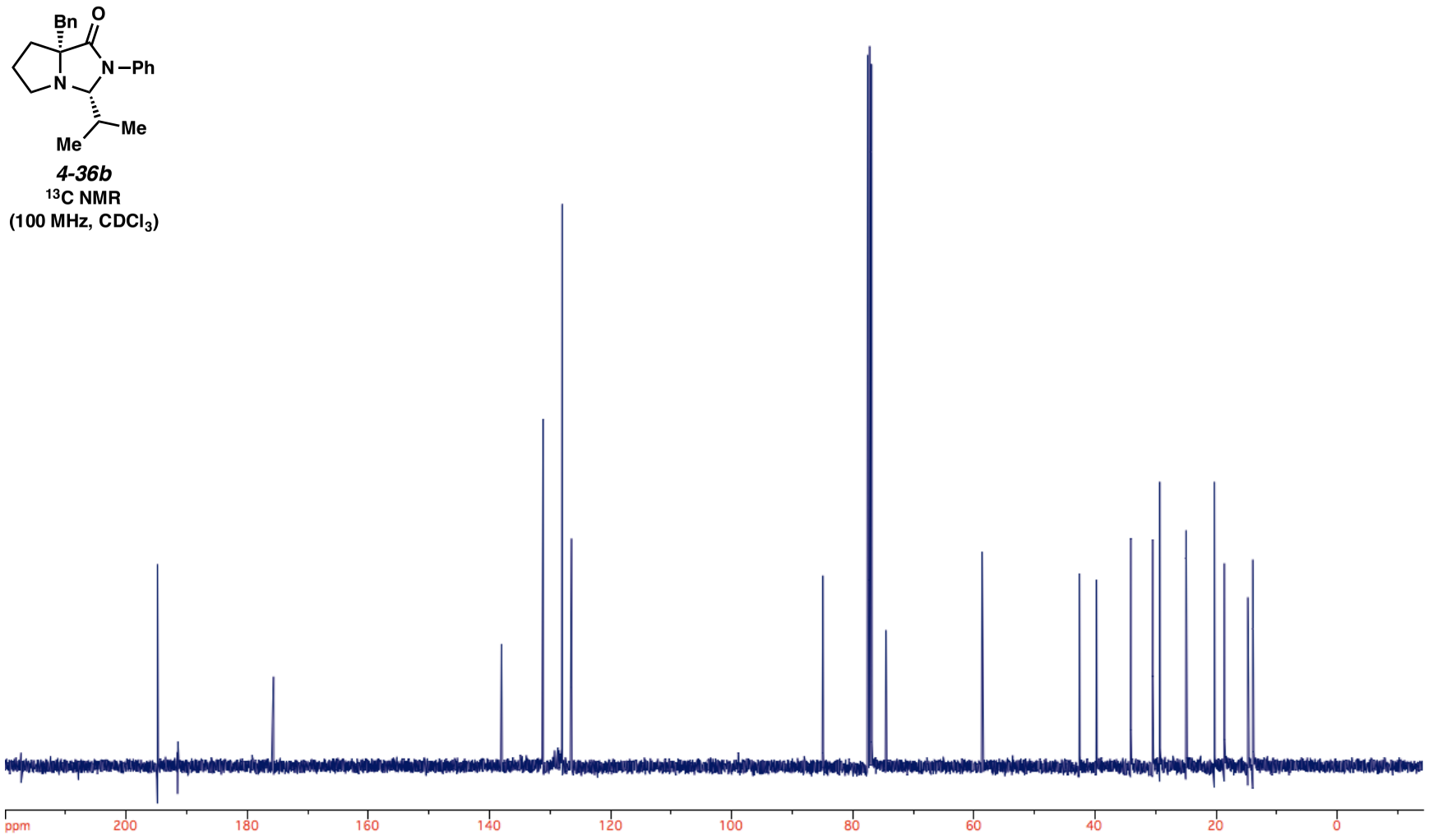


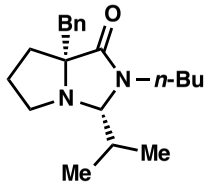
4-36b

^{1}H NMR

(400 MHz, $CDCl_3$)



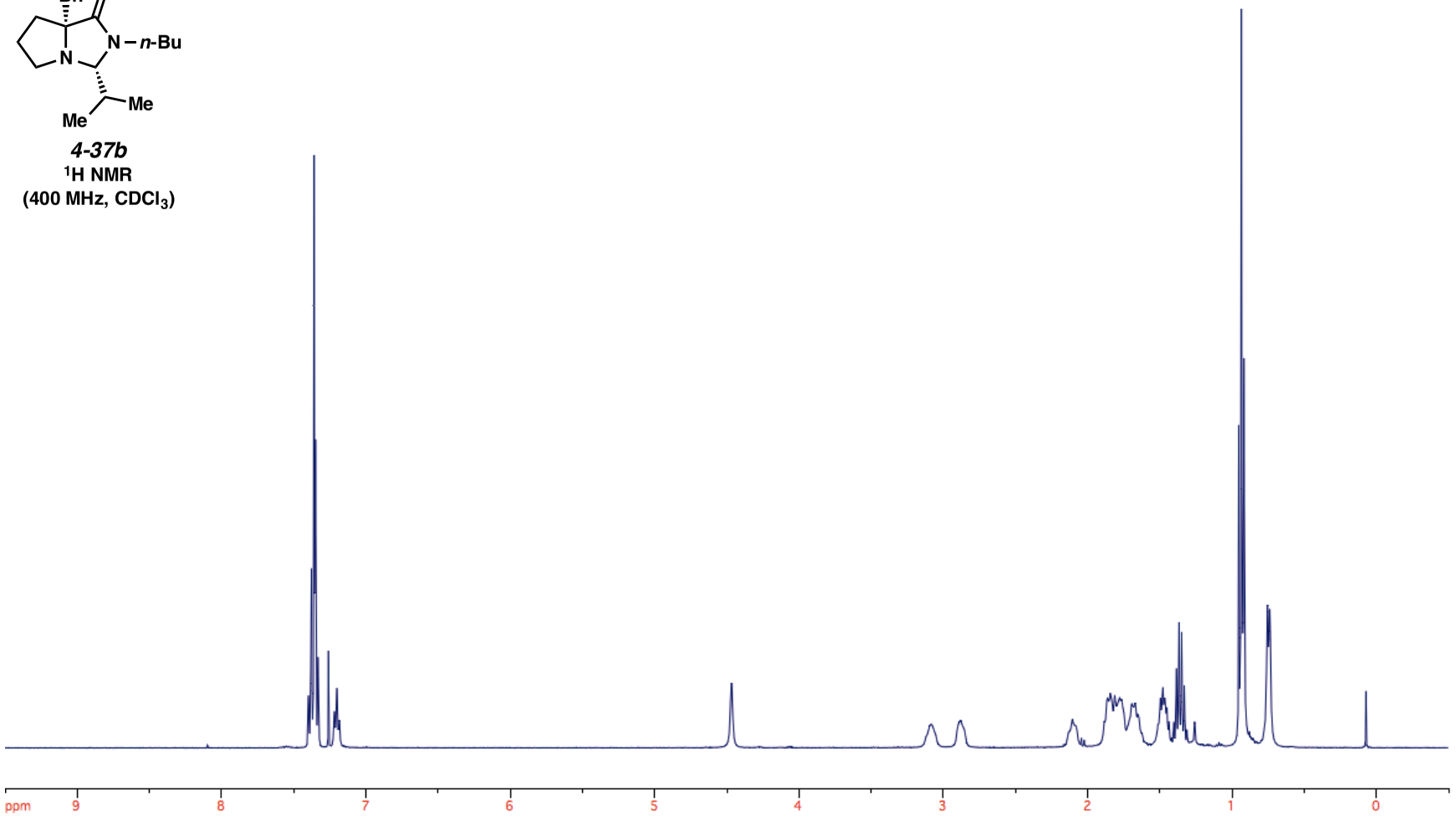

Bn
O
N
N–Ph
Me
Me
4-36b
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

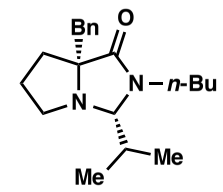


4-37b

^{1}H NMR

(400 MHz, $CDCl_3$)

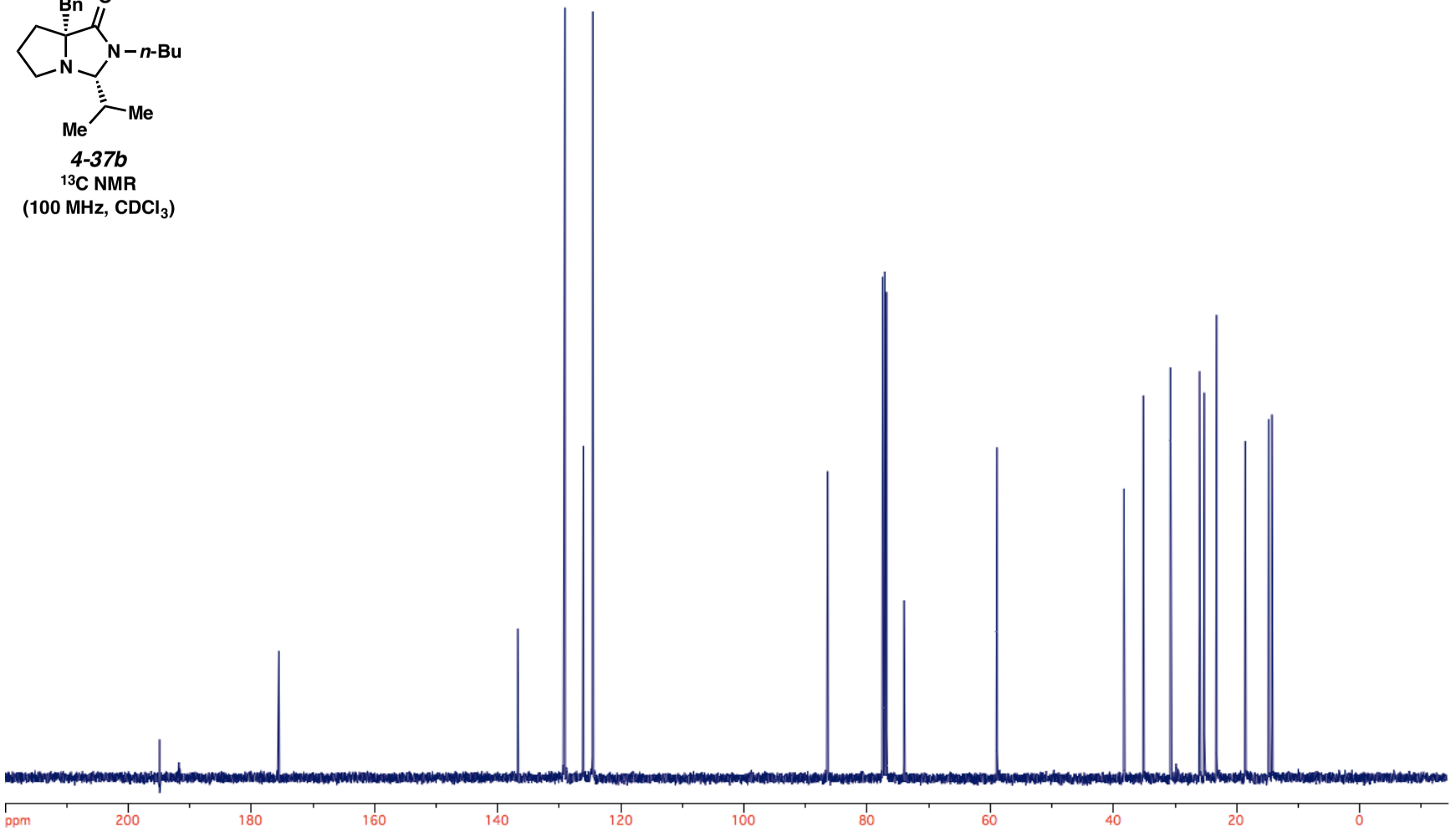


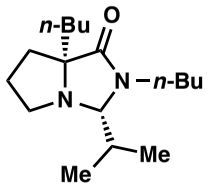


4-37b

^{13}C NMR

(100 MHz, $CDCl_3$)

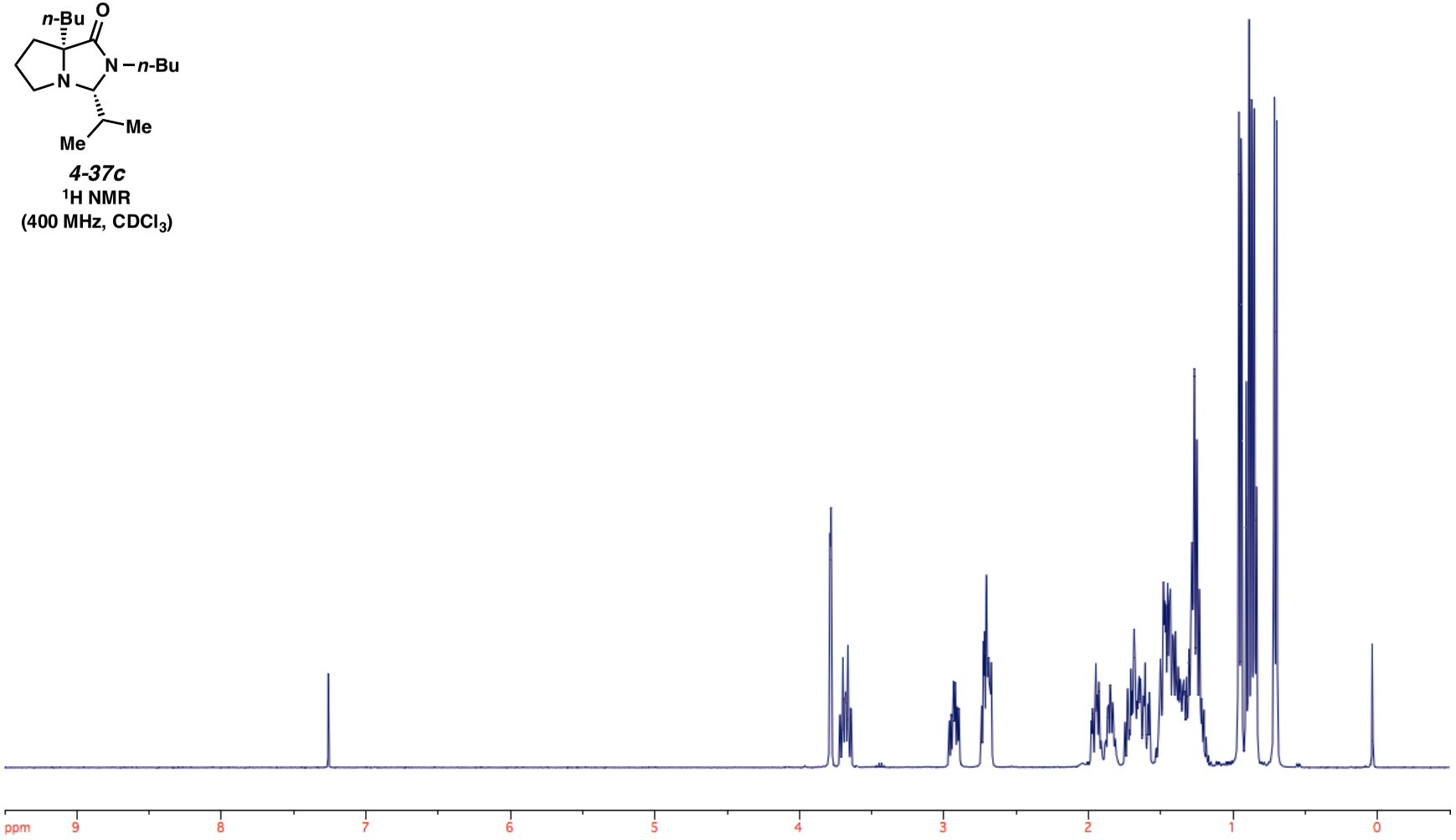


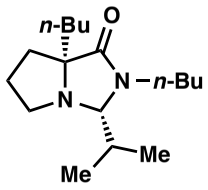


4-37c

^{1}H NMR

(400 MHz, $CDCl_3$)

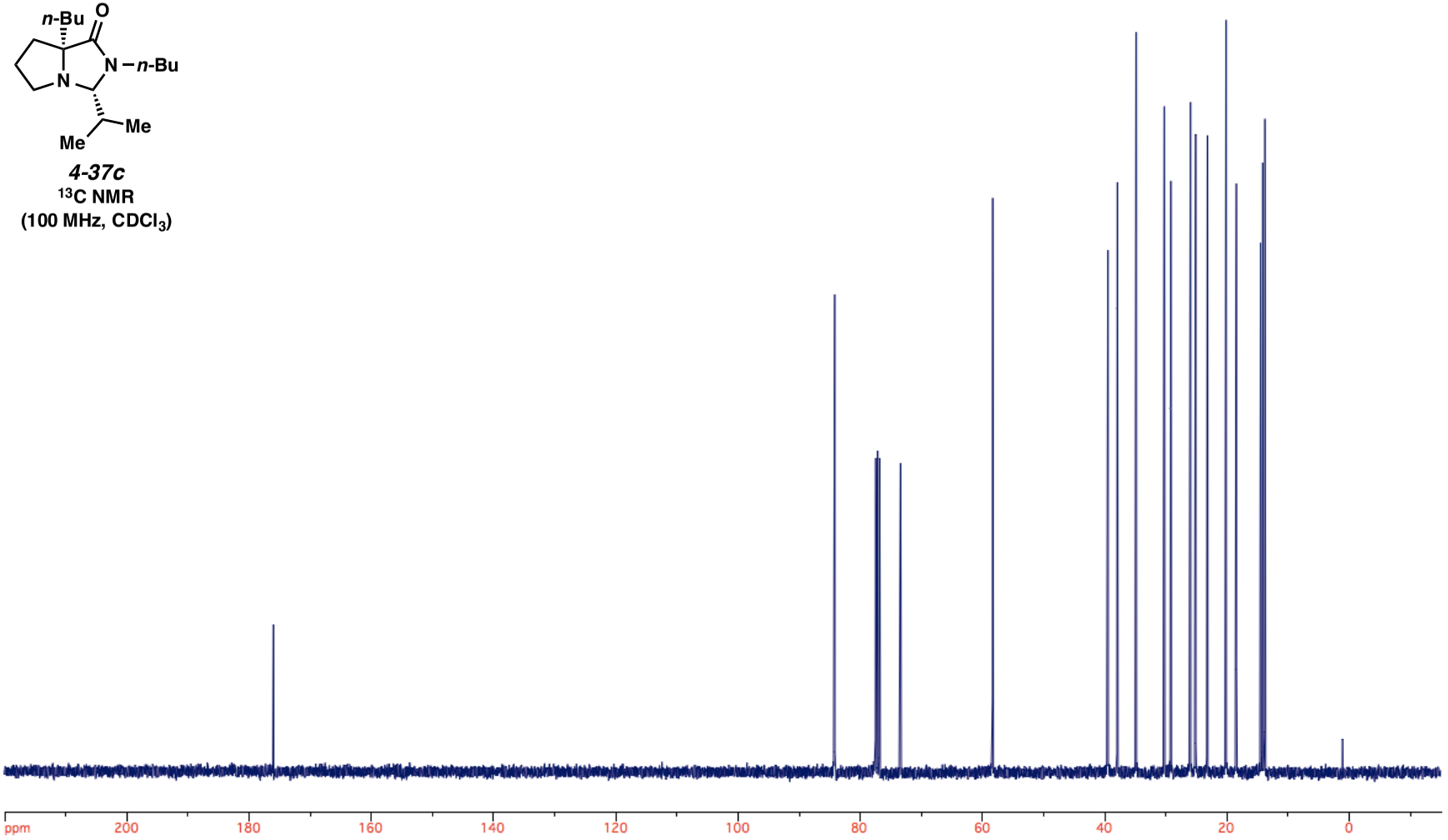


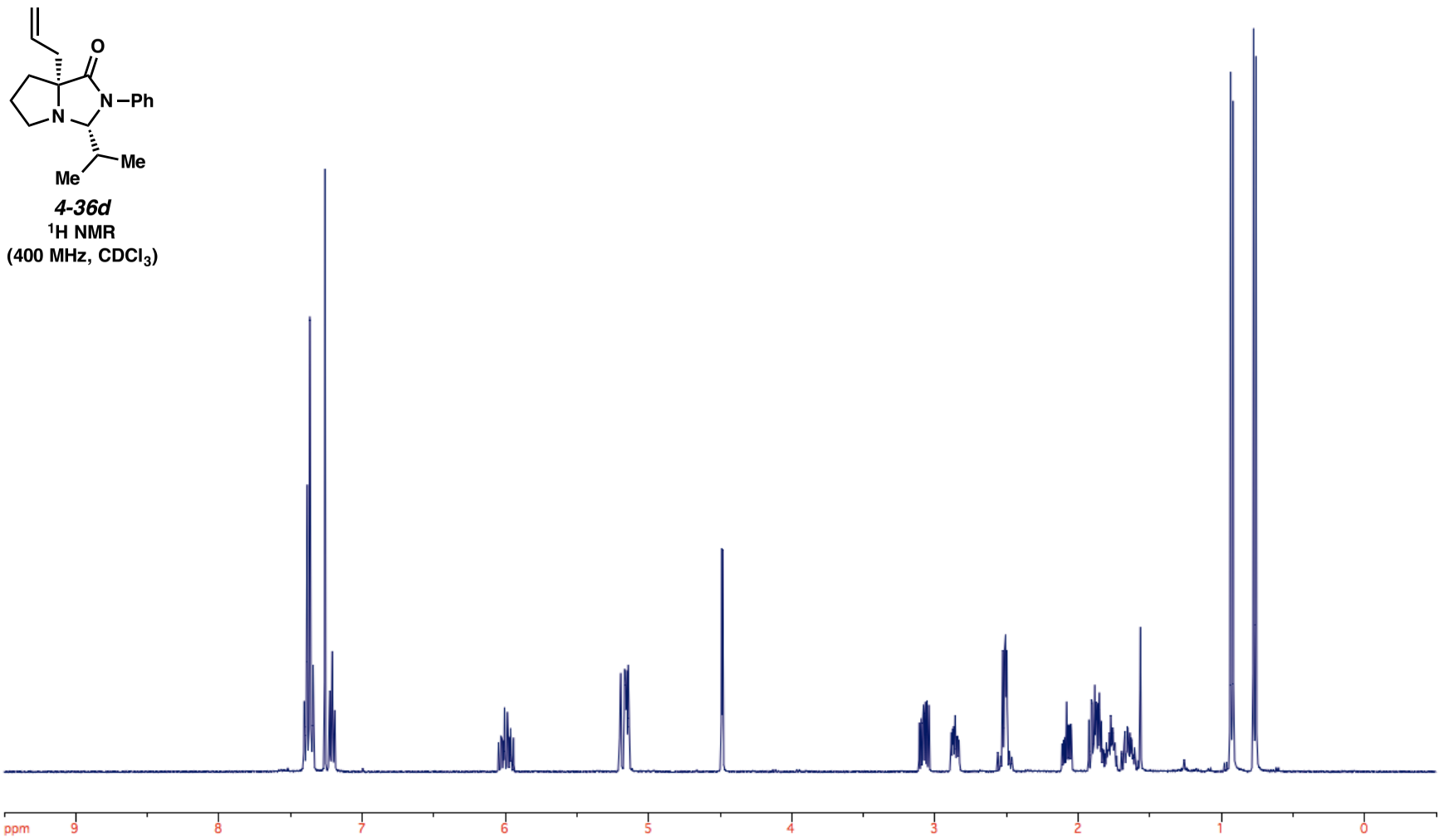


4-37c

^{13}C NMR

(100 MHz, $CDCl_3$)





4-36d

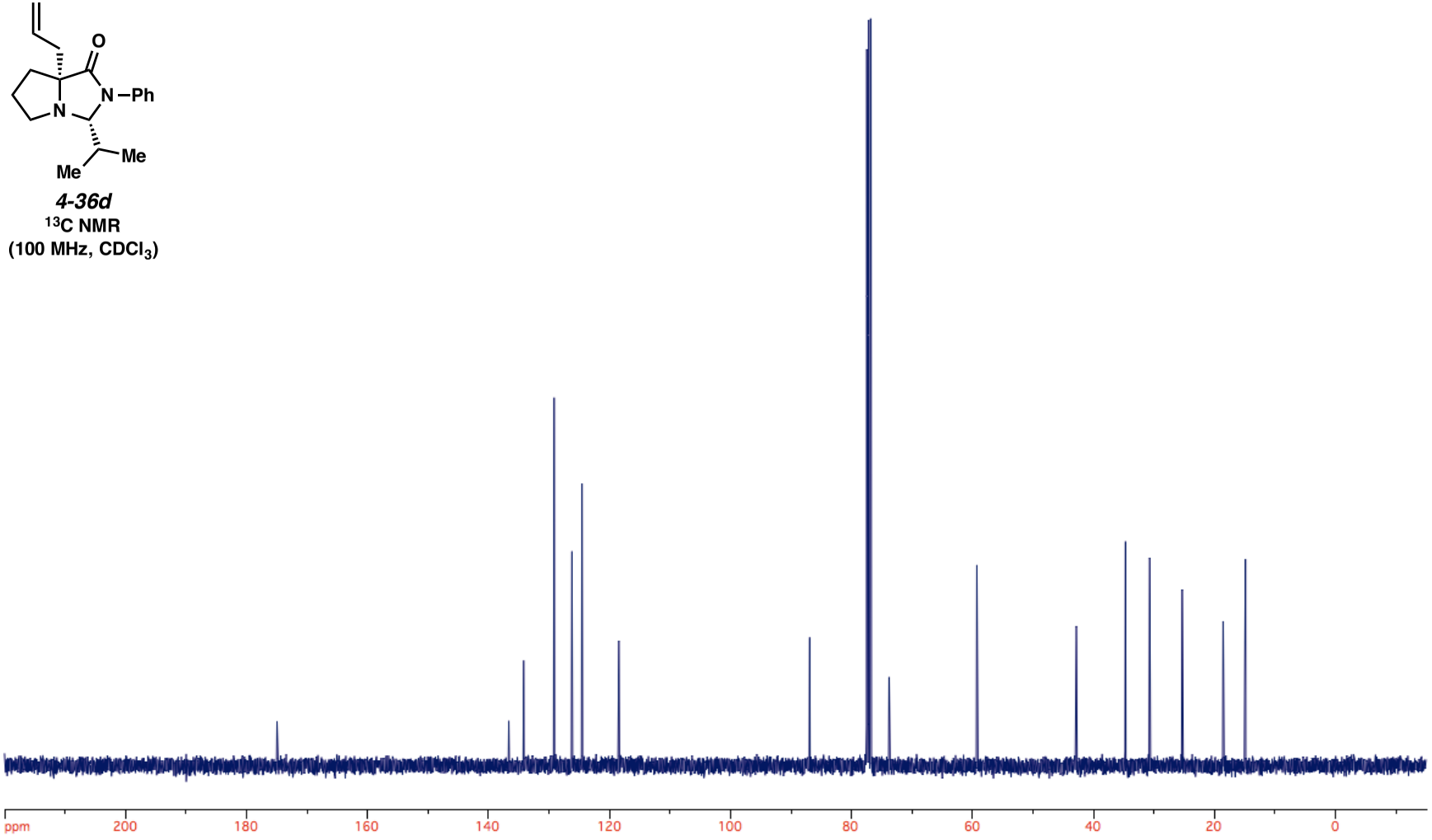
^{1}H NMR

(400 MHz, $CDCl_3$)

4-36d

^{13}C NMR

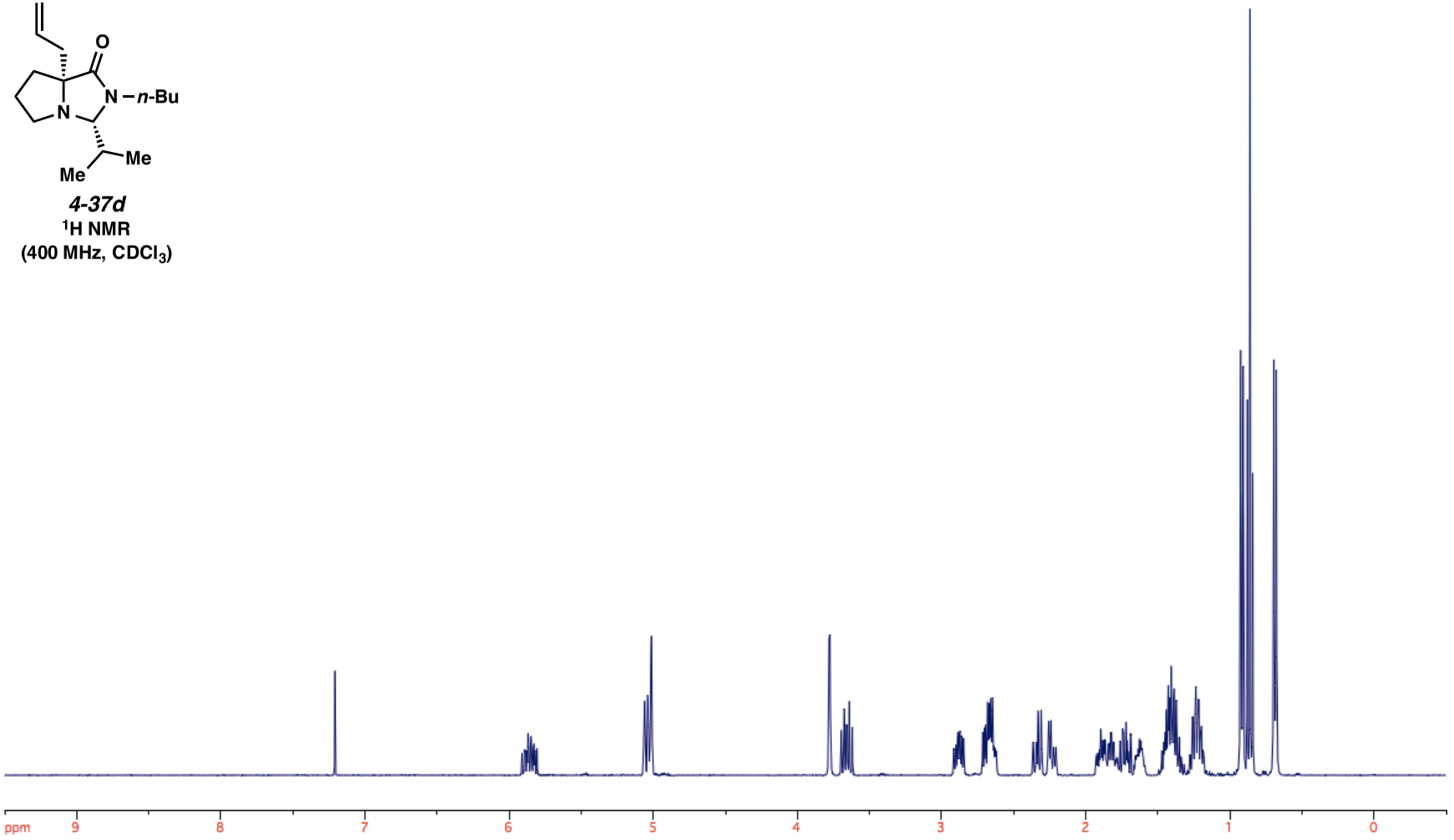
(100 MHz, $CDCl_3$)

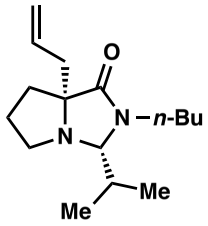


4-37d

^{1}H NMR

(400 MHz, $CDCl_3$)

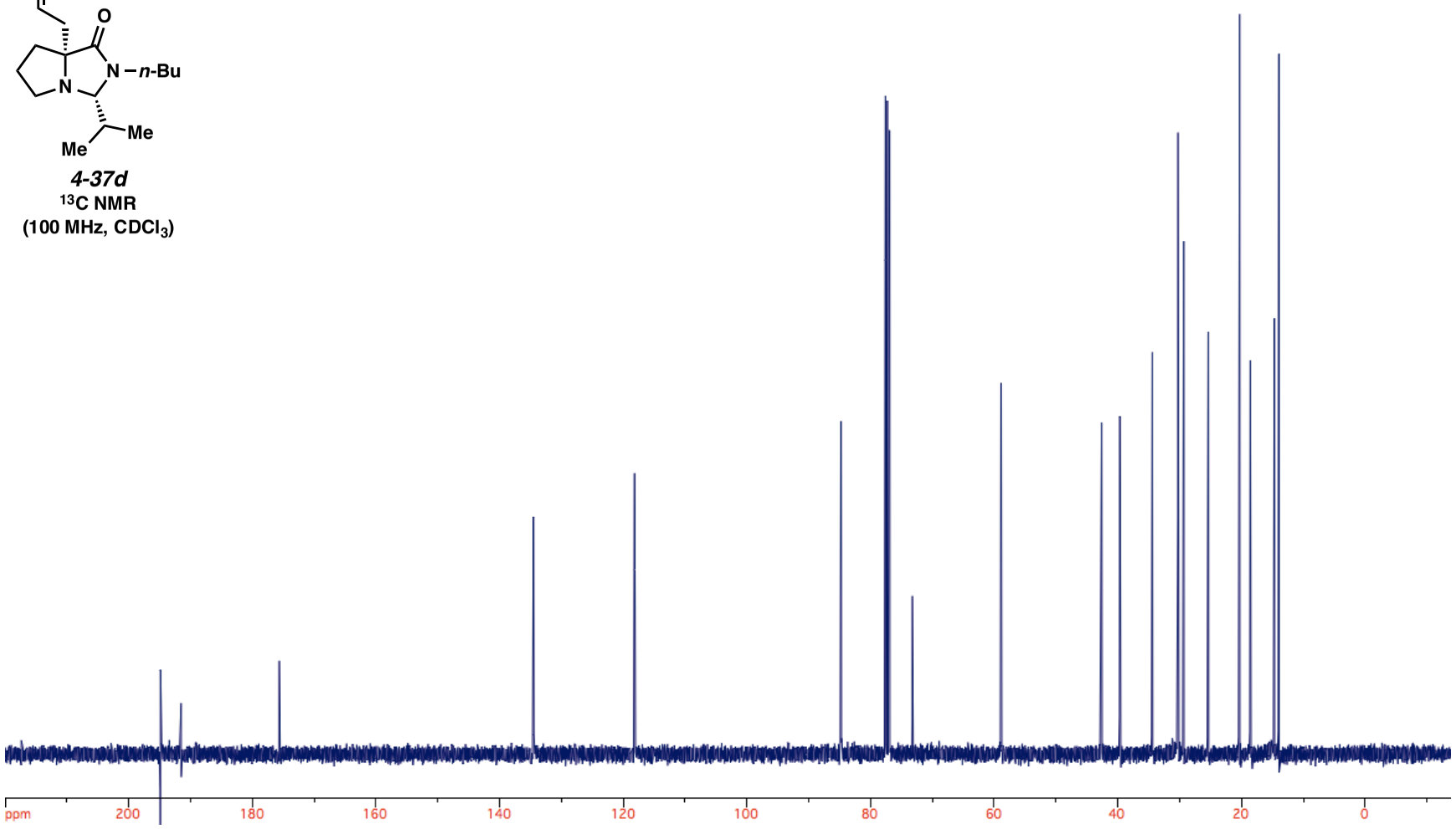


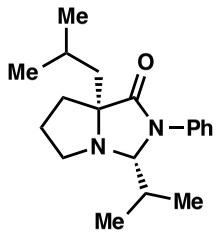


4-37d

^{13}C NMR

(100 MHz, $CDCl_3$)

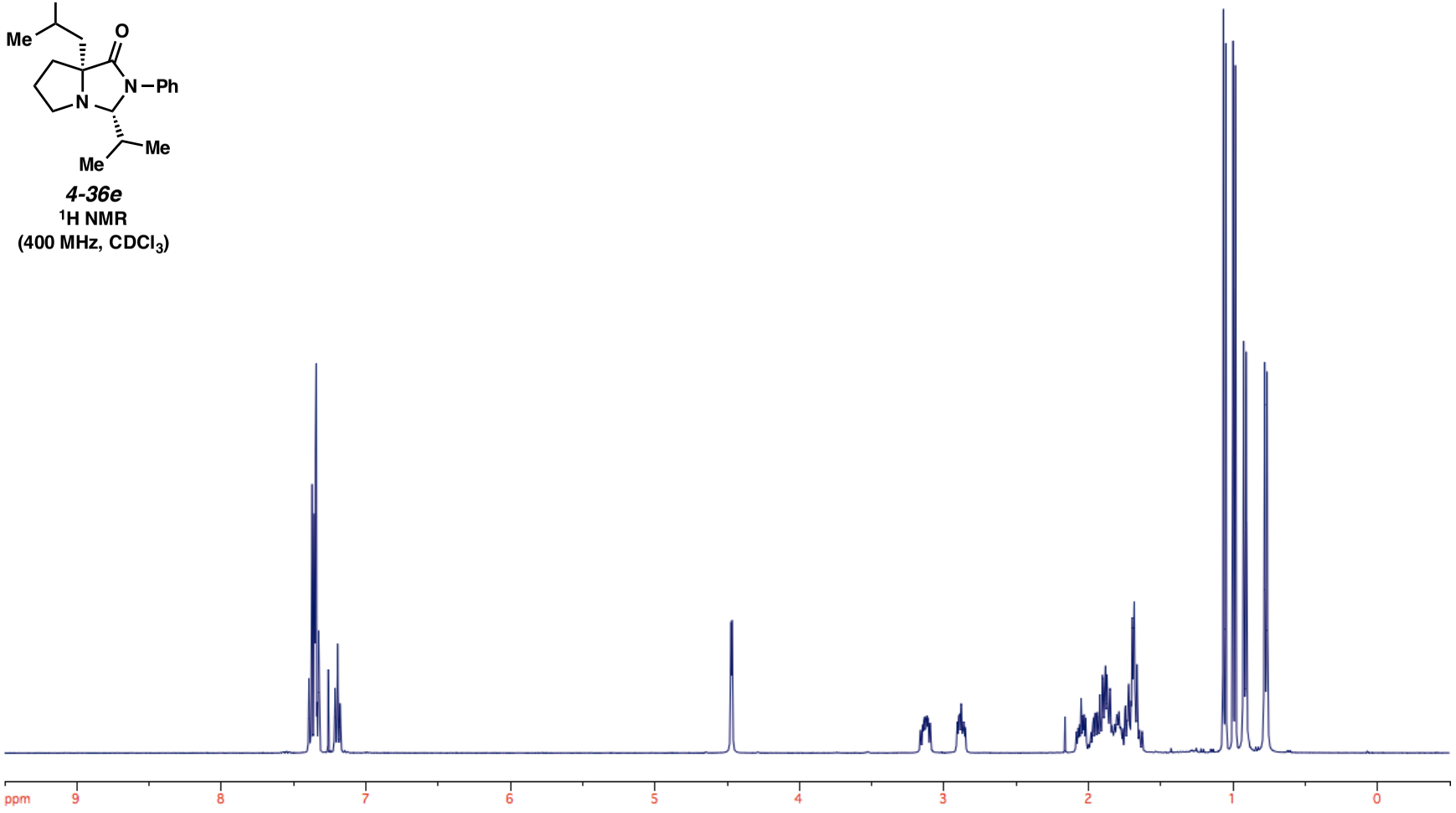




4-36e

^{1}H NMR

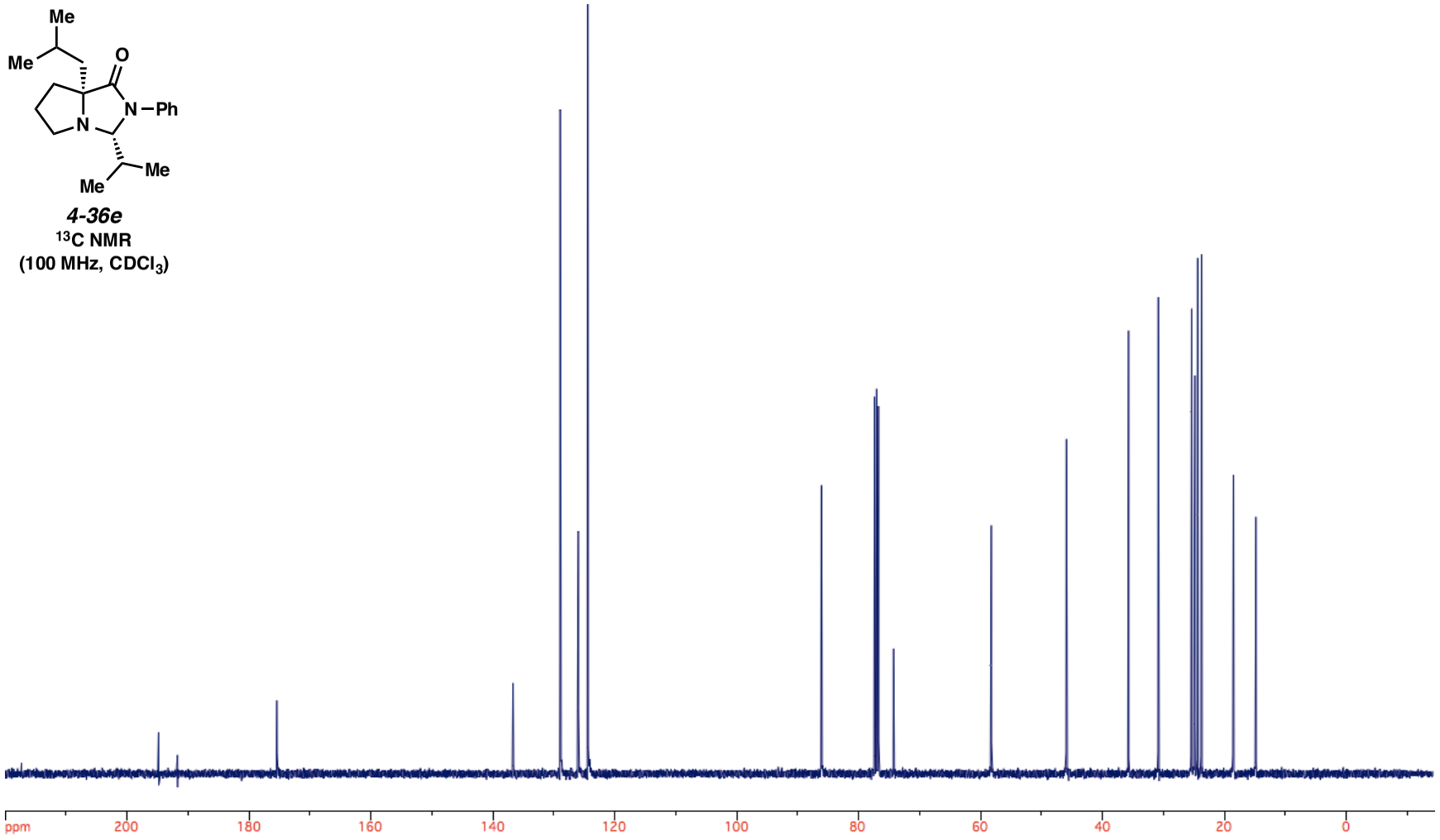
(400 MHz, $CDCl_3$)

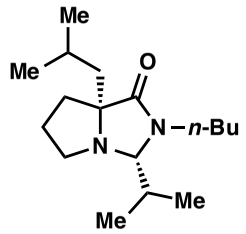


4-36e

^{13}C NMR

(100 MHz, $CDCl_3$)

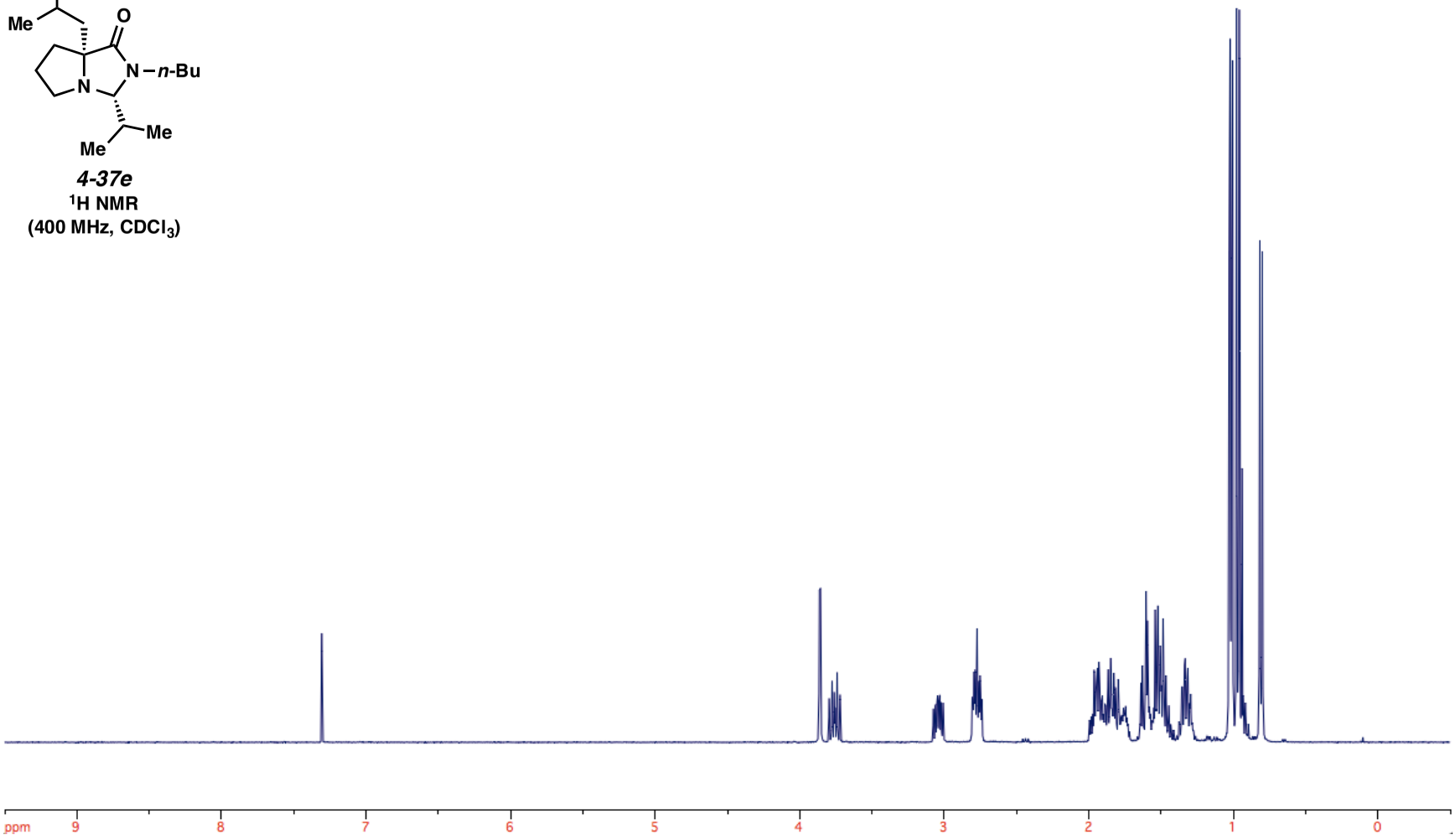




4-37e

^{1}H NMR

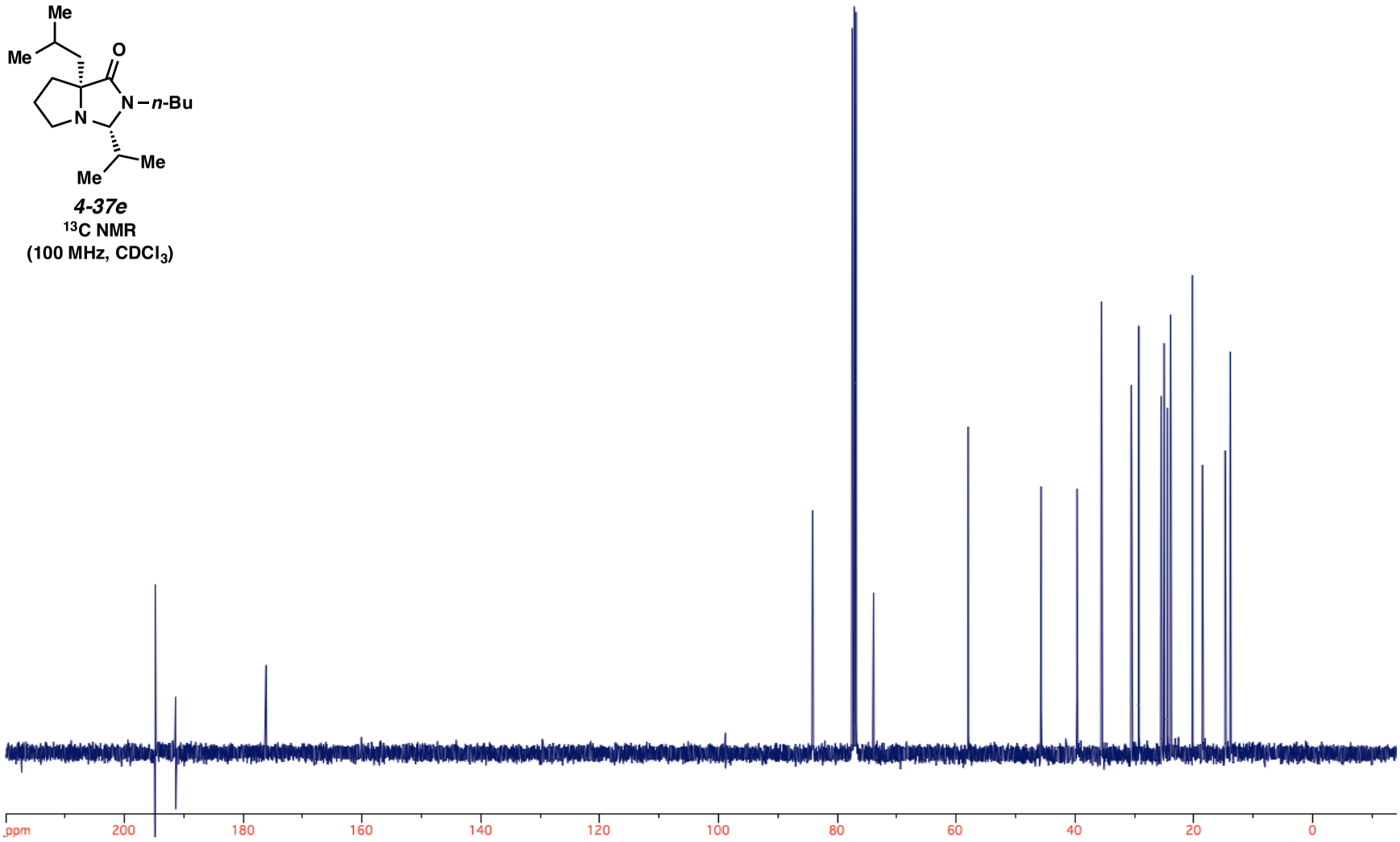
(400 MHz, $CDCl_3$)

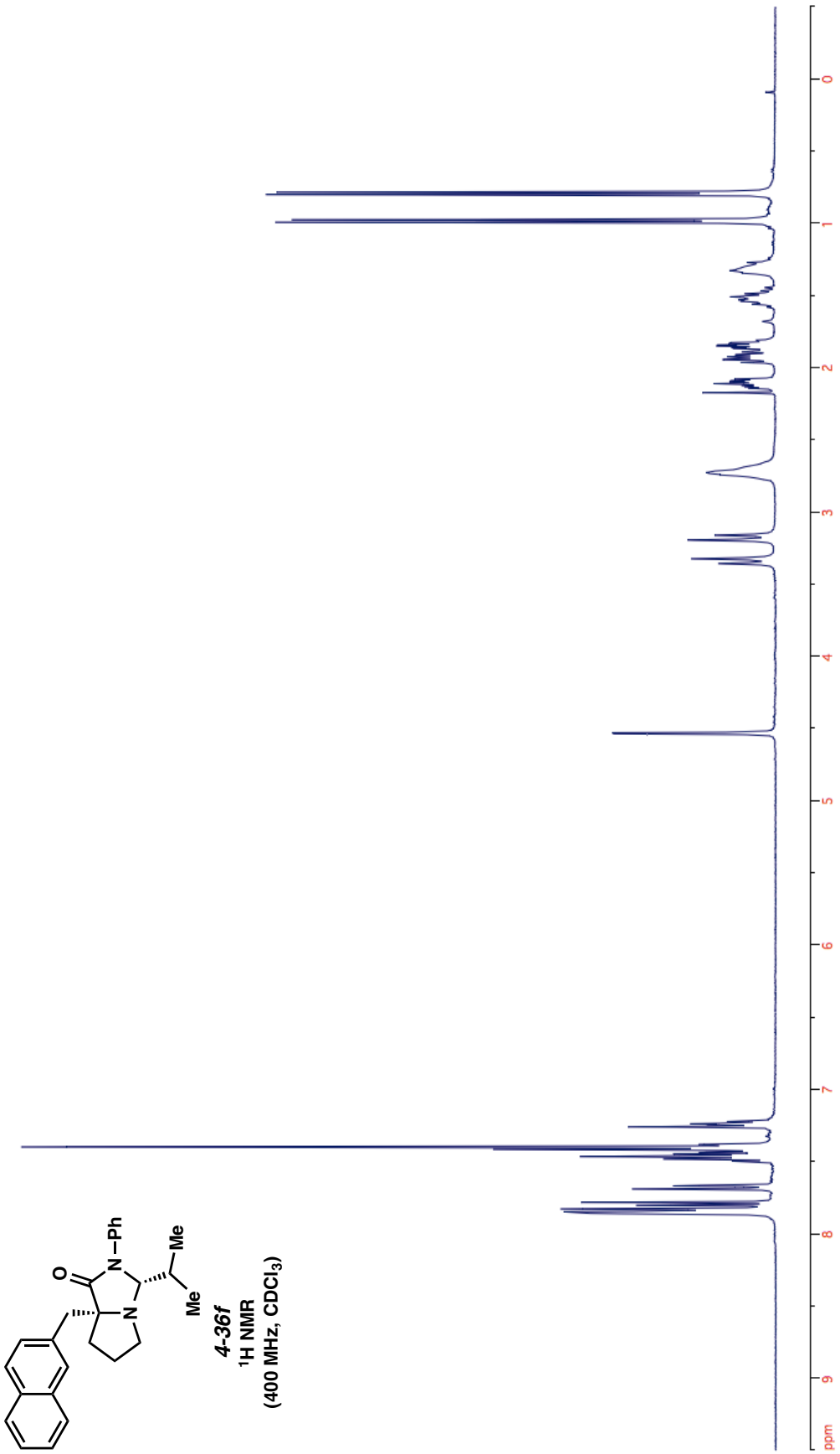


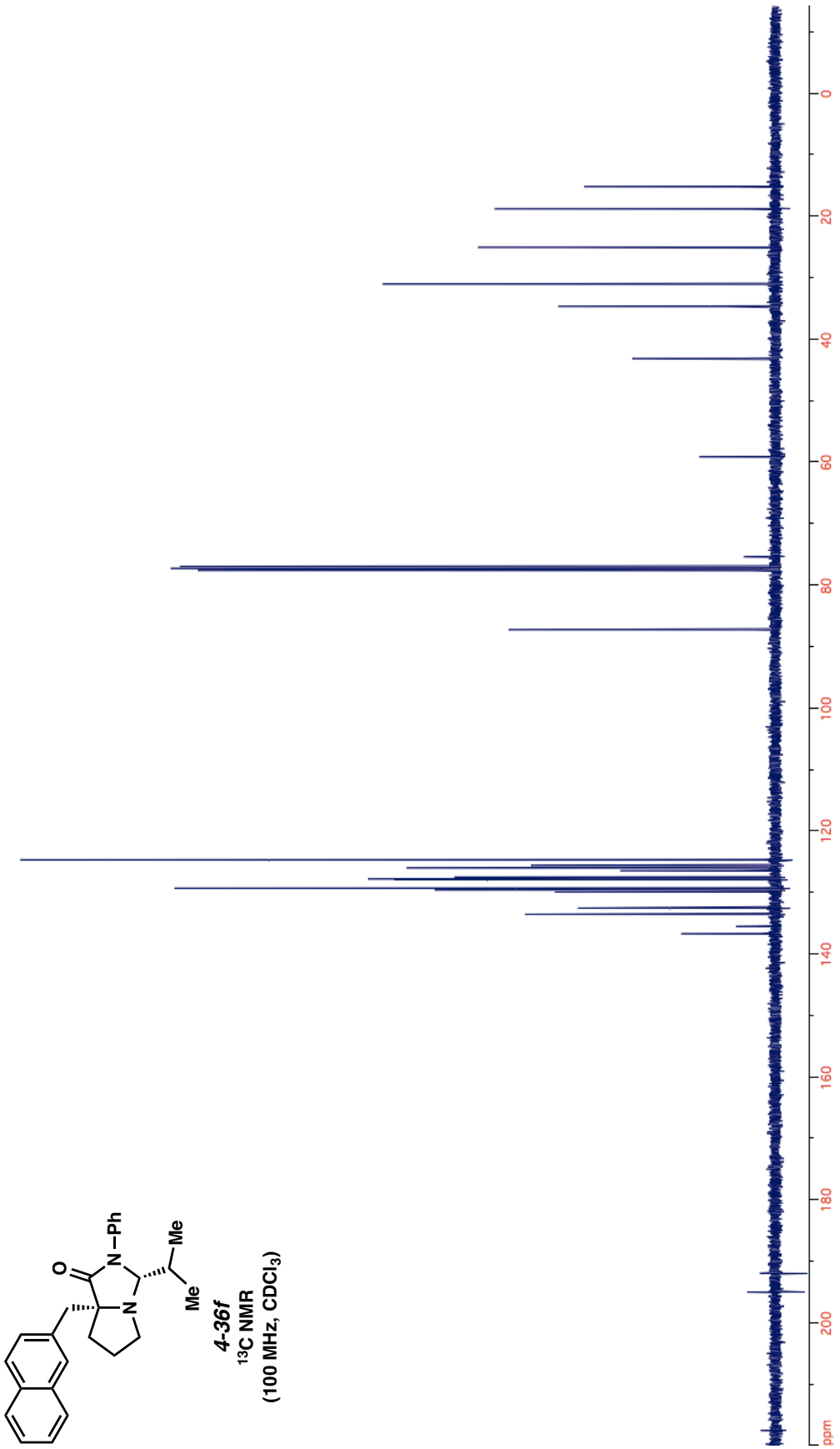
4-37e

^{13}C NMR

(100 MHz, $CDCl_3$)



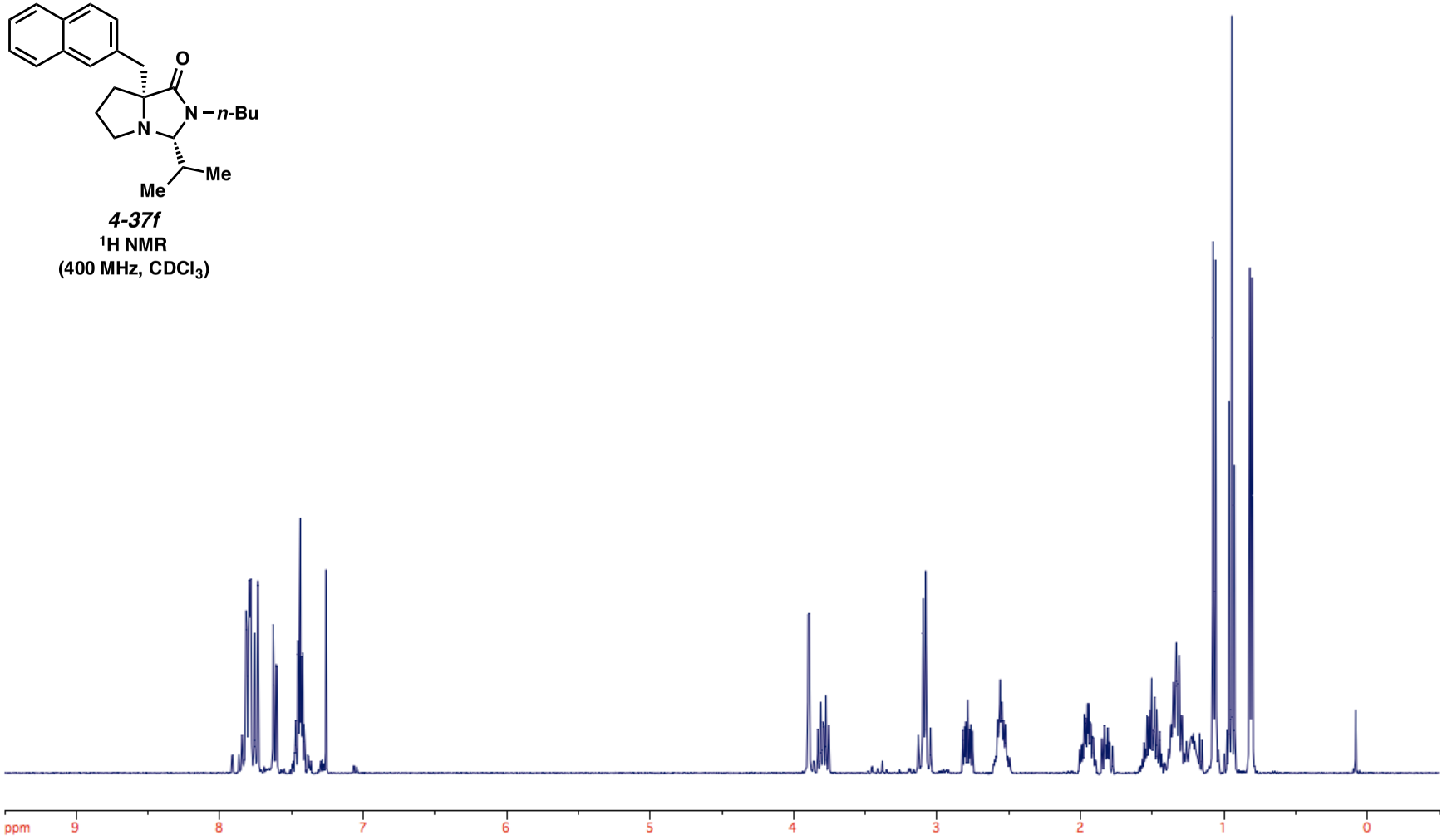

O
N–Ph
N
Me
Me
4-36f
^{1}H NMR
(400 MHz, $CDCl_3$)
ppm
0
1
2
3
4
5
6
7
8
9

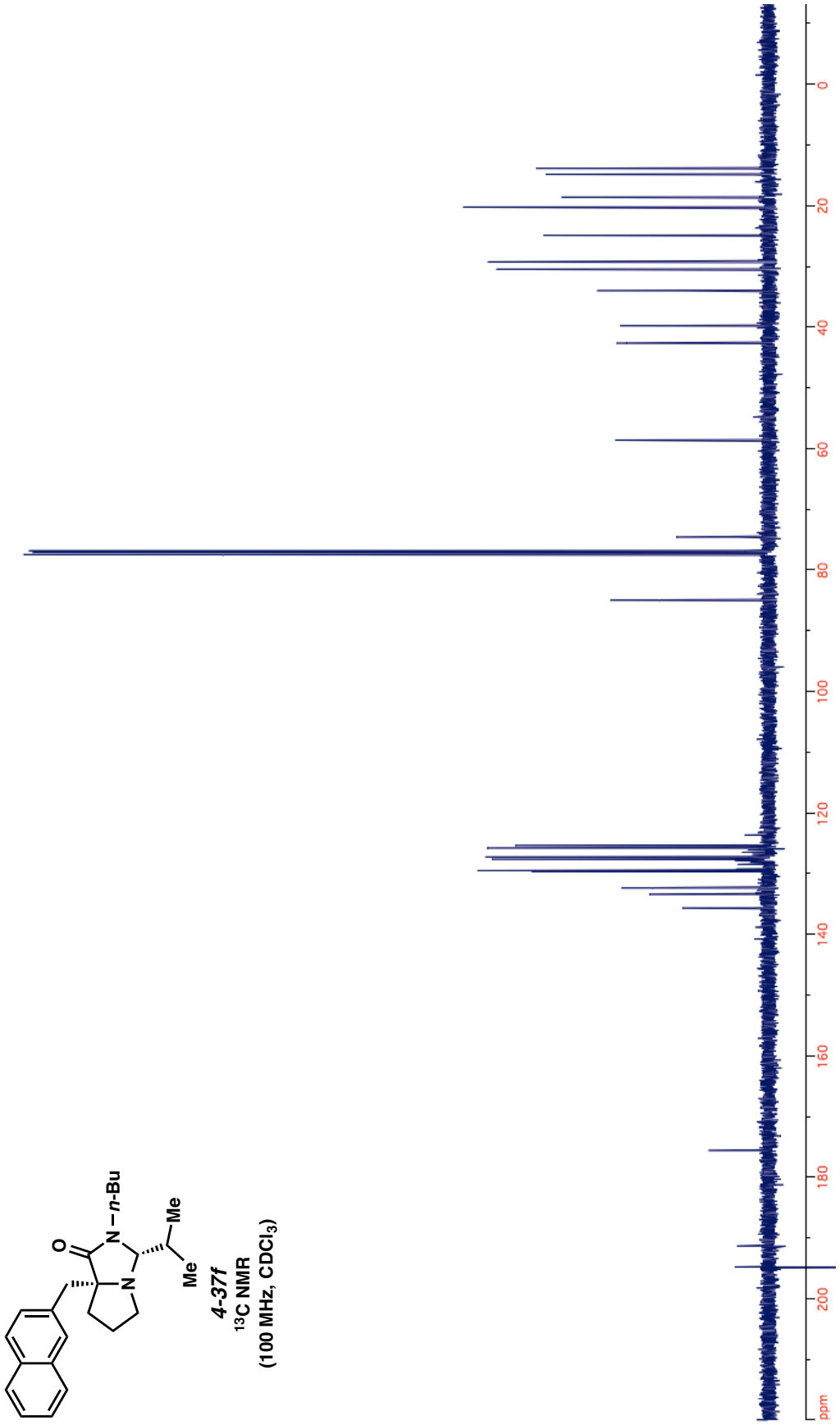

O
N–Ph
N
Me
Me
4-36f
13C NMR
(100 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

4-37f

^{1}H NMR

(400 MHz, $CDCl_3$)

