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Michael R. Emmett, *The University of Western Ontario*

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

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

(Thesis format: Monograph)

by

Michael R. Emmett

Graduate Program in Chemistry

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

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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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-cyclopropanediester. 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: Cyclopropanediester, 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.

I have been fortunate enough to mentor three undergraduate students with their fourth year honours projects. I would like to thank them for their constant effort and hopefully we learned a lot together on their respective projects.

I would like to thank the support staff at Western for their expertise and their assistance over my six years: Dr. Mat Willans (NMR), Ron Maslen and Robin Hall (lab technicians), Darlene McDonald (graduate secretary), and Marylou Hart, Sherrie McPhee and Don Yakobchuck at ChemBiostores for aiding me in the acquisition of the chemicals that I required.

I would like to thank my friends outside of chemistry that I have had the pleasure of interacting with. The times that we have shared outside of the lab have helped keep me sane over my time here and I don't know if I could be the person I am today without all of you.

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 unwavering 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.

Finally, I would like to thank Polydoros and Huck for their assistance editing this dissertation. This document would never have been completed without their help. I would also like to thank the members of my thesis examination committee, for their patience in my lack of meeting deadlines (except this one) and for helping me complete my degree.

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List of Abbreviations

1,2-C ₆ H ₄ Cl ₂	1,2-dichlorobenzene
[α] _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	<i>tert</i> -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	$\alpha,\alpha',\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid
Et	Ethyl
Et ₂ O	Diethyl ether
EtOAc	Ethyl acetate
FT-IR	Fourier Transform Infrared
G2	Grubbs 2 nd Generation Catalyst
GABA	<i>gamma</i> -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–trioxazoline
IBX	2-Iodoxybenzoic acid
<i>i</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
<i>n</i> -Bu	Butyl
NDMBA	N,N'-dimethylbarbituric acid
NEt ₃	Triethylamine
NMR	Nuclear Magnetic Resonance
NTf ₂	Triflimide
Nu	Nucleophile
OTf	Triflate
P1	Amidoporphyrin ligand
<i>p</i> -ABSA	<i>para</i> -Acetamidobenzenesulfonyl azide
PDC	Pyridinium dichromate

Ph	Phenyl
PhCN	Benzonitrile
Pg	Protecting group
PMP	<i>para</i> -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 _N 1	Unimolecular Nucleophilic Substitution
S _N 2	Bimolecular Nucleophilic Substitution
TBAF	<i>tetra</i> -butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl; bis(salicylidene- <i>tert</i> -butylamine)
TBSCl	<i>tert</i> -butyldimethylsilyl chloride
<i>t</i> Bu	<i>tert</i> -butyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Tol.	Toluene
Ts	<i>para</i> -toluenesulfonyl
TsCl	<i>para</i> -toluenesulfonyl chloride
TsOH	<i>para</i> -toluenesulfonic acid

Chapter 1 The Synthesis and Reactivity of Cyclopropane Hemimalonates

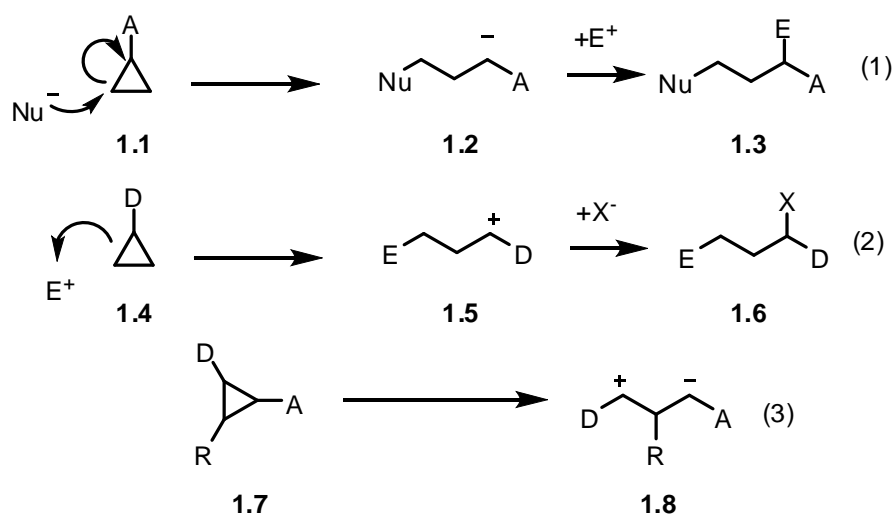
Chapter 1 describes the development of a new type of donor-acceptor cyclopropane and the expansion of current group methodology through the nucleophilic ring opening of cyclopropane hemimalonates with indole under ultra-high pressure conditions. A brief overview of the structure and bonding of cyclopropanes 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 1.6² and 1.7³ 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 bond⁴. This bonding phenomenon has been used to explain the observation that cyclopropanes display reactivity common to olefins⁵. 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 nucleophile 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

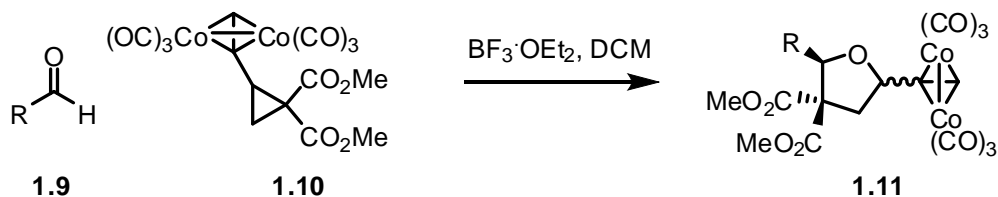
This dipole can react with another dipole to form annulated products, or it can simply react with a nucleophile to form acyclic products. Donor-acceptor cyclopropanes were first investigated in the 1960s and 1970s primarily by the groups of Stork⁷⁻¹⁰ and Danishefsky¹¹⁻¹⁴, but it wasn't until the 1980s when the groups of Wenkert¹⁵⁻¹⁶ and Reissig¹⁷⁻²⁵ 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

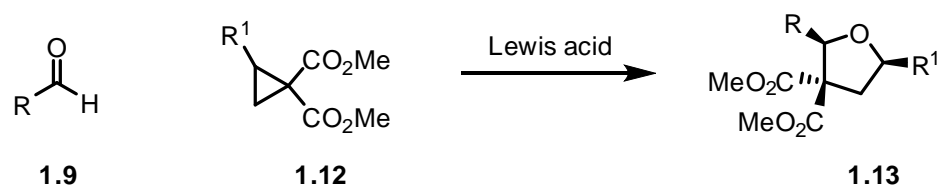
Carbonyls have been shown to be suitable dipoles for the formation of tetrahydrofurans with 1,1-cyclopropanediester. The Christie group formed 1,2,5-tetrahydrofurans **1.11**²⁶ from the reaction of Nicholas activated cyclopropanes **1.10** and aldehydes **1.9** (Scheme 1.2). The alkynyl substituted cyclopropanes 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.



Scheme 1.2: Christie Group Tetrahydrofuran Synthesis

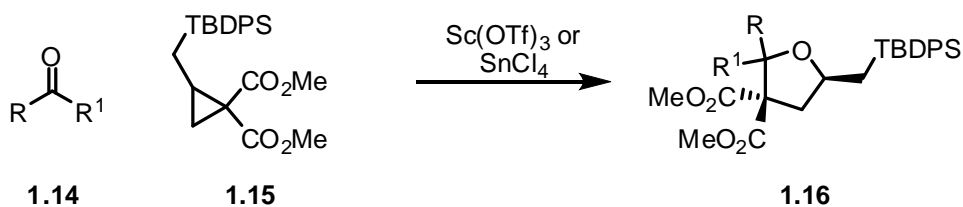
The Johnson group at the University of North Carolina has been one of the pioneers in the field of tetrahydrofuran syntheses from cyclopropanes. They initially developed the cyclization of aryl and vinyl cyclopropanediester **1.12** with a variety of aldehydes **1.9** (Scheme 1.3). Under tin triflate 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.



Scheme 1.3: Johnson Group Tetrahydrofuran Syntheses

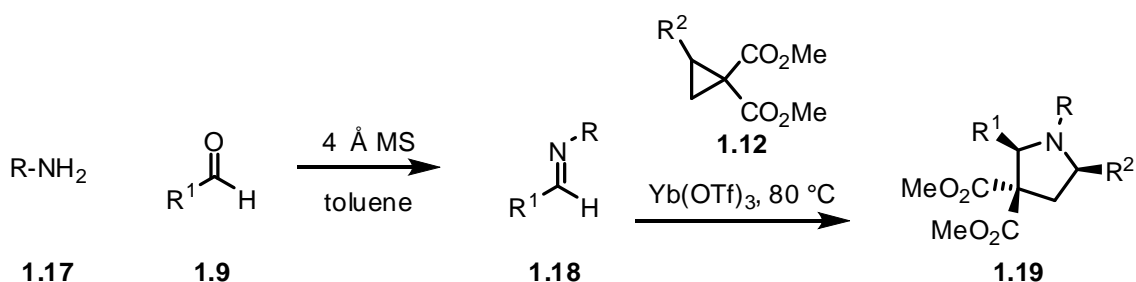
In 2006, the Yadav group developed cyclopropanes with an aliphatic silane as the donor group, **1.15**.³¹ By using the beta-silicon effect they could stabilize the generated positive charge, under scandium triflate catalysis, to form tetrahydrofurans **1.16** with aldehydes or cyclic ketones **1.14** (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.



Scheme 1.4: Yadav Group Synthesis of Tetrahydrofurans

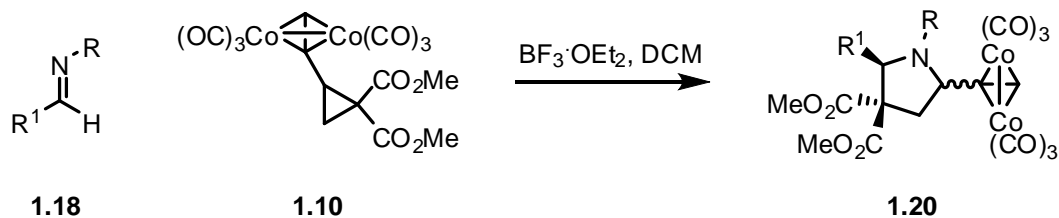
Section 1.2.2 Formation of Pyrrolidines

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-cyclopropanediester 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.

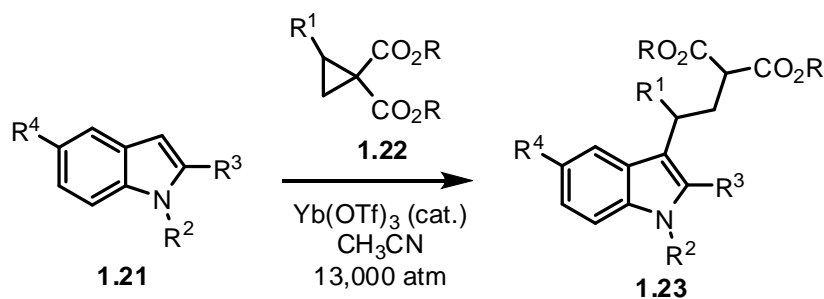


Scheme 1.6: Christie Group's Analogous Pyrrolidine Synthesis

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

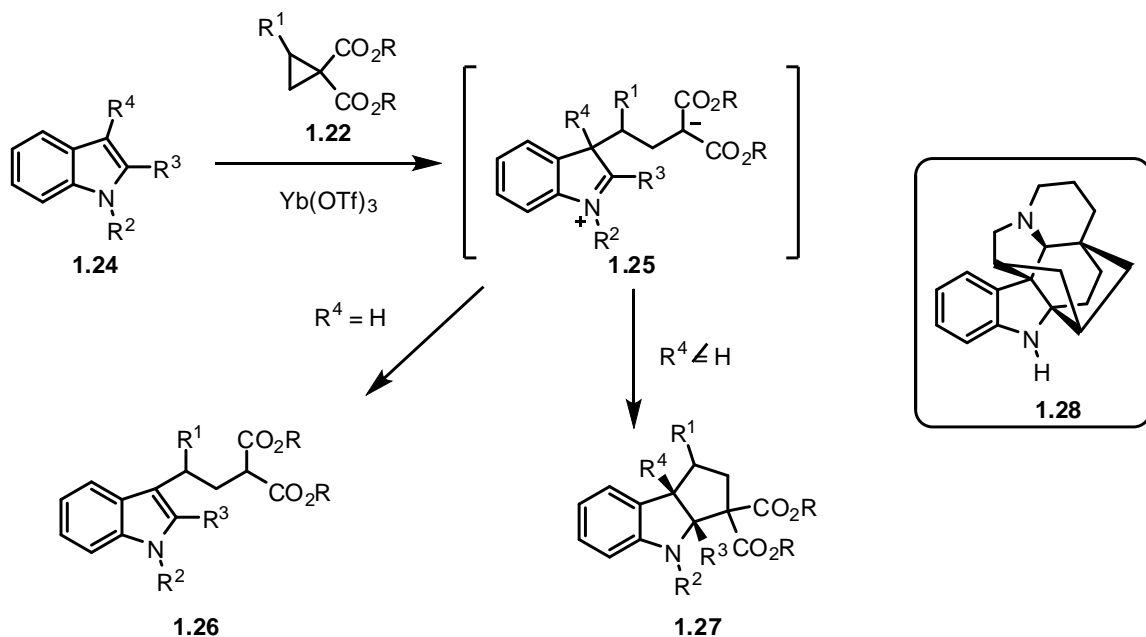


Scheme 1.7: The Reaction of Substituted Indoles with Cyclopropanediester under Ultra-high Pressures and Lewis Acid Catalysis

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

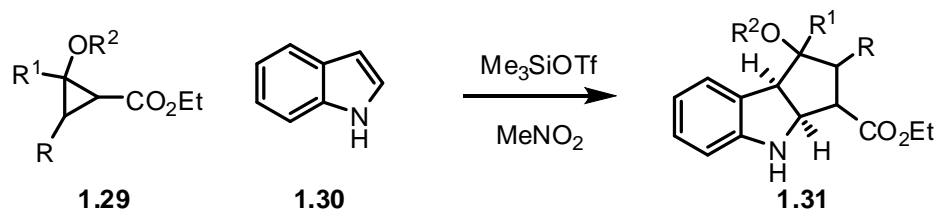
inhibited. This is contrary to previous reports that water was a good co-solvent for reactions at high pressures.³⁷ It was also contrary to the fact that ytterbium triflate showed no inhibition of Lewis acidity in the presence of water.³⁸ A small scope was investigated as only three cyclopropanes were tested. It is of note that the parent cyclopropanediester 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**.



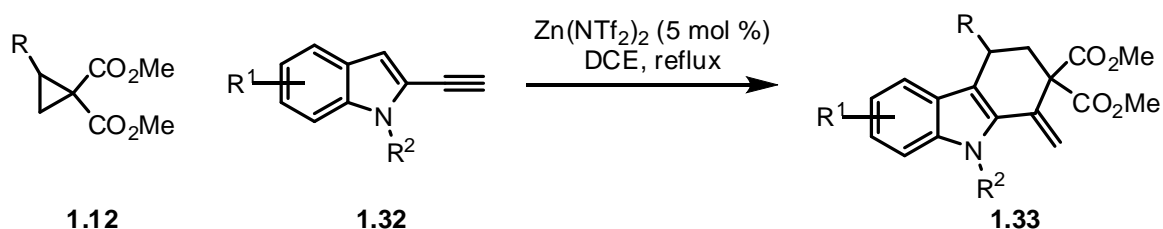
Scheme 1.8: The Reaction of Cyclopropanediesters with Substituted Indoles

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 iminal with the nitrogen.



Scheme 1.9: Pagenkopf Group Ring Opening of Cyclopropanes with Indoles

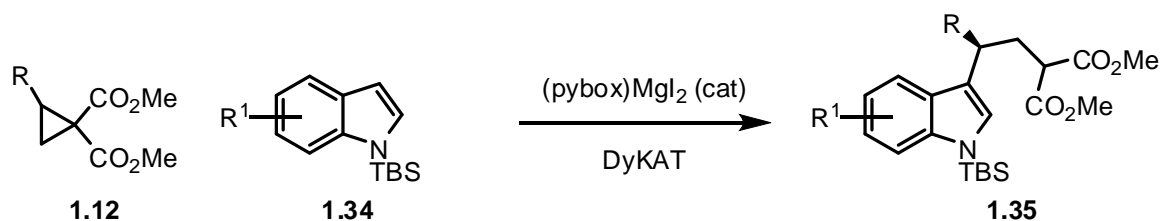
In 2009, the Kerr group developed a new concept where they could tether a nucleophile and an orthogonal electrophile together to receive pyrans⁴⁰ and piperidines.⁴¹ In 2011, the Kerr group extended this concept by attaching an alkyne to the 2-position of the indole ring **1.32** (Scheme 1.10).⁴³ With 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 cyclopropanediester 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

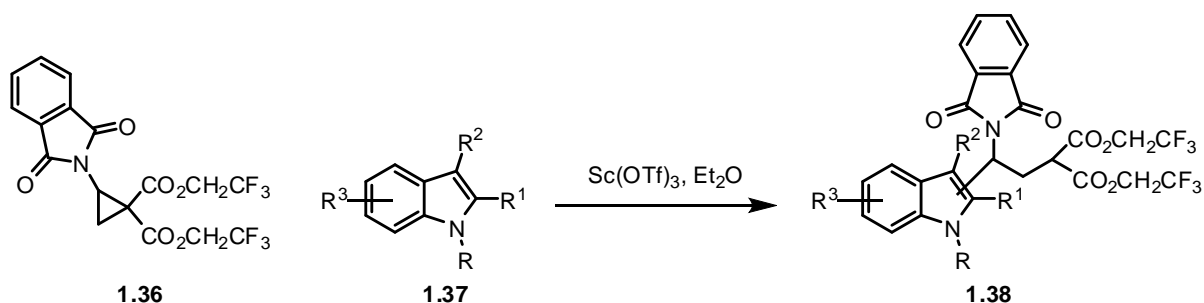
protecting groups on indole. They quickly learned that they needed to temper the reactivity of the indole so that the racemization of their starting cyclopropane was a competitive process to the indole alkylation. After optimization, it was found that a TBS-protected indole **1.34** worked the best for 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 cyclopropanediester 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.



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

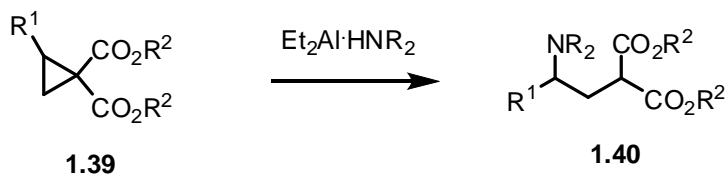
could produce a wide variety of different indole adducts. It is of note that when they used the skatole derived indole in this case, they did not see pentannulation, but simple C-3 to C-2 migration of the ring opened framework.



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

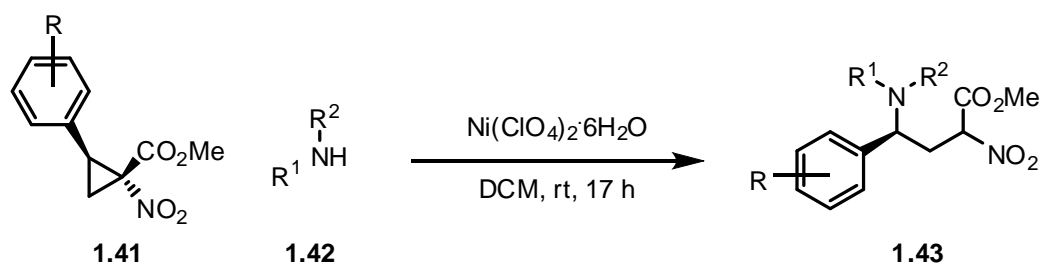
Section 1.3.2 Ring Opening of Cyclopropanes with Amines to form gamma-aminobutyric acid (GABA) analogues

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.



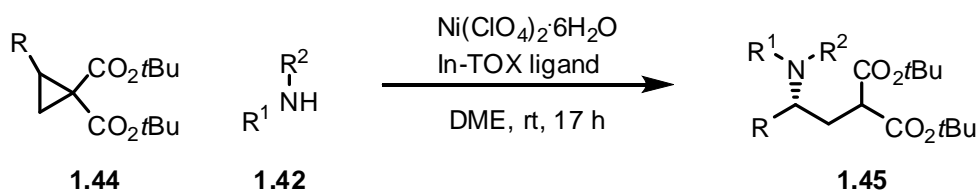
Scheme 1.13: Schneider's Aminolysis of Cyclopropanes

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.)



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

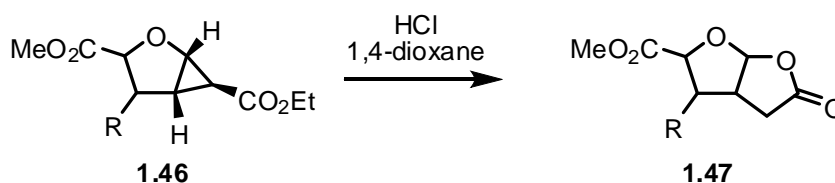
In 2012, Tang further advanced this field of donor-acceptor cyclopropane chemistry by developing a nickel catalyzed enantioselective ring opening of cyclopropanes **1.44** with amines **1.42** (Scheme 1.15).⁴⁸ While the previous methodology by Charette focused on secondary amines and anilines, the goal 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.



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

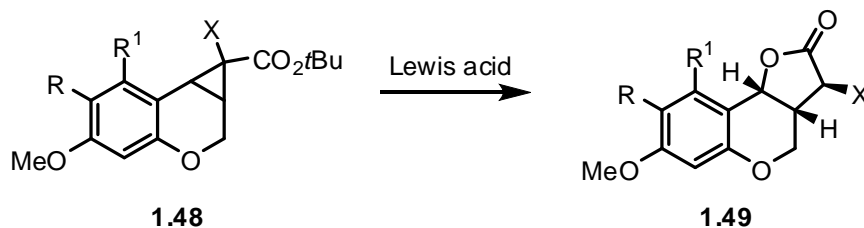
Section 1.4 Ring Expansions of Cyclopropanes to Form Lactones

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 Theodorakis⁵² and co-workers. Towards a more decorated substructure they need to reflux **1.46** in acid to induce the rearrangement.



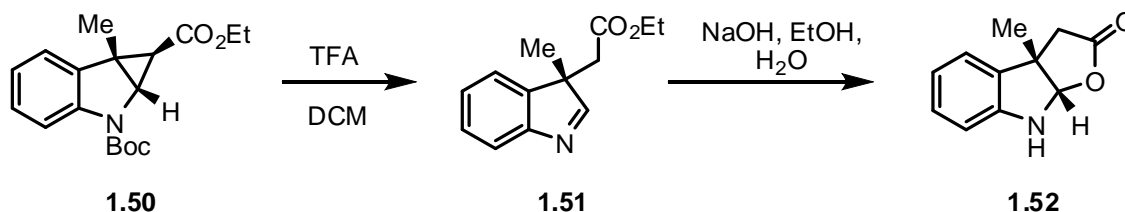
Scheme 1.16: Reiser's Lactone Formation

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.



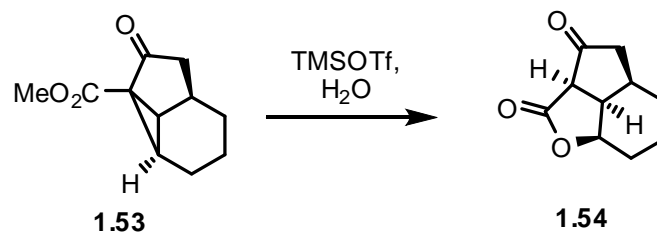
Scheme 1.17: Mead's Lactone Formation

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).



Scheme 1.18: Boysen's Stepwise Lactone Formation

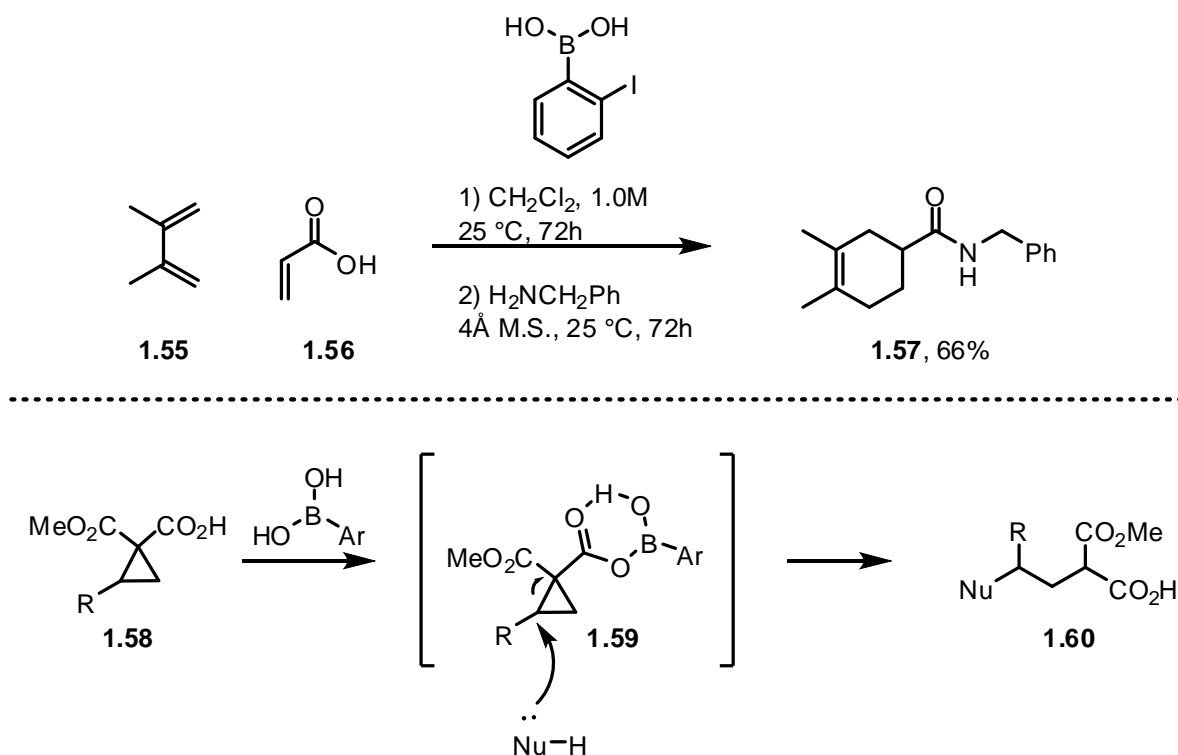
In 2013, Corey described the synthesis of fused lactones from fused cyclopropanes. In multiple steps they could make their desired starting materials, then a triflic acid mediated ring expansion/lactonization event occurred.⁵⁵ This skeletal rearrangement worked well for a variety of different substrates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



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 numerous 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-cyclopropanediester 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.

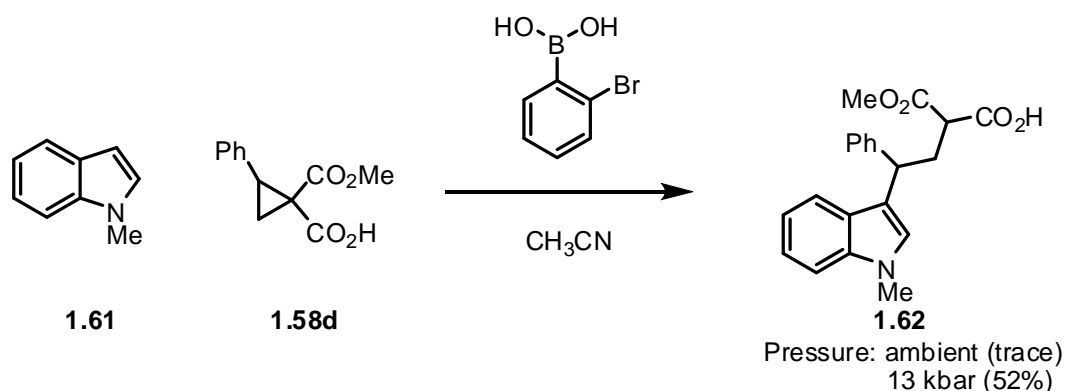


Scheme 1.20: Indole Ring Opening Project Inspiration

Section 1.5.1 Results and Discussion

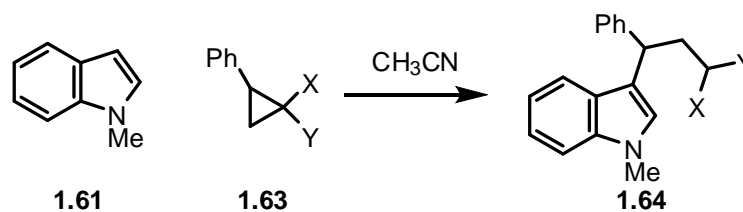
Section 1.5.1.1 Reaction Optimization

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-cyclopropanediester 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.

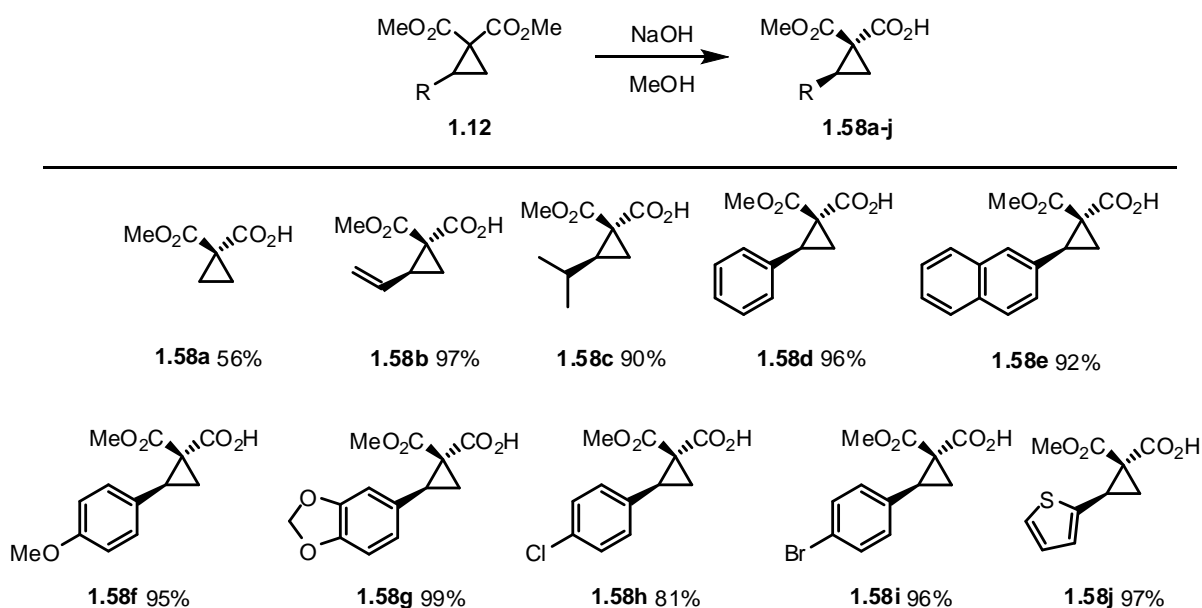
Table 1.1: Optimization Study for Ring Opening Reaction

Entry	Cyclopropane (1.63)	Temp. (°C)	Indole Equiv.	Conditions	Conversion (by NMR)	Yield
1	X= CO ₂ Me Y= CO ₂ H	25	2	24 h	0 %	N/A
2	X= CO ₂ Me Y= CO ₂ H	82	2	24 h	0 %	N/A
3	X= CO ₂ Me Y= CO ₂ H	80	2	30 min, mW	0 %	N/A
4	X= CO ₂ Me Y= CO ₂ H	25	2	48 h, 13 kbar	100 %	70 %
5	X= CO ₂ Me Y= CO ₂ H	25	1.2	48 h, 13 kbar	50 %	Not Determined
6	X=Y= CO ₂ Me	25	2	48 h, 13 kbar	0 %	N/A
7	X = CO ₂ H Y = H	25	2	48 h, 13 kbar	0 %	N/A
8	X= CO ₂ Me Y= CO ₂ H	50	2	1 h, 13 kbar	100 %	76 %
9	X= CO₂Me Y= CO₂H	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

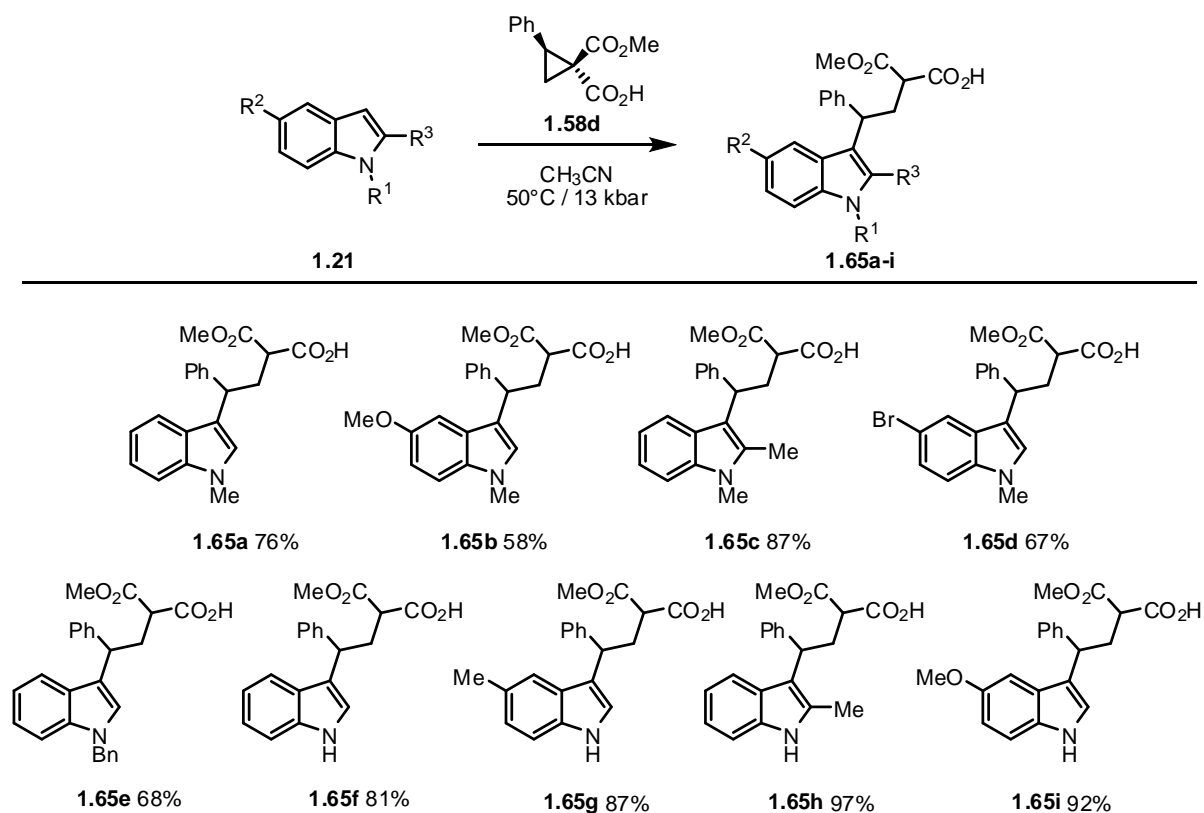


Scheme 1.22: Synthesis of a Library of Cyclopropane Hemimalonates

Section 1.5.1.3 Investigating the Scope of the Reaction

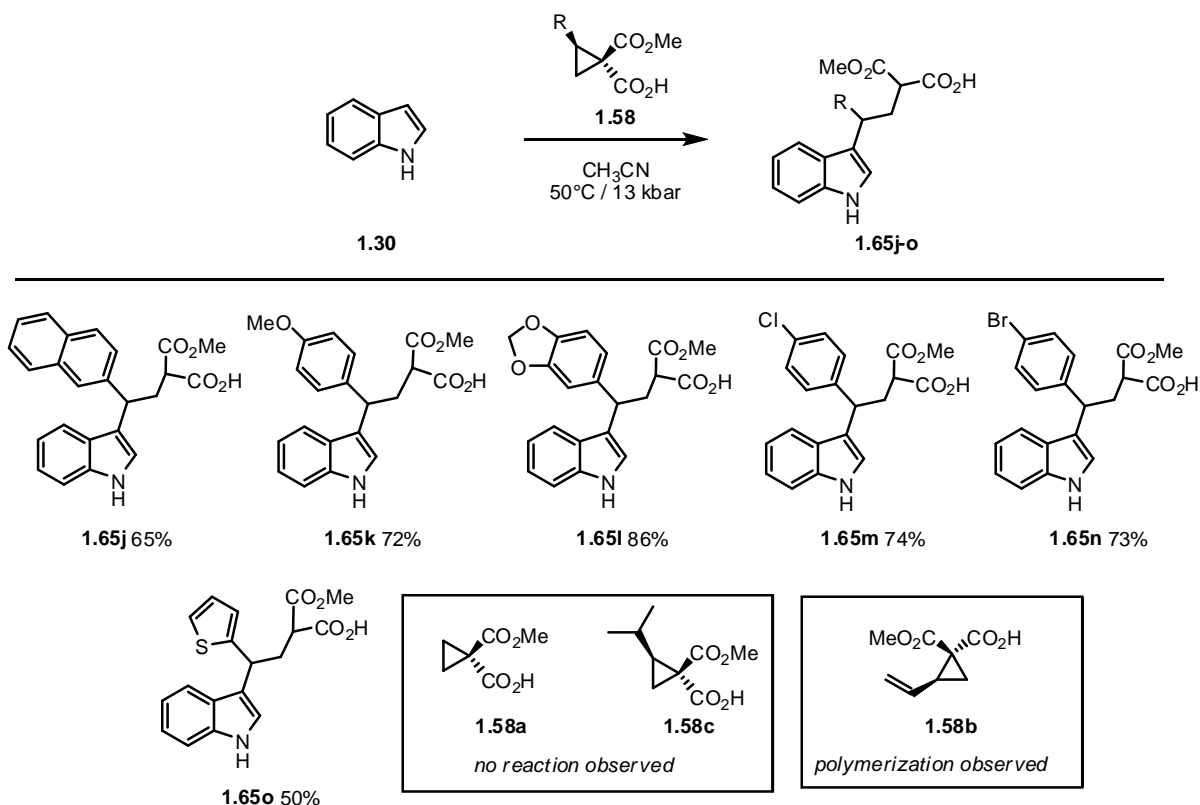
Looking into the scope of this new reaction, we first investigated what substitution patterns would be tolerated on our indole species (Scheme 1.23). For the most part the reaction was tolerant to all substitution patterns that we tried. Due to the instability of the 5-methoxy-1-methylindole, it was 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

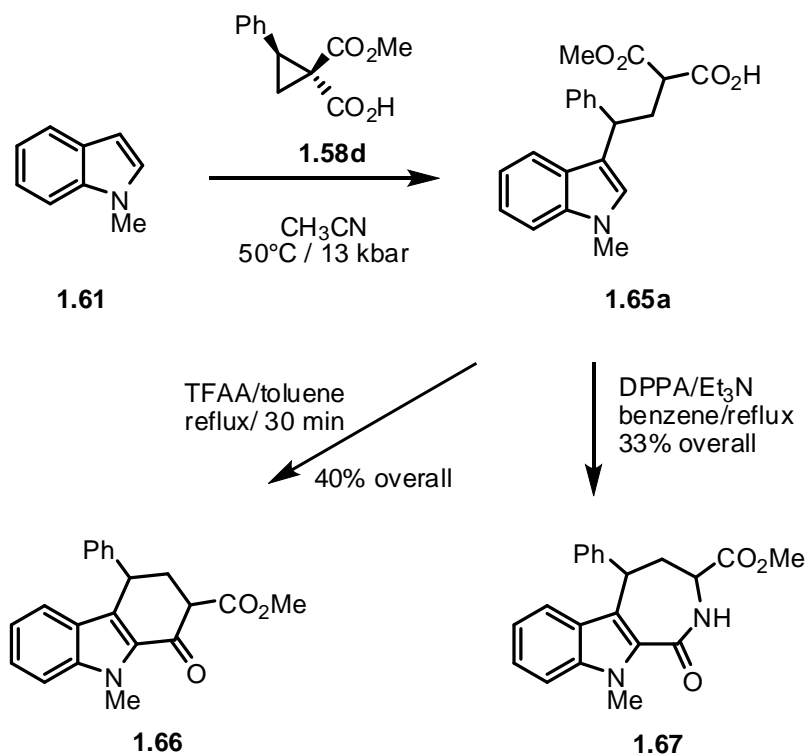
With indole appearing to be the optimal nucleophile, we decided to test the scope of cyclopropanes that could be utilized in this reaction. Aryl and heteroaryl cyclopropane substitution was well-tolerated giving good to excellent yields of products. Unfortunately the vinyl cyclopropane **1.58b**, polymerized 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**.



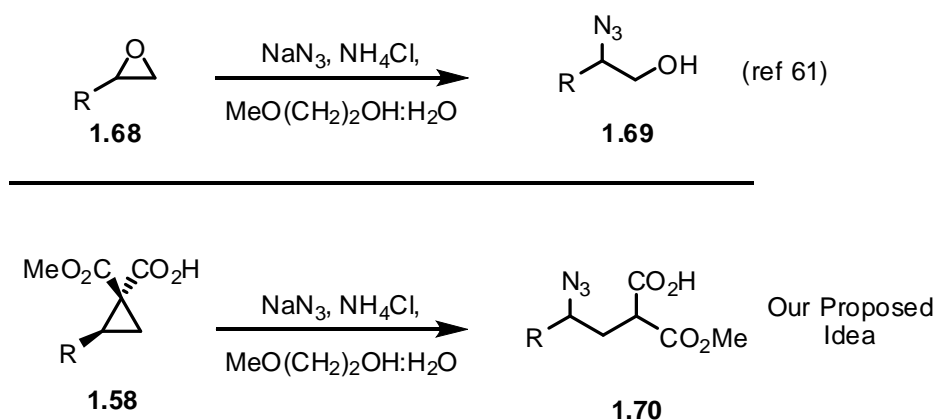
Scheme 1.25 Elaboration of Ring Opened Adduct **1.65a**

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 Bäckvall⁶¹ 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**.

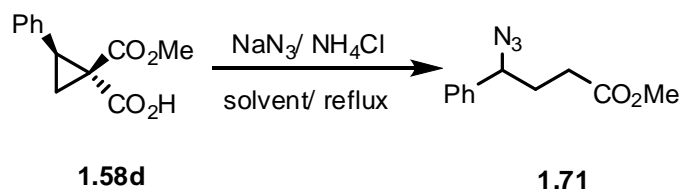


Scheme 1.26 New Ring Opening Proposal with Azides

Section 1.6.1 Results and Discussion

Section 1.6.1.1 Reaction Optimization

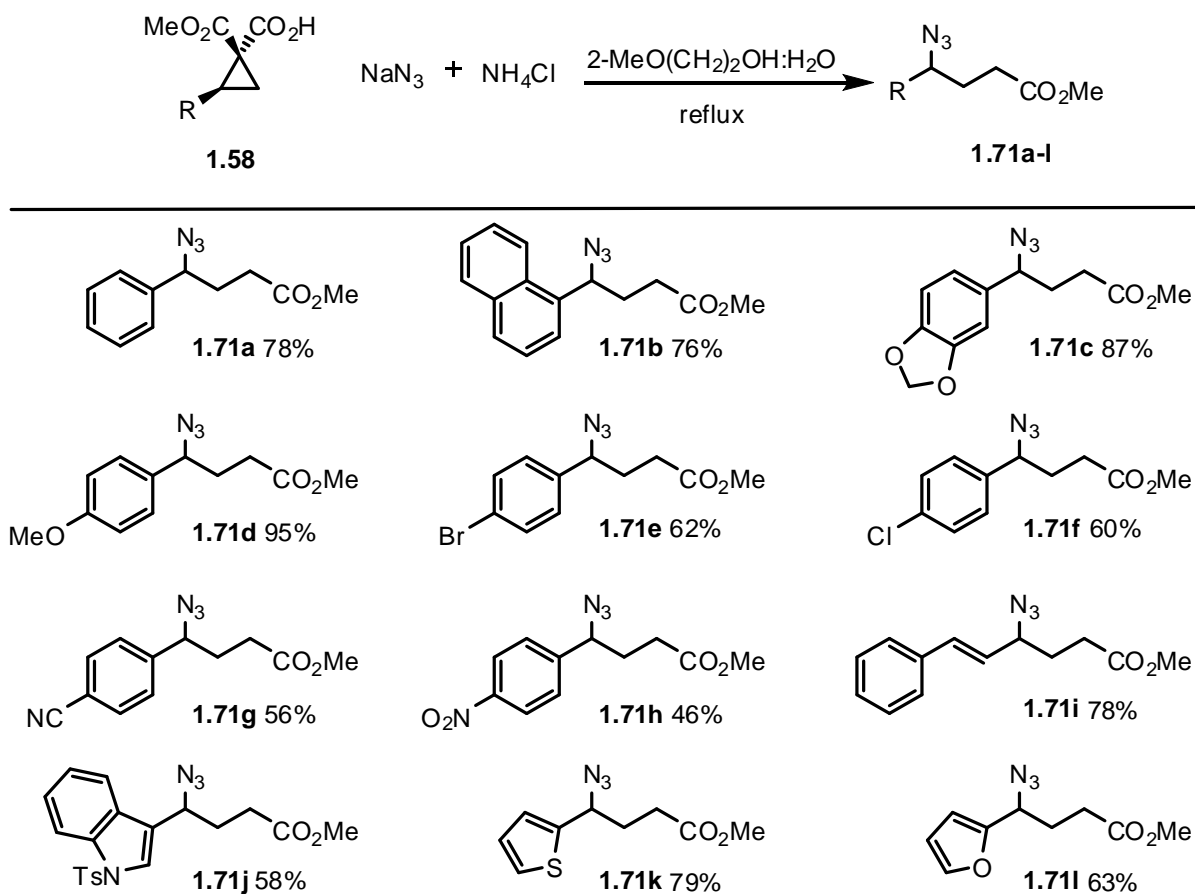
Using Bäckvall's conditions as a starting point for the reaction we obtained a 70 % yield of a ring opened product that had concurrently undergone decarboxylation **1.71**. Removal of the ammonium chloride led to a decrease in the formation of product. Attempting to use other organic solvents that are 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-cyclopropanediester 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

Entry	Azide (equiv)	NH ₄ Cl (equiv)	Solvent	Yield(%)
1	1	1.4	2-MeO(CH ₂) ₂ OH:H ₂ O (10:1)	70
2	1	0	2-MeO(CH ₂) ₂ OH:H ₂ O (10:1)	N/A
3	1	0	2-MeO(CH ₂) ₂ OH	30
4	1	1.4	C ₆ H ₆	no rxn
5	1	1.4	CH ₃ CN	no rxn
6	1	1.4	THF	no rxn
7	1.2	1.4	2-MeO(CH₂)₂OH:H₂O (10:1)	78
8	2	1.4	2-MeO(CH ₂) ₂ OH:H ₂ O (10:1)	73
9	2	3	2-MeO(CH ₂) ₂ OH:H ₂ O (10:1)	74
10	1.2	1.4	2-MeO(CH ₂) ₂ OH:H ₂ O (10:1)	50
11	1.2	1.4	2-MeO(CH ₂) ₂ OH:H ₂ O (5:1)	74
12	1.2	1.4	2-MeO(CH ₂) ₂ OH:H ₂ O (1:1)	60
13*	1.2	1.4	2-MeO(CH ₂) ₂ OH:H ₂ O (10:1)	50

Section 1.6.1.2 Investigating the Scope of the Reaction

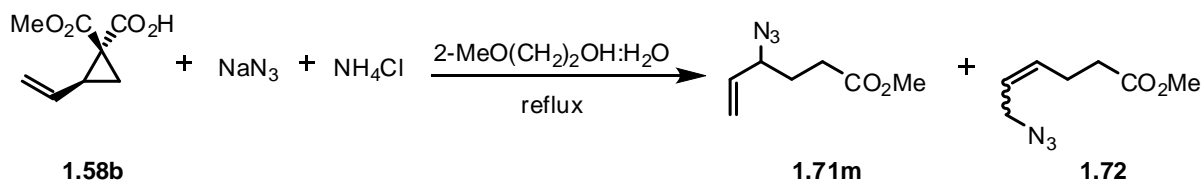
With our optimal conditions in hand (Table 1.2, entry 7), we surveyed our new library of cyclopropane hemimalonates to determine the generality of this method. The reaction worked well for aromatic substituted cyclopropanes as well as heteroaromatic cyclopropanes. The reaction worked extremely well with 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

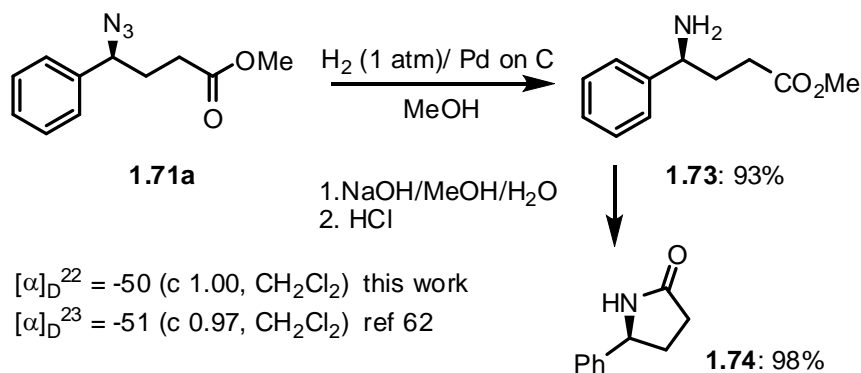
One interesting result was that even though the styrenyl cyclopropane underwent this transformation, issues arose when we attempted to use the vinyl substituted cyclopropane. In this example, we obtained an intractable mixture of our expected product **1.71m** and a S_{N}' addition product **1.72**.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

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



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

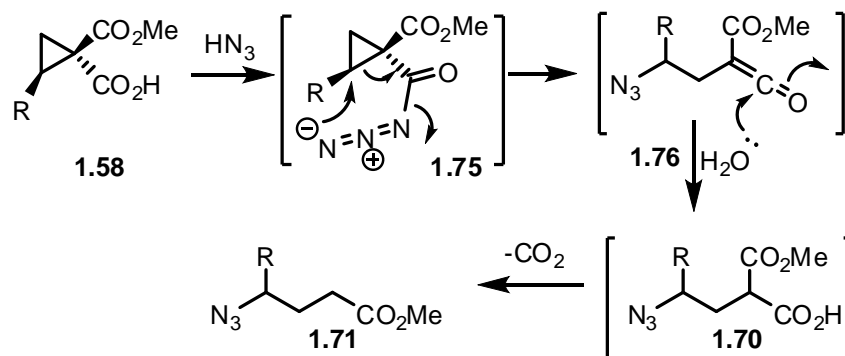
It is of note that the optically enriched phenyl cyclopropane (S)-**1.58d** (90% ee) underwent this transformation with full retention of enantiopurity (*vide supra*) to give (S)-**1.71a**. Finally, cyclopropanes where the substitution was aliphatic or unsubstituted were unreactive under these conditions 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

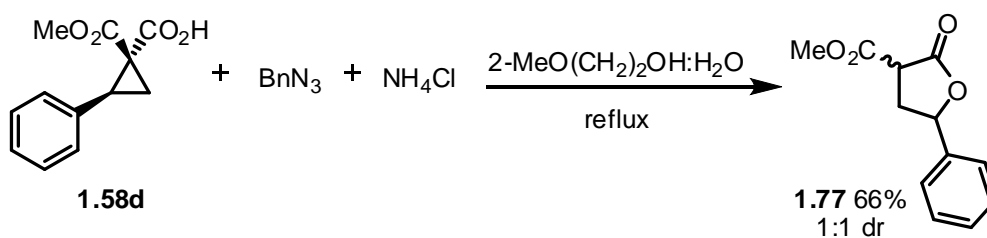
The fact that the hemimalonates are effective substrates and the diesters are not, is surprising to us. In our previous report in which we described the nucleophilic opening of these species with indoles, we were able to rationalize the results by invoking a high pressure induced intramolecular hydrogen 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 decarboxylated **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 maintaining 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

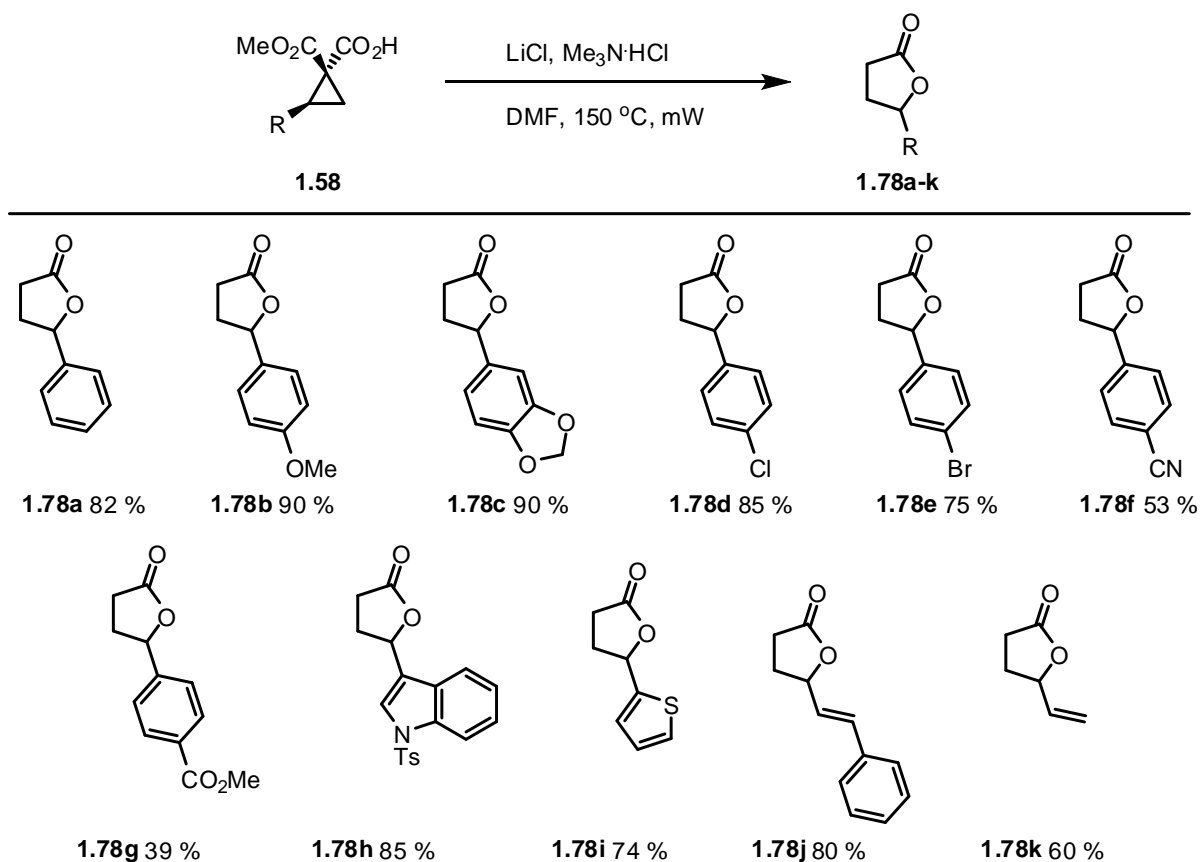


Entry	Additive (1.4 equiv.)	Solvent / Temp. (°C)	Time (h)	Product (%)
1	NH ₄ Cl	2-MeO(CH ₂) ₂ OH/reflux	2	82 1.77 , trace 1.78
2	NH ₄ Cl	DMSO / 135	1	87 1.77 , trace 1.78
3	NH ₄ Cl	(5:1) DMSO:H ₂ O/135	1	mixture
4	NaCl	DMSO / 135	1	mixture
5	KCl	DMSO / 135	1	mixture
6	LiCl	DMSO / 135	24	mixture
7	NaCN	DMSO / 135	24	no rxn
8	Me ₃ NHCl	DMSO / 135	24	mixture
9	NH ₄ Cl / NaCN	DMSO / 135	1 / 6	65 1.78
10	LiCl /	DMSO / 135	24	mixture

	Me ₃ NHCl			
11	LiCl /	DMSO / reflux	24	mixture
	Me ₃ NHCl			
12	LiCl /	DMSO / 150, mW	0.66	71 1.78
	Me ₃ NHCl			
13	LiCl /	DMF / 150, mW	0.66	82 1.78
	Me₃NHCl			
14	LiCl /	DMF / 150, mW	0.66	45 1.78
	Me ₃ NHCl			

Section 1.7.1.2 Investigating the Scope of the Rearrangement

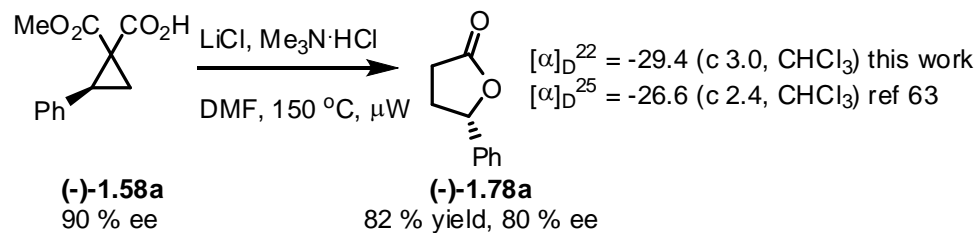
Once again, having our vast library of cyclopropane hemimalonates, we were able to explore the utility of this transformation. Both electron donating and halogen substituted phenyl cyclopropanes underwent the butanolide formation in moderate to excellent yields. Conversely, the electron withdrawing phenyl 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.



Scheme 1.32 Reaction Scope of the Butanolide Rearrangement

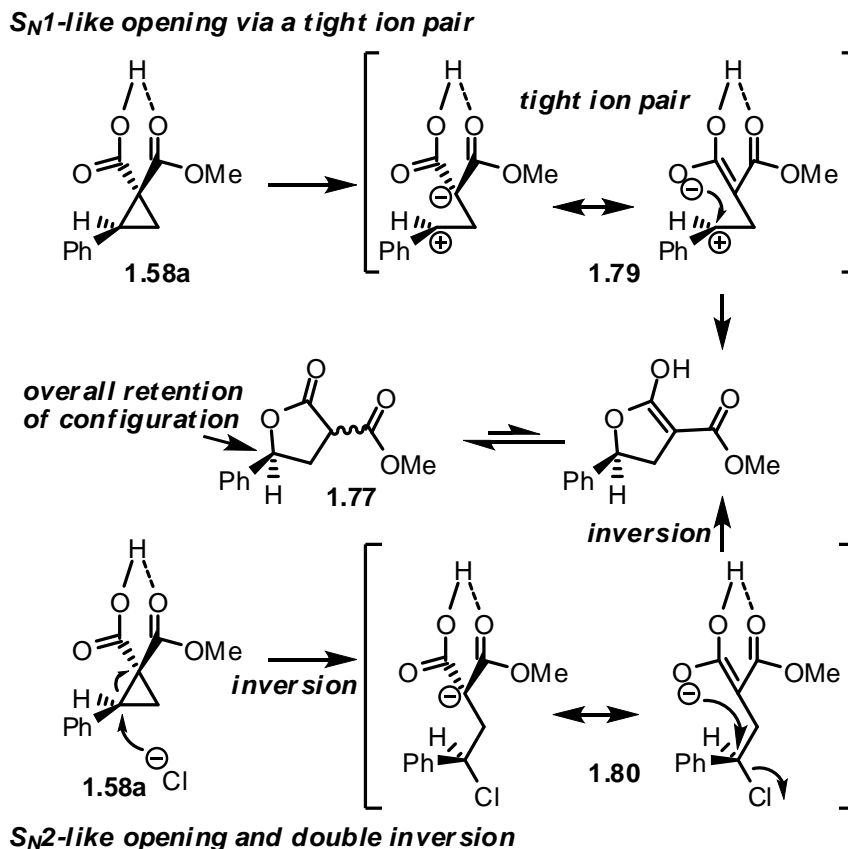
Section 1.7.1.3 Reaction Mechanism

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 solvolytic 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).

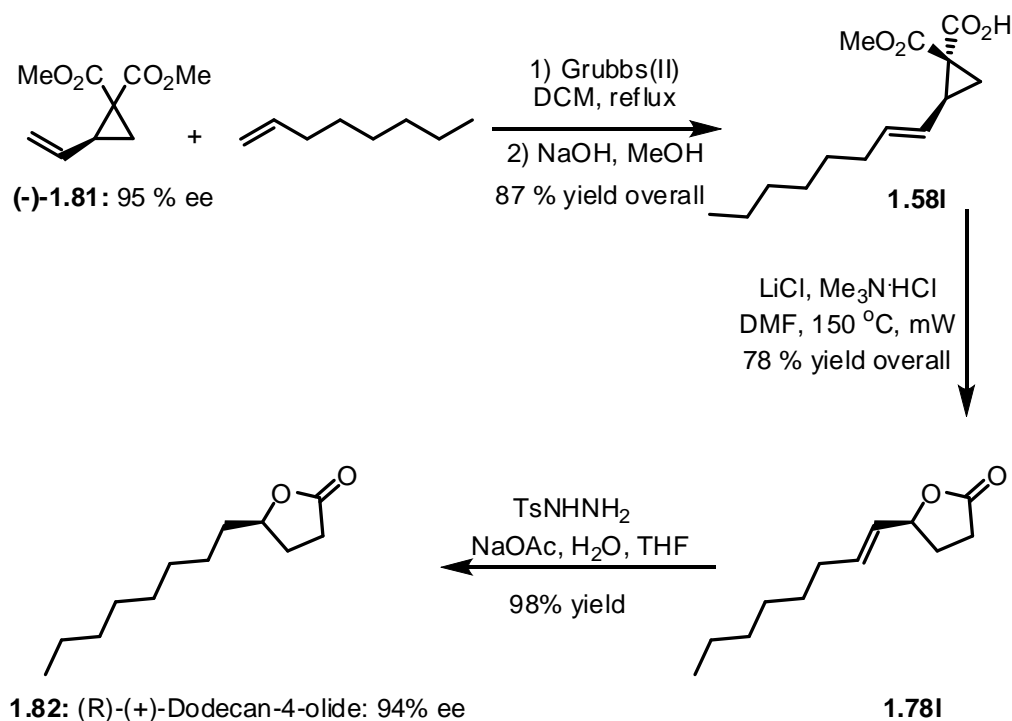


Scheme 1.34 Possible Mechanistic Pathways for the Butanolide Rearrangement

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 PtO₂. The π -system reduction of butanolide **1.78I** 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).

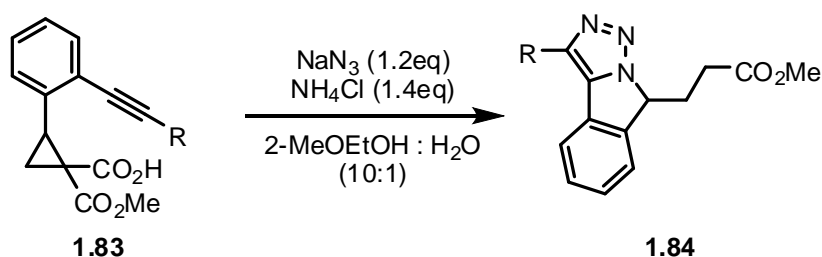


Scheme 1.35 Total Synthesis of (R)-(+)-dodecan-4-olide

Section 1.8 Summary and Future Work

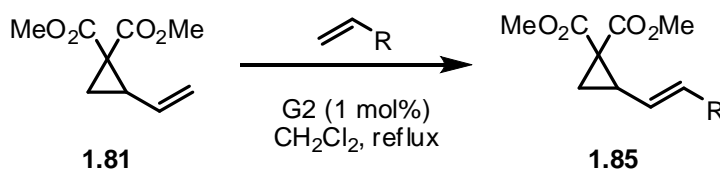
In summary, we have been able to synthesize and develop a new type of donor-acceptor cyclopropane and develop its reactivity. The hemimalonates do not need a Lewis acid to activate them and they can react under transition metal free, aqueous conditions. Under ultra-high pressure conditions, we were able 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



Scheme 1.36 Extension of the Azide Methodology to Synthesize Triazoles

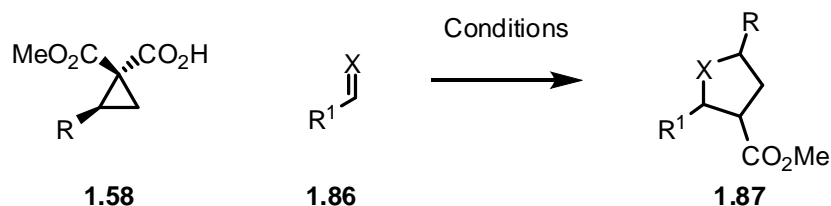
Without the presence of an external nucleophile, the hemimalonates **1.58**, can rearrange to form γ -butanolides in 39-90% yields. This reaction allowed for the total synthesis of (R)-(+)-dodecan-4-olide in 4 synthetic operations in a 67% overall yield. We believe the development of the cyclopropane 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



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.



Scheme 1.38 Potential Decarboxylative Dipolar Cycloaddition

Section 1.9 Experimental

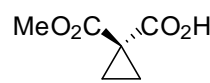
General

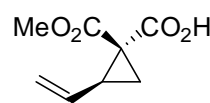
Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. ^1H , ^{19}F , and ^{13}C NMR experiments were performed on Varian Mercury 400, Varian Inova 400 and Inova 600 instruments and samples were obtained in CDCl_3 (referenced to 7.26 ppm for ^1H and 77.0 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 F₂₅₄) 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 LECOTM Tempres High-Pressure chemical reactor. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor.

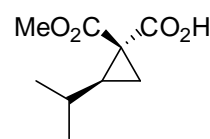
Section 1.9.1 The Ring Opening of Cyclopropane Hemimalonates by Indole

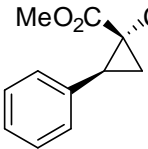
General Procedure for the mono-saponification of 1,1-cyclopropanediester

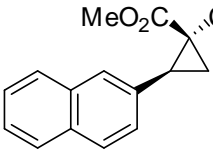
Cyclopropanes were dissolved in MeOH and 1.7M NaOH (1.2 eq.) with constant stirring. The solution was stirred for 1.5 h then was diluted with EtOAc and water to separate layers. The aqueous layer was the acidified with 5% HCl to reach pH 2, then extracted three times with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated.⁶⁰

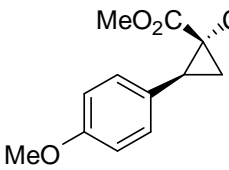

 Reagents employed: **1.12a** (0.356 g, 2.25 mmol); NaOH (1.60 mL, 2.72 mmol); MeOH (2 mL); Yielded **1.58a** as a clear oil, 56 % (0.181 g, 1.26 mmol). Spectral properties are identical to those previously reported.⁷⁷

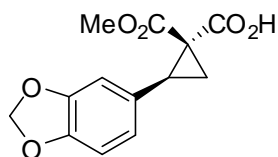

 Reagents employed: **1.12b** (0.541 g, 2.94 mmol); NaOH (2.25 mL, 3.50 mmol); MeOH (2.25 mL); Yielded **1.58b** as a clear oil, 91% (0.453 g, 2.66 mmol). Spectral properties are identical to those previously reported.⁷⁸


 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). ¹H-NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₉H₁₄O₄ = 186.0892, found 186.0887

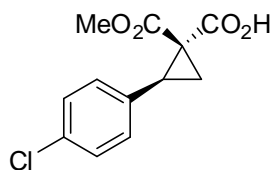

 Reagents employed: diester **1.12d** (1.02 g, 4.34 mmol); NaOH (3.00 mL, 5.17 mmol); MeOH (3 mL); Yielded **1.58d** as a clear oil, 93% (0.890 g, 4.04 mmol). Spectral properties are identical to those previously reported.⁷⁹


 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). ¹H-NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₁₆H₁₄O₄ = 270.0892, found 270.0893

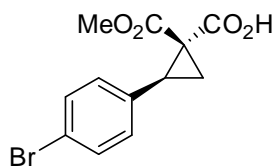

 Reagents employed: **1.12f** (0.997 g, 3.77 mmol); NaOH (2.65 mL, 4.50 mmol); MeOH (3 mL); Yielded **1.58f** as a white powder, 95% (0.903 g, 3.61 mmol). ¹H-NMR (400 MHz, CDCl₃): δ = 7.15 (d, J = 8.2 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.34 (dd, J = 9.0 Hz, 9.0 Hz, 1H), 3.31 (s, 3H), 2.38 (dd, J = 8.6 Hz, 4.7 Hz, 1H), 2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₄O₅ = 250.0841, found 250.0840



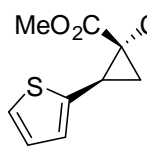
Reagents employed: **1.12g** (0.379 g, 1.36 mmol); NaOH (1.00 mL, 1.70 mmol); MeOH (1 mL); Yielded **1.58g** as a yellow powder, 98% (0.352g, 1.33 mmol). ¹H-NMR (600 MHz, CDCl₃): δ 6.75-6.68 (m, 3H), 5.95 (s, 2H), 3.38 (s, 3H), 3.30 (dd, J = 9.0 Hz, 9.0 Hz, 1H), 2.32 (dd, J = 8.6 Hz, 5.1 Hz, 1H), 2.23 (dd, J = 9.4 Hz, 5.1 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): 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 C₁₃H₁₂O₆ = 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). ¹H-NMR (600 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₁ClO₄ = 254.0346, found 254.0343

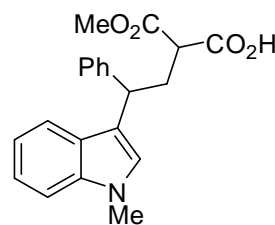


Reagents employed: **1.12i** (0.322 g, 1.03 mmol); NaOH (1.00 mL, 1.70 mmol); MeOH (1 mL); Yielded **1.58i** as a white solid, 96% (0.296 g, 0.988 mmol). ¹H-NMR (600 MHz, CDCl₃): δ 7.42 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 3.34 (s, 3H), 3.30 (dd, J = 8.8 Hz, 8.8 Hz, 1H), 2.33 (dd, J = 8.2 Hz, 4.7 Hz, 1H), 2.20 (dd, J = 9.4 Hz, 5.3 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): 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 C₁₂H₁₁BrO₄ = 297.9841, found 297.9843

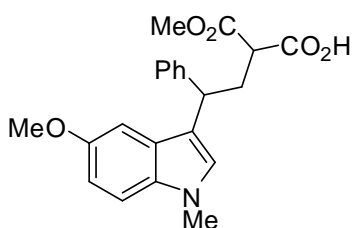

 Reagents employed: **1.12j** (1.12 g, 4.66 mmol); NaOH (3.26 mL, 5.54 mmol); MeOH (3.3 mL); Yielded **1.58j** as a yellow-brown oil, 97% (1.021 g, 4.52 mmol). ¹H-NMR (600 MHz, CDCl₃): δ = 7.22 (m, 1H), 6.94 (m, 2H), 3.43 (s, 3H), 3.35 (dd, J = 8.8 Hz, 8.8 Hz, 1H), 2.31 (dd, J = 8.2 Hz, 5.3 Hz, 2H), 2.19 (dd, J = 9.4 Hz, 4.7 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): 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 C₁₀H₁₀O₄S = 226.0300, found 226.0300

General Procedure for the Ring Opening of Cyclopropane Hemimalonates with Indole

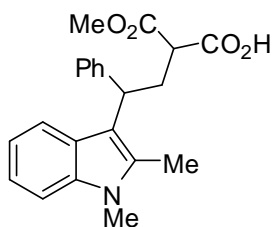
Indoles and cyclopropanes were measured into a length of heat shrinkable Teflon tubing closed at one end with a brass clamp. The tube was sealed with another brass clamp and placed in a LECO Tempres high-pressure chemical reactor and the reactor was heated to 50 °C, then pressurized. After a period of 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). ¹H-NMR (400 MHz, CDCl₃) 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 $\text{C}_{21}\text{H}_{21}\text{NO}_4$ = 351.1471, found = 351.1459

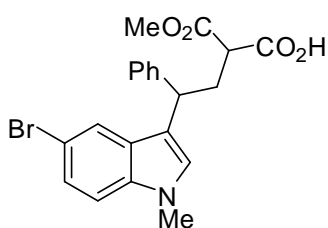


Reagents employed: **1.21a** (0.099 g, 0.612 mmol); **1.58d** (0.107 g, 0.486 mmol); acetonitrile (3 mL); Yielded **1.65b** as a reddish-brown oil, 58% (0.108 g, 0.282 mmol). ^1H -NMR (400 MHz, CDCl_3) Diastereomer A: δ = 7.38-7.28 (m, 4H), 7.25-7.20 (m, 1H), 7.16 (s, 1H), 6.94-6.90 (dd, J = 9.0 Hz, 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 $\text{C}_{22}\text{H}_{23}\text{NO}_5$ = 381.1576, found = 381.1589

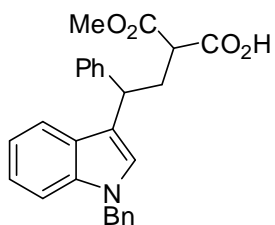


Reagents employed: **1.21b** (0.083 g, 0.574 mmol); **1.58d** (0.104 g, 0.471 mmol); acetonitrile (3 mL); Yielded **1.65c** as a dark red oil, 87% (0.150 g, 0.409 mmol). ^1H -NMR (400 MHz, CDCl_3) Diastereomer A: δ = 7.58-7.54 (broad dd, J = 7.8 Hz, 2.4Hz, 1H), 7.45 (s, 1H) 7.43 (s, 1H), 7.35-7.27 (m,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

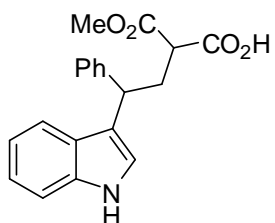
1H), 4.45-4.36 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.45-3.39 (m, 1H), 3.05-2.97 (m, 2H), 2.39 (s, 3H); Diastereomer B: δ = 7.58-7.54 (broad dd, J = 7.8 Hz, 2.4Hz, 1H), 7.45 (1s, 1H), 7.43 (s, 1H), 7.35-7.27 (m, 3H), 7.25-7.16 (m, 2H), 7.08-7.04 (d, J = 7.0 Hz, 1H), 4.45-4.36 (m, 1H), 3.67 (s, 3H), 3.59 (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 $\text{C}_{22}\text{H}_{23}\text{NO}_4$ = 365.1627, found = 365.1615



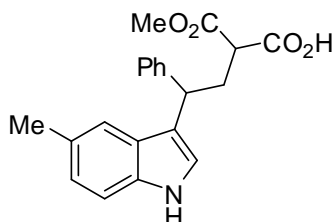
Reagents employed: **1.21c** (0.116 g, 0.552 mmol); **1.58d** (0.101 g, 0.460 mmol); acetonitrile (3 mL); Yielded **1.65d** as a dark yellow oil, 67% (0.132 g, 0.308 mmol); ^1H -NMR (400 MHz, CDCl_3) Diastereomer A: δ = 7.57 (d, J = 2.0 Hz, 1H), 7.32-7.28 (m, 4H), 7.25-7.18 (m, 2H), 7.13 (s, 1H), 6.93 (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 $\text{C}_{21}\text{H}_{20}\text{BrNO}_4$ = 429.0576 found = 429.0563



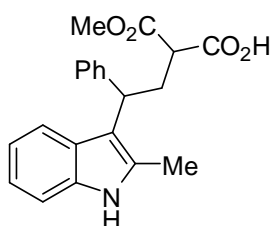
Reagents employed: **1.21d** (0.116 g, 0.561 mmol); **1.58d** (0.103 g, 0.467 mmol); acetonitrile (3 mL); Yielded **1.65e** as an orange oil, 68% (0.135 g, 0.316 mmol). $^1\text{H-NMR}$ (400 MHz, CDCl_3) Diastereomer A: $\delta = 7.50\text{-}7.43$ (m, 1H), $7.35\text{-}7.23$ (m, 7H), $7.21\text{-}7.17$ (m, 2H), $7.13\text{-}7.06$ (m, 3H), $7.03\text{-}6.98$ (m, 2H), 5.24 (s, 2H), $4.35\text{-}4.25$ (m, 1H), 3.64 (s, 3H), $3.45\text{-}3.41$ (m, 1H), $2.92\text{-}2.81$ (m, 1H), $2.69\text{-}2.59$ (m, 1H); Diastereomer B: $7.50\text{-}7.43$ (m, 1H), $7.35\text{-}7.23$ (m, 7H), $7.21\text{-}7.17$ (m, 2H), $7.13\text{-}7.06$ (m, 3H), $7.03\text{-}6.98$ (m, 2H), 5.24 (s, 2H), $4.35\text{-}4.25$ (m, 1H), 3.72 (s, 3H), $3.45\text{-}3.41$ (m, 1H), $2.92\text{-}2.81$ (m, 1H), $2.69\text{-}2.59$ (m, 1H); Diastereomeric Mixture: $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 175.2$, 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 $\text{C}_{27}\text{H}_{25}\text{NO}_4 = 427.1784$, 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). $^1\text{H-NMR}$ (400 MHz, CDCl_3) Diastereomer A: $\delta = 8.06\text{-}8.01$ (broad s, 1H), $7.47\text{-}7.41$ (m, 1H), $7.35\text{-}7.27$ (m, 4H), $7.25\text{-}7.12$ (m, 2H), $7.08\text{-}6.99$ (m, 2H), $4.30\text{-}4.23$ (m, 1H), 3.65 (s, 3H), $3.46\text{-}3.40$ (m, 1H), $2.91\text{-}2.80$ (m, 1H) $2.70\text{-}2.59$ (m, 1H); Diastereomer B: $\delta = 8.06\text{-}8.01$ (broad s, 1H), $7.47\text{-}7.41$ (m, 1H), $7.35\text{-}7.27$ (m, 4H), $7.25\text{-}7.12$ (m, 2H), $7.08\text{-}6.99$ (m, 2H), $4.30\text{-}4.23$ (m, 1H), 3.73 (s, 3H), $3.46\text{-}3.40$ (m, 1H), $2.91\text{-}2.80$ (m, 1H) $2.70\text{-}2.59$ (m, 1H); Diastereomeric Mixture: $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 174.1$, 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 $\text{C}_{20}\text{H}_{19}\text{NO}_4 = 337.1314$, found = 337.1305

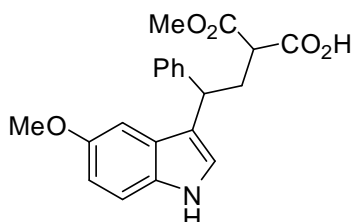


Reagents employed: **1.21f** (0.072 g, 0.551 mmol); **1.58d** (0.101 g, 0.460 mmol); acetonitrile (3 mL); Yielded **1.65g** as a dark green oil, 87% (0.141 g, 0.401 mmol). ¹H-NMR (400 MHz, CDCl₃) Diastereomer A: δ = 7.97 (br s, 1H), 7.33-7.27 (m, 4H), 7.24-7.19 (m, 3H), 7.00-6.95 (m, 2H), 4.27-4.20 (m, 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: ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₂₁NO₄ = 351.1471, found = 351.1472

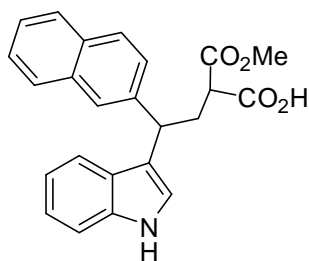


Reagents employed: **1.21g** (0.0722 g, 0.55 mmol); **1.58d** (0.1010 g, 0.46 mmol); acetonitrile (3 mL); Yielded **1.65h** as a dark orange oil, 97% (0.1564 g, 0.44 mmol). ¹H-NMR (400 MHz, CDCl₃) Diastereomer A: δ = 7.99-7.92 (d, J = 13.7 Hz, 1H), 7.55-7.50 (d, J = 8.2 Hz, 1H), 7.44-7.39 (d, J = 7.4 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: ¹³C NMR (100 MHz, CDCl₃) 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 $\text{C}_{21}\text{H}_{21}\text{NO}_4 = 351.1471$, found = 351.1463

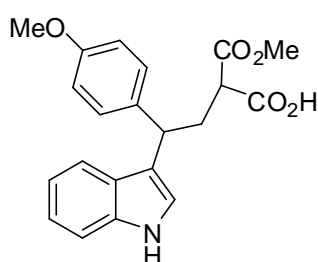


Reagents employed: **1.21h** (0.080 g, 0.546 mmol); **1.58d** (0.100 g, 0.455 mmol); acetonitrile (3 mL); Yielded **1.65i** as a dark brown oil, 92% (0.154 g, 0.419 mmol). $^1\text{H-NMR}$ (400 MHz, CDCl_3) Diastereomer A: $\delta = 7.94$ (br s, 1H), 7.32-7.28 (m, 3H), 7.23-7.17 (m, 3H), 7.02-6.99 (m, 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: $\delta = 7.95$ (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: $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 173.9, 173.9, 170.1, 170.0, 153.5, 143.3, 143.1, 131.7, 128.5, 128.4, 127.9, 127.9, 127.1, 127.0, 126.5, 126.4, 122.3, 122.2, 117.9, 117.8, 112.0, 111.8, 101.3, 101.2, 55.7, 55.7, 52.6, 52.5, 50.1, 50.0, 40.7, 40.6, 34.8, 34.6$; 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 $\text{C}_{21}\text{H}_{21}\text{NO}_5 = 367.1420$, found = 367.1414

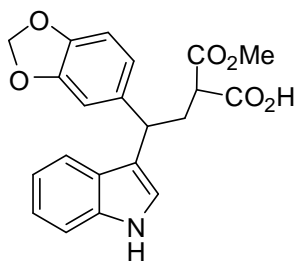


Reagents employed: **1.21e** (0.054 g, 0.456 mmol); **1.58e** (0.103 g, 0.380 mmol); acetonitrile (3 mL); Yielded **1.65j** as pink oil, 65% (0.096 g, 0.248 mmol). $^1\text{H-NMR}$ (400 MHz, CDCl_3) Diastereomer A: $\delta = 8.35$ -6.86 (aromatic region is a mixture of diastereomers as well as atropisomers),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

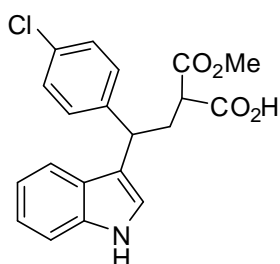
MHz, CDCl₃) δ = 170.7, 170.1, 139.4, 139.0, 136.5, 136.4, 134.0, 131.8, 131.7, 128.8, 127.2, 127.2, 126.8, 126.8, 126.4, 126.3, 126.1, 126.0, 125.9, 125.4, 125.1, 124.5, 124.4, 123.4, 122.9, 122.3, 122.1, 122.0, 121.6, 119.7, 119.5, 119.4, 119.4, 119.3, 119.0, 118.9, 118.3, 117.9, 52.7, 52.5, 35.7, 35.5, 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 C₂₄H₂₁NO₄ = 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). ¹H-NMR (400 MHz, CDCl₃) 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: ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₂₁NO₅ = 367.1420, found = 367.1418

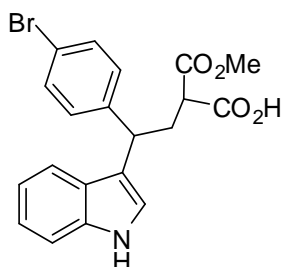


Reagents employed: **1.21e** (0.054 g, 0.464 mmol); **1.58g** (0.102 g, 0.387 mmol); acetonitrile (3 mL); Yielded **1.65l** as clear oil, 86% (0.128 g, 0.334 mmol). $^1\text{H-NMR}$ (400 MHz, CDCl_3) Diastereomer A: δ = 8.14 (br s, 1H), 7.43 (t, J = 9.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.17-7.11 (m, 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: $^{13}\text{C NMR}$ (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 $\text{C}_{21}\text{H}_{19}\text{NO}_6$ = 381.1212, found = 381.1219

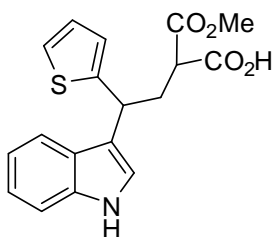


Reagents employed: **1.21e** (0.056 g, 0.474 mmol); **1.58h** (0.101 g, 0.395 mmol); acetonitrile (3 mL); Yielded **1.65m** as an orange oil, 74% (0.108 g, 0.291 mmol). $^1\text{H-NMR}$ (400 MHz, CDCl_3) Diastereomer A: δ = 8.20 (br s, 1H), 7.41-7.35 (m, 1H), 7.33-7.29 (m, 1H), 7.22 (s, 3H), 7.18-7.13 (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: $^{13}\text{C NMR}$ (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 C₂₀H₁₈ClNO₄ = 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). ¹H-NMR (400 MHz, CDCl₃) 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: ¹³C NMR (100 MHz, CDCl₃) 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

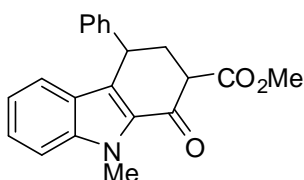


Reagents employed: **1.21e** (0.064 g, 0.542 mmol); **1.58j** (0.102 g, 0.452 mmol); acetonitrile (3 mL); Yielded **1.65o** as brown oil, 50% (0.077 g, 0.224 mmol). ¹H-NMR (600 MHz, CDCl₃) Diastereomer A: δ = 8.08 (br s, 1H), 7.95 (br s, 1H), 7.53 (t, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.32-7.28 (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: ¹³C NMR (100 MHz, CDCl₃) 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 $\text{C}_{18}\text{H}_{17}\text{NO}_4\text{S}$ = 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.

