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The Synthesis and Reactivity of Novel Donor-Acceptor Cyclopropanes and Progress Towards Pyrrolidine Alkaloids

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Graduate Program in Chemistry
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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by

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Abstract and Key Words

Abstract – The first chapter of this thesis focuses on the synthesis and reactivity of cyclopropane hemimalonates. The cyclopropane hemimalonates can easily be synthesized from 1,1-cyclopropanediesters. The reactivity of cyclopropane hemimalonates with indole under ultra-high pressure conditions leads to ring opened adducts that are complementary to previous research in the Kerr group. The tandem ring opening decarboxylation reaction of cyclopropane hemimalonates led to the synthesis of γ-aminobutyric acid analogues. When an external nucleophile was not present, the cyclopropane hemimalonates could rearrange to form butyrolactones in good to excellent yields. The stereochemical integrity of the cyclopropane hemimalonate is retained through this process, which is not usually seen in cyclopropane reactivity.

The second chapter describes the progress towards the synthesis of Kainic acid. While the progress towards this natural product appeared to be going well, after closer analysis of the products, a new reactivity of diazo species and cyclopentadiene was realized.

In the third chapter, the progress towards the synthesis of Actinophyllic acid is provided. Synthesis of advanced intermediates was completed, however the key formation of a 1,4-dicarbonyl species of the pyrrolidine ring eluded this study.

Key Words: Cyclopropanediesters, Cyclopropane Hemimalonate, γ-aminobutyric acid, Butyrolactone, Methodology, Natural Product, Kainic Acid, Pyrrolidine, Actinophyllic acid, Total Synthesis

Co-Authorship

Chapter 1 involves some collaborative work with Huck Grover. In Section 1.6, Huck completed the syntheses of the electron neutral and electron-poor aryl products. In Section 1.7, Huck completed the synthesis of the electron-rich aryl butyrolactones and the total synthesis of (R)-(+)-dodecan-4-olide, while I completed the degradation studies to determine the rotation and the enantiomeric excess of the starting material and product for the total synthesis. The total synthesis has been placed in this thesis to provide the application of the transformation.

Acknowledgements

I would like to thank my supervisor, Mike Kerr, for taking me on as his first graduate student in four years. Our relationship really grew when I became the senior Kerr group student after only a one year of grad school and your enthusiasm for chemistry has been an inspiration over the last six years. I would also like to thank him for the many late night talks over many glasses of scotch that helped me keep my priorities in order throughout the years.

I would like to thank all of the members of the Kerr research group, who would help keep things light in the lab when it was needed. In particular, I have to thank Huck Grover, who not only collaborated with me on two publications, but has also been one of the best friends anyone could ask for. We had to learn and grow as chemists a lot faster than I think we had originally attended and I know I couldn't have gotten to where I am today without you. I would also thank Katarina Sapeta, who supervised me when I entered the Kerr lab for my fourth year honours project. I had zero knowledge of synthetic organic chemistry when I entered the lab and you didn't hold it against me. Although we didn't leave on the best of terms, I cannot thank you enough for making me feel like a member of the Kerr group from day one. To the past members of the Kerr group (Dr. Cheryl Carson, Dr. Andrew Leduc, Dr. Terry Lebold, Dr. Michael Johansen and Dr. Avedis Karadeolian), you all set such impressive examples to try and live up to and the work ethic shown by all of you had a positive effect on my time in the group. To my current lab mates (Huck Grover, Erin Armstrong, Michelle Flisar, Joanne Curiel-Tejeda and Matt Vriesen) thank you for your support throughout the years and I hope I have been able to assist you in your studies so far, I know we have big things in the pipeline that should come to fruition soon. To the boys down the hall (Polydoros Kyriacou, and B-Ryan Landschoot), we have had a lot of fun over our time together. Poly, apparently we took classes together in undergrad, but you have been a great friend over the years. B-Ryan, always quick with a joke or a funny story, you have made the last two years of my time in the group a blast.

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I would like to thank my family for always supporting me over the last nine years here at Western. I don't know if you agreed with me when I informed you that I was going to Western to pursue a degree in chemistry, or when I said I would be pursuing a graduate degree, but your love and support remained unwaivered and I couldn't have completed this without you.

I would also like to thank my girlfriend Jess Avery. She has always supported my decisions throughout my career here and has helped knock me down a few pegs when it was necessary. Without you, I don't know where I would be today, but I know I am a better person today because of you. I am very fortunate to have met you in our third year of undergrad and cannot wait to see what our future holds together.

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List of Abbreviations

1,2-$C_6H_4Cl_2$	1,2-dichlorobenzene
$[\alpha]_D^{23}$	Specific Rotation in degrees at 23˚C
A	Acceptor
Å	Angstrom
Ac	Acetyl
acac	Acetylacetone
Alloc	Allyloxycarbonyl
CAN	1,1'-Azobiscyclohexanecarbonitrile
AcOH	Acetic acid
Ar	Aryl
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
c	Concentration
C	Celsius
calc'd	Calculated
CAN	Ceric ammonium nitrate
cat.	Catalyst
Cbz	Carboxybenzyl
Cp	Cyclopentadiene
COD	Cyclooctadiene
COSY	Correlation spectroscopy
CPU	Carboxypeptidase U
d	Doublet
D	Donor
DBU	1,8-Diazabicycloundec-7-ene

DCC	Dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DIBAL-H	Diisobutylaluminum hydride
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMP	Dess-Martin Periodinane
DPPA	Diphenylphosphoryl azide
dppb	1,4-Bis(diphenylphosphino)butane
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
dt	double of triplets
DyKAT	Dynamic Kinetic Asymmetric Transformation
E	Electrophile
ee	Enantiomeric excess
eq	Equivalents
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
FT-IR	Fourier Transform Infrared
G2	Grubbs 2nd Generation Catalyst
GABA	*gamma*-aminobutyric acid
h	hours
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMDS	Hexamethyldisilyl

HMPA	Hexamethylphosphoramide
HPLC	High-performance Liquid Chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
In-TOX	Indane−trisoxazoline
IBX	2-Iodoxybenzoic acid
i-Pr	isopropyl
J	Coupling constant
kbar	Kilobar
LDA	Lithium diisopropylamide
LG	Leaving group
m	multiplet
M	Metal or molar concentration
Me	Methyl
MeOH	Methanol
$MeNO_2$	Nitromethane
MS	Molecular Sieves
MsCl	Methanesulfonyl chloride
mW	Microwave
n-Bu	Butyl
NDMBA	N,N'-dimethylbarbituric acid
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
NTf_2	Triflimide
Nu	Nucleophile
OTf	Triflate
P1	Amidoporphyrin ligand
p-ABSA	*para*-Acetamidobenzenesulfonyl azide
PDC	Pyridinium dichromate

Ph	Phenyl
PhCN	Benzonitrile
Pg	Protecting group
PMP	*para*-methoxyphenyl
ppm	Parts per million
Py	Pyridine
pybox	Pyridine bis(oxazoline)
q	quartet
R,X	Generic Atoms
s	singlet
Sal	Salen ligand
S_N'	Nucleophilic Substitution at an adjacent position
S_N1	Unimolecular Nucleophilic Substitution
S_N2	Biomolecular Nucleophilic Substitution
TBAF	*tetra*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl; bis(salicylidene-*tert*-butylamine)
TBSCl	*tert*-butyldimethylsilyl chloride
*t*Bu	*tert*-butyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TFAA	Trifluoracetic anhydride
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Tol.	Toluene
Ts	*para*-toluenesulfonyl
TsCl	*para*-toluenesulfonyl chloride
TsOH	*para*-toluenesulfonic acid

Chapter 1 The Synthesis and Reactivity of Cyclopropane Hemimalonates

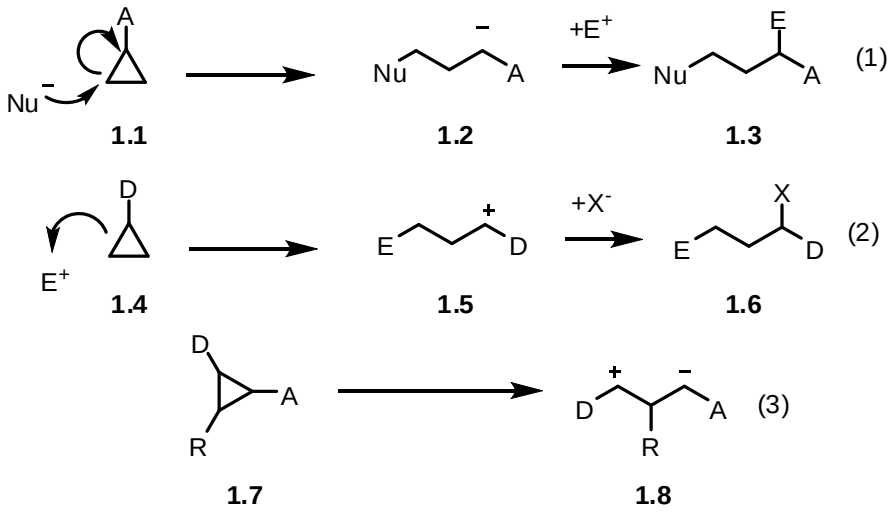
Chapter 1 describes the development of a new type of donor-acceptor cyclopropane and the expansion of current group methodology through the nucleophilic ring opening of cyclopropane hemimalonates with indole under ultra-high pressure conditions. A brief overview of the structure and bonding of cyclopropanes as well as their reactivity with indole and dipoles to form five-membered rings will be provided. This is followed by the ring opening of cyclopropanes to form γ-aminobutyric acid (GABA) products and the synthesis of γ-butanolides from cyclopropanes. The research presented in Section 1.5 was completed by myself alone and the results have been published in a peer reviewed journal.[1] Reproduced in part with permission from Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180-4183. Copyright 2011 American Chemical Society. The research presented in Sections 1.6 and 1.7 was completed in collaboration with Huck Grover. The results from Sections 1.6[2] and 1.7[3] have been published in peer reviewed journals. Section 1.6 was reproduced in part with permission from Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem.* **2012**, *77*, 6634-6637. Copyright 2012 American Chemical Society. Section 1.7 was reproduced in part with permission from Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Lett.***2013**, *15*, 4838-4841. Copyright 2013 American Chemical Society.

Section 1.1 Introduction

Section 1.1.1 Structure and Bonding of Cyclopropanes

Cyclopropanes are three-membered carbocycles that display a variety of different reactivity. Simplistically they are drawn as equilateral triangles with bond angles of 60°, which is a large deviation from the standard tetrahedral bond angle of 109.5. Due to the constraints on this ring system, it is believed that the electron densities of the cyclopropyl bonds are off-center and resemble more of a banana-type bond[4]. This bonding phenomenon has been used to explain the observation that cyclopropanes display reactivity common to olefins[5]. Though these three membered rings have a large amount of angular ring strain, 115 kJ/mol,[6] the bonds are kinetically inert without substitution or activation. The substitution pattern about the three membered rings governs the reactivity of these molecules and they are classed as such: acceptor, donor or donor-acceptor

cyclopropanes. Acceptor groups are typically electron-withdrawing groups with the ability to stabilize an adjacent negative charge through resonance. Examples include carbonyls, nitro or sulfonyl groups. Acceptor cyclopropanes **1.1** pull electron-density out of the ring, which can allow nucleophilic attack vicinal to the acceptor group (Scheme 1.1, equation 1). The donor class of cyclopropanes provides electron density to the cyclopropane ring, and hence gives the ring nucleophilic character. The ring-opening event creates a positive charge geminal to the donor group **1.5**, which stabilizes the charge, and allows for the addition of a nucleophiles at the geminal carbon **1.6** (Scheme 1.1, equation 2). The donor-acceptor class **1.7** highlights the best features of each of the previous classes, activating the ring in a synergistic fashion to allow a push-pull type mechanism to allow formation of a 1,3-dipole **1.8**.



Scheme 1.1: The Reactivity of Acceptor, Donor and Donor-acceptor Cyclopropanes

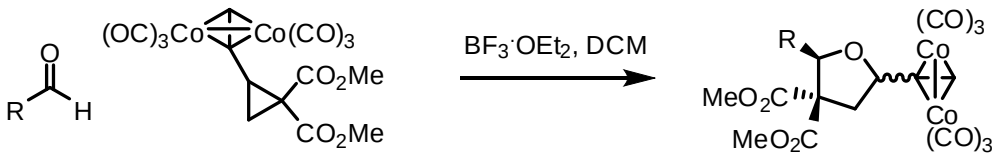
This dipole can react with another dipole to form annulated products, or it can simply react with a nucleophile to form acyclic products. Donor-acceptor cyclopropanes were first investigated in the 1960s and 1970s primarily by the groups of Stork[7-10] and Danishefsky[11-14], but it wasn't until the 1980s when the groups of Wenkert[15-16] and Reissig[17-25] investigated these molecules did they come to the forefront of organic chemistry. The ring opening of the donor-acceptor class of cyclopropanes will be the focus of the next section.

Section 1.2 Formation of Five Membered Heterocycles from Cyclopropanes

The ring expansion of donor-acceptor cyclopropanes have been applied to numerous synthetic applications and have also been used to make a number of natural products. This section will highlight the synthesis of five-membered heterocycles from aldehydes and aldimines. The use of nitriles or isocyanates have been omitted.

Section 1.2.1 Formation of Tetrahydrofurans

Carbonyls have been shown to be suitable dipoles for the formation of tetrahydrofurans with 1,1-cyclopropanediesters. The Christie group formed 1,2,5-tetrahydrofurans **1.11**[26] from the reaction of Nicholas activated cyclopropanes **1.10** and aldehydes **1.9** (Scheme 1.2). The alkynyl substituted cyclopropanes are complexed with cobalt which helps stabilize the developing positive charge at the 2-position of the cyclopropane under Lewis acid activation. Electron poor and aliphatic aldehydes participate in this reaction, while electron rich aldehydes are not compatible with the reaction conditions. An excess of Lewis acid is required to prevent cyclopropyl lactonization.

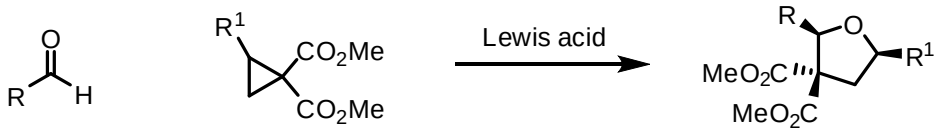


1.9 **1.10** **1.11**

Scheme 1.2: Christie Group Tetrahydrofuran Synthesis

The Johnson group at the University of North Carolina has been one of the pioneers in the field of tetrahydrofuran syntheses from cyclopropanes. They initially developed the cyclization of aryl and vinyl cyclopropanediesters **1.12** with a variety of aldehydes **1.9** (Scheme 1.3). Under tin triflate catalysis, they received excellent yields and *cis*-diastereoselectivity.[27,28] However, when an aliphatic aldehyde was a desired reaction partner tin tetrachloride was necessary to activate the cyclopropane, and under these

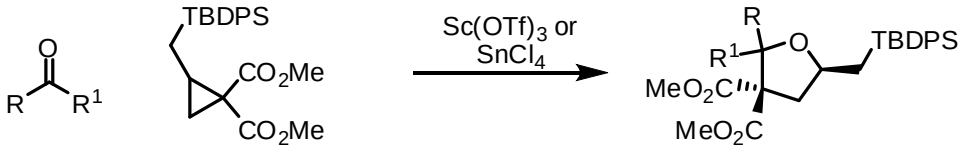
conditions the diastereoselectivity was suppressed. They also explored ketones for this reaction with their only success coming from the use of acetone. While investigating the mechanism of this transformation, they noticed that they were getting racemization of their starting material cyclopropanes.[29] This led them to the development of a Dynamic Kinetic Asymmetric Transformation (DyKAT) of this cycloaddition.[30] When using Magnesium Iodide as the Lewis acid and a chiral pybox ligand, they could form enantioenriched products from racemic cyclopropanes.



1.9 **1.12** **1.13**

Scheme 1.3: Johnson Group Tetrahydrofuran Syntheses

In 2006, the Yadav group developed cyclopropanes with an aliphatic silane as the donor group, **1.15**.[31] By using the beta-silicon effect they could stabilize the generated positive charge, under scandium triflate catalysis, to form tetrahydrofurans **1.16** with aldehydes or cyclic ketones **1.14** (Scheme 1.4). When an acyclic ketone was used, it was necessary to use tin tetrachloride. Once again, the diastereoselectivity was *cis* with respect to the 2 and 5 positions of the tetrahydrofuran ring.

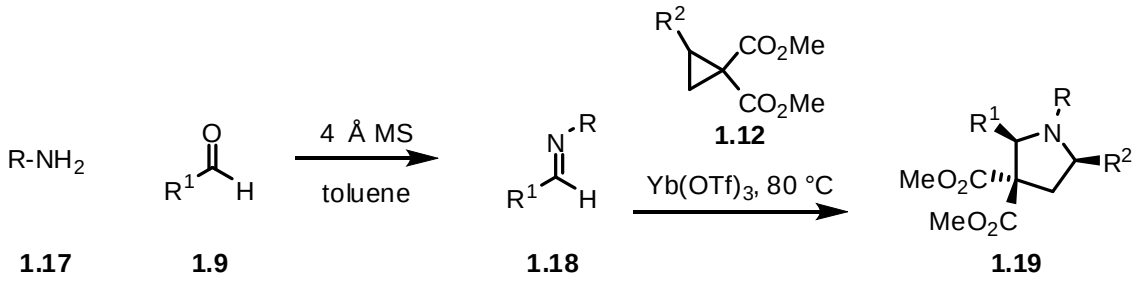


1.14 **1.15** **1.16**

Scheme 1.4: Yadav Group Synthesis of Tetrahydrofurans

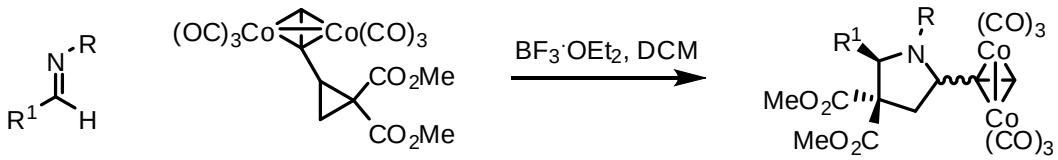
Section 1.2.2 Formation of Pyrrolidines

The analogous reaction using imines as the dipolar reaction partner has also been a well-developed reaction. In 2005, the Kerr group developed the reaction of aldimines and 1,1-cyclopropanediesters under ytterbium triflate catalysis to form 2,5-*cis*-pyrrolidines **1.19** (Scheme 1.5).[32] The aldimines **1.18** were formed in situ from the parent aldehyde **1.9** and an amine **1.17** by stirring over molecular sieves before the cyclopropane **1.12** was introduced to the reaction media. A wide variety of amines were amenable to the reaction conditions, but the aldehyde needed to be aromatic. Also, when the cyclopropane was unsubstituted, an aniline was necessary as the amine partner to form the pyrrolidine ring.



Scheme 1.5: Kerr Group Pyrrolidine Synthesis

The Tang group also developed a similar pyrrolidine synthesis using scandium triflate as their Lewis acid and dichloromethane (DCM) as their solvent.[33] Interestingly in their study, ytterbium triflate was not a catalyst that allowed their reaction to proceed. Once again a *cis*-diastereoselectivity was observed for this cycloaddition. Following their cyclizations of aldehydes with cyclopropanes, the Christie group also developed the synthesis of pyrrolidines **1.20** with the formation of aldimines **1.18**.[34] Once again they used Nicholas activated cyclopropanes **1.10** for these cyclizations. Though only a few examples were described in this report, the dependence on the temperature of the reaction was also studied. While the temperature used did not affect the selectivity of the reaction, only aromatic aldehydes could be used.



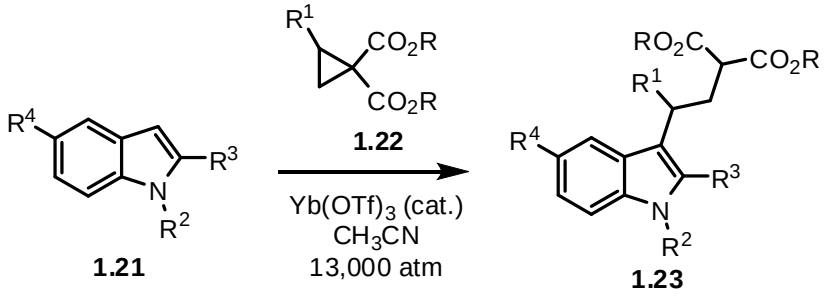
1.18 **1.10** **1.20**

Scheme 1.6: Christie Group's Analogous Pyrrolidine Synthesis

Section 1.3 Ring Opening of Cyclopropanes to Form Acyclic Adducts

Section 1.3.1 Ring Opening of Cyclopropanes with Indoles

While the cycloadditions of dipoles and cyclopropanes have been thoroughly investigated, the ring opening of cyclopropanes with various nucleophiles to form acyclic adducts has not been taken advantage of. The Kerr group has been interested in donor-acceptor cyclopropanes since 1997, when they discovered the ring opening of cyclopropanes **1.22** with indoles **1.21** at ultra-high pressures (Scheme 1.7).[35] This work was inspired by the ultra-high pressure reactions of indoles with electron-deficient olefins.[36]

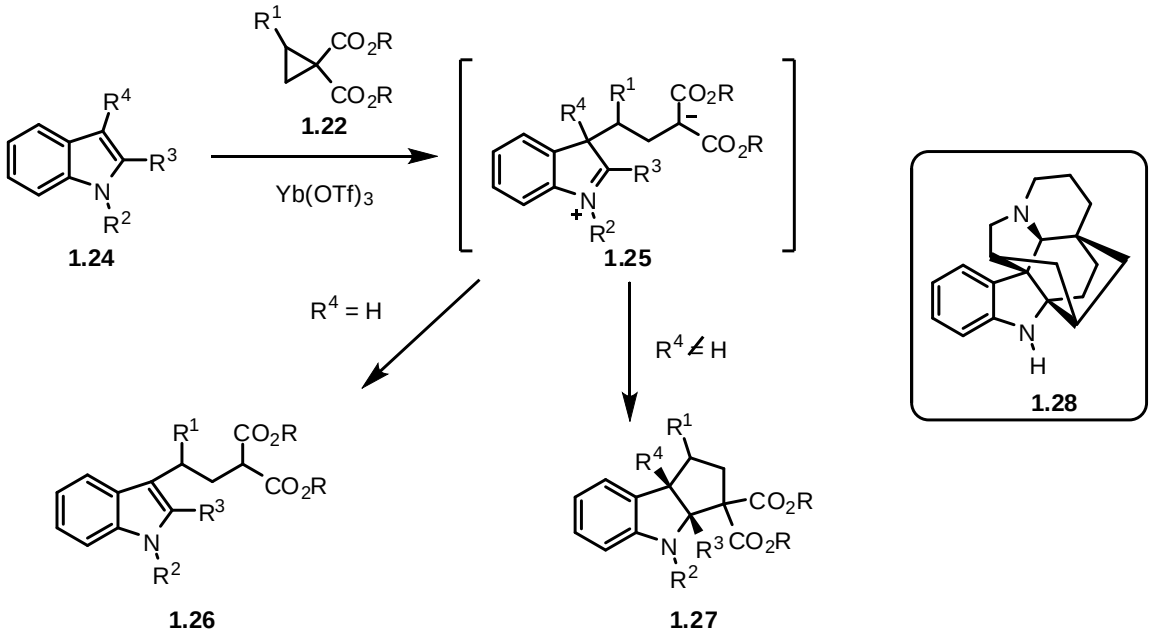


Scheme 1.7: The Reaction of Substituted Indoles with Cyclopropanediesters under Ultra-high Pressures and Lewis Acid Catalysis

Using the conditions from the previous report of Michael additions of indoles to electron poor acceptors as a starting point, the reaction was optimized. Through a scanning of solvents it was observed that acetonitrile was the optimal solvent. Interestingly, when trace amounts of water were present in the mixture the reaction was

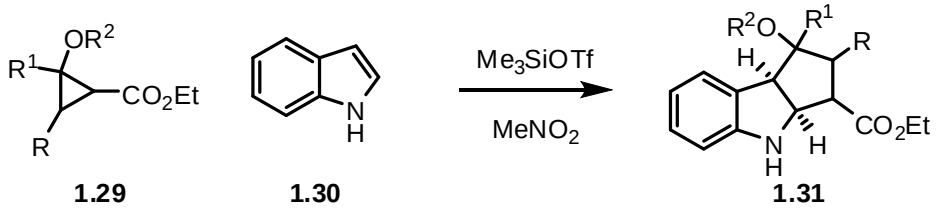
inhibited. This is contrary to previous reports that water was a good co-solvent for reactions at high pressures.[37] It was also contrary to the fact that ytterbium triflate showed no inhibition of Lewis acidity in the presence of water.[38] A small scope was investigated as only three cyclopropanes were tested. It is of note that the parent cyclopropanediesters reacted more efficiently than the alkyl substituted cyclopropane, as there was no group to stabilize the generated positive charge. Also of note was that the more electron-rich indole substrates produced products in higher yields.

In 1999, Kerr and Keddy further investigated this newly found reactivity by substituting the 3-position of the indole.[39] It was found that the cyclopropanes would ring open as before, but instead of a re-aromatization event occurring the malonyl anion **1.25** formed would close onto the iminium ion to form a pentannulated product **1.27** (Scheme 1.8). Gratifyingly, this reaction could be easily tested due to skatole, 3-methylindole, being commercially available. An early observation was that substitution was required at the nitrogen of the skatole, as a mixture of pentannulated and N-alkylated products were observed. This nitrogen was simply methylated or benzylated to solve this issue. Upon crystallization of the adducts, it was found that the ring formation was *cis* and the protecting group on the nitrogen did not affect the reaction. When there was substitution at the 2 and 3-positions of the indole as well, hyperbaric conditions were needed to force the reaction to proceed. It is of note that when higher temperatures were employed a C-3 to C-2 migration was observed. The substructure of the annulated product can be seen in the core of Kopsane **1.28**.



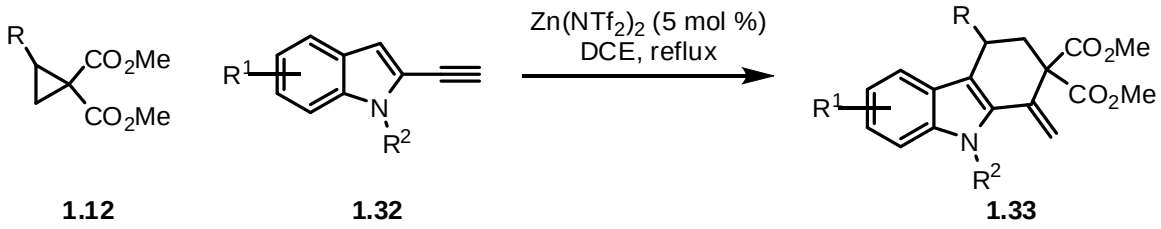
Scheme 1.8: The Reaction of Cyclopropanediesters with Substituted Indoles

In 2007, Pagenkopf and co-workers developed a slightly different modification on the cyclopropane and investigated their opening with indoles.[40] The modification involved increasing electron-donating ability of this group by simply using enol-ether derived cyclopropanes **1.29**, instead of using cyclopropanes with π-electron donating groups. These more activated cyclopropanes underwent smooth ring opening and annulation onto the 2-position of the indole ring **1.31** (Scheme 1.9). This is a nice contrast to the previously described example as substitution is not necessary on the 3-position to have the annulation proceed. This reaction worked smoothly for a variety of different substituted cyclopropanes, such as cyclic ethers, exocyclic ethers or non-cyclic ethers. When skatole was utilized, they produced addition products at the 2-position with elimination of the ether moiety. These adducts could be treated with either base to cyclize onto the nitrogen of the indole to form an amide or the ester could be reduced and the resulting aldehyde could be trapped by the nitrogen to form an aminal with the nitrogen.



Scheme 1.9: Pagenkopf Group Ring Opening of Cyclopropanes with Indoles

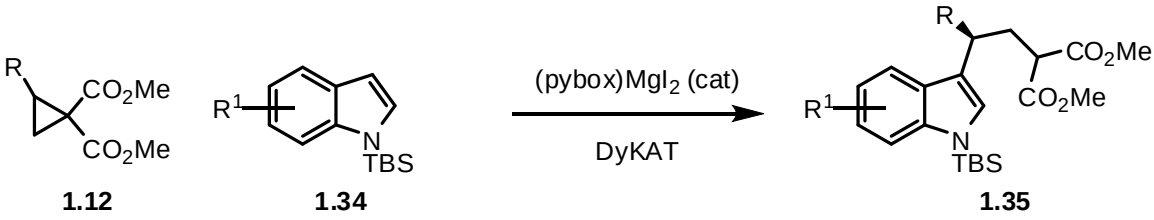
In 2009, the Kerr group developed a new concept where they could tether a nucleophile and an orthogonal electrophile together to receive pyrans[40] and piperidines.[41] In 2011, the Kerr group extended this concept by attaching an alkyne to the 2-position of the indole ring **1.32** (Scheme 1.10).[43] With the ring-opening process already being well developed in the group, the challenge became whether or not the same Lewis acid could be oxophilic enough to activate the diesters and soft enough to activate the alkyne towards cyclization to give **1.33**. With the previous methodologies already developed, it didn't take long to find that the optimal catalyst to complete both reactions was zinc triflimide. This reaction worked well for a wide scope of different cyclopropanes **1.12**, with the parent cyclopropanediesters proceeding in a 14% yield. An investigation into the substitution pattern on the alkyne as well as the mechanism of the reaction was investigated.



Scheme 1.10: Kerr Group Tandem Indole Ring Opening/Conia-ene Sequence

In 2013, Johnson developed a DyKAT in which they took racemic cyclopropanes and could open them with indoles to receive enantioenriched adducts (Scheme 1.11).[44] As the Johnson group has been well versed on DyKAT reactions of donor-acceptor cyclopropanes, they started with their standard MgI_2·pyBox catalyst, and tested the role of

protecting groups on indole. They quickly learned that they needed to temper the reactivity of the indole so that the racemization of their starting cyclopropane was a competitive process to the indole alkylation. After optimization, it was found that a TBS-protected indole **1.34** worked the best for this process. In their substrate scope, they found that a wide variety of cyclopropanes would undergo this DyKAT with good to excellent enantiomeric ratios. The DyKAT is working by a type I method; the catalyst combines with their starting material (cyclopropane in this case) and one of the diastereomeric metal complexes reacts faster than the other. This was verified through a test study where they took the racemic and both enantiomers of the phenyl-substituted cyclopropanediesters and tested them under their reaction conditions and what was observed was that the S-enantiomer of their starting material reacted approximately 5 times faster than the R enantiomer.

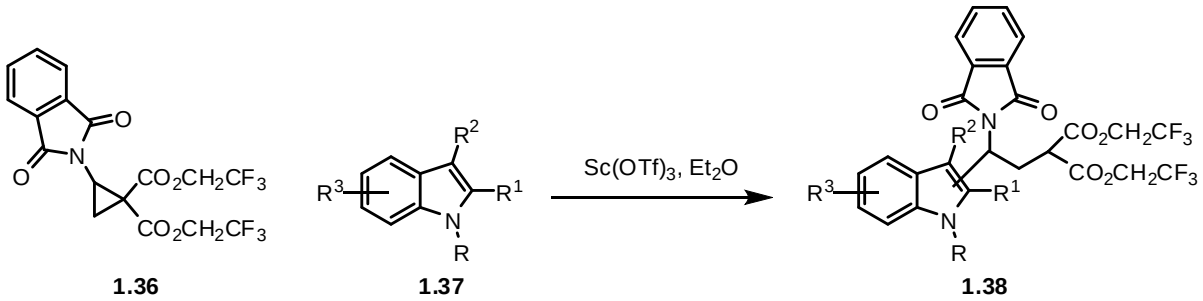


1.12 **1.34** **1.35**

Scheme 1.11: Johnson Group DyKAT Ring Opening of Cyclopropanes with Indoles

In 2013, Waser proposed a different donating group on the cyclopropane in order to furnish reactivity.[45] The idea was analogous to the Pagenkopf cyclopropane example (Scheme 1.9), where they put an amine functionality as the donating group for the cyclopropanes. This worked as both an advantage and a disadvantage as the amine products formed could easily undergo a gramine fragmentation to form various di-indolemethanes. They found that if they could increase the reactivity of the cyclopropane so that it was faster than the di-indolemethane formation, they could inhibit the latter process. They attempted to adjust the electronics on the phthalimide group to no avail. The only other option was to adjust the accepting group of the cyclopropane. By changing the diester moiety to a di-trifluoroethylester moiety **1.36**, they could sufficiently increase the alkylation reactivity (Scheme 1.12). With this modification in hand they

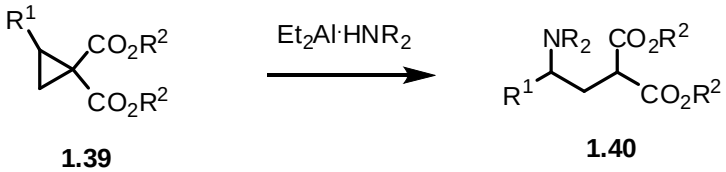
could produce a wide variety of different indole adducts. It is of note that when they used the skatole derived indole in this case, they did not see pentannulation, but simple C-3 to C-2 migration of the ring opened framework.



Scheme 1.12: Waser Group Ring Opening of Amino-cyclopropanes with Indole

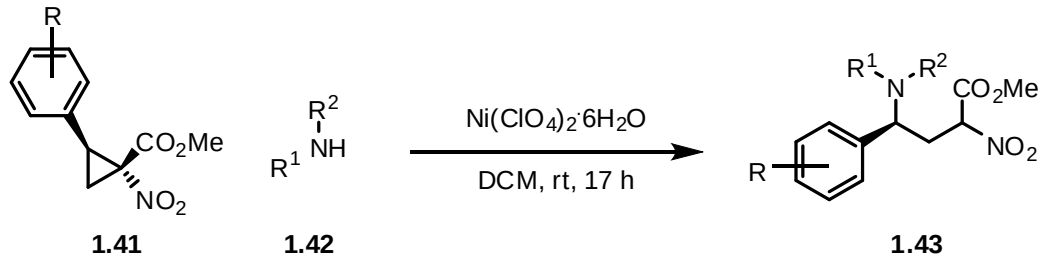
Section 1.3.2 Ring Opening of Cyclopropanes with Amines to form gamma-aminobutryic acid (GABA) analogues

In 1986, Schneider developed a reaction in which donor-acceptor cyclopropanes could be opened by amines to form GABA analogues.[46] By treating the reaction with a 1:1 mixture of amine and diethylaluminum chloride, they obtained aminolysis of the cyclopropane **1.40**. When this ratio was not equivalent, the primary product of the reaction was aminolysis of the esters on the cyclopropane. They proposed that the diethylaluminum and the amine make a complex, which then reacts with the cyclopropane **1.39**. This reaction worked well for a variety of different cyclopropanes and amines, however when the cyclopropane was alkyl substituted the yield suffered. It is of note that when they used a 2,2-disubstituted cyclopropane they did receive a modest yield over their ring opened product.



Scheme 1.13: Schneider's Aminolysis of Cyclopropanes

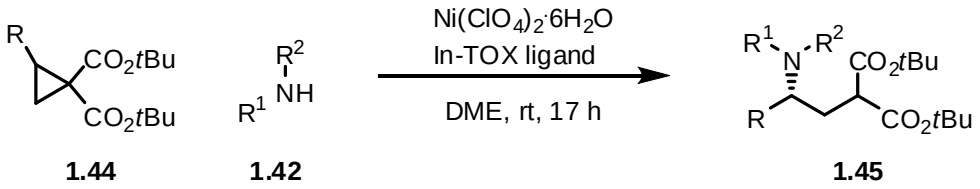
In 2008, Charette and co-workers set to open donor-acceptor cyclopropanes with a variety of different amines.[47] Originally, they found that they could take different cyclopropanes **1.41** and thermally open them with aniline, but if they started with an enantioenriched cyclopropane they lost selectivity through the course of the reaction (Scheme 1.14). This suggests a thermal racemization of their starting material in the absence of a Lewis acid. To prevent this issue, they decided to investigate Lewis acid catalysis, in order to lower the temperature of the reaction. They found that nickel perchlorate was the optimal catalyst and they used it as their catalyst for the scope of the reaction (Scheme 1.14). Though they did not explore a wide variety of cyclopropanes, they tested a vast number of amines **1.42** with success (anilines, secondary amines, indoline, etc.)



1.41 **1.42** **1.43**

Scheme 1.14: Charette's Ring Opening of Cyclopropanes with Amines

In 2012, Tang further advanced this field of donor-acceptor cyclopropane chemistry by developing a nickel catalyzed enantioselective ring opening of cyclopropanes **1.44** with amines **1.42** (Scheme 1.15).[48] While the previous methodology by Charette focused on secondary amines and anilines, the goal of this project was to asymmetrically open the cyclopropanes with aliphatic amines. This reaction gave excellent yields and enantioselectivity for all cyclopropanes and amines used. It is of note that when less than an extra equivalent of cyclopropane was used, a kinetic resolution took place. The product and the recovered starting material cyclopropane could be isolated in high yield and high enantioselectivity. This explains why the full fold excess of cyclopropane was necessary, as only one enantiomer of the cyclopropane was reactive when it was coordinated with the metal-ligand complex.

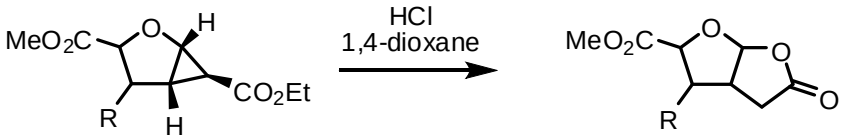


1.44 **1.42** **1.45**

Scheme 1.15: Tang's Chiral Ligand Cyclopropane Ring Opening with Aliphatic Amines

Section 1.4 Ring Expansions of Cyclopropanes to Form Lactones

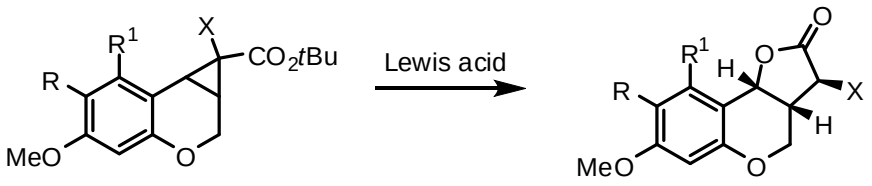
Rearrangements of cyclopropanes are a well investigated field, with the vinyl cyclopropane rearrangement being the predominantly investigated method.[49,50] While the synthesis of lactones from cyclopropanes has been seen many times, very rarely is taken advantage of. In 2005, Reiser and co-workers were working towards the core of the Spongiane diterpenoid substructure when they used a cyclopropane ring expansion.[51] With a dihydrofuran based cyclopropane for their model study, they could treat this with HCl to induce lactonization **1.47** (Scheme 1.16). This idea was a modification of the previously reported lactonization by Theodorakis[52] and co-workers. Towards a more decorated substructure they need to reflux **1.46** in acid to induce the rearrangement.



1.46 **1.47**

Scheme 1.16: Reiser's Lactone Formation

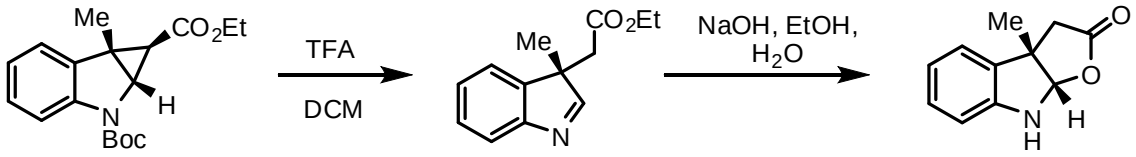
In 2010, Mead and co-workers employed a lactonization of cyclopropanated 2H-chromenes **1.48** under Lewis acid catalysis (Scheme 1.17).[53] Good yields of lactones **1.49** were isolated by this method, but 50 mol% of catalyst was necessary for this reaction to occur. It was proposed that the *t*-butyl ester was de-alkylated under the acidic conditions and the acid that was formed cyclized onto the benzylic position of the chromene.



1.48 **1.49**

Scheme 1.17: Mead's Lactone Formation

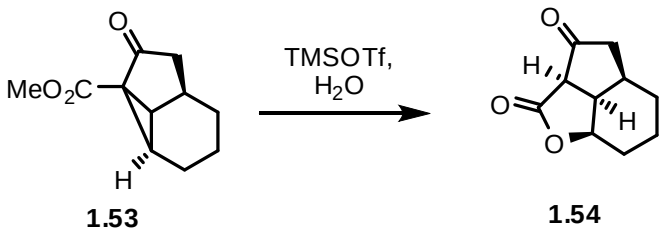
In 2012, Boysen reported the cyclopropanation of indoles that were followed by ring-opening and lactonization.[54] Interestingly, in this case the lactonization was not mediated by an external acid, but by using an intramolecular acid. When they removed the Boc protecting group from **1.50** under acidic conditions, the cyclopropane opened and left an indolenine product **1.51**. The ester was then saponified and then a cyclization event occurred to form the desired lactone **1.52** (Scheme 1.18).



1.50 **1.51** **1.52**

Scheme 1.18: Boysen's Stepwise Lactone Formation

In 2013, Corey described the synthesis of fused lactones from fused cyclopropanes. In multiple steps they could make their desired starting materials, then a triflic acid mediated ring expansion/lactonization event occurred.[55] This skeletal rearrangement worked well for a variety of different substrates under these acidic conditions to form a variety of different ring systems; an example is shown in Scheme 1.19.

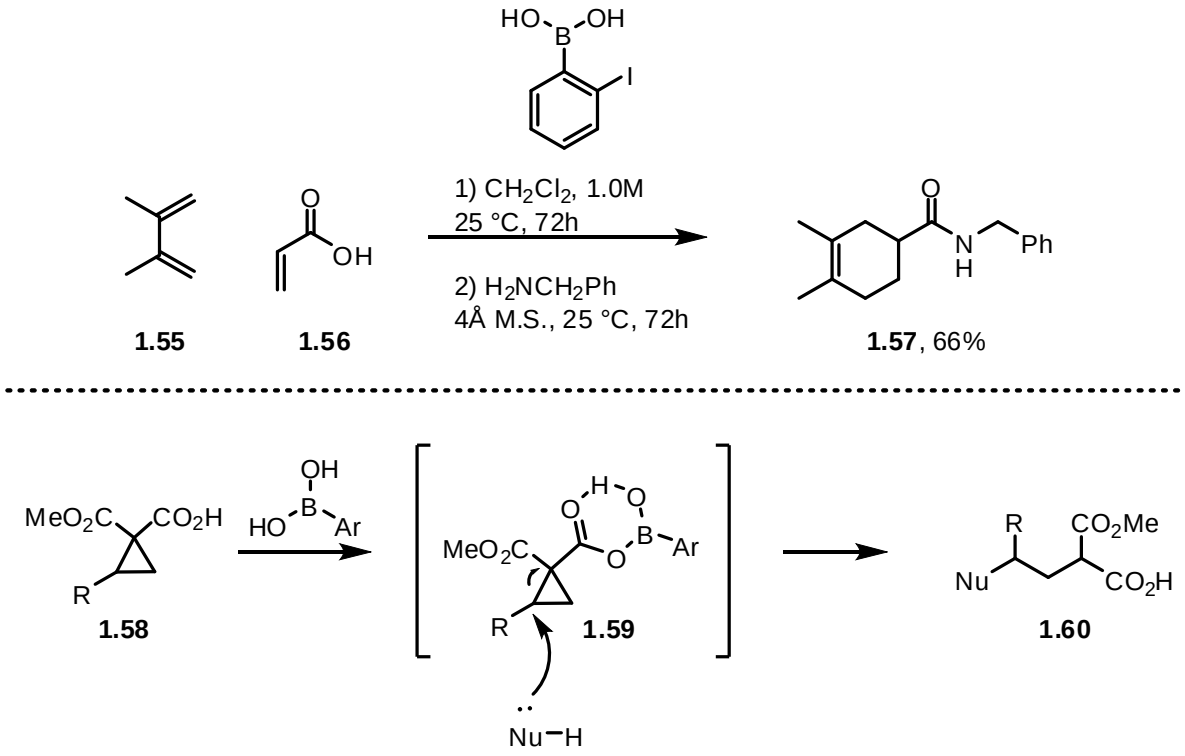


1.53 **1.54**

Scheme 1.19: Corey's Tricyclic Lactone Formation

Section 1.5 Ring Opening of Cyclopropane Hemimalonates by Indole

Due to the presence of indole as a core structure in numberous pharmaceuticals efficient means of functionalization remain as a challenge in synthetic organic chemistry.[56-58] With the Kerr group's history of opening 1,1-cyclopropanediesters with indole (*vide supra),* we were interested in a new mode of activation for cyclopropanes. Inspired by the work of Dennis Hall (Scheme 1.20),[59] we proposed that if we simply saponify one the esters on our cyclopropane perhaps we could activate it towards ring opening with a boronic acid.

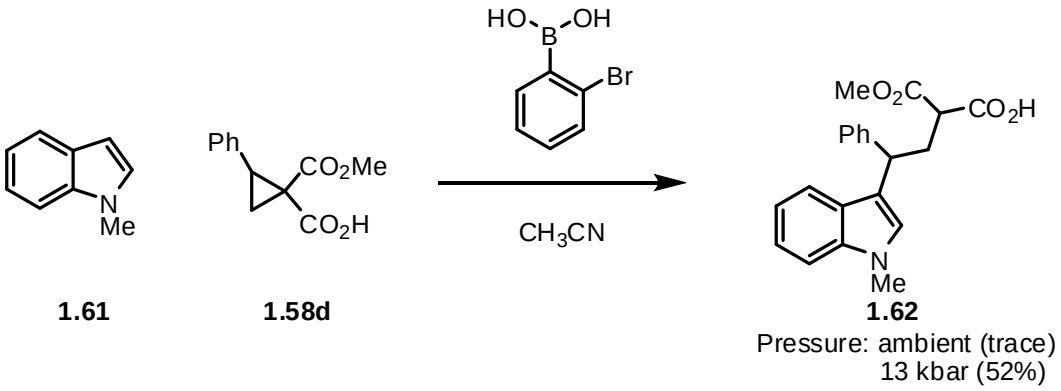


Scheme 1.20: Indole Ring Opening Project Inspiration

Section 1.5.1 Results and Discussion

Section 1.5.1.1 Reaction Optimization

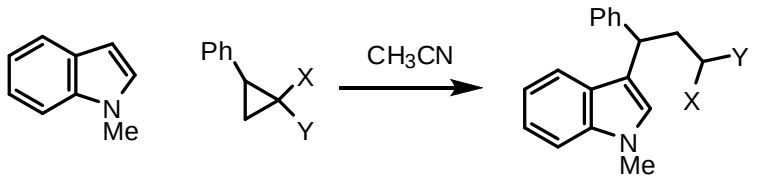
Having a vast library of cyclopropanes at hand, we attempted to replicate the conditions developed by Hall for our reaction, omitting the amine addition following the initial reaction. We used 2-bromophenylboronic acid as our catalyst, 1-methylindole **1.61** as our nucleophile and the phenylcyclopropane hemimalonate **1.58d** for our cyclopropane; unfortunately the reaction did not proceed at room temperature (Scheme 1.21). We used the phenyl cyclopropane hemimalonate as our test substrate, as in most of our methodologies this is the substrate which best describes the reactivity of this class of molecules. We switched the solvent from DCM to acetonitrile and observed trace product by NMR spectroscopy. With access to an ultra-high pressure reactor and given the previous success in the group using these conditions (*vide supra*), we attempted to modify the original conditions replacing the Lewis acid with the boronic acid. To our delight, this reaction did in fact work to give **1.62**, in a modest 52 % yield.



Scheme 1.21: Attempted Ring Opening Using a Boronic Acid as a Catalyst

While in the process of optimizing this new activation, we attempted the reaction without a boronic acid present at ultra-high pressures and we obtained a 70 % yield of our desired product after 2 days at 13 kbar. Therefore, the boronic acid was in fact unnecessary for the reaction to proceed and if anything it may be hindering the reaction. With this being the first reactivity of cyclopropane hemimalonates, we went back and looked at reaction conditions at ambient temperature and pressures. No reactivity was observed from room temperature to refluxing in acetonitrile. When we attempted the reaction using a microwave reactor (table 1.1, entry 3), we also saw no reactivity. Lowering the stoichiometry of the indole starting material, resulted in incomplete reactions over the 2 days for the reaction. We then decided to look back at our original entry into this field and were gratified to find the 1,1-cyclopropanediesters did not undergo this reaction in the absence of a Lewis acid. In order to determine whether both the ester and the acid were necessary for the reactivity we tried a cyclopropane with only an acid functionality as the electron-withdrawing group and this also did not undergo the ring opening event. Finally, we tried heating the reaction only to realize that the reaction time could be substantially decreased when heated to 50 degrees (2 days to 1 hour, table 1.1 entry 8). We could also lower the equivalents of indole down to 1.2 and did not see an appreciable decrease in yield.

Table 1.1: Optimization Study for Ring Opening Reaction



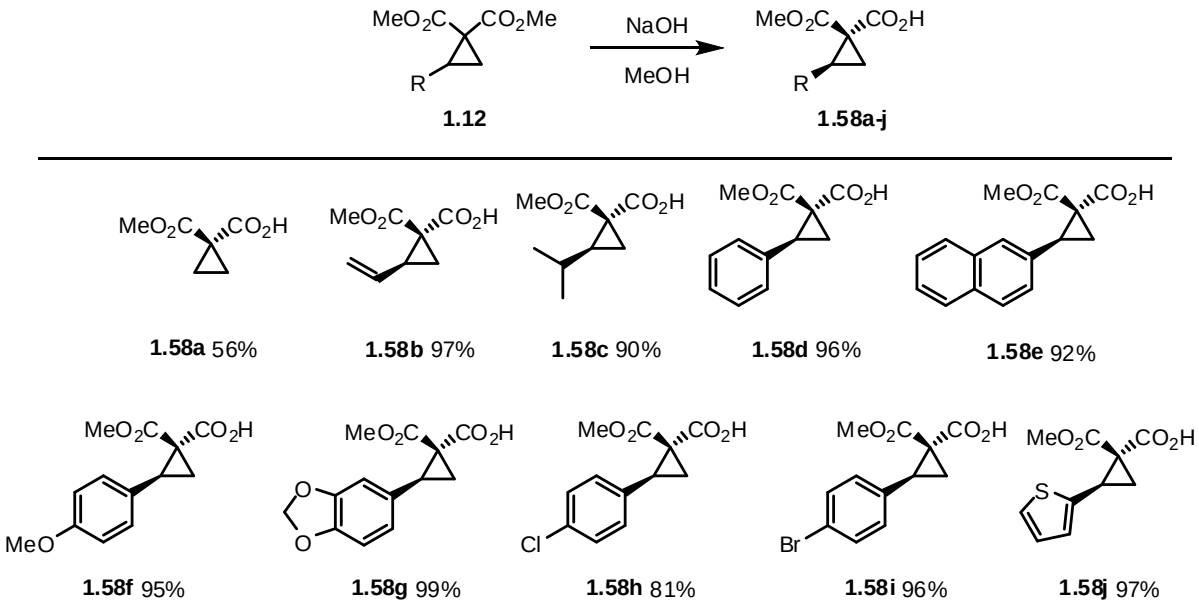
1.61 **1.63** **1.64**

Entry	Cyclopropane (**1.64**)	Temp. (°C)	Indole Equiv.	Conditions	Conversion (by NMR)	Yield
1	X= CO_2Me Y= CO_2H	25	2	24 h	0 %	N/A
2	X= CO_2Me Y= CO_2H	82	2	24 h	0 %	N/A
3	X= CO_2Me Y= CO_2H	80	2	30 min, mW	0 %	N/A
4	X= CO_2Me Y= CO_2H	25	2	48 h, 13 kbar	100 %	70 %
5	X= CO_2Me Y= CO_2H	25	1.2	48 h, 13 kbar	50 %	Not Determined
6	X=Y= CO_2Me	25	2	48 h, 13 kbar	0 %	N/A
7	X = CO_2H Y = H	25	2	48 h, 13 kbar	0 %	N/A
8	X= CO_2Me Y= CO_2H	50	2	1 h, 13 kbar	100 %	76 %
9	**X= CO_2Me Y= CO_2H**	**50**	**1.2**	**1 h, 13 kbar**	**100 %**	**73 %**

Section 1.5.1.2 Synthesis of Cyclopropane Hemimalonates

With our optimal conditions in hand (Table 1.1, entry 9), it was necessary to now create a library of cyclopropane hemimalonates, which were prepared in methanolic

sodium hydroxide. While we could form the cyclopropane with no substituents, we were also able to form a vast number of cyclopropane hemimalonates that were vicinally substituted with alkyl, aryl, heteroaryl and vinyl groups, all formed in modest to excellent yields (Scheme 1.22). The saponification occurs at the ester that is *trans* to the vicinal cyclopropyl substitution with reasonable diastereoselection.[60]

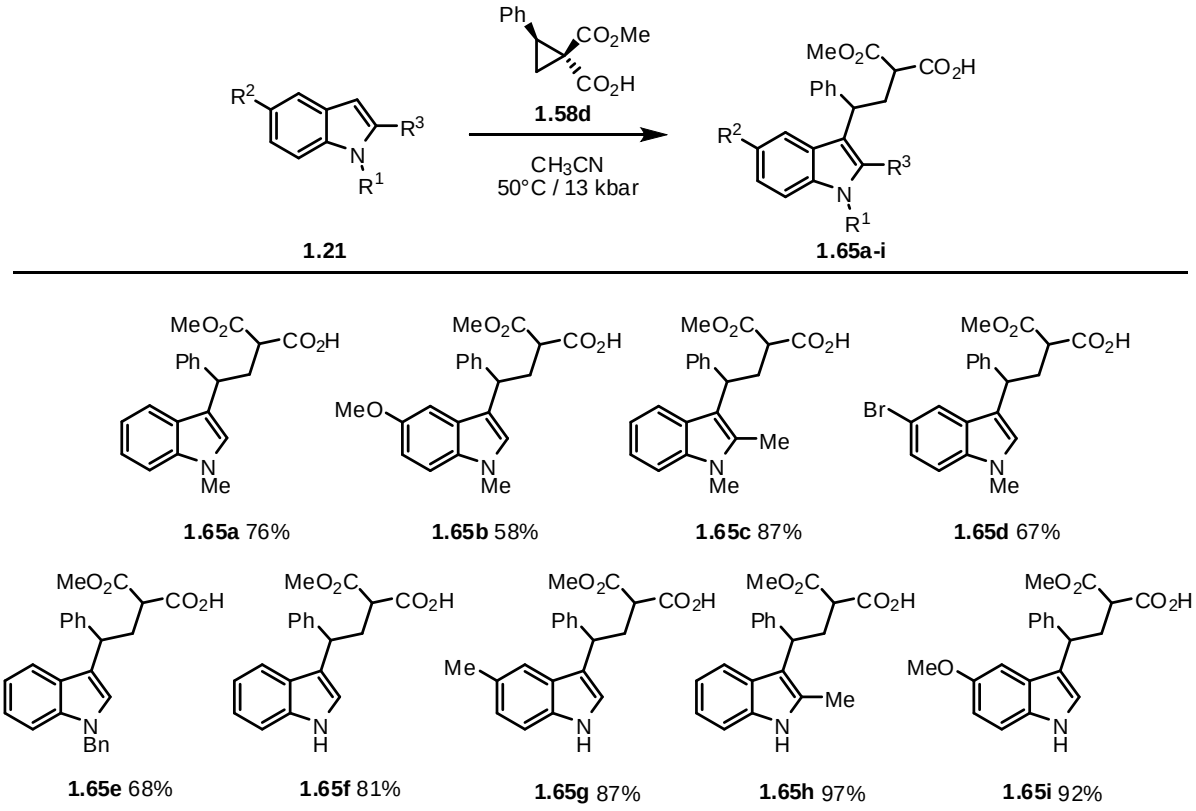


Scheme 1.22: Synthesis of a Library of Cyclopropane Hemimalonates

Section 1.5.1.3 Investigating the Scope of the Reaction

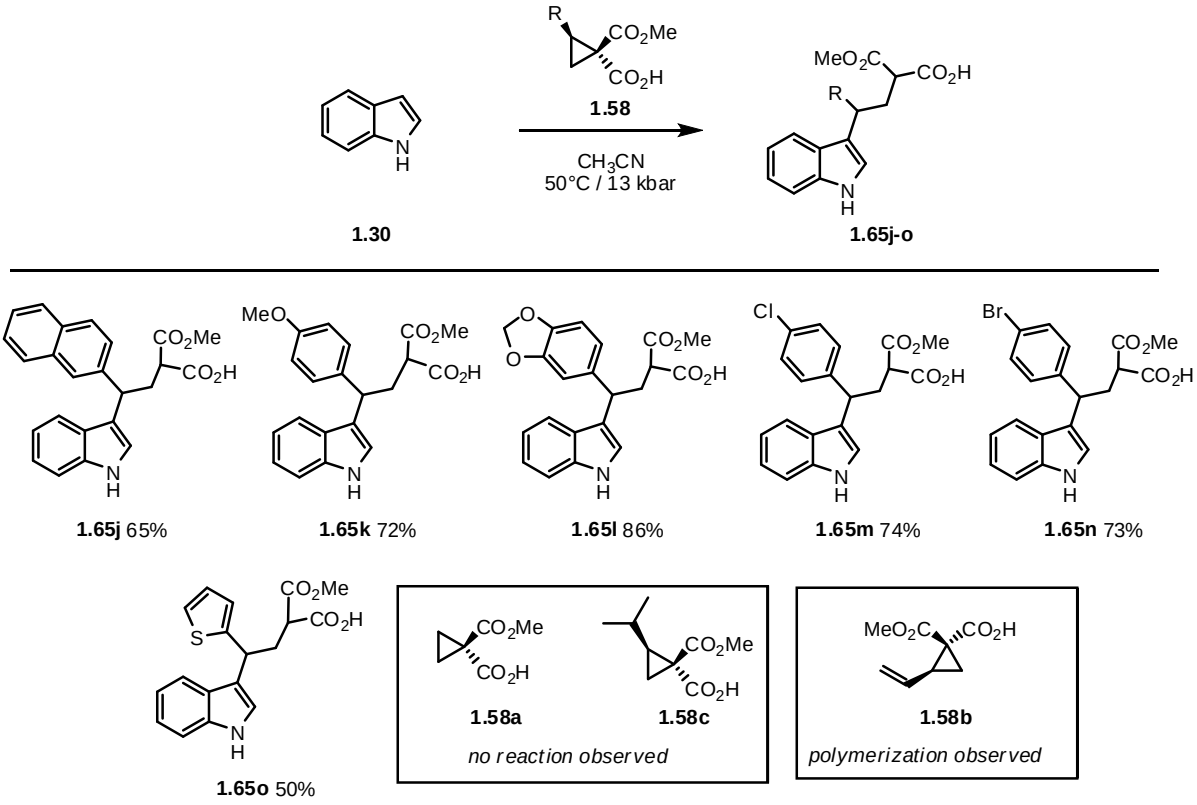
Looking into the scope of this new reaction, we first investigated what substitution patterns would be tolerated on our indole species (Scheme 1.23). For the most part the reaction was tolerant to all substitution patterns that we tried. Due to the instability of the 5-methoxy-1-methylindole, it was unsurprising that only a modest yield was obtained for **1.65b**. The most important thing to note was that indoles with no substitution at the nitrogen gave the highest yields of all the substituted examples. Unsurprisingly, when the Boc protected indole was used the reactivity of the indole was suppressed and no productive results were obtained. Methyl substitution at the 2-position **1.65h** appeared to enhance the reactivity of the indole, presumably by stabilizing the

iminium ion that was formed by the ring opening reaction. Skatole, 3-methylindole, was unsuccessful in completing this transformation.



Scheme 1.23 Variation of the Indole Nucleophile

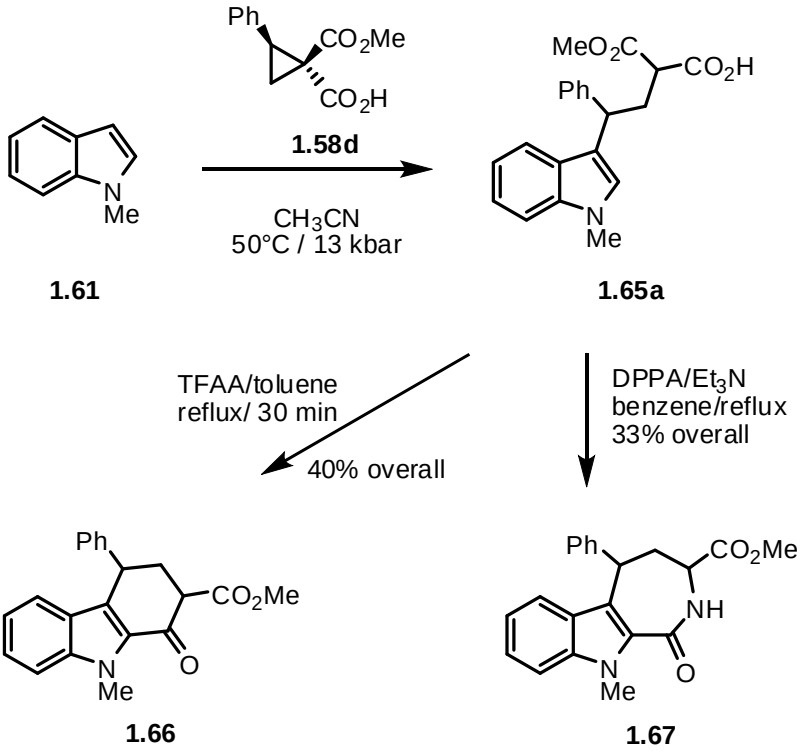
With indole appearing to be the optimal nucleophile, we decided to test the scope of cyclopropanes that could be utilized in this reaction. Aryl and heteroaryl cyclopropane substitution was well-tolerated giving good to excellent yields of products. Unfortunately the vinyl cyclopropane **1.58b**, polymerized under the reaction conditions. Alkyl **1.58c** and the parent cyclopropane **1.58a** failed to undergo the reaction. This is consistent with the cyclopropyl substitution being able to stabilize the developing positive charge in the reaction transition state (Scheme 1.24).



Scheme 1.24 Variation of the Cyclopropyl Electrophile

Section 1.5.1.4 Elaboration of Ring Opened Adducts and Mechanistic Discussion

We became interested in what we could do with our differentiable acceptor groups to show the potential utility of these hemimalonate products. When the groups are diesters the manipulations you can do to them are limited. With our acid functionality we were able to smoothly convert the adducts to the diesters by simple esterification of the acid with TMS-diazomethane. We were also curious as to whether or not these products would be amenable to different transformations. We found that treatment of the hemimalonate adduct **1.65a** with trifluoroacetic anhydride (TFAA) allowed for a cyclization onto the 2-position of the indole to produce tetrahydrocarbazoles **1.66** (Scheme 1.25). We could also treat **1.65a** with diphenylphosphoryl azide (DPPA) and what we noticed here was the isocyanate intermediate was once again trapped by the 2-position of the indoles to form these interesting azepinoindoles **1.67** in 33 % overall yield from cyclopropane **1.58d**.



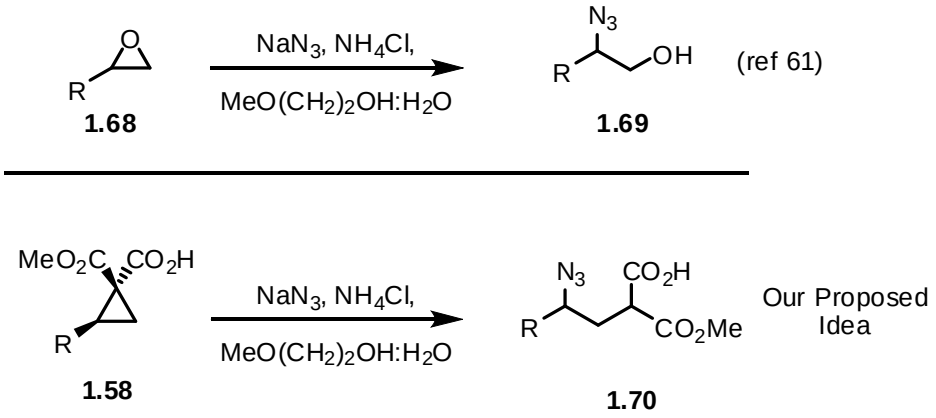
Scheme 1.25 Elaboration of Ring Opened Adduct **1.65a**

While the use of ultra-high pressures to induce reactivity was unsurprising, the fact that the reaction did not work at all thermally was quite interesting. In the Lewis acid catalyzed reaction of the 1,1-cyclopropanediesters, thermal conditions were effective at achieving this transformation. We propose that in fact under the ultra-high pressure conditions, a hydrogen bonding interaction may be taking place in order to activate the bond polarization of the cyclopropane.

Section 1.6 Tandem Ring Opening/Decarboxylation of Cyclopropane Hemimalonates with Sodium Azide

While looking to investigate new reactivity of cyclopropanes with different nucleophiles, it sometimes helps to look into what reactivity other three-membered rings have. The inspiration for this project came from the azide opening of epoxides **1.68** by Bäckvall[61] under aqueous conditions. We proposed that if we took our newly developed

cyclopropane hemimalonates **1.58** under these conditions, perhaps we could induce the same ring opening transformation to form **1.70**.



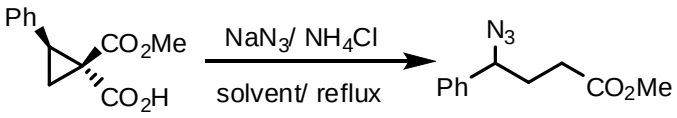
Scheme 1.26 New Ring Opening Proposal with Azides

Section 1.6.1 Results and Discussion

Section 1.6.1.1 Reaction Optimization

Using Bäckvall's conditions as a starting point for the reaction we obtained a 70 % yield of a ring opened product that had concurrently undergone decarboxylation **1.71**. Removal of the ammonium chloride led to a decrease in the formation of product. Attempting to use other organic solvents that are typically used for cyclopropane transformations led to no product whatsoever (Table 1.2, entries 4-6). We investigated the equivalents of sodium azide and quickly realized that a slight excess led to an increase in yield, but adding another full equivalent was unsuccessful in increasing the yield further. Due to the elevated temperatures required we attempted the reaction in a microwave reactor. Unfortunately while we still obtained product, it was not in an increased yield (Table 1.2, entry 10) We also looked into the solvent ratio of 2-methoxyethanol to water, and a 10:1 mixture gave the best results (Table 1.2, entries 11-12). We attempted the reaction with the 1,1-cyclopropanediesters and the reaction did not proceed. When we added a Lewis acid (ytterbium triflate) to the mixture we obtained the ring opened diester product, but in a modest 50 % yield (Table 1.2, entry 13).

Table 1.2: Optimization Study for Azide Ring Opening/ Decarboxylation

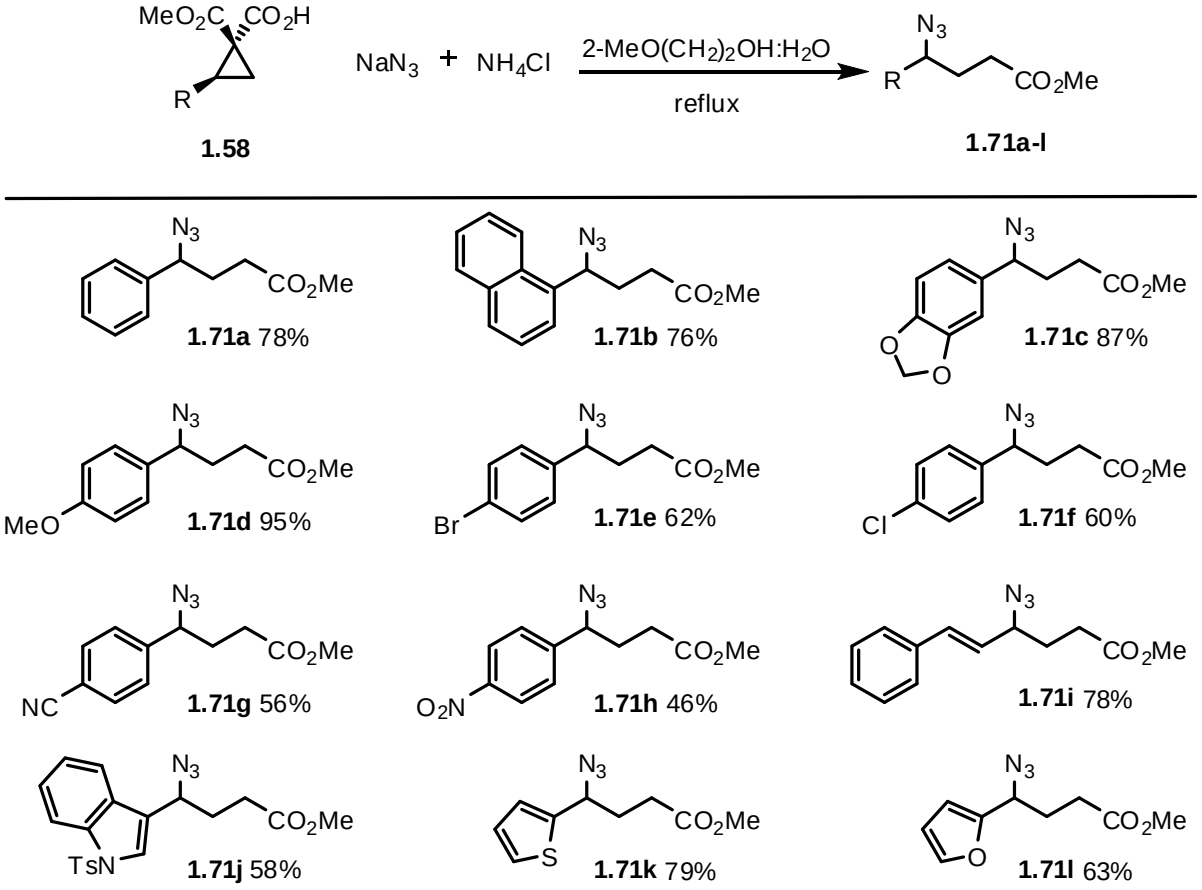


1.58d **1.71**

Entry	Azide (equiv)	NH_4Cl (equiv)	Solvent	Yield(%)
1	1	1.4	2-MeO$(CH_2)_2$OH:H_2O (10:1)	70
2	1	0	2-MeO$(CH_2)_2$OH:H_2O (10:1)	N/A
3	1	0	2-MeO$(CH_2)_2$OH	30
4	1	1.4	C_6H_6	no rxn
5	1	1.4	CH_3CN	no rxn
6	1	1.4	THF	no rxn
7	**1.2**	**1.4**	**2-MeO$(CH_2)_2$OH:H_2O (10:1)**	**78**
8	2	1.4	2-MeO$(CH_2)_2$OH:H_2O (10:1)	73
9	2	3	2-MeO$(CH_2)_2$OH:H_2O (10:1)	74
10	1.2	1.4	2-MeO$(CH_2)_2$OH:H_2O (10:1)	50
11	1.2	1.4	2-MeO$(CH_2)_2$OH:H_2O (5:1)	74
12	1.2	1.4	2-MeO$(CH_2)_2$OH:H_2O (1:1)	60
13*	1.2	1.4	2-MeO$(CH_2)_2$OH:H_2O (10:1)	50

Section 1.6.1.2 Investigating the Scope of the Reaction

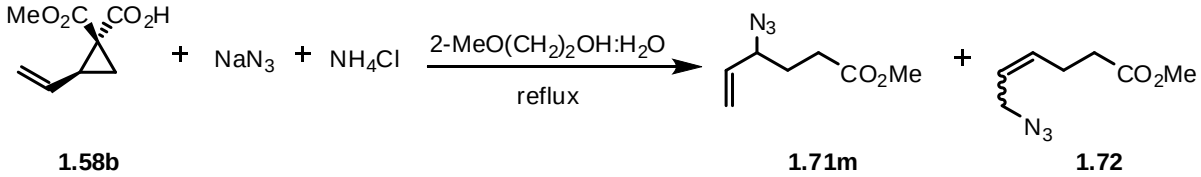
With our optimal conditions in hand (Table 1.2, entry 7), we surveyed our new library of cyclopropane hemimalonates to determine the generality of this method. The reaction worked well for aromatic substituted cyclopropanes as well as heteroaromatic cyclopropanes. The reaction worked extremely well with electron rich aromatic cyclopropanes, nearing almost quantitative results for **1.71d**. The yields were modest for the electron poor aromatic cyclopropanes.



Scheme 1.27 Reaction Scope of the Azide Transformation

One interesting result was that even though the styrenyl cyclopropane underwent this transformation, issues arose when we attempted to use the vinyl substituted cyclopropane. In this example, we obtained an intractable mixture of our expected product **1.71m** and a S_N' addition product **1.72**. At this point we are not sure why

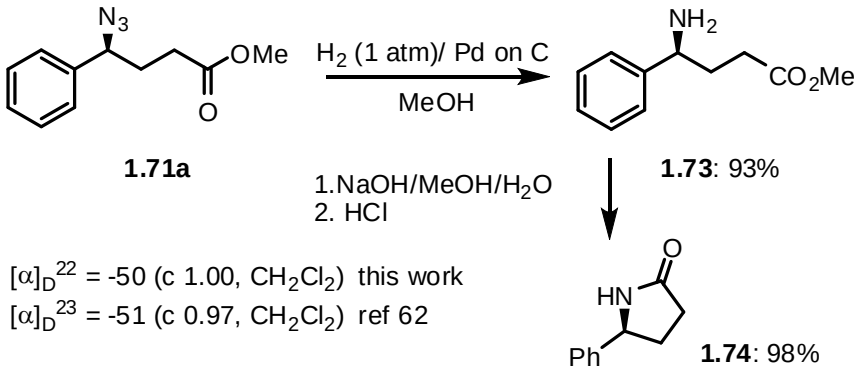
substitution at the terminal position of the vinyl group changes the reactivity of the cyclopropane.



1.58b **1.71m** **1.72**

Scheme 1.28 Mixture of Products when Using the Vinyl Cyclopropane Hemimalonate **1.58b**

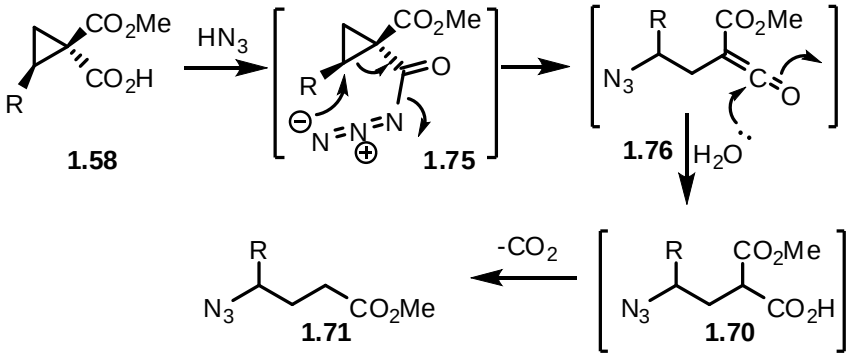
It is of note that the optically enriched phenyl cyclopropane (S)-**1.58d** (90% ee) underwent this transformation with full retention of enantiopurity (*vide supra*) to give (S)-**1.71a**. Finally, cyclopropanes where the substitution was aliphatic or unsubstituted were unreactive under these conditions and starting material was recovered intact. To prove that these adducts were viable precursors for GABA esters, we simply reduced azide **1.71a** to the primary amine **1.73** using palladium on carbon. It was at this point that the enantiopurity of the product was tested as the azide-ester products were difficult to separate by HPLC. The enantiopurity was tested by making the Mosher's amide (*vide infra*) of the amine-ester product. To determine the absolute stereochemical outcome of the reaction, **1.73** was converted to the lactam **1.74** and the optical rotation was found to be in agreement with literature (Scheme 1.29).[62]



Scheme 1.29 Testing of Enantiopurity and Absolute Stereochemistry

Section 1.6.1.3 Reaction Mechanism

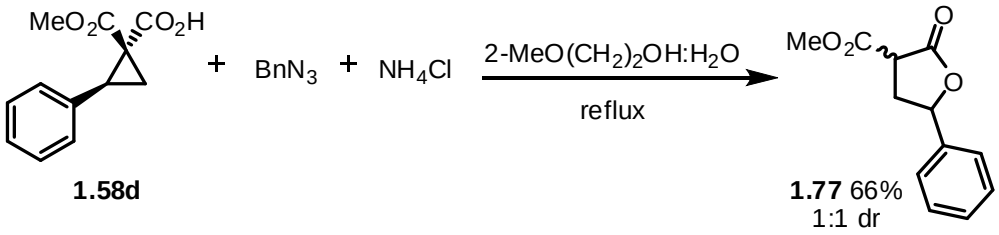
The fact that the hemimalonates are effective substrates and the diesters are not, is surprising to us. In our previous report in which we described the nucleophilic opening of these species with indoles, we were able to rationalize the results by invoking a high pressure induced intramolecular hydrogen bond between the carboxylic acid and the ester. The effect of this would be to stereoelectronically align the carbonyls for the ring-opening event. It is hard to make such a rationalization in this case since the reaction takes place in a refluxing protic medium. It puzzles us then, why the carboxylic acid moiety is a requirement for this reaction. One explanation (Scheme 1.30) is that the reaction was proceeding via an acyl azide **1.75** which could undergo a [3,3]-sigmatropic rearrangement to yield ketene **1.76**, which in turn would be intercepted by water to regenerate the acid. Decarboxylation of the resulting monoester **1.70** could then ensue, yielding the observed product **1.71**. We have attempted to prepare and isolate the acylazide, and subject it to the reaction conditions in order to prove this hypothesis; however the results were inconclusive due to extensive decomposition.



Scheme 1.30 Possible Mechanistic Explanation

Section 1.7 Synthesis of Butanolides from Cyclopropane Hemimalonates

In the process of optimizing the reaction of sodium azide with cyclopropane hemimalonates, we wanted to try to react a substituted azide with our hemimalonates to try and expand the scope of the reaction further. What we quickly realized was that another process was taking place; the hemimalonate **1.58d** was undergoing a ring expansion rearrangement to form a butanolide **1.77** (Scheme 1.31).



Scheme 1.31 Discovery of the Cyclopropane Hemimalonate Rearrangement

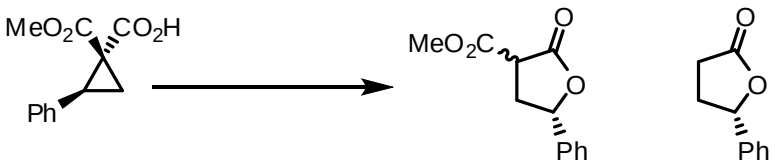
Section 1.7.1 Results and Discussion

Section 1.7.1.1 Reaction Optimization

Initial attempts to optimize this reaction worked quite well obtaining an 82 % yield of **1.77**. Changing the solvent from 2-methoxyethanol to DMSO increased the yield to 87 %. Testing other organic solvents did not help this reaction to proceed. We attempted using a variety of salts and while reactions went to completion, they all went to a mixture of products: the cyclized **1.77** and the decarboxyalted **1.78** butanolides.

Unfortunately, we never obtained **1.77**, as the sole product of any of these reactions. Frustrated by this result we decided to try and optimize the reaction for **1.78** instead. The reaction conditions were modified to more standard types of Krapcho dealkoxycarbonylation conditions. In a two-step protocol, we were able to rearrange the cyclopropane in one step, and then subsequently decarboxylate the product in a 65 % yield. Desiring a one pot procedure and still maintaing a mixture of products we decided to try and irradiate our starting materials in a microwave reactor. While DMSO was the optimal solvent at standard thermal conditions, DMF led to our desired product in our highest yield of 82% in the microwave reactor. We attempted this transformation as well with the parent diester compound and while we did obtain product in a 45 % yield, significant decomposition of the cyclopropane was realized (Table 1.3, entry 14).

Table 1.3: Optimization Study for Hemimalonate Rearrangement



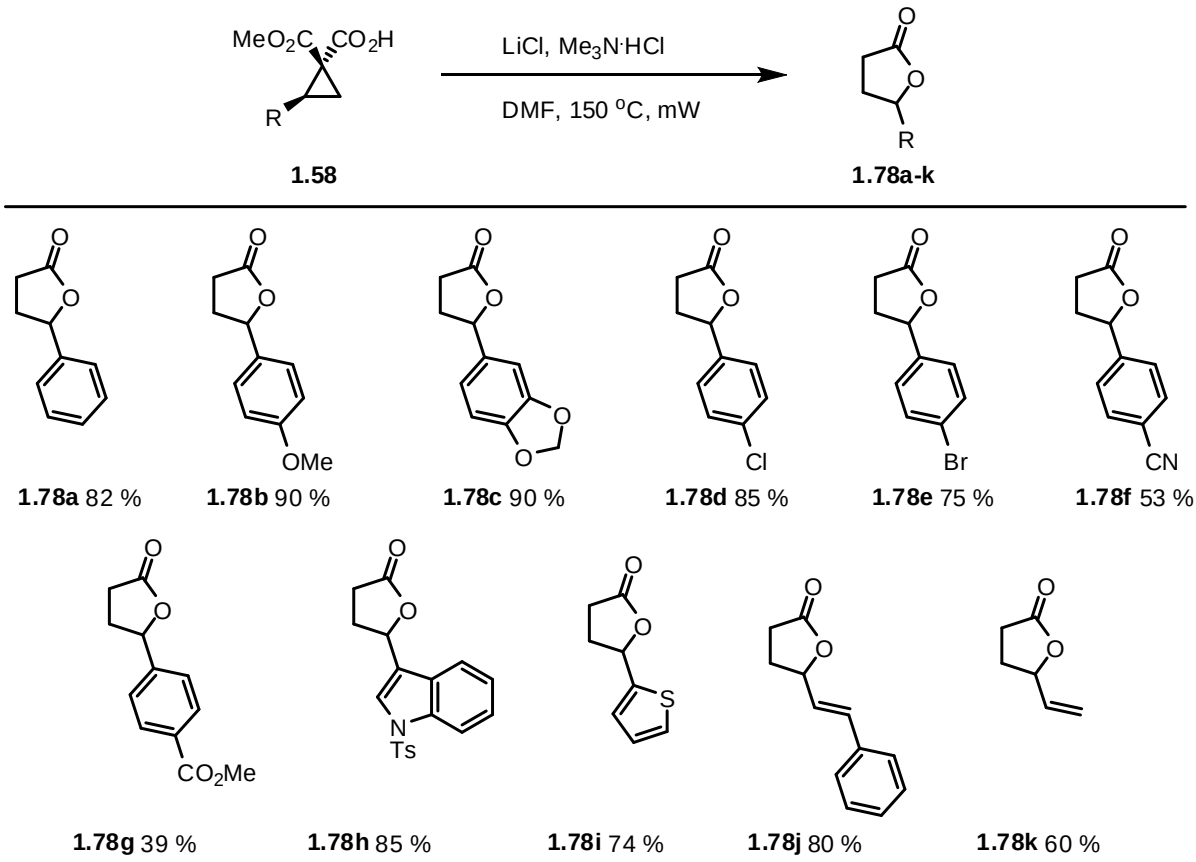
1.58d **1.77** **1.78**

Entry	Additive (1.4 equiv.)	Solvent / Temp. (^{o}C)	Time (h)	Product (%)
1	NH_4Cl	2-$MeO(CH_2)_2OH$/reflux	2	82 **1.77**, trace **1.78**
2	NH_4Cl	DMSO / 135	1	87 **1.77**, trace **1.78**
3	NH_4Cl	(5:1) DMSO:H_2O/135	1	mixture
4	NaCl	DMSO / 135	1	mixture
5	KCl	DMSO / 135	1	mixture
6	LiCl	DMSO / 135	24	mixture
7	NaCN	DMSO / 135	24	no rxn
8	$Me_3N{\cdot}HCl$	DMSO / 135	24	mixture
9	NH_4Cl / NaCN	DMSO / 135	1 / 6	65 **1.78**
10	LiCl /	DMSO / 135	24	mixture

	$Me_3N{\cdot}HCl$			
11	LiCl /	DMSO / reflux	24	mixture
	$Me_3N{\cdot}HCl$			
12	LiCl /	DMSO / 150, mW	0.66	71 **1.78**
	$Me_3N{\cdot}HCl$			
13	**LiCl /**	**DMF / 150, mW**	**0.66**	**82 1.78**
	$Me_3N{\cdot}HCl$			
14	LiCl /	DMF / 150, mW	0.66	45 **1.78**
	$Me_3N{\cdot}HCl$			

Section 1.7.1.2 Investigating the Scope of the Rearrangement

Once again, having our vast library of cyclopropane hemimalonates, we were able to explore the utility of this transformation. Both electron donating and halogen substituted phenyl cyclopropanes underwent the butanolide formation in moderate to excellent yields. Conversely, the electron withdrawing phenyl cyclopropanes gave only modest yields of the desired butanolides. The heteroaromatic cyclopropanes provided butanolides in excellent yield as did the styrenyl substituted cyclopropane. Interestingly, for this transformation the vinyl cyclopropane was amenable to our reaction conditions. The lower yield in this example can be explained by **1.58b** being highly reactive nature towards polymerization. Unfortunately, alkyl **1.58c** and unsubstituted cyclopropanes **1.58a**, do not yield the butanolide products.



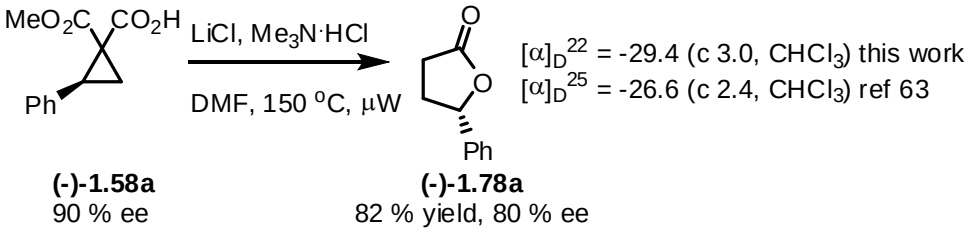
1.78a 82 % **1.78b** 90 % **1.78c** 90 % **1.78d** 85 % **1.78e** 75 % **1.78f** 53 %

1.78g 39 % **1.78h** 85 % **1.78i** 74 % **1.78j** 80 % **1.78k** 60 %

Scheme 1.32 Reaction Scope of the Butanolide Rearrangement

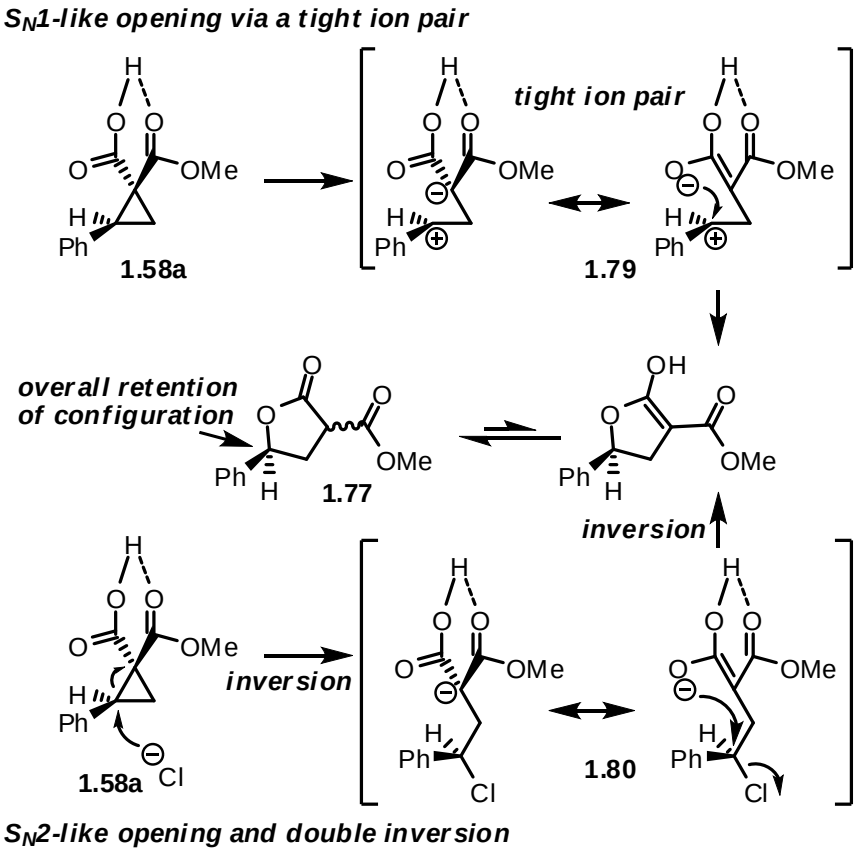
Section 1.7.1.3 Reaction Mechanism

To shed light onto the mechanism, optically enriched phenyl cyclopropane (-)-**1.58d** was subjected to the reaction conditions (Scheme 1.33). Smooth transformation lead to an isolated 82% yield of enriched butanolide **1.78a**, with only slight erosion of enantiomeric excess (determined by a Mosher's ester sequence, *vide infra*). Optical rotation analyses of the product support the (S) isomer butanolide being isolated.[63] This outcome suggests that the reaction occurs with retention of stereochemistry, a result unusual in donor-acceptor cyclopropane chemistry.