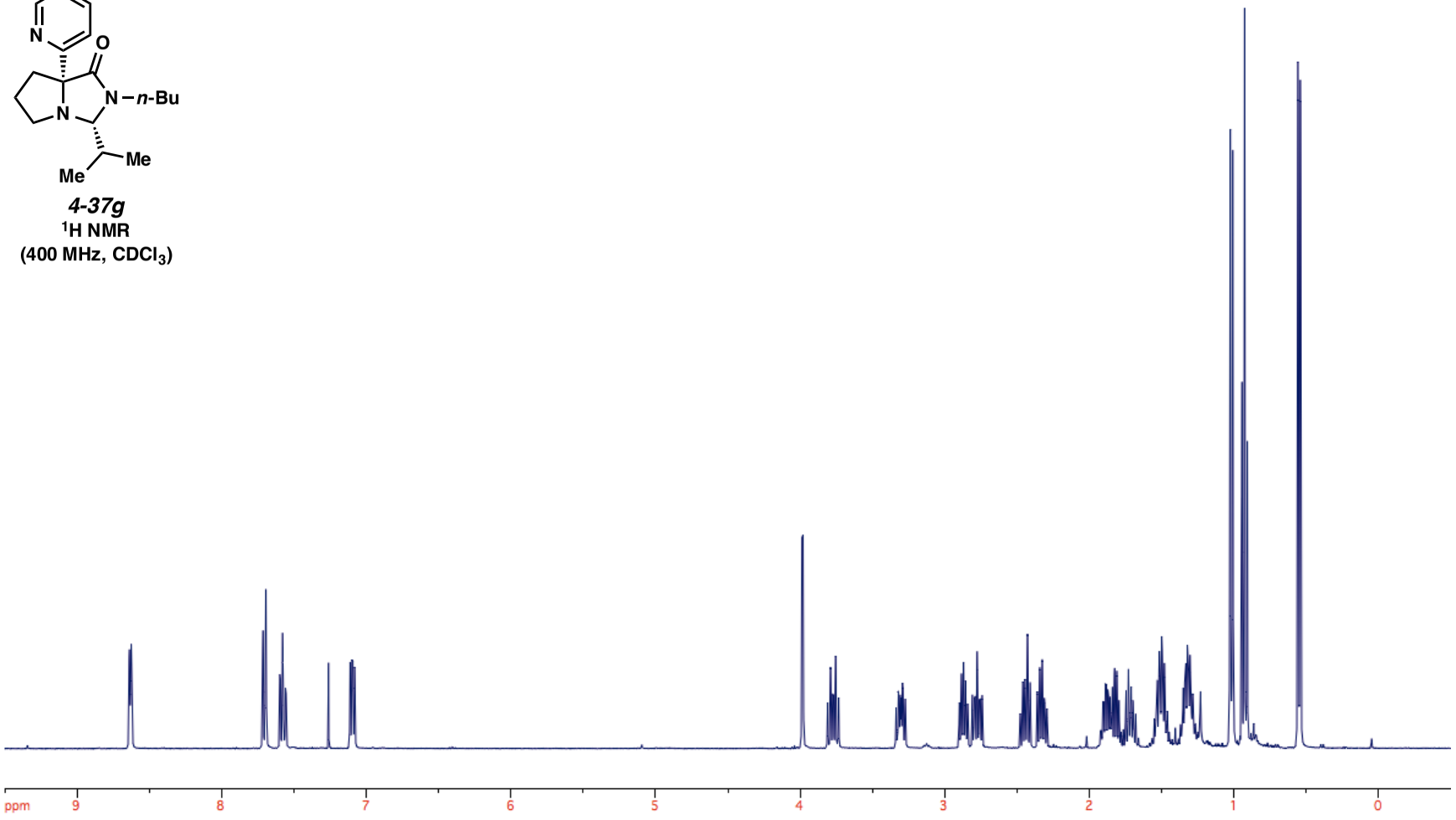



O
N – n-Bu
N
Me
Me
4-37f
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

4-37g

^{1}H NMR

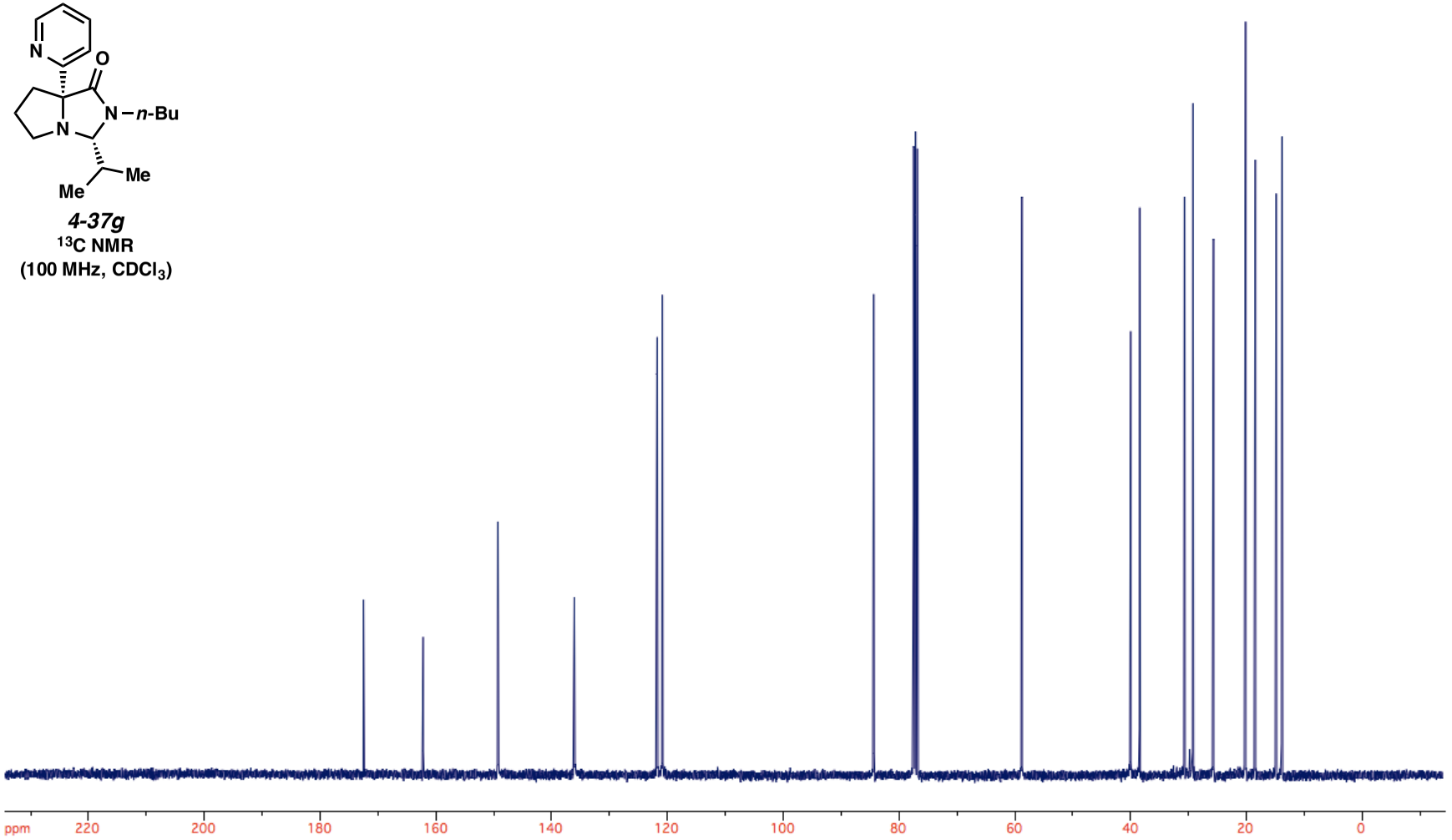
(400 MHz, $CDCl_3$)

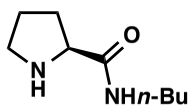


4-37g

^{13}C NMR

(100 MHz, $CDCl_3$)

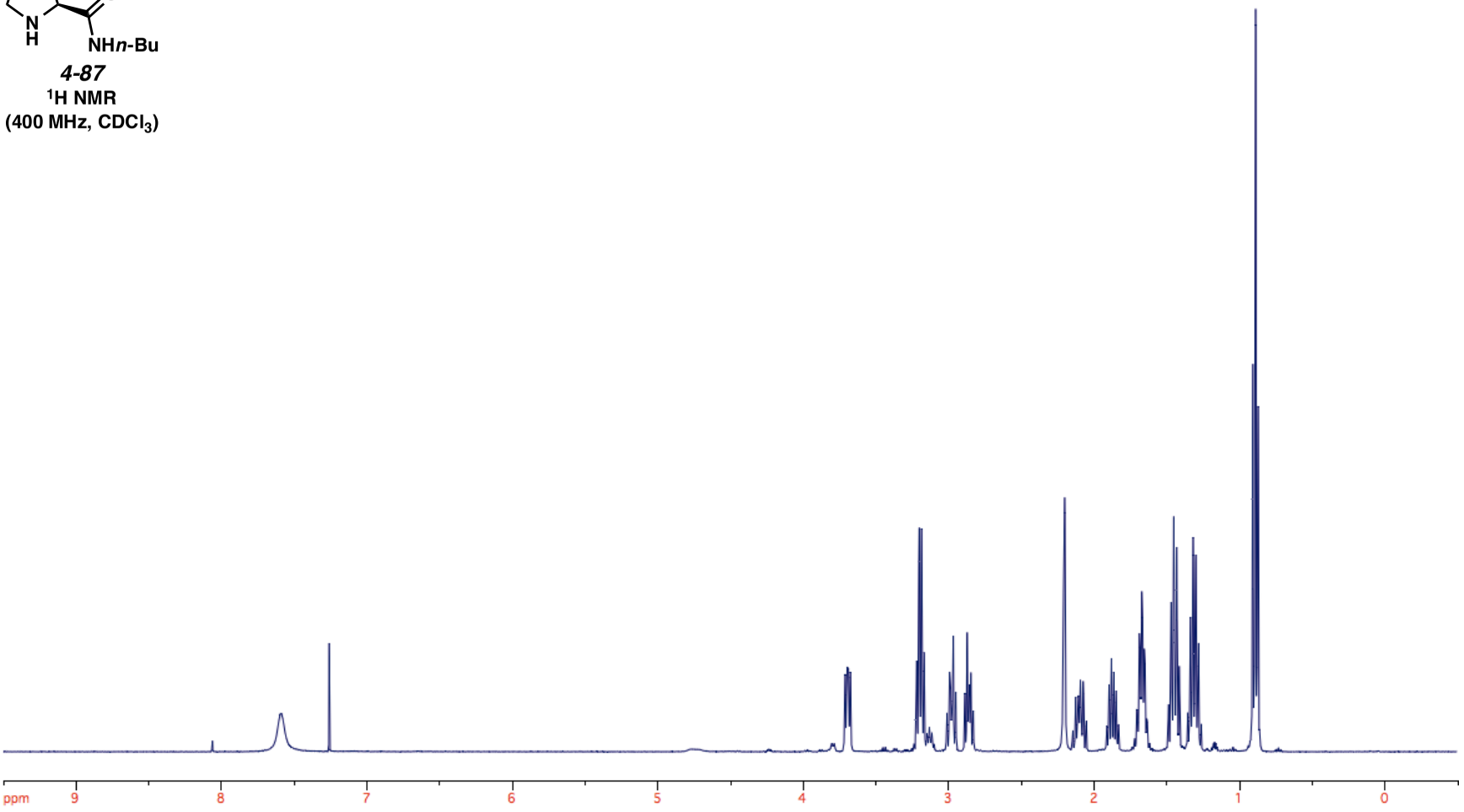


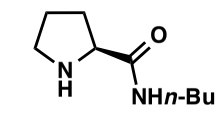


4-87

^{1}H NMR

(400 MHz, $CDCl_3$)

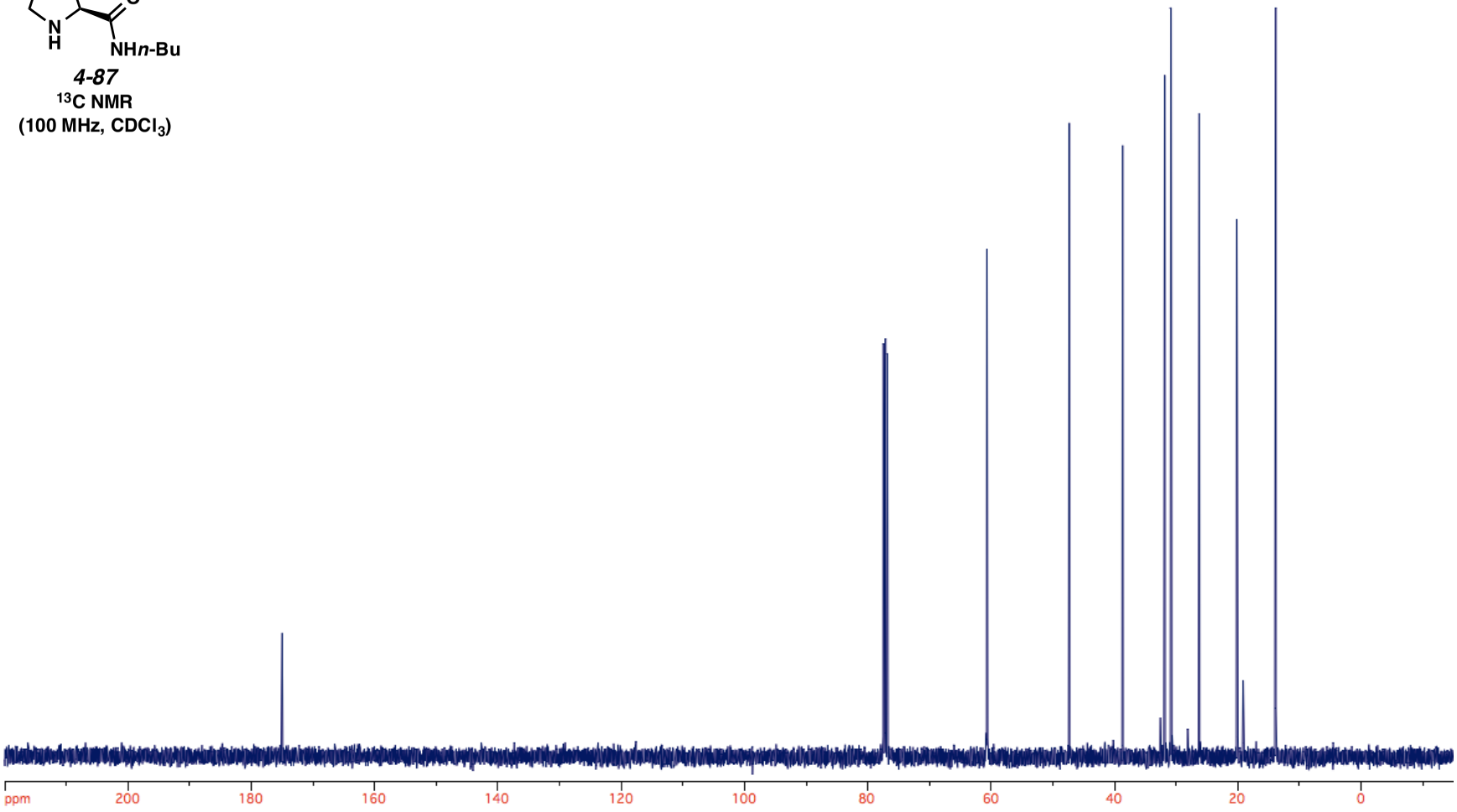




4-87

^{13}C NMR

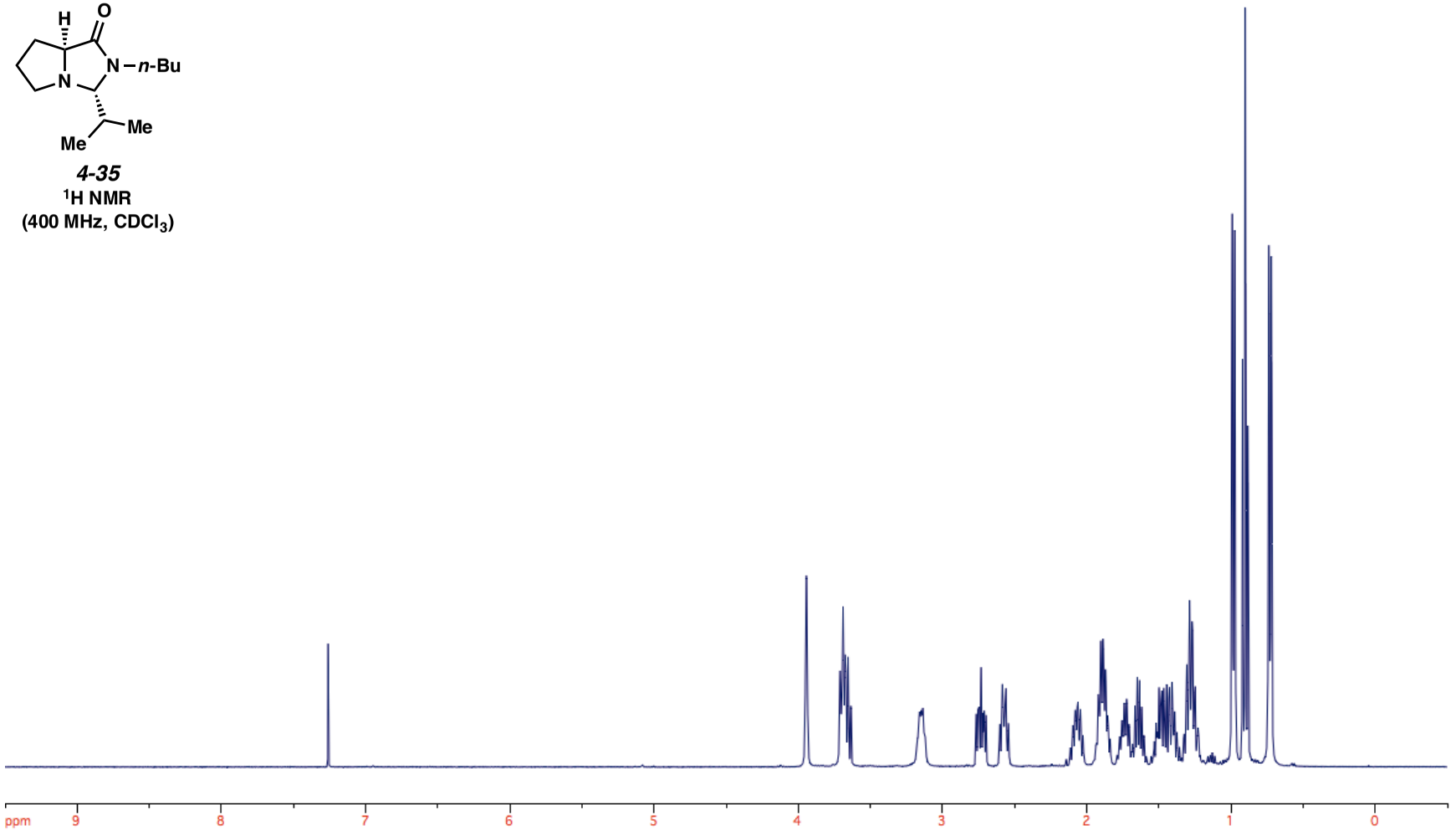
(100 MHz, $CDCl_3$)



4-35

^{1}H NMR

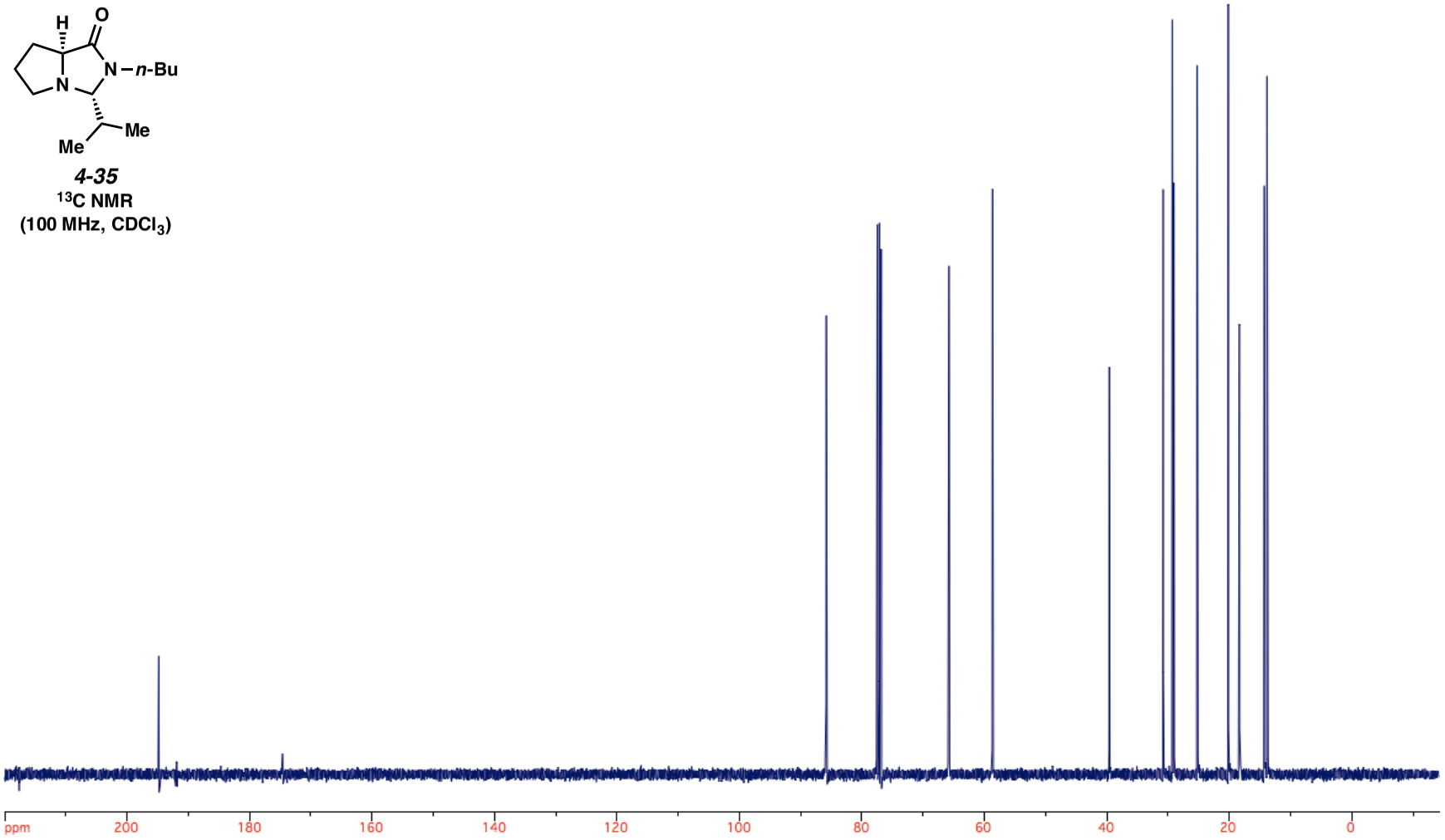
(400 MHz, $CDCl_3$)

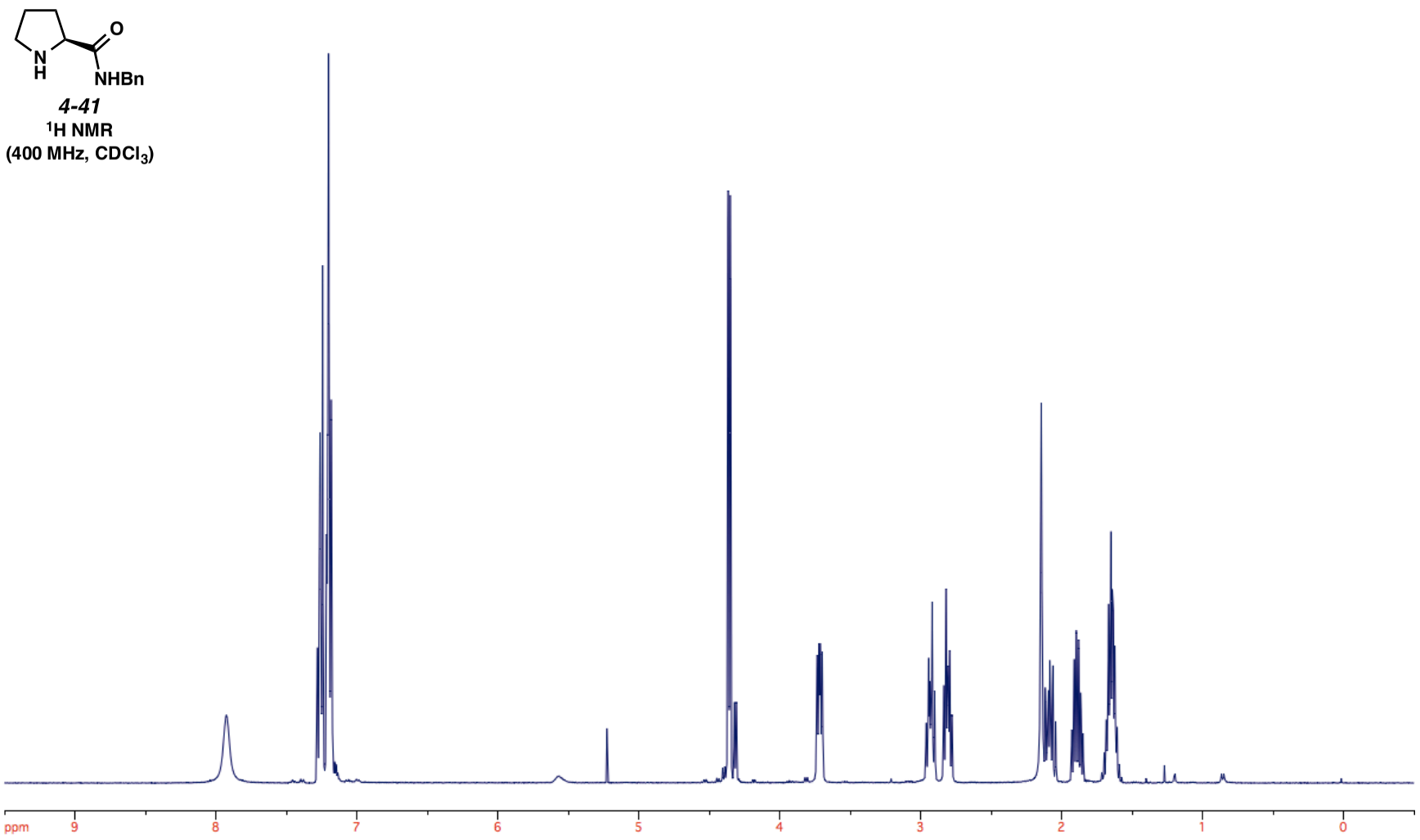


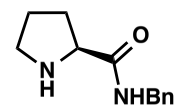
4-35

^{13}C NMR

(100 MHz, $CDCl_3$)



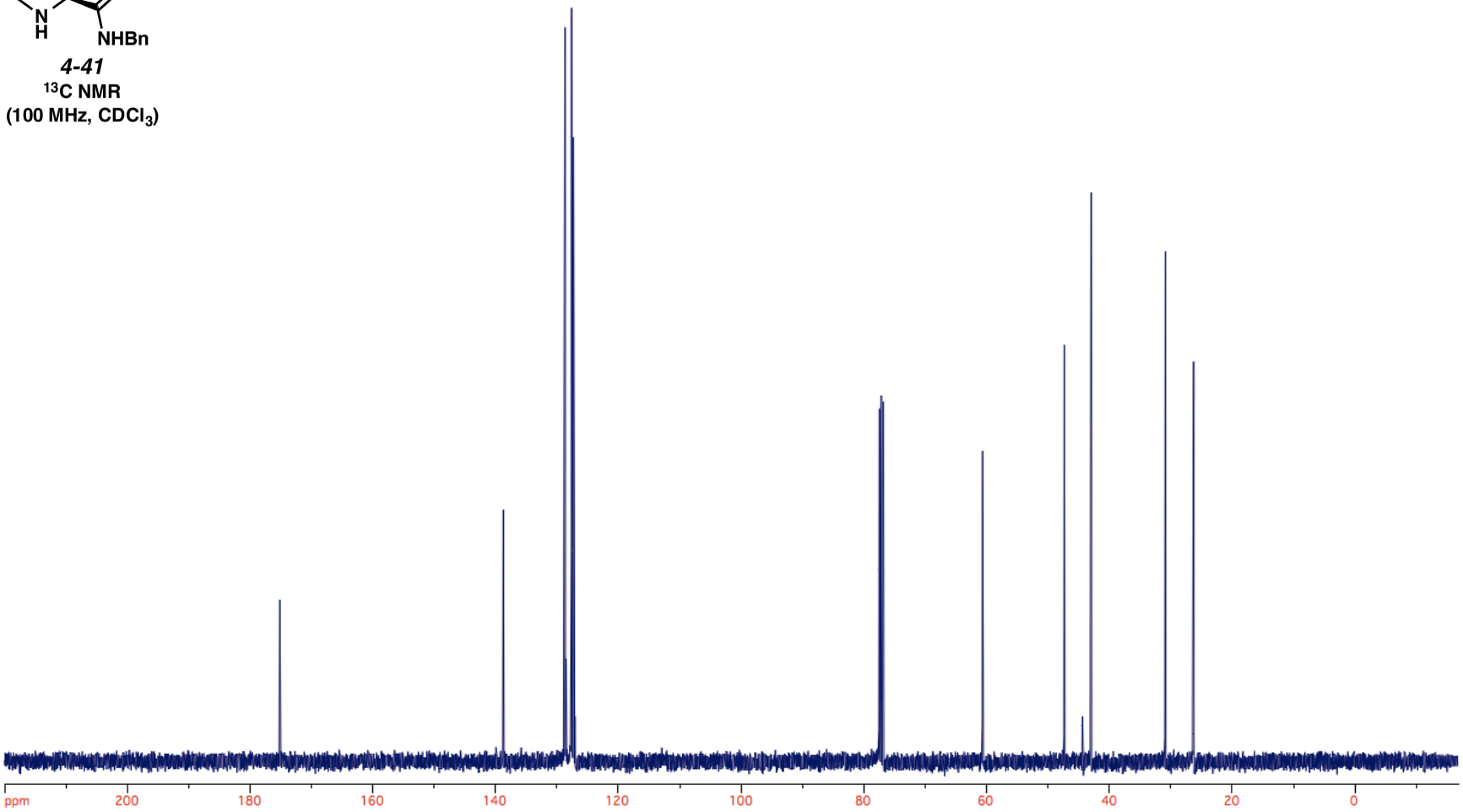

O
N
H
NHBn
4-41
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0

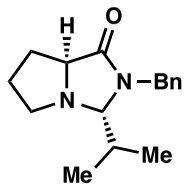


4-41

^{13}C NMR

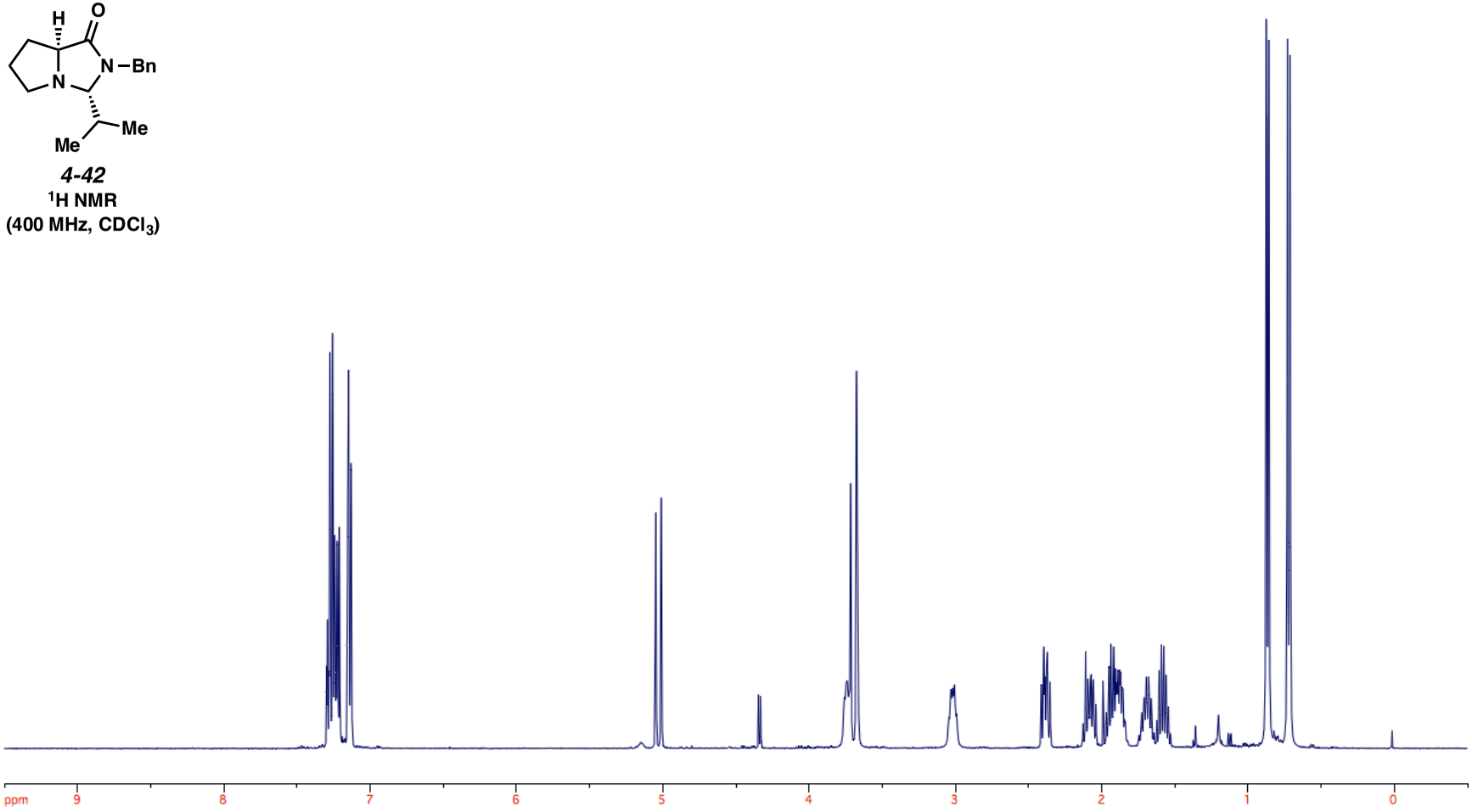
(100 MHz, $CDCl_3$)

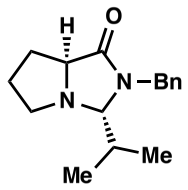




4-42

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

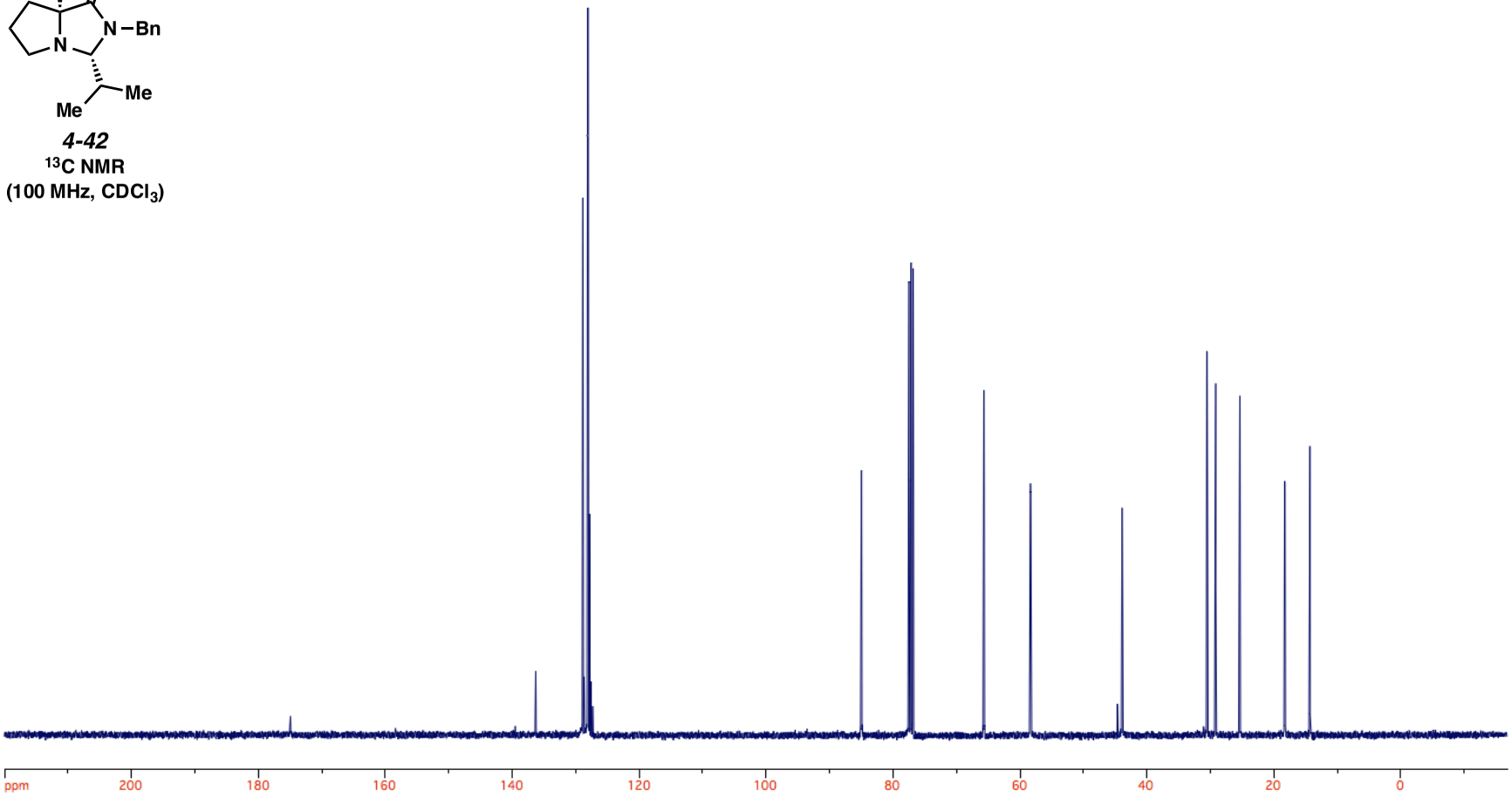


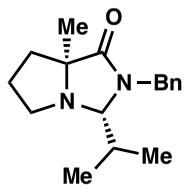


4-42

^{13}C NMR

(100 MHz, $CDCl_3$)

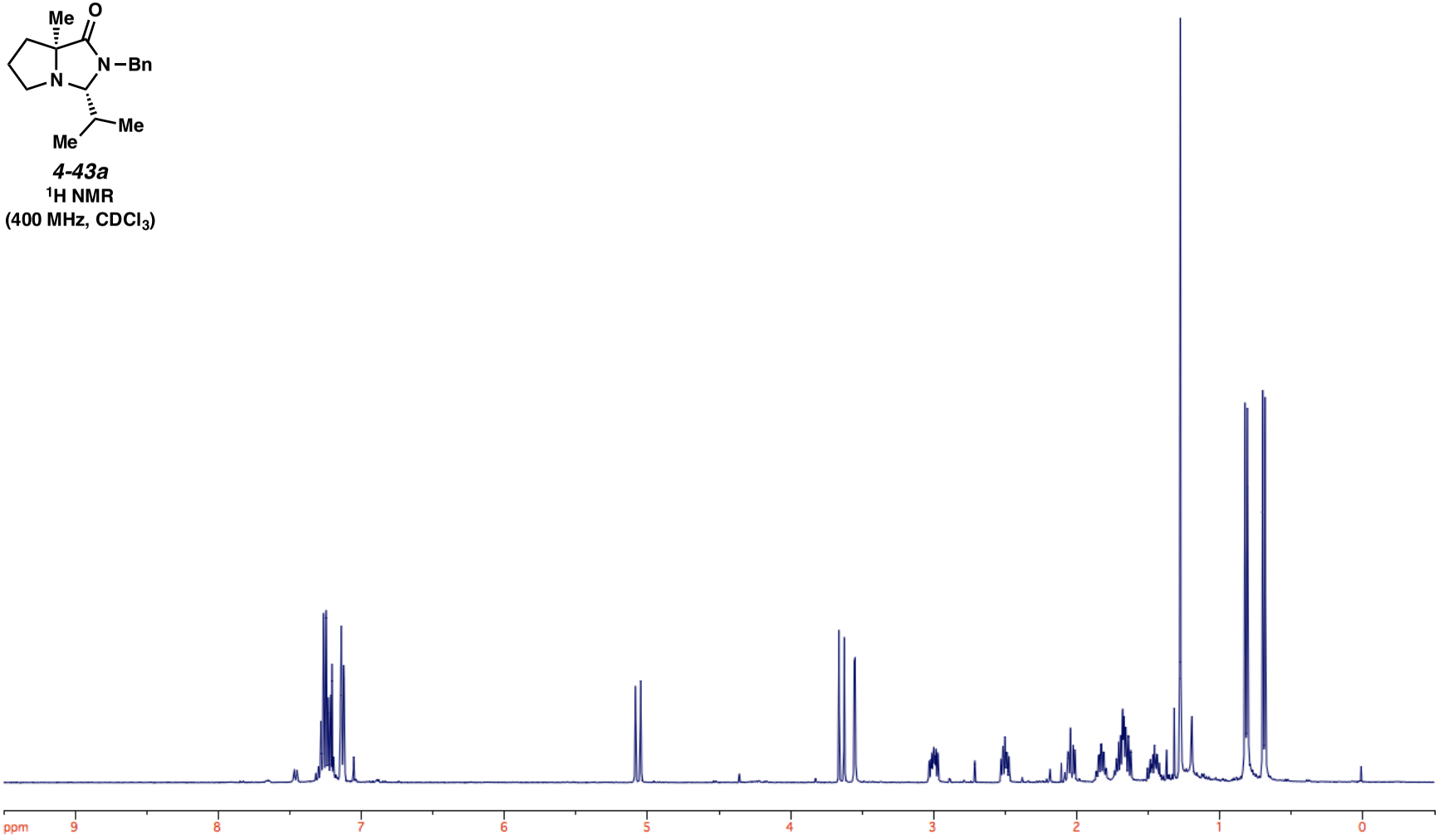


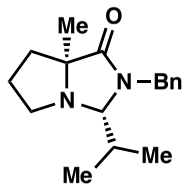


4-43a

^{1}H NMR

(400 MHz, $CDCl_3$)

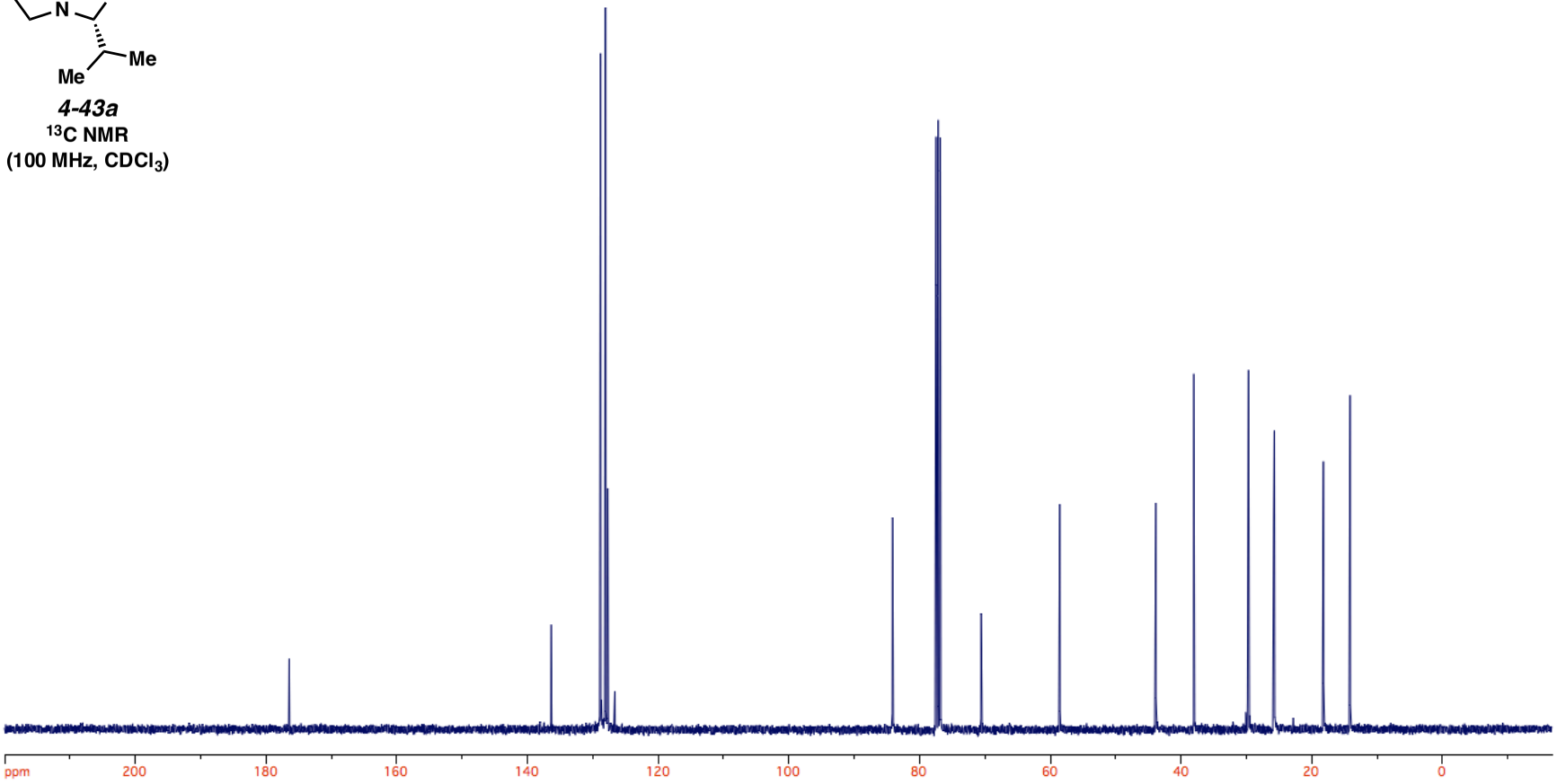


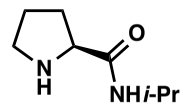


4-43a

^{13}C NMR

(100 MHz, $CDCl_3$)

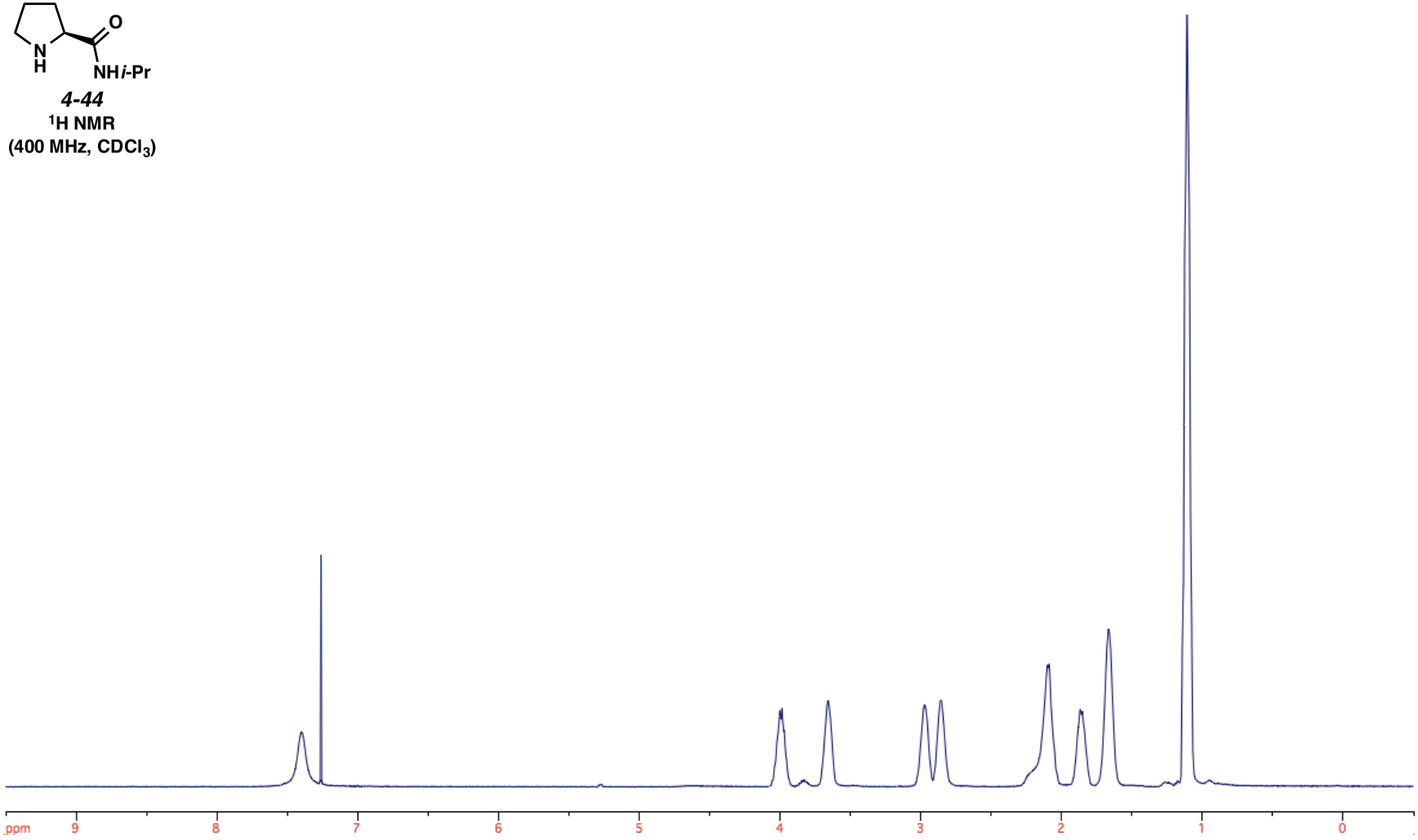


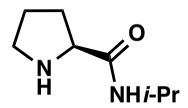


4-44

^{1}H NMR

(400 MHz, $CDCl_3$)

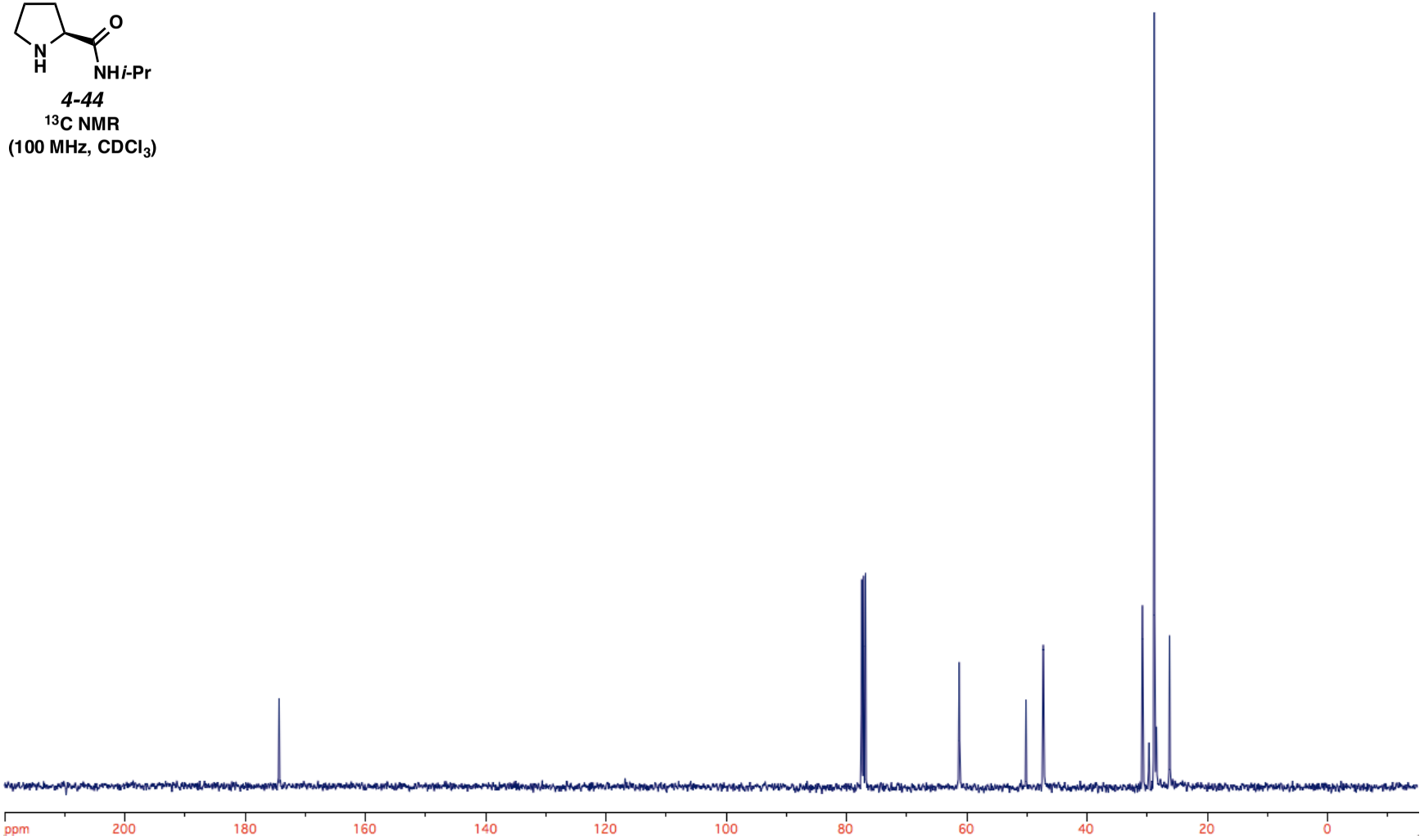


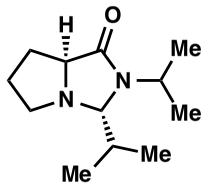


4-44

^{13}C NMR

(100 MHz, $CDCl_3$)

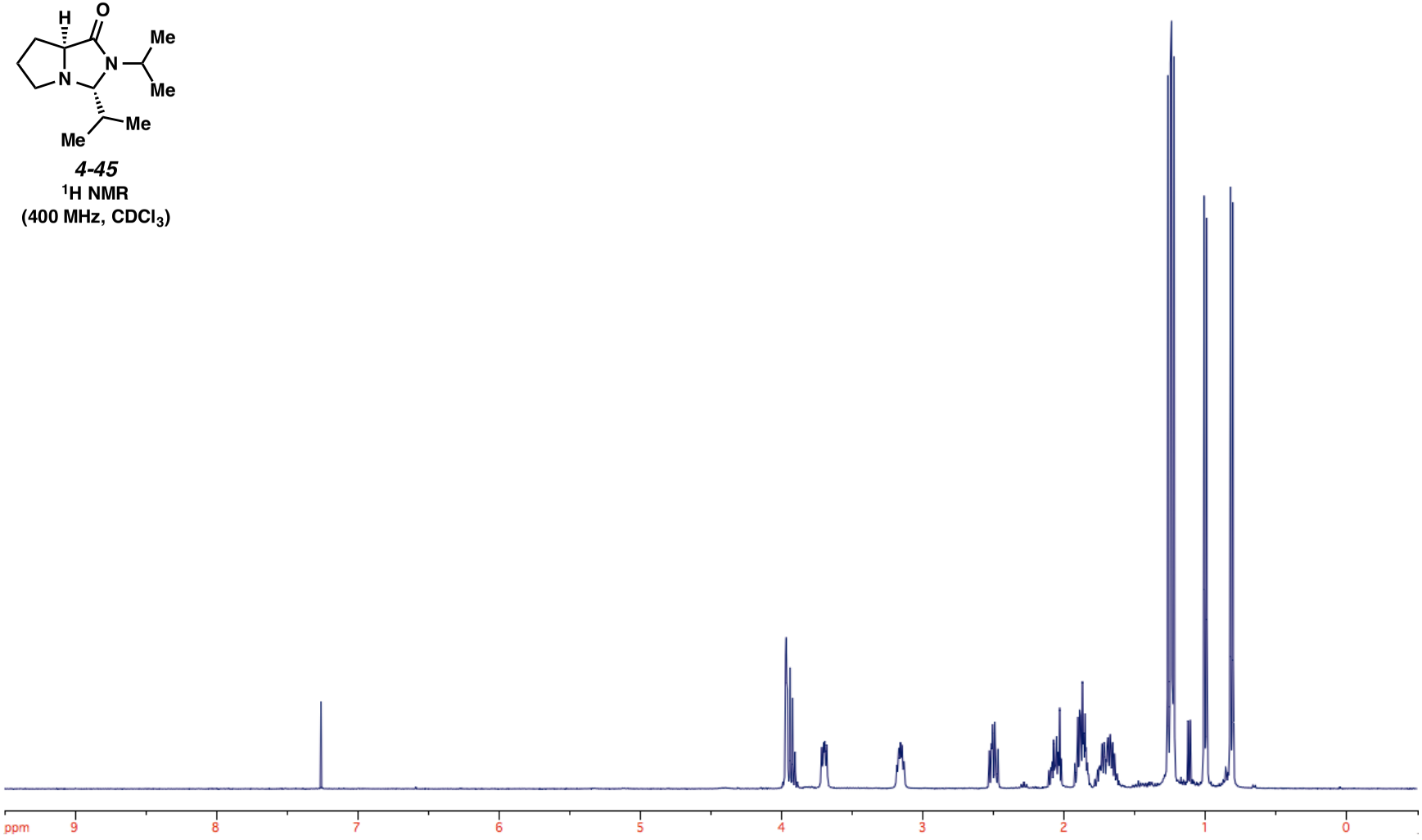


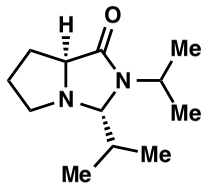


4-45

^{1}H NMR

(400 MHz, $CDCl_3$)

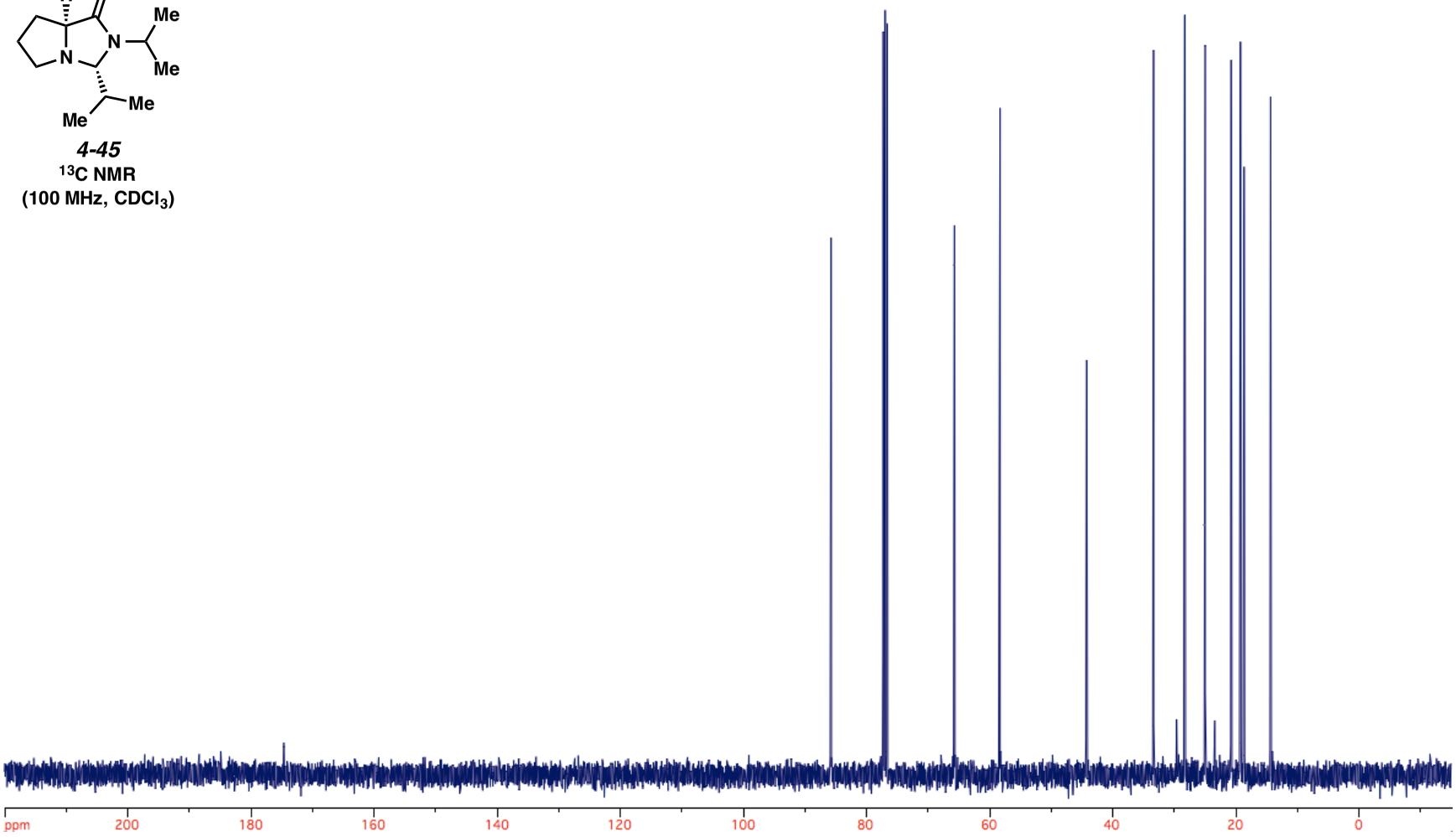


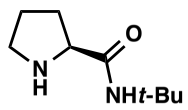


4-45

^{13}C NMR

(100 MHz, $CDCl_3$)

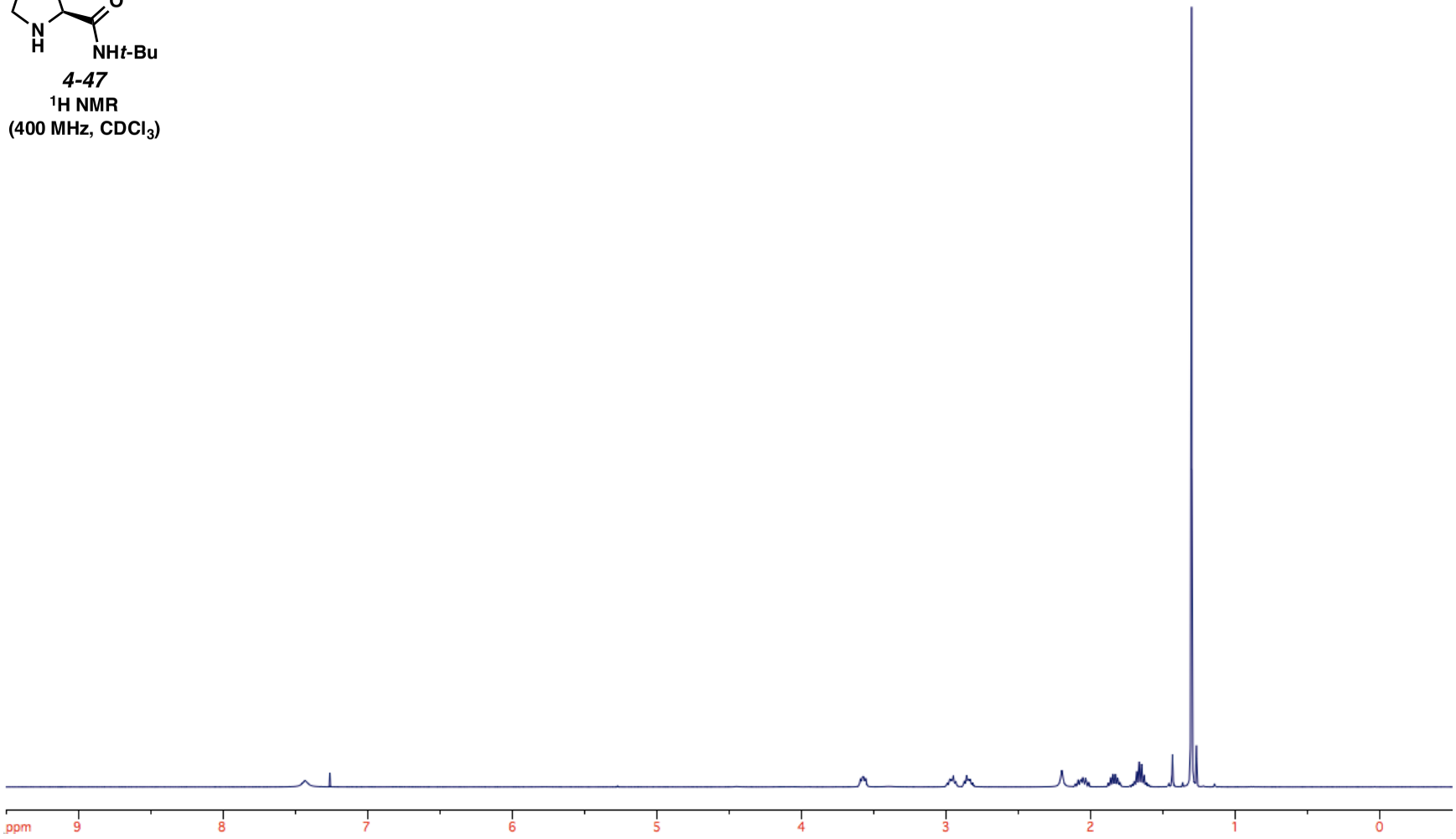


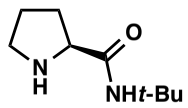


4-47

^{1}H NMR

(400 MHz, $CDCl_3$)

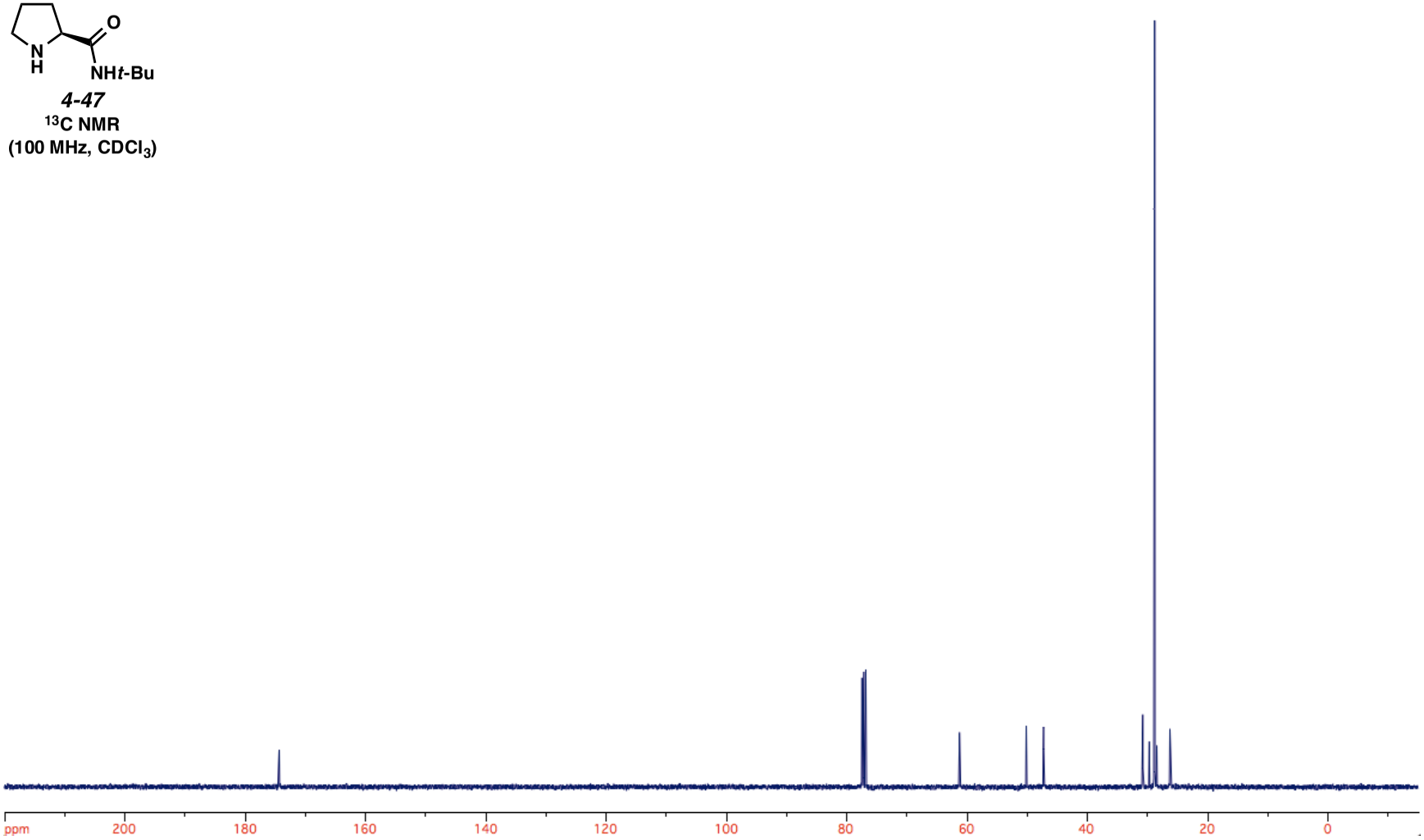




4-47

^{13}C NMR

(100 MHz, $CDCl_3$)

