10-30-2019 12:00 PM

The Synthesis of Heterocycles and Carbocycles and Work Towards Kainic Acid

Mathew L. Piotrowski
The University of Western Ontario

Supervisor
Kerr, Michael A.
The University of Western Ontario

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

Abstract

This thesis focuses on the synthesis of a variety of heterocycles and carbocycles such as pyrrolidines, dihydrofurans, dihydropyrroles, cyclopentenes, and 2,5-dihydrooxepines. Traditional synthetic methods are discussed first, followed by the manipulation of donor-acceptor cyclopropanes towards the above-mentioned compounds. This leads to a discussion about an important pyrrolidine-containing natural product known as kainic acid. Kainic acid has been studied in the neuroscience field for its biological properties which have led to a better understanding of common human neurological disorders like epilepsy, Huntington's disease and the after-effects of strokes.

Chapter two focuses on a common rearrangement of donor-acceptor cyclopropanes known as the Cloke-Wilson reaction. Without isolating the desired cyclopropane, two modes of reactivity were observed which depended solely on the choice of starting reagent. The first was the traditional Cloke-Wilson rearrangement generating dihydrofurans and the second was a vinylogous variant forming 2,5-dihydrooxepines. It was discovered that with careful choice of Lewis acid or transition metal catalysts, each of the obtained compounds can be manipulated to other dihydrofuran derivatives or dihydropyrrole heterocycles. One of the dihydropyrrole compounds obtained was deemed as a viable synthetic precursor towards kainic acid.

Chapter three describes the synthetic efforts towards kainic acid utilizing the methodology from chapter two. The difficulties towards this natural molecule will be presented with the major issue resulting from stereochemical constraints. This resulted in the successful synthesis of β-allokainic acid which is one of the less active isomers of naturally occurring kainic acid.

Chapter four discloses a single-step manipulation of the dihydrofurans synthesized via Cloke-Wilson rearrangement to their corresponding cyclopentenes. Extensive screening of Lewis acids and solvents provided insights into the possible mechanism of this reaction.

Keywords

Donor-Acceptor Cyclopropanes, Carbocycles, Heterocycles, Pyrrolidines, Dihydropyrroles, Dihydrofurans, Cyclopentenes, Dihydrooxepines, Cycloaddition, Annulation, Rearrangement, Cloke-Wilson Rearrangement, Vinylogous Cloke-Wilson Rearrangement, Rearrangement of Heterocycles, Kainic Acid, β-Allo-Kainic Acid

Lay Audience Abstract

This thesis describes the synthesis of molecules known as carbocycles and heterocycles. These types of compounds are abundant in products obtained from natural sources and are highly sought in the pharmaceutical industry. Finding new ways of synthesizing carbocycles and heterocycles is always in high demand. Common synthetic procedures are discussed, followed by how cyclopropanes can be utilized towards the mentioned compounds. This leads to a discussion about a heterocycle-containing natural product known as kainic acid. The biological properties of this compound were studied which lead to a better understanding of common human neurological disorders such as epilepsy, Huntington's disease and the after-effects of strokes.

Chapter two focuses on a common reaction involving cyclopropanes and their rearrangement to heterocycles of value. The reaction proceeds by a famous transformation known as the Cloke-Wilson rearrangement. It was discovered that with a careful choice of catalyst, each of the compounds can be manipulated to other heterocycles that are seen in desired pharmaceuticals and natural products. We determined one of the compounds to be a useful starting reagent towards the synthesis of kainic acid.

Chapter three describes the synthetic efforts towards kainic acid. Initial synthetic problems are discussed with the most significant issue arising once the relative three-dimensional arrangement of atoms on a specific intermediate was determined, also known as stereochemistry. Attempts at obtaining the correct stereochemistry failed which resulted in the synthesis of one of the isomers of kainic acid known as β-allokainic acid.

Chapter four discloses the rearrangement of products obtained in chapter two to their corresponding cyclopentene derivatives. An extensive testing of catalysts and solvents were preformed which helped obtain the cyclopentenes in high yields and provided insights into the possible mechanism of the rearrangement.

Acknowledgments

Firstly, I would like to thank Dr. Kerr for giving me the opportunity to be part of your group. I have learned a lot from you, and I would like to thank you for believing in me throughout the many years I spent in your lab, especially during the days where I was very critical of myself. You shaped me into the chemists I am today which will greatly help in my future endeavors.

Next, I would like to thank Dr. Pagenkopf for letting me volunteer in his lab when I was in my third-year undergrad and then letting me work for him during the summer. I was able to get a taste of a graduate life style and gain valuable experience and knowledge which gave me an edge in my fourth-year thesis project. I would like to thank the graduate student mentors I had during this time. Geoff Phillips, thank you for taking me on during the summer months. I learned a lot from you and enjoyed working with you. Naresh Vemula, thank you for taking me on as a volunteer. You are a great mentor and I learned a great deal from you. I am happy that we remain in touch and I consider you a good friend.

I would like to thank the past and current Kerr group members for your constant support and making the entire graduate experience an enjoyable time. For the past members, I would like to thank Joanne Curiel-Tejeda for being my 4491 graduate mentor and becoming a great friend throughout the years. You've taught me a lot and you were the person I always sought advice from. I miss the fun salsa music in the lab and your Dominican nights at your place with those amazing plantain chips. I would like to thank Poly Kyriacou for your support and your funny jokes and random videos you always shared. You always managed to find music that matched the specific mood of the lab, some of which were hilarious. I miss the "go-pro" days back in 217. Matthew Vriesen, my twin, thank you for teaching me how to do proper columns. I always looked up to you as a chemist and I appreciate all your help. You're a great friend and I hope to share many more uncontrollable laughs with you. Jeff Kerkovius, thanks for those mechanism fun days you started. It was nice to have the brain juices flowing.

For the current group members, I would like to give a big thanks to Lauren Irwin. I appreciate all the times we were able to discuss chemistry and bounce ideas off one another. I am extremely happy that I got to know you and that I can call you my friend. We got to share

a lot of good memories together with my two favorites being the ringing of the dinner bell in Halifax and our hilarious and awkward elevator ride after TAing. I still start laughing whenever I think about it. I want to also thank you for always including me in parties and other hangouts. I wouldn't have got to know and become friends with other people in the department if it wasn't for you. You are an unbelievably talented chemist and I wish nothing but the best for you. I hope that we can stay in touch throughout the years.

I would like to thank my mom and my sister for their unconditional support and always being interested in my day even though you never understood what I was talking about. I appreciate all the help you gave me; delicious home cooked meals so I never had to worry about making dinner, driving me sometimes all the way home, or letting me crash at your place whenever I stayed very late in the lab, and simply how both of you always shared in my excitement whenever something ended up working in the lab and when I got my first publication. I love you both.

To my beautiful and loving fiancé, words can't express how grateful I am to have had you by my side during my graduate studies. You were always there for me during my bad days in the lab and always managed to make me feel better with your loving hugs and by making me laugh with the many silly faces you do and the silly jokes you say. You always listened to me vent my frustrations and knew exactly what to say to make me feel better. You were the first person I wanted to share any good news with. You seemed to be always more excited than I was which made me laugh. I cherish the memories I made with you more than anything else in the world and I look forward for the many more memories we'll share. You are my best friend and I love you with all my heart.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Appendices

List of Abbreviations

(R)-(-)-BDHP	(R)-(-)-1,1’-Binaphthyl-2,2’-diyl hydrogenphosphate
2,2-DMP	2,2-dimethoxypropane
2,4-DNPH	2,4-dinitrophenylhydrazine
6-$(Me)_2$biPy	6,6'-dimethyl-2,2'-bipyridine
A	acceptor
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Ar	Aryl group
Bn	Benzyl
CBZ-Cl	Benzyl chloroformate
COBI	Oxzazborolidinim ion
CSA	Camphursulfonic acid
D	Donor
DA	Donor-acceptor
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEPC	Diethyl pyrocarbonate
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine

DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPA	Diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
dr	Diastereomeric ratio
DYKAT	Dynamic kinetic asymmetric transformation
ee	Enantiomeric excess
EtAOc	Ethylacetate
EtOH	Ethanol
ETP	Epidithiodiketopiperazines
EWG	Electron withdrawing group
HFIP	Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
IBX	2-iodoxybenzoic acid
iGluRs	Ionotropic glutamate receptors
*i*PrNEt	Isopropylethylamine
*i*PrOH	Isopropanol
KHMDS	Potassium bis(trimethylsilyl)amide
LA	Lewis acid
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
$LiAlH(OtBu)_3$	Lithium tri-tert-butoxyaluminum hydride

LiHMDS	Lithium bis(trimethylsilyl)amide
LTMP	Lithium tetramethylpiperidide
MBH	Mortia-Baylis-Hillman
MCR	Multicomponent Reactions
MeCN	acetonitrile
MeMgBr	Methyl magnesiumbromide
$MeNO_2$	Nitromethane
MeOH	Methanol
mGluRs	Metabotropic glutamate receptors
$Mn(OAc)_3$	Manganese triacetate
MOMCl	Chloromethyl methyl ether
MS	Molecular Sieves
MsCl	Methanesulfonyl chloride
MTBE	Methyl tert-butyl ether
MW	Microwave
NaOAc	Sodium acetate
NaOEt	Sodium ethoxide
n-BuLi	Butyl lithium
NMO	N-methylmorpholine N-oxide
o-QMs	*o*-Quinone methides
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II) dichloride
Pd-TMM	Palladium- trimethylenemethane
PhCl	Chlorobenzene

$PhI(OAc)_2$	(diacetoxyiodo)benzene
PhSeCl	Benzeneselenenyl chloride
PPh_3	Triphenylphosphine
PPTS	Pyridium p-toluenensulfonate
p-$TsOH \cdot H_2O$	*p*-toluenesulfonic acid monohydrate
$Rh_2(esp)_2$	Bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]
$Rh_2(OAc)_4$	Rhodium(II)acetate
RNA	Ribonucleic acid
SET	Single electron transfer
TBAF	Tetrabutylammonium fluoride
TBHP	Tert-butyl hydrogen peroxide
TBPB	Tert-butyl peroxybenzoate
TBSCl	Tert-butyldimethylsilyl chloride
t-$BuCO_2H$	Pivalic acid
t-BuOH	Tert-butanol
t-BuOK	Potassium tert-butoxide
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
TMSCN	Trimethylsilyl cyanide
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

Chapter 1

1 The Importance of Heterocycles and Carbocycles in Life and Synthesis

Structures that are studied for their important biological properties, whether isolated from natural sources or synthesized in the lab, typically have one or more cyclic motifs either fused together or connected by a small linker chain[1–3]. Due to the rigidity of cyclic structures, better interactions with the binding sites are typically obtained since the active conformation is locked in place. Acyclic systems however, contain multiple rotating bonds resulting in many different conformations, only one of which results in the desired binding interaction[3]. Therefore, ideal pharmaceutical candidates contain heterocyclic or carbocyclic structures.

Cyclic compounds are extremely important for normal life functions[1,2,4]. DNA, which contains the genetic information of all life forms on our planet, is made of heterocyclic compounds, nucleic acids and carbohydrates (Figure **1-1a**). Amino acids, which are the building blocks of proteins also contain several cyclic motifs (Figure **1-1b**). Important porphyrins, which are heterocyclic macrocycles, such as chlorophyll-a and heme are vital compounds for photosynthesis and the transfer of oxygen to body tissues respectively (Figure **1-1c**). Drugs that many people take on a regular basis to maintain a healthy lifestyle like vitamins are all composed of heterocyclic systems (Figure **1-1d**).

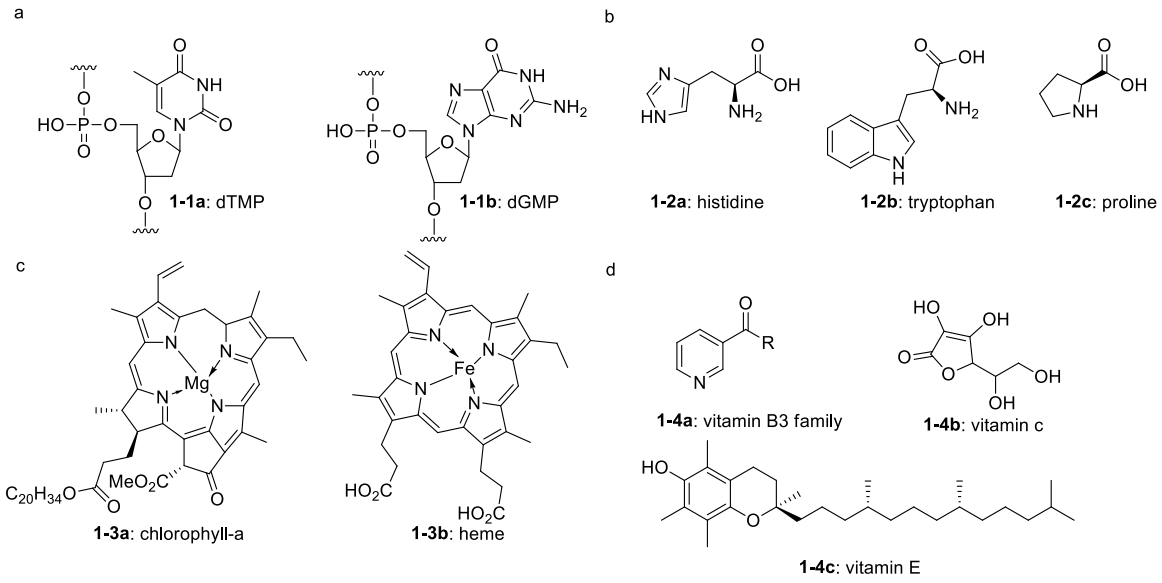


Figure 1-1. Important biological compounds. [a] Nucleic acids and carbohydrate segment of DNA. [b] Amino acids. [c] Heterocyclic macrocycles responsible for photosynthesis and transfer of oxygen to blood. [d] Vitamins

Since cyclic structures are so important in life and highly desirable in the pharmaceutical industry, ways of synthesizing hetero- and carbocycles is one of the most explored fields of organic chemistry. New methodologies are published on a regular basis that can provide easy access to complex cyclic motifs towards natural product synthesis or for pharmaceutical studies. From the vast array of hetero- and carbocycles, only a select few are discussed in this dissertation. This includes five-membered carbo- and heterocyclic rings and seven-membered oxacycles (Figure **1-2**). Examples of such structures in natural products and pharmaceuticals will be presented.

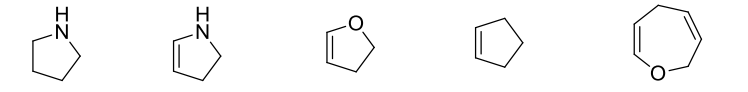


Figure 1-2. The hetero- and carbocycles of interest

1.1 Synthesis of Five-Membered Carbocycles and Heterocycles

1.1.1 Synthesis of Pyrrolidines

Pyrrolidines are among the most important heterocyclic compounds that are featured in a wide array of naturally occurring and synthesized compounds that contain many biological properties.[5–7] (Figure **1-3a**). Paraherquamide A[8] (**1-10**) is a potent anthelmintic agent with activity against drug resistant intestinal parasites. γ-Carboxyglutamic derivatives[9] (**1-11**) have been shown to be useful towards the synthesis of neuroprotective agents. Kainic acid[10] (**1-12**) possesses important neuroexcitatory properties that will be discussed in greater detail in the upcoming sections. Enantiomerically pure pyrrolidines (**1-13** to **1-15**) also have a dominant role as organocatalysts[11,12] (Figure **1-3b**).

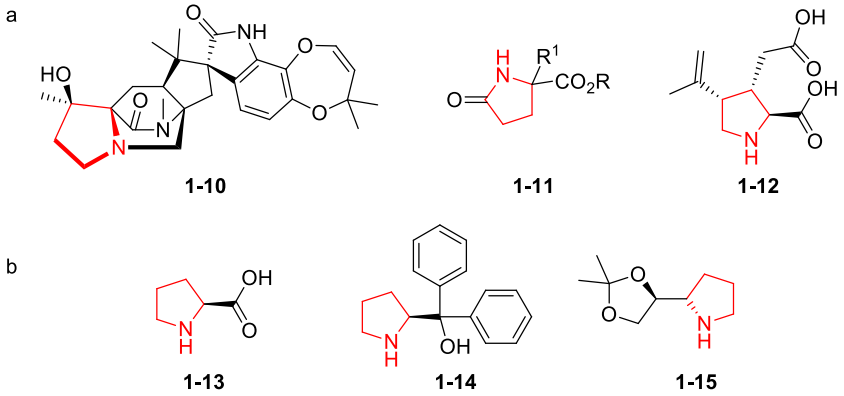
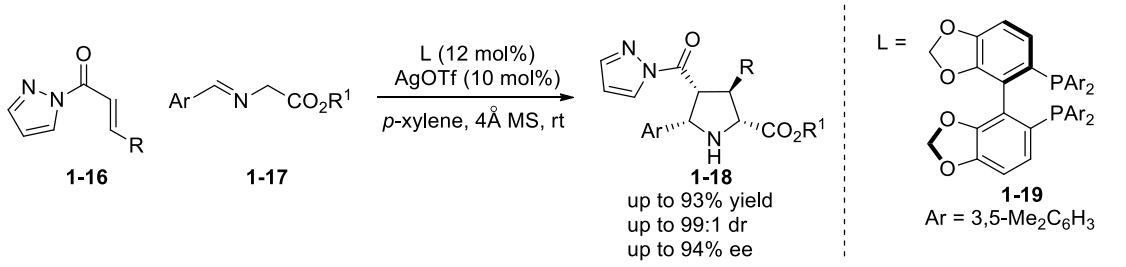


Figure 1-3. [a] Select examples of naturally occurring and synthetically made compounds with biological properties. [b] Examples of organocatalysts.

Thus, discovering ways of synthesizing pyrrolidines can have a great impact in synthetic and pharmaceutical communities. The most common synthetic strategy of forming the pyrrolidine core is by [3+2]-cycloaddition and annulation chemistry.[11–19]

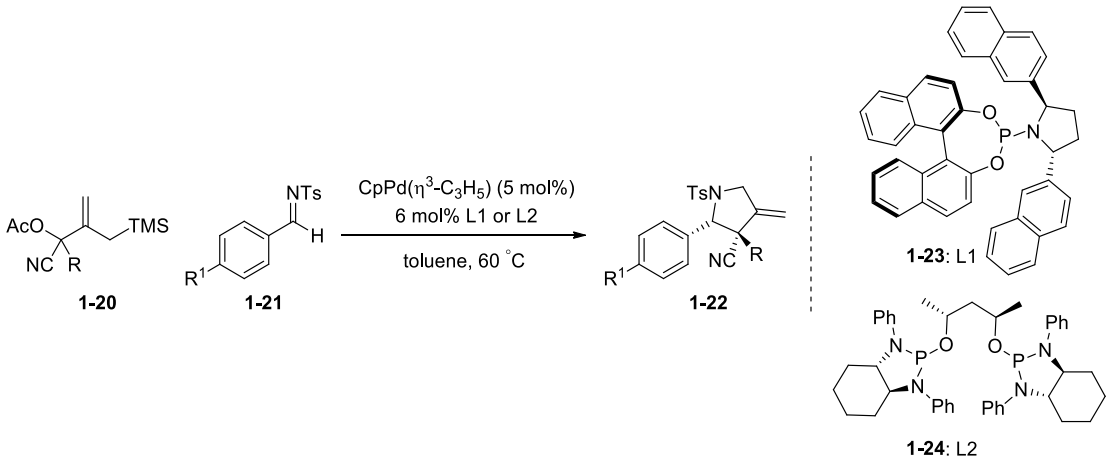
Recently, Singh and co-workers showed a synthesis of pyrrolidines rings (**1-18**) by a [3+2]-cycloaddition between α,β-unsaturated pyrazolamide (**1-16**) and azomethine ylides (**1-17**) using a Ag(I) catalyst and chiral ligand (**1-19**) (Scheme **1-1**).[20]



Scheme 1-1. Diastereo- and enantioselective synthesis of highly substituted pyrrolidines using a chiral Ag(I) catalyst

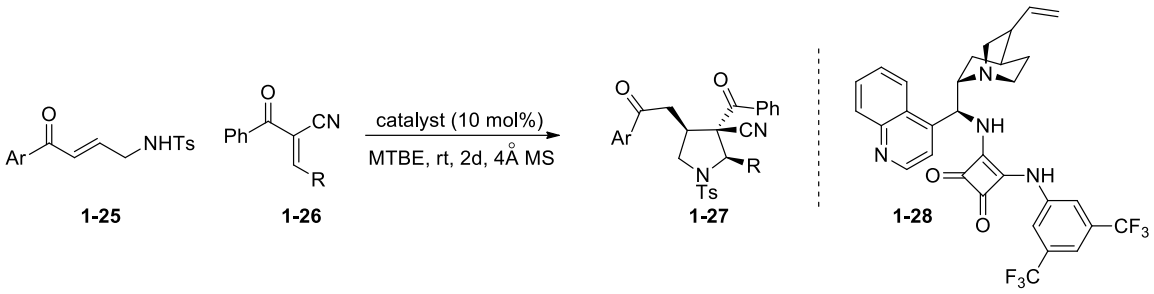
The pyrrolidines synthesized contained four contiguous stereogenic centers and were produced in excellent diastereoselectivity, high yields, and enantioselectivities. The group also showcased transformations of the pyrrolidine products to various synthetically useful advanced intermediates.

Since the first introduction of Pd-trimethylenemethane (Pd-TMM) complexes by Trost and Chan[21], their utility as three-carbon synthons for [3+2]-cycloaddition chemistry has grown significantly with the formation of a variety of carbo- and heterocycles of various ring sizes.[16,17,22,23] Trost *et al.* recently published an enantioselective synthesis of pyrrolidines (**1-22**) containing a quaternary center with the first use of disubstituted donors (**1-20**) in a Pd-TMM cycloaddition with imines (**1-21**).[24] The reaction was made possible with the use of diamidophosphite ligands (**1-23** and **1-24**) (Scheme **1-2**).



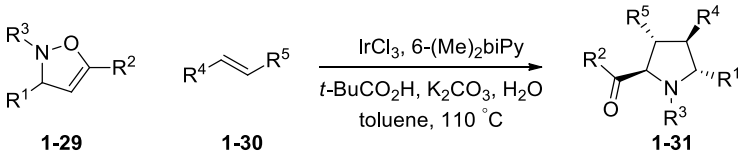
Scheme 1-2. Pd-TMM cycloaddition with disubstituted TMM-donors and imines forming enantioselective pyrrolidines containing quaternary centers

Continuing with the synthesis of pyrrolidines containing quaternary centers, Chandra Pan and co-workers utilized an organocatalyzed double Michael addition/annulation chemistry towards highly enantioselective pyrrolidines.[25] Using a cinchonidine derived bifunctional amino-squaramide catalyst (**1-28**), both N-tosyl amino-methyl enones (**1-25**) and *trans*-α-cyano-α,β-unsaturated ketones (**1-26**) were activated simultaneously towards a double Michael addition reaction to form pyrrolidines (**1-27**) (Scheme **1-3**).



Scheme 1-3. Organocatalyzed enantioselective double Michael addition towards highly substituted pyrrolidines

Although not enantioselective, Kang and co-workers were able to show the conversion of 2,3-dihydroisoxazoles (**1-29**) to fully substituted pyrrolidines (**1-31**) through an iridium-complex catalyzed N-O bond cleavage/rearrangement/cyclization of (**1-29**) with various alkenes (**1-30**)[26] (Scheme **1-4**).



Scheme 1-4. Single step transformation of 1,3-dihydroisoxazoles to pyrrolidines

The reaction was found to work with a variety of substrates bearing aromatic substituents; however, any alkyl substituents except for (R^3) resulted in no observed product. The iridium catalyst used could be recycled up to seven times with only a slight drop in yield which can be advantageous in industrial-scale reactions.

1.1.2 Synthesis of Dihydropyrroles

Similar to pyrrolidines, except with an extra unit of unsaturation, dihydropyrroles are another class of five-membered heterocycles that have a prominent role in natural products and pharmaceuticals (Figure **1-4**). Anthramycin (**1-32**) has been shown to interact in the minor groove of DNA to form covalent bonds with guanine bases. This interrupts biological processes that involve transcription factors and RNA polymerase which can aid in the treatment of various cancers.[27] Dihydropyrrole (**1-33**) has been proven to inhibit protein geranylgeranyltransferase type I which is an enzyme that is important for the regulation of many protein functions.[28,29] Dihydropyrrole (**1-34**) is an example of nonpeptide peptidomimetics which are an important class of compounds that mimic natural peptide strands and overcome the limitations of these peptides in therapeutic interventions.[30]

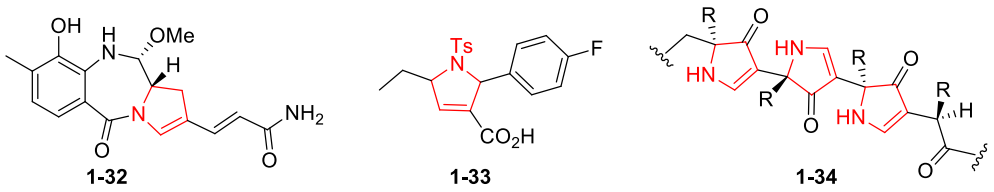
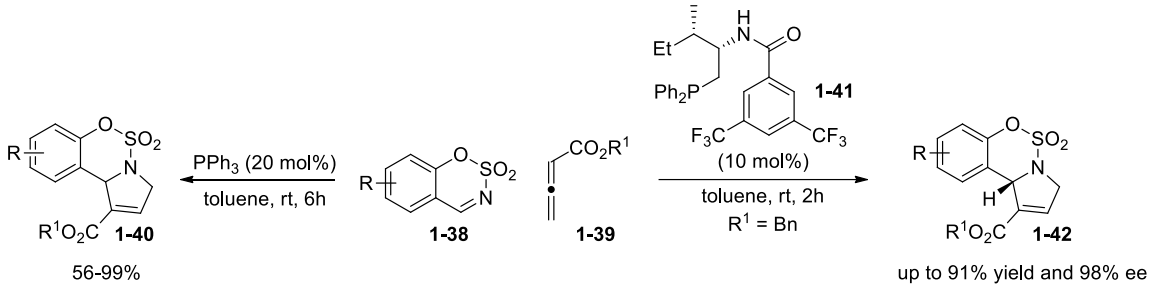


Figure 1-4. Natural and synthetic dihydropyrroles with important biological properties

Dihydropyrroles are commonly synthesized through cycloaddition and annulation chemistry. However, cycloisomerization reactions are also prevalent. Wender *et al.* were able to showcase the formation of dihydropyrroles (**1-37**) by treating aziridines (**1-35**) with silver or Bronsted acid catalysts. This resulted in the formation of 1,3-dipoles which reacted with a variety of alkynes (**1-36**) in a formal [3+2]-cycloaddition.[31] The reaction was shown to be highly regioselective (Scheme **1-5**).

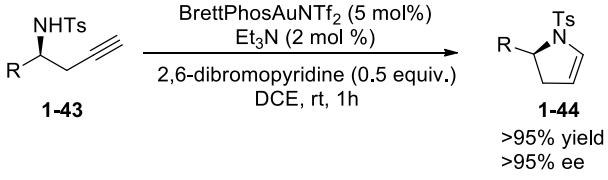
Scheme 1-5. Highly regioselective formation of dihydropyrroles through a formal [3+2]-cycloaddition

Asymmetric formal cycloadditions towards dihydropyrrole derivatives are also possible. Recently, Guo and co-workers performed a Ph_3P catalyzed [3+2]-cycloaddition with sulfamate derived cyclic imines (**1-38**) and allenoates (**1-39**) forming sulfamate fused dihydropyrroles (**1-40**) in high yields.[32] Using a phosphine chiral catalyst (**1-41**), an asymmetric version was developed forming the desired products in high enantiomeric purity (**1-42**) (Scheme **1-6**). Sulfamate fused dihydropyrroles are interesting heterocycles that could potentially be used in the pharmaceutical industry.[33]



Scheme 1-6. Phosphine catalyzed [3+2]-cycloaddition of sulfamate derived cyclic imines with allenoates

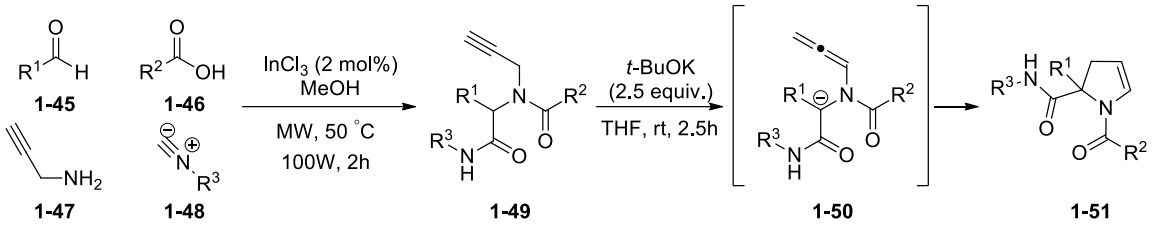
As mentioned above, cycloisomerizations are another common technique used towards dihydropyrrole synthesis. Ye and co-workers performed a gold catalyzed cycloisomerization of chiral homopropargyl sulfonamides (**1-43**) forming enantiopure dihydropyrroles (**1-44**)[34] (Scheme **1-7**). The reaction proceeded through an anti-Markovnikov addition. With careful examination of reaction conditions, the authors determined that adding a catalytic amount of base suppressed an undesirable dimerization reaction.[35]



Scheme 1-7. Cycloisomerization reaction producing enantiopure dihydropyrroles

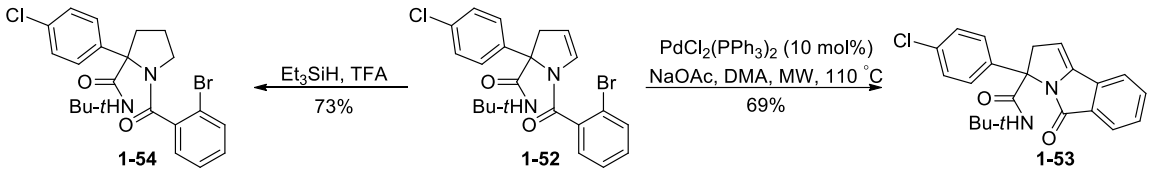
Multicomponent reactions (MCRs) are useful techniques that involve the reaction of three or more reactants in a single reaction vessel to produce a single product containing

majority of the reactants.[36] MCRs are a great way to form a variety of complex heterocycles and carbocycles since the reaction is highly chemo- and regioselective, atom economical, and step efficient.[36] Miranda *et al.* were able to show a four component Ugi reaction forming a propargyl-Ugi product (**1-49**). This was then treated with a strong base forming a Ugi-allenamide intermediate (**1-50**) that underwent a cycloisomerization to form dihydropyrrole derivatives (**1-51**)[37] (Scheme **1-8**).