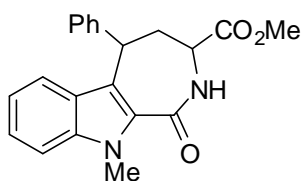


Reagents employed: **1.65a** (0.055 g, 0.157 mmol); TFAA (24 μL , 1.73 mmol); Toluene (5 ml); NaH (0.023 g, 0.575 mmol); DMF (3 mL); Yielded **1.66** as brown oil, 40% (0.061 g, 0.183 mmol). ¹H-NMR (400 MHz, CDCl_3) Diastereomer A: δ = 7.26-

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: ¹³C 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 $\text{C}_{21}\text{H}_{19}\text{NO}_3$ = 333.1365, found = 333.1372

Procedure for the Conversion of 1.65a to Azepinoindole 1.67⁸²

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 MgSO₄, filtered and purified by flash chromatography on silica gel.

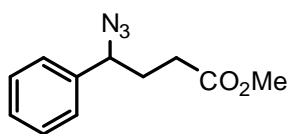


Reagents employed: **1.65a** (0.160 g, 0.454 mmol); DPPA (97 μ L, 0.454 mmol); triethylamine (69 μ L, 0.498 mmol); Benzene (5 mL); Yielded **1.67** as a yellow oil, 33% (0.052 g, 0.149 mmol). ¹H-NMR (400 MHz, CDCl₃) Diastereomeric mixture: δ = 7.45-7.40 (m, 1H), 7.34-7.27 (m, 4H), 7.24-7.16 (m, 2H), 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: ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₂₀N₂O₃ = 348.1474, found = 348.1476

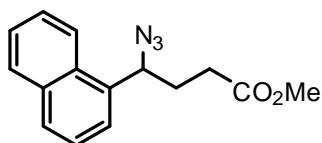
Section 1.9.2 The Tandem Ring Opening/Decarboxylation of Cyclopropane Hemimalonates with Sodium Azide**General Experimental Procedure for the synthesis of azidoesters 1.71a-l**

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

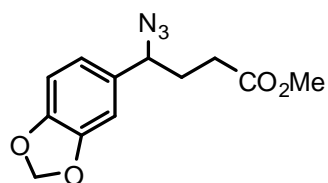
extracted with ether (3 times). The organic layers were then combined and dried with magnesium sulfate. Following filtration, the solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (EtOAc:Hexanes, 20:80) to yield the desired products **1.71a-l**.



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

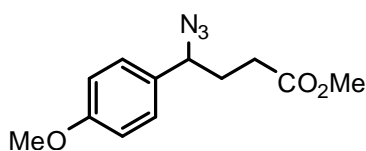


Reagents employed: **1.58e** (0.119 g, 0.440 mmol); sodium azide (0.035 g, 0.538 mmol); ammonium chloride (0.033 g, 0.617 mmol); 2-methoxyethanol:water; Yield **1.71b** as a clear oil, 76% (0.090 g, 0.334 mmol) as a clear oil. $R_f = 0.58$, 30% EtOAc in hexanes; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 8.16$ (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); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 173.3$, 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 $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2 = 269.1164$, found = 269.1159.

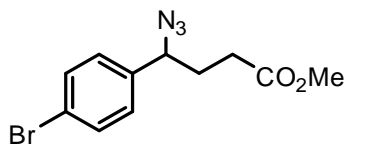


Reagents employed: **1.58g** (0.097 g, 0.367 mmol); sodium azide (0.029 g, 0.446 mmol); ammonium chloride (0.027 g, 0.505 mmol); 2-methoxyethanol:water; Yielded **1.71c** as a clear oil, 87% (0.084 g, 0.319 mmol). $R_f = 0.58$, 30% EtOAc in hexanes; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 6.80$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

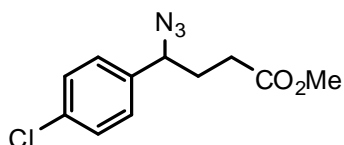
(d, $J = 1.6$ Hz, 1H) 5.97 (s, 2H), 4.44 (dd, $J = 7.8, 6.2$ Hz, 1H), 3.66 (s, 3H), 3.76 (t, $J = 7.4, 2H$), 2.11-1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 173.1, 148.2, 147.7, 132.7, 120.7, 108.3, 106.9, 101.2, 65.1, 51.7, 31.3, 30.5$; IR (thin film): 3459, 3323, 2953, 2101, 1739, 1505, 1490, 1443, 1342, 1328, 1252, 1170, 1102, 1042, 933, 863, 813, 661; HRMS (EI) calc'd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_4 = 263.0906$, found = 263.0905.



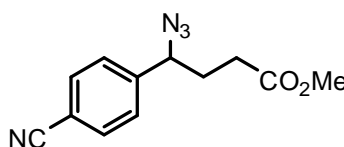
Reagents employed: **1.58f** (0.100 g, 0.400 mmol); sodium azide (0.031 g, 0.477 mmol); ammonium chloride (0.030 g, 0.561 mmol); 2-methoxyethanol:water; Yielded **1.71d** as a clear oil, 95% (0.095 g, 0.381 mmol). $R_f = 0.54$, 30% EtOAc in hexanes; ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.25$ -7.21 and 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) $\delta = 173.1, 159.6, 130.8, 128.1, 114.2, 64.8, 55.2, 51.6, 31.2, 30.5$; IR (thin film): 3451, 3319, 2953, 2839, 2482, 2101, 1739, 1611, 1529, 1438, 1245, 1174, 1034, 832, 545; HRMS (EI) calc'd for $\text{C}_{12}\text{H}_{15}\text{NO}_3 = 221.1052$, found = 221.1050. (M-N₂)



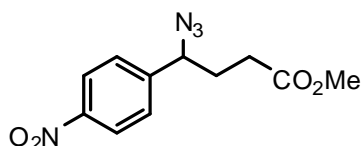
Reagents employed: **1.58i** (0.095 g, 0.318 mmol); sodium azide (0.025 g, 0.385 mmol), ammonium chloride (0.024 g, 0.449 mmol); 2-methoxyethanol:water; Yielded **1.71e** as a clear oil, 62% (0.059 g, 0.198 mmol). $R_f = 0.53$, 30% EtOAc in hexanes; ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.53$ -7.50 and 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) $\delta = 173.0, 183.0, 132.0, 128.5, 122.4, 64.6, 51.7, 31.3, 30.3$; IR (thin film): 3455, 3319, 2951, 2101, 1737, 1489, 1437, 1250, 1201, 1171, 1044, 1011, 822, 532; HRMS (EI) calc'd for $\text{C}_{11}\text{H}_{13}\text{BrN}_3\text{O}_2 = 298.0191$, found = 298.0185. (M+H)



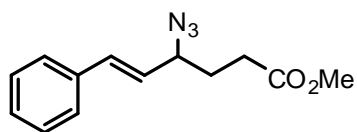
Reagents employed: **1.58h** (0.105 g, 0.412 mmol); sodium azide (0.032 g, 0.538 mmol); ammonium chloride (0.030 g, 0.561 mmol); 2-methoxyethanol:water; Yielded **1.71f** as a clear oil, 60% (0.063 g, 0.248 mmol). $R_f = 0.56$, 30% EtOAc in hexanes; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.38\text{-}7.35$ and $7.26\text{-}7.23$ (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); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 173.0, 137.5, 134.2, 129.1, 128.2, 64.5, 51.7, 31.3, 30.3$; IR (thin film): 2952, 2101, 1739, 1493, 1437, 1325, 1249, 1202, 1171, 1092, 1015, 826, 534; HRMS (EI) calc'd for $\text{C}_{11}\text{H}_{13}\text{ClN}_3\text{O}_2 = 254.0696$, found = 254.0710. (M+H)



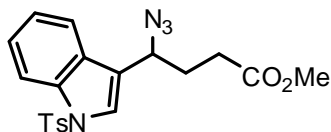
Reagents employed: **1.58k** (0.116 g, 0.473 mmol); sodium azide (0.037 g, 0.569 mmol), ammonium chloride (0.035 g, 0.654 mmol); 2-methoxyethanol:water; Yielded **1.71g** as a clear oil, 56% (0.065 g, 0.266 mmol). $R_f = 0.46$, 30% EtOAc in hexanes; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.69\text{-}7.66$ and $7.44\text{-}7.41$ (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); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 172.7, 144.4, 132.7, 127.5, 118.2, 112.3, 64.4, 51.7, 31.3, 30.0$; IR (thin film): 2953, 2230, 2100, 1734, 1609, 1438, 1417, 1308, 1252, 1200, 1174, 1019, 835, 566; HRMS (EI) calc'd for $\text{C}_{12}\text{H}_{13}\text{N}_4\text{O}_2 = 245.1039$, found = 245.1045. (M+H)



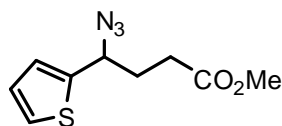
Reagents employed: **1.58l** (0.116 g, 0.437 mmol); sodium azide (0.034 g, 0.523 mmol); ammonium chloride (0.033 g, 0.617 mmol); 2-methoxyethanol:water; Yielded **1.71h** as a clear oil, 46% (0.053 g, 0.201 mmol). $R_f = 0.44$, 30% EtOAc in hexanes; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 8.26\text{-}8.23$ and $7.52\text{-}7.49$ (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); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 172.7, 147.8, 146.4, 127.7, 124.1, 64.3, 51.8, 31.5, 30.0$; IR (thin film): 2953, 2926, 2100, 1735, 1607, 1522, 1437, 1348, 1253, 1200, 1172, 853, 700; HRMS (EI) calc'd for $\text{C}_{11}\text{H}_{13}\text{N}_4\text{O}_4 = 265.0937$, 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; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.37$ (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) $\delta = 173.2, 135.7, 133.9, 128.6, 128.2, 126.7, 126.1, 63.9, 51.7, 30.2, 29.8$; IR (thin film): 3027, 2952, 2105, 1739, 1493, 1437, 1239, 1170, 1112, 1071, 969, 888, 751, 694; HRMS (EI) calc'd for $\text{C}_{13}\text{H}_{14}\text{NO}_2 = 216.1030$, found = 216.1030. (M-N₂, H)

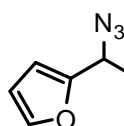


Reagents employed: **1.58m** (0.098 g, 0.237 mmol); sodium azide (0.018 g, 0.277 mmol); ammonium chloride (0.018 g, 0.337 mmol); 2-methoxyethanol:water; Yielded **1.71j** as a clear oil, 58% (0.057 g, 0.138 mmol). $R_f = 0.54$, 30% EtOAc in hexanes; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.99$ (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) $\delta = 173.0, 145.2, 135.5, 134.8, 129.9, 128.4, 126.8, 125.3, 124.0, 123.5, 120.2, 120.0, 113.9, 57.8, 51.7, 30.4, 29.4, 21.5$; IR (thin film): 2953, 2925, 2109, 1735, 1448, 1372, 1256, 1178, 1123, 1089, 749, 669, 574, 538; HRMS (EI) calc'd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_4\text{S} = 412.1205$, 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; $^1\text{H-NMR}$ (400 MHz,

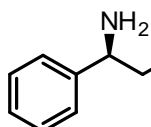
CDCl₃): δ = 7.30 (dd, J = 5.0, 1.2 Hz, 1H), 7.04-7.03 (m, 1H), 7.01-6.98 (m, 1H), 4.9 (dd, J = 7.0, 7.0 Hz, 1H), 3.67 (s, 3H), 2.44 (dd, J = 7.4, 1.2 Hz, 2H), 2.23-2.10 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.8, 141.7, 126.8, 125.8, 125.6, 60.3, 51.6, 31.6, 30.4; IR (thin film): 2952, 2099, 1736, 1437, 1367, 1328, 1240, 1173, 854, 835, 707; HRMS (EI) calc'd for C₉H₁₁NO₂S = 197.0510, found = 197.0511. (M-N₂)



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 **1.71I** as a clear oil, 63% (0.079 g, 0.378 mmol). R_f = 0.54, 30% EtOAc in hexanes; ¹H-NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₉H₁₁NO₃ = 181.0739, found = 181.0739. (M-N₂)

Procedure for the azide reduction to GABA esters

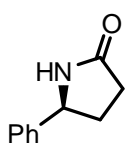
To a solution of azide (1 equiv) in MeOH was added 10% palladium on activated carbon. The solution was stirred under a balloon of hydrogen for two hours. The mixture was then passed through celite and the solvent was removed under reduced pressure to give GABA ester **1.73**.



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

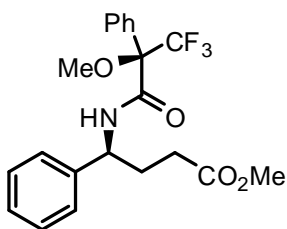
To a solution of optically enriched methyl 4-amino-4-phenylbutanoate **1.71a** (0.259 mmol) in MeOH, was added 1.7 M NaOH (0.389 mmol) dropwise. The solution was stirred for 2 hours, and then diluted with EtOAc and water to separate layers. The aqueous layer was then acidified with 5% HCl to reach pH 2, and then extracted three times with EtOAc. The combined organic layers were washed with brine, dried of MgSO₄, 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

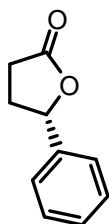
To a solution of methyl 4-amino-4-phenylbutanoate **1.73** (0.068 mmol) in THF (1 mL), was added Mosher's Acid (0.071 mmol), DCC (0.081 mmol) and DMAP (0.0041 mmol). The solution was stirred at room temperature overnight. The solution was filtered and the solvent was removed under reduced pressure, to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



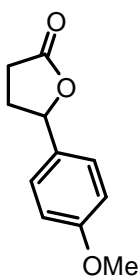
Reagents employed: **1.73** (0.013 g, 0.068 mmol); Mosher's Acid (0.017 g, 0.071 mmol); DCC (0.017 g, 0.081 mmol); DMAP (0.001 g, 0.0041 mmol); Yield 61% (0.017 g, 0.042 mmol). ¹H-NMR (400 MHz, CDCl₃): δ = 7.56-7.54 (m, 2H), 7.42-7.41 (m, 3H), 7.37-7.34 (m, 2H), 7.31-7.29 (m, 3H), 7.19 (d, J = 8.2 Hz, 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). ¹⁹F-NMR (376 MHz, CDCl₃): δ = -68.8 (s, 3F), -68.9 (s, 0.16F). The enantiomeric excess was determined to be 90% by Mosher's amide (¹H, ¹⁹F-NMR).

Section 1.9.3 The Synthesis of Butanolides from Cyclopropane Hemimalonates

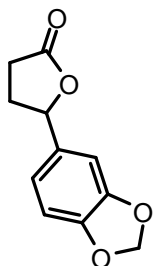
General Experimental Procedure: Cyclopropane hemimalonates **1.58**, LiCl, and Me₃NHCl were added to a microwave vial and dissolved in DMF. The vial was sealed and heated for 40 minutes at 150 °C. After the required reaction time the reaction was quenched with H₂O and extracted with ether. The organic 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.



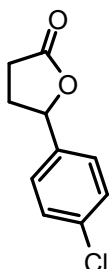
Reagents employed: **1.58d** (0.075 g, 0.341 mmol); LiCl (0.029 g, 0.684 mmol); Me₃NHCl (0.046 g, 0.481 mmol); DMF (4 mL); Yielded **1.78a** as a clear oil, 82% (0.045 g, 0.279 mmol). Spectral properties are identical to those previously reported.⁶³ 80% ee calculated from Mosher's ester. ¹⁹F-NMR (376 MHz, CDCl₃): δ = -71.31 (s, 90), -71.59 (s, 10).



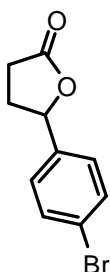
Reagents employed: **1.58f** (0.077 g, 0.308 mmol); LiCl (0.026 g, 0.613 mmol); Me₃NHCl (0.041 g, 0.429 mmol); DMF (4 mL); Yielded **1.78b** as a yellow oil, 91% (0.054 g, 0.281 mmol). R_f = 0.25, 30% EtOAc/hexanes. ¹H-NMR (400 MHz, CDCl₃): δ = 7.26 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.45 (dd, J = 8.6, 6.2 Hz, 1H), 3.80 (s, 3H), 2.68-2.56 (m, 3H), 2.26-2.14 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): 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 C₁₁H₁₂O₃ = 192.0786, found = 192.0783.



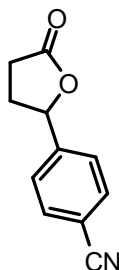
Reagents employed: **1.58g** (0.078 g, 0.295 mmol); LiCl (0.025 g, 0.590 mmol); Me₃N·HCl (0.040 g, 0.419 mmol); DMF (4 mL); Yielded **1.78c** as a brown oil, 90% (0.055 g, 0.267 mmol). R_f = 0.22, 30% EtOAc/hexanes. ¹H-NMR (400 MHz, CDCl₃): δ = 6.81-6.78 (m, 3H), 5.96 (s, 2H), 5.40 (dd, J = 8.6, 6.2 Hz, 1H), 2.66-2.54 (m, 3H), 2.22-2.09 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): 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 C₁₁H₁₀O₄ = 206.0579, found = 206.0575.



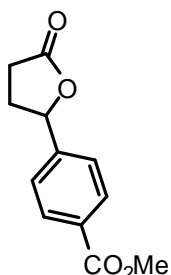
Reagents employed: **1.58h** (0.075 g, 0.294 mmol); LiCl (0.025 g, 0.590 mmol); Me₃N·HCl (0.039 g, 0.408 mmol); DMF (4 mL); Yielded **1.78d** as a yellow oil, 81% (0.047 g, 0.239 mmol). R_f = 0.16, 30% EtOAc/hexanes. ¹H-NMR (400 MHz, CDCl₃): δ = 7.36 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.48 (dd, J = 8.6, 6.2 Hz, 1H), 2.70-2.61 (m, 3H), 2.20-2.07 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): 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 C₁₀H₉ClO₂ = 196.0291, found = 196.0299.



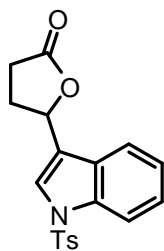
Reagents employed: **1.58i** (0.076 g, 0.254 mmol); LiCl (0.022 g, 0.519 mmol); Me₃N·HCl (0.035 g, 0.366 mmol); DMF (4 mL); Yielded **1.78e** as a yellow oil, 74% (0.045 g, 0.187 mmol). R_f = 0.29, 30% EtOAc/hexanes. ¹H-NMR (400 MHz, CDCl₃): δ = 7.51 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 5.46 (dd, J = 8.2, 6.2 Hz, 1H), 2.71-2.61 (m, 3H), 2.21-2.07 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): 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 C₁₀H₉BrO₂ = 239.9786, found = 239.9794.



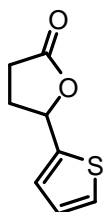
Reagents employed: **1.58k** (0.075 g, 0.306 mmol); LiCl (0.026 g, 0.613 mmol); Me₃N·HCl (0.041 g, 0.429 mmol); DMF (4 mL); Yielded **1.78f** as a clear oil, 52% (0.030 g, 0.160 mmol). R_f = 0.11, 30% EtOAc/hexanes. ¹H-NMR (600 MHz, CDCl₃): δ = 7.69 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 5.55-5.51 (m, 1H), 2.76-2.60 (m, 3H), 2.16-2.07 (m, 1H). ¹³C-NMR (150 MHz, CDCl₃): 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 C₁₁H₉NO₂ = 187.0633, found = 187.0639.



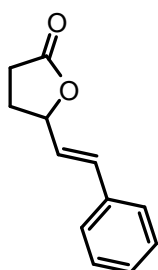
Reagents employed: **1.58o** (0.075 g, 0.270 mmol); LiCl (0.023 g, 0.543 mmol); Me₃N·HCl (0.036 g, 0.377 mmol); DMF (4 mL); Yielded **1.78g** as a clear oil, 39% (0.023 g, 0.104 mmol). R_f = 0.16, 30% EtOAc/hexanes. ¹H-NMR (400 MHz, CDCl₃): δ = 8.06 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 5.59-5.53 (m, 1H), 3.92 (s, 3H), 2.76-2.63 (m, 3H), 2.21-2.12 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): 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 C₁₂H₁₂O₄ = 220.0736, found = 220.0720.



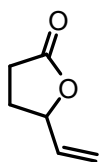
Reagents employed: **1.58m** (0.082 g, 0.198 mmol); LiCl (0.017 g, 0.401 mmol); Me₃N·HCl (0.027 g, 0.283 mmol); DMF (4 mL); Yielded **1.78h** as a yellow oil, 85% (0.060 g, 0.169 mmol). R_f = 0.24, 30% EtOAc/hexanes. ¹H-NMR (400 MHz, CDCl₃): δ = 7.99 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.59 (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). ¹³C-NMR (100 MHz, CDCl₃): 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 C₁₉H₁₇NO₄S = 355.0878, found = 355.0879.



Reagents employed: **1.58j** (0.068 g, 0.301 mmol); LiCl (0.025 g, 0.590 mmol); Me₃N·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. ¹H-NMR (400 MHz, CDCl₃): 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). ¹³C-NMR (100 MHz, CDCl₃): 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 C₈H₈O₂S = 168.0245, found = 168.0243.



Reagents employed: **1.58m** (0.098 g, 0.398 mmol); LiCl (0.034 g, 0.802 mmol); Me₃N·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. ¹H-NMR (600 MHz, CDCl₃): 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). ¹³C-NMR (100 MHz, CDCl₃): 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 C₁₂H₁₂O₂ = 188.0837, found = 188.0837.

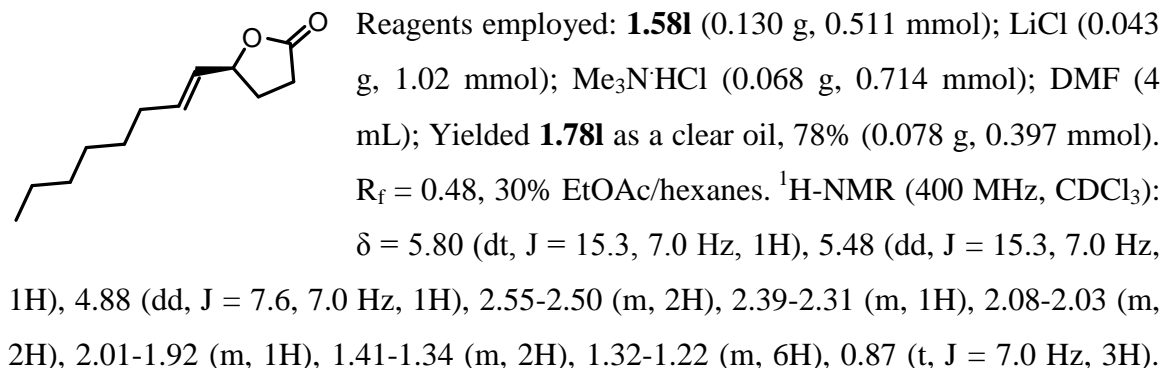
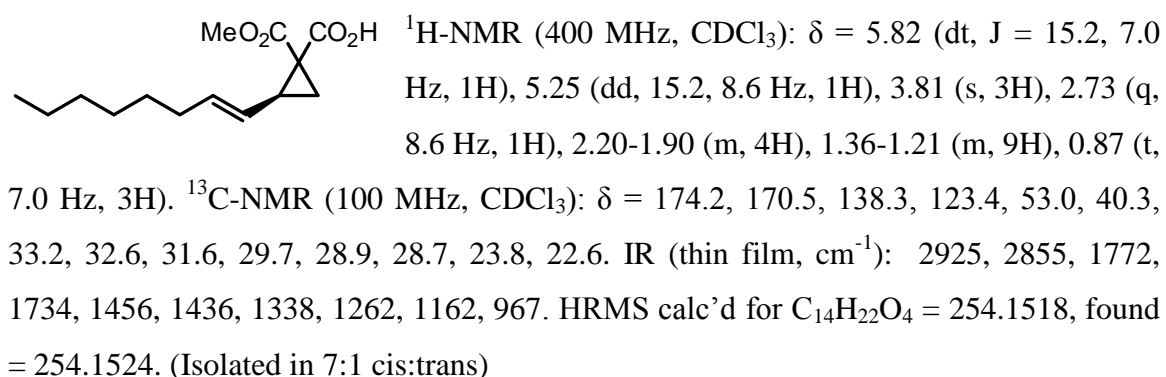


Reagents employed: **1.58b** (0.086 g, 0.505 mmol); LiCl (0.043 g, 1.01 mmol); Me₃N·HCl (0.068 g, 0.712 mmol); DMF (4 mL); Yielded **1.78k** as a clear oil, 60% (0.034 g, 0.303 mmol). R_f = 0.33, 30% EtOAc/hexanes. ¹H-NMR (400 MHz, CDCl₃): δ = 5.87 (ddd, J = 16.8, 10.5 Hz, 5.9 Hz, 1H), 5.36 (dt, J = 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, 1H), 2.04-1.94 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): 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 C₆H₈O₂ = 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.

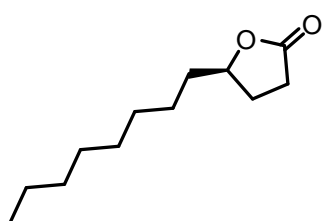
The crude octenyl cyclopropane was taken up in MeOH (5 mL) and treated with 1.7 M NaOH (1.6 mL, 2.72 mmol). The reaction was stirred at room temperature for 2.5 hours, and then the reaction was quenched with H₂O. The organic was extracted with EtOAc, and the aqueous layer was acidified with 5% HCl. The aqueous was extracted 3x with EtOAc to obtain the product. The organic was dried with MgSO₄, filtered and concentrated to obtain **1.581** (0.300 g, 1.18 mmol) in an 87% yield over the two steps.



^{13}C -NMR (100 MHz, CDCl_3): $\delta = 177.0, 135.8, 127.3, 110.0, 81.1, 32.1, 31.6, 28.8, 28.8, 28.7, 22.6, 14.1$. IR (thin film, cm^{-1}): 2926, 2855, 1773, 1734, 1457, 1176, 969. HRMS calc'd for $\text{C}_{12}\text{H}_{20}\text{O}_2 = 196.1463$, found = 196.1460. (Isolated in 7:1 cis:trans)

Reduction of Olefin:

Lactone **12** (0.175 g, 0.892 mmol) was dissolved in THF:H₂O (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. ^1H -NMR (600 MHz, CDCl_3): $\delta = 4.51\text{-}4.44$ (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): $\delta = 177.3, 81.0, 35.6, 31.8, 29.4, 29.3, 29.2, 28.9, 28.0, 25.2, 22.6, 14.1$. IR (thin film, cm^{-1}): 2926, 2855, 1776, 1458, 1352, 1179, 1017, 914. HRMS calc'd for $\text{C}_{12}\text{H}_{22}\text{O}_2 = 199.1698$, found = 199.1703 (M + H). 94% ee calculated from Mosher's ester. ^{19}F -NMR (376 MHz, CDCl_3): $\delta = -71.29$ (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 Takemoto¹ 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 alga². 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, Morimoto⁵ deduced the relative stereochemistry around the pyrrolidine core; his stereochemical assignment was confirmed a few years later by X-ray analysis². The first total synthesis by Oppolzer⁶ (*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.

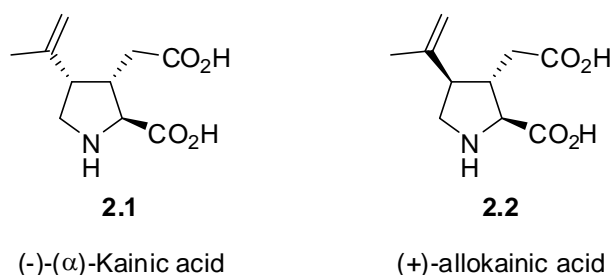


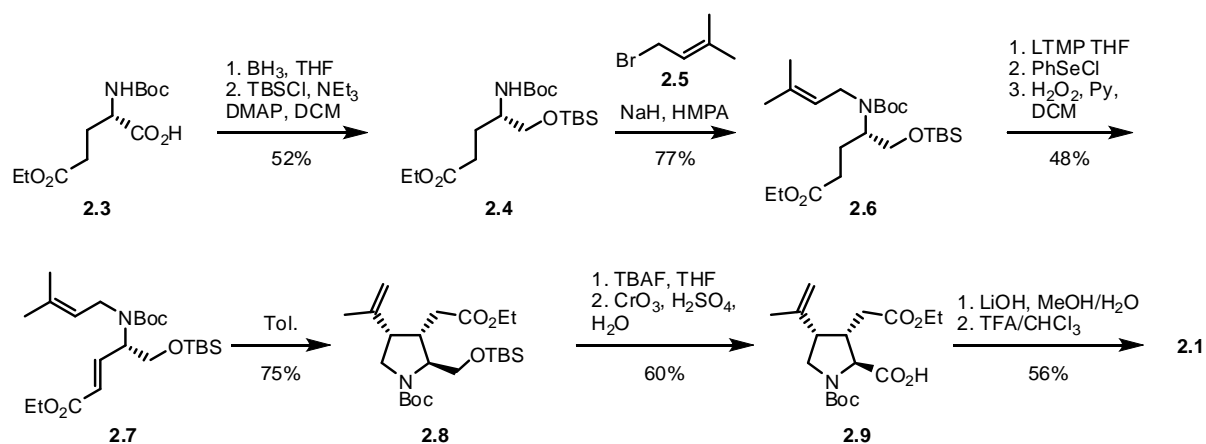
Figure 2.1 Structures of Kainic Acid and Allokainic Acid

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 anthihelminthic drug at the time, with virtually no side effects². 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.

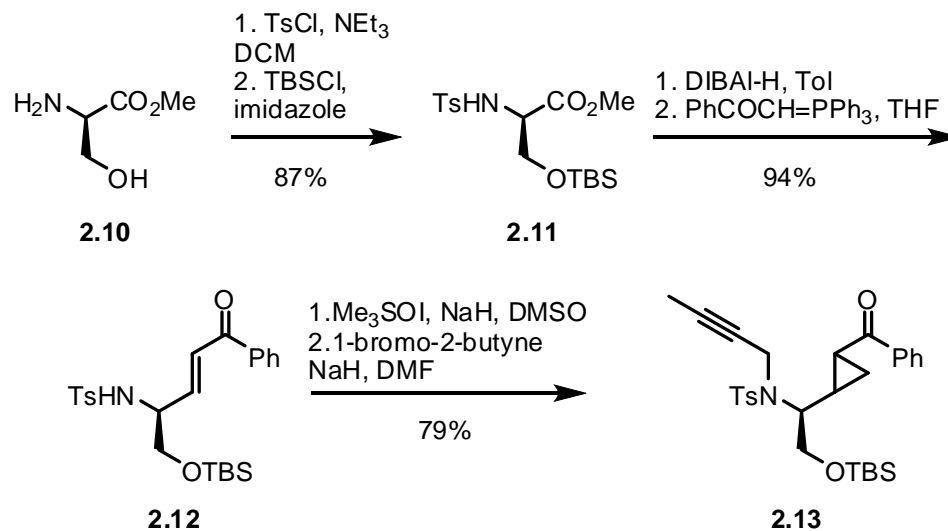
Section 2.2 Total Syntheses of Kainic acid

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.



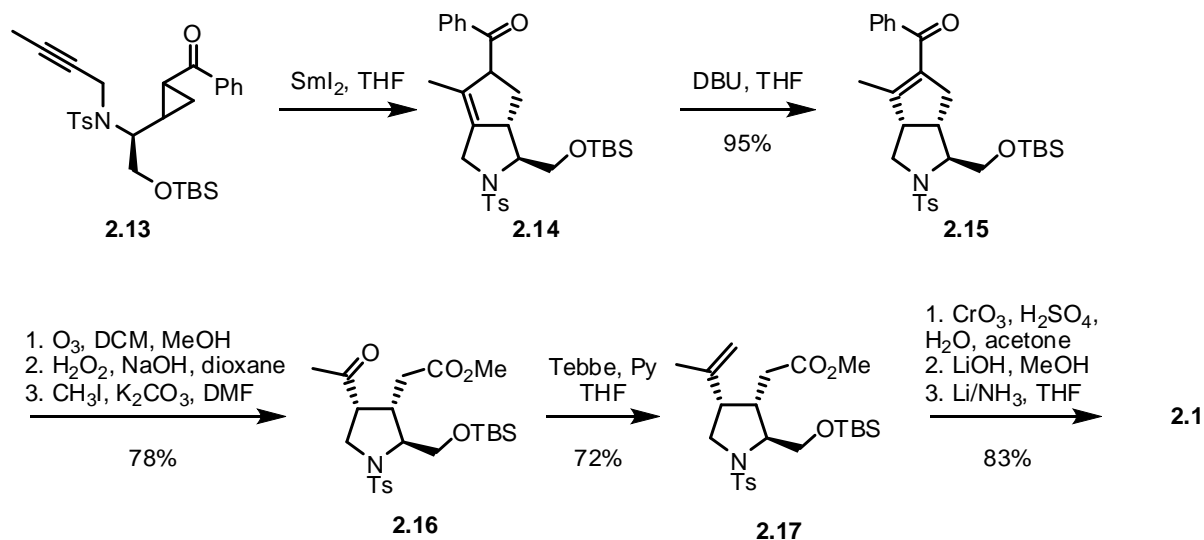
Scheme 2.1 Oppolzer's Total Synthesis of (-)-(α)-kainic Acid

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.



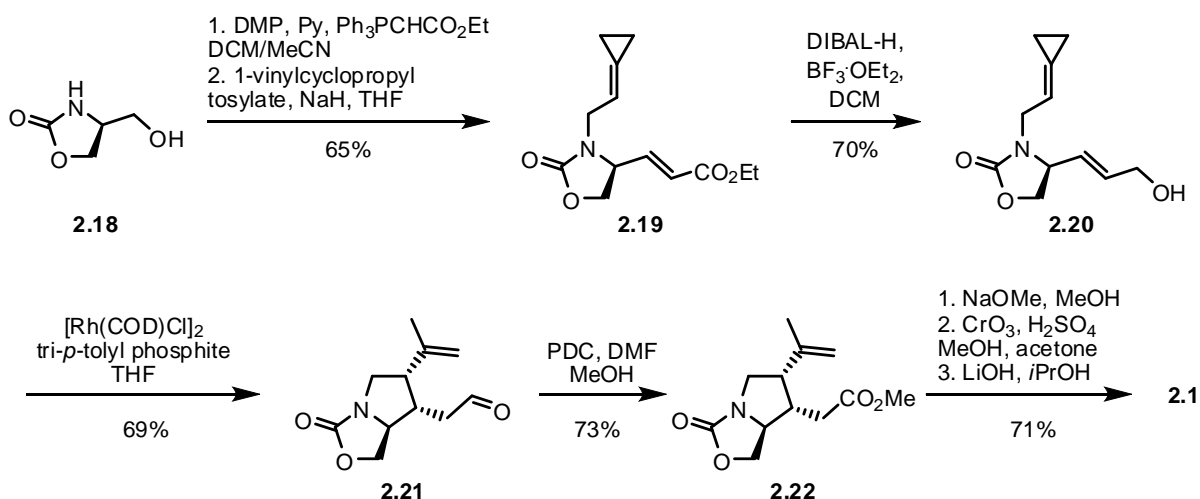
Scheme 2.2 Li's Formation of [3+2] Cyclization Precursor

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.



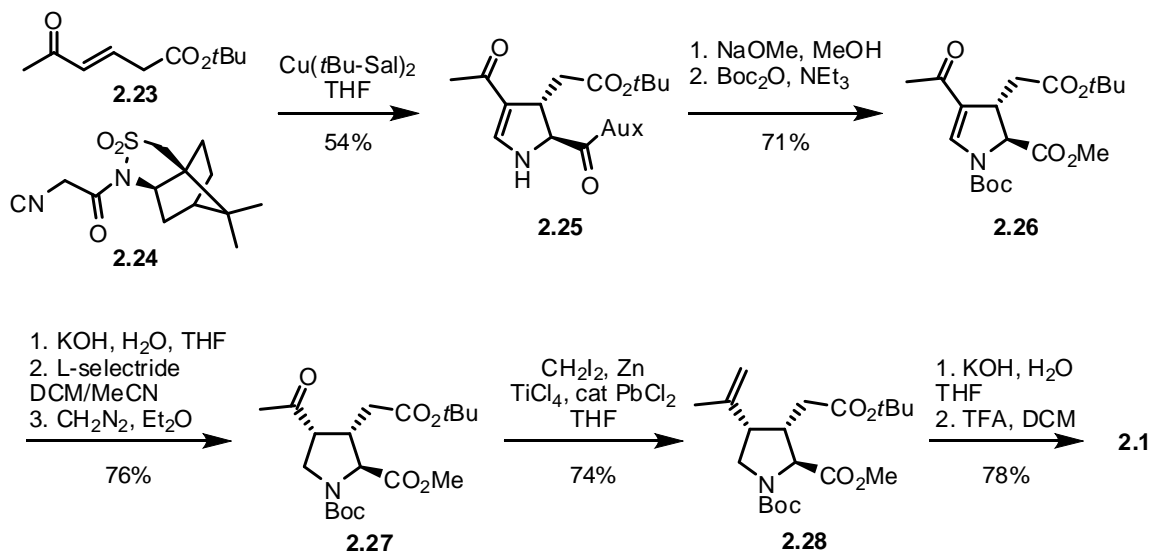
Scheme 2.3 Li's Completed Total Synthesis

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 Wittig 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 carbamyl 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

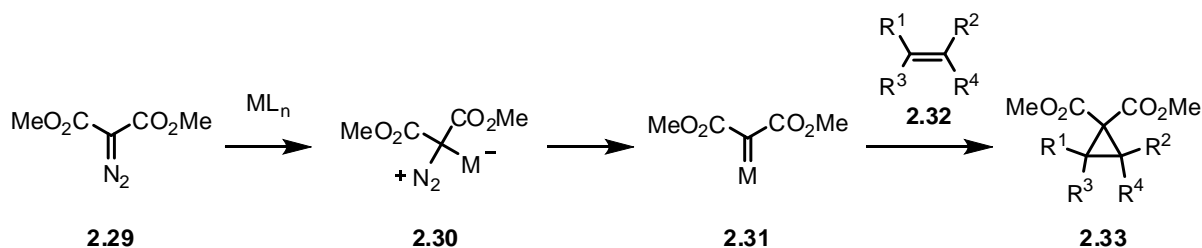
In 2014, Shinada and co-workers developed a copper catalyzed Michael addition-cyclization of a chiral isocyanide **2.24** and an α,β -unsaturated ketone **2.23** to access the pyrrolidine core of Kainic acid (Scheme 2.5).⁹ Using chiral isocyanide **2.24**, they attempted to form the pyrrolidine ring under basic conditions; this led primarily to auxiliary 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 auxiliary 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

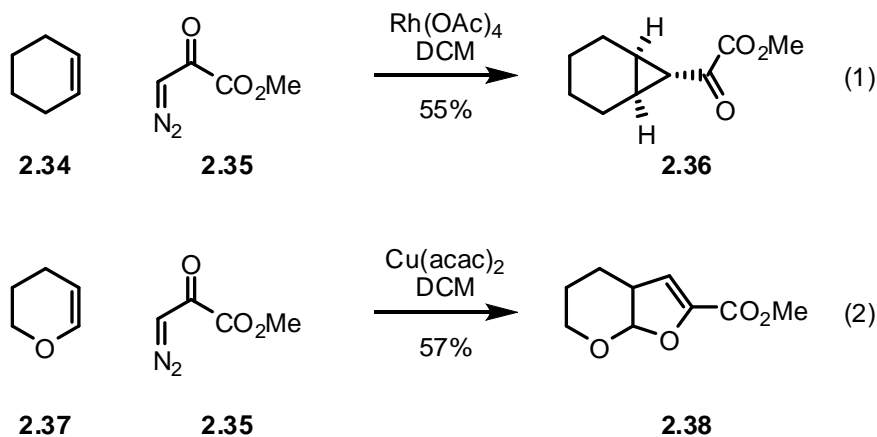
Since the seminal review on the cyclopropanation of alkenes and aromatics with ethyl diazoacetate,¹⁰ this field of chemistry has blossomed into a wide variety of different areas. Specifically, advances in catalyst design can arrive at chemo-, diastereo-, or enantioselective products as desired. Diazomalonates 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.

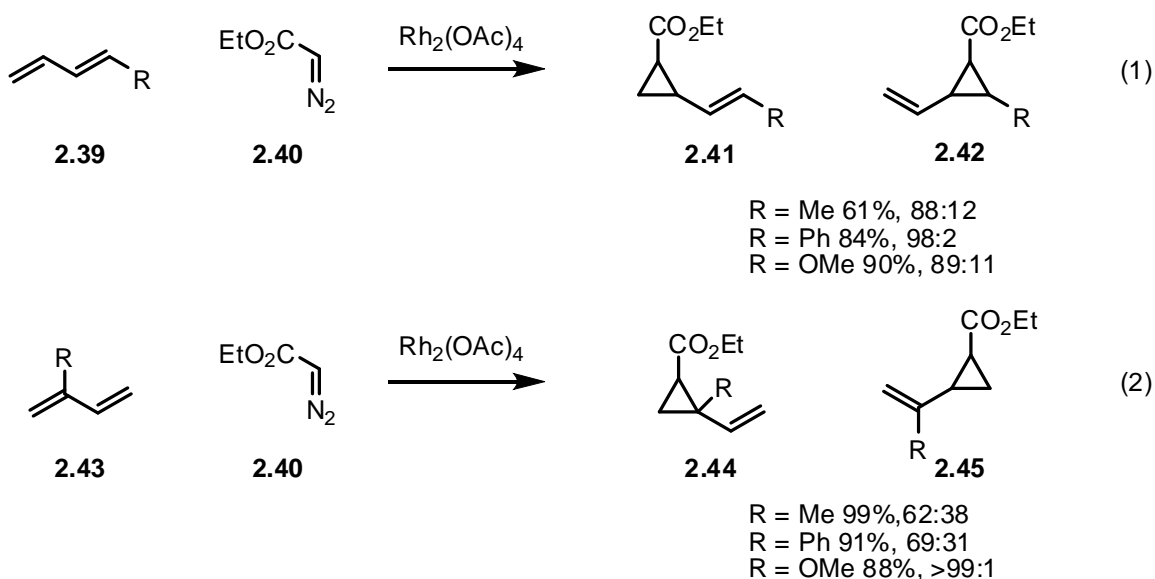


Scheme 2.7 Reactivity of Diazo Species with Olefins

Section 2.3.2 Reactivity of Diazo Species with Dienes

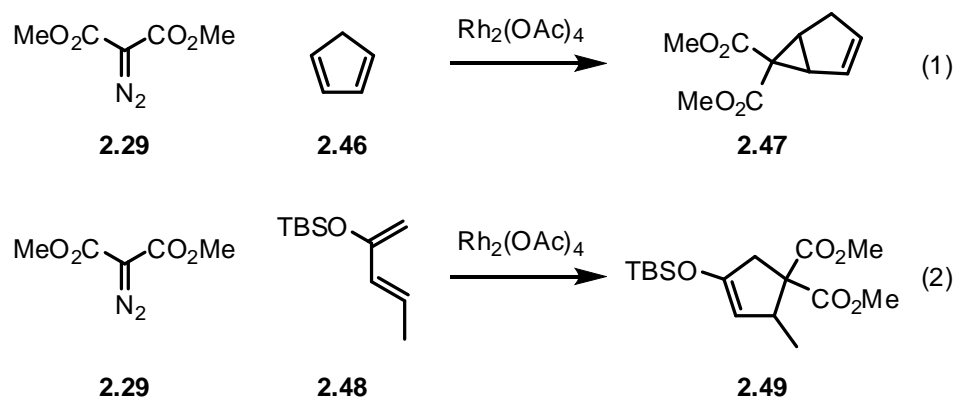
Dienes can be useful cyclopropanation partners as the products lead to vinyl substituted cyclopropanes which can be manipulated in subsequent synthetic steps.¹⁴ The

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

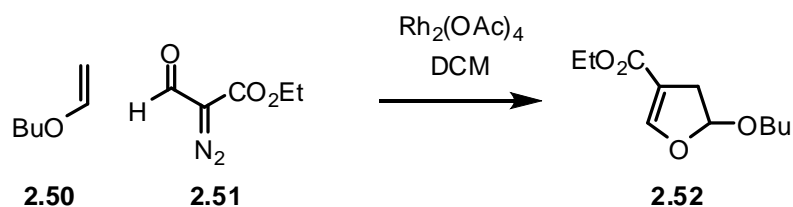
The effects of diene substitutions are different when diazomalonates **2.29** are employed as the cyclopropanation precursor (Scheme 2.9). A reaction with cyclopentadiene **2.46** for example, the expected cyclopropanation is observed **2.45** due to the unpolarised nature of the diene.¹⁶ However, when 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

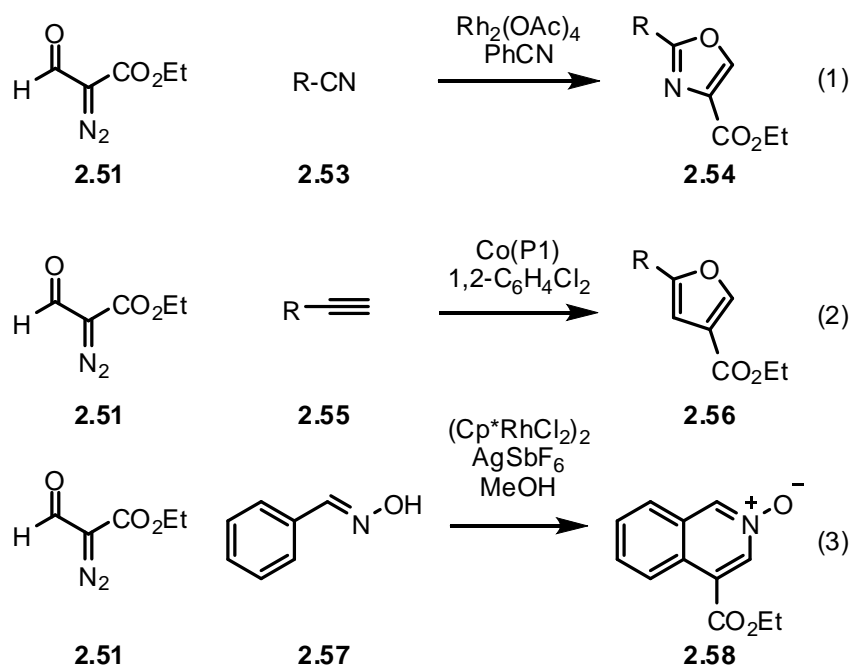
Section 2.3.3 Reactivity of Aldehyde-ester Diazo Compounds

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**

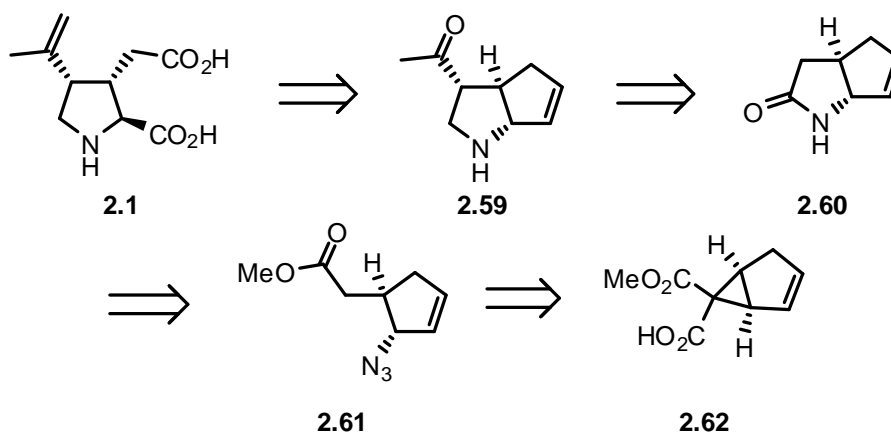
Since the seminal work of Wenkert, diazospecies **2.51** has been utilized in the synthesis of several different heterocycles. It has been reacted with nitriles **2.53**,¹⁹ alkynes **2.55**²⁰ and aryl oximes **2.57**²¹, to form 1,3-oxazoles **2.54**, furans **2.56** and pyridine N-oxides **2.58**, respectively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



Scheme 2.11 Recent Transformations of **2.51**

Section 2.4 Our Retrosynthetic Proposal

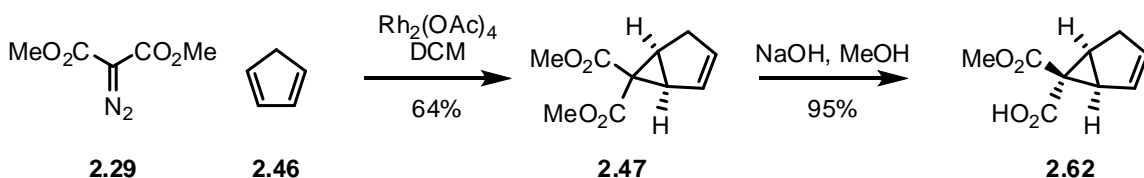
With the knowledge in hand that cyclopentadiene will undergo a smooth diazomalonate mediated cyclopropanation, and that asymmetric cyclopropanations are possible, we proposed a new cyclopropane route to Kainic acid. It was envisioned that the isopropenyl group could be installed through some previously 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

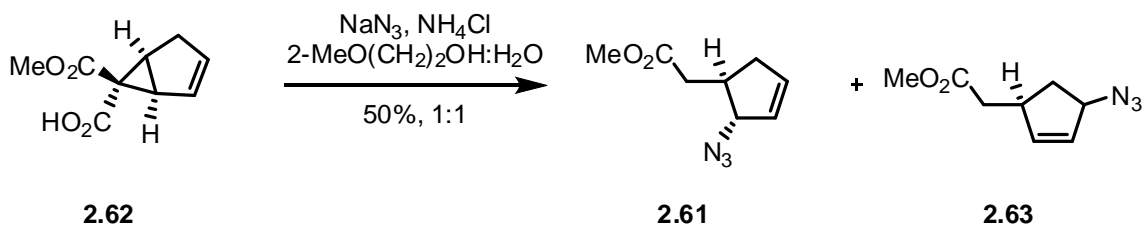
To begin our synthesis we focused on the synthesis of **2.62**, which could be achieved in a two-step process. Cyclopentene cyclopropane **2.45** was synthesized from diazomalonate **2.29**, cyclopentadiene **2.46**, and $\text{Rh}_2(\text{OAc})_4$, (1 mol%) in a 64 % yield. Cyclopropanediester **2.47** 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**

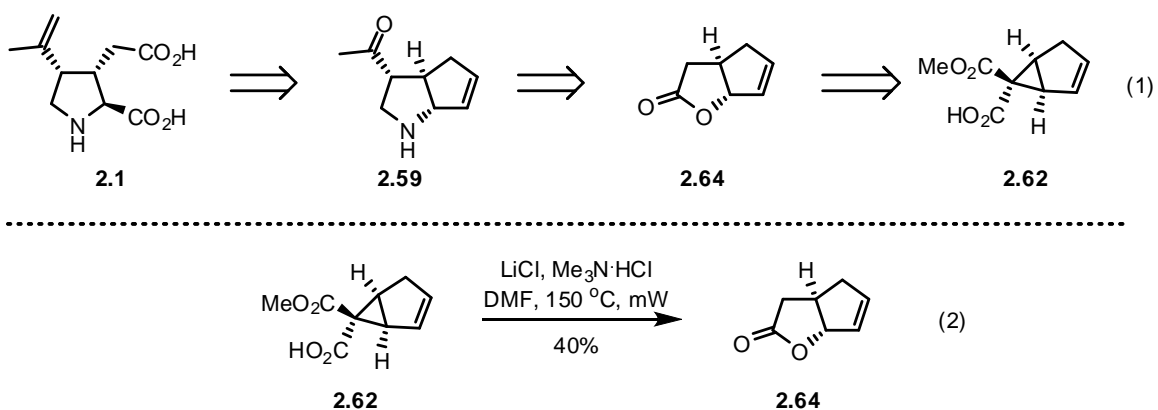
Having our desired hemimalonate **2.62** in hand, we began the investigation into the azide ring opening of this substrate. Unfortunately, when we attempted the tandem ring opening dealkoxycarbonylation sequence, we obtained a mixture of products in a 50 % yield. This appeared to be an equal intractable 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.



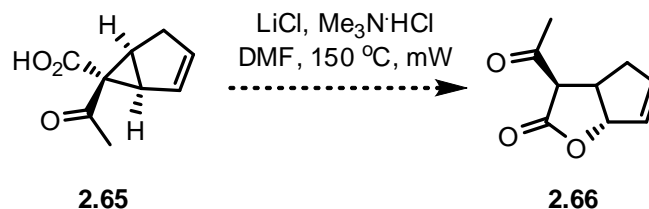
Scheme 2.14 Tandem Azide Ring Opening Dealkoxycarbonylation of **2.62**

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 formation²⁴ 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.



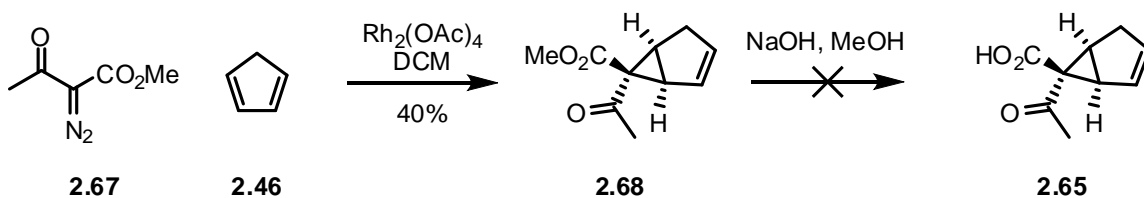
Scheme 2.15 Second Generation Retrosynthesis and Result

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).



Scheme 2.16 Potential Keto-Ester Lactonization Reaction

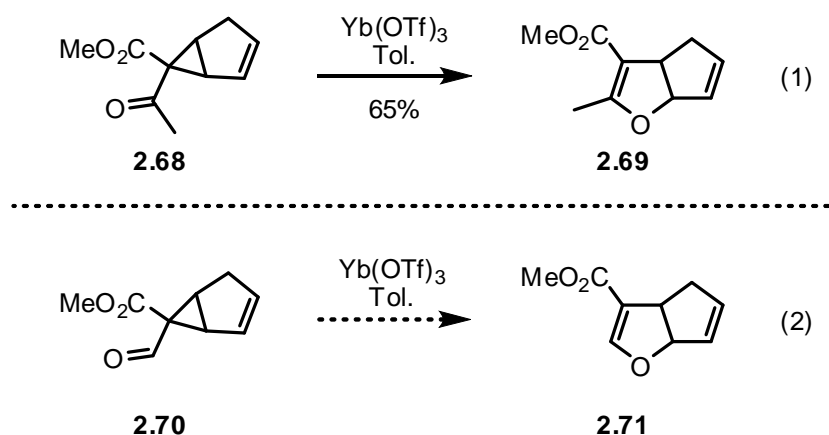
Starting from keto-ester diazo species **2.67**, a rhodium catalyzed cyclopropanation reaction occurred again with cyclopentadiene **2.46**, which proceeded to give **2.68** in a modest 40 % yield. We then tried to saponify this material anyways to give **2.65**, but we were unsuccessful under either 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.



Scheme 2.17 Attempting to Pre-install the Ketone Functionality

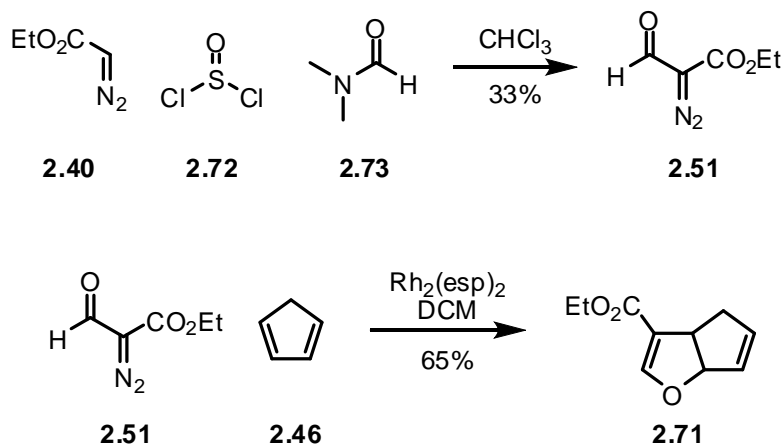
While this was a discouraging result, we thought that perhaps we could still utilize compound **2.68**. There is precedence for ketone-cyclopropane rearrangements to form a

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).



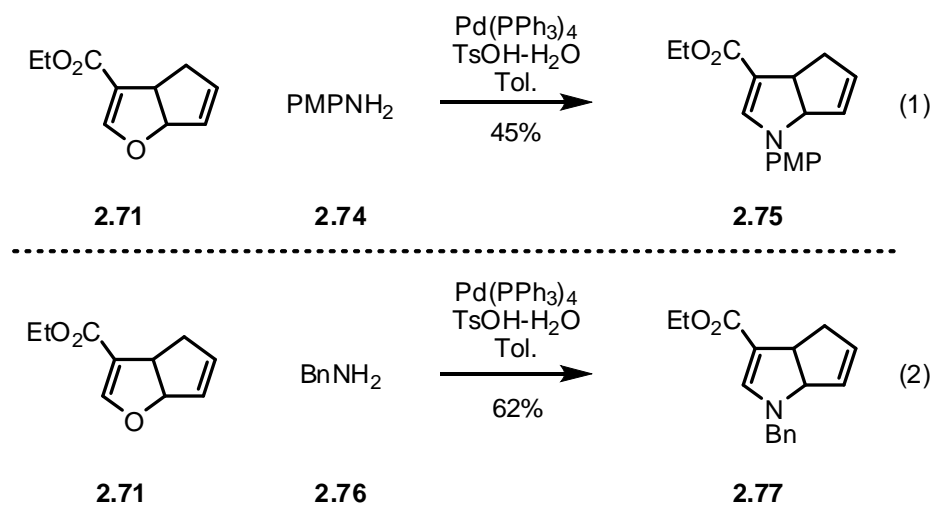
Scheme 2.18 Ketone Rearrangement and Possible Aldehyde Rearrangement

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 be our desired cyclized adduct **2.71** (*vide infra*) in 65 % yield. The same reaction with $\text{Rh}_2(\text{OAc})_4$ 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**

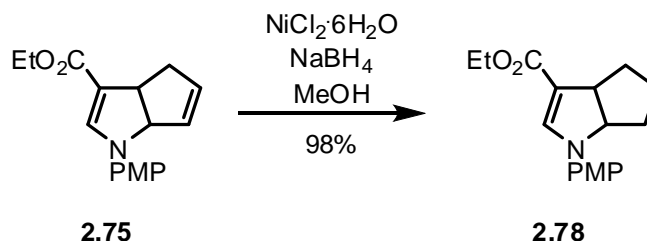
We then converted the dihydrofuran **2.69** to dihydropyrroles **2.71** using a palladium catalyzed procedure²⁸ with *p*-anisidine **2.70** in 45 % yield (Scheme 2.20, eq. 1). By switching the amine source from *p*-anisidine to benzyl amine **2.72**, we could increase the yield of dihydropyrrole formation to 62 % (Scheme 2.20, eq. 2).



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

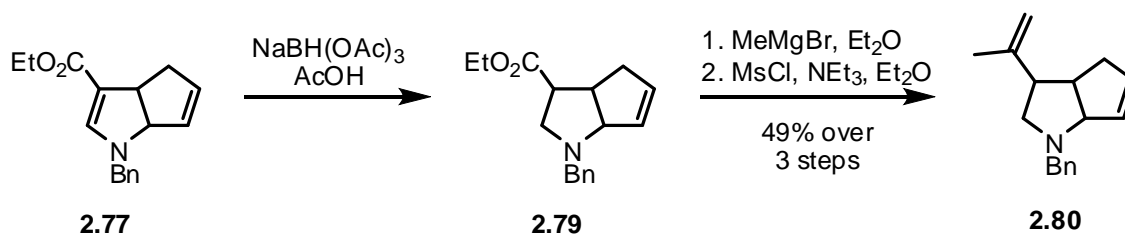
Having the core framework desired for Kainic acid, we decided to try to manipulate the ester functionality to the isopropylidene. We attempted to saponify the

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).



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 group³⁰ **2.80** in an overall yield of 49% over the three steps.



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**.

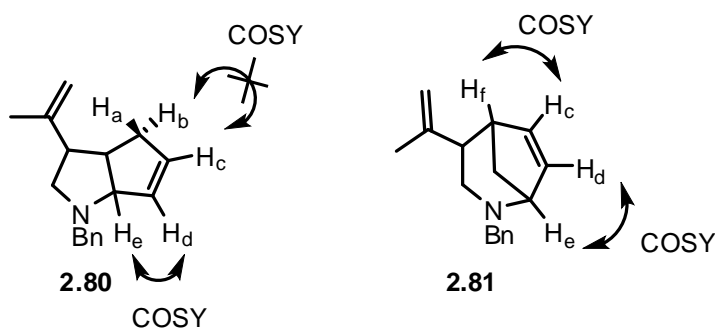


Figure 2.2 Structural Reassignment Based on 2-D NMR Studies

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**.

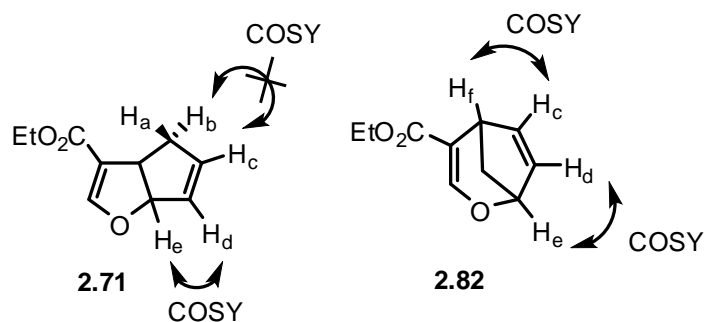


Figure 2.3 Structural Reassignment of **2.71** to **2.82**

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 bicyclic 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

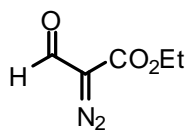
Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. ^1H , and ^{13}C NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl_3 (referenced to 7.26 ppm for ^1H and 77.0 for ^{13}C). 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 F₂₅₄) 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 LECOTM 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 °C 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 °C 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

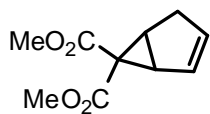
sulfuric acid (10%), brine and dried over MgSO₄. The resulting yellow oil (0.420 g, 2.96 mmol, 33%) was used without further purification with data as reported in the literature.



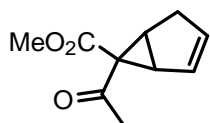
Reagents employed: **2.72** (0.653 mL, 9.00 mmol); **2.73** (0.697 mL, 9.04 mmol); **2.40** (1.91 mL, 18.2 mmol); chloroform (4 mL); Yielded **2.51** as a yellow oil, 33% (0.420 g, 2.96 mmol). Spectral properties are identical to those previously reported.²⁷

General Procedure for the Reaction of Diazo Species with Cyclopentadiene

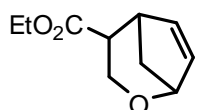
Cyclopentadiene **2.46** was distilled from dicyclopentadiene prior to use, due to dimerization of **2.46** at room temperature. Rhodium catalyst (2 mol %) was added to a solution of cyclopentadiene and DCM at room temperature. The diazo species in DCM was added dropwise and the solution was heated to 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); Rh₂OAc₄ (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



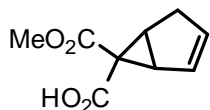
Reagents employed: **2.46** (1.05 g, 15.9 mmol); Rh₂OAc₄ (0.047 g, 1.06 mmol); **2.67** (1.50 g, 10.6 mmol); DCM (15 mL); Yielded **2.68** as a colourless oil, 40% (0.760 g, 4.22 mmol). ¹H-NMR (400 MHz, CDCl₃): δ = 5.82-5.78 (m, 1H), 5.68-5.63 (m, 1H), 3.68 (s, 3H), 2.83-2.78 (m, 1H), 2.75-2.73 (m, 1H), 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); Rh₂esp₂ (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). ¹H-NMR (600 MHz, CDCl₃): 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); ¹³C NMR (150 MHz, CDCl₃): 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 C₁₀H₁₂O₃ = 180.0786, found 180.0791.

Procedure for the saponification of **2.47**

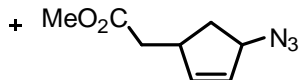
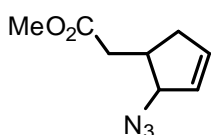
Cyclopropanes were dissolved in MeOH and 1.7M NaOH (1.2 eq.) with constant stirring. The solution was stirred for 1.5 h then was diluted with EtOAc and water to separate layers. The aqueous layer was the acidified with 5% HCl to reach pH 2, then extracted three times with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, 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). ¹H-NMR (600 MHz, CDCl₃): 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.

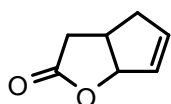


Reagents employed: **2.62** (0.101 g, 0.554 mmol); sodium azide (0.043 g, 0.661 mmol); ammonium chloride (0.042 g,

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). ¹H-NMR (600 MHz, CDCl₃): (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

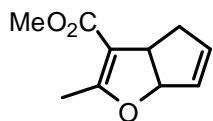
Cyclopropane hemimalonate, LiCl, and Me₃N·HCl were added to a microwave vial and dissolved in DMF. The vial was sealed and heated for 40 minutes at 150 °C. After the required reaction time the reaction was quenched with H₂O and extracted with ether. The organic layer was dried and the solvent was removed. 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); Me₃NHCl (0.073 g, 0.764 mmol); DMF (3 mL); Yielded **2.64** as a yellow oil, 40% (0.027 g, 0.217 mmol). ¹H-NMR (600 MHz, CDCl₃): 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). ¹³C NMR (150 MHz, CDCl₃): δ = 177.1, 136.8, 129.0, 89.6, 39.5, 36.0, 35.1.

Procedure for the Ketone Cyclopropane Rearrangement

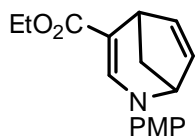
YbOTf₃ (20 mol %) was added to a solution of keto-ester cyclopropane **2.68** in toluene. The mixture was stirred at room temperature until the reaction was complete (as determined by TLC analysis). The solution was purified via flash chromatography on silica gel and the product was isolated.



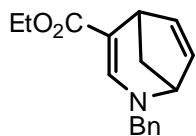
Reagents employed: **2.68** (0.107 g, 0.594 mmol); YbOTf₃ (0.074 g, 0.119 mmol); Toluene (3 mL); Yielded **2.69** as a yellow oil, 65% (0.070 g, 0.388 mmol). ¹H-NMR (600 MHz, CDCl₃): δ = 6.07-6.04 (m, 1H), 5.79-5.76 (m, 1H), 5.62 (br d, J = 9.4 Hz, 1H), 3.84-3.80 (m, 1H), 3.71 (s, 3H), 2.75-2.68 (m, 1H), 2.50-2.45 (m, 1H), 2.17 (s, 3H). ¹³C NMR (150 MHz, CDCl₃): 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·H₂O, Pd(PPh₃)₄, toluene and oxepane were added sequentially to a round bottom flask. Then the resulting mixture was stirred at 70 °C 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·H₂O (0.010 g, 0.053 mmol); Pd(PPh₃)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). ¹H-NMR (600 MHz, CDCl₃): 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). ¹³C NMR (150 MHz, CDCl₃): 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.

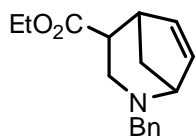


Reagents employed: **2.76** (0.097 g, 0.905 mmol); *p*-TsOH·H₂O (0.010 g, 0.053 mmol); Pd(PPh₃)₄ (0.021 g, 0.018 mmol); **2.82** (0.050 g, 0.301 mmol); Toluene (5 mL); Yielded oxepane as an orange oil, 62% (0.050 g, 0.186 mmol). ¹H-NMR (600 MHz, CDCl₃): δ = 7.38-7.34 (m, 2H), 7.32-7.29 (m, 1H), 7.26-7.23 (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). ¹³C NMR (150 MHz, CDCl₃): 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 C₁₇H₁₉NO₂ = 269.1416, found 269.1409.

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

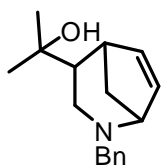
A solution of azapane in THF was added dropwise to a solution of NaBH(OAc)₃ in AcOH. After the reaction was complete as monitored by TLC (30% EtOAc:hexanes), the solution was diluted with EtOAc and the layers were separated. The aqueous layer

was neutralized with saturated sodium hydrogen carbonate and then extracted three times with EtOAc. The combined organic layers were dried with MgSO₄ and the solvent was removed.



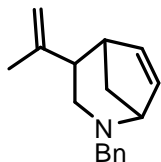
Reagents employed: azapane (0.310 g, 1.15 mmol); NaBH(OAc)₃ (0.732 g, 0.345 mmol); AcOH (3.5 mL); THF (5 mL); Crude ester divided into three parts and one of them taken forward for the Grignard addition.

The crude ester was then dissolved in ether and cooled to 0°C. 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 MgSO₄ and the solvent was removed.



Reagents employed: crude ester (0.098 g, 0.361 mmol); MeMgBr (0.4 mL, 1.20 mmol); Et₂O (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°C and NEt₃ 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 MgSO₄. 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); NEt₃ (0.489 g, 4.83 mmol); Et₂O (3 mL); Yielded **2.81** as a colourless oil, 49% over three steps (0.038 g, 0.159 mmol). ¹H-NMR (600 MHz, CDCl₃): 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). ¹³C NMR (150 MHz, CDCl₃): 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.

Section 2.8 References

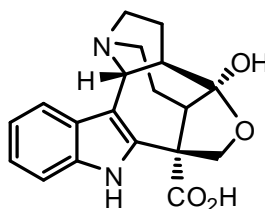
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Chapter 3 Actinophyllic Acid

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

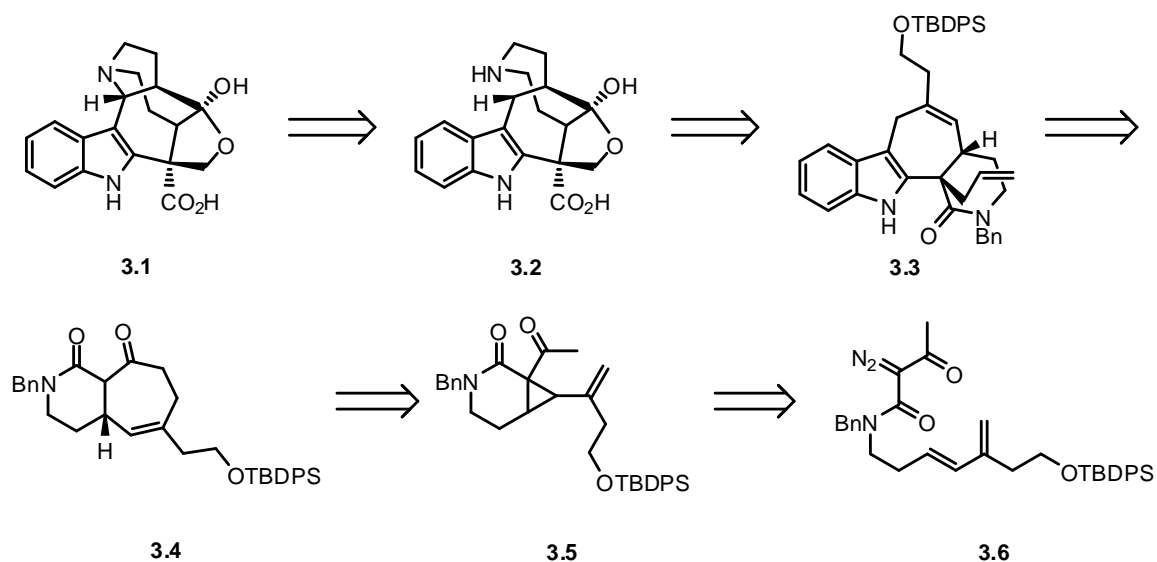
Figure 3.1 Actinophyllic Acid, **3.1**

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 its 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

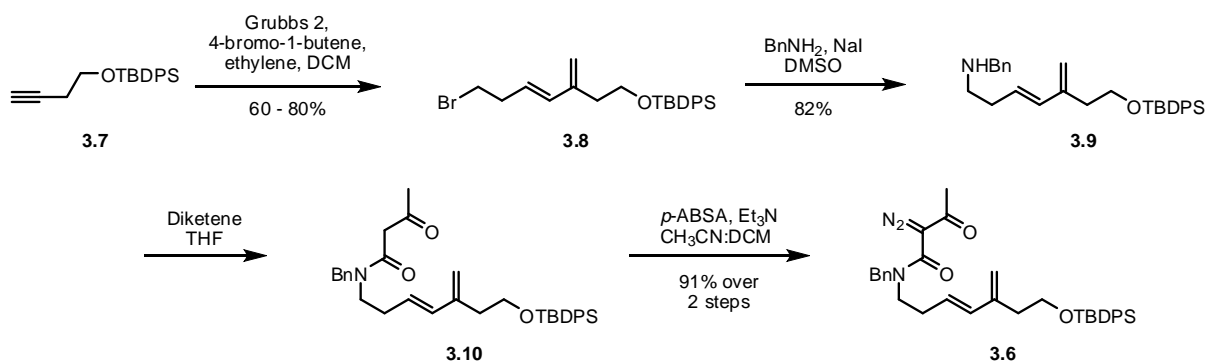
In 2009, Wood and co-workers revealed their synthetic plan for the synthesis of Actinophyllic Acid (Scheme 3.1).⁷ They envisioned creating the large eight membered ring via a ring closing reaction of secondary amine **3.2** and an indole-quinonemethide species to furnish **3.1**. They believed that they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



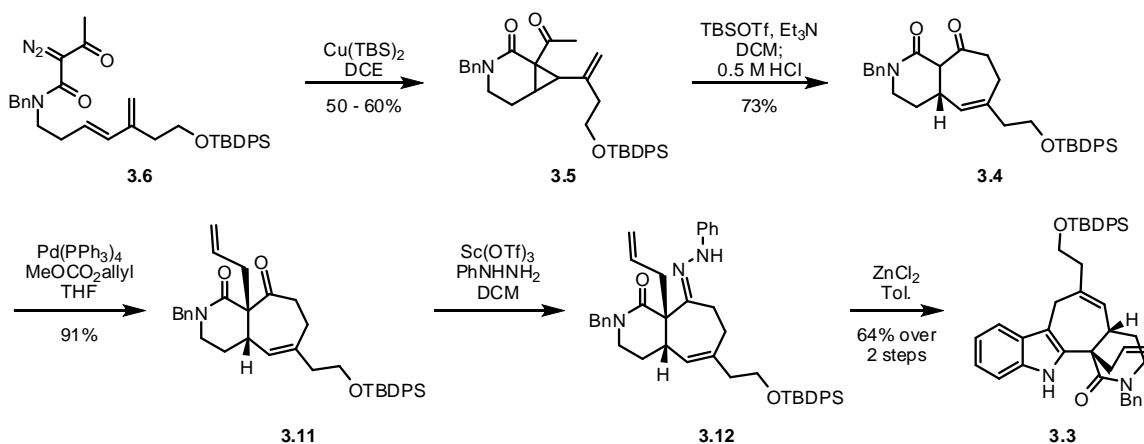
Scheme 3.1 Wood's Retrosynthetic Plan

In the forward sense, starting from protected homo-propargyl 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.



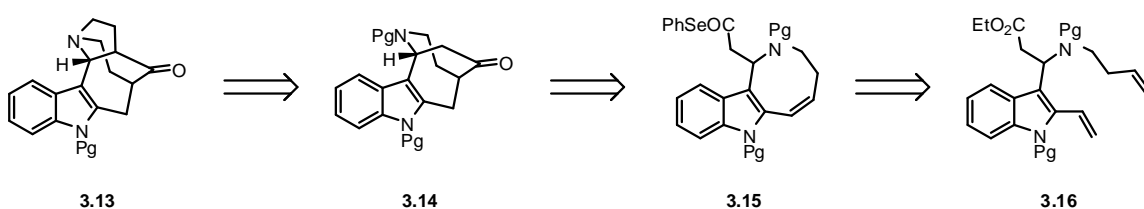
Scheme 3.2 Synthesis of Cyclopropanation Precursor

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.