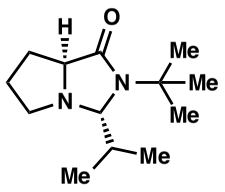


4-48

^{1}H NMR

(400 MHz, $CDCl_3$)

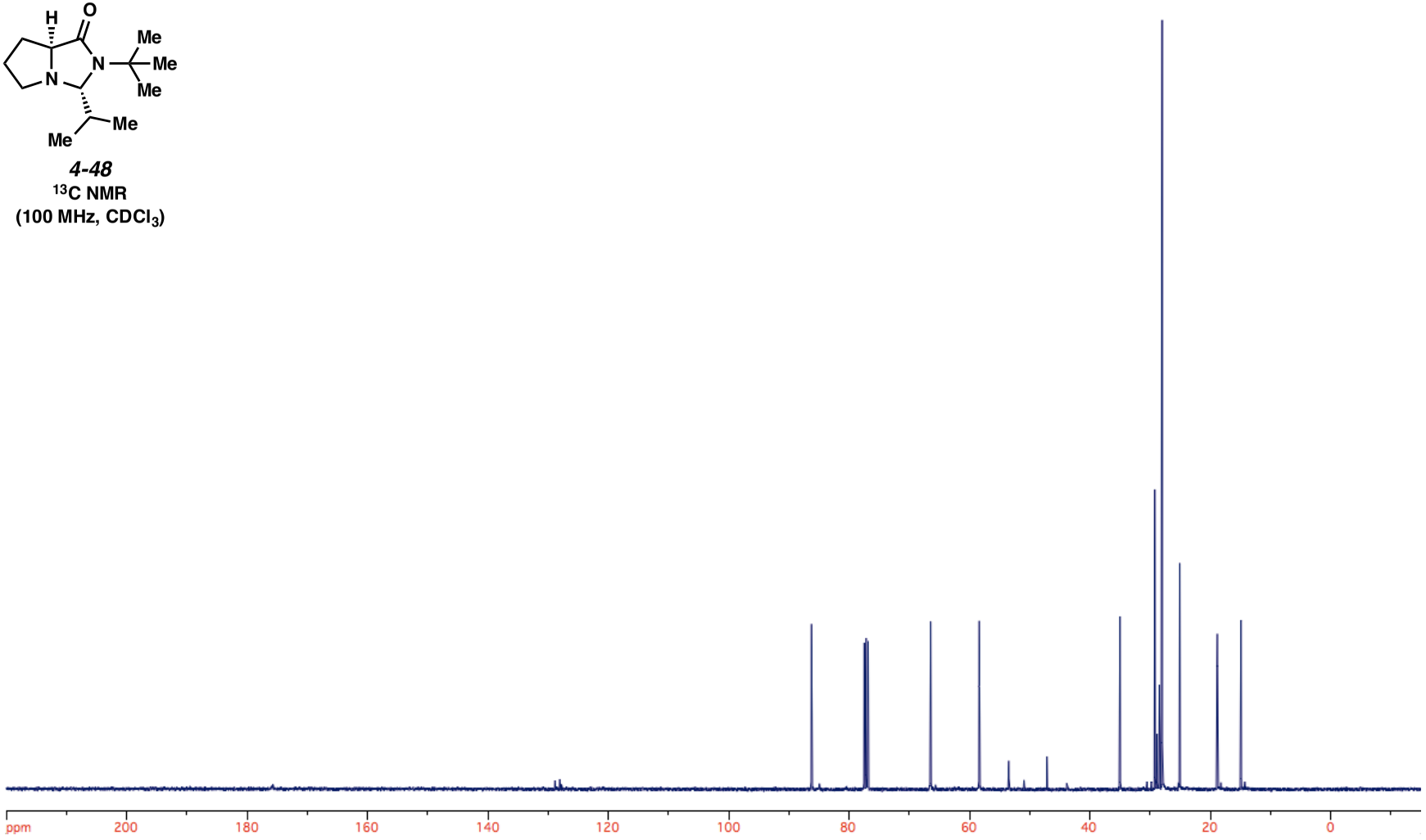


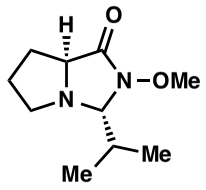


4-48

^{13}C NMR

(100 MHz, $CDCl_3$)

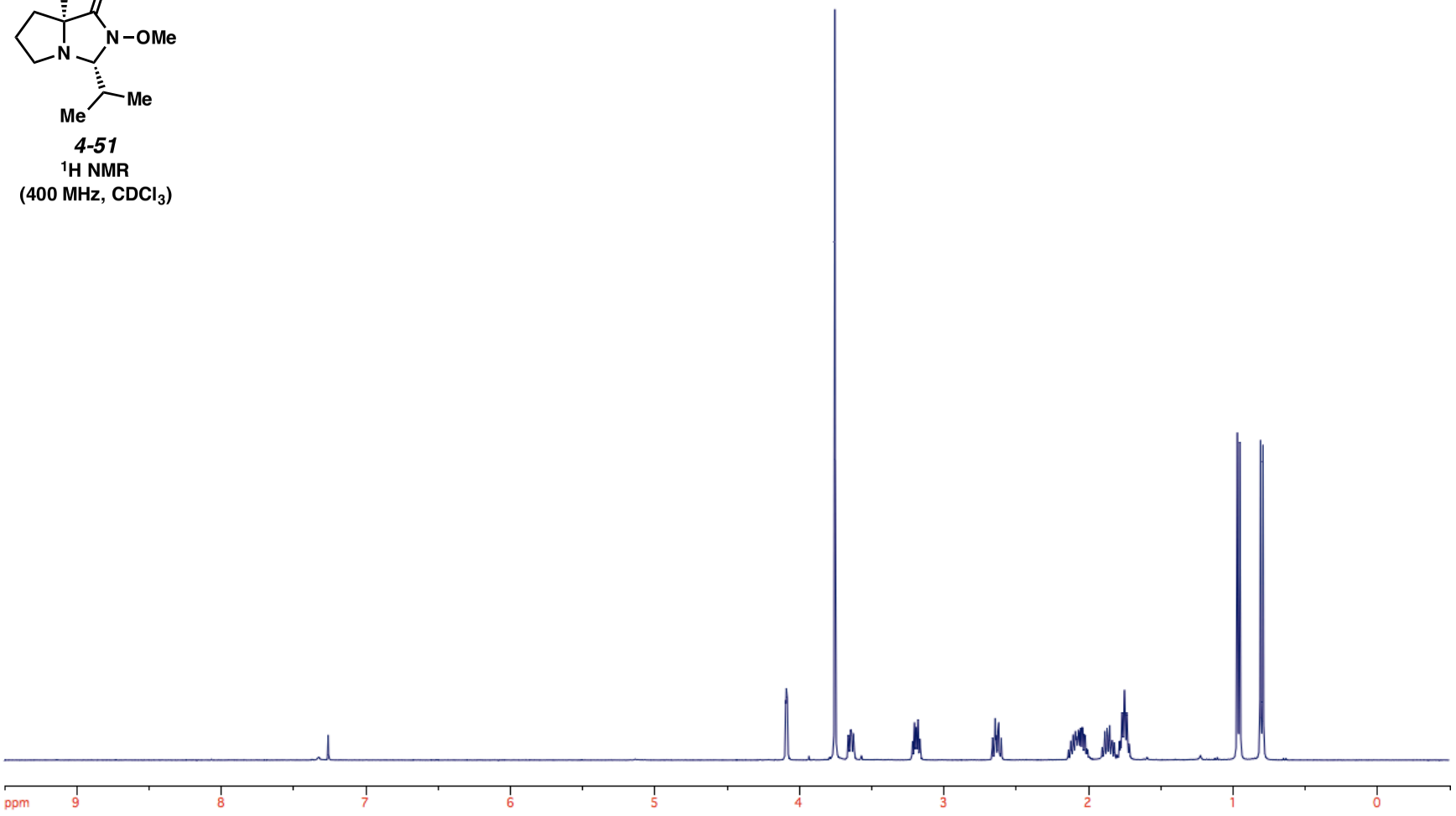


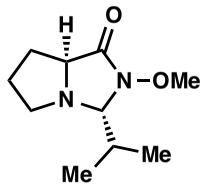


4-51

^{1}H NMR

(400 MHz, $CDCl_3$)

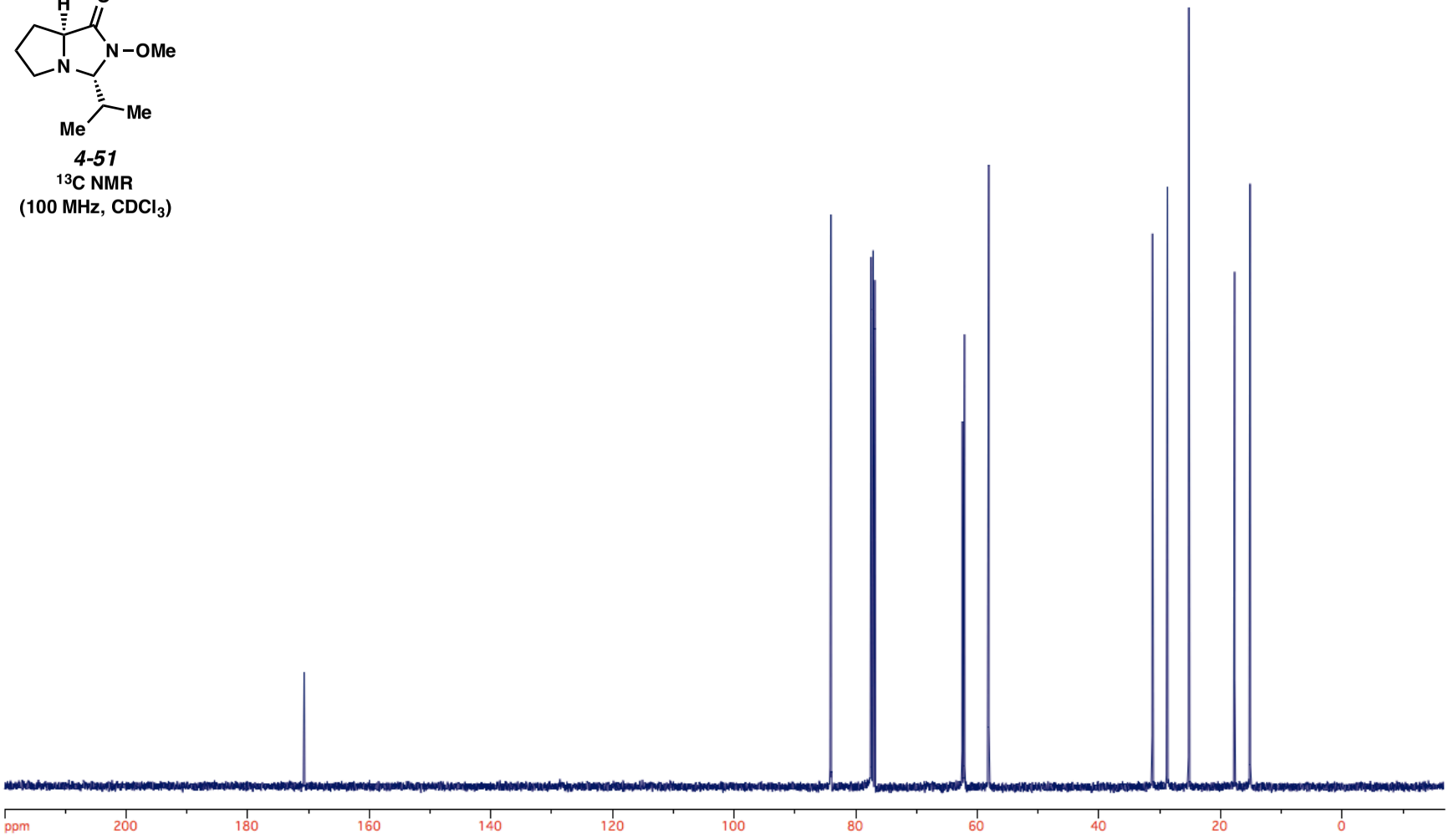


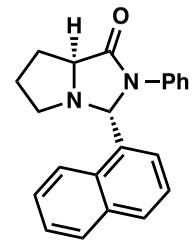


4-51

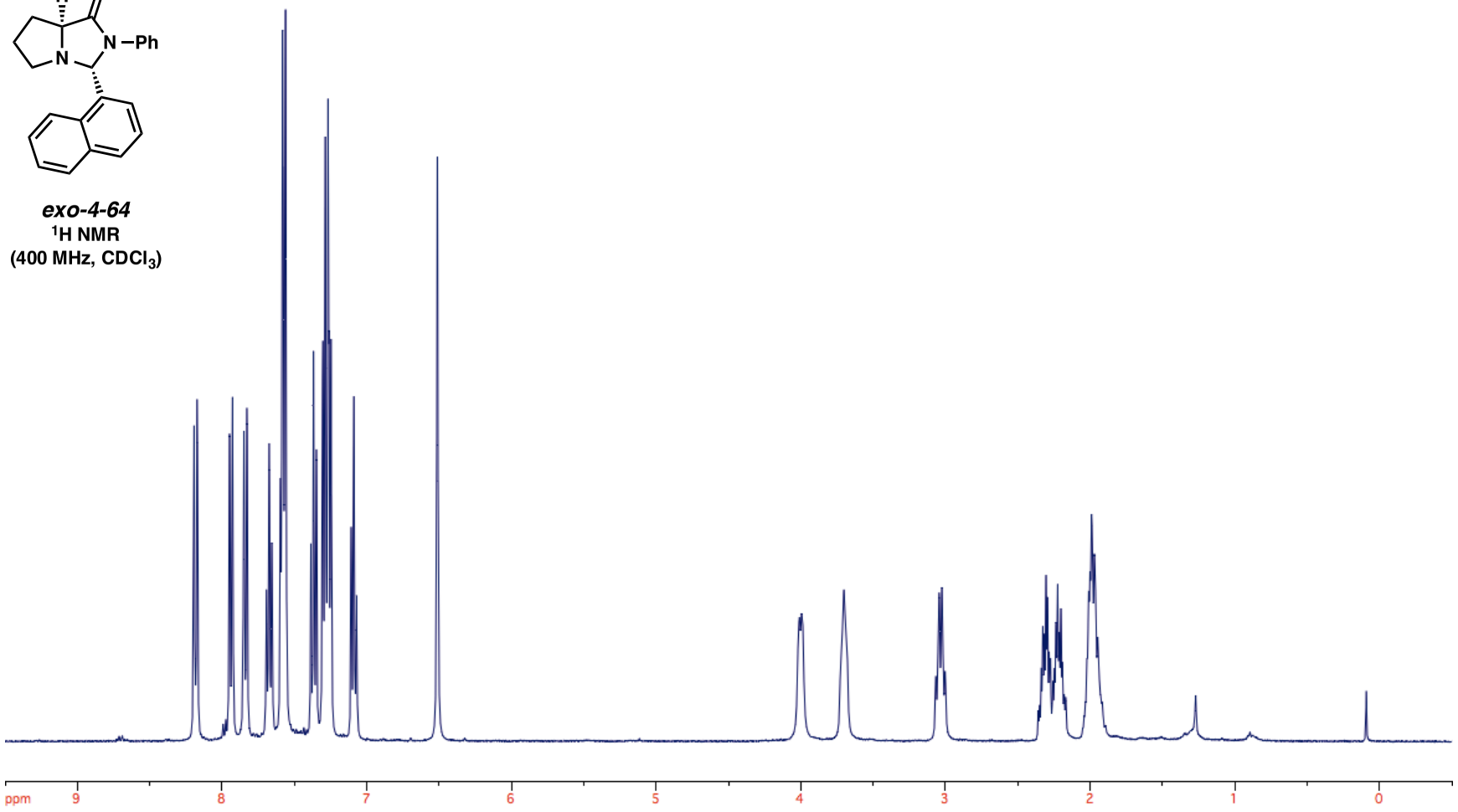
^{13}C NMR

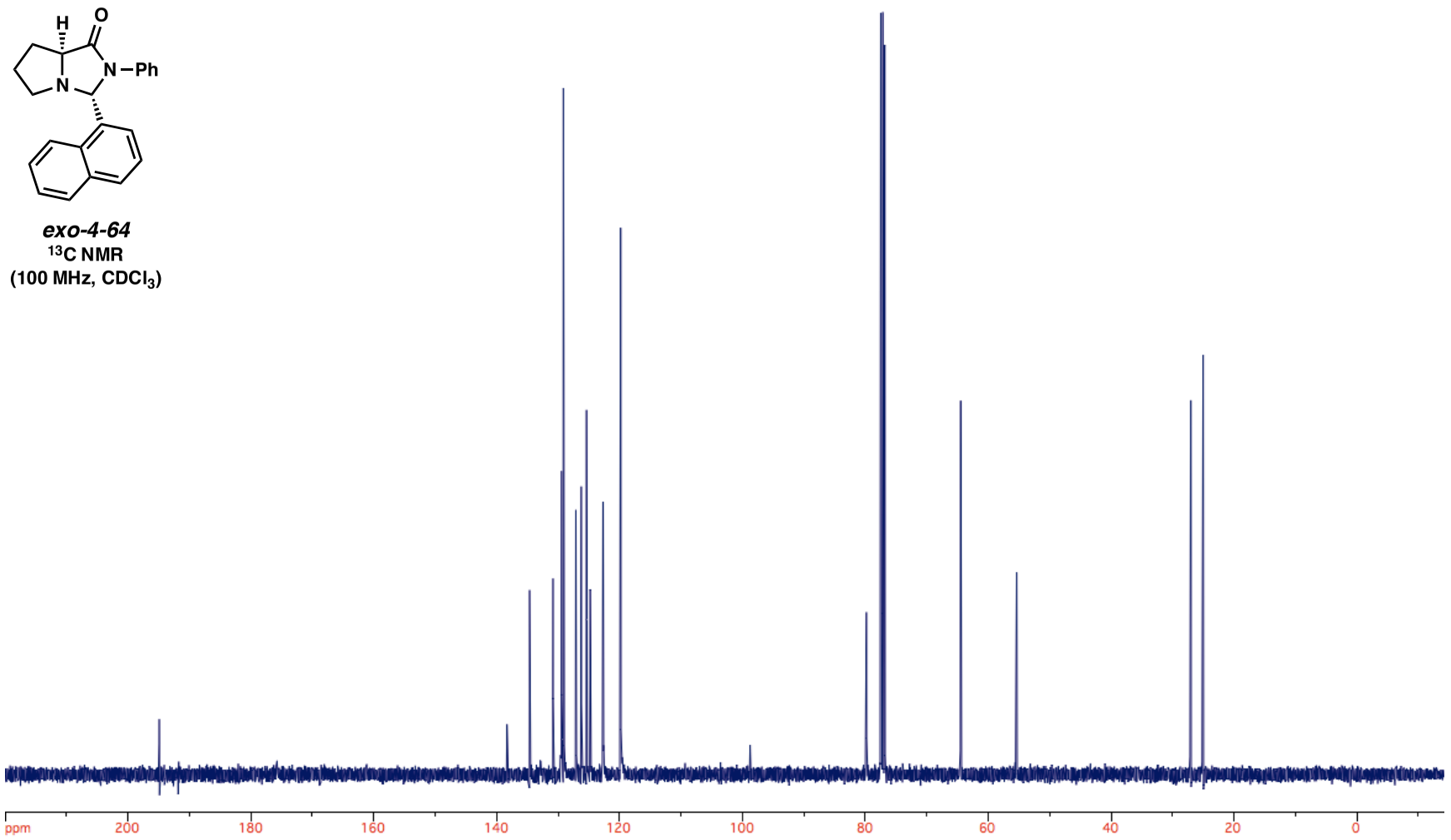
(100 MHz, $CDCl_3$)





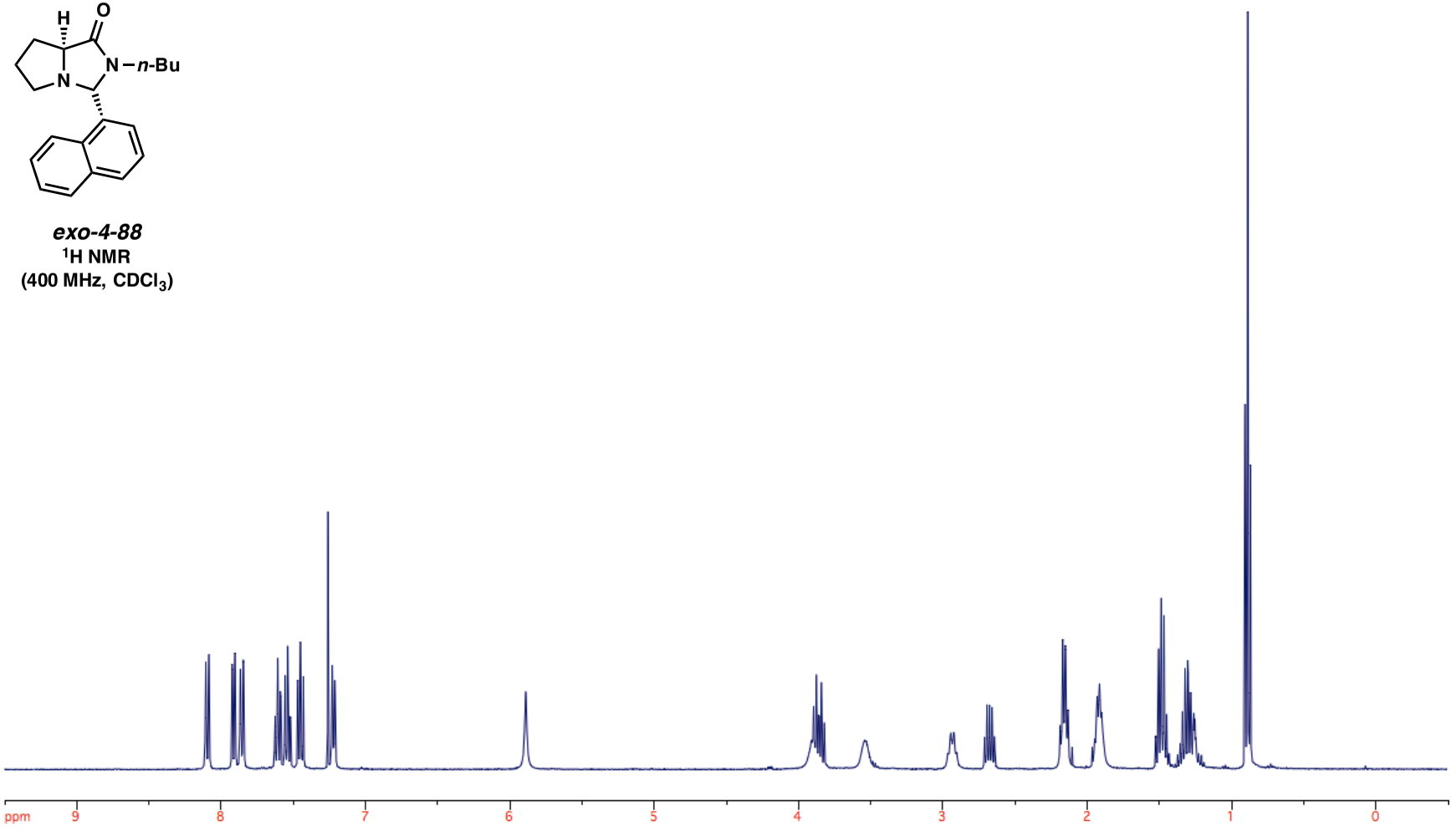
exo-4-64
^{1}H NMR
(400 MHz, $CDCl_3$)



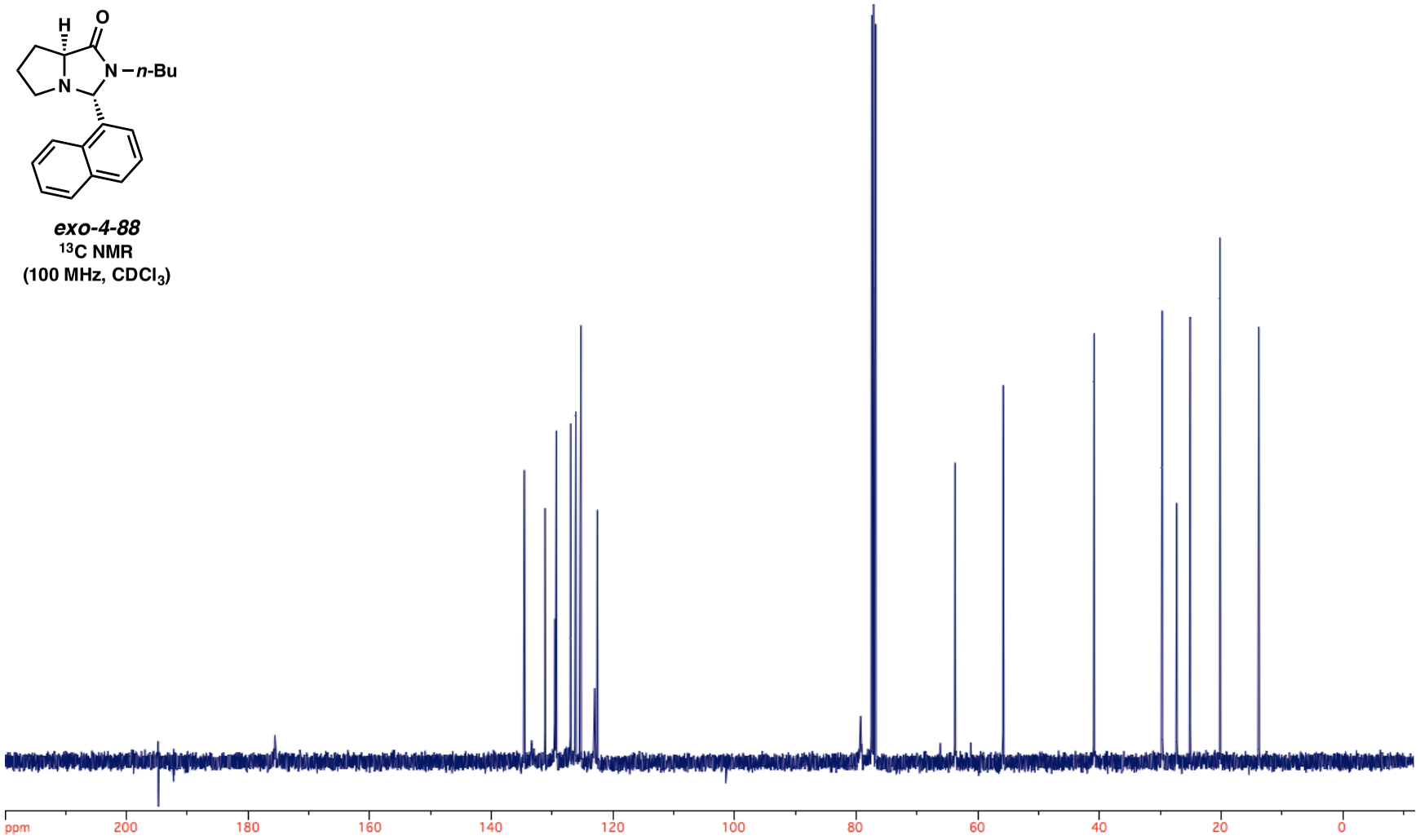


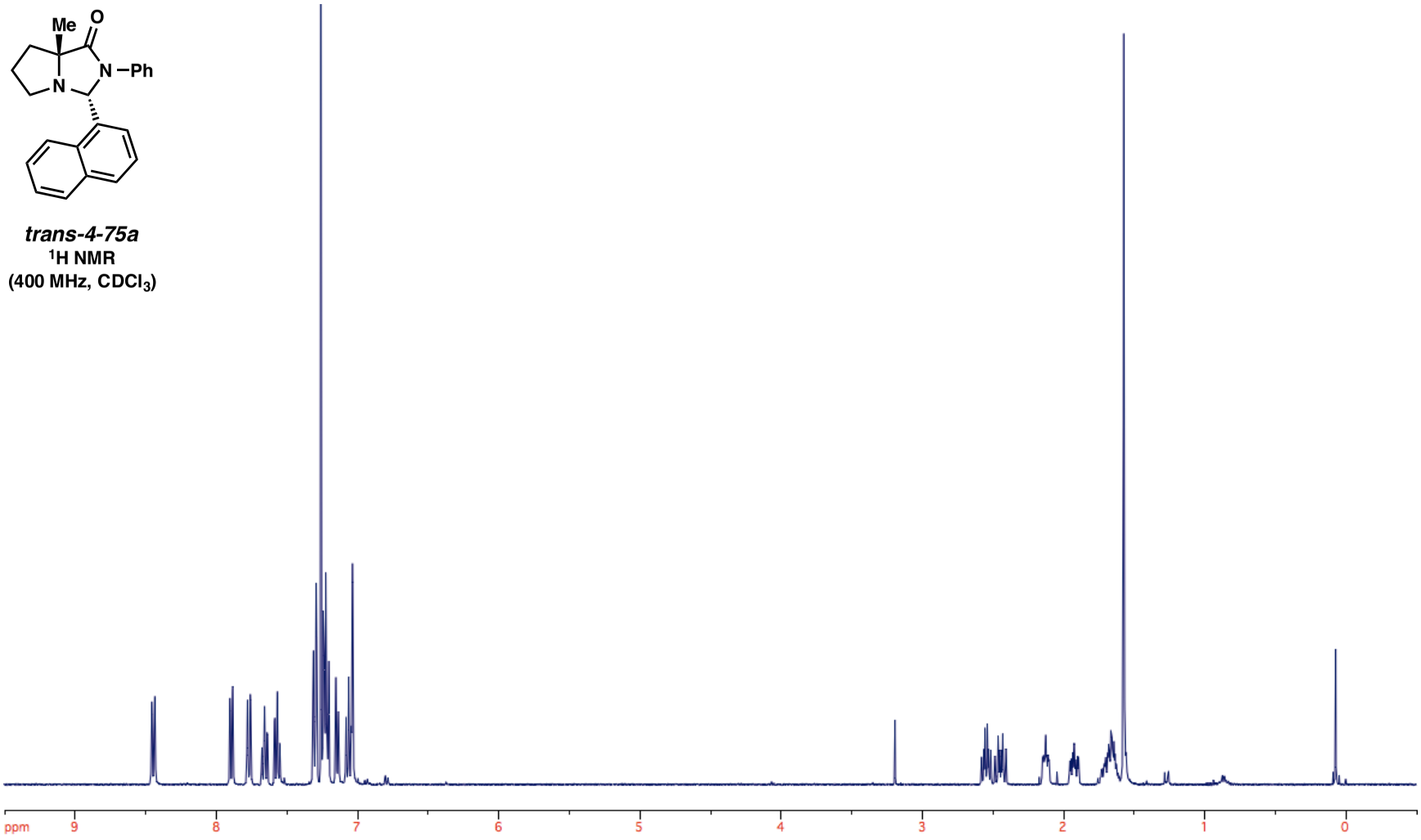
exo-4-64
^{13}C NMR
(100 MHz, $CDCl_3$)

exo-4-88
^{1}H NMR
(400 MHz, $CDCl_3$)



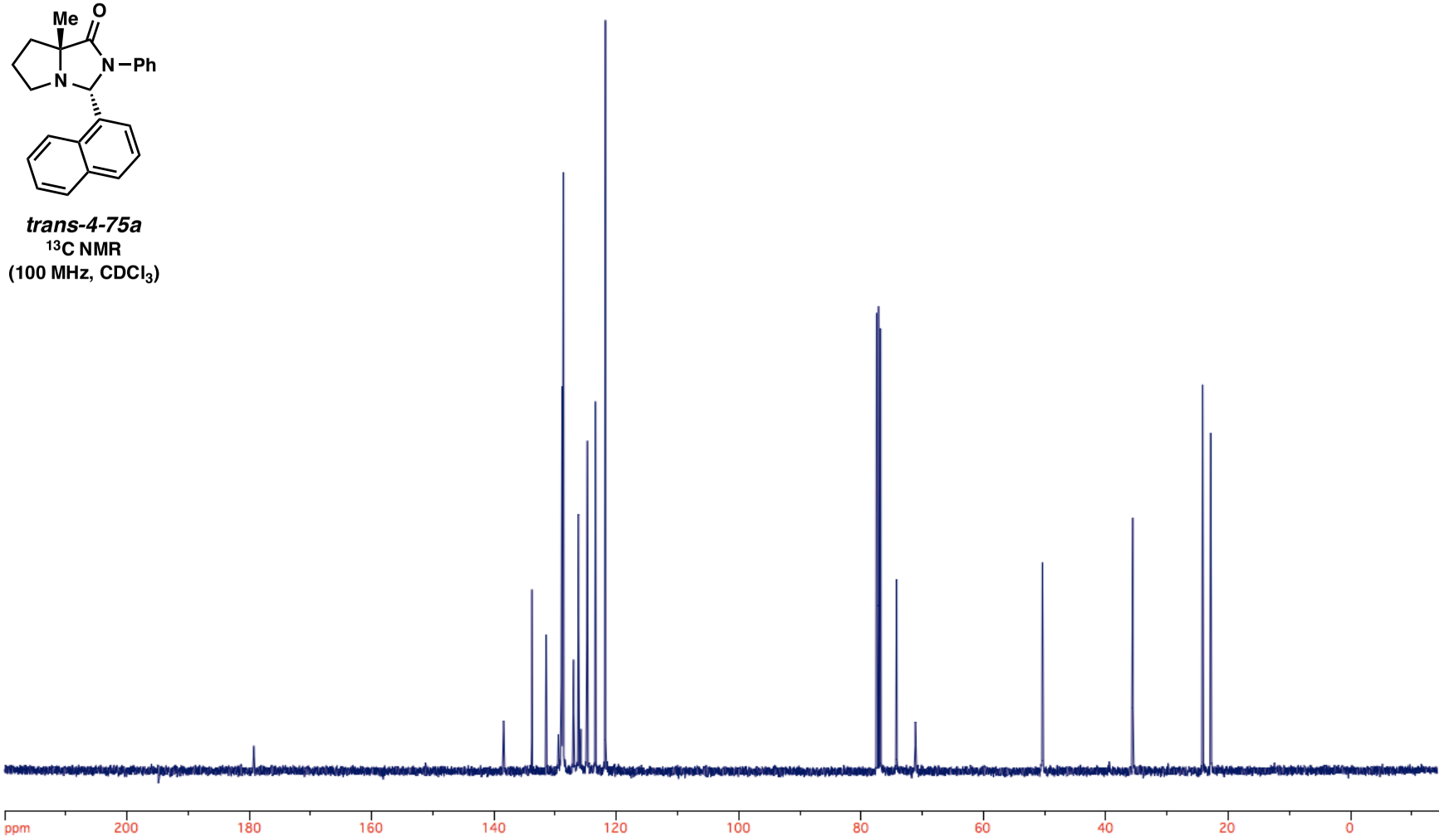
exo-4-88
^{13}C NMR
(100 MHz, $CDCl_3$)



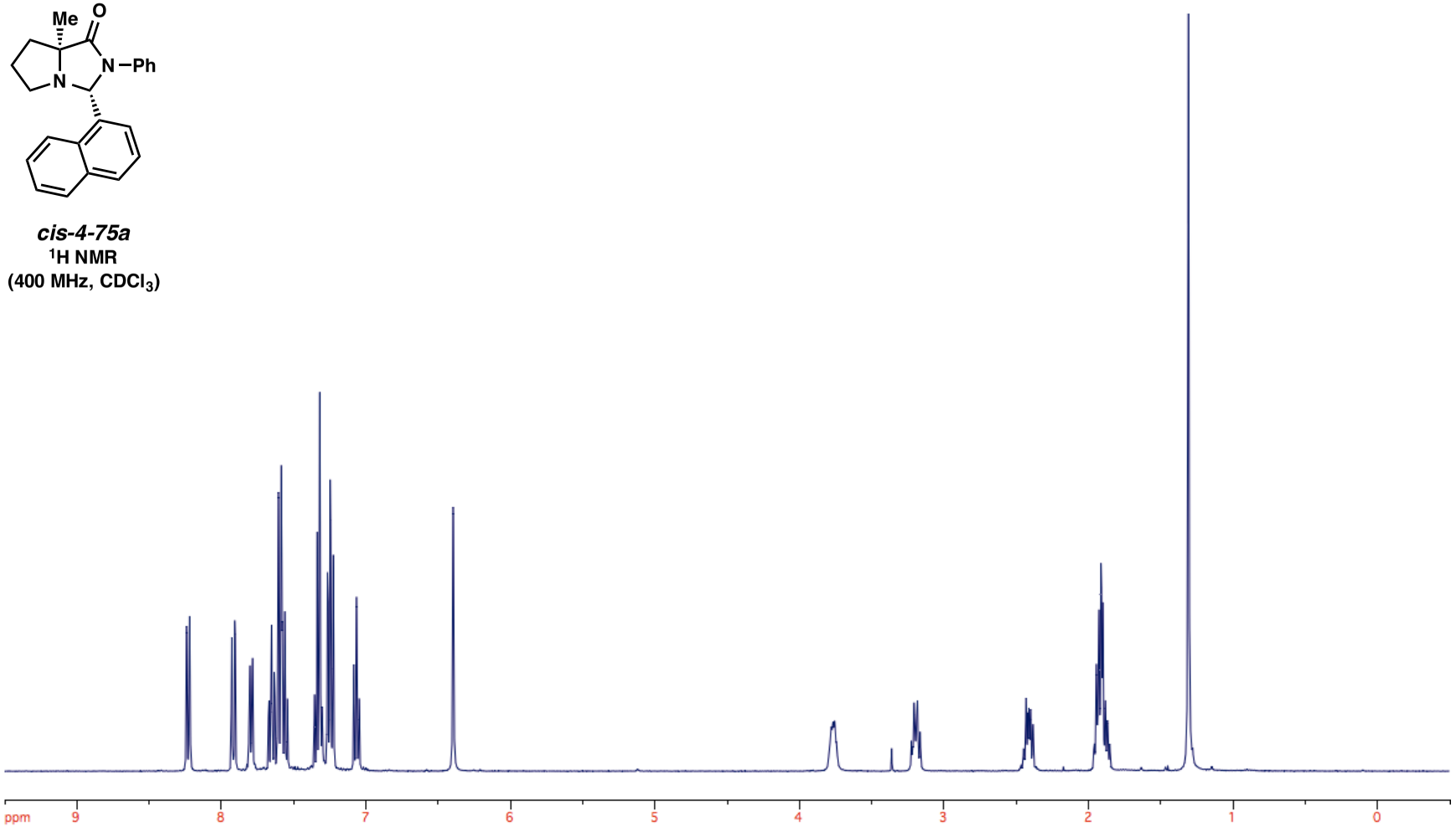


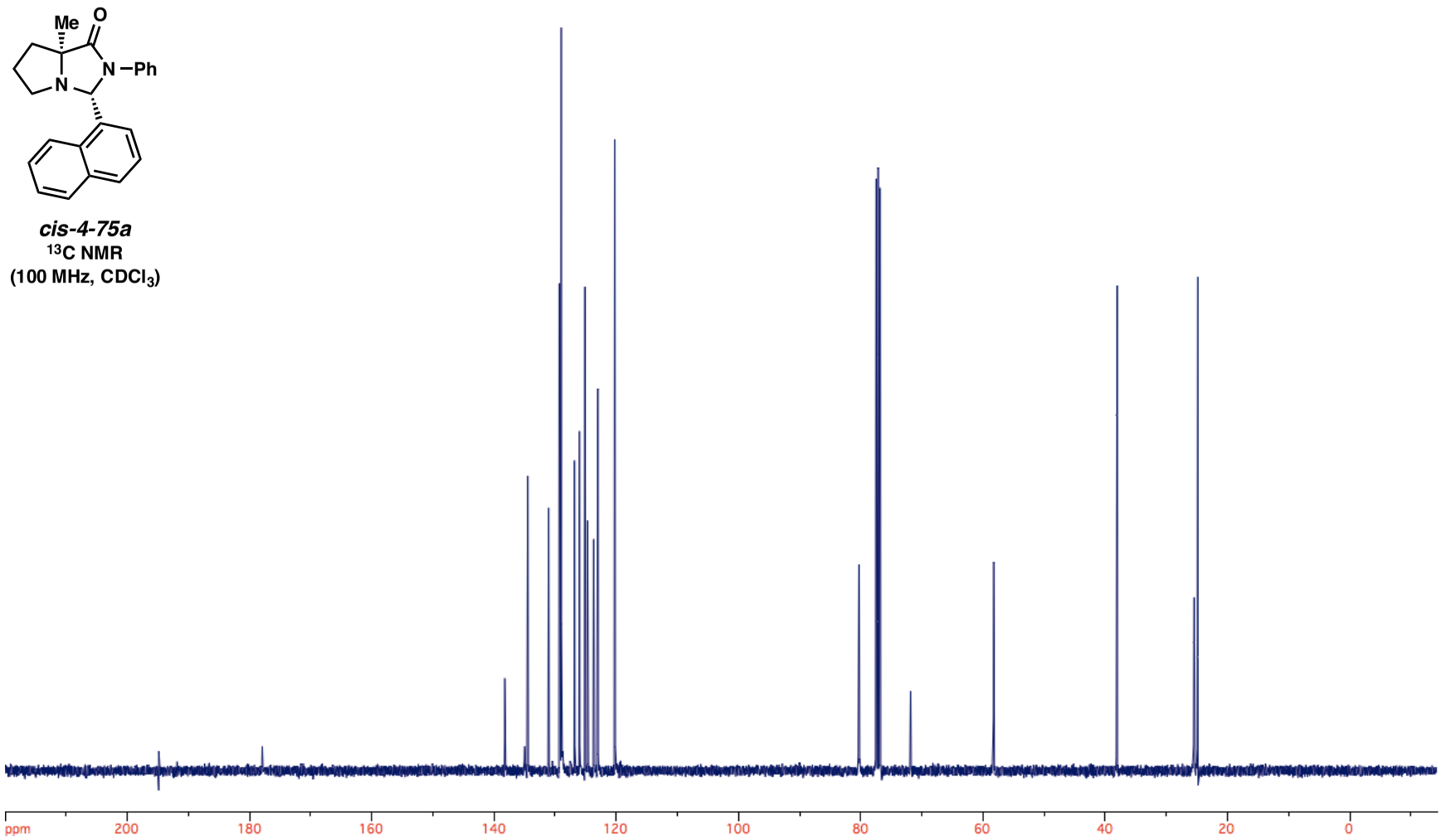
trans-4-75a
^{1}H NMR
(400 MHz, $CDCl_3$)

trans-4-75a
^{13}C NMR
(100 MHz, $CDCl_3$)



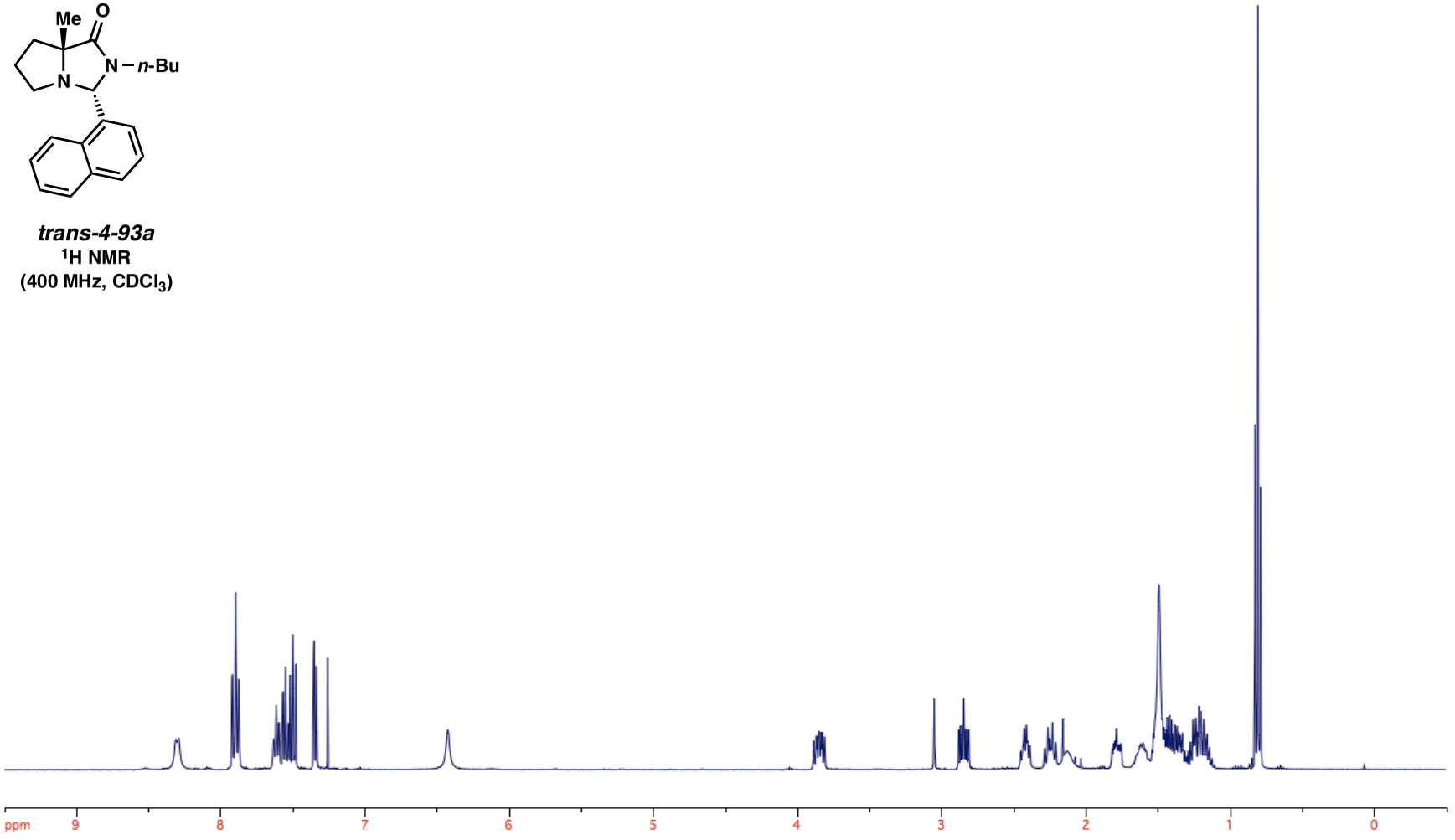
cis-4-75a
^{1}H NMR
(400 MHz, $CDCl_3$)

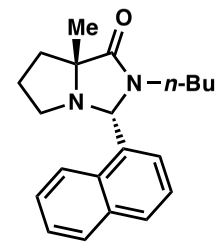




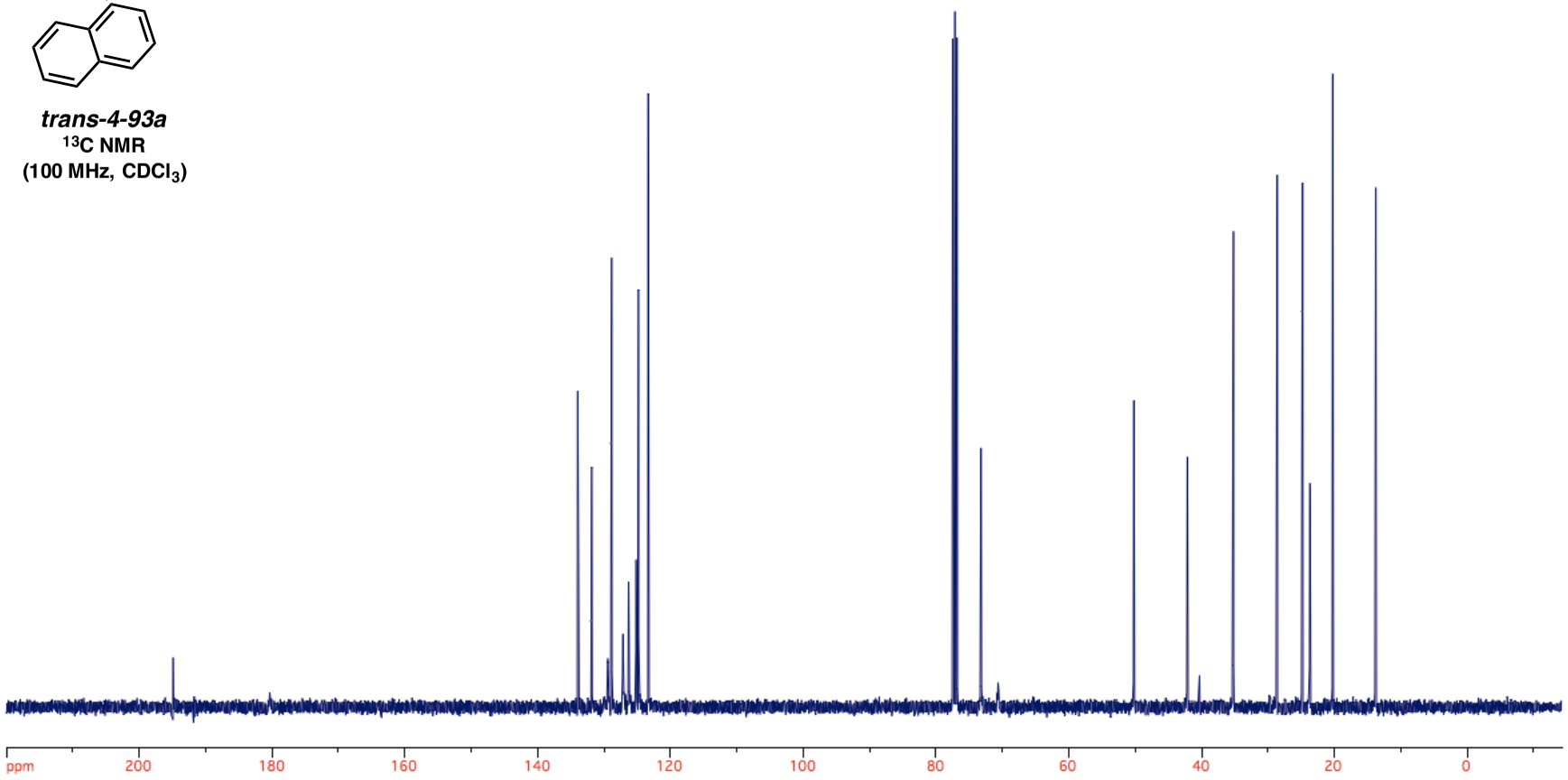
cis-4-75a
^{13}C NMR
(100 MHz, $CDCl_3$)

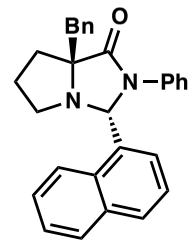
trans-4-93a
^{1}H NMR
(400 MHz, $CDCl_3$)



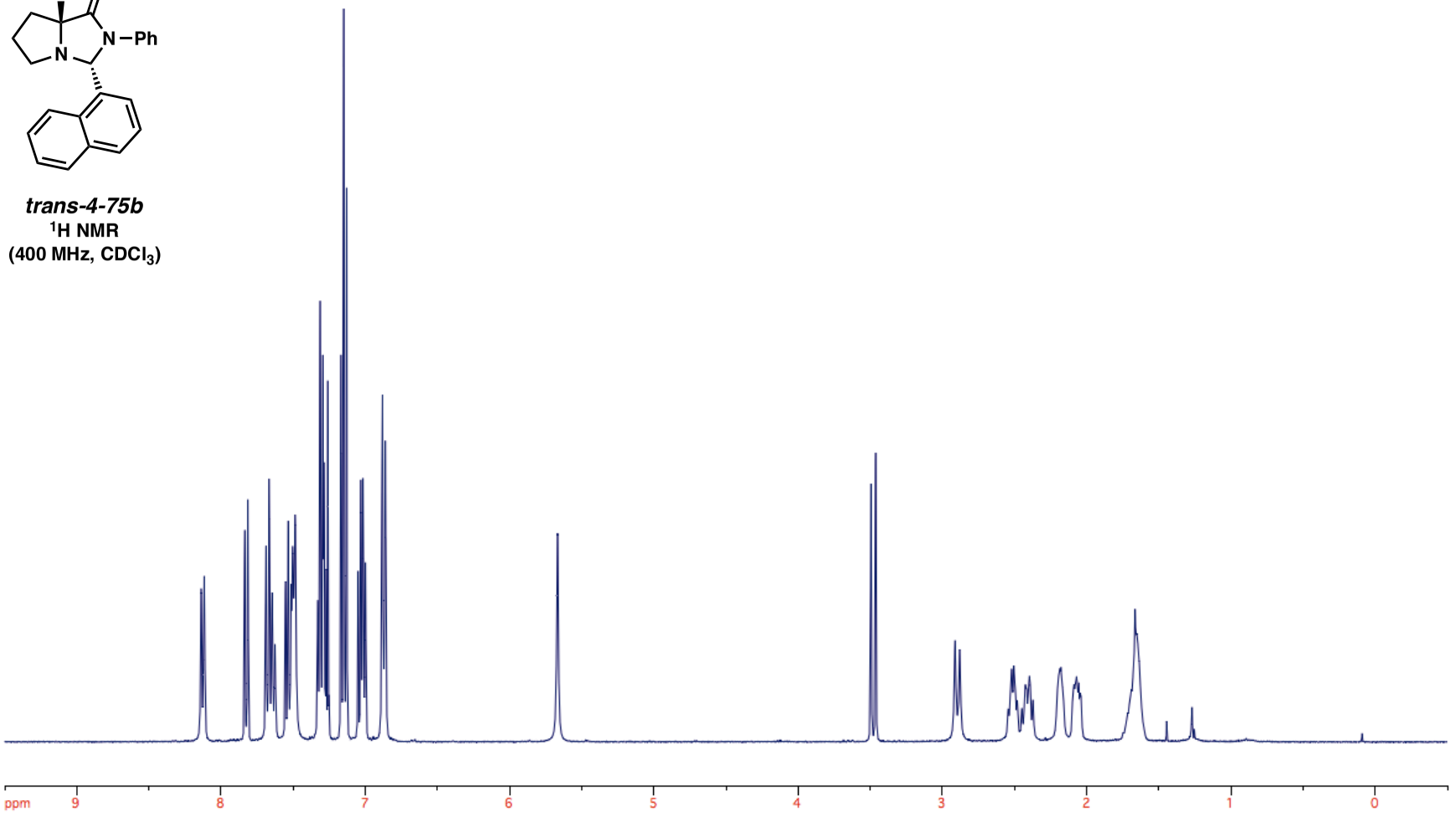


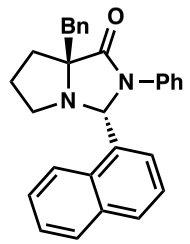
trans-4-93a
^{13}C NMR
(100 MHz, $CDCl_3$)



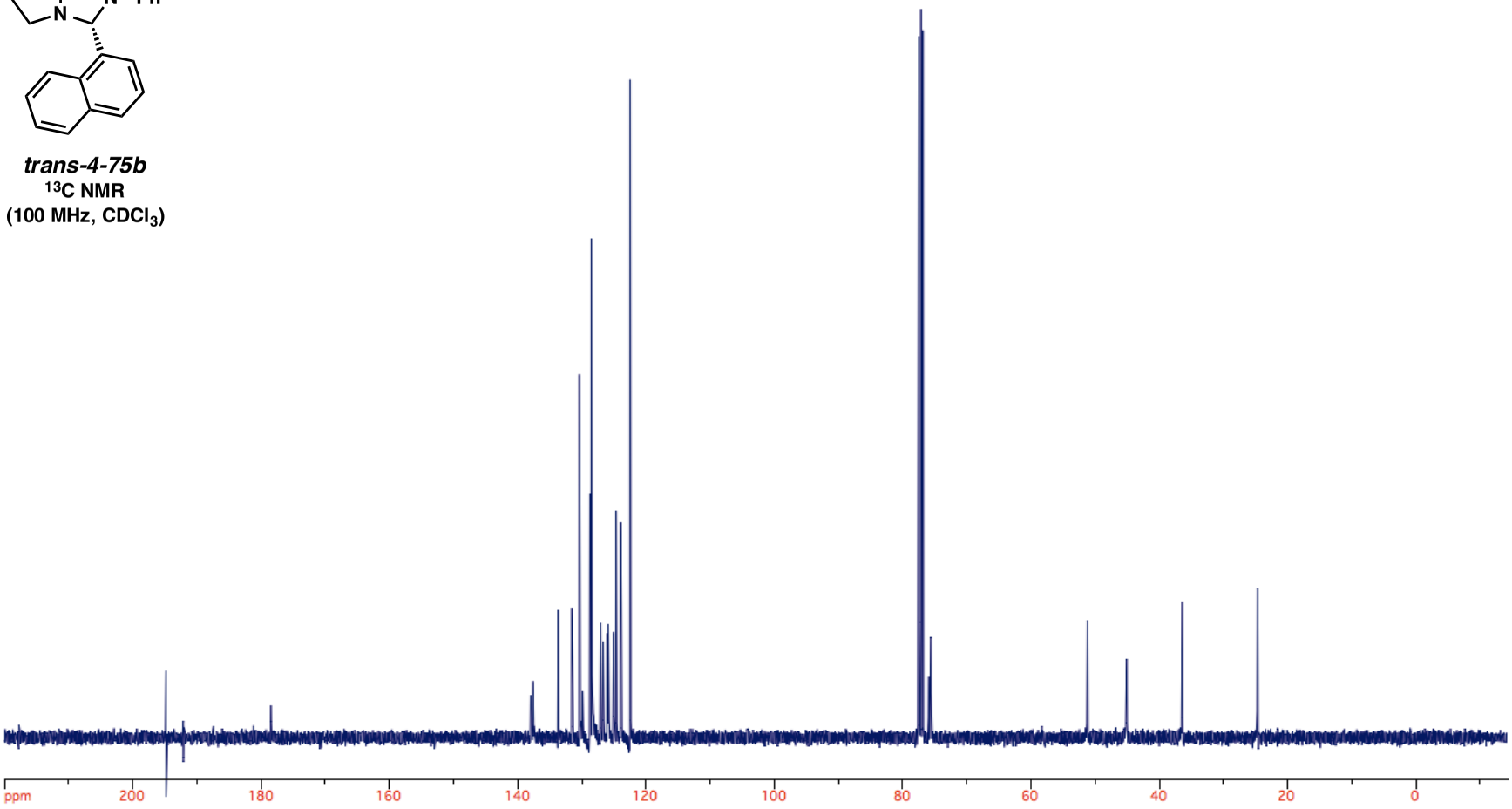


trans-4-75b
^{1}H NMR
(400 MHz, $CDCl_3$)

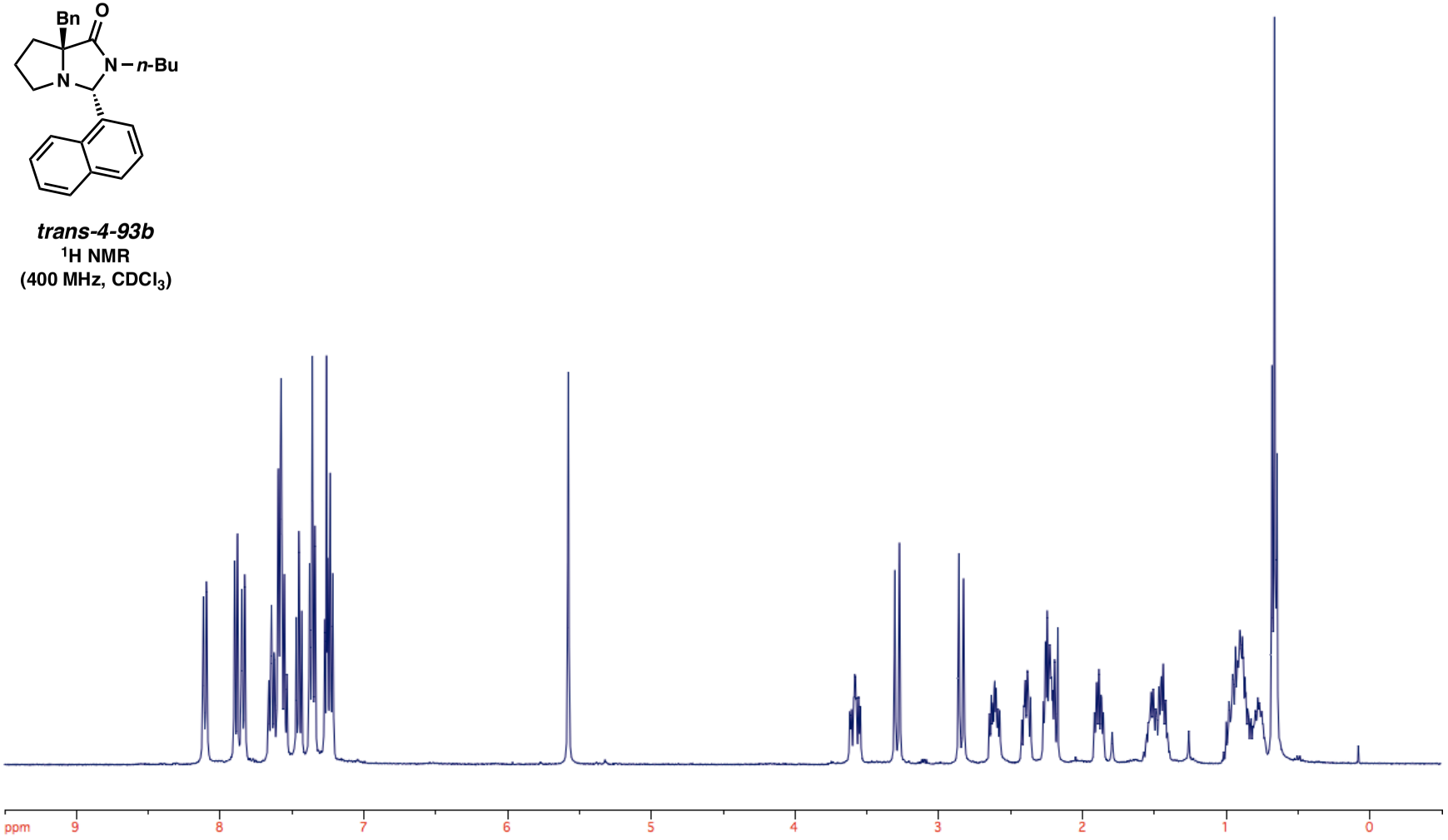


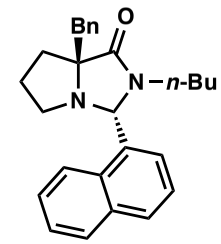


trans-4-75b
^{13}C NMR
(100 MHz, $CDCl_3$)

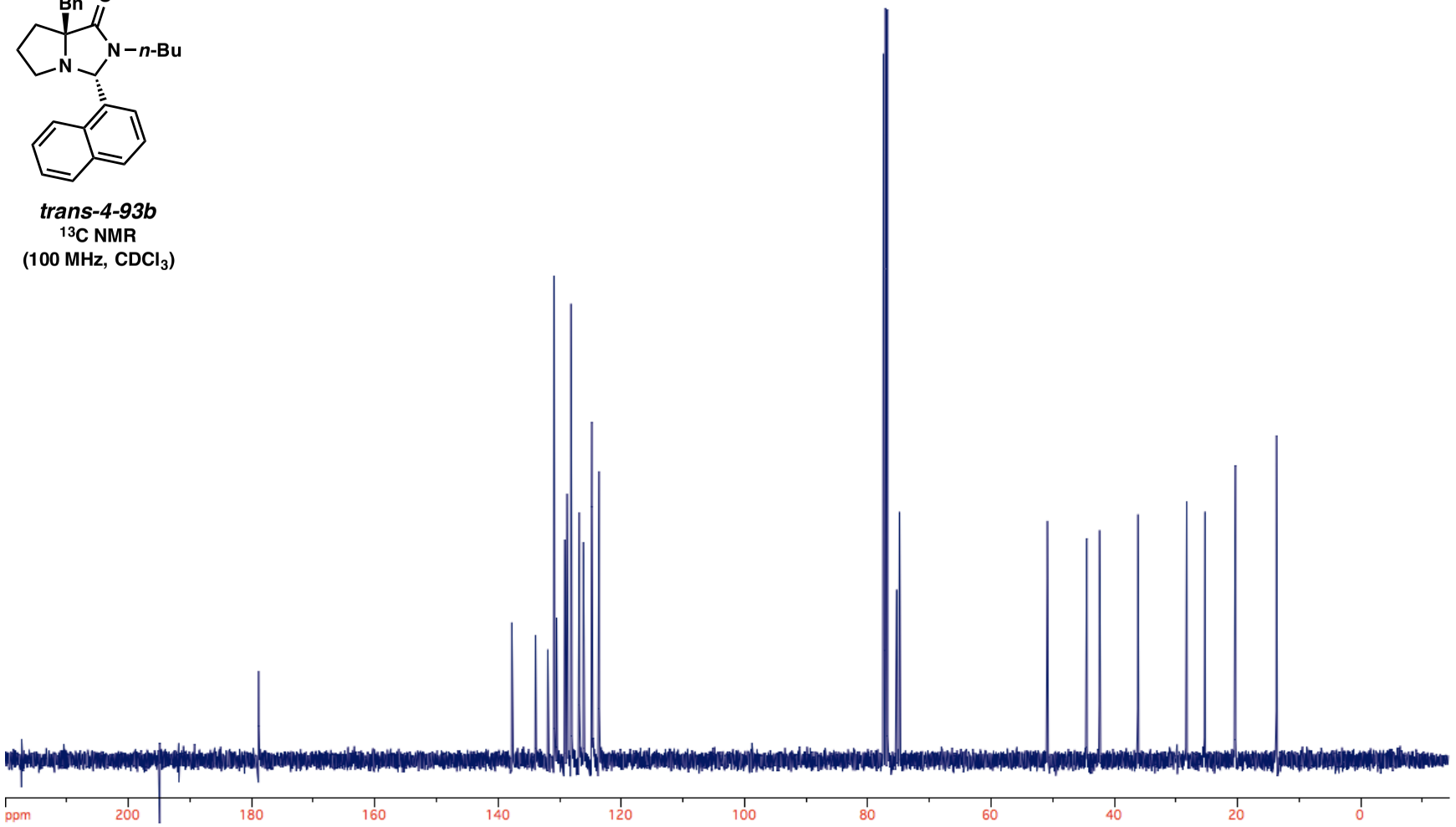


trans-4-93b
^{1}H NMR
(400 MHz, $CDCl_3$)

