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The Application of Novel Donor Acceptor Cyclopropanes in the Synthesis of Linearly Fused Tricyclic Triazoles

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Graduate Program in Chemistry
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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THE APPLICATION OF NOVEL DONOR ACCEPTOR CYCLOPROPANES IN THE
SYNTHESIS OF LINEARLY FUSED TRICYCLIC TRIAZOLES

(Thesis format: Integrated Article)

by

Michelle Elaine Flisar

Graduate Program in Chemistry

A thesis submitted in partial fulfillment
of the requirements for the degree of
Masters of Science

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

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Abstract

Previous work in the Kerr group has shown the success of donor-acceptor cyclopropanes as substrates in a variety of synthetic reactions; this document will apply the use of donor acceptor cyclopropanes in various synthetic reactions. This was done using a 2-substituted 1,1-cyclopropanediester, in the Overman Rearrangement, which has yet to be explored using DA cyclopropanes. Another useful DA cyclopropane is the novel acetylene-bearing donor acceptor diester cyclopropanes which would be synthetically useful in a wide variety of reactions. In particular, the Conia-ene cyclization occurred intramolecularly with this alkyne DA cyclopropane with a large library of nucleophiles. Finally, taking this acetylene-bearing DA cyclopropane, it was converted to the hemimalonate version, and subjected to a ring-opening by azide as the nucleophile to generate an alkyl azide; which then underwent a [3+2] dipolar cycloaddition with the alkyne to form novel linearly fused tricyclic triazoles.

Keywords

Donor acceptor cyclopropanes, heterocycles, triazole, Click chemistry, cycloaddition, Overman Rearrangement, Conia-ene cyclization, annulation, organic synthesis.

Co-Authorship Statement

The work in Chapter 4 was submitted in the following article:

Flisar, M. E.; Emmett, M. R.; *Kerr, M. A. “The Catalyst-free Tandem Ring-opening/Click Reaction of Acetylene-Bearing Donor Acceptor Cyclopropanes” *Synlett* **2014**, manuscript was accepted to Synlett and awaiting publication.

The original draft of this manuscript was prepared by the authors and Dr. M.A. Kerr. The initial concept and trial reaction were completed by M. R. Emmett, and all experimental synthesis and characterization was completed by the first author.

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List of Abbreviations

A	Acceptor (group)
AAC	Azide-Alkyne Cycloaddition
app	Apparent
Ar	Aryl (group)
Bn	Benzyl (group)
calc'd	Calculated
CuACC	Copper-catalyzed Azide-Alkyne Cycloaddition
d	day
d	doublet
D	Donor (group)
DA	Donor-Acceptor
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DMSO	Dimethylsulfoxide
Decomp.	Decomposition
E/E ⁺	Electrophile
EDG	Electron Donating Group
EI	Electron Impact
EtOAc	Ethyl Acetate
EWG	Electron Donating Group
FCM	Förster-Coulson-Moffit
FT-IR	Fourier Transform Infrared Spectroscopy
g	grams

h	hours
HIV	Human Immunodeficiency Virus
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
<i>J</i>	Coupling constant
kBar	kilobar
kJ	kilojoule
L	Ligand
m	multiplet
M	Molarity
MeOH	Methanol
mg	milligram
MHz	Megahertz
mL	milliliters
mmol	millimol
MP	Melting Point
MS	Mass Spectrometry
NBS	<i>N</i> -Bromosuccinimide
NMO	4-Methylmorpholine <i>N</i> -oxide
NMR	Nuclear Magnetic Resonance
Nu/Nu ⁻	Nucleophile
o/n	Overnight
<i>p</i>	para
q	Quartet
R	Any functional group

R_f	Retention Factor
rt	room temperature
s	singlet
SM	Starting Material
S_N	Nucleophilic Substitution
t	triplet
Tf	triflate
TFA	Trifluoroacetic Acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
UV	Ultraviolet
X	Halogen group
α	Alpha
β	Beta
σ	Sigma
π	Pi
μ L	MicroLiter

1 Introduction to Donor Acceptor Cyclopropanes

1.1 Donor Acceptor Cyclopropanes

1.1.1 Structure and Bonding in Cyclopropanes

The highly strained cyclopropane ring was discovered back in 1881 by Freund, and has been a widely used synthetic tool in chemistry for over a century.¹ This is due to cyclopropanes highly reactive nature, caused by the strain energy on this three-membered ring system; this reactivity is analogous to the reactive nature seen in olefins. Cyclopropanes have been known to react with a wide variety of electrophiles, nucleophiles, and radical species and therefore have become a useful tool in creating new and exciting chemical transformations.¹

The concept of bent bonds in cyclopropanes was first described by Ingold in an effort to explain the stability of tetrahedrane (Figure 1.1).² The strongly bent bonds in tetrahedrane lead to poor orbital overlap and weak C-C bonds.³

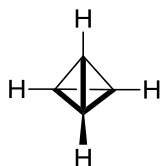


Figure 1.1 Structure of Tetrahedrane

The reactive qualities of a cyclopropane ring can be attributed to its unique chemical and physical properties. In terms of physical properties, a cyclopropane ring significantly deviates from the ideal 109.5° tetrahedral bond geometry value for a sp^3 carbon; the bond angles in a cyclopropane ring being only approximately 60° (Figure 1.2). This angular ring strain accounts for approximately 118 kJ/mol of energy in a cyclopropane ring. It is this strain on the ring that causes the cyclopropane to react similarly to olefins.⁴



Figure 1.2 Angle Strain of a Cyclopropane

This angular strain present in each cyclopropane must be alleviated by increasing the amount of p character in the ring. Since bent bonds would lead to poor overlap and weak C-C bonds, Förster, Coulson and Moffitt (FCM) came up with a model to describe the bonding within a cyclopropane ring (Figure 1.3). FCM calculated that the C-C bonds contained more p character, while the C-H bonds contained more s character. In order for this to be possible the C-C bonds must be shorter and have hybridization values of approximately 80 % p and 20 % s character; and the C-H bonds must have hybridization values of 70 % p and 30 % s character. These results were first based off of computational studies, and later further proven by experimental ones. From this model of bonding (Figure 1.3), the overlap of the p orbital's are relatively off centered and ineffective, thus resulting in the cyclopropanes unique reactivity in comparison to a standard alkane. Ultimately the FCM model explains that weakening the C-C bonds, along with the strain of the three-membered ring, leads to overall bond weakening.^{1,3}

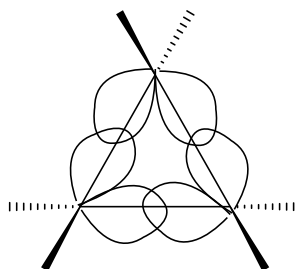


Figure 1.3 Förster-Coulson-Moffitt Model of a Cyclopropane Ring

These weakened bonds are what make cyclopropane a more reactive substrate; when compared to other cycloalkane systems, the reactivity of cyclopropane is much more reactive than a typical alkane bond (355 vs. 255 kJ/mol). This increase in reactivity makes cyclopropanes great substrates for reactions with nucleophiles, electrophiles and radical species, much like olefins.^{4,5}

Within a cyclopropane ring there are three different types of strain. Previously mentioned was angular strain (Figure 1.2); Figure 1.5 illustrates the other two types of strain, caused by the repulsions of electrons between different substituents, known as torsional and steric strain. Torsional strain occurs in the ring system as different substituents eclipse one another. Similarly, steric strain occurs in highly substituted cyclopropane rings and therefore repulsions occur when the neighboring atoms are too close together (Figure 1.4).⁴

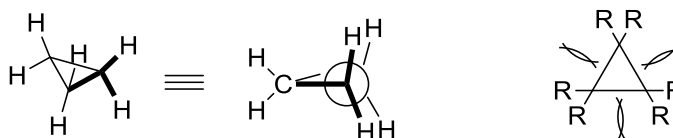


Figure 1.4 Torsional/Steric Strain of Cyclopropanes

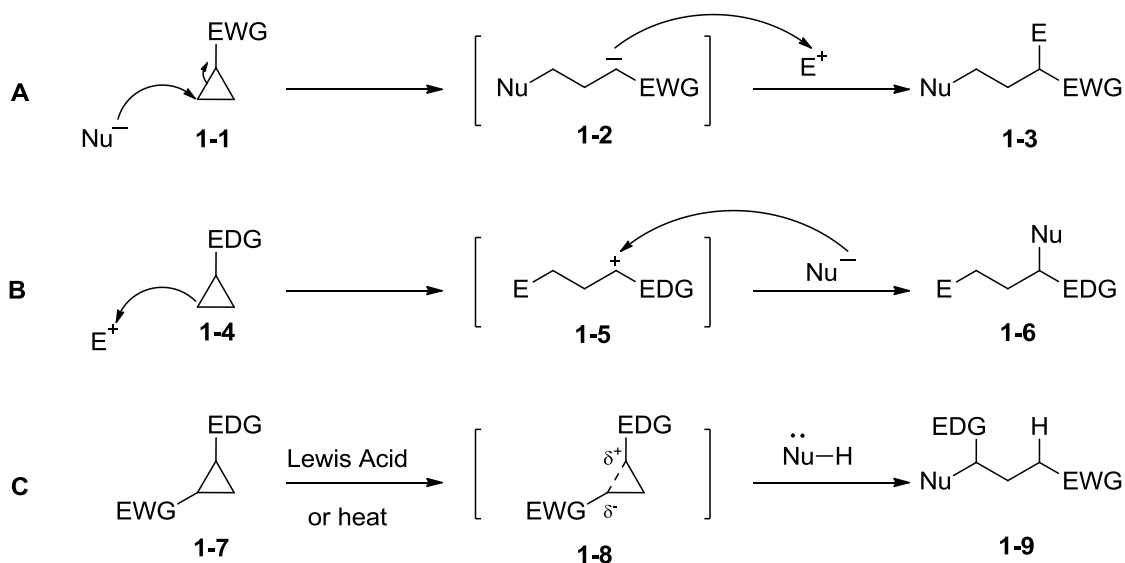
1.1.2 Types and Reactivity of Cyclopropanes

Even with large amounts of strain energy, cyclopropanes are often rather slow to react. Previous research has suggested that cyclopropanes need to be activated in order to increase the reactivity rates. This activation usually comes from a combination of electron withdrawing substituents and/or electron donating substituents attached to the cyclopropane ring. Activated cyclopropanes have become synthetic building blocks in organic chemistry and allow for the generation of new carbon-carbon bonds. Based on the different types of activation sources, there are three main types of activated cyclopropanes:^{6,7}

- I. Acceptor Cyclopropanes
- II. Donor Cyclopropanes
- III. Donor-Acceptor Cyclopropanes

Acceptor cyclopropanes contain electron withdrawing functional substituents (EWG) which allows for the stabilization of a negative charge generated after nucleophilic ring opening on the vicinal carbon (Scheme 1.1A). Trapping with an electrophile can lead to

the homo-Michael product **1-3**. Donor cyclopropanes, are the opposite, in that they contain electron donating functional groups (EDG), which allows electron density to be distributed throughout the ring and therefore increases the nucleophilicity of the cyclopropane ring (Scheme **1.1B**). Therefore in the presence of an electrophile, nucleophilic attack by cyclopropane **1-4** can occur to give a carbocation intermediate **1-5**. This charge is stabilized by the EDG which can be further reacted with a nucleophile to give **1-6**.^{6,7}



Scheme 1.1 The Reactivity of Cyclopropanes

The third and final type is donor-acceptor (DA) cyclopropanes, which contains both electron donating and electron withdrawing functional groups; this type of cyclopropane is considered the most synthetically useful of the three types due to the formation of a 1,3-dipole (**1-8**) which can readily react with nucleophiles (Scheme **1.1C**). Under Lewis acid conditions, vicinal DA cyclopropanes are doubly activated and can undergo formal retro-aldol rearrangements to create a 1,3 dipole synthon for homo-Michael reactions. The vicinal ED and EW groups on cyclopropane **1-7** allows for the stabilization of possible ring opening (**1-8**) and therefore nucleophile attack can occur.⁷

DA cyclopropanes can be divided into two separate categories: geminal and vicinal DA cyclopropanes (Figure 1.5). Geminal refers to the substituents residing on the same carbon, whereas vicinal refers to them being on adjacent carbons. Geminal DA cyclopropanes are not commonly used in synthetic chemistry due to the substituents on the cyclopropane ring not being able to act in a synergic manner. Vicinal DA cyclopropanes exhibit an electron push-pull relationship, therefore having reactivity analogous to a 1,3-dipole, making them more synthetically useful than geminal DA cyclopropanes.^{6,7} Geminally substituted DA cyclopropanes however, do display important structural significance for amino acid synthesis, as well as in the synthesis of phytohormone ethene.⁸

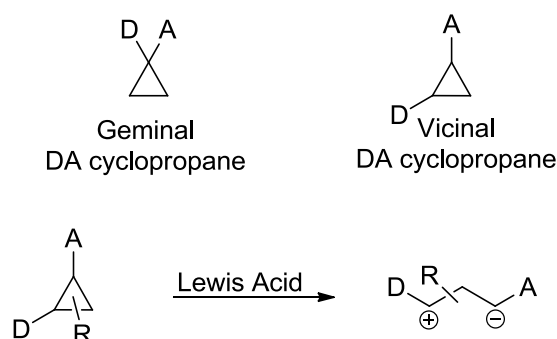


Figure 1.5 Geminal and Vicinal DA Cyclopropanes and the Mode of Reactivity

1.1.3 Synthesis of DA cyclopropanes

1.1.3.1 History of synthesis of DA cyclopropane

The synthesis of cyclopropanes centers mainly on carbene chemistry, as four of the six major methods involve these substrates (**1-4**, Figure 1.6⁹). Three of the four carbene methods involve a direct [2+1] cycloaddition, changing the location of the donor and acceptor functionality groups between the carbene and the olefin (**1-3**).

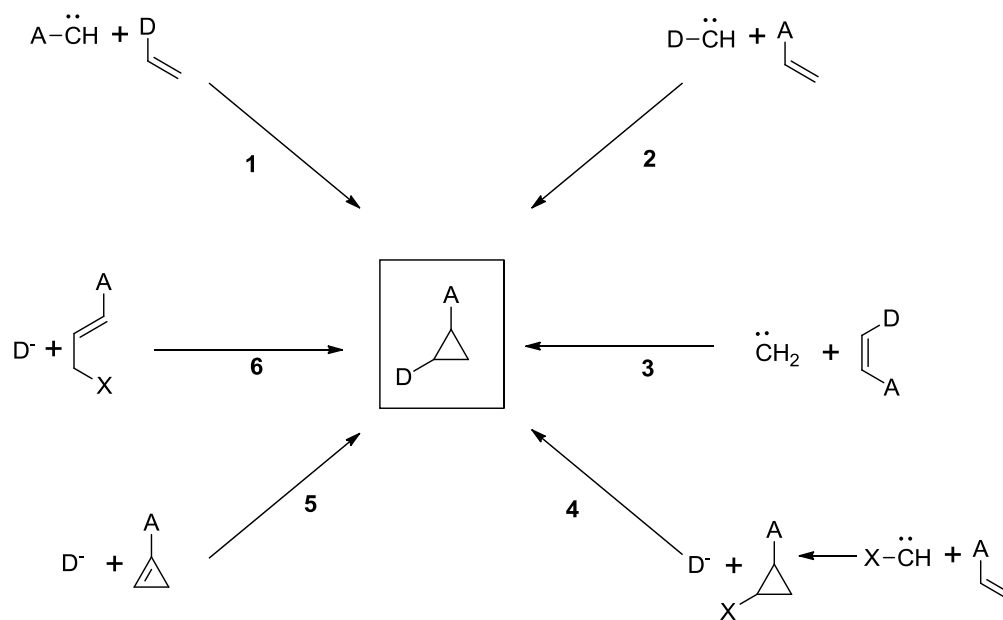


Figure 1.6 The various ways to make DA Cyclopropanes

Path **1** involves the reaction between an acceptor-substituted carbene with an electron-rich olefin, whereas path **2** is the opposite, involving a donor-substituted carbene with an electron-poor olefin. The use of an olefin containing both the donor and acceptor functional groups on it can undergo methylenation with a carbene to give a DA cyclopropane seen in path **3**. For paths **2** & **3**, the use of the donor-substituted carbene, as well as methylenation of a DA-olefin, is rather difficult and not very efficient due to the low reactivity of these substrates. Using a halogenated cyclopropane (path **4**) as a precursor to the target molecule has increased the scope of DA cyclopropanes. This route goes through a halocarbene, which reacts with an olefin to give an acceptor cyclopropane; donor functionalities can substitute the halogen group by treatment with various nucleophiles. The use of cyclopropanes by activation with electron withdrawing substituents is also of lesser importance due to the involvement of starting material which is not readily available (path **5**). The very first synthesis of DA cyclopropanes (route **6**) occurred by a Michael addition of a nucleophile followed by an intramolecular substitution to create the three-membered ring. This process could be described as an intramolecular S_N ring closure reaction. Since all carbon atoms were already assembled in

the starting material, and the reaction was not general enough and therefore has not received very much attention.^{6,9}

The easiest and most convenient source of carbenes is diazoalkanes, which decompose in the presence of a metal catalyst to form reactive carbene complexes (carbenoids) that can then undergo [2+1] cycloadditions with olefins to yield the desired cyclopropane. Using acceptor-substituted diazoalkanes (diazocarbonyls) can yield DA cyclopropanes when reacted with electron rich alkenes (Figure 1.7⁶).^{6,9}

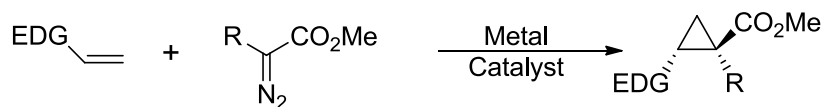
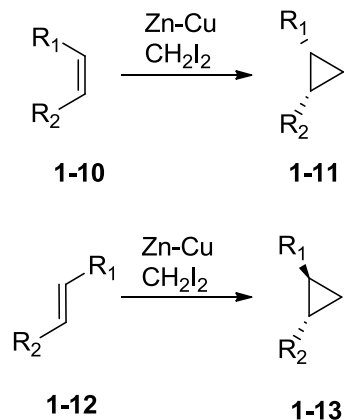


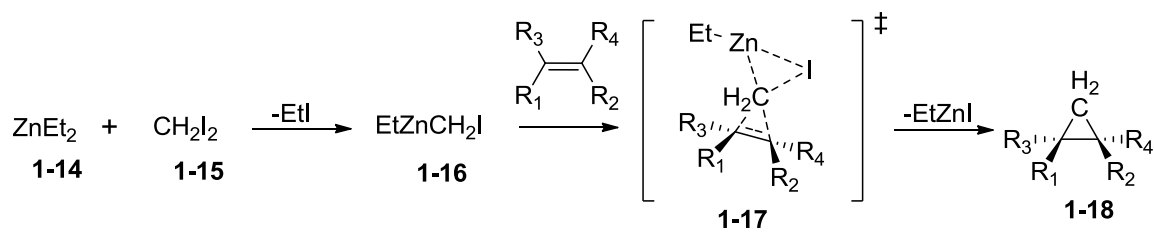
Figure 1.7 The use of Diazo-Species to form DA Cyclopropanes

1.1.3.2 Simmons-Smith Cyclopropanation

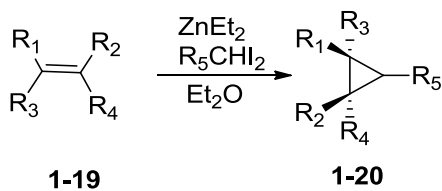
A very well known cyclopropanation in organic chemistry is the Simmons-Smith cyclopropanation. This reaction was named after the discoverers H.E. Simmons and R.D. Smith, who back in 1958, were the first to use diiodomethane (CH₂I₂) in the presence of a zinc-copper amalgam to stereospecifically convert an un-functionalized alkene into a cyclopropane (Scheme 1.2).¹⁰ The reaction mechanism goes through a three-centered “butterfly type” transition state 1-17 (Scheme 1.3¹⁰), and agrees with both theoretical studies as well as the stereochemical outcome produced for all reactions. Since 1958, many modifications have been made, the major one being by Furukawa in 1966, who replaced the Zn-Cu system with diethyl zinc, making the reaction much less complex (Scheme 1.4¹⁰).¹⁰



Scheme 1.2 The Simmons-Smith Cyclopropanation



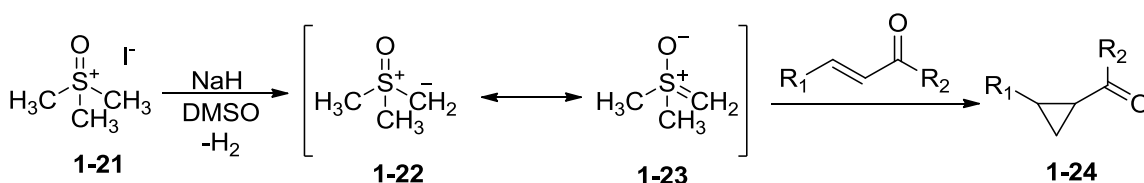
Scheme 1.3 The Proposed Mechanism for the Simmons-Smith Cyclopropanation



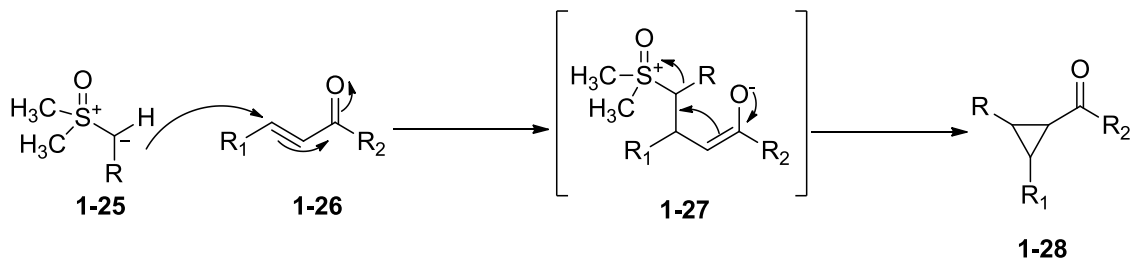
Scheme 1.4 The Simmons-Smith Cyclopropanation with Furukawa Modifications

1.1.3.3 Corey-Chaykovsky Cyclopropanation

Another unique and commonly used cyclopropanation is the Corey-Chaykovsky reaction. Developed in 1962 by E. J. Corey and M. Chaykovsky, it was discovered that the deprotonation of trimethylsulfoxonium halides could occur using powdered sodium hydride, under nitrogen atmosphere at room temperature, thereby generating a dimethylsulfoxonium methylide (Scheme 1.5¹¹). When this ylide **1-25** was mixed with α,β -unsaturated carbonyl compounds **1-26**, and a conjugate addition followed by the expelling of the ylide (**1-27**) produced cyclopropane **1-28** as the product (Scheme 1.6).¹¹



Scheme 1.5 General Reaction for the Corey-Chaykovsky Cyclopropanation

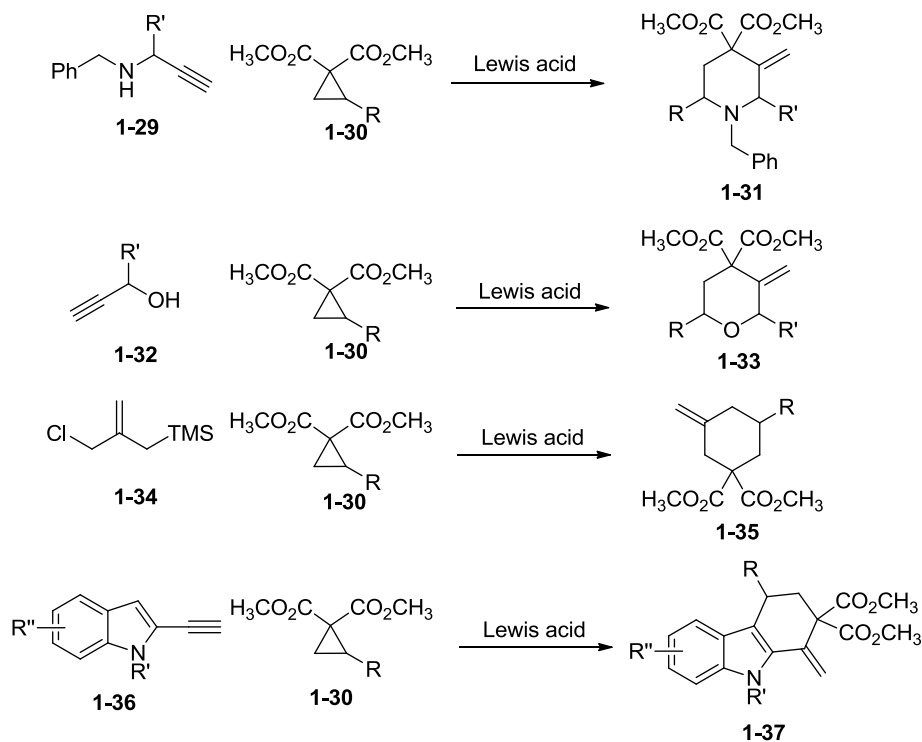


Scheme 1.6 Proposed Mechanism of the Corey-Chaykovsky Cyclopropanation

The Corey-Chaykovsky cyclopropanation is the synthesis used for this thesis work, as it is the most cost effective and efficient synthesis of DA cyclopropanes. This is due to the absence of catalyst, mild conditions, high yields and readily synthesized starting materials.

1.1.4 Applications of Donor Acceptor Cyclopropanes

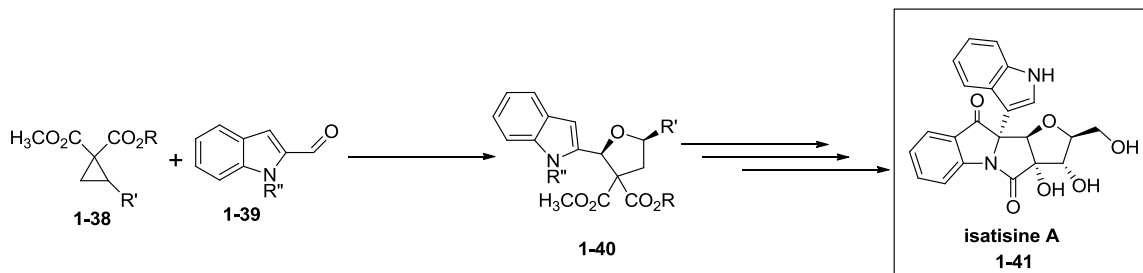
To this day, DA cyclopropanes are extremely useful for synthetic chemists as they can be valuable building blocks in a wide variety of natural product syntheses. In particular, DA cyclopropanes are of substantial importance in the area of ring-opening/annulation reactions. This has allowed for easy access to a variety of synthetic products such as piperidines **1-31**¹², tetrahydropyrans **1-33**¹³, cyclohexanes **1-35**¹⁴ and tetrahydrocarbazoles **1-37**,¹⁵ respectively (Scheme 1.7). These reactions offer a suitable way to access a variety of carbocyclic and heterocyclic products.



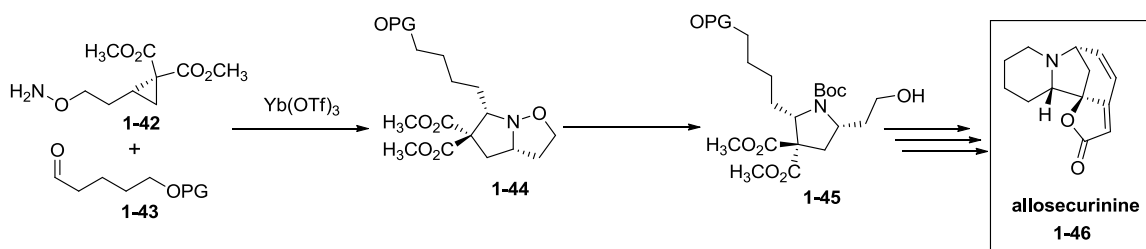
Scheme 1.7 Reactions of DA Diester Cyclopropanes

Scheme 1.7 illustrates a wide range of organic substrates that can be easily functionalized by the use of DA cyclopropanes. In the Kerr group, methodologies have been developed for a variety of annulation reactions described in Scheme 1.7.

These reactions have allowed for the formation of a diverse library of organic compounds, some of which have been directly applied to natural product synthesis, such as Isatisine A¹⁶ and Allosecurinine¹⁷. These natural products were synthesized in the Kerr lab by A. Karadeolian and A. Leduc, respectively (Schemes 1.8 & 1.9). DA cyclopropanes have been and will continue to be one of organic synthesis greatest building tools.



Scheme 1.8 Synthesis of Isatisine A



Scheme 1.9 Synthesis of Allosecurinine

1.2 The 1,3-dipolar Huisgen Cycloaddition & Click Chemistry

1.2.1 History of the 1,3-dipolar Huisgen cycloaddition

Back in 1933, Linus Pauling, was the first to discover the dipolar nature of azides.¹⁸ L. Pauling describes methyl azide as having two distinct structural formulas, one in which the nitrogen atoms form a ring and the other as an open chain. Based off of the crystal structure of sodium azide, it was determined that the azide ion obtains a linear configuration and this structure can be extended to organic azides as well. Based off of these findings, Pauling determined that methyl azide is in fact a linear configuration.¹⁸

Since then, many discoveries about 1,3-dipoles have been made, especially by Rolf Huisgen, who has extensively studied 1,3-dipoles both mechanistically and kinetically.^{19,20} In 1963, R. Huisgen, described 1,3-dipoles as an *a-b-c* system, where *a* must own an electron sextet, in other words, have an incomplete valence shell and a formal positive charge; *b* can remain neutral; and *c* must have a formal negative charge cause by a pair of shared electrons. The 1,3-dipole can then undergo many reactions, the most popular one being the cycloaddition.

Cycloadditions are classified by the number of new σ -bonds formed and/or in relation to the size of the newly formed ring. Generally cycloadditions occur from the breaking of two π -bonds to form two new σ -bonds. Typically a [3 + 2] cycloaddition leads to an uncharged five-membered ring, which will not occur with stable reactants containing full octets and no formal charges. This is where the 1,3-dipole can be used to overcome such challenges.¹⁹ In order to understand the mechanism behind the 1,3-dipolar cycloaddition, it must be compared to the mechanistic interpretations of other cycloadditions. The key investigation with the 1,3-dipolar cycloaddition, is determining if the two new σ -bonds close simultaneously or one after the other, to form the five-membered ring. Based on experimental findings by Huisgen, the favorable mechanism is one which is a concerted mechanism, with a cyclic electron shift. Similar one-step reactions of this type include the Diels-Alder and the Claisen/Cope rearrangements. The energy profile of these one-step reactions, contain only a single activation peak between the reactants and the products.²⁰

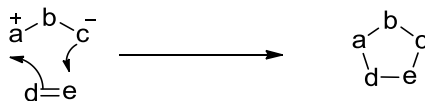


Figure 1.8 The 1,3-dipole described by Huisgen

When a 1,3-dipole is combined with a multiple bond system ($d-e$), Figure 1.8²⁰, this successfully forms a five-membered ring, and the dipolarophile can be either a double or triple bond. A 1,3-dipolar cycloaddition contains a zwitterionic all-octet resonance structure, which can display both electrophilic and nucleophilic activity making it ambivalent. The 1,3-dipole is more stable if atom b can share an unpaired set of electrons with atom a to form an additional bond.²¹

An excellent example of a stable 1,3-dipole is the organic azide. As previously describe, the resonance structure was determined back in 1933 by L. Pauling, however the first preparation is dated back to 1884 by P. Griess. This azide molecule, having three adjoining nitrogen atoms with two opposing charges, was a fascinating discovery as not only is it stable, it is also easily available to react in a variety of reactions, and now has developed into what is known as azide chemistry.¹⁹

A common Huisgen 1,3-dipolar cycloaddition would be between azides and alkynes to give the five-member triazole ring. Azides serve as a reliable way to introduce a nitrogen substituent into a substrate and are desired reagents for click chemistry, as they are extremely stable towards aqueous and aerobic synthetic conditions.²²

1.2.2 Click Chemistry

The term “click chemistry” was first coined in 1998 by K. B. Sharpless, and since then numerous reviews and research has been done in this field of chemistry. The term “click chemistry” refers to a general method of generating products by joining smaller subunits in a single transformation. This chemistry is commonly seen through-out nature to link together subunits through C-C linkages.²¹

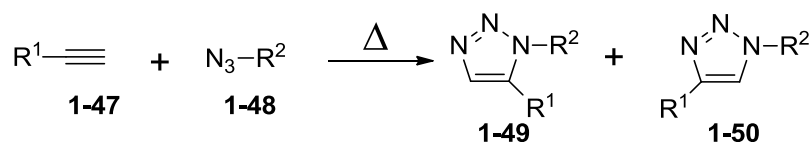
In the past, in order for a reaction to be considered click chemistry, it had to follow a specific set of criteria. The criteria was that the reaction must be modular, give moderately high yields, be wide in scope, generate only inoffensive byproducts which can be removed by non-chromatographic purification methods, and be stereospecific. The reaction conditions and products were required to be stable under physiological conditions, insensitive to oxygen and water, and must use easily available starting material and reagents, contain water or an easily removed solvent (or no solvent at all), and simple product isolation. Click chemistry reactions have been known to be strongly exothermic, highly tolerated and often accelerated by the presence of water. Today, click chemistry still follows this set of criteria, however there are many reactions which follow most (not all) of the criteria, and are still considered a part of click chemistry community.²³

There are many different types of click reactions, some of the most common examples include: ^{21,22,24}

- I. Cycloadditions of unsaturated species, especially 1,3-dipolar cycloadditions as well as the Diels-Alder reaction
- II. Nucleophilic substitution chemistry, mainly ring-opening reactions of strained heterocyclic compounds, giving the formation of new carbon-heteroatom bonds (epoxides, aziridines, aziridinium ions, episulfonium ions)
- III. Non-aldol carbonyl chemistry, such as thio-urea, oxime ether, hydrazone, aromatic heterocycles, and amide formations
- IV. Additions to carbon-carbon multiple bonds, epoxidations, aziridinations, dihydroxylations, sulfenyl halide additions, and Michael additions of Nu-H reactant

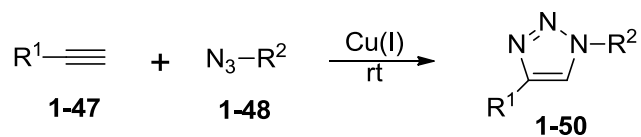
1.2.3 Copper-Catalyzed Azide-Alkyne Cycloaddition

As previously described, there are many different types of click reactions, new ones being discovered every year. The most well-known of all the click reactions would be the Copper-catalyzed Azide-Alkyne Cycloaddition (CuAAC). This click reaction was published back in 2001 by Meldal, and received a lot of attention from Sharpless and other chemists immediately.²⁵ The CuACC click reaction fulfills all the requirements for a click reaction, and has enormous potential in biological, chemical and material sciences.²¹ The Azide-alkyne Cycloaddition (ACC) is highly relevant for biological applications, however the use of copper in these reactions, can be toxic for living organisms. The search for copper-free ACC reactions have been developed, but the downfalls include higher temperatures, slow reaction times and poor regioselectivity (scheme 1.10).



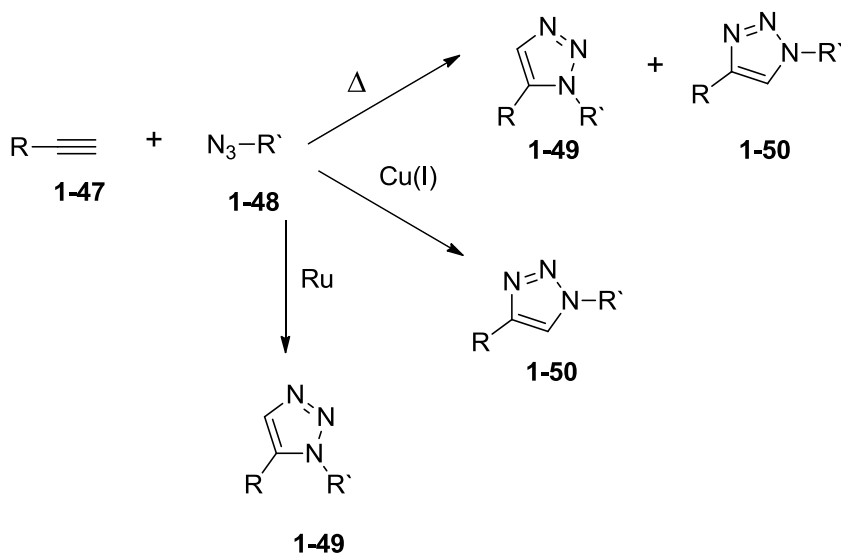
Scheme 1.10 Azide-Alkyne Cycloaddition (AAC)

The copper-catalyzed azide-alkyne cycloaddition, results in the formation of a five-membered ring known as a triazole. Unlike its parent reaction, the Huisgen 1,3-dipolar cycloaddition which is slow at the formation of triazoles at room temperature, the addition of the copper-catalyst accelerated the reaction rate by a factor of 10^7 , as well as allowed the reaction to be done in an aqueous medium. CuACC also produces only one regioisomer of the triazoles, the 1,4-disubstituted triazole (**1-50**), whereas a standard cycloaddition results in the formation of 1,4- and 1,5- regioisomers. Another great feature of the CuACC reaction is the excellent yield of the 1,4-disubstituted 1,2,3-triazole formed and the lack of effect electronics and sterics have on this reaction. The active copper species used for these reactions varies, the most common being Cu(I), however Cu(0) and Cu(II) may also be used. Generally, Cu(II) salts are used as they can be easily reduced to Cu(I) *in situ*, in the presence of reducing agents. Cu(I) salts are less commonly used because of the instability of the Cu(I) species under aerobic conditions.²¹



Scheme 1.11 The Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)

The main focus of CuAAC has been on the development of biocompatible methods in order to accelerate the ACC reaction and improve regioselectivity without using biohazardous material. The future of click chemistry, in particular the ACC reaction, is to find methods of preparing these substrates in copper or transition-metal free environment.²¹



Scheme 1.12 A Summary of the Azide-Alkyne Cycloadditions²⁴

The success of this reaction was due to its high yielding, robust, and suitable for biomolecular ligation properties. The triazole product formed is chemically inert to many reactive conditions, such as hydrolysis, oxidation and reduction.²⁵

So far, the benefits of the CuACC reaction have made an enormous effect on click chemistry thus far. Some biological applications of the CuACC reaction include the discovery of Amprenavir, through combinatorial screening using CuACC (Figure 1.9²⁶).

Amprenavir is a HIV-protease inhibitor which has been clinically used since 1997. It prevents HIV-proteases from cleaving proteins, which inhibits the HIV virus.²⁶

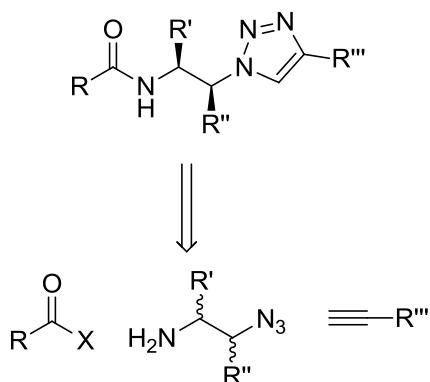


Figure 1.9 Reterosynthesis of Inhibitors of HIV-Protease by CuAAC

Click chemistry is the new approach to being able to synthesize large and vast libraries of building blocks for possible drug discovery. A computation study by Guida et al²⁷ suggest that the pool of “drug-like” compounds could be as large as 10^{63} . In order to be a ‘drug-like’ compound, the compound must have less than 30 non-hydrogen atoms, be no more than 500 Daltons in size, contain only H, C, N, O, P, S, F, Cl and Br, and be stable in the presence of oxygen and water. Currently of the 10^{63} compounds out there, only around 10^7 compounds have been discovered to fulfill these criteria. Click reactions could be the new frontier for being able to easily and relatively quickly way to be able to discovery more ‘drug-like’ compounds.²⁸

1.2.4 History and Uses of Triazoles

As previously described the copper (I)-catalyzed click reaction between an azide and a terminal alkyne leads to the formation of the 1,2,3-triazole moiety. This motif (Figure 1.10), has been well studied for its biologically active nature. This click reaction has been a key tool in the mass formation of this triazole scaffold, due to the high degree of reliability, specificity, and biocompatibility of the starting reactants. This specific click reaction is the reason that click chemistry is such a powerful tool for drug discovery and the synthesis of drug candidates.²³

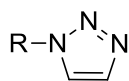


Figure 1.10 The Triazole Motif

The importance of the triazole moiety in drug candidates has been seen prior to the discovery of click chemistry. Over 7000 triazole containing compounds were reported before the initial copper-catalyzed click reaction was discovered. In medicinal chemistry, triazoles have shown to be stable towards acid and base hydrolysis, as well as under oxidative and reductive conditions. This indicated the high aromatic stability of the triazole moiety. Triazoles also are quite resistant to metabolic degradation, making them perfect substrates for drug candidacy. A well known triazole containing compound would be Tazobactam (Figure 1.11), a β -lactamase inhibitor, which in combination with the antibiotic piperacillin, is commonly known as Tazocin; a treatment against many gram positive and gram negative pathogens.²⁹

The triazole moiety has proved to be a useful tool in improving pharmacokinetic properties of desired drugs. Overall the triazole scaffold can be found in a number of biologically active compounds, and has been shown to exhibit anti-HIV properties, as well as in antibacterial, antibiotic and antiviral activities.²⁹ By linking a triazole moiety to a drug core, it can increase a variety pharmacokinetic factors, such as with cephalosporins which is endowed with good oral availability when linked to a triazole moiety (Figure 1.11²⁹). Antiviral and cytotoxic properties have been reported for the triazole, making it a useful analogue for pyrimidine nucleosides.²⁹

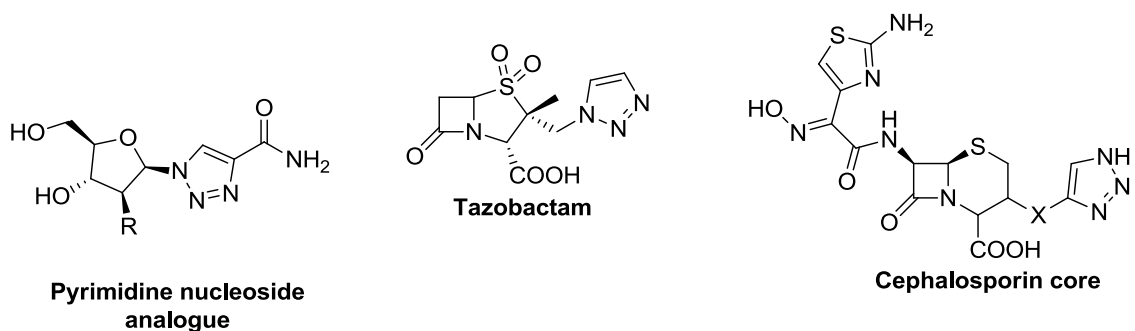
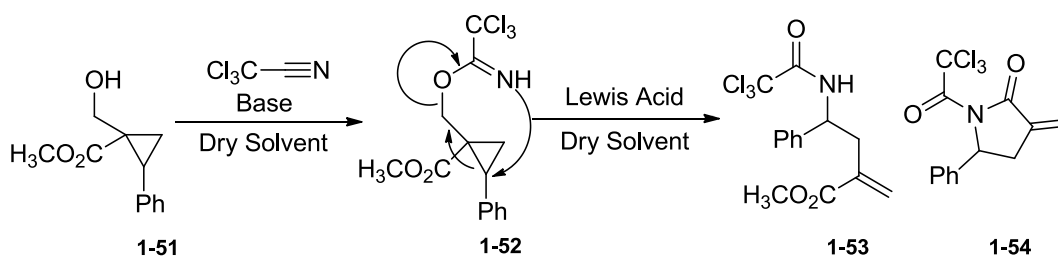


Figure 1.11 Different Biologically Active Substrates containing the Triazole Moiety

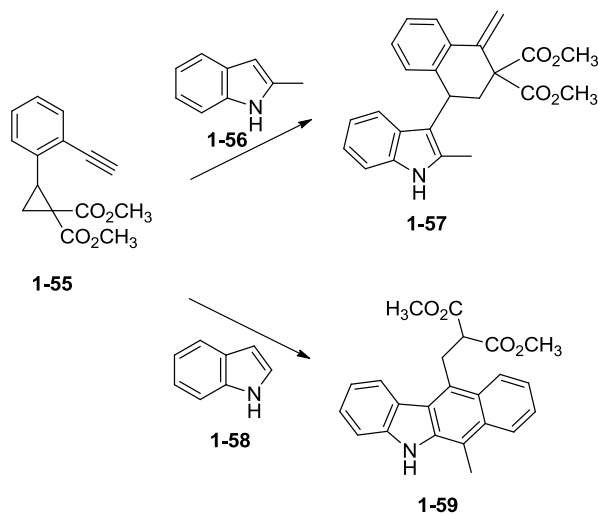
1.3 Description of Thesis

The work described in this thesis can be divided into three chapters, all of which focus around DA cyclopropanes and the various ring-opening reactions that can occur with them. The second chapter will be an exploration of the Overman rearrangement, involving the synthesis of an allylic alcohol into an acetimidate, followed by a [3,3]-sigmatropic rearrangement known as the Overman Rearrangement.³⁰⁻³²



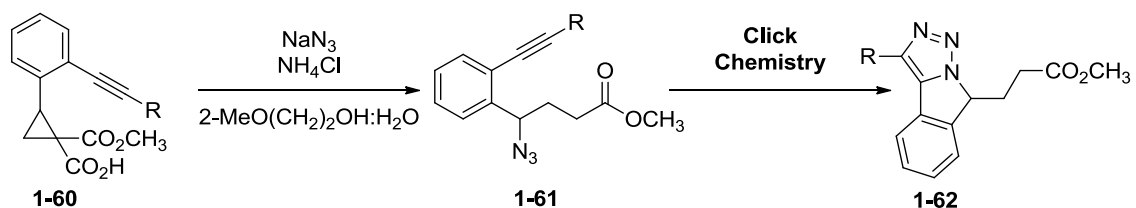
Scheme 1.13 Chapter Two: The Overman Rearrangement

The third chapter will focus on the use of DA cyclopropanes, in the Conia-ene reaction, as well as the investigation into the different types of reactivity these DA cyclopropanes have with various different types of Lewis Acids.³³



Scheme 1.14 Chapter 3: The Investigation into DA Cyclopropanes and the Conia-ene/Annulation Reaction

Finally, the fourth chapter will focus on the synthesis of a wide variety of substituted triazole compounds, made by the tandem ring-opening and catalyst-free click reaction of our DA cyclopropane with sodium azide.^{34,35}



Scheme 1.15 Chapter 4: The Catalyst-Free Tandem Ring-Opening and Click Reaction of an Acetylene-Bearing Donor Acceptor Cyclopropanes

1.4 Chapter One References

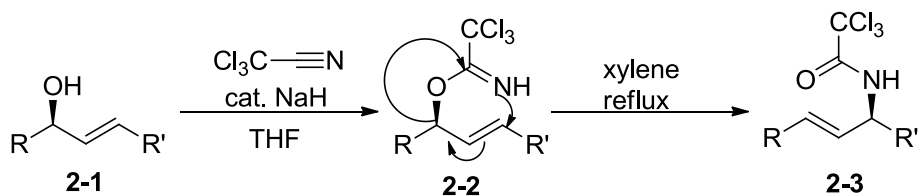
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2 Using DA Cyclopropanes in the Investigation with the Overman Rearrangement

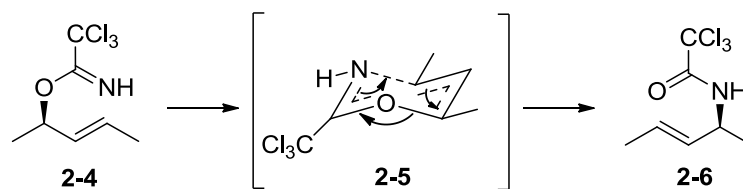
2.1 Introduction

The Overman Rearrangement is a thermal [3,3]-sigmatropic rearrangement of an allylic trichloroacetimidate to an allylic trichloroacetamide (Scheme 2.1). This reaction was originally reported in 1974 as the rearrangement of allylic alcohol **2-1** to the corresponding amine **2-3**.¹ These allylic amines can be synthetically useful for the construction of a variety of biologically active nitrogen-containing molecules such as unnatural amino acids, antibiotics and alkaloids. The transformation was the first of its kind, for making these types of compounds, and is stereo- and regio-specific. The Overman rearrangement proceeds similar to typical [3,3]-sigmatropic rearrangements and it is believed that it occurs in a chair-like transition state, allowing for chirality transfer to occur.¹⁻⁵



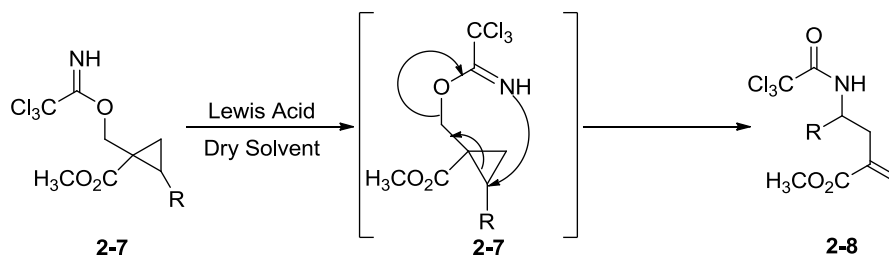
Scheme 2.1 The Overman Rearrangement

The first reported example of a [3,3]-sigmatropic rearrangement was back in 1912, discovered by R. L. Claisen and today is well known as the Claisen rearrangement. It has become a powerful tool for forming new carbon-carbon bonds. [3,3]-sigmatropic rearrangements are a unique class of pericyclic reactions involving the movement of a sigma-bond from one place to another during the reaction course. It is the chair-like transition state (Scheme 2.2) that dictates the resulting double bond to favor the trans (E) geometry over the cis (Z), due to the stability of substituents being in the equatorial position on the chair.⁴⁻⁵



Scheme 2.2 The Transition State of the Overman Rearrangement

Donor-acceptor cyclopropanes have been well studied and reported in a large number of synthetic reactions. The Overman rearrangement has yet to be investigated with DA cyclopropanes as a substrate. The similarity of DA cyclopropanes to olefins supports the hypothesis that these cyclopropanes would be able to successfully undergo the Overman Rearrangement (Scheme 2.3).

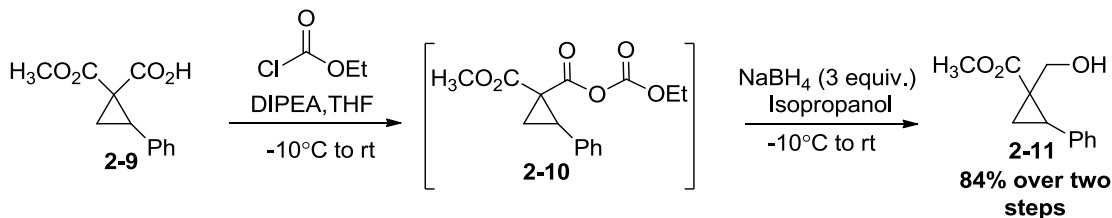


Scheme 2.3 The Initial Research Hypothesis of the use of DA Cyclopropanes in the Overman Rearrangement

2.2 Results and Discussion

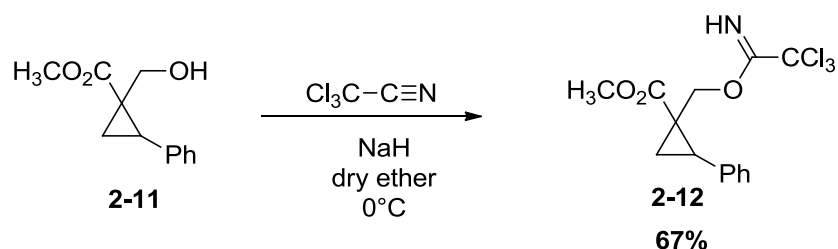
2.2.1 Synthesis of the Acetimidate Intermediate

The substrate 2-phenyl 1,1-cyclopropane hemimalonate was chosen as the ideal starting material for the initial studies of this project due to the success with this substrate in previous DA cyclopropane reactions. In the efforts towards the Overman rearrangement using DA cyclopropanes, alcohol **2-11** had to be synthesized from **2-9**, the cyclopropane hemimalonate (Scheme 2.4). Substrate **2-11** was synthesized through a two-step, one-pot procedure, forming the mixed anhydride **2-10**, and then reducing it to give the desired alcohol **2-11**. After an exhaustive search for modifying the temperature, equivalents, base and solvent, the ideal conditions were found for a scalable synthesis of the alcohol as seen in Scheme 2.4.⁶⁻⁷



Scheme 2.4 Synthesis of the Cyclopropyl Alcohol 2-11

The synthesis of acetimidate **2-12**, was achieved using the initial conditions done by Overman (Scheme **2.5**), involving trichloroacetonitrile and sodium hydride.¹⁻³

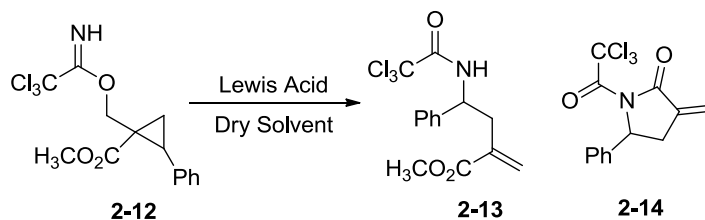


Scheme 2.5 Synthesis of the Cyclopropyl Acetimidate 2-12

2.2.2 Investigation into the Homo-Overman Rearrangement using DA cyclopropanes

With the desired starting material in hand, the next step was to find the ideal conditions to promote the Overman rearrangement with the DA cyclopropane **2-12**. Table **2.1** shows the investigation of this reaction, involving assortment of different reaction conditions. Initially the first reaction done used the very first Overman rearrangement conditions which yielded no formation of product (entry **1**). Next the affect of Lewis acids on the reaction was investigated; starting with scandium triflate, the reaction was done initially at room temperature which resulted in trace product formation (entry **2**). The product observed was not the amide **2-13**, as predicted, however the result from an *in situ* lactamization occurred to give product **2-14**. Using similar conditions to entry **2**, the temperature was increased for entry **3**, leading to only decomposition.