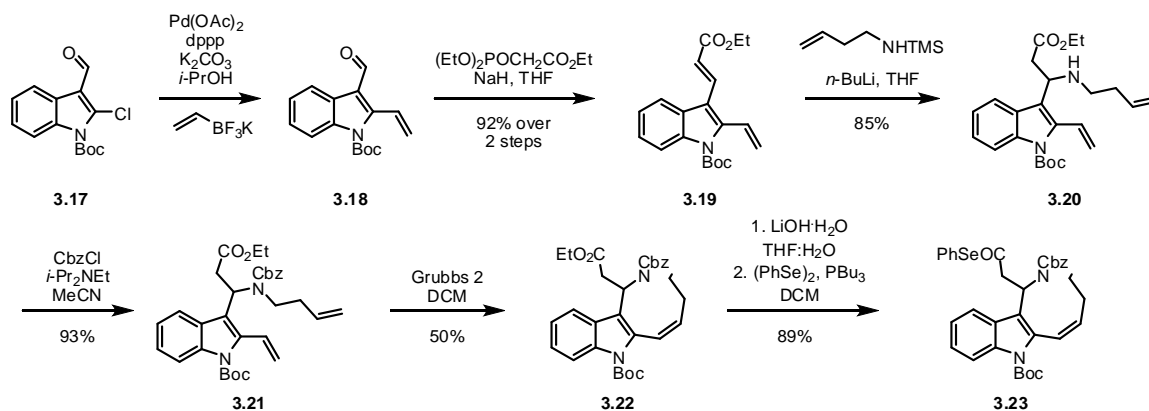
Scheme 3.3 Synthesis of Key Indole Intermediate 3.3

In 2012, Taniguchi developed a transannular acyl radical cyclization 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**.



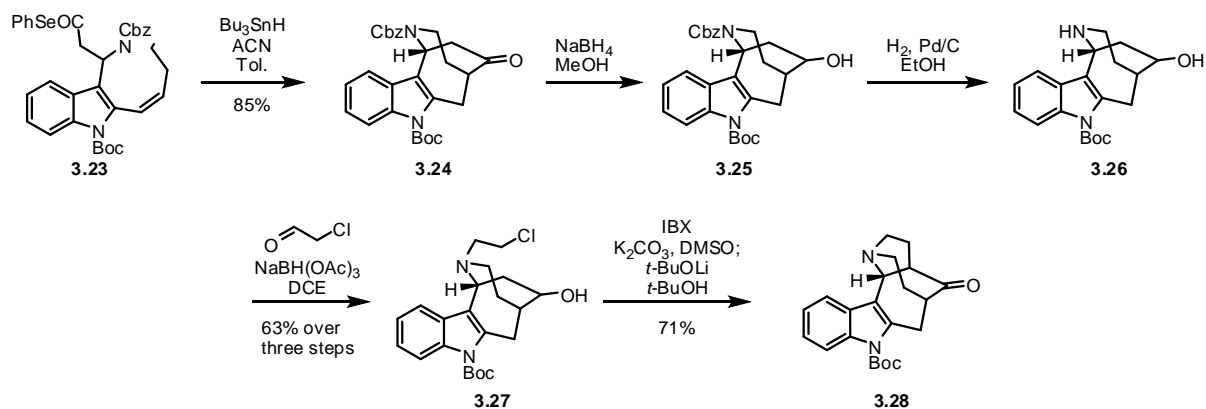
Scheme 3.4 Taniguchi's Retrosynthetic Plan

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**.



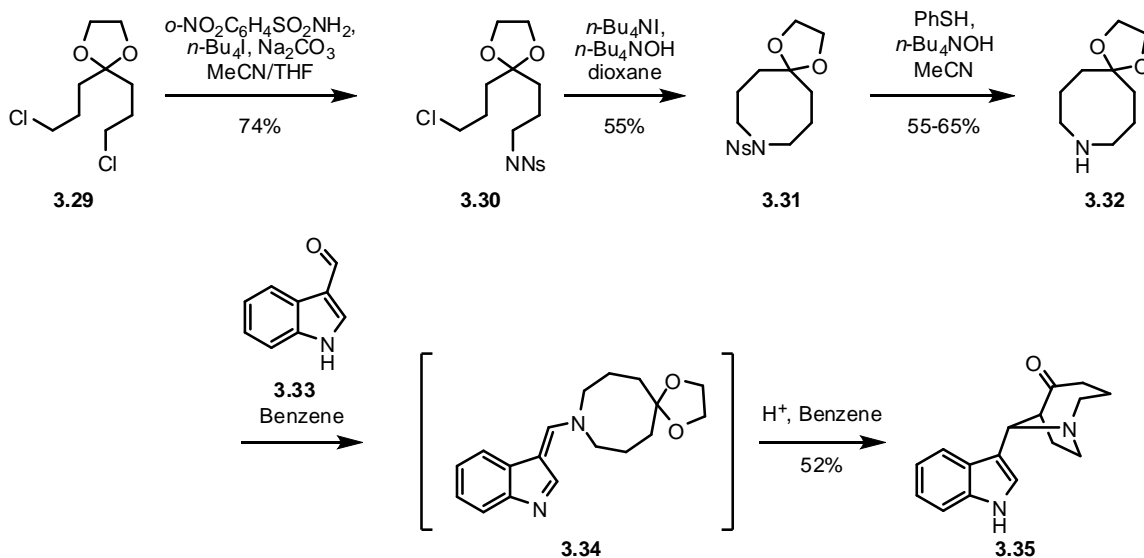
Scheme 3.5 Synthesis of Acyl Radical Precursor

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.



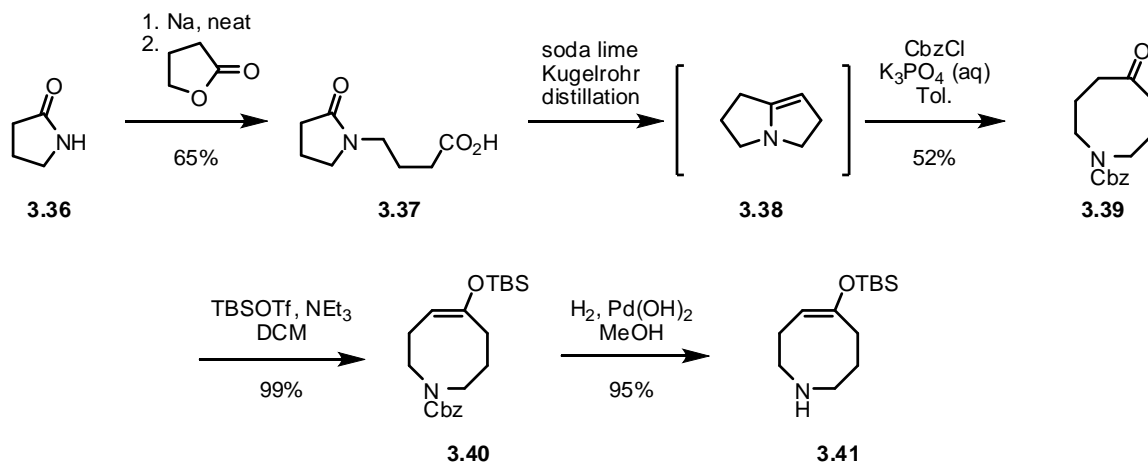
Scheme 3.6 Acyl Radical Cyclization and Synthesis of Advanced intermediate **3.28**

The group of Maldonado and co-workers believed that they could form the 1-azabicyclo[4.2.1]nonane core of Actinophyllic acid⁹ 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.



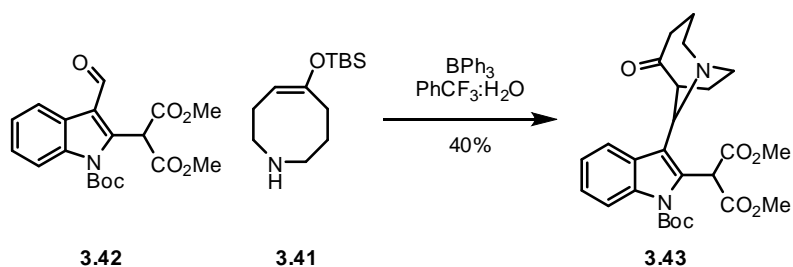
Scheme 3.7 Maldonado's Synthesis of the Actinophyllic Acid Core

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.



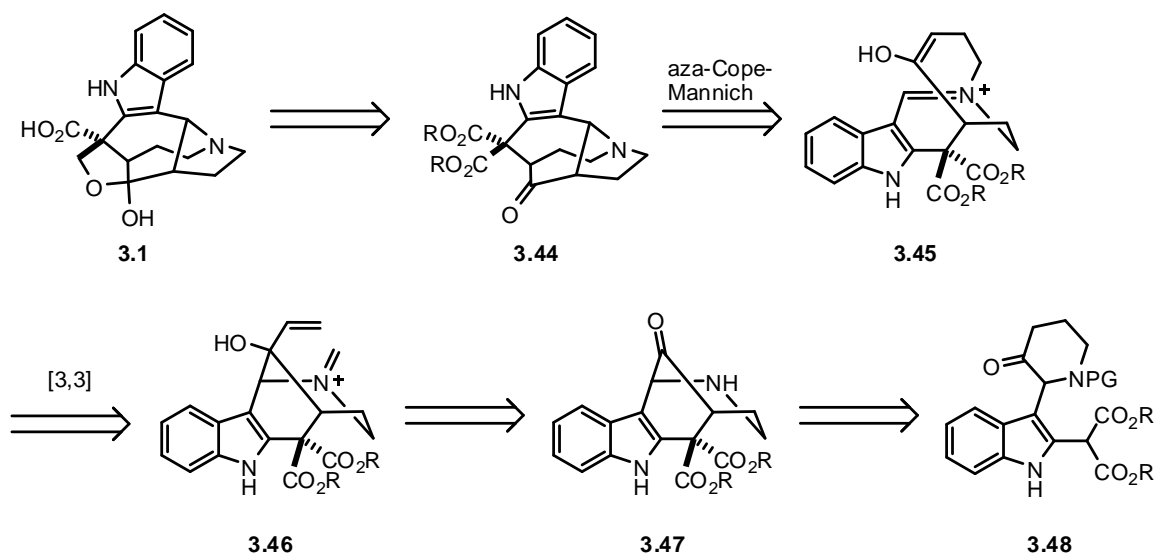
Scheme 3.9 Coldham's Synthesis of the Core of Actinophyllic Acid

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 2013¹⁴ will be described herein.

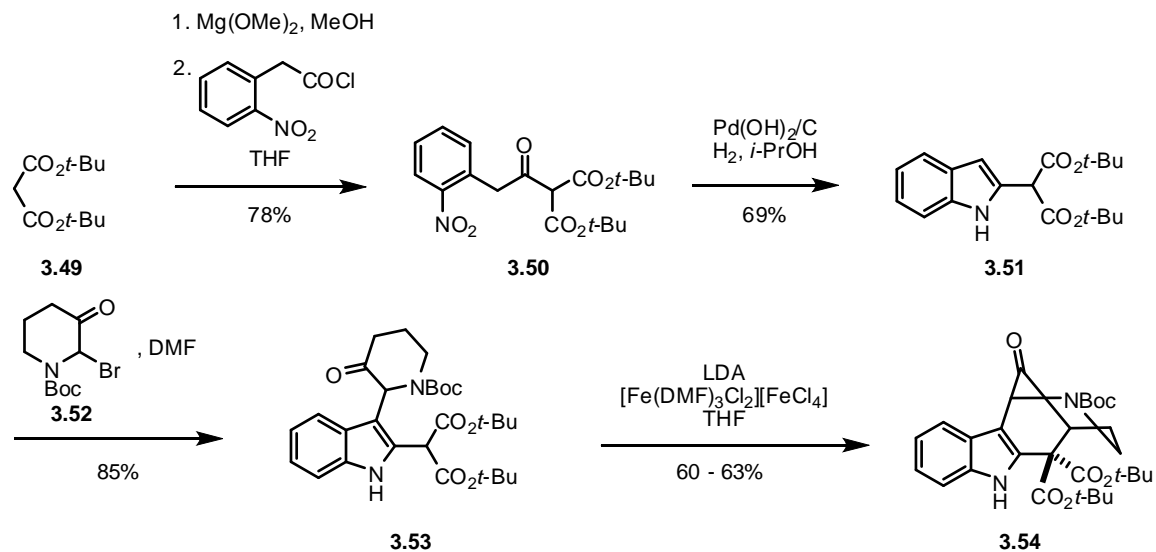
Section 3.3.1 Overman's Total Synthesis of Actinophyllic Acid

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 cyclization 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**.



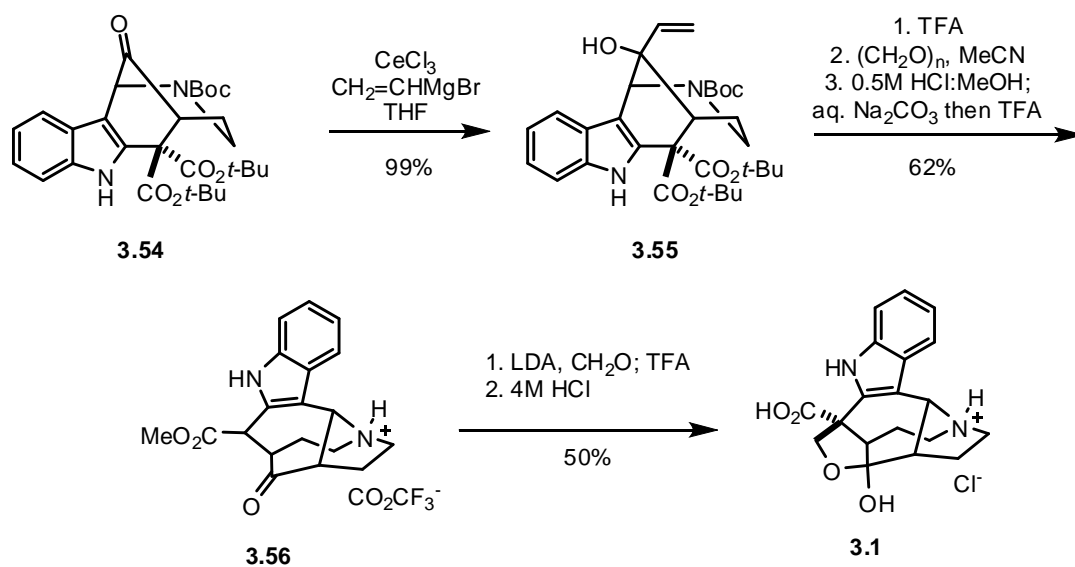
Scheme 3.10 Overman's Retrosynthetic Strategy

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

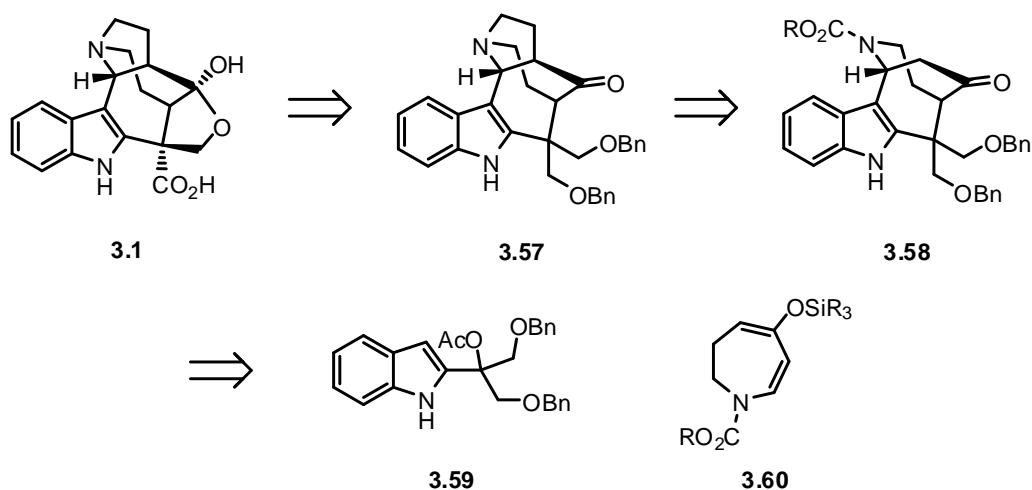
A Luche mediated Grignard addition to ketone **3.54** provided access to their key rearrangement substrate **3.55**. Removal of the Boc protecting group, followed by iminium formation with *p*-formaldehyde set up their rearrangement/aza-Cope-Mannich cascade to form **3.56** in a superb 62% yield. Next **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

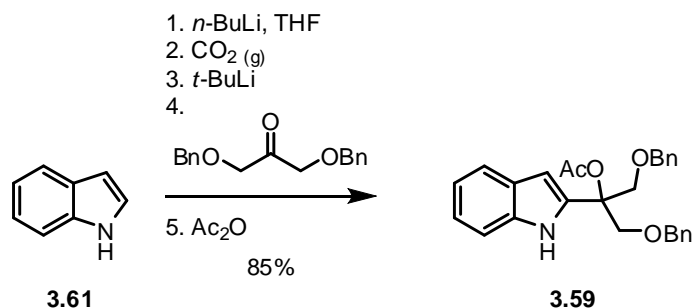
Section 3.3.2 Martin's Total Synthesis

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

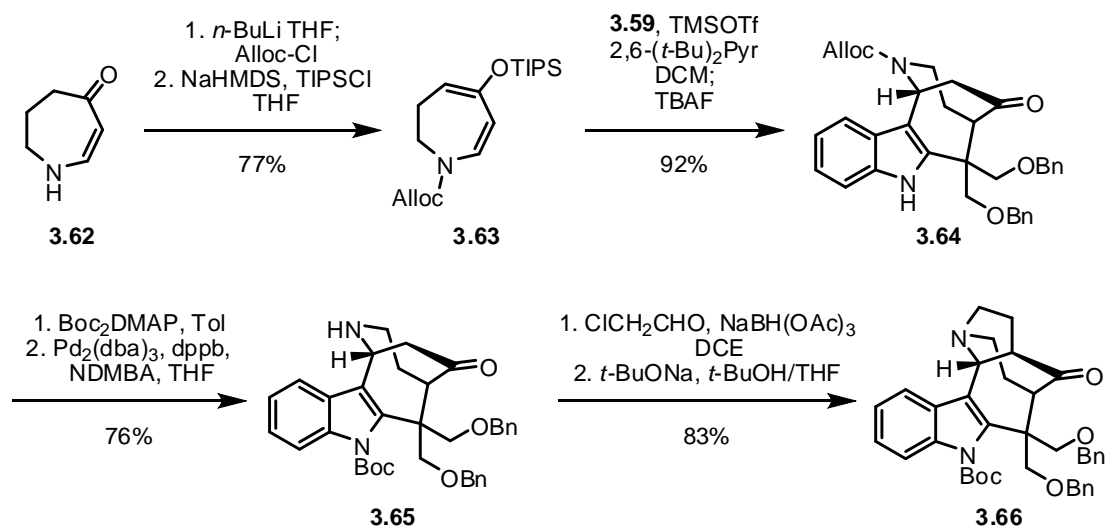
Taking indole **3.61**, they could form the dianionic species, which was added into 1,3-dibenzoyloxyacetone. The product of was then protected in situ to form **3.59** in an 85% yield (Scheme 3.14).



Scheme 3.14 Synthesis of Cyclization Precursor

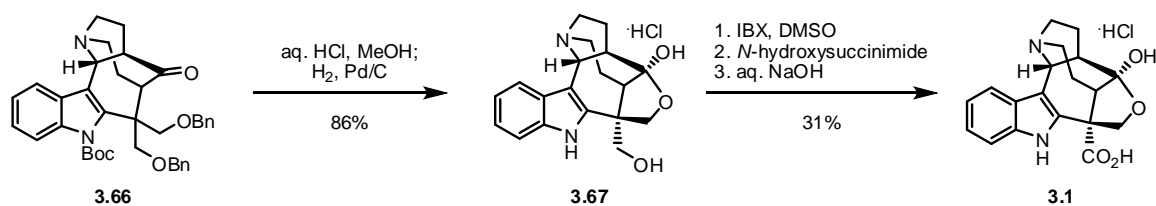
Azepinone **3.62** was protected with Alloc-Cl and trapped as the silyl enol ether to form the desired diene **3.63** for the cyclization (Scheme 3.15). After extensive optimization of conditions, the cascade was promoted with TMSOTf, followed by addition of TBAF to remove the silyl protecting group 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

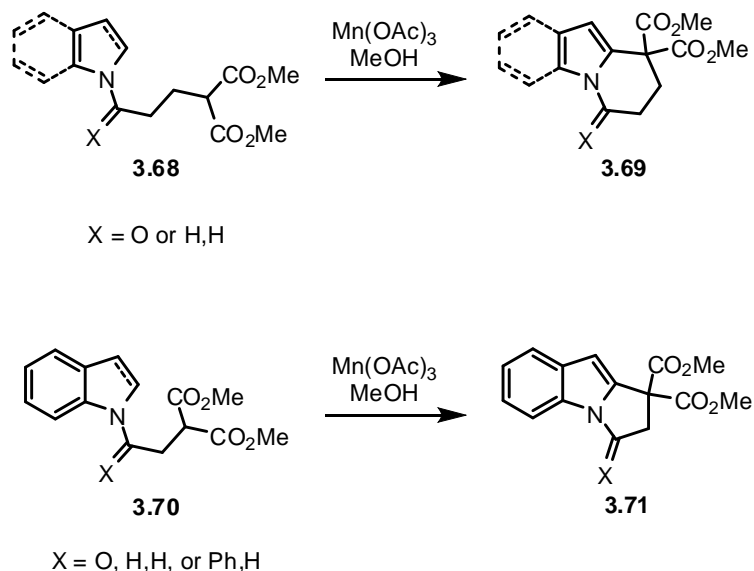
Removal of the Boc group on the indole and removal of the benzyl protecting groups provided **3.67** as the HCl salt; all that remained was oxidation of the neopentyl alcohol to form Actinophyllic acid. After many attempts, they could oxidize the alcohol to the aldehyde with IBX, followed by addition 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

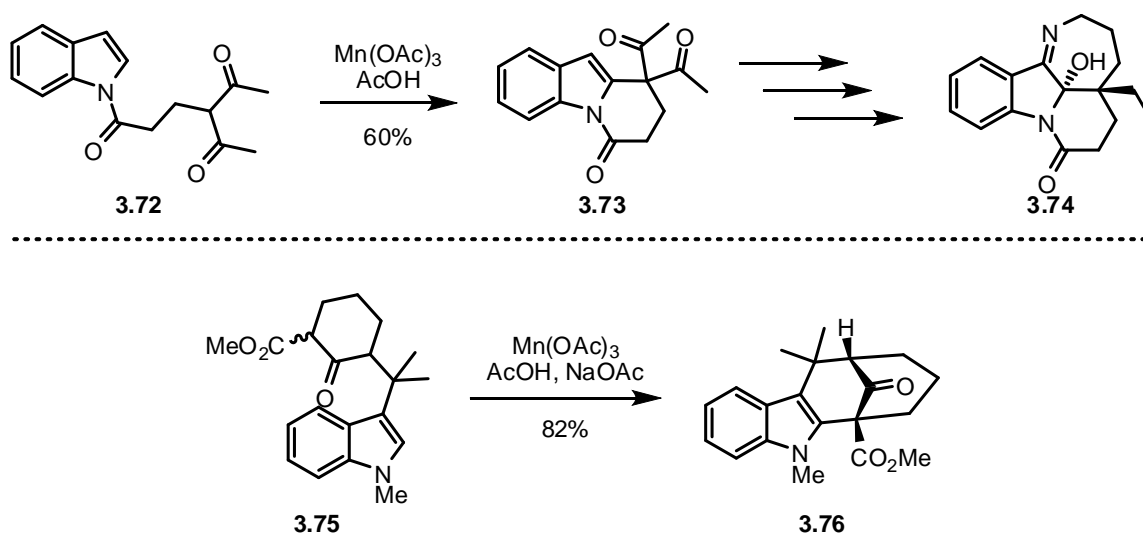
Section 3.4 Oxidative Radical Cyclizations

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 compounds 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

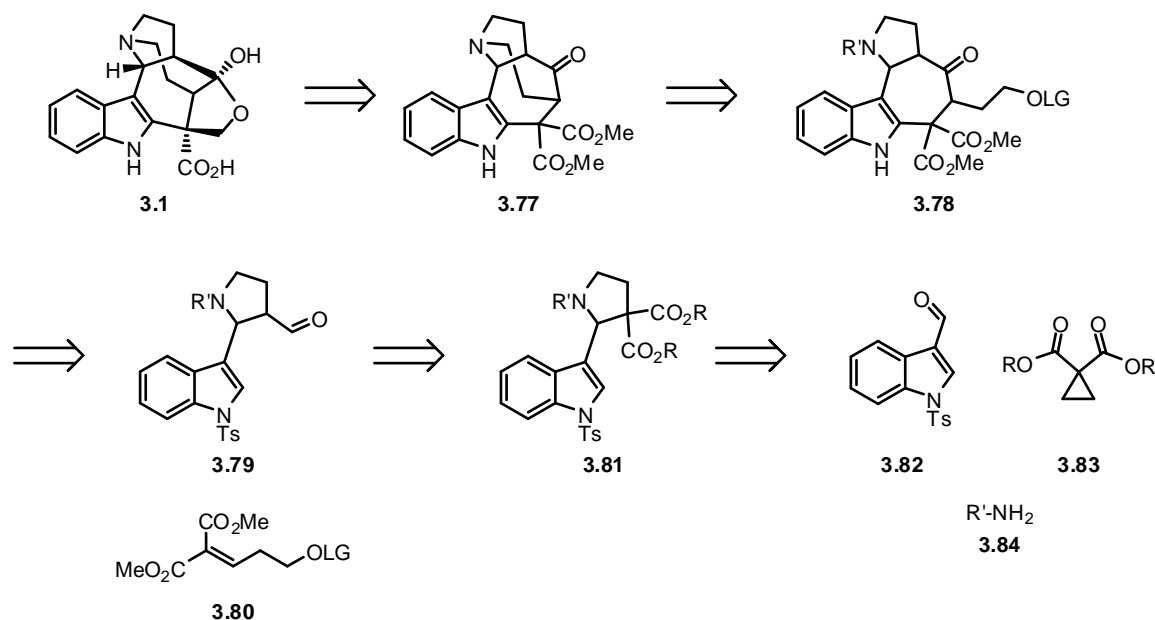


Scheme 3.18 Applications of the Manganese Mediated Oxidative Cyclization

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

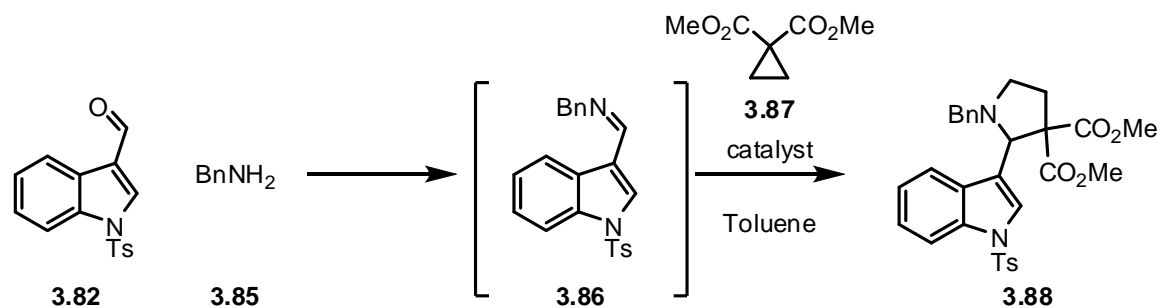
Section 3.6 Results and Discussion

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-methide²¹ 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-cyclopropanediester 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).

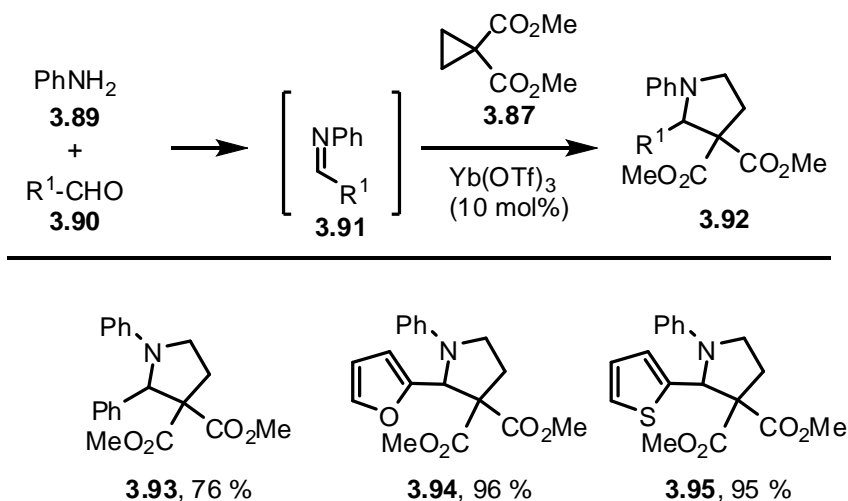
Table 3.1 Pyrrolidine Ring Formation Attempts



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

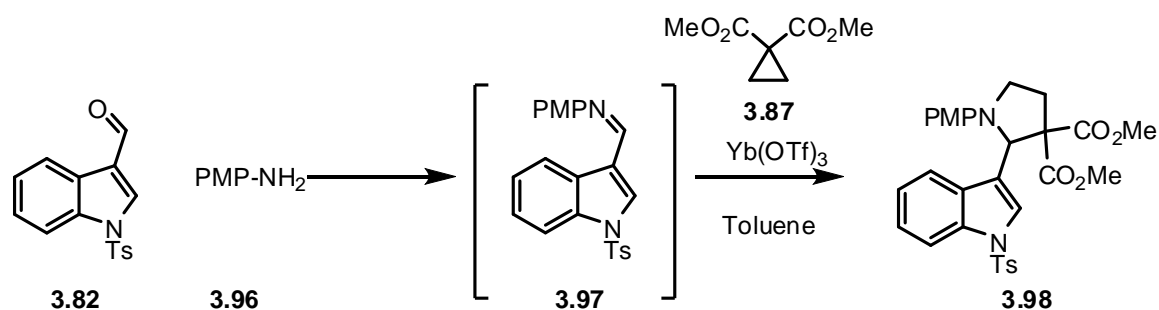
Having no success at completing the three-component coupling required for Actinophyllic acid, we re-examined the pyrrolidine methodology.²² Upon further

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



Scheme 3.20 Selected Examples from Kerr's Pyrrolidine Methodology

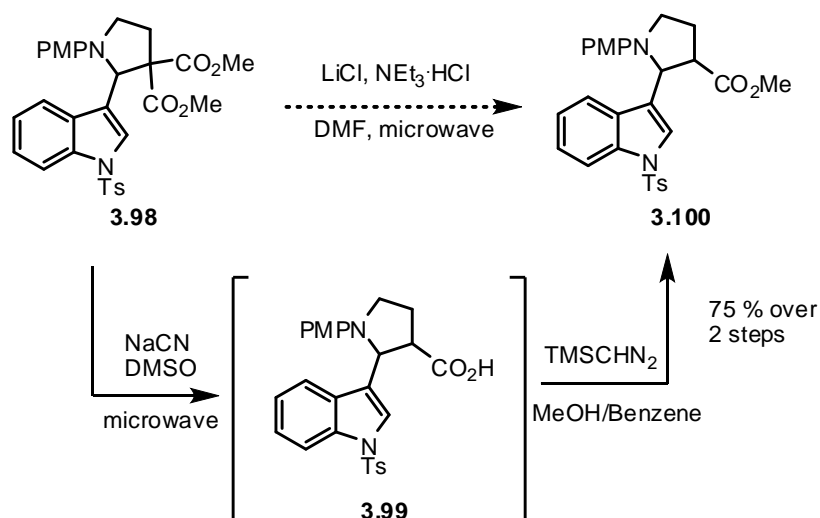
From this observation, we decided to use *p*-anisidine **3.96** as our amine source as the aromatic ring could be cleavable at a later time, as well as it would give us a diagnostic methyl peak in our NMR spectra. By making this adjustment, we were able to generate desired pyrrolidine **3.98** in an 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-

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

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

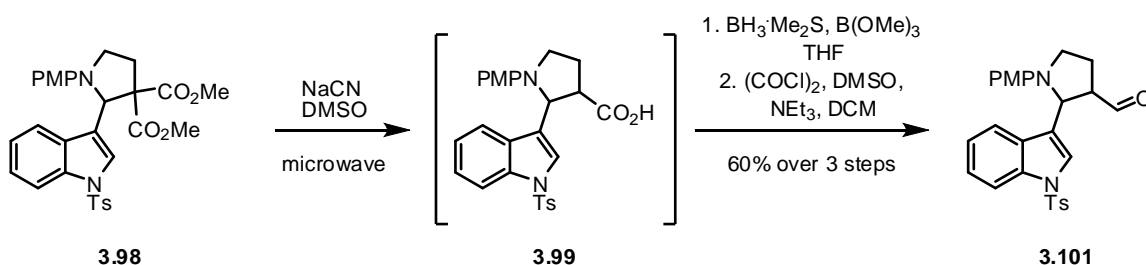
Section 3.6.2 Progress Towards Actinophyllic Acid

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 dealkoxycarbonylation²⁴ 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

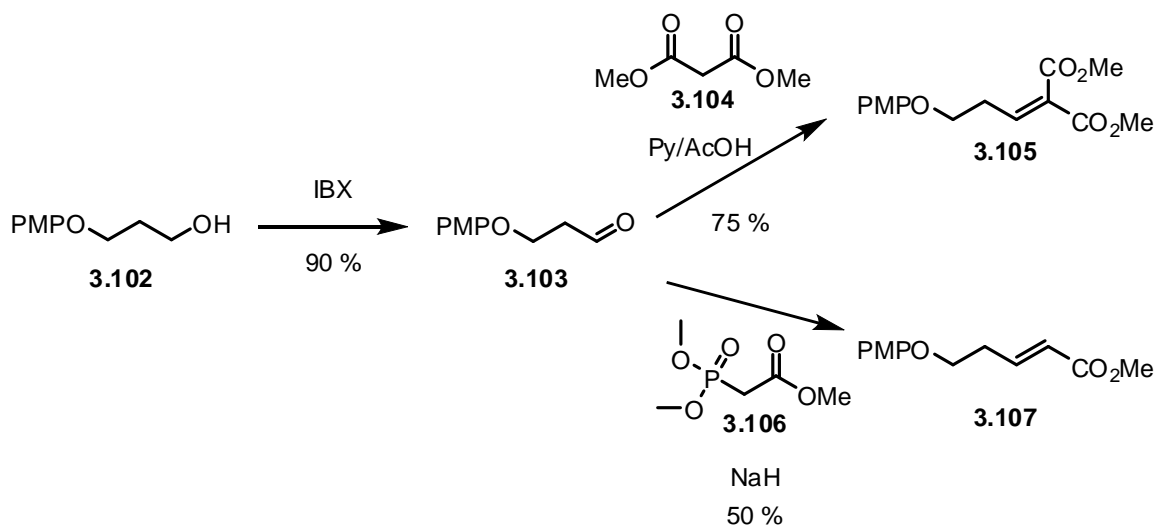
With the realization that under the Krapcho conditions we could generate a single acid functionality, we thought that this would be a good intermediate for the synthesis of our desired aldehyde. Using the same conditions as stated above, we reduced the acid using borane and oxidized the resultant alcohol 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**

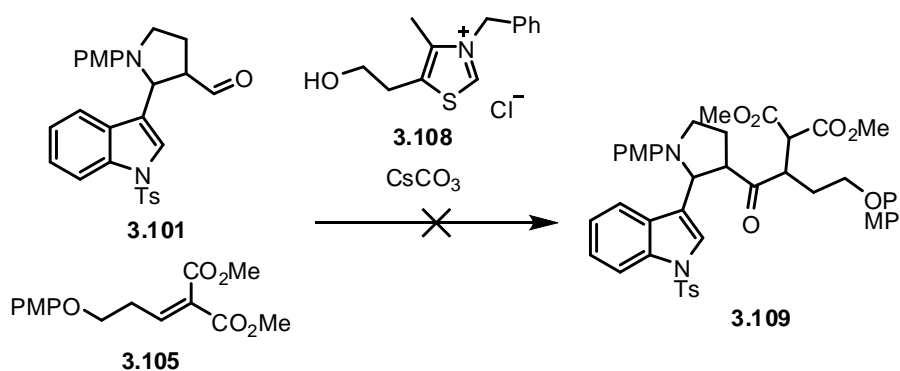
We decided to synthesize two different acceptors both of which could be carried forward for the Stetter reaction. Taking mono-protected propanediol, we oxidized the remaining alcohol up to the aldehyde in 90% yield using IBX (Scheme 3.23). From there

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



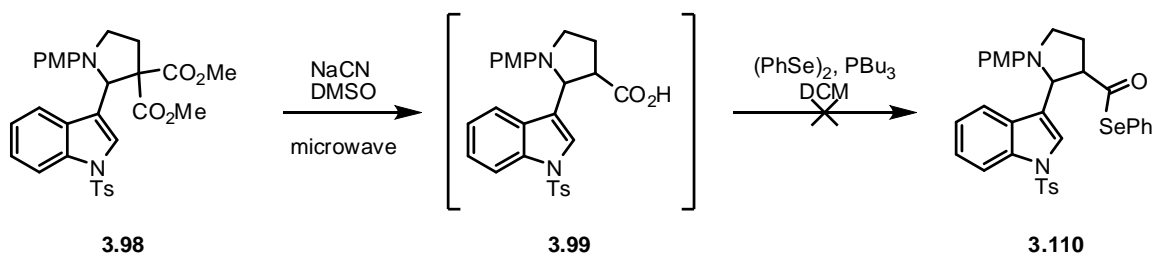
Scheme 3.23 Synthesis of Potential Stetter/Acyl Radical Acceptors

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.



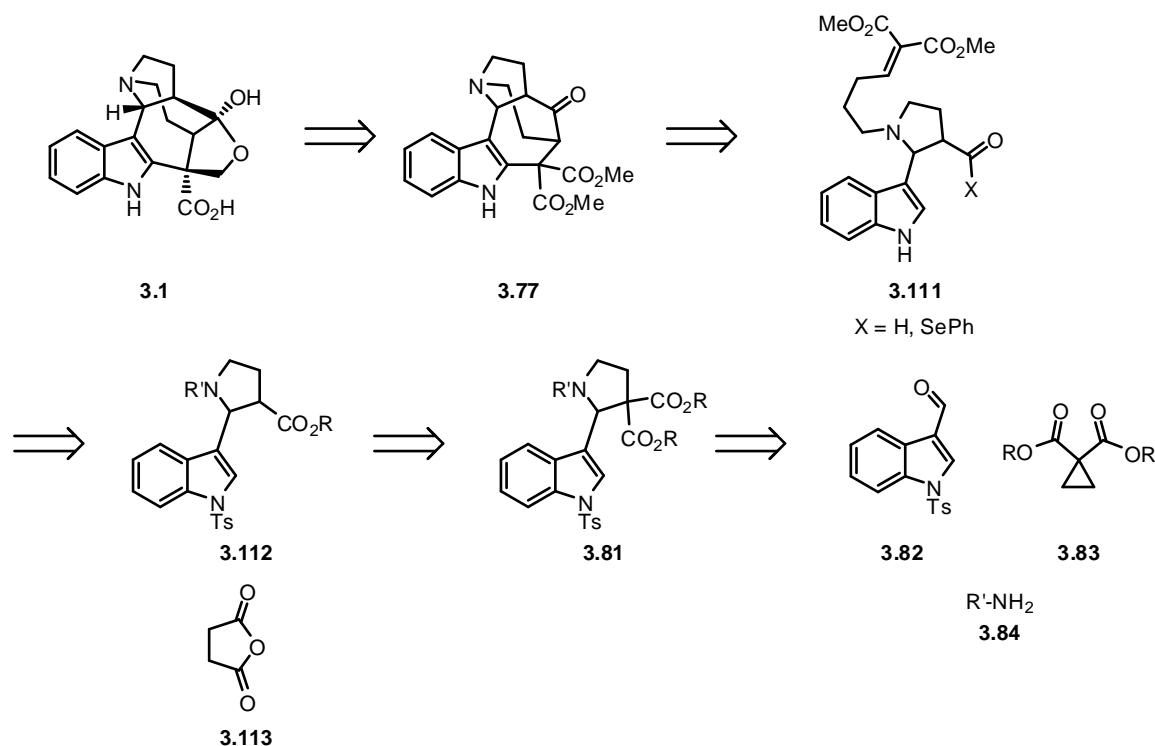
Scheme 3.24 Stetter Reaction Attempt

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).



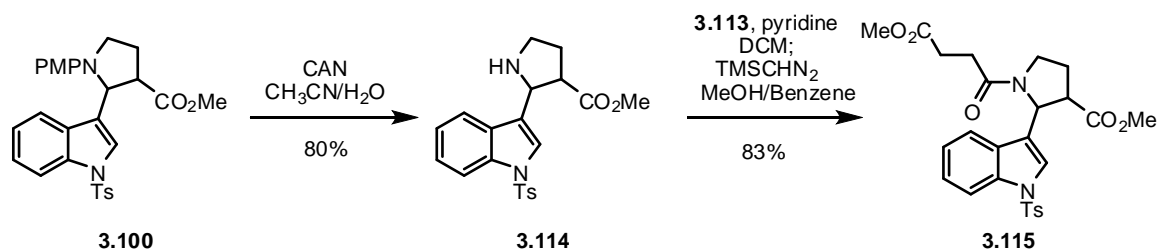
Scheme 3.25 Attempted Synthesis of Selenoester **3.110**

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

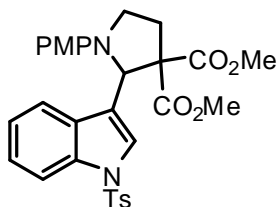
Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. ^1H , and ^{13}C NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl_3 (referenced to 7.26 ppm for ^1H and 77.0 for ^{13}C). 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 F₂₅₄) 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 LECOTM 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 YbOTf₃ (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).



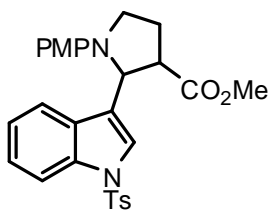
Reagents employed: **3.82** (0.379 g, 1.26 mmol); **3.96** (0.156 g, 1.27 mmol); YbOTf₃ (0.078 g, 0.126 mmol); **3.87** (0.100 g, 0.632 mmol); Toluene (3 mL); Yielded **3.98** as a yellowish foam, 86% (0.307 g, 0.546 mmol). ¹H-NMR (400 MHz, CDCl₃): δ = 7.91-7.87 (m, 1H), 7.67-7.63 (m, 1H), 7.48 (d, J = 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

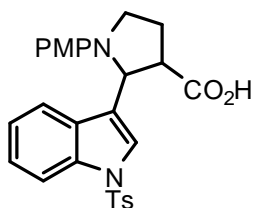
To a solution of diester in wet DMSO was added NaCN. The reaction mixture was then heated to 140 °C under microwave irradiation for 3 h. The reaction was poured into water and extracted three times with Et₂O. The combined extracts were then washed twice with water, once with brine and dried over MgSO₄. The aqueous layer was then acidified and re-extracted with Et₂O 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 TMSCHN₂ 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); TMSCHN₂ (0.105 mL, 0.210 mmol); Yielded **3.100** as an orange oil, 86% (0.046 g, 0.091 mmol). ¹H-NMR (600 MHz, CDCl₃): $\delta = 7.98$ (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).

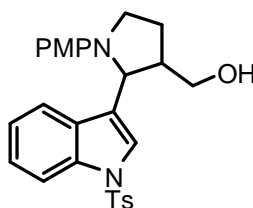
Procedure for the conversion of 3.96 to 3.99

To a solution of diester in wet DMSO was added NaCN. The reaction mixture was then heated to 140 °C under microwave irradiation for 3 h. The reaction was poured into water and extracted three times with Et₂O. The combined extracts were then washed twice with water, once with brine and dried over MgSO₄. The aqueous layer was then acidified and re-extracted with Et₂O 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.



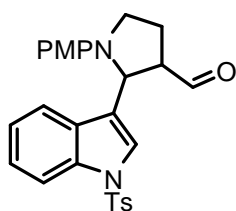
Reagents employed: **3.98** (0.270 g, 0.480 mmol); NaCN (0.118 g, 2.41 mmol); DMSO (3 mL); Crude acid taken forward for the reduction to primary alcohol.

A solution of crude acid in THF was added slowly to a cooled solution (0 °C) of BH₃·SMe₂ 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); BH₃·SMe₂ (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).

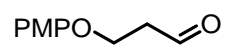


Reagents employed: alcohol (0.229 g, 0.480 mmol); oxalyl chloride (0.167 mL, 1.91 mmol); DMSO (0.272 mL, 3.84 mmol); NEt_3 (0.668 mL, 4.79 mmol); DCM (10 mL); Yielded **3.101** as a yellow oil, 60% over the three steps (0.135 g, 0.284 mmol). $^1\text{H-NMR}$ (600 MHz,

CDCl_3): (mixture of diastereomers) $\delta = 9.85$ (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).

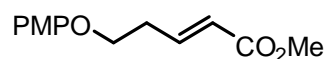
Procedure for the oxidation of alcohol **3.102** to aldehyde **3.103**

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). ¹H-NMR (400 MHz, CDCl₃): 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 H₂ 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 MgSO₄. The crude residue was then purified by flash column chromatography (elution with EtOAc/hexanes mixtures).

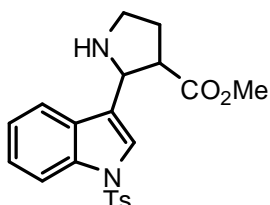

 Reagents employed: **3.103** (0.819 g, 4.54 mmol); **3.106** (1.00 mL, 6.82 mmol); NaH (0.303 g, 7.58 mmol); THF (10 mL); DCM (1 mL); Yielded **3.107** as a yellow oil, 50% (0.537 g, 2.27 mmol). ¹H-NMR (400 MHz, CDCl₃): δ = 7.05 (dt, J = 15.6, 7.0 Hz, 1H), 6.83 (s, 4H), 5.96 (dt, J = 15.6, 1.6 Hz, 1H), 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

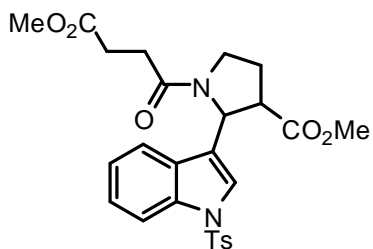
layers were separated. The organic was washed with water, brine and then dried over MgSO_4 . The crude residue was purified by flash column chromatography (elution of EtOAc/hexanes mixtures).



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). $^1\text{H-NMR}$ (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); TMSCHN₂ (0.123 mL, 0.246 mmol); Yielded **3.115** as a colourless oil, 83% (0.052 g, 0.101 mmol). ¹H-NMR (600 MHz, CDCl₃): (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

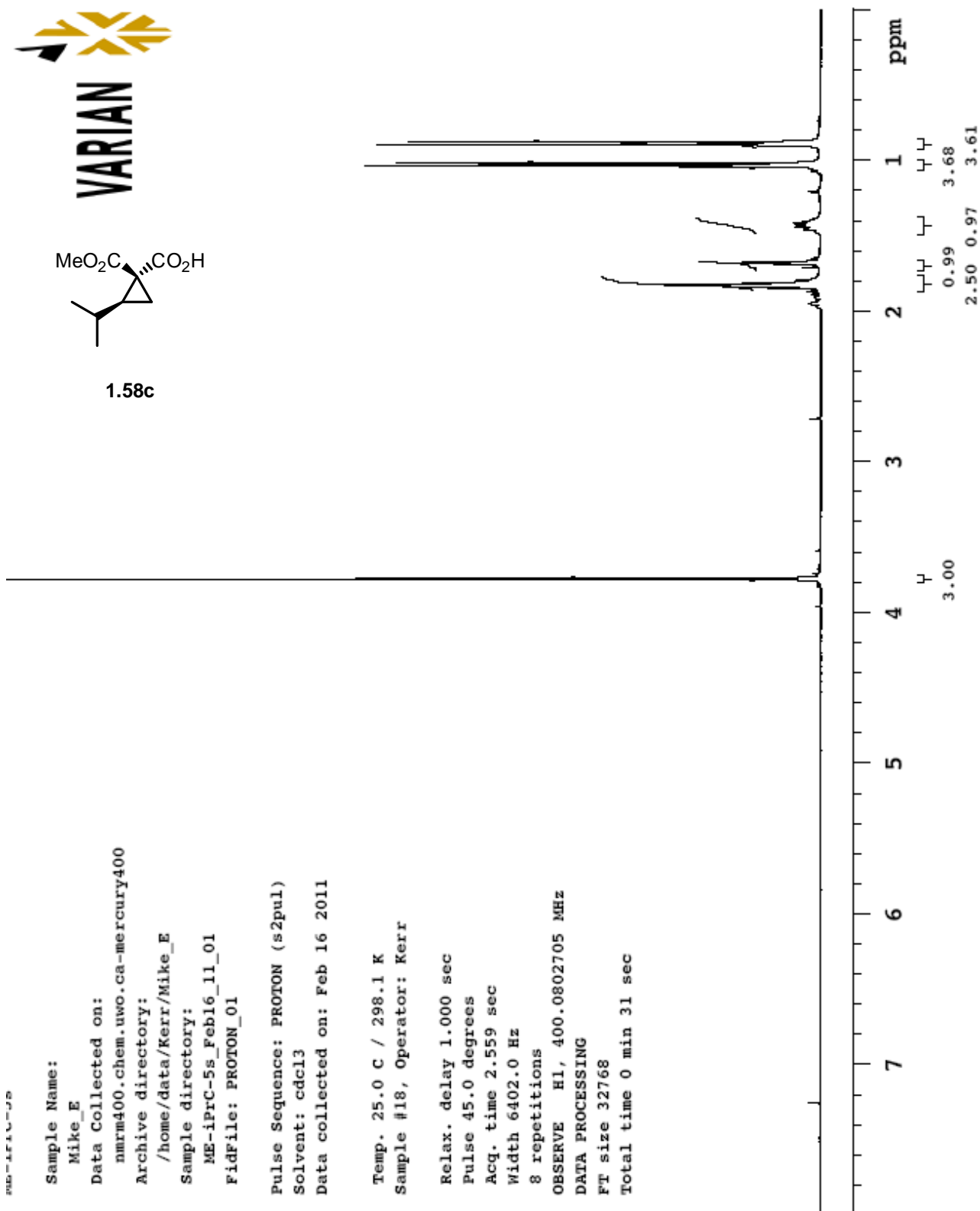
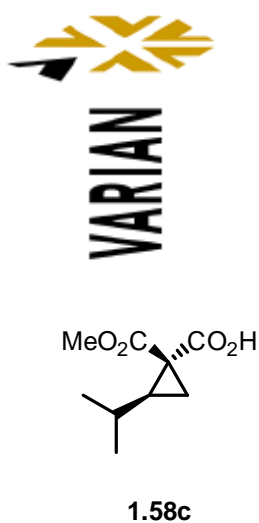
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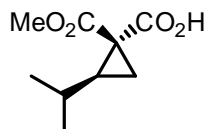
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Total time 0 min 31 sec





VARIAN



1.58c

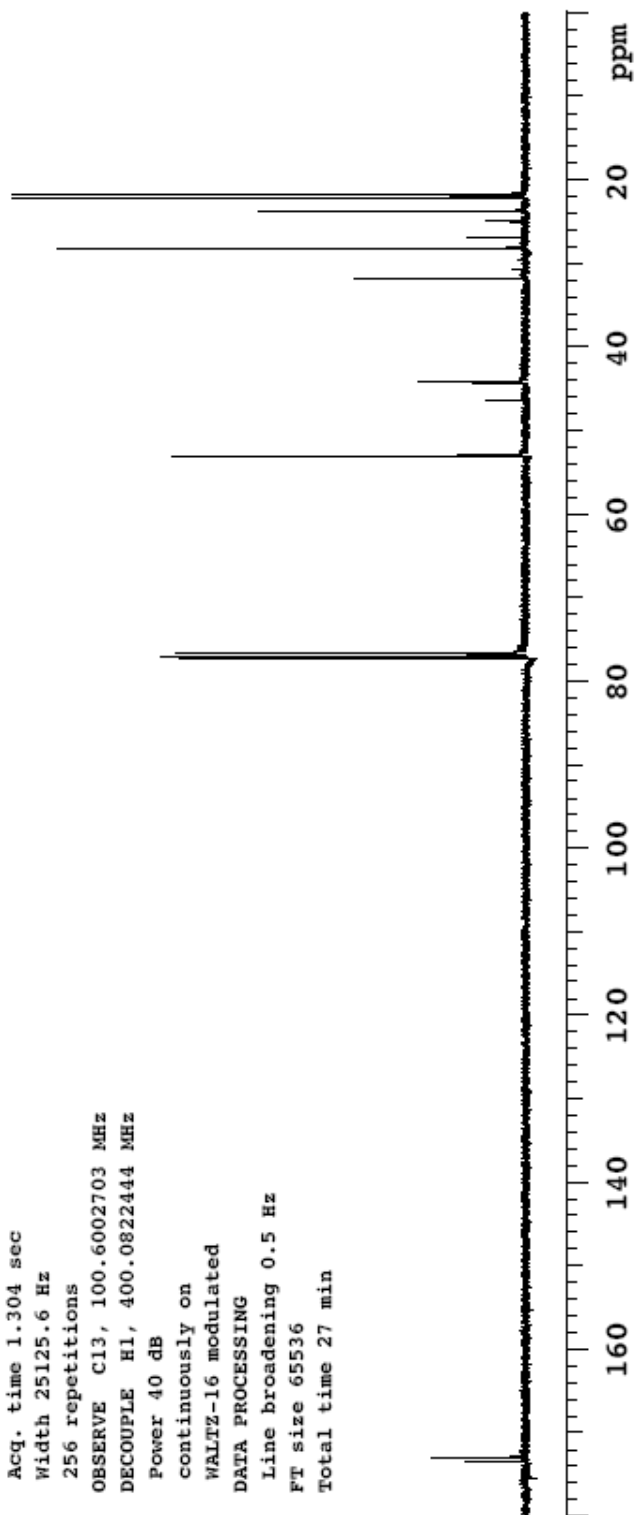
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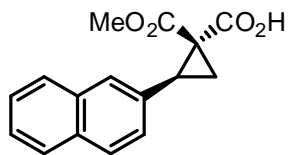
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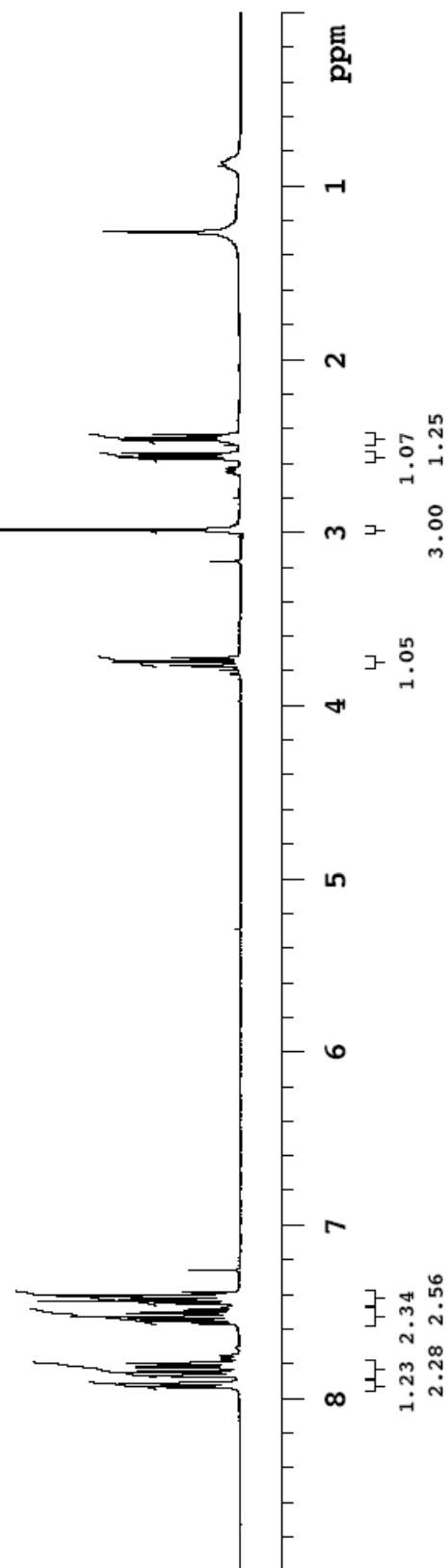
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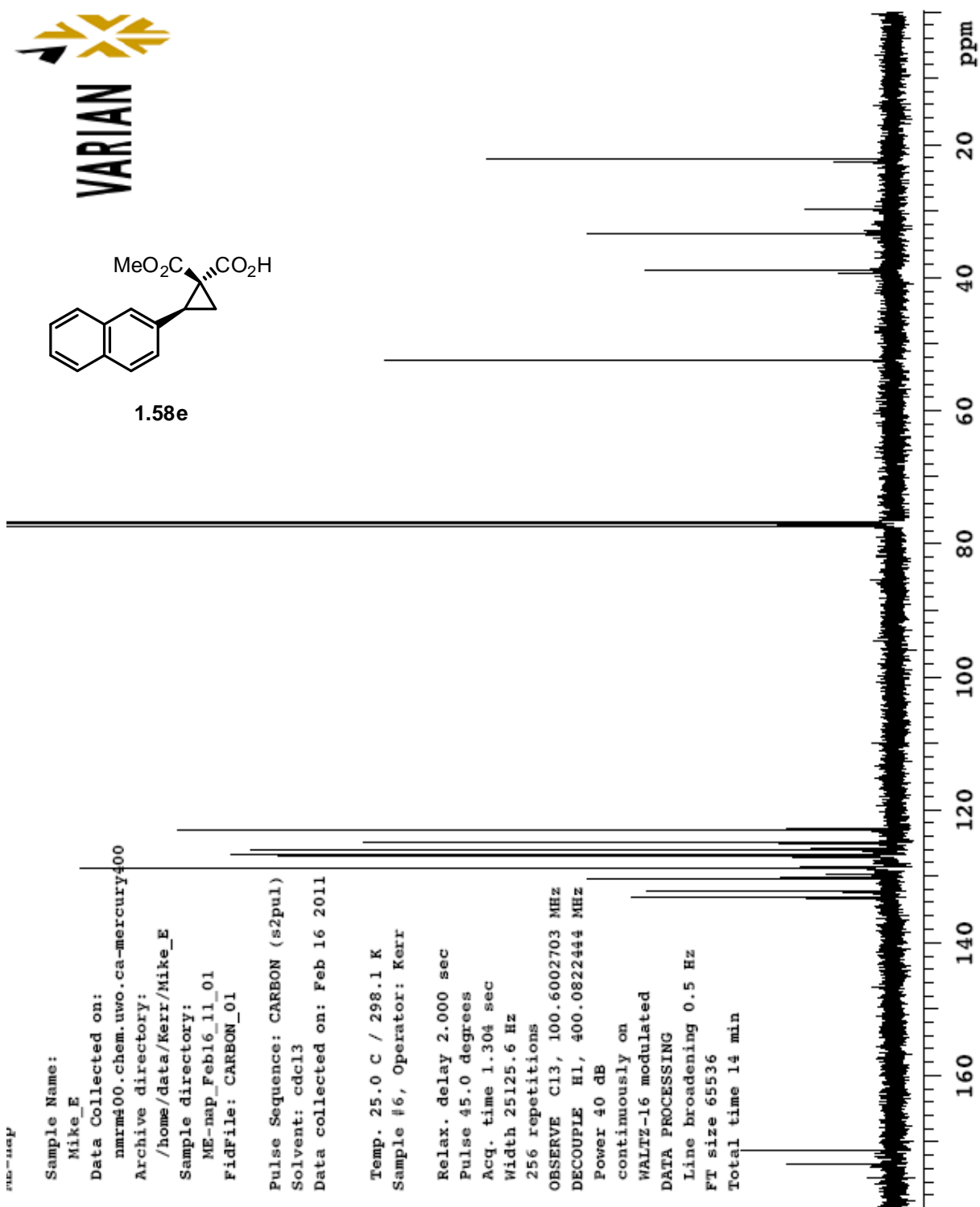
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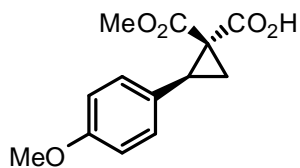
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1.58f

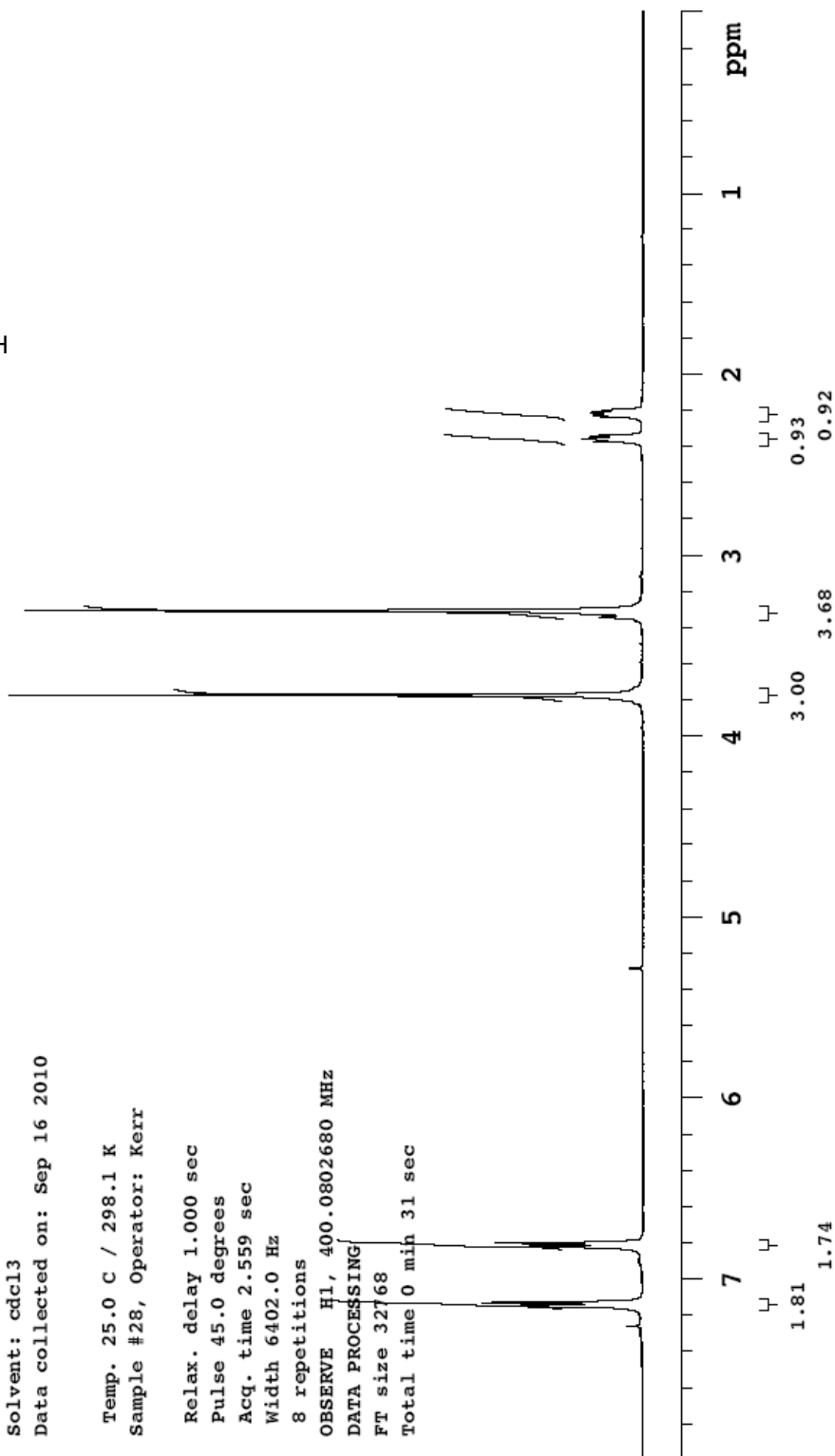
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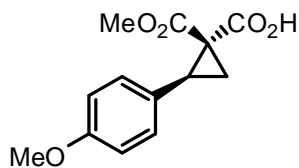
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1.58f

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 DECOUPLE H1, 400.0822444 MHz
 Power 40 dB
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 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 27 min

*** F-F ***

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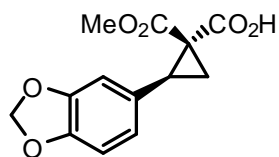
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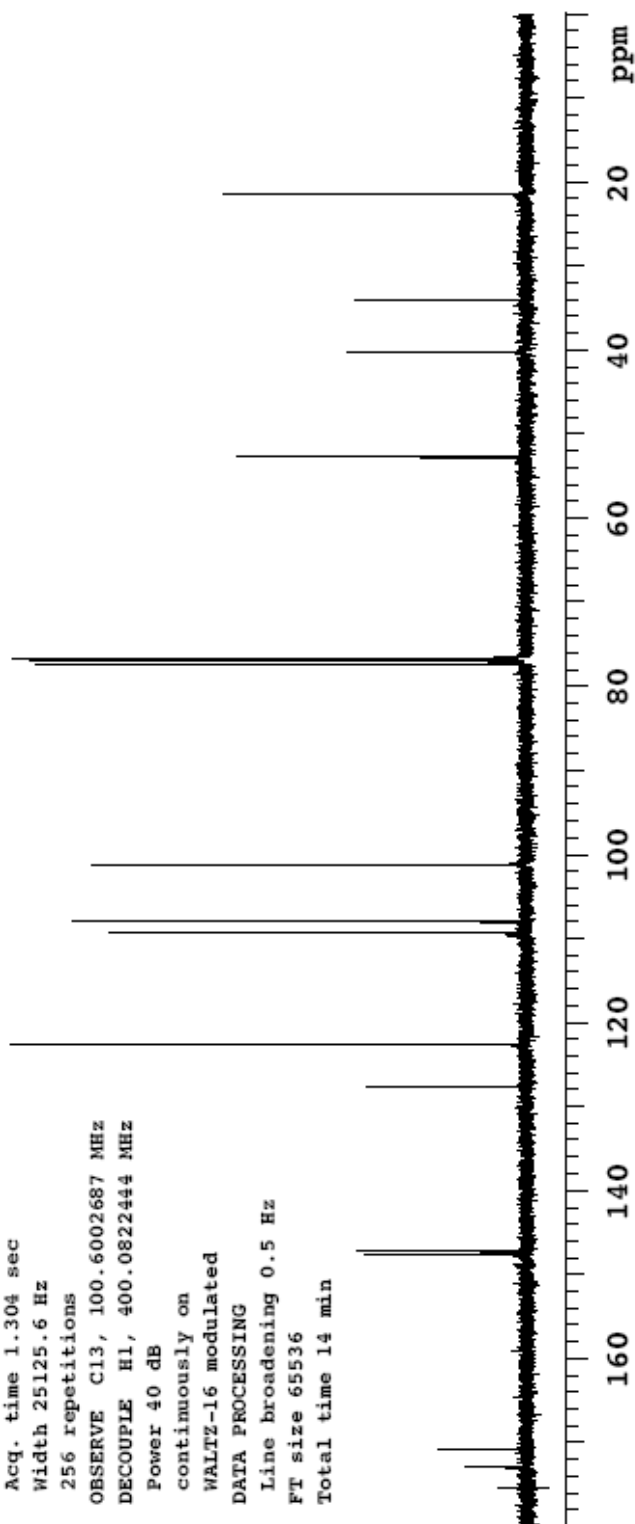
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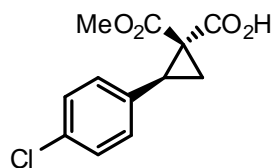


VARIAN



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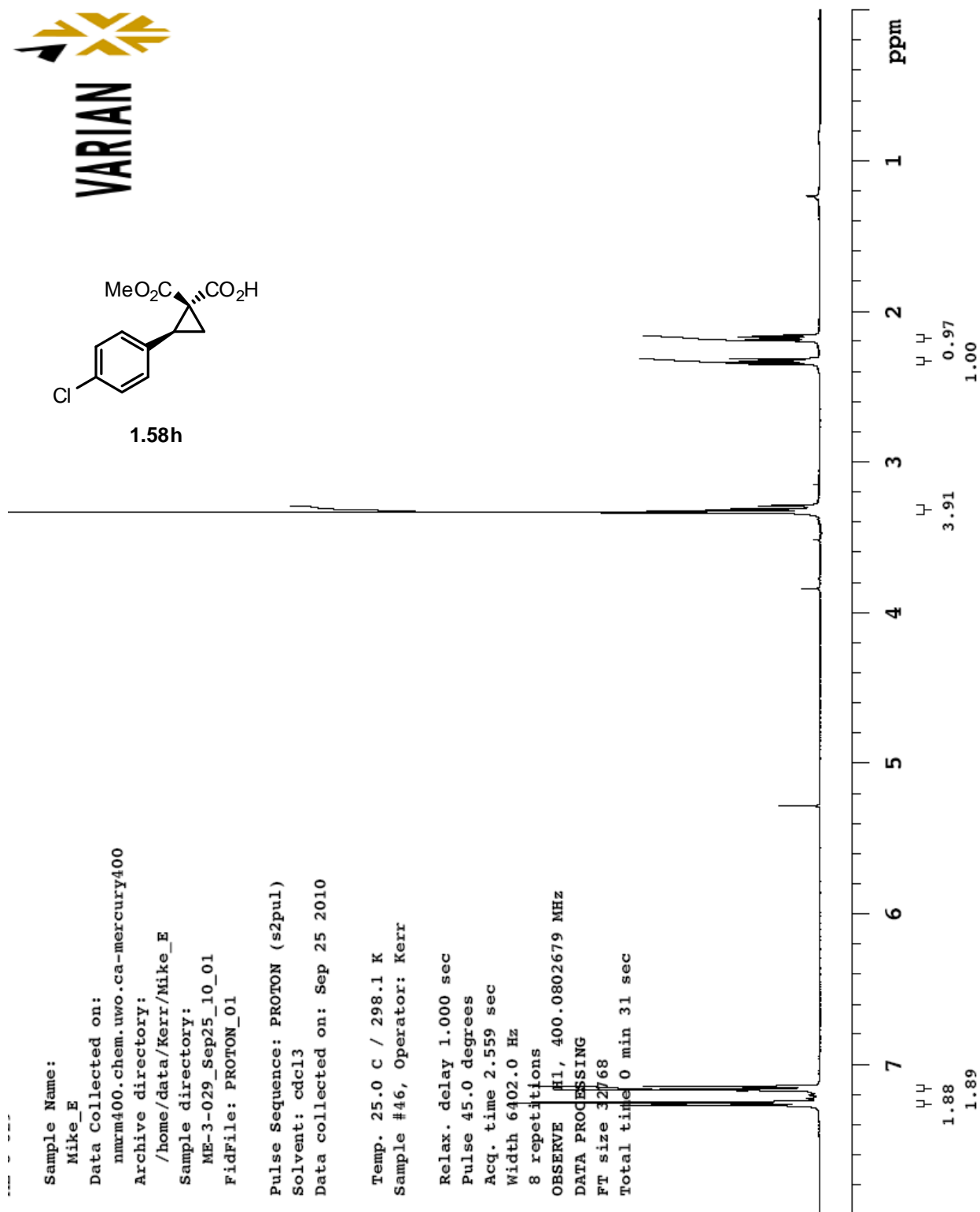
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2

3

4

5

6

7

H H

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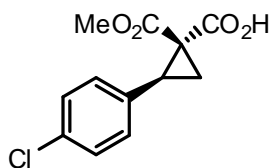
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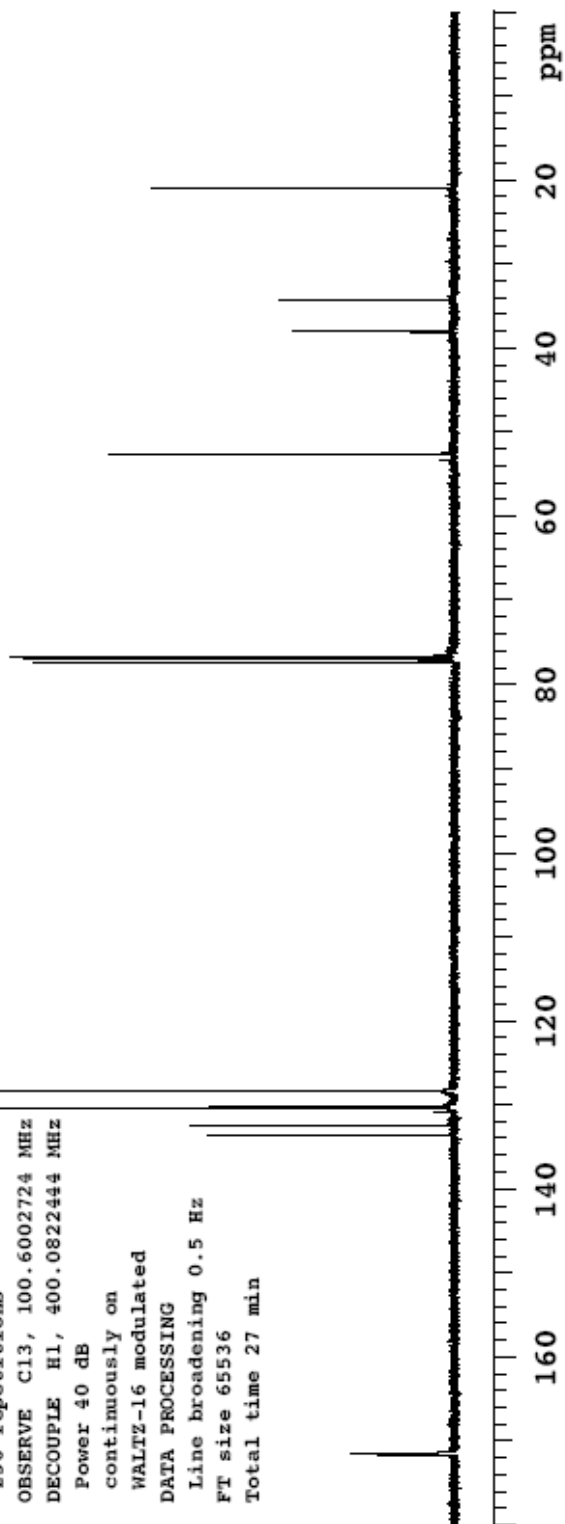
0.97

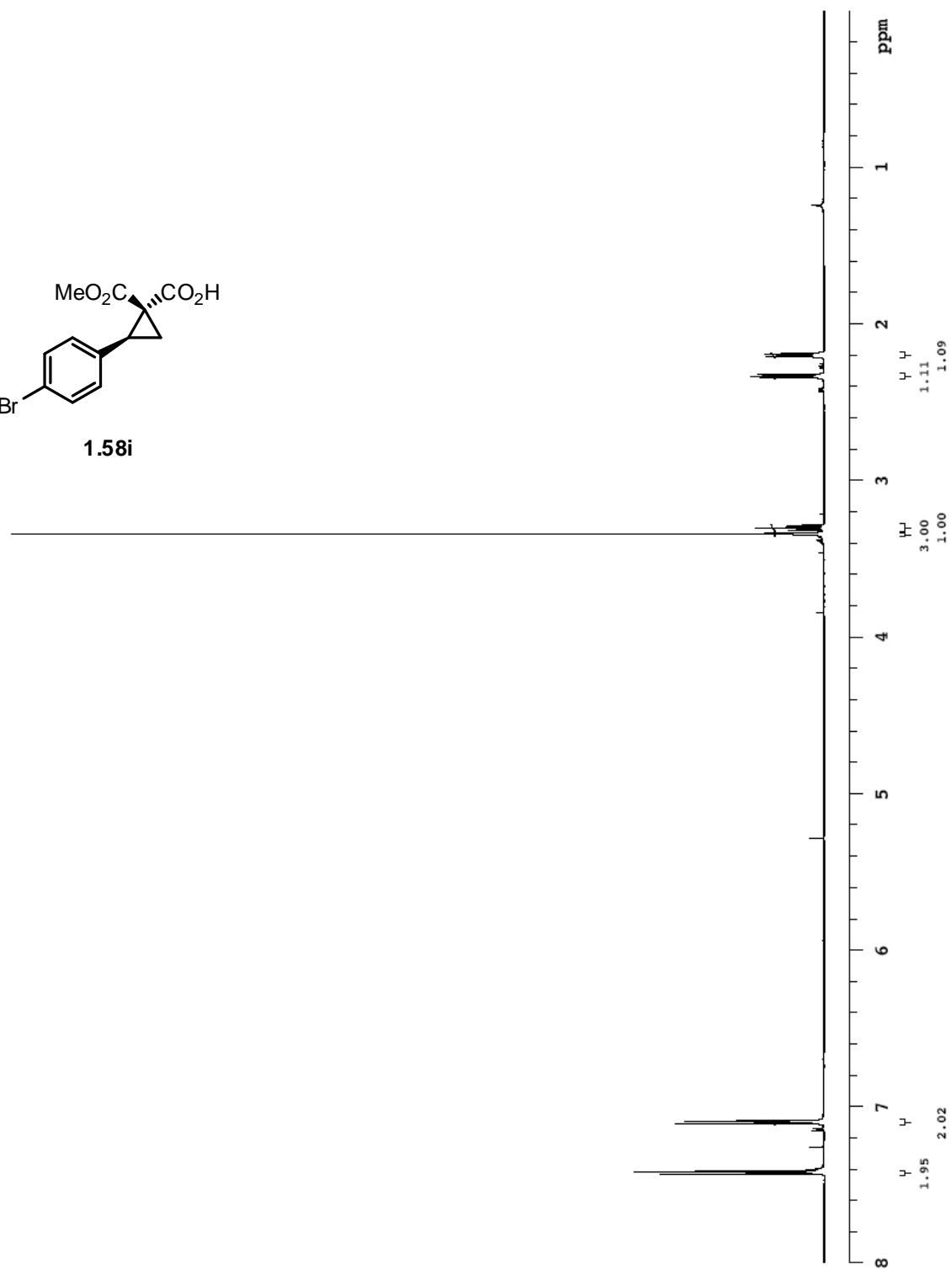
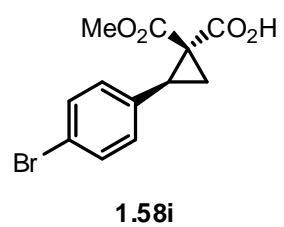
1.00

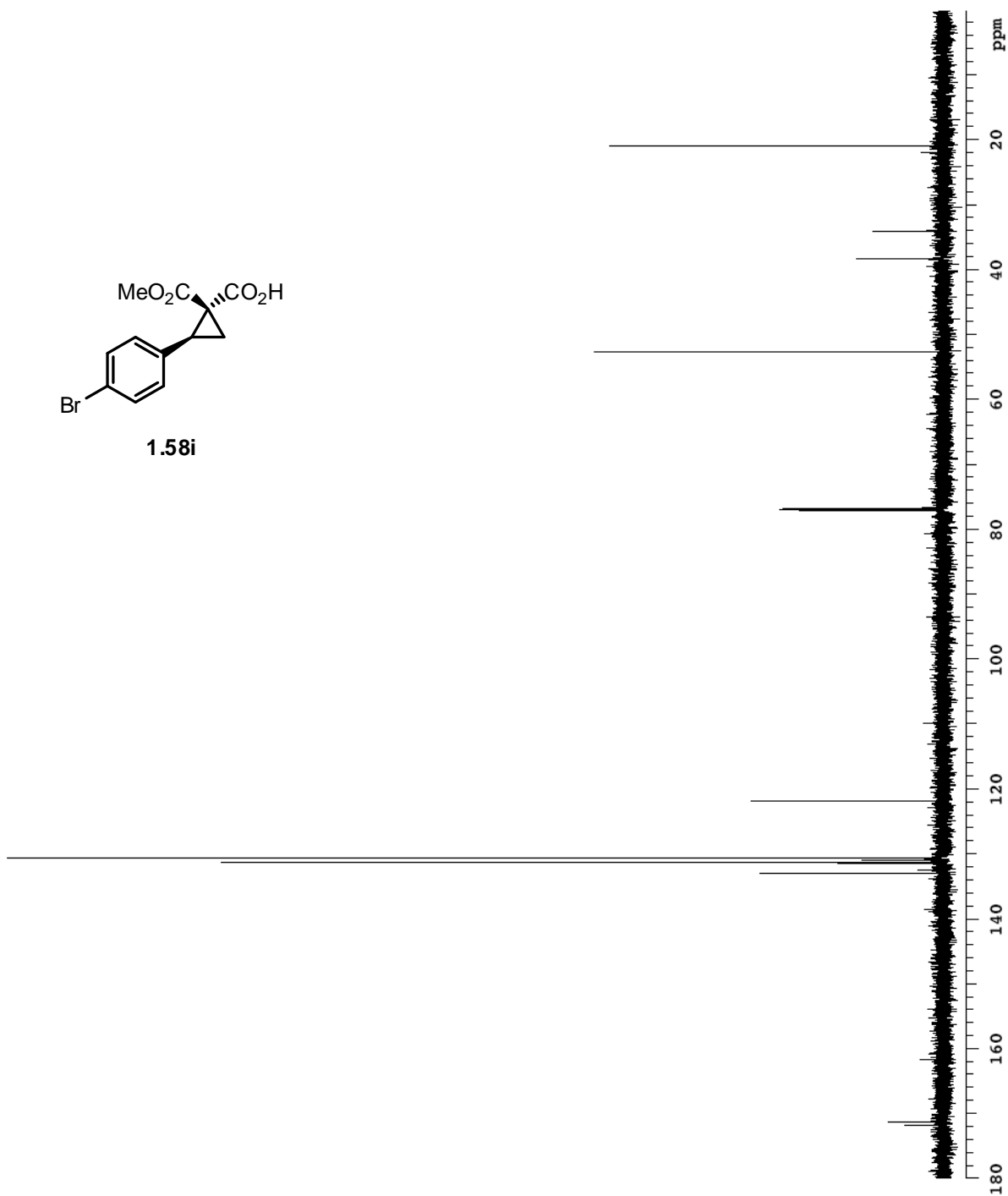
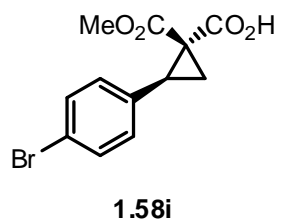