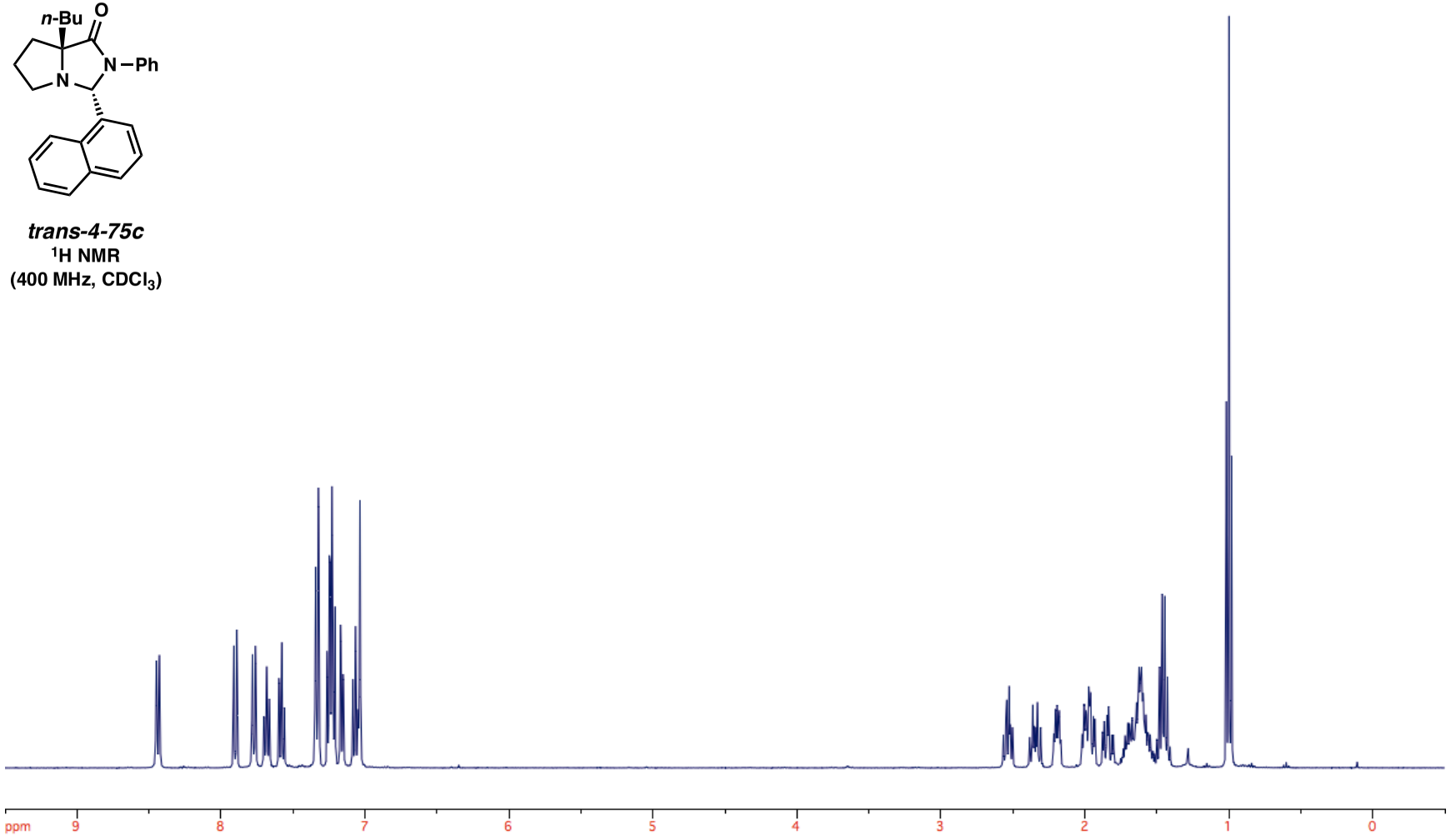


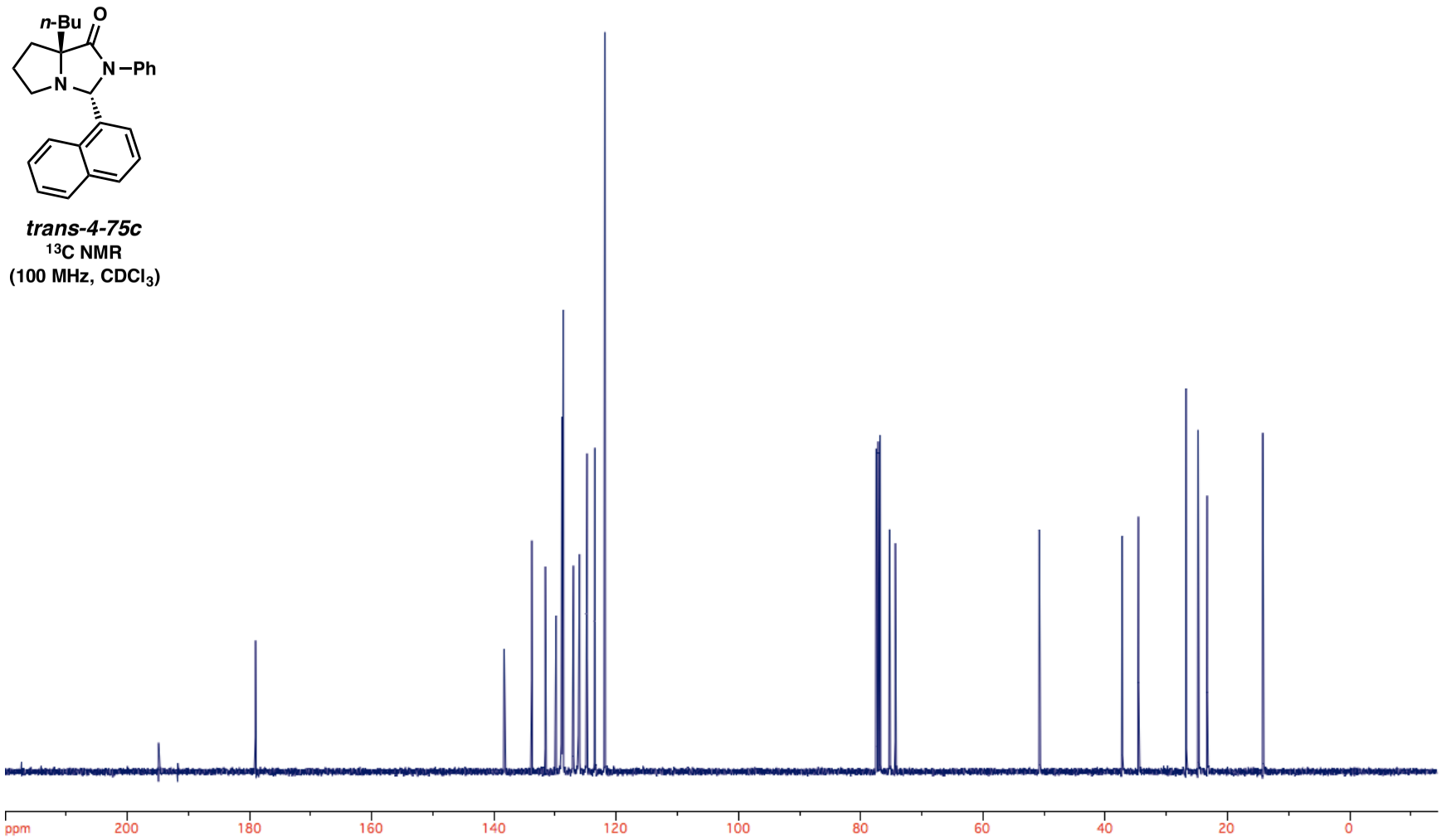


trans-4-93b
^{13}C NMR
(100 MHz, $CDCl_3$)

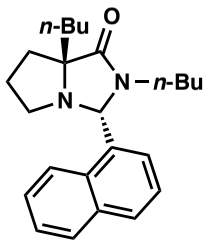


trans-4-75c
^{1}H NMR
(400 MHz, $CDCl_3$)

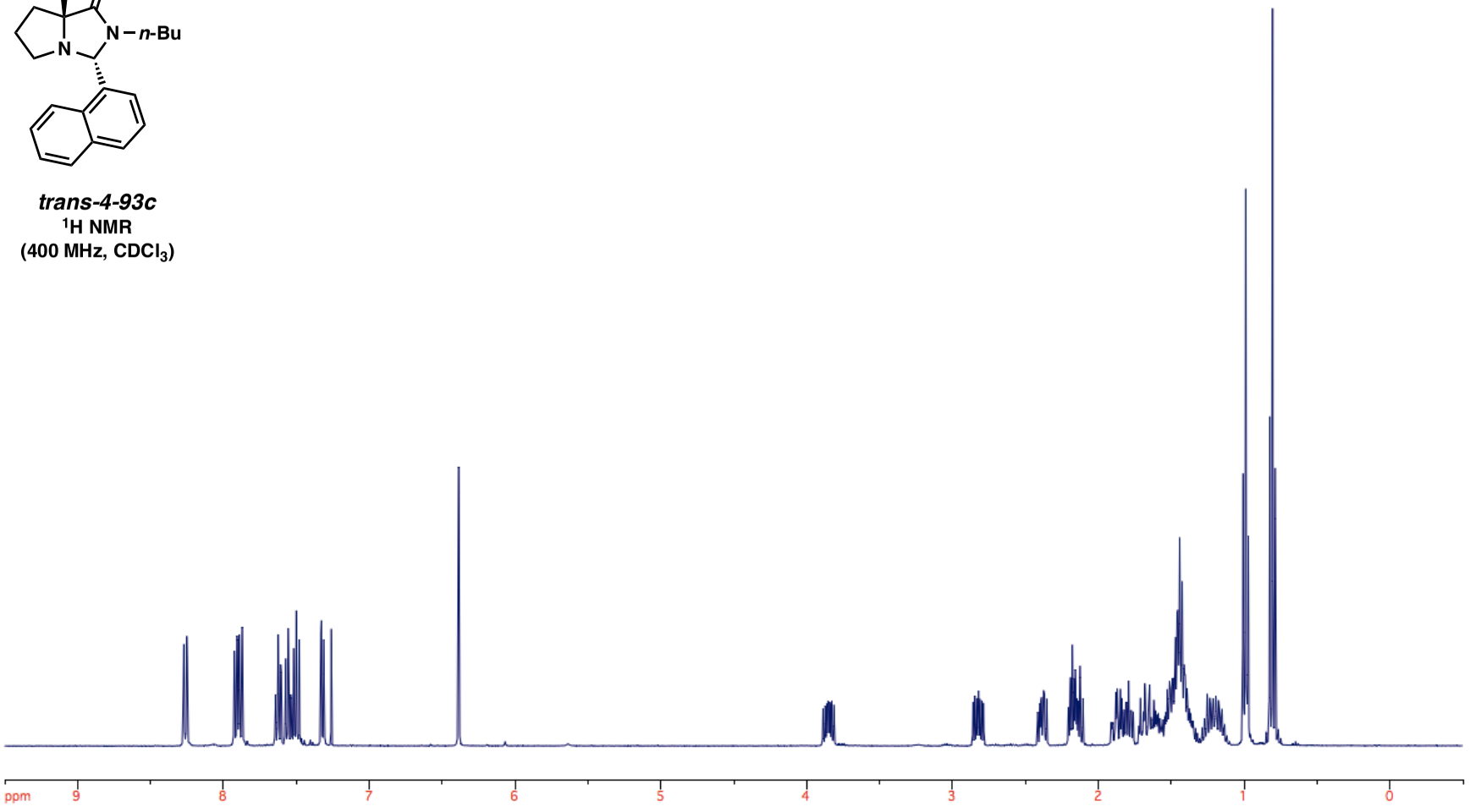


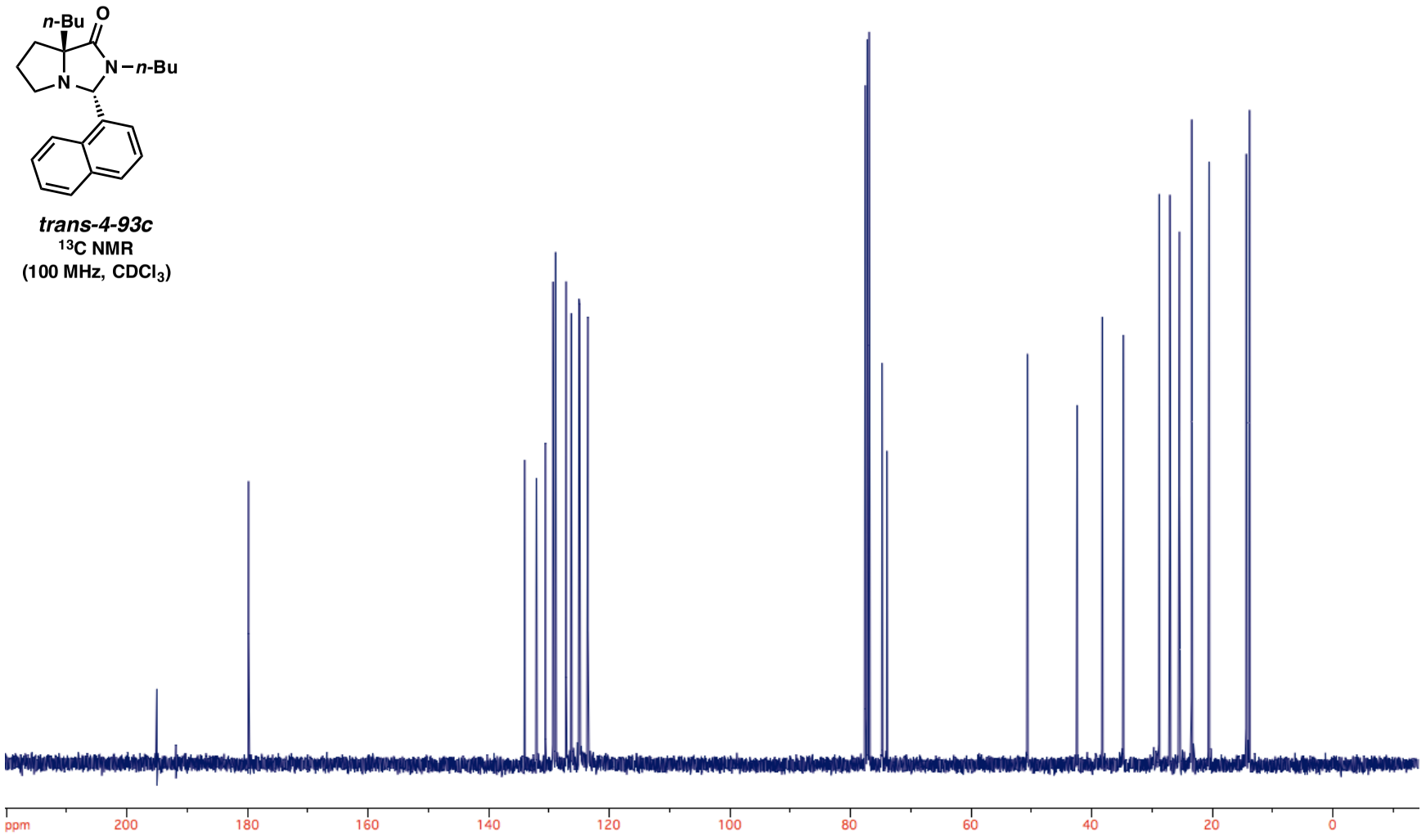


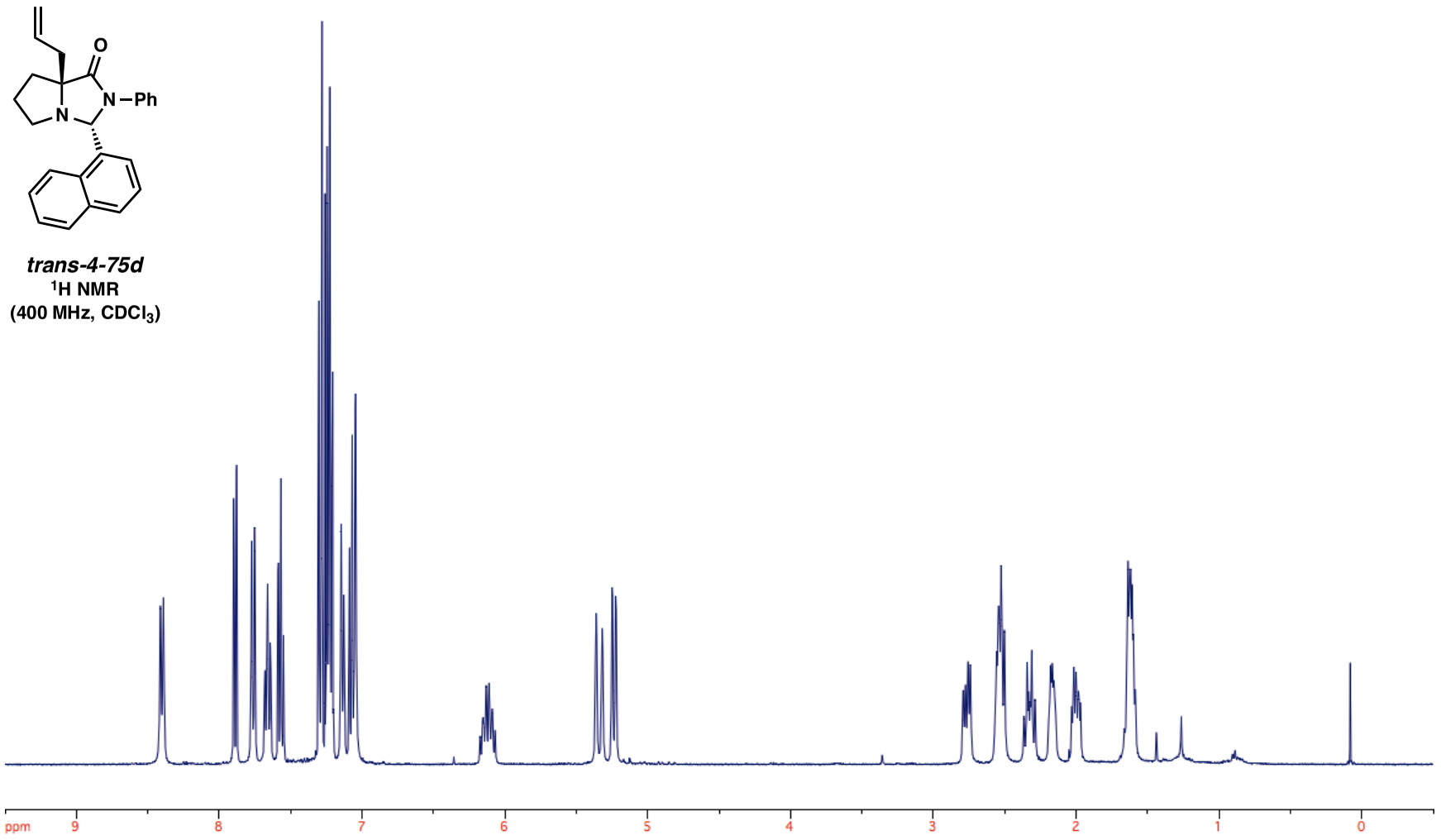
trans-4-75c
^{13}C NMR
(100 MHz, $CDCl_3$)



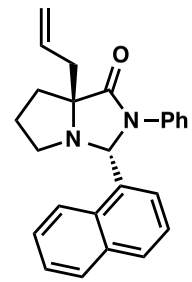
trans-4-93c
^{1}H NMR
(400 MHz, $CDCl_3$)



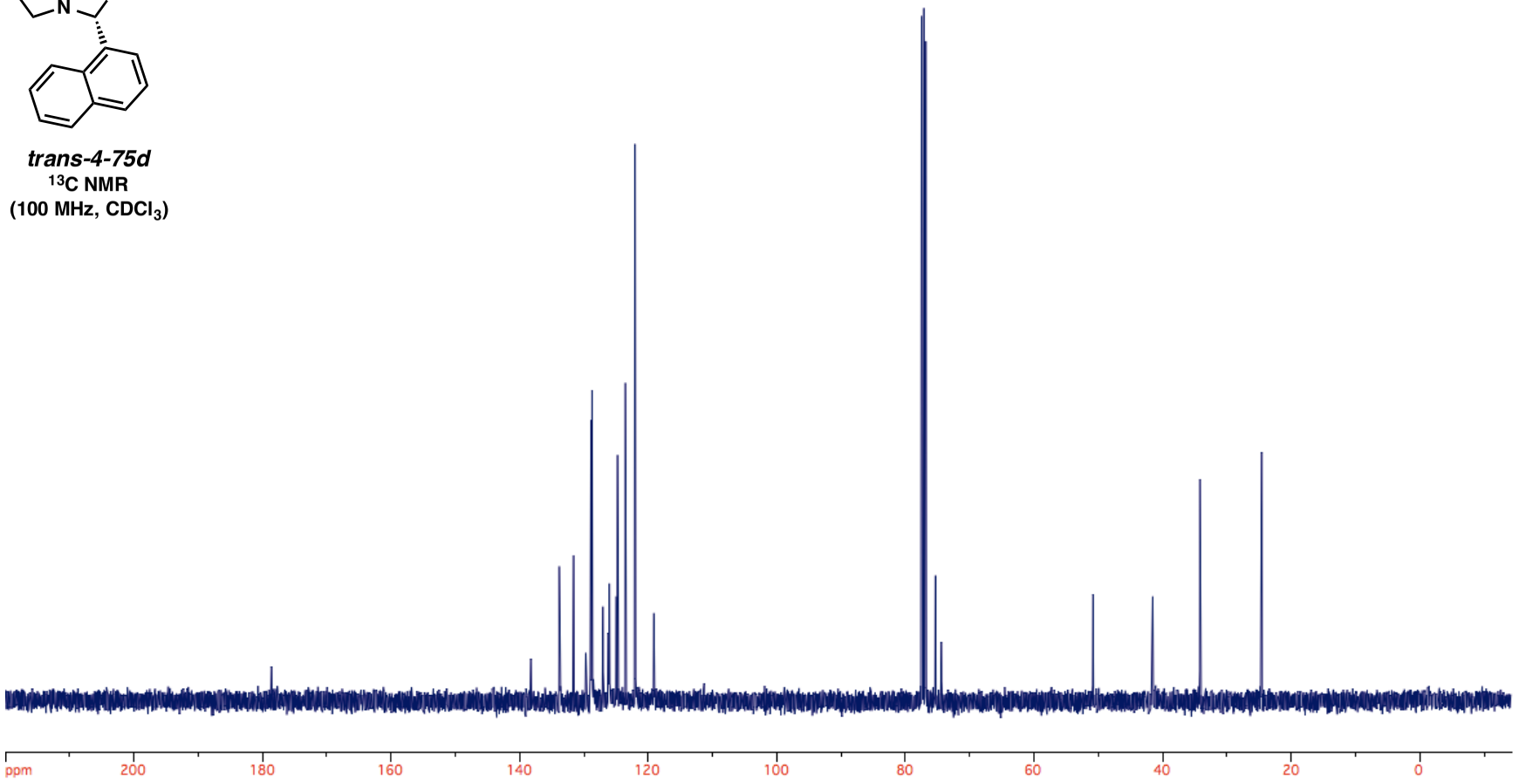

n-Bu
O
N
N–n-Bu
trans-4-93c
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

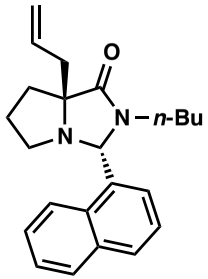


trans-4-75d
^{1}H NMR
(400 MHz, $CDCl_3$)

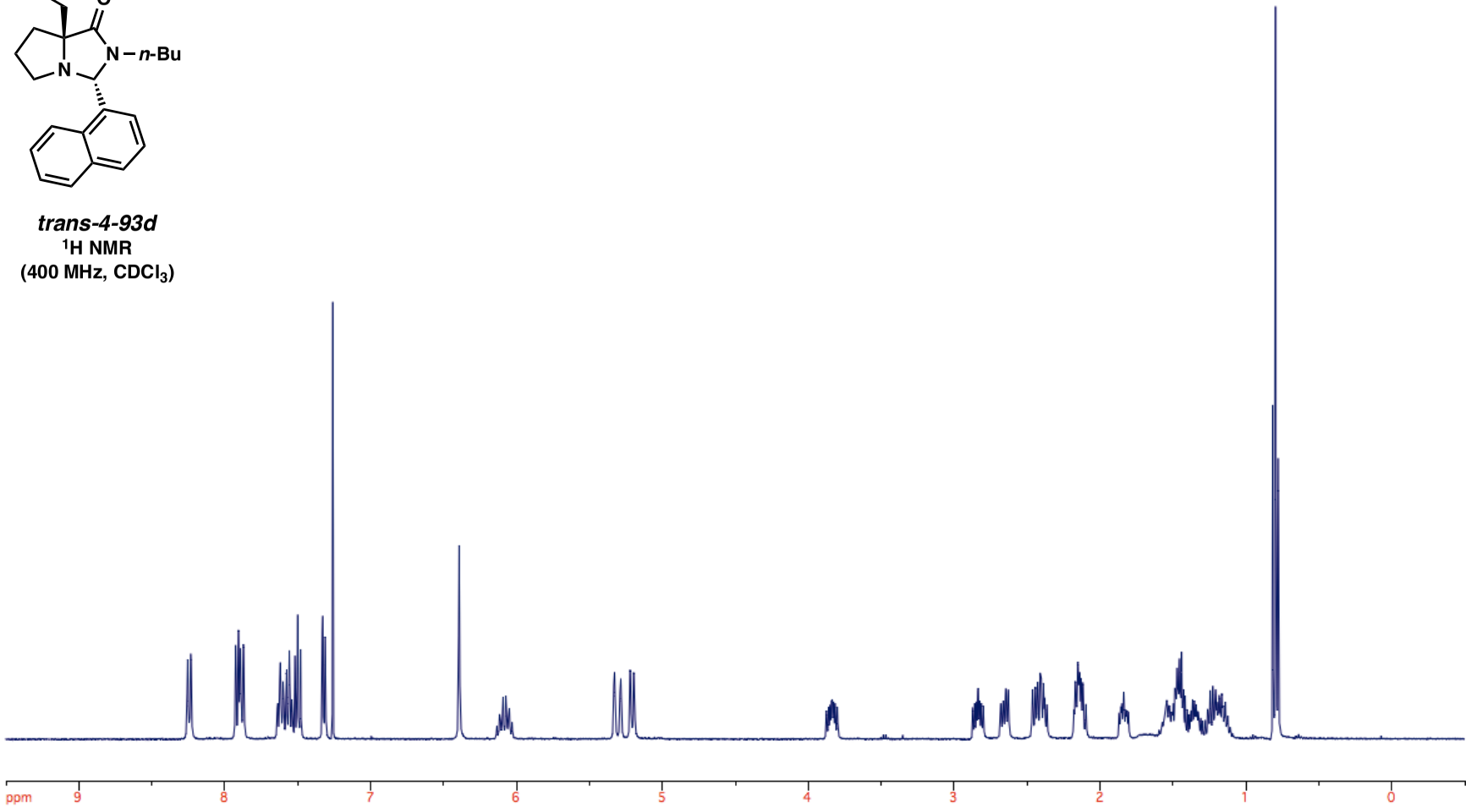


trans-4-75d
^{13}C NMR
(100 MHz, $CDCl_3$)

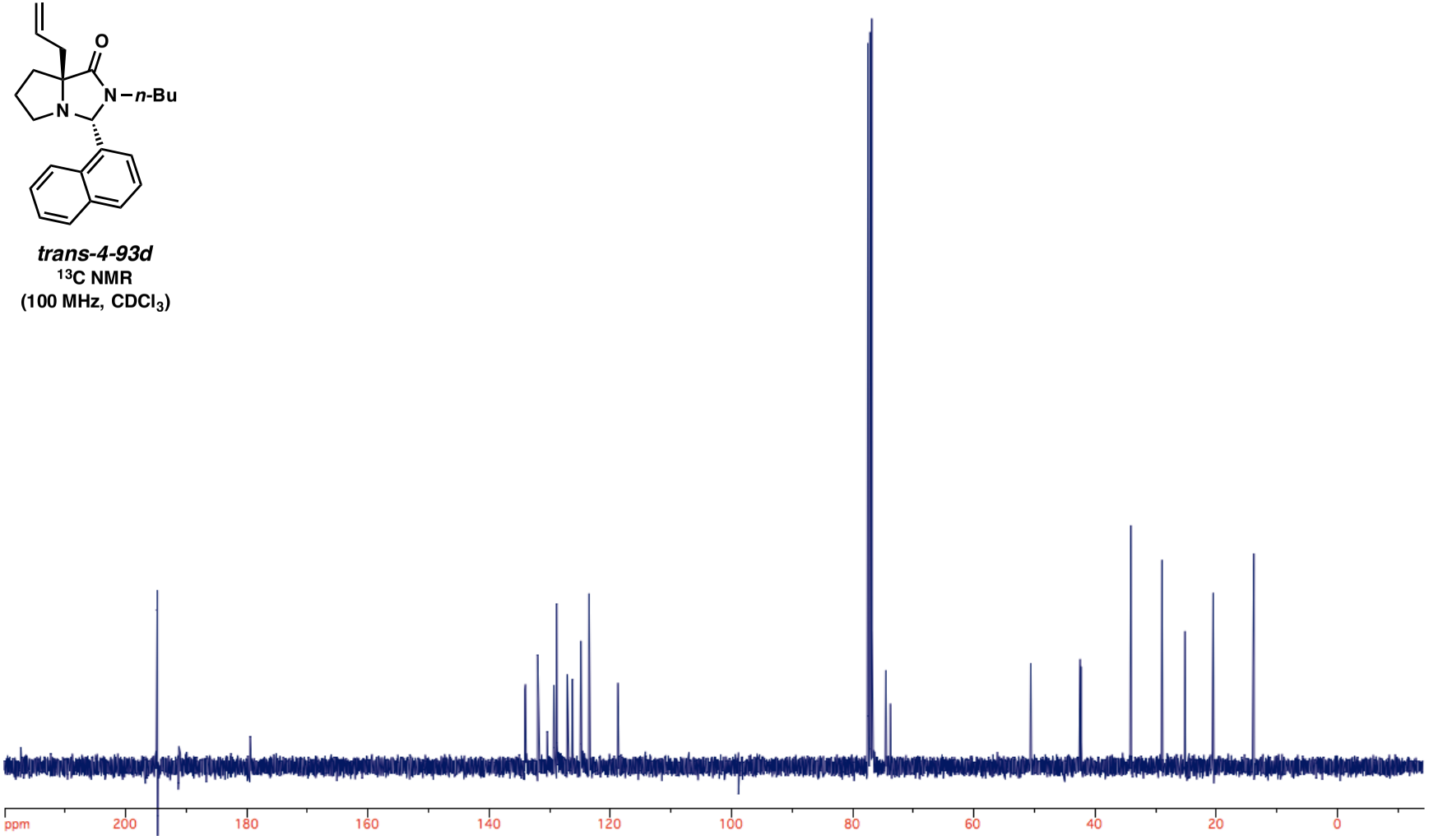




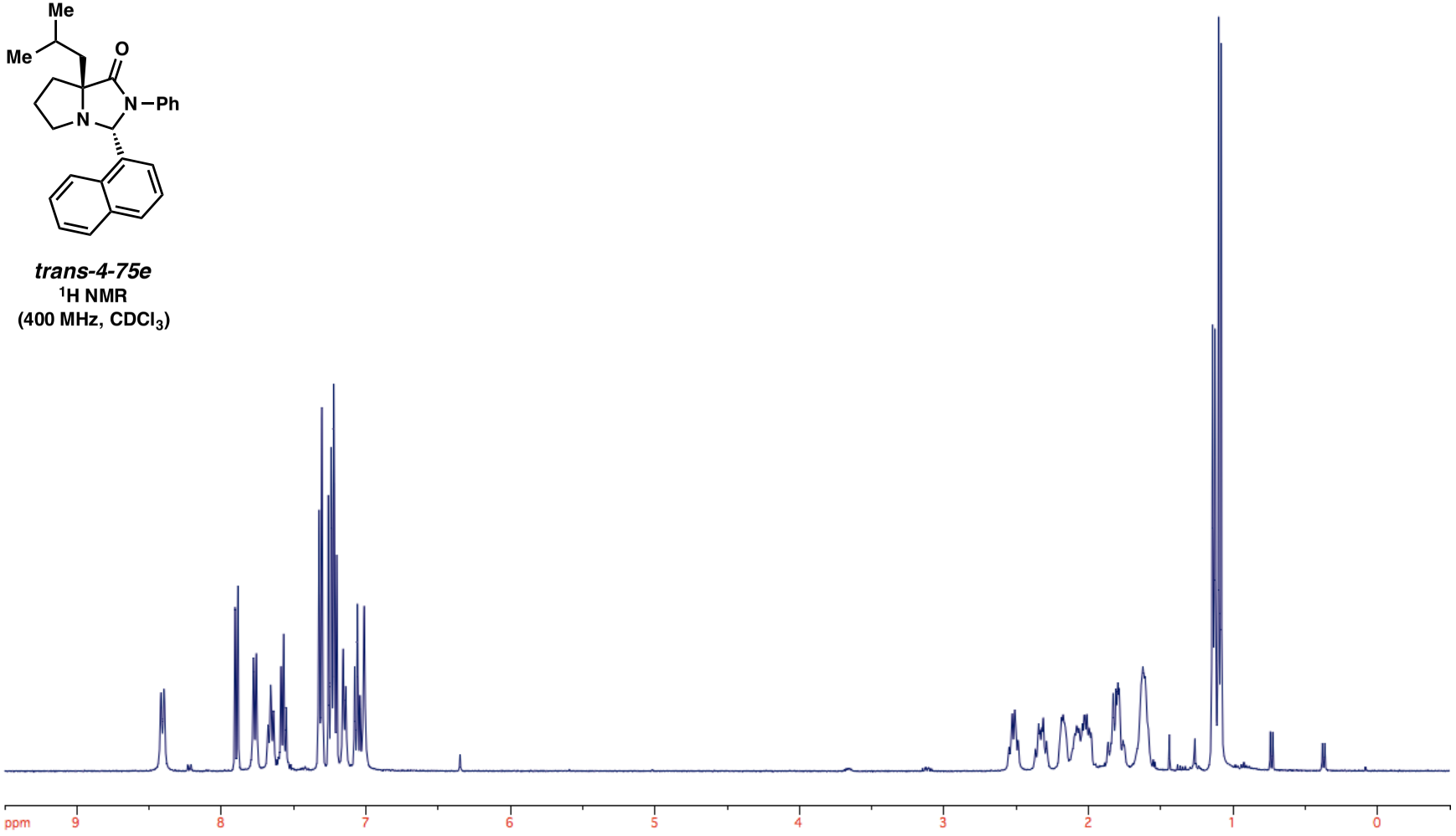
trans-4-93d
^{1}H NMR
(400 MHz, $CDCl_3$)

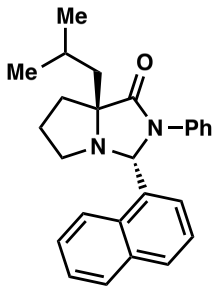


trans-4-93d
^{13}C NMR
(100 MHz, $CDCl_3$)

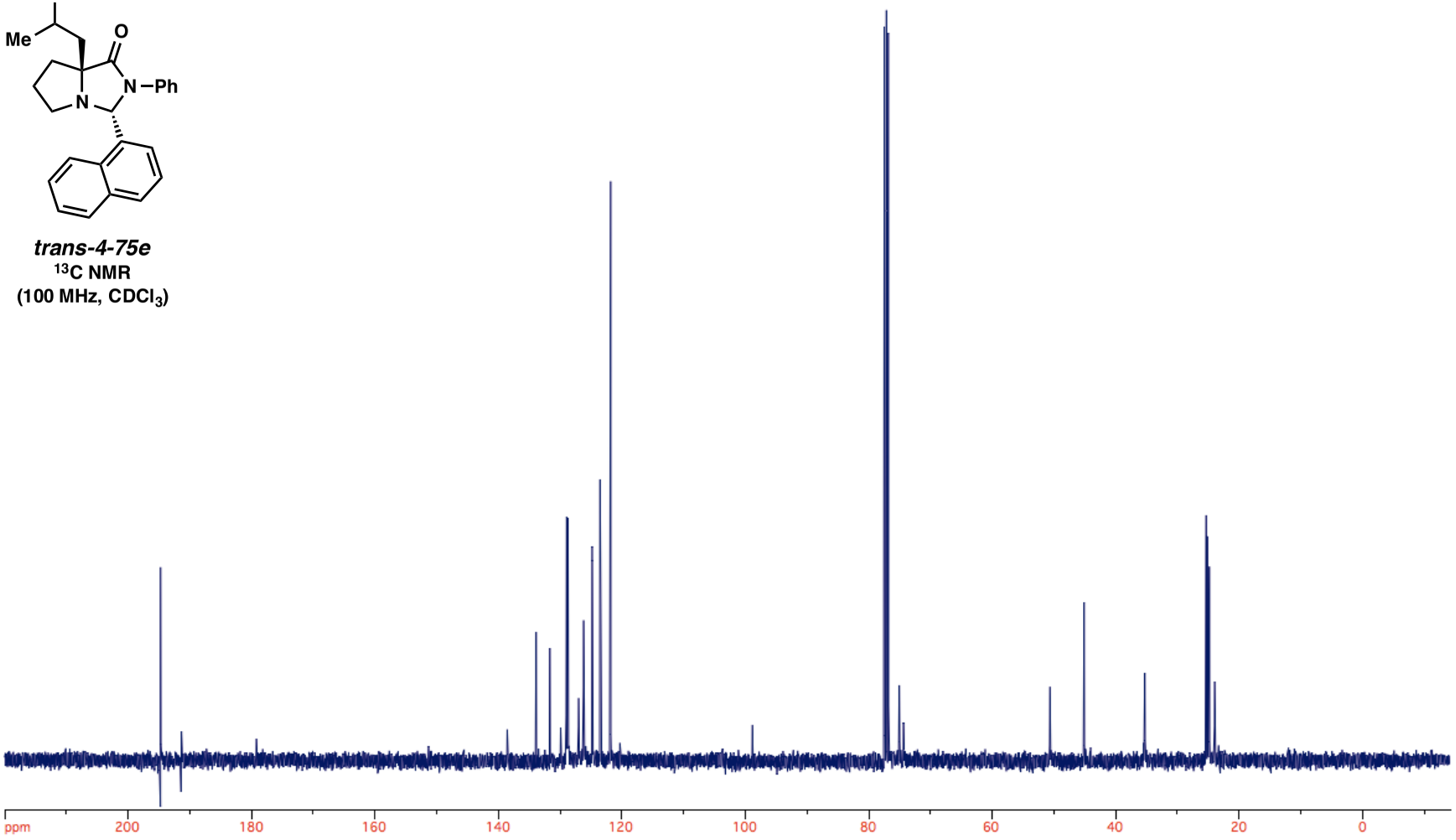


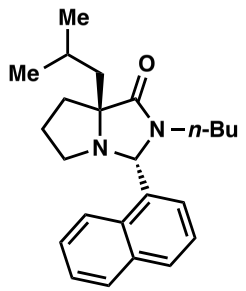
trans-4-75e
^{1}H NMR
(400 MHz, $CDCl_3$)



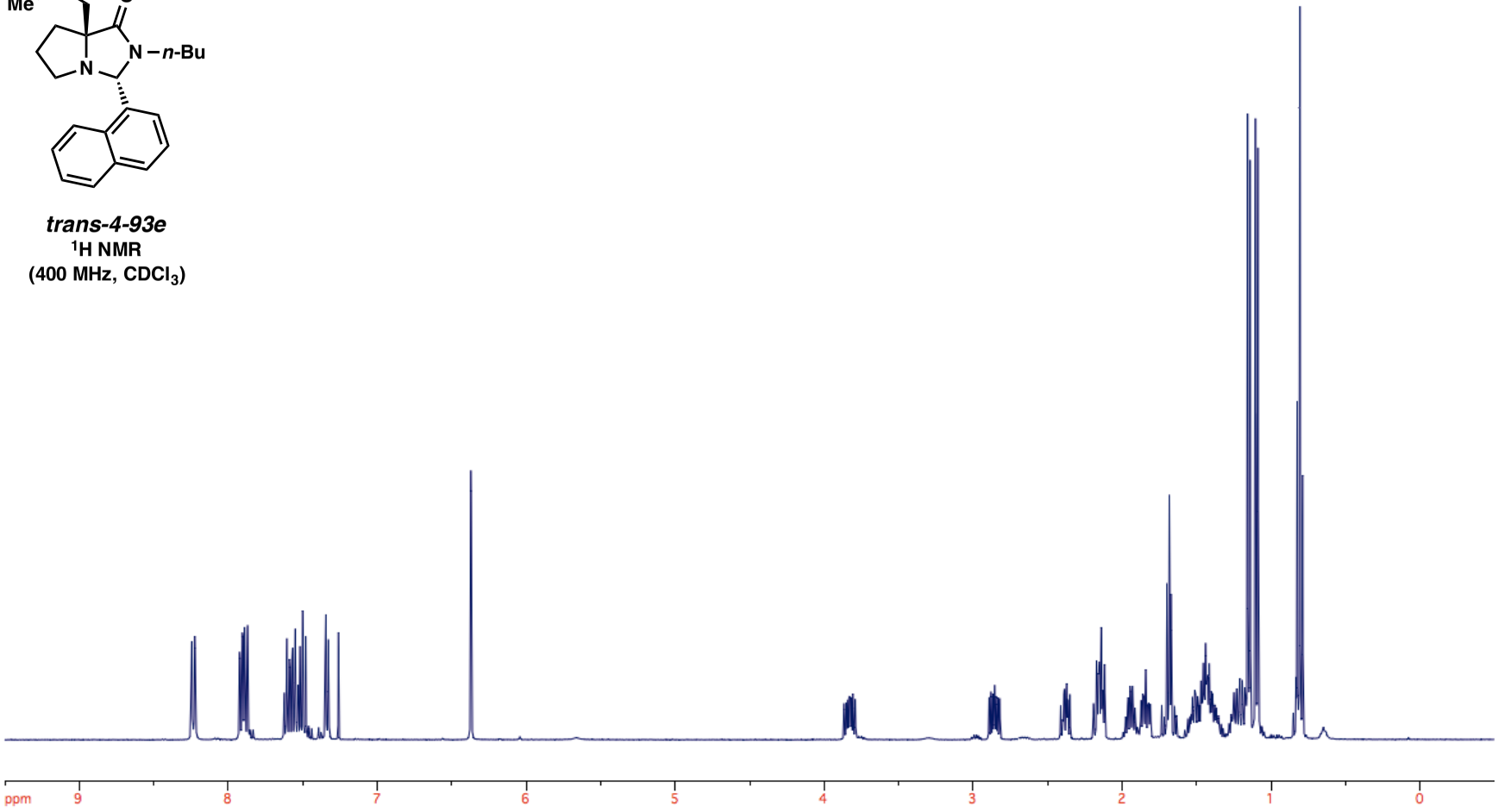


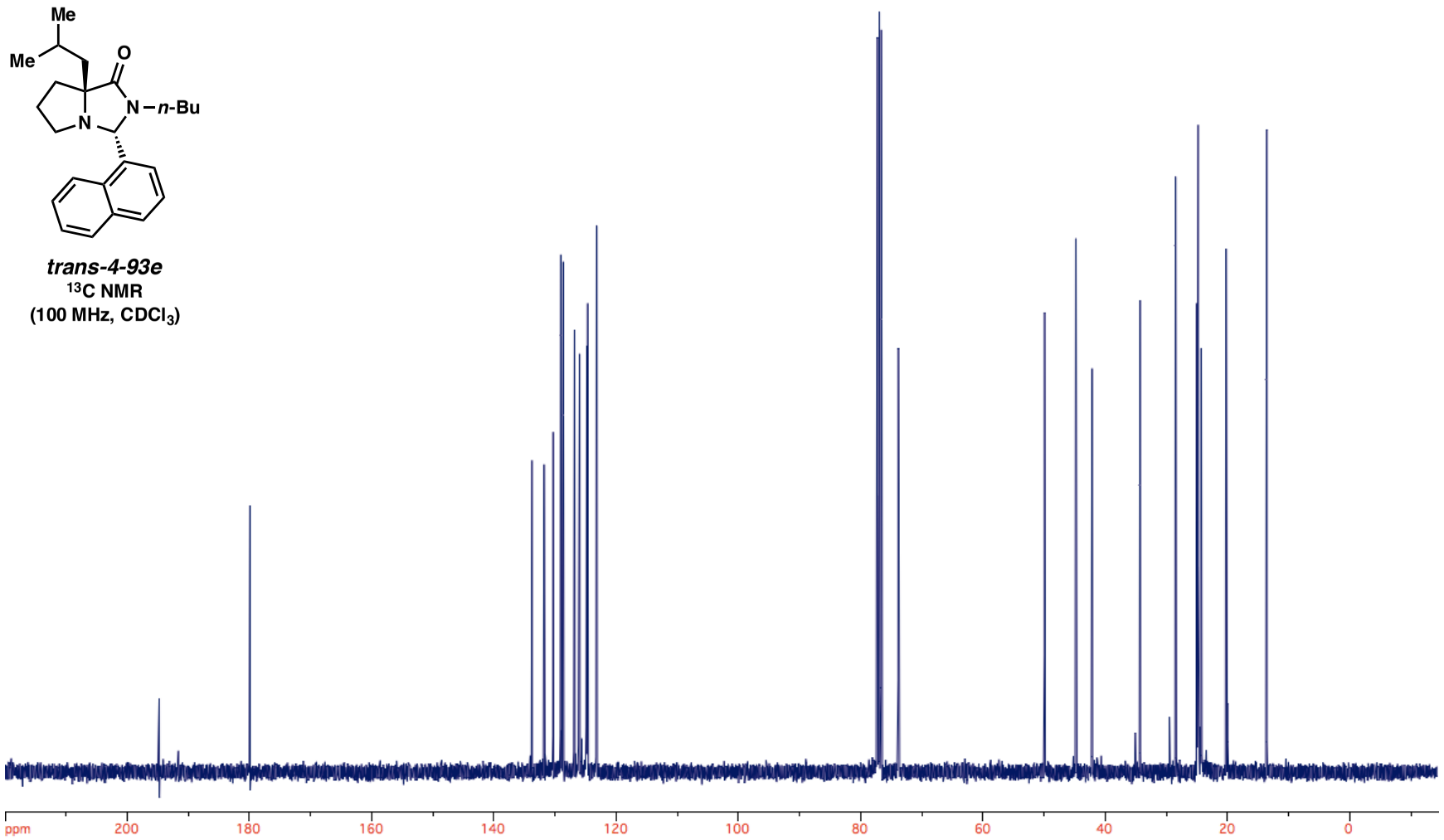
trans-4-75e
^{13}C NMR
(100 MHz, $CDCl_3$)



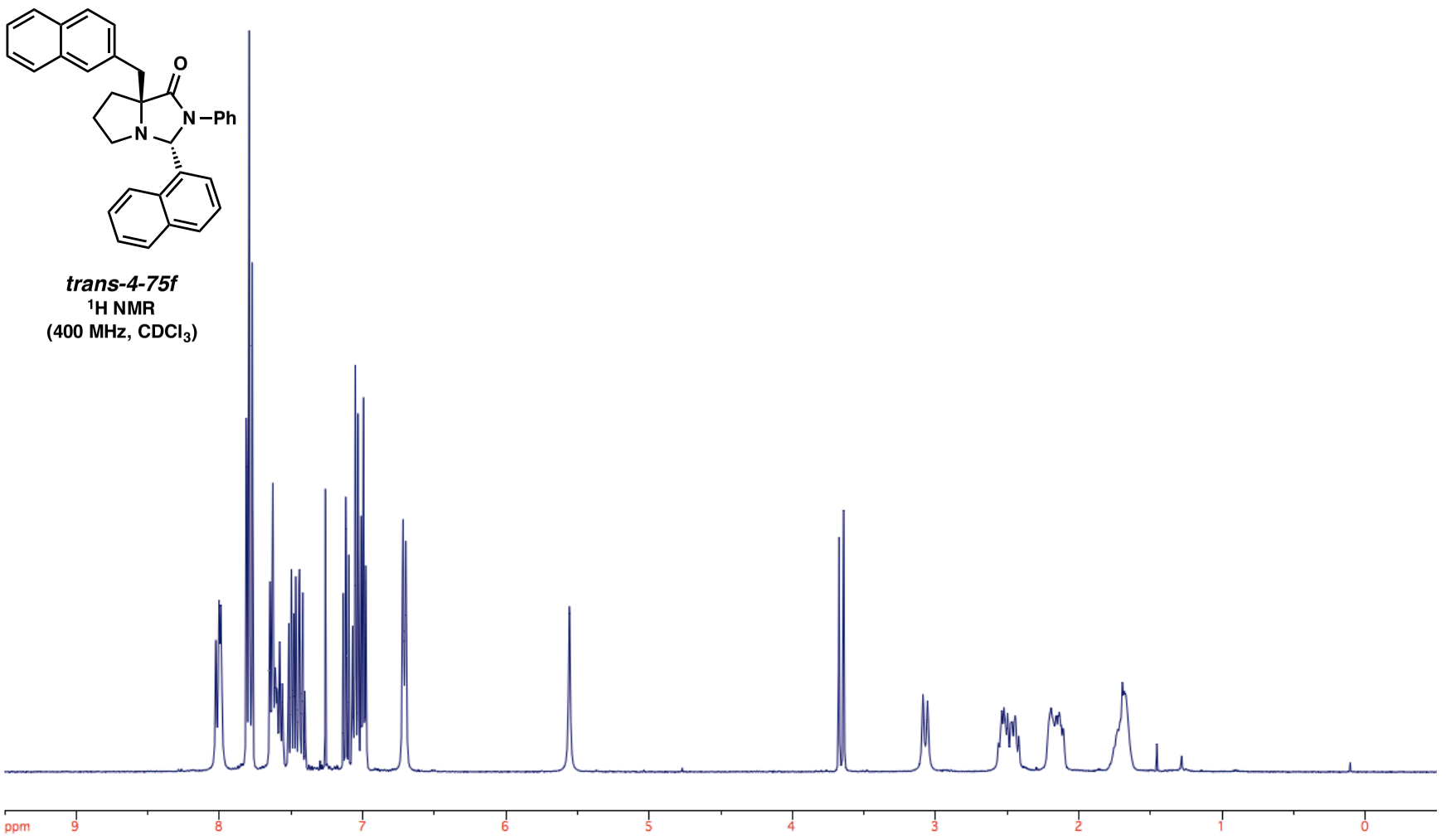


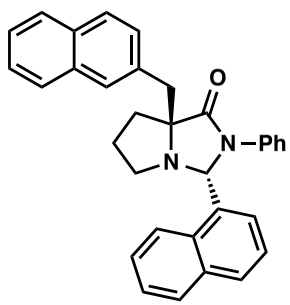
trans-4-93e
^{1}H NMR
(400 MHz, $CDCl_3$)



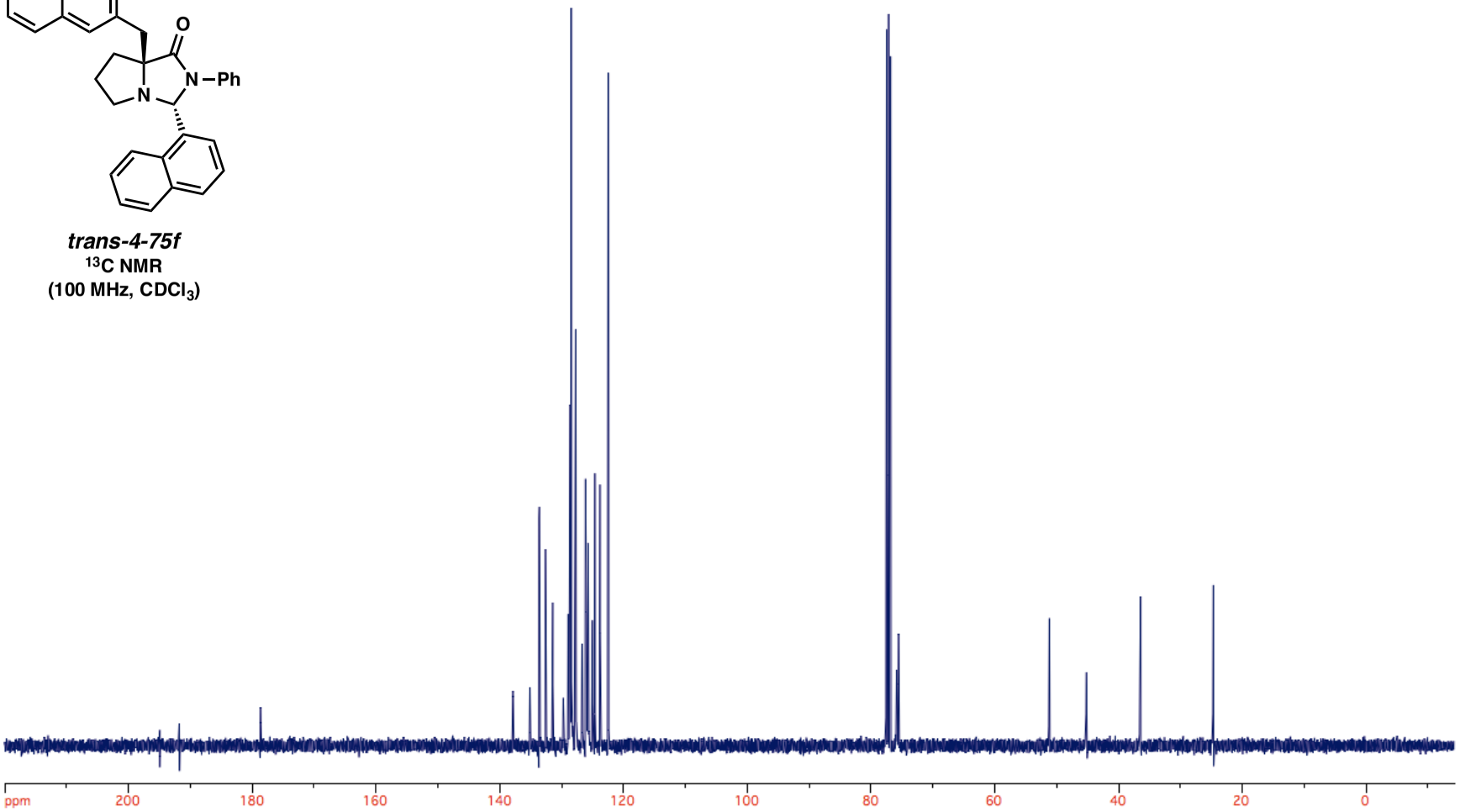


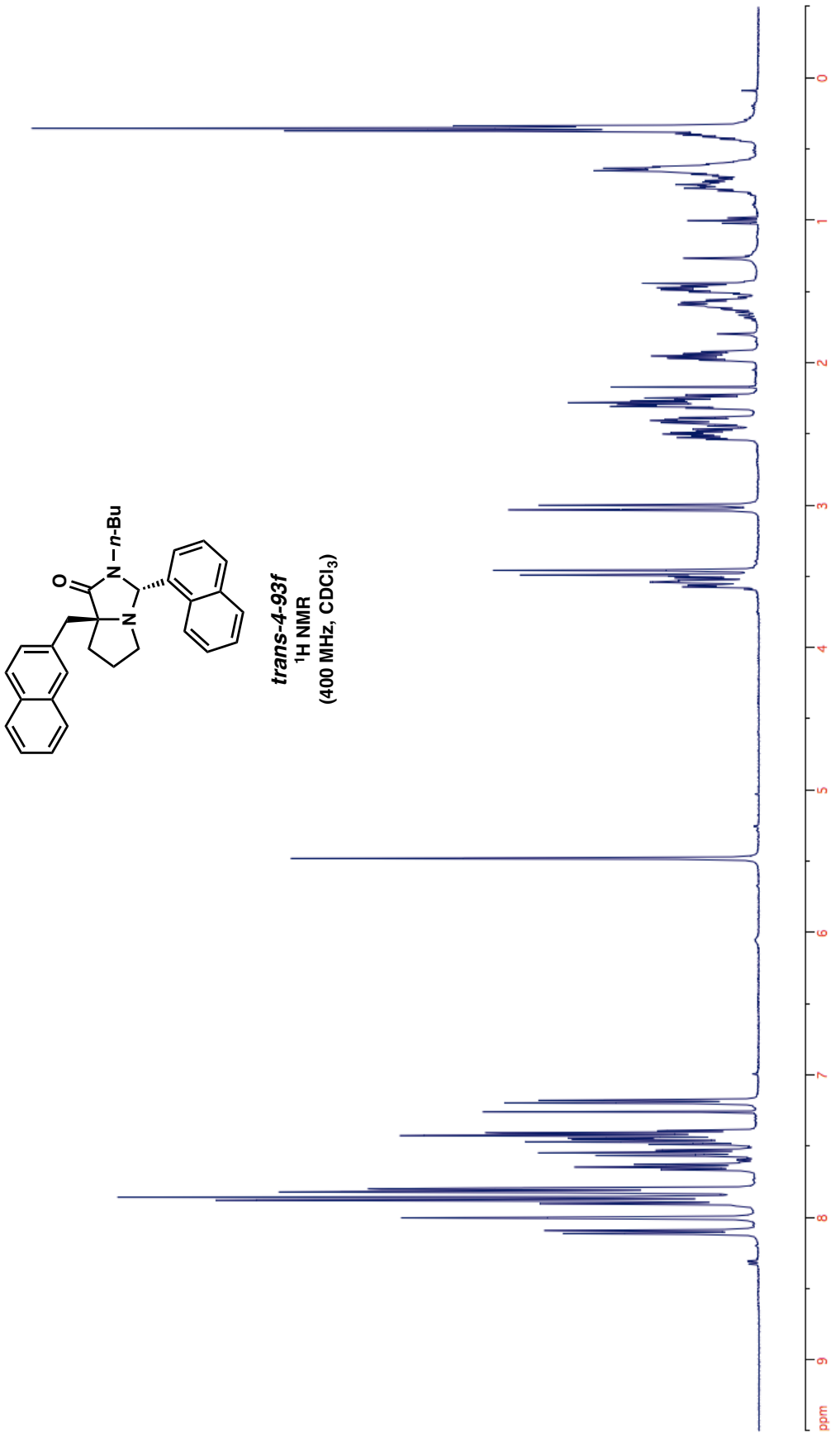
trans-4-93e
^{13}C NMR
(100 MHz, $CDCl_3$)

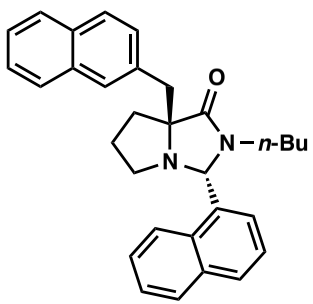

O
N–Ph
N
trans-4-75f
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0



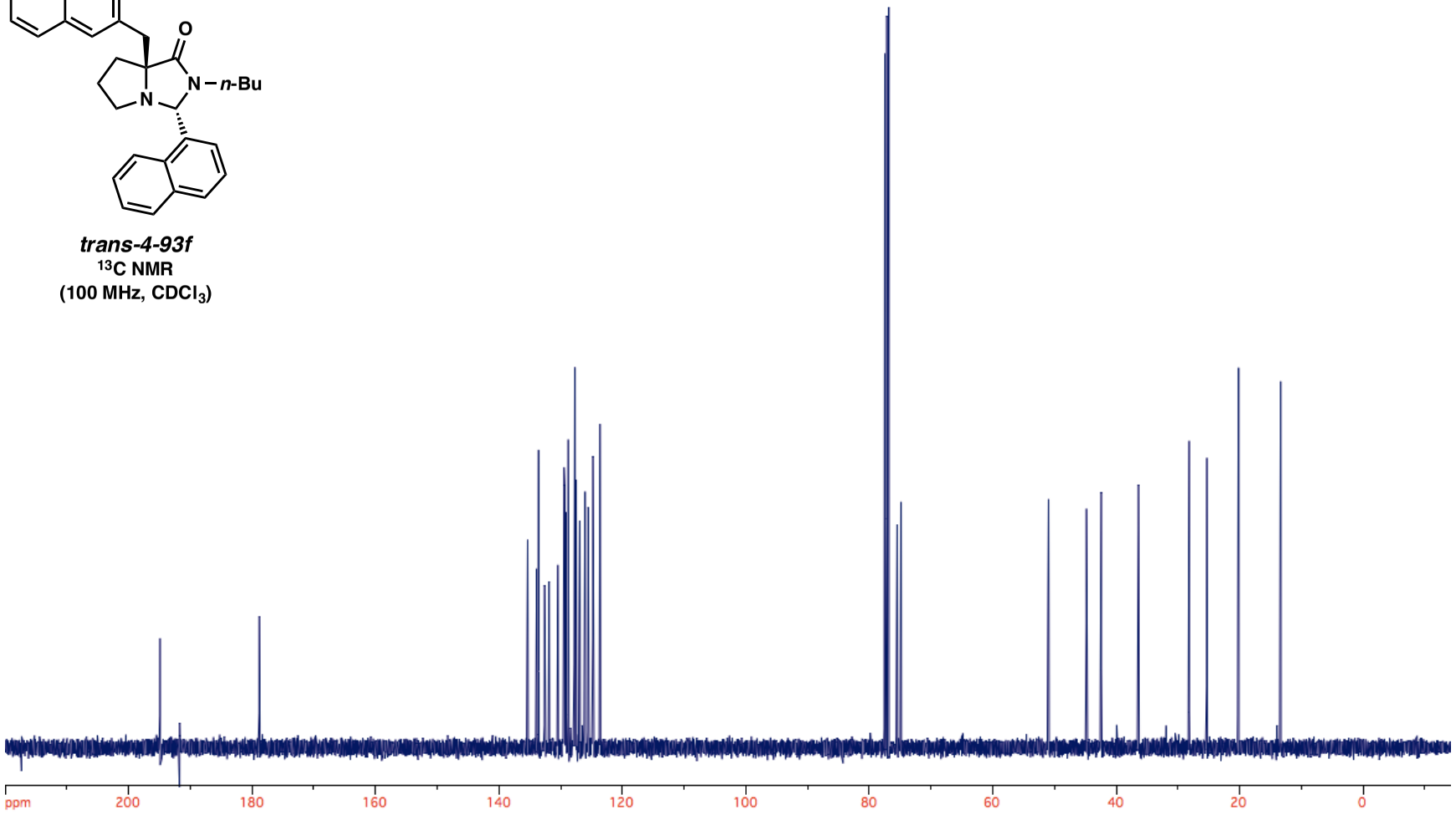
trans-4-75f
^{13}C NMR
(100 MHz, $CDCl_3$)

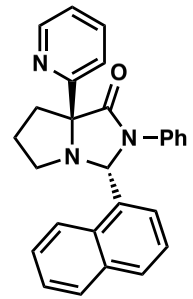



O
N
n-Bu
N
trans-4-93f
1H NMR
(400 MHz, CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9

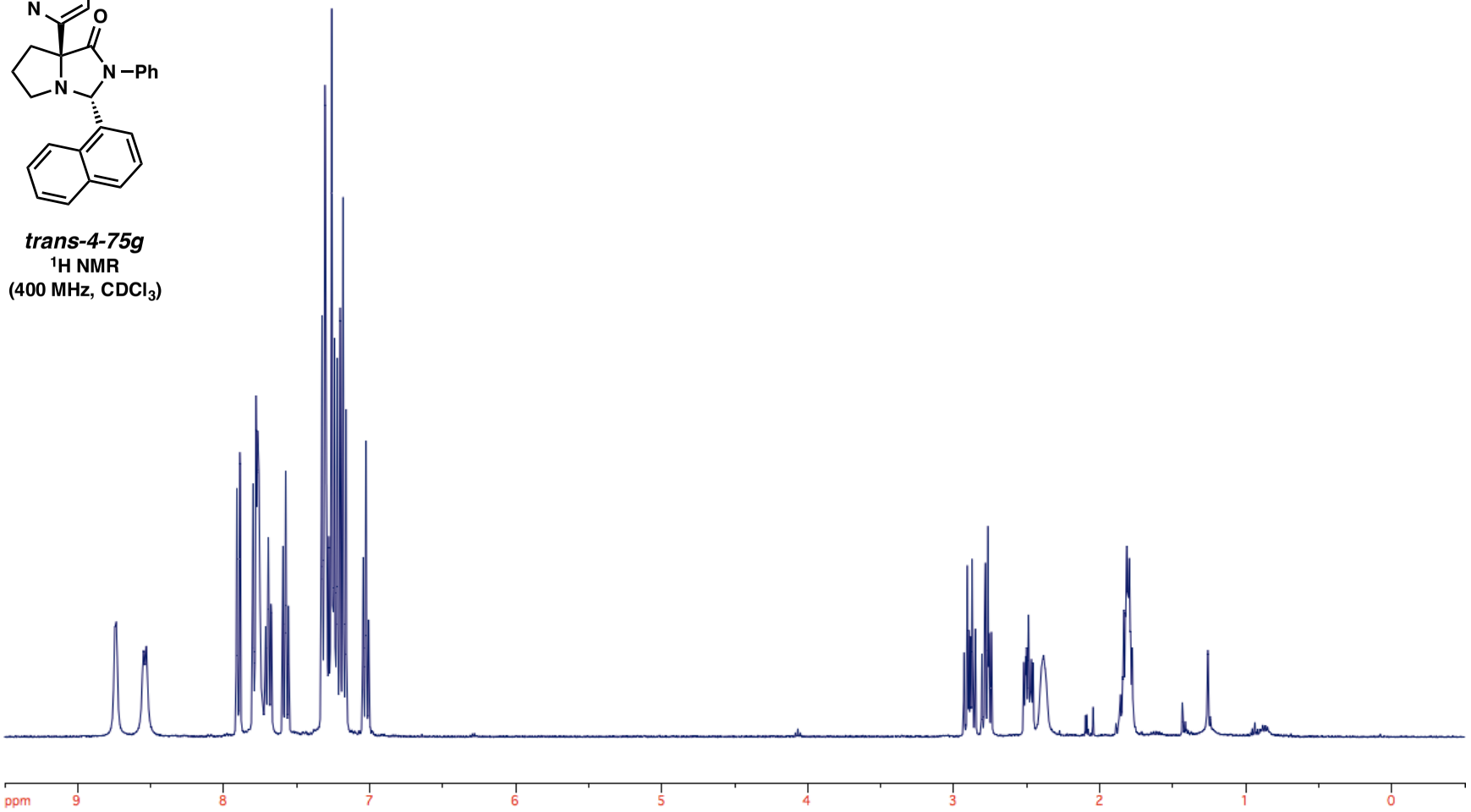


trans-4-93f
^{13}C NMR
(100 MHz, $CDCl_3$)