Table 2.1 Optimization of the Overman Rearrangement



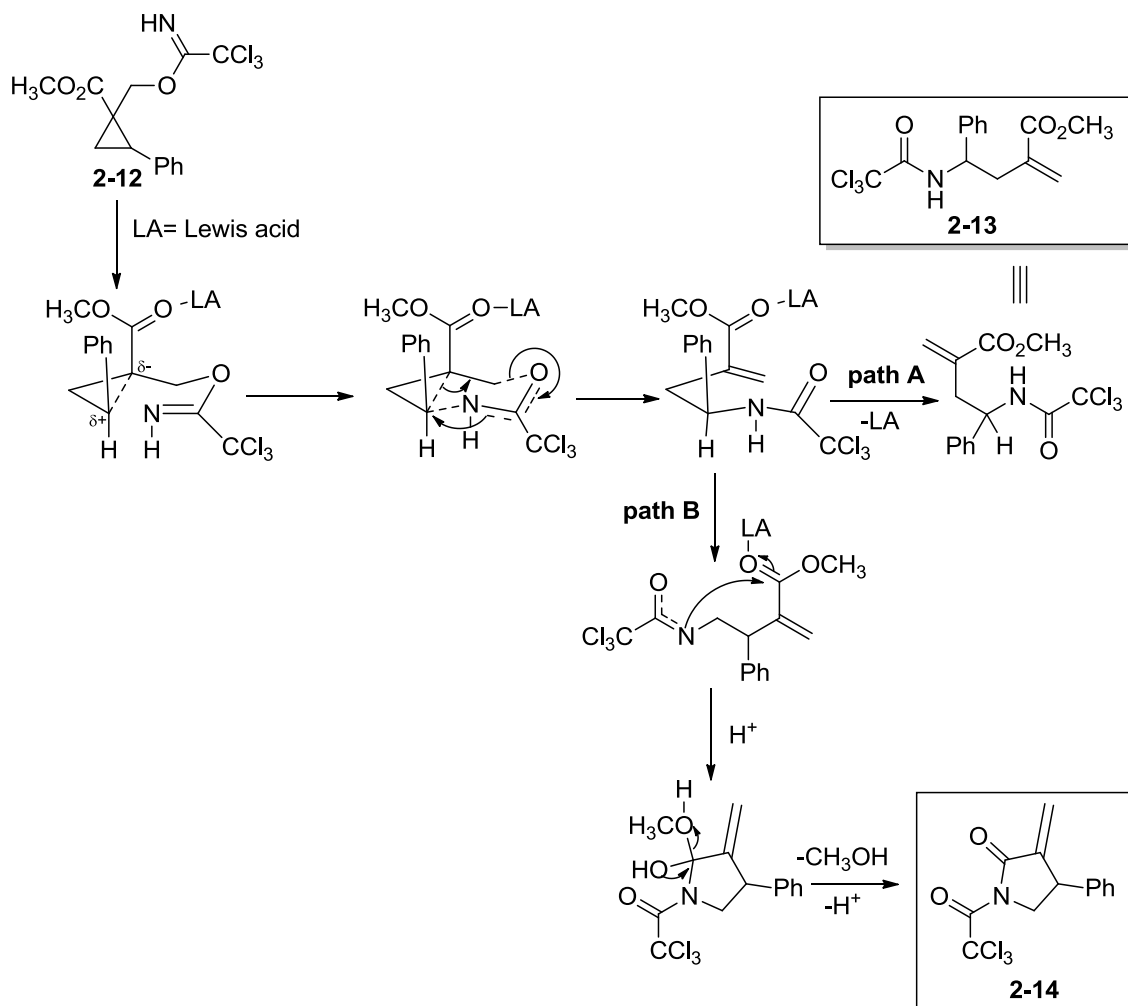
Entry	Catalyst (10 mol %)	Conditions (solvent, temperature)		Time	Yield (%)	Compound #
1	None	Toluene	reflux	3 h	-	-
2	Sc(OTf) ₃	Toluene	rt	2 h	Trace	2-14
3	Sc(OTf) ₃	Toluene	65 °C	3 h	-	-
4	Sc(OTf) ₃	Toluene	rt - 65 °C	2 d	Trace	2-14
5	Sc(OTf) ₃	CH ₂ Cl ₂	rt	2 h	-	-
6	Sc(OTf) ₃	CH ₃ CN	rt -reflux	1 d	Trace	2-14
7	Sc(OTf) ₃	CH ₃ CN	reflux	1 d	Trace	2-14
8 ^a	Sc(OTf) ₃ , DBU	Toluene	reflux	1 d	-	-
9 ^b	Sc(OTf) ₃	CH ₃ CN	rt	1 d	-	-
10	Sc(OTf) ₃	Toluene	rt	3 d	Trace	2-14
11	Yb(OTf) ₃	CH ₂ Cl ₂	rt	7 h	-	-
12	TiCl ₄	DCE	reflux	1 d	Trace	2-13
13	TiCl ₄	DCE	reflux	1 d	19 %	2-13
14 ^c	BF ₃ OEt ₂	DCE	reflux	1 d	Trace	2-13
15	BF ₃ OEt ₂	DCE	60 °C	2 h	Trace	2-13
16	BF ₃ OEt ₂	DCE	reflux	1 d	-	-

a: 1.1 equivalent of DBU used; b: reaction done in high pressure reactor at 13 kBar; c: 1.0 equivalent of catalysts used

Entry 4 explored the same conditions however starting at room temperature and eventually increasing the heat. This also gave product 2-14, however only trace amounts. Entries 5-6 explored the use of different solvents, one yielding no product, the other trace amounts. The use of acetonitrile as a successful solvent, lead us to explore varying temperatures however both resulted in only trace product of 2-14 (entries 6-7).

Entries **8** and **9**, explored other conditions; one involving a base (entry **8**) the other with the use of a high pressure reactor (entry **9**). Both reactions lead to no product and only decomposition. Entry **10** mimicked the successful conditions from entry **2** this time leaving the reaction for numerous days. The increase in reaction time did not increase the yield, and only trace product **2-14** was isolated. Switching to different Lewis acids, entry **11** employed the use of ytterbium triflate, which even at room temperature gave decomposition. Exploring more Lewis acids, entries **12** and **13** used TiCl_4 , which was successful in the formation of product **2-13**. Initially only trace amounts of product **2-13** were formed (entry **12**), however when the reaction was increased in amount of starting material used, a definitive yield of 19% was isolated. Finally, entries **14-16**, used the Lewis acid BF_3OEt_2 , which also gave trace amounts of product **2-13**. Varying the temperature, equivalents and size of the reaction did not aid in increasing the yield of product formed.

The formation of two different products, one formed by only the Overman rearrangement, the other formed by the rearrangement and an additional *in situ* lactamization, can be explained best by the mechanism in Scheme **2.6**. The main role in determining if the reaction will continue to react and lactamize is with the coordination of the Lewis acid to the ester functionality groups. When the Lewis acid has a strong attachment to the carbonyl oxygen of the ester moiety, it will remain coordinated even after the formation of the homo-allylic amide **2-13**. This coordination allows for the newly formed amide nitrogen to further react and attack the carbonyl carbon, therefore forming the five-membered lactam ring **2-14**. With other Lewis Acids (such as TiCl_4 and BF_3OEt_2) the coordination only occurs for the ring-opening, and therefore only the amide product **2-13** is formed.



**Scheme 2.6 The Proposed Mechanism for the formation of Overman
Rearrangement Products 2-13 & 2-14**

Although the Overman rearrangement did work with DA cyclopropanes, it resulted in very low yields. After many attempts to improve this reaction, with very little success in improving the yields, it was therefore decided that in our hands DA cyclopropanes were not the best candidates for this intriguing [3,3]-sigmatropic rearrangement.

2.3 Conclusions

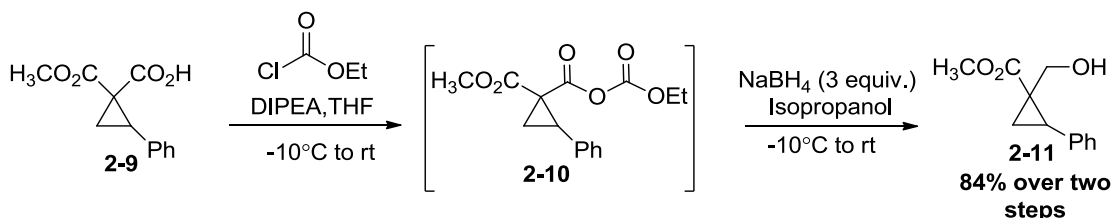
In summary, we were only able to achieve small success with the use of DA cyclopanes as a new substrate in the Overman rearrangement. The result yielded either a homo-allylic amide or a lactam ring; both products were only isolated in small yields (< 20 %). In the future if modifications and improvements can be found, a library of these compounds could possibly be made. These modifications would have to promote the ring opening of the DA cyclopane, possibly by changing the ester functionality group to one which is more electron withdrawing.

2.4 Experimental

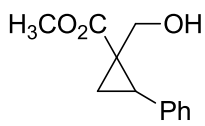
2.4.1 General Considerations

All solvents for routine isolation of products and chromatography were reagent grade. Reagents used were purchased from Sigma Aldrich, Alfa Aesar, Caledon or VWR. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (60F-254) visualizing under UV light and developed using acidic *p*-anisaldehyde stain. All flash column chromatography was performed using silica gel (230-400 mesh) with indicated solvents. ¹H and ¹³C NMR spectra were recorded on either a 400 MHz or on a 600 MHz NMR spectrometer. Chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constants in hertz (Hz), and number of protons. HRMS were measured with electron impact (EI) ionization and quadrupole mass analyzer. Melting points were determined using a Gallenkamp melting point apparatus and was uncorrected. Infrared spectra were obtained using thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and were reported in frequency of absorption (cm⁻¹).

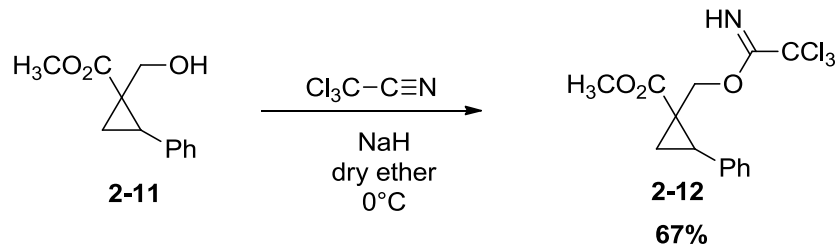
2.4.2 Experimental Procedure and Spectral Data for Alcohol **2-11**



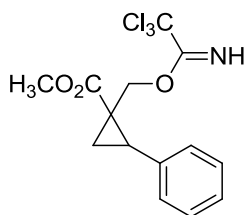
To a flask containing dry THF, 1-methoxycarbonyl-2-phenylcyclopropanecarboxylic acid (**2-9**) (1 equivalent) was added, and the reaction mixture was cooled to -10°C . Diisopropyl ethyl amine (1 equivalent) was added and stirred at -10°C . After 15 minutes, ethyl chloroformate (1.1 equivalent) was slowly added drop-wise over 5 minutes. The reaction mixture was slowly warmed up to room temperature and after 3 hours NaBH_4 (3 equivalent) and Isopropanol were added. The reaction mixture was left stirring at room temperature overnight (12-14 h). Water was added to the reaction mixture, and the aqueous layer was extracted with EtOAc 3 times. The organic phases were combined and dried with MgSO_4 , filtered and the solvent was removed. The residue was purified by flash column chromatography (gradient elution, EtOAc/Hexanes) to yield the desired compound (**2-11**).


Methyl 1-(hydroxymethyl)-2-phenylcyclopropanecarboxylate (2-11): Reagents employed: 1-methoxycarbonyl-2-phenylcyclopropanecarboxylic acid (**2-9**) (0.130 g, 0.600 mmol), diisopropyl ethyl amine (0.125 mL, 0.720 mmol), ethyl chloroformate (0.064 mL, 0.670 mmol), THF, NaBH_4 (0.070 g, 1.80 mmol), Isopropanol; yield 84% (0.103 g, 0.499 mmol) as a white solid; $R_f = 0.20$, 30% EtOAc in hexanes; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 7.19\text{--}7.29$ (m, 5H), 3.97 (d, $J = 12.1$ Hz, 1H), 3.58 (d, $J = 12.1$ Hz, 1H), 3.32 (s, 3H), 2.84 (br s, OH, 1H) 2.64 (t, $J = 8.2$ Hz, 1H), 2.02 (dd, $J = 7.8, 5.5$ Hz, 1H) 1.33 (d, $J = 9.0, 5.1$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) $\delta = 172.6, 136.2, 129.1, 127.9, 126.7, 67.0, 51.4, 34.4, 31.0, 16.6$.

2.4.3 Experimental Procedure and Spectral Data for Acetimidate **2-12**



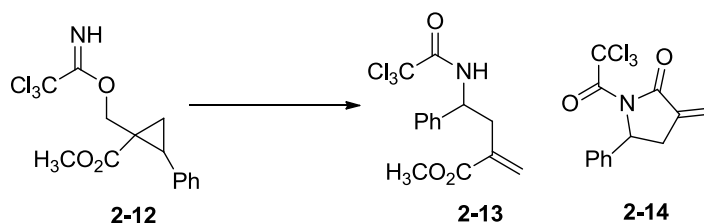
Alcohol **2-11** (1 equivalent) was added to a flask containing ether and cooled to 0°C. To the reaction mixture, sodium hydride (NaH, in 60% mineral oil) (1.1 equivalent) was slowly added and stirred at 0°C. Once the formation of H_{2(g)} had ceased, trichloroacetonitrile (1.2 equivalent) was slowly added drop-wise over 2 minutes. The reaction was stirred at 0°C and warmed-up slowly to room temperature. Once evidence of starting material was gone by TLC analysis (~3h) the reaction mixture was filtered through a pad of Celite and the solvent was removed. The residue was purified by flash column chromatography (30% EtOAc/Hexanes) to yield the desired compound (**2-12**).



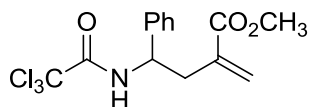
Methyl 2-phenyl-1-((2,2,2-trichloro-1-iminoethoxy)methyl)cyclopropanecarboxylate (2-12):

Reagents employed: Methyl 1-(hydroxymethyl)-2-phenylcyclopropanecarboxylate (**2-11**) (0.100 g, 0.480 mmol), NaH (in 60% mineral oil, 0.013 g, 0.530 mmol), trichloroacetonitrile (0.058 mL, 0.580 mmol), ether: yield 67% (0.114 g, 0.325 mmol) as a yellow oil; $R_f = 0.60$, 30% EtOAc in hexanes; ¹H-NMR (400 MHz, CDCl₃): $\delta = 8.35$ (br s, 1H), 7.15-7.30 (m, 5H), 4.76 (d, $J = 10.9$ Hz, 1H), 4.47 (d, $J = 11.3$ Hz, 1H), 3.38 (s, 3H), 2.71 (t, $J = 8.6$ Hz, 1H), 2.13 (dd, $J = 7.8, 5.5$ Hz, 1H), 1.53 (dd, $J = 9.4, 5.5$ Hz, 1H).

2.4.4 General Procedure and Spectral Data for the Homo-Overman Rearrangement products **2-13** & **2-14**



Methyl 2-phenyl-1-((2,2,2-trichloro-1-iminoethoxy)methyl)cyclopropanecarboxylate (**2-12**) (1 equivalent) was dissolved in the solvent used, and the Lewis acid was added (10 mol%, unless otherwise indicated). The reaction conditions are as described in Table 2.1. Once reaction was complete, determined by TLC analysis, the reaction mixture was quenched with water. The mixture was extracted three times with EtOAc, dried with MgSO₄, filtered through a pad of Celite and the solvent was removed. The residue was purified by flash column chromatography (gradient elution, EtOAc/Hexanes) to yield the desired compound (**2-13** or **2-14**).

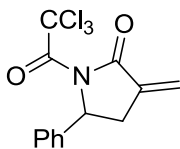


Methyl

2-methylene-2-phenyl-4-(2,2,2-

trichloroacetyl)butanoate (2-13): colorless oil; $R_f =$

0.68, 30% EtOAc in hexanes; ¹H-NMR (400 MHz, CDCl₃): $\delta = 7.40$ (d, $J = 7.0$ Hz, 2H), 7.35 (t, $J = 7.0$ Hz, 2H), 7.30 (t, $J = 7.6$ Hz, 1H), 6.26 (d, $J = 1.2$ Hz, 1H), 5.63 (d, $J = 1.2$ Hz, 1H), 5.01 (dd, $J = 8.2, 5.9$ Hz, 1H), 3.76 (s, 3H), 3.08-3.00 (m, 2H).



3-Methylene-5-phenyl-1-(2,2,2-trichloroacetyl)pyrrolidin-2-one

(2-14): colorless oil; $R_f = 0.55$, 30% EtOAc in hexanes; ¹H-NMR

(600 MHz, CDCl₃): $\delta = 7.40$ (t, $J = 7.0$ Hz, 2H), 7.36 (d, $J = 7.6$ Hz, 1H), 7.33 (t, $J = 7.0$ Hz, 2H), 6.32 (t, $J = 2.9$ Hz, 1H), 5.69 (t, $J = 2.4$ Hz, 1H), 5.53 (t, $J = 7.6$ Hz, 1H), 3.40 (m, 1H), 2.94 (m, 1H).

2.5 Chapter Two References

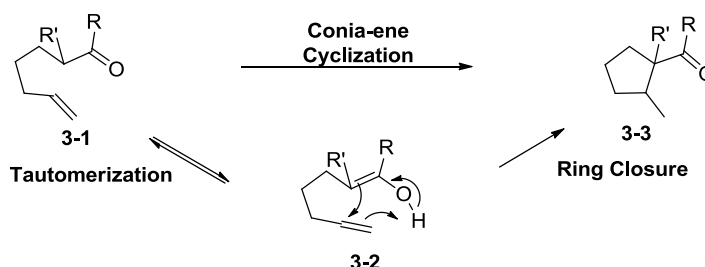
- (1) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.
- (2) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.
- (3) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.
- (4) Claisen, L.; *Ber.* **1912**, *45*, 3157.
- (5) Clayden, Greeves, Warren, Wothers, *Organic Chemistry* 1st ed., Oxford University Press, New York City, 2007.
- (6) Fadel, A., Garcia-Argote, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1159.
- (7) Soai, K., Yokoyama, S., Moshida, K. *Synthesis* **1987**, *43*, 3972.

3 Donor-Acceptor Cyclopropanes in the Conia-ene Cyclization Reaction

3.1 Introduction

3.1.1 The Conia-ene Cyclization Reaction

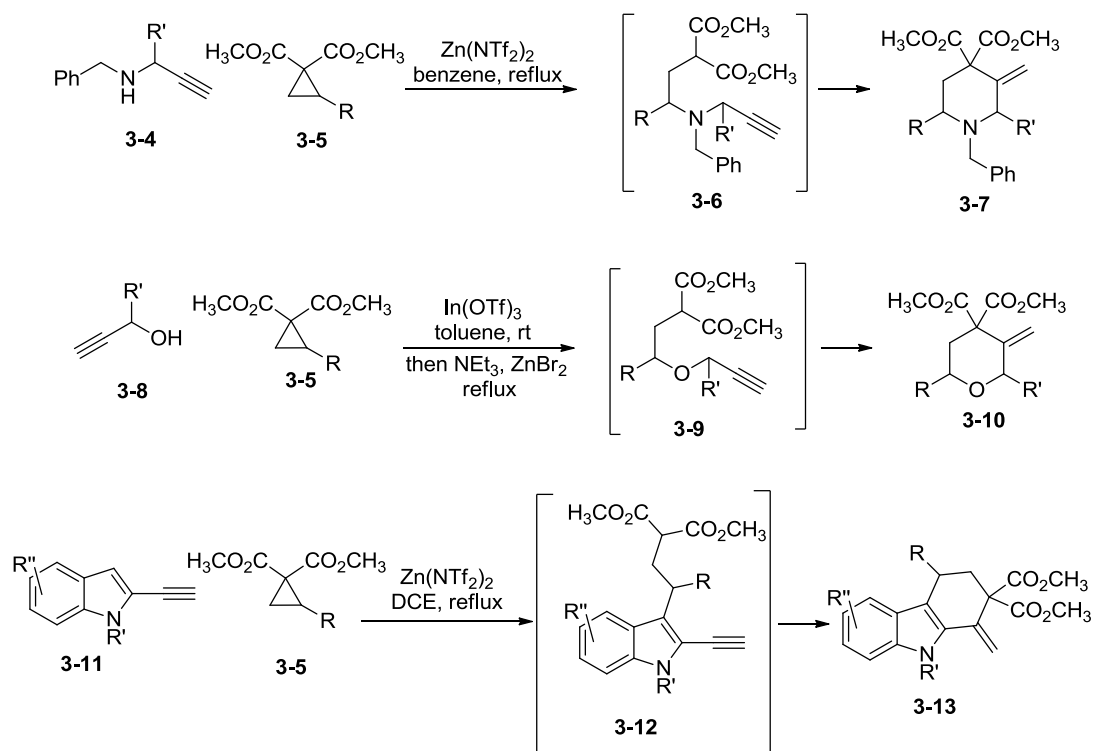
The Conia-ene reaction is an intramolecular ene reaction catalyzed by Lewis acids or heat. Early work done by J. M. Conia and P. Le Perchec in 1975 indicated that these reactions could only be done at very high temperatures, therefore limiting the synthetic utility of this reaction in organic synthesis.¹ The Conia-ene cyclization was originally done using unsaturated carbonyl compounds to yield cyclic products (Scheme 3.1¹). This reaction is a well known tool in organic synthesis for carbon-carbon bond formation with alkenes as well as alkynes.² There currently has been extensive work forming five-membered rings, however much less research has been done forming larger ring systems.³



Scheme 3.1 Conia-ene Cyclization

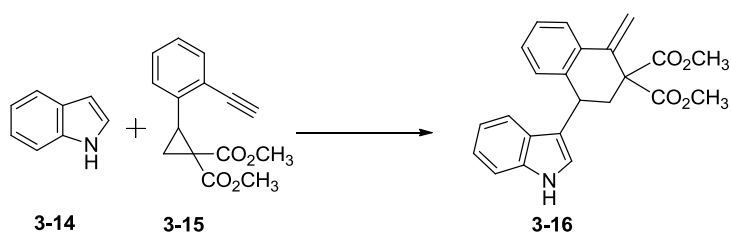
3.2 Previous work on the Conia-ene Reaction

Recently, the Kerr group has utilized the Conia-ene reaction in conjunction with DA cyclopropanes to form a variety of hetero- and carbo-cyclic compounds (Scheme 3.2). These reactions involve a nucleophilic cyclopropane ring-opening followed by a subsequent Conia-ene reaction with the pendant alkyne moiety. This one-pot reaction has led to the facile production of piperidines **3-7**⁴, tetrahydropyrans **3-10**⁵ and tetrahydrocarbazoles **3-13**⁶ respectively.



Scheme 3.2 Precedents for the Conia-ene Reaction with DA Cyclopropanes

With growing success in the area of cyclopropane ring-opening and Conia-ene reactions, the next investigation involved the use of a new DA cyclopropane. The nucleophiles **3-4**, **3-8**, and **3-11** all contained the acetylene group; this investigation explored the use of the acetylene on the DA cyclopropane. This new substrate, an acetylene-bearing donor acceptor cyclopropane **3-15** can be seen in Scheme 3.3.



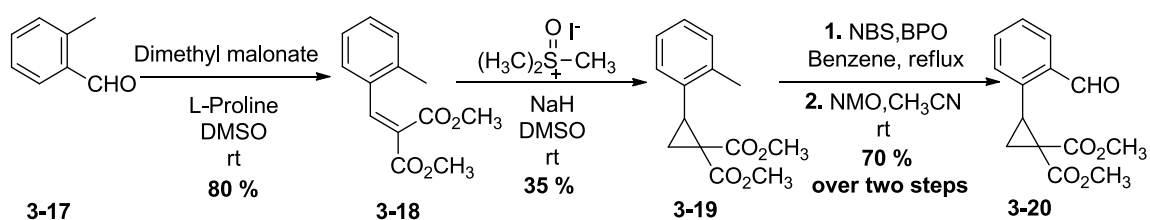
Scheme 3.3 The Investigation of Acetylene-Bearing DA Cyclopropane in the Conia-ene Reaction

3.3 Results and Discussion

3.3.1 Synthesis of the Acetylene-Bearing DA Cyclopropane

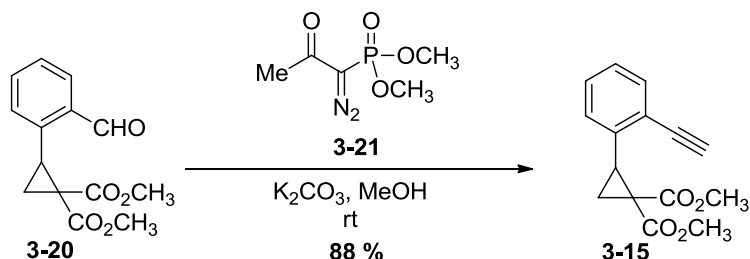
In order to begin the investigation of the acetylene-bearing DA cyclopropane with a variety of nucleophiles in the Conia-ene reaction, the DA cyclopropane **3-15** had to be synthesized in a 5-step procedure.

Aldehyde **3-20**, was synthesized by modifications to a known procedure⁷. A Knoevenagel condensation of commercially available 2-methylbenzaldehyde **3-17**, followed by a Corey-Chaykovsky cyclopropanation⁸ gave cyclopropane substrate **3-19**. Mono-bromination of **3-19**, followed by oxidations gave the corresponding aldehyde **3-20** over the two steps (Scheme 3.4).



Scheme 3.4 Synthesis of Aldehyde 3-20

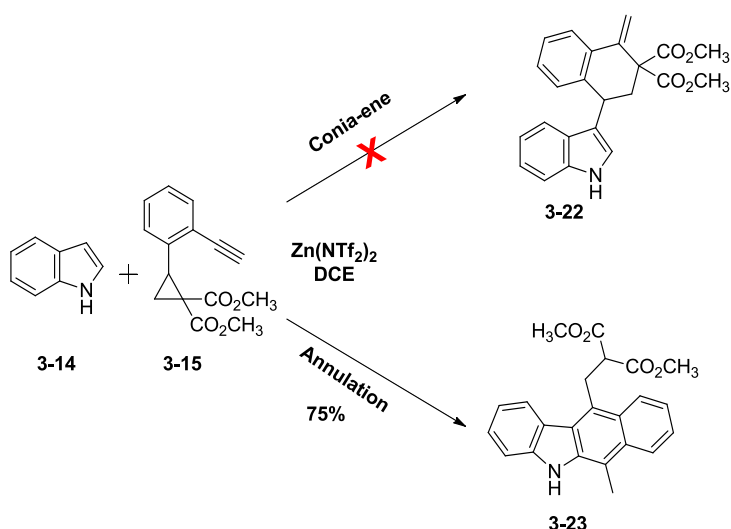
Aldehyde **3-20** could be homologated in one step using the O'hira-Bestman reagent **3-21**, which lead to the desired alkyne (Scheme 3.6).⁹



Scheme 3.5 Synthesis of DA Cyclopropane 3-15

3.3.2 Investigation into Conia-ene Cyclization

Based on previous success with Lewis acids and the Conia-ene reaction⁴⁻⁶, the first attempt with DA cyclopropane **3-15** started out with the Lewis acid zinc bistriflimide ($\text{Zn}(\text{NTf}_2)_2$). The initial hypothesis was the formation of product **3-22**, as a result from a Conia-ene cyclization. The result obtained after a test reaction involving the $\text{Zn}(\text{NTf}_2)_2$ with indole **3-14** as the nucleophile, gave a much different product **3-23**. This newly formed product is a result of an indole annulation with the acetylene-bearing DA cyclopropane **3-15** (Scheme 3.7).



Scheme 3.6 Preliminary Result for Nucleophilic Attack on the DA Cyclopropane

Although this newly formed product **3-23**, was not initially the desired product, the core of **3-23** is intriguing due to its similarity in a variety of natural products, including Ellipticine (Figure 3.1). This natural product has been shown to exhibit antitumor and anti-HIV activity.¹⁰

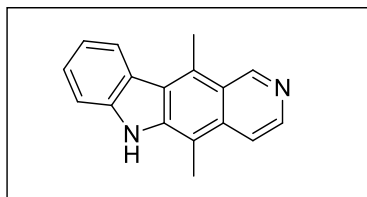
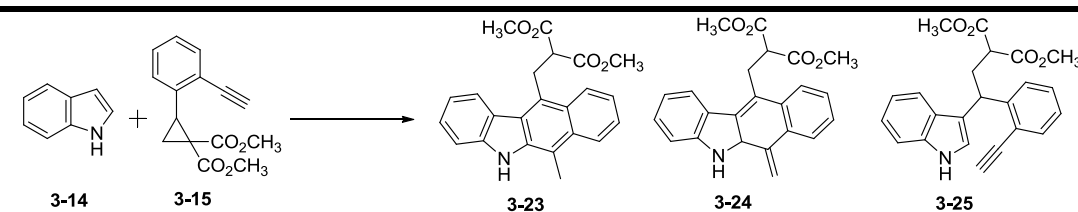


Figure 3.1 Ellipticine

Due to the potential use for this product **3-23** in natural product synthesis, the investigation was altered to focus on the annulation product. The next step was to try and optimize the conditions; Table **3.1** shows this investigation, involving a variety of different reaction conditions. It is to be noted that four different products occurred during this optimization; the annulation product **3-23**, the non-aromatic product **3-24**, the ring-opened product **3-25**, as well as in some cases the Conia-ene product **3-22**.

Table 3.1 Results from the Optimization of the Annulation Reaction



Entry	Catalyst (10 mol %)	Conditions	Results
1 ¹	Zn(NTf ₂) ₂	DCE, reflux, 1.5 h	75% 3-23 ; 5% 3-24
2	Zn(NTf ₂) ₂ , 1 drop TFA	DCE, reflux, 2 h	25% 3-23 ; 11% 3-24
3	Zn(NTf ₂) ₂ , 1 drop TFA	DCE, reflux, 3 h	30% 3-23 ; 6% 3-24
4	Zn(NTf ₂) ₂	CH ₃ CN, reflux, 2 h	Trace 3-25 ; Decomp.
5	Zn(NTf ₂) ₂	Toluene, reflux, 2h	56% 3-23
6	Zn(NTf ₂) ₂	CH ₂ Cl ₂ , reflux, 4h	Decomposition
7	Sc(OTf) ₃	DCE, rt, 3 h	50% 3-25
8	Yb(OTf) ₃	DCE, reflux, 1 d	75% 3-25
9	Zn(OTf) ₂	DCE, reflux, 1d	Decomp.
10	Cu(OTf) ₂	DCE, reflux, 4 h	SM, Decomp.
11	ZnBr ₂	DCE, reflux, 2 h	Trace 3-22 ; Decomp.
12	InBr ₃	DCE, reflux, 4 h	45% 3-23 ; 32% 3-22
13	MnCl ₂ ·4H ₂ O	DCE, reflux, 1 d	Trace 3-22 , Decomp.
14 ¹	GaCl ₃	DCE, reflux, 1 d	27% 3-23 ; Trace 3-22
15	Cis-PtCl ₂ (PPh ₃) ₂	DCE, reflux, 1 d	SM
16	Ca(NTf ₂) ₂	DCE, reflux, 1 d	SM
17 ²	Ca(NTf ₂) ₂ , Bu ₄ NPF ₆	DCE, reflux, 1 d	SM
18	AuCl ₃ -DMSO	DCE, reflux, 1 d	SM

Entry	Catalyst (10 mol %)	Conditions	Results
19 ²	Ag(TMS) AuCl(PPh ₃)	DCE, reflux, 1 d	SM, Decomp.
20	AuCl ₃ (PPh ₃)	DCE, reflux, 1 d	SM
21 ³	Cu(OTf) ₂ AuCl(PPh ₃)	Toluene, reflux, 1 d	SM, Decomp.
22	Zn(NTf ₂) ₂	DCE, reflux, 6 h	40% 3-23 ; 5 % 3-24
23	Zn(NTf ₂) ₂	DCE, 155°C, 30 min	Decomp.

μ W

1: 20 mol % **2**: 5 mol % each **3**: 20 mol % and 0.2 mol % respectively

To start the investigation, a variety of Lewis acids were thoroughly examined. Entries **1-6** explore the catalyst, zinc bistriflimide, with entry **1** giving the best result of a 75% yield of the product **3-23**, with only trace amount of the non-aromatic species **3-24**. The addition of TFA was done in the attempt to provide a proton source for rearomatization; this was not successful, and resulted in a loss of yield of the desired product **3-23**. Switching to other polar aprotic solvents, with slightly different boiling points (entries **4** & **6**), did not improve the results; using a non-polar solvent (entry **5**) was successful at obtaining product **3-23**; however the yield did not increase from entry **1**. From there a series of different Lewis acids were tested (entries **7-10**), and either gave ring opened product **3-25**, or starting material/decomposition. Since only ring-opened product was made, this indicates that these particular Lewis acids used were not successfully able to coordinate to the alkyne, and therefore were not able to proceed to the annulation product. Moving forward we sought out to examine more Lewis acids commonly used in our research. Entries **11-14** were unsuccessful in giving a high yields of the desired product **3-23**, however after further examination gave us a mix of **3-23** and the Conia-ene product **3-22**. This is not surprising as these Lewis acids used were previously used in our lab for the Conia-ene reaction. Entries **15-17**, used Lewis acids with evidence of promoting a similar reaction cascade, however no products were formed and only starting material remained.

It is known that gold salts can activate alkynes by coordination, thus began the investigation into gold catalysts for entries **18-21**.¹¹⁻¹² Several different attempts were done involving different gold catalysts, with different ligands and additives, and

unfortunately none of the gold catalysts appeared to give any product, only starting material remained. This could be due to the fact that the gold catalysts were not able to coordinate to the esters, and therefore resulted in no ring opening to occur, and thus the reaction itself could not proceed.

Returning back to zinc bistriflimide, the next attempt was to leave the reaction longer to try and promote the non-aromatic species **3-24** to become the aromatic **3-23**; however this just led to a decrease in yield of **3-23** overall. Finally entry **23**, used microwave conditions, and only gave decomposition and was the last attempt in the investigation. After examining our efforts, the best results remain from entry **1**, and these conditions were therefore used in the efforts towards applying this reaction to a wide variety of different nucleophiles.

3.3.3 Exploration into the Scope of the Annulation Reaction

The scope was initially done on a variety of substituted indoles. Entries **2** and **3** have functional groups off of the indole nitrogen (R_1). Both gave evidence of the desired product **3-27** as well as side product of the Conia-ene reaction. Focusing on substitutions at positions R_2 and R_3 , the functional groups were varied in terms of the electronic effects. Entry **4**, gave a rather low yield of product **3-27**, as well as some ring-opened product as a mixture. Switching to electron-donating, the methoxy indole in entry **5**, also appeared to give annulation product as well as Conia-ene product, also as a mixture. Entry **6** was not easy to separate, and was a mixture of different products. Entries **7-8**, were more electron-withdrawing functional groups, and gave only evidence of the Conia-ene product with no annulation product being formed at all.

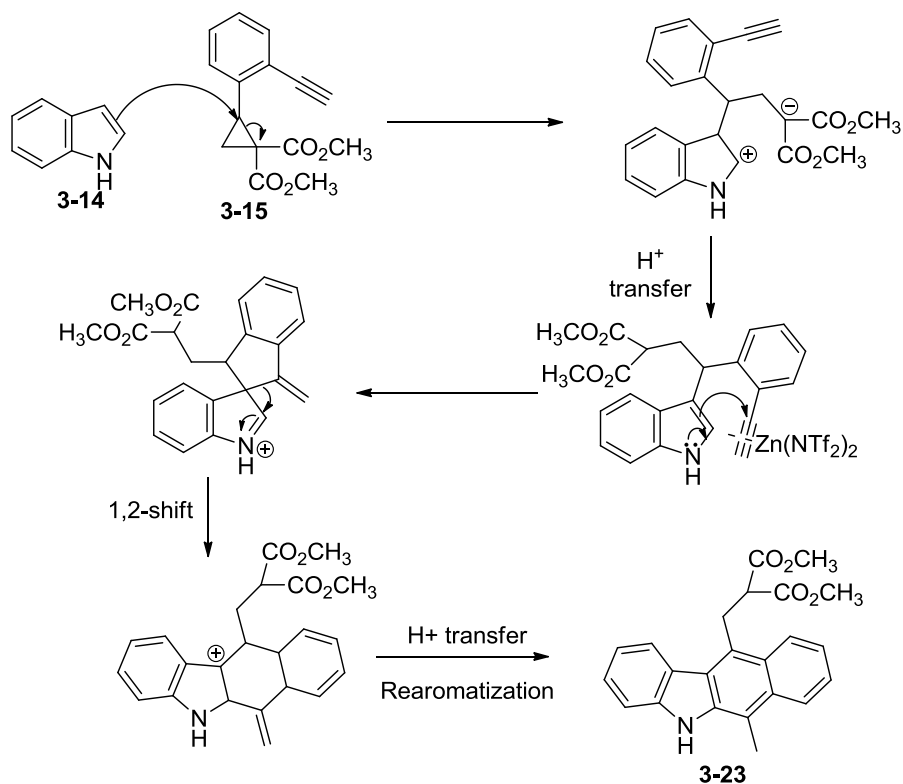
Table 3.2 The Substrate Scope for the Annulation Reaction

Reaction scheme: Substituted indole **3-26** (with substituents R₁, R₂, R₃) reacts with DA cyclopropane **3-15** (with two CO₂CH₃ groups) in the presence of Zn(NTf₂)₂ in DCE at reflux for 1.5 h to yield product **3-27**, which is a fused tricyclic system with a benzene ring fused to the indole system and a cyclohexene ring fused to the benzene ring, with two CO₂CH₃ groups on the cyclohexene ring.

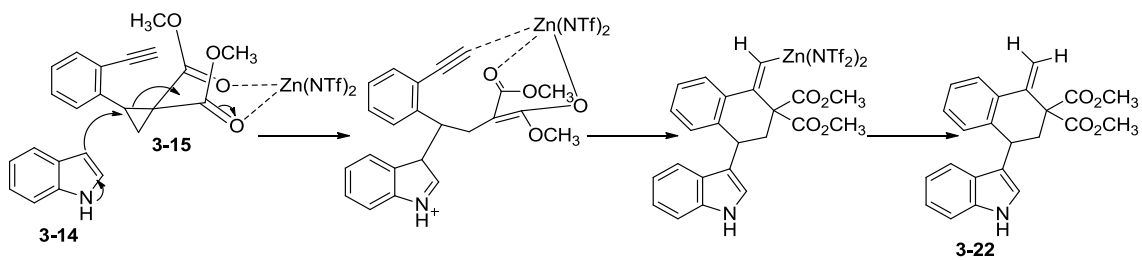
Entry	Compound #	R ₁	R ₂	R ₃	Yield (%)	Results
1	3-27a	H	H	H	75	-
2	3-27b	Bn	H	H	-	Trace Conia-ene
3	3-27c	CH ₃	H	H	74	-
4	3-27d	H	Br	H	-	Trace Ring Opened
5	3-27e	H	MeO	H	-	Inseparable
6	3-27f	H	OH	H	-	Inseparable
7	3-27g	H	H	Cl	-	45% Conia-ene
8	3-27h	H	NO ₂	H	-	34% Conia-ene

3.3.4 Proposed Mechanism for the Annulation and Conia-ene Reactions

The use of DA cyclopropane **3-15** in the Conia-ene reaction initially led the investigation towards a new process, the annulation reaction. After finding the ideal conditions, the annulation process was applied to a variety of different substituted indoles, and the results from Table **3.2**, have indicated that these substitutions play a role in the mechanism and can therefore change the mechanism from the annulation reaction to the Conia-ene. The two proposed mechanisms (Scheme **3.7** & **3.8**) can give some insight into the reasons for the mixture of the two products; the annulation and the Conia-ene products.



Scheme 3.7 Proposed Nucleophilic Ring-Opening and Annulation Mechanism



Scheme 3.8 Proposed Nucleophilic Ring-Opening and Conia-ene Mechanism

In the two proposed mechanisms, the key step is if the nitrogen on the indole has enough electron density to support the attack from the alkyne functionality group. This will impact the direction the mechanism takes; the indole plays a role in the annulation process from proceeding, whereas with the Conia-ene the indole nitrogen is no longer needed after the initial ring-opening attack.

3.3.5 Investigation of the Conia-ene with DA cyclopropane **3-15**

Since our efforts towards expanding the substrate scope of the annulation reaction were unsuccessful, the next step was to explore the Conia-ene reaction again, this time using nucleophiles which cannot undergo the annulation reaction. The initial optimization involved the use of 3-methylindole as the nucleophile, and although we explored some different Lewis acids, the best results occurred with $\text{Zn}(\text{NTf}_2)_2$. Table **3.3** explores the different nucleophiles used in the investigation of the Conia-ene reaction.

Table 3.3 Substrate Scope for the Conia-ene Reaction

Entry	Product #	Starting material (nucleophile)	Result
1	3-28a	 3-29	40 %
2	3-28b	 3-30	36 %
3	3-28c	 3-31	SM
4	3-28d	 3-32	Decomposition
5	3-28e	 3-33	SM

After a short scope of different nucleophiles, it was evident that most of these reactions were unsuccessful, undergoing no reaction at all (entries **3** & **5**), giving low yields (entries **1** & **2**) or only giving decomposition (entry **4**). With entry **1**, this nucleophile was chosen as the methyl group blocks the 2-position on the indole and this will therefore prevent any formation of the annulation product. With entries **2-5** these all contain nucleophilic atoms with lone pair electrons, which will promote the ring-opening reaction and allow for the Conia-ene to occur.

After an exhaustive attempt at optimizing both the annulation and Conia-ene reactions with the acetylene-bearing DA cyclopropane, the results were not successful enough to move forward with this research. It was therefore decided to end this project and attempt using the DA cyclopropane **3-15** in other valuable synthetic reactions.

3.4 Chapter Three Conclusions

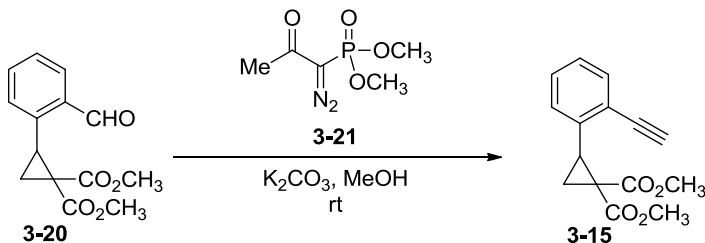
In summary the formation of the annulation adduct **3-23** was successful, which led to a yield of 75 %. As for the initial hypothesis of making the Conia-ene product **3-22**, initially this was not successful, however after changing the nucleophiles was achieved in a 40 % yield using 3-methylindole. For the future of this methodology, many factors could be changed to try and make this reaction more efficient. For the annulation reaction, being able to get only product **3-23** with no non-aromatic **3-24** or ring-opened **3-25** side products from occurring would be the ideal situation. This may involve reevaluating the optimization of conditions and try new Lewis acids. As for the Conia-ene reaction, more attempts could be made with both the conditions used as well as the scope of nucleophiles, in order to achieve success with this reaction and the DA cyclopropane **3-15**.

3.5 Experimental Details for Chapter 3

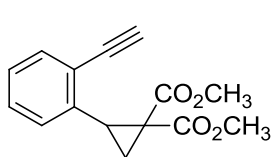
3.5.1 General Considerations

For general considerations refer to section 2.4.1 General Considerations from Chapter 2.

3.5.2 Experimental Procedure and Spectral Data for Acetylene-Bearing DA Cyclopropane **3-15**



Dimethyl 2-(2-formylphenyl)cyclopropane-1,1-dicarboxylate (**3-20**) (1 equivalent) was dissolved in methanol and slightly heated for 10 minutes until the starting material was fully dissolved. Once removed from heat, potassium carbonate was added (2.5 equivalent) and the reaction mixture was stirred at room temperature. Dimethyl (1-diazo-2-oxopropyl)phosphonate (**3-21**) (2.5 equivalent) was dissolved in methanol and slowly added drop wise over 5 minutes. Reaction mixture was left to stir at room temperature, and was quenched with brine once deemed complete by TLC analysis (approx. 18 h). Brine was added to the reaction mixture and the aqueous layer was extracted with EtOAc 3 times. The organic phases were combined and dried with MgSO₄, filtered and the solvent was removed. The residue was purified by flash column chromatography (gradient elution, EtOAc/Hexanes) to yield the desired compound (**3-15**).



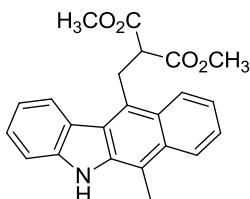
Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate

(3-15): Reagents employed: dimethyl 2-(2-formylphenyl)cyclopropane-1,1-dicarboxylate (**3-20**) (1.00 g, 3.81 mmol), potassium carbonate (1.32 g, 9.50 mmol), dimethyl (1-diazo-2-oxopropyl)phosphonate (**3-21**) (1.83 g, 9.50 mmol), methanol: yield 88 % (0.857 g, 3.32 mmol) as a light red solid; MP: 70°C, R_f = 0.50, 30% EtOAc in hexanes; ¹H-NMR (400 MHz, CDCl₃) δ = 7.48 (dd, *J* = 7.8, 7.4 Hz, 1H), 7.28-7.19 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 1H), 3.80 (s, 3H), 3.53 (dd, *J* = 8.8, 8.6 Hz, 1H), 3.35 (s, 3H), 3.32 (s, 1H), 2.26 (dd, *J* =

8.2, 5.1 Hz, 1H), 1.79 (dd, $J = 9.0, 5.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 170.0, 167.1, 137.3, 132.5, 128.4, 127.2, 126.7, 124.1, 82.3, 81.5, 52.7, 52.2, 36.9, 31.8, 19.1$; IR (thin film, cm^{-1}) 3286, 3027, 2953, 1727, 1437, 1334, 1132; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{14}\text{O}_4$ 258.0892, found 258.0901.

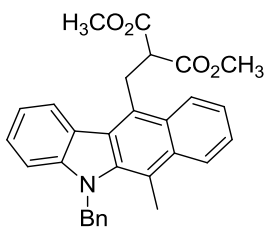
3.5.3 General Experimental Procedures and Spectral Data for Annulation products **3-27**

Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (1 equivalent) was added to a flask containing DCE, and the flask was flushed with Argon gas. To the reaction mixture indole (1.2 equivalent) was added followed by the catalyst zinc bistriflimide ($\text{Zn}(\text{NTf}_2)_2$) (0.1 equivalent). The reaction mixture was stirred at reflux for approximately 2 hours, after starting material no longer remained based on TLC analysis. The reaction mixture was cooled to room temperature and the crude solution was purified by flash column chromatography (gradient elution, EtOAc/Hexanes) to yield the desired annulation compound (**3-27a-h**).

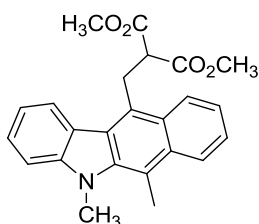


Dimethyl 2-((6-methyl-5H-benzo[b]carbazol-11-yl)methyl)malonate (3-23/3-27a): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.075 g, 0.290 mmol), Indole (0.041g, 0.350 mmol),

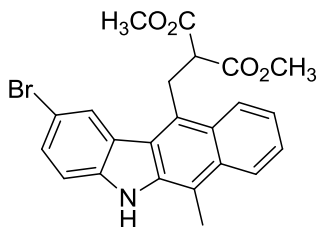
$\text{Zn}(\text{NTf}_2)_2$ (0.019 g, 0.03 mmol), DCE: yield 75% (0.081 g, 0.234 mmol) of a yellow solid; $R_f = 0.40$, 30% EtOAc in hexanes; ^1H -NMR (600 MHz, CDCl_3) $\delta = 8.29$ (t, $J = 7.81$ Hz, 2H), 8.09 (d, $J = 8.60$ Hz, 1H), 7.94 (br, s, 1H) 7.53 (t, $J = 7.8$ Hz, 1H), 7.46 (dd, $J = 8.2, 7.0$ Hz, 2H), 7.38 (d, $J = 7.4$ Hz, 1H), 7.27 (d, $J = 15.2$ Hz, 1H), 4.41 (d, $J = 7.8$ Hz, 2H), 4.06 (t, $J = 7.8$ Hz, 1H), 3.58 (s, 6H), 2.72 (s, 3H).



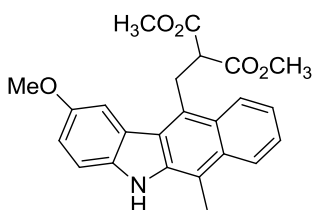
Dimethyl 2-((5-benzyl-6-methyl-5H-benzo[b]carbazol-11-yl)methyl)malonate (3-27b): Reagents used: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.075 g, 0.29 mmol), benzyl-Indole (0.072 g, 0.35 mmol), Zn(NTf₂)₂ (0.019 g, 0.03 mmol), DCE: yield 56 % (0.073 g, 0.156 mmol) as a colorless solid; $R_f = 0.40$, 30% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃) (mixture of products) $\delta = 8.31$ (dd, $J = 7.6, 5.72$ Hz, 2H), 8.12 (d, $J = 8.2$ Hz, 1H), 7.60 (d, $J = 8.2$ Hz, 1H), 7.51 (d, $J = 7.0$ Hz, 1H), 7.47-7.44 (m, 2H), 7.34 (d, $J = 7.6$ Hz, 2H), 7.31-7.28 (m, 5H), 7.22-7.19 (m, 2H), 7.15-7.08 (m, 4H), 7.05 (d, $J = 7.6$ Hz, 1H), 7.00 (t, $J = 7.0$ Hz, 2H), 6.90 (s, 1H), 5.87 (s, 1H), 5.72 (s, 2H), 5.26 (s, 2H), 5.13 (s, 1H), 4.14 (d, $J = 7.6$ Hz, 2H), 4.38 (dd, $J = 10.5, 5.9$ Hz, 1H), 4.06 (t, $J = 7.6$ Hz, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 3.58 (s, 6H), 2.88 (s, 3H), 2.86-2.83 (m, 2H).



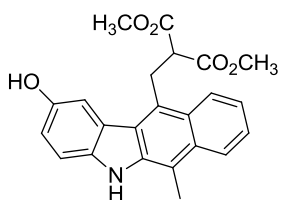
Dimethyl 2-((5,6-dimethyl-5H-benzo[b]carbazol-11-yl)methyl)malonate (3-27c): Reagents used: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.093 g, 0.360 mmol), methyl-indole (0.056g, 0.430 mmol), Zn(NTf₂)₂ (0.025 g, 0.040 mmol), DCE: yield 68 % (0.104 g, 0.267 mmol) of a colorless solid; $R_f = 0.40$, 30% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃) $\delta = 8.28$ (t, $J = 8.2$ Hz, 2H), 8.20 (d, $J = 8.2$ Hz, 2H), 7.56-7.52 (m, 2H), 7.47-7.44 (m, 1H), 7.40 (d, $J = 8.2$ Hz, 1H), 4.42 (d, $J = 7.6$ Hz, 1H), 4.13 (s, 3H), 4.01 (t, $J = 7.6$ Hz, 1H), 3.56 (s, 6H), 3.13 (s, 3H).



Dimethyl 2-((2-bromo-6-methyl-5H-benzo[b]carbazol-11-yl)methyl)malonate (3-27d): Reagents used: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.075 g, 0.290 mmol), 5-bromoindole (0.069 g, 0.350 mmol), Zn(NTf₂)₂ (0.018 g, 0.030 mmol), DCE: yield 32% (0.042 g, 0.092 mmol) as a solid; $R_f = 0.40$, 30% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃) (mixture of products) $\delta = 8.94$ (s, 1H), 8.42 (s, 1H), 8.30 (d, $J = 8.8$ Hz, 1H), 8.07 (t, $J = 8.8$ Hz, 1H), 7.97 (s, 1H), 7.53-7.47 (m, 4H), 4.33 (d, $J = 7.0$ Hz, 2H), 4.01 (t, $J = 7.6$ Hz, 1H), 3.97 (s, 6H), 3.71 (s, 2H), 2.62 (br s, 3H).

