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One-Pot Synthesis of Bicyclic Piperidines from Donor Acceptor Cyclopropanes

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Abstract

The efficient synthesis of heterocyclic compounds is of great importance to organic chemistry. One method for achieving efficiency is through the use and development of one-pot reactions. This thesis describes the planning and development of an extension to the tandem cyclopropane opening Conia-ene reactivity previously reported. A search for a substrate capable of undergoing the reaction was undertaken and the reaction was optimized. The highest yielding conditions tested used catalytic $Sc(OTf)_3$ and superstoichiometric $ZnBr_2$, but other catalyst systems also worked. The optimized reaction conditions tolerated 6-membered rings well in addition to 7-membered rings in some rotationally restricted cases. Heteroatom linkers such as oxygen and protected amines were also well tolerated. This protocol provides efficient access to bicyclic piperidines that can be mapped onto natural products.

Keywords: bicyclic piperidines, cyclopropane annulation, donor acceptor cyclopropane, Conia-ene reaction, nucleophilic opening cyclopropanes, quinolizidine, one-pot reaction.

Summary for Lay Audience

Man-made pharmaceuticals need to be synthesized efficiently for the compounds to be commercially or medicinally relevant. These pharmaceuticals are nearly universally made through multistep synthesis. One way to make the synthesis of these compounds more efficient is by reducing the number of isolation and cleaning steps. Nearly every distinct reaction step necessitates purification of the product and inevitably some loss of material occurs. Therefore, a reaction method that involves more than one chemical change in a single vessel without isolation is desirable. This thesis describes the development of an efficient synthesis of a complicated chemical structure.

Acknowledgements

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A – acceptor

Ac – acetyl

AcOH – acetic acid

ACN – acetonitrile

Ad – adamantyl

Ar – aryl

Boc – *tert*-butoxycarbonyl

Boc_2O – di-*tert*-butyl decarbonate

Bn – benzyl

CSA – camphorsulfonic acid

D – donor

DA – donor-acceptor

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE – 1,2-dichloroethane

DCM – dichloromethane

DME – 1,2-dimethoxyethane

DMF – *N*,*N*-dimethylformamide

DMPU – *N*,*N*'-dimethylpropyleneurea

DMS – dimethyl sulfide

DMSO – dimethyl sulfoxide

DNs – 2,4-dinitrobenzenesulfonyl

dr – diastereomeric ratio

DTBAD – ditertbutylazodicarboxylate

E – electrophile

ee – enantiomeric excess

Et – ethyl

EtOAc – ethyl acetate

g – grams

h – hours

HRMS – high resolution mass spectrometry

IBX – 2-iodoxybenzoic acid

In-TOX – indane-trixoxazoline

*i*Pr – isopropyl

IR – infrared

LAH – lithium aluminum hydride

LDA – lithium diisopropylamide

Me – methyl

min – minutes

mmol – millimole

MOM – methoxymethyl

Ms – methanesulfonyl

µmol – micromole

µW – microwave

NBS – *N*-bromosuccinimide

NIS – *N*-iodosuccinimide

NMR – nuclear magnetic resonance spectroscopy

Ns – 2-nitrobenzenesulfonyl

NTf_2 – bis(trifluoromethyl)sulfonimide

Nu – nucleophile

OTf – trifluoromethanesulfonate

Ph – phenyl

rt – room temperature

Sia – 1,2-dimethylpropyl

STAB – sodium Triacetoxyborohydride

TBAF – tetrabutylammonium fluoride

TBS – *tert*-butyldimethylsilyl

t-Bu – *tert*-butyl

t-BuOK – potassium *tert*-butoxide

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TIPS – triisopropylsilyl

TLC – thin–layer chromatography

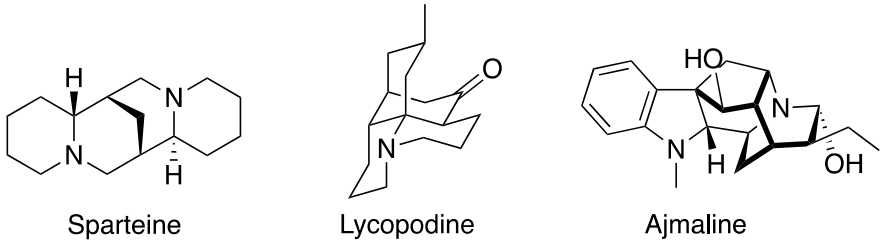
TMS – trimethylsilyl

Ts – toluenesulfonyl

Chapter 1 Introduction

1.1 Heterocycles in Natural Products

Heterocyclic moieties are highly abundant in pharmaceuticals and bioactive natural products of interest. A recent study found that around 59% of unique small molecule drugs contain a nitrogen heterocycle.[1] The biological effects of these alkaloids can be quite useful and widely varied. For example, sparteine acts as a sodium channel blocker,[2] Lycopodine exhibits anticholinestererase activity,[3] and ajmaline is used to treat heart arrhythmias.[4]



Sparteine Lycopodine Ajmaline

Figure 1.1. Selected heterocyclic natural products with biological effects.

It is sometimes challenging to obtain useful quantities of these products from natural sources. This difficulty can be because a compound is of low abundance or because the organism itself is rare or difficult to farm. As a result, it can be necessary to synthesize these natural products if they are desired for testing or pharmaceutical uses. Due to the aforementioned abundance of heterocycles in pharmaceuticals, efficient synthesis of these moieties is of significant importance to pharmaceutical chemistry. The efficiency of organic syntheses can be improved in many ways, but one popular approach is the use of one-pot reactions. In a one-pot reaction, more than one transformation occurs sequentially without isolation of intermediates.[5] Performing more than one transformation in one pot can lead to a significant reduction in the number of steps in a synthetic pathway.[6] For example, in a hypothetical synthesis of a final product, if 2 steps could be performed in one vessel, the one-pot synthesis would require fewer purification steps than the stepwise process (Figure 1.2). Due to the lessened purification requirments, syntheses that involve these one-pot protocols are in general shorter, more efficient, and greener. The improved

step economy also leads to overall more efficient and cost-effective synthetic pathways. This combination of factors makes designing one-pot protocols desirable.

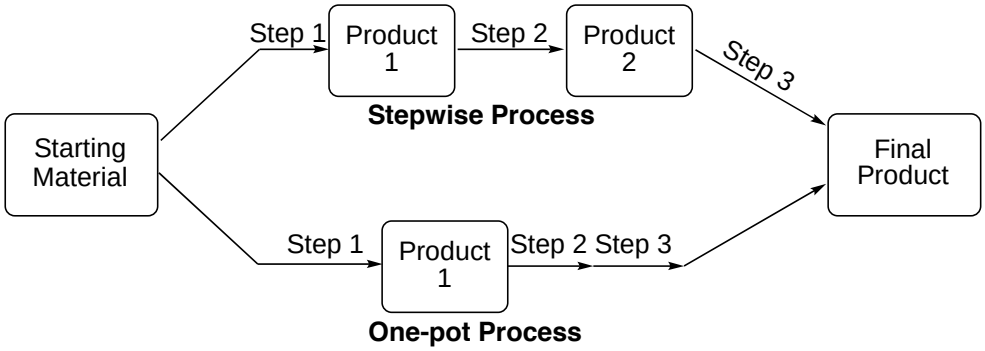
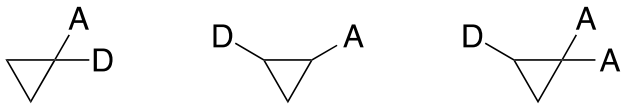


Figure 1.2. Efficiency of one-pot or tandem reactions.

1.2 Donor-Acceptor Cyclopropanes

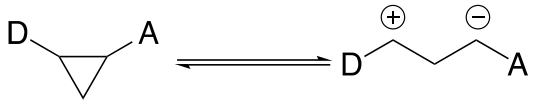
Cyclopropane is a highly strained molecule due to its bond angles of 60 degrees deviating significantly from the expected 109.5 degrees of an sp^3 hybridized carbon.[7] The arrangement of atoms also causes significant torsional strain as the hydrogen atoms are forced to be eclipsed.[8] These two factors in combination lead to a ring strain of an estimated 27.5 kcal/mol. This ring strain provides a strong driving force for ring-opening reactions. Despite this strain, cyclopropane itself is quite kinetically inert. This inertness can be altered by changing the substituents on the cyclopropane ring. A cyclopropane ring possessing both donor groups (electron donating groups) and acceptor groups (electron withdrawing groups) is referred to as a donor-acceptor (DA) cyclopropane. Geminal DA cyclopropanes are in general rather uninteresting compounds from a standpoint of reactivity **1.1** (Figure 1.3). However, if a donor group and an acceptor group are positioned on vicinal carbons on a cyclopropane ring, the resulting compound has unique reactivity **1.2**. The donor and acceptor groups work together to polarize the C-C bond between the groups through a tandem push-pull effect. This polarization activates the DA cyclopropane towards ring-opening reactions. DA cyclopropanes often also have two acceptor groups such as in **1.3**, but the reactivity is similar, and they are still referred to as DA cyclopropanes.



1.1 **1.2** **1.3**

Figure 1.3. General structure of DA cyclopropanes.

The ease of ring opening is further rationalized through a relationship with zwitterionic form **1.4** (Figure 1.4). The donor group provides electron density to the positively charged carbon and the acceptor group(s) stabilize the negative charge on the negatively charged carbon. In general, heteroatom donor groups are better at stabilizing the transition state than aryl donor groups, which are better than alkyl donor groups. A Lewis or Brønsted acid can be used to further polarize the C-C bond and activate the DA cyclopropane towards ring-opening reactions.

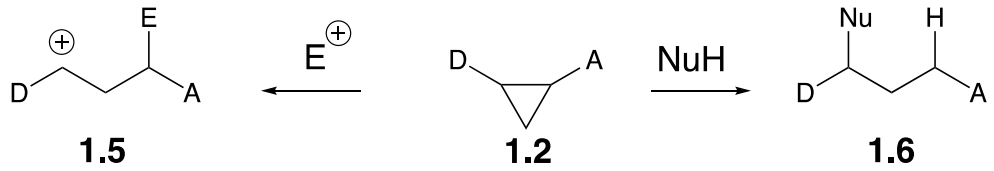


1.2 **1.4**

Figure 1.4. Zwitterionic relationship of DA cyclopropanes.

1.3 Ring Opening Reactions of Donor-Acceptor Cyclopropanes

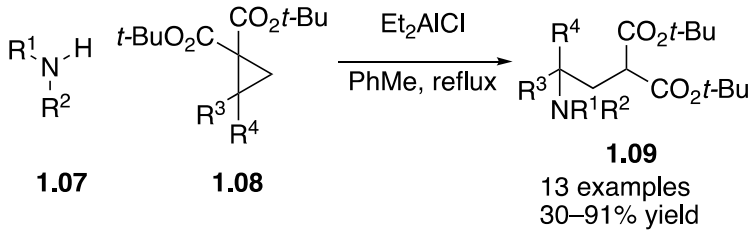
DA cyclopropanes can be opened with a wide variety of nucleophiles and electrophiles. Electrophiles add to the carbon attached to the acceptor group and nucleophiles add to the carbon attached to the donor group (Scheme 1.1). DA cyclopropanes react with nucleophiles to yield homo-Michael adducts **1.6**. Heteroatom nucleophiles such as amines and carbon nucleophiles such as indoles react well with DA cyclopropanes. Reviews have been published on the reactivity of DA cyclopropanes.[7] This thesis will focus exclusively on the opening of DA cyclopropanes with nucleophiles.



Scheme 1.1. Reactions of DA cyclopropanes with electrophiles and nucleophiles.

1.3.1 Ring Opening Reactions of DA Cyclopropanes with Amines

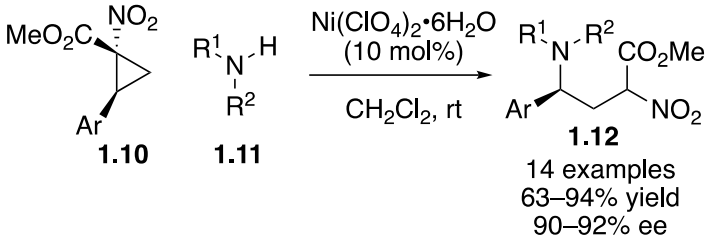
Amines are a commonly utilized class of nucleophile in ring opening reactions of DA cyclopropanes. The first reported example in the literature was by Schnieder and Blanchard.[9] In this protocol, stoichiometric Et_2AlCl was used to activate a series of cyclopropanes **1.08** and form ring-opened products **1.09** (Scheme 1.2). Ammonia as well as primary and secondary amines **1.07** were able to easily react with the cyclopropanes and form aminomalonates **1.09**. The reaction is thought to occur via the aluminum adduct of the amines.



Scheme 1.2. Reaction of DA cyclopropanes with amines mediated by Et_2AlCl.

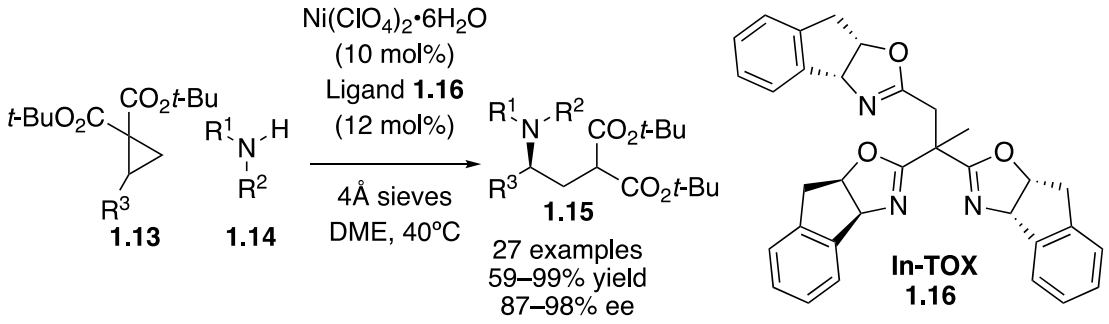
More recently, milder reaction conditions have been developed for opening DA cyclopropanes. A protocol developed by Charette and Lifchits can be used to open optically enriched DA cyclopropanes **1.10** with amines **1.11** at room temperature yielding ring-opened products **1.12** with no loss of enantiomeric excess at the electrophilic position of the cyclopropane (Scheme 1.3).[10] There was loss of chiral information at the carbon attached to the nitro group due to its enolizability. A number of Lewis acids were tested and $Ni(ClO_4)_2 \cdot 6H_2O$ provided the best yields while preserving the enantiomeric excess. The general conditions worked well for most amines, but piperidine, pyrrolidine as well as the very electron poor *p*-nitroaniline required longer reaction times. The slower-reacting amines still provided ring-opened products in good yields. Other aliphatic amines

complexed too strongly with the catalyst and slowed the reaction to the point of unfeasibility. Piperidine and pyrrolidine only reacted appreciably due to their high nucleophilicity. The reaction was tolerant of other aryl amines with a variety of electron donating and electron withdrawing groups. Interestingly, Boc protected amine substituents were also stable under the reaction conditions. This Boc protected amine handle could allow for particularly facile derivatization of the reaction products.



Scheme 1.3. Ring opening of DA cyclopropanes with amines catalyzed by $Ni(ClO_4)•6H_2O$.

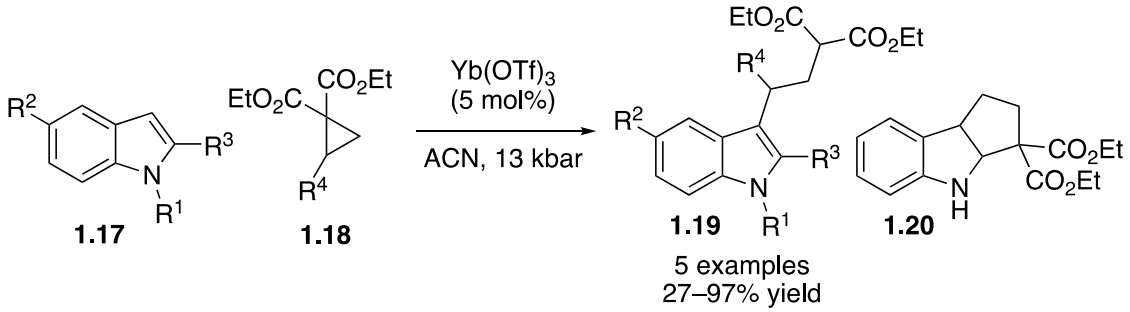
If an appropriate chiral catalyst is selected for the reaction, a racemic cyclopropane can be resolved into a nearly homochiral ring-opened product (Scheme 1.4). A protocol published by Tang *et al.* describes the use of a chiral catalyst to perform asymmetric induction. A Ni complex of an indane-trisoxazoline (In-TOX) ligand **1.16** was used to open DA cyclopropanes **1.13** with secondary amines **1.14** and yield enantioenriched γ-substituted γ-amino acid derivatives **1.15**. The compatible cyclopropanes included aryl, heteroaryl, and alkyl, and alkenyl substituted examples. Only cyclopropanes bearing an *o*-substituted aryl ring was problematic presumably due to steric effects. All the cyclopropanes converted to γ-substituted γ-amino acid derivatives with excellent enantioselectivity regardless of yield.



Scheme 1.4. Enantioselective ring opening of racemic DA cyclopropane.

1.3.2 Ring Opening Reactions of DA Cyclopropanes with Indole

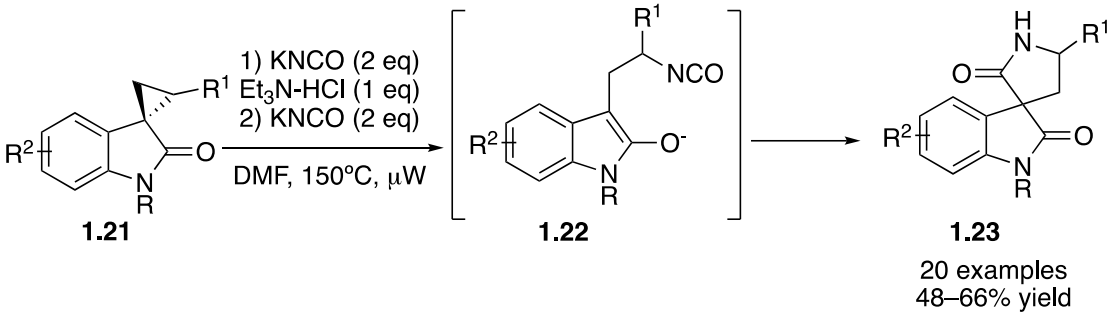
Indoles are another effective class of nucleophile for opening DA cyclopropanes. Homo-Michael adducts **1.19** of indoles **1.17** and DA cyclopropanes **1.18** were first reported by Kerr and Harrington (Scheme 1.5).[11] The reactions were performed under hyperbaric conditions with a $Yb(OTf)_3$ catalyst. Several cyclopropane substitutions were tested (R^4 = Me, H, and phenyl) and several substitutions on the indole nitrogen were tolerated (R^1 = Me, TIPS). The highest yield was obtained when a phenyl substituted cyclopropane was used. Of the indoles tested, *N*-methyl indole was the highest yielding. In the case of R^1 = TIPS, the yield was moderate, but there was some amount of desilylated product isolated. It was also noted that the yield was dramatically lower when the indole was *N*-unsubstituted (R^1 = H) due to the competing formation of **1.20**.



Scheme 1.5. Ring opening reactions of DA cyclopropanes with indole.

1.3.3 Ring Opening Reactions of DA Cyclopropanes with Isocyanates

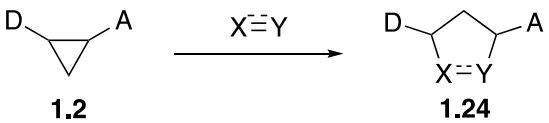
Nucleophilic DA cyclopropane opening initially yields a ring-opened product but this intermediate can react further and form cyclized products if additional chemistry occurs. In the case of the ring-opening of DA cyclopropanes **1.21** with isocyanate nucleophiles, the intermediate ring-opened product **1.21** undergoes a cyclization forming a spiro compound **1.22** (Scheme 1.6).[12] In this reaction, the isocyanate is trapped by the enolate generated by the cyclopropane opening. A number of aromatic donor groups were tolerated on the cyclopropane (R^1) including electron donating group and electron withdrawing group substituted rings and heteroaromatics. Only the electron deficient *p*-nitrophenyl cyclopropane failed to react with the isocyanate. This reaction is an example of a complex transformation achieved through a tandem reaction.



Scheme 1.6. Tandem reaction of DA cyclopropanes forming spirooxindoles.

1.4 [3+2] Annulation Reactions of DA Cyclopropanes

DA cyclopropanes **1.2** can undergo [3+2] annulation reactions with an appropriate unsaturated group (Scheme 1.7) forming 5-membered rings **1.24**. These annulation reactions are widely used in the synthesis of both carbocycles and heterocycles.



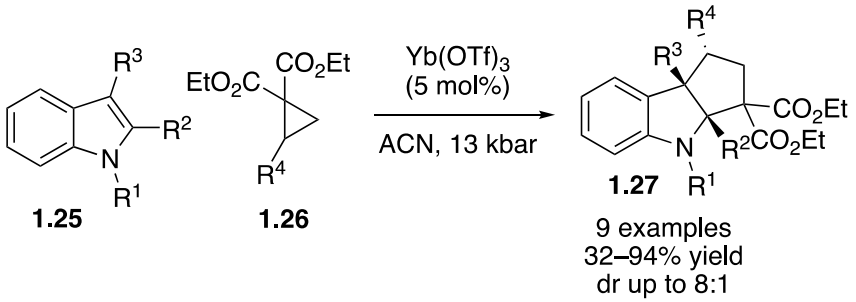
1.2 **1.24**

Scheme 1.7. General scheme for annulation reactions of DA cyclopropanes.

For example, annulation reactions with cyclopropanes can be performed with aldehydes,[13] imines,[14] ynamides,[15] nitriles,[16] indoles,[17] alkenes,[18] and many other suitable groups. These reactions typically require a Lewis acid catalyst to activate the DA cyclopropane.

1.4.1 [3+2] Annulation of 3-Alkylindoles with DA Cyclopropanes

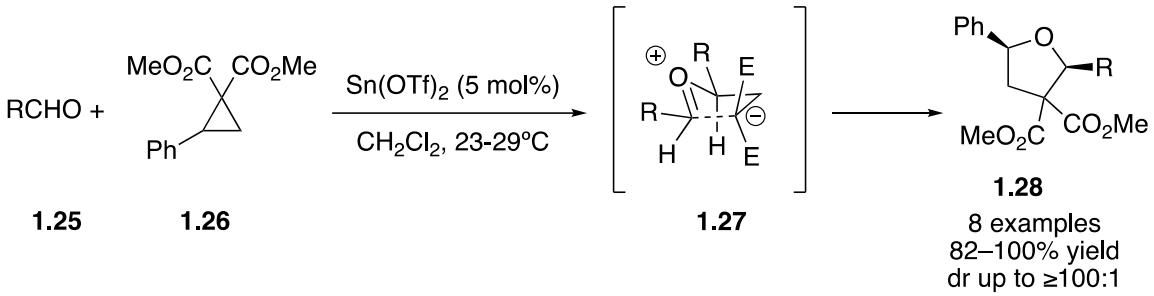
A minor side product isolated from Kerr and Harrington's work involving the ring opening of DA cyclopropanes with indole was an annulated product **1.20**.[11] This reaction pathway was explored in depth with more substituted indoles by Kerr and Keddy.[17] In the transformation, cyclopropane **1.25** reacted with indole **1.26** forming annulated product **1.27**. In the course of the reaction, the intermediate iminium ion generated after cylopropane ring-opening is intercepted by the malonate group. The overall transformation is a [3+2] annulation. This annulation was a minor reaction pathway when the indole was not 3-substituted as the competing rearomatization is rapid. It was realized that in the case of 3-alkylindoles, the annulated compound could be isolated as the major product. In many cases, the reaction was performed at atmospheric pressure, but in sterically demanding cases ($R^2 \neq H$), hyperbaric conditions improved the yield. Methyl substituted cyclopropanes and cyclopropanes without a donor group reacted with the indoles, but phenyl substituted cyclopropanes provided the highest yield and the best diastereoselectivity. The relative stereochemistry of the major diastereomer was as shown in **1.27**. The minor diastereomer had R^2 and R^3 cis to R^4.



Scheme 1.8. [3+2] annulation of 3-alkylindoles with DA cyclopropanes.

1.4.2 [3+2] Annulation of DA Cyclopropanes with Aldehydes

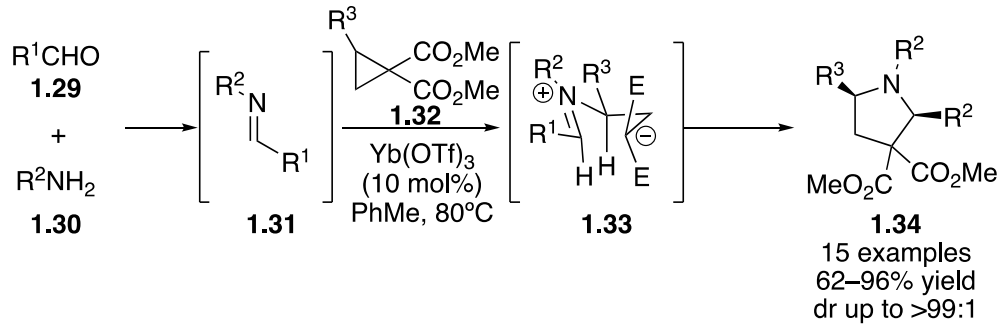
The [3+2] annulation pathway of DA cyclopropanes was extended to aldehydes by Polhaus and Johnson. When aldehydes **1.25** were reacted with DA cyclopropanes **1.26** in the presence of a $Sn(OTf)_2$ catalyst, the cyclopropane undergoes a [3+2] annulation forming 2,5-cis tetrahydrofurans **1.28** (Scheme 1.9).[13] The reaction had very good yields and moderate to excellent *cis:trans* diastereoselectivity (over 100:1) depending on the R group of the aldehyde (Scheme 1.2). Other catalysts promoted the reaction including $Cu(OTf)_2$, $Sc(OTf)_3$ and $SnCl_4$ albeit with lower *cis:trans* diastereoselectivity (59:1, 3:1, and 31:1 respectively) and longer reaction times. Harsher Lewis acids such as $AlCl_3$ and $TiCl_4$ caused decomposition of the DA cyclopropane. Milder Lewis acids such as $SnCl_2$, $ZnCl_2$, $Mg(OTf)_2$, and $La(OTf)_3$ were unable to promote the reaction. The reaction tolerated a number of different aldehydes including heteroaryl, alkenyl, and alkynyl substituents as well as electron rich, electron deficient, and electron neutral aryl substituents. It was noted that the rather electron poor 4-nitrobenzaldehyde required longer reaction times and additional catalyst. The diastereoselectivity of the reaction is proposed to be caused by a steric clash from the placement of the R group of the aldehyde in a pseudoaxial position in the transition state leading to the trans diastereomer **1.27**. The R group is placed in a more stable pseudoequatorial position in the transition state leading to the cis diastereomer **1.28**.



Scheme 1.9. One-pot tetrahydrofuran synthesis with DA cyclopropanes.

1.4.3 [3+2] Annulation of DA Cyclopropanes with Imines

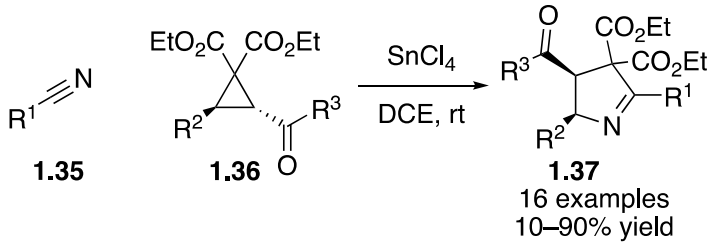
Another extension of the annulation chemistry of DA cyclopropanes was published by Kerr and Carson. The paper outlined the reaction of an aldehyde **1.29**, amine **1.30**, and DA cyclopropane **1.32** in the presence of a $Yb(OTf)_3$ catalyst forming 2,5-cis pyrroldines **1.34** (Scheme 1.10). This reaction proceeds via the intermediacy of the imine **1.31**. Preformed imines were also able to react directly with the cyclopropanes to furnish pyrrolidines but forming the imines *in situ* was found to be higher yielding. The cyclopropane and the $Yb(OTf)_3$ catalyst had to be added after imine formation since both the aldehyde and amine are capable of opening the DA cyclopropane under Lewis acid conditions. The mechanism follows the same general reaction mechanism as aldehydes. Phenyl, vinyl, and furanyl as well as donor free cyclopropanes reacted well under the conditions tested. A wide range of heteroaryl as well as electron neutral and electron rich aryl aldehydes were also tolerated. It was noted that the presence of the strongly electron withdrawing nitro group on the aldehyde prevented the formation of the annulated product. Analogous to the reaction of DA cyclopropanes with aldehydes, annulation reactions with aldimines were highly diastereoselective. This diastereoselectivity is also attributed to the greater stability of the transition state **1.33** leading to the cis pyrrolidine. Note that the bulky substituent (R^1) is placed in a pseudoequatorial. Diastereoselectivity was best in the case of R^1 = Ph and R^2 = alkyl. Heteroaryl aldehydes provided much poorer diastereoselectivity as did *N*-aryl aldimines. An explanation for this observation was not provided.



Scheme 1.10. Synthesis of pyrrolidines from DA cyclopropanes and aldimines.

1.4.4 [3+2] Annulation of DA Cyclopropanes with Nitriles

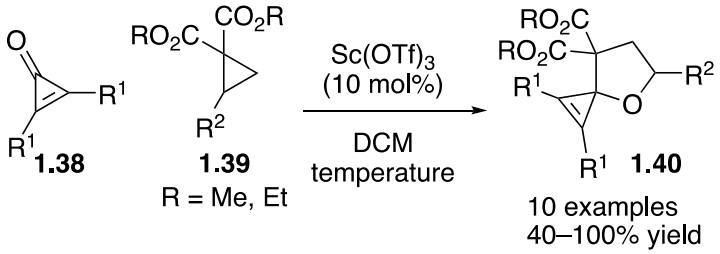
Nitriles are another useful class of dipolarophile that can undergo annulation reactions with DA cyclopropanes. The annulations of DA cyclopropanes with nitriles have been studied widely and a review has been published on the subject.[19] A representative example was published by Srinivasan and Sathishkanna.[20] In the protocol, nitriles **1.35** were able to undergo a $SnCl_4$ mediated [3+2] annulation reaction with DA cyclopropanes **1.36** forming highly substituted pyrrolines **1.37** (Scheme 1.11). The yields were moderate to high for all DA cyclopropane substrates except when R^2 = *p*-nitrophenyl. This reduced yield is presumed to be due to the lessened ability to stabilize the ring opening. There was a strong improvement in yield when acetonitrile was used over the other nitriles tested due to its different steric and electronic factors. The high diastereoselectivity of the reaction comes from the chirality of the starting DA cyclopropanes. There is inversion of configuration of the stereocenter at R^2 and retention of configuration at the R^3 carbonyl group.



Scheme 1.11. Synthesis of pyrrolines from [3+2] annulation of DA cyclopropanes with nitriles.

1.4.5 [3+2] Annulation of DA Cyclopropanes with Cyclopropenone

Annulation reactions of DA cyclopropanes have more recently been extended to other carbonyls such as cyclopropenones by Sierra *et al*.[21] In the protocol, cyclopropenone **1.38** undergoes a [3+2] annulation with a DA cyclopropane **1.39** forming oxaspiric compound **1.40** (Scheme 1.12). A number of substituents on the DA cyclopropanes were tested, with electron rich substituents increasing the yield and electron poor substituents slightly decreasing it. The extremely electron rich phthalimidyl group was extremely effective at promoting cyclopropane ring opening and provided exceptional yields (R^2 = phthalimidyl). While a nitro substituted aryl group on the DA cyclopropane completely prevented the desired reaction from occurring. The reaction also tolerated alkyl and aryl groups on the cyclopropenone.

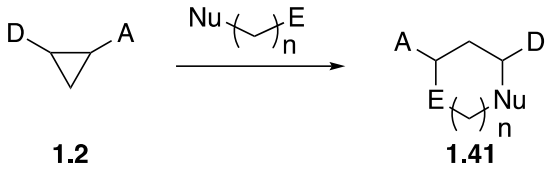


Scheme 1.12. Formation of spiro compounds by from DA cyclopropanes and cycloproenone.

1.5 Annulation Reactions of DA Cyclopropanes Forming Larger Rings

The [3+2] annulations of DA cyclopropanes are commonplace and the 5-membered ring containing reaction products are often useful compounds. A less well explored area is the [3+3] annulation of DA cyclopropanes (Scheme 1.13). Annulation reactions of this type form useful 6-membered rings and a number of protocols have been published in recent years. These [3+3] annulations can be used to synthesize either heterocycles or carbocycles. Annulations forming 6-membered rings have been performed with nitrones,[22] diaziridines,[23] carbonyl ylides,[24] 2-chloromethyl allylsilanes,[25] nitrosoarenes,[26] indonyl

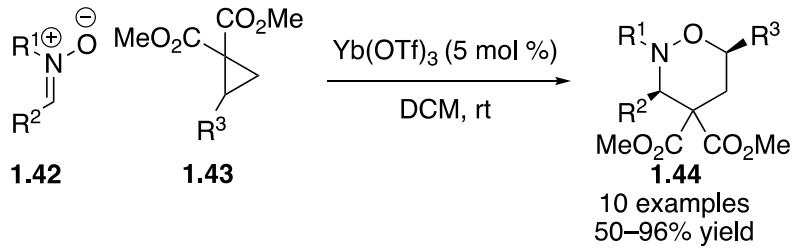
alcohols,[27] tronopnes,[28] and many other suitable dipolarophiles. Larger rings can also be formed if an appropriate dipolarophile is used.



Scheme 1.13. Annulation reactions of DA cyclopropanes forming 6-membered and larger rings.

1.5.1 Homo [3+2] Annulation DA Cyclopropanes with Nitrones

The homo [3+2] annulation of DA cyclopropanes to form 6-membered rings was first reported by Kerr and Young.[22] The paper discusses cycloaddition of nitrones **1.42** and DA cyclopropanes **1.43** forming tetrahydro-1,2-oxazines **1.44** in the presence of catalytic $Yb(OTf)_3$ (Scheme 1.14). Several other Lewis acids were tested but $Yb(OTf)_3$ had the best performance. Multiple nitrones were tested and it was found that the *N*-(*p*-tolyl) nitrones were the most reactive and provided the highest yields. Cyclopropanes without a donor group as well as vinyl, styryl, and phenyl substituted cyclopropanes reacted under the conditions and were converted to oxazines in moderate to excellent yield. The phenyl, styryl, and vinyl substituted cyclopropanes greatly reduced the reaction time required for conversion. The phenyl and styryl substituted cyclopropanes were also higher yielding. The lower yields in the case of vinyl substituted cyclopropanes were attributed to Lewis acid promoted polymerization. All the products possessed the same regiochemistry and were isolated as the cis diastereomer **1.44**.

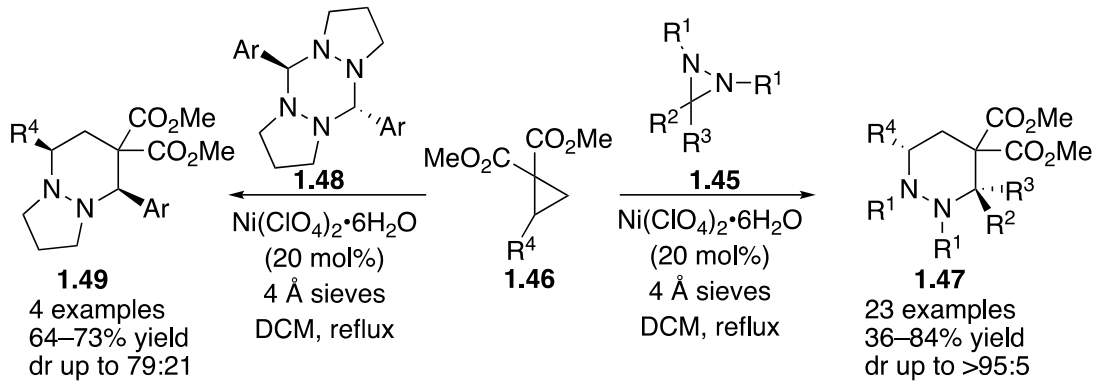


1.42 **1.43** **1.44**

Scheme 1.14. Homo [3+2] annulation of nitrones with DA cyclopropanes.

1.5.2 [3+3] Annulation DA Cyclopropanes with Diaziridines

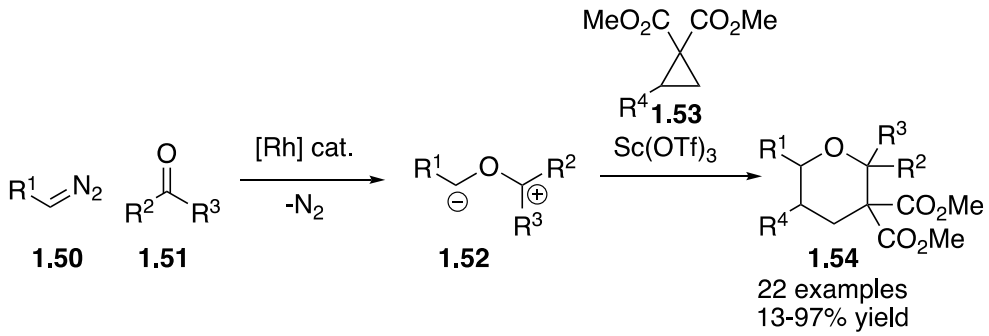
A recent advancement in the field of cyclopropane annulation was reported by Trushkov *et al*. The paper describes the first [3+3] annulation reaction between two different saturated 3-membered rings (Scheme 1.15).[23] In the reaction, a diaziridine **1.45** and a DA cyclopropane **1.46** combined to form a perhydropyridazine **1.47**. Of the Lewis acids tested, $Sc(OTf)_3$ was able to promote the reaction, but $Ni(ClO_4)_2{\cdot}6H_2O$ was more effective and provided better diastereoselectivity. Harsher Sn based Lewis acids such as caused decomposition of the diaziridine resulting in lower yields while the milder $Ni(OTf)_2$ failed to promote the reaction efficiently. A wide range of aryl, heteroaryl, and alkenyl DA cyclopropanes were tolerated as were several different substituents on the diaziridine. Diaziridines bearing no substituents on the ring carbon (R^2, R^3 = H) reacted efficiently under the conditions as did diaziridines with a quaternary ring carbon. Bicyclic diaziridines (R^1 = $(CH_2)_3$) reacted much more effectively than the acyclic diethyl derivative (R^1 = Et). This enhanced reactivity is attributed to the likely trans arrangement of the groups on the diaziridine hindering attack on the DA cyclopropane. In cases where R^3 = H, the reaction product was primarily the trans diastereomer. Diaziridines can dimerize with each other and form pyrazolo[1,2-a]pyridazines **1.48** and these dimers can also react with DA cyclopropanes. Interestingly, there was a reversal of the diastereoselectivity when these dimers were reacted with preference for the cis diastereomer **1.49**. The reactivity of the dimers **1.48** may be due to their relationship with azomethine imines.



Scheme 1.15. [3+3] annulation of DA cyclopropanes with diaziridines.

1.5.3 [3+3] Annulation of DA Cyclopropanes with Carbonyl Ylides

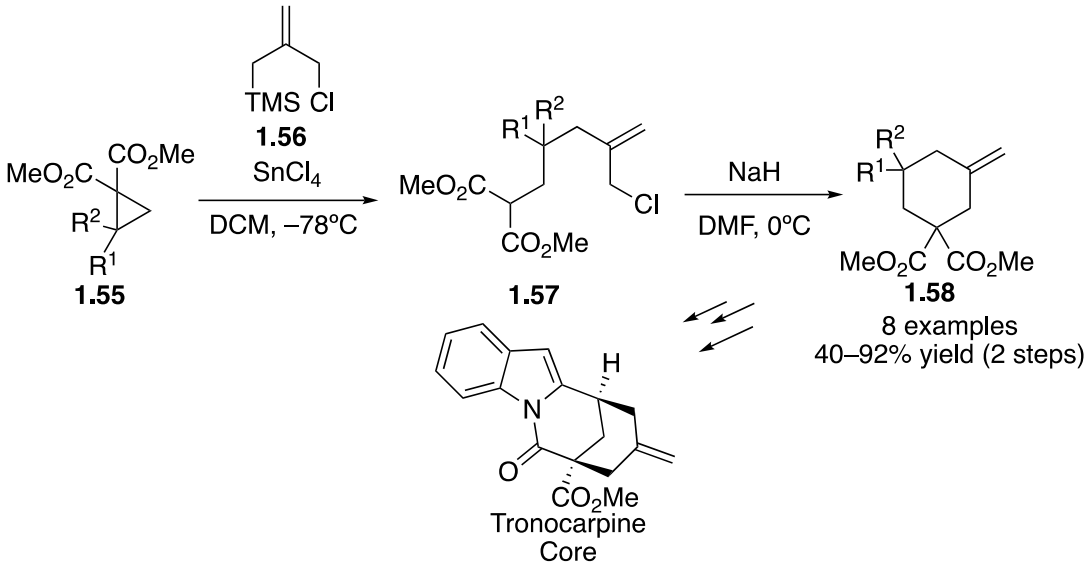
An interesting application of reactive intermediates in the annulation reactions of DA cyclopropanes was demonstrated by Werz, Jones, and Petzold.[24] The paper describes the reaction of carbonyl ylides **1.52** with DA cyclopropanes **1.53** forming tetrahydropyrans **1.54** (Scheme 1.16). The reaction required two catalysts; a Rh(II) catalyst to perform the metal carbenoid chemistry and a Lewis acid to activate the DA cyclopropane. Somewhat more exotic Rh(II) catalysts were also tested, but none performed better than the simple $Rh_2(OAc)_4$. Of the two Lewis acids tested individually, $Sc(OTf)_3$ was found to have better performance than $Yb(OTf)_3$. Interestingly, it was found that adding a small portion of $Yb(OTf)_3$ to the $Sc(OTf)_3$ catalyst provided the highest yields. In the tested case, the carbonyl and diazo compound are part of the same compound. A range of aryl substituents were tolerated on the DA cyclopropanes. The cyclopropanes bearing heteroaromatic or aryl substituents with weak or strong donor groups provided the best yields in the reaction. Any electron withdrawing substituent on the phenyl ring of the cyclopropane reduced the yield dramatically. Careful testing of temperature led to the conclusion that reacting the components at 30ºC was most preferred. Higher temperatures (70ºC) completely prevented the desired transformation. In testing, several diazo tethered methyl esters were utilized, and the solvent of choice depended on the length of the chain connecting the groups. The reaction was moderately to strongly diastereoselective depending on the diazo compound tested. This diastereoselectivity was attributed more to solvent effects than any other factor since the solvent selected was different based on the substrate tested.



Scheme 1.16. Synthesis of tetrahydropyrans from DA cyclopropanes and carbonyl ylides

1.5.4 [3+3] Annulation of DA Cyclopropanes with 2-Chloromethyl Allylsilanes

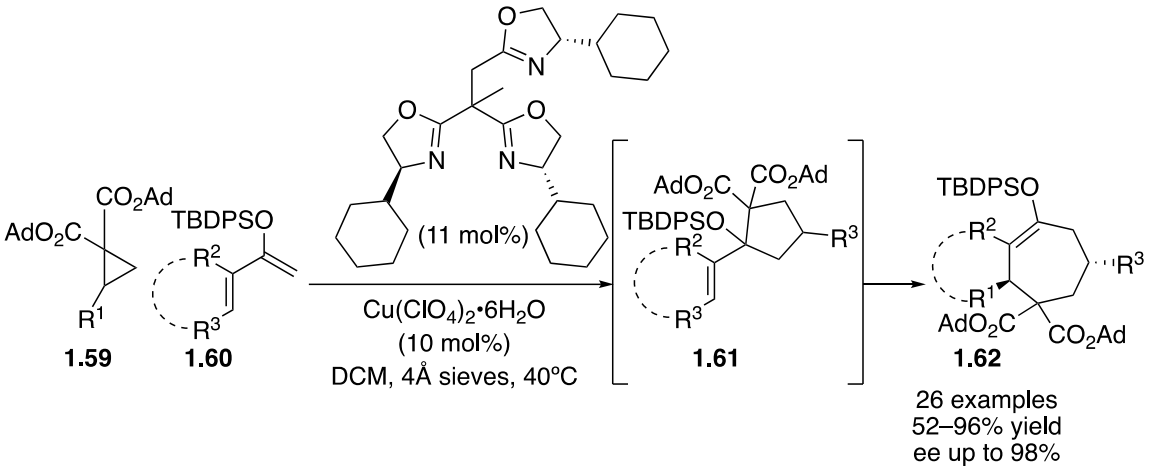
A two-step annulation of DA cyclopropanes with 2-chloromethyl allylsilanes forming cyclohexanes was reported by Kerr and Sapeta.[25] The original goal of the transformation was to use a Pd-trimethylenemethane complex to annulate the DA cyclopropane. Unfortunately, all attempts at Pd catalysis did not yield the desired product. Fortunately, after some testing, a two-step protocol that achieved the transformation was discovered. The process began by first opening the DA cyclopropanes **1.55** with the allylsilane **1.56** in the presence of $SnCl_4$ giving yields from 62 to 92% (Scheme 1.17). The ring opened products **1.57** was isolated and then treated with NaH to afford the final cyclohexanes **1.58** in yields from 75 to 97%. Unsubstituted, heteroatom substituted, and monoalkyl substituted cyclopropanes underwent ring opening by a chloride and produced no allylated product **1.57** under reaction conditions. Phenyl and heteroaryl substituted cyclopropanes were well tolerated by the reaction and the products were isolated in high yield. The reaction was more problematic for the spiro cyclohexyl cyclopropane (R^1, R^2 = $(CH_2)_5$). Some amount of the underwent elimination to form an inseparable byproduct. The allylated material still converted to the desired cyclohexane **1.58**. The utility of the reaction products was demonstrated by using the protocol to synthesize the core of tronocarpine.



Scheme 1.17. Synthesis of exomethylene cyclohexanes from DA cyclopropanes and 2-chloromethyl allylsilanes.

1.5.5 [4+3] Annulation of DA Cyclopropanes with Dienes

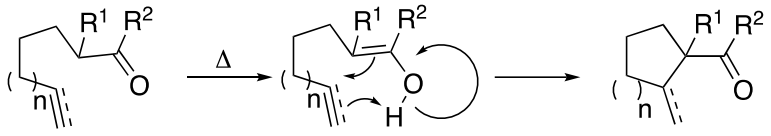
An example of an annulation of DA cyclopropanes forming 7-membered rings was published by Tang *et al.*[29] In the reaction, a DA cyclopropane **1.59** reacts with a diene **1.60** to form cycloheptenes or [*n*,5,0]carbobicycles **1.62** (Scheme 1.18). Mechanistic studies were undertaken, and it was found that the reaction proceeds in two parts. First, a [3+2] cycloaddition takes place forming **1.61** which then undergoes an intramolecular cyclization forming **1.62**. The second intramolecular cyclization was confirmed by exposing purified **1.61** to the reaction conditions. Based on the results of the experiments, the [3+2] product is the kinetic product and the [4+3] product is the thermodynamic one. The reaction was highly enantioselective when a chiral ligand was used.



Scheme 1.18. [4+3] annulation of DA cyclopropanes with dienes.

1.6 Conia-ene Chemistry

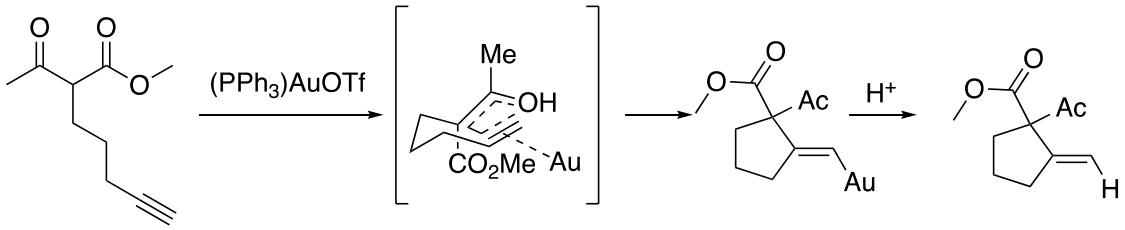
The Conia-ene reaction is an intramolecular C-C bond forming reaction in which an enol reacts with a tethered alkene or alkyne. In the reaction, cyclization occurs through a concerted 1,5 hydrogen shift.[30] The Alder-ene reaction is mechanistically similar to the thermal Conia-ene reaction. This reaction was first reported in the 1970s as a thermal process (Scheme 1.19). Unfortunately, this version of the reaction is mostly unsuitable for complex synthetic protocols as it requires extremely high temperatures. The thermal Conia-ene reaction only proceeds at an appreciable rate at temperatures exceeding 300ºC. At these elevated temperatures, many functional groups tend to undergo pyrolysis. The yield can also be quite low, especially for larger rings.



Scheme 1.19. Mechanism of the thermal Conia-ene reaction.

It was discovered that including a Lewis acid to activate the alkyne or alkene significantly reduced the temperatures required for the reaction.[31] Cyclizations that previously required temperatures near 300ºC could be realized at or near room temperature with the simple addition of a gold catalyst (Scheme 1.20). The Lewis acid catalyzed reaction occurs in two

steps with cyclization occurring first followed by protodeauration. Stereochemical outcome of the addition is as shown with the Au atom trans to the dicarbonyl in the intermediate. In the case of reactions with a tethered alkyne, the product is a beta-gamma unsaturated carbonyl compound. The reaction is particularly well suited to forming 5 and 6-membered rings.

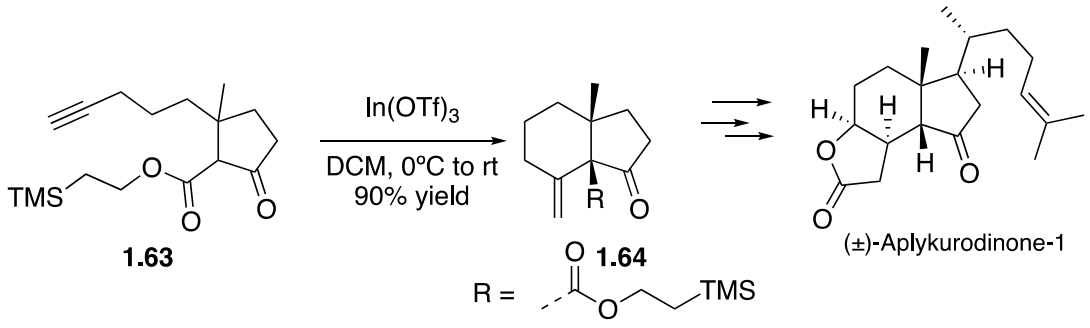


Scheme 1.20. Lewis acid catalyzed Conia-ene reaction proceeds at room temperature.

The catalytic Conia-ene reaction has seen significant use in organic synthesis and reviews have been published.[32] Conia-ene chemistry is also used in the synthesis of heterocycles and has been applied in the total synthesis of many compounds.

1.6.1 Total Synthesis of (±)-Aplykurodinone-1 with the Conia-Ene Reaction

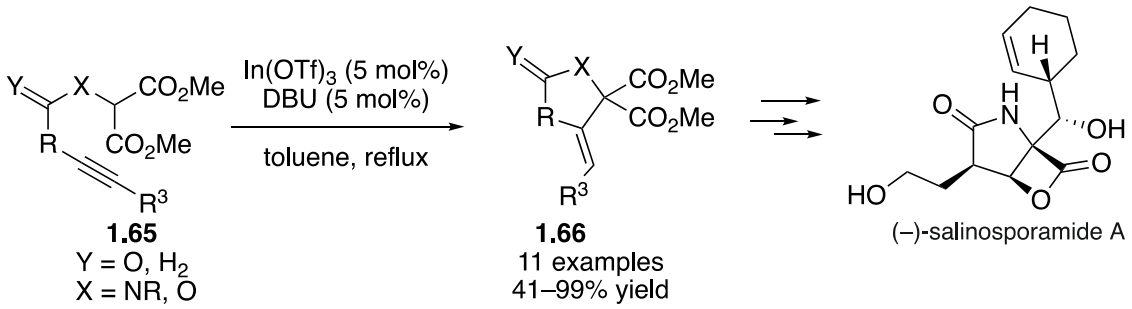
The Conia-ene reaction has also been applied to more complicated systems as in the case of a formal total synthesis of (±)-aplykurodinone-1 reported by Huang *et al.* In one of the key steps of the transformation, an alkyne **1.63** was cyclized to a bicyclic compound **1.64** using Conia-ene chemistry (Scheme 1.21). A significant amount of optimization was required to attain high yields and conversion. The best additive was found to be stoichiometric $In(OTf)_3$. Other harsher Lewis acids caused decomposition of the intermediate **1.63**. In the optimization study, $Cu(OTf)_2$ and $InCl_3$ were the only other Lewis acids capable of promoting the transformation.



Scheme 1.21. The total synthesis of (±)-aplykurodinone-1 using the Conia-ene reaction.

1.6.2 Synthesis of Heterocycles via Conia-Ene Chemistry

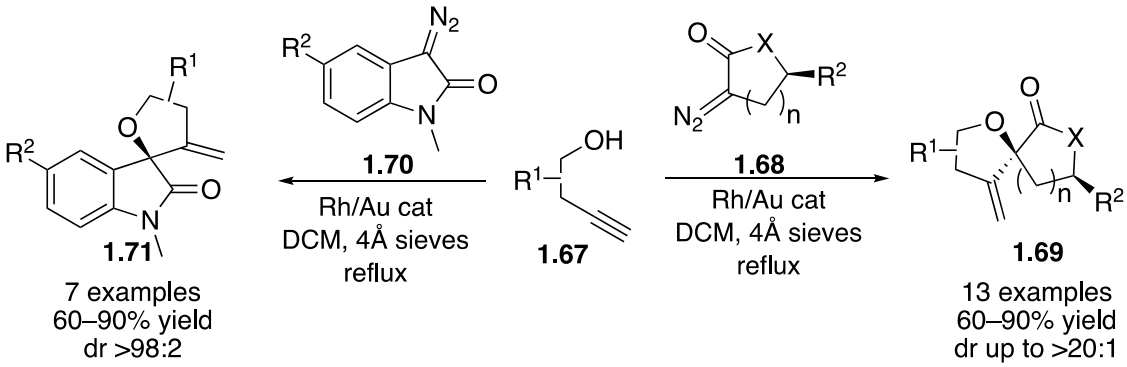
Another implementation of the Conia-ene reaction was detailed by Hatakeyama *et al*.[33] In the protocol, malonates **1.65** were cyclized under Conia-ene conditions forming heterocycles **1.66** (Scheme 1.22). The heterocycles formed had either an amide, amine, or ether group. The reaction was able to form 5 and 6-membered rings efficiently and 7-membered rings were tolerated albeit with lower yield. When a starting material with a chiral linking R group was used, the cyclization occurred with no erosion of enantiomeric excess. These highly functionalized heterocycles are potentially useful as synthetic intermediates. To showcase this, one of the Conia-ene products was elaborated into a natural product (−)-salinosporamide A.



Scheme 1.22. $In(OTf)_3$ catalyzed Conia-ene reaction of malonates forming heterocycles.

1.6.3 Synthesis of Spiroethers Using the Conia-ene Reaction

Another use of the Conia-ene reaction has been published by Sharma *et al.*[34] The paper outlines the use of a dual catalyst system to form spiroethers **1.69** and **1.71** from diazo compounds **1.68** or **1.70** and a homopropargyl alcohol **1.67 (**Scheme 1.23). When the products **1.69** could exhibit stereoisomersim, the reaction was highly diastereoselective and afforded products with the bulky R^2 group opposite the alkene moiety. A number of amino acid-derived diazo compounds **1.68** were tested and provided spiroethers **1.69** in high yields. The authors were able to force a steric mismatch with a chiral propargyl alcohol and a chiral starting material where the bulky groups were on opposite sides in the product. In that case, the yield was much lower and diastereoselectivity suffered. Isatin derived diazo compounds **1.70** also reacted efficiently giving spirooxindoles **1.71**. The reaction was tolerant of a number of different substituents on the isatin including electron donating and electron withdrawing groups. In the deuterium labelling experiments, the alkyne proton was syn to the carbonyl in the intermediate as was observed by Toste *et al.*[31]

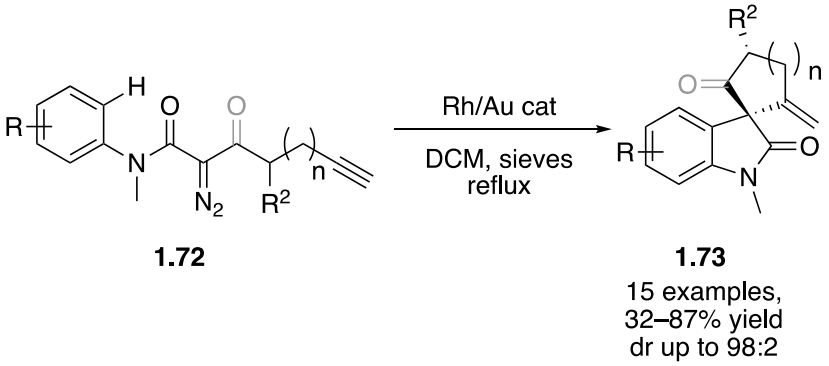


Scheme 1.23. Synthesis of spiroethers using a tandem protocol involving the Conia-ene reaction.

1.6.4 Synthesis of Spirocarbocycles Using the Conia-ene Reaction

The tandem Conia-ene diazo decomposition methodology has also been extended to carbocycles by Sharma *et al.* (Scheme 1.24).[35] In this paper, the authors used the Conia-ene reaction in tandem with a C-H insertion to convert diazo compounds **1.72** to 5-, 6-, and 7-memebered spirocarbocycles **1.73**. The authors tested a variety of different substituents

and were able to isolate the spirocycles in generally good yields. The reaction required additional catalyst when forming 7-membered rings. Most substrates were tolerated well except for the substrate with R = CN. This substrate required significantly longer reaction times as the cyano group hindered C-H insertion step. Excellent diastereoselectivity was observed when R^2 was not H.

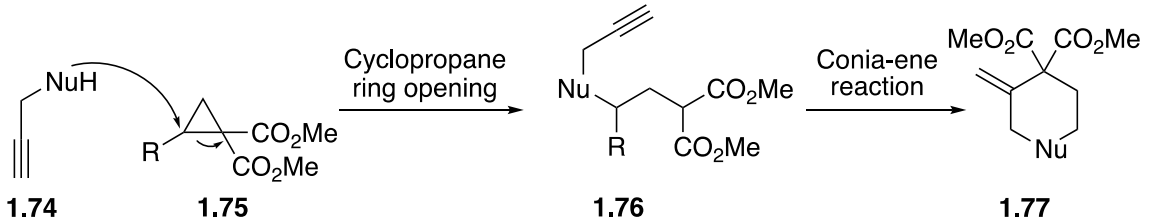


1.72 **1.73**

Scheme 1.24. Synthesis of spirocarbocycles using a tandem protocol involving the Conia-ene reaction.

1.7 Tandem DA Cyclopropane Opening/Conia-Ene Chemistry

It was realized by Kerr *et al.* that if a nucleophile with a tethered alkyne **1.74** was reacted with a DA cyclopropane **1.75**, it would form an intermediate **1.76** that would be capable of undergoing a Conia-ene reaction (Scheme 1.25). The product of this overall transformation would be 6-membered rings **1.77**. This methodology has been applied to the synthesis of both heterocyclic and carbocyclic moieties.

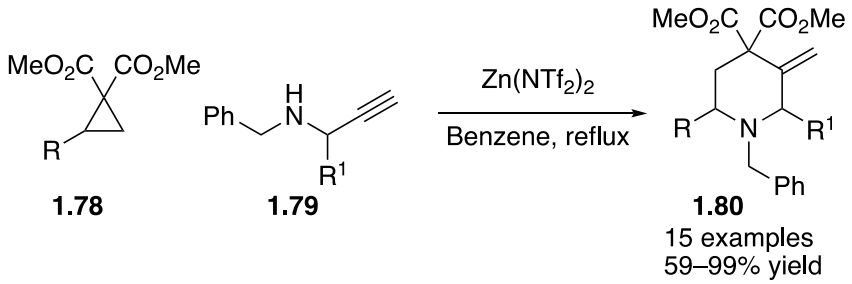


1.74 **1.75** **1.76** **1.77**

Scheme 1.25. General scheme of tandem nucleophilic cyclopropane opening and Conia-ene reaction.

1.7.1 Synthesis of Piperidines from DA Cyclopropanes

The first paper to explore this chemistry tested the reaction between various DA cyclopropanes and N-benzyl propargylamine catalyzed by $Zn(NTf_2)_2$ (Scheme 1.26).[36] It was found that a single Zn catalyst was able to promote both reactions effectively in a one-pot reaction. This discovery was quite fortunate since a hard Lewis acid is typically required to promote the cyclopropane opening and a soft Lewis acid is required to activate the alkyne. The reaction tolerated a wide range of donor groups on the cyclopropane and the piperidines were isolated in excellent yields. All of the alkenyl, aryl, and heteroaryl substituted cyclopropanes provided the product in superb yields, but the aryl substituents with electron withdrawing groups required additional amine and catalyst. These more forcing conditions were also required for methyl substituted cyclopropane and the unsubstituted cyclopropane. These cyclopropanes also provided noticeably lower yields. This lessened reactivity is likely due to the ring opening reaction not proceeding as easily. The stereospecificity of the reaction was tested using homochiral DA cyclopropanes and α-chiral propargylamines. The reaction proceeded with retention of configuration of the propargylamine and inversion of configuration of the cyclopropane.

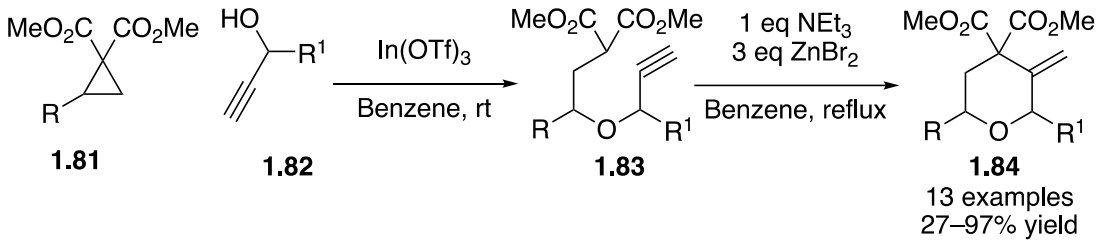


Scheme 1.26. Synthesis of piperidines from DA cyclopropanes and propargylamines.

1.7.2 Synthesis of Tetrahydropyrans from DA Cyclopropanes

A similar procedure using propargyl alcohol **1.82** and DA cyclopropanes **1.81** to form tetrahydropyrans **1.84** was later reported (Scheme 1.27).[37] The reaction of propargyl

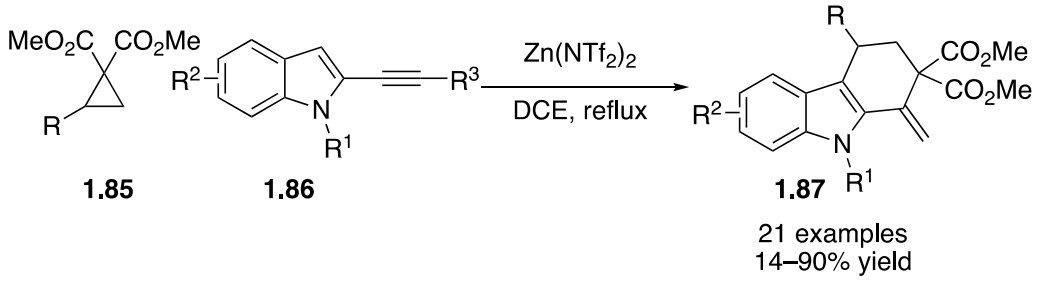
alcohol with the cyclopropane required the use of two catalysts sequentially. This dual catalyst system was used because the propargyl alcohol required a stronger Lewis acid, $In(OTf)_3$ to activate the cyclopropane and allow for ring-opening. $In(OTf)_3$ is also capable of promoting the Conia-ene reaction and a one-pot tandem protocol was successful in simple cases where the aryl substituent had electron neutral or electron withdrawing groups. In testing, it was found that the stronger Lewis acid eventually caused the decomposition of the intermediate with heating if the R group did not possess an electron withdrawing group. The addition of $ZnBr_2$ and NEt_3 allowed for conversion of the ring opened intermediate **1.83** of more electron rich cyclopropanes to the tetrahydropyrans. With the dual catalyst system, the authors were able to isolate an array of substituted tetrahydropyrans in good yields. Cyclopropanes bearing aryl groups with electron withdrawing substituents required additional catalyst allow the ring opening to proceed more readily. Additionally, in general, electron rich aromatic substituents were lower yielding and the particularly electron-rich 2-furanyl substituent decomposed under reaction conditions. Tests with homochiral cyclopropanes determined that the cyclopropane opening proceeds with inversion of configuration. A racemic mixture of α-chiral propargyl alcohol and racemic cyclopropane yielded a 1:1 mixture of diastereomers. These results confirm the mechanism proceeds as predicted with retention of configuration of the α-chiral propargyl alcohol.



Scheme 1.27. Synthesis of tetrahydropyrans from DA cyclopropanes and propargyl alcohol.

1.7.3 Synthesis of Tetrahydrocarbazoles from DA Cyclopropanes

The most recent entry in this series of tandem and one-pot reactions is the conversion of DA cyclopropanes **1.85** and 2-alkynylindoles **1.86** to tetrahydrocarbazoles **1.87** (Scheme 1.28).[38] This reaction was also tolerant of many unsaturated functional groups on the cyclopropane including electron neutral and electron rich and slightly electron deficient aryl groups along with alkenyl and heteroaryl groups. The worst performing cyclopropane was the one lacking a donor group (R = H). This cyclopropane required additional catalyst to achieve conversion. The reaction was also tolerant of unprotected indoles (R^1 = H) as well as electron withdrawing groups on the indole. Attempts were made to perform the Conia-ene reaction on ring opened substrates bearing substituted alkynes ($R^4 \neq$ H) but no cyclization occurred except when the substituent was a carbomethoxy group (R^4 = CO_2Me). The authors attributed, this cyclization to conjugate addition instead of Conia-ene reactivity.



Scheme 1.28. Tandem cyclopropane opening Conia-ene one pot reaction with 2-alkynylindoles.

1.8 Scope of Thesis

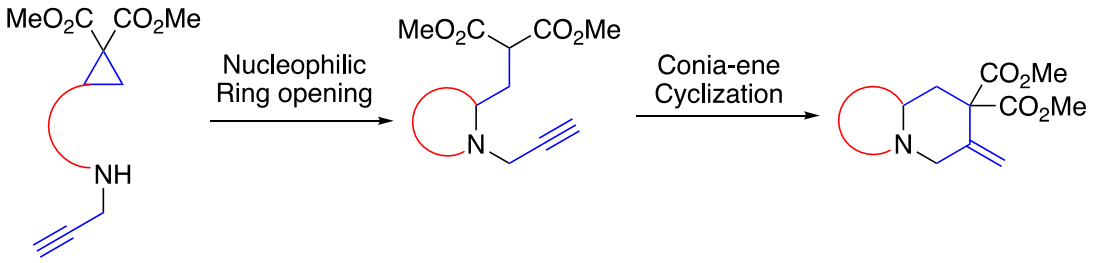
All of the examples of tandem DA cyclopropane Conia-ene chemistry were performed intermolecularly. An intermolecular process results in formation of a single ring in the overall transformation. However, the tandem reaction does not necessarily have to be performed intermolecularly. If a cyclopropane tethered to a nucleophile undergoes ring opening, a new ring is be formed. This intermediate could form an additional ring if it could

undergo a subsequent Conia-ene cyclization. This thesis describes the optimization and testing of a protocol for synthesizing bicyclic piperidines using tandem DA cyclopropane Conia-ene chemistry.

Chapter 2 Results and Discussion

2.1 Synthesis of Model Substrate and Optimization of Reaction Conditions

It was realized that based on the previous papers using DA cyclopropanes and propargyl nucleophiles, tethering a cyclopropane to propargylamine should allow for the rapid synthesis of bicyclic piperidines. Therefore, a protocol for an intramolecular cyclopropane opening Conia-ene process was targeted. The products of this reaction would be highly functionalized bicyclic piperidines (Scheme 2.1). This reaction would make bioactive natural products and synthetic compounds containing these bicyclic piperidines more accessible.

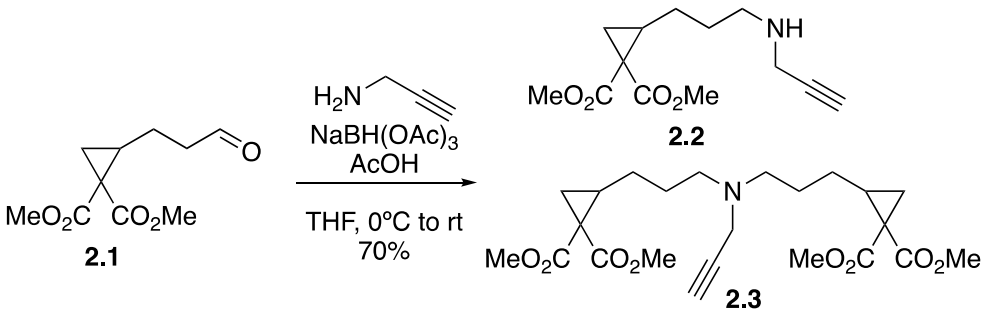


Scheme 2.1. Hypothesized nucleophilic ring opening Conia-ene process.

2.1.1 Synthesis and Testing of 5-Membered Ring Forming Substrate **2.2**

With the goal of developing access to piperidines, a model substrate **2.2** was targeted for testing our hypothesized reaction and to optimize the potential results (Scheme 2.2). A propargyl amine was targeted instead of an allyl amine due to the presence of an additional functional handle in the proposed product. Aldehyde **2.1** had been previously synthesized

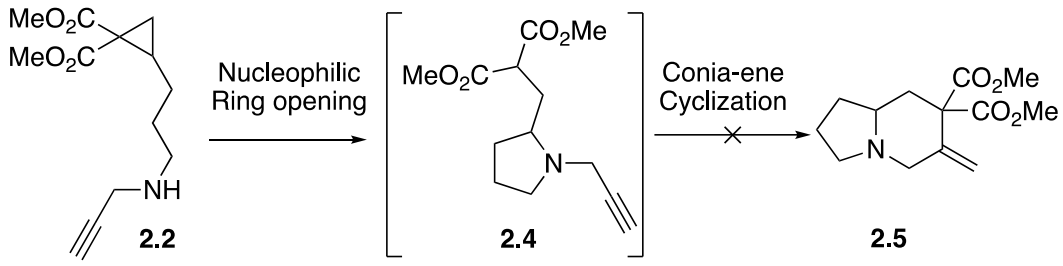
and was easily obtained from 4-penten-1-ol in four synthetic steps based on modified literature procedures.[39] The reductive amination of aldehyde **2.1** proved challenging and several reaction conditions from the literature were tested before amine **2.2** was obtained in appreciable yield. Several protocols involving the more common $NaCNBH_3$ were tested, but no amine was isolated despite consumption of the starting material.[40-41] Another approach involving imine formation followed by reduction furnished the amine **2.2** in very small, but detectable quantities.[42] This protocol was decided to be unworkable as the yield was consistently low (<5%) despite multiple attempts. Attempts to recover additional material by increasing the scale of the reaction proved unsuccessful. The amine was also not cleanly isolable from the reaction byproducts. Additionally, none of the byproducts could be definitively identified. Finally, based on a literature report, a reduction with sodium triacetoxyborohydride (STAB) was tested.[43] This protocol afforded significantly higher yields of **2.2** (30%). The balance of the starting material could be accounted for as a significant amount of **2.3** was isolated. From this, it was realized that the low yield was caused by the competing formation of **2.3**, the dialkylated amine. Using a larger excess (4.0 equivalents) of propargylamine in the reaction mixture greatly reduced the proportion of **2.3** formed. This modification improved the yield of **2.2** to 70% at gram scale.