Scheme 1.33 Reaction of Optically Enriched **1.58a**

It occurred to us that there were two possible mechanistic explanations for such a transformation. The first being a solvolitic cleavage of the cyclopropane bond to form a benzylic cation and a malonyl anion. The cation would undergo attack from the malonate in an O-alkylation to produce the desired butanolide. A dealkoxycarbonylative event would follow this transformation, but would have no effect on the outcome of the reaction. Another possibility would be that the chloride anion from our salt opens the cyclopropane to get an inversion of stereochemistry. This event could be followed by an O-alkylation from the malonyl group with inversion again to retain the required stereochemistry (Scheme 1.34).

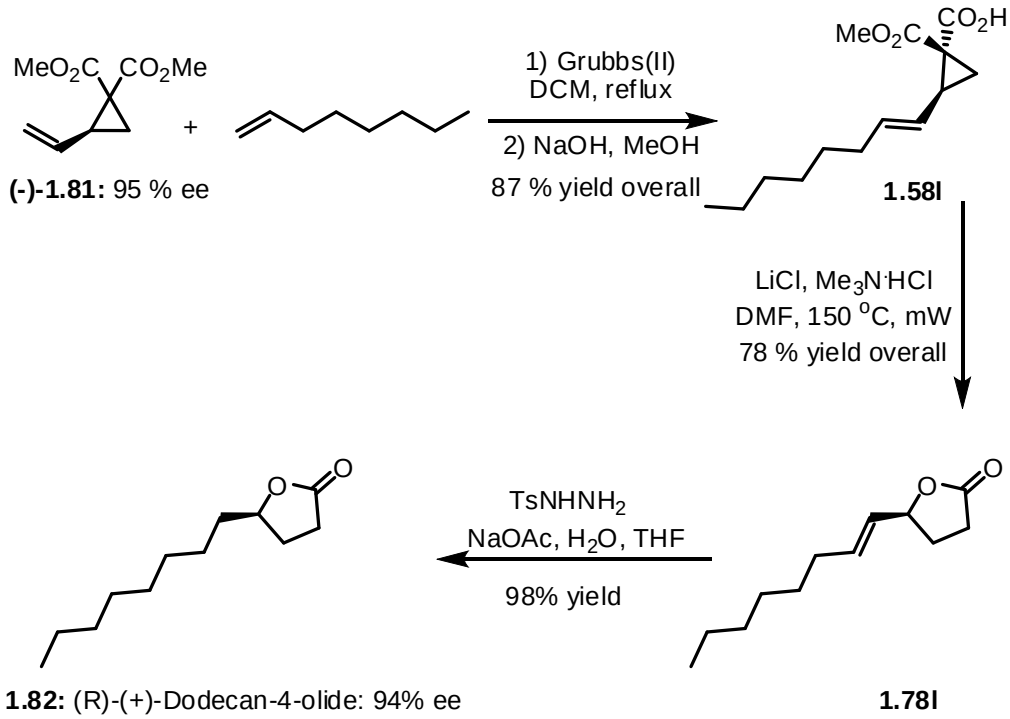


Scheme 1.34 Possible Mechanistic Pathways for the Butanolide Rearrangement

Section 1.7.1.4 Total Synthesis of (R)-(+)-dodecan-4-olide

A unique and naturally reoccurring butanolide is (R)-dodecan-4-olide **1.82**. Isolated from an array of natural sources including the pygidial glands of rove beetles,[64] fruits,[65] butterfat,[66] and the territorial marking fluid of the Bengal tiger,[67] dodecan-4-olide is a small natural product which plays a role in many different biological functions.[68,69] Due to this compound's abundance in nature, dodecan-4-olide is one of the most common butanolides targeted for small molecule synthesis.[70-74] Readily available dimethyl ester vinyl cyclopropane **1.81** was subjected to cross metathesis conditions with oct-1-ene in the presence of Grubbs 2nd generation ruthenium catalyst to access the crude octenyl cyclopropane. Following monosaponification, cyclopropane hemimalonate **1.58k** was isolated in an 87% yield over two steps. Hemimalonate **1.58k** was then exposed to the standard butanolide synthesis conditions and alkenyl butanolide **1.78l** was isolated in

78% yield. Reduction of the π-system proved to be the most difficult step in synthesis resulting in over reduction of the lactone ring under standard conditions including hydrogenation over Pd on carbon or PtO_2. The π-system reduction of butanolide **1.78l** was finally achieved using tosylhydrazide as a hydrazine source allowing access to (R)-dodecan-4-olide **1.82** in 98% yield and 94% ee (determined by a Mosher's ester sequence).

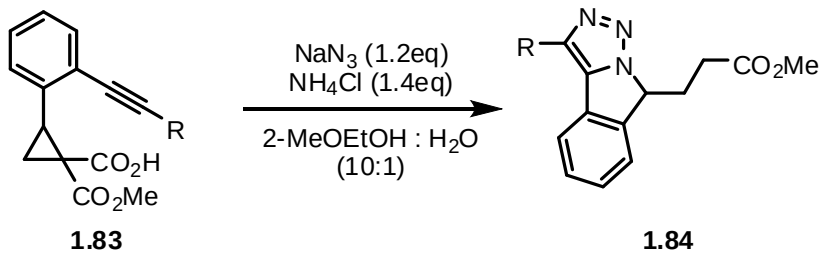


Scheme 1.35 Total Synthesis of (R)-(+)-dodecan-4-olide

Section 1.8 Summary and Future Work

In summary, we have been able to synthesize and develop a new type of donor-acceptor cyclopropane and develop its reactivity. The hemimalonates do not need a Lewis acid to activate them and they can react under transition metal free, aqueous conditions. Under ultra-high pressure conditions, we were able to open cyclopropane hemimalonates **1.58** with indoles to access 15 ring opened adducts **1.65** in yields ranging from 50-97%. These adducts could also be converted to carbazoles or azepinoindoles in short order. Taking the hemimalonates with sodium azide and ammonium chloride, we

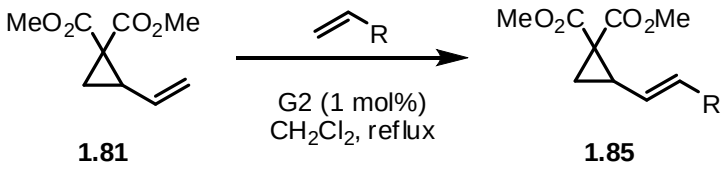
were able to access 12 different azido-esters **1.71** in 46-95% yield depending on the substrate. These azido-esters could easily be converted to GABA analogues by hydrogenation, allowing access to a wide scope of unnatural amino acids. This methodology has since been extended to alkynyl-aryl cyclopropane hemimalonates **1.83** to a synthesis of triazoles **1.84**.[75]



1.83 **1.84**

Scheme 1.36 Extension of the Azide Methodology to Synthesize Triazoles

Without the presence of an external nucleophile, the hemimalonates **1.58**, can rearrange to form γ-butanolides in 39-90% yields. This reaction allowed for the total synthesis of (R)-(+)-dodecan-4-olide in 4 synthetic operations in a 67% overall yield. We believe the development of the cyclopropane cross metathesis reaction has solved the issue with alkyl cyclopropanes having sluggish reactivity towards nucleophiles. This reaction was developed further and reactivities were compared between the alkyl and the substituted alkenyl cyclopropanes.[76]

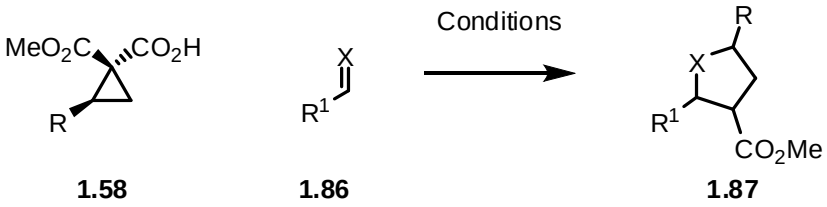


1.81 **1.85**

Scheme 1.37 Cross Metathesis of Vinyl Cyclopropanes

In future studies, the cyclopropane hemimalonate reactivity needs to be further investigated with attention towards cycloaddition chemistry. With their proclivity for

decarboxylation, under the appropriate conditions a decarboxylative cycloadditions could be possible.



1.58 **1.86** **1.87**

Scheme 1.38 Potential Decarboxylative Dipolar Cycloaddition

Section 1.9 Experimental

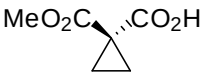
General

Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. ^{1}H, ^{19}F, and ^{13}C NMR experiments were performed on Varian Mercury 400, Varian Inova 400 and Inova 600 instruments and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Toluene, tetrahydrofuran (THF), ether, acetonitrile (MeCN) and dichloromethane (DCM) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Alfa Aesar, or Caledon. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F_{254}) visualizing with UV light, and the plates developed using acidic anisaldehyde. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh). High-pressure reactions were carried out on a LECO^{TM} Tempres High-Pressure chemical reactor. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor.

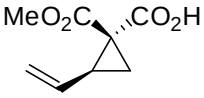
Section 1.9.1 The Ring Opening of Cyclopropane Hemimalonates by Indole

General Procedure for the mono-sapofication of 1,1-cyclopropanediesters

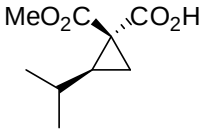
Cyclopropanes were dissolved in MeOH and 1.7M NaOH (1.2 eq.) with constant stirring. The solution was stirred for 1.5 h then was diluted with EtOAc and water to separate layers. The aqueous layer was the acidified with 5% HCl to reach pH 2, then extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated.[60]



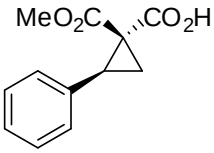
Reagents employed: **1.12a** (0.356 g, 2.25 mmol); NaOH (1.60 mL, 2.72 mmol); MeOH (2 mL); Yielded **1.58a** as a clear oil, 56 % (0.181 g, 1.26 mmol). Spectral properties are identical to those previously reported.[77]



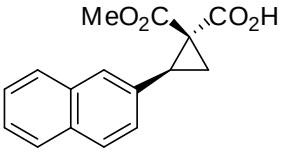
Reagents employed: **1.12b** (0.541 g, 2.94 mmol); NaOH (2.25 mL, 3.50 mmol); MeOH (2.25 mL); Yielded **1.58b** as a clear oil, 91% (0.453 g, 2.66 mmol). Spectral properties are identical to those previously reported.[78]



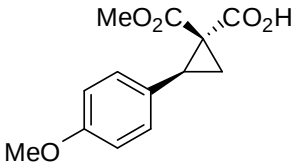
Reagents employed: **1.12c** (0.337 g, 1.68 mmol); NaOH (1.20 mL, 2.04 mmol); MeOH (1.2 mL); Yielded **1.58c** as a clear oil, 90% (0.281 g, 1.43 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 2.01 (dd, J = 9.0 Hz, 3.9 Hz, 1H), 1.87-1.95 (m, 1H), 1.78 (dd, J = 8.6 Hz, 3.9 Hz, 1H), 1.55-1.62 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 172.9, 53.0, 44.2, 31.9, 28.2, 23.7, 22.1, 21.7; IR (thin film, cm^{-1}): 3101, 3006, 2962, 2874, 1736, 1697, 1438, 1385, 1360, 1329, 1282, 1209, 1146, 1033, 968, 952, 907, 868, 808, 768; HRMS calc'd for $C_9H_{14}O_4$ = 186.0892, found 186.0887



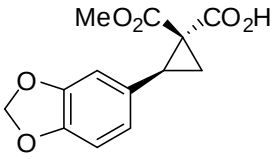
Reagents employed: diester **1.12d** (1.02 g, 4.34 mmol); NaOH (3.00 mL, 5.17 mmol); MeOH (3 mL); Yielded **1.58d** as a clear oil, 93% (0.890 g, 4.04 mmol). Spectral properties are identical to those previously reported.[79]



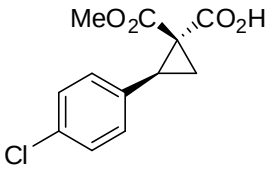
Reagents employed: **1.12e** (0.507 g, 1.78 mmol); NaOH (1.30 mL, 2.21 mmol); MeOH (1.3 mL); Yielded **1.58e** as a pink oil, 92% (0.442 g, 1.63 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.6 Hz, 1H), 7.88-7.79 (m, 2H), 7.58-7.49 (m, 2H), 7.46-7.41 (m, 2H), 3.76 (dd, J = 8.8 Hz, 8.8 Hz, 1H), 2.99 (s, 3H), 2.57 (dd, J = 8.6 Hz, 4.7 Hz, 1H), 2.51 (dd, J = 9.4 Hz, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 171.3, 133.2, 132.3, 130.3, 128.7, 128.6, 126.9, 126.8, 126.1, 124.9, 123.0, 52.5, 38.8, 33.4, 22.0; IR (thin film, cm^{-1}): 3098, 3050, 3016, 2954, 2925, 2854, 1735, 1701, 1686, 1675, 1655, 1597, 1509, 1446, 1367, 1344, 1330, 1295, 1266, 1242, 1210, 1147, 1047, 1021, 987, 973, 951, 898, 866, 843, 802, 780, 736, 702; HRMS calc'd for $C_{16}H_{14}O_4$ = 270.0892, found 270.0893



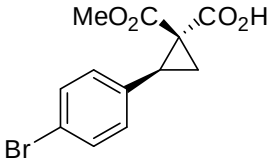
Reagents employed: **1.12f** (0.997 g, 3.77 mmol); NaOH (2.65 mL, 4.50 mmol); MeOH (3 mL); Yielded **1.58f** as a white powder, 95% (0.903 g, 3.61 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.2 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.34 (dd, J = 9.0 Hz, 9.0 Hz, 1H), 3.31 (s, 3H), 2.38 (dd, J = 8.6 Hz, 4.7 Hz, 1H), 2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 171.1, 159.1, 130.2, 125.7, 113.5, 55.2, 52.5, 39.7, 34.2, 21.1; IR (thin film, cm^{-1}): 3009, 2956, 2839, 2586, 1734, 1695, 1612, 1584, 1551, 1517, 1438, 1377, 1331, 1304, 1251, 1223, 1199, 1179, 1146, 1033, 974, 943, 902, 835, 811, 767, 704; HRMS calc'd for $C_{13}H_{14}O_5$ = 250.0841, found 250.0840



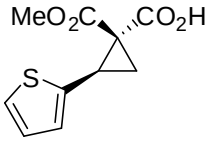
Reagents employed: **1.12g** (0.379 g, 1.36 mmol); NaOH (1.00 mL, 1.70 mmol); MeOH (1 mL); Yielded **1.58g** as a yellow powder, 98% (0.352g, 1.33 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.75-6.68 (m, 3H), 5.95 (s, 2H), 3.38 (s, 3H), 3.30 (dd, J = 9.0 Hz, 9.0 Hz, 1H), 2.32 (dd, J = 8.6 Hz, 5.1 Hz, 1H), 2.23 (dd, J = 9.4 Hz, 5.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9, 170.8, 147.5, 147.2, 127.6, 122.6, 109.4, 108.0, 101.2, 52.7, 40.3, 33.9, 21.4; IR (thin film, cm^{-1}): 3096, 3011, 2959, 2899, 2698, 1737, 1685, 1609, 1506, 1495, 1440, 1330, 1240, 1212, 1147, 1104, 1074, 1037, 1020, 955, 933, 909, 899, 869, 861, 824, 809, 760; HRMS calc'd for $C_{13}H_{12}O_6$ = 264.0634, found 264.0635



Reagents employed: **1.12h** (0.368 g, 1.37 mmol); NaOH (1 mL, 1.70 mmol); MeOH (1 mL); Yielded **1.58h** as a clear oil, 81% (0.283 g, 1.11 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.29 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 3.37 (t, J = 8.6 Hz, 1H), 3.33 (s, 3H), 2.38 (dd, J = 8.6 Hz, 4.7 Hz, 1H), 2.32 (dd, J = 9.4 Hz, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 171.4, 133.7, 132.5, 130.3, 128.4, 52.6, 38.0, 34.2, 21.0; IR (thin film, cm^{-1}): 3102, 3030, 2953, 2853, 1735, 1697, 1654, 1593, 1491, 1438, 1398, 1333, 1292, 1219, 1177, 1145, 1073, 1012, 970, 943, 899, 855, 834, 813, 786, 760. HRMS calc'd for $C_{12}H_{11}ClO_4$ = 254.0346, found 254.0343



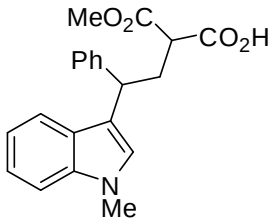
Reagents employed: **1.12i** (0.322 g, 1.03 mmol); NaOH (1.00 mL, 1.70 mmol); MeOH (1 mL); Yielded **1.58i** as a white solid, 96% (0.296 g, 0.988 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.42 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 3.34 (s, 3H), 3.30 (dd, J = 8.8 Hz, 8.8 Hz, 1H), 2.33 (dd, J = 8.2 Hz, 4.7 Hz, 1H), 2.20 (dd, J = 9.4 Hz, 5.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.8, 171.3 133.0, 131.4, 131.3, 131.0, 130.6, 121.9, 52.6, 38.4, 34.1, 21.0; IR (thin film, cm^{-1}): 3102, 3030, 2953, 2853, 1735, 1697, 1654, 1593, 1491, 1438, 1398, 1333, 1292, 1219, 1177, 1145, 1073, 1012, 970, 943, 899, 855, 834, 813, 786, 760. HRMS calc'd for $C_{12}H_{11}BrO_4$ = 297.9841, found 297.9843



Reagents employed: **1.12j** (1.12 g, 4.66 mmol); NaOH (3.26 mL, 5.54 mmol); MeOH (3.3 mL); Yielded **1.58j** as a yellow-brown oil, 97% (1.021 g, 4.52 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.22 (m, 1H), 6.94 (m, 2H), 3.43 (s, 3H), 3.35 (dd, J = 8.8 Hz, 8.8 Hz, 1H), 2.31 (dd, J = 8.2 Hz, 5.3 Hz, 2H), 2.19 (dd, J = 9.4 Hz, 4.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.2, 170.7, 137.2, 127.2, 126.6, 125.5, 52.6, 35.5, 32.5, 22.2; IR (thin film, cm^{-1}): 3108, 3012, 2954, 2849, 1781, 1738, 1699, 1576, 1559, 1539, 1437, 1386, 1332, 1243 1211, 1150, 1092, 1079, 1041, 988, 932, 914, 898, 707; HRMS calc'd for $C_{10}H_{10}O_4S$ = 226.0300, found 226.0300

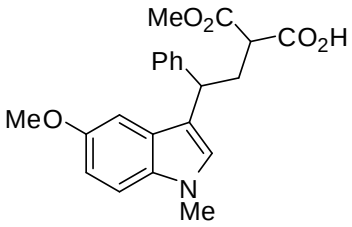
General Procedure for the Ring Opening of Cyclopropane Hemimalonates with Indole

Indoles and cyclopropanes were measured into a length of heat shrinkable Teflon tubing closed at one end with a brass clamp. The tube was sealed with another brass clamp and placed in a LECO Tempres high-pressure chemical reactor and the reactor was heated to 50 °C, then pressurized. After a period of time the mixture was depressurized and the solvent removed. The residue was subjected to flash chromatography on silica gel and the product isolated as an oil and mixture of diastereomers.

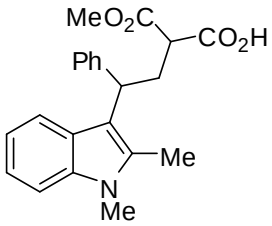


Reagents employed: **1.61** (0.072 g, 0.547 mmol); **1.58d** (0.100 g, 0.456 mmol); acetonitrile (3 mL); Yielded **1.65a** as a red oil, 73% (0.117 g, 0.332 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 9.83-9.30 (broad s, 1H), 7.56-7.49 (m, 1H), 7.43-7.21 (m, 7H), 7.13-7.05 (m, 1H), 6.94 (s, 1H), 4.37-4.29 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.56-3.48 (m, 1H), 2.97-2.87 (m, 1H), 2.77-2.66 (m, 1H); Diastereomer B: δ = 9.83-9.30 (broad s, 1H), 7.56-7.49 (m, 1H), 7.43-7.21 (m, 7H), 7.13-7.05 (m, 1H), 6.97 (s, 1H),

4.37-4.29 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.56-3.48 (m, 1H), 2.97-2.87 (m, 1H), 2.77-2.66 (m, 1H); Diastereomeric mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.2, 169.6, 169.6, 143.3, 143.2, 137.2, 128.5, 128.5, 127.9, 127.8, 127.0, 127.0, 126.5, 126.4, 126.1, 126.0, 121.6, 119.4, 119.4, 118.8, 116.9, 116.8, 109.1, 52.6, 52.6, 50.0, 40.5, 34.9, 34.8, 32.6 IR (thin film, cm^{-1}): 3062, 3027, 2952, 1744, 1602, 1547, 1489, 1458, 1452, 1374, 1328, 1265, 1157, 1087, 1014, 926, 740, 703; HRMS calc'd for $C_{21}H_{21}NO_4$ = 351.1471, found = 351.1459

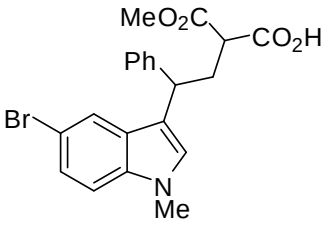


Reagents employed: **1.21a** (0.099 g, 0.612 mmol); **1.58d** (0.107 g, 0.486 mmol); acetonitrile (3 mL); Yielded **1.65b** as a reddish-brown oil, 58% (0.108 g, 0.282 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.38-7.28 (m, 4H), 7.25-7.20 (m, 1H), 7.16 (s, 1H), 6.94-6.90 (dd, J = 9.0 Hz, 2.0Hz, 1H), 6.89-6.85 (m, 2H), 4.29-4.19 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.50-3.44 (m, 1H), 2.92-2.81 (m, 1H) 2.70-2.59 (m, 1H); Diastereomer B: δ = 7.38-7.28 (m, 4H), 7.25-7.20 (m, 1H), 7.18 (s, 1H), 6.94-6.90 (dd, J = 9.0 Hz, 2.0Hz, 1H), 6.89-6.85 (m, 2H), 4.29-4.19 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.50-3.44 (m, 1H), 2.92-2.81 (m, 1H) 2.70-2.59 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.1, 174.9 169.7, 169.6, 153.5, 143.2, 143.2, 132.6, 128.5, 127.9, 127.9, 127.3, 127.3, 126.7, 126.6, 126.5, 116.4, 116.4, 111.8, 111.8, 109.9, 101.4, 101.3, 55.8, 55.7, 52.6, 49.9, 40.6, 40.5, 34.8, 34.7, 32.8; IR (thin film, cm^{-1}): 2957, 2925, 1735, 1622, 1577, 1492, 1452, 1424, 1271, 1219, 1173, 1061, 1036, 796, 736, 702; HRMS calc'd for $C_{22}H_{23}NO_5$ = 381.1576, found = 381.1589

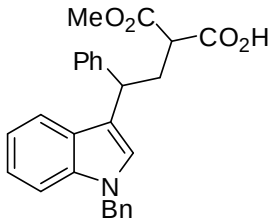


Reagents employed: **1.21b** (0.083 g, 0.574 mmol); **1.58d** (0.104 g, 0.471 mmol); acetonitrile (3 mL); Yielded **1.65c** as a dark red oil, 87% (0.150 g, 0.409 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.58-7.54 (broad dd, J = 7.8 Hz, 2.4Hz, 1H), 7.45 (s, 1H) 7.43 (s, 1H), 7.35-7.27 (m, 3H), 7.25-7.16 (m, 2H), 7.10-7.06 (d, J = 7.8 Hz,

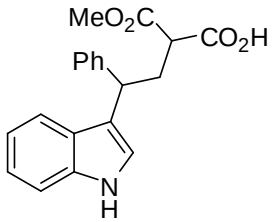
1H), 4.45-4.36 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.45-3.39 (m, 1H), 3.05-2.97 (m, 2H), 2.39 (s, 3H); Diastereomer B: δ = 7.58-7.54 (broad dd, J = 7.8 Hz, 2.4Hz, 1H), 7.45 (1s, 1H), 7.43 (s, 1H), 7.35-7.27 (m, 3H), 7.25-7.16 (m, 2H), 7.08-7.04 (d, J = 7.0 Hz, 1H), 4.45-4.36 (m, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 3.45-3.39 (m, 1H), 3.05-2.97 (m, 2H), 2.39 (s, 3H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.0, 169.9, 169.7, 144.0, 136.9, 136.9, 134.2, 134.1, 128.2, 127.4, 126.3, 126.3, 125.9, 120.4, 120.4, 119.3, 119.2, 118.8, 118.8, 110.8, 110.7, 108.7, 108.6, 52.4, 52.4, 50.4, 50.2, 39.5, 39.4, 33.2, 29.4, 10.4, 10.4; IR (thin film, cm^{-1}): 3062, 3026, 2950, 1739, 1712, 1612, 1559, 1494, 1471, 1436, 1408, 1369, 1335, 1252, 1158, 1061, 1031, 923, 740, 701; HRMS calc'd for $C_{22}H_{23}NO_4$ = 365.1627, found = 365.1615



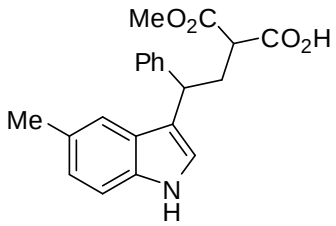
Reagents employed: **1.21c** (0.116 g, 0.552 mmol); **1.58d** (0.101 g, 0.460 mmol); acetonitrile (3 mL); Yielded **1.65d** as a dark yellow oil, 67% (0.132 g, 0.308 mmol); ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.57 (d, J = 2.0 Hz, 1H), 7.32-7.28 (m, 4H), 7.25-7.18 (m, 2H), 7.13 (s, 1H), 6.93 (s, 1H), 4.22-4.15 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.44-3.38 (m, 1H), 2.83-2.72 (m, 1H) 2.68-2.57 (m, 1H); Diastereomer B: δ = 7.53 (d, J = 1.6 Hz, 1H), 7.32-7.28 (m, 4H), 7.25-7.18 (m, 2H), 7.11 (s, 1H), 6.90 (s, 1H), 4.22-4.15 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.44-3.38 (m, 1H), 2.83-2.72 (m, 1H) 2.68-2.57 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.8, 169.6, 142.9, 142.8, 135.9, 135.8, 129.0, 128.7, 128.6, 128.6, 127.8, 127.2, 127.1, 126.7, 126.7, 124.5, 121.9, 121.8, 116.7, 116.6, 112.3, 110.7, 52.7, 52.7, 49.9, 40.3, 40.3, 34.9, 34.8, 32.8, 32.8; IR (thin film, cm^{-1}): 3058, 3027, 2951, 1739, 1711, 1612, 1559, 1477, 1437, 1371, 1336, 1267, 1228, 1158, 1040, 866, 794, 739, 702; HRMS calc'd for $C_{21}H_{20}BrNO_4$ = 429.0576 found = 429.0563



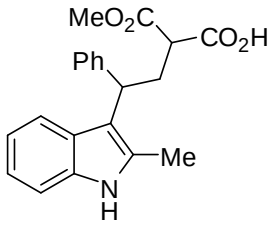
Reagents employed: **1.21d** (0.116 g, 0.561 mmol); **1.58d** (0.103 g, 0.467 mmol); acetonitrile (3 mL); Yielded **1.65e** as an orange oil, 68% (0.135 g, 0.316 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.50-7.43 (m, 1H), 7.35-7.23 (m, 7H), 7.21-7.17 (m, 2H), 7.13-7.06 (m, 3H), 7.03-6.98 (m, 2H), 5.24 (s, 2H), 4.35-4.25 (m, 1H), 3.64 (s, 3H), 3.45-3.41 (m, 1H), 2.92-2.81 (m, 1H), 2.69-2.59 (m, 1H); Diastereomer B: 7.50-7.43 (m, 1H), 7.35-7.23 (m, 7H), 7.21-7.17 (m, 2H), 7.13-7.06 (m, 3H), 7.03-6.98 (m, 2H), 5.24 (s, 2H), 4.35-4.25 (m, 1H), 3.72 (s, 3H), 3.45-3.41 (m, 1H), 2.92-2.81 (m, 1H), 2.69-2.59 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.2, 175.1, 169.6, 169.5, 143.2, 143.1, 137.5, 136.9, 128.6, 128.5, 128.5, 127.9, 127.9, 127.4, 127.3, 127.3, 126.5, 126.5, 125.5, 125.4, 121.9, 121.9, 119.6, 119.6, 119.1, 117.6, 117.5, 109.6, 52.6, 52.6, 49.9, 49.9, 40.6, 40.6, 34.8, 34.8; IR (thin film, cm^{-1}): 3060, 3028, 2952, 2928, 1739, 1712, 1613, 1603, 1495, 1481, 1467, 1453, 1438, 1418, 1393, 1355, 1332, 1300, 1265, 1233, 1201, 1176, 1028, 739, 700; HRMS calc'd for $C_{27}H_{25}NO_4$ = 427.1784, found = 427.1778



Reagents employed: **1.21e** (0.064 g, 0.548 mmol); **1.58d** (0.101 g, 0.457 mmol); acetonitrile (3 mL); Yielded **1.65f** as a brown oil, 81% (0.125 g, 0.371 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 8.06-8.01(broad s, 1H), 7.47-7.41 (m, 1H), 7.35-7.27 (m, 4H), 7.25-7.12 (m, 2H), 7.08-6.99 (m, 2H), 4.30-4.23 (m, 1H), 3.65 (s, 3H), 3.46-3.40 (m, 1H), 2.91-2.80 (m, 1H) 2.70-2.59 (m, 1H); Diastereomer B: δ = 8.06-8.01 (broad s, 1H), 7.47-7.41 (m, 1H), 7.35-7.27 (m, 4H), 7.25-7.12 (m, 2H), 7.08-6.99 (m, 2H), 4.30-4.23 (m, 1H), 3.73 (s, 3H), 3.46-3.40 (m, 1H), 2.91-2.80 (m, 1H) 2.70-2.59 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 170.1, 143.5, 143.2, 136.5, 128.8, 128.7, 128.5, 128.4, 127.9, 126.7, 126.5, 126.4, 126.4, 121.9, 121.6, 121.4, 119.3, 119.2, 118.1, 118.0, 111.1, 52.6, 52.5, 50.1, 40.6, 40.5, 34.9 34.7; IR (thin film, cm^{-1}): 3412, 3058, 3029, 2952, 2928, 1736, 1621, 1608, 1583, 1493, 1456, 1436, 1420, 1337, 1265, 1227, 1164, 1128, 1099, 1080, 1011, 741, 701; HRMS calc'd for $C_{20}H_{19}NO_4$ = 337.1314, found = 337.1305

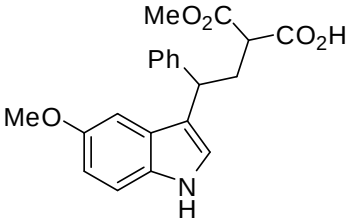


Reagents employed: **1.21f** (0.072 g, 0.551 mmol); **1.58d** (0.101 g, 0.460 mmol); acetonitrile (3 mL); Yielded **1.65g** as a dark green oil, 87% (0.141 g, 0.401 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.97 (br s, 1H), 7.33-7.27 (m, 4H), 7.24-7.19 (m, 3H), 7.00-6.95 (m, 2H), 4.27-4.20 (m, 1H), 3.67 (s, 1H), 3.47-3.41 (m, 1H), 2.88-2.77 (m, 1H), 2.69-2.59 (m, 1H), 2.38 (s, 3H); Diastereomer B: δ = 8.00 (br s, 1H), 7.33-7.27 (m, 4H), 7.24-7.19 (m, 3H), 7.00-6.95 (m, 2H), 4.27-4.20 (m, 1H), 3.73 (s, 1H), 3.47-3.41 (m, 1H), 2.88-2.77 (m, 1H), 2.69-2.59 (m, 1H), 2.37 (s, 3H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0, 173.8, 170.1, 170.1, 143.6, 143.4, 134.8, 128.4, 128.4, 128.3, 128.3, 127.8, 126.9, 126.8, 123.6, 121.7, 121.5, 118.8, 118.8, 117.5, 117.3, 110.8, 52.5, 52.5, 50.1, 50.1, 40.5, 40.5, 35.0, 34.8, 21.5, 21.4; IR (thin film, cm^{-1}): 3408, 3028, 2952, 2922, 2860, 1735, 1653, 1603, 1583, 1494, 1436, 1640, 1265, 1227, 1165, 1099, 1031, 797, 756, 736, 701; HRMS calc'd for $C_{21}H_{21}NO_4$ = 351.1471, found = 351.1472

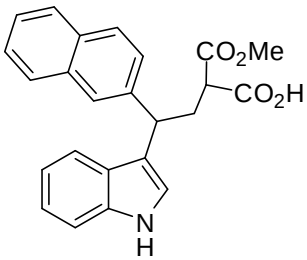


Reagents employed: **1.21g** (0.0722 g, 0.55 mmol); **1.58d** (0.1010 g, 0.46 mmol); acetonitrile (3 mL); Yielded **1.65h** as a dark orange oil, 97% (0.1564 g, 0.44 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.99-7.92 (d, J = 13.7 Hz, 1H), 7.55-7.50 (d, J = 8.2 Hz, 1H), 7.44-7.39 (d, J = 7.4 Hz, 2H), 7.33-7.27 (t, J = 7.4 Hz, 2H), 7.24-7.18 (m, 1H), 7.16-7.09 (m, 1H), 7.08-7.02 (t, J = 7.4 Hz, 1H), 4.38-4.30 (m, 1H), 3.58 (s, 3H), 3.44-3.37 (m, 1H), 3.05-2.89 (m, 2H), 2.34 (s, 3H); Diastereomer B: δ = 7.99-7.92 (d, J = 13.7 Hz, 1H), 7.55-7.50 (d, J = 8.2 Hz, 1H), 7.44-7.39 (d, J = 7.4 Hz, 2H), 7.33-7.27 (t, J = 7.4 Hz, 2H), 7.24-7.18 (m, 1H), 7.16-7.09 (m, 1H), 7.08-7.02 (t, J = 7.4 Hz, 1H), 4.38-4.30 (m, 1H), 3.74 (s, 3H), 3.44-3.37 (m, 1H), 3.05-2.89 (m, 2H), 2.34 (s, 3H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.8, 170.0, 169.7, 143.8, 135.5, 135.4, 132.5, 132.4, 128.3, 127.5, 127.3, 127.2, 126.0, 120.9, 120.8, 119.3, 119.2, 119.2, 111.4, 111.4, 110.4, 110.4, 52.6, 52.5, 50.4, 50.2, 39.3, 39.2, 33.2, 11.9,

11.9; IR (thin film, cm^{-1}): 3403, 3057, 3026, 2952, 2924, 1733, 1716, 1619, 1601, 1583, 1559, 1494, 1460, 1436, 1388, 1342, 1302, 1266, 1244, 1161, 1046, 1031, 1022, 741, 701; HRMS calc'd for $C_{21}H_{21}NO_4$ = 351.1471, found = 351.1463

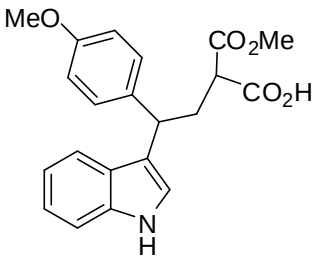


Reagents employed: **1.21h** (0.080 g, 0.546 mmol); **1.58d** (0.100 g, 0.455 mmol); acetonitrile (3 mL); Yielded **1.65i** as a dark brown oil, 92% (0.154 g, 0.419 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.94 (br s, 1H), 7.32-7.28 (m, 3H), 7.23-7.17 (m, 3H), 7.02-6.99 (m, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.82-6.79 (m, 1H), 4.24-4.18 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.46-3.41 (m, 1H), 2.89-2.79 (m, 1H), 2.67-2.58 (m, 1H); Diastereomer B: δ = 7.95 (br s, 1H), 7.32-7.28 (m, 3H), 7.23-7.17 (m, 3H), 7.02-6.99 (m, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.82-6.79 (m, 1H), 4.24-4.18 (m, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 3.46-3.41 (m, 1H), 2.89-2.79 (m, 1H), 2.67-2.58 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9, 173.9, 170.1, 170.0, 153.5, 143.3, 143.1, 131.7, 128.5, 128.4, 127.9, 127.9, 127.1, 127.0, 126.5, 126.4, 122.3, 122.2, 117.9, 117.8, 112.0, 111.8, 101.3, 101.2, 55.7, 55.7, 52.6, 52.5, 50.1, 50.0, 40.7, 40.6, 34.8, 34.6; IR (thin film, cm^{-1}): 3411, 3059, 3028, 3000, 2952, 2833, 1735, 1624, 1604, 1583, 1485, 1454, 1439, 1341, 1288, 1266, 1213, 1172, 1094, 1063, 1031, 922, 834, 800, 752, 736, 702; HRMS calc'd for $C_{21}H_{21}NO_5$ = 367.1420, found = 367.1414

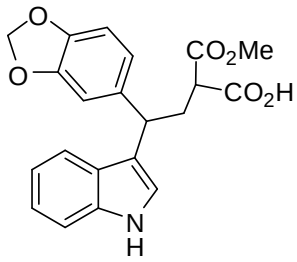


Reagents employed: **1.21e** (0.054 g, 0.456 mmol); **1.58e** (0.103 g, 0.380 mmol); acetonitrile (3 mL); Yielded **1.65j** as pink oil, 65% (0.096 g, 0.248 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 8.35-6.86 (aromatic region is a mixture of diastereomers as well as atropisomers), 5.23-5.18 (m, 1H), 3.65 (s, 3H), 3.61-3.56 (m, 1H), 2.99-2.78 (m, 2H); Diastereomer B: δ = 8.35-6.86 (aromatic region is a mixture of diastereomers as well as atropisomers), 5.23-5.18 (m, 1H), 3.70 (s, 3H), 3.61-3.56 (m, 1H), 2.99-2.78 (m, 2H); Diastereomeric Mixture: ^{13}C NMR (100

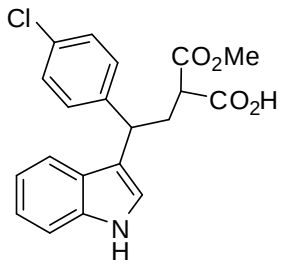
MHz, $CDCl_3$) δ = 170.7, 170.1, 139.4, 139.0, 136.5, 136.4, 134.0, 131.8, 131.7, 128.8, 127.2, 127.2, 126.8, 126.8, 126.4, 126.3, 126.1, 126.0, 125.9, 125.4, 125.1, 124.5, 124.4, 123.4, 122.9, 122.3, 122.1, 122.0, 121.6, 119.7, 119.5, 119.4, 119.4, 119.3, 119.0, 118.9, 118.3, 117.9, 52.7, 52.5, 35.7, 35.5, 34.7, 34.6, 29.7; IR (thin film, cm^{-1}): 3412, 3054, 2951, 2925, 1734, 1700, 1684, 1653, 1636, 1617, 1598, 1576, 1558, 1540, 1507, 1490, 1457, 1436, 1419, 1396, 1265, 1227, 1167, 1097, 1011, 801, 780, 741, 702; HRMS calc'd for $C_{24}H_{21}NO_4$ = 387.1471, found = 387.1475



Reagents employed: **1.21e** (0.056 g, 0.482 mmol); **1.58f** (0.100 g, 0.402 mmol); acetonitrile (3 mL); Yielded **1.65k** as a light brown oil, 72% (0.106 g, 0.289 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.93 (br s, 1H), 7.39-7.34 (m, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.17-7.13 (m, 2H), 7.10-7.06 (m, 1H), 6.99-6.93 (m, 2H), 6.75 (d, J = 8.2 Hz, 2H), 4.18-4.12 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.39-3.34 (m, 1H), 2.81-2.74 (m, 1H), 2.57-2.50 (m, 1H); Diastereomer B: δ = 7.95 (br s, 1H), 7.39-7.34 (m, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.17-7.13 (m, 2H), 7.10-7.06 (m, 1H), 6.99-6.93 (m, 2H), 6.75 (d, J = 8.2 Hz, 2H), 4.18-4.12 (m, 1H), 3.69 (s, 3H), 3.59 (s, 3H), 3.39-3.34 (m, 1H), 2.81-2.74 (m, 1H), 2.57-2.50 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.5, 170.1, 158.1, 158.0, 136.5, 135.5, 135.2, 128.9, 126.7, 126.5, 122.0, 121.4, 121.3, 119.4, 119.4, 119.2, 118.6, 118.4, 113.8, 113.8, 111.1, 55.1, 52.6, 50.1, 50.0, 39.8, 39.8; IR (thin film, cm^{-1}): 3410, 3057, 3002, 2953, 2837, 1734, 1611, 1584, 1512, 1489, 1458, 1437, 1339, 1302, 1249, 1178, 1110, 1099, 834, 743; HRMS calc'd for $C_{21}H_{21}NO_5$ = 367.1420, found = 367.1418

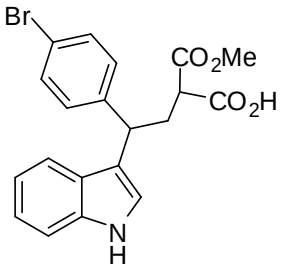


Reagents employed: **1.21e** (0.054 g, 0.464 mmol); **1.58g** (0.102 g, 0.387 mmol); acetonitrile (3 mL); Yielded **1.65l** as clear oil, 86% (0.128 g, 0.334 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 8.14 (br s, 1H), 7.43 (t, J = 9.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.17-7.11 (m, 1H), 7.05-6.99 (m, 2H), 6.82-6.78 (m, 1H), 6.75-6.70 (m, 2H), 5.89-5.85 (m, 2H), 4.22-4.14 (m, 1H), 3.73 (s, 3H), 3.49-3.41 (m, 1H), 2.86-2.75 (m, 1H), 2.61-2.51 (m, 1H); Diastereomer B: δ = 8.17 (br s, 1H), 7.43 (t, J = 9.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.17-7.11 (m, 1H), 7.05-6.99 (m, 2H), 6.82-6.78 (m, 1H), 6.75-6.70 (m, 2H), 5.89-5.85 (m, 2H), 4.22-4.14 (m, 1H), 3.68 (s, 3H), 3.49-3.41 (m, 1H), 2.86-2.75 (m, 1H), 2.61-2.51 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.4, 169.9, 147.7, 147.7, 137.4, 137.2, 136.5, 126.6, 126.5, 122.1, 121.2, 121.1, 121.0, 121.0, 119.3, 119.3, 118.4, 118.3, 111.1, 108.2, 108.0, 100.8, 52.6, 49.9, 40.3, 34.9, 34.8, 31.5, 29.6, 25.2, 22.6, 14.1; IR (thin film, cm^{-1}): 3412, 3057, 2953, 2925, 2855, 1733, 1558, 1503, 1487, 1457, 1440, 1339, 1242, 1163, 1127, 1099, 1038, 934, 865, 813, 743, 702; HRMS calc'd for $C_{21}H_{19}NO_6$ = 381.1212, found = 381.1219

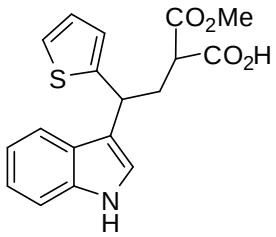


Reagents employed: **1.21e** (0.056 g, 0.474 mmol); **1.58h** (0.101 g, 0.395 mmol); acetonitrile (3 mL); Yielded **1.65m** as an orange oil, 74% (0.108 g, 0.291 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 8.20 (br s, 1H), 7.41-7.35 (m, 1H), 7.33-7.29 (m, 1H), 7.22 (s, 3H), 7.18-7.13 (m, 2H), 7.05-6.96 (m, 2H), 4.27-4.20 (m, 1H), 3.67 (s, 3H), 3.46-3.39 (m, 1H), 2.88-2.76 (m, 1H), 2.65-2.54 (m, 1H); Diastereomer B: δ = 8.20 (br s, 1H), 7.41-7.35 (m, 1H), 7.33-7.29 (m, 1H), 7.22 (s, 3H), 7.18-7.13 (m, 2H), 7.05-6.96 (m, 2H), 4.27-4.20 (m, 1H), 3.71 (s, 3H), 3.46-3.39 (m, 1H), 2.88-2.76 (m, 1H), 2.65-2.54 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0, 169.8, 141.9, 141.8, 136.5, 132.1, 132.1, 129.2, 129.2, 128.6, 128.6, 126.4, 126.3, 122.2, 121.5, 121.4, 119.4, 119.2, 119.1, 117.6, 117.5, 111.2, 52.7, 52.6, 49.9, 40.0, 34.7, 34.5; IR (thin film, cm^{-1}): 3409, 3057, 2952, 2901, 2795, 1734,

1653, 1599, 1577, 1558, 1491, 1457, 1436, 1418, 1339, 1265, 1227, 1163, 1092, 1014, 1032, 831, 765, 742, 702; HRMS calc'd for $C_{20}H_{18}ClNO_4$ = 371.0924, found = 371.0922



Reagents employed: **1.21e** (0.048 g, 0.409 mmol); **1.58i** (0.102 g, 0.341 mmol); acetonitrile (3 mL); Yielded **1.65n** as an orange oil, 73% (0.103 g, 0.249 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 8.13 (br s, 1H), 7.42-7.36 (m, 3H), 7.34-7.28 (m, 2H), 7.19-7.15 (m, 2H), 7.05-6.97 (m, 2H), 4.26-4.20 (m, 1H), 3.68 (s, 3H), 3.45-3.40 (m, 1H), 2.88-2.77 (m, 1H), 2.66-2.55 (m, 1H); Diastereomer B: δ = 8.12 (br s, 1H), 7.42-7.36 (m, 3H), 7.34-7.28 (m, 2H), 7.19-7.15 (m, 2H), 7.05-6.97 (m, 2H), 4.26-4.20 (m, 1H), 3.73 (s, 3H), 3.45-3.40 (m, 1H), 2.88-2.77 (m, 1H), 2.66-2.55 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 174.0, 169.8, 169.7, 142.4, 142.3, 136.5, 131.6, 131.6, 129.7, 129.7, 126.4, 126.4, 122.3, 121.5, 121.4, 120.3, 120.3, 119.5, 119.3, 119.2, 117.6, 117.5, 111.2, 52.7, 52.7, 49.8, 40.1, 34.6, 34.5; IR (thin film, cm^{-1}): 3412, 3054, 2952, 2925, 1734, 1598, 1558, 1510, 1489, 1456, 1435, 1418, 1353, 1337, 1265, 1245, 1168, 1095, 1011, 896, 801, 780, 767, 742, 702

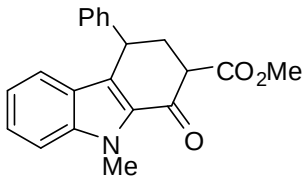


Reagents employed: **1.21e** (0.064 g, 0.542 mmol); **1.58j** (0.102 g, 0.452 mmol); acetonitrile (3 mL); Yielded **1.65o** as brown oil, 50% (0.077 g, 0.224 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$) Diastereomer A: δ = 8.08 (br s, 1H), 7.95 (br s, 1H), 7.53 (t, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.32-7.28 (m, 1H), 7.14-6.89 (m, 5H), 4.61-4.54 (m, 1H), 3.67 (s, 3H), 3.51-3.45 (m, 1H), 2.93-2.83 (m, 1H), 2.79-2.68 (m, 1H); Diastereomer B: δ = 8.12 (br s, 1H), 7.95 (br s, 1H), 7.53 (t, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.32-7.28 (m, 1H), 7.14-6.89 (m, 5H), 4.61-4.54 (m, 1H), 3.68 (s, 3H), 3.51-3.45 (m, 1H), 2.93-2.83 (m, 1H), 2.79-2.68 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0, 169.9, 169.8, 148.0, 147.8, 136.5, 136.4, 126.5, 126.2, 126.1, 124.4, 124.4, 123.8, 122.1, 121.9, 121.7, 119.5,

119.4, 119.2, 119.0, 117.7, 111.3, 111.1, 52.6, 52.6, 50.0, 50.0, 36.1, 36.0, 35.8, 35.6; IR (thin film, cm^{-1}): 3410, 3108, 3057, 2952, 2926, 2854, 1733, 1619, 1558, 1507, 1489, 1457, 1436, 1339, 1265, 1228, 1165, 1099, 1032, 1012, 850, 742, 702; HRMS calc'd for $C_{18}H_{17}NO_4S$ = 343.0878, found = 343.0870

Procedure For the Conversion of 1.65a to Tetrahydrocarbazole 1.66

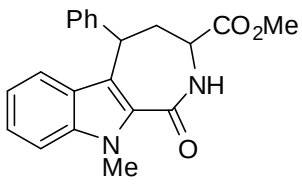
Crude mixture of indole hemi-malonate **1.65a** and indole **1.61** were dissolved in toluene. Trifluoroacetic anhydride (TFAA) was added to the solution, the mixture was stirred for 30 mins and cold water was added. The aqueous layer was extracted three times with DCM, then the combined organic layers were dried over $MgSO_4$, filtered and solvent was removed in vacuo.[80] The residue was then added to a suspension of NaH in wet DMF.[81] After stirring for 15 mins at 70 °C, the mixture was poured over ice and extracted with ether three times. The combined organic layers were dried over $MgSO_4$, filtered and solvent was removed in vacuo. The residue was then purified by flash chromatography on silica gel.



Reagents employed: **1.65a** (0.055 g, 0.157 mmol); TFAA (24 µL, 1.73 mmol); Toluene (5 ml); NaH (0.023 g, 0.575 mmol); DMF (3 mL); Yielded **1.66** as brown oil, 40% (0.061 g, 0.183 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomer A: δ = 7.26-7.43(m, 6H), 7.18 (d, J = 8.2 Hz, 1H), 6.84-6.89 (m, 1H), 6.68 (d, J = 8.2 Hz, 1H), 4.44 (dd, J = 11.0 Hz, 4.7 Hz, 1H), 4.12 (s, 3H), 3.84 (dd, J = 12.9 Hz, 4.3 Hz, 1H), 3.79 (s, 3H), 2.79-7.69 (m, 1H), 2.64-2.57 (m, 1H); Diastereomer B: δ = 7.26-7.43(m, 6H), 7.09 (d, J = 8.2 Hz, 1H), 6.96-7.01 (m, 1H), 6.68 (d, J = 8.2 Hz, 1H), 4.68-4.73 (m, 1H), 4.14 (s, 3H), 3.78 (s, 3H), 3.73 (dd, J = 9.0 Hz, 4.7 Hz, 1H), 2.95-3.03 (m, 1H), 2.45-2.52 (m, 1H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.9, 186.6, 170.7, 170.6, 143.1, 142.2, 140.4, 140.3, 130.6, 129.9, 129.7, 129.6, 128.7, 128.6, 128.3, 128.0, 127.1, 127.0, 126.9, 126.8, 124.3, 124.1 122.8, 122.3, 110.3, 110.2, 52.4, 52.4, 41.1, 37.7, 37.2, 31.6, 31.5; HRMS calc'd for $C_{21}H_{19}NO_3$ = 333.1365, found = 333.1372

Procedure for the Conversion of 1.65a to Azepinoindole 1.67[82]

Crude mixture of indole hemi-malonate **1.65a** and indole **1.61** were dissolved in benzene. Diphenylphosphoryl azide (DPPA) and triethylamine were added and the reaction was stirred for 10 mins. The reaction was then heated to reflux for 15 hrs. The solvent was removed in vacuo, the remaining residue was dissolved in EtOAc and washed with a solution of 5% HCl. The organic layer was dried over $MgSO_4$, filtered and purified by flash chromatography on silica gel.



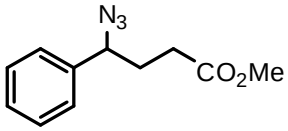
Reagents employed: **1.65a** (0.160 g, 0.454 mmol); DPPA (97 µL, 0.454 mmol); triethylamine (69 µL, 0.498 mmol); Benzene (5 mL); Yielded **1.67** as a yellow oil, 33% (0.052 g, 0.149 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) Diastereomeric mixture: δ = 7.45-7.40 (m, 1H), 7.34-7.27 (m, 4H), 7.24-7.16 (m, 2H), 7.06-7.01 (m, 1H), 6.90 (d, J = 5.5 Hz, 1H), 5.57-5.47 (overlapping br d, 1H), 4.53-4.41 (m, 1H), 4.33-4.26 (m, 1H), 3.75, 3.75 (overlapping s, 3H), 3.63, 3.62 (overlapping s, 3H), 2.85-2.40 (overlapping m, 2H); Diastereomeric Mixture: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 172.0, 156.1, 156.1, 143.6, 143.2, 137.4, 137.3, 128.6, 128.5, 127.9, 127.8, 126.6, 126.5, 126.2, 126.1, 121.8, 119.2, 118.9, 109.3, 109.2, 52.8, 52.4, 39.3, 39.2, 38.2, 38.1, 32.7, 32.7; HRMS calc'd for $C_{21}H_{20}N_2O_3$ = 348.1474, found = 348.1476

Section 1.9.2 The Tandem Ring Opening/Decarboxylation of Cyclopropane Hemimalonates with Sodium Azide

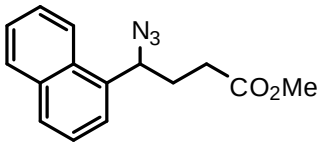
General Experimental Procedure for the synthesis of azidoesters 1.71a-l

Sodium azide (1.2 equiv.) and ammonium chloride (1.4 equiv.) were added to a solution of cyclopropane hemimalonate (1.0 equiv.) in 2-methoxyethanol:water (5.0 ml:0.5 ml). The mixture was stirred at reflux (125 °C) until the reaction was complete (as determined by TLC analysis). The reaction was then quenched with water and

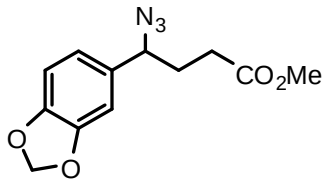
extracted with ether (3 times). The organic layers were then combined and dried with magnesium sulfate. Following filtration, the solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (EtOAc:Hexanes, 20:80) to yield the desired products **1.71a-l**.



Reagents employed: **1.58d** (0.104 g, 0.473 mmol); sodium azide (0.037 g, 0.569 mmol); ammonium chloride (0.036 g, 0.673 mmol); 2-methoxyethanol:water; Yielded **1.71 a** as a clear oil, 78% (0.081 g, 0.369 mmol). The data for this compound matched that previously reported.[83]

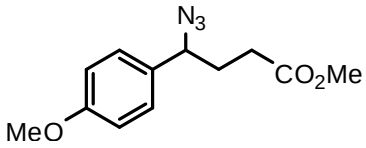


Reagents employed: **1.58e** (0.119 g, 0.440 mmol); sodium azide (0.035 g, 0.538 mmol); ammonium chloride (0.033 g, 0.617 mmol); 2-methoxyethanol:water; Yield **1.71b** as a clear oil, 76% (0.090 g, 0.334 mmol) as a clear oil. R_f = 0.58, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.6, 1H), 7.90 (dd, J = 7.8, 1.6 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.60-7.48 (m, 4H), 5.37 (dd, J = 8.6, 5.8 Hz, 1H), 3.69 (s, 3H), 2.60-2.43 (m, 2H), 2.36-2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.3, 134.7, 134.0, 130.6, 129.1, 128.95, 126.6, 125.9, 125.3, 124.3, 122.9, 62.0, 51.7, 30.71, 30.6; IR (thin film): 3050, 2953, 2926, 2852, 2101, 1736, 1437, 1364, 1325, 1252, 1201, 1173, 801, 779; HRMS (EI) calc'd for $C_{15}H_{15}N_3O_2$ = 269.1164, found = 269.1159.

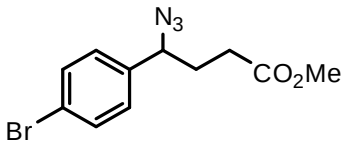


Reagents employed: **1.58g** (0.097 g, 0.367 mmol); sodium azide (0.029 g, 0.446 mmol); ammonium chloride (0.027 g, 0.505 mmol); 2-methoxyethanol:water; Yielded **1.71c** as a clear oil, 87% (0.084 g, 0.319 mmol). R_f = 0.58, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, J = 1.6 Hz, 1H), 6.78 (s, 1H) 6.76

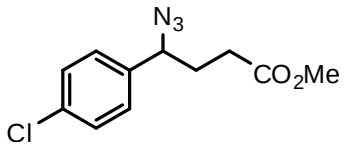
(d, J = 1.6 Hz, 1H) 5.97 (s, 2H), 4.44 (dd, J = 7.8, 6.2 Hz, 1H), 3.66 (s, 3H), 3.76 (t, J = 7.4, 2H), 2.11-1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1, 148.2, 147.7, 132.7, 120.7, 108.3, 106.9, 101.2, 65.1, 51.7, 31.3, 30.5; IR (thin film): 3459, 3323, 2953, 2101, 1739, 1505, 1490, 1443, 1342, 1328, 1252, 1170, 1102, 1042, 933, 863, 813, 661; HRMS (EI) calc'd for $C_{12}H_{13}N_3O_4$ = 263.0906, found = 263.0905.



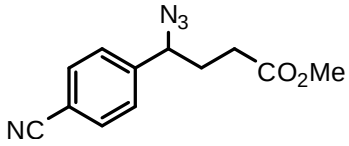
Reagents employed: **1.58f** (0.100 g, 0.400 mmol); sodium azide (0.031 g, 0.477 mmol); ammonium chloride (0.030 g, 0.561 mmol); 2-methoxyethanol:water; Yielded **1.71d** as a clear oil, 95% (0.095 g, 0.381 mmol). R_f = 0.54, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25-7.21 and 6.92-6.89 (m, AA'BB', 4H), 4.47 (dd, J = 7.8, 6.3 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.36 (t, J = 7.4, 2H), 2.15-1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1, 159.6, 130.8, 128.1, 114.2, 64.8, 55.2, 51.6, 31.2, 30.5; IR (thin film): 3451, 3319, 2953, 2839, 2482, 2101, 1739, 1611, 1529, 1438, 1245, 1174, 1034, 832, 545; HRMS (EI) calc'd for $C_{12}H_{15}NO_3$ = 221.1052, found = 221.1050. (M-N_2)



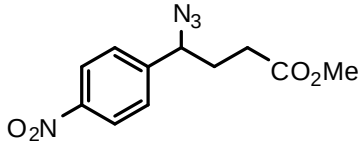
Reagents employed: **1.58i** (0.095 g, 0.318 mmol); sodium azide (0.025 g, 0.385 mmol), ammonium chloride (0.024 g, 0.449 mmol); 2-methoxyethanol:water; Yielded **1.71e** as a clear oil, 62% (0.059 g, 0.198 mmol). R_f = 0.53, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53-7.50 and 7.20-7.17 (m, AA'BB', 4H), 4.52 (dd, J = 8.2, 6.3 Hz, 1H), 3.66 (s, 3H), 2.37 (ddd, J = 9.8, 7.8, 3.1 Hz, 2H), 2.12-1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 183.0, 132.0, 128.5, 122.4, 64.6, 51.7, 31.3, 30.3; IR (thin film): 3455, 3319, 2951, 2101, 1737, 1489, 1437, 1250, 1201, 1171, 1044, 1011, 822, 532; HRMS (EI) calc'd for $C_{11}H_{13}BrN_3O_2$ = 298.0191, found = 298.0185. (M+H)



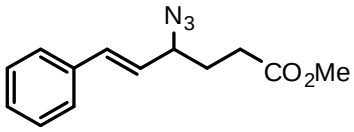
Reagents employed: **1.58h** (0.105 g, 0.412 mmol); sodium azide (0.032 g, 0.538 mmol); ammonium chloride (0.030 g, 0.561 mmol); 2-methoxyethanol:water; Yielded **1.71f** as a clear oil, 60% (0.063 g, 0.248 mmol). R_f = 0.56, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38-7.35 and 7.26-7.23 (m, AA'BB', 4H), 4.53 (dd, J = 7.8, 6.3 Hz, 1H), 3.67 (s, 3H), 2.38 (ddd, J = 9.4, 7.4, 2.3 Hz, 2H), 2.13-1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 137.5, 134.2, 129.1, 128.2, 64.5, 51.7, 31.3, 30.3; IR (thin film): 2952, 2101, 1739, 1493, 1437, 1325, 1249, 1202, 1171, 1092, 1015, 826, 534; HRMS (EI) calc'd for $C_{11}H_{13}ClN_3O_2$ = 254.0696, found = 254.0710. (M+H)



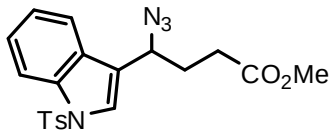
Reagents employed: **1.58k** (0.116 g, 0.473 mmol); sodium azide (0.037 g, 0.569 mmol), ammonium chloride (0.035 g, 0.654 mmol); 2-methoxyethanol:water; Yielded **1.71g** as a clear oil, 56% (0.065 g, 0.266 mmol). R_f = 0.46, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69-7.66 and 7.44-7.41 (m, AA'BB', 4H), 4.63 (dd, J = 7.0, 7.0 Hz, 1H), 3.66 (s, 3H), 2.46-2.32 (m, 2H), 2.07-2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 144.4, 132.7, 127.5, 118.2, 112.3, 64.4, 51.7, 31.3, 30.0; IR (thin film): 2953, 2230, 2100, 1734, 1609, 1438, 1417, 1308, 1252, 1200, 1174, 1019, 835, 566; HRMS (EI) calc'd for $C_{12}H_{13}N_4O_2$ = 245.1039, found = 245.1045. (M+H)



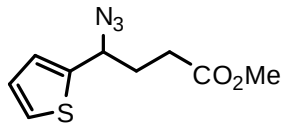
Reagents employed: **1.58l** (0.116 g, 0.437 mmol); sodium azide (0.034 g, 0.523mmol); ammonium chloride (0.033 g, 0.617 mmol); 2-methoxyethanol:water; Yielded **1.71h** as a clear oil, 46% (0.053 g, 0.201 mmol). R_f = 0.44, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26-8.23 and 7.52-7.49 (m, AA'BB', 4H), 4.71 (dd, J = 7.0, 7.0 Hz, 1H), 3.68 (s, 3H), 2.49-2.34 (m, 2H), 2.08 (q, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 147.8, 146.4, 127.7, 124.1, 64.3, 51.8, 31.5, 30.0; IR (thin film): 2953, 2926, 2100, 1735, 1607, 1522, 1437, 1348, 1253, 1200, 1172, 853, 700; HRMS (EI) calc'd for $C_{11}H_{13}N_4O_4$ = 265.0937, found = 265.0935. (M+H)



Reagents employed: **1.58m** (0.101 g, 0.410 mmol); sodium azide (0.032 g, 0.492 mmol); ammonium chloride (0.030 g, 0.561 mmol); 2-methoxyethanol:water; Yielded **1.71i** as a clear oil, 78% (0.078 g, 0.318 mmol). R_f = 0.50, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.26-7.22 (m, 1H), 6.60 (d, J = 15.6 Hz, 1H), 6.06 (dd, J = 16.0, 8.2 Hz, 1H) 4.08 (dd, J = 14.9, 7.4 Hz, 1H), 3.64 (s, 3H), 2.41 (t, J = 7.4 Hz, 2H), 1.94-1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.2, 135.7, 133.9, 128.6, 128.2, 126.7, 126.1, 63.9, 51.7, 30.2, 29.8; IR (thin film): 3027, 2952, 2105, 1739, 1493, 1437, 1239, 1170, 1112, 1071, 969, 888, 751, 694; HRMS (EI) calc'd for $C_{13}H_{14}NO_2$ = 216.1030, found = 216.1030. (M-N_2, H)

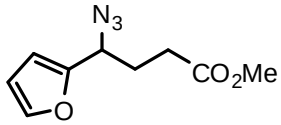


Reagents employed: **1.58m** (0.098 g, 0.237 mmol); sodium azide (0.018 g, 0.277 mmol); ammonium chloride (0.018 g, 0.337 mmol); 2-methoxyethanol:water; Yielded **1.71j** as a clear oil, 58% (0.057 g, 0.138 mmol). R_f = 0.54, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 1 Hz, 1H), 7.58 (s, 1H), 7.35 (ddd, J = 8.6, 7.4, 1.2 Hz, 1H), 7.26 (ddd, J = 8.2, 8.2, 0.8 Hz, 1H), 7.23-7.21 (m, 2H), 4.76 (dd, J = 7.0, 7.0 Hz, 1H), 3.68 (s, 3H), 2.51-2.38 (m, 2H), 2.33 (s, 3H), 2.27-2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 145.2, 135.5, 134.8, 129.9, 128.4, 126.8, 125.3, 124.0, 123.5, 120.2, 120.0, 113.9, 57.8, 51.7, 30.4, 29.4, 21.5; IR (thin film): 2953, 2925, 2109, 1735, 1448, 1372, 1256, 1178, 1123, 1089, 749, 669, 574, 538; HRMS (EI) calc'd for $C_{20}H_{20}N_4O_4S$ = 412.1205, found = 412.1190.



Reagents employed: **1.58j** (0.135 g, 0.597 mmol); sodium azide (0.047 g, 0.723 mmol); ammonium chloride (0.045 g, 0.841 mmol); 2-methoxyethanol:water; Yielded **1.71k** as a clear oil, 79% (0.106 g, 0.471 mmol). R_f = 0.47, 30% EtOAc in hexanes; ^{1}H-NMR (400 MHz,

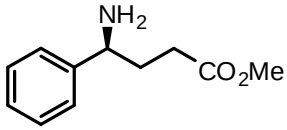
$CDCl_3$): δ= 7.30 (dd, J = 5.0, 1.2 Hz, 1H), 7.04-7.03 (m, 1H), 7.01-6.98 (m, 1H), 4.9 (dd, J = 7.0, 7.0 Hz, 1H), 3.67 (s, 3H), 2.44 (dd, J = 7.4, 1.2 Hz, 2H), 2.23-2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 141.7, 126.8, 125.8, 125.6, 60.3, 51.6, 31.6, 30.4; IR (thin film): 2952, 2099, 1736, 1437, 1367, 1328, 1240, 1173, 854, 835, 707; HRMS (EI) calc'd for $C_9H_{11}NO_2S$ = 197.0510, found = 197.0511. ($M-N_2$)



Reagents employed: **1.58n** (0.126 g, 0.599 mmol); sodium azide (0.047 g, 0.723 mmol); ammonium chloride (0.045 g, 0.841 mmol); 2-methoxyethanol:water; Yielded **1.71l** as a clear oil, 63% (0.079 g, 0.378 mmol). R_f = 0.54, 30% EtOAc in hexanes; ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, J = 1 Hz, 1H), 6.36 (dd, J = 3.1, 1.8 Hz, 1H), 6.33 (d, J = 3.1 Hz, 1H), 4.53 (dd, 7.2, 7.2 Hz, 1H), 3.68 (s, 3H), 2.43 (ddd, J = 7.6, 7.6, 0.8 Hz, 2H), 2.25-3.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.9, 151.5, 143.0, 110.2, 108.1, 57.9, 51.7, 30.2, 27.8; IR (thin film): 2954, 2102, 1736, 1438, 1338, 1239, 1210, 1173, 1013, 745; HRMS (EI) calc'd for $C_9H_{11}NO_3$ = 181.0739, found = 181.0739. ($M-N_2$)

Procedure for the azide reduction to GABA esters

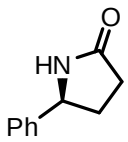
To a solution of azide (1 equiv) in MeOH was added 10% palladium on activated carbon. The solution was stirred under a balloon of hydrogen for two hours. The mixture was then passed through celite and the solvent was removed under reduced pressure to give GABA ester **1.73**.



Reagents employed: **1.71a** (0.066 g, 0.301 mmol); 10% palladium on activated carbon (0.003 g); Yielded **1.73** as a yellow oil, 93% (0.054 g, 0.279 mmol). The data for this compound matched that previously reported.[84]

Lactamization Procedure

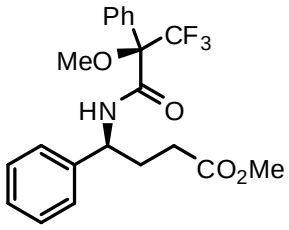
To a solution of optically enriched methyl 4-amino-4-phenylbutanoate **1.71a** (0.259 mmol) in MeOH, was added 1.7 M NaOH (0.389 mmol) dropwise. The solution was stirred for 2 hours, and then diluted with EtOAc and water to separate layers. The aqueous layer was then acidified with 5% HCl to reach pH 2, and then extracted three times with EtOAc. The combined organic layers were washed with brine, dried of $MgSO_4$, filtered and concentrated.



Reagents employed: **1.73** (0.050 g, 0.259 mmol); 1.7 M NaOH (0.5 mL, 0.389 mmol); Yielded **1.74** as a yellow oil, 96% (0.040 g, 0.248 mmol). The data for this compound matched the previously reported.[62]

Mosher's Amide Procedure

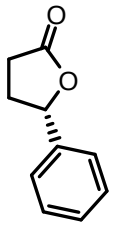
To a solution of methyl 4-amino-4-phenylbutanoate **1.73** (0.068 mmol) in THF (1 mL), was added Mosher's Acid (0.071 mmol), DCC (0.081 mmol) and DMAP (0.0041 mmol). The solution was stirred at room temperature overnight. The solution was filtered and the solvent was removed under reduced pressure, to which the mixture was purified by flash chromatography (EtOAc:Hexanes, 20:80) to yield Mosher's Amide.



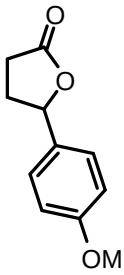
Reagents employed: **1.73** (0.013 g, 0.068 mmol); Mosher's Acid (0.017 g, 0.071 mmol); DCC (0.017 g, 0.081 mmol); DMAP (0.001 g, 0.0041 mmol); Yield 61% (0.017 g, 0.042 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.56-7.54 (m, 2H), 7.42-7.41 (m, 3H), 7.37-7.34 (m, 2H), 7.31-7.29 (m, 3H), 7.19 (d, J = 8.2 Hz, 1H), 5.01 (br dd J = 15.2, 7.8 Hz, 1H), 3.67 (s, 0.19H), 3.59 (s, 3H), 3.40 (s, 0.22H), 3.37 (s, 3H), 2.30-2.26 (m, 3H), 2.17-2.11 (m, 2H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -68.8 (s, 3F), -68.9 (s, 0.16F). The enantiomeric excess was determined to be 90% by Mosher's amide (^{1}H, ^{19}F-NMR).

Section 1.9.3 The Synthesis of Butanolides from Cyclopropane Hemimalonates

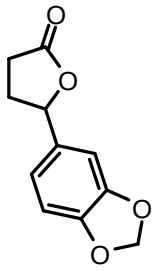
General Experimental Procedure: Cyclopropane hemimalonates **1.58**, LiCl, and $Me_3N{\cdot}HCl$ were added to a microwave vial and dissolved in DMF. The vial was sealed and heated for 40 minutes at 150 °C. After the required reaction time the reaction was quenched with H_2O and extracted with ether. The organic layer was dried and the solvent was removed. The residue was subjected to flash chromatography on silica gel and the product **1.78** was isolated.



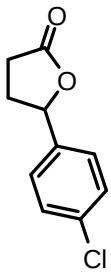
Reagents employed: **1.58d** (0.075 g, 0.341 mmol); LiCl (0.029 g, 0.684 mmol); $Me_3N{\cdot}HCl$ (0.046 g, 0.481 mmol); DMF (4 mL); Yielded **1.78a** as a clear oil, 82% (0.045 g, 0.279 mmol). Spectral properties are identical to those previously reported.[63] 80% ee calculated from Mosher's ester. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -71.31 (s, 90), -71.59 (s, 10).



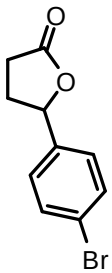
Reagents employed: **1.58f** (0.077 g, 0.308 mmol); LiCl (0.026 g, 0.613 mmol); $Me_3N{\cdot}HCl$ (0.041 g, 0.429 mmol); DMF (4 mL); Yielded **1.78b** as a yellow oil, 91% (0.054 g, 0.281 mmol). R_f = 0.25, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.45 (dd, J = 8.6, 6.2 Hz, 1H), 3.80 (s, 3H), 2.68-2.56 (m, 3H), 2.26-2.14 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.9, 159.7, 131.1, 126.9, 114.0, 81.3, 55.3, 30.8, 29.2. IR (thin film, cm^{-1}): 3129, 1771, 1517, 1400, 1250, 1175, 1141, 1112, 1032. HRMS calc'd for $C_{11}H_{12}O_3$ = 192.0786, found = 192.0783.



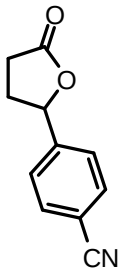
Reagents employed: **1.58g** (0.078 g, 0.295 mmol); LiCl (0.025 g, 0.590 mmol); $Me_3N{\cdot}HCl$ (0.040 g, 0.419 mmol); DMF (4 mL); Yielded **1.78c** as a brown oil, 90% (0.055 g, 0.267 mmol). R_f = 0.22, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.81-6.78 (m, 3H), 5.96 (s, 2H), 5.40 (dd, J = 8.6, 6.2 Hz, 1H), 2.66-2.54 (m, 3H), 2.22-2.09 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7, 148.0, 147.7, 133.0, 119.1, 108.2, 105.9, 101.2, 81.2, 30.9, 29.0. IR (thin film, cm^{-1}): 3135, 2992, 1771, 1505, 1446, 1400, 1245, 1141, 1037. HRMS calc'd for $C_{11}H_{10}O_4$ = 206.0579, found = 206.0575.



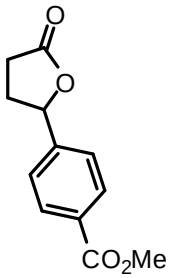
Reagents employed: **1.58h** (0.075 g, 0.294 mmol); LiCl (0.025 g, 0.590 mmol); $Me_3N{\cdot}HCl$ (0.039 g, 0.408 mmol); DMF (4 mL); Yielded **1.78d** as a yellow oil, 81% (0.047 g, 0.239 mmol). R_f = 0.16, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.48 (dd, J = 8.6, 6.2 Hz, 1H), 2.70-2.61 (m, 3H), 2.20-2.07 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.5, 137.8, 134.2, 128.9, 126.6, 80.4, 30.9, 28.8. IR (thin film, cm^{-1}): 3135, 2924, 1773, 1402, 1173, 1138, 1091, 1035. HRMS calc'd for $C_{10}H_9ClO_2$ = 196.0291, found = 196.0299.



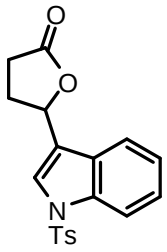
Reagents employed: **1.58i** (0.076 g, 0.254 mmol); LiCl (0.022 g, 0.519 mmol); $Me_3N{\cdot}HCl$ (0.035 g, 0.366 mmol); DMF (4 mL); Yielded **1.78e** as a yellow oil, 74% (0.045 g, 0.187 mmol). R_f = 0.29, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 5.46 (dd, J = 8.2, 6.2 Hz, 1H), 2.71-2.61 (m, 3H), 2.21-2.07 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.5, 138.4, 131.9, 126.9, 122.3, 80.4, 30.9, 28.8. IR (thin film, cm^{-1}): 3136, 2923, 1781, 1402, 1173, 1140, 1035, 1010. HRMS calc'd for $C_{10}H_9BrO_2$ = 239.9786, found = 239.9794.



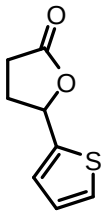
Reagents employed: **1.58k** (0.075 g, 0.306 mmol); LiCl (0.026 g, 0.613 mmol); $Me_3N{\cdot}HCl$ (0.041 g, 0.429 mmol); DMF (4 mL); Yielded **1.78f** as a clear oil, 52% (0.030 g, 0.160 mmol). R_f = 0.11, 30% EtOAc/hexanes. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 5.55-5.51 (m, 1H), 2.76-2.60 (m, 3H), 2.16-2.07 (m, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 176.0, 144.7, 132.6, 125.8, 118.3, 112.3, 79.8, 30.8, 28.6. IR (thin film, cm^{-1}): 2954, 2924, 1772, 1653, 1457, 1174, 1019, 525. HRMS calc'd for $C_{11}H_9NO_2$ = 187.0633, found = 187.0639.



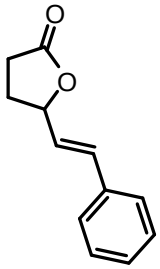
Reagents employed: **1.58o** (0.075 g, 0.270 mmol); LiCl (0.023 g, 0.543 mmol); $Me_3N{\cdot}HCl$ (0.036 g, 0.377 mmol); DMF (4 mL); Yielded **1.78g** as a clear oil, 39% (0.023 g, 0.104 mmol). R_f = 0.16, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 5.59-5.53 (m, 1H), 3.92 (s, 3H), 2.76-2.63 (m, 3H), 2.21-2.12 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.5, 166.5, 144.4, 130.2, 130.1, 125.0, 80.4, 52.2, 30.9, 28.7. IR (thin film, cm^{-1}): 2998, 1785, 1721, 1613, 1436, 1283, 1178, 1142, 1113, 1019, 940, 768, 706. HRMS calc'd for $C_{12}H_{12}O_4$ = 220.0736, found = 220.0720.



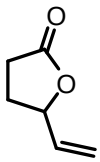
Reagents employed: **1.58m** (0.082 g, 0.198 mmol); LiCl (0.017 g, 0.401 mmol); $Me_3N{\cdot}HCl$ (0.027 g, 0.283 mmol); DMF (4 mL); Yielded **1.78h** as a yellow oil, 85% (0.060 g, 0.169 mmol). R_f = 0.24, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ =7.99 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.59 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.35 (dt, J = 8.6, 1.2 Hz, 1H), 7.28-7.20 (m, 3H), 5.75-5.69 (m, 1H), 2.72-2.64 (m, 3H), 2.47-2.35 (m, 1H), 2.33 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.4, 145.3, 135.3, 134.9, 130.0, 128.0, 126.8, 125.3, 123.4, 123.0, 120.5, 119.8, 113.7, 75.4, 28.5, 28.2, 21.5. IR (thin film, cm^{-1}): 3115, 1775, 1447, 1400, 1371, 1174, 1124, 1100, 1036. HRMS calc'd for $C_{19}H_{17}NO_4S$ = 355.0878, found = 355.0879.



Reagents employed: **1.58j** (0.068 g, 0.301 mmol); LiCl (0.025 g, 0.590 mmol); $Me_3N{\cdot}HCl$ (0.040 g, 0.418 mmol); DMF (4 mL); Yielded **1.78i** as an orange oil, 74% (0.037 g, 0.220 mmol). R_f = 0.24, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (dd, J = 5.1, 1.6 Hz, 1H), 7.09 (d, J = 3.5 Hz, 1H), 7.00 (dd, J = 4.7, 3.5 Hz, 1H), 5.76-5.69 (m, 1H), 2.74-2.60 (m, 3H), 2.45-2.31 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.1, 141.7, 126.9, 126.2, 125.9, 77.3, 30.7, 28.9. IR (thin film, cm^{-1}): 3108, 2923, 2851, 1777, 1401, 1172, 1135, 1015, 921. HRMS calc'd for $C_8H_8O_2S$ = 168.0245, found = 168.0243.



Reagents employed: **1.58m** (0.098 g, 0.398 mmol); LiCl (0.034 g, 0.802 mmol); $Me_3N{\cdot}HCl$ (0.053 g, 0.555 mmol); DMF (4 mL); Yielded **1.78j** as a clear oil, 80% (0.060 g, 0.319 mmol). R_f = 0.28, 30% EtOAc/hexanes. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.39 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.29 (d, J = 7.0 Hz, 1H), 6.68 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 15.8, 7.0 Hz, 1H), 5.13-5.09 (m, 1H), 2.62-2.57 (m, 2H), 2.51-2.44 (m, 1H), 2.13-2.06 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.8, 135.6, 132.8, 128.6, 128.3, 126.7, 126.4, 80.6, 28.8, 28.5. IR (thin film, cm^{-1}): 2924, 1768, 1073, 1032, 974, 758. HRMS calc'd for $C_{12}H_{12}O_2$ = 188.0837, found = 188.0837.

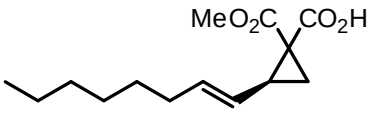


Reagents employed: **1.58b** (0.086 g, 0.505 mmol); LiCl (0.043 g, 1.01 mmol); $Me_3N{\cdot}HCl$ (0.068 g, 0.712 mmol); DMF (4 mL); Yielded **1.78k** as a clear oil, 60% (0.034 g, 0.303 mmol). R_f = 0.33, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddd, J = 16.8, 10.5 Hz, 5.9 Hz, 1H), 5.36 (dt, J = 17.2, 1.2 Hz, 1H), 5.25 (dt, J = 10.5, 1.2 Hz, 1H), 4.96-4.90 (m, 1H), 2.56-2.50 (m, 2H), 2.41 (dt, J = 12.5, 6.6 Hz, 1 H), 2.04-1.94 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.9, 135.5, 117.4, 80.4, 28.2, 28.2. IR (thin film, cm^{-1}): 2957, 2921, 2851, 1772, 1734, 1558, 1457. HRMS calc'd for $C_6H_8O_2$ = 112.0524, found = 112.0520

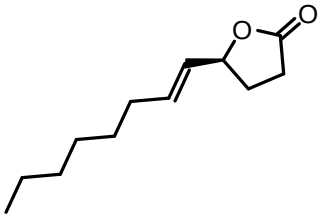
Synthesis of Cyclopropane Hemimalonate for Dodecanolide:

Vinyl cyclopropane **(-)-1.81** (0.250 g, 1.36 mmol) and 1-octene (0.26 mL, 1.63 mmol) were dissolved in DCM and the reaction vessel was purged with Argon. Grubbs II (0.056 g, 0.068 mmol) was added as one portion. The purple solution was heated to reflux for 3 hours. Florisil® was added and the mixture was stirred for another 20 minutes. The reaction mixture was filtered, concentrated and flushed through a plug of silica.

The crude octenyl cyclopropane was taken up in MeOH (5 mL) and treated with 1.7 M NaOH (1.6 mL, 2.72 mmol). The reaction was stirred at room temperature for 2.5 hours, and then the reaction was quenched with H_2O. The organic was extracted with EtOAc, and the aqueous layer was acidified with 5% HCl. The aqueous was extracted 3x with EtOAc to obtain the product. The organic was dried with $MgSO_4$, filtered and concentrated to obtain **1.58l** (0.300 g, 1.18 mmol) in an 87% yield over the two steps.



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82 (dt, J = 15.2, 7.0 Hz, 1H), 5.25 (dd, 15.2, 8.6 Hz, 1H), 3.81 (s, 3H), 2.73 (q, 8.6 Hz, 1H), 2.20-1.90 (m, 4H), 1.36-1.21 (m, 9H), 0.87 (t, 7.0 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.2, 170.5, 138.3, 123.4, 53.0, 40.3, 33.2, 32.6, 31.6, 29.7, 28.9, 28.7, 23.8, 22.6. IR (thin film, cm^{-1}): 2925, 2855, 1772, 1734, 1456, 1436, 1338, 1262, 1162, 967. HRMS calc'd for $C_{14}H_{22}O_4$ = 254.1518, found = 254.1524. (Isolated in 7:1 cis:trans)

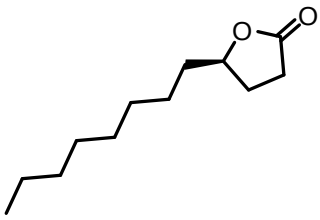


Reagents employed: **1.58l** (0.130 g, 0.511 mmol); LiCl (0.043 g, 1.02 mmol); $Me_3N{\cdot}HCl$ (0.068 g, 0.714 mmol); DMF (4 mL); Yielded **1.78l** as a clear oil, 78% (0.078 g, 0.397 mmol). R_f = 0.48, 30% EtOAc/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.80 (dt, J = 15.3, 7.0 Hz, 1H), 5.48 (dd, J = 15.3, 7.0 Hz, 1H), 4.88 (dd, J = 7.6, 7.0 Hz, 1H), 2.55-2.50 (m, 2H), 2.39-2.31 (m, 1H), 2.08-2.03 (m, 2H), 2.01-1.92 (m, 1H), 1.41-1.34 (m, 2H), 1.32-1.22 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0, 135.8, 127.3, 110.0, 81.1, 32.1, 31.6, 28.8, 28.8, 28.7, 22.6, 14.1. IR (thin film, cm^{-1}): 2926, 2855, 1773, 1734, 1457, 1176, 969. HRMS calc'd for $C_{12}H_{20}O_2$ = 196.1463, found = 196.1460. (Isolated in 7:1 cis:trans)

Reduction of Olefin:

Lactone **12** (0.175 g, 0.892 mmol) was dissolved in THF:H_2O (8:8 mL). Tosylhydrazine (1.66 g, 8.91 mmol) and sodium acetate (0.951 g, 11.6 mmol) were added and the reaction mixture was heated to reflux for 24 hours. Water was added to quench the reaction and the aqueous was extracted with ether 4x. The organic was dried with $MgSO_4$, filtered and subjected to column chromatography. The product **1.82** (0.173 g, 0.867 mmol) was isolated in a 98 % yield.



R_f = 0.49, 30% EtOAc/hexanes. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 4.51-4.44 (m, 1H), 2.56-2.48 (m, 2H), 2.35-2.26 (m, 1H), 1.77-1.70 (m, 1H), 1.62-1.55 (m, 1H), 1.49-1.41 (m, 1H), 1.40-1.22 (m, 12H), 0.88 (t, 7.0 Hz, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 177.3, 81.0, 35.6, 31.8, 29.4, 29.3, 29.2, 28.9, 28.0, 25.2, 22.6, 14.1. IR (thin film, cm^{-1}): 2926, 2855, 1776, 1458, 1352, 1179, 1017, 914. HRMS calc'd for $C_{12}H_{22}O_2$ = 199.1698, found = 199.1703 (M + H). 94% ee calculated from Mosher's ester. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -71.29 (s, 97), -71.36 (s, 3).

Section 1.10 References

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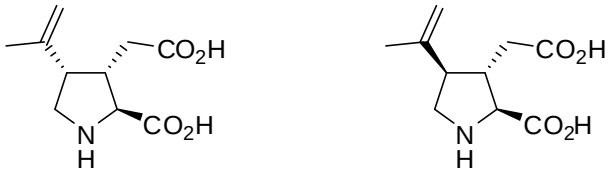
Chapter 2. Kainic Acid

Section 2.1 Isolation and Biological Activity

(-)-(α)-Kainic acid **2.1** was first isolated in 1953 by the group of Takemoto[1] from the marine alga *Diginea simplex*, along with its C-4 epimer (+)-allokainic acid **2.2**. It was named after 'Kaininso', the Japanese name of the mother alga[2]. Over two decades later, in 1975, it was isolated again from related alga *Centrocerus clavulatum*[3] and as well the Corsican moss *Alsidium helminthocorton*[4] in the early 1980s. Shortly after the isolation of (-)-(α)-Kainic acid, Morimoto[5] deduced the relative stereochemistry around the pyrrolidine core; his stereochemical assignment was confirmed a few years later by X-ray analysis[2]. The first total synthesis by Oppolzer[6] (*vide infra*) defined the absolute stereochemistry of the pyrrolidine ring as (*S*, *S*, *S*) in relation to the C-2, C-3, and C-4 carbons.