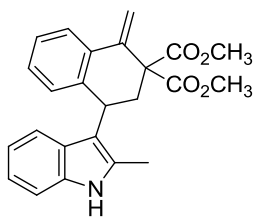


Dimethyl 2-((2-methoxy-6-methyl-5H-benzo[b]carbazol-11-yl)methyl)malonate (3-27e): Reagents used: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.045 g, 0.180 mmol), 5-methoxyindole (0.032 g, 0.220 mmol), Zn(NTf₂)₂ (0.012 g, 0.018 mmol), DCE: yield 48% (35 mg, 0.086 mmol) of a solid; $R_f = 0.40$, 30% EtOAc in hexanes; yield N/A. Mixture was not cleanly separated.



Dimethyl 2-((2-hydroxy-6-methyl-5H-benzo[b]carbazol-11-yl)methyl)malonate (3-27f): Reagents used: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.075 g, 0.29 mmol), 5-hydroxyindole (0.047 g, 0.35 mmol), Zn(NTf₂)₂ (0.018 g, 0.030 mmol), DCE: yield N/A. Mixture was not cleanly separated.

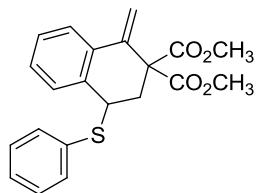
3.5.4 Experimental and spectral data for Conia-ene reaction



Dimethyl 4-(2-methyl-1H-indol-3-yl)-1-methylene-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (3-28a): Reagents

employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.100 g, 0.390 mmol), 2-methylindole (0.061 g,

0.460 mmol), Zn(NTf₂)₂ (0.025 g, 0.040 mmol), DCE: yield 40 % (0.061 g, 0.157 mmol) as a colorless oil; R_f = 0.53, 30% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ: 7.53-7.51 (m, 1H), 7.28-7.25 (m, 3H), 7.17-7.15 (m, 1H), 7.06 (t, *J* = 7.8 Hz, 1H) 6.90 (d, *J* = 7.4 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 5.82 (s, 1H), 4.90 (s, 1H), 3.72 (br d, *J* = 9.0 Hz, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 3.10 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.58 (dd, *J* = 13.7, 2.0 Hz, 1H) 1.61 (s, 3H).



Dimethyl 1-methylene-4-(phenylthio)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (3-28b): Reagents

employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate **3-15** (0.100 g, 0.390 mmol), thiophenol (0.047 mL,

0.460 mmol), Zn(NTf₂)₂ (0.025 g, 0.040 mmol), DCE: yield 36 % (0.062 g, 0.168 mmol) as a yellow oil. R_f = 0.53, 30% EtOAc in hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 7.65 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.58 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.38-7.36 (m, 2H), 7.28-7.22 (m, 4H), 5.71 (s, 1H), 5.02 (s, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 2.90 (dd, *J* = 14.1, 5.5 Hz, 1H), 2.64 (dd, *J* = 14.1, 8.6 Hz, 1H).

3.6 Chapter Three References

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4 The Catalyst-Free Tandem Ring-Opening/Click Reaction of Acetylene-Bearing Donor Acceptor Cyclopropanes

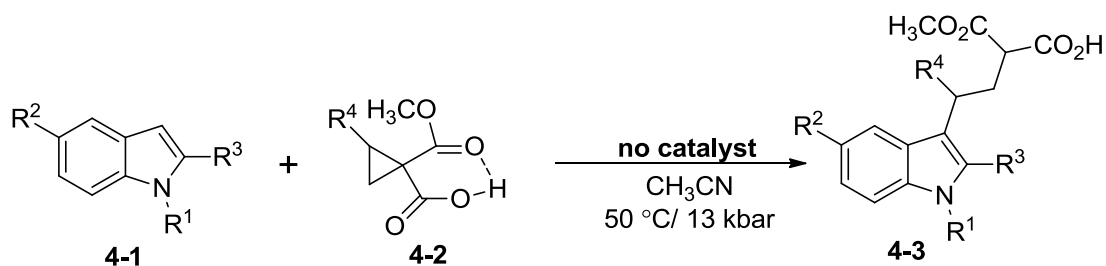
4.1 Introduction

Previous research done from Chapter 3, with the acetylene-bearing DA cyclopropane lead the exploration of using this substrate in the next phase of the investigation of novel DA cyclopropanes.

4.1.1 Donor Acceptor Cyclopropane Hemimalonates

The use of the DA diester cyclopropane, is well known and is well used among chemists in organic synthesis. Changing one of the ester functionalities to a carboxylic acid, has shown to improve the reactivity of these DA cyclopropanes.¹⁻³ As a result, ring-opening reactions which may not occur with the standard diester cyclopropane, may react with the hemimalonate cyclopropane.

Reported back in 2011, M. R. Emmett and M. A. Kerr (Scheme 4.1¹), discovered new modes of DA cyclopropane activation converting one of the geminal esters to a carboxylic acid to give a hemimalonate cyclopropane. This new cyclopropane can react as an electrophile, and in the presence of indole underwent ring opening in the absence of a Lewis acid.¹



Scheme 4.1 Previous Work on Cyclopropane Hemimalonates

There were many speculations into the reasoning behind the success with these hemimalonate cyclopropanes. The first assumption was that the presence of the carboxylic acid moiety, allowed for the formation of a favorable hydrogen bond (Figure 4.1). It was assumed that this hydrogen bonding resulted in the enhancement of the electron-withdrawing capabilities of the ester moiety, and therefore helped facilitate the nucleophilic ring-opening reaction. This however would come at the expense of depositing an equal amount of electron density on the carboxylate moiety, thus making it less electron-withdrawing, and therefore the net activation would be closer to zero.¹

A more likely reason for the increased reactivity of these hemimalonates would be that the hydrogen bond stereoelectronically aligns the carbonyl groups, which allows the receiving of electron density in the ring-opening reaction to occur. The resulting zwitterions from the cyclopropane ring-opening would be a highly delocalized six-electron species.¹

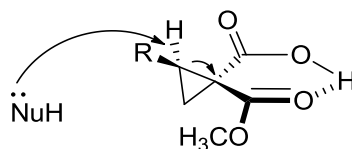
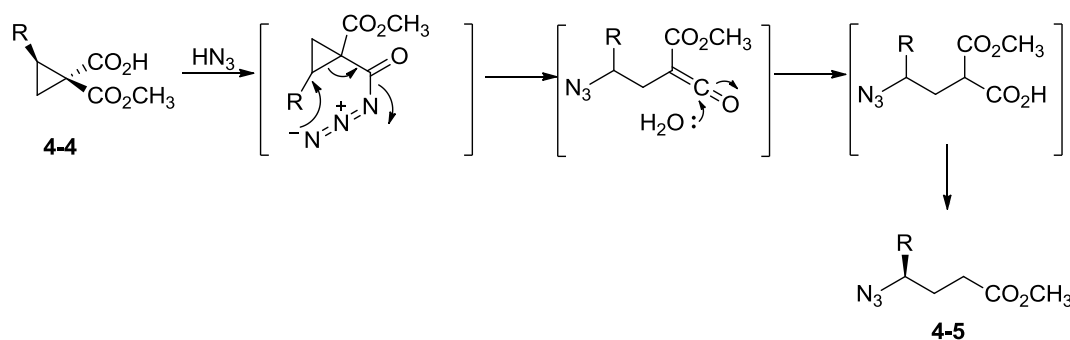


Figure 4.1 The Effects of Intramolecular Hydrogen Bonds on Nucleophilic Ring-Opening of DA Cyclopropane

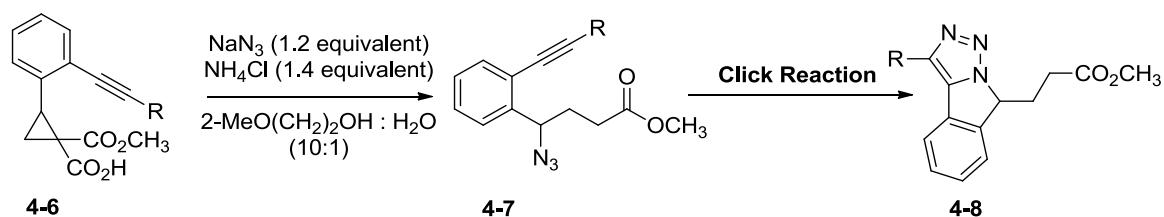
The use of hemimalonates over the diester cyclopropane was also reported in 2012, with nucleophilic ring opening by sodium azide.² In this report, the diester cyclopropane did not undergo successful ring-opening, only the hemimalonate cyclopropane did. For this reaction, the previous assumptions about hydrogen bonding and the stereoelectronic alignment of the carbonyls would not make sense in this case, as it was done in a refluxing protic environment. Other possible reasons for the required carboxylic acid moiety for this reaction could be due to the acyl azide would undergo a [3,3]-sigmatropic rearrangement to yield a ketene (Scheme 4.2²). This would in turn regenerate the acid by water, followed by decarboxylation. This proposed mechanism seems plausible, however the acylazide was never isolate and therefore the mechanism is still inconclusive.²



Scheme 4.2 Proposed Mechanism for Azide Ring-Opening of DA Cyclopropane Hemimalonates

4.1.2 Research Objective

The focus of this chapter will be on the acetylene-bearing DA cyclopropane **4-6** in a tandem ring-opening/click reaction to form new triazole containing compounds. After the extensive research done with diester substrate **4-6** from Chapter 3, this novel DA cyclopropane was subjected to the conditions from previous work using hemimalonates.^{1,2,3} As with the previous work done, the cyclopropane was required to be the hemimalonate version rather than the diester one. The conditions employed¹ were catalyst free and the initial hypothesis was that this reaction would only lead to substrate **4-7**. The initial hypothesis was partially correct, however after the ring-opening and decarboxylation a 1,3-dipolar cycloaddition occurred to give the triazole product **4-8** (Scheme 4.3).

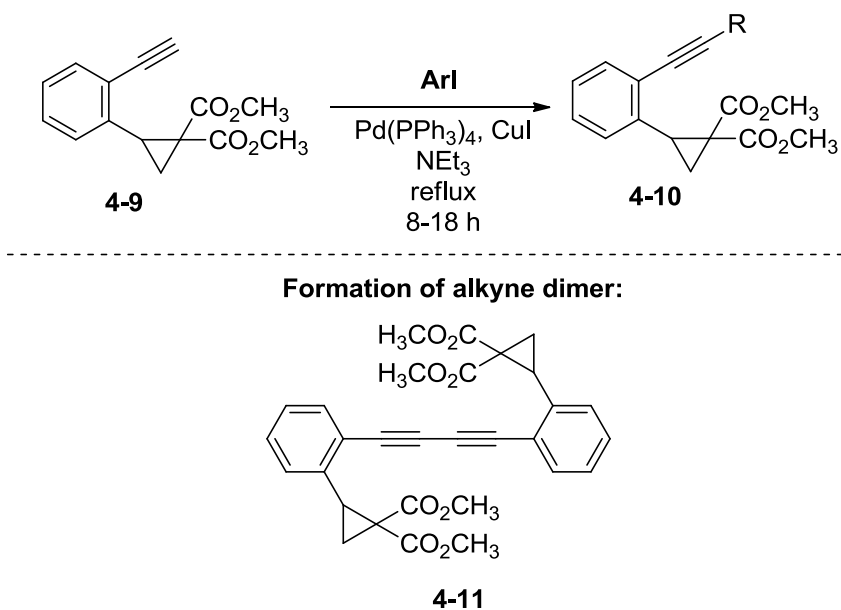


Scheme 4.3 The Efforts towards Novel Linearly Fused Tricyclic Triazoles using Donor Acceptor Cyclopropane Hemimalonates

4.2 Results and Discussion

4.2.1 Synthesis of DA Cyclopropanes Precursors

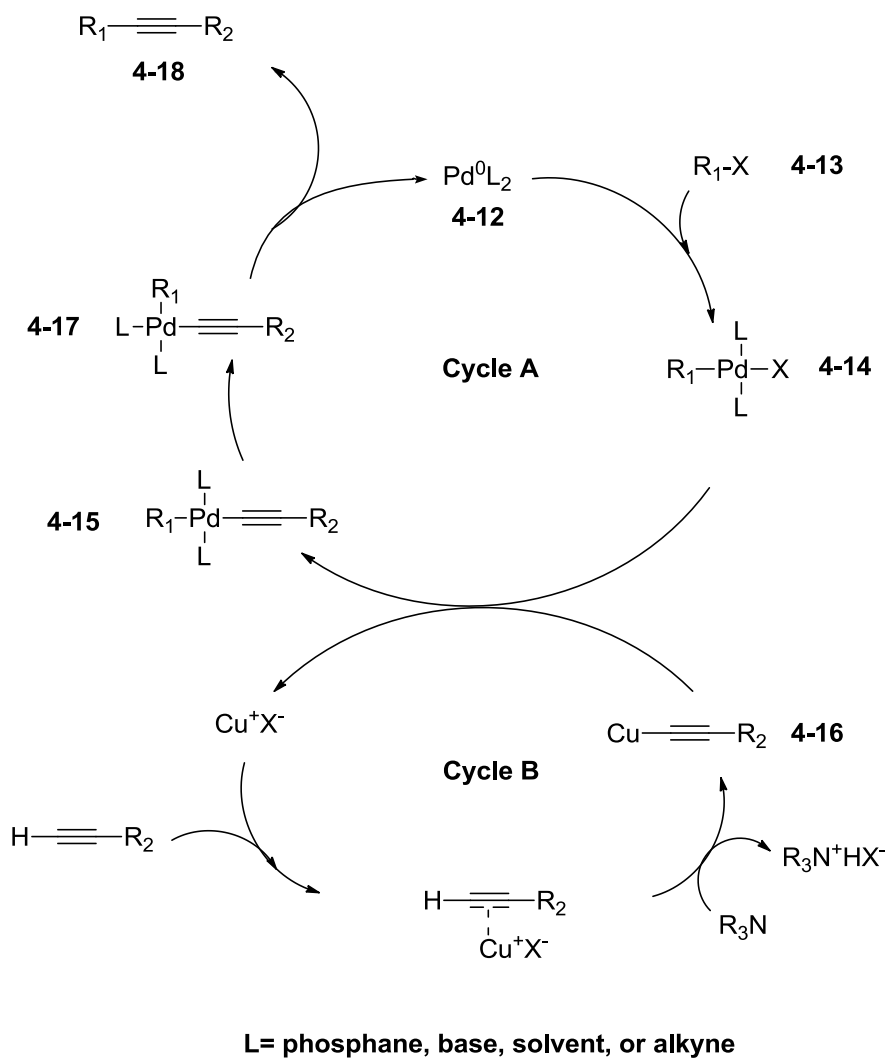
To start this project, a variety of different DA cyclopropanes had to be synthesized. Initially we believed that a large library of cyclopropanes could be easily accessed through a simple cross coupling reaction of the alkyne **4-9** and an aryl halide (Scheme 4.4). This synthetic route proved to be successful, only when the aryl halide used was an iodo-species. The iodo-species was more successful as it helped reduce the amount of dimer formed between two of the alkyne species (**4-11**). The bromo-substrates resulted in lower yields of the desired product **4-10** and higher yields of the dimer **4-11**; thus the iodo-species was used for most examples.



Scheme 4.4 The Sonogashira Cross Coupling Reaction with DA Cyclopropane 4-9

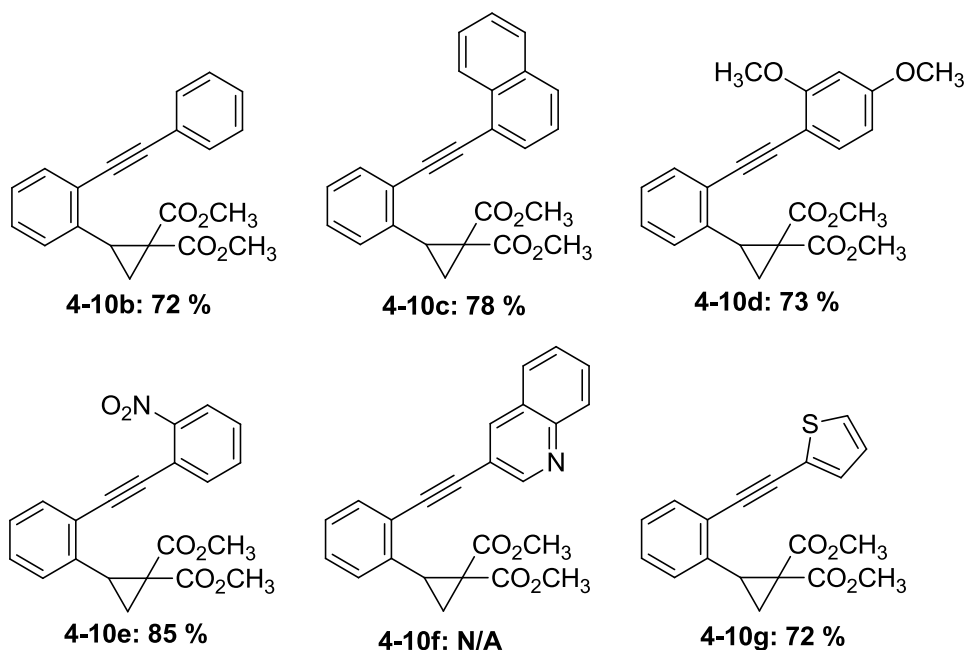
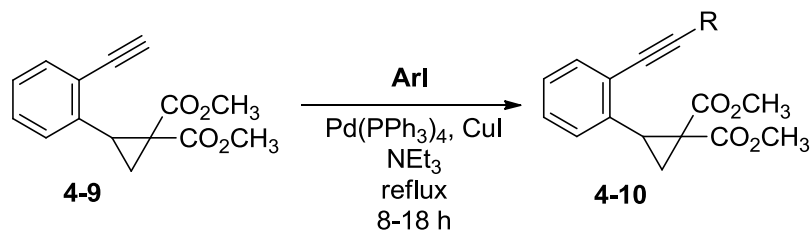
The Sonogashira cross coupling reaction received its' name back in 1975 from the discovery by Sonogashira, Tohda, and Hagihara.⁴ They determined that the coupling could be easily done at room temperature using a palladium source as the catalyst, and combined with an amine as the solvent and a co-catalytic amount of copper iodide. Although Sonogashira reactions are generally considered to be done with copper, "copper-free" options may need to be considered in order to avoid the undesirable formation of alkyne homo-coupling cause by the copper-mediated Hay/Glaser reaction.⁵ The term "Sonogashira Reaction" has been used as a description for any palladium(0)-catalysed coupling of an sp^2 (or sp^3) halide or triflate with a terminal alkyne, without the presence of copper-salts.

The proposed mechanism, is thought to have the two catalysts act independently to one another, the first cycle being the palladium-cycle or cycle A, and the second being the copper-cycle or cycle B (Figure 4.2⁶). Cycle A follows a classic C-C palladium cross-coupling formation.⁶⁻⁷ The cycle starts with the catalytically active Pd(0)L₂ species (**4-12**), which can be formed from a variety of Pd(0) complexes, such as Pd(PPh₃)₄, or can be created from Pd(II) complexes through reductive elimination. The amine solvent/base, can also aid in the reduction of Pd(II) to Pd(0) through the formation of iminium cations.^{6,8} Once the desired Pd(0)L₂ species has been formed, the first step of the cycle is initiated by oxidative addition of the aryl or vinyl halide (**4-13**). This is considered to be the rate-determining step of the entire catalytic cycle. Once the halogen species binds, it creates the adduct **4-14**, which can then be transformed into **4-15** after transmetalation with the copper acetylide **4-16**, formed in Cycle B. From there, reductive elimination occurs, after cis/trans-isomerization to the final alkyne (**4-17**), to give the desired product **4-18** and regeneration of the palladium catalyst (**4-12**).⁶



Scheme 4.5 The Proposed Sonogashira Mechanism

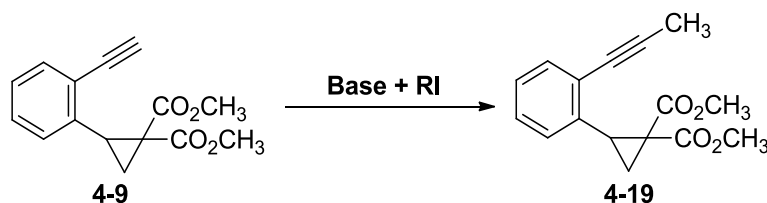
Table 4.1 Synthesis of Internal Alkynes via Sonogashira Cross-Coupling.



Under standard conditions⁴, using aryl halides, the Sonogashira cross coupling reaction with acetylene-bearing DA cyclopropane **4-9**, worked relatively well for most of the substrates. In the case of the heteroaromatic substrate **4-10f**, which was successfully made, however the clean separation of the alkyne and the dimer formed was not achieved. For this reason a yield cannot be reported, and the product mixture was moved onto the next synthetic step.

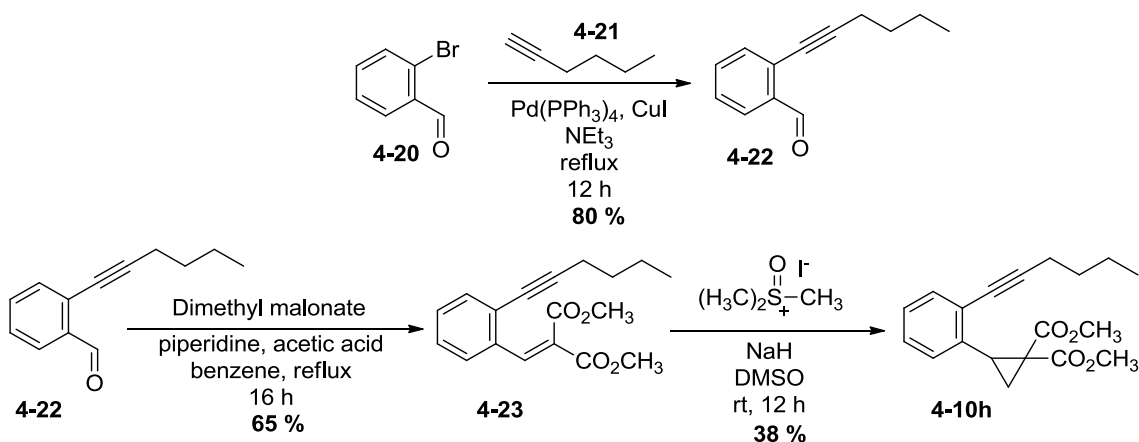
4.2.2 Synthesis of the Alkyl-Substituted Acetylene-Bearing DA Cyclopropane

As previously mentioned, the Sonogashira reaction can only work with sp^2 aryl halides. Our goal was to find alternative ways to introduce an alkyl chain (C_nXH_{2n+1} , $n = 1-6$) onto our alkyne. Our initial attempts began with trying to deprotonate the alkyne and introduce an alkyl chain electrophile (Scheme 4.6). These attempts were never successful and therefore other methods had to be investigated.



Scheme 4.6 Attempt to make Substrate 4-19 from Alkyne 4-9

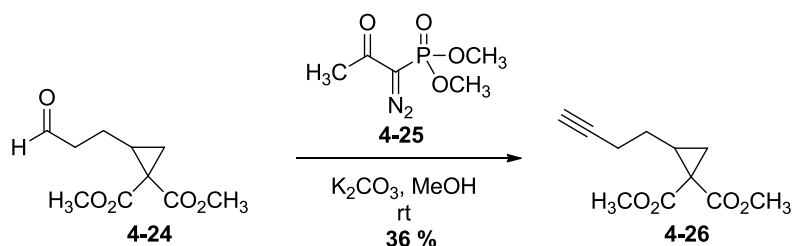
To make cyclopropane **4-10h** the synthetic route had to start from the beginning with a Sonogashira cross coupling reaction of readily available bromobenzaldehyde **4-20** with hexyne **4-21**, followed by the standard synthesis⁹⁻¹⁰ of the cyclopropane moiety. This route, albeit lengthy in steps, had precedence that it would be successful as substrates **4-22** and **4-23** had been successfully made by other research groups.¹¹⁻¹²



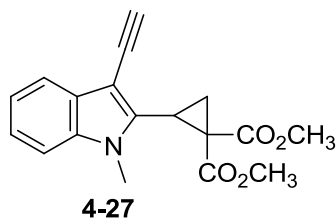
Scheme 4.7 The Synthetic Route towards the DA Cyclopropane 4-10h

4.2.3 Synthesis of additional DA cyclopropanes

In addition to the aliphatic alkyne, two other cyclopropanes were synthesized. Starting with readily available aldehyde **4-24** (Scheme 4.9) an O'Hira-Bestmann homologation¹³ was done to give the alkyne **4-26**. Substrate **4-27** was available and was carried forward in the synthesis of the triazole compounds.

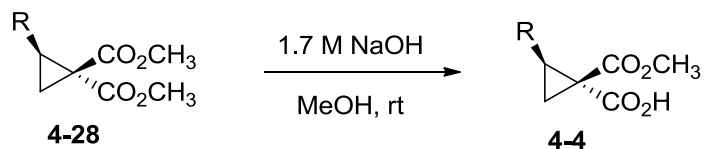


Scheme 4.8 Synthesis towards DA Cyclopropane 4-26



Scheme 4.9 Acetylene-Bearing Indole DA Cyclopropane

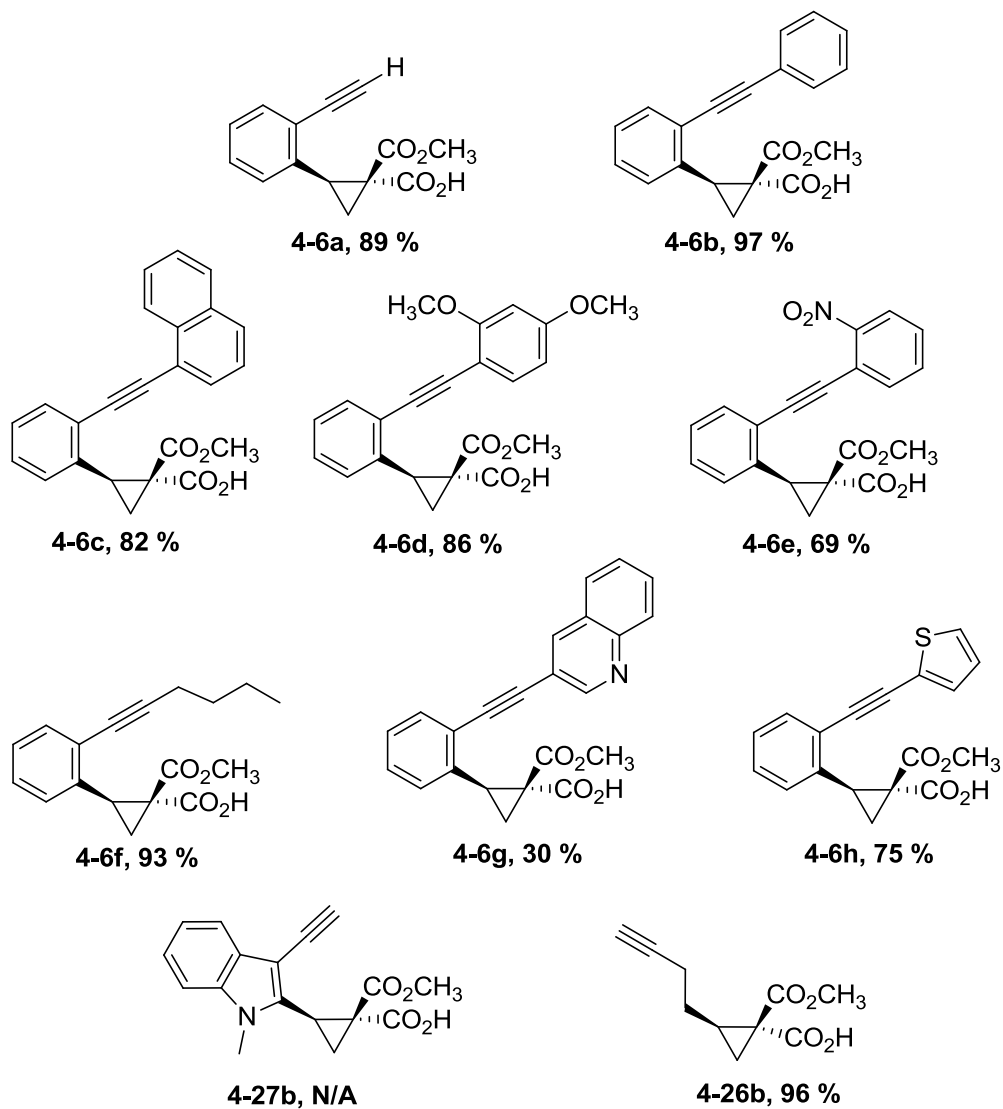
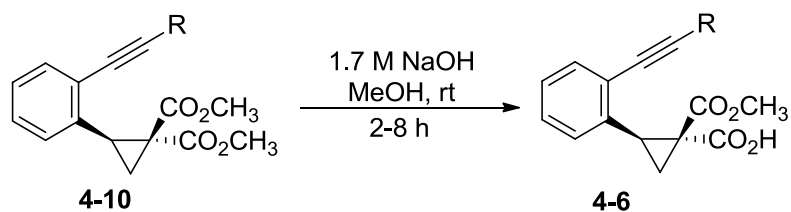
4.2.4 Synthesis of DA cyclopropane hemimalonates



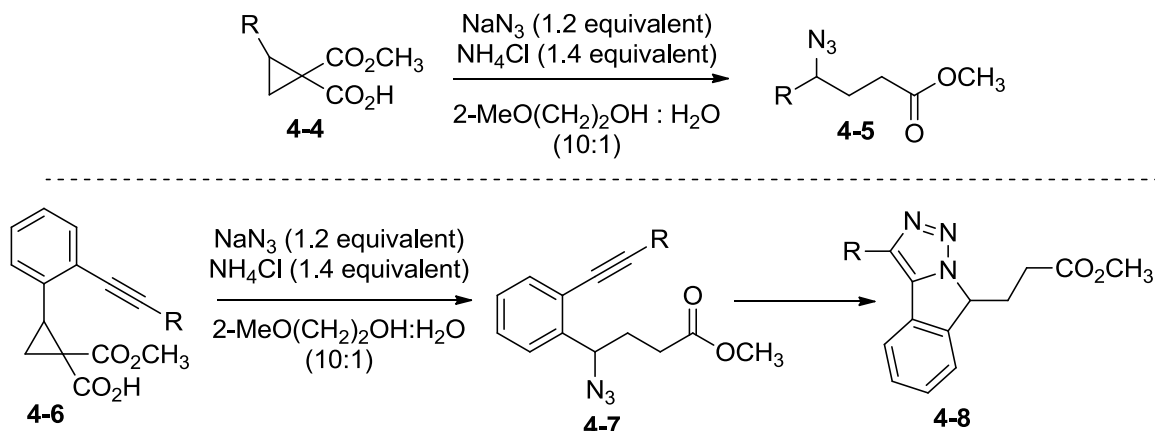
Scheme 4.10 Selective Trans-Saponification of DA Cyclopropane Diester Substrates

As previously mentioned, the diester cyclopropane would not successfully undergo ring-opening with sodium azide.² In order for the ring-opening to occur, an ester-acid cyclopropane (**4-4**) must be used, to help promote the nucleophilic attack by the azide. This conversion of one of the esters to an acid, is done by a simple saponification using basic conditions. Previous studies have shown, through the use of deuterium labeling, that the rate of saponification between the two esters favors the trans-ester over the cis-ester.¹⁴ Due to this rate difference, mono-saponification can be done easily without the concern of making the diacid cyclopropane. This reaction proceeded well for all substrates except with substrate **4-27b**, which may have decomposed after the work-up. It is worthy to note that the yields were reduced for the electron-withdrawing substituent (NO₂, **4-6e**) as well as with the heteroaromatic species (**4-6f**) due to the starting material **4-10f** being carried forward as a mixture (Table 4.2).

Table 4.2 Synthesis of DA Cyclopropane Hemimalonates



4.2.5 Synthesis of the triazole substrates

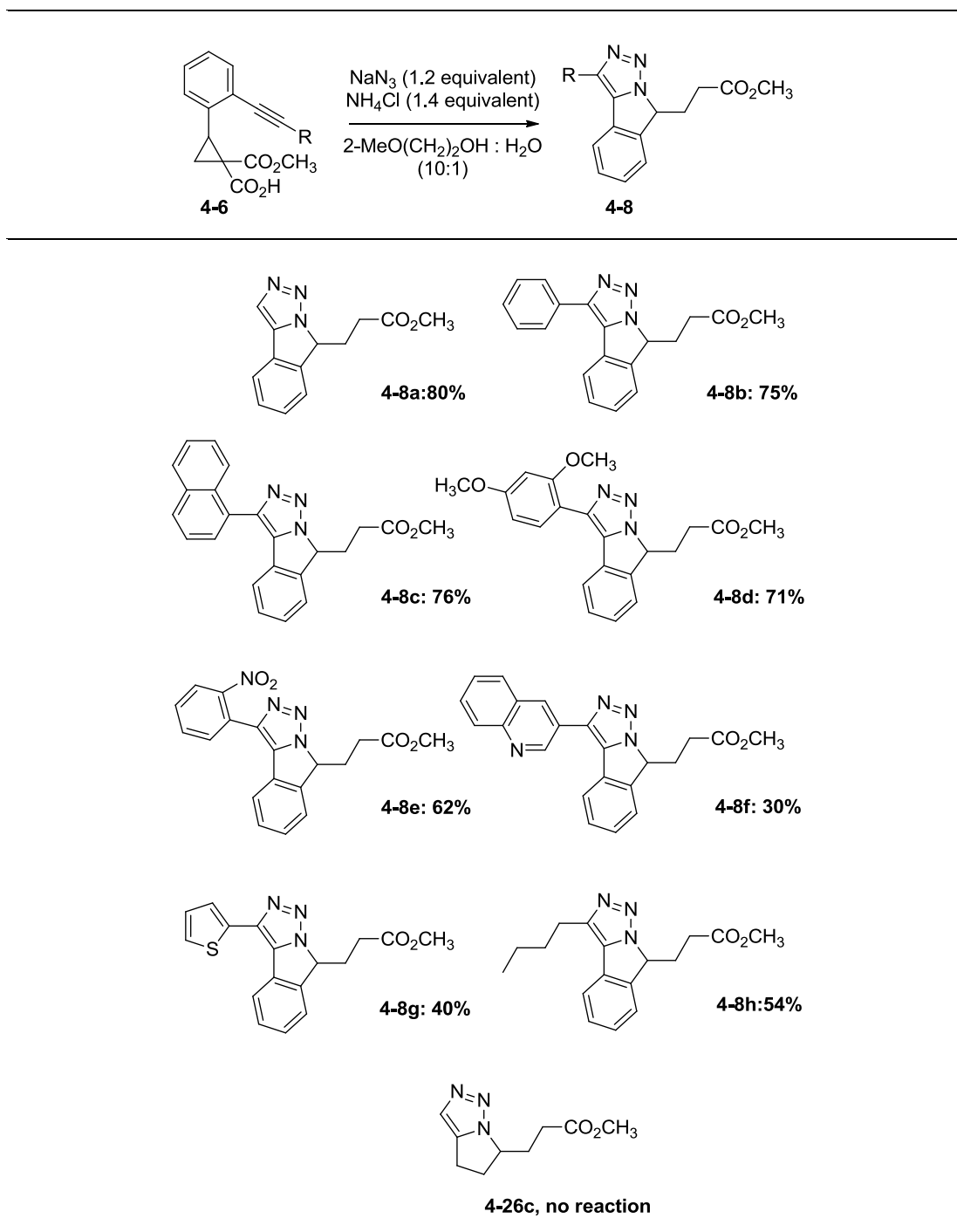


Scheme 4.11 The Synthetic Route towards the Triazole Substrates

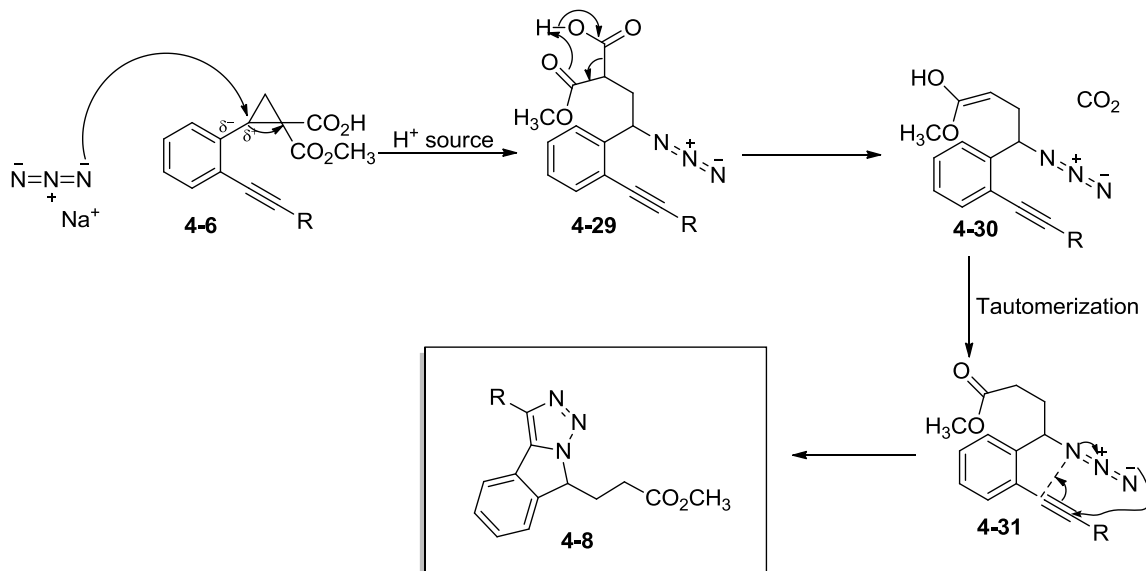
The alkyne substrate **4-6** was subjected to conditions previously used with DA cyclopropane hemimalonates and azide as the nucleophile.² To our delight DA cyclopropane **4-6** underwent the predicted ring-opening and decarboxylation, as well as a 1,3-dipolar cycloaddition commonly referred to as click chemistry. This reaction was clean and efficient, catalyst-free and gave great yields for this three-step process. Table **4.4** shows the substrate scope for the formation of triazoles. This reaction went relatively smoothly with most substituents, however the heteroaromatic substituents **4-8g** and **4-8h**, gave a much lower yield. This could be accounted for the fact that the starting material was more difficult to make, difficult to separate, and resulted in lower the yields of starting material **4-6**. It is to be noted that when there was an electron-withdrawing group, NO₂, on the phenyl ring of the R group **4-8e** this resulted in a lower yield, whereas electron-donating substrates such as **4-8c** and **4-8d** had the opposite effect and increased the yield of the triazole product. The cyclopropane with the aliphatic chain at the R position **4-8h** did give triazole product, however in a lower yield than other substrates. It is also important to take note of **4-26c**, which features no phenyl group off of the cyclopropane, resulted in no yield of the triazole product, and the lack of reaction from this substrate can be explained by the proposed mechanism, Scheme **4-11**. In this proposed mechanism, the cyclopropane opening is much better facilitated when there is the benzene ring present. This can be explained by the π -electrons in the benzene ring,

which help stabilize the transition state of the reaction, allowing for ring opening to occur by supporting the δ^+ charge on the donor-acceptor cyclopropane. Substrate **4-26c**, without the benzene ring there to support the cyclopropane, the ring opening will not occur and therefore the reaction itself will not proceed.

Table 4.3 Reaction Scope of Triazoles



4.2.6 Proposed Mechanism of the Catalyst-Free Tandem Ring-opening/Click Reaction Donor Acceptor Cyclopropanes



Scheme 4.12 The Proposed Mechanism of the Reaction with DA Cyclopropane 4-6 and Sodium Azide

The results from Table 4.4 have proven that this reaction was extremely successful, especially since the reaction undergoes three mechanistic steps in one-pot. The first step is the nucleophilic ring-opening by azide, to give substrate 4-29, which next underwent decarboxylation to give 4-30, that can tautomerize to 4-31. Substrate 4-31 can then undergo the 1,3-dipolar cycloaddition to give the triazole product 4-8. This reaction mechanism is notable as it does not require any catalyst and is also done intramolecularly.

4.3 Conclusions

As demonstrated, DA cyclopropanes, in particular the acetylene-bearing DA cyclopropane hemimalonate, has proven to be exceptional substrates for the catalyst-free tandem ring-opening/click reaction. This reaction resulted in a variety of novel linearly fused tricyclic triazoles to be successfully made, in excellent yields for this one-pot, three-step procedure.

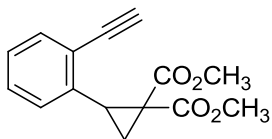
In summary, we have described a new reaction involving a tandem ring-opening/cycloaddition reaction with donor-acceptor cyclopropanes. The reaction was technically simple and generated molecular complexity in a rapid fashion. The newly formed products were novel tricyclic triazoles which have shown fluorescent behavior, and these triazole compounds have been shown in research to become fluorescent probes for metal detection.¹⁵ Work is underway to determine the fluorescence behavior of these compounds as well as potential bio-activity.

4.4 Experimental

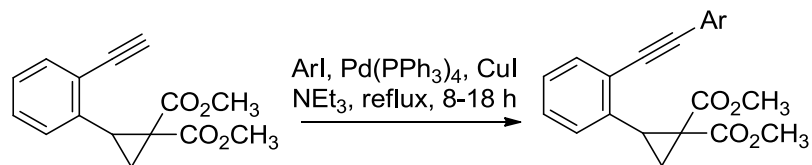
4.4.1 General Considerations

For general considerations refer to section **2.4.1** General Considerations from Chapter 2

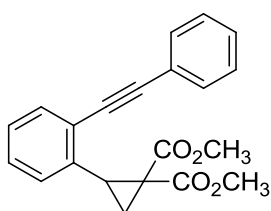
4.4.2 General Procedure and Spectral Data for Cyclopropanes 4-10a-g



Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (4-9/4-10a): See Chapter 3 compound **3-15** for experimental procedure and spectral data.



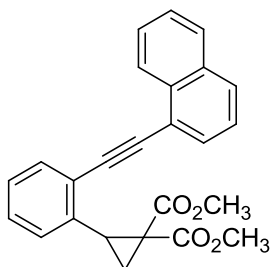
Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (1 equivalent) was dissolved in triethylamine ($C = 0.890$ mM), followed by the addition of the aryl halide (1.2 equivalent), copper iodide (CuI) (5 mol %) and tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$) (2.5 mol %). The reaction mixture was heated to reflux under Argon atmosphere, for 8 to 18 hours depending on the substrate. Upon completion deemed by TLC analysis, the reaction was cooled to room temperature and the solvent was removed. The crude product was dissolved in dichloromethane and washed with water 3 times. The organic phase was dried with MgSO_4 , filtered, and the solvent was removed. The residue was purified by flash column chromatography (EtOAc/Hexanes) to yield the desired compounds (**4-10b-g**).



Dimethyl 2-(2-(phenylethynyl)phenyl)cyclopropane-1,1-

dicarboxylate (4-10b): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (0.100 g, 0.387 mmol), iodobenzene (0.052 mL, 0.465 mmol), $\text{Pd}(\text{PPh}_3)_4$

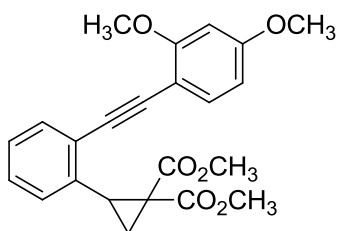
(0.010 g, 0.009 mmol), CuI (0.003 g, 0.018 mmol), triethylamine (0.500 mL, $C = 0.890$ mM): yield 61% (0.079 g, 0.236 mmol) as a clear oil; $R_f = 0.51$, 30% EtOAc in hexanes; ^1H NMR (600 MHz, CDCl_3) $\delta = 7.57\text{-}7.52$ (m, 3H), 7.38-7.34 (m, 3H), 7.27-7.25 (m, 2H), 7.11-7.09 (m, 1H), 3.71 (s, 3H), 3.64 (t, $J = 8.8$ Hz, 1H), 3.37 (s, 3H), 2.30 (dd, $J = 8.2, 5.3$ Hz, 1H), 1.80 (dd, $J = 9.4, 5.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 170.2, 167.1, 136.6, 131.7, 131.6, 128.3, 127.9, 127.3, 127.0, 125.3, 123.3, 110.0, 94.6, 87.3, 52.6, 52.2, 36.8, 32.4, 19.2$; IR (thin film, cm^{-1}) 3061, 2951, 1728, 1495, 1436, 1332, 1284, 1215, 1130, 757, 692; HRMS (EI) calc'd for $\text{C}_{21}\text{H}_{18}\text{O}_4$ 334.1205, found 334.1209.



Dimethyl 2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropane-

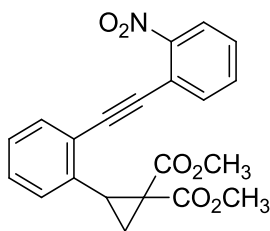
1,1-dicarboxylate (4-10c): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (0.150 g, 0.581 mmol), 1-iodonaphthalene (0.102 mL, 0.699 mmol), Pd(PPh₃)₄ (0.015 g, 0.013 mmol), CuI (0.006 g, 0.030 mmol), triethylamine (0.700 mL, C = 0.890 mM): yield 78% (0.175 g,

0.455 mmol) as a clear oil; $R_f = 0.46$, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) $\delta = 8.46$ (d, $J = 8.2$ Hz, 1H), 7.87 (dd, $J = 10.6, 8.8$ Hz, 2H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.66-7.65 (m, 1H), 7.62 (t, $J = 7.0$ Hz, 1H), 7.54 (t, $J = 7.0$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 7.30-7.29 (m, 2H), 7.13-7.12 (m, 1H), 3.72 (dd, $J = 8.8, 8.2$ Hz, 1H), 3.54 (s, 1H), 3.40 (s, 1H), 2.35 (dd, $J = 8.2, 5.3$ Hz, 1H), 1.85 (dd, $J = 9.4, 5.3$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) $\delta = 170.0, 167.1, 136.4, 133.1, 132.0, 130.6, 128.7, 128.1, 128.0, 127.3, 126.9, 126.7, 126.3, 125.4, 125.2, 120.9, 92.6, 92.1, 52.5, 52.2, 37.0, 32.2, 19.1$; IR (thin film, cm⁻¹) 3057, 2951, 1728, 1436, 1283, 1130, 802; HRMS (EI) calc'd for C₂₅H₂₀O₄ 384.1362, found 384.1363.

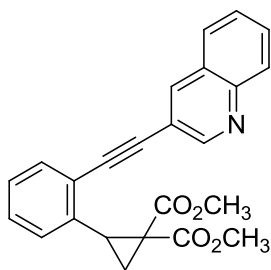


Dimethyl 2-(2-((2,4-dimethoxyphenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (4-10d): Reagents

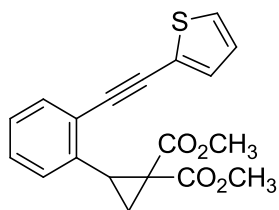
employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (0.125 g, 0.484 mmol), 1-Iodo-2,4-dimethoxybenzene (0.153 g, 0.581 mmol), Pd(PPh₃)₄ (0.014 g, 0.012 mmol), CuI (0.005 g, 0.024 mmol), triethylamine (0.600 mL, C = 0.890 mM): yield 57% (0.108 g, 0.274 mmol) as a clear oil; $R_f = 0.29$, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) $\delta = 7.53$ -7.51 (m, 1H), 7.43 (d, $J = 8.2$ Hz, 1H), 7.21-7.19 (m, 2H), 7.05-7.02 (m, 1H), 6.50-6.45 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 3.64 (dd, $J = 9.0, 8.6$ Hz, 1H), 3.36 (s, 3H), 2.32 (dd, $J = 8.6, 5.1$ Hz, 1H), 1.84 (dd, $J = 9.4, 5.1$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) $\delta = 167.3, 161.1, 136.2, 134.4, 131.7, 127.3, 127.1, 126.7, 125.9, 110.0, 105.3, 104.8, 98.4, 91.1, 90.1, 55.8, 55.4, 52.5, 52.1, 36.9, 32.3, 19.4$; IR (thin film, cm⁻¹) 2951, 2210, 1727, 1608, 1509, 1300, 1211, 1124, 1030, 758; HRMS (EI) calc'd for C₂₃H₂₂O₆ 394.1416, found 394.1412.



Dimethyl 2-(2-((2-nitrophenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (4-10e): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (0.050 g, 0.190 mmol), 1-Iodo-2-nitrobenzene (0.057 g, 0.230 mmol), Pd(PPh₃)₄ (0.006 g, 0.005 mmol), CuI (0.002 g, 0.009 mmol), triethylamine (0.300 mL, C = 0.890 mM): yield 85 % (0.061 g, 0.161 mmol) as a clear oil; R_f = 0.29, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 8.10 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.61 (dt, *J* = 7.4, 1.6 Hz, 2H), 7.49-7.45 (m, 1H), 7.33-7.27 (m, 2H), 7.09 (br d, *J* = 7.4, 1.6 Hz, 1H), 3.70 (s, 3H), 3.64 (t, *J* = 8.6 Hz, 1H), 3.36 (s, 3H), 2.31 (dd, *J* = 8.2, 5.1 Hz, 1H) 1.84 (dd, *J* = 9.4, 5.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.0, 167.0, 149.2, 137.0, 134.9, 132.8, 132.6, 128.9, 128.6, 127.4, 127.0, 124.6, 124.4, 118.8, 95.1, 89.6, 52.6, 52.2, 37.1, 31.8, 19.1; IR (thin film, cm⁻¹) 2952, 2853, 2217, 1727, 1525, 1342, 1286, 1216, 1130, 746; HRMS (EI) calc'd for C₂₁H₁₇NO₆ 379.1056, found 380.1136.

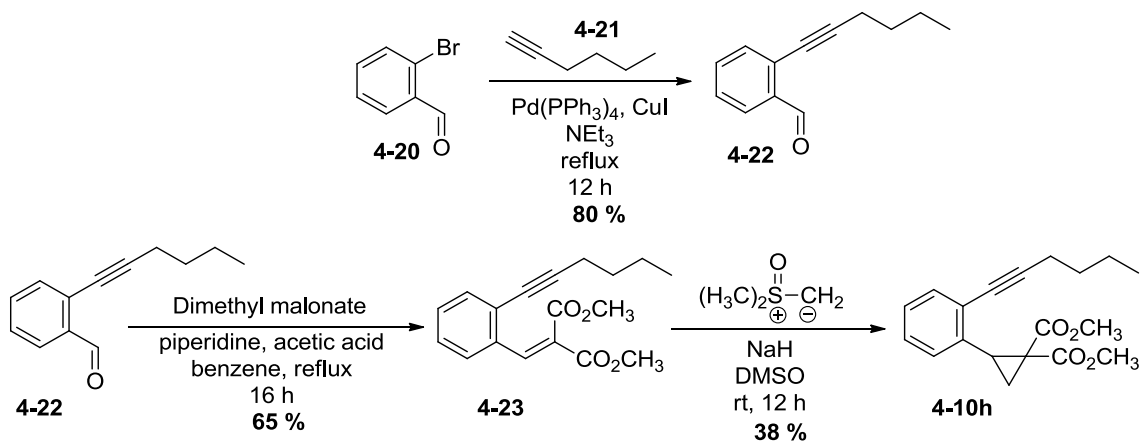


Dimethyl 2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (4-10f): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (0.100 g, 0.390 mmol), 3-iodoquinoline (0.128 g, 0.500 mmol), Pd(PPh₃)₄ (0.012 g, 0.010 mmol), CuI (0.004 g, 0.020 mmol), triethylamine (0.500 mL, C = 0.890 mM): (0.025 g product, 0.062 g of dimer isolated), as a clear oil; R_f = 0.24, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) (mixture of products) δ = 8.98 (br s, 1H), 8.32 (br s, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.71 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.60-7.56 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.28 (br t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 3.82 (br s, 2H), 3.71 (s, 3H), 3.65 (dd, *J* = 8.8, 8.2 Hz, 1H), 3.48 (br t, 1H), 3.39 (br s, 2H), 3.35 (s, 3H), 2.36 (dd, *J* = 9.4, 5.5 Hz, 1H), 2.33 (dd, *J* = 7.6, 5.3 Hz, 1H), 1.89-1.82 (br m, 2H).

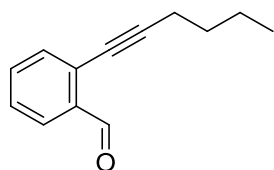


Dimethyl 2-(2-(thiophen-2-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (4-10g): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (0.075 g, 0.290 mmol), 2-bromothiophene (0.042 mL, 0.430 mmol), Pd(PPh₃)₄ (0.006 g, 0.006 mmol), CuI (0.003 g, 0.002 mmol), triethylamine (0.350 mL, C = 0.890 mM): yield 72% (0.071 g, 0.209 mmol) as a clear oil; R_f = 0.42, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.48 (br dd, *J* = 7.0, 2.4 Hz, 1H), 7.29 (d, *J* = 4.1 Hz, 2H), 7.25-7.22 (m, 2H), 7.09 (br d, *J* = 7.0, 1.8 Hz, 1H), 7.02 (t, *J* = 4.7 Hz, 1H), 3.74 (s, 3H), 3.57 (t, *J* = 8.8 Hz, 1H), 3.36 (s, 3H), 2.29 (dd, *J* = 8.2, 5.3 Hz, 1H), 1.80 (dd, *J* = 9.4, 5.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.0, 167.1, 136.5, 132.0, 131.4, 128.0, 127.3, 127.2, 127.1, 127.0, 124.9, 123.2, 91.0, 87.8, 52.6, 52.1, 36.7, 32.1, 19.1; IR (thin film, cm⁻¹) 2950, 1725, 1434, 1383, 1127; HRMS (EI) calc'd for C₁₉H₁₆O₄S 340.0769, found 340.0770.