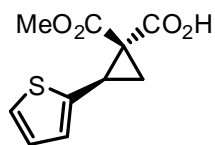
1.58h

Sample Name:
 Mike_E
 Data Collected on:
 nrm400.chem.uwo.ca-mercury400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-3-029_Sep25_10_01
 FidFile: CARBON_01
 Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Sep 25 2010
 Temp. 25.0 C / 298.1 K
 Sample #46, Operator: Kerr
 Relax. delay 5.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 256 repetitions
 OBSERVE C13, 100.6002724 MHz
 DECOUPLE H1, 400.0822444 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 27 min

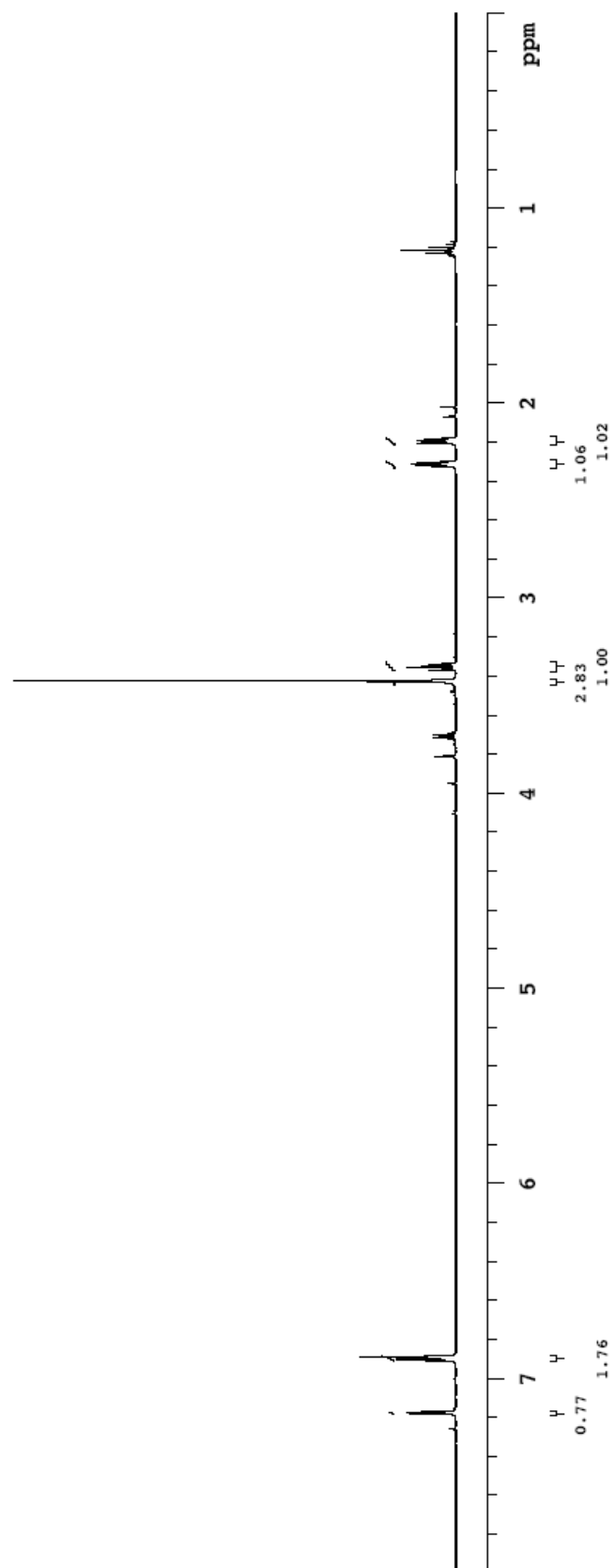


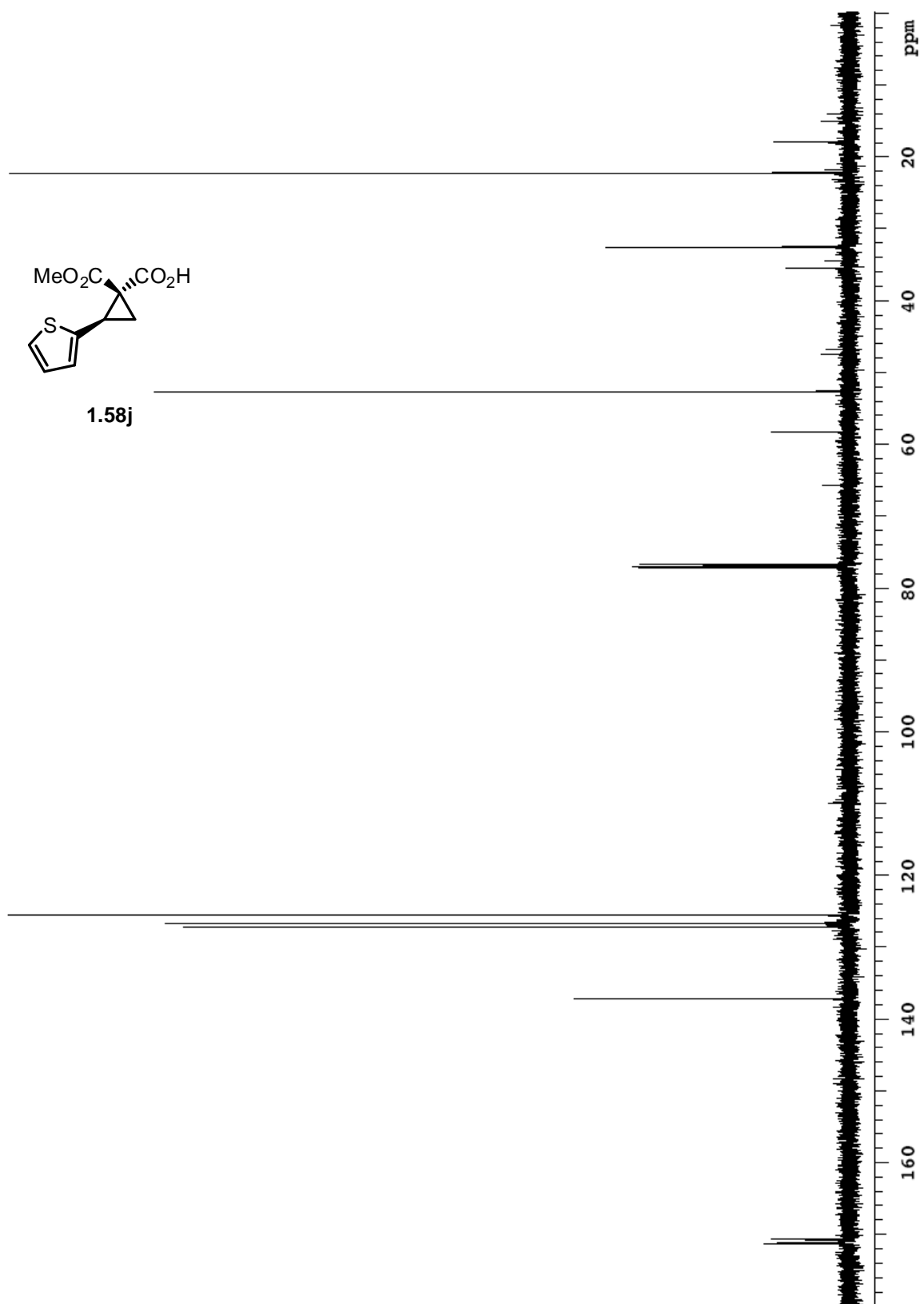






1.58j





ME-PbCNMe

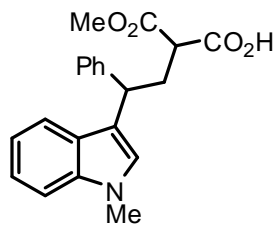
Sample Name:
Mike_E
Data Collected on:
mmrh400.chem.uwo.ca-inova400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-PbCNMe-2_Mar7_11_01
FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 7 2011

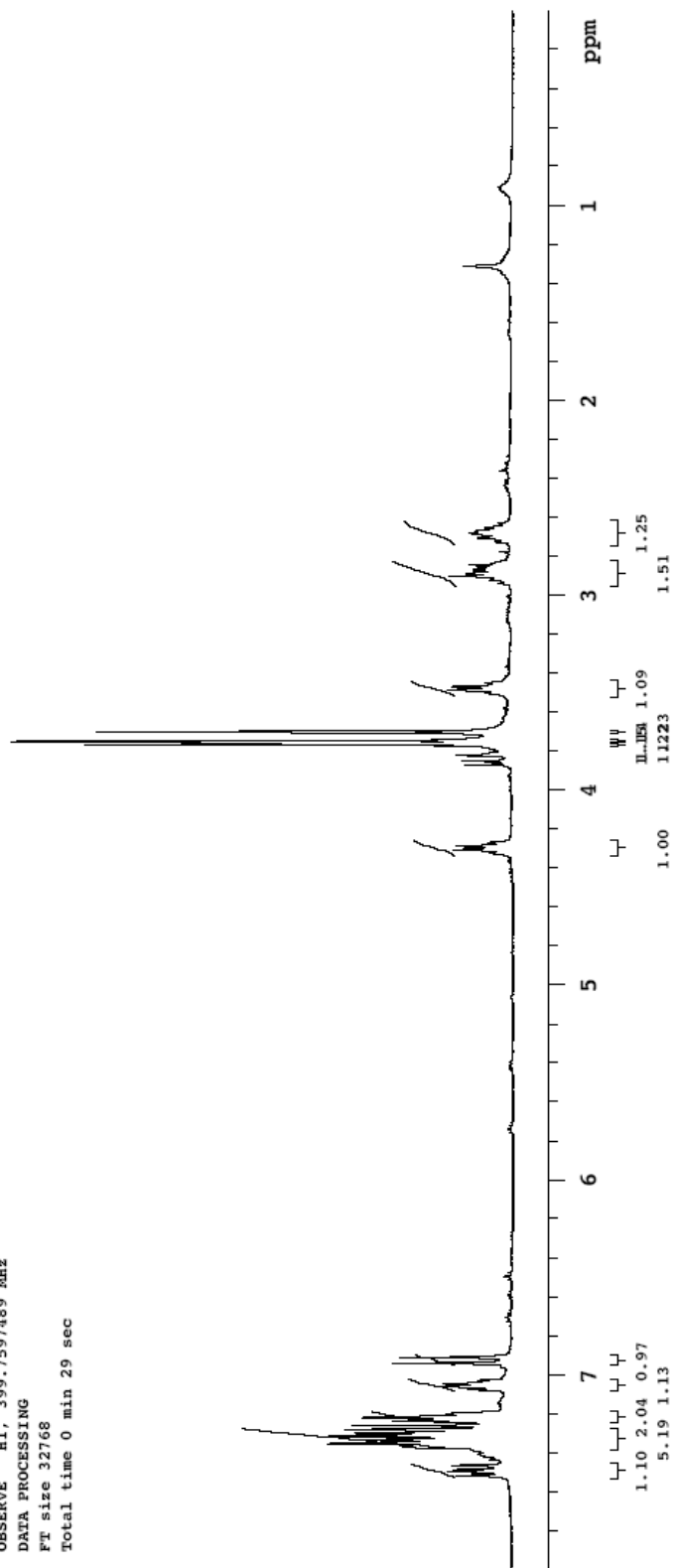
Temp. 25.0 C / 298.1 K
Operator: Kerr

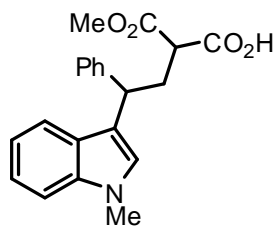
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.6 Hz
8 repetitions

OBSERVE H1, 399.7597489 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 29 sec



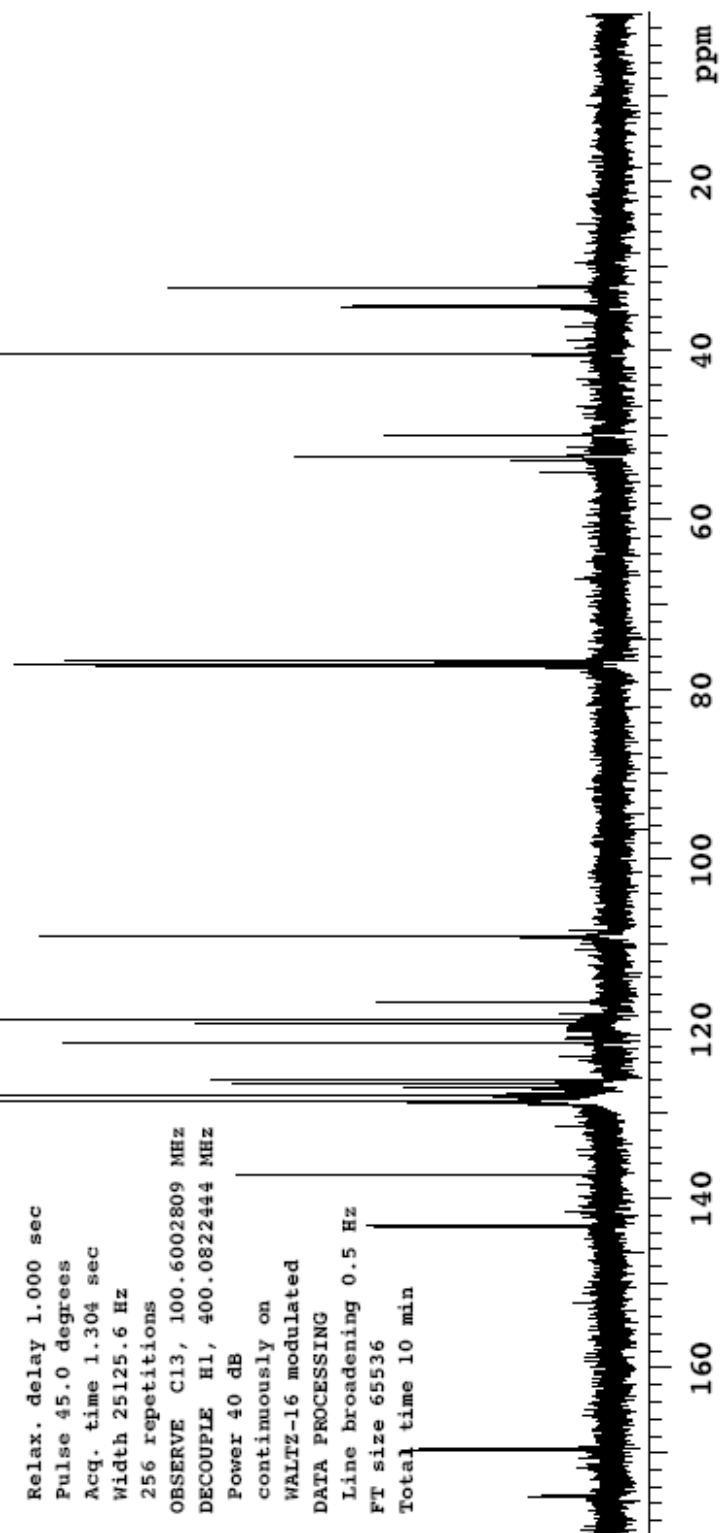
1.65a

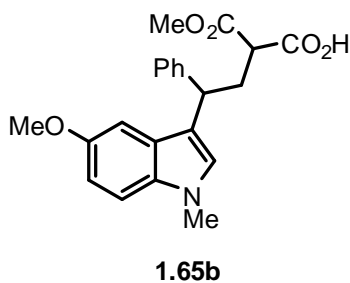




1.65a

Sample Name:
 Mike_E
 Data Collected on:
 nmr400.chem.uwo.ca-mercury400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-2-187col_jun8_10_01
 Fidfile: CARBON_01
 Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Jun 8 2010
 Temp. 25.0 C / 298.1 K
 Sample #8, Operator: Kerr
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 256 repetitions
 OBSERVE C13, 100.6002809 MHz
 DECOUPLE H1, 400.0822444 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 10 min



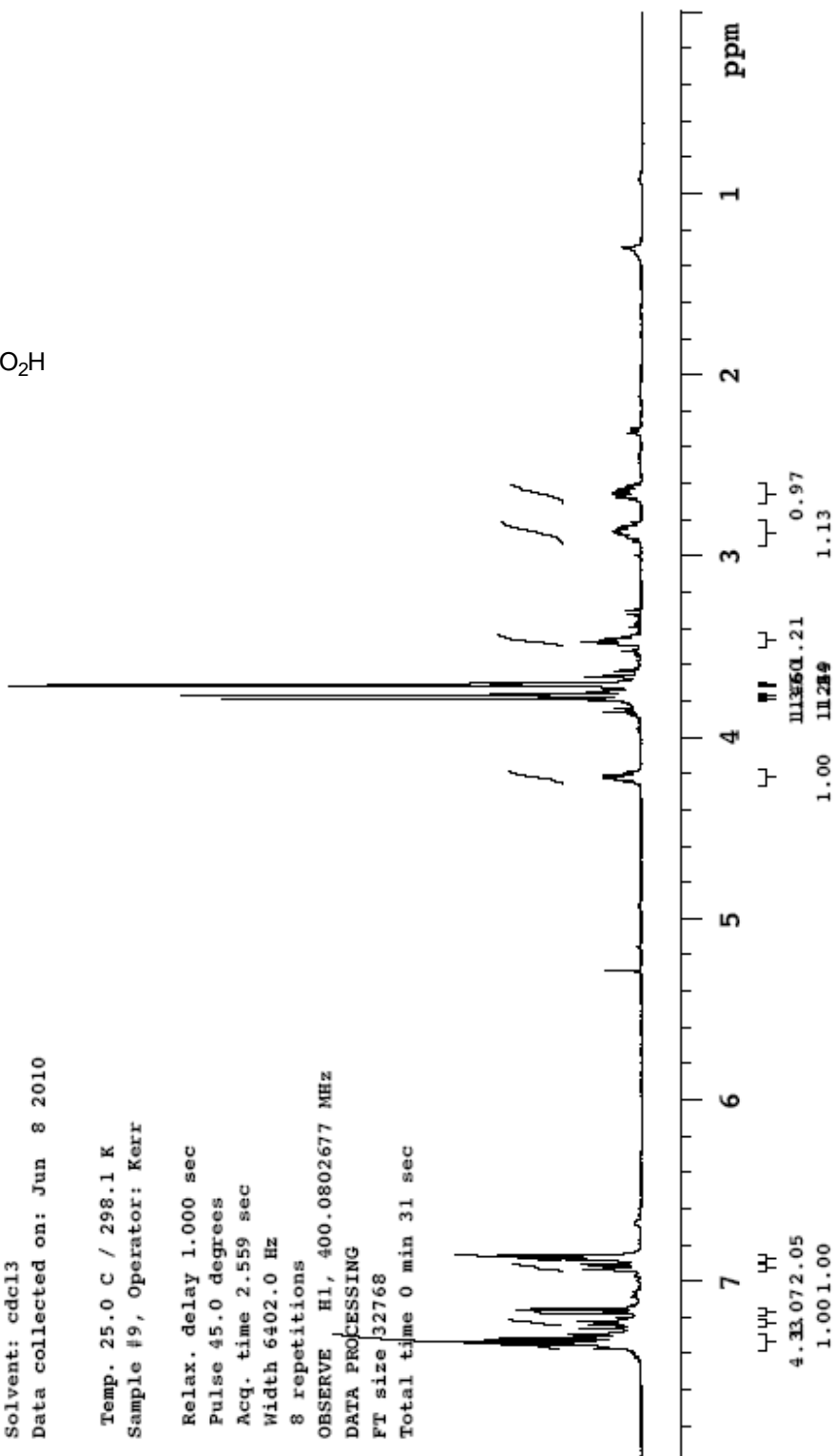


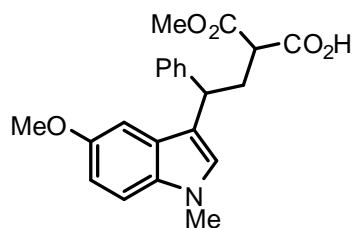
Sample Name:
Mike_E
Data Collected on:
nmrmf00.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-2-191col_Jun8_10_01
Fidfile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 8 2010

Temp. 25.0 C / 298.1 K
Sample #9, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802677 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec



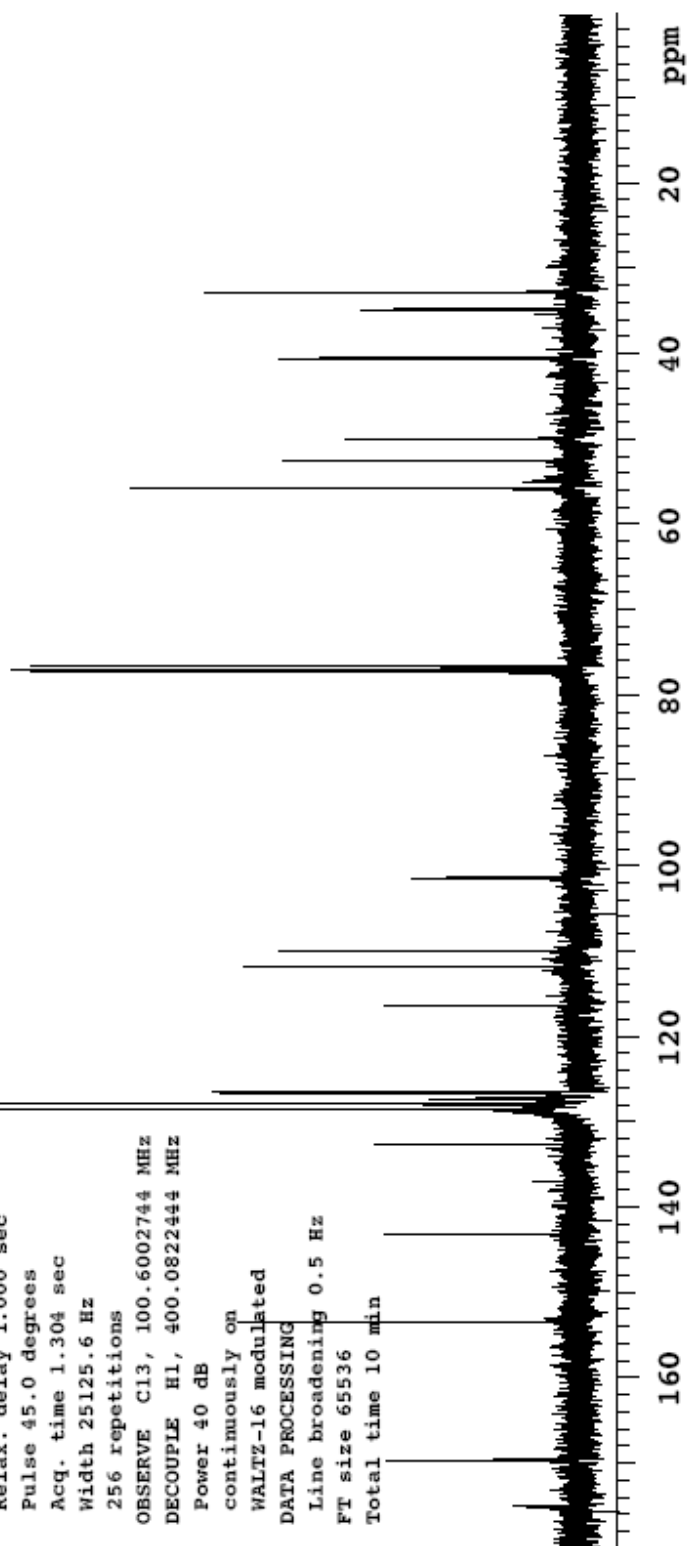


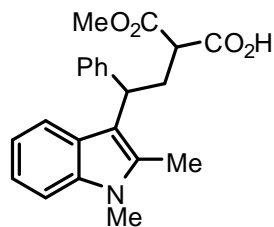
1.65b

Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-2-191col_Jun8_10_01
FidFile: CARBON_01
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 8 2010

Temp. 25.0 C / 298.1 K
Sample #9, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.6002744 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 10 min





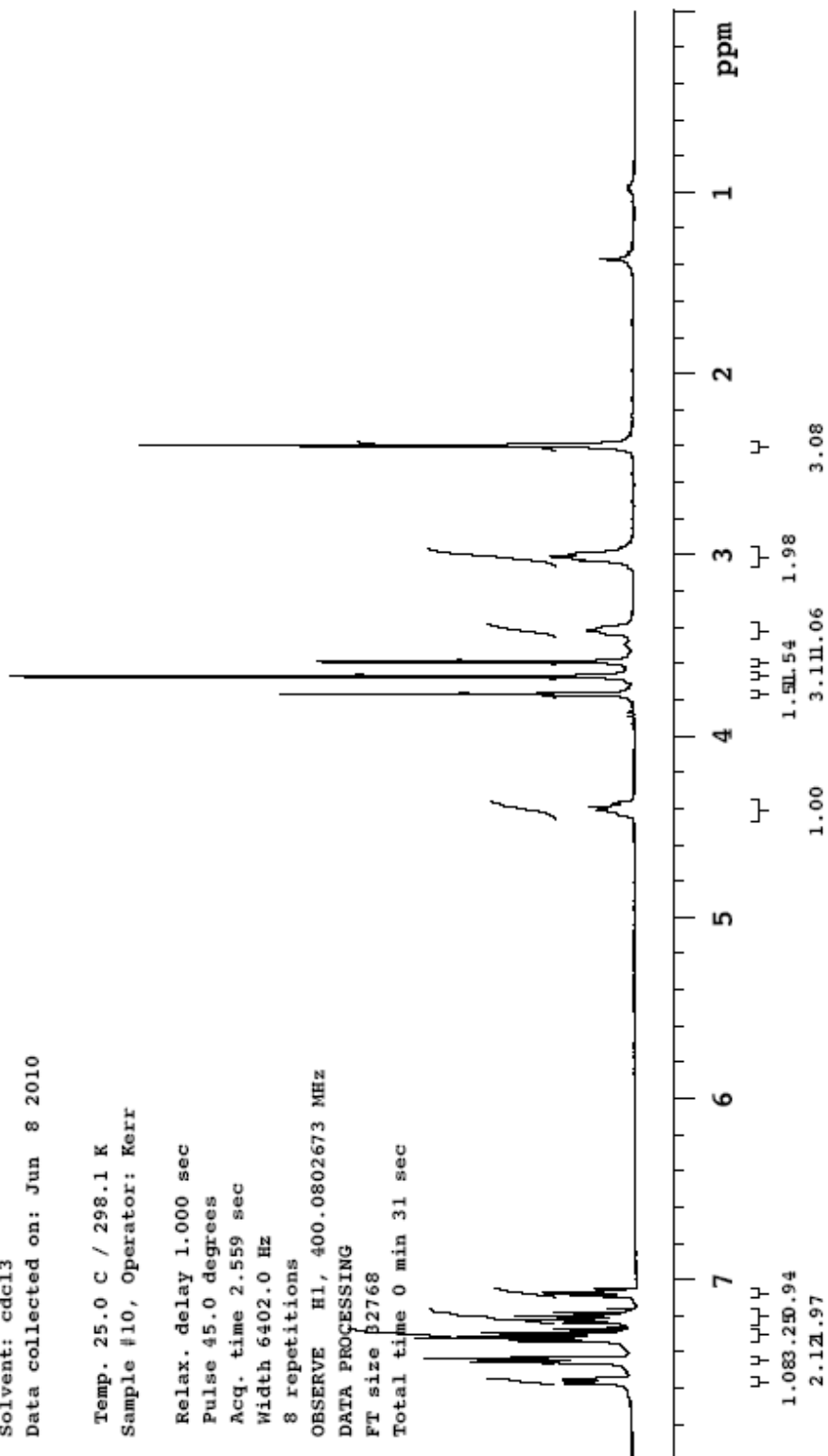
1.65c

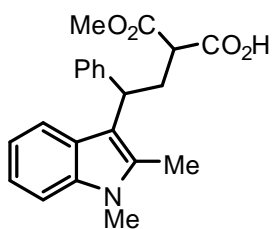
Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-2-195col_Jun8_10_01
FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 8 2010

Temp. 25.0 C / 298.1 K
Sample #10, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802673 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec

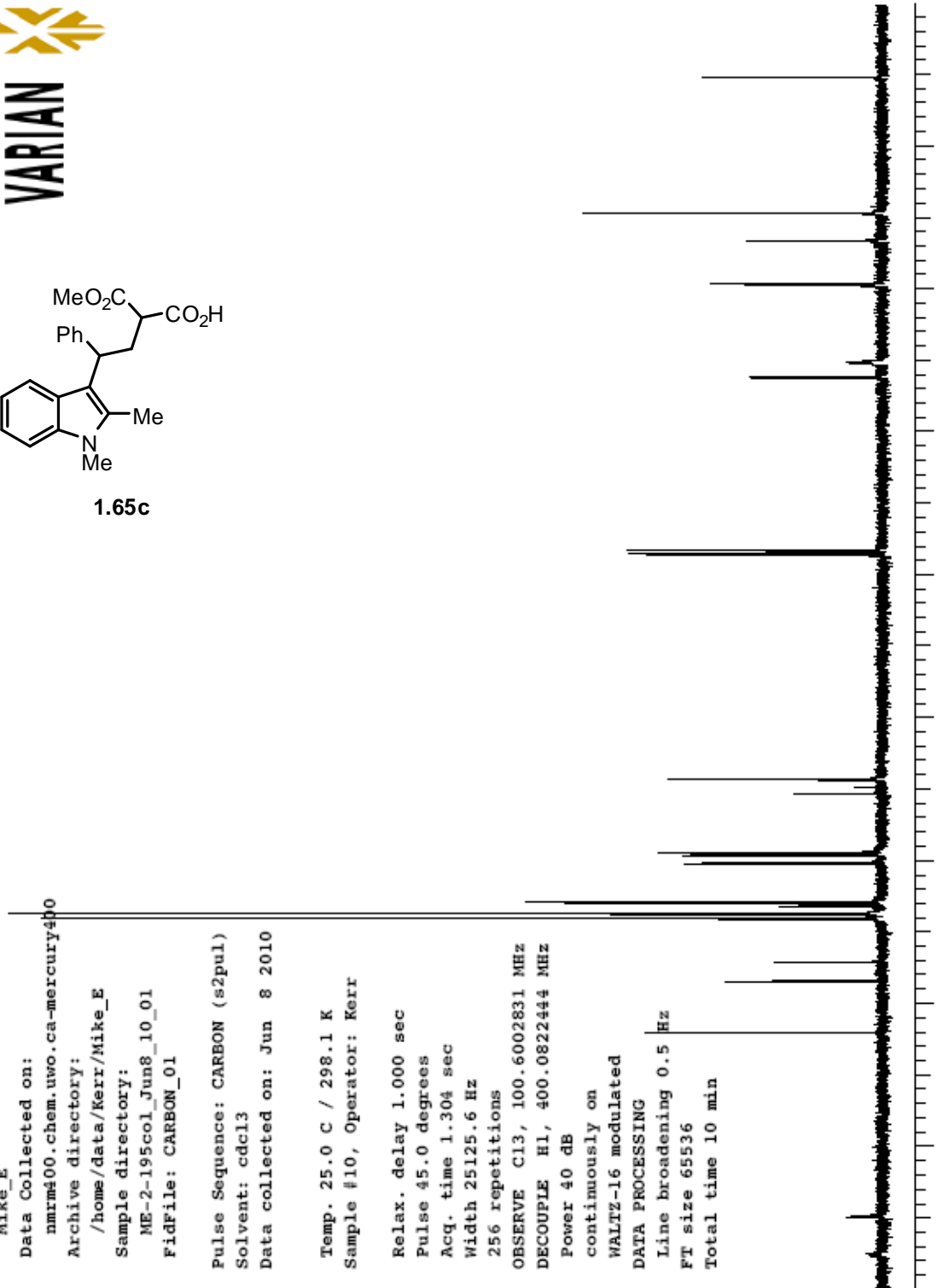


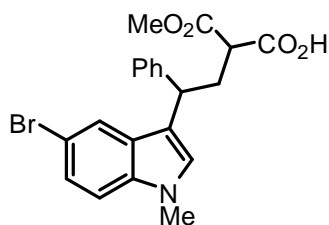


1.65c

Sample Name:
 Mike_E
 Data Collected on:
 nmrm400.chem.uwo.ca-mercury400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-2-195col_Jun8_10_01
 FidFile: CARBON_01
 Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Jun 8 2010
 Temp. 25.0 C / 298.1 K
 Sample #10, Operator: Kerr
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 256 repetitions
 OBSERVE C13, 100.6002831 MHz
 DECOUPLE H1, 400.0822444 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 10 min

160 140 120 100 80 60 40 20 ppm



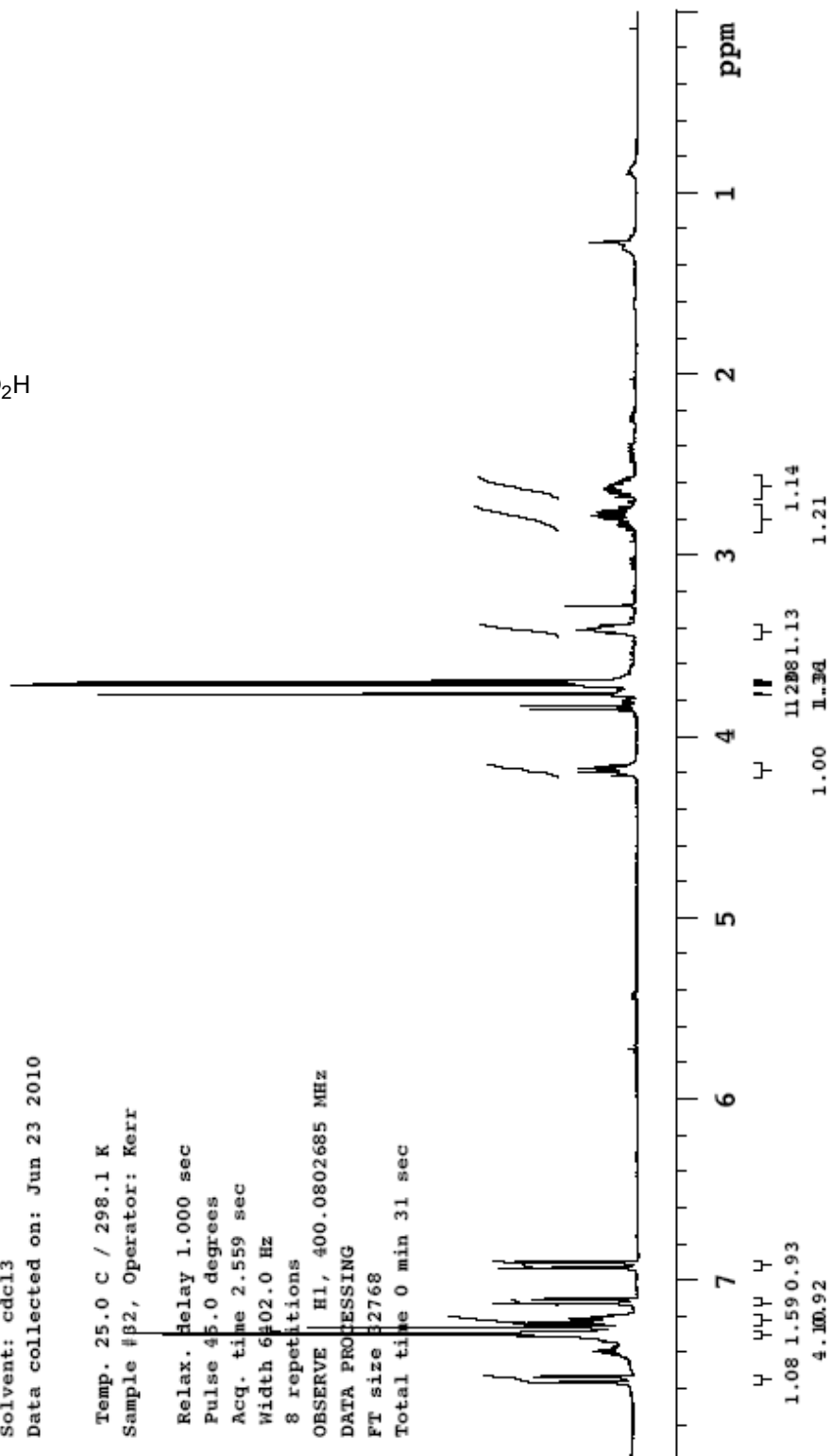


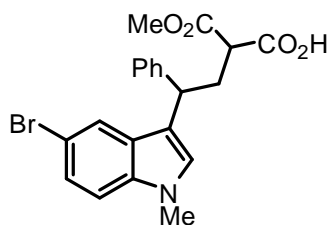
1.65d

Sample Name:
Mike_E
Data Collected on:
nrmr400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-003p_Jun23_10_01
FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 23 2010

Temp. 25.0 C / 298.1 K
Sample #82, Operator: Kerr
Relax. Helay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802685 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec

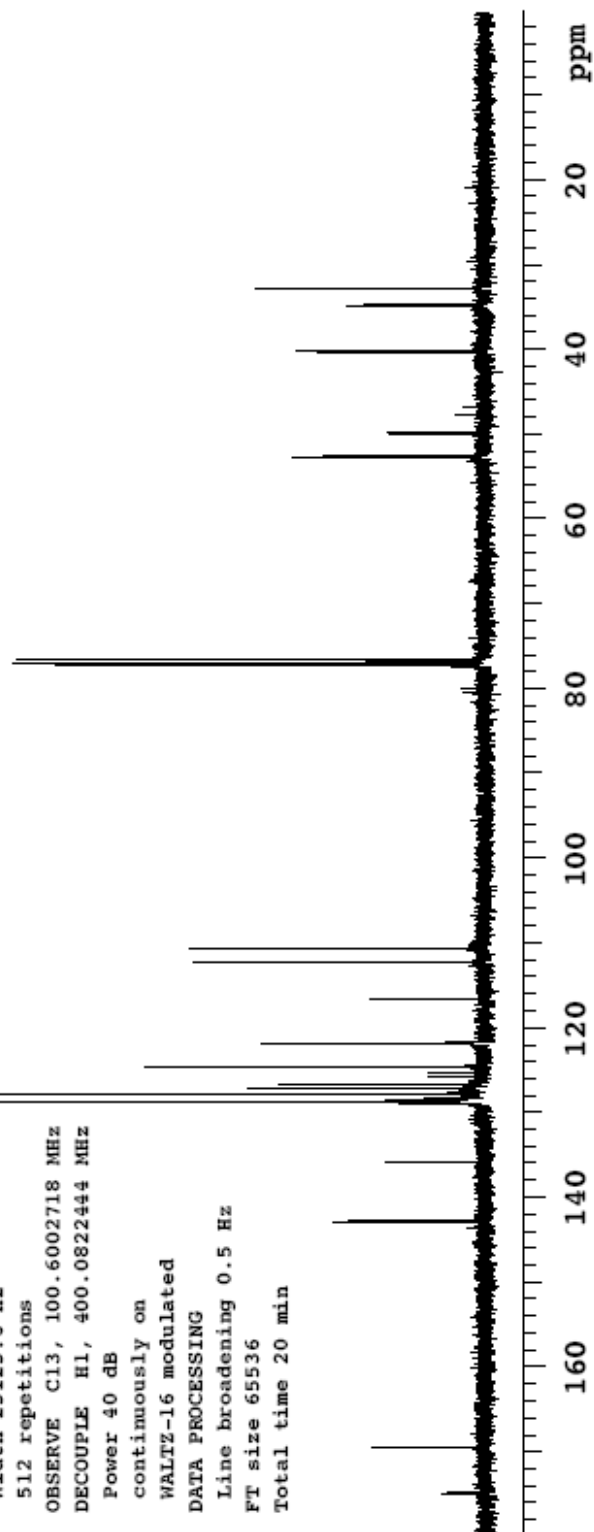


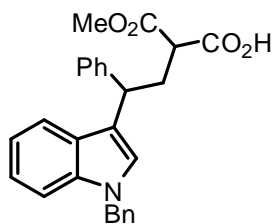


1.65d

Sample Name:
 Mike_E
 Data Collected on:
 nmrm400.chem.uwo.ca-mercury400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-2-199char_Jun16_10_01
 FidFile: CARBON_01
 Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Jun 16 2010
 Temp. 25.0 C / 298.1 K
 Sample #17, Operator: Kerr

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 512 repetitions
 OBSERVE C13, 100.6002718 MHz
 DECOUPLE H1, 400.0822444 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 20 min





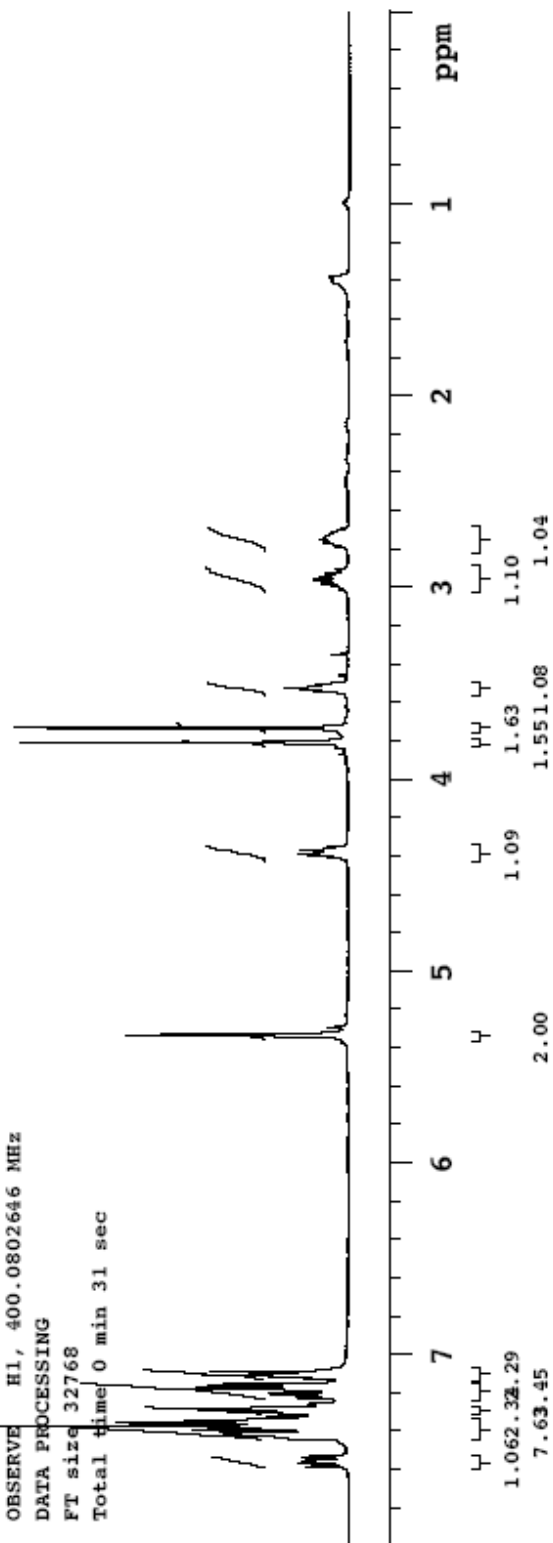
1.65e

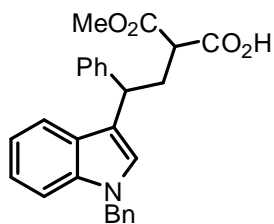
Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-007p_Jun24_10_01
FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jun 24 2010

Temp. 25.0 C / 298.1 K
Sample #7, Operator: Kerr

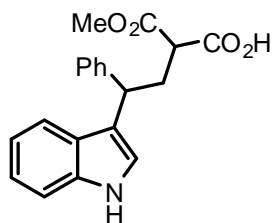
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 5402.0 Hz
8 repetitions
OBSERVE H1, 400.0802646 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





1.65e

Sample Name: Mike_E
 Data Collected on: nmrm400.chem.uwo.ca-mercury400
 Archive directory: /home/data/kerr/Mike_E
 Sample directory: ME-3-007P_Jun24_10_01
 FidFile: CARBON_01
 Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Jun 24 2010
 Temp. 25.0 C / 298.1 K
 Sample #7, Operator: Kerr
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 512 repetitions
 OBSERVE C13, 100.6002822 MHz
 DECOUPLE H1, 400.0822444 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 20 min



1.65f

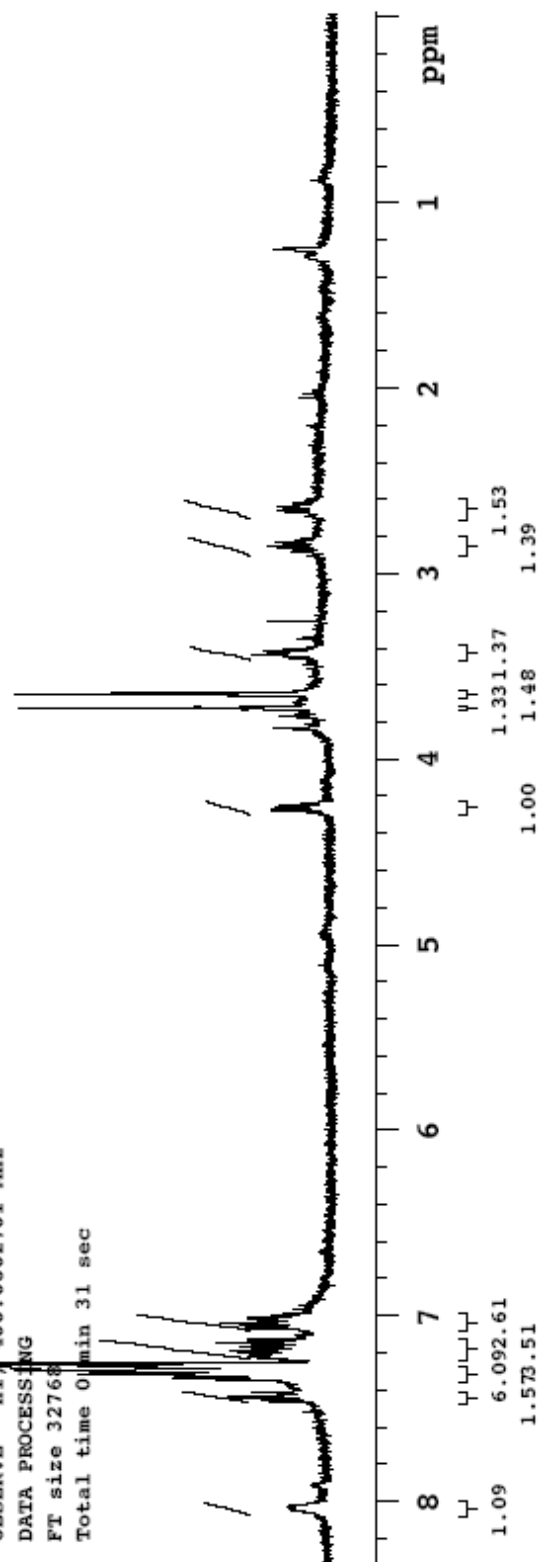
Sample Name: Mike_E
 Data Collected on: nmrms00.chem.uwo.ca-mercury400
 Archive directory: /home/data/Kerr/Mike_E
 Sample directory: ME-2-205p_Jun21_10_01
 FidFile: PROTON_01

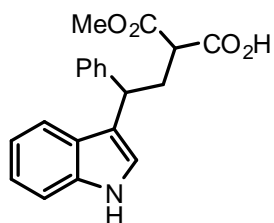
Pulse Sequences: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jun 21 2010

Temp. 25.0 C / 298.1 K
 Sample #5, Operator: Kerr

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.559 sec
 Width 6402.0 Hz
 8 repetitions

OBSERVE H1 / 400.0802701 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0min 31 sec





1.65f

Sample Name:
Mike_E

Data Collected on:
nmrm400.chem.uwo.ca-mercury400

Archive directory:
/home/data/kerr/Mike_E

Sample directory:
ME-2-205char_Jun16_10_01

FidFile: CARBON_01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jun 16 2010

Temp. 25.0 C / 298.1 K

Sample #18, Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.304 sec

Width 25125.6 Hz

512 repetitions

OBSERVE C13, 100.6002757 MHz

DECOUPLE H1, 400.0822444 MHz

Power 40 dB

continuously on

WALTZ-16 modulated

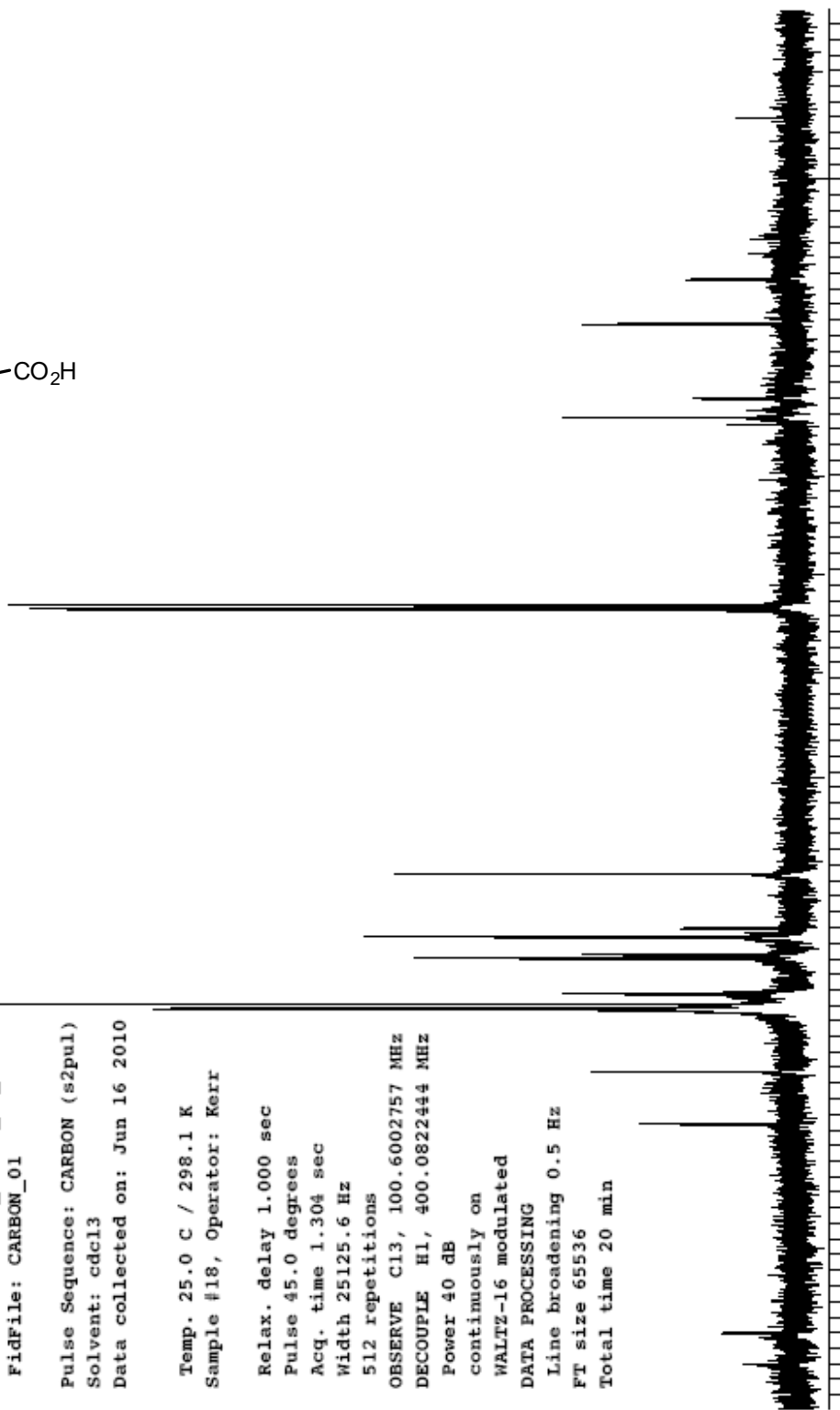
DATA PROCESSING

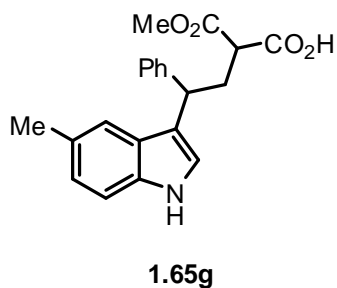
Line broadening 0.5 Hz

FT size 65536

Total time 20 min

160 140 120 100 80 60 40 20 ppm





Sample Name:
Mike_E

Data Collected on:
nmrms400.chem.uwo.ca-mercury400

Archive directory:
/home/data/Kerr/Mike_E

Sample directory:
ME-5MeNHPh-2_Mar9_11_01

FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Mar 9 2011

Temp. 25.0 C / 298.1 K

Sample #9, Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.559 sec

Width 6402.0 Hz

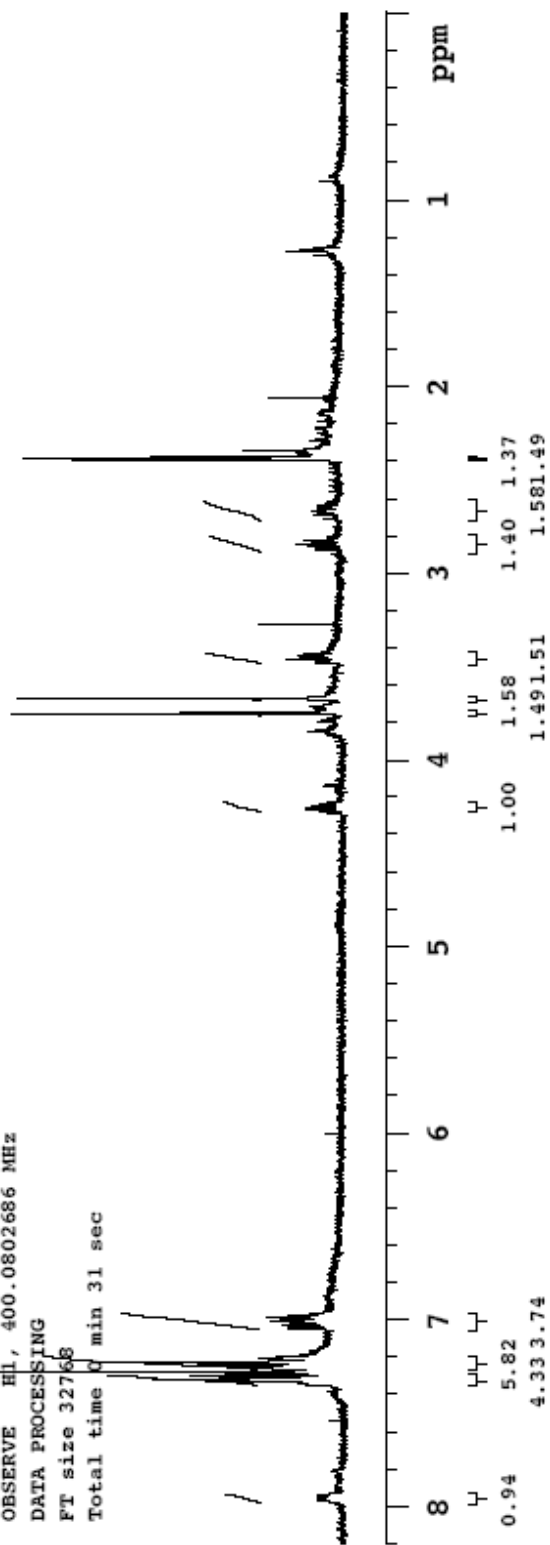
8 repetitions

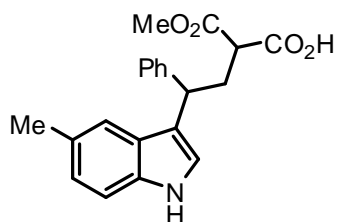
OBSERVE H1, 400.0802686 MHz

DATA PROCESSING

FT size 32768

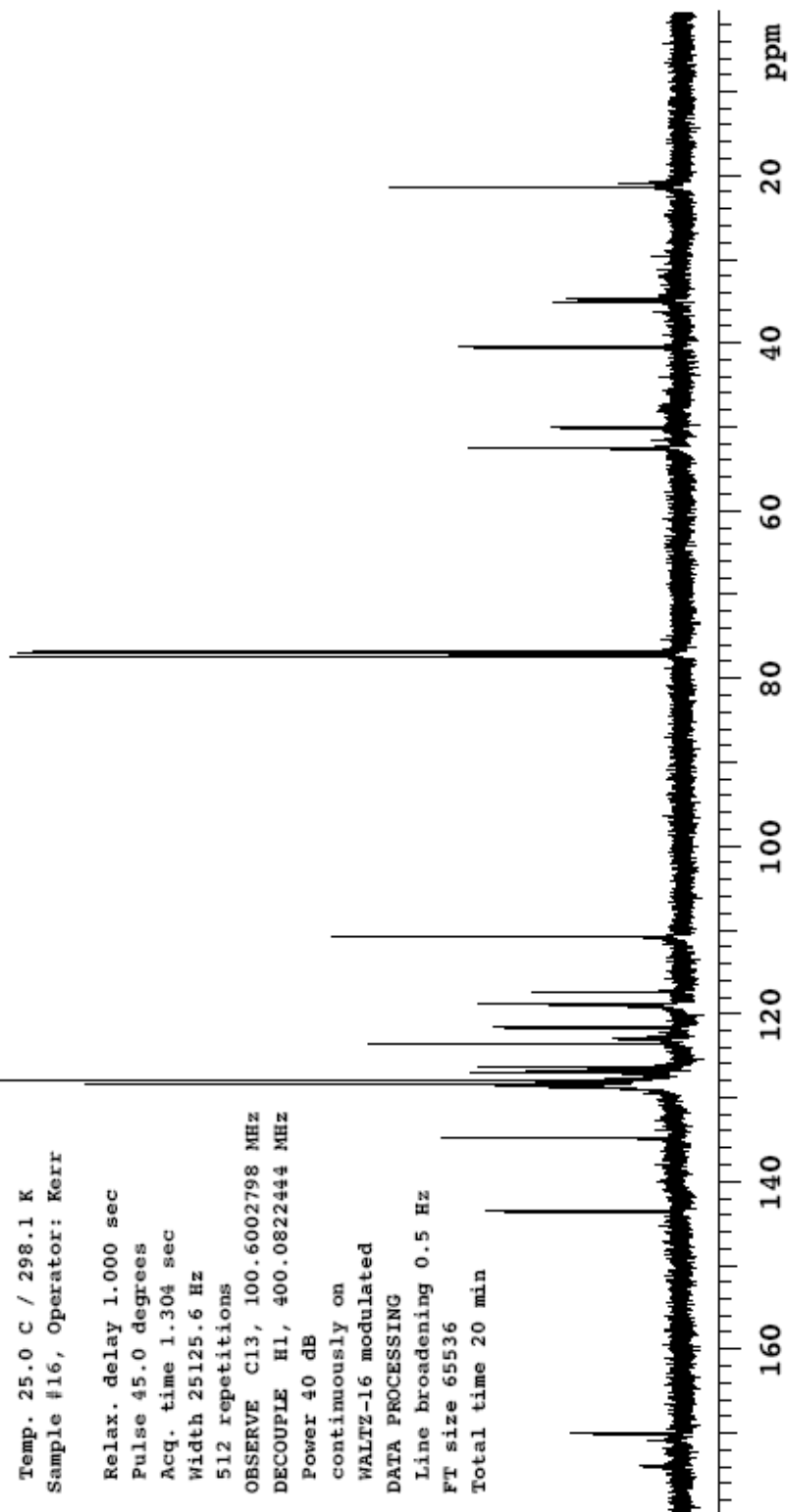
Total time 0 min 31 sec

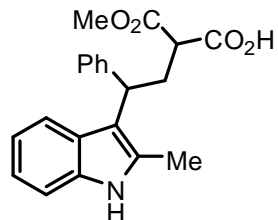




1.65g

Sample Name:
 Mike_E
 Data Collected on:
 nmrm400.chem.uwo.ca-mercury400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-3-01lp_Jun29_10_01
 FidFile: CARBON_01
 Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Jun 29 2010
 Temp. 25.0 C / 298.1 K
 Sample #16, Operator: Kerr
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.304 sec
 Width 25125.6 Hz
 512 repetitions
 OBSERVE C13, 100.6002798 MHz
 DECOUPLE H1, 400.0822444 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 20 min





1.65h

ME-3-003

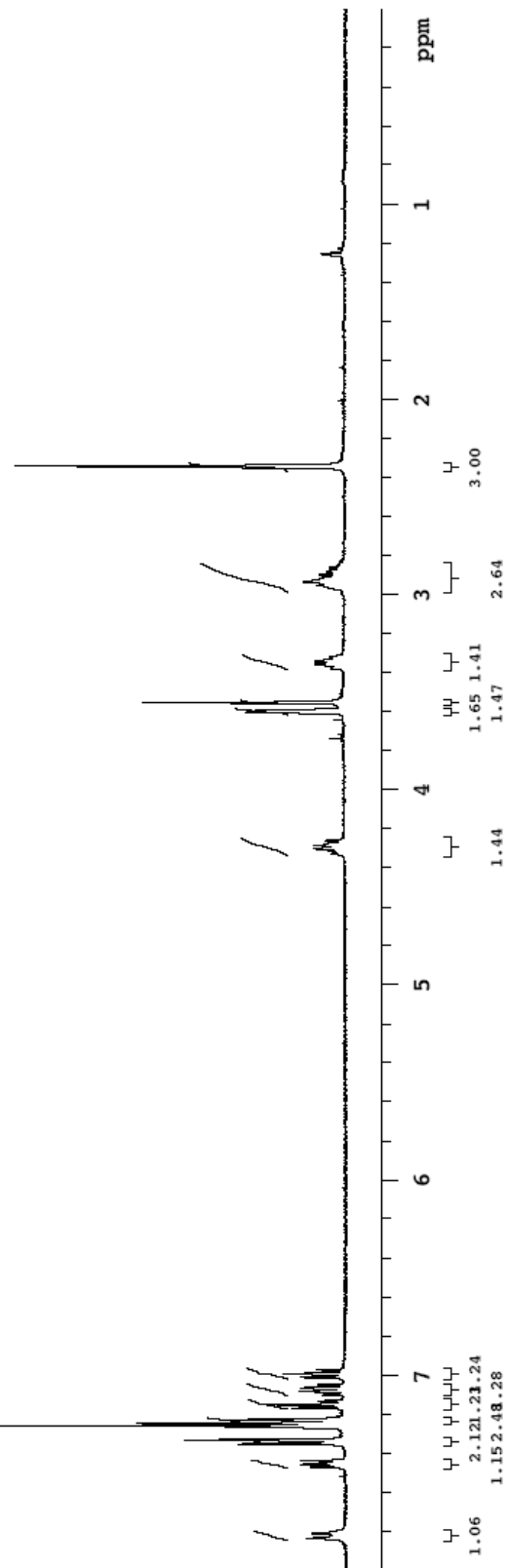
Sample Name: Mike_E
 Data Collected on: nmrrh400.chem.uwo.ca-inova400
 Archive directory: /home/data/Kerr/Mike_E
 Sample directory: ME-3-003_sep15_10_01
 Fidfile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Sep 15 2010

Temp. 25.0 C / 298.1 K
 Operator: Keir

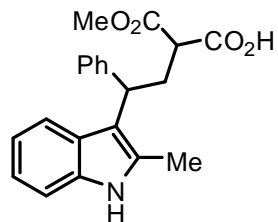
Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.559 sec
 Width 6402.6 Hz
 8 repetitions

OBSERVE H1 399.7597473 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 29 sec





VARIAN



1.65h

Sample Name:
Mike_E
Data Collected on:
nmrmd00.chem.uwo.ca-mercury400

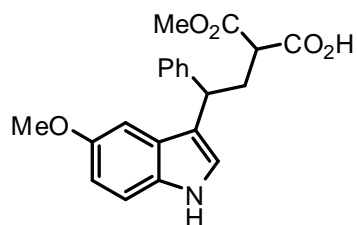
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-003p_Jun21_10_01
FidFile: CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 21 2010

Temp. 25.0 C / 298.1 K
Sample #6, Operator: Kerr

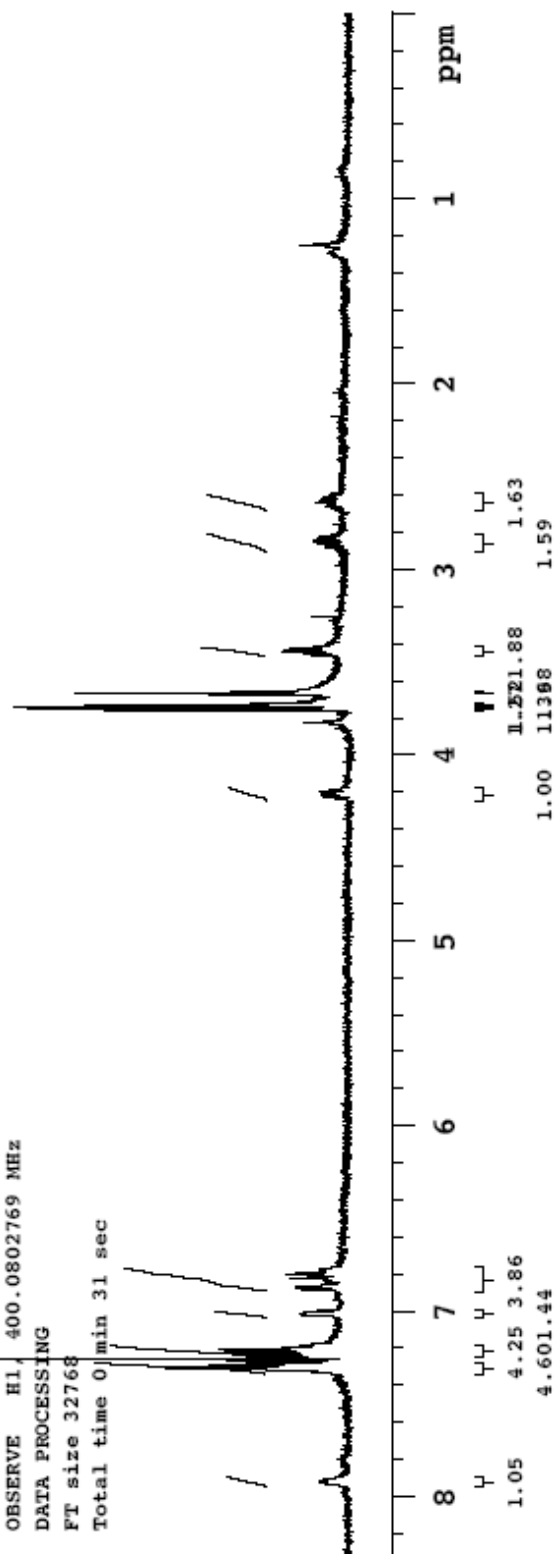
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
512 repetitions
OBSERVE C13, 100.6002755 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 20 min

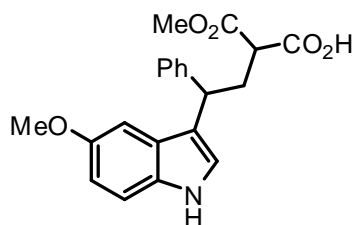




1.65i

Sample Name:
 Mike_E
 Data Collected on:
 nmr00.chem.uwo.ca-mercury400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-5MeOHPh_Mar9_11_01
 FidFile: PROTON_01
 Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Mar 9 2011
 Temp. 25.0 C / 298.1 K
 Sample #10, Operator: Kerr
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.559 sec
 Width 6402.0 Hz
 8 repetitions
 OBSERVE H1, 400.0802769 MHZ
 DATA PROCESSING
 FT size 32768
 Total time 0 min 31 sec





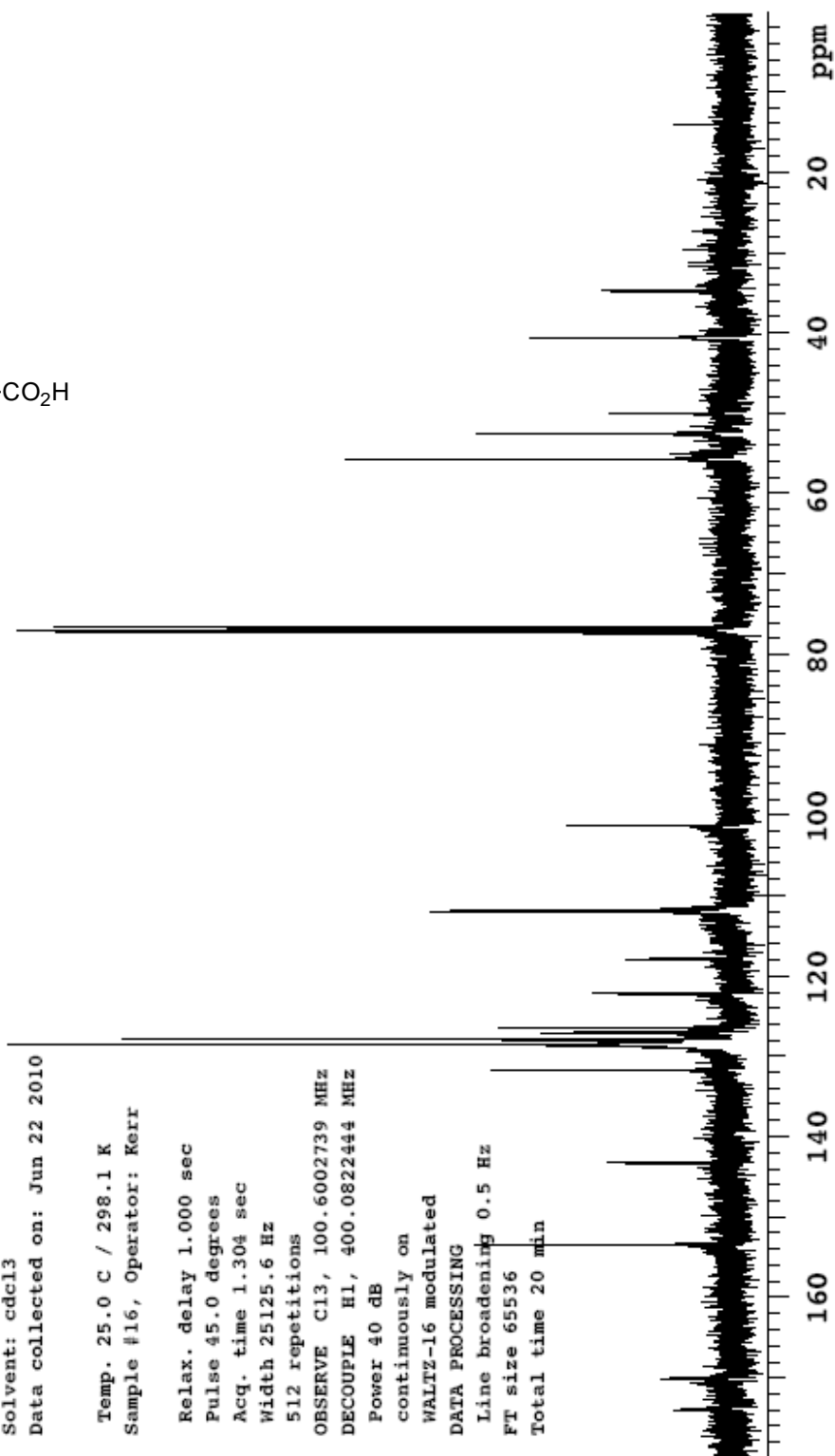
1.65i

Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-005p_Jun22_10_02
FidFile: CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 22 2010

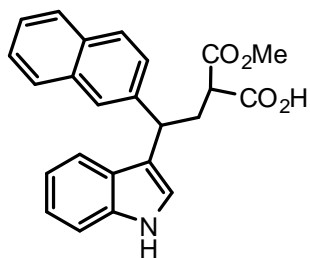
Temp. 25.0 C / 298.1 K
Sample #16, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
512 repetitions
OBSERVE C13, 100.6002739 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 20 min





VARIAN

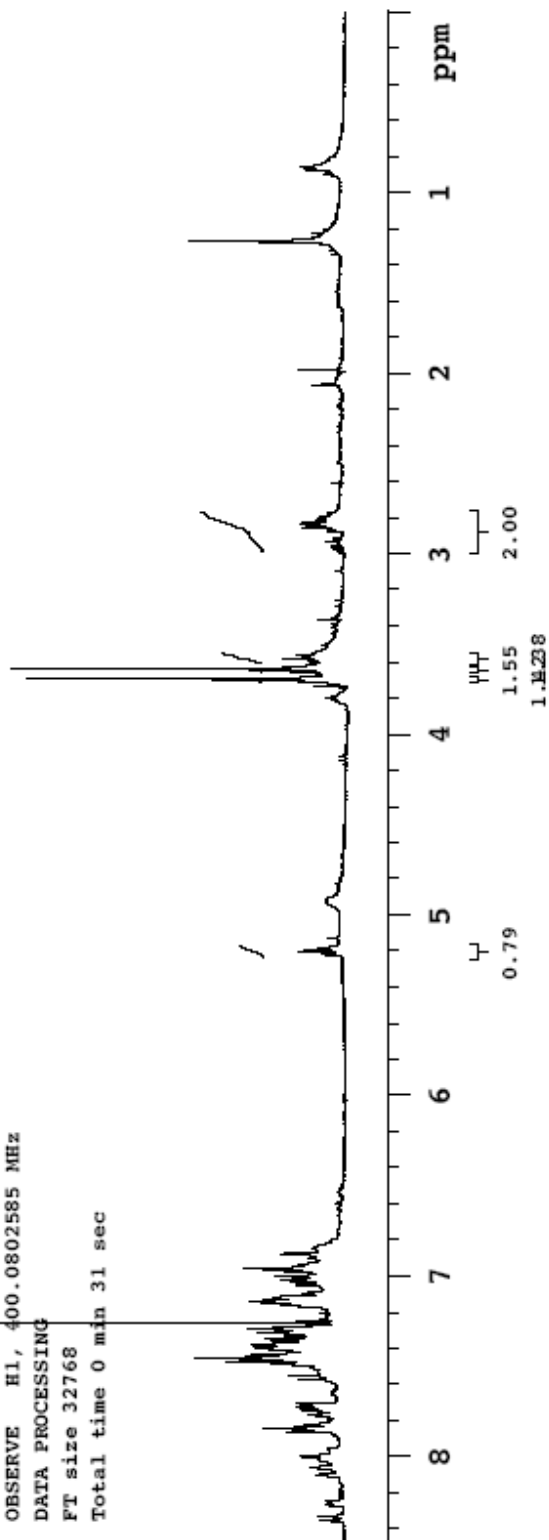


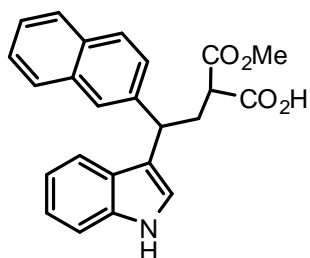
1.65j

Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-065n_Aug31_10_01
FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2010

Temp. 25.0 C / 298.1 K
Sample #29, Operator: Kerr
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802585 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





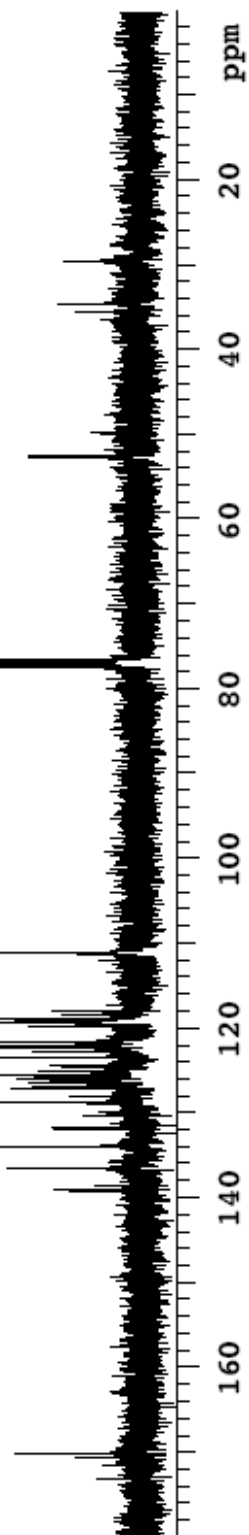
1.65j

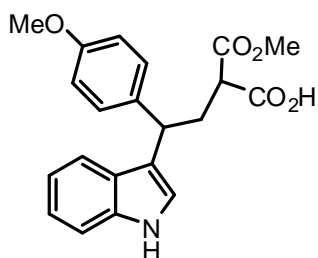
Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-065n_Aug31_10_01
FidFile: CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Aug 31 2010

Temp. 25.0 C / 298.1 K
Sample #29, Operator: Kerr

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
1000 repetitions
OBSERVE C13, 100.6002656 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min





1.65k

ME-NHP-MeOPh

Sample Name:

Mike_E

Data Collected on:

nmrrb400.chem.uwo.ca-inova400

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

ME-NHP-MeOPh_Mar9_11_01

Fidfile: PROTON01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Mar 9 2011

Temp. 25.0 C / 298.1 K

Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.559 sec

Width 6402.6 Hz

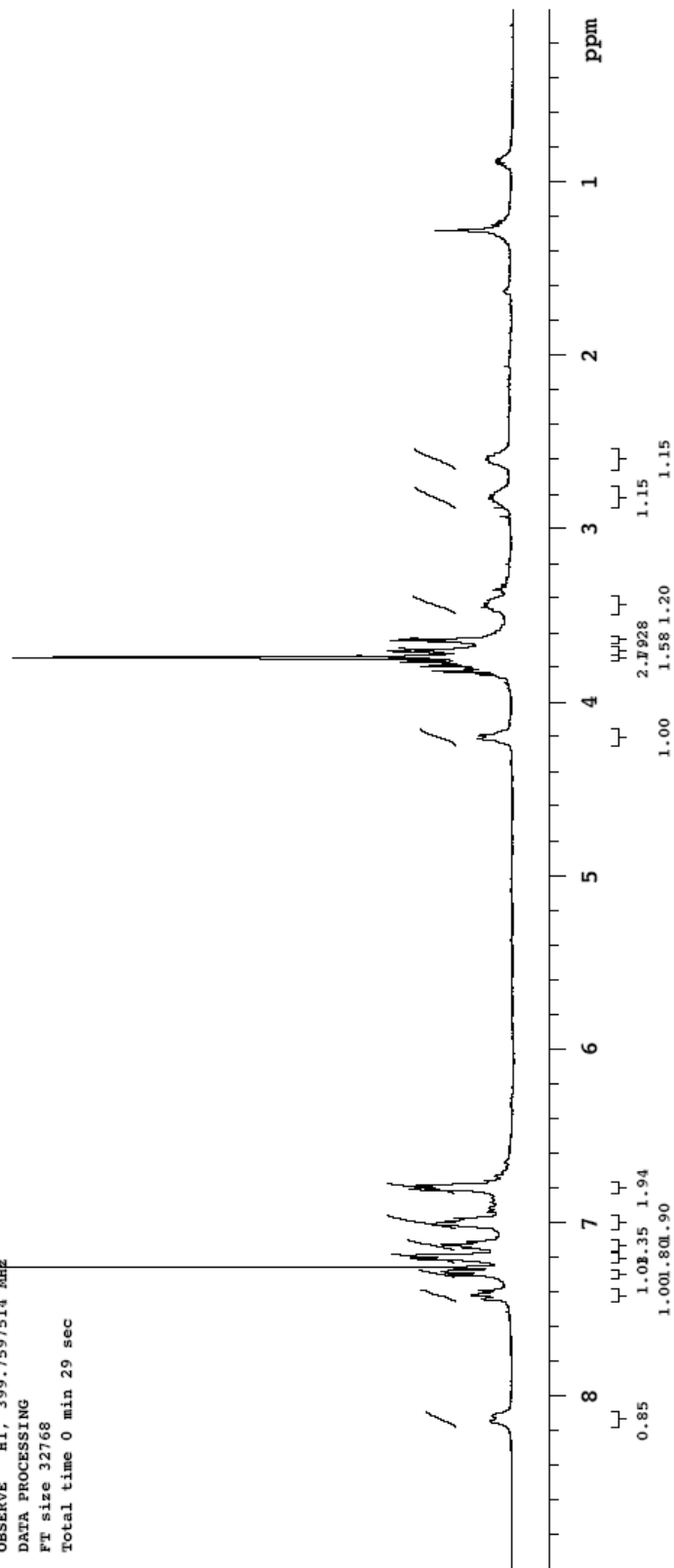
8 repetitions

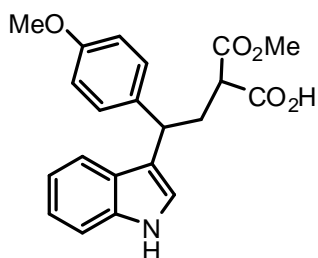
OBSERVE H1, 399.7597514 MHZ

DATA PROCESSING

FT size 32768

Total time 0 min 29 sec





1.65k

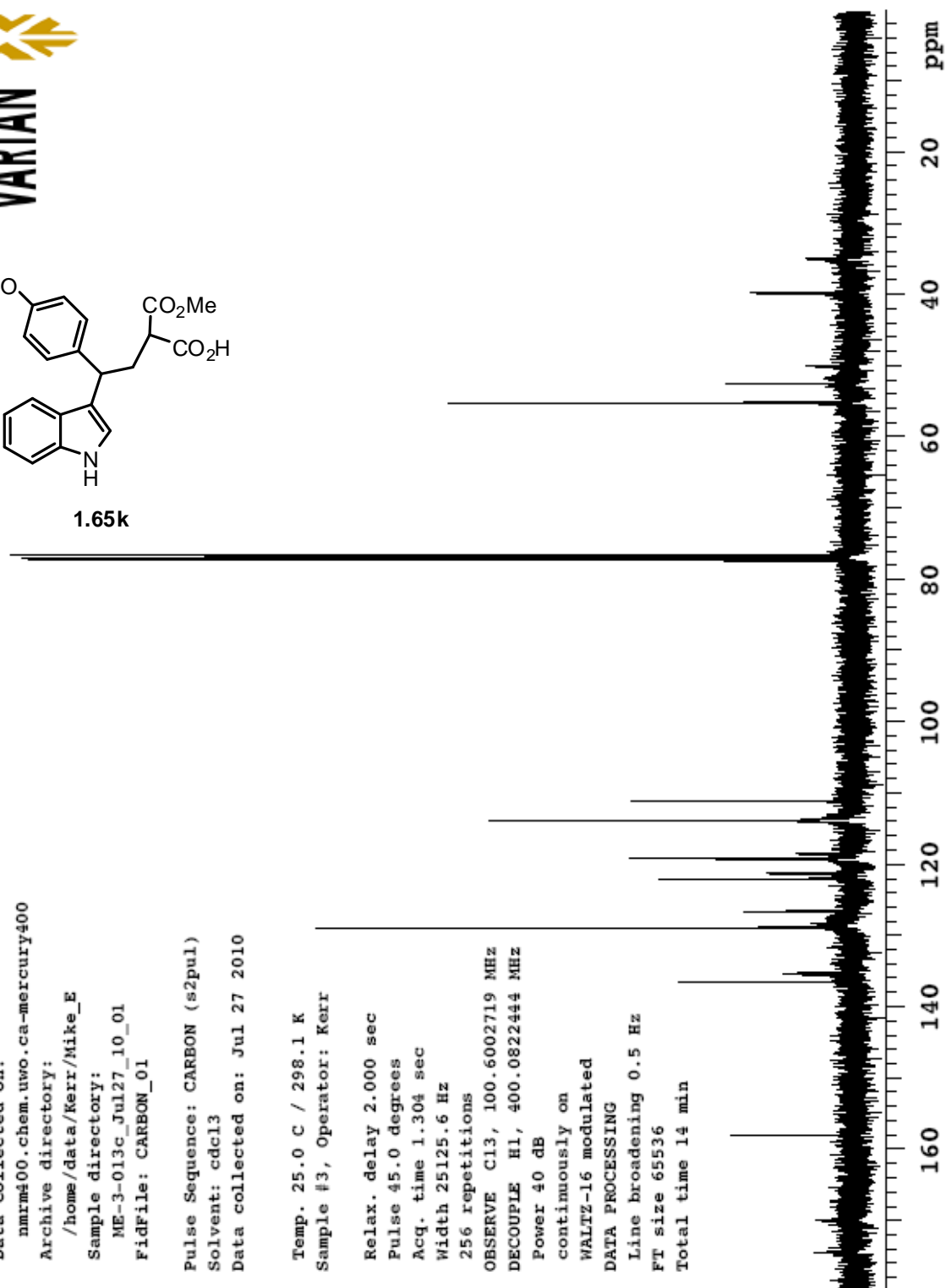
Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-013c_Jul27_10_01
FidFile: CARBON_01

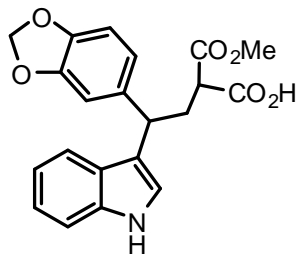
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2010

Temp. 25.0 C / 298.1 K
Sample #3, Operator: Kerr

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.6002719 MHz
DECOUPLE H1, 400.0822444 MHz

Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 14 min





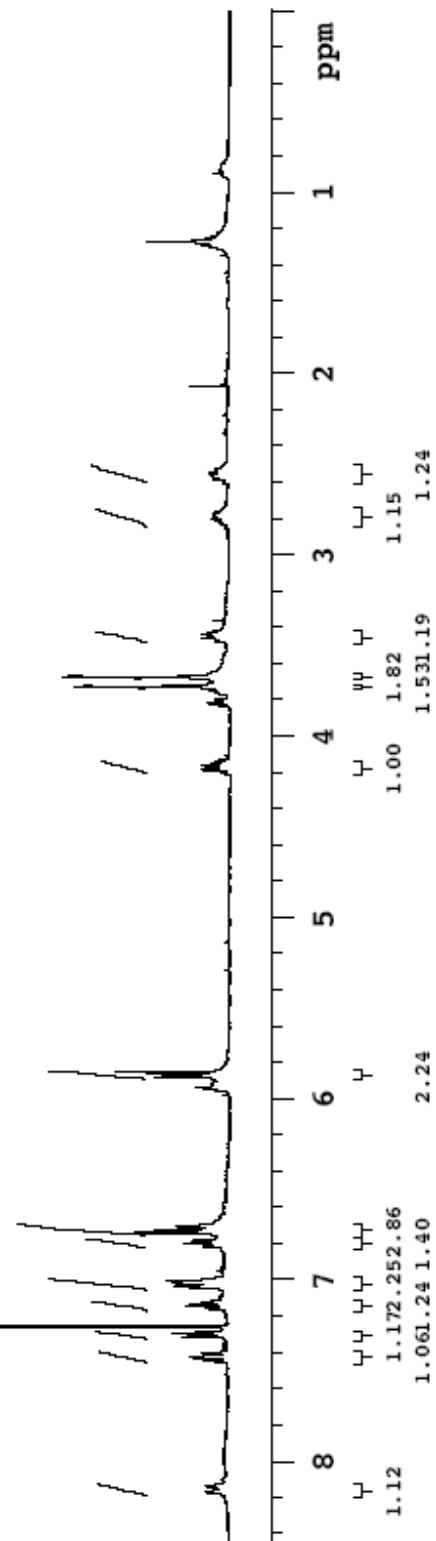
1.651

Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-053p_Jul22_10_01
Fidfile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 22 2010

Temp. 25.0 C / 298.1 K
Sample #47, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802692 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec



ME-3-0536

Sample Name:
Mike_E
Data Collected on:
nmr400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-0536_Jul27_10_01
FidFile: CARBON_01

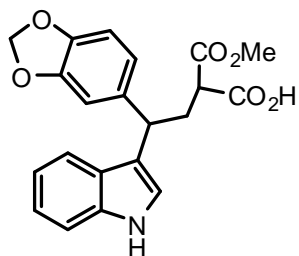
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2010

Temp. 25.0 C / 298.1 K
Sample #24, Operator: Kerr

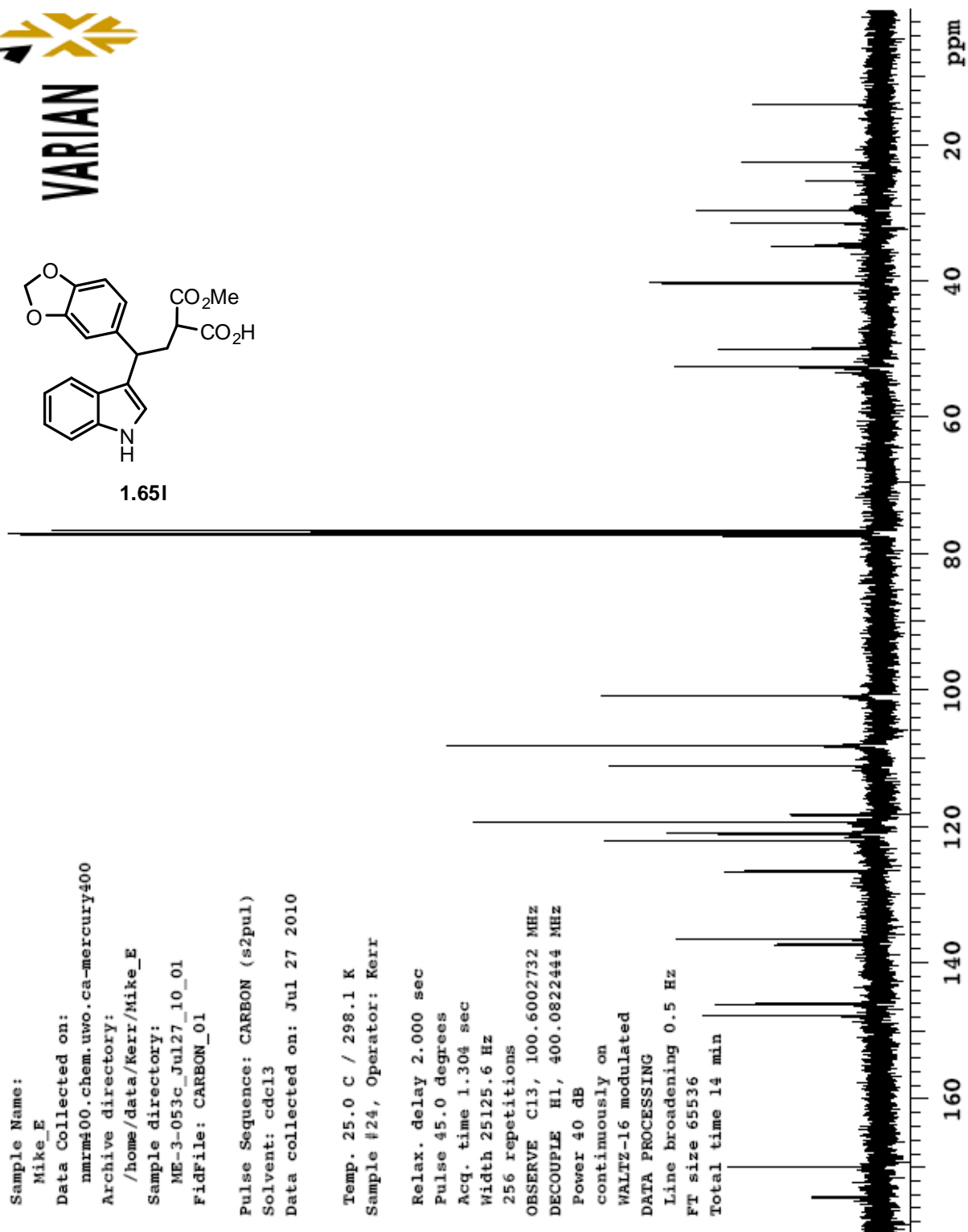
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.6002732 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 14 min

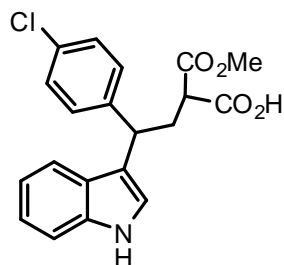


VARIAN



1.651





1.65m

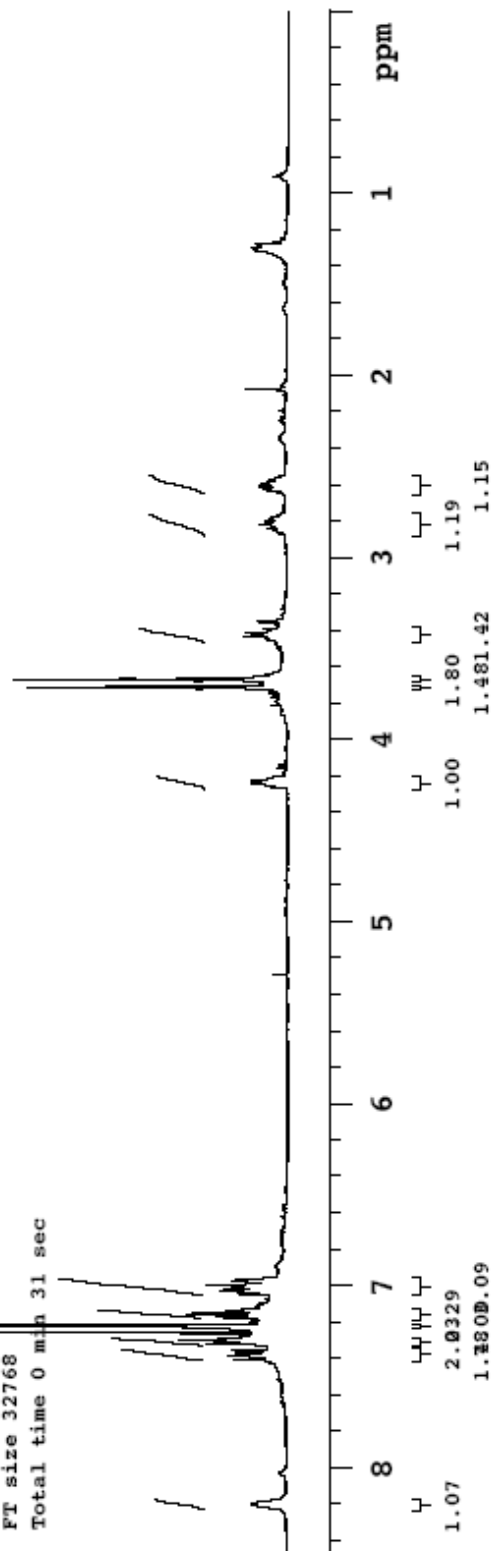
Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-035c_Jul27_10_01
FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2010

Temp. 25.0 C / 298.1 K
Sample #30, Operator: Kerr

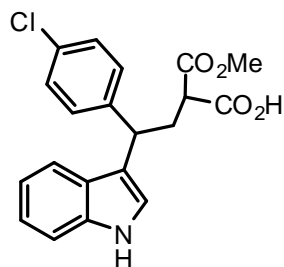
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions

OBSERVE H1, 400.0802697 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





VARIAN



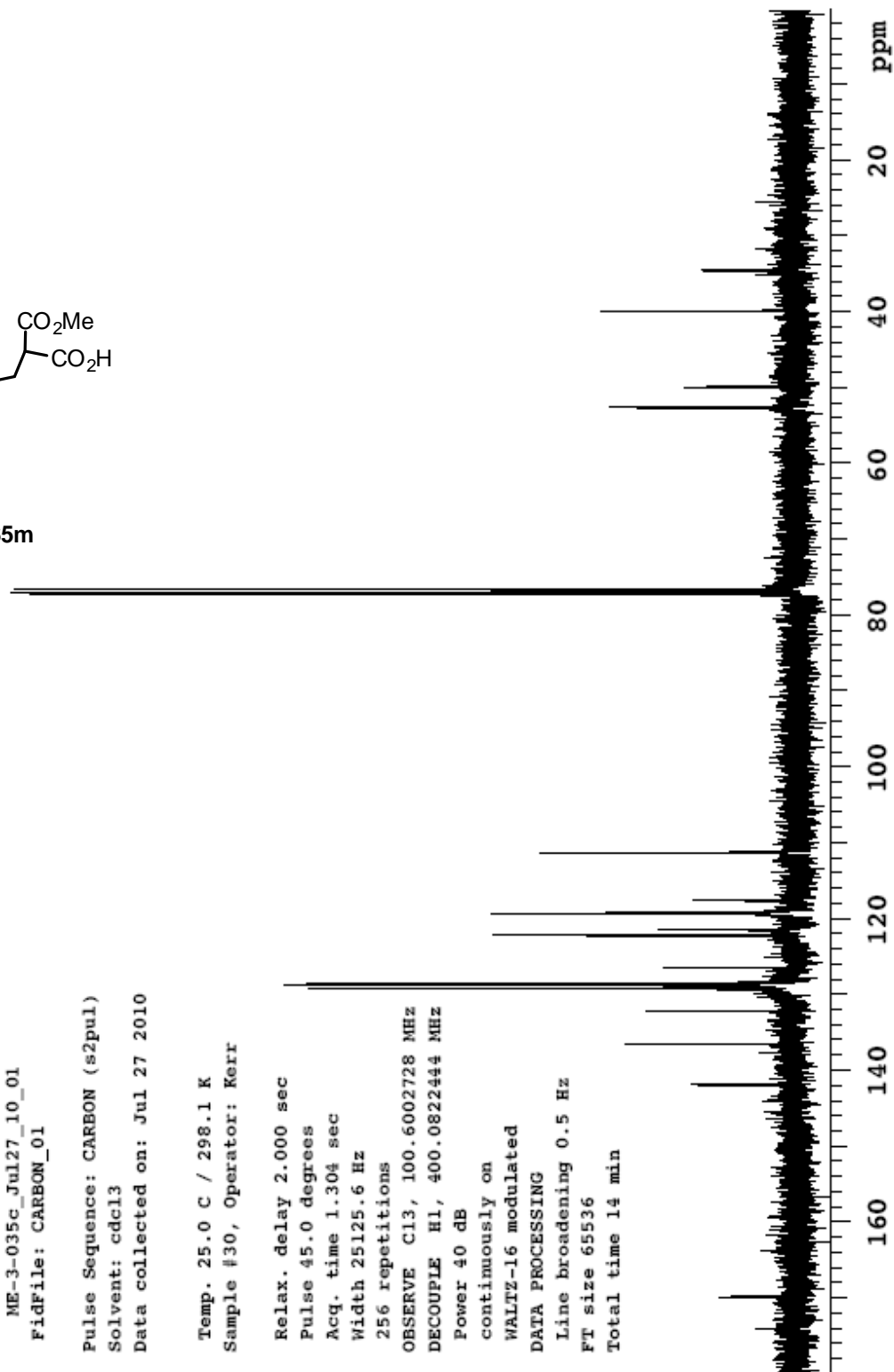
1.65m

Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-3-035c_Jul27_10_01
FidFile: CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 27 2010

Temp. 25.0 C / 298.1 K
Sample #30, Operator: Kerr

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.6002728 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 14 min



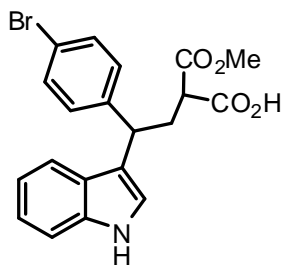
ME-4-18/1W

Sample Name:
Mike_E
Data Collected on:
nmrrh400.Chem.uwo.ca-inova400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-4-187w_May24_11_01
FidFile: PROTON01

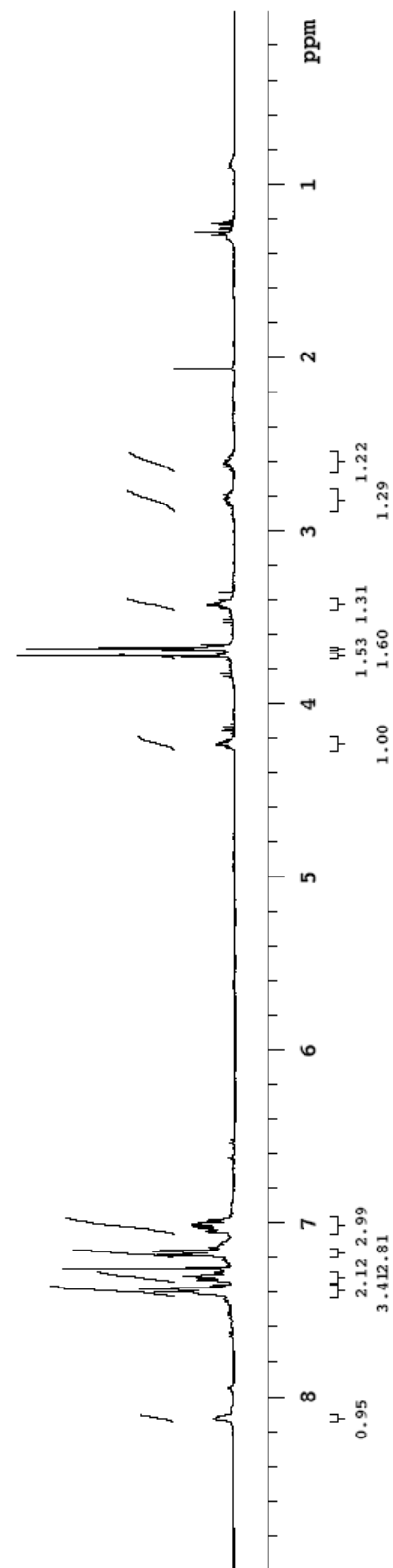
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 24 2011

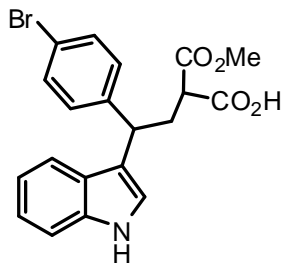
Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.6 Hz
8 repetitions
OBSERVE H1, 399.7597492 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 29 sec



1.65n





1.65n

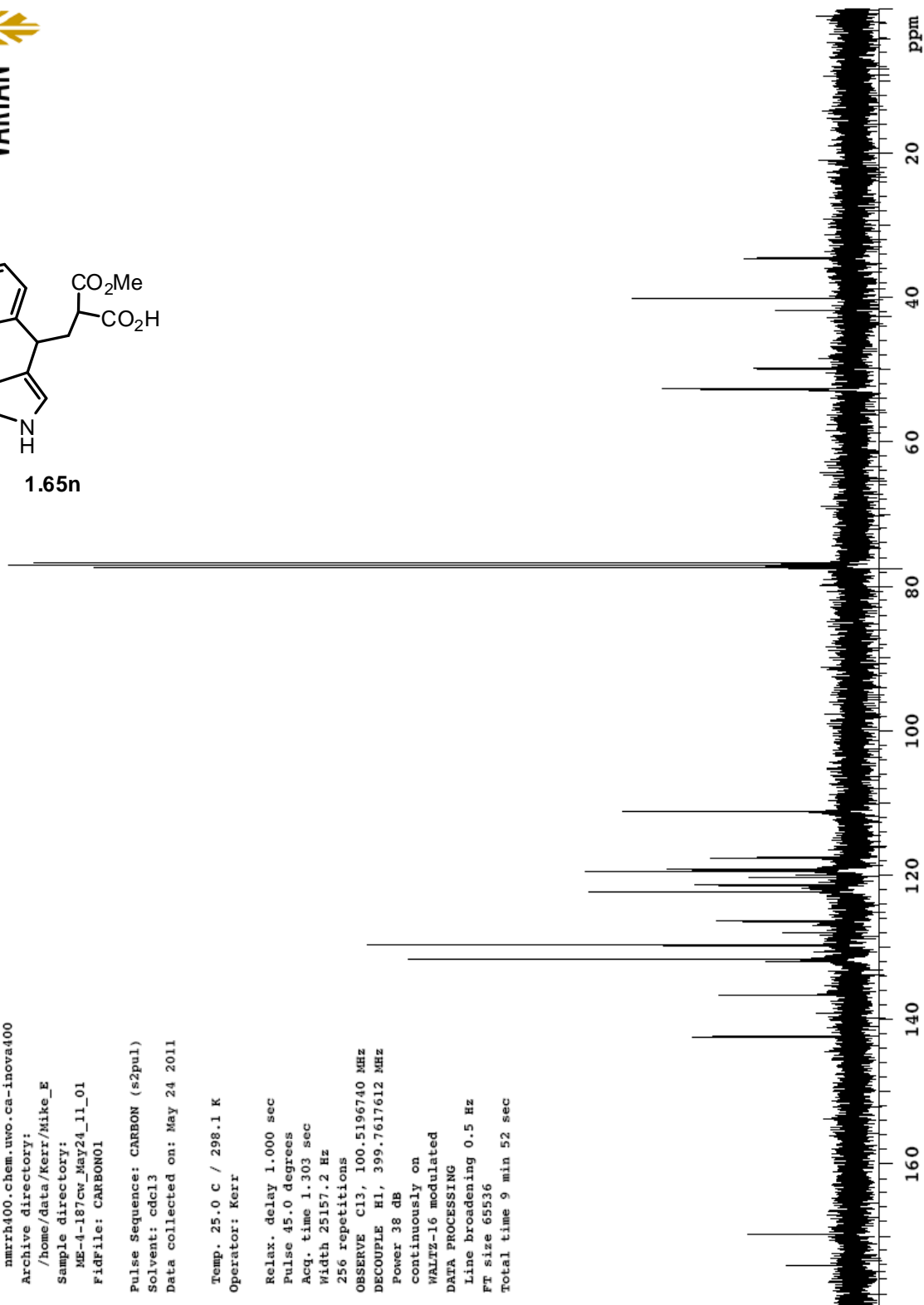
ME-4-187CW

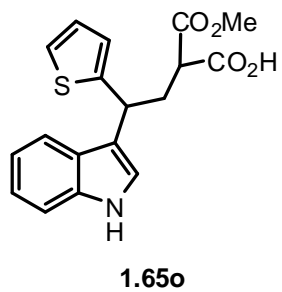
Sample Name:
Mike_E
Data Collected on:
nmrrh400.chem.uwo.ca-inova400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-4-187cw_May24_11_01
FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 24 2011

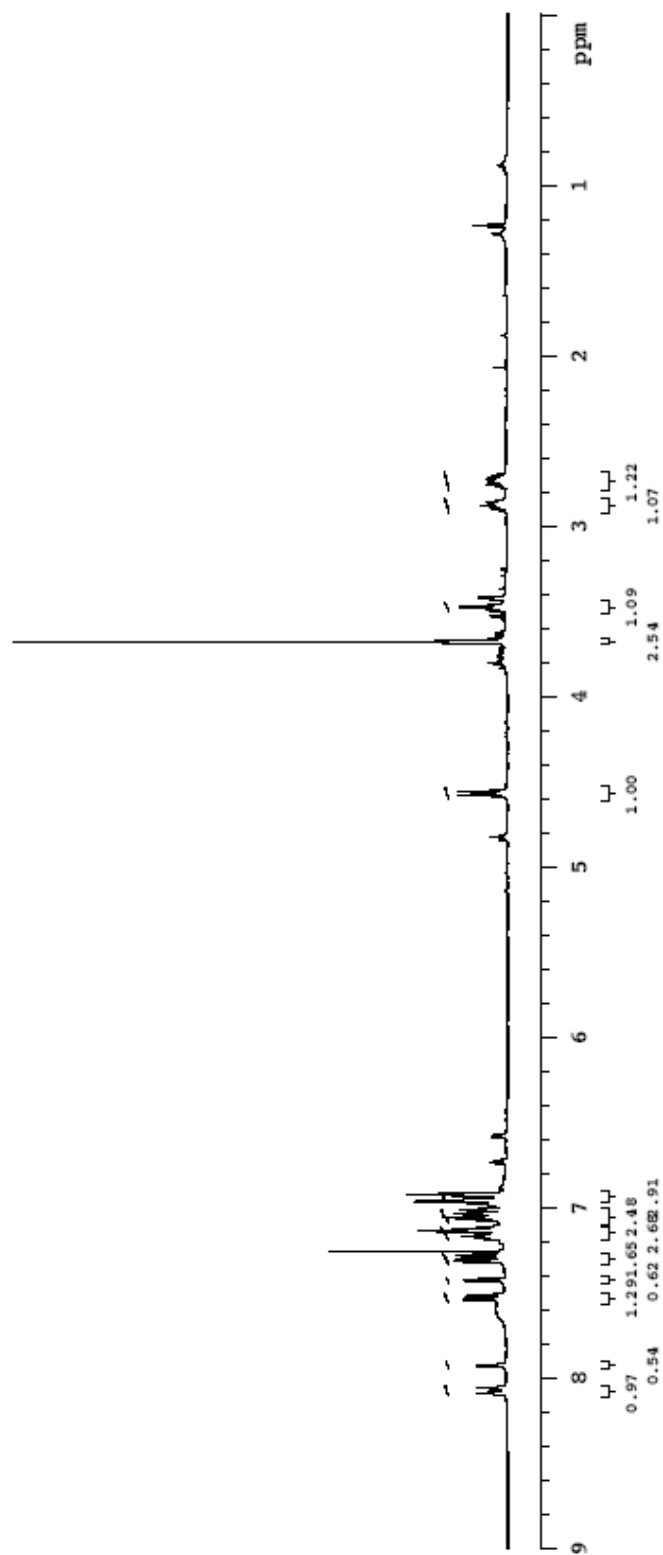
Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.303 sec
Width 25157.2 Hz
256 repetitions
OBSERVE C13, 100.5196740 MHz
DECOUPLE H1, 399.7617612 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min 52 sec





1.65o



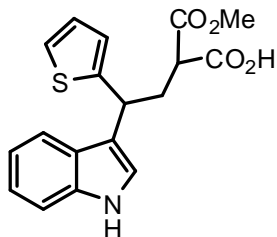
ME-4-187-2c

Sample Name:
Mike_E
Data Collected on:
nmrrh400.chem.uwo.ca-inova400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-4-187-2c_May24_11_01
FidFile: CARBON01

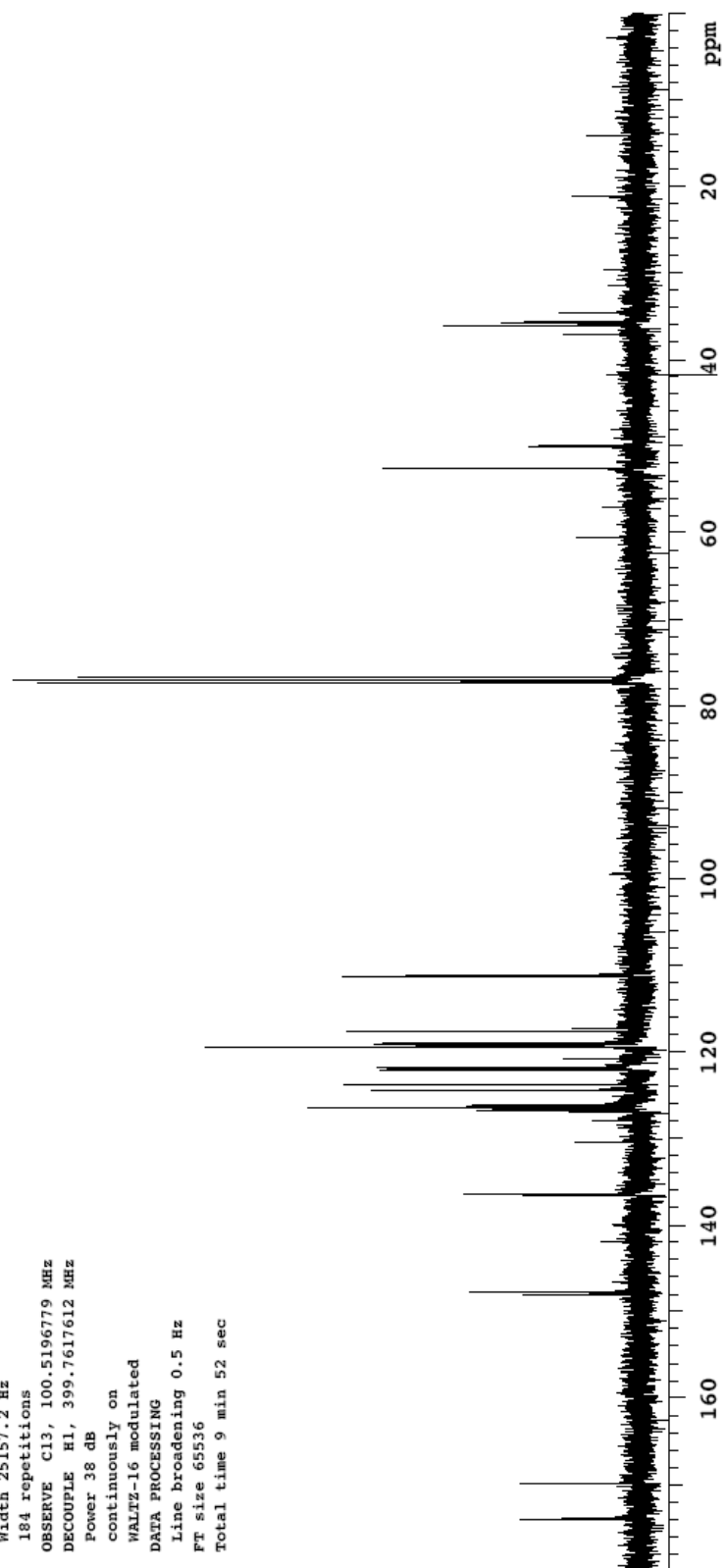
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 24 2011

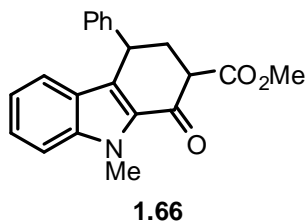
Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.303 sec
Width 25157.2 Hz
184 repetitions
OBSERVE C13, 100.5196779 MHz
DECOUPLE H1, 399.7617612 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min 52 sec



1.65o





ME-2-041col

Sample Name:

Mike_E

Data Collected on:

nrm400.chem.uwo.ca-mercury400

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

ME-2-041col_Feb26_10_01

FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Feb 26 2010

Temp. 25.0 C / 298.1 K

Sample #15, Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.559 sec

Width 6402.0 Hz

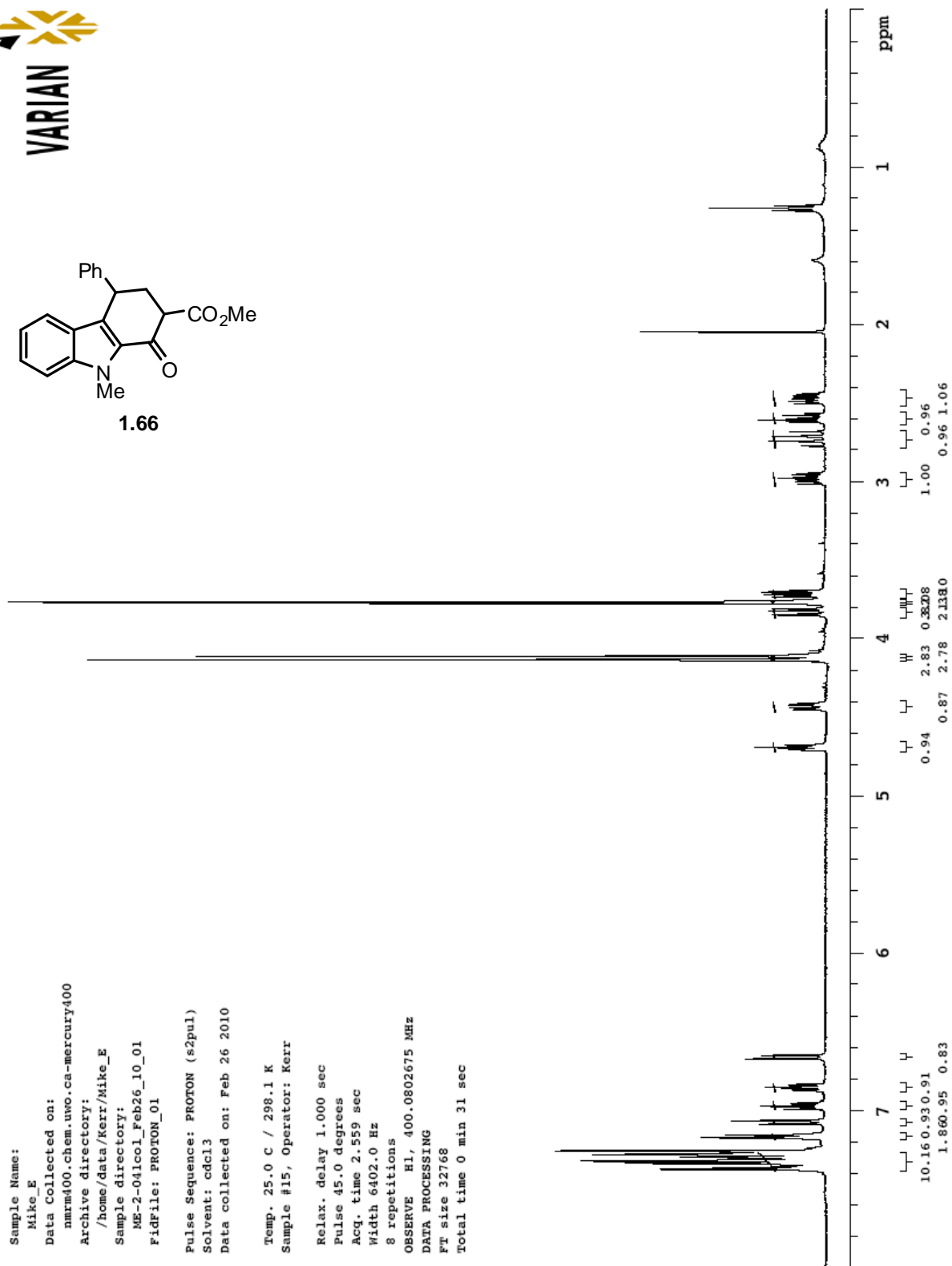
8 repetitions

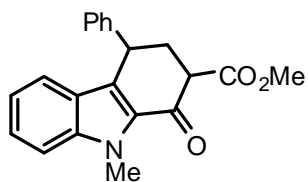
OBSERVE H1, 400.0802675 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 31 sec





1.66

ME-1-171colC

Sample Name:

Mike_E

Data Collected on:

nmrh400.chem.uwo.ca-inova400

Archive directory:

/home/data/kerr/Mike_E

Sample directory:

ME-1-171colC_Dec15_0901

FidFile: CARBON01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Dec 15 2009

Temp. 25.0 C / 298.1 K

Operator: kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.304 sec

Width 25133.5 Hz

256 repetitions

OBSERVE C13, 100.5196741 MHz

DECOUPLE H1, 399.7617612 MHz

Power 38 dB

continuously on

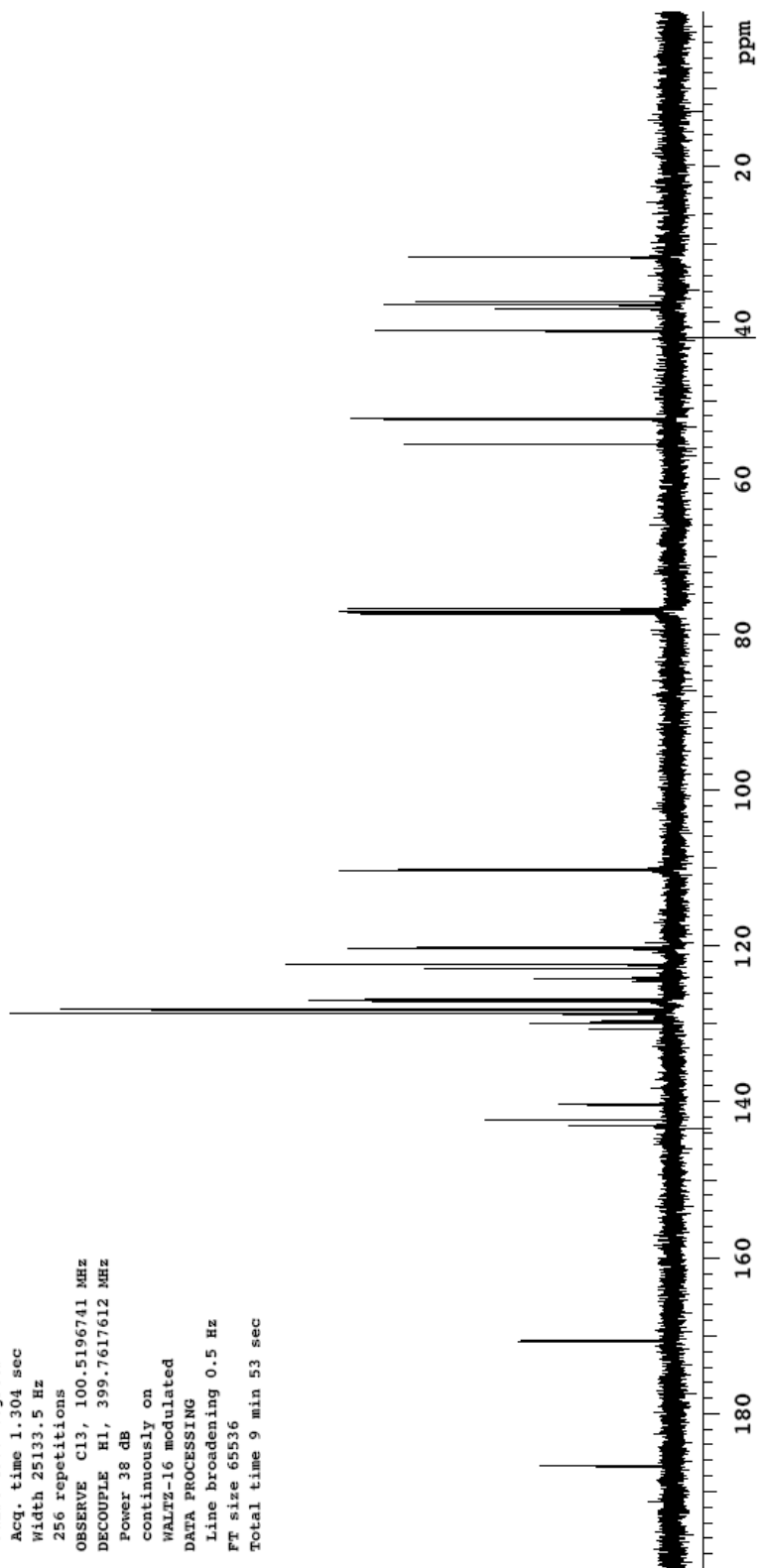
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 9 min 53 sec



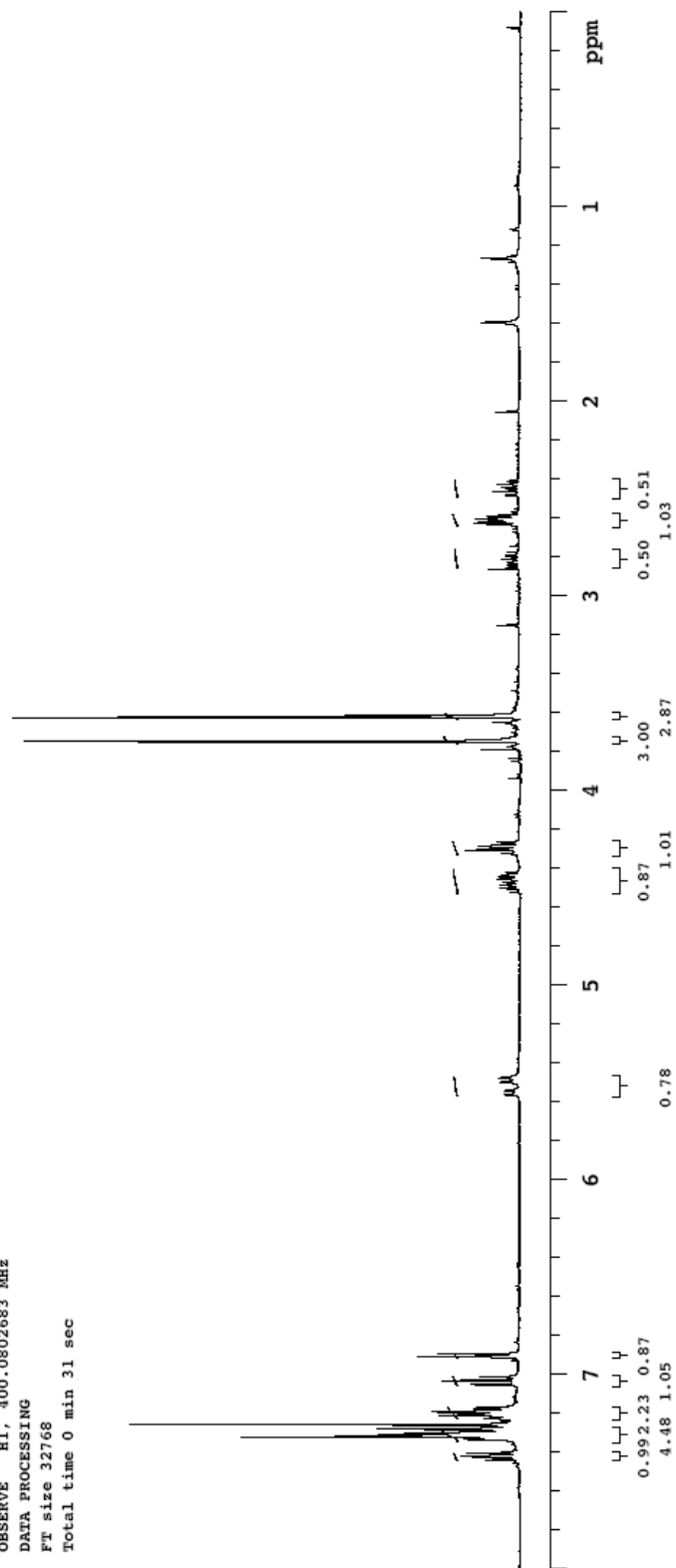
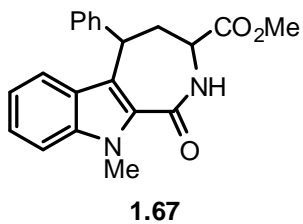
ME-1-141carb2

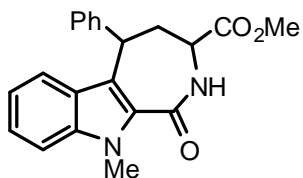
Sample Name:
Mike E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-1-141carb2_Oct13_0901
FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 13 2009

Temp. 25.0 C / 298.1 K
Sample #2, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802683 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





1.67

ME-1-141carb2

Sample Name:

Mike_E

Data Collected on:

nmrm400.chem.uwo.ca-mercury400

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

ME-1-141carb2_Oct13_0901

FidFile: CARBON_01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Oct 13 2009

Temp. 25.0 C / 298.1 K

Sample #2, Operator: Kerr

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.304 sec

Width 25125.6 Hz

1000 repetitions

OBSERVE C13, 100.6002650 MHZ

DECOUPLE H1, 400.0822444 MHZ

Power 42 dB

continuously on

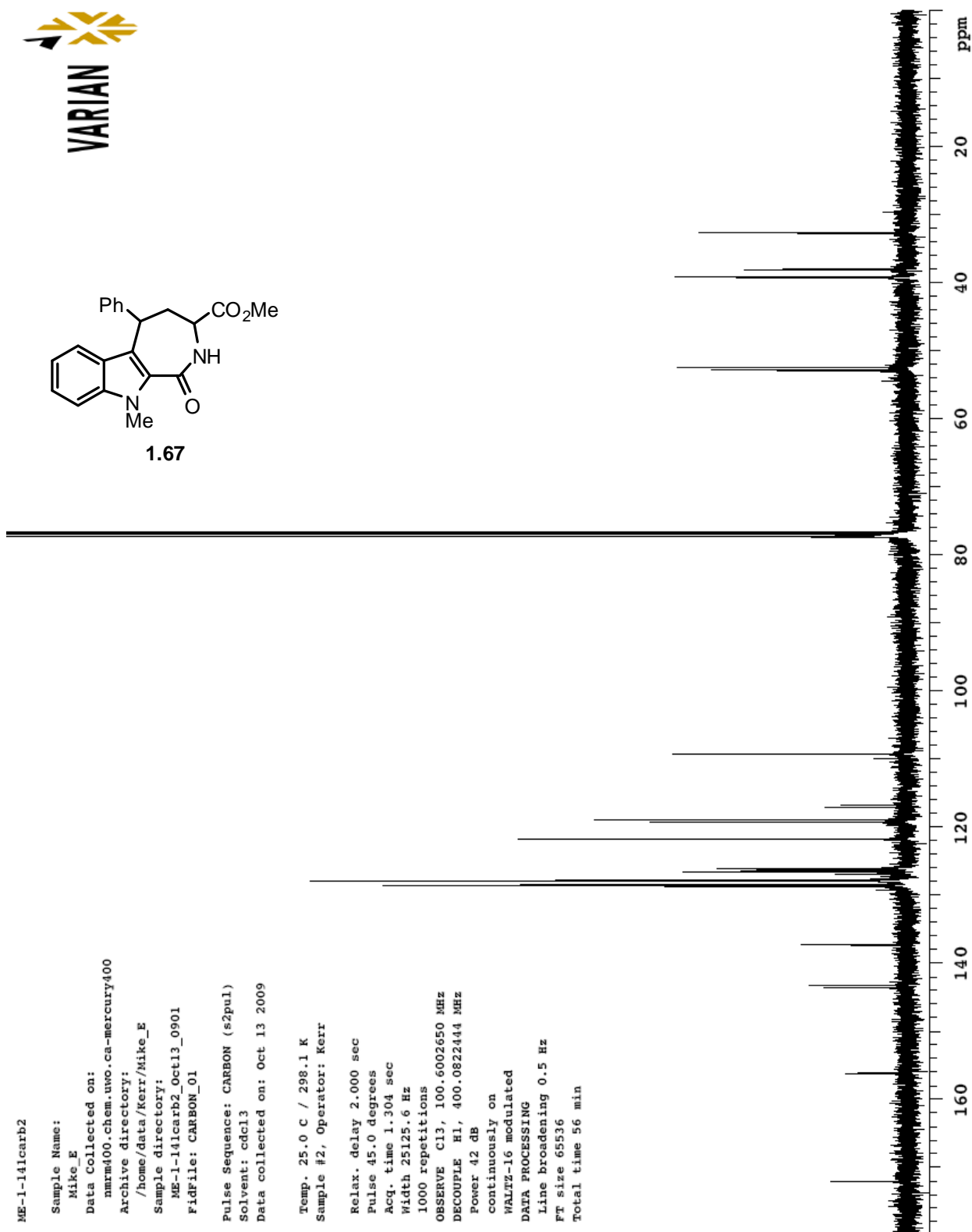
WALTZ-16 modulated

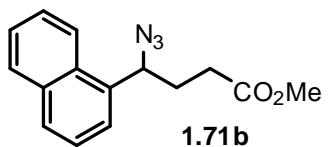
DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 56 min



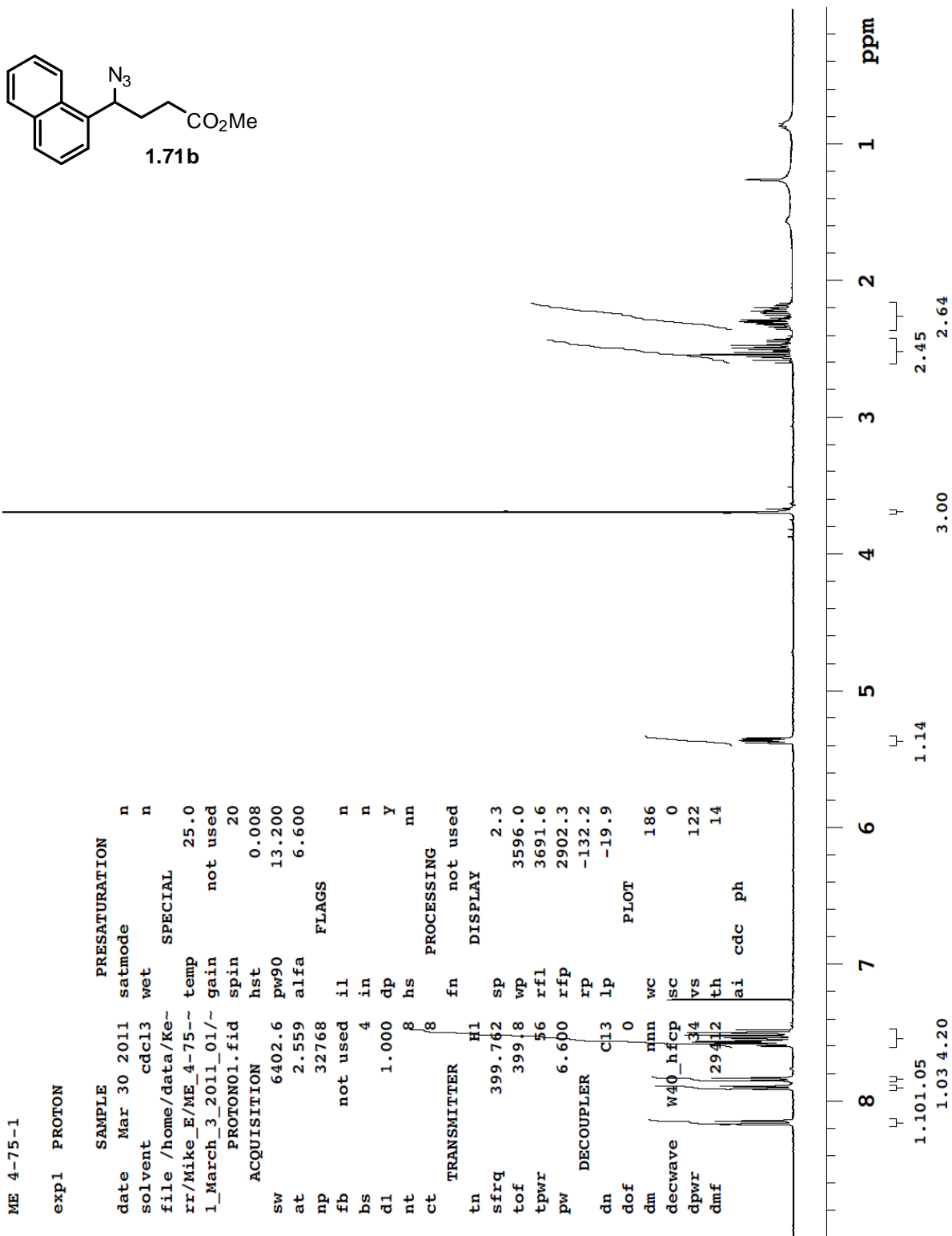


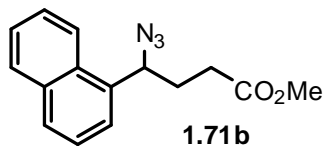
ME 4-75-1

exp1 PROTON

```

SAMPLE          PRESATURATION
date  Mar 30 2011  satmode      n
solvent  cdcl3  wet            n
file  /home/data/Ke~
rr/Mike_E/ME_4-75-~  temp      25.0
1_March_3_2011_01/~  gain      not used
PROTON01.fid  spin      20
ACQUISITION
sw  6402.6  pw90      13.200
at  2.559  alfa      6.600
np  32768  FLAGS
fb  not used  il      n
bs  4      in      n
dl  1.000  dp      Y
nt  8      hs      nn
ct  8      fn      not used
TRANSMITTER     H1      DISPLAY
tn              399.762  sp      2.3
sfrq            399.8  wp      3596.0
tpwr            56    rfl      3691.6
pw             6.600  rfp      2902.3
DECOUPLER       rp      -132.2
dn              Cl3  lp      -19.9
dof             0
dm              mnn  wc      186
decwave         W40_hfcp  sc      0
dpwr            34    vs      122
dmf             29412  th      14
ai  cdc  ph
    
```

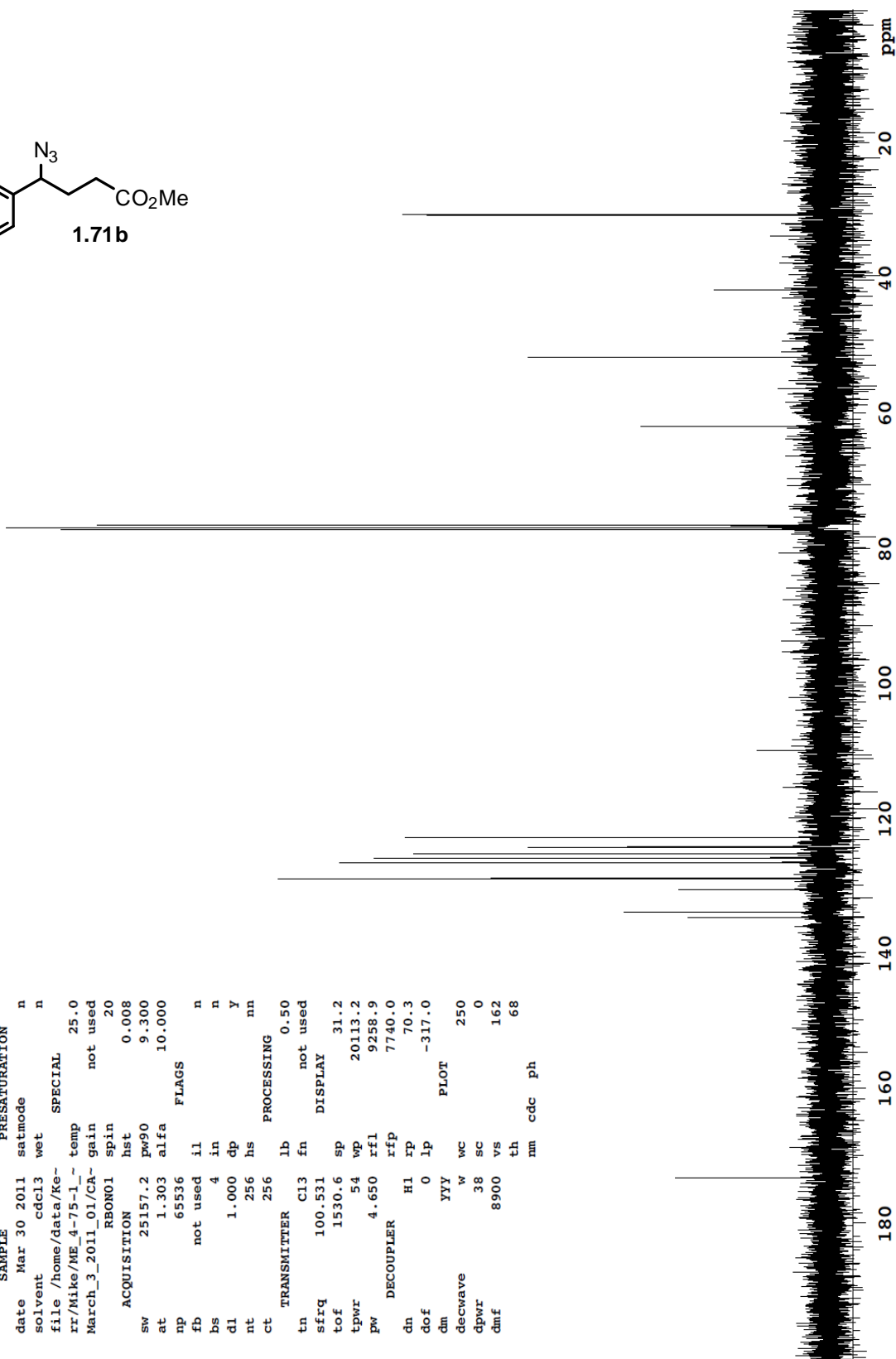


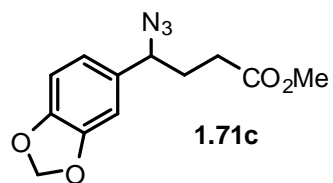


ME 4-75-1

exp1 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	
RBON01	spin	20	
ACQUISITION			
sw	25157.2	hst	0.008
at	1.303	pw90	9.300
np	6536	alfa	10.000
fb	not used	il	n
bs	4	in	n
dl	1.000	dp	y
nt	256	hs	nn
ct	256	PROCESSING	
tn	C13	lb	0.50
fn	not used	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	r1p	r1p	7740.0
dn	H1	fp	70.3
dof	0	lp	-317.0
dm	YYY	PLOT	
decwave	w	wc	250
dpwr	38	sc	0
dmf	8900	vs	162
th		mm	cdc
ph			68

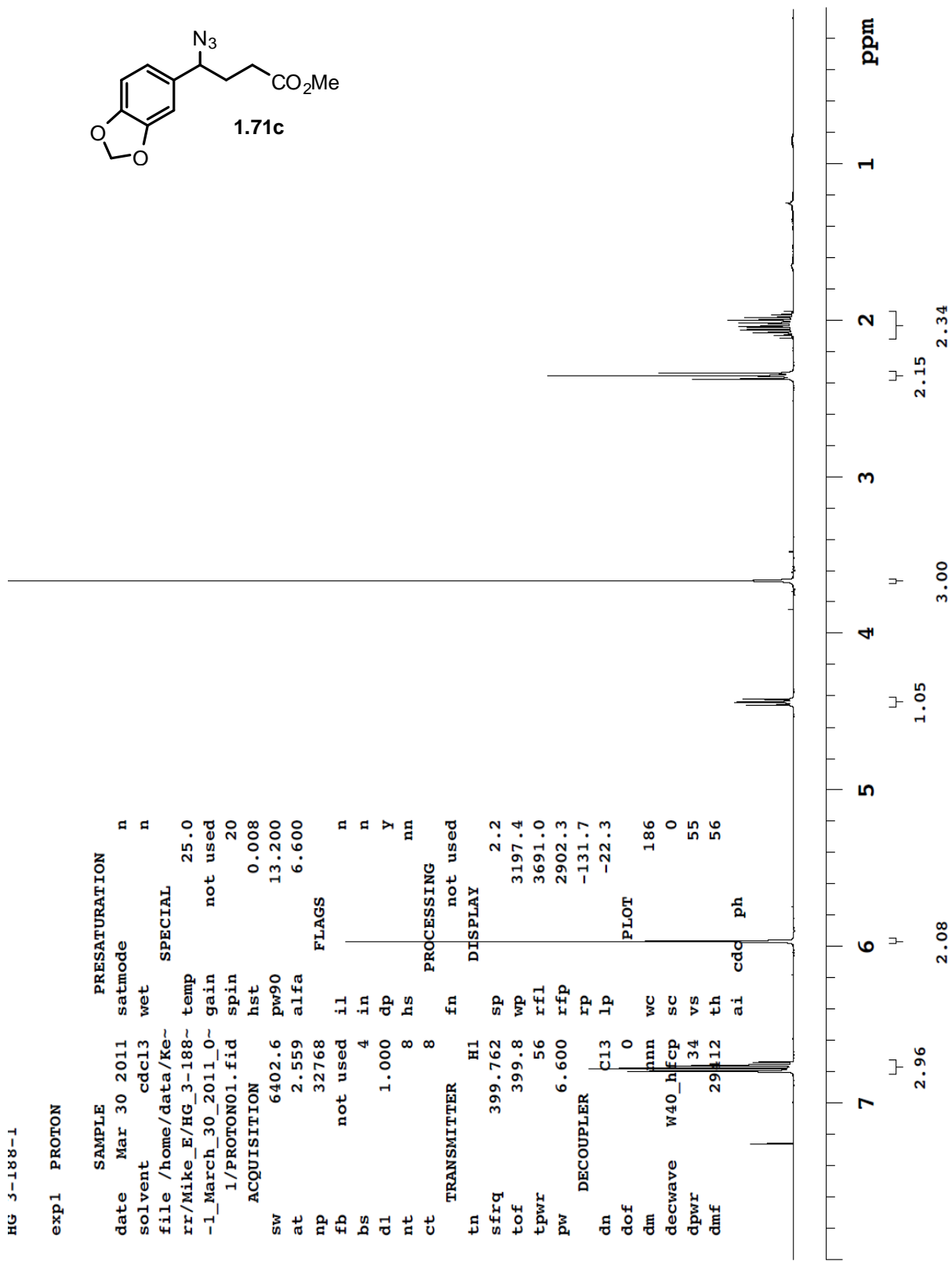


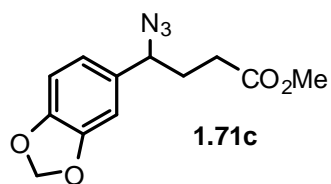


HG 3-188-1

exp1 PROTON

date	Mar 30 2011	satmode	n	PRESATURATION
solvent	cdcl3	wet	n	
file	/home/data/Ke-	SPECIAL		
rr/Mike_E/HG_3-188-	temp	25.0		
-1_March_30_2011_0~	gain	not used		
1/PROTON01.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	
dl	1.000	dp	y	
nt	8	hs	nn	
ct	8	PROCESSING		
TRANSMITTER	fn	not used		
tn	H1	DISPLAY		
sfrq	399.762	sp	2.2	
tof	399.8	wp	3197.4	
tpwr	56	rfl	3691.0	
pw	6.600	rfp	2902.3	
DECOUPLER	rp		-131.7	
dn	c13	lp	-22.3	
dof	0	PLOT		
dm	hnn	wc	186	
decwave	W40_hfcp	sc	0	
dpwr	34	vs	55	
dmf	29	th	56	
	ai	cdd		
		ph		