Scheme 2.2. Synthesis of **2.1** from literature compounds.

With the successful synthesis of amine **2.2**, the next step was proving the tandem reaction was viable and then optimizing conditions. Based on previous work, a hard Lewis acid, typically a lanthanide triflate was selected to promote the ring opening reaction. $Sc(OTf)_3$ was used extensively due to its enhanced Lewis acidity relative to other lanthanide triflates.[44] Other harsher hard Lewis acids were also tested including $SnCl_4$ and $TiCl_4$ in

some cases. Soft Lewis acidic compounds such as gold and zinc salts were selected to promote the Conia-ene reaction. $Zn(NTf_2)_2$ was also tested as both a hard and soft Lewis acid since it was able to promote both the cyclopropane opening and the Conia-ene reaction in previous work.[36-38] Based on these criteria, conditions were selected and tested to test the one-pot reaction of **2.2** and the results of this optimization study are outlined in Table 2.1. The optimized reaction conditions from the papers using the cyclopropane opening Conia-ene process were also tested (Table 2.1, entries 2, 3, 6). No Conia-ene product was isolated. The formation of the Conia-ene product is confirmed by the appearance of the exocyclic methylene group in the ^{1}H NMR spectrum. These peaks appear as two singlets around 5 ppm are very diagnostic for the formation of a Conia-ene product. The tested conditions produced the ring-opened product **2.4** or caused either partial or complete decomposition of the material into an uncharacterizable tar. Formation of an uncharacterizable tar was commonly encountered in the testing of substrates. Any subsequent mention of decomposition refers to tar formation unless otherwise noted. The identity of the ring-opened product was confirmed by treating **2.2** with $Sc(OTf)_3$ in DCM or toluene (Scheme 2.3). This reaction afforded **2.4** in 75% yield after purification (Table 2.1, entry 1). IR spectroscopy was also used to confirm the presence of an alkyne. Further confirmation was provided by complete analysis of the 2D NMR spectra of the compound. The ring-opened product **2.4** did not convert to the Conia-ene product **2.5** under any of the tested conditions.



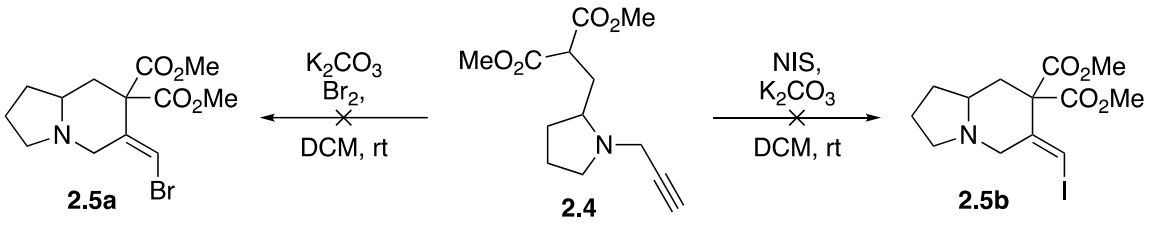
Scheme 2.3. Hypothesized nucleophilic ring opening Conia-ene process for **2.2**.

Table 2.1. Attempted ring-opening Conia-ene cyclization of **2.2**.

Entry	Solvent	Time	Catalyst(s) or Additive(s)	Temperature	Yield of 2.4
1	Benzene	12 h	$Sc(OTf)_3$ (0.1 eq)	rt	75%
2	Benzene	24 h	$Zn(NTf_2)_2$ (0.15 eq)	reflux	60%
3	Benzene	12 h rt 16 h heat	1) $Sc(OTf)_3$ (0.1 eq) 2) $ZnBr_2$ (1.0 eq)	rt then reflux	65%
4	Toluene	12 h rt 24 h heat	1) $Sc(OTf)_3$ (0.1 eq) 2) $ZnBr_2$ (1.0 eq)	rt then reflux	Decomp
5	Benzene	12 h 24 h	1) $Sc(OTf)_3$ (0.1 eq) 2) $PPh_3Au(NTf_2)$ (0.05 eq)	rt	70%
6	Toluene	24 h	1) $In(OTf)_3$ (0.1 eq), NEt_3 (1 eq) 2) $ZnBr_2$ (2.0 eq)	rt then reflux	60%
7	Toluene	48 h	1) $In(OTf)_3$(0.1 eq), NEt_3 (1 eq) 2) $ZnBr_2$ (2.0 eq)	rt then reflux	Decomp
8	DCE	24 h	1) $Sc(OTf)_3$ (0.1 eq) 2) $PPh_3Au(NTf_2)$ (0.05 eq)	rt then reflux	70%

Given the lack of reactivity of **2.2** under catalytic or stoichiometric Lewis acidic conditions, direct cyclization of the ring-opened intermediate **2.4** was attempted instead. The cyclization tests with **2.4** all resulted either in the isolation of starting material or complete decomposition of the mixture with no detectable conversion to **2.5**. The results of these trials are summarized in Table 2.2. Several Lewis acids known to promote the Conia-ene reaction were tested. $Mn(OAc)_3$ was also tested as a single-electron transfer agent (Table 2.2, entry 7,8) was explored as a radical based alternative to the Conia-ene reaction.[45] The $Mn(OAc)_3$ additive forms a malonyl radical that has been able to cyclize with a tethered alkyne in other systems. $SnCl_4$ mediated ring closing was also tested (Table 2.2, entry 9) and also resulted in decomposition.[46] Attempts were also made to form **2.5a** and **2.5b** with bromolactonization and iodolactonization type chemistry respectively (Scheme 2.4).[47-49] These approaches were also ineffective at forming **2.5** and resulted in either decomposition

of the material in the case of bromolactonization or no detectable reaction in the case of iodolactonization.



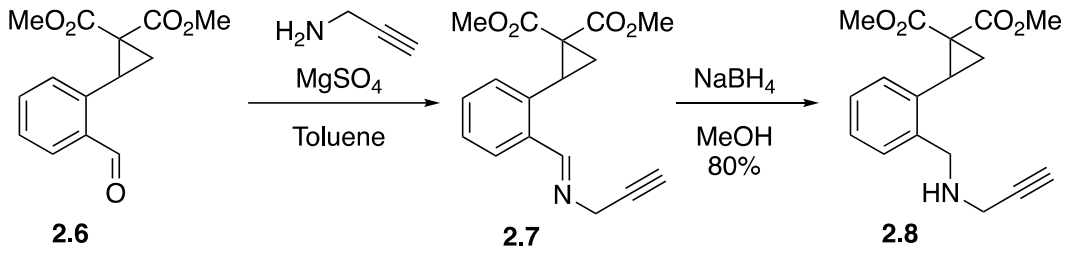
Scheme 2.4. Attempted bromolactonization and iodolactonization of **2.4**.

Table 2.2. Attempted Conia-ene reaction of **2.4**.

Entry	Solvent	Time	Catalyst(s) or Additive(s)	Temperature	Result
1	DCE	12 h	$PPh_3Au(NTf_2)$ (0.05 eq)	rt	SM recovered
2	Toluene	24 h	$ZnBr_2$ (2.0 eq)	100ºC	SM recovered
3	Benzene	24 h	$Zn(NTf_2)_2$ (0.1 eq)	reflux	SM recovered
4	Toluene	24 h	$Zn(NTf_2)_2$ (0.3 eq)	reflux	SM recovered
5	Xylene	12 h	$ZnBr_2$ (2.0 eq)	150ºC	Decomp
6	Xylene	30 min	$Zn(NTf_2)_2$ (0.1 eq)	170ºC (microwave)	Decomp
7	MeOH	3 h	$Mn(OAc)_3$ (2.1 eq), $Cu(OAc)_2$ (1.0 eq)	reflux	SM recovered
8	MeOH	6 h	$Mn(OAc)_3$ (2.1 eq)	reflux	SM recovered
9	DCM	10 min	1) $SnCl_4$ (1.8 eq) 2) NEt_3	rt	Decomp

2.1.2 Synthesis and Testing of 5-Membered Ring Forming Benzo Linked Substrate **2.8**

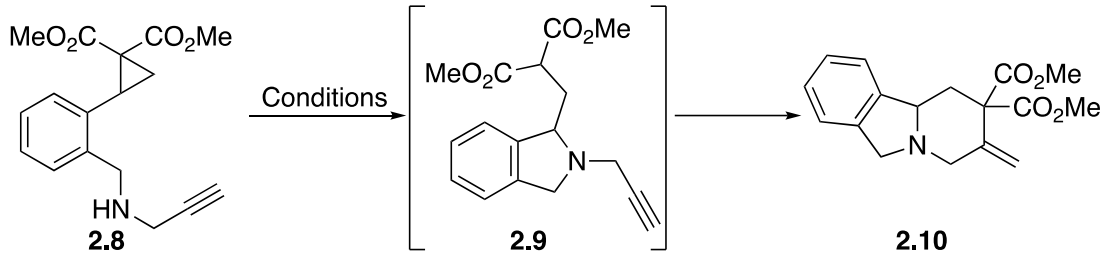
Since the ring-opened product **2.4** did not undergo the Conia-ene reaction, a new substrate, **2.8** was targeted. This substrate was targeted based on the use of *N*-benzyl propargylamine in the previous precedent.[36] It was hoped that by more closely mimicking the previous conditions, the Conia-ene reaction would be made more favourable. Aldehyde **2.6** was synthesized from *o*-tolualdehyde in four synthetic steps (Scheme 2.5).[39] From aldehyde **2.6**, reductive amination using STAB with the previously optimized conditions was attempted. All the starting material was consumed based on the crude ^{1}H NMR spectrum, but **2.8** was not formed. To address this, the aldehyde was first condensed with propargylamine to form intermediate **2.7**. The intermediate was then subjected to borohydride reduction and afforded the ring opened product **2.9** in 60% yield. To attempt to isolate the amine, the reaction time was shortened, and the reaction was performed at a lower temperature. With these changes, **2.8** was successfully collected in an 80% yield.



Scheme 2.5. Synthesis of **2.8** from known compounds.

Amine **2.8** proved able to form the ring opened product **2.9** readily upon treatment with $Sc(OTf)_3$ (Scheme 2.6). Significant conversion to the ring opened product **2.9** was observed after two weeks of storage at –20ºC. Upon exposure of **2.9** to the Conia-ene conditions, a product possessing the exocyclic methylene group was observed; this was identified as **2.10**. Unfortunately, the formation of this product was accompanied by significant decomposition. Attempts were made at optimizing this reaction, but the decomposition made purification difficult and caused low yields (Table 2.3). Additionally, the Conia-ene reaction of **2.9** never went to completion and the ring-opened material **2.9** was always present. Despite testing multiple catalysts, solvents, and temperatures, only traces of the Conia-ene product **2.10** were ever isolated. The zinc catalyst is poorly soluble in toluene and due to the apparent decomposition of the material, it was hypothesized that catalyst

deactivation was the cause of the incomplete reaction. Multiple additions of catalyst did not improve the yield of the reaction (Table 2.3, entry 5). THF was also tested as the reaction solvent to attempt to address catalyst deactivation (Table 2.3, entry 7). Using THF as the solvent only hastened the decomposition. The $Sc(OTf)_3/ZnBr_2$ dual catalyst system proved to be marginally better than the other tested systems. The attempts at reaction optimization are summarized in Table 2.3.



Scheme 2.6. Nucleophilic ring opening Conia-ene reaction of **2.8**.

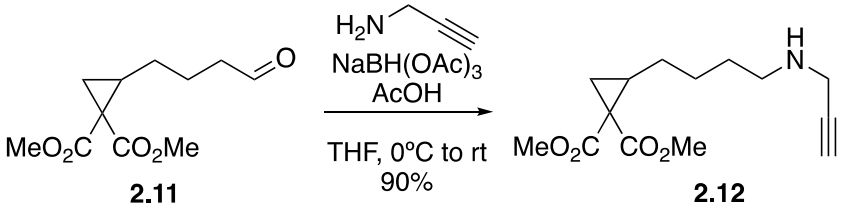
Table 2.3. Attempted optimization of tandem nucleophilic cyclopropane opening Conia-ene process of **2.8**.

Entry	Solvent	Time	Catalyst(s)	Temperature	Result
1	Toluene	12 h	$Sc(OTf)_3$ (0.1 eq)	rt	8% **2.9**
2	Toluene	12 h	$Zn(NTf_2)_2$ (0.1 eq)	90ºC	Trace **2.10**
3	Benzene	16 h	$Zn(NTf_2)_2$ (0.1 eq)	reflux	5% **2.10**
4	Benzene	10 h 12 h	1) $Sc(OTf)_3$ (0.1 eq) 2) $ZnBr_2$ (2.0 eq)	rt reflux	5% **2.10**
5	Toluene	10 h 12 h	1) $Sc(OTf)_3$ (0.1 eq) 2) $ZnBr_2$ (2.0 eq)	rt 100ºC	13% **2.10**
6	Toluene	12 h 4 h	1) $Sc(OTf)_3$ (0.1 eq) 2) $ZnBr_2$ (2.0 eq), NEt_3 (1.0 eq)	rt 100ºC	35% **2.10**
7	THF	12 h	$ZnBr_2$ (2.0 eq)	reflux	Decomp

From the difficulties encountered in optimizing the Conia-ene reaction of **2.9** and its noticeable instability under the reaction conditions, it was clear that a new substrate needed to be synthesized.

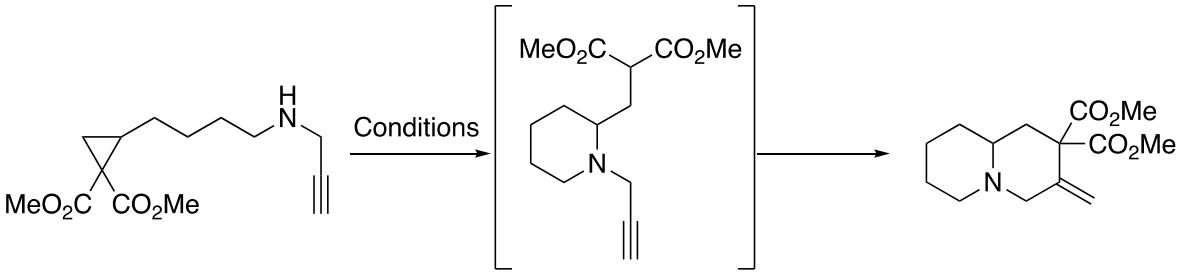
2.1.3 Synthesis and Testing of 6-Membered Ring Forming Substrate **2.12**

With the results from substrates **2.2** and **2.8**, it was postulated that the indolizidine system was too strained, preventing **2.4** and **2.9** from cyclizing well under Conia-ene conditions. With this hypothesis in mind, a substrate with a longer carbon chain was targeted. Aldehyde **2.11** was synthesized from 5-hexen-1-ol in four synthetic steps (Scheme 2.7). Amine **2.12** was obtained from **2.11** in high yield using the previously optimized reductive amination procedure.



Scheme 2.7. Synthesis of **2.12** from previously synthesized compounds.

The tandem reaction worked well on **2.12** and the Conia-ene product **2.14** was obtained in high yield (Scheme 2.8). The substrate was also tested with several other Lewis acids, but none outperformed the $Sc(OTf)_3/ZnBr_2$ dual catalyst system (Table 2.4). Unlike for **2.8**, the addition of NEt_3 had no appreciable effect on the yield in this system. A 93% yield of **2.14** was obtained with no detectable decomposition using $Sc(OTf)_3$ and $ZnBr_2$ at elevated temperatures (Table 2.4 entry 3). The results of the optimization trials are summarized in Table 2.4. With the success, attempts at optimizing the synthesis of **2.10** were not pursued further.



2.12 **2.13** **2.14**

Scheme 2.8. Conversion of **2.12** to the Conia-ene product **2.14**.

Table 2.4. Optimization of reaction conditions for substrate **2.12**. Reactions were performed on a 50 mg scale unless otherwise noted * = decomposition noted. [a] = 150 mg scale.

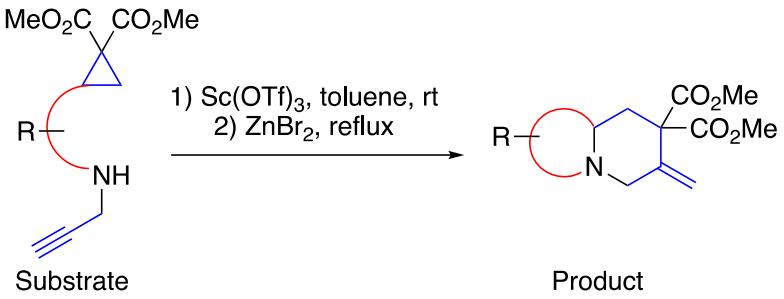
Entry	Solvent	Time	Catalyst(s)	Temperature	Yield
1	Toluene	12 h 12 h	$Zn(NTf_2)_2$ (0.1 eq)	rt 100ºC	43%
2	Toluene	12 h	$Zn(NTf_2)_2$ (0.1 eq)	100ºC	40%*
3[a]	Toluene	12 h 5 h	1) $Sc(OTf)_3$ (0.1 eq) 2) $ZnBr_2$ (2.0 eq)	rt 100ºC	93%
4	Toluene	14 h	$Sc(OTf)_3$ (0.1 eq), $ZnBr_2$ (2.0 eq)	100ºC	45%*
5	Toluene	12 h 8 h	1) $In(OTf)_3$ (0.2 eq) 2) $ZnBr_2$ (2.0 eq)	rt 100ºC	20%*
6	Toluene	12 h 14 h	1) $In(OTf)_3$ (0.2 eq) 2) $ZnBr_2$ (2.0 eq)	rt 100ºC	13%*
7	Toluene	12 h 5 h	1) $Sc(OTf)_3$ (0.1 eq) 2) $ZnBr_2$ (2.0 eq), NEt_3 (1.0 eq)	rt 100ºC	89%

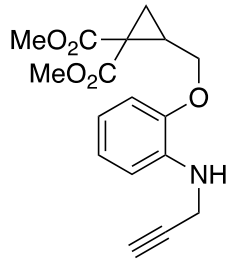
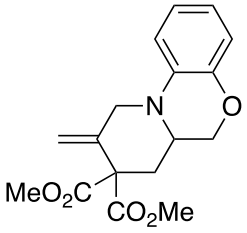
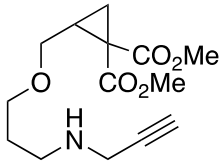
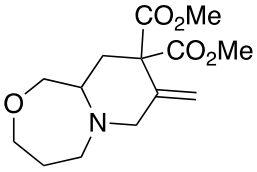
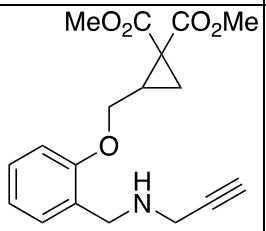
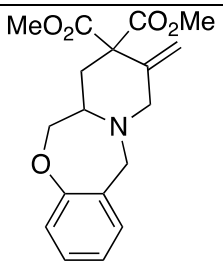
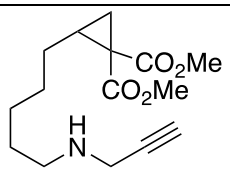
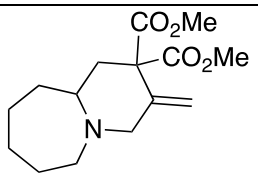
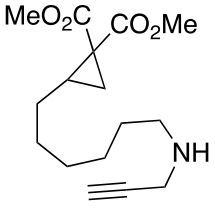
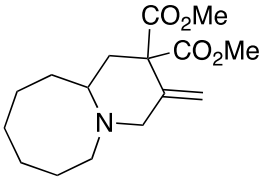
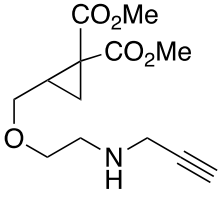
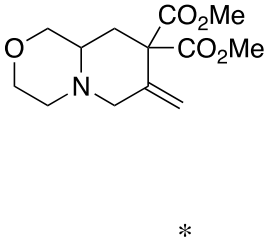
2.2 Synthesis of Additional Substrates

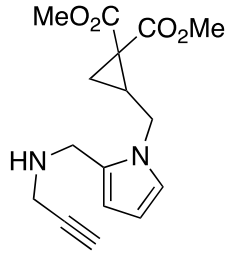
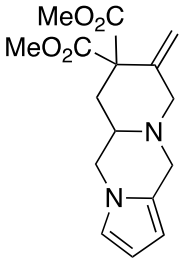
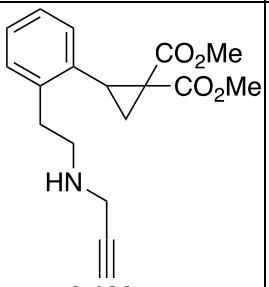
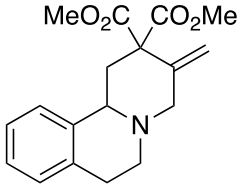
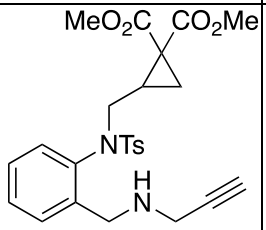
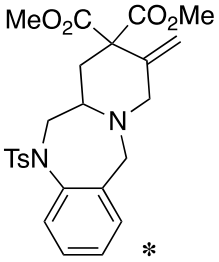
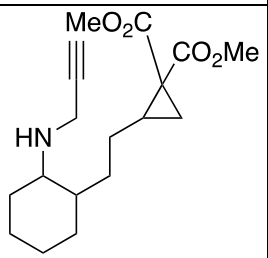
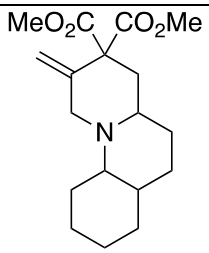
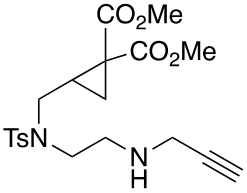
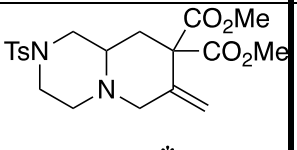
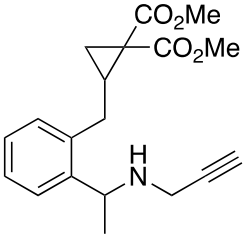
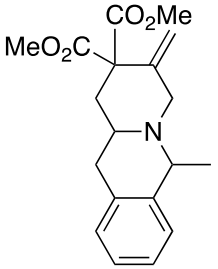
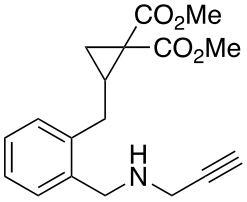
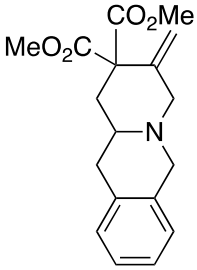
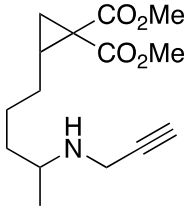
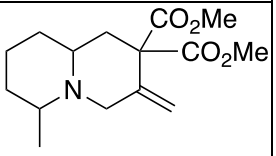
With the success of the tandem reaction on **2.12**, the next step was to explore substrate scope for the reaction. Given the lack of reactivity of **2.4** and **2.9** under Conia-ene conditions, only substrates that would form 6-or 7-memebered rings during the cyclopropane opening step were targeted. In the pursuit of testing the reaction scope, a number of substrates were designed and synthesized to test the effects of ring size and the presence of heteroatoms and the nucleophilicity of the amine (Table 2.5). Our proposed

research plan to explore the suitability of this methodology is outlined in Table 2.5. The structure of each substrate and its proposed structure of the Conia-ene product are shown.

Table 2.5. General reaction scheme and substrates and idealized Conia-ene products. * = Conia-ene product isolated.

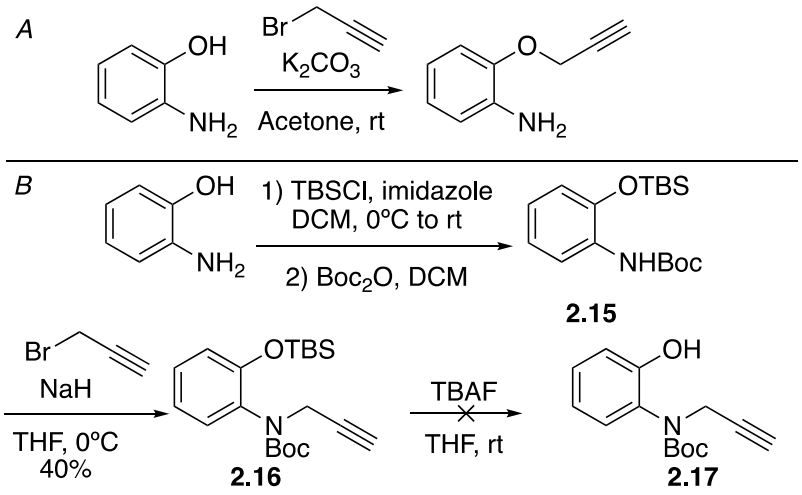


Substrate	Desired Product	Substrate	Desired Product
 **2.19**	 **2.21**	 **2.39**	 **2.41**
 **2.25**	 **2.27** *	 **2.51**	 **2.53**
 **2.31**	 **2.33**	 **2.64**	 * **2.66**

Substrate	Desired Product	Substrate	Desired Product
 **2.68**	 **2.70**	 **2.132**	 * **2.134**
 **2.83**	 * **2.85**	 **2.138**	 **2.142**
 **2.97**	 * **2.99**	 **2.141**	 **2.143**
 **2.118**	 **2.120**	 **2.143**	 **2.145**

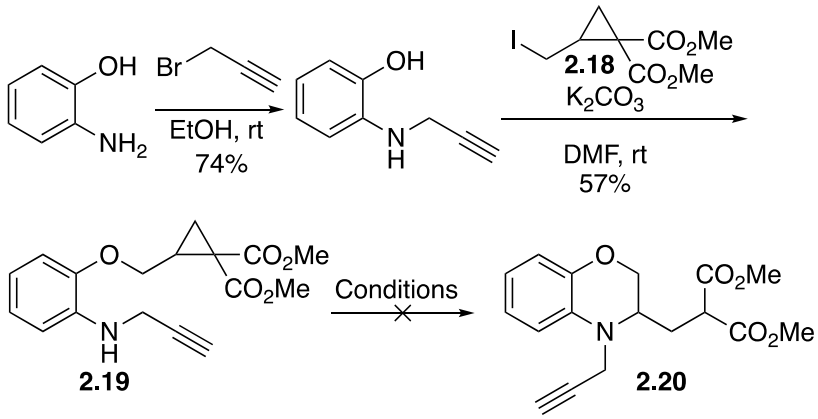
2.2.1 Synthesis and Testing of *o*-Aminophenol Derived Substrate **2.19**

An important consideration for this reaction is the nature of the nucleophile used for the ring-opening reaction. To test the viability of aniline nucleophiles for the ring-opening Conia-ene reaction, potential substrate **2.18** was targeted (Scheme 2.9). Given the position of the oxygen on the ring relative to the nitrogen, **2.18** should be more nucleophilic than aniline. Attempted alkylation of 2-aminophenol with propargyl bromide in acetone with K_2CO_3 resulted in the isolation of O-propargyl-2-aminophenol (Scheme 2.9 A). To address this selectivity issue, a new strategy involving protecting groups was tested. TBS and Boc protection of aminophenol smoothly affording **2.15** in near quantitative yield (Scheme 2.9 B). However, **2.15** proved slow to alkylate under a variety of conditions. Conversion to **2.16** was eventually realized, but the compound appeared to undergo significant decomposition under TBS deprotection conditions. The deprotected product **2.17** was part of a complex mixture of products and could not be isolated. While this instability could likely be addressed through the use of milder deprotection conditions, it was realized that a new strategy using no protecting groups was possible.



Scheme 2.9. Attempted synthesis of substrate **2.18.**

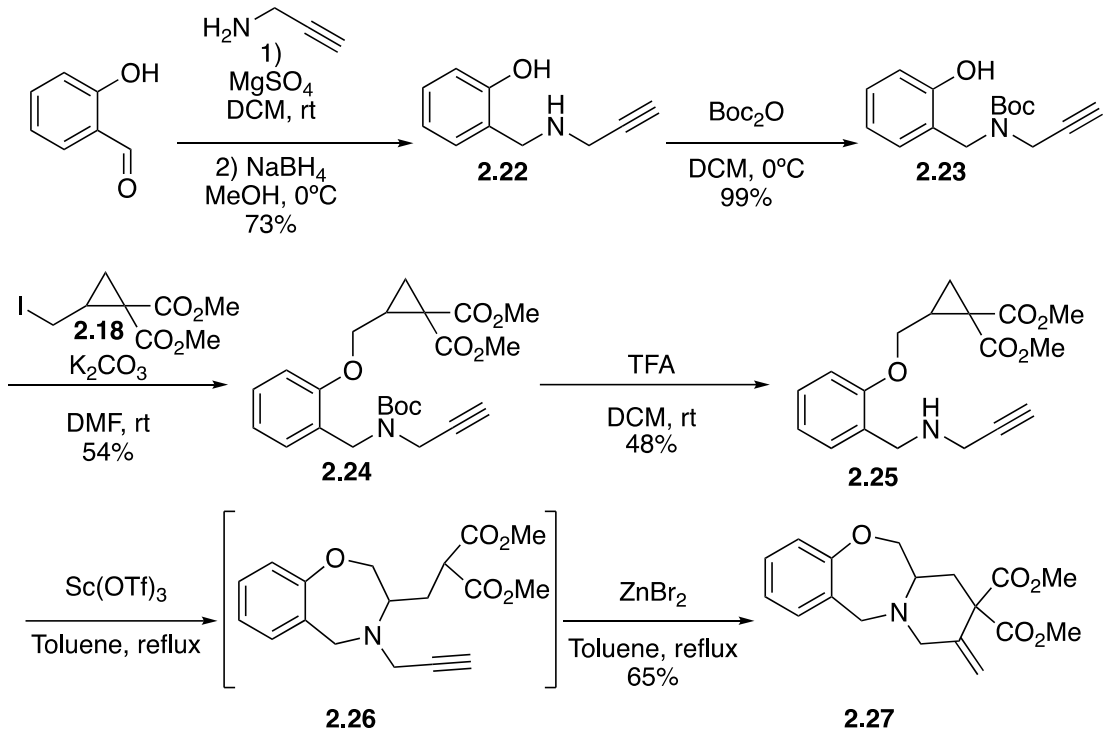
Based on literature reports, 2-aminophenol could be selectively N-alkylated without protecting groups (Scheme 2.10).[50] Using this alternative approach, the N-propargyl 2-aminophenol was isolated in good yield. Using standard O-alkylation conditions, **2.19** was obtained easily. However, when subjected to the optimized conditions, the compound did not undergo nucleophilic ring opening at room temperature or at elevated temperatures. Increasing the catalyst loading above 20 mol% did not yield the ring-opened product **2.20**. Several sets of literature conditions were tested including work using indolines to open cyclopropanes. The catalyst best suited to opening DA cyclopropanes with indolines, $Yb(OTf)_3$ also did not yield any ring opened material.[51] Harsher Lewis acids such as $SnCl_4$ resulted in direct decomposition of the material with no apparent conversion to the ring-opened product. The decomposition due to $SnCl_4$ still occurred at 0ºC. Given this, no other harsh Lewis acids were tested. Increasing the nucleophilicity of the amine via deprotonation was also tested, but no conversion to the ring opened material **2.20** occurred. The lack of reactivity is likely due to inductive deactivation of the cyclopropane due to the position of the ether oxygen atom. This deactivation combined with the comparative ineffectiveness of alkyl substituents as donor groups makes this DA cyclopropane particularly unreactive. Combined with the lack of nucleophilicity of anilines compared to aliphatic amines, an intramolecular reaction is extremely unlikely. With this result, no further tests were performed with this substrate and **2.21** was not isolated.



Scheme 2.10. Synthesis and testing of **2.19**.

2.2.2 Synthesis and Testing of Salicylaldehyde Derived Substrate **2.26**

Based on the results of testing **2.19**, a substrate with a similar structure was targeted to test if the inductive deactivation of the cyclopropane by the oxygen was the sole reason for the lack of reactivity. A highly similar substrate, **2.25** was targeted to address these concerns. The nucleophilicity of the aliphatic amine in **2.25** is much greater than that of the amine in **2.19**. Starting from salicylaldehyde, reductive amination afforded amine **2.22** (Scheme 2.11). Next, alkylation of **2.22** was attempted with **2.18**. However, **2.22** could not be selectively O-alkylated without first protecting the nitrogen. Further, the crude material from these attempts was obtained in low yield. To address both of these issues, the amine **2.22** was Boc protected affording **2.23**. The O-alkylation conditions from the aminophenol derived substrate worked well to access intermediate **2.24**. Boc deprotection using standard conditions worked well and furnished **2.25**.[52] The substrate did not convert to the ring-opened product at room temperature with the optimized conditions from the first test substrate. Since 10 mol% $Sc(OTf)_3$ did not open the cyclopropane in a reasonable time frame, moderate heating in toluene (90ºC) was tested. Unfortunately, the increased temperature also did not fully convert the substrate to the ring-opened intermediate **2.26** in 24 hours. Some slight decomposition of the material was also observed. Complete conversion to the ring opened product was achieved after heating at reflux in toluene for 24 h with 20 mol% $Sc(OTf)_3$. The Zn-promoted Conia-ene reaction worked well and **2.27** was isolated in 65% yield.

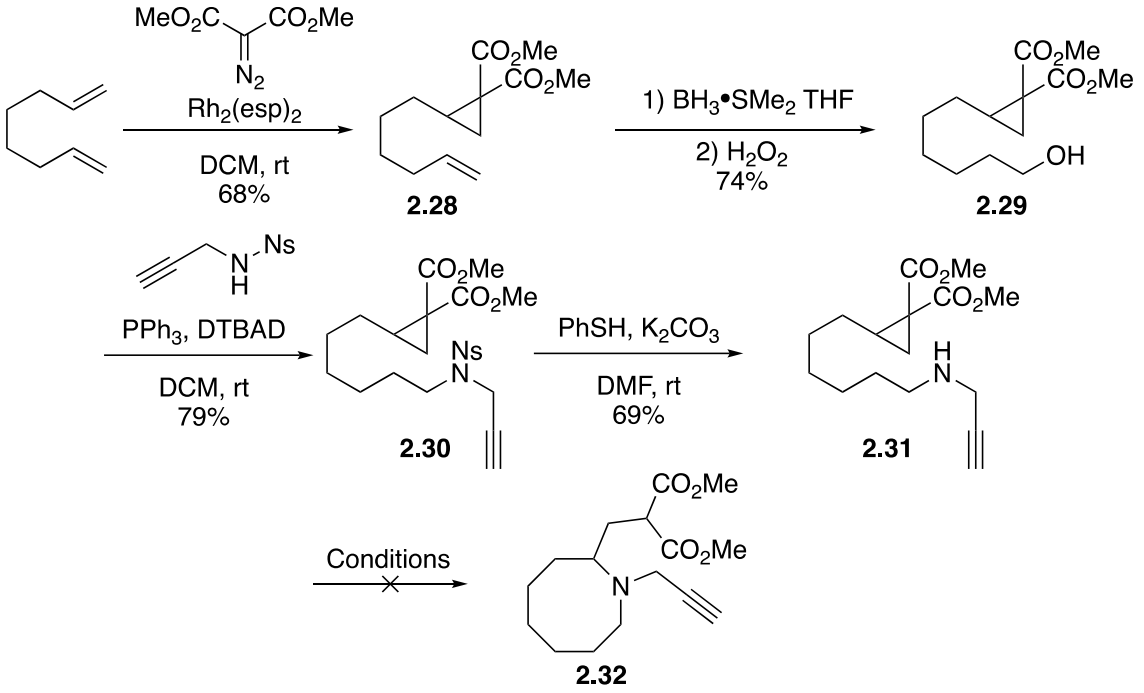


Scheme 2.11. Synthesis of substrate **2.25** from known compounds and conversion to the Conia-ene product **2.27**.

1.2.2.3 Synthesis and Testing of Octadiene Derived Substrate **2.31.**

With the success of the salicylaldehyde derived substrate **2.25**, it appeared that 7 membered rings were tolerated by the reaction conditions. The next question was whether 8 membered rings would be tolerated. This potential avenue was explored via the synthesis and testing of substrate **2.31** (Scheme 2.12). The substrate was synthesized using a Mitsunobu reaction of an activated amine as a critical step.[53] This reaction is occasionally referred to as the Fukuyama amine synthesis. In the synthesis of **2.31**, 1,7-octadiene was first desymmetrized by cyclopropanation affording alkene **2.28**. This alkene was then hydroborated under standard conditions and alcohol **2.29** was isolated. The alcohol was then converted to the Ns protected amine **2.30** under Fukuyama conditions. After deprotection using PhSH, the amine **2.31** was isolated. **2.31** did not undergo ring opening under any tested conditions. Even with very high catalyst loadings (40 mol% $Sc(OTf)_3$), no traces of proposed ring opened product **2.32** were isolated. Microwave heating up to 140°C was tested also

afforded no ring opened product. In general, the harsher conditions resulted in no conversion with slow decomposition. It is likely that the transition state to form the 8-membered ring is too unfavourable to happen at an appreciable rate. Given the unfavourable ring size, it is not surprising that **2.33** was not obtained. With this result, no further tests were performed on **2.31**, and the synthetic focus moved to other substrates.

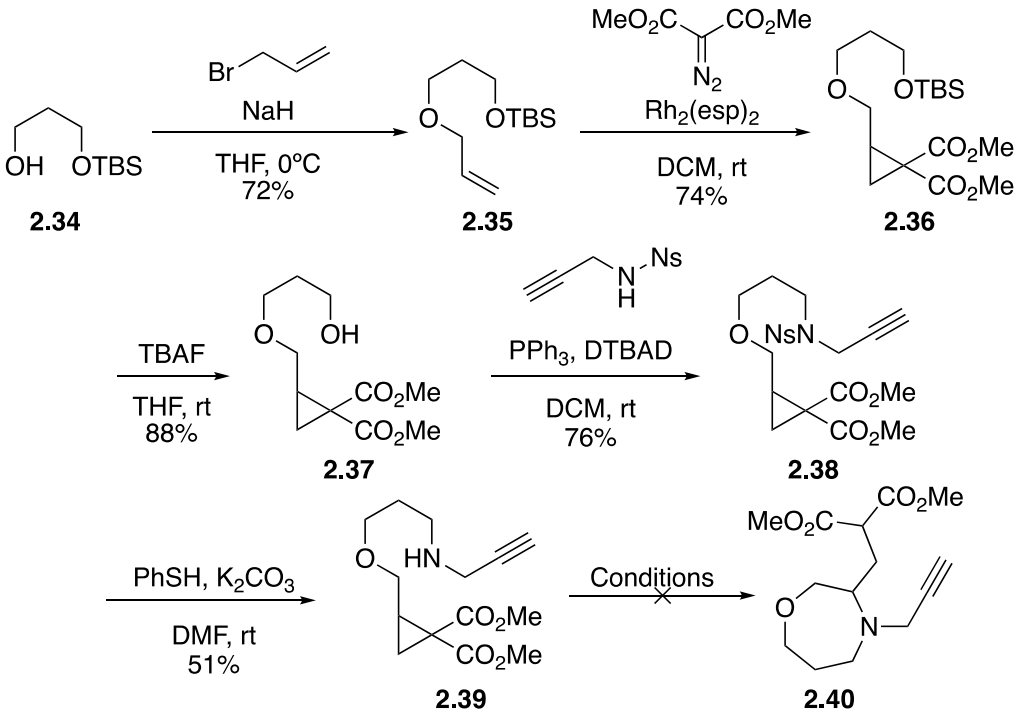


Scheme 2.12. Synthesis and testing of **2.31**.

1.2.2.4 Synthesis and Testing of 7-Membered Ring Forming Substrate **2.39**

Based on the results from the 8-membered test substrate, a synthetically simple 7-membered substrate without a benzo linker **2.39** was targeted (Scheme 2.13). This substrate was targeted to determine if the rotational restriction of the benzo group allowed the ring opening to proceed easily or if an 8-membered ring was the problem. If the substrate were to react as hoped, it would yield Conia-ene product **2.41**. Starting from propane-1,3-diol, monoprotection afforded the alcohol **2.34**. The alcohol was allylated under standard conditions affording ether **2.35**. This ether was then cyclopropanated affording **2.36**. TBS

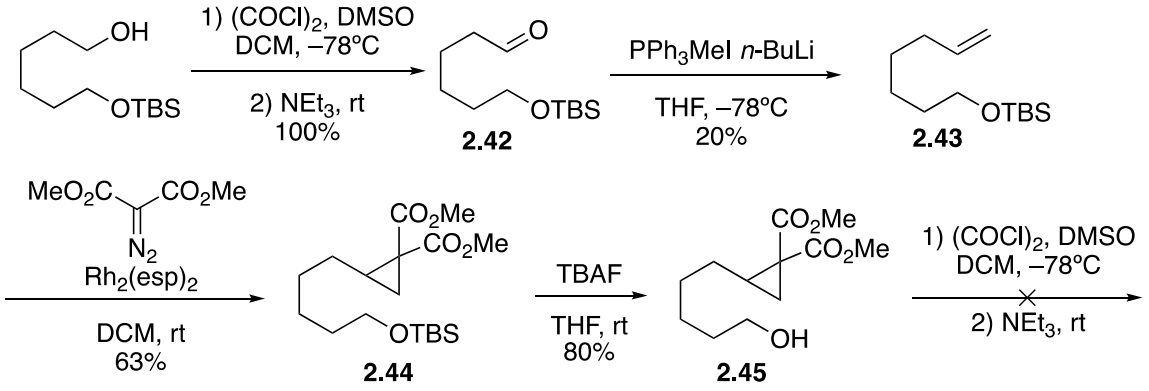
deprotection afforded cyclopropyl alcohol **2.37**. Fukuyama amination afforded Ns protected amine **2.38**. Deprotection of this amine afforded substrate **2.39**. This substrate proved unreactive under Lewis acid conditions. As expected from the results of **2.25**, there was no apparent ring-opening at room temperature. The conditions used for the earlier synthesized 7-membered ring forming substrate **2.25**, 20 mol% $Sc(OTf)_3$ in PhMe at reflux for 24 h also did not yield any ring opened material **2.40**. Longer reaction times caused no conversion or appreciable change in the TLC plate until sudden decomposition of the material. Higher temperatures caused faster decomposition. Other catalysts such as $Zn(NTf_2)_2$ and $SnCl_4$ also did not convert **2.39** to the proposed ring opened material **2.40**. It was realized that this could be because the oxygen in the backbone deactivates the cyclopropane towards opening sufficiently that the already unfavourable 7-membered ring forming event cannot proceed. With this realization, testing was ceased on **2.39** and another substrate was targeted.



Scheme 2.13. Synthesis and testing of 7-membered ring forming substrate **2.39**.

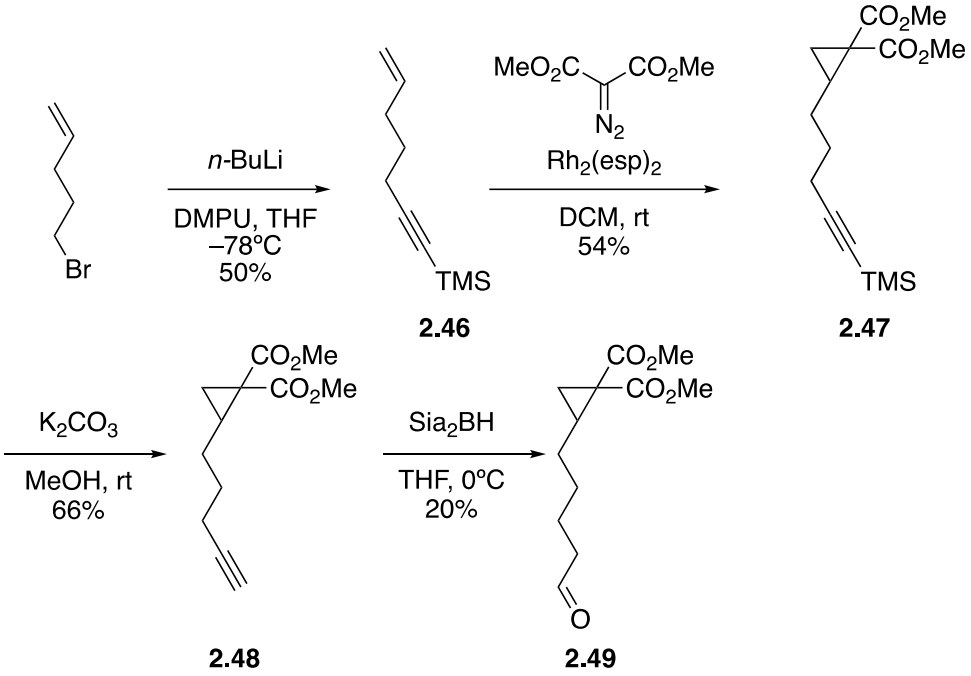
2.2.5 Synthesis and Testing of 7-Membered Ring Forming Substrate **2.51**

Substrate **2.39** showed that 7-membered rings are not as compatible with the synthetic protocol as initially hoped. However, there was a confounding variable in the mix; the oxygen that made **2.39** so easy to synthesize also deactivated the cyclopropane towards opening. This deactivation had not been a problem in the salicylaldehyde derived substrate **2.25** presumably because of the rotational restriction provided by the benzo linker in the backbone. To determine whether it was the oxygen linker or the lack of rotational restriction, substrate **2.41** was targeted (Scheme 2.14). In pursuit of this, aldehyde **2.42** was synthesized based on literature procedures from monoprotected hexane-1,6-diol.[54] A Wittig reaction on **2.42** afforded alkene **2.43** in an initially poor and unreproducible yield. Several sets of conditions were tested, including using *t*-BuOK instead of *n*-BuLi, but the yield was no better. The synthesis of this aldehyde required the use of a Swern oxidation, and the residual traces of dimethyl sulfide poisoned the Rh catalyst and the cyclopropanation was initially unsuccessful. This issue with residual DMS was addressed by using a higher loading and purifying the material by column chromatography several times prior to use. Cyclopropanation of the purified alkene **2.43** afforded cyclopropane **2.44** in 63% yield. TBS deprotection of this afforded alcohol **2.45** in good yield. Swern oxidation of **2.45** was performed, but it appeared that no aldehyde was formed. While this result was likely anomalous, due to the low overall yield of this approach combined with the difficulty in removing residual DMS made further testing of this route undesirable.



Scheme 2.14. Synthesis of cyclopropane alcohol **2.45** and attempted Swern oxidation.

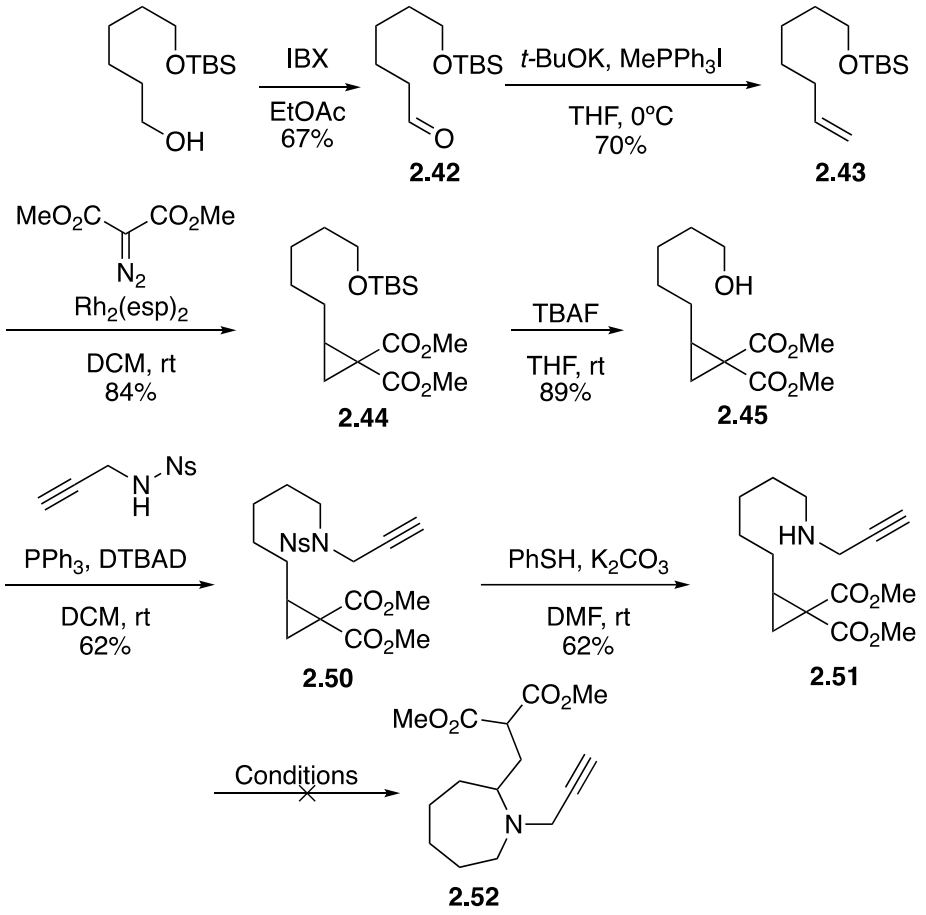
An alternate approach involving hydroboration of an alkyne was also tested. Based on literature procedures, alkene **2.46** was synthesized (Scheme 2.15).[55] This alkene was cyclopropanated to afford alkyne **2.47**. The methanolic deprotection of the alkyne proceeded smoothly and free alkyne **2.48** was obtained. This alkyne was then treated with several sets of hydroboration conditions. While up to 20% conversion to aldehyde **2.49** was obtained at a 100 mg scale with the use of Sia_2BH, this was decided to be unworkable as the yield dropped sharply with an increase in scale. With this result, an alternate strategy was pursued.



Scheme 2.15. Synthesis of aldehyde **2.49**.

It was realized that an IBX oxidation of monoprotected hexane-1,6-diol would avoid the issue of DMS poisoning the catalyst. A new set of attempts with freshly synthesized PPh_3MeI and newly purchased t-BuOK proved more successful and the yield of **2.43** was much higher (Scheme 2.16). The cyclopropanation of the alkene proceeded easily and the cyclopropane **2.44** was again isolated. Deprotection of this cyclopropane was facile and **2.45** was isolated in similarly high yield. With this alcohol in hand, a Mitusnobu reaction

with *N*-nosyl-propargylamine afforded protected amine **2.50**. This amine was easily deprotected with the PhSH and substrate **2.51** was isolated. On testing of **2.51**, no catalysts were able to promote formation of **2.52**. The compound instead underwent sudden decomposition similarly to **2.39**. Based on the results of testing of **2.51**, it appeared that only rotationally restricted 7-membered rings were compatible with the reaction.

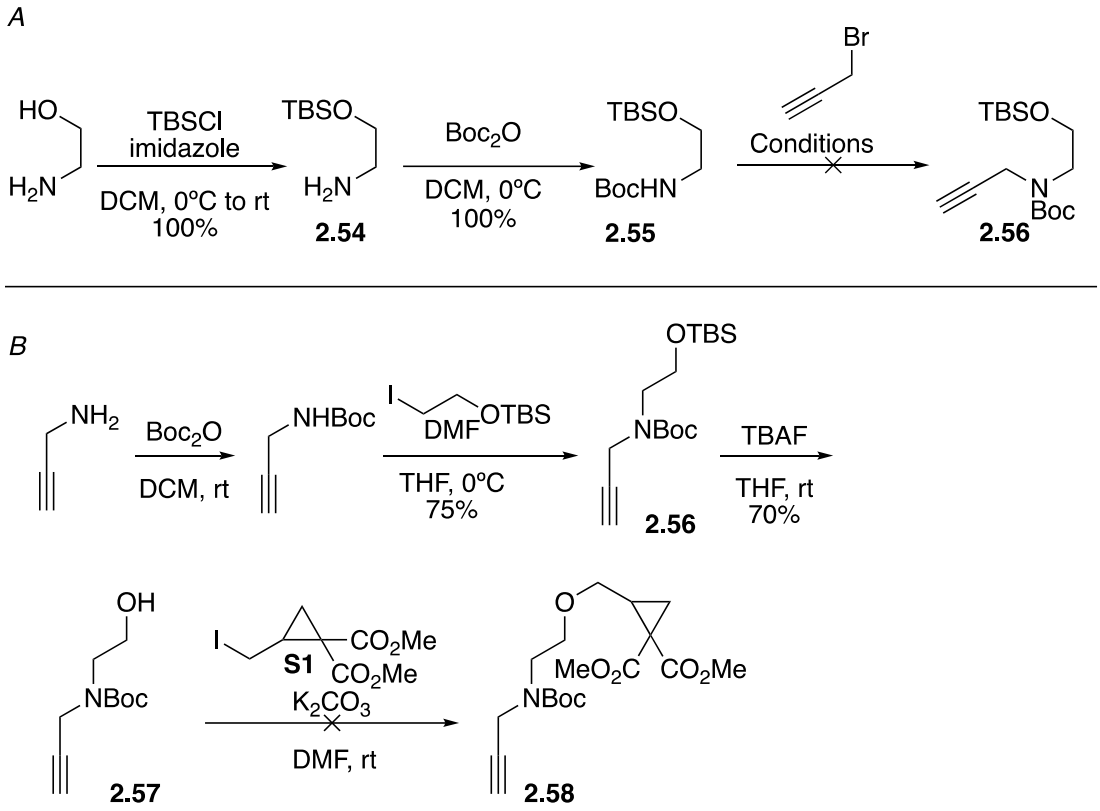


Scheme 2.16. Synthesis and testing of 7-membered ring forming substrate **2.51**.

2.2.6 Synthesis and Testing of 6-Membered Ring Forming Ether Linked Substrate **2.64**

Based on the results of substrate **2.25**, it was clear that oxygen atoms were tolerated in the backbone in specific cases. This discovery left the possibility of synthesizing a 6-membered ring forming substrate with an oxygen in the backbone, **2.64**. A new approach

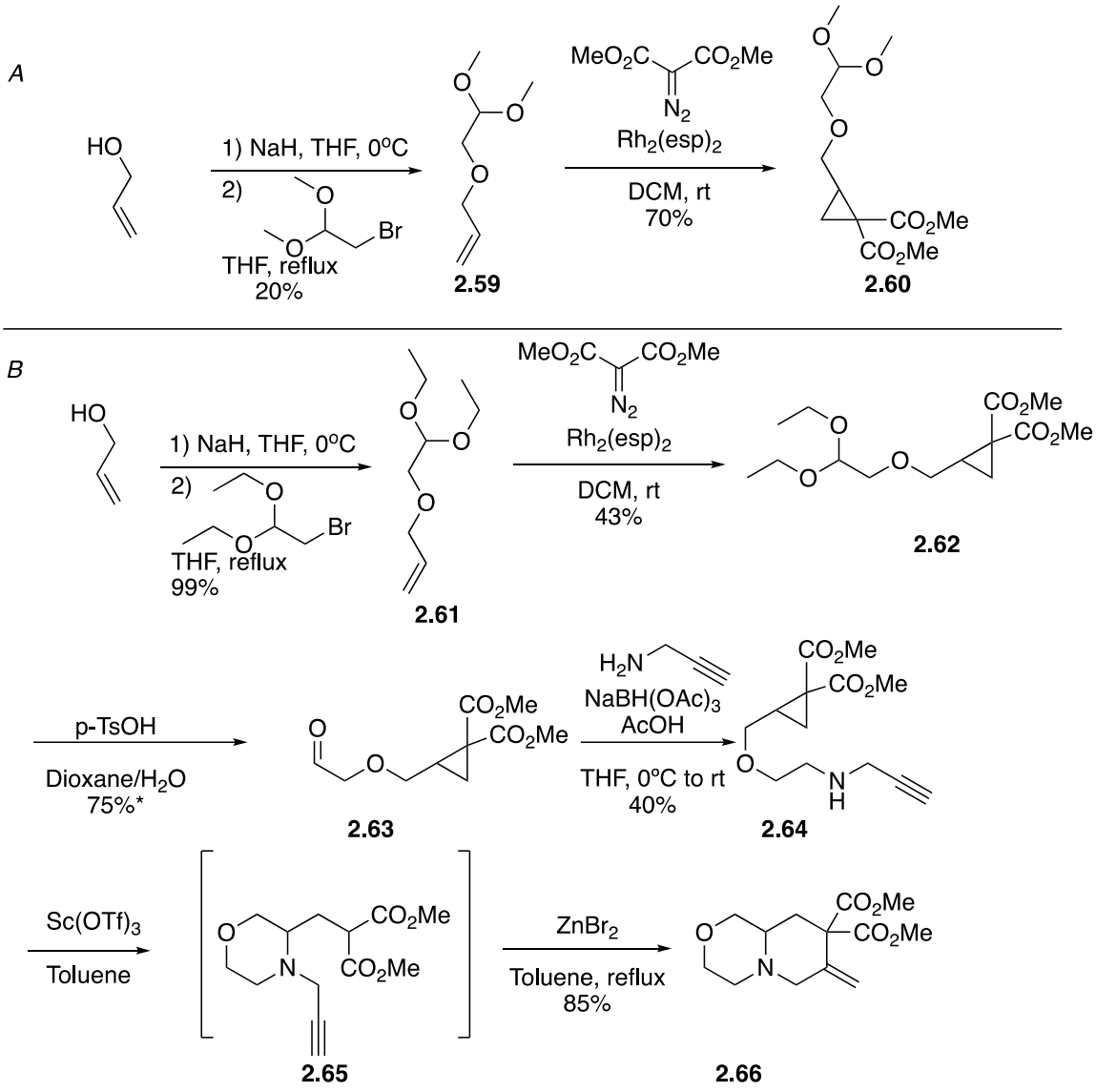
had to be planned to synthesize this substrate and the first attempt started by protecting ethanolamine (Scheme 2.17 A). It was realized that if ethanolamine was treated with propargyl bromide, it could lead to a mixture of products. Therefore, a strategy to mitigate this was pursued. It is known that Boc protected amines can be deprotonated and alkylated with an appropriate electrophile. TBS protection of 2-aminoethanol with standard conditions afforded **2.54** and Boc protection of this amine afforded **2.55**. Alkylation of the sodium salt of **2.55** with propargyl bromide was attempted, but no **2.56** was isolated after multiple attempts. Propargyl iodide is not commercially available and is difficult to prepare so the quality of the electrophile cannot be conveniently improved. Given the difficulty of alkylating **2.56**, another approach to synthesizing the substrate was tested based on N-Boc-propargylamine (Scheme 2.17 B). N-Boc-propargylamine alkylated smoothly with TBS-protected 2-iodoethanol affording **2.56**. TBS deprotection was also facile and **2.57** was isolated in good yield. However, the resulting alcohol proved difficult to alkylate with dimethyl-2-(iodomethyl)-cyclopropane-1,1-dicarboxylate **2.18**. No conversion was achieved under very mild conditions with K_2CO_3 as the base. More forcing conditions with NaH appeared to decompose cyclopropane **2.18** and no **2.58** was isolated.



Scheme 2.17. Attempted synthesis of **2.64**.

Given the difficulties encountered in the first synthetic pathway to **2.64**, an alternate approach was pursued (Scheme 2.18). The alkylation of allyl alcohol with bromoacetaldehyde derivatives has been performed before.[56] Unfortunately, the alkylation of the sodium salt of allyl alcohol with bromoacetaldehyde dimethyl acetal was complicated by the apparent volatility of **2.59** as well as its slow formation (Scheme 2.18 A). Significant conversion took upwards of 3 days to achieve. The crude yield was modest (~30%) in most attempts but the material required purification by column chromatography to be cyclopropanated successfully. There was significant loss of material even when a more volatile solvent system consisting of pentane and Et_2O was utilized. As a result, the purified yield of **2.59** was very low. A small amount of this material was successfully cyclopropanated, but this approach did not provide **2.60** in sufficient quantities to allow for synthesis of significant amounts of **2.64**. Acetal deprotection of **2.60** was also slow to progress and low yielding. These combined factors meant that the volatility had to be addressed. The issues with volatility were addressed by substituting bromoacetaldehyde

diethyl acetal for the dimethyl acetal. With this change, the yield of the reaction forming **2.61** was near quantitative using the same conditions (Scheme 2.18 B). Cyclopropanation of **2.61** worked well and cyclopropane **2.62** was isolated in high yield. The acetal group on **2.62** was slow to hydrolyze under milder conditions and a reaction time of 5 days at 50ºC was required to achieve significant conversion to the aldehyde **2.63**. The aldehyde was also extremely difficult to isolate and separate from unreacted acetal presumably due to its reactivity. Fortunately, the crude mixture of the aldehyde **2.63** and the acetal **2.62** when treated with reductive amination conditions afforded **2.64** in moderate yield. Amine cyclopropanediester **2.64** converted readily to the ring opened intermediate **2.65** and the Conia-ene product **2.66** under optimized conditions. Due to the smoothness of the transformation, **2.65** never had to be isolated to confirm its structure.

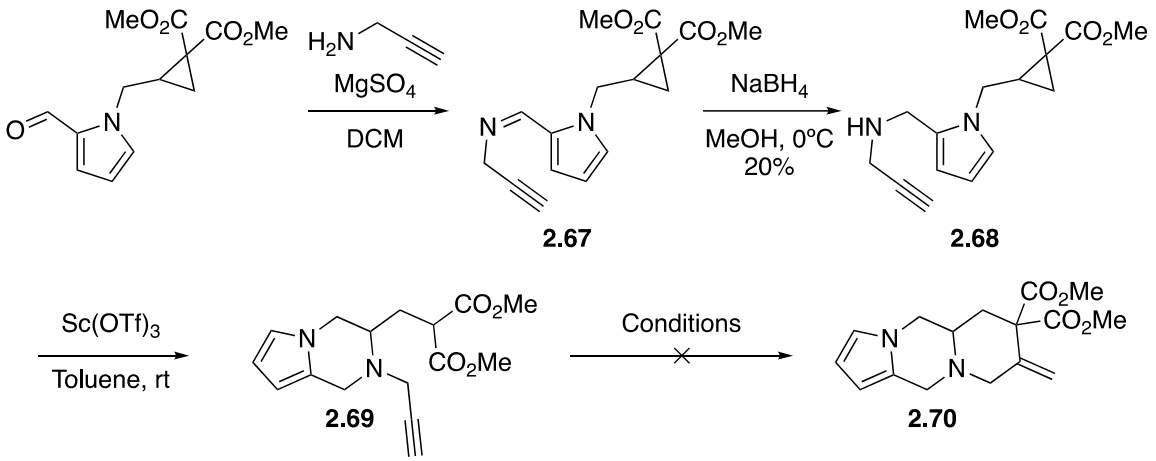


Scheme 2.18. Synthesis and testing of substrate **2.64**. * = crude yield.

2.2.7 Synthesis and Testing of Pyrrole Linked Substrate **2.68**

Another easy to synthesize substrate was identified based on previous literature reports. A pyrrole tethered cyclopropane could be accessed rapidly from known compounds and converted to the imine **2.67** (Scheme 2.19). This imine was easily reduced affording **2.68**. This amine was able to undergo ring opening to form intermediate **2.69** under mild conditions. The ring-opened intermediate was not stable under either $ZnBr_2$ or $Zn(NTf_2)_2$ Conia-ene conditions. Even with very mild heating, significant decomposition was

observed and no traces of **2.70** were observed. The instability of **2.69** is attributed to the tendency of pyrroles to polymerize. Compound **2.68** was also observed to darken on standing in $CDCl_3$ at room temperature. Given the instability of ring opened material **2.69** towards Lewis acids, no further tests were performed.

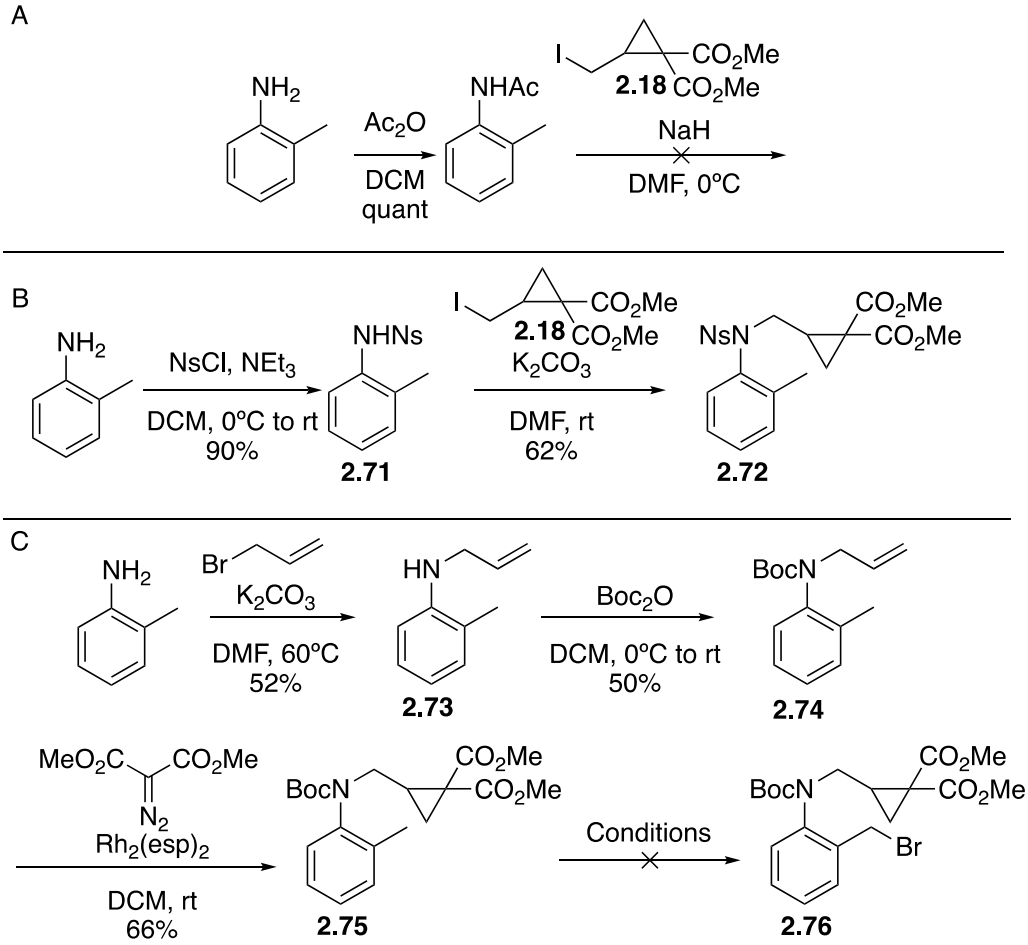


Scheme 2.19. Synthesis and testing of **2.68**.

2.2.8 Synthesis and Testing of 7-Membered Ring Forming Amine Substrate **2.83**

Based on the results of **2.24**, it was hoped that the reaction conditions would tolerate a protected nitrogen in the backbone. In pursuit of this, a substrate was targeted to have a benzo linker and a protected amide in the backbone. An initial series of synthetic attempts were made based on *o*-toluidine. Several protecting groups were tested and were found to be problematic for a variety of reasons. The first protecting group tested was an acetyl group (Scheme 2.20 A). 2-methylacetanilide was easily accessed by treating *o*-toluidine with acetic anhydride. The acetanilide was difficult to allylate under several sets of conditions and did not react cleanly with iodomethyl cyclopropane **2.18**. Instead, **2.18** appeared to slowly decompose under the reaction conditions. This difficulty of alkylation was not present in the Ns protected amide **2.71**, but it was realized that the reactivity of the amine rendered the compound unsuitable for further manipulation (Scheme 2.20 B). It was also realized that for conversion to a usable precursor, the more exotic and expensive DNs

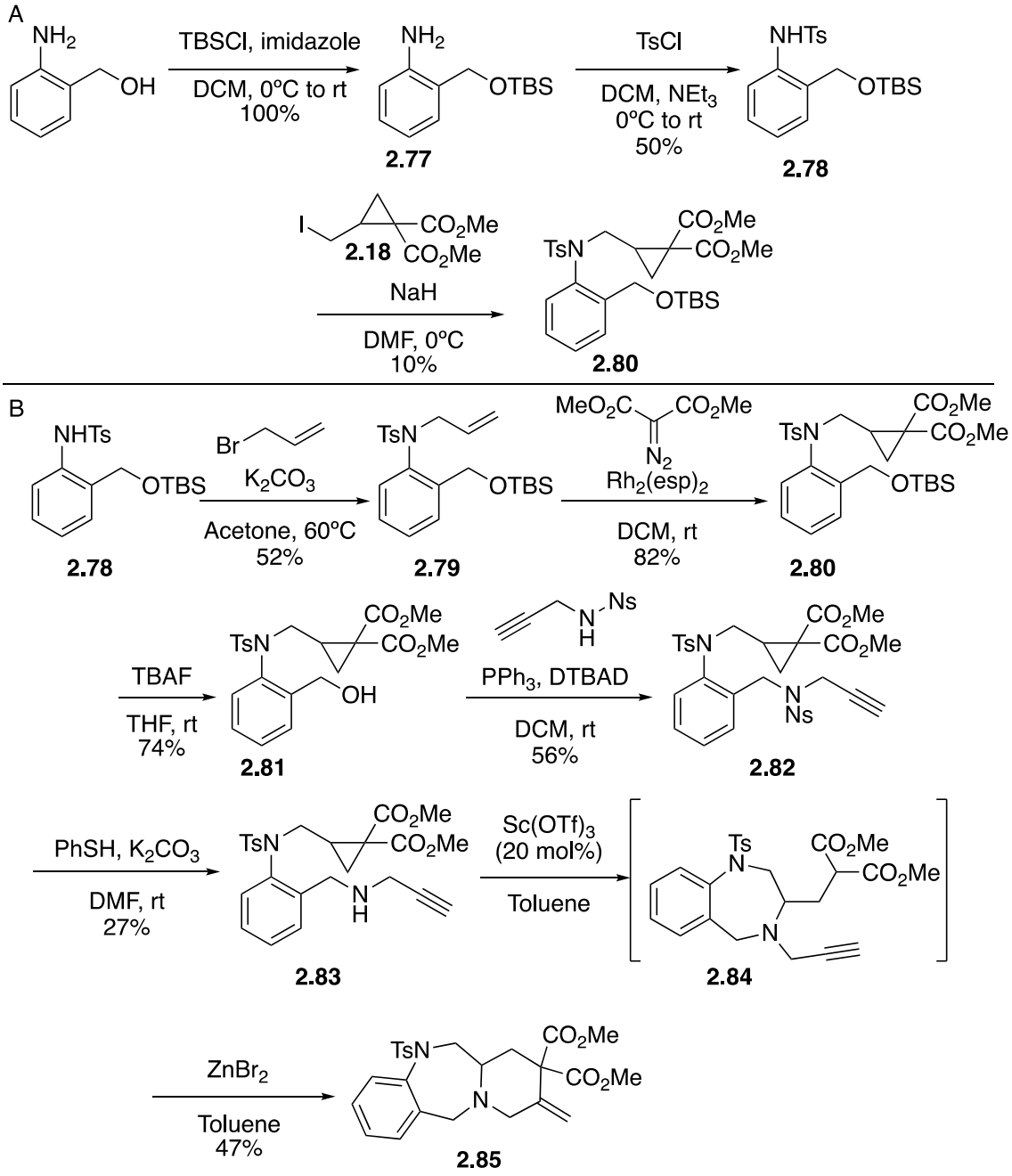
protecting group would be required due to the need to use the Fukuyama reaction. A DNs group is the only common amine protecting group that both activates the amine to alkylation and can be removed in the presence of a Ns group. In another approach, *o*-toluidine was monoallylated to **2.74** and converted to the Boc protected amine **2.75** (Scheme 2.20 C). The protected amine was then cyclopropanated under standard conditions to afford cyclopropane **2.76**. Several attempts were made to convert **2.76** to the benzyl bromide **2.77**, but all attempts resulted in decomposition of the material with no discernable conversion.



Scheme 2.20. Attempted synthesis of **2.83**.