4.4.3 General Experimental Procedure for the Synthesis of Substrate 14h



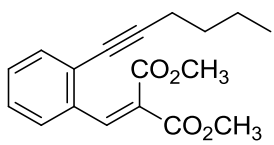
2-bromobenzaldehyde (**4-20**) (1 equivalent) was dissolved in triethylamine (3.0 mL) under Argon atmosphere. To this solution, 1-hexyne (**4-21**) (1.2 equivalent), Tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄) (2 mol %) and copper iodide (CuI) (1 mol %) were added. The solution was stirred at 50 °C for 4 hours, than cooled to room temperature. The reaction mixture was filtered and the solid remaining was rinsed with ether. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired compound (**4-22**).



2-(hex-1-yn-1-yl)benzaldehyde (4-22): Reagents employed: 2-bromobenzaldehyde (**4-20**) (0.095 mL, 0.811 mmol), 1-hexyne (**4-21**) (0.112 mL, 0.975 mmol), Pd(PPh₃)₄ (0.018 g, 0.016 mmol), CuI (0.002 g, 0.008 mmol), triethylamine (3.0 mL): yield 80 % (0.121 g, 0.649 mmol) as a yellow oil: data matched that of previously reported¹¹

General Experimental Procedure for the Synthesis of Substrate 17.

2-(hex-1-yn-1-yl)benzaldehyde (**4-22**) (1 equivalent) was dissolved in benzene (5 mL) and dimethyl malonate (1.3 equivalent) was added. In a separate flask, the piperidine (0.1 equivalent) and acetic acid (0.1 equivalent) were added together, this was added to the reaction flask and the reaction mixture was heated to reflux overnight using a Dean-Stark apparatus. After 16- 18 hours, upon completion by TLC analysis, the reaction was cooled and water was added and the aqueous was extracted with EtOAc 3 times. The organic layers were combined and washed with 1M NaOH solution 4 times, followed by a water wash. From there the organic layers were dried with MgSO₄, filtered and the solvent was removed. This yielded the desired compound (**4-23**).

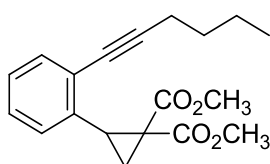


Dimethyl 2-(2-(hex-1-yn-1-yl)benzylidene)malonate (4-23): Reagents employed: 2-(hex-1-yn-1-yl)benzaldehyde (**4-22**) (0.075 g, 0.403 mmol), dimethyl malonate (0.068 g, 0.515 mmol), piperidine (0.003 g, 0.040 mmol), acetic acid (0.002 g, 0.040 mmol), benzene: yield 65% (0.078 g, 0.262 mmol) as a yellow oil: data matched that of previously reported¹²

General Experimental Procedure for the Synthesis of Substrate 4-10h.

Dimethyl 2-(2-(hex-1-yn-1-yl)benzylidene)malonate (**4-23**) (1 equivalent) was dissolved in DMSO (2 mL). In a separate reaction flask, the Corey-Chaykovsky ylide (1.7 equivalent) was dissolved in DMSO (5 mL) and sodium hydride (1.7 equivalent, in 60% mineral oil) was added portionwise and stirred until the evolution of H₂ ceased. The starting material solution was slowly added dropwise over 5 minutes, the reaction mixture was stirred at room temperature for 6 hours and as the reaction was complete by

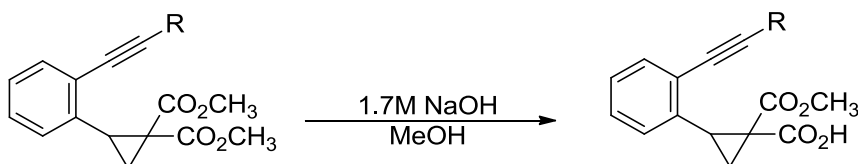
TLC analysis. Water was added to the reaction and the aqueous was extracted 4 times with ether. The organic phases were combined and washed 4 times with brine, and 3 times with water. The organic phases were dried with $MgSO_4$, filtered, and the solvent was removed. The residue needed no further purification to yield the desired compound **4-10h**.



Dimethyl 2-(2-(hex-1-yn-1-yl)phenyl)cyclopropane-1,1-dicarboxylate (4-10h): Reagents employed: dimethyl 2-(2-(hex-1-yn-1-yl)benzylidene)malonate (**4-23**) (0.075 g, 0.250 mmol), Dimethyloxosulfonium methylide (Corey-Chaykovsky Reagent)

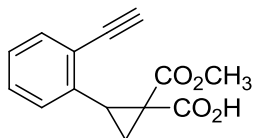
(0.092 g, 0.420 mmol), sodium hydride (in 60% mineral oil, 0.016 g, 0.420 mmol), DMSO: yield 38 % (0.030 mg, 0.095 mmol) as a clear oil; $R_f = 0.53$, 30% EtOAc in hexanes; 1H NMR (400 MHz, $CDCl_3$) $\delta = 7.37-7.35$ (m, 1H), 7.18-7.14 (m, 2H), 7.01-6.99 (m, 1H), 3.78 (s, 3H), 3.51 (t, $J = 8.8$ Hz, 1H), 3.34 (s, 3H), 2.42 (t, $J = 7.0$ Hz, 2H), 2.26 (dd, $J = 8.8, 5.3$ Hz, 1H) 1.77 (dd, $J = 9.4, 5.3$ Hz, 1H), 1.60-1.56 (m, 2H), 1.50-1.45 (m, 2H), 0.95 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 170.1, 167.2, 136.4, 131.7, 127.1, 126.6, 126.1, 95.9, 78.4, 52.6, 52.1, 36.7, 32.3, 30.7, 22.0, 19.3, 13.6$; IR (thin film, cm^{-1}) 2954, 2932, 2872, 1730, 1436, 1332, 1282, 1212, 1130, 756; HRMS (EI) calc'd for $C_{19}H_{22}O_4$ 314.1518, found 314.1517.

4.4.4 General Procedure and Spectral Data for Hemimalonates

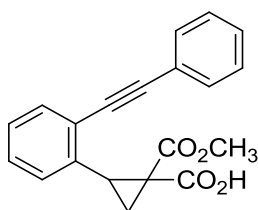


The general procedure for the saponification of compounds **4-10a-h** was done using standard basic conditions. Subjecting the alkyne-bearing cyclopropane diesters **14a-h**, the starting material (1 equivalent) was dissolved in methanol and 1.7 M NaOH was added (1.7 equivalent). The reaction mixture was stirred at room temperature until completion determined by TLC analysis. Once reaction was done, water was added and the reaction was extracted with ethyl acetate. The aqueous layer was acidified and extracted 3 times with ethyl acetate. The combined organic layer was washed with water and dried with

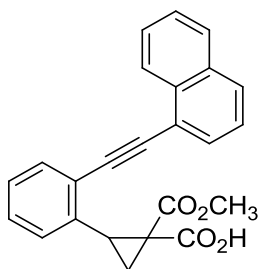
MgSO₄, filtered and the solvent was removed. No further purification was needed, yielding the desired cyclopropane hemimalonates **4-6a-h**.



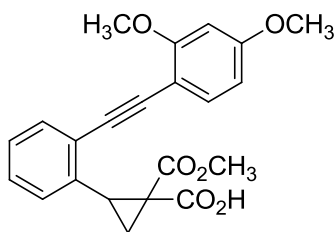
(2-ethynylphenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (4-6a): Reagents employed: dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (**4-9**) (0.120 g, 0.465 mmol), 1.7 M NaOH (0.465 mL, 0.790 mmol), methanol: yield 88 % (0.100 mg, 0.409 mmol) to give a white solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.44 (br d, *J* = 7.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.26-7.22 (m, 2H), 3.51 (dd, *J* = 9.4, 9.0 Hz, 1H), 3.37 (s, 1H), 3.25 (s, 3H), 2.41-2.33 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.9, 170.9, 137.5, 132.2, 128.7, 128.5, 127.7, 127.7, 83.6, 80.7, 52.6, 40.3, 33.1, 22.2; IR (thin film, cm⁻¹) 3283, 3028, 2955, 1754, 1675, 1447, 1352, 1146, 759; HRMS (EI) calc'd for C₁₄H₁₃O₄ 245.0814, found 245.0807 (M+H).



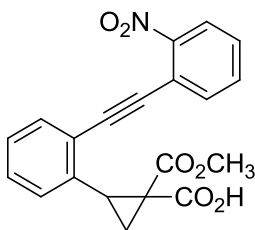
1-(methoxycarbonyl)-2-(2-(phenylethynyl)phenyl)cyclopropanecarboxylic acid (4-6b): Reagents employed: dimethyl 2-(2-(phenylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (**4-10b**) (0.075 g, 0.224 mmol), 1.7 M NaOH (0.230 mL, 0.381 mmol), methanol: yield 95 % (0.068 g, 0.212 mmol) to give a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.52-7.48 (m, 3H), 7.34-7.30 (m, 3H), 7.28-7.22 (m, 3H), 3.60 (t, *J* = 9.0 Hz, 1H), 3.23 (s, 3H), 2.43-2.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.9, 170.6, 136.2, 131.9, 131.8, 131.6, 128.8, 128.6, 128.4, 128.0, 127.8, 122.5, 110.0, 95.7, 86.3, 52.6, 40.5, 33.2, 22.4; IR (thin film, cm⁻¹) 3060, 2922, 1757, 1675, 1443, 1216, 1146, 756, 691; HRMS (EI) calc'd for C₂₀H₁₆O₄ 320.1049, found 320.1046.



1-(methoxycarbonyl)-2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropanecarboxylic acid (4-6c): Reagents employed: dimethyl 2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (**4-10c**) (0.175 g, 0.460 mmol), 1.7 M NaOH (0.460 mL, 0.770 mmol), methanol: yield 80 % (0.137 g, 0.370 mmol) to give a yellow oil; ^1H NMR (600 MHz, CDCl_3) δ = 8.37 (d, J = 8.8 Hz, 1H), 7.86 (t, J = 7.0 Hz, 2H), 7.80 (d, J = 7.0 Hz, 1H), 7.68 (br t, 1H), 7.61 (dd, J = 8.2, 7.0 Hz, 1H), 7.52 (dt, J = 22.3, 8.2, 7.0 Hz, 2H), 7.30-7.35 (m, 3H), 3.73 (t, J = 8.8 Hz, 1H), 3.30 (s, 3H), 2.50-2.48 (m, 1H), 2.45-2.43 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.4, 171.0, 136.1, 133.1, 132.2, 131.0, 129.1, 128.8, 128.3, 128.0, 127.9, 126.8, 126.4, 126.0, 125.5, 125.4, 120.2, 93.6, 91.3, 52.6, 40.0, 33.6, 22.2; IR (thin film, cm^{-1}) 3058, 2953, 2853, 1755, 1675, 1445, 1217, 1145, 755; HRMS (EI) calcd for $\text{C}_{24}\text{H}_{18}\text{O}_4$ 370.1205, found 370.1203.

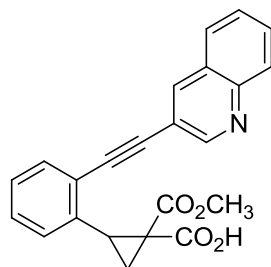


2-(2-((2,4-dimethoxyphenyl)ethynyl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (4-6d): Reagents employed: dimethyl 2-(2-((2,4-dimethoxyphenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (**4-10d**) (0.100 g, 0.250 mmol), 1.7 M NaOH (0.250 mL, 0.430 mmol), methanol: yield 86 % (0.082 g, 0.216 mmol) to give a clear oil; ^1H NMR (600 MHz, CDCl_3) δ = 7.54-7.52 (m, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.25-7.21 (m, 3H), 6.52 (dd, J = 8.2, 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.64 (t, J = 9.4 Hz, 1H), 3.27 (s, 3H), 2.47-2.40 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 174.0, 170.3, 161.5, 135.9, 134.4, 131.8, 128.8, 127.6, 127.2, 125.6, 104.9, 104.5, 98.3, 89.1, 55.7, 55.4, 52.5, 40.5, 33.2, 22.3; IR (thin film, cm^{-1}) 2925, 2853, 2208, 1735, 1608, 1509, 1439, 1211, 1030; HRMS (EI) calc'd for $\text{C}_{22}\text{H}_{20}\text{O}_6$ 380.1260, found 380.1265.



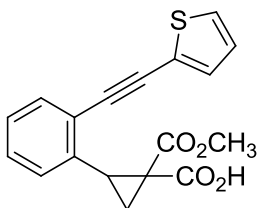
1-(methoxycarbonyl)-2-(2-((2-nitrophenyl)ethynyl)phenyl)cyclopropanecarboxylic acid (4-6e): Reagents employed: dimethyl 2-(2-((2-nitrophenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (**4-10e**) (0.060 g, 0.160 mmol), 1.7 M NaOH (0.160 mL, 0.270 mmol), methanol: yield 68 % (0.040 mg, 0.109 mmol)

to give a yellow oil; ^1H NMR (600 MHz, CDCl_3) δ = 8.08 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.65-7.60 (m, 2H), 7.47 (dd, J = 8.2, 7.6 Hz, 1H), 7.37-7.27 (m, 3H), 3.65 (dd, J = 9.4, 8.8 Hz, 1H), 3.28 (s, 3H), 2.46 (dd, J = 8.8, 4.7 Hz, 1H), 2.39 (dd, J = 9.4, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.9, 170.3, 136.7, 134.8, 133.2, 132.7, 129.0, 128.8, 128.0, 124.7, 93.7, 90.5, 52.7, 40.3, 29.7, 22.3; IR (thin film, cm^{-1}) 3025, 2925, 2854, 2217, 1737, 1525, 1342, 1217, 1145, 746; HRMS (EI) calc'd for $\text{C}_{20}\text{H}_{16}\text{NO}_6$ 366.0978, found 366.0973 (M+H).



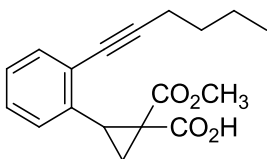
1-(methoxycarbonyl)-2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropanecarboxylic acid (4-6f): Reagents employed: dimethyl 2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (**4-10f**) (0.025 g, 0.065 mmol), 1.7 M NaOH (0.065 mL, 0.111 mmol), methanol: yield 58% (0.014 g, 0.038

mmol) to give a yellow oil; ^1H -NMR (400 MHz, CDCl_3): δ = 9.00 (br s, 1H), 8.37 (br s, 1H), 8.07 (br d, J = 8.2 Hz, 1H), 7.86 (br d, J = 8.2 Hz, 1H), 7.71 (br t, J = 7.6 Hz, 1H), 7.56 (dd, J = 8.6 Hz, 1H), 7.37 (t, J = 7.0 Hz, 1H), 7.31 (t, J = 7.6 Hz, 2H), 3.69 (t, J = 9.0 Hz, 1H), 3.30 (s, 3H), 2.48 (dd, J = 8.2, 4.7 Hz, 1H), 2.41-2.38 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.7, 171.3, 138.2, 136.9, 133.2, 132.0, 129.0, 128.7, 128.4, 127.9, 127.8, 123.9, 123.4, 123.2, 113.9, 80.4, 80.2, 52.7, 39.1, 33.5, 21.9; IR (thin film, cm^{-1}) 2923, 1958, 1731, 1445, 1333, 1217, 1141, 755; HRMS (EI) calc'd for $\text{C}_{23}\text{H}_{17}\text{NO}_4$ 371.1158, found 371.1169.



**1-(methoxycarbonyl)-2-(2-(thiophen-2-ylethynyl)phenyl)
cyclopropanecarboxylic acid (4-6g):** Reagents employed:

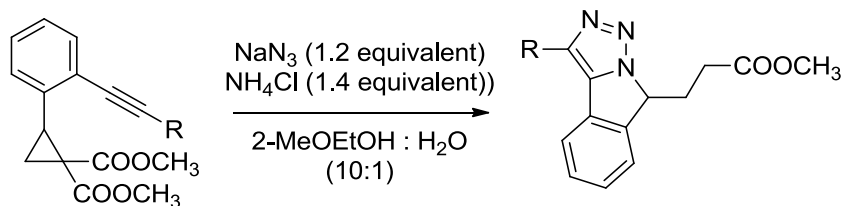
dimethyl 2-(2-(thiophen-2-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (**4-10g**) (0.071 g, 0.210 mmol), 1.7 M NaOH (0.210 mL, 0.360 mmol), methanol: yield 75 % (0.051 mg, 0.157 mmol) to give a clear oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.50 (d, *J* = 5.5 Hz, 1H), 7.37 (d, *J* = 3.5 Hz, 1H), 7.32-7.28 (m, 3H), 7.13 (br d, 1H), 7.03 (t, *J* = 4.7 Hz, 1H), 6.80 (br d, 1H), 3.59 (t, *J* = 9.0 Hz, 1H), 3.27 (s, 3H), 2.46-2.40 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.7, 170.9, 136.1, 132.9, 132.6, 131.5, 129.2, 128.8, 127.9, 127.8, 127.3, 127.2, 90.0, 88.9, 52.6, 40.3, 3.2, 22.4; IR (thin film, cm⁻¹) 3105, 2953, 2201, 1753, 1447, 1216, 1147, 853, 755, 704; HRMS (EI) calcd for C₁₈H₁₄O₄S 326.0613, found 326.0210.



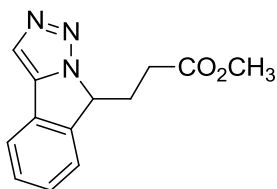
**2-(2-(hex-1-yn-1-yl)phenyl)-1-(methoxycarbonyl)
cyclopropanecarboxylic acid (4-6h):** Reagents employed:

dimethyl-2-(2-(hex-1-yn-1-yl)phenyl) cyclopropane-1,1-dicarboxylate (**4-10h**) (0.030 g, 0.100 mmol), 1.7 M NaOH (0.100 mL, 0.160 mmol), methanol: yield 90 % (0.027 g, 0.090 mmol) to give a yellow oil; ¹H-NMR (600 MHz, CDCl₃) δ = 7.36 (br d, *J* = 7.6 Hz, 1H), 7.24-7.19 (m, 3H), 3.48 (dd, *J* = 9.4, 8.8 Hz, 1H), 3.24 (s, 3H), 2.43 (dd, *J* = 7.6, 7.0 Hz, 2H), 2.40-2.35 (m, 2H), 1.61-1.56 (m, 2H), 1.48-1.43 (m, 2H), 0.94 (dd, *J* = 7.6, 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 174.1, 170.8, 136.4, 131.5, 128.6, 127.6, 127.1, 125.7, 97.4, 77.7, 52.5, 40.9, 33.1, 30.6, 29.7, 22.3, 22.1, 19.3, 13.6; IR (thin film, cm⁻¹) 2924, 2853, 1735, 1449, 1248, 755; HRMS (EI) calcd for C₁₈H₂₀O₄ 300.1362, found 300.1350.

4.4.5 General Procedure and Spectral Data for Triazoles



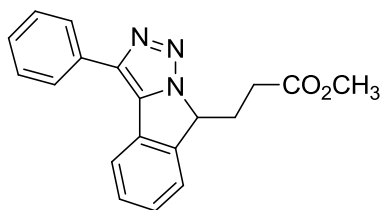
Cyclopropane hemimalonate (**4-6a-h**) (1 equivalent) was dissolved in a solution of 2-methoxyethanol:water (10:1) and then sodium azide (NaN_3) (1.2 equivalent) and ammonium chloride (NH_4Cl) (1.4 equivalent) were added. The mixture was heated to reflux and monitored until completion by TLC analysis (1.5 – 2 h). The reaction mixture was cooled to room temperature, and water was added. The reaction was extracted 3 times with ether. The organic layers were combined and dried with MgSO_4 , filtered and the solvent was removed. The residue was purified by flash column chromatography (EtOAc/hexanes) to yield the desired triazole (**4-8a-h**).



Methyl 3-(8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate

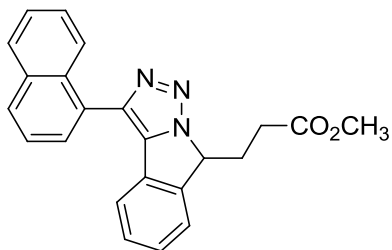
(4-8a): Reagents employed: 2-(2-ethynylphenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (**4-6a**) (0.080 g, 0.328 mmol), NaN_3 (0.026 g, 0.394 mmol), NH_4Cl (0.025 g,

0.459 mmol), 2-methoxyethanol/water: yield 80% (0.064 g, 0.263 mmol) as a clear oil; R_f = 0.12, 30% EtOAc in hexanes; ^1H NMR (600 MHz, CDCl_3) δ = 7.82 (s, 1H), 7.63 (d, J = 7.0 Hz, 1H), 7.50-7.40 (m, 3H), 5.54 (dd, J = 7.8, 3.9 Hz, 1H), 3.64 (s, 3H), 2.81-2.73 (m, 1H), 2.60-2.52 (m, 1H), 2.47-2.40 (m, 1H), 2.29-2.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.8, 144.8, 129.1, 128.6, 127.1, 124.3, 123.8, 121.7, 61.9, 51.8, 28.8, 28.5; IR (thin film, cm^{-1}) 3136, 3057, 2998, 2951, 2850, 1734, 1624, 1471, 1437, 1416, 1379, 1245, 1205, 1094; HRMS (EI) calc'd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_2$ 243.1008, found 243.1006



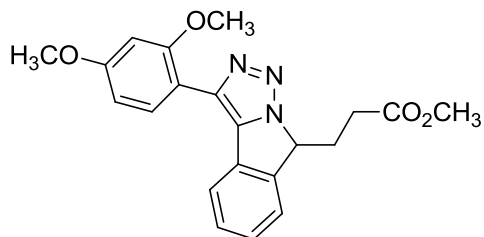
Methyl 3-(3-phenyl-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (4-8b): Reagents employed:

1-(methoxycarbonyl)-2-(2-(phenylethynyl)phenyl)cyclopropanecarboxylic acid (**4-6b**) (0.046 g, 0.143 mmol), NaN₃ (0.011 g, 0.172 mmol), NH₄Cl (0.013 g, 0.242 mmol), 2-methoxyethanol/water: yield 77% (0.035 g, 0.110 mmol) as a white solid; R_f = 0.17, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.96 (d, *J* = 7.04 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 3H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.45-7.40 (m, 2H), 5.58 (dd, *J* = 7.0, 4.1 Hz, 1H), 3.65 (s, 3H), 2.84-2.78 (m, 1H), 2.63-2.58 (m, 1H), 2.50-2.45 (m, 1H), 2.34-2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.9, 145.0, 133.9, 131.0, 129.1, 128.9, 128.5, 127.7, 127.6, 126.6, 126.2, 125.8, 125.4, 123.6, 122.1, 62.0, 51.9, 29.0, 28.8; IR (thin film, cm⁻¹) 3853, 3058, 2950, 2852, 1735, 1609, 1446, 1358, 1174; HRMS (EI) calc'd for C₁₉H₁₇N₃O₂ 319.1321, found 319.1324.



Methyl 3-(3-(naphthalen-1-yl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (4-8c): Reagents employed:

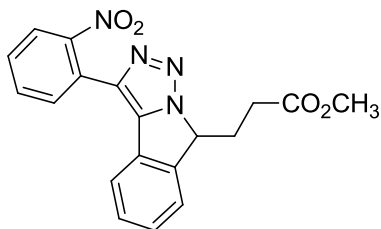
1-(methoxycarbonyl)-2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropanecarboxylic acid (**4-6c**) (0.021 g, 0.060 mmol), NaN₃ (0.005 g, 0.070 mmol), NH₄Cl (0.005 g, 0.080 mmol), 2-methoxyethanol/water: yield 72% (0.016 g, 0.043 mmol) as a clear oil; R_f = 0.17, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 8.18 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.20 Hz, 2H), 7.88 (br s, 1H), 7.64 (br s, 1H), 7.54 (dt, *J* = 7.8, 7.0 Hz, 3H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 5.64 (br s, 1H), 3.68 (s, 3H), 2.92-2.83 (br m, 1H), 2.76-2.68 (m, 1H), 2.62-2.54 (m, 1H), 2.42-2.33 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.9, 145.0, 133.9, 131.0, 129.1, 128.9, 128.5, 127.7, 127.6, 126.6, 126.2, 125.8, 125.4, 123.6, 122.1, 62.0, 51.9, 29.0, 28.8; IR (thin film, cm⁻¹) 2925, 2853, 1753, 1437, 1171, 778; HRMS (EI) calc'd for C₂₃H₁₉N₃O₂ 369.1477, found 369.1473.



Methyl 3-(3-(2,4-dimethoxyphenyl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (4-8d):

Reagents employed: 2-(2-((2,4-dimethoxyphenyl)ethynyl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid

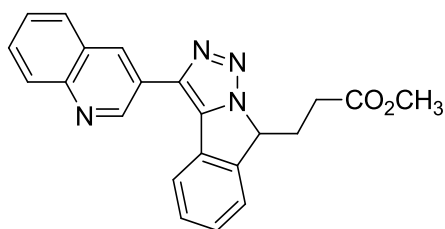
(**4-6d**) (0.021 g, 0.055 mmol), NaN₃ (0.005 g, 0.070 mmol), NH₄Cl (0.005 g, 0.080 mmol), 2-methoxyethanol/water: yield 73% (0.015 g, 0.040 mmol) as a clear oil; R_f = 0.10, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.78 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.67 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 5.55 (dd, *J* = 7.6, 4.1 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H), 2.87-2.77 (br m, 1H), 2.65-2.59 (m, 1H), 2.52-2.47 (m, 1H), 2.34-2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.0, 161.4, 157.4, 144.8, 139.1, 135.1, 131.2, 128.7, 127.7, 123.2, 113.3, 105.0, 98.6, 61.5, 55.5, 55.2, 51.8, 28.9, 28.7; IR (thin film, cm⁻¹): 3445, 3001, 2924, 2850, 1735, 1617, 1580, 1509, 1454, 1308, 1210, 1161, 1117, 1032; HRMS (EI) calc'd for C₂₁H₂₁N₃O₄ 379.1532, found 379.1527.



Methyl 3-(3-(2-nitrophenyl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (4-8e):

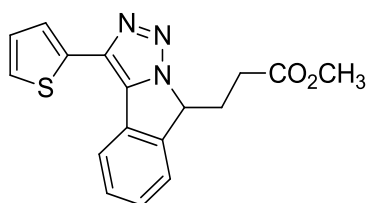
Reagents employed: 1-(methoxycarbonyl)-2-(2-((2-nitrophenyl)ethynyl)phenyl)cyclopropanecarboxylic acid

(**4-6e**) (0.068 g, 0.190 mmol), NaN₃ (0.015 g, 0.220 mmol), NH₄Cl (0.014 g, 0.260 mmol), 2-methoxyethanol/water: yield 61% (0.042 g, 0.115 mmol) as a clear oil; R_f = 0.12, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 8.08 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.0 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.44-7.38 (m, 3H), 5.60 (q, *J* = 7.0, 3.5 Hz, 1H), 3.65 (s, 3H), 2.84-2.78 (br m, 1H), 2.64-2.59 (m, 1H), 2.51-2.46 (m, 1H), 2.34-2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.9, 144.9, 133.0, 132.2, 129.4, 129.1, 128.9, 127.1, 124.9, 123.8, 121.5, 120.7, 119.6, 112.5, 62.1, 58.5, 29.7, 28.8, 28.6; IR (thin film, cm⁻¹) 2922, 2851, 1735, 1529, 1438, 1361, 754; HRMS (EI) calc'd for C₁₉H₁₆N₄O₄ 364.1172, found 364.1166.



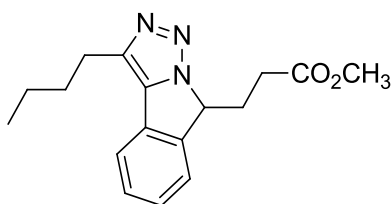
Methyl 3-(3-(quinolin-3-yl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (4-8f): Reagents used: 1-(methoxycarbonyl)-2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropanecarboxylic acid (**4-6f**) (0.027 g, 0.073 mmol), NaN₃ (0.006 g, 0.087 mmol),

NH₄Cl (0.006 g, 0.100 mmol), 2-methoxyethanol/water: yield 30% (0.008 g, 0.022 mmol) as a clear oil; R_f = 0.07, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 9.52 (br s, 1H), 8.76 (br s, 1H), 8.20 (br d, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H) 7.52 (t, *J* = 7.4 Hz, 2H), 5.66 (dd, *J* = 7.4, 3.9 Hz, 1H), 3.68 (s, 3H), 2.89-2.81 (br m, 1H), 2.70-2.62 (m, 1H), 2.56-2.48 (m, 1H), 2.38-2.31 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.8, 149.2, 147.7, 145.1, 138.8, 136.3, 133.3, 129.8, 129.4, 129.3, 129.0, 128.1, 128.0, 127.3, 127.2, 124.6, 124.1, 121.3, 62.0, 51.9, 28.9, 28.6; IR (thin film, cm⁻¹) 3361, 2924, 2853, 2362, 1734, 1594, 1419, 1375, 1123, 1043; HRMS (EI) calc'd for C₂₂H₁₈N₄O₂ 370.1430, found 370.1443.



Methyl 3-(3-(thiophen-2-yl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (4-8g): Reagents employed: 1-(methoxycarbonyl)-2-(2-(thiophen-2-ylethynyl)phenyl)cyclopropanecarboxylic acid (**4-6g**)

(0.035 g, 0.110 mmol), NaN₃ (0.009 g, 0.130 mmol), NH₄Cl (0.008 g, 0.150 mmol), 2-methoxyethanol/water: yield 39% (0.014 g, 0.043 mmol) as a clear oil; R_f = 0.22, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 8.03 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 2.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.47-7.43 (m, 1H), 7.41 (d, *J* = 4.1 Hz, 1H), 7.20-7.18 (m, 1H), 5.58 (dd, *J* = 5.3, 3.5 Hz, 1H), 3.65 (s, 3H), 2.83-2.78 (br m, 1H), 2.62-2.56 (m, 1H), 2.48-2.43 (m, 1H), 2.33-2.29 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.8, 144.8, 137.2, 133.9, 133.2, 129.1, 128.6, 127.8, 127.2, 125.3, 125.1, 123.8, 121.6, 61.9, 51.8, 28.9, 28.5; IR (thin film, cm⁻¹) 3421, 2918, 2849, 2361, 2336, 1735, 1458, 1084; HRMS (EI) calc'd for C₁₇H₁₅N₃O₂S 325.0885 found 325.0877.



Methyl 3-(3-butyl-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (4-8h): Reagents employed:

2-(2-(hex-1-yn-1-yl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (**4-6h**) (0.027 g, 0.089 mmol), NaN₃ (0.007 g, 0.108 mmol), NH₄Cl (0.008 g, 0.151 mmol), 2-methoxyethanol/water: yield 53% (0.014 g, 0.047 mmol) as a clear oil; R_f = 0.17, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 7.60 (d, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 7.8, 7.4 Hz, 2H), 7.38 (dd, *J* = 7.8, 7.0 Hz, 1H), 5.48 (dd, *J* = 7.4, 4.3 Hz, 1H), 3.64 (s, 3H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.80-2.71 (m, 1H), 2.58-2.50 (m, 1H), 2.46-2.38 (m, 1H), 2.29-2.20 (m, 1H), 1.83-1.76 (m, 1H), 1.49-1.40 (m, 1H), 0.97 (t, *J* = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 163.3, 154.7, 129.0, 127.8, 123.8, 120.8, 93.2, 61.7, 51.8, 31.7, 28.9, 28.5, 25.6, 22.4, 13.9; IR (thin film, cm⁻¹) 2954, 2925, 2854, 1737, 1457, 1437, 1378, 1170, 767; HRMS (EI) calcd for C₁₇H₂₁N₃O₂ was 299.1634, found 299.1632.

4.5 Chapter Four References

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- (2) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem.* **2012**, *77*, 6634.
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- (12) Gao, K.; Wu, J. *Org. Lett.* **2008**, *10*, 2251.
- (13) a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.(b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.(c) Pietruszka, J.; Witt, A.; *Synthesis* **2006**, *24*, 4266.
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5 Summary of Thesis

This body of work explored some of the potential uses of DA cyclopropanes in organic synthesis. Today, there are numerous reviews¹ on various aspects of cyclopropanes, and continued research should be done on these DA cyclopropanes, as they continue to succeed in organic synthesis in a wide variety of reactions.

Although the actual DA cyclopropanes investigated throughout this body of work were not the same substrate for each investigation, all DA cyclopropanes used served the same purpose; that is to determine the vast scope of reactions that DA cyclopropanes can be applied too. Firstly, the Overman rearrangement was done using an acetimidate DA cyclopropane, and although this reaction saw some success, it was not enough to make it a candidate for further exploration into this rearrangement.

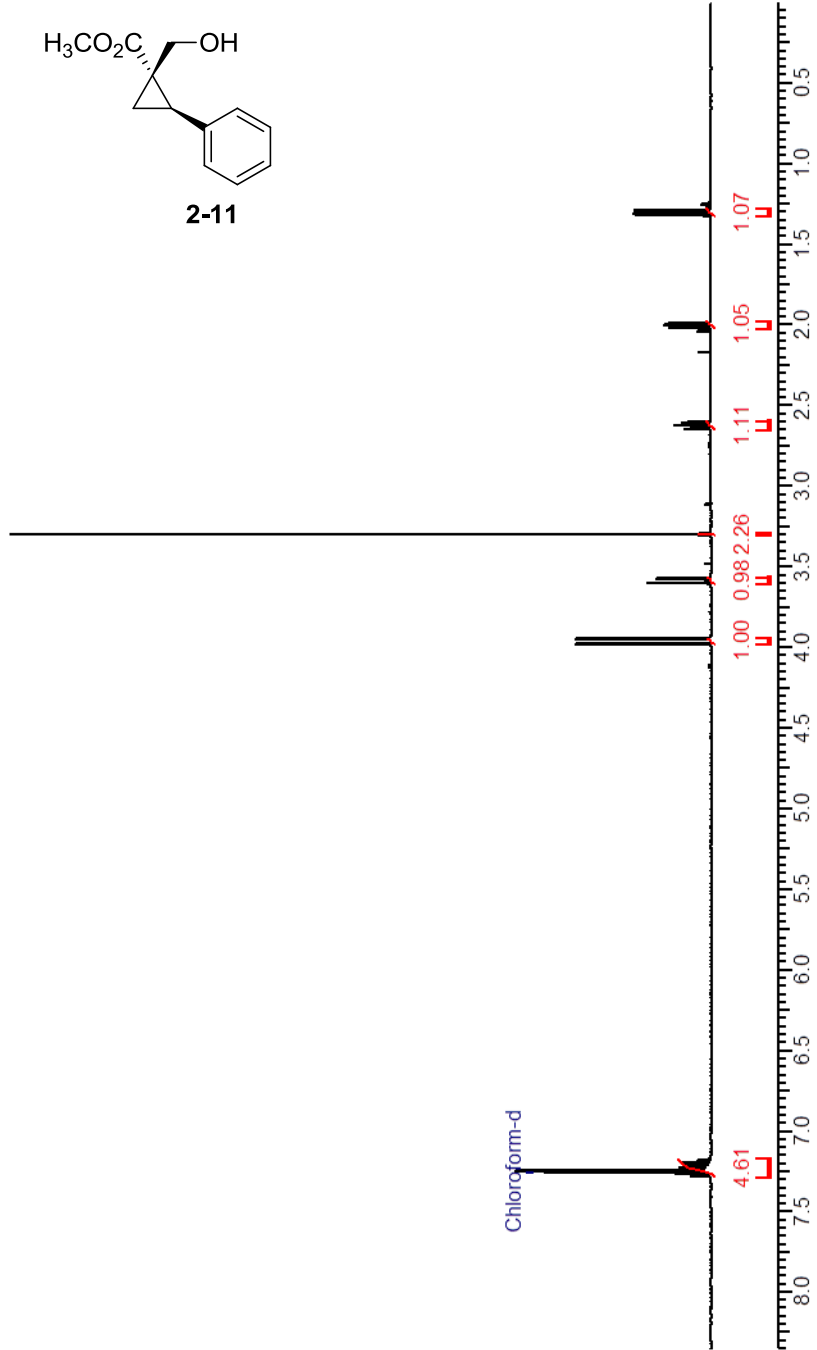
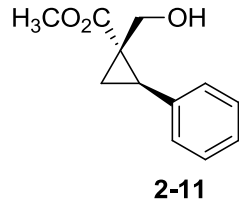
The following two projects described in this thesis employed the use of an acetylene bearing DA cyclopropane. This cyclopropane was initially investigated in the annulation and Conia-ene reactions. This unique DA cyclopropane had the ability to react via nucleophilic ring-opening as well as undergo further intramolecular reactions to form the annulation and Conia-ene products. The success from these two projects could be further explored with exploration of different substrates as nucleophiles; however for this body of work these reactions were no longer explored.

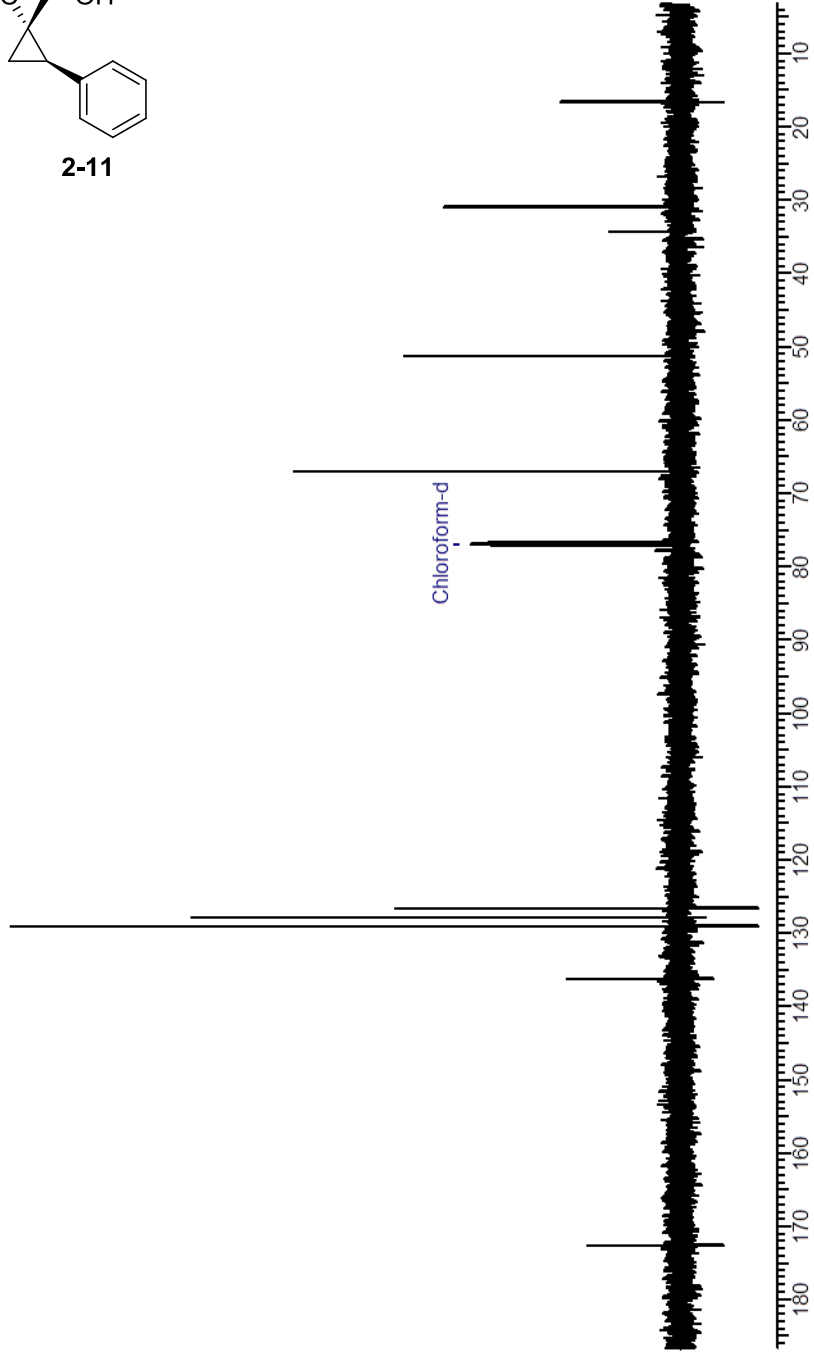
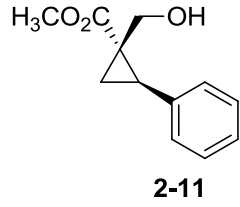
Finally, using the acetylene bearing DA cyclopropane, success came in the form of 1,2,3-triazole compounds.² This project required the synthesis of the hemimalonate cyclopropanes, and it allowed for the success of the three transformations in one-pot with the use of no metal-catalysts. These newly formed linearly fused tricyclic triazoles could potentially be biologically active, and the synthetic handle containing the ester functionality could be functionalized to a variety of amino acids, peptides, proteins and possibly DNA.² This multi-step reaction sequence provided excellent proof to the chemistry community how valuable and versatile DA cyclopropanes really are.

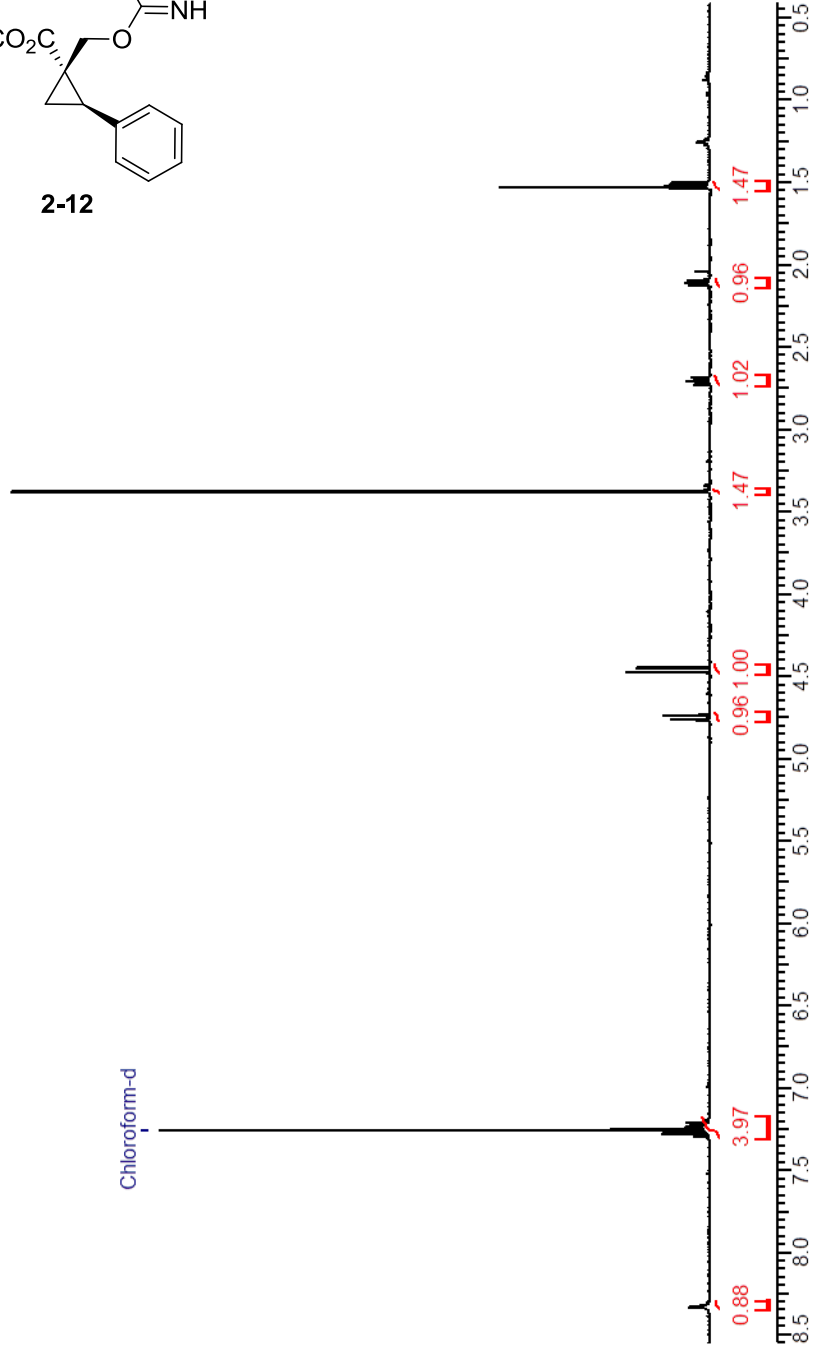
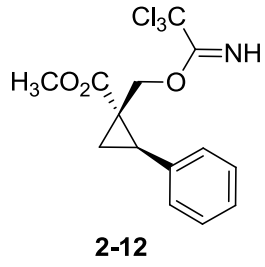
5.1 Chapter Five References

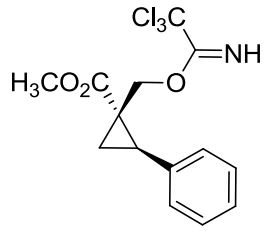
- (1) For reviews on donor-acceptor cyclopropanes, see: (a) Cavitt, M.A.; Phun, L.H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (b) Schneider, T.F.; Kaschel, J.; Werz, D.B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. (c) Lebold, T.P.; Kerr, M.A. *Pure Appl. Chem.*, **2010**, *82*,1797. (d) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (e) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (f) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (g) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (h) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.
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- (3) For information on triazoles, see: (a) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. **2007**, *28*, 278. (b) Singh, H.; Sindhu, J.; Khurana, J.M; *Sensor Actuat B-Chem* **2014**, 192 536 (c)Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905.