2.1 (-)-(α)-Kainic acid **2.2** (+)-allokainic acid

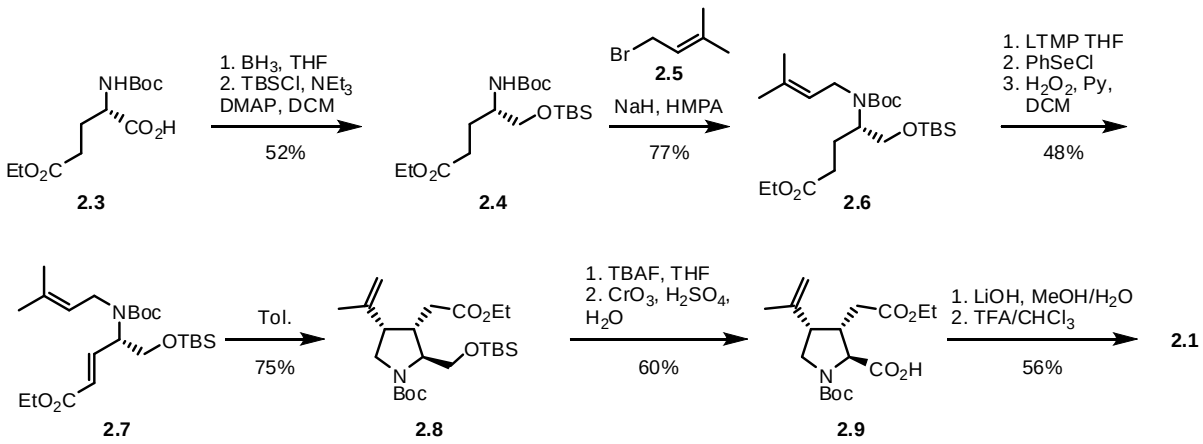
Figure 2.1 Structures of Kainic Acid and Allokainic Acid

Over the last 20 years there have been over 30 total syntheses of Kainic acid reported due to its unique biological activity. The *Diginea* simplex alga has been used for over a 1000 years in Japan for its anthelmintic (anti-intestinal worm) properties. It wasn't until much later that it was discovered that the active ingredient, Kainic acid, was much stronger than the santonin, the best anthihelmintic drug at the time, with virtually no side effects[2]. Kainic acid has also been shown to mimic the biological activity of L-Glutamic acid. They both activate ionotropic glutamic receptors which upon overexposure can lead to cell death. Not long after the similarity between kainic acid and glutamic acid was discovered, kainic acid was tested on animals to determine its potential neurological effects. It was found to induce motor hyperactivity as well as cause seizures in the

animals. The neurons that had come in contact with kainic acid had succumbed to cell death; this feature mimics the effects of a variety of different neurological disorders present in humans, such as strokes, epilepsy and Huntington's disease. The ever increasing interest in the biological activity of Kainic acid has led to it being a target of great interest to the synthetic organic community.

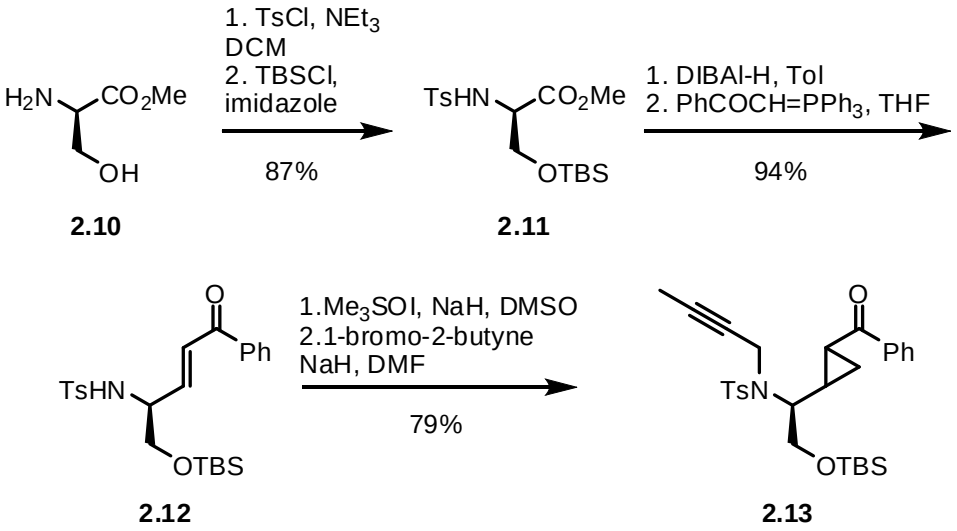
Section 2.2 Total Syntheses of Kainic acid

Due to the vast number of total syntheses of kainic acid, this section will describe the very first total synthesis, followed by a number of recent total syntheses. The first total synthesis was completed by Oppolzer and Thirring in 1982, starting from a derivative of (S)-glutamic acid and highlighted by an intramolecular ene reaction. To establish the core pyrrolidine ring (Scheme 2.1), Boc-protected (S)-glutamic acid **2.3**, was reduced with borane and subsequently protected with a TBS group to yield **2.4** in a 52% yield over the two steps. **2.4** was then alkylated with **2.5**, in a 77% yield. To set up the required 1,6-diene **2.7** for their ene-type reaction, they needed to form an α,β–unsaturated ester. They completed this transformation by first selenation of an enolate, followed by oxidation and selenoxide elimination to form desired **2.7** in a 48% yield over the 3 steps. Diene **2.7** was then smoothly converted to pyrrolidine **2.8** via an intramolecular ene reaction in a 70% yield, while installing the required stereochemistry for Kainic acid. Simple TBS removal, followed by oxidation up to carboxylic acid **2.9**, after saponification and a Boc-deprotection furnished kainic acid in an overall 5% yield. Although Oppolzer's total synthesis is quite a few more steps than what is commonly seen today, this synthesis set the bar for the following syntheses that will be described herein.



Scheme 2.1 Oppolzer's Total Synthesis of (-)-(α)-kainic Acid

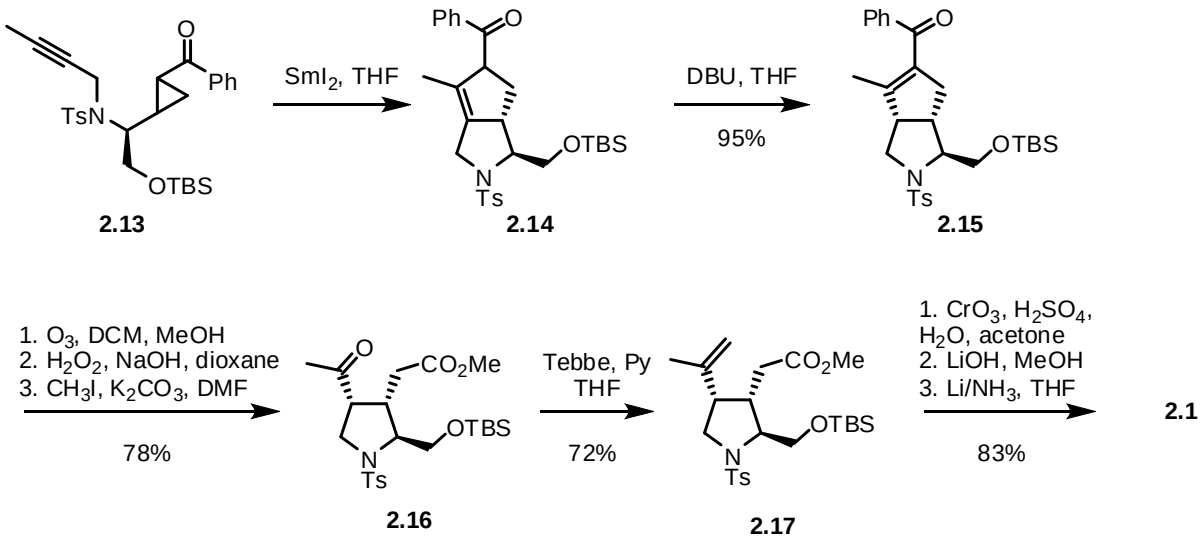
In 2012, Li's group developed a novel [3+2] samarium iodide mediated radical cyclization of a cyclopropyl ketone and an alkyne.[7] Starting from D-Serine methyl ester **2.10**, the amine functionality was tosyl protected followed by TBS protection of the alcohol to form **2.11** in 87% over the two steps (Scheme 2.3). The ester was then reduced to the aldehyde which was then subjected to Wittig olefination to form α,β–unsaturated ketone **2.12**. The ketone was taken through a Corey-Chaykovsky cyclopropanation and the amine was alkylated with 1-bromo-2-butyne, to give **2.13** as a mixture of diastereomers in 79% yield over 2 steps.



2.10 **2.11** **2.12** **2.13**

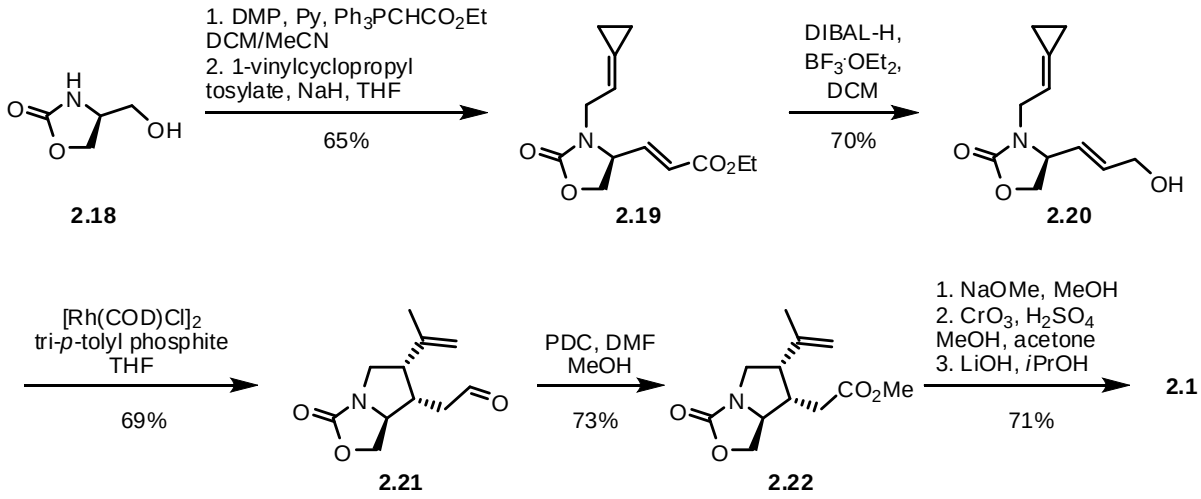
Scheme 2.2 Li's Formation of [3+2] Cyclization Precursor

With the cyclization precursor **2.13** in hand, they investigated their key reaction. After optimization, they were able to isolate their desired cyclized ketone **2.14** in 81% yield as a mixture of inconsequential diastereomers (Scheme 2.3). The olefin was isomerized into conjugation **2.15** using DBU, providing the necessary stereochemistry at the C-3 and C-4 positions. The olefin underwent ozonolysis followed by an oxidative work up to reveal a carboxylic acid, which was then protected as the methyl ester to give **2.16** in a 78% yield. The remaining ketone was converted to the isopropenyl group **2.17** using a Tebbe olefination in a 72% yield. A one-pot TBS deprotection, Jones oxidation revealed the acid at the C-2 position, and then deprotection of both the methyl ester at the C-3 position and the tosylated amine provided kainic acid in 83% yield over the 3 synthetic operations. The synthesis was completed in 15 linear steps in an overall 24% yield. While this synthesis is quite a bit longer than Oppolzer's, the isolated yield of Kainic acid is significantly higher over the entire process.



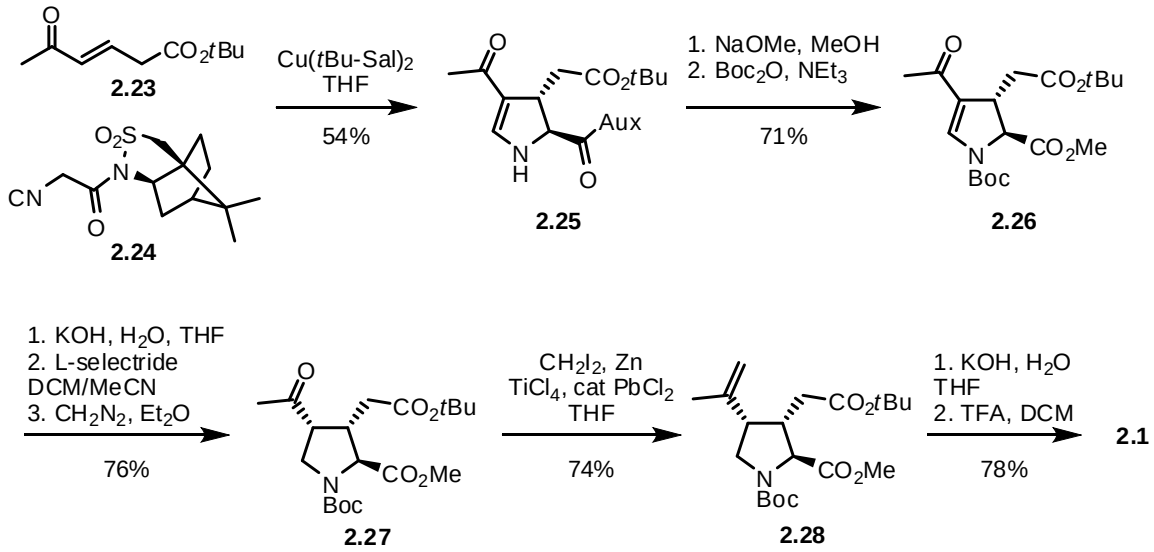
Scheme 2.3 Li's Completed Total Synthesis

Also in 2012, Evans developed a rhodium catalyzed ene-cycloisomerization using alkylidene cyclopropanes (Scheme 2.4).[8] The synthesis starts with alcohol **2.18**, which underwent a Dess-Martin oxidation followed by an in situ Witting olefination to form the desired α,β-unsaturated ester. The carbamyl nitrogen was then alkylated with 1-vinylcyclopropyl tosylate to install the cyclopropane moiety **2.19** in an 84% yield. The ester was reduced with DIBAL-H to provide their ene-cycloisomerization precursor **2.20**. The rhodium catalyzed alkylidene cyclopropane ene-rearrangement formed the desired pyrrolidine **2.21** in a 69% yield. **2.21** was then oxidized to the corresponding methyl ester **2.22** using a modified Corey procedure. The cabamyl ring was solvolitically cleaved to give a primary alcohol that was oxidized to the acid using Jones reagent, and finally kainic acid was revealed by a global deprotection using base. The sequence took 8 steps and provided the natural product in a 17 % overall yield.



Scheme 2.4 Evans' Total Synthesis of Kainic Acid

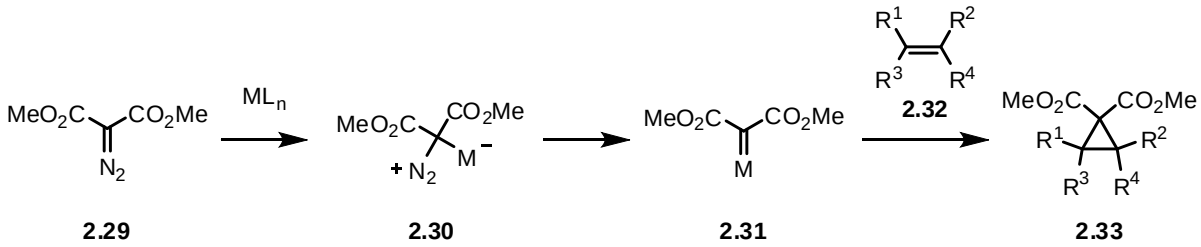
In 2014, Shinada and co-workers developed a copper catalyzed Michael addition-cyclization of a chiral isocyanide **2.24** and an α,β–unsaturated ketone **2.23** to access the pyrrolidine core of Kainic acid (Scheme 2.5).[9] Using chiral isocyanide **2.24**, they attempted to form the pyrrolidine ring under basic conditions; this led primarily to auxillary cleavage. When they tried the reaction without base, they were able to isolate the desired pyrroline **2.25** in a 54% yield. With pyrroline **2.25** in hand, they next cleaved the sultam auxillary and protected the nitrogen with a Boc group to give **2.26**. The ester was then saponified and conjugate reduction was completed with L-selectride. Direct conjugate reduction of the methyl ester substrate **2.26** led to the wrong epimer at C-4. The acid was re-esterified and the ketone was homologated using the Nozaki reagent to give **2.28**. The methyl ester was once again saponified and the substrate was treated with TFA to cleave both the *t*-butyl ester as well as the Boc protecting group. This series of reactions led to Kainic acid in 9 linear steps in an overall yield of 17 %.



Scheme 2.5 Shinada`s Total Synthesis of Kainic Acid

Section 2.3 Diazomalonate Cyclopropanations and Reactivity of Related Diazo Compounds

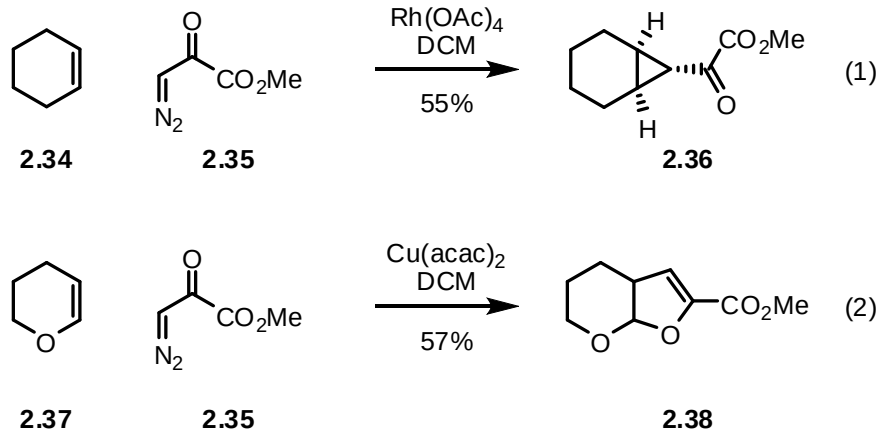
Since the seminal review on the cyclopropanation of alkenes and aromatics with ethyl diazoacetate,[10] this field of chemistry has blossomed into a wide variety of different areas. Specifically, advances in catalyst design can arrive at chemo-, diastereo-, or enantioselective products as desired. Diazomalonates are an interesting class of compounds as they can provide not only a more reaction diazo species, but also another functional handle for further chemical manipulations. The mechanism of cyclopropanation of diazo compounds is well understood.[11] Starting from diazo compound **2.29**, a diazonium complex forms with the metal to provide **2.30** (Scheme 2.6). This complex can then extrude N_2 gas to produce metal carbenoid **2.31**. Due to the highly electrophilic nature of diazomalonates, the olefin **2.32** will attack the metal carbenoid forming a negative charge on the carbenoid carbon. This species can then attack back onto the newly formed carbocation to provide cyclopropane **2.33**.



Scheme 2.6 Diazomalonate Cyclopropanation Mechanism

Section 2.3.1 Reactivity of Diazo Species with Olefins

The stereoselectivity of the products obtained from the reaction of diazo species and olefins can be predicted by the electronics of the olefin. Electron neutral olefins **2.34** primarily give cyclopropanated products **2.36** (Scheme 2.7, eq. 1).[12] However, when the olefin is electron-rich **2.37**, the product obtained appears to be the result of a [3+2] cycloaddition **2.38** (Scheme 2.7, eq. 2).[13] It is believed that the olefin is first cyclopropanated, but due to the electronics of the product, the ring can be rearranged through the development of an oxocarbenium ion.

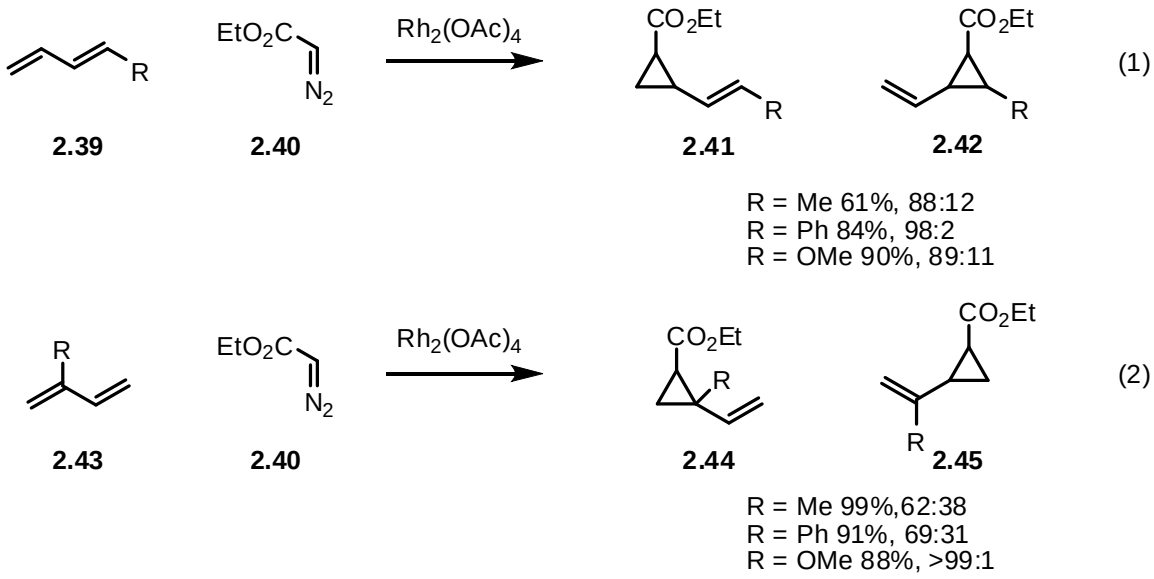


Scheme 2.7 Reactivity of Diazo Species with Olefins

Section 2.3.2 Reactivity of Diazo Species with Dienes

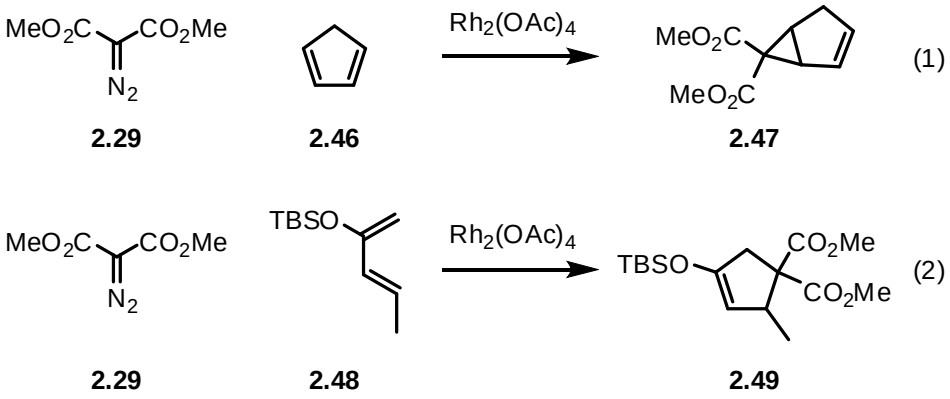
Dienes can be useful cyclopropanation partners as the products lead to vinyl substituted cyclopropanes which can be manipulated in subsequent synthetic steps.[14] The

main obstacle of these reactions are the competitive reactivity of the diazo species and each olefin in the system. With ethyldiazoacetate **2.40** and terminally substituted dienes **2.39**, the regiochemical preference is the less sterically hindered double bond **2.41** (Scheme 2.8, eq. 1).[15] However, when the substitution is internal, at the 2-position **2.43**, the preference is now for the substituted double bond **2.44**, with greater selectivity for electron-rich olefins (Scheme 2.8, eq. 2).



Scheme 2.8 Effects of Diene Substitution with Ethyldiazoacetate

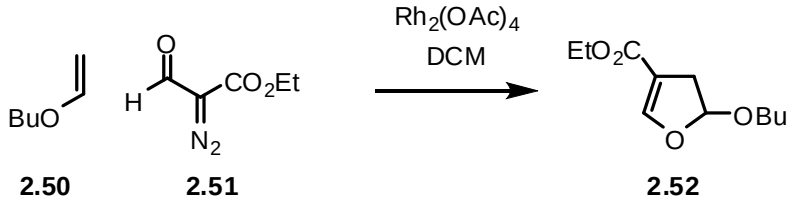
The effects of diene substitutions are different when diazomalonates **2.29** are employed as the cyclopropanation precursor (Scheme 2.9). A reaction with cyclopentadiene **2.46** for example, the expected cyclopropanation is observed **2.45** due to the unpolarised nature of the diene.[16] However, when an electron-rich diene **2.48** is used, cyclopropanation is not observed and an annulated product is seen as the sole product **2.49**. This is believed to be due to the stability of the zwitterionic intermediates developed in the reaction.[17]



Scheme 2.9 Diene Reactivity with Diazomalonate

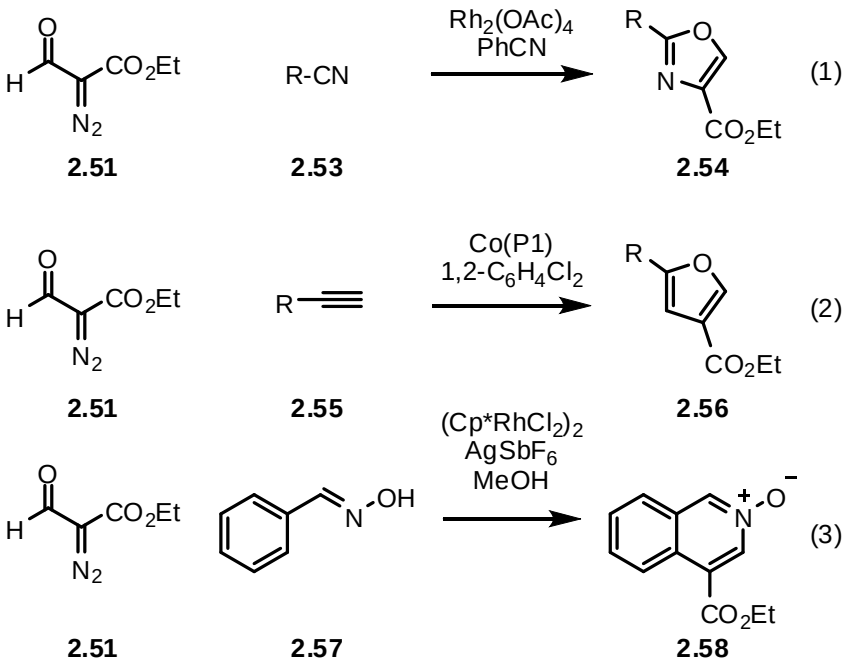
Section 2.3.3 Reactivity of Aldehyde-ester Diazo Compounds

In 1988, Wenkert developed the reactivity of a new type of diazo species, one that had a geminally substituted ester and aldehyde **2.50**. When it was reacted with butylvinylether **2.48**, it did not undergo a cyclopropanation event, but a cyclization to form dihydrofurans **2.50** (Scheme 2.10).[18]



Scheme 2.10 Wenkert's Cycloaddition of **2.51** with Butylvinyl Ether **2.50**

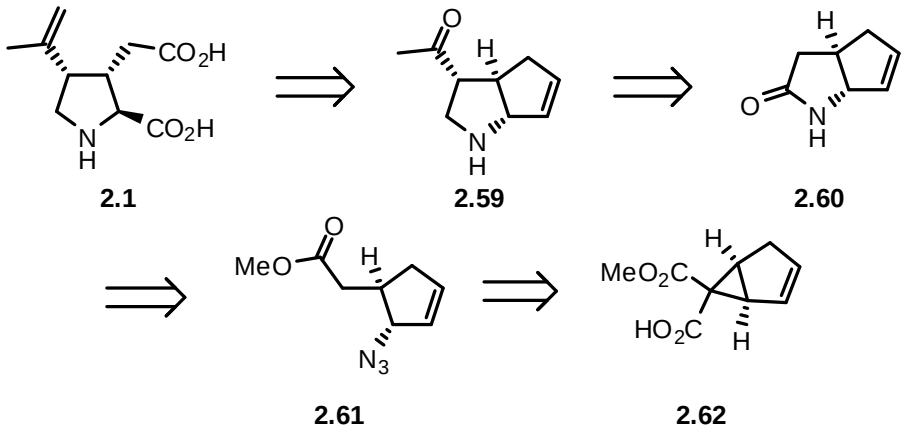
Since the seminal work of Wenkert, diazospecies **2.51** has been utilized in the synthesis of several different heterocycles. It has been reacted with nitriles **2.53**,[19] alkynes **2.55**[20] and aryl oximes **2.57**[21], to form 1,3-oxazoles **2.54**, furans **2.56** and pyridine N-oxides **2.58**, respectively as products (Scheme 2.11).



Scheme 2.11 Recent Transformations of **2.51**

Section 2.4 Our Retrosynthetic Proposal

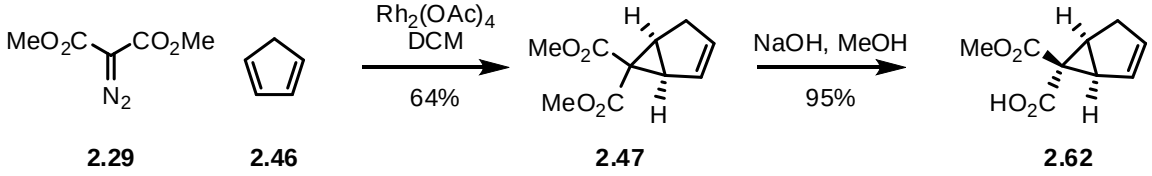
With the knowledge in hand that cyclopentadiene will undergo a smooth diazomalonate mediated cyclopropanation, and that asymmetric cyclopropanations are possible, we proposed a new cyclopropane route to Kainic acid. It was envisioned that the isopropenyl group could be installed through some previously developed chemistry, through a Tebbe olefination or use of the Nozaki reagent. The di-acid moiety we envisioned arising from ozonolysis or a dihydroxylation and cleavage of a cyclopentene unit **2.59** (Scheme 2.12). We thought that pyrrolidine of kainic acid could come from a lactamization on the appropriate amine and the ketone functionality could be introduced to **2.60**. The amine moiety could be installed via our previously established azide ring opening methodology,[22] which would arrive us back at a cyclopentene-derived cyclopropane hemimalonate **2.62**.



Scheme 2.12 Our Retrosynthetic Analysis

Section 2.5 Results and Discussion

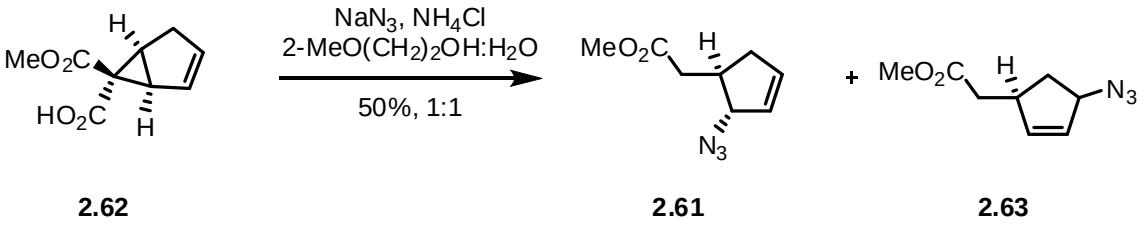
To begin our synthesis we focused on the synthesis of **2.62**, which could be achieved in a two-step process. Cyclopentene cyclopropane **2.45** was synthesized from diazomalonate **2.29**, cyclopentadiene **2.46**, and $Rh_2(OAc)_4$, (1 mol%) in a 64 % yield. Cyclopropanediesters **2.47** was then saponified under the standard conditions to furnish hemimalonate **2.62** in a 95 % yield.



Scheme 2.13 Formation of Cyclopentene Cyclopropane Hemimalonate **2.62**

Having our desired hemimalonate **2.62** in hand, we began the investigation into the azide ring opening of this substrate. Unfortunately, when we attempted the tandem ring opening dealkoxycarbonylation sequence, we obtained a mixture of products in a 50 % yield. This appeared to be an equal intractable mixture of our desired compound **2.61** and the S_N' addition product **2.63** (Scheme 2.14). This was not a too surprising result, as a further analysis of the literature showed that these cyclopropanes are prone to S_N'

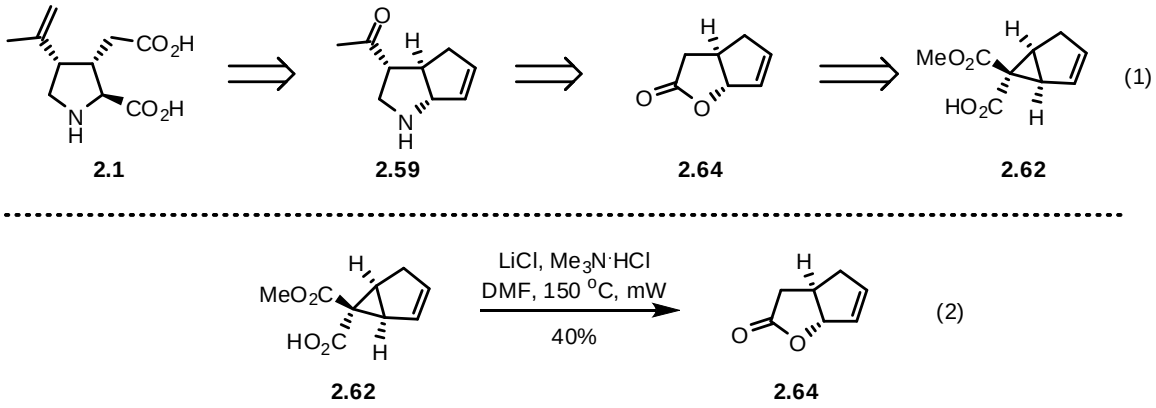
nucleophilic additions.[16,23] This reactivity was also evident in our initial work with the vinylcyclopropane hemimalonate.



2.62 **2.61** **2.63**

Scheme 2.14 Tandem Azide Ring Opening Dealkoxycarbonylation of **2.62**

We were not discouraged by this result; we thought that maybe by just changing our choice of methodology, perhaps we could still obtain kainic acid. What we next envisioned was that our cyclopropane rearrangement lactone formation[24] could result in formation of a key substrate **2.61** and based on the lactone methodology the regioselectivity in this case, should not be an issue (Scheme 2.15, eq.1). With lactone in hand, we could convert **2.64** to lactam **2.60**, and install the ketone afterwards. When we took **2.52** using our optimized conditions for lactone formation we did see lactone **2.64**, but only in a 40 % yield (Scheme 2.15, eq. 2). Unfortunately, this yield could not be improved upon and did not seem like a great start to our synthesis.

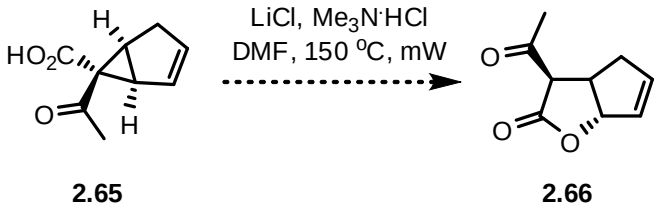


2.1 **2.59** **2.64** **2.62**

2.62 **2.64**

Scheme 2.15 Second Generation Retrosynthesis and Result

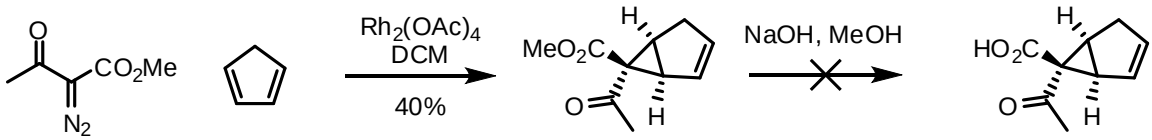
Due to the poor yield we obtained, we thought that if we had a ketone in the starting material **2.65**, instead of getting a decarboxylation to occur, perhaps the ketone would remain on our product **2.66** and we would not have to install it at a later time. This idea would require the use a keto-ester diazo compound as our starting material (Scheme 2.16.



2.65 **2.66**

Scheme 2.16 Potential Keto-Ester Lactonization Reaction

Starting from keto-ester diazo species **2.67**, a rhodium catalyzed cyclopropanation reaction occurred again with cyclopentadiene **2.46**, which proceeded to give **2.68** in a modest 40 % yield. We then tried to saponify this material anyways to give **2.65**, but we were unsuccessful under either our standard conditions or under more forcing conditions, which led to decomposition. The problem with saponification can be attributed to the diastereoselective formation of the cyclopropane. As per Charette's research on directing groups of acetoacetate diazo compounds,[25] the ketone has a preference for being *trans* to the substitution on the olefin. This would put the ester in the face of the cyclopentene unit, perhaps making it more difficult to saponify.

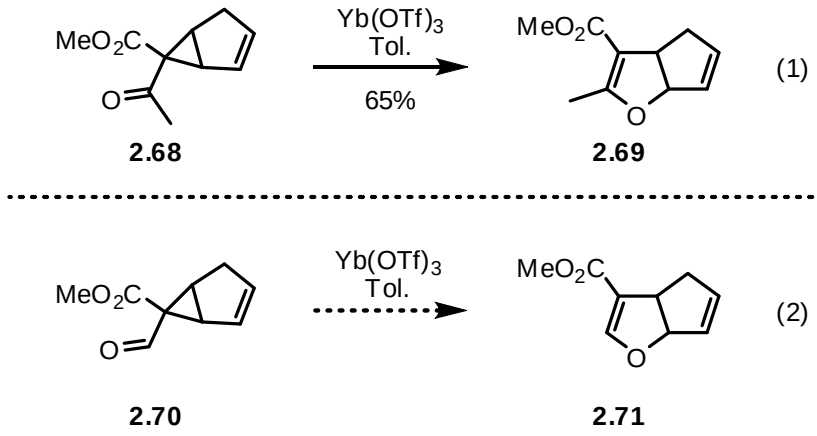


2.67 **2.46** **2.68** **2.65**

Scheme 2.17 Attempting to Pre-install the Ketone Functionality

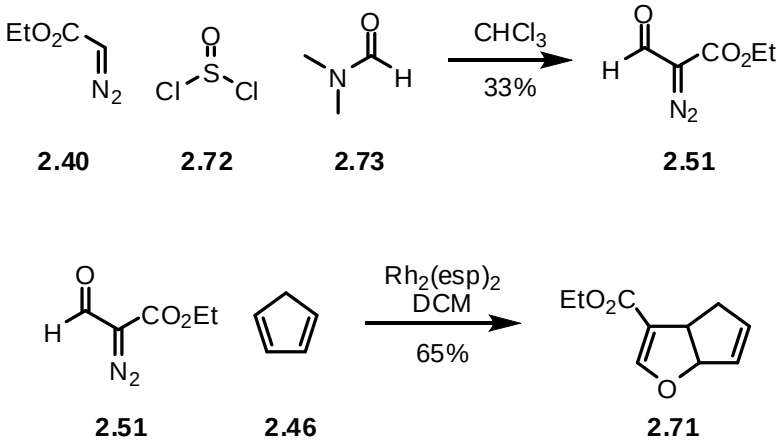
While this was a discouraging result, we thought that perhaps we could still utilize compound **2.68**. There is precedence for ketone-cyclopropane rearrangements to form a

variety of different dihydrofurans.[26] Taking compound **2.68** and with ytterbium triflate in toluene, we were able to synthesize the dihydrofuran **2.69** in a 65 % yield (Scheme 2.18, eq. 1). While there is no methyl group at the C-5 position of Kainic acid, we were encouraged by the success of this rearrangement. Perhaps if we had an aldehyde-ester diazo compound similar to that of **2.51,** as shown in the work of Wenkert (*vide supra*), we could cyclopropanate cyclopentadiene **2.46** and then rearrange the aldehyde **2.70** to form dihydrofuran **2.71** which maps onto Kainic acid perfectly (Scheme 2.18, eq. 2).



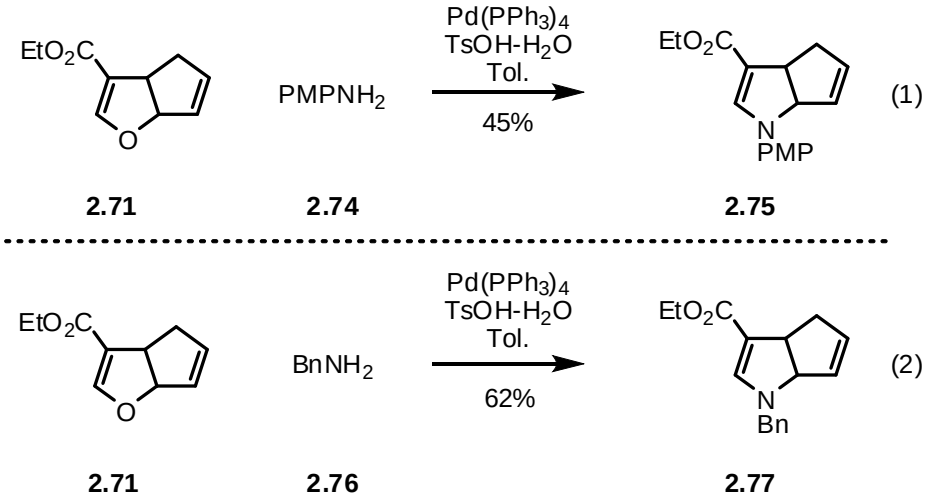
Scheme 2.18 Ketone Rearrangement and Possible Aldehyde Rearrangement

The synthesis of diazo compound **2.51** starts with taking thionyl chloride **2.72** and DMF **2.73** to form the Vilsmeier-Haack reagent (Scheme 2.19). The reagent is taken in chloroform and reacted with ethyldiazoacetate to form compound **2.51** in a 33% yield.[27] Next we intended to make cyclopropane **2.70**, but we observed a different result. **2.51** was then reacted with cyclopentadiene **2.46** in the presence of Rh_2esp_2 (1 mol %) and gratifyingly received what appeared to by our desired cyclized adduct **2.71** (*vide infra*) in 65 % yield. The same reaction with $Rh_2(OAc)_4$ as the catalyst, was much lower yielding for this reaction. This result appears to follow the pattern of reactivity with **2.51**, where cycloadditions are the main products of these reactions.



Scheme 2.19 Formation of **2.51** and Dihydrofuran **2.71**

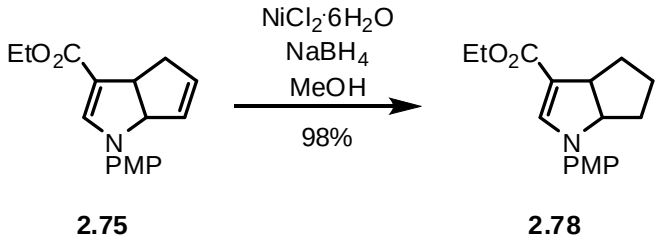
We then converted the dihydrofuran **2.69** to dihydropyrroles **2.71** using a palladium catalyzed procedure[28] with *p*-anisidine **2.70** in 45 % yield (Scheme 2.20, eq. 1). By switching the amine source from *p*-anisidine to benzyl amine **2.72**, we could increase the yield of dihydropyrrole formation to 62 % (Scheme 2.20, eq. 2).



Scheme 2.20 Formation of Dihydropyrroles **2.75** and **2.77** from Dihydrofuran **2.71**

Having the core framework desired for Kainic acid, we decided to try to manipulate the ester functionality to the isopropylidene. We attempted to saponify the

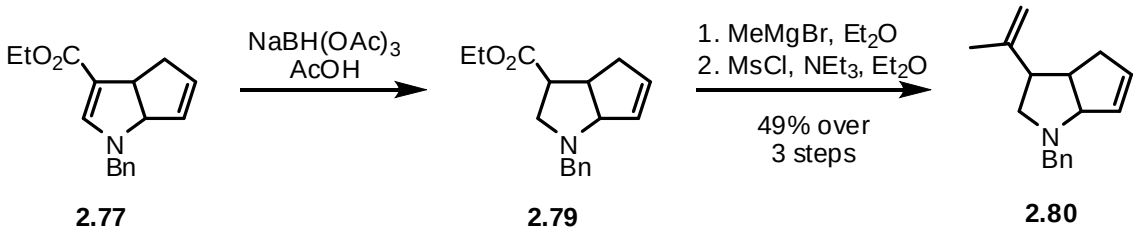
ester in order to convert it to the Weinreb amide, however this was unsuccessful. We attempted to make the Weinreb directly by using Weinreb's amine and phenyl magnesium chloride,[29] but this also did not work. Finally, we tried to add methyl Grignard directly to the ester and in this case decomposition of the starting material **2.75** was observed. When analyzing compound **2.75** again, we had maybe thought about this functional group incorrectly. While at first blush it looks like an α,β-unsaturated ester, it could also be thought of as a vinylogous carbamate. In order to access the ester, we needed to reduce the conjugated double bond, while not disturbing our cyclopentene double bond. To reduce the conjugated double bond we first tried nickel borohydride, but unfortunately it reduced the wrong olefin (Scheme 2.21).



2.75 **2.78**

Scheme 2.21 Nickel Borohydride Reduction of **2.75**

Reducing with sodium cyanoborohydride resulted in no reaction at all. Finally, taking **2.73** with sodium triacetoxyborohydride in acetic acid allowed for reduction of the conjugated olefin to compound **2.74** (Scheme 2.22). Due to purification issues of **2.79**, we took the product crude and treated it with excess methyl Grignard to dialkylate the ester. Once again, this substrate was difficult to purify by column chromatography. Taking the crude material of this compound, we added mesyl chloride and triethylamine and dehydrated the tertiary alcohol to the required isopropenyl group[30] **2.80** in an overall yield of 49% over the three steps.



2.77 **2.79** **2.80**

Scheme 2.22 Conversion of Carbamate **2.77** to Isopropenyl Tertiary Amine **2.80**

It was at this point that we were interested in the relative stereochemistry of the three chiral centres in compound **2.80**. Due to the splitting patterns that we could see in the proton NMR, we thought that getting 2-D NMR data on this compound (COSY, HSQC, and HMBC) we would be able to determine orientation of product **2.80**. Upon analysis of the 2-D NMR data, it was determined that our skeletal assignment was incorrect. The key correlations that we observed are highlighted in Figure 2.2. We could not find any COSY correlations between what we had originally assigned as either of the methylene protons (H_a and H_b) and our internal olefin proton (H_c). However, we could see correlations between both bridgehead protons and both internal olefin protons (H_f and H_c, H_d and H_e). That led us to structure **2.81** as being our product instead of **2.80**.

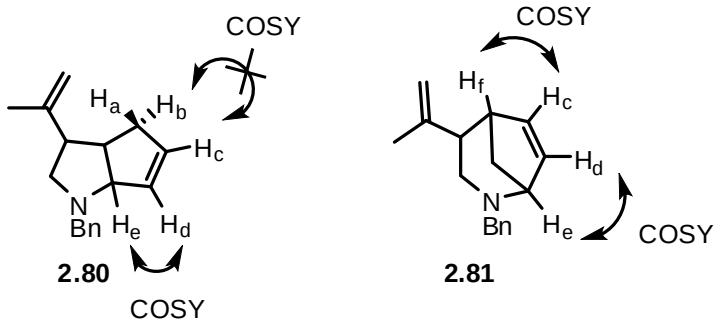


Figure 2.2 Structural Reassignment Based on 2-D NMR Studies

Based on the new structural information we had obtained on **2.81**, this led us to believe that in the conversion from dihydrofuran **2.71** to dihydropyrrole **2.77**, we did not get our desired rearrangement, but the same S_N' type of addition we had seen in our azide

reaction (Scheme 2.14). We decided to go back and get the same 2-D NMR data on our dihydrofuran **2.71** as well and to our dismay, once again the COSY correlations that we observed were not what we had expected. The methylene protons (H_a and H_b) did not have a correlation with the olefin proton H_c. We did see a COSY correlation between bridgehead proton H_f and olefin proton H_c, leading us to reassign the structure of dihydrofuran **2.71** to bicyclic oxepine **2.82**.

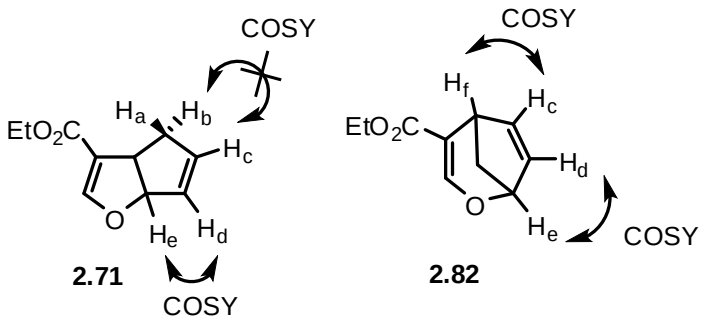


Figure 2.3 Structural Reassignment of **2.71** to **2.82**

Section 2.6 Summary and Future Work

In summary, while we were unsuccessful in completing the total synthesis of Kainic acid, we did discover a reaction that, to our knowledge, has not been explored yet. We could take diazo species **2.51** with cyclopentadiene and from **2.82** cleanly and in 65% yield. What is more interesting is that taking oxepane **2.82**, we were able to convert it an azepane while still retaining the bicylic product. We believe that if we could form pyrroline **2.75**, we have developed a solution of converting the vinylogous carbamyl group to the required isopropenyl group in Kainic acid. Future work would be to attempt this oxepine formation with other cyclic and acyclic dienes to determine the generality of this reaction.

Section 2.7 Experimental

General

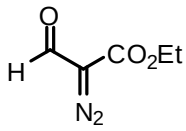
Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. ^{1}H, and ^{13}C NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Toluene, tetrahydrofuran (THF), ether, acetonitrile (MeCN) and dichloromethane (DCM) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Alfa Aesar, or Caledon. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F_{254}) visualizing with UV light, and the plates developed using acidic anisaldehyde. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh). High-pressure reactions were carried out on a LECO^{TM} Tempres High-Pressure chemical reactor. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor.

Procedure for the Synthesis of Diazo Species 2.51

2.51 was synthesized using a literature procedure.[27]

Thionyl chloride (1 equiv.) was added dropwise to anhydrous DMF (1 equiv.) and the mixture was heated at 40℃ for 2 h. The reaction mixture was then evaporated to give an off-white solid. The solid was dissolved in chloroform and ethyl diazoacetate (2 equiv.) was added dropwise over a period of 5 min at 0℃ and stirring continued for 1 h at room temperature. The chloroform was removed, ether added and the white precipitate filtered off. The white precipitate was dissolved in acetic acid (10%) and stirred overnight at room temperature. The aqueous solution was extracted with ether twice, the combined organic layers washed with aqueous saturated sodium hydrogen carbonate, aqueous

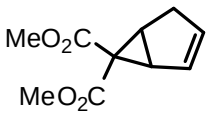
sulfuric acid (10%), brine and dried over $MgSO_4$. The resulting yellow oil (0.420 g, 2.96 mmol, 33%) was used without further purification with data as reported in the literature.



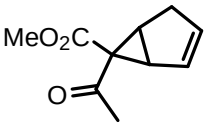
Reagents employed: **2.72** (0.653 mL, 9.00 mmol); **2.73** (0.697 mL, 9.04 mmol); **2.40** (1.91 mL, 18.2 mmol); chloroform (4 mL); Yielded **2.51** as a yellow oil, 33% (0.420 g, 2.96 mmol). Spectral properties are identical to those previously reported.[27]

General Procedure for the Reaction of Diazo Species with Cyclopentadiene

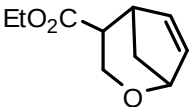
Cyclopentadiene **2.46** was distilled from dicyclopentadiene prior to use, due to dimerization of **2.46** at room temperature. Rhodium catalyst (2 mol %) was added to a solution of cyclopentadiene and DCM at room temperature. The diazo species in DCM was added dropwise and the solution was heated to reflux. After the reaction was deemed to be complete by TLC analysis, the solution was purified via flash chromatography on silica gel and the product was isolated.



Reagents employed: **2.46** (1.00 g, 15.1 mmol); Rh_2OAc_4 (0.033 g, 0.747 mmol); **2.29** (1.20 g, 7.59 mmol); DCM (15 mL); Yielded **2.47** as a colourless oil, 65% (0.968 g, 4.93 mmol). Spectral properties are identical to those previously reported.[31]



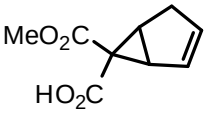
Reagents employed: **2.46** (1.05 g, 15.9 mmol); Rh_2OAc_4 (0.047 g, 1.06 mmol); **2.67** (1.50 g, 10.6 mmol); DCM (15 mL); Yielded **2.68** as a colourless oil, 40% (0.760 g, 4.22 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82-5.78 (m, 1H), 5.68-5.63 (m, 1H), 3.68 (s, 3H), 2.83-2.78 (m, 1H), 2.75-2.73 (m, 1H), 2.72-2.69 (m, 1H), 2.43 (dt, J = 6.2, 1.2 Hz, 1H), 2.25 (s, 3H)



Reagents employed: **2.46** (0.059 mL, 0.702 mmol); Rh_2esp_2 (0.001 g, 0.014 mmol); **2.51** (0.200 g, 1.41 mmol); DCM (3 mL); Yielded **2.82** as an orange oil, 65% (0.082 g, 0.455 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.10 (d, J = 1.2 Hz, 1H), 6.50 (dd, J = 5.3, 2.3 Hz, 1H), 5.52 (dd, J = 5.3, 2.3 Hz, 1H), 5.03 (m, 1H), 4.14 (q, J = 7.0 Hz, 2 H), 3.33 (m, 1H), 2.01 (m, 1H), 1.82 (d, 10.6 Hz, 1H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.1, 152.4, 143.3, 121.7, 111.7, 81.4, 59.8, 35.7, 34.7, 14.3. HRMS calc'd for $C_{10}H_{12}O_3$ = 180.0786, found 180.0791.

Procedure for the saponification of 2.47

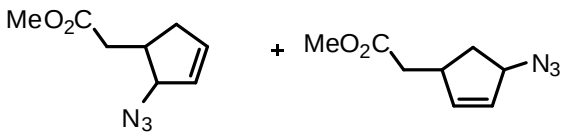
Cyclopropanes were dissolved in MeOH and 1.7M NaOH (1.2 eq.) with constant stirring. The solution was stirred for 1.5 h then was diluted with EtOAc and water to separate layers. The aqueous layer was the acidified with 5% HCl to reach pH 2, then extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated.[32]



Reagents employed: **2.47** (1.13 g, 5.76 mmol); NaOH (5 mL, 8.60 mmol); MeOH (5 mL); Yielded **2.62** as a colourless oil, 95% (1.00 g, 5.49 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.83-5.80 (m, 1H), 5.68-5.65 (m, 1H), 3.65 (s, 3H), 2.90 (dt, J = 6.5, 2.3 Hz, 1H), 2.84-2.79 (m, 1H), 2.74-2.68 (m, 1H), 2.54 (dd, J = 6.5, 6.5 Hz, 1H).

Procedure for Azide ring opening of 2.62

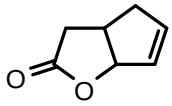
Sodium azide (1.2 equiv.) and ammonium chloride (1.4 equiv.) were added to a solution of cyclopropane hemimalonate (1.0 equiv.) in 2-methoxyethanol:water (5.0 ml:0.5 ml). The mixture was stirred at reflux (125 °C) until the reaction was complete (as determined by TLC analysis). The reaction was then quenched with water and extracted with ether (3 times). The organic layers were then combined and dried with magnesium sulfate. Following filtration, the solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (EtOAc:Hexanes, 20:80) to yield the ring opened product as a mixture of regioisomers.



Reagents employed: **2.62** (0.101 g, 0.554 mmol); sodium azide (0.043 g, 0.661 mmol); ammonium chloride (0.042 g, 0.785 mmol); 2-methoxyethanol:water; Yielded **2.61**/**2.63** as a 1:1 mixture of isomers, 50% (0.050 g, 0.276 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): (Both isomers) δ = 6.07-6.05 (m, 1H), 6.03-6.01 (m, 1H), 5.82-5.80 (m, 1H), 5.73-5.70 (m, 1H), 4.40-4.37 (m, 1H), 4.06 (br s, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.31-3.26 (m, 1H), 2.79-2.73 (m, 1H), 2.63-2.57 (m, 1H), 2.52 (dd, J = 15.2, 7.0 Hz), 2.43-2.38 (m, 2H), 2.31 (dd, J = 15.8, 8.2 Hz, 1H), 2.21 (ddd, J = 14.0 7.6, 2.9 Hz, 1H), 2.07-2.02 (m, 1H), 1.89-1.84 (m, 1H).

Procedure for Lactone Formation

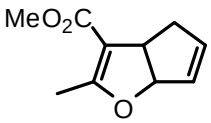
Cyclopropane hemimalonate, LiCl, and $Me_3N{\cdot}HCl$ were added to a microwave vial and dissolved in DMF. The vial was sealed and heated for 40 minutes at 150 °C. After the required reaction time the reaction was quenched with H_2O and extracted with ether. The organic layer was dried and the solvent was removed. The residue was subjected to flash chromatography on silica gel and the product was isolated.



Reagents employed: **2.62** (0.100 g, 0.549 mmol); LiCl (0.047 g, 1.11 mmol); $Me_3N{\cdot}HCl$ (0.073 g, 0.764 mmol); DMF (3 mL); Yielded **2.64** as a yellow oil, 40% (0.027 g, 0.217 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.09-6.05 (m, 1H), 5.87-5.84 (m, 1H), 5.50 (d, J = 7.6 Hz), 3.15-3.09 (m, 1H), 2.81 (dd, J = 18.2, 10.6 Hz, 1H), 2.75 (dd, J = 18.2, 8.2 Hz, 1H), 2.33-2.26 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.1, 136.8, 129.0, 89.6, 39.5, 36.0, 35.1.

Procedure for the Ketone Cyclopropane Rearrangement

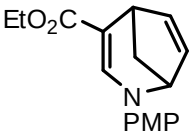
$YbOTf_3$ (20 mol %) was added to a solution of keto-ester cyclopropane **2.68** in toluene. The mixture was stirred at room temperature until the reaction was complete (as determined by TLC analysis). The solution was purified via flash chromatography on silica gel and the product was isolated.



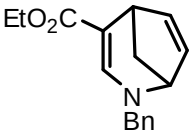
Reagents employed: **2.68** (0.107 g, 0.594 mmol); $YbOTf_3$ (0.074 g, 0.119 mmol); Toluene (3 mL); Yielded **2.69** as a yellow oil, 65% (0.070 g, 0.388 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.07-6.04 (m, 1H), 5.79-5.76 (m, 1H), 5.62 (br d, J = 9.4 Hz, 1H), 3.84-3.80 (m, 1H), 3.71 (s, 3H), 2.75-2.68 (m, 1H), 2.50-2.45 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.3, 166.7, 136.8, 106.2, 91.8, 50.7, 43.7, 40.0, 14.3.

General Procedure for the Palladium catalyzed azepane formation

Amine, *p*-$TsOH{\cdot}H_2O$, $Pd(PPh_3)_4$, toluene and oxepane were added sequentially to a round bottom flask. Then the resulting mixture was stirred at 70℃ overnight. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the reaction mixture was evaporated and purified via flash chromatography on silica gel.[28]



Reagents employed: **2.74** (0.111 g, 0.901 mmol); *p*-TsOH·H_2O (0.010 g, 0.053 mmol); $Pd(PPh_3)_4$ (0.021 g, 0.018 mmol); **2.82** (0.050 g, 0.301 mmol); Toluene (5 mL); Yielded oxepane as an orange oil, 45% (0.039 g, 0.137 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.31-7.30 (m, 1H), 7.07-7.04 and 6.88-6.85 (m, AA'BB', 4H), 6.12 (dd, J = 5.3, 2.9 Hz, 1H), 5.41 (dd, J = 5.3, 2.4 Hz, 1H), 4.51 (m, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.79 (s, 3H), 3.47-3.45 (m, 1H), 1.99 (dt, J = 10.6, 4.1 Hz, 1H), 1.72 (d, J = 10.6 Hz, 1H), 1.27 (t, J = 7.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.9, 156.3, 139.3, 137.2, 135.6, 121.6, 119.7, 114.6, 102.0, 63.2, 59.3, 55.5, 35.9, 34.3, 14.6.

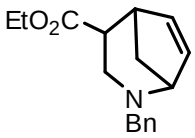


Reagents employed: **2.76** (0.097 g, 0.905 mmol); *p*-TsOH·H_2O (0.010 g, 0.053 mmol); $Pd(PPh_3)_4$ (0.021 g, 0.018 mmol); **2.82** (0.050 g, 0.301 mmol); Toluene (5 mL); Yielded oxepane as an orange oil, 62% (0.050 g, 0.186 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.38-7.34 (m, 2H), 7.32-7.29 (m, 1H), 7.26-7.23 (m, 2H), 7.17 (s, 1H), 5.99 (dd, J = 5.3, 2.9 Hz, 1H), 5.06 (dd, J = 5.3 Hz, 2.4 Hz, 1H), 4.44-4.32 (AB system, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.82-3.80 (m, 1H), 3.38-3.36 (m, 1H), 1.81 (dt, J = 10.0, 4.1 Hz, 1H), 1.50 (d, J = 10.0 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 141.1, 137.7, 134.6, 128.7, 127.9, 127.6, 119.5, 60.2, 59.2, 59.0, 35.6, 33.9, 14.7. HRMS calc'd for $C_{17}H_{19}NO_2$ = 269.1416, found 269.1409.

Procedure for the Conversion of the Vinylogous Carbamate to the Isopropenyl Group

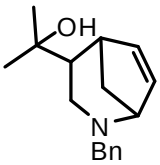
A solution of azapane in THF was added dropwise to a solution of $NaBH(OAc)_3$ in AcOH. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the solution was diluted with EtOAc and the layers were separated. The aqueous layer

was neutralized with saturated sodium hydrogen carbonate and then extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$ and the solvent was removed.



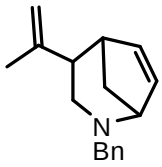
Reagents employed: azapane (0.310 g, 1.15 mmol); $NaBH(OAc)_3$ (0.732 g, 0.345 mmol); AcOH (3.5 mL); THF (5 mL); Crude ester divided into three parts and one of them taken forward for the Grignard addition.

The crude ester was then dissolved in ether and cooled to 0℃. A 3M solution of MeMgBr was added dropwise over 5 minutes and the solution was warmed to room temperature. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the solution was diluted with EtOAc and the layers were separated. The aqueous layer was neutralized with a 5% solution of HCl and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$ and the solvent was removed.



Reagents employed: crude ester (0.098 g, 0.361 mmol); MeMgBr (0.4 mL, 1.20 mmol); Et_2O (3 mL); Crude tertiary alcohol was carried forward in the next step.

The crude tertiary alcohol was dissolved in ether and MsCl was added to the solution. The reaction was then cooled to 0℃ and NEt_3 was added dropwise to the solution. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the solution was diluted with EtOAc. The aqueous layer was extracted three times with EtOAc and the combined organic layers were dried with $MgSO_4$. The solvent was removed and the residue was purified via flash chromatography on silica gel.



Reagents employed: crude tertiary alcohol; MsCl (0.081 g, 0.0707 mmol); NEt_3 (0.489 g, 4.83 mmol); Et_2O (3 mL); Yielded **2.81** as a colourless oil, 49% over three steps (0.038 g, 0.159 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.37-7.34 (m, 2H), 7.33-7.29 (m, 2H), 7.25-7.22 (m, 1H), 6.31 (dd, J = 5.3, 2.9 Hz, 1H), 5.89 (dd, J = 5.9, 1.8 Hz, 1H), 5.20 (s, 1H), 4.91 (s, 1H), 3.58-3.56 (m, 1H), 3.55-3.24 (AB system, 2H), 2.79 (d, J = 11.7 Hz, 1H), 2.65-2.62 (m, 1H), 2.43 (dd, J = 11.7, 5.9 Hz, 1H), 2.09-2.06 (m, 1H), 2.00 (d, J = 10.0 Hz, 1H), 1.73 (s, 3H), 1.61-1.57 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.6, 139.7, 137.1, 128.7, 128.1, 126.7, 126.6, 111.5, 63.3, 61.2, 50.4, 41.3, 40.8, 38.4, 22.8.

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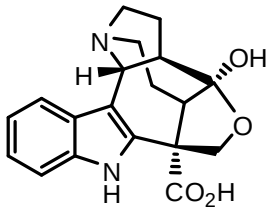
Chapter 3 Actinophyllic Acid

Section 3.1 Isolation and Biological Activity

In 2005, Carroll and co-workers were screening natural products with the intention of determining which ones could upregulate fibrinolysis.[1] In this study, they came across the natural product Actinophyllic Acid **3.1**.



3.1

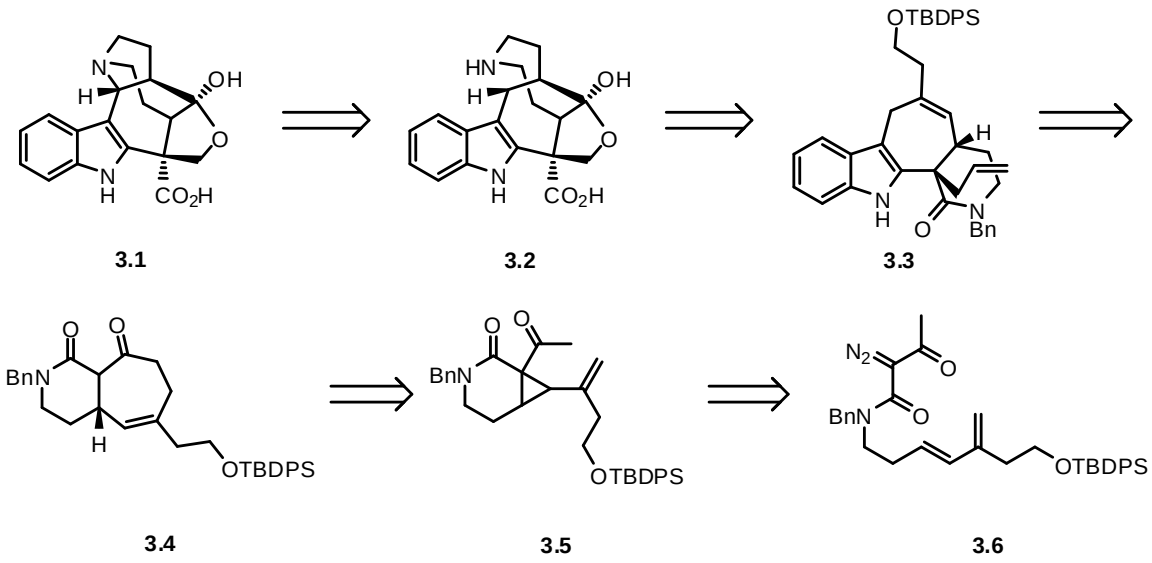
Figure 3.1 Actinophyllic Acid, **3.1**

It was isolated from the leaves of *Alstonia actinophylla*, which was growing on the Cape York Peninsula, Far North Queensland, Australia. The importance of this study was due to the presence of thrombotic diseases in the developed world. Fibrinolysis is the body's process of breaking down blood clots in the blood stream. While Actinophyllic acid does not act directly on blood clots themselves, it does interact with is carboxypeptidase U (CPU) that inhibits fibrinolysis.[2] A suppression of fibrinolysis can lead to a variety of different pathological consequences, such as pulmonary embolism and myocardial infarction.[3-6] Due to the biological activity and unique structural framework of Actinophyllic acid, many studies have been developed methods to synthesize it. These synthetic methods as well as the completed total syntheses will be described herein.

Section 3.2 Studies Towards the Synthesis of Actinophyllic Acid

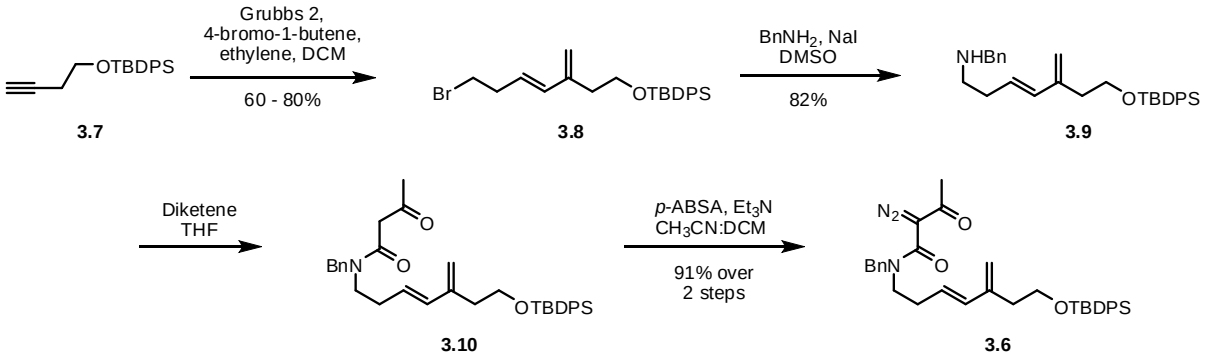
In 2009, Wood and co-workers revealed their synthetic plan for the synthesis of Actinophyllic Acid (Scheme 3.1).[7] They envisioned creating the large eight membered ring via a ring closing reaction of secondary amine **3.2** and an indole-quinonemethide species to furnish **3.1**. They believed that they could arrive at pentacyclic amine **3.2** from

indole lactam **3.3**. The indole and the quaternary center they believed they could introduce through selective alkylation and indole formation procedures of bicyclic β-ketoamide **3.4**, which could be synthesized from a divinyl-cyclopropane rearrangement of cyclopropane **3.5**. Compound **3.5** could be formed from an intramolecular diazoacetoacetamide cyclopropanation of **3.6**.



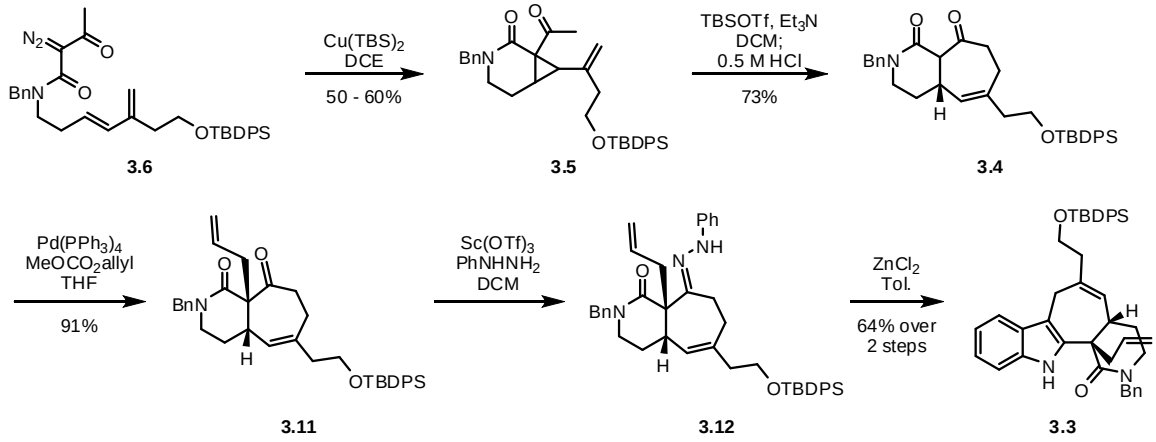
Scheme 3.1 Wood's Retrosynthetic Plan

In the forward sense, starting from protected homo-propagyl alcohol **3.7**, an enyne cross metathesis furnished diene **3.8** in a 60-80% yield. Displacement of the bromide with benzylamine produced amine **3.9** in an 82% yield. This amine was then treated with diketene to form a β-ketoamide, which was then subjected to Regitz diazo transfer to furnish their cyclopropanation precursor **3.6** in 91% yield over the two steps.



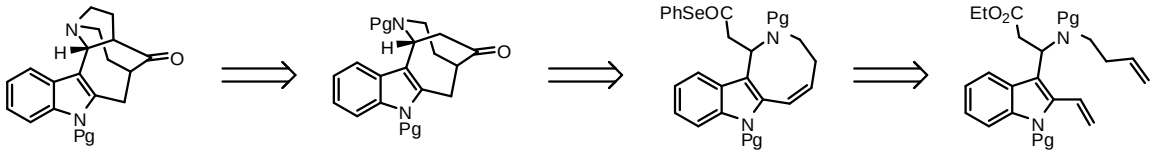
Scheme 3.2 Synthesis of Cyclopropanation Precursor

Through a vigorous catalyst screening, they eventually were able to synthesize cyclopropane **3.5** in a 50-60% yield using copper(TBS)$_2$. Enolization of **3.5** with TBSOTf, followed by treatment with acid allowed for the divinylcyclopropane rearrangement to form **3.4** in a 73% yield. The bicyclic β-ketoamide **3.4** was alkylated using a Tsuji-Trost allylation to arrive at **3.11** in a 91% yield. Under scandium triflate catalyzed hydrazone synthesis, indolization was realized in a 64 % yield to give them advanced intermediate **3.3**. This brought an end of their synthetic study as they were able to form the core seven-membered ring of Actinophyllic acid.



Scheme 3.3 Synthesis of Key Indole Intermediate **3.3**

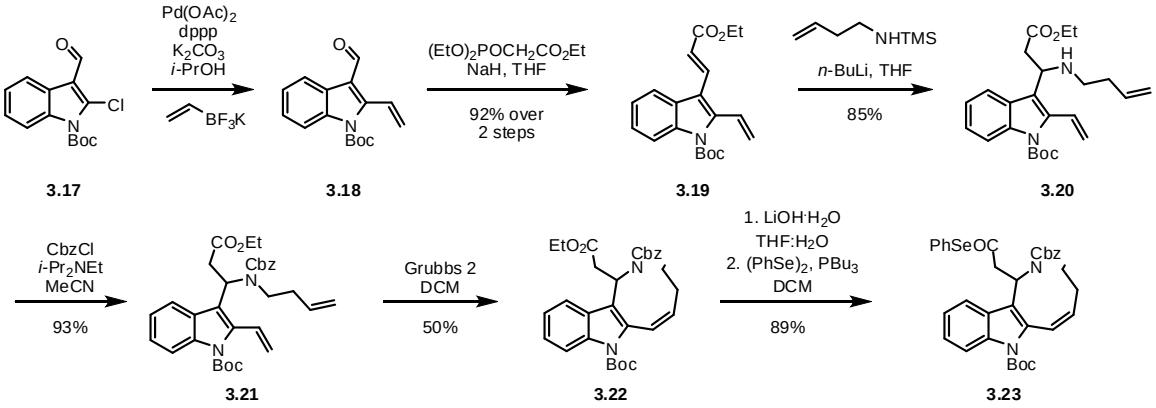
In 2012, Taniguchi developed a transannular acyl radical cylization protocol to produce the core of Actinophyllic acid.[8] Their target compound **3.13** would result from sequential dialkylation of an amine and at the α-position of ketone **3.14** (Scheme 3.4). It was thought that **3.14** would be produced from the transannular acyl radical cyclization of **3.15**. The cyclization precursor **3.15** would be produced from a ring closing metathesis and selenoester formation of **3.16**.



3.13 **3.14** **3.15** **3.16**

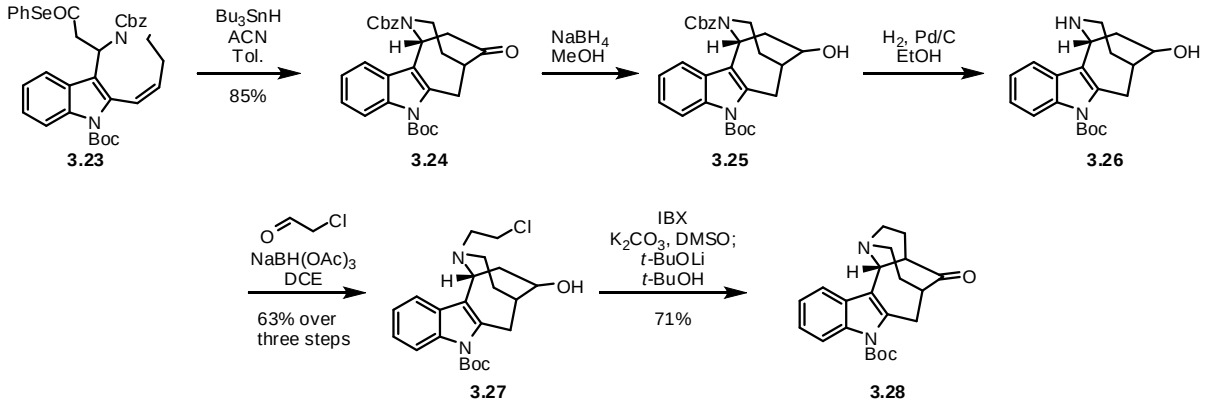
Scheme 3.4 Taniguchi's Retrosynthetic Plan

From chloroindole **3.17**, a Suzuki-Miyaura cross coupling produced vinyl indole **3.18**, which was carried forward crude to a Horner-Wadworth-Emmons homologation to provide α,β-unsaturated ester **3.19** in a 92% yield over the two steps (Scheme 3.5). Michael addition with TMS-protected homo-propargyl amine furnished **3.20** in an 85% yield. The amine was re-protected with a Cbz group to give **3.21**, which was subjected to ring-closing metathesis to provide **3.22** with the required eight-membered ring. Ester saponification followed by selenoester formation provided them with the radical cyclization precursor **3.23**.



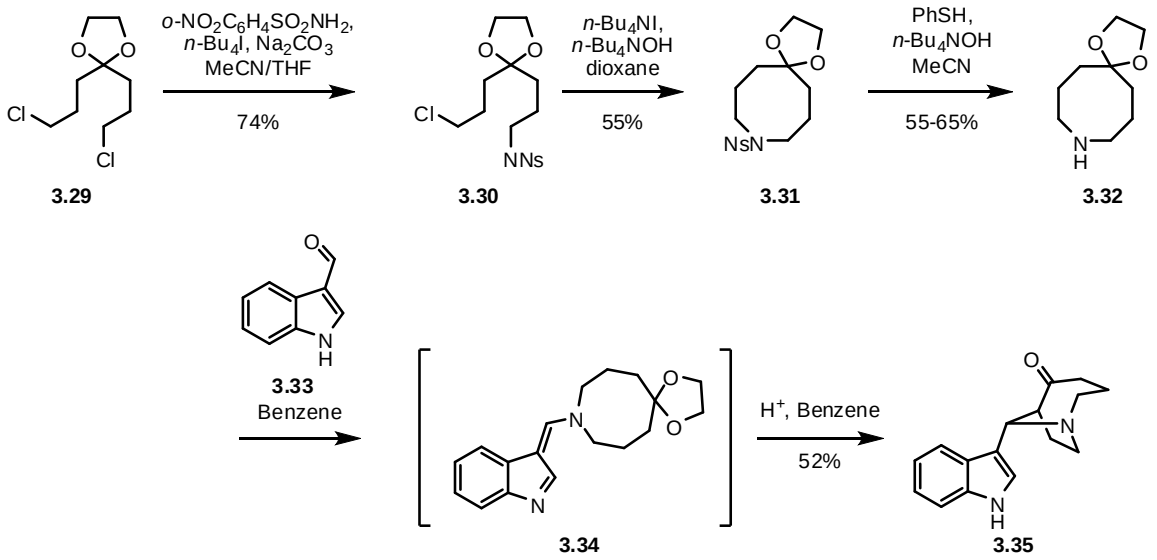
Scheme 3.5 Synthesis of Acyl Radical Precursor

Gratifyingly, the radical cyclization to form the tetracyclic core of Actinophyllic acid **3.24,** worked well giving the correct regiochemistry of radical attack (Scheme 3.6). This is not too surprising as the radical formed after cyclization would be more stable α to the indole due its resonance with the benzylic C-3 position of the indole. Reduction of ketone **3.24** with sodium borohydride, Cbz deprotection of **3.25** followed by reductive amination led to aminoalcohol **3.27**. The secondary alcohol was then oxidized back up to the ketone, which underwent alkylation to form the pentacyclic core of Actinophyllic acid **3.28**. Due to the lack of functionalization adjacent to the 2-position of the indole, this would be the end of their synthetic study.



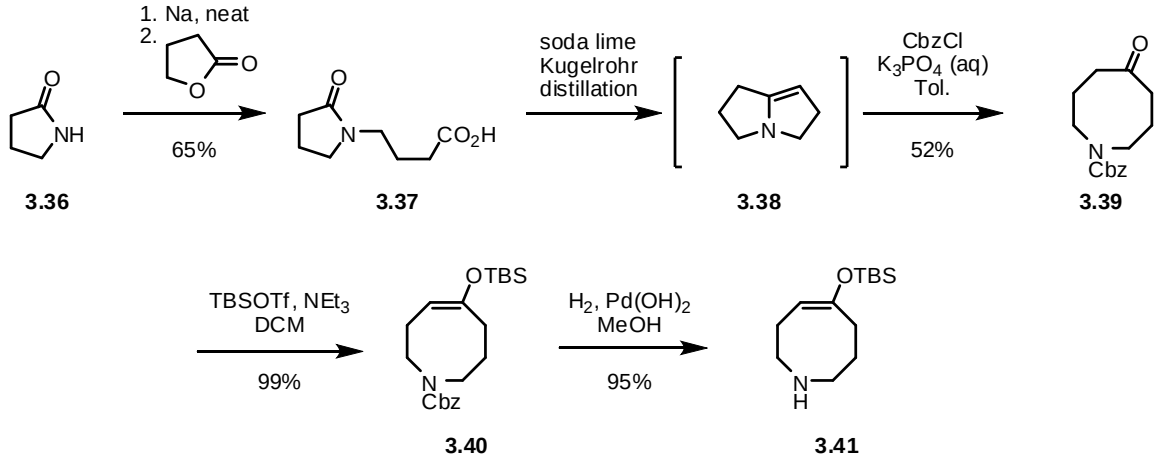
Scheme 3.6 Acyl Radical Cyclization and Synthesis of Advanced intermediate **3.28**

The group of Maldonado and co-workers believed that they could form the 1-azabicyclo[4.2.1]nonane core of Actinophyllic acid[9] through a non-carbonyl mediated Mannich reaction that was previously developed by Wenkert.[10] Starting from symmetric dichloride **3.29**, they were able to mono-alkylated with *o*-nitrobenzenesulfonamide to form **3.30** (Scheme 3.7). This was then subjected to macrocyclization to form their desired protected cyclization precursor **3.31**. Simple treatment with benzenethiol allowed for deprotection of the *o*-nosyl protecting group **3.32**, readying their substrate for cyclization. Taking **3.32** with indole-3-carboxaldehyde **3.33** and heating in toluene, followed by addition of acid furnished **3.35**. While they did get the cyclization they expected, the seven-membered ring is *anti* with respect to the indole. They are currently looking into methods to attempt to reverse this chemoselectivity.



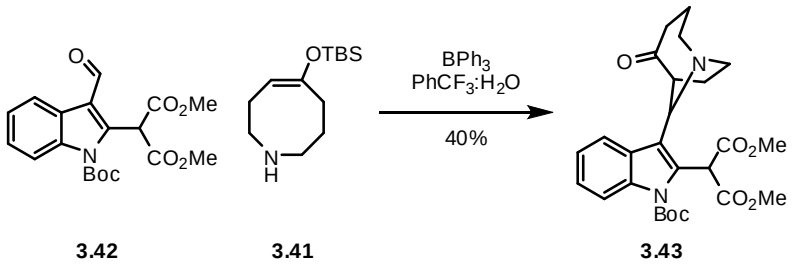
Scheme 3.7 Maldonado's Synthesis of the Actinophyllic Acid Core

Coldham developed a comparable route to Maldonado where the envisioned making a similar bicyclic core.[11] Taking pyrrolidinone **3.36** neat with sodium metal, and adding butyrolactone gave them acid **3.37**. Treating this under dehydrating conditions provided them with tetrahydropyrrolizine **3.38**, which then could be ring-opened with a biphasic solution of potassium phosphate and CbzCl to form azocinone **3.39**. Silyl enol ether formation followed by deprotection of the Cbz group gave key substrate **3.41** for their Mannich cyclization.



Scheme 3.8 Synthesis of Addition Precursor

Taking indole **3.42** and **3.41** under Brønsted acidic conditions only furnished their Mannich adduct **3.43** in a 40% optimized yield. Similar to the result observed by Maldonado, the carbonyl functionality is *anti* to the malonyl on the 2-position of the indole.



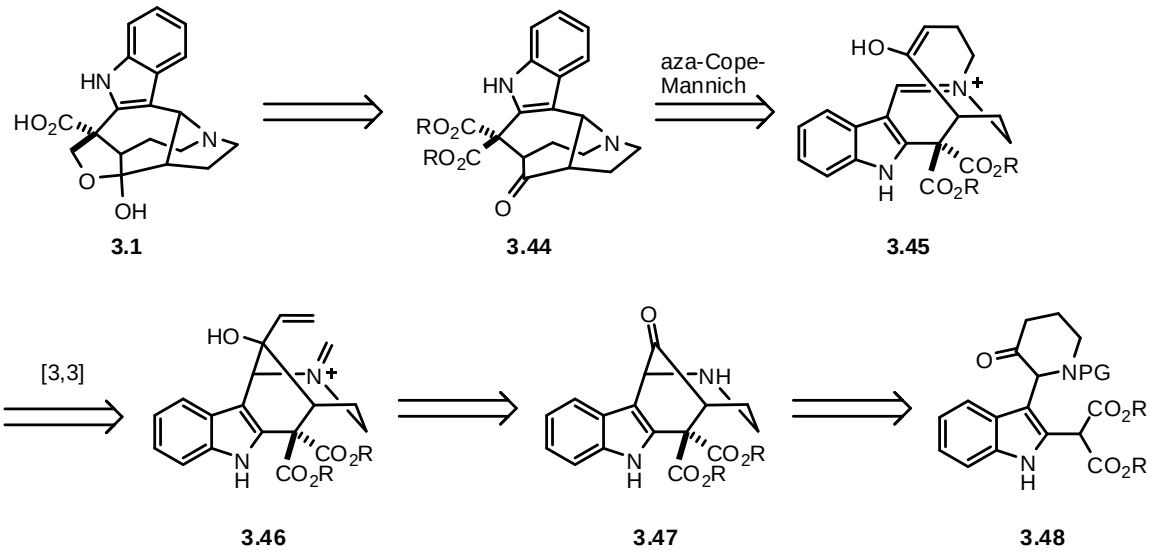
Scheme 3.9 Coldham's Synthesis of the Core of Actinophyllic Acid

Section 3.3 Total Syntheses of Actinophyllic Acid

Overman first synthesized Actinophyllic acid in 2008,[12] and improved the end game of their synthesis in 2010.[13] The seminal total synthesis of Overman and the total synthesis reported by Martin in 2013[14] will be described herein.

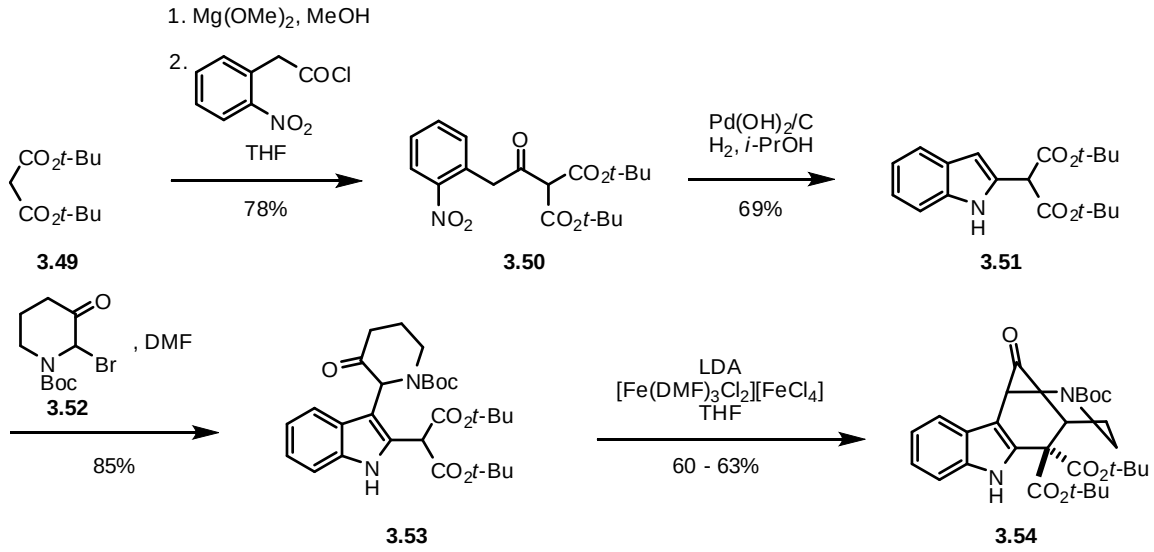
Section 3.3.1 Overman's Total Synthesis of Actinophyllic Acid

The retrosynthetic plan for the synthesis of actinophyllic acid is shown below in Scheme 3.10. The proposed final step would be a tetrahydrofuran-ketal ring closing which would lead back to diester **3.44**. **3.44** could be formed through an aza-Cope-Mannich cylization of **3.45**, which could be generated from a [3,3] rearrangement of iminium **3.46**. Formation of **3.47** would arise from an oxidative enolate cyclization of **3.48**.