With the realization that **2.76** was unstable under Wohl-Ziegler conditions, a new approach was formulated based on 2-aminobenzyl alcohol. 2-aminobenzyl alcohol was easily doubly protected to afford **2.78** (Scheme 2.21 A). Attempts were made to alkylate this amine with

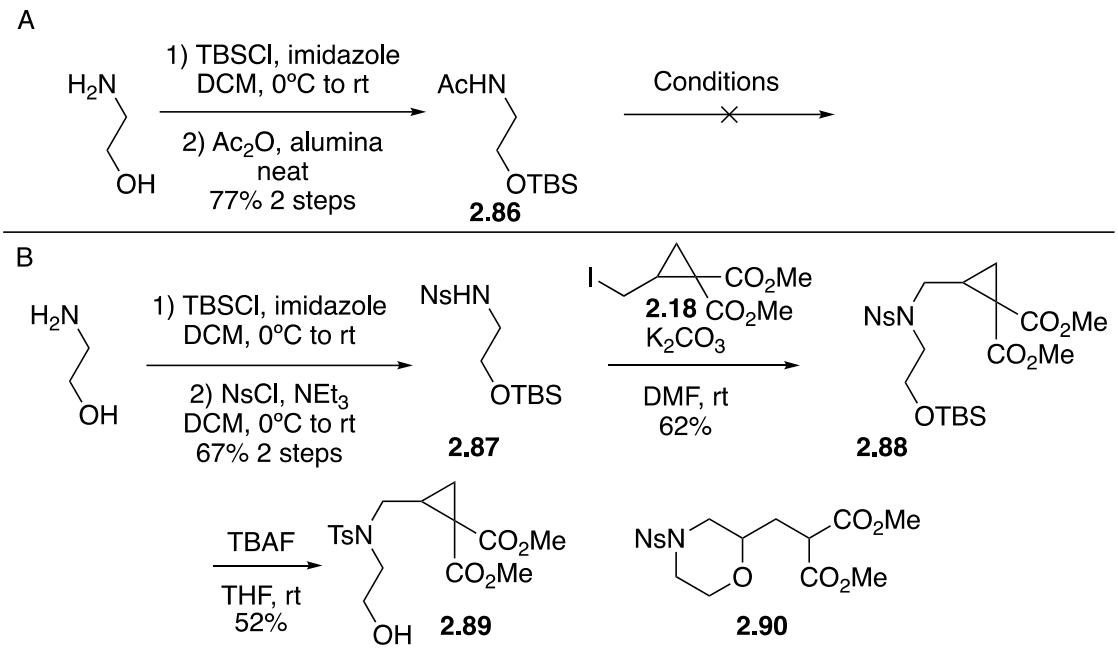
dimethyl-2-(iodomethyl)-cyclopropane-1,1-dicarboxylate, but the reaction appeared to decompose the cyclopropane. This attempted alkylation resulted in a very low yield (<30%) of a difficult to separate mixture of products that contained some **2.80**. With this result, **2.78** was instead allylated affording **2.79** (Scheme 2.21 B).[57] This material was easily cyclopropanated to afford **2.80**. The deprotection of **2.80** proceeded smoothly with the addition of TBAF and afforded alcohol **2.81**. This alcohol was easily converted to Ns amine **2.82** with Mitsunobu conditions with *N*-nosyl-propargylamine. The Ns amine was treated with PhSH and the substrate **2.83** was isolated in low yield. Similar to **2.24**, this substrate required harsher conditions to form the ring-opened product **2.84**. $ZnBr_2$ converted the ring-opened material to the Conia-ene product **2.85** in modest yield.



Scheme 2.21. Synthesis and testing of amine linked 7-atom ring forming substrate **2.83**.

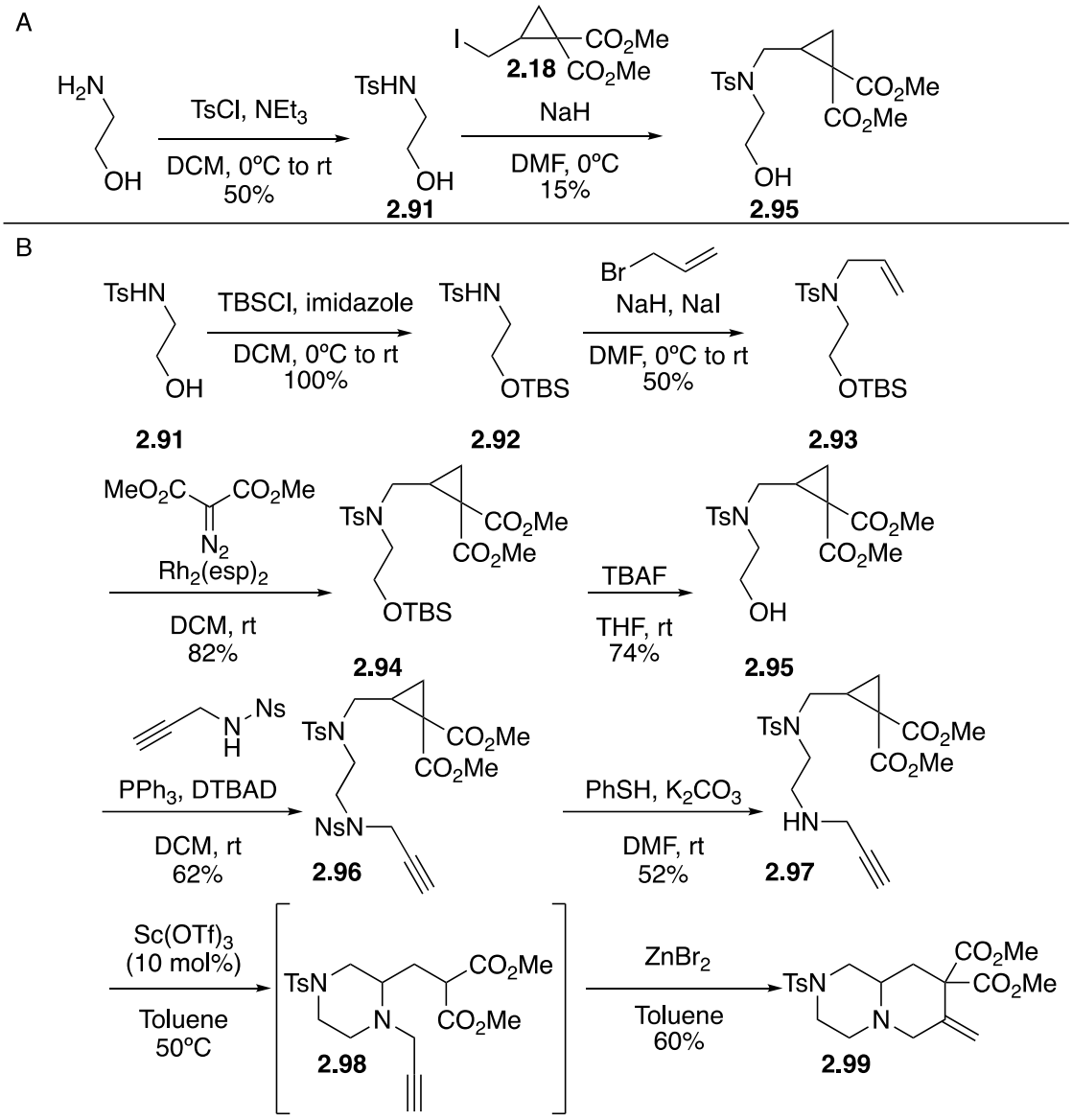
2.2.9 Synthesis and Testing of 6-Membered Ring Forming Amine Substrate **2.97**

It was also hoped that a substrate with a protected amino group in the same position as the oxygen of **2.64** would be compatible with the reaction. Initial attempts were made starting by doubly protecting ethanolamine with TBS and acetyl protecting groups **2.86** (Scheme 2.22 A). This acetamide proved quite unreactive and effective alkylation was never realized even with the highly reactive allyl bromide. An easier to alkylate compound was obtained when a Ns group was used instead of an acetyl group affording **2.87** (Scheme 2.22 B). This compound alkylated smoothly with the cyclopropane **2.18** affording **2.88**. TBAF deprotection of the TBS alcohol did not result in the isolation of a significant amount of alcohol **2.89**. Instead, the near complete conversion to a ring-opened product **2.90** was observed. It was also realized that even if the deprotection to proceed successfully, there would be no easy way of adding the propargylamine functionality and obtaining **2.97** without the use of a DNs group. While this approach would be possible with the use of a DNs group, with the destruction of much of the material, a new strategy was employed instead.



Scheme 2.22. Attempted synthesis of **2.97**.

A Ts protecting group strategy was tried instead to avoid the deprotection issues with the Ns group. Initially, ethanolamine was Ts protected affording **2.90** (Scheme 2.23 A). Several attempts were made to alkylate this compound with cyclopropane **2.18**, but alcohol **2.95** was only isolated in extremely low yield as part of a mixture of uncharacterized products. To address the difficulties in alkylating **2.90**, the Ts protected amine was TBS protected affording **2.92** (Scheme 2.23 B). To avoid the use of the problematic cyclopropane **2.18**, the material was instead allylated affording **2.93**. Cyclopropanation proceeded smoothly and **2.94** was isolated. A TBAF deprotection of **2.93** buffered with AcOH provided the alcohol **2.95** in good yield with no detectable ring-opened material. This alcohol converted easily to the Ns protected substrate **2.96** under Mitsunobu conditions. Deprotection proceeded in low yield and the substrate **2.97** was isolated. The substrate converted cleanly to the ring-opened material **2.98** under mild $Sc(OTf)_3$ conditions. The Conia-ene reaction of the ring-opened material proceeded well under the optimized conditions and **2.99** was isolated in moderate yield.

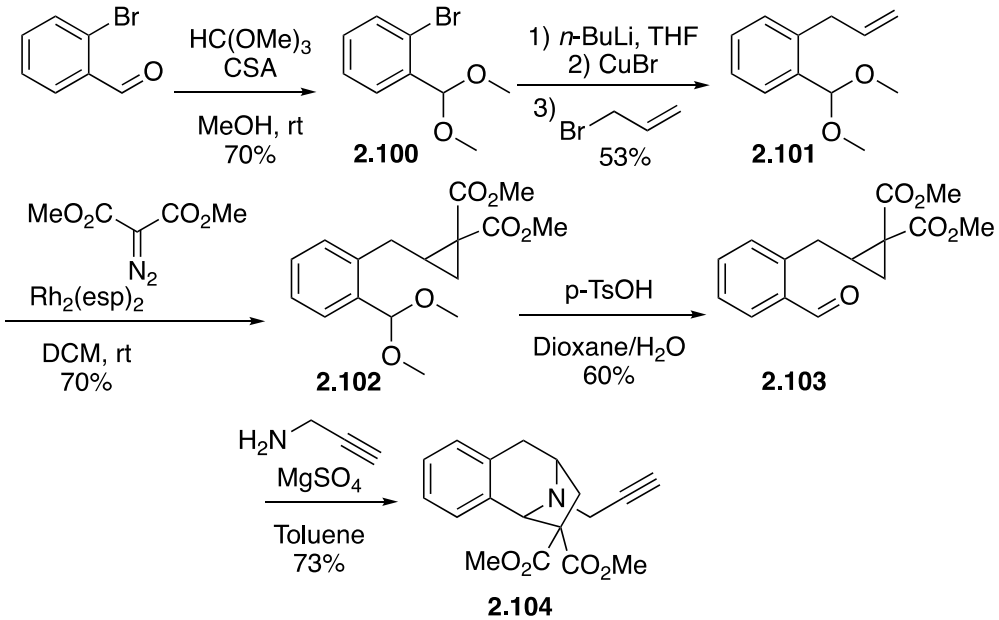


Scheme 2.23. Synthesis and testing of amine-linked 6-membered ring forming substrate **2.97**.

2.2.10 Synthesis and Testing of Benzo Linked Substrate **2.120**

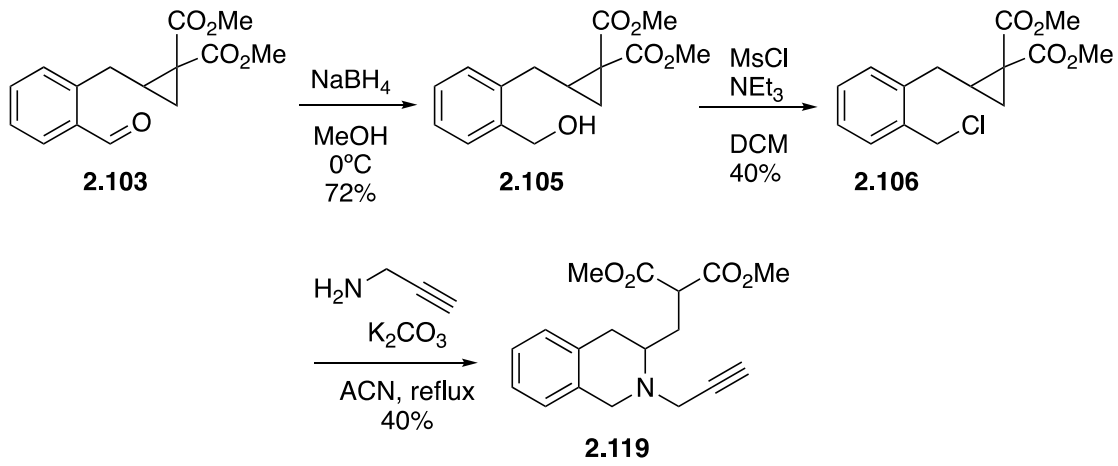
With the difficulties encountered in cyclizing intermediate **2.9**, a different benzo-linked substrate was targeted. This substrate was targeted based on the observation that the substrates that form a 6-membered ring in the first step worked significantly better than those that make 5-membered rings. Synthesis of **2.120** began with acetal protection of 2-

bromobenzaldehyde affording **2.100** in high yield (Scheme 2.24). The alkene was then lithiated and converted to an organocopper reagent. This intermediate reacted with allyl bromide to afford **2.101**.[58] The allylbenzene **2.101** was obtained in initially poor yields using this modified literature procedure. It was realized that this reaction is very sensitive to the quality of the CuBr. Performing the reaction with old samples of CuBr with significant Cu(II) content resulted in poor yields. It was possible to purify the old sample of CuBr given enough effort, but the reagent is inexpensive enough that purchasing a new sample was affordable. Using this new sample of CuBr improved the yields of the allylation dramatically. Cyclopropanation of **2.101** proceeded easily and afforded cyclopropane **2.102** in a 70% yield. The acetal **2.102** was hydrolysed to **2.103** with TsOH in water and dioxane. Aldehyde **2.103** underwent a spontaneous reaction forming a tricyclic compound **2.104** when exposed to propargylamine in the presence of $MgSO_4$. The reaction was rapid, and the imine intermediate was never isolated. This reaction occurred when either $MgSO_4$ or molecular sieves were used as the dehydrating agent. The formation of **2.104** in the presence of molecular sieves is surprising since ring opening reactions of DA cyclopropanes typically require a Lewis acid catalyst. **2.103** is known to convert to tricyclic compounds analogous to **2.104** in the presence of amines and Lewis acids.[59]



Scheme 2.24. Attempts towards synthesis of **2.118**.

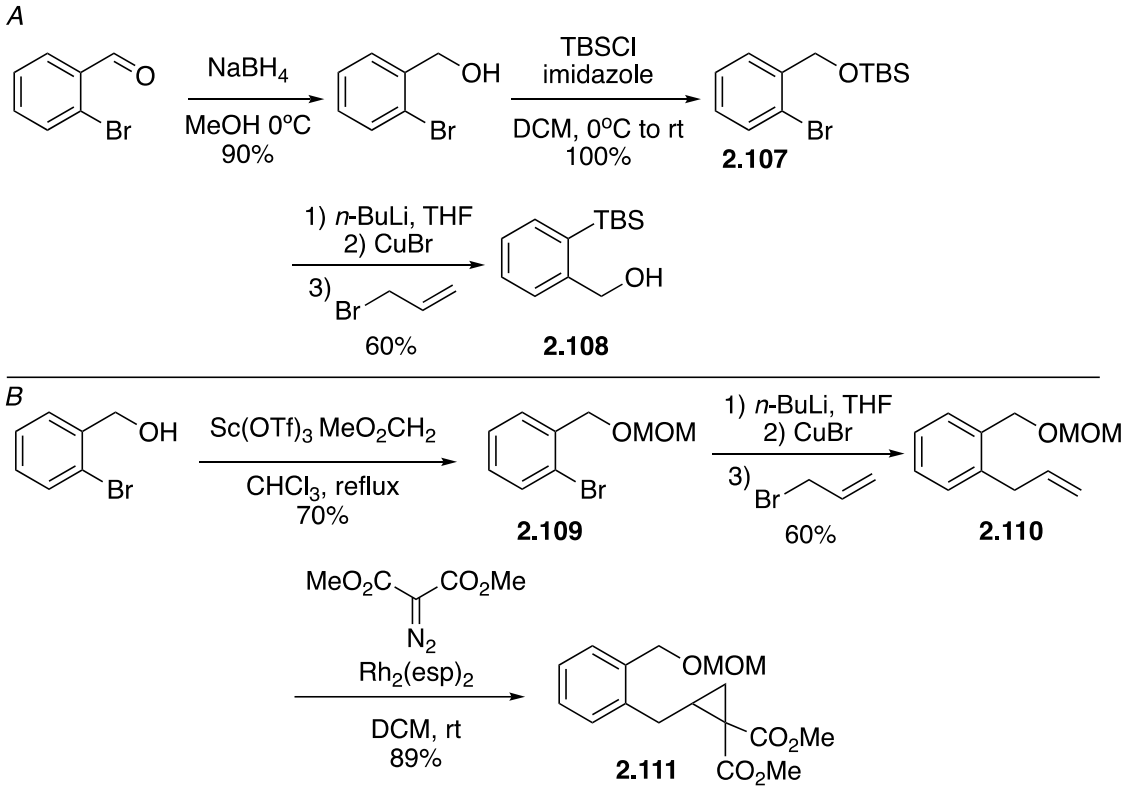
Since the imine could not be isolated, aldehyde **2.103** was subjected to the optimized reductive amination conditions used to synthesize **2.2**. No cyclopropane was isolated, and it appeared that the compound instead underwent slow decomposition forming a mixture of unidentifiable products and a significant quantity of tricyclic compound **2.104**. With the difficulties encountered in reductive amination, a third attempt involving the displacement of a leaving group was tested. In this approach, the aldehyde group was first reduced with $NaBH_4$ affording alcohol **2.105** (Scheme 2.25). Mesylation of **2.105** was attempted, but the starting material took over 24 hours to be consumed and mesylate was not isolated. Upon workup, the material was determined to be benzyl chloride **2.106**. Treatment of the benzyl chloride with propargylamine under alkylation conditions afforded no **2.118**. Instead, a small quantity of ring opened product **2.119** was obtained. However, given the low overall yield of this pathway, a new approach was considered.



Scheme 2.25. Synthetic progress towards substrate **2.118**.

The propensity of aldehyde **2.103** to undergo side reactions was noted and to attempt to avoid this problem, an approach was crafted to avoid its intermediacy. In this attempt, 2-bromobenzaldehyde was reduced with $NaBH_4$ affording 2-bromobenzyl alcohol (Scheme 2.26 A). This alcohol was then protected with TBSCl affording **2.107**. The protected alcohol was subjected to the allylation conditions used in the synthesis of **2.101**. Under the reaction conditions, a Brook rearrangement occurred affording **2.108**. This reaction pathway consumed all the starting material and no allylated material was obtained. Some attempts were made at modifying the conditions to favour allylation instead of

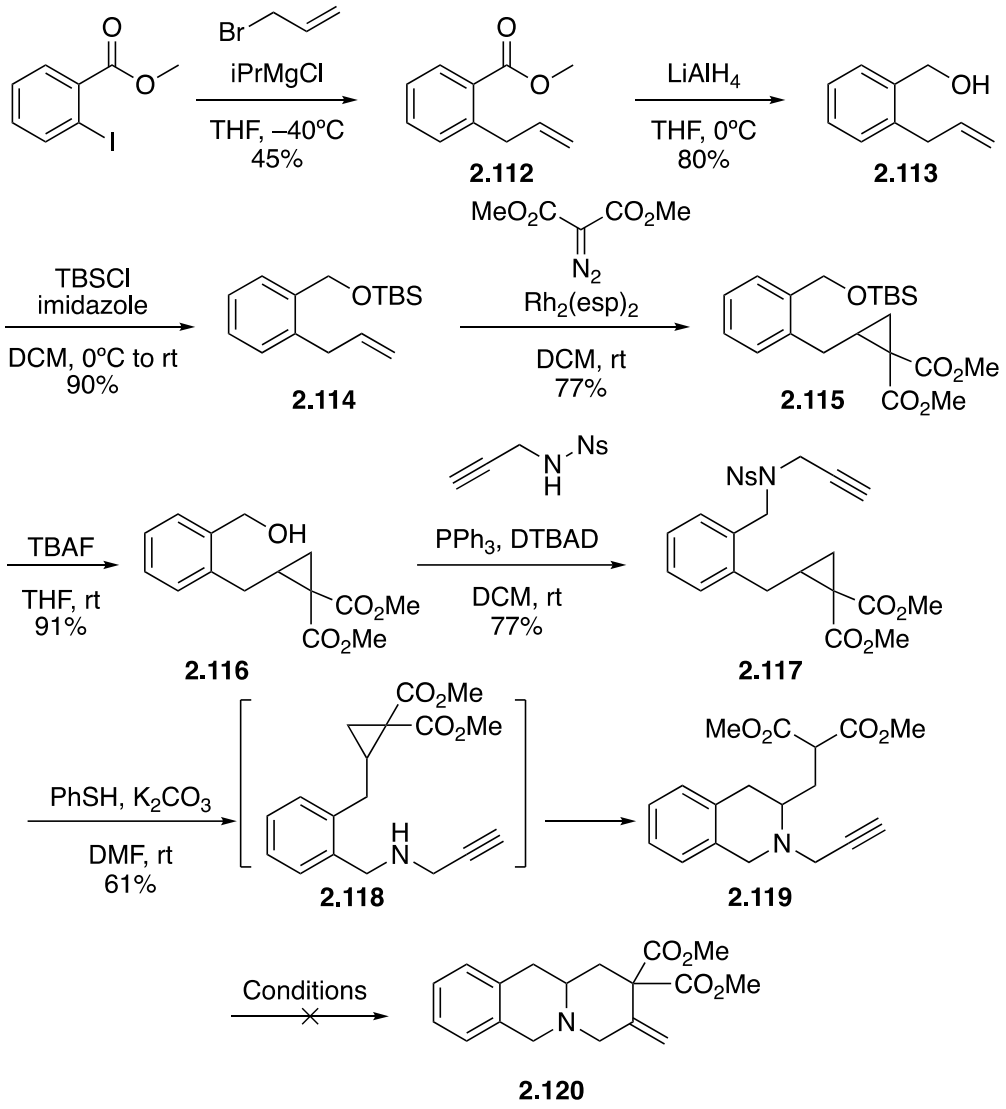
rearrangement, but no allylbenzene product was ever obtained. An alternative route involving a Grignard reaction was tested, but the Grignard of **2.107** proved extremely difficult to make reliably. An alternative protecting group, a MOM ether was tested (Scheme 2.26 B). The ether **2.109** was formed easily based on a literature procedure. This MOM ether was allylated easily affording **2.110**. Unfortunately, cyclopropanation of this protected alcohol was very low yielding. No byproducts could be isolated from the reaction. Although a small amount of **2.111** could be isolated, this approach was abandoned due to the consistently low yield of the reaction.



Scheme 2.26. Alternate attempts at synthesis of **2.118**.

A new approach was devised starting from methyl 2-iodobenzoate. After magnesium halogen exchange, and allylation, **2.112** was isolated (Scheme 2.27). This material was then reduced with $LiAlH_4$ to afford the benzyl alcohol **2.113**. The alcohol was protected with TBSCl affording **2.114** in quantitative yield. This alkene was then cyclopropanated under standard conditions affording **2.115**. The TBAF mediated deprotection proceeded well and **2.116** was isolated. This alcohol reacted well under Mitsunobu conditions with

the Ns amine affording **2.117**. Unfortunately, the deprotection of this amine with PhSH was difficult. The reaction proceeded very slowly and yielded the ring opened product **2.119** instead of substrate **2.118**. Based on the isolation of **2.119**, it was clear that any **2.118** formed was transitory in nature. Fortunately, the isolation of the ring opened material was sufficient to allow for testing of this substrate under Conia-ene conditions. The ring-opened material **2.119** did not cyclize under the Zn catalyzed or promoted Conia-ene conditions and instead slowly decomposed to a complex mixture of products. This lack of reactivity is likely due to a poor spatial arrangement in the preferred conformer of **2.119** that does not allow proper alignment of the atoms for forming the desired Conia-ene product **2.120**. The Conia-ene reaction is notoriously sensitive to the relative arrangement of the reacting groups. With this result, further testing of **2.119** was abandoned.

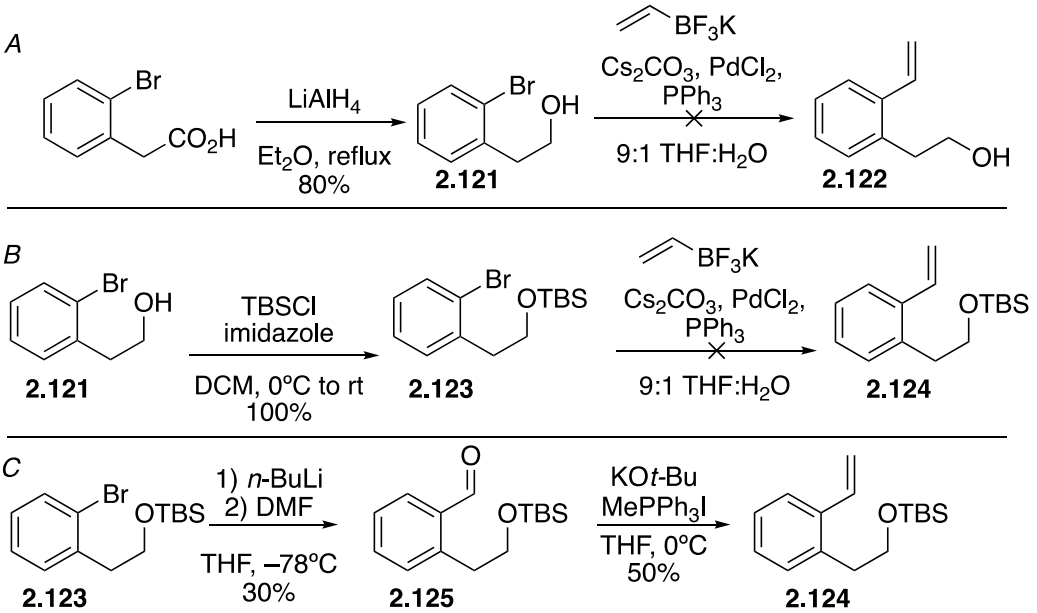


Scheme 2.27. Synthesis and testing of **2.119**.

2.2.11 Synthesis and Testing of Phenylcyclopropane Substrate **2.132**

Substrate **2.132** was targeted to test the viability of phenylcyclopropanes for the tandem reaction. Starting from 2-bromophenylacetic acid, phenethyl alcohol **2.121** was obtained by $LiAlH_4$ reduction (Scheme 2.28 A). Suzuki coupling was attempted with the alcohol **2.121**. Unfortunately, alcohol **2.121** did not undergo coupling readily under the tested conditions despite several attempts and different sets of conditions. Traces of the styrene

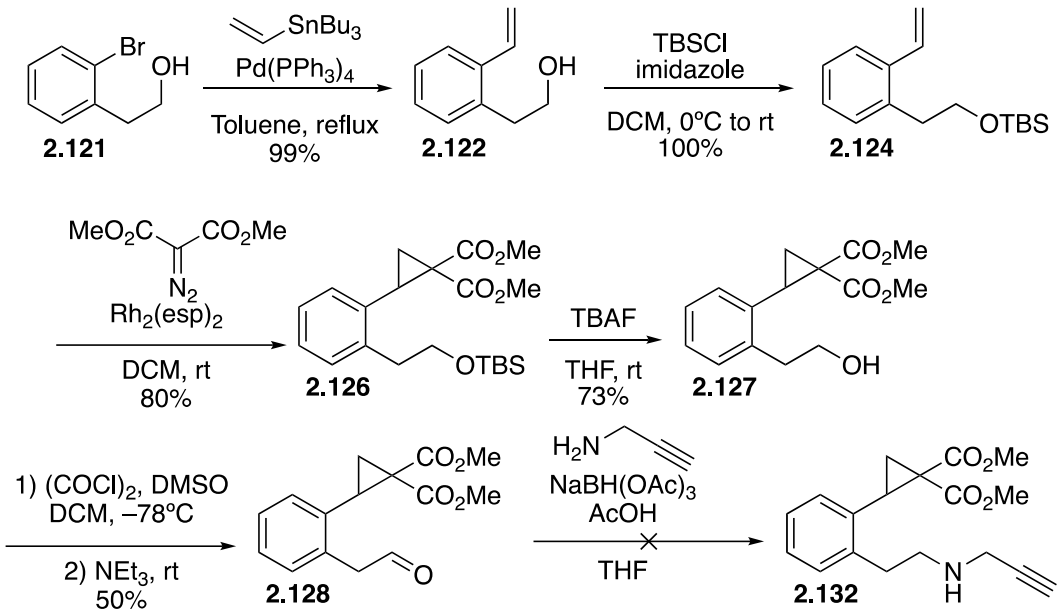
2.122 were observed in the ^{1}H NMR spectrum, however the reaction never went to completion. The yield was not improved with supplementary additions of catalyst, increasing the equivalence of the coupling partner, changing the temperature, changing the concentration, or increasing the starting catalyst loading. Styrene **2.122** and the starting bromoarene **2.121** were also found to be entirely inseparable by column chromatography. To determine if the lack of conversion was due to the free alcohol group, TBS protection was performed (Scheme 2.28 B). With standard conditions, **2.121** was TBS protected furnishing **2.123** in quantitative yield. Treatment of the TBS protected alcohol **2.123** with Suzuki conditions did not furnish even traces of the styrene **2.124** and this approach was abandoned. Given the difficulties encountered, an alternative approach involving formylation of the silyl protected alcohol **2.123** was tested (Scheme 2.28 C). While some **2.125** was isolated, the formylation of **2.123** proved to be quite low yielding. The Wittig reaction of **2.125** was also not high yielding. Given the low yields of this pathway, a new route was devised.



Scheme 2.28. Attempted synthesis of styrene derivatives.

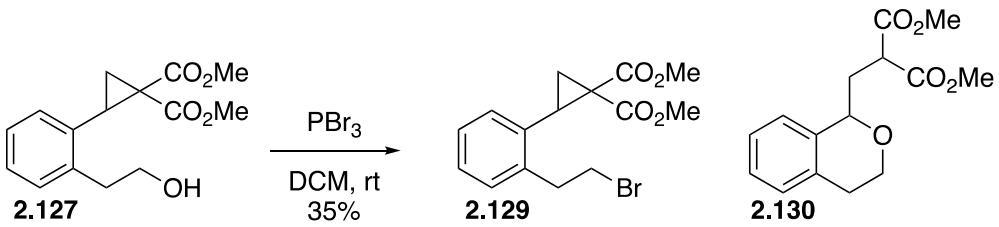
Given the difficulties in performing a Suzuki coupling, Stille coupling conditions were tested instead. On testing, alcohol **2.121** reacted readily under Stille conditions, and styrene **2.122** was isolated in quantitative yield after purification by column chromatography

(Scheme 2.29). TBS protection proceeded in good yield and protected alcohol **2.124** was isolated. The rhodium catalyzed cyclopropanation reaction on this substrate never went to completion, but enough **2.126** was isolated to continue with substrate testing. Deprotection of **2.126** afforded alcohol **2.127** in 73% yield. Swern oxidation of **2.127** afforded the aldehyde **2.128** in under 50% yield and numerous byproducts were observed via TLC. This instability is believed to be the result of the of the enolizable aldehyde. Despite the significant decomposition, sufficient material was isolated to attempt reductive amination to synthesize **2.132** with the optimized conditions. After workup, a propargyl group was observed in the ^{1}H NMR spectrum of the product mixture after workup. However, the material proposed to be amine **2.132** could not be isolated from the reaction mixture.



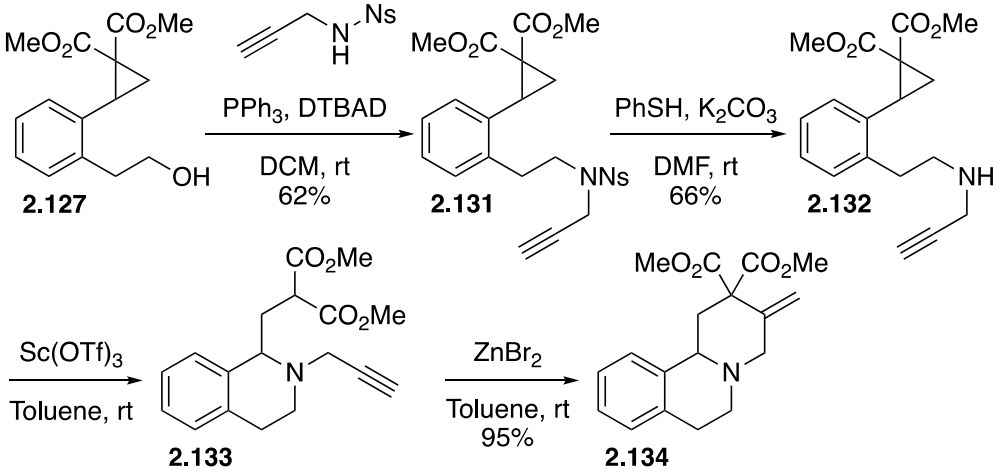
Scheme 2.29. Attempted synthesis of substrate **2.132**.

In an attempt to address the difficulties with using aldehyde **2.128,** a new approach was tested using PBr_3 to form alkyl bromide **2.129** (Scheme 2.30). This attempt resulted in formation of proposed ring opened material **2.130** as the major product. The mixture of products was also obtained in low yield and proved to be virtually inseparable with a ratio of **2.130** to **2.129** of about 3:1. It was realized that an Appel reaction was likely to furnish the alkyl bromide cleanly, but this approach was sidelined in favour of a Mitsunobu based approach.



Scheme 2.30. Alternative attempts at synthesis of **2.132**.

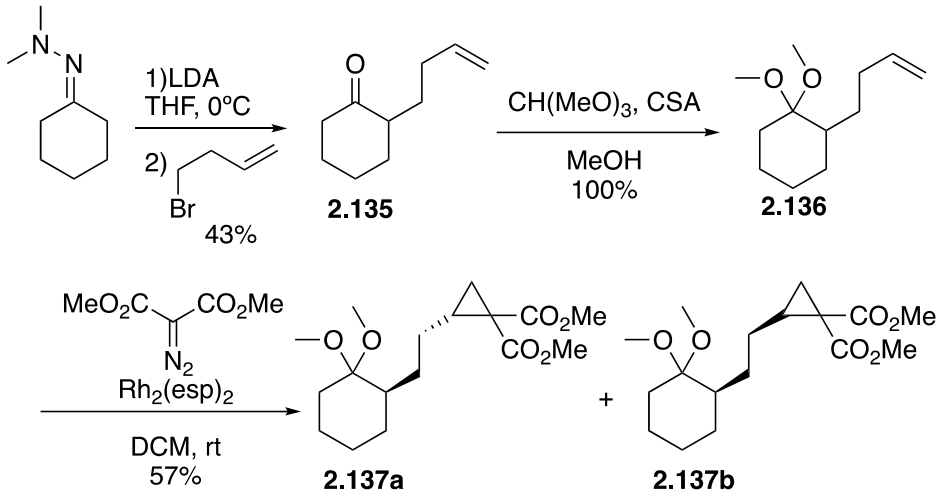
In a new attempt starting from the cyclopropyl alcohol **2.127**, a Mitsunobu reaction afforded protected amine **2.131** (Scheme 2.31). Initial attempts at deprotecting **2.131** with PhSH at elevated temperature afforded significant amounts of an unknown and inseparable byproduct. Using milder conditions, **2.131** was easily deprotected using PhSH in DMF at room temperature to afford the substrate **2.132**. The substrate converted easily to the ring-opened intermediate **2.133**. The formation of ring opened material **2.133** was observed and some material was isolated to confirm the identity, but it was not fully characterized. When subjected to optimized reaction conditions, **2.132** converted easily to product **2.134** in high yield without the need to isolate **2.133**.



Scheme 2.31. Synthesis and testing of **2.132**.

2.2.12 Attempted Synthesis of **2.138**

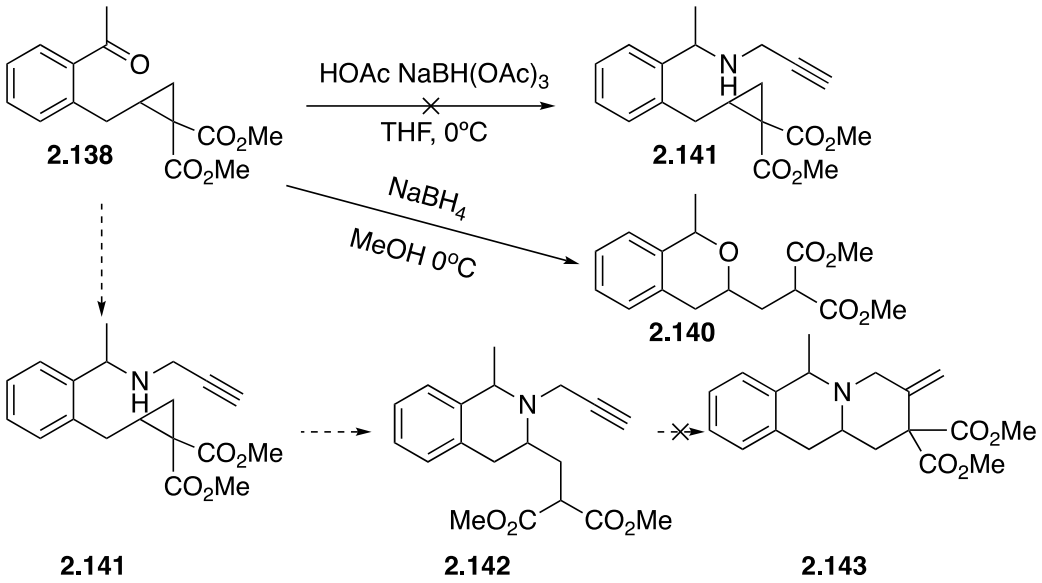
It was wondered if the reaction occurred with clean inversion of configuration of the chiral cyclopropane carbon retention or if scrambling occurred. To test the stereochemical outcome of the reaction, a substrate with separable diastereomers could have its diastereomers resolved and tested individually. It would also be interesting to test if there is a difference in the rate of reaction between the diastereomers. A cyclohexanone derived substrate **2.138** was targeted as a simple to synthesize candidate (Scheme 2.32). Cyclohexanone was converted to the dimethyl hydrazone based on previous literature precedent.[60] The Li salt of this hydrazone was easily alkylated with 4-bromo-1-butene affording **2.135**. Acetal formation was facile and **2.136** was isolated. However, an issue arose when the alkene was converted to the cyclopropane **2.137**. The cyclopropanation formed two difficult to separate diastereomers, **2.137a** and **2.137b**. The presence of both of these diastereomers also made the NMR spectrum nearly indecipherable. It was also realized that the following reductive amination step was likely to produce 4 sets of diastereomers that would be extremely difficult to separate and test individually. Additionally, the diastereomers would be very difficult to differentiate by NMR techniques as the alkyl region of the ^{1}H NMR spectrum is particularly complex in this series of compounds. Work on this substrate was discontinued after this stereochemical issue was considered.



Scheme 2.32. Attempted synthesis of a cyclohexanone-based substrate.

2.2.13 Attempted Synthesis of **2.142**

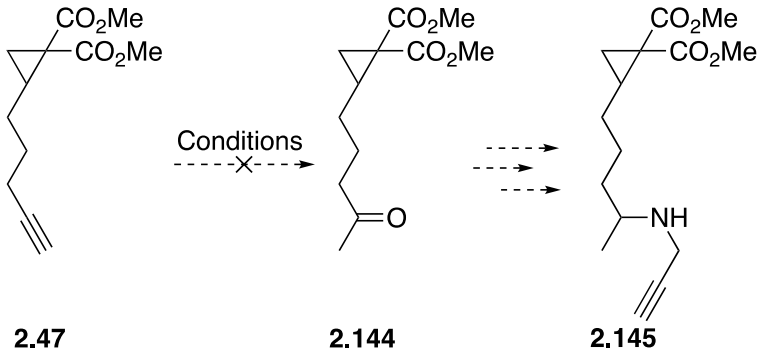
To attempt to address the issues with potential substrate **2.138**, a new benzo-linked substrate was targeted to test diastereoselectivity. Based on previous reports, ketone **2.139** was prepared.[59] Treating this ketone with reductive amination conditions caused no conversion to the desired **2.141** and only starting material was recovered (Scheme 2.33). This lack of reactivity was thought to be due to the steric hindrance of the ketone and several sets of more forcing conditions were tested to try to achieve amination. These more forcing results caused the decomposition of the starting material with no conversion to **2.141**. All attempts at imine formation also resulted in isolation of only starting material instead of the desired **2.141**. Several attempts were made to convert the ketone to an alcohol and perform a Mitsunobu reaction. However, all attempts at reduction of the ketone resulted in ring-opening of the cyclopropane. Reduction of the ketone under very mild conditions with $NaBH_4$ also resulted in complete conversion to a ring-opened product **2.140**. The difficulty in using the ketone would have necessitated a new approach but the pursuit of **2.141** was based on the results of the highly similar substrate **2.118**, the proposed ring opened material **2.142** would be unlikely to cyclize to **2.143** under Conia-ene conditions. Therefore, based on the results of **2.118**, further attempts at synthesizing **2.141** were not made.



Scheme 2.33. Attempted synthesis of **2.141**.

2.2.14 Attempted Synthesis of **2.143**

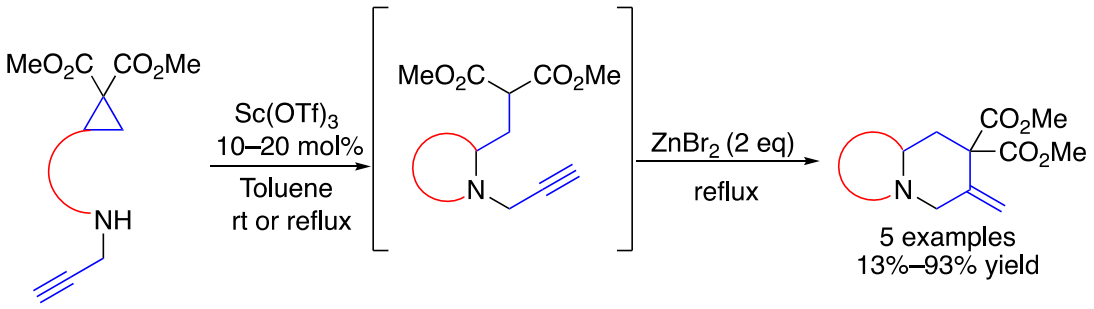
A final attempt was made at synthesizing a substrate to test the diastereoselectivity of the reaction based on **2.47** (Scheme 2.34). A number of attempts were made to hydrate the alkyne of **2.47**, including catalytic attempts, but no **2.144** was observed.[61] All tested conditions resulted in decomposition of the starting cyclopropane. This hydration approach is likely unviable and a new approach to the compound is necessary.



Scheme 2.34. Attempted synthesis of **2.145** from **2.47**.

Chapter 3 Conclusion and Future Work

In the pursuit of extending the previously developed one-pot DA cyclopropane opening Conia-ene reaction, a synthetic protocol for a one-pot conversion of cyclopropane tethered amines to bicyclic piperidines was planned and tested (Scheme 3.1). Initial studies with substrates that would ideally form indolizine scaffolds were either unstable or unreactive under Conia-ene conditions. Substrates that formed 6-membered rings in the DA cyclopropane opening step were most successful. In the optimization study, a two catalyst system of $Sc(OTf)_3$ and $ZnBr_2$ was most successful. In cases where the molecule was rotationally restricted, substrates forming 7-membered rings were also successfully converted to the Conia-ene product. Protected amines and oxygen linkers were well tolerated by the reaction as well. In total, 7 substrates were synthesized that successfully converted to the Conia-ene product. A number of other substrates were synthesized that either could not open the cyclopropane ring or could not undergo Conia-ene cyclization.



Scheme 3.1. One-pot synthesis of bicyclic piperidines from propargylamine tethered DA cyclopropanes.

Based on the insights from the substrate scope, compounds highly similar to other successful substrates such as **3.1** and could be targeted (Figure 3.1) The Conia-ene product **3.2** is highly similar to both **2.27** and **2.85**.

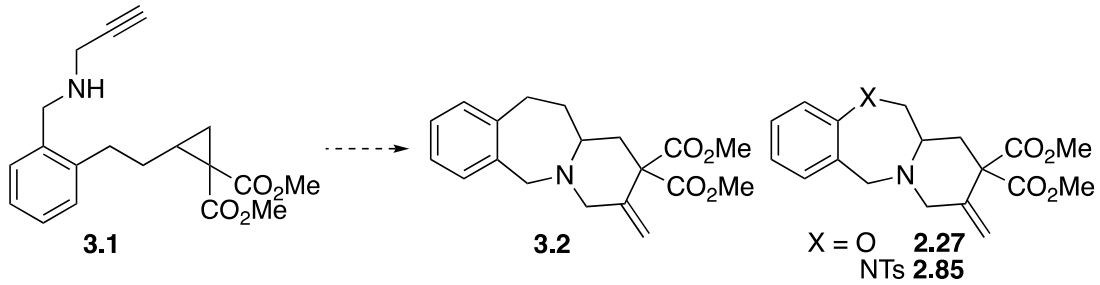


Figure 3.1. Structures of potential substrate **3.1** and Conia-ene product **3.2**, and highly similar substrates.

Other substrates unrelated to any successful substrate such as **3.3** could be targeted. Substrates based on **3.3** have all the attributes of a successful substrate and the Conia-ene product **3.4** contains a rotationally restricted 7-membered ring (Figure 3.2). Heteroatom linkers (X = NR, O) and alkyl linkers (X = CH_2) are likely to be tolerated and should also be relatively simple to synthesize for testing.

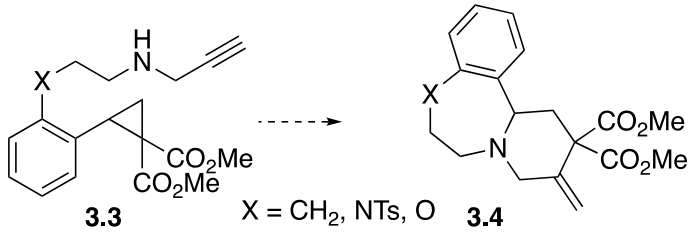


Figure 3.2. Structure of potential substrate **3.3** and Conia-ene product **3.4**.

It should also be possible to synthesize substituted versions of the successful substrates. For example, substrate **3.5** is structurally similar to **2.132** (Figure 3.3). The reaction conditions are likely to be tolerant of some functional groups easily introduced to aromatic rings such as halides, and nitro groups. **3.5** would convert under reaction conditions to **3.6**.

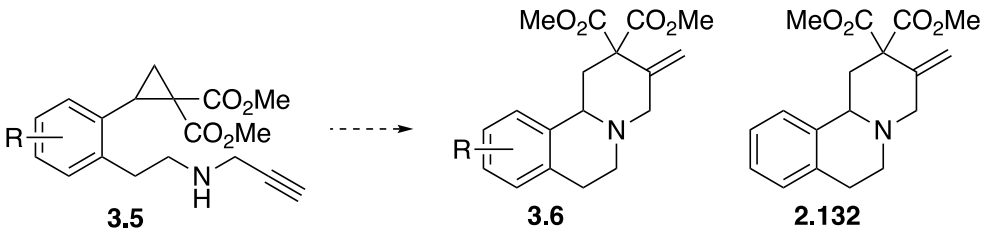


Figure 3.3. Structure of potential substrate **3.5**, Conia-ene product **3.6**, and analogous substrate **2.132**.

There also is potential to synthesize a substrate that has multiple diastereomers such as **2.145** (Figure 3.4). If the diastereomers could be resolved, the individual compounds could react at different rates in the tandem reaction. If the reactivities of the diastereomers is sufficiently different, it could provide some insight into the mechanism of the reaction.

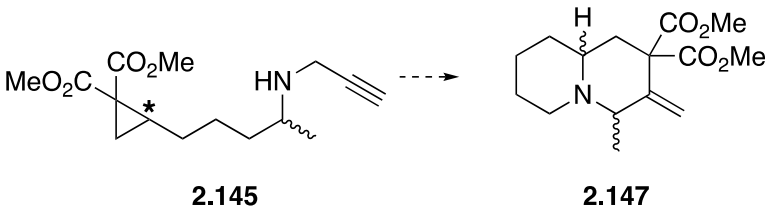


Figure 3.4. Diastereotopic substrate **2.145** and Conia-ene product.

Finally, given how these bicyclic piperidines can be mapped onto natural products, it may be possible to use one of these substrates in a total synthesis (Figure 3.5). Even if it was decided that no currently available substrate could be converted to a natural product, there is still the potential for synthesizing a new substrate and pursuing a total synthesis. There are a large number of natural products containing the bicyclic piperidine system furnished by the protocol.

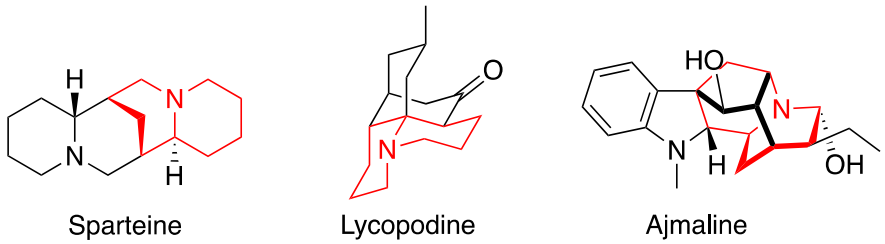


Figure 3.5. Selected bioactive natural products containing a bicyclic piperidine moiety. Bicyclic moiety highlighted in red.

Chapter 4 Experimental

General

All manipulations were performed under an atmosphere of argon unless otherwise indicated. Reaction flasks were oven-dried at 110ºC and cooled in a desiccator prior to use. Toluene, tetrahydrofuran (THF), diethyl ether, dichloromethane (DCM), *N*,*N*-dimethylformamide (DMF), dioxane, acetonitrile, and benzene were dried and deoxygenated by passing the nitrogen purged solvents through an activated alumina column. Dimethyl-2-(iodomethyl)-cyclopropane-1,1-dicarboxylate (**2.18**),[62] *N*-nosyl propargylamine,[63] and dimethyl diazomalonate [64] were synthesized according to literature procedures. All other reagents and solvents were purchased from commercial sources and used without further purification. Reaction progress was monitored by thin layer chromatography (TLC) (Merck, TLC silica gel 60 F254) visualized with UV light, and the plates were developed using acidic p-anisaldehyde, basic $KMnO_4$, or I_2. Flash chromatography was performed with silica gel purchased from Silicycle Chemical Division Inc. (230–400 mesh). Yields are reported after purification unless otherwise noted. High-resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact or electrospray ionization. NMR experiments were performed on 400 or 600 MHz Varian INOVA spectrometers or a 400 MHz Bruker spectrometer at 25ºC. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were referenced internally using residual solvent signals to TMS at $\delta = 0$ $CDCl_3$ (^{1}H, 7.26 ppm; $^{13}C\{^{1}H\}$, 77.2 ppm). Multiplicities of the signals are noted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

General Procedure A: Reductive amination of aldehydes.

To a solution of aldehyde (1.0 eq) in THF (0.1 M) was added AcOH (1.0 eq), and propargylamine (4.0 eq). The solution was cooled to 0ºC and STAB (1.5 eq) was added portion wise over 10 minutes. The flask was allowed to warm to room temperature and was stirred overnight. 3 M NaOH was added, and the mixture was extracted with EtOAc. The organic fraction was dried with $MgSO_4$ solvent was evaporated. The material was purified by column chromatography (EtOAc/hexanes).

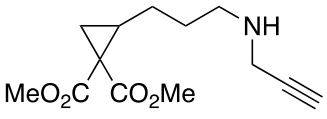
General Procedure B: Tandem cyclopropane opening Conia-ene reaction.

Amine cyclopropanediester (1.0 eq) was dissolved in toluene (0.05 M). To this solution was added $Sc(OTf)_3$ (0.1 eq). The reaction was stirred at room temperature until the TLC indicated completion of ring opening. $ZnBr_2$ (2.0 eq) was added and the solution was heated to 100ºC. The reaction was stirred at 100ºC until TLC indicated completion. Water was added and the mixture was extracted three times with EtOAc. The combined organic layers were washed two times with water and once with brine. The organic fraction was then dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude product. The crude material was purified by column chromatography using EtOAc/hexanes as the eluent.

General Procedure C: Mitsunobu Reaction of Ns Protected Amines.

According to a modification of a literature procedure:[53] Alcohol (1.0 eq), *N*-nosyl-propargylamine (1.0 eq), and PPh_3 (1.0 eq) were dissolved in DCM (0.1 M). To this solution was added DTBAD (1.0 eq) and the reaction was stirred overnight. 4 N HCl in dioxane was added and the mixture was stirred for 1 h at room temperature. Solvent was then evaporated. The residue was dissolved in DCM. The mixture was washed with 3 M HCl 3 times. The organic layer was dried with $MgSO_4$. The solids were filtered off and the solvent was evaporated affording a residue. This was purified by column chromatography (Hexanes:EtOAc).

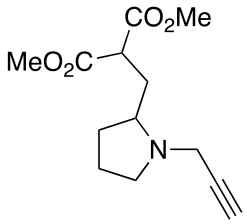
Synthesis and Characterization Data



Dimethyl 2-(3-(prop-2-yn-1-ylamino)propyl)cyclopropane-1,1-dicarboxylate

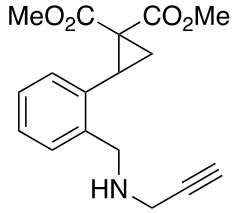
2.1[39] (1.09 g, 4.95 mmol) was treated with propargylamine (1.27 mL, 19.8 mmol), acetic acid (0.28 mL, 4.95 mmol), and STAB (1.57 g, 7.43 mmol) according to General Procedure B. The crude material was purified by column chromatography using EtOAc/hexanes (9:1) with 1% NH_3 in MeOH as the eluent. **2.2** was isolated as a yellow oil (880 mg, 70%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.76 (s, 3H), 3.72 (s, 3H), 3.41 (d, *J* = 2.4 Hz, 2H), 2.70 (td,

J = 7.3, 1.5 Hz, 2H), 2.20 (t, *J* = 2.4 Hz, 1H), 1.91 (dtd, *J* = 9.0, 7.9, 6.3 Hz, 1H), 1.69 – 1.48 (m, 3H), 1.46 – 1.33 (m, 2H) 1.26 (t, *J* = 7.1 Hz, 1H).



Dimethyl 2-((1-(prop-2-yn-1-yl)pyrrolidin-2-yl)methyl)malonate

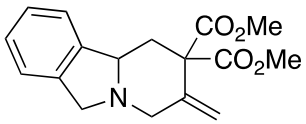
2.2 (238 mg, 0.94 mmol) was dissolved in DCM (18.8 mL). To this was added $Sc(OTf)_3$ (23 mg, 0.09 mmol). The reaction was stirred until ring opening was complete by TLC analysis. The reaction was filtered, and solvent was evaporated. The crude material was purified by column chromatography (40% EtOAc in Hexanes) affording **2.4** as a yellow oil (172 mg, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.73 (s, 3H), 3.71 (s, 3H), 3.54 – 3.27 (m, 3H), 2.95 (ddd, J = 9.8, 7.3, 2.9 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.57 (td, J = 9.2, 7.7 Hz, 1H), 2.24 – 2.09 (m, 2H), 2.04 – 1.87 (m, 2H), 1.82 – 1.63 (m, 2H), 1.46 (dddd, J = 12.0, 9.2, 6.8, 4.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.1, 170.1, 79.3, 72.5, 58.9, 52.9, 52.7, 52.6, 48.9, 40.7, 32.7, 30.3, 22.9.



Dimethyl 2-(2-((prop-2-yn-1-ylamino)methyl)phenyl)cyclopropane-1,1-dicarboxylate (2.8).

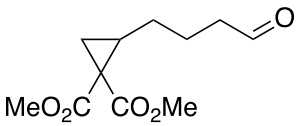
Aldehyde **2.6** [39] (1.2 g, 4.57 mmol) was dissolved in toluene (10 mL). To this solution was added propargyl amine (0.35 mL, 5.50 mmol) and $MgSO_4$ (1.5 g). This mixture was stirred overnight at room temperature. The $MgSO_4$ was then filtered off and the solvent was removed under vacuum to afford the crude material. A portion of this material (0.51 g, 1.7 mmol) was dissolved in MeOH (17 mL) and cooled to 0ºC. To this mixture was added $NaBH_4$ (97 mg, 2.55 mmol) in three portions over 4 min. This was stirred at 0ºC for 15 min. Solvent was evaporated and a residue was obtained. The residue was suspended in H_2O (20 mL). This mixture was extracted three times with DCM. The combined organic layers were washed with water and brine before they were dried with $MgSO_4$. Solids were filtered off and the solvent was removed under reduced pressure to afford the crude product. The crude material was purified by column chromatography using EtOAc/hexanes (1:1) as the eluent to give cyclopropyl amine **2.7** (410 mg, 80%). **^{1}H NMR**

(400 MHz, $CDCl_3$) δ = 7.39 – 7.32 (m, 1H), 7.24 – 7.15 (m, 2H), 7.08 – 7.03 (m, 1H), 3.96 (s, 2H), 3.81 (s, 3H), 3.44 (dd, *J* = 5.5, 2.4 Hz, 2H), 3.29 (s, 3H), 2.32 (dd, *J* = 8.3, 5.2 Hz, 1H), 1.75 (dd, *J* = 9.2, 5.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.3, 167.2, 140.0, 133.0, 129.3, 127.8, 127.5, 127.1, 82.3, 71.7, 53.0, 52.3, 49.9, 37.9, 37.0, 30.5, 18.6. **FTIR** (thin film, cm^{-1}) 3284, 2952, 1727, 1435, 1331, 1277, 1229, 1203, 1133. **HRMS** Calc'd for $C_{17}H_{19}NO_4$ = 301.1314, found 301.1316.



Dimethyl 3-methylene-3,4,6,10b-tetrahydropyrido[2,1-*a*]isoindole-2,2(1*H*)-dicarboxylate (2.10).

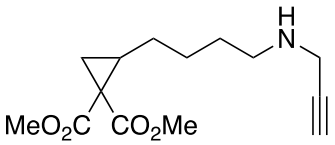
2.8 (151 mg, 0.5 mmol) was treated according to General Procedure A with $Sc(OTf)_3$ (24.6 mg, 0.05 mmol) and $ZnBr_2$ (226 mg, 1.0 mmol) The crude material was purified by column chromatography using EtOAc/hexanes (50%). (53 mg, 35%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.26 – 7.20 (m, 4H) (Overlapped with $CDCl_3$), 5.30 (s, 1H), 4.95 (s, 1H), 4.14 (d, J = 12.2 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 2.86 (dd, J = 13.4, 3.0 Hz, 1H), 2.29 (dd, J = 13.3, 11.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.55, 170.42, 143.07, 140.30, 140.14, 127.20, 126.86, 122.76, 121.20, 114.47, 66.01, 62.39, 61.17, 56.25, 55.97, 53.22, 52.90, 35.79, 31.74, 22.80, 15.43, 14.27. **FTIR** (thin film, cm^{-1}) 2952, 2889, 2777, 1732, 1651, 1461, 1435, 1245, 1173, 1085, 1066, 1034, 909, 748. **HRMS** Calc'd for $C_{17}H_{19}NO_4$ = 301.1314, found 301.1316.



Dimethyl 2-(4-oxobutyl)cyclopropane-1,1-dicarboxylate (2.11).

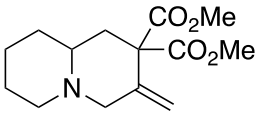
2.11 has been made before.[65] DMSO (0.42 mL, 5.90 mmol) was dissolved in DCM (25 mL) and cooled to –78ºC. To this was added oxalyl chloride (0.29 mL, 3.37 mmol) dropwise. Dimethyl 2-(4-hydroxybutyl)cyclopropane-1,1-dicarboxylate[66] (647 mg, 2.8 mmol) was dissolved in DCM (2.3 mL) and added dropwise. The reaction mixture was stirred at –78ºC for 30 min. NEt_3 (2.0 mL, 14.1 mmol) was added slowly and the reaction was stirred for 45 min. The flask was allowed to slowly warm to room temperature and was stirred for 3 h. The pH of the reaction was brought to 7 with the addition of 1 M HCl.

The mixture was then extracted 3 times with DCM. The combined organic layers were washed with water and brine. The organic layers were dried with $MgSO_4$. Solids were filtered off and solvent was evaporated affording **2.11** as a yellow oil (633 mg, 99%). Compound was used without further purification. Spectral data in agreement with literature.



Dimethyl 2-(4-(prop-2-yn-1-ylamino)butyl)cyclopropane-1,1-dicarboxylate (2.12).

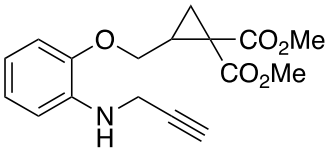
2.11 (1.04 g, 4.6 mmol) was treated with propargylamine (1.16 mL, 18.2 mmol), acetic acid (0.26 mL, 4.6 mmol) and STAB (1.45 g, 6.84 mmol) according to General Procedure B. The crude material was purified by column chromatography using EtOAc as the eluent. **2.12** was obtained as a yellow oil (0.79 g, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.73 (s, 3H), 3.69 (s, 3H), 3.39 (d, *J* = 2.4 Hz, 2H), 2.82 – 2.55 (m, 2H), 2.18 (t, *J* = 2.4 Hz, 1H), 1.87 (dtd, *J* = 8.9, 7.8, 5.7 Hz, 1H), 1.50 – 1.40 (m, 6H), 1.41 – 1.28 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.93, 168.76, 82.33, 71.32, 52.65, 52.55, 48.50, 38.22, 33.95, 29.49, 28.65, 28.63, 26.61, 21.40. **FTIR** (thin film, cm^{-1}) 3282, 2935, 2858, 1728, 1436, 1276, 1211, 1128. **HRMS** Calc'd for $C_{14}H_{21}NO_4$ = 267.1471, found 267.1471.



Dimethyl 3-methyleneoctahydro-2H-quinolizine-2,2-dicarboxylate (2.14).

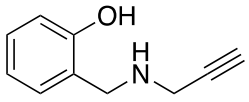
2.12 (134 mg, 0.5 mmol) was treated with $Sc(OTf)_3$ (25 mg, 0.05 mmol) and $ZnBr_2$ (225 mg, 1.0 mmol) according to General Procedure C. The crude material was purified by column chromatography using EtOAc/Hexanes (3:2). **2.14** was obtained as a yellow oil (124 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.18 (d, J = 1.5 Hz, 1H), 4.77 (s, 1H), 3.78 (d, J = 7.9 Hz, 6H), 3.26 (d, J = 12.6 Hz, 1H), 2.84 (t, J = 12.8 Hz, 2H), 2.30 (dd, J = 13.6, 2.3 Hz, 1H), 2.15 – 1.91 (m, 2H), 1.75 (t, J = 11.4 Hz, 2H), 1.69 – 1.56 (m, 2H), 1.40 – 1.18 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl^3$) δ = 170.5, 170.3, 140.6, 113.7, 61.2, 61.1, 58.7, 55.8, 52.9, 52.6, 39.4, 32.5, 29.7, 25.4, 24.2. **FTIR** (thin film, cm^{-1}) 2932, 2854, 2789,

1733, 1654, 1436, 1259, 1240, 1199, 1132, 1092, 1050, 915. **HRMS** Calc'd for $C_{14}H_{21}NO_4$ = 267.1471, found 267.1462.



Dimethyl 2-((2-(prop-2-yn-1-ylamino)phenoxy)methyl)cyclopropane-1,1-dicarboxylate (2.19).

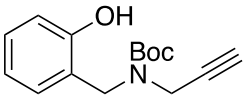
This procedure is based on a literature report.[59] *N*-propargyl-*o*-aminophenol **2.17** (147 mg, 1.0 mmol) was dissolved in DMF. To this was added K_2CO_3 (276 mg, 2.0 mmol). **2.18** (298 mg, 1.0 mmol) was added in one portion and the mixture was stirred for 24 h at room temperature. Water was added and the mixture was extracted with Et_2O 3 times. The combined organic layers were washed with water and dried with brine and $MgSO_4$. Solids were filtered off and solvent was evaporated. The crude material was purified by column chromatography (EtOAc in Hexanes) affording **2.19** as a yellow oil (180 mg, 57 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.06 – 6.57 (m, 4H), 4.23 (dd, J = 10.3, 5.0 Hz, 1H), 3.99 (d, J = 2.4 Hz, 2H), 3.94 (dd, J = 10.4, 7.2 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 2.44 (dtd, J = 9.3, 7.4, 5.0 Hz, 1H), 2.19 (t, J = 2.4 Hz, 1H), 1.73 (dd, J = 7.6, 4.9 Hz, 1H), 1.54 (dd, J = 9.3, 4.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.3, 168.7, 146.1, 136.8, 122.0, 118.0, 111.5, 111.3, 81.1, 71.2, 66.1, 53.1, 53.0, 33.4, 33.0, 26.9, 18.8. **FTIR** (thin film, cm^{-1}) 3413, 3284, 3009, 2953, 2923, 2851, 1722, 1603, 1579, 1511, 1436, 1333, 1286, 1245, 1208, 1127.



2-((prop-2-yn-1-ylamino)methyl)phenol (2.22).

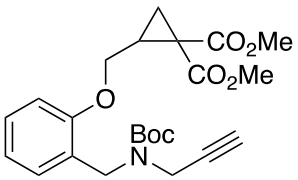
Salicylaldehyde (2.61 mL, 25 mmol) was dissolved in DCM (47 mL). To this solution was added propargylamine (1.9 mL, 30 mmol) and $MgSO_4$ (3 g). The suspension was stirred overnight at room temperature. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure to afford the crude imine. The imine was then dissolved in MeOH (250 mL) and cooled to 0ºC. To this solution was added $NaBH_4$ (1.99 g, 52.5 mmol) in three portions over 5 min. This mixture was then stirred for 3 h at 0ºC. After

stirring at 0ºC, the solvent was evaporated. Water was added to the residue and the mixture was diluted with DCM. The aqueous layer was extracted with DCM two additional times. The combined organic layers were dried with anhydrous $MgSO_4$ and solvent was evaporated affording **2.22** as a white solid (2.94 g, 73%). The crude material was used without further purification. **MP** = 54–57ºC. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.18 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 7.03 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.79 (td, *J* = 7.4, 1.2 Hz, 1H), 4.10 (s, 2H), 3.47 (d, *J* = 2.5 Hz, 2H), 2.30 (t, *J* = 2.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 158.11, 129.18, 129.01, 121.73, 119.46, 116.60, 80.29, 72.92, 50.95, 36.69. **HRMS** Calc'd for $C_{10}H_{11}NO$ 162.0919, found 162.0916.



***Tert*-butyl (2-hydroxybenzyl)(prop-2-yn-1-yl)carbamate (2.23).**

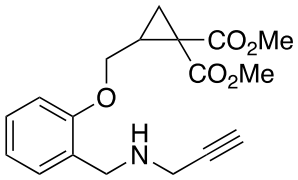
Amine **2.22** (2.94 g, 18.2 mmol) was dissolved in DCM (36.4 mL) and was cooled to 0ºC. To this solution was added Boc_2O dropwise over 3 min. The reaction was warmed to room temperature and stirred for 1 hour. Solvent was evaporated under reduced pressure. The residue was purified by column chromatography (12% EtOAc in Hexanes) affording **2.23** as a colourless oil (4.76 g, 99 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.92 (s, 1H), 7.19 (td, J = 7.8, 1.8 Hz, 1H), 7.11 (dd, J = 7.5, 1.7 Hz, 1H), 6.89 (dd, J = 8.2, 1.2 Hz, 1H), 6.78 (td, J = 7.4, 1.2 Hz, 1H), 4.42 (s, 2H), 3.94 (d, J = 2.5 Hz, 2H), 2.24 (t, J = 2.5 Hz, 1H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 156.4, 131.5, 130.3, 122.3, 122.0, 119.5, 117.6, 82.7, 78.7, 72.4, 46.1, 35.7, 28.5, 28.4, 27.8. **FTIR** (thin film, cm^{-1}) 3290, 2978, 2934, 1654, 1486, 1456, 1441, 1418, 1367, 1251, 1159, 1124, 871, 756. **HRMS** Calc'd for $C_{15}H_{19}NO_3$ = 261.1365, found 261.1359.



Dimethyl 2-((2-(((*tert*-butoxycarbonyl)(prop-2-yn-1-yl)amino)methyl)phenoxy)methyl)cyclopropane-1,1-dicarboxylate (2.24).

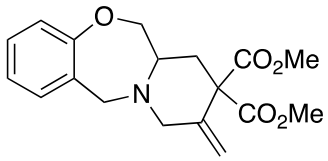
2.23 (979 mg, 3.7 mmol) was dissolved in DMF (18.5 mL). To this solution was added **2.18** (1.103g, 3.7 mmol) and K_2CO_3 (1.04 g, 7.5 mmol). The suspension was stirred at room temperature overnight. The reaction was quenched with the addition of water and the mixture was extracted 3 times with Et_2O. The combined organic

layers were dried with $MgSO_4$ and solvent was evaporated under reduced pressure affording a colourless oil. Crude material was then purified by column chromatography (17% EtOAc in Hexanes) affording **2.24** as a pale-yellow oil as a mixture of rotamers (860 mg, 54%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.23 – 7.10 (m, 1H), 6.92 (td, J = 7.5, 1.1 Hz, 1H), 6.77 (dd, J = 8.3, 1.1 Hz, 1H), 4.52 (s, 2H), 4.20 – 4.03 (m, 2H), 3.95 (dd, J = 10.4, 7.6 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 2.46 (dtd, J = 9.3, 7.6, 5.8 Hz, 1H), 1.69 (dd, J = 7.5, 4.9 Hz, 1H), 1.59 – 1.53 (m, 1H), 1.53 – 1.38 (m, 9H). **FTIR** (thin film, cm^{-1}) 3286, 2977, 2954, 2930, 1728, 1694, 1455, 1437, 1408, 1286, 1240, 1213, 1163, 1128. **HRMS** Calc'd for $C_{23}H_{29}NO_7$ = 431.1944, found 431.1926.



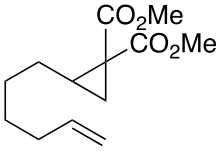
Dimethyl 2-((2-((prop-2-yn-1-ylamino)methyl)phenoxy)methyl)cyclopropane-1,1-dicarboxylate (2.25).

2.24 (860 mg, 2.0 mmol) was dissolved in DCM (10 mL). To this was added TFA (10 mL). The mixture was stirred for 12 h at room temperature. Solvent was evaporated under vacuum to afford a residue. The residue was dissolved in EtOAc and basified to pH ≥9 with 2M NaOH. EtOAc was separated from the water and dried with $MgSO_4$. Solvent was evaporated under reduced pressure to afford **2.25** as a brown oil (320 mg, 48%). The compound was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.32 – 7.18 (m, 2H), 6.93 (td, J = 7.4, 1.1 Hz, 1H), 6.78 (dd, J = 8.3, 1.1 Hz, 1H), 4.27 (dd, J = 10.5, 5.2 Hz, 1H), 4.03 – 3.85 (m, 2H), 3.82 (dd, J = 10.5, 8.4 Hz, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.50 (t, J = 2.4 Hz, 2H), 2.56 – 2.37 (m, 1H), 2.27 (t, J = 2.5 Hz, 1H), 2.17 (s, 2H), 1.68 (dd, J = 7.5, 5.0 Hz, 1H), 1.58 (dd, J = 9.3, 5.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.15, 168.46, 156.54, 130.85, 129.08, 121.27, 111.22, 72.41, 66.10, 53.08, 53.05, 47.85, 37.47, 33.20, 31.08, 26.94, 18.85. **FTIR** (thin film, cm^{-1}) 3286, 2953, 1725, 1689, 1603, 1494, 1454, 1437, 1289, 1241, 1213, 1129. **HRMS** Calc'd for $C_{18}H_{21}NO_5$ = 331.1412, found 331.1426.