Appendix 1: ^1H and ^{13}C NMR Spectra for Chapter 2

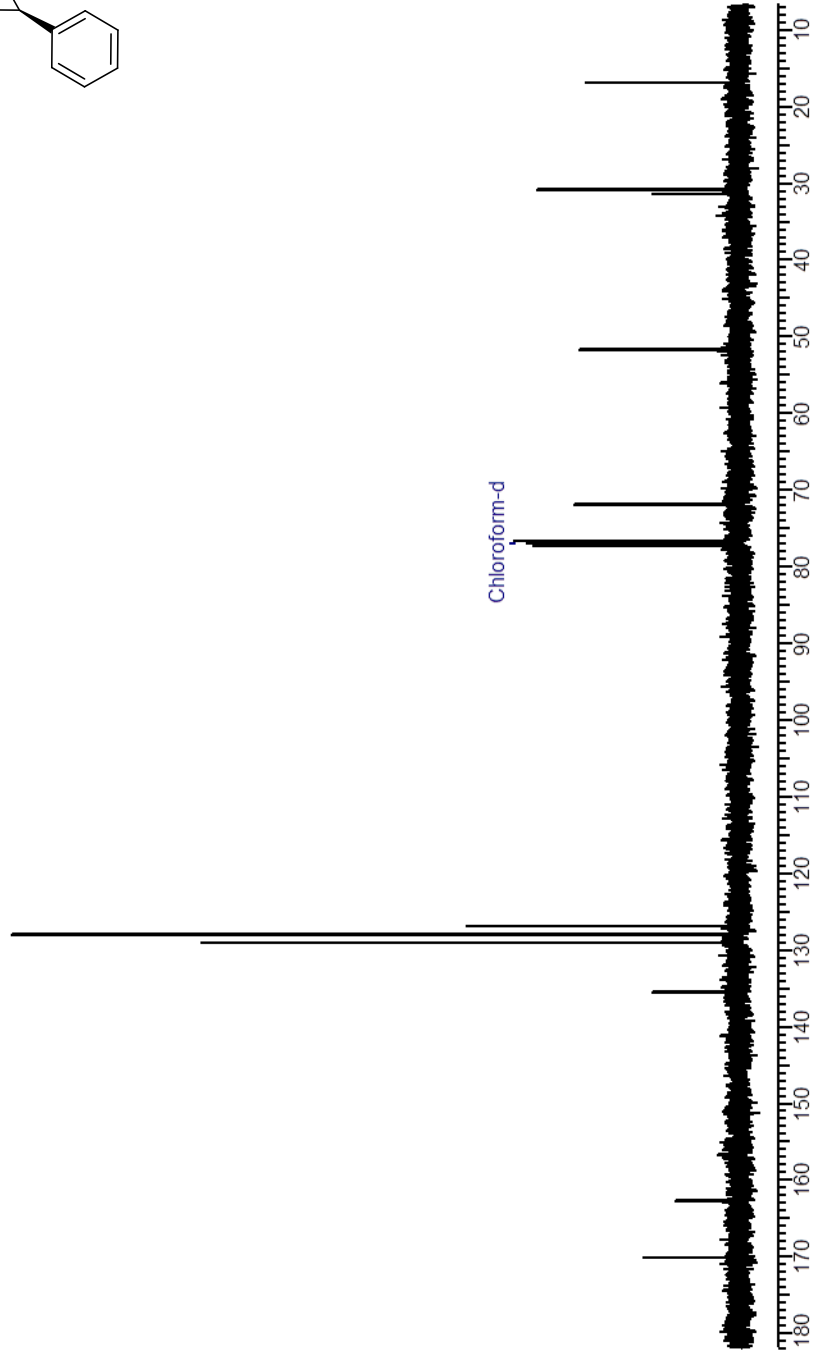


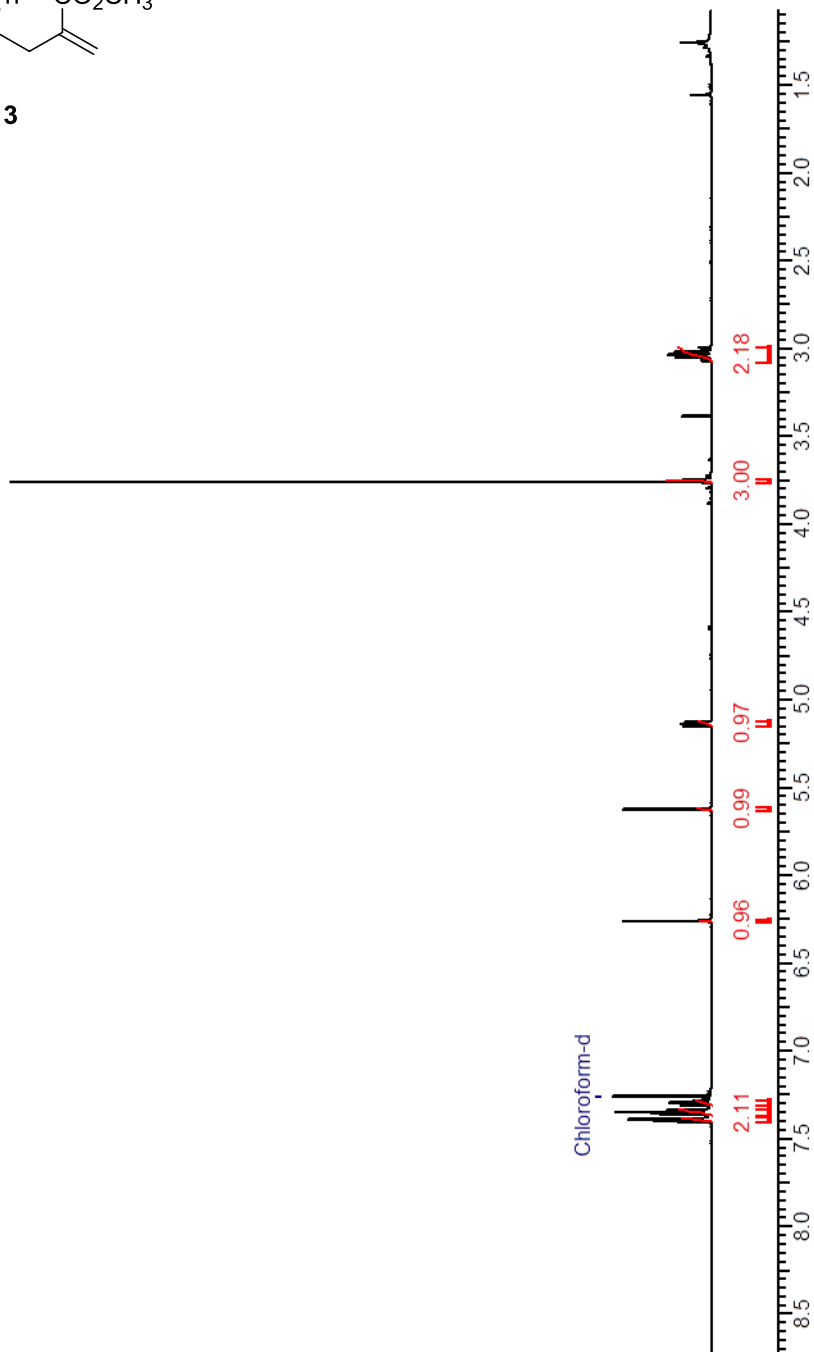
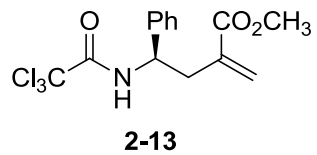


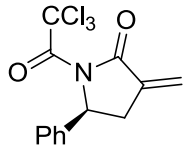




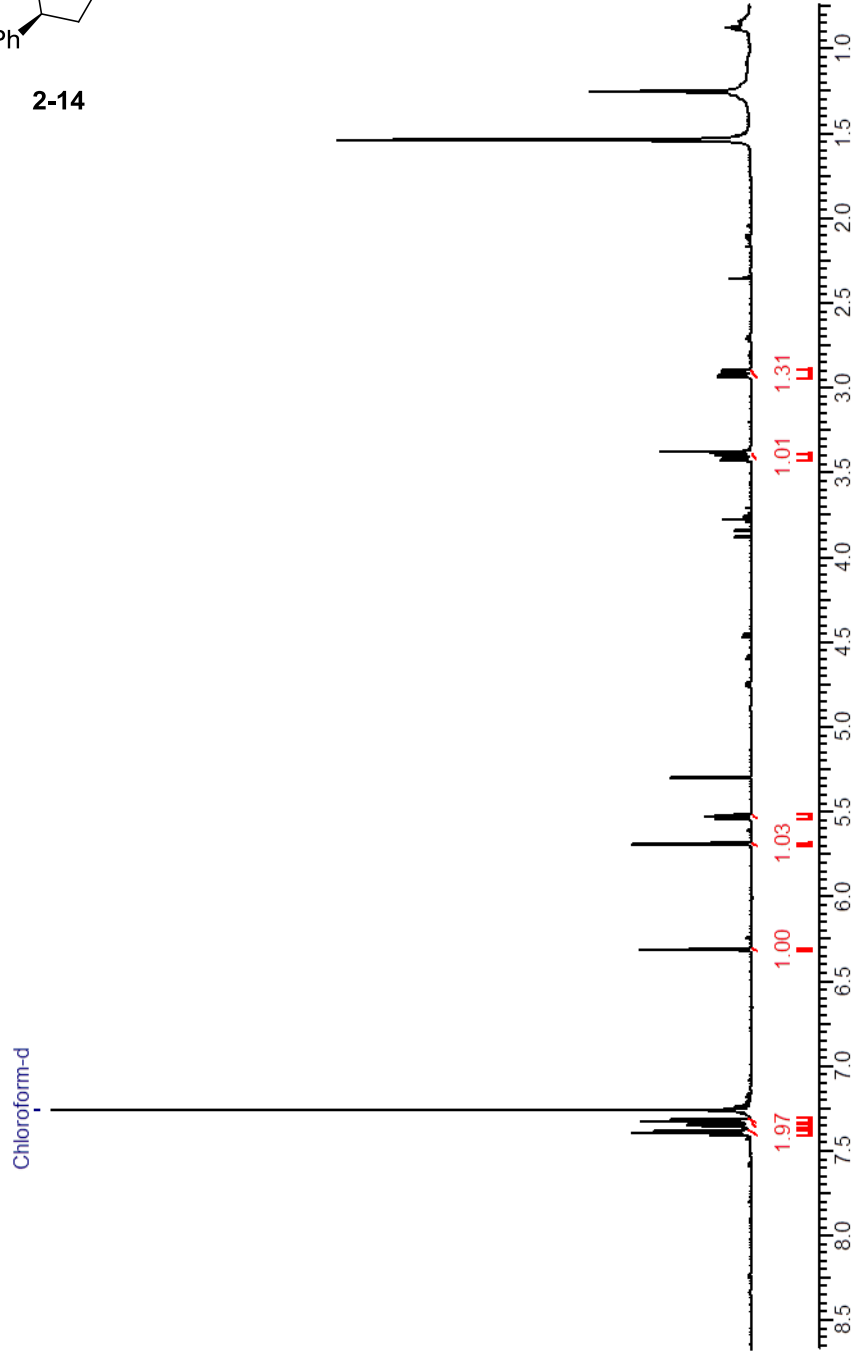
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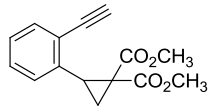




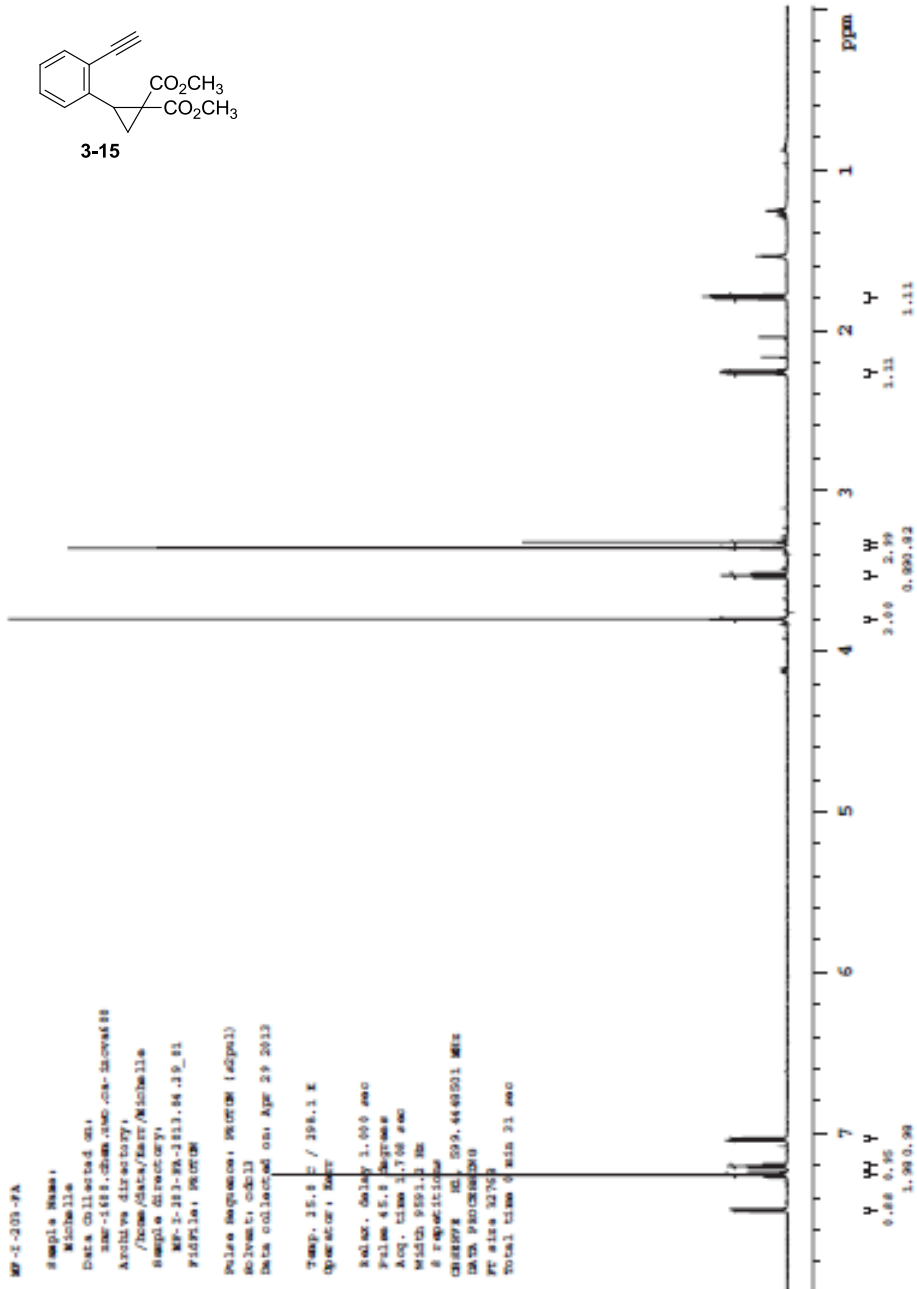
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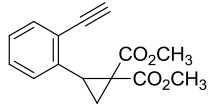
Appendix 2: ^1H and ^{13}C NMR Spectra for Chapter 3



3-15

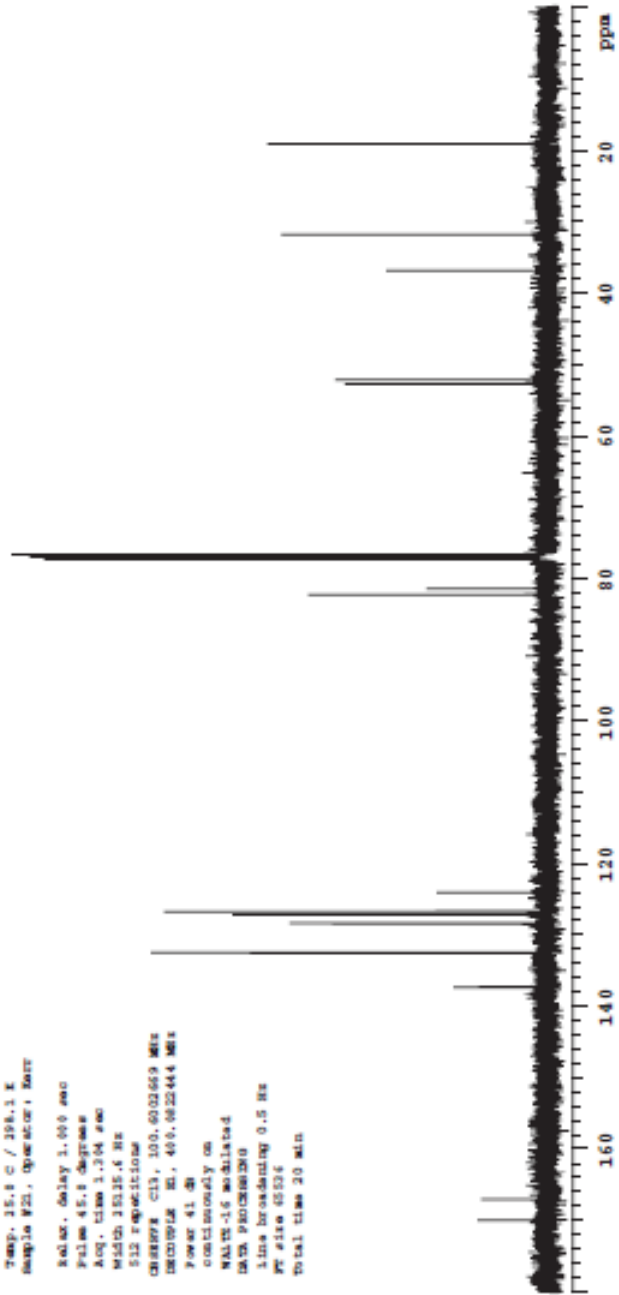


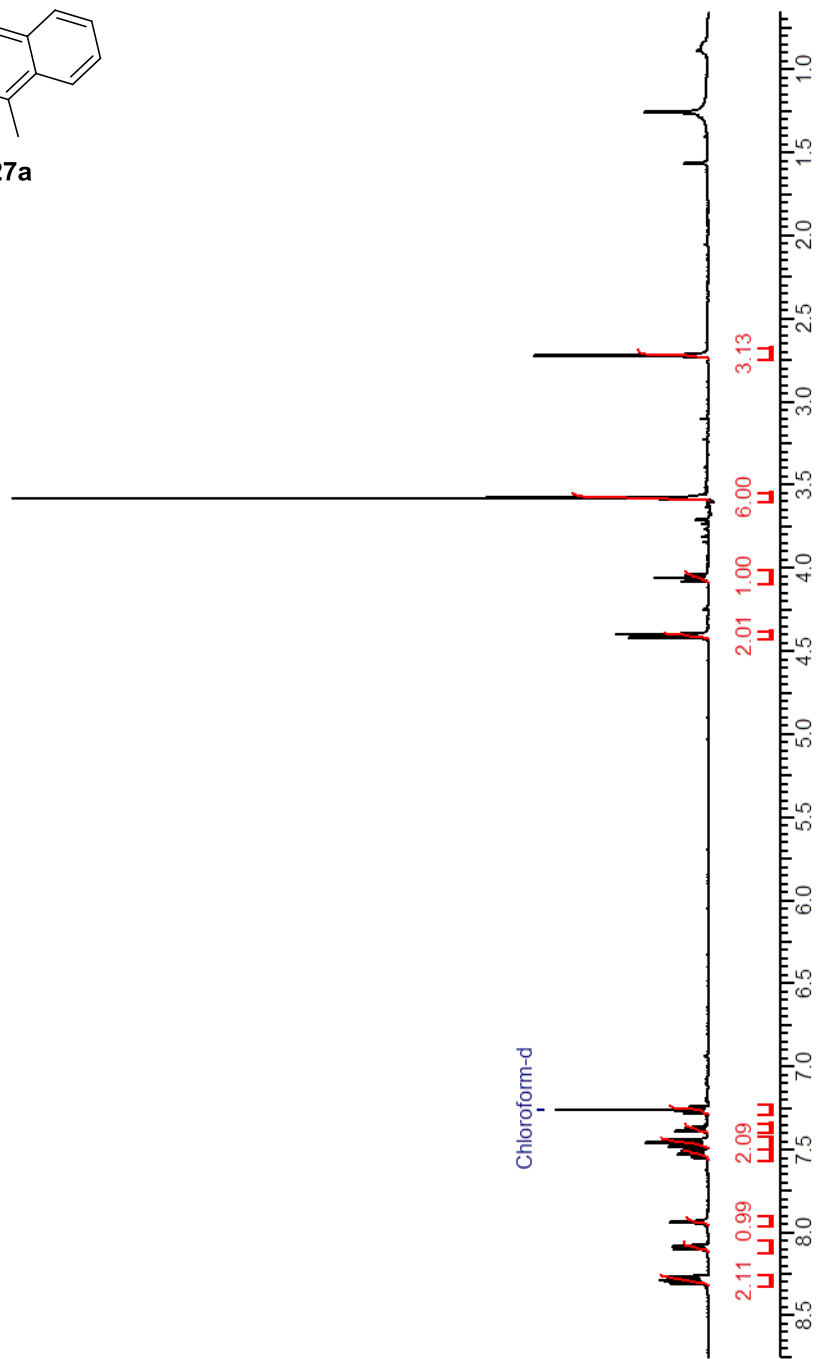
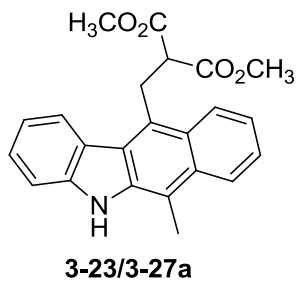
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 /home/data/karr/Michelle
 Sample directory:
 MF-5-203-FA-2013.04.19_01
 File(s): PLOT08
 Pulse Sequence: PLOT08 (adp01)
 solvent: cdcl3
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 Temp: 25.2 C / 398.1 K
 Operator: karr
 Solar Delay: 1.000 sec
 Pulse: 45.8 degrees
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 # repetitions:
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 PE size: 32768
 Total time: 0 min 31 sec

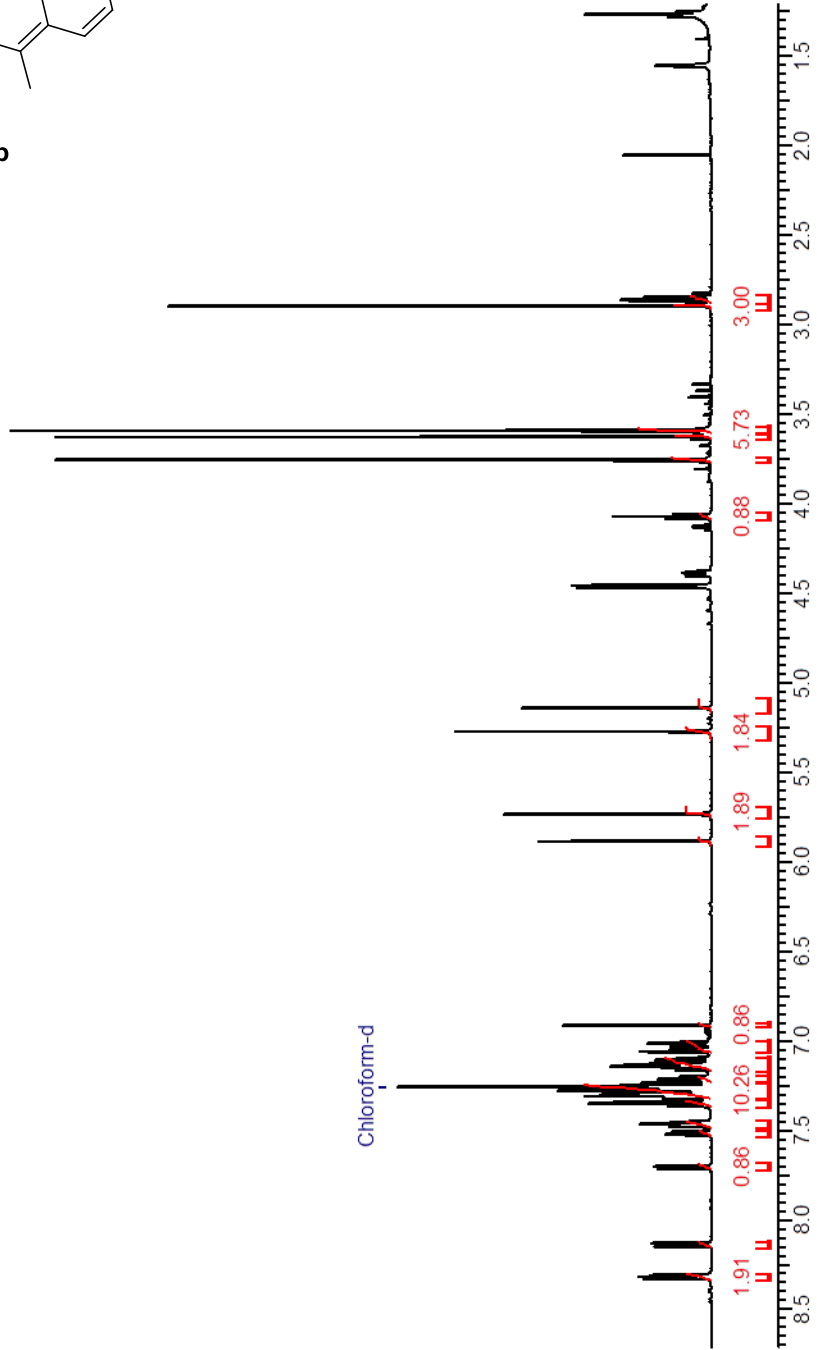
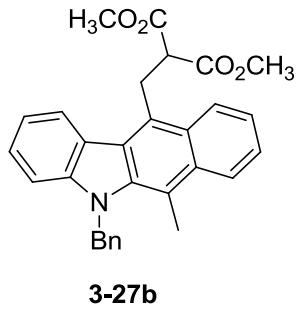


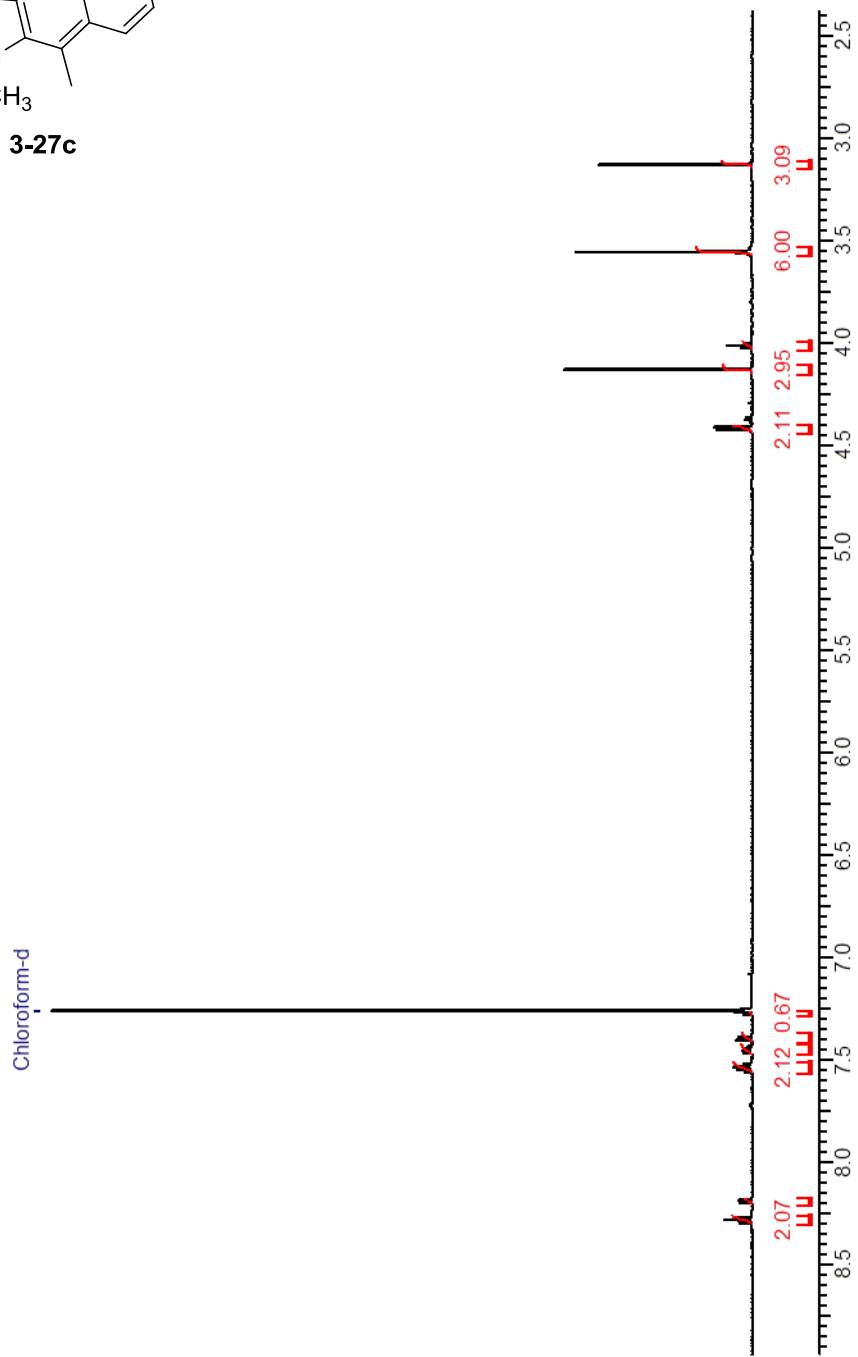
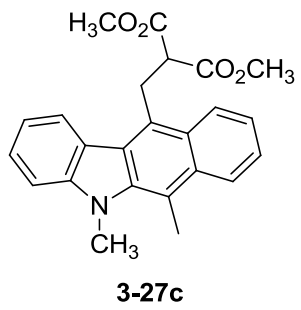
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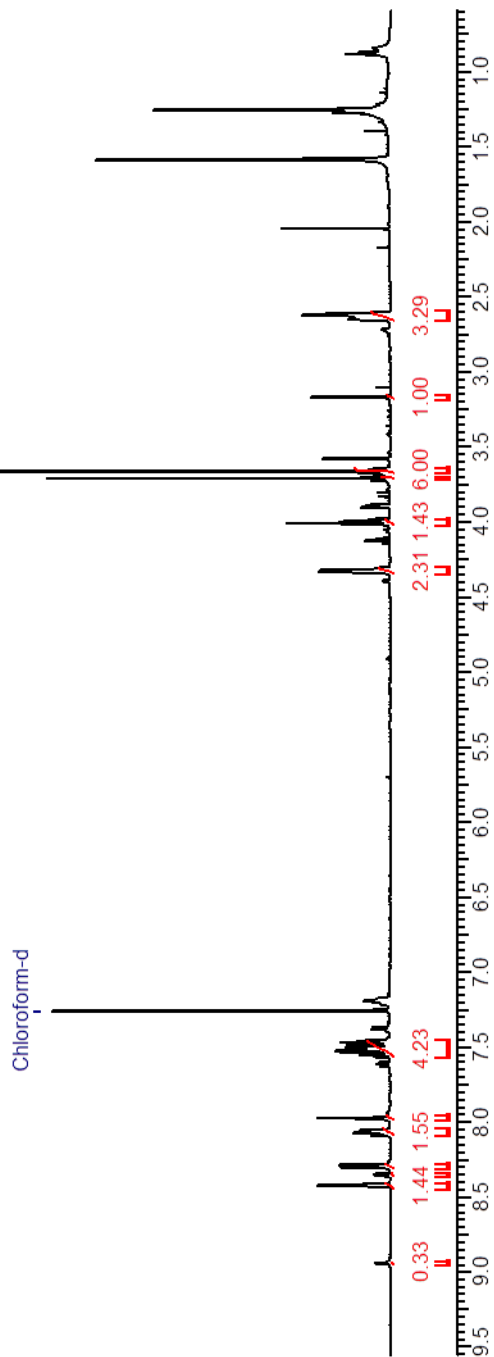
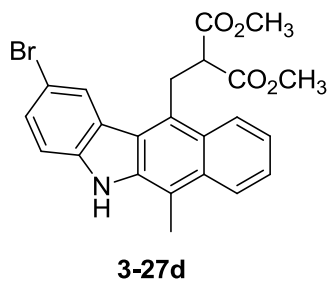
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 /home/dsfs/memo/Michelle
 Sample directory:
 KP-3-AUCY08-C13-2014.03.18_01
 File(s): CH0008
 Pulse sequence: CH0008 (40ppm)
 Solvent: cdcl3
 Data collected on: Mar 18 2014
 Temp: 35.8 C / 96.4 F
 Sample #21, Operator: Mary
 Relax. Delay: 1.000 sec
 Pulse: 45.8 degrees
 Acq. time: 1.204 sec
 Width: 25325.6 Hz
 S12 repetitions:
 CHANNEL: C13, 100.625659 MHz
 DECOUPLE: H1, 499.022444 MHz
 Power: 41 dB
 continuously on
 NMR3-15: modulated
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 Line broadening: 0.5 Hz
 FT size: 65536
 Total time: 20 min

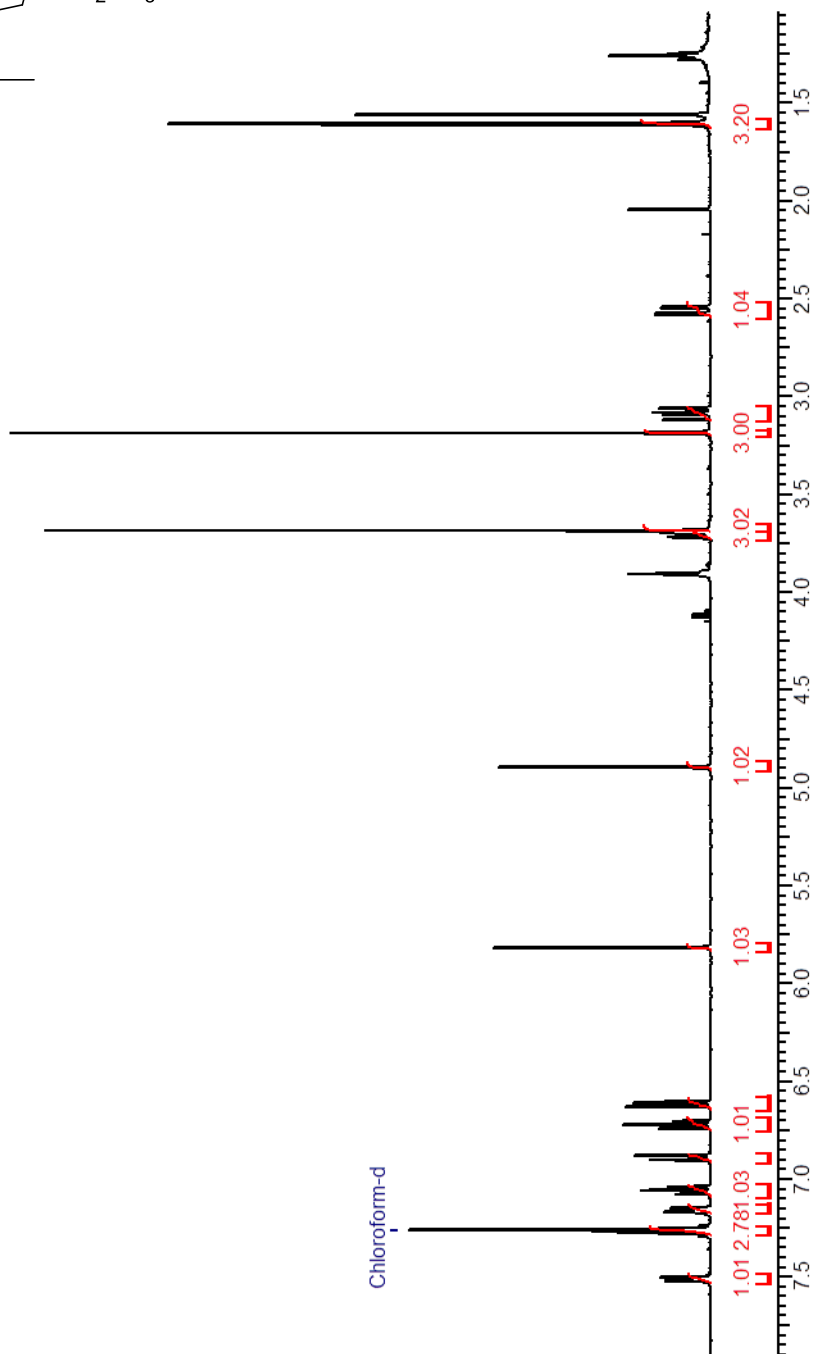
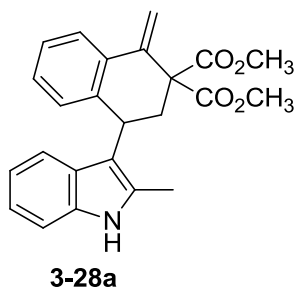


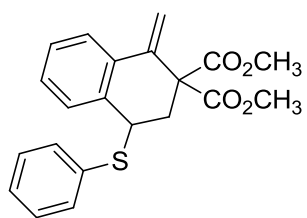




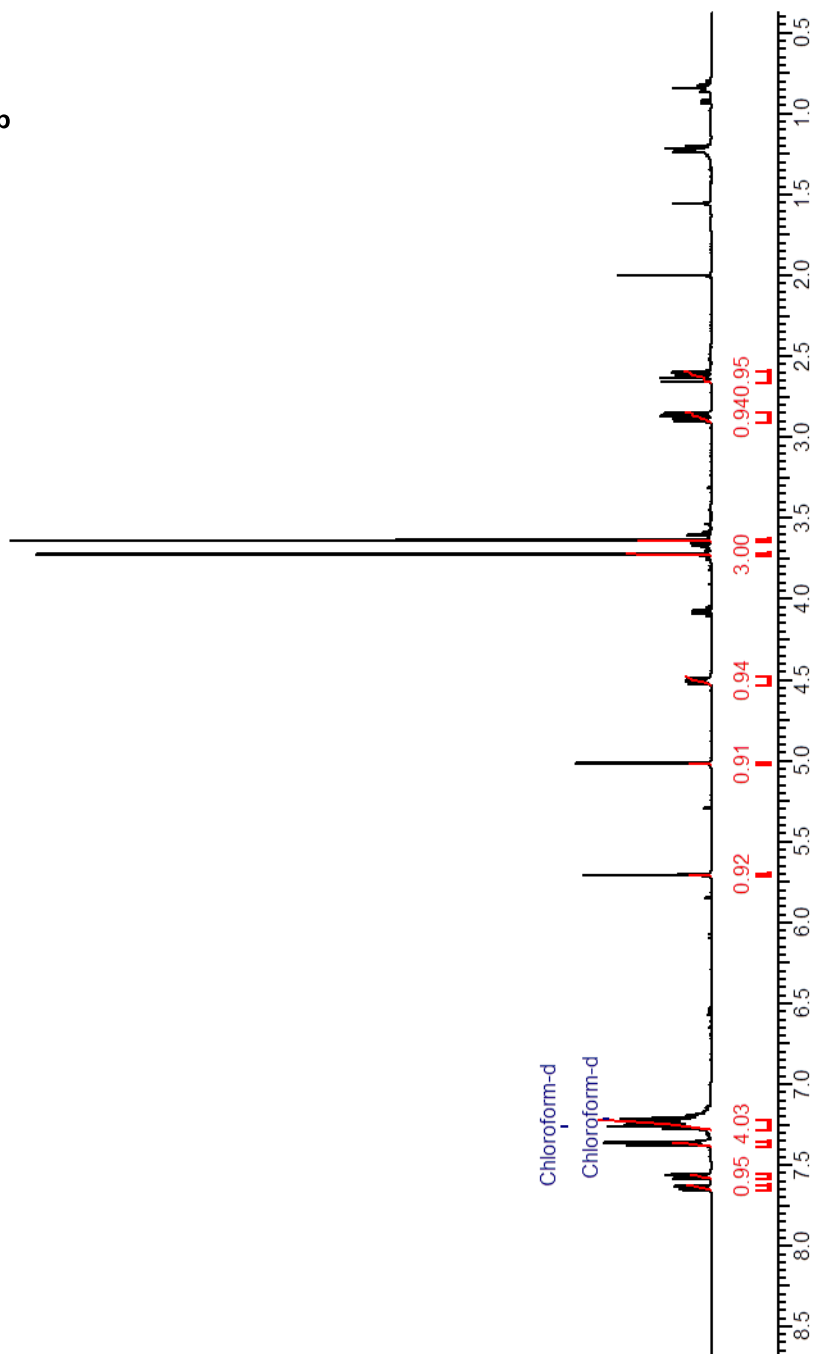




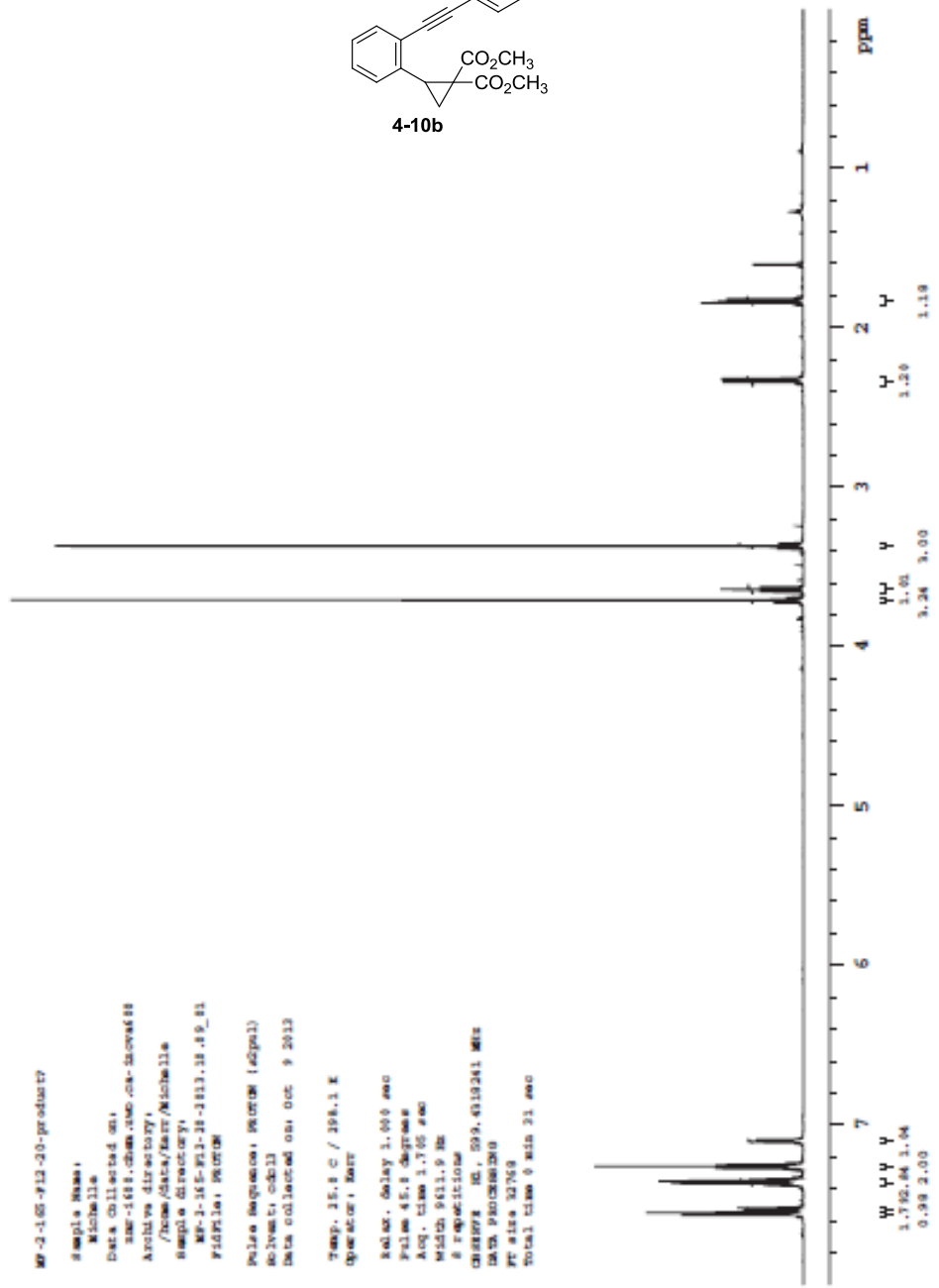
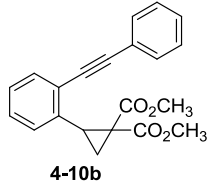




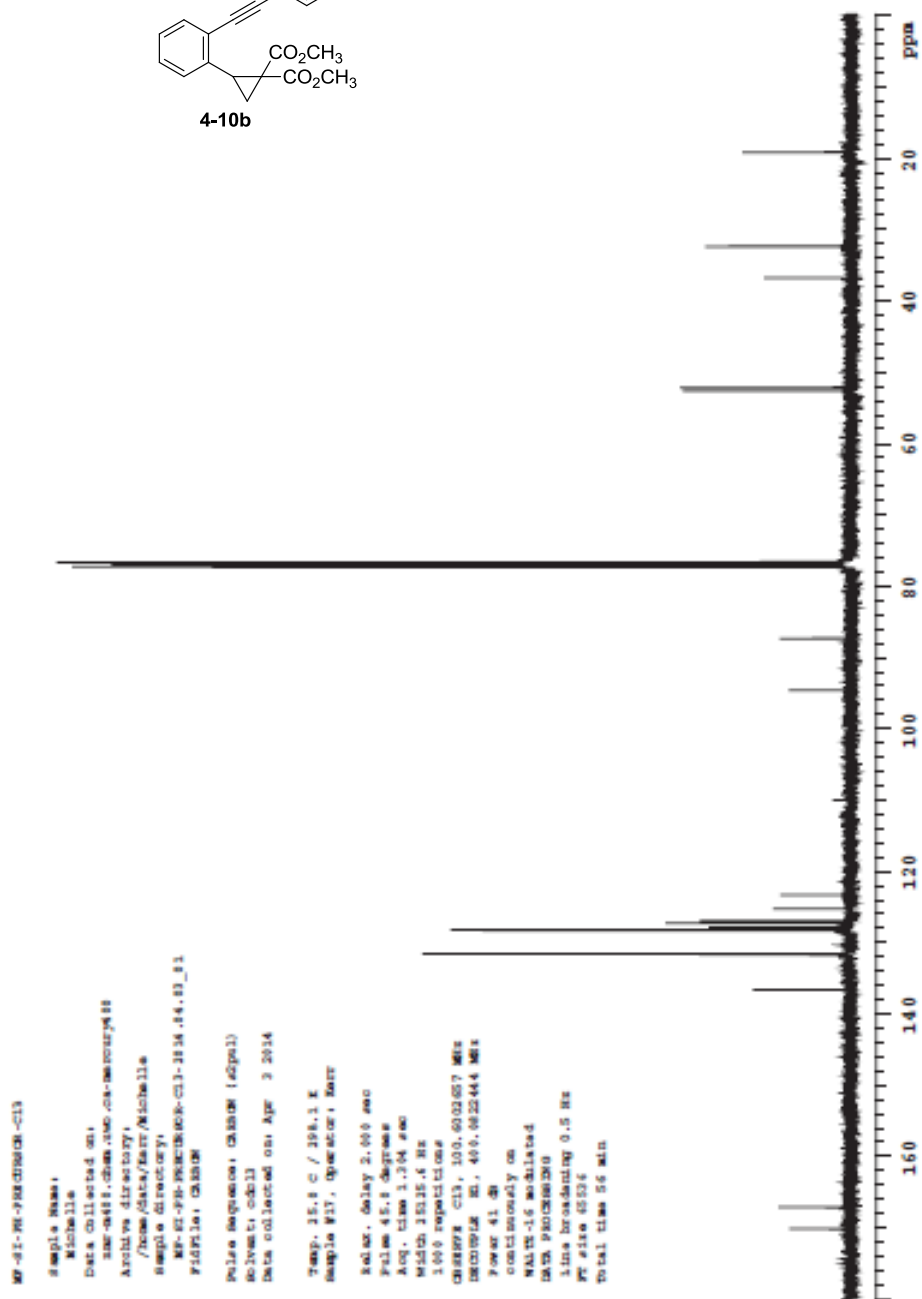
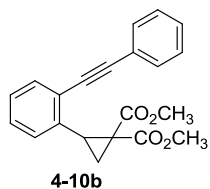
3-28b

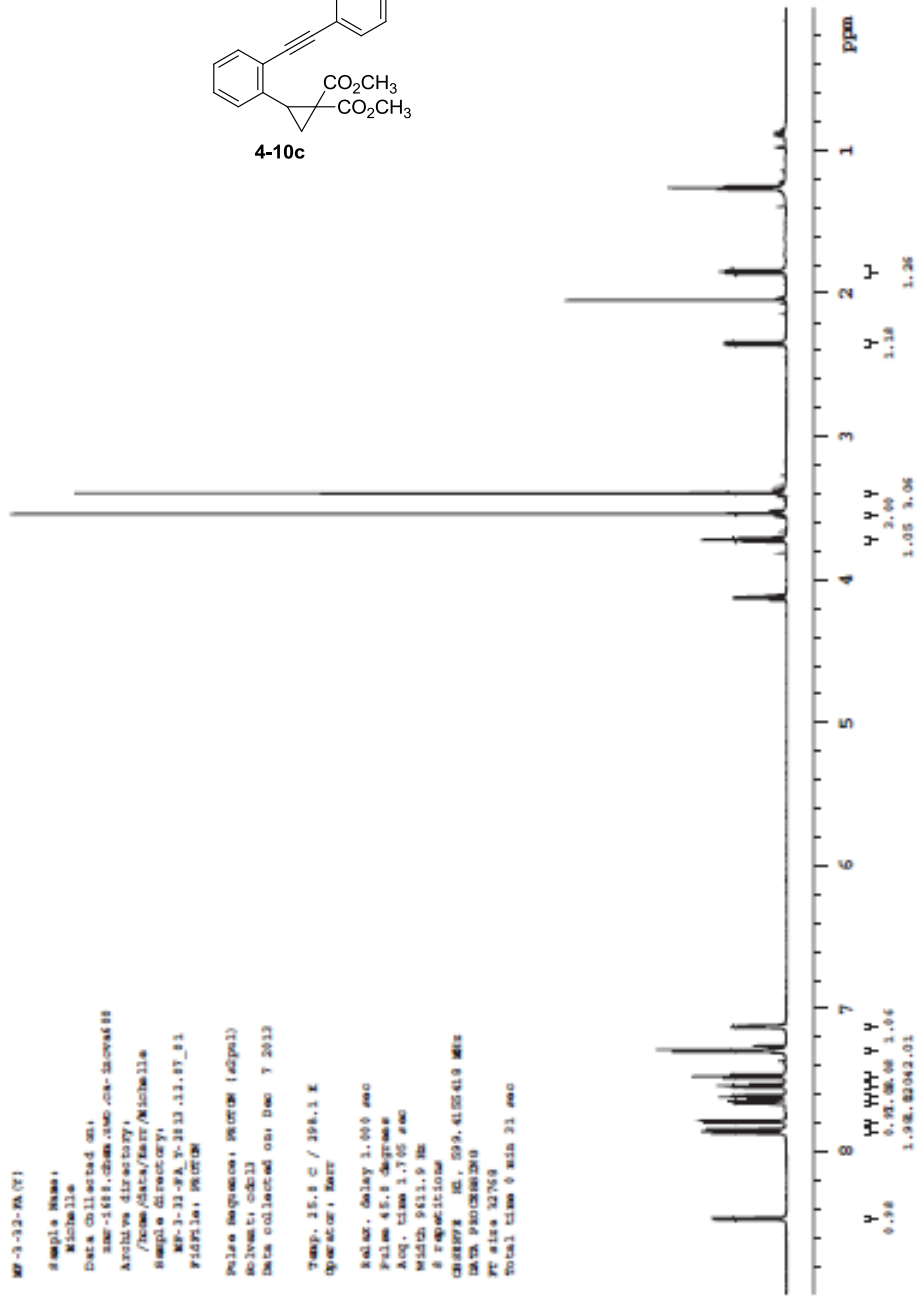
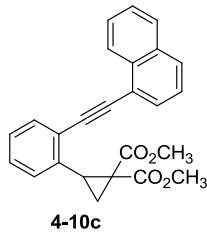


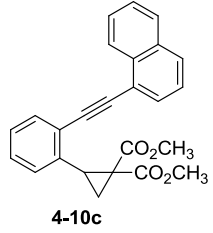
Appendix 3: ^1H and ^{13}C NMR Spectra for Chapter 4



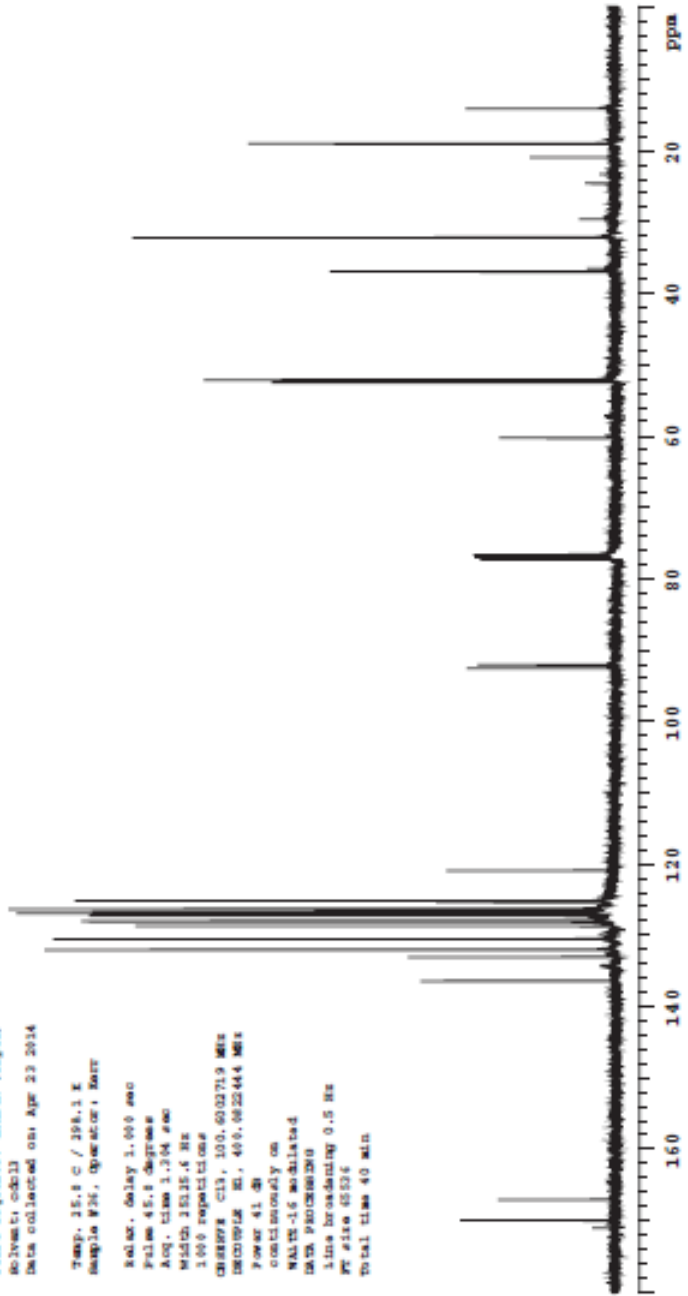
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 Sample directory:
 00-2-165-913-20-2013.18.89_81
 File(s): 00000
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 Solvent: cdcl3
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 Temp.: 35.8 C / 396.1 K
 Operator: Marr
 Relax. delay: 3.000 sec
 Pulse: 45.8 degrees
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 DATA PROCESSING
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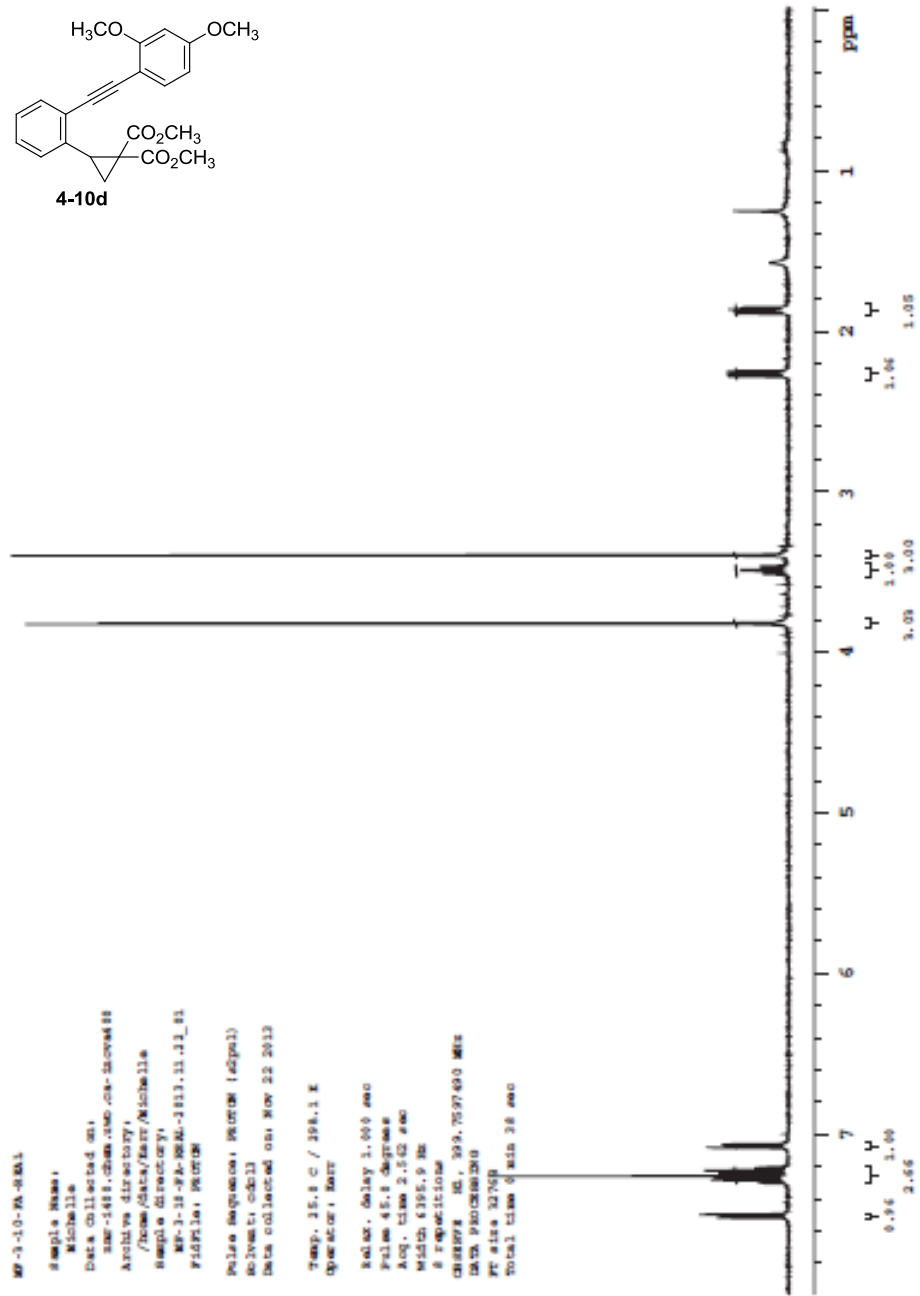
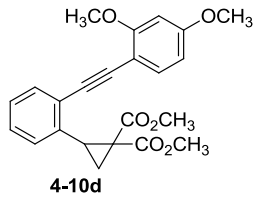






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 Sample directory:
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 File(s): CH30M
 Pulse sequence: CH30M (c2pr1)
 Solvent: cdcl3
 Data collected on: Apr 23 2014
 Temp: 35.8 C / 96.4 F
 Sample Wt: Operator: Karr
 Relax. Delay: 1.000 sec
 Pulse: Galay 1.000 sec
 Pulse: 45.8 degrees
 Acq. time: 1.204 sec
 Width: 15335.6 Hz
 1000 repetitions
 Channels: CH3, 100.625719 MHz
 DECOUPLE: RL, 400.002544 MHz
 Power: 41 dB
 conditionally on
 WALTZ-16 modulated
 DATA PROCBIND0
 Line broadening: 0.5 Hz
 FT size: 65536
 Total time: 40 min





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 Data Collected on: 10/14/11 08:00:00
 Archive directory: /home/data/terr/Michelle
 Sample directory: MF-3-10-FA-00A1-11.11.11_01
 File(s): 000001