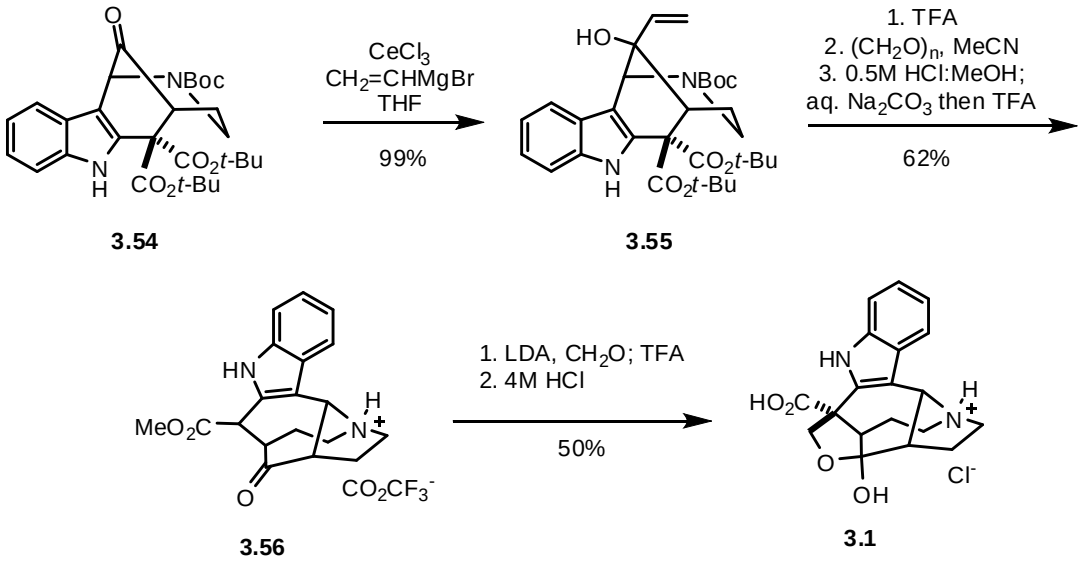
Scheme 3.10 Overman's Retrosynthetic Strategy

The magnesium-generated enolate of *t*-butyl malonate **3.49**, was added into *o*-nitrophenyl acetyl chloride, to form keto-ester **3.50** (Scheme 3.11). Reduction of the nitro group followed by cyclization onto the ketone gave indole-2-malonate **3.51**. Taking bromo-piperidinone **3.52** and indole **3.51**, alkylation at the 3-position formed **3.53** which was now ready for the desired oxidative enolate cyclization. Treatment of **3.53** with LDA and an iron (III) oxidant furnished tetracyclic ketone **3.54** in a 60-63% yield, which could be completed on a multigram scale.



Scheme 3.11 Oxidative Enolate Coupling

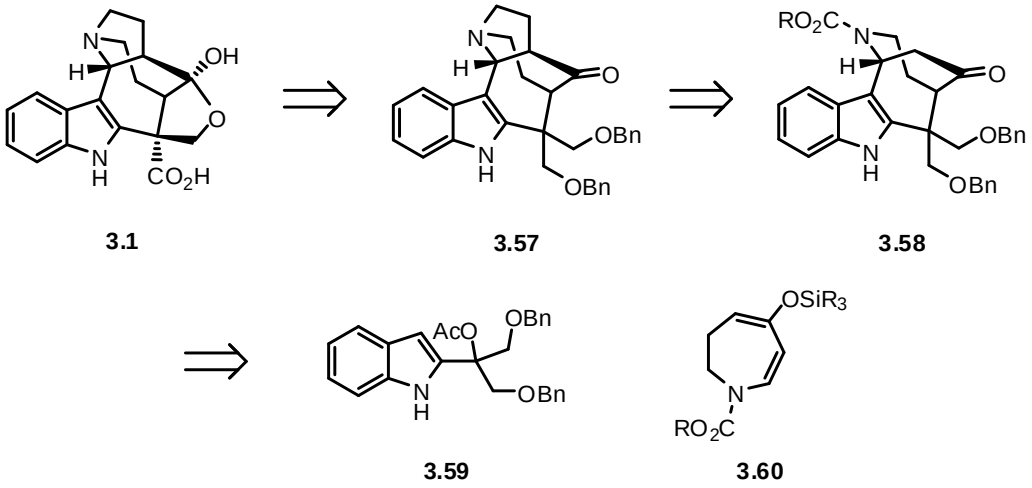
A Luche mediated Grignard addition to ketone **3.54** provided access to their key rearrangement substrate **3.55**. Removal of the Boc protecting group, followed by iminium formation with *p*-formaldehyde set up their rearrangement/aza-Cope-Mannich cascade to form **3.56** in a superb 62% yield. Next **3.56** was deprotonated to give a stereoselective enolate which was then trapped with monomeric formaldehyde and subsequently cyclized onto the ketone to form Actinophyllic acid. This completed the first total synthesis of Actinophyllic acid in an 8% overall yield with the isolation of only 7 intermediates.



Scheme 3.12 Overman's Completed Total Synthesis of Actinophyllic Acid

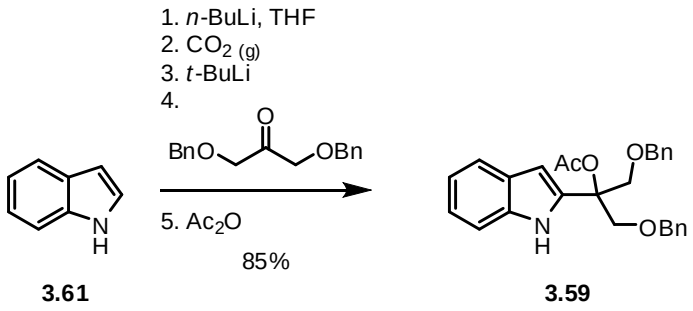
Section 3.3.2 Martin's Total Synthesis

In 2013, Martin developed an elegant synthesis of Actinophyllic acid which employed the use of a cascade reaction protocol. They envisioned that **3.1** could be made through refunctionalization of **3.57**. Synthesis of the pyrrolidine ring from **3.58** could be formed in a similar method to that of Taniguchi (*vide supra*). Formation of **3.58** would come from a carbocation/π-nucleophile cascade reaction from indole **3.59** and diene **3.60**.



Scheme 3.13 Martin's Retrosynthetic Analysis

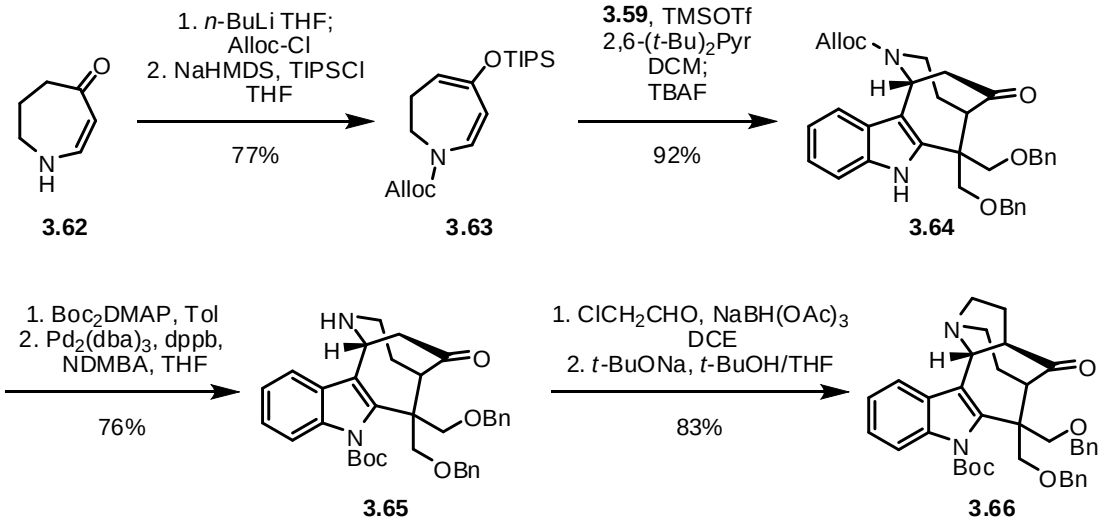
Taking indole **3.61**, they could form the dianionic species, which was added into 1,3-dibenzyloxyacetone. The product of was then protected in situ to form **3.59** in an 85% yield (Scheme 3.14).



Scheme 3.14 Synthesis of Cyclization Precursor

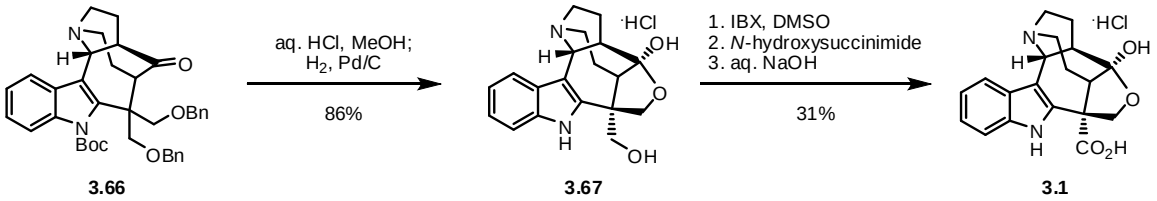
Azepinone **3.62** was protected with Alloc-Cl and trapped as the silyl enol ether to form the desired diene **3.63** for the cyclization (Scheme 3.15). After extensive optimization of conditions, the cascade was promoted with TMSOTf, followed by addition of TBAF to remove the silyl protecting group provided ketone **3.64** in an excellent 92% yield. Boc protection of the indole, followed by alloc deprotection

provided secondary amine **3.65**. Pyrrolidine ring formation was completed in a similar fashion to Taniguchi (*vide supra*) to arrive at **3.66** in an 83% yield.



Scheme 3.15 Carbocation/π-nucleophile Cascade

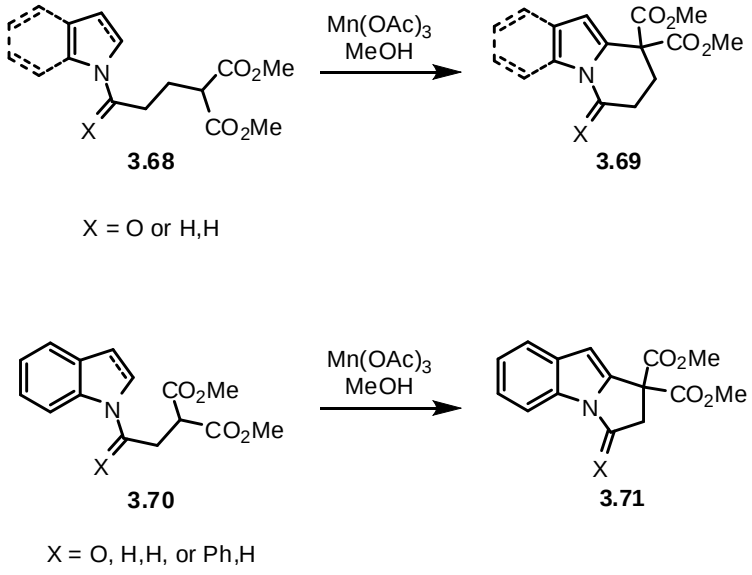
Removal of the Boc group on the indole and removal of the benzyl protecting groups provided **3.67** as the HCl salt; all that remained was oxidation of the neopentyl alcohol to form Actinophyllic acid. After many attempts, they could oxidize the alcohol to the aldehyde with IBX, followed by addition of N-hydroxysuccinimide in the presence of excess IBX allowed for formation of the succinic ester. This underwent simple saponification to form Actinophyllic acid **3.1** in only 10 overall steps. Analogues of Actinophyllic acid were generated using this protocol, as the choice of substitution on amine **3.62** can lead to a library of products.



Scheme 3.16 Martin's End Game

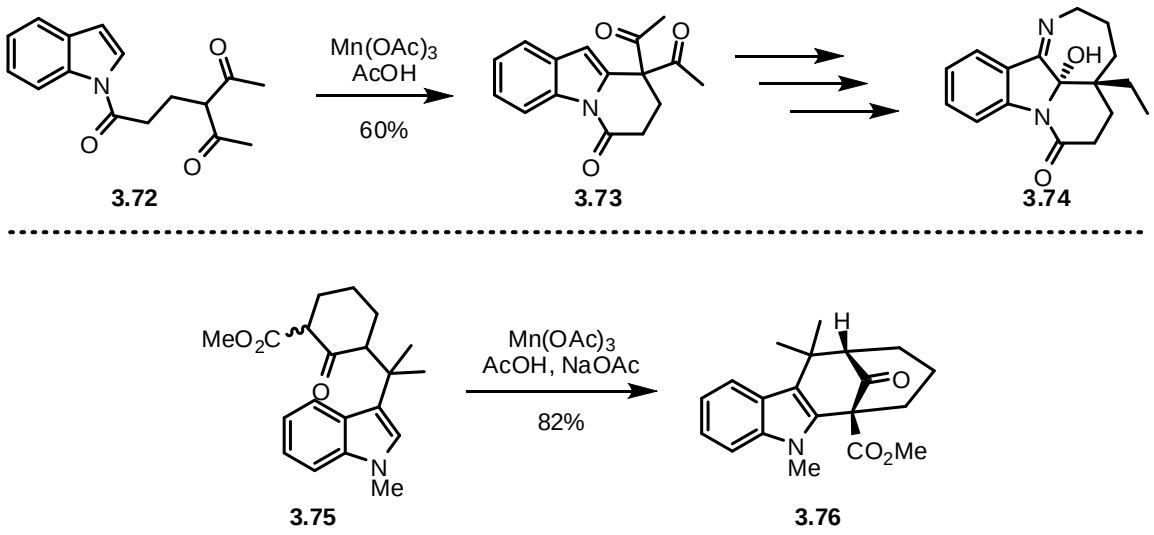
Section 3.4 Oxidative Radical Cyclizations

Oxidative radical cyclizations of 1,3-diones, β-keto-esters and malonates into a variety of different aromatic systems have been thoroughly investigated by the groups of Chuang and Snider.[15-17] The Kerr group has investigated this reaction as well by using tethered malonate and β-keto-ester componds under superstoichiometric manganese (III) acetate and cyclizing them into indoles, pyrroles and indolines (Scheme 3.17).[18] The tether was always from the nitrogen atom of the heterocycle and the yield of the transformation was not deteriorated by the electron-withdrawing nature of the amide functionality.



Scheme 3.17 Manganese Mediated Oxidative Cyclizations

Though only a few pyrrole examples were tested, when there was substitution on the pyrrole ring, a mixture of regiochemical isomers was obtained. While substitution on the 5-position of the indole was well tolerated, electron-deficient substitution at the 3-position of the indole was not amenable to these reaction conditions. Interestingly, with a slightly larger excess of manganese (III) acetate, indoline could also be used in this reaction. The indoline was oxidized to the indole under these conditions and subsequently cyclized onto the indole ring. The success of this methodology has lent itself to the study of natural product synthesis. The Kerr group used this methodology to complete the total synthesis of mersicarpine.[19] A similar cyclization was used by the Rawal group towards the synthesis of the core of the welwitindolinones.[20]

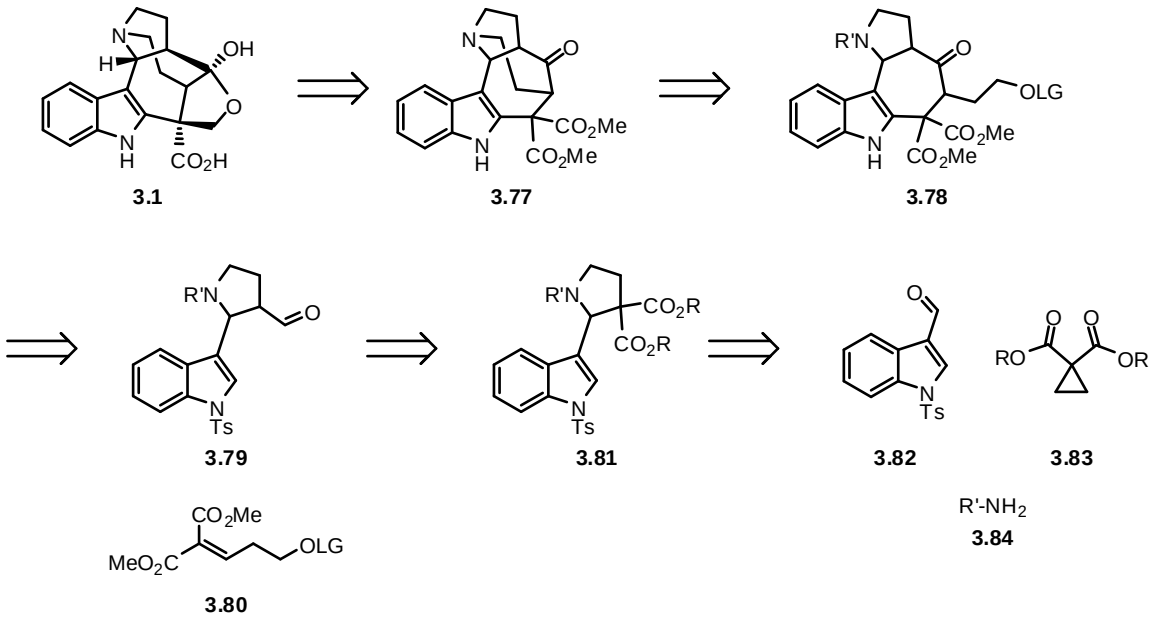


Scheme 3.18 Applications of the Manganese Mediated Oxidative Cyclization

Section 3.5 Retrosynthetic Proposal for Actinophyllic Acid

Upon initial inspection of Actinophyllic Acid we deemed that our end game could coincide with the synthesis of Overman and simply finish with the tetrahydrofuran ring formation (Scheme 3.19). **3.77** would come from a deprotection and N-alkylation of the pyrrolidine **3.78**. We believed that the next bond disconnection would be the most difficult one to form (**3.78**-**3.79**), due to the necessary formation of a 1,4-dicarbonyl species. We envisioned that this functionality could be installed by either an

intermolecular acyl radical addition or a Stetter reaction between **3.79** and **3.80** followed by a manganese mediated radical cyclization. **3.79** could be formed by a Krapcho dealkoxycarbonylation and ester reduction of **3.81**. Pyrrolidine **3.81** could come from the previously established three-component coupling developed by the Kerr group (as described in Chapter 1), from easily accessible starting materials.



Scheme 3.19 Proposed Retrosynthetic Plan for Actinophyllic Acid

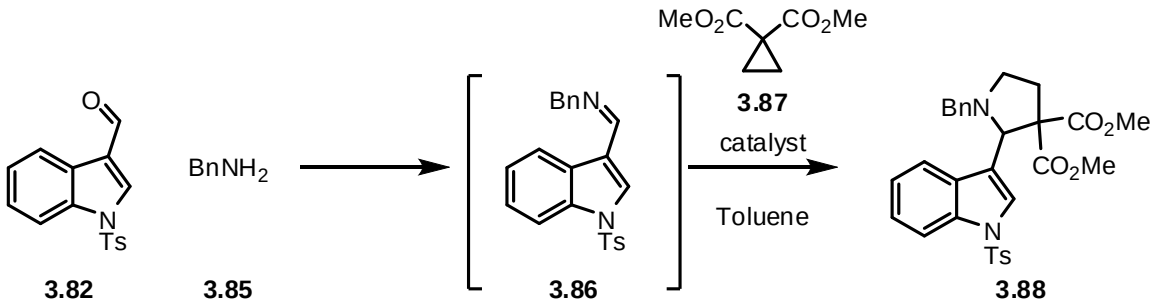
Section 3.6 Results and Discussion

Section 3.6.1 Pyrrolidine Ring Formation

Upon investigation of the pyrrolidine ring formation, the components of the reaction had to be selected carefully. First, we need to use an amine that had either substitution that could be directly converted to a desired functionality later, or a cleavable functionality so that the amine could be manipulated later. Also, we needed to consider substitution on the indole ring as the product that we would be forming would have a gramine-type framework, which have been known to fragment as an indolequinone-methide[21] as described in the earlier synthetic studies. We decided upon N-tosylindole-3-carboxaldehyde as our indole partner, as this protection should attenuate the

nucleophilicity of the indole ring and stop any gramine-type fragmentation. We also decided to start with benzylamine as this protecting group could easily be removed later for further manipulations. We attempted to use the optimized conditions from the methodology, but unfortunately we saw no product formation (Table 3.1, entry 1. We next attempted Lewis acids that have been known to activate 1,1-cyclopropanediesters towards ring opening events. Once again, none of these conditions formed any of the desired pyrrolidine ring under both thermal and microwave conditions (Table 3.1, entries 2-8).

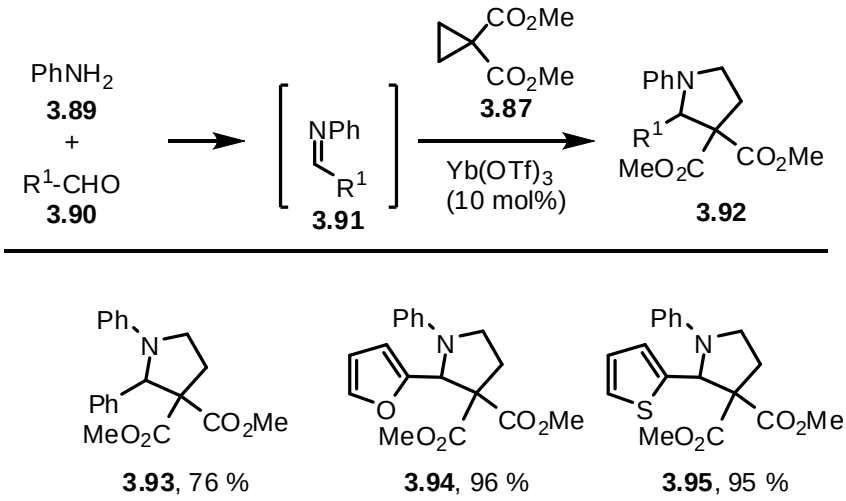
Table 3.1 Pyrrolidine Ring Formation Attempts



Entry	Lewis Acid (20 mol %)	Conditions	Time (h)	Result
1	$Yb(OTf)_3$	80℃ to 110℃	16	No Reaction
2	$Yb(OTf)_3$	Microwave, 140℃	1	No Reaction
3	$Sc(OTf)_3$	80℃ to 110℃	16	No Reaction
4	$Sc(OTf)_3$	Microwave, 140℃	1	No Reaction
5	$Sn(OTf)_2$	80℃ to 110℃	16	No Reaction
6	$Sn(OTf)_2$	Microwave, 140℃	1	No Reaction
7	$AlCl_3$	80℃ to 110℃	16	No Reaction
8	$AlCl_3$	Microwave, 140℃	1	No Reaction

Having no success at completing the three-component coupling required for Actinophyllic acid, we re-examined the pyrrolidine methodology.[22] Upon further

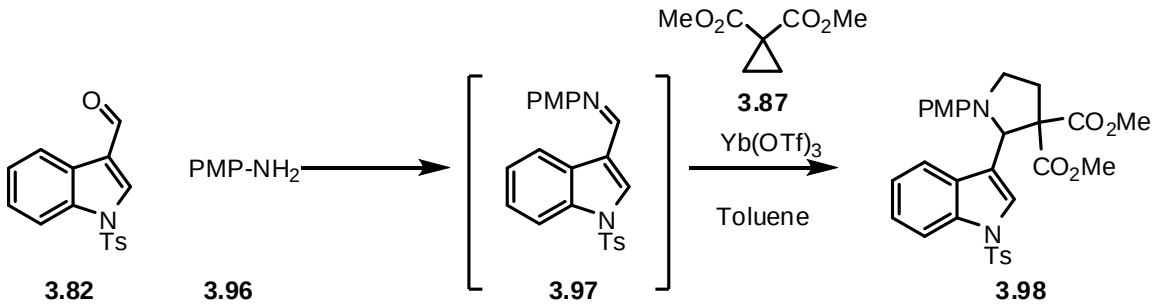
inspection, when the parent 1,1-cyclopropanediesters was used, only an aniline were used to complete the cycloaddition (Scheme 3.20).



Scheme 3.20 Selected Examples from Kerr's Pyrrolidine Methodology

From this observation, we decided to use *p*-anisidine **3.96** as our amine source as the aromatic ring could be cleavable at a later time, as well as it would give us a diagnostic methyl peak in our NMR spectra. By making this adjustment, we were able to generate desired pyrrolidine **3.98** in an 18% yield using the previously optimized conditions (Table 3.2, entry 1). Completing the reaction using a microwave reactor allowed for an increase in the yield to 61 % (Table 3.2, entry 2). And finally, increasing the equivalents of the aldehyde and the amine from 1.2:1.2:1 to 2:2:1, the yield was increased again to an 87 % yield. Now that we had completed an efficient synthesis of our desired pyrrolidine **3.98**, we next focused our attention on the synthesis of 1,4-dicarbonyl species.

Table 3.2 Optimization of *p*-anisidine Pyrrolidine Ring Formation

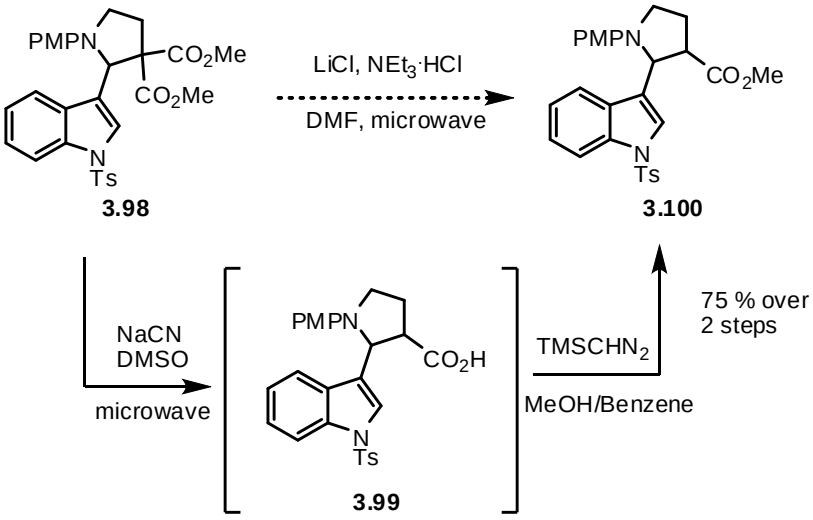


3.82 **3.96** **3.97** **3.98**

Entry	Equivalents (Amine:Aldehyde:Cyclopropane)	Conditions	Time (h)	Isolated Yield (%)
1	1.2:1.2:1	110℃	16	18
2	1.2:1.2:1	Microwave, 140℃	3	61
3	2:2:1	Microwave, 140℃	3	86

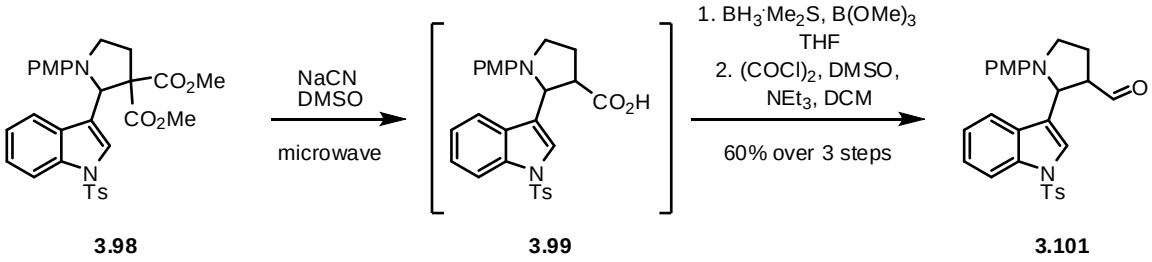
Section 3.6.2 Progress Towards Actinophyllic Acid

We first decided to work on the synthesis of the aldehyde substituted pyrrolidine partner **3.79**. To achieve this, we would first need to eliminate one of our ester functionalities. Initial attempts to remove the ester using LiCl and NEt_3[23] lead to no decarboxylated product with slow decomposition starting material (Scheme 3.21). We next attempted to use a sodium cyanide mediated Krapcho dealkoxycarbonylation[24] and from the crude NMR we appeared to be successful. For simplicity of purification, we converted the acid generated by the reaction to the methyl ester by using TMS-diazomethane.



Scheme 3.21 Removal of one of the ester functionalities by Krapcho Dealkoxycarbonylation

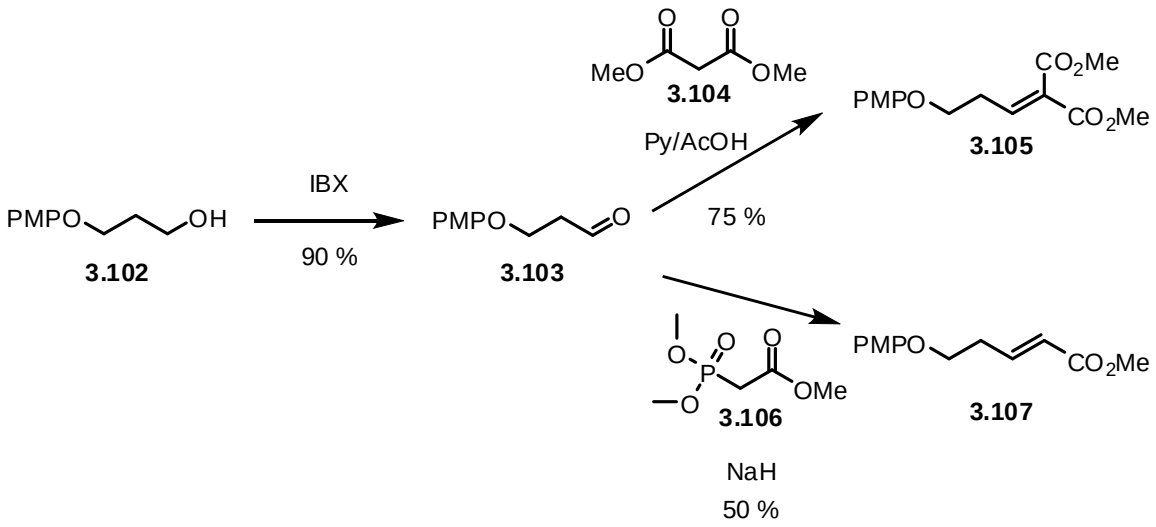
With the realization that under the Krapcho conditions we could generate a single acid functionality, we thought that this would be a good intermediate for the synthesis of our desired aldehyde. Using the same conditions as stated above, we reduced the acid using borane and oxidized the resultant alcohol to the aldehyde using Swern conditions to **3.101** in a 60% isolated yield over the three steps (Scheme 3.22).



Scheme 3.22 Synthesis of Stetter Nucleophile **3.101**

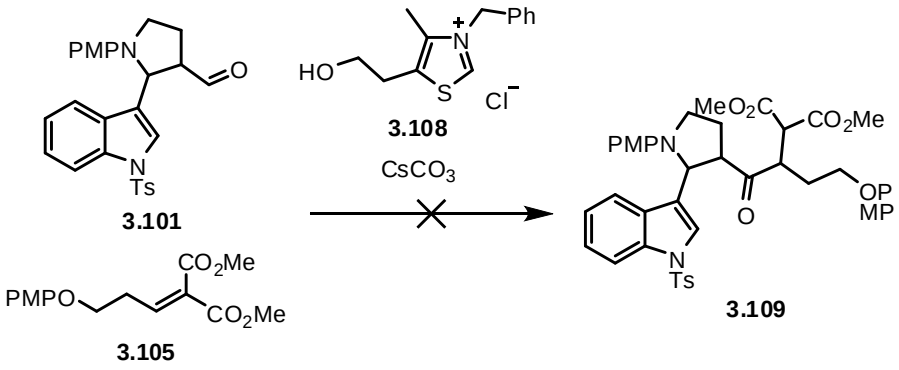
We decided to synthesize two different acceptors both of which could be carried forward for the Stetter reaction. Taking mono-protected propanediol, we oxidized the remaining alcohol up to the aldehyde in 90% yield using IBX (Scheme 3.23). From there

we generated two separate acceptors, one using a Knoevenagel condensation to from diester **3.105** and the other a Horner-Wadsworth-Emmons homologation to form monoester **3.107**.



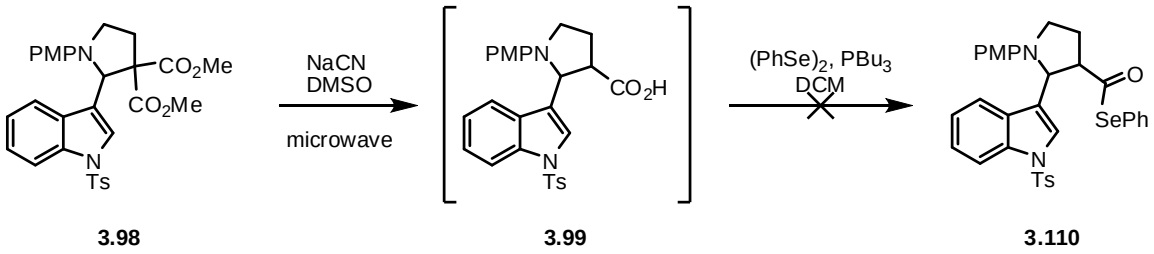
Scheme 3.23 Synthesis of Potential Stetter/Acyl Radical Acceptors

With both reactive partners in hand, we attempted a Stetter reaction to build the required 1,4-dicarbonyl species using alkylidene malonate **3.105**, aldehyde **3.101** and thiazolium catalyst **3.108**, but unfortunately we did not obtain any product in the reaction. Due to the difficult in scaling up the synthesis of **3.101**, only one attempt at the Stetter reaction was tried.



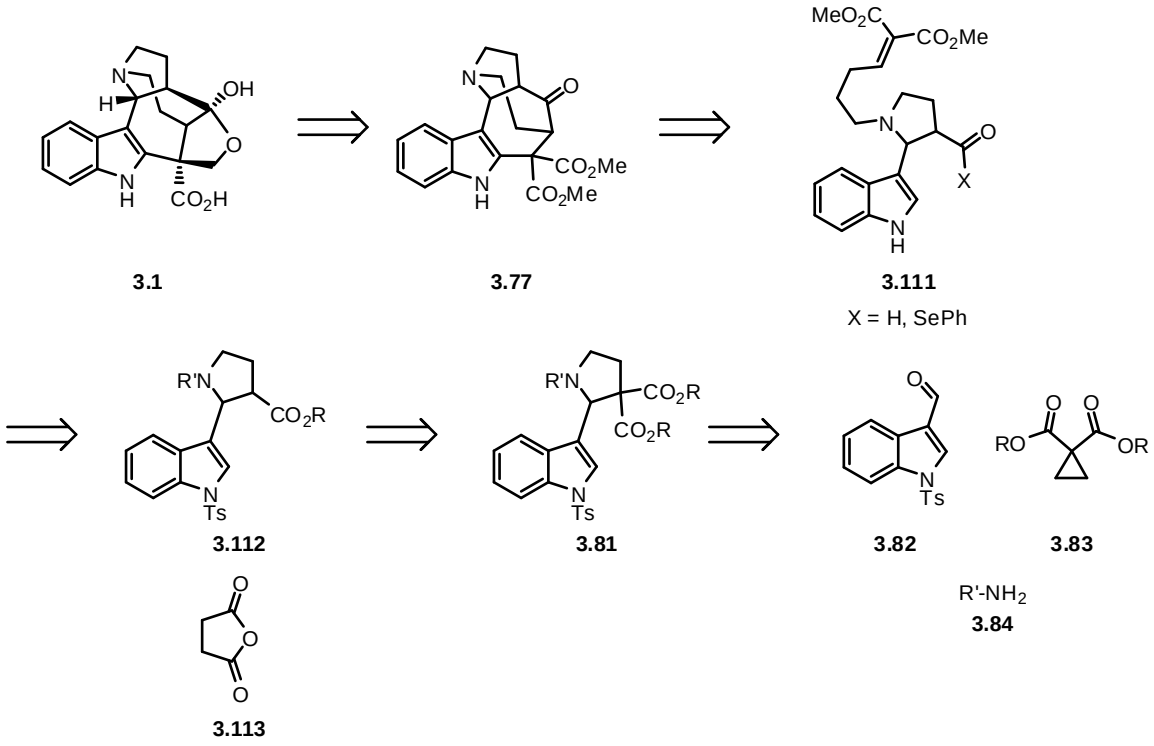
Scheme 3.24 Stetter Reaction Attempt

However, having synthesized both **3.105** and **3.107**, we thought that maybe the acyl radical addition could also be possible into either of them. Knowing that we could form carboxylic acid **3.99** and also having the knowledge that we could manipulate this acid a variety of ways, we envisioned generating a selenoester, which could undergo an acyl radical addition into acceptor **3.105**. We attempted to convert carboxylic acid **3.99** to the corresponding selenoester **3.110**; however under a variety of different conditions the selenoester was never detected and only decomposition was observed (Scheme 3.25).



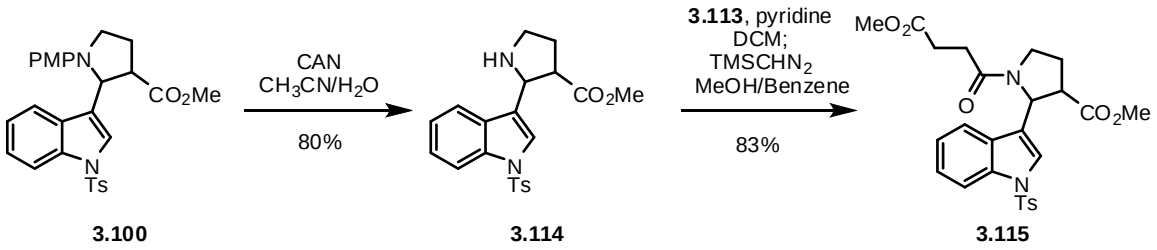
Scheme 3.25 Attempted Synthesis of Selenoester **3.110**

Having run into these difficulties with our intermolecular proposal, we believed that we could synthesize a precursor for an intramolecular addition, similar to what we had originally proposed. By adding the acceptor group to the pyrrolidine after deprotection would give **3.111**, which would now be prepared for the intramolecular addition. The previous steps in the synthesis would remain the same (Scheme 3.26).



Scheme 3.26 Second Generation Retrosynthetic Plan

Taking monoester-pyrrolidine **3.100**, we removed the PMP protecting group using ceric ammonium nitrate (CAN)[25] to provide **3.114** in an 80% yield (Scheme 3.27). Having **3.114** in hand, we attempted to acylate the nitrogen using acryloyl chloride, but no product was observed. We also attempted a reductive amination using octanal (to determine the potential for the reaction), but once again no product was detected. However, when attempting the acylation with succinic anhydride, we obtained our desired acylated product. Due to purification issues, we converted the acid to the methyl ester using TMS-diazomethane and obtained the diester product **3.115** in an 83 % yield. Due to time constraints, this is where the forward progress for this project ended.



Scheme 3.26 Pyrrolidine Acylation

Section 3.7 Summary and Future Work

In summary, we have developed a route to an advanced synthetic intermediate on the pathway toward the synthesis of Actinophyllic acid. We further developed the three component pyrrolidine reaction and taken advantage of the requirement of an aniline derived amine for reactivity with cyclopropane **3.83**. The removal of one of the ester groups has been completed efficiently and the conversion of the remaining carbonyl functionality to an aldehyde has been completed. The removal of the PMP protecting group and acylation with succinic anhydride has allowed for the investigation of an intramolecular variant for the forward synthesis. Future work for this project would be converting the remaining ester on **3.98** to selenoester **3.110** and determining if an intermolecular acyl radical addition would be possible. Also, taking the diester **3.115** and homologating the amide chain, would allow access to an intramolecular variant of either the Stetter reaction or acyl radical addition.

Section 3.8 Experimental

General

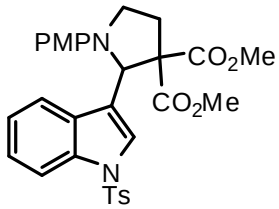
Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. ^{1}H, and ^{13}C NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra

(HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Toluene, tetrahydrofuran (THF), ether, acetonitrile (MeCN) and dichloromethane (DCM) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Alfa Aesar, or Caledon. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F_{254}) visualizing with UV light, and the plates developed using acidic anisaldehyde. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh). High-pressure reactions were carried out on a LECO^{TM} Tempres High-Pressure chemical reactor. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor.

Procedure for Pyrrolidine Ring Formation

The procedure is adapted from the literature.[22]

N-tosylindole-3-carboxaldehyde **3.82** and *p*-anisidine **3.95** were dissolved in dry toluene and stirred over activated 4 Å molecular sieves for 1 h. The imine solution was then transferred to a microwave vial, then $YbOTf_3$ (20 mol %) and cyclopropane **3.86** were added, and the mixture was heated to 140˚C for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered and the solvent was removed. The crude residue was purified by flash column chromatography (elution with EtOAc/hexanes mixtures).



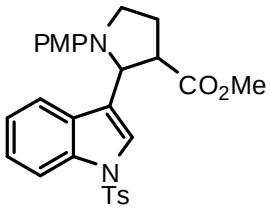
Reagents employed: **3.82** (0.379 g, 1.26 mmol); **3.96** (0.156 g, 1.27 mmol); $YbOTf_3$ (0.078 g, 0.126 mmol); **3.87** (0.100 g, 0.632 mmol); Toluene (3 mL); Yielded **3.98** as a yellowish foam, 86% (0.307 g, 0.546 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91-7.87 (m, 1H), 7.67-7.63 (m, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.40 (s, 1H), 7.30-7.20 (m, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.68-6.63 and 6.38-6.33 (m, AA'BB', 4H), 5.67 (s, 1H),

3.81 (t, J = 7.8 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.30-3.21 (m, 1H), 3.07-2.97 (m, 1H), 2.89 (s, 3H), 2.58 (dd, J = 12.1, 5.1 Hz, 1H), 2.31 (s, 3H).

Procedure of the Conversion of 3.98 to 3.100

The procedure was adapted from the literature.[24]

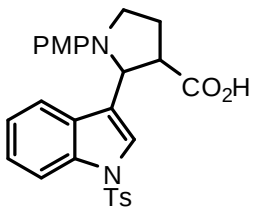
To a solution of diester in wet DMSO was added NaCN. The reaction mixture was then heated to 140℃ under microwave irradiation for 3 h. The reaction was poured into water and extracted three times with Et_2O. The combined extracts were then washed twice with water, once with brine and dried over $MgSO_4$. The aqueous layer was then acidified and re-extracted with Et_2O three times. The combined extracts were then washed once with brine and concentrated. The resultant mixture was found to contain the dealkoxycarbonylated mono-acid product. This acid was then dissolved in benzene and methanol (2:1) and treated with 2.0 M solution of $TMSCHN_2$ to reform the required methyl ester. The solution was then concentrated and then purified via flash column chromatography (elution with EtOAc/hexanes mixtures).



Reagents employed: **3.98** (0.059 g, 0.105 mmol); NaCN (0.026 g, 0.531 mmol); DMSO (3 mL); $TMSCHN_2$ (0.105 mL, 0.210 mmol); Yielded **3.100** as an orange oil, 86% (0.046 g, 0.091 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.58-7.55 and 7.16-7.13 (m, AA'BB', 4H), 7.36-7.32 (m, 1H), 7.31 (s, 1H), 7.29-7.27 (m, 1H), 6.73-6.70 and 6.44-6.41 (m, AA'BB', 4H), 5.13 (s, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 3.74-3.70 (m, 1H), 3.50-3.45 (m, 1H), 3.15-3.13 (m, 1H), 2.47-2.40 (m, 1H), 2.34 (s, 3H), 2.30-2.23 (m, 1H).

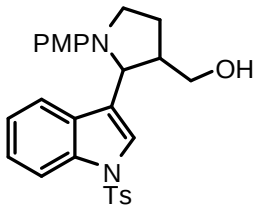
Procedure for the conversion of 3.96 to 3.99

To a solution of diester in wet DMSO was added NaCN. The reaction mixture was then heated to 140℃ under microwave irradiation for 3 h. The reaction was poured into water and extracted three times with Et_2O. The combined extracts were then washed twice with water, once with brine and dried over $MgSO_4$. The aqueous layer was then acidified and re-extracted with Et_2O three times. The comined extracts were then washed once with brine and concentrated. The resultant mixture was found to contain the dealkoxycarbonylated mono-acid product.



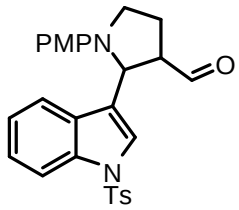
Reagents employed: **3.98** (0.270 g, 0.480 mmol); NaCN (0.118 g, 2.41 mmol); DMSO (3 mL); Crude acid taken forward for the reduction to primary alcohol.

A solution of crude acid in THF was added slowly to a cooled solution (0˚C) of $BH_3{\cdot}SMe_2$ and $B(OMe)_3$ in THF. The reaction mixture was stirred overnight and quenched with methanol. The solvent was removed and the crude primary alcohol residue was carried forward for oxidation.



Reagents employed: **3.99** (0.235 g, 0.479 mmol); $BH_3{\cdot}SMe_2$ (0.062 g, 0.816 mmol); $B(OMe)_3$ (0.084 g, 0.808 mmol); THF (5 mL); The crude alcohol was carried forward to the next step.

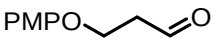
To a solution of oxalyl chloride in DCM at -78˚C was slowly added a solution of DMSO in DCM. After stirring for 10 mins, a solution of alcohol in DMC was added and stirred for 30 mins. NEt_3 was then added and after 10 mins the reaction was warmed to 0˚C and a 1:10 H_2O:DCM mixture was added. The aqueous layer was extracted three times with DCM, the combined organic layers were washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$ and concentrated. The residue was then purified via flash column chromatography (elution of EtOAc/hexanes mixtures).



Reagents employed: alcohol (0.229 g, 0.480 mmol); oxalyl chloride (0.167 mL, 1.91 mmol); DMSO (0.272 mL, 3.84 mmol); NEt_3 (0.668 mL, 4.79 mmol); DCM (10 mL); Yielded **3.101** as a yellow oil, 60% over the three steps (0.135 g, 0.284 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): (mixture of diastereomers) δ = 9.85 (s, 1H), 9.82 (s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.59-7.55 (m, 3H), 7.52-7.48 (m, 3H), 7.36-7.32 (m, 2H), 7.28-7.23 (m, 2H), 7.20-7.16 (m, 1H), 7.16-7.13 (m, 2H), 7.08 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 2.9 Hz, 1H), 6.74-6.71 and 6.47-6.44 (m, AA'BB', 4H), 6.53 (dd, J = 8.8, 2.9 Hz, 1H), 5.23 (s, 1H), 5.20 (d, J = 7.0 Hz, 1H), 4.01-3.97 (m, 1H), 3.75 (s, 3H), 3.74-3.70 (m, 2H), 3.69 (s, 3H), 3.51-3.47 (m, AB, 1H), 3.30-3.22 (m, 2H), 3.08 (br d, J = 7.6 Hz, 1H), 2.90-2.86 (m, AB, 1H), 2.45-2.40 (m, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 2.28-2.23 (m, 1H).

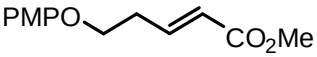
Procedure for the oxidation of alcohol 3.102 to aldehyde 3.103

The alcohol was dissolved in EtOAc and IBX was added to the solution. The reaction was heated to reflux (77˚C) for 3 h. The reaction mixture was then filtered through Celite and the solvent was removed. The crude residue was pure enough to carry forward.

 Reagents employed: **3.102** (0.210 g, 1.15 mmol); IBX (0.644 g, 2.30 mmol); EtOAc (4 mL); Yielded **3.103** as a colourless oil, 90% (0.178 g, 0.988 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.87 (t, J = 1.6 Hz, 1H), 6.85-6.84 (m, AA'BB', 4H), 4.27 (t, J = 6.3 Hz, 2H), 3.77 (s, 3H), 2.88 (dt, J = 6.3, 1.6 Hz, 2H).

Procedure for the Horner-Wadsworth-Emmons homologation of 3.101

NaH was added portionwise to a solution of phosphonate in THF at 0˚C. The solution was stirred for 30 mins, until the evolution of H_2 ceased. The aldehyde was dissolved in DCM and added dropwise to the reaction mixture. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the reaction was quenched with water. EtOAc was added at the layers were separated. The aqueous layer was extracted three times with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. The crude residue was then purified by flash column chromatography (elution with EtOAc/hexanes mixtures).

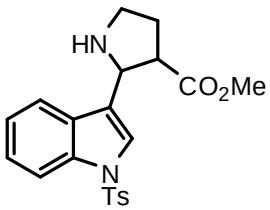
 Reagents employed: **3.103** (0.819 g, 4.54 mmol); **3.106** (1.00 mL, 6.82 mmol); NaH (0.303 g, 7.58 mmol); THF (10 mL); DCM (1 mL); Yielded **3.107** as a yellow oil, 50% (0.537 g, 2.27 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.05 (dt, J = 15.6, 7.0 Hz, 1H), 6.83 (s, 4H), 5.96 (dt, J = 15.6, 1.6 Hz, 1H), 4.03 (t, J = 6.2 Hz, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 2.65 (ddt, J = 7.0, 6.2, 1.6 Hz, 2H).

Procedure for the removal of the PMP protecting group

The procedure was following a literature procedure.[25]

A solution of PMP protected amine in acetonitrile was cooled to 0˚C and ceric ammonium nitrate in water was added dropwise. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the solution was diluted with EtOAc and the

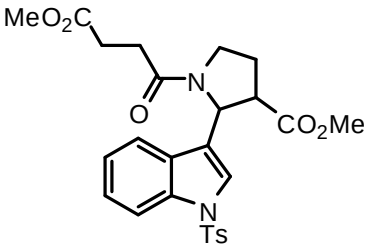
layers were separated. The organic was washed with water, brine and then dried over $MgSO_4$. The crude residue was purified by flash column chromatography (elution of EtOAc/hexanes mixtures).



Reagents employed: **3.100** (0.068 g, 0.135 mmol); ceric ammonium nitrate (0.223 g, 0.407 mmol); acetonitrile (4 mL); water (1 mL); Yielded **3.114** as a yellow oil, 80% (0.043 g, 0.108 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.2 Hz, 1H), 7.76-7.73 and 7.21-7.18 (m, AA'BB', 4H), 7.60 (d, J = 8.2 Hz, 1H), 7.56 (s, 1H), 7.32-7.28 (m, 1H), 7.23-7.21 (m, 1H), 6.63 (s, 1H), 4.64 (d, J = 6.4 Hz, 1H), 3.68 (s, 3H), 3.22-3.17 (m, 2H), 3.10-3.06 (m, 1H), 2.32 (s, 3H), 2.25-2.14 (m, 2H).

Procedure for the acylation of 3.109

Succinic anhydride was added to a solution of pyrrolidine in DCM. Pyridine was added to the solution and the reaction was heated to reflux (115˚C) overnight. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the solution was diluted with EtOAc, washed with aqueous $CuSO_4$ and the layers were separated. The organic layer was washed two more times with aqueous $CuSO_4$, once with brine and dried over $MgSO_4$. The residue was found to contain an acid, for ease of isolation the acid was converted to the methyl ester. This acid was then dissolved in benzene and methanol (2:1) and treated with 2.0 M solution of $TMSCHN_2$ to reform the required methyl ester. The solution was then concentrated and then purified via flash column chromatography (elution with EtOAc/hexanes mixtures, followed by 1% MeOH/DCM eluent).



Reagents employed: **3.114** (0.049 g, 0.123 mmol); **3.113** (0.025 g, 0.250 mmol); DCM (1 mL); pyridine (3 mL); $TMSCHN_2$ (0.123 mL, 0.246 mmol); Yielded **3.115** as a colourless oil, 83% (0.052 g, 0.101 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$): (mixture of rotomers) δ = 7.99 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.79-7.76 (m, 2H), 7.72-7.69 (m, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.38-7.35 (m, 2H), 7.30-7.25 (m, 3H), 7.24-7.18 (m, 4H), 5.69 (s, 1H), 5.53 (s, 1H), 3.97-3.92 (m, 1H), 3.85-3.79 (m, 1H), 3.78 (2s, 6H), 3.69 (s, 3H), 3.64 (s, 3H), 3.14-3.11 (m, 1H), 3.11-3.08 (m, 1H), 2.81-2.74 (m, 2H), 2.64-2.58 (m, 2H), 2.55-2.48 (m, 3H), 2.41-2.35 (m, 1H) 2.33 (s, 3H), 2.31 (s, 3H), 2.30-2.22 (m, 2H), 2.21-2.14 (m, 2H), 2.13-2.06 (m, 2H).

Section 3.9 References

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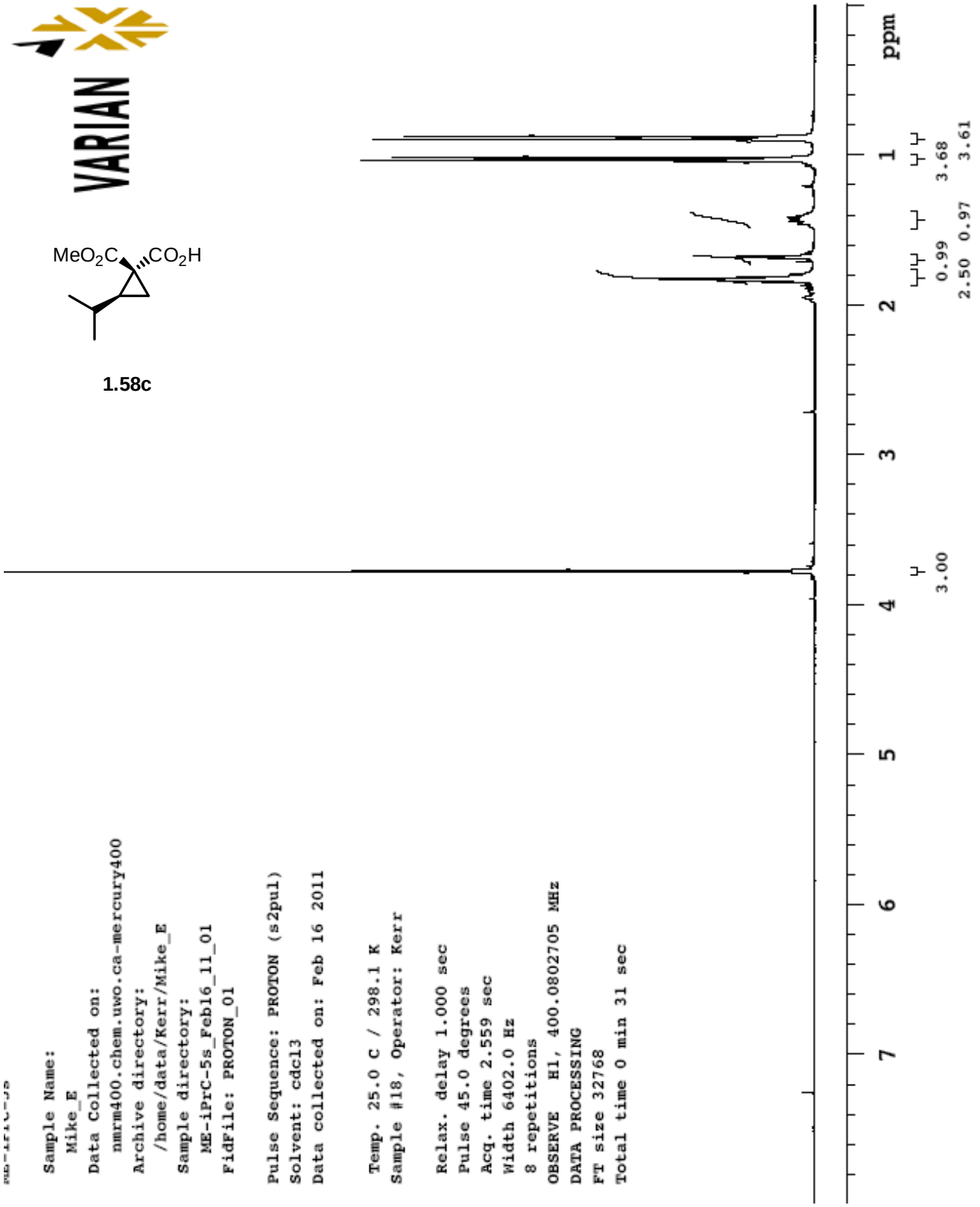
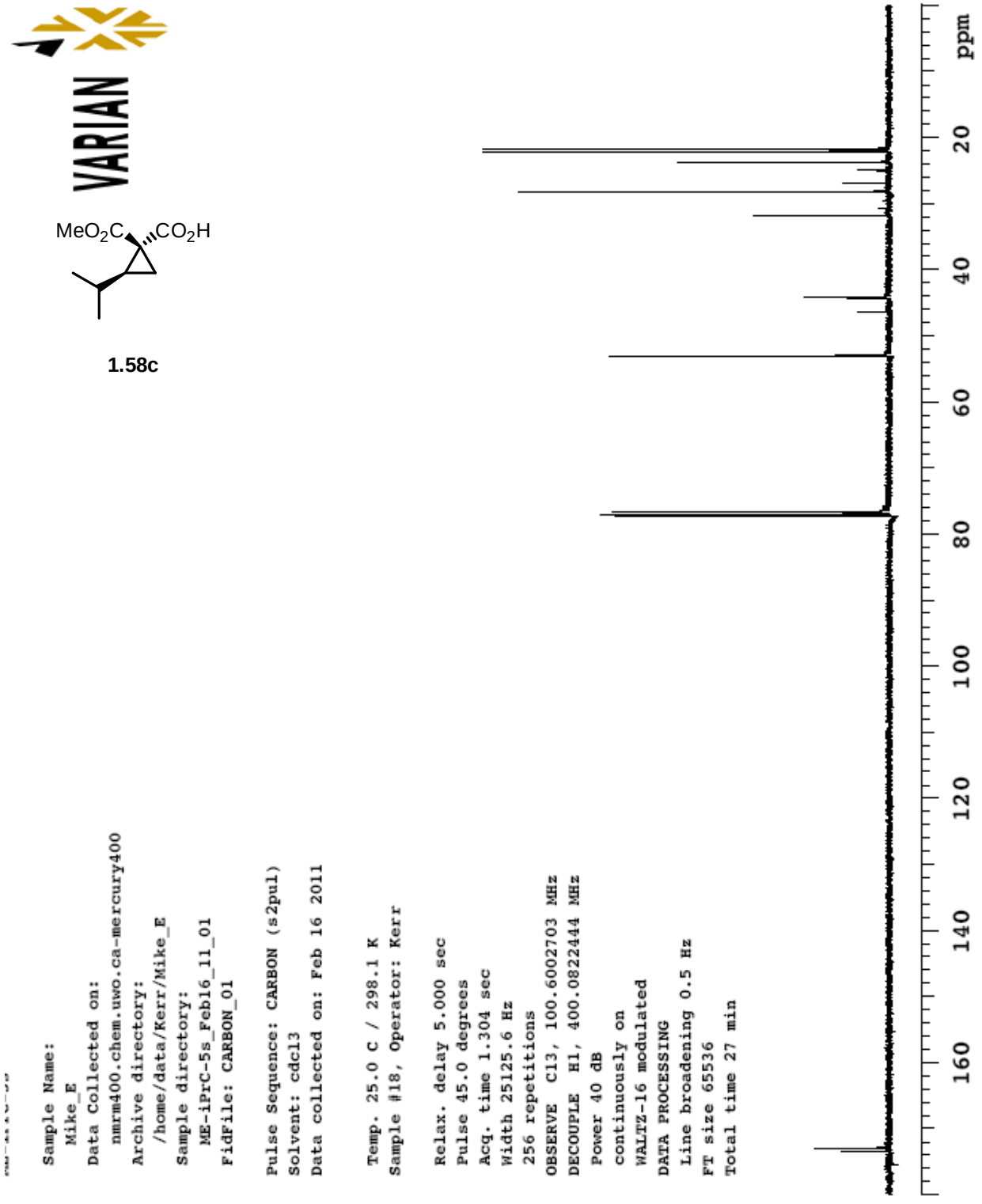
Appendix 1 – NMR Spectral Data for Chapter 1





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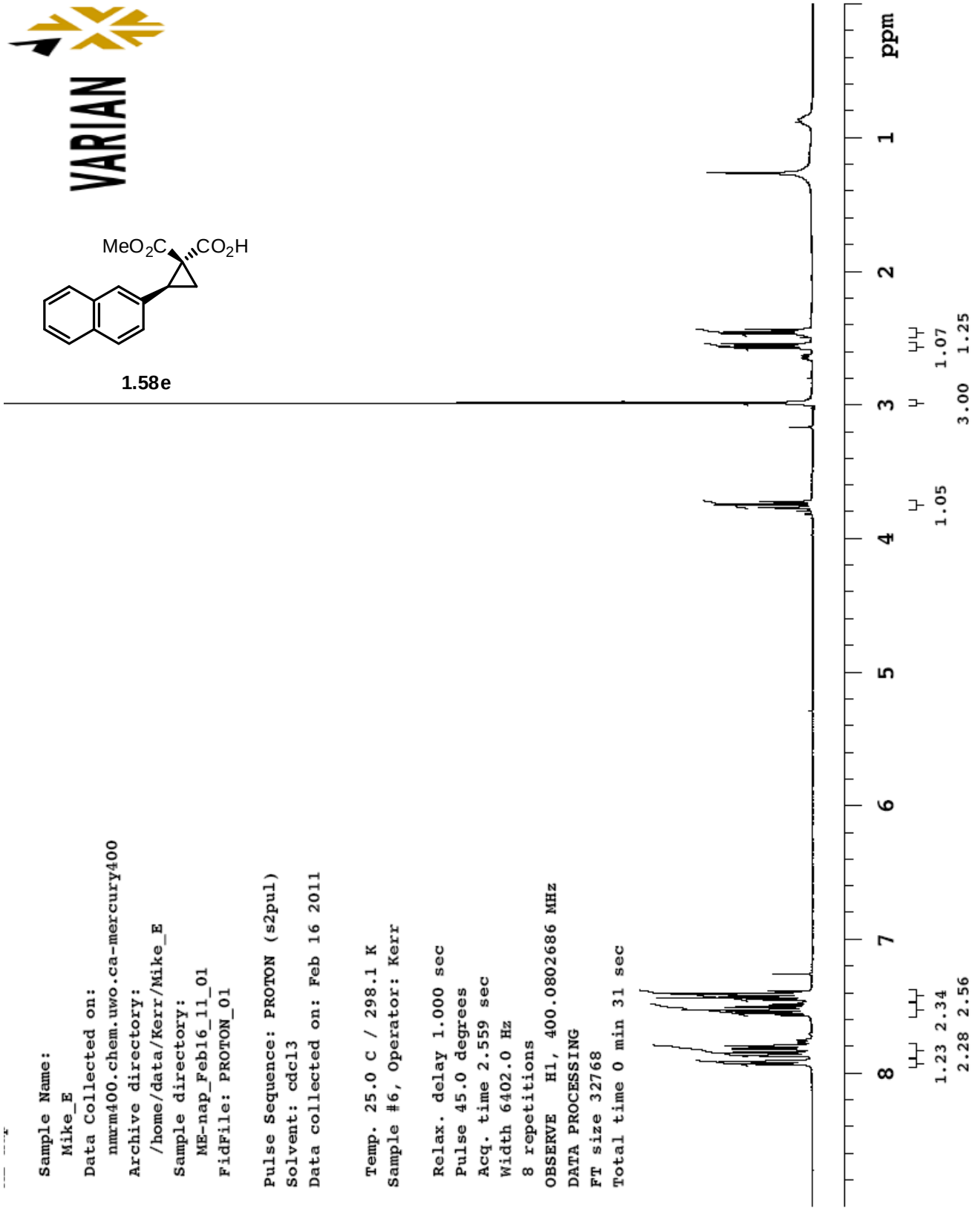

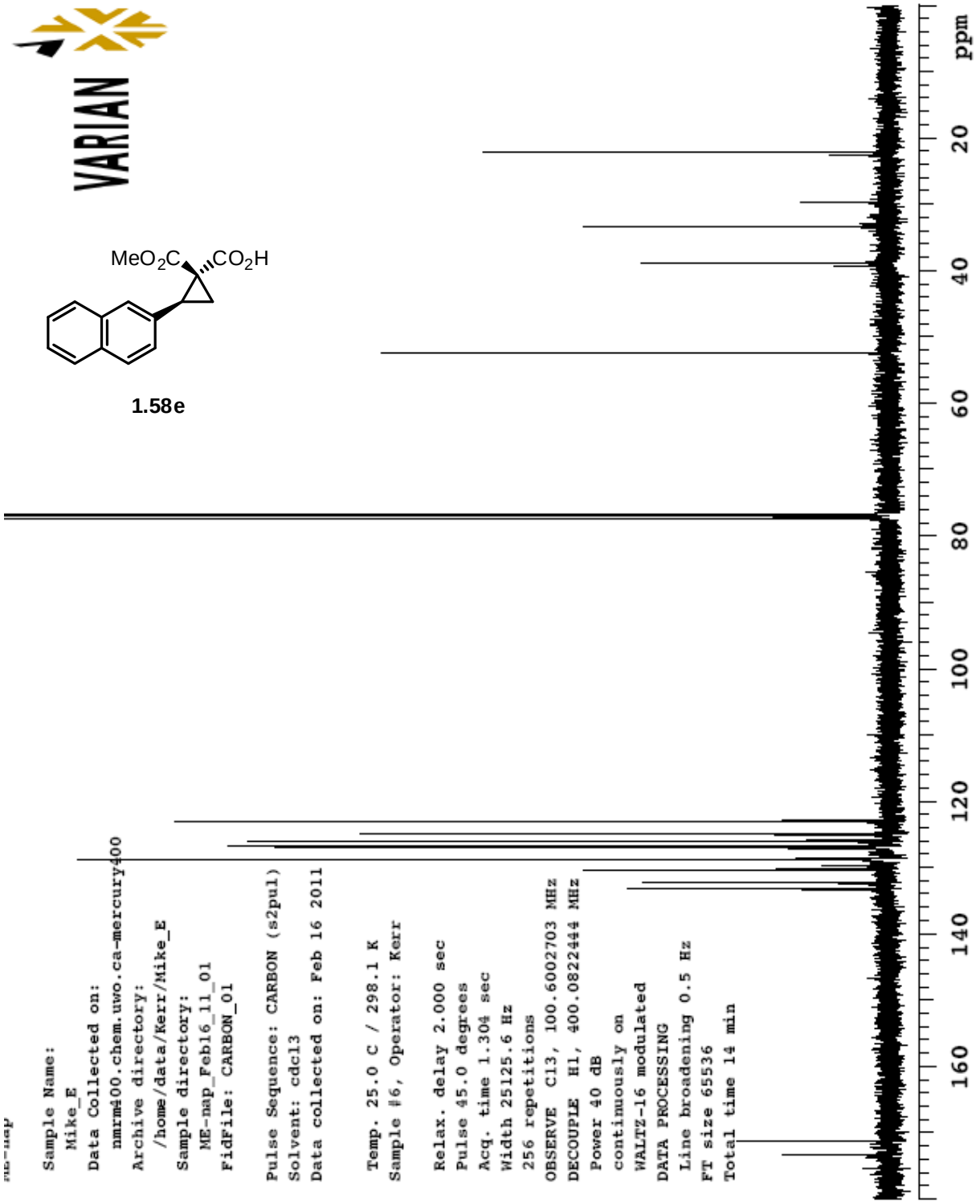

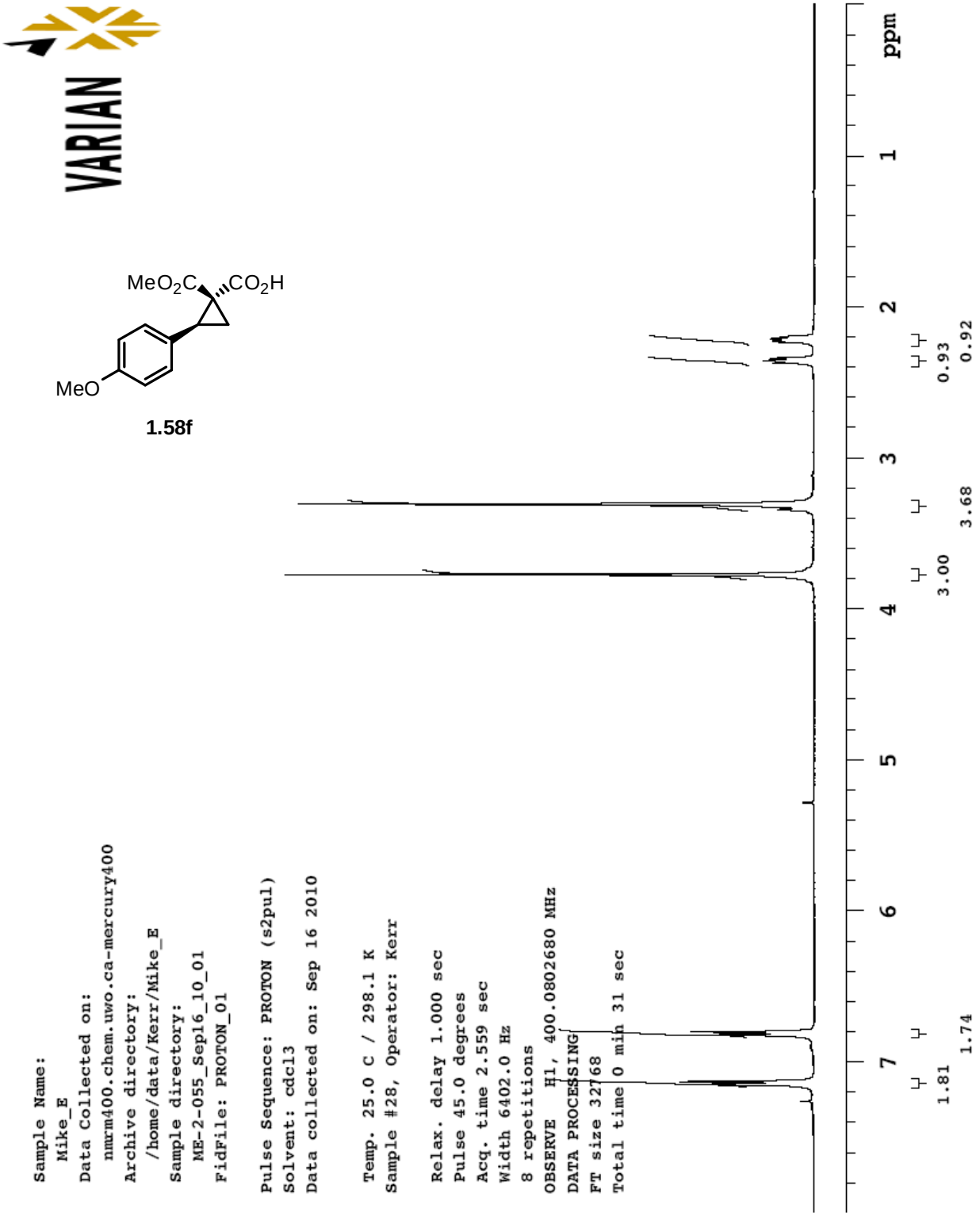

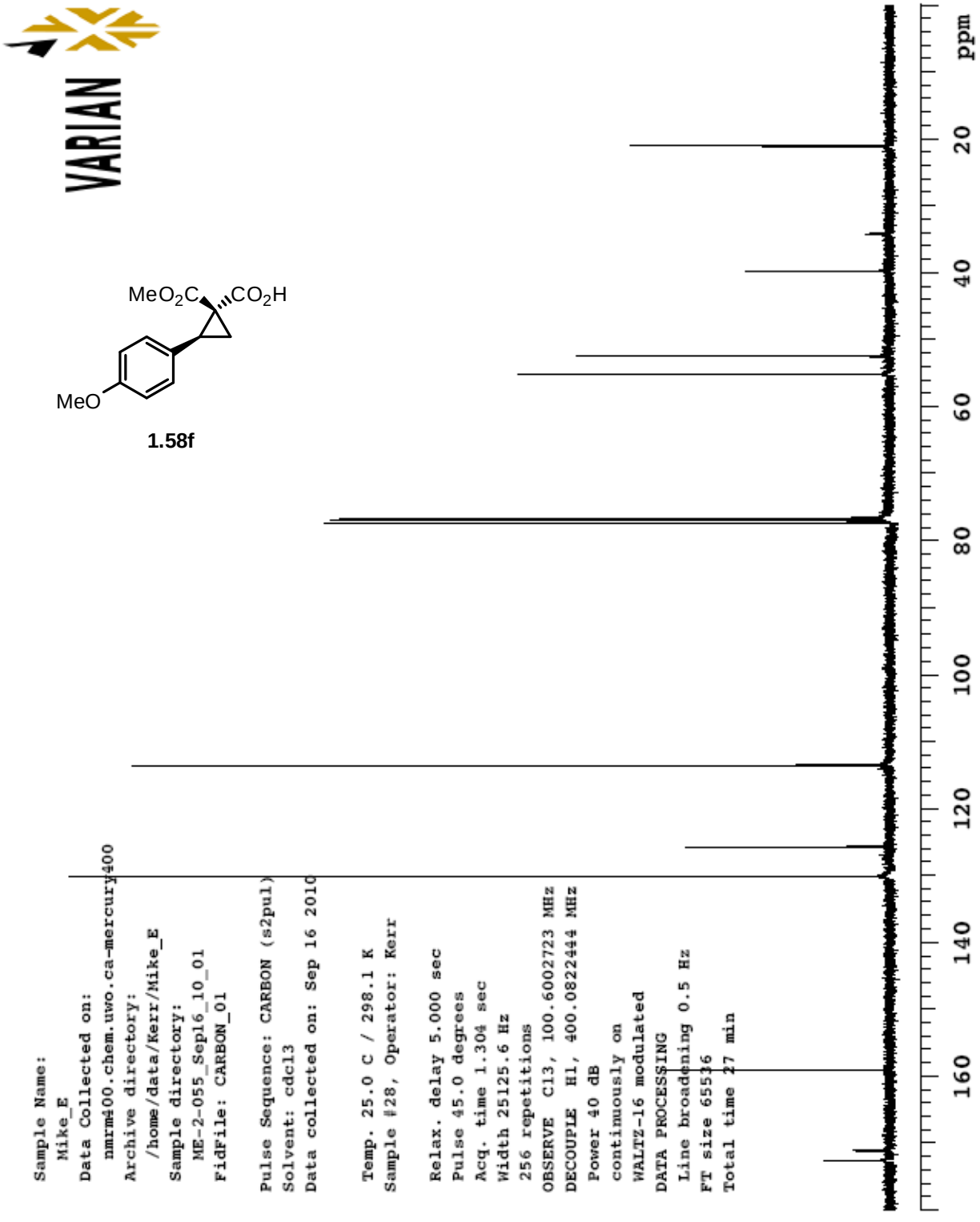

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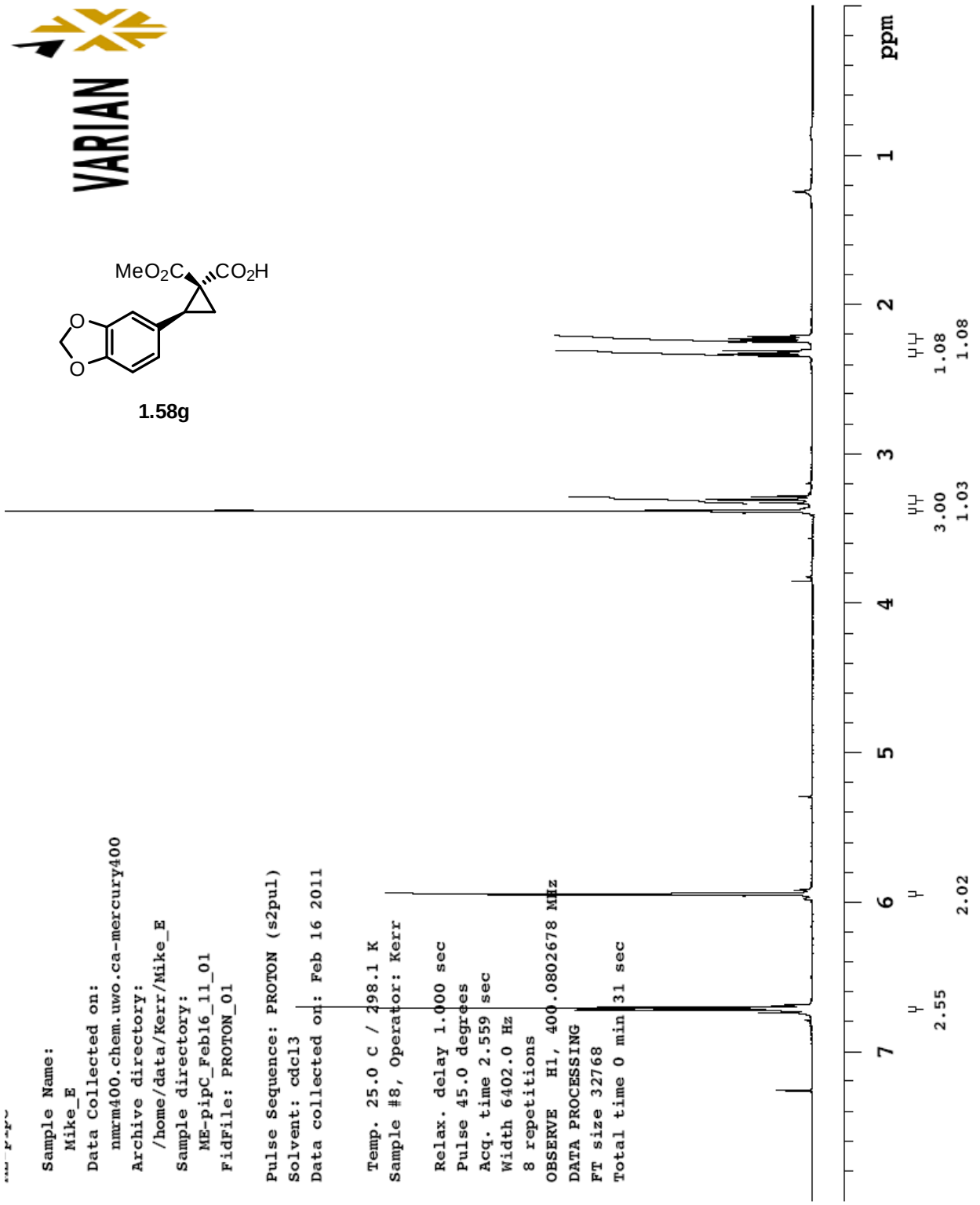

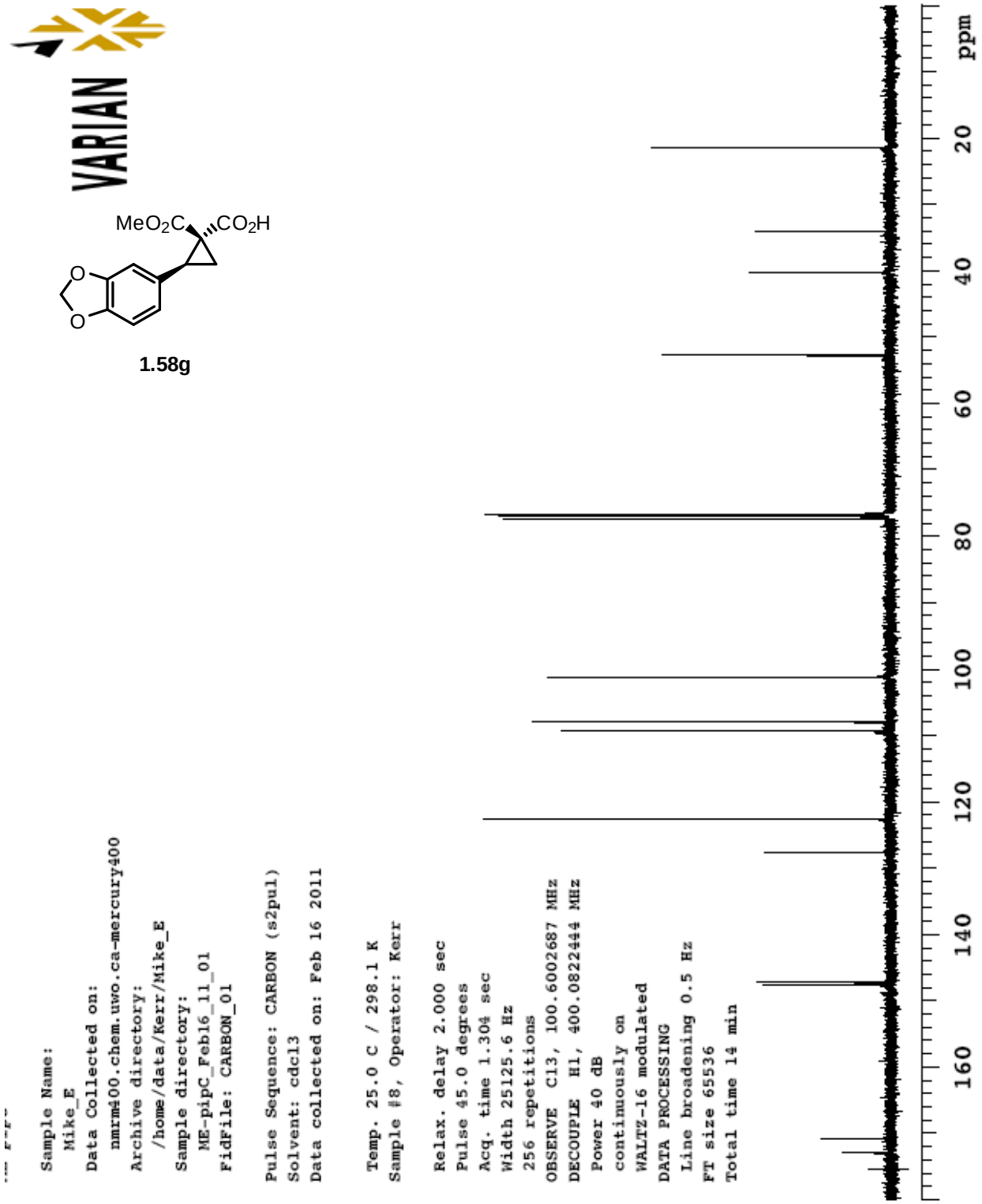

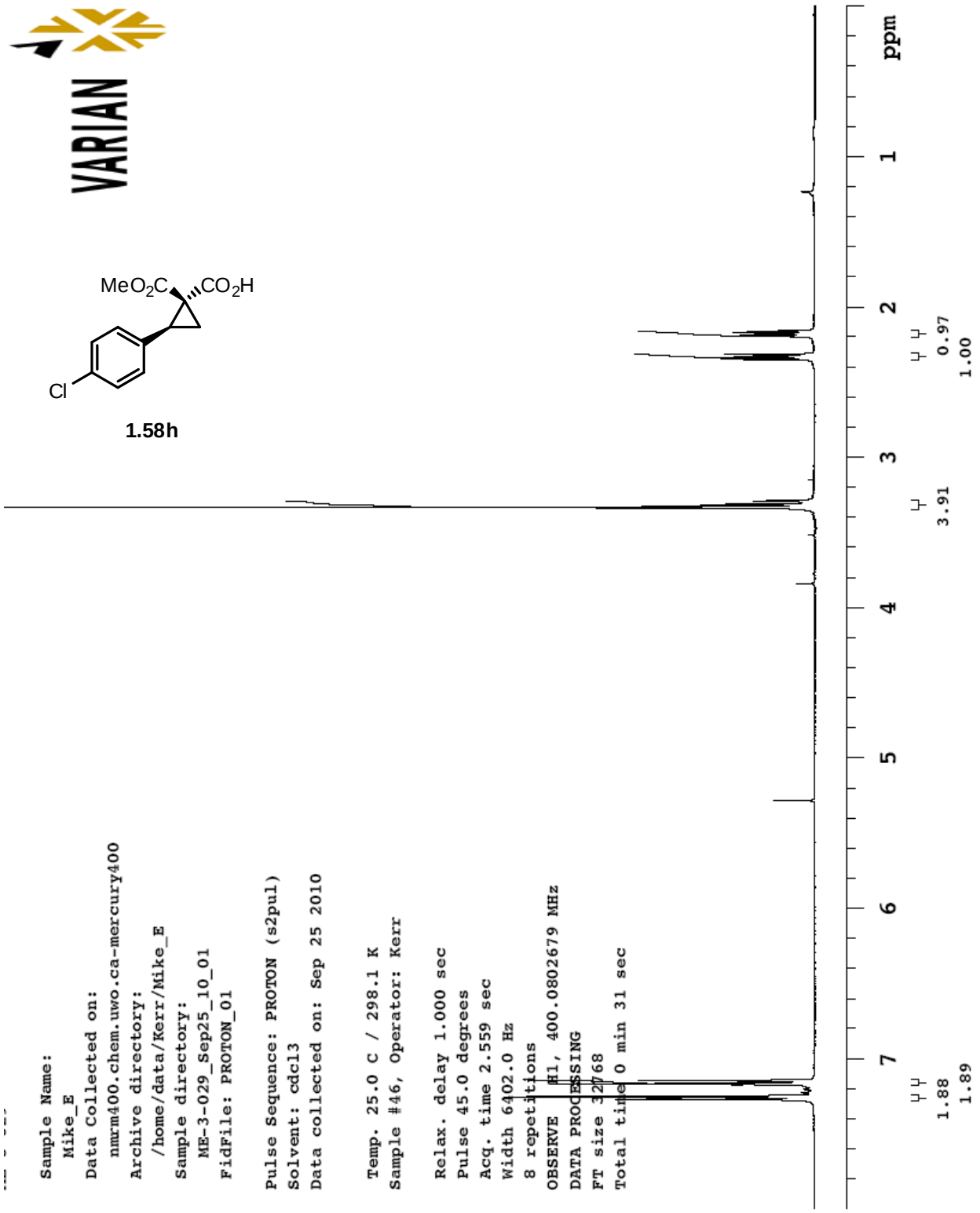

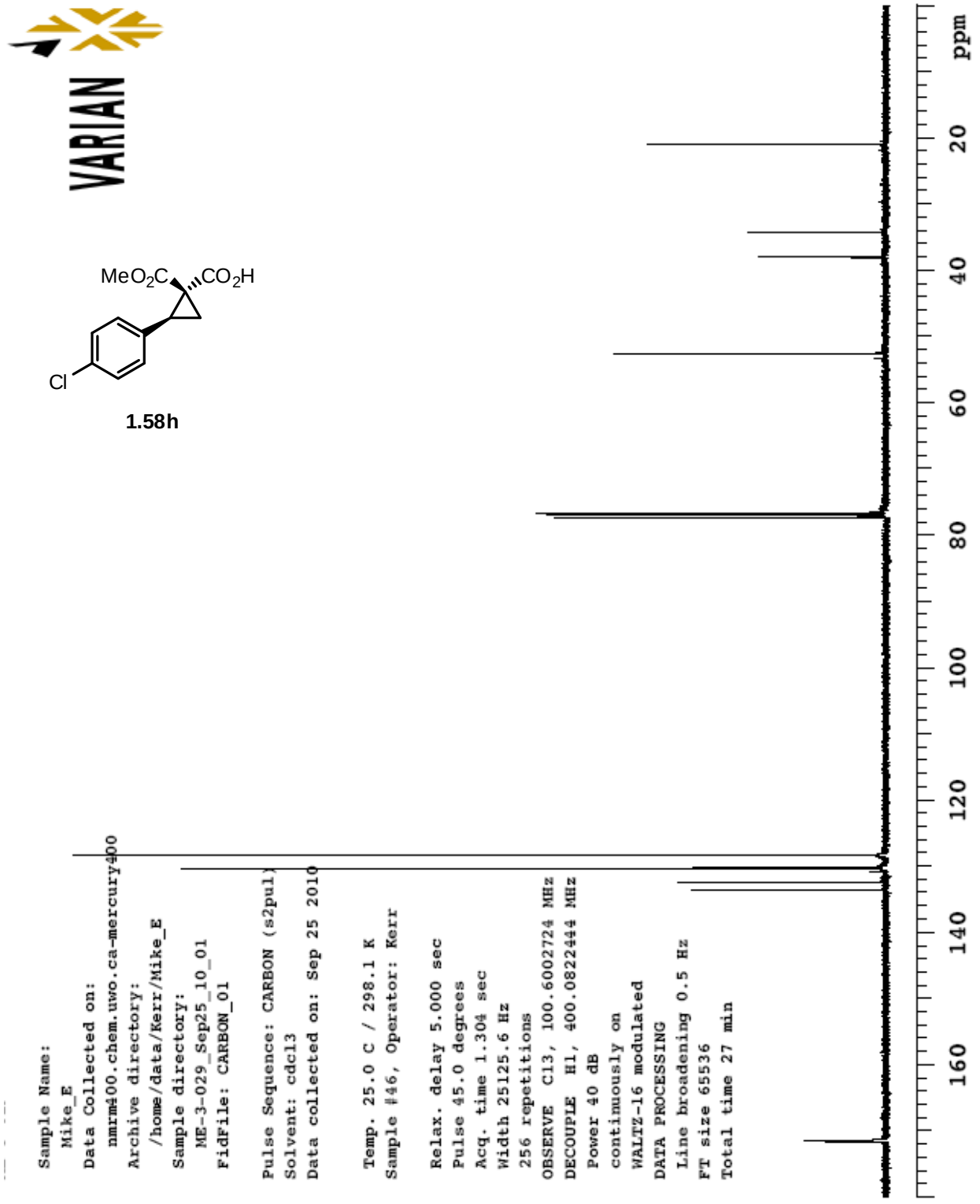

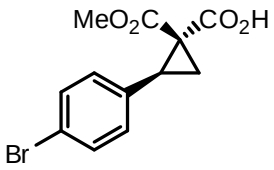

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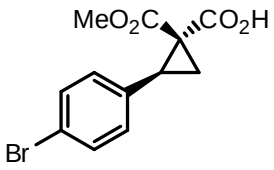