Dimethyl 9-methylene-6a,7,9,10-tetrahydro-12*H*-benzo[f]pyrido[2,1-*c*][1,4]oxazepine-8,8(6*H*)-dicarboxylate (2.27).

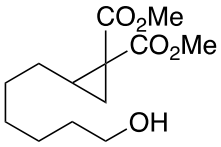
2.25 was treated according to a modification of General Procedure A. **2.24** (166 mg, 0.5 mmol) was dissolved in toluene (10 mL) and $Sc(OTf)_3$ 0.2 eq (49 mg, 0.1 mmol) was added. The reaction was stirred at reflux in PhMe until ring opening was complete by TLC analysis. $ZnBr_2$ (225 mg, 1.0 mmol) was added to the ring opened product and the remainder of the procedure was performed per General Procedure A. (40% EtOAc in Hexanes). **2.27** was obtained as a colourless oil (108 mg, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.22 – 7.10 (m, 2H), 7.05 – 6.91 (m, 2H), 5.22 (d, *J* = 1.4 Hz, 1H), 4.82 (d, *J* = 0.8 Hz, 1H), 4.20 (dd, *J* = 12.7, 2.5 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.77 – 3.65 (m, 2H), 3.59 (dd, *J* = 12.6, 9.0 Hz, 1H), 3.50 (dd, *J* = 14.9, 13.2 Hz, 2H), 3.28 – 3.09 (m, 1H), 2.63 (ddt, *J* = 11.6, 8.9, 2.6 Hz, 1H), 2.27 (dd, *J* = 13.6, 2.7 Hz, 1H), 2.13 – 1.92 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.2, 170.1, 160.2, 140.3, 131.2, 130.7, 128.9, 123.8, 120.2, 114.3, 62.1, 61.0, 60.6, 60.3, 53.3, 52.9, 34.4. **FTIR** (thin film, cm^{-1}) 2951, 2804, 2769, 1730, 1492, 1455, 1436, 1269, 1238, 1195, 1117, 1096, 1073, 1055, 1014, 914, 765, 729. **HRMS** Calc'd for $C_{18}H_{21}NO_5$ = 331.1412, found 331.1428.



Dimethyl 2-(hex-5-en-1-yl)cyclopropane-1,1-dicarboxylate (2.28).

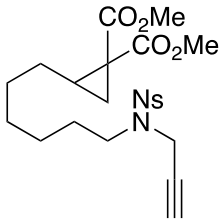
1,7-octadiene (2.95 mL, 20 mmol) and $Rh_2(esp)_2$ (19 mg, 2.5 μmol) were dissolved in DCM (200 mL). A solution of dimethyl diazomalonate (1.58 g, 10 mmol) in DCM (14.5 mL) was added in portions over 1 h. The reaction was stirred overnight. Solvent was evaporated and the crude material was purified by column chromatography (8% EtOAc in Hexanes) affording **2.28** as a colourless oil (1.66 g, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (ddt, J = 16.9, 2.0, 1.5 Hz, 1H), 4.94 (ddt, J = 10.2, 2.3, 1.2 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.03 (tdd, J = 6.8, 5.4, 1.4 Hz, 2H), 1.96 – 1.78 (m, 1H), 1.50 – 1.30 (m, 8H), 1.23 – 1.11 (m, 1H). **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 171.1, 168.9, 138.9, 114.6, 52.7, 52.6, 34.1, 33.7, 28.9, 28.7, 28.6, 28.4, 21.5. **FTIR** (thin film, cm^{-1}) 3076, 2930, 2858, 1726, 1436, 1329, 1210, 1130.



Dimethyl 2-(6-hydroxyhexyl)cyclopropane-1,1-dicarboxylate (2.29).

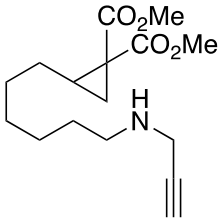
This procedure is based on a literature protocol.[59] **2.28** (721 mg, 3.0 mmol) in THF (3.4 mL) was added dropwise to the solution. The mixture was stirred at 0ºC for 2.5 h. The reaction was quenched with the addition of 1:1 MeOH:THF (1.65 mL). A buffer solution of KH_2PO_4 (0.825 g, 6.06 mmol) and NaOH (139 mg, 3.48 mmol) in H_2O (6.6 mL). 30% H_2O_2 (1.83 mL) was added and the reaction was stirred overnight. Water was then added, and the mixture was extracted with EtOAc 3 times. The organic layers were washed with saturated aqueous Na_2SO_3 and brine. The organic layer was then dried with $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (40% EtOAc in Hexanes) affording **2.29** as a colourless oil (577 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.75 (s, 3H), 3.72 (s, 3H), 3.63 (t, J = 6.6 Hz, 2H), 2.04 – 1.74 (m, 1H), 1.67 – 1.51 (m, 2H), 1.49 – 1.26 (m, 12H), 1.25 – 1.10 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 168.9, 63.1, 52.7, 52.6, 34.0, 32.8, 29.2, 28.9, 28.9, 28.7, 25.7, 21.5. **FTIR** (thin film, cm^{-1}) 3424, 2931, 2858, 1722, 1437, 1284, 1210, 1128.



Dimethyl 2-(6-((4-nitro-N-(prop-2-yn-1-yl)phenyl)sulfonamido)hexyl)cyclopropane-1,1-dicarboxylate (2.30).

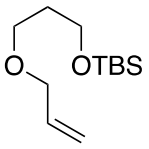
Following general procedure C, **2.29** (577 mg, 2.23 mmol), *N*-nosyl-propargylamine (536 mg, 2.23 mmol), and PPh_3 (585 mg, 2.23 mmol) were dissolved in DCM (22 mL). DTBAD (514 mg, 2.23 mmol) was then added. The reaction was stirred at room temperature overnight. (50% EtOAc in Hexanes). **2.30** was obtained as a viscous yellow oil (846 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.56 – 7.93 (m, 1H), 7.93 – 7.53 (m, 3H), 4.19 (d, J = 2.5 Hz, 2H), 3.75 (s, 4H), 3.72 (s, 4H), 3.41 – 3.36 (m, 2H), 2.16 (t, J = 2.4 Hz, 1H), 1.86 (ddd, J = 9.0, 7.9, 6.2 Hz, 1H), 1.63 – 1.56 (m, 3H), 1.51 – 1.21

(m, 11H), 1.23 – 1.08 (m, 1H**).** **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.1, 168.9, 148.7, 133.7, 133.0, 131.7, 131.0, 124.3, 73.9, 52.7, 52.6, 46.9, 36.3, 34.0, 28.8, 28.8, 28.7, 27.4, 26.4, 21.5. **FTIR** (thin film, cm^{-1}) 3286, 2934, 2860, 1723, 1545, 1438, 1371, 1358, 1340, 1286, 1213, 1165, 1129.



Dimethyl 2-(6-(prop-2-yn-1-ylamino)hexyl)cyclopropane-1,1-dicarboxylate (2.31).

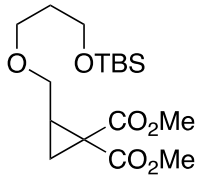
2.30 (480 mg, 1.0 mmol) was dissolved in DMF (3.0 mL). To this was added K_2CO_3 (414 mg, 3.0 mmol). PhSH (120 µL, 1.2 mmol) was added dropwise and the reaction was stirred at room temperature until the TLC indicated completion. Water was added and the mixture was extracted with Et_2O 3 times. The organic layers were washed with water and brine. The solution was then dried with $MgSO_4$, solids were filtered off and solvent was evaporated. The crude material was purified by column chromatography (EtOAc) affording **2.31** as a yellow oil (205 mg, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.75 (s, 3H), 3.72 (s, 3H), 3.42 (d, J = 2.4 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.20 (t, J = 2.4 Hz, 1H), 1.88 (ddd, J = 8.9, 7.8, 6.1 Hz, 1H), 1.57 – 1.08 (m, 13H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.1, 168.9, 82.5, 71.3, 52.7, 52.6, 48.8, 38.3, 34.0, 29.9, 29.3, 28.9, 28.9, 28.8, 27.3, 21.6. **FTIR** (thin film, cm^{-1}) 3287, 2928, 2856, 1723, 1437, 1330, 1282, 1211, 1129.



(3-(allyloxy)propoxy)(*tert*-butyl)dimethylsilane (2.35).

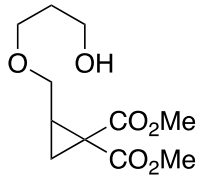
According to a literature procedure,[67] NaH (60% in mineral oil) (252 mg, 6.30 mmol) was suspended in THF (9.0 mL) and cooled to 0ºC. To this was added monoprotected diol **2.34**[68] (1.0 g, 5.25 mmol) dissolved in THF (4.5 mL). This solution was stirred at 0ºC for 20 min. Allyl bromide (0.59 mL, 6.83 mmol) was added dropwise. The solution was warmed to room temperature and stirred overnight. Saturated NH_4Cl was added and the mixture was extracted with Et_2O. The organic layers were dried with bring and $MgSO_4$. Solids were filtered off and solvent was evaporated. The crude material was purified by column chromatography (10% EtOAc in Hexanes) affording **2.35** as a

colourless oil (874 mg, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.92 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.27 (dq, J = 17.2, 1.7 Hz, 1H), 5.16 (dq, J = 10.4, 1.4 Hz, 1H), 3.96 (dt, J = 5.6, 1.4 Hz, 2H), 3.71 (t, J = 6.2 Hz, 2H), 3.52 (t, J = 6.3 Hz, 2H), 1.79 (p, J = 6.3 Hz, 2H), 0.89 (s, 10H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 135.2, 116.8, 72.0, 67.1, 60.1, 33.1, 26.1, 18.5, -5.2. **FTIR** (thin film, cm^{-1}) 2954, 2928, 2857, 1472, 1254, 1092, 1005, 833, 774.



Dimethyl 2-((3-((*tert*-butyldimethylsilyl)oxy)propoxy)methyl)cyclopropane-1,1-dicarboxylate (2.36).

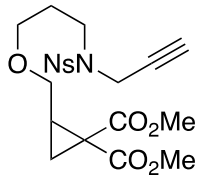
Alkene **2.35** (847 mg, 3.80 mmol) and $Rh_2(esp)_2$ (7.2 mg, 9.5 µmol) were dissolved in DCM (38 mL). A solution of dimethyl diazomalonate in DCM (6.1 mL) was added in portions over 1 h. The reaction was stirred overnight. Solvent was evaporated and the crude material was purified by column chromatography (30% EtOAc in Hexanes) affording **2.36** as a colourless oil (1.01 g, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.75 (s, 3H), 3.73 (s, 3H), 3.66 (t, J = 6.2 Hz, 2H), 3.47 (t, J = 6.3 Hz, 4H), 2.20 (ddt, J = 9.2, 7.5, 6.2 Hz, 1H), 1.73 (p, J = 6.3 Hz, 2H), 1.56 (dd, J = 7.6, 4.7 Hz, 1H), 1.45 (dd, J = 9.2, 4.7 Hz, 1H), 0.88 (s, 9H), 0.04 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.6, 168.4, 68.5, 67.8, 60.0, 52.8, 52.7, 33.0, 32.7, 27.5, 26.1, 19.1, 18.5, -5.2. **FTIR** (thin film, cm^{-1}) 2953, 1723, 1437, 1320, 1287, 1211, 1129.



Dimethyl 2-((3-hydroxypropoxy)methyl)cyclopropane-1,1-dicarboxylate (2.37).

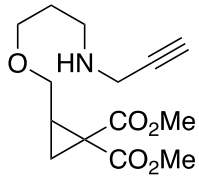
Protected alcohol **2.36** (1.01 g, 2.80 mmol) was dissolved in THF (9.3 mL). A 1.0 M solution of TBAF in THF (3.92 mL, 3.92 mmol) was added dropwise. The reaction was stirred at room temperature until TLC indicated completion. Water was added and the mixture was extracted 3 times with DCM. The combined organic layers were washed with water and brine. The solution was dried with $MgSO_4$ and solids were filtered off. Solvent was evaporated and the crude material was purified by column

chromatography (50% EtOAc in Hexanes) affording **2.37** as a colourless oil (610 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.86 – 3.70 (m, 8H), 3.66 – 3.48 (m, 3H), 3.41 (dd, J = 10.7, 7.5 Hz, 1H), 2.39 – 2.12 (m, 2H), 1.87 – 1.68 (m, 2H), 1.55 (dd, J = 7.6, 4.8 Hz, 1H), 1.45 (dd, J = 9.3, 4.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.4, 168.5, 70.0, 68.9, 61.7, 52.9, 52.8, 32.9, 32.2, 27.3, 19.0. **FTIR** (thin film, cm^{-1}) 3457, 2953, 2873, 1723, 1437, 1332, 1211, 1129.



Dimethyl 2-((3-((4-nitro-N-(prop-2-yn-1-yl)phenyl)sulfonamido)propoxy)methyl)cyclopropane-1,1-dicarboxylate (2.38).

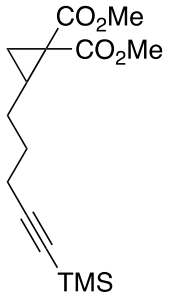
Following general procedure C, **2.37** (610 mg, 2.47 mmol), *N*-nosyl-propargylamine (593 mg, 2.47 mmol), and PPh_3 (648 mg, 2.47 mmol) were dissolved in DCM (24.7 mL). DTBAD (569 mg, 2.47 mmol) was then added. The reaction was stirred at room temperature overnight. (50% EtOAc in Hexanes). **2.38** was obtained as a viscous yellow oil (880 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.13 – 7.92 (m, 1H), 7.74 – 7.67 (m, 2H), 7.67 – 7.58 (m, 1H), 4.21 (d, J = 2.5 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.53 – 3.22 (m, 6H), 2.25 – 2.05 (m, 2H), 1.94 – 1.74 (m, 2H), 1.61 – 1.51 (m, 1H), 1.44 (dd, J = 9.2, 4.7 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ = 170.5, 168.4, 148.5, 133.8, 132.9, 131.8, 131.2, 124.3, 74.0, 68.5, 67.7, 52.9, 52.8, 44.5, 36.8, 32.8, 28.0, 27.3, 19.0. **FTIR** (thin film, cm^{-1}) 3285, 2954, 2876, 1726, 1545, 1438, 1340, 1290, 1196, 1166, 1131.



Dimethyl 2-((3-(prop-2-yn-1-ylamino)propoxy)methyl)cyclopropane-1,1-dicarboxylate (2.39).

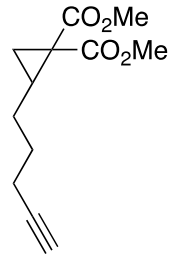
Ns amine **2.38** (468 mg, 1.0 mmol) was dissolved in DMF (3.0 mL). To this was added K_2CO_3 (414 mg, 3.0 mmol). PhSH (120 µL, 1.2 mmol) was added dropwise and the reaction was stirred at room temperature until the TLC indicated completion. Water was added and the mixture was extracted with Et_2O 3 times. The organic layers were washed with water and brine. The solution was then dried with $MgSO_4$, solids were filtered off and solvent was evaporated. The crude material was purified by column

chromatography (EtOAc) affording **2.39** as a yellow oil (144 mg, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.76 (s, 3H), 3.73 (s, 3H), 3.54 – 3.38 (m, 6H), 2.75 (t, J = 6.9 Hz, 2H), 2.27 – 2.10 (m, 2H), 1.78 – 1.65 (m, 2H), 1.56 (dd, J = 7.6, 4.7 Hz, 1H), 1.44 (dd, J = 9.2, 4.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.5, 168.4, 82.4, 71.3, 69.5, 68.5, 52.9, 52.8, 46.1, 38.3, 32.8, 29.9, 27.4, 19.1. **FTIR** (thin film, cm^{-1}) 3279, 2952, 2865, 1725, 1437, 1332, 1288, 1212, 1130.



Dimethyl 2-(5-(trimethylsilyl)pent-4-yn-1-yl)cyclopropane-1,1-dicarboxylate (2.47).

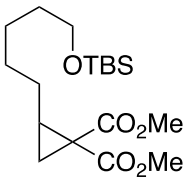
Enyne **2.46**[55] and $Rh_2(esp)_2$ (45 mg, 0.06 mmol) were dissolved in DCM (120 mL). A solution of dimethyl diazomalonate (2.07 g, 13.1 mmol) in DCM (19 mL) was added in portions over 1 h. The reaction was stirred overnight at room temperature. Solvent was evaporated and the crude material was purified by column chromatography (10% EtOAc in Hexanes) affording **2.47** as a colourless oil (1.93 g, 54%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.76 (s, 3H), 3.72 (s, 3H), 2.25 (t, J = 6.9 Hz, 2H), 1.95 – 1.81 (m, 1H), 1.74 – 1.48 (m, 3H), 1.41 (dd, J = 8.3, 3.2 Hz, 2H), 1.35 – 1.09 (m, 1H), 0.14 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.0, 168.7, 106.8, 85.2, 53.6, 52.8, 52.6, 34.0, 28.2, 27.9, 21.4, 19.6, 0.3. **FTIR** (thin film, cm^{-1}) 2954, 2902, 2865, 2173, 1726, 1437, 1328, 1275, 1249, 1210, 1132, 840, 760.



Dimethyl 2-(pent-4-yn-1-yl)cyclopropane-1,1-dicarboxylate 2.48).

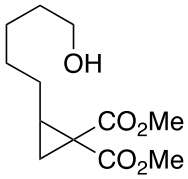
TMS protected alkyne **2.47** (1.00 g, 3.4 mmol) was dissolved in MeOH (7 mL). To this was added K_2CO_3 (470 mg, 3.4 mmol) and the reaction was stirred at room temperature until deprotection was complete. Water was added and the mixture was extracted with DCM 3 times. The combined organic layers were dried with $MgSO_4$ and solids were filtered. Solvent was evaporated affording pure **2.47**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.79 (s, 3H), 3.75 (s, 3H), 2.24 (tdd, J = 6.9, 2.7, 0.9 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.74 – 1.65 (m, 2H), 1.63 – 1.52 (m, 1H), 1.48 – 1.28 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.0, 168.7, 84.0, 68.9, 52.8,

52.7, 34.0, 28.1, 27.8, 27.7, 21.3, 18.2. **FTIR** (thin film, cm^{-1}) 3292, 3005, 2953, 2866, 1726, 1437, 1331, 1290, 1275, 1213, 1135.



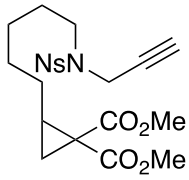
Dimethyl 2-(5-((*tert*-butyldimethylsilyl)oxy)pentyl)cyclopropane-1,1-dicarboxylate (2.44).

Alkene **2.43** (779 mg, 3.41 mmol) and $Rh_2(esp)_2$ (6 mg, 0.017 mmol) were dissolved in DCM (34 mL). A solution of dimethyl diazomalonate (593 mg, 3.75 mmol) in DCM (5.4 mL) was added in portions over 1 h. The reaction was stirred overnight at room temperature. Solvent was evaporated and the crude material was purified by column chromatography (8% EtOAc in Hexanes) affording **2.44** as a clear colourless oil (1.02 g, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.75 (s, 3H), 3.72 (s, 3H), 3.59 (t, J = 6.5 Hz, 2H), 2.11 – 1.74 (m, 1H), 1.62 – 1.25 (m, 9H), 1.23 – 1.09 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.1, 168.9, 63.2, 52.7, 52.6, 34.0, 32.9, 28.9, 28.9, 28.8, 26.1, 25.6, 21.6, 18.5, -5.1. **FTIR** (thin film, cm^{-1}) 2952, 2931, 2988, 2857, 1727, 1436, 1210, 1128, 1095, 833, 774. **HRMS** Calc'd for $C_{18}H_{34}O_5Si$ = 358.2176 found 358.2177.



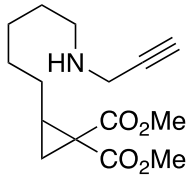
Dimethyl 2-(5-hydroxypentyl)cyclopropane-1,1-dicarboxylate (2.45).

Protected alcohol **2.44** (359 mg, 2.85 mmol) was dissolved in THF (9.5 mL). To this was added 1 M TBAF in THF (3.9 mL, 3.9 mmol) dropwise. This solution was stirred until TLC indicated completion. Water was added and the mixture was extracted with DCM 3 times. The organic layers were dried with $MgSO_4$ and solids were filtered. Solvent was evaporated and the crude material was purified by column chromatography (35% EtOAc in hexanes) affording **2.45** as a colourless oil (619 mg, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.75 (s, 3H), 3.72 (s, 3H), 3.63 (t, J = 6.5 Hz, 2H), 2.01 – 1.82 (m, 1H), 1.71 – 1.51 (m, 2H), 1.50 – 1.32 (m, 7H), 1.28 – 1.10 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.1, 168.9, 63.0, 52.7, 52.6, 34.0, 32.7, 28.8, 28.8, 28.7, 25.5, 21.5. **FTIR** (thin film, cm^{-1}) 3380, 2980, 2934, 2861, 1723, 1437, 1332, 1284, 1212, 1130.



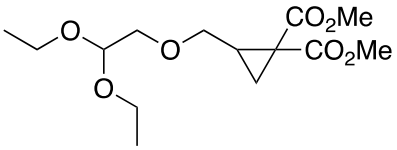
Dimethyl 2-(5-((4-nitro-N-(prop-2-yn-1-yl)phenyl)sulfonamido)pentyl)cyclopropane-1,1-dicarboxylate (2.46).

Following general procedure C, alcohol **2.45** (244 mg, 1.0 mmol), *N*-nosyl-propargylamine (240 mg, 1.0 mmol), and PPh_3 (262 mg, 1.0 mmol) were dissolved in DCM (10 mL). DTBAD (230 mg, 1.0 mmol) was then added. The reaction was stirred at room temperature overnight. (40% EtOAc in Hexanes). **2.46** was obtained as a viscous yellow oil (287 mg, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.37 – 7.95 (m, 1H), 7.95 – 7.58 (m, 3H), 4.19 (d, J = 2.5 Hz, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.55 – 3.29 (m, 2H), 2.16 (t, J = 2.5 Hz, 1H), 1.94 – 1.74 (m, 1H), 1.59 (q, J = 7.5 Hz, 3H), 1.48 – 1.23 (m, 6H), 1.22 – 1.09 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.0, 168.8, 133.8, 133.0, 131.7, 131.0, 124.3, 77.0, 73.9, 52.8, 52.7, 46.9, 36.4, 28.7, 28.6, 28.5, 27.4, 26.2, 21.5. **FTIR** (thin film, cm^{-1}) 3283, 2936, 2862, 1723, 1544, 1438, 1372, 1358, 1340, 1287, 1213, 1165, 1130.



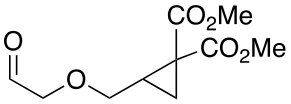
Dimethyl 2-(5-(prop-2-yn-1-ylamino)pentyl)cyclopropane-1,1-dicarboxylate (2.47).

Ns amine **2.46** (287 mg, 0.62 mmol) was dissolved in DMF (1.9 mL). To this was added K_2CO_3 (255 mg, 1.86 mmol). PhSH (76 µL, 0.74 mmol) was added dropwise and the reaction was stirred at room temperature until the TLC indicated completion. Water was added and the mixture was extracted with Et_2O 3 times. The organic layers were washed with water and brine. The solution was then dried with $MgSO_4$, solids were filtered off and solvent was evaporated. The crude material was purified by column chromatography (80% EtOAc in Hexanes) affording **2.46** as a yellow oil (108 mg, 62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.75 (s, 3H), 3.72 (s, 3H), 3.42 (d, J = 2.4 Hz, 2H), 2.67 (t, J = 7.1 Hz, 2H), 2.20 (t, J = 2.4 Hz, 1H), 2.02 – 1.79 (m, 1H), 1.65 – 1.27 (m, 9H), 1.26 – 1.09 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.1, 168.9, 82.5, 71.3, 52.7, 52.6, 48.7, 38.3, 34.0, 29.9, 28.9, 28.8, 28.8, 27.1, 21.5. **FTIR** (thin film, cm^{-1}) 3284, 2930, 2857, 1725, 1437, 1330, 1285, 1212, 1130.



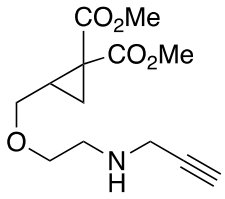
Dimethyl 2-((2,2-diethoxyethoxy)methyl)cyclopropane-1,1-dicarboxylate (2.62).

Alkene **2.61**[56] (1.74 g, 10 mmol) and $Rh_2(esp)_2$ (57 mg, 0.075 mmol) were dissolved in DCM (100 mL). A solution of dimethyl diazomalonate in DCM (30 mL) was added slowly over 1 h. The reaction was stirred overnight at room temperature. The solvent was evaporated, and the crude material was purified by column chromatography (27% EtOAc in hexanes) affording **2.62** as a colourless oil (1.32 g, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.56 (t, J = 5.2 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.68 (ddd, J = 9.3, 7.1, 2.2 Hz, 2H), 3.60 – 3.49 (m, 4H), 3.48 – 3.36 (m, 2H), 2.21 (ddt, J = 9.2, 7.6, 6.4 Hz, 1H), 1.56 (dd, J = 7.6, 4.8 Hz, 1H), 1.45 (dd, J = 9.2, 4.7 Hz, 1H), 1.30 – 1.17 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.5, 168.3, 101.3, 71.7, 69.3, 62.5, 62.5, 52.8, 52.8, 32.8, 27.4, 19.1, 15.5. **FTIR** (thin film, cm^{-1}) 2976, 2955, 2926, 2880, 1728, 1438, 1330, 1289, 1212, 1130, 1066.



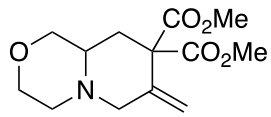
Dimethyl 2-((2-oxoethoxy)methyl)cyclopropane-1,1-dicarboxylate (2.63).

Acetal **2.62** (1.29 g, 4.23 mmol) was dissolved in dioxane (5.4 mL). Water (2.9 mL), and tosylic acid hydrate (81 mg, 0.42 mmol) were added. The reaction was heated to 50ºC and stirred until the starting material was mostly consumed (ca. 5 days). Brine was added to the reaction mixture and the solution was extracted with Et_2O 3 times. The organic layers were dried with $MgSO_4$. Solvent was evaporated affording the crude aldehyde **2.63** (0.73 g, 75%). **2.63** was unstable towards column conditions and was used in later reactions as the crude material. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.70 (t, J = 0.9 Hz, 1H), 4.07 (dd, J = 3.7, 0.8 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.69 (dd, J = 10.6, 5.7 Hz, 1H), 3.64 – 3.55 (m, 1H), 2.29 (dtd, J = 9.3, 7.5, 5.8 Hz, 1H), 1.61 (dd, J = 7.6, 4.9 Hz, 1H), 1.52 (dd, J = 9.3, 4.9 Hz, 1H).



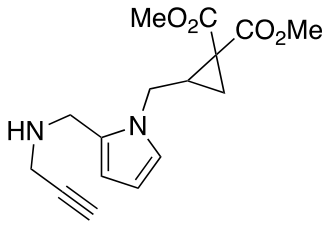
Dimethyl 2-((2-(prop-2-yn-1-ylamino)ethoxy)methyl)cyclopropane-1,1-dicarboxylate (2.64).

Aldehyde **2.63** (230 mg, 1 mmol) was treated with AcOH (58 µL, 1 mmol), STAB (318 mg, 1.5 mmol), and propargylamine (0.26 mL, 4 mmol) according to General Procedure A. rf = 0.35 in 100% EtOAc. **2.64** isolated as a yellow oil (107 mg, 40%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.79 (s, 3H), 3.75 (s, 3H), 3.63 – 3.43 (m, 6H), 2.84 (ddd, *J* = 5.8, 4.4, 1.4 Hz, 2H), 2.33 – 2.16 (m, 2H), 1.59 (dd, *J* = 7.6, 4.7 Hz, 1H), 1.47 (dd, *J* = 9.2, 4.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.5, 168.4, 82.2, 71.5, 70.2, 68.6, 52.9, 52.8, 48.1, 38.4, 32.8, 27.4, 19.0. **FTIR** (thin film, cm^{-1}) 3275, 3001, 2954, 2922, 2853, 1727, 1607, 1437, 1333, 1279, 1213, 1130. **HRMS** Calc'd for $C_{13}H_{19}NO_5$ = 269.1263, found 269.1263.



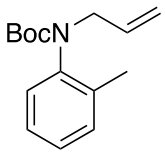
Dimethyl 7-methylenehexahydropyrido[2,1-*c*][1,4]oxazine-8,8(1*H*)-dicarboxylate (2.66).

Amine tethered cyclopropane **2.64** was treated according to General Procedure A. **2.64** (166 mg, 0.5 mmol), $Sc(OTf)_3$ (25 mg, 0.05 mmol), $ZnBr_2$ (226 mg, 1.0 mmol). Purified by column chromatography using 100% EtOAc affording **2.66** as a yellow oil (141 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.24 (d, *J* = 1.5 Hz, 1H), 4.84 (d, *J* = 0.7 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 – 3.61 (m, 3H), 3.42 – 3.24 (m, 2H), 3.00 (d, *J* = 12.4 Hz, 1H), 2.70 (dt, *J* = 11.6, 2.0 Hz, 1H), 2.36 (td, *J* = 11.5, 3.5 Hz, 1H), 2.22 (dd, *J* = 13.0, 2.2 Hz, 1H), 2.15 (tt, *J* = 9.6, 2.7 Hz, 1H), 1.98 (t, *J* = 12.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.1, 169.9, 139.8, 114.2, 71.1, 66.8, 60.8, 60.3, 57.3, 54.0, 53.1, 52.8, 33.9. **FTIR** (thin film, cm^{-1}) 2953, 2851, 2803, 1730, 1653, 1435, 1241, 1181, 1121, 1079, 1031, 923, 888, 734, 616. **HRMS** Calc'd for $C_{13}H_{19}NO_5$ = 269.1263, found 269.1260.



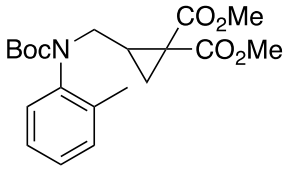
Dimethyl 2-((2-((prop-2-yn-1-ylamino)methyl)-1H-pyrrol-1-yl)methyl)cyclopropane-1,1-dicarboxylate (2.68).

Dimethyl 2-((2-formyl-1H-pyrrol-1-yl)methyl)cyclopropane-1,1-dicarboxylate[59] (270 mg, 1.01 mmol) was dissolved in DCM (1.9 mL). To this was added propargylamine (268 µL, 4.04 mmol) and $MgSO_4$ (1.4 g). This mixture was stirred for 3 days at room temperature until TLC indicated consumption of starting material. The solution was filtered, and solvent was evaporated. The residue was dissolved in MeOH (10 mL) and cooled to 0ºC. $NaBH_4$ (31 mg, 0.82 mmol) was added in one portion and the reaction was stirred for 25 minutes at 0ºC then solvent was evaporated. The residue was dissolved in DCM and water. The mixture was extracted with DCM 3 times. The organic layers were washed with brine and dried with $MgSO_4$. Solids were filtered off and solvent was evaporated. The crude material was purified by column chromatography (35% EtOAc in Hexanes) affording **2.68** as a yellow oil (60 mg, 20% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.65 (t, J = 2.3 Hz, 1H), 6.36 – 5.86 (m, 2H), 4.13 (dd, J = 14.6, 6.4 Hz, 1H), 3.88 (dd, J = 14.7, 7.9 Hz, 1H), 3.84 (d, J = 1.6 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.39 (d, J = 2.4 Hz, 2H), 2.40 (dtd, J = 9.1, 7.7, 6.4 Hz, 1H), 2.25 (t, J = 2.4 Hz, 1H), 1.66 (dd, J = 7.7, 4.9 Hz, 1H), 1.51 (dd, J = 9.2, 4.9 Hz, 1H). **FTIR** (thin film, cm^{-1}) 3281, 2953, 2924, 2849, 1723, 1489, 1435, 1327, 1290, 1212, 1127, 711.



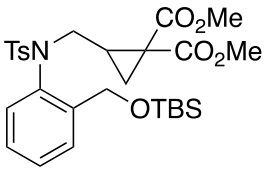
***Tert*-butyl allyl(o-tolyl)carbamate (2.74).**

This compound has been made before. *N*-allyl-2-methylaniline **2.73** (930 mg, 6.3 mmol) was dissolved in DCM (12.5 mL). The solution was cooled to 0ºC and Boc_2O was added dropwise. Solvent was evaporated and the crude material was purified by column chromatography (7% EtOAc in Hexanes) affording **2.74** as a colourless oil which solidified in the freezer (779 mg, 50%). Spectral data in accordance with literature.



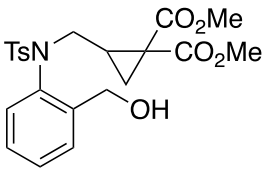
Dimethyl 2-(((*tert*-butoxycarbonyl)(*o*-tolyl)amino)methyl)cyclopropane-1,1-dicarboxylate (2.75).

Alkene **2.74** (247 mg, 1.0 mmol) and $Rh_2(esp)_2$ (2 mg, 2.5µmol) were dissolved in DCM (10 mL). A solution of dimethyl diazomalonate (174 mg, 1.1 mmol) in DCM (1.6 mL) was added portion wise over 1 hour. The reaction was stirred overnight. Solvent was evaporated and the crude material was purified by column chromatography (17% EtOAc in Hexanes) affording **2.75** as a colourless oil (248 mg, 66%) as a mixture of rotamers. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.26 – 7.03 (m, 4H), 3.73 (s, 3H), 3.62 (s, 2H), 3.58 (s, 2H), 3.48 (dd, J = 14.5, 7.2 Hz, 1H), 2.23 (s, 2H), 1.58 (d, J = 22.4 Hz, 4H), 1.34 (s, 9H). **FTIR** (thin film, cm^{-1}) 2976, 2954, 1728, 1696, 1437, 1381, 1292, 1279, 1212, 1154, 1131.



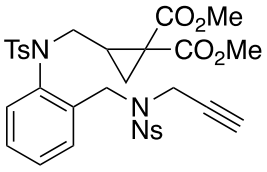
Dimethyl 2-(((*N*-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-4-methylphenyl)sulfonamido)methyl)cyclopropane-1,1-dicarboxylate (2.80).

Doubly protected *N*-allyl-2-aminobenzyl alcohol **2.79** (1.02 g, 2.4 mmol) was dissolved in DCM (24 mL). To this was added $Rh_2(esp)_2$. A solution of dimethyl diazomalonate in DCM (3.8 mL) was added portion wise over 1 h. The reaction was stirred overnight. Solvent was evaporated and the crude material was purified by column chromatography (10% EtOAc in Hexanes) affording **2.80** as a colourless oil (1.11 g, 82%) as a 1:1 mixture of rotamers. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.69 (d, J = 8.0 Hz, 2H), 7.57 – 7.48 (m, 4H), 7.43 – 7.33 (m, 2H), 7.30 (s, 3H), 7.12 (td, J = 7.7, 1.6 Hz, 2H), 6.53 (ddd, J = 8.0, 4.1, 1.2 Hz, 2H), 5.11 – 4.80 (m, 4H), 3.85 (dd, J = 13.9, 7.7 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.69 (s, 2H), 3.61 (dd, J = 14.3, 7.9 Hz, 1H), 3.56 (s, 2H), 3.52 – 3.41 (m, 1H), 3.26 (dd, J = 13.9, 6.6 Hz, 1H), 2.46 (s, 6H), 2.17 – 2.06 (m, 1H), 2.02 (q, J = 7.9 Hz, 1H), 1.54 – 1.39 (m, 2H), 1.28 (td, J = 7.9, 7.5, 2.8 Hz, 4H), 1.07 – 0.86 (m, 18H), 0.36 – 0.11 (m, 12H). **FTIR** (thin film, cm^{-1}) 2955, 2928, 2918, 2851, 1728, 1457, 1437, 1349, 1279, 1267, 1215, 1163, 1131, 1085, 911, 838, 815, 778, 734, 713, 657, 577, 552.



Dimethyl 2-(((*N*-(2-(hydroxymethyl)phenyl)-4-methylphenyl)sulfonamido)methyl)cyclopropane-1,1-dicarboxylate (2.81).

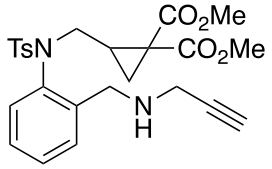
Protected alcohol **2.80** (1.24 g, 2.2 mmol) was dissolved in THF (7.3 mL). A 1.0 M solution of TBAF in THF (3.1 mL, 3.1 mmol) was added dropwise. The reaction was stirred until TLC indicated completion. Water was added and the mixture was extracted 3 times with DCM. The organic layers were dried with $MgSO_4$ and solids were filtered. Solvent was evaporated and the crude material was purified by column chromatography (65% EtOAc in Hexanes) affording **2.81** as a 1:1 mixture of rotamers (730 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.66 (dt, J = 7.7, 2.0 Hz, 2H), 7.55 – 7.44 (m, 4H), 7.36 (qd, J = 7.5, 1.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 4H), 7.13 (dtd, J = 9.0, 7.5, 1.6 Hz, 2H), 6.41 (ddd, J = 22.2, 8.0, 1.2 Hz, 2H), 4.94 (ddd, J = 17.1, 12.6, 4.9 Hz, 2H), 4.67 (ddd, J = 16.9, 12.6, 8.9 Hz, 2H), 3.99 (dd, J = 14.5, 6.0 Hz, 1H), 3.91 – 3.78 (m, 4H), 3.70 (s, 3H), 3.69 (s, 2H), 3.40 – 3.24 (m, 4H), 3.09 (ddd, J = 20.9, 8.9, 4.9 Hz, 2H), 2.45 (s, 5H), 2.27 – 2.14 (m, 1H), 1.87 (tdd, J = 9.3, 7.7, 5.1 Hz, 1H), 1.51 – 1.41 (m, 2H), 1.37 (dd, J = 7.8, 5.0 Hz, 1H), 1.30 – 1.20 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.0, 169.5, 168.2, 168.0, 144.2, 144.2, 143.4, 143.3, 137.4, 136.7, 134.8, 134.5, 131.4, 131.2, 129.8, 129.7, 129.4, 129.2, 128.5, 128.3, 128.2, 128.1, 127.7, 126.9, 61.1, 60.9, 53.4, 53.1, 53.0, 52.7, 50.8, 50.4, 33.6, 33.6, 28.4, 25.8, 21.7, 19.2, 19.1. **FTIR** (thin film, cm^{-1}) 3526, 2955, 2924, 2853, 1723, 1308, 1284, 1157, 1133, 1091, 1051, 911, 816, 732, 699, 657, 575, 553.



Dimethyl 2-(((4-methyl-N-(2-(((4-nitro-N-(prop-2-yn-1-yl)phenyl)sulfonamido)methyl)phenyl)phenyl)sulfonamido) methyl)cyclopropane-1,1-dicarboxylate (**2.82).**

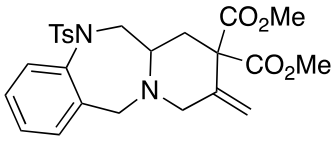
Following general procedure C, alcohol **2.81** (730 mg, 1.63 mmol), *N*-nosyl-propargylamine (392 mg, 1.63 mmol), and PPh_3 (428 mg, 1.63 mmol) were dissolved in DCM (16 mL). DTBAD (375 mg, 1.63 mmol) was then added. The reaction was stirred at room temperature overnight. (45% EtOAc in Hexanes). **2.82** was obtained as a viscous yellow oil (614 mg, 56%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.15 (ddd, J = 5.8, 4.5, 3.5 Hz, 2H), 7.78 – 7.58 (m, 6H), 7.54 – 7.47 (m, 4H), 7.39 – 7.27 (m, 6H), 7.14 (tt, J = 7.6, 2.3 Hz, 2H), 6.51 (ddd, J = 7.7, 6.3, 1.3 Hz, 2H), 5.43 – 4.83 (m, 4H), 4.37 – 4.07 (m, 4H), 3.96 (dd, J = 13.8, 7.0 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 3.65 – 3.46 (m,

4H), 3.18 (dd, J = 13.8, 7.3 Hz, 1H), 2.45 (s, 6H), 2.13 (dt, J = 4.7, 2.4 Hz, 2H), 2.06 (td, J = 8.6, 7.2 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.31 (dd, J = 9.1, 5.0 Hz, 1H), 1.17 (dd, J = 7.7, 5.0 Hz, 1H).



Dimethyl 2-(((4-methyl-N-(2-((prop-2-yn-1-ylamino)methyl)phenyl)phenyl)sulfonamido)methyl)cyclopropane-1,1-dicarboxylate (2.83).

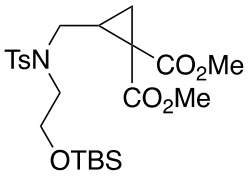
Ns protected amine **2.82** (614 mg, 0.92 mmol) was dissolved in DMF (2.8 mL). To this was added K_2CO_3 (381 mg, 2.76 mmol) then PhSH (110 µL, 1.09 mmol) dropwise. The mixture was stirred until TLC indicated consumption of starting material. Water was added and the mixture was extracted with Et_2O 3 times. The combined organic layers were dried with $MgSO_4$. Solids were filtered off and the solvent was evaporated. The crude material was purified by column chromatography (3% MeOH in DCM) affording **2.83** as a yellow oil (120 mg, 27%). This compound appears as a 1:1 mixture of rotamers. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.71 – 7.60 (m, 1H), 7.56 – 7.47 (m, 4H), 7.37 – 7.28 (m, 5H), 7.11 (tt, J = 7.6, 1.9 Hz, 2H), 6.53 (td, J = 7.8, 1.3 Hz, 2H), 5.30 (s, 4H), 4.08 (dd, J = 15.6, 13.3 Hz, 2H), 4.01 – 3.82 (m, 3H), 3.83 – 3.66 (m, 10H), 3.58 – 3.36 (m, 7H), 3.29 (dd, J = 14.0, 6.1 Hz, 1H), 2.44 (s, 6H), 2.28 (dt, J = 3.7, 2.4 Hz, 2H), 2.15 (p, J = 7.7 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.80 (s, 2H), 1.44 (d, J = 8.5 Hz, 2H), 1.31 – 1.23 (m, 2H). **FTIR** (thin film, cm^{-1}) 3289, 2954, 2925, 2871, 1723, 1437, 1343, 1281, 1215, 1157, 1131, 1091, 910, 815, 731, 711, 577, 547.



Dimethyl 9-methylene-5-tosyl-5,6*a*,7,9,10,12-hexahydrobenzo[*e*]pyrido[1,2-*a*][1,4]diazepine-8,8(6*H*)-dicarboxylate (2.85).

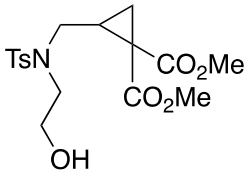
2.83 was treated according to a modification of General Procedure A. **2.83** (100 mg, 0.2 mmol) was dissolved in toluene (4 mL) and $Sc(OTf)_3$ 0.2 eq (20 mg, 0.04 mmol) was added. The reaction was stirred at reflux in PhMe until ring opening was complete by TLC analysis. $ZnBr_2$ (90 mg, 0.4 mmol) was added to the ring opened product and the remainder of the procedure was performed per General Procedure A. (60% EtOAc in Hexanes). **2.86**

was obtained as a yellow oil (47 mg, 47%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.61 (d, J = 7.9 Hz, 2H), 7.28 (s, 1H), 7.23 – 7.09 (m, 2H), 5.15 (d, J = 1.3 Hz, 1H), 4.76 (s, 1H), 4.21 (s, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.73 – 3.70 (m, 1H), 3.37 – 3.15 (m, 2H), 3.01 (d, J = 12.6 Hz, 1H), 2.48 (d, J = 17.7 Hz, 2H), 2.43 (s, 3H), 2.40 – 2.24 (m, 1H), 1.91 (dd, J = 23.2, 11.0 Hz, 1H) (3 protons missing due to overlap with solvent).



Dimethyl 2-(((*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-methylphenyl)sulfonamido)methyl)cyclopropane-1,1-dicarboxylate (2.94).

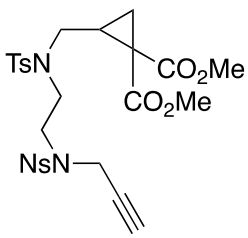
Alkene **2.93**[69] (1.66 g, 4.5 mmol) and $Rh_2(esp)_2$ (17 mg, 22.5 µmol) were dissolved in DCM (45 mL). A solution of dimethyl diazomalonate (783 mg, 4.95 mmol) in DCM (7.2 mL) was added portion wise over 1 h. The reaction was stirred overnight at room temperature. Solvent was evaporated and the crude material was purified by column chromatography (20% EtOAc in Hexanes) affording **2.94** as a colourless oil (1.84 g, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.3 Hz, 2H), 7.37 – 7.30 (m, 2H), 3.80 – 3.70 (m, 6H), 3.56 (dd, J = 14.8, 5.4 Hz, 1H), 3.32 (td, J = 6.3, 3.5 Hz, 2H), 3.10 (dd, J = 14.8, 8.2 Hz, 1H), 2.44 (s, 3H), 2.15 (dtd, J = 9.1, 7.9, 5.4 Hz, 1H), 1.57 – 1.42 (m, 2H), 0.88 (s, 9H), 0.05 (d, J = 1.2 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.0, 168.1, 143.5, 137.2, 129.9, 127.3, 62.5, 52.9, 52.9, 50.3, 48.4, 33.3, 26.7, 26.0, 21.6, 20.7, 18.3, -5.4. **FTIR** (thin film, cm^{-1}) 3052, 2954, 1727, 1339, 1272, 1258, 1215, 1157, 1107, 1090, 836, 813, 778, 731, 652, 549.



Dimethyl 2-(((*N*-(2-hydroxyethyl)-4-methylphenyl)sulfonamido)methyl)cyclopropane-1,1-dicarboxylate (2.95).

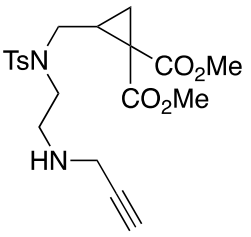
Protected alcohol **2.94** (1.00 g, 2.0 mmol) was dissolved in THF (6.8 mL). AcOH (0.16 mL) was added. A 1.0 M solution of TBAF in THF (2.8 mL, 2.8 mmol) was added dropwise. The reaction was stirred until TLC indicated completion (ca. 3 h). Water was added and the mixture was extracted 3 times with DCM. The organic layers were washed with saturated aqueous $NaHCO_3$ 2 times. The organic layers were dried with brine and

$MgSO_4$. Solids were filtered and the solvent was evaporated. The crude material was purified by column chromatography (50% EtOAc in Hexanes) affording **2.95** as a colourless oil (771 mg, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.3 Hz, 3H), 7.37 – 7.30 (m, 3H), 3.94 – 3.67 (m, 8H), 3.45 (dd, J = 14.7, 7.0 Hz, 1H), 3.35 (ddd, J = 15.1, 6.0, 4.5 Hz, 1H), 3.29 – 3.08 (m, 3H), 2.45 (s, 5H), 2.15 (dq, J = 9.2, 7.1 Hz, 1H), 1.61 – 1.44 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 169.9, 168.2, 143.9, 135.8, 130.0, 127.5, 61.6, 53.2, 53.1, 51.1, 48.7, 33.6, 26.8, 21.7, 20.4. **FTIR** (thin film, cm^{-1}) 3528, 2954, 2923, 2852, 1725, 1437, 1334, 1277, 1156, 1133, 727, 654, 549.



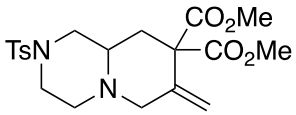
Dimethyl 2-(((4-methyl-*N*-(2-((4-nitro-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)ethyl)phenyl)sulfonamido)methyl) cyclopropane-1,1-dicarboxylate (2.96).

Following general procedure C, alcohol **2.95** (771 mg, 2.0 mmol), *N*-nosyl-propargylamine (480 mg, 2.0 mmol), and PPh_3 (525 mg, 2.0 mmol) were dissolved in DCM (20 mL). DTBAD (461 mg, 2.0 mmol) was then added. The reaction was stirred at room temperature overnight. (65% EtOAc in Hexanes). **2.96** was obtained as a viscous yellow oil (756 mg, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.20 – 8.06 (m, 1H), 7.82 – 7.58 (m, 5H), 7.39 – 7.29 (m, 2H), 4.27 (t, J = 2.4 Hz, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.64 (t, J = 7.3 Hz, 2H), 3.57 – 3.46 (m, 2H), 3.36 (dt, J = 14.7, 7.4 Hz, 1H), 2.94 (dd, J = 14.6, 7.9 Hz, 1H), 2.43 (s, 3H), 2.24 (t, J = 2.5 Hz, 1H), 2.17 – 1.93 (m, 1H), 1.65 – 1.44 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 169.8, 168.0, 148.4, 144.0, 135.6, 134.0, 132.3, 132.0, 131.6, 130.1, 127.5, 124.4, 74.3, 53.1, 53.0, 48.5, 47.1, 47.0, 38.5, 33.4, 26.3, 21.7, 20.4. **FTIR** (thin film, cm^{-1}) 3276, 3095, 2955, 2925, 1727, 1545, 1438, 1345, 1294, 1160, 1135, 733, 654.



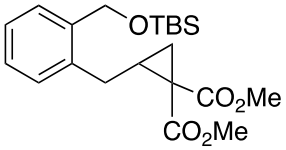
Dimethyl 2-(((4-methyl-*N*-(2-(prop-2-yn-1-ylamino)ethyl)phenyl)sulfonamido)methyl)cyclopropane-1,1-dicarboxylate (2.97).

Ns amine **2.95** (786 mg, 1.30 mmol) was dissolved in DMF (3.9 mL). To this was added K_2CO_3 (537 mg, 3.88 mmol) then PhSH dropwise (158 µL, 1.55 mmol). This reaction was stirred until TLC indicated completion. Water was added and the mixture was extracted with Et_2O 3 times. The organic layers were washed with water and dried with $MgSO_4$. Solids were filtered and solvent was evaporated. The crude material was purified by column chromatography (85% EtOAc in Hexanes with 1% NEt_3) affording **2.97** as a yellow oil (283 mg, 52%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.68 (d, J = 8.3 Hz, 2H), 7.35 – 7.28 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.46 (dd, J = 14.9, 5.8 Hz, 1H), 3.42 (d, J = 2.4 Hz, 2H), 3.33 (dt, J = 14.3, 6.5 Hz, 1H), 3.21 (dt, J = 14.4, 6.3 Hz, 1H), 3.02 (dd, J = 14.9, 7.9 Hz, 1H), 2.89 (t, J = 6.4 Hz, 2H), 2.42 (s, 3H), 2.22 (t, J = 2.4 Hz, 1H), 2.17 – 2.05 (m, 1H), 1.57 – 1.44 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 169.8, 168.2, 143.7, 136.4, 129.9, 127.4, 82.0, 71.8, 62.1, 53.0, 53.0, 48.5, 48.0, 47.1, 38.1, 33.5, 26.8, 21.7, 20.6, 14.1. **FTIR** (thin film, cm^{-1}) 3280, 2954, 2852, 2257, 1723, 1598, 1437, 1333, 1277, 1215, 1155, 1131, 1090, 980, 873, 728, 653.



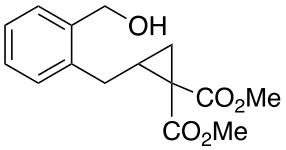
Dimethyl 7-methylene-2-tosyloctahydro-8*H*-pyrido[1,2-*a*]pyrazine-8,8-dicarboxylate (2.99).

Amine tethered cyclopropane **2.97** was treated according to General Procedure A. **2.97** (100 mg, 0.24 mmol), $Sc(OTf)_3$ (13 mg, 0.025 mmol), $ZnBr_2$ (113 mg, 0.5 mmol). Purified by column chromatography using 60% EtOAc in Hexanes. **2.99** was isolated as a yellow oil (60 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.70 – 7.58 (m, 2H), 7.54 – 7.28 (m, 2H), 5.14 (d, J = 1.4 Hz, 1H), 4.75 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.61 (ddt, J = 12.9, 10.9, 2.3 Hz, 2H), 3.23 (d, J = 12.5 Hz, 1H), 2.95 (d, J = 12.4 Hz, 1H), 2.76 (dt, J = 11.2, 2.5 Hz, 1H), 2.42 (s, 4H), 2.35 (dd, J = 11.3, 2.8 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.15 (ddt, J = 12.2, 9.8, 2.6 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.89 (dd, J = 13.3, 11.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 169.8, 169.8, 144.0, 139.8, 131.9, 129.8, 128.0, 114.4, 60.5, 59.8, 56.4, 53.4, 53.3, 53.0, 50.9, 45.8, 35.9, 21.6. **FTIR** (thin film, cm^{-1}) 2952, 2851, 2813, 1731, 1455, 1332, 1244, 1165, 1124, 1075, 1018, 922, 816, 765, 732, 656, 601, 538.



Dimethyl 2-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)benzyl)cyclopropane-1,1-dicarboxylate (2.115).

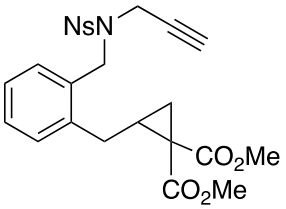
Alkene **2.114** (Synthesized in three steps from methyl 2-iodobenzoate by allylation,[70] reduction,[71] and TBS protection[39]) (1.05 g, 4.0 mmol) and $Rh_2(esp)_2$ (8 mg, 10 µmol) were dissolved in DCM (40 mL). A solution of dimethyl diazomalonate (696 mg, 4.4 mmol) in DCM (6.4 mL) was added portion wise over 1 h. The reaction was stirred overnight at room temperature. Solvent was evaporated and the crude material was purified by column chromatography (7% EtOAc in Hexanes) affording **2.115** as a colourless oil (1.21 g, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 – 7.37 (m, 1H), 7.25 – 7.20 (m, 3H), 4.71 (s, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 2.92 (dd, *J* = 15.4, 5.8 Hz, 1H), 2.46 (dd, *J* = 15.4, 8.7 Hz, 1H), 2.24 (tdd, *J* = 8.8, 7.7, 5.8 Hz, 1H), 1.60 (dd, *J* = 7.7, 4.7 Hz, 1H), 1.51 (dd, *J* = 9.0, 4.7 Hz, 1H), 0.93 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.7, 168.7, 138.8, 137.1, 128.6, 127.5, 127.5, 126.6, 63.4, 52.8, 52.7, 34.3, 30.6, 28.3, 26.1, 21.8, 18.5, -5.1. **FTIR** (thin film, cm^{-1}) 2954, 2930, 2886, 2856, 1727, 1436, 1323, 1272, 1255, 1212, 1126, 1075, 836.



Dimethyl 2-(2-(hydroxymethyl)benzyl)cyclopropane-1,1-dicarboxylate (2.116).

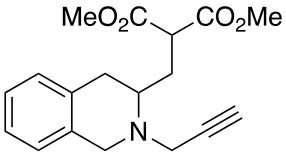
Protected alcohol **2.115** (1.21 g, 3.1 mmol) was dissolved in THF (10.3 mL). To this was added a 1.0 M solution of TBAF in THF (4.3 mL, 4.3 mmol). The reaction was stirred at room temperature until TLC indicated completion. Water was added and the mixture was extracted with DCM 3 times. The organic layers were washed with brine and dried with $MgSO_4$. Solids were filtered off and solvent was evaporated. The crude material was purified by column chromatography (45% EtOAc in Hexanes) affording **2.116** as a colourless oil (787 mg, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.37 (dd, J = 6.8, 1.7 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.23 (dd, J = 6.9, 2.4 Hz, 1H), 4.70 (d, J = 1.3 Hz, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 2.98 (dd, J = 15.4, 6.2 Hz, 1H), 2.60 (dd, J = 15.4, 8.5 Hz, 1H), 2.28 (tdd,

J = 8.5, 7.7, 6.2 Hz, 1H), 1.68 – 1.59 (m, 2H), 1.51 (dd, J = 9.0, 4.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.6, 168.9, 138.4, 138.0, 129.1, 128.6, 128.4, 126.9, 63.4, 52.9, 52.8, 34.3, 30.5, 28.4, 21.8. **FTIR** (thin film, cm^{-1}) 3507, 2955, 1723, 1437, 1324, 1278, 1215, 1127.



Dimethyl 2-(2-(((4-nitro-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)methyl)benzyl)cyclopropane-1,1-dicarboxylate (2.117).

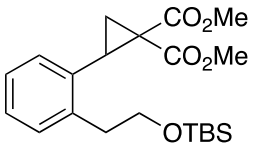
Following general procedure C, alcohol **2.116** (278 mg, 1.0 mmol), *N*-nosyl-propargylamine (240 mg, 1.0 mmol), and PPh_3 (262 mg, 1.0 mmol) were dissolved in DCM (10 mL). DTBAD (230 mg, 1.0 mmol) was then added. The reaction was stirred at room temperature overnight. (40% EtOAc in Hexanes). **2.37** was obtained as a viscous yellow oil (385 mg, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.04 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.86 – 7.57 (m, 3H), 7.57 – 7.28 (m, 3H), 7.21 (td, *J* = 7.4, 1.7 Hz, 1H), 4.70 – 4.51 (m, 2H), 4.14 – 3.90 (m, 2H), 3.76 – 3.73 (m, 6H), 3.02 (dd, *J* = 15.9, 5.8 Hz, 1H), 2.56 (dd, *J* = 16.0, 8.7 Hz, 1H), 2.19 (tdd, *J* = 8.7, 7.6, 5.7 Hz, 1H), 2.11 (t, *J* = 2.4 Hz, 1H), 1.64 – 1.42 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 168.6, 148.6, 139.3, 133.9, 132.4, 131.8, 131.7, 131.5, 130.2, 129.2, 128.9, 127.0, 124.3, 76.5, 74.6, 52.9, 48.5, 36.0, 34.3, 30.5, 27.9, 21.6. **FTIR** (thin film, cm^{-1}) 3285, 2980, 2971, 2956, 2923, 2359, 1724, 1545, 1437, 1372, 1360, 1338, 1291, 1273, 1216, 1167, 1127.



Dimethyl 2-((2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)malonate (2.119).

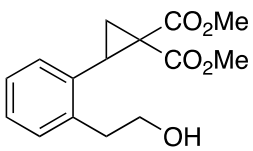
Ns protected amine **2.117** (234 mg, 0.467 mmol) was dissolved in DMF (1.4 mL). To this was added K_2CO_3 (242 mg, 1.75 mmol). PhSH (71µL, 0.71 mmol) was the added dropwise and the reaction was stirred until consumption of the starting material was confirmed by TLC. Water was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried with $MgSO_4$. Solids were filtered off and the crude material was purified by column chromatography (25% EtOAc in Hexanes) affording

2.119 (90 mg, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.19 – 6.97 (m, 4H), 3.91 (s, 2H), 3.74 (d, *J* = 0.8 Hz, 6H), 3.68 (t, *J* = 7.3 Hz, 1H), 3.54 (dd, *J* = 16.8, 2.5 Hz, 1H), 3.34 (dd, *J* = 16.8, 2.5 Hz, 1H), 3.08 (qd, *J* = 6.7, 5.2 Hz, 1H), 2.95 (dd, *J* = 16.5, 5.2 Hz, 1H), 2.55 (dd, *J* = 16.4, 6.5 Hz, 1H), 2.27 (dt, J = 14.1, 7.4 Hz, 1H), 2.21 (t, J = 2.4 Hz, 1H), 1.98 (dt, J = 13.9, 6.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.1, 170.0, 133.9, 133.2, 129.0, 126.8, 126.5, 126.2, 80.0, 72.7, 72.7, 54.0, 52.8, 51.4, 48.8, 41.8, 31.1, 30.9. **FTIR** (thin film, cm^{-1}) 3282, 2980, 2970, 2954, 1748, 1435, 1347, 1274, 1231, 1199, 1154.



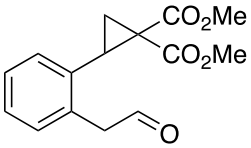
Dimethyl 2-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)cyclopropane-1,1-dicarboxylate (2.126).

Alkene **2.124** (Synthesized in three steps from 2-bromophenylacetic acid by reduction, Stille coupling,[72] and TBS protection[39]) (1.41 g, 5.37 mmol) was dissolved in DCM (54 mL). To this solution was added $Rh_2(esp)_2$ (31 mg, 0.004 mmol). A solution of dimethyl diazomalonate (0.943 g, 5.91 mmol) in DCM (mL) was added slowly over the course of an hour. After the addition, the reaction was stirred at room temperature overnight. Solvent was then removed under vacuum. The residue was purified by column chromatography (10% EtOAc in Hexanes) affording **2.126** as a yellow oil (1.627 g, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.15 (ddd, *J* = 8.8, 6.0, 2.8 Hz, 1H), 7.13 – 6.99 (m, 1H), 3.97 – 3.85 (m, 2H), 3.84 (s, 3H), 3.38 (t, *J* = 8.7 Hz, 1H), 3.32 (s, 3H), 3.09 (dt, *J* = 14.2, 7.2 Hz, 1H), 2.85 (ddd, *J* = 13.7, 7.3, 6.1 Hz, 1H), 2.33 (dd, *J* = 8.2, 5.1 Hz, 1H), 1.76 (dd, *J* = 9.2, 5.1 Hz, 1H), 0.90 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.23, 167.01, 140.10, 132.63, 129.68, 127.52, 127.29, 125.91, 63.62, 52.82, 52.10, 36.73, 36.04, 30.88, 25.92, 18.87, 18.30, -5.44, -5.52. **FTIR** (thin film, cm^{-1}) 3021, 2996, 2953, 2930, 2888, 2857, 1730, 1437, 1330, 1281, 1255, 1228, 1202, 1130, 1093. **HRMS** Calc'd for $C_{21}H_{32}O_5Si$ = 392.2019, found 392.2016.



Dimethyl 2-(2-(2-hydroxyethyl)phenyl)cyclopropane-1,1-dicarboxylate (2.127).

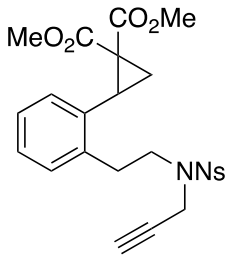
Protected alcohol **2.126** (411 mg, 1.05 mmol) was dissolved in THF (3.5 mL). To this solution was added a 1.0 M solution of TBAF in THF (1.47 mL). The reaction was stirred at room temperature until TLC indicated consumption of starting material. The reaction was quenched with the addition of H_2O and the mixture was extracted three times with DCM. The combined organic layers were washed with water and then dried with $MgSO_4$. The solvent was removed in vacuo affording the crude product. The crude material was purified by column chromatography (45% EtOAc in Hexanes) affording **2.127** as a colourless oil (239 mg, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 1H), 7.22 – 7.14 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 3.93 (d, *J* = 5.0 Hz, 1H), 3.84 (s, 2H), 3.35 (s, 2H), 3.31 (t, *J* = 8.7 Hz, 1H), 3.19 – 2.84 (m, 1H), 2.35 (dd, *J* = 8.2, 5.2 Hz, 1H), 1.79 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.61 (s, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ 170.37, 167.31, 139.52, 132.92, 129.80, 127.93, 127.35, 126.41, 62.74, 53.13, 52.38, 37.17, 36.21, 30.86, 18.89. **FTIR** (thin film, cm^{-1}) 3427, 3021, 3004, 2953, 2925, 2879, 2852, 1722, 1436, 1329, 1278, 1228, 1200, 1128, 1044. **HRMS** Calc'd for $C_{15}H_{19}O_5Si$ = 279.1233, found 279.1230.



Dimethyl 2-(2-(2-oxoethyl)phenyl)cyclopropane-1,1-dicarboxylate (2.128).

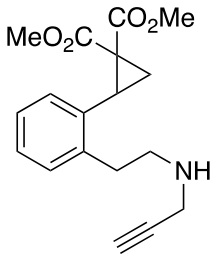
This compound degrades rapidly once synthesized. DMSO (0.15 mL, 2.1 mmol) was dissolved in DCM (9.1 mL). This solution was cooled to –78ºC with a dry ice bath. To this chilled solution was added oxalyl chloride (0.1 mL, 1.2 mmol) dropwise. The solution was stirred for 10 min at –78ºC. **2.127** (278 mg, 1 mmol) was dissolved in DCM (0.8 mL) and added dropwise to the solution of DMSO. The combined solution was stirred for 30 min at –78ºC. NEt_3 (0.7 mL, 5 mmol) was added dropwise. The reaction was stirred at –78ºC for 30 min. The flask was then allowed to come to room temperature and was stirred for 3 h. The reaction was then acidified to pH 7 with the addition of 1 M HCl. The mixture was extracted three times with DCM. The combined organic layers were washed with water three times and brine one time. The organic layers were then dried with $MgSO_4$. The solvent was removed under vacuum and a crude oil was obtained. The crude material was purified by column chromatography (30% EtOAc in Hexanes) affording **2.128** as a yellow oil (110 mg, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.76 (t, *J* = 2.0 Hz, 1H), 7.34 – 7.22

(m, 2H), 7.20-7.13 (m, 2H), 3.95 – 3.75 (m, 5H), 3.31 (s, 3H), 3.12 (t, *J* = 8.6 Hz, 1H), 2.30 (dd, *J* = 8.1, 5.2 Hz, 1H), 1.75 (dd, *J* = 9.2, 5.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) = δ 199.21, 170.03, 166.95, 133.54, 133.37, 130.54, 128.42, 128.27, 127.59, 53.17, 52.40, 48.02, 36.82, 30.68, 18.74. **HRMS** Calc'd for $C_{15}H_{16}O_5$ = 276.0998, found 276.0990.



Dimethyl 2-(2-(2-((4-nitro-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)ethyl)phenyl)cyclopropane-1,1-dicarboxylate (2.131).

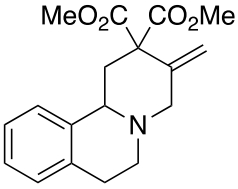
Following general procedure C, alcohol **2.127** (647 mg, 2.33 mmol), *N*-nosyl-propargylamine (560 mg, 2.33 mmol), and PPh_3 (611 mg, 2.33 mmol) were dissolved in DCM (23 mL). DTBAD (537 mg, 2.33 mmol) was then added. The reaction was stirred at room temperature overnight. (45% EtOAc in Hexanes). **2.131** was obtained as a viscous yellow oil (728 mg, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.24 – 7.89 (m, 1H), 7.88 – 7.54 (m, 3H), 7.22 – 6.91 (m, 4H), 4.27 (d, *J* = 2.5 Hz, 2H), 3.81 (s, 3H), 3.69 (ddd, *J* = 14.4, 10.5, 6.1 Hz, 1H), 3.60 – 3.49 (m, 1H), 3.29 (s, 3H), 3.23 (t, *J* = 8.6 Hz, 1H), 3.19 – 3.09 (m, 1H), 3.01 (ddd, *J* = 13.5, 10.7, 6.1 Hz, 1H), 2.30 (dd, *J* = 8.1, 5.2 Hz, 1H), 2.19 (t, *J* = 2.4 Hz, 1H), 1.76 (dd, *J* = 9.2, 5.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 167.0, 148.4, 138.7, 133.7, 133.1, 132.6, 131.8, 131.1, 129.7, 128.2, 128.0, 126.8, 124.3, 74.0, 53.1, 52.3, 47.8, 37.1, 37.0, 31.6, 30.4, 18.7. **FTIR** (thin film, cm^{-1}) 3285, 3097, 3074, 3024, 3003, 2953, 2122, 1725, 1543, 1437, 1359, 1339, 1281, 1163, 1127.



Dimethyl 2-(2-(2-(prop-2-yn-1-ylamino)ethyl)phenyl)cyclopropane-1,1-dicarboxylate (2.132).

Ns protected amine **2.131** (728 mg, 1.45 mmol) was dissolved in DMF (4.4 mL). K_2CO_3 (601 mg, 4.35 mmol) was added followed by the dropwise addition of PhSH (178µL, 1.74 mmol). The reaction was stirred at room temperature until TLC indicated completion. Water was added and the mixture was extracted 3 times with Et_2O. The organic layers were washed with water and dried with $MgSO_4$. Solids were filtered off and solvent was evaporated. The crude material was

purified by column chromatography (4% MeOH in DCM) affording **2.132** as a colourless oil (303 mg, 66% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.24 – 7.18 (m, 2H), 7.18 – 7.08 (m, 1H), 7.08 – 7.01 (m, 1H), 3.81 (s, 3H), 3.46 (d, J = 2.4 Hz, 2H), 3.31 (s, 3H), 3.27 (t, J = 8.8 Hz, 1H), 3.06 – 2.94 (m, 3H), 2.86 (ddd, J = 11.7, 9.4, 7.2 Hz, 1H), 2.31 (dd, J = 8.2, 5.2 Hz, 1H), 2.20 (t, J = 2.4 Hz, 1H), 1.74 (dd, J = 9.2, 5.1 Hz, 1H), 1.32 – 1.09 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.4, 167.1, 140.6, 132.6, 129.2, 127.9, 127.6, 126.2, 82.3, 71.4, 53.1, 52.3, 48.7, 38.3, 37.0, 33.0, 30.7, 18.9. **FTIR** (thin film, cm^{-1}) 3288, 2953, 2921, 2848, 1726, 1437, 1331, 1281, 1229, 1203, 1130, 1098, 753.



Dimethyl 3-methylene-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline-2,2-dicarboxylate (2.134).

Amine tethered cyclopropane **2.132** was treated according to General Procedure A. **2.132** (158 mg, 0.5 mmol), $Sc(OTf)_3$ (25 mg, 0.05 mmol), $ZnBr_2$ (225 mg, 1.0 mmol). Purified by column chromatography using 50% EtOAc in Hexanes. **2.134** was isolated as a yellow oil (150 mg, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.22 – 6.97 (m, 4H), 5.22 (d, J = 1.4 Hz, 1H), 4.85 (d, J = 0.8 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.51 – 3.25 (m, 3H), 3.11 (ddd, J = 15.9, 10.1, 5.6 Hz, 1H), 3.05 – 2.97 (m, 1H), 2.93 (dd, J = 13.5, 2.5 Hz, 1H), 2.77 (dt, J = 16.1, 4.0 Hz, 1H), 2.53 (ddd, J = 11.2, 9.9, 4.3 Hz, 1H), 2.30 (dd, J = 13.6, 12.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.6, 170.3, 140.0, 136.7, 134.6, 129.1, 126.6, 126.0, 125.6, 114.1, 61.9, 61.4, 59.1, 53.2, 52.9, 50.2, 37.8, 31.1, 29.6. **FTIR** (thin film, cm^{-1}) 2951, 2924, 2852, 1733, 1454, 1435, 1255, 1122, 1086, 1069, 913, 745.