Pulse Sequence: 000001 (40001)
 Solvent: 0013
 Data collected on: Nov 22 2013

Temp: 35.0 C / 295.1 K
 Operator: terr

Retard. Delay: 1.00 sec
 Pulse: 45.8 degrees
 Acq. time: 2.50 sec
 Width: 6395.9 Hz
 # repetitions: 8
 Channel ID: 309.7577400 MHz
 Data: 000000000
 File size: 31750
 Total time: 0 min 26 sec

MF-4-Dimethoxy-Precurser

Sample Name:
Michelle

Data collected on:
sat-0811.dms.ncb.ca-mcoursy488
Archive directory:
/New/Data/Bar/Michelle
Sample directory:
MF-4-Dimethoxy-Precurser-2014-04-21_91
FIDFILE: CH3OH

Pulse sequence: CH3OH (409ul)

solvent: cdcl3

Data collected on: Apr 21 2014

Temp: 25.8 C / 798.1 K

Sample P5, Operator: Kerr

Solvent delay 1.00 sec

Pulse 45.8 degree

Acq. time 1.264 sec

MSD00 15335.6 Hz

512 repetitions

CH3OH: ch3, 100.602643 MHz

DECOUPLE: H1, 400.0822444 MHz

Power 41 dB

continuously on

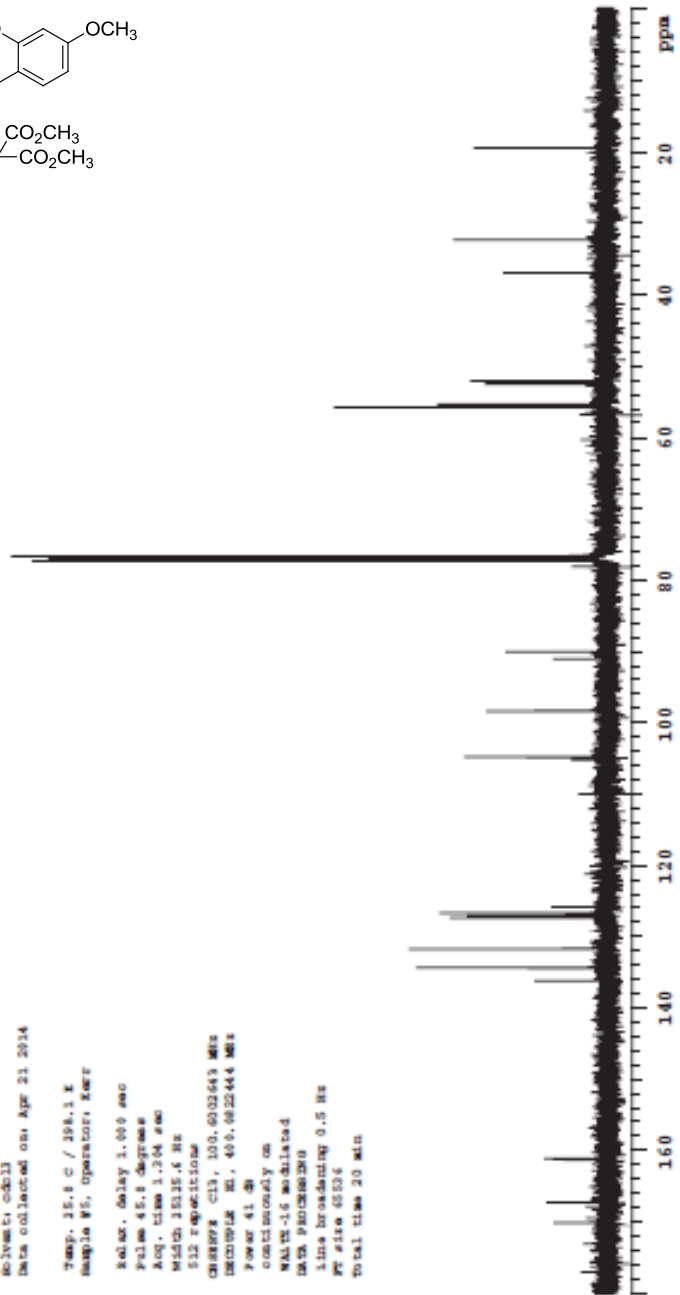
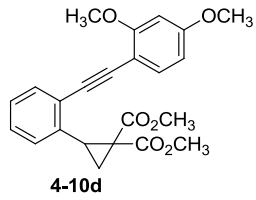
WALTZ-16 modulated

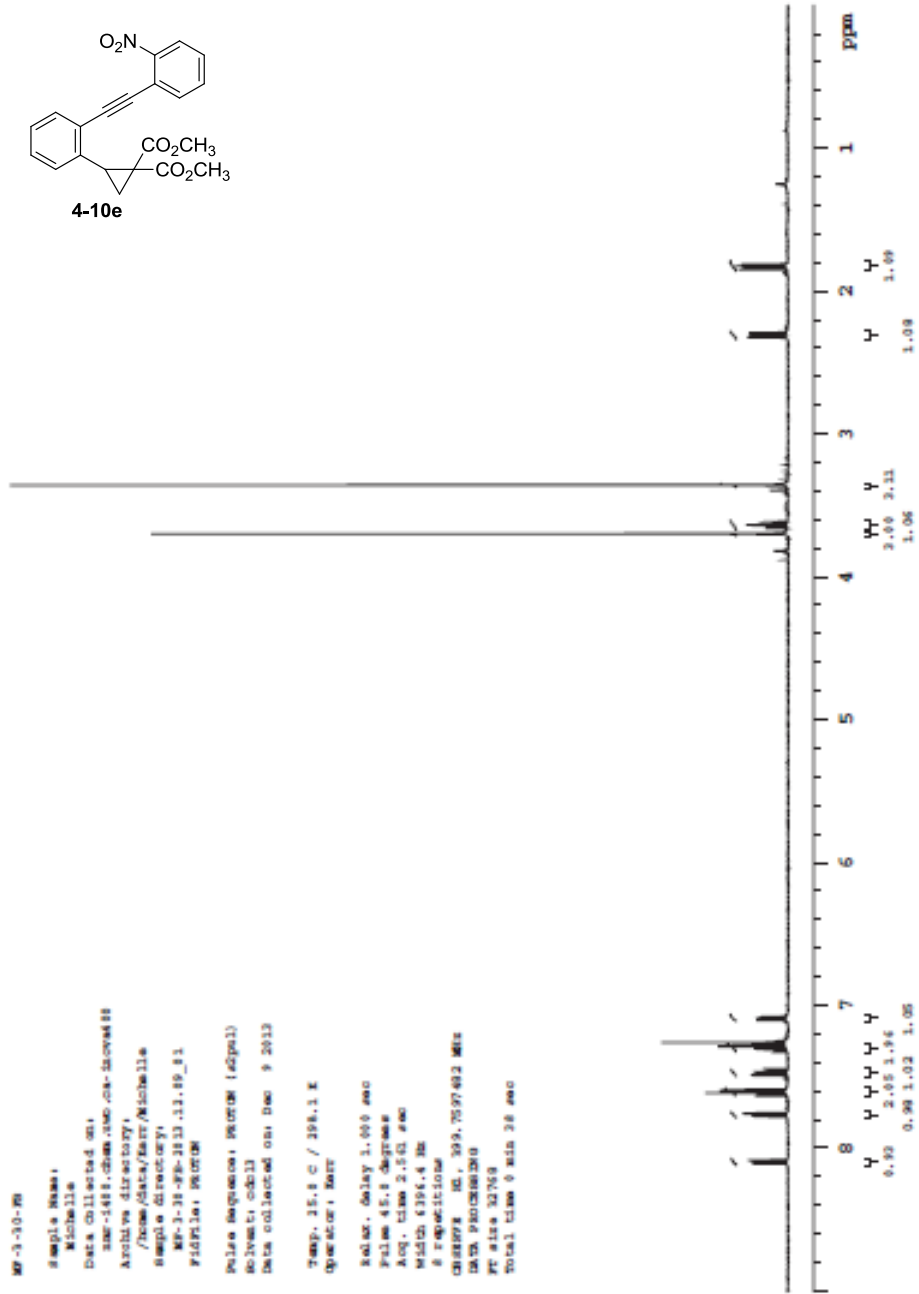
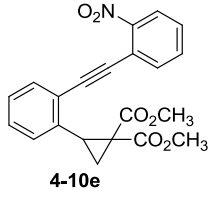
DATA F80C080200

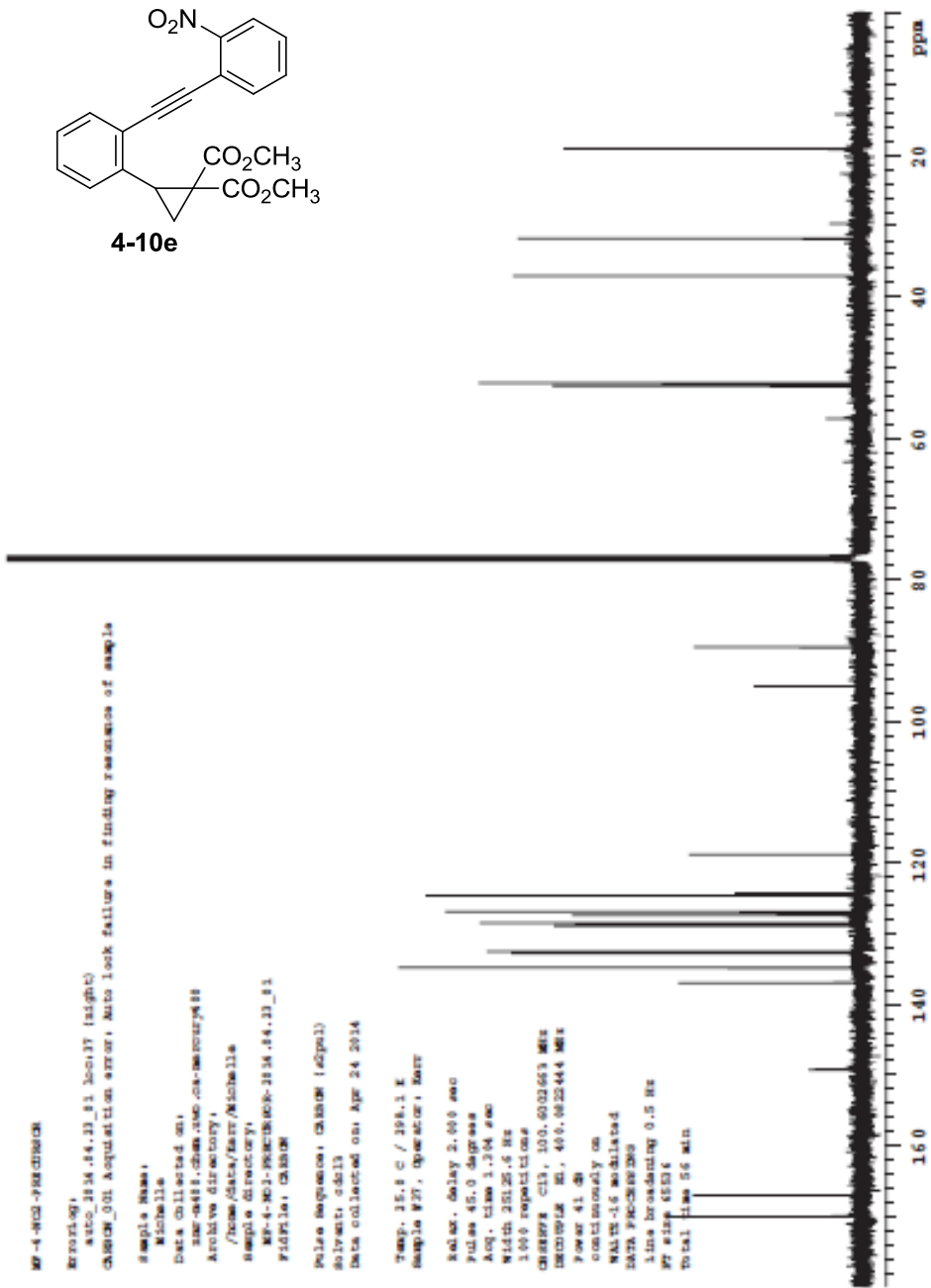
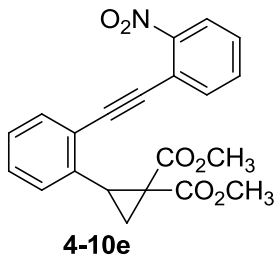
line broadening 0.5 Hz

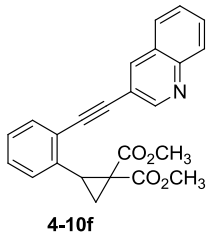
RF size 65936

Total time 20 min

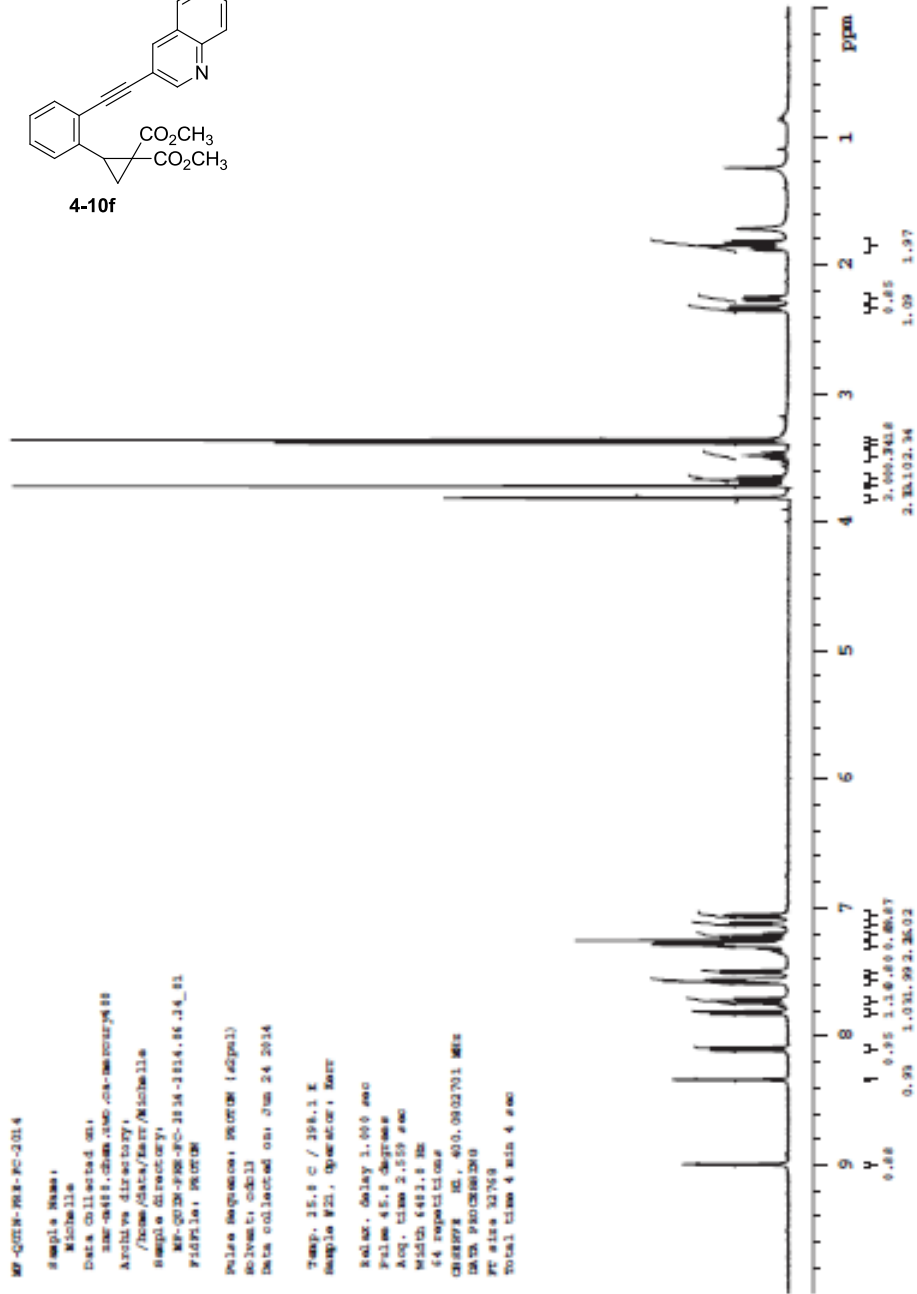


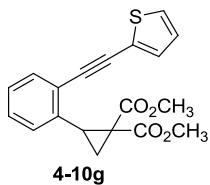




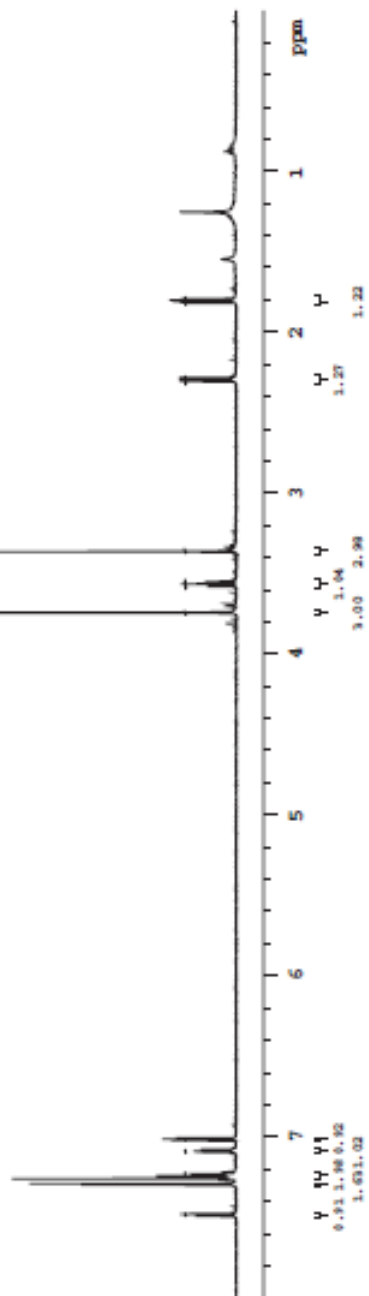


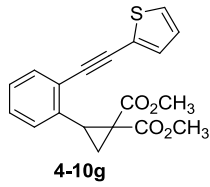
MF-Q02N-F08-PC-2014
 Sample Name: Michelle
 Data collected on: 2014-08-11 10:48:11
 Archive directory: /home/Data/Karr/Michelle
 Sample directory: MF-Q02N-F08-PC-2014-2014-08-11_01
 FID011a: 060208
 Pulse sequence: 060208 (62pm1)
 solvent: cdcl3
 Data collected on: 08/24/2014
 Temp: 35.0 C / 196.0 K
 Sample #20, Operator: Karr
 Relax. delay 3.000 sec
 Pulse 45.0 degrees
 Acq. time 2.559 sec
 Width 4492.0 Hz
 64 repetitions
 060208_00_400_0902701.MS
 Data: 0602080200
 File size 32760
 Total time 4 min 4 sec





MF-3-06-20
 Sample Name: Michelle
 Data collected on: 2012-11-13 13:16:51
 Archive directory: /home/data/farr/Michelle
 Sample directory: MF-3-06-20-11-13-16_51
 File(s): PR0706
 Pulse Sequence: PR0706 (a2ppl)
 Solvent: cdcl3
 Data collected on: Dec 6 2012
 Temp: 25.1 C / 78.1 F
 Operator: Farr
 Relax. Delay: 1.00 sec
 Pulse: 45.1 degrees
 Acq. time: 1.705 sec
 Match: 9611.9 Hz
 # Repetitions: 8
 Channels: 02, 03, 41, 05, 41, 9
 Data: PR0706.D
 File size: 92760
 Total time: 0 min 21 sec





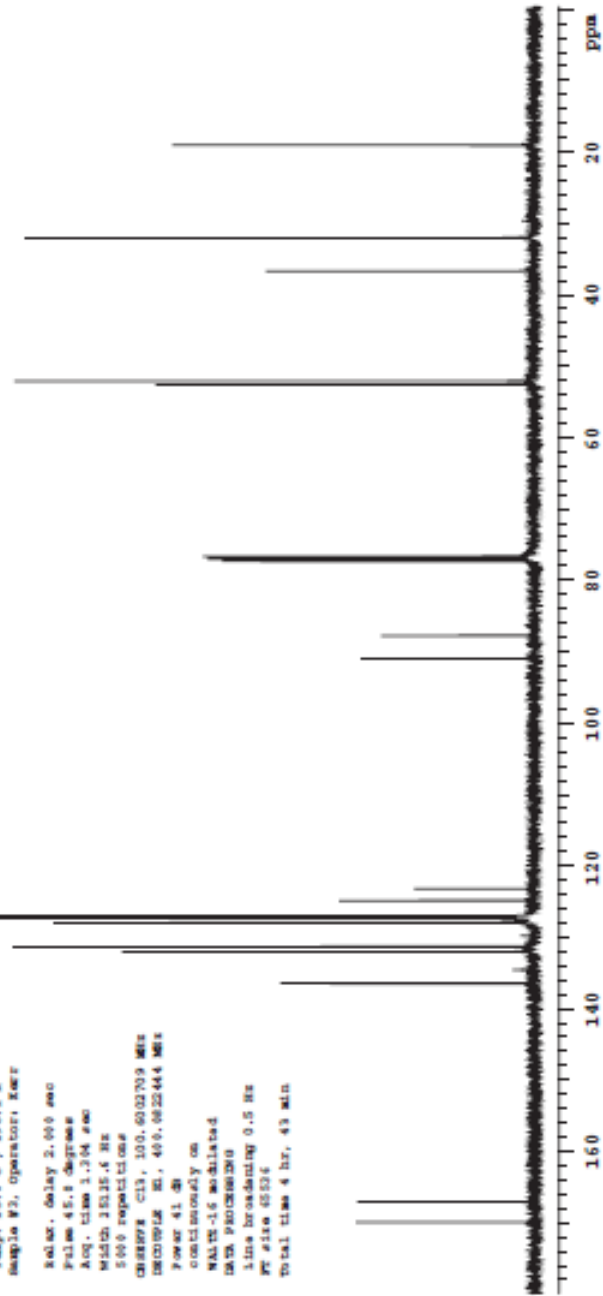
```

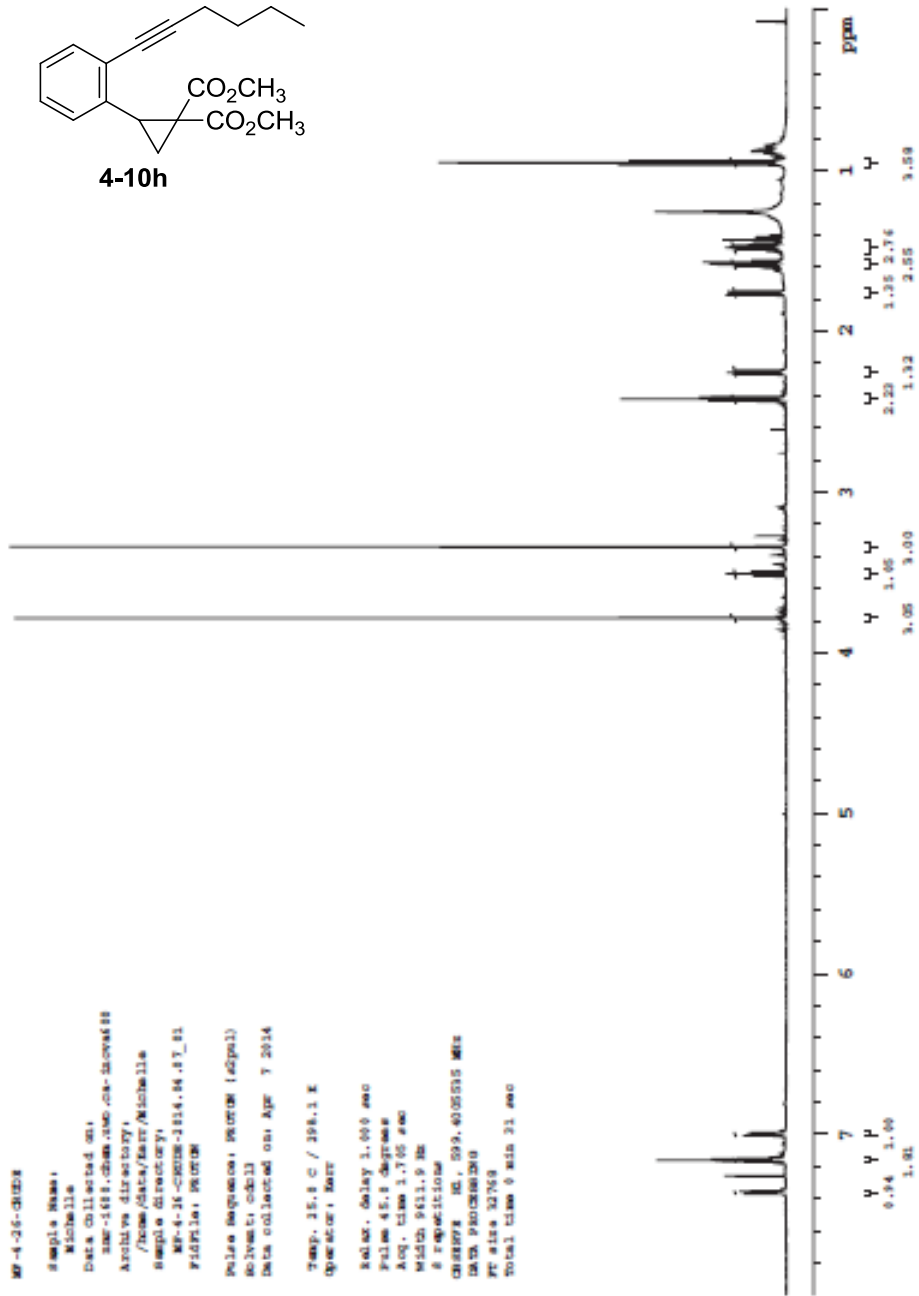
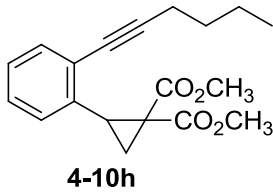
mf-thio-pre-ple-work
Sample Name:
Michelle
Data collected on:
Tue-04-08-2014 10:00:00 AM
Archive directory:
/home/data/karr/Michelle
Sample directory:
mf-thio-pre-ple-work-2014-07-06_01
File(s): CH001

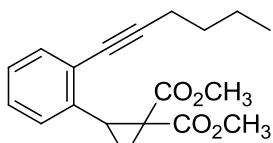
Pulse sequence: zgpg30 (zgpg30)
Solvent: cdcl3
Data collected on: Jul 6 2014

Temp: 25.8 C / 79.1 F
Sample Wt, Operator: Kerr
Relax. Delay 2.000 sec
Pulse 45.8 degrees
Acq. time 1.204 sec
Width 15120.0 Hz
5000 repetitions
CH001F2 CH3, 100.602709 MHz
CH001F2 H1, 400.0022444 MHz
Power 41 dB
conditionally on
WALTZ-16 modulated
Data PROCM0300
line broadening 0.5 Hz
PT size 65526
Total time 4 hr, 43 min

```







4-10h

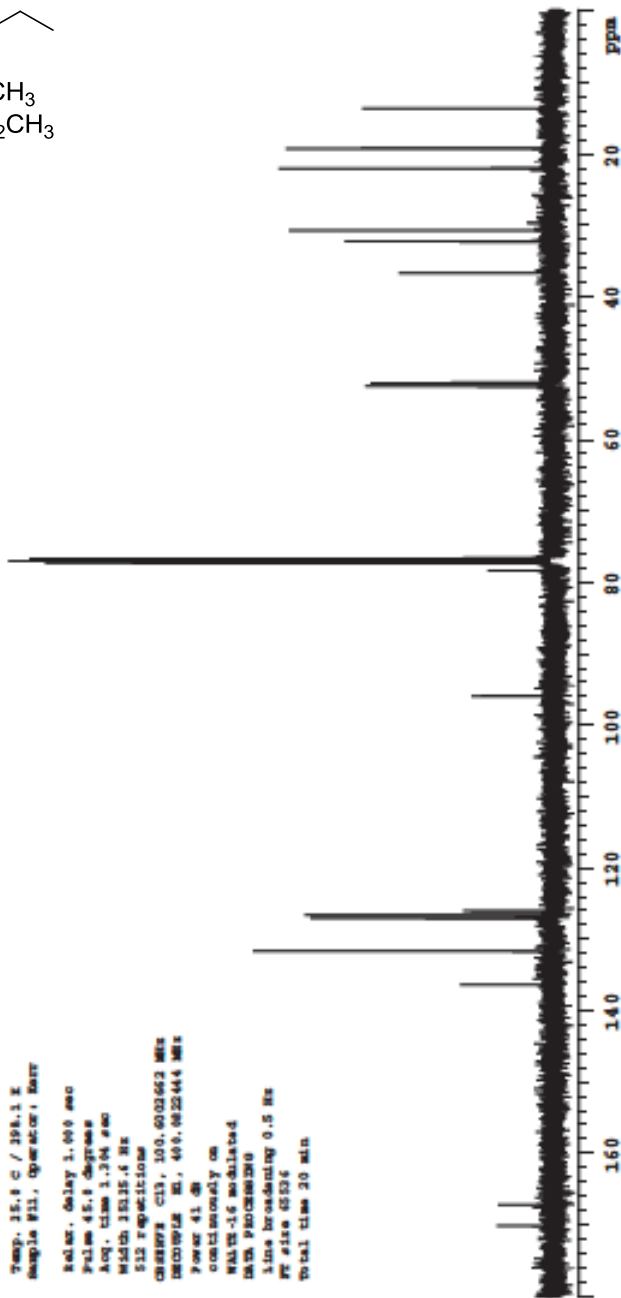
MS-4-111570-783CD1028
 Sample Name:
 Michelle
 Data Collected on:
 ms-411570.chm.nci.ca-micro7488
 Archive directory:
 /home/data/terr/Michelle
 Sample directory:
 MS-4-111570-783CD1028-1114_15_05_11
 FIDFile: CH100

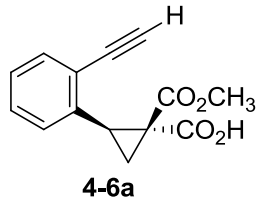
Pulse Sequence: CH100 (cdpm)
 Solvent: cdcl3
 Data collected on: May 5 2014

Temp: 35.0 C / 100.1 F
 Sample #11, Operator: terr

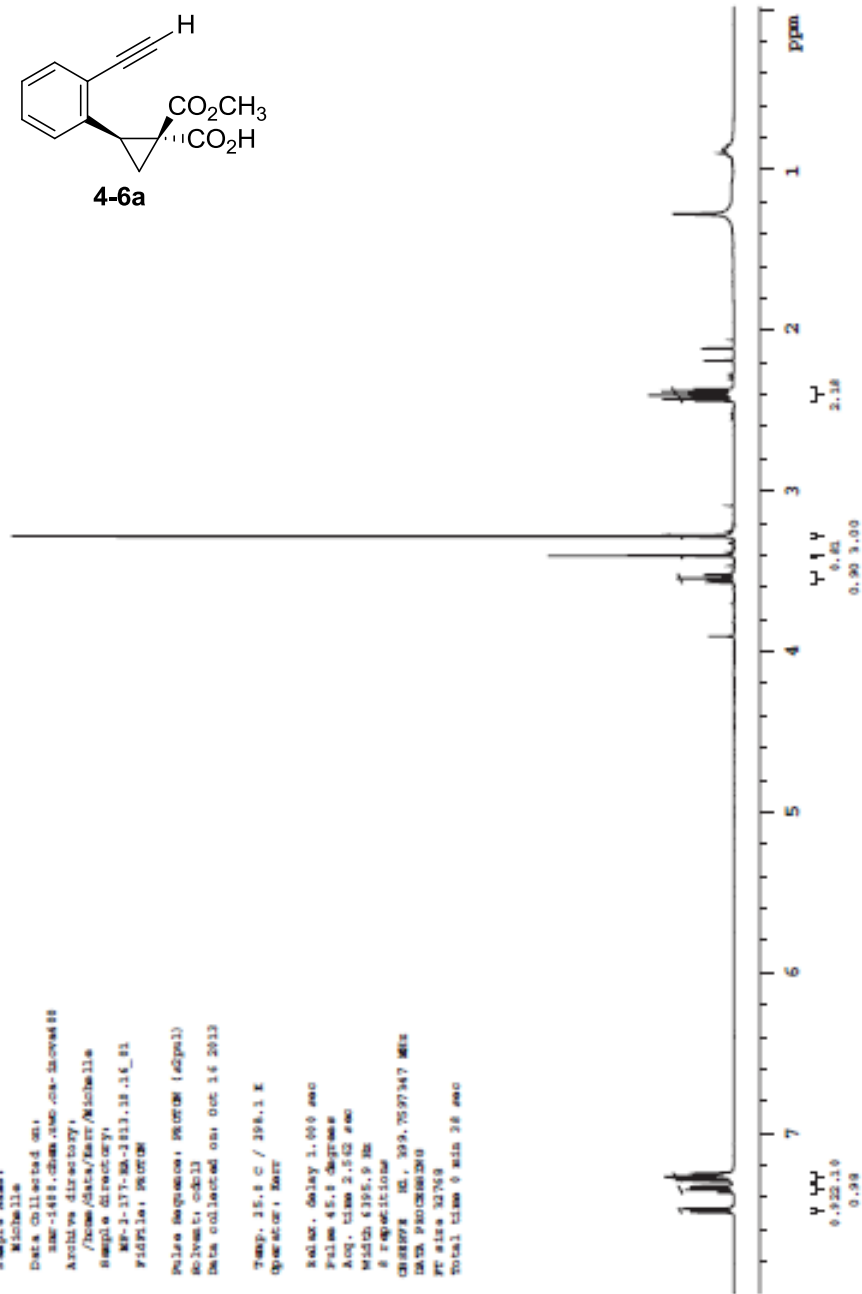
Relax. Delay: 1.000 sec
 Pulse: 45.0 degrees
 Acq. time: 1.204 sec
 Width: 30315.4 Hz
 512 repetitions

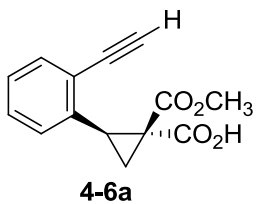
CHANNELS: CH1, 100.6000000 MHz
 DECOUPLE: RL, 499.9025444 MHz
 Power: 41.00
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening: 0.5 Hz
 F2 file: 45336
 Total time: 30 min



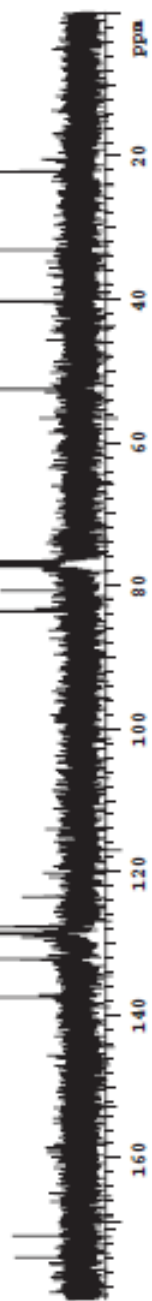


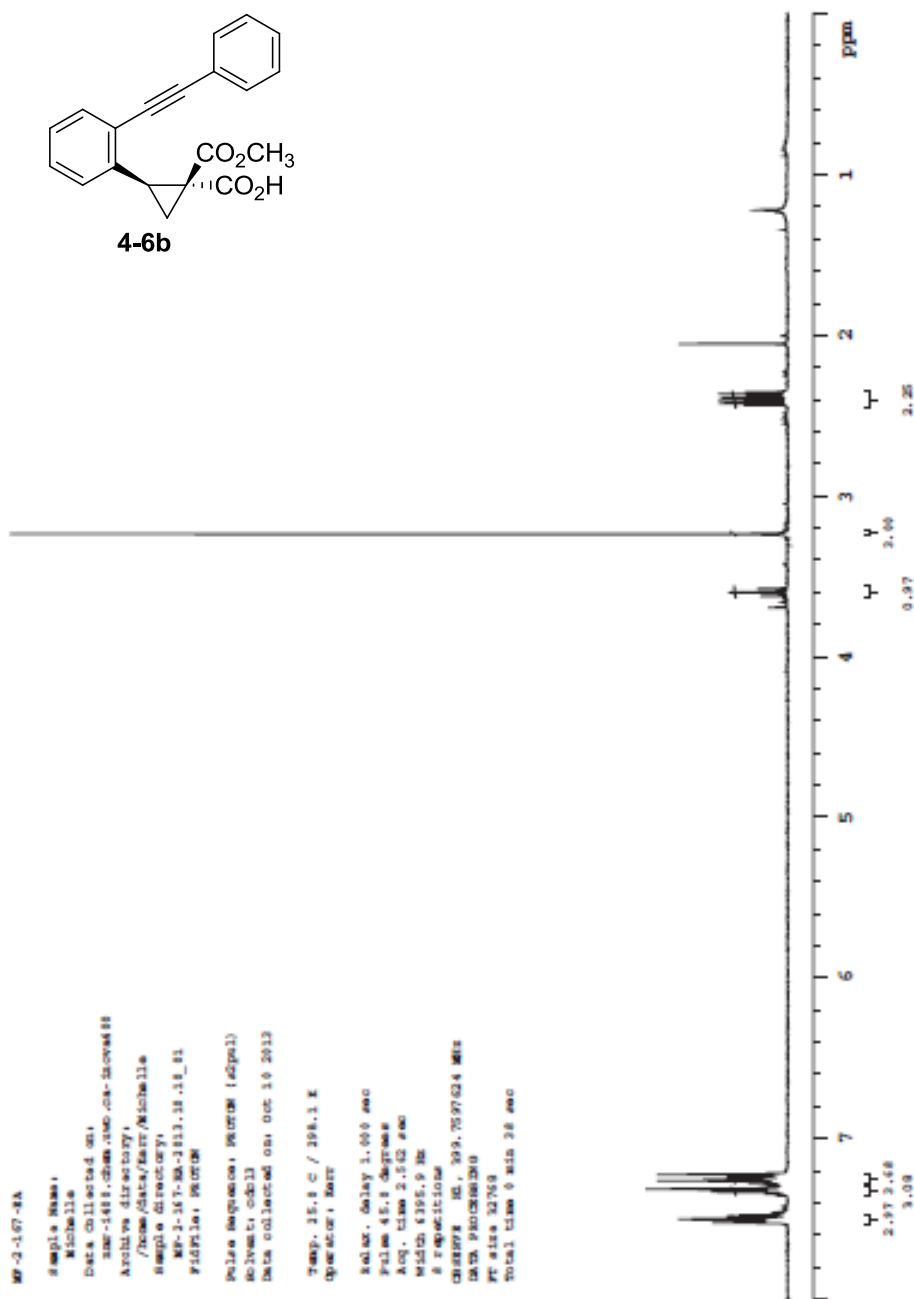
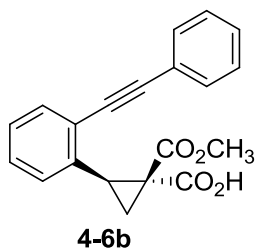
MF-2-177-2A
 Sample Name:
 Michelle
 Data collected on:
 sar-1488.chms.ncs-lacvms08
 Archive directory:
 /home/data/lacv/Michelle
 Sample directory:
 MF-2-177-2A-111.18.16_01
 File(s): PR0708
 Pulse Sequence: PR0708 (62pel)
 solvent: cdcl3
 Data collected on: Oct 16 2013
 Temp: 35.8 C / 96.4 F
 Operator: Marc
 Solvent Delay: 1.00 sec
 Pulse: Galley 1.00 sec
 Pulse: 45.1 degree
 Acq. time: 2.542 sec
 MHz: 639.9 MHz
 # Repetitions:
 8
 CHERRY: ID: 399, 7597347 MHz
 DATA PROCESSING
 FT size: 32753
 Total time: 0 min 26 sec

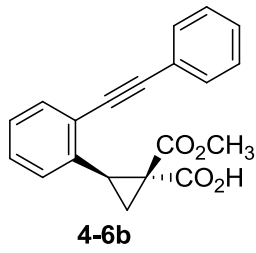




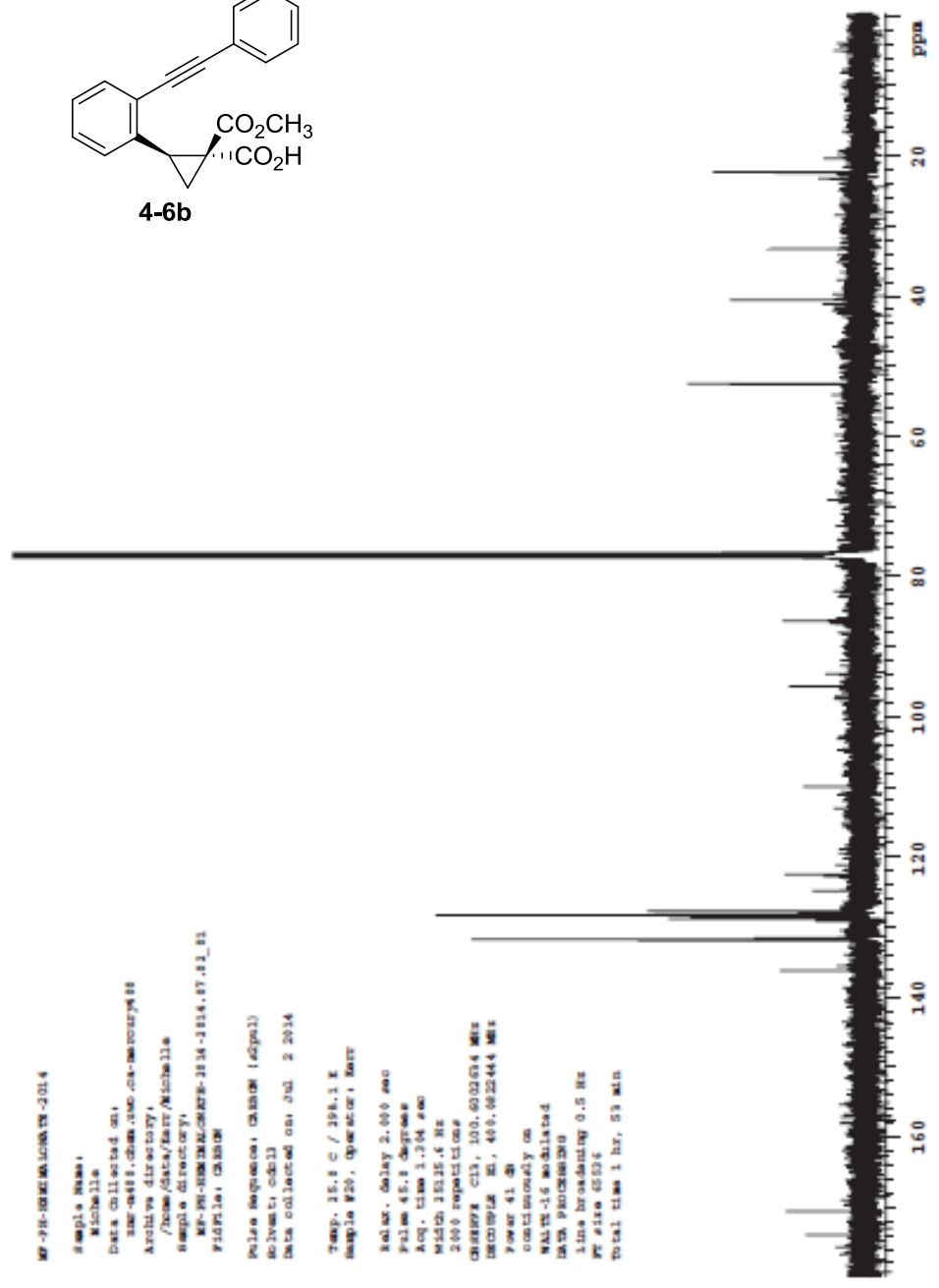
NP-4-ALKYNE-01
 Sample Name:
 Michelle
 Data collected on:
 04/25/2014 08:48:00 AM
 Archive directory:
 /home/data/farr/Michelle
 Sample directory:
 NP-4-ALKYNE-01-2014_04_25_01
 File(s): 01.D
 Pulse sequence: CASHM (62pul)
 Solvent: cdcl3
 Data collected on: Apr 25 2014
 Temp: 35.1 C / 94.1 K
 Sample Wt, Operator: KMR
 Relax. delay: 1.000 sec
 Pulse: 45.1 degrees
 Acq. time: 1.704 sec
 Width: 25125.6 Hz
 SIZ: 1 Repetition
 CHANNELS: C13, 100.6203016 MHz
 DECOUPLE: H1, 400.0822444 MHz
 Power: 41.00
 continuously on
 WALTZ-16 enabled
 DATA PROCESSING
 Line broadening: 0.5 Hz
 FT size: 65536
 Total time: 20 min

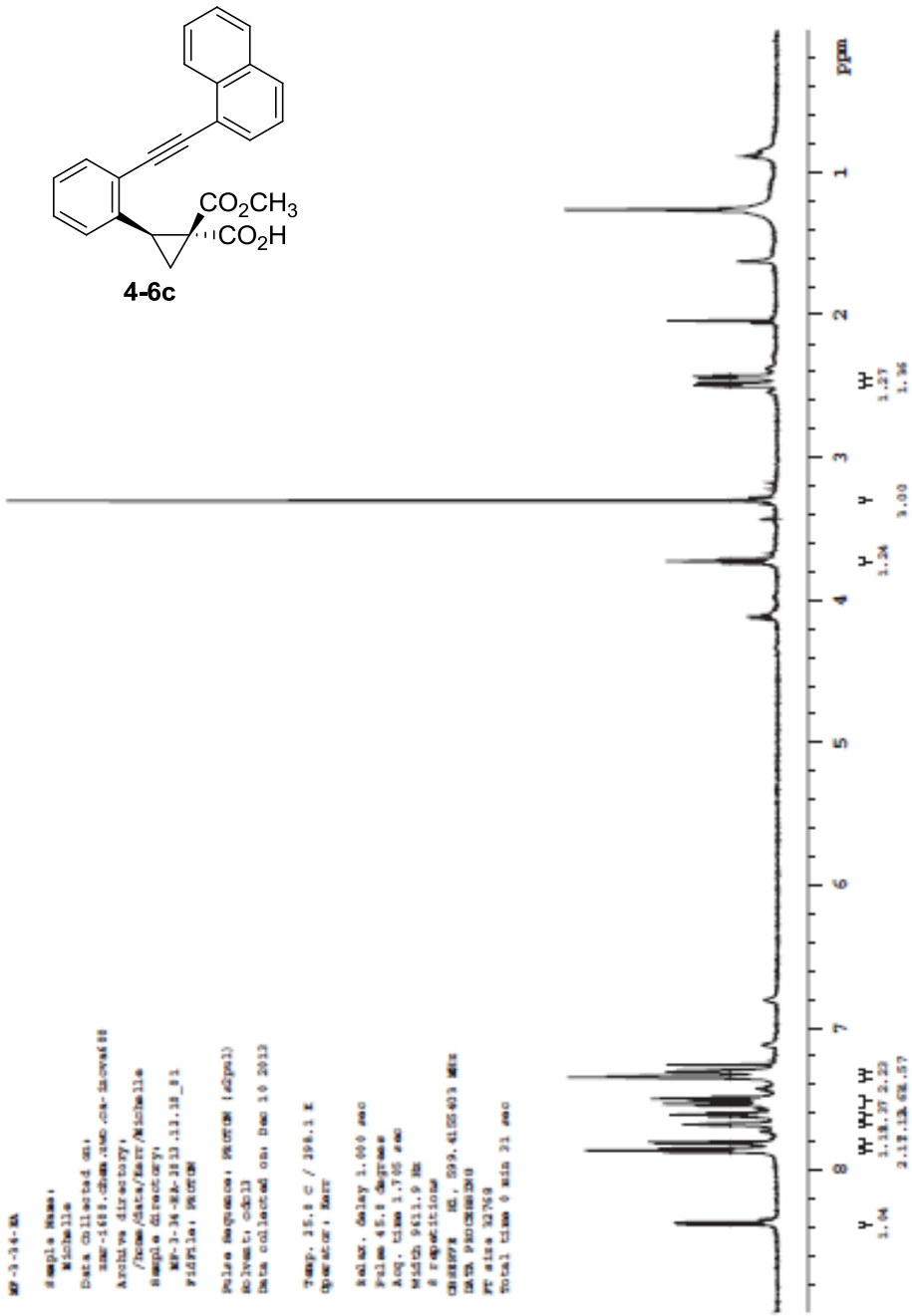


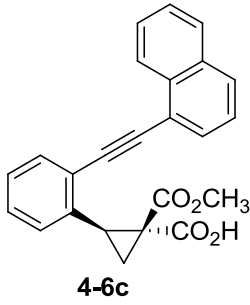




NP-05-000000000000-2014
 Sample Name:
 Michelle
 Data collected on:
 08-04-08 08:00:00
 Archive directory:
 /home/datta/Barr/Michelle
 Sample directory:
 NP-05-000000000000-2014-07-01_01
 File(s): CH3OH
 Pulse sequence: zgpg30 (zgpg30)
 Solvent: cdcl3
 Data collected on: Jul 2 2014
 Temp: 30.3 C / 298.1 K
 Sample M20, Operator: Barr
 Relax: delay 2.000 sec
 Pulse: delay 45.0 degrees
 Acq. time: 1.204 sec
 Width: 15125.6 Hz
 2000 repetitions
 CHANNELS: CH3, 100.6202634 MHz
 PROCPAR: SI, 400.0822444 MHz
 Power: 41.0W
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening: 0.5 Hz
 FT size: 65536
 Total time: 1 hr, 53 min



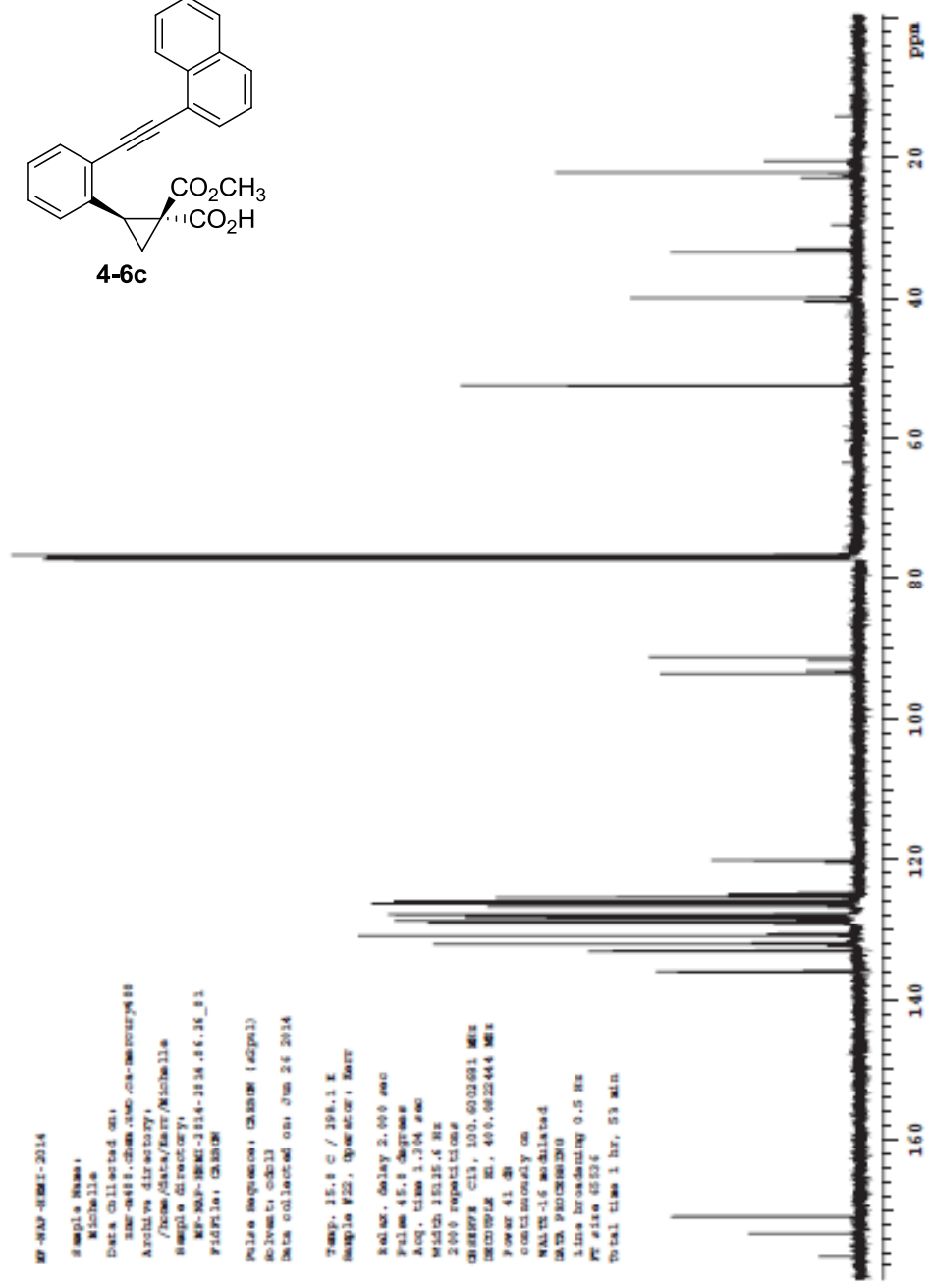


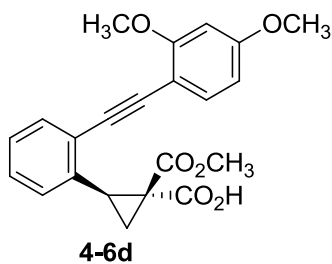


MS-003-0001-2014
 Sample Name:
 Michelle
 Data collected on:
 MAR-04-11-08AM.WAD-0A-00000748
 Archive directory:
 /Home/Data/MSR/Michelle
 Sample directory:
 MS-003-0001-2014-04-16_01
 File(s): 00000