Scheme 1-8. Four component Ugi reaction followed by base mediated cycloisomerization towards dihydropyrrole derivatives

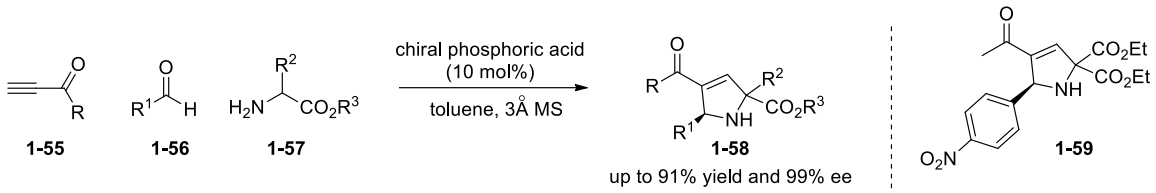
The utility of this transformation has been expanded by synthesizing advanced intermediates in a single step (Scheme **1-9**). Using dihydropyrrole (**1-52**), the group was able to form a bicyclic structure (**1-53**) by performing a Heck cross-coupling reaction. 2-arylpyrrolidine (**1-54**) was formed through a reduction using triethylsilane hydride which are pharmacologically important compounds.[38]



Scheme 1-9. Subsequent transformations of dihydropyrroles

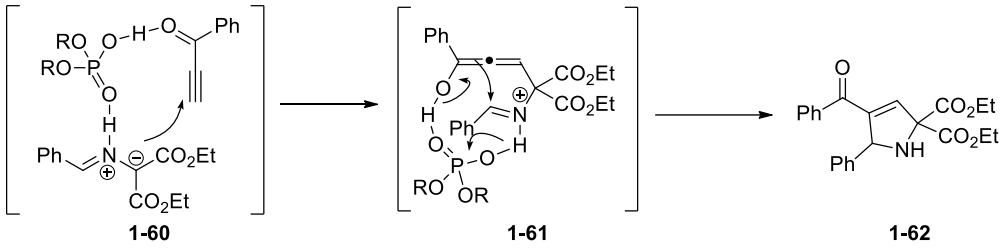
Another interesting MCR was developed by Gong *et al.* resulting in the first catalytic asymmetric formal [3+2] cycloaddition of electron deficient alkynes and azomethine ylides under chiral phosphoric acid conditions.[39] The use of various aldehydes (**1-56**) and α-amino esters (**1-57**) generated the desired azomethine ylide *in-situ* which reacted with various alkynes (**1-55**) forming dihydropyrrole (**1-58**) derivatives in high yields and high

enantioselectivities (Scheme **1-10**). Compound (**1-59**) showed to have potential bioactivities *in vitro* against mammary carcinoma cell line, MCF7.



Scheme 1-10. First catalytic asymmetric formal [3+2]-cycloaddition using electron deficient alkynes and azomethine ylides to form dihydropyrroles

DFT studies showed that the chiral phosphoric acid has a duel role in the reaction: it behaves as a Bronsted acid and Lewis base (Scheme **1-11**). The alkyne becomes more electron deficient once the carbonyl oxygen interacted with the OH group on the phosphorus through H-bonding. Simultaneously, the anion of the azomethine ylide became more reactive through H-bonding between the N-H of the ylide and the Lewis basic phosphoryl oxygen (**1-60**). This resulted in a conjugate addition of the azomethine ylide to the alkyne followed by a Mannich-type cyclization (**1-61**) forming dihydropyrrole (**1-62**).

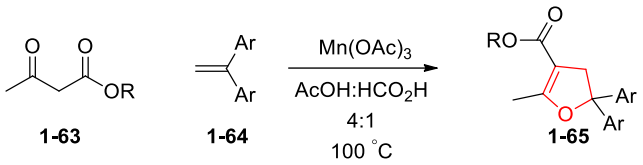


Scheme 1-11. Proposed mechanism towards dihydropyrrole formation showcasing the dual role of the chiral phosphoric acid

1.1.3 Synthesis of Dihydrofurans

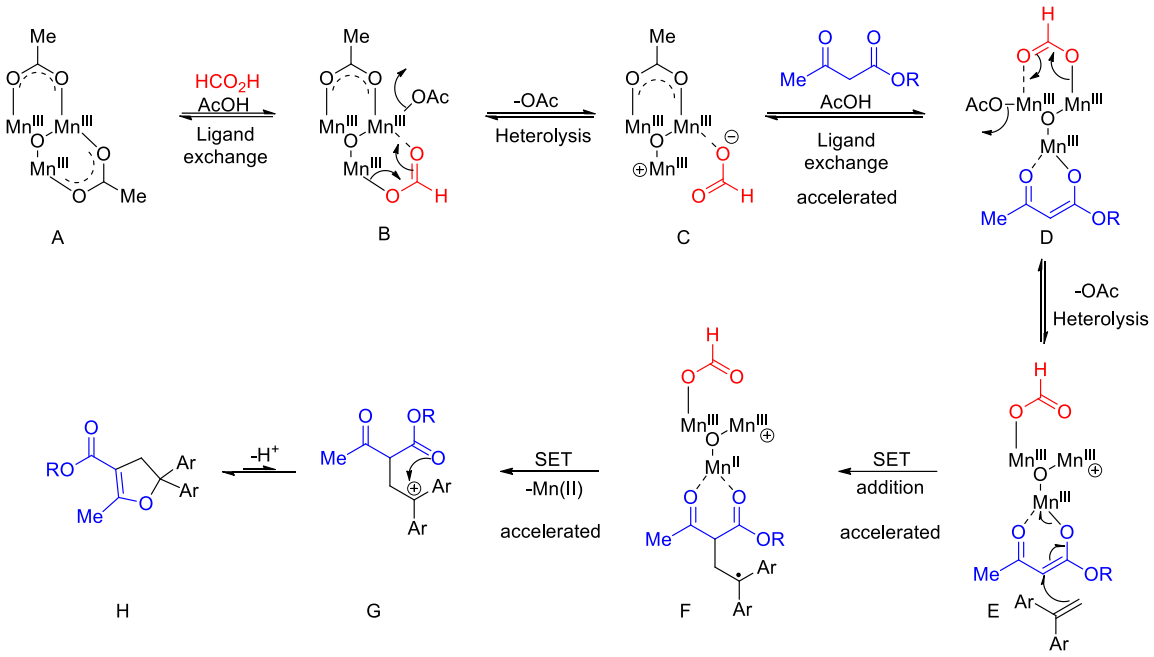
Dihydrofurans are found in numerous natural products and pharmaceuticals but also serve as precursors in an array of organic transformations.[40,41] Radical-induced cyclizations between 1,3-dicarbonyl species or similar variants and alkenes is a common way of synthesizing dihydrofurans. Nishino and co-workers reported an oxidative radical

cyclization of a variety of 1,3-dicarbonyl compounds (**1-63**) and 1,1-diarylethene (**1-64**) promoted by $Mn(OAc)_3$ in an AcOH-HCO_2H media forming dihydrofurans containing a quaternary center (**1-65**) (Scheme **1-12**).[42]



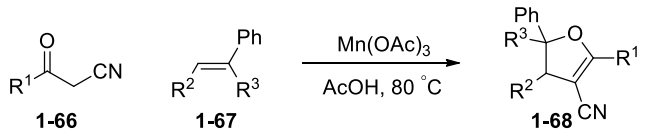
Scheme 1-12. Oxidative radical cyclization forming dihydrofuran derivatives

The addition of formic acid results in increased reaction rates and yields. The explanation of the rate enhancement with the addition of a secondary strong acid was explained by Kochi (Scheme **1-13**).[43] Under typical reaction conditions involving acetic acid (AcOH), complex A is thought to undergo ligand exchange with the 1,3-dicarbonyl species generating Mn(III)-enolate complex, which was found to be the rate-limiting step. However, with the introduction of formic acid, ligand exchange between complex A occurs forming complex C. Due to the production of both ion-pair and cationic Mn(III) species, the reactivity of the intermediate is increased resulting in a rate-enhancement for the 1,3-dicarbonyl ligand exchange forming complex D. This is followed by two SET additions that resulted in carbocation G which underwent cyclization forming the final product H.



Scheme 1-13. Rate-enhancement of the oxidative radical cyclization with the introduction of formic acid

In a similar reaction, Yilmaz and co-workers performed an oxidative radical cyclization between 3-oxopropanenitriles (**1-66**) and various alkenes (**1-67**) induced by $Mn(OAc)_3$ which furnished a variety of 3-cyanodihydrofuran derivatives (**1-68**) (Scheme **1-14**).[44]

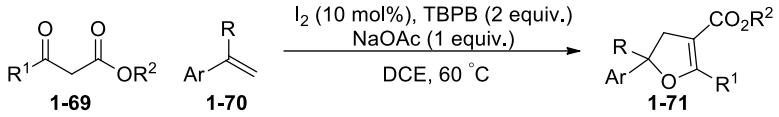


Scheme 1-14. Formation of 3-cyanodihydrofuran derivatives via oxidative radical cyclization

Biological studies were conducted with the compounds synthesized against a variety of Gram-positive and Gram-negative bacteria. The results obtained showed that all 3-cyanodihydrofuran derivatives had stronger antimicrobial activity against the bacteria studied when comparing to more traditional antibiotics such as the β-lactams or tetracyclines.

The main limitation of performing these and similar reactions is the need to use large excess of transition metal oxidants, which upon scale-up can be costly. With recent

reports of iodine serving as an alternative catalyst to transition metals in many reactions[45], the group of Lei wanted to see if they could substitute the typical transition metals used in oxidative radical cyclizations between 1,3-dicarbonyls (**1-69**) and alkenes (**1-70**) with iodine to form various dihydrofuran compounds (**1-71**).[46] After screening many conditions, it was found that I_2 and *tert*-butyl peroxybenzoate (TBPB), with NaOAc as an additive, furnished dihydrofurans in good yields (Scheme **1-15**).

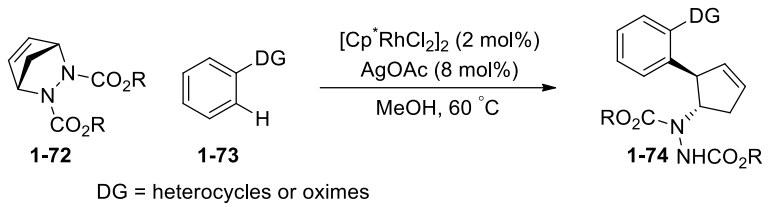


Scheme 1-15. The use of iodine towards an oxidative radical cyclization

1.1.4 Synthesis of Cyclopentenes

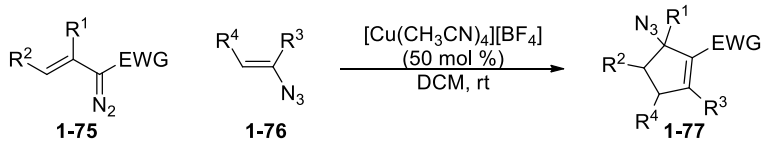
Although heterocyclic compounds have a greater presence in the pharmaceutical industries than their carbocyclic counterparts, cyclopentane and cyclopentene motifs have been utilized as the main scaffold in several medicinally active compounds.[47–49] The five membered carbocycle is also present in many naturally occurring compounds each with their own unique biological properties.[47,49–51] Many of these compounds contain highly substituted cyclo-pentane or -pentene cores, thus synthetic efforts for synthesizing complex five membered carbocycles gained considerable interest in the chemical community. There are a number of different ways that five-membered carbocycles can be synthesized: cycloaddition reactions, electrocyclizations, transition metal mediated cyclizations, rearrangements, and Aldol-type reactions.[51]

The presence of functionalized cyclopentenes in natural products or pharmaceuticals is limited compared to its saturated counterpart; however, the ability to synthesize cyclopentene cores can serve as key intermediates towards cyclopentane motifs. An important example is the synthesis of vicinal 2-arylated cyclopentenylamines.[48] The work by Zhang *et al.* showcased the formation of such cyclopentenes (**1-74**) by performing a Rh(III) catalyzed directing group (DG) assisted C-H functionalization of arenes (**1-73**) and desymmetrization of diazabicycles (**1-72**) (Scheme **1-16**).[48] The products were obtained under mild conditions and high yields.



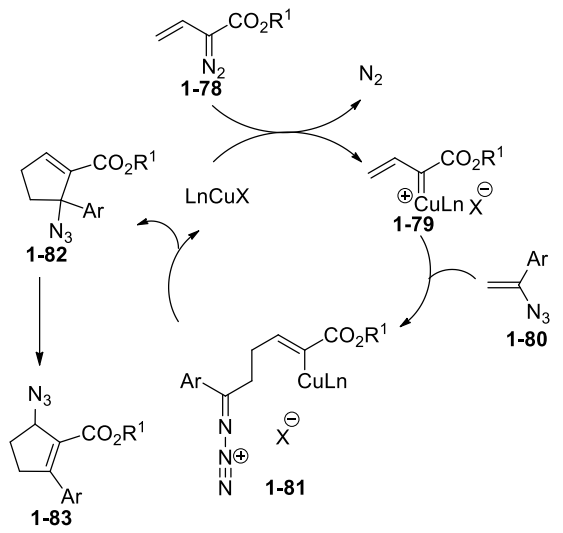
Scheme 1-16. Rh(III)-catalyzed C-H activation/desymmetrization of diazabicycles with arenes towards the synthesis of functionalized cyclopentenes

Recently, the Lopez group reported the synthesis of functionalized cyclopentenes (**1-77**) by reacting vinylazides (**1-76**) with alkenyldiazo compounds (**1-75**) in the presence of a copper catalyst in a formal [3+2]-cycloaddition/allylic azide rearrangement (Scheme **1-17**)[52].



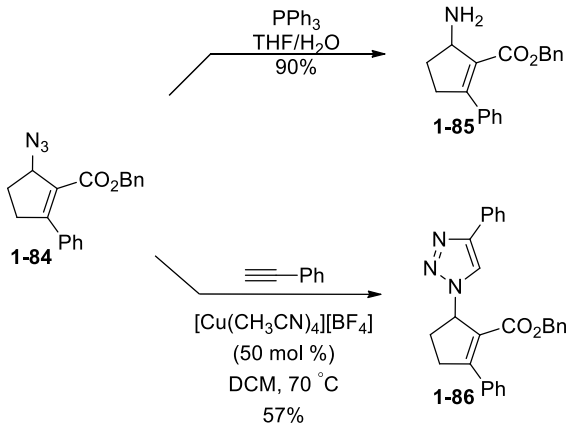
Scheme 1-17. [3+2]-cycloaddition/allylic azide rearrangement towards cyclopentenes

The first step in the proposed mechanism involves generation of a copper carbene complex (**1-79**) (Scheme **1-18**). The vinylazide (**1-80**) reacted with the carbene complex as an enamine-type nucleophile forming intermediate (**1-81**) followed by cyclization generating cycloadduct (**1-82**). This cycloadduct underwent a [3+3]-sigmatropic isomerization forming the final product (**1-83**).



Scheme 1-18. Proposed mechanism towards cyclopentene formation

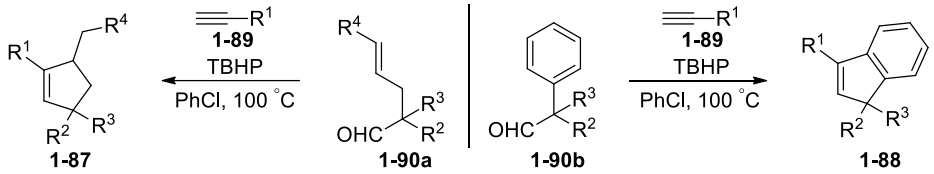
Due to the retention of the azide functionality, further chemical manipulations were studied. Under Staudinger conditions, the azide (**1-84**) was reduced to the amino derivative (**1-85**). An azide-click reaction was also performed forming triazole derivative (**1-86**) and this reaction was efficiently executed in a one-pot fashion (Scheme **1-19**).



Scheme 1-19. Manipulations of the azide functionality to amino and triazole derivatives

Cycloadditions involving metal-free conditions can provide easy access to complex products in a cost-effective process. Recently, Li and co-workers were able to show the synthesis of highly substituted cyclopentenes (**1-87**) or indenes (**1-88**) via a metal-free

oxidative decarbonylative [3+2]-annulation of terminal alkynes (**1-89**) with tertiary alkyl aldehydes (**1-90a,b**) (Scheme **1-20**)[53].



Scheme 1-20. Metal free oxidative decarbonylation, [3+2]-annulation between tertiary aldehydes and terminal alkynes towards functionalized cyclopentenes and indenes

The reactions worked well with a variety of (hetero)aryl and alkyl alkynes, as well as with a variety of alkyl aldehydes. Secondary alkyl aldehydes failed to provide any desired products and the reaction temperature seemed to play an important role as small deviations from 100 °C resulted in irreproducible results.

1.2 Synthesis of Seven-Membered Oxacycles

Compounds containing a seven membered oxacycle are found in numerous natural products that were found to possess antiviral (**1-91**)[54], inhibition of histamine release from mast cells (**1-92**)[55], and anti-inflammatory properties (**1-93**)[56] (Figure **1-5**).

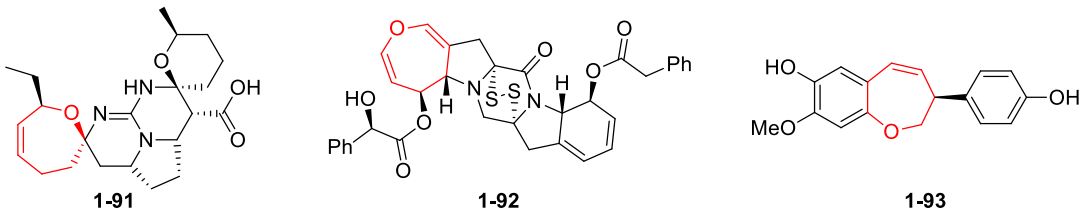
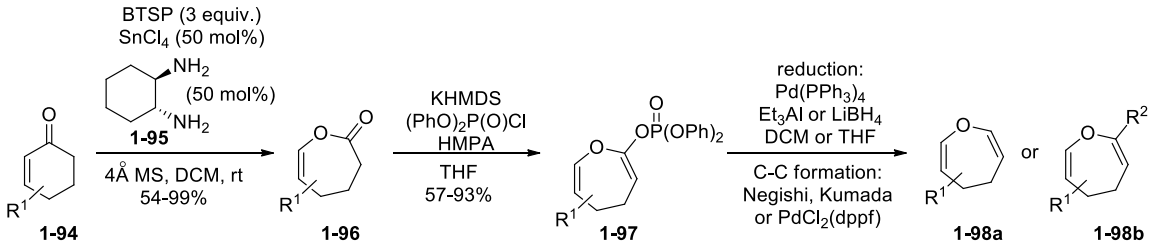


Figure 1-5. Bioactive natural products containing a seven-membered oxacycle

The structural complexity and biological properties of these seven-membered oxacycles resulted in considerable synthetic efforts.[54,57,58] Nicolaou *et al*. showed a mild three step sequence towards the synthesis of a variety of 4,5-dihydrooxepines[59]. Beginning with an array of cyclohexenones (**1-94**), a regioselective Baeyer-Villiger oxidation was achieved forming enol lactone (**1-96**) in good yields. The enol lactone was then converted to an enol phosphate (**1-97**) that was either reduced under palladium catalysis and a suitable

reducing agent or various C-C bond forming reactions were done furnishing the desired dihydrooxepines (**1-98a,b**) (Scheme **1-21**).

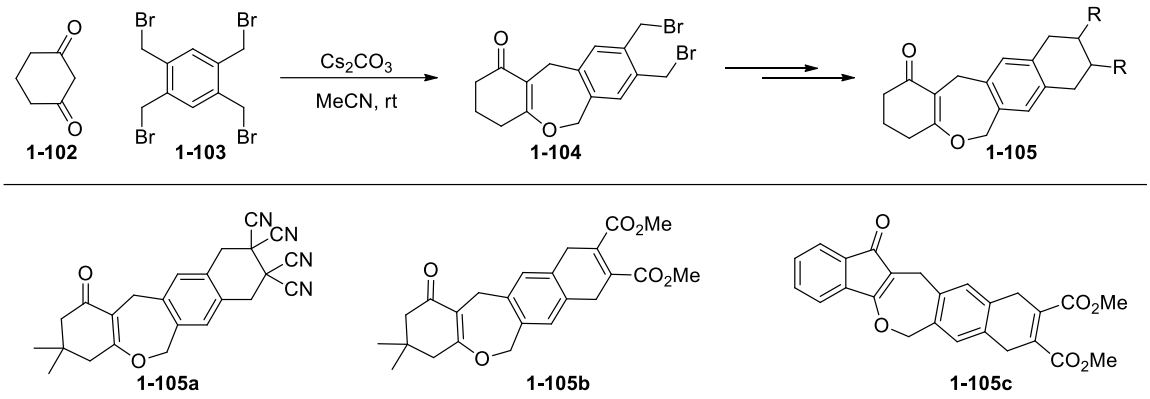


Scheme 1-21. Three step sequence towards dihydrooxepines

The complex structure of epidithiodiketopiperazines (ETP) such as (**1-92**) (Figure **1-5**) has attracted many research groups towards its total synthesis. Liang and co-workers recently reported the synthesis of dihydrooxepines (**1-101**) through a radical [2+2+3]-annulation of 1,6-enynes (**1-99**) with α-bromo-1,3-dicarbonyl compounds (**1-100**) (Scheme **1-22**).[60] The products were formed in good yields and were identified as important scaffolds for the ETP class of natural products.

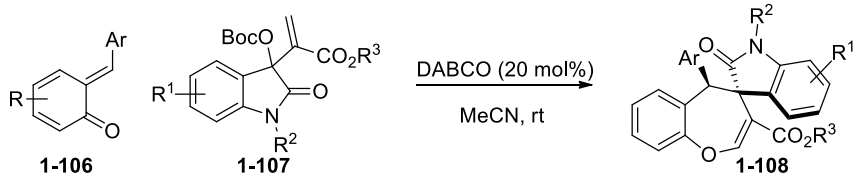
Scheme 1-22. Radical annulation towards dihydrooxepines

Benzooxepines such as (**1-93**) (Figure **1-5**) are another common structural scaffold found in numerous natural products and pharmaceuticals. Recently, Kotha *et al.* devised a simple synthetic method towards benzooxepines.[61] Under basic conditions, a variety of cyclic 1,3-diones (**1-102**) were reacted with 1,2,4,5-tetrakis(bromomethylbenzene) (**1-103**) providing benzooxepines (**1-104**) in moderate yields (Scheme **1-23**). With the functional handles presented, subsequent steps were performed in high yields providing an array of polycyclic benzooxepines (**105a,b,c**).



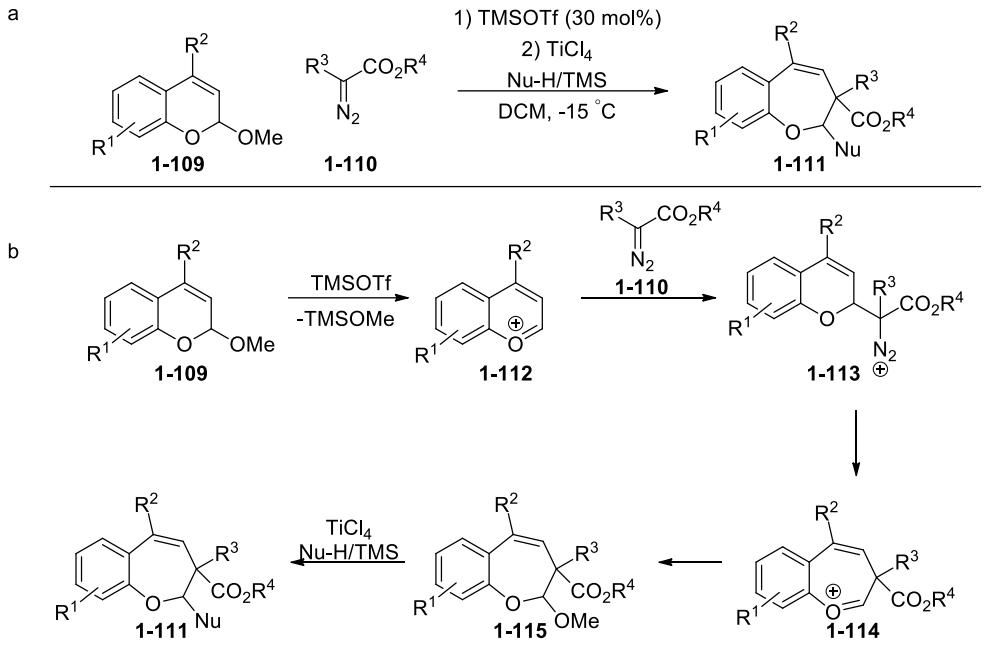
Scheme 1-23. Synthesis of benzooxepines and subsequent steps towards polycyclic benzooxepines

The work by Du and co-workers showed the synthesis of spirocyclic benzooxepines (**1-108**) bearing oxindole scaffolds in good to excellent yields and good diastereoselectivities.[62] This was accomplished by a Lewis base catalyzed [4+3]-annulation of *o*-Quinone methides (*o*-QMs) (**1-106**) and Morita-Baylis-Hillman (MBH) carbonates (**1-107**) (Scheme **1-24**). The reaction worked regardless of variation in the substitution pattern. Only a slight decrease in yields were seen when larger ester groups were present in (**1-107**).



Scheme 1-24. [4+3]-annulation between *o*-QMs and MBH carbonates under Lewis basic conditions towards spirocyclic benzooxepines

The Lecourt group showcased the synthesis of highly functionalized benzooxepines (**1-111**) containing a quaternary center through a ring expansion of chromene derivatives (**1-109**) with donor-acceptor diazo compounds (**1-110**)[63] (Scheme **1-25**a).



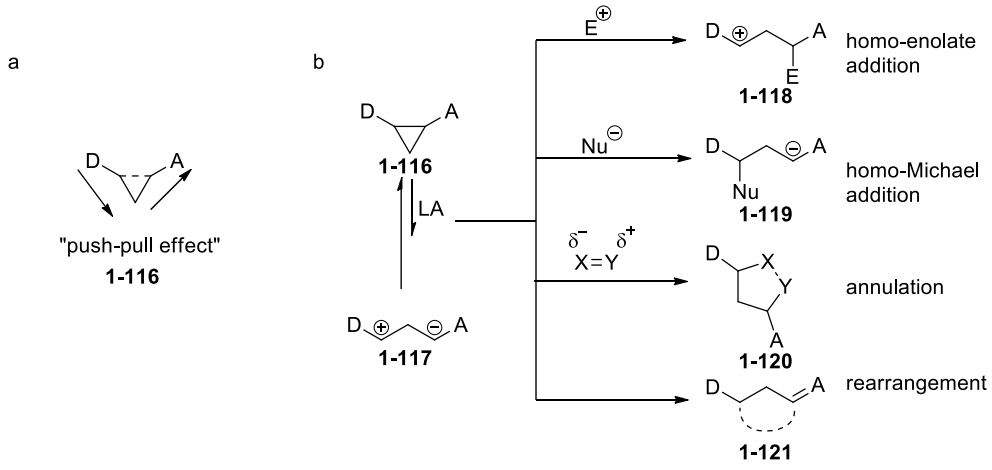
Scheme 1-25. [a] Synthesis of benzooxepines through the ring expansion of chromene derivatives. [b] Proposed mechanism of the reaction.

Treating chromene derivatives (**1-109**) under a Lewis acid formed benzopyrylium (**1-112**) followed by addition of the diazo species (**1-110**) forming (**1-113**). A 1,2-migration of the endocyclic C-C bond resulted in the oxocarbenium ion (**1-114**) with the extrusion of nitrogen gas. Trapping (**1-114**) with the initially generated TMSOMe formed (**1-115**) and in the same pot, treating (**1-115**) with $TiCl_4$ reformed the oxocarbenium ion (**1-114**) which was trapped with various nucleophiles forming (**1-111**) (Scheme **1-25b**).

Structures containing pyrrolidines, dihydropyrroles, dihydrofurans, cyclopentenes, and dihydrooxepines in their scaffolds have numerous biological applications and are found in many natural products. Thus, the discovery of new synthetic methodologies towards these highly desirable structural motifs is a major focus in the synthetic community and pharmaceutical research. An area of research providing several advancements in methodologies towards the abovementioned structures is the use of donor-acceptor (DA) cyclopropanes.

1.3 Reactivity of Donor-Acceptor Cyclopropanes and Their Uses in the Formation of Hetero- and Carbo-cycles

Cyclopropanes have emerged to be useful synthetic building blocks in organic chemistry because of its highly strained three-membered ring.[64–73] Cyclopropanes that contain donor (D) and acceptor (A) groups located vicinally to one another are termed DA cyclopropanes (**1-116**).[74] The presence of the DA groups amplifies the reactivity of the cyclopropane ring due to a synergistic electron "push-pull" effect which greatly weakens the vicinal C-C bond (Scheme **1-26a**). Typically, moieties with electron-rich aryl groups, heteroatoms, alkyl or alkenyl serve as the donor group and electron withdrawing moieties such as carbonyl, sulfonyl, and nitro serve as the acceptor group.[72] Upon treatment with a Lewis acid, the DA cyclopropane is proposed to undergo ring opening forming a 1,3-dipole (**1-117**) and depending on the reaction conditions, many different products can be obtained (Scheme **1-26b**).[66,71,72] A high regioselectivity is observed within these reactions due to the added stability of the positive and negative charges imparted by the D and A groups.



Scheme 1-26. [a] DA cyclopropane showing the weakened vicinal C-C bond due to the push-pull effect. [b] Reactivity of DA cyclopropanes.

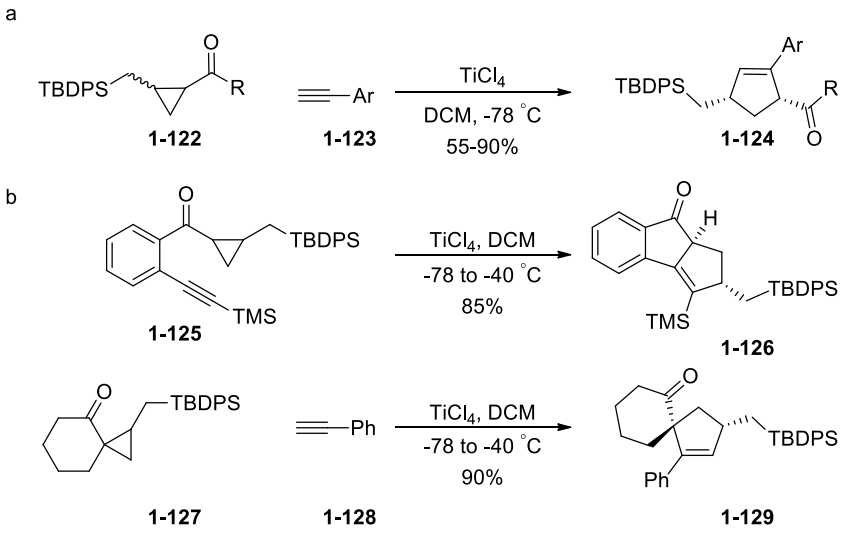
Of interest, are annulation and rearrangement reactions involving DA cyclopropanes as this readily allows the formation of a variety of carbo- and heterocycles of various ring sizes.

1.3.1 Annulation reactions involving DA-Cyclopropanes

Annulation reactions of DA-cyclopropanes with dipolarophiles, 1,3-dipoles, and dienes have been reported to highlight the formation of carbo- and heterocycles in pharmaceuticals or target oriented synthesis. The utilization of these transformations will be featured towards the formation of cyclopentenes, pyrrolidines and dihydropyrroles.