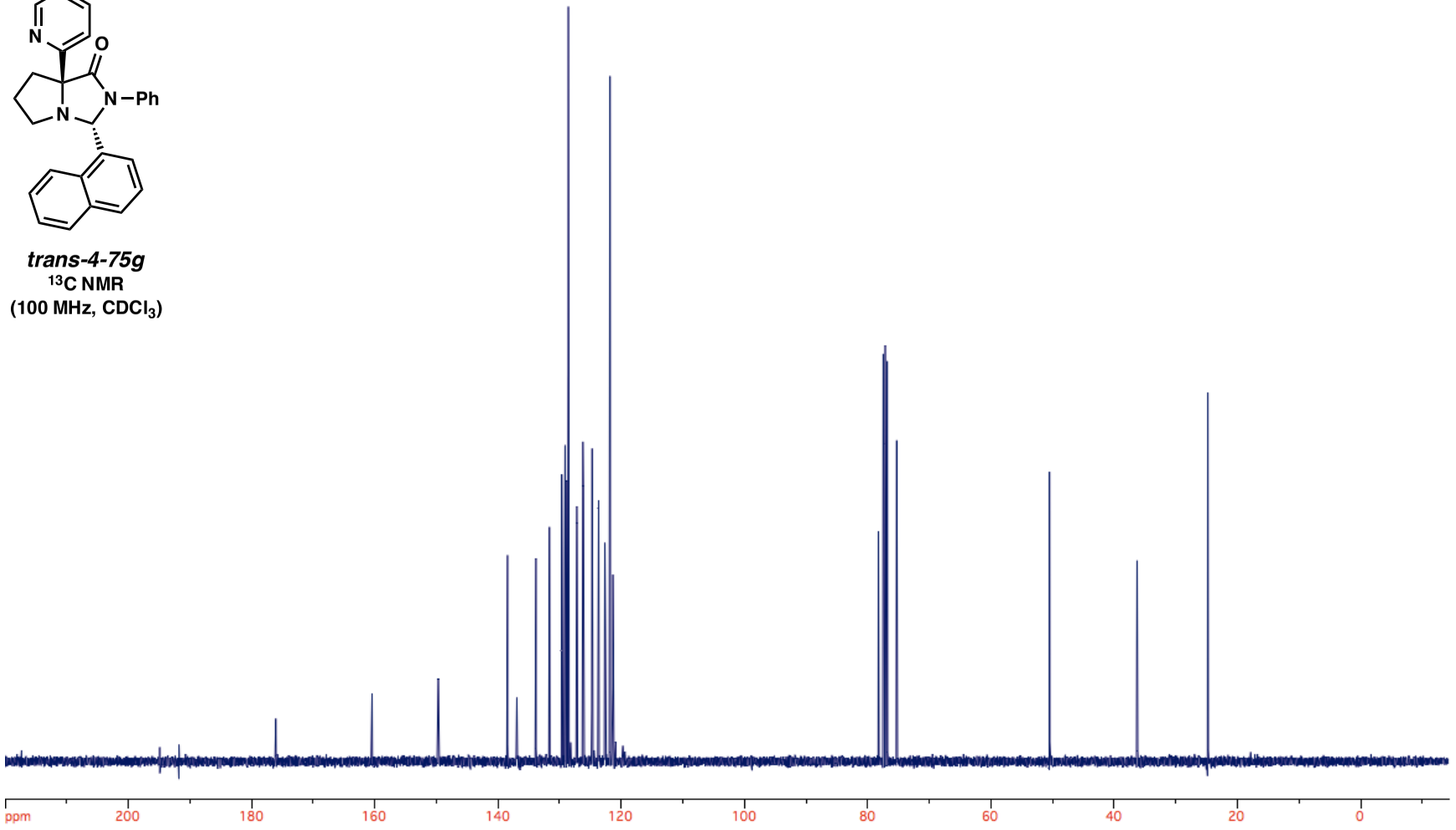




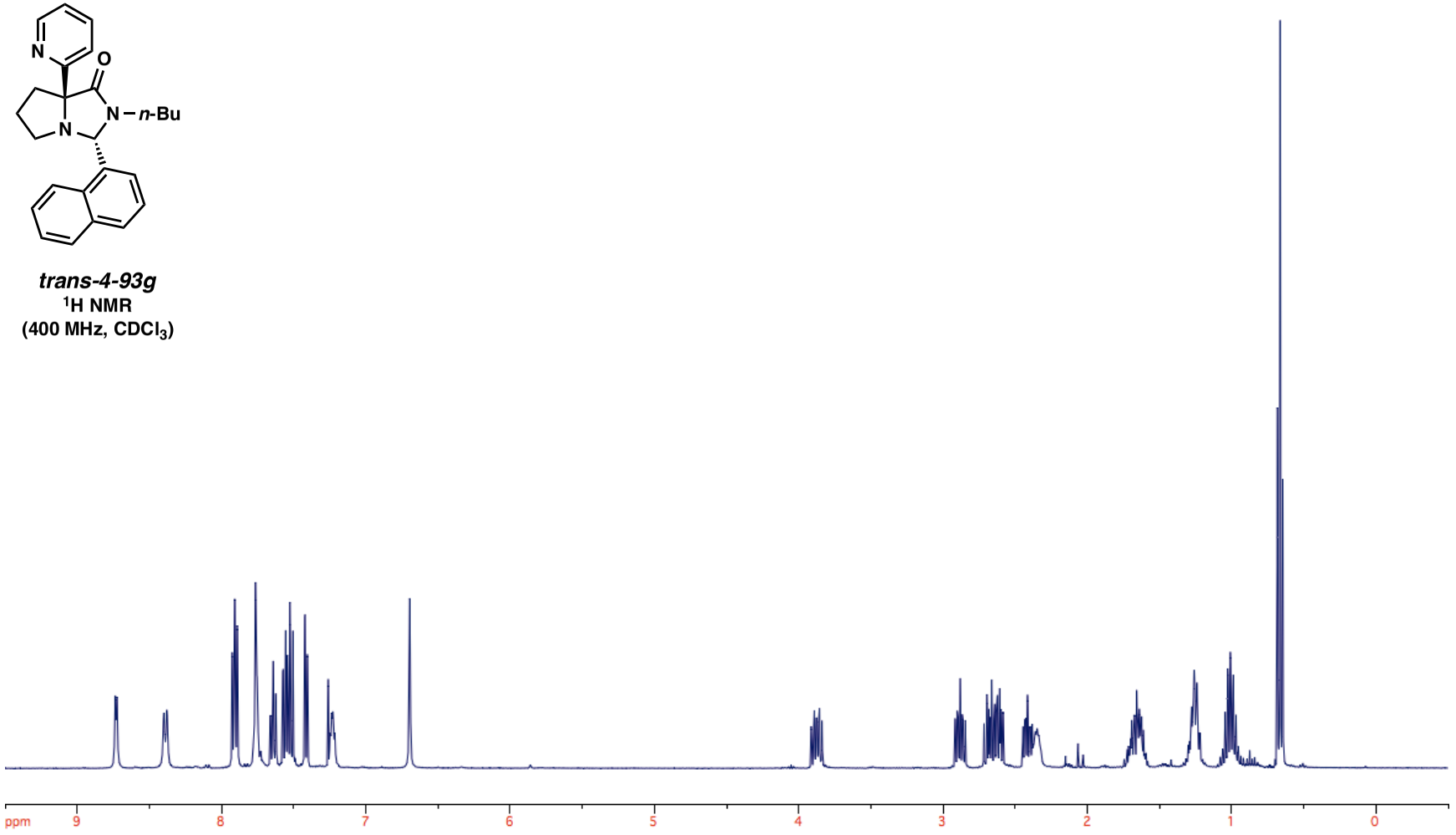
trans-4-75g
^{1}H NMR
(400 MHz, $CDCl_3$)



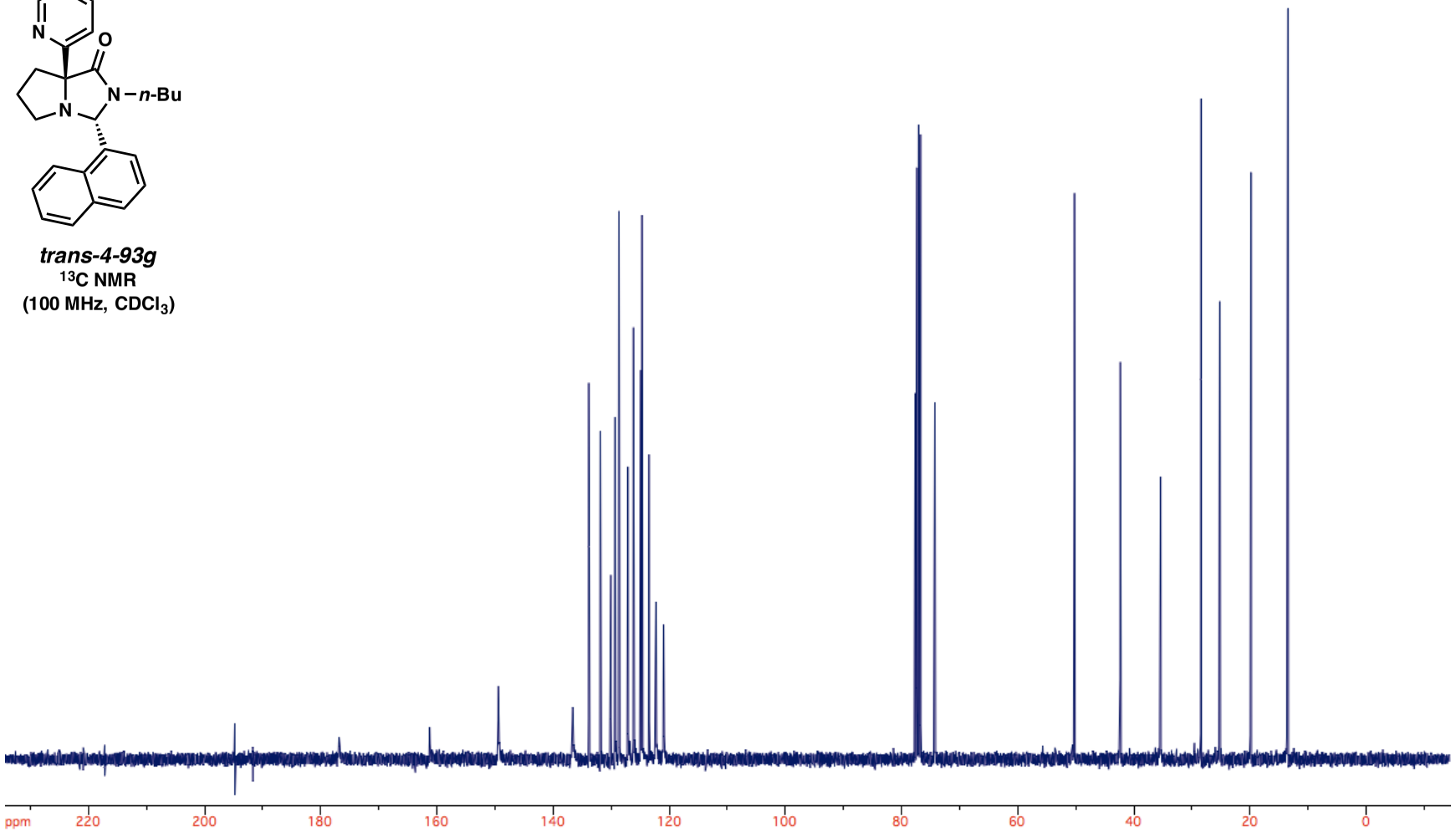
trans-4-75g
^{13}C NMR
(100 MHz, $CDCl_3$)

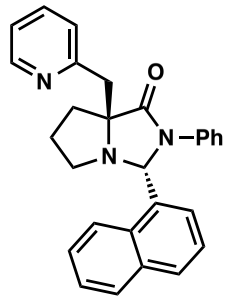


trans-4-93g
^{1}H NMR
(400 MHz, $CDCl_3$)

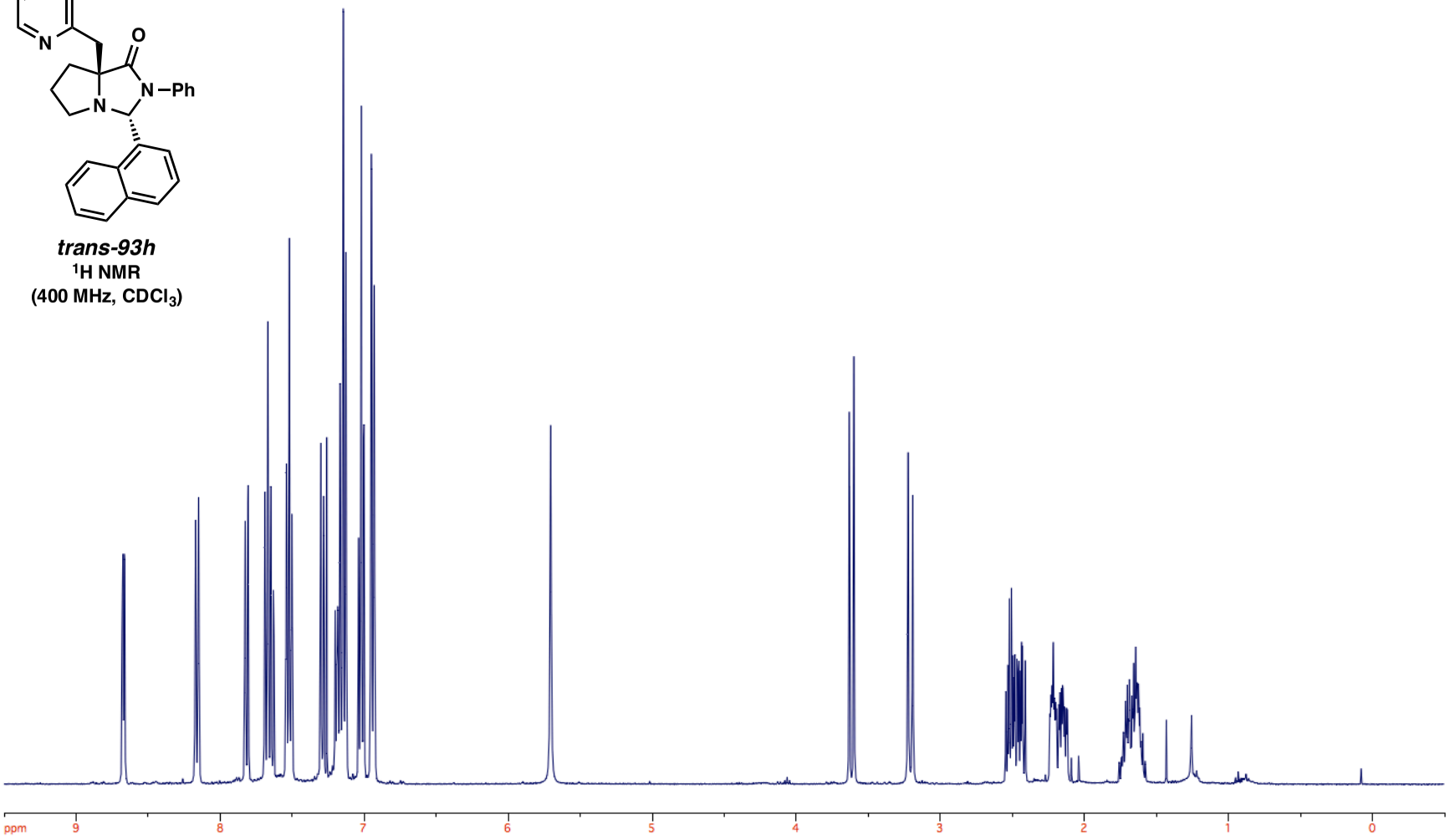


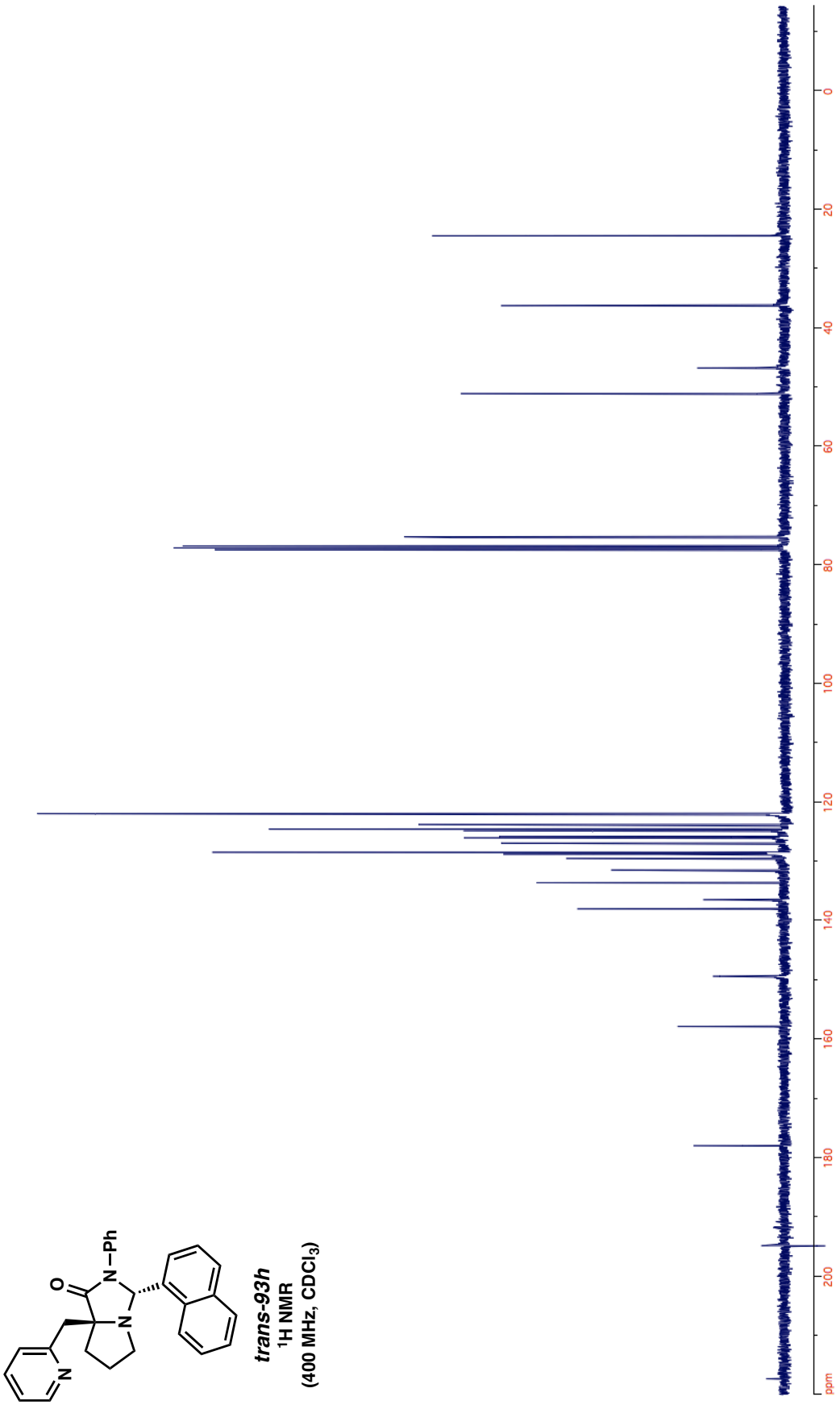
trans-4-93g
^{13}C NMR
(100 MHz, $CDCl_3$)



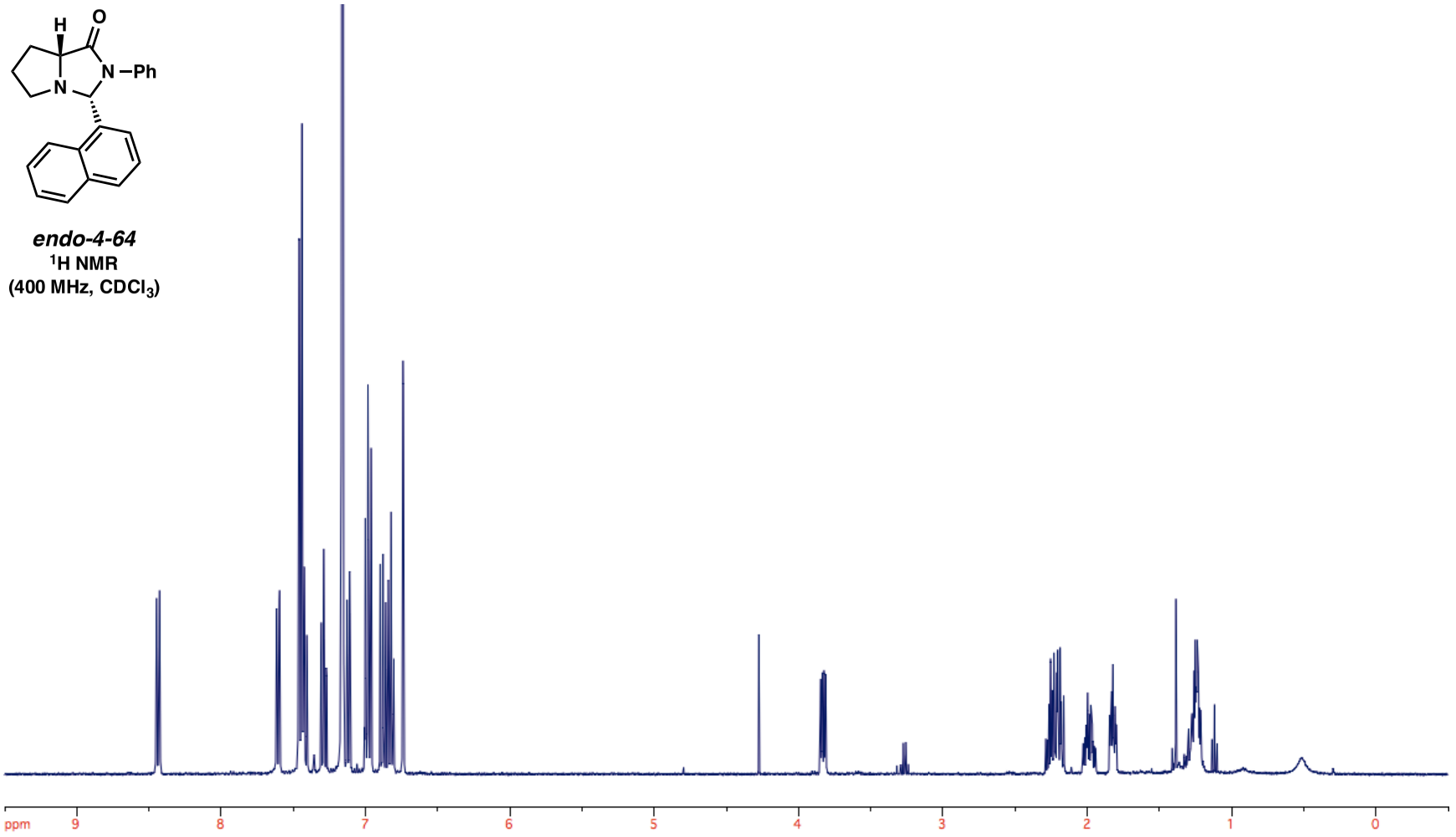


trans-93h
^{1}H NMR
(400 MHz, $CDCl_3$)

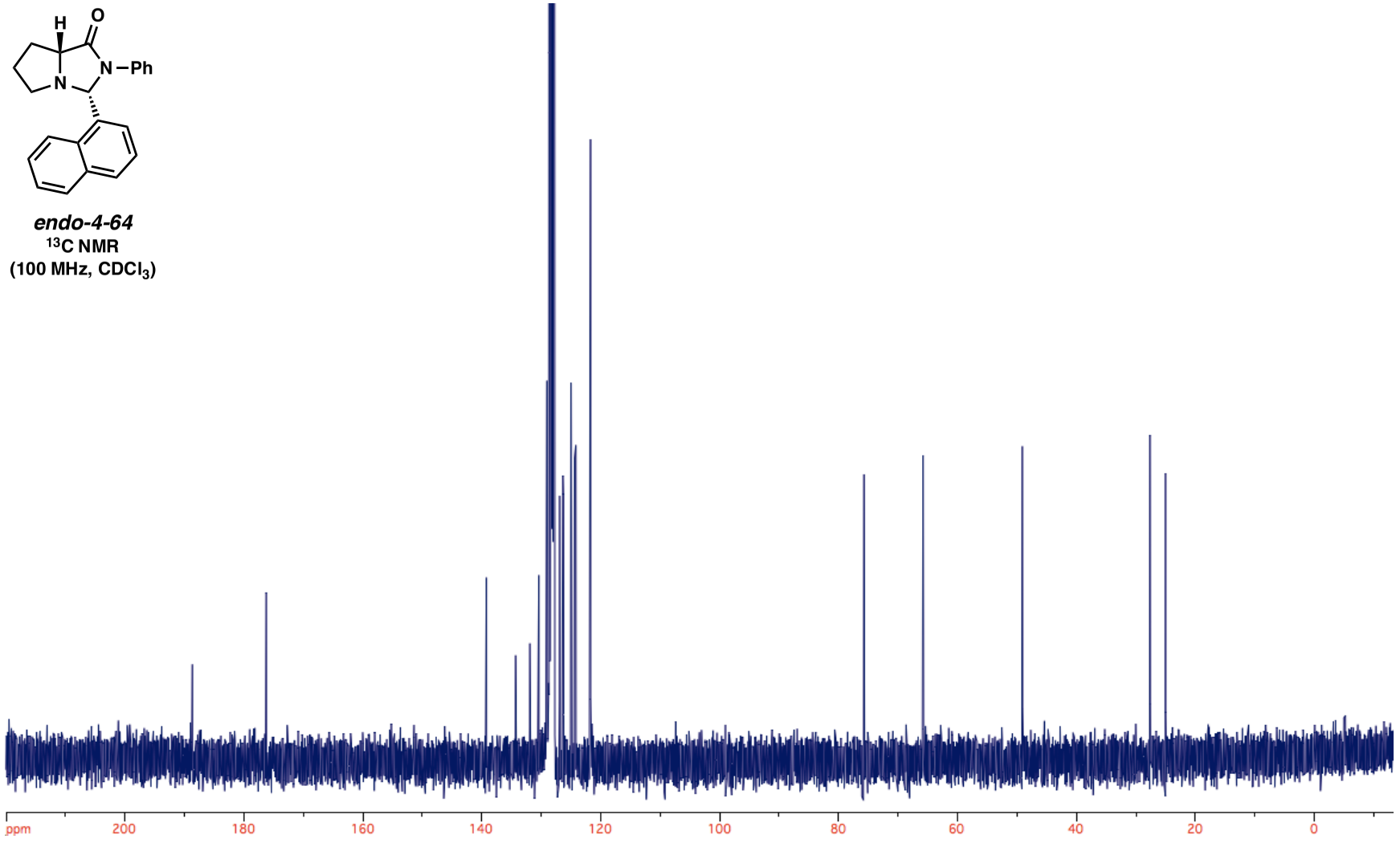




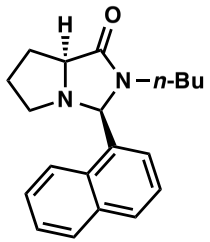
trans-93h
^{1}H NMR
(400 MHz, $CDCl_3$)



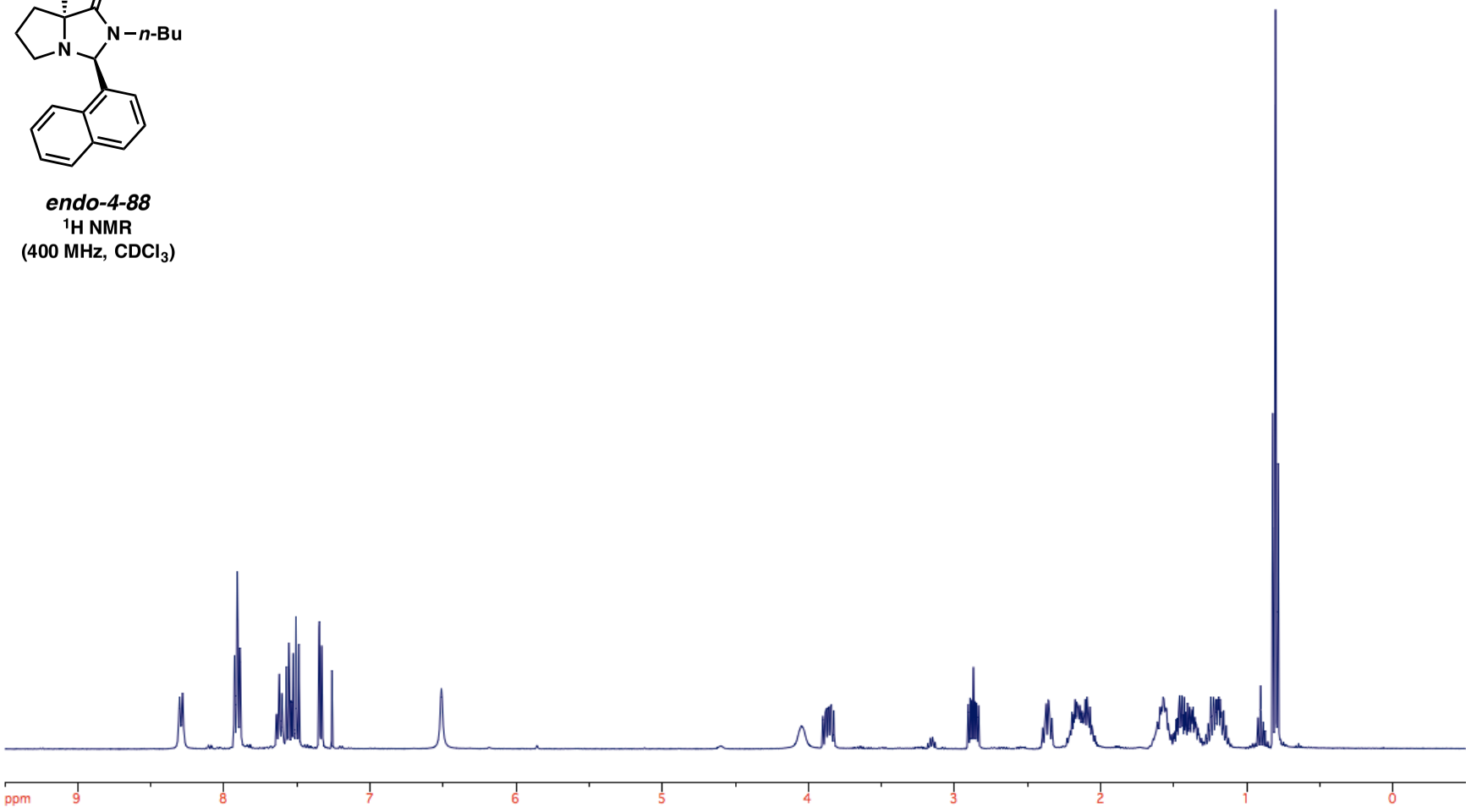
endo-4-64
^{1}H NMR
(400 MHz, $CDCl_3$)

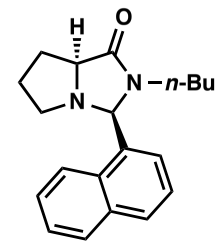


endo-4-64
^{13}C NMR
(100 MHz, $CDCl_3$)

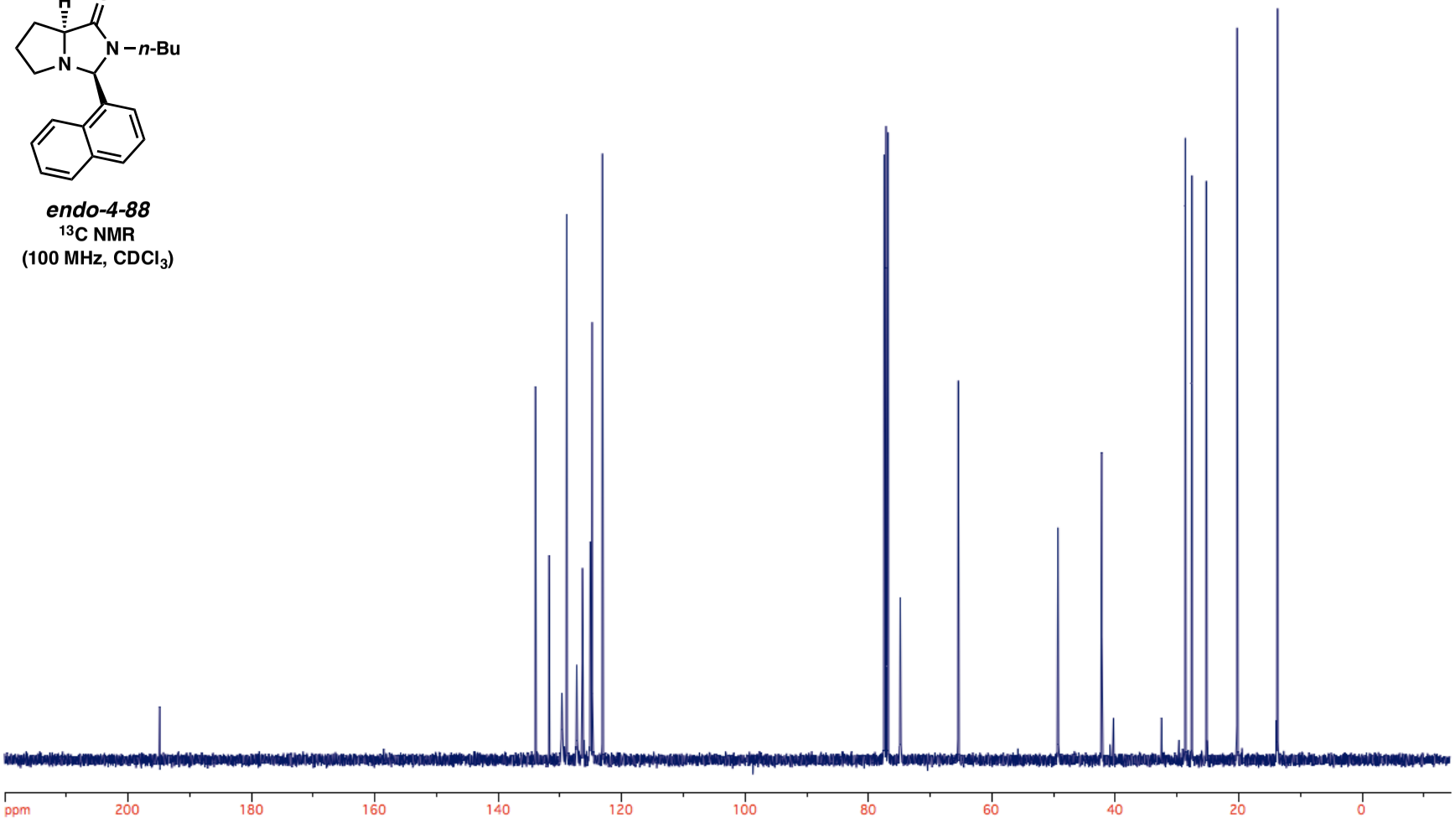


endo-4-88
^{1}H NMR
(400 MHz, $CDCl_3$)

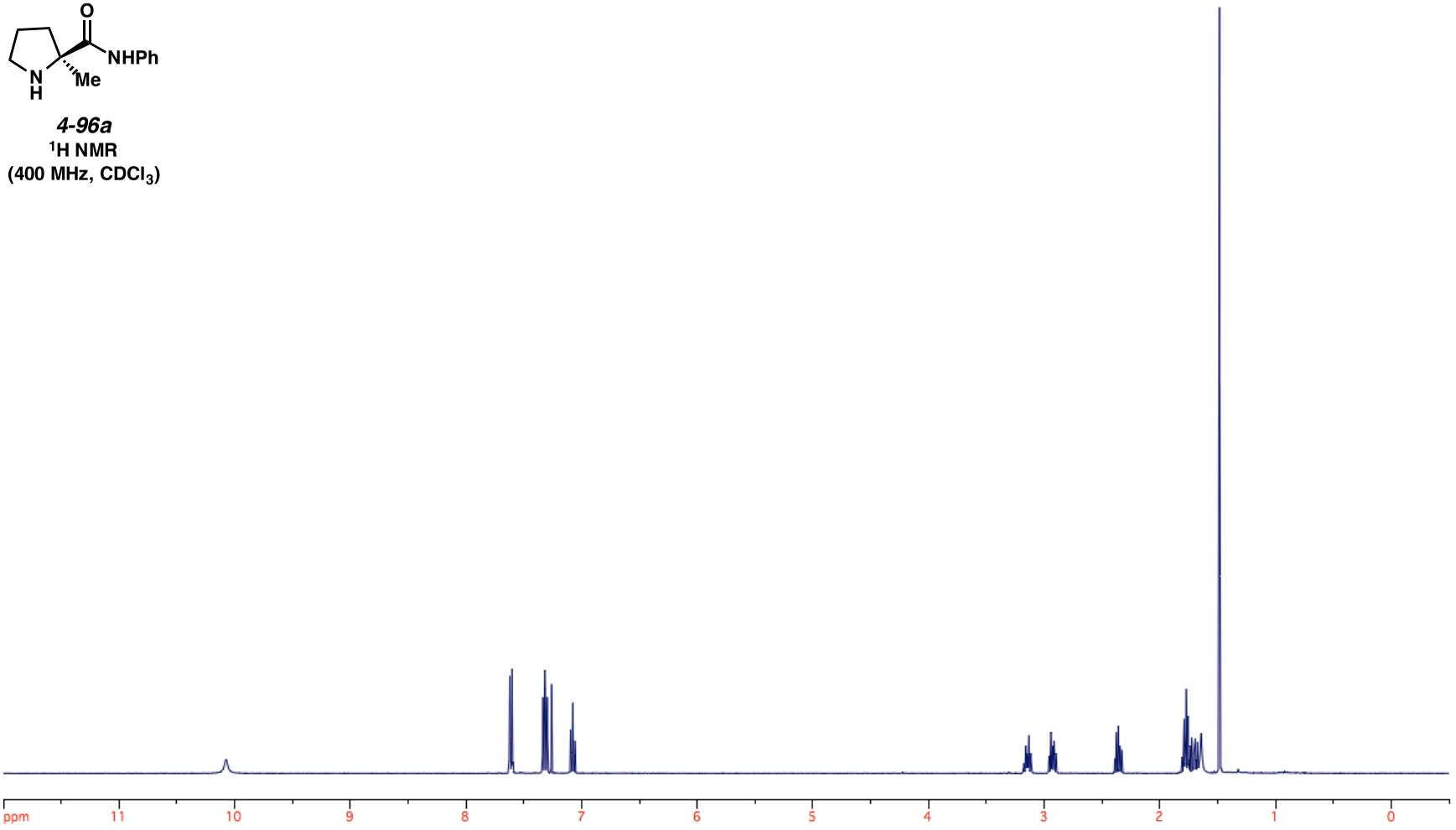


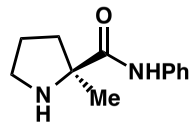


endo-4-88
^{13}C NMR
(100 MHz, $CDCl_3$)



4-96a
^{1}H NMR
(400 MHz, $CDCl_3$)

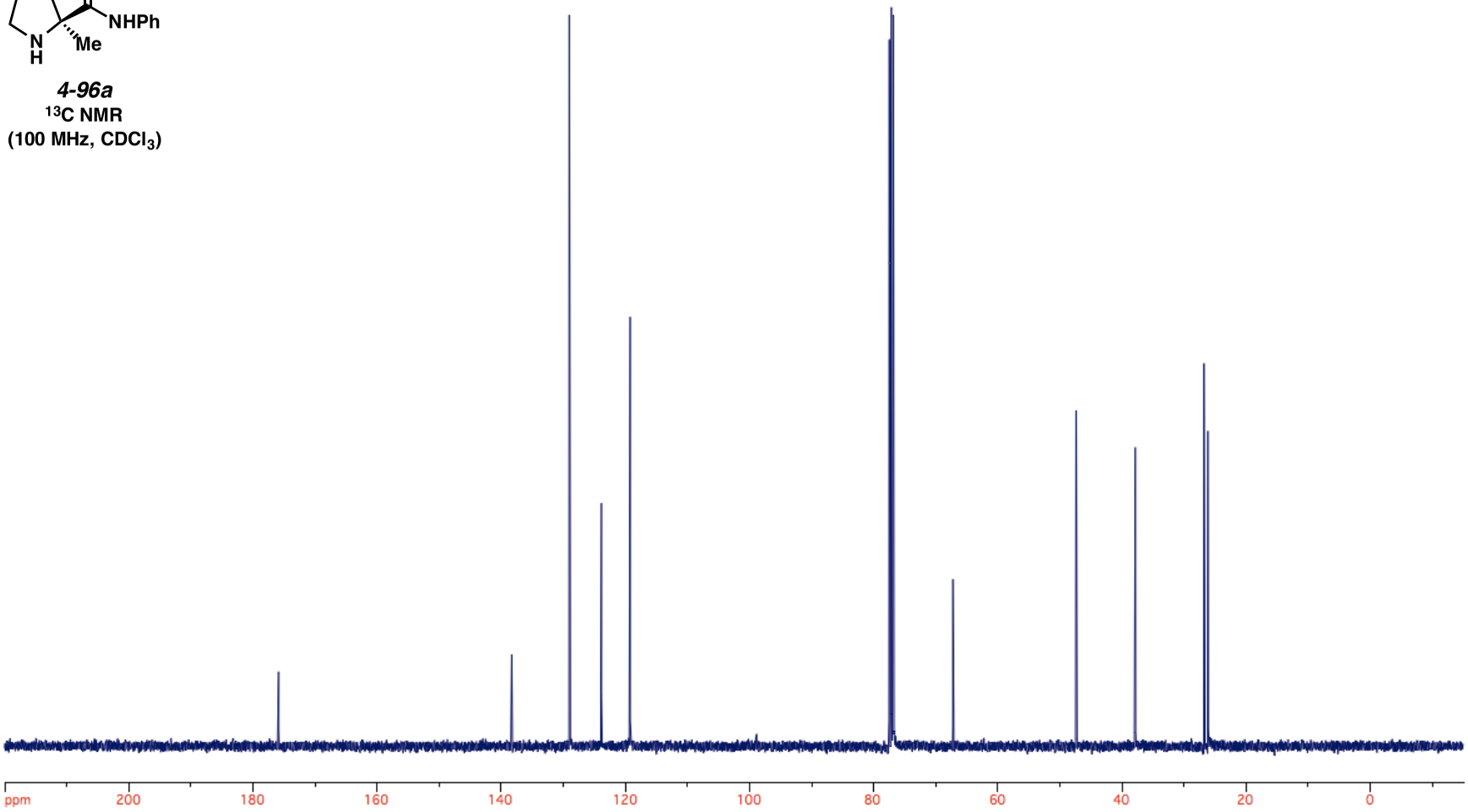


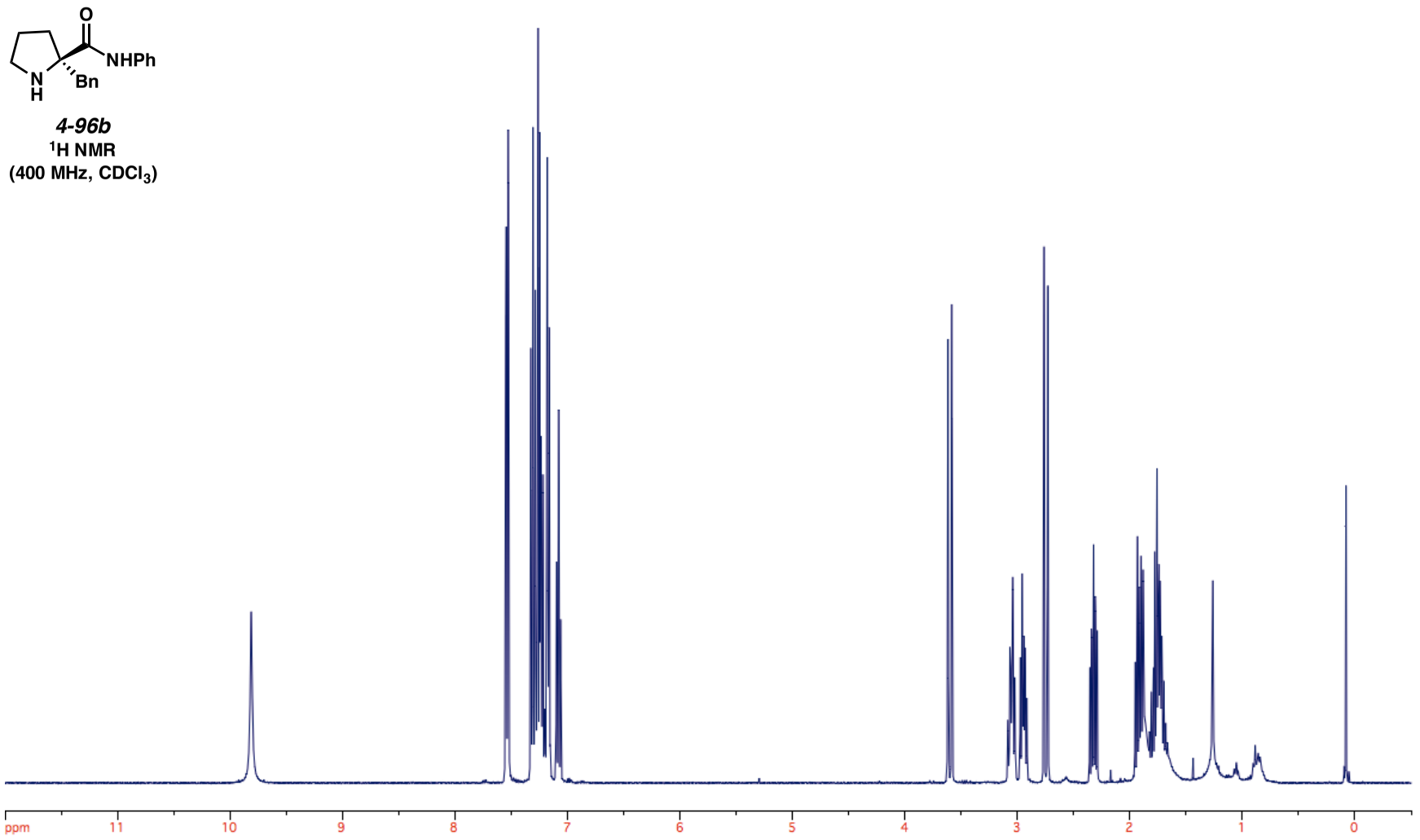


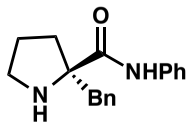
4-96a

^{13}C NMR

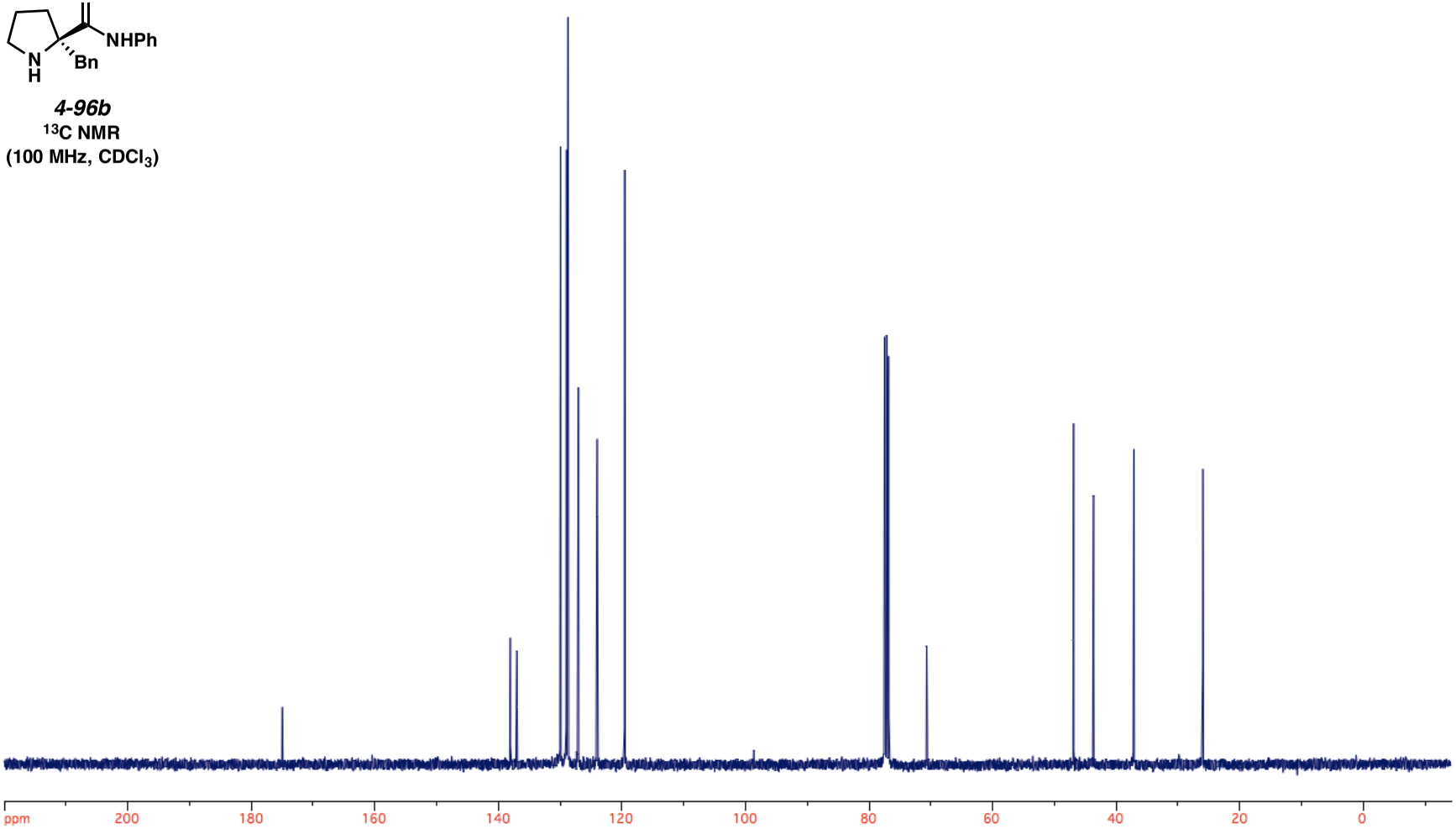
(100 MHz, $CDCl_3$)

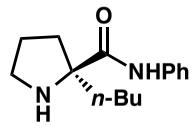



O
NHPh
N
H
Bn
4-96b
1H NMR
(400 MHz, CDCl3)
ppm
11
10
9
8
7
6
5
4
3
2
1
0

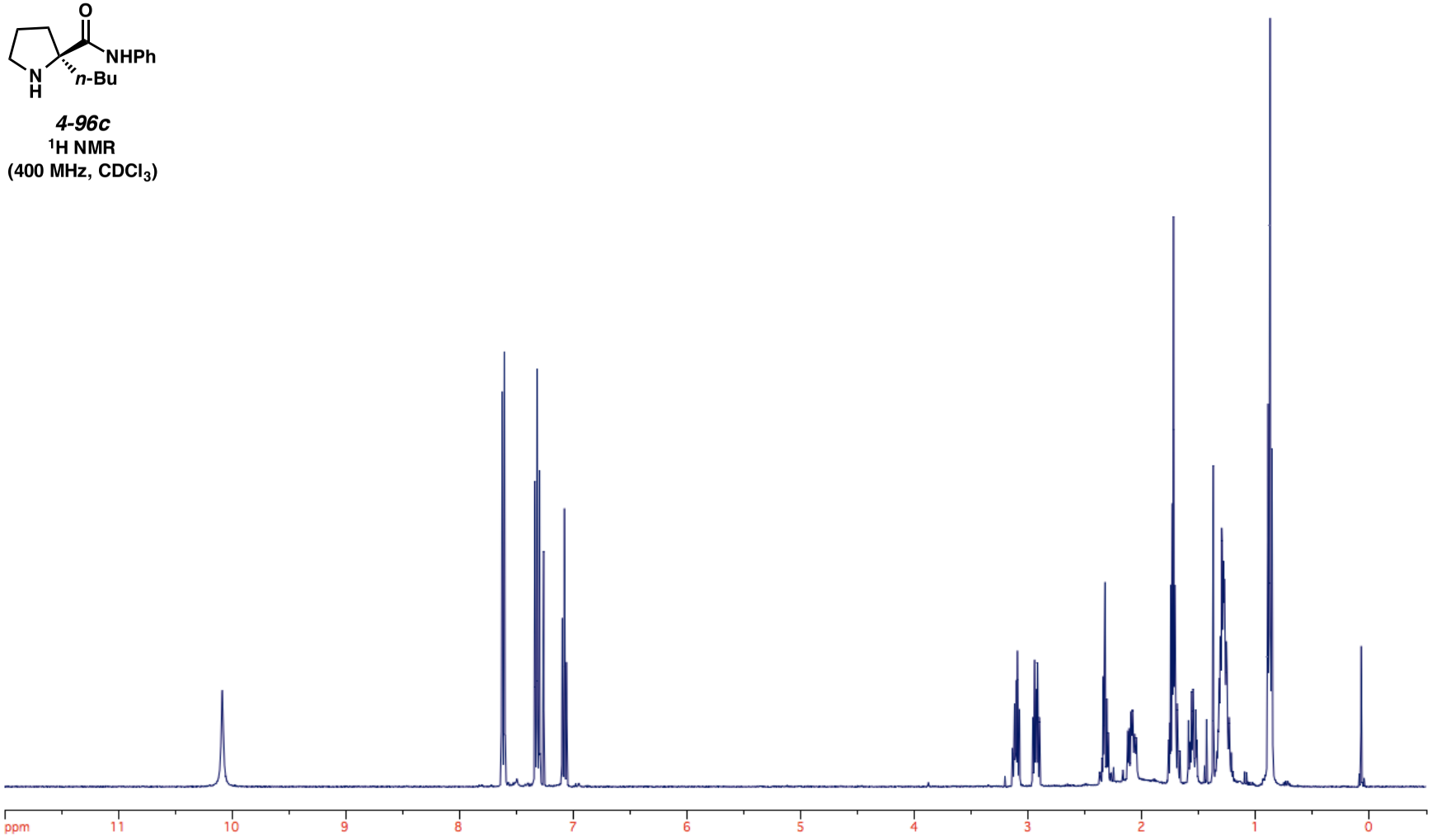


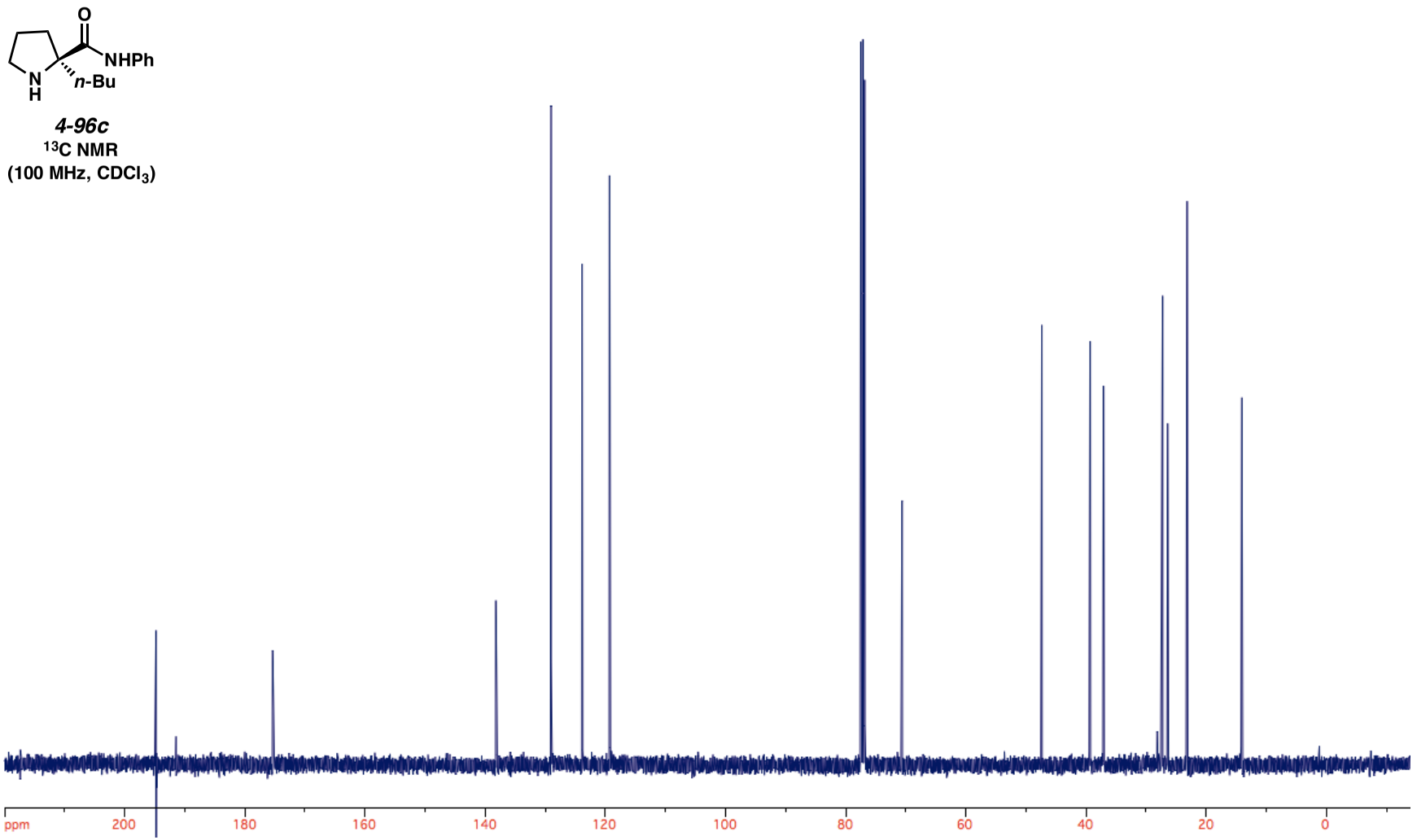
4-96b
^{13}C NMR
(100 MHz, $CDCl_3$)



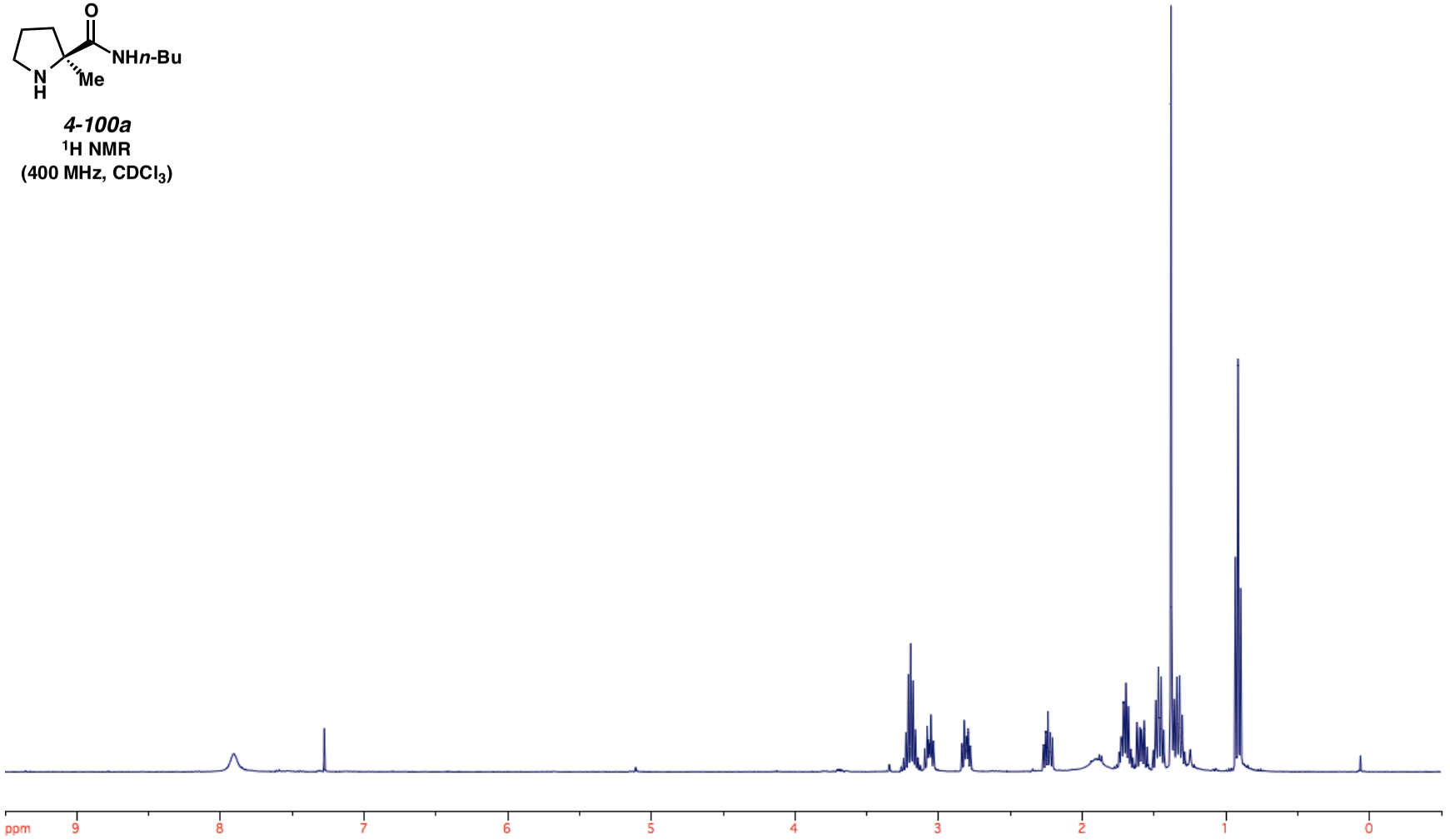


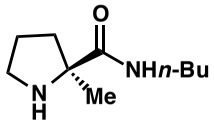
4-96c
^{1}H NMR
(400 MHz, $CDCl_3$)




O
NHPh
N
H
n-Bu
4-96c
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

4-100a
^{1}H NMR
(400 MHz, $CDCl_3$)

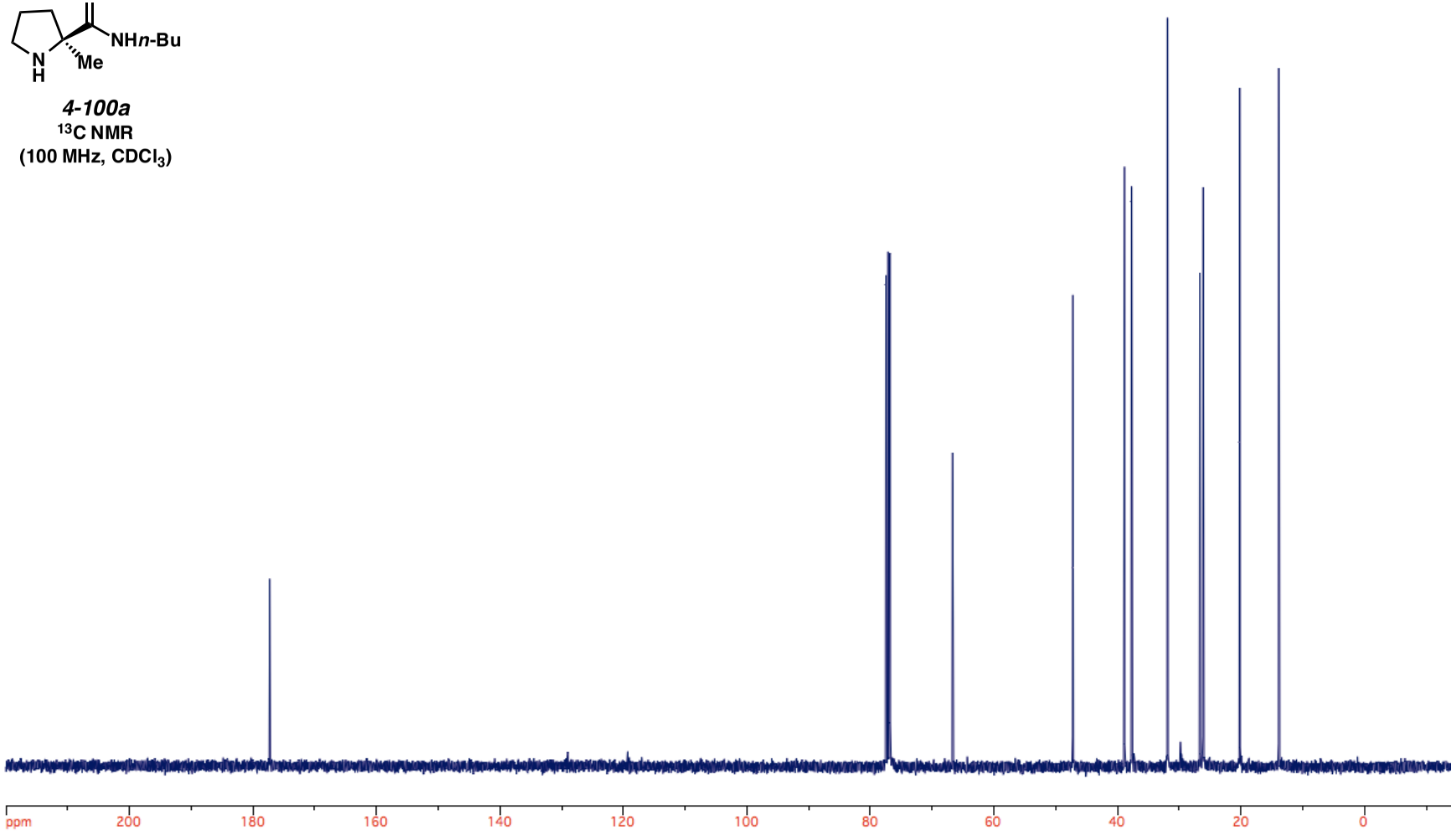


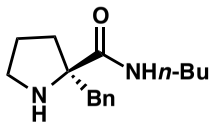


4-100a

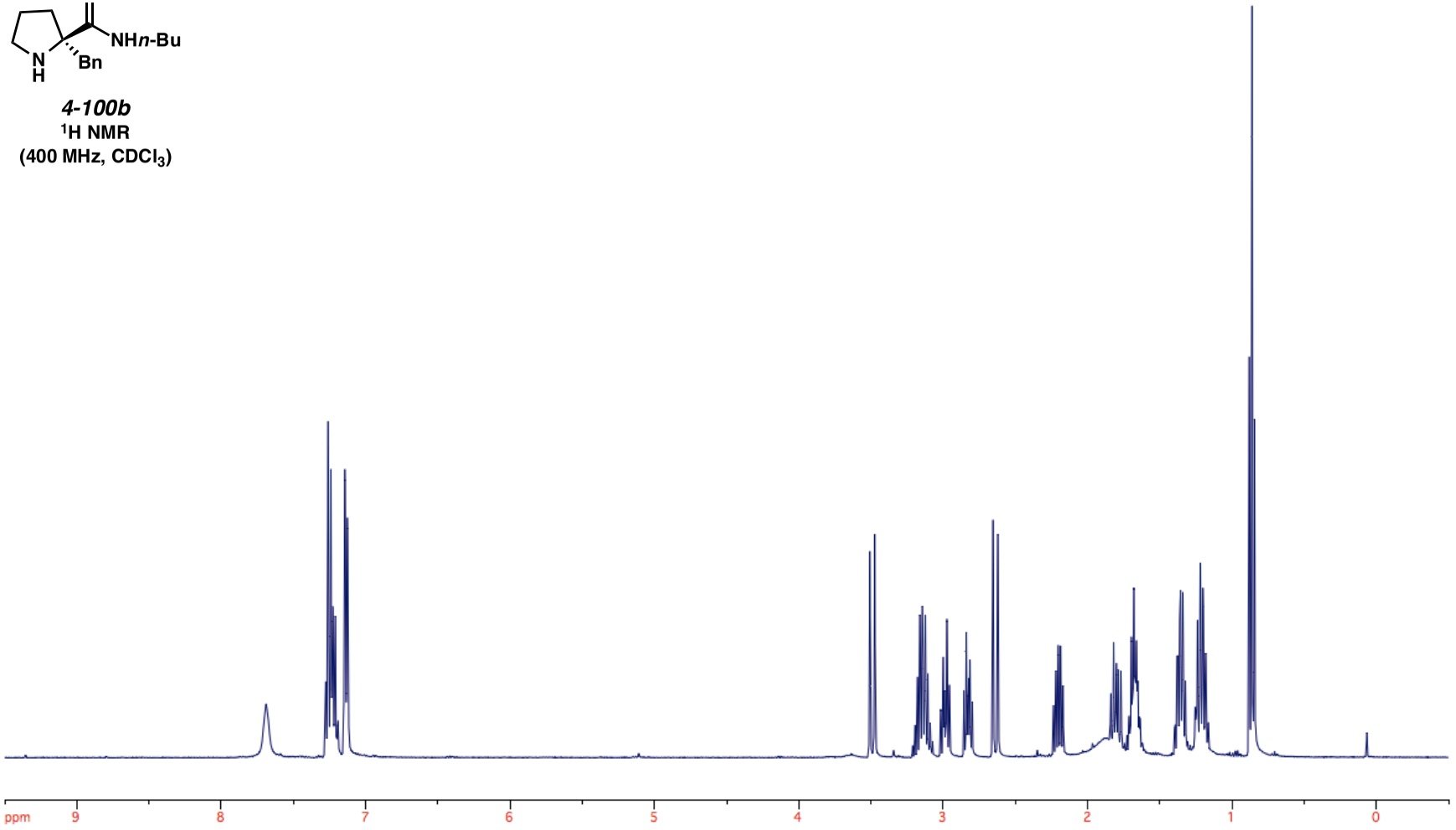
^{13}C NMR

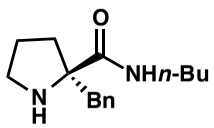
(100 MHz, $CDCl_3$)