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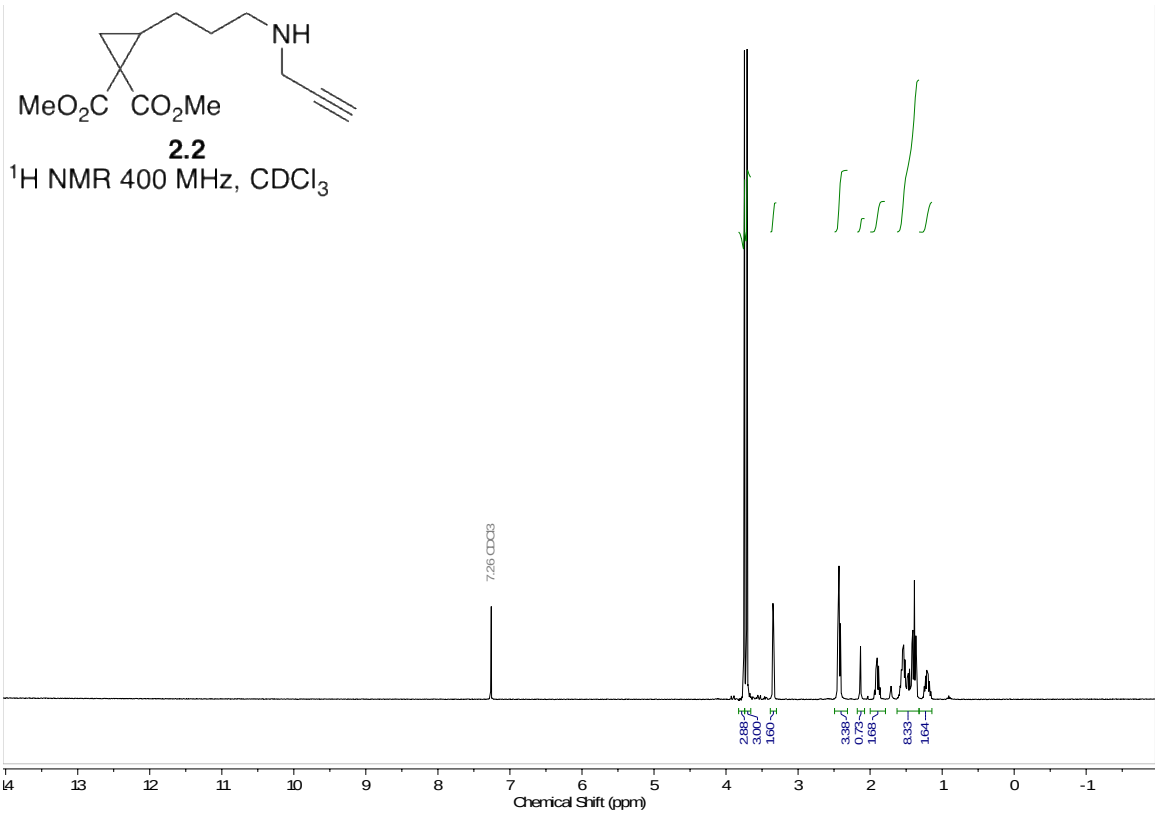
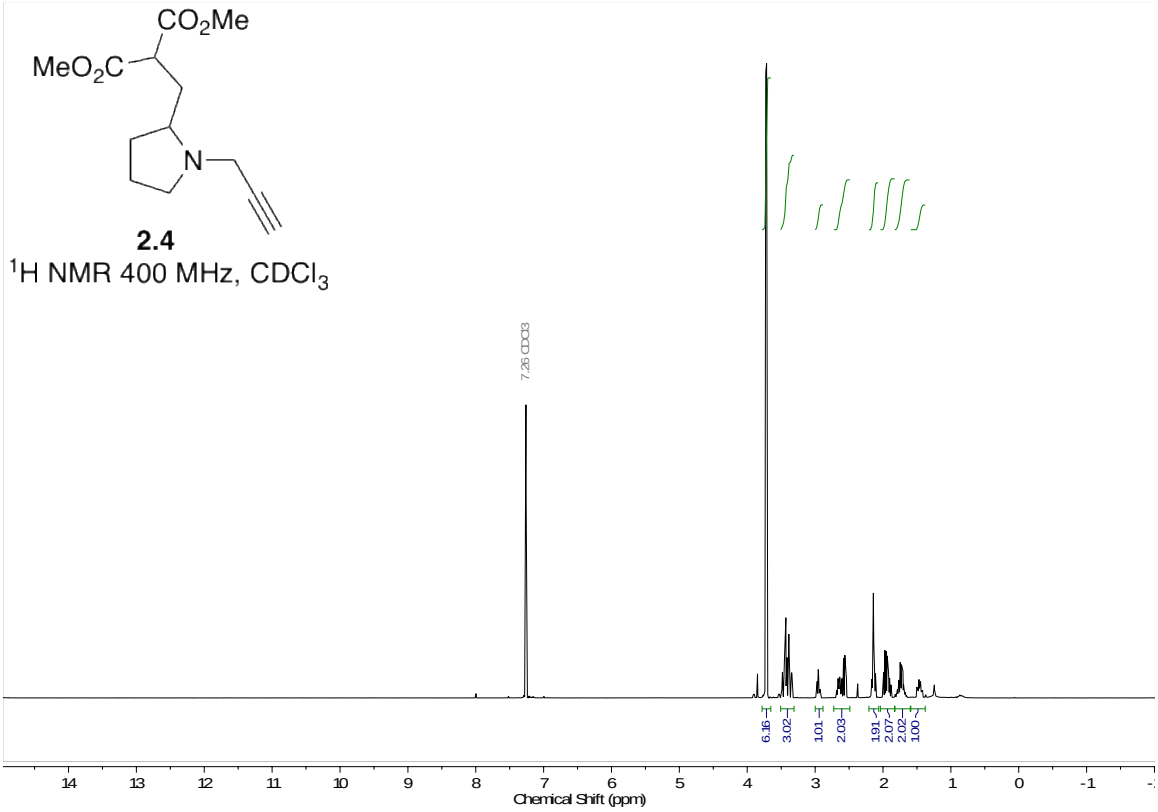
Appendix I – One-Pot Synthesis of Bicyclic Piperidines ^{1}H NMR and ^{13}C NMR



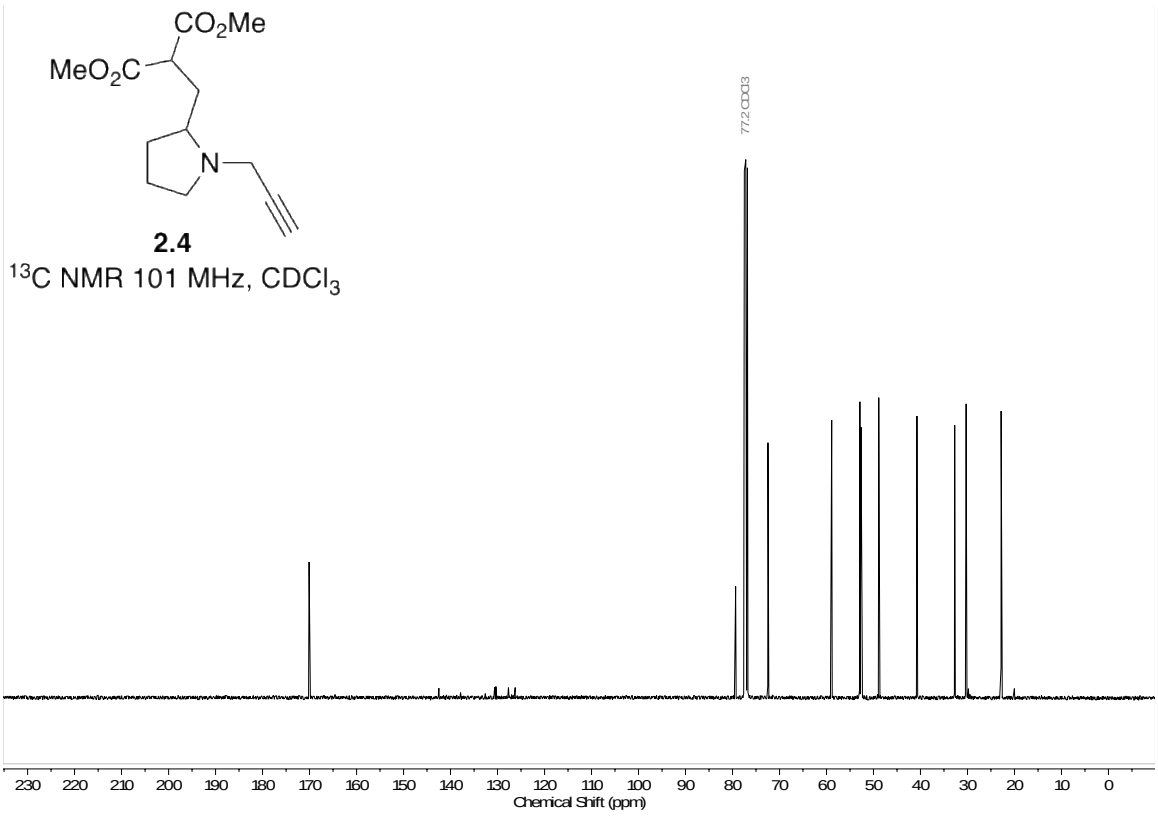
2.2

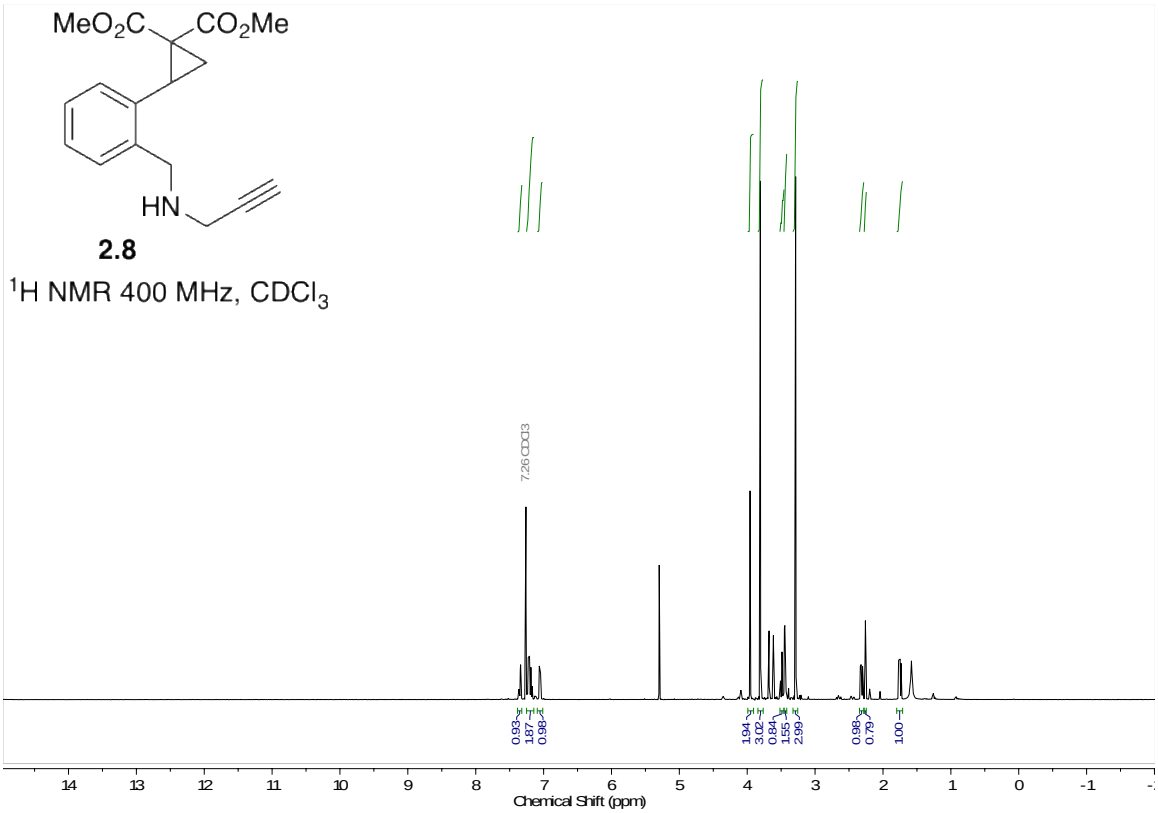
^{1}H NMR 400 MHz, $CDCl_3$

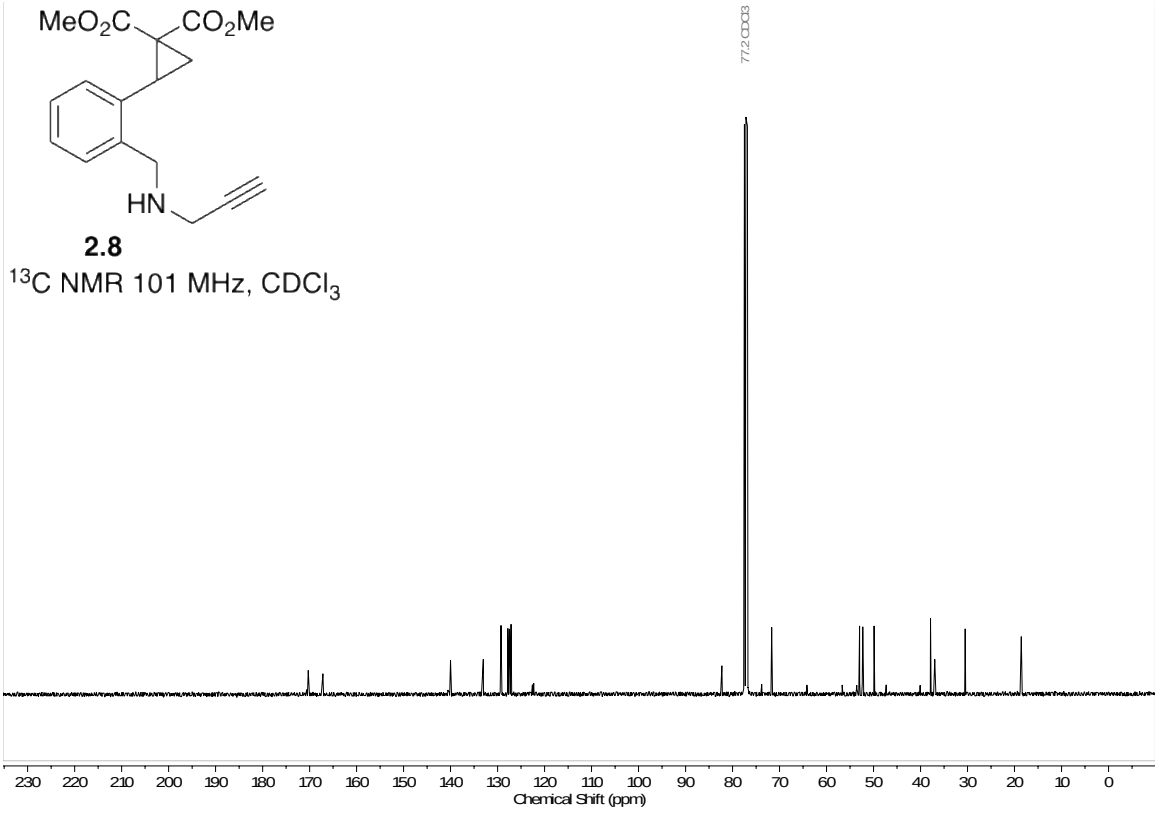


2.4

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

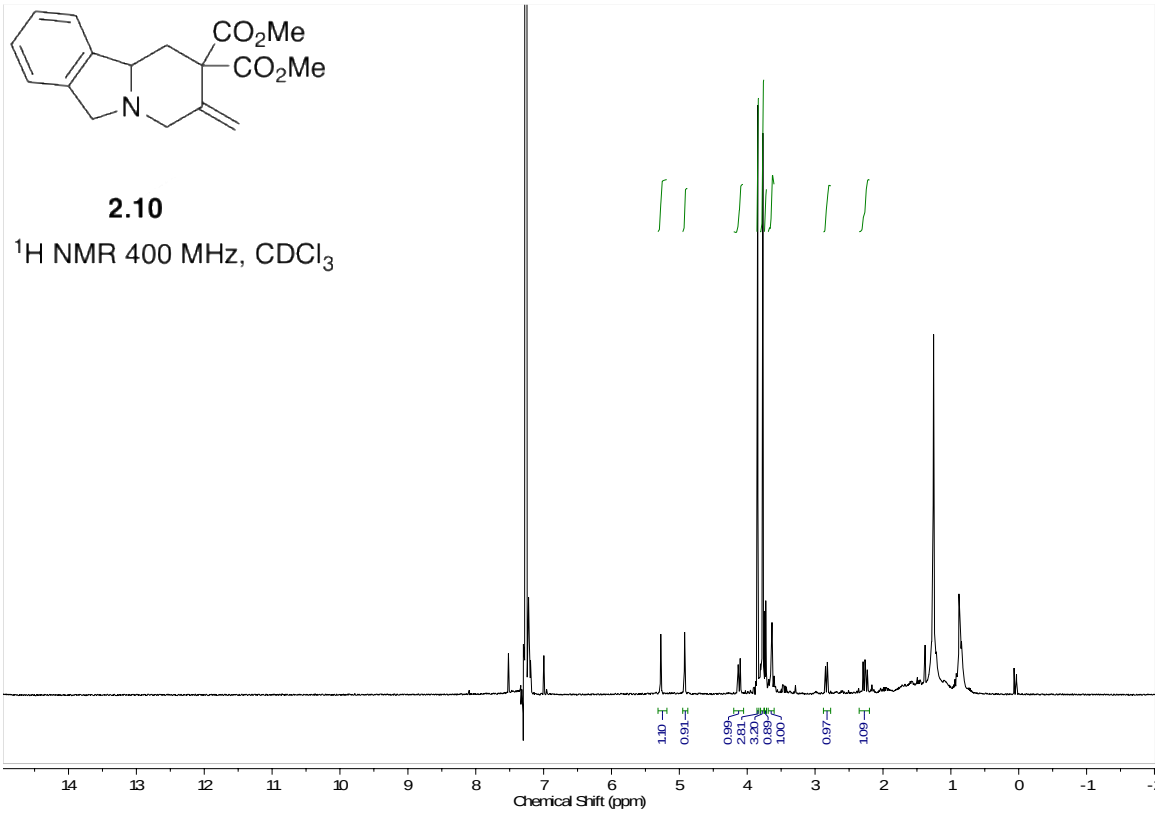

CO2Me
MeO2C
N
2.4
13C NMR 101 MHz, CDCl3
77.2 CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


MeO2C
CO2Me
HN
2.8
1H NMR 400 MHz, CDCl3
7.26 CDCl3
0.93
1.87
0.98
1.94
3.02
0.84
1.55
2.99
0.98
0.79
1.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)



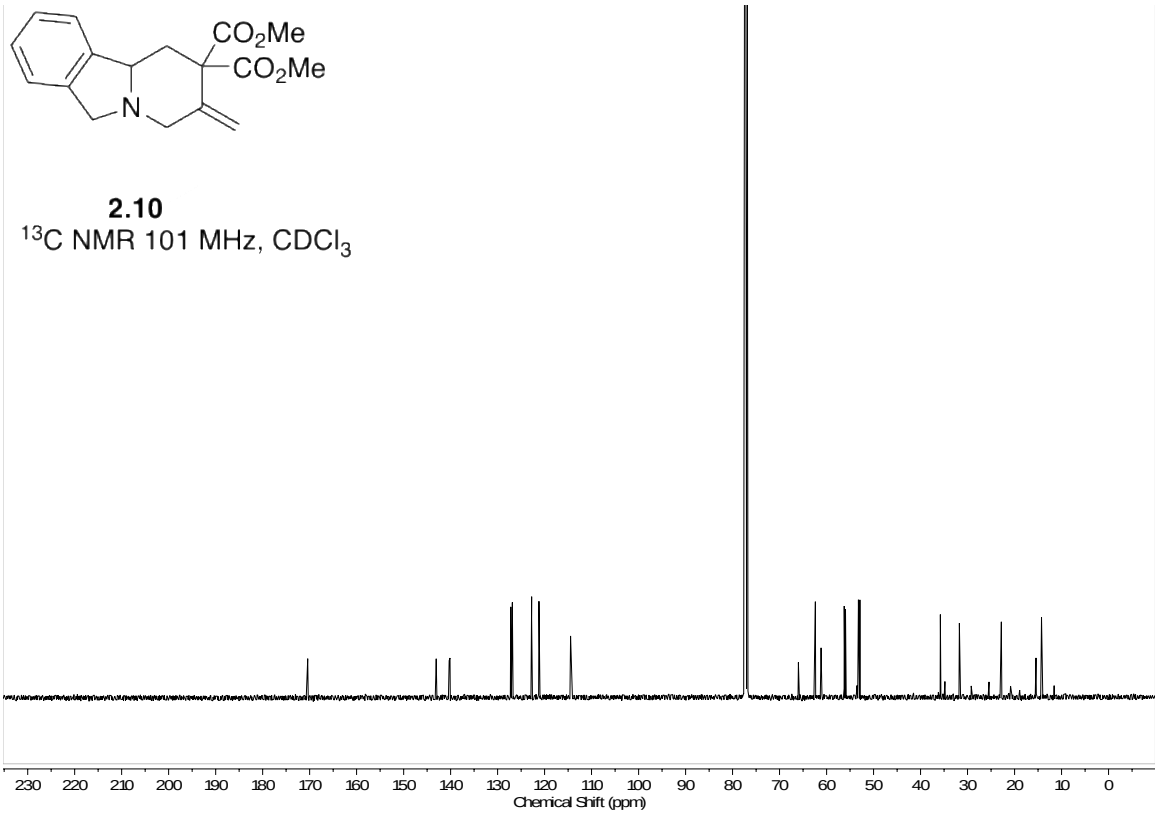
2.8

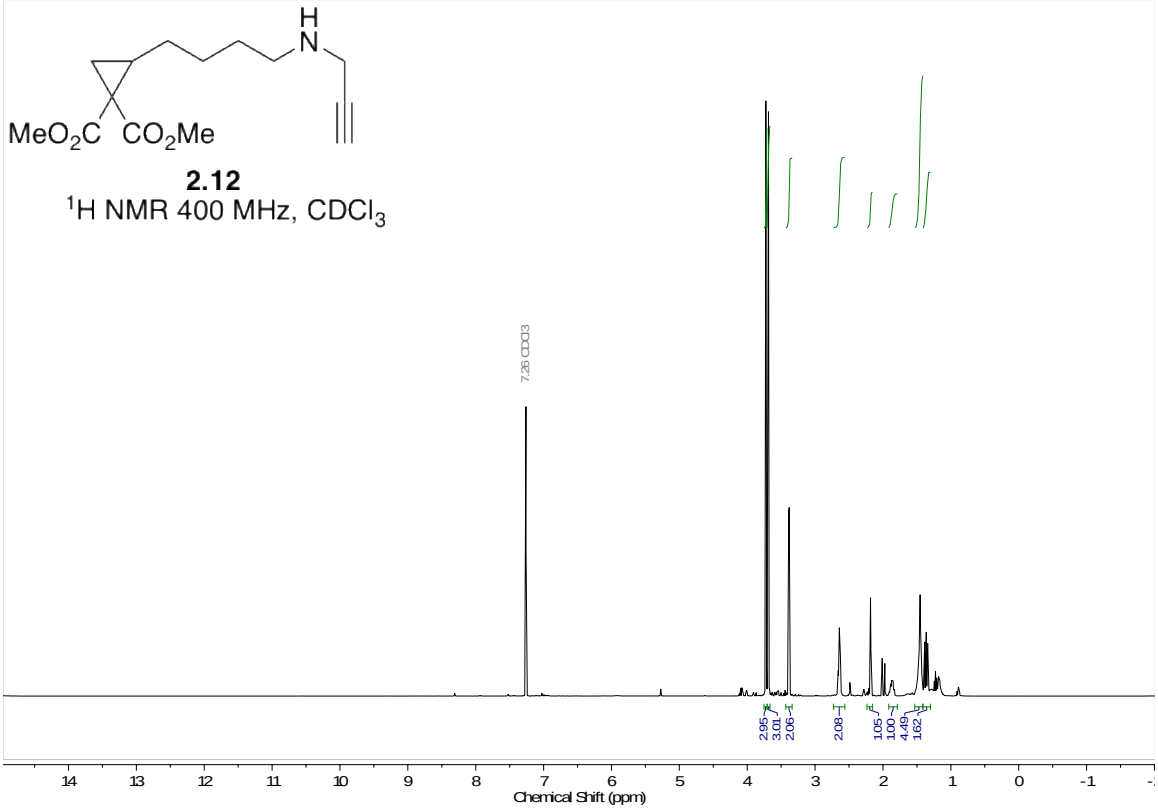
^{13}C NMR 101 MHz, $CDCl_3$

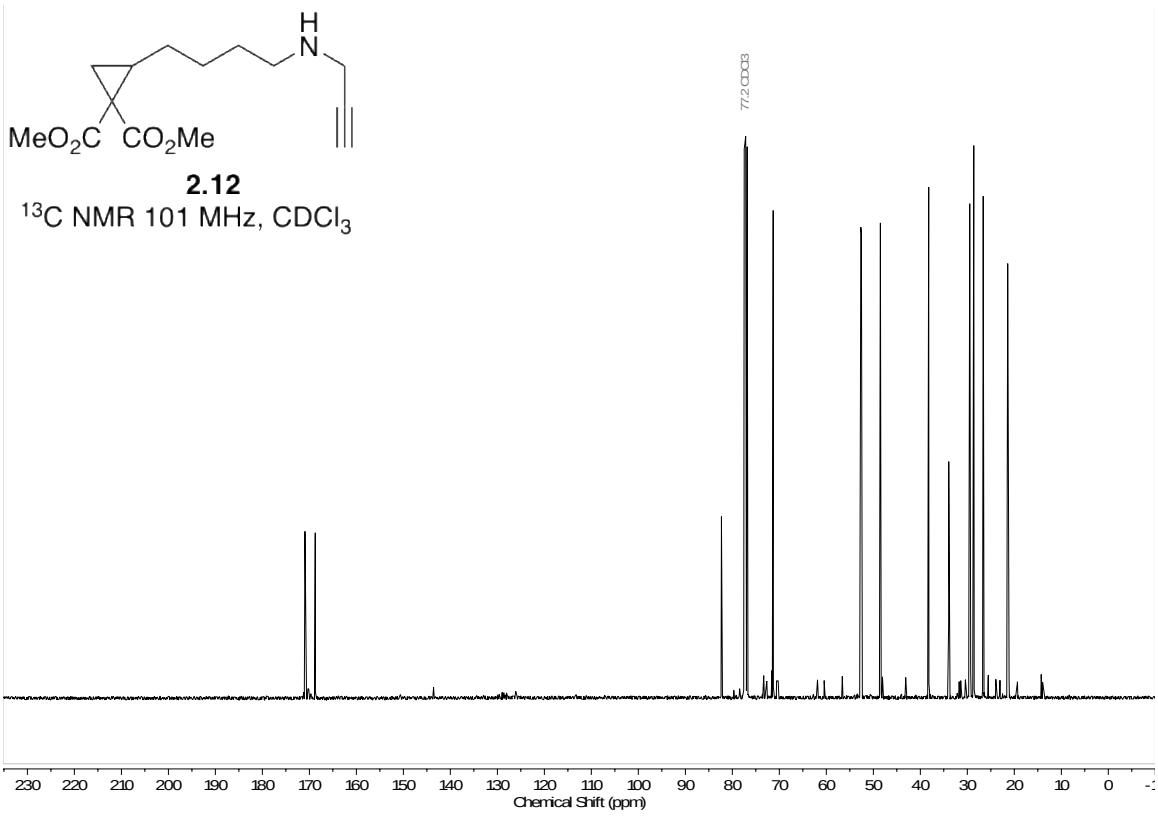


2.10

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

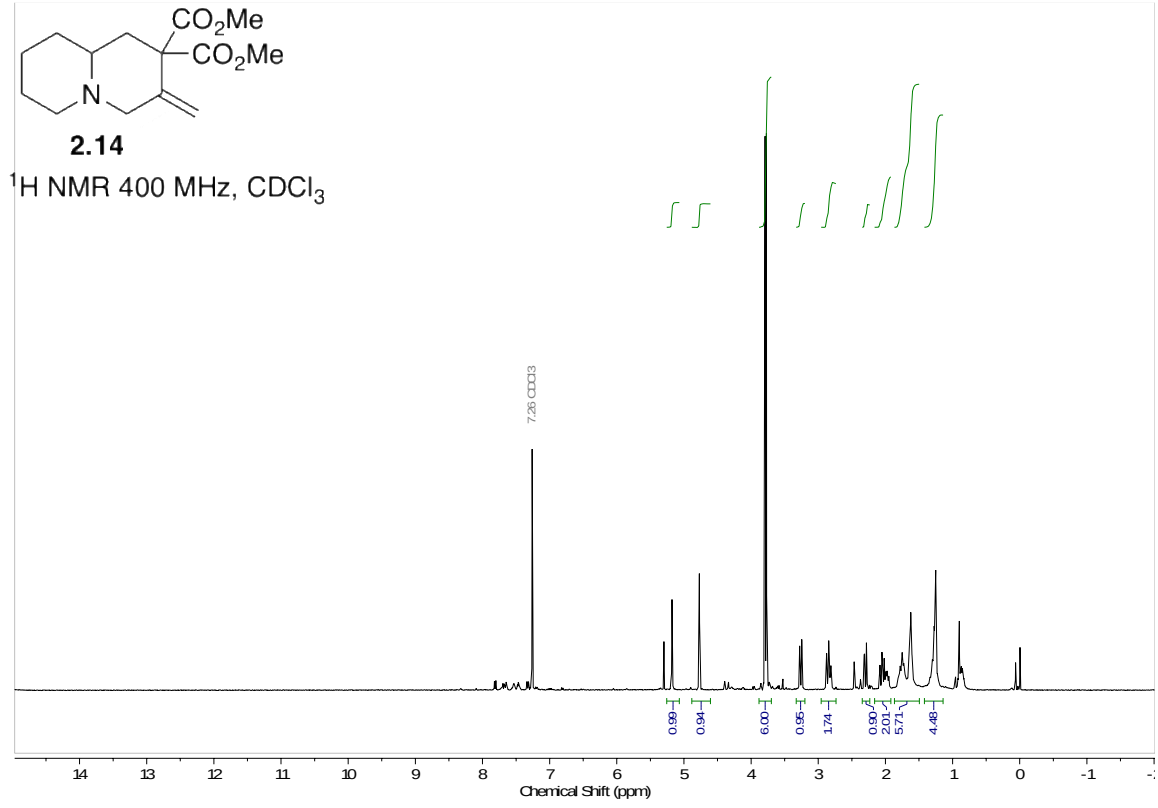

CO2Me
CO2Me
N
2.10
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)


H
N
MeO2C CO2Me
2.12
1H NMR 400 MHz, CDCl3
7.26 CDCl3
Chemical Shift (ppm)



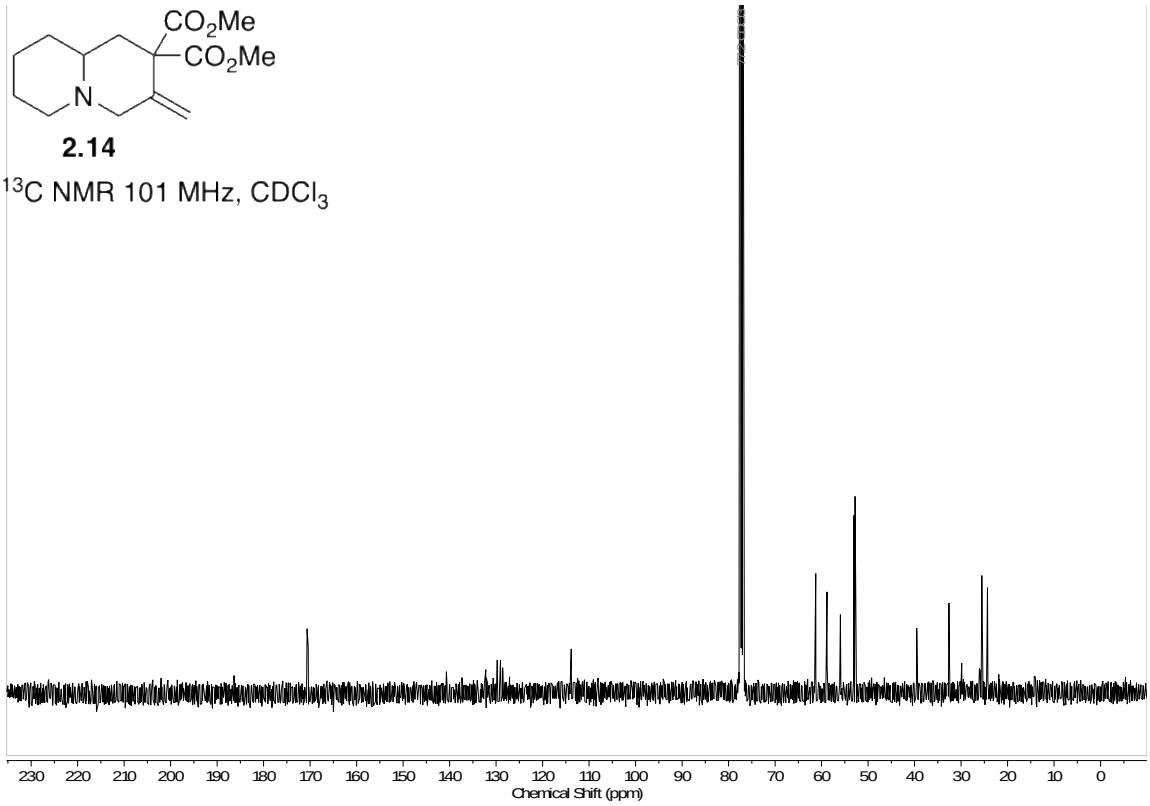
2.12

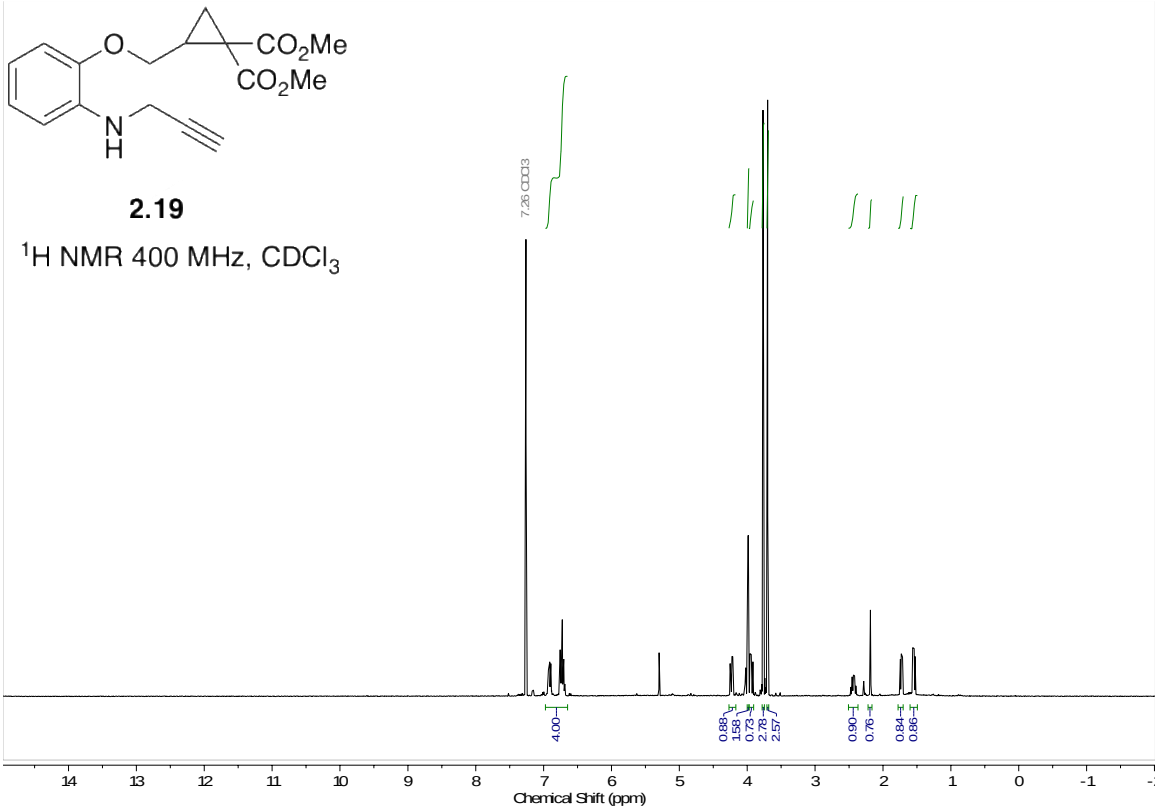
^{13}C NMR 101 MHz, $CDCl_3$

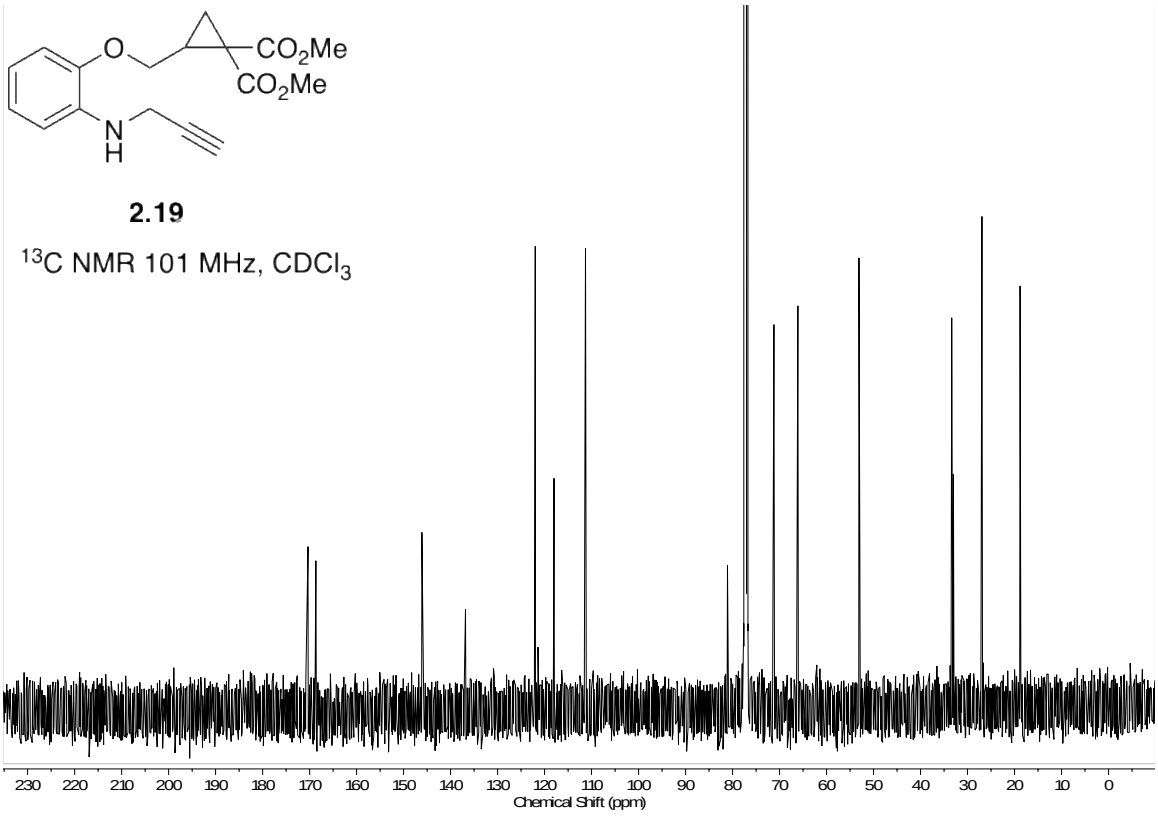


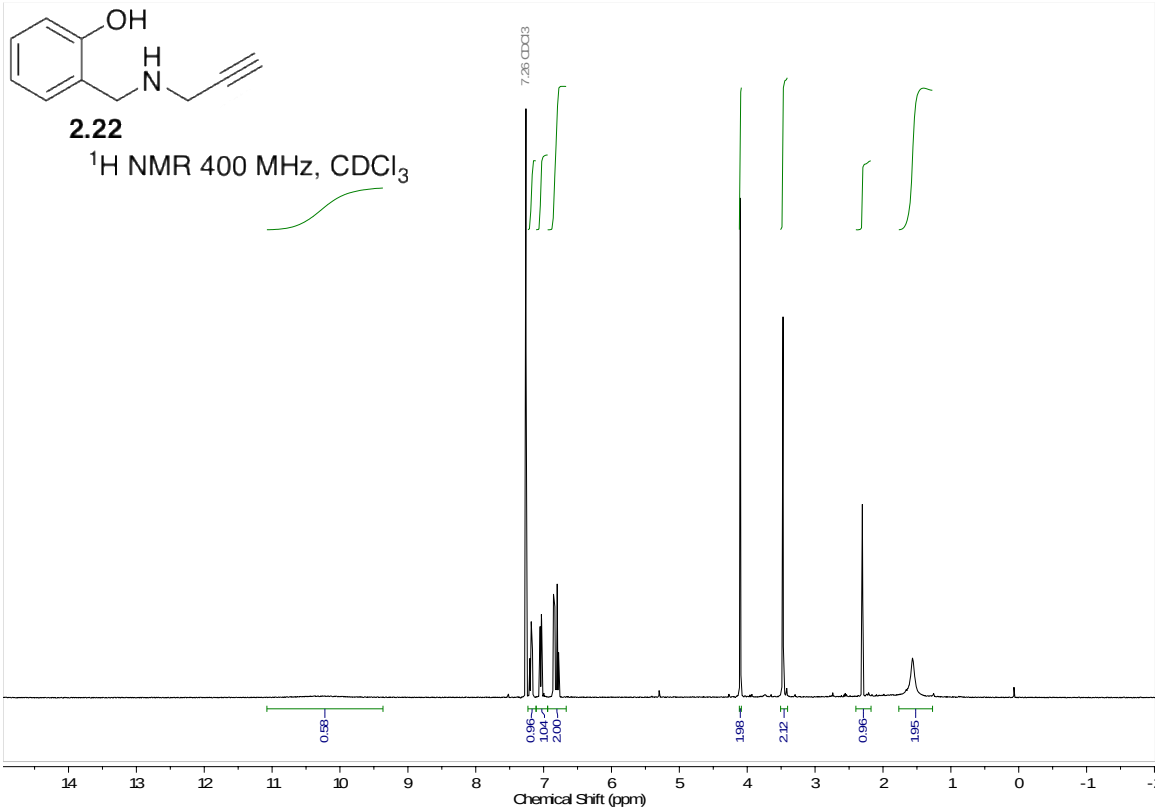
2.14

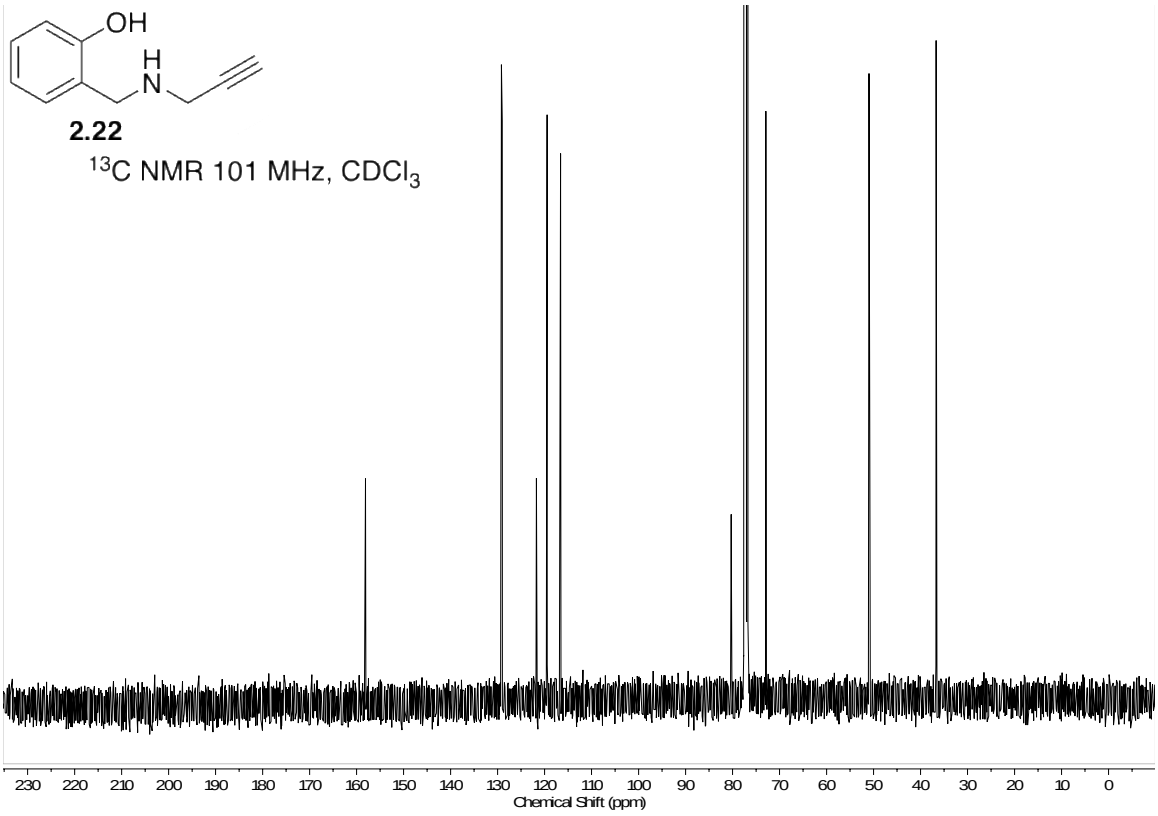
^{1}H NMR 400 MHz, $CDCl_3$

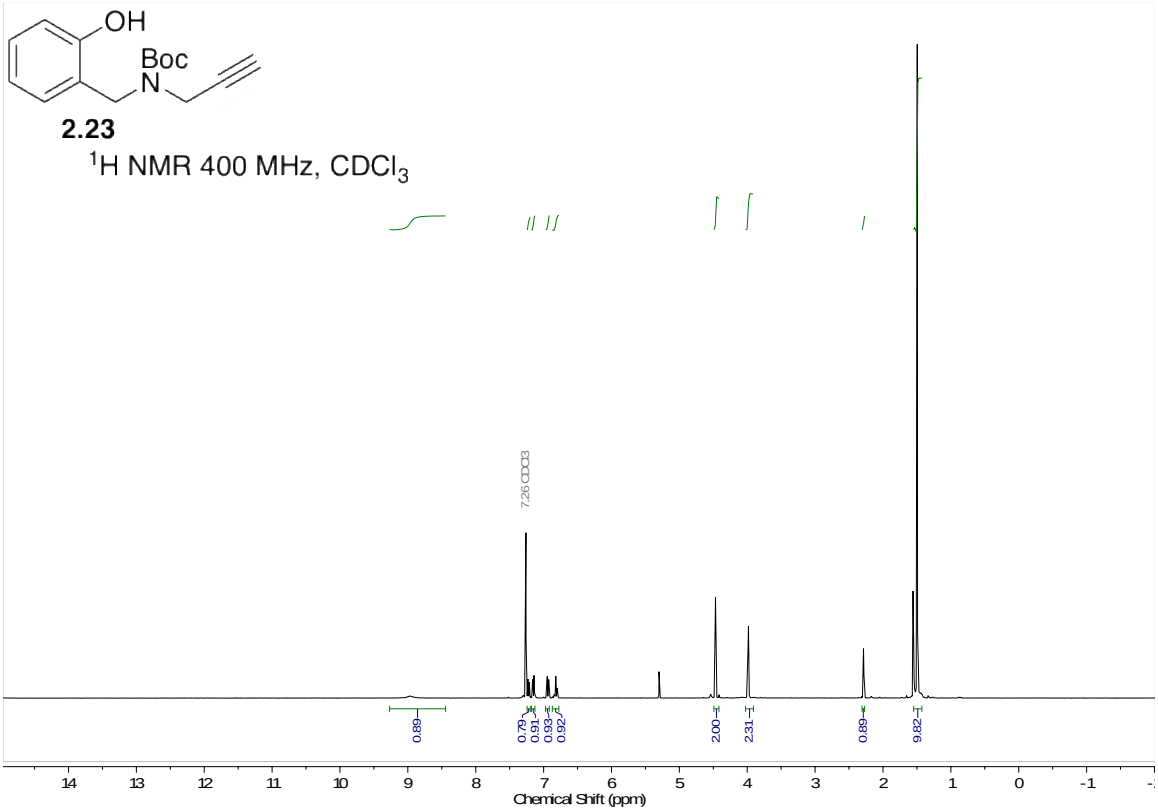

CO2Me
CO2Me
N
2.14
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

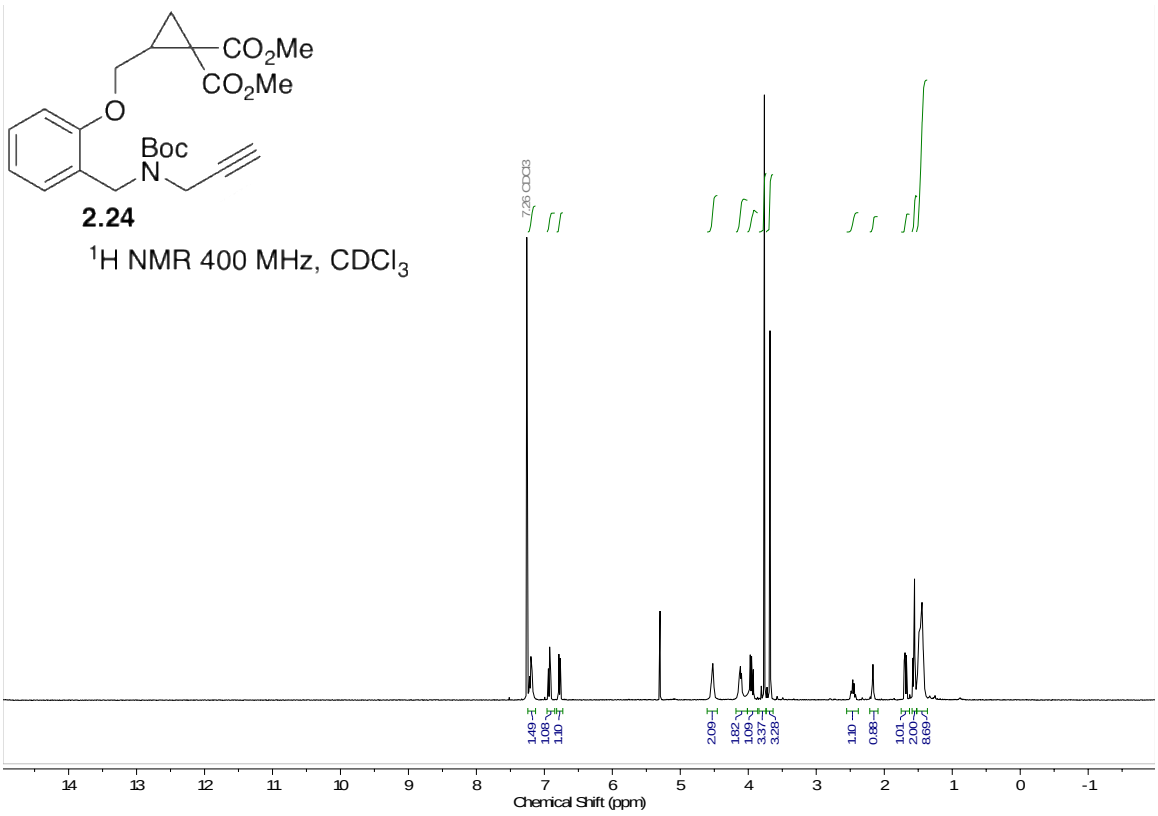

O
CO2Me
CO2Me
N
H
2.19
1H NMR 400 MHz, CDCl3
7.26 CDCl3
4.00
0.98
1.58
0.73
2.78
2.57
0.90
0.76
0.84
0.86
Chemical Shift (ppm)

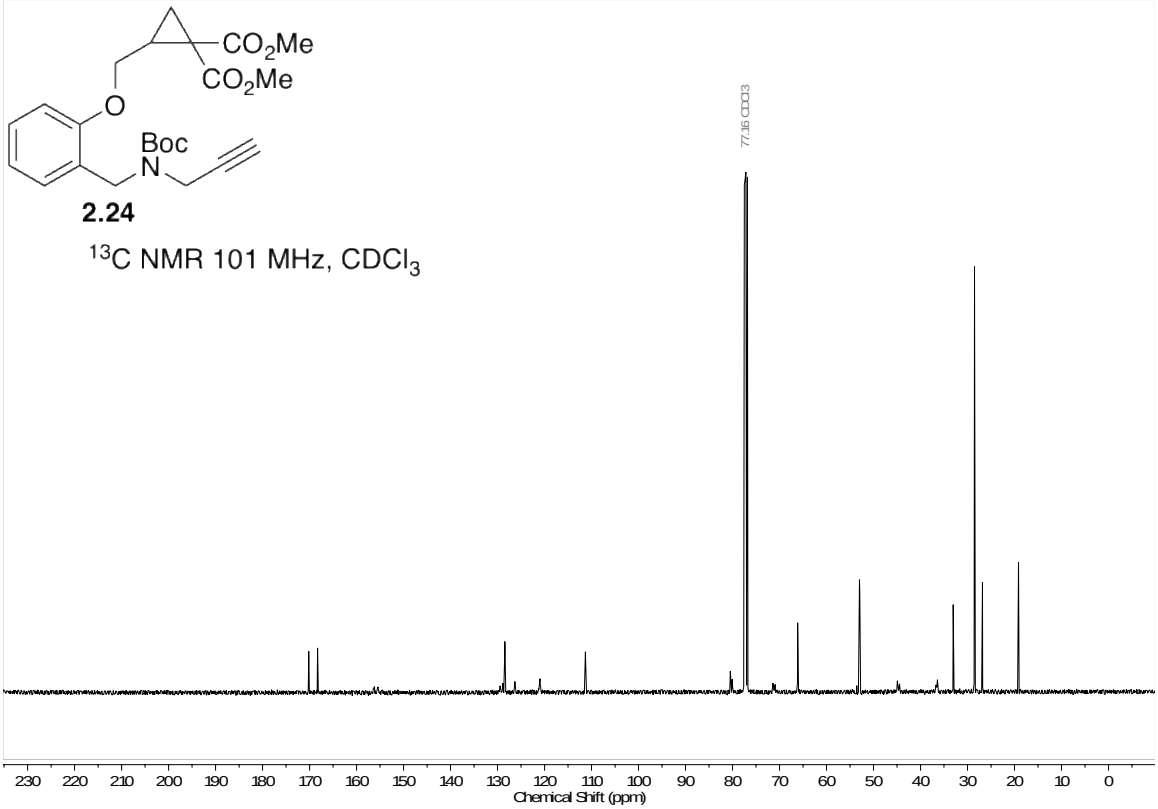

O
CO2Me
CO2Me
N
H
2.19
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

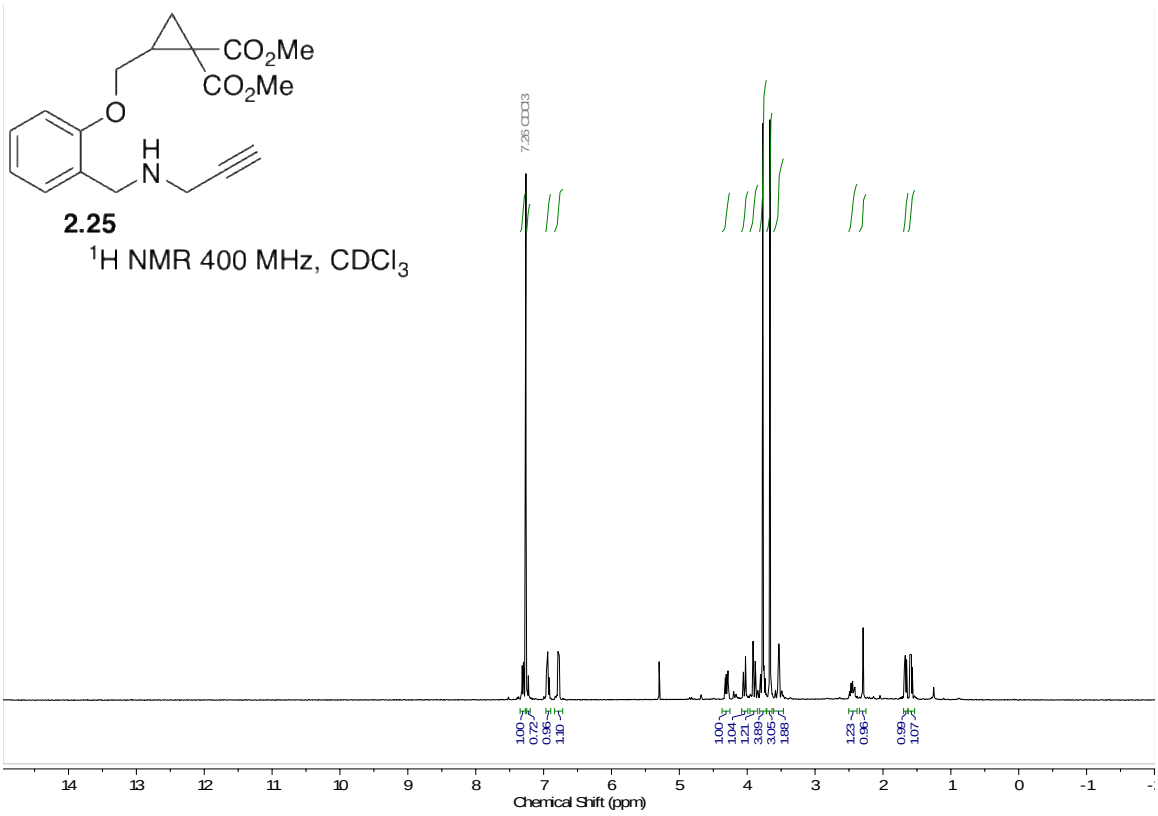

OH
H
N
2.22
1H NMR 400 MHz, CDCl3
7.26 CDCl3
0.93
0.96
1.04
2.00
1.98
2.12
0.96
1.95
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

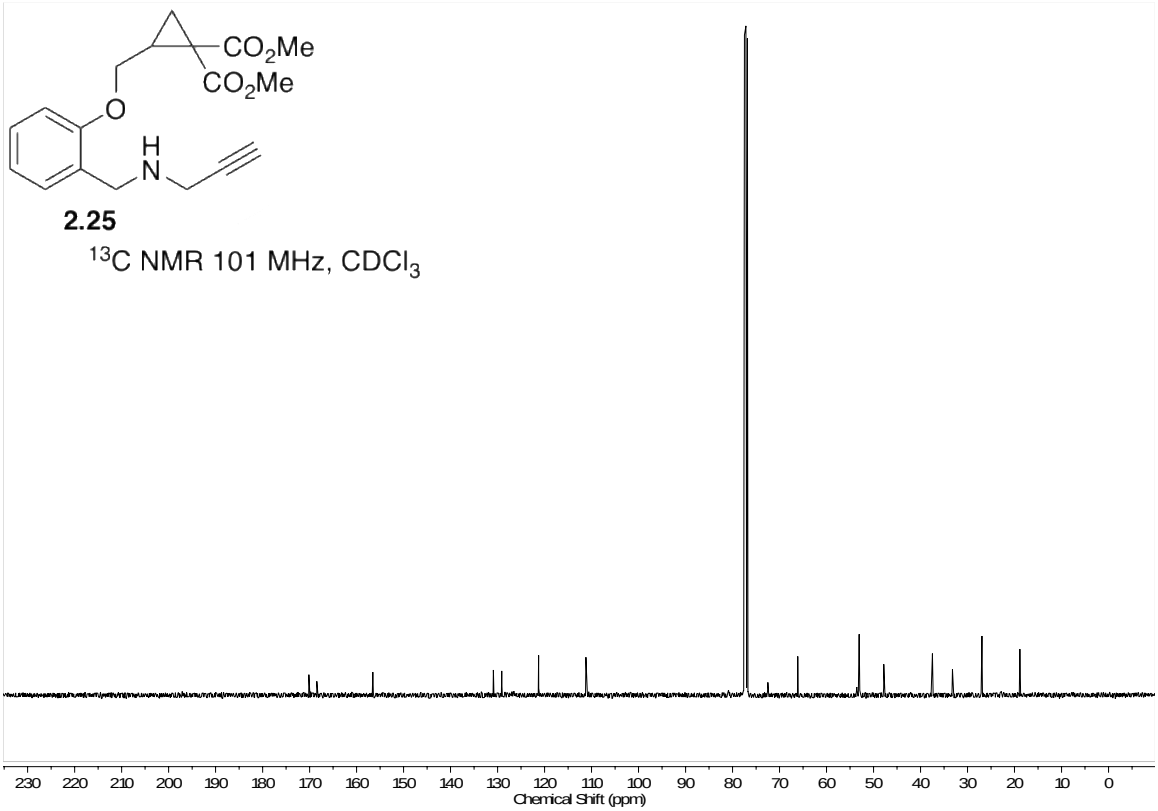

OH
H
N
2.22
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

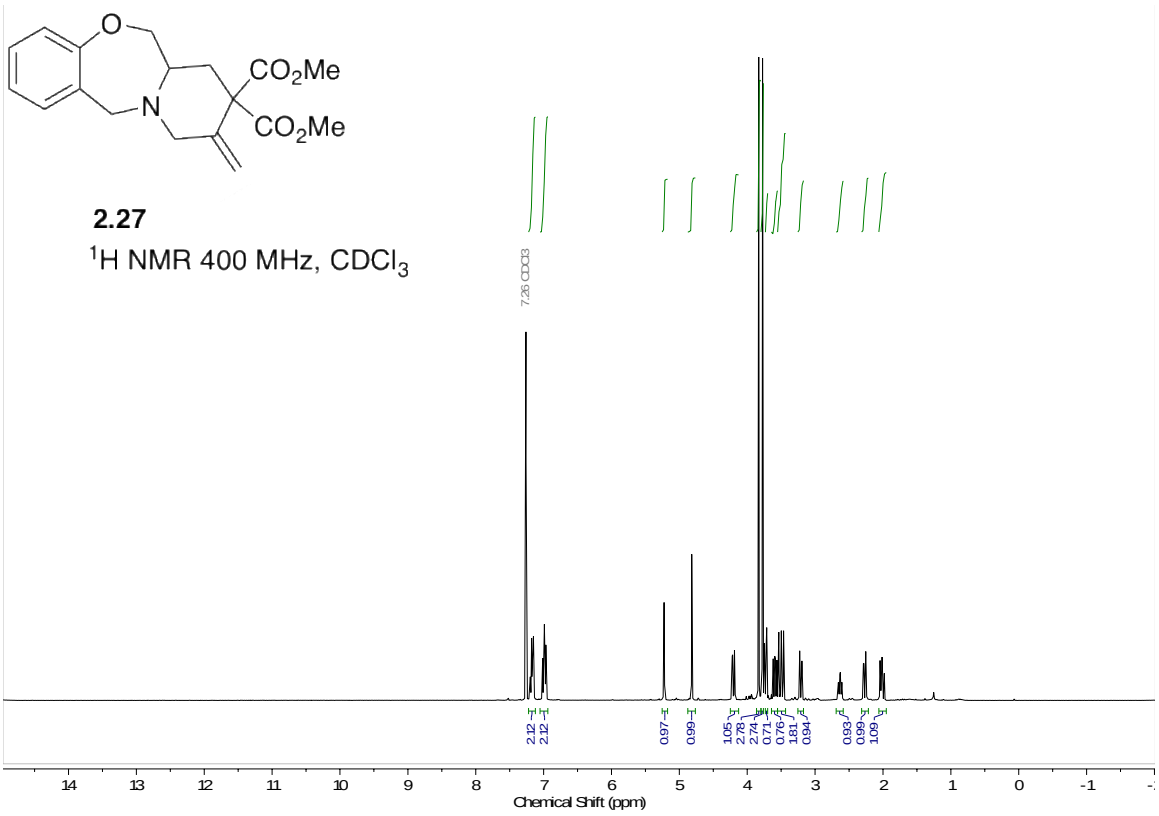

OH
Boc
N
2.23
1H NMR 400 MHz, CDCl3
7.26 CDCl3
0.89
0.79
0.91
0.93
0.92
2.00
2.31
0.89
9.82
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

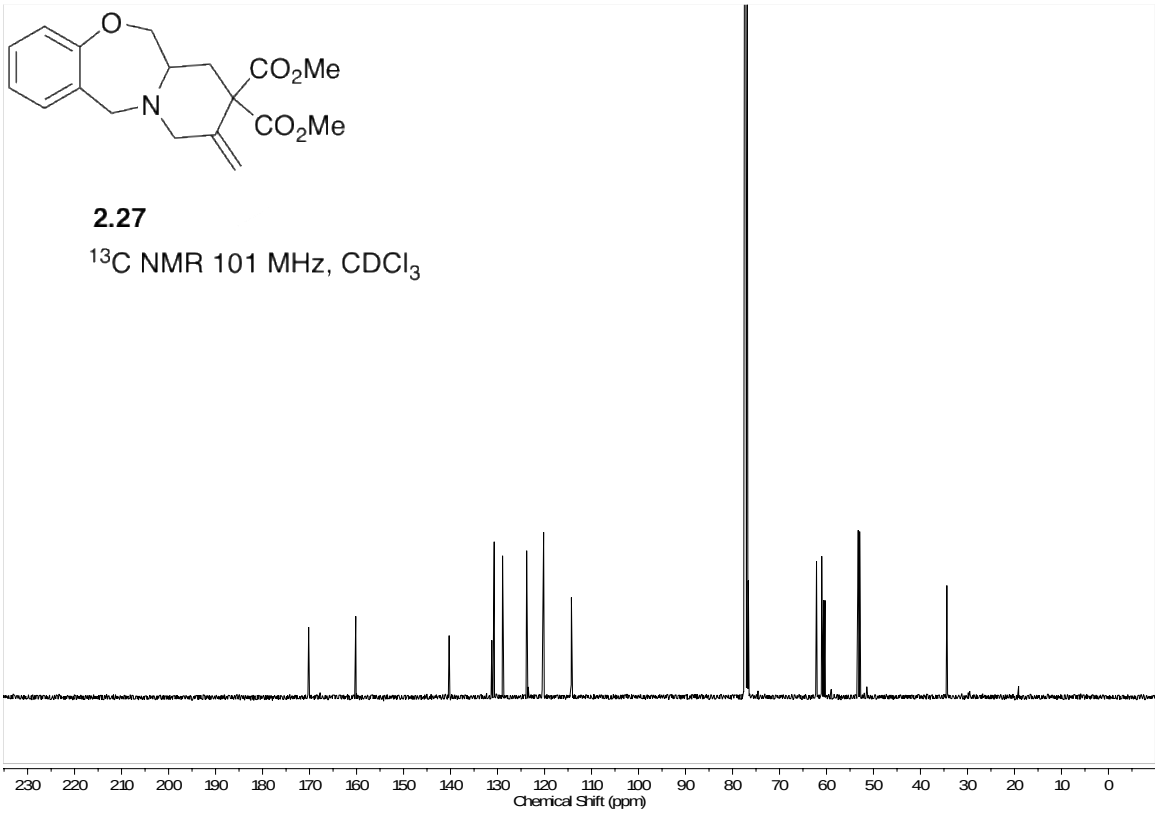

CO2Me
CO2Me
O
Boc
N
2.24
1H NMR 400 MHz, CDCl3
7.26 CDCl3
1.49
1.08
1.10
2.09
1.82
1.09
3.37
3.28
1.10
0.88
1.01
2.00
8.69
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

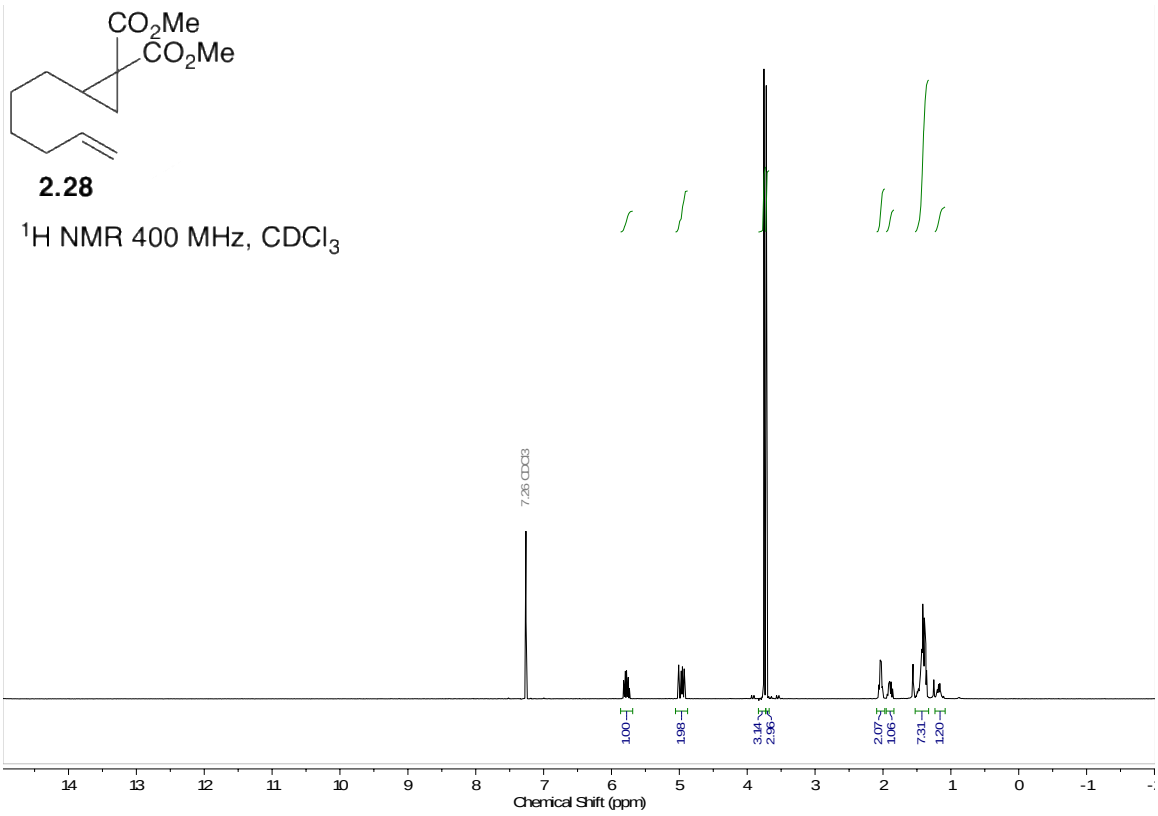

CO2Me
CO2Me
O
Boc
N
2.24
13C NMR 101 MHz, CDCl3
77.16 CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

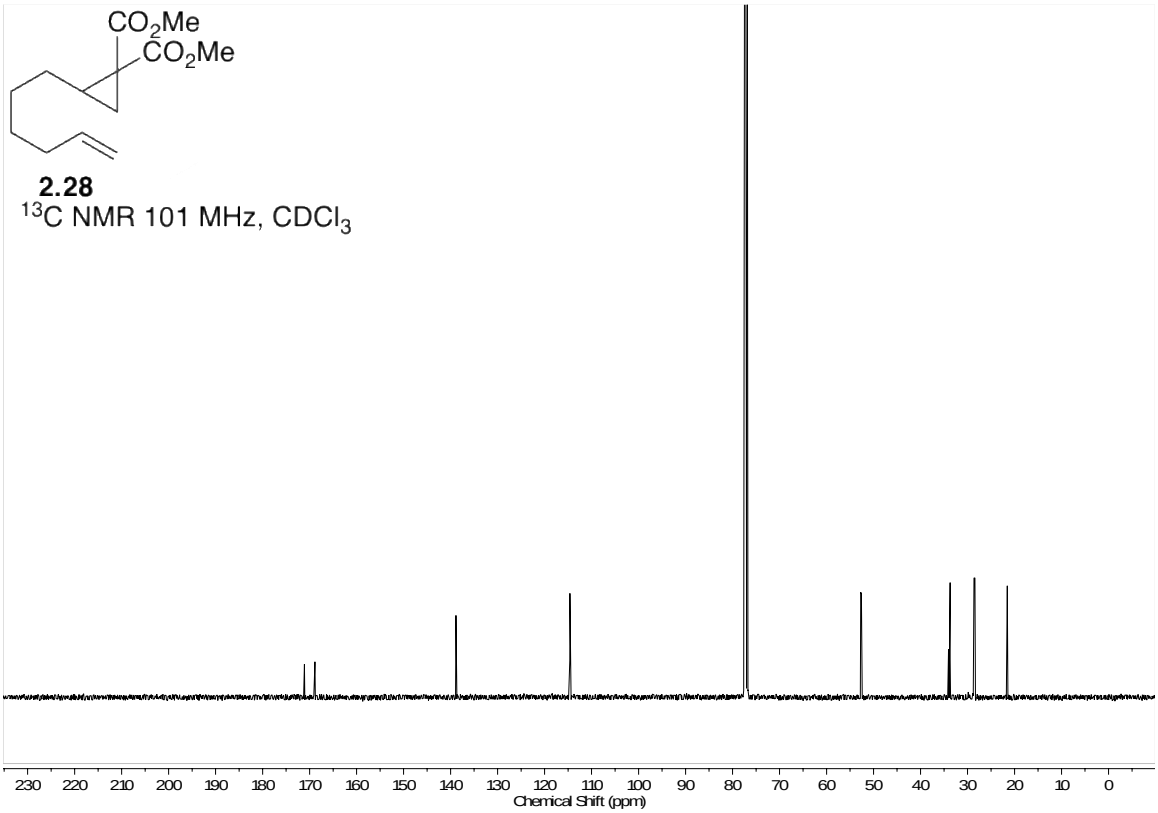

CO2Me
CO2Me
O
H
N
2.25
1H NMR 400 MHz, CDCl3
7.26 CDCl3
1.00
0.72
0.96
1.10
1.00
1.04
1.21
3.89
3.05
1.88
1.23
0.90
0.99
1.07
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