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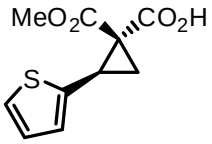

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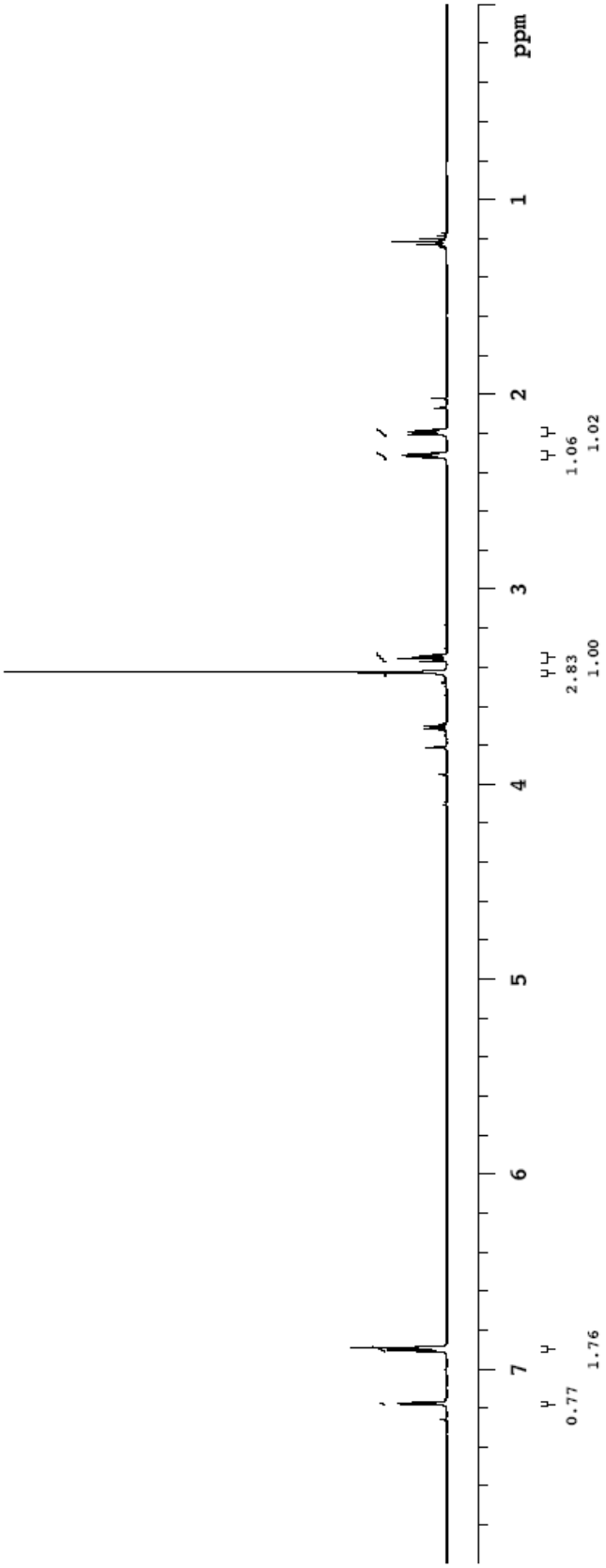

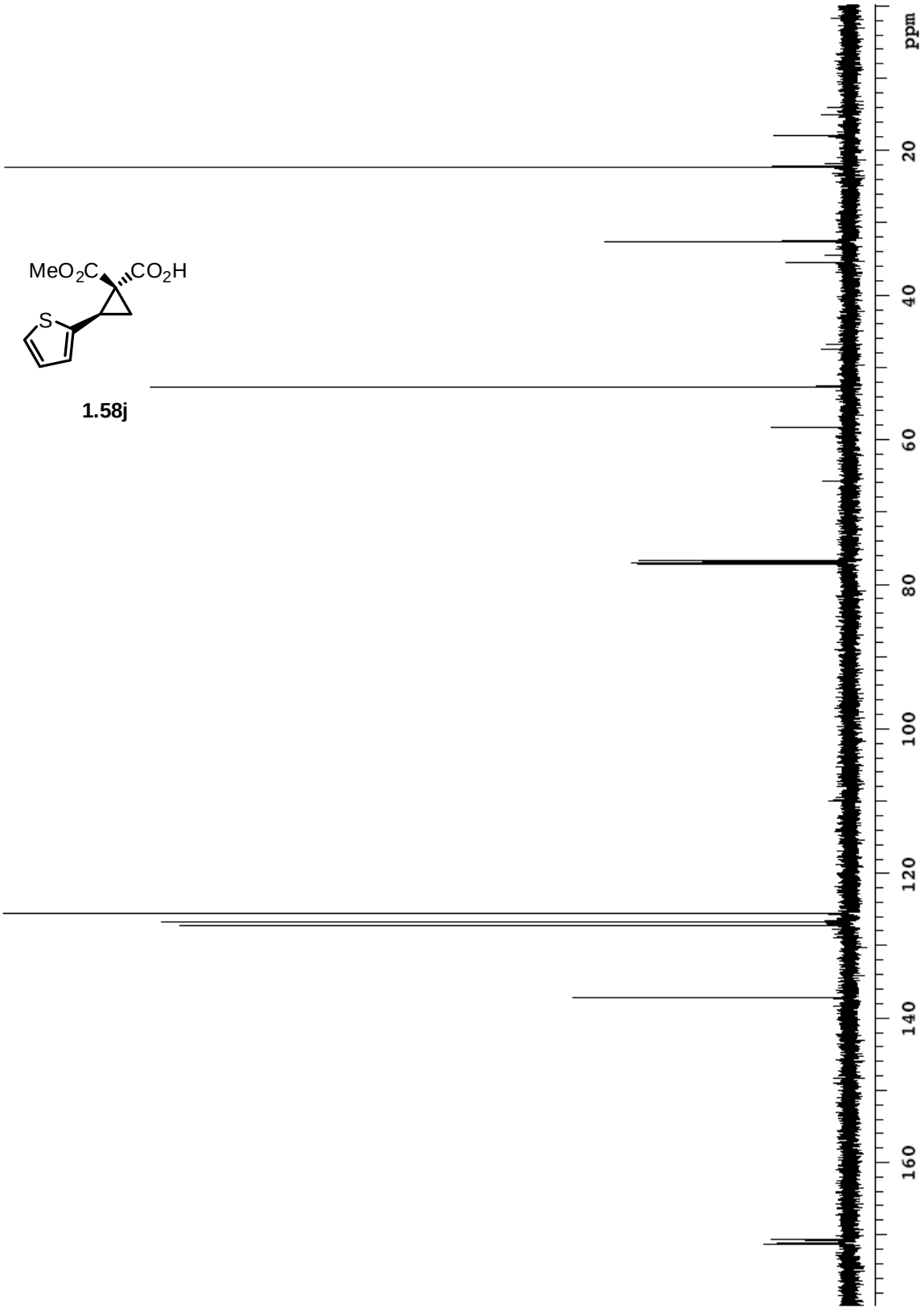

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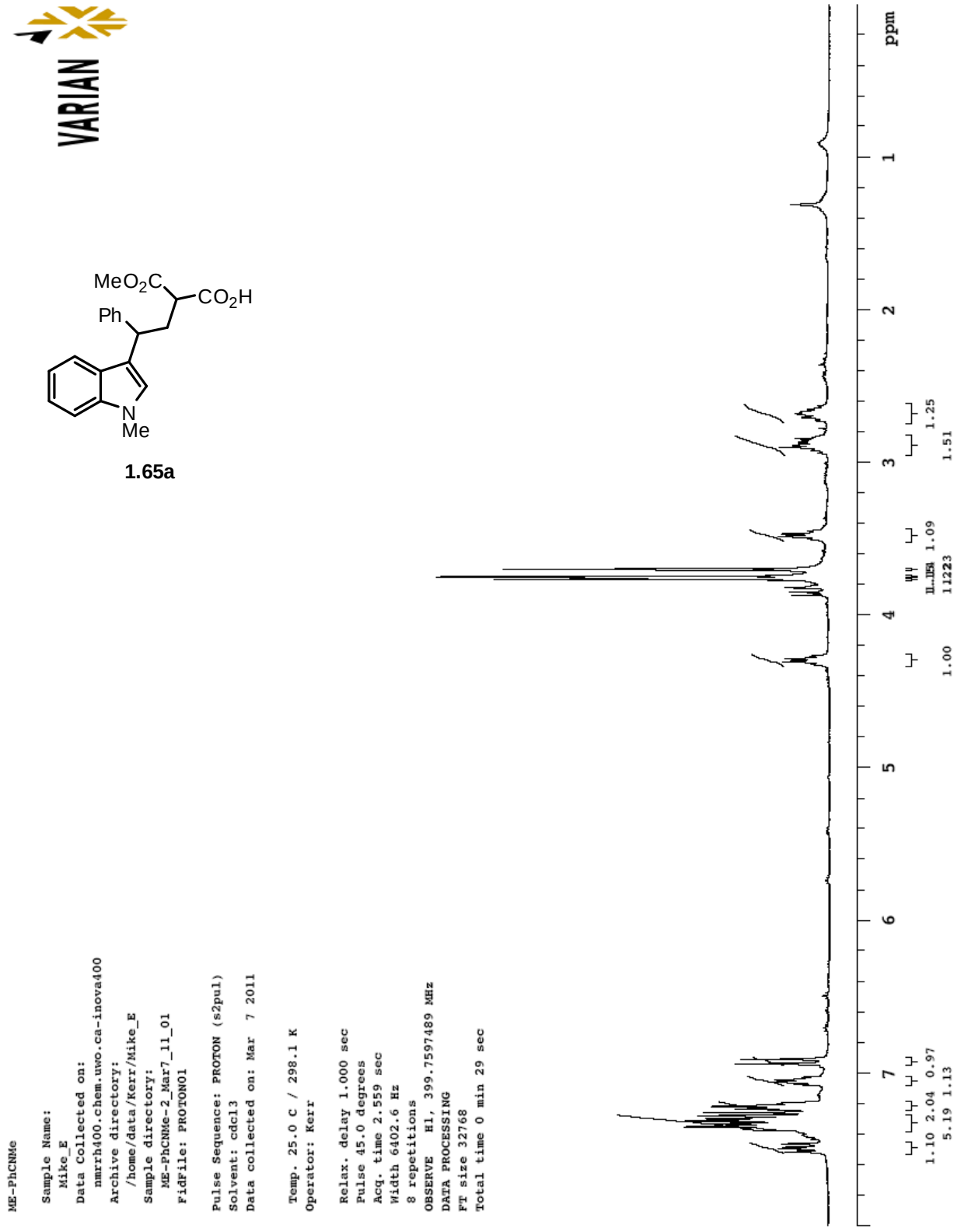

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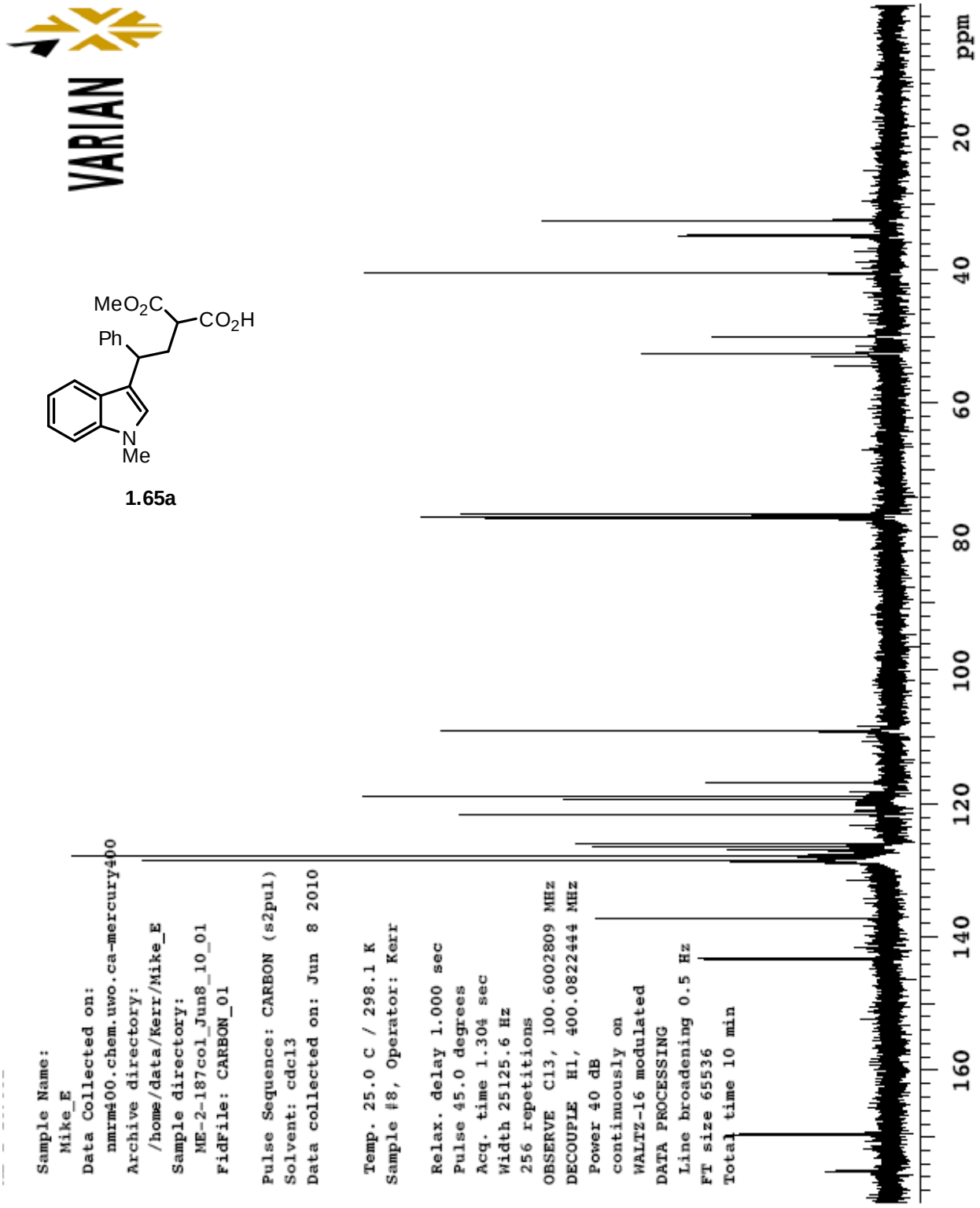

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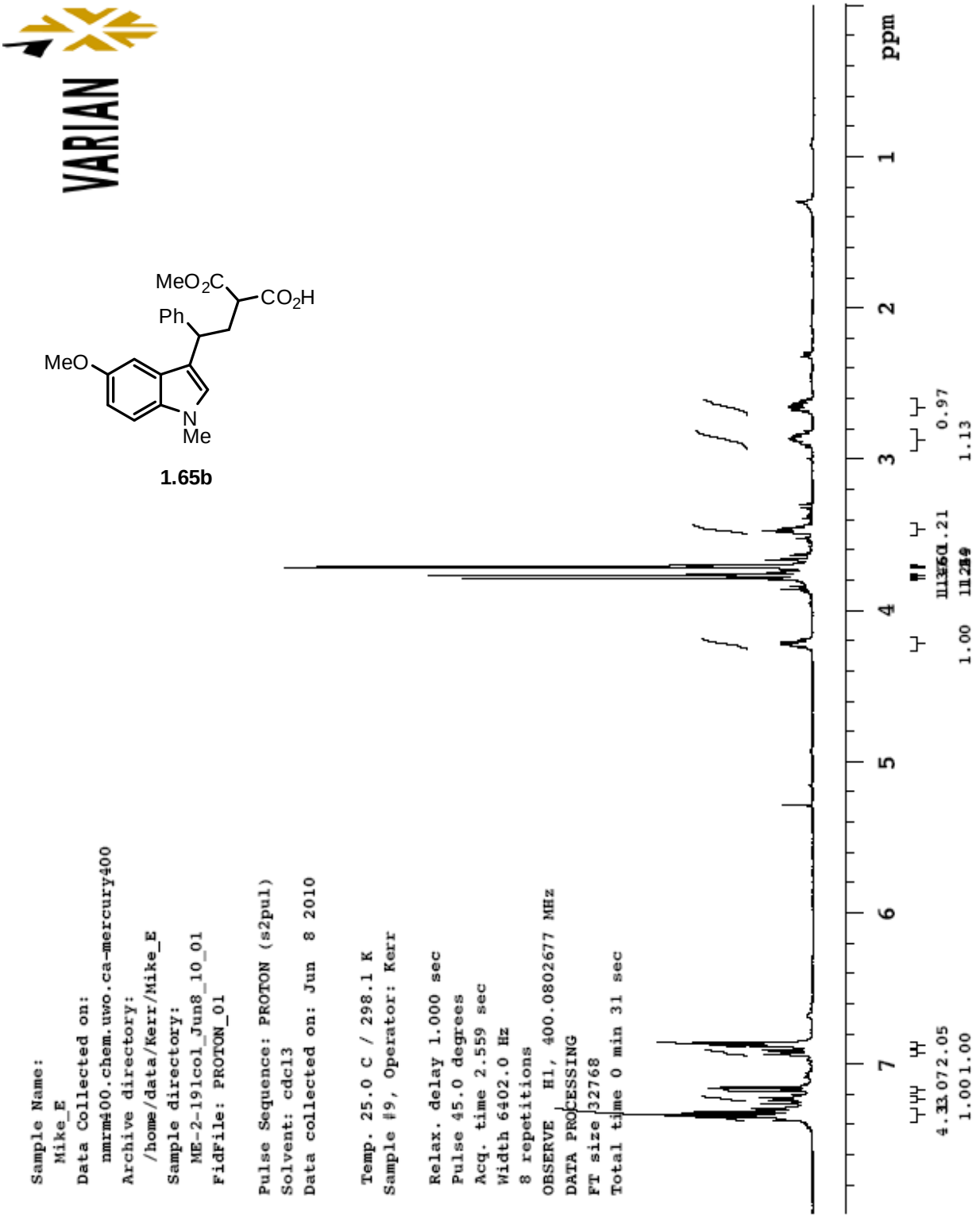

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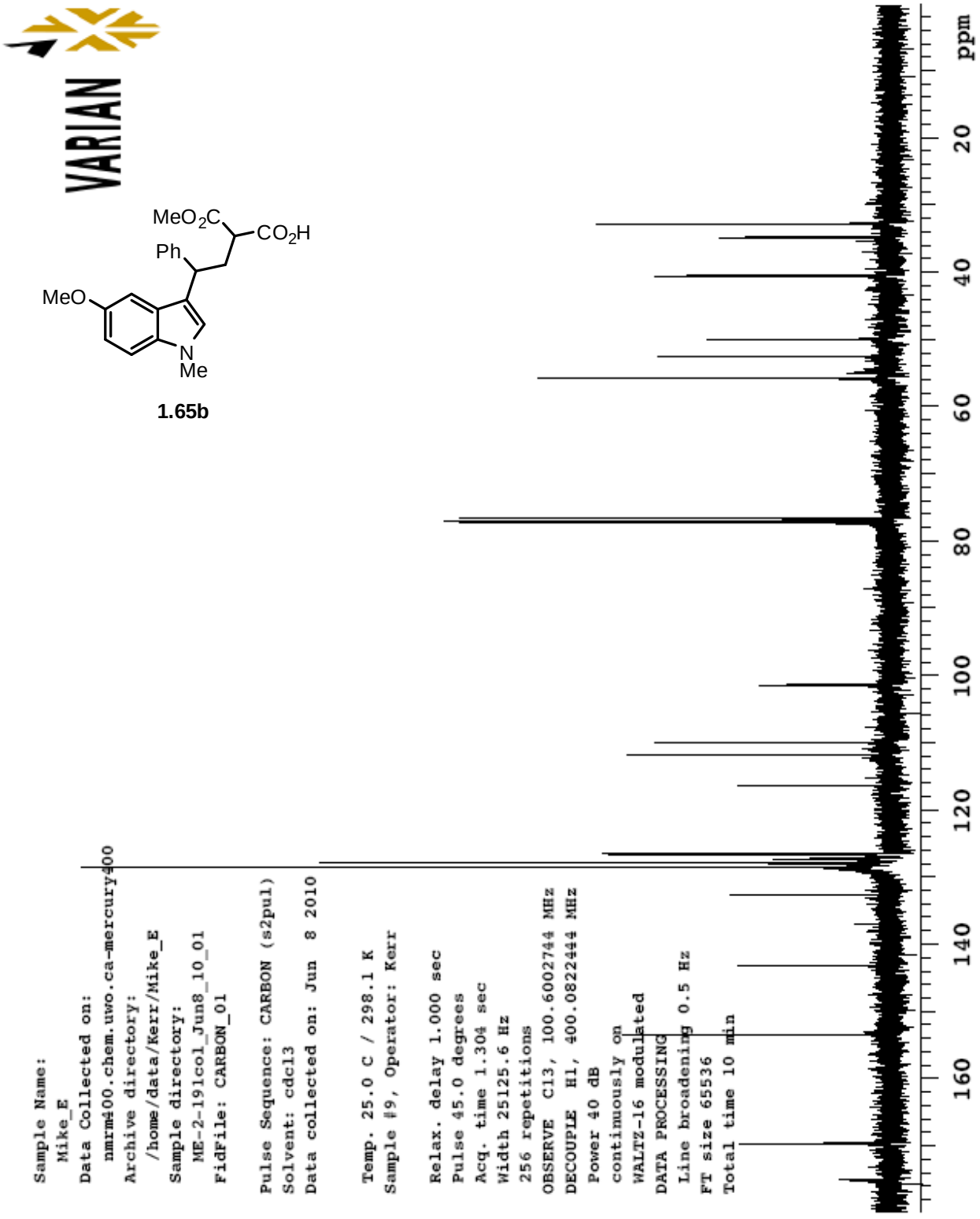

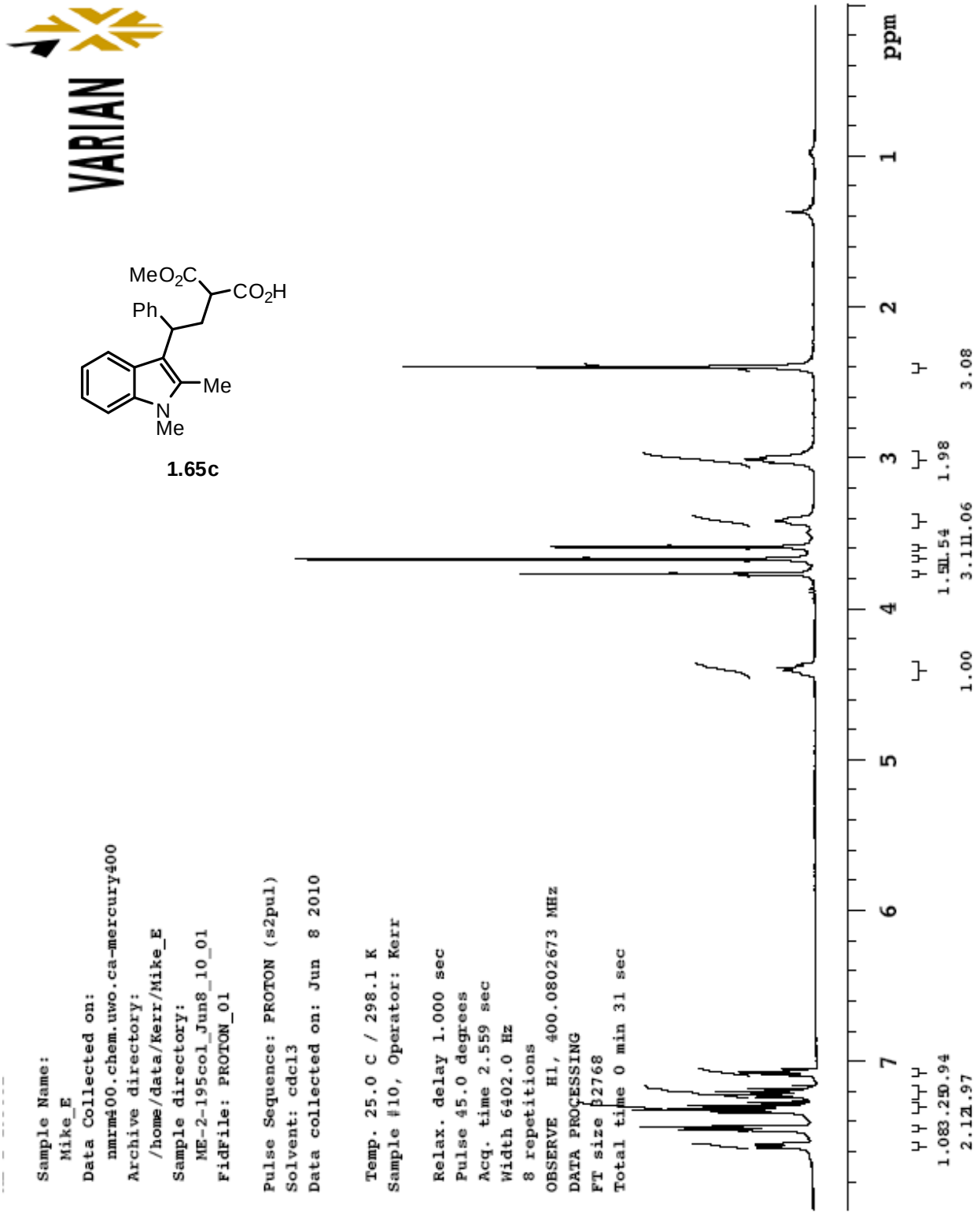

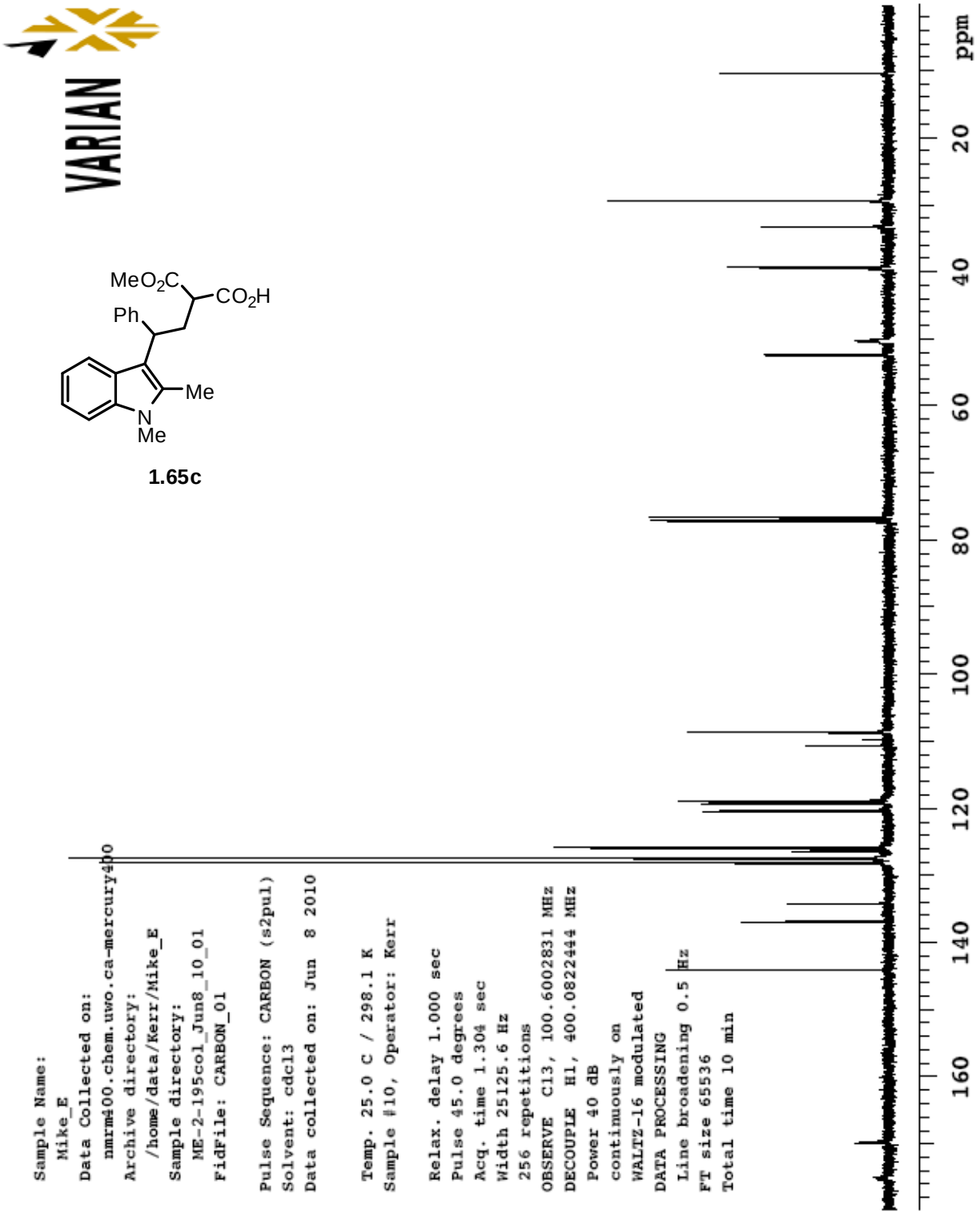

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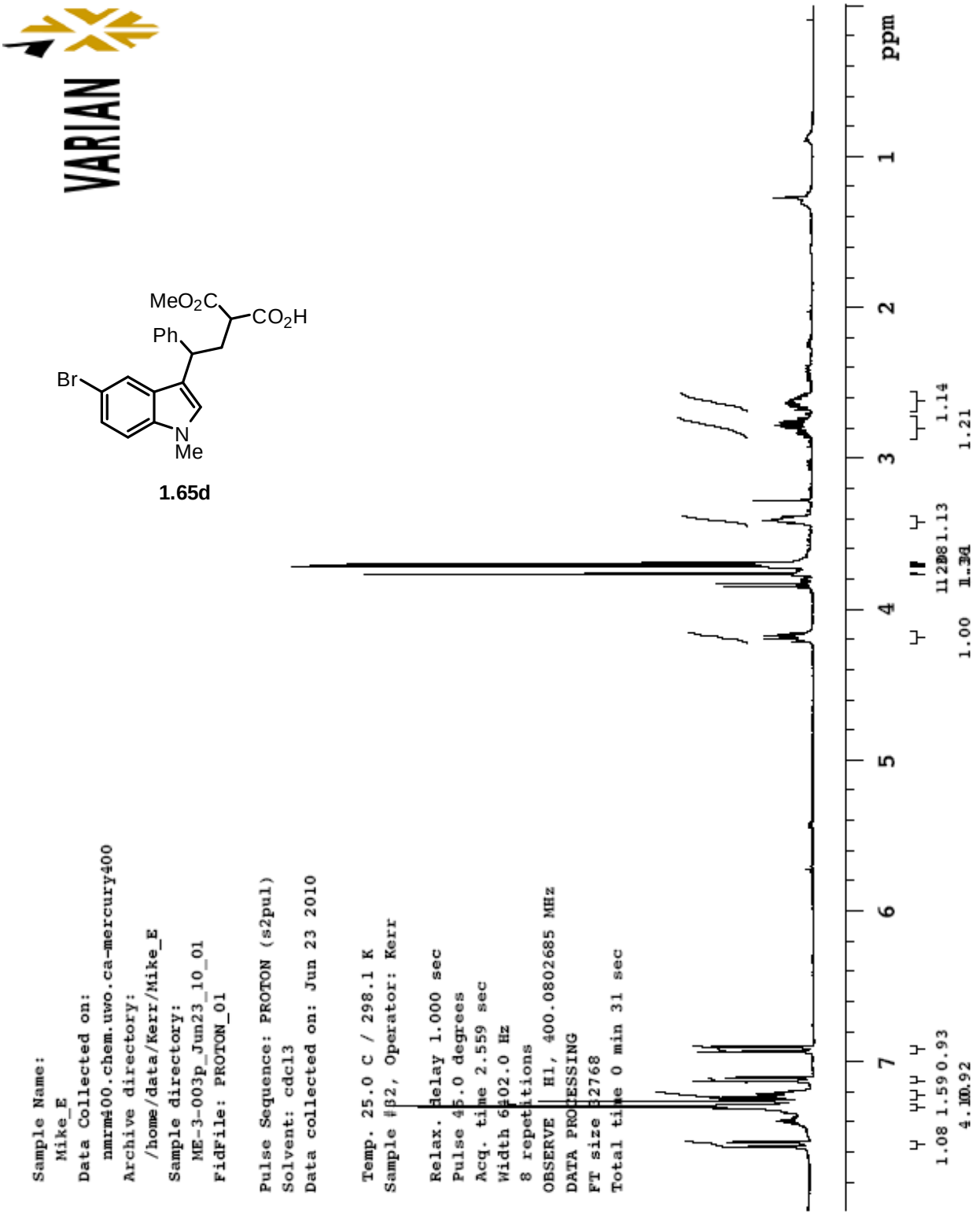

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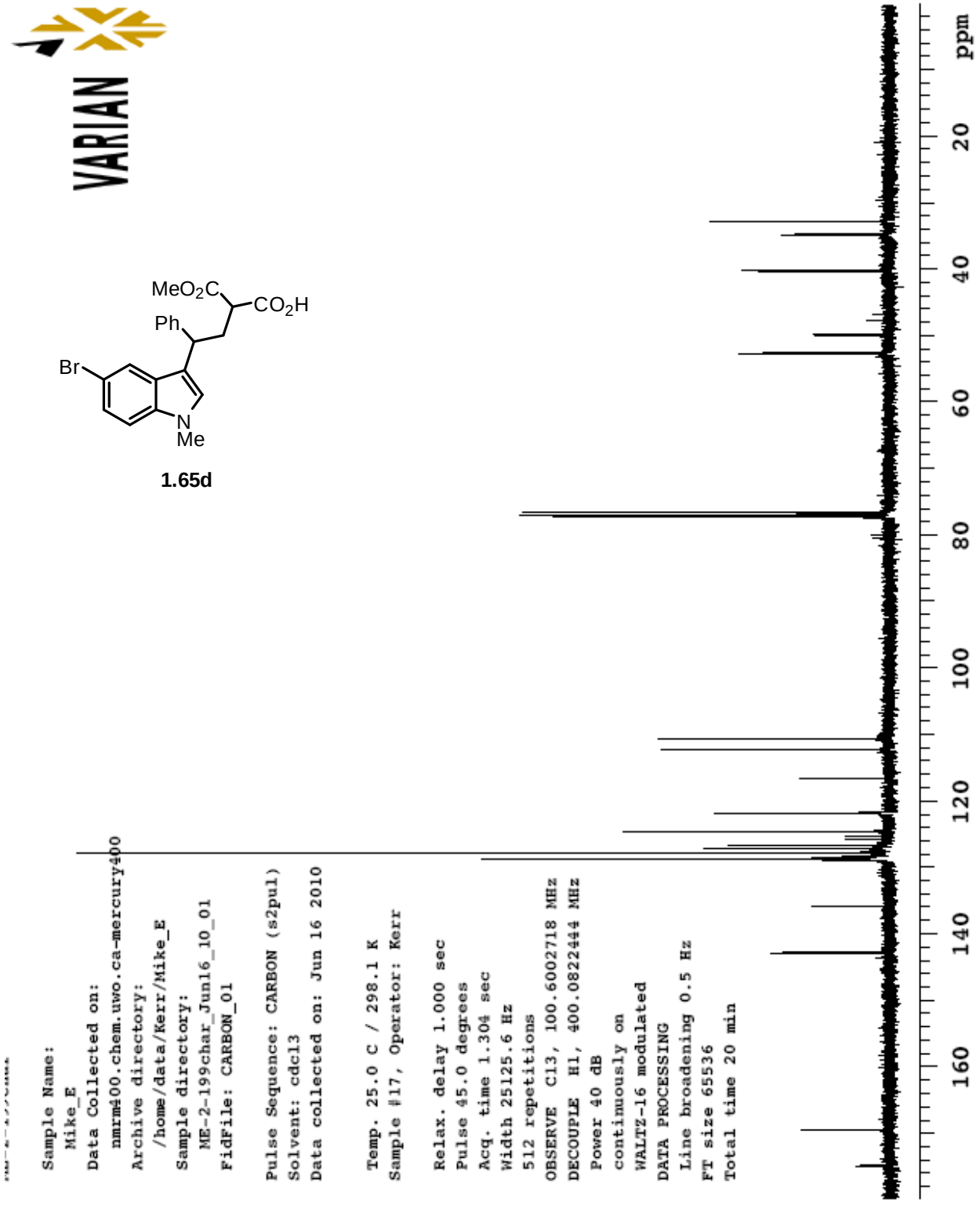

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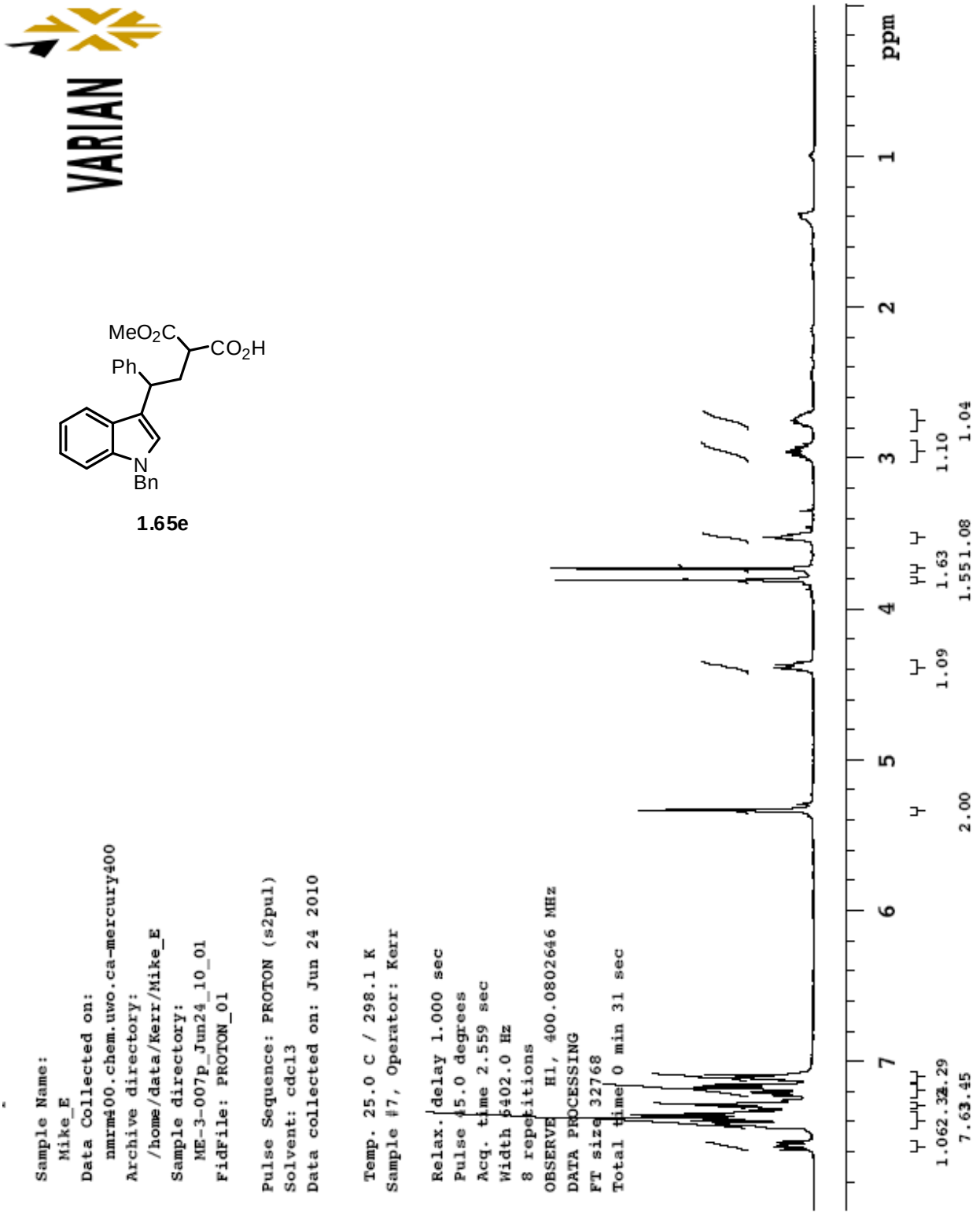
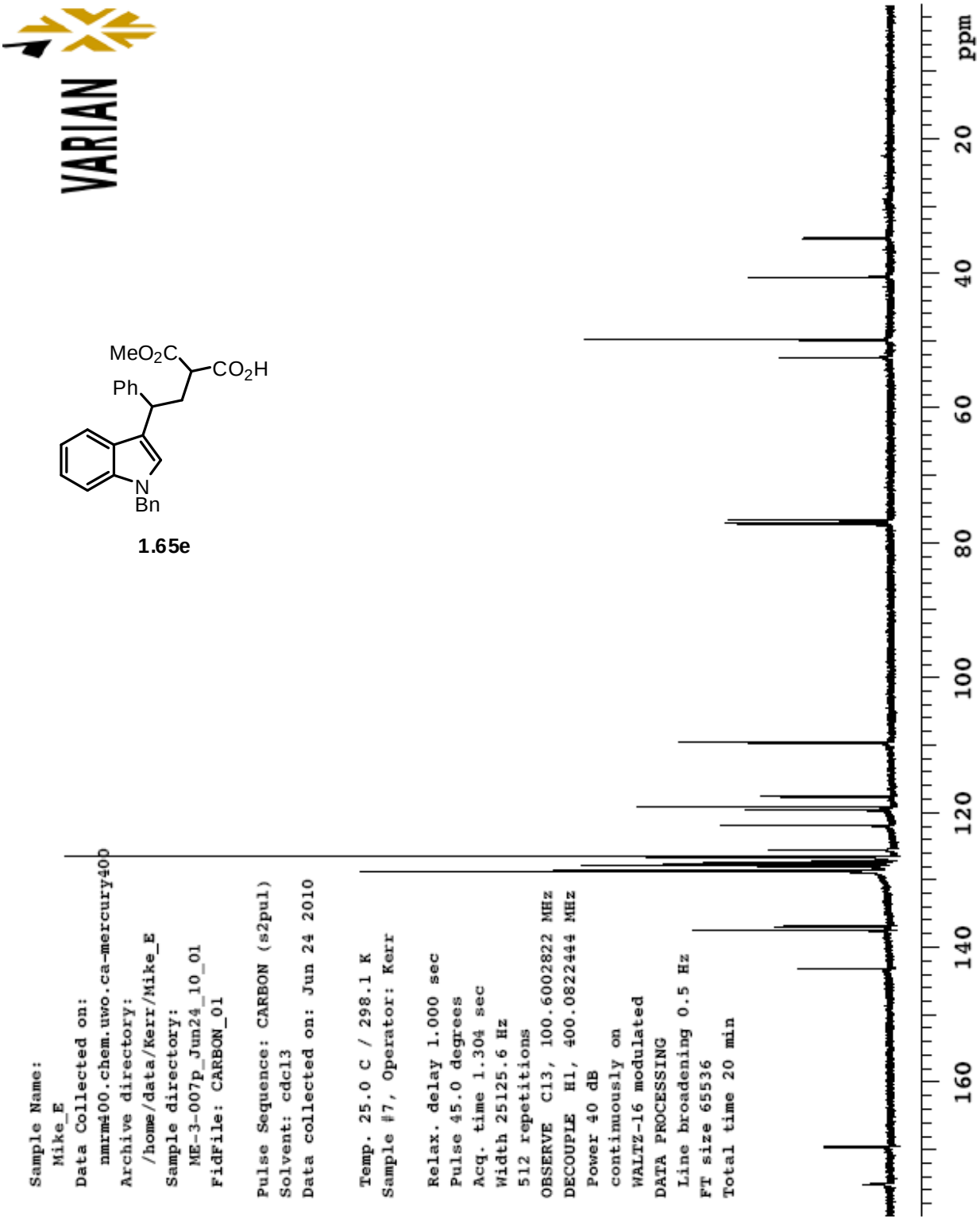
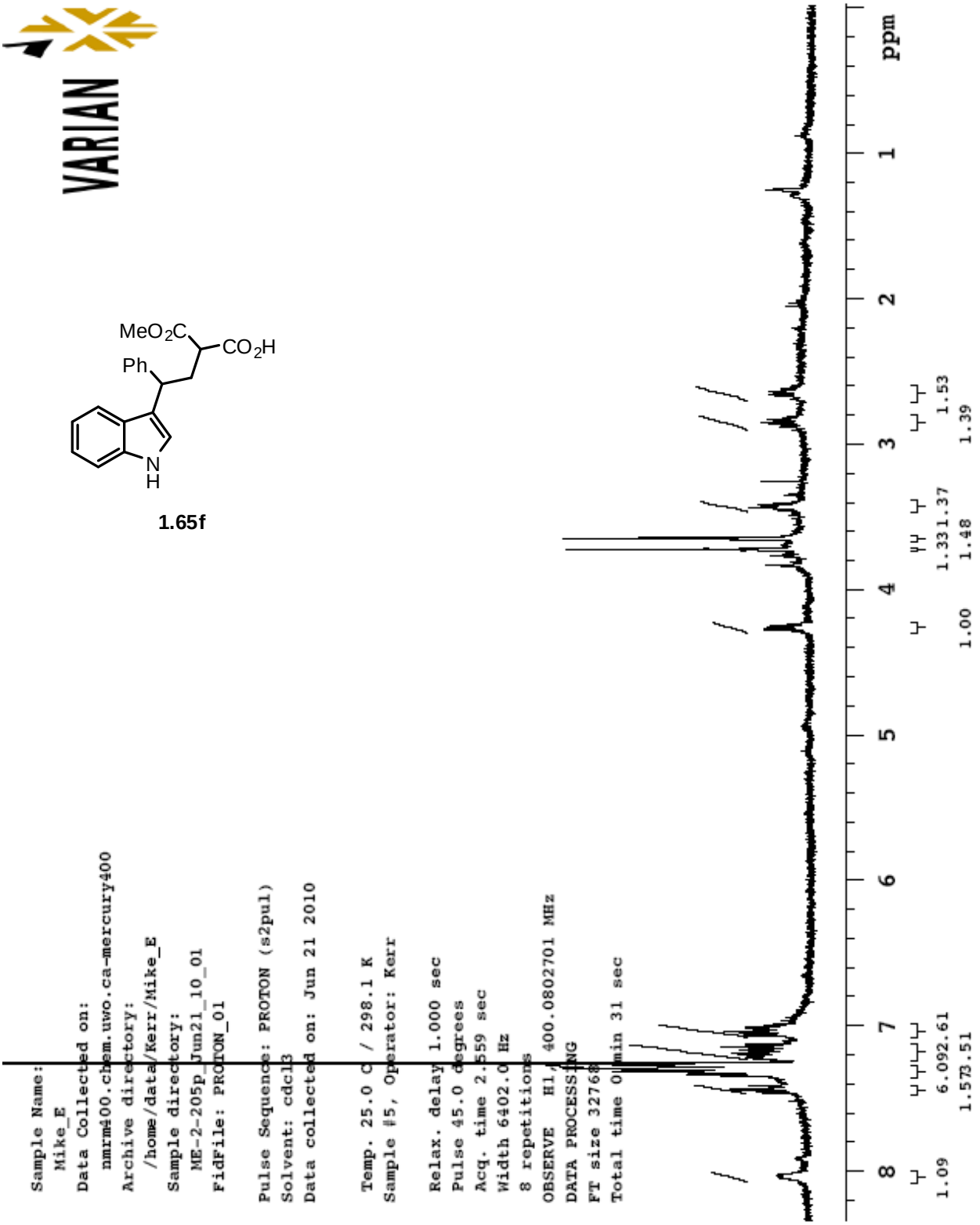
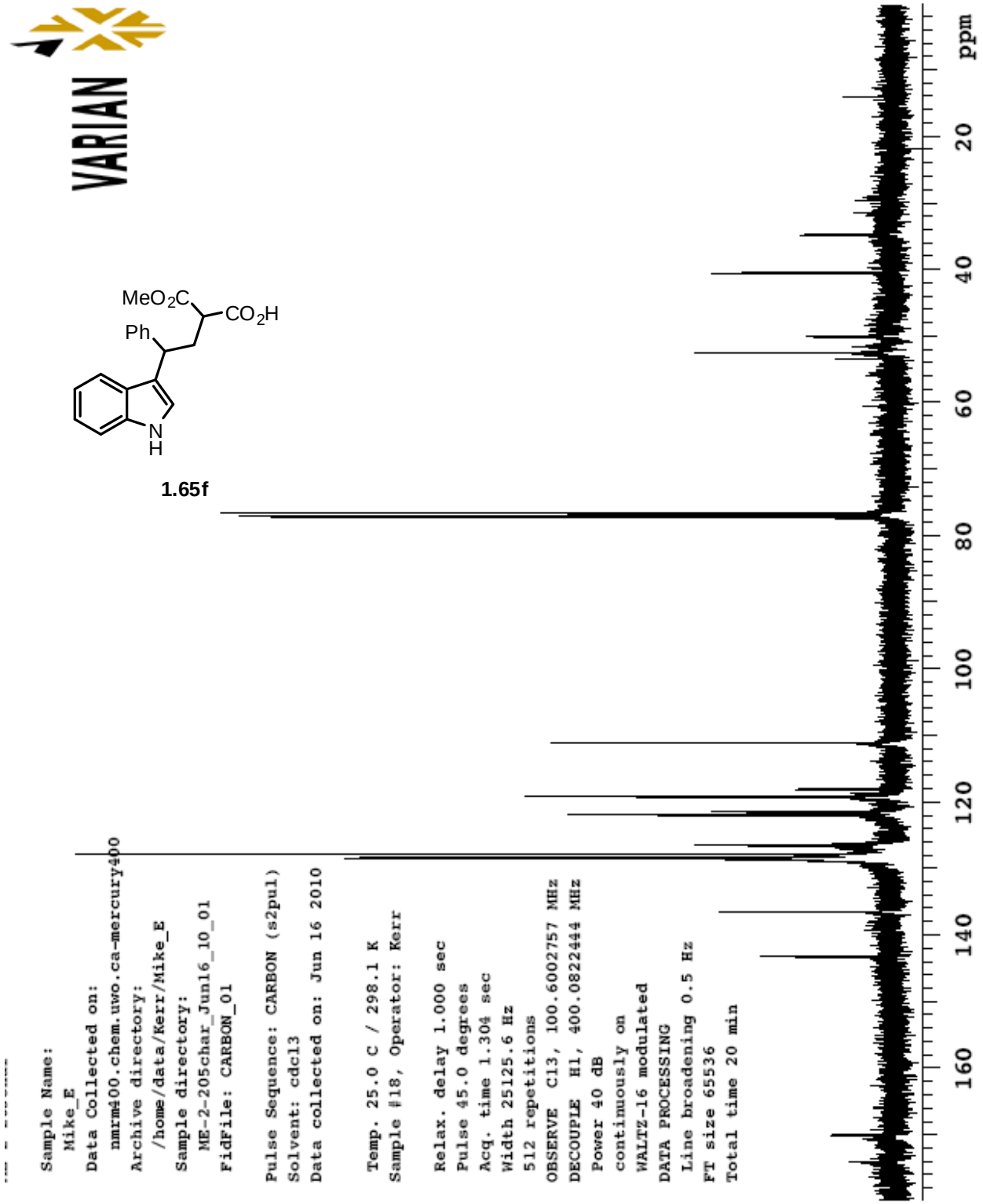
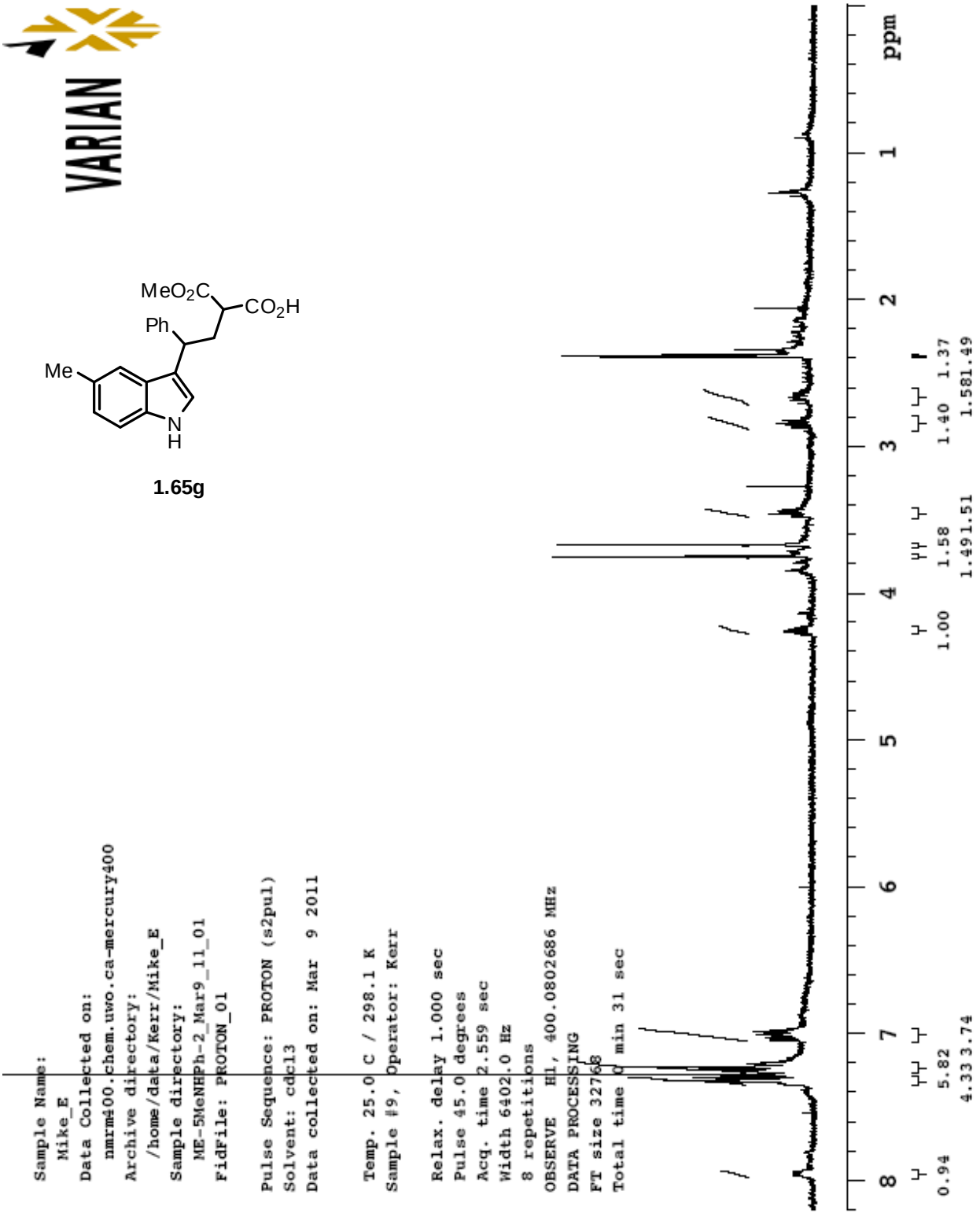




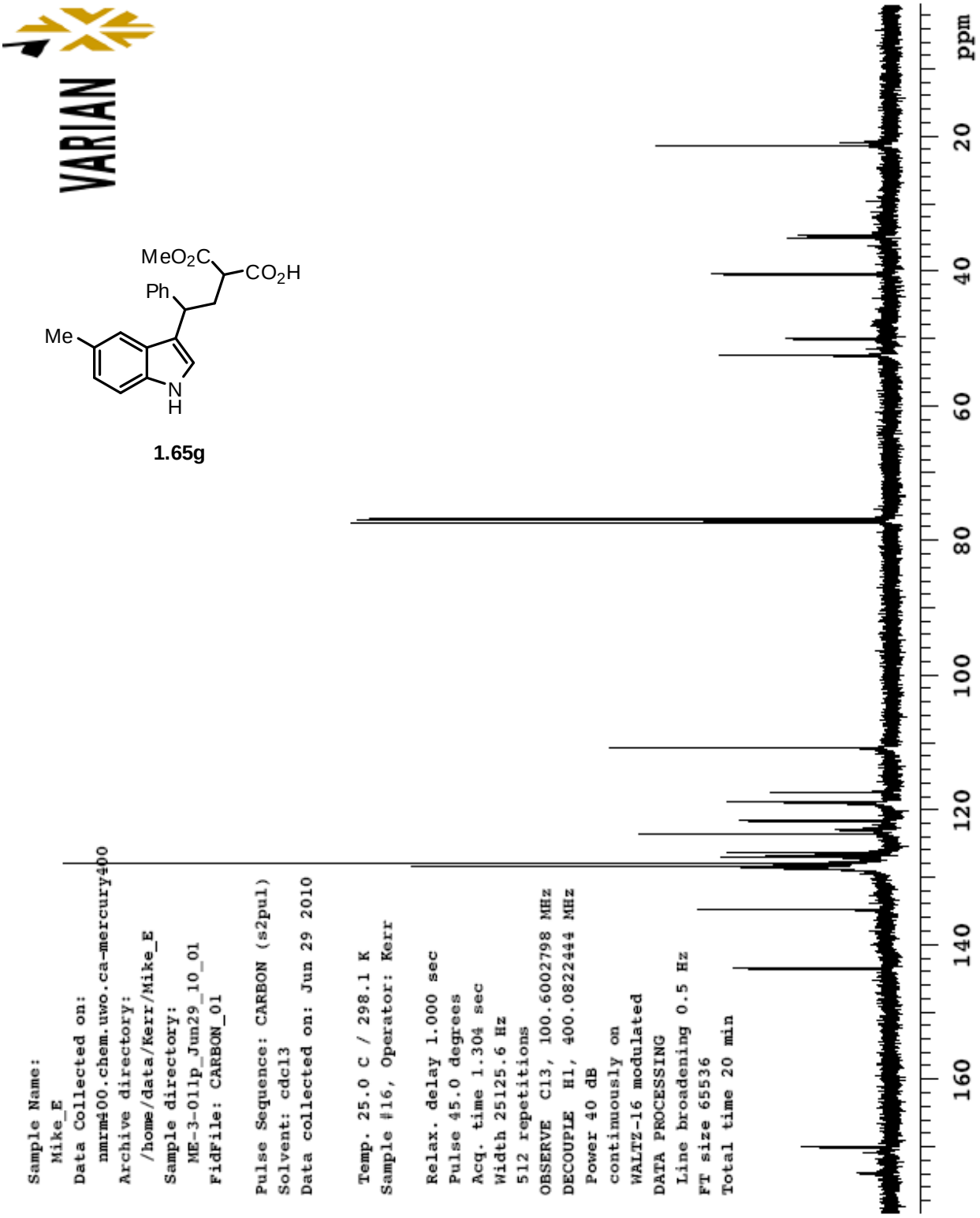


1.65f

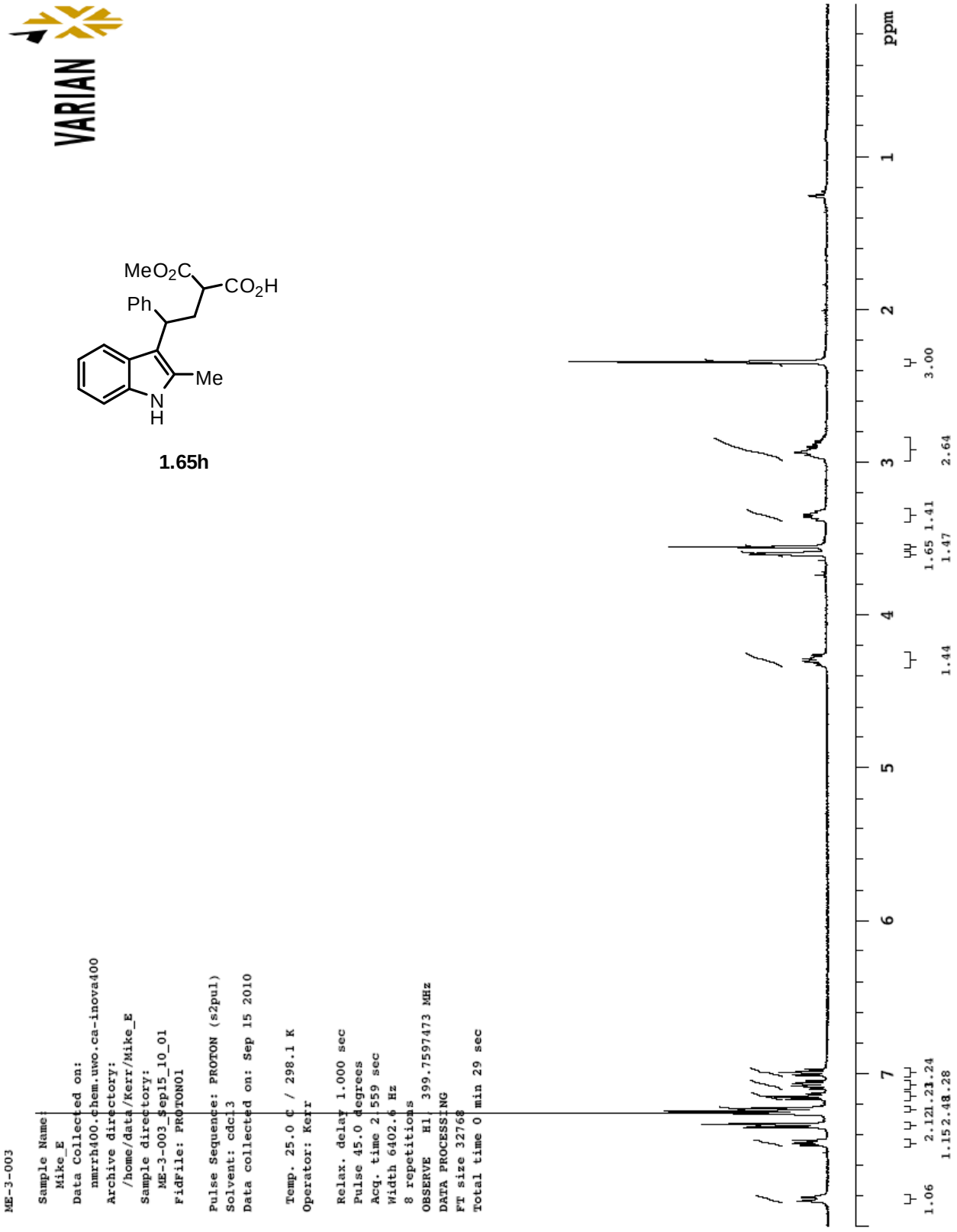


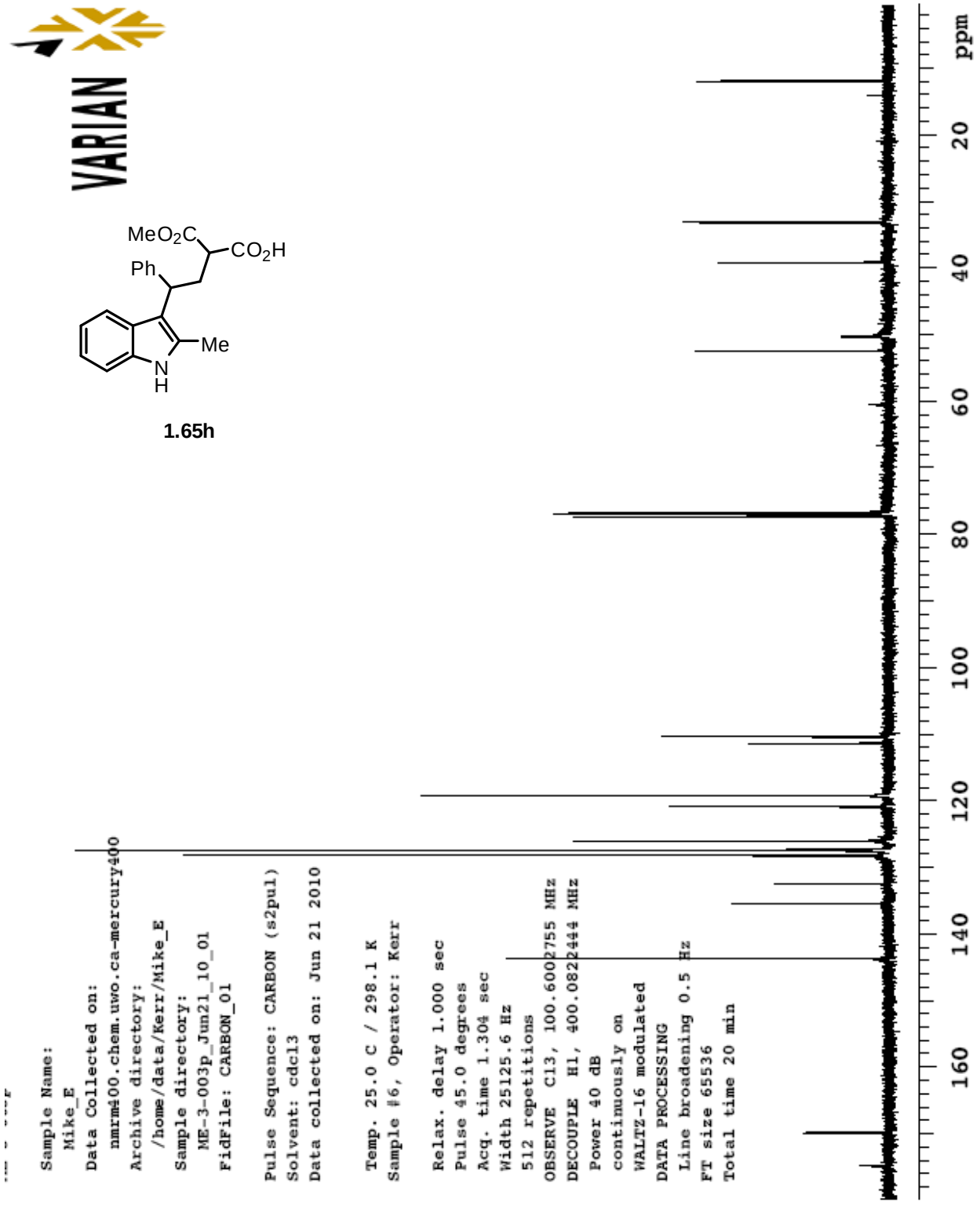


1.65g

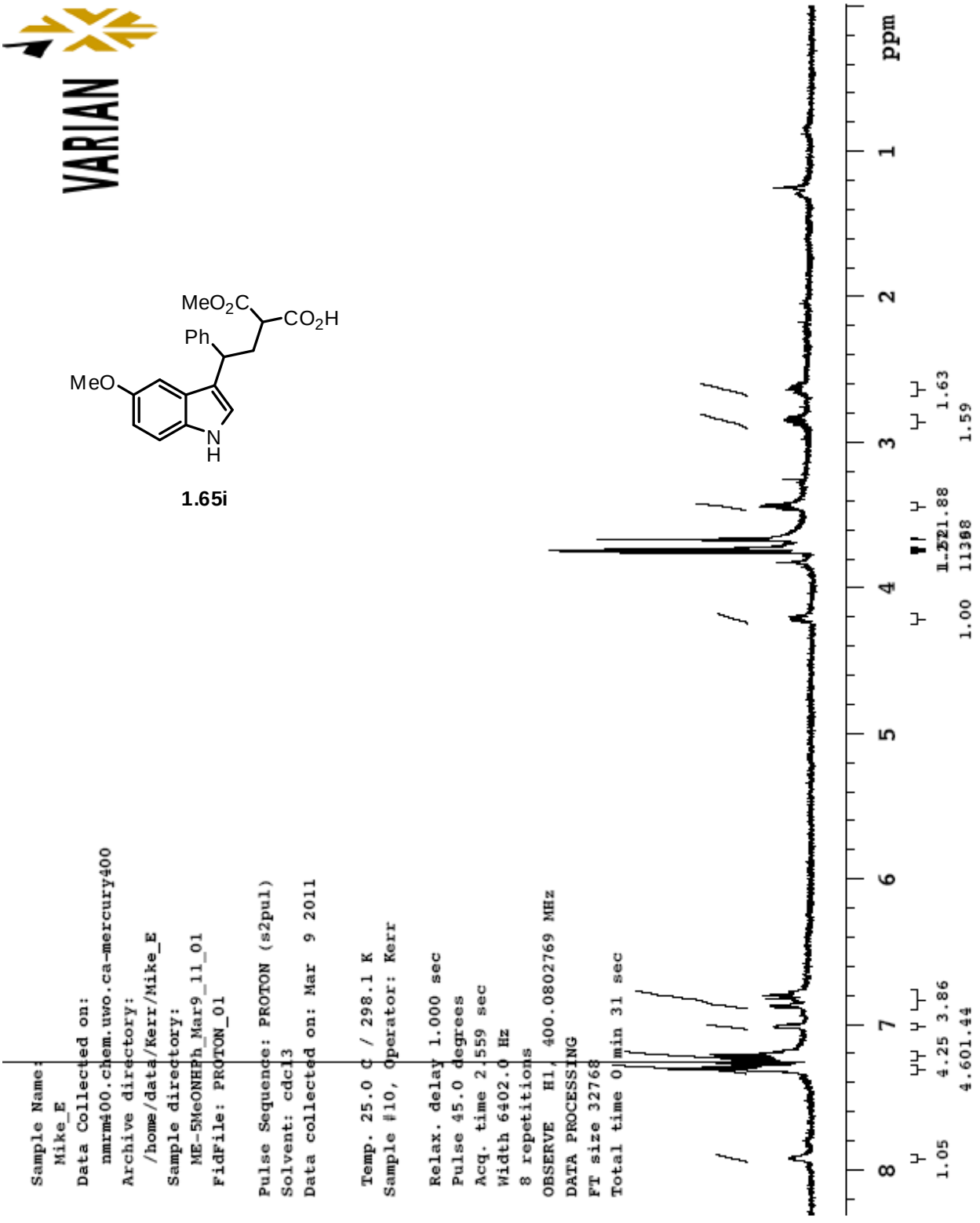


1.65g

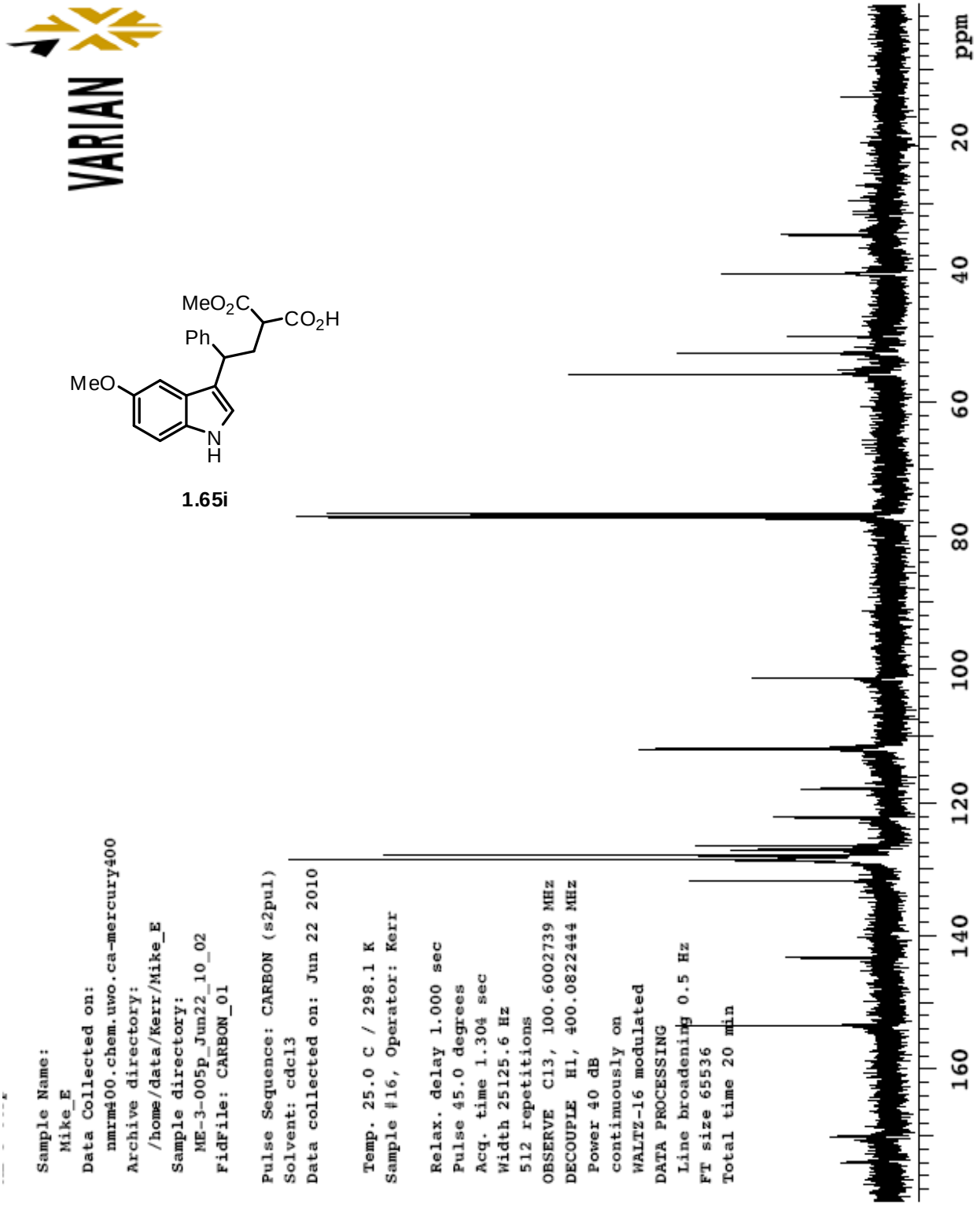


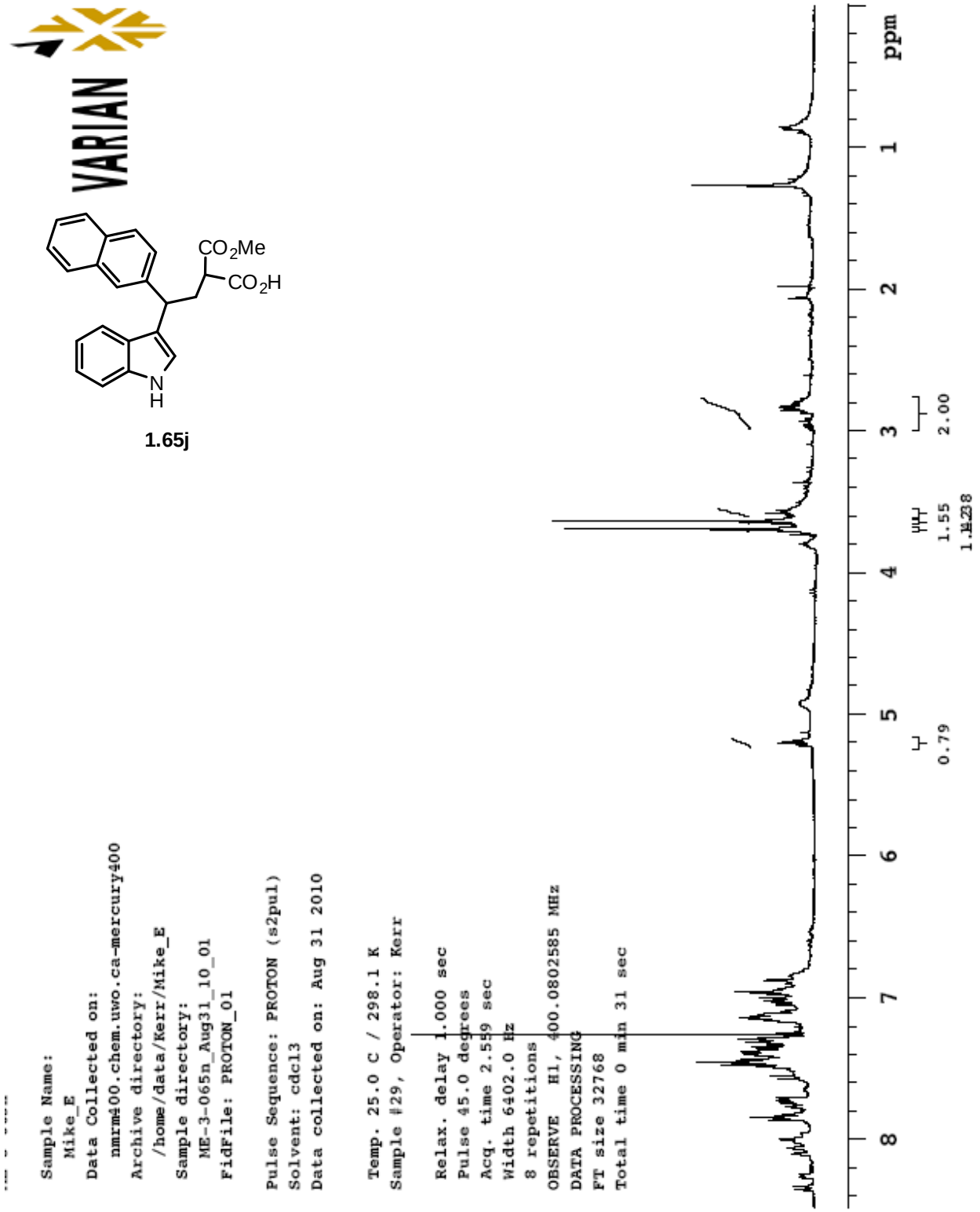


1.65h



1.65i





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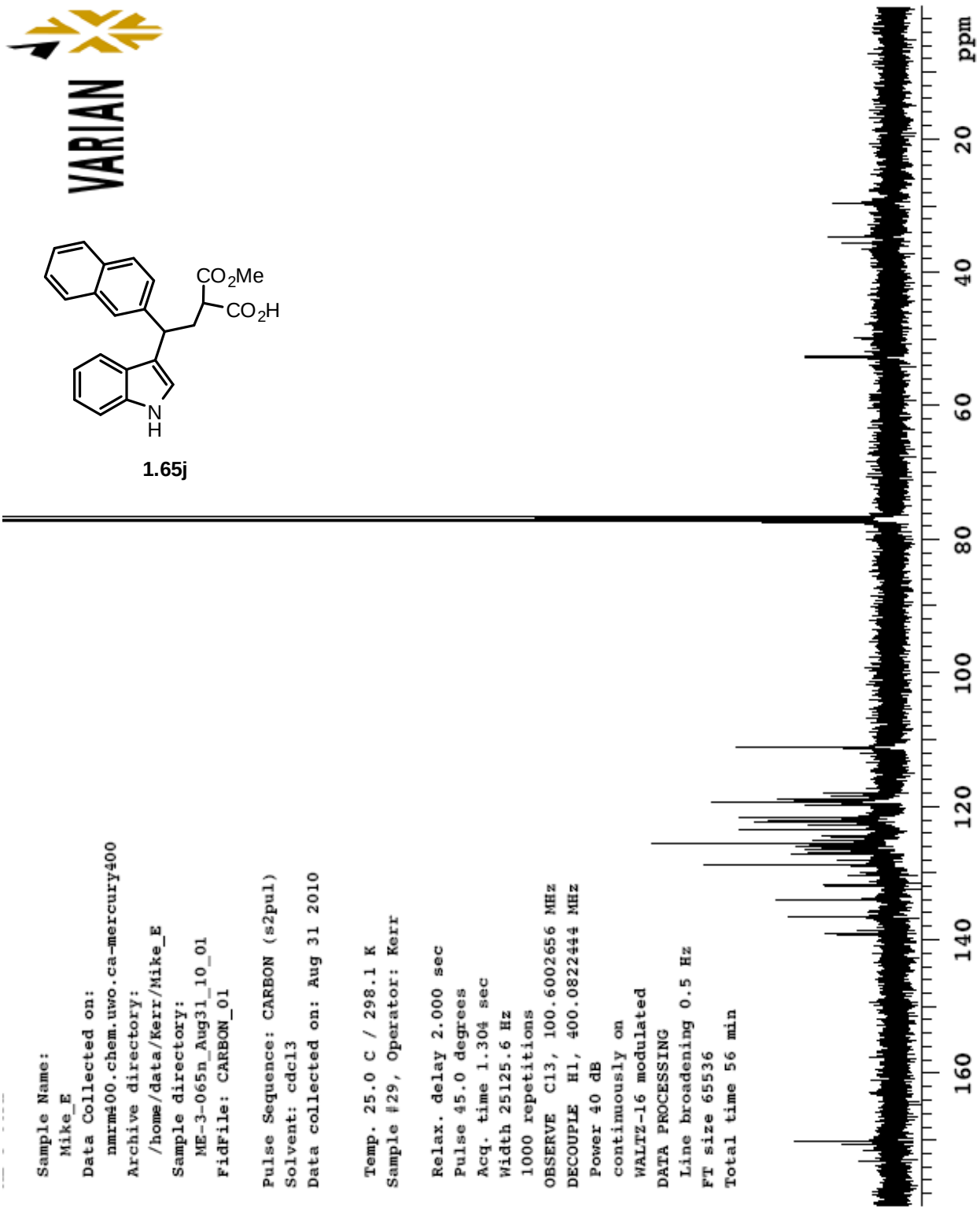
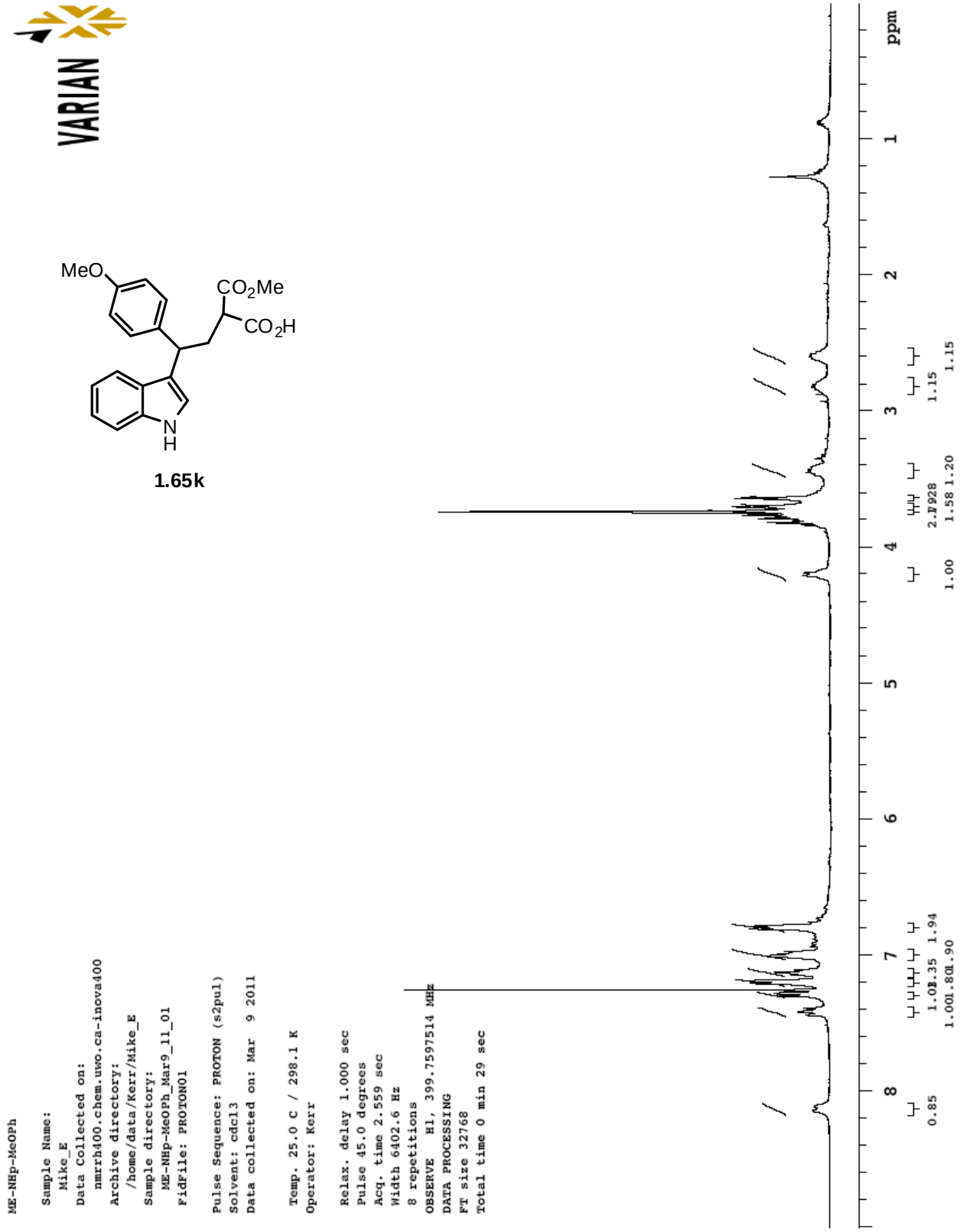
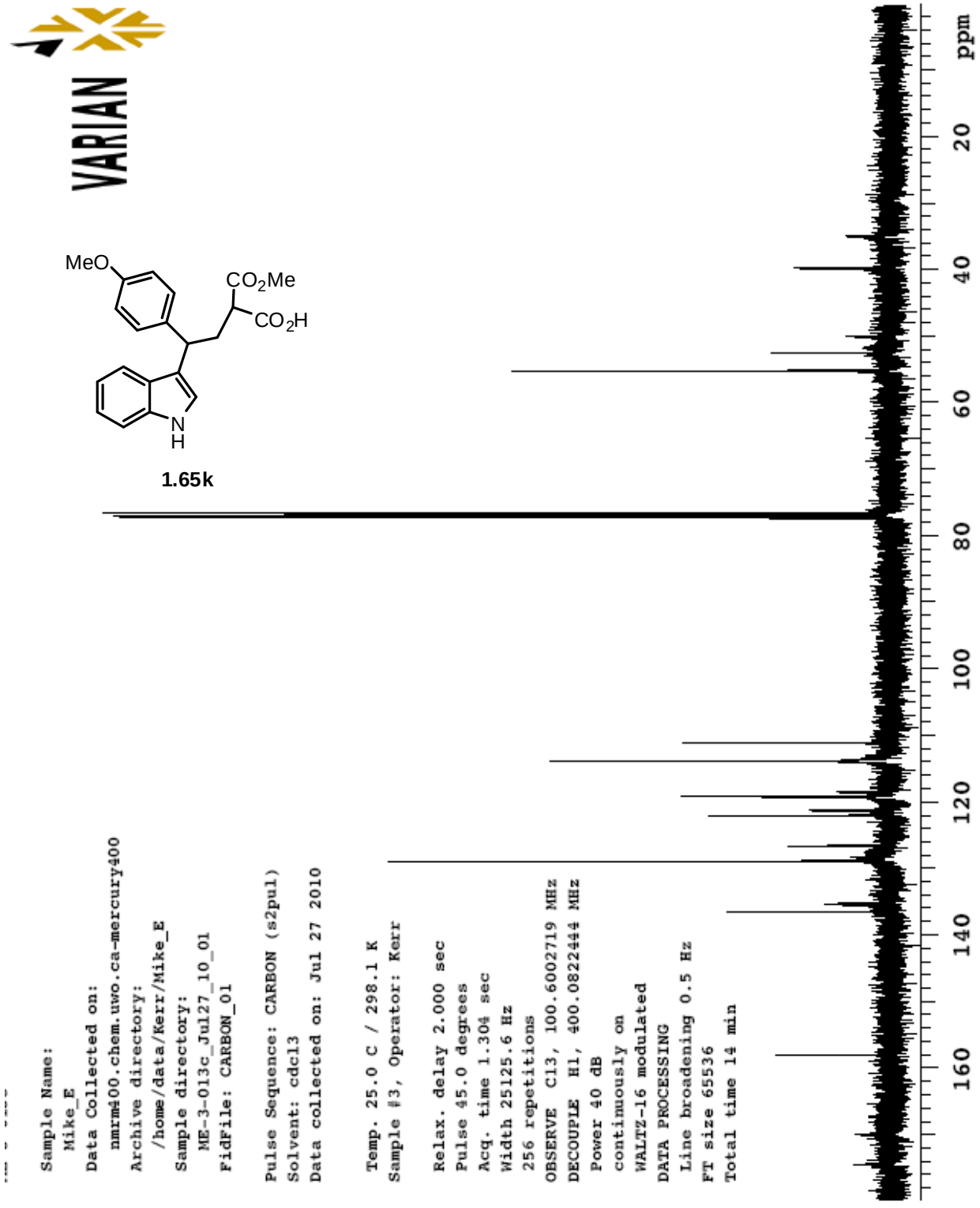
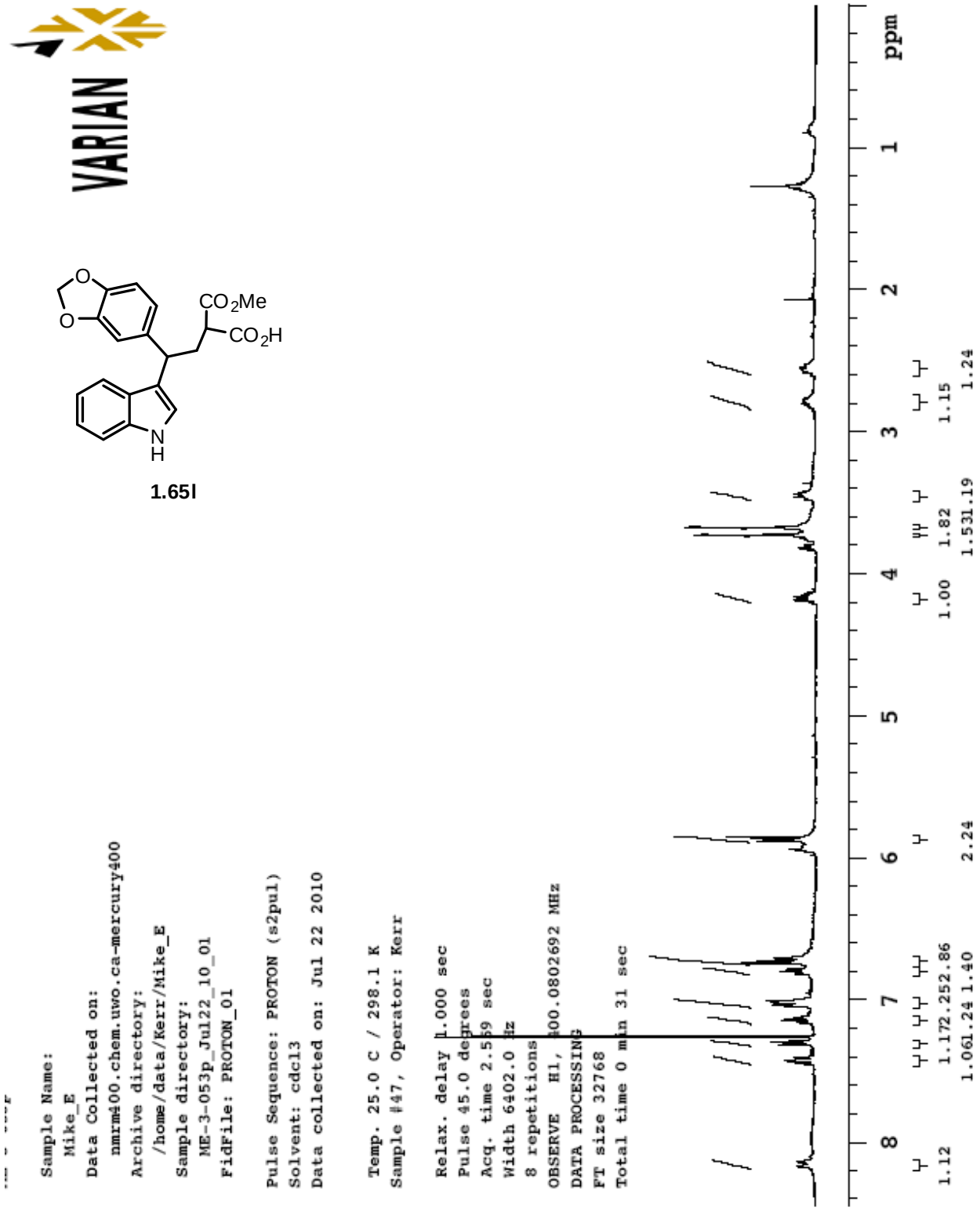