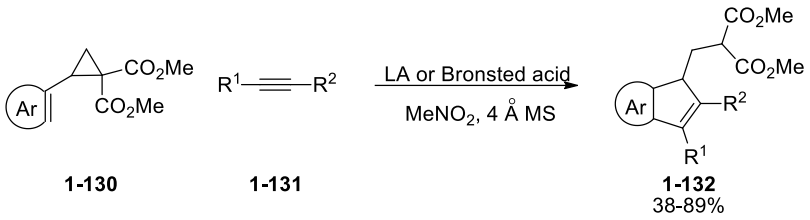
1.3.1.1 Synthesis of Cyclopentenes

Unlike the formation of heterocycles, the formation of carbocycles is much less prevalent since the cyclopropane ring-opening event is less favorable with carbon nucleophiles.[71] Nevertheless, DA cyclopropanes have been shown to react with a variety of carbon-based dipolarophiles in [3+2]-annulation chemistry to make cyclopentene rings.[67,75] Yadav was able to take advantage of this reactivity by using aryl acetylene nucleophiles (**1-123**) and a stoichiometric amount of Lewis acid generating substituted cyclopentenes (**1-124**) in moderate to good yields and *cis* selectivity up to 95:5 (Scheme **1-27a**).[76] Intramolecular variants were also subjected to the reaction conditions which formed polycyclic (**1-126**) and spirocyclic motifs (**1-129**), the latter of which are found in many natural compounds (Scheme **1-27b**).[77]



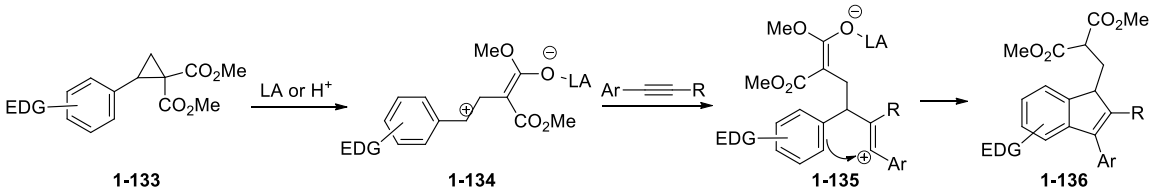
Scheme 1-27. [a] Synthesis of cyclopentenes through a [3+2]-annulation of DA cyclopropanes and acetylenes. [b] Intramolecular variants.

Budynina expanded these examples with doubly-substituted alkynes (**1-131**) and DA cyclopropanes (**1-130**) in a [3+2]-annulation initiated using a Lewis acid or Bronsted acid towards the formation of indenes (**1-132**). These classes of compounds are important for their bioactivities and fluorescent properties (Scheme **1-28**).



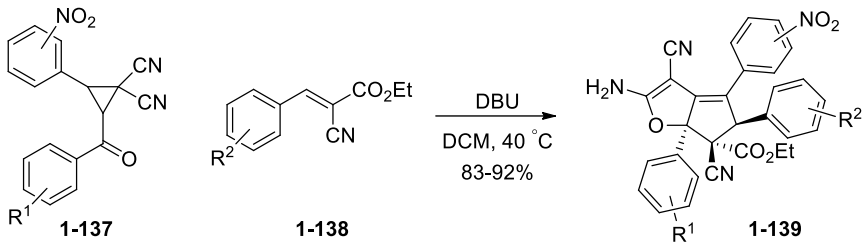
Scheme 1-28. [3+2] annulation between DA cyclopropane and alkynes forming indenes

The proposed mechanism involved formation of the 1,3-dipole equivalent (**1-134**) upon treating the cyclopropane (**1-133**) with a Lewis acid or Bronsted acid. Nucleophilic attack by the alkyne formed vinyl cation intermediate (**1-135**) which underwent an intramolecular Friedel-Crafts reaction onto the vinyl cation affording the final indene product (**1-136**) (Scheme **1-29**).[78]



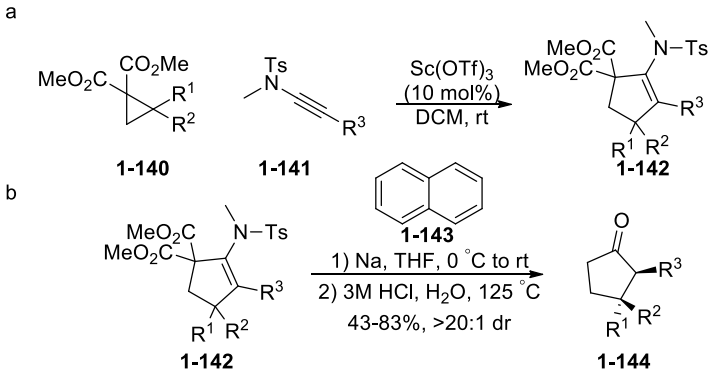
Scheme 1-29. Proposed mechanism for indene formation

Recently, Wang *et al.* was able to showcase the formation of highly functionalized cyclopenta[*b*]furans (**1-139**) through a DBU promoted cascade annulation of nitroarylcyclopropane-1,1-dicarbonitriles (**1-137**) and 3-aryl-2-cyanoacrylates (**1-138**)[79] (Scheme **1-30**). For cyclopropane derivatives (**1-137**), only *o*- or *p*-nitro groups were tolerated since the negative charge from deprotonation of the α-proton was stabilized by the strong inductive and conjugative effects of the nitro group which was not seen for *m*-nitro positions.



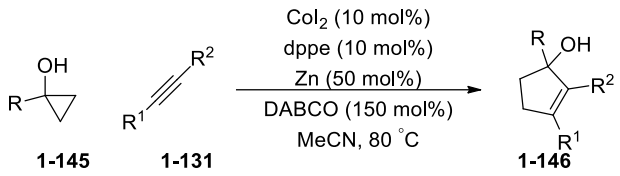
Scheme 1-30. Highly stereoselective formation of cyclopenta[*b*]furan rings from DA cyclopropanes

Johnson *et al.* were able to react a variety of DA cyclopropanes (**1-140**) and ynamides (**1-141**) in a [3+2]-annulation in the presence of a Lewis acid forming highly substituted cyclopentene sulfonamides (**1-142**) (Scheme **1-31a**).[80] With the use of enantiopure cyclopropanes, complete inversion of stereochemistry was observed at the donor site of the cyclopropane. These cyclopentene sulfonamides were efficiently converted to their cyclopentanone counterparts (**1-144**) as a single diastereomer via two-step sequence of tosyl removal followed by enamine hydrolysis with concurrent decarboxylations (Scheme **1-31b**).



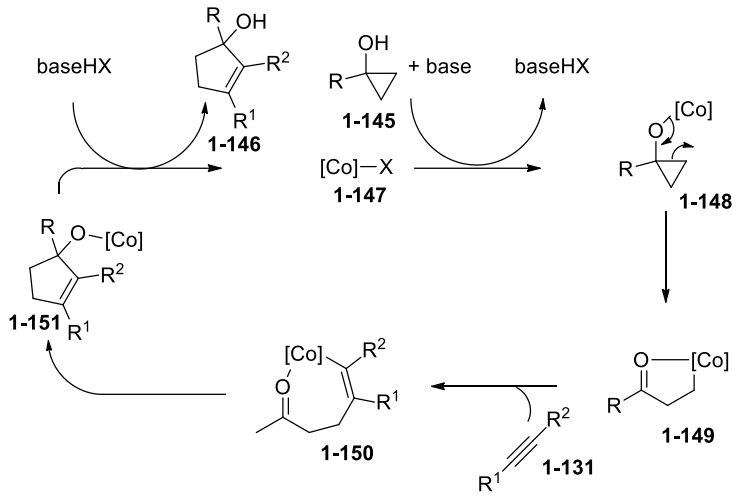
Scheme 1-31. [a] [3+2]-annulation between DA cyclopropanes and ynamides. [b] conversion of cyclopentene sulfonamides to cyclopentanones.

The work by Yoshikai and co-workers showed the first reported example of an intermolecular coupling between cyclopropanols (**1-145**) and unfunctionalized alkynes (**1-131**) producing cyclopentenols (**1-146**) (Scheme **1-32**).[81]



Scheme 1-32. Reaction between cyclopropanols and unfunctionalized alkynes to furnish cyclopentenols

The proposed catalytic cycle began with the generation of the active Co(I) species (**1-147**) from the Co(II) pre-catalyst and Zn. Deprotonation with DABCO formed a cobalt cyclopropoxide species (**1-148**) that underwent ring-opening which resulted in a cobalt homoenolate complex (**1-149**). Insertion of the alkyne gave an alkenylcobalt species (**1-150**) which underwent an intramolecular carbonyl addition (**1-151**) followed by protodemetallation affording the final product (**1-146**) (Scheme **1-33**).

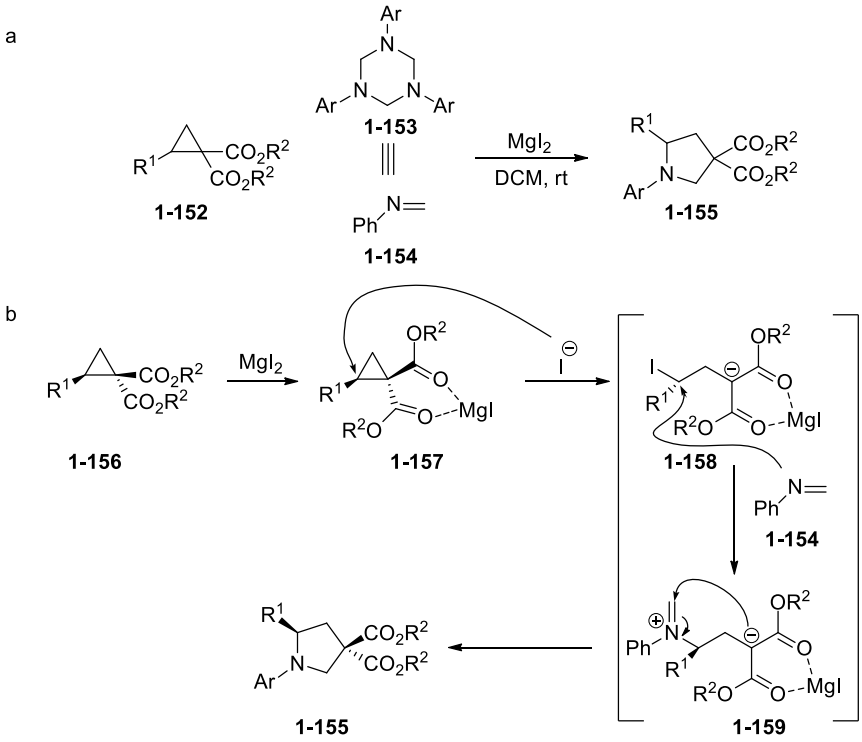


Scheme 1-33. Proposed catalytic cycle for the formation of cyclopentenols

1.3.1.2 Formation of Five-Membered Heterocycles

The ability to find new ways of forming heterocycles constitutes one of the largest areas of research in organic chemistry. The unique reactivity of DA cyclopropane derivatives has been exploited throughout the years towards the synthesis of compounds that may be of interest from structural or biological standpoints.

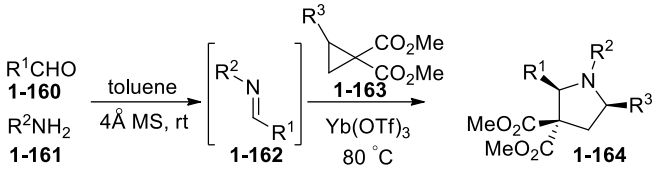
As mentioned earlier, pyrrolidines are an important class of heterocycles due to their presence in natural products and pharmaceuticals. It is not surprising that the reactivity of DA cyclopropanes has been exploited towards pyrrolidine synthesis. The Werz group showed the synthesis of pyrrolidines (**1-155**) by reacting DA cyclopropanes (**1-152**) with a formaldimine surrogate (**1-154**), 1,3,5-triazinanes (**1-153**), under Lewis acid catalysis (Scheme **1-34a**).[82] A variety of alkyl and (hetero)aryl cyclopropanes were tolerated and various 1,3,5-triazinanes worked as well. When using enantiopure cyclopropane under these reaction conditions, complete retention of stereochemistry was observed indicating a double S_N2-type mechanism (Scheme **1-34b**).



Scheme 1-34. [a] Synthesis of pyrrolidines via the reaction of DA cyclopropanes and 1,3,5-triazinanes. [b] Proposed double S_N2-type mechanism.

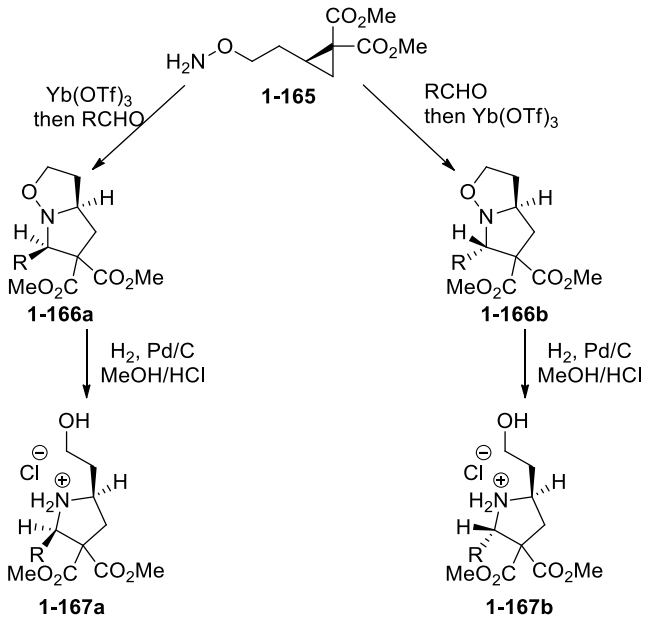
In a similar reaction involving aldimines as the dipolarophile in a [3+2]-annulation, the Kerr group showcased a highly diastereoselective synthesis of 2,5-*cis*-pyrrolidines (**1-164**) through the ring-opening of DA cyclopropanes (**1-163**). This was accomplished with *in-situ* generated aldimines (**1-162**) under Lewis acid catalysis (Scheme **1-35**).[83] Aryl or heteroaryl aldehydes (**1-160**) provided the best results whereas both primary alkylamines

and anilines (**1-161**) were also well tolerated. This research was showcased in the total synthesis of FR901483.[84]



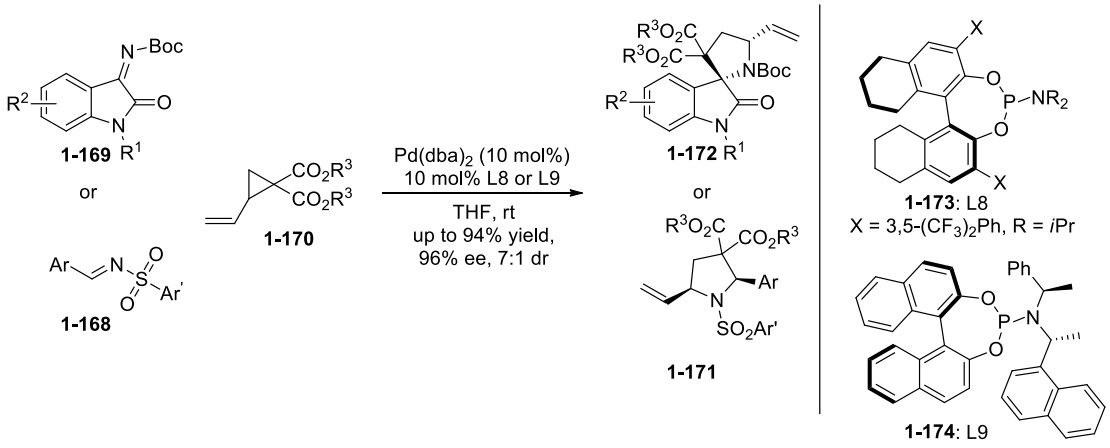
Scheme 1-35. Formation of *cis*-2,5-pyrrolidine rings through ring-opening of DA cyclopropanes with aldimines

The Kerr group expanded the synthesis of pyrrolidines with the use of DA cyclopropanes tethered to alkoxyamines (**1-165**) (Scheme **1-36**).[85] This intramolecular reaction resulted in the diastereoselective formation of substituted pyrrolo-isoxazolidines with high enantiopurity (**1-166a,b**). Reversing the addition order of catalyst and substrate resulted in the formation of two discrete diastereomers which were subjected to N-O bond cleavage providing highly substituted 2,5-*trans*- (**1-167a**) or 2,5-*cis*-pyrrolidines (**1-167b**) in a predictable manner. In order to avoid epimerization during the N-O bond cleavage, methanolic HCl was used which likely suppressed the retro-Mannich isomerization pathway.



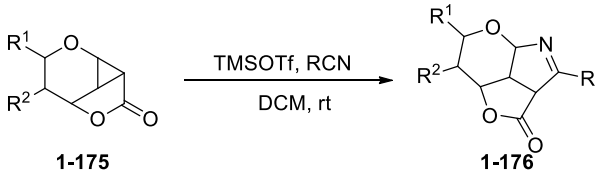
Scheme 1-36. Highly diastereo- and enantioselective formation of pyrrolidines with the use of tethered DA cyclopropanes-alkoxyamines

Liu *et al*. recently showed a formal [3+2]-cycloaddition of vinylcyclopropanes (**1-170**) and aldimines (**1-168**) or isatin-derived ketimines (**1-169**) under palladium catalysis and chiral phosphoramidite ligands (**1-173**, **1-174**) towards the formation of highly functionalized and optically enriched pyrrolidines (**1-171**) or spiro-[pyrrolidin-3,2'-oxindole] derivatives (**1-172**) (Scheme **1-37**).[86] This was the first enantioselective example involving ketimines as the dipolarophile in a formal [3+2]-cycloaddition involving DA cyclopropanes.



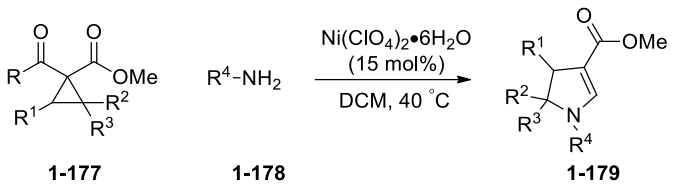
Scheme 1-37. Formal [3+2]-cycloaddition between DA cyclopropanes and aldimines or ketimines

The reactivity of DA cyclopropanes can also be utilized in annulation reactions towards dihydropyrroles. The Pagenkopf group utilized glycal-derived DA cyclopropanes (**1-175**) and were the first to perform formal [3+2]-cycloadditions with a variety of nitriles providing complex dihydropyrroles (**1-176**) in high yields (Scheme **1-38**).[87]



Scheme 1-38. Formal [3+2]-cycloadditions with glycal derived DA cyclopropanes and nitriles towards dihydropyrroles

More recently, France and co-workers showed a nucleophilic ring-opening of DA cyclopropanes (**1-177**) with primary amines (**1-178**) followed by cyclization forming dihydropyrroles (**1-179**) in good to excellent yields (Scheme **1-39**).[88] However, it can be argued that imine formation occurs prior to cyclization which would be followed by a Cloke-Wilson type rearrangement through a zwitterionic intermediate. This process will be discussed in greater detail in the following section.

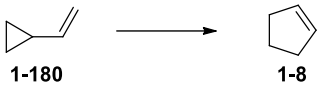


Scheme 1-39. Ring-opening/cyclization of DA cyclopropanes with primary amines

Annulation reactions involving DA cyclopropanes towards the synthesis of various carbocycles and heterocycles is a vast area of ongoing research with unique scaffolds being synthesized regularly.

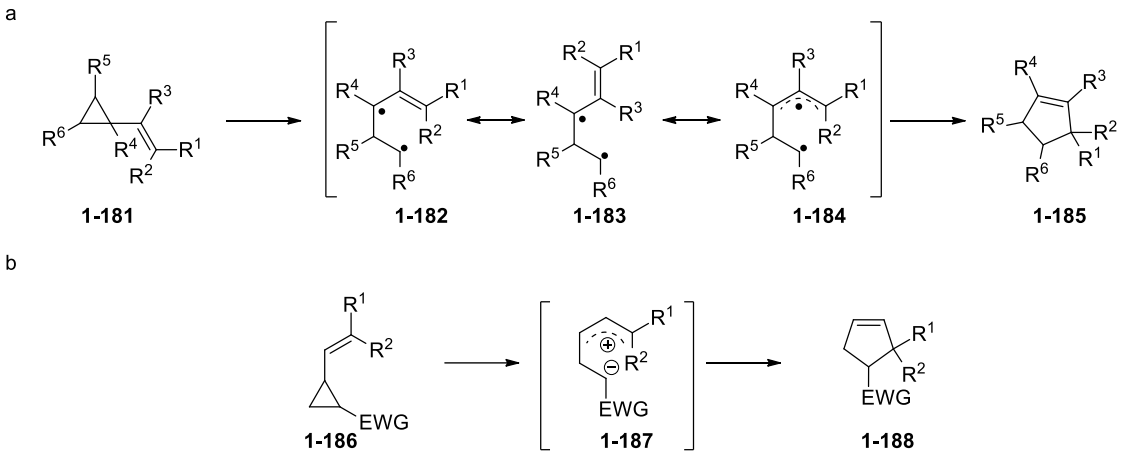
1.3.2 Rearrangements of DA Cyclopropanes

Rearrangements of DA cyclopropanes is another large area of research in organic chemistry since it allows the formation of various cyclic structures in a quick and atom economical manner. One of the most famous examples of cyclopropane rearrangements is the vinylcyclopropane-cyclopentene rearrangement[64,65,89–93] (Scheme **1-40**).



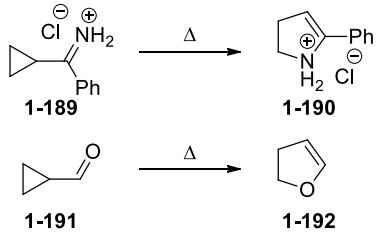
Scheme 1-40. Vinylcyclopropane-cyclopentene rearrangement

Since the discovery of this reaction, numerous reviews were published which debated its exact mechanism. Today, the majority of the evidence suggests a diradical mechanism or through zwitterionic intermediates (Scheme **1-41**); however, a concerted [1,3] process is still argued.[94–96]



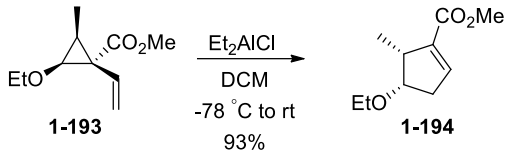
Scheme 1-41. Vinylcyclopropane-cyclopentene rearrangement. [a] diradical mechanism. [b] zwitterionic intermediate mechanism.

A much less known variant of this reaction is the heteroatom version known as the Cloke-Wilson reaction. Cloke discovered the formation of 2-phenylpyrroline hydrochloride (**1-190**) when he attempted to distill phenyl cyclopropyl ketimine hydrochloride (**1-189**) under vacuum. Wilson separately reported the formation of dihydrofurans (**1-192**) from the thermal rearrangement of cyclopropylcarboxaldehyde (**1-191**) (Scheme **1-42**).[92]



Scheme 1-42. Cloke-Wilson rearrangements towards the formation of dihydropyrroles and dihydrofurans

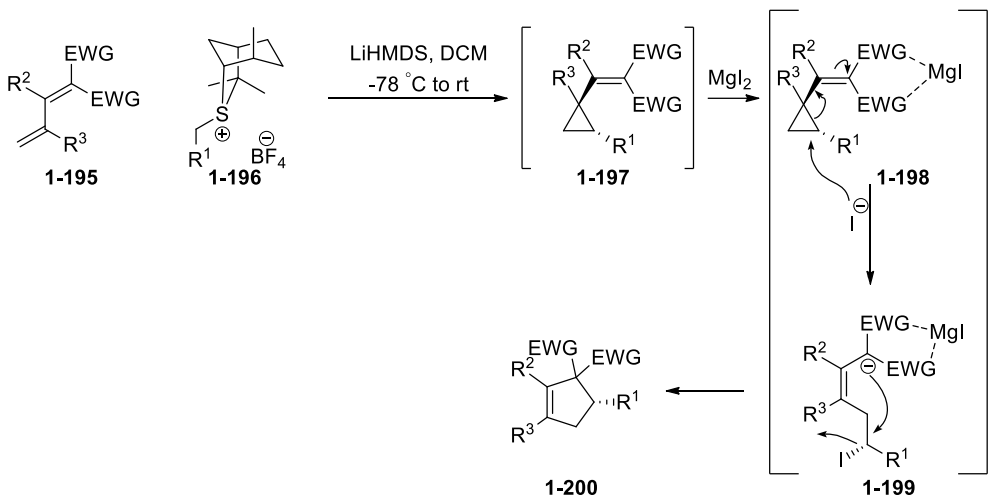
The vinylcyclopropane-cyclopentene and Cloke-Wilson rearrangements were not widely applicable due to the extremely high temperatures required to induce the rearrangement.[92] However, with the introduction of DA cyclopropanes, these types of rearrangements could be carried out under much milder conditions. Davies *et al.* showed a highly stereoselective formation of cyclopentenes (**1-194**) using vinyl DA cyclopropane (**1-193**) under mild conditions in the presence of an aluminum catalyst (Scheme **1-43**).[95]



Scheme 1-43. Stereoselective vinylcyclopropane-cyclopentene rearrangement under mild conditions

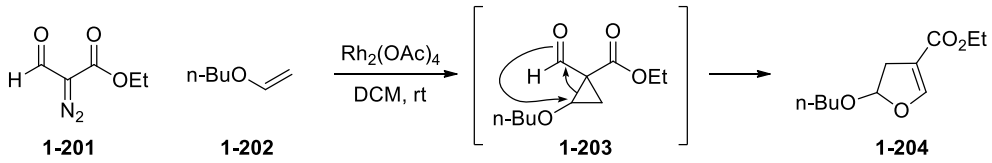
To explain the high stereoselectivity of the rearrangement, Davies proposed that the rearrangement underwent a formal [1,3]-sigmatropic rearrangement proceeding suprafacially with retention of configuration. However, it was also proposed that the DA cyclopropane underwent ring-opening to the zwitterionic intermediate and re-closed to the cyclopentene before any bond rotation occurred. This may be possible due to the extremely low temperature the reaction was performed in.

Recently, Robiette *et al.* developed a highly diastereo- and enantioselective one-pot protocol that gave cyclopentenes (**1-200**) via the vinylcyclopropane-cyclopentene rearrangement. Chiral sulfur ylides (**1-196**) underwent a formal [4+1]-annulation with 1,1-bis-activated 1,3-dienes (**1-195**) to yield *in situ* vinylcyclopropane (**1-197**). The cyclopropane was then treated with MgI_2 which resulted in a vinylcyclopropane-cyclopentene rearrangement with complete retention of stereochemistry (Scheme **1-44**).[97] Computational studies were conducted to gain insight into the mechanism and results suggested that the reaction underwent two S_N2 reactions which accounted for the stereochemistry. Upon coordination of MgI_2 onto the EWG of the cyclopropane (**1-198**), the displaced iodide opened the cyclopropane in an S_N2 fashion (**1-199**) followed by ring closure with expulsion of the iodide in a second S_N2 reaction to form the cyclopentene ring (**1-200**).



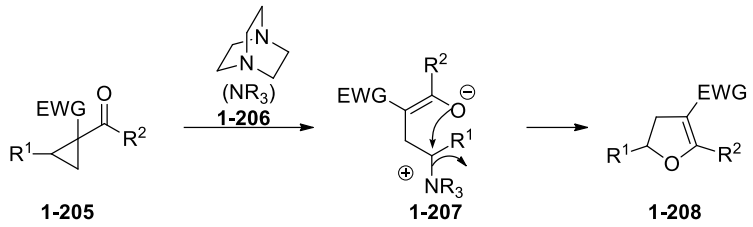
Scheme 1-44. Diastereo- and enantioselective vinylcyclopropane-cyclopentene rearrangement undergoing a double S_N2 displacement

Wenkert was able to utilize the reactivity of DA cyclopropanes and perform the Cloke-Wilson rearrangement under mild conditions forming various dihydrofurans.[98] Ethylformyldiazoacetate (**1-201**) was reacted with *n*-butylvinyl ethers (**1-202**) under metal carbenoid chemistry forming cyclopropane intermediate (**1-203**) that underwent the Cloke-Wilson rearrangement which furnished dihydrofuran (**1-204**) in good yields (Scheme **1-45**).



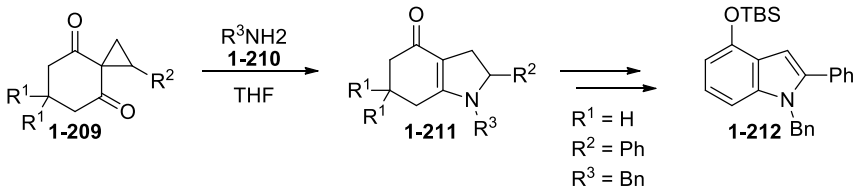
Scheme 1-45. Cloke-Wilson rearrangement of DA cyclopropane to dihydrofuran

Recently, the group of Xu showcased a high yielding organocatalytic Cloke-Wilson rearrangement of cyclopropyl ketones (**1-205**) to dihydrofurans (**1-208**) with the use of DABCO (**1-206**) (Scheme **1-46**).[99] The products were obtained in high yields and mechanistic studies supported a S_N1 type (zwitterionic) (**1-207**) mechanism.



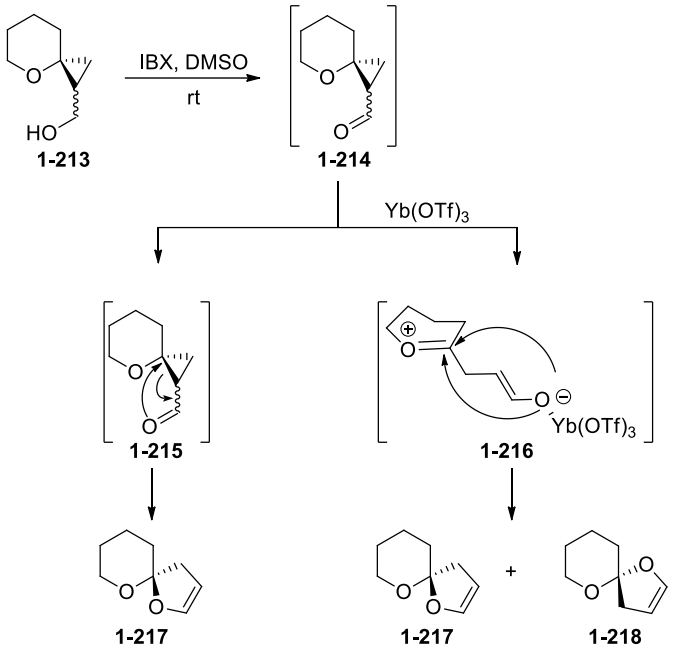
Scheme 1-46. Proposed mechanism for the organocatalyzed Cloke-Wilson rearrangement

Formation of dihydropyrroles via the Cloke-Wilson rearrangement was employed under mild conditions upon introduction of DA cyclopropanes. Spirocyclic DA cyclopropanes (**1-209**) were reacted with a variety of primary amines (**1-210**) at room temperature without any catalyst forming bicyclic dihydropyrroles (**1-211**) in excellent yields (Scheme **1-47**).[100] To show the utility of these transformations, the group transformed a select example to its corresponding indole derivative (**1-212**).



Scheme 1-47. Cloke-Wilson rearrangement of DA cyclopropanes to dihydropyrroles

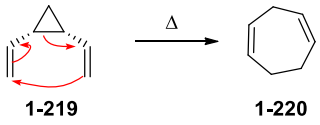
DFT studies were conducted for the Cloke-Wilson rearrangement involving up to 72 DA cyclopropanes.[71,101] It was found that in the absence of a catalyst, the rearrangement occurred through a concerted process.[101,102] The corresponding zwitterionic or biradical intermediates were shown to have higher activation barriers in all cases.[101] An example of this is shown by Werz and co-workers where they synthesized [n,5]-spiroketals (**1-217**, **1-218**) (n = 5 or 6) through the Cloke-Wilson rearrangement of DA cyclopropanes (**1-214**)[103] (Scheme **1-48**).