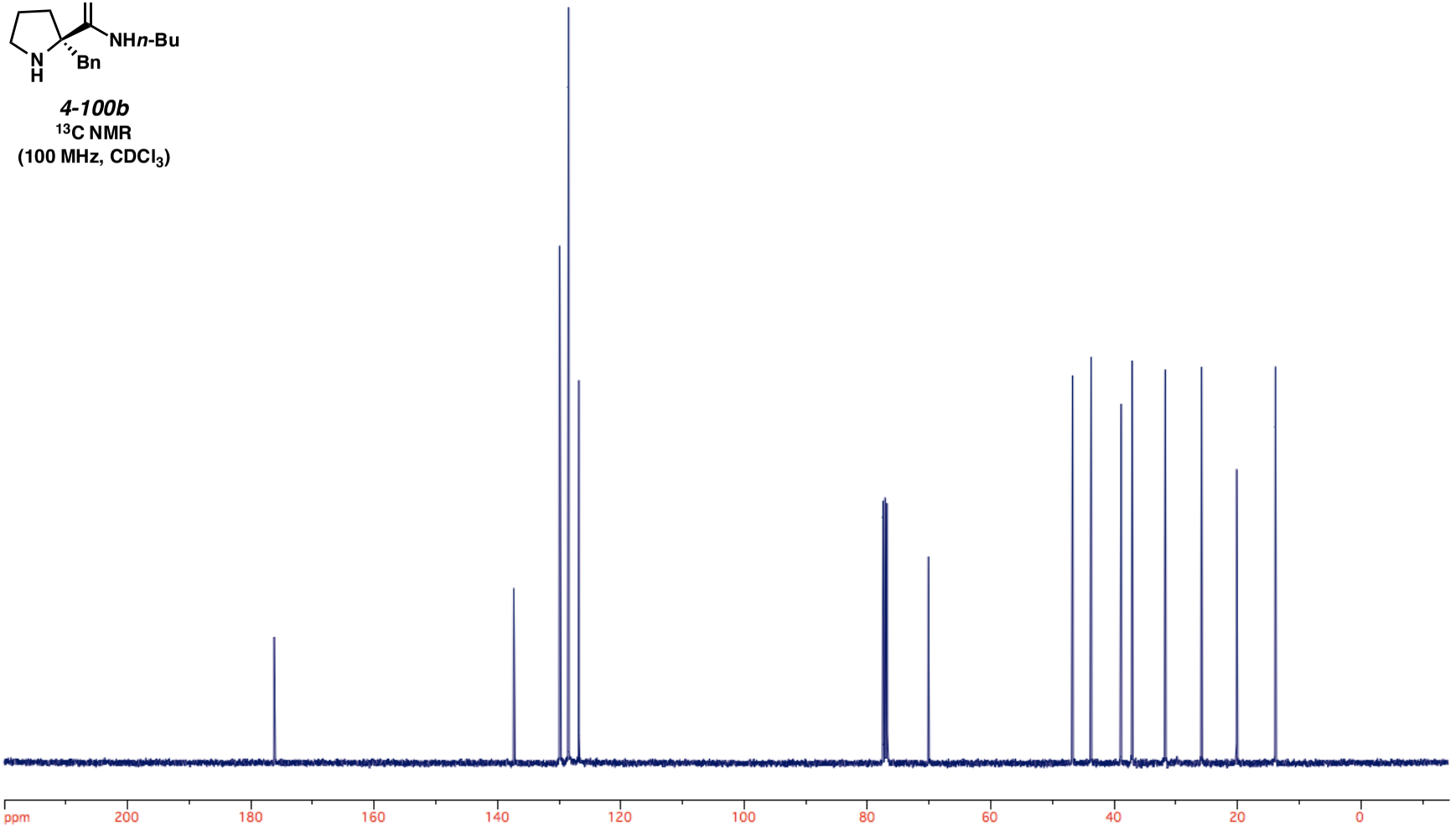


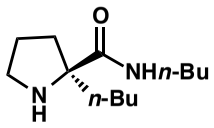
4-100b
^{1}H NMR
(400 MHz, $CDCl_3$)



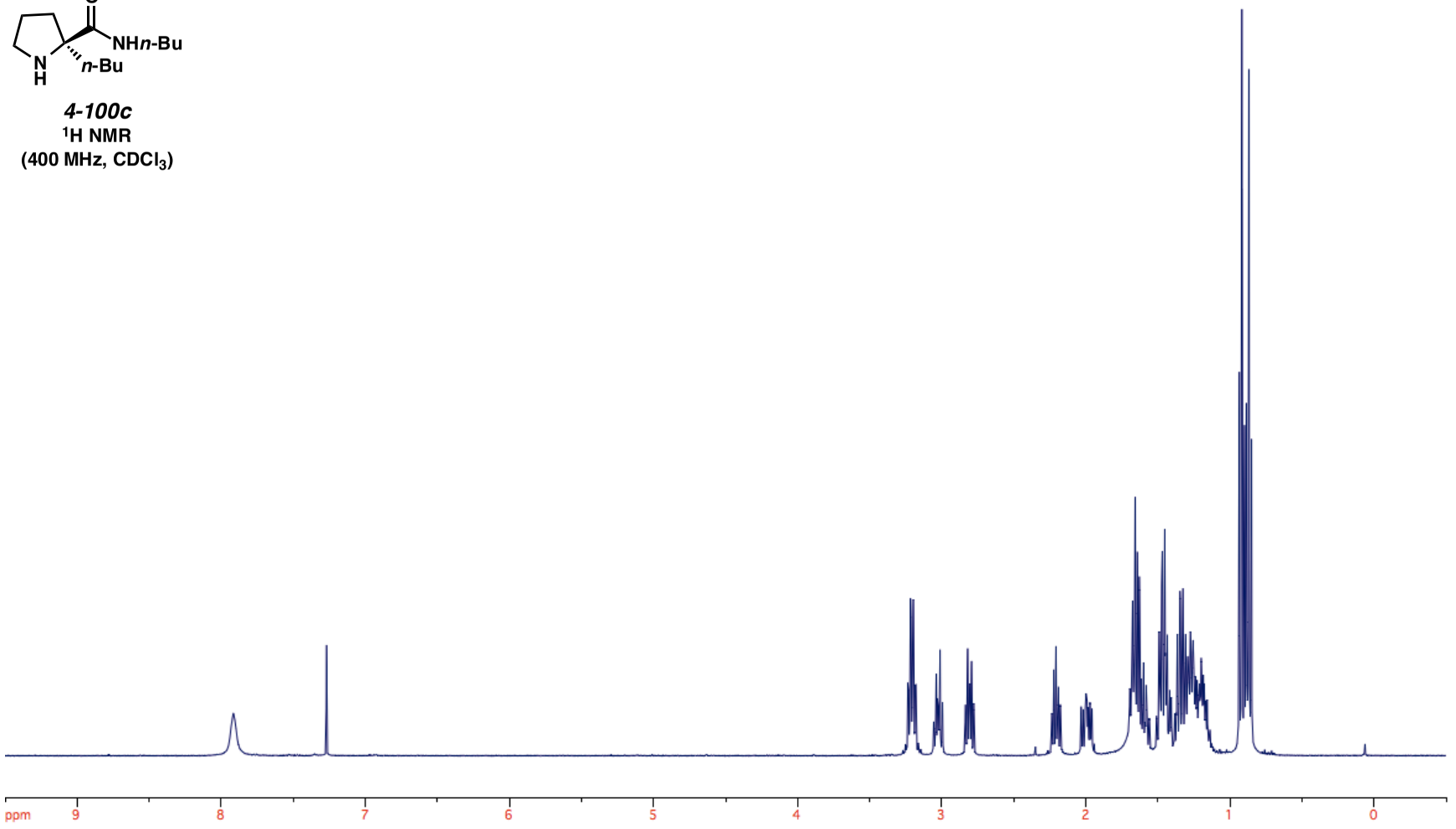


4-100b
^{13}C NMR
(100 MHz, $CDCl_3$)

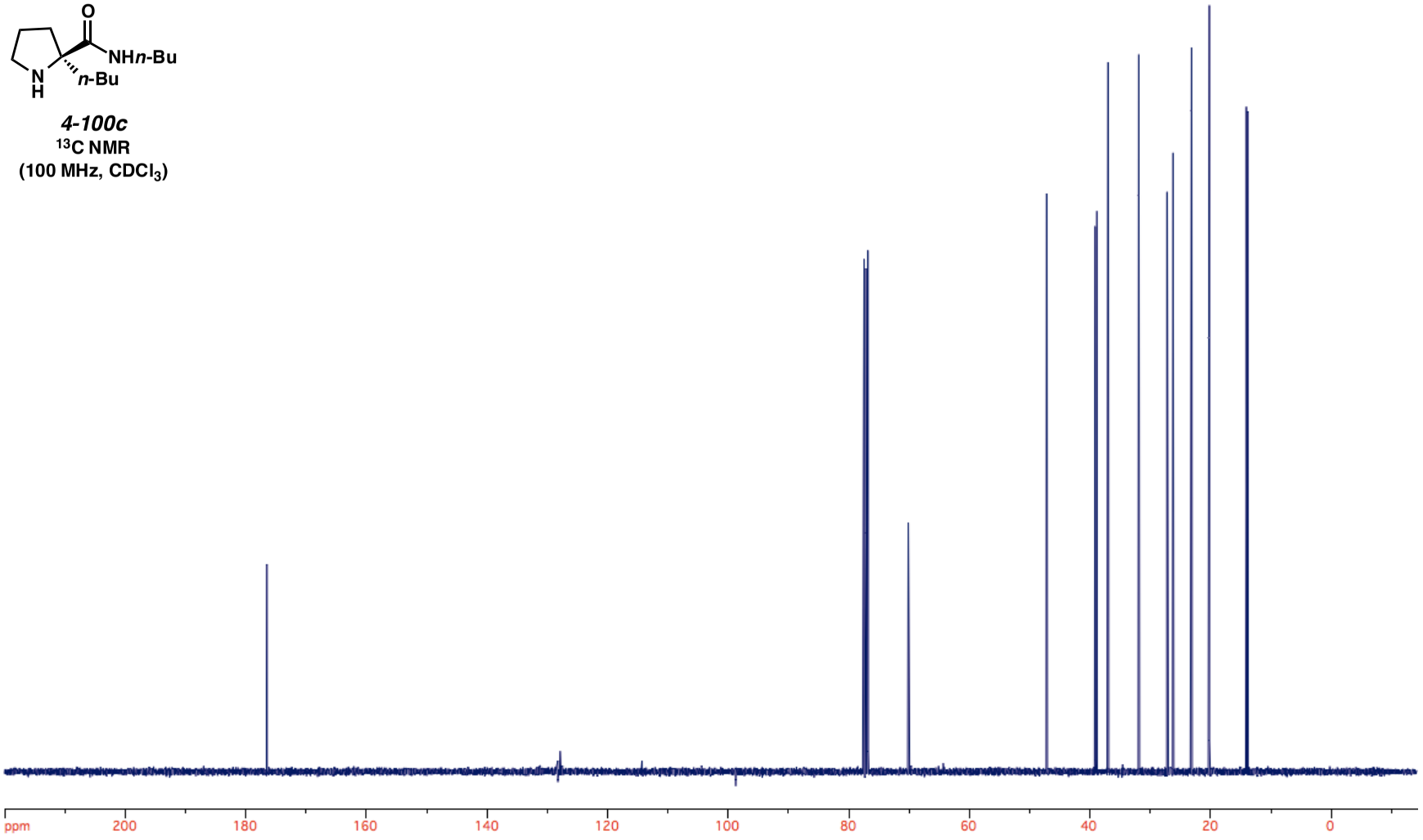


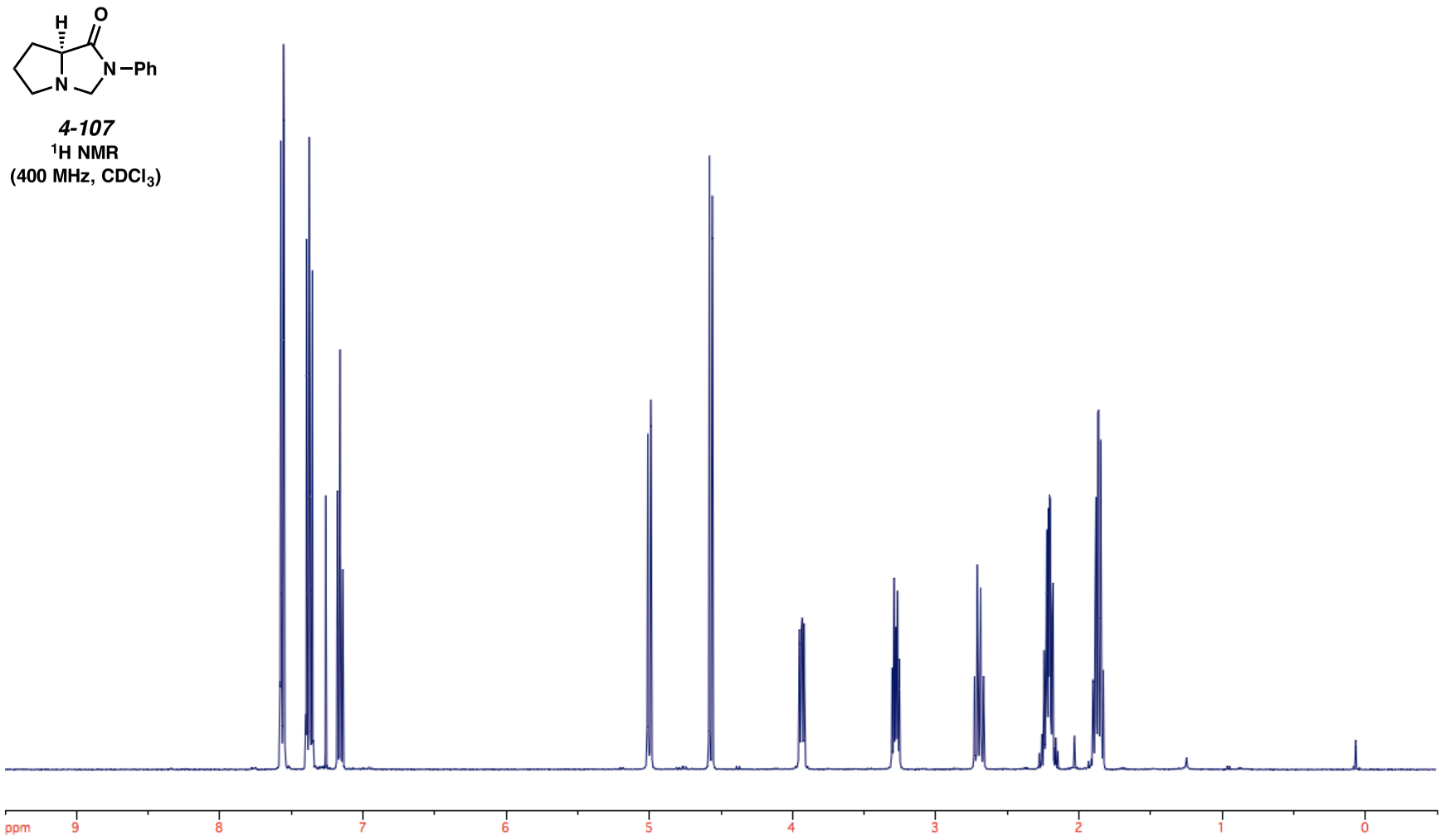


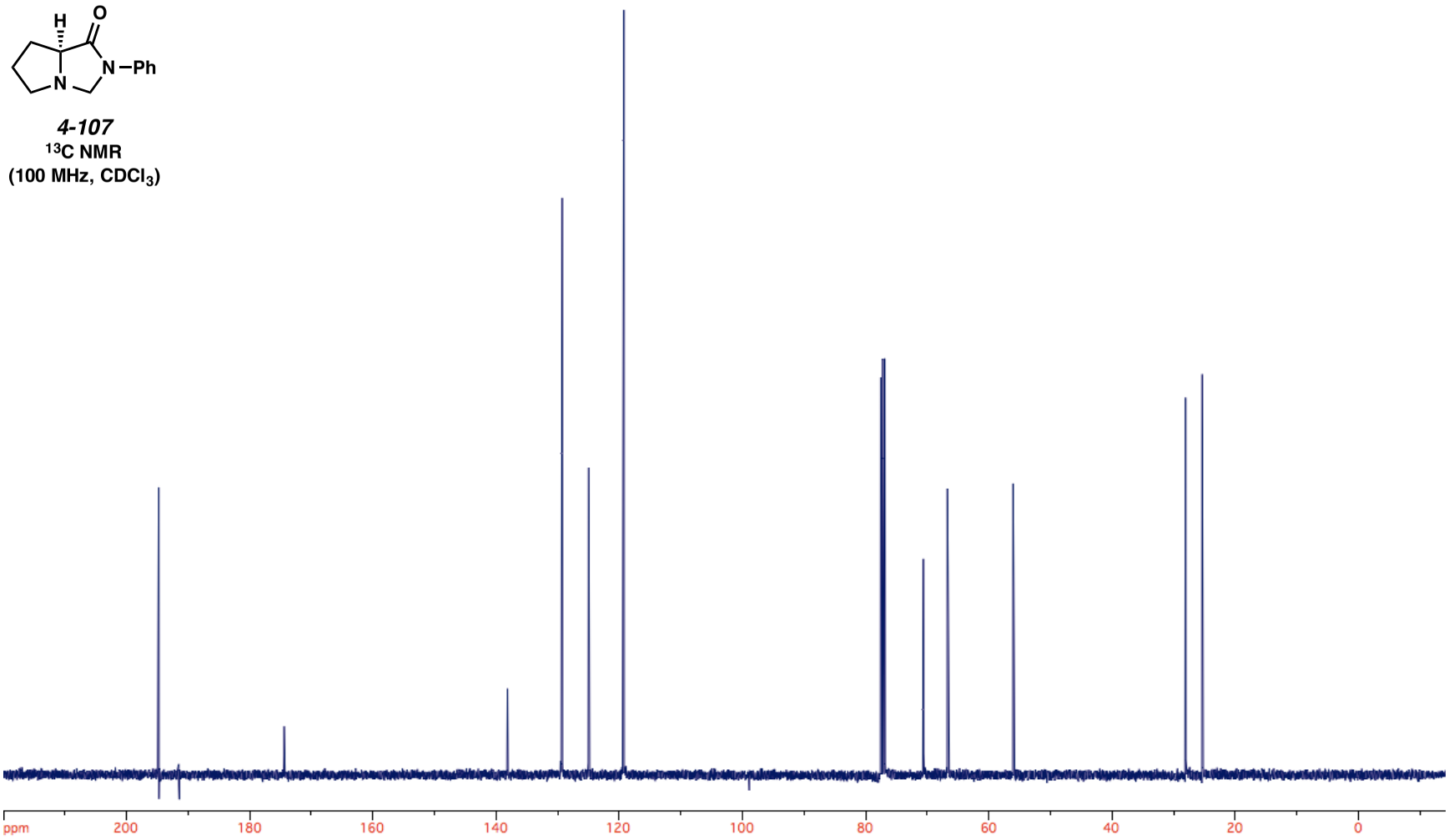
4-100c
^{1}H NMR
(400 MHz, $CDCl_3$)



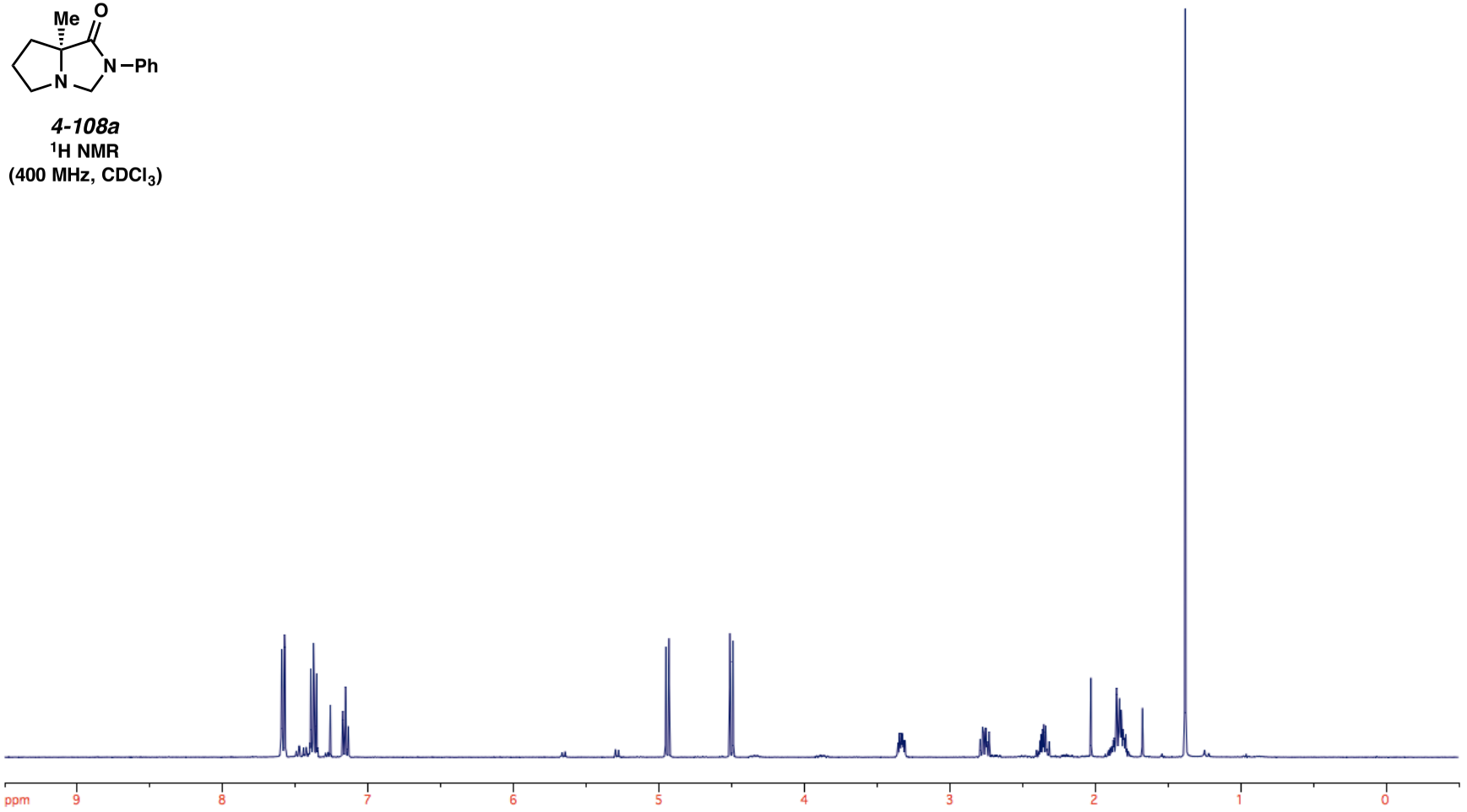
4-100c
^{13}C NMR
(100 MHz, $CDCl_3$)

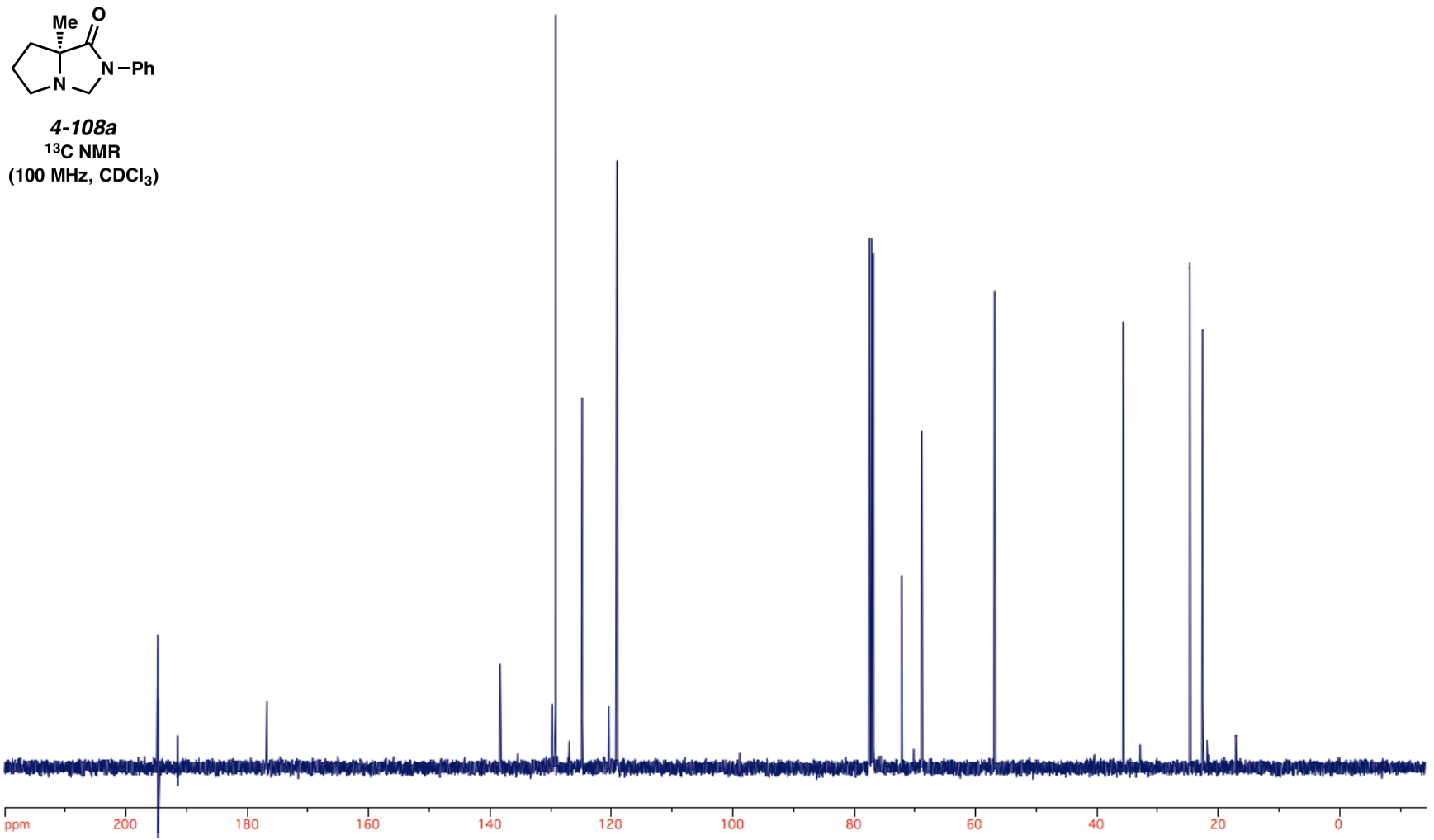


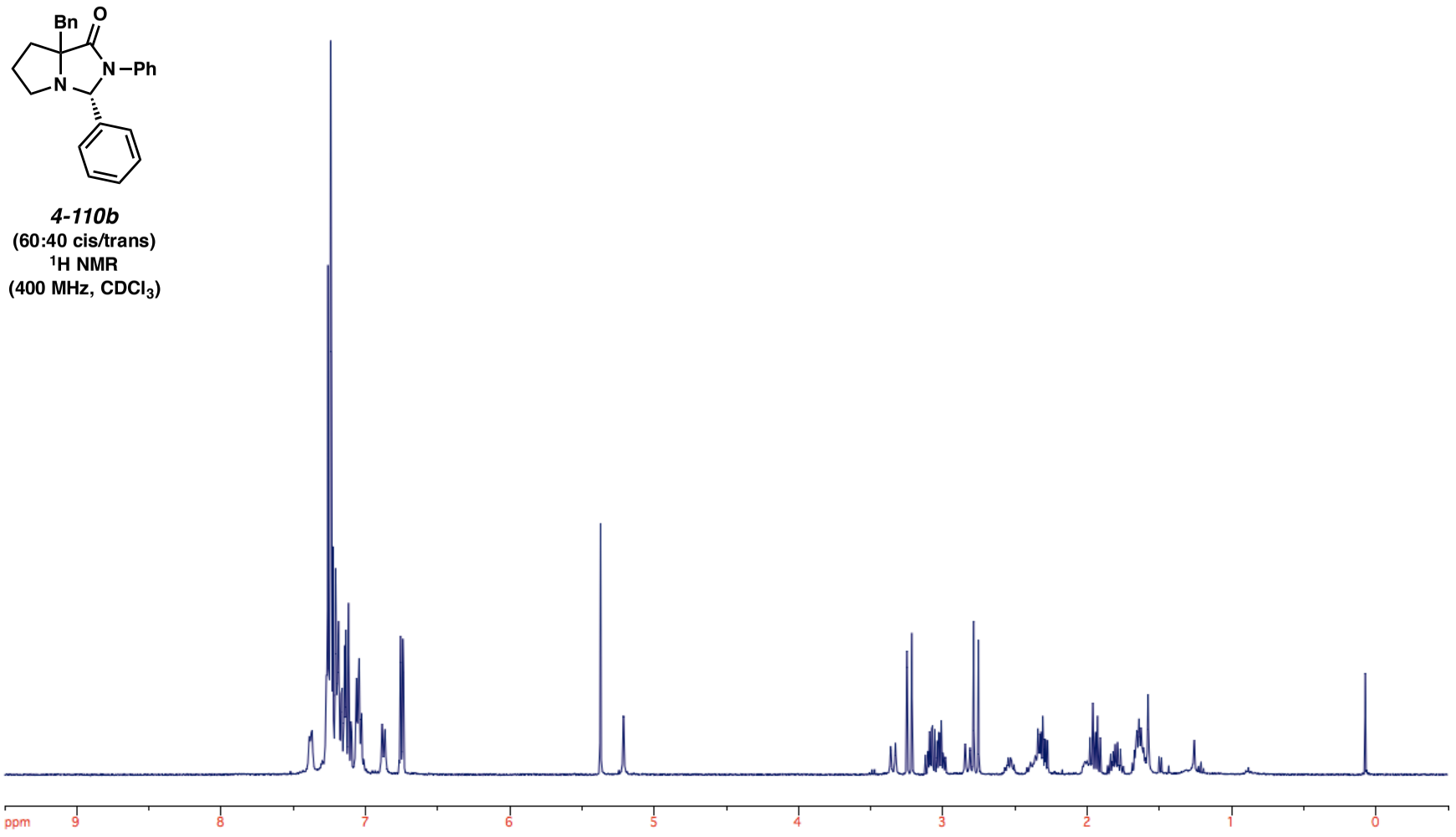

H
O
N
N–Ph
4-107
1H NMR
(400 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1
0


H
O
N
N–Ph
4-107
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

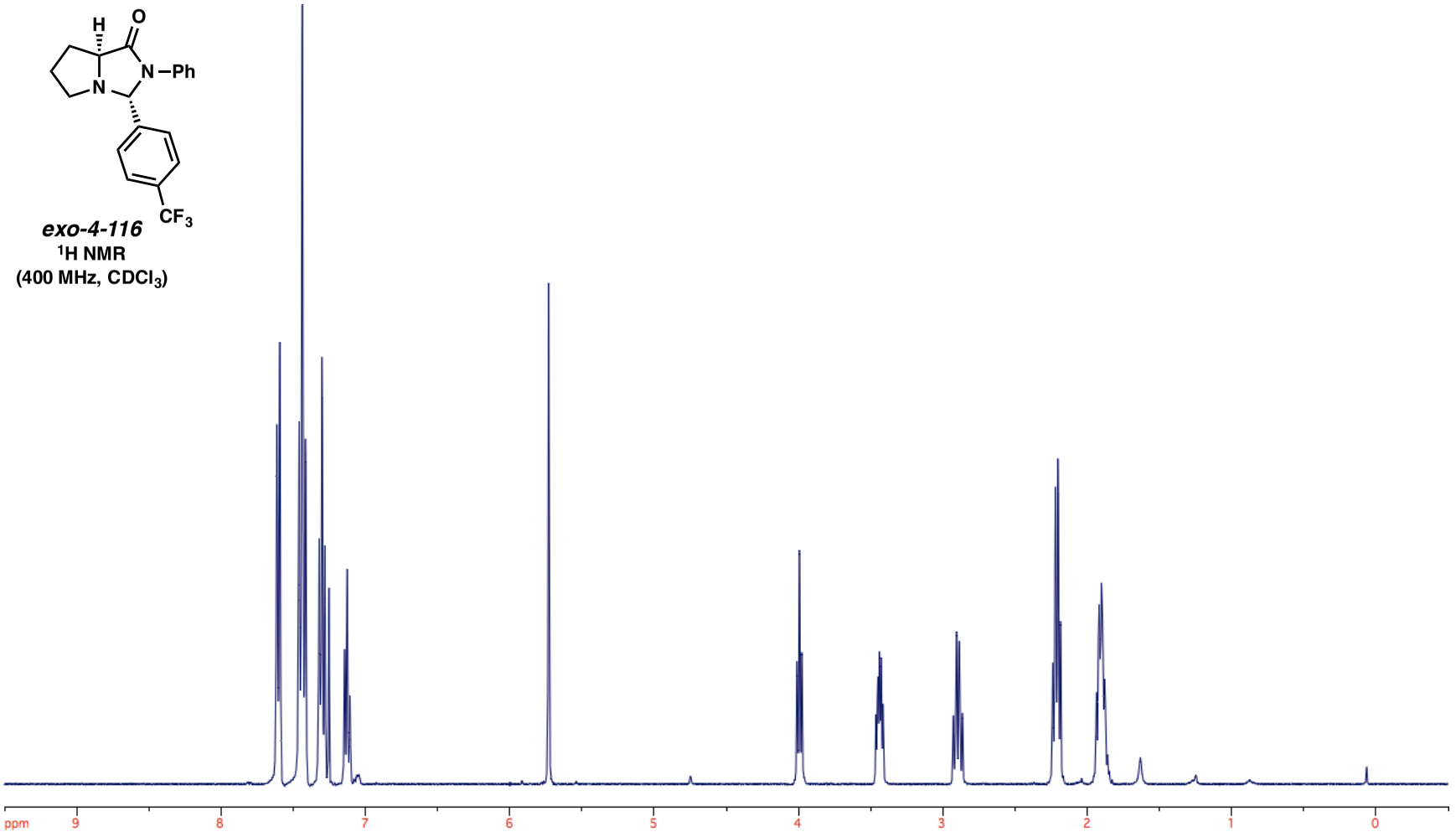
4-108a
^{1}H NMR
(400 MHz, $CDCl_3$)




Me
O
N
N–Ph
4-108a
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0



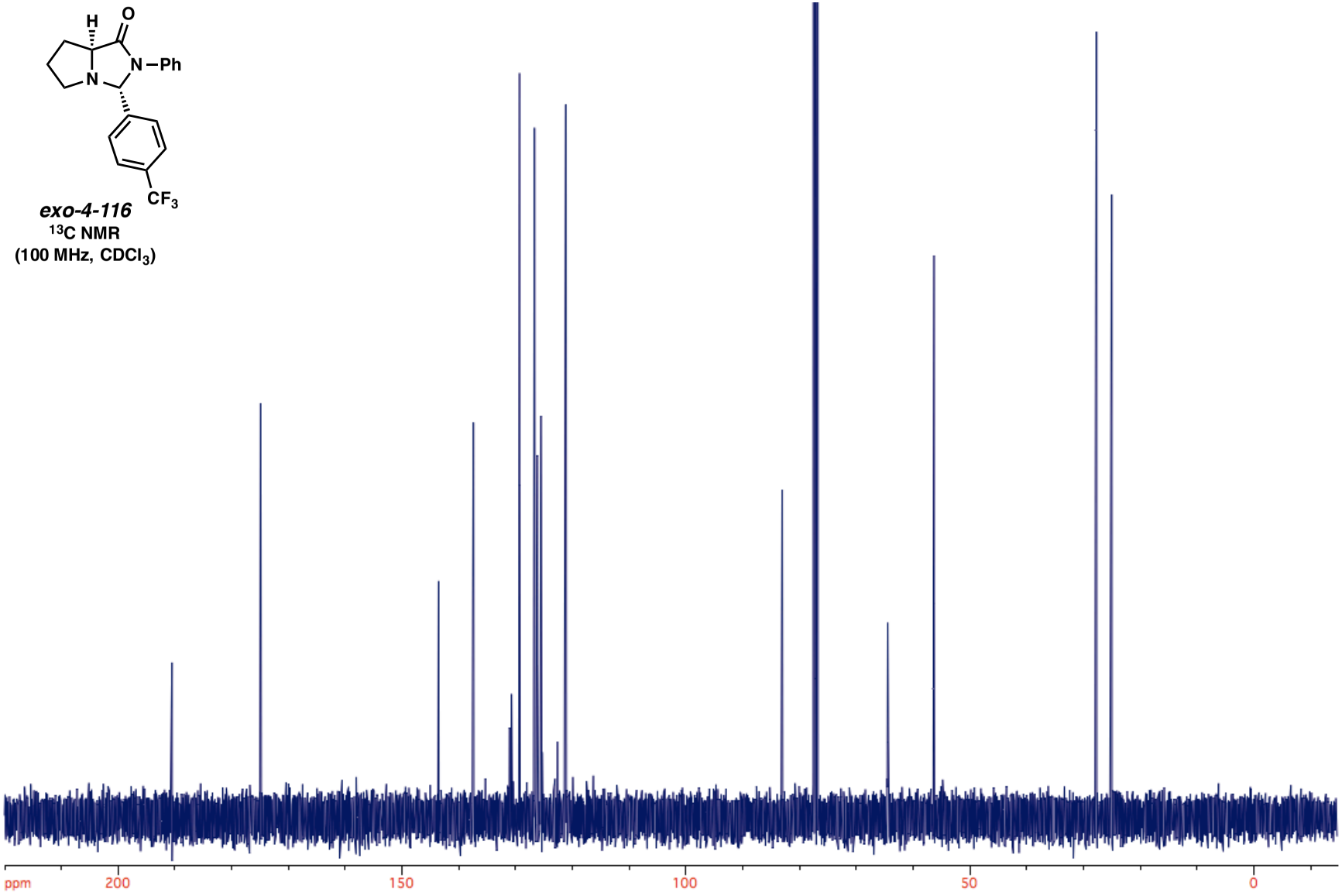
4-110b
(60:40 cis/trans)
^{1}H NMR
(400 MHz, $CDCl_3$)



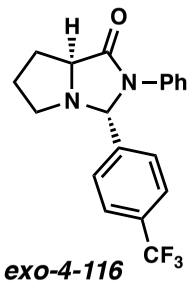
exo-4-116

^{1}H NMR

(400 MHz, $CDCl_3$)



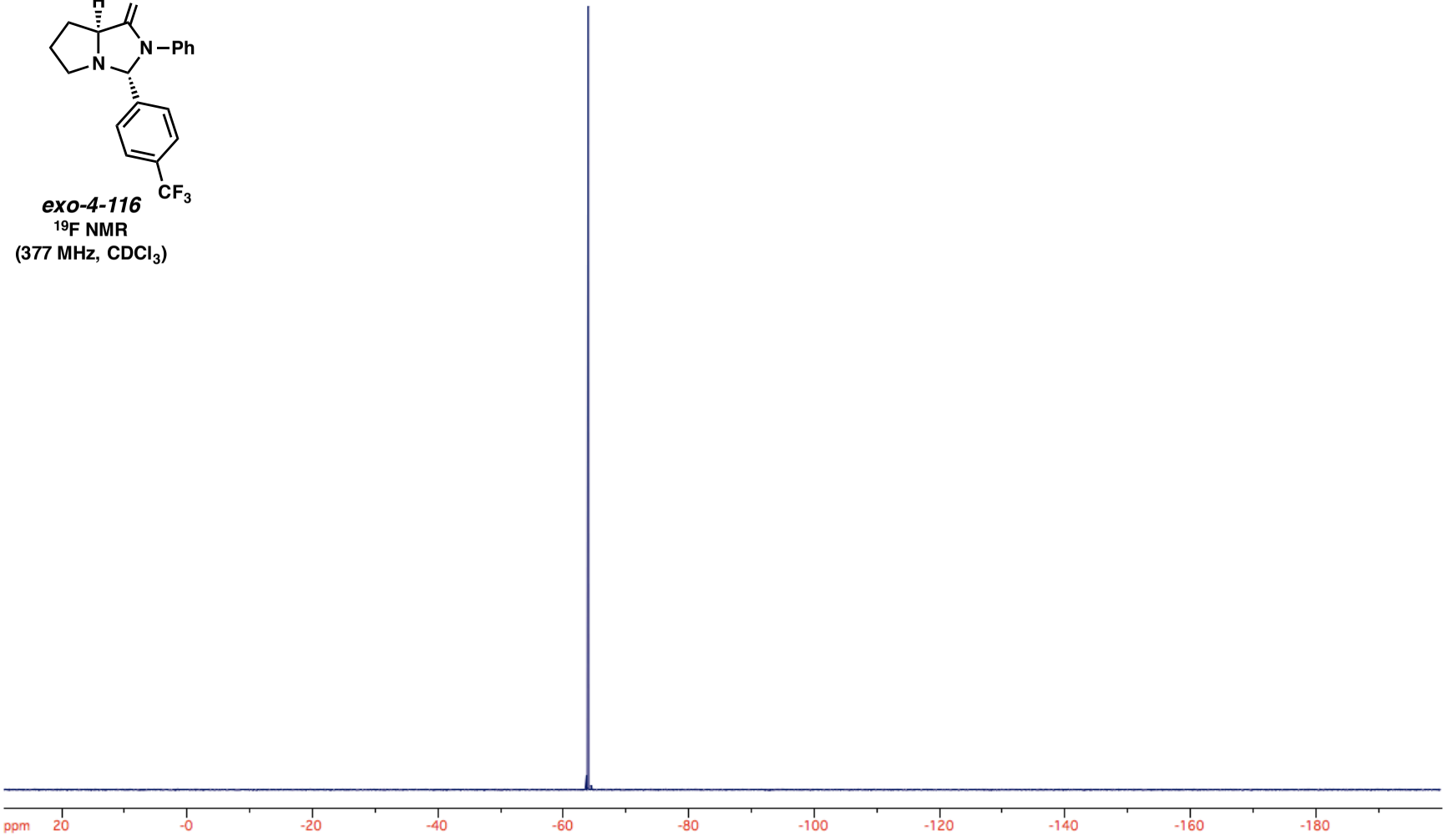
exo-4-116
^{13}C NMR
(100 MHz, $CDCl_3$)

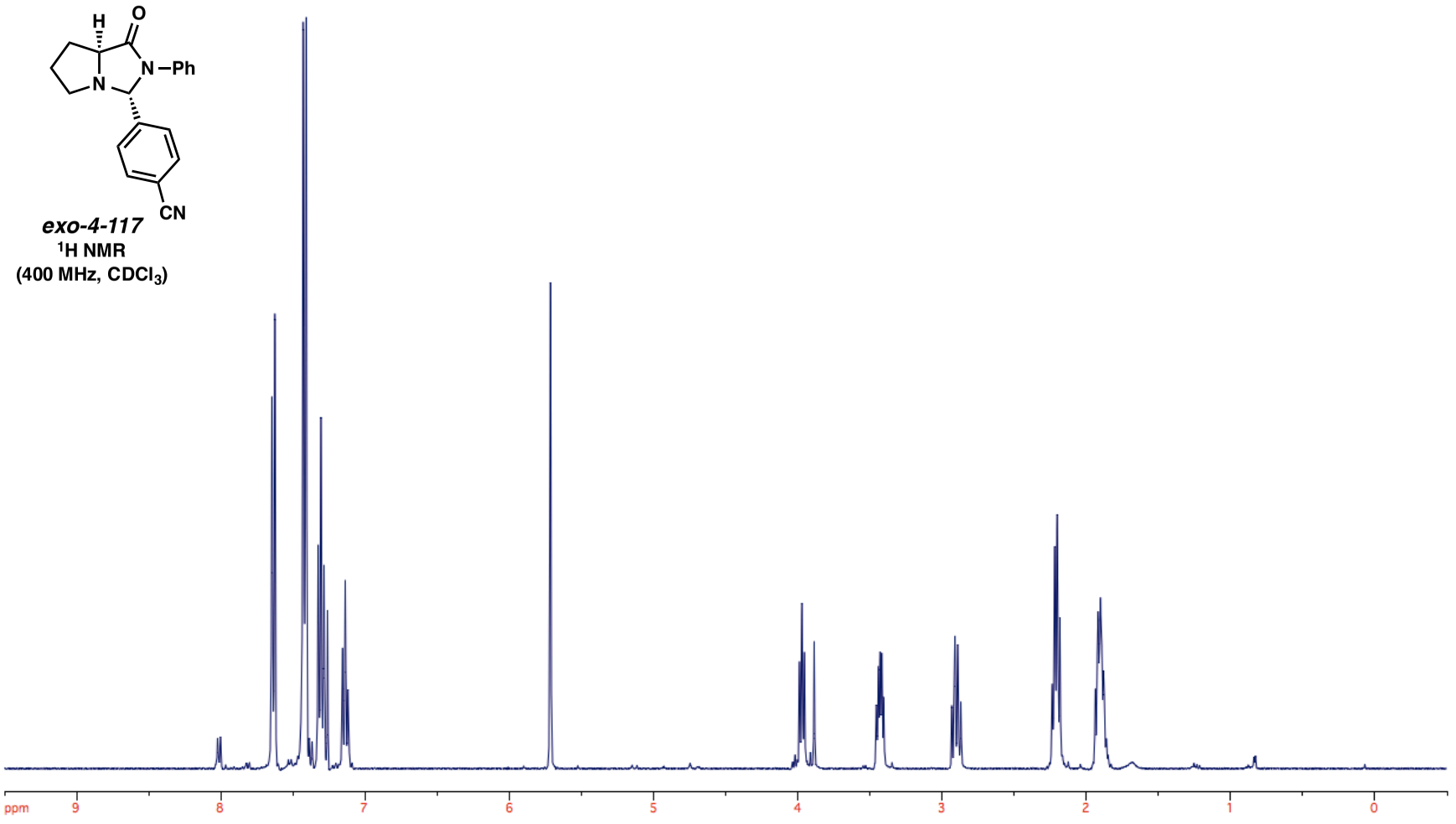


exo-4-116

^{19}F NMR

(377 MHz, $CDCl_3$)

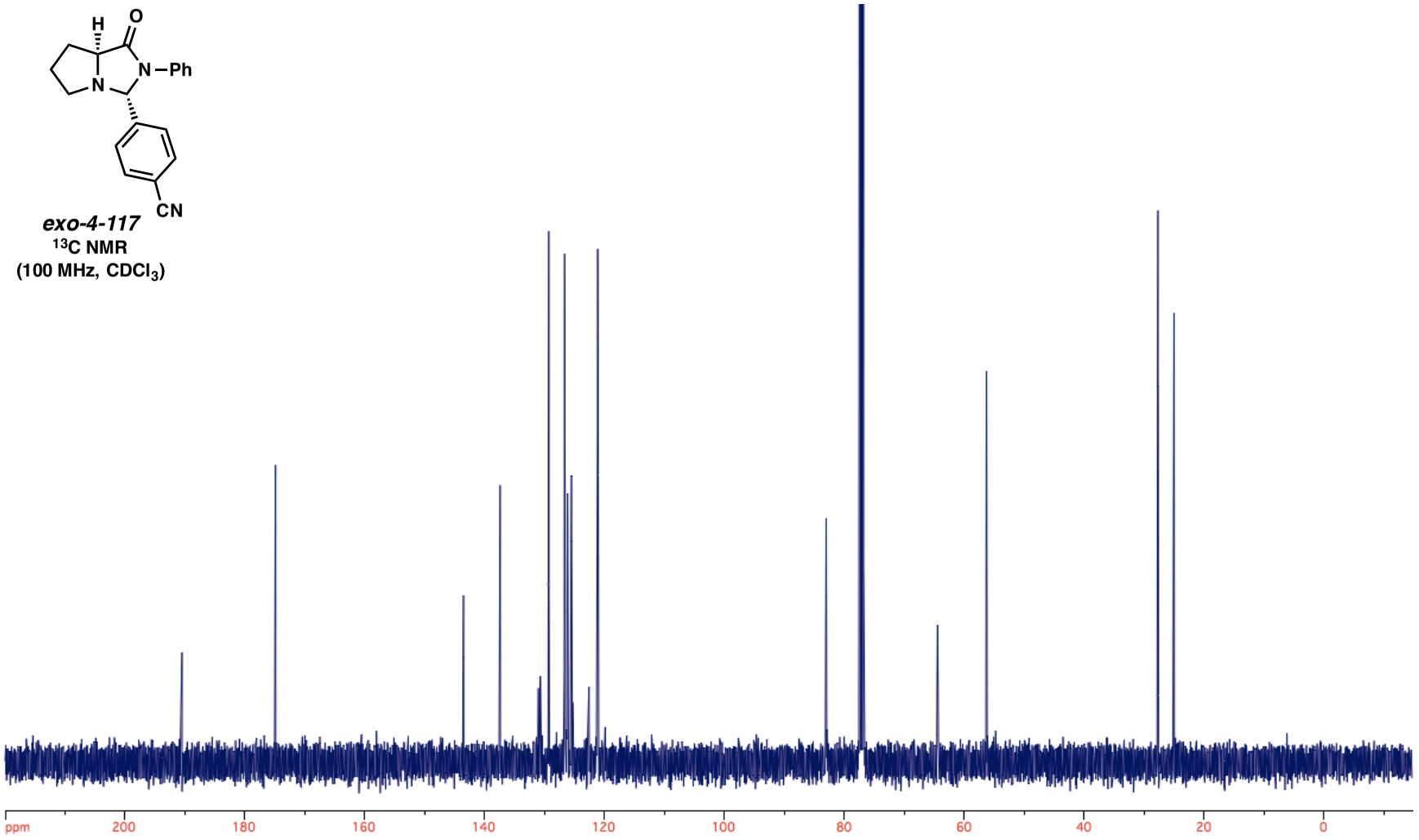




exo-4-117

^{1}H NMR

(400 MHz, $CDCl_3$)



exo-4-117

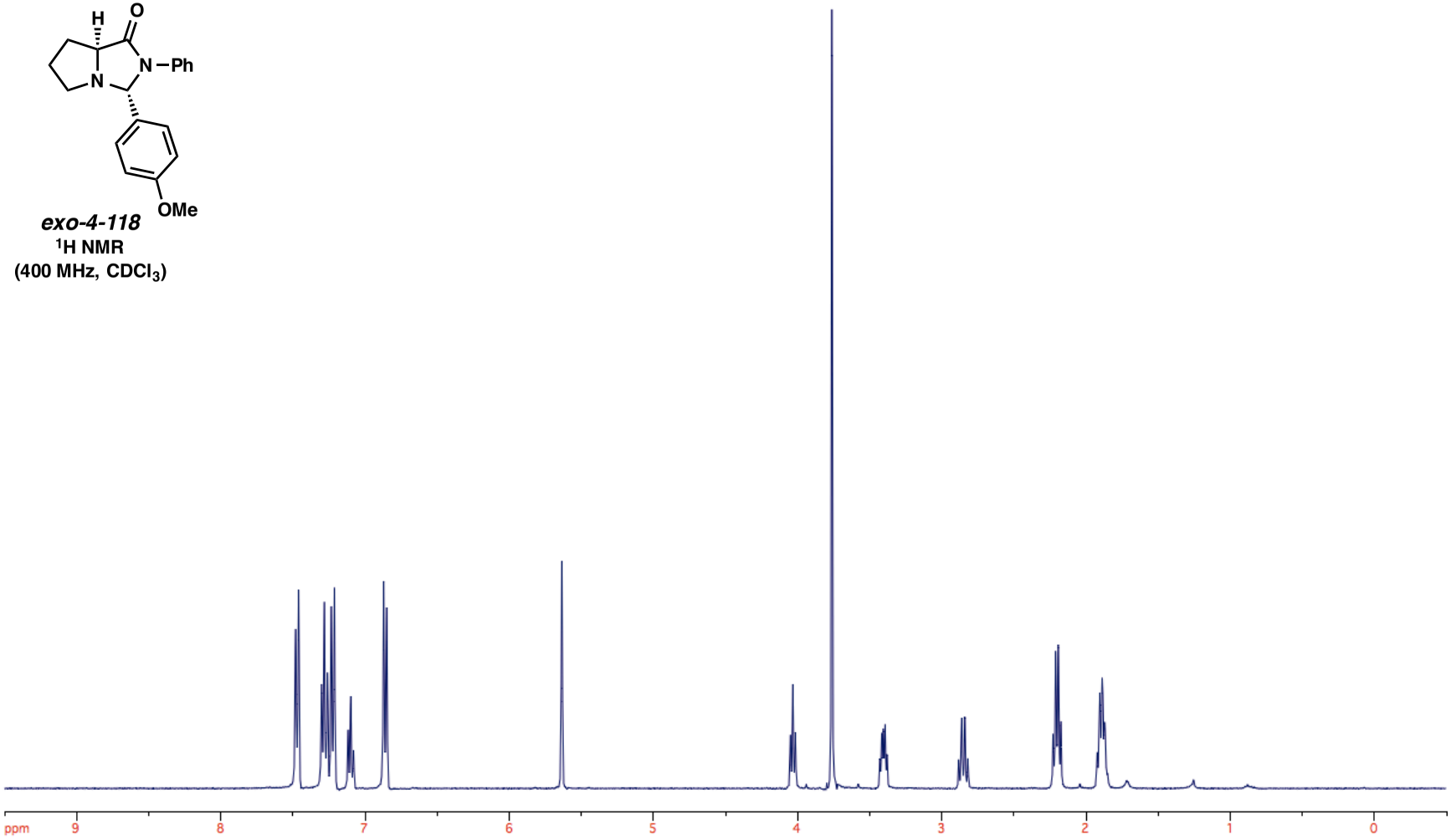
^{13}C NMR

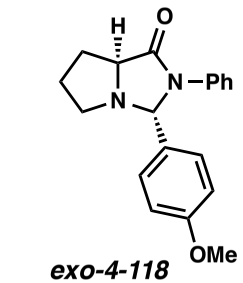
(100 MHz, $CDCl_3$)

exo-4-118

^{1}H NMR

(400 MHz, $CDCl_3$)

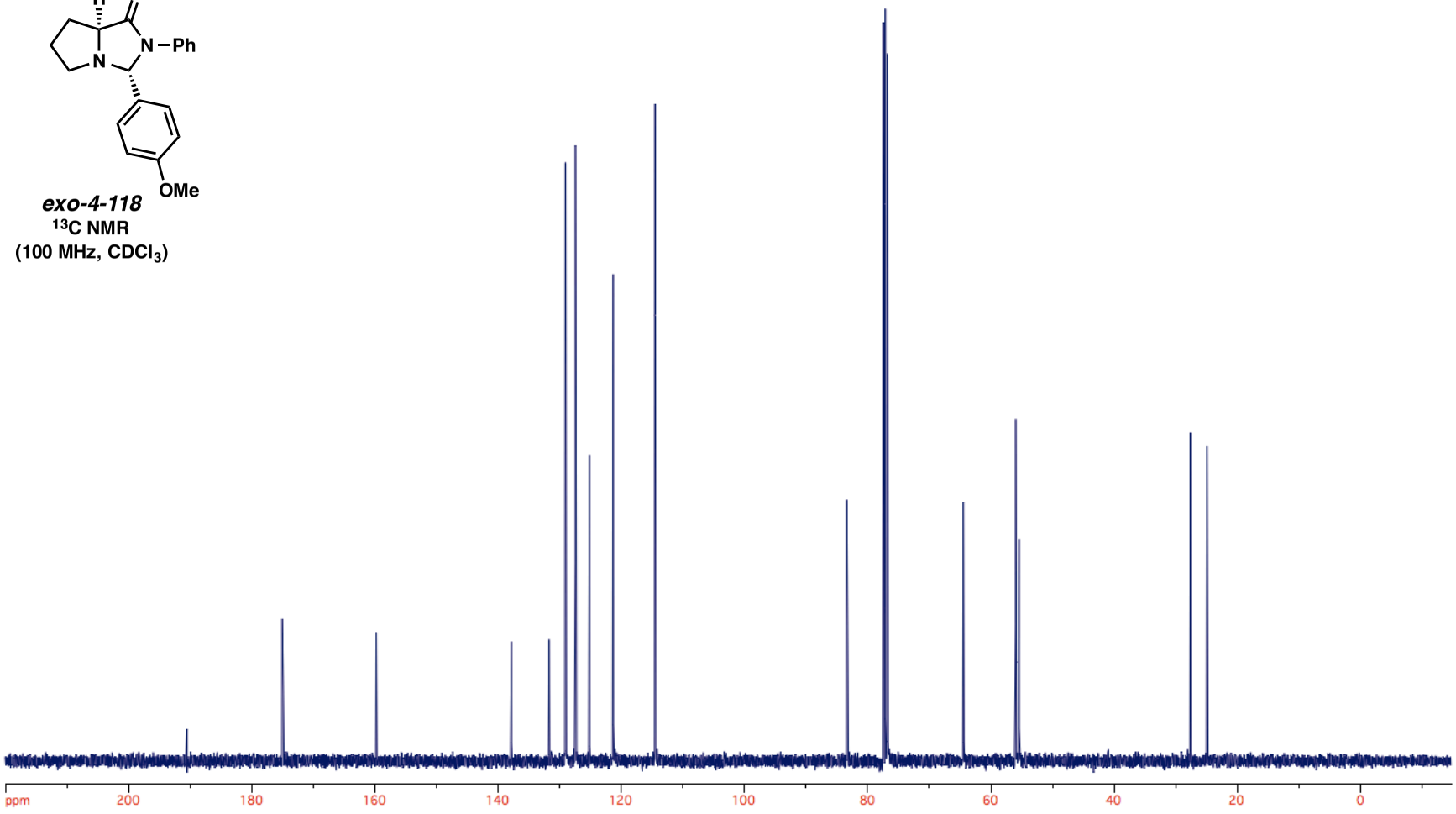


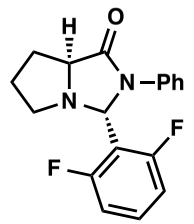


exo-4-118

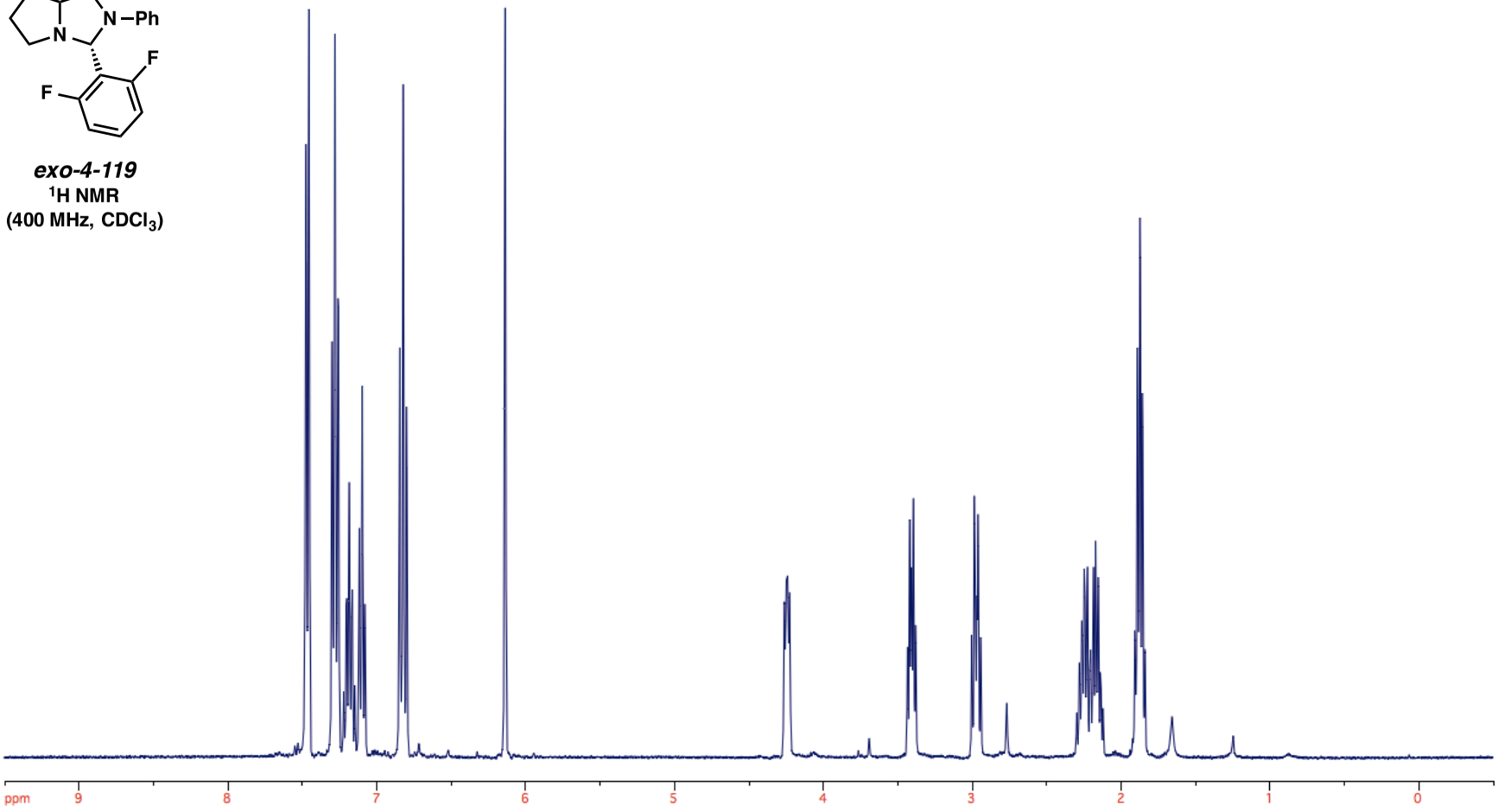
^{13}C NMR

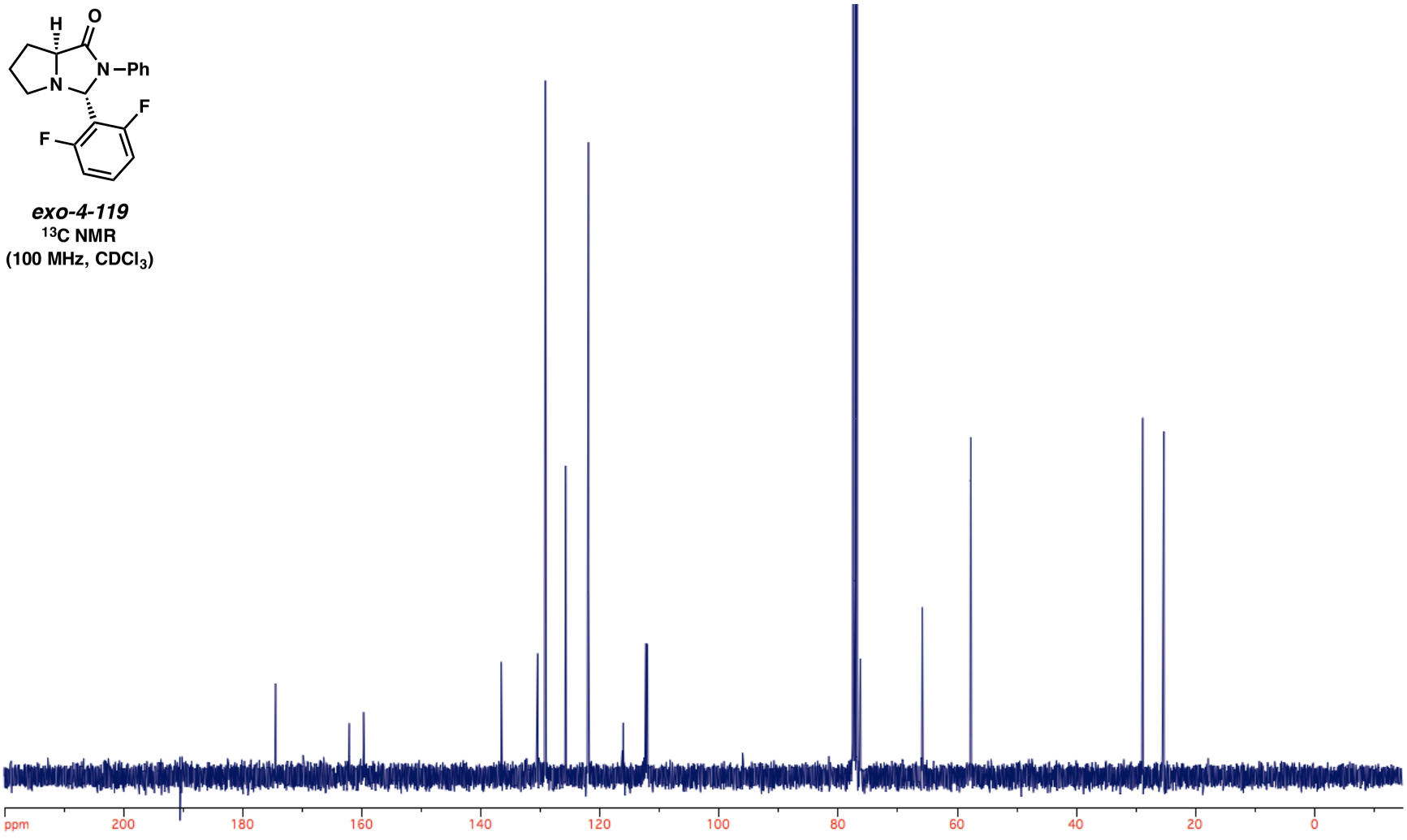
(100 MHz, $CDCl_3$)



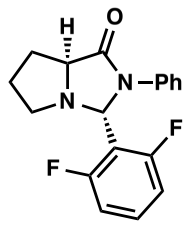


exo-4-119
^{1}H NMR
(400 MHz, $CDCl_3$)