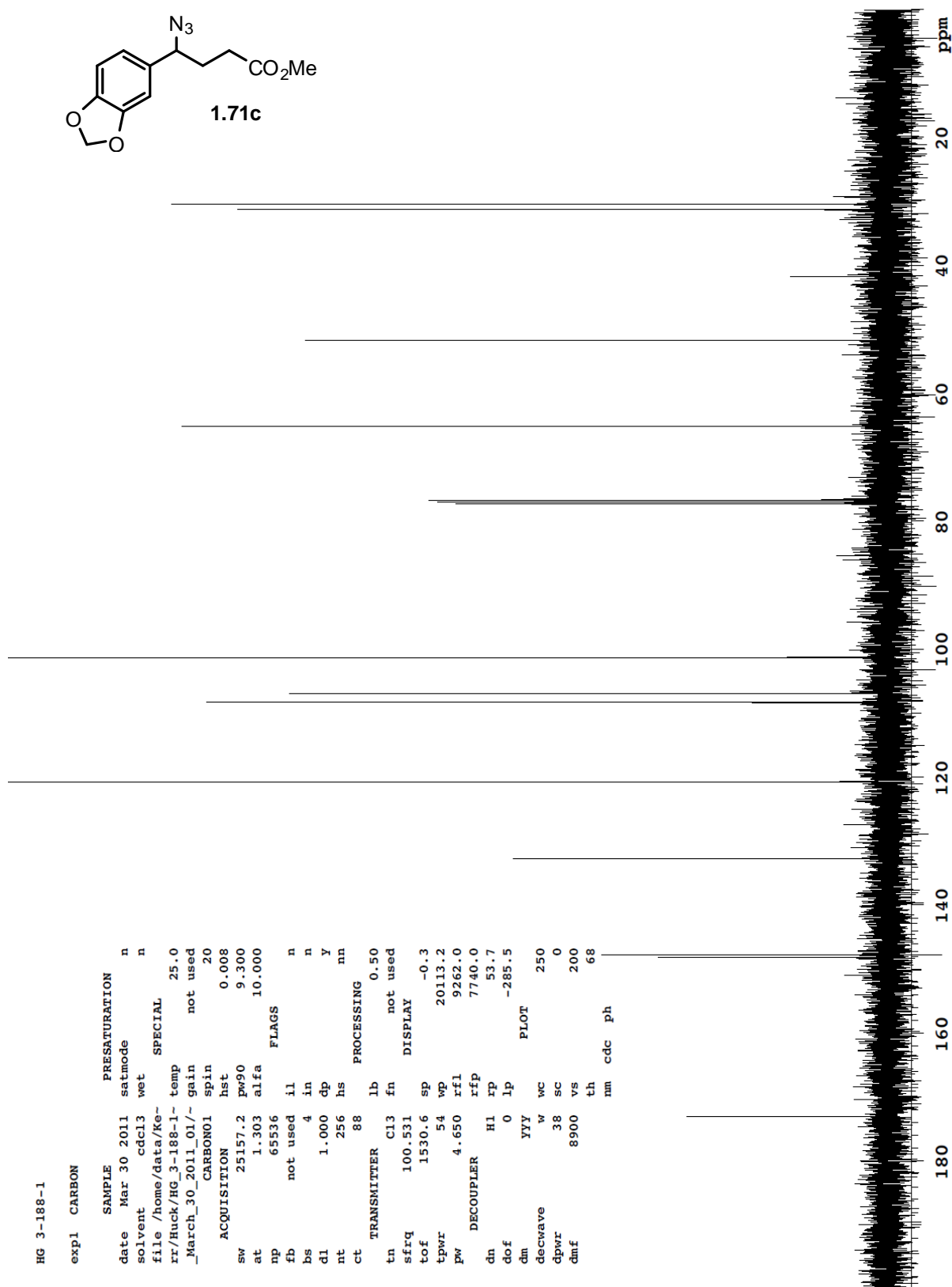


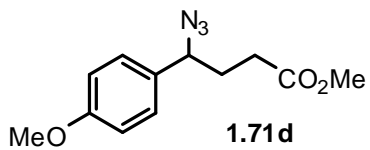


```

HG 3-188-1
exp1 CARBON
SAMPLE PRESATURATION
date Mar 30 2011 satmode n
solvent cdcl3 wet n
file /home/data/Ke- SPECIAL
rr/Huck/HG_3-188-1- 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
dl 1.000 dp y
nt 256 hs nn
ct 88 PROCESSING
TRANSMITTER lb 0.50
tn C13 in not used
sfrq 100.531 DISPLAY
tof 1530.6 sp -0.3
tpwr 54 vp 20113.2
pw 4.650 rf1 9262.0
DECOUPLER H1 rp 7740.0
dn dof 0 lp 53.7
dm YYY -285.5 PLOT
decwave w wc 250
dpwr 38 sc 0
dmf 8900 vs 200
th nm cdc ph 68

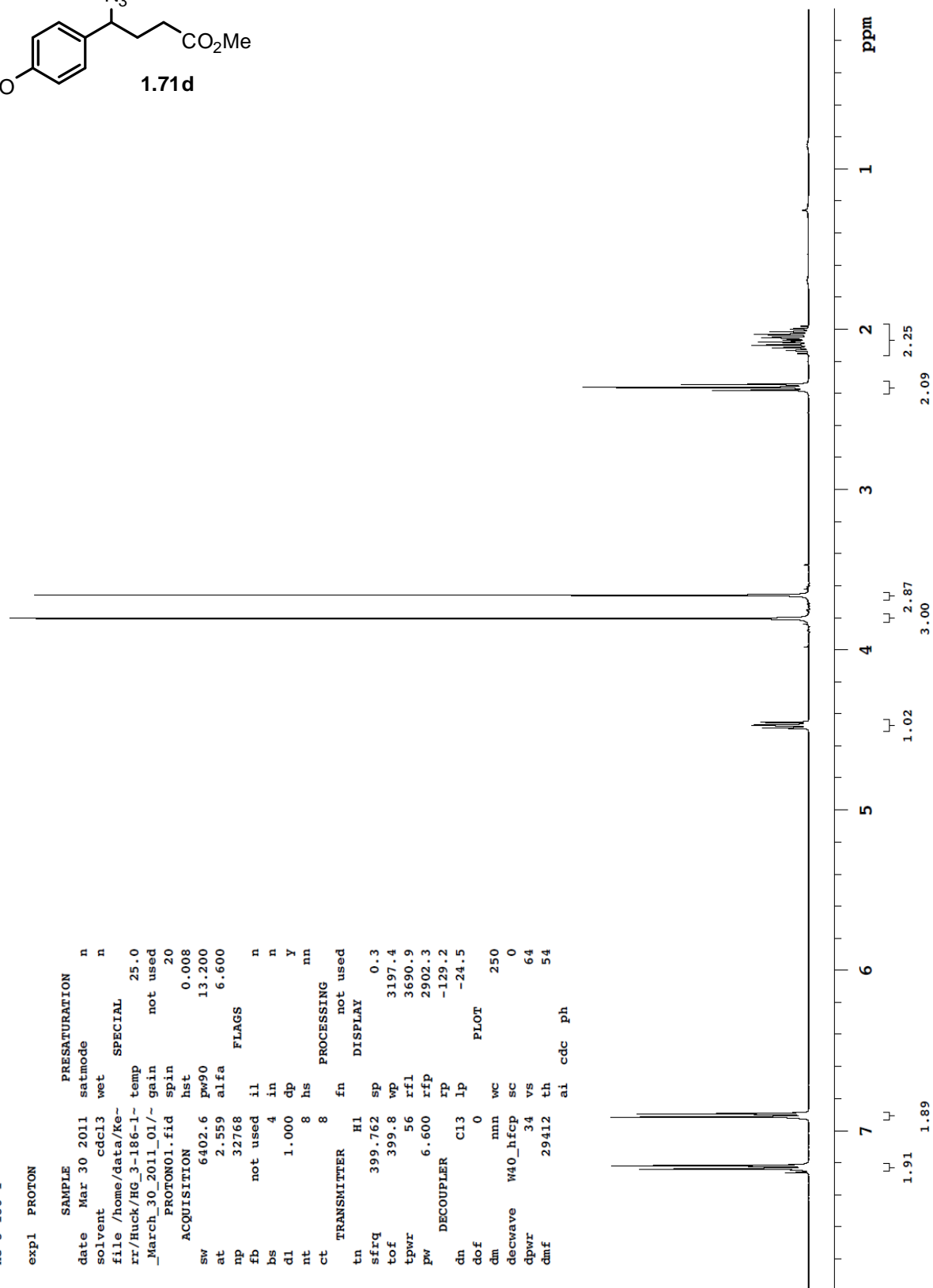
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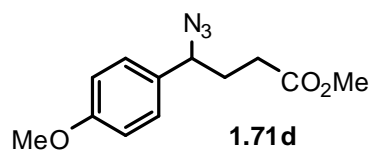




HG 3-186-1
 exp1 PROTON

SAMPLE	PRESATURATION	
date Mar 30 2011	satmode n	
solvent cdcl3	wet n	
file /home/data/Ke-	SPECIAL	
rt/Huck/HG_3-186-1-	temp 25.0	
_March_30_2011_01/-	gain not used	
PROTON01.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 0.3	
tof 399.8	wp 3197.4	
tpwr 56	rfl 3690.9	
pw 6.600	rfp 2902.3	
DECOUPLER	rp -129.2	
dn C13	lp -24.5	
dof 0	PLOT	
dm nnn	wc 250	
decwave W40_hfcp	sc 0	
dpwr 34	vs 64	
dmf 29412	th 54	
	ai cdc	ph



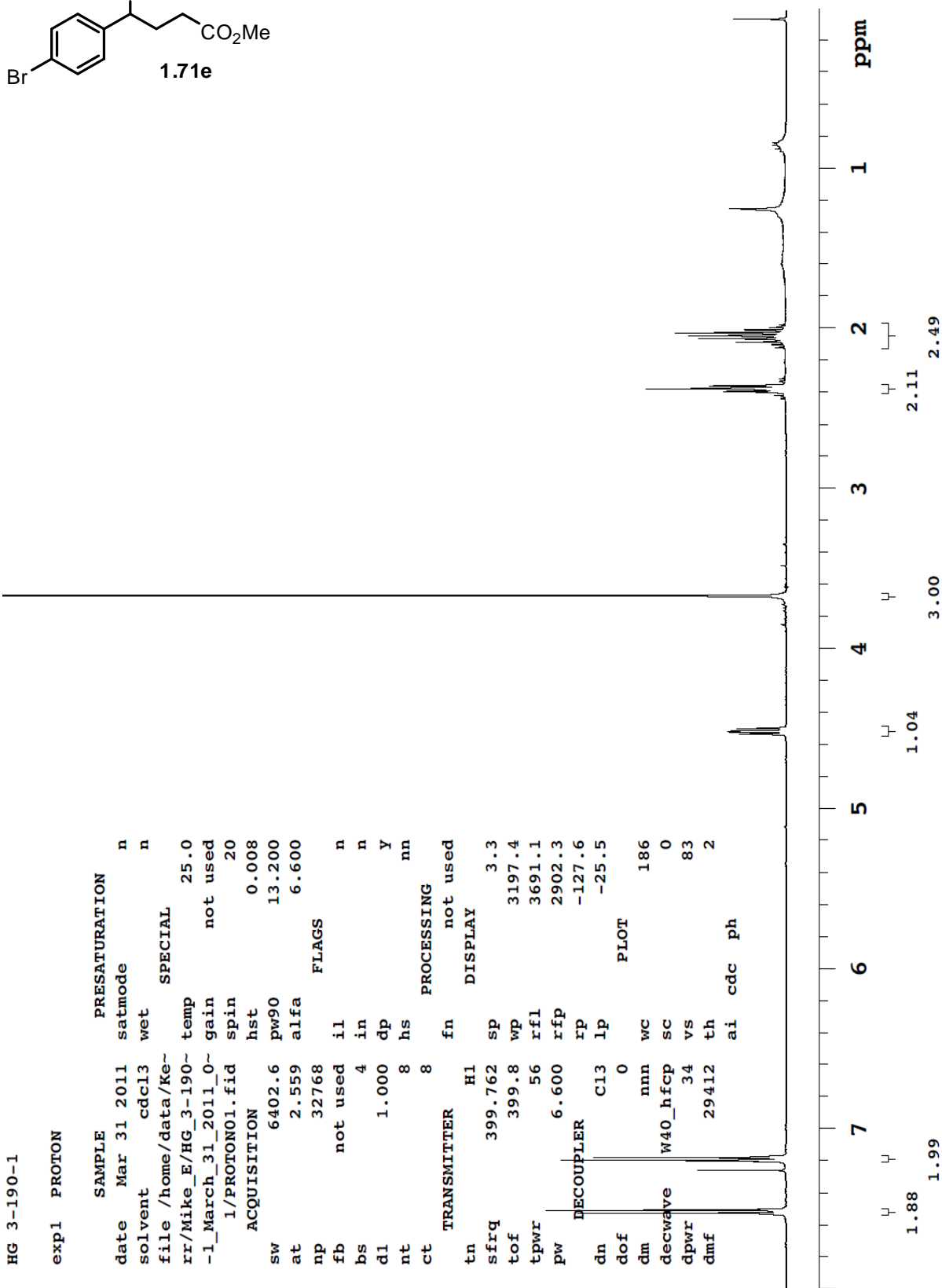
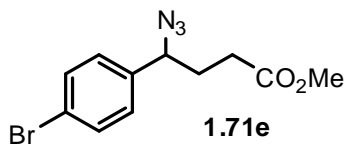


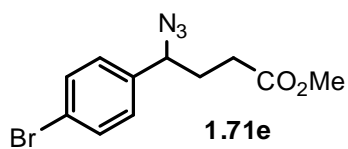
HG 3-186-1

exp1 CARBON

SAMPLE		PRESATURATION	
date	Mar 30 2011	satmode	n
solvent	cdcl3	wet	n
file	/home/data/Ke~	SPECIAL	
ir/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
dl	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	cdc	68
	ph		

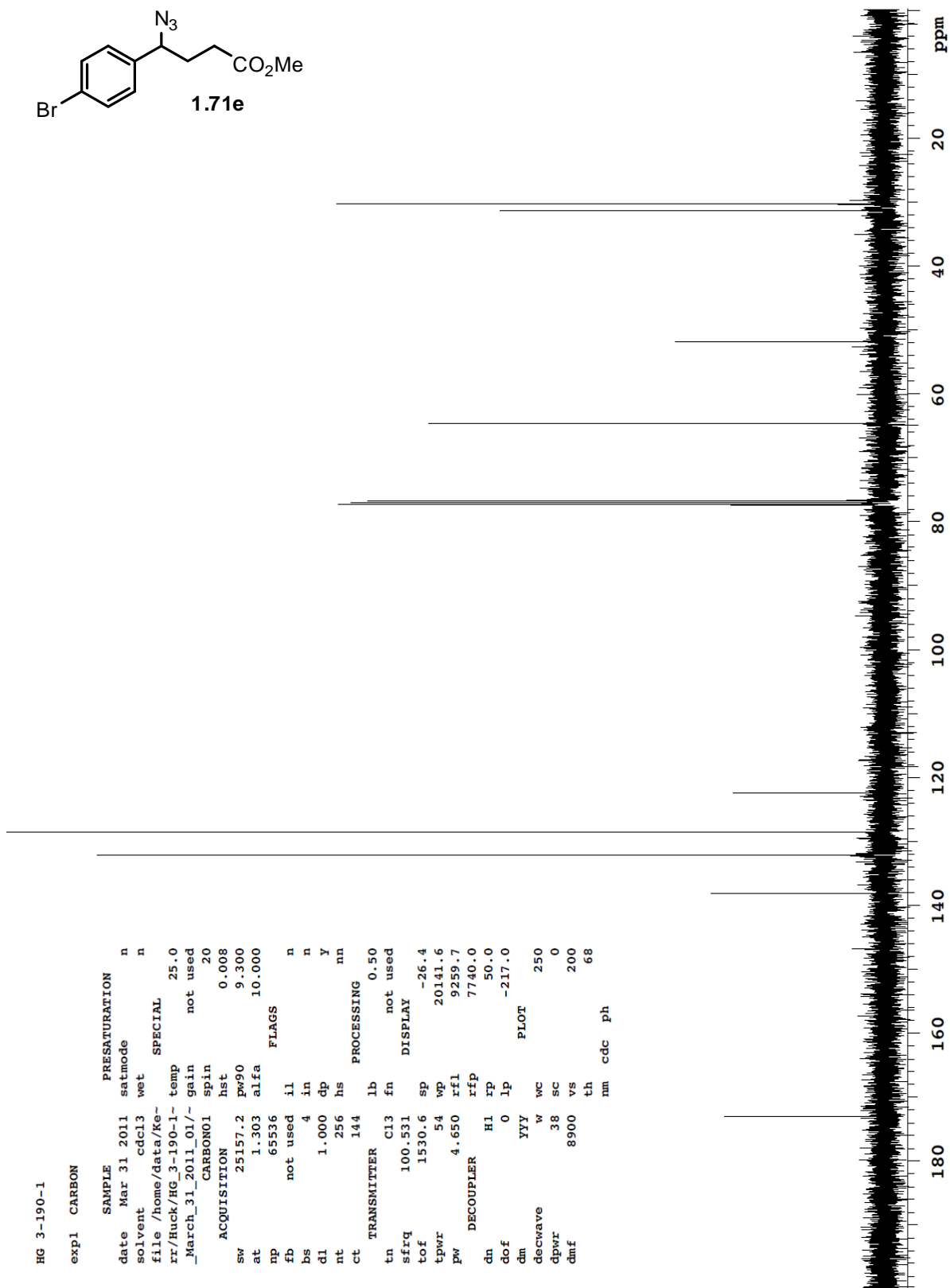
ppm

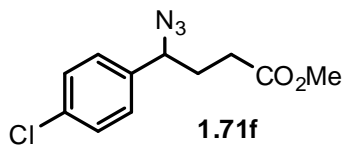




HG 3-190-1
 exp1 CARBON

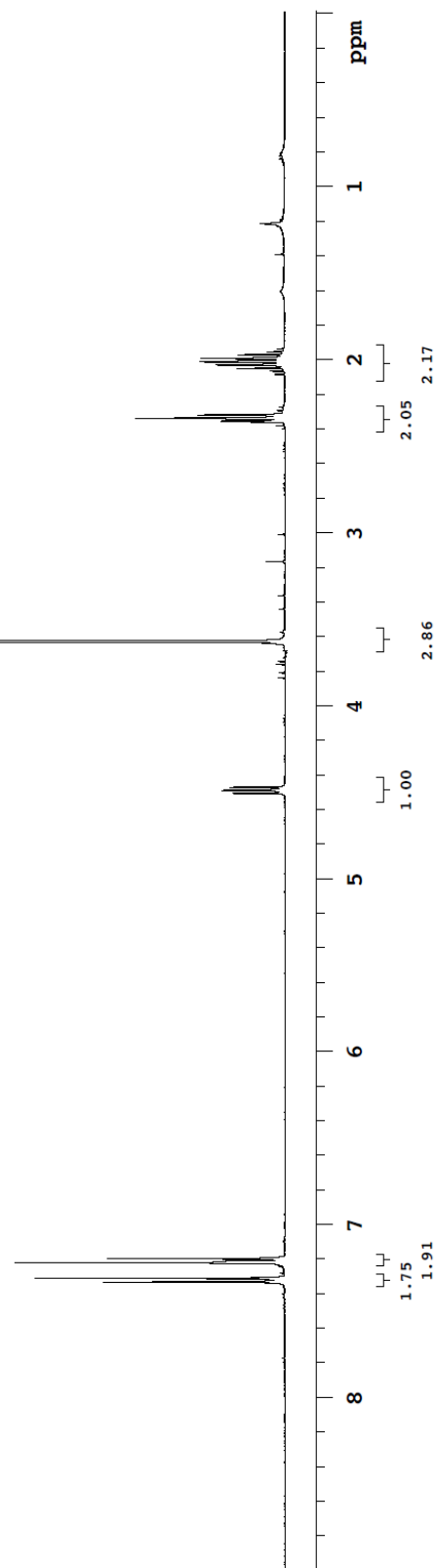
SAMPLE		PRESATURATION	
date	Mar 31 2011	satmode	n
solvent	cdcl3	wet	n
file	/home/data/Ke-	SPECIAL	
ir/Huck/HG_3-190-1-	temp	25.0	
_March_31_2011_01/-	gain	not used	
CARBON01	spin	20	
ACQUISITION	hst	0.008	
sw	25157.2	pw90	9.300
at	1.303	alfa	10.000
np	65536	FLAGS	
fb	not used	il	n
bs	4	in	n
d1	1.000	dp	Y
nt	256	hs	nn
ct	144	PROCESSING	
TRANSMITTER	lb	0.50	
tn	Cl3	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	vc	250
dpwr	38	sc	0
dmf	8900	vs	200
	th	nm	68
	cdc	ph	

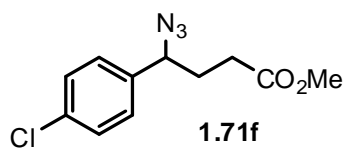




HG 4-54-1
 exp1 PROTON

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/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
dl 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	

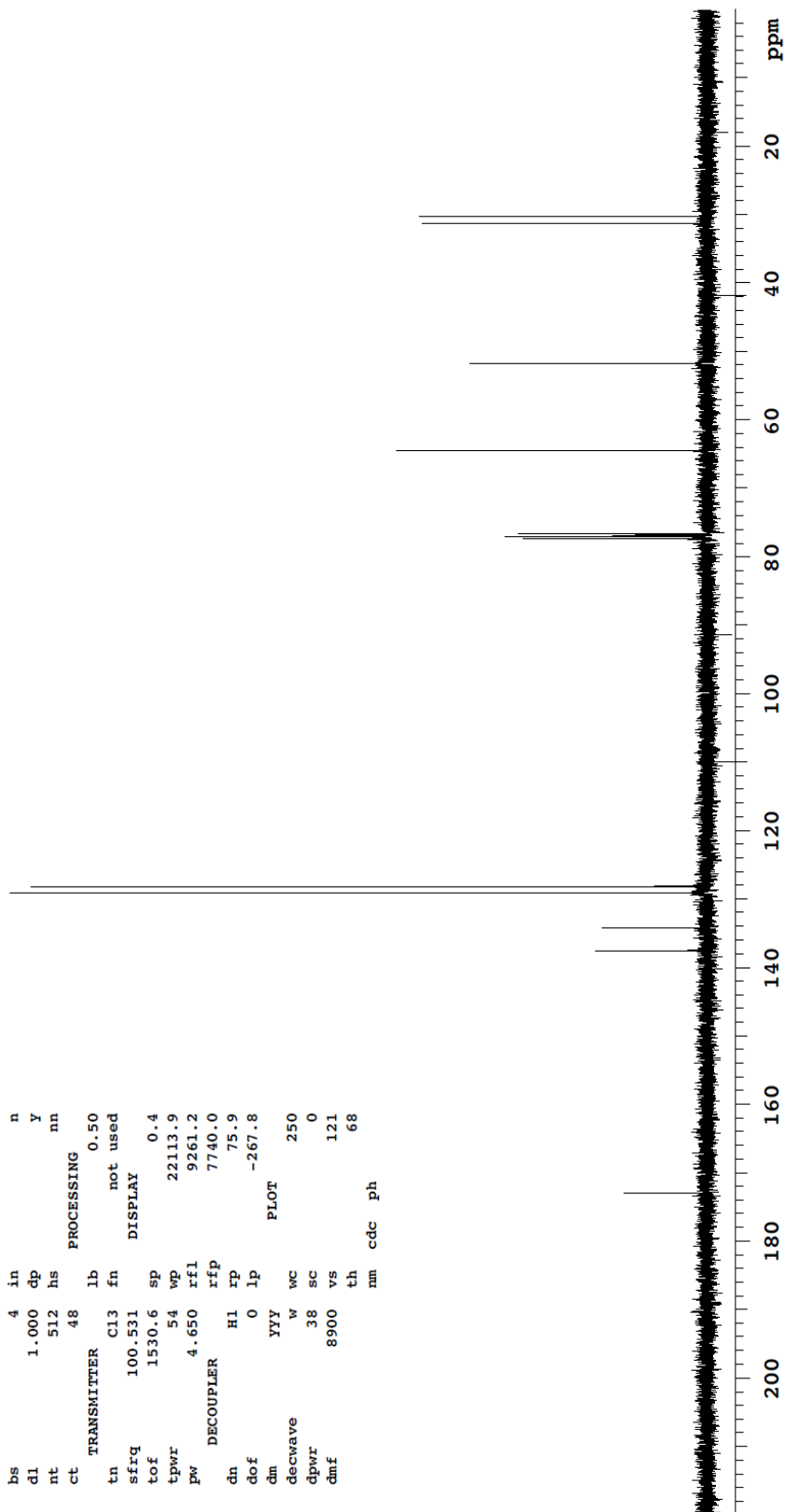


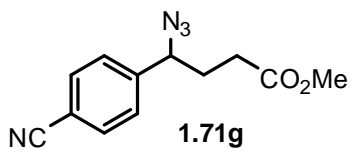


HG 4-54-1

expl CARBON

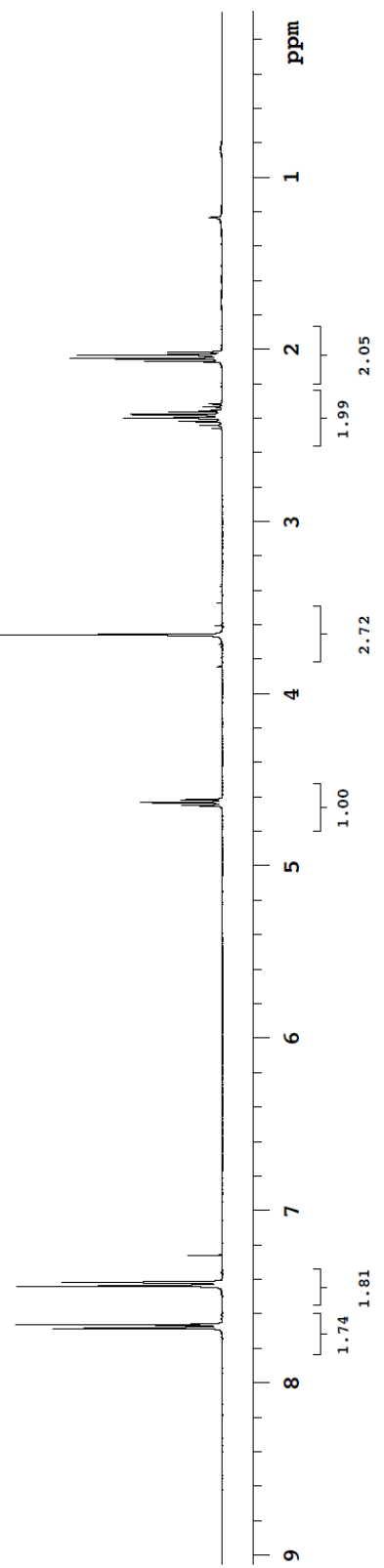
SAMPLE	PRESATURATION	n
date Apr 23 2011	satmode	n
solvent cdcl3	wet	SPECIAL
file /home/data/ke-	temp	25.0
rr/Huck/HG_4-54-1-	gain	not used
April_23_2011_01/C-	spin	20
ARBONO1.fid	hst	0.008
ACQUISITION	pw90	9.300
sw 25157.2	alfa	10.000
at 1.303	FLAGS	
np 65536		
fb not used	il	n
bs 4	in	n
d1 1.000	dp	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	rfl	9261.2
DECOUPLER	rfp	7740.0
dn H1	fp	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

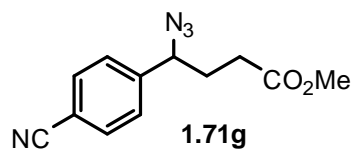




HG 4-80-1
 expl PROTON

SAMPLE	PRESATURATION	n
date Apr 29 2011	satmode	n
solvent cdcl3	wet	n
file /home/data/ke-	SPECIAL	
rr/Huck/HG 4-80-1-	temp	25.0
April_29_2011_01/P-	gain	not used
ROTON01.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	14.8
tof 399.8	vp	3606.1
tpwr 56	rfl	3690.5
pw 6.550	rfp	2902.3
DECOUPLER	fp	-116.0
dn C13	lp	-21.8
dof 0	PLOT	
dnn nnn	wc	250
decwave W40_hfcp	sc	0
dpwr 34	vs	39
dmf 29412	th	14
	al	cdc
	ph	

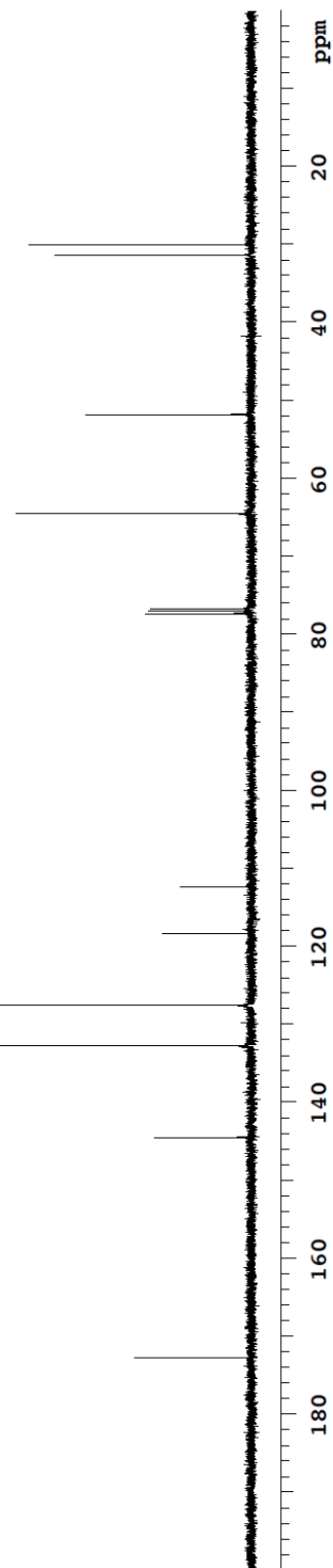


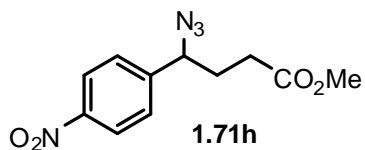


```

HG 4-80-1
expl CARBON
SAMPLE PRESATURATION
date Apr 29 2011 satmode n
solvent cdcl3 wet n
file /home/data/Ke- SPECIAL
ir/Huck/HG_4-80-1_ temp 25.0
April_29_2011_01/C- gain not used
ARBONO1.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
dl 1.000 dp y
nt 512 hs nn
ct 64 PROCESSING
TRANSMITTER lb 0.50
tn C13 fn not used
sfrq 100.531 DISPLAY
tof 1530.6 sp 0.2
tpwr 54 wp 20113.2
pw 4.600 rfl 1521.4
DECOUPLER rfp 0
dn H1 rp 57.3
dof 0 lp -234.1
dm YY PLOT
decwae w wc 250
dpwr 38 sc 0
dmf 9100 vs 94
th cdc ph 68

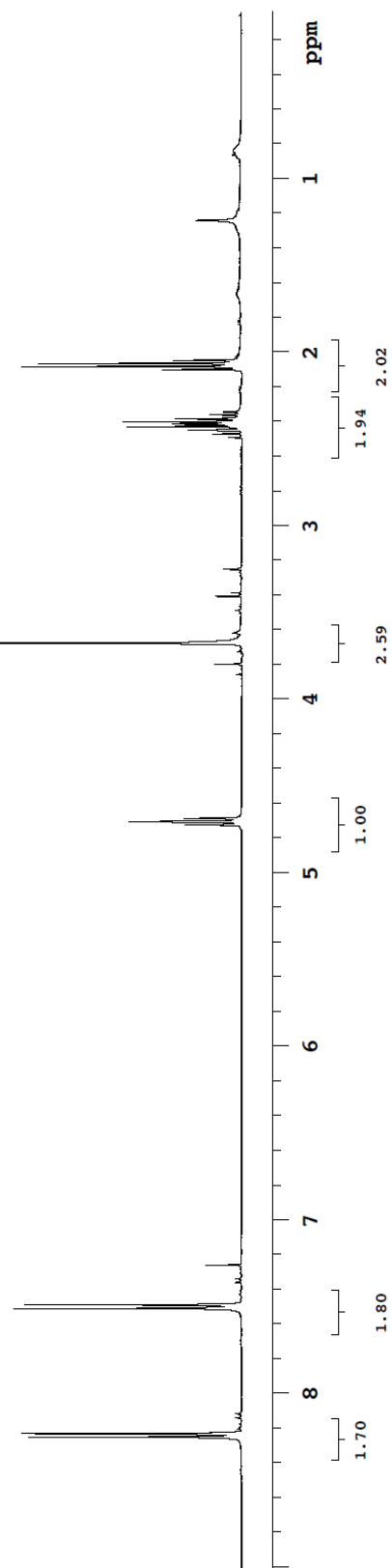
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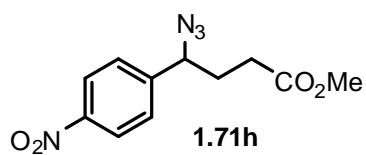




HG_4-78-1
 exp1 PROTON

SAMPLE	PRESATURATION	n
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/P-	gain	not used
ROTON01.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	15.2
tof 399.8	wp	3591.7
tpwr 56	rfl	3690.1
pw 6.550	rfp	2902.3
DECOUPLER	rfp	-124.9
dn C13	lp	-7.6
dof 0	PLOT	
dm nnn	wc	250
decwave W40_hfcp	sc	0
dpwr 34	vs	101
dmf 29412	th	27
	ai	cdc
	ph	





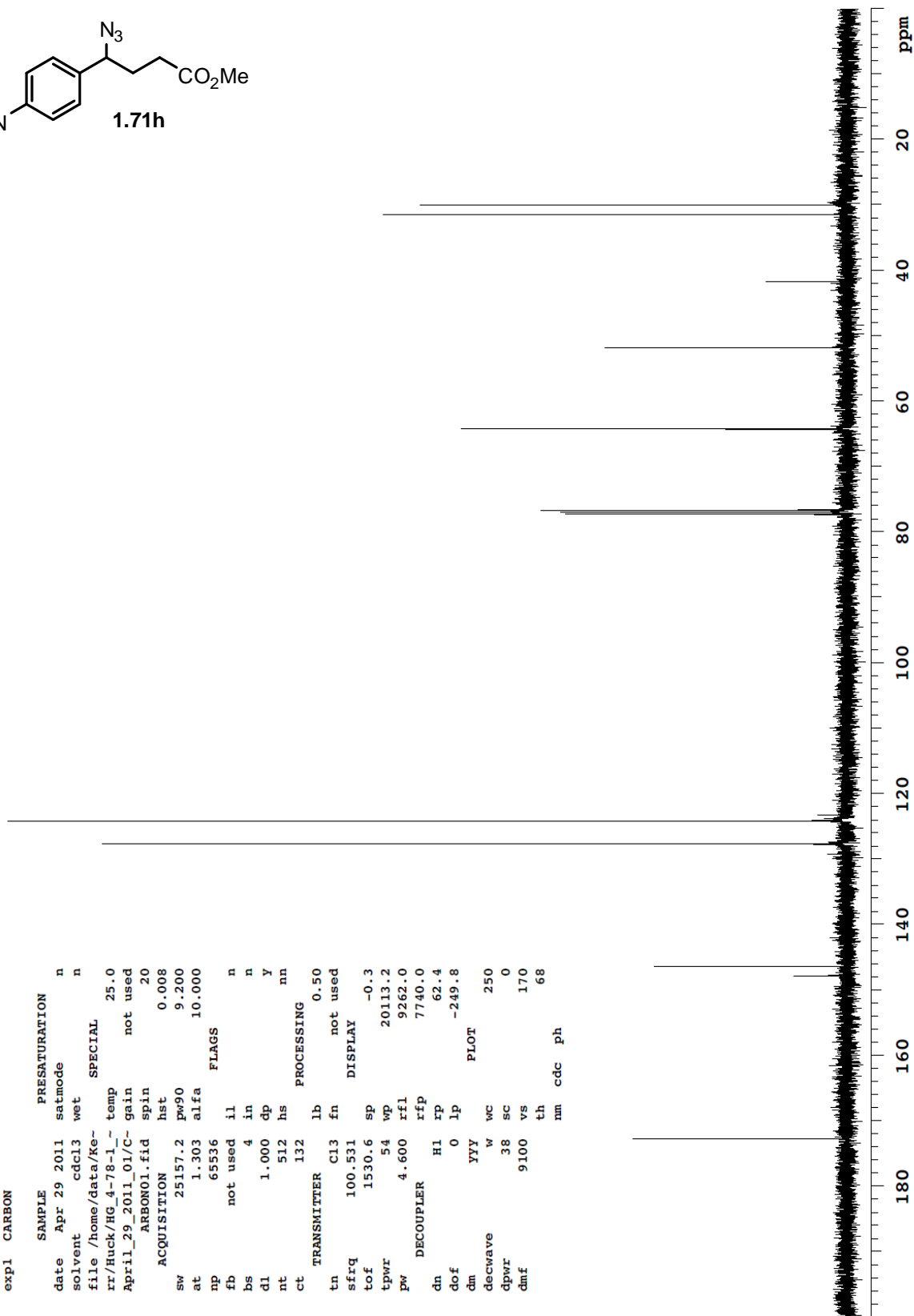
HG_4-78-1

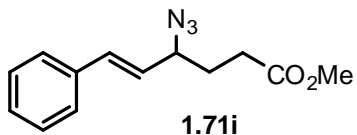
expl CARBON

```

SAMPLE PRESATURATION
date Apr 29 2011 satmode n
solvent cdcl3 wet n
file /home/data/Ke- SPECIAL 25.0
rr/Huck/HG_4-78-1_- temp not used
April_29_2011_01/C- gain 20
ARBONO1.fid spin 0.008
ACQUISITION hst 9.200
sw 25157.2 pw90 10.000
at 1.303 alfa FLAGS
np 65536
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 rfl 9262.0
DECOUPLER H1 rfp 7740.0
dn 0 lp 62.4
dm YYY PLOT -249.8
deccwve w wc 250
dpwr 38 sc 0
dmf 9100 vs 170
mm cdc ph 68

```

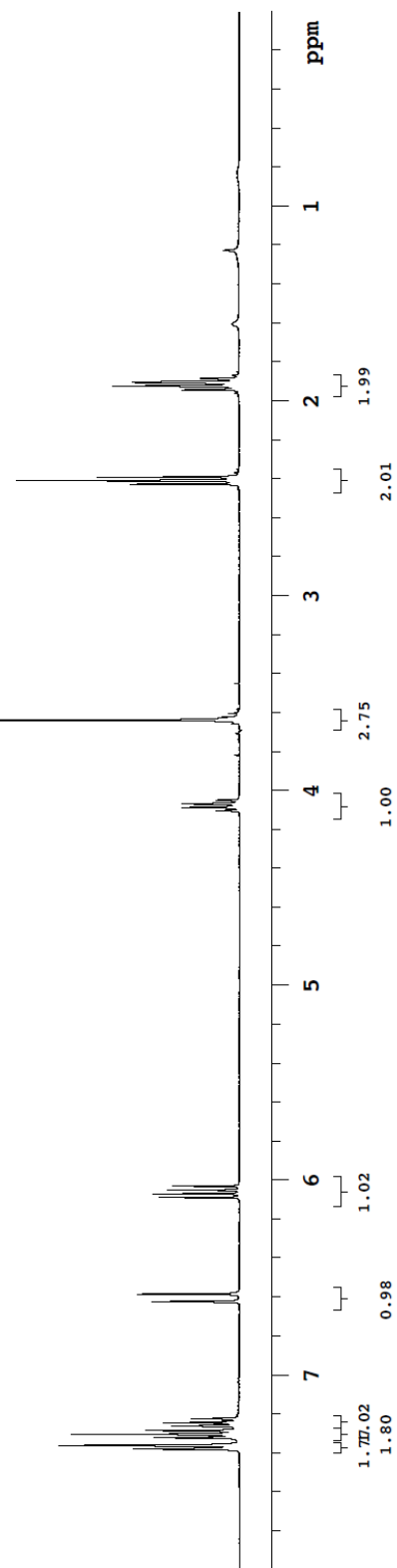


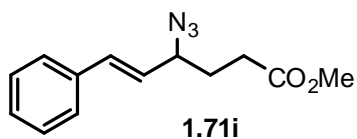


```

HG_4-58-1
exp1  PROTON
SAMPLE      PRESATURATION
date  Apr 23 2011  satmode  n
solvent  cdcl3  wet  n
file  /home/data/Ke-rr/Huck/HG_4-58-1_
rr/Huck/HG_4-58-1_  temp  25.0
April_23_2011_01/P- gain  not used
ROTOR01.fid  spin  20
ACQUISITION  hst  0.008
sw  6402.6  pw90  13.200
at  2.559  alfa  6.600
np  32768
fb  not used  il  n
bs  4  in  n
dl  1.000  dp  Y
nt  8  hs  nn
ct  8  PROCESSING
tn  H1  fn  not used
sfrq  399.762  sp  0.3
tof  399.8  wp  3197.4
tpwr  56  rfl  802.7
pw  6.600  rfp  0
dn  DECOUPLER  C13  lp  -131.0
dof  0  PLOT  -23.5
dm  nnn  wc  250
decwave  W40_hfcp  sc  0
dpwr  34  vs  74
dmf  29412  th  ai  cdc  ph  27

```

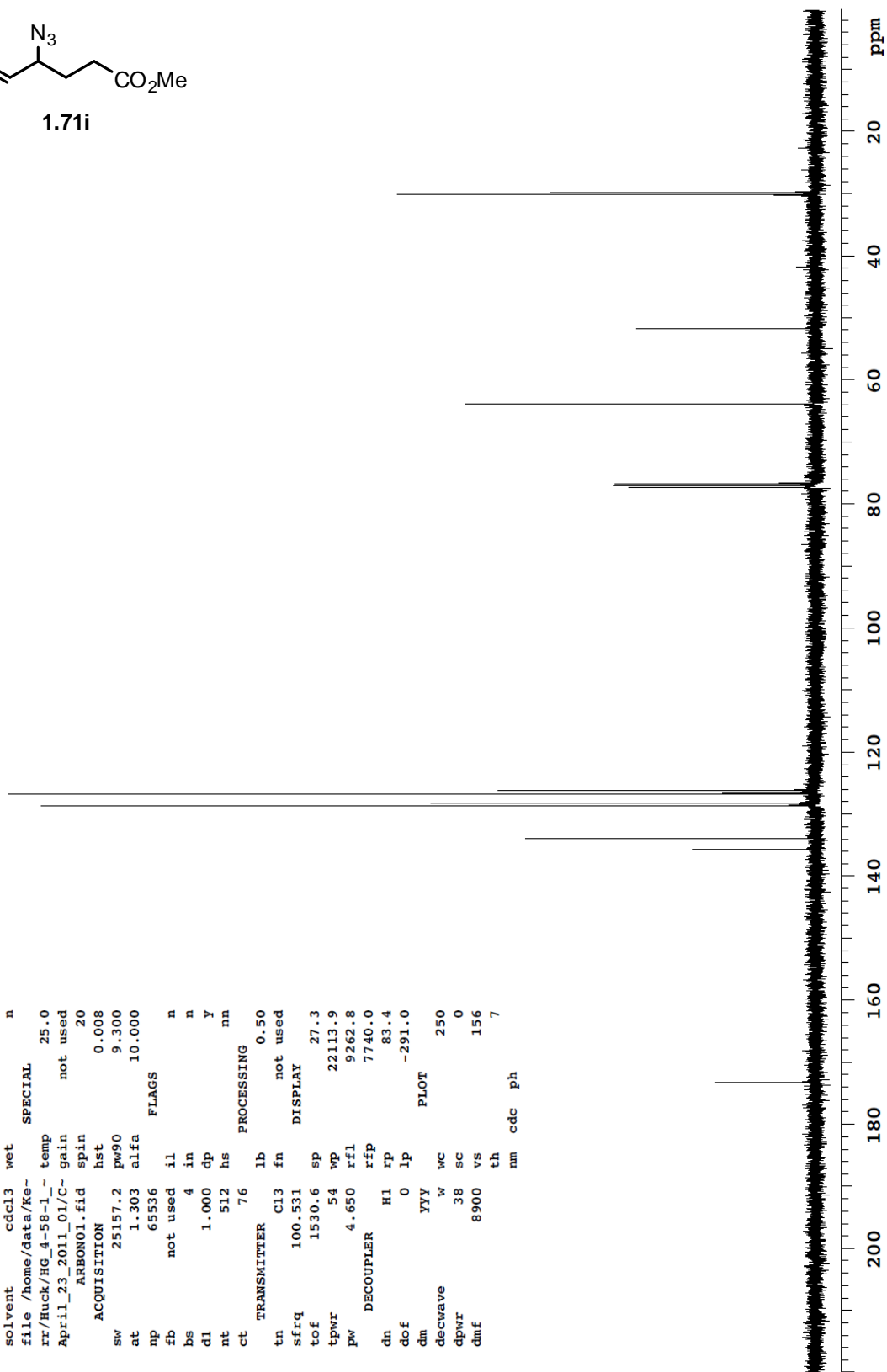


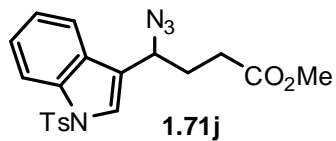


```

HG_4-58-1
exp1 CARBON
SAMPLE PRESATURATION
date Apr 23 2011 satmode n
solvent cdcl3 wet n
file /home/data/ke- SPECIAL
rr/Huck/HG_4-58-1~ temp 25.0
April_23_2011_01/C~ gain not used
ARBONO1.fid spin 20
ACQUISITION hst 0.008
sw 25157.2 pw90 9.300
at 1.303 alfa 10.000
np 65536
fb not used il FLAGS
bs 4 in n
dl 1.000 dp y
nt 512 hs nn
ct 76 PROCESSING
TRANSMITTER lb 0.50
tn CI3 fn not used
sfrq 100.531 DISPLAY
tof 1530.6 sp 27.3
tpwr 54 wp 22113.9
pw 4.650 rfl 9262.8
DECOUPLER rfp 7740.0
dn H1 rp 83.4
dof 0 lp -291.0
dm YYY PLOT
decwave w wc 250
dpwr 38 sc 0
dmf 8900 vs 156
th cdc ph 7

```

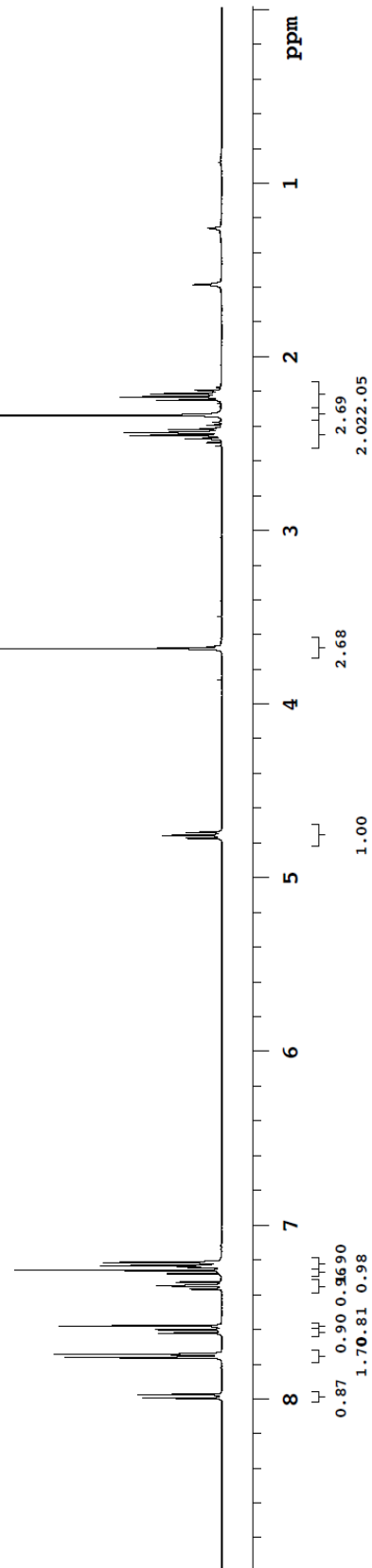


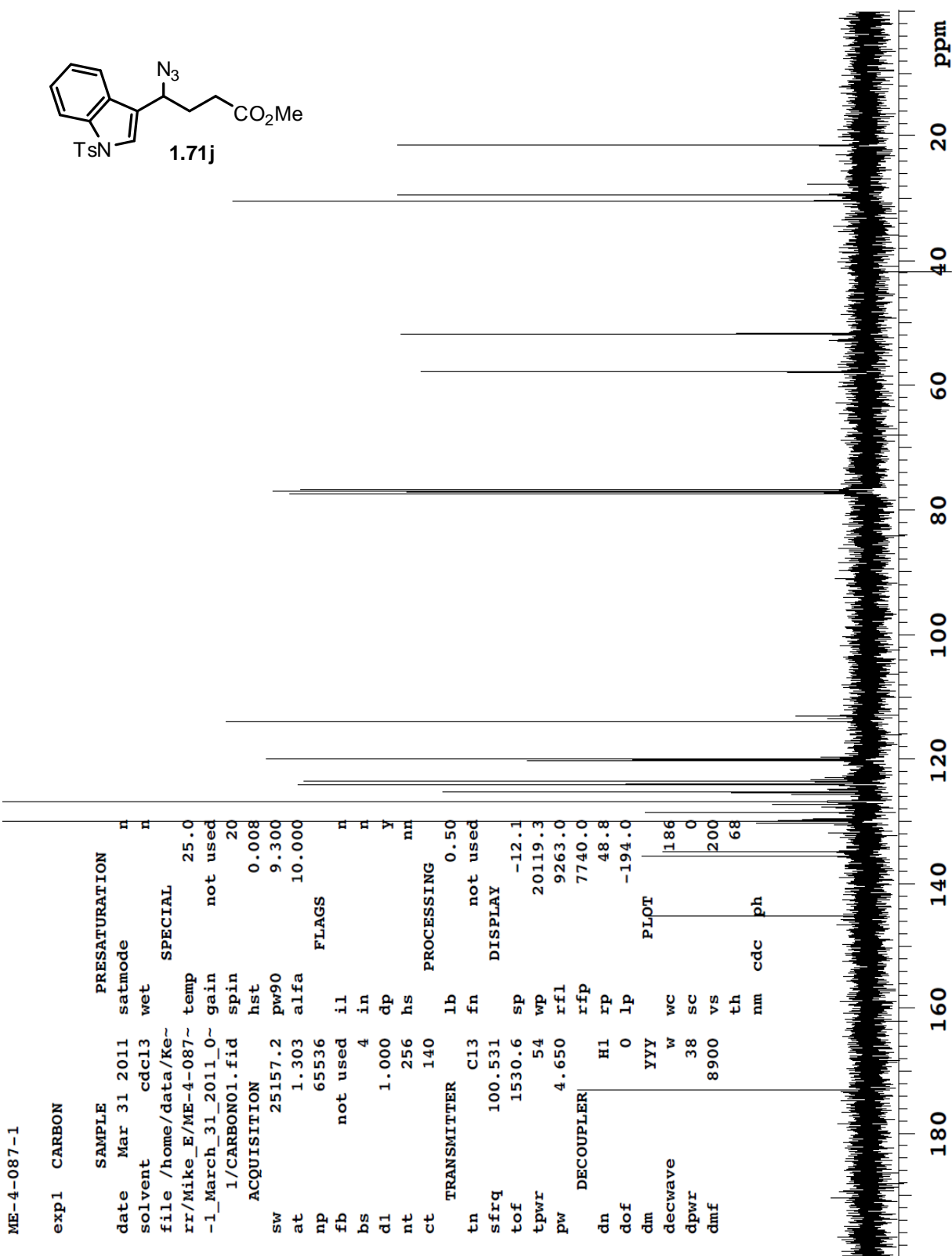


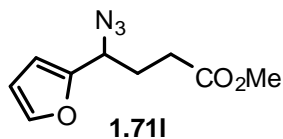
HG 4-56-1

exp1 PROTON

date	Apr 23 2011	satmode	n	PRESATURATION
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	
dl	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	rfl	3689.8	
pw	6.600	rfp	2902.3	
DECOUPLER	rp		-131.6	
dn	CI3	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	







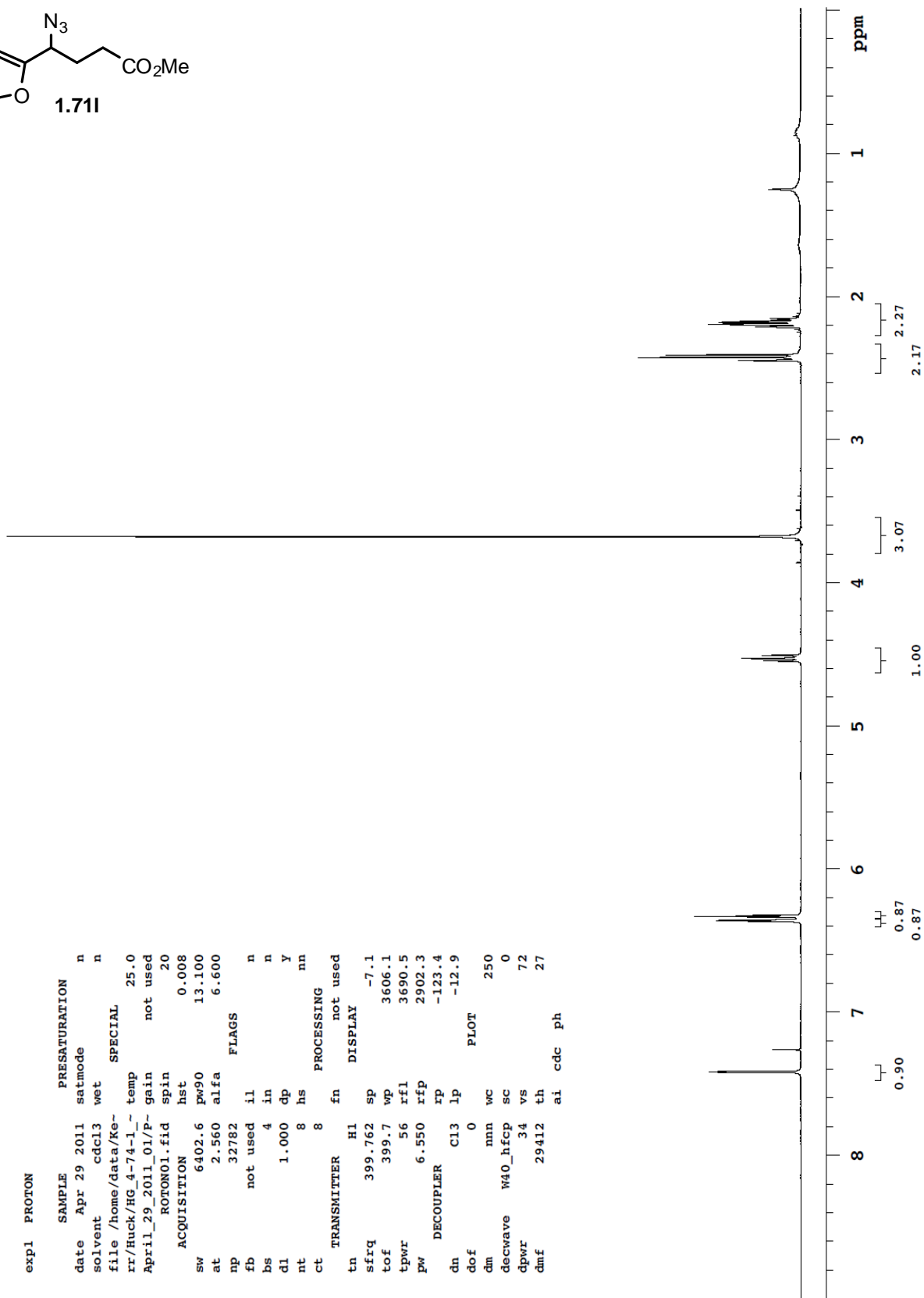
HG 4-74-1

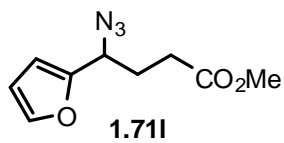
exp1 PROTON

```

SAMPLE          PRESATURATION
date  Apr 29 2011  satmode  n
solvent  cdcl3  wet  n
file  /home/data/Ke-
rr/Huck/HG 4-74-1_  SPECIAL
April_29_2011_01/P-  temp  25.0
          ROTON01.fid  gain  not used
          spin  20
          hst  0.008
ACQUISITION
sw  6402.6  pw90  13.100
at  2.560  alfa  6.600
np  32782
fb  not used  il  n
bs  4  in  n
dl  1.000  dp  Y
nt  8  hs  nn
ct  8  PROCESSING
          fn  not used
          HI  DISPLAY
tn  399.762  sp  -7.1
sfrq  399.7  wp  3606.1
tpwr  56  rfl  3690.5
pw  6.550  rfp  2902.3
          rp  -123.4
          lp  -12.9
          C13  PLOT
dof  0
dm  nnn  wc  250
decwave  W40_hfcp  sc  0
dpwr  34  vs  72
dmf  29412  th  ai  cdc  ph  27

```



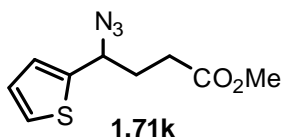


HG 4-74-1
 exp1 CARBON

date	Apr 29 2011	satmode	n
solvent	cdcl3	wet	n
file	/home/data/ke-	SPECIAL	
rr/Huck/HG_4-74-1_	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
dl	1.000	dp	y
nt	512	hs	nn
ct	92	PROCESSING	
TRANSMITTER	lb	0.50	
tn	C13	fn	not used
sfrq	100.531	DISPLAY	
tof	1530.6	sp	5.1
tpwr	54	wp	20071.0
pw	4.600	xf1	9260.5
DECOUPLER	rfp	7740.0	
dn	H1	rp	61.6
dof	0	lp	-251.4
dm	YYY	PLOT	
decwave	w	wc	250
dpwr	38	sc	0
dmf	9100	vs	84
		th	68
		nm	cdc
		ph	

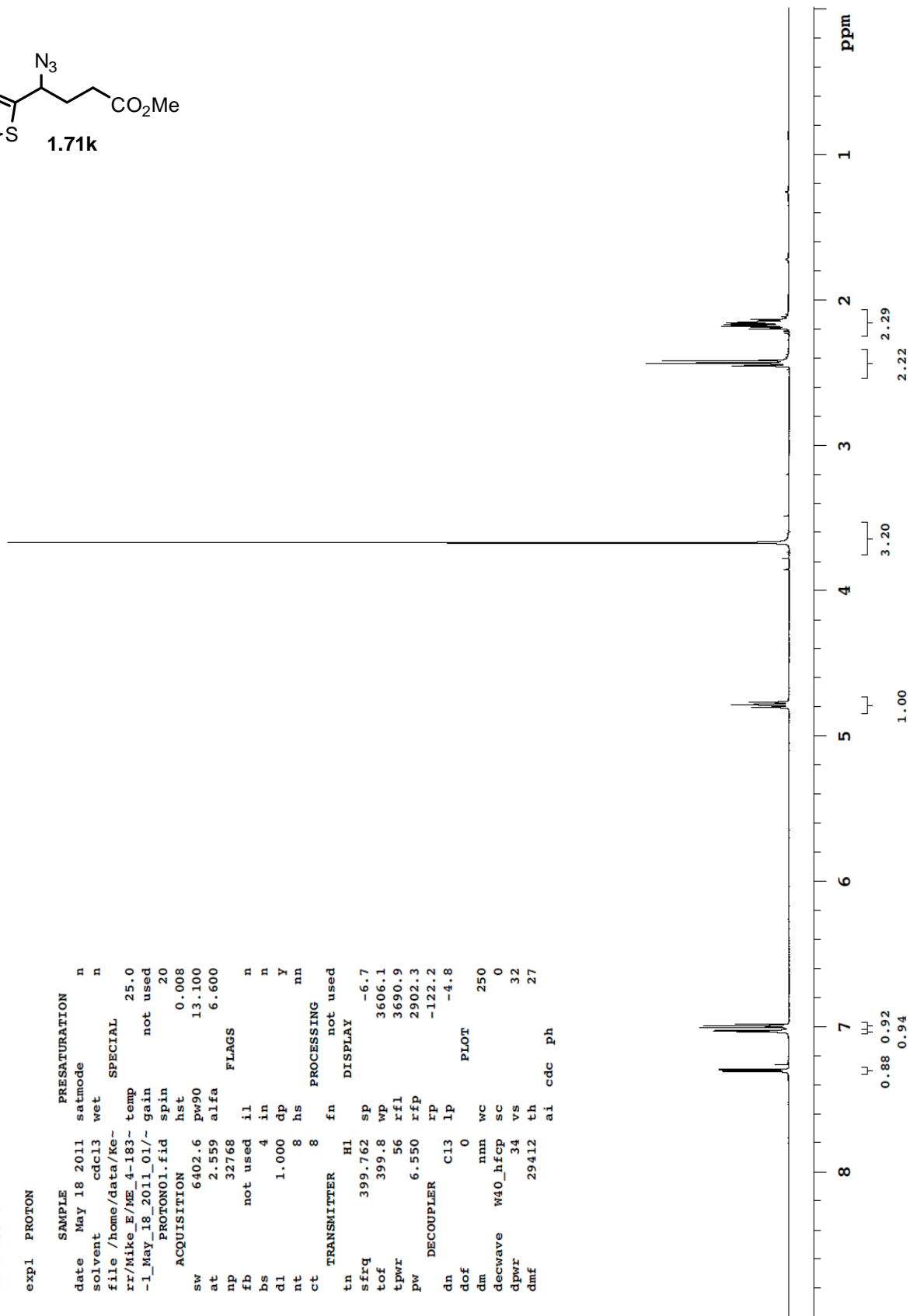
180 160 140 120 100 80 60 40 20 ppm

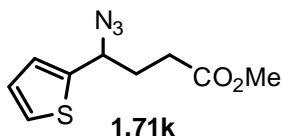




```

ME 4-183-1
expl  PROTON
      SAMPLE      PRESATURATION
date  May 18 2011 satmode   n
solvent cdcl3 wet        n
file  /home/data/Re-rr/Mike_E/ME_4-183-1
      SPECIAL 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
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
      H1 DISPLAY
tn 399.762 sp -6.7
sfrq 399.8 wp 3606.1
tpwr 56 rfl 3690.9
pw 6.550 rfp 2902.3
      DECOUPLER xp -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 ai cdc ph
  
```





ME 4-183-1

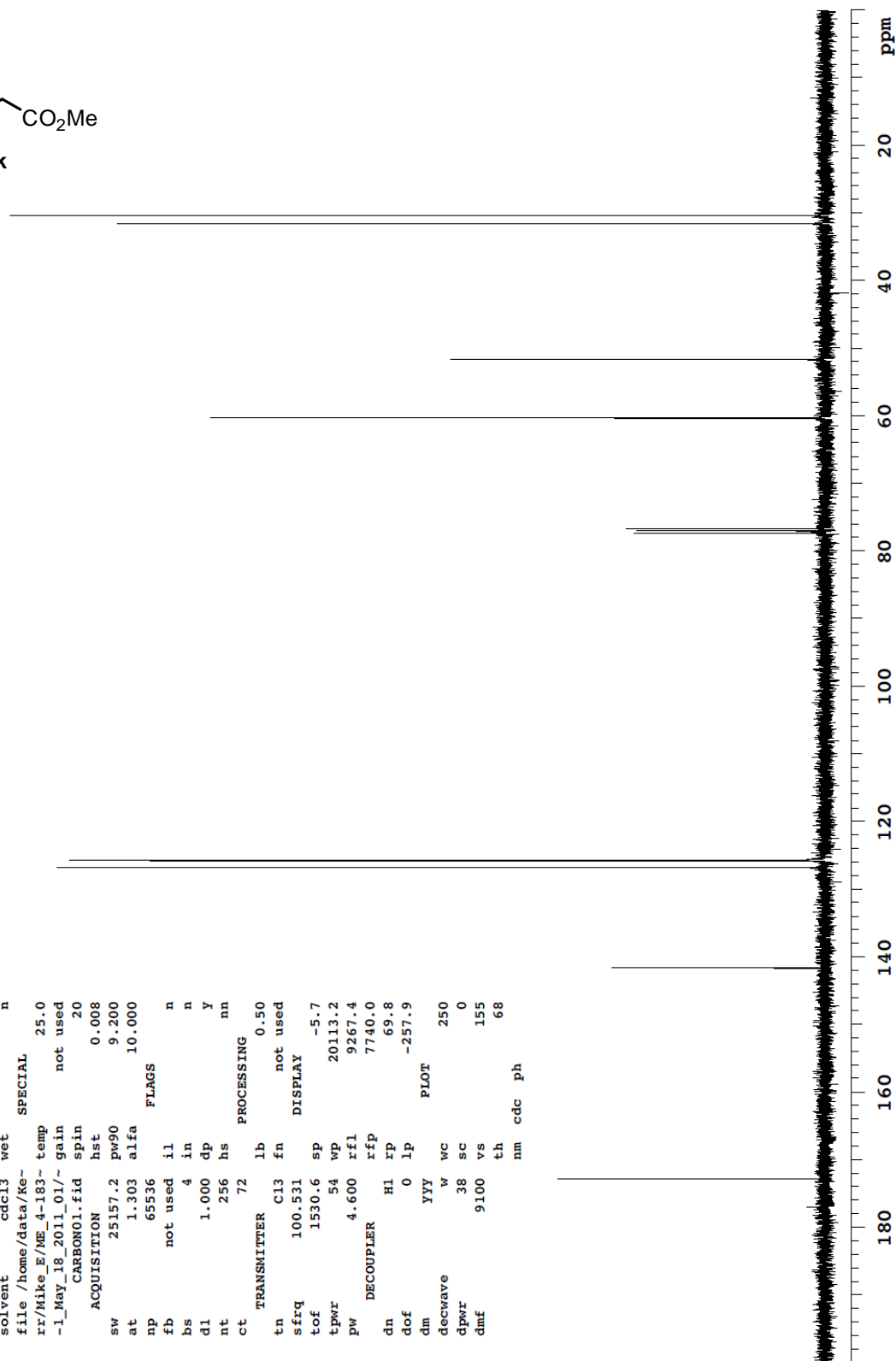
exp1 CARBON

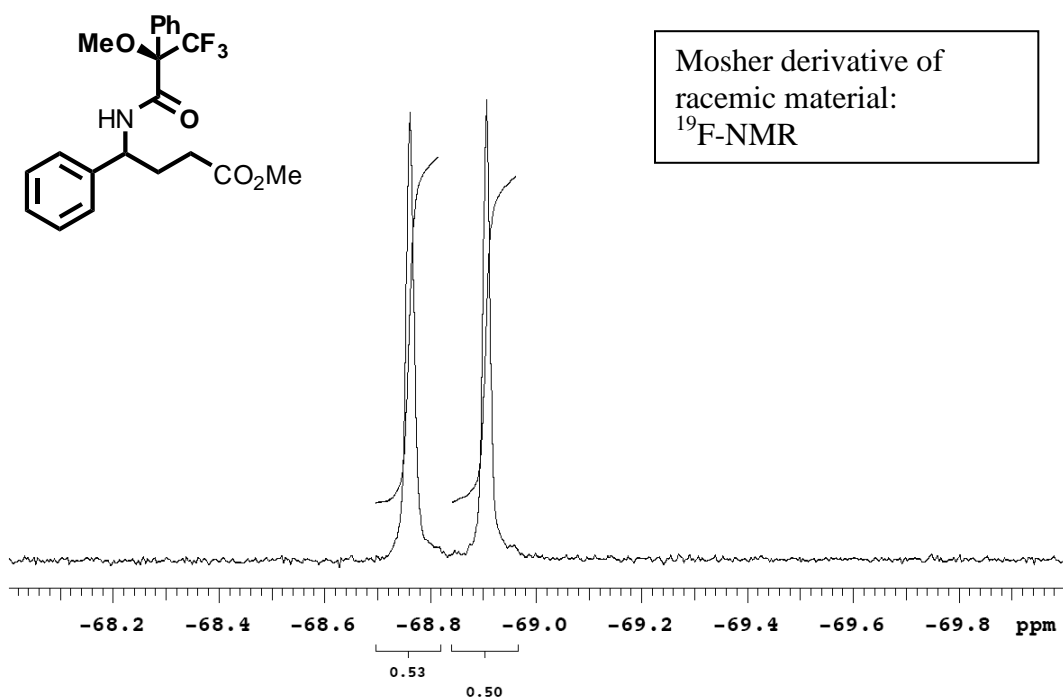
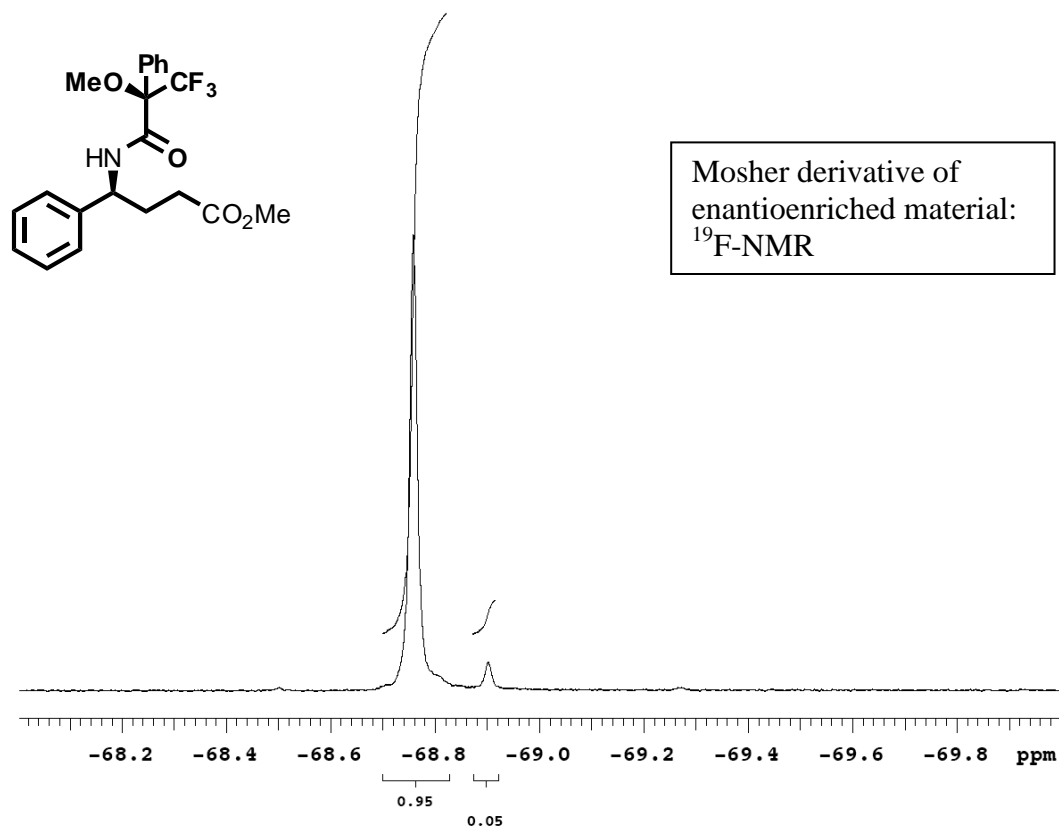
```

SAMPLE          PRESATURATION
date  May 18 2011  satmode      n
solvent  cdcl3  wet      n
file  /home/data/ke-
rr/Mike_E/ME_4-183-
-1_May_18_2011_01/~ gain  25.0
CARBON01.fid spin  not used
                hst      20
ACQUISITION    hst      0.008
sw  25157.2  pw90      9.200
at  1.303  alfa      10.000
np  65536
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  rfl  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

```





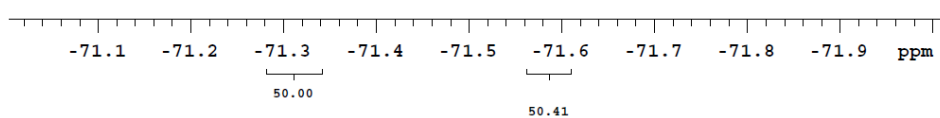
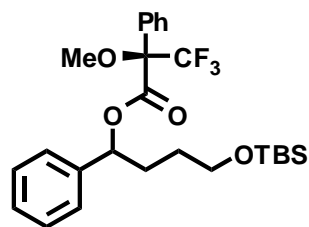
HG 9-204-1

Sample Name:
Huck
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Huck
Sample directory:
HG 9-204-1 Feb 5 2013_01
FidFile: FLUORINE

Pulse Sequence: FLUORINE (s2pul)
Solvent: cdcl3
Data collected on: Feb 5 2013

Temp. 25.0 C / 298.1 K
Sample #7, Operator: Kerr

Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 0.736 sec
Width 86956.5 Hz
32 repetitions
OBSERVE F19, 376.4515719 MHz
DATA PROCESSING
FT size 131072
Total time 1 min 36 sec



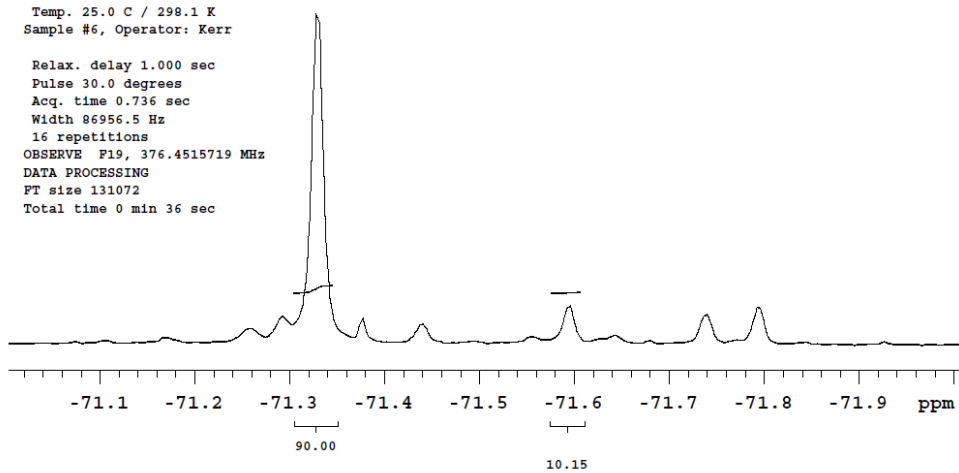
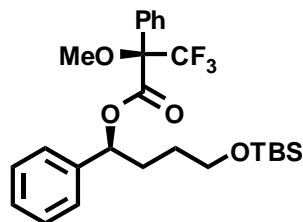
ME 8-205

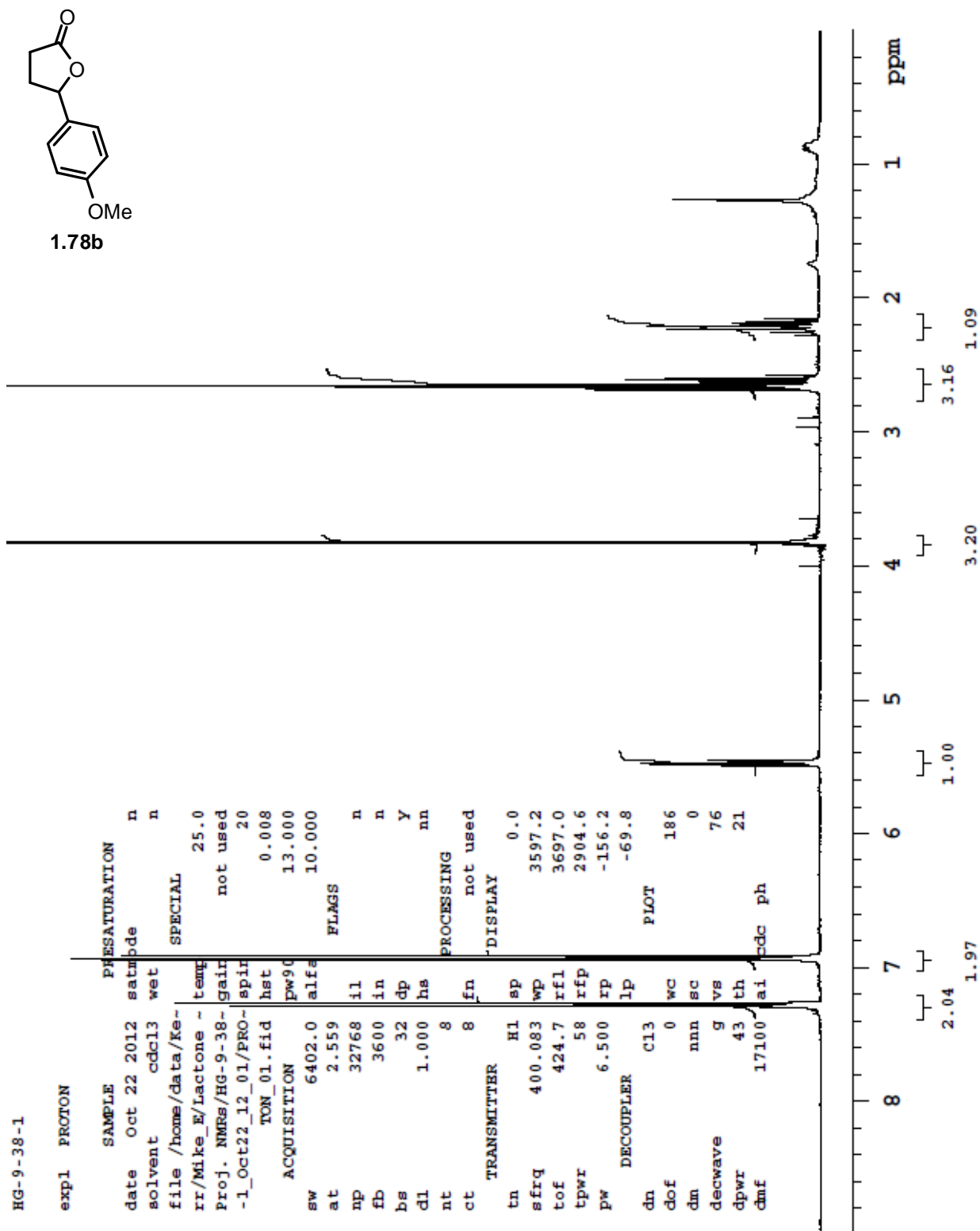
Sample Name:
Huck
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Huck
Sample directory:
ME 8-205 Feb 5 2013_01
FidFile: FLUORINE

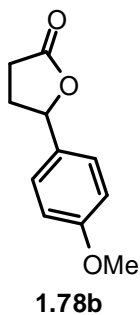
Pulse Sequence: FLUORINE (s2pul)
Solvent: cdcl3
Data collected on: Feb 5 2013

Temp. 25.0 C / 298.1 K
Sample #6, Operator: Kerr

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 0.736 sec
Width 86956.5 Hz
16 repetitions
OBSERVE F19, 376.4515719 MHz
DATA PROCESSING
FT size 131072
Total time 0 min 36 sec



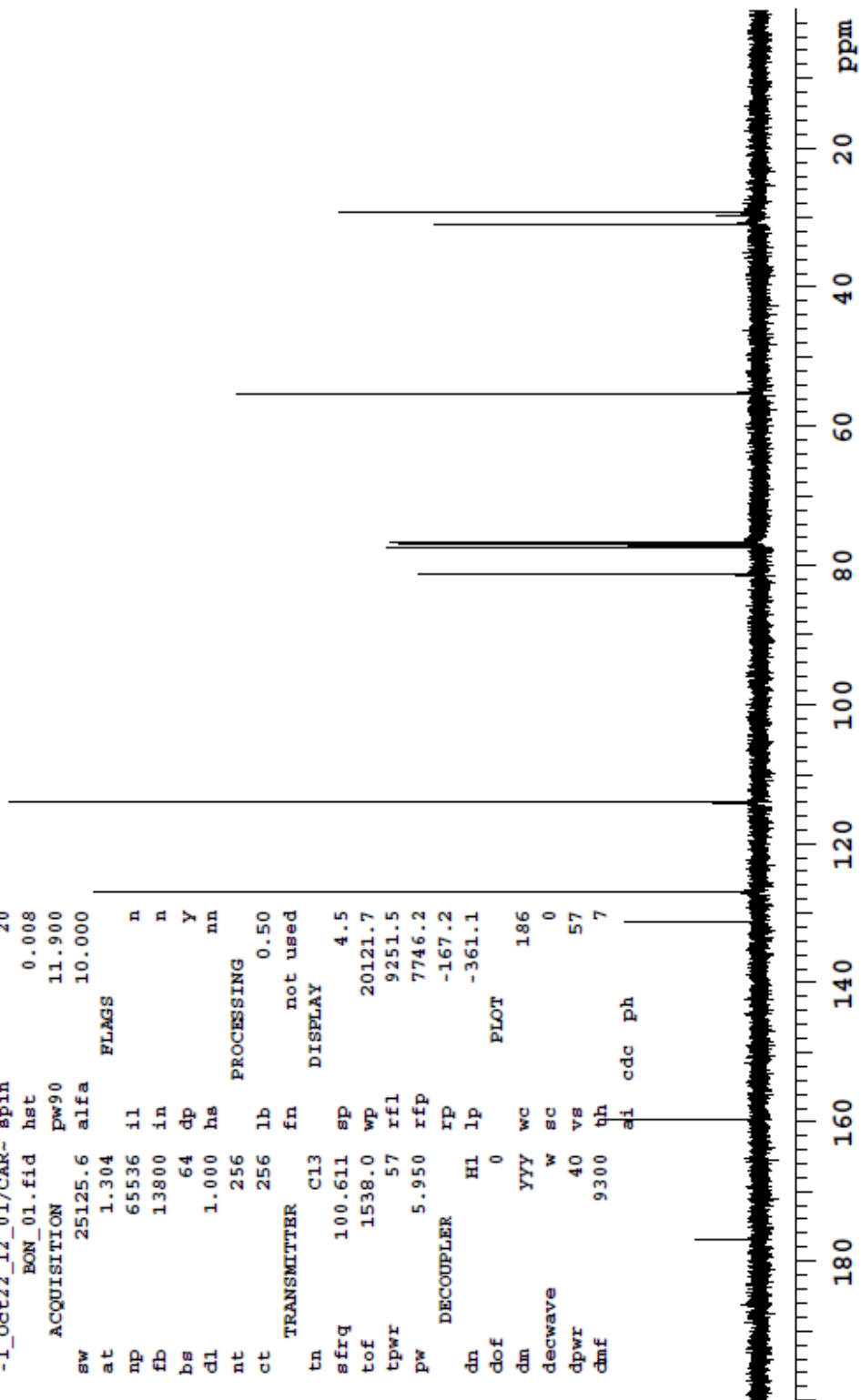


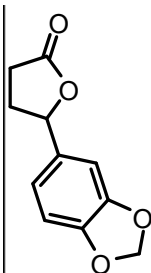


HG-9-38-1

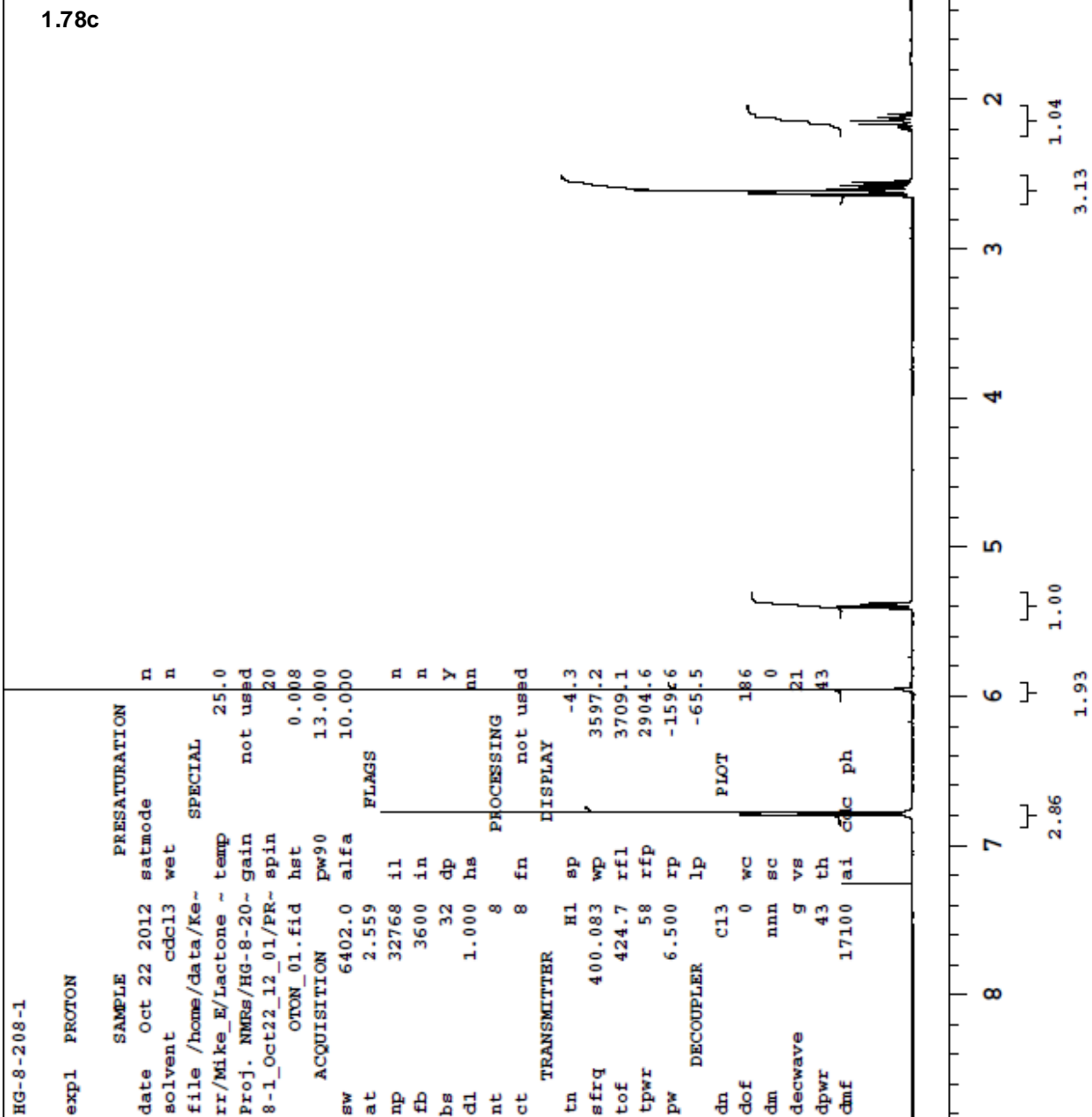
expl CARBON

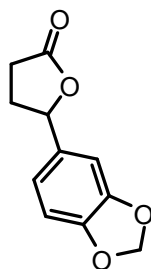
SAMPLE		PRESATURATION	
date	Oct 22 2012	satmode	n
solvent	cdcl3	wet	n
file	/home/data/Ke-	SPECIAL	
ir/Mike_E/Lactone	- temp		25.0
Proj. NMRs/HG-9-38-	gain	not used	
-1_Oct22_12_01/CAR-	spin		20
	BON_01.fid	hst	0.008
ACQUISITION		pw90	11.900
sw	25125.6	alfa	10.000
at	1.304	FLAGS	
np	65536	il	n
fb	13800	in	n
bs	64	dp	y
dl	1.000	hs	nn
nt	256	PROCESSING	
ct	256	lb	0.50
TRANSMITTER		fn	not used
tn	CL3	DISPLAY	
sfrq	100.611	sp	4.5
tof	1538.0	wp	20121.7
tpwr	57	rfl	9251.5
pw	5.950	rfp	7746.2
DECOUPLER		rp	-167.2
dn	H1	lp	-361.1
dof	0	PLOT	
dm	YY	wc	186
decwave	w	sc	0
dpwr	40	vs	57
dmf	9300	th	7
		ai	cdc
		ph	





1.78c





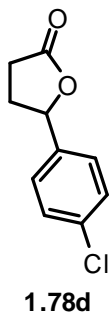
1.78c

HG-8-208-1

exp1 CARBON

SAMPLE		PRESATURATION	
date	Oct 22 2012	satmode	n
solvent	cdcl3	wet	n
file	/home/data/Ke-	SPECIAL	
rr/Mike_E/Lactone ~ temp			25.0
Proj. NMRS/HG-8-20-	gain	not used	
8-1_Oct22_12_01/CA-	spin	20	
RBON_01.fid	hst	0.008	
ACQUISITION	pw90	11.900	
sw	25125.6	alfa	10.000
at	1.304	FLMGS	
np	65536	il	n
fb	13800	in	n
bs	64	dp	y
dl	1.000	hs	nn
nt	256	PROCESSING	
ct	256	lb	0.50
TRANSMITTER	fn	not used	
tn	Cl3	DISPLAY	
sfrq	100.611	sp	4.2
tof	1538.0	wp	20121.7
tpwr	57	rf1	9251.8
pw	5.950	rfp	7746.2
DECOUPLER	rp		-153.9
dn	H1	lp	-383.2
dof	0	PLOT	
dm	YYY	wc	186
decwave	w	sc	0
dpwr	40	vs	57
dmf	9300	th	6
	ai	cdc	ph

180 160 140 120 100 80 60 40 20 ppm



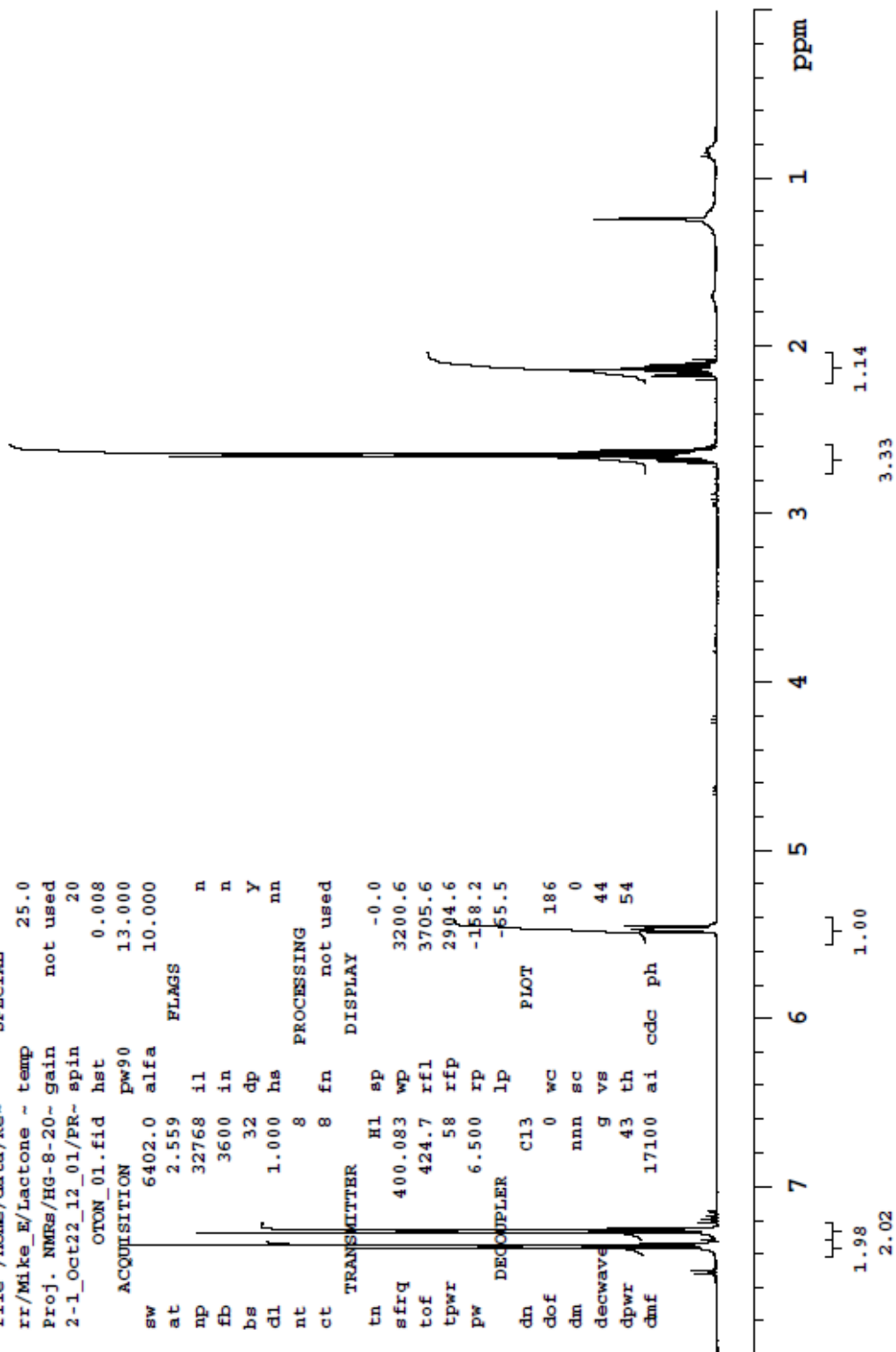
HG-8-202-1

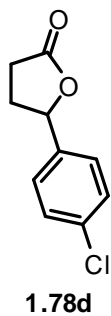
exp1 PROTON

```

SAMPLE          PRESATURATION
date   Oct 22 2012  satmode      n
solvent  cdcl3  wet             n
file /home/data/ke-          SPECIAL
rr/Mike_E/Lactone ~ temp    25.0
Proj. NMRs/HG-8-20~ gain    not used
2-1_Oct22_12_01/PR~ spin    20
OTON_01.fid  hst             0.008
ACQUISITION  pw90            13.000
              alfa           10.000
              FLAGS
at           2.559
np           32768  il      n
fb           3600  in      n
bs           32    dp      y
d1           1.000  hs      nn
nt           8
ct           8  fn      not used
              PROCESSING
              DISPLAY
TRANSMITTER  H1  sp      -0.0
              400.083  wp    3200.6
              424.7  rf1   3705.6
              58    rfp   2904.6
              6.500  rp   -158.2
              DECOUPLER  lp   -65.5
              c13      PLOT
dn           0  wc      186
dm           nnn  sc      0
decwave     g  vs      44
dpwr        43  th      54
dmf        17100 ai  cdc  ph