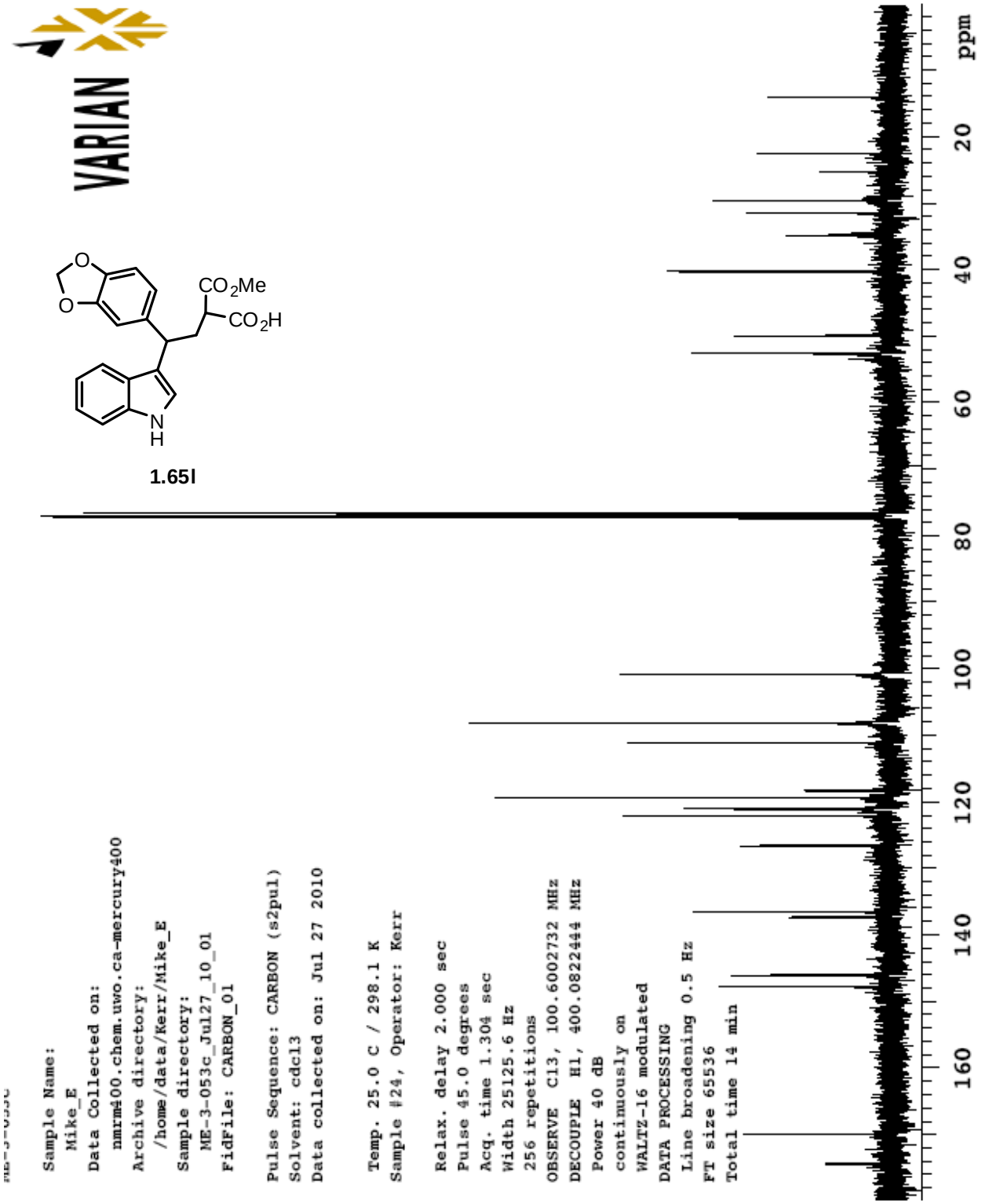
1.65j

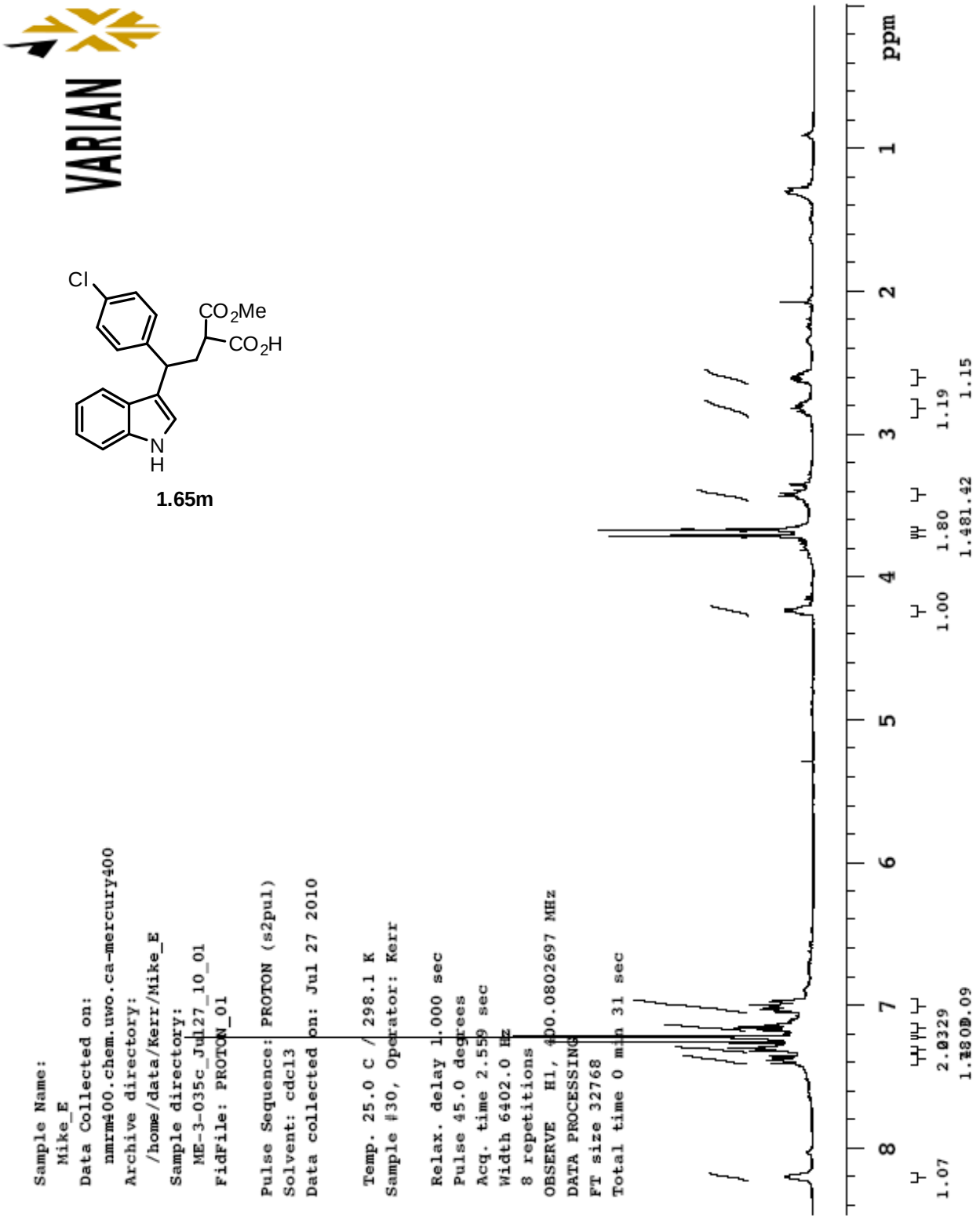






1.65l





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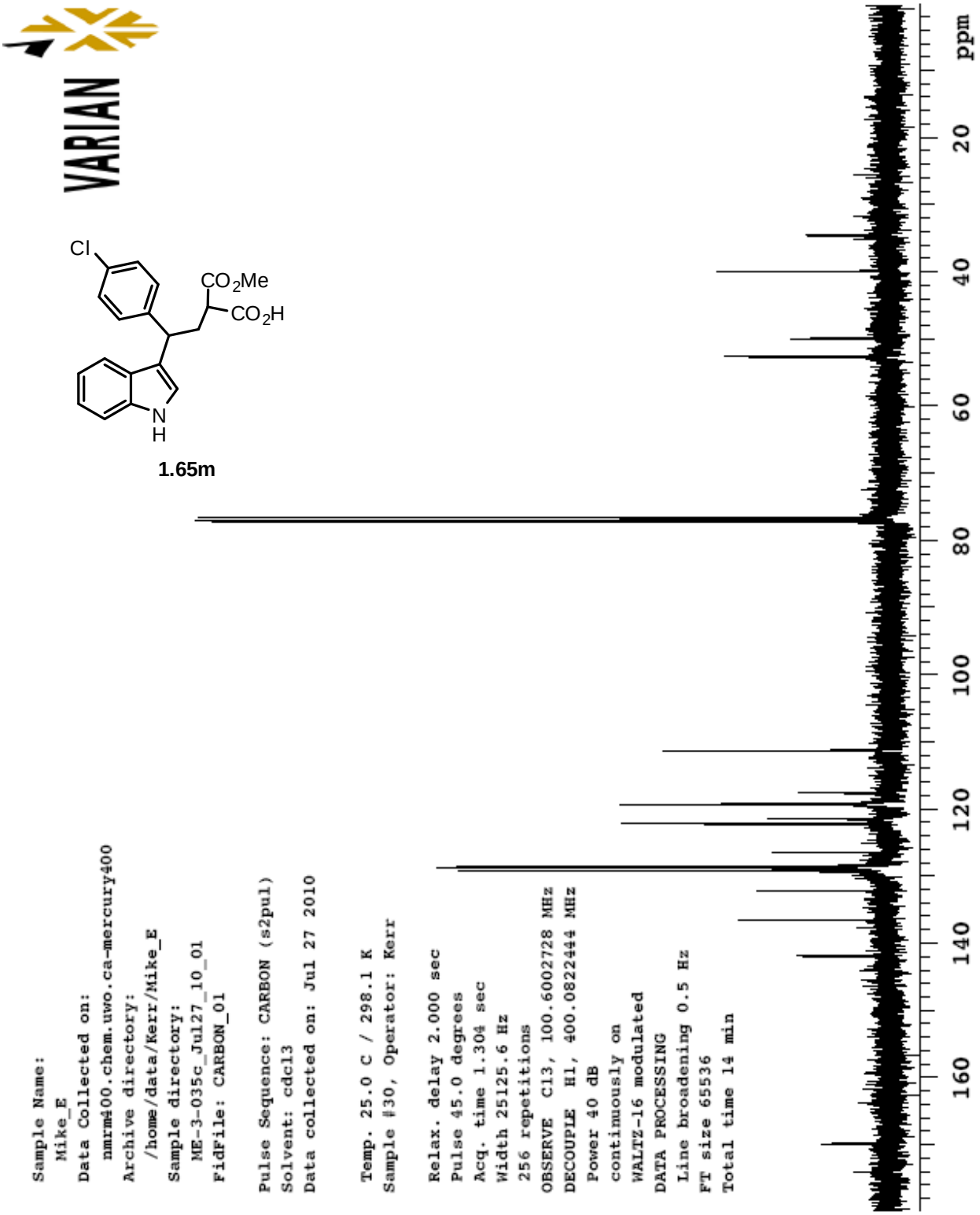

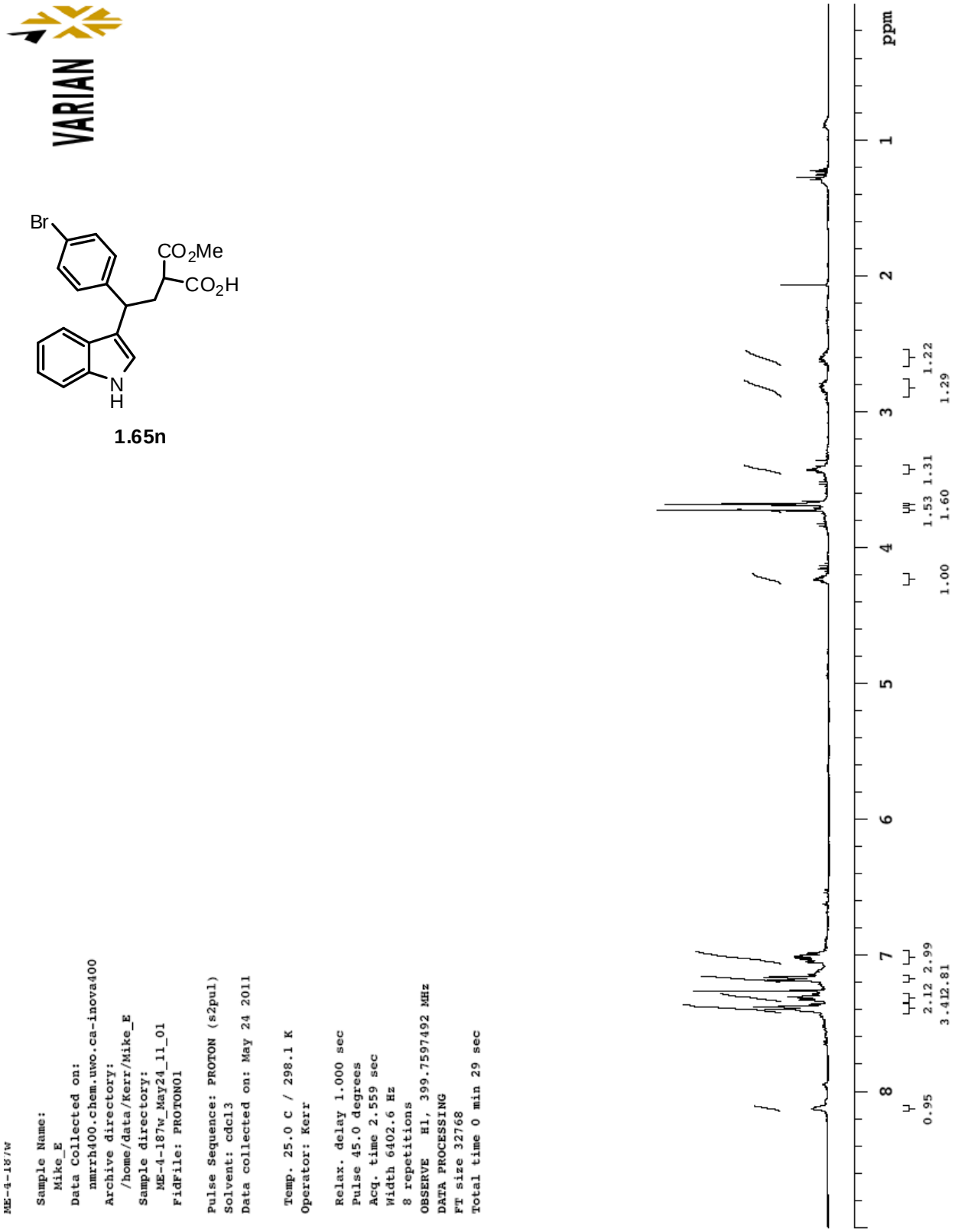

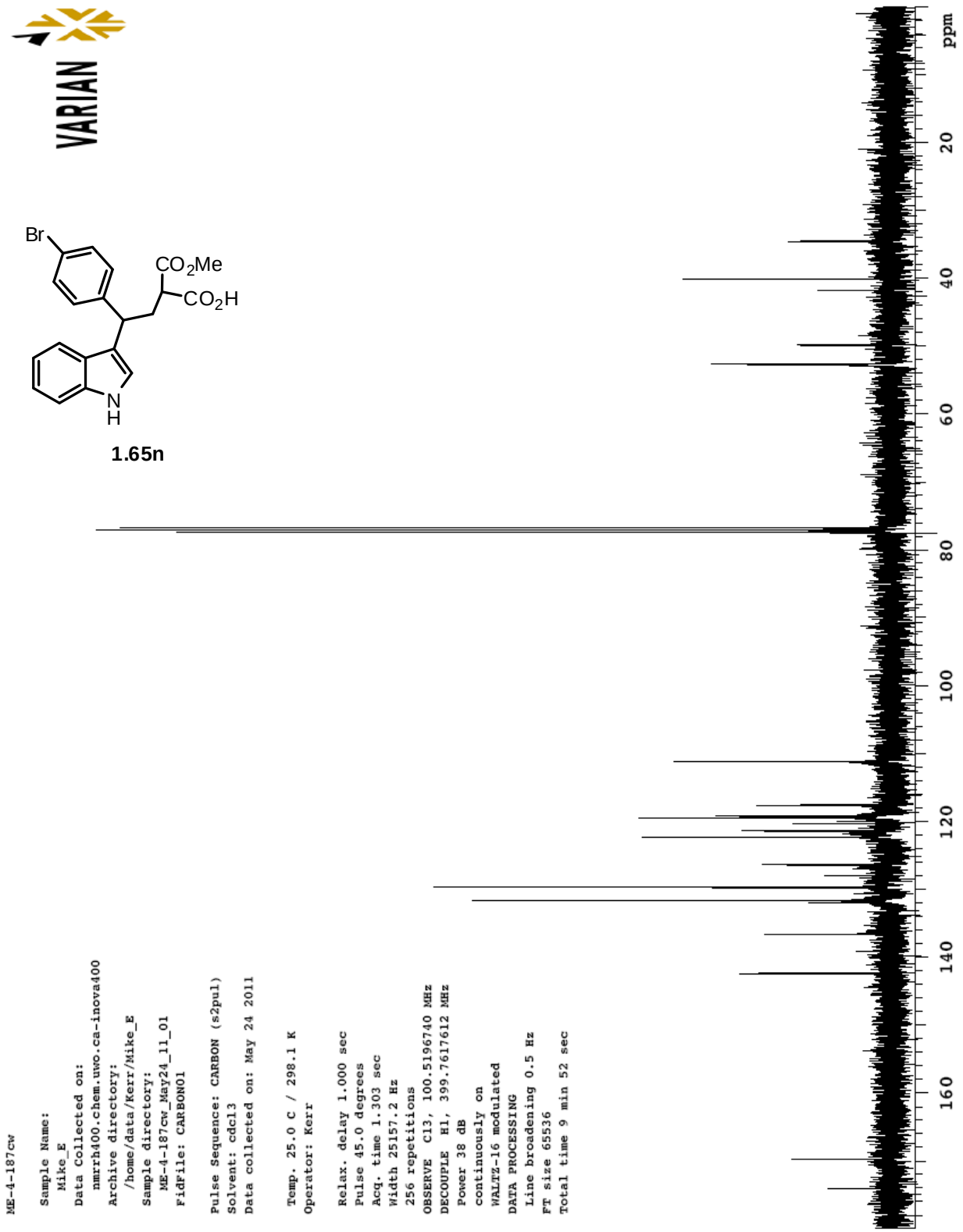

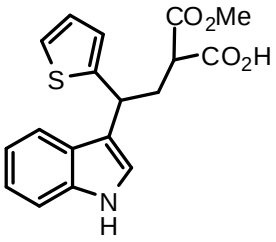

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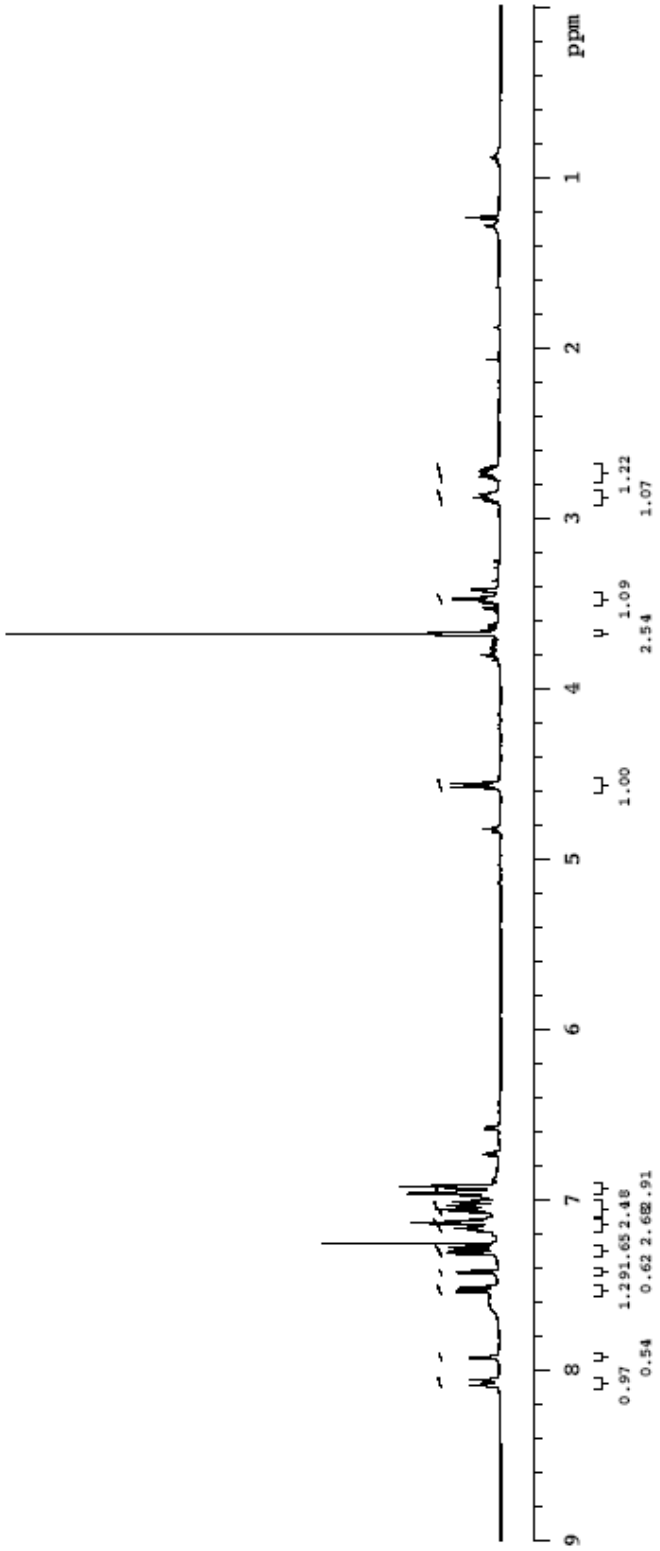
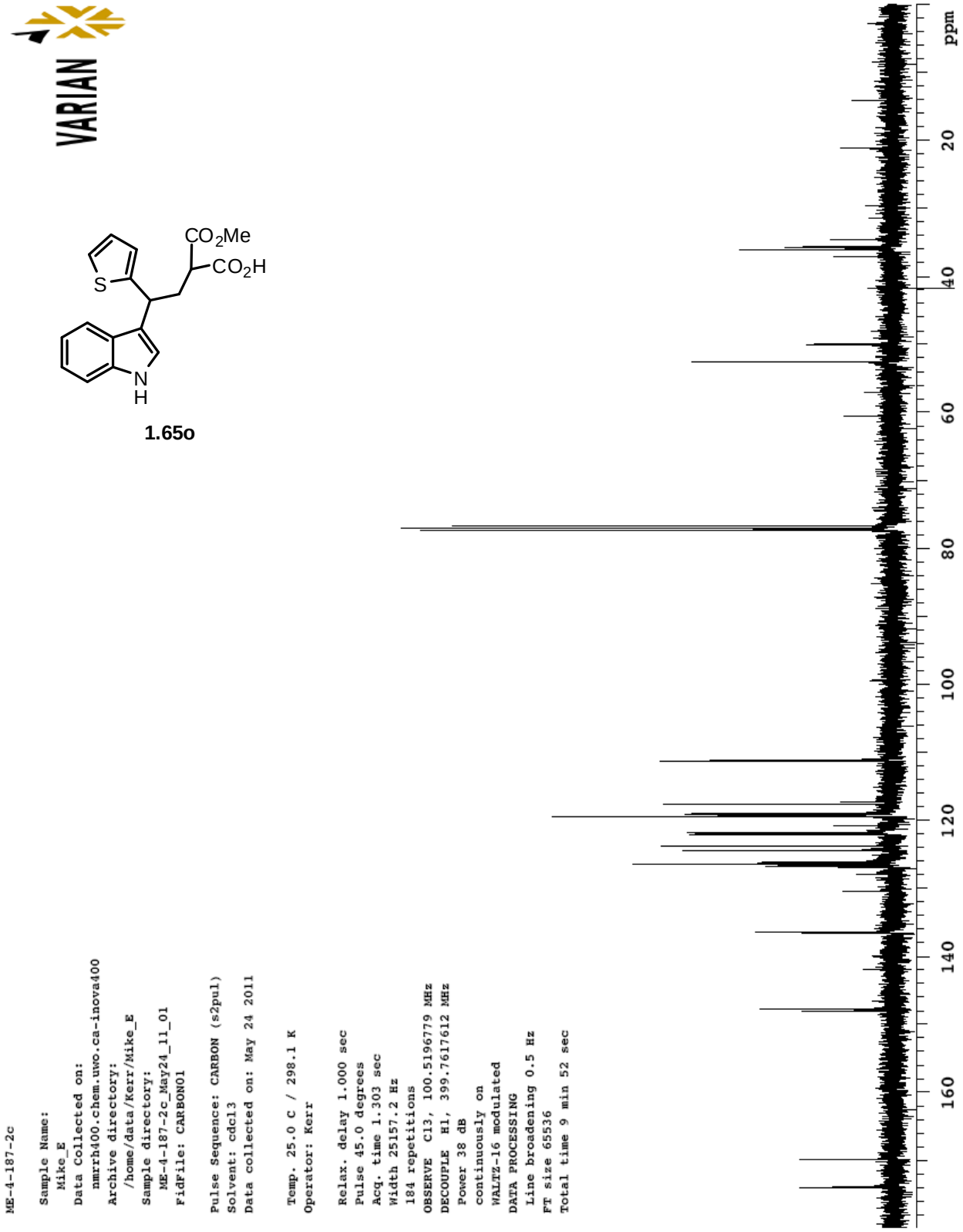
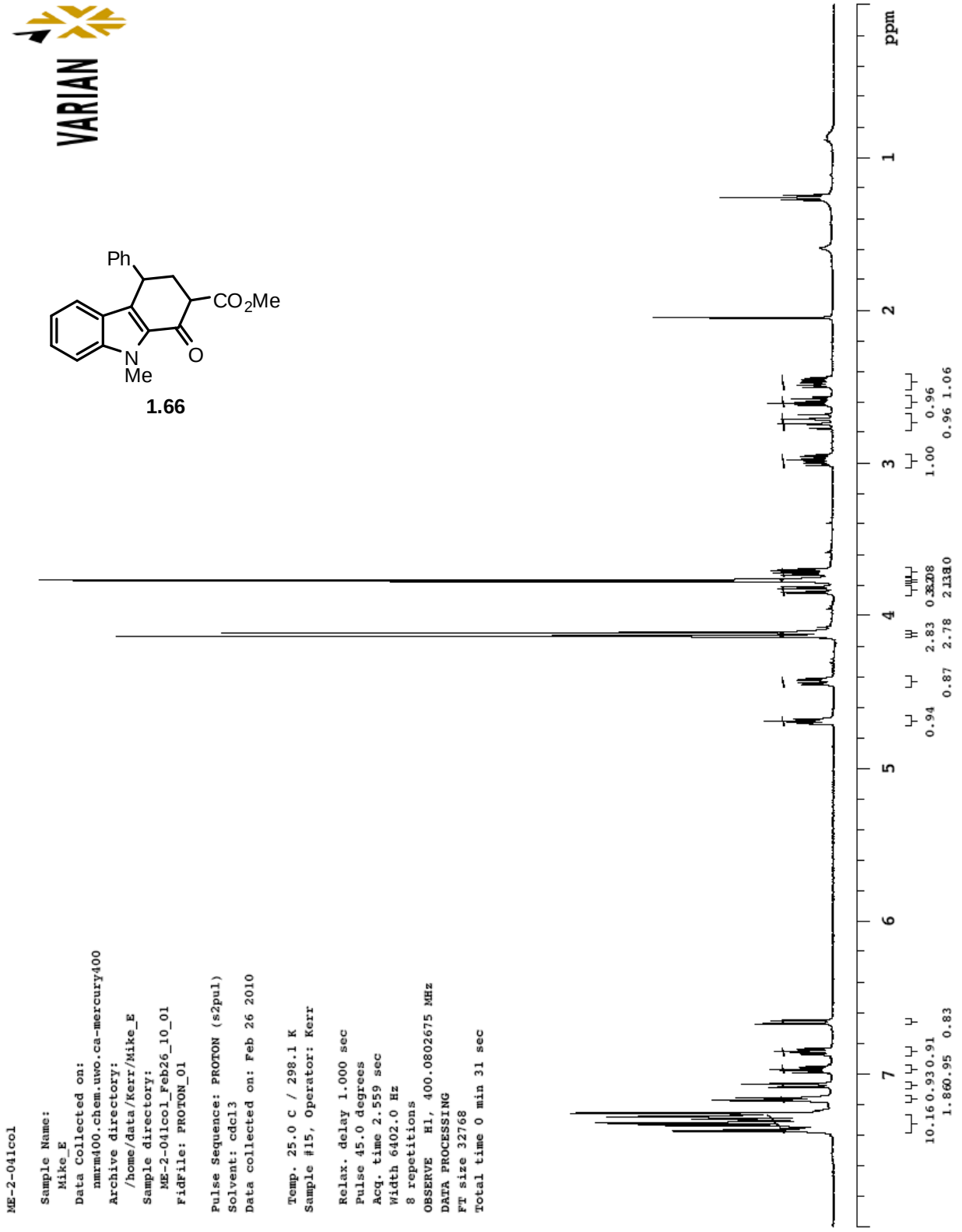
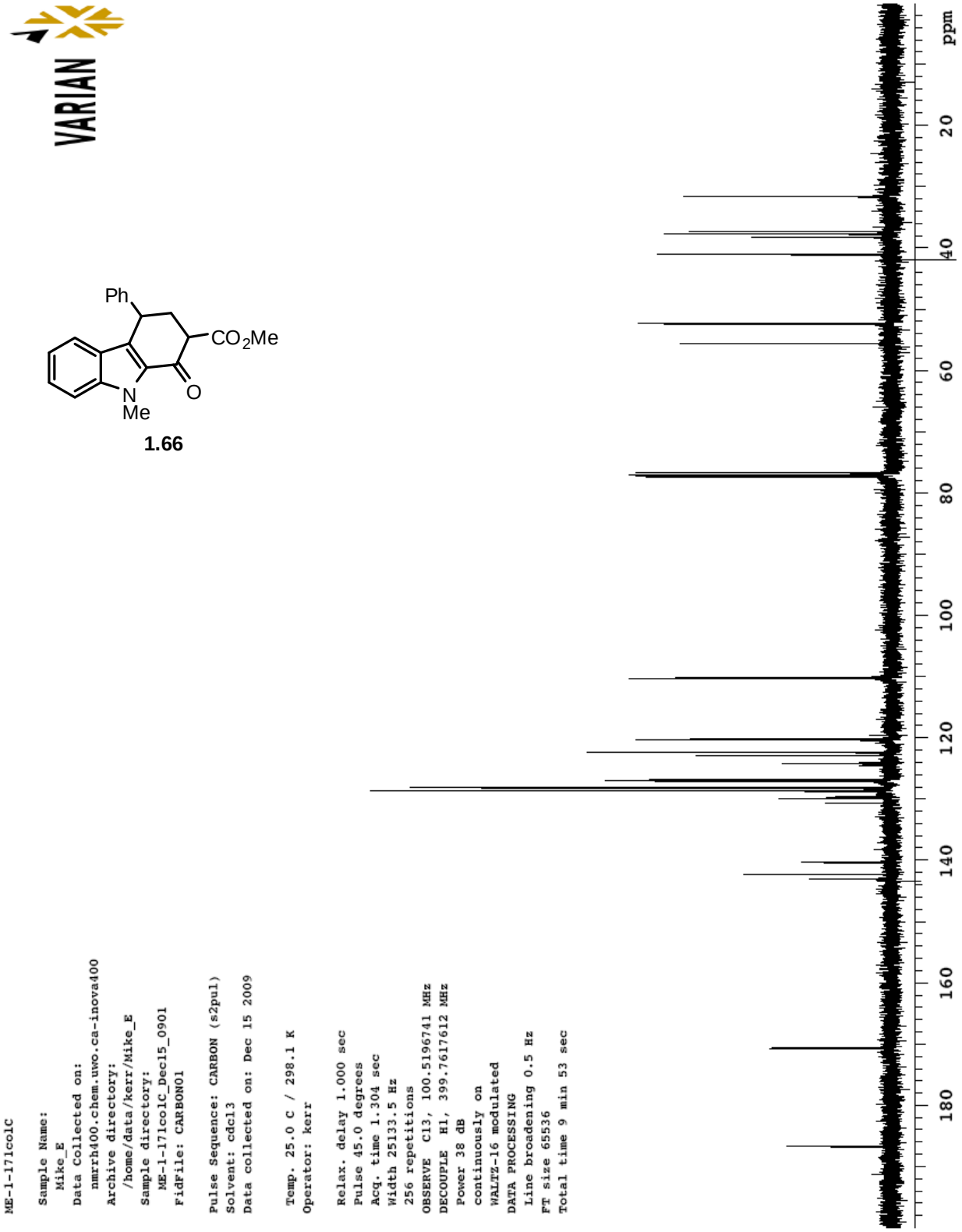
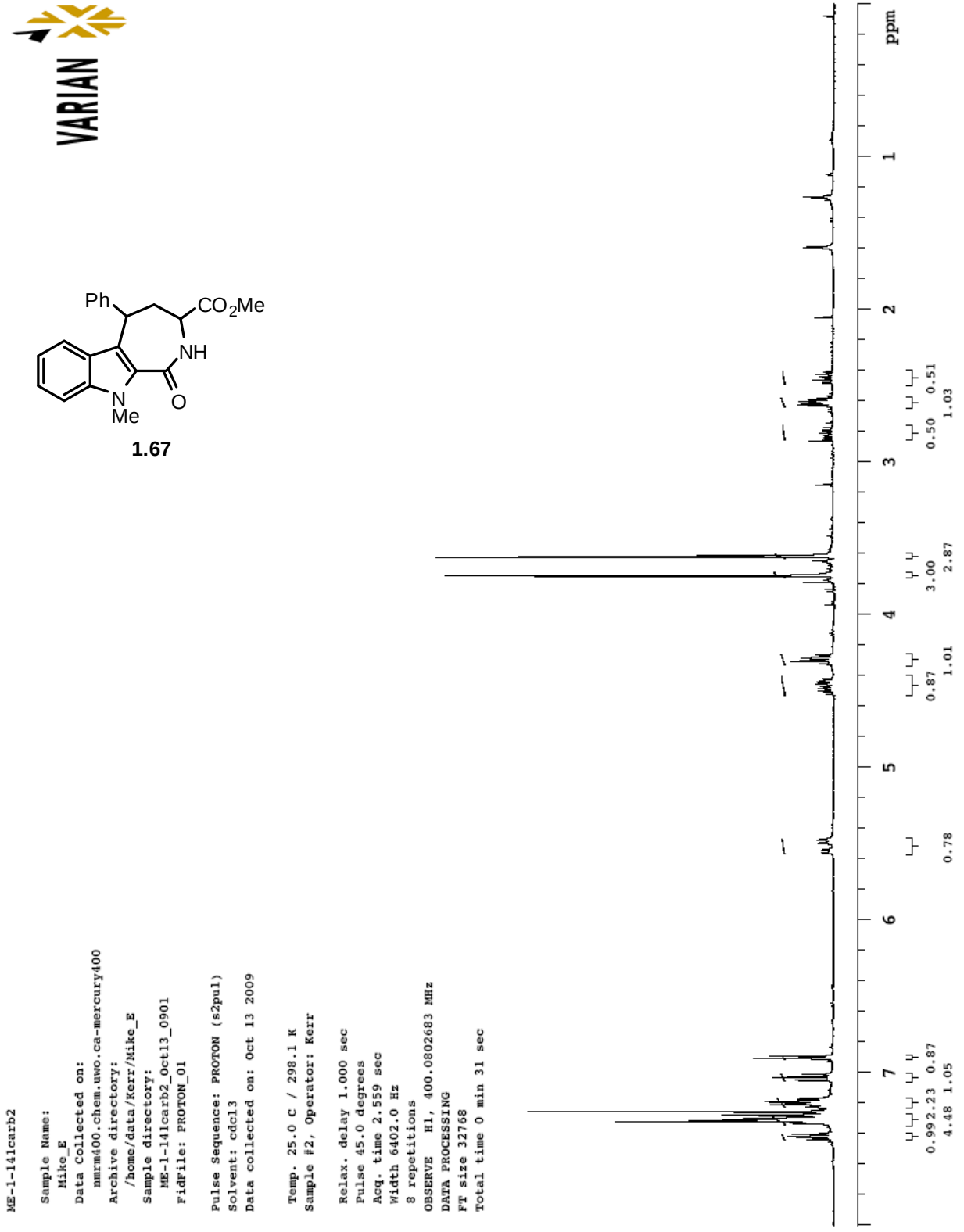


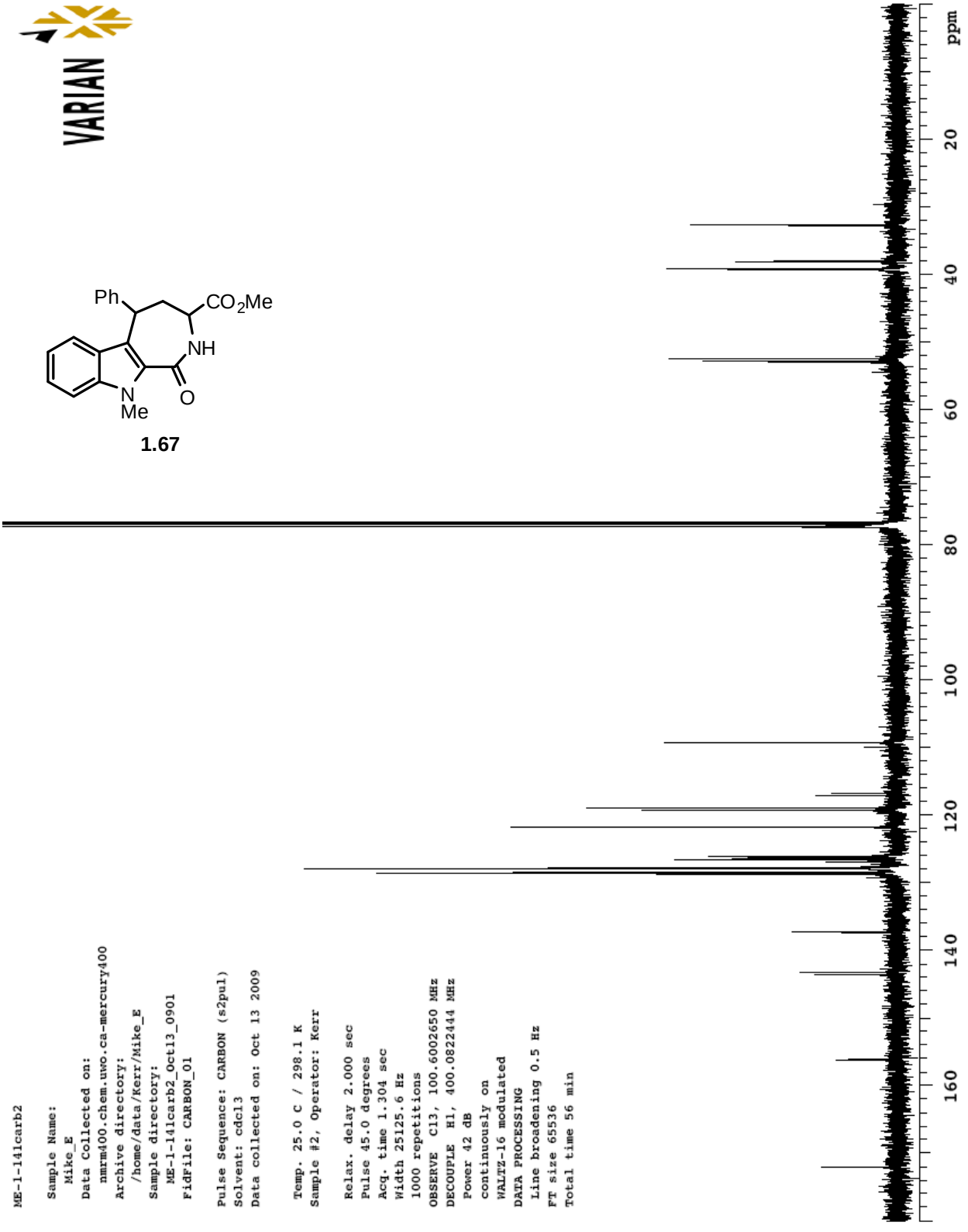


1.65o

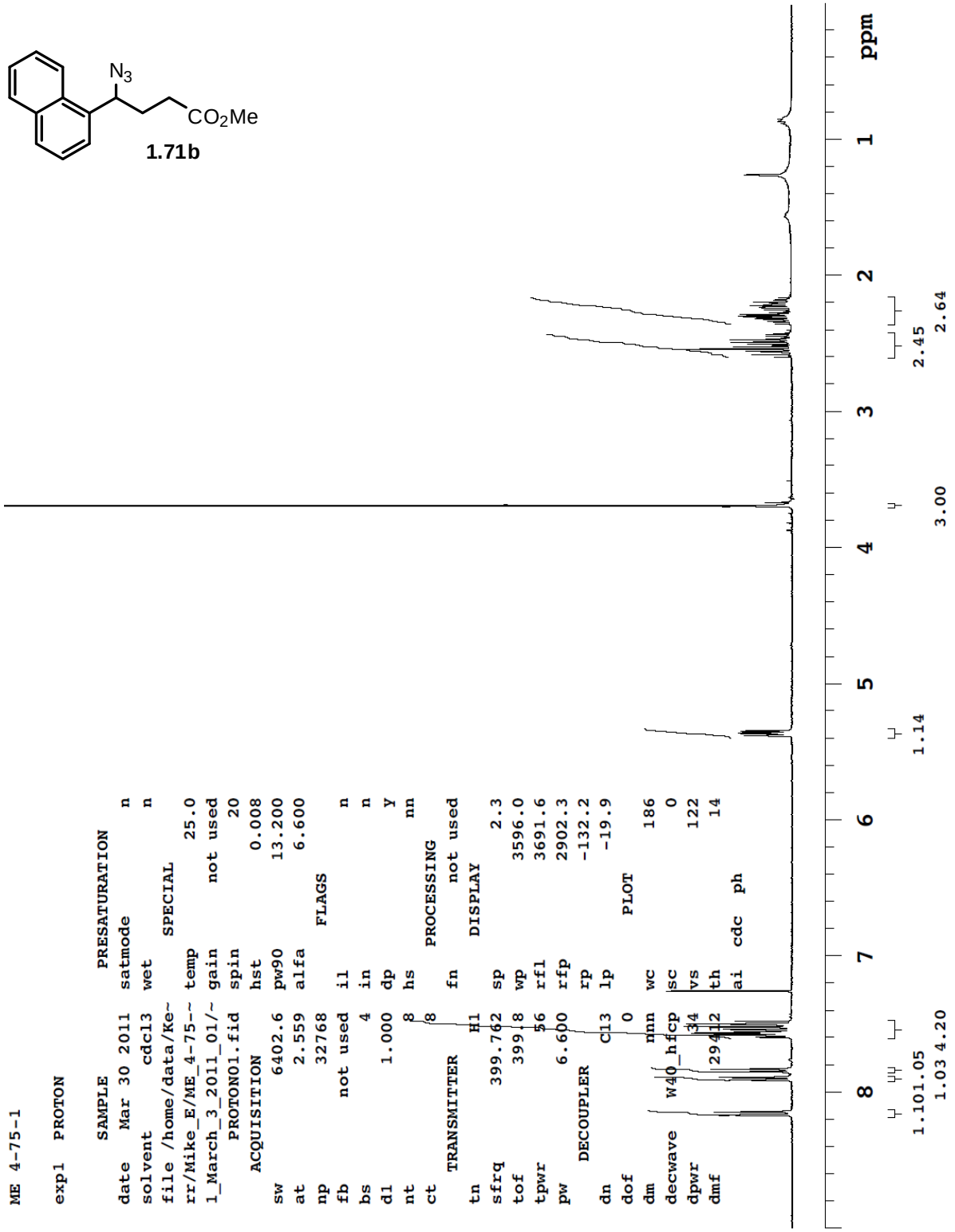


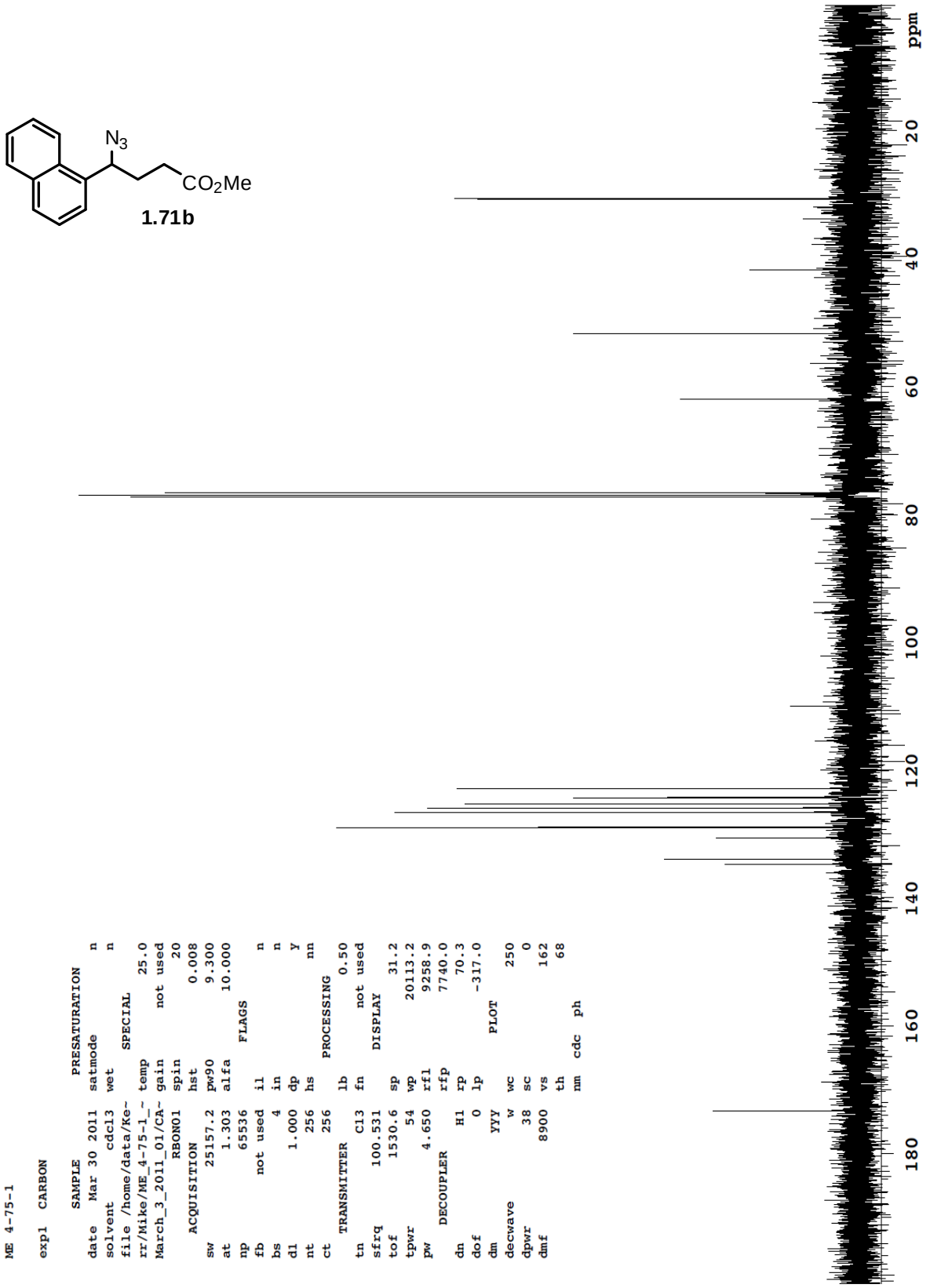




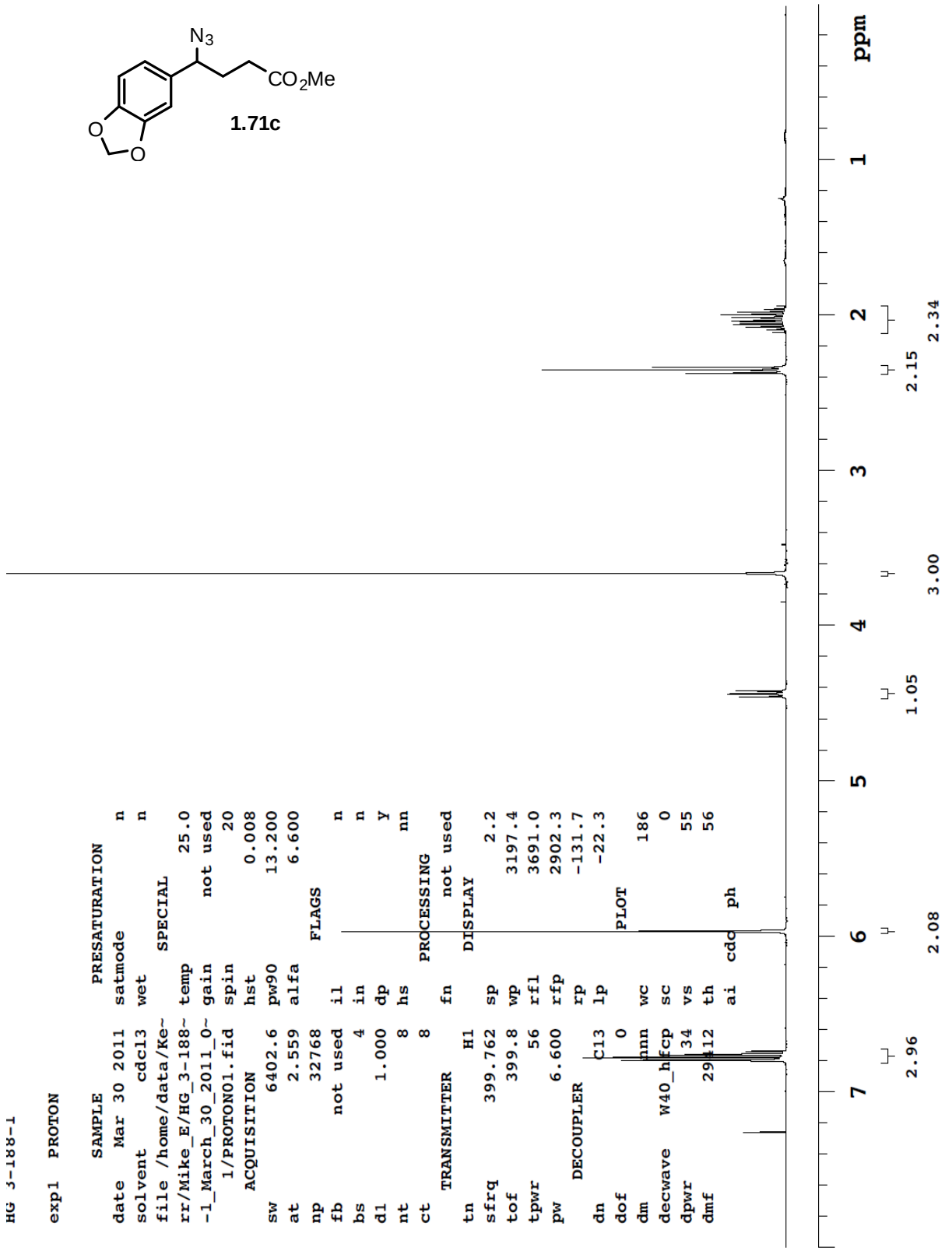


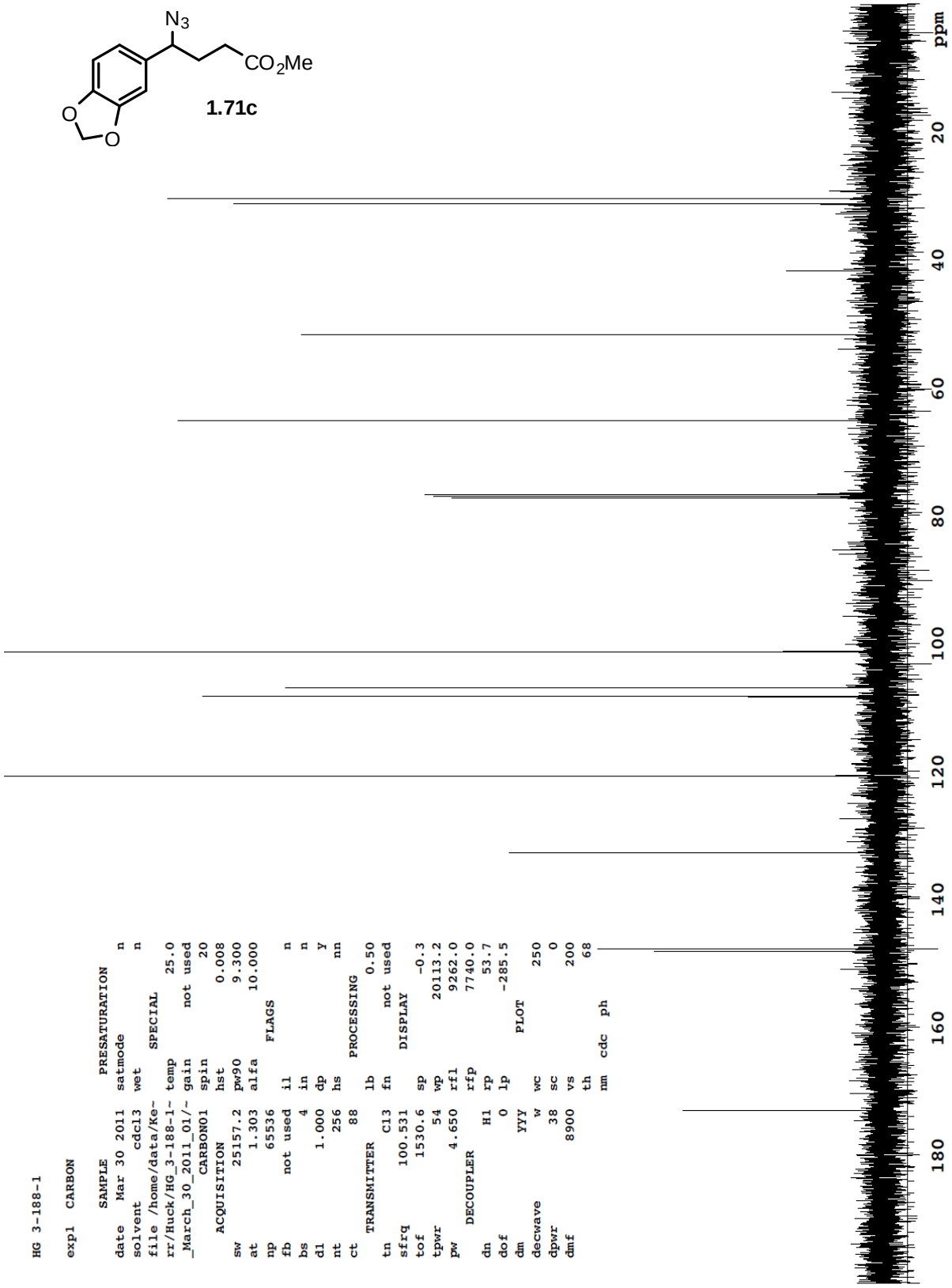
1.67

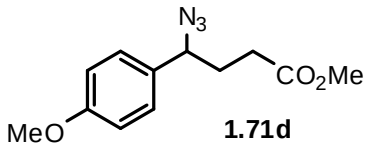




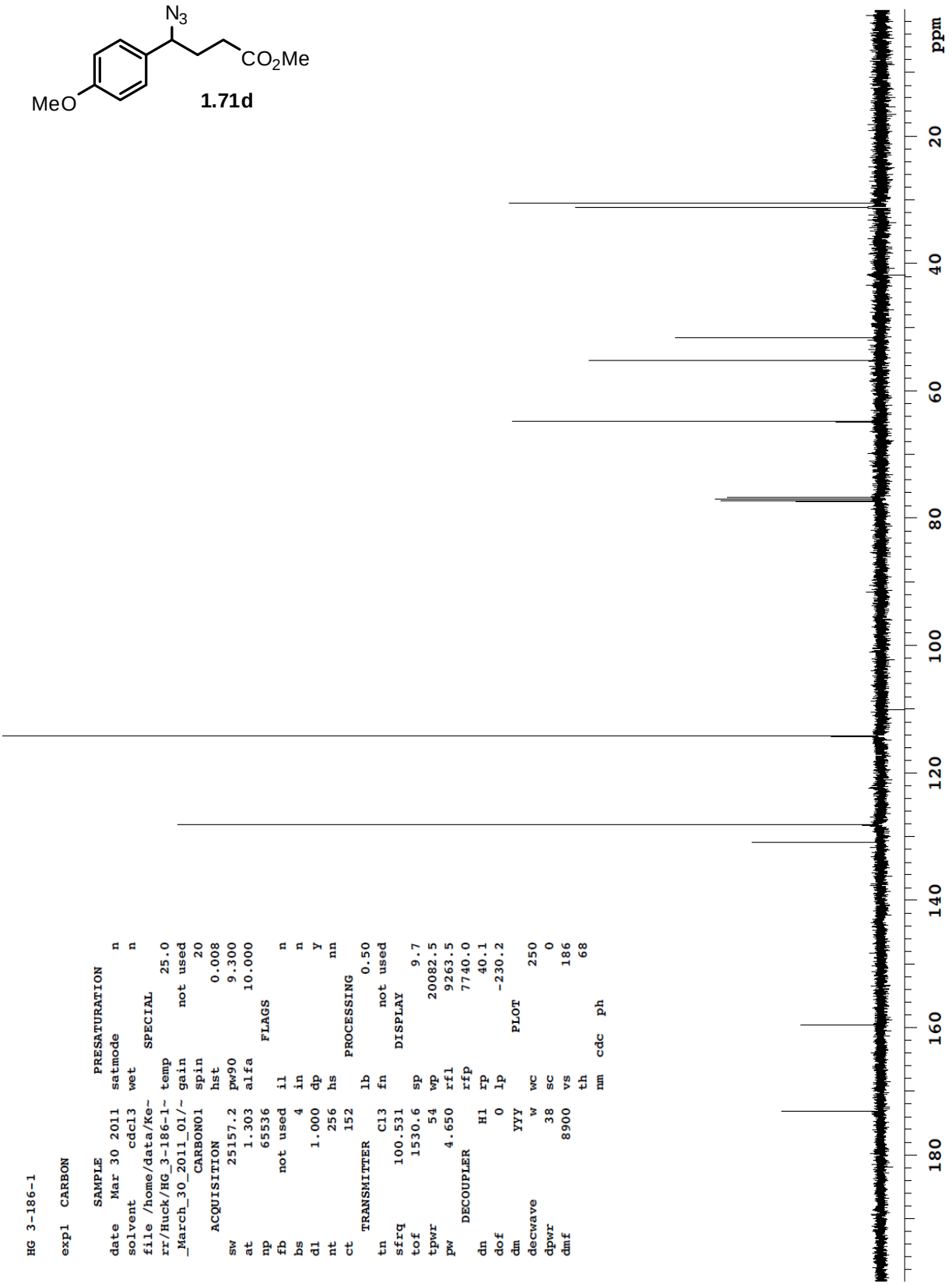

```
ME 4-75-1

expl  CARBON

      SAMPLE                PRESATURATION
date   Mar 30 2011  satmode          n
solvent      cdcl3  wet              n
file /home/data/Ke-          SPECIAL
rr/Mike/ME_4-75-1_~ temp          25.0
March_3_2011_01/CA~ gain      not used
         RBNO1    spin              20
   ACQUISITION       hst           0.008
sw       25157.2  pw90           9.300
at           1.303  alfa        10.000
np           65536          FLAGS
fb       not used  il               n
bs              4  in               n
d1          1.000  dp               y
nt            256  hs              nn
ct            256          PROCESSING
   TRANSMITTER       lb            0.50
tn           C13  fn       not used
sfrq      100.531          DISPLAY
tof      1530.6   sp              31.2
tpwr          54  wp           20113.2
pw         4.650  rfl           9258.9
   DECOUPLER       rfp           7740.0
dn             H1  rp              70.3
dof             0  lp            -317.0
dm            yyy          PLOT
decwave         w  wc             250
dpwr           38  sc               0
dmf          8900  vs             162
                   th              68
                      nm  cdc  ph
```



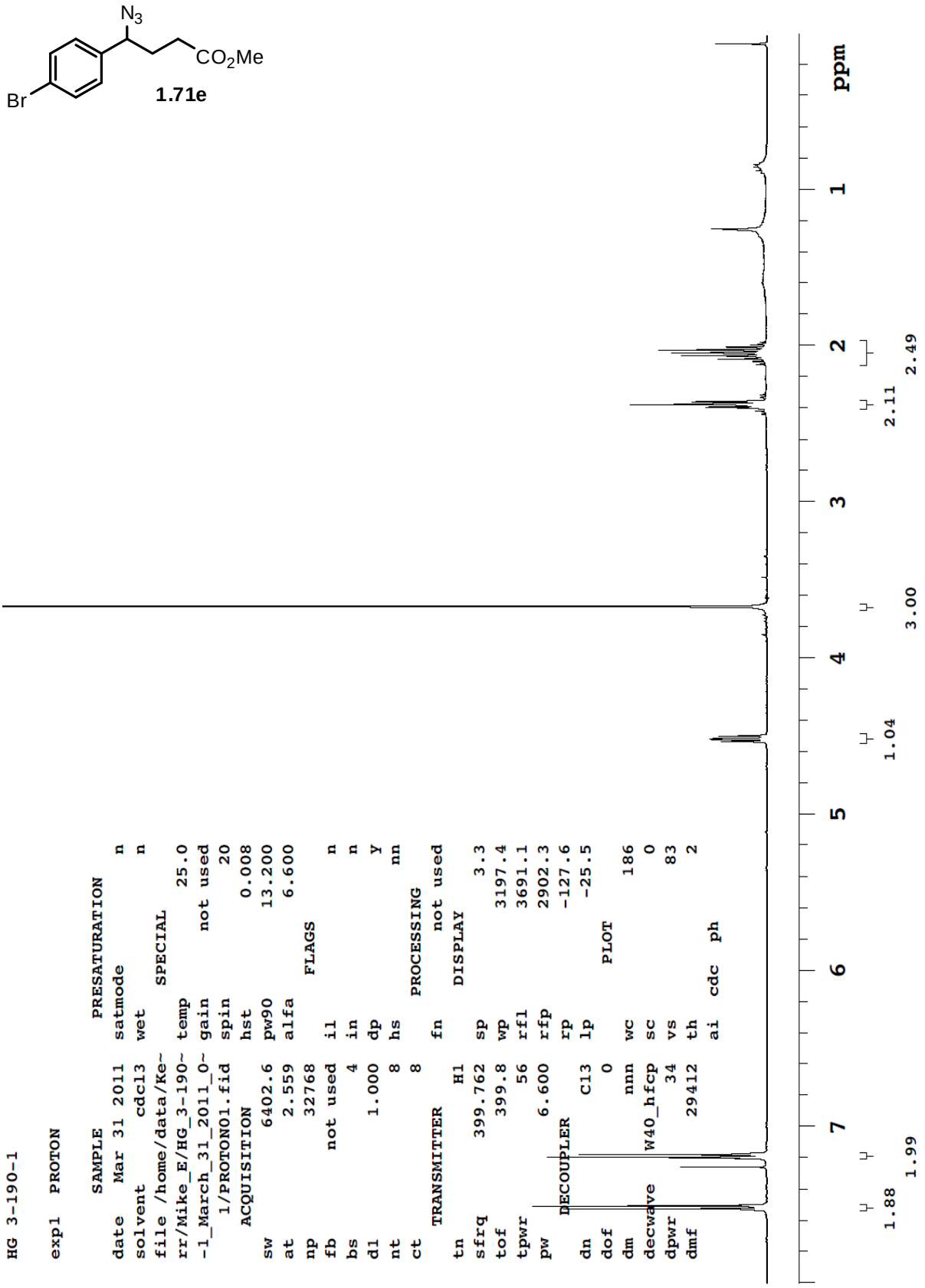


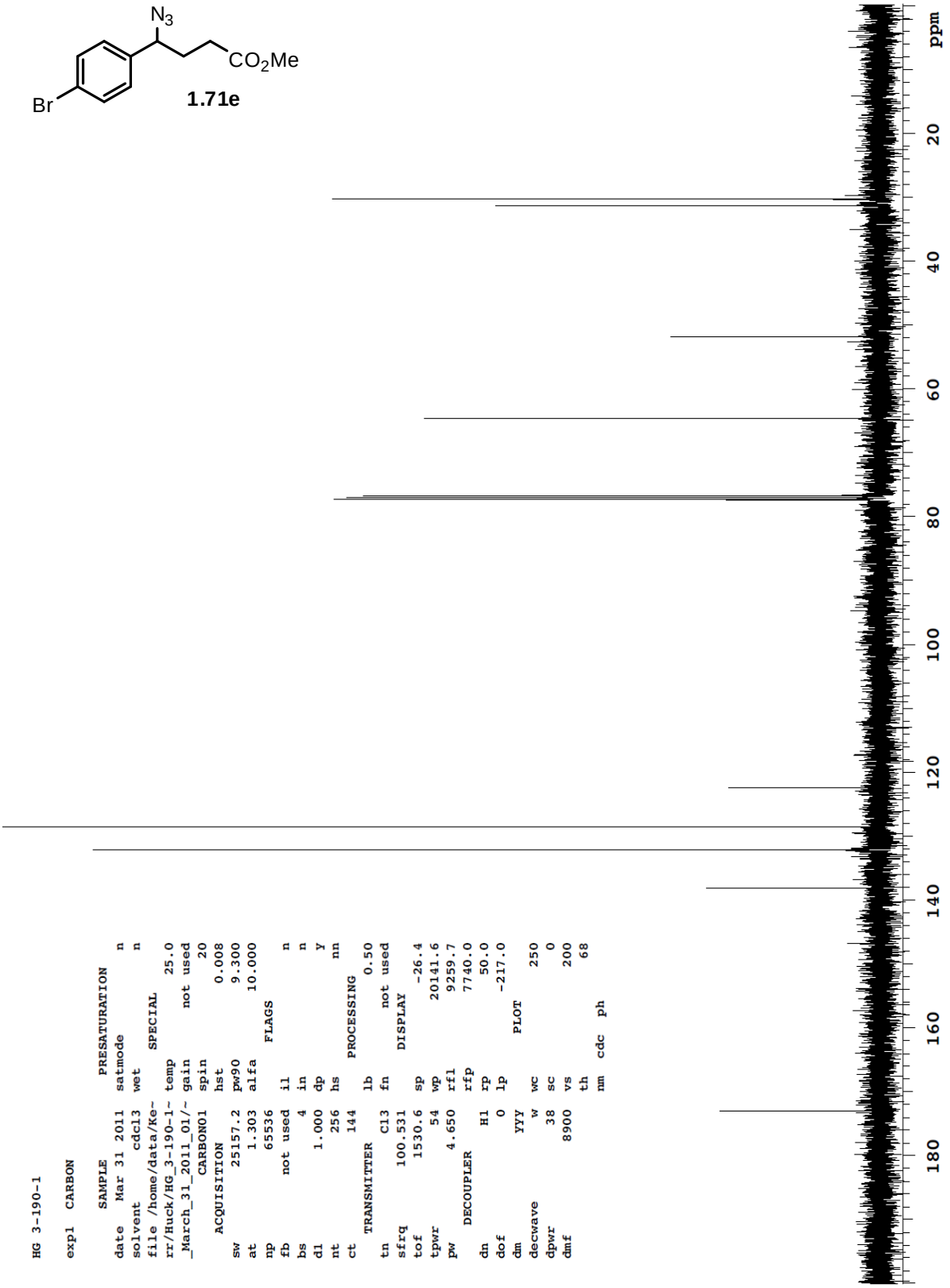


1.71d

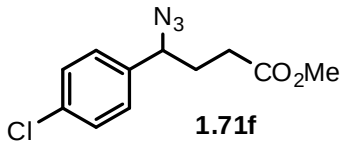



```
HG 3-186-1

exp1  CARBON

      SAMPLE                PRESATURATION
date   Mar 30 2011  satmode          n
solvent     cdcl3   wet              n
file /home/data/Ke-              SPECIAL
rr/Huck/HG_3-186-1~ temp            25.0
_March_30_2011_01/~ gain         not used
         CARBON01   spin               20
    ACQUISITION     hst             0.008
sw        25157.2   pw90            9.300
at            1.303 alfa           10.000
np            65536           FLAGS
fb       not used   il                 n
bs              4   in                 n
d1          1.000   dp                 y
nt            256   hs                nn
ct            152           PROCESSING
   TRANSMITTER      lb              0.50
tn             C13  fn          not used
sfrq        100.531           DISPLAY
tof          1530.6  sp              9.7
tpwr           54    wp          20082.5
pw           4.650   rfl          9263.5
   DECOUPLER        rfp          7740.0
dn             H1    rp             40.1
dof             0    lp           -230.2
dm             yyy           PLOT
decwave          w   wc              250
dpwr            38   sc                0
dmf           8900   vs              186
                     th               68
                     nm  cdc  ph
```



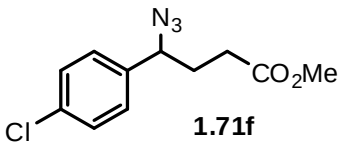



```
HG 3-190-1

expl  CARBON

   SAMPLE          PRESATURATION
date   Mar 31 2011  satmode          n
solvent      cdcl3  wet              n
file /home/data/Ke-          SPECIAL
rr/Huck/HG_3-190-1-  temp         25.0
_March_31_2011_01/-  gain      not used
          CARBON01  spin             20
   ACQUISITION     hst           0.008
sw         25157.2  pw90          9.300
at             1.303  alfa       10.000
np             65536          FLAGS
fb       not used  il               n
bs             4   in               n
d1             1.000  dp           y
nt             256  hs             nn
ct             144          PROCESSING
  TRANSMITTER      lb            0.50
tn           C13  fn       not used
sfrq       100.531       DISPLAY
tof        1530.6  sp          -26.4
tpwr           54  wp        20141.6
pw             4.650  rfl      9259.7
   DECOUPLER       rfp         7740.0
dn           H1  rp             50.0
dof            0  lp           -217.0
dm           yyy          PLOT
decwave          w  wc           250
dpwr            38  sc             0
dmf           8900  vs           200
                    th            68
                    nm  cdc  ph
```



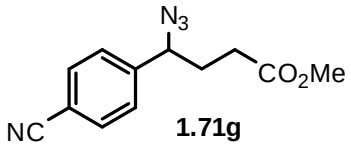
1.71f


```
HG 4-54-1

exp1  PROTON

      SAMPLE          PRESATURATION
date   Apr 23 2011  satmode          n
solvent    cdcl3    wet              n
file /home/data/Ke~          SPECIAL
rr/Huck/HG_4-54-1_~ temp         25.0
April_23_2011_01/P~ gain      not used
      ROTON01.fid   spin           20
   ACQUISITION      hst         0.008
sw        6402.6    pw90       13.200
at         2.559    alfa        6.600
np         32768          FLAGS
fb     not used    il             n
bs            4    in             n
d1        1.000    dp             y
nt            8    hs            nn
ct            8          PROCESSING
   TRANSMITTER      fn      not used
tn           H1          DISPLAY
sfrq     399.762    sp         -6.7
tof        399.8    wp      3606.1
tpwr          56    rfl      802.7
pw         6.600    rfp          0
   DECOUPLER      rp       -135.1
dn           C13    lp        -15.0
dof            0          PLOT
dm           nnn    wc          250
decwave  W40_hfcp    sc            0
dpwr          34    vs           76
dmf        29412    th           27
                    ai   cdc   ph
```

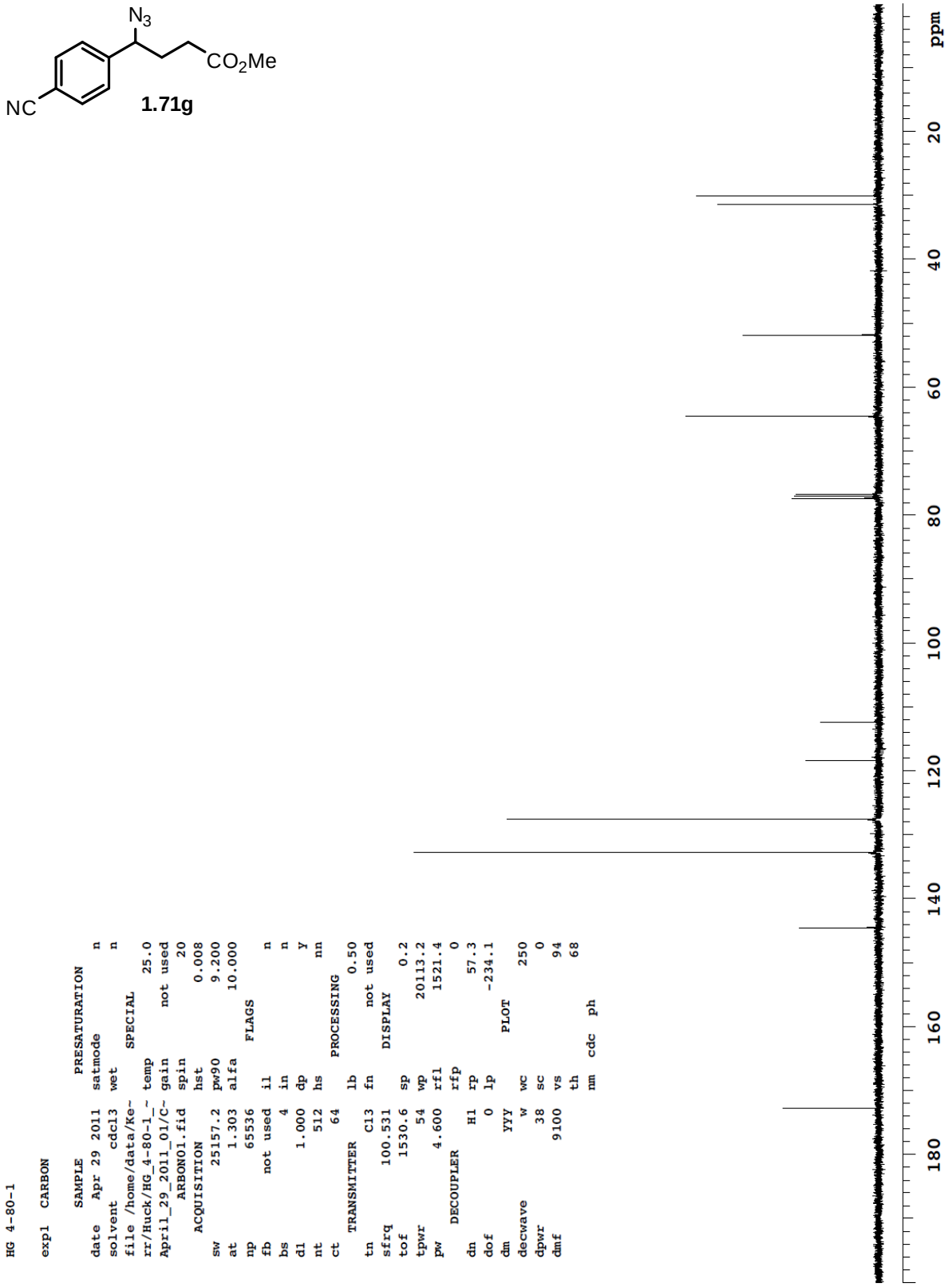


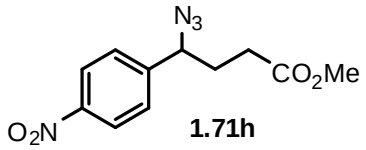
1.71f


```
HG 4-54-1

exp1  CARBON

      SAMPLE          PRESATURATION          n
date  Apr 23 2011    satmode                n
solvent    cdcl3     wet                    n
file /home/data/Ke-          SPECIAL
rr/Huck/HG_4-54-1_~  temp          25.0
April_23_2011_01/C~  gain      not used
      ARBON01.fid    spin            20
   ACQUISITION       hst          0.008
sw        25157.2    pw90         9.300
at            1.303  alfa        10.000
np          65536          FLAGS
fb       not used    il             n
bs              4    in             n
dl          1.000    dp             y
nt            512    hs            nn
ct             48          PROCESSING
   TRANSMITTER       lb           0.50
tn             C13    fn       not used
sfrq      100.531          DISPLAY
tof      1530.6    sp             0.4
tpwr           54    wp       22113.9
pw          4.650    rf1       9261.2
   DECOUPLER         rfp       7740.0
dn             H1     rp          75.9
dof             0     lp       -267.8
dm            yyy          PLOT
decwave         w     wc           250
dpwr           38     sc             0
dmf          8900     vs           121
                      th            68
                         nm   cdc   ph
```

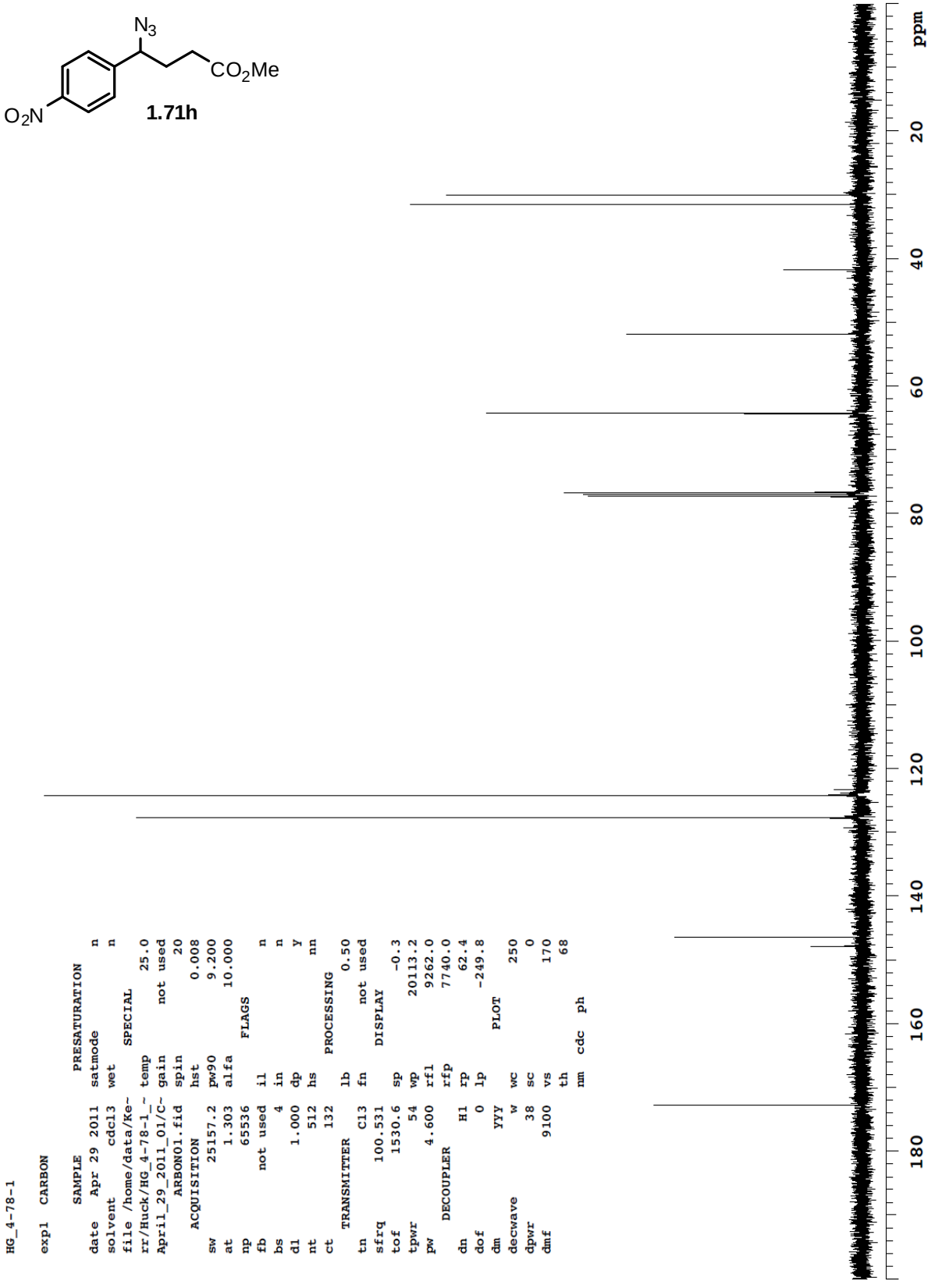


1.71g

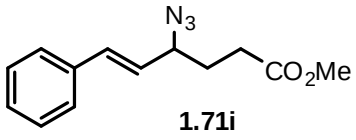




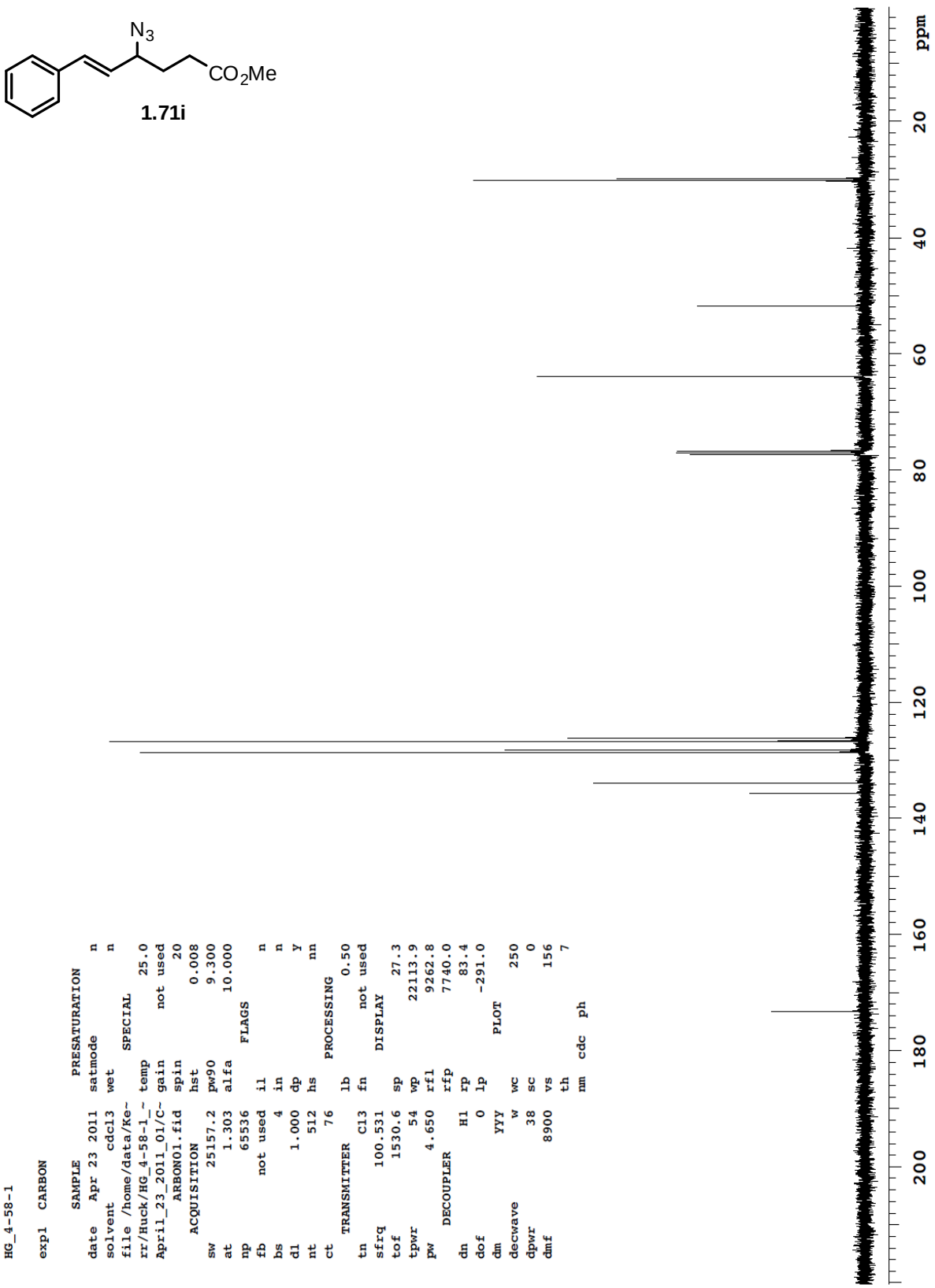
1.71h

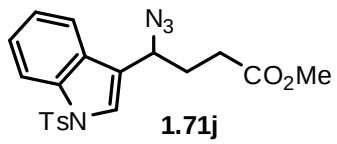



```
HG_4-78-1

expl  CARBON

      SAMPLE                PRESATURATION
date    Apr 29 2011  satmode          n
solvent     cdcl3    wet              n
file /home/data/Ke~          SPECIAL
rr/Huck/HG_4-78-1_~ temp          25.0
April_29_2011_01/C~ gain      not used
      ARBON01.fid  spin            20
   ACQUISITION          hst       0.008
sw        25157.2  pw90          9.200
at            1.303  alfa       10.000
np            65536          FLAGS
fb        not used  il               n
bs               4  in               n
d1           1.000  dp               y
nt             512  hs              nn
ct             132          PROCESSING
   TRANSMITTER     lb            0.50
tn          C13   fn        not used
sfrq     100.531          DISPLAY
tof       1530.6  sp            -0.3
tpwr          54  wp         20113.2
pw         4.600  rf1         9262.0
   DECOUPLER          rfp       7740.0
dn             H1  rp            62.4
dof             0  lp          -249.8
dm                yyy          PLOT
decwave          w  wc             250
dpwr            38  sc               0
dmf           9100  vs             170
                    th              68
                    nm  cdc  ph
```