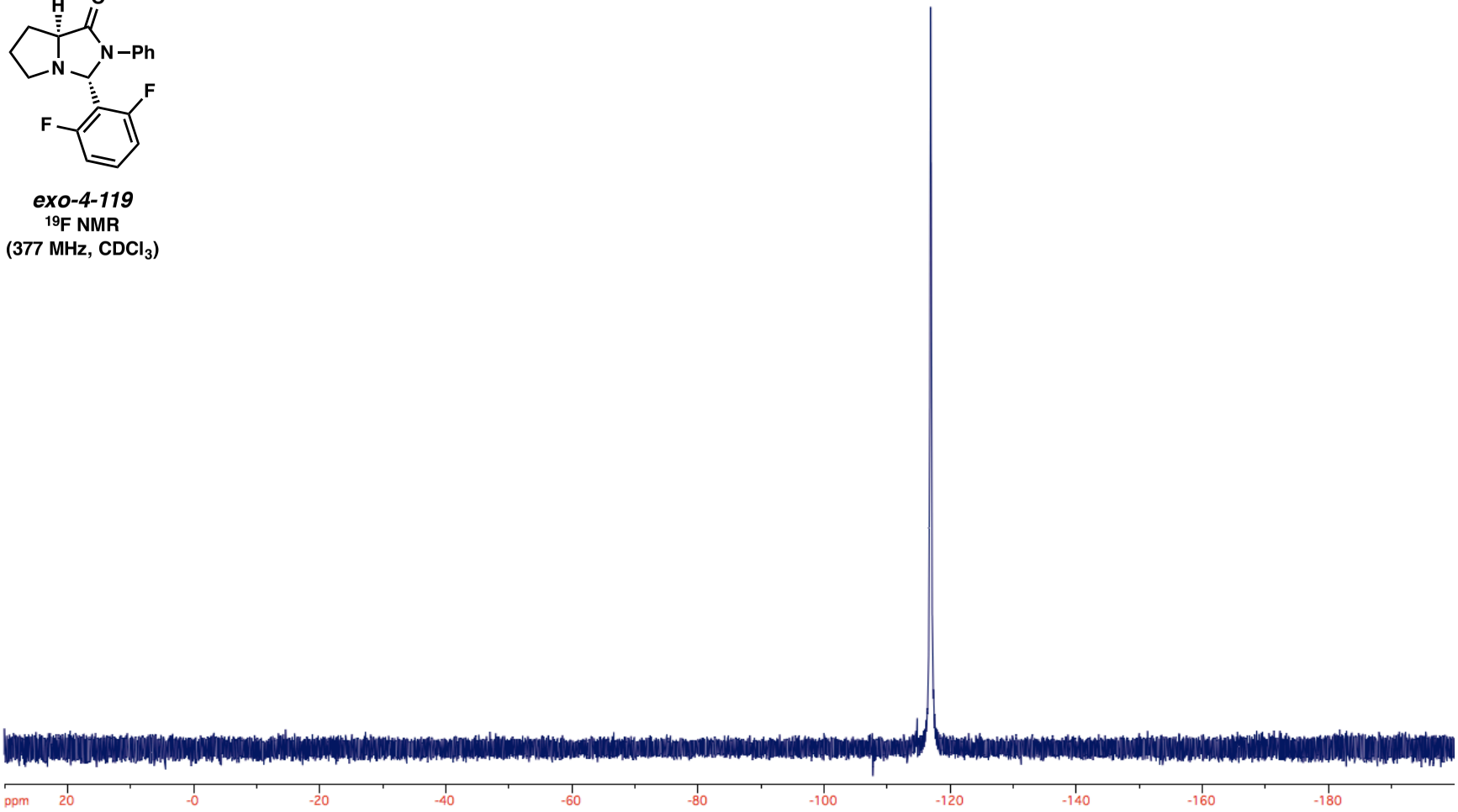
exo-4-119
^{13}C NMR
(100 MHz, $CDCl_3$)



exo-4-119

^{19}F NMR

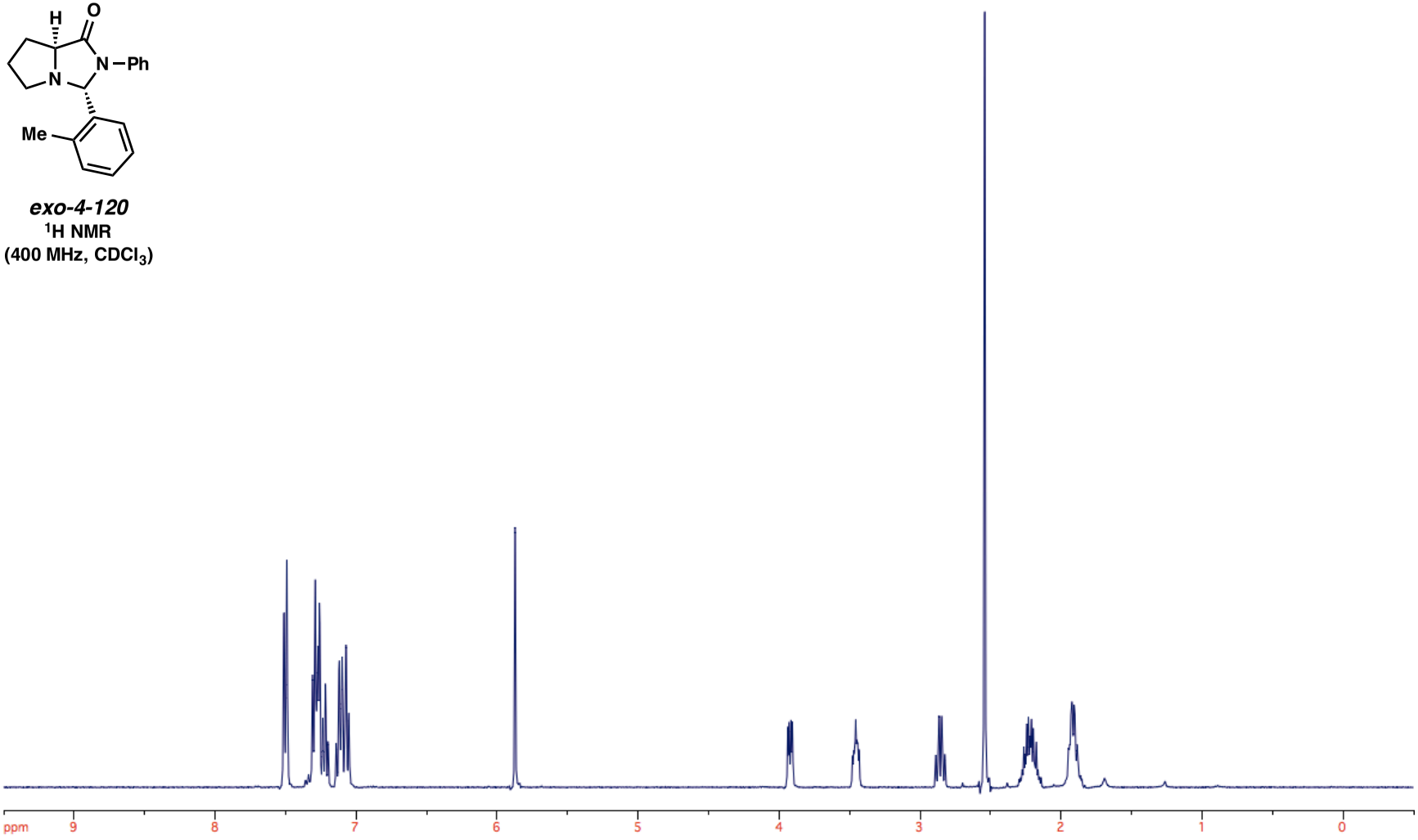
(377 MHz, $CDCl_3$)

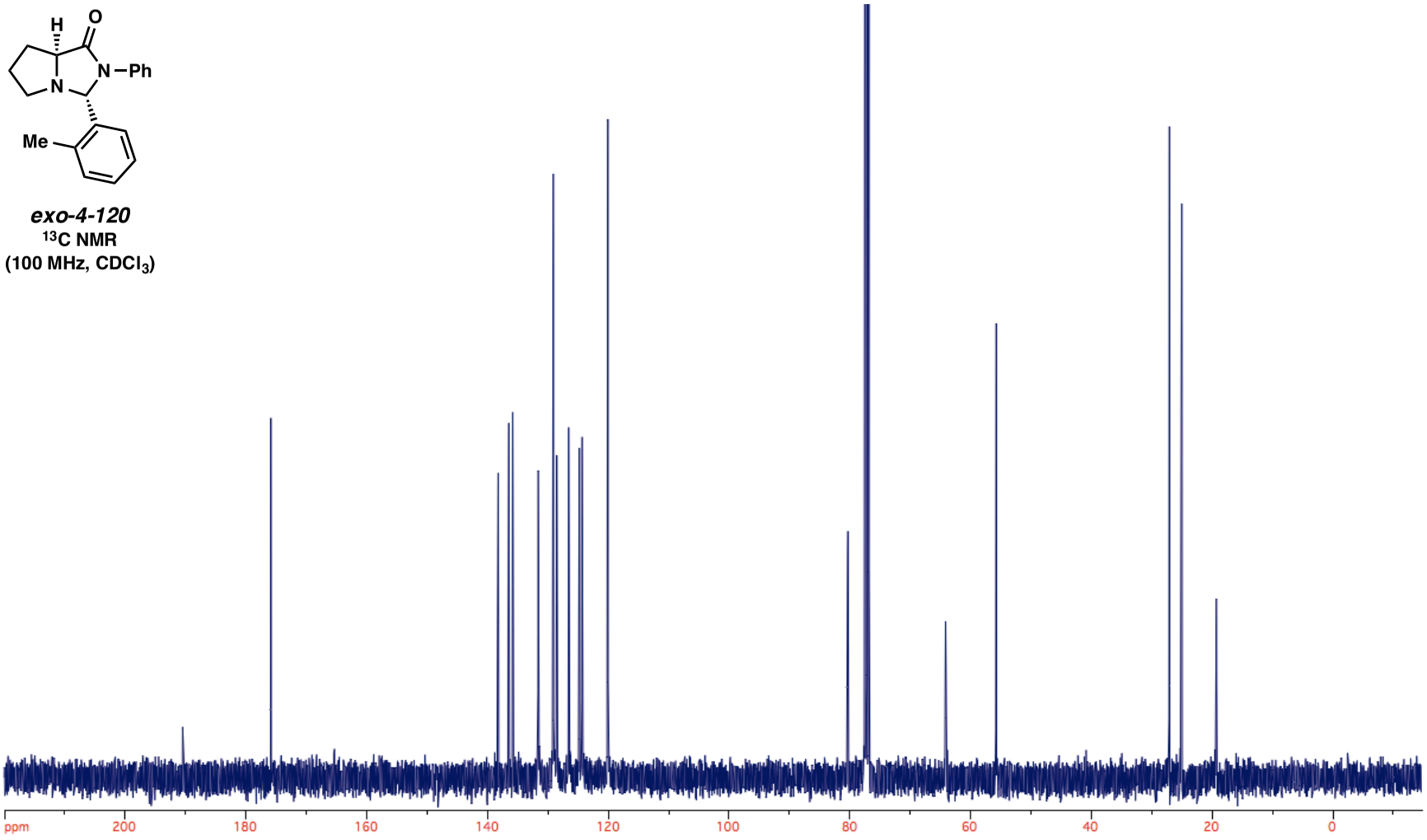


exo-4-120

^{1}H NMR

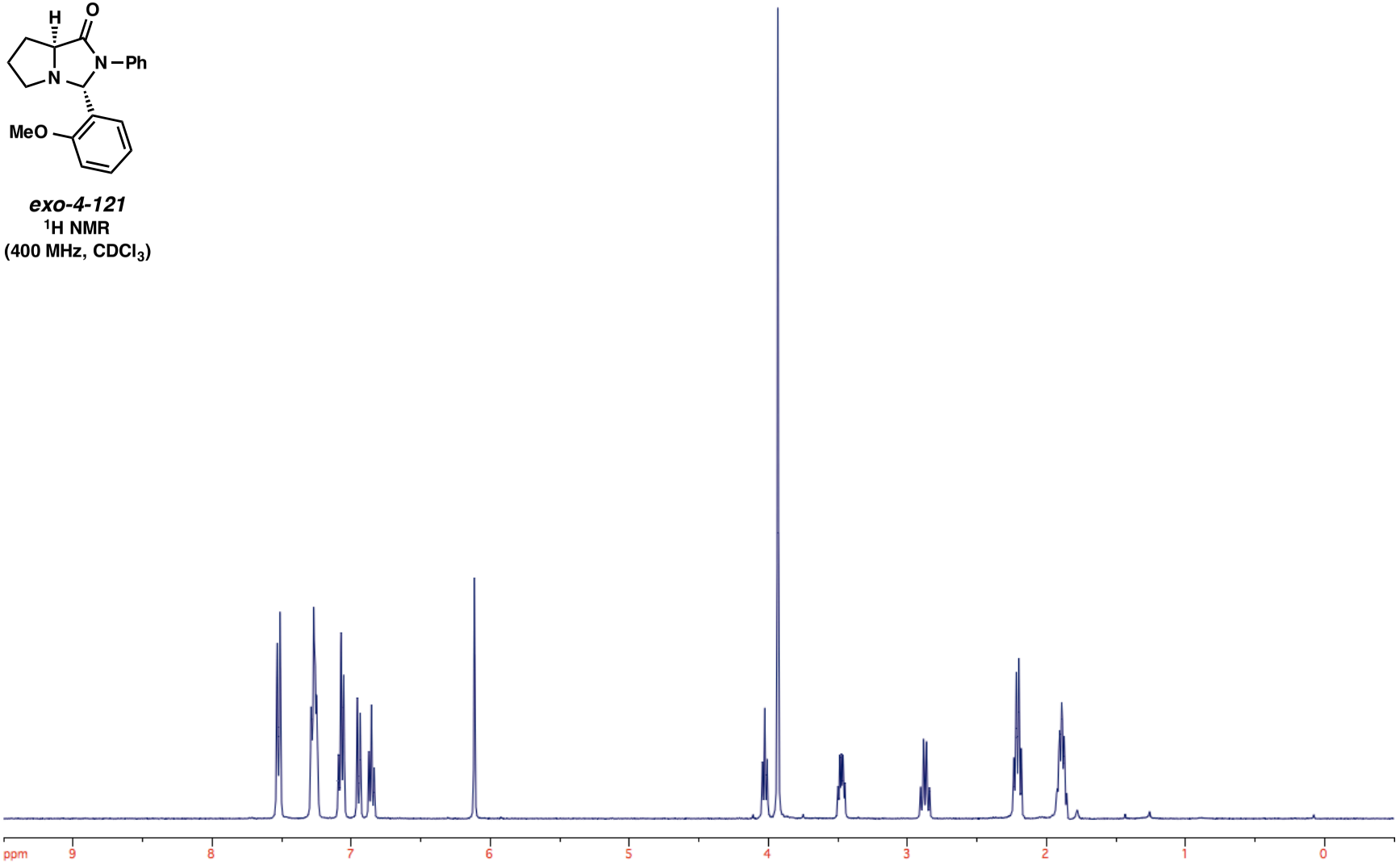
(400 MHz, $CDCl_3$)

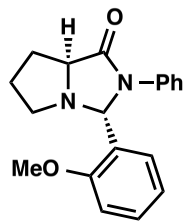




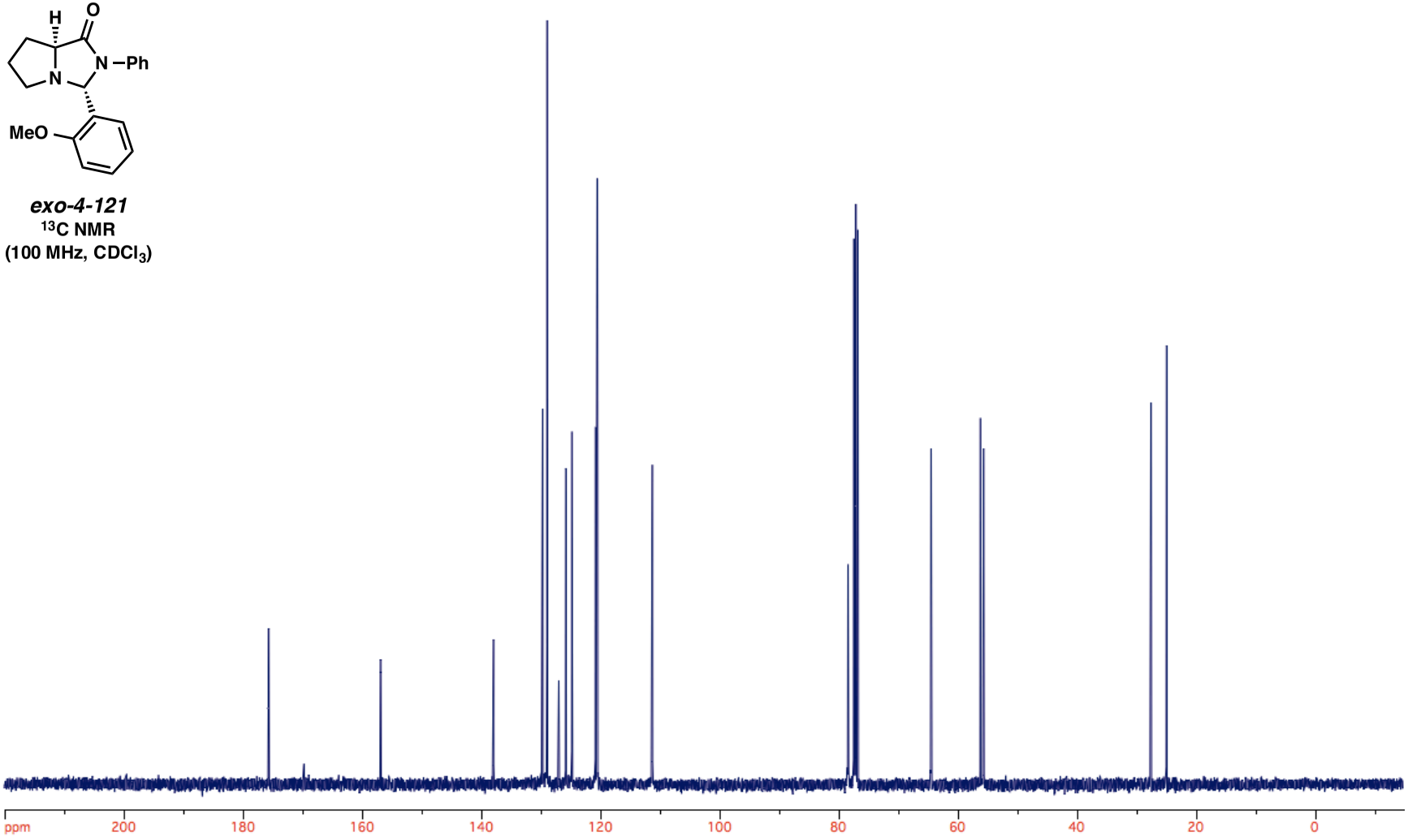
exo-4-120
^{13}C NMR
(100 MHz, $CDCl_3$)

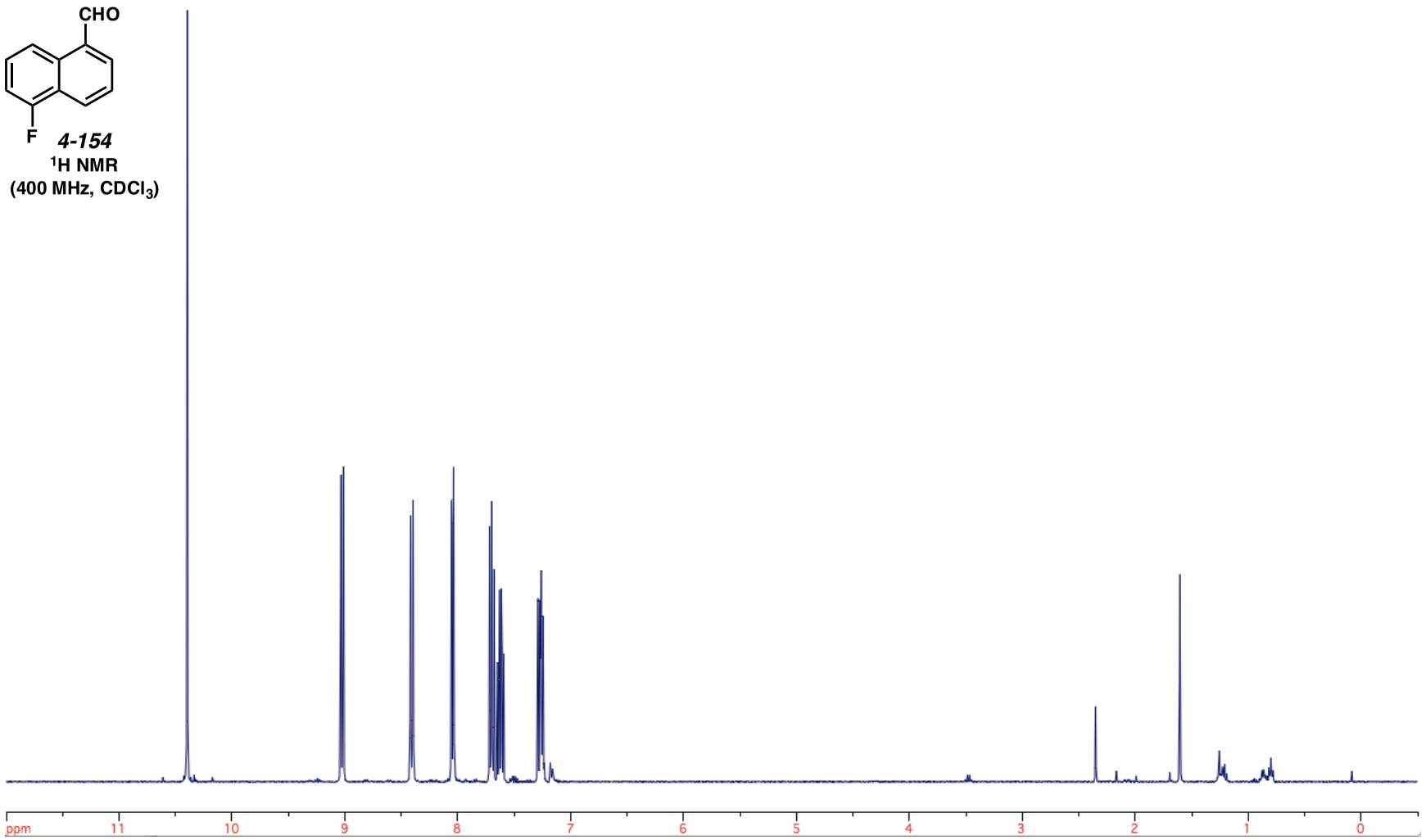
exo-4-121
^{1}H NMR
(400 MHz, $CDCl_3$)

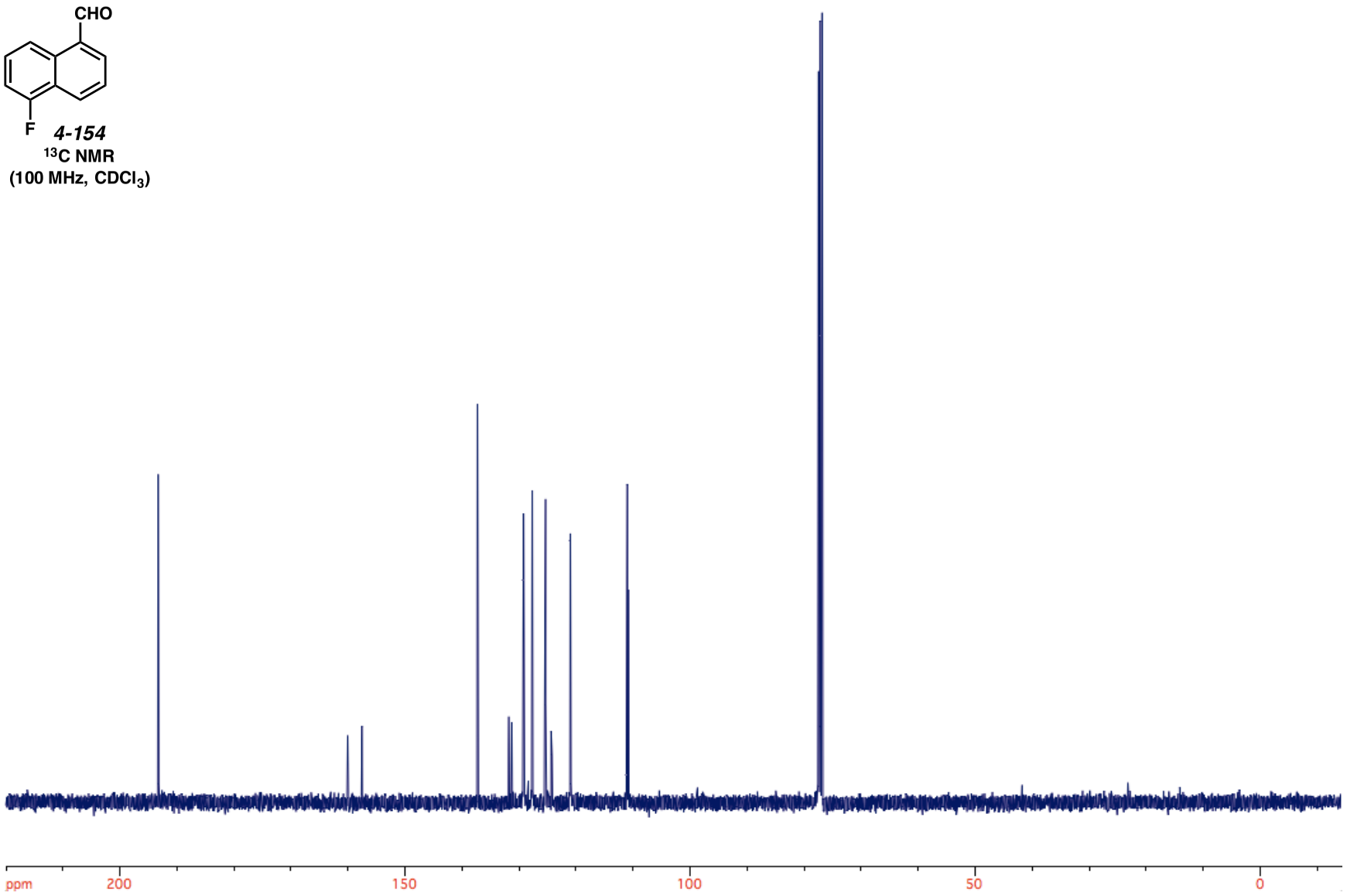


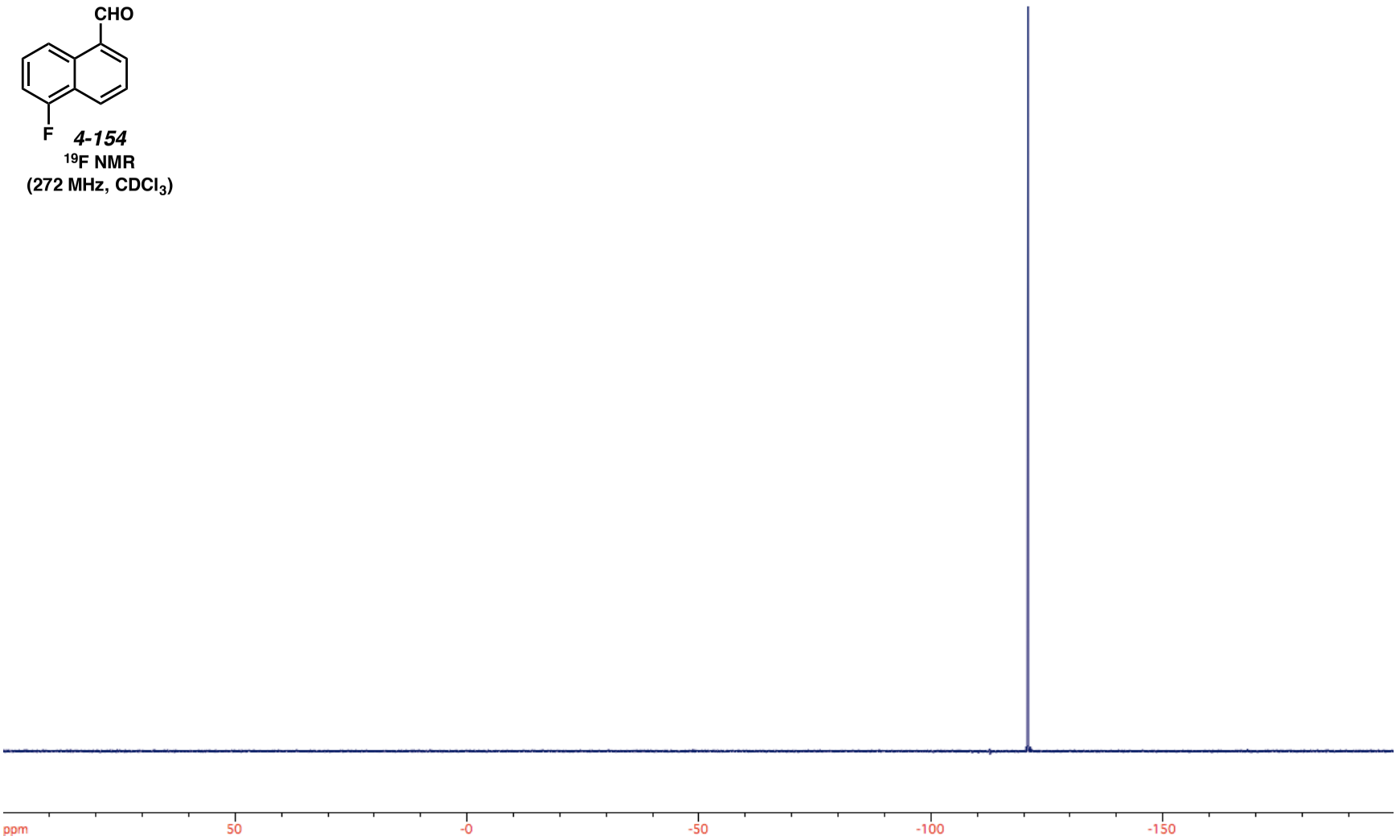


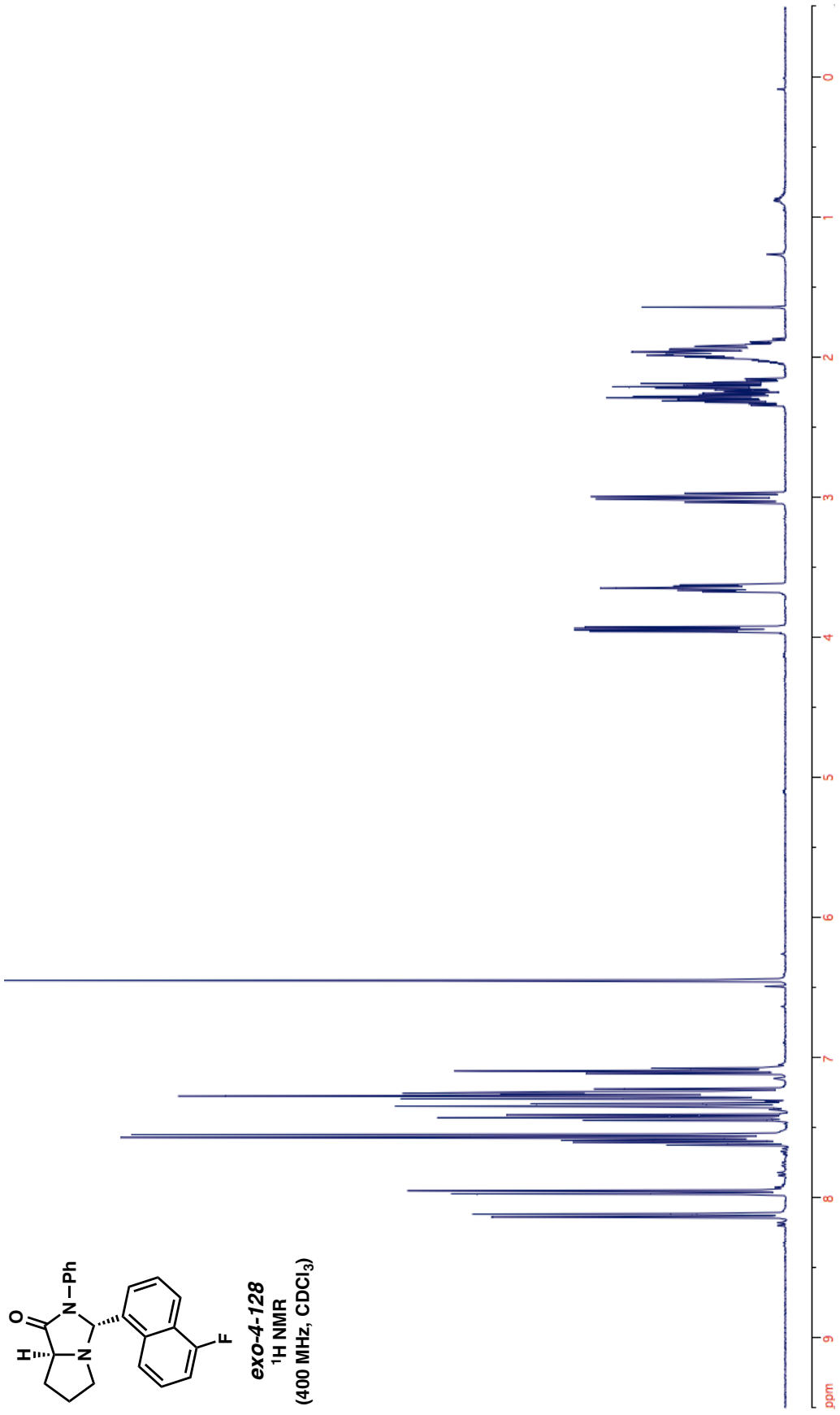
exo-4-121
^{13}C NMR
(100 MHz, $CDCl_3$)




CHO
F
4-154
1H NMR
(400 MHz, CDCl3)
ppm
11
10
9
8
7
6
5
4
3
2
1
0

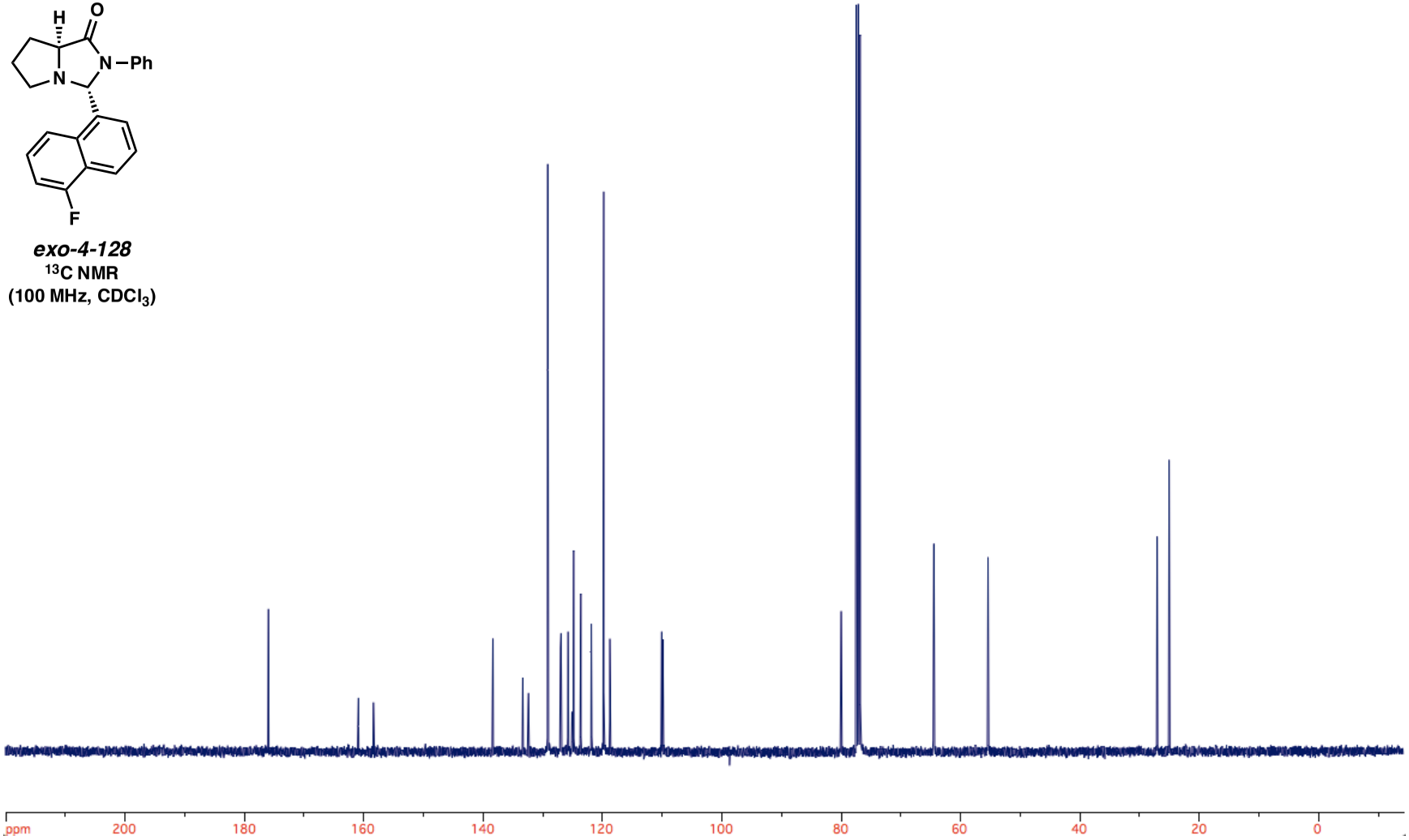

CHO
F
4-154
13C NMR
(100 MHz, CDCl3)
ppm
200
150
100
50
0


CHO
F
4-154
19F NMR
(272 MHz, CDCl3)
ppm
50
-0
-50
-100
-150

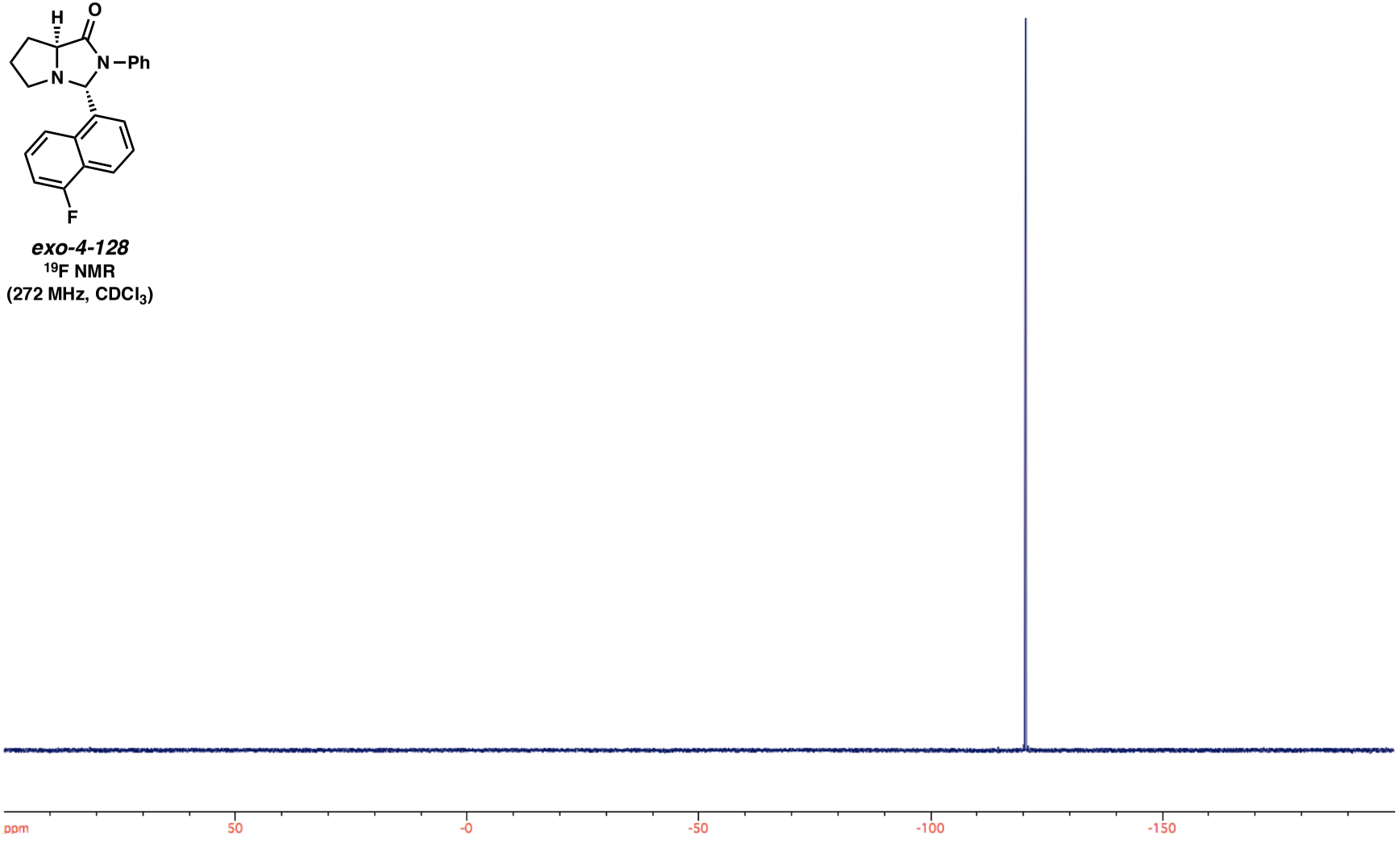


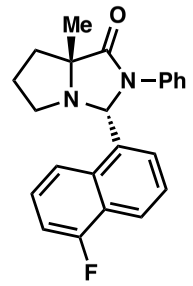
exo-4-128
^{1}H NMR
(400 MHz, $CDCl_3$)

exo-4-128
^{13}C NMR
(100 MHz, $CDCl_3$)



exo-4-128
^{19}F NMR
(272 MHz, $CDCl_3$)

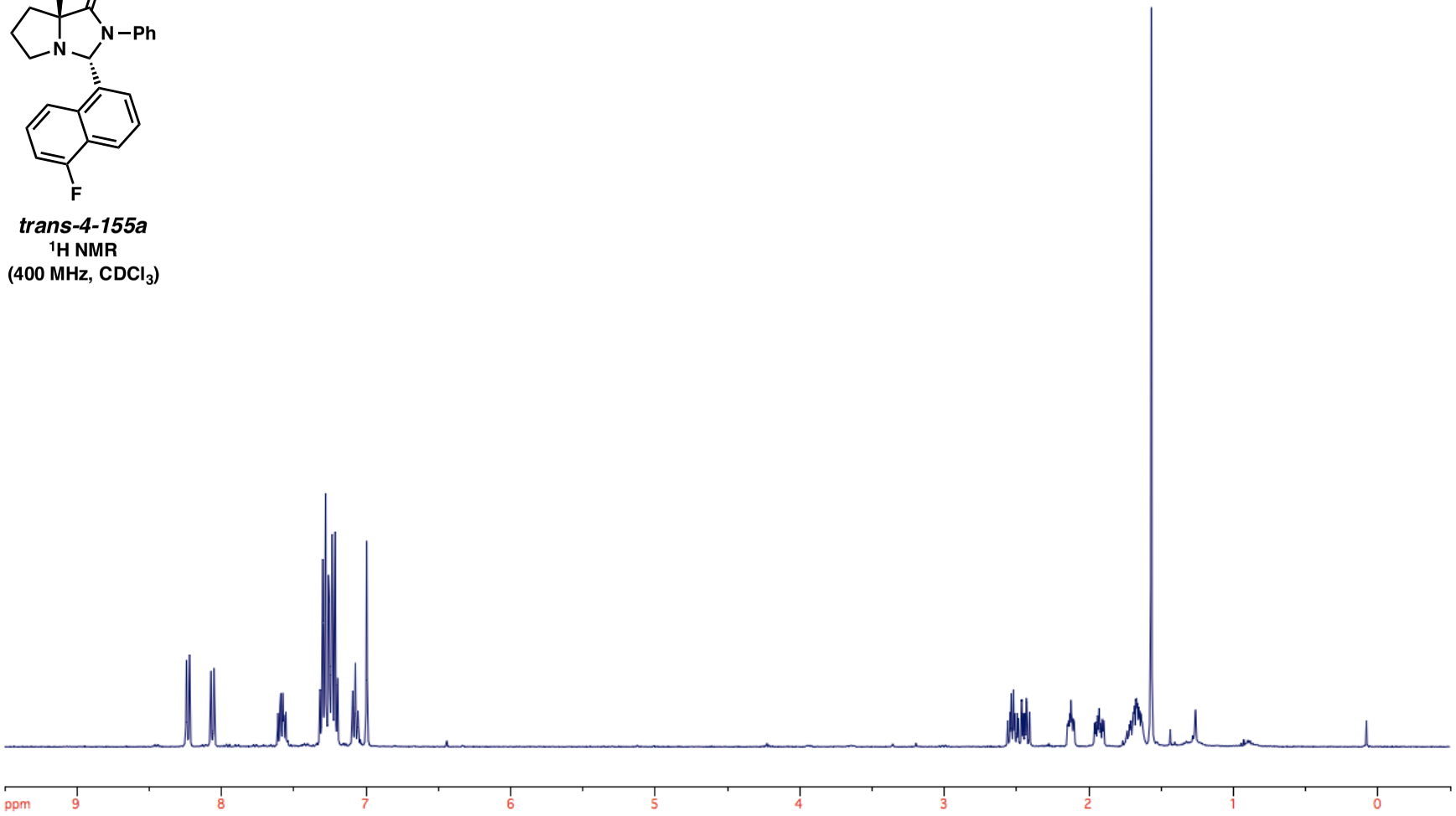


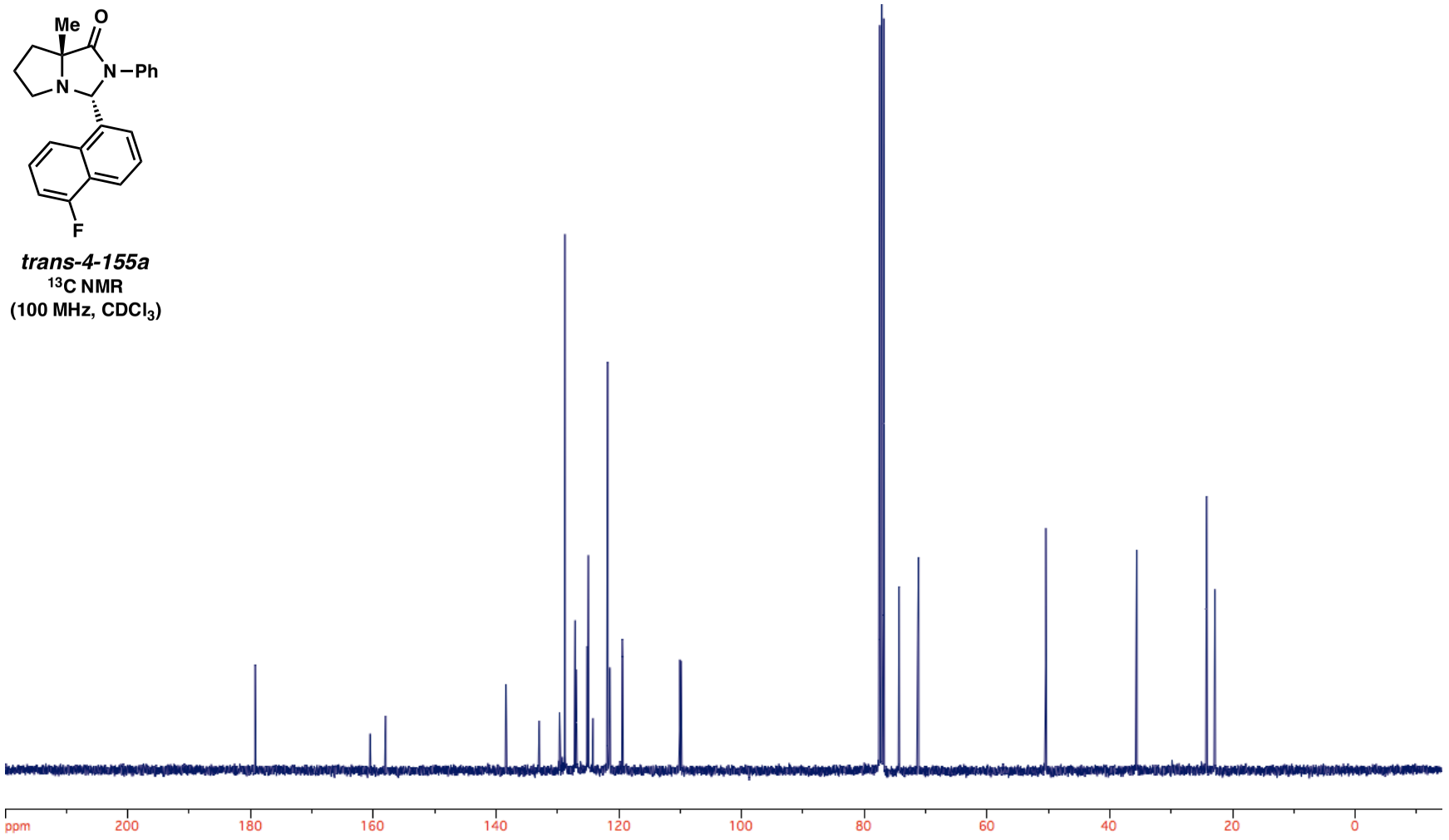


trans-4-155a

^{1}H NMR

(400 MHz, $CDCl_3$)



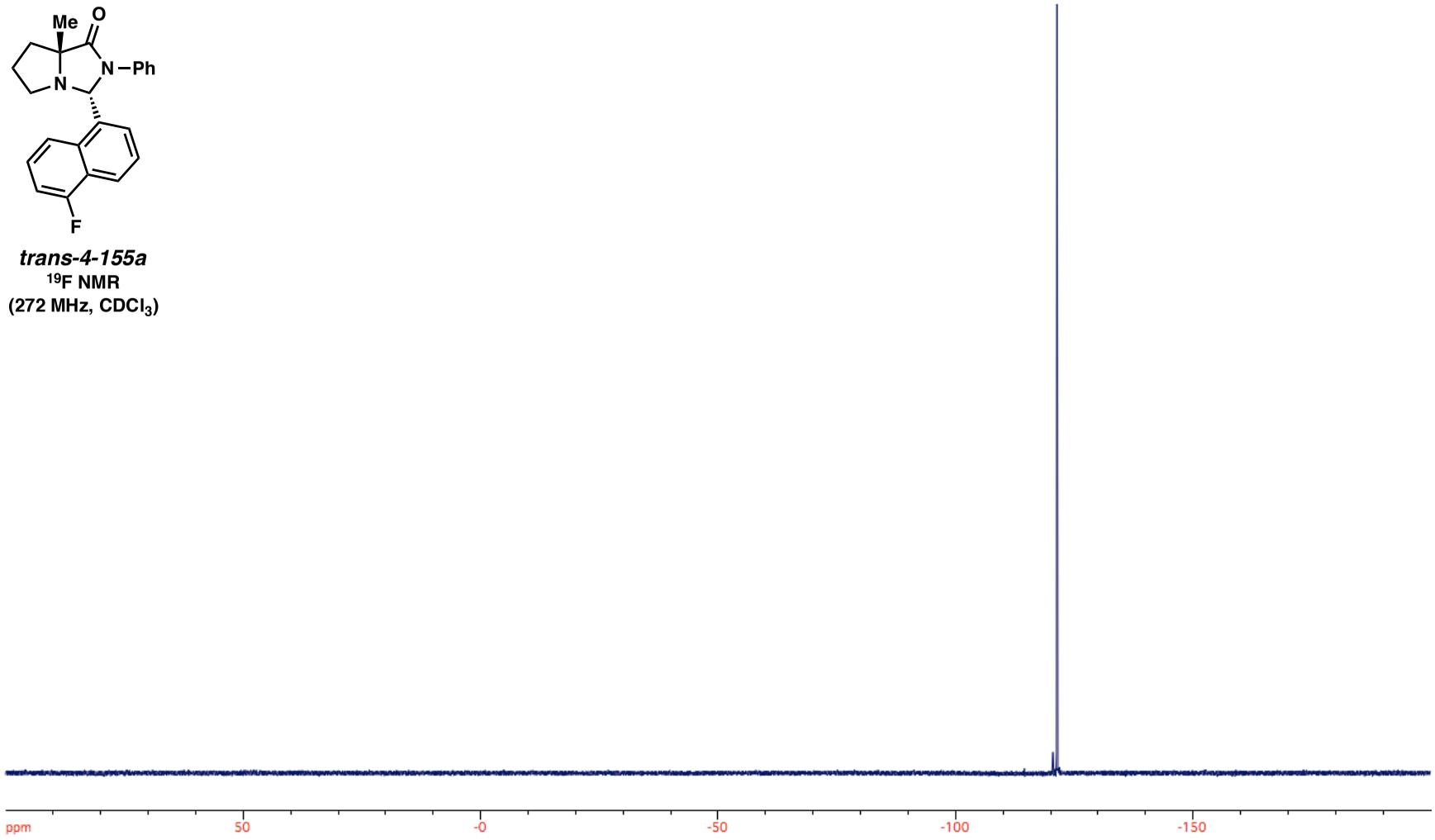


trans-4-155a
^{13}C NMR
(100 MHz, $CDCl_3$)

trans-4-155a

^{19}F NMR

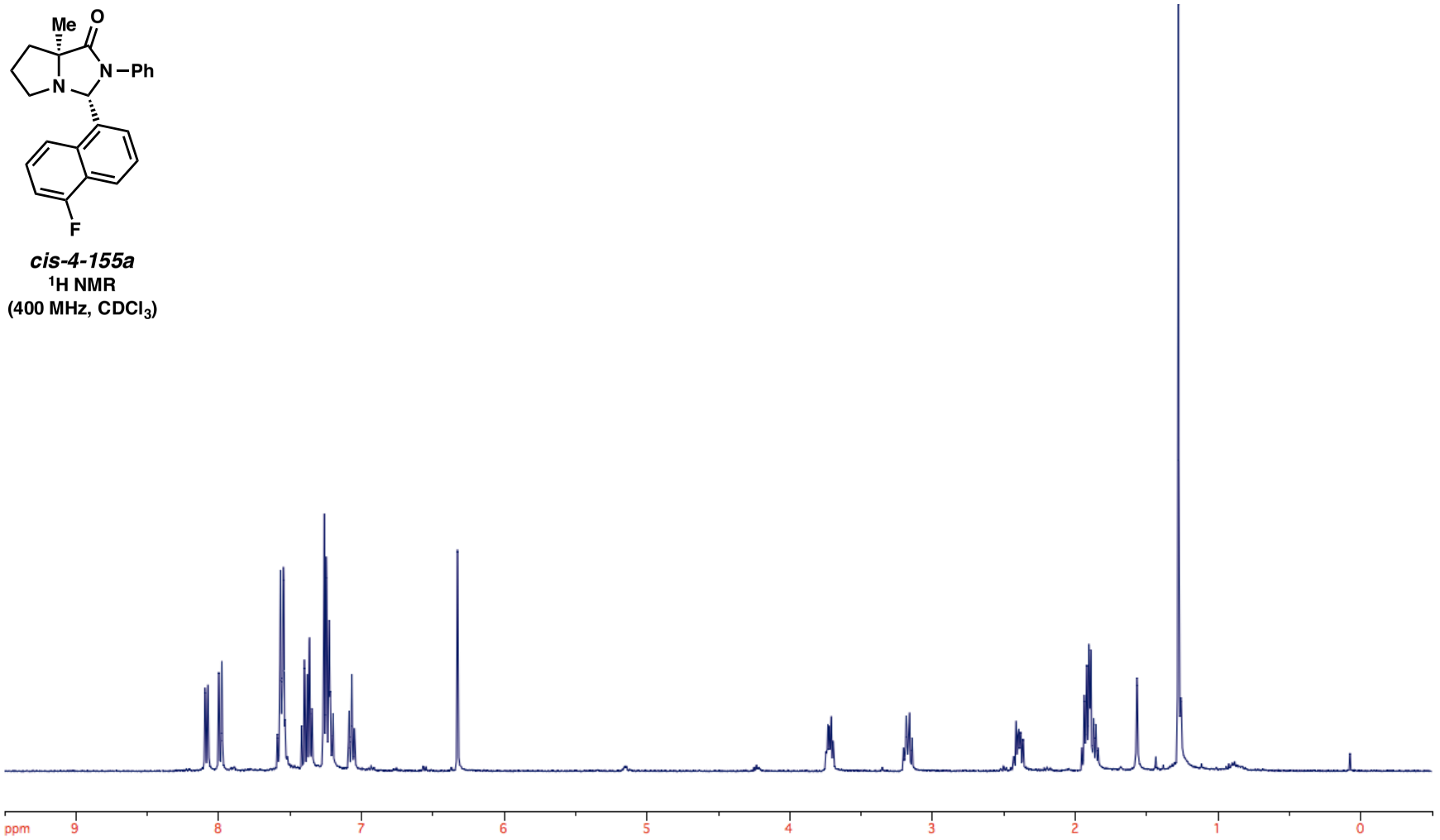
(272 MHz, $CDCl_3$)



cis-4-155a

^{1}H NMR

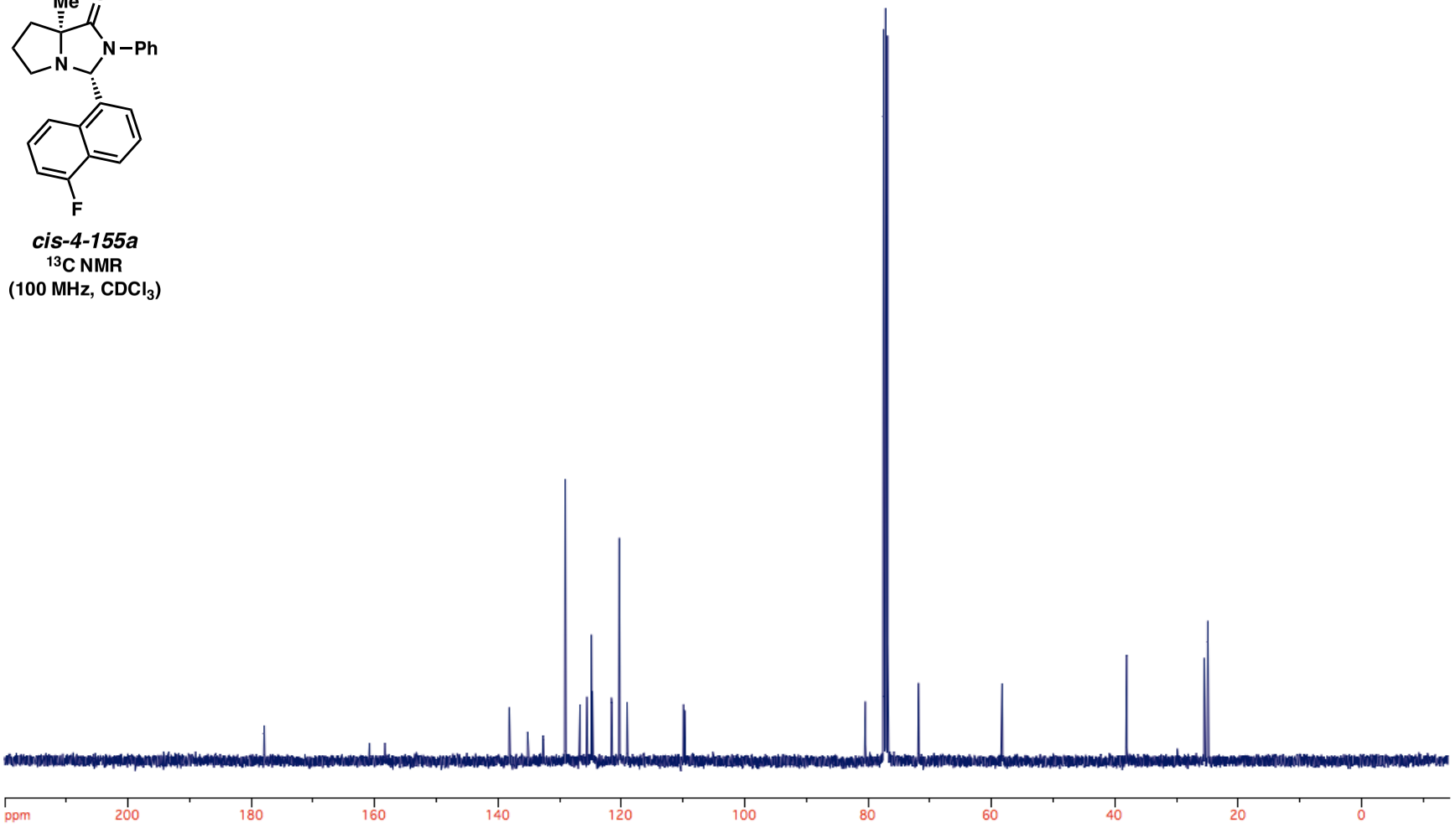
(400 MHz, $CDCl_3$)



cis-4-155a

^{13}C NMR

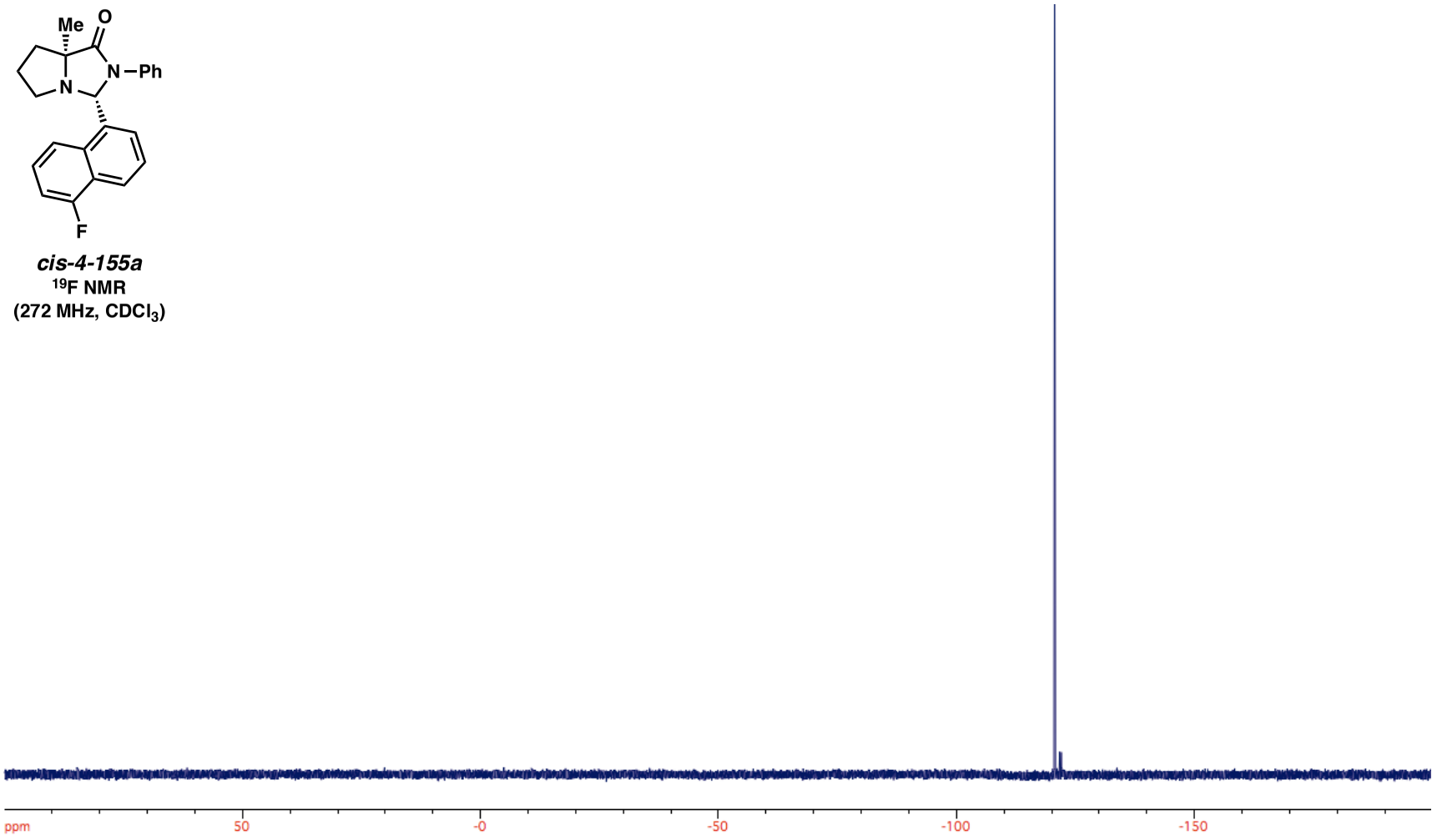
(100 MHz, $CDCl_3$)



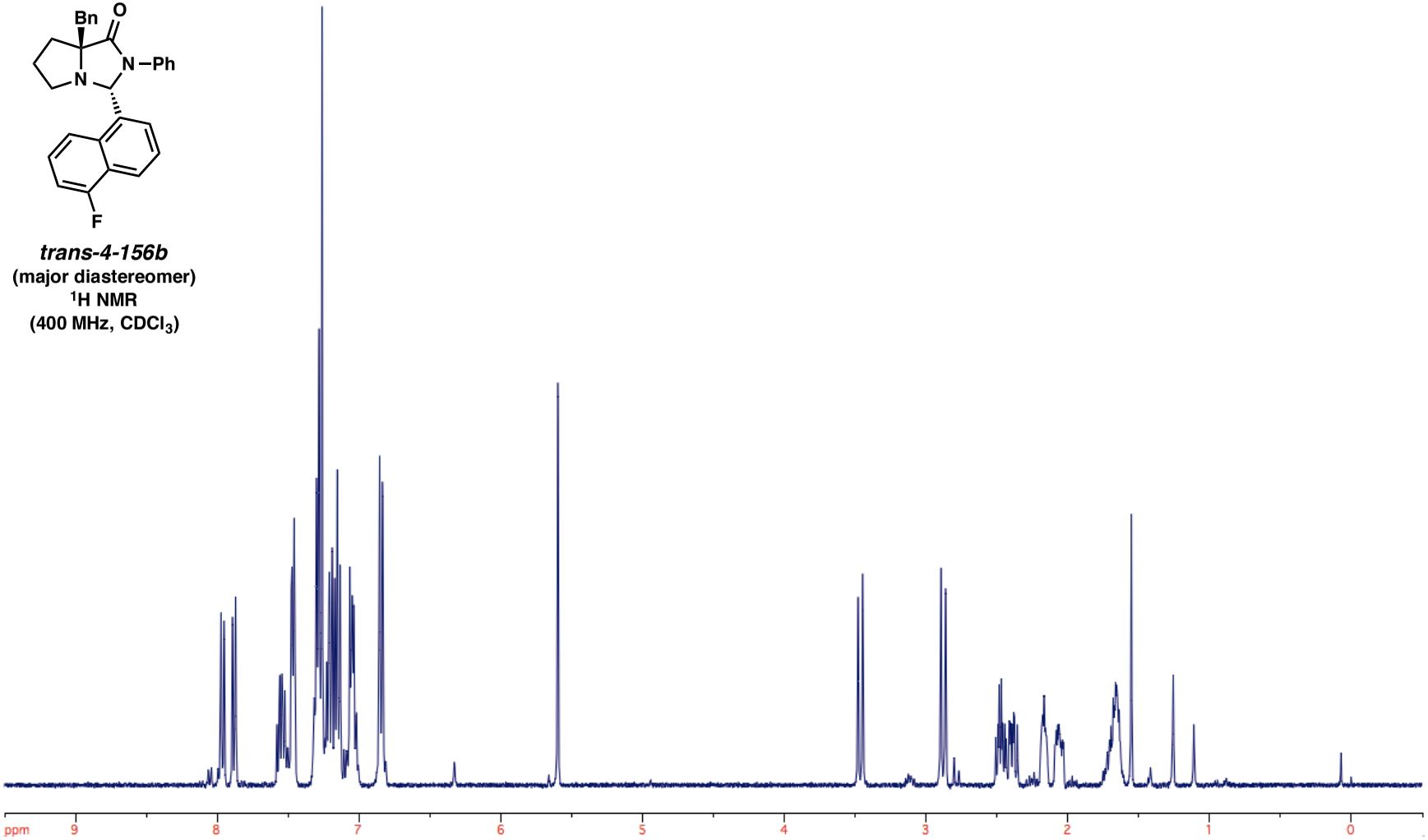
cis-4-155a

^{19}F NMR

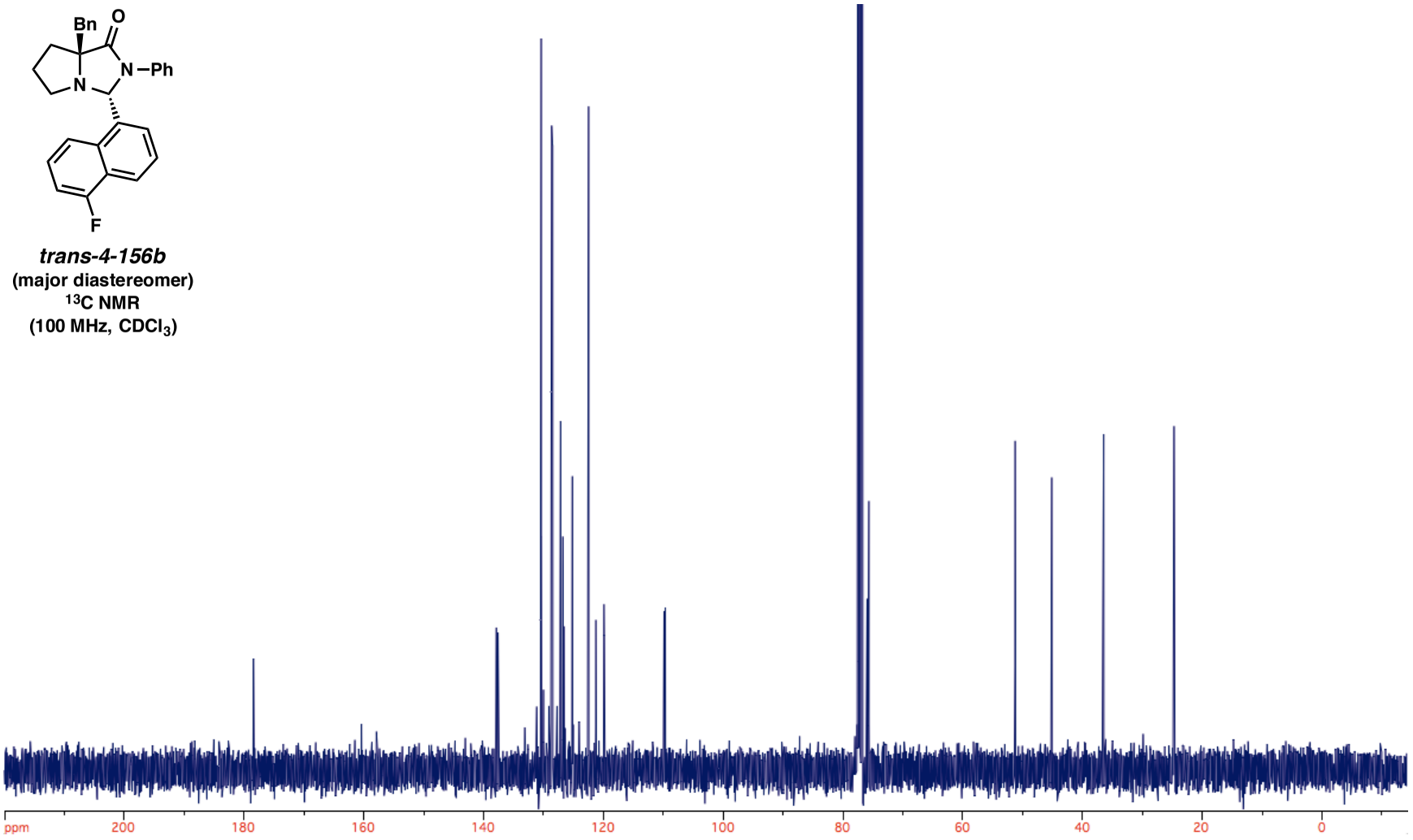
(272 MHz, $CDCl_3$)