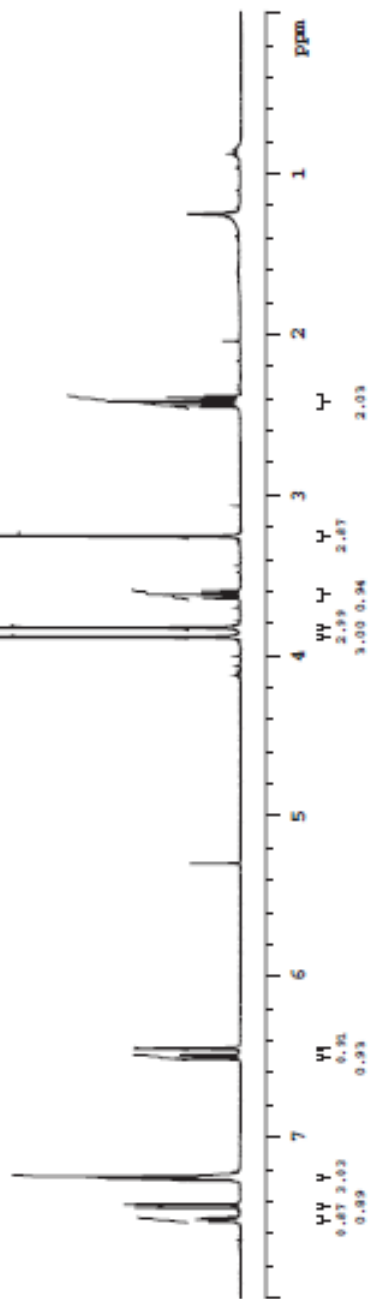
Pulse sequence: zgpg30 (zgpg3)
 solvent: cdcl3
 Data collected on: Sun 26 2014

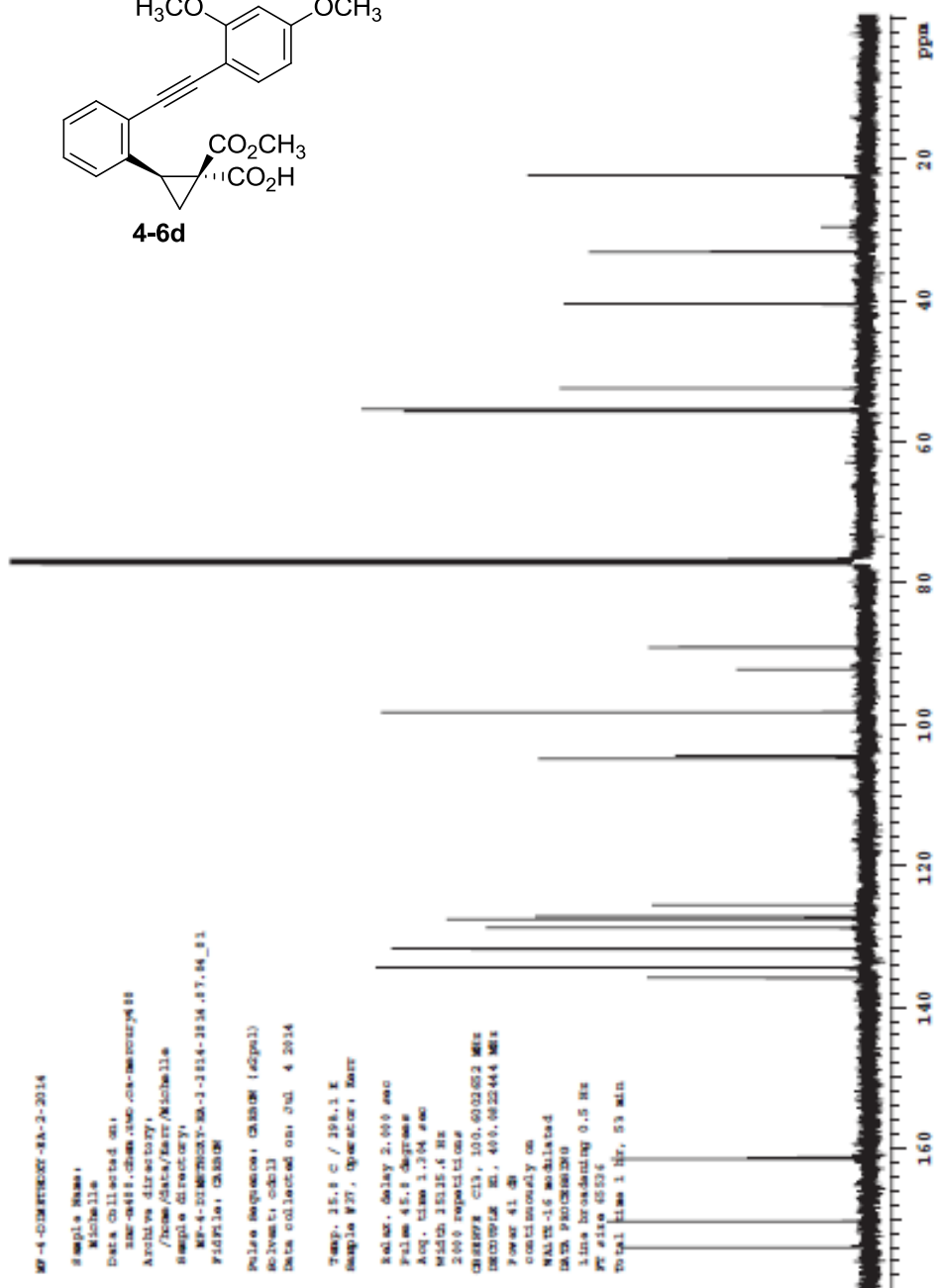
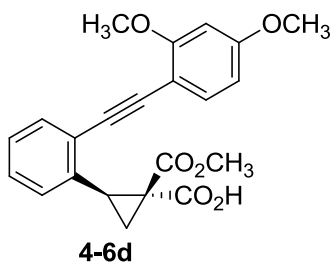
Temp: 25.0 C / 298.1 K
 Sample #22, Operator: Barr
 Relax delay 2.000 sec
 Pulse 45.0 degrees
 Acq. time 1.264 sec
 Width 13135.6 Hz
 200 repetitions
 CHANNEL C13, 100.620201 MHz
 INCOUPLER IN, 400.0022444 MHz
 Power 41.00
 continuously on
 WALTZ-16 Modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 1 hr, 53 min

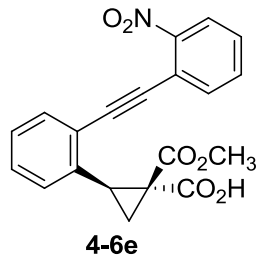


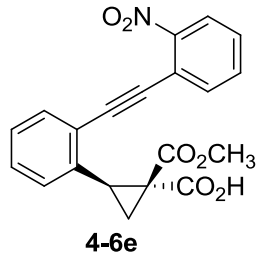


MF-4-0187000-BA-3-2014
 Sample Name: Michelle
 Data Collected on: sun-0411-08h30m-04h-00m-00s-000
 Archive directory: /home/data/Barr/Michelle
 Sample directory: MF-4-0187000-BA-3-2014-07-04_01
 FIDAP file: PLOT08
 Pulse sequence: PLOT08 (ad2p11)
 solvent: cdcl3
 Data collected on: Jul 4 2014
 Temp: 15.0 C / 398.1 K
 Sample #27, Operator: Barr
 Relax. delay: 1.000 sec
 Pules: 45.0 degrees
 Acq. time: 2.559 sec
 Wdth: 6481.8 Hz
 32 repetitions
 CHIRP: HS, 400.0902695 MHz
 DATA PROCESSING
 FT size: 32768
 Total time: 2 min 7 sec

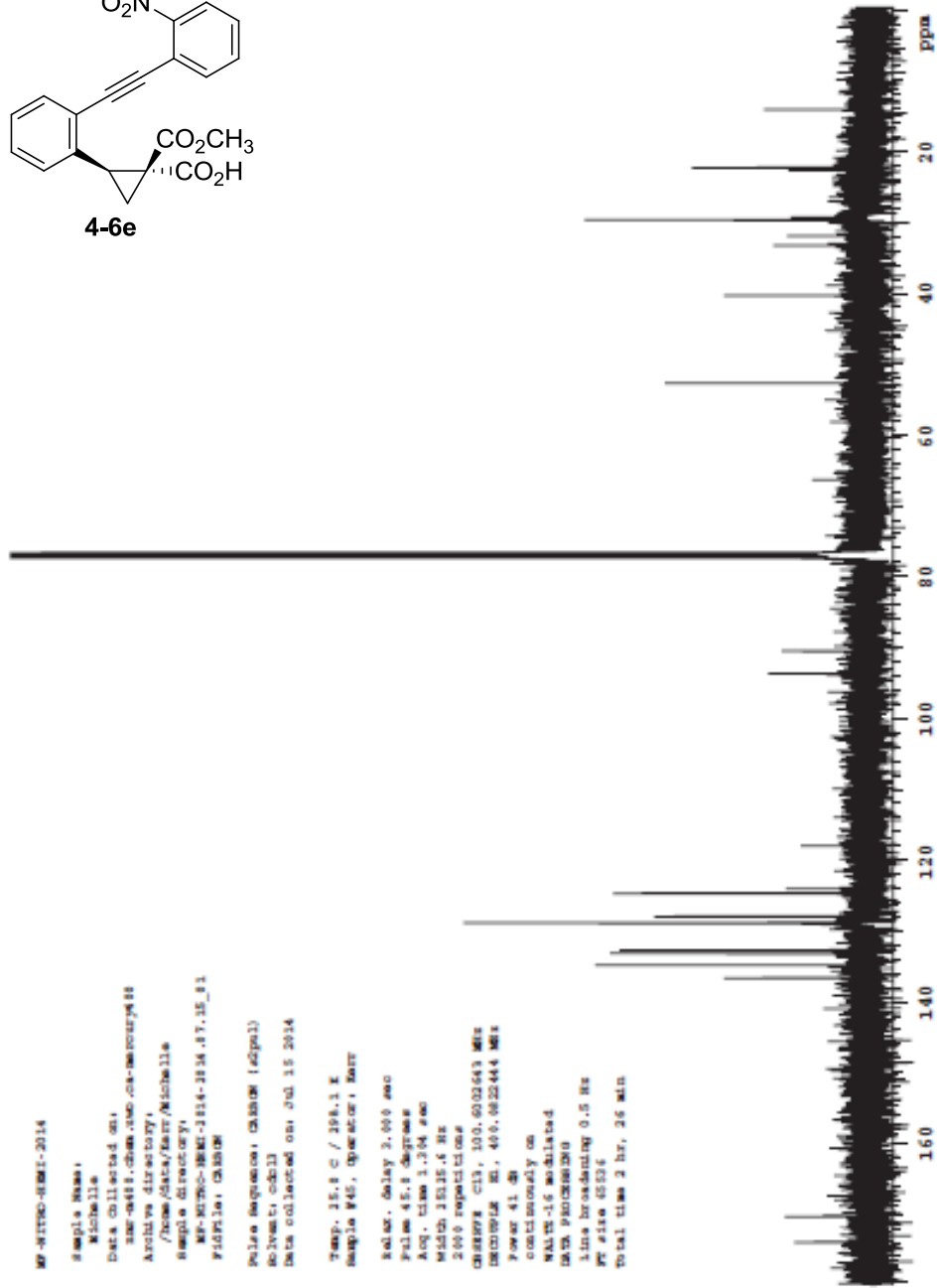


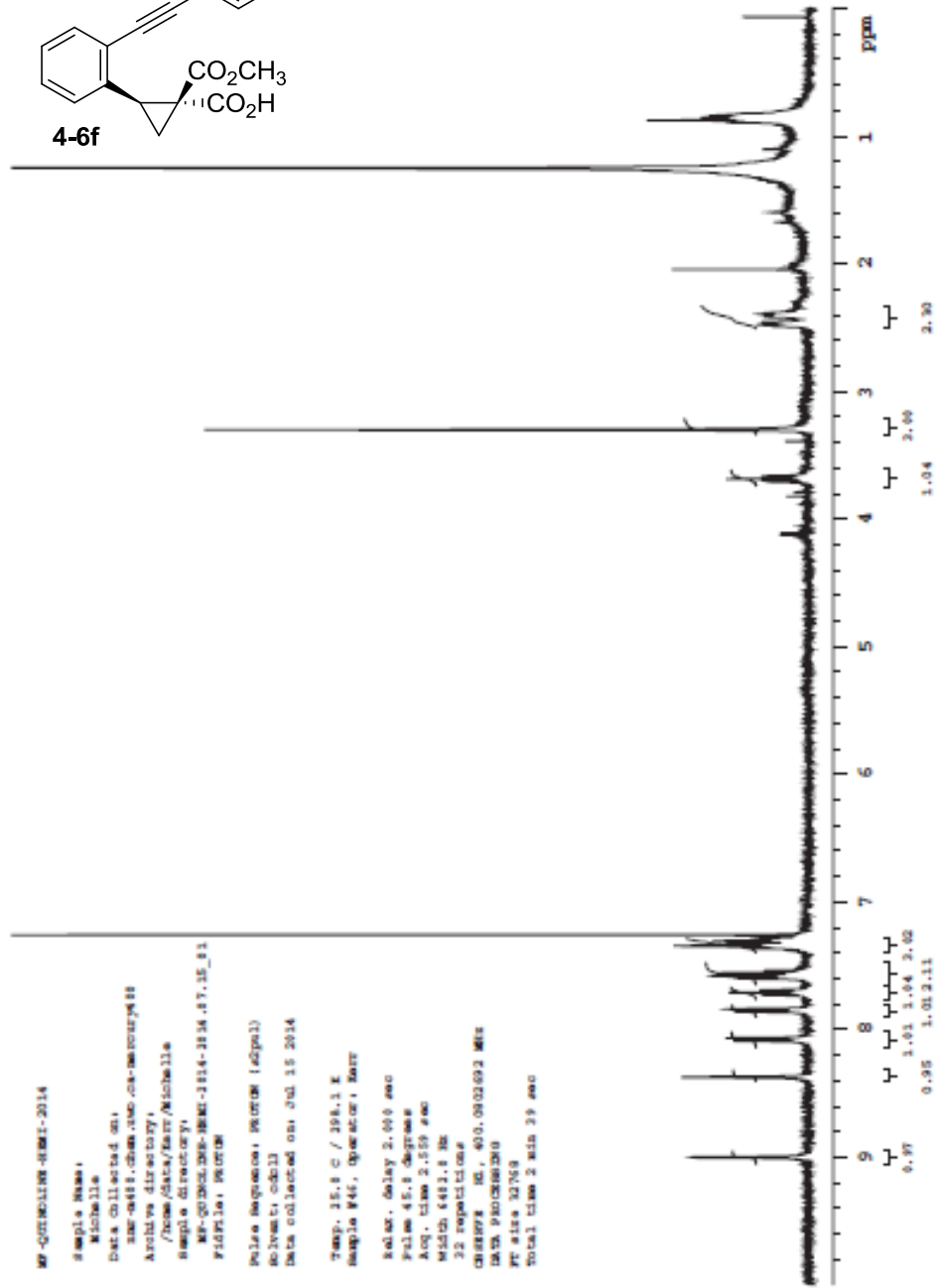
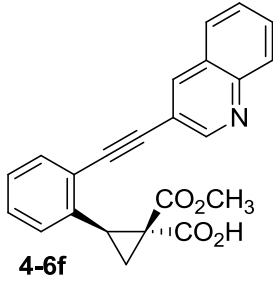


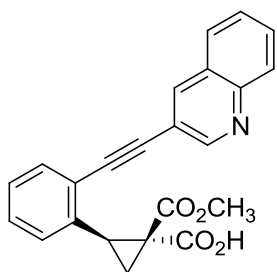




MF-NITRO-HEMI-2014
 Sample Name: Michelle
 Data Collected on: sun-0418-08am.usd.ca-micro2488
 Archive directory: /home/data/farr/Michelle
 Sample directory: MF-NITRO-HEMI-2014-2014-07-15_01
 FIDFILE: CH3OH
 Pulse sequence: CH3OH (40ppm)
 Solvent: cdcl3
 Data collected on: Jul 15 2014
 Temp: 15.3 C / 298.1 K
 Sample #45, Operator: Farr
 Soler. delay 2.000 sec
 Pulse delay 45.0 degrees
 Acq. time 1.704 sec
 Width 15125.6 Hz
 2000 repetitions
 CH3OH c13, 100.622543 MHz
 INCOUPLR M1, 400.002244 MHz
 Power 41.0W
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 2 hr, 26 min







4-6f

MF-4-Q02M-BA-CL3
 Sample Name:
 Michelle
 Data collected on:
 MAR-04-11-08AM.WED.CA-060007488
 Archive directory:
 /Home/Data/BA/Michelle
 Sample directory:
 MF-4-Q02M-BA-CL3-2014.05.19_01
 File(s): CH3OH

Pulse sequence: CH3OH (zgpg1)
 solvent: cdcl3
 Data collected on: May 19 2014

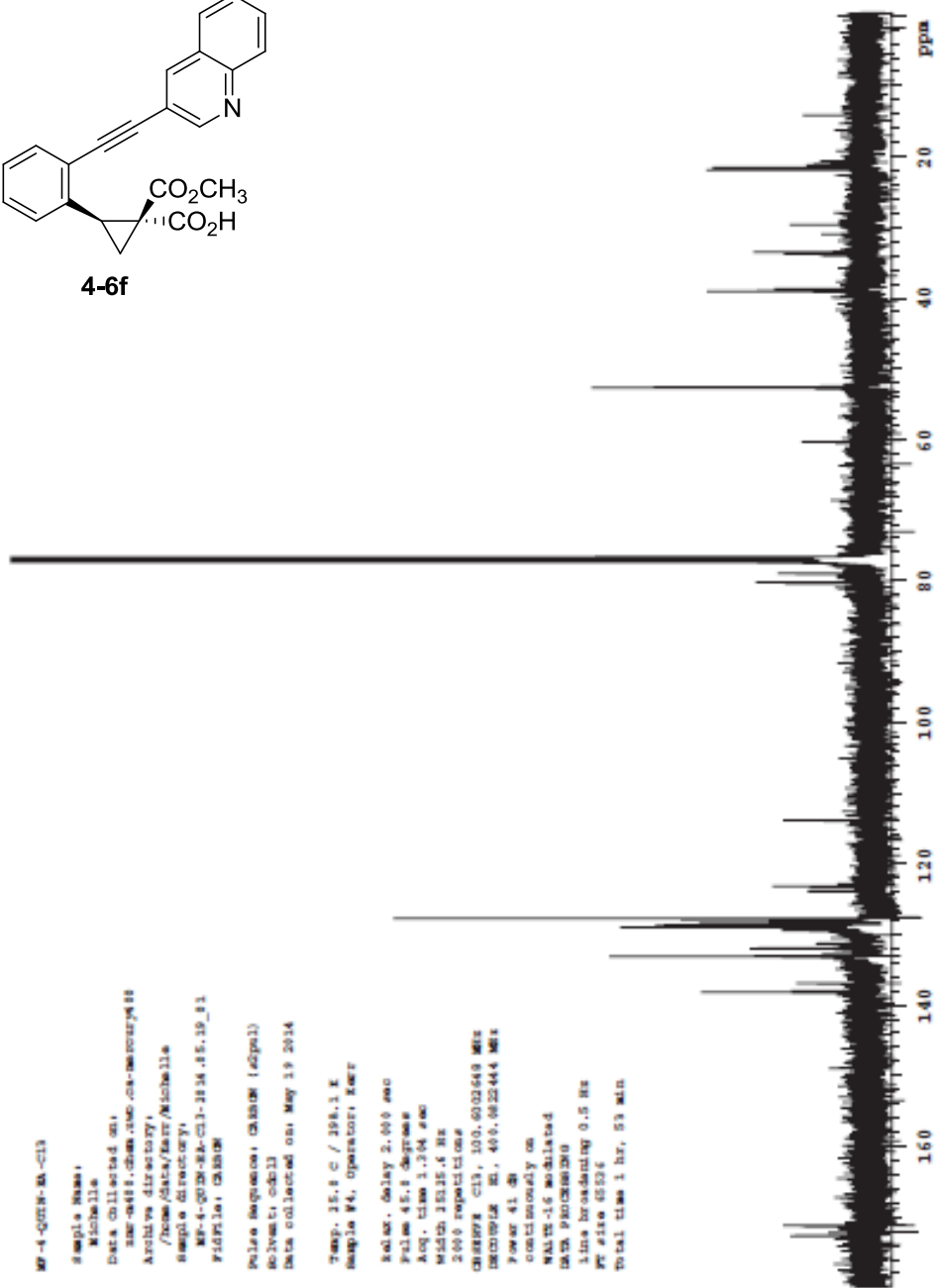
Temp: 25.0 C / 798.1 K
 Sample #4, Operator: Kerr

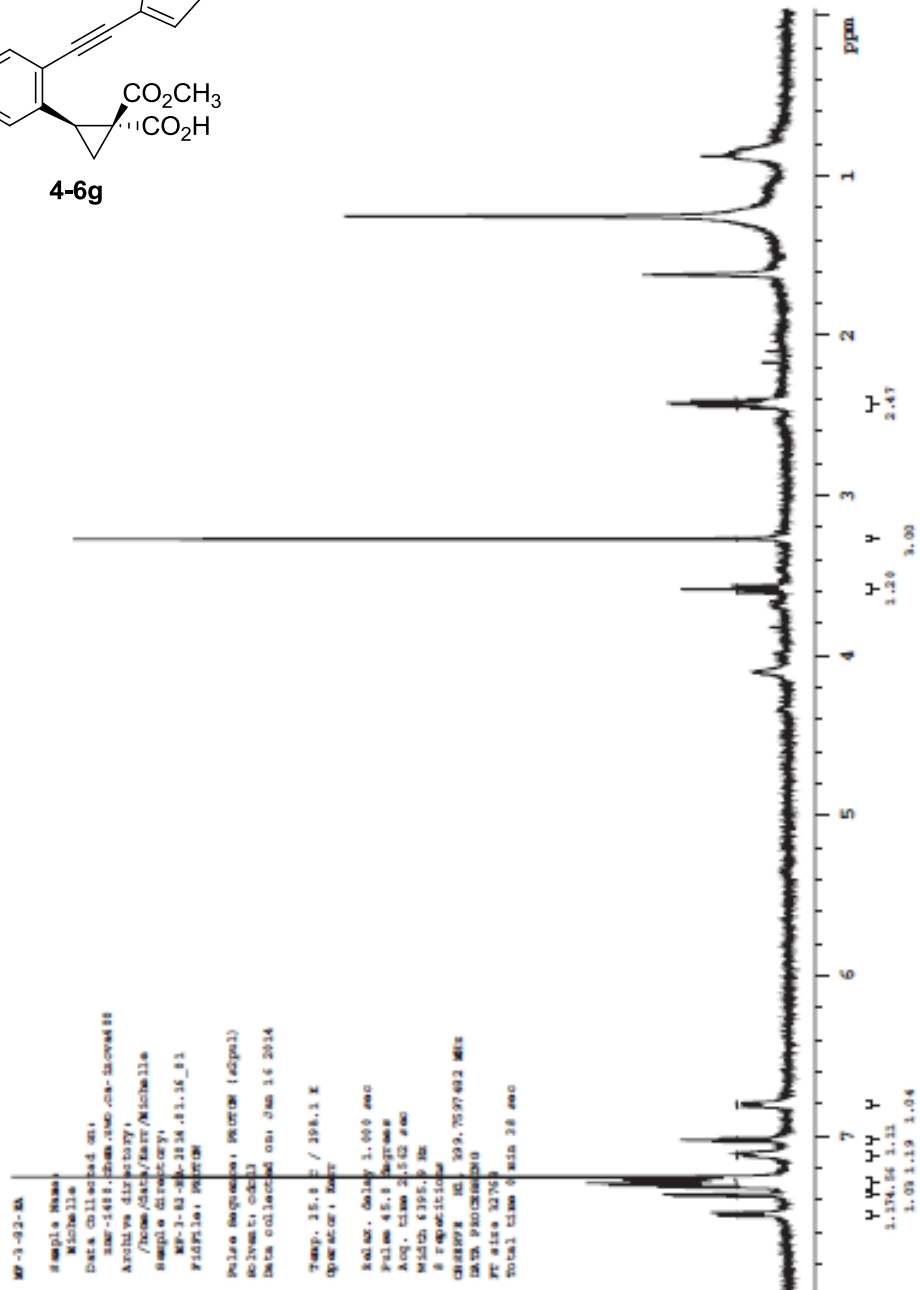
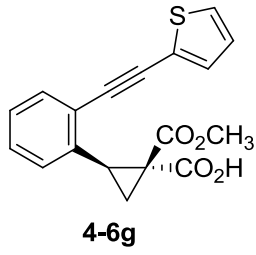
Solvent delay 2.000 sec
 Pulse 45.0 degrees
 Acq. time 1.204 sec
 Width 10215.6 Hz
 200 repetitions

CHANNEL C13, 100.622649 MHz
 INVERSE M1, 400.002244 MHz

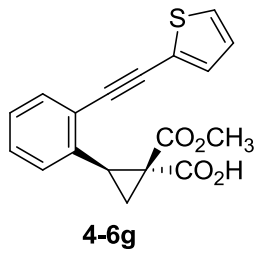
Power 41.00
 continuously on

NMR-16 irradiated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 4534
 Total time 1 hr, 53 min





MS-3-02-04
 Sample Name: Michellie
 Data collected on: 11/14/14 11:48:00 AM
 Archive directory: /home/dick/Harr/Michellie
 Sample directory: MS-3-02-04-1114
 File: MS-3-02-04-1114_01.D
 Pulse sequence: PROCES (edit)
 solvent: CH2Cl2
 Data collected on: Jan 16 2014
 Temp: 15.8 C / 298.1 K
 Operator: Barr
 Solvent delay: 1.000 sec
 Valve 45.8 degrees
 Acq. time 2.532 sec
 Watch 6395.9 Hz
 6 replicates
 channel: 01 109.7597493 MHz
 DATA PROCESSED
 RT size 32768
 Total time 6 min 36 sec

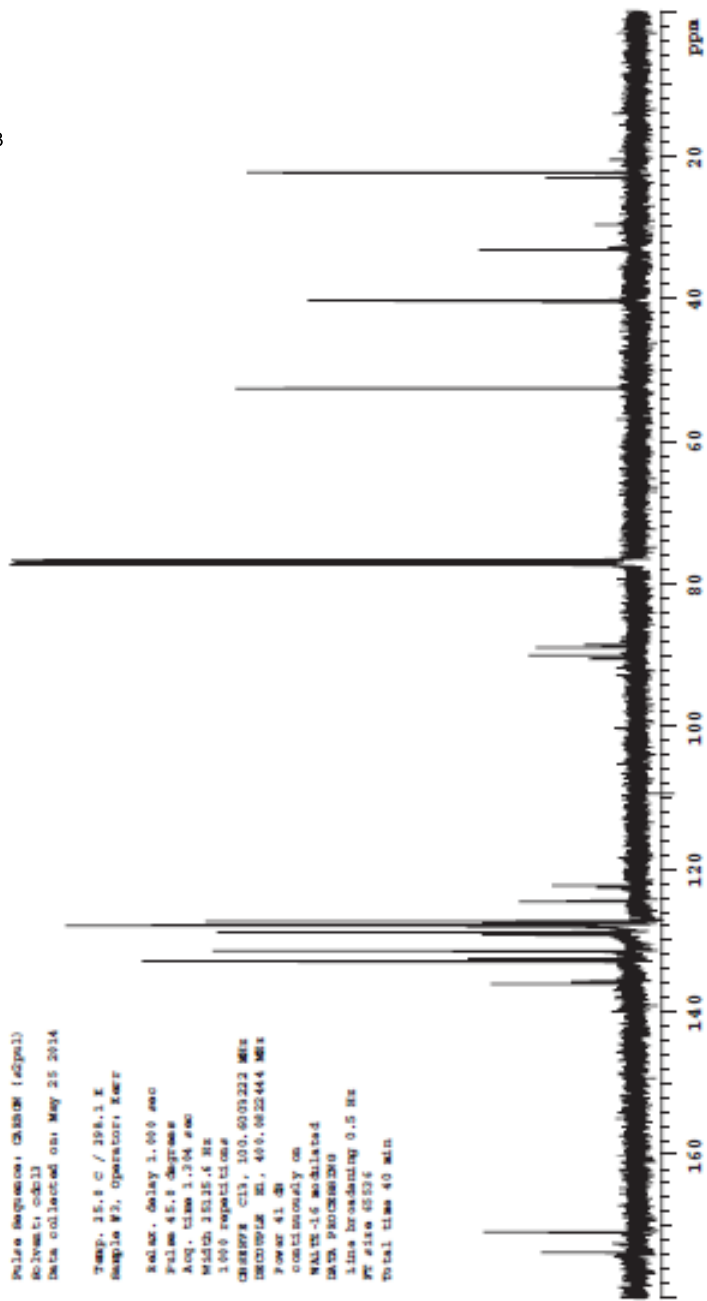


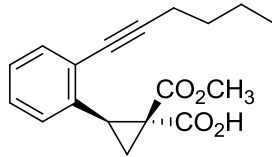
MF-4-TRIC-BA-C-13-2
 Sample Name:
 Michelle
 Data collected on:
 mar-0411.08am.tmo.ca-manary@11
 Archive directory:
 /home/data/karr/Michelle
 Sample directory:
 MF-4-TRIC-BA-C-13-2-1314.15.15_01
 File(s): 03008

Pulse Sequence: zgpg30 (42pt1)
 Solvent: cdcl3
 Data collected on: May 25 2014

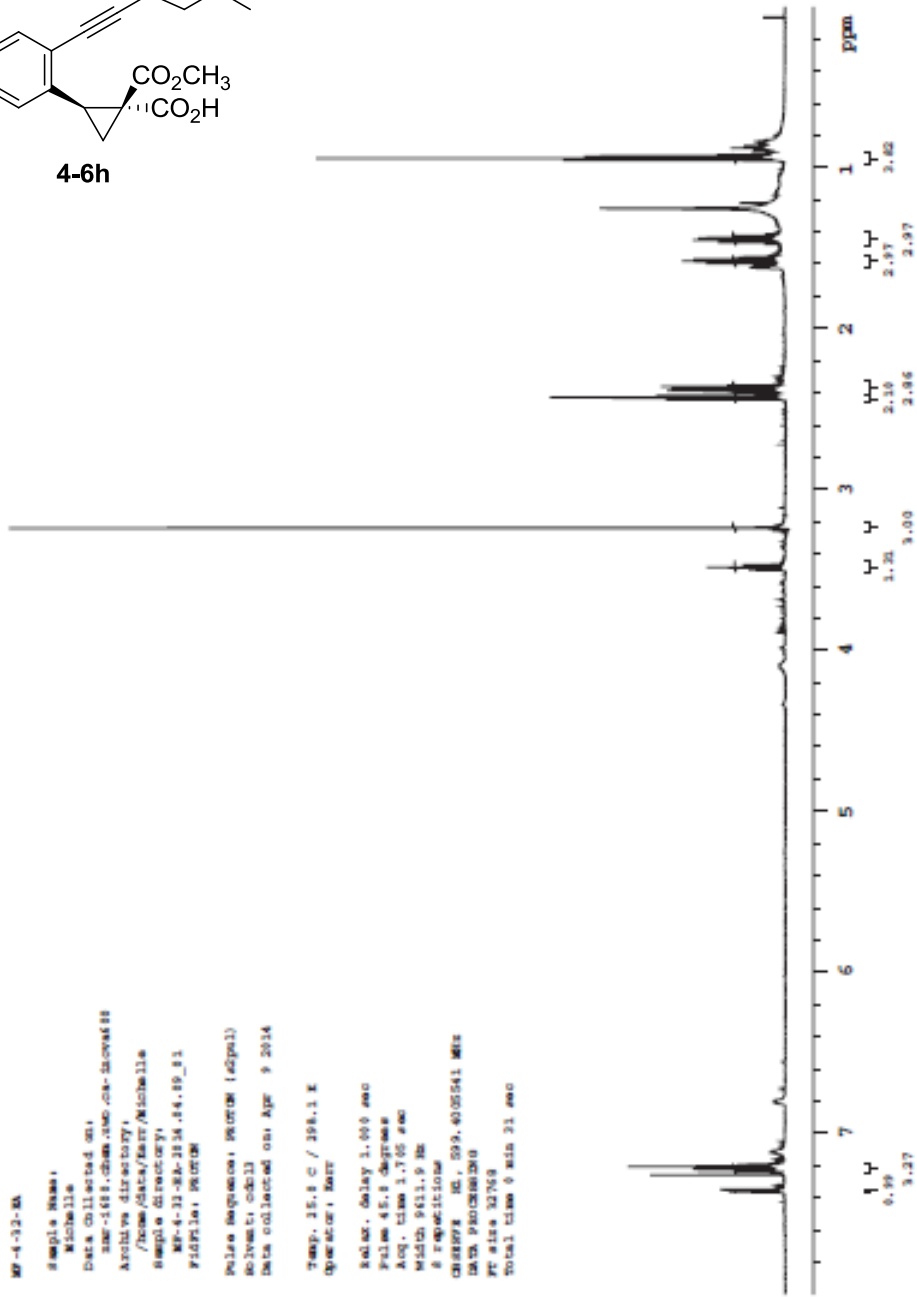
Temp: 25.0 C / 298.1 K
 Sample #2, Operator: Karr

Solvent Delay: 3.000 sec
 Pulse: 45.1 degrees
 Acq. time: 1.264 sec
 Width: 15135.6 Hz
 1000 repetitions
 CHANNEL F13, 100.620322 MHz
 DECUPLE M1, 400.002244 MHz
 Power 41 dB
 continuously on
 WALTZ-16 simulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65534
 Total time 40 min

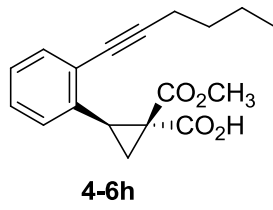




4-6h



MF-4-32-NA
 Sample Name:
 Michelle
 Data Collected on:
 sat-1001.chm.tms.chs-tmsvaf88
 Archive directory:
 /home/Data/Estr/Michelle
 Sample directory:
 MF-4-32-NA-2014.04.09_01
 FIDPRIN1 PR070M
 Pulse Sequence: PR070M (e2ps13)
 solvent: cdcl3
 Data collected on: Apr 9 2014
 Temp: 30.0 C / 86.0 F
 Operator: Barr
 Relax. Delay 3.000 sec
 Pulse 45.0 degrees
 Acq. time 3.700 sec
 Width 9413.9 Hz
 # Repetitions
 CHANNELS: MS, QP2, 4025541 MHz
 DATA PROCESSING
 FT size 32750
 Total time 0 min 31 sec

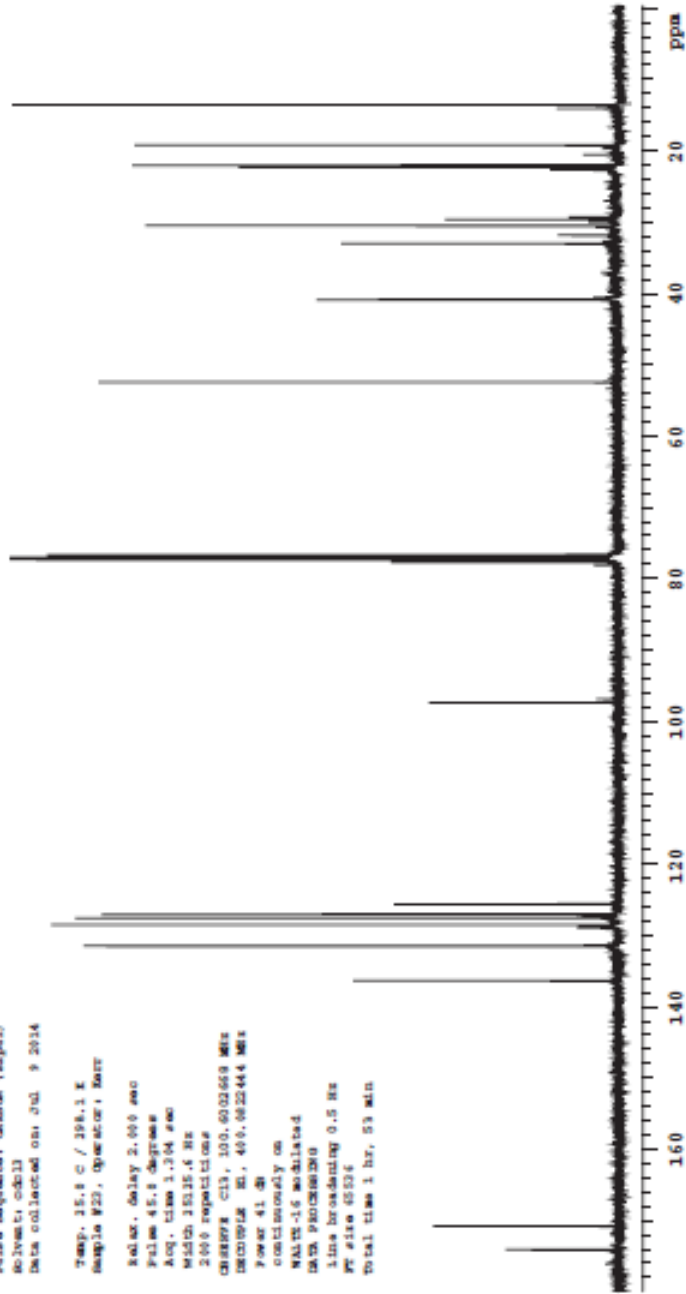


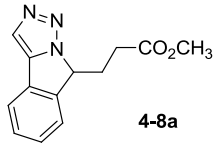
MP-4-MULTI-2A-2014
 Sample Name:
 Michelle
 Data collected on:
 xmr-0418.chm.tmo.ch-mchoury@is
 Archive directory:
 /home/dhaka/karr/Michelle
 Sample directory:
 MP-4-MULTI-2A-2014-2014.07.08_01
 FIDFile: CH308

Pulse sequence: CH308 (4091)
 solvent: cdcl3
 Data collected on: Jul 9 2014

Temp: 25.8 C / 398.1 K
 Sample V23, Operator: Karr
 Relax. delay: 2.000 sec
 Pulse: 45.8 degrees
 Acq. time: 3.004 sec
 Width: 15125.8 Hz
 2000 repetitions
 CH308F2 C13, 100.602659 MHz
 INCD097A M1, 400.002244 MHz
 Power: 41 dB
 continuously on