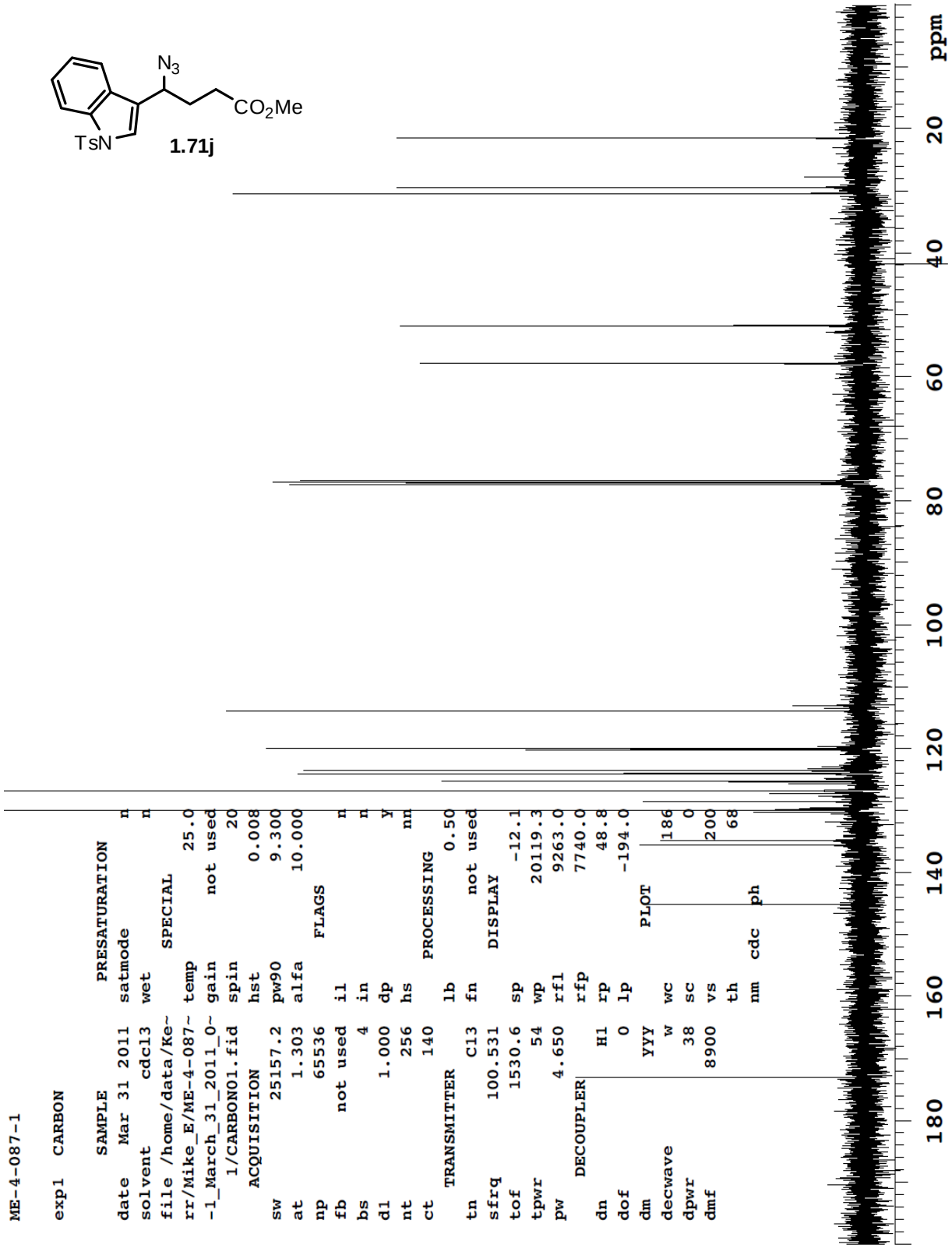
1.71i





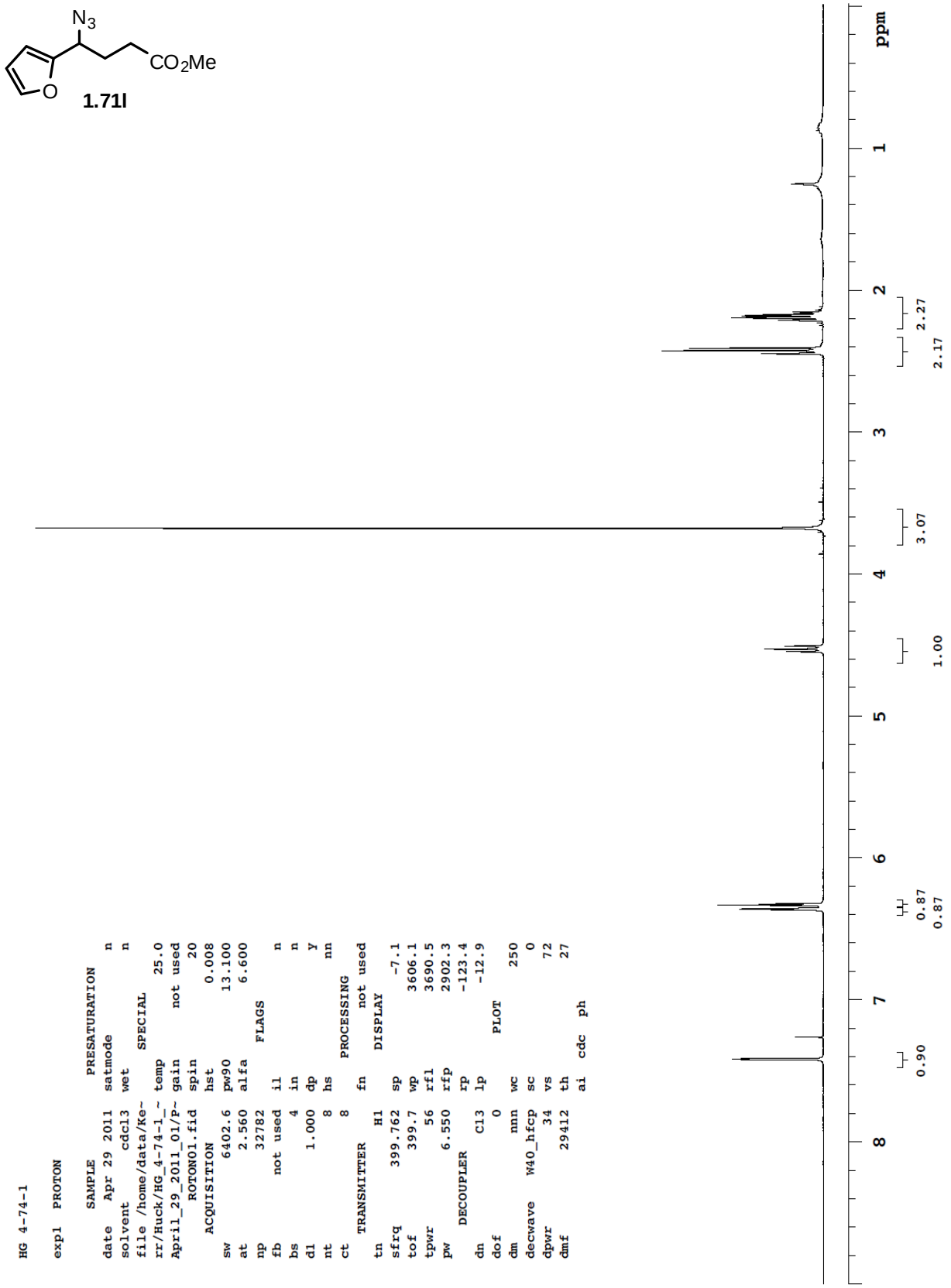
1.71j

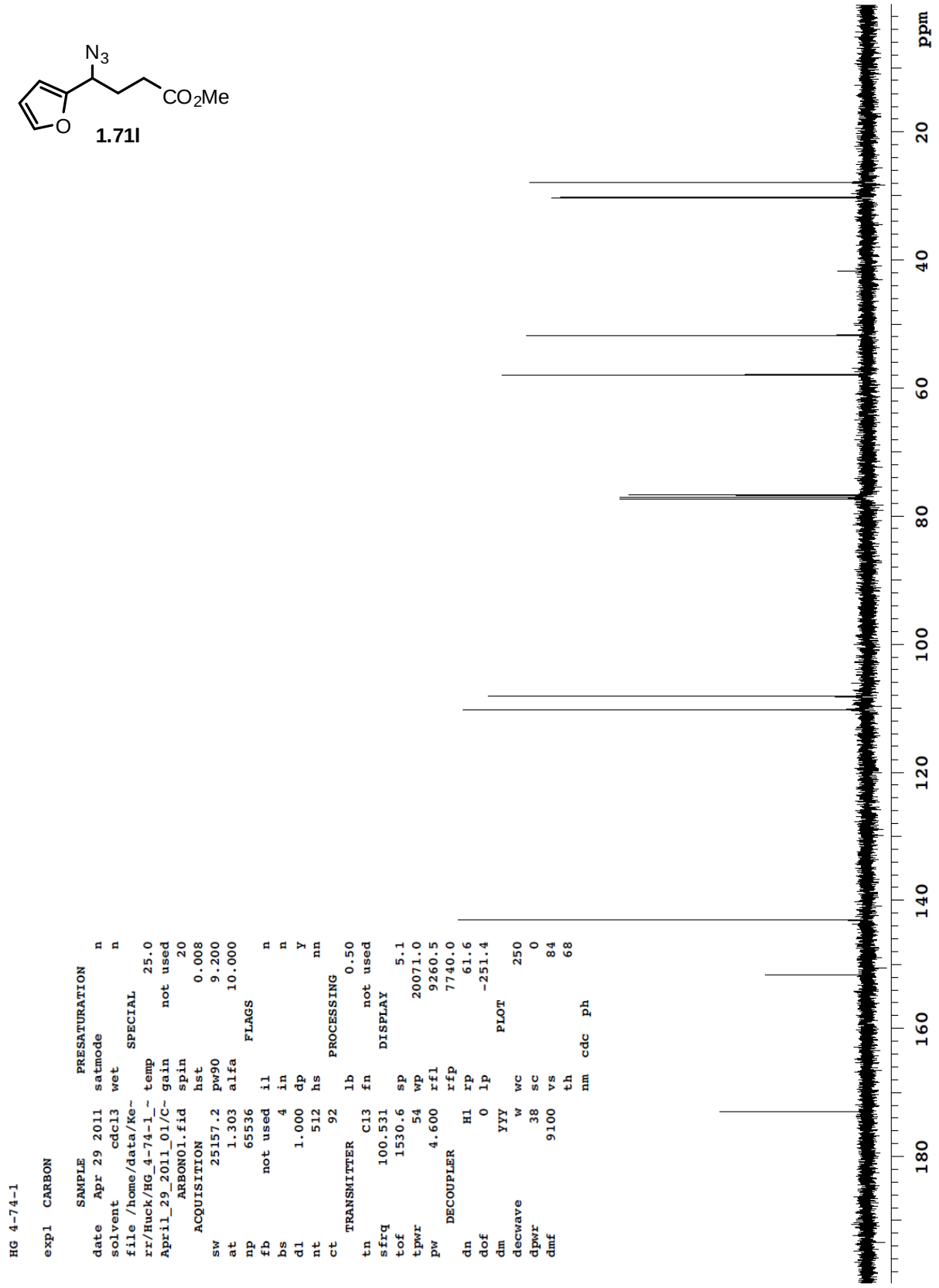

```
HG 4-56-1

expl  PROTON

      SAMPLE                  PRESATURATION
date   Apr 23 2011  satmode              n
solvent      cdcl3  wet                  n
file /home/data/Ke~          SPECIAL
rr/Huck/HG_4-56-1_~  temp                25.0
April_23_2011_01/P~  gain        not used
      ROTON01.fid  spin                 20
   ACQUISITION     hst               0.008
sw          6402.6  pw90             13.200
at           2.559  alfa              6.600
np           32768          FLAGS
fb       not used  il                   n
bs              4  in                   n
d1          1.000  dp                   y
nt              8  hs                  nn
ct              8          PROCESSING
   TRANSMITTER             fn       not used
tn              H1          DISPLAY
sfrq       399.762  sp                -6.7
tof          399.8  wp             3598.7
tpwr            56  rf1            3689.8
pw           6.600  rfp            2902.3
   DECOUPLER       rp             -131.6
dn              C13  lp               -19.9
dof               0          PLOT
dm              nnn  wc                250
decwave   W40_hfcp  sc                  0
dpwr             34  vs                 99
dmf           29412  th                 54
                     ai  cdc  ph
```

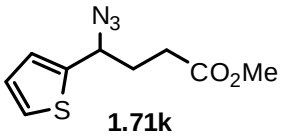


ME-4-087-1

```
expl  CARBON

      SAMPLE          PRESATURATION
date   Mar 31 2011  satmode          n
solvent     cdcl3   wet              n
file /home/data/Ke~      SPECIAL
rr/Mike_E/ME-4-087~ temp                25.0
-1_March_31_2011_0~ gain         not used
   1/CARBON01.fid   spin                20
   ACQUISITION      hst               0.008
sw          25157.2  pw90              9.300
at            1.303  alfa             10.000
np            65536          FLAGS
fb        not used   il               n
bs               4   in               n
d1           1.000   dp               y
nt             256   hs               nn
ct             140        PROCESSING
   TRANSMITTER          lb              0.50
tn              C13     fn         not used
sfrq         100.531          DISPLAY
tof         1530.6   sp                -12.1
tpwr            54   wp             20119.3
pw           4.650   rfl             9263.0
   DECOUPLER        rfp             7740.0
dn                H1  rp                48.8
dof                0  lp              -194.0
dm               yyy          PLOT
decwave            w  wc                186
dpwr              38  sc                  0
dmf             8900  vs                200
                      th                 68
                      nm  cdc  ph
```

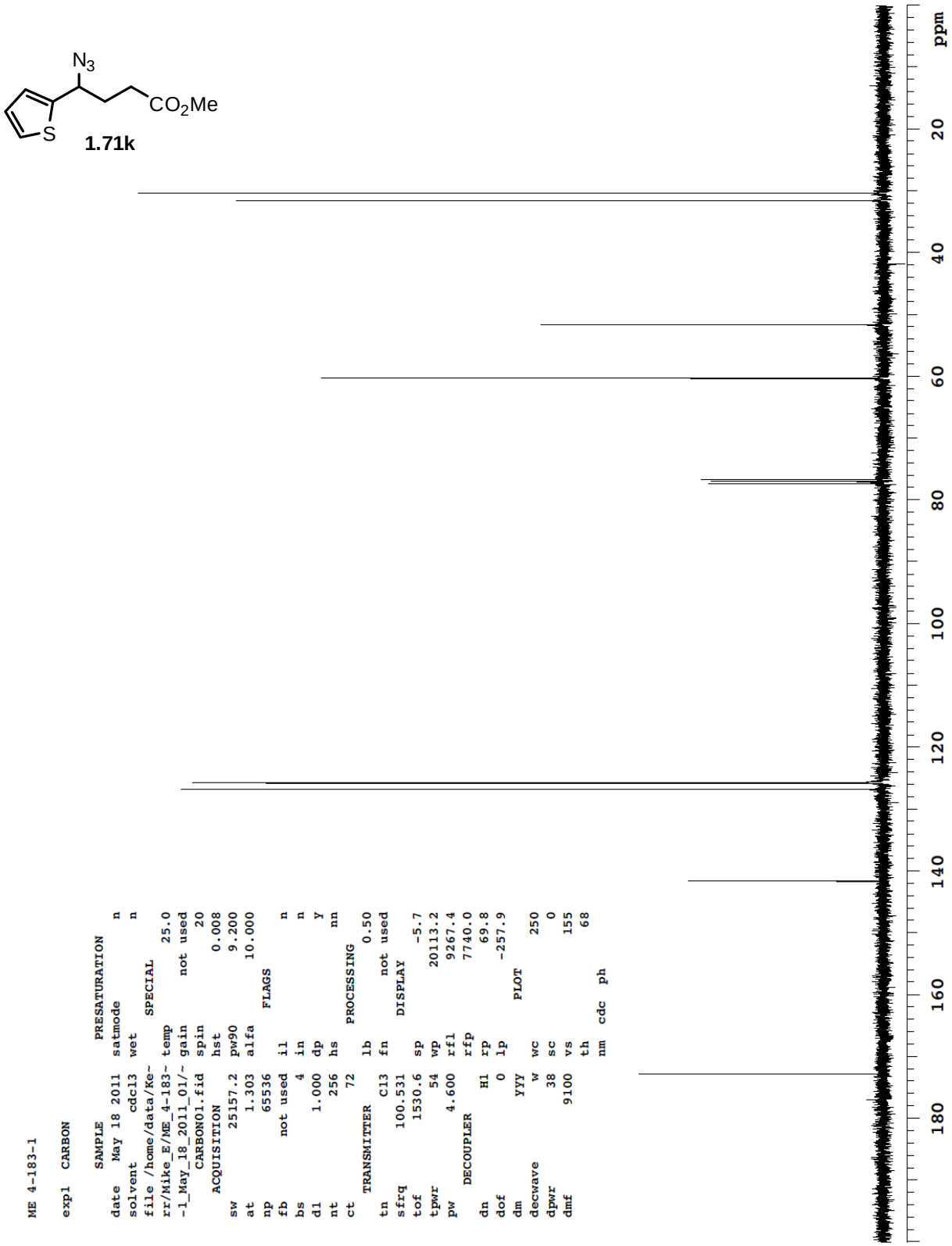




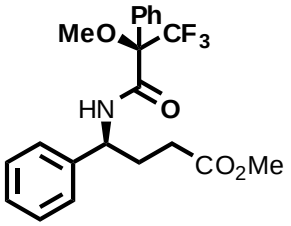


1.71k

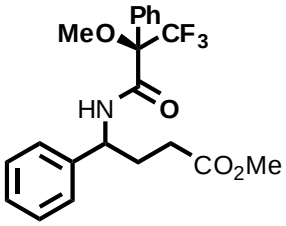

```
ME 4-183-1

  expl  PROTON

        SAMPLE          PRESATURATION          n
  date   May 18 2011    satmode                n
  solvent    cdcl3      wet
  file /home/data/Ke-                SPECIAL
  rr/Mike_E/ME_4-183-  temp                25.0
  -1_May_18_2011_01/~  gain            not used
     PROTON01.fid      spin                  20
    ACQUISITION        hst                0.008
  sw          6402.6   pw90               13.100
  at           2.559   alfa                6.600
  np           32768                FLAGS
  fb       not used    il                     n
  bs              4    in                     n
  d1          1.000    dp                     y
  nt              8    hs                    nn
  ct              8                PROCESSING
     TRANSMITTER          fn          not used
  tn              H1          DISPLAY
  sfrq       399.762   sp                  -6.7
  tof          399.8   wp                3606.1
  tpwr            56   rfl               3690.9
  pw           6.550   rfp               2902.3
     DECOUPLER        rp                 -122.2
  dn              C13   lp                  -4.8
  dof               0               PLOT
  dm              nnn   wc                  250
  decwave   W40_hfcp   sc                    0
  dpwr             34   vs                   32
  dmf           29412   th                   27
                        ai   cdc  ph
```



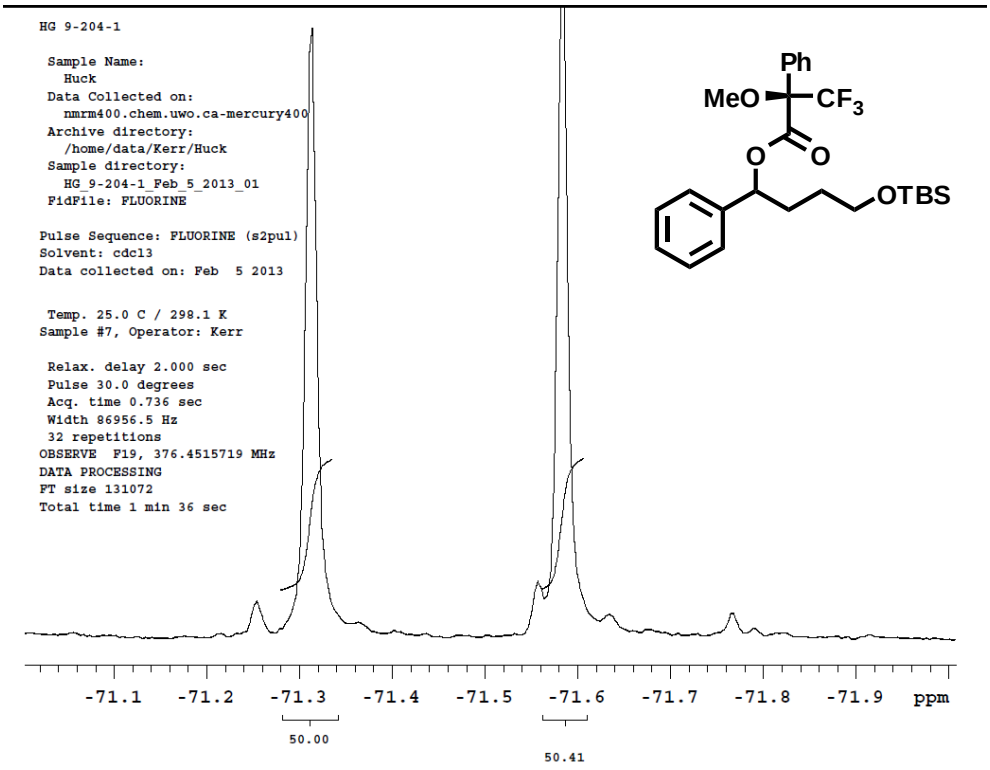

```
ME 4-183-1

expl  CARBON

        SAMPLE              PRESATURATION
date    May 18 2011 satmode          n
solvent     cdcl3   wet              n
file /home/data/Ke-         SPECIAL
rr/Mike_E/ME_4-183- temp            25.0
-1_May_18_2011_01/- gain        not used
      CARBON01.fid  spin              20
    ACQUISITION     hst           0.008
sw        25157.2   pw90          9.200
at          1.303   alfa         10.000
np          65536           FLAGS
fb      not used    il               n
bs             4    in               n
d1         1.000    dp               y
nt           256    hs              nn
ct            72             PROCESSING
    TRANSMITTER     lb            0.50
tn            C13   fn        not used
sfrq       100.531          DISPLAY
tof       1530.6    sp            -5.7
tpwr          54    wp         20113.2
pw         4.600    rf1         9267.4
    DECOUPLER       rfp         7740.0
dn             H1   rp            69.8
dof             0   lp          -257.9
dm            yyy           PLOT
decwave         w   wc             250
dpwr           38   sc               0
dmf          9100   vs             155
                    th              68
                    nm  cdc  ph
```

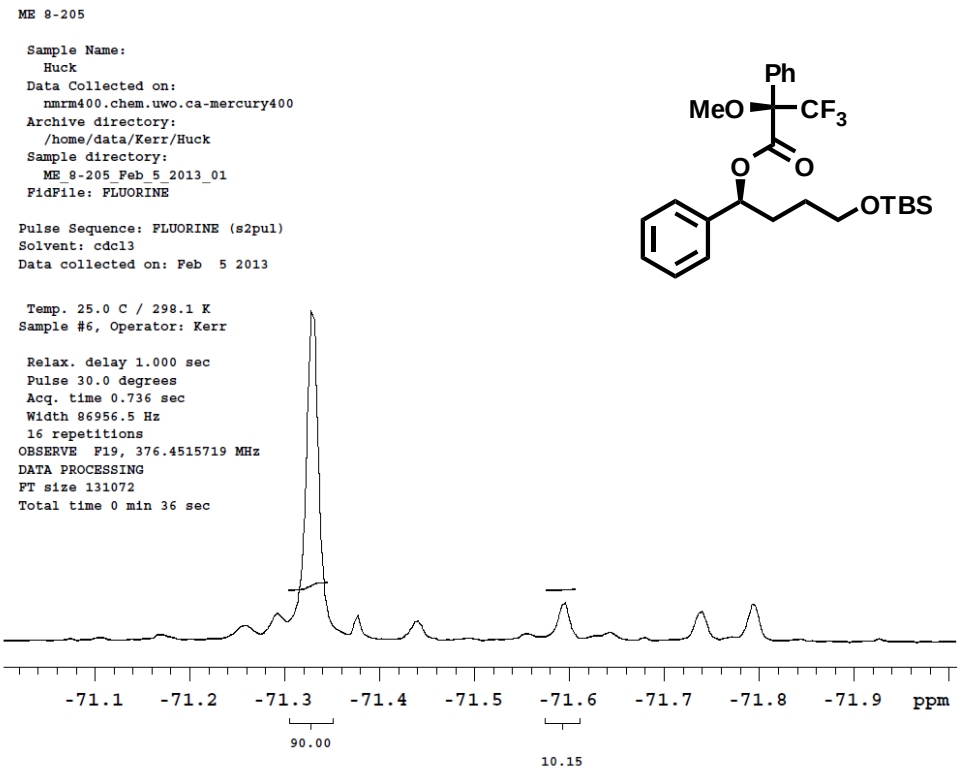


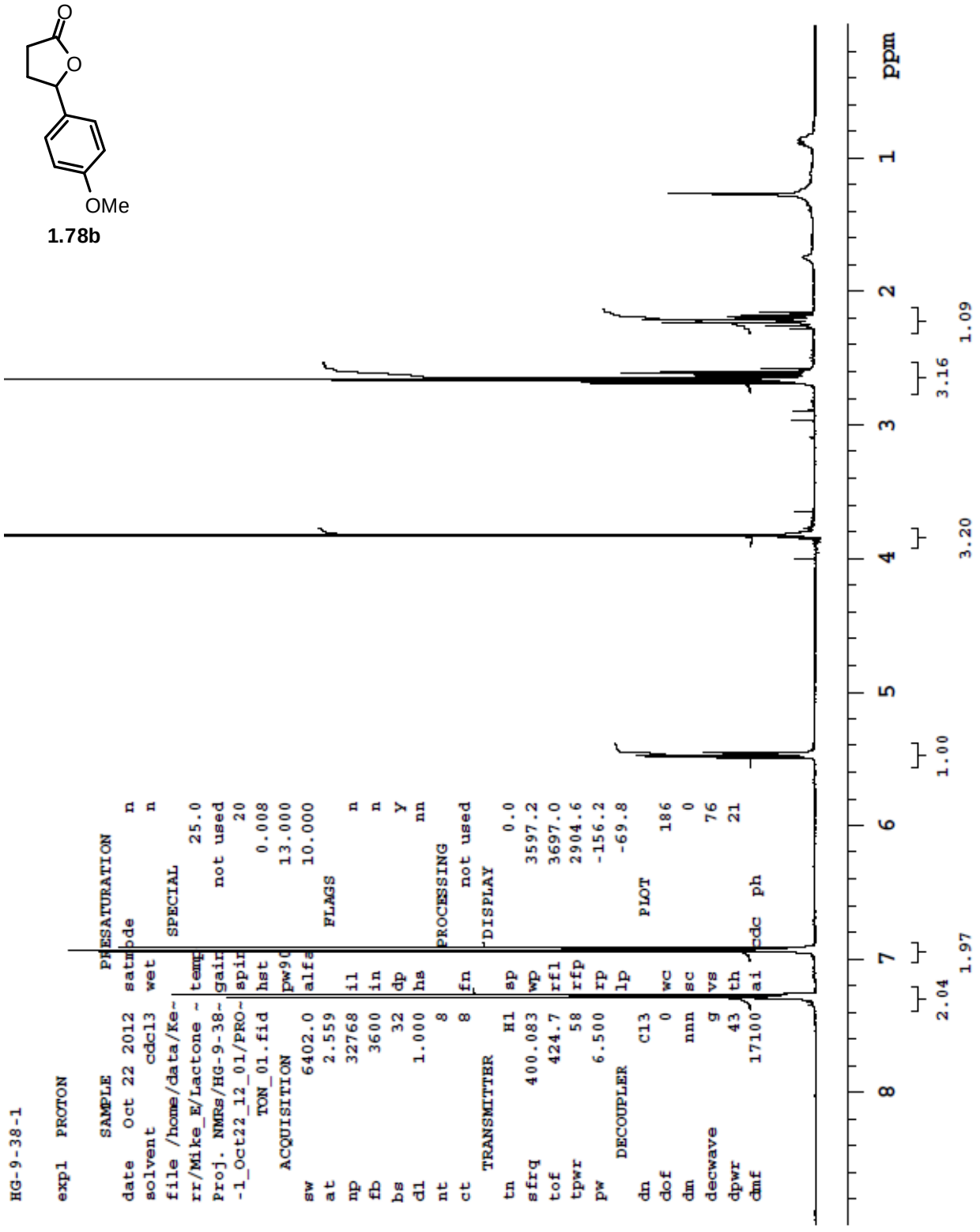
Mosher derivative of enantioenriched material: ^{19}F-NMR

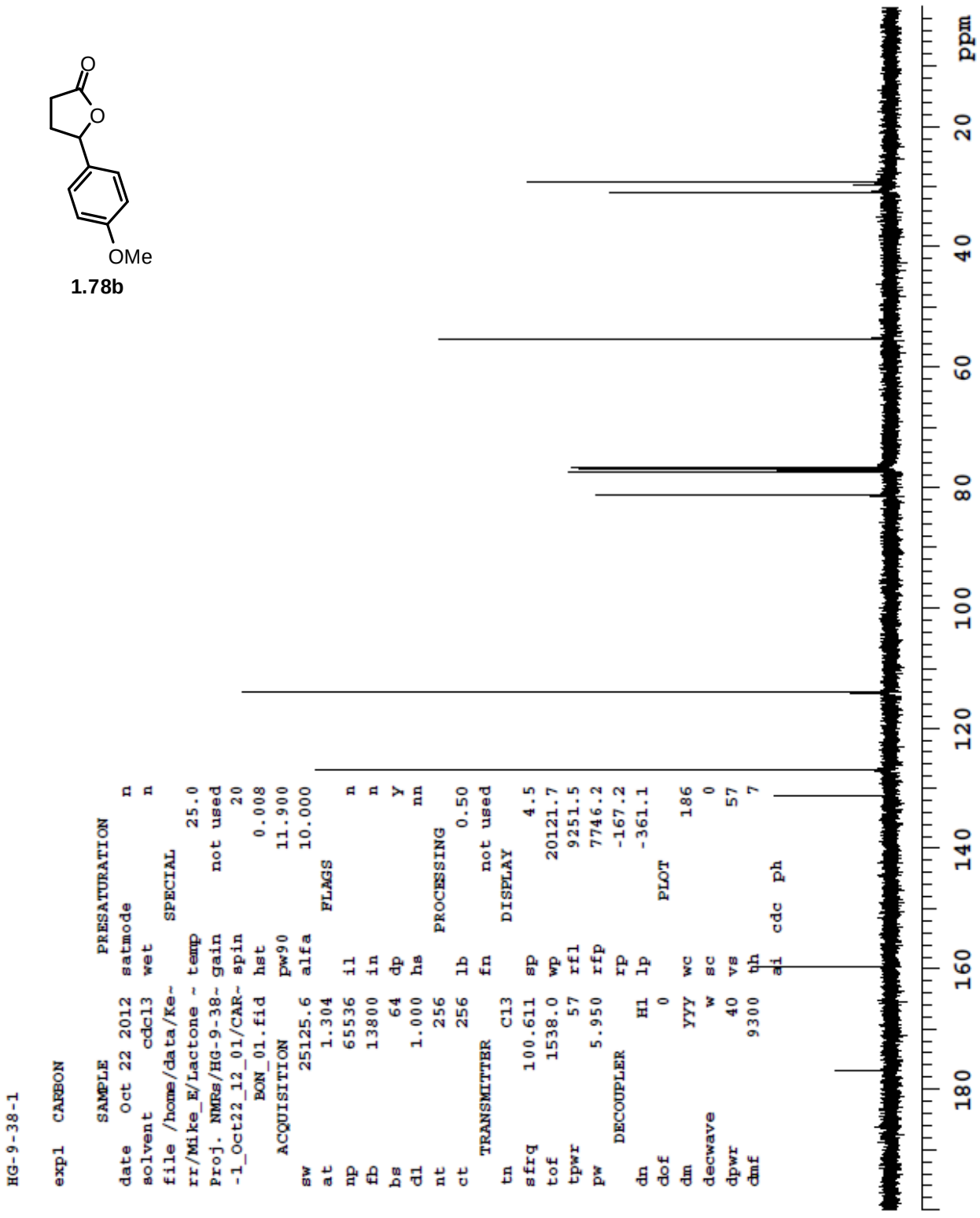


Mosher derivative of racemic material: ^{19}F-NMR

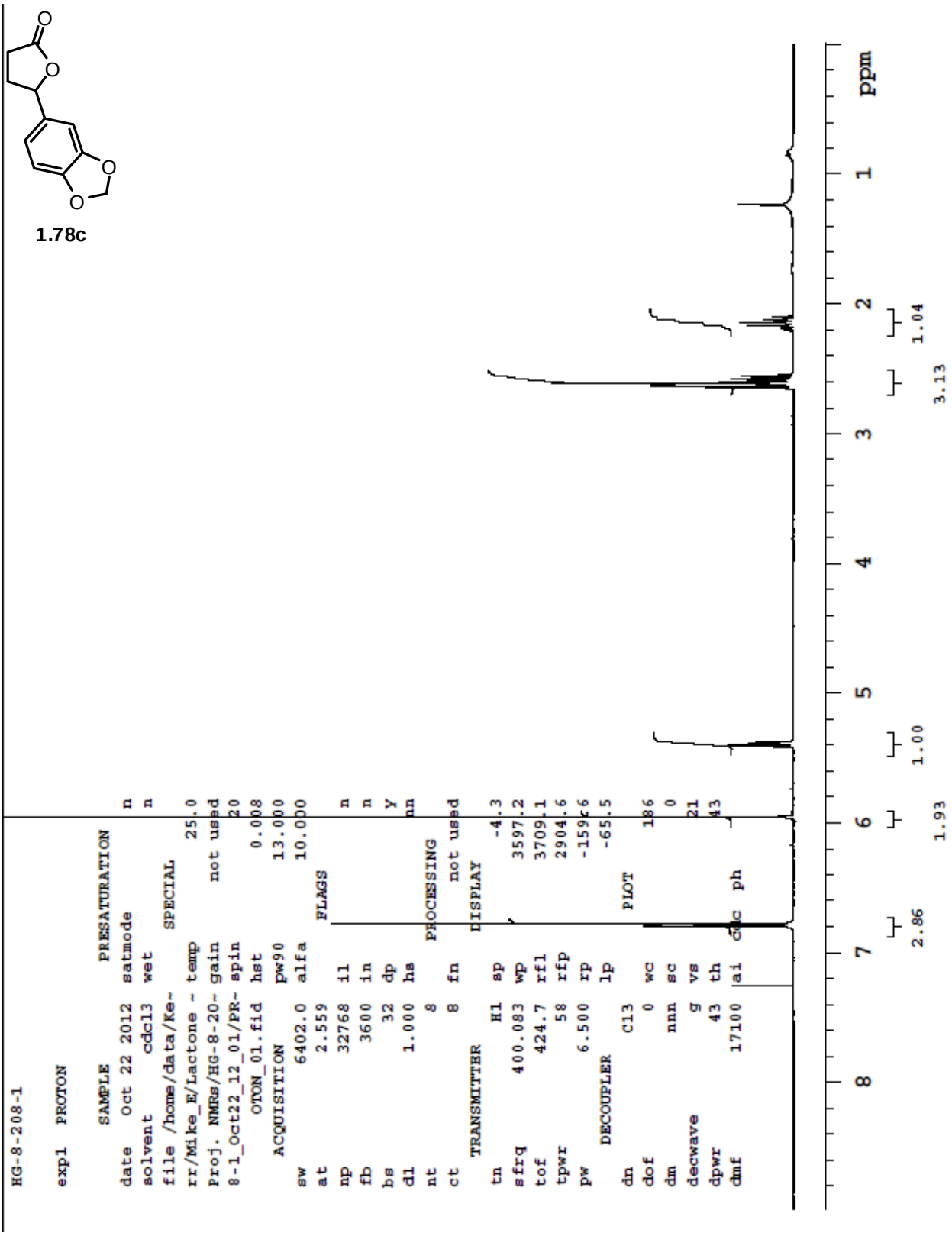


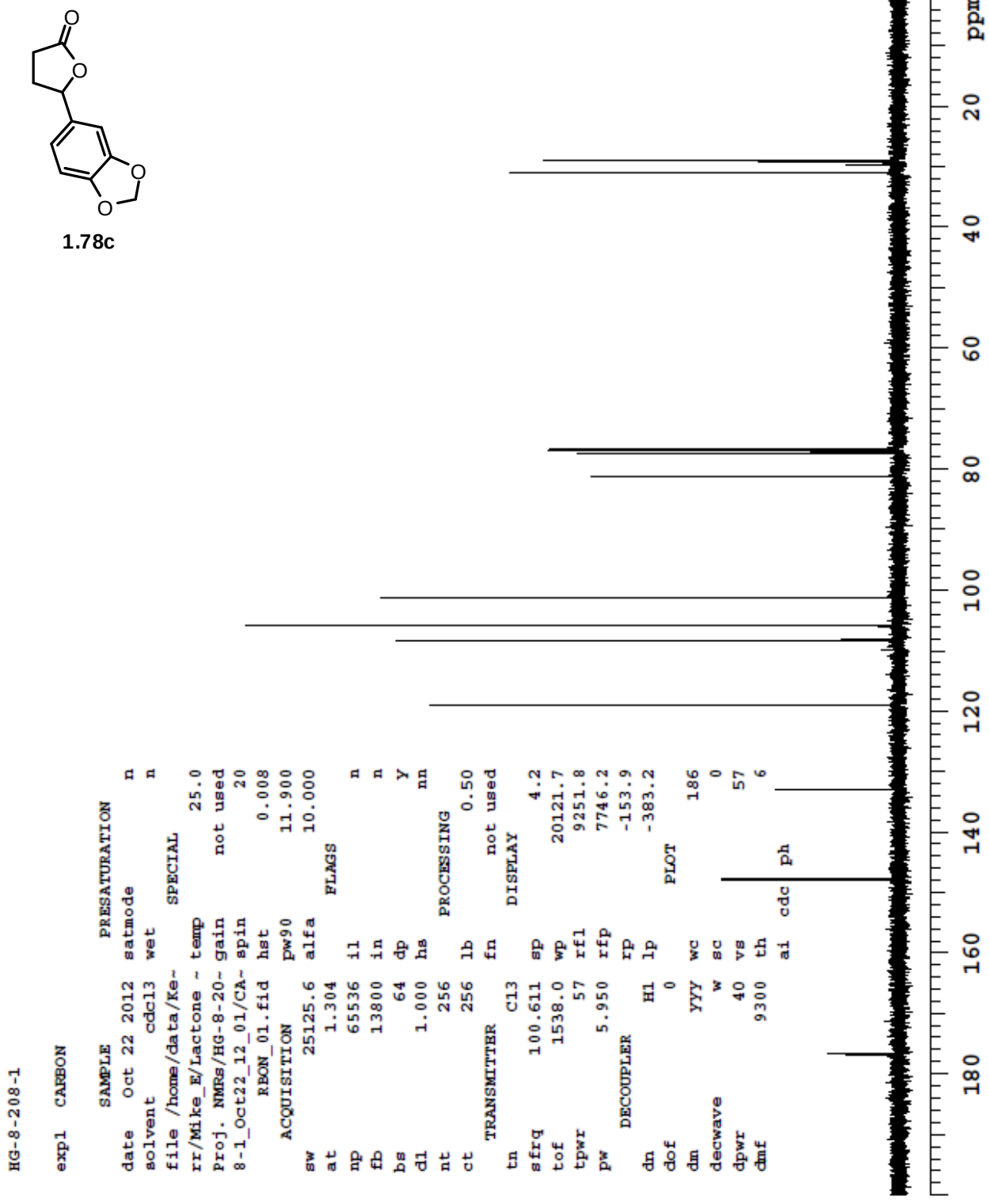


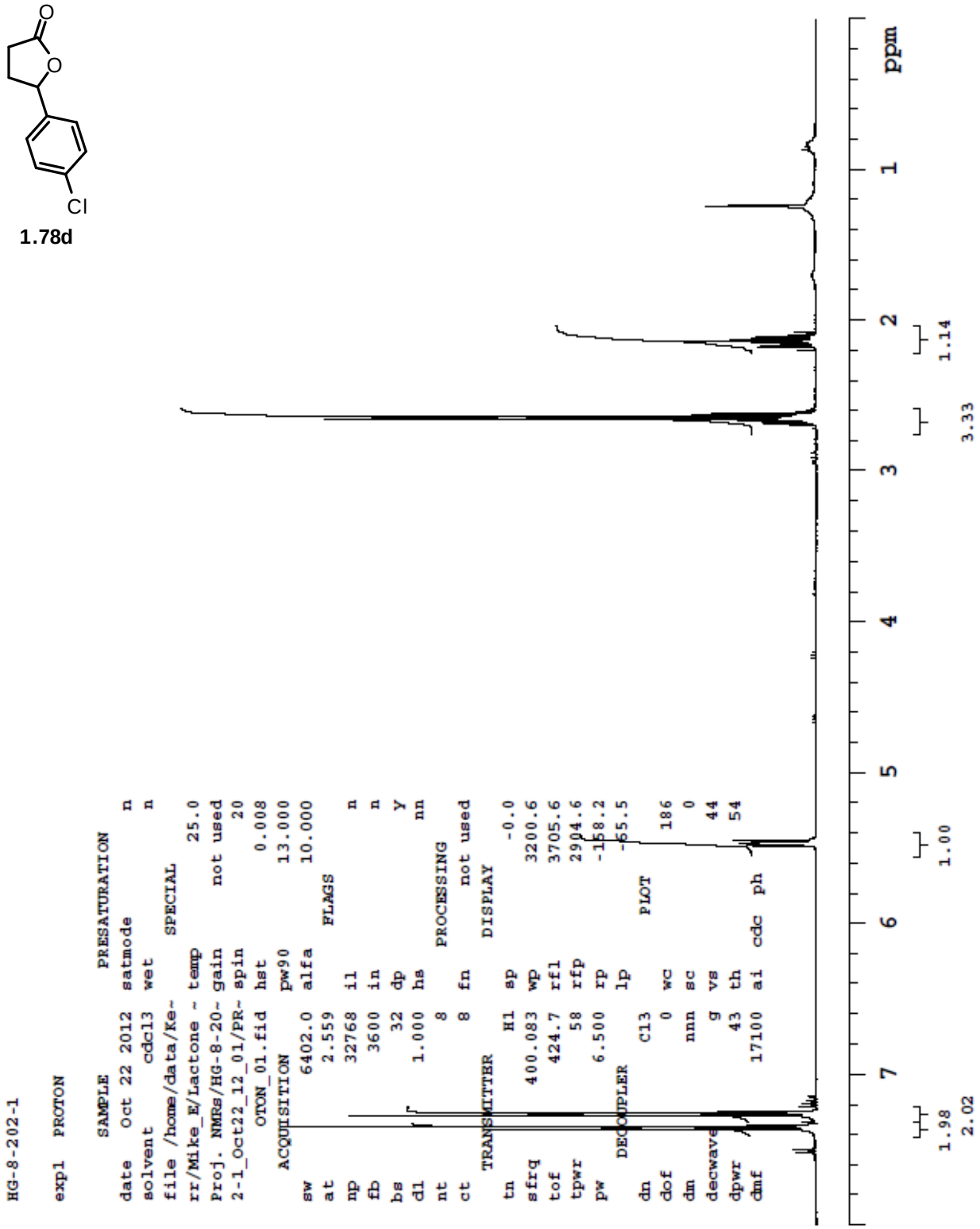


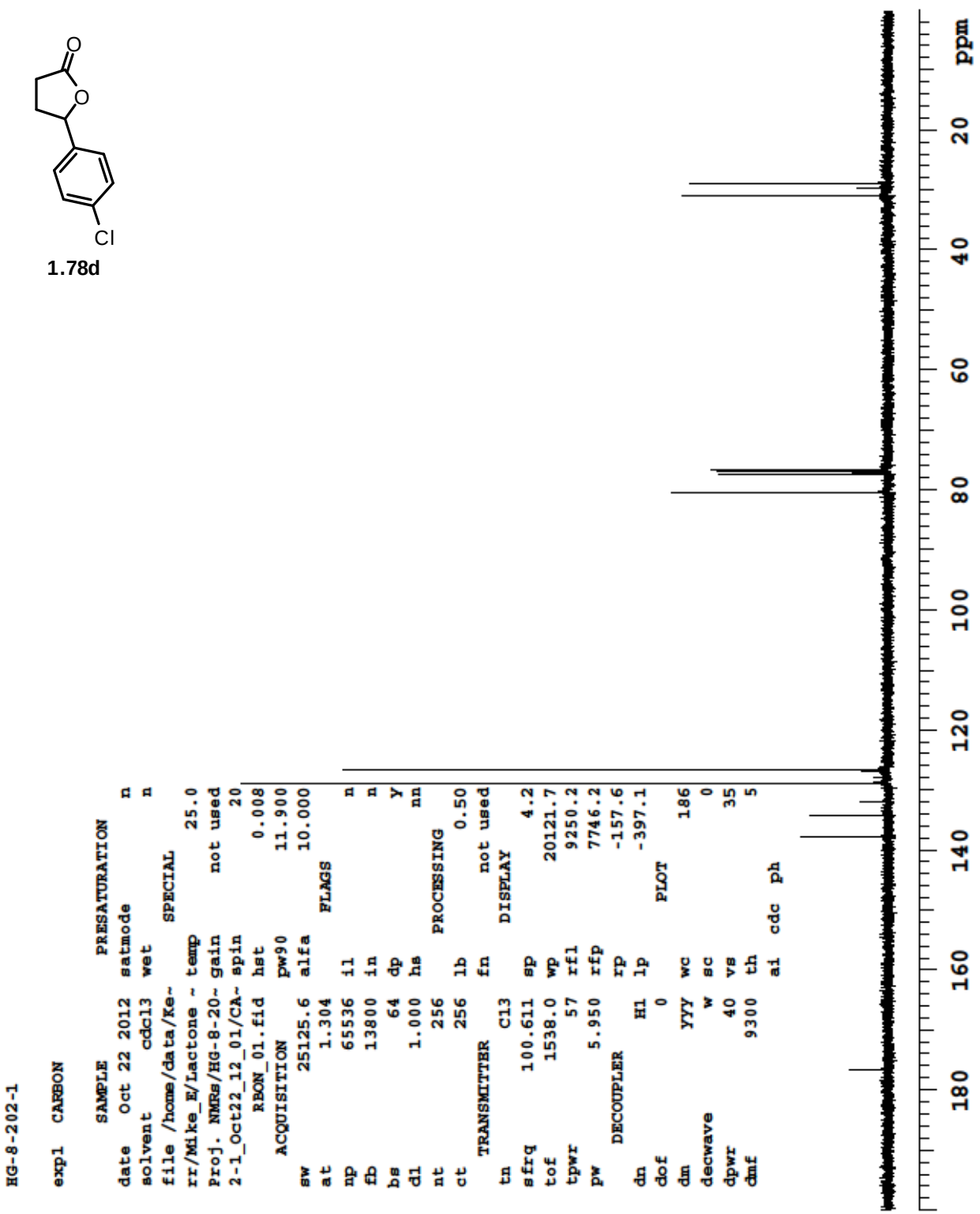


1.78b

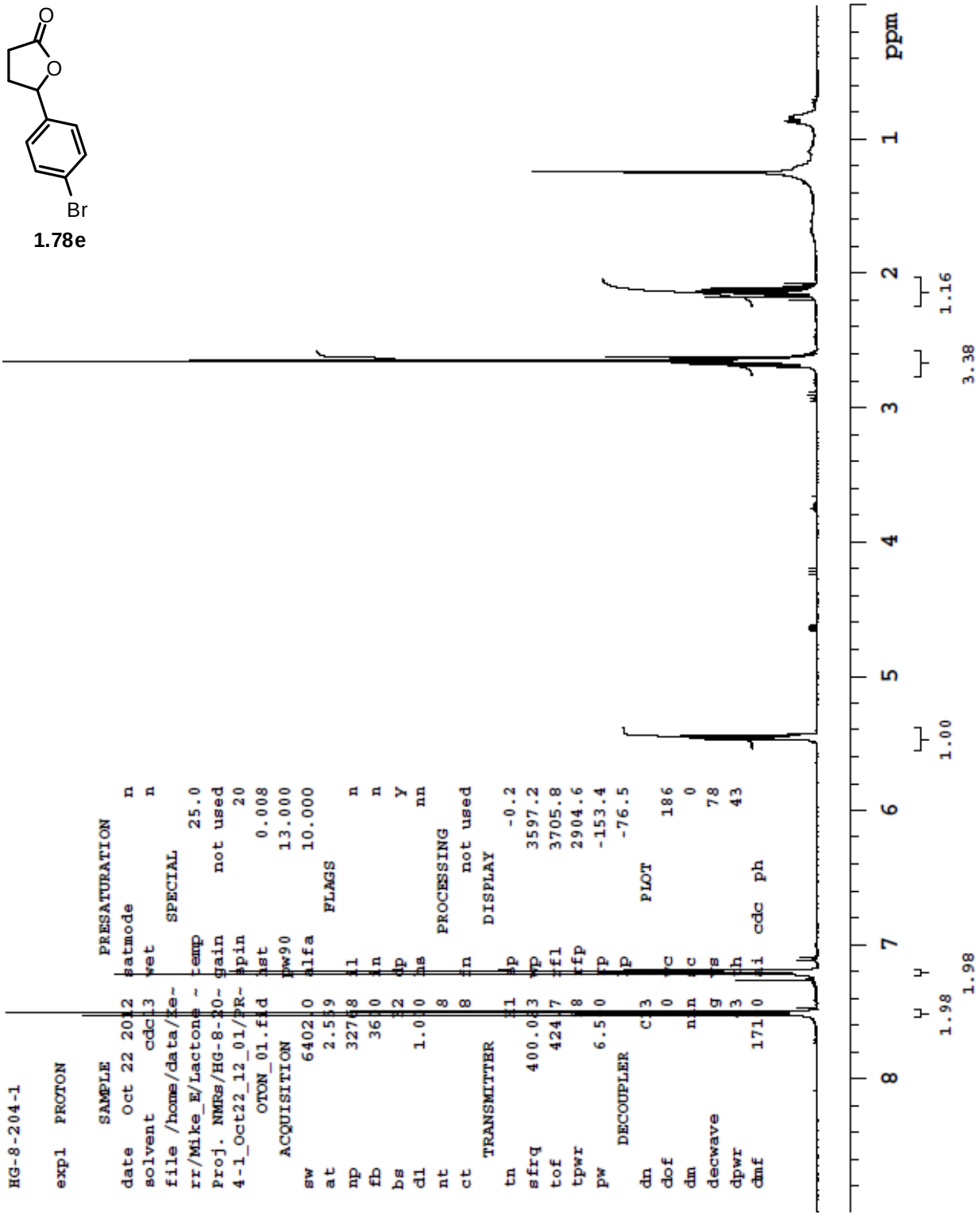


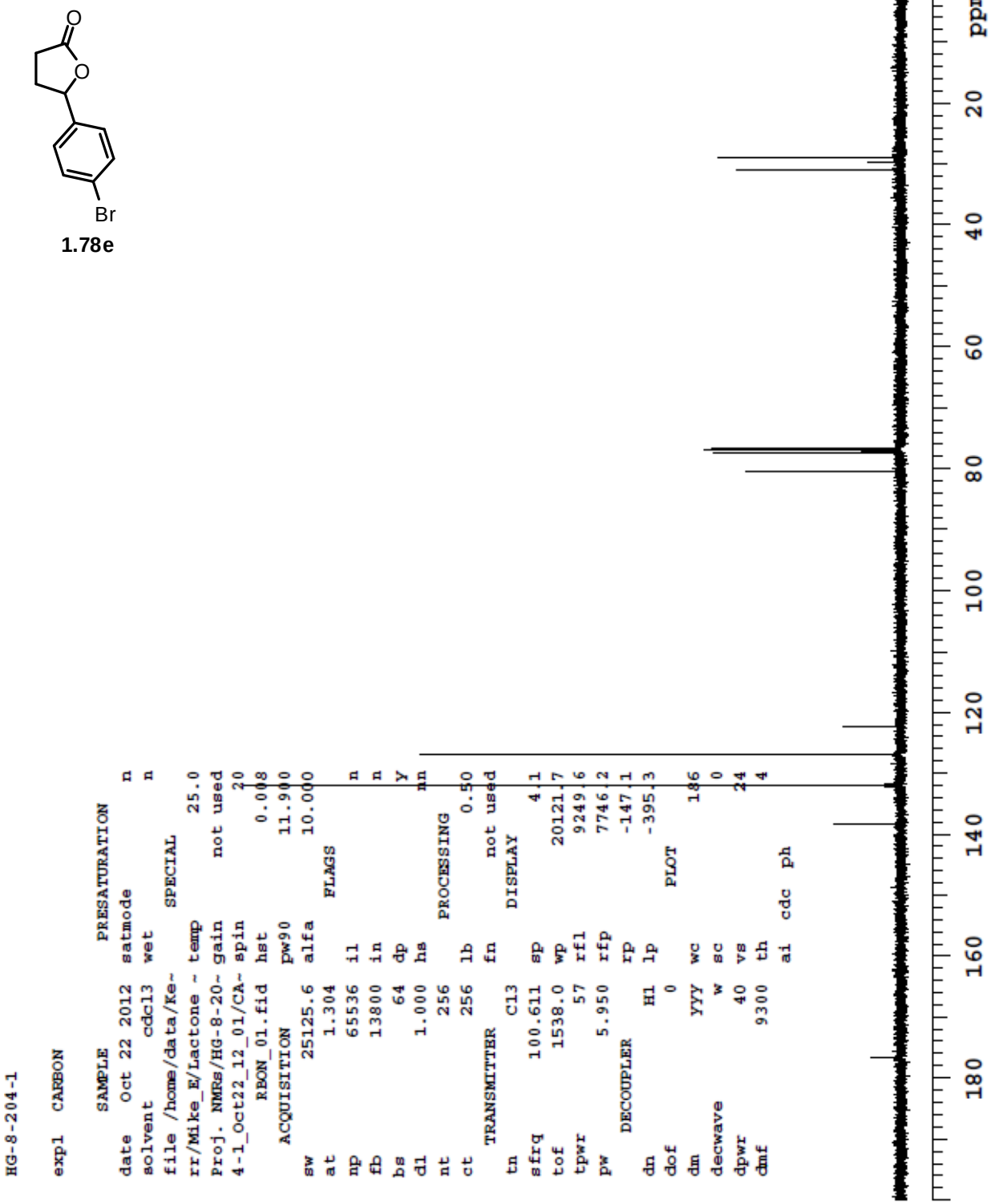


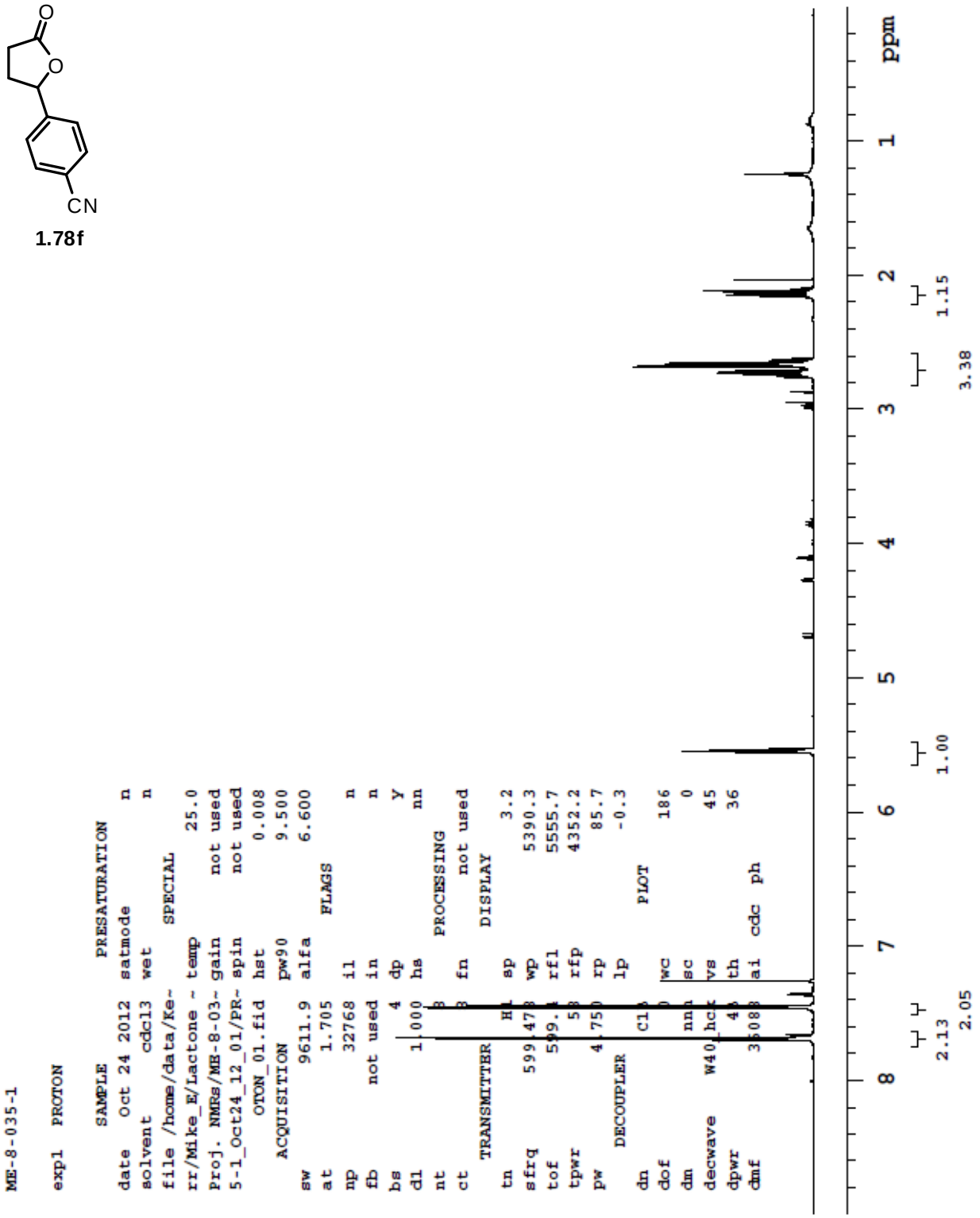


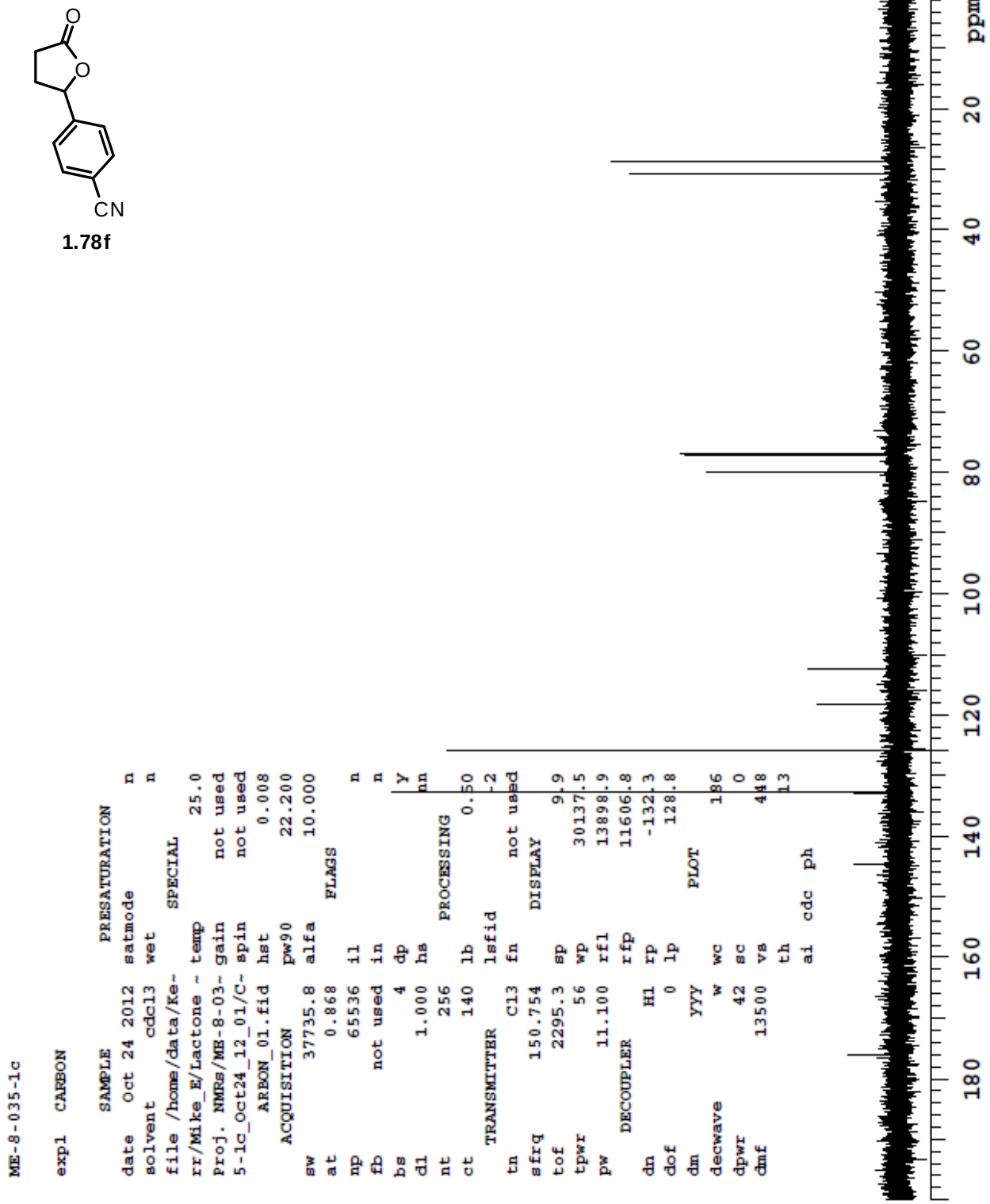


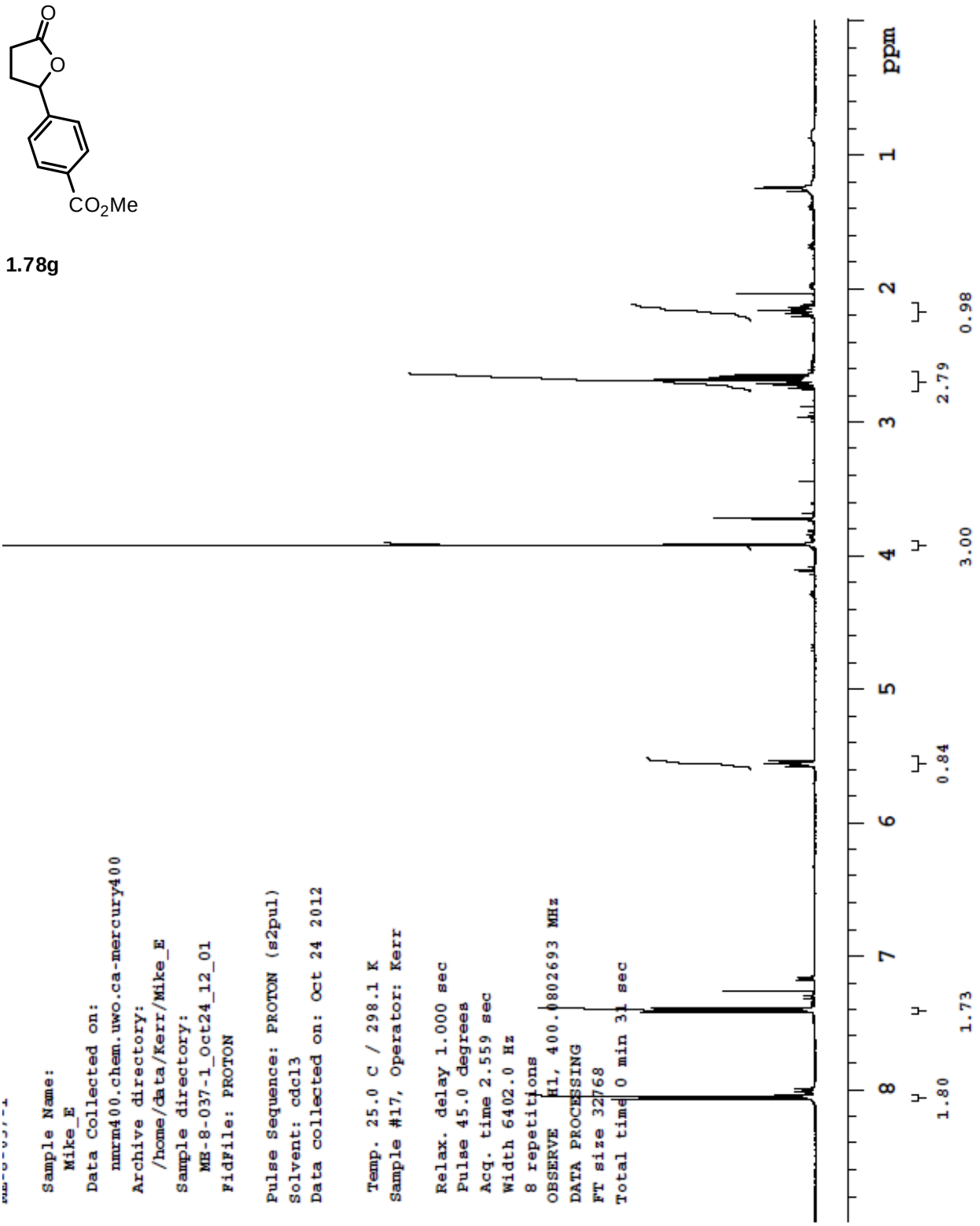
1.78d

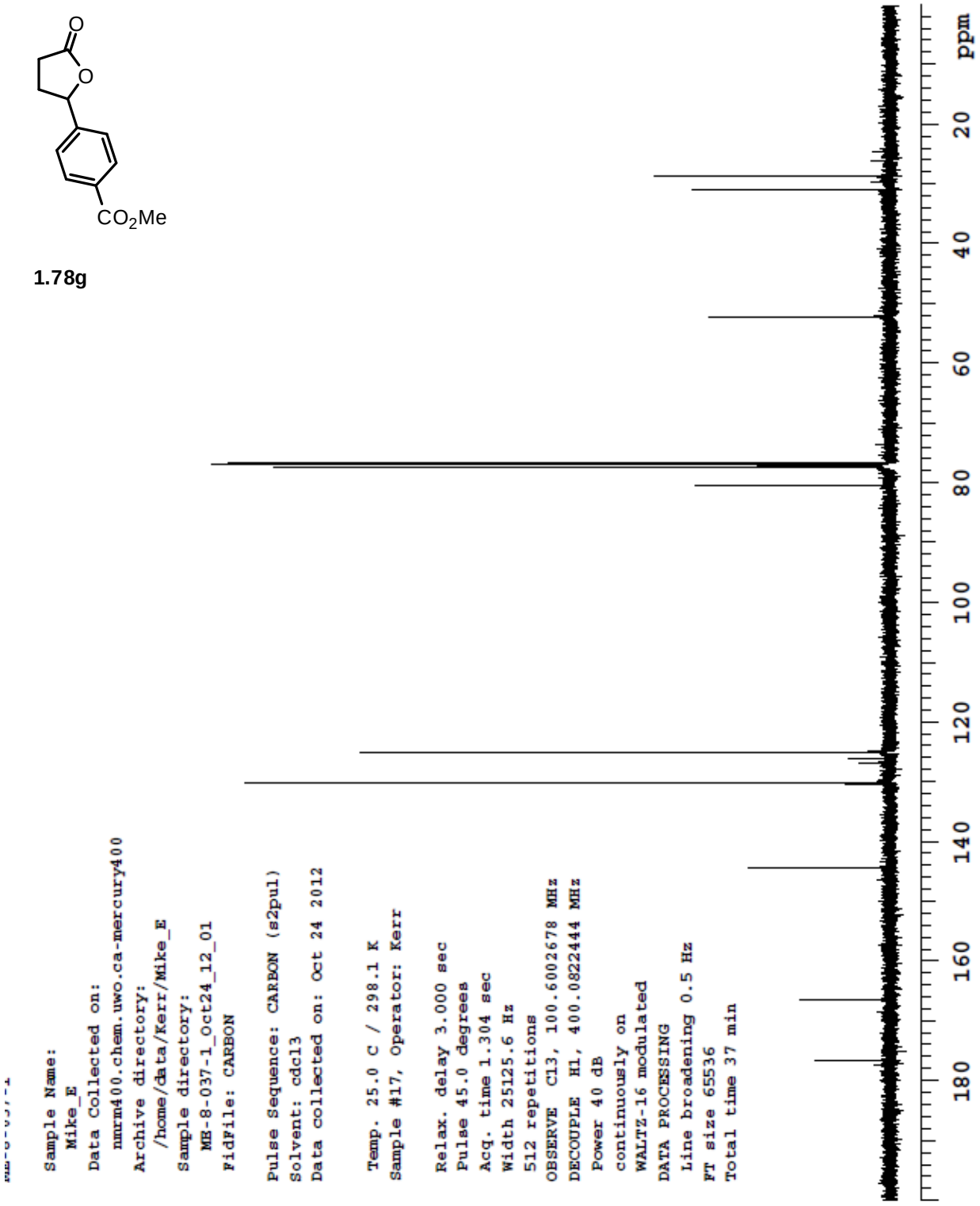


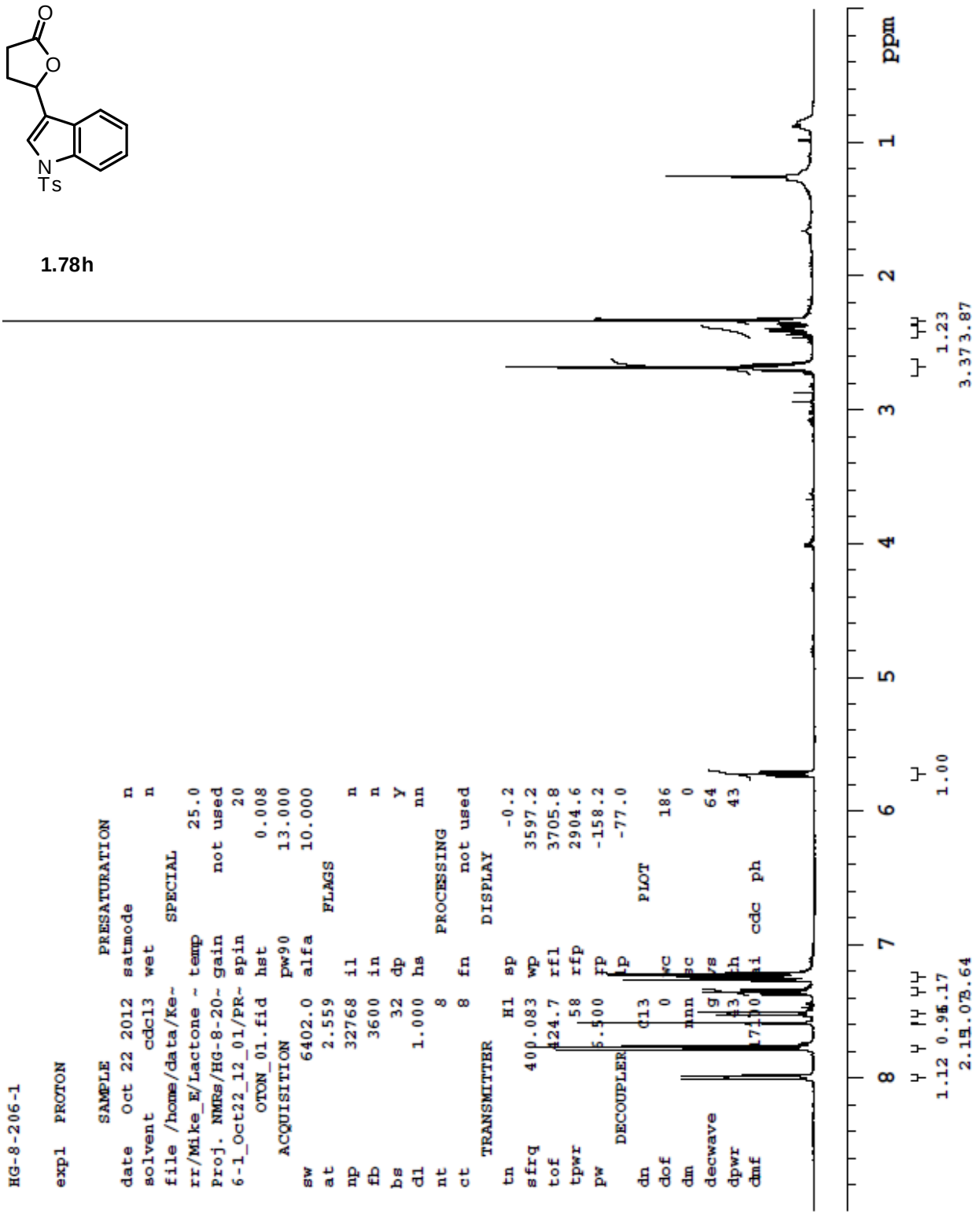


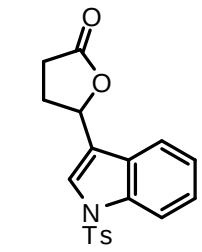












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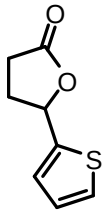

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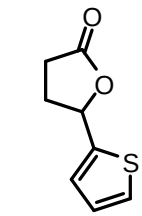
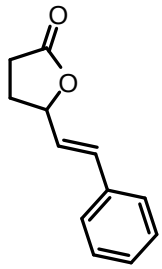


1.78i



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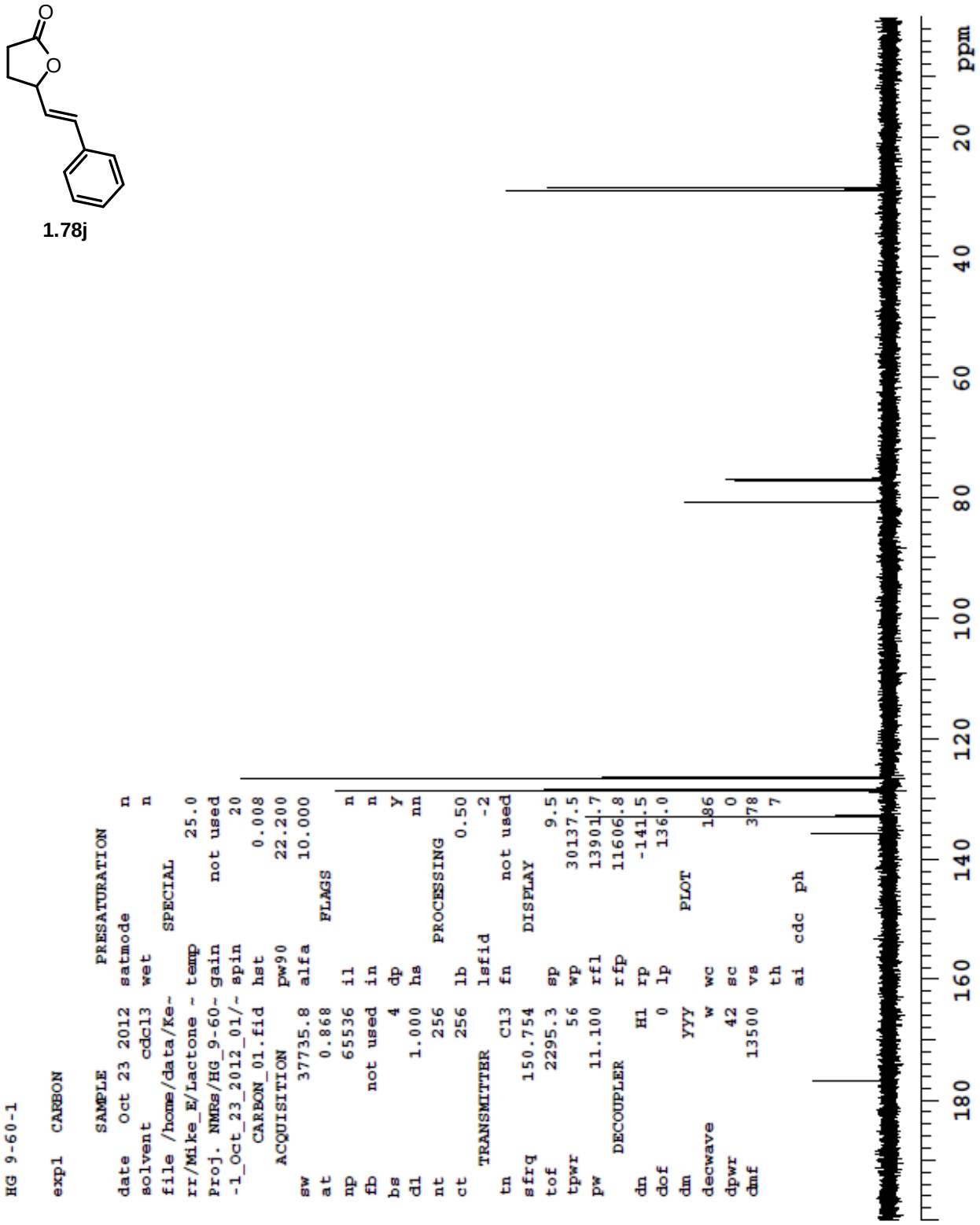
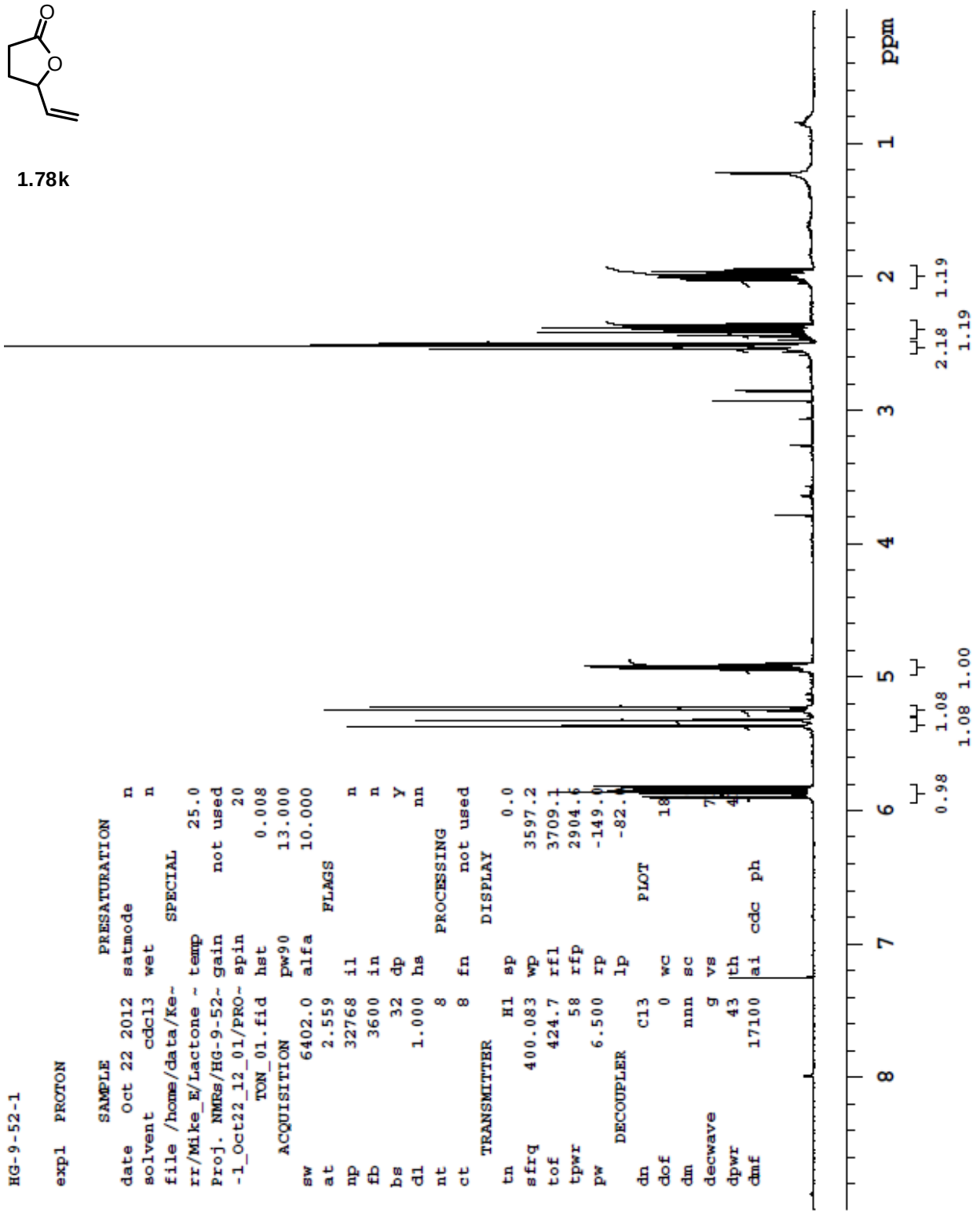
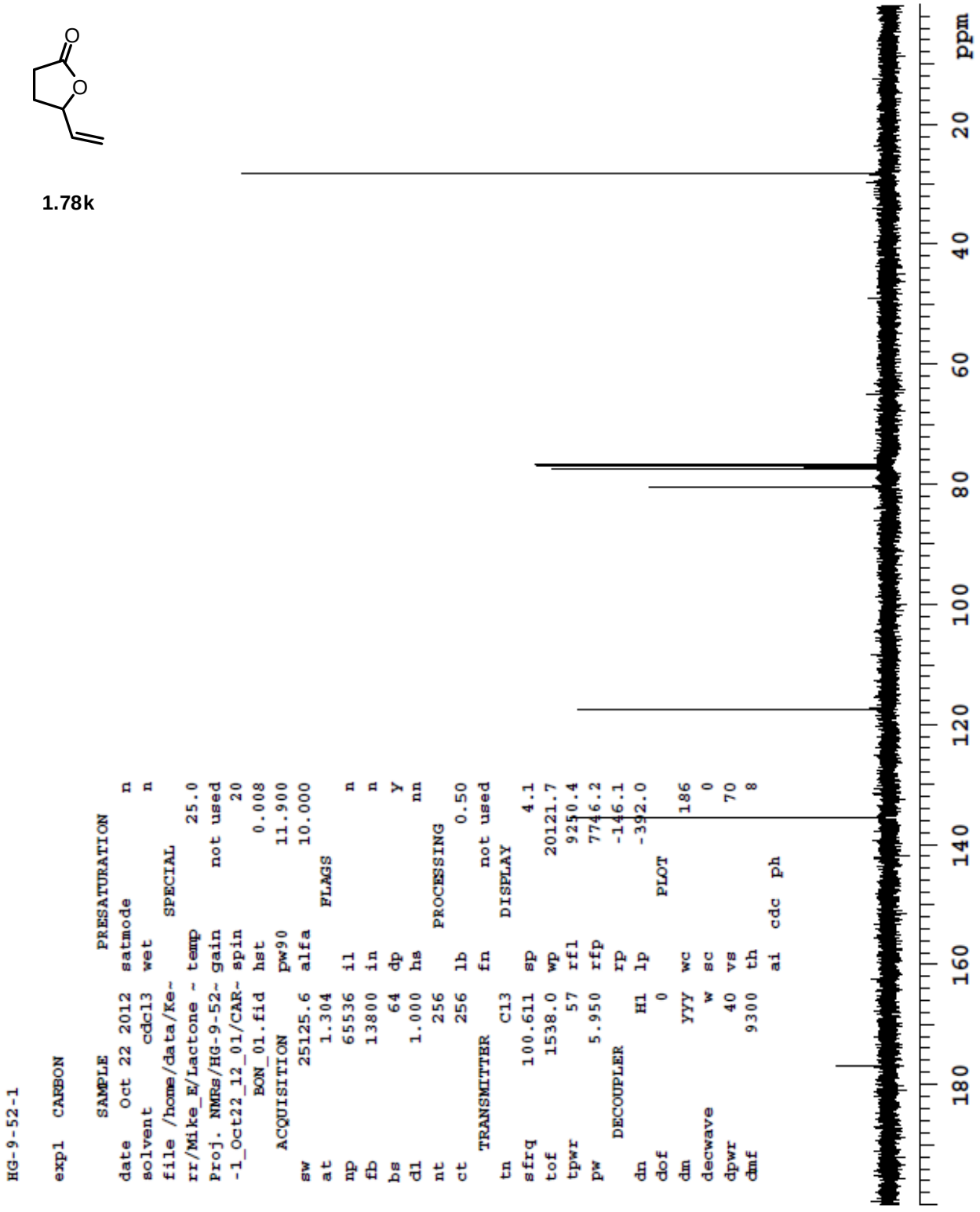
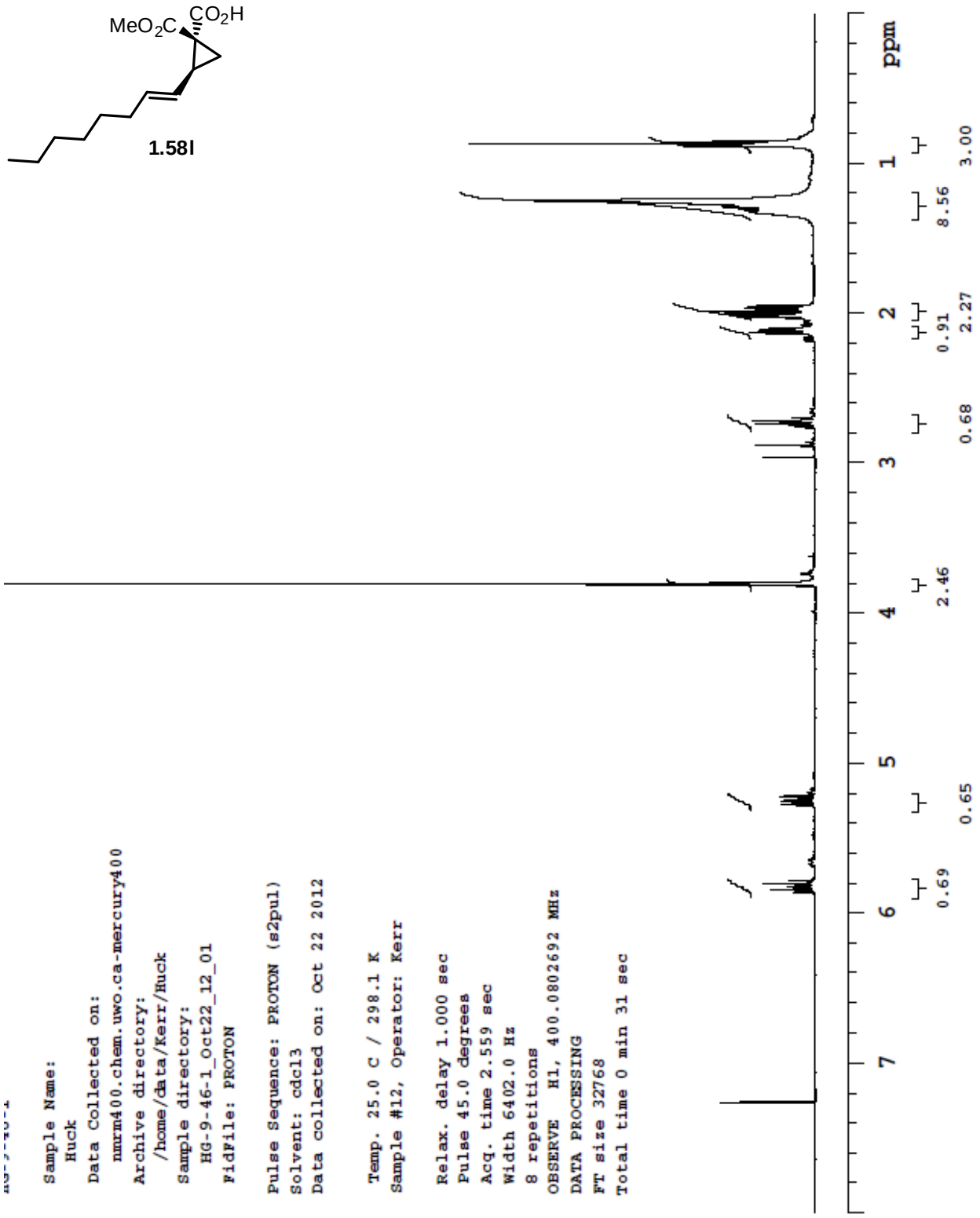
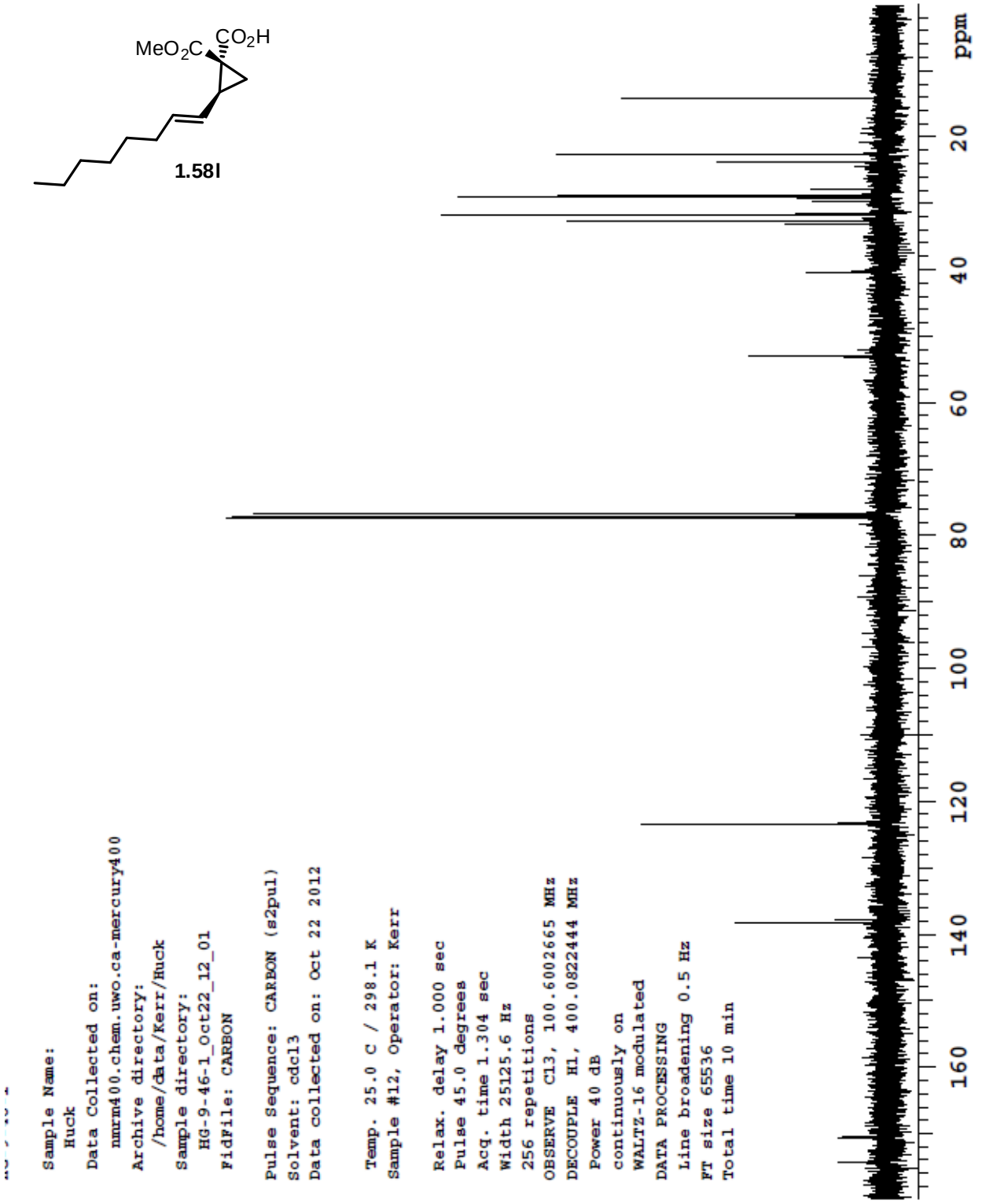
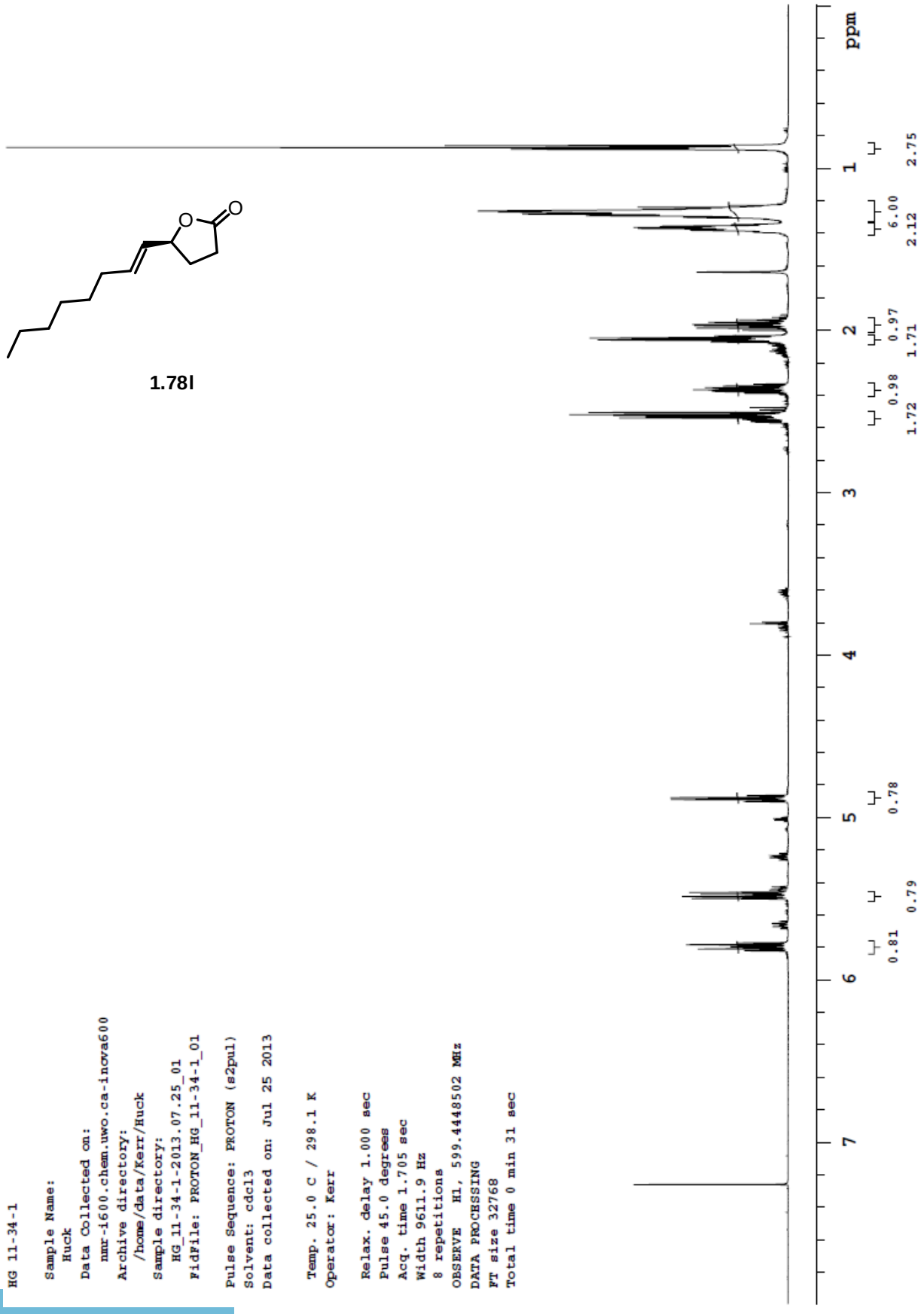