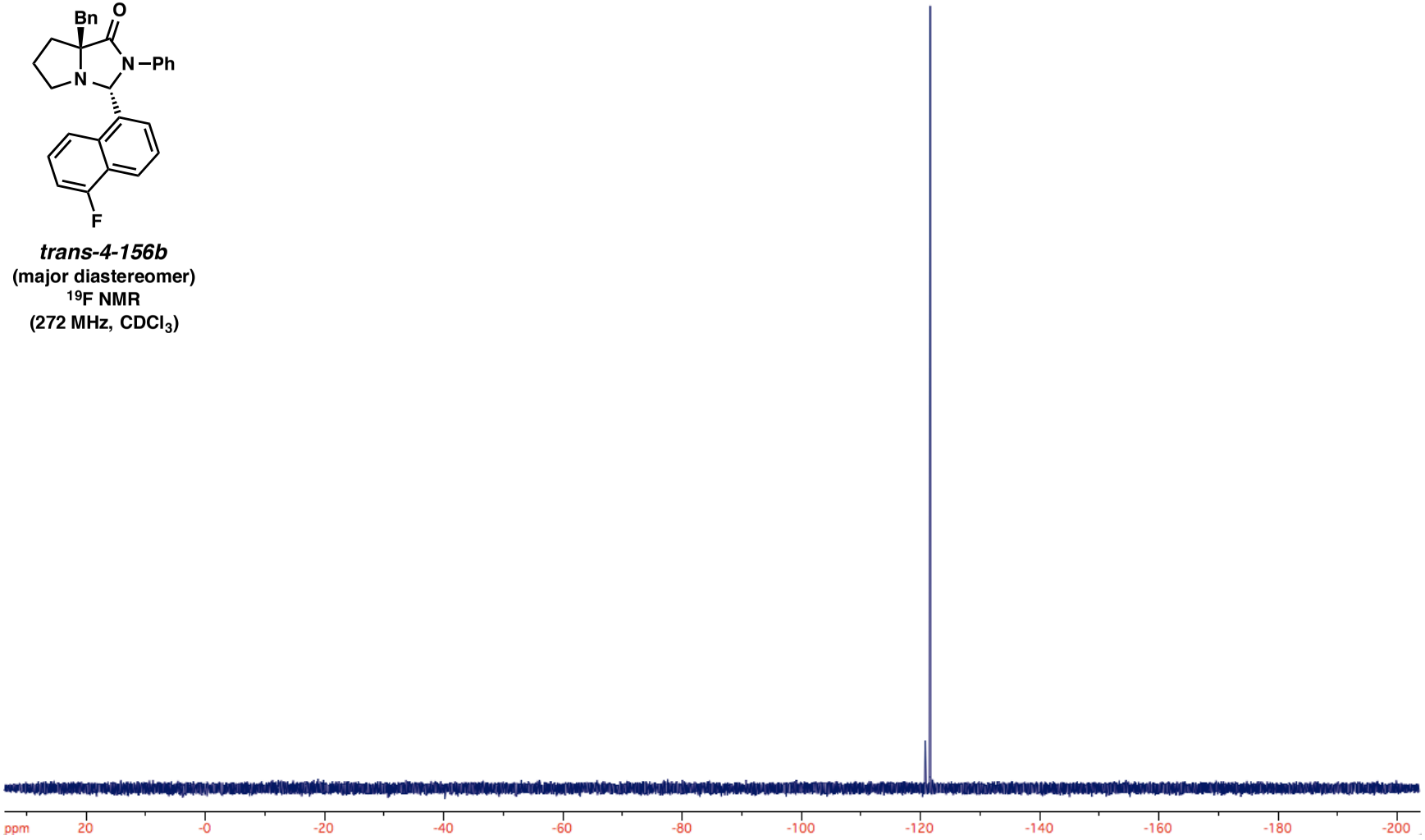
trans-4-156b
(major diastereomer)
^{1}H NMR
(400 MHz, $CDCl_3$)

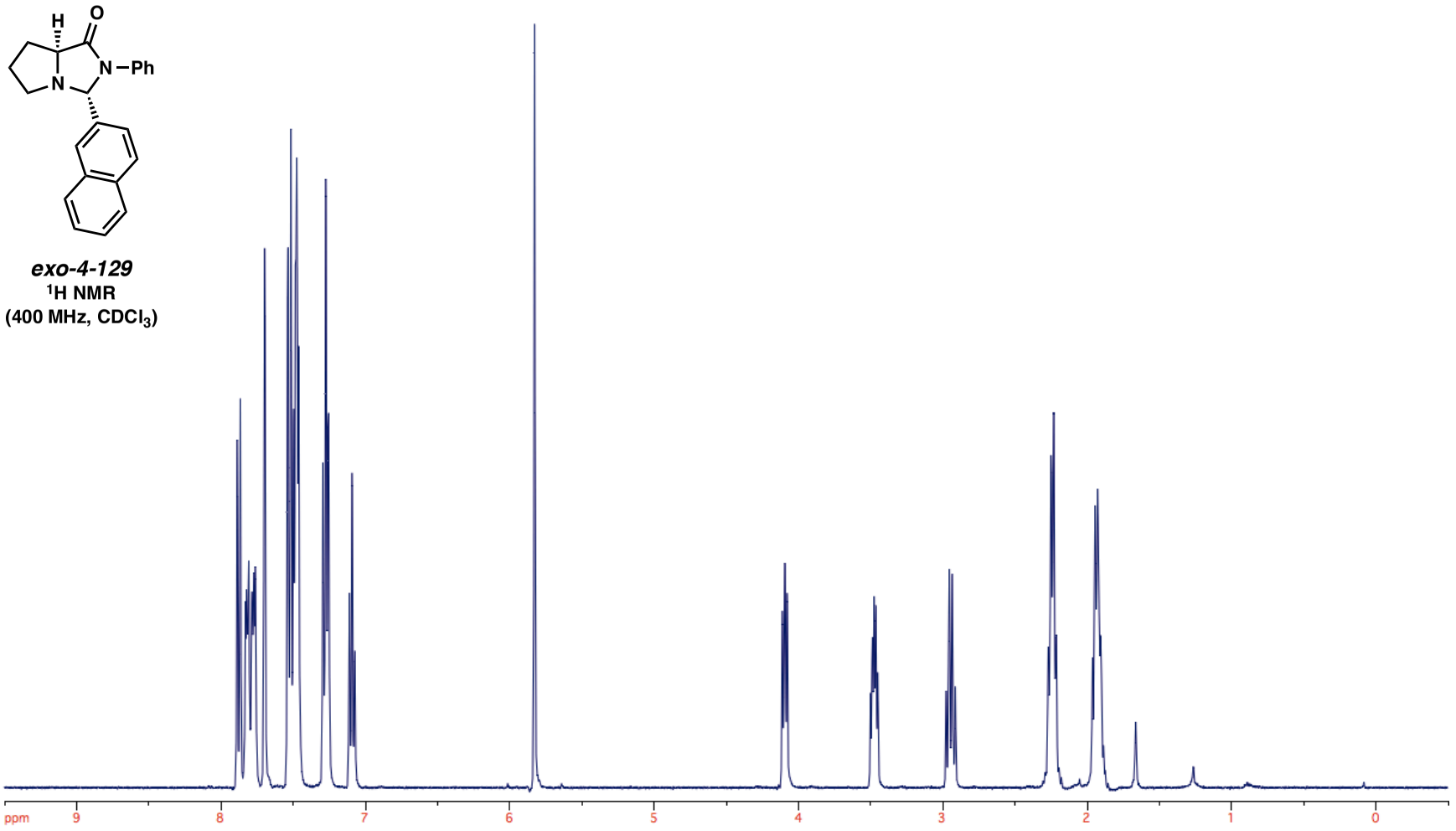


trans-4-156b
(major diastereomer)
^{13}C NMR
(100 MHz, $CDCl_3$)

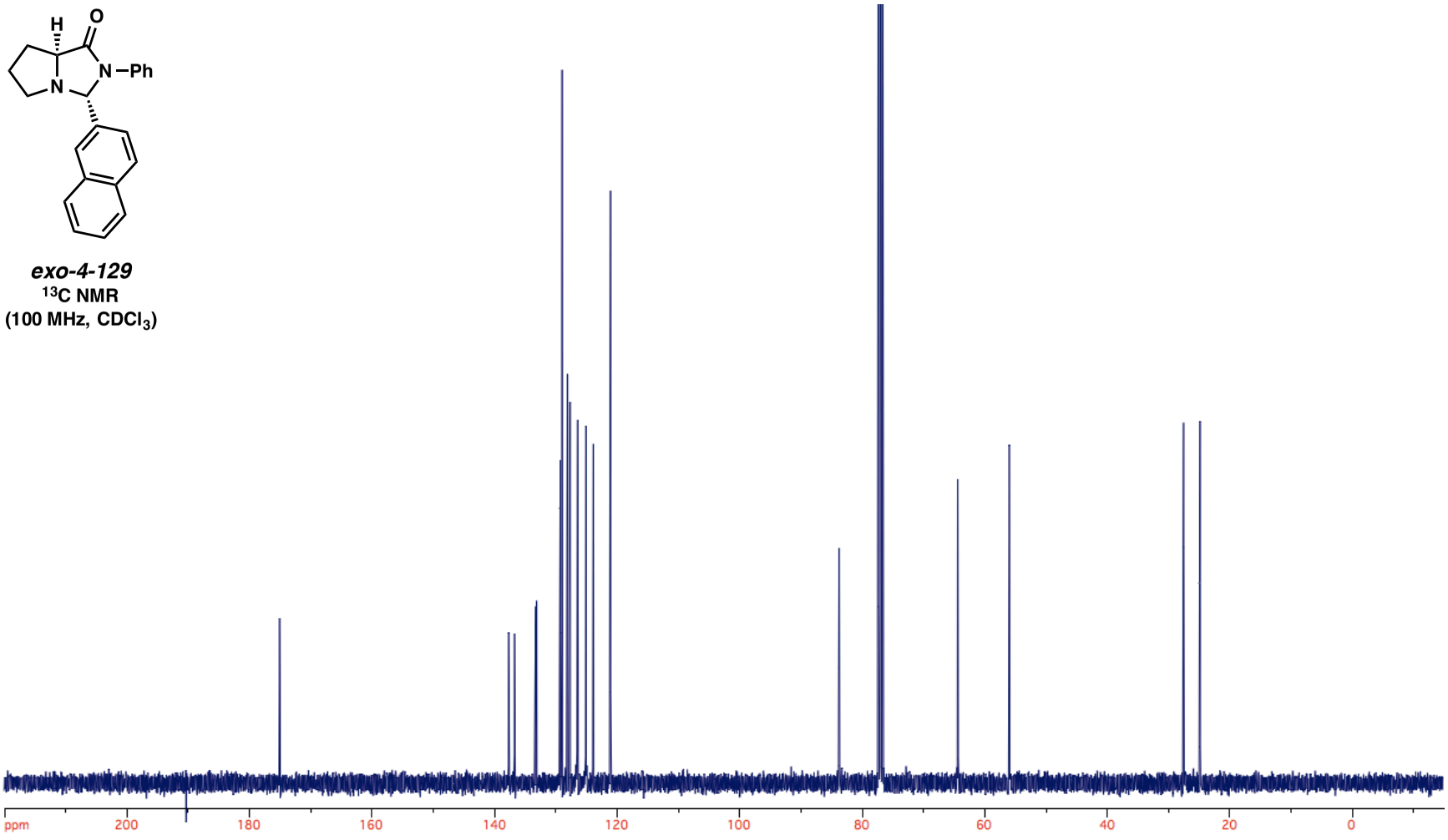


trans-4-156b
(major diastereomer)
^{19}F NMR
(272 MHz, $CDCl_3$)



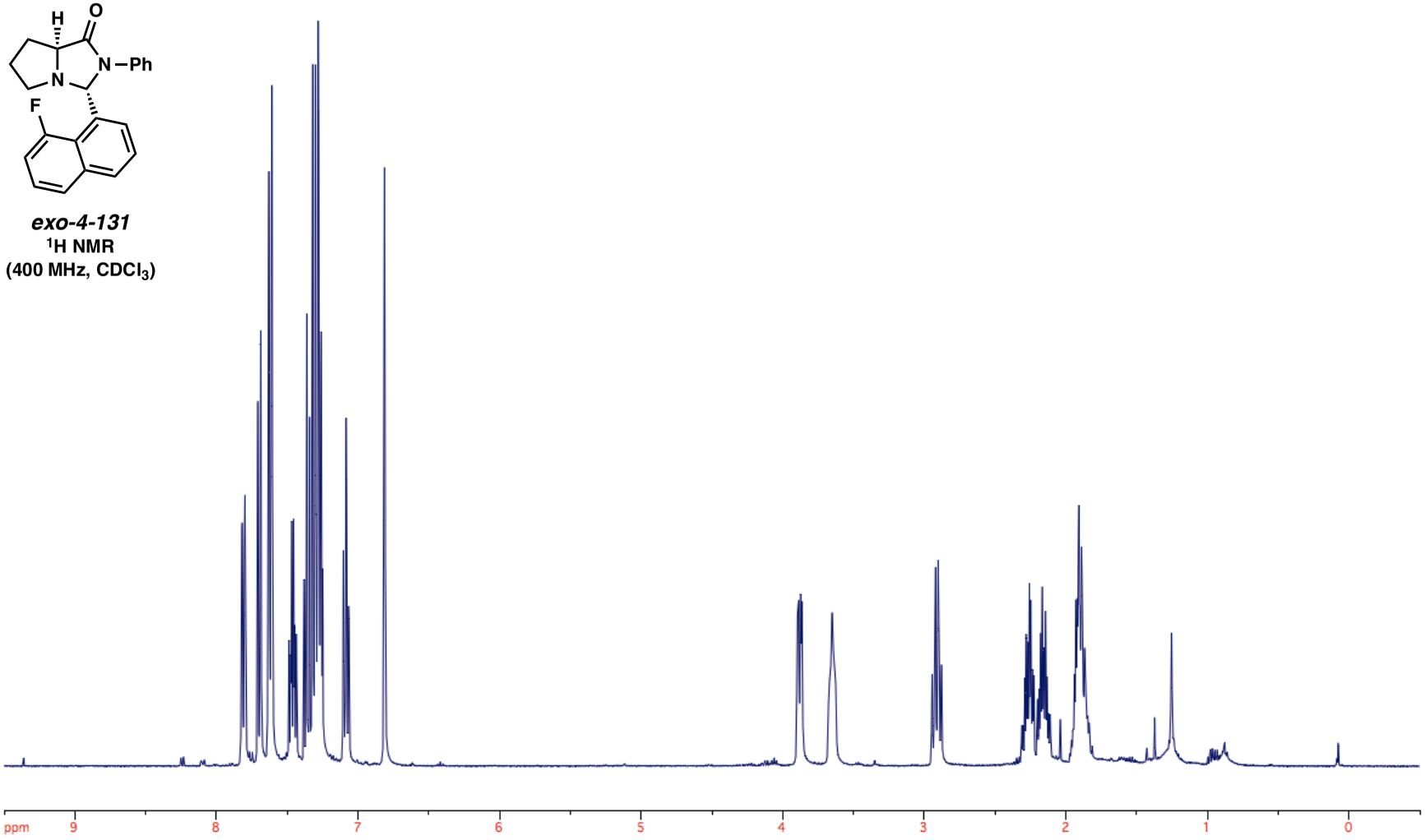


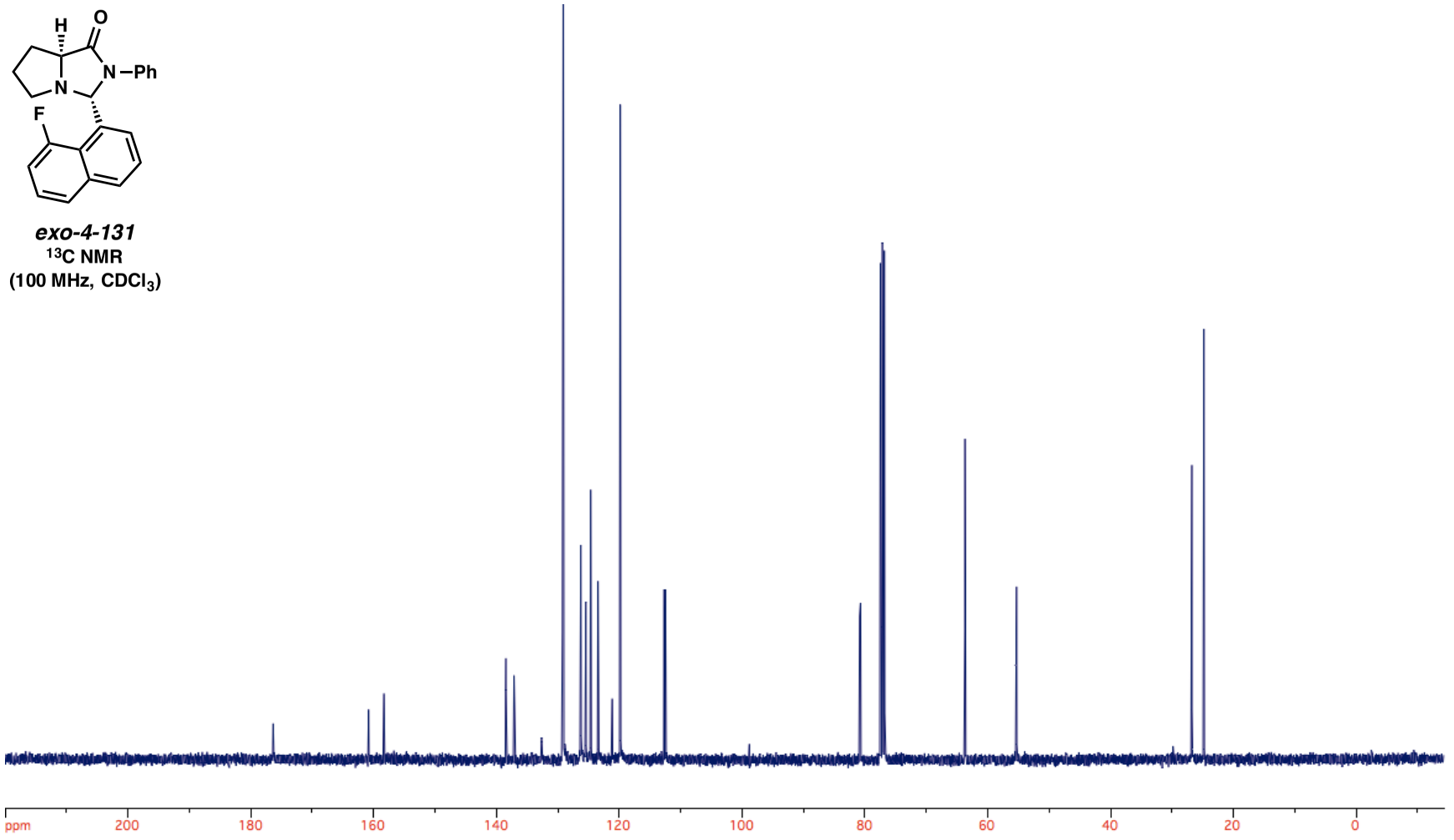
exo-4-129
^{1}H NMR
(400 MHz, $CDCl_3$)



exo-4-129
^{13}C NMR
(100 MHz, $CDCl_3$)

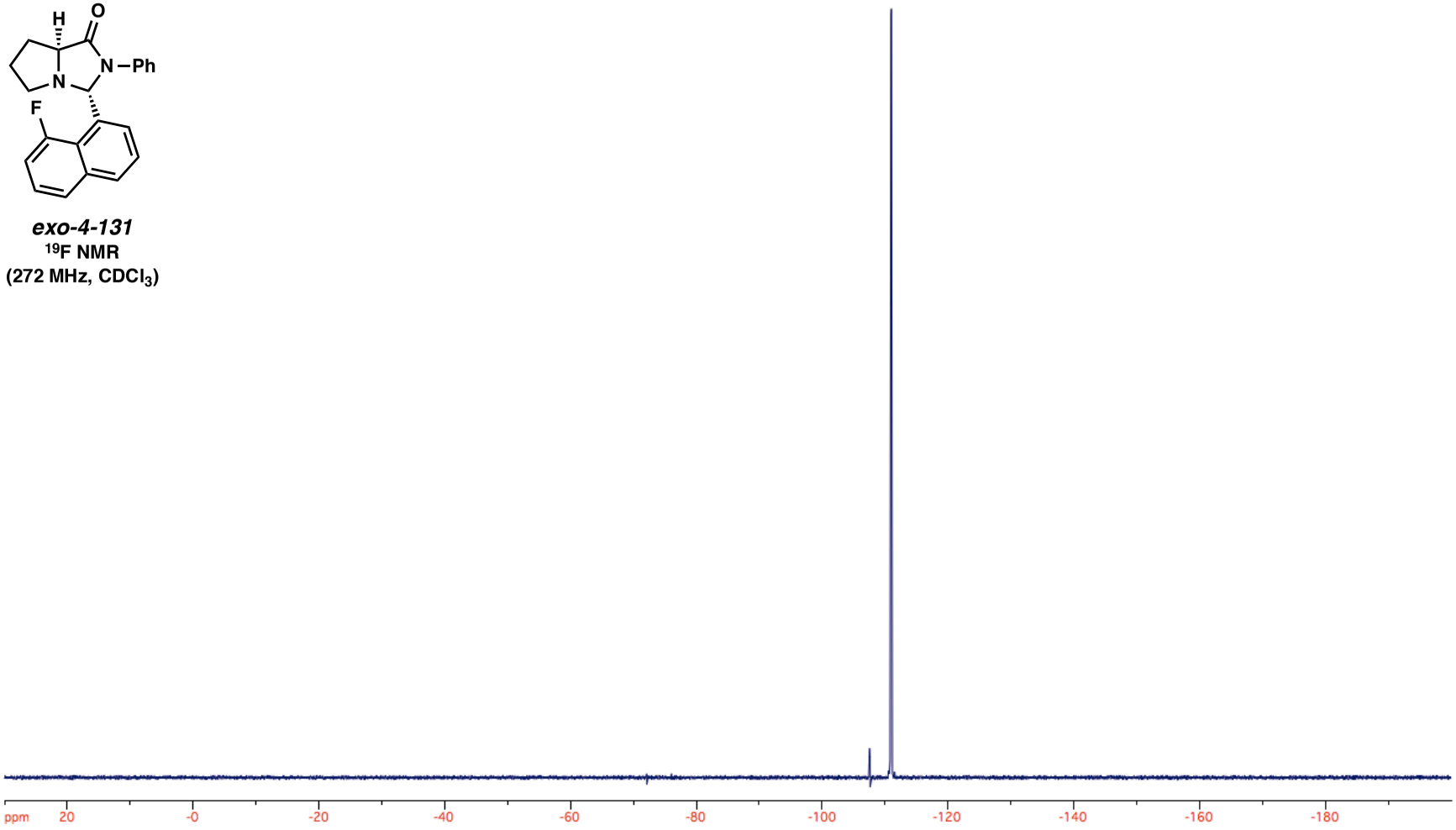
exo-4-131
^{1}H NMR
(400 MHz, $CDCl_3$)



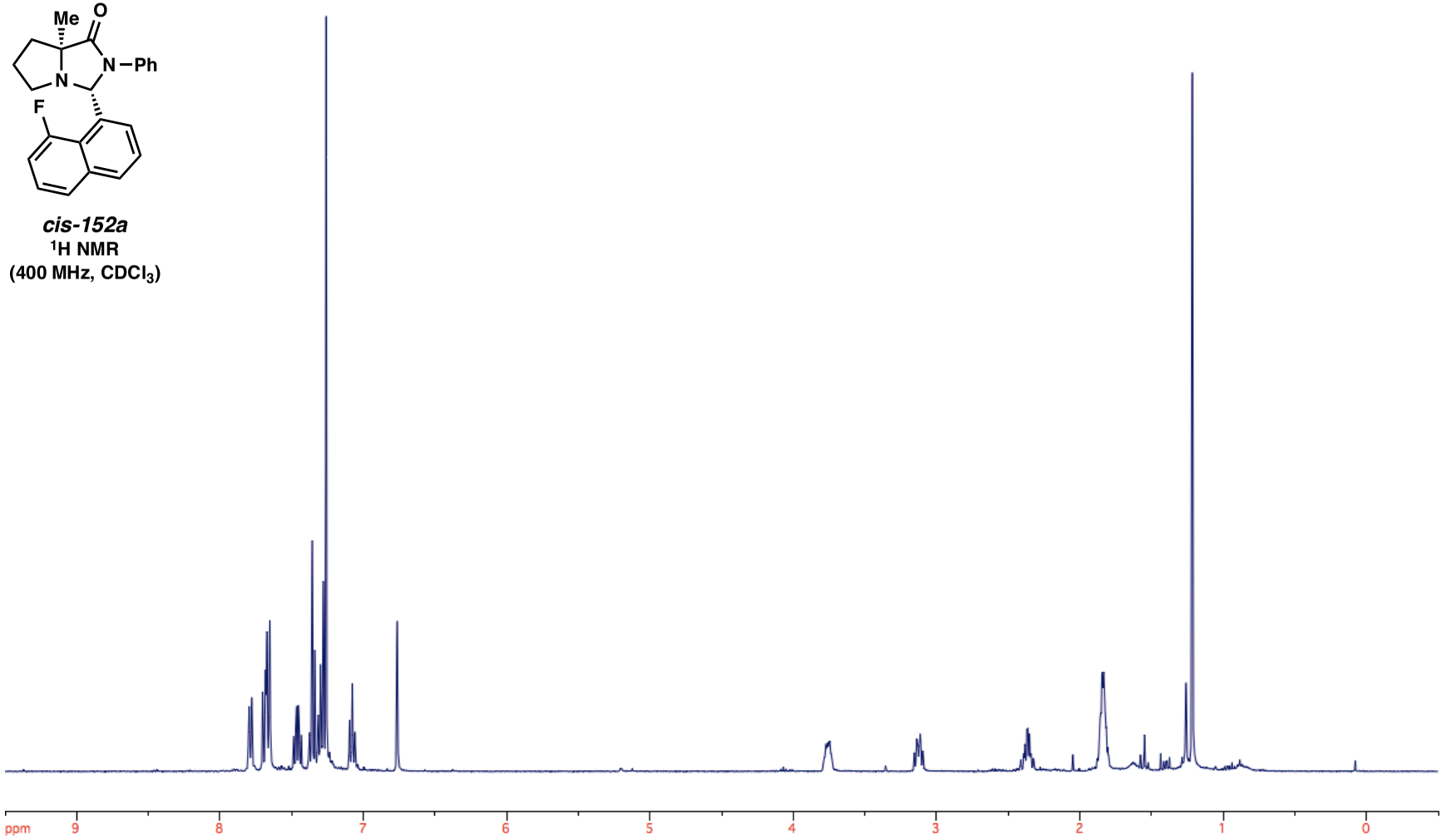


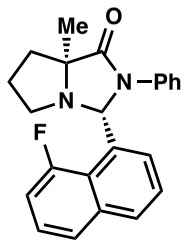
exo-4-131
^{13}C NMR
(100 MHz, $CDCl_3$)

exo-4-131
^{19}F NMR
(272 MHz, $CDCl_3$)

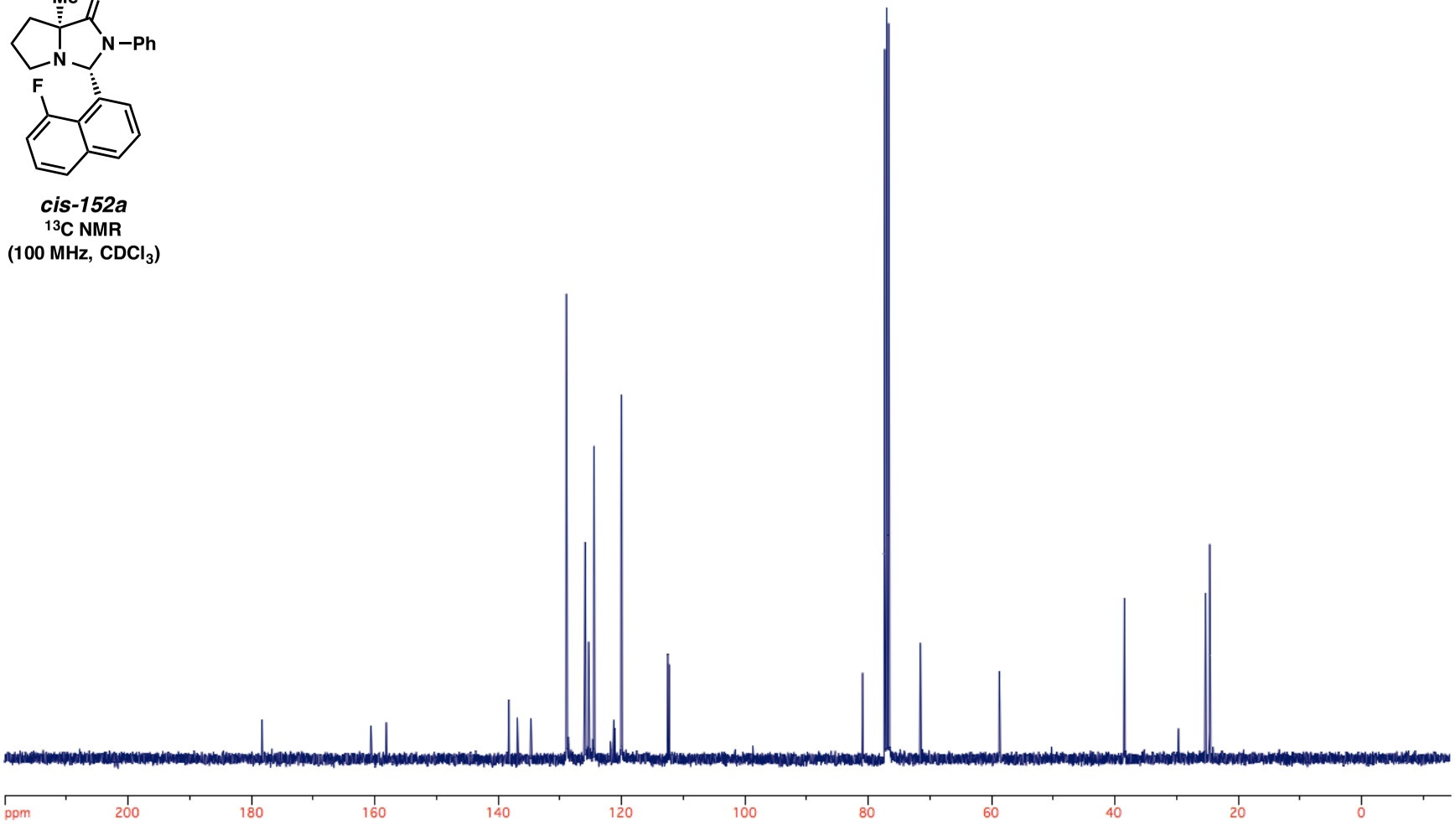


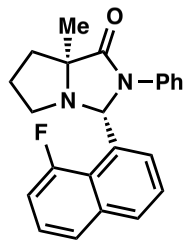
cis-152a
^{1}H NMR
(400 MHz, $CDCl_3$)



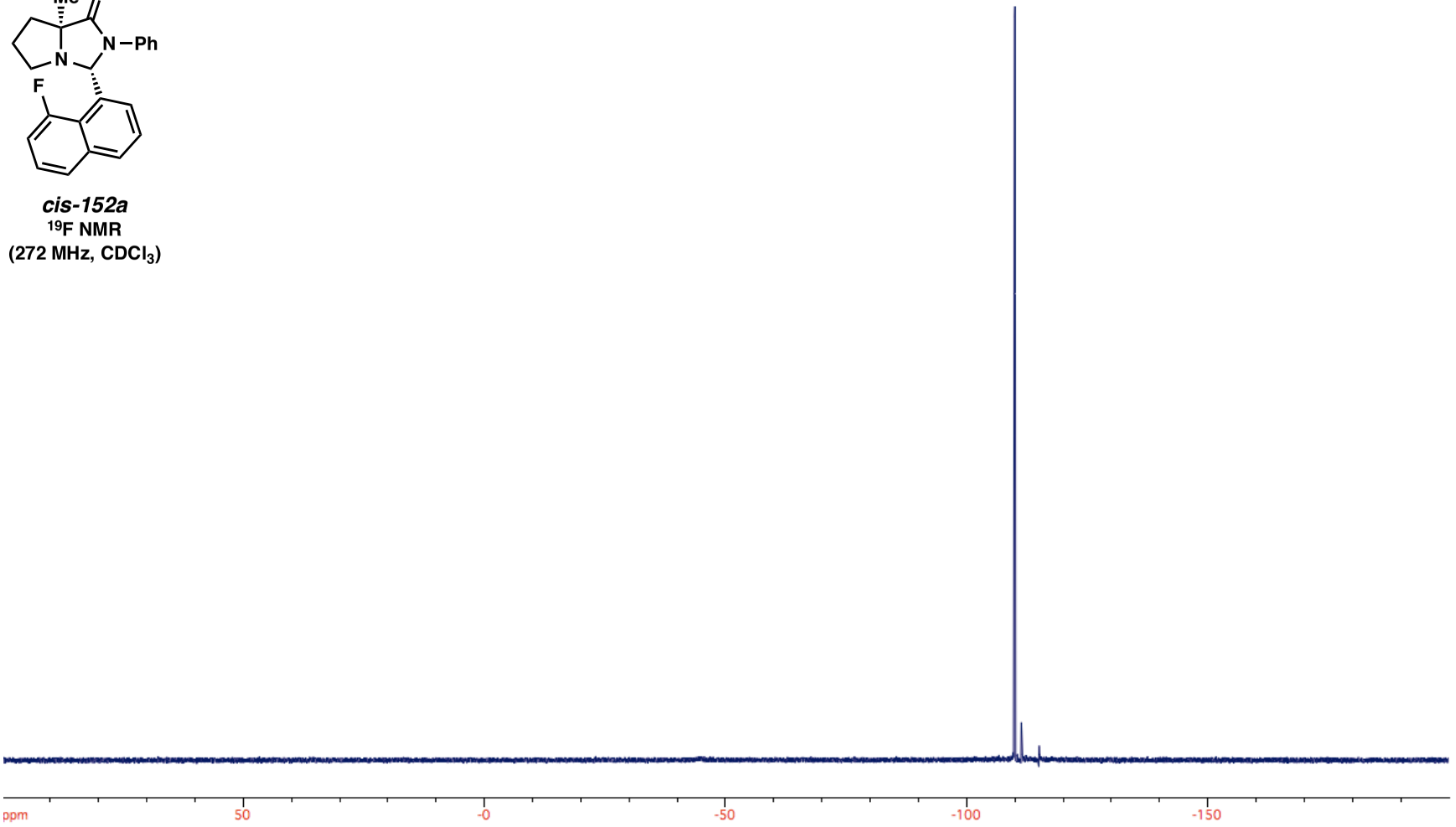


cis-152a
^{13}C NMR
(100 MHz, $CDCl_3$)

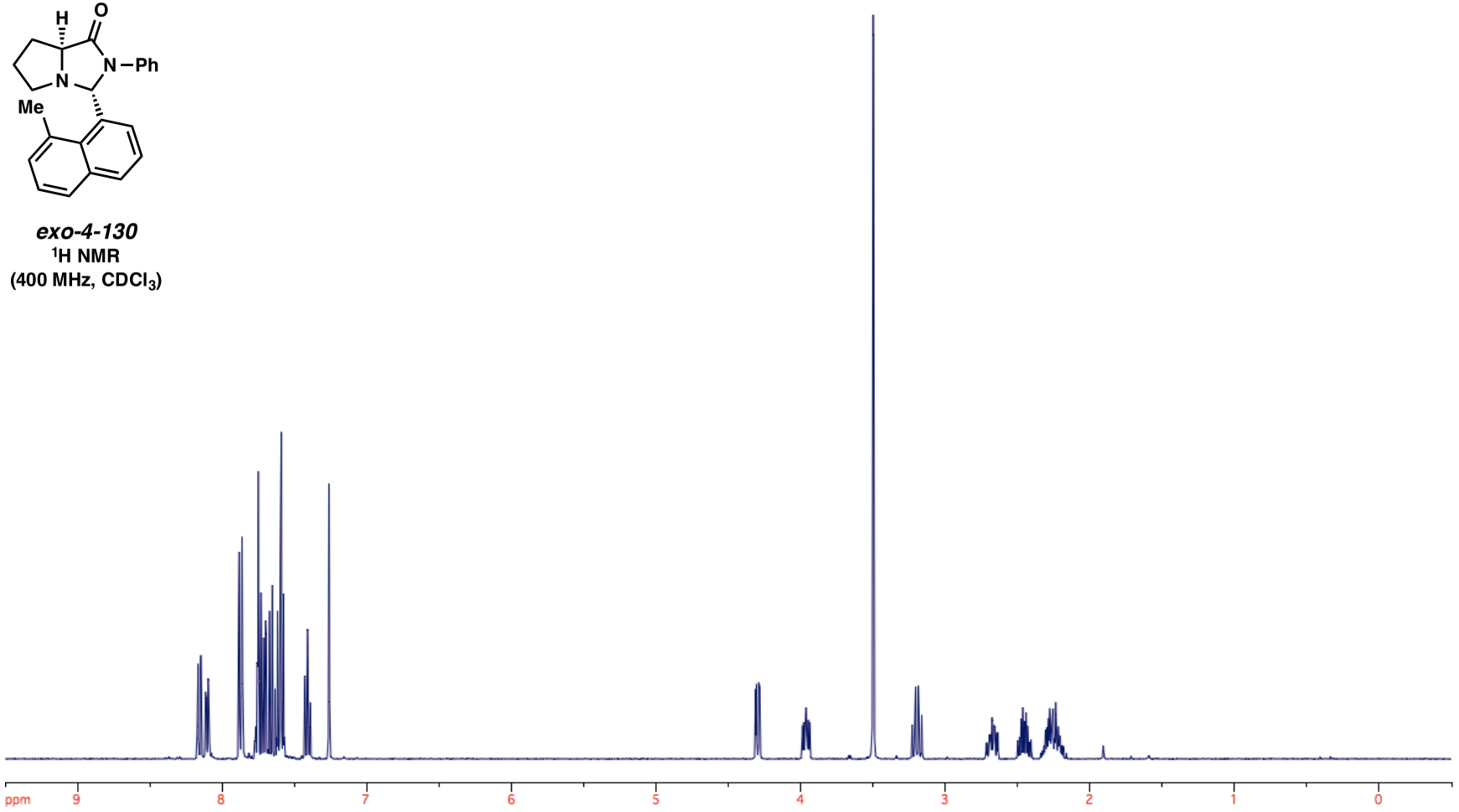




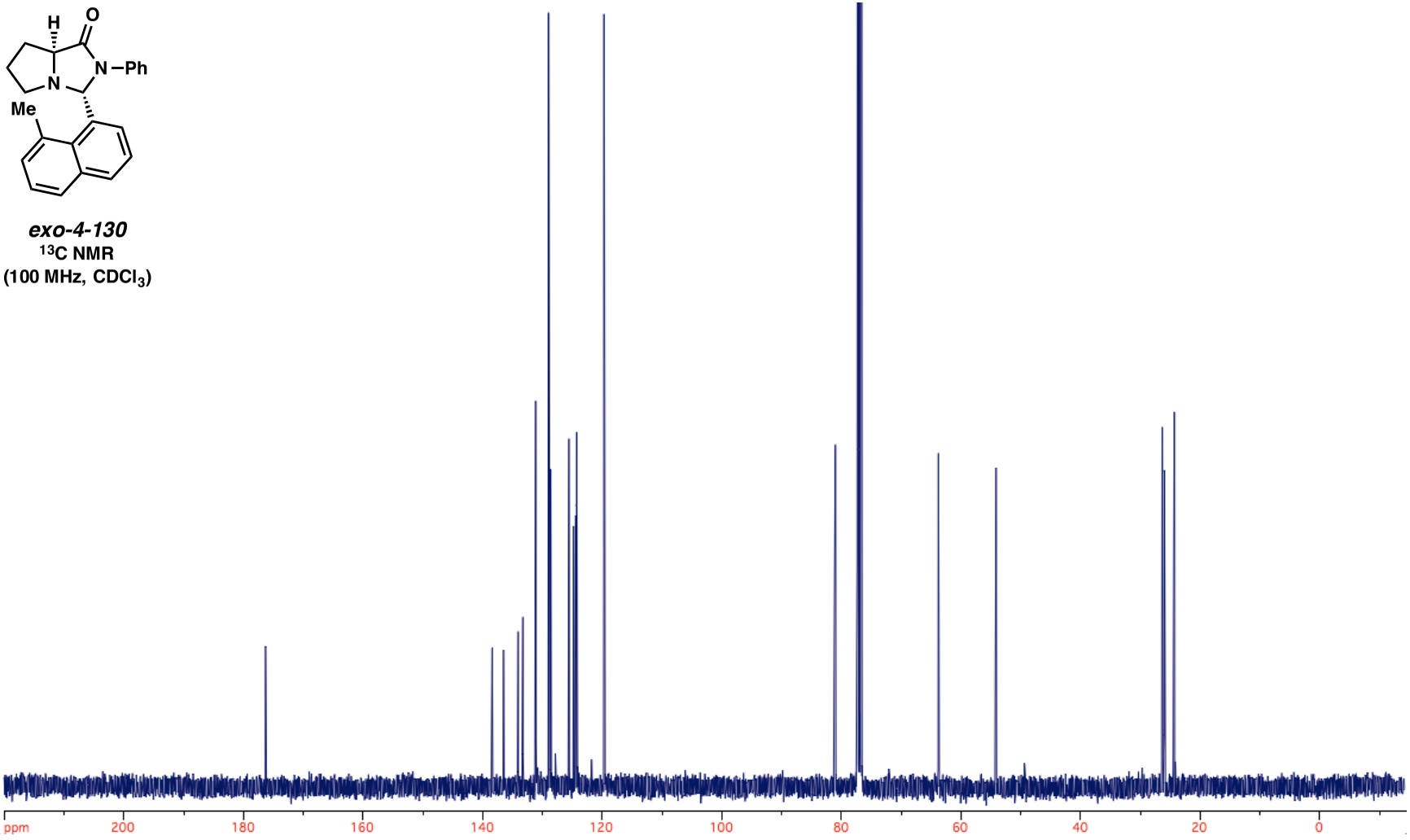
cis-152a
^{19}F NMR
(272 MHz, $CDCl_3$)



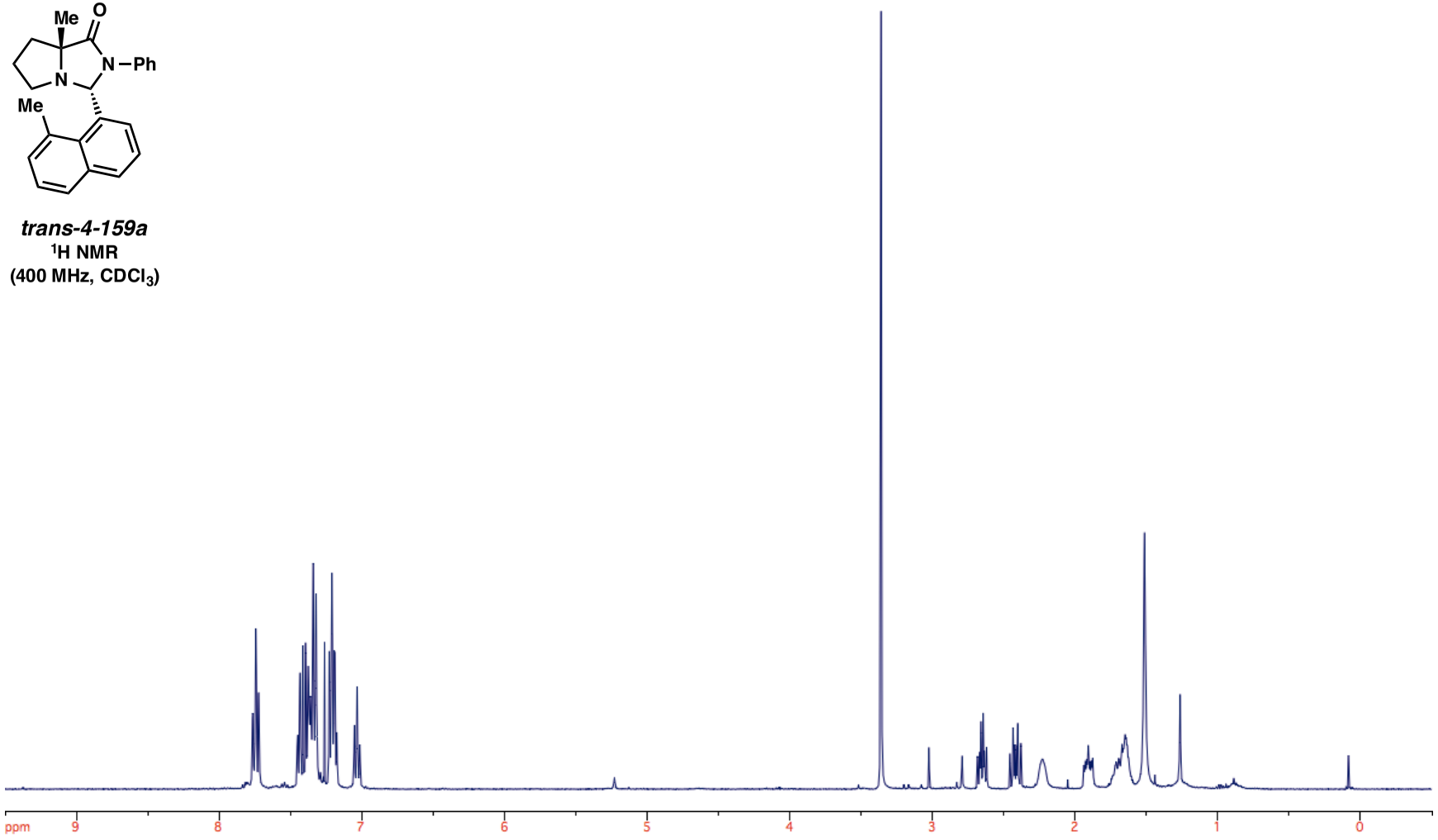
exo-4-130
^{1}H NMR
(400 MHz, $CDCl_3$)

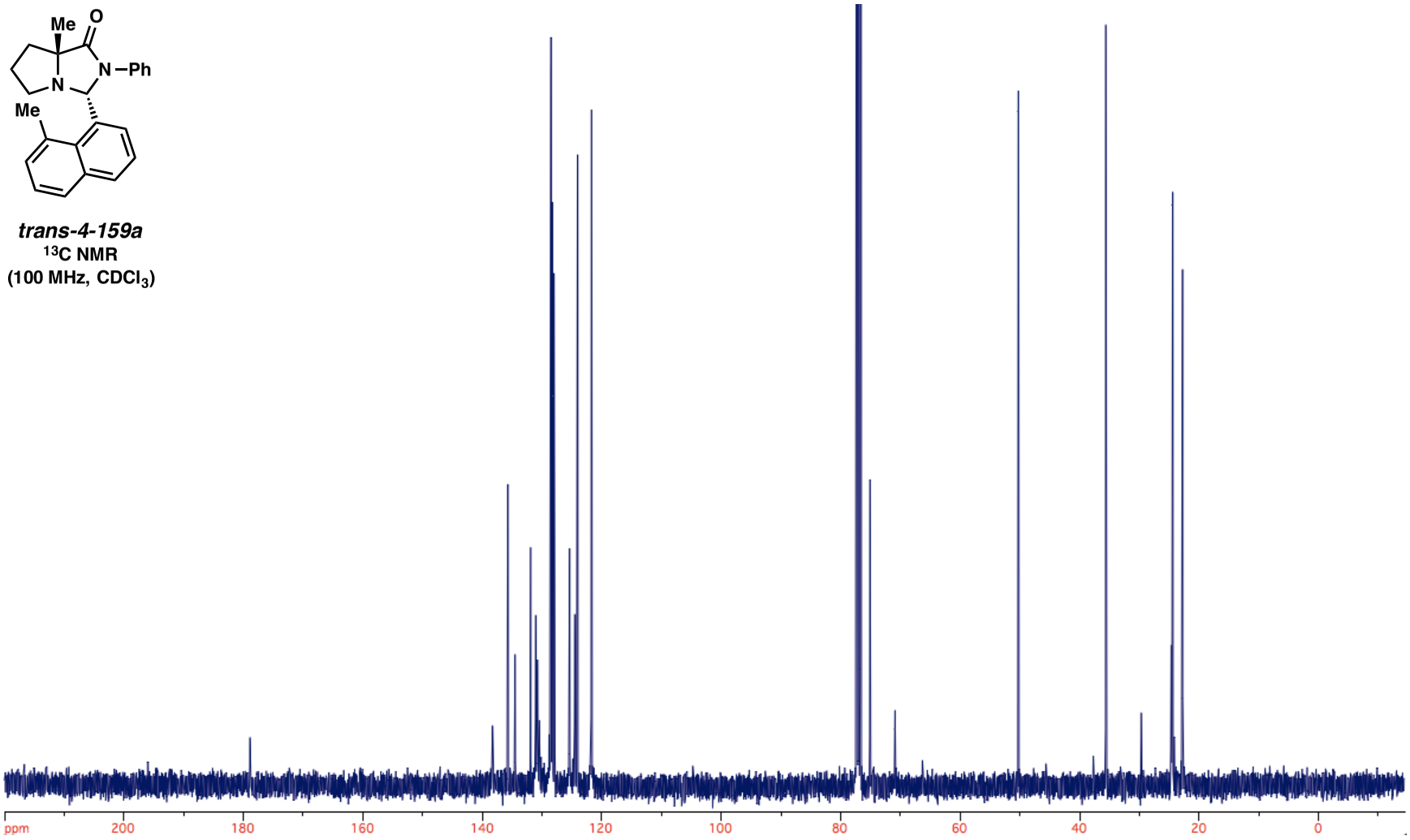


exo-4-130
^{13}C NMR
(100 MHz, $CDCl_3$)

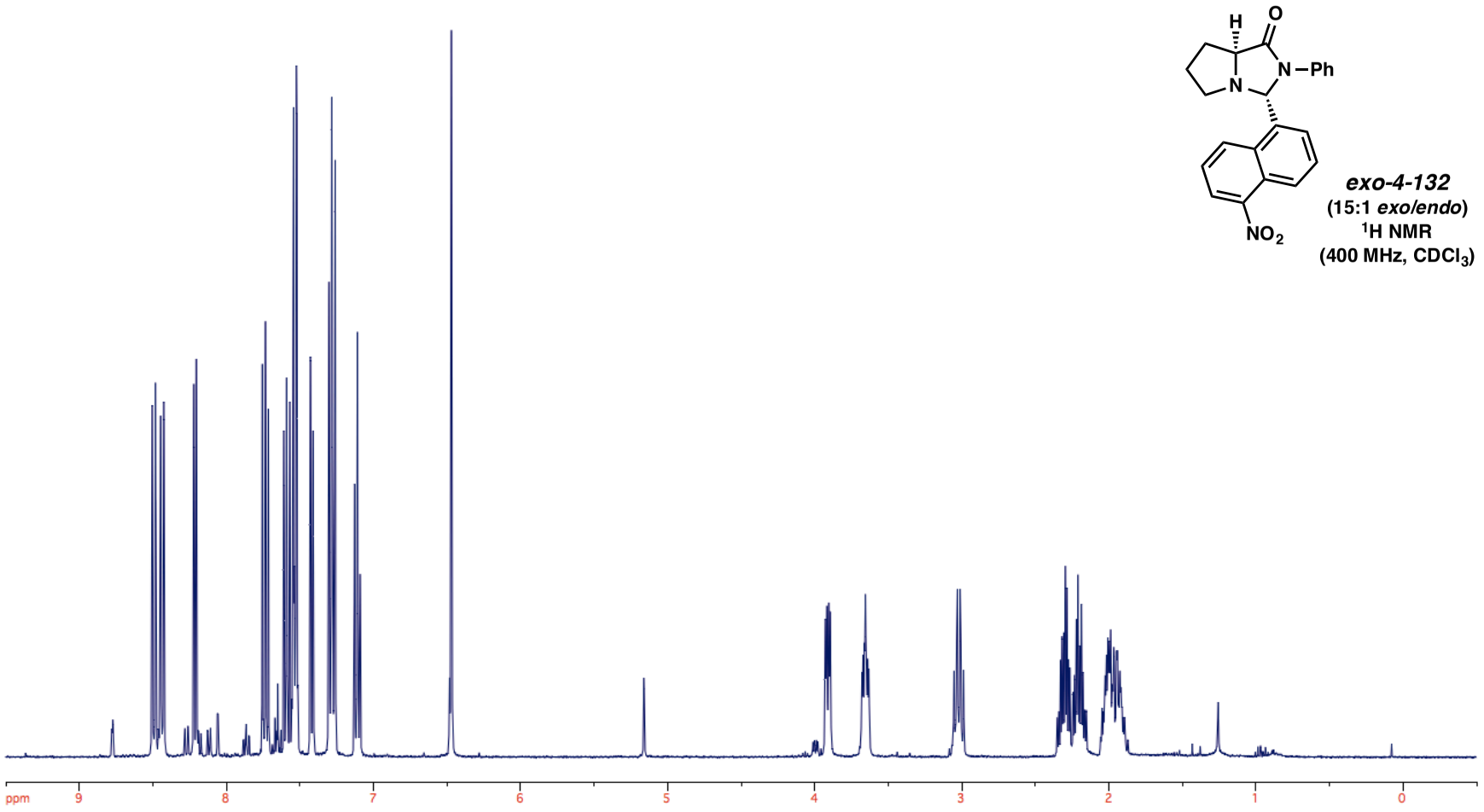


trans-4-159a
^{1}H NMR
(400 MHz, $CDCl_3$)

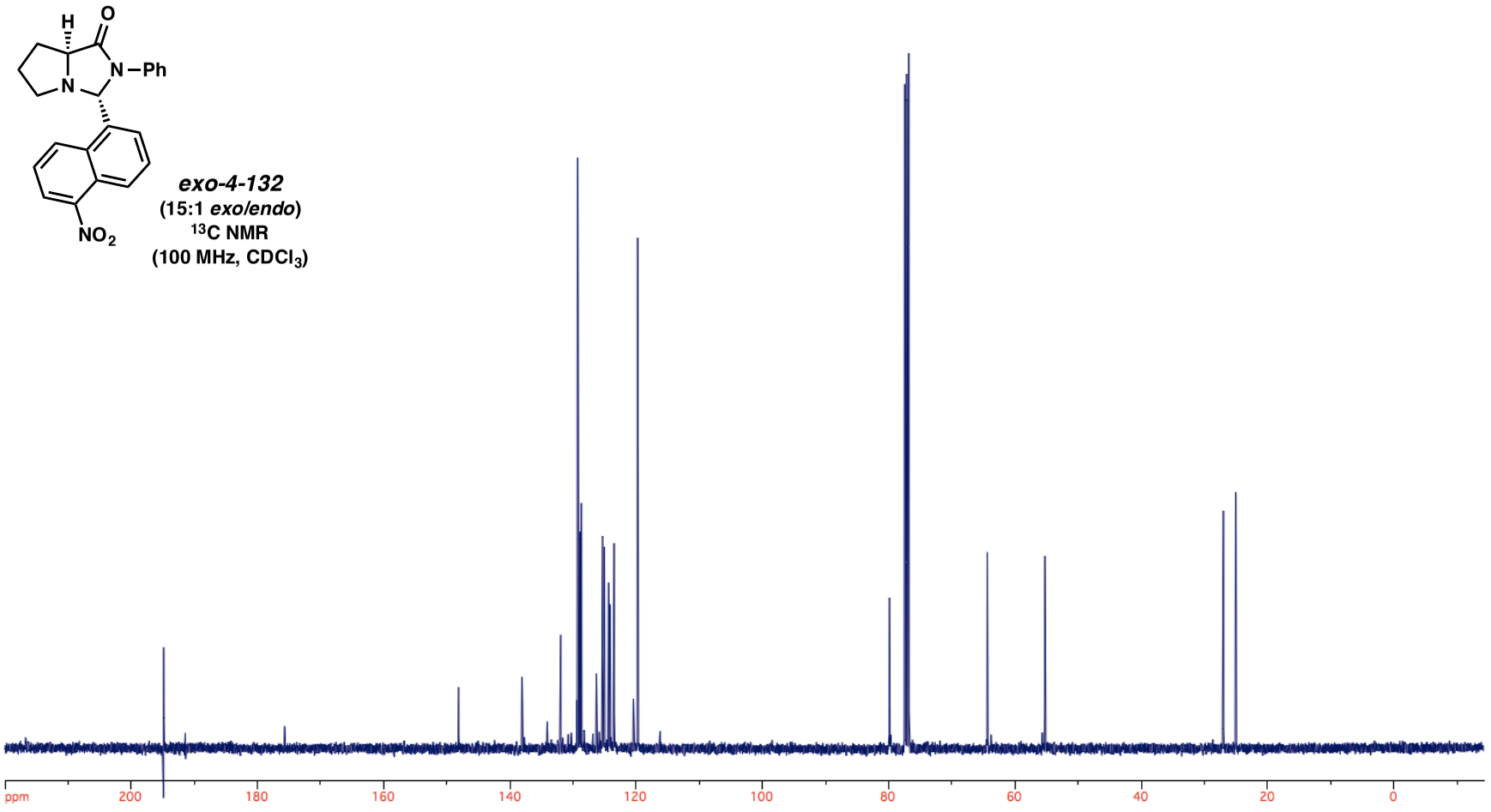




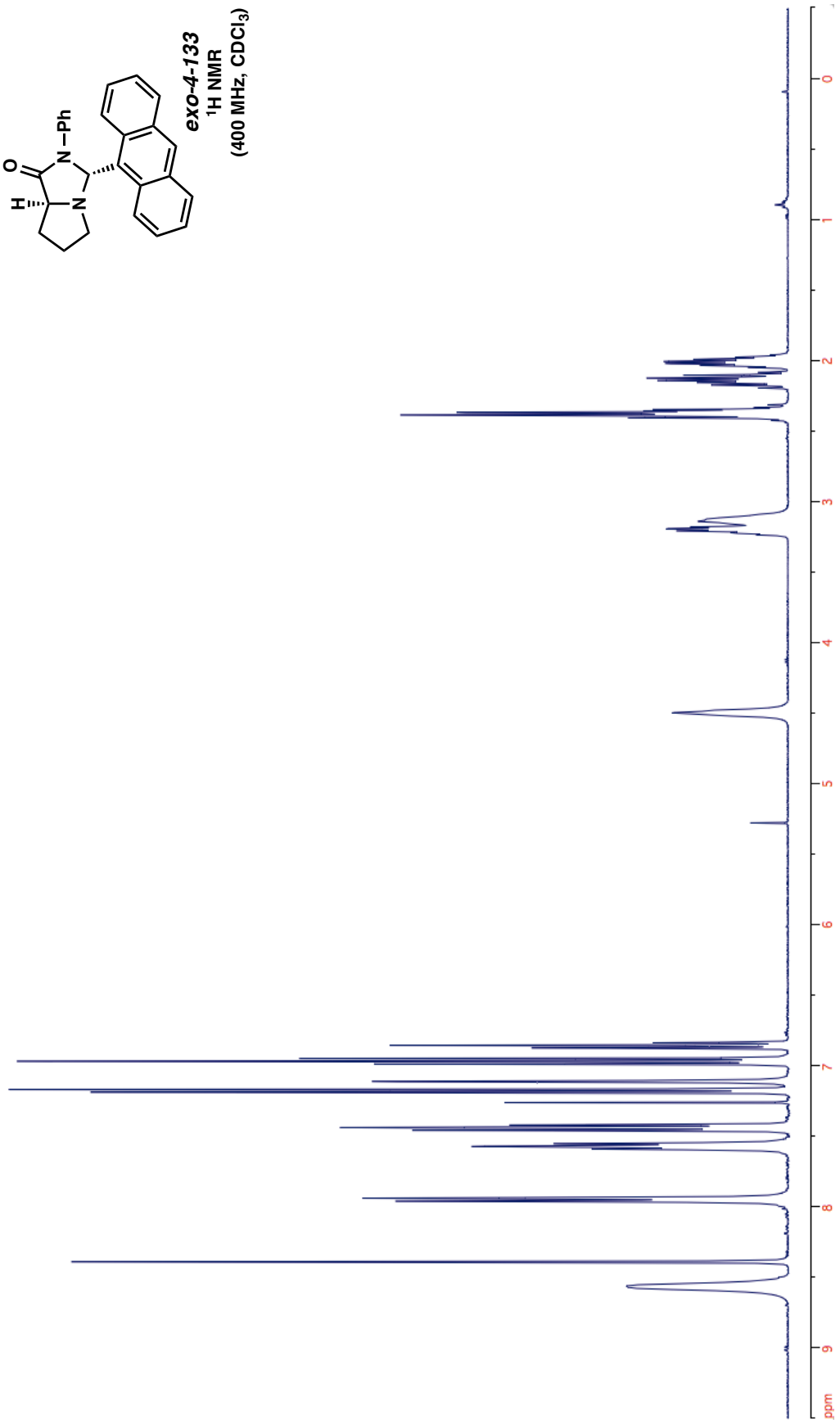
trans-4-159a
^{13}C NMR
(100 MHz, $CDCl_3$)

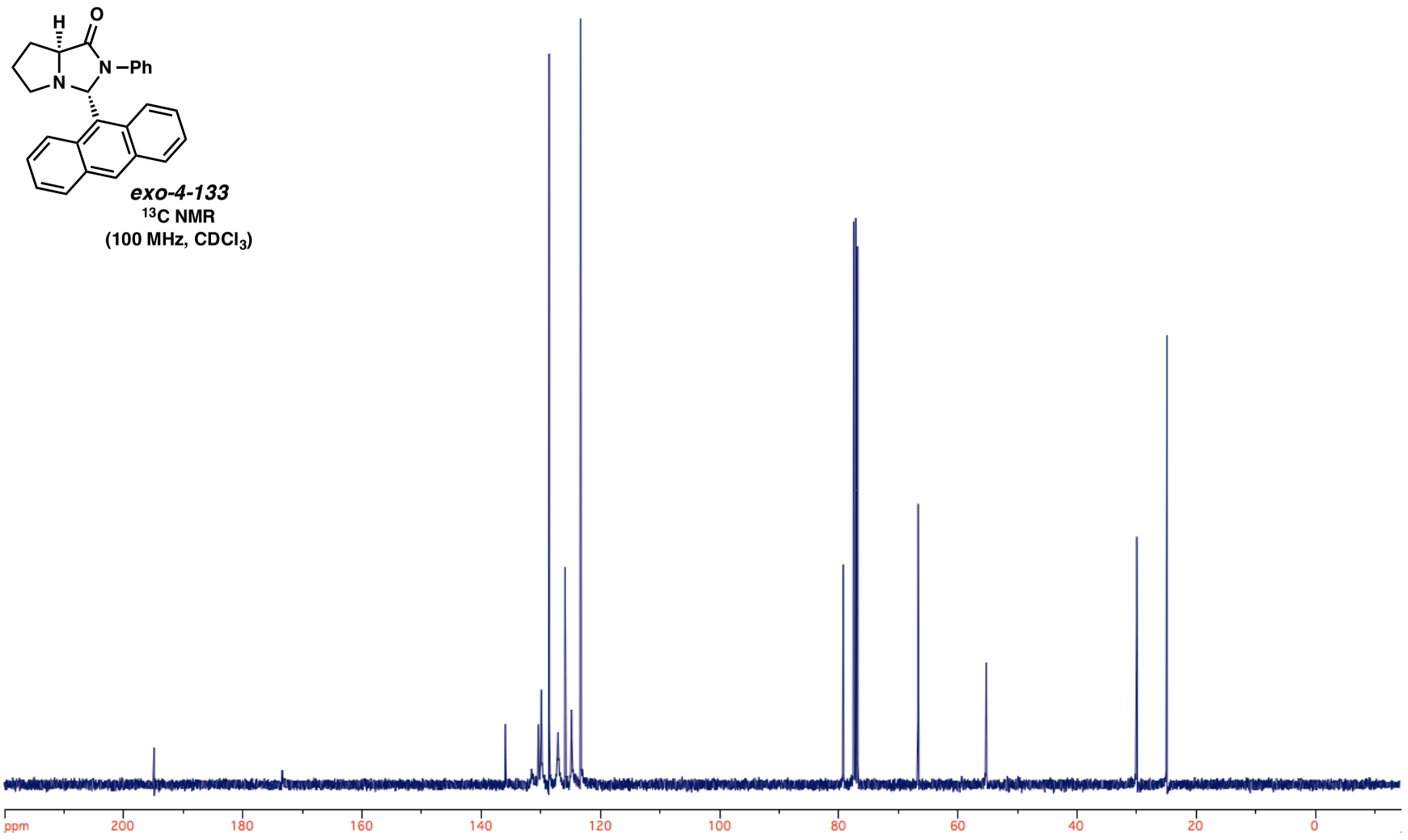


exo-4-132
(15:1 *exo/endo*)
^{1}H NMR
(400 MHz, $CDCl_3$)



exo-4-132
(15:1 *exo/endo*)
^{13}C NMR
(100 MHz, $CDCl_3$)


exo-4-133
^{1}H NMR
(400 MHz, $CDCl_3$)
O
H
N
N
Ph
ppm
0
1
2
3
4
5
6
7
8
9



exo-4-133

^{13}C NMR

(100 MHz, $CDCl_3$)

4.7 References and Notes

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(16) Pyramidalization of both nitrogens of the imidazolidinone should occur upon enolization. This orientation is aligned with a proposed transition state in the alkylations of imidazolidinones based on glycine derivatives. See: Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237−261.

(17) This orientation is aligned with a proposed transition state in the alkylations of imidazolidinones based on glycine derivatives. See: Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237−261.

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