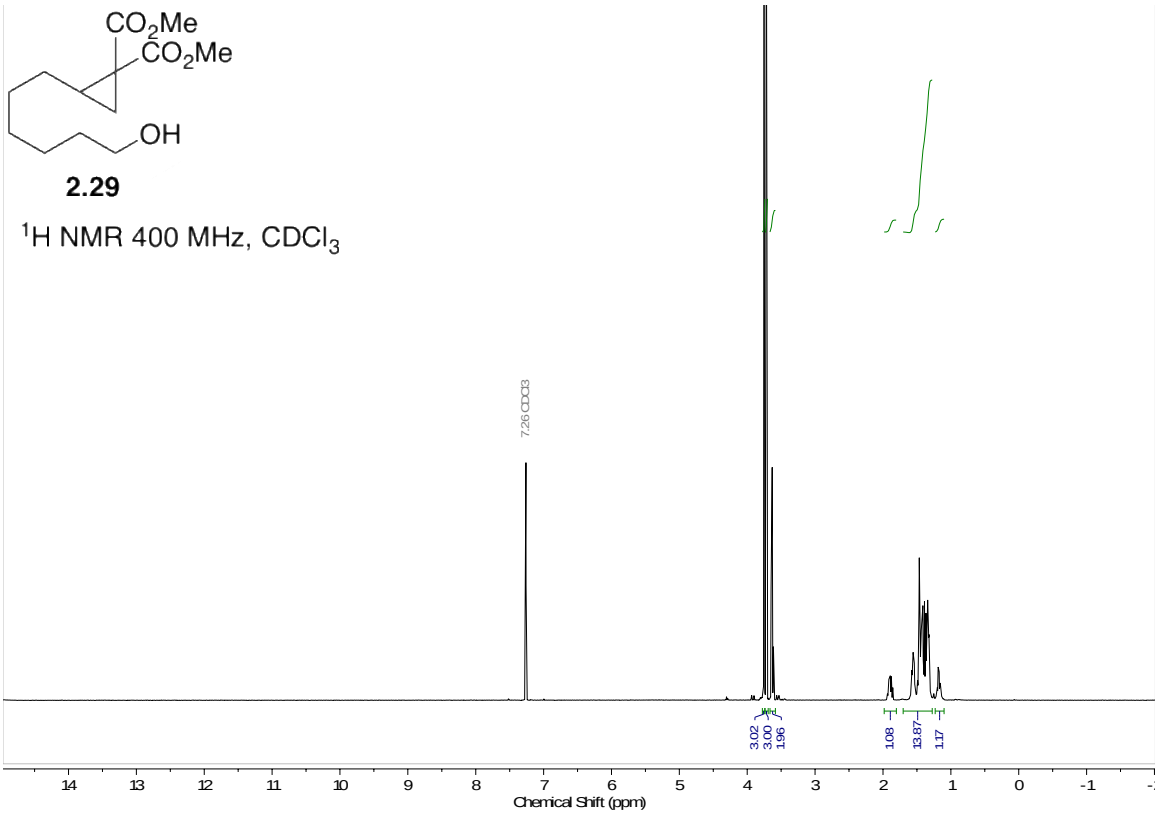

CO2Me
CO2Me
O
H
N
2.25
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

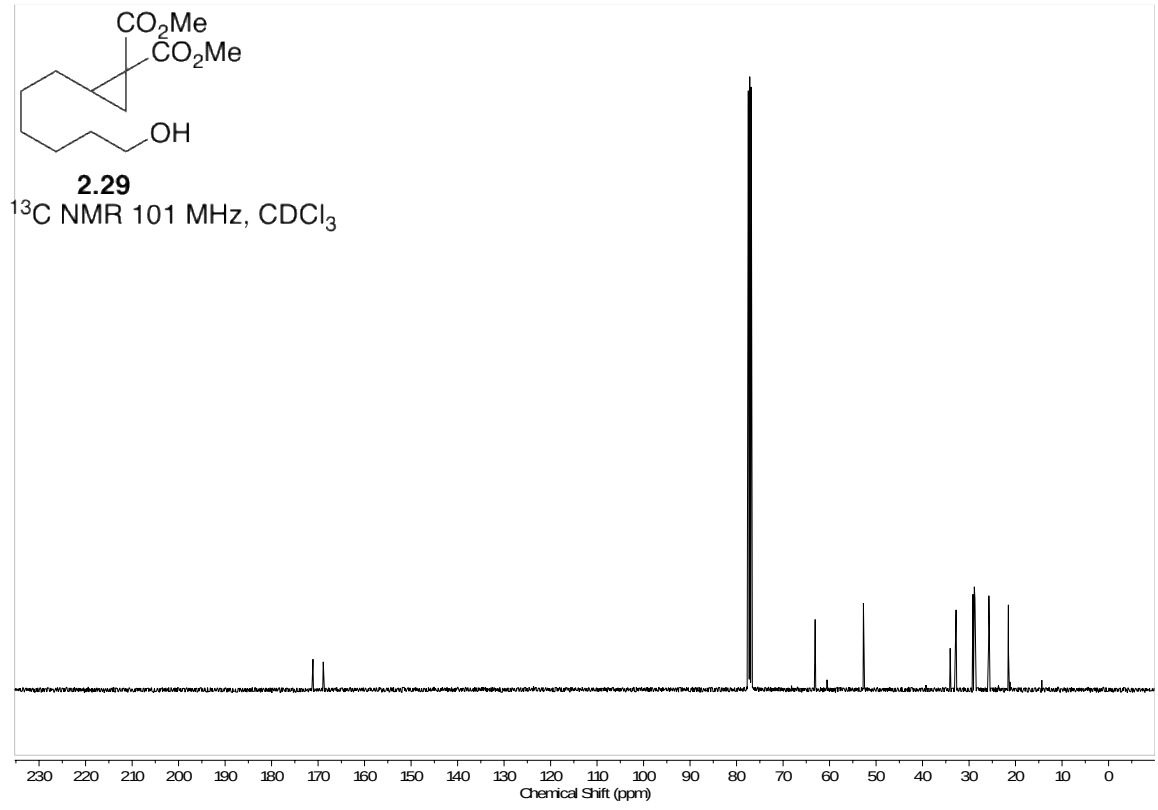

O
N
CO2Me
CO2Me
2.27
1H NMR 400 MHz, CDCl3
7.26 CDCl3
2.12
2.12
0.97
0.99
1.05
2.78
2.74
0.71
0.76
1.81
0.94
0.93
0.99
1.09
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

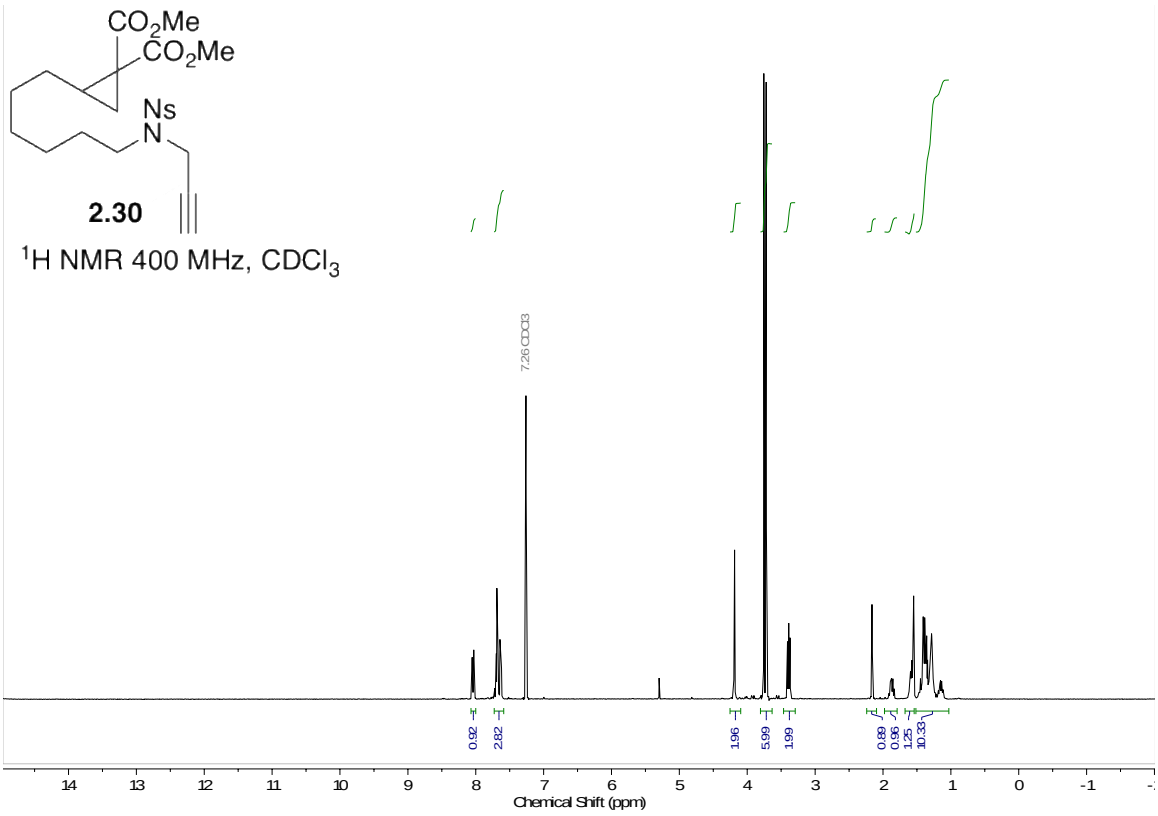

O
N
CO2Me
CO2Me
2.27
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

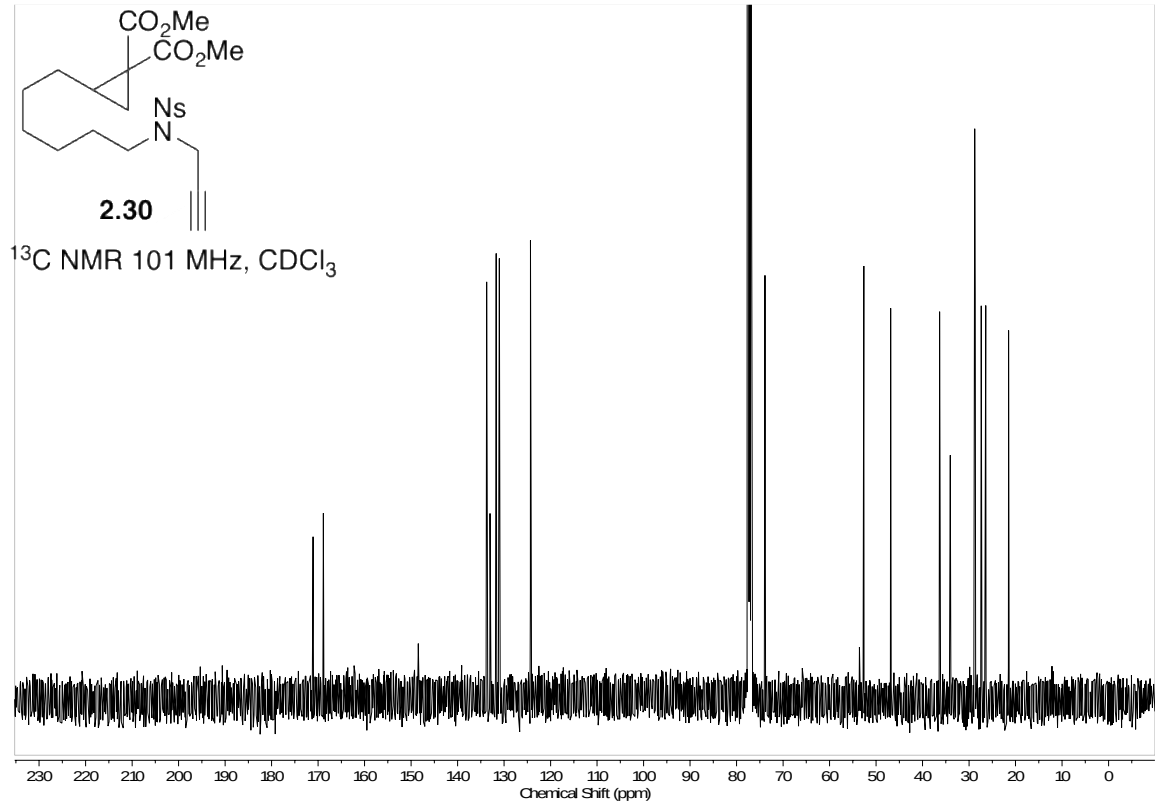

CO2Me
CO2Me
2.28
1H NMR 400 MHz, CDCl3
7.26 CDCl3
1.00
1.98
3.14
2.99
2.07
1.06
7.31
1.20
Chemical Shift (ppm)

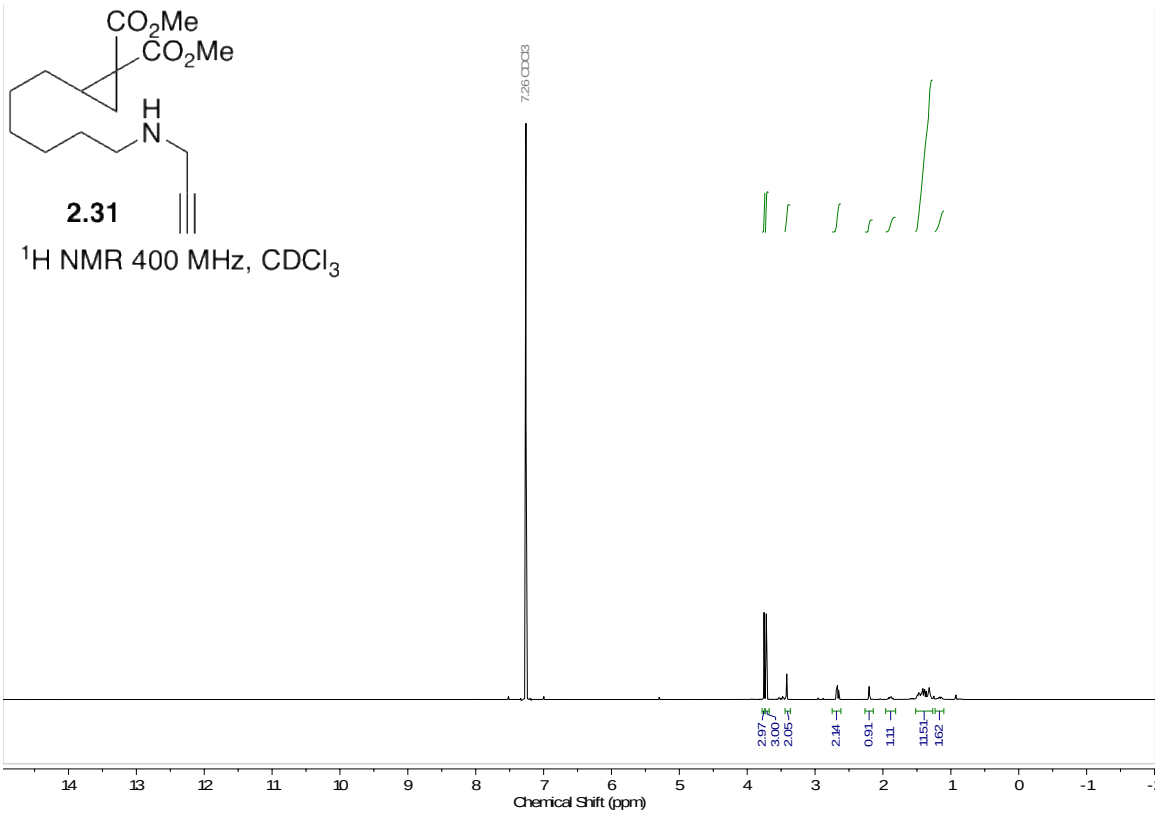

CO2Me
CO2Me
2.28
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

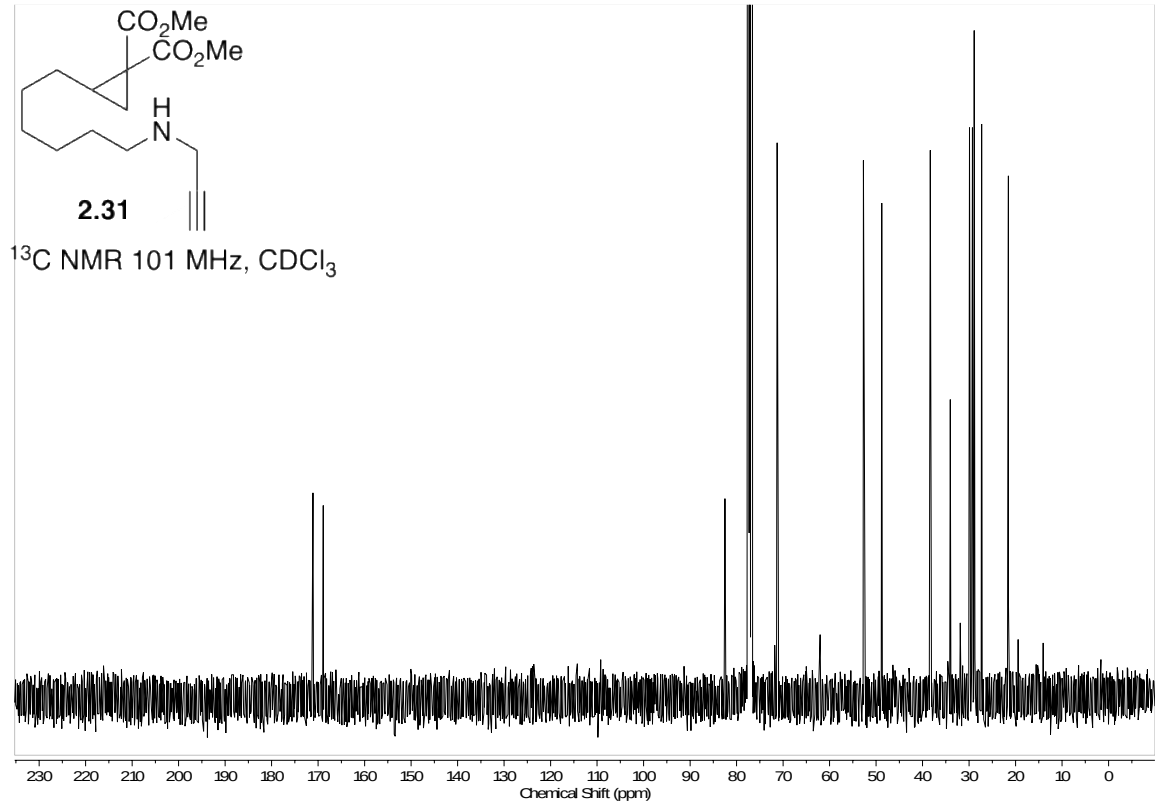

CO2Me
CO2Me
OH
2.29
1H NMR 400 MHz, CDCl3
7.26 CDCl3
3.02
3.00
1.96
1.08
13.87
1.17
Chemical Shift (ppm)

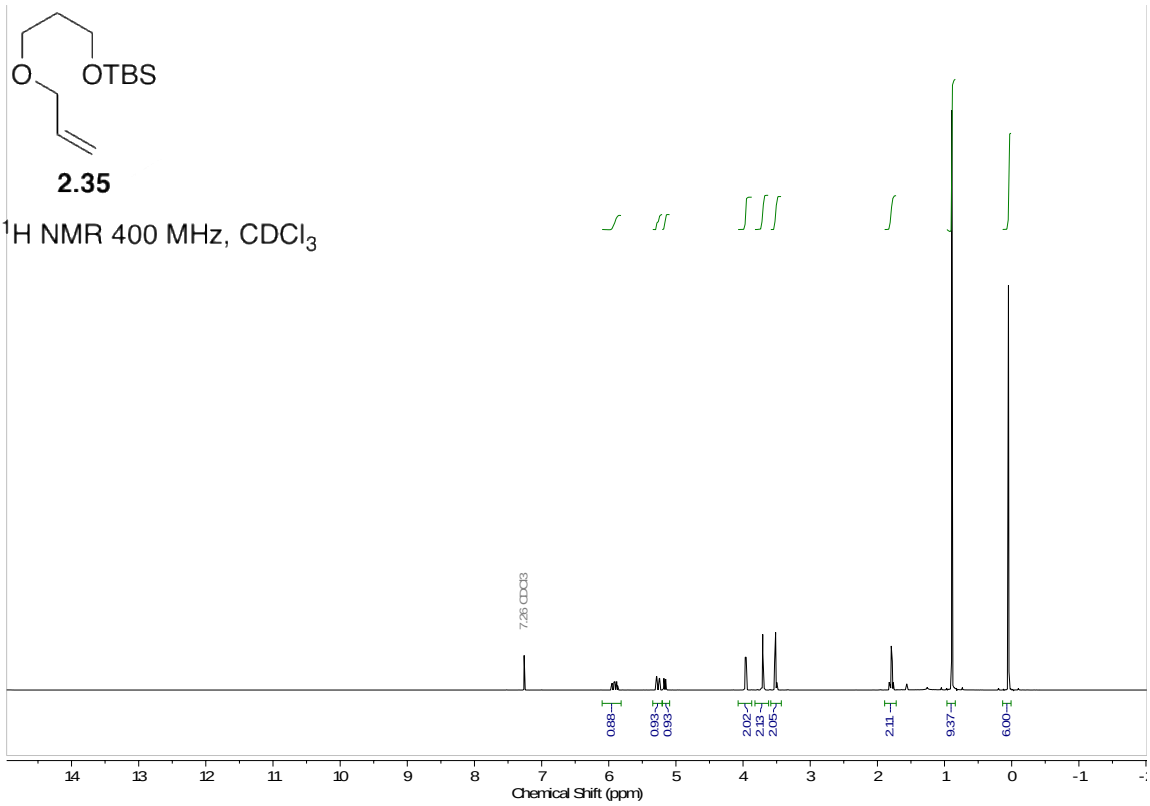

CO2Me
CO2Me
OH
2.29
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

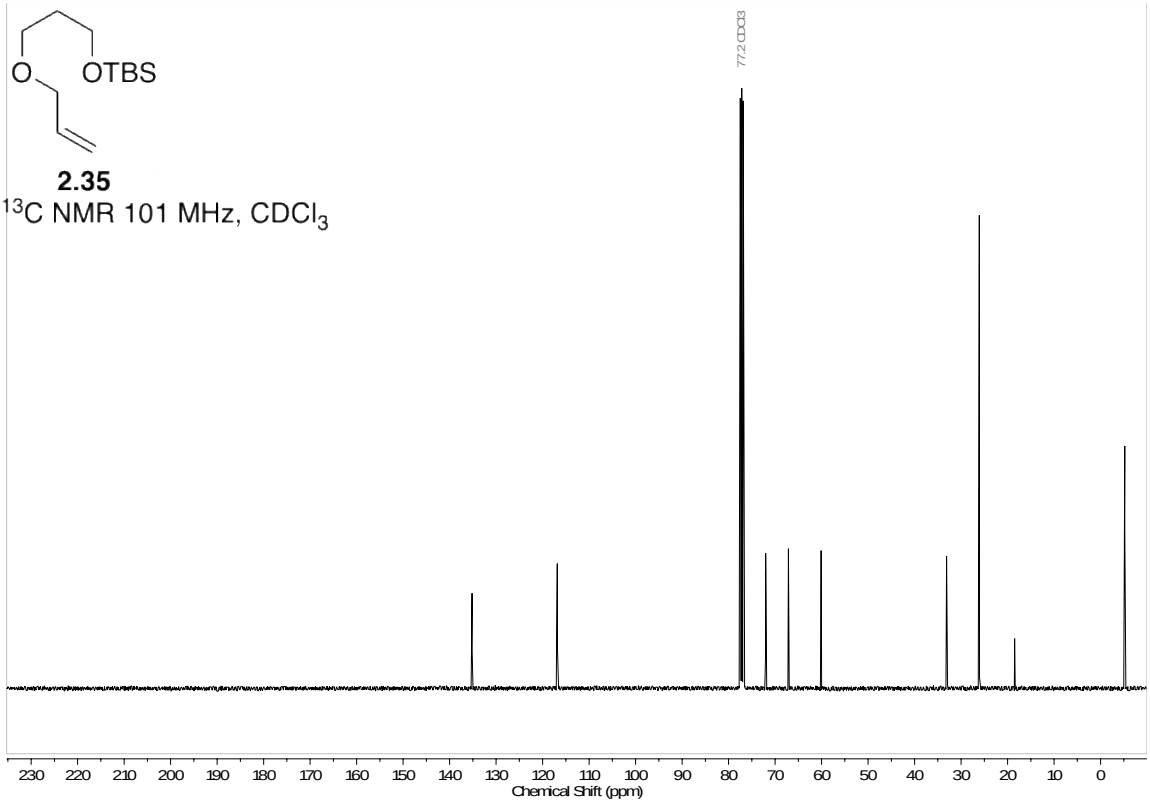

CO2Me
CO2Me
Ns
N
2.30
1H NMR 400 MHz, CDCl3
7.26 CDCl3
0.92
2.82
1.96
5.99
1.99
0.89
0.96
1.25
10.33
Chemical Shift (ppm)

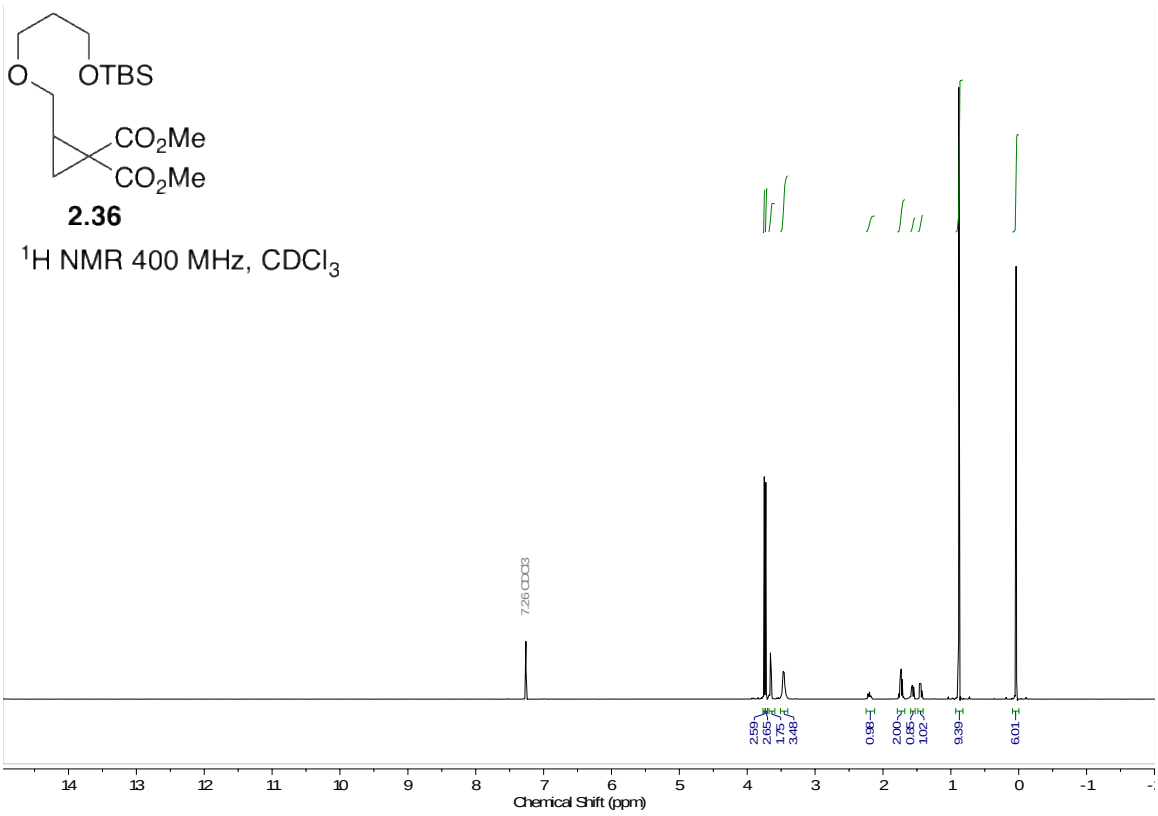

CO2Me
CO2Me
Ns
N
2.30
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

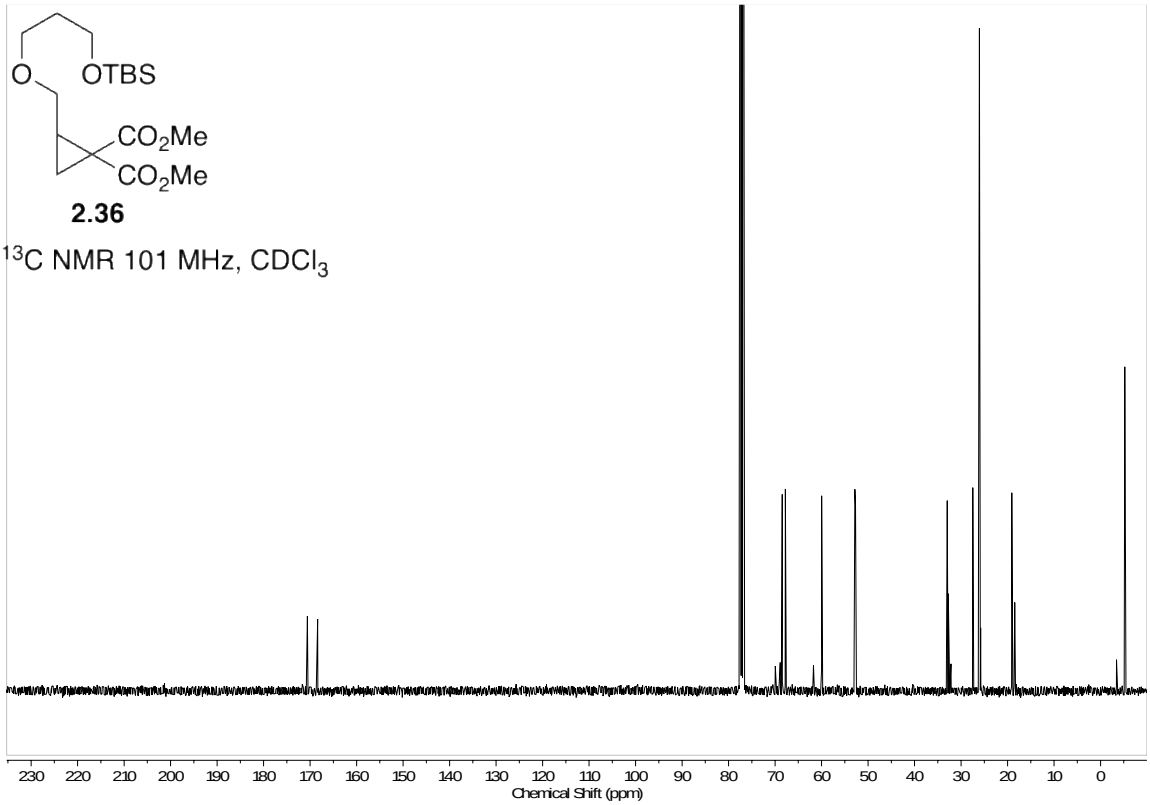

CO2Me
CO2Me
H
N
2.31
1H NMR 400 MHz, CDCl3
7.26 CDCl3
2.97
3.00
2.05
2.14
0.91
1.11
1.51
1.62
Chemical Shift (ppm)

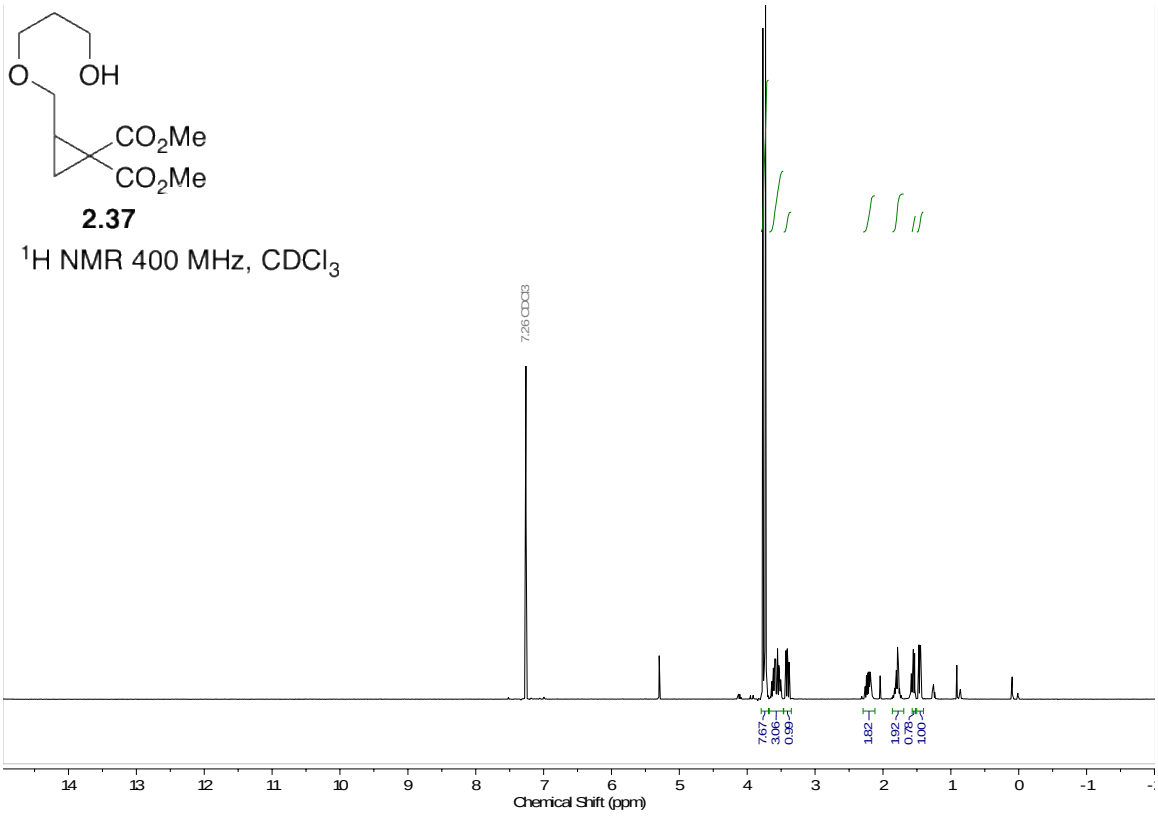

CO2Me
CO2Me
H
N
2.31
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

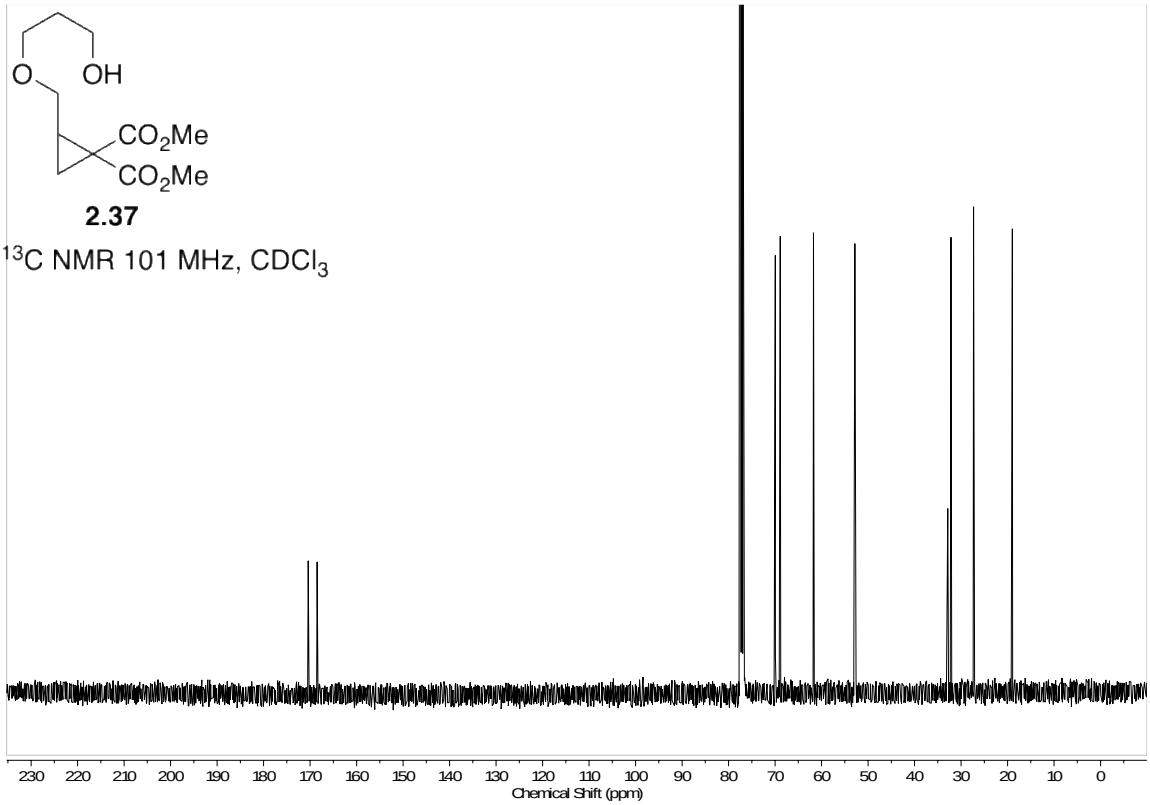

O
OTBS
2.35
1H NMR 400 MHz, CDCl3
7.26 CDCl3
0.88
0.93
0.93
2.02
2.13
2.05
2.11
9.37
6.00
Chemical Shift (ppm)

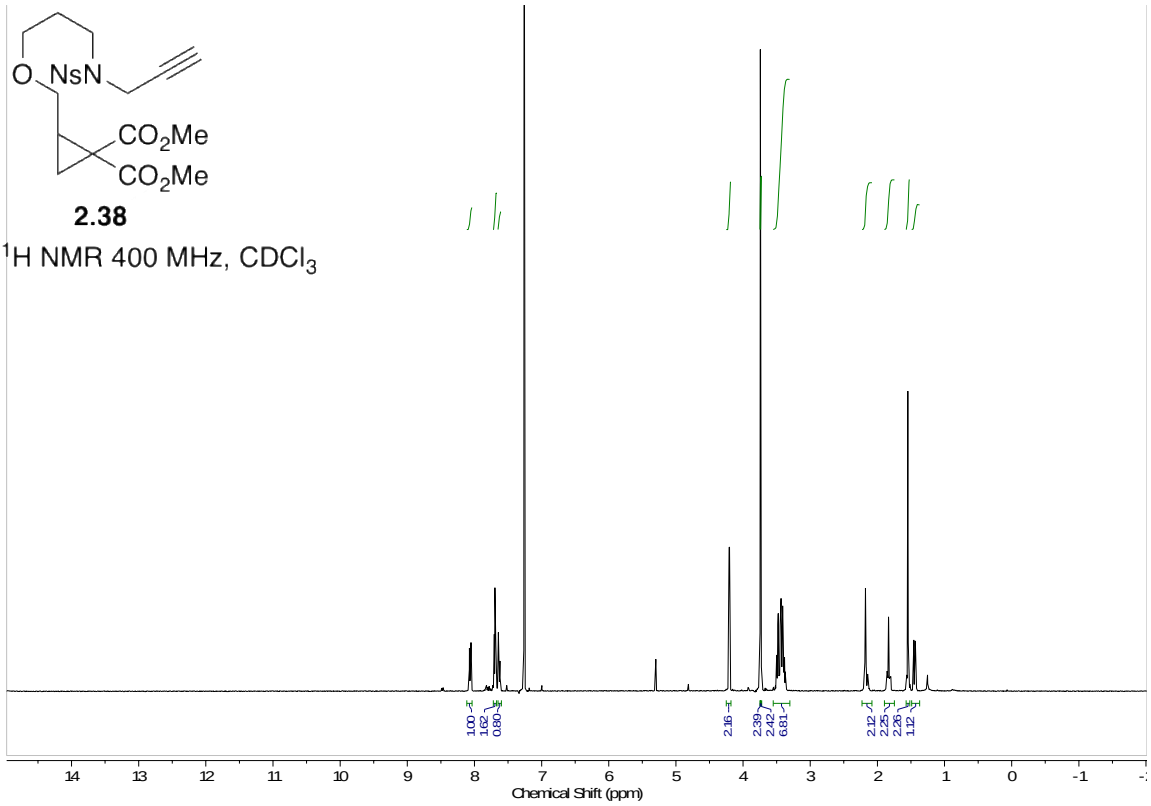

O
OTBS
2.35
13C NMR 101 MHz, CDCl3
77.2 CDCl3
Chemical Shift (ppm)

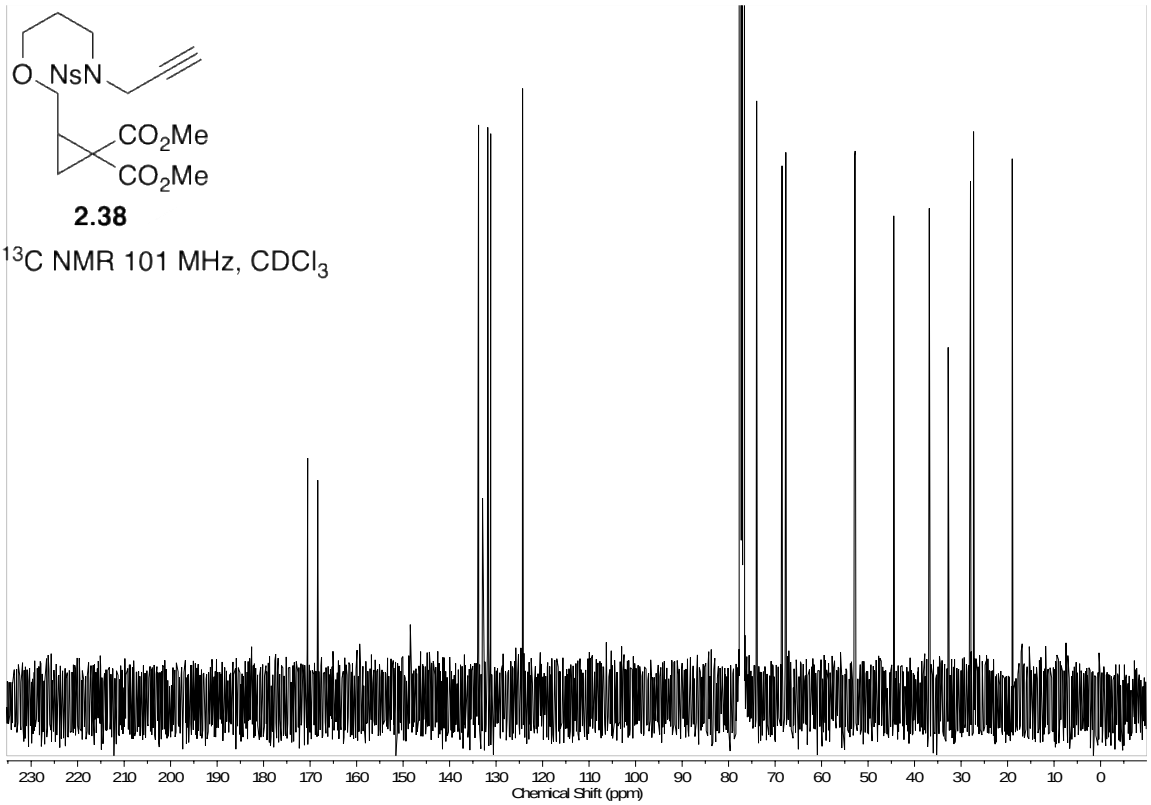

O
OTBS
CO2Me
CO2Me
2.36
1H NMR 400 MHz, CDCl3
7.26 CDCl3
2.59
2.65
1.75
3.48
0.98
2.00
0.85
1.02
9.39
6.01
Chemical Shift (ppm)

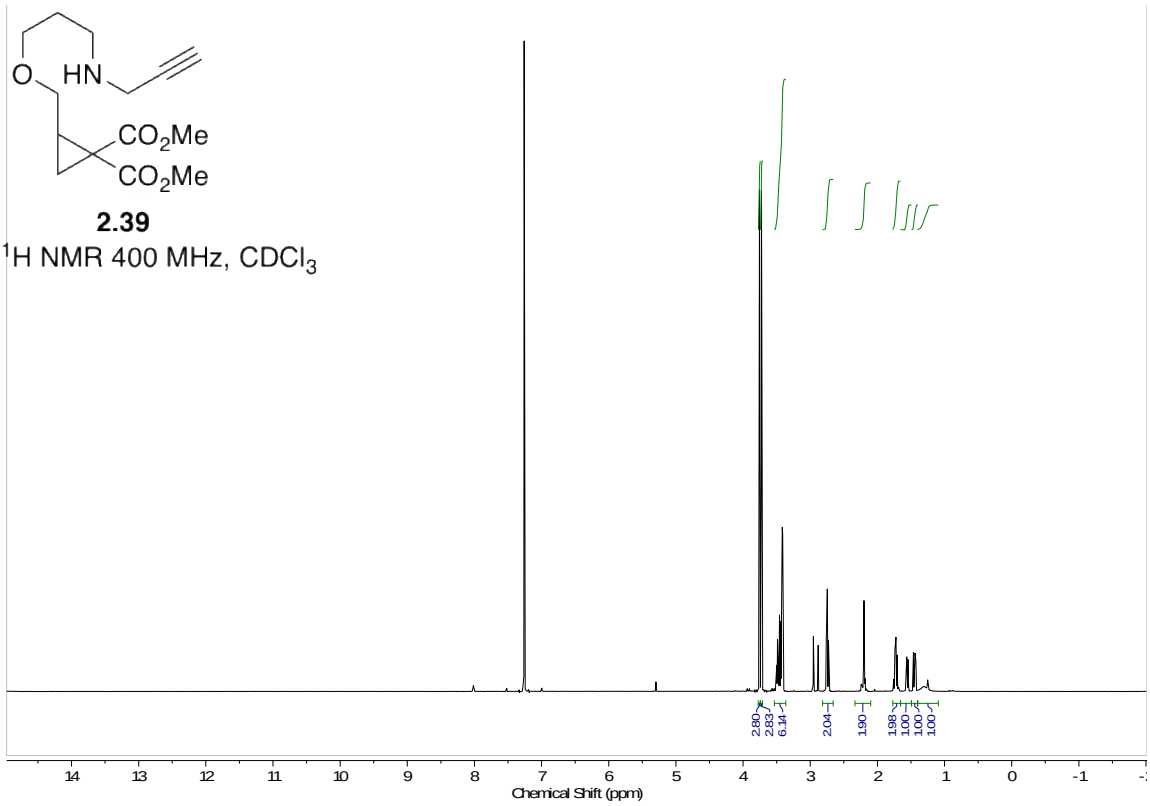

O
OTBS
CO2Me
CO2Me
2.36
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

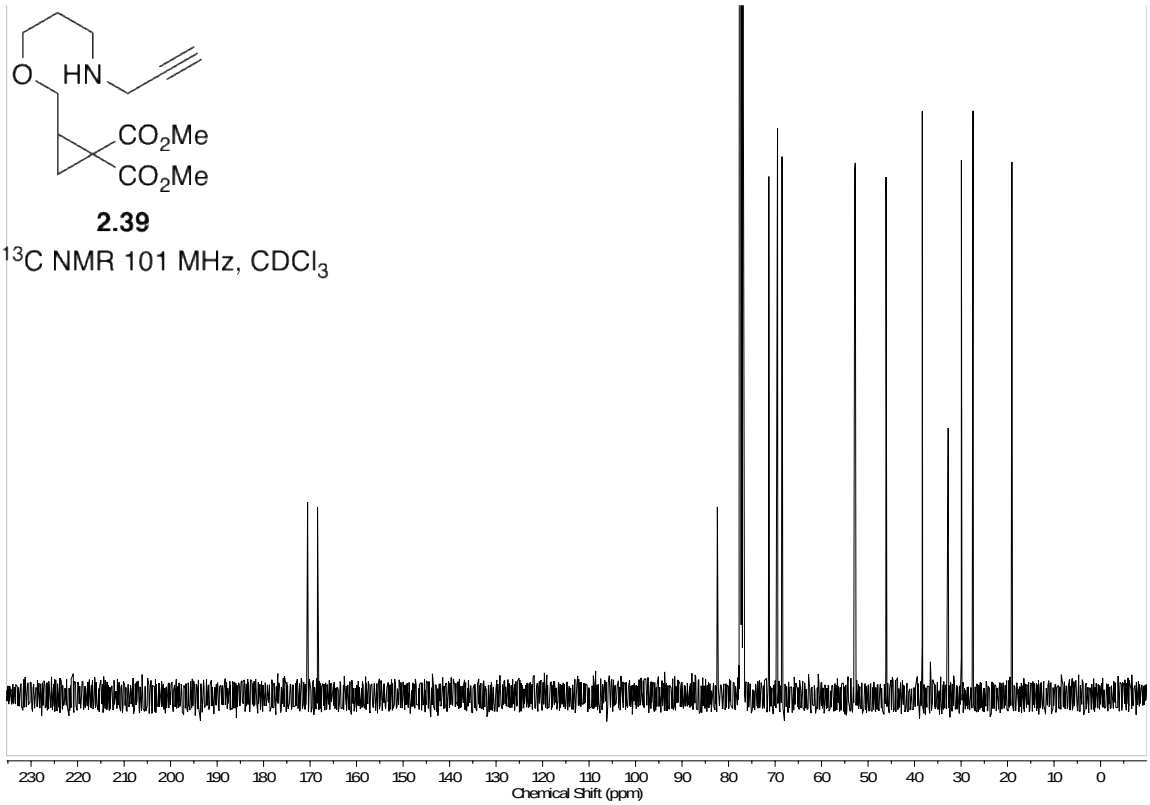

O
OH
CO2Me
CO2Me
2.37
1H NMR 400 MHz, CDCl3
7.26 CDCl3
7.67
3.06
0.99
1.82
1.92
0.78
1.00
Chemical Shift (ppm)

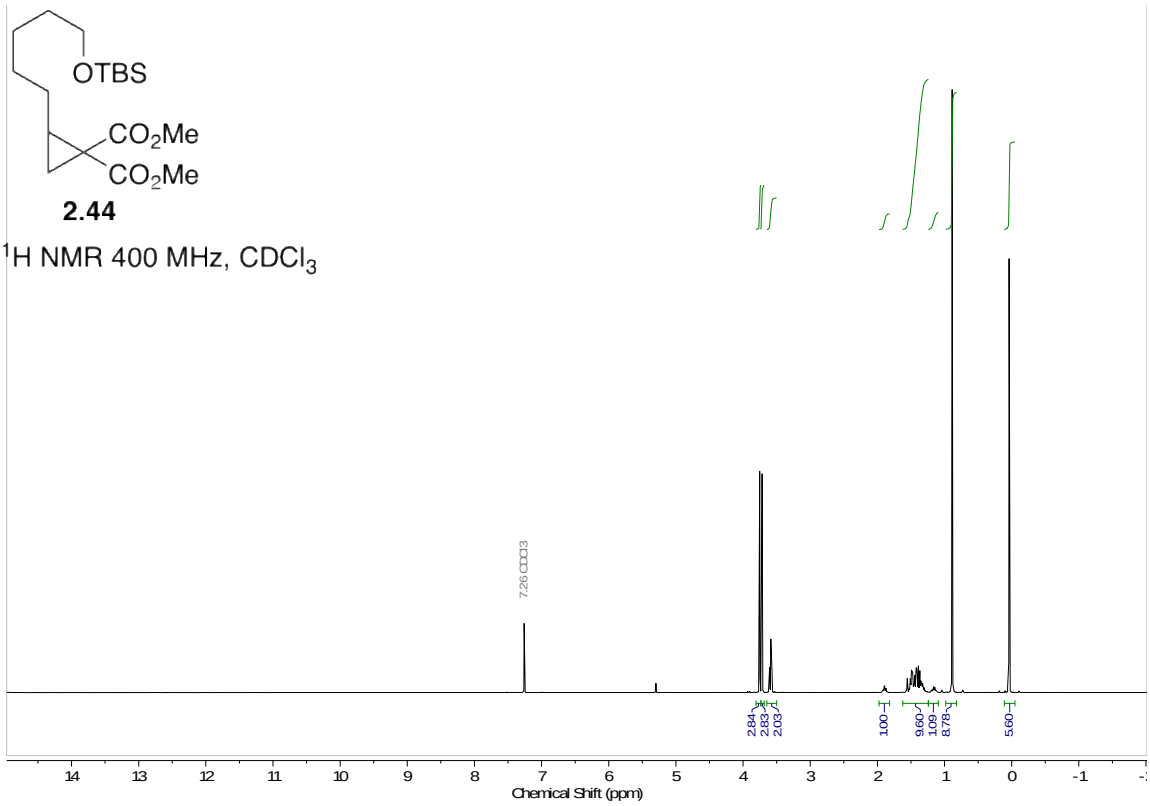

O
OH
CO2Me
CO2Me
2.37
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

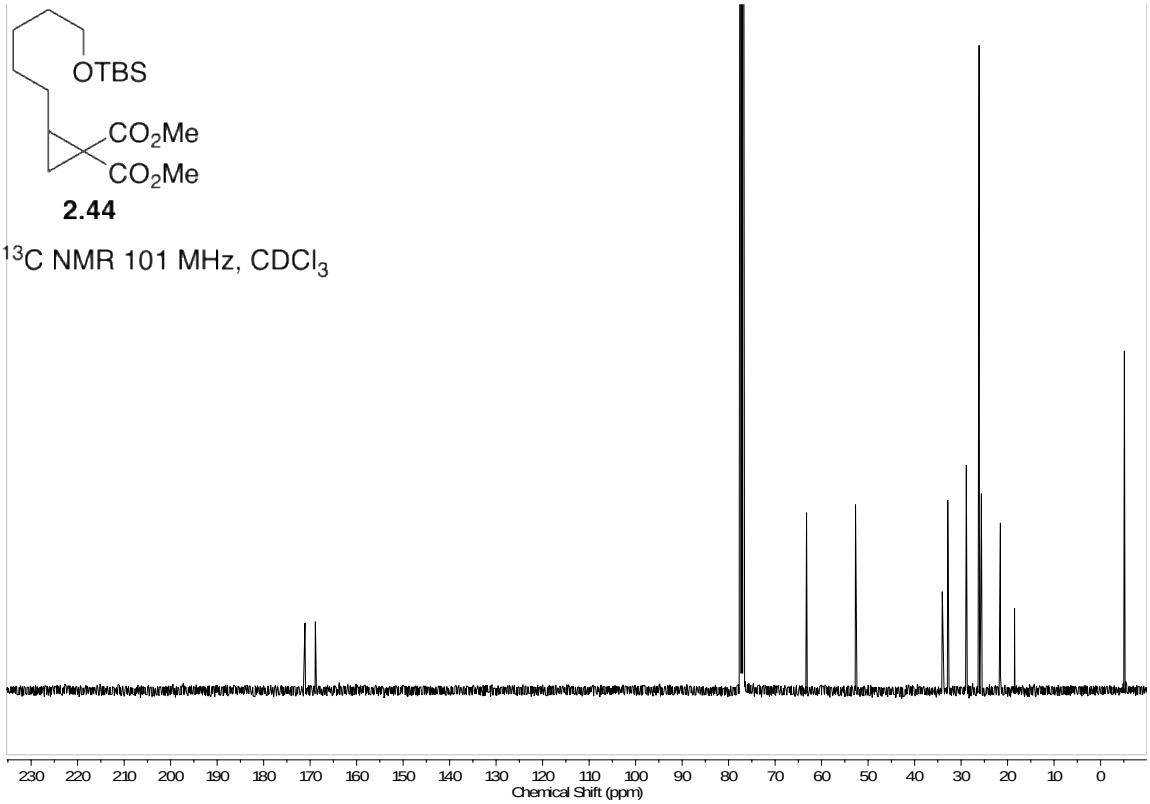

O NsN
CO2Me
CO2Me
2.38
1H NMR 400 MHz, CDCl3
1.00
1.62
0.80
2.16
2.39
2.42
6.81
2.12
2.25
2.26
1.12
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

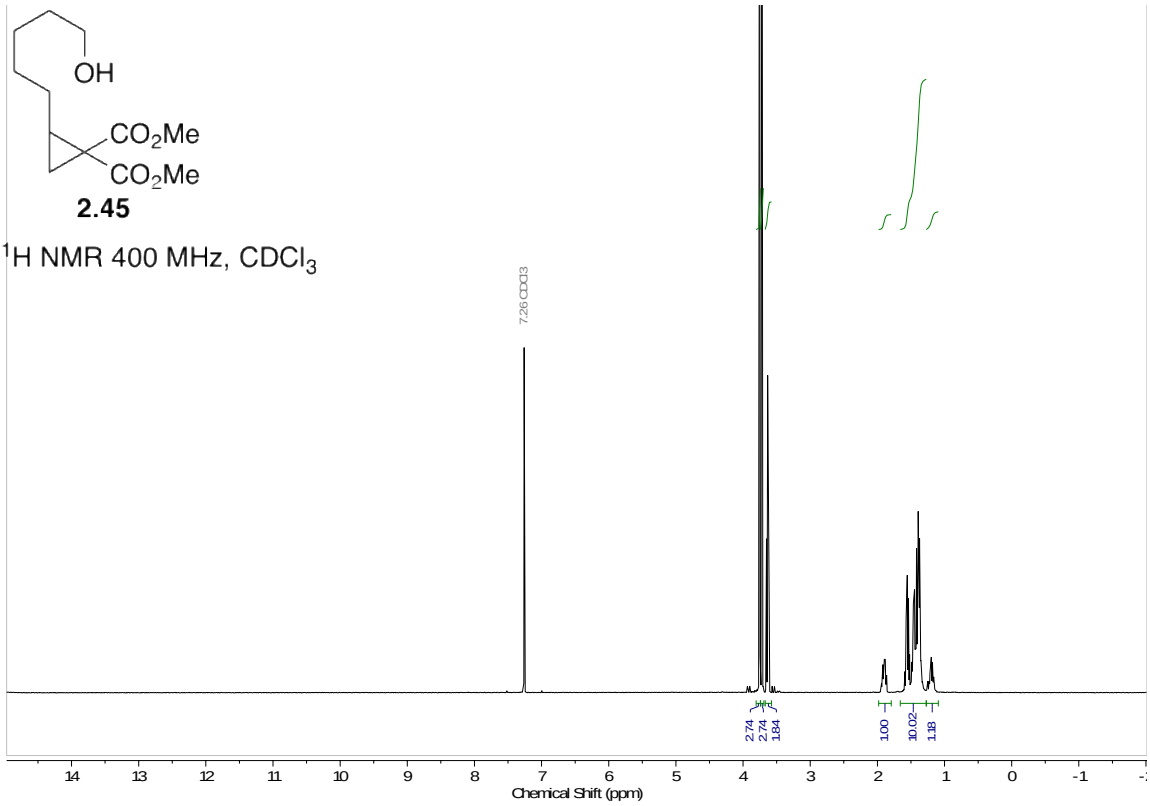

O NsN
CO2Me
CO2Me
2.38
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

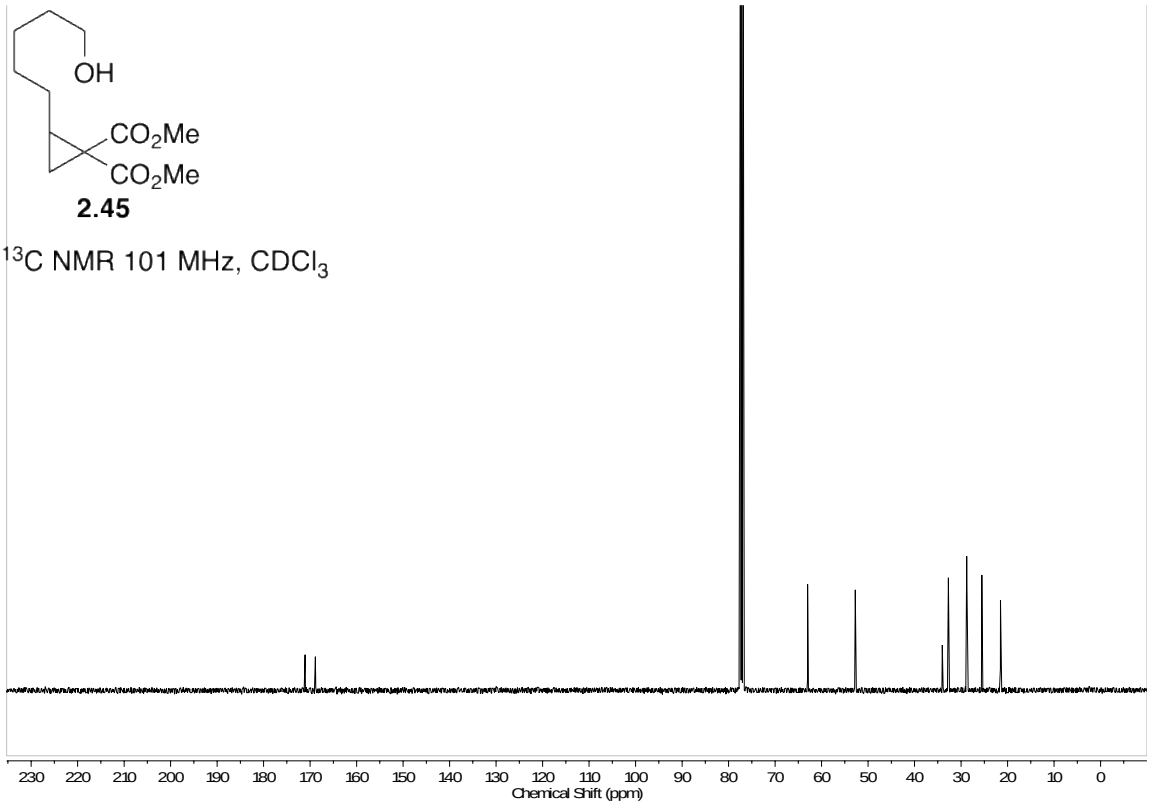

O
HN
CO2Me
CO2Me
2.39
1H NMR 400 MHz, CDCl3
2.80
2.83
6.14
2.04
1.90
1.98
1.00
1.00
1.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

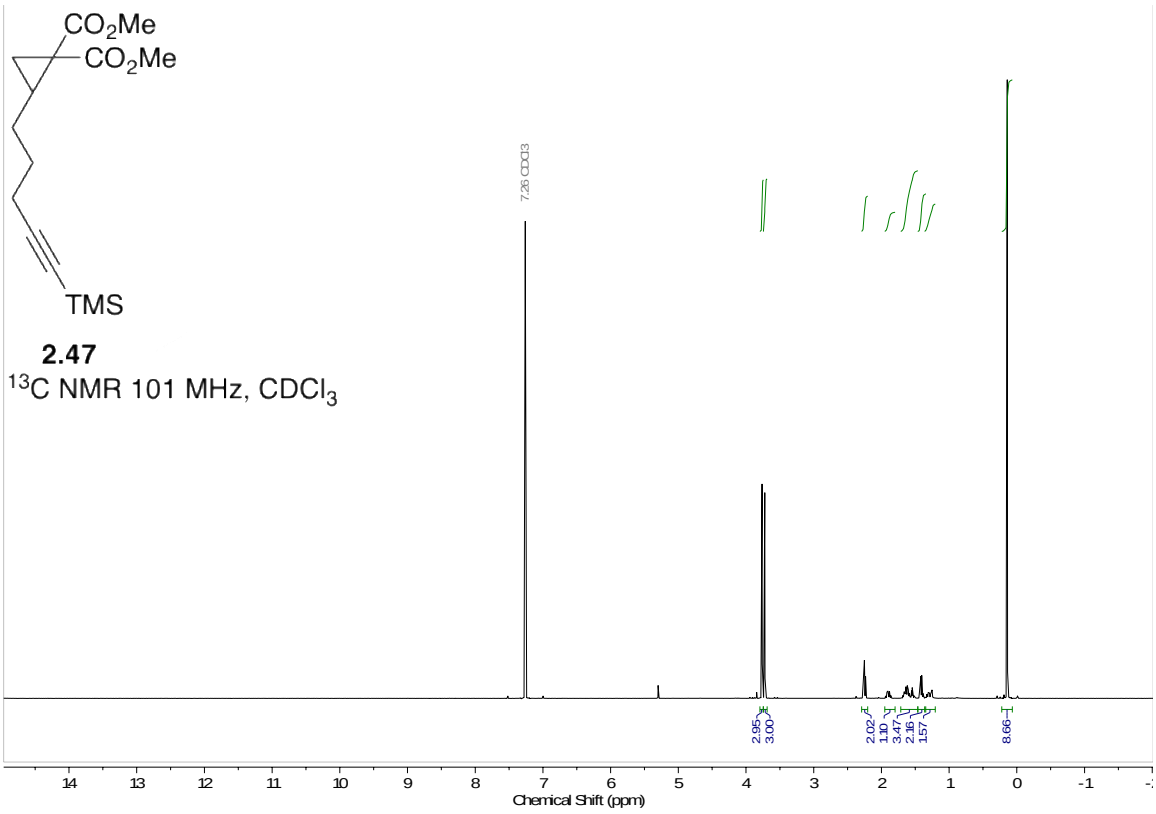

O
HN
CO2Me
CO2Me
2.39
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

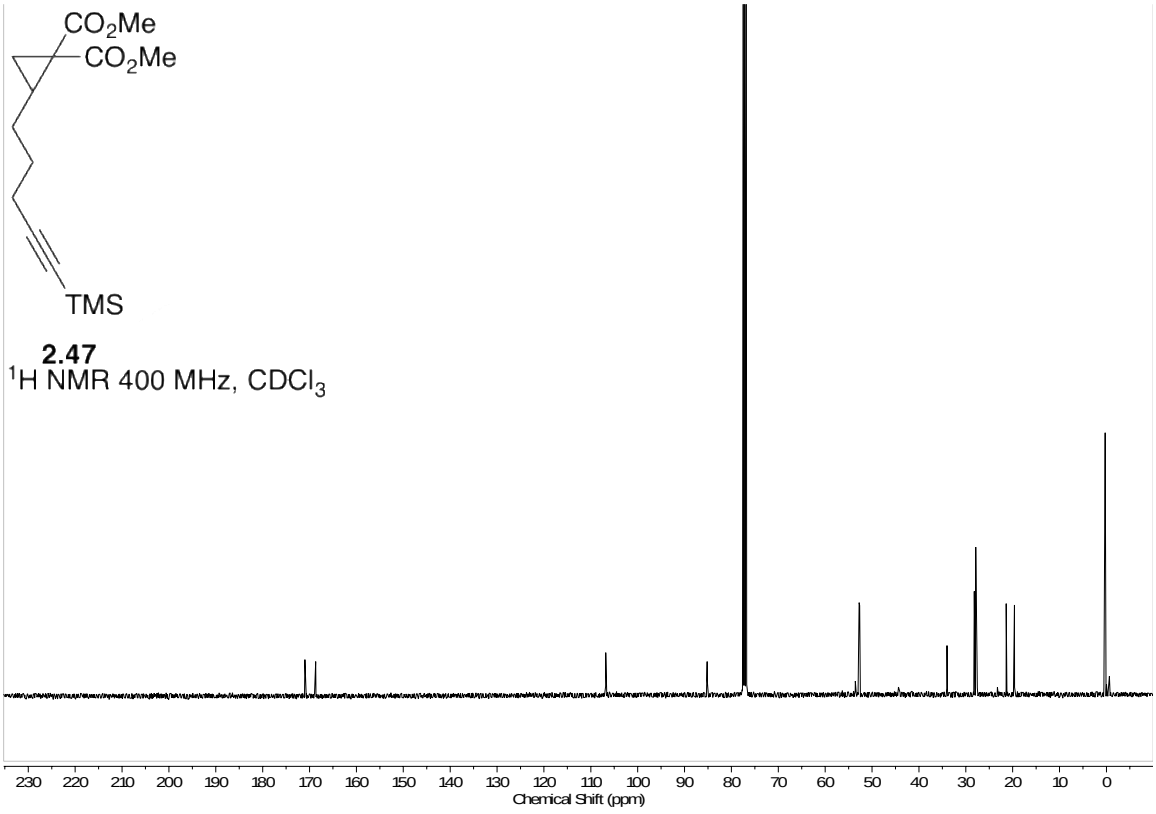

OTBS
CO2Me
CO2Me
2.44
1H NMR 400 MHz, CDCl3
7.26 CDCl3
2.84
2.83
2.03
1.00
9.60
1.09
8.78
5.60
Chemical Shift (ppm)