Scheme 1-48. Rearrangement of DA cyclopropanes to spiroketals

When no Lewis acid was used, high diastereoselectivity was observed supporting a concerted mechanism (**1-215**). In the presence of a Lewis acid, the yields increased and a mixture of diastereomers (**1-217**, **1-218**) was observed, supporting a zwitterionic intermediate (**1-216**).

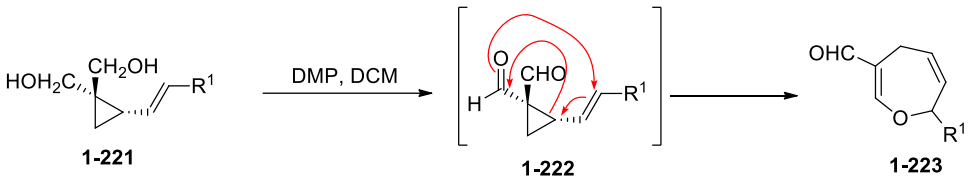
Larger ring systems can be formed with the use of divinylcyclopropanes (**1-219**) which undergo a Cope rearrangement to furnish cycloheptadiene compounds (**1-220**)[104] (Scheme **1-49**).



Scheme 1-49. Divinylcyclopropane-cycloheptadiene rearrangement

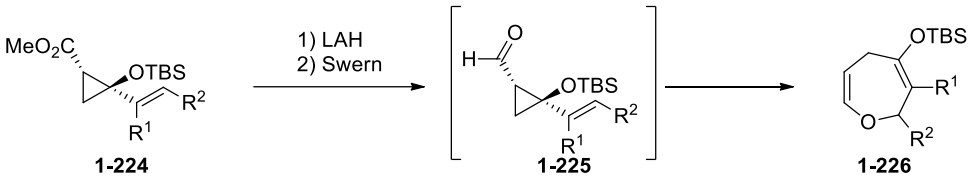
The heteroatom version of the divinylcyclopropane-cycloheptadiene rearrangement is also known and useful for making 7-membered heterocycles. This work was pioneered by Reissig and Boeckman in the mid 1990s. Boeckman synthesized vinylcyclopropane (**1-221**) and after oxidation with DMP he formed the required (hetero)-

divinylcyclopropane (**1-222**) which instantly underwent a retro-Claisen rearrangement furnishing 2,5-dihydrooxepines (**1-223**) in good to excellent yields (Scheme **1-50**).[105]



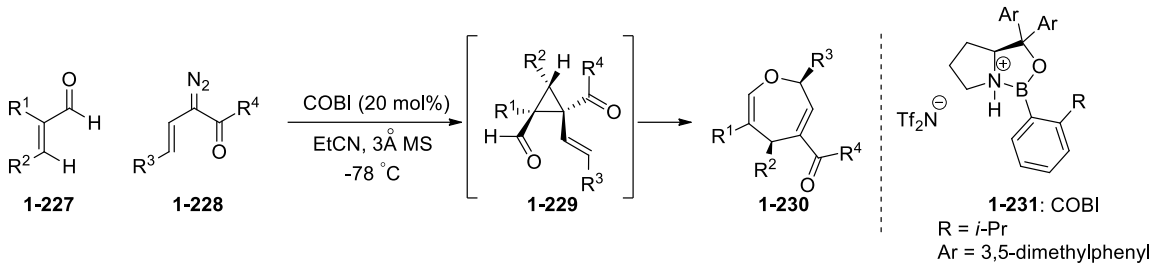
Scheme 1-50. Boeckman's (hetero)-divinylcyclopropane rearrangement to 2,5-dihydrooxepines

Similarly, Reissig synthesized vinylcyclopropane (**1-224**) and after further chemical transformations he formed the required (hetero)-divinylcyclopropane (**1-225**). This intermediate instantly underwent a retro-Claisen rearrangement furnishing 2,5-dihydrooxepines (**1-226**) in moderate to good yields (Scheme **1-51**).[106]



Scheme 1-51. Reissig's (hetero)-divinylcyclopropane rearrangement to 2,5-dihydrooxepines

An enantioselective version of this transformation was recently reported by the Ryu group. The required enantiopure DA cyclopropane (**1-229**) was formed via a Michael addition initiated cyclopropanation between substituted acroleins (**1-227**) and vinyldiazoesters (**1-228**) under chiral oxazaborolidinium ion (COBI) (**1-231**) catalyst (Scheme **1-52**).[107] The cyclopropane instantly underwent a retro-Claisen rearrangement generating 2,5-dihydrooxepines (**1-230**) in high yields and enantioselectivities. This was the first reported example of a catalytic asymmetric formation of 2,5-dihydrooxepines through tandem cyclopropanation/retro-Claisen rearrangement.



Scheme 1-52. First enantioselective formation of dihydrooxepines through a tandem cyclopropanation/retro-Claisen rearrangement

DA cyclopropanes are synthons whose innate dipole moments are appropriate to produce carbocyclic and heterocyclic compounds. Rearrangement reactions are important since they allow the formation of said compounds in an atom economical process. Many of these examples require only mild conditions without the need of any catalysts. These types of rearrangements will be the main focus of the upcoming chapters, which ultimately leads into the work towards pyrrolidine-containing product kainic acid.

1.4 Kainic Acid

1.4.1 Isolation and biological activity

The kainoid amino acids are densely functionalized pyrrolidine motifs that are structurally related to glutamic acid (**1-232h**), which is an excitatory neurotransmitter (Figure **1-6**).[108–111] The parent of the kainoids, α-kainic acid (**1-232a**), was first isolated by Takemoto in 1953 from the Japanese marine algae *Digenea simplex* along with its C-4 epimer α-allokainic acid (**1-232b**).[108–111] A few years after its isolation, Morimoto was the first to deduce the relative stereochemistry of the pyrrolidine ring through X-ray analysis and it was not until the first total synthesis by Oppolzer and Thirring in 1982 where the absolute stereochemistry was confirmed.[108–112]

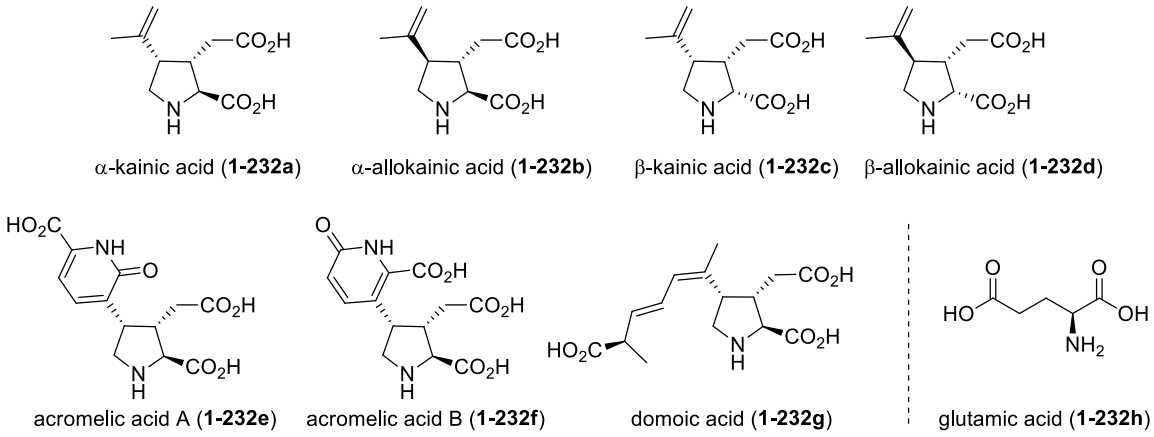


Figure 1-6. Kainoid amino acid family and their resemblance to glutamic acid

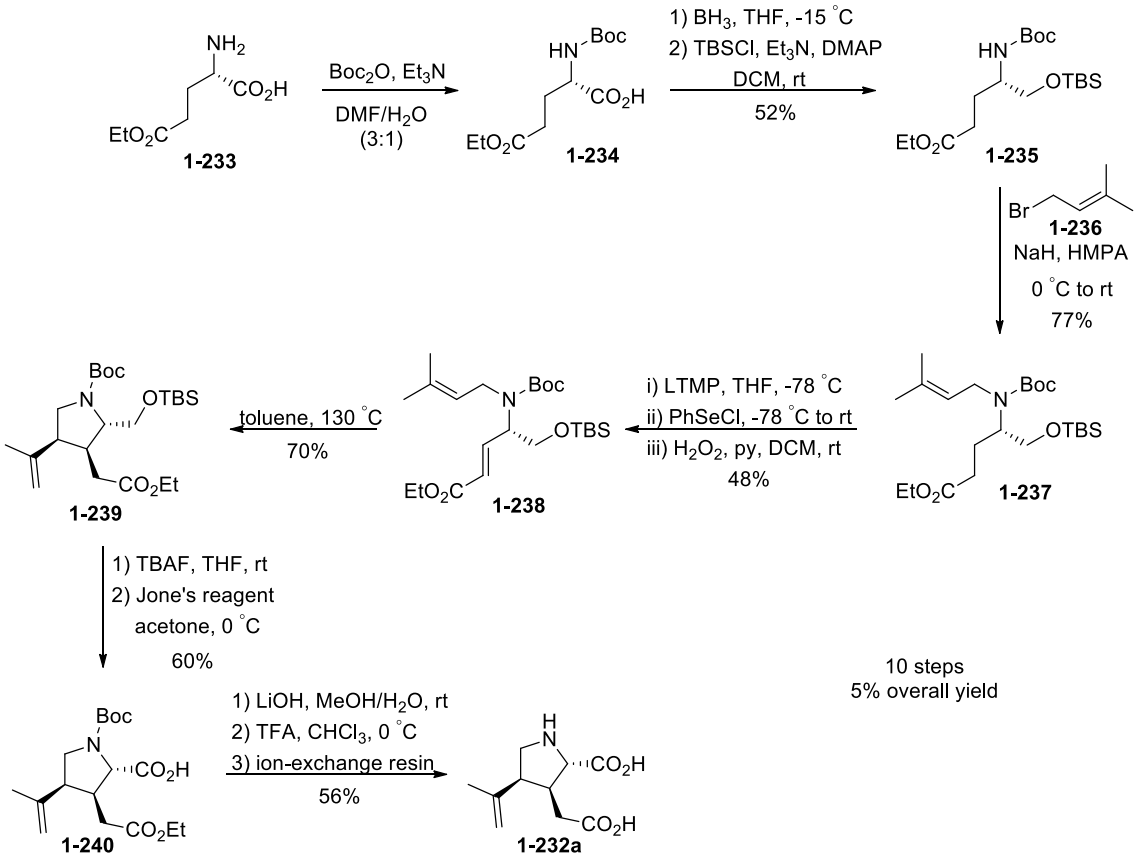
Since the initial isolation of kainic acid, the compound received attention from chemists and biologist due to its neuroexcitatory properties. L-glutamic acid (**1-232h**), which is the most abundant excitatory neurotransmitter, interacts with two classes of receptors. The first are called ionotropic glutamate receptors (iGluRs), which are coupled to ion channels that control the flux of ions to nerve cells and are capable of millisecond or faster response times. The second are metabotropic glutamate receptors (mGluRs) which have slower response times compared to the first, but produce long lasting changes to nerve cells.[109] When L-glutamic acid (**1-232h**) was administered subcutaneously to animals, it destroyed neurons of the inner retina which suggested that excessive activation of iGluRs can cause a cascade of events that leads to cell death.[109] When kainic acid (**1-232a**) was administered, it was discovered that it behaved as an agonist for the iGluRs, mediating the effects caused by glutamic acid which helped to elucidate the neurophysiological role of glutamic acid.[109,113] It was later understood that when in direct contact with neurons, kainic acid induced motor hyperactivity and seizures, as well as destroyed neurons in specific regions of the brain that contained high concentrations of the molecule.[108,109] It was then realized that these symptoms resembled several human pathological conditions which resulted in creating model conditions for the better understanding of epilepsy, stroke and Huntington's chorea.[109,111]

With its interesting biological properties, kainic acid became high in demand in the neuroscience field; however, limited supply from natural sources resulted in a shortage

and high price (50mg from sigma-aldrich costs $1260.00). Due to this demand, kainic acid sparked interest in organic chemists, resulting in over 70 published synthetic routes.[114]

1.4.2 Total syntheses of Kainic acid

Oppolzer and Thirring's kainic acid synthesis was instrumental for the determination of its absolute stereochemistry (Scheme **1-53**).[112]

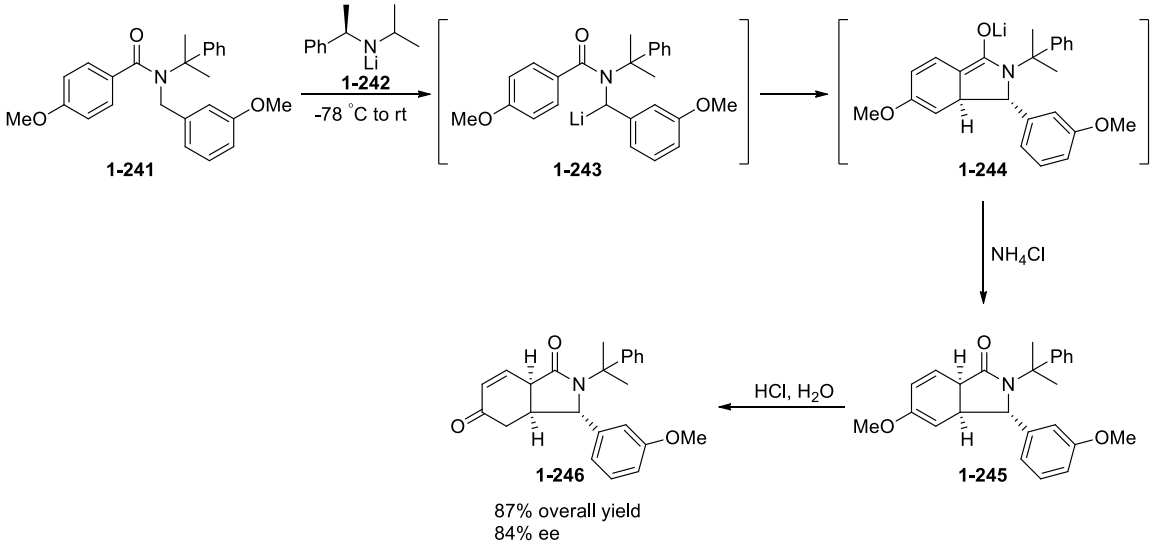


Scheme 1-53. First total synthesis of kainic acid

Starting from a derivative of L-glutamic acid (**1-233**), Boc protection of the primary amine resulted in carboxylic acid (**1-234**). Reduction of the carboxylic acid with borane followed by protection of the resulting primary alcohol with TBSCl furnished (**1-235**) in 52% overall yield. N-alkylation was then performed with (**1-236**) to provide tertiary amine (**1-237**) in good yield. The α,β-unsaturated ester (**1-238**) was formed by treating (**1-237**) under strong basic conditions with an organoselenium reagent, followed by

Grieco elimination. A key stereocontrolled intramolecular ene reaction was performed by heating (**1-238**) in toluene which furnished the desired pyrrolidine core (**1-239**) with the correct stereochemistry. Deprotection of the silyl group followed by oxidation to the acid formed (**1-240**) in 60% overall yield. Finally, saponification of the ester followed by cleavage of the Boc group and purification using ion-exchange resin gave the final product (**1-232a**) in an overall yield of 5%.

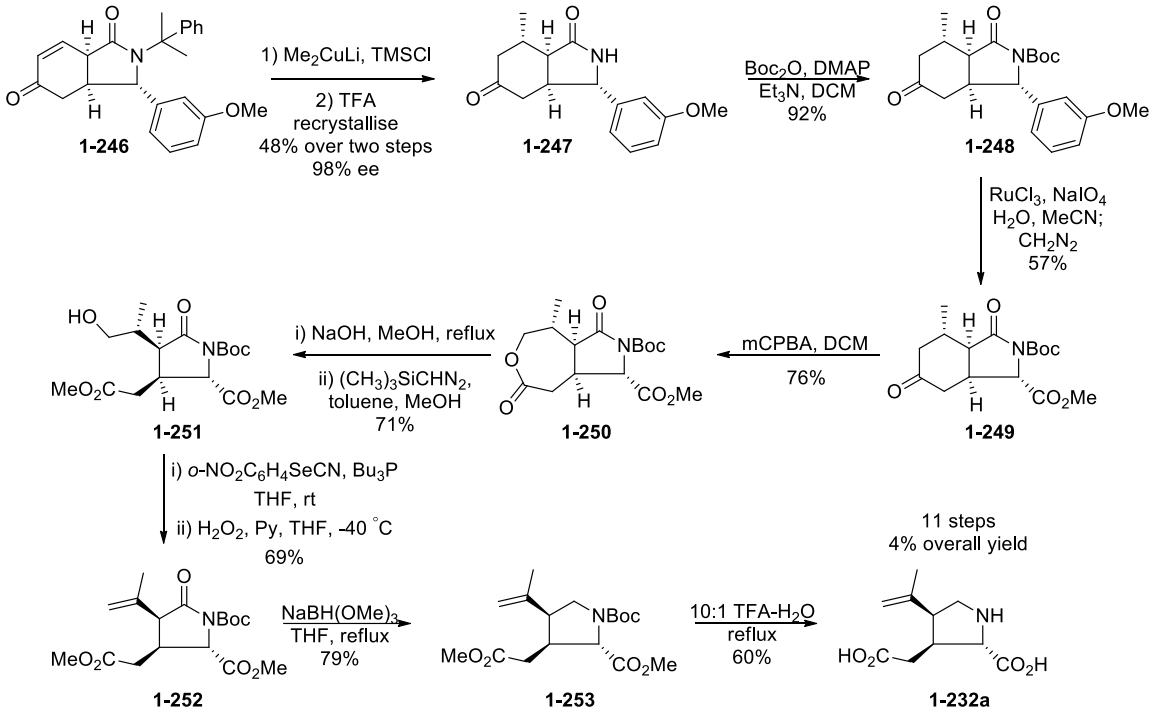
Since the pioneering work by Oppolzer and Thirring[112], several highly efficient total syntheses of kainic acid have been reported. In 2002, Clayden reported an enantioselective synthesis of kainic acid which featured an asymmetric dearomatizing cyclization forming isoindolinones as the key substrate[115] (Scheme **1-54**). Beginning with a N-benzyl benzamide derivative (**1-241**), the asymmetric dearomatizing cyclization was made possible with chiral lithium amide (**1-242**) generating lithium enolate (**1-244**). This intermediate was then protonated (**1-245**) and hydrolyzed forming isoindolinone (**1-246**).



Scheme 1-54. Asymmetric dearomatizing cyclization towards enantioenriched isoindolinone

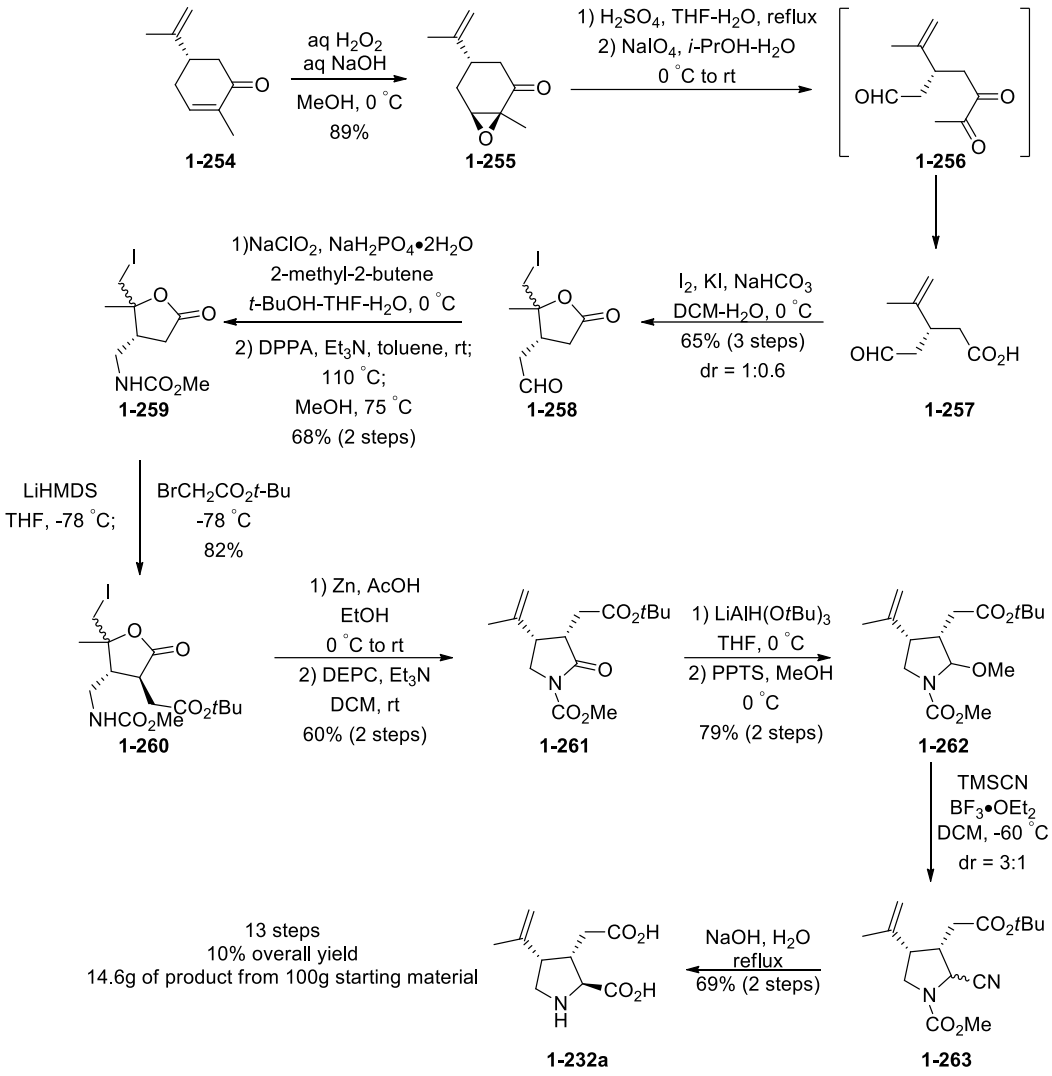
Following the groups previously reported racemic kainic acid synthesis[116] (Scheme **1-55**), the enantioenriched isoindolinone (**1-246**) was treated with an organocuprate in the presence of TMSCl which formed an enol ether derivative that was hydrolyzed with subsequent deprotection forming lactam (**1-247**). After recrystallization of this intermediate, the product lactam was obtained in a 48% yield with 98% ee. Lactam (**1-**

247) was then Boc protected forming (**1-248**) followed by an oxidative removal of the aromatic ring generating a carboxylic acid derivative which was esterified with diazomethane forming methyl ester (**1-249**). Baeyer-Villiger oxidation formed lactone (**1-250**) regioselectively which was hydrolyzed and esterified forming dimethyl ester (**1-251**). Grieco dehydration of (**1-251**) to give isopropenyl (**1-252**) was achieved in one step by treating the primary alcohol with an organoselenium reagent which was oxidized to a selenoxide followed by its elimination. Selective reduction of the lactam with sodium trimethoxyborohydride formed Boc-protected pyrrolidine (**1-253**) which was deprotected with subsequent hydrolysis of the methyl esters using a trifluoroacetic acid/water mixture forming kainic acid (**1-232a**) in 11 steps with an overall yield of 4%.



Scheme 1-55. Synthesis of kainic acid utilizing the asymmetric dearomatizing cyclization methodology

In 2011, Fukuyama reported a multigram total synthesis of kainic acid which featured a stereoselective alkylation and hydrolysis of a nitrile derivative accompanied by epimerization[117] (Scheme **1-56**).

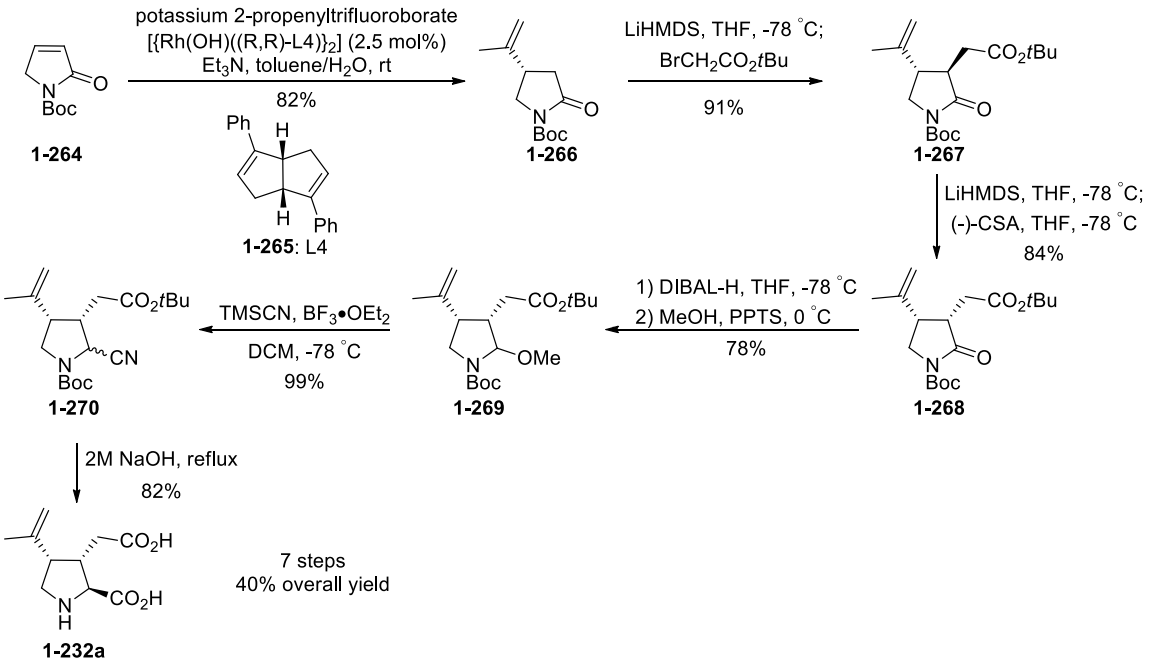


Scheme 1-56. Fukuyama's multigram synthesis of kainic acid

The synthesis involved epoxidation of (+)-carvone (**1-254**) to epoxide (**1-255**) in high yield. The epoxide was then hydrolyzed under acidic conditions producing a diastereomeric mixture of diols, which was subjected to oxidative cleavage forming a 1,2-diketone intermediate (**1-256**). The diketone intermediate was further oxidized to acid (**1-257**) followed by cyclization involving iodine and base to produce iodolactone (**1-258**). Treatment of (**1-258**) under standard Pinnick conditions followed by Curtius rearrangement formed carbamate (**1-259**). The stereoselective alkylation was then performed under basic conditions with *tert*-butylbromoacetate forming ester (**1-260**). Reductive ring-opening of (**1-260**) with Zn produced a carboxylic acid intermediate that

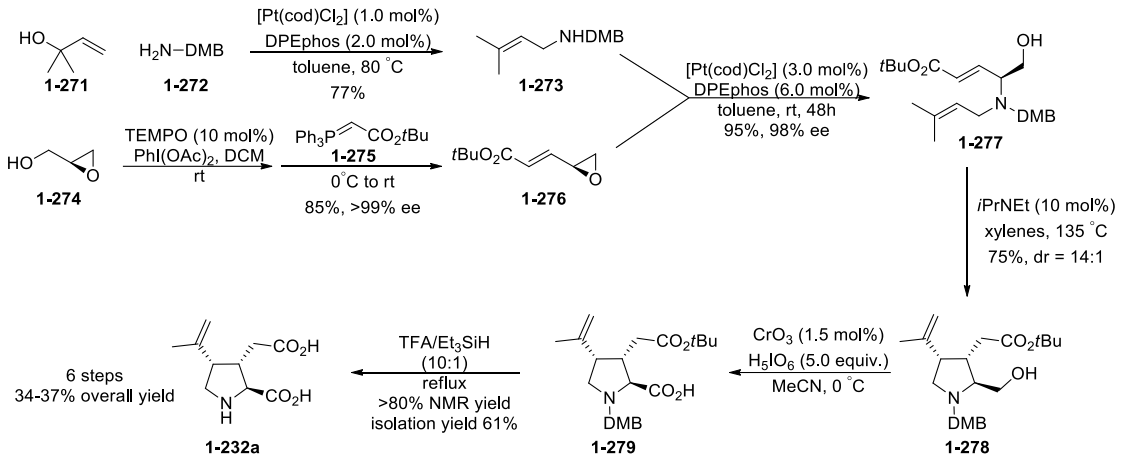
underwent cyclization with DEPC to form lactam (**1-261**). Selectively reducing the lactam and treating the resulting hemiaminal with methanol and acid formed (**1-262**) as a single diastereomer. Treatment of (**1-262**) with TMSCN and Lewis acid gave, via an acyliminium ion, aminonitrile (**1-263**) as a 3:1 mixture of diastereomers. This was not an issue since epimerization of the unwanted diastereomer occurred during the final hydrolysis step producing kainic acid (**1-232a**) in 13 steps with an overall yield of 10%, providing up to 14.6g of product when beginning with 100g of (+)-carvone.

Lin and co-workers reported the highest overall yield of kainic acid in just seven steps with the instrumental step being an asymmetric alkenylation of cyclic α,β-unsaturated carbonyl compounds (Scheme **1-57**).[118] Beginning with lactam (**1-264**), the asymmetric alkenylation was performed forming lactam (**1-266**) in 82% yield and 99% ee. Next, alkylation of (**1-266**) with *tert*-butylbromoacetate gave *trans*-3,4-substituted ester (**1-267**). To acquire the *syn* relationship between C3 and C4 (**1-268**), a dynamic protonation process was executed by deprotonating (**1-267**) at -78 °C followed by protonation with (-)-CSA. The next final steps followed a similar procedure to that reported by Fukuyama providing kainic acid (**1-232a**) in seven steps with a 40% overall yield.



Scheme 1-57. Lin *et al.* synthesis of kainic acid with high overall yield

In 2014, Ohshima *et al*. reported the shortest synthesis of kainic acid to date with a high overall yield and the ability to perform the reactions on gram scale without affecting yield or enantioselectivity[119] (Scheme **1-58**). The key steps featured sequential platinum catalyzed direct allylic aminations and a thermal ene cyclization.



Scheme 1-58. Oshima's total synthesis of kainic acid

The synthesis began with the direct amination of allylic alcohol (**1-271**) and 2,4-dimethoxybenzylamine (DMB) (**1-272**) under platinum catalysis forming allylamine (**1-273**). The enantiopure epoxide (**1-276**) required for the second platinum allylation was formed in one-pot beginning with oxidizing epoxide (**1-274**) with TEMPO followed by a Wittig olefination with (**1-275**) to form (**1-276**) in high yields. With the enantiopure epoxide in hand, the second platinum catalyzed allylation was accomplished forming diallylamine (**1-277**). The ene-cyclization was then performed which constructed the desired pyrrolidine ring (**1-278**) with three continuous stereocenters. Upon scale-up, a catalytic amount of base was added to avoid partial decomposition of the substrate. Oxidizing the primary alcohol to the carboxylic acid (**1-279**) under Jones conditions followed by treatment of the crude material with triethylsilane and TFA resulted in the deprotection of the DMB and *tert*-butyl groups forming the final product (**1-232a**) in six steps with an overall yield of 34-37%.

Each of the synthetic routes to kainic acid presented have had a great impact in the synthetic community. With the goal to synthesize the compound in a quick and efficient

manner, new synthetic methodologies were discovered which can potentially be useful for other synthetic targets. The ability to provide this compound in multigram scale and high overall yields can allow for further biological studies to be conducted.

1.5 References

(1) Quin, L. D.; Tyrell, J. A. *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2010.