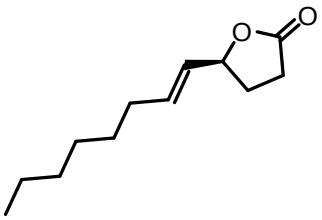






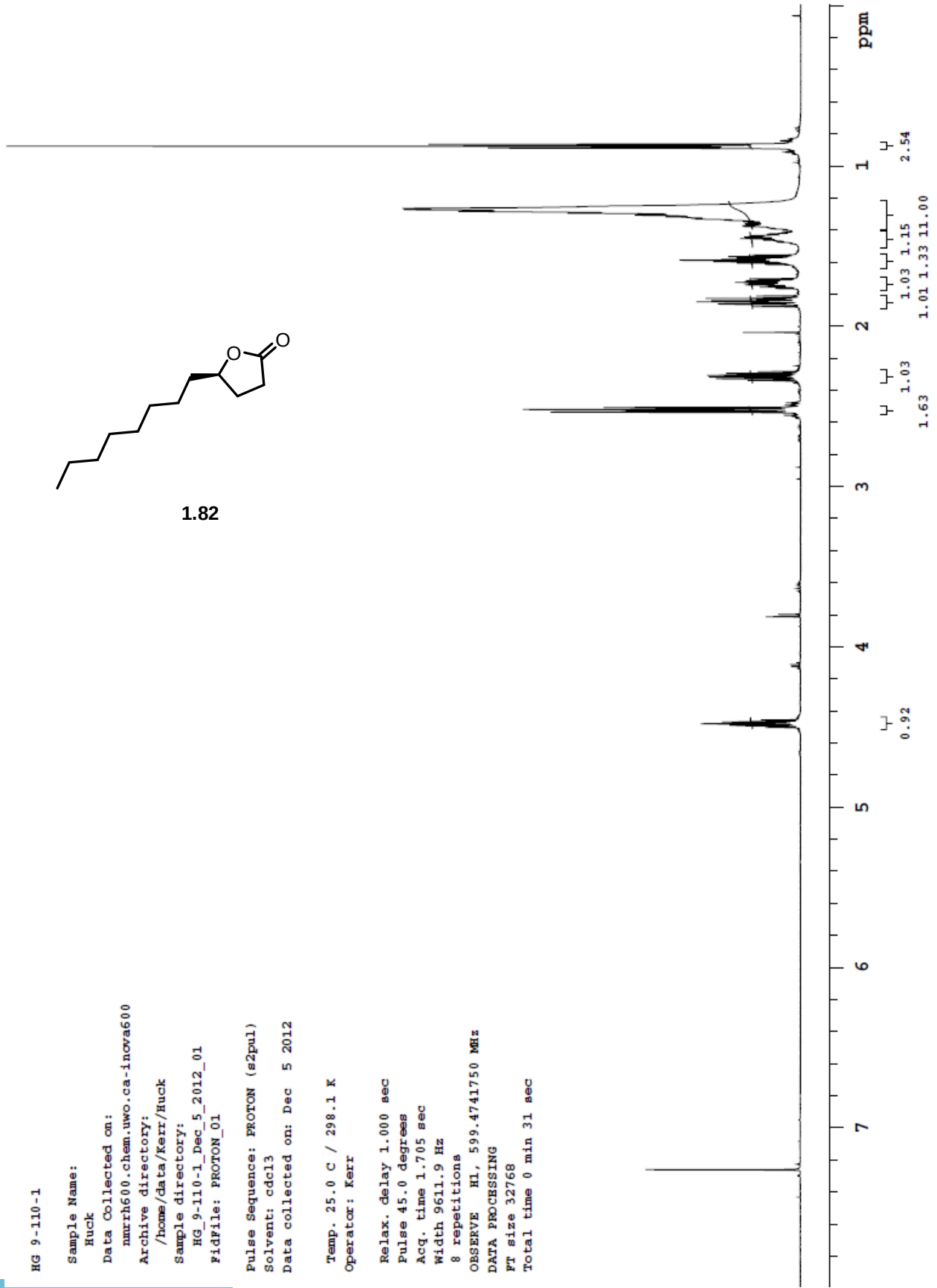


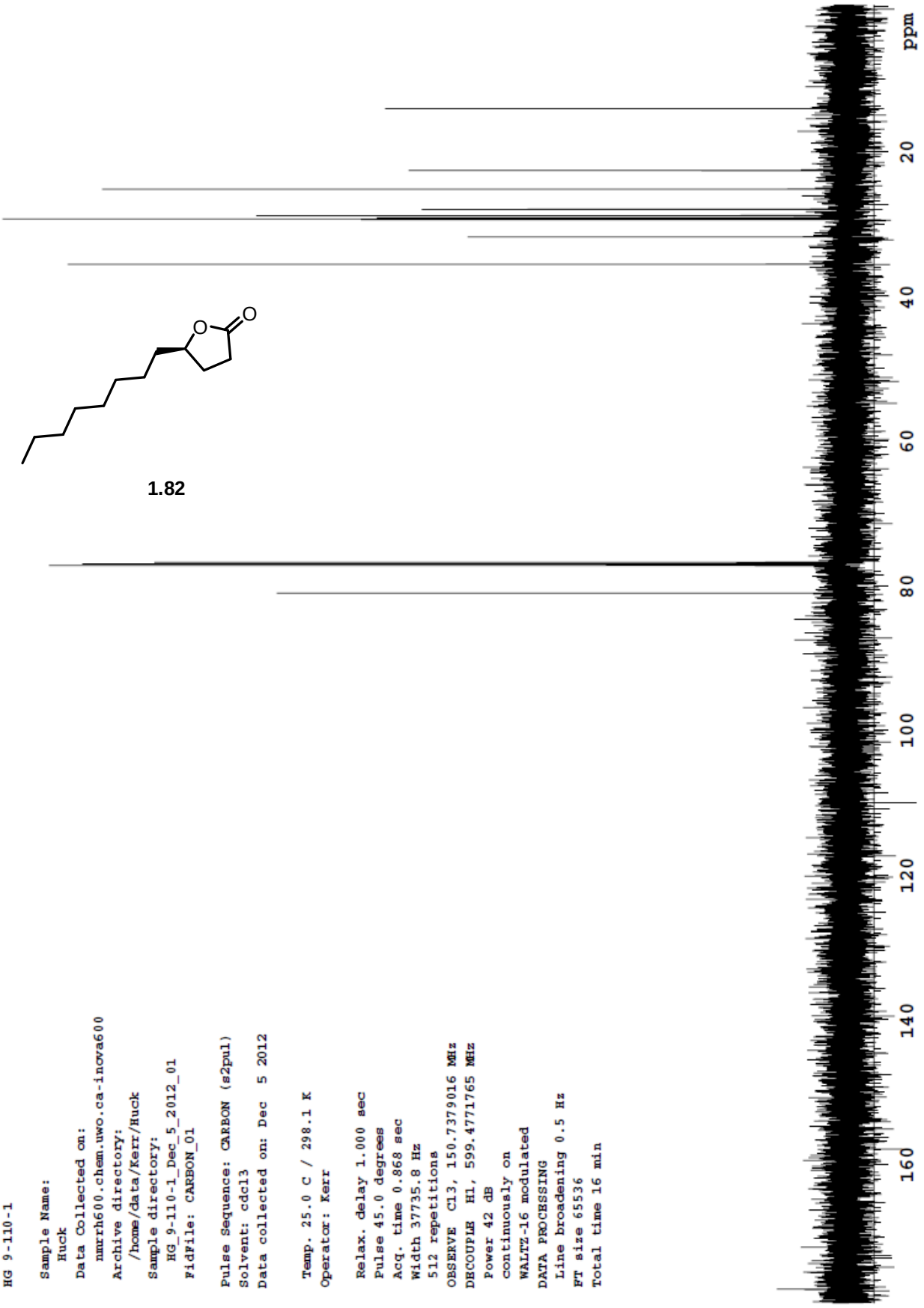


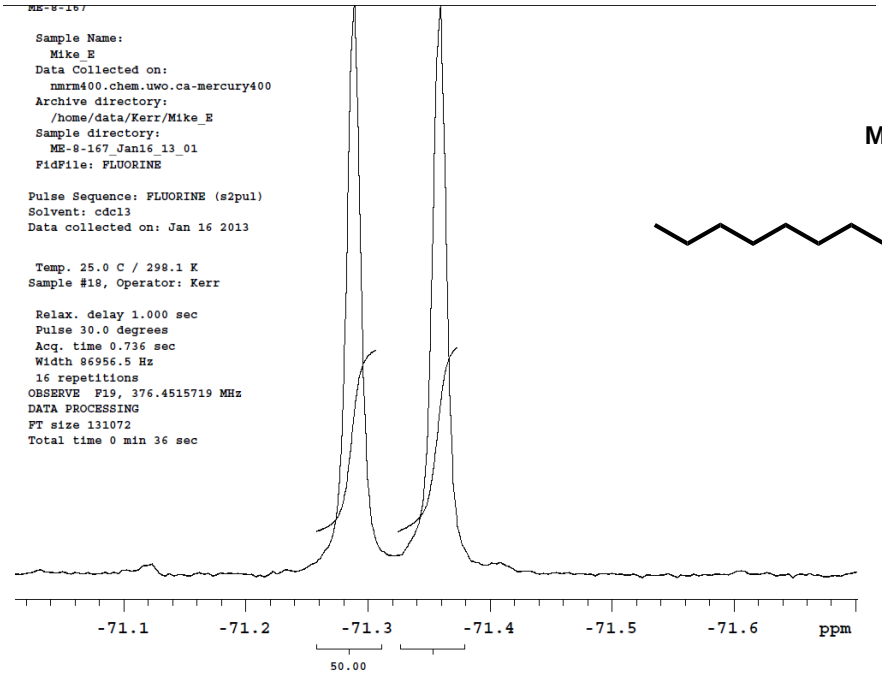


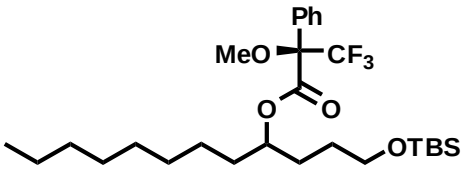
1.78l

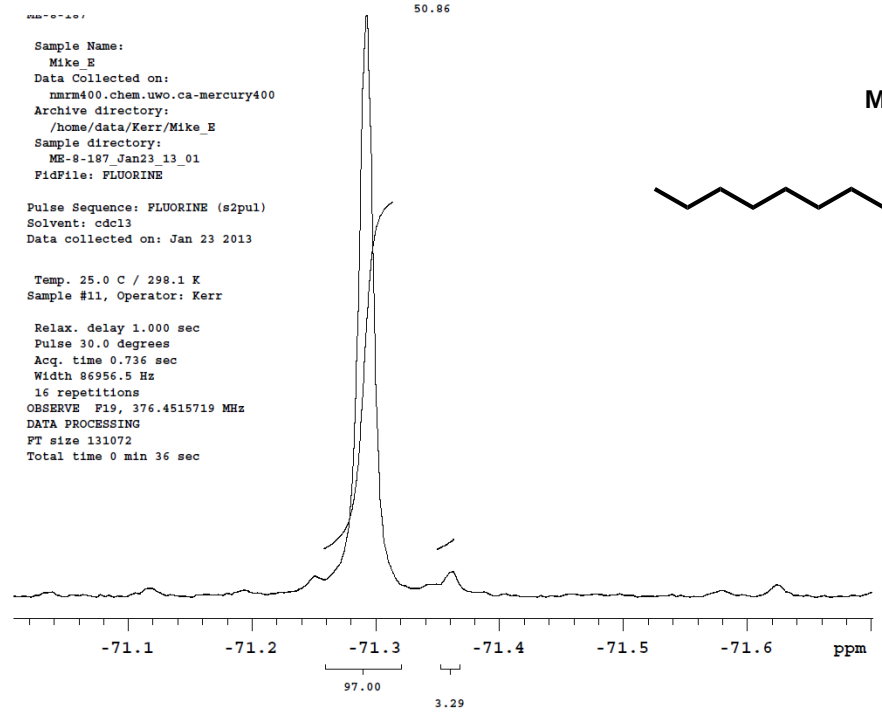
```
HG 11-34-1

  Sample Name:
    Huck
  Data Collected on:
    nmr-i600.chem.uwo.ca-inova600
  Archive directory:
    /home/data/Kerr/Huck
  Sample directory:
    HG_11-34-1-2013.07.25_01
  FidFile: CARBON_HG_11-34-1_01

  Pulse Sequence: CARBON (s2pul)
  Solvent: cdcl3
  Data collected on: Jul 25 2013

  Temp. 25.0 C / 298.1 K
  Operator: Kerr

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 0.868 sec
  Width 37735.8 Hz
    512 repetitions
  OBSERVE C13, 150.7305296 MHz
  DECOUPLE H1, 599.4478617 MHz
    Power 43 dB
    continuously on
    WALTZ-16 modulated
  DATA PROCESSING
    Line broadening 0.5 Hz
  FT size 65536
  Total time 16 min
```

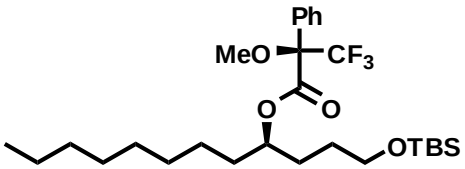




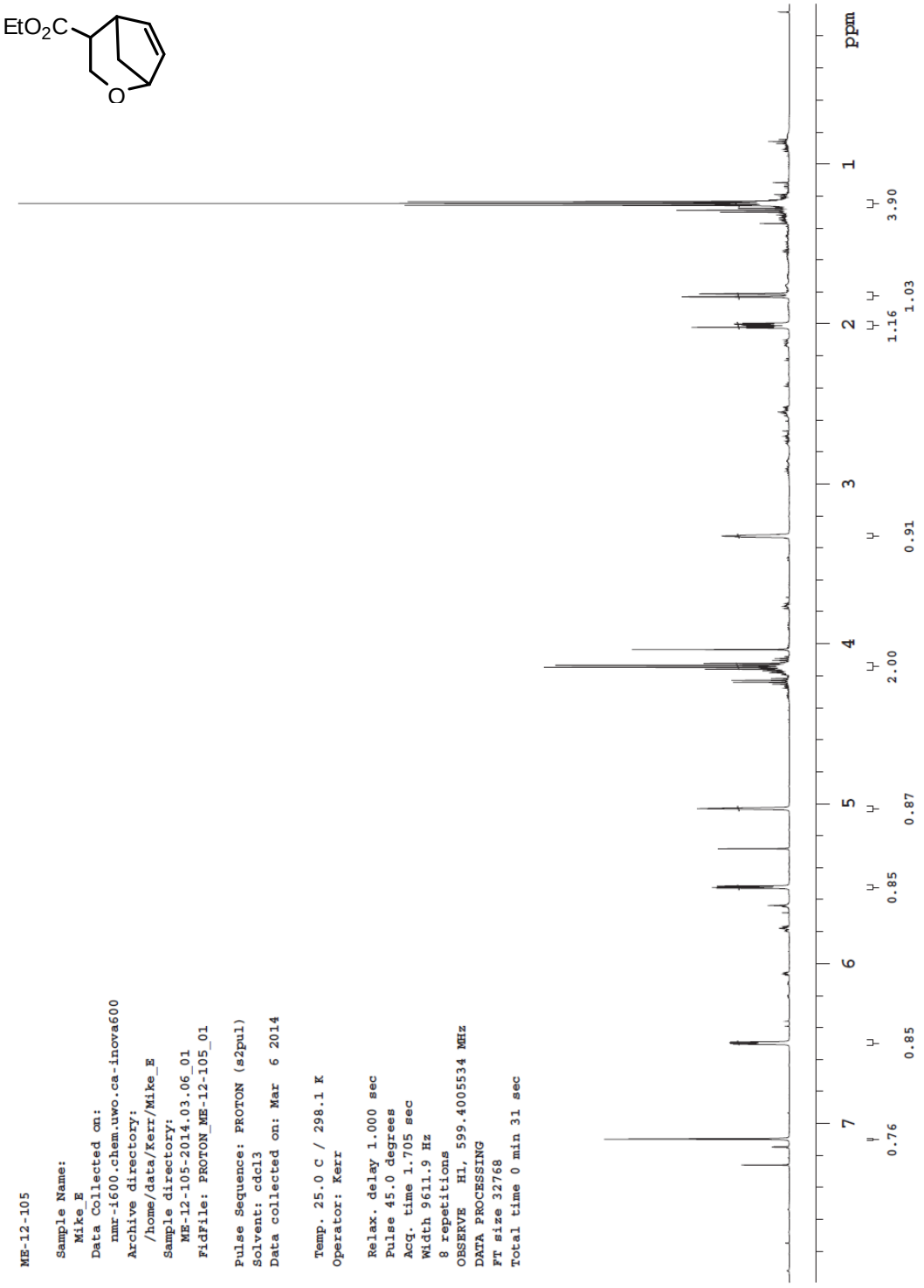








Appendix 2 – NMR Spectral Data for Chapter 2



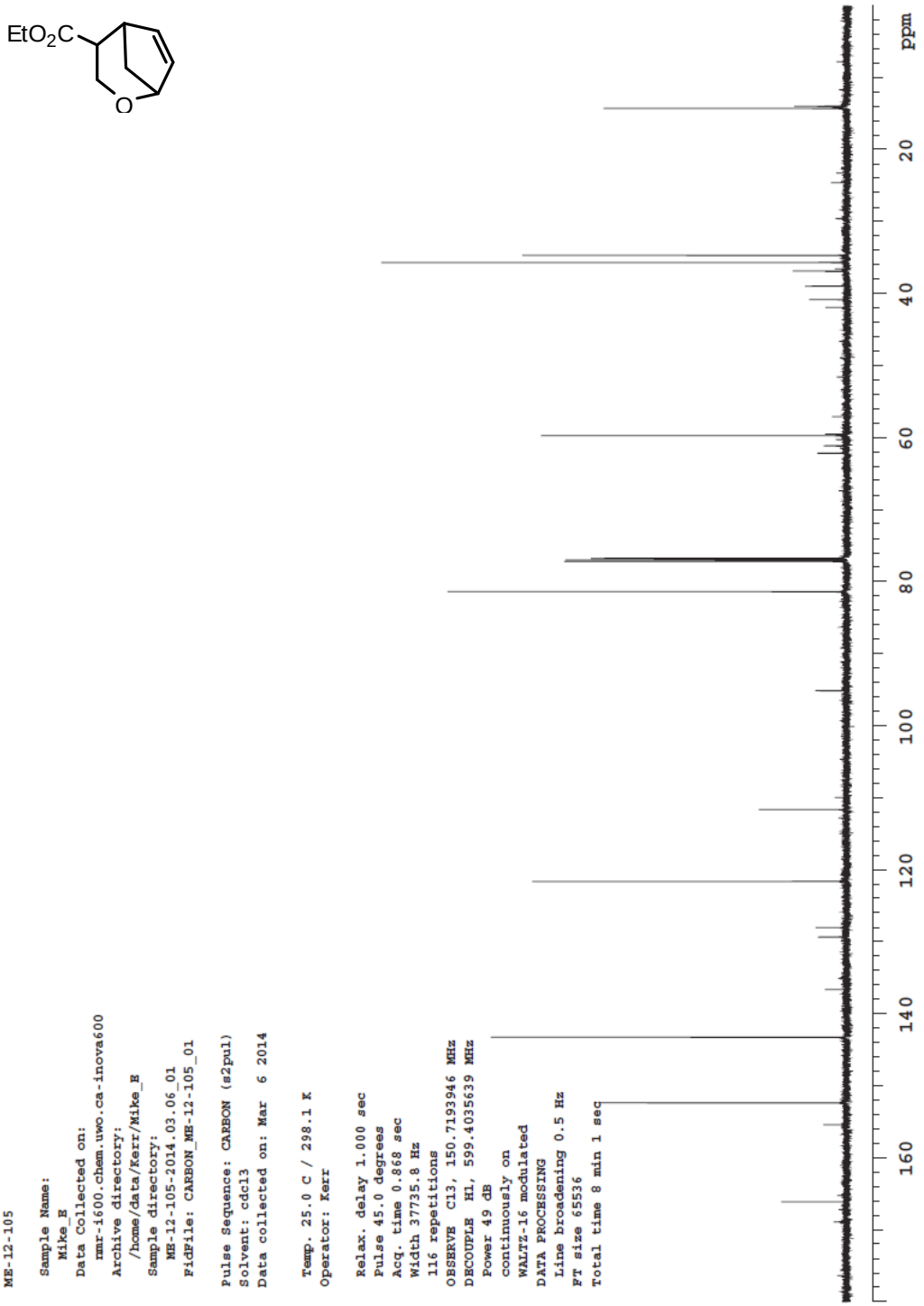
ME-12-105

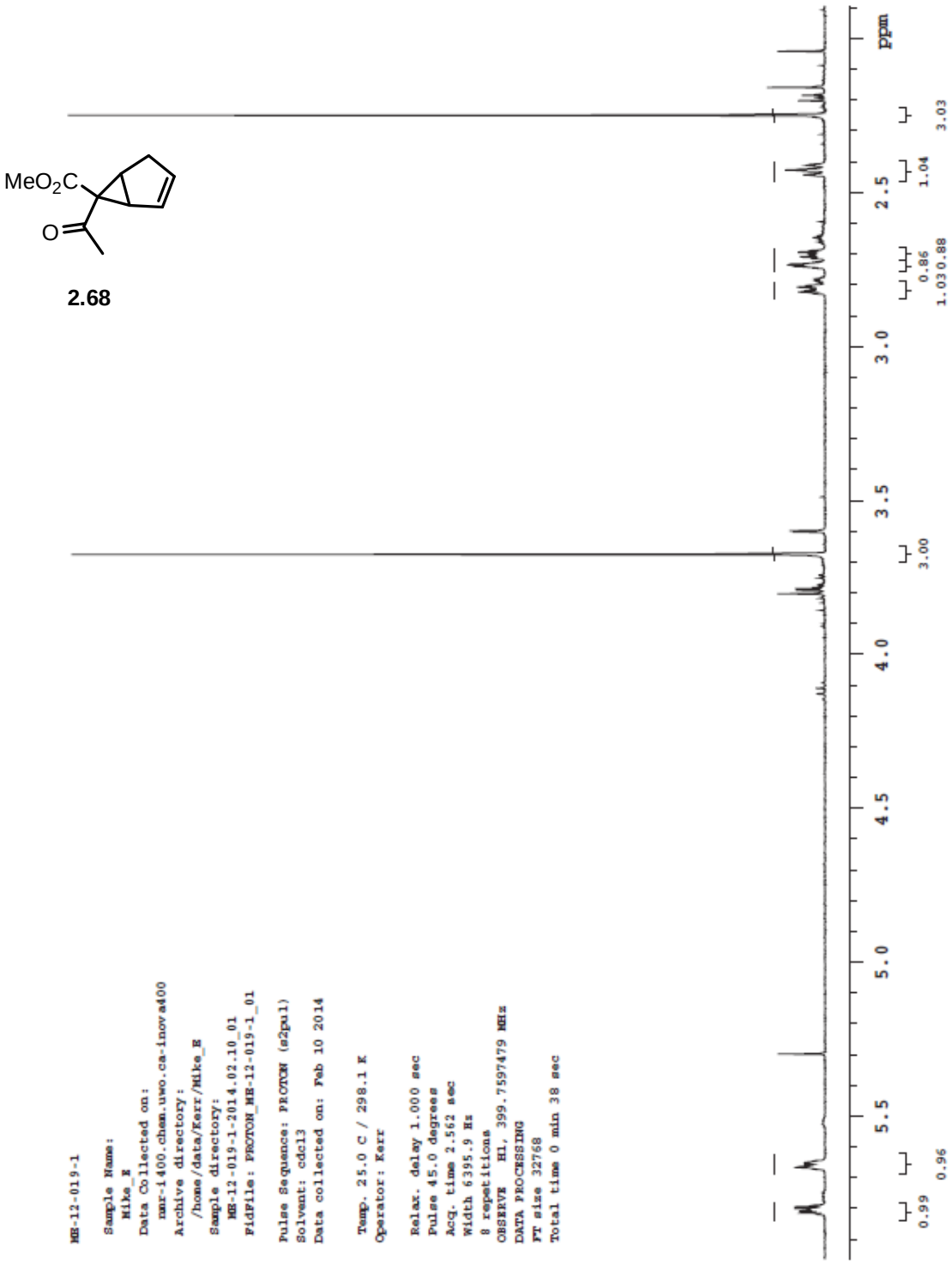
Sample Name:
Mike_E
Data Collected on:
nmr-1600.chem.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-12-105-2014.03.06_01
FidFile: PROTON_ME-12-105_01

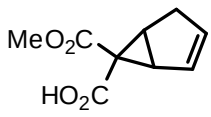
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 6 2014

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.705 sec
Width 9611.9 Hz
8 repetitions
OBSERVE H1, 599.4005534 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec







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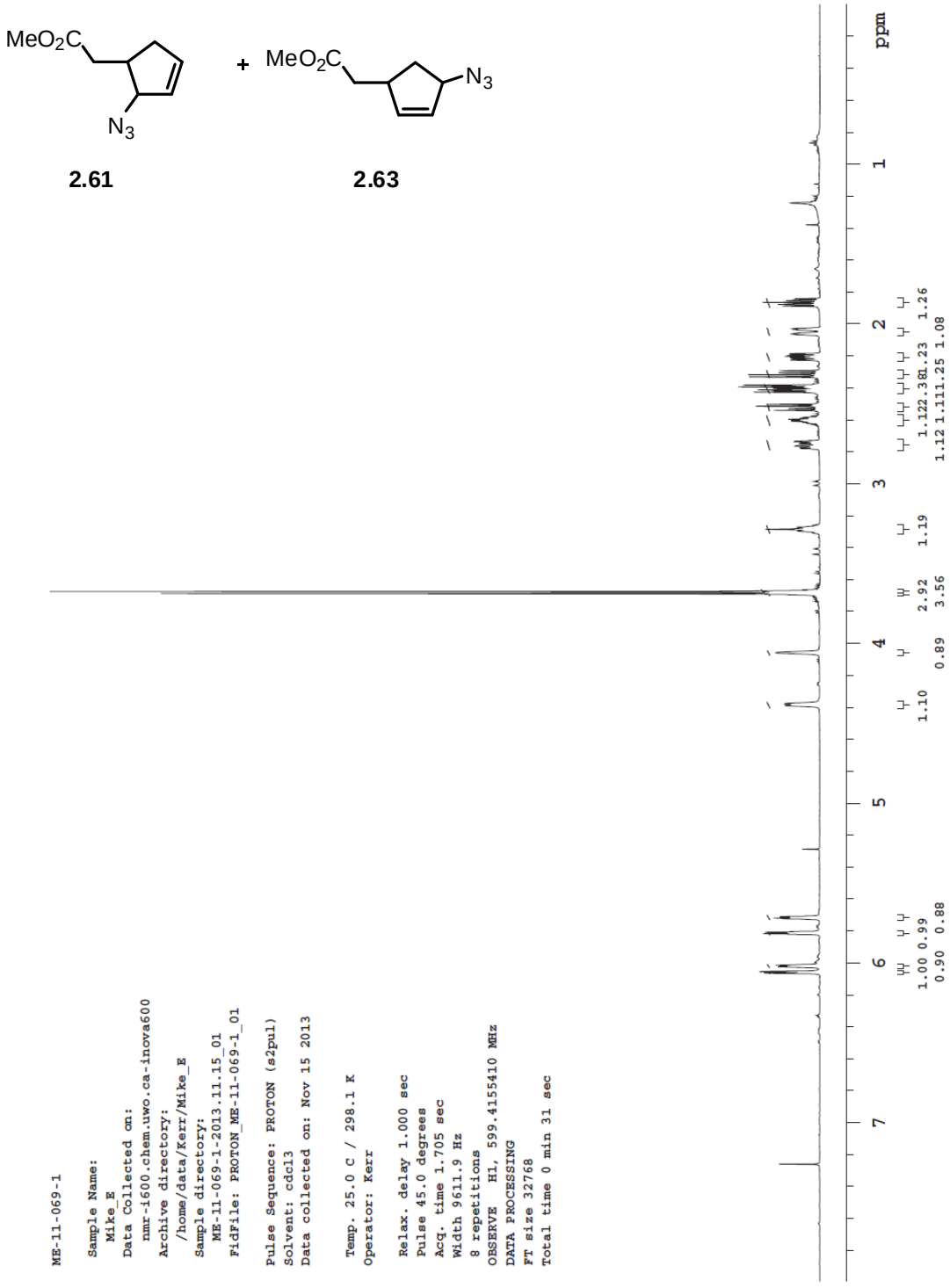
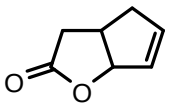




2.64

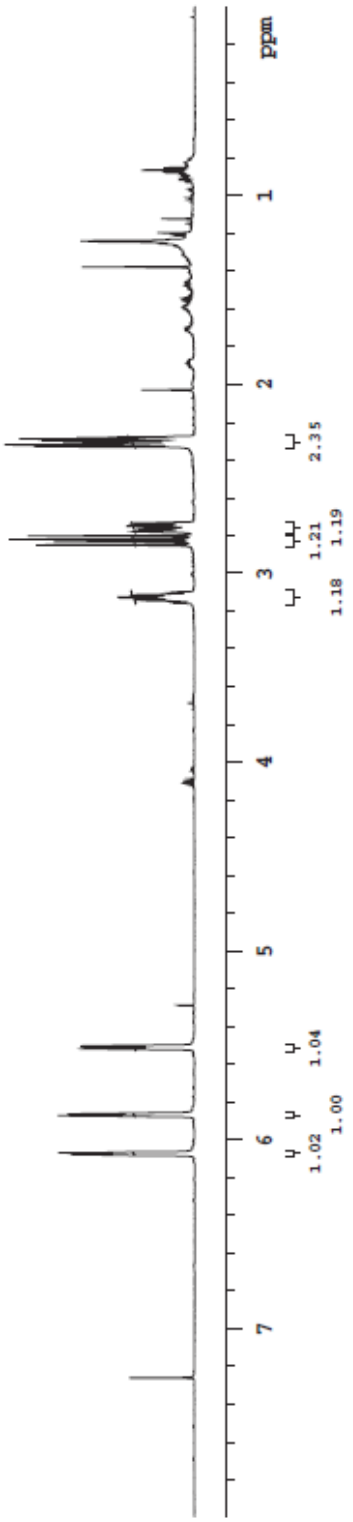
MR-11-173-1

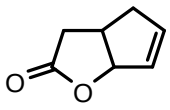
Sample Name:
Mike_E
Data Collected on:
nmr-1600.chem.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
MR-11-173-1-2014.01.27_01
FidFile: PROTON_MR-11-173-1_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jan 27 2014

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.705 sec
Width 9611.9 Hz
8 repetitions
OBSERVE H1, 599.4155445 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





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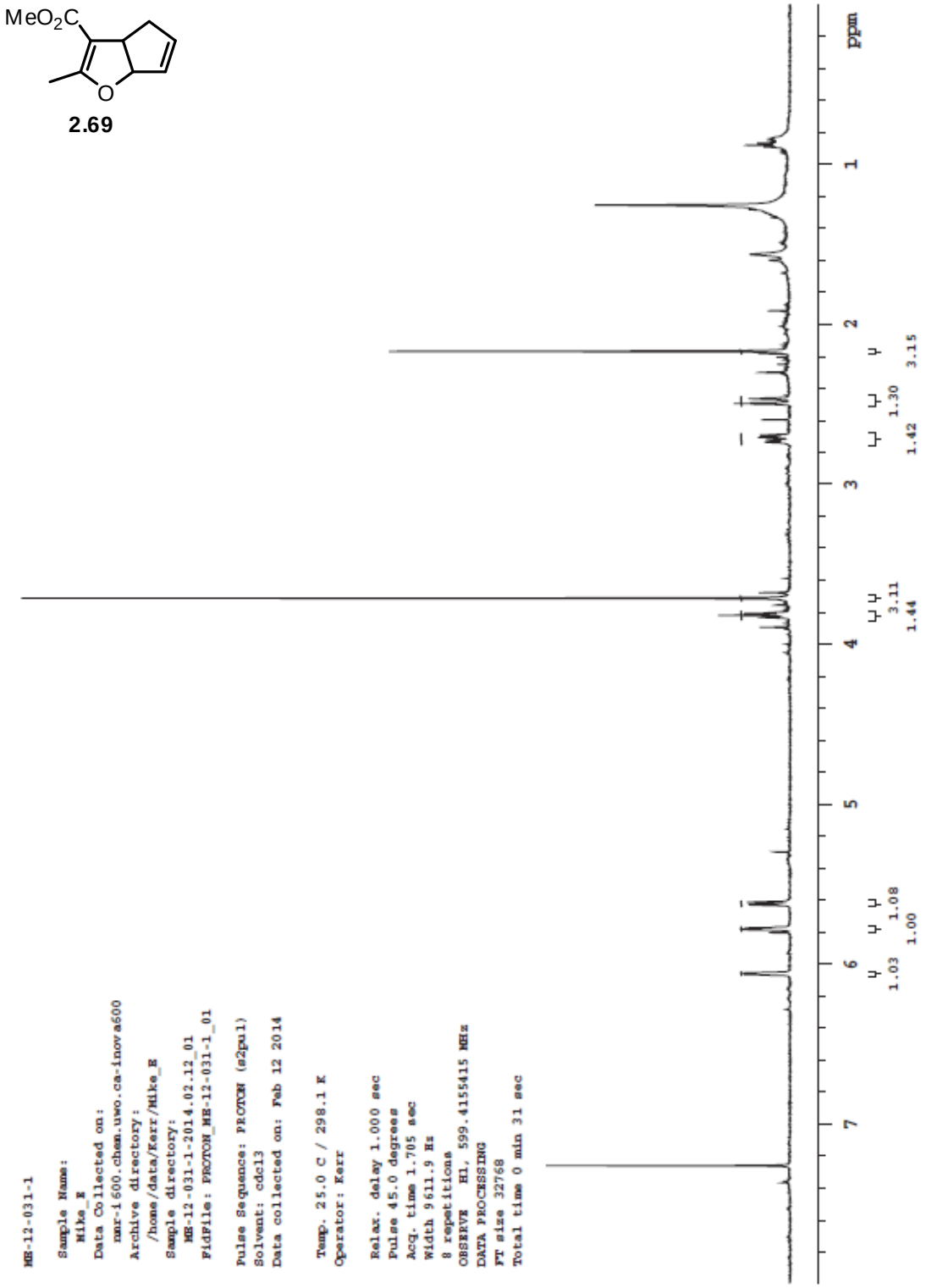
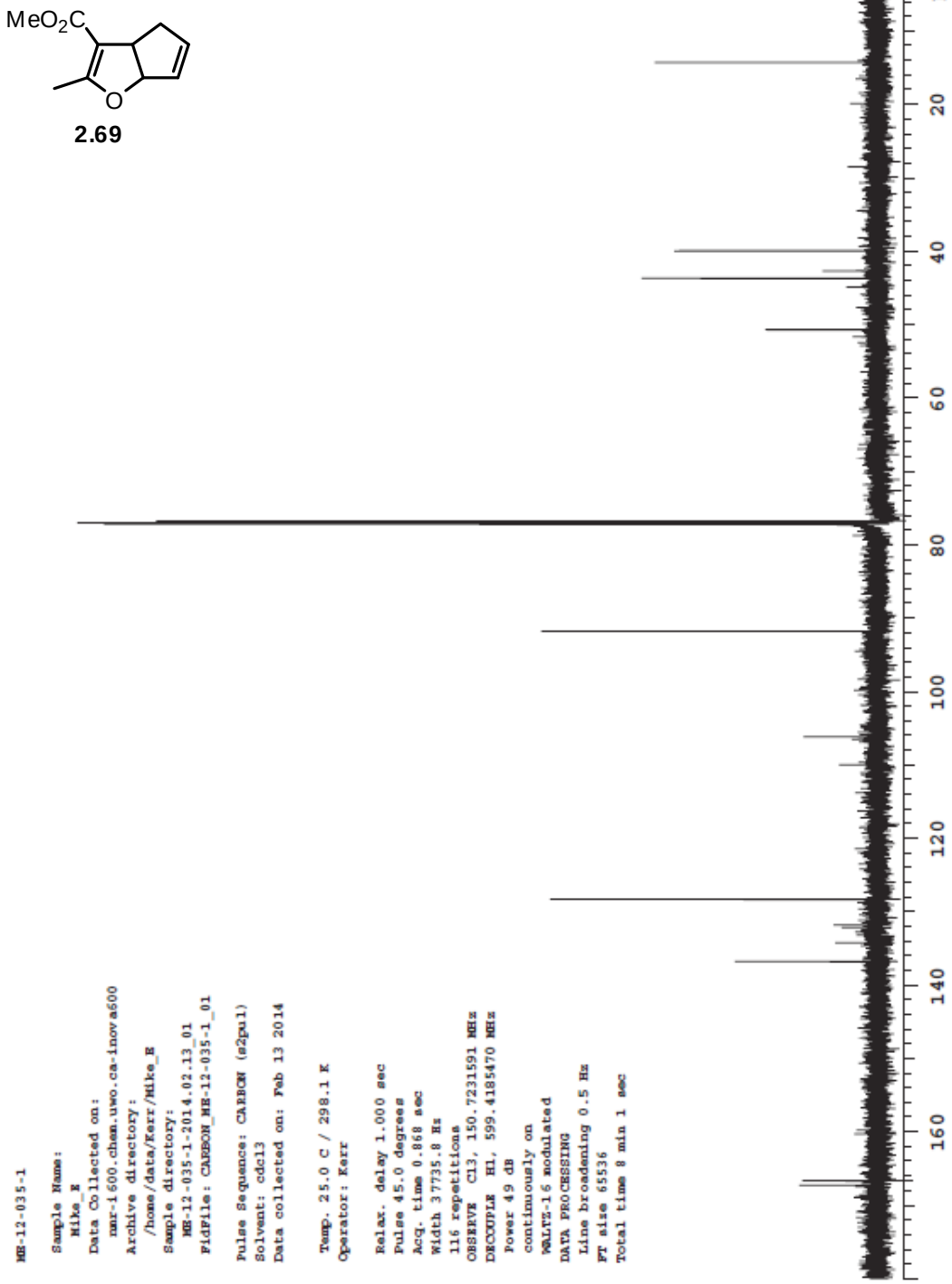
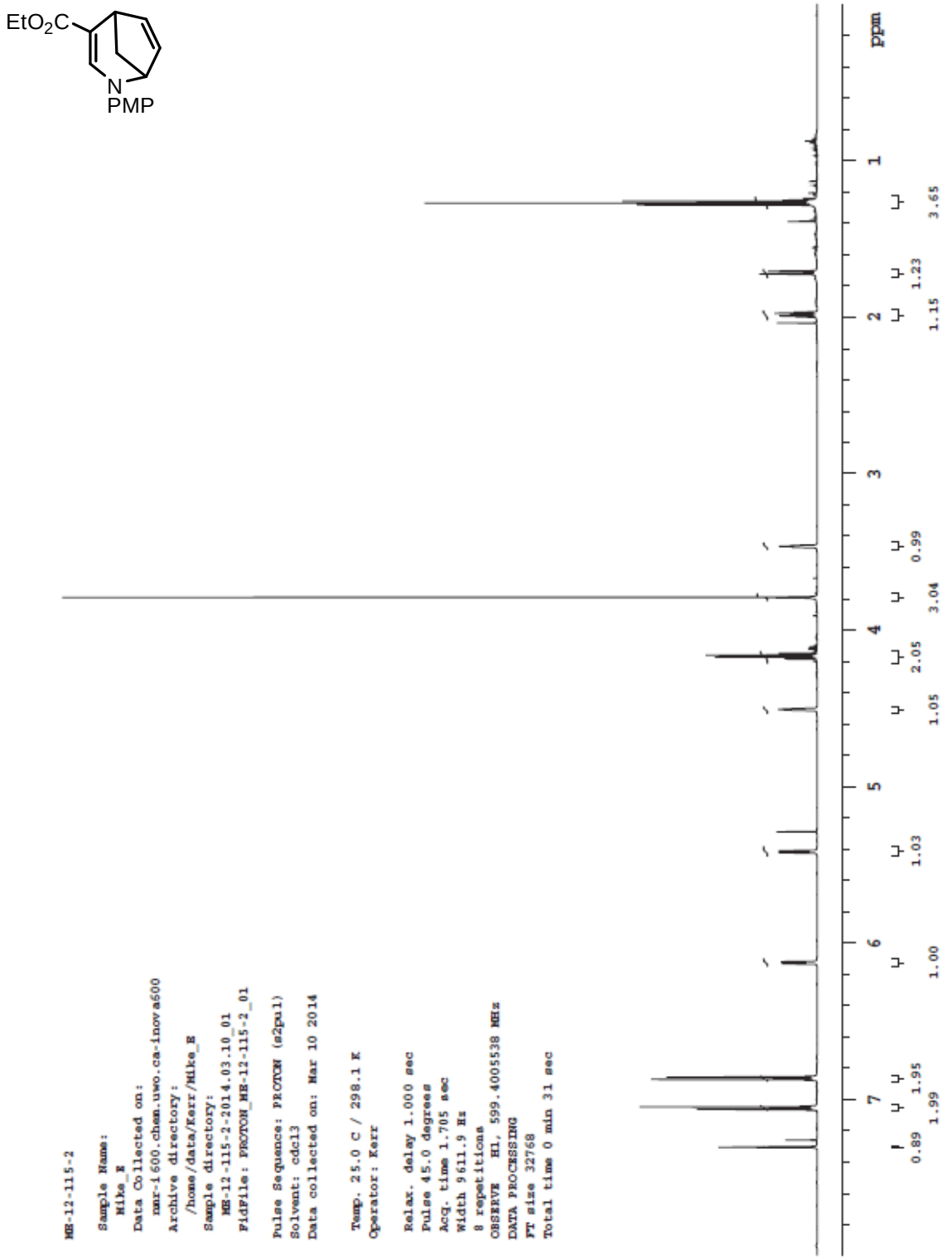
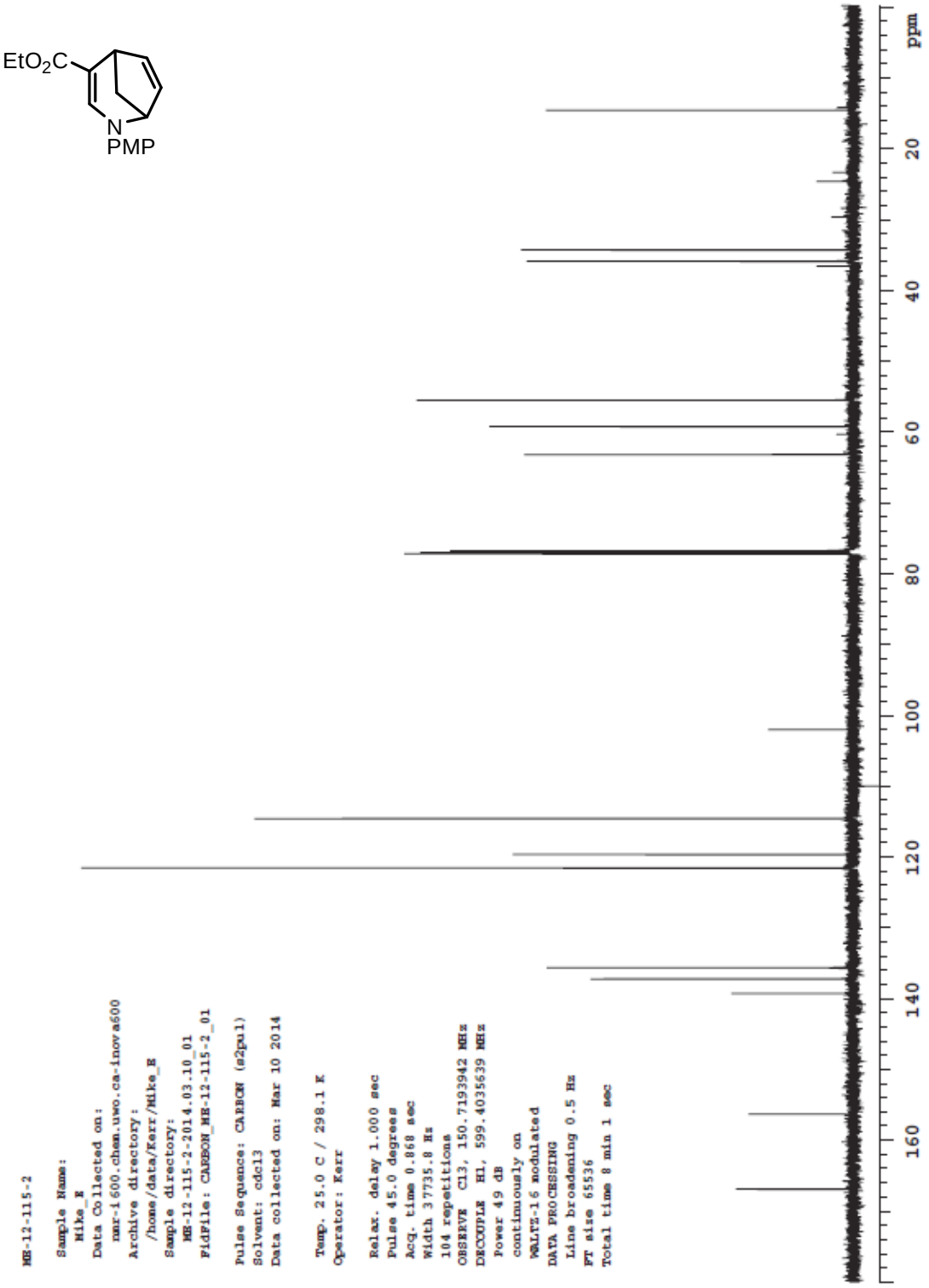
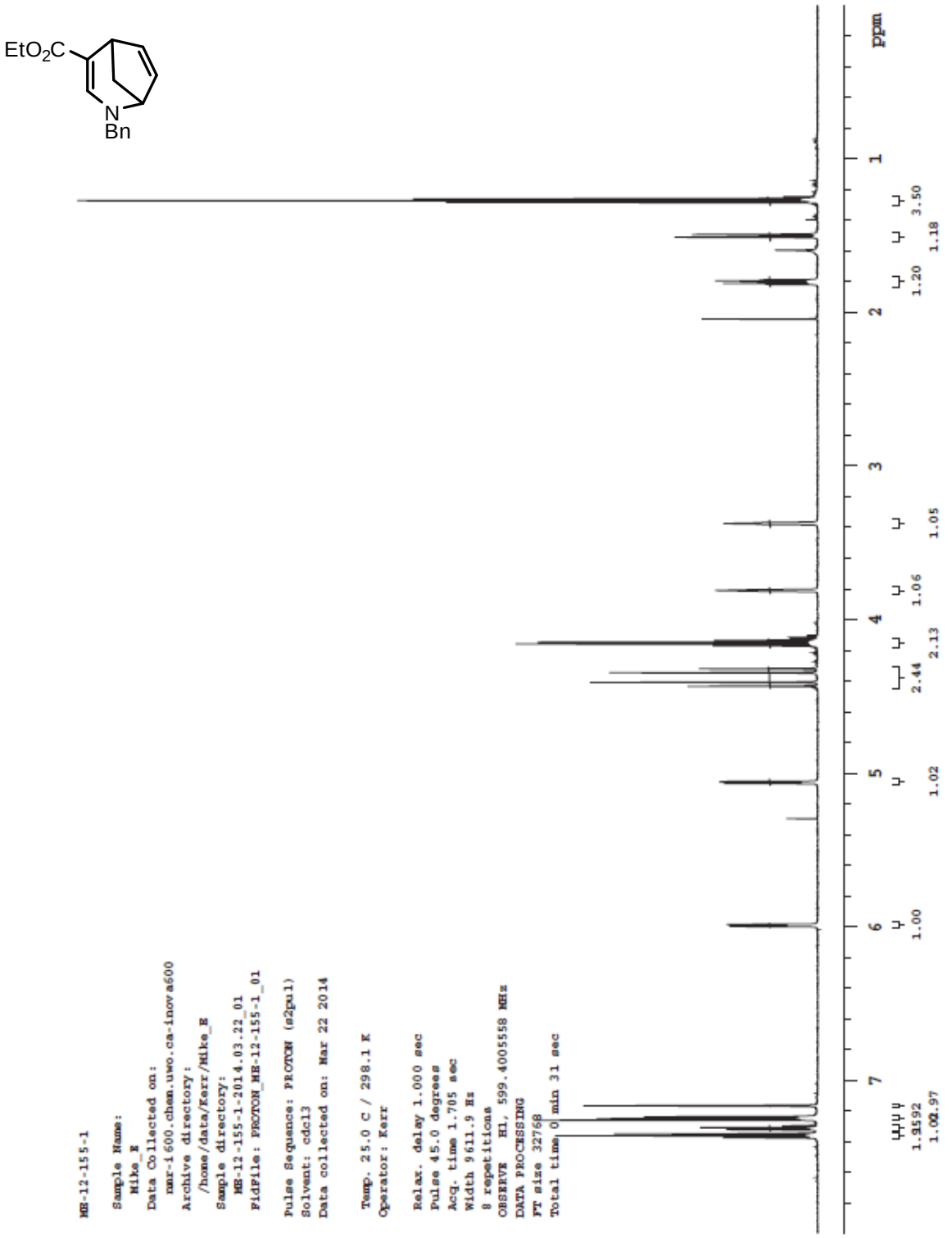
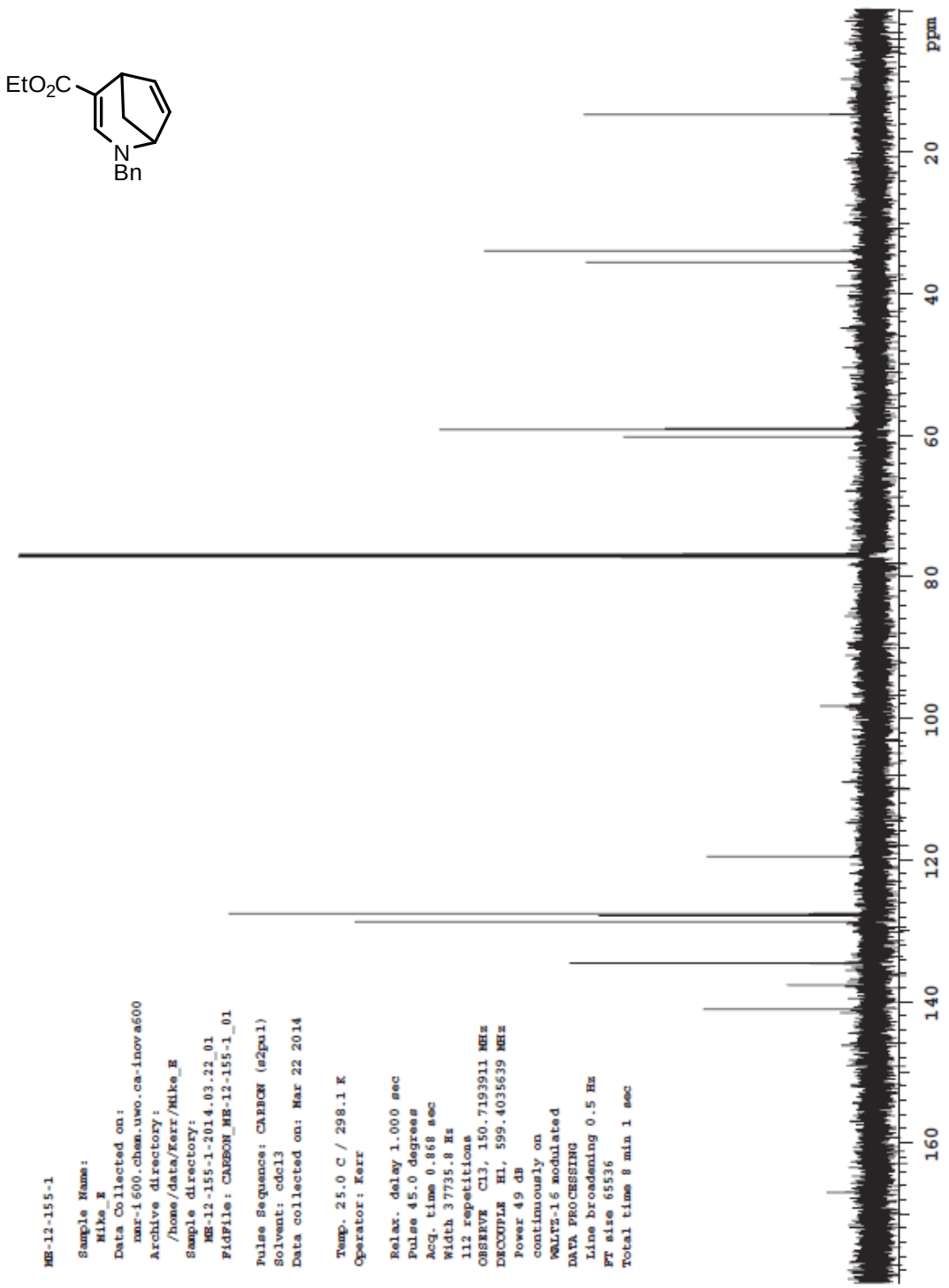


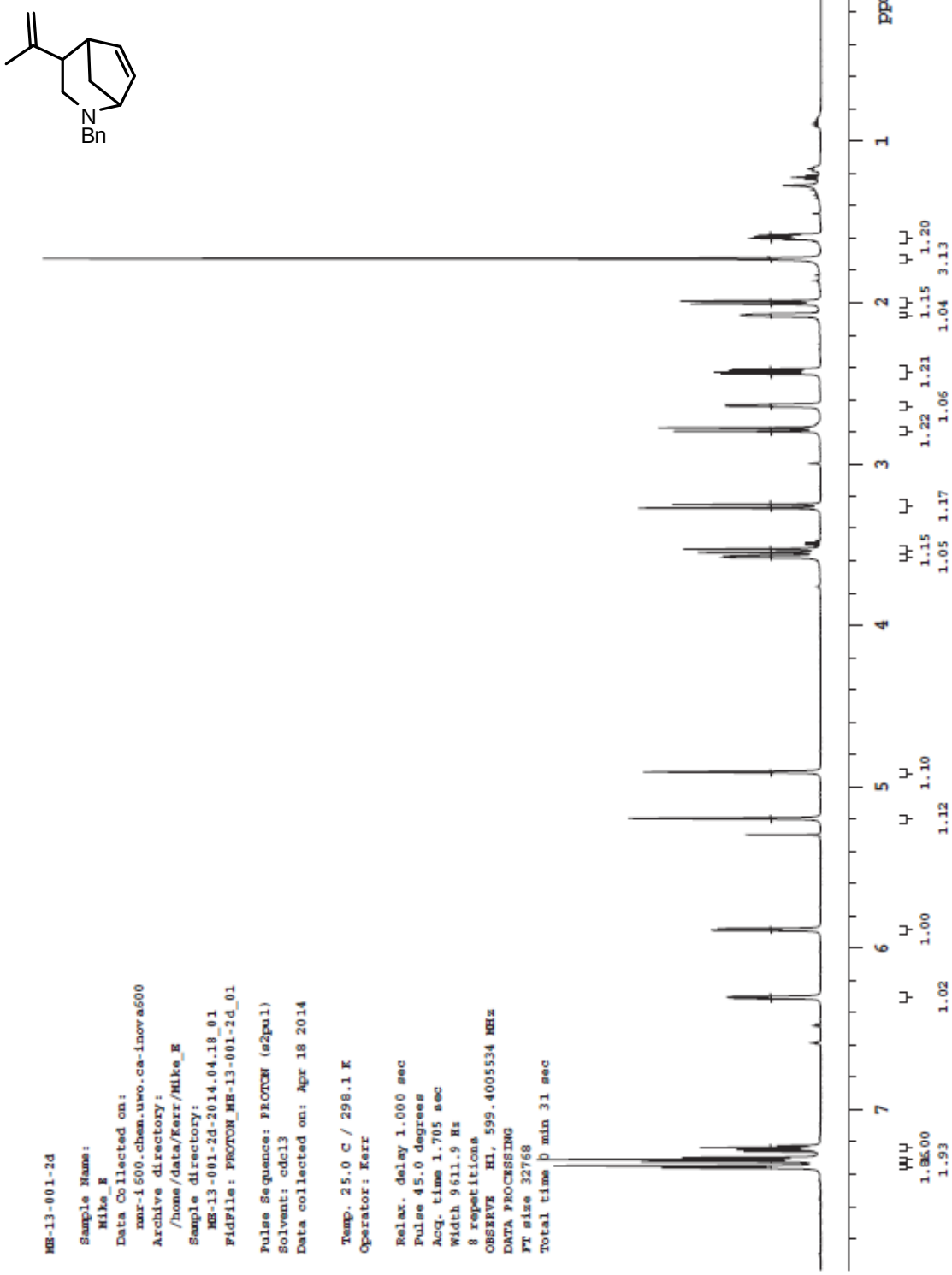


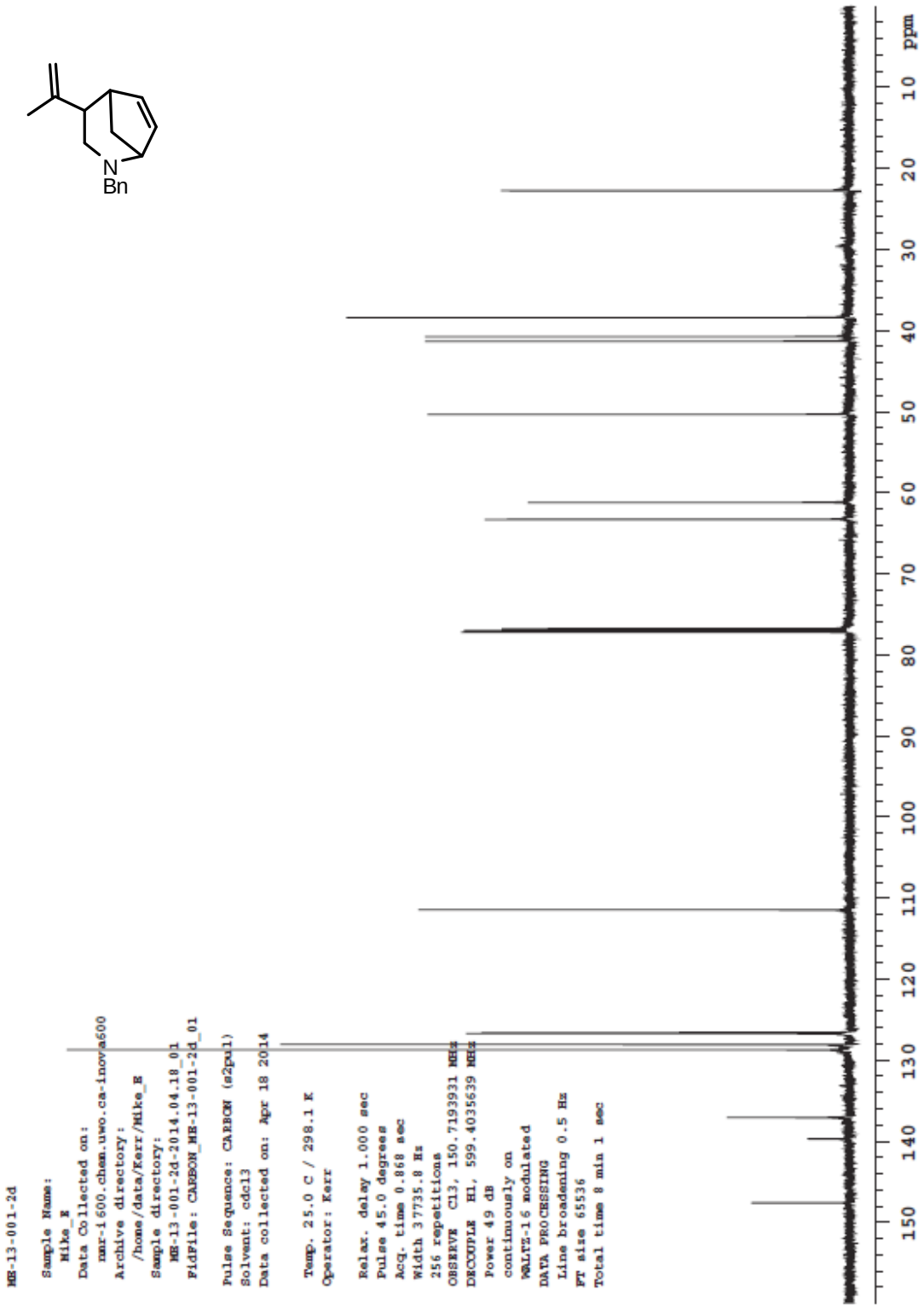




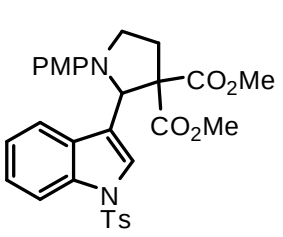








Appendix 3 – NMR Spectral Data for Chapter 3



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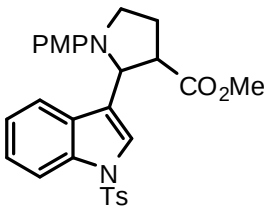

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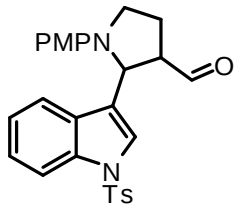

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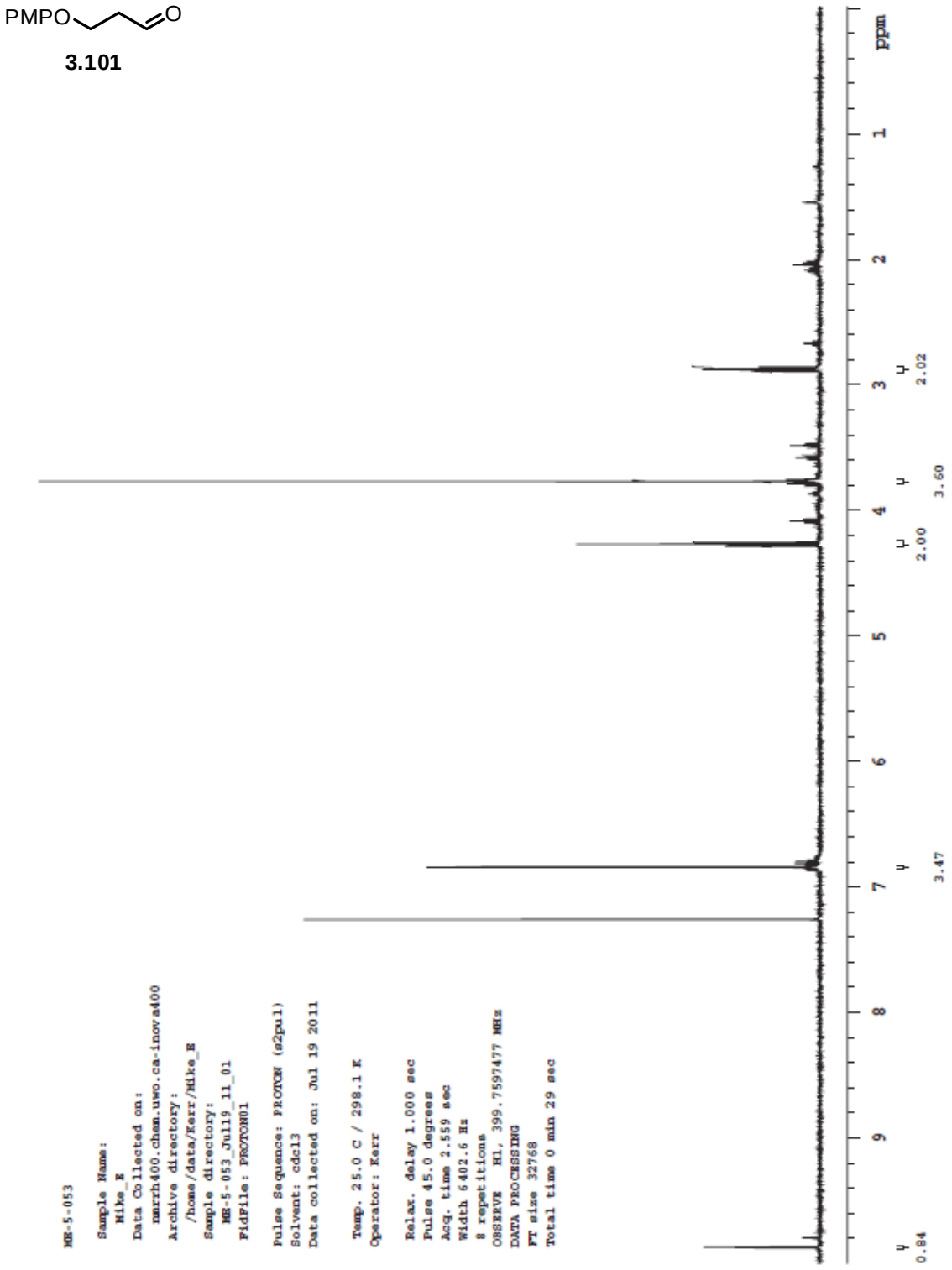

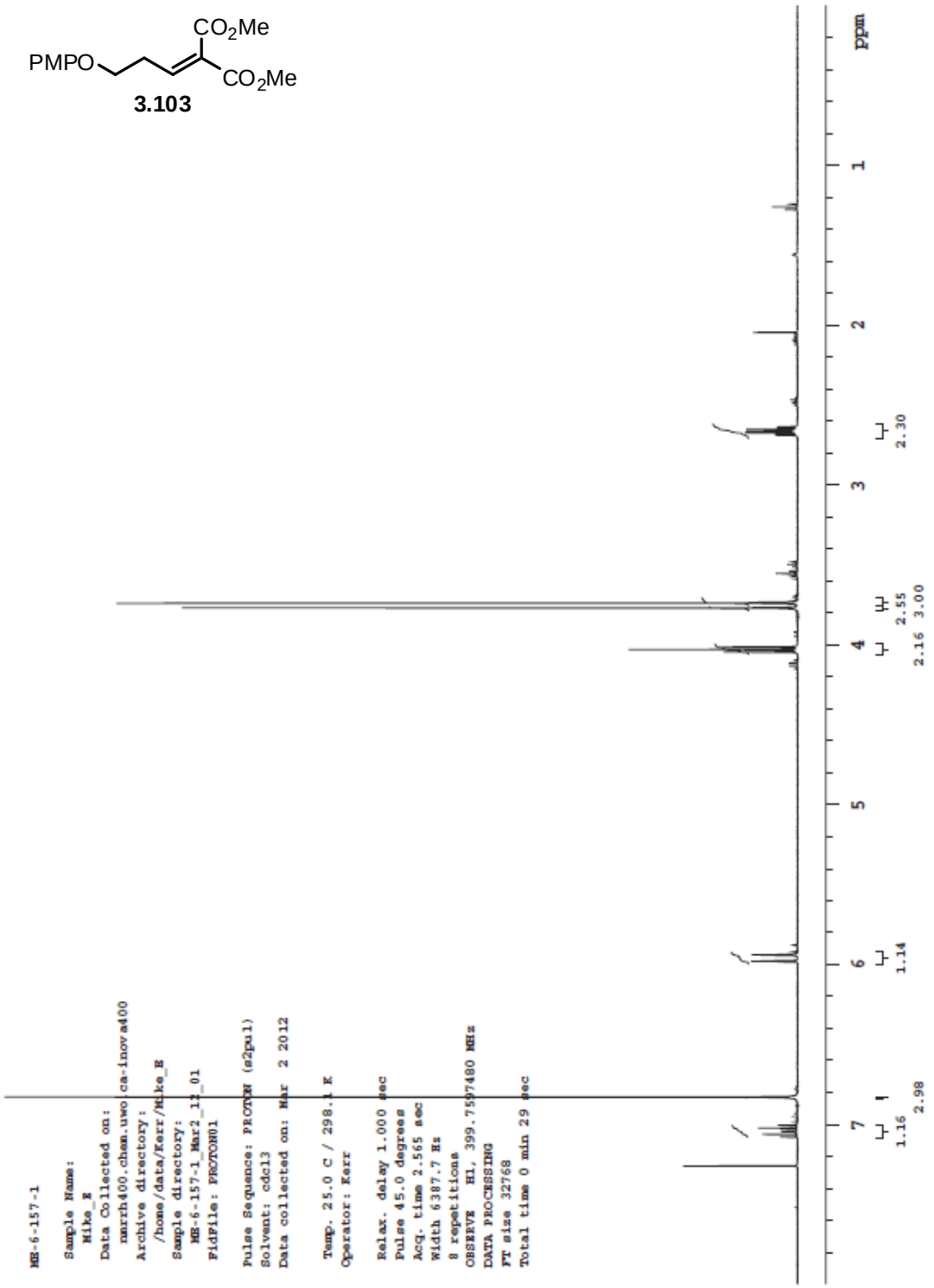

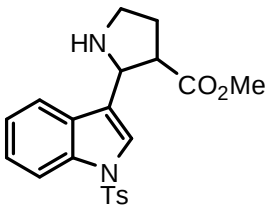

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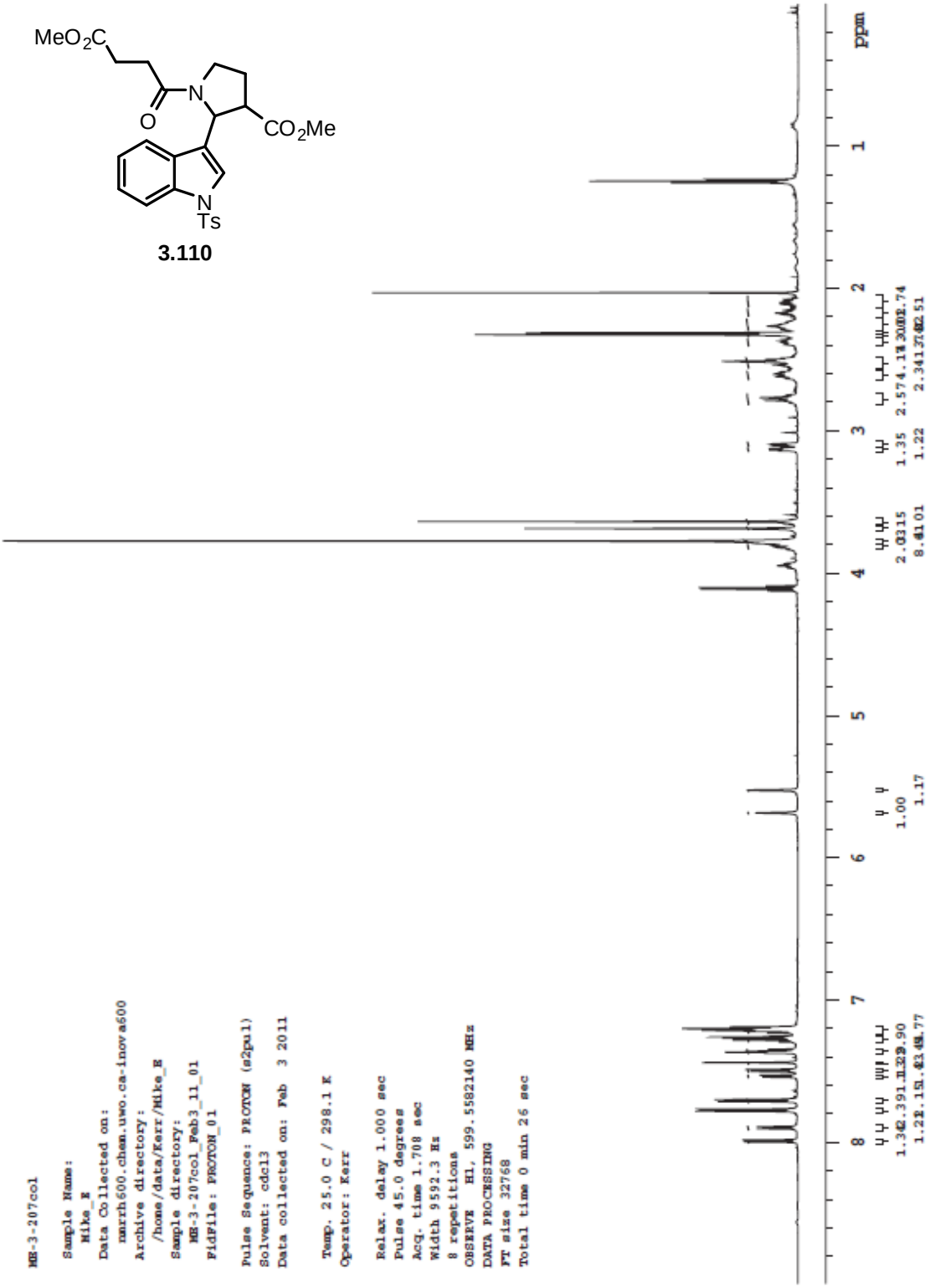

3.110

Curriculum Vitae for Michael R. Emmett

A) Education

The University of Western Ontario (Sept. 2009 – present). Ph. D. in Chemistry
Research Advisor: Professor Michael A. Kerr

The University of Western Ontario (Sept. 2005 – April 2009). Honors B.Sc. (Honors Specialization Chemistry)
Thesis Title: Activation of Cyclopropanes towards Nucleophilic Ring Opening Using Internal Brønsted Acids
Undergraduate Honors Supervisor: Professor Michael A. Kerr

B) Research and Relevant Work Experience

The University of Western Ontario, Department of Chemistry (2009 – present)
Teaching Assistant, Chemistry 3373, 2283, 1050.

The University of Western Ontario, (2009 – present) Research Assistant
Research Supervisor: Professor Michael A. Kerr

The University of Western Ontario (2010 – present)
Undergraduate Thesis Supervisor for Chemistry 4491 Chemistry Students

C) Publications

1) Flisar, M. E.; Emmett, M. R.; Kerr, M. A. The Catalyst-free Tandem Ring-opening/Click Reaction of Acetylene-Bearing Donor Acceptor Cyclopropanes *Synlett Manuscript Accepted*

2) Grover, H. K.; Emmett, M. R.; Kerr, M. A. γ-Substituted Butanolides from Cyclopropane Hemimalonates: An Expedient Synthesis of Natural (R)-Dodecan-4-olide *Org. Lett*. **2013**, *15*, 4838.

3) Emmett, M. R.; Grover, H. K.; Kerr, M. A. Tandem Ring-Opening/Decarboxylation of Cyclopropane Hemimalonates with Sodium Azide: A Short Route to γ-Aminobutyric Acid Esters *J. Org. Chem.* **2012**, *77*, 6634.

4) Emmett, M. R.; Kerr, M. A. Nucleophilic Ring Opening of Cyclopropanes Using Internal Brønsted Acid Activation *Org. Lett.* **2011**. *13*, 4180.

D) Presentations

5) **Emmett, M. R.***, Grover, H. K., Kerr, M. A. (2014) The Reactivity of Cyclopropane Hemimalonates. The 97th Canadian Society for Chemistry Conference, Vancouver, British Columbia, Oral Presentation (Ph. D. Work)

6) **Emmett, M. R.***, Kerr, M. A. (2014) Progress Towards Actinophyllic Acid. The 97th Canadian Society for Chemistry Conference, Vancouver, British Columbia, Poster Presentation (Ph. D. Work)

7) **Emmett, M. R.***, Kerr, M. A. (2012) The Reactivity of Cyclopropane Hemimalonates. The 95th Canadian Society for Chemistry Conference, Calgary, Alberta, Oral Presentation (Ph. D. Work)

8) **Emmett, M. R.*,** Kerr, M. A. (2012) Early Progress Towards Actinophyllic Acid. 15th Symposium on the Latest Trends in Organic Synthesis. St. Catharines, Ontario, Poster Presentation (Ph. D. Work)

9) Grover, H. K.*, **Emmett, M. R.**, Kerr, M. A. (2012) The Reactivity of Cyclopropane Hemimalonates. 15th Symposium on the Latest Trends in Organic Synthesis. St. Catharines, Ontario, Poster Presentation (Ph. D. Work)

10) **Emmett, M. R.***, Kerr, M. A. (2011) Progress Towards Actinophyllic Acid. The 94th Canadian Society for Chemistry Conference, Montreal, Quebec, Oral Presentation (Ph. D. Work)

11) **Emmett, M. R.***, Sapeta, K. A., Kerr, M. A. (2010) Nucleophilic Ring Opening of Cyclopropanes Using Internal Brønsted Acid Activation. 14th Symposium on the Latest Trends in Organic Synthesis. St. Catharines, Ontario, Poster Presentation (Ph. D. Work)

12) **Emmett, M. R.***, Sapeta, K. A., Kerr, M. A. (2010) Nucleophilic Ring Opening of Cyclopropanes Using Internal Brønsted Acid Activation. The 93rd Canadian Society for Chemistry Conference, Toronto, Ontario, Poster Presentation (Ph. D. Work)

13) **Emmett, M. R.***, Kerr, M. A. (2009) Activation of Cyclopropanes towards Nucleophilic Ring Opening Using Internal Brønsted Acids. Fourth Year Defense, University of Western Ontario, London, Ontario, Oral Presentation (B. Sc. Work)

E) Awards

Name of Award	Value (/yr)	Location of Tenure	Period Held
1st Place CSC Organic Chemistry Oral Award	$100	U. Western Ontario	N/A
NSERC PGS-D Scholarship	$21000	U. Western Ontario	May 2013-present
Ontario Graduate Scholarship	$15000	U. Western Ontario	Declined (May 2013-present)
UWO Teaching Assistant Award	-	U. Western Ontario	Nominated (2012-2013)
NSERC PGS-D Scholarship	$21000	U. Western Ontario	Waitlisted (May 2012)
Ontario Graduate Scholarship	$15000	U. Western Ontario	Waitlisted (May 2012)
UWO Teaching Assistant Award	-	U. Western Ontario	Nominated (2011-2012)
Graduate Tuition Scholarship	~$7000	U. Western Ontario	Sept. 2009 – Apr. 2012
Western Entrance Scholarship	$2000	U. Western Ontario	Sept. 2005