WALTZ-16 modulated
 DATA PROCESSING
 Line broadening: 0.5 Hz
 FT size: 65536
 Total time: 1 hr, 53 min





```

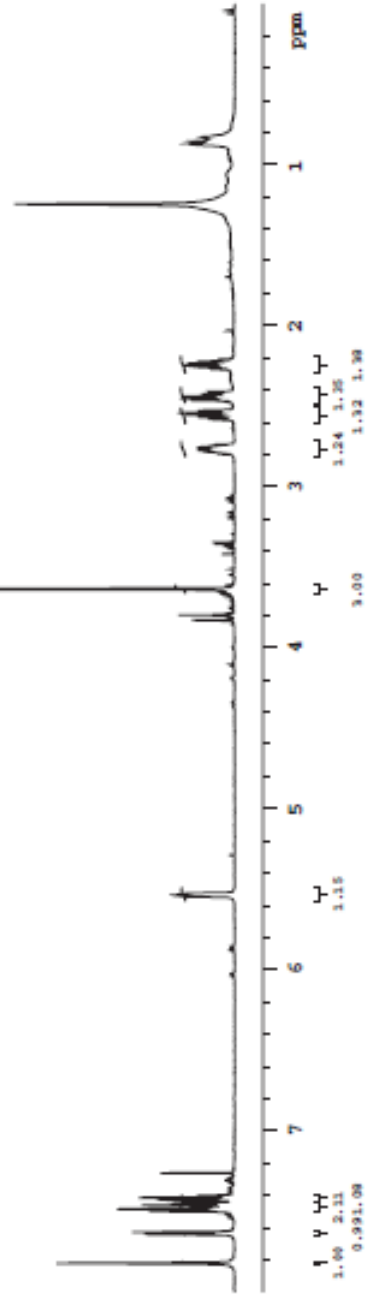
MF-2-1-97-CUMAM
Sample Name:
Mischelle
Data collected on:
mf-1681.dmsa.twe.ch-14064688
Archive directory:
/home/data/karr/Mischelle
Sample directory:
MF-2-1-97-CUMAM-1681.11.11_81
V16P11a.k

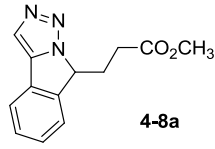
Pulse Sequence: PRCORM (40pm1)
Solvent: cdcl3
Data collected on: Oct 21 2013

Temp: 35.8 C / 396.3 K
Operator: karr

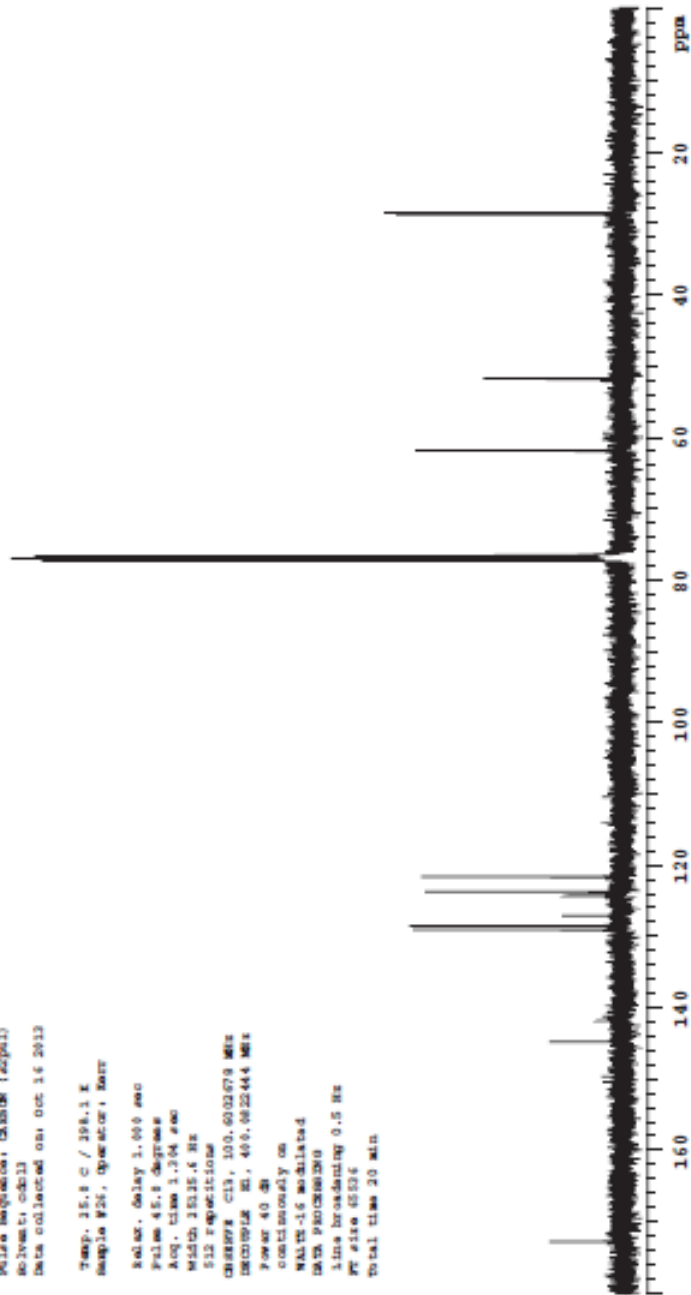
Acq. delay: 1.00 sec
Pulse: 45.8 degrees
Acq. time: 1.705 sec
Width: 9431.9 Hz
# FREQ: 510.1304
CHARGE: 05. 599. 0119324 MHz
DATA PROCESSING:
PT size: 32768
Total time: 0 min 21 sec

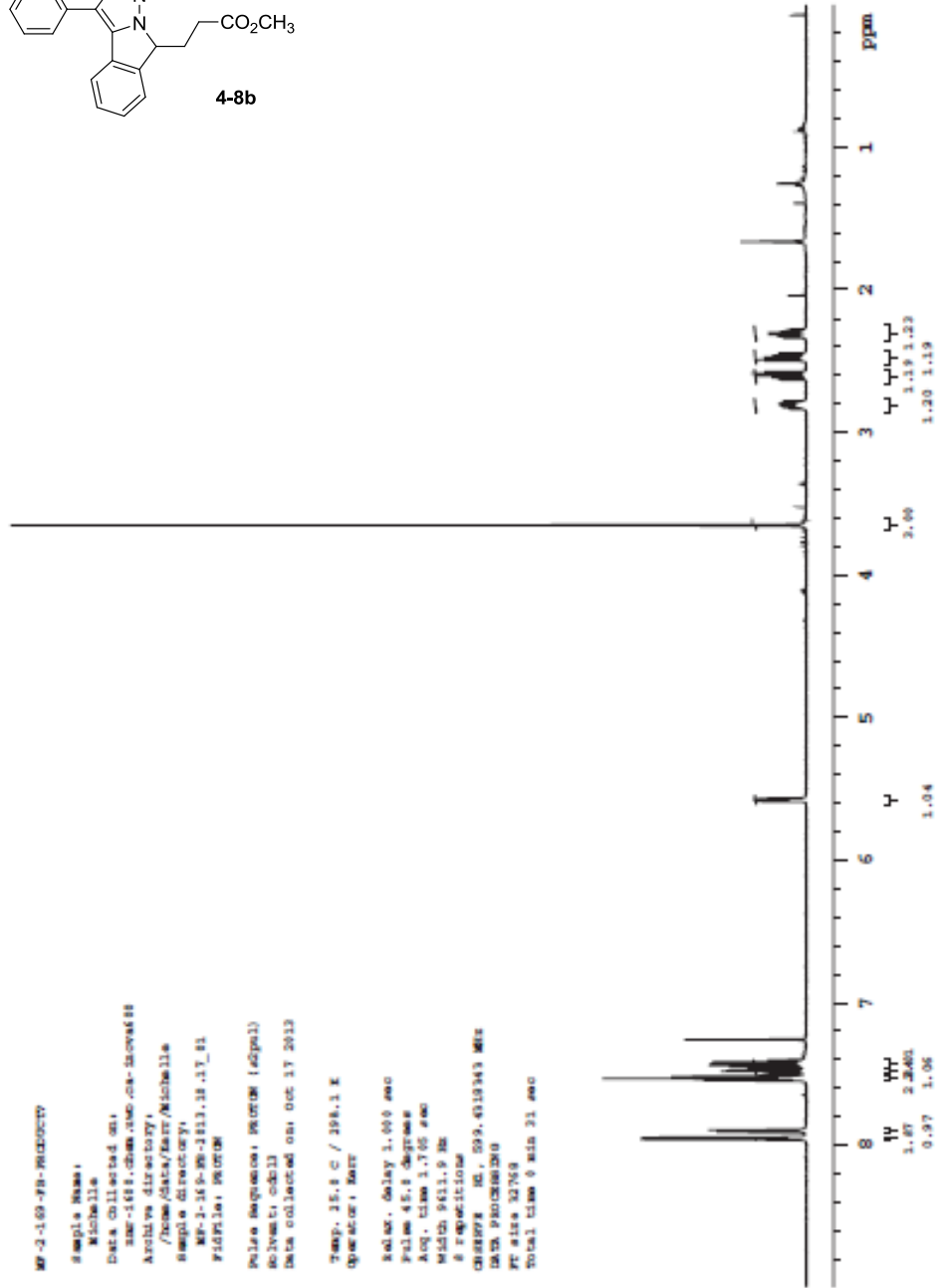
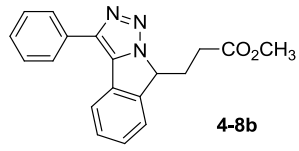
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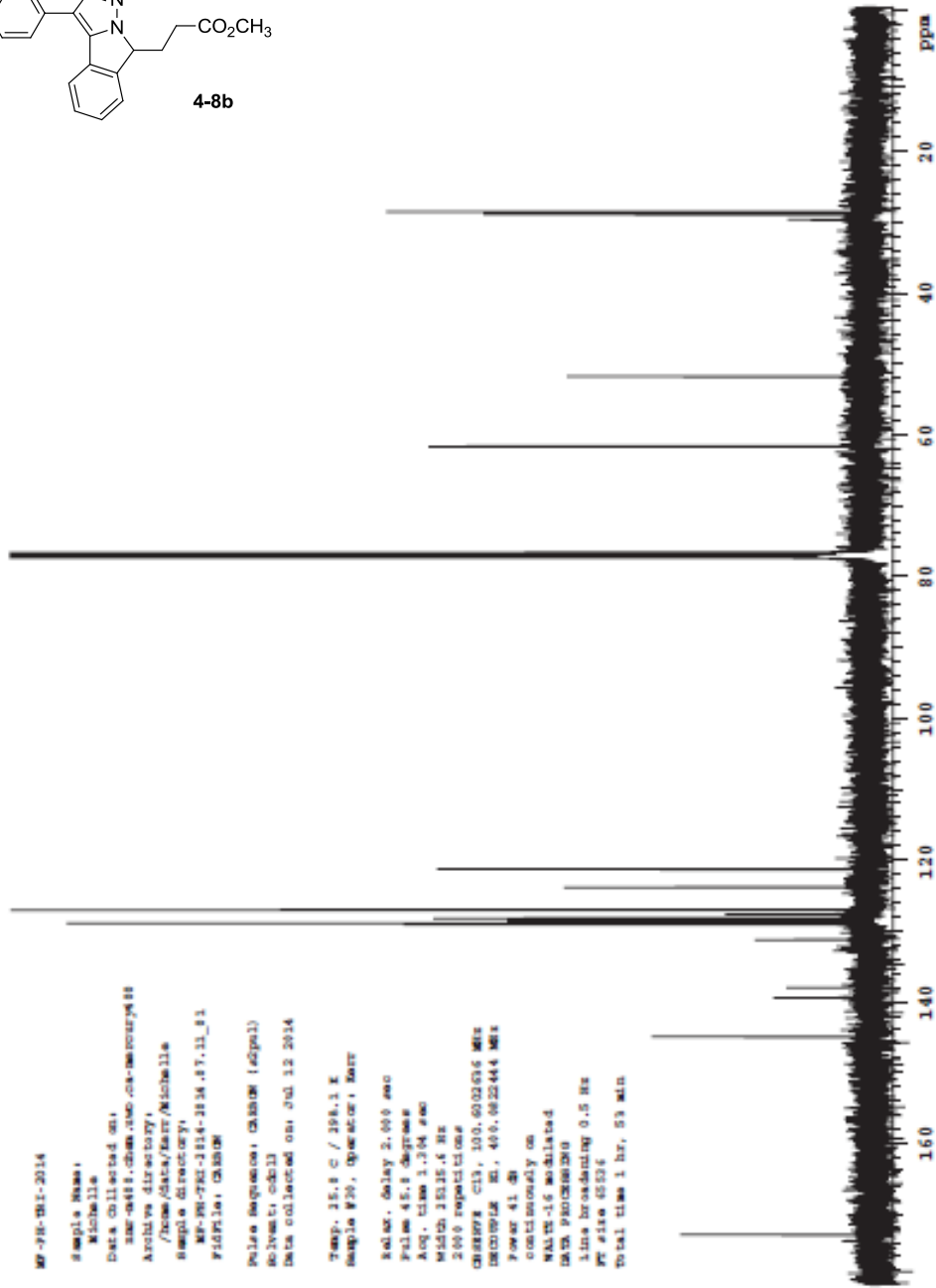
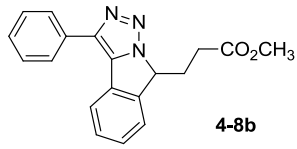




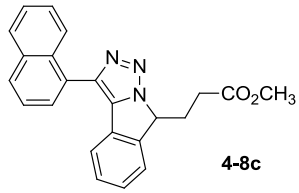
MF-3-173-PRODUCT
 Sample Name:
 Michella
 Data collected on:
 Tue-04-11-2013 10:00:00 AM
 Archive directory:
 /home/data/Bar/Michella
 Sample directory:
 MF-3-173-PRODUCT-2013-10-16_01
 FIDFILE, CHH001
 Pulse sequence: CHH001 (20201)
 Solvent: cdcl3
 Data collected on: Oct 16 2013
 Temp: 35.8 C / 96.4 F
 Sample #26, Operator: Bar
 Relax. delay: 3.000 sec
 Pulses: 45.8 degrees
 Acq. time: 1.354 sec
 Width: 15315.6 Hz
 512 repetitions
 CHANNEL: C13, 100.6202679 MHz
 DECUPLE: EL, 400.0020444 MHz
 Power: 40 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening: 0.5 Hz
 FT size: 65536
 Total time: 20 min



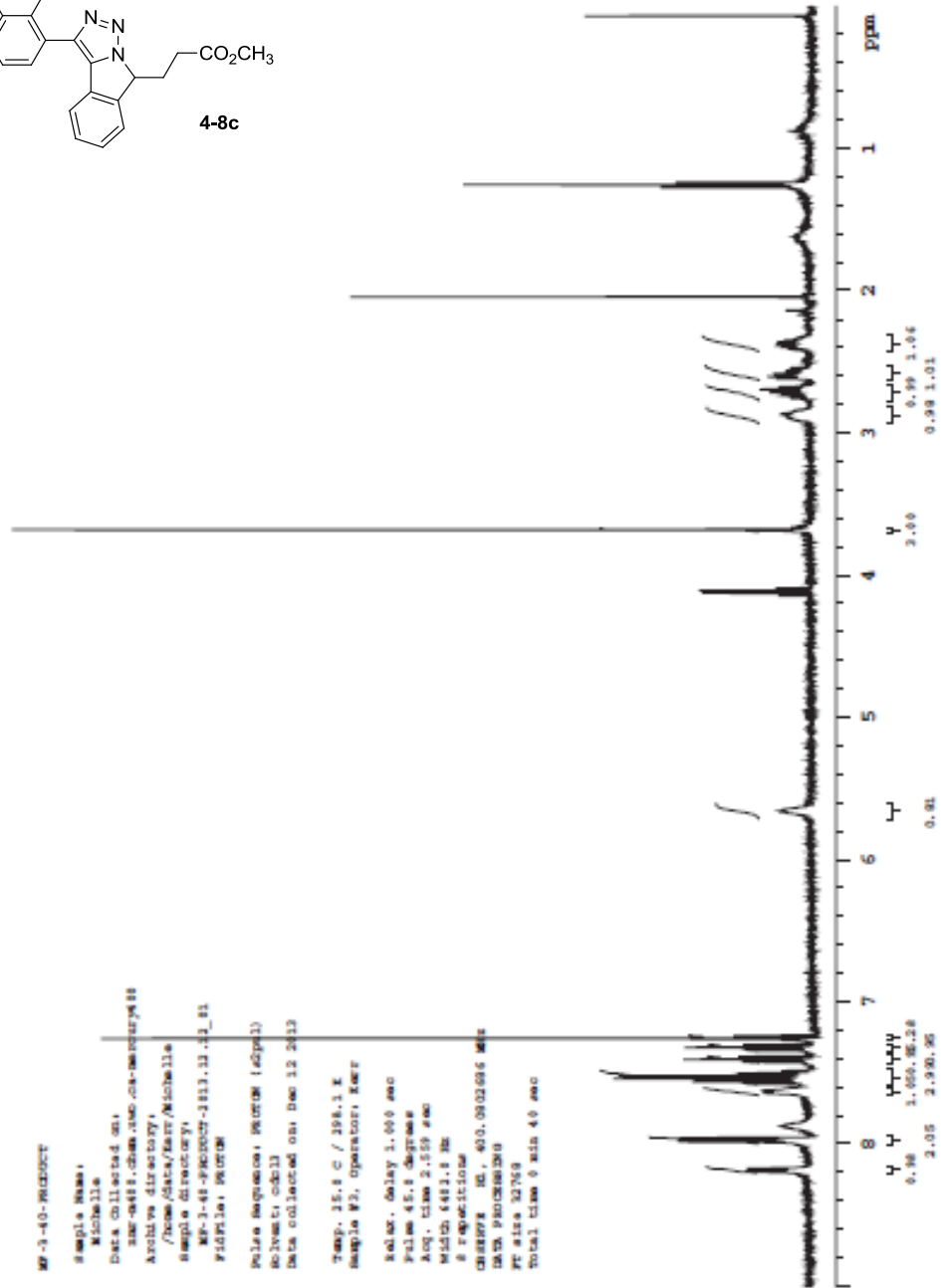


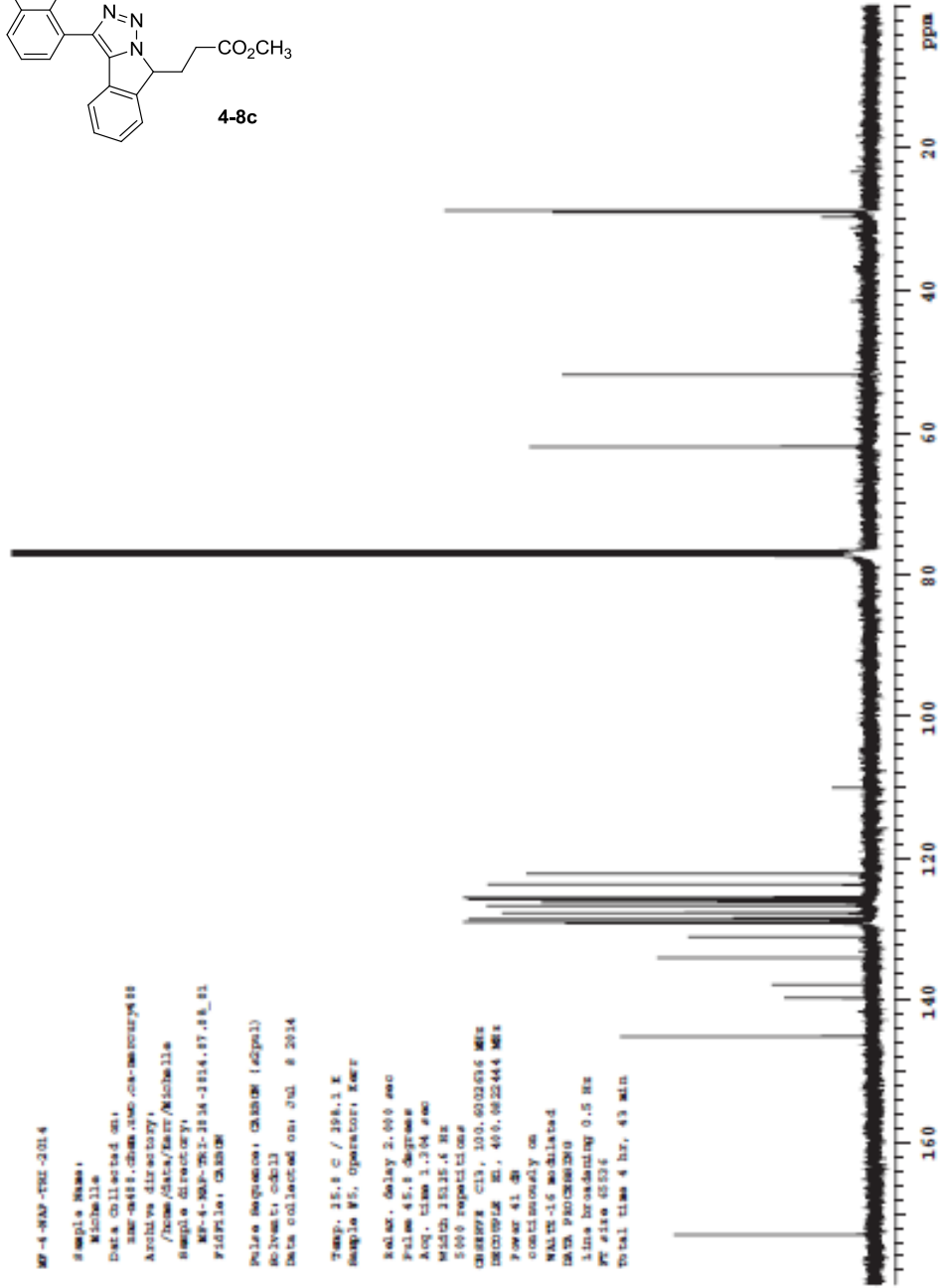
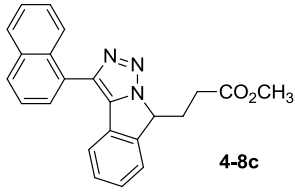


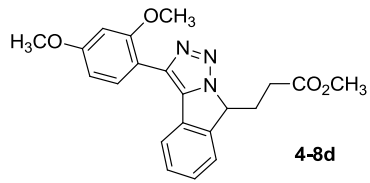
MF-781-2014
 Sample Name: Michelle
 Data collected on: mar-04-11-08am.140.ca-1400000488
 Archive directory: /home/Data/Karr/Michelle
 Sample directory: MF-781-2014-2014-07-11_11
 File(s): CH3001
 Pulse sequence: CH3001 (40p01)
 Solvent: cdcl3
 Data collected on: Jul 12 2014
 Temp: 35.8 C / 96.4 F
 Sample #20, Operator: Karr
 Relax. Delay 2.000 sec
 Pulse 45.8 degrees
 Acq. time 1.204 sec
 Width 15135.6 Hz
 2000 repetitions
 channels: C13, 100.620365 MHz
 DECOUPLER: NS, 400.0022444 MHz
 Power 41 dB
 continuously on
 WALTZ-16 stabilized
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 65536
 Total time 1 hr, 53 min



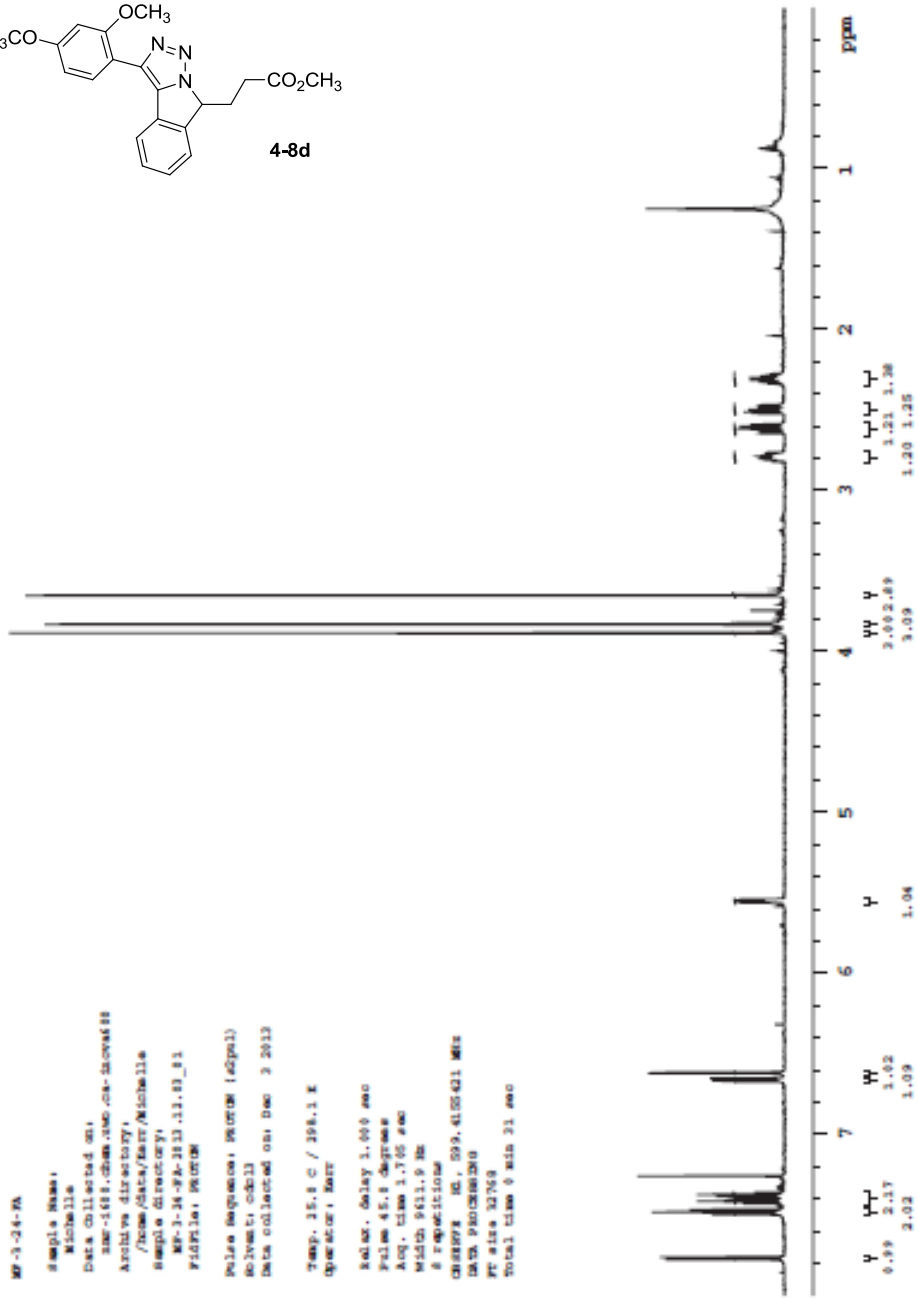
MF-3-40-PRODUCT
 Sample Name: Michella
 Data collected on: sar-0488.chan.vac.ca-0602070488
 Archive directory: /home/data/karr/Michella
 Sample directory: MF-3-40-PRODUCT-2013.12.13_01
 File(s): PRODUCT
 Pulse Sequence: MURCH (40ppl)
 solvent: cdcl3
 Data collected on: Dec 12 2013
 Temp: 15.3 C / 198.1 K
 Sample #2, operator: Kerr
 Solvent Delay: 1.000 sec
 Pulse: 45.8 degrees
 Acq. time: 2.559 sec
 MSCR: 602.8 Hz
 8 repetitions
 CHANNELS: HC, 400.0002096 MHz
 DATA PROCESSING
 FT size: 32759
 Total time: 0 min 40 sec

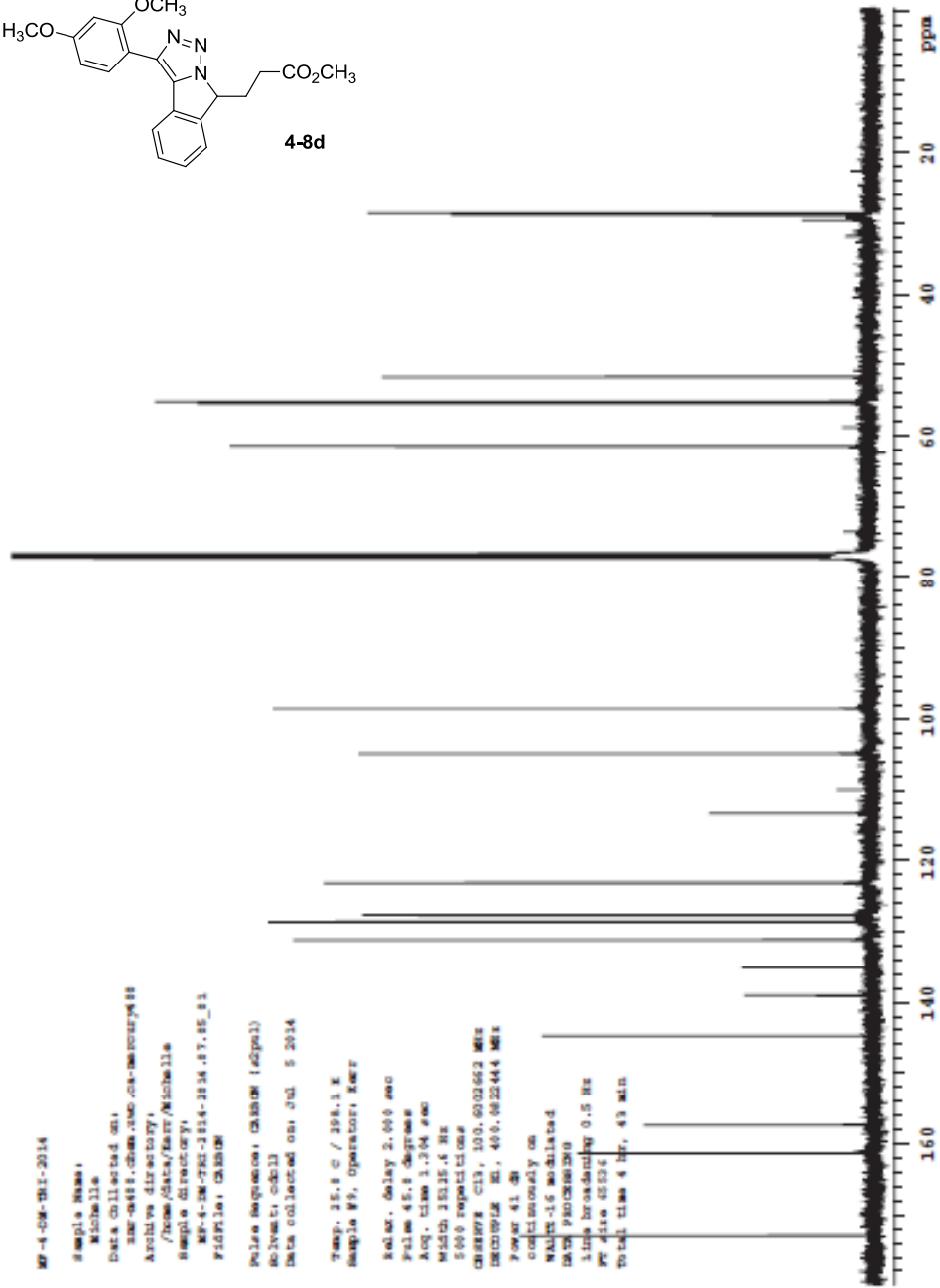
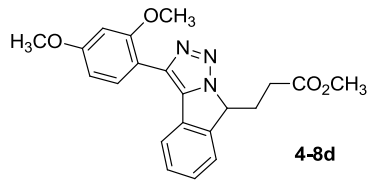


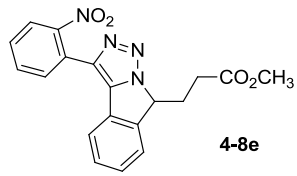




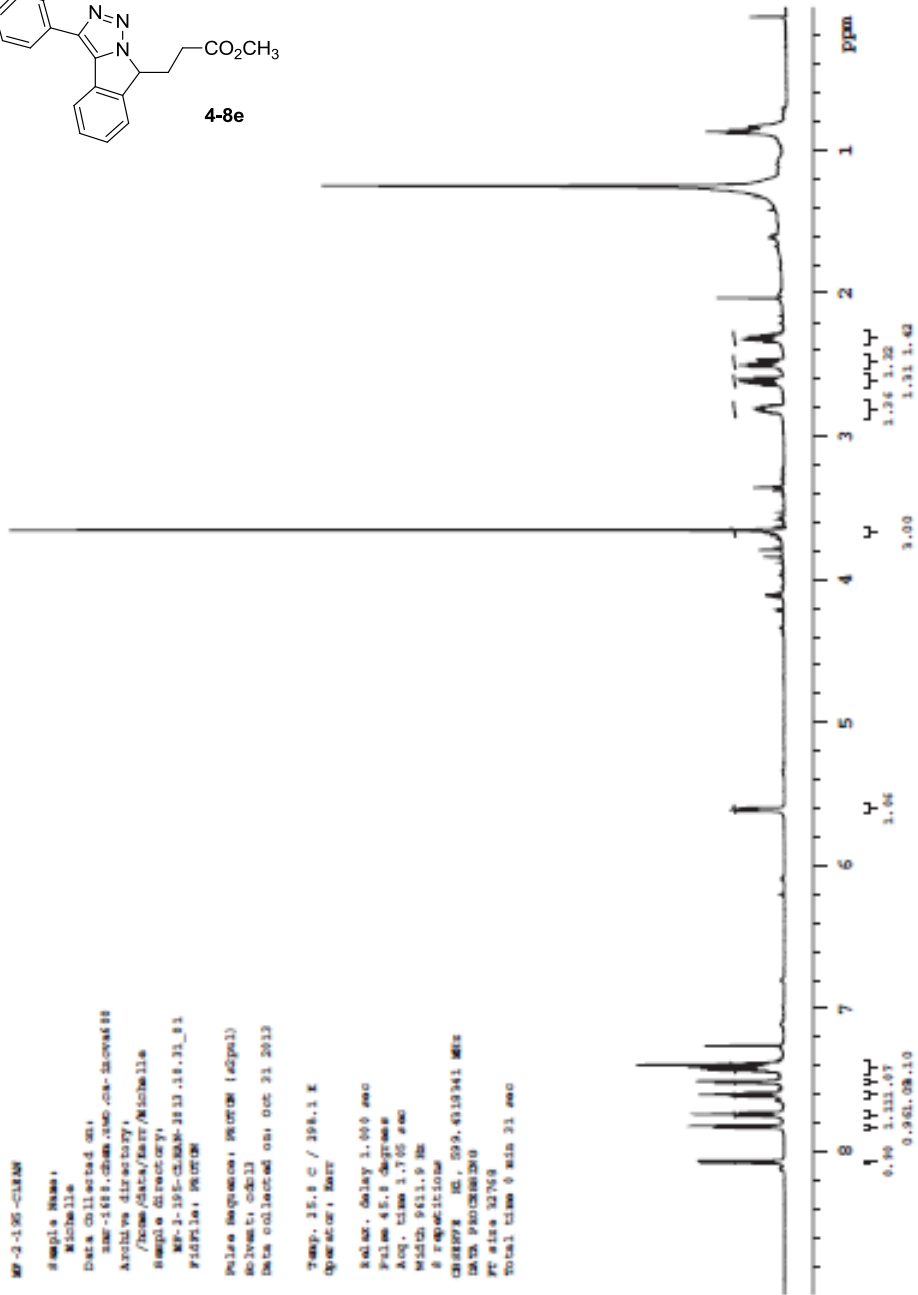
MF-3-24-FA
 Sample Name:
 Michelle
 Data collected on:
 2013-12-03 10:00:00
 Archive directory:
 /home/Data/FArr/Michelle
 Sample directory:
 MF-3-24-FA-2013-12-03_01
 FIDFILE: PR0708
 Pulse Sequence: PR0708 (40961)
 solvent: cdcl3
 Data collected on: Dec 3 2013
 Temp: 25.0 C / 77.0 K
 Operator: Farr
 Relax. Delay 1.000 sec
 Pulse 45.0 degree
 Acq. time 1.705 sec
 Width 9411.0 Hz
 6 repetitions
 Channels: 01, 009, 4105431 MHz
 DATA PROCESSING
 FT size 32768
 Total time 9 min 31 sec

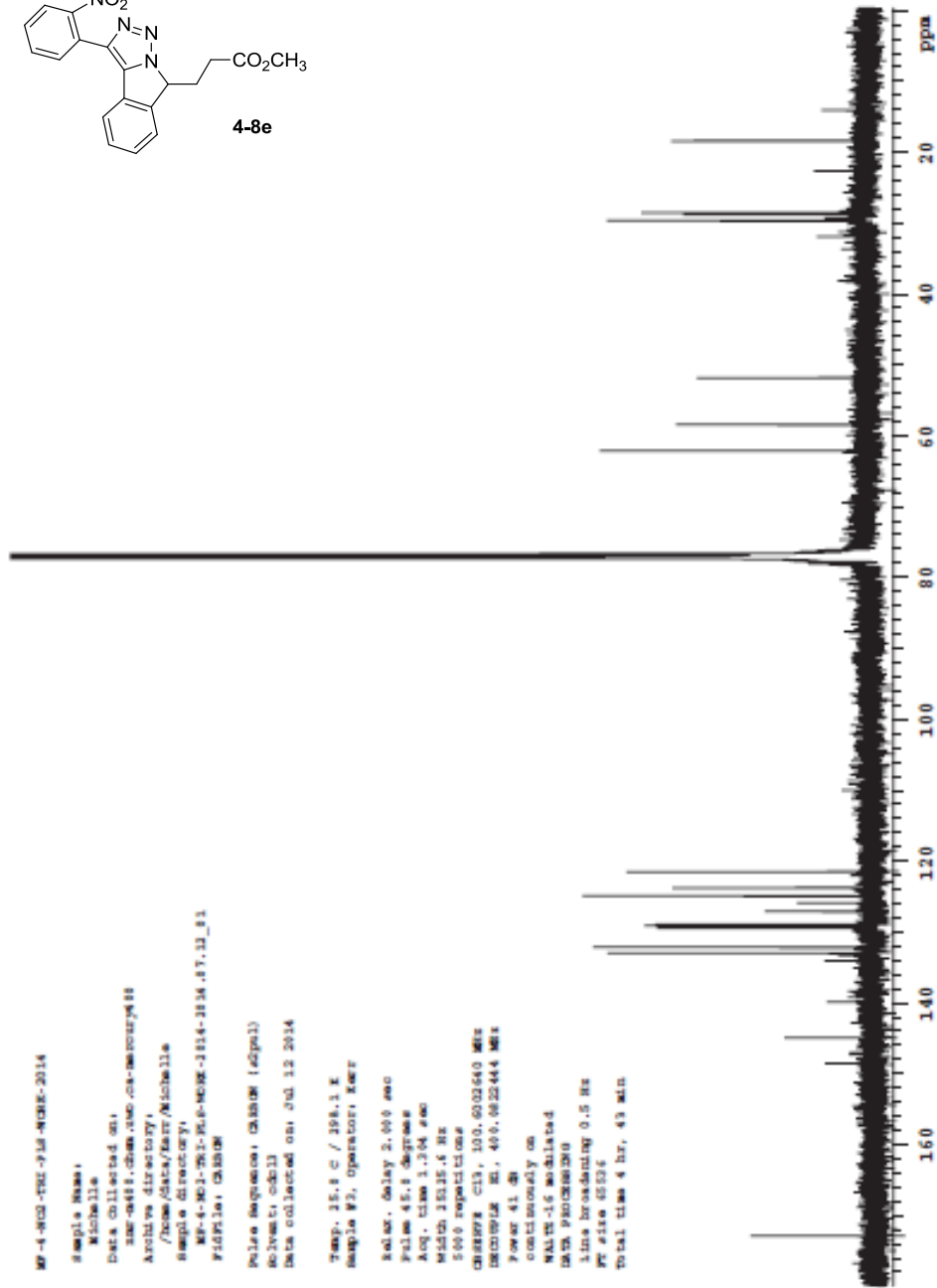
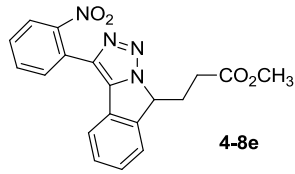


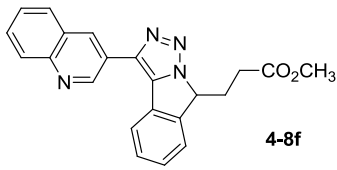




MF-2-195-CHAM
 Sample Name:
 Michelle
 Data collected on:
 mar-16-11 08:46:00 ca-1606488
 Archive directory:
 /home/data/Bar/Michelle
 Sample directory:
 MF-2-195-CHAM-1813.18.31_81
 P54P7616, PROTOM
 Pulse sequence: PROTOM (40961)
 solvent: CDCl3
 Data collected on: Oct 31 2013
 Temp: 25.8 C / 798.1 K
 Operator: Bar
 Solvent delay: 3.00 sec
 Pulse: delay 45.8 degrees
 Acq. time: 1.765 sec
 Width: 9811.9 Hz
 # repetitions:
 channels: 16, 099, 4310341 MHz
 DATA PROCESEDU
 FT size: 32758
 Total time: 0 min 31 sec







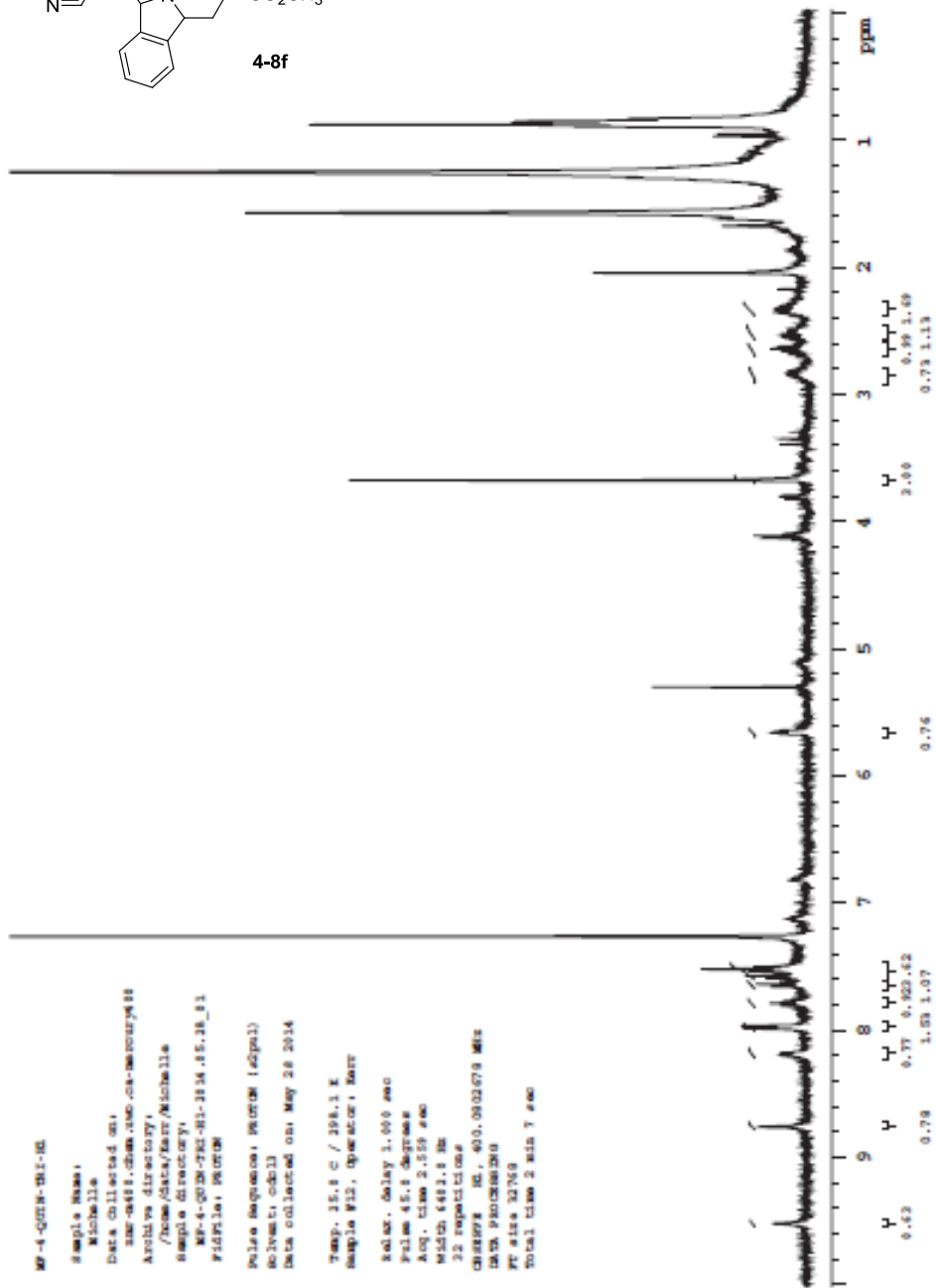
MF-4-Q228-181-02
 Sample Name:
 Michelle
 Data collected on:
 Tue-04/11/2014 14:00:00
 Archive directory:
 /home/data/Bar/Michelle
 Sample directory:
 MF-4-Q228-181-1814-05_18_01
 File(s): PLOT01

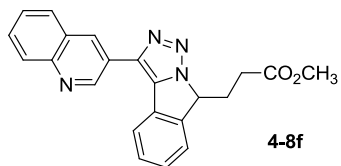
Pulse sequence: PLOT01 (adp11)
 solvent: cdcl3
 Data collected on: May 28 2014

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

Solvent delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.550 sec
 Width 6400.0 Hz
 32 repetitions

CHANNEL 01, 400.0002679 MHz
 DATA PROCESSING
 FT size 32768
 Total time 2 min 7 sec





KP-3-103-78-PRODCT-QTDC0328
 Sample Name:
 Michelle
 Data collected on:
 sat-0418-2014
 Archive directory:
 /home/data/kerr/Michelle
 Sample directory:
 KP-3-103-78-PRODCT-QTDC0328-03_18_14
 File(s): CH3OH

Pulse sequence: CH3OH (cp1)
 Solvent: cdcl3
 Data collected on: Jan 20 2014

Temp: 25.0 C / 298.1 K
 Sample Wt, Operator: Kerr

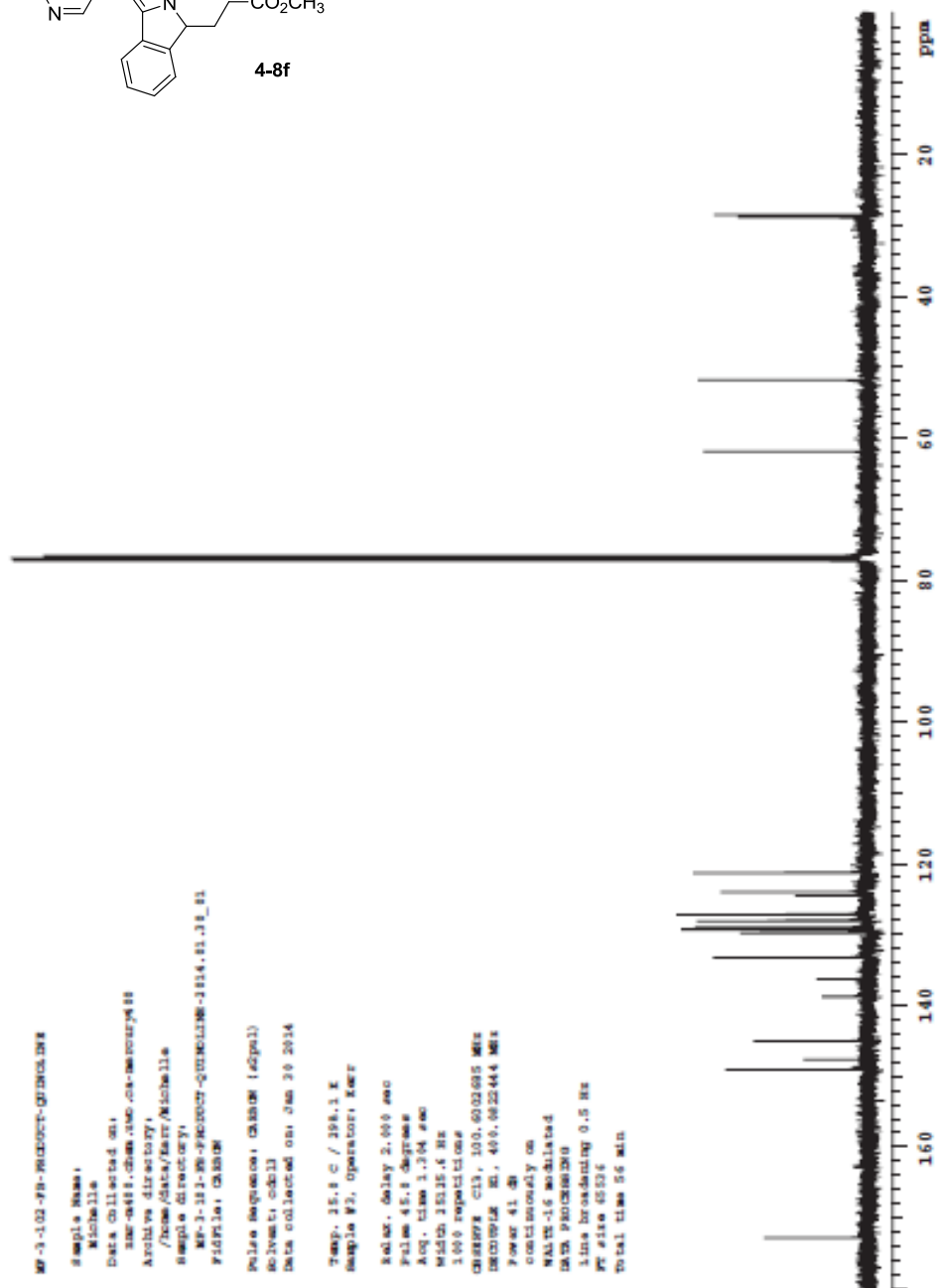
Relax. Delay 2.00 sec
 Pulse 45.8 degrees
 Acq. time 1.204 sec
 Width 15215.4 Hz
 1000 repetitions

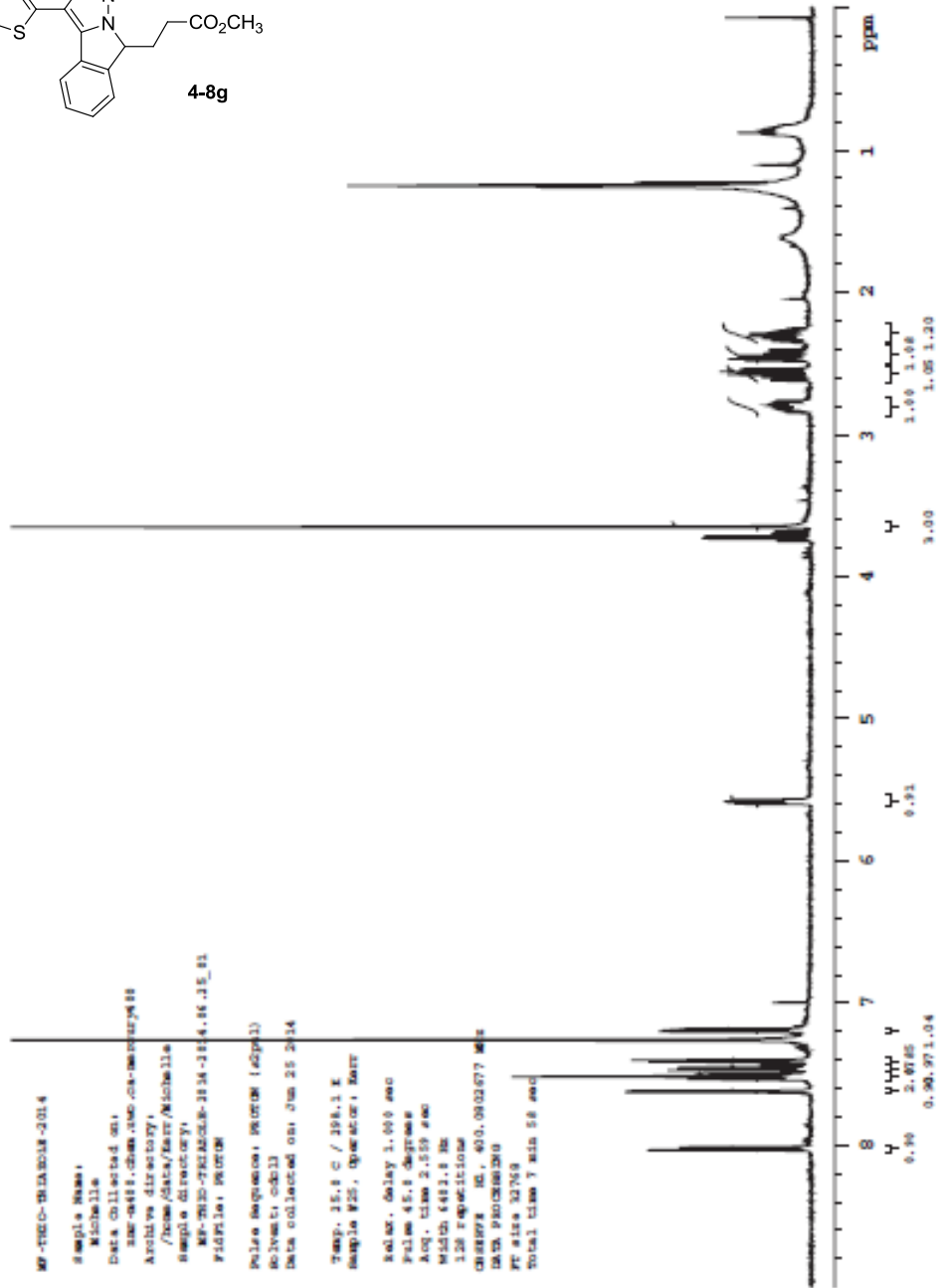
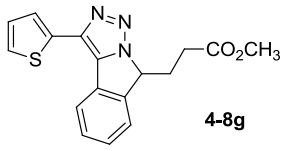
CHANNEL C13, 100.622605 MHz
 DECOUPLE H1, 400.002244 MHz

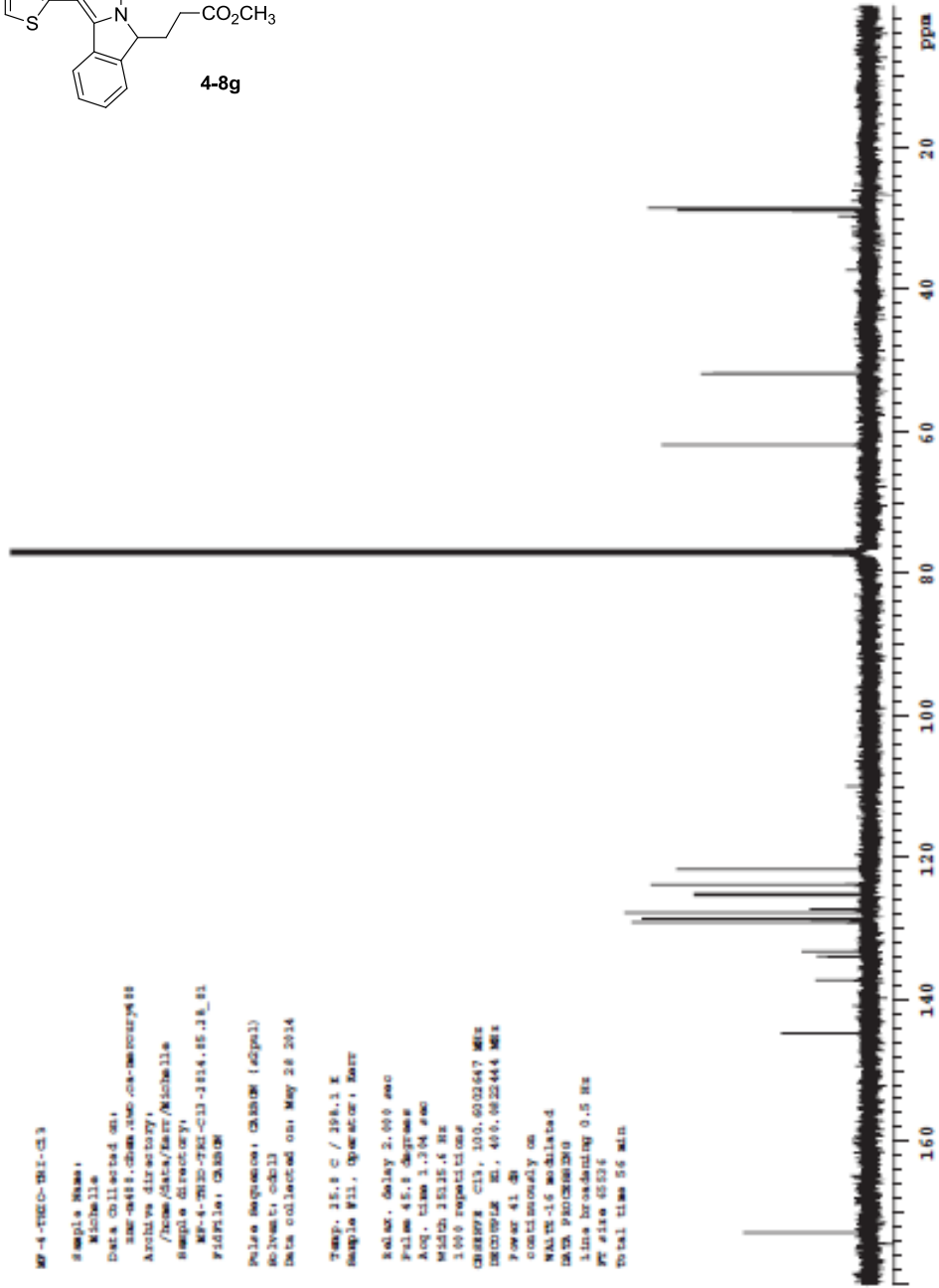
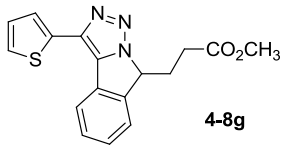
Power 41 dB
 conditionally on

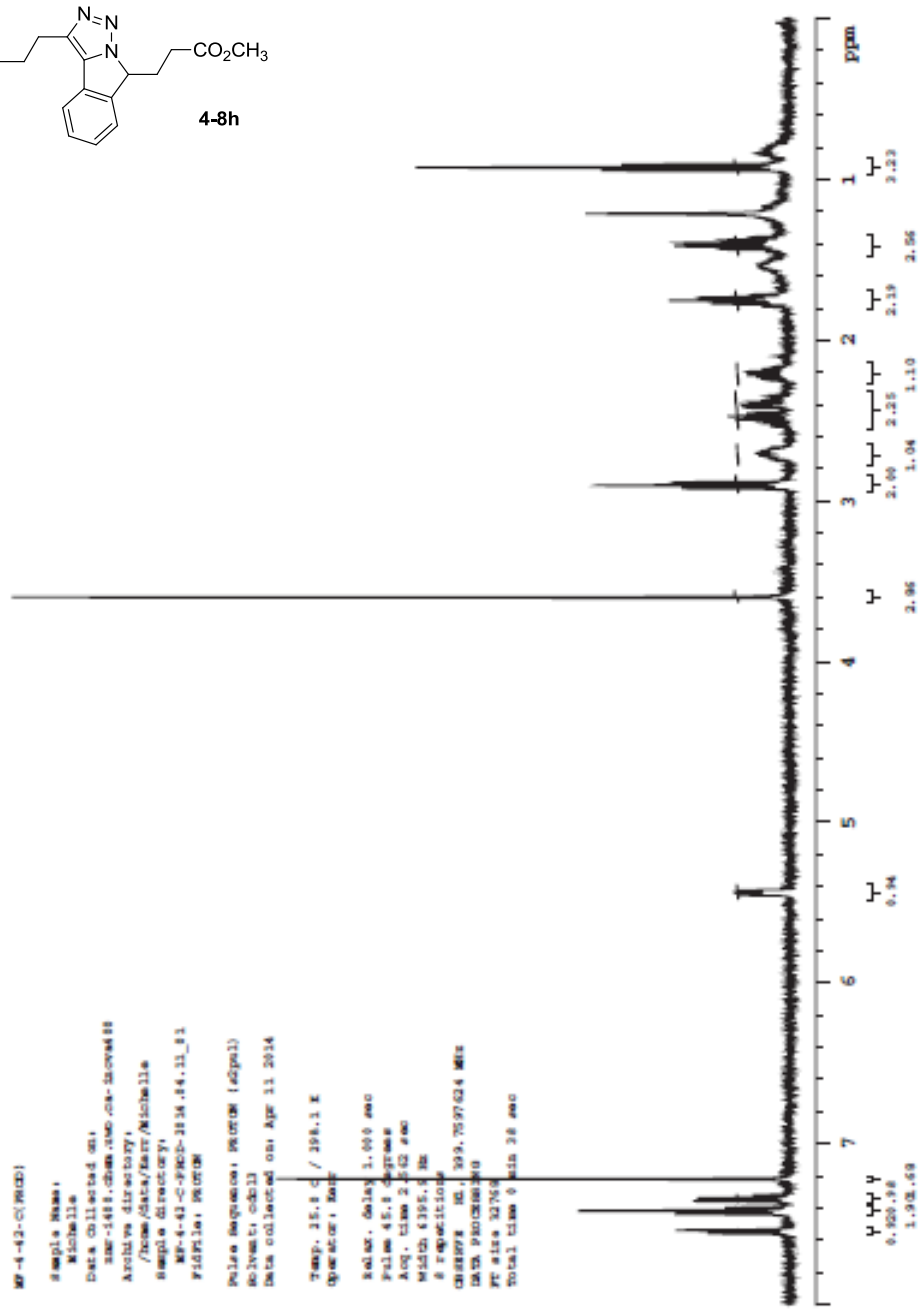
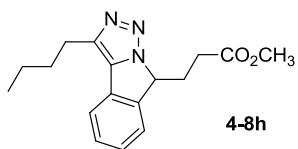
WALTZ-16 modulated
 DATA PROCESSING

Line broadening 0.5 Hz
 FT size 6556
 Total time 56 min







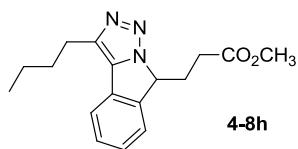


MP-4-42-C(1000)
 Sample Name:
 Michélla
 Data collected on:
 sun-148.chan.ncs-12000488
 Archive directory:
 /home/data/ncs/Michélla
 Sample directory:
 MP-4-42-C(1000)-2014.04.11_11
 File(s): 10000

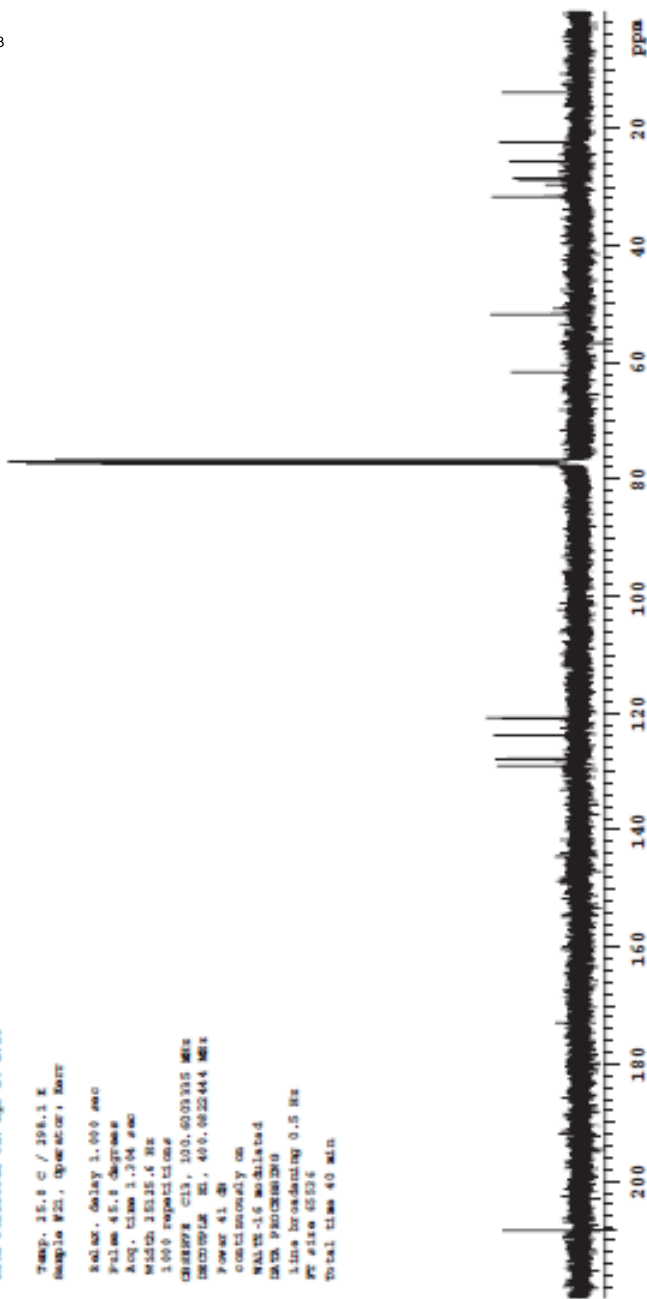
Pulse sequence: 10000 (adpnl)
 solvent: cdcl3
 Data collected on: Apr 11 2014

Temp: 35.0 C / 398.1 K
 Operator: kmp

Solvent delay: 3.00 sec
 P1: 45.1 sec
 Acq. time: 2.362 sec
 MTD: 6395.0 Hz
 S: 8 repetitions
 CHIRP: 10, 399, 7597624 MHz
 DATA PROCESSING
 FT size: 32752
 Total time: 0 min 38 sec



MF-4-NMPL-TRIAXIS
 Sample Name: Michelle
 Data collected on: mar-24-11.08:45:00.ca-00000468
 Archive directory: /Home/Data/Karr/Michelle
 Sample directory: MF-4-NMPL-TRIAXIS-214_04_19_01
 F54P101, CH3OH
 Pulse sequence: CH3OH (zgpg31)
 solvent: CDCl3
 Data collected on: Apr 29 2014
 Temp: 25.8 C / 798.1 K
 Sample #21, Operator: Karr
 Solvent delay: 3.000 sec
 Pulse delay: 45.8 degrees
 Acq. time: 3.264 sec
 Width: 10335.6 Hz
 1000 repetitions
 channels: C13, 100.603035 MHz
 decouple: H1, 400.0022444 MHz
 Power: 41.0
 continuously on
 WALTZ-16 modulated
 INVA: F80C00300
 Line broadening: 0.5 Hz
 FT size: 65536
 Total time: 40 min



Curriculum Vitae

Name: Michelle Flisar

Post-secondary Education and Degrees: Wilfrid Laurier University
Waterloo, Ontario, Canada
2008-2012 B.Sc. Biochemistry and Biotechnology

The University of Western Ontario
London, Ontario, Canada
2012-Present M.Sc. Chemistry

Honours and Awards: Deans Honour Roll, Wilfrid Laurier University
2010-2012

Related Work Experience

Teaching Assistant
The University of Western Ontario
2012-2014

Research Assistant
Wilfrid Laurier University
2010-2012 (May-August)

Publications:

Flisar, M. E.; Emmett, M. R.; *Kerr, M. A. "The Catalyst-free Tandem Ring-opening/Click Reaction of Acetylene-Bearing Donor Acceptor Cyclopropanes" *Synlett* **2014**, manuscript was accepted to Synlett and awaiting publication.