```

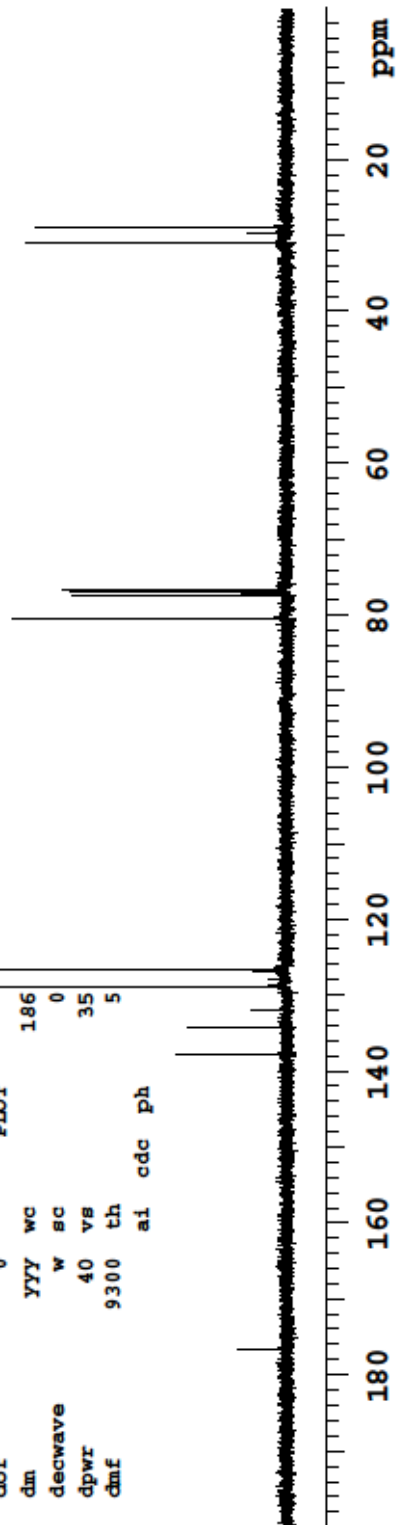


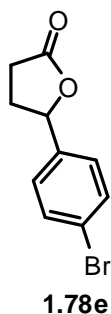


HG-8-202-1

exp1 CARBON

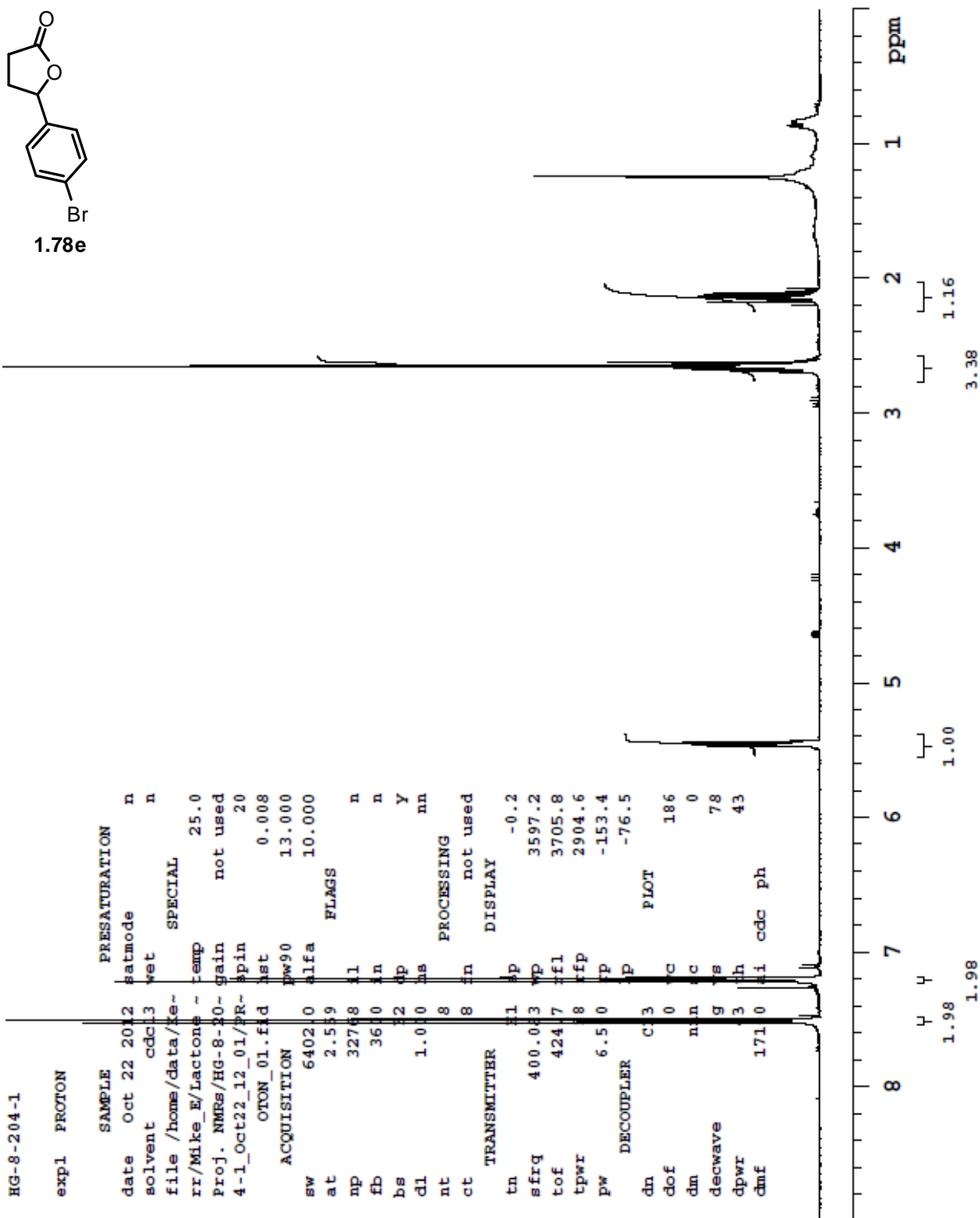
SAMPLE		PRESATURATION	
date	Oct 22 2012	satmode	n
solvent	cdcl3	wet	n
file	/home/data/Ke-	SPECIAL	
ir/Mike_E/Lactone	~ temp	25.0	
Proj.	NMRs/HG-8-20-	Gain	not used
2-1_Oct22_12_01/CA-	spin	20	
RBON_01.fid	hst	0.008	
ACQUISITION			
pw90	11.900		
sw	25125.6	alfa	10.000
at	1.304	FLAGS	
np	65536	il	n
fb	13800	in	n
bs	64	dp	y
d1	1.000	hs	nn
nt	256	PROCESSING	
ct	256	lb	0.50
TRANSMITTER			
tn	C13	fn	not used
DISPLAY			
sfrq	100.611	sp	4.2
tof	1538.0	wp	20121.7
tpwr	57	rf1	9250.2
pw	5.950	rfp	7746.2
DECOUPLER			
dn	H1	rp	-157.6
dof	0	lp	-397.1
PLOT			
dm	yyy	wc	186
decwave	w	sc	0
dpwr	40	vs	35
dmf	9300	th	5
ai cdc ph			

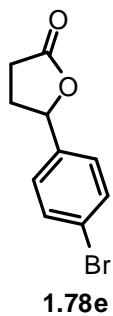




HG-8-204-1
exp1 PROTON

SAMPLE		PRESATURATION	
date	Oct 22 2012	satmode	n
solvent	cdcl3	wet	n
file	/home/data/ke-	SPECIAL	
ir/Mike_E/Lactone	- temp	25.0	
Proj.	NMRs/HG-8-10-	gain	not used
4-1_Oct22_12_01/PR-	spin	20	
OTON_01.fid	ast	0.008	
ACQUISITION		FLAGS	
sw	6402.0	pw90	13.000
at	2.559	alfa	10.000
np	32768	l1	n
fb	3600	in	n
bs	32	dp	y
d1	1.000	hs	nn
nt	8	in	not used
ct	8	in	not used
TRANSMITTER		DISPLAY	
tn	fl	fp	-0.2
sfrq	400.083	fp	3597.2
tof	424.7	fl1	3705.8
tpwr	8	rfp	2904.6
pw	6.50	fp	-153.4
DECOUPLER		PLOT	
dn	C13	pc	186
dof	0	pc	0
dm	nm	pc	78
decwave	9	ts	43
dpwr	3	h	
dmf	171.0	si	cdc ph

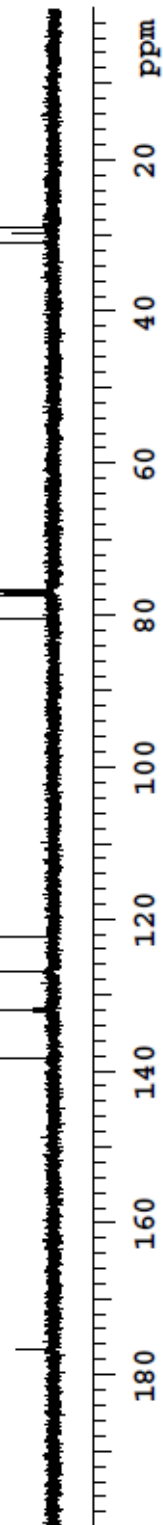


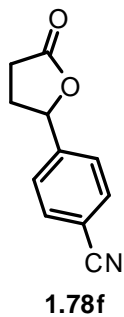


HG-8-204-1

expl CARBON

SAMPLE	PRESATURATION
date Oct 22 2012	satmode n
solvent cdcl3	wet n
file /home/data/Ke-	SPECIAL
ir/Mike_E/Lactone - temp	25.0
Proj. NMRS/HG-8-20-	Gain not used
4-1_Oct22_12_01/CA-	spin 20
RBON_01.fid	hst 0.008
ACQUISITION	PW90 11.900
sw 25125.6	alfa 10.000
at 1.304	FLAGS
np 65536	il n
fb 13800	in n
bs 64	dp Y
d1 1.000	hs nn
nt 256	PROCESSING
ct 256	lb 0.50
TRANSMITTER	fn not used
tn C13	DISPLAY
sfrq 100.611	sp 4.1
tof 1538.0	wp 20121.7
tpwr 57	rf1 9249.6
pw 5.950	rfp 7746.2
DECOUPLER	rp -147.1
dn H1	lp -395.3
dof 0	PILOT
dm YYY	wc 1.86
decwave w	sc 0
dpwr 40	vs 24
dmf 9300	th 4
	ai cdc ph





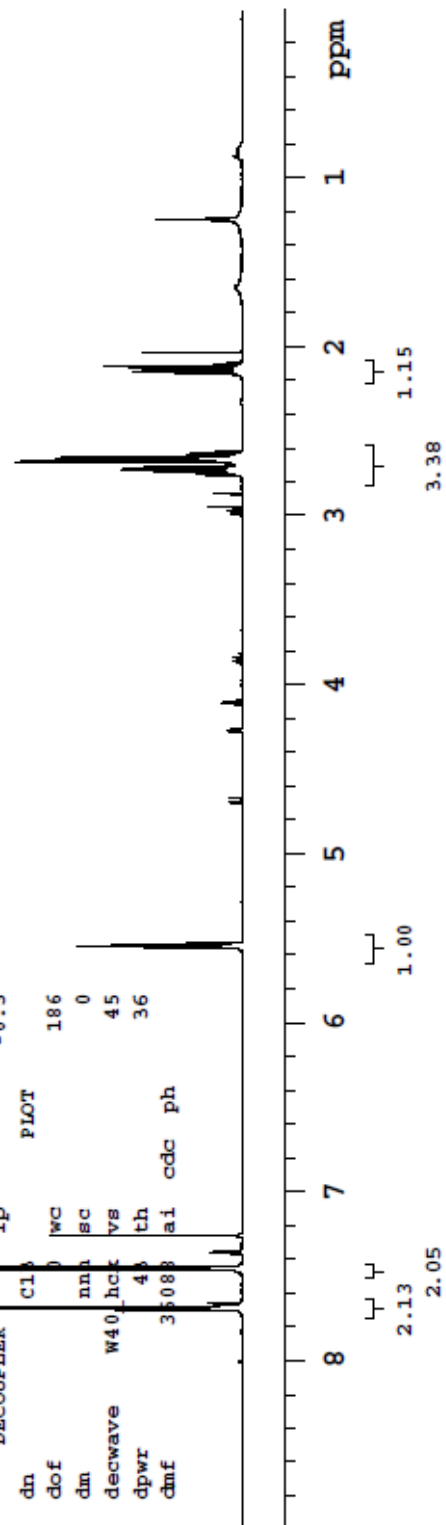
ME-8-035-1

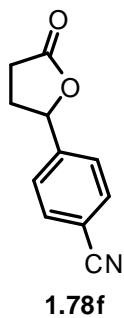
exp1 PROTON

```

SAMPLE          PRESATURATION
date  Oct 24 2012  satmode      n
solvent  cdcl3  wet           n
file  /home/data/Ke-rr/Mike_E/Lactone ~ temp 25.0
Proj.  NMRs/ME-8-03- gain      not used
5-1_Oct24_12_01/PR- spin      not used
      OTON_01.fid  hst         0.008
ACQUISITION    pw90         9.500
sw  9611.9  alfa         6.600
at  1.705
np  32768  il
fb  not used  in      n
bs  4      dp      y
d1  1.000  hs      nn
nt
ct  8      fn      not used
      8      fn      not used
      8      fn      not used
TRANSMITTER    H1  sp      3.2
sfrq  599.478  wp      5390.3
tof   599.478  rfl      5555.7
tpwr  58      rfp      4352.2
pw    4.750  rp      85.7
      DECOUPLER  lp      -0.3
dn
dof
dm
decwave  W40  hc      186
dpwr    40  vs      0
dmf     35088  ai  cdc  ph  45
      36

```





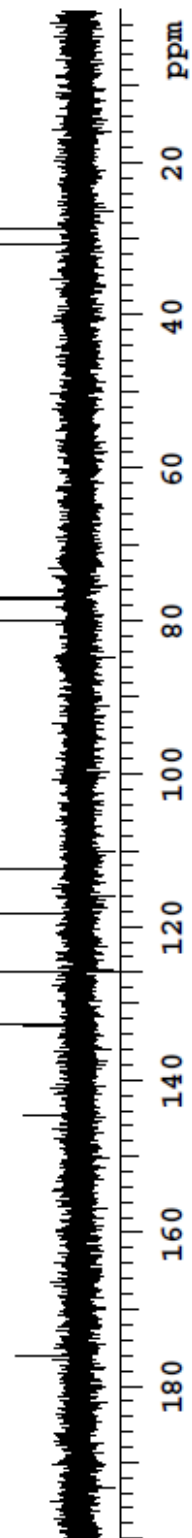
ME-8-035-1c

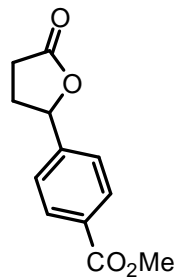
exp1 CARBON

```

SAMPLE      PRESATURATION
date Oct 24 2012 satmode n
solvent cdcl3 wet n
file /home/data/Ke- SPECIAL
rr/Mike_E/Lactone - temp 25.0
Proj. NMRs/ME-8-03- gain not used
5-1c_Oct24_12_01/C- spin not used
ARBON_01.fid hst 0.008
ACQUISITION pw90 22.200
sw 37735.8 alfa 10.000
at 0.868 FLAGS
np 65536 il n
fb not used in n
bs 4 dp Y
dl 1.000 hs nn
nt 256 PROCESSING
ct 140 lb 0.50
tn TRANSMITTER lsfid -2
sfrq 150.754 fn not used DISPLAY
tof 2295.3 sp 9.9
tpwr 56 wp 30137.5
pw 11.100 rfl 13898.9
DECOUPLER rfp 11606.8
dn H1 rp -132.3
dof 0 lp 128.8
dm YYY PLOT
decwave w wc 186
dpwr 42 sc 0
dmf 13500 vs 488
th 13
ai cdc ph

```





1.78g

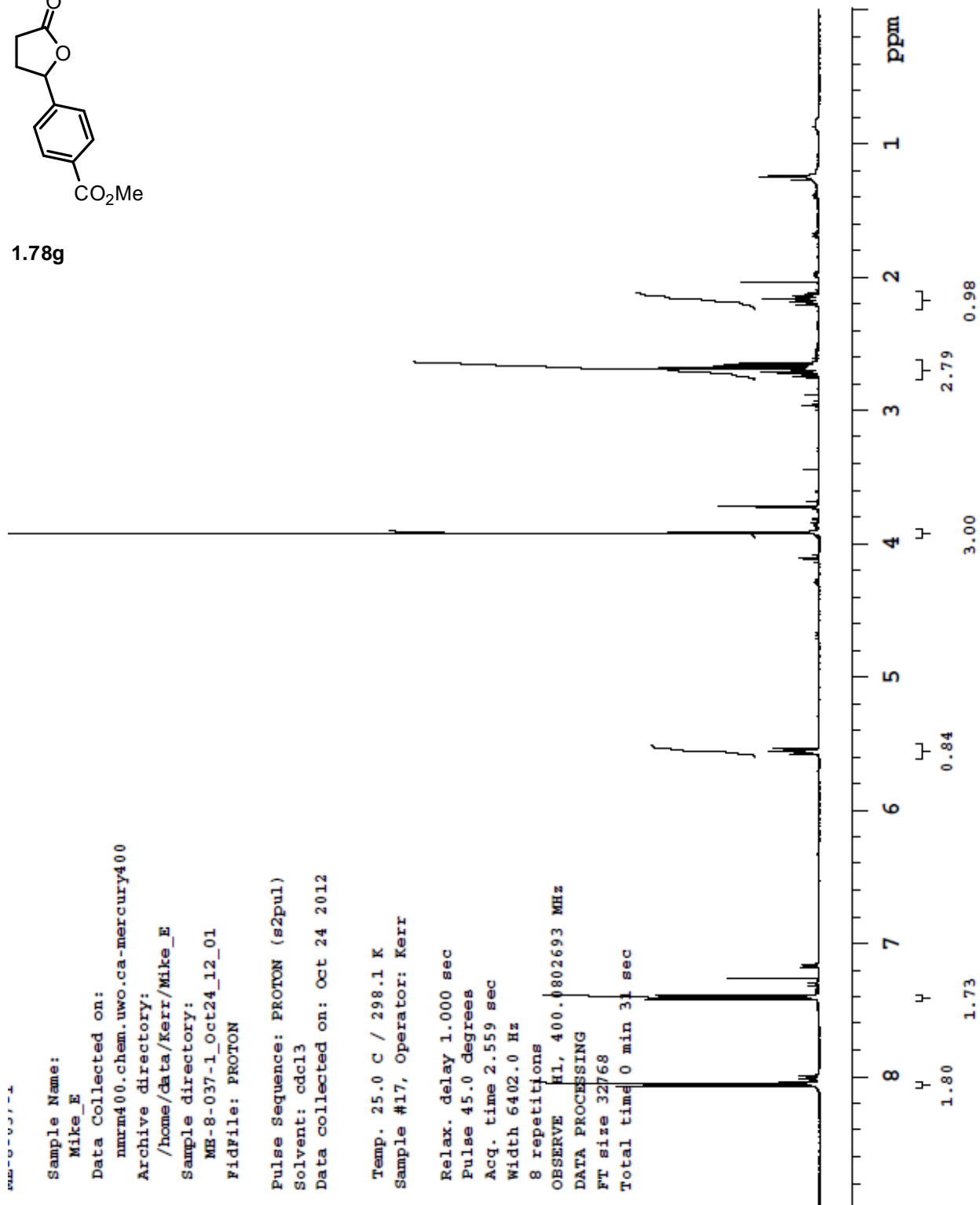
MB-8-037-1

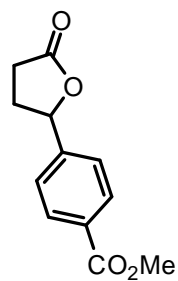
Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
MB-8-037-1_Oct24_12_01
Fidfile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 24 2012

Temp. 25.0 C / 298.1 K
Sample #17, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802693 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





1.78g

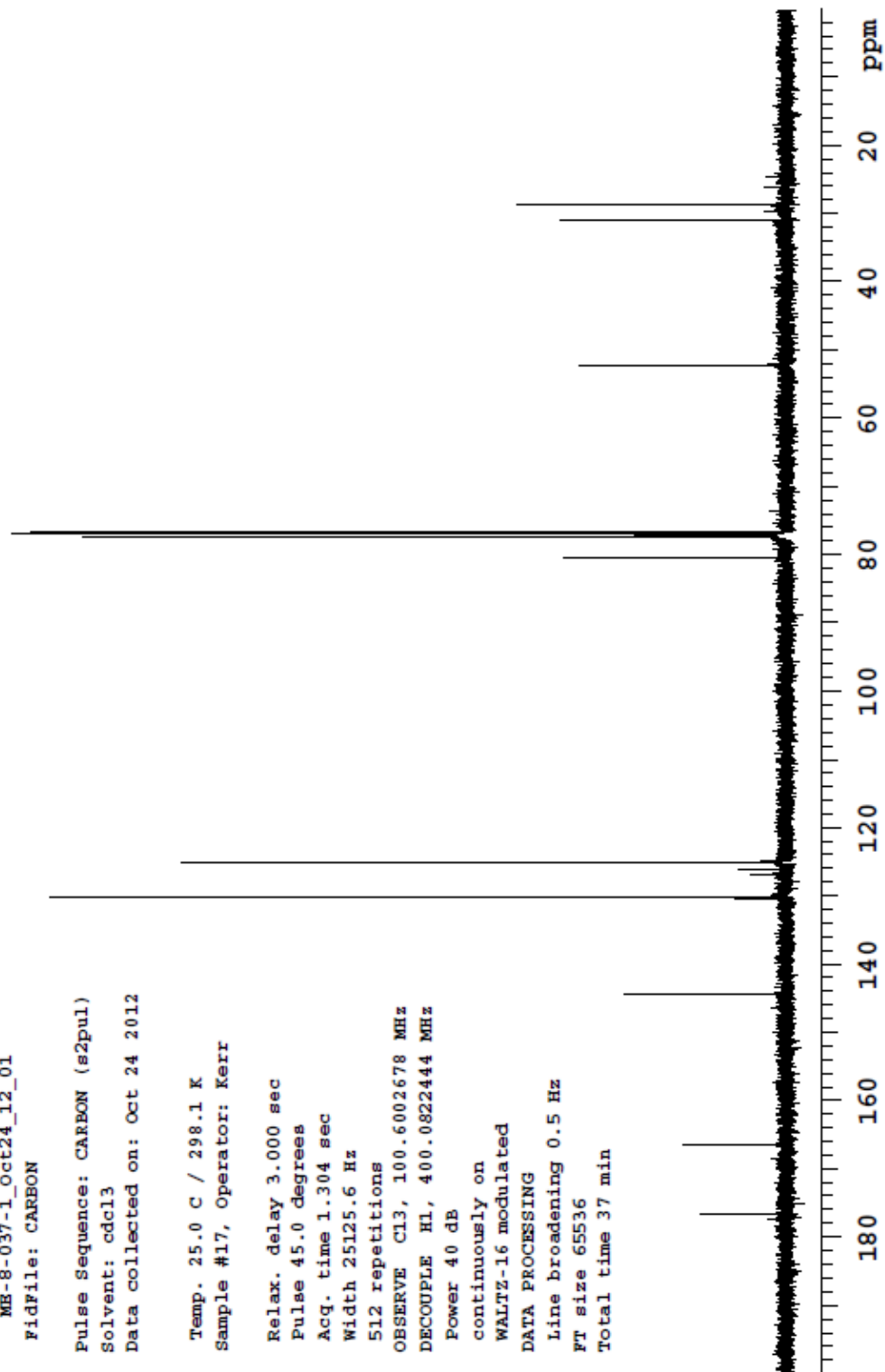
nmr-0-0011-1

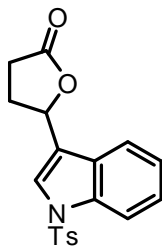
Sample Name:
Mike_E
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
MB-8-037-1_Oct24_12_01
FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 24 2012

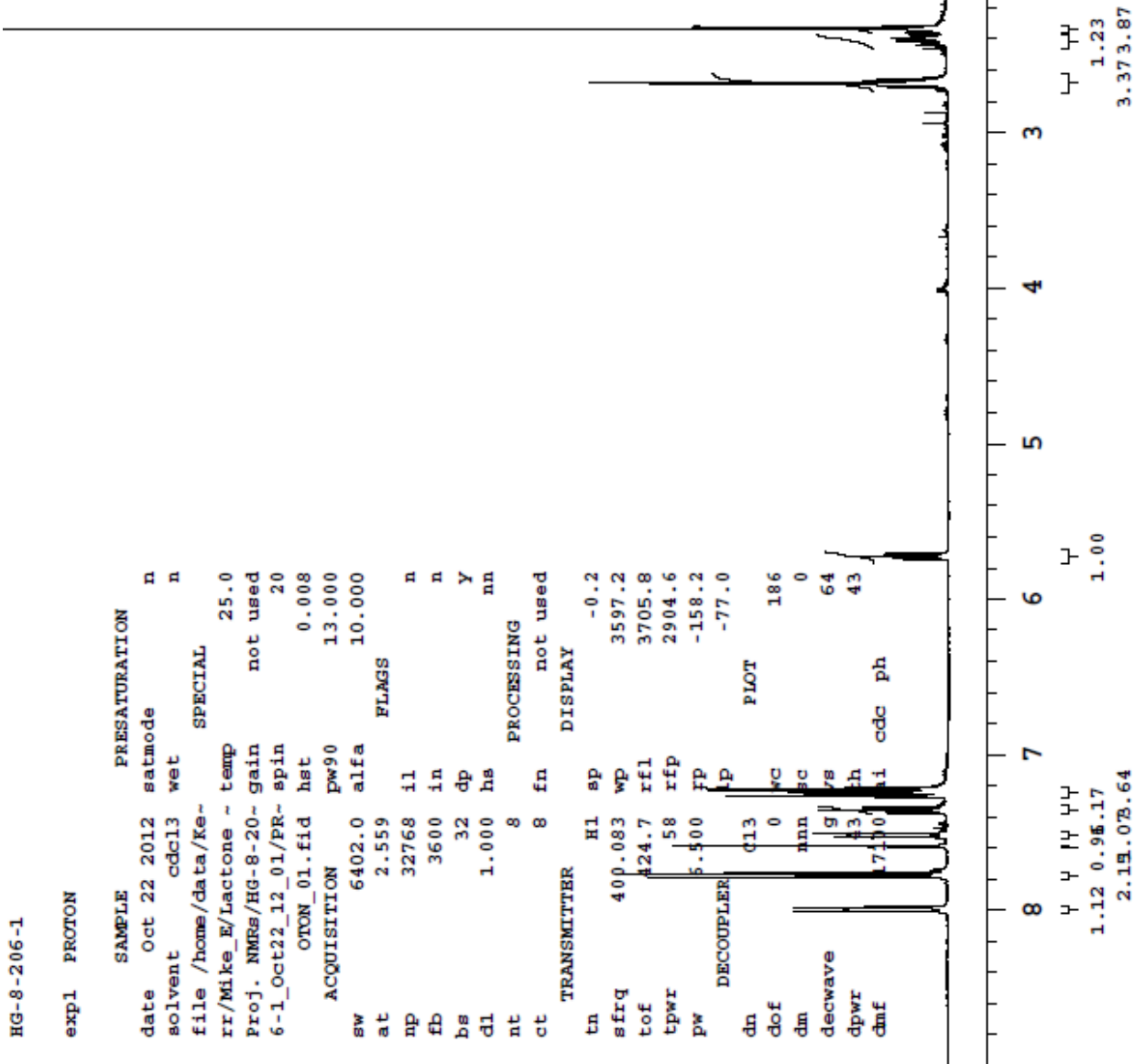
Temp. 25.0 C / 298.1 K
Sample #17, Operator: Kerr

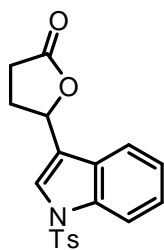
Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
512 repetitions
OBSERVE C13, 100.6002678 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 37 min





1.78h





1.78h

HG-8-206-1

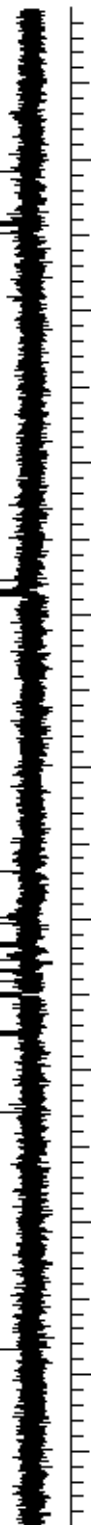
exp1 CARBON

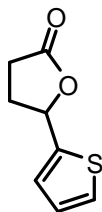
```

SAMPLE      PRESATURATION
date  Oct 22 2012  satmode      n
solvent  cdcl3  wet           n
file  /home/data/Ke-          SPECIAL
ir/Mike_E/Lactone ~ temp      25.0
Proj.  NMRs/HG-8-20- gain      not used
6-1_Oct22_12_01/CA- spin      20
RBON_01.fid hst              0.008
ACQUISITION pw90             11.900
sw          25125.6  alfa      10.000
at          1.304
np          65536  il
fb          13800  in
bs          64    dp
dl          1.000  hs
nt          256
ct          256  lb
TRANSMITTER C13             fn      not used
tn
sfrq       100.611  sp          4.6
tof        1538.0  wp          20121.7
tpwr       57     rf1          9251.4
pw         5.950  rfp          7746.2
DECOUPLER  rp          -139.8
dn         H1    lp          -387.0
dof        0
dm        yyy   wc          186
decwave   w    sc
dpwr      40   vs          75
dmf       9300 th          8
ai cdc ph

```

180 160 140 120 100 80 60 40 20 ppm





1.78i

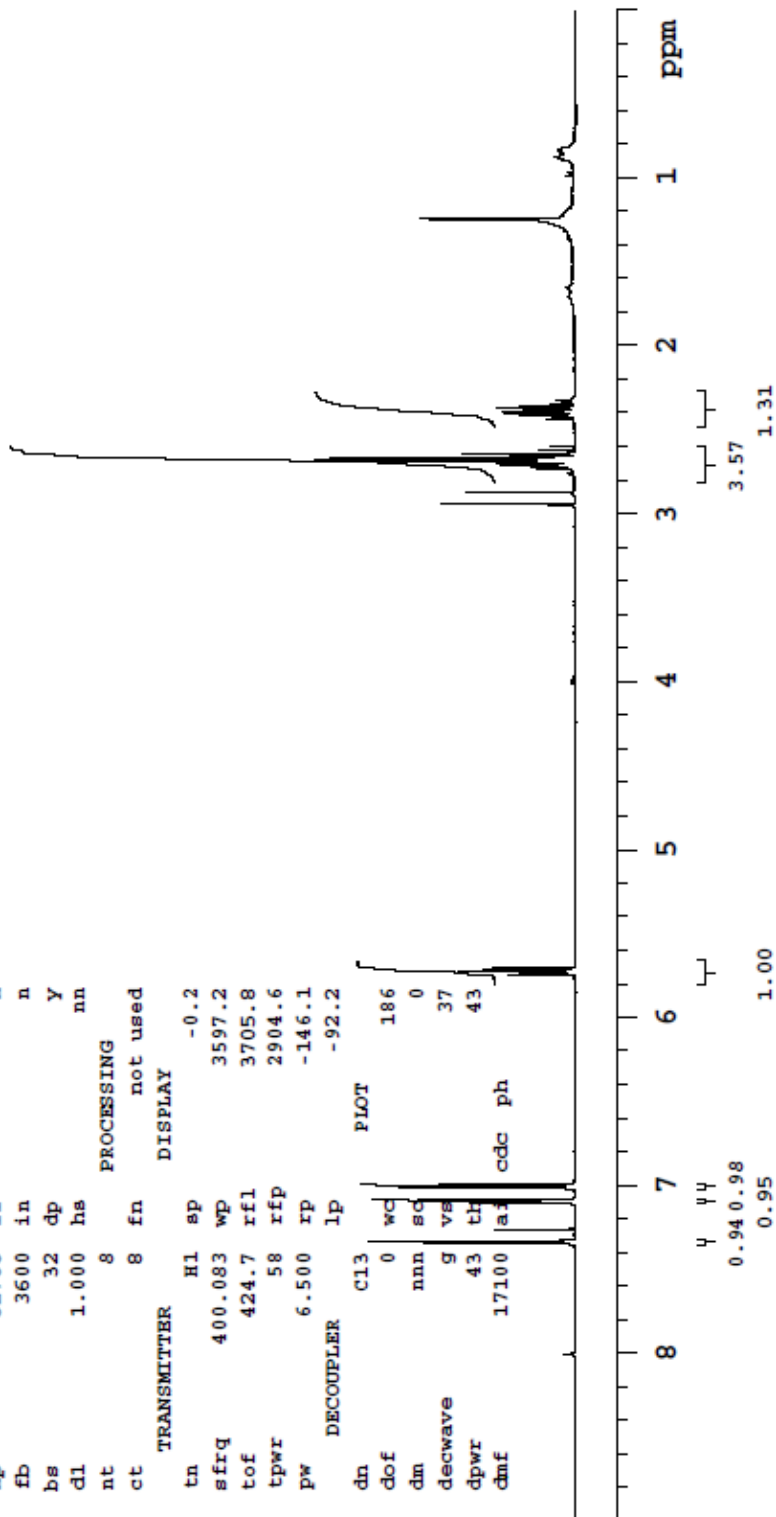
HG-9-32-1

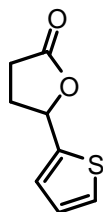
exp1 PROTON

```

SAMPLE          PRESATURATION
date   Oct 22 2012  satmode      n
solvent cdcl3      wet          n
file   /home/data/Ke-          SPECIAL
ir/Mike_E/Lactone ~ temp      25.0
Proj.  NMRs/HG-9-32- gain      not used
-1_Oct22_12_01/PRO- spin      20
      TON_01.fid hst          0.008
ACQUISITION
sw     6402.0  alfa          13.000
at     2.559
np     32768  il            n
fb     3600   in            n
bs     32     dp            Y
dl     1.000  hs            nn
nt     8
ct     8     fn            not used
      TRANSMITTER          DISPLAY
tn     H1   sp            -0.2
sfrq   400.083 wp          3597.2
tof    424.7  rf1         3705.8
tpwr   58     rfp         2904.6
pw     6.500  rp          -146.1
      DECOUPLER           lp          -92.2
dn     C13
dof    0     wc          186
dm     nnn   sc          0
decwave g    vs          37
dpwr   43    th          43
dmf    17100  ai          cdc ph

```





1.78i

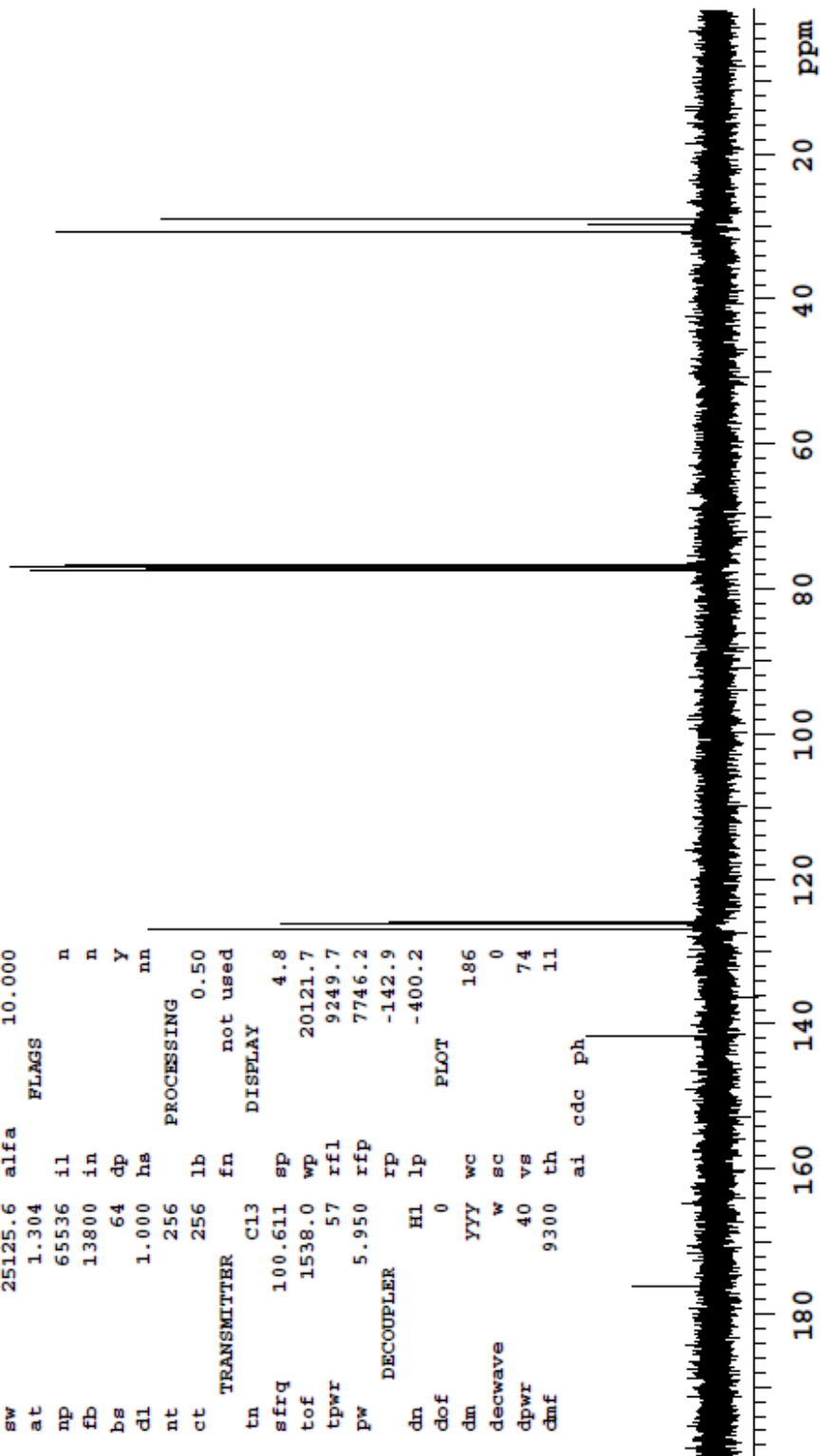
HG-9-32-1

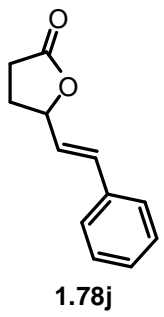
exp1 CARBON

```

SAMPLE      PRESATURATION
date Oct 22 2012 satmode n
solvent cdcl3 wet n
file /home/data/Ke- SPECIAL
rr/Mike_E/Lactone ~ temp 25.0
Proj. NMRS/HG-9-32~ gain not used
-1_Oct22_12_01/CAR~ spin 20
BON_01.fid hst 0.008
ACQUISITION pw90 11.900
sw 25125.6 alfa 10.000
at 1.304 FLAGS
np 65536 il n
fb 13800 in n
bs 64 dp Y
dl 1.000 ha nn
nt 256
ct 256 lb 0.50
TRANSMITTER fn not used
tn CL3 DISPLAY
sfrq 100.611 sp 4.8
tof 1538.0 wp 20121.7
tpwr 57 rfl 9249.7
pw 5.950 rfp 7746.2
DECOUPLER ip -142.9
dn H1 lp -400.2
dof 0 PLOT
dm YYY wc 186
decwave w sc 0
dpwr 40 vs 74
dmf 9300 th 11
ai cdc ph

```





HG 9-60-1

exp1 PROTON

SAMPLE PRESATURATION

date Oct 23 2012 satmode n

solvent cdcl3 wet n

file /home/data/Ke- SPECIAL

rr/Mike_E/Lactone - temp 25.0

Proj. NMRs/HG_9-60- gain not used

-1_Oct_23_2012_01/~ spin 20

PROTON_01.fid hst 0.008

ACQUISITION pw90 9.500

sw 9611.9 alfa 6.600

at 1.705 FLAGS

np 32768 il n

fb not used in n

bs 4 dp Y

dl 1.000 hs nn

nt 8

ct 8 fn not used

TRANSMITTER DISPLAY

tn H1 sp 3.0

sfrq 599.478 wp 5390.3

tof 599.5 rfl 5560.6

tpwr 58 rfp 4352.2

pw 4.750 rp 98.4

DECOUPLER lp -20.8

PLOT

dn C13

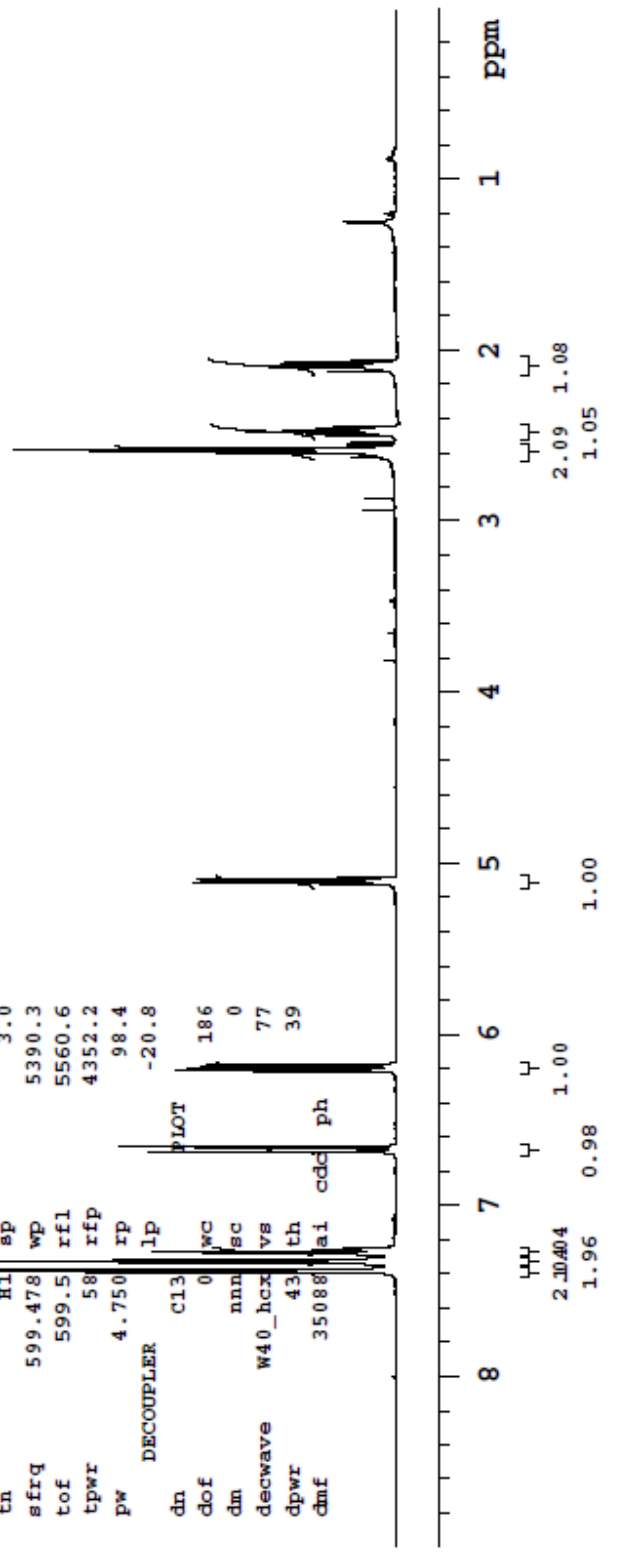
dof 0 WC 186

dm nnn SC 0

decwave W40_hcx vs 77

dpwr 43 th 39

dmf 35088 ai cdc ph



8

7

6

5

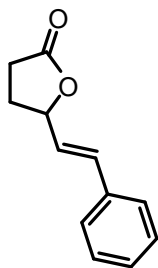
4

3

2

1

ppm



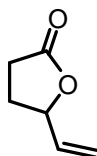
1.78j

HG 9-60-1

expl CARBON

SAMPLE		PRESATURATION	
date	Oct 23 2012	satmode	n
solvent	cdcl3	wet	n
file	/home/data/Ke-	SPECIAL	
rr/Mike_E/Lactone	~ temp	25.0	
Proj.	NMRs/HG_9-60~	gain	not used
-1_Oct_23_2012_01/~	spin	20	
CARBON_01.fid	hst	0.008	
ACQUISITION	Pw90	22.200	
sw	37735.8	alfa	10.000
at	0.868	FLAGS	
np	65536	il	n
fb	not used	in	n
bs	4	dp	Y
d1	1.000	hs	nn
nt	256	PROCESSING	
ct	256	lb	0.50
TRANSMITTER	lsfid		
tn	CL3	fn	not used
sfrq	150.754	DISPLAY	
tof	2295.3	sp	9.5
tpwr	56	wp	30137.5
pw	11.100	rfl	13901.7
DECOUPLER	rfp		11606.8
dn	H1	rp	-141.5
dof	0	lp	136.0
dm	YYY	PLOT	
decwave	w	wc	186
dpwr	42	sc	0
dmf	13500	vs	378
	th	th	7
	ai	cdc	ph

180 160 140 120 100 80 60 40 20 ppm



1.78k

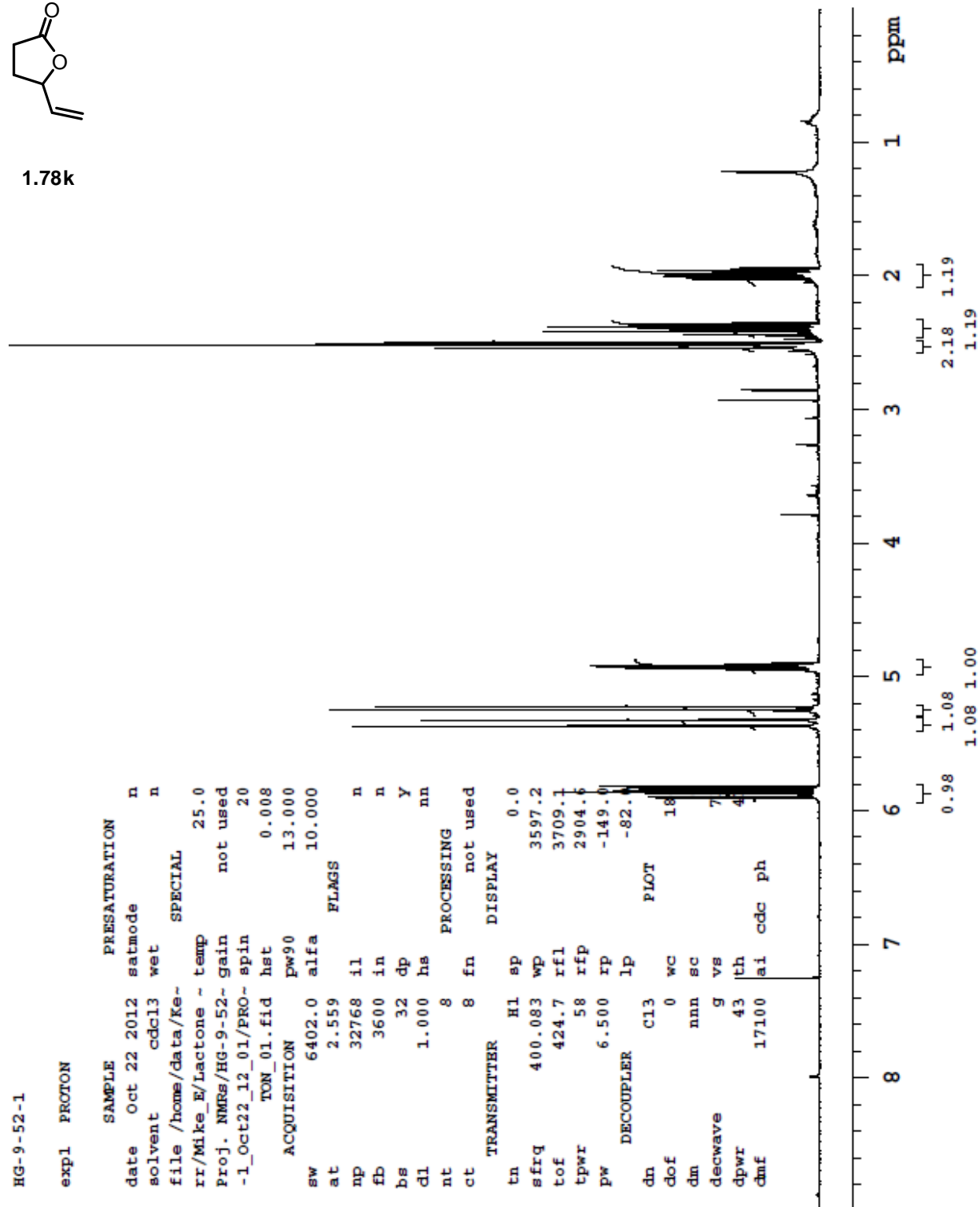
HG-9-52-1

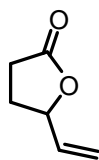
exp1 PROTON

```

SAMPLE          PRESATURATION
date   Oct 22 2012   satmode   n
solvent cdcl3      wet        n
file   /home/data/Ke-   SPECIAL
rr/Mike_E/Lactone - temp    25.0
Proj.  NMRs/HG-9-52- gain   not used
-1_Oct22_12_01/PRO- spin    20
      TON_01.fid  hst      0.008
ACQUISITION      pw90     13.000
sw      6402.0  alfa     10.000
at      2.559
np      32768  il
fb      3600   in      n
bs      32     dp      y
dl      1.000  hs      nn
nt      8
ct      8     fn      not used
      TRANSMITTER      DISPLAY
tn      H1   sp      0.0
sfrq    400.083  wp     3597.2
tof     424.7   rfl     3709.1
tpwr    58     rfp     2904.6
pw      6.500   rp     -149.0
      DECOUPLER      lp     -82.0
dn      C13
dof     0     wc     18
dm      nnn   sc
decwave g     vs     7
dpwr    43   th     4
dmf     17100 ai   cdc   ph

```





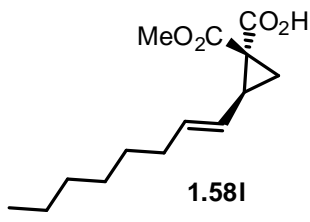
1.78k

HG-9-52-1

exp1 CARBON

SAMPLE		PRESATURATION	
date	Oct 22 2012	satmode	n
solvent	cdcl3	wet	n
file	/home/data/Ke-	SPECIAL	
ir/Mike_E/Lactone	- temp	25.0	
Proj.	NMRS/HG-9-52-	gain	not used
-1_Oct22_12_01/CAR-	spin	20	
	BON_01.fid	hst	0.008
ACQUISITION	pw90	11.900	
sw	25125.6	alfa	10.000
at	1.304		FLAGS
np	65536	il	n
fb	13800	in	n
bs	64	dp	y
dl	1.000	hs	nn
nt	256		PROCESSING
ct	256	lb	0.50
TRANSMITTER	fn		not used
tn	C13		DISPLAY
sfrq	100.611	sp	4.1
tof	1538.0	wp	20121.7
tpwr	57	rf1	9250.4
pw	5.950	rfp	7746.2
DECOUPLER	rp		-146.1
dn	H1	lp	-392.0
dof	0		PLOT
dm	YYY	wc	186
decwave	w	sc	0
dpwr	40	vs	70
dmf	9300	th	8
	ai	cdc	ph





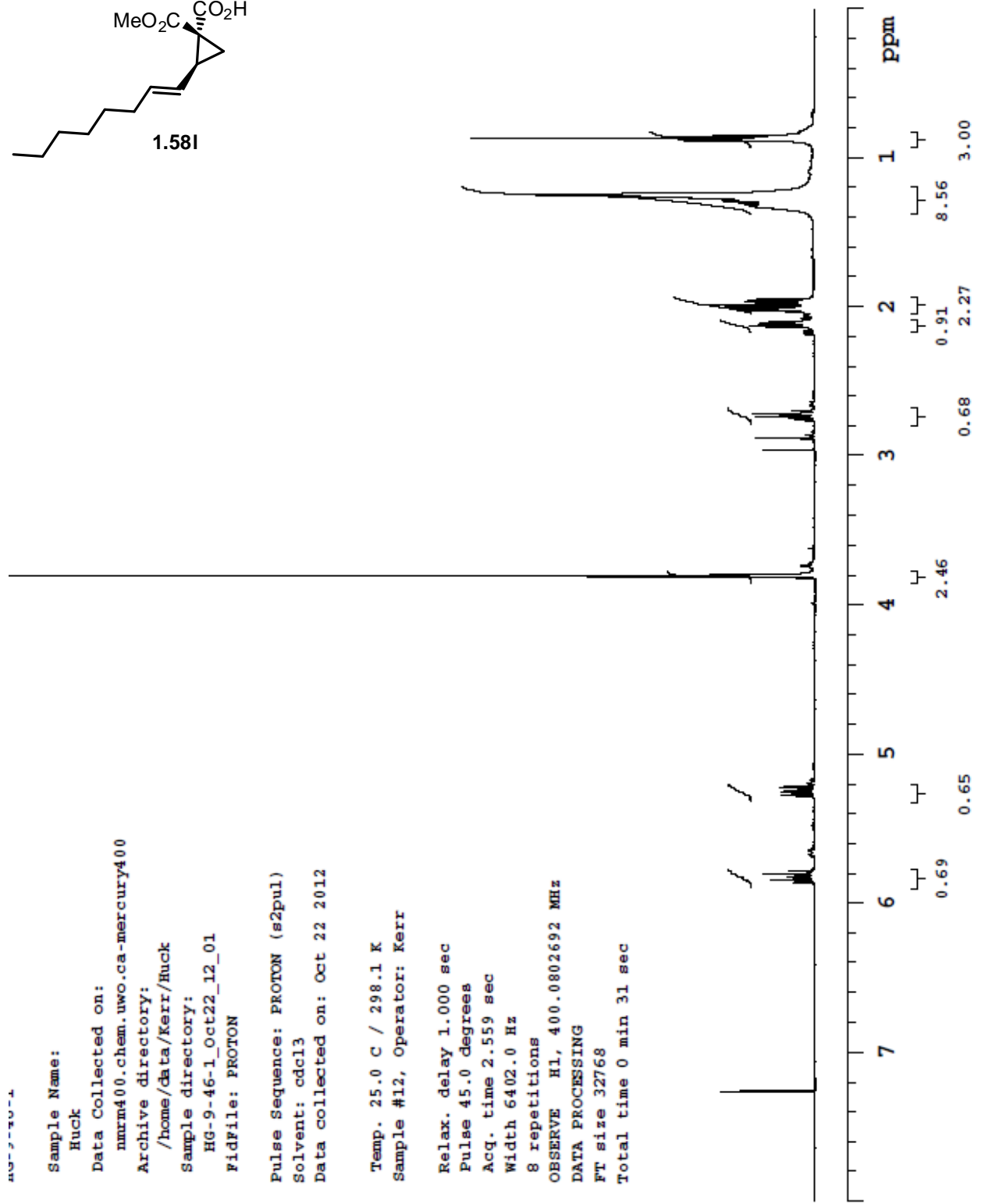
407-7-10-1

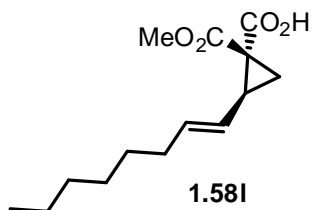
Sample Name:
Huck
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Huck
Sample directory:
HG-9-46-1_Oct22_12_01
Fidfile: PROTON

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 22 2012

Temp. 25.0 C / 298.1 K
Sample #12, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.559 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.0802692 MHz
DATA PROCESSING
Ft size 32768
Total time 0 min 31 sec



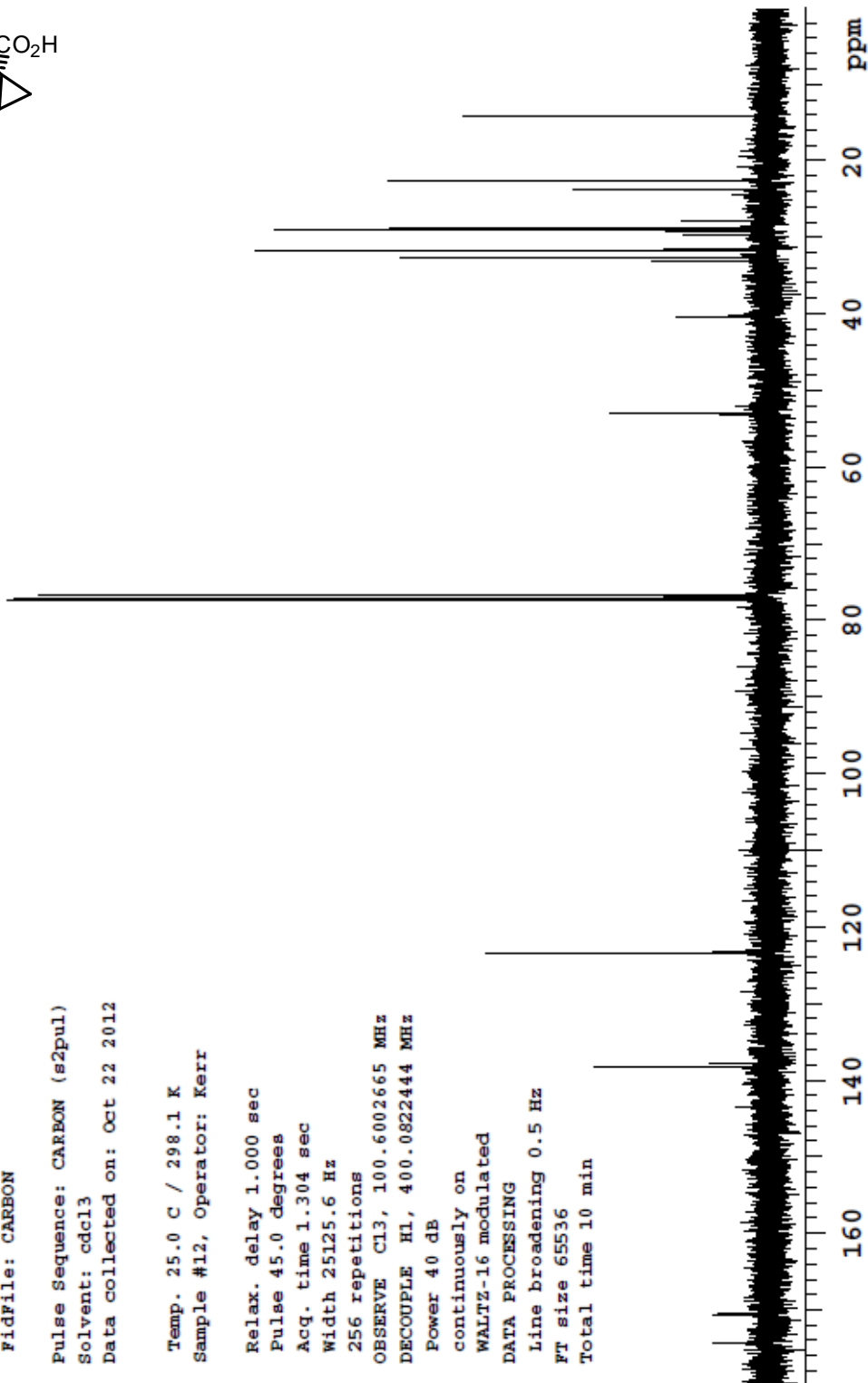


Sample Name:
Huck
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Kerr/Huck
Sample directory:
HG-9-46-1_Oct22_12_01
Fidfile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 22 2012

Temp. 25.0 C / 298.1 K
Sample #12, Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.6002665 MHz
DECOUPLE H1, 400.0822444 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 10 min



HG 11-34-1

Sample Name:

Ruck

Data Collected on:

nmr-1600.chem.uwo.ca-inova600

Archive directory:

/home/data/Kerr/Ruck

Sample directory:

HG_11-34-1-2013.07.25_01

Fidfile: PROTON_HG_11-34-1_01

Pulse Sequence: PROTON (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 1.705 sec

Width 9611.9 Hz

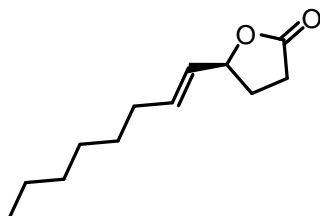
8 repetitions

OBSERVE H1, 599.4448502 MHz

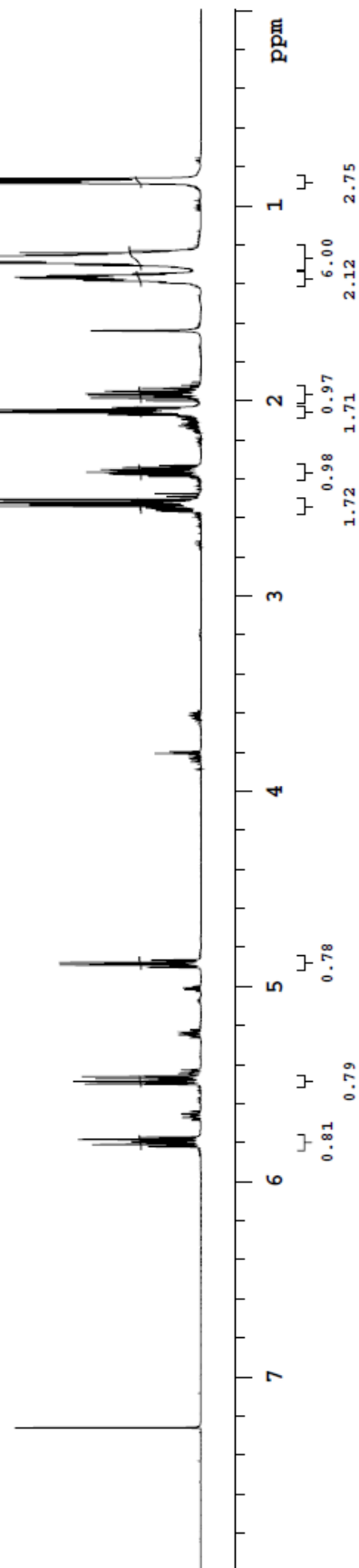
DATA PROCESSING

FT size 32768

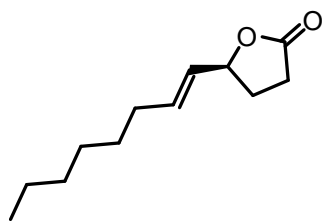
Total time 0 min 31 sec



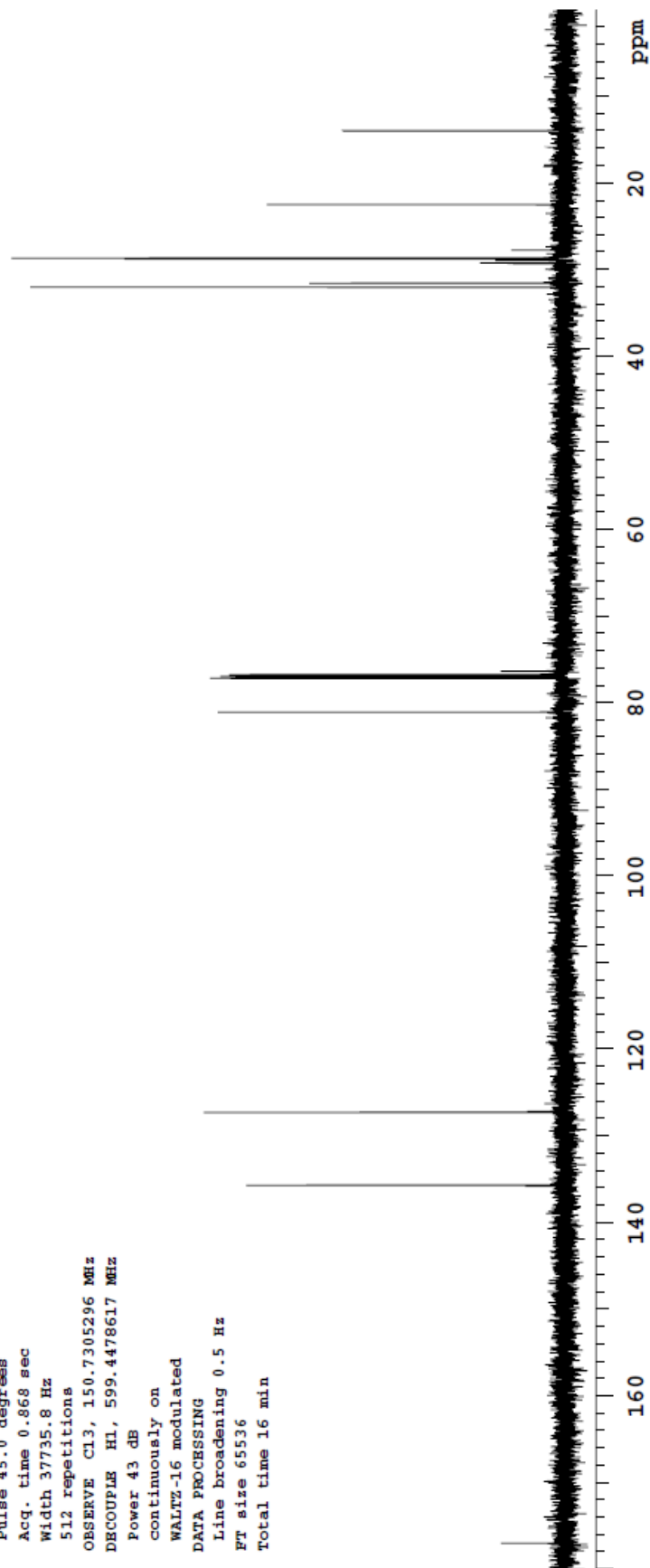
1.781



HG 11-34-1

Sample Name:
HuckData Collected on:
nmr-i600.chem.uwo.ca-inova600
Archive directory:
/home/data/Keir/HuckSample directory:
HG 11-34-1-2013.07.25_01
FidFile: CARBON_HG_11-34-1_01Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 25 2013Temp. 25.0 C / 298.1 K
Operator: KerrRelax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 37735.8 Hz
512 repetitionsOBSERVE C13, 150.7305296 MHz
DECOUPLE H1, 599.4478617 MHz
Power 43 dBcontinuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 16 min

1.781



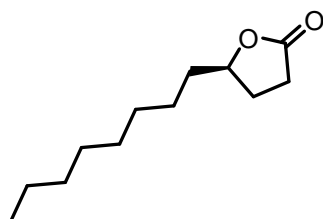
HG 9-110-1

Sample Name:
Huck
Data Collected on:
nmrhh600.chem.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Huck
Sample directory:
HG_9-110-1_Dec_5_2012_01
Fidfile: PROTON_01

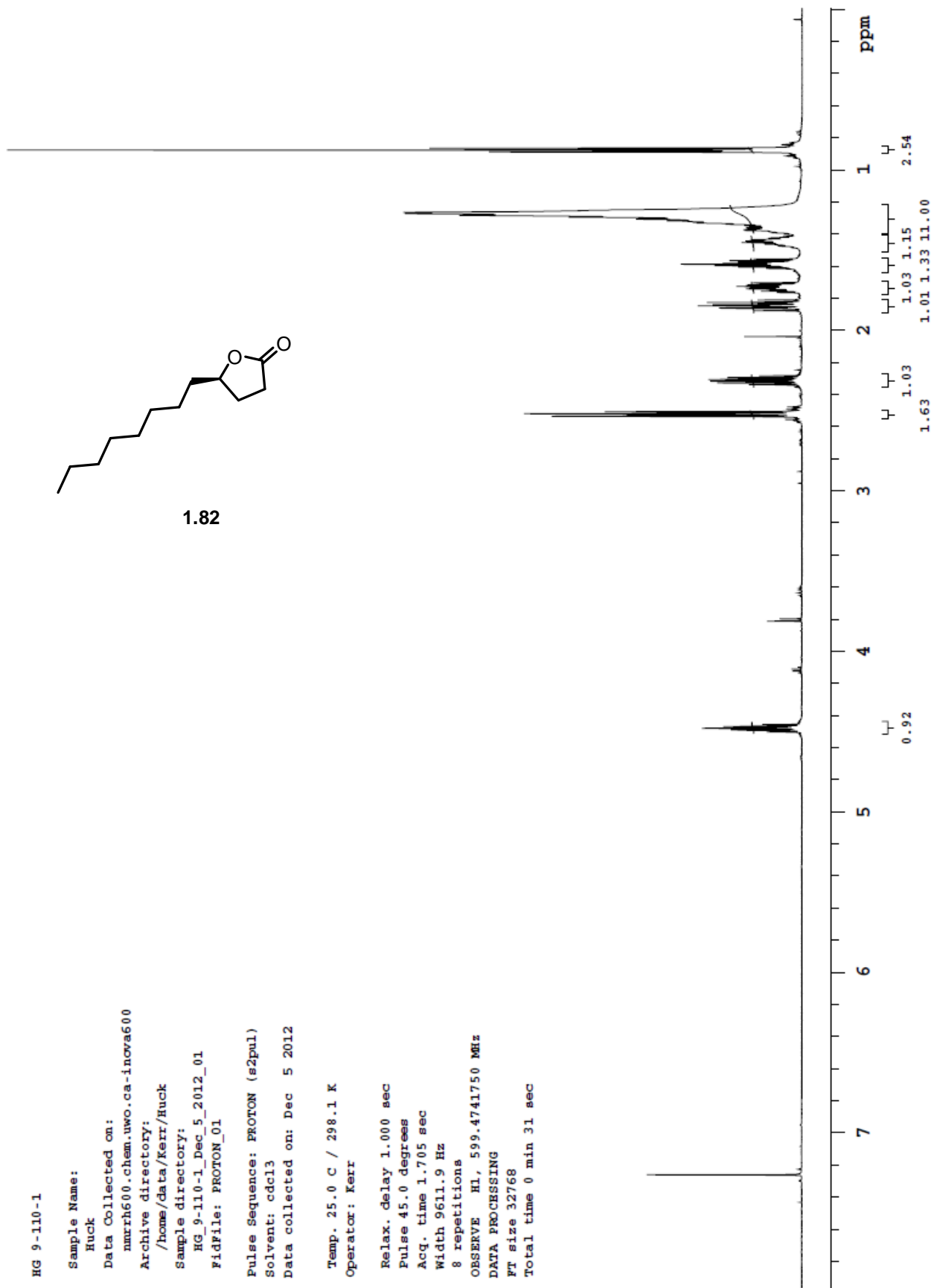
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Dec 5 2012

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, 599.4741750 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec



1.82



HG 9-110-1

Sample Name:

Huck

Data Collected on:

nmrh600.chem.uwo.ca-incova600

Archive directory:

/home/data/Kerr/Huck

Sample directory:

HG_9-110-1_Dec_5_2012_01

FidFile: CARBON_01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Dec 5 2012

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, 150.7379016 MHz

DECOUPLE H1, 599.4771765 MHz

Power 42 dB

continuously on

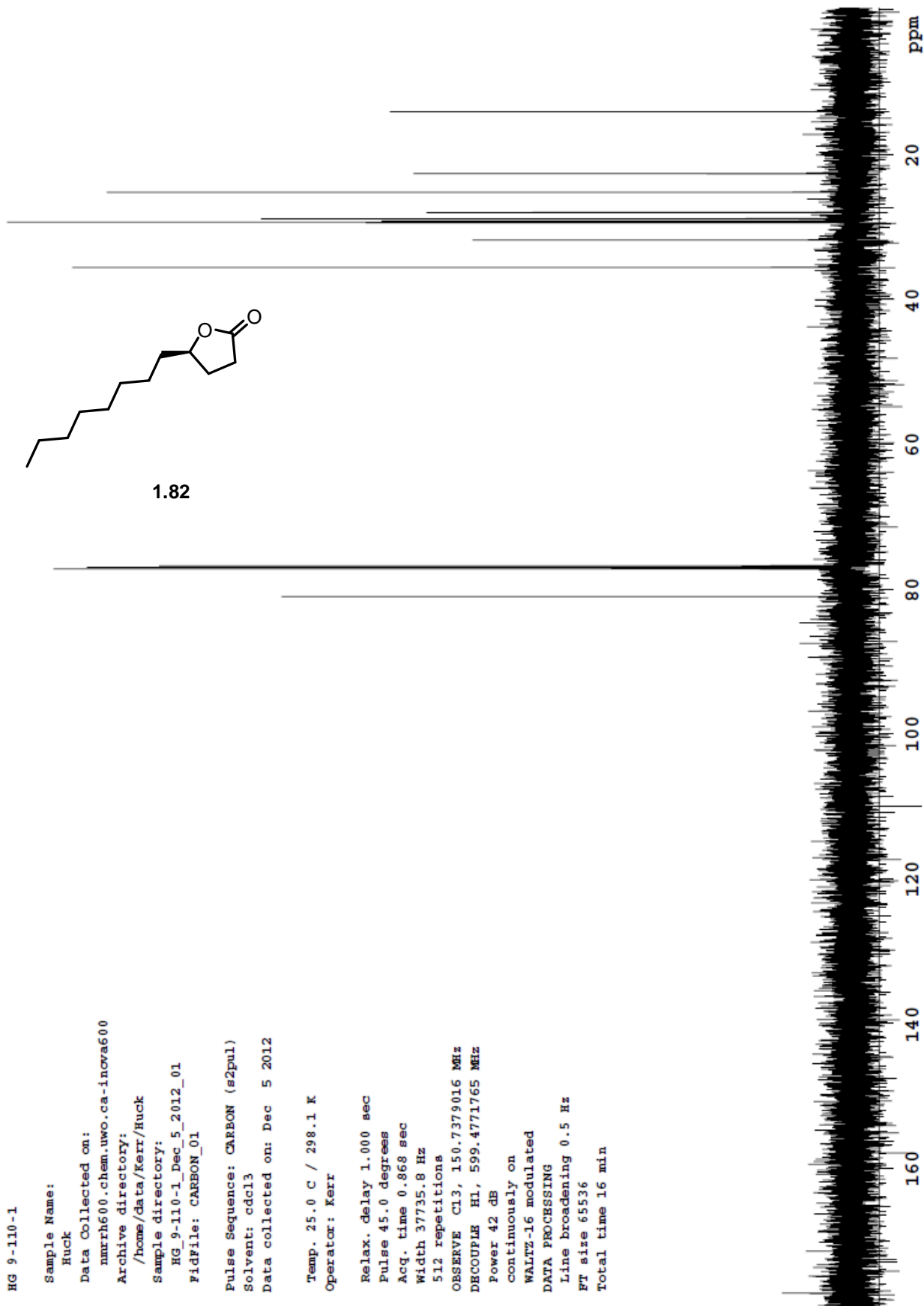
WALTZ-16 modulated

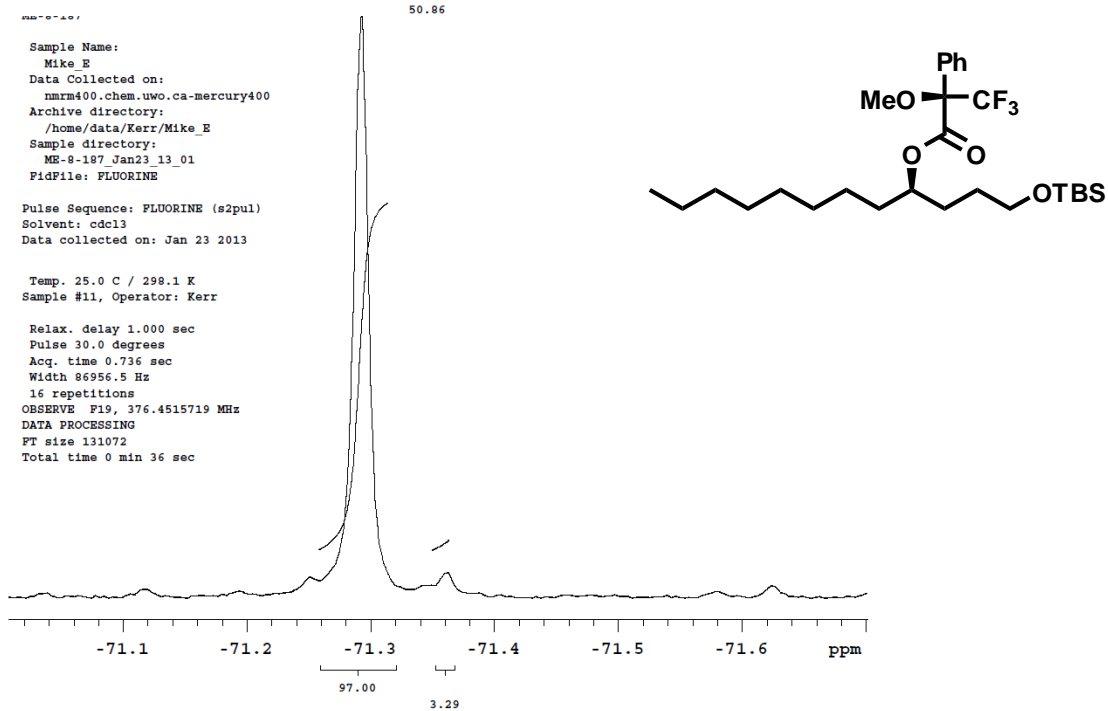
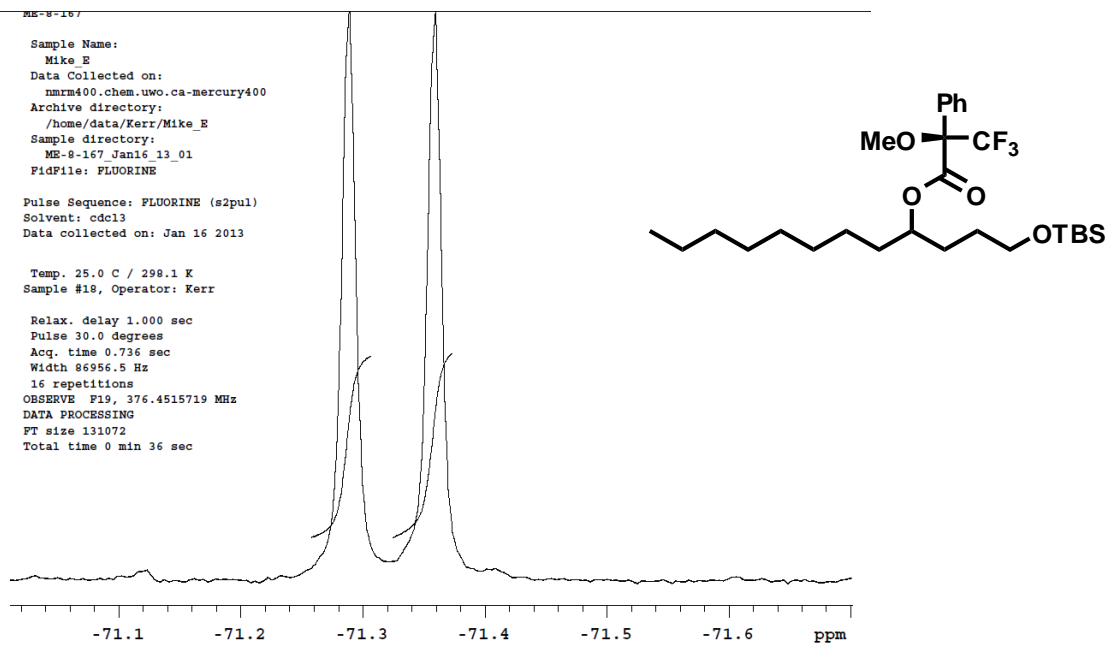
DATA PROCESSING

Line broadening 0.5 Hz

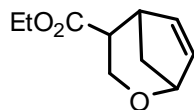
FT size 65536

Total time 16 min





Appendix 2 – NMR Spectral Data for Chapter 2



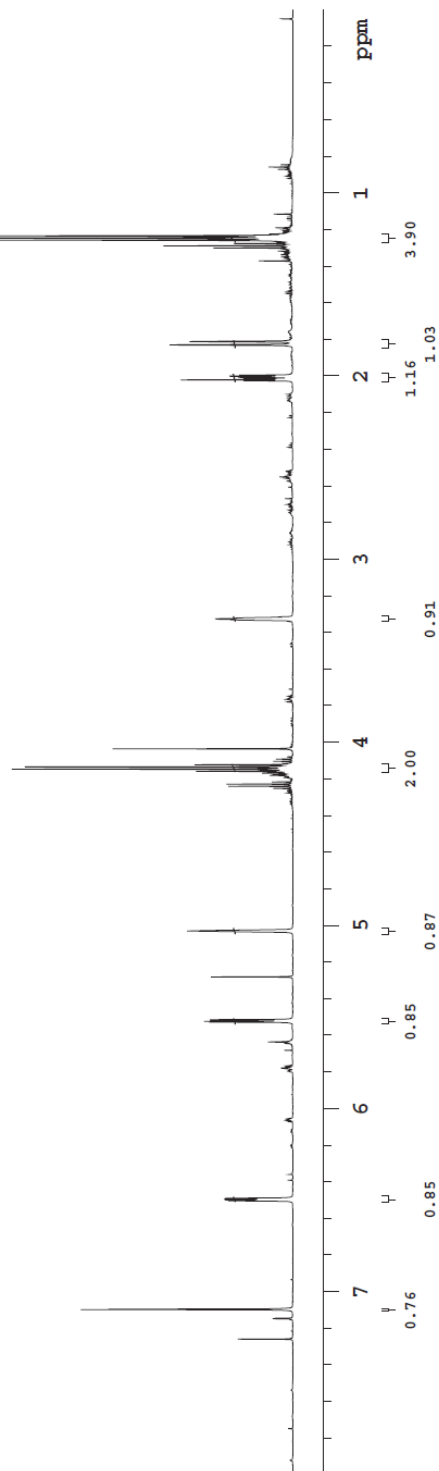
ME-12-105

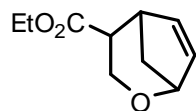
Sample Name:
Mike_E
Data Collected on:
nmr-1600.chem.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-12-105-2014.03.06_01
F1File: PROTON_ME-12-105_01

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
ORSEVE HL 599.4005534 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