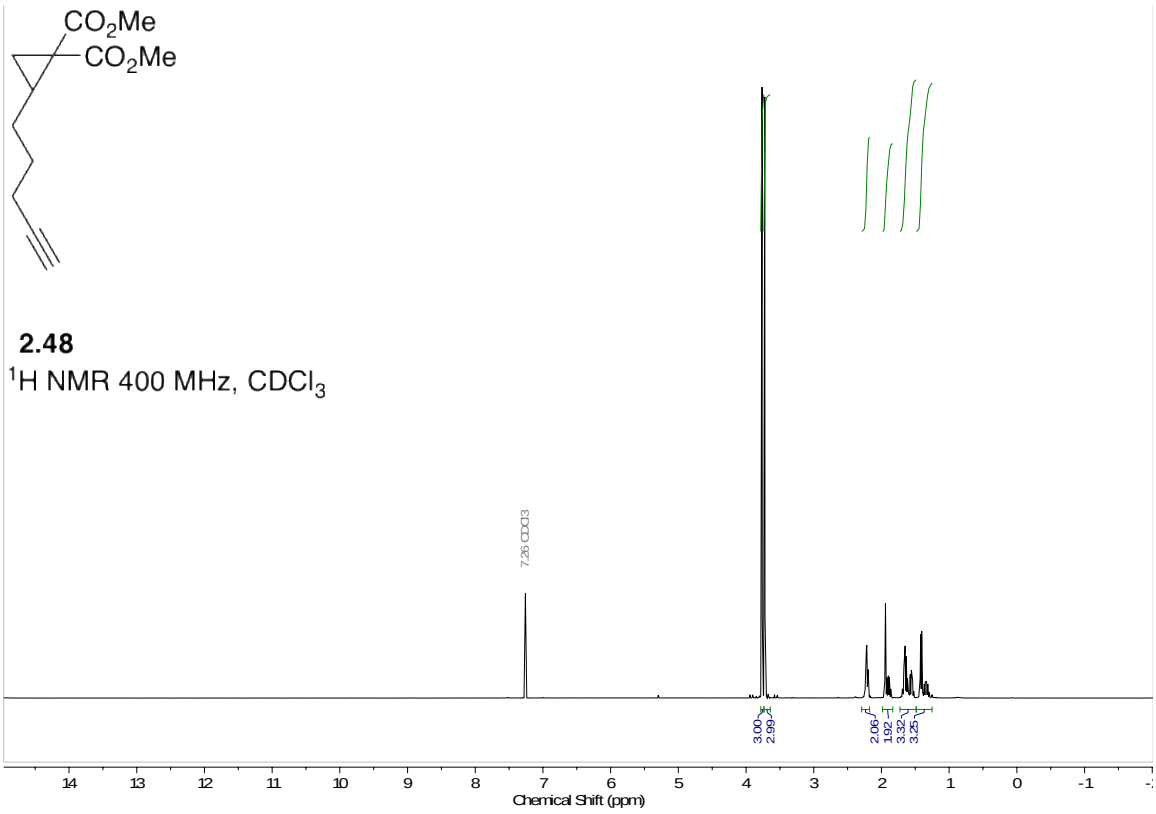

OTBS
CO2Me
CO2Me
2.44
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

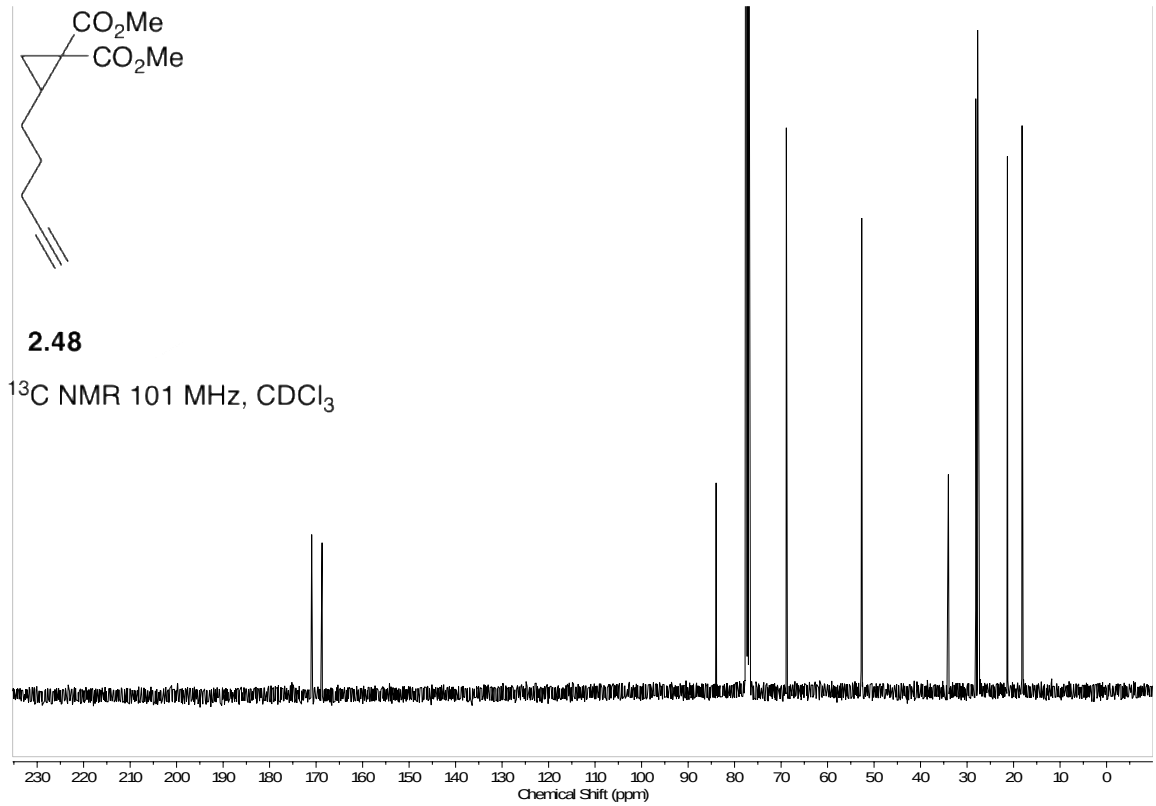

OH
CO2Me
CO2Me
2.45
1H NMR 400 MHz, CDCl3
7.26 CDCl3
2.74
2.74
1.84
1.00
10.02
1.18
Chemical Shift (ppm)

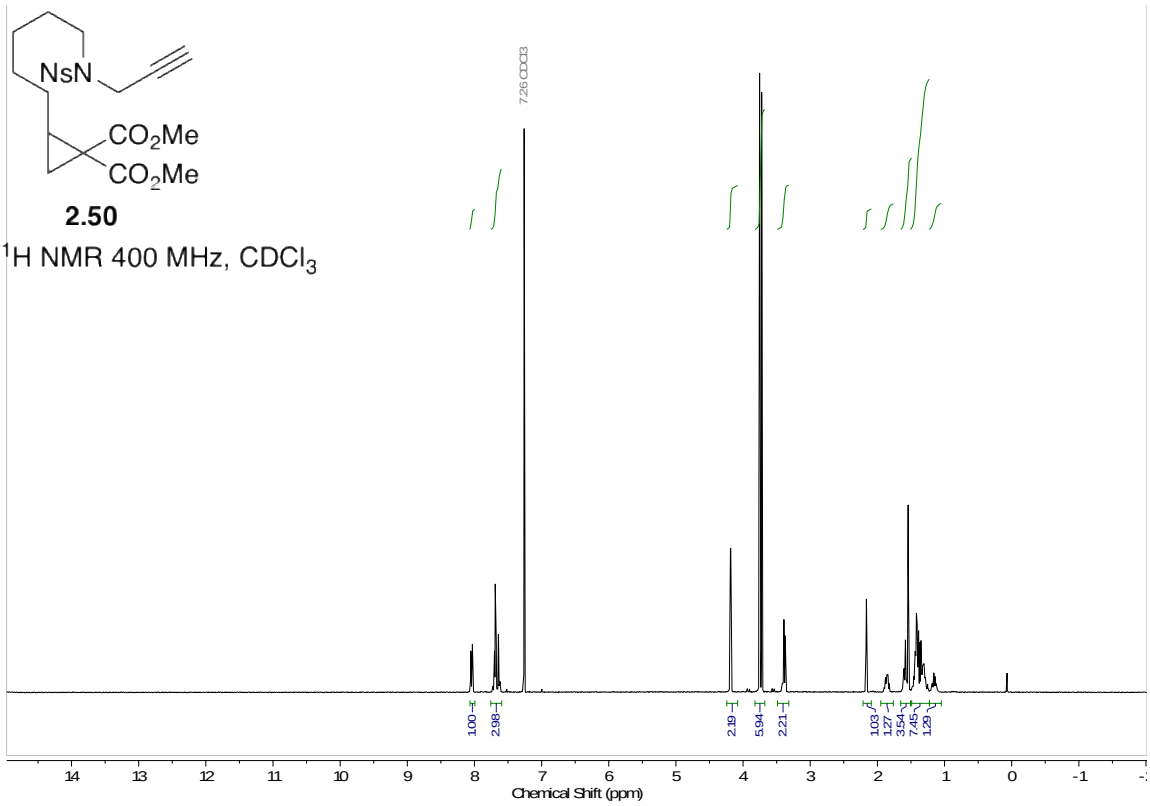

OH
CO2Me
CO2Me
2.45
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

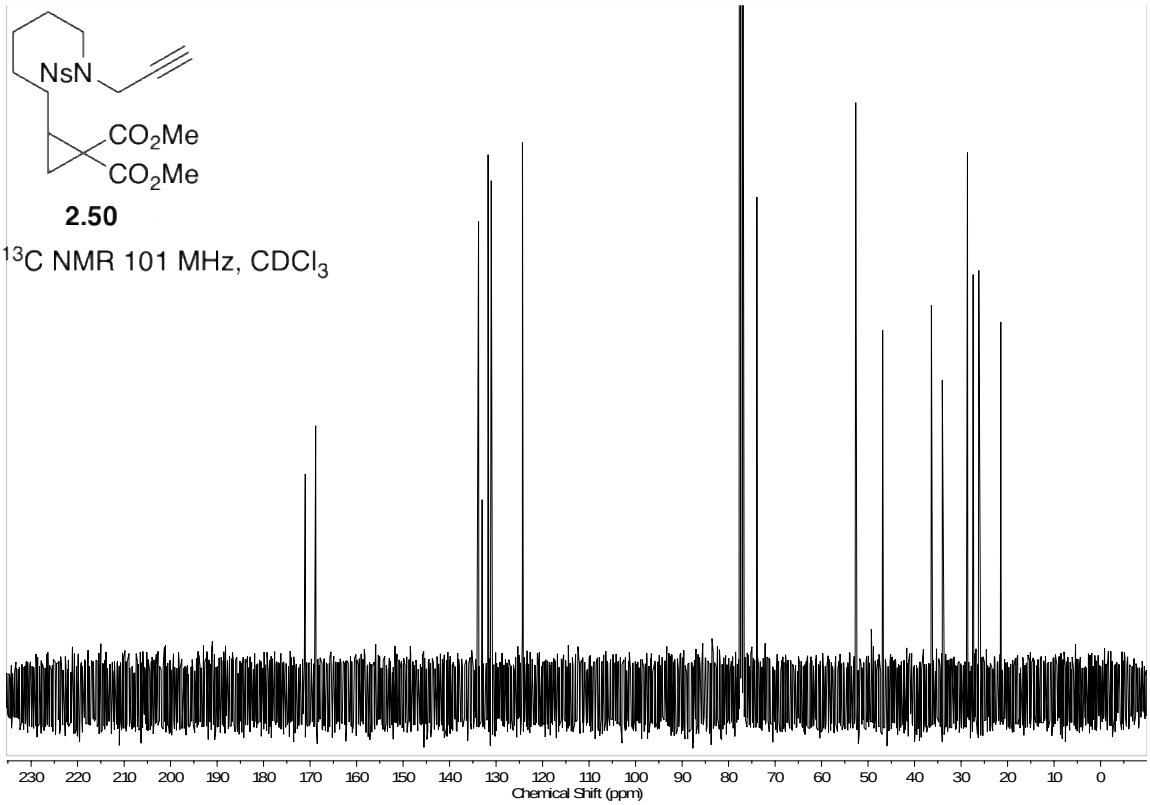

CO2Me
CO2Me
TMS
2.47
13C NMR 101 MHz, CDCl3
7.26 CDCl3
2.95
3.00
2.02
1.10
3.47
2.16
1.57
8.66
Chemical Shift (ppm)

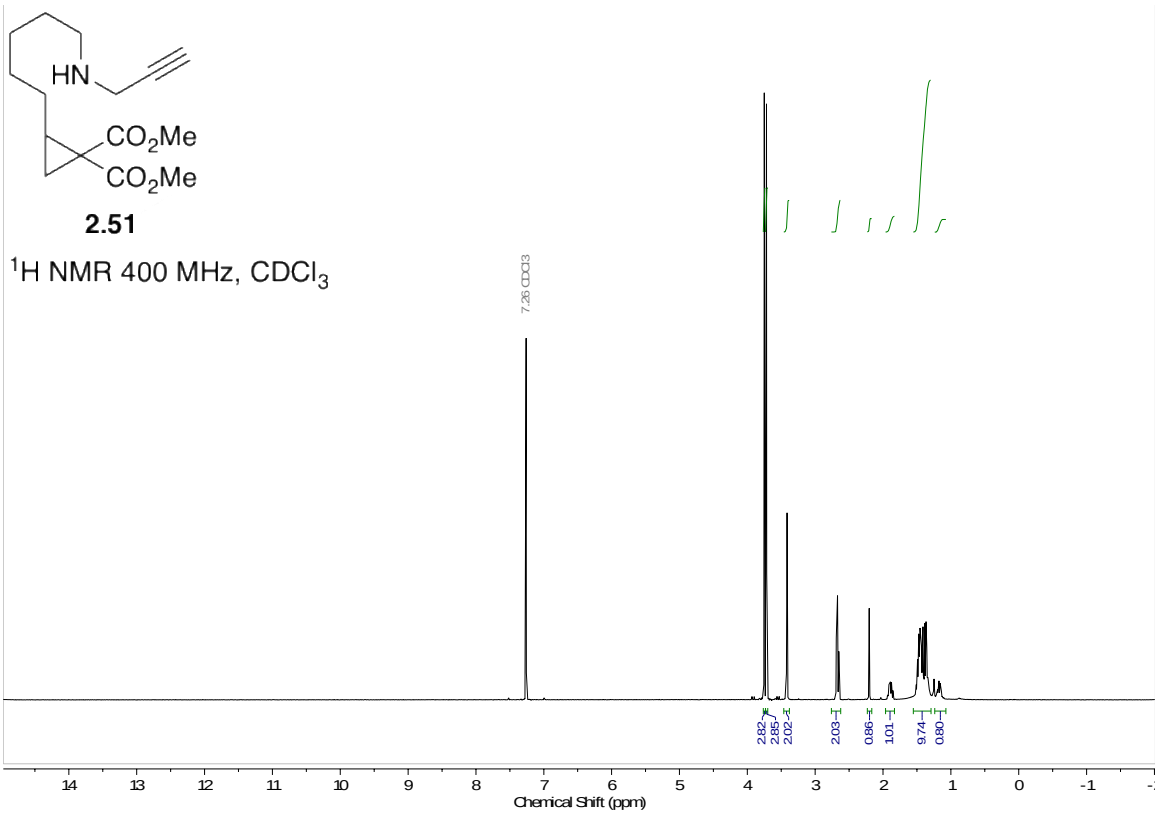

CO2Me
CO2Me
TMS
2.47
1H NMR 400 MHz, CDCl3
Chemical Shift (ppm)

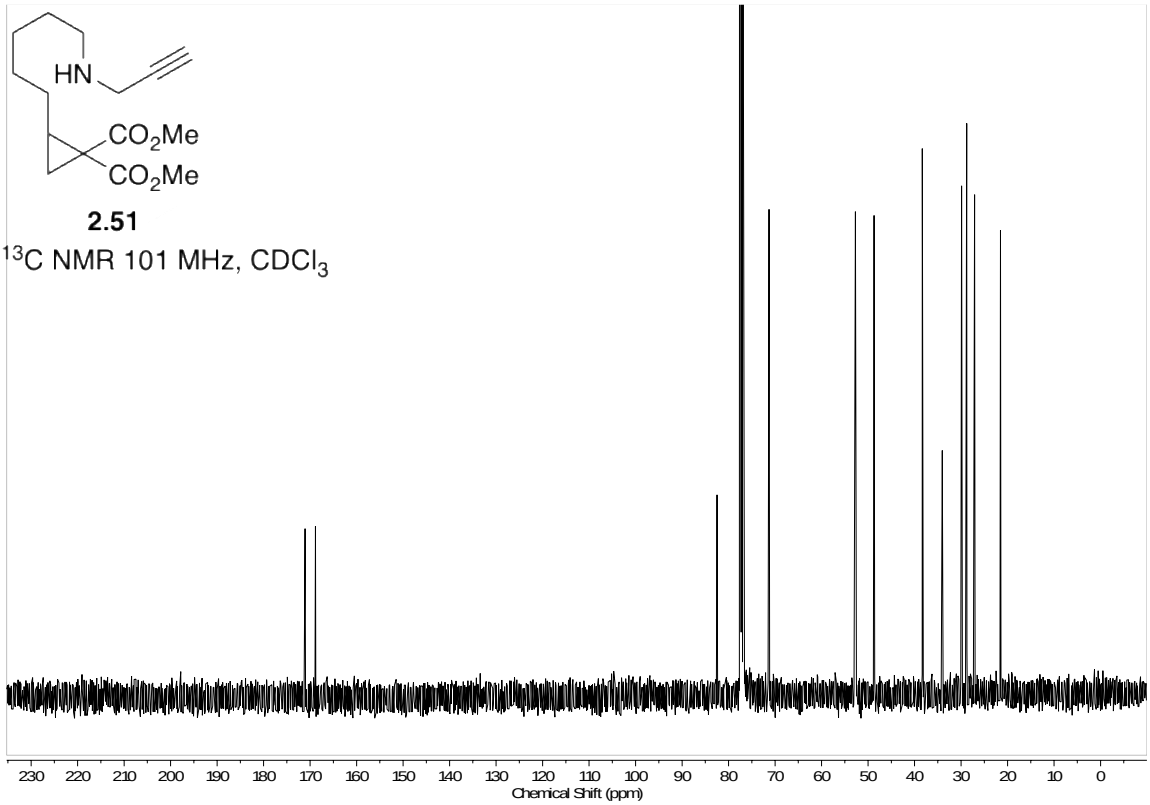

CO2Me
CO2Me
2.48
1H NMR 400 MHz, CDCl3
7.26 CDCl3
3.00
2.99
2.06
1.92
3.32
3.25
Chemical Shift (ppm)

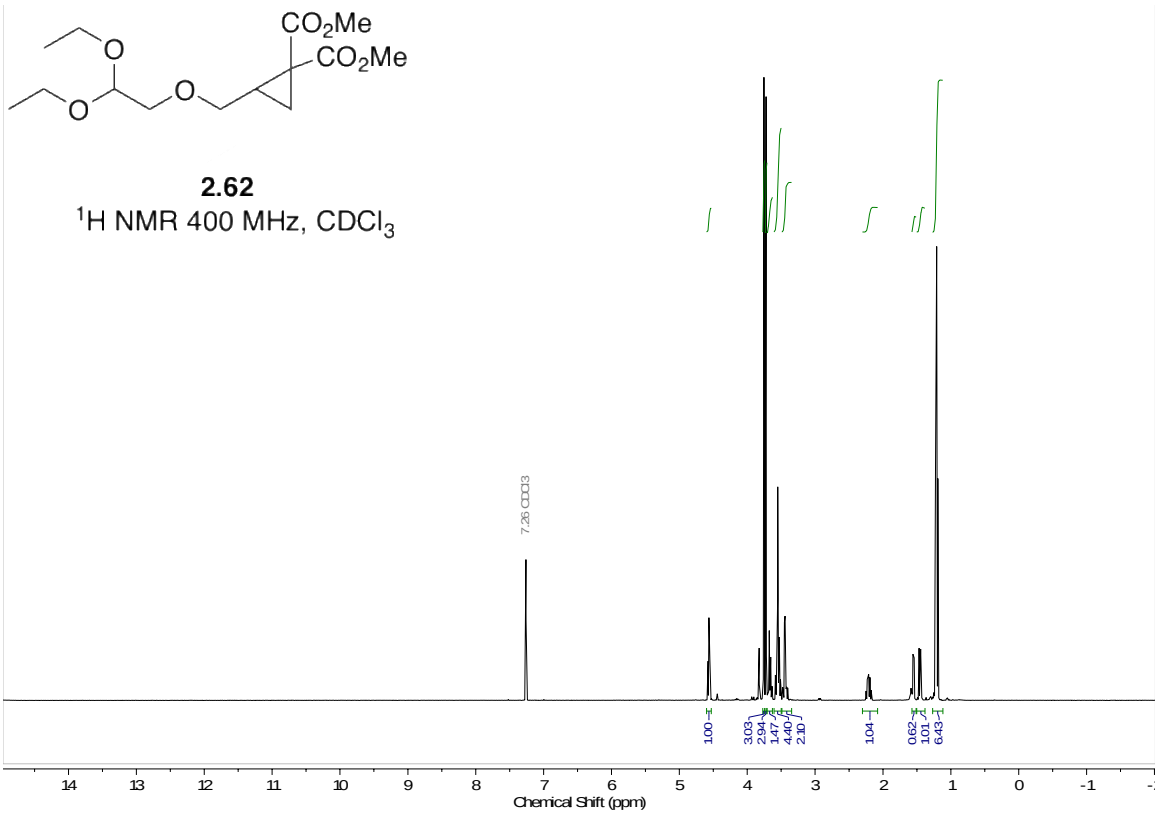

CO2Me
CO2Me
2.48
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

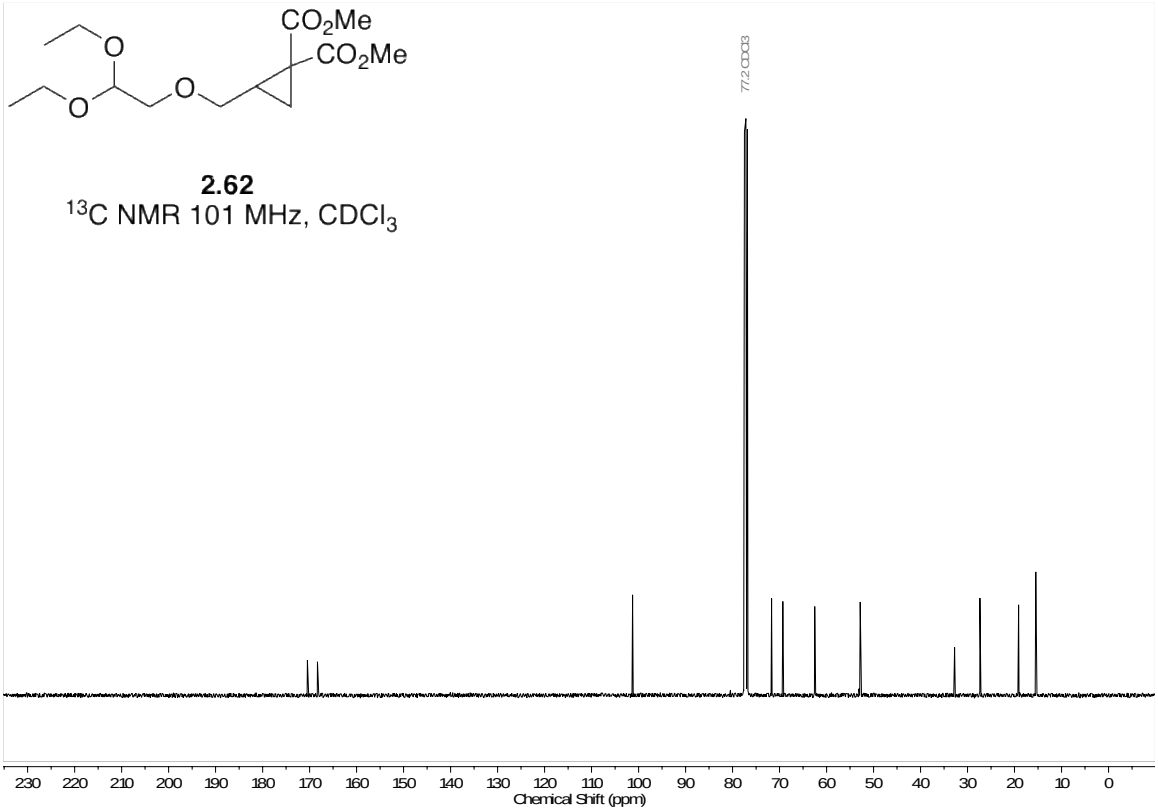

NsN
CO2Me
CO2Me
2.50
1H NMR 400 MHz, CDCl3
7.26 CDCl3
1.00
2.98
2.19
5.94
2.21
1.03
1.27
3.54
7.45
1.29
Chemical Shift (ppm)

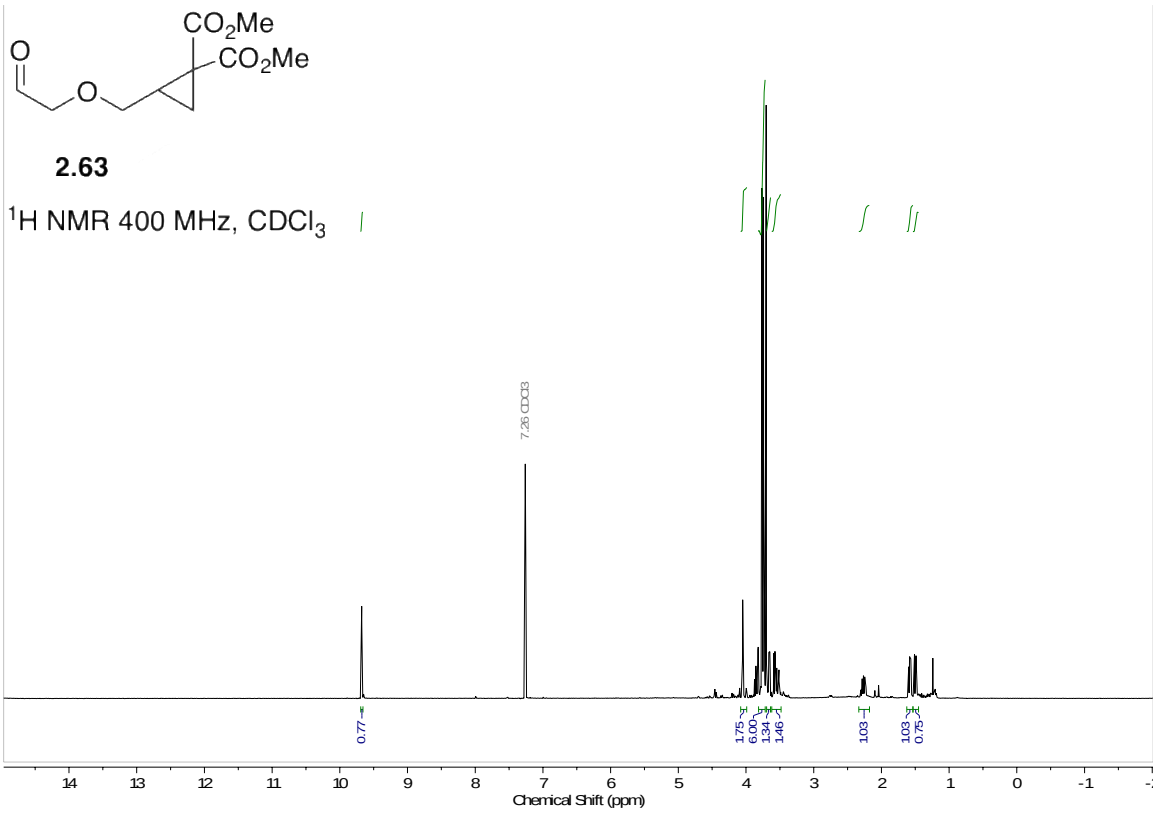

NsN
CO2Me
CO2Me
2.50
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

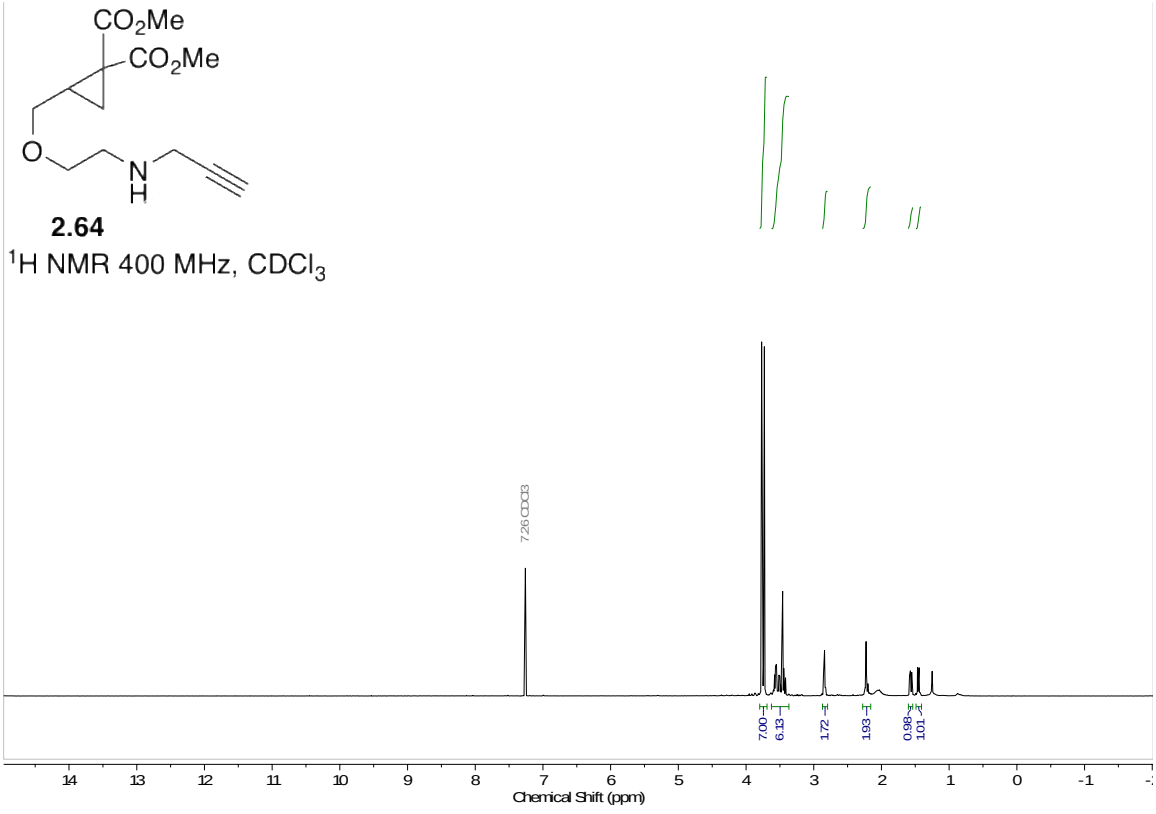

HN
CO2Me
CO2Me
2.51
1H NMR 400 MHz, CDCl3
7.26 CDCl3
2.82
2.85
2.02
2.03
0.86
1.01
9.74
0.80
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

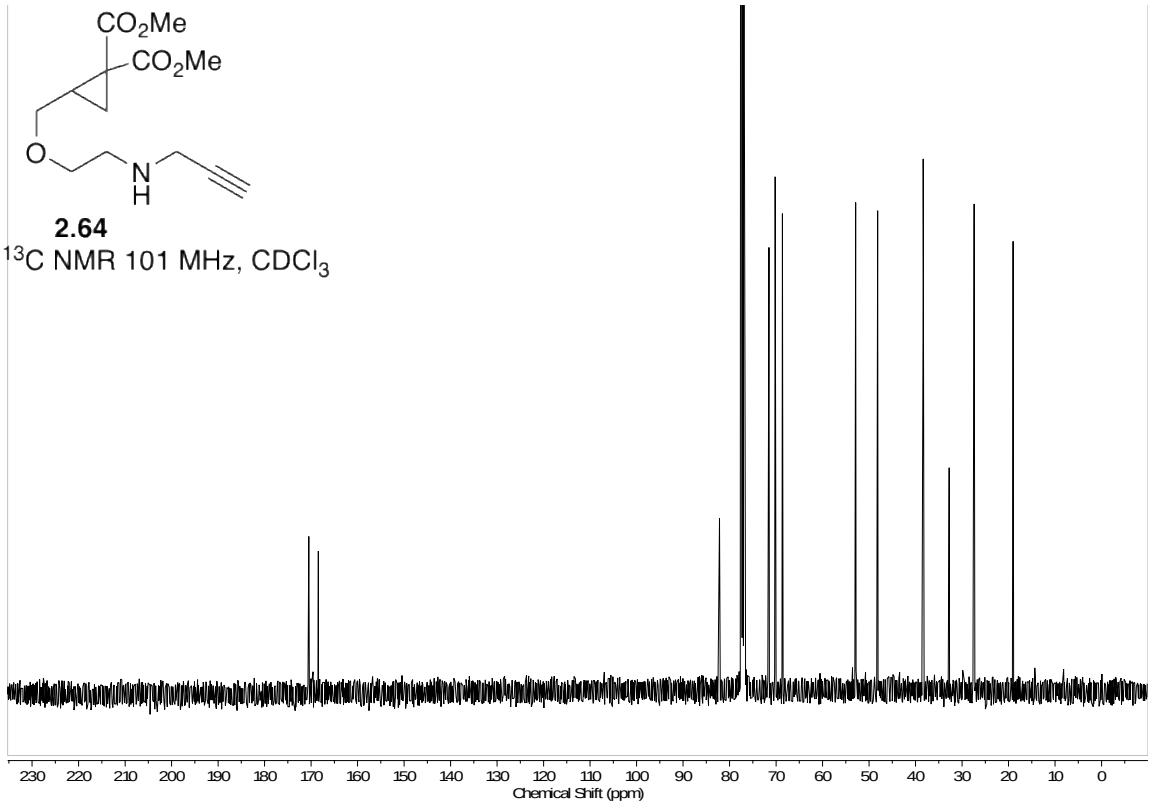

HN
CO2Me
CO2Me
2.51
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


CO2Me
CO2Me
O
O
O
2.62
1H NMR 400 MHz, CDCl3
7.26 CDCl3
100
3.03
2.94
1.47
4.40
2.10
1.04
0.62
1.01
6.43
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)


CO2Me
CO2Me
O
O
O
2.62
13C NMR 101 MHz, CDCl3
77.2 CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

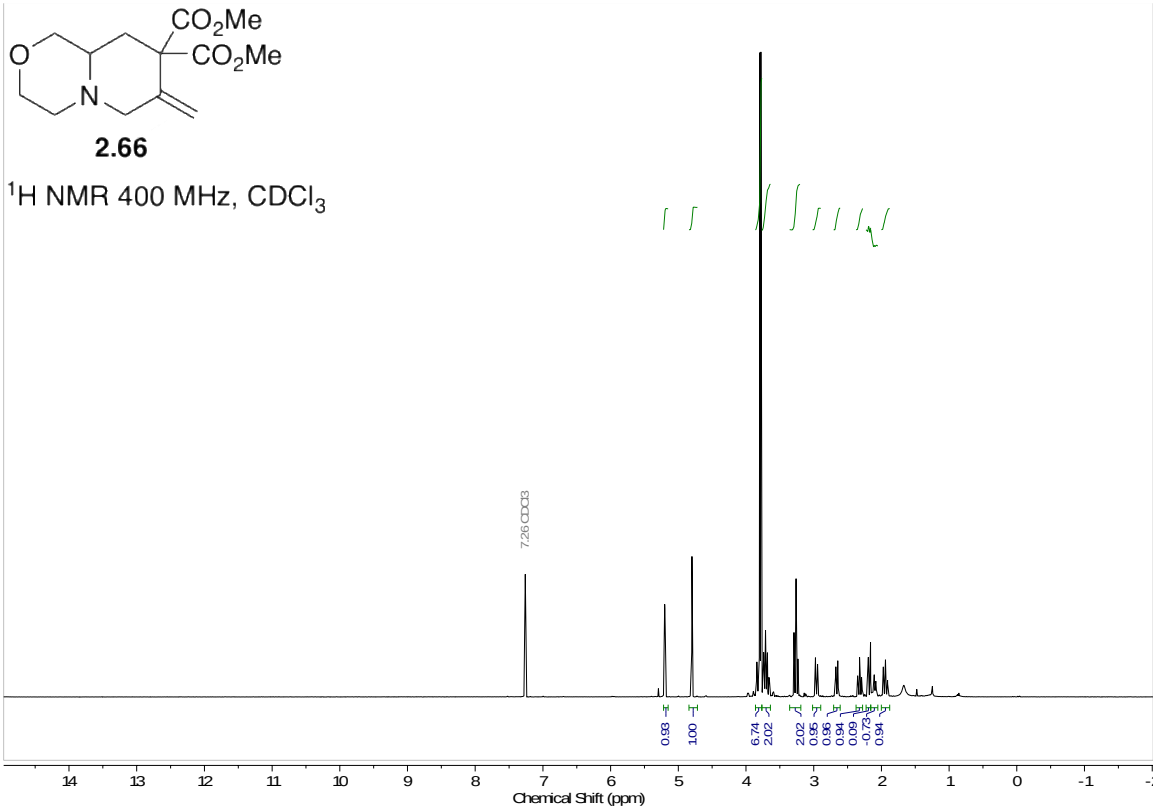

CO2Me
CO2Me
O
O
2.63
1H NMR 400 MHz, CDCl3
7.26 CDCl3
0.77
1.75
6.00
1.34
1.46
1.03
1.03
0.75
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)


CO2Me
CO2Me
O
N
H
2.64
1H NMR 400 MHz, CDCl3
7.26 CDCl3
7.00
6.13
1.72
1.93
0.98
1.01
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)



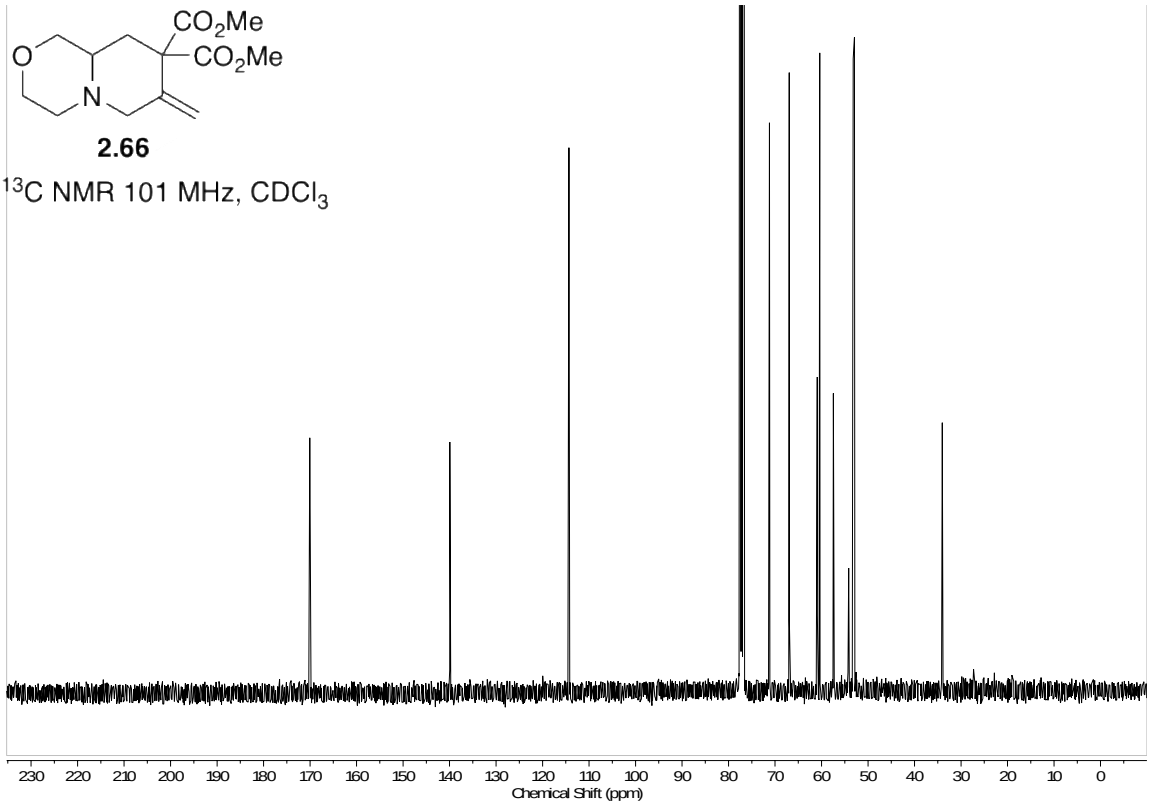
2.64

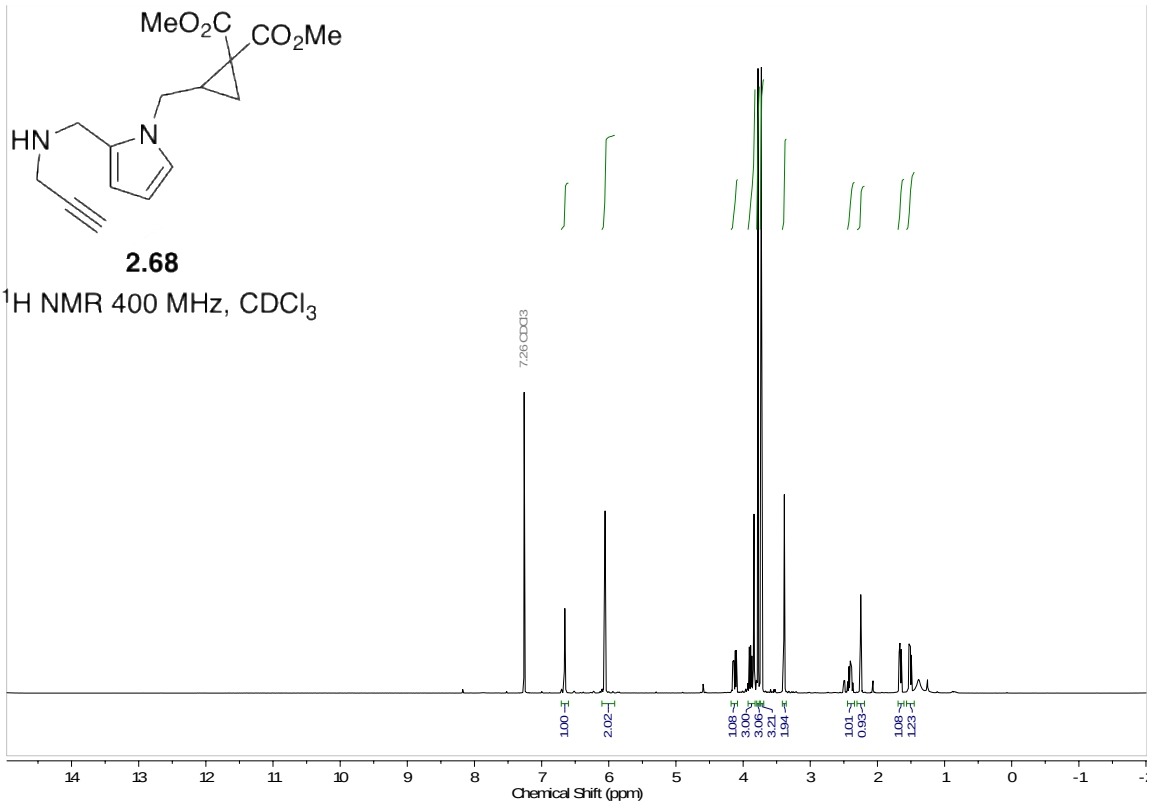
^{13}C NMR 101 MHz, $CDCl_3$

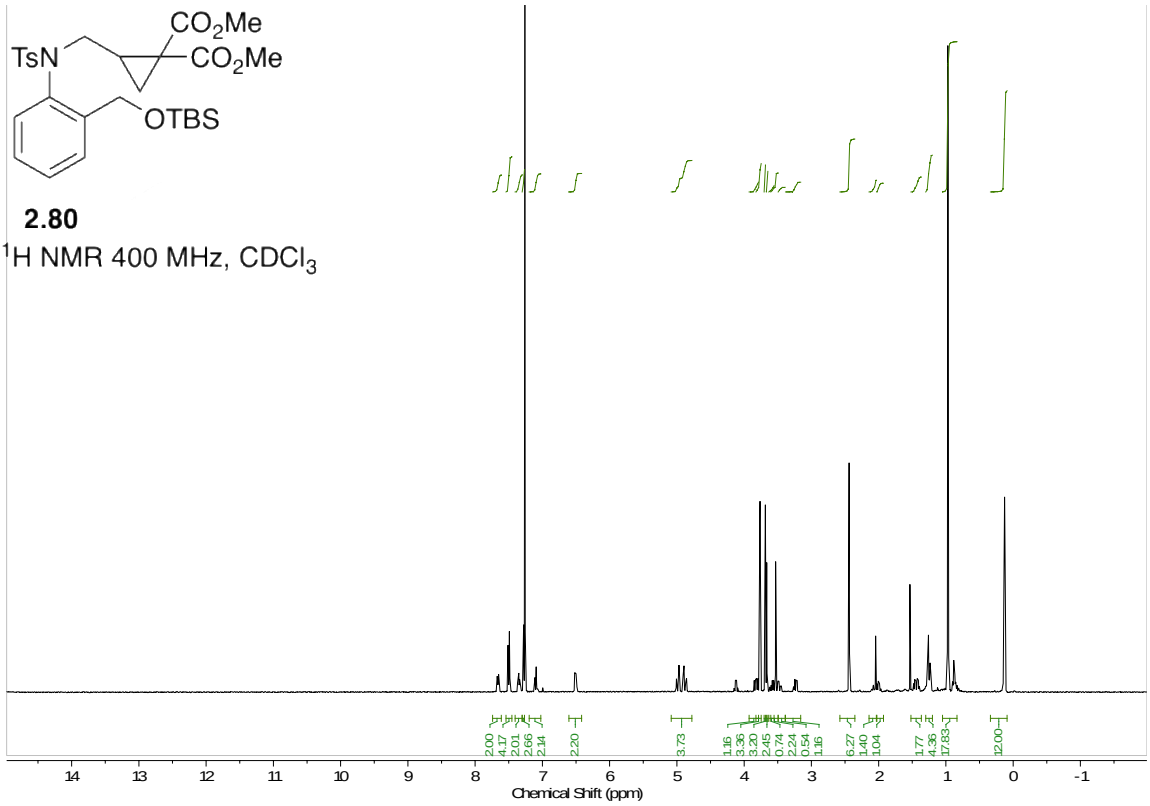


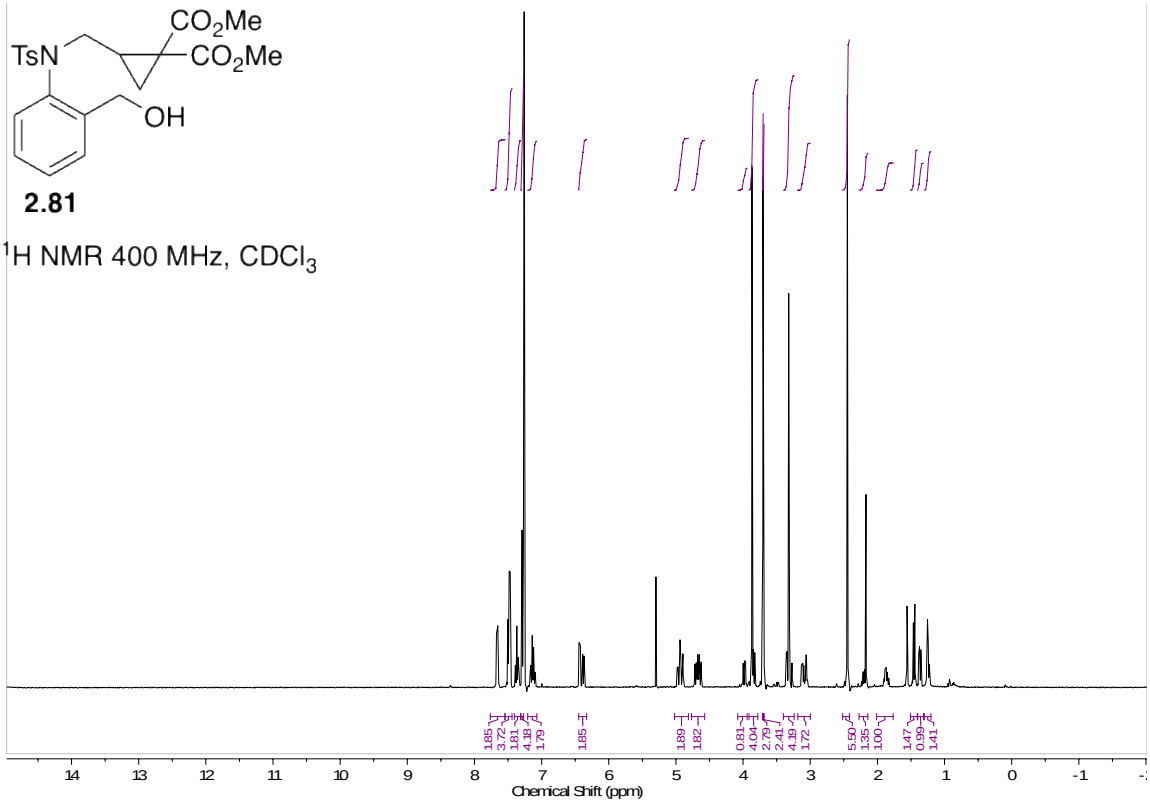
2.66

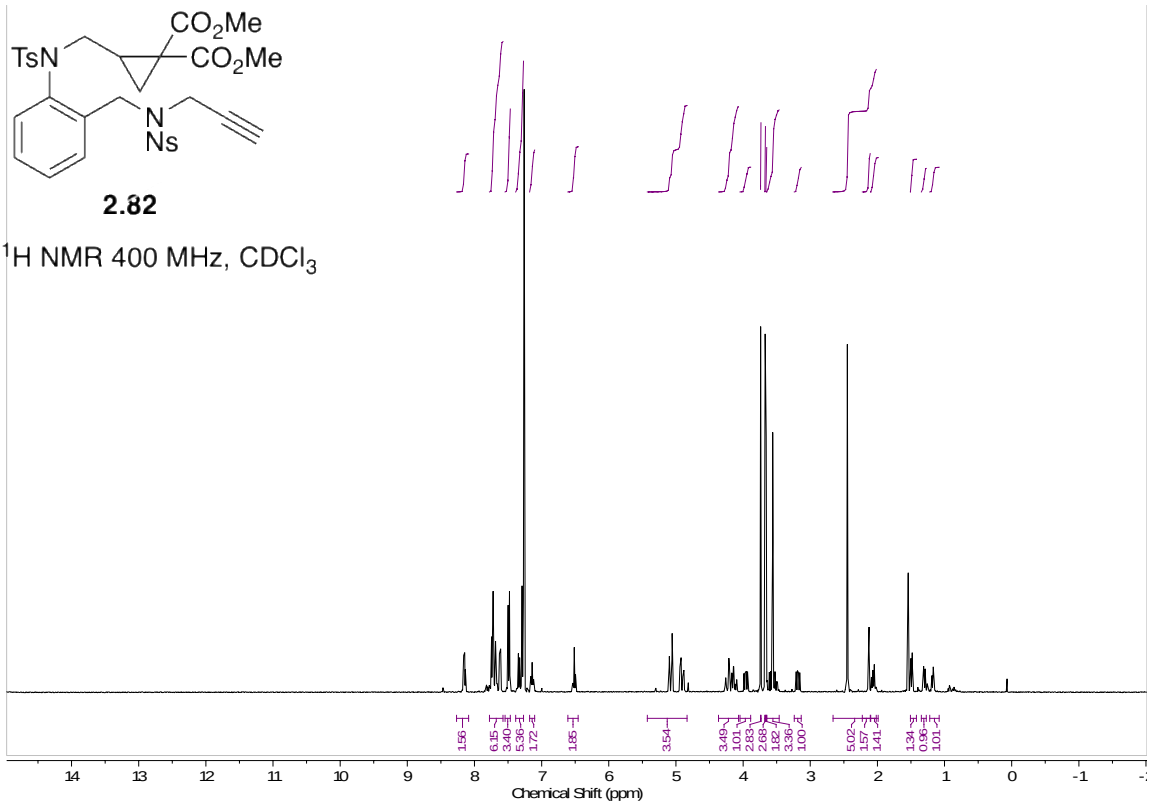
^{1}H NMR 400 MHz, $CDCl_3$


CO2Me
CO2Me
O
N
2.66
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


MeO2C
CO2Me
HN
N
2.68
1H NMR 400 MHz, CDCl3
7.26 CDCl3
1.00
2.02
1.08
3.00
3.06
3.21
1.94
1.01
0.93
1.08
1.23
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

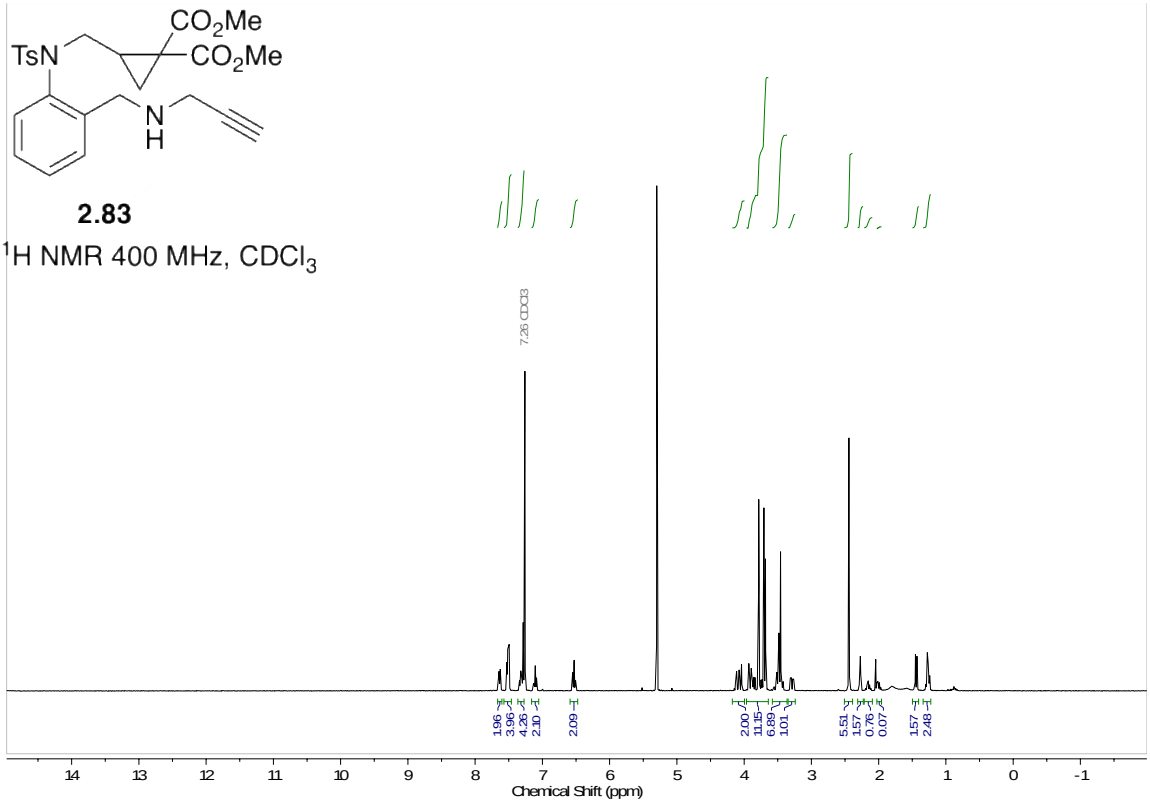

CO2Me
TsN
CO2Me
OTBS
2.80
1H NMR 400 MHz, CDCl3
Chemical Shift (ppm)


CO2Me
TsN
CO2Me
OH
2.81
1H NMR 400 MHz, CDCl3
Chemical Shift (ppm)



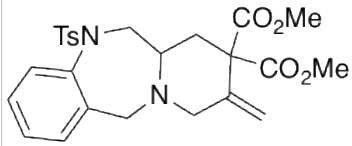
2.82

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



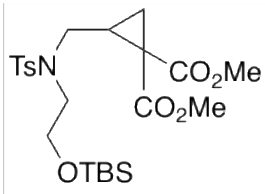
2.83

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



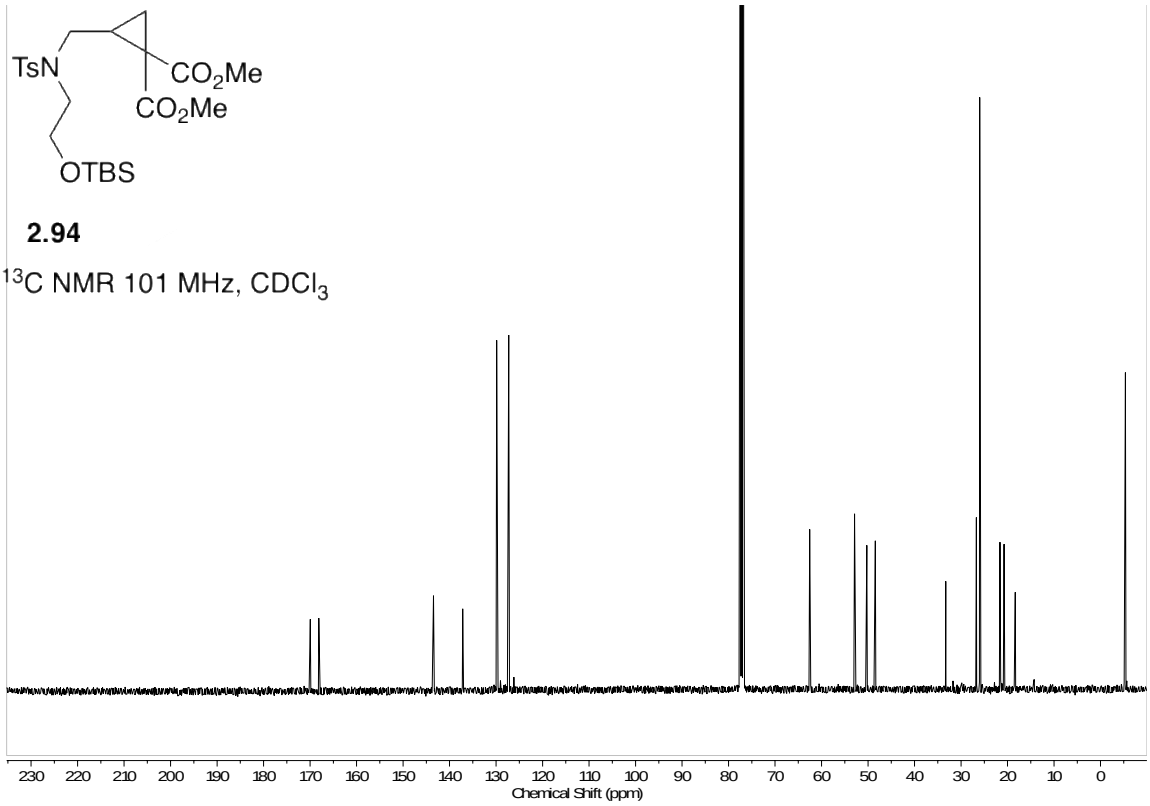
2.85

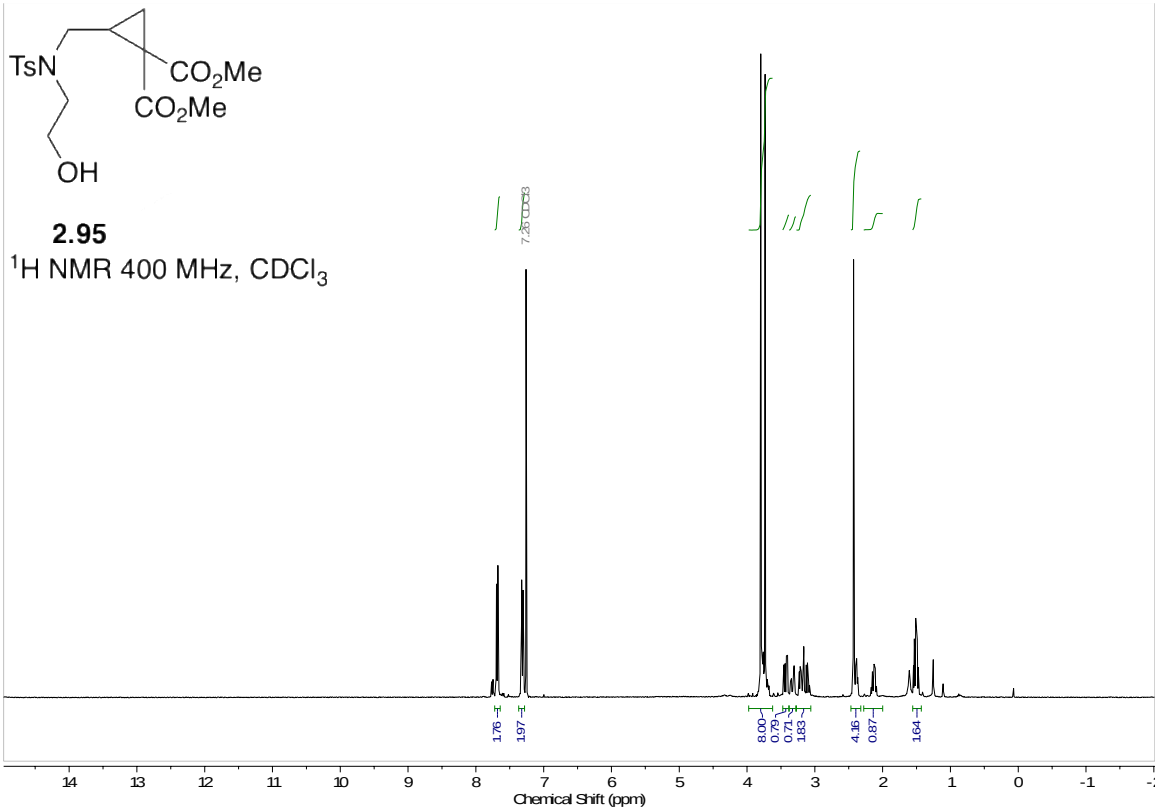
^{1}H NMR 400 MHz, $CDCl_3$

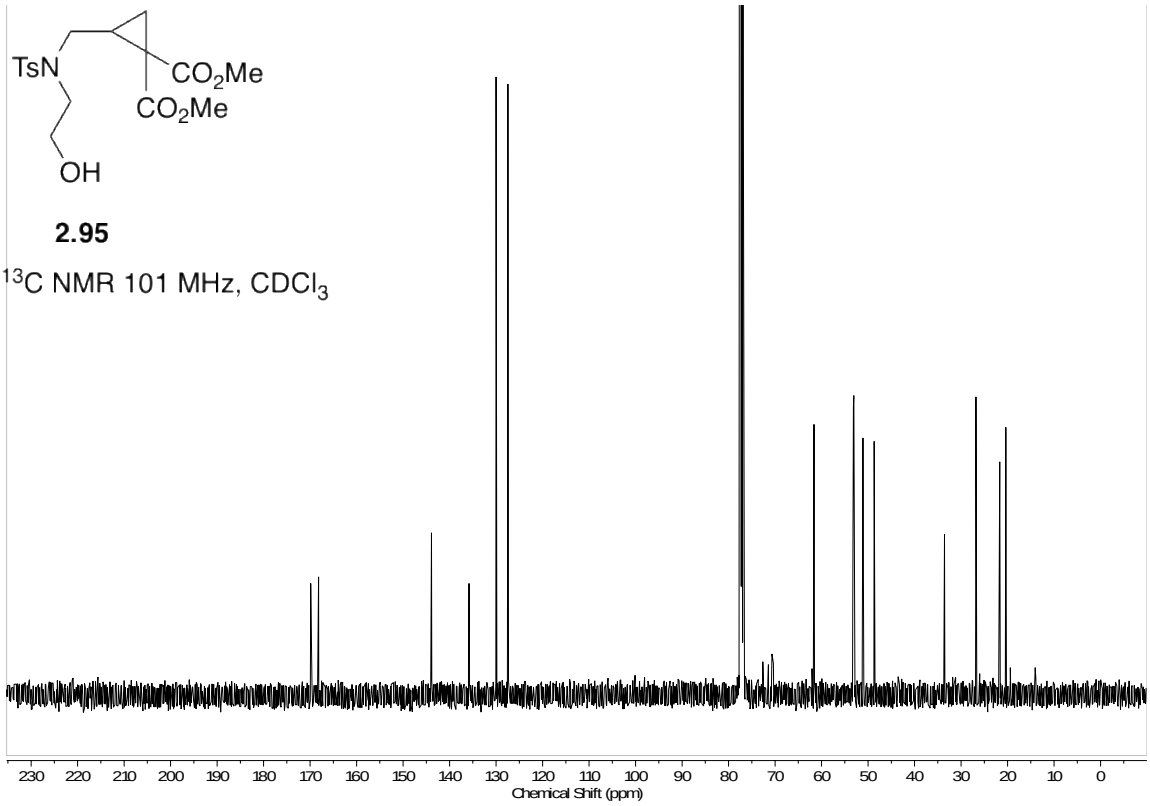


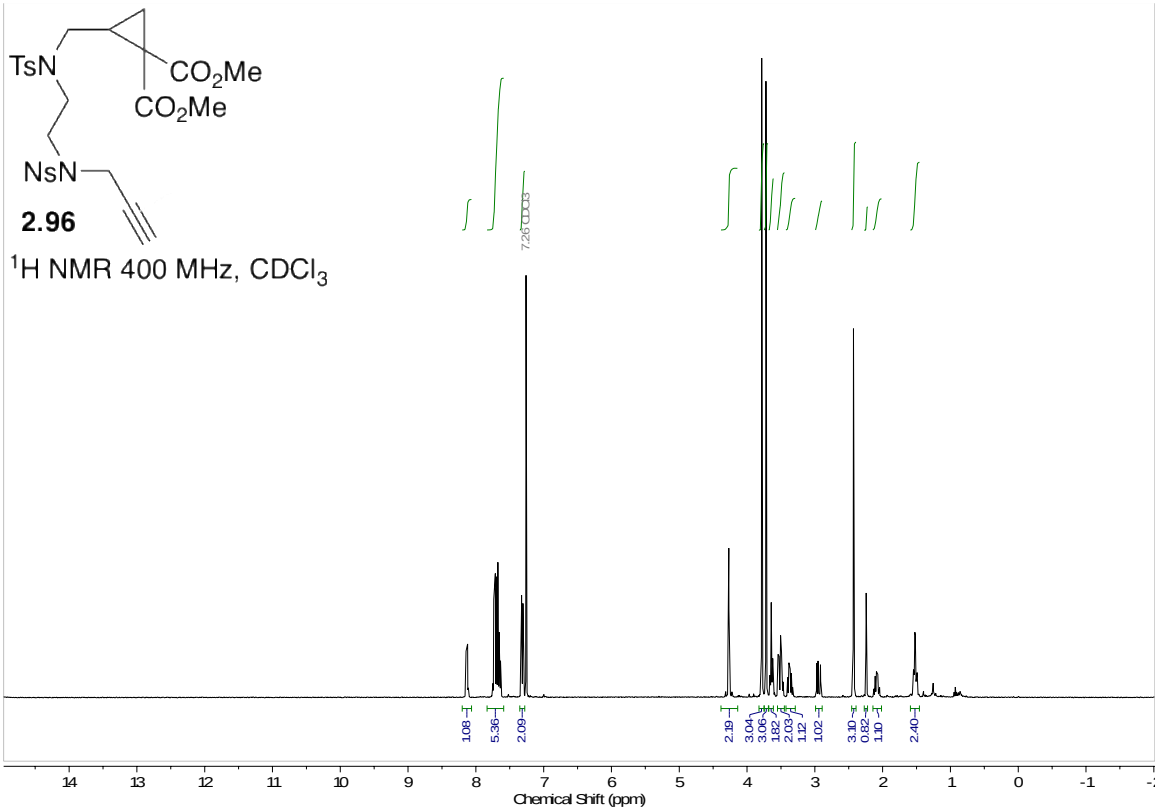
2.94

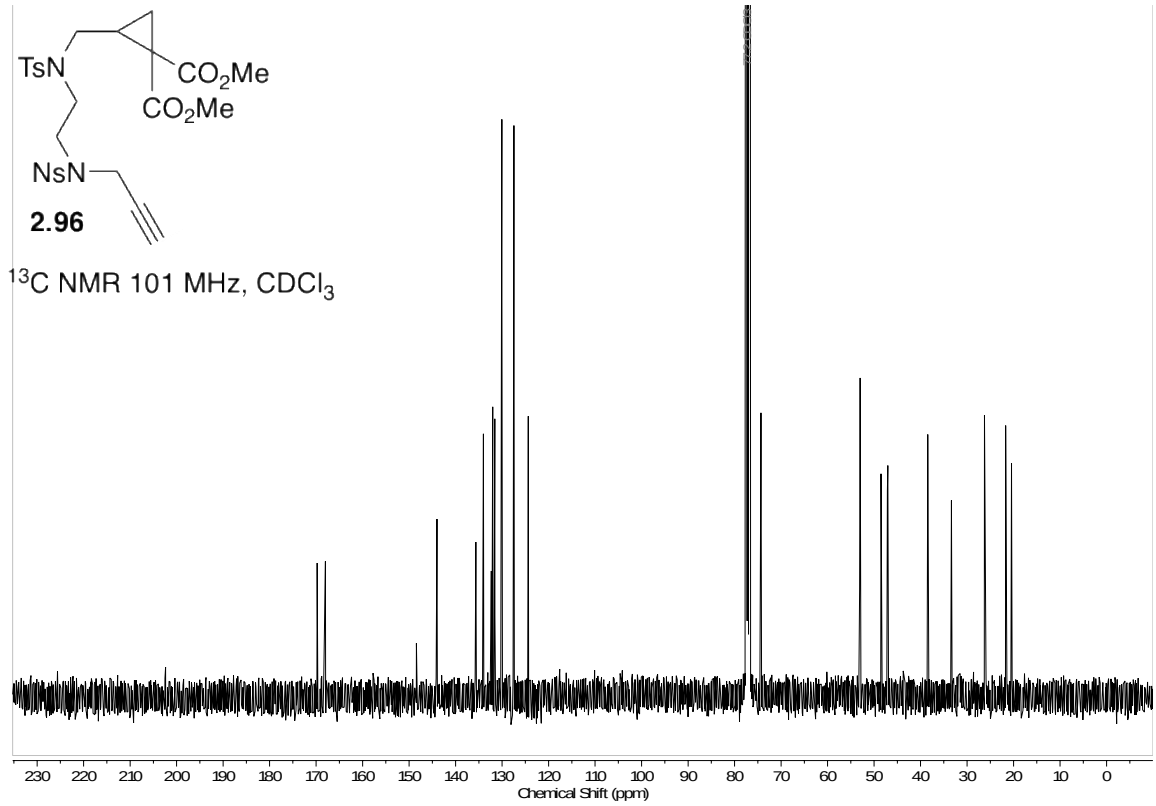
^{1}H NMR 400 MHz, $CDCl_3$

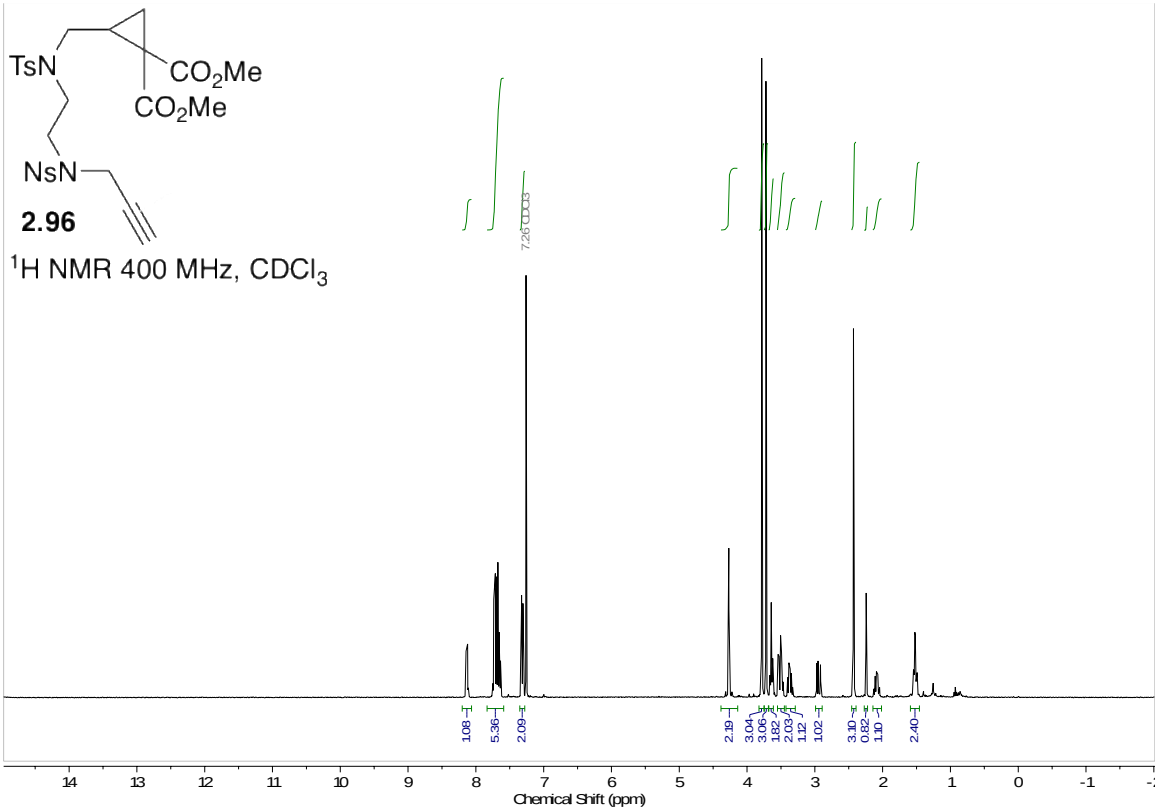

TsN
CO2Me
CO2Me
OTBS
2.94
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

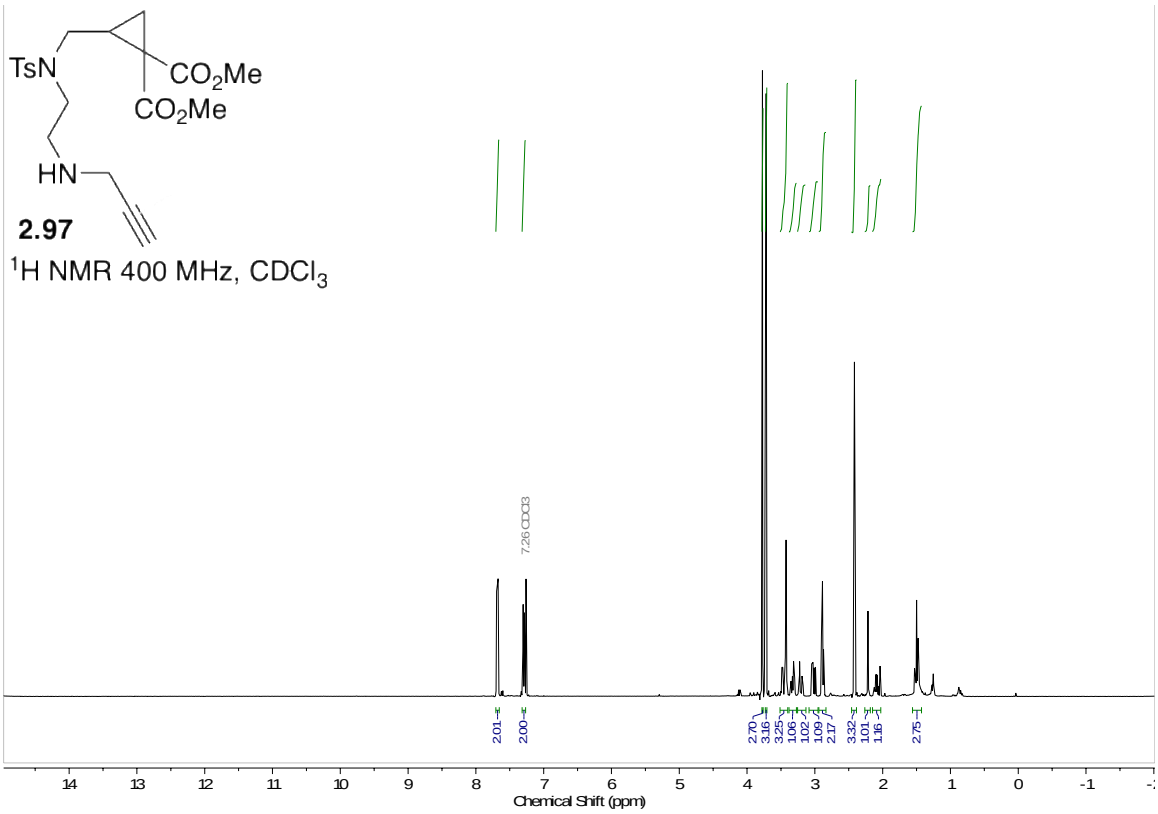

TsN
CO2Me
CO2Me
OH
2.95
1H NMR 400 MHz, CDCl3
Chemical Shift (ppm)

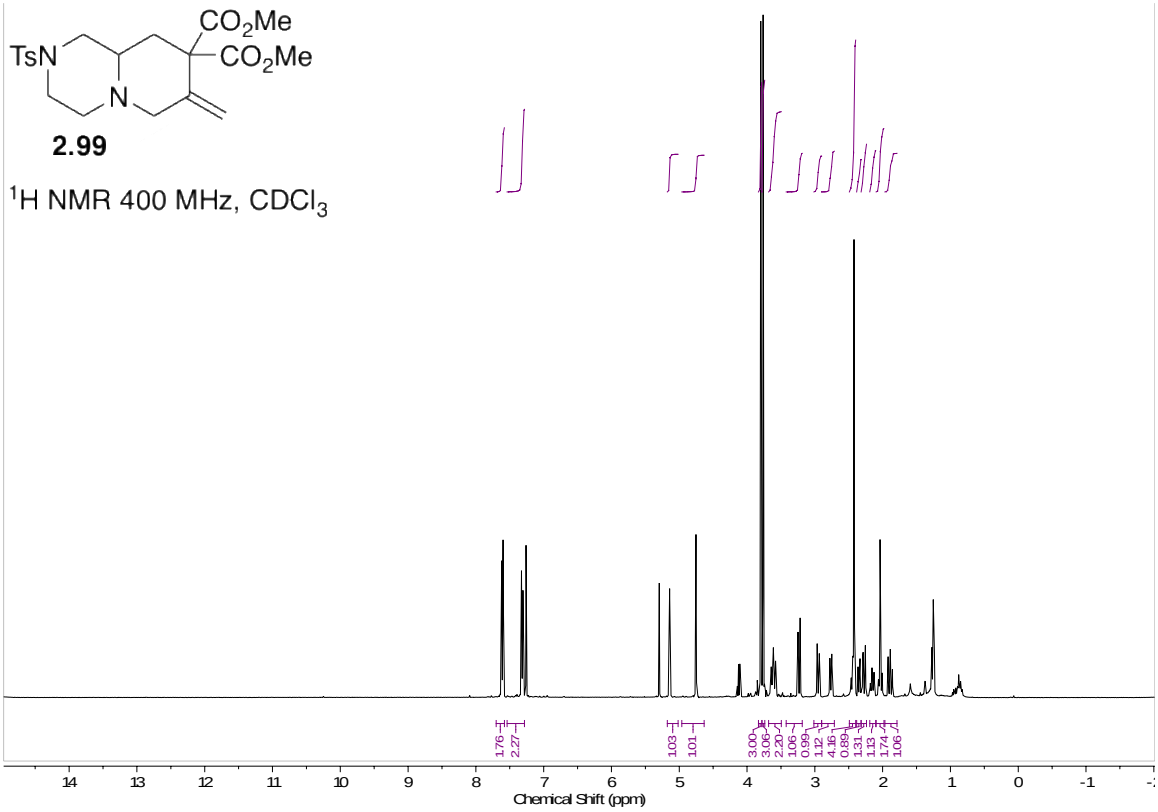

TsN
CO2Me
CO2Me
OH
2.95
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

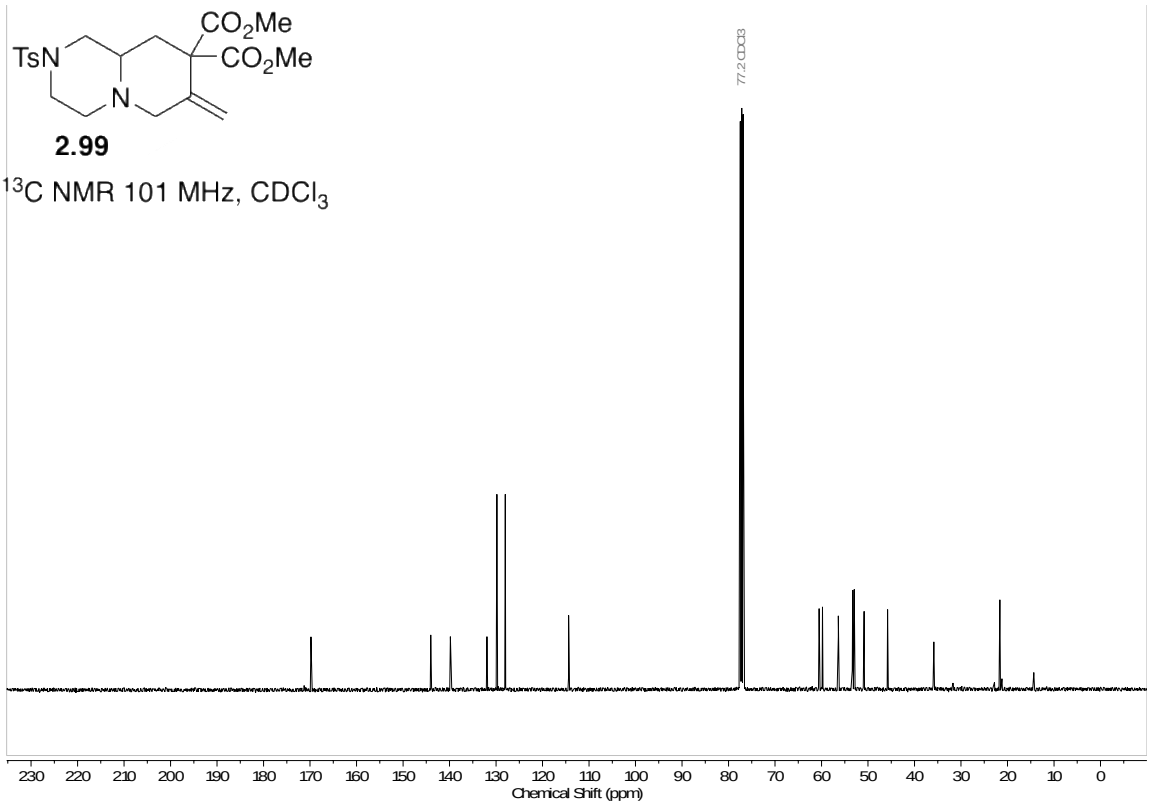

TsN
CO2Me
CO2Me
NsN
2.96
1H NMR 400 MHz, CDCl3
7.26 CDCl3
1.08
5.36
2.09
2.19
3.04
3.06
1.82
2.03
1.12
1.02
3.10
0.82
1.10
2.40
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)


TsN
CO2Me
CO2Me
NsN
2.96
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)


TsN
CO2Me
CO2Me
NsN
2.96
1H NMR 400 MHz, CDCl3
7.26 CDCl3
Chemical Shift (ppm)

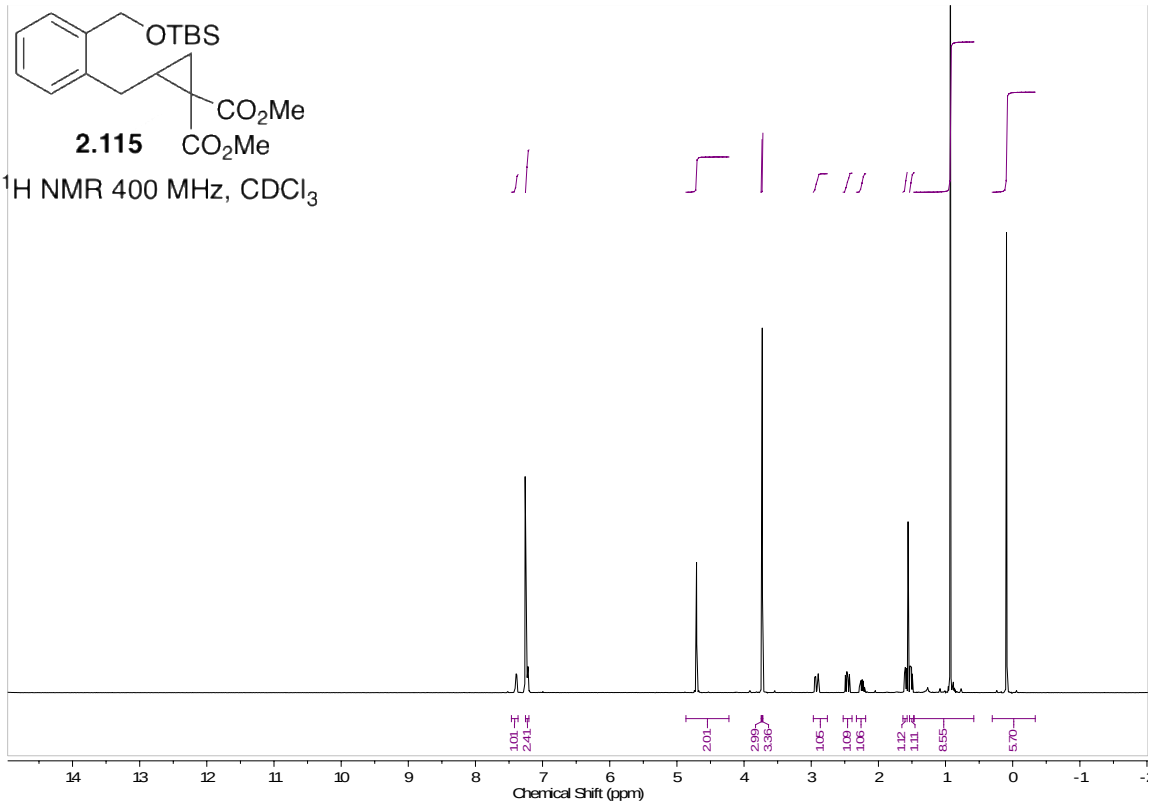

TsN
CO2Me
CO2Me
HN
2.97
1H NMR 400 MHz, CDCl3
7.26 CDCl3
Chemical Shift (ppm)


TsN
CO2Me
CO2Me
N
2.99
1H NMR 400 MHz, CDCl3
Chemical Shift (ppm)



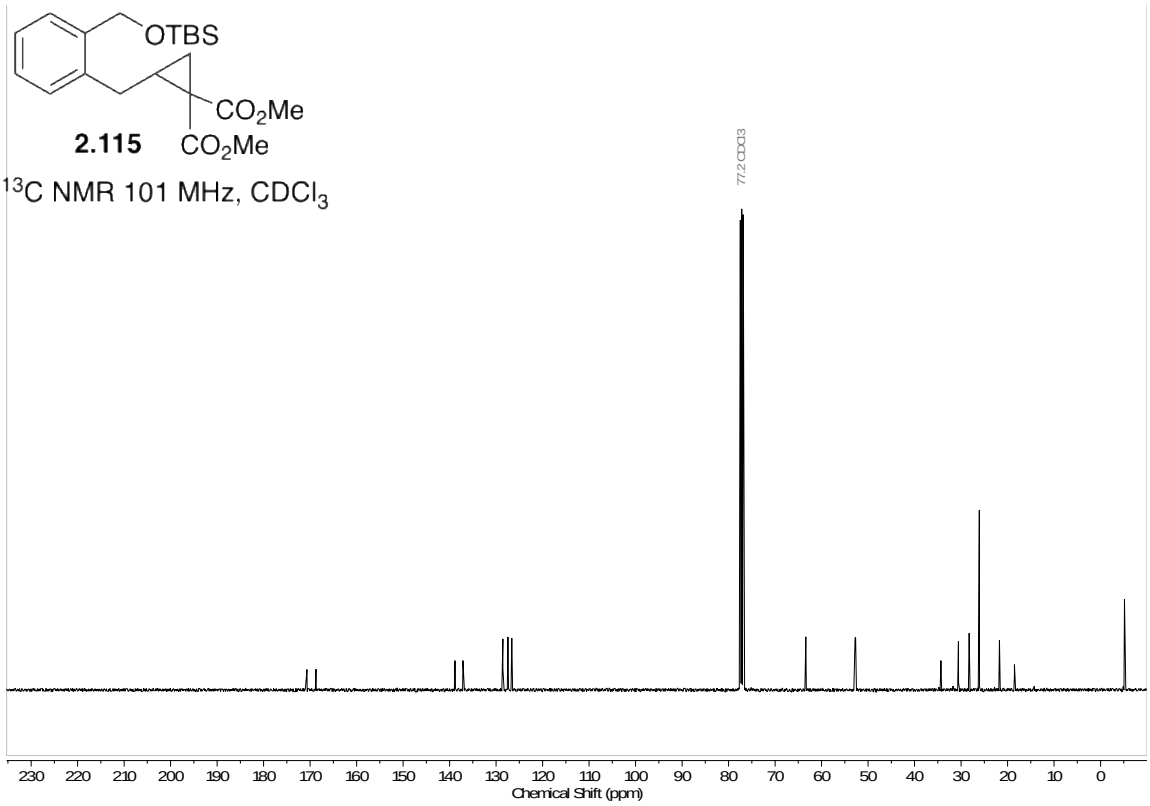
2.99

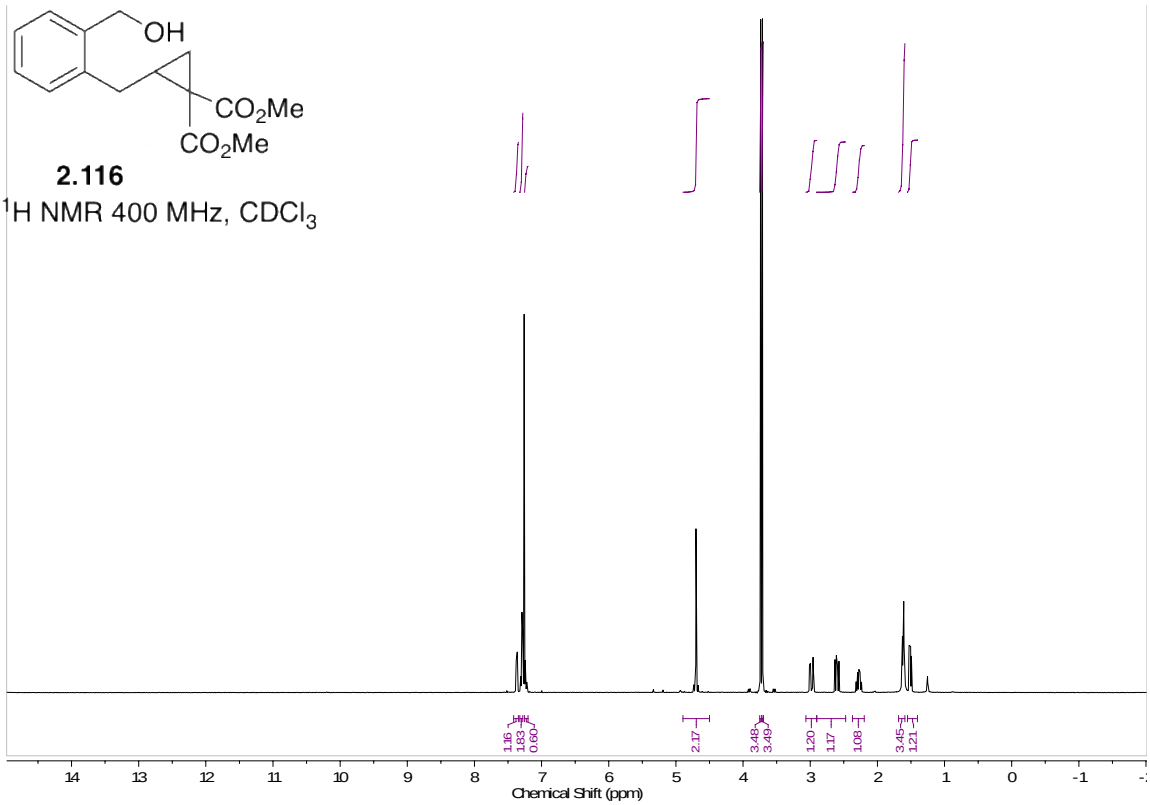
^{13}C NMR 101 MHz, $CDCl_3$

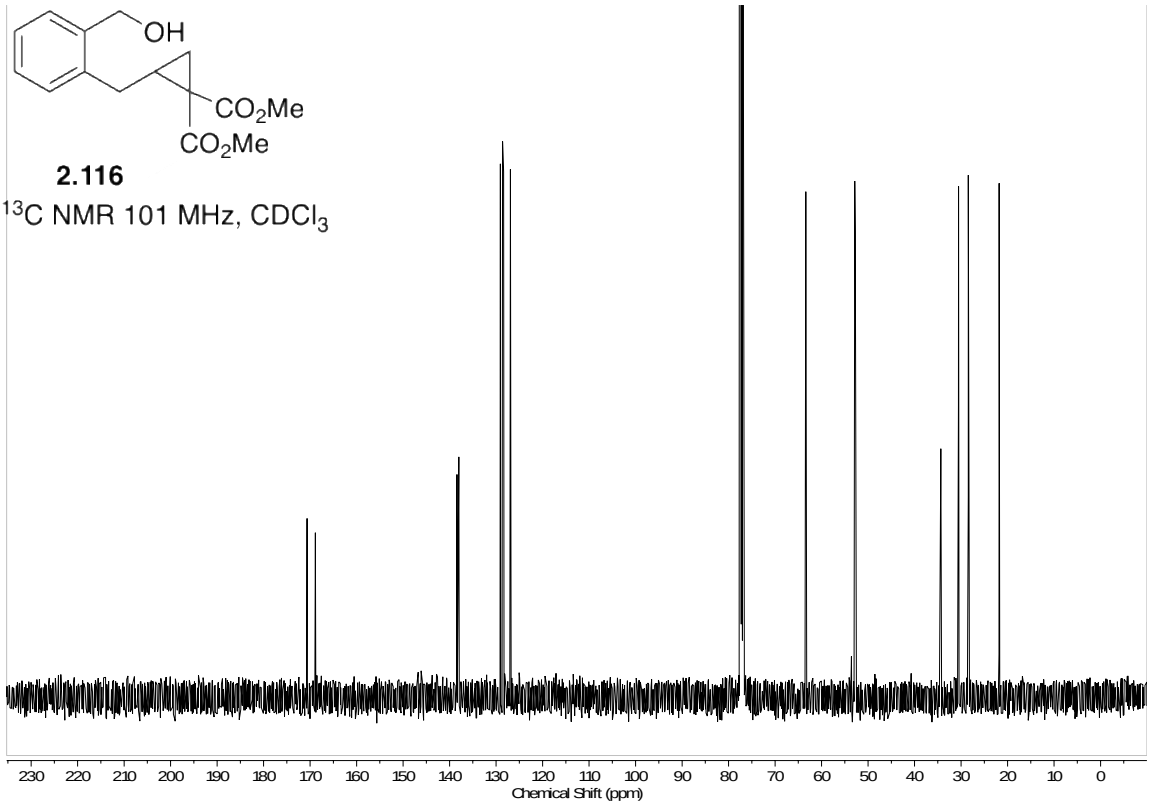


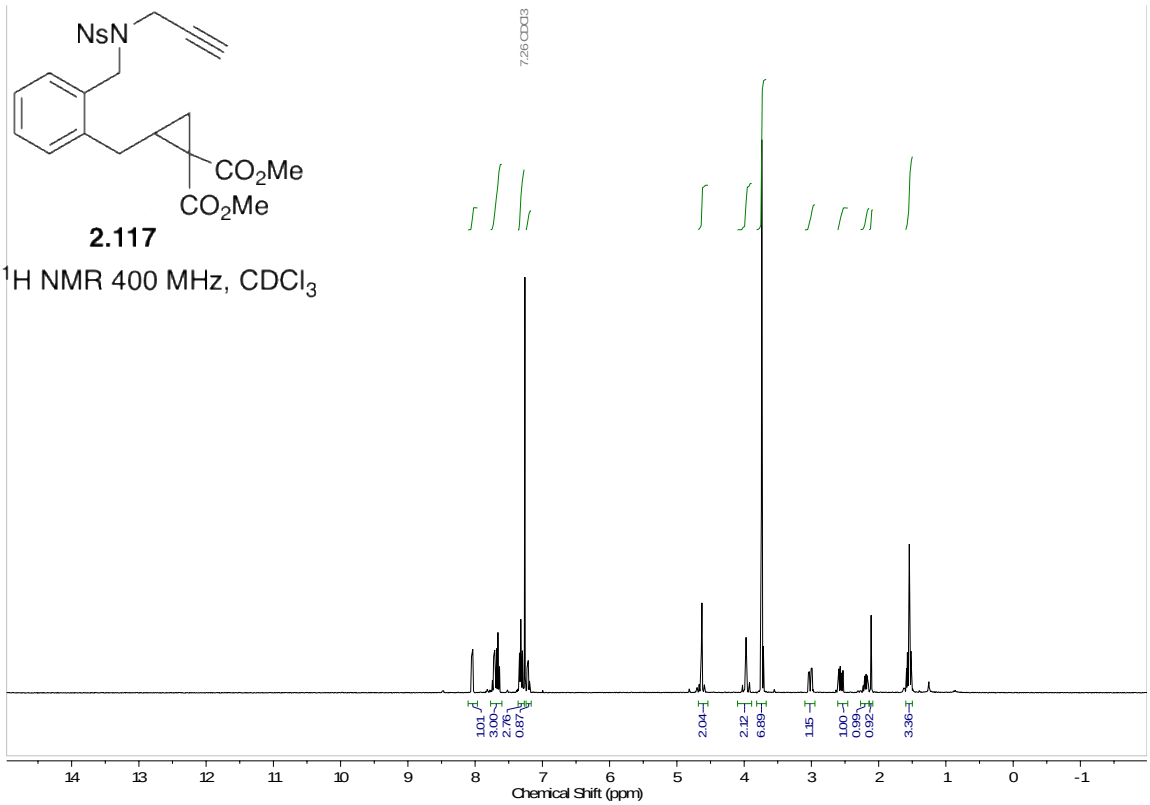
2.115

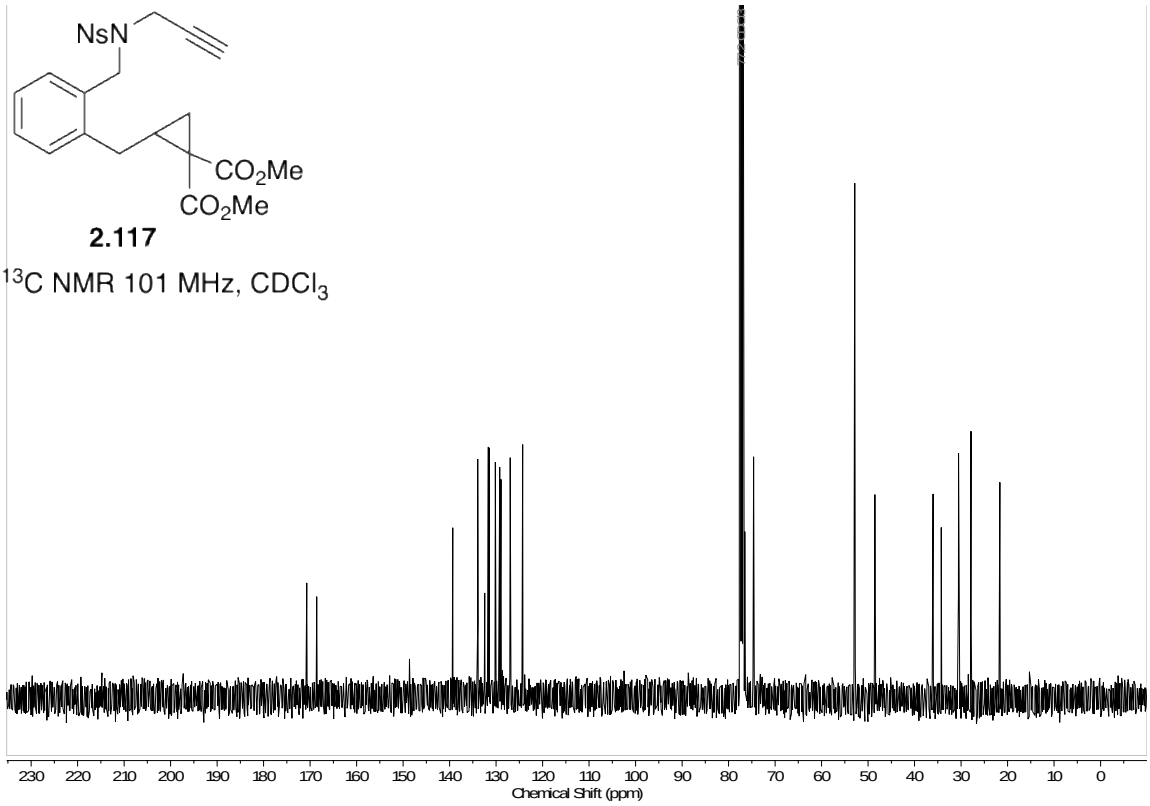
^{1}H NMR 400 MHz, $CDCl_3$


OTBS
CO2Me
CO2Me
2.115
13C NMR 101 MHz, CDCl3
77.2 CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


OH
CO2Me
CO2Me
2.116
1H NMR 400 MHz, CDCl3
1.16
1.83
0.60
2.17
3.48
3.49
1.20
1.17
1.08
3.45
1.21
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

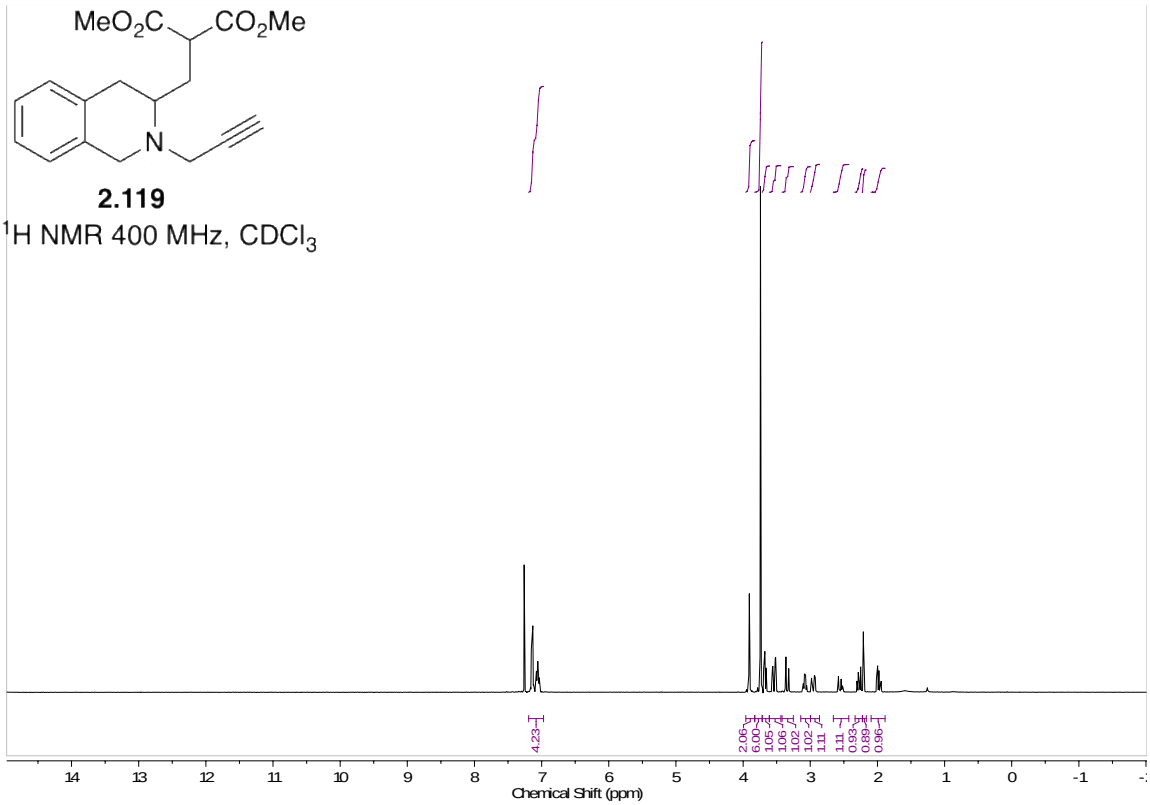

OH
CO2Me
CO2Me
2.116
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


NsN
CO2Me
CO2Me
2.117
1H NMR 400 MHz, CDCl3
7.26 CDCl3
1.01
3.00
2.76
0.87
2.04
2.12
6.89
1.15
1.00
0.99
0.92
3.36
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)



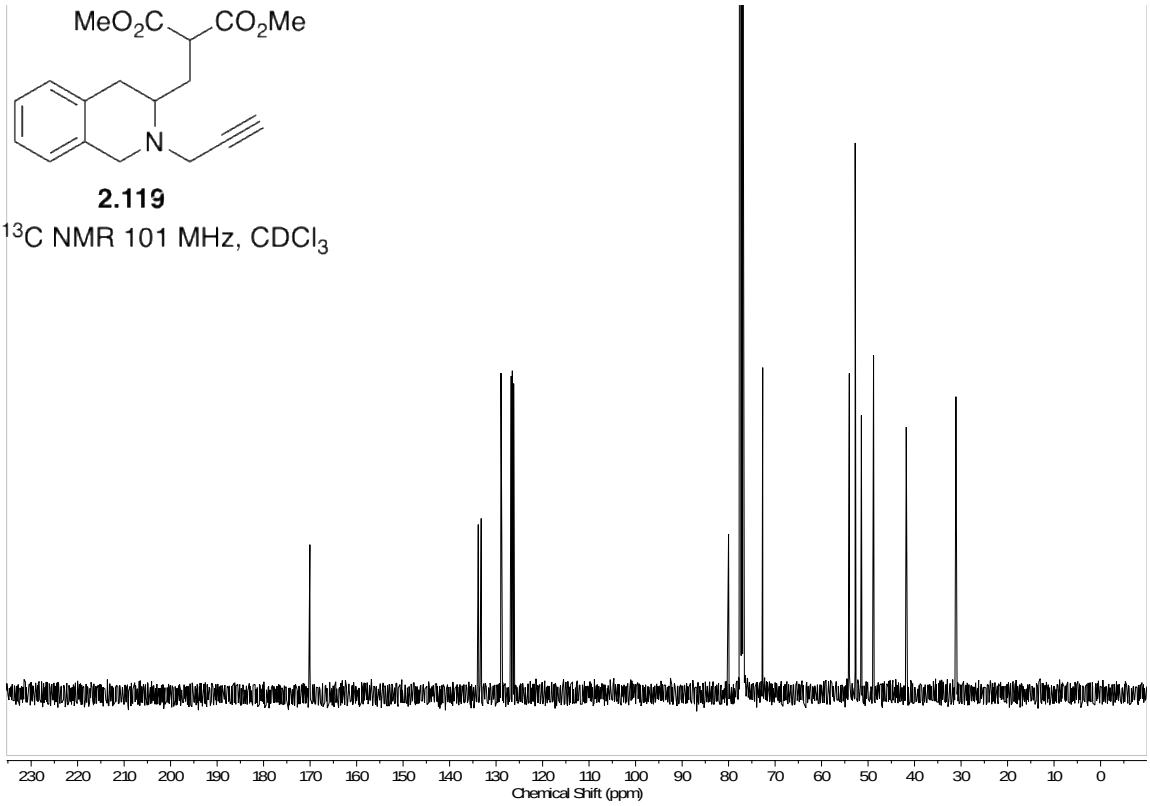
2.117

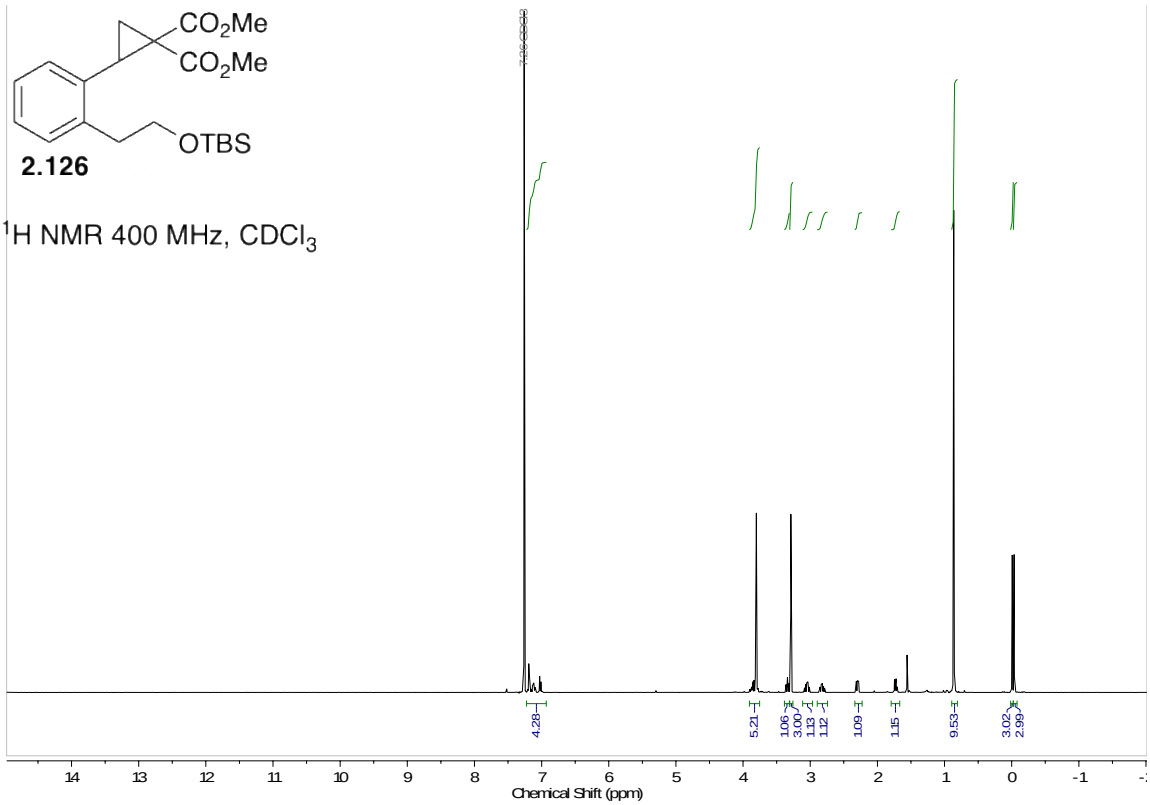
^{13}C NMR 101 MHz, $CDCl_3$

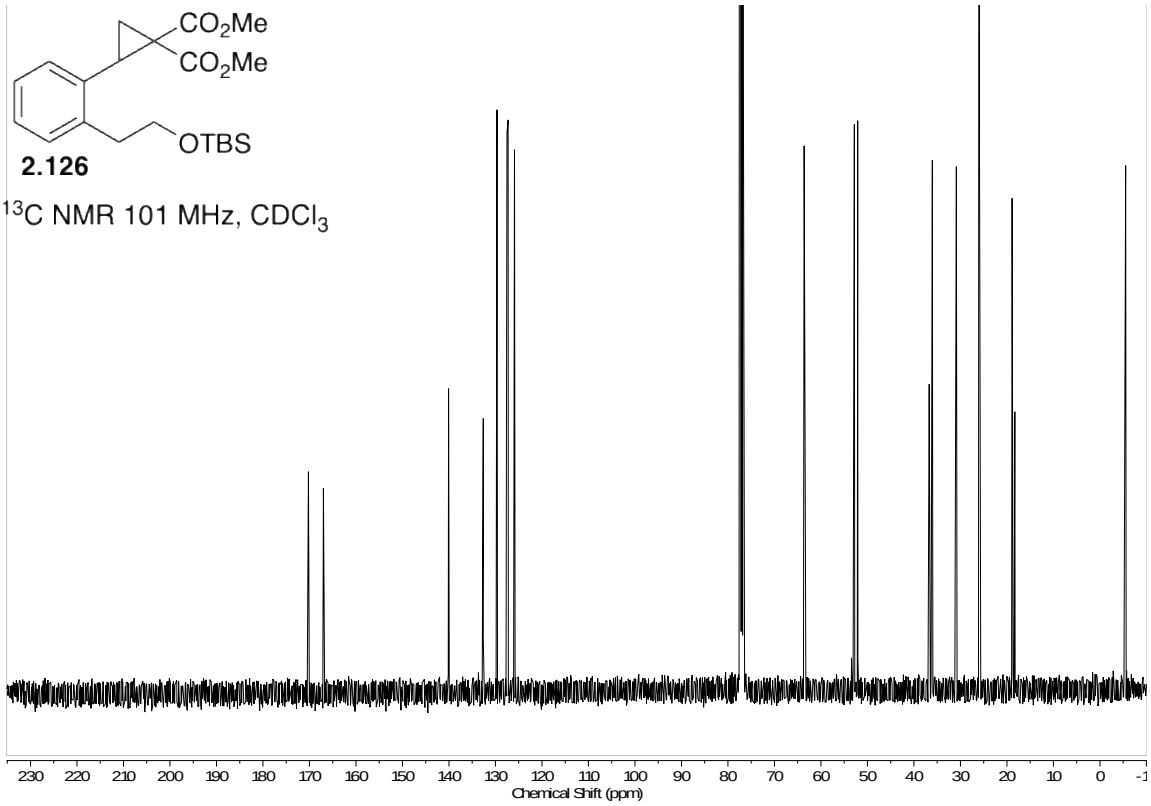


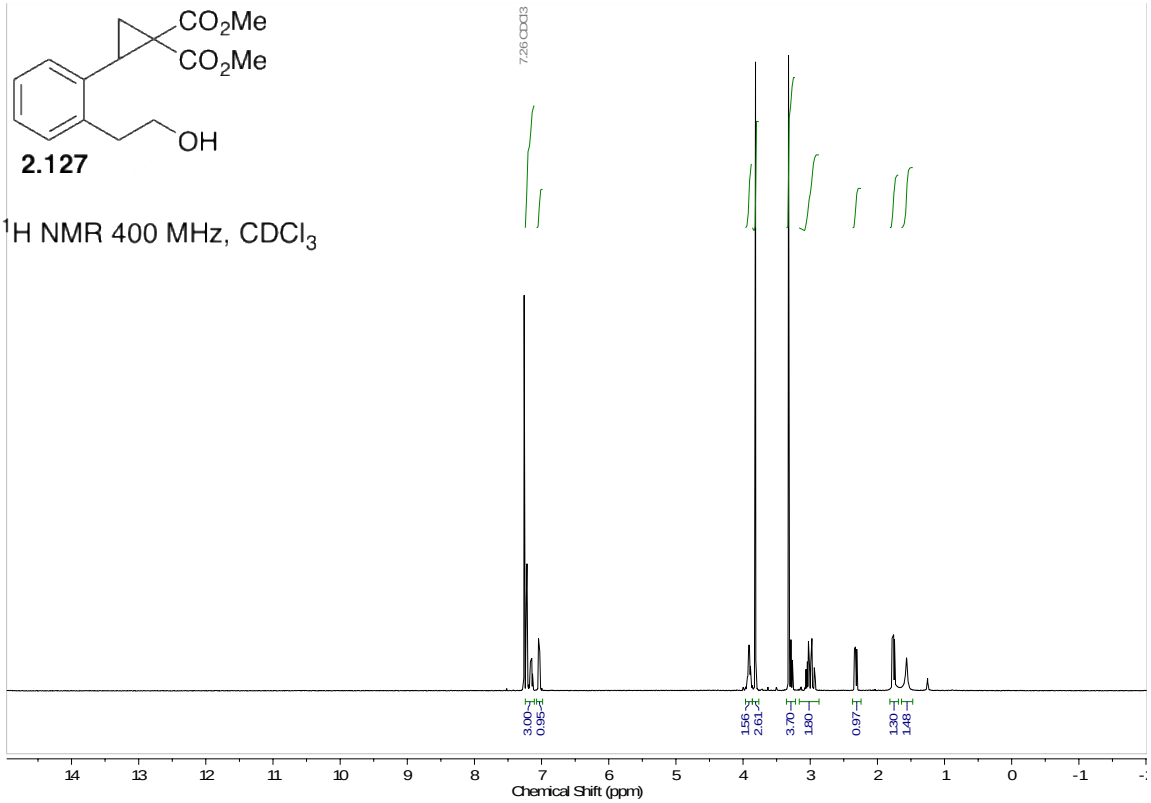
2.119

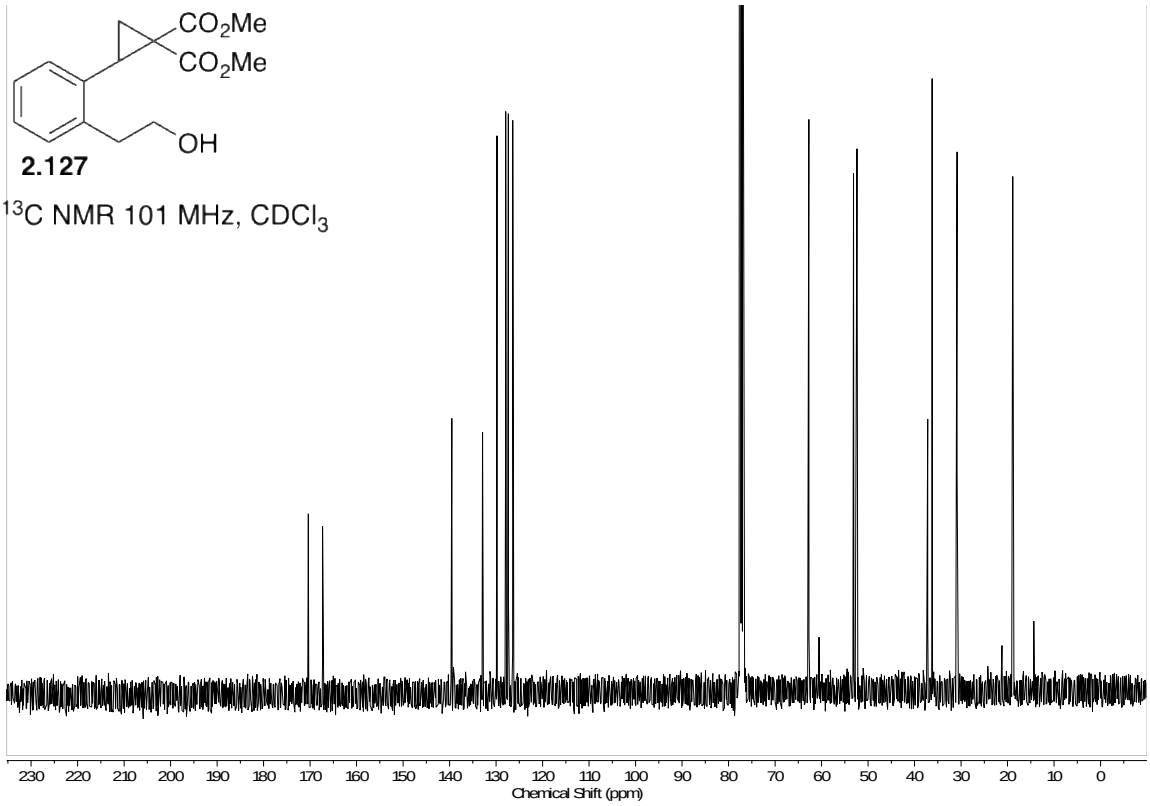
^{1}H NMR 400 MHz, $CDCl_3$

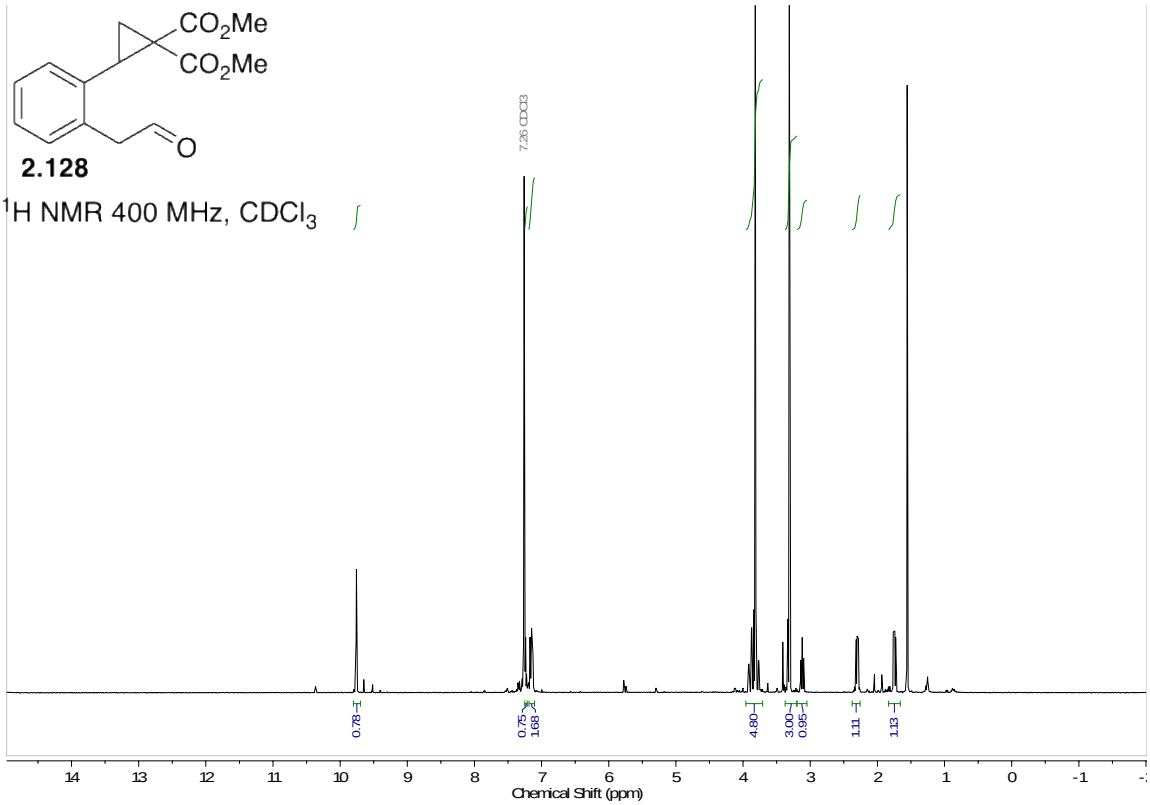

MeO2C
CO2Me
N
2.119
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

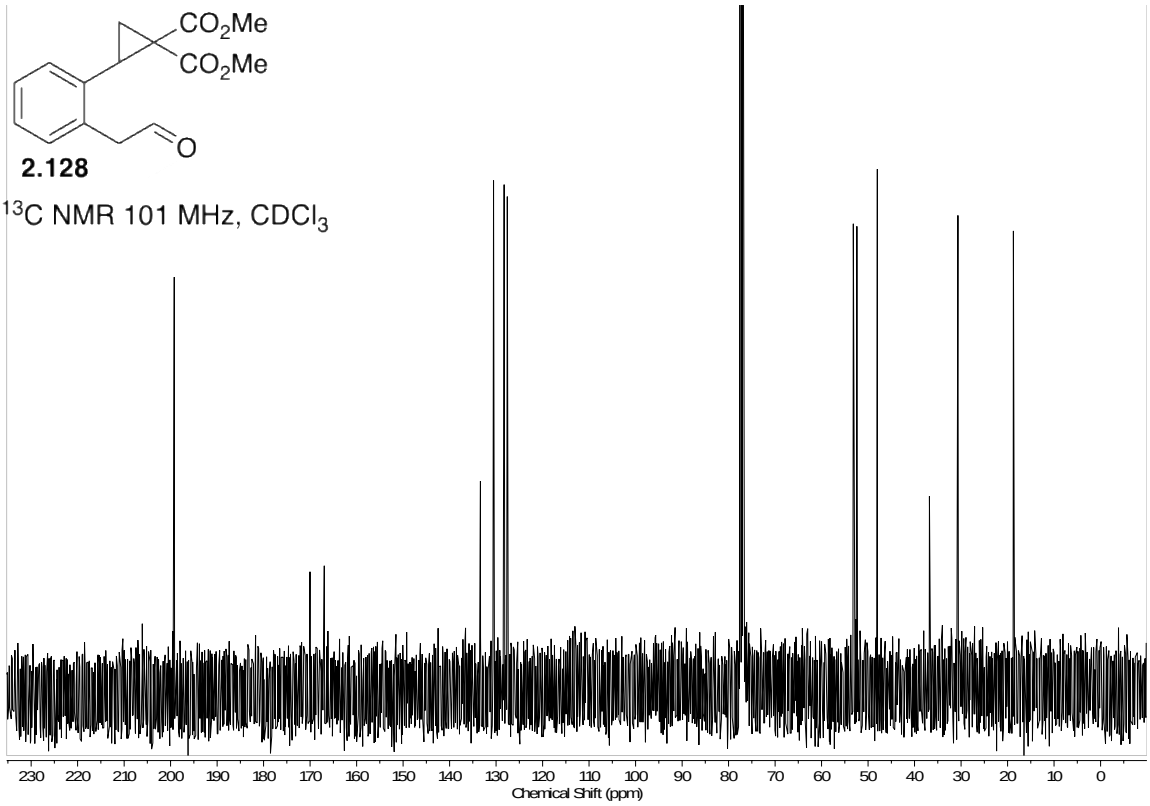

CO2Me
CO2Me
OTBS
2.126
1H NMR 400 MHz, CDCl3
4.28
5.21
1.06
3.00
1.13
1.12
1.09
1.15
9.53
3.02
2.99
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)

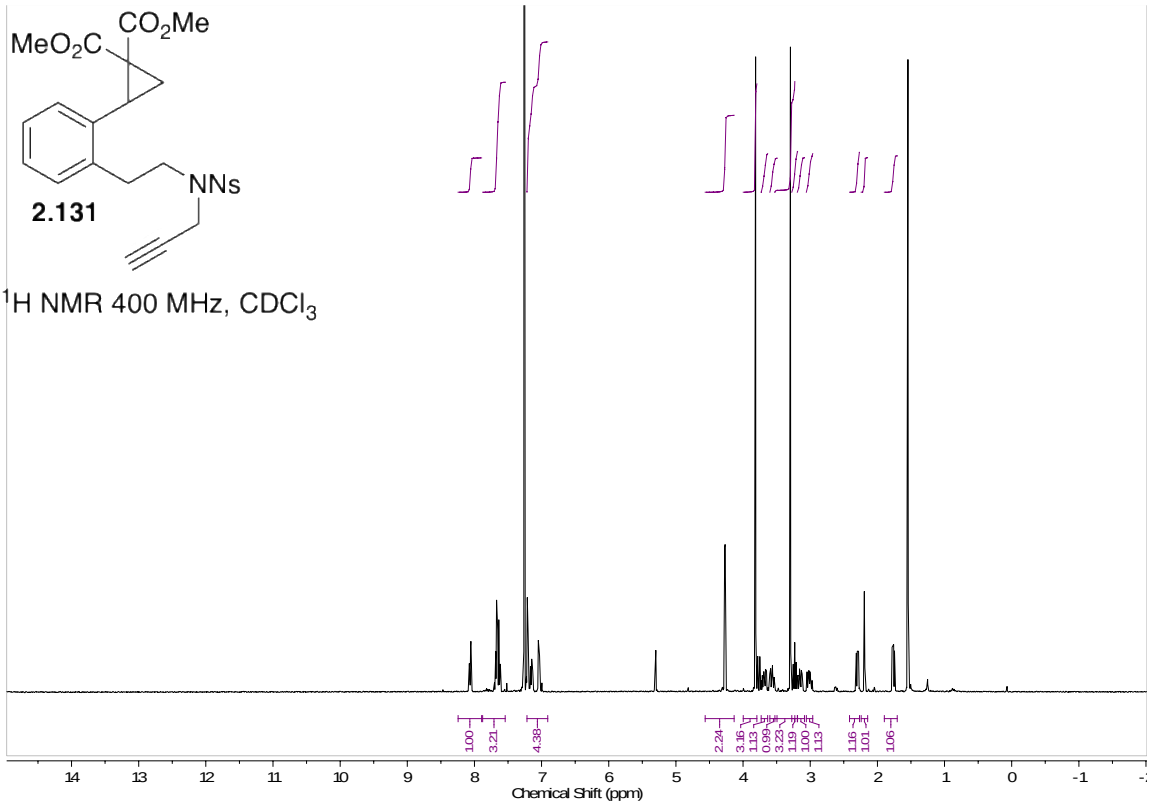

CO2Me
CO2Me
OTBS
2.126
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

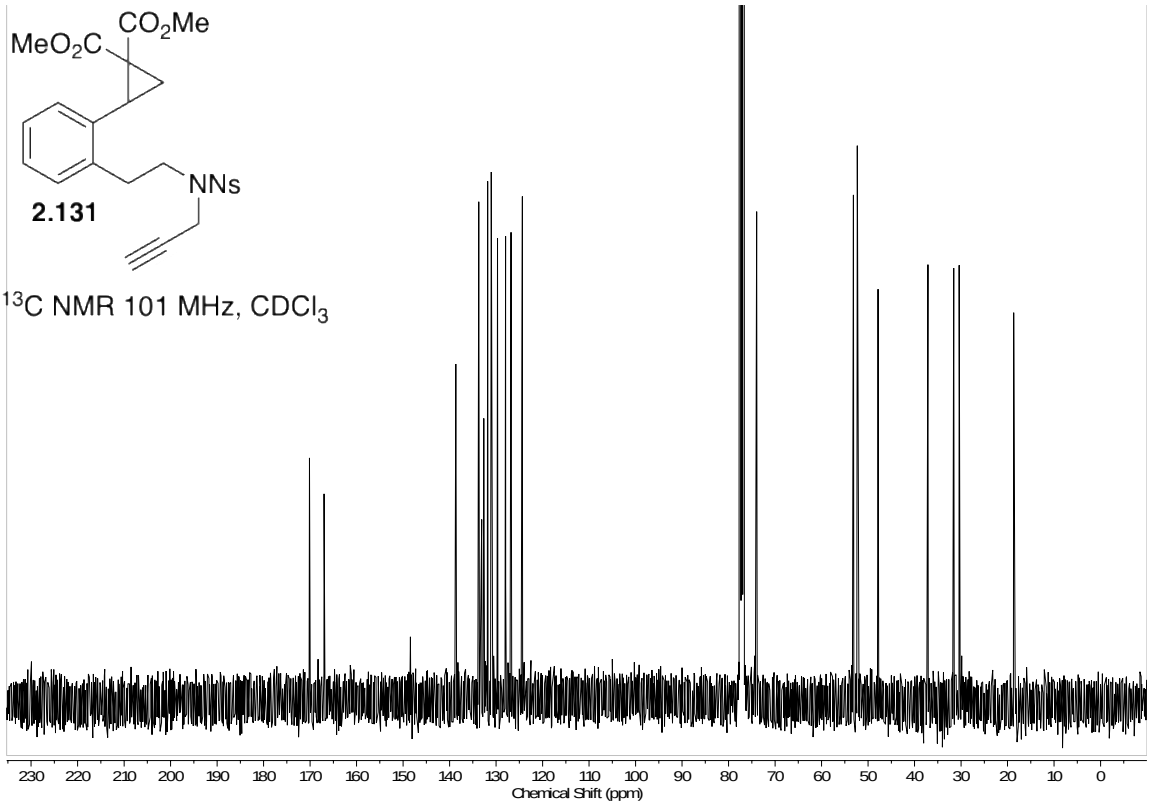

CO2Me
CO2Me
OH
2.127
1H NMR 400 MHz, CDCl3
7.26 CDCl3
3.00
0.95
1.56
2.61
3.70
1.80
0.97
1.30
1.48
Chemical Shift (ppm)

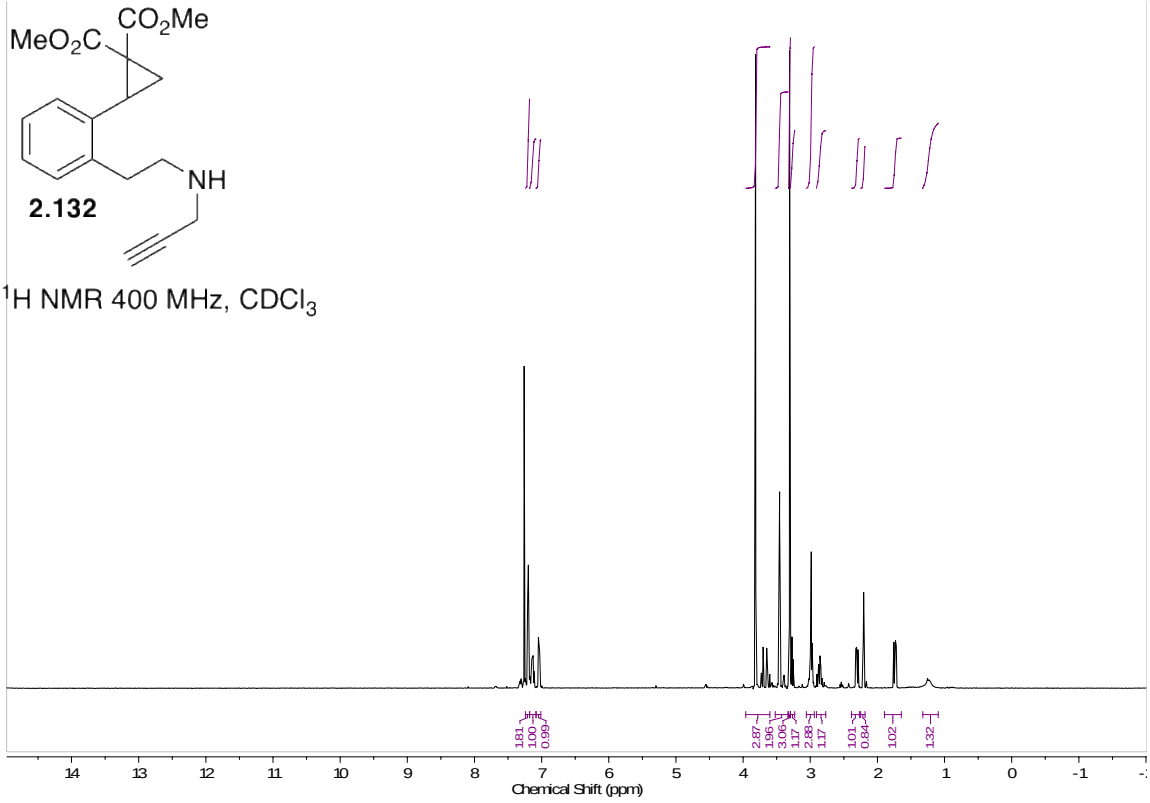

CO2Me
CO2Me
OH
2.127
13C NMR 101 MHz, CDCl3
Chemical Shift (ppm)

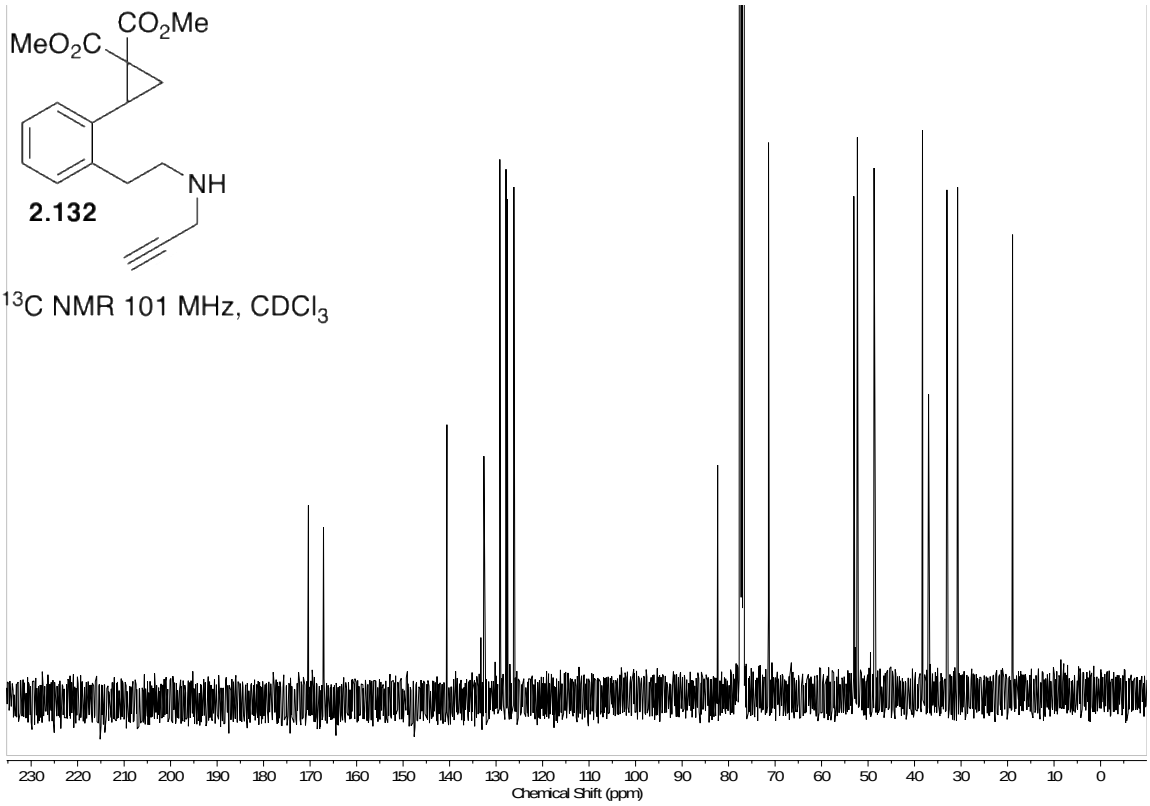

CO2Me
CO2Me
O
2.128
1H NMR 400 MHz, CDCl3
7.26 CDCl3
0.78
0.75
1.68
4.80
3.00
0.95
1.11
1.13
Chemical Shift (ppm)

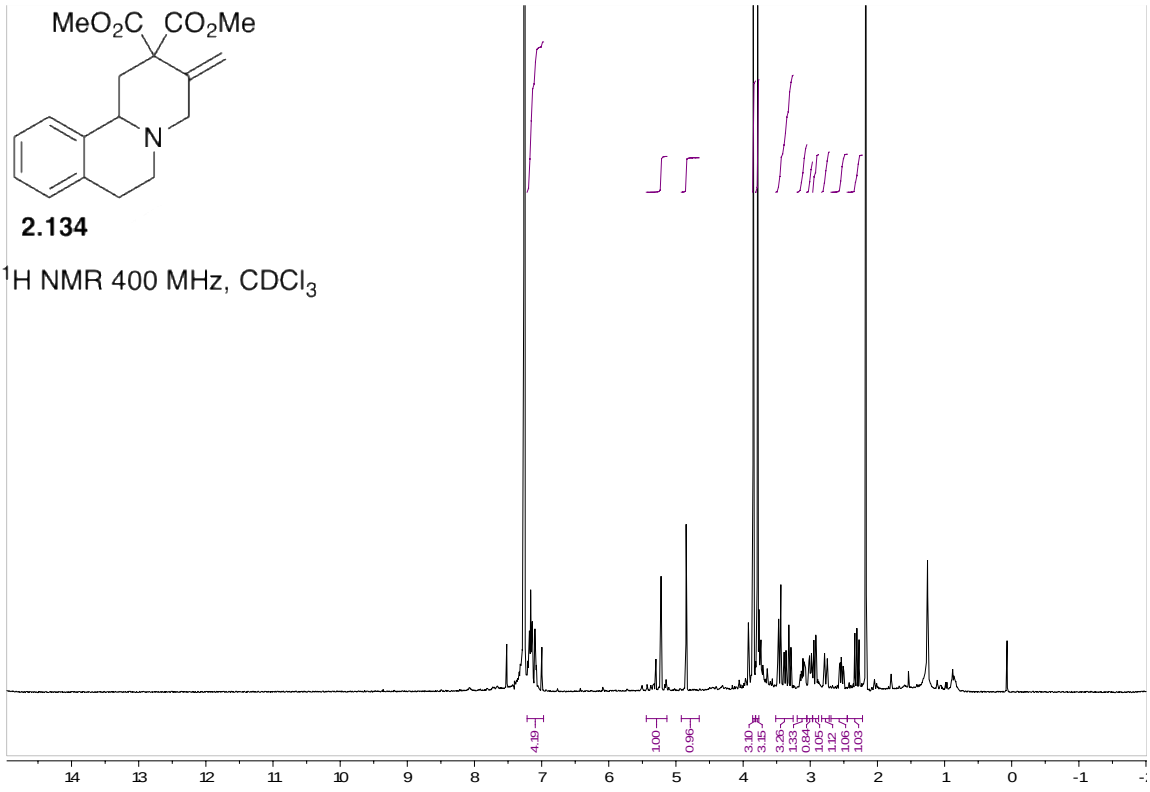

CO2Me
CO2Me
O
2.128
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

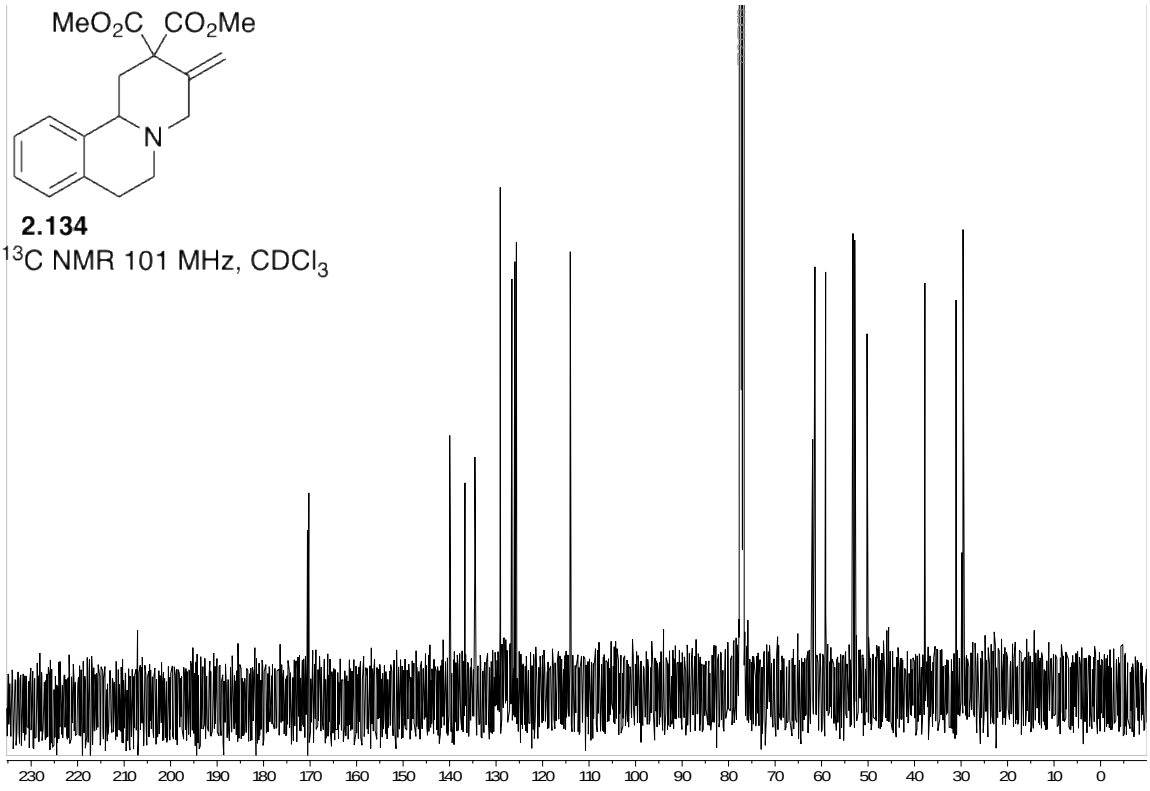

MeO2C
CO2Me
NNs
2.131
1H NMR 400 MHz, CDCl3
100
3.21
4.38
2.24
3.16
1.13
0.99
3.23
1.19
1.00
1.13
1.16
1.01
1.06
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)


MeO2C
CO2Me
NNs
2.131
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


MeO2C
CO2Me
NH
2.132
1H NMR 400 MHz, CDCl3
1.81
1.00
0.99
2.87
1.96
3.06
1.17
2.88
1.17
1.01
0.84
1.02
1.32
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)


MeO2C
CO2Me
NH
2.132
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


MeO2C
CO2Me
N
2.134
1H NMR 400 MHz, CDCl3
4.19
1.00
0.96
3.10
3.15
3.28
1.33
0.84
1.05
1.12
1.06
1.03
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1


MeO2C CO2Me
N
2.134
13C NMR 101 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Curriculum Vitae

EDUCATION

Bachelor of Science, Honours Specialization in Biochemistry and Chemistry Sept. 2014 – May 2018
The University of Western Ontario, London, Ontario

Master of Science Chemistry, Organic Sept 2018 – Present
The University of Western Ontario, London, Ontario
Research Supervisor: M. A. Kerr.

RESEARCH EXPERIENCE

Masters Student Sept. 2018 – Present
The University of Western Ontario, London, Ontario
Research Supervisor: M. A. Kerr

- Developed a new synthetic protocol for forming bicyclic piperidines from donor-acceptor cyclopropanes using a one-pot reaction
- Synthesized multiple new organic compounds using named reactions

Chemistry Thesis Research Project Sept 2017 – March 2018
The University of Western Ontario, London, Ontario
Research Supervisor: J. M. Blacquiere

- Synthesized and studied the reactivity of a Pd(II) 1-azaallyl species
- Worked with highly reactive compounds in a glovebox
- Attempted copolymerization of carbon monoxide with polar monomers with Pd(II) species

Summer Research Position
The University of Western Ontario, London, Ontario Summer 2017
Research Supervisor: K. M. Baines

- Synthesized and tested reactivity of novel tin catecholate complexes thermally and mechanochemically

Summer Research Position
The University of Western Ontario, London, Ontario Summer 2018
Research Supervisor: J. B. Gilroy

- Synthesized new metal formazanate compounds
- Tested the spectroscopic and electrochemical properties of formazanate compounds

PUBLICATIONS

- Maar, R. R.; Zhang, R.; Stephens, D. G.; Ding, Z.; Gilroy, J. B., *Angew. Chem. Int. Ed.* **2019**, *131*, 1064-1068.

AWARDS

- NSERC Summer Research Grant 2017, 2018
- Dean's List, *The University of Western Ontario*, London, Ontario 2015, 2016, 2018

EMPLOYMENT

Teaching Assistant – Western University Sept 2018 – April 2020

- Supervised laboratory activities and provided guidance to students
- Graded assignments for Organic Chemistry for Life Sciences I and Organic Chemistry II