(2) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society. An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, Second.; John Wiley & Sons Ltd: Chichester, West Sussex, 2011.

(3) Patrick, G. L. *An Introduction to Drug Synthesis*; Oxford University Press: New York, New York, 2014.

(4) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. *Advan. Biol. Res.* **2011**, *5* (3), 120–144.

(5) Marson, C. M. *Saturated Heterocycles with Applications in Medicinal Chemistry*; Elsevier Ltd, 2017; Vol. 121.

(6) Zhang, T. Y. *The Evolving Landscape of Heterocycles in Drugs and Drug Candidates*; Elsevier Ltd, 2017; Vol. 121.

(7) Chen, W.; Zhan, P.; De Clercq, E.; Liu, X. *Curr. Pharm. Des.* **2012**, *18* (1), 100–112.

(8) Williams, R. M.; Cao, J.; Tsujishima, H. *J. Am. Chem. Soc.* **2003**, *125*, 12172–12178.

(9) Alvarez-Ibarra, C.; Csàkÿ, A. G.; De Silanes, I. L.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62* (3), 479–484.

(10) Nicolle, S. M.; Lewis, W.; Hayes, C. J.; Moody, C. J. *Angew. Chem. Int. Ed.* **2016**,

55 (11), 3749–3753.

(11) Kumar, I. *RSC Adv.* **2014**, *4* (32), 16397–16408.

(12) Bhat, C.; Tilve, S. G. *RSC Adv.* **2014**, *4* (11), 5405–5452.

(13) Padwa, A.; Bur, S. *Recent Advances of 1,3-Dipolar Cycloaddition Chemistry for Alkaloid Synthesis*; Elsevier Ltd, 2016; Vol. 119.

(14) Bdiri, B.; Zhao, B. J.; Zhou, Z. M. *Tetrahedron Asymmetry* **2017**, *28* (7), 876–899.

(15) Narayan, R.; Potowski, M.; Jia, Z. J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47* (4), 1296–1310.

(16) Kobayashi, S.; Jorgensen, K. A. *Cycloaddition Reaction in Organic Synthesis*; Wiley, 2001.

(17) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96* (1), 49–92.

(18) Dennis, N. *Organic Reaction Mechanims 2015: An Annual Survey Covering the Literature Dated January to December 2015*; C., K. A., Ed.; John Wiley & Sons Ltd, 2019.

(19) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115* (11), 5366–5412.

(20) Ray, S. K.; Biswas, R. G.; Suneja, A.; Sadhu, M. M.; Singh, V. K. *J. Org. Chem.* **2018**, *83* (4), 2293–2308.

(21) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101* (21), 6429–6432.

(22) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902–5915.

(23) Trost, B. M.; Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636–6645.

(24) Trost, B. M.; Lam, T. M.; Herbage, M. A. *J. Am. Chem. Soc.* **2013**, *135* (7), 2459–2461.

(25) Mukhopadhyay, S.; Pan, S. C. *Org. Biomol. Chem.* **2018**, *16* (48), 9349–9353.

(26) Xiao, Z. F.; Ding, T. H.; Mao, S. W.; Shah, Z.; Ning, X. S.; Kang, Y. B. *Org. Lett.* **2016**, *18* (21), 5672–5675.

(27) Antonow, D.; Thurston, D. E. *Chem. Rev.* **2011**, *111* (4), 2815–2864.

(28) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; De Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129* (18), 5843–5845.

(29) Magedov, I. V.; Luchetti, G.; Evdokimov, N. M.; Manpadi, M.; Steelant, W. F. A.; Van slambrouck, S.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. *Bioorganic Med. Chem. Lett.* **2008**, *18* (4), 1392–1396.

(30) Smith, A. B.; Charnley, A. K.; Hirschmann, R. *Acc. Chem. Res.* **2011**, *44* (3), 180–193.

(31) Wender, P. A.; Strand, D. *J. Am. Chem. Soc.* **2009**, *131* (22), 7528–7529.

(32) Yu, H.; Zhang, L.; Yang, Z.; Li, Z.; Zhao, Y.; Xiao, Y.; Guo, H. *J. Org. Chem.* **2013**, *78* (17), 8427–8436.

(33) Winum, J. Y.; Scozzafava, A.; Montero, J. L.; Supuran, C. T. *Med. Res. Rev.* **2005**, *25* (2), 186–228.

(34) Yu, Y. F.; Shu, C.; Zhou, B.; Li, J. Q.; Zhou, J. M.; Ye, L. W. *Chem. Commun.* **2015**, *51* (11), 2126–2129.

(35) Yu, Y. F.; Shu, C.; Shen, C. H.; Li, T. Y.; Ye, L. W. *Chem. - An Asian J.* **2013**, *8* (12), 2920–2924.

(36) Masson, G.; Neuville, L.; Bughin, C.; Fayol, A.; Zhu, J. Multicomponent Synthesis of Macrocycles. In *Synthesis of Heterocycles via Multicomponent Reactions II*; Maes, B. U. W., Ruijter, E., Orru, R. V. A., Enders, D., Ley, S. V., Mehta, G., Nicolaou, K. C., Noyori, R., Overman, L. E., Padwa, A., et al., Eds.; Springer, 2010; pp 1–5.

(37) Polindara-García, L. A.; Miranda, L. D. *Org. Lett.* **2012**, *14* (21), 5408–5411.

(38) Elliot, R. L.; Kopecka, H.; Lin, N.-H.; He, Y.; Garvey, D. S. *Synthesis* **1995**, No. 7, 772–774.

(39) Shi, F.; Luo, S. W.; Tao, Z. L.; He, L.; Yu, J.; Tu, S. J.; Gong, L. Z. *Org. Lett.* **2011**, *13* (17), 4680–4683.

(40) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100* (6), 2407–2473.

(41) Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. *Eur. J. Org. Chem.* **2005**, No. 23, 4929–4949.

(42) Matsumoto, R.; Nishino, H. *Synth. Commun.* **2015**, *45* (15), 1807–1816.

(43) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **2005**, *92* (8), 2450–2460.

(44) Loğoğlu, E.; Yilmaz, M.; Katircioğlu, H.; Yakut, M.; Mercan, S. *Med. Chem. Res.* **2010**, *19* (5), 490–497.

(45) Liu, D.; Lei, A. *Chem. Asian J.* **2015**, *10* (4), 806–823.

(46) Tang, S.; Liu, K.; Long, Y.; Gao, X.; Gao, M.; Lei, A. *Org. Lett.* **2015**, *17* (10), 2404–2407.

(47) Heasley, B. *Curr. Org. Chem.* **2014**, *18* (6), 641–686.

(48) Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2014**, *5*, 297–302.

(49) Barrero, A.; Quilez del Moral, J.; Herrador, M.; Rodriguez, H.; Perez Morales, M. *Curr. Org. Chem.* **2009**, *13* (12), 1164–1181.

(50) Heasley, B. *Eur. J. Org. Chem.* **2009**, No. 10, 1477–1489.

(51) Ferreira, A. J.; Beaudry, C. M. *Tetrahedron* **2017**, *73* (8), 965–1084.

(52) López, E.; López, L. A. *Angew. Chem. Int. Ed.* **2017**, *56* (18), 5121–5124.

(53) Zou, H. X.; Li, Y.; Yang, X. H.; Xiang, J.; Li, J. H. *J. Org. Chem.* **2018**, *83* (15), 8581–8588.

(54) Snyder, N. L.; Haines, H. M.; Peczuh, M. W. *Tetrahedron* **2006**, *62* (40), 9301–9320.

(55) Kawahara, N.; Nakajima, S.; Yamazaki, M.; Kawai, K. *Chem. Pharm. Bull.* **1989**, *37* (10), 2592–2595.

(56) Herrmann, J. M.; Untergehrer, M.; Jürgenliemk, G.; Heilmann, J.; König, B. *Eur. J. Org. Chem.* **2014**, *2014* (15), 3170–3181.

(57) Elliott, M., C. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2301–2323.

(58) Olivera, R.; Sanmartin, R.; Churruca, F.; Domínguez, E. *Org. Prep. Proced. Int.* **2004**, *36* (4), 297–330.

(59) Nicolaou, K. C.; Yu, R.; Shi, L.; Cai, Q.; Lu, M.; Heretsch, P. *Org. Lett.* **2013**, *15* (8), 1994–1997.

(60) Zheng, L.; Liang, Y. M. *J. Org. Chem.* **2017**, *82* (13), 7000–7007.

(61) Kotha, S.; Khedkar, P.; Dommaraju, Y. *Tetrahedron Lett.* **2019**, *60* (9), 631–648.

(62) Du, J. Y.; Ma, Y. H.; Meng, F. X.; Zhang, R. R.; Wang, R. N.; Shi, H. L.; Wang, Q.; Fan, Y. X.; Huang, H. L.; Cui, J. C.; et al. *Org. Lett.* **2019**, *21* (2), 465–468.

(63) Courant, T.; Pasco, M.; Lecourt, T. *Org. Lett.* **2018**, *20* (9), 2757–2761.

(64) Wong, H. N. C.; Hon, M.; Tse, C.; Yip, Y.; Tank, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198.

(65) Reissig, H.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196.

(66) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61* (2), 321–347.

(67) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem.* **2015**, *13* (3), 655–

671.

(68) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060.

(69) O'Connor, N. R.; Wood, J. L.; Stoltz, B. M. *Isr. J. Chem.* **2016**, *56* (6–7), 431–444.

(70) Pagenkopf, B. L.; Vemula, N. *Eur. J. Org. Chem.* **2017**, *2017* (18), 2561–2567.

(71) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53* (22), 5504–5523.

(72) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43* (3), 804–818.

(73) Gharpure, S. J.; Nanda, L. N. *Tetrahedron Lett.* **2017**, *58* (8), 711–720.

(74) Reissig, H.; Hirsch, E. *Angew. Chem. Int. Ed.* **1980**, *19* (10), 814–816.

(75) Ivanova, O. A.; Trushkov, I. V. *Chem. Rec.* **2019**, *19*, 1–21.

(76) Yadav, V. K.; Sriramurthy, V. *Angew. Chem. Int. Ed.* **2004**, *43* (20), 2669–2671.

(77) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007–9071.

(78) Rakhmankulov, E. R.; Ivanov, K. L.; Budynina, E. M.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Latyshev, G. V.; Trushkov, I. V.; Melnikov, M. Y. *Org. Lett.* **2015**, *17* (4), 770–773.

(79) Qian, S.; Xie, Z.; Liu, J.; Li, M.; Wang, S.; Luo, N.; Wang, C. *J. Org. Chem.* **2018**, *83* (23), 14768–14776.

(80) Mackay, W. D.; Fistikci, M.; Carris, R. M.; Johnson, J. S. *Org. Lett.* **2014**, *16* (6), 1626–1629.

(81) Yang, J.; Shen, Y.; Lim, Y. J.; Yoshikai, N. *Chem. Sci.* **2018**, *9* (34), 6928–6934.

(82) Garve, L. K. B.; Kreft, A.; Jones, P. G.; Werz, D. B. *J. Org. Chem.* **2017**, *82* (17),

9235–9242.

(83) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70* (20), 8242–8244.

(84) Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777–779.

(85) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130* (12), 4196–4201.

(86) Huang, X. B.; Li, X. J.; Li, T. T.; Chen, B.; Chu, W. D.; He, L.; Liu, Q. Z. *Org. Lett.* **2019**, *21* (6), 1713–1716.

(87) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125* (27), 8122–8123.

(88) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79* (7), 3030–3039.

(89) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. The Vinylcyclopropane-Cyclopentene Rearrangement. In *Organic Reactions*; Kende, A. S., Ed.; John Wiley & Sons Ltd, 1985; pp 248–331.

(90) Baldwin, J. E. *Chem. Rev.* **2003**, *103* (4), 1197–1212.

(91) Baldwin, J. E.; Leber, P. A. *Org. Biomol. Chem.* **2008**, *6* (1), 36–47.

(92) Hudlicky, T.; Reed, J. W. *Angew. Chem. Int. Ed.* **2010**, *49* (29), 4864–4876.

(93) Hudlicky, T. *ACS Omega* **2018**, *3* (12), 17326–17340.

(94) Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, *98* (21), 6705–6706.

(95) Davies, H. M. L.; Baihua, H. *J. Org. Chem.* **1992**, *57* (11), 3186–3190.

(96) Bulo, R. E.; Ehlers, A. W.; Grimme, S.; Lammertsma, K. *J. Am. Chem. Soc.* **2002**, *124* (46), 13903–13910.

(97) Clergue, S.; Rousseau, O.; Delaunay, T.; Dequirez, G.; Tran, T. Van; Aakchioui, S. El; Barozzino-Consiglio, G.; Robiette, R. *Chem. Eur. J.* **2018**, *24* (44), 11417–

11425.

(98) Wenkert, E.; Ananthanarayan, T. P.; Ferreira, V. F.; Hoffmann, M. G.; Kim, H. *J. Org. Chem.* **1990**, *55*, 4975–4976.

(99) Zhang, J.; Tang, Y.; Wei, W.; Wu, Y.; Li, Y.; Zhang, J.; Zheng, Y.; Xu, S. *Org. Lett.* **2017**, *19* (12), 3043–3046.

(100) Nambu, H.; Fukumoto, M.; Hirota, W.; Yakura, T. *Org. Lett.* **2014**, *16* (15), 4012–4015.

(101) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848–1851.

(102) Sperling, D.; Reißig, H.-U.; Fabian, J. *Eur. J. Org. Chem.* **1999**, *1999*, 1107–1114.

(103) Brand, C.; Rauch, G.; Zanoni, M.; Dittrich, B.; Werz, D. B. *J. Org. Chem.* **2009**, *74* (22), 8779–8786.

(104) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. Divinylcyclopropane-CycloheptadieneRearrangement. *Organic Reactions*. 2004, pp 1–133.

(105) Boeckman, R. K.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem.* **1993**, *58* (6), 1295–1297.

(106) Hofmann, B.; Reissig, H.-U. *Synlett* **1993**, 27–29.

(107) Shim, S. Y.; Cho, S. M.; Venkateswarlu, A.; Ryu, D. H. *Angew. Chem. Int. Ed.* **2017**, *56* (30), 8663–8666.

(108) Parsons, A. F. *Tetrahedron* **1996**, *52* (12), 4149–4174.

(109) Stathakis, C. I.; Yioti, E. G.; Gallos, J. K. *Eur. J. Org. Chem.* **2012**, No. 25, 4661–4673.

(110) Bhat, C.; Kumar, A. *Asian J. Org. Chem.* **2015**, *4* (2), 102–115.

(111) Majik, M. S.; Mandrekar, V. K. *Curr. Org. Chem.* **2016**, *20*, 939–951.

(112) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104* (18), 4978–4979.

(113) Hashimoto, K.; Konno, K.; Shirahama, H. *J. Org. Chem.* **1996**, *61* (14), 4685–4692.

(114) Chekan, J. R.; McKinnie, S. M. K.; Moore, M. L.; Poplawski, S. G.; Michael, T. P.; Moore, B. S. *Angew. Chem. Int. Ed.* **2019**, *58* (25), 8454–8457.

(115) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38–39.

(116) Clayden, J.; Tchabanenko, K. *Chem. Commun.* **2000**, 317–318.

(117) Takita, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13* (8), 2068–2070.

(118) Yu, H. J.; Shao, C.; Cui, Z.; Feng, C. G.; Lin, G. Q. *Chem. Eur. J.* **2012**, *18* (42), 13274–13278.

(119) Zhang, M.; Watanabe, K.; Tsukamoto, M.; Shibuya, R.; Morimoto, H.; Ohshima, T. *Chem. Eur. J.* **2014**, *21* (10), 3937–3941.

Chapter 2

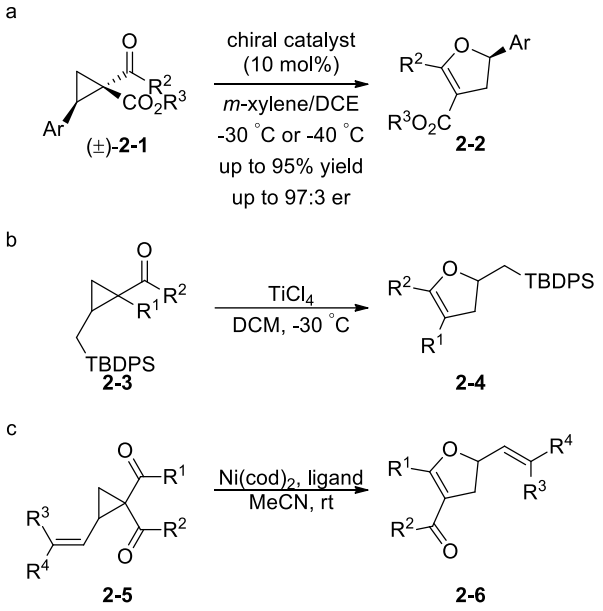
2 The Tandem Cyclopropanation/Vinylogous Cloke-Wilson Rearrangement for the Synthesis of Heterocyclic Scaffolds

This chapter was adapted from the following manuscript:

Piotrowski, M. L.; Kerr, M. A. *Org. Lett.* **2018**, *20*, 7624-7627

2.1 Introduction

The ring strain inherent in DA cyclopropanes and the weakened vicinal C-C bond due to the synergistic electron push-pull relationship between the D and A groups has been exploited for decades. Simple nucleophilic ring-opening of a DA cyclopropane (a homo-Michael addition) or electrophilic ring-opening (homo-enolate addition) results in linear compounds, while reaction with dipolar species can result in hetero- or carbocyclic products. Rearrangement reactions of DA cyclopropanes represents another class of reactivity for an expedient method to access complex chemical structures in an atom economical manner.[64–73] Perhaps one of the most well-established processes is the vinylcyclopropane-cyclopentene rearrangement which results in five membered ring products.[92] A much less studied variant of this reaction is the Cloke-Wilson rearrangement (Scheme **1-42**). In 1929, Cloke reported that treatment of cyclopropyl phenyl ketone with ammonium chloride resulted in the formation of a dihydropyrrole.[120] In 1947 Wilson was able to induce rearrangement of cyclopropane carboxyaldehyde to dihydrofuran.[121] Since these initial discoveries, there have been notable advancements including organocatalysis (Scheme **1-46**)[99], DYKAT (Scheme **2-1a**)[122], silicon promotion (Scheme **2-1b**)[123], and transition metal catalysis (Scheme **2-1c**).[124]

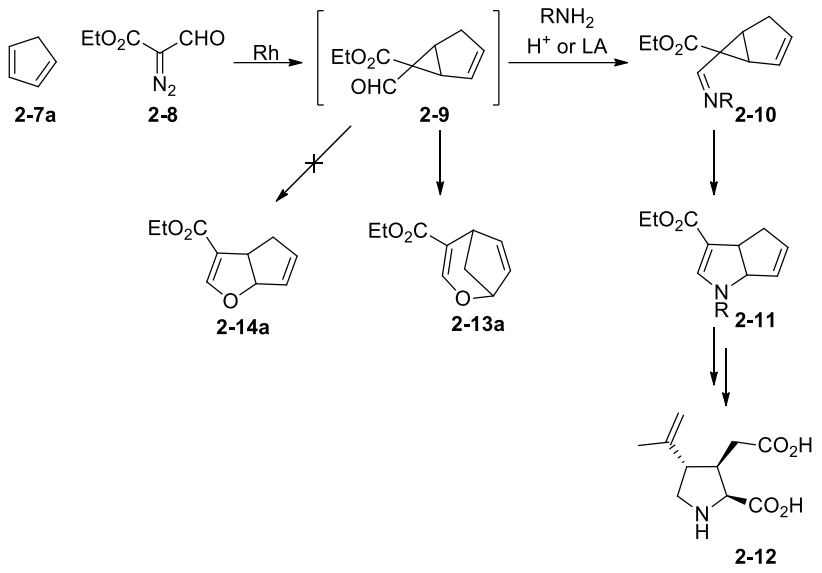


Scheme 2-1. Recent advances in the Cloke-Wilson rearrangement to dihydrofurans

Herein we report a tandem cyclopropanation/Cloke-Wilson rearrangement as well as a rarer but not unprecedented[105,106,125–128] vinylogous variant (a retro-Claisen rearrangement) to form seven-membered oxacycles.

2.2 Results and Discussion

The discovery of the title reactions came about while exploring a route to kainic acid. The original plan was to cyclopropanate cyclopentadiene (**2-7**) with (**2-8**) to produce (**2-9**). The aldehyde would then be converted to aldimine (**2-10**) and subjected to a Cloke-Wilson rearrangement to produce (**2-11**) which we deemed a possible synthetic precursor to kainic acid (**2-12**) (Scheme **2-2**). When subjecting the reactants under metal-carbenoid cyclopropanation conditions, the desired cyclopropane was not isolable but formed a new product *in situ* which we first assigned to a Cloke-Wilson product such as (**2-14a**). Extensive NMR analysis, however showed that the product was in fact a 2,5-dihydrooxepine (**2-13a**), the product of a vinylogous Cloke-Wilson reaction. With this interesting lead result in hand, we sought to explore the reaction for substrate scope and mechanistic understanding.



Scheme 2-2. Vinylogous Cloke-Wilson rearrangement to 2,5-dihydrooxepines

Our study commenced with the treatment of 1,3-cyclohexadiene (**2-7b**) with 2-formyl ethyl diazoacetate (**2-8**) (Table **1**). Zero-addition of all reagents in DCM at 40 °C provided dihydrooxepine (**2-13b**) in low yield along with an unknown by-product (entry 1). It was later realized that the unknown by-product is the dimerization of (**2-8**) forming (**2-15**) which is a common occurrence in metal carbenoid chemistry (Figure **2-1**).[129,130]

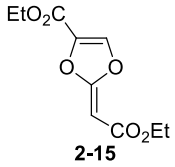
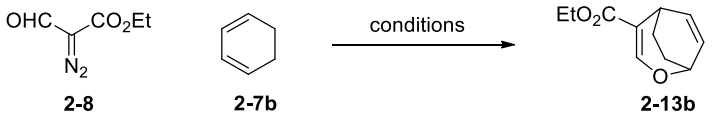


Figure 2-1. Dimerization product of 2-formyl ethyl diazoacetate

With this information in mind, it was decided to add (**2-8**) over an extended period of time to minimize this side reaction. Addition of the diazo species over a period of 30 minutes did not show an improved yield (entry 2). Extending the addition time to one hour (entry 3) and two hours (entry 4) improved the yield slightly; however, the dimerization was still an issue. A switch in equivalence between cyclopentadiene and diazo showed an improvement in yield (entry 5). Lowering the reaction temperature to 25 °C with a two-hour addition time drastically improved the yield (entry 6) while extending

the addition time to ten hours did not improve the results (entry 7). Cooling the reaction to 0 °C in order to minimize the dimerization even further proved to be effective; however, the yield did not improve due to a great deal of decomposition (entry 9). Lowering the amount of catalyst to 1 mol % with an addition time of two hours at 25 °C proved to be the most effective (entry 8). Other catalysts such as $Rh_2(OAc)_4$ provided the product in lower yields (entry 10) or were ineffective (entry 12-14).

Table 1. Tandem cyclopropanation/vinylogous Cloke-Wilson rearrangement with formyldiazoacetate and 1,3-cyclohexadiene



2-8 **2-7b** **2-13b**

Entry	Solvent	Temp (°C)	Addition time of diazo (hours)	Catalyst (mol %)	Diene:diazo	Isolated yield (%)
1	DCM	40	0	$Rh_2(esp)_2$ (2)	2:1	22
2	DCM	40	0.5	$Rh_2(esp)_2$ (2)	2:1	28
3	DCM	40	1	$Rh_2(esp)_2$ (2)	2:1	30
4	DCM	40	2	$Rh_2(esp)_2$ (2)	2:1	34
5	DCM	40	2	$Rh_2(esp)_2$ (2)	1:2	40
6	DCM	25	2	$Rh_2(esp)_2$ (2)	1:2	64
7	DCM	25	10	$Rh_2(esp)_2$ (2)	1:2	60
8	DCM	25	2	$Rh_2(esp)_2$ (1)	1:2	62
9	DCM	0	2	$Rh_2(esp)_2$ (1)	1:2	50

10	DCM	25	2	$Rh_2(OAc)_4$ (1)	1:2	20
11	DCM	25	2	$Rh_2(esp)_2$ (1)	4:1	50
12	DCM	25	2	$Cu(OTf)_2$ (5)	1:2	No rxn
13	DCE	85	2	$Cu(OTf)_2$ (5)	1:2	Decomp.
14	DCE	85	2	$Cu(OTf)_2$ (5)	4:1	Decomp.
15	DCM	25	2	$Rh_2(esp)_2$ (1)	1:3	62

Treating a variety of readily available butadienes (**2-7**) with 2-formyl ethyl diazoacetate (**2-8**) under the conditions shown in entry 8 (Table **1**), provided the corresponding 2,5-dihydrooxepines in modest but acceptable yields given the rapid formation of molecular complexity (Figure **2-2**).

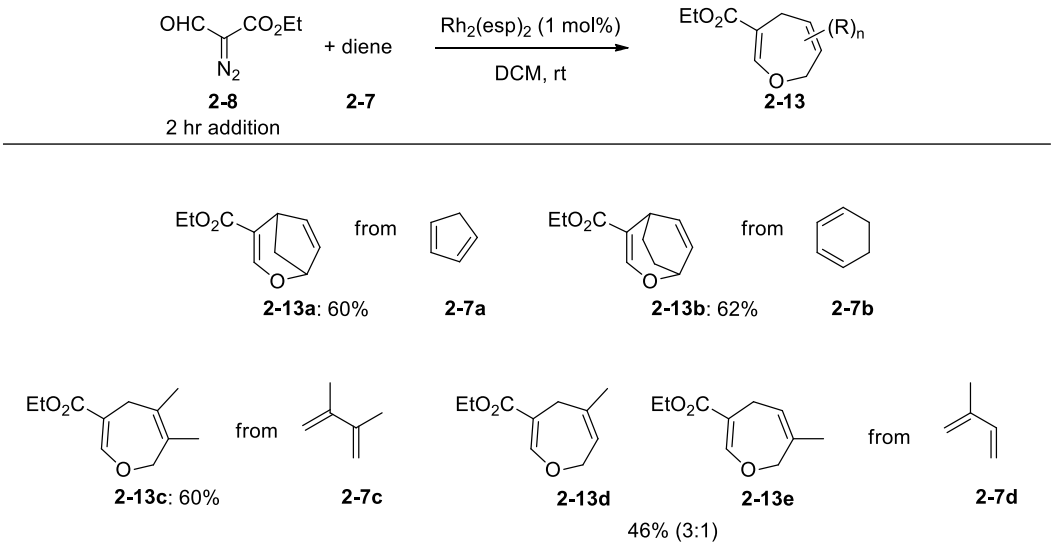
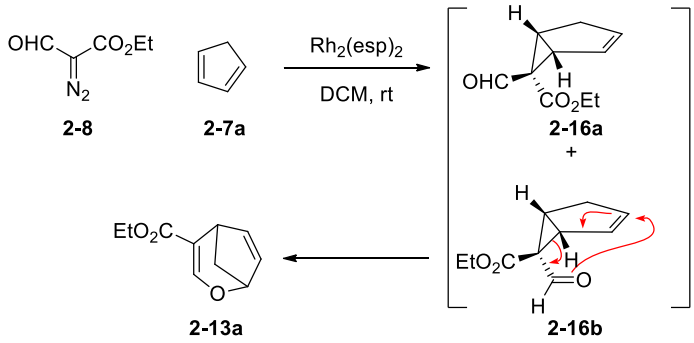


Figure 2-2. Tandem cyclopropanation/vinylogous Cloke-Wilson rearrangement towards 2,5-dihydrooxepines

The modest yields can be explained by the formation of diastereomers during the cyclopropanation stage (Scheme **2-3**). For the rearrangement to occur, an endo relationship between the aldehyde and the vinyl group is necessary.[104,105,131] While one

diastereomer (**2-16b**) would be well positioned to undergo the rearrangement, the other (**2-16a**) would not. At this stage, this is merely a hypothesis as we have never been able to isolate products derived from (**2-16a**).



Scheme 2-3. Mechanistic hypothesis

We were surprised to see a different reactivity pattern when aryl substituted butadienes (**2-17**) were employed. Rather than the vinylogous reaction pathway, a tandem cyclopropanation/Cloke-Wilson process occurred (Figure **2-3**). The most electron rich butadienes (yielding **2-18b**,**c**) underwent spontaneous rearrangement to the dihydrofurans, while the others required treatment with a Lewis acid such as $Sc(OTf)_3$ to promote the cyclization.

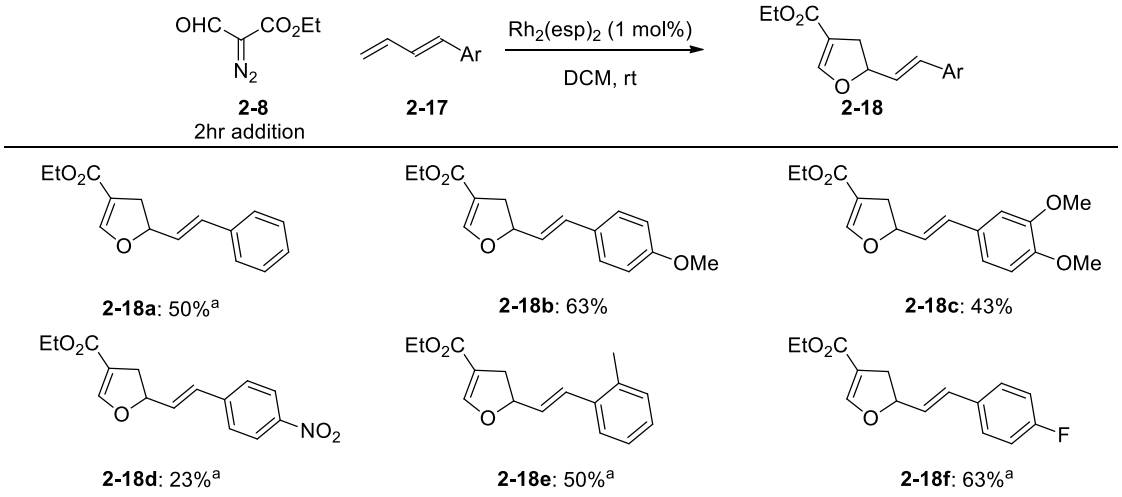


Figure 2-3. Tandem cyclopropanation/Cloke-Wilson rearrangement towards dihydrofurans. [a] Product obtained as a mixture with cyclopropane; required treatment with 5 mol% $Sc(OTf)_3$ in DCM at 40 °C to complete cyclization.

Interestingly, the dihydrooxepines from (Figure **2-1**) underwent rearrangement to their dihydrofuran counterparts (**2-14**) upon treatment with a Lewis acid (Figure **2-4**), likely via a 1,3-oxygen migration involving an allyl cation (Scheme **2-4**). Several things are worthy of note. The bicyclic dihydrooxepines underwent this process in exceedingly high yields, likely due the favorable strain relief in going from a seven-membered ring to a five-membered ring. When the regioisomeric mixture of (**2-13d**) and (**2-13e**) was subjected to the reaction conditions, only (**2-13d**) underwent rearrangement. This result is likely due the fact that (**2-13d**) may form a 3° carbocation while (**2-13e**) would require a higher energy 2° cation.

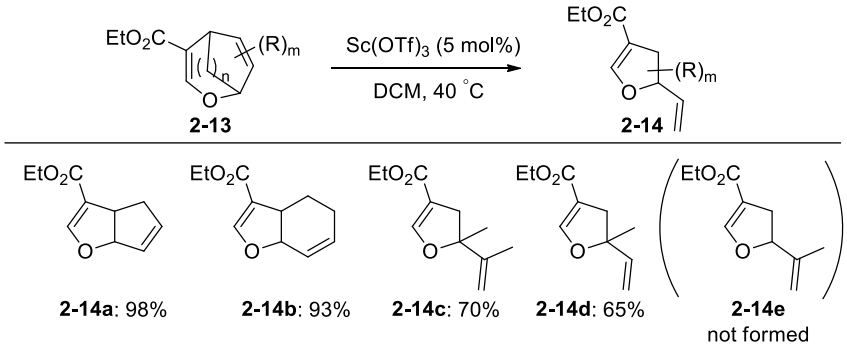
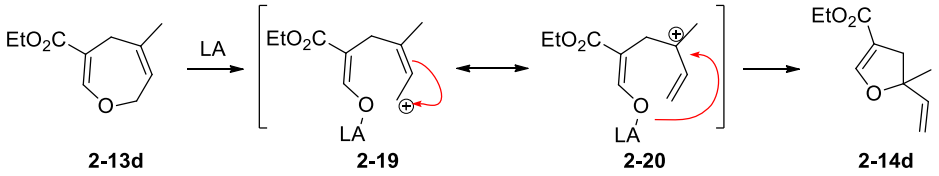


Figure 2-4. Rearrangement of dihydrooxepines to dihydrofurans



Scheme 2-4. Proposed mechanism for the rearrangement of dihydrooxepines to dihydrofurans

Inspired by a report by the Ma group[132], we sought to perform an oxygen to nitrogen transposition to access aza-heterocycles (**2-21**). The Ma communication reported only a single example as a mechanistic study and so this is (to the best of our knowledge) an unexplored reaction. Using slightly modified conditions, we subjected the dihydrofurans from (Figures **2-3** and **2-4**) and were delighted with the results (Figure **2-5**). We limited this study to the use of benzylamine except for a single case where *p*-anisidine was

employed successfully. Ma's paper provides a reasonable mechanism which involves a π-allyl intermediate.

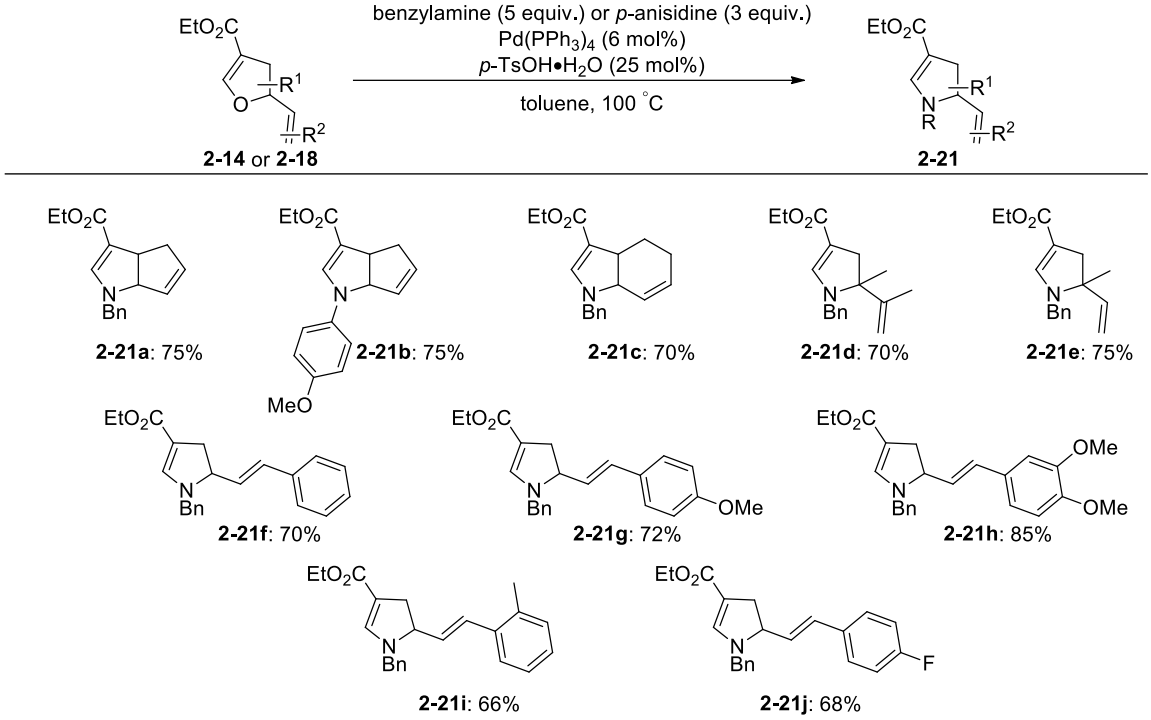


Figure 2-5. Conversion of dihydrofurans to dihydropyrroles

To improve the efficiency of the rearrangements described above, we sought ways to shorten the number of steps involved (Figure **2-6**). When testing a one-pot protocol for the tandem cyclopropanation/vinylogous Cloke-Wilson rearrangement followed by the 1,3-allylic migration, formation of (**2-14a**) was achieved, however the overall yield was inferior. Also, when the oxygen to nitrogen transposition was attempted on dihydrooxepine (**2-13a**), rearrangement was concurrent with nitrogen insertion. The yield for the one-step process was similar to that of the sequential reactions.

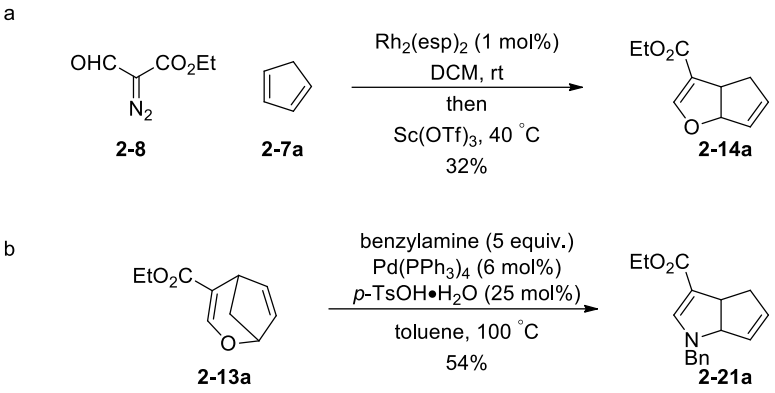


Figure 2-6. [a] One-pot cyclopropanation/vinylogous Cloke-Wilson rearrangement/1,3-allylic migration. [b] Direct conversion of dihydrooxepine to dihydropyrrole.

2.3 Conclusion

In summary, we have described a tandem cyclopropanation/Cloke-Wilson rearrangement as well as the associated vinylogous Cloke-Wilson rearrangement to provide access to 2,5-dihydrooxepine and dihydrofuran scaffolds. Moreover, the dihydrofurans were converted to dihydropyrroles via a relatively unknown palladium-catalyzed oxygen to nitrogen transposition.

2.4 References

(120) Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51* (4), 1174–1187.

(121) Wilson, C. L. *J. Am. Chem. Soc.* **1947**, *69* (12), 3002–3004.

(122) Ortega, A.; Manzano, R.; Uria, U.; Carrillo, L.; Reyes, E.; Tejero, T.; Merino, P.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2018**, *57* (27), 8225–8229.

(123) Yadav, V. K.; Balamurugan, R.. *Org. Lett.* **2001**, *3* (17), 2717–2718.

(124) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8* (4), 573–576.

(125) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133* (4), 774–776.

(126) Feng, J. J.; Zhang, J. *J. Am. Chem. Soc.* **2011**, *133* (19), 7304–7307.

(127) Lee, Y. R.; Hwang, J. C. *Eur. J. Org. Chem.* **2005**, No. 8, 1568–1577.

(128) Chaplin, D. A.; Fox, M. E.; Kroll, S. H. B. *Chem. Commun.* **2014**, *50* (44), 5858–5860.

(129) Connell, R. D.; Tebbe, M.; Gangloff, A. R.; Helquist, P. *Tetrahedron* **1993**, *49* (25), 5445–5459.

(130) Linder, J.; Garner, T. P.; Williams, H. E. L.; Searle, M. S.; Moody, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 1044–1051.

(131) Boeckman, R. K.; Reeder, M. R. *J. Org. Chem.* **1997**, *62* (19), 6456–6457.

(132) Cheng, J.; Jiang, X.; Zhu, C.; Ma, S. *Adv. Synth. Catal.* **2011**, *353* (10), 1676–1682.

2.5 Experimental

2.5.1 General Considerations

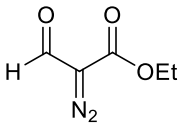
All reactions were conducted under an atmosphere of argon unless otherwise indicated. DCM, toluene, DMF, and THF were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other solvents and reagents were used as purchased from Sigma Aldrich, Alfa Aesar, Caledon, VWR or Oakwood Chemicals and used as received. Reaction progress was followed by thin layer chromatography (TLC) (Merck, TLC silica gel 60 F254) visualized with UV light, and the plates developed with *p*-anisaldehyde, vanillin, basic potassium permanganate or DMP stains. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc).

NMR experiments were performed on Varian Mercury 400, Bruker AvIII 400, Inova 400 and Inova 600 MHz instruments with ^{13}C operating frequencies of 100, 100, 100, and 150 MHz respectively. Chemical shifts are reported in ppm relative to the residual solvent signal; $CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.1$ for ^{13}C. Coupling constants (*J*) are reported in Hz, and multiplicities of the signals are described

using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization. Melting points were determined using a Digimelt MPA160 melting point apparatus from Stanford Research Systems (SRS). Infrared spectra were obtained using a Bruker Alpha II Platinum ATR spectrometer or as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}).

2.5.2 Experimental procedures and characterization data

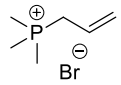
General procedure for the synthesis of formyldiazoacetate **2-8**



Thionyl chloride (1 equiv, 90 mmol) was added dropwise to anhydrous DMF (1 equiv, 90 mmol) at room temperature. Once added, the reaction mixture was heated to 40° C for three hours. The reaction mixture was placed directly under high vacuum until a colourless precipitate was formed. The precipitate was dissolved in chloroform (40ml) and cooled to -20° C using an ice/acetone bath. To the cooled solution, ethyl diazoacetate (2 equiv, 180 mmol) was added dropwise over a period of 30 minutes and the reaction mixture was stirred at room temperature for an hour. Solvent was removed and the orange precipitate was washed with cold ether (50ml) followed by vacuum filtration. The precipitate was washed with 100ml cold ether, collected and dissolved in 10% aqueous acetic acid (40ml) and stirred overnight at room temperature. The aqueous solution was extracted with ether and the combined organic layers were washed with aqueous saturated sodium hydrogen carbonate (40ml), 10% aqueous sulfuric acid solution (40ml), brine, and dried using $MgSO_4$. The resulting yellow oil was used without further purification (36%, 4.5940g). Full characterization can be found in the published articles[a-c]. Note: if all the α-chloroethyl acetate by product hasn't been removed during the vacuum filtration washes with ether, the product obtained after the completed workup can be passed through a silica plug eluting with ethyl acetate.

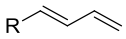
Synthesis of 1,3-dienes

Procedure for the formation of allyltrimethylphosphonium bromide



Trimethylphosphine (1M in THF) (30ml, 30mmol) in dry DCM (30ml) under Argon gas was cooled to 0 ˚C. Allyl bromide (2.6ml, 30mmol) was added dropwise and the reaction was stirred at room temperature for 2.5 hours. The solvent was removed under reduced pressure to yield the desired compound (quant. 5.9g)[d, e].

General procedure for the synthesis of 1,3-dienes



Allyltrimethylphosphonium bromide (0.25g, 1.25mmol) under argon gas in 6.25ml THF was cooled to 0 ˚C. Butyl lithium (2.5M in hexanes) (0.5ml, 1.25mmol) added dropwise and stirred for 15mins. Aldehyde (0.11g, 1.0mmol) in 1.25ml THF was added dropwise and stirred for one hour at 0 ˚C followed by stirring at room temperature until reaction completion monitored by TLC analysis. The reaction mixture was quenched with saturated NH_4Cl and extracted with ether. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude material was filtered through a silica plug eluting with 10% Et_2O/pentane providing the final diene (0.1555g, 0.97mmol)[f].

Full characterization of these starting materials can be found in the following references:

a) F. M. Stojanovic, Z. Arnold, *Collect. Czechoslov. Chem. Commun.* **1967**, 32, 2155-2160.

b) L. Jiang, A. Davison, G. Tennant, R. Ramage, *Tetrahedron* **1998**, 54, 14233-14254.

c) J. Linder, T. P. Garner, H. E. L. Williams, M. S. Searle, C. J. Moody, *J. Am. Chem. Soc.* **2011**, 133, 1044-1051.

d) R. Tamura, K. Saegusa, M. Kakihana, D. Oda, *J. Org. Chem.* **1988**, 53, 2723-2728.

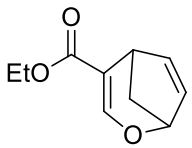
e) J. McNulty, P. Das, *Tetrahedron Lett.* **2009**, 50, 5737-5740.

f) A. Lishchynskyi, K. Muniz, *Chem. Eur. J.* **2012**, 18, 2212-2216.

General procedure for the formation of dihydrooxepine and dihydrofuran compounds (**2-13** and **2-18**)

To a round bottom flask containing a stir bar, $Rh_2(esp)_2$ catalyst (1 mol %) was added and purged with argon gas. DCM (0.35M) was added followed by the addition of the 1,3-diene (1 equiv). Formyldiazoacetate **2-8** (2 equiv) in DCM (0.35M) was added at room temperature via syringe pump over a period of 2 hours. The reaction mixture was stirred at room temperature until completion monitored by TLC analysis. Solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/Hexanes; unless otherwise indicated) to yield the desired compounds. For dihydrofurans (**2-18a**, **d-f**), additional treatment with $Sc(OTf)_3$ in DCM at 40 °C for one hour was required to complete the cyclization. The mixture was then filtered through a silica plug eluting with EtOAc/Hexanes.

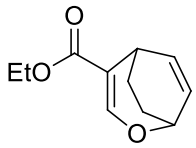
Ethyl 2-oxabicyclo[3.2.1]octa-3,6-diene-4-carboxylate 2-13a



Reagents employed: formyldiazoacetate **2-8** (0.2g, 1.4 mmol), cyclopentadiene (0.06ml, 0.7 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (5mg, 0.007 mmol), DCM (6ml): yield 60% (0.075g, 0.42 mmol) as a yellow oil; Rf = 0.59, 30% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.11 (d, J = 1.5 Hz, 1H), 6.51 (dd, J =

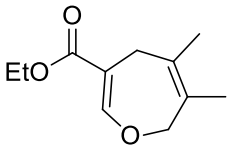
5.3, 2.4 Hz, 1H), 5.55 (dd, J = 5.3, 2.4 Hz, 1H), 5.05 (m, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.35 (br s, 1H), 2.05 (ddd, J = 11.2, 4.1, 2.9 Hz, 1H), 1.85 (d, J = 11.2 Hz, 1H) 1.27 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3, 152.6, 143.4, 121.8, 111.8, 81.6, 59.9, 35.8, 34.8, 14.5; **IR** (thin film, cm^{-1}) 2981, 1703, 1605, 1249, 1078; **HRMS** (EI) calc'd for $C_{10}H_{12}O_3$ 180.0786, found 180.0781.

Ethyl 2-oxabicyclo[3.2.2]nona-3,6-diene-4-carboxylate 2-13b



Reagents employed: formyldiazoacetate **2-8** (0.2g, 1.4mmol), 1,3-cyclohexadiene (0.07ml, 0.7mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (5mg, 0.007mmol), DCM (6ml): yield 62% (0.084g, 0.43 mmol) as a yellow oil; Rf = 0.62, 30% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, J = 1.3 Hz, 1 H) 6.70 (ddd, J = 8.8, 6.4, 1.1 Hz, 1 H) 5.97 (ddd, J = 8.8, 6.4, 1.1 Hz, 1 H) 4.62 (ddt, J = 6.5, 5.2, 1.4 Hz, 1 H) 4.14 (q, J = 7.2 Hz, 2 H) 3.23-3.19 (m, 1 H) 2.51 (dddd, J = 15.4, 9.3, 6.2, 1.4 Hz, 1 H) 2.24-2.17 (m, 1 H) 1.95-1.87 (m, 1 H) 1.77 (dddd, J = 12.9, 11.3, 6.2, 4.0 Hz, 1 H) 1.25 (t, J = 7.2 Hz, 3 H**); ^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 156.3, 141.7, 123.2, 111.5, 72.5, 60.2, 29.3, 28.6, 27.8, 14.5; **IR** (thin film, cm^{-1}) 2979, 1697, 1615, 1196, 1063, 891; **HRMS** (EI) calc'd for $C_{11}H_{14}O_3$ 194.0943, found 194.0944.

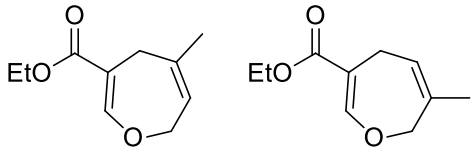
Ethyl 5,6-dimethyl-4,7-dihydrooxepine-3-carboxylate 2-13c



Reagents employed: formyldiazoacetate **2-8** (0.2g, 1.4 mmol), 2,3-dimethyl-1,3-butadiene (0.08ml, 0.7 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (5mg, 0.007 mmol), DCM (6ml): purified with column chromatography using 5% Et_2O/pentane; yield 60% (0.083g, 0.42 mmol) as a yellow oil; Rf = 0.64, 30% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 (s, 1H), 4.60 (s, 2H), 4.15 (q, J =

7.1 Hz, 2H), 3.19 (s, 2H), 1.80 (br s, 6H), 1.26 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 168.9, 158.0, 139.0, 126.4, 106.4, 71.9, 60.2, 30.0, 20.8, 18.4, 14.4; **IR** (thin film, cm^{-1}) 2981, 1698, 1626, 1251, 1210, 1071; **HRMS** (EI) calc'd for $C_{11}H_{16}O_3$ 196.1099, found 196.1100.

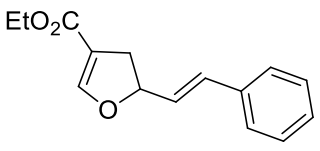
Ethyl 6-methyl-4,7-dihydrooxepine-3-carboxylate 2-13d and **2-13e**



2-13d **2-13e**

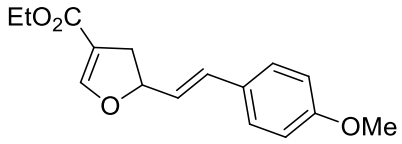
Reagents employed: formyldiazoacetate **2-8** (0.43g, 3.0 mmol), isoprene (0.15ml, 1.5 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (0.011g, 0.015 mmol), DCM (13ml): purified with column chromatography using 5% Et_2O/pentane; yield 46% (0.12g, 0.69 mmol) as an inseparable mixture of isomers (3:1) as a yellow oil; Rf = 0.68, 30% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$, **2-13d**) δ = 7.52 (t, J = 1.0 Hz, 1H), 5.74 (t, J = 7.1 Hz, 1H), 4.57 (d, J = 7.1 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.22 (s, 2H), 1.86 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); **^{1}H NMR** (400 MHz, $CDCl_3$, **2-13e**) δ = 7.50 (t, J = 1.0 Hz, 1H), 5.93 (tq, J = 6.3, 1.7 Hz, 1H), 4.60 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.15-3.12 (m, 2H), 1.82 (q, J = 1.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, **2-13d**) δ = 168.8, 158.4, 148.4, 120.0, 105.3, 65.8, 60.3, 29.1, 25.0, 14.5; **^{13}C NMR** (100MHz, $CDCl_3$, **2-13e**) δ = 168.8, 158.2, 134.9, 130.0, 107.3, 70.4, 62.4, 41.0, 23.3, 22.4, 14.2; **IR** (thin film, cm^{-1}) 2978, 1698, 1625, 1223, 1095, 1065; **HRMS** (EI) calc'd for $C_{10}H_{14}O_3$ 182.0943, found 182.0942.

(E)-ethyl 5-styryl-4,5-dihydrofuran-3-carboxylate 2-18a



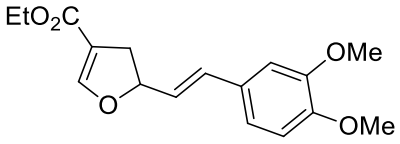
Reagents employed: formyldiazoacetate **2-8** (0.22g, 1.54 mmol), (E)-buta-1,3-dien-1-ylbenzene (0.1g, 0.77 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (6mg, 0.0077mmol), DCM (7ml); yield 50% (0.095g, 0.39 mmol) as a mixture of cyclopropane and dihydrofuran; Rf = 0.61, 30% EtOAc/hexanes; **Reagents employed**: Cyclopropane/dihydrofuran mixture (0.095g, 0.39 mmol), $Sc(OTf)_3$ (0.01g, 0.019 mmol), DCM (3ml): yield 100% (0.095g, 0.39 mmol) as a yellow oil; Rf = 0.61, 30% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.35-7.31 (m, 2H), 7.30-7.27 (m, 2H), 6.64 (d, J = 15.9 Hz, 1H), 6.28 (dd, J = 15.8, 7.3 Hz, 1H), 5.39 (dt, J = 9.5, 7.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.11 (ddd, J = 14.7, 10.6, 1.9 Hz, 1H), 2.74 (ddd, J = 14.7, 8.0, 1.9 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.3, 156.3, 136.0, 132.6, 128.7, 128.3, 127.4, 126.8, 108.9, 85.8, 59.9, 34.2, 14.5; **IR** (thin film, cm^{-1}) 2980, 1701, 1624, 1102, 751, 692; **HRMS** (EI) calc'd for $C_{15}H_{16}O_3$ 244.1099, found 244.1098.

(E)-ethyl 5-(4-methoxystyryl)-4,5-dihydrofuran-3-carboxylate 2-18b



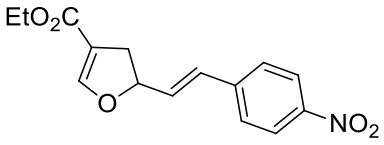
Reagents employed: formyldiazoacetate **2-8** (0.26g, 1.88 mmol), (E)-1-(buta-1,3-dien-1-yl)-4-methoxybenzene (0.15g, 0.94 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (7mg, 0.0094 mmol), DCM (8ml): yield 63% (0.16g, 0.59 mmol) as a green/yellowish solid; Rf = 0.45, 30% EtOAc/hexanes; **melting point**: 64.4-64.6 °C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (AA'BB', 2H), 7.27 (t, J = 1.9 Hz, 1H), 6.88-6.84 (AA'BB', 2H), 6.58 (d, J = 15.6 Hz, 1H), 6.14 (dd, J = 15.8, 7.5 Hz, 1H), 5.36 (dt, J = 10.4, 7.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.08 (ddd, J = 14.7, 10.4, 1.9 Hz, 1H), 2.72 (ddd, J = 14.4, 8.0, 1.8 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 159.8, 156.3, 132.4, 128.7, 128.1, 125.2, 114.1, 108.9, 86.2, 59.9, 55.4, 34.2, 14.5; **IR** (thin film, cm^{-1}) 2980, 1700, 1624, 1512, 1249, 1102, 1032; **HRMS** (EI) calc'd for $C_{16}H_{18}O_4$ 274.1205, found 274.1207.

(E)-ethyl 5-(3,4-dimethoxystyryl)-4,5-dihydrofuran-3-carboxylate 2-18c



Reagents employed: formyldiazoacetate **2-8** (0.27g, 1.9 mmol), (E)-4-(buta-1,3-dien-1-yl)-1,2-dimethoxybenzene (0.18g, 0.97 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (7mg, 0.0097 mmol), DCM (8ml): yield 43% (0.12g, 0.42 mmol) as a yellow oil; Rf = 0.28, 30% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (t, J = 1.9 Hz, 1H), 6.95-6.92 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.15 (dd, J = 15.7, 7.4 Hz, 1H), 5.37 (dt, J = 9.6, 7.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.10 (ddd, J = 14.8, 10.5, 1.9 Hz, 1H), 2.74, (ddd, J = 14.8, 7.8, 1.8 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 165.2, 156.3, 149.4, 149.1, 132.6, 129.0, 125.3, 120.3, 111.1, 108.9, 108.8, 86.1, 59.8, 56.0, 55.9, 34.1, 14.5; **IR** (thin film, cm^{-1}) 2935, 1698, 1623, 1515, 1265, 1101, 1025; **HRMS** (EI) calc'd for $C_{17}H_{20}O_5$ 304.1311, found 304.1311.

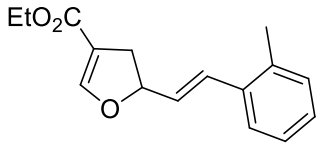
(E)-ethyl 5-(4-nitrostyryl)-4,5-dihydrofuran-3-carboxylate 2-18d



Reagents employed: formyldiazoacetate **2-8** (0.19g, 1.4 mmol), (E)-1-(buta-1,3-dien-1-yl)-4-nitrobenzene (0.054g, 0.31 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (2mg, 0.0031 mmol), DCM (5ml): yield 29% (0.026g, 0.09 mmol) as a dark orange oil; Rf = 0.41, 20% EtOAc/hexanes; **Reagents employed**: cyclopropane/dihydrofuran mixture (0.026g, 0.09 mmol), $Sc(OTf)_3$ (2mg, 0.0045 mmol), DCM (0.75ml): yield 100% (0.026g, 0.09 mmol) as a dark yellow oil; Rf = 0.41, 20% EtOAc/hexanes; **^{1}H NMR** δ 8.21-8.16 (m, 2H), 7.54-7.51 (m, 2H), 7.28 (brs, 1H), 6.69 (d, J = 15.8 Hz, 1H), 6.44 (dd, J = 15.9, 6.5 Hz, 1H), 5.42 (dt, J = 10.6, 7.1 Hz, 4.19 (q, J = 7.1 Hz, 2H), 3.15 (ddd, J = 14.7, 10.7, 1.4 Hz, 1H), 2.74 (ddd, J = 14.8, 7.7, 1.5 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.1, 156.1, 147.4, 142.5,

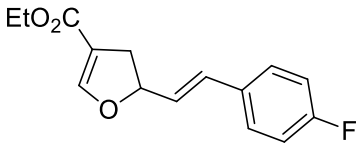
132.3, 129.8, 127.4, 124.2, 109.0, 84.7, 60.1, 34.2, 14.5; **IR** (cm^{-1}) 2981, 1698, 1514, 1340, 1097; **HRMS** (EI) calc'd for $C_{15}H_{15}NO_5$ 289.0950, found 289.0963.

(E)-ethyl 5-(2-methylstyryl)-4,5-dihydrofuran-3-carboxylate 2-18e



Reagents employed: formyldiazoacetate **2-8** (0.24g, 1.7 mmol), (E)-1-(buta-1,3-dien-1-yl)-2-methylbenzene (0.12g, 0.86 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (6mg, 0.0086 mmol), DCM (7.4ml): yield 50% (0.11g, 0.43 mmol) as a yellow oil; Rf = 0.5, 20% EtOAc/hexanes; **Reagents employed**: cyclopropane/dihydrofuran mixture (0.11g, 0.43 mmol), $Sc(OTf)_3$ (0.01g, 0.022 mmol), DCM (3ml): yield 100% (0.11g, 0.43 mmol) as a dark yellow oil; Rf = 0.5, 20% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46-7.43 (m, 1H), 7.29 (br s, 1H), 7.19-7.14 (m, 3H), 6.86 (d, J = 15.6 Hz, 1H), 6.17 (dd, J = 15.7, 7.3 Hz, 1H), 5.41 (dt, J = 10.3, 8.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.12 (ddd, J = 14.8, 10.5, 1.9 Hz, 1H), 2.75 (ddd, J = 14.7, 8.1, 1.9 Hz, 1H), 2.36 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 156.5, 135.8, 135.0, 130.5, 130.4, 128.6, 128.1, 126.2, 125.8, 108.8, 86.1, 59.9, 34.2, 19.8, 14.4; **IR** (cm^{-1}) 2980, 1699, 1622, 1095, 749; **HRMS** (EI) calc'd for $C_{16}H_{18}O_3$ 258.1256, found 258.1257.

(E)-ethyl 5-(4-fluorostyryl)-4,5-dihydrofuran-3-carboxylate 2-18f



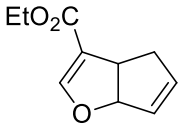
Reagents employed: formyldiazoacetate **2-8** (0.25g, 1.8 mmol), (E)-1-(buta-1,3-dien-1-yl)-4-fluorobenzene (0.13g, 0.88 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (7mg, 0.0088 mmol), DCM (7.5ml): yield 65% (0.15g, 0.57 mmol) as a yellow oil and mixture of cyclopropane and oxepine; Rf = 0.52, 30% EtOAc/hexanes; **Reagents employed**: cyclopropane/dihydrofuran mixture (0.15g, 0.57

mmol), $Sc(OTf)_3$ (0.014g, 0.028 mmol), DCM (3ml): yield 98% (0.14g, 0.56 mmol) as a yellow oil; Rf = 0.52, 30% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37-7.36 ($AA^{'}BB^{'}$, 2 H), 7.27 (t, J = 1.8 Hz, 1 H), 7.03-7.00 ($AA^{'}BB^{'}$, 2 H), 6.60 (d, J = 15.8 Hz, 1 H), 6.19 (dd, J = 15.8, 7.2 Hz, 1 H), 5.36 (dt, J = 9.9, 7.5 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 3.10 (ddd, J = 14.8, 10.5, 1.8 Hz, 1 H), 2.73 (ddd, J = 14.8, 7.9, 1.8 Hz, 1 H), 1.28 (t, J = 7.1 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.2, 162.7 (d, $^1J_{CF}$ = 247.7 Hz), 156.3, 132.2 (d, $^4J_{CF}$ = 3.4 Hz), 131.4, 128.4 (d, $J^3_{C\text{-}F}$ = 8.1 Hz), 127.2, 115.7 (d, $^2J_{CF}$ = 21.7 Hz), 108.9, 85.6, 59.9, 34.1, 14.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.42-(-113.34); **IR** (thin film, cm^{-1}) 2982, 1700, 1625, 1509, 1229, 1108, 755; **HRMS** (EI) calc'd for $C_{15}H_{15}FO_3$ 262.1005, found 262.0996.

General procedure for the conversion of dihydrooxepines to dihydrofurans (**2-14**)

In a round bottom flask containing the starting dihydrooxepine and stir bar was added DCM (0.12M) and $Sc(OTf)_3$ (5 mol%) under argon gas. The reaction was heated to reflux for the allotted time. The reaction was then cooled to room temperature and filtered through celite eluting with DCM. Solvent was then removed under reduced pressure or with a stream of nitrogen gas for the more volatile compounds. The compounds either required no further purification or column chromatography eluting with EtOAc/hexanes or Et_2O/pentane.

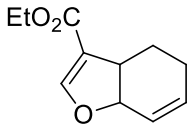
Ethyl 4,6a-dihydro-3aH-cyclopenta[b]furan-3-carboxylate 2-14a



Reagents employed: Dihydrooxepine **2-13a** (0.11g, 0.63 mmol), $Sc(OTf)_3$ (0.016g, 0.032mmol), DCM (5ml): yield 98% (0.11g, 0.63 mmol) as a dark purple oil with a reaction time of one hour with no further purification required; Rf = 0.59, 30% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, J = 1.4 Hz, 1H), 6.08-6.05 (m, 1H), 5.81-5.76 (m, 2H), 4.17 (q, J = 7.4 Hz, 2H), 3.79-3.74 (m, 1H), 2.76-2.68 (m, 1H), 2.57-2.50 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.5, 155.6,

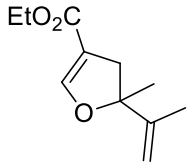
136.9, 128.3, 113.1, 95.4, 59.8, 42.2, 39.2, 14.6; **IR** (thin film, cm^{-1}) 2931, 1702, 1622, 1104, 1028, 775; **HRMS** (EI) calc'd for $C_{10}H_{12}O_3$ 180.0786, found 180.0791.

Ethyl 3a,4,5,7a-tetrahydrobenzofuran-3-carboxylate 2-14b



Reagents employed: Dihydrooxepine **2-13b** (0.084g, 0.43 mmol), $Sc(OTf)_3$ (0.011g, 0.022 mmol), DCM (3.6ml): yield 93% (0.078g, 0.4 mmol) as a dark purple oil with a reaction time of one hour and purified by column chromatography eluting with 15% EtOAc in hexanes; Rf = 0.61, 30% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (brs, 1H), 6.25-6.21 (m, 1H), 5.98-5.95 (m, 1H), 4.92-4.89 (m, 1H), 4.24-4.19 (m, 2H), 3.10-3.06 (m, 1H), 2.17-2.08 (m, 2H), 1.96-1.89 (m, 1H), 1.38-1.34 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H); **^{13}C NMR** δ 165.4, 157.1, 134.8, 123.2, 114.2, 81.0, 59.7, 38.6, 24.8, 23.1, 14.5; **IR** (thin film, cm^{-1}) 2929, 1708, 1616, 1098, 905, 766; **HRMS** (EI) calc'd for $C_{11}H_{14}O_3$ 194.0943, found 194.0942.

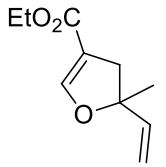
Ethyl 5-methyl-5-(prop-1-en-2-yl)-4,5-dihydrofuran-3-carboxylate 2-14c



Reagents employed: Dihydrooxepine **2-13c** (0.05g, 0.25 mmol), $Sc(OTf)_3$ (6mg, 0.012 mmol), DCM (2ml): yield 74% (0.037g, 0.19 mmol) as a yellow oil with a reaction time of five hours and purified by column chromatography eluting with 5% Et_2O in pentane and concentrated with nitrogen gas; Rf = 0.33, 10% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (t, J = 2.0 Hz, 1H), 4.99 (brs, 1H), 4.83 (brs, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.87, 2.63 (AB_q, J_{AB} = 14.6 Hz, 2H; with each signal split into a doublet due to $^4J_{CH}$ = 1.8 Hz coupling with the methine proton), 1.78 (s, 3H), 1.49 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.6, 155.5, 146.9, 110.2, 107.9, 93.2,

59.9, 39.5, 26.2, 18.5, 14.6; **IR** (cm^{-1}) 2978, 1700, 1624, 1101; **HRMS** (EI) calc'd for C11H16O3 196.1099, found 196.1102.

Ethyl 5-methyl-5-vinyl-4,5-dihydrofuran-3-carboxylate 2-14d

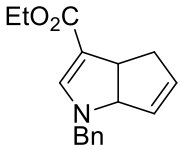


Reagents employed: Dihydrooxepine (**2-13d,e**) (0.12g, 0.69 mmol), $Sc(OTf)_3$ (0.017g, 0.034 mmol), DCM (6ml): yield 65% (0.082g, 0.45 mmol) as a yellow oil purified by column chromatography eluting with 5% Et_2O in pentane and concentrated with nitrogen gas; Rf = 0.54, 10% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.18 (t, J = 1.8 Hz, 1H), 5.95 (dd, J = 17.2, 10.8 Hz, 1H), 5.21 (d, J = 17.3 Hz, 1H), 5.08 (d, J = 10.8 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.81, 2.65 (AB_q, J_{AB} = 14.6 Hz, 2H; with each signal split into a doublet due to $^4J_{CH}$ = 1.8 Hz coupling with the methine proton), 1.46 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 155.4, 140.9, 113.0, 107.9, 90.8, 59.8, 39.9, 26.4, 14.5; **IR** (cm^{-1}) 2978, 1700, 1622, 1099; **HRMS** (EI) calc'd for $C_{10}H_{14}O_3$ 182.0943, found 182.0945.

General procedure for the conversion of dihydrofuran to dihydropyrrole (**2-21**)

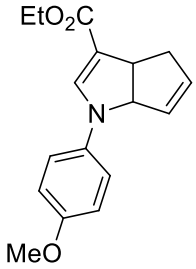
In a microwave vial or sealed tube containing magnetic stir bar and capped with a rubber septum under argon gas was added the starting dihydrofuran (1 equiv.) followed by dry toluene (0.12M). In the following order was added benzylamine or *p*-anisidine (5 equiv. or 3 equiv. respectively), *p*-$TsOH \cdot H_2O$ (0.25 mol%) and $Pd(PPh_3)_4$ (6 mol%) under argon. The rubber septum was replaced with a microwave vial cap or sealed tube cap and heated to 100 °C overnight. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/Hexanes) to yield the desired compounds (**2-21a-j**).

Ethyl 1-benzyl-1,3a,4,6a-tetrahydrocyclopenta[b]pyrrole-3-carboxylate 2-21a



Reagents employed: dihydrofuran **2-14a** (0.37g, 2.0 mmol), benzylamine (1.0ml, 10.0 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.14g, 0.12 mmol), *p*-Toluenesulfonic acid monohydrate (0.095g, 0.5 mmol), toluene (17ml): yield 75% (0.41g, 1.5 mmol) as an orange oil; Rf = 0.37, 30% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38-7.27 (m, 4H), 7.26-7.25 (m, 1H), 7.04 (d, J = 1.0 Hz, 1H), 5.99-5.96 (m, 1H), 5.66-5.63 (m, 1 H), 5.72-5.68 (m, 1 H), 4.36, 4.28 (AB_q, J_{AB} = 15.0, 2H), 4.19-4.06 (m, 2 H), 3.88 (dddd, J = 10.6, 8.3, 2.7, 1.0 Hz, 1 H), 2.81-2.73 (m, 1 H), 2.62-2.55 (m, 1 H), 1.24 (t, J = 7.1 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 148.9, 137.0, 135.6, 128.9, 128.1, 127.9, 126.9, 103.9, 73.5, 58.8, 52.6, 43.3, 40.9, 14.8; **IR** (thin film, cm^{-1}) 2918, 1671, 1582, 1167, 1086, 698; **HRMS** (EI) calc'd for $C_{17}H_{19}NO_2$ 269.1416, found 269.1417.

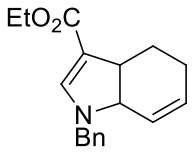
Ethyl 1-(4-methoxyphenyl)-1,3a,4,6a-tetrahydrocyclopenta[b]pyrrole-3-carboxylate 2-21b



Reagents employed: dihydrofuran (**2-14a**) (1.32g, 7.4 mmol), 4-methoxyaniline (2.82g, 22.9 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.51g, 0.44 mmol), *p*-Toluenesulfonic acid monohydrate (0.35g, 1.8 mmol), toluene (62ml): yield 75% (1.58g, 5.5 mmol) as a pale brown solid; Rf = 0.44, 30% EtOAc/hexanes; **melting point**: 61.6-62.0 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, J = 1.2 Hz, 1H), 6.93-6.91 (AA'BB', 2H), 6.86-6.83 (AA'BB' m, 2H), 6.03-6.01 (m, 1H), 5.88-5.85 (m, 1H), 5.33=5.30 (m, 1H), 4.22-4.13 (m, 2H), 3.97 (br t, J = 9.1 Hz, 1H), 3.76 (s, 3H), 2.87-2.81 (m, 1H), 2.66-2.64 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.4, 154.6, 140.7, 135.9, 134.9, 126.6, 116.2, 166.0, 115.1, 108.9, 72.8, 59.2, 55.7, 42.9, 40.2, 14.8;

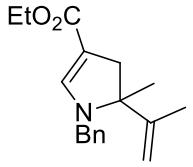
IR (thin film, cm^{-1}) 2928, 1679, 1596, 1514, 1243, 1211, 1100, 1034, 819; **HRMS** (EI) calc'd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1367.

Ethyl 1-benzyl-3a,4,5,7a-tetrahydro-1H-indole-3-carboxylate 2-21c



Reagents employed: dihydrofuran (**2-14b**) (0.078g, 0.4 mmol), benzylamine (0.22ml, 2 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.028g, 0.024 mmol), *p*-Toluenesulfonic acid monohydrate (0.019g, 0.1 mmol) toluene (3.3ml): yield 70% (0.079g, 0.28 mmol) as a yellow oil; Rf = 0.4, 20% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.30-7.27 (m, 1H), 7.25-7.23 (m, 2H), 7.13 (s, 1H), 6.10-6.07 (m, 1H), 5.79-5.76 (m, 1H), 4.35 (AB_q, J_{AB} = 15.0 Hz, 1H), 4.18-4.09 (overlapped of quartet with AB_q, 3H), 3.77-3.74 (m, 1H), 2.99 (ddd, J = 11.5, 9.5, 4.5 Hz, 1H), 2.10-2.05 (m, 1H), 2.01-1.97 (m, 1H), 1.95-1.88 (m, 2H), 1.36 (qd, J = 11.7, 4.5 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.4, 150.3, 136.6, 133.4, 128.9, 128.8, 128.2, 127.9, 121.9, 105.9, 60.0, 58.9, 51.9, 39.4, 24.5, 23.6, 14.8; **IR** (cm^{-1}) 2925, 1669, 1578, 1139; **HRMS** (EI) calc'd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1558.

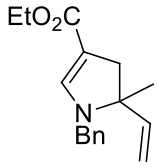
Ethyl 1-benzyl-5-methyl-5-(prop-1-en-2-yl)-4,5-dihydro-1H-pyrrole-3-carboxylate 2-21d



Reagents employed: dihydrofuran (**2-14c**) (0.048g, 0.24 mmol), benzylamine (0.13ml, 1.2 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.017g, 0.014 mmol), *p*-Toluenesulfonic acid monohydrate (0.011g, 0.06 mmol) toluene (2ml): yield 70% (0.047g, 0.16 mmol) as a yellow oil; Rf = 0.47, 20% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36-7.33 (m, 3H), 7.30-7.28 (m, 1H), 7.25-7.24 (m, 2H), 7.00 (br s, 1H),

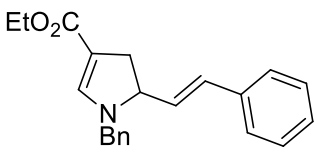
4.98 (d, J = 8.4 Hz, 2H), 4.12-4.08 (overlapped of quartet with AB_q, 3H) 3.99 (AB_q, J_{AB} = 14.6 Hz, 1H), 2.94, 2.63 (AB_q, J_{AB} = 15.0 Hz, 2H; with each signal split into a doublet due to $^4J_{CH}$ = 1.3 Hz coupling with the methine proton), 1.79 (s, 3H), 1.40 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 148.8, 146.8, 137.8, 128.9, 128.4, 127.8, 112.8, 98.4, 71.6, 58.9, 48.5, 41.6, 23.6, 19.0, 14.8; **IR** (cm^{-1}) 2977, 1633, 1591, 1145; **HRMS** (EI) calc'd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1716.

Ethyl 1-benzyl-5-methyl-5-vinyl-4,5-dihydro-1H-pyrrole-3-carboxylate 2-21e



Reagents employed: dihydrofuran (**2-14d**) (0.051g, 0.28 mmol), benzylamine (0.15ml, 1.4 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.019g, 0.017 mmol), *p*-Toluenesulfonic acid monohydrate (0.013g, 0.07 mmol), toluene (2.3ml): yield 75% (0.057g, 0.21 mmol) as a red oil; Rf = 0.39, 20% EtOAc/hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.30-7.27 (m, 1H), 7.25-7.24 (m, 2H), 6.97 (br s, 1H), 5.98 (dd, J = 17.4, 10.7 Hz, 1H), 5.20 (d, J = 14.7 Hz, 1H), 5.17 (d, J = 7.9 Hz, 1H), 4.14-4.08 (overlapped of quartet with AB_q, 3H), 4.05 (AB_q, J_{AB} = 14.8 Hz, 1H), 2.85, 2.72 (AB_q, J_{AB} = 14.7 Hz, 2H), 1.36 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.7, 148.8, 141.5, 138.2, 128.8, 128.2, 127.7, 114.5, 98.7, 69.4, 58.9, 48.5, 43.0, 22.1, 14.8; **IR** (cm^{-1}) 2975, 1671, 1590, 1146, 1075; **HRMS** (EI) calc'd for $C_{17}H_{21}NO_2$ 271.1572, found 271.1571.

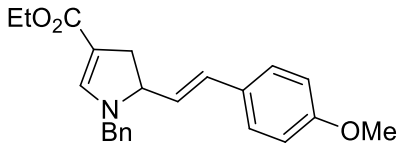
(E)-ethyl 1-benzyl-5-styryl-4,5-dihydro-1H-pyrrole-3-carboxylate 2-21f



Reagents employed: dihydrofuran (**2-18a**) (0.095g, 0.39 mmol), benzylamine (0.21ml, 1.9 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.027g, 0.023 mmol), *p*-

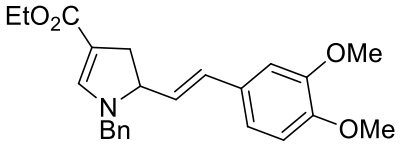
Toluenesulfonic acid monohydrate (0.018g, 0.097 mmol), toluene (3.2ml): yield 70% (0.091g, 0.27 mmol) as an orange oil; Rf = 0.42, 20% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 7H), 7.25-7.21 (m, 2H), 7.17 (brs, 1H), 6.43 (d, J = 15.8 Hz, 1H), 6.18 (dd, J = 15.8, 8.7 Hz, 1H), 4.31 (AB_q, J_{AB} = 14.9 Hz, 1H), 4.24 (dt, J = 10.8, 9.1 Hz, 1H), 4.17-4.08 (overlapped of quartet with AB_q, 3H), 3.07 (ddd, J = 14.9, 11.1, 1.1 Hz, 1H), 2.68 (ddd, J = 14.9, 9.2, 1.3 Hz, 1H), 1.26 (t, J = 7.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.4, 150.3, 136.8, 136.4, 133.3, 128.9, 128.8, 128.5, 128.3, 128.1, 127.8, 126.6, 100.6, 66.1, 59.1, 51.8, 35.4, 14.8; **IR** (cm^{-1}) 2977, 1669, 1589, 1167, 1070; **HRMS** (EI) calc'd for $C_{22}H_{23}NO_2$ 333.1729, found 333.1730.

(E)-ethyl 1-benzyl-5-(4-methoxystyryl)-4,5-dihydro-1H-pyrrole-3-carboxylate 2-21g



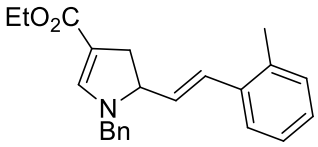
Reagents employed: dihydrofuran (**2-18b**) (0.043g, 0.16 mmol), benzylamine (0.08ml, 0.8 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.012g, 0.01 mmol), *p*-Toluenesulfonic acid monohydrate (6mg, 0.03 mmol), toluene (1.3ml): yield 72% (0.042g, 0.11 mmol) as a yellow oil; Rf = 0.38, 30% EtOAc/hexanes; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.36-7.33 (m, 2H), 7.31-7.28 (m, 3H), 7.23-7.21 (m, 2H), 7.17 (br s, 1H), 6.88-6.85 (AA'BB', 2H), 6.37 (d, J = 15.7 Hz, 1H), 6.03 (dd, J = 15.7, 8.8 Hz, 1H), 4.29, 4.10 (AB_q, J_{AB} = 14.9 Hz, 2H), 4.21 (dt, J = 11.0, 9.0 Hz, 1H), 4.14 (qd, J = 7.1, 2.3 Hz, 2H), 3.82 (s, 3H), 3.05 (ddd, J = 15.0, 11.1, 1.1 Hz, 1H), 2.66 (ddd, J = 14.9, 9.3, 1.3 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5, 159.6, 150.3, 136.9, 132.8, 129.1, 128.8, 128.3, 127.9, 127.8, 126.3, 114.2, 100.5, 66.3, 59.0, 55.4, 51.7, 35.5, 14.8; **IR** (thin film, cm^{-1}) 2930, 1674, 1592, 1511, 1248, 1178, 1075, 700; **HRMS** (EI) calc'd for $C_{23}H_{23}NO_3$ 363.1834, found 363.1824.

(E)-ethyl 1-benzyl-5-(3,4-dimethoxystyryl)-4,5-dihydro-1H-pyrrole-3-carboxylate 2-18h



Reagents employed: dihydrofuran (**2-18c**) (0.05g, 0.16 mmol), benzylamine (0.09ml, 0.8 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.011g, 0.0096 mmol), *p*-Toluenesulfonic acid monohydrate (8mg, 0.04 mmol), toluene (1.3ml): yield 85% (0.054g, 0.14 mmol) as a light yellow oil; Rf = 0.24, 30% EtOAc/hexanes; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.36-7.33 (m, 2H), 7.31-7.28 (m, 1H), 7.24-7.22 (m, 2H), 7.18 (brs, 1H), 6.91-6.88 (m, 2H), 6.82 (d, J = 8.2 Hz, 1H), 6.36 (d, J = 15.7 Hz, 1H), 6.03 (dd, J = 15.7, 8.8 Hz, 1H), 4.30 (AB_q, J_{AB} = 15.0 Hz, 1H), 4.23 (dt, J = 11.3, 9.0 Hz, 1H), 4.16-4.10 (overlapped of quartet with AB_q, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.06 (ddd, J = 15.0, 11.1, 1.1 Hz, 1H), 2.68 (ddd, J = 15.0, 9.1, 1.3 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.5, 150.4, 149.3, 149.2, 136.9, 132.9, 129.5, 128.9, 128.3, 127.8, 126.5, 120.0, 111.2, 108.8, 100.5, 66.3, 59.1, 56.1, 56.0, 51.8, 35.5, 14.8; **IR** (cm^{-1}) 2933, 1669, 1588, 1512, 1263, 1137, 1071; **HRMS** (EI) calc'd for C24H27NO4 393.1940, found 393.1921.

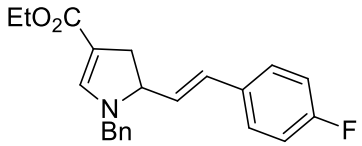
(E)-ethyl 1-benzyl-5-(2-methylstyryl)-4,5-dihydro-1H-pyrrole-3-carboxylate 2-21i



Reagents employed: dihydrofuran (**2-18e**) (0.05g, 0.19 mmol), benzylamine (0.1ml, 0.95 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.013g, 0.011 mmol), *p*-Toluenesulfonic acid monohydrate (9mg, 0.047 mmol), toluene (1.6ml): yield 66% (0.043g, 0.12 mmol) as a dark yellow oil; Rf = 0.4, 20% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.29 (m, 4H), 7.26-7.15 (m, 6H), 6.65 (d, J = 15.6 Hz, 1H), 6.07 (dd, J = 15.6, 8.8 Hz, 1H), 4.33 (AB_q, J_{AB} = 14.9 Hz, 1H), 4.27 (dt, J = 11.0, 9.3 Hz, 1H), 4.19-4.12 (overlapped of quartet with AB_q, 3H), 3.09 (dd, J = 14.8, 11.2 Hz, 1H), 2.70 (ddd, J = 14.9, 9.3, 1.3 Hz, 1H), 2.33 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 150.4, 136.8, 135.6, 135.5, 131.2, 130.4, 129.8, 128.8, 128.3,

127.9, 127.8, 126.3, 125.9, 100.5, 66.3, 59.1, 51.8, 35.5, 19.9, 14.8; **IR** (cm^{-1}) 2977, 1670, 1590, 1168, 1072; **HRMS** (EI) calc'd for $C_{23}H_{25}NO_2$ 347.1885, found 347.1883.

(E)-ethyl 1-benzyl-5-(4-fluorostyryl)-4,5-dihydro-1H-pyrrole-3-carboxylate 2-21j



Reagents employed: dihydrofuran (**2-18f**) (0.08g, 0.3 mmol), benzylamine (0.16ml, 1.5 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.021g, 0.018 mmol), *p*-Toluenesulfonic acid monohydrate (0.014g, 0.075 mmol), toluene (2.5ml): yield 68% (0.072g, 0.2 mmol) as an orange oil; Rf = 0.34, 20% EtOAc/hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H, 7.23-7.21 (m, 2H), 7.17 (t, J = 1.2 Hz, 1H), 7.04-6.99 (m, 2H), 6.39 (d, J = 15.8 Hz, 1H), 6.08 (dd, J = 15.8, 8.7 Hz, 1H), 4.30 (AB_q, J_{AB} = 14.9 Hz, 1H), 4.22 (dt, J = 10.8, 9.0 Hz, 1H), 4.17-4.08 (overlapped of quartet with AB_q, 3H), 3.06 (ddd, J = 15.0, 11.1, 1.1 Hz, 1H), 2.66 (ddd, J = 15.0, 9.3, 1.3 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** 166.4, 162.6 (d, $^{1}J_{CF}$ = 247.4 Hz), 150.3, 136.8, 132.5 (d, $^{4}J_{CF}$ = 3.4 Hz), 132.0, 128.8, 128.33, 128.31, 128.26, 128.23, 128.1, 127.8, 115.7 (d, $^{2}J_{CF}$ = 21.6 Hz), 100.6, 66.1, 59.1, 51.9, 35.4, 14.8 ; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -113.73; **IR** (cm^{-1}) 2923, 1671, 1590, 1507, 1226, 1168, 1071; **HRMS** (EI) calc'd for C22H22FNO2 351.1635, found 351.1629.

Chapter 3

3 Synthesis of (±)-β-Allokainic Acid

This chapter was adapted from the following manuscript:

Piotrowski, M. L.; Kerr, M. A. *Eur. J. Org. Chem.* **2019**, 3122-3126.

3.1 Introduction

The kainoid amino acids are a family of compounds that have gained considerable attention due to their biological properties such as neuroexcitatory and excitotoxic activities.[108–111] α-kainic acid (**3-1a**) and its related structures (Figure **3-1**) have been found to behave as agonists for the glutamate receptors mediating the effects of L-glutamic acid and thus have been extensively used for the elucidation of the neurophysiological role of glutamic acid.[109,113]

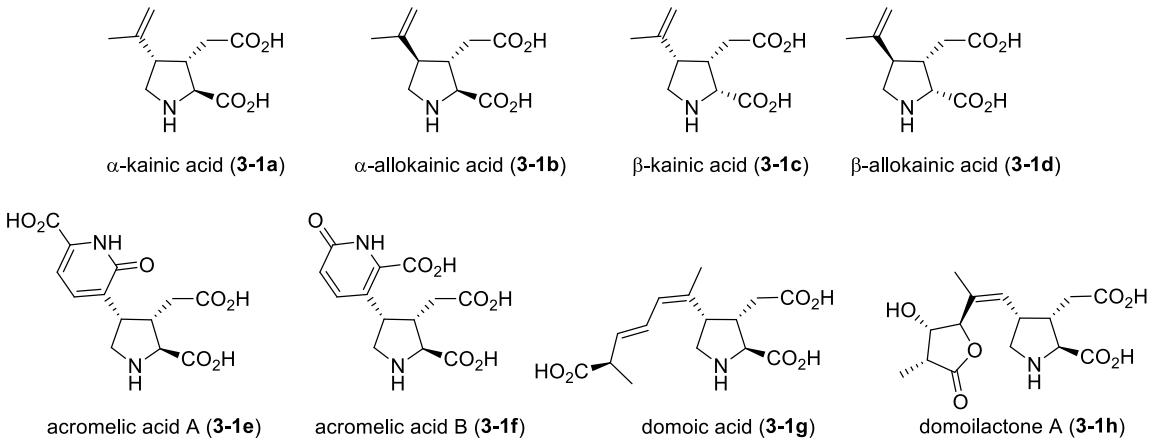
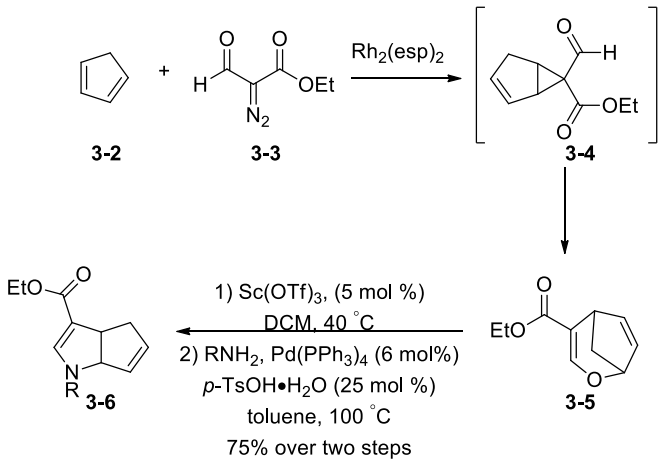


Figure 3-1. Kainoid family of compounds. Natural and unnatural

It has been shown that when in direct contact with neurons, α-kainic acid can induce motor hyperactivity and seizures and can destroy neurons in specific regions that contain high concentrations of the molecule.[108,109] This discovery helped to create model conditions for human diseases such as epilepsy, Huntington's chorea and stroke.[109,111] Through the continuous study of the biological properties of the family of kainoid compounds, a better understanding of the structure activity relationship was obtained. It

was found that the stereochemistry around the pyrrolidine ring plays an important part in the biological activity of the molecule; the 2,3-*trans*-3,4-*cis* compounds showed potent activity whereas in 3-epi (2,3-*cis*) or 4-epi (3,4-*trans*) showed a dramatic reduction in activity.[113]

We have recently shown the formation of substituted 2,5-dihydrooxepine rings (**3-5**) through a vinylogous Cloke-Wilson rearrangement (Scheme **3-1**) of donor-acceptor cyclopropanes such as (**3-4**) and subsequent transformations that offer ready formation of dihydropyrroles such as (**3-6**).[133] This compound was deemed a viable synthetic precursor to target the kainoid family of compounds. Our efforts towards the synthesis of members of the kainoids, resulting in the successful synthesis of (±)-β-allokainic acid, are described herein.

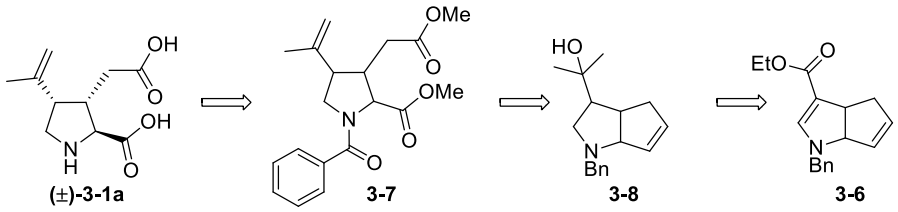


Scheme 3-1. Formation of 2,5-dihydrooxepines through a vinylogous Cloke-Wilson rearrangement of donor-acceptor cyclopropanes and subsequent steps towards dihydropyrrole

3.2 Results and Discussion

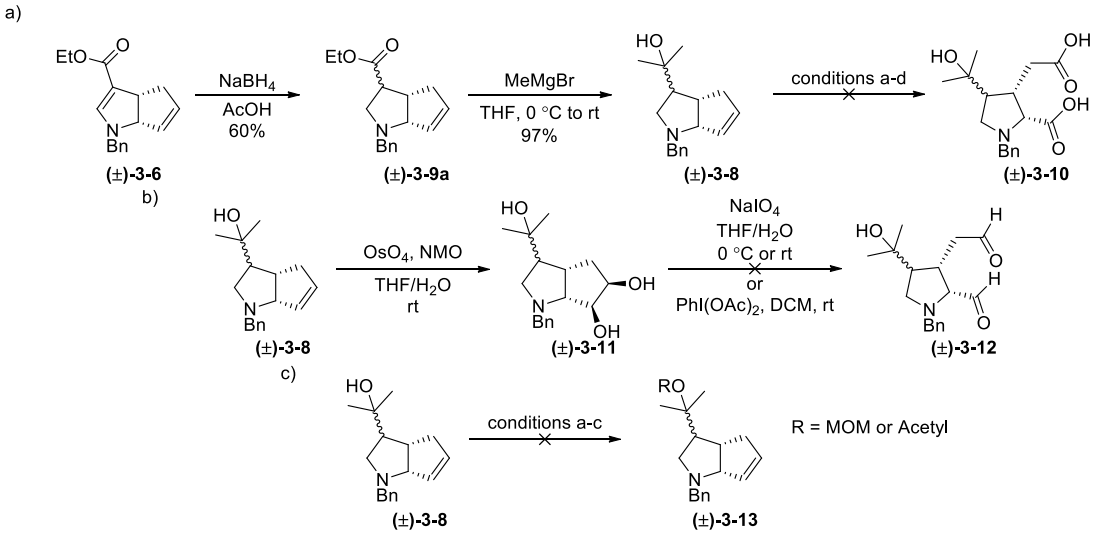
Our original target compound was (±)-α-kainic acid (**3-1a**)[134–139] which was envisioned to be obtained by basic hydrolysis of intermediate (**3-7**) which could be obtained from (**3-8**) through oxidatively cleaving the olefin to the di-acid followed by esterification (Scheme **3-2**). The benzyl group in this oxidation step will most likely oxidize to a benzoyl group. The isopropenyl moiety can be formed via dehydration of the tertiary alcohol. Compound (**3-8**) would be obtained from (**3-6**) through a vinylogous carbamate double bond

reduction and Grignard addition with methylmagnesium bromide to form the tertiary alcohol. And finally, compound (**3-6**) can be obtained as shown in our previous work (Scheme **3-1**).



Scheme 3-2. Retrosynthetic analysis towards kainic acid

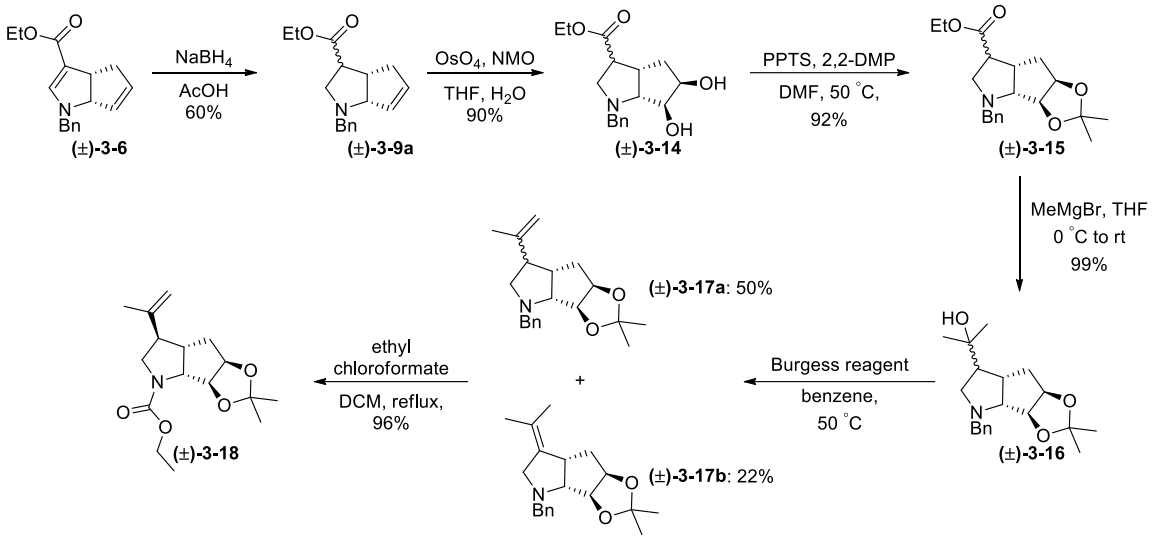
The vinylogous carbamate double bond in (**3-6**) was reduced with sodium borohydride in acetic acid[140] providing the major diastereomer (**3-9a**) in a 60% yield and minor diastereomer (**3-9b**) in a 4% yield. At this time, it was still unclear as to which diastereomer was obtained. Treatment of (**3-9a**) with methylmagnesium bromide furnished the tertiary alcohol (**3-8**). Subjecting this compound to a variety of oxidative reactions resulted in extensive decomposition (Scheme **3-3a**). Taking compound (**3-8**) and subjecting it towards Upjohn dihydroxylation conditions did furnish the desired diol (**3-11**); however, attempts at cleaving the diol to the di-aldehyde (**3-12**) resulted in decomposition (Scheme **3-3b**). Attempts at protecting the tertiary alcohol (**3-8**) prior to the oxidation step was also unsuccessful (Scheme **3-3c**).



Scheme 3-3. (a) Synthetic efforts towards the di-acid moiety. Conditions: (a) Oxone, OsO_4, DMF; (b) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O; (c) RuO_2, $NaIO_4$, EtOAc, H_2O; (d) 1) O_3 2) HCO_2H, H_2O_2; (3b) Attempted Johnson-Lemieux oxidation; (3c). Attempts at tertiary alcohol protection. Conditions: (a) MOMCl, NaI, DIPEA, DME; (b) Ac_2O, DMAP, DCM; (c) Ac_2O, NaOAc, 140 °C, MW.

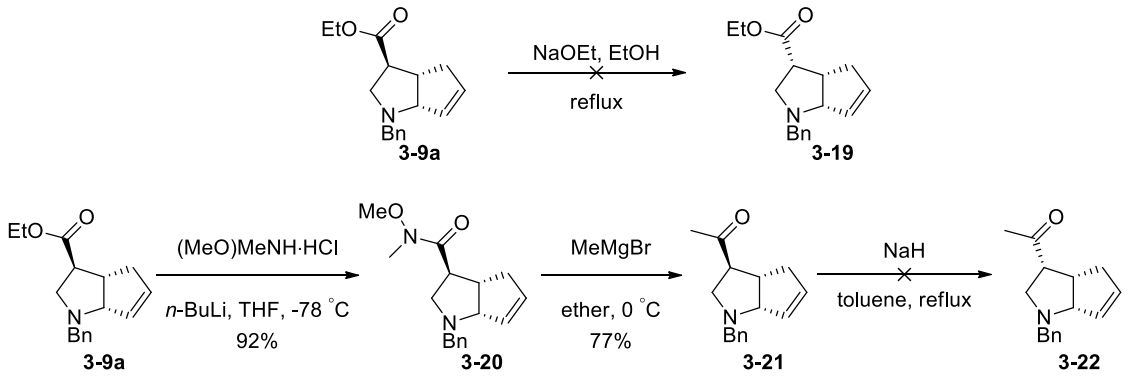
Due to the electron donating ability of the benzyl group, it is believed that under oxidative conditions, not only can the benzyl group oxidize to a benzoyl, but the C-5 position on the pyrrolidine ring could also potentially oxidize forming a lactam, which could cause a mixture of products.[141] Therefore, the removal of the benzyl group prior to the oxidative cleavage step would be ideal.

Treatment of (**3-9a**) under Upjohn dihydroxylation conditions produced diol (**3-14**) followed by acetonide protection using 2,2-dimethoxylpropane (2,2-DMP) and PPTS producing acetonide (**3-15**). Transformation of the ester into the isopropenyl moiety began by treating (**3-15**) with excess methylmagnesium bromide forming tertiary alcohol (**3-16**). The use of Burgess reagent, known to be a very strong dehydrating agent for tertiary alcohols[142], provided the isopropenyl compound (**3-17a**) as the major isomer in a 50 % yield along with minor isopropylidene isomer (**3-17b**) in a 22% yield. After chromatographic separation of the two isomers, (**3-17a**) was treated with ethyl chloroformate forming carbamate (**3-18**)[143] (Scheme **3-4**).



Scheme 3-4. Synthetic route to carbamate 3-18 and ultimate stereochemical confirmation

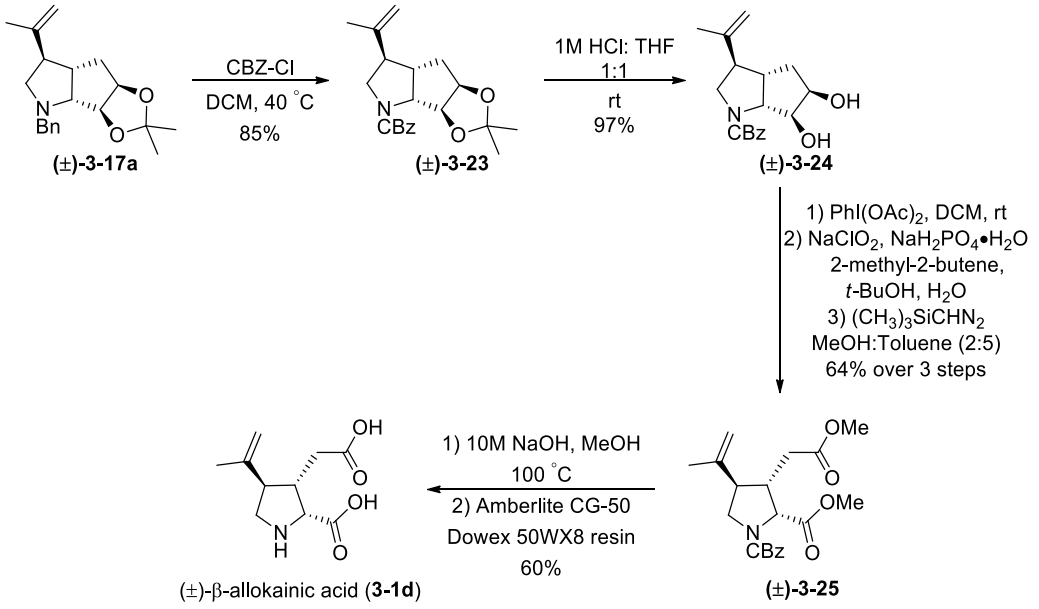
The stereochemistry of compound (**3-18**) was confirmed by comparing it with data published by the Coldham group during their work towards kainic acid[143]. The assigned stereochemistry was a disappointing revelation since the configuration of the isopropenyl moiety would need to be epimeric to access kainic acid. Epimerization of the ester moiety in (**3-9a**) or similar compounds was unsuccessful (Scheme **3-5**). With this information in hand we diverted our task to the synthesis of β-allokainic acid (**3-1d**).[144]



Scheme 3-5. Attempted epimerization's

Starting from compound (**3-17a**), the benzyl group was replaced with a benzyloxycarbonyl group, forming carbamate (**3-23**) (Scheme **3-6**). Acetonide removal yielded diol (**3-24**) which set the stage for oxidative cleavage. Many conditions involving

sodium periodate were explored with all leading to decomposition. A switch in oxidant to $PhI(OAc)_2$ in DCM provided the crude di-aldehyde[145] which was subjected to a double Pinnick oxidation[146] followed by derivatization as the methyl esters for ease of purification. Thus, (**3-25**) was produced as a 1:1 mixture of rotamers (presumably as a result of the CBz group) in an overall yield of 64% over the three steps. Finally, basic hydrolysis provided (±)-β-allokainic acid (**3-1d**) in 60% yield.[118,147]



Scheme 3-6. Final synthetic steps towards (±)-β-allokainic acid

3.3 Conclusion

In summary, a synthesis of (±)-β-allokainic acid has been achieved in a linear sequence of 12 steps with an overall yield of 3.5%. The synthesis of the pyrrolidine core (**3-6**) can be achieved in three chemical operations employing our previously reported vinylogous Cloke-Wilson rearrangement. Further manipulation to the final product is achieved through simple chemical transformations with minimal purification steps required.

3.4 References

(133) Piotrowski, M. L.; Kerr, M. A. *Org. Lett.* **2018**, *20* (23), 7624–7627.

(134) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 3635–3638.

(135) Reddy, N. K.; Chandrasekhar, S. *J. Org. Chem.* **2013**, *78*, 3355–3360.

(136) Oe, K.; Ohfune, Y.; Shinada, T. *Org. Lett.* **2014**, *16*, 2550–2553.

(137) Shi, H.; Li, J.; Liu, Y.; Du, Z.; Huang, Z.; Zhao, N.; Li, N.; Yang, J. *Tetrahedron* **2016**, *72* (35), 5502–5506.

(138) Suzuki, J.; Miyano, N.; Yashiro, S.; Umezawa, T.; Matsuda, F. *Org. Biomol. Chem.* **2017**, *15*, 6557–6566.

(139) Lei, H.; Xin, S.; Qiu, Y.; Zhang, X. *Chem. Commun.* **2018**, *54*, 727–730.

(140) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317–384.

(141) Murahashi, S.; Komiya, N. Oxidation Reactions. In *Ruthenium in Organic Synthesis*; Murahashi, S., Ed.; Wiley-VCH: Weinheim, 2004; pp 53–93.

(142) Burgess, E. M.; Penton, H. R. J.; Taylor, E. A. *J. Org. Chem.* **1973**, *38* (1), 26–31.

(143) Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem.* **2003**, *1*, 2111–2119.

(144) Liang, Y.; Chung, C.; Liao, D.; Lee, W.; Tu, Y.; Uang, B. *J. Org. Chem.* **2018**, *83*, 10564–10572.

(145) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12* (7), 1552–1555.

(146) Maison, W. *Eur. J. Org. Chem.* **2007**, 2276–2284.

(147) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467–6471.

3.5 Experimental

3.5.1 General Considerations

All reactions were conducted under an atmosphere of argon unless otherwise indicated. DCM, toluene, DMF, THF, and benzene were dried and deoxygenated by passing the

nitrogen purged solvents through activated alumina columns. All other solvents and reagents were used as purchased from Sigma Aldrich, Alfa Aesar, Caledon, VWR or Oakwood Chemicals and used as received. Reaction progress was monitored by TLC (EM Science, silica gel 60 F254), visualized with UV light, and the plates developed with p-anisaldehyde, vanillin, basic potassium permanganate or DMP stains. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc).

NMR experiments were performed on Varian Mercury 400, Bruker AvIII 400, Inova 400 and Inova 600 MHz instruments with ^{13}C operating frequencies of 100, 100, 100, and 125 MHz respectively. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.1$ for ^{13}C; D_2O referenced at $\delta = 4.79$ for ^{1}H). Coupling constants (J) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization. Melting points were determined using a Digimelt MPA160 melting point apparatus from Stanford Research Systems (SRS). Infrared spectra were obtained using a Bruker Alpha II Platinum ATR spectrometer or as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}).

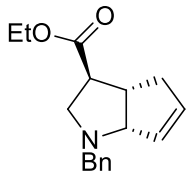
3.5.2 Procedures and characterization data

Procedure for vinylogous carbamate double bond reduction (**3-9a,b**):

A round bottom flask containing **3-6** (1.13g, 4.2 mmol) was dissolved in acetic acid (35ml) under an open atmosphere. $NaBH_4$ (0.79g, 21 mmol) was added slowly in small portions at room temperature and the reaction was stirred for one hour. The reaction was slowly quenched with water and extracted with DCM. The organic layers were washed twice with saturated $NaHCO_3$, once with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The major isomer **3-9a** was separated by flash chromatography (EtOAc/hexanes); yield: 60% (0.68g, 2.5 mmol) as an orange oil; $Rf_{major} = 0.32$, 20%

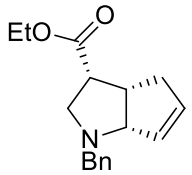
EtOAc in hexanes; yield minor **3-9b**: 4% (0.04g, 0.17 mmol) as an orange oil; Rf_{minor} = 0.18, 20% EtOAc in hexanes.

(±)-(3S,3aS,6aS)-ethyl 1-benzyl-1,2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole-3-carboxylate (3-9a)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H), 7.25-7.23 (m, 1H), 5.70-5.68 (m, 1H), 5.42 (dq, J = 6.1, 2.1 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.84 (br d, J = 8.8 Hz, 1H) 3.75 (ABq, J_{AB} = 12.8 Hz, 2H), 3.10-3.02 (m, 2H), 2.72-2.65 (m, 2H), 2.63-2.55 (m, 1H), 2.28 (dquin, J = 17.4, 2.4 Hz, 1H), 1.25 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.3, 139.2, 131.4, 131.2, 129.2, 128.3, 127.1, 74.8, 60.6, 59.5, 56.6, 51.0, 43.3, 38.6, 14.3; **IR** (cm^{-1}) 2799, 1729, 1159, 697; **HRMS** (EI) *m/z* calc'd for $C_{17}H_{21}NO_2$ 271.1572 (M^+): found 271.1564.

(±)-(3R,3aS,6aS)-ethyl 1-benzyl-1,2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole-3-carboxylate (3-9b)

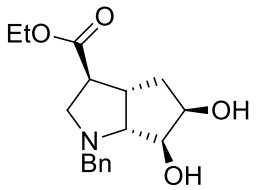


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 4H), 7.25-7.22 (m, 1H), 5.91-5.88 (m, 1H), 5.68 (dq, J = 5.8, 2.2 Hz, 1H), 4.30 (br s, 1H), 4.14 (ddquin, J = 10.8, 7.2, 3.6 Hz, 2H), 3.79, 3.65 (ABq, J_{AB} = 13.1 Hz, 2H), 3.24-3.15 (m, 2H), 2.89-2.85 (m, 1H), 2.69-2.61 (m, 1H), 2.50-2.43 (m, 1H), 2.14-2.07 (m, 1H), 1.26 (t, 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 173.0, 134.5, 129.2, 128.7, 128.4, 128.1, 127.0, 72.8, 60.3, 56.6, 51.5, 47.5, 41.3, 35.9, 14.4; **IR** (cm^{-1}) 2956, 1729, 1179, 697; **HRMS** (EI, source temp 250 °C) *m/z* calc'd for $C_{17}H_{21}NO_2$ 271.1572 (M^+): found 271.1569.

Procedure for dihydroxylation reaction **(3-14)**

A round bottom flask containing **3-9a** (1.36g, 5.0 mmol) was dissolved in 4:3 mixture of THF:H_2O (29:21ml) under an open atmosphere. A small crystal of OsO_4 was added and the reaction stirred for 10 minutes. NMO (0.7g, 6.0 mmol) was added and the reaction was stirred overnight. Sodium sulfite (12 equiv.) was added and the reaction was stirred for one hour. The reaction was diluted with brine and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure providing the corresponding diol **3-14** as a white solid without the need for further purification; yield = 90% (1.37g, 4.5 mmol); Rf = 0.15, 50% EtOAc in hexanes; melting point: 119.8-120.2 °C.

(±)-(3S,3aS,5R,6S,6aR)-ethyl 1-benzyl-5,6-dihydroxyoctahydrocyclopenta[b]pyrrole-3-carboxylate (3-14)



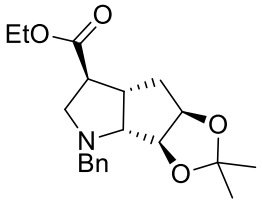
^{1}H **NMR** (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 4.36 (br s, 1H), 4.11 (qd, J = 7.1, 1.1 Hz, 2H), 3.87, 3.52 (ABq, J_{AB} = 13.0 Hz, 2H), 3.78 (br t, J = 3.3 Hz, 1H), 3.10 (dd, J = 8.9, 6.4 Hz, 1H), 3.06-3.01 (m, 2H), 2.66-2.58 (m, 1H), 2.43 (dd, J = 10.9, 8.9 Hz, 1H), 2.06-1.96 (m, 2H), 1.91 (br s, 1H), 2.03-1.98 (m, 2H), 1.83 (ddd, J = 13.5, 6.1, 2.4 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.7, 138.9, 128.9, 128.5, 127.4, 77.3, 77.2, 74.0, 60.7, 59.4, 57.7, 50.1, 42.9, 36.7, 14.3; **IR** (cm^{-1}) 3404, 3315, 2966, 1734, 1100; **HRMS** (EI) *m/z* calc'd for $C_{17}H_{23}NO_4$ 305.1627 (M^+), found 305.1628.

Procedure for acetonide protection (**3-15**)

Diol **3-14** (1.46g, 4.8 mmol) was placed in a round bottom flask under an argon gas atmosphere. DMF (40ml) was added followed by 2,2-dimethoxypropane (40ml). PPTS (1.20g, 4.8 mmol) was added and the reaction was warmed to 50 ˚C overnight. The

reaction was cooled to room temperature, diluted with water and extracted with ether. The organic extracts were washed with saturated $NaHCO_3$, water, brine, dried with Na_2SO_4 and concentrated. Column chromatography eluting with EtOAc/hexanes provided the final product as a yellow oil; yield 92% (1.51g, 4.4 mmol); Rf = 0.31, 20% EtOAc in hexanes.

(±)-(3aS,3bR,6S,6aS,7aR)-ethyl 4-benzyl-2,2-dimethyloctahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrole-6-carboxylate (3-15)



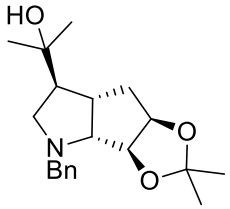
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H), 7.25-7.22 (m, 1H), 4.81 (t, J = 5.3 Hz, 1H), 4.46 (d, J = 5.3 Hz, 1H), 4.13-4.09 (q, J = 7.1 Hz, overlapped with AB_q, J = 13.3 Hz, 3H), 3.27 (ABq, J = 13.4 Hz, 1H), 3.20 (dd, J = 9.6, 7.9 Hz, 1H), 3.10-3.06 (m, 1H), 3.01 (d, J = 7.2 Hz, 1H), 2.68 (td, J = 8.2, 3.5 Hz, 1H), 2.42 (dd, J = 9.7, 8.5 Hz, 1H), 2.30 (dd, J = 13.9, 7.8 Hz, 1H), 1.81 (ddd, J = 14.4, 10.1, 4.8 Hz, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 138.9, 128.7, 128.4, 127.1, 110.0, 83.9, 83.0, 76.2, 60.8, 58.1, 57.4, 47.6, 45.3, 39.3, 26.9, 24.6, 14.3; **IR** (cm^{-1}) 2981, 1730, 1370, 1158, 1048, 700; **HRMS** (EI) *m/z* calc'd for $C_{20}H_{27}NO_4$ 345.1940 (M^+), found 345.1938.

Procedure for Grignard addition (**3-16**)

Starting material **3-15** (1.51g, 4.4 mmol) was placed in round bottom flask under an argon gas atmosphere. THF (37ml) was added and the reaction was cooled to 0 ˚C in an ice/water bath. MeMgBr (3.0M in diethyl ether, 7.2 ml, 21.8 mmol) was added dropwise over five minutes. The ice/water bath was removed, and the reaction was stirred at room temperature for 1.5 hours. The reaction was cooled back to 0 ˚C and slowly quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, and

concentrated to give **3-16** as a yellow oil without the need of any further purification; yield = 99% (1.43g, 4.3 mmol); Rf = 0.07, 30% EtOAc in hexanes.

(±)-2-((3aS,3bR,6S,6aS,7aR)-4-benzyl-2,2-dimethyloctahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrol-6-yl)propan-2-ol (3-16)

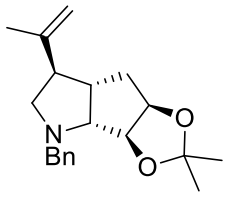


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.25 (m, 4H), 7.23-7.18 (m, 1H), 4.77 (t, J = 5.1 Hz, 1H), 4.42 (d, J = 5.1 Hz, 1H), 4.07, 3.14 (ABq, J = 13.3 Hz, 2H), 2.97 (dd, J = 9.4, 7.8 Hz, 1H), 2.80 (d, J = 7.4 Hz, 1H), 2.74-2.67 (m, 1H), 2.22 (dd, J = 14.1, 8.2 Hz, 1H), 2.07 (t, J = 9.4 Hz, 1H), 1.87-1.74 (m, 2H), 1.43 (s, 3H), 1.28 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.2, 128.7, 128.3, 126.9, 109.7, 84.1, 83.4, 77.2, 71.4, 58.4, 56.8, 54.9, 43.1, 40.8, 28.4, 27.9, 26.9, 24.6; **IR** (cm^{-1}) 3493, 2973, 2928, 1370, 1049; **HRMS** (EI) *m/z* calc'd for $C_{20}H_{29}NO_3$ 331.2147 (M^+), found 331.2145.

Procedure for dehydration reaction (**3-17a,b**)

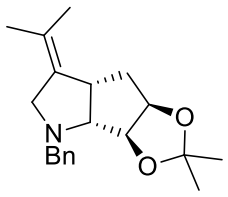
Tertiary alcohol **3-16** (0.73g, 2.2 mmol) was placed in round bottom flask under an argon gas atmosphere. Benzene was added (31ml) followed by Burgess reagent (1.04g, 4.4 mmol) and the reaction was stirred at 50 ˚C for two hours. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The product was purified by column chromatography eluting with EtOAc/hexanes providing (**3-17a,b**) as yellow oils; yield **3-17a =** 50% (0.34g, 1.1 mmol), yield **3-17b** = 22% (0.15g, 0.48 mmol); Rf **3-17a** = 0.53, Rf **3-17b** = 0.66, 30% EtOAc in hexanes.

(±)-(3aS,3bR,6R,6aS,7aR)-4-benzyl-2,2-dimethyl-6-(prop-1-en-2-yl)octahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrole (3-17a)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 4H), 7.25-7.22 (m, 1H), 4.81 (td, J = 5.1, 1.2 Hz, 1H), 4.68-4.66 (m, 2H), 4.45 (d, J = 5.1 Hz, 1H), 4.09, 3.24 (ABq, J = 13.3 Hz, 2H), 3.06 (dd, J = 9.4, 7.4 Hz, 1H), 2.95 (d, J = 7.8 Hz, 1H), 2.77-2.70 (m, 1H), 2.47-2.42 (m, 1H), 2.25 (ddd, J = 14.1, 8.2, 1.2 Hz, 1H), 2.13 (t, J = 9.3 Hz, 1H), 1.84 (ddd, J = 14.1, 9.4, 5.1 Hz, 1H), 1.69 (br s, 3H), 1.46 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.5, 139.2, 128.8, 128.3, 127.0, 109.9, 109.6, 84.6, 83.3, 76.6, 59.6, 58.5, 51.0, 46.3, 39.9, 27.1, 24.8, 21.3; **IR** (cm^{-1}) 3027, 2984, 1645, 1370, 1056; **HRMS** (EI) *m/z* calc'd for $C_{20}H_{27}NO_2$ 313.2042 (M^+), found 313. 2036.

(±)-(3aS,3bR,6aS,7aR)-4-benzyl-2,2-dimethyl-6-(propan-2-ylidene)octahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrole (3-17b)

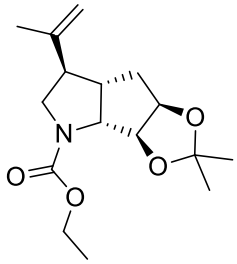


^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.29 (m, 4H), 7.25-7.22 (m, 1H), 4.84 (t, J = 5.0 Hz, 1H), 4.50 (d, J = 5.4 Hz, 1H), 4.14, 3.25 (ABq, J = 13.6 Hz, 2H), 3.54, 2.79 (ABq, J = 13.4 Hz, 2H), 3.35-3.29 (m, 1H), 3.01 (d, J = 6.2 Hz, 1H), 2.55 (dd, J = 14.0, 7.7 Hz, 1H), 1.78 (ddd, J = 14.2, 10.9, 4.7 Hz, 1H), 1.64 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.4, 133.6, 128.5, 128.3, 126.9, 122.0, 109.6, 83.9, 83.4, 76.9, 58.4, 58.0, 44.9, 37.9, 26.8, 24.4, 21.0, 20.8; **IR** (cm^{-1}) 2979, 2931, 1741, 1370, 1047; **HRMS** (EI) *m/z* calc'd for $C_{20}H_{27}NO_2$ 313.2042 (M^+), found 313.2041.

Procedure for the conversion of a benzyl group to a carbamate (**3-18** and **3-23**)

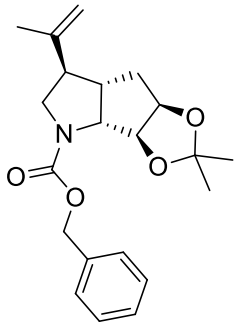
To a round bottom flask containing acetonide **3-17a** (1 equiv.) under argon gas was added DCM (0.1M). The corresponding chloroformate (6 equiv.) was added and reaction was heated to 40 ˚C for 19 hours with ethyl chloroformate and 24 hours with benzyl chloroformate. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The product was purified by flash chromatography eluting with EtOAc/hexanes.

(±)-(3aS,3bR,6R,6aS,7aR)-ethyl 2,2-dimethyl-6-(prop-1-en-2-yl)hexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrole-4(3aH)-carboxylate (3-18)



Reagents employed: Acetonide **3-17a** (0.093g, 0.3 mmol), ethyl chloroformate (0.17ml, 1.8 mmol), DCM (3ml): yield 92% (0.081g, 0.27 mmol) as an oil; Rf = 0.32, 30% EtOAc in hexanes; Full characterization can be found in the following published article[143].

(±)-(3aS,3bR,6R,6aS,7aR)-benzyl 2,2-dimethyl-6-(prop-1-en-2-yl)hexahydro-[1,3]dioxolo[4',5':4,5]cyclopenta[1,2-b]pyrrole-4(3aH)-carboxylate (3-23)



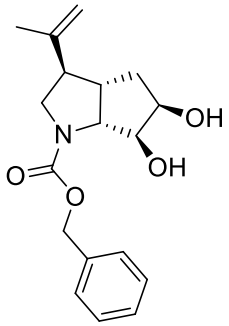
Reagents employed: Acetonide **3-17a** (0.4964g, 1.6 mmol), benzyl chloroformate (1.4 ml, 9.6 mmol), DCM (16ml): yield 89% (0.5108g, 1.4 mmol) as a white solid; Rf = 0.27, 20% EtOAc in hexanes; melting point: 86.5-87.1 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ

7.44-7.29 (m, 5H), 5.30 (br d, J = 12.8 Hz, 1H), 5.15 (br s, 1H), 4.76 (br s, 1H), 4.69-4.58 (m, 3H), 4.07 (d, J = 7.0 Hz, 1H), 3.64 (br d, J = 11.7 Hz, 1H), 3.57-3.52 (m, 1H), 2.93-2.88 (m, 1H), 2.42 (br s, 1H), 2.16 (dt, J = 14.3, 7.5 Hz, 1H), 1.72 (br s, 3H), 1.68-1.60 (m, 1H), 1.47 (br s, 3H), 1.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) mixture of rotamers; δ 155.0, 154.9, 145.8, 145.5, 137.1, 136.9, 128.6, 128.5, 128.2, 128.1, 127.8, 127.6, 110.6, 110.5, 110.4, 86.4, 85.4, 81.2, 69.1, 68.4, 67.0, 66.9, 50.4, 50.0, 48.1, 47.4, 46.8, 46.0, 36.6, 36.5, 26.9, 24.5, 21.5; **IR** (cm^{-1}) 2937, 1696, 1648, 1411, 1357, 1205, 1059; **HRMS** (EI) *m/z* calc'd for $C_{21}H_{27}NO_4$ 357.1940, found 357.1935.

Procedure for acetonide deprotection (**3-24**)

Acetonide **3-23** (0.49g, 1.4 mmol) was dissolved in THF (7 ml) under an open atmosphere. Aqueous 1M HCl (7 ml) was added and the reaction was stirred at room temperature for 24 hours. The reaction was diluted with water and extracted with ethyl acetate, washed with saturated $NaHCO_3$, brine and dried with Na_2SO_4. The solvent was removed under reduced pressure providing diol **3-24** as a white solid without the need for further purification; Yield = 97% (0.43g, 0.63 mmol); Rf = 0.19, 30% EtOAc in hexanes; melting point: 85.0-85.4 °C.

(±)-(3R,3aS,5R,6S,6aR)-benzyl 5,6-dihydroxy-3-(prop-1-en-2-yl)hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (3-24)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5H), 5.15 (ABq, J_{AB} = 12.3 Hz, 2H, $\Delta\delta_{AB}$ = 0.01), 4.92 (s, 1H), 4.79 (br s, 1H), 4.74 (br s, 1H), 4.27 (t, J = 3.9 Hz, 1H), 4.22 (dd, J = 10.2, 7.2 Hz, 1H), 3.97 (dd, J = 7.2, 3.7 Hz, 1H), 3.81 (dd, J = 10.8, 7.3 Hz, 1H), 3.30 (t, J = 10.7 Hz, 1H), 2.92-2.87 (m, 1H), 2.85 (br s, 1H), 2.49 (td, J = 10.1, 7.3 Hz, 1H), 2.15

(dd, J = 14.6, 9.1 Hz, 1H), 1.70 (s, 3H), 1.62 (dt, J = 14.7, 5.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.8, 142.9, 136.3, 128.7, 128.3, 128.1, 111.8, 80.6, 75.9, 69.0, 67.5, 53.4, 52.9, 43.4, 36.0, 20.7; **IR** (cm^{-1}) 3433, 3344, 2932, 2891, 1678, 1424, 1355, 1149; **HRMS** (EI) *m/z* calc'd for $C_{18}H_{23}NO_4$ 317.1627 (M^+), found 317.1619.

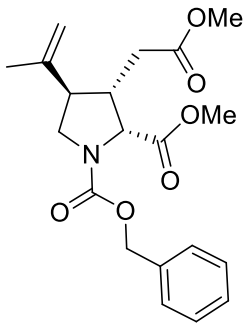
Procedure for the synthesis of protected β-allokainic acid dimethylester (**3-25**)

Diol **3-24** (0.42g, 1.3 mmol) placed in a round bottom flask was dissolved in reagent grade DCM (13 ml) under an open atmosphere. Iodobenzene diacetate (0.50g, 1.6 mmol) was added in a single portion and stirred at room temperature for two hours. Solvent was removed under reduced pressure and the crude material was taken to the next step.

Assuming full conversion, the crude di-aldehyde (0.41g, 1.3 mmol) was dissolved in tert-butanol (93 ml) under an open atmosphere. 2-methyl-2-butene (0.55 ml, 5.2 mmol) was added followed by an aqueous mixture of sodium chlorite (0.30g, 3.4 mmol) and sodium phosphate monobasic monohydrate (0.43g, 3.1 mmol) in 14 ml of water using a glass pipette. The reaction was stirred at room temperature for 18 hours. Solvent was removed under reduced pressure and the residue was dissolved in 20 ml of 0.1M NaOH and extracted with DCM. The aqueous layer was acidified to pH 1 with concentrated HCl and extracted with ethyl acetate collecting in a different flask. The combined ethyl acetate layers were washed with brine and dried with Na_2SO_4. The solvent was removed providing the crude di-acid as a foamy white solid. The crude material was taken to the next step.

The crude di-acid (0.36g, 1.0 mmol) was dissolved in a 2:5 mixture of methanol: toluene (6.2: 15.6 ml) under an atmosphere of argon. Trimethylsilyl diazomethane (2.0M in diethyl ether, 1.6 ml, 3.1 mmol) was added dropwise at room temperature. The reaction was stirred for 30 minutes and few drops of acetic acid was added until the bright yellow colour disappeared. Solvent was removed under reduced pressure. Residue was dissolved in methanol and washed with a small amount of HPLC grade hexanes. Methanol was removed under reduced pressure providing the product **3-25** (1:1 mixture of rotamers) as a