ME-12-105

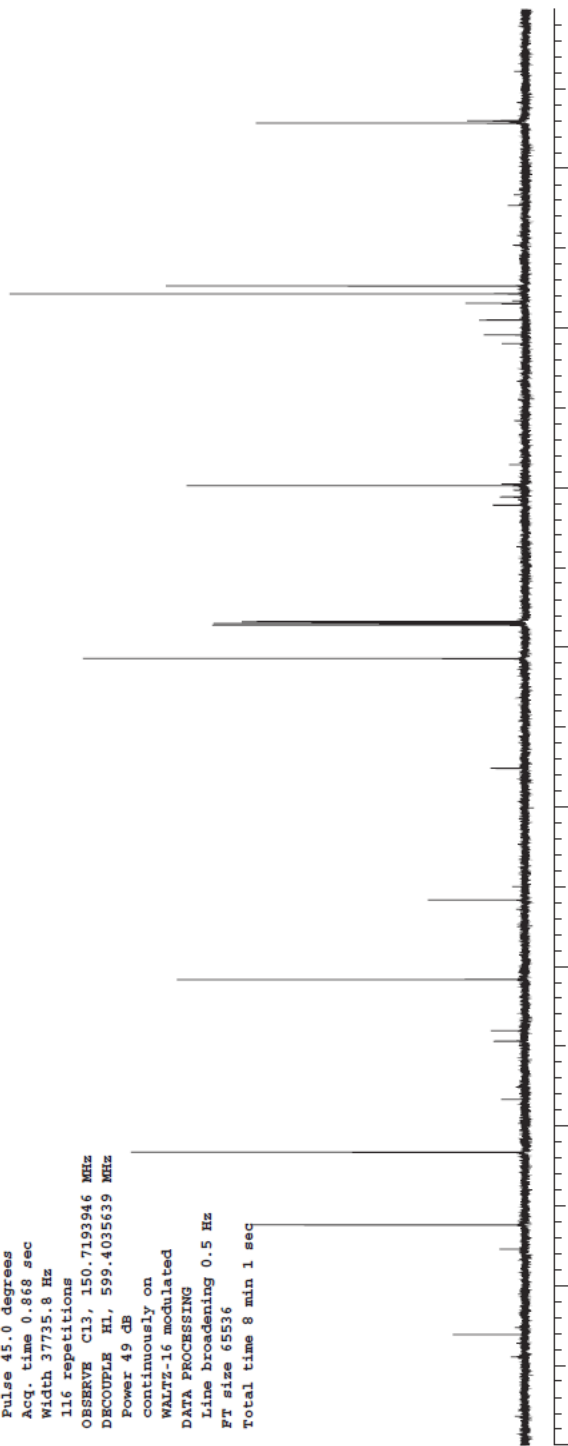
Sample Name:
Mike E
Data Collected on:
mmr-1600.chem.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-12-105-2014.03.06_01
FIDFile: CARBON_ME-12-105_01

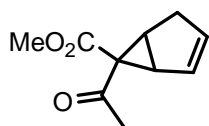
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 6 2014

Temp. 25.0 C / 298.1 K
Operator: Kerr

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 37735.8 Hz
116 repetitions
OBSERVE C13, 150.7193946 MHz
DECOUPLE H1, 599.4035639 MHz
Power 49 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 8 min 1 sec

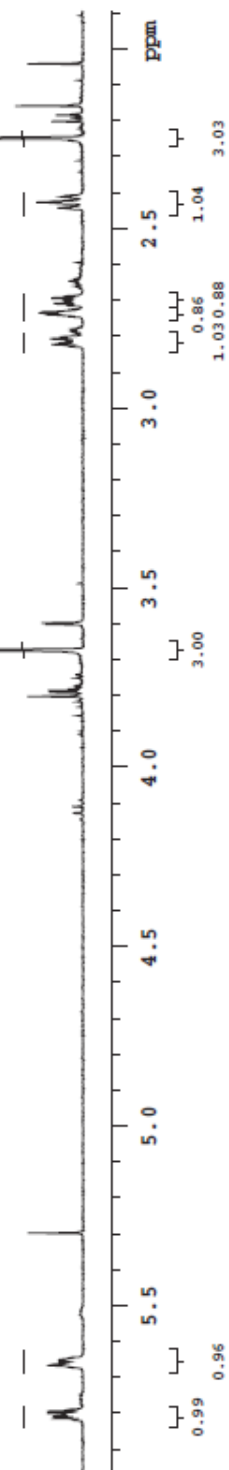
160 140 120 100 80 60 40 20 ppm

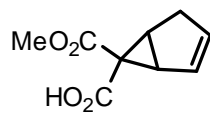




2.68

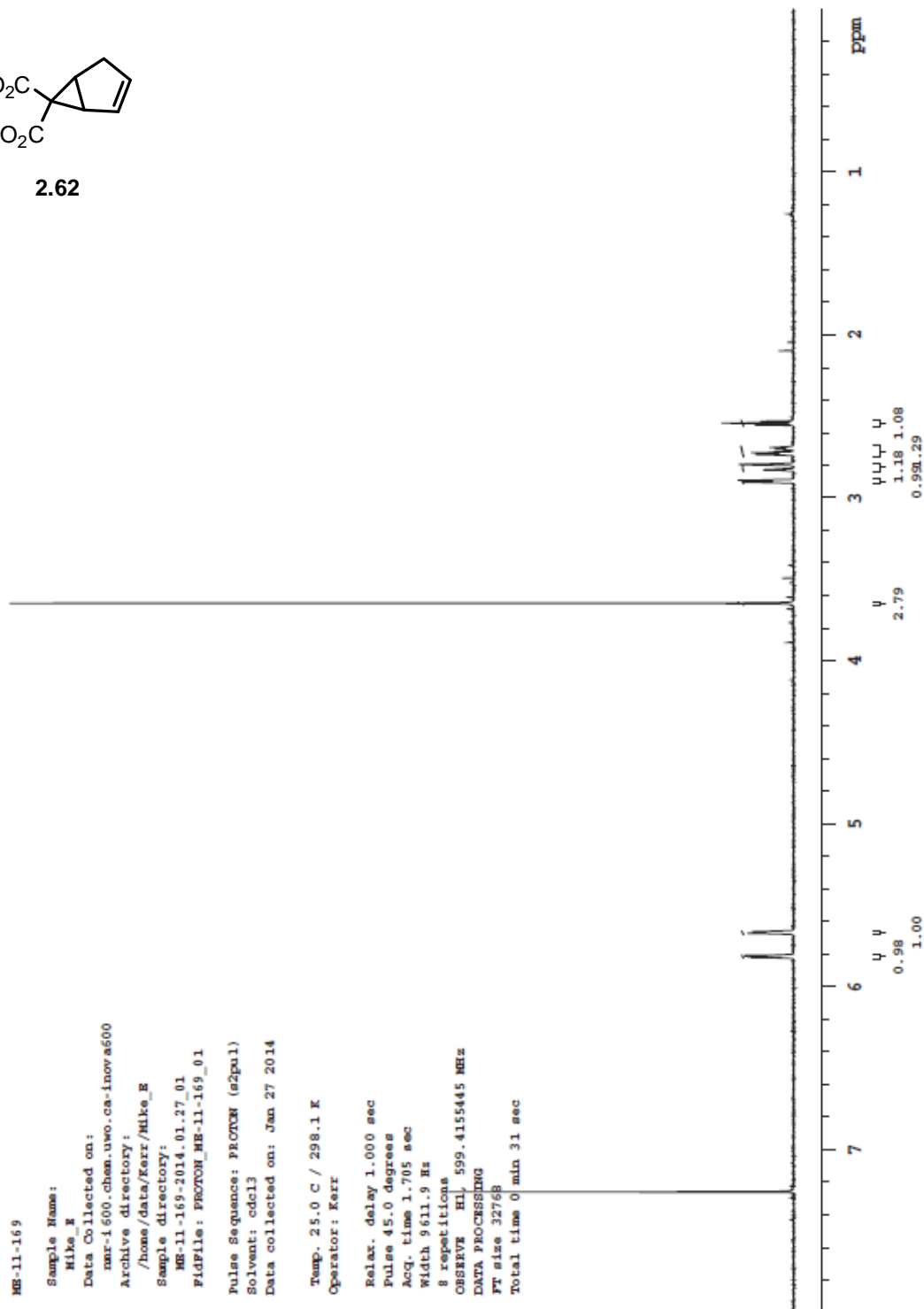
MS-12-019-1
 Sample Name:
 Mike_R
 Data Collected on:
 mar-1400.chem.uwo.ca-inova400
 Archive directory:
 /home/data/Kerr/Mike_R
 Sample directory:
 MS-12-019-1-2014.02.10.01
 FIDFile: PROTON_MS-12-019-1_01
 Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Feb 10 2014
 Temp. 25.0 C / 298.1 K
 Operator: Kerr
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.562 sec
 Width 6395.9 Hz
 8 repetitions
 OBSERVE HL, 399.7597479 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 38 sec

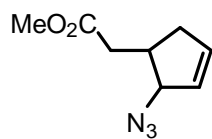




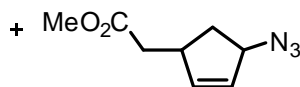
2.62

ME-11-169
 Sample Name:
 Mike_E
 Data Collected on:
 nar-i600.chem.uwo.ca-inova600
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-11-169-2014.01.27_01
 FIDFile: PROTON_ME-11-169_01
 Pulse Sequence: PROTON (s2pu1)
 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 HL, 599.4155445 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 31 sec





2.61



2.63

ME-11-069-1

Sample Name:

Mike_E

Data Collected on:

nmr-i600.chem.uwo.ca-inova600

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

ME-11-069-1-2013.11.15_01

FidFile: PROTON_ME-11-069-1_01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Nov 15 2013

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

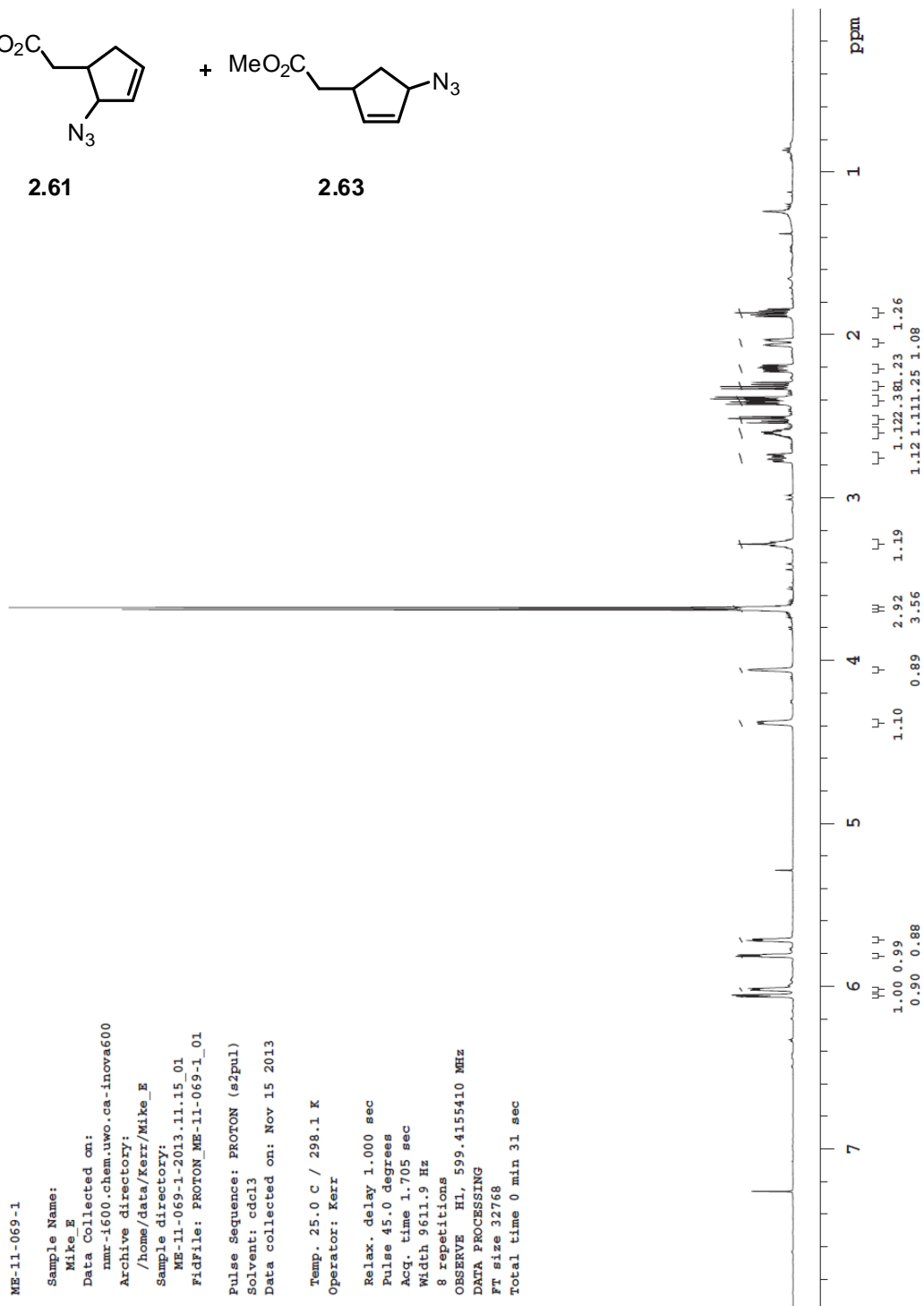
8 repetitions

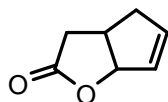
OBSERVE H1, 599.4155410 MHz

DATA PROCESSING

FT size 32768

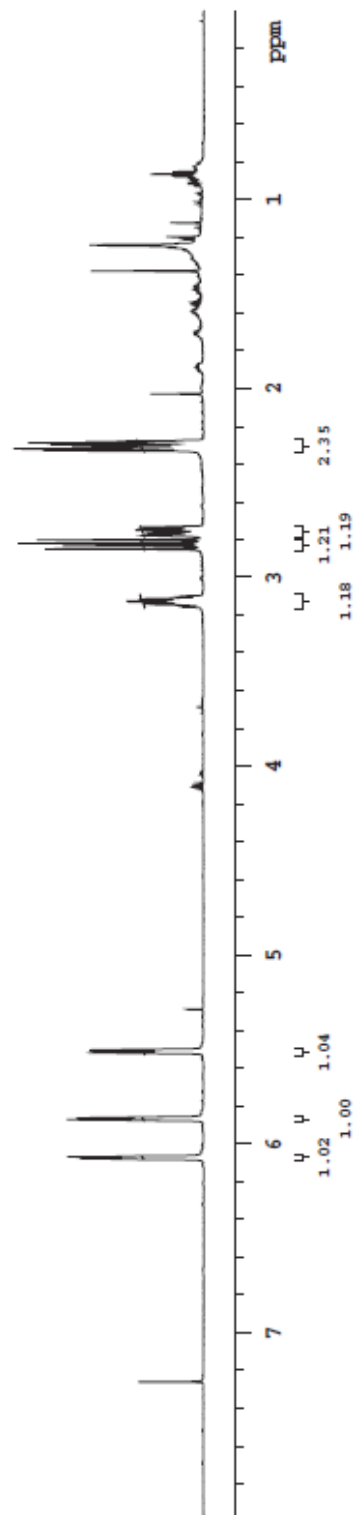
Total time 0 min 31 sec

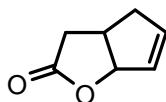




2.64

MB-11-173-1
 Sample Name:
 Mike_E
 Data Collected on:
 nar-i600.chem.usc.ca-inova600
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 MB-11-173-1-2014.01.27.01
 Fidfile: PROTON_MB-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





2.64

MS-11-173-1

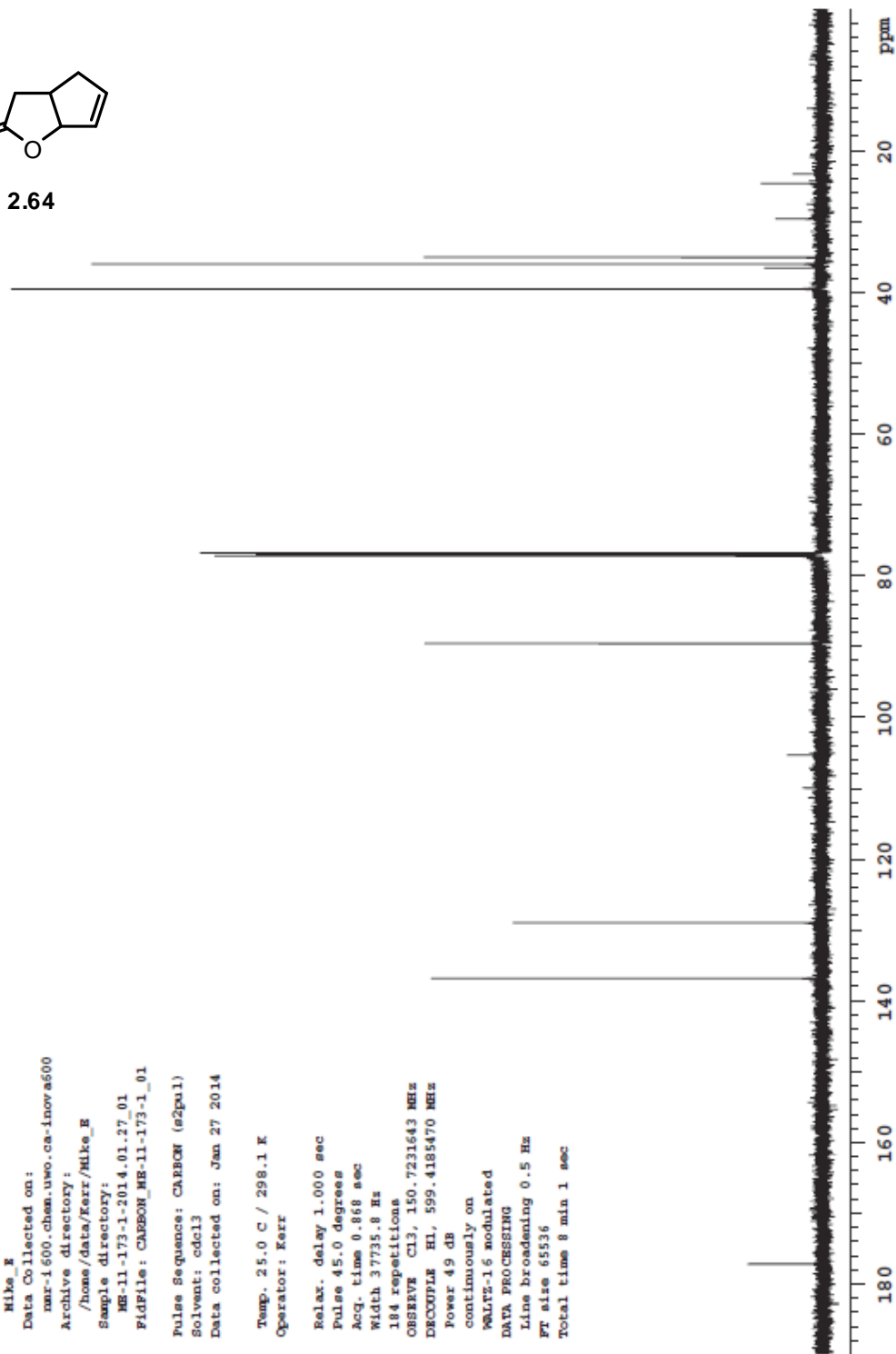
Sample Name: Mike_E
 Data Collected on: nmr-1600.chan.uwo.ca-inova500
 Archive directory: /home/data/Kerr/Mike_E
 Sample directory: MS-11-173-1-2014.01.27_01
 F1F1file: CARBON_MS-11-173-1_01

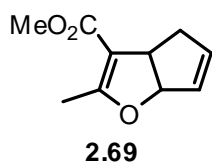
Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Jan 27 2014

Temp. 25.0 C / 298.1 K
 Operator: Kerr

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 0.868 sec
 Width 37735.8 Hz
 184 repetitions

OBSERVE CL3, 150.7231643 MHz
 DECOUPLE H1, 599.4185470 MHz
 Power 49 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 8 min 1 sec





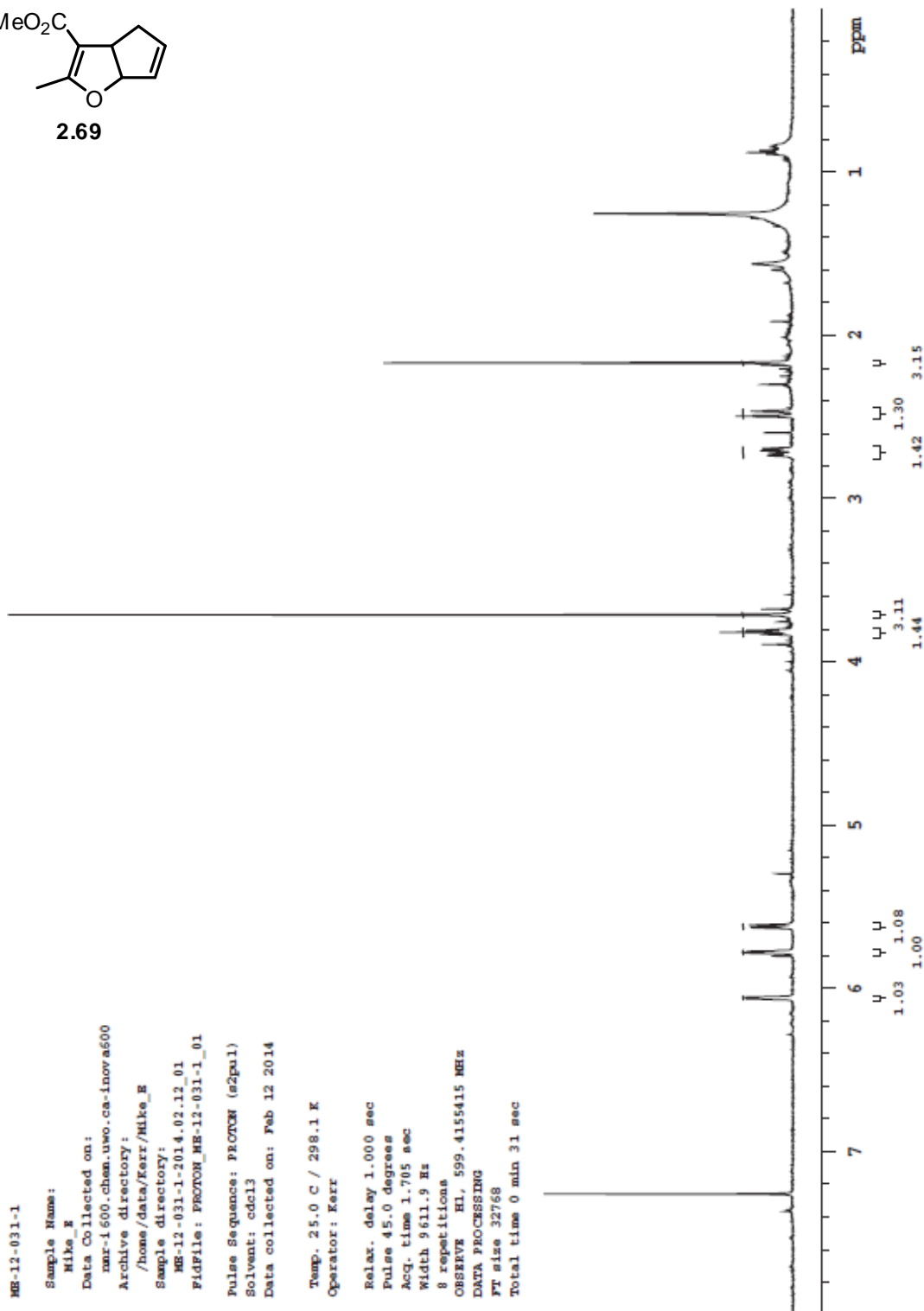
MB-12-031-1
 Sample Name: Mike_E
 Data Collected on: nmr-1600.chem.uwo.ca-inova600
 Archive directory: /home/data/Kerr/Mike_E
 Sample directory: MB-12-031-1-2014.02.12_01
 Fidfile: PROTON_MB-12-031-1_01

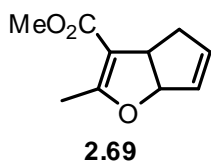
Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Feb 12 2014

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, 599.4155415 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 31 sec



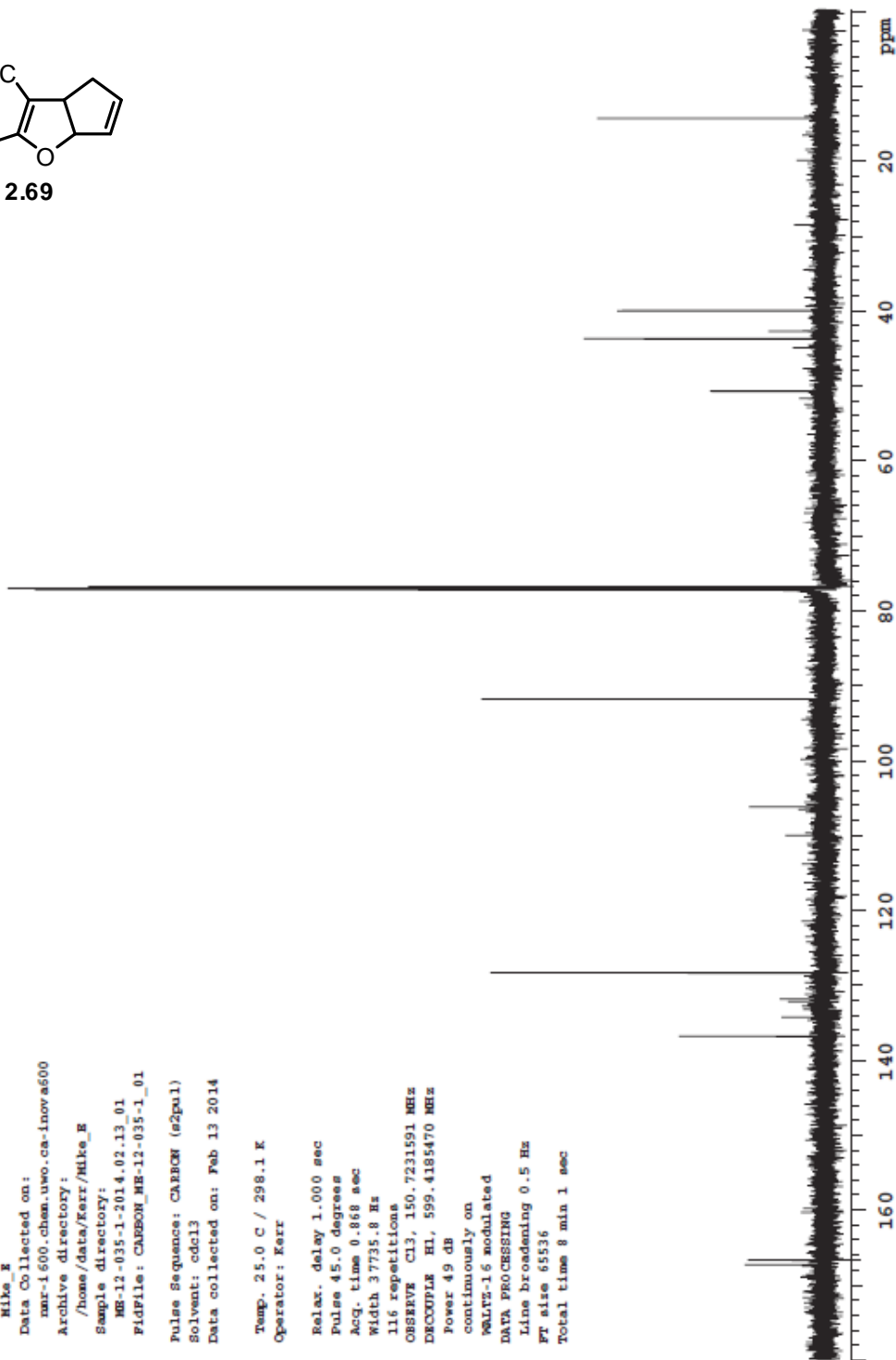


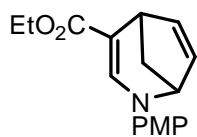
ME-12-035-1

Sample Name:
Mike_E
Data Collected on:
nmr-1600.chem.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
ME-12-035-1-2014.02.13.01
FIDFile: CARBON_ME-12-035-1_01
Pulse Sequence: CARBON (s2pu1)
Solvent: cdcl3
Data collected on: Feb 13 2014

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
116 repetitions
OBSERVE C13, 150.7231591 MHz
DECOUPLE H1, 599.4185470 MHz
Power 49 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
Ft size 65536
Total time 8 min 1 sec





ME-12-115-2

Sample Name:
Mike_E

Data Collected on:
mr-1600.chem.uwo.ca-inova600

Archive directory:
/home/data/Karr/Mike_E

Sample directory:
ME-12-115-2-2014.03.10.01

Fidfile: PROTON_ME-12-115-2_01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Mar 10 2014

Temp. 25.0 C / 298.1 K

Operator: Karr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.705 sec

Width 9611.9 Hz

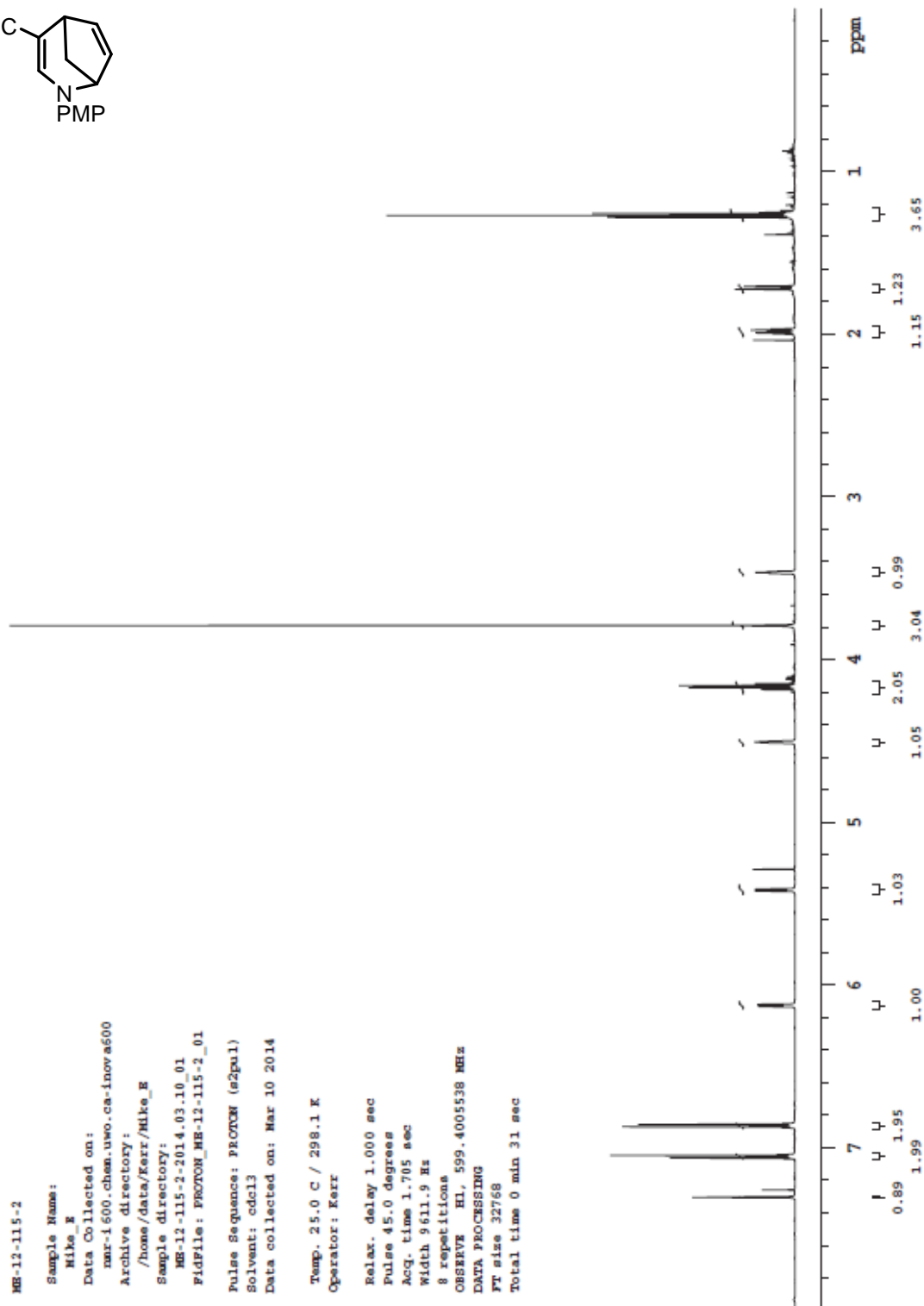
8 repetitions

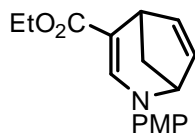
OBSERVE H1, 599.4005538 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 31 sec





MR-12-115-2

Sample Name:

Mike_E

Data Collected on:

mar-1600.chen.uwo.ca-inova600

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

MR-12-115-2-2014.03.10.01

FIDFile: CARBON_MR-12-115-2_01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Mar 10 2014

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

104 repetitions

OBSERVE CH3, 150.7193942 MHz

DECOUPLE H1, 599.4035639 MHz

Power 49 dB

continuously on

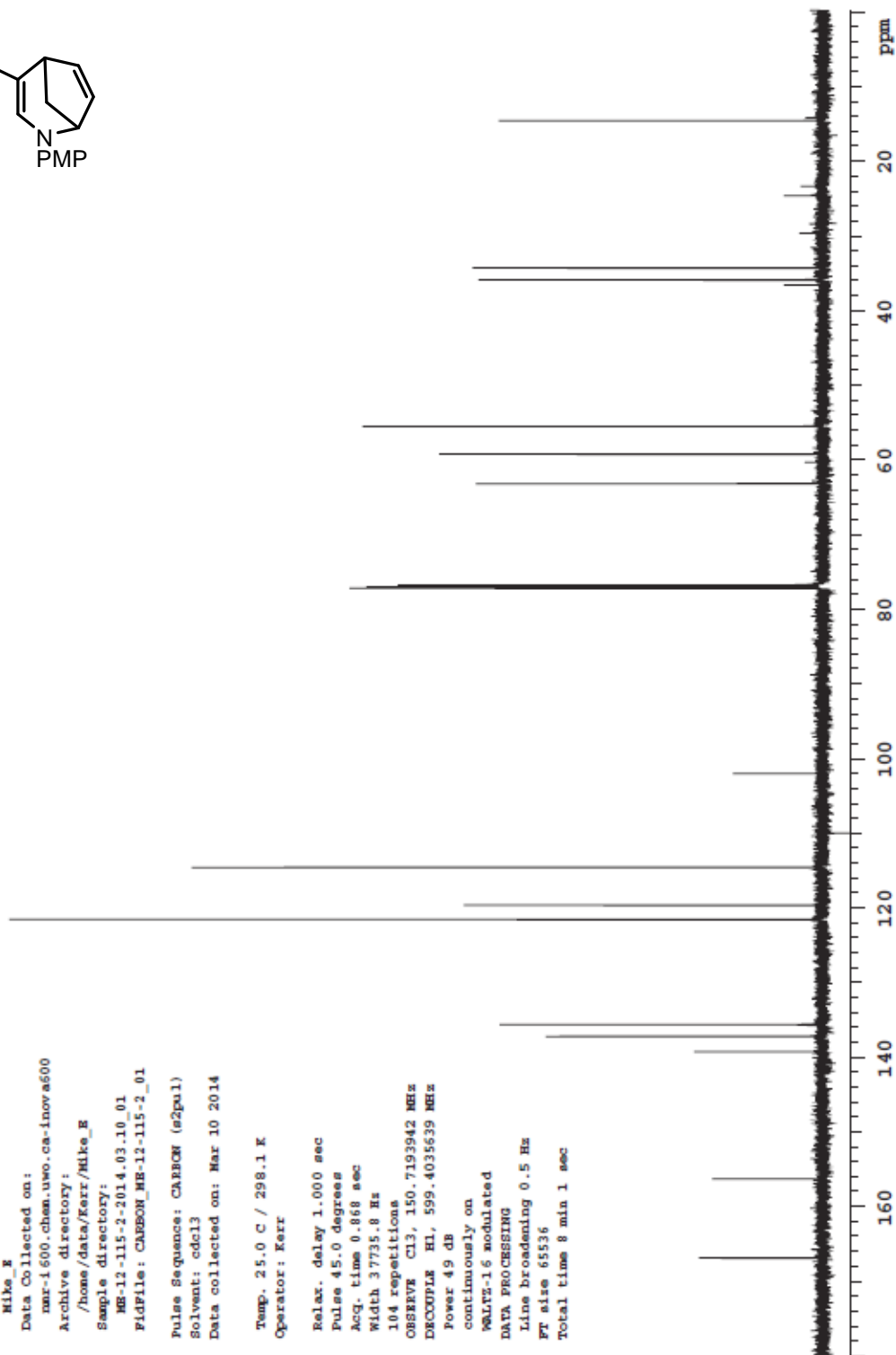
WALTZ-16 modulated

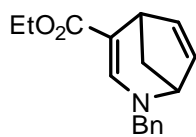
DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 8 min 1 sec

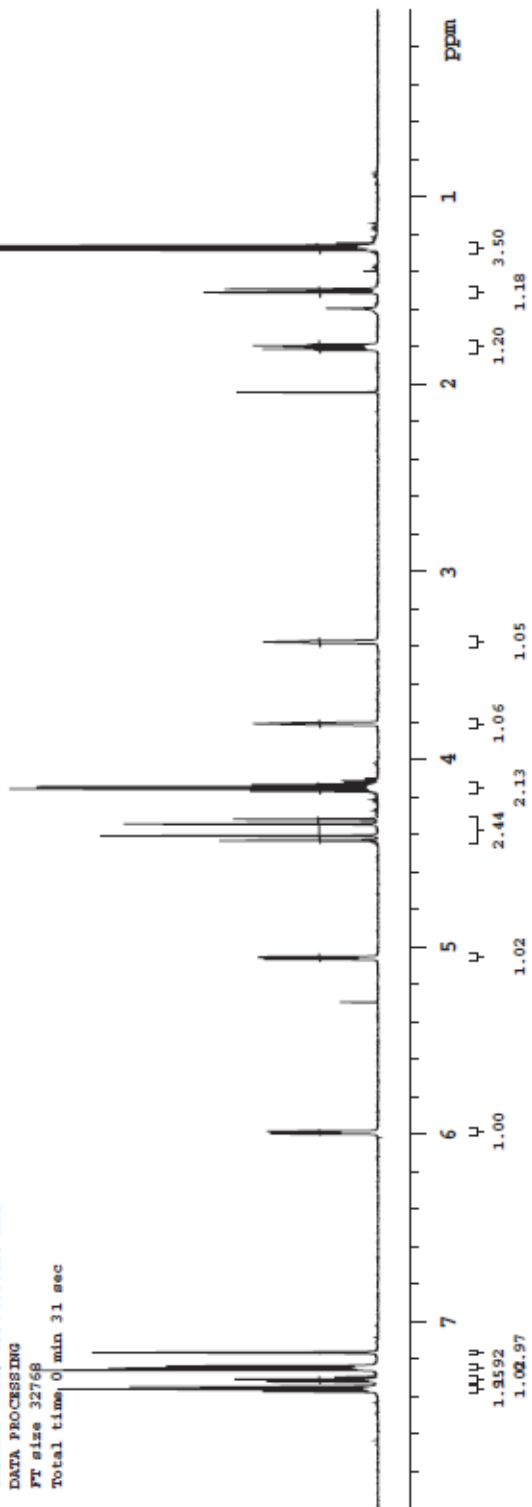


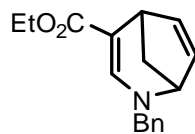


MB-12-155-1
Sample Name:
Mike_E
Data Collected on:
mar-1600.chen.uwo.ca-inova600
Archive directory:
/home/data/Kerr/Mike_E
Sample directory:
MB-12-155-1-2014.03.22_01
FIDFile: PROTON_MB-12-155-1_01
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Mar 22 2014

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 HL, 599.4005558 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 31 sec





MB-12-155-1

Sample Name:
Mike_E

Data Collected on:
mar-1600.chan.uwo.ca-inova600

Archive directory:
/home/data/Kerr/Mike_E

Sample directory:
MB-12-155-1-2014.03.22.01

FIDFile: CARBON_MB-12-155-1_01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Mar 22 2014

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

112 repetitions

OBSERVE C13, 150.7193911 MHz

DECOUPLE H1, 599.4036639 MHz

Power 49 dB

continuously on

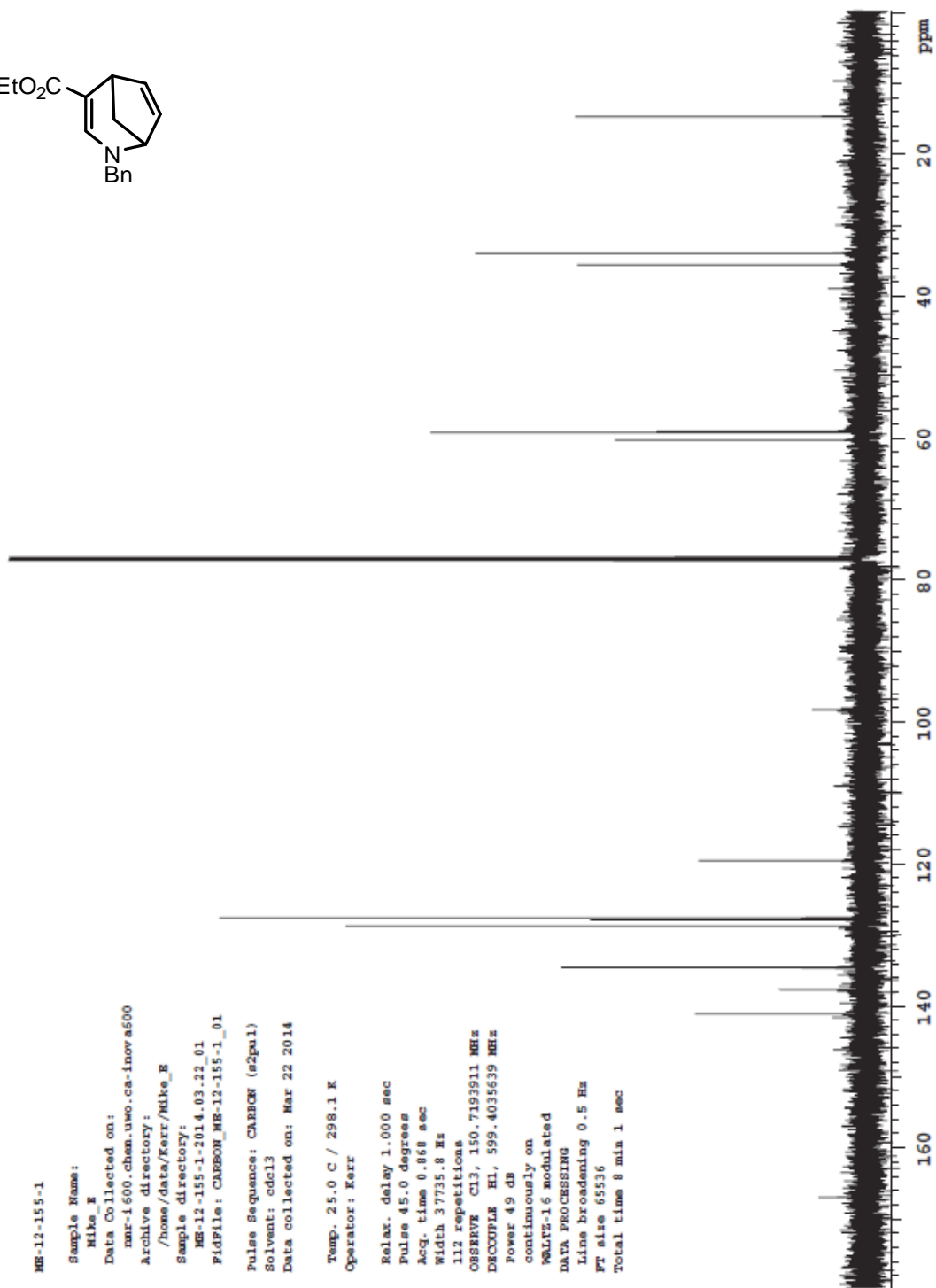
WALTZ-16 modulated

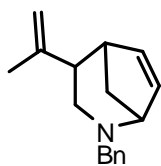
DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 8 min 1 sec





MB-13-001-2d

Sample Name:

Mike_E

Data Collected on:

nmr-1600.chem.uwo.ca-inova600

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

MB-13-001-2d-2014.04.18_01

File: PROTON_MB-13-001-2d_01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Apr 18 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

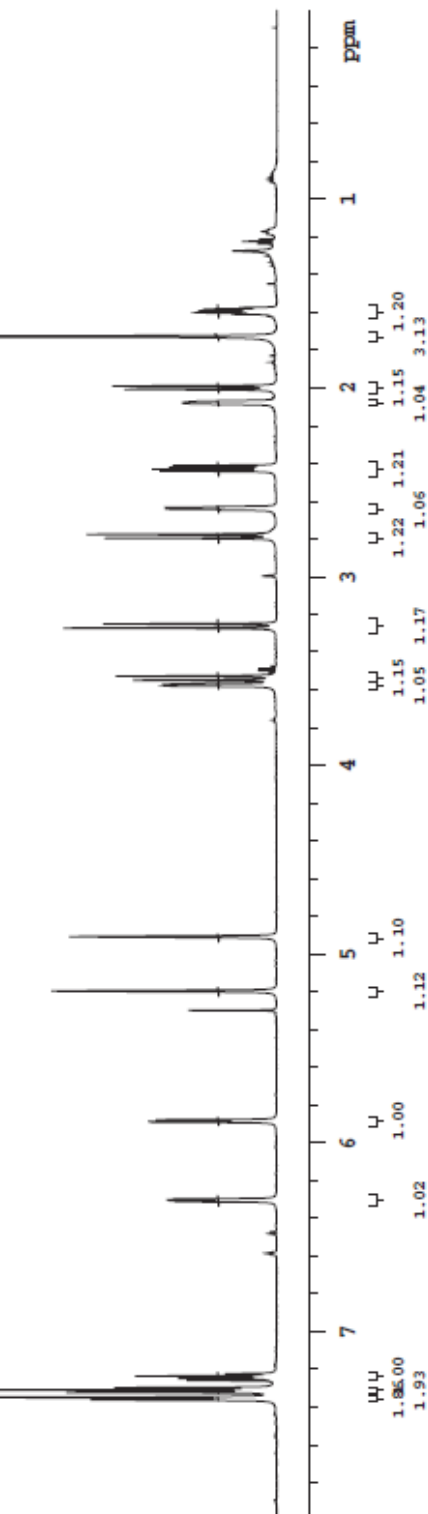
8 repetitions

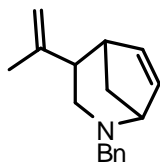
OBSERVE HL 599.4005534 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 31 sec





ME-13-001-2d
 Sample Name:
 Mike_E
 Data Collected on:
 mar-1600.chem.uwo.ca-innov/s600
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-13-001-2d-2014.04.18_01
 FIDFile: CARBON_ME-13-001-2d_01

Pulse Sequence: CARBON (s2pul)
 Solvent: cdcl3
 Data collected on: Apr 18 2014

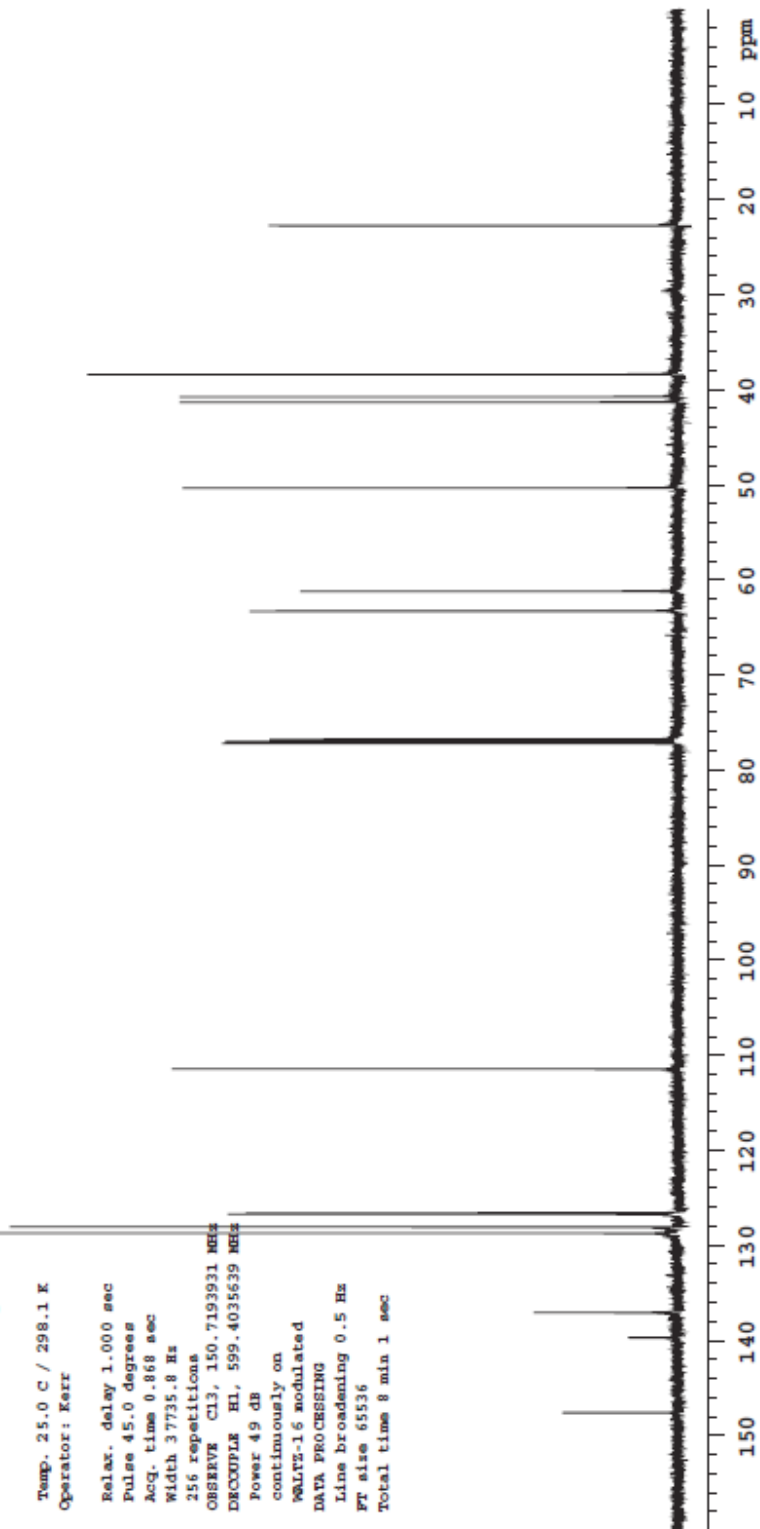
Temp. 25.0 C / 298.1 K
 Operator: Kerr

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 0.868 sec
 Width 37735.8 Hz

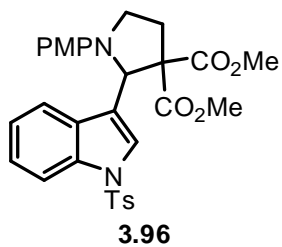
256 repetitions
 OBSERVE C13, 150.7193931 MHz
 DECOUPLE H1, 599.4035639 MHz

Power 49 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 8 min 1 sec



Appendix 3 – NMR Spectral Data for Chapter 3

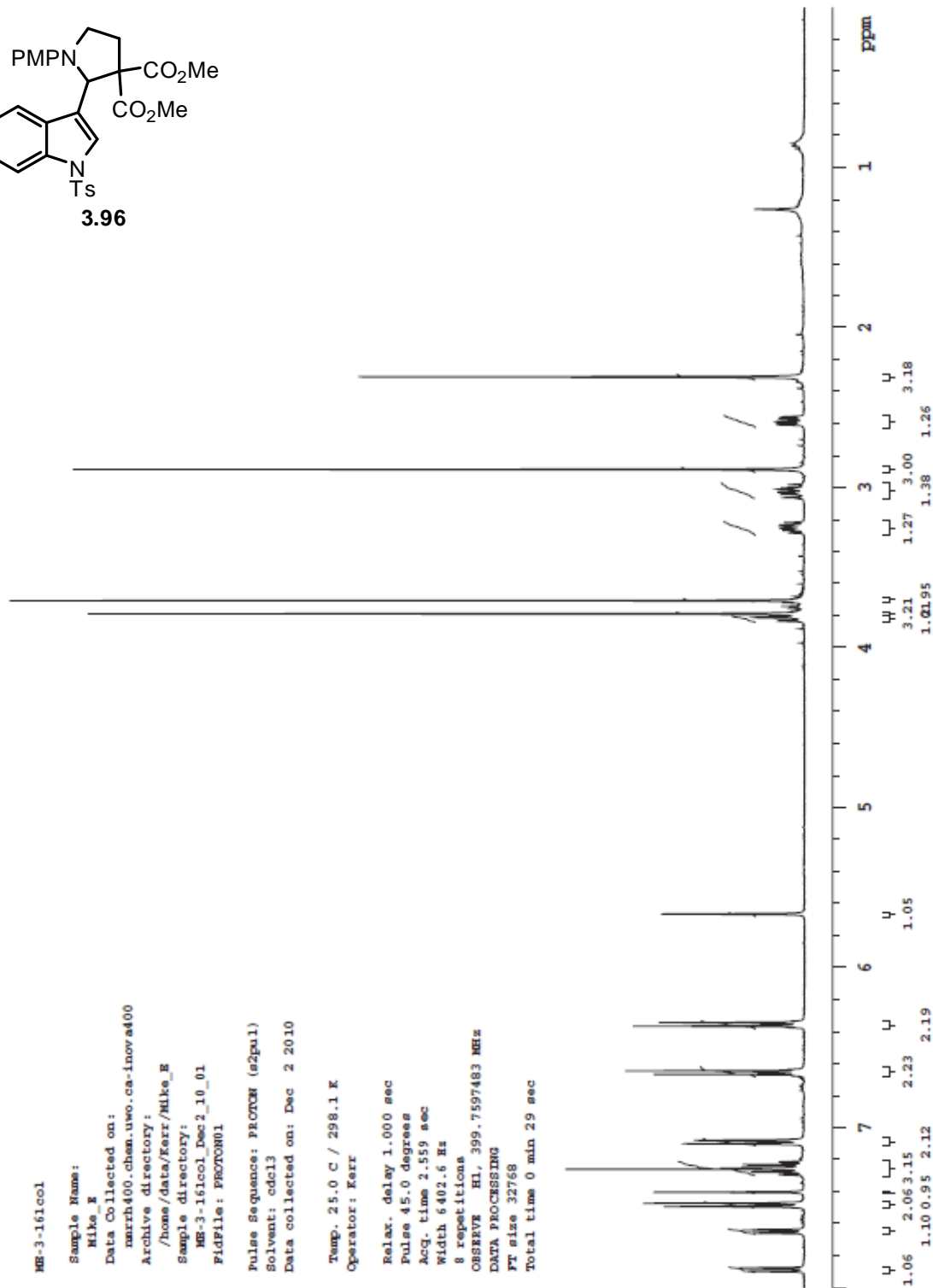


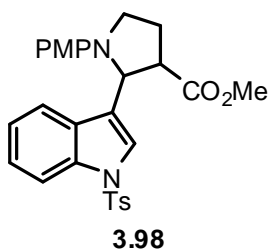
MS-3-161col
 Sample Name:
 Mike_E
 Data Collected on:
 nmrh400.chem.uwo.ca-inova400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 MS-3-161col_Dec2_10_01
 FidFile: PROTON01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Dec 2 2010

Temp. 25.0 C / 298.1 K
 Operator: Kerr

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.559 sec
 Width 6402.6 Hz
 8 repetitions
 OBSERVE H1, 399.7597483 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 29 sec





ME-3-169

Sample Name:
Mike_E

Data Collected on:
narrh500.chem.usc.ca-inova600

Archive directory:
/home/data/Kerr/Mike_E

Sample directory:
ME-3-169_Dec3_10_01

File: PROTON_01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Dec 3 2010

Temp. 25.0 C / 298.1 K

Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.708 sec

Width 9592.3 Hz

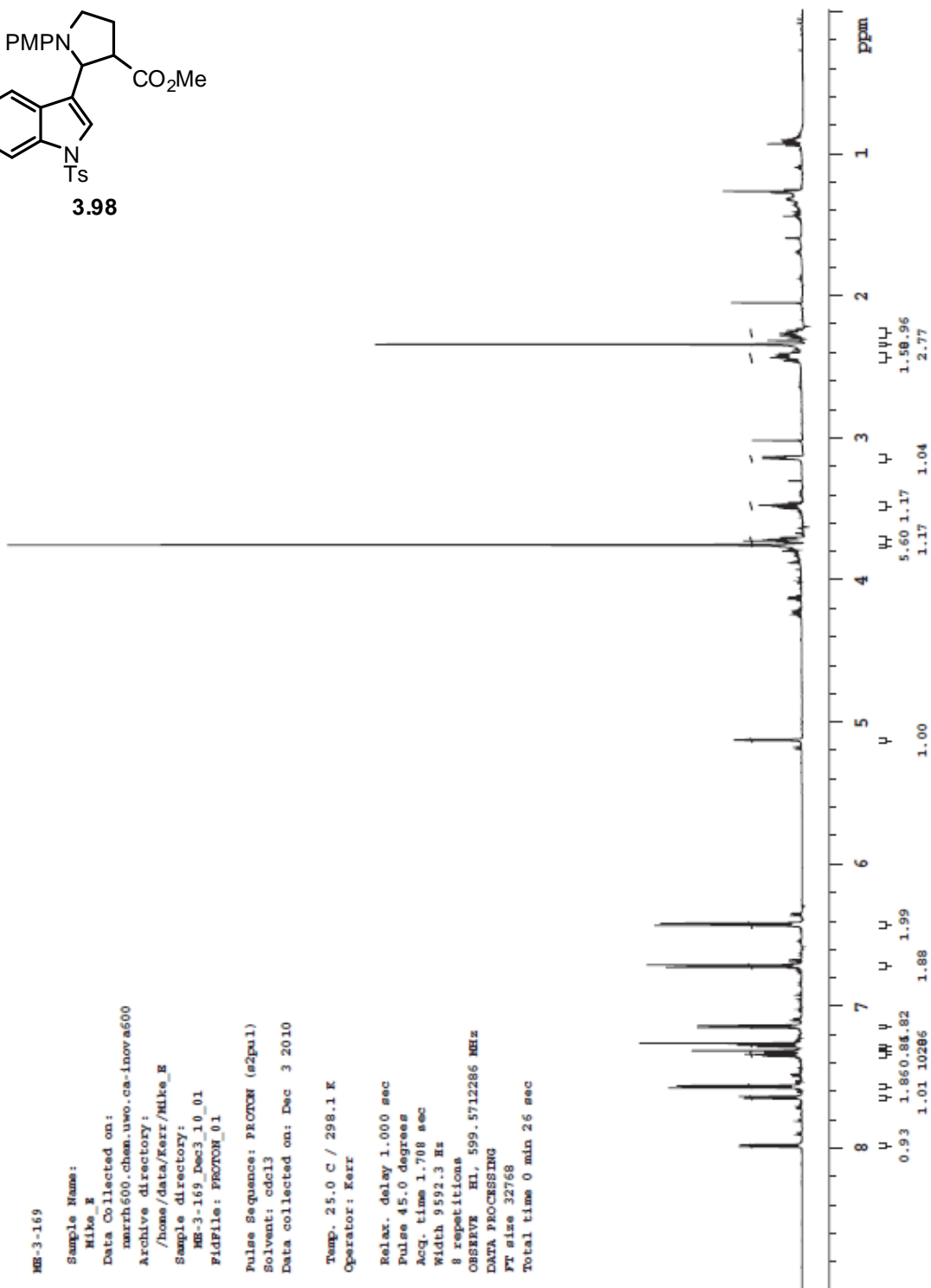
8 repetitions

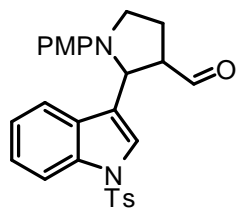
OBSERVE HL, 599.5712286 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 26 sec





3.99

ME-5-005

Sample Name:

Mike_E

Data Collected on:

marh600.chen.uwo.ca-inova600

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

ME-5-005_Jun16_11_01

Fidfile: PROTON_01

Pulse Sequence: PROTON (s2pul)

Solvent: cdcl3

Data collected on: Jun 16 2011

Temp. 25.0 C / 298.1 K

Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.708 sec

Width 9592.3 Hz

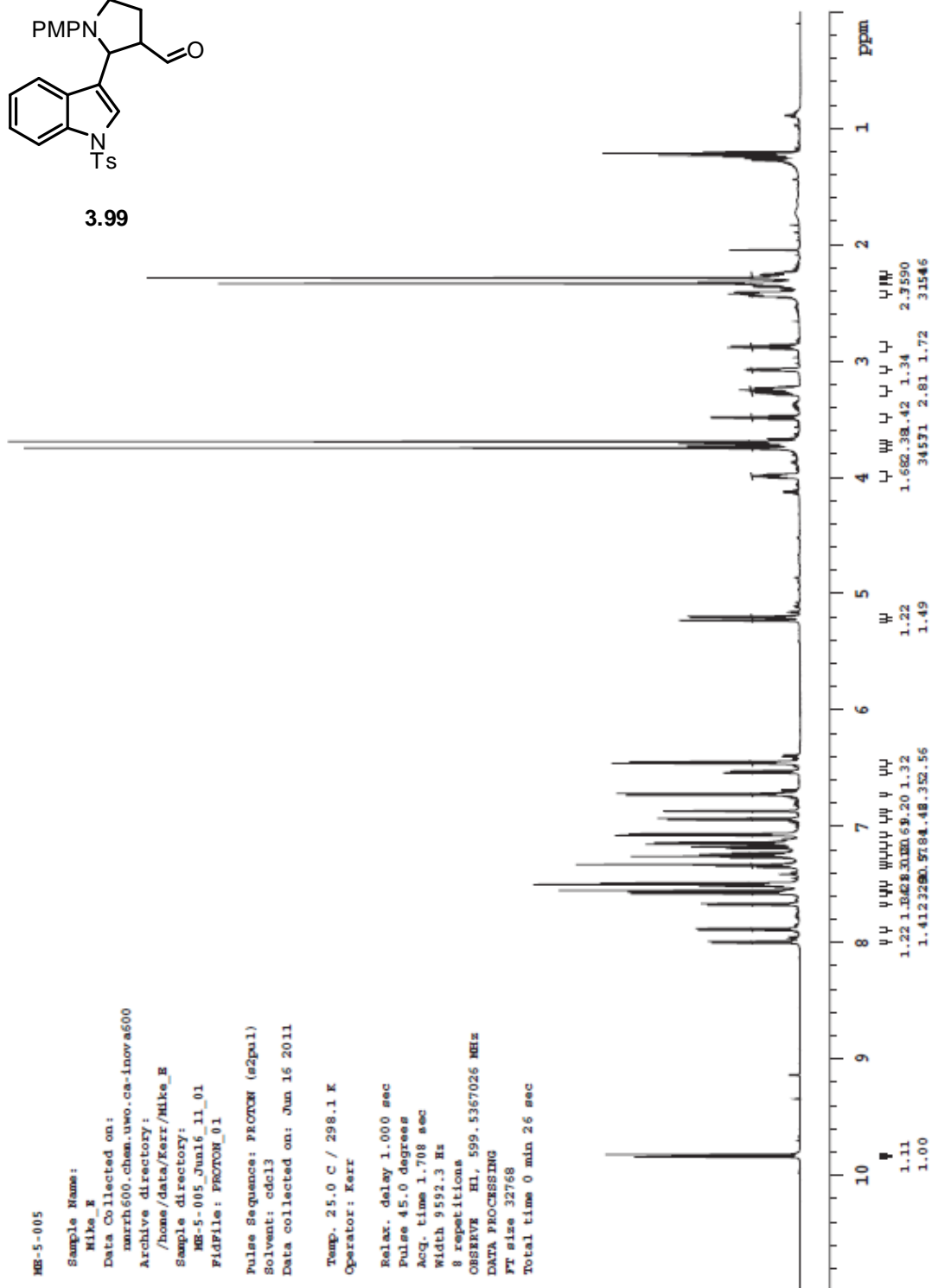
8 repetitions

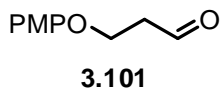
OBSERVE H1, 599.5367026 MHz

DATA PROCESSING

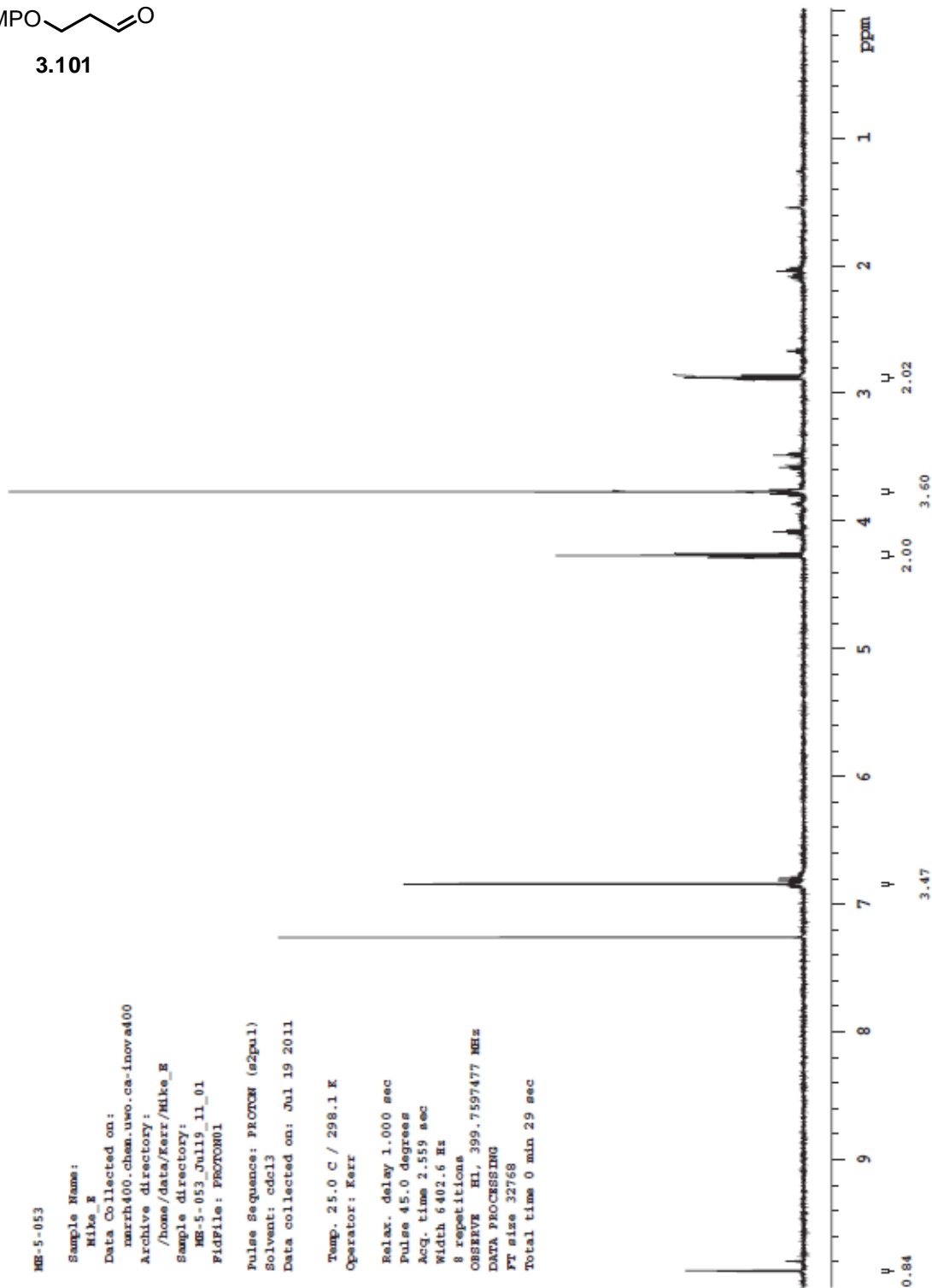
FT size 32768

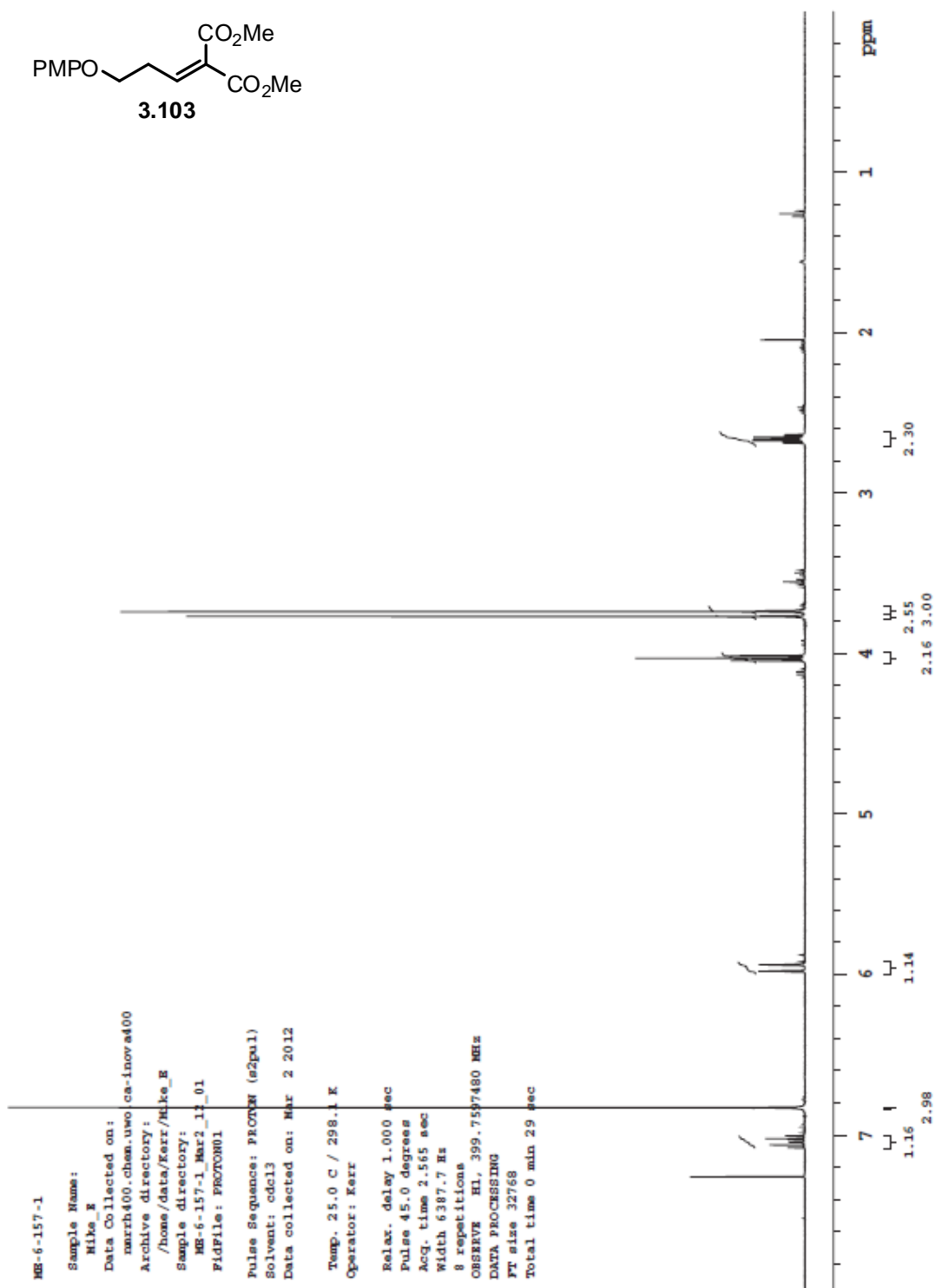
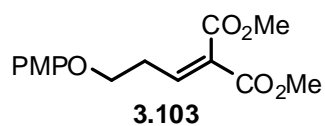
Total time 0 min 26 sec

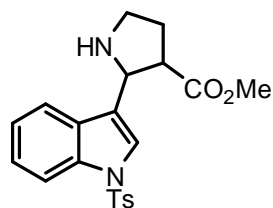




MB-5-053
 Sample Name:
 Mike_E
 Data Collected on:
 marh400.chem.uwo.ca-inova400
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 MB-5-053_Jul19_11_01
 FIDfile: PROTON01
 Pulse Sequence: PROTON (s2pul)
 Solvent: cdcl3
 Data collected on: Jul 19 2011
 Temp. 25.0 C / 298.1 K
 Operator: Kerr
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.559 sec
 Width 6402.6 Hz
 8 repetitions
 OBSERVE H1, 399.7597477 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 29 sec







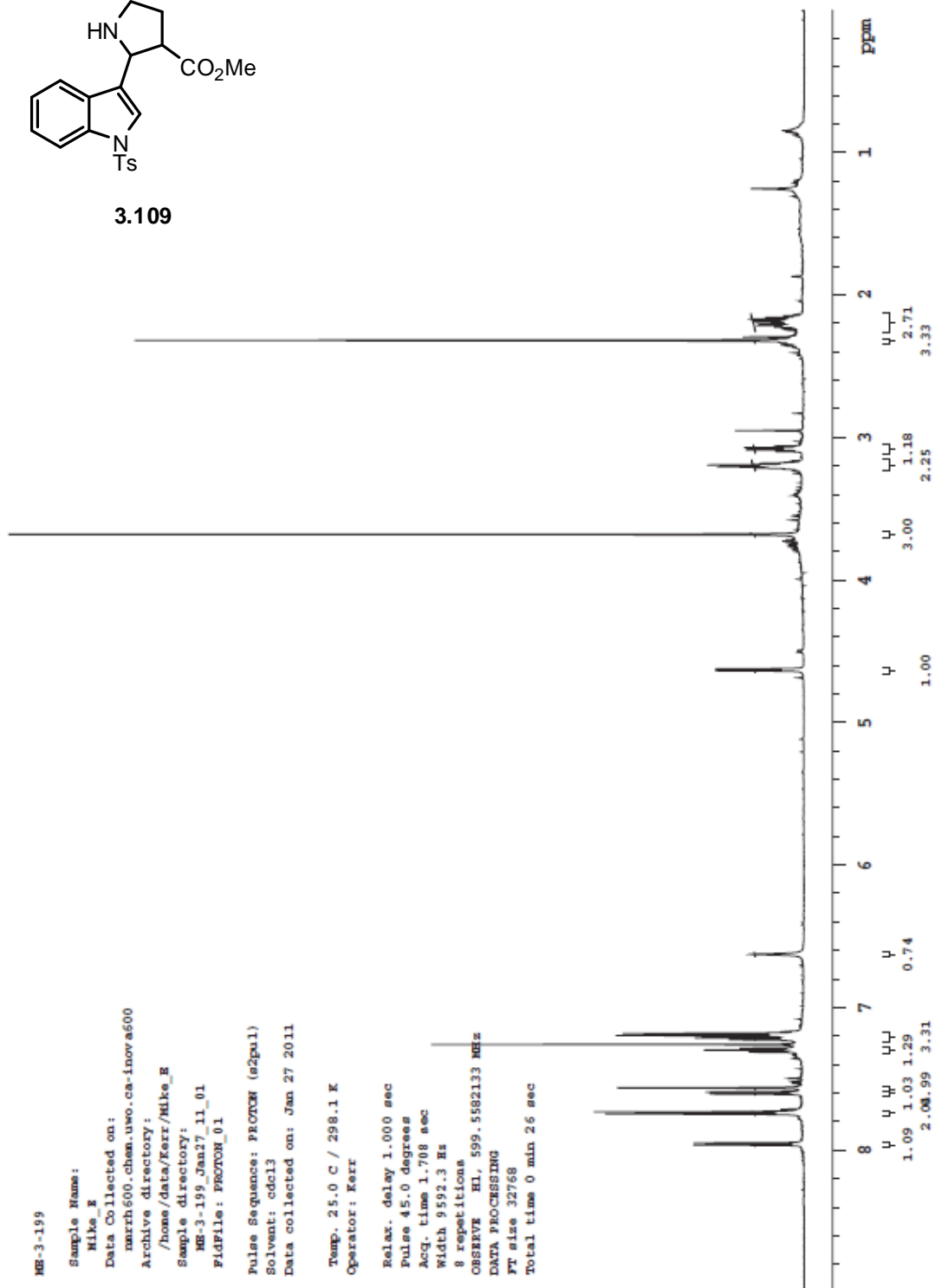
3.109

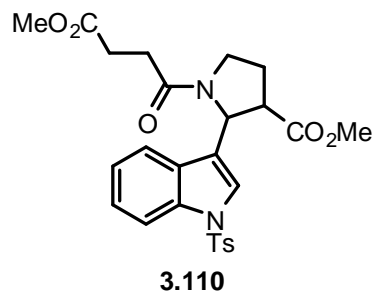
ME-3-199
 Sample Name:
 Mike_E
 Data Collected on:
 marh500.chem.uwo.ca-inova500
 Archive directory:
 /home/data/Kerr/Mike_E
 Sample directory:
 ME-3-199_Jan27_11_01
 Fidfile: PROTON_01

Pulse Sequence: PROTON (s2pul)
 Solvent: cdc13
 Data collected on: Jan 27 2011

Temp. 25.0 C / 298.1 K
 Operator: Kerr

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.708 sec
 Width 9592.3 Hz
 8 repetitions
 OBSERVE H1, 599.5582133 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min 26 sec





MS-3-207col

Sample Name:

Mike_E

Data Collected on:

marth600.chen.uwo.ca-inova600

Archive directory:

/home/data/Kerr/Mike_E

Sample directory:

MS-3-207col_Feb3_11_01

FIDFile: FRETION_01

Pulse Sequence: FRETION (s2pul)

Solvent: cdcl3

Data collected on: Feb 3 2011

Temp. 25.0 C / 298.1 K

Operator: Kerr

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.708 sec

Width 9592.3 Hz

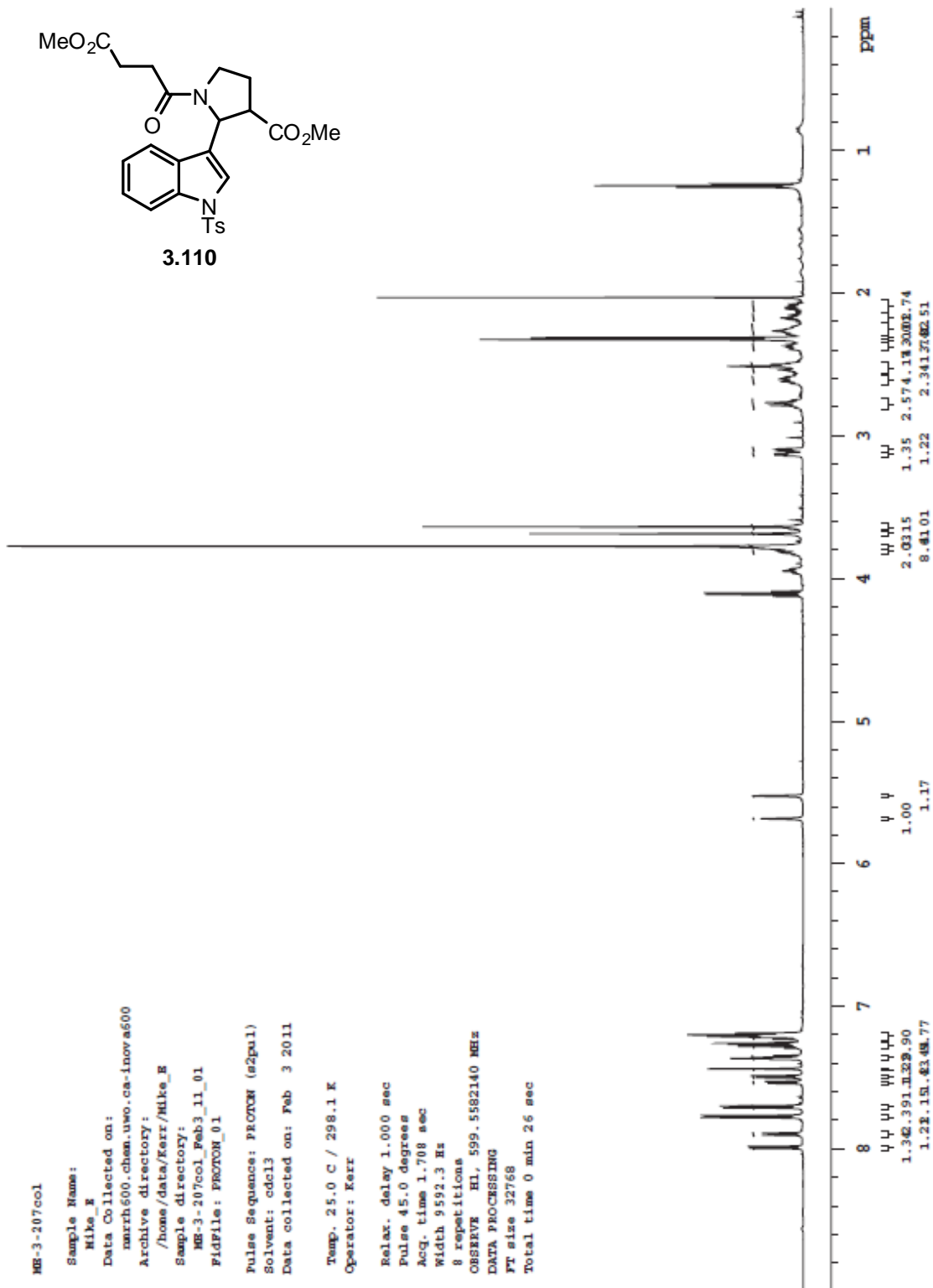
8 repetitions

OBSERVE H1, 599.582140 MHz

DATA PROCESSING

FT size 32768

Total time 0 min 26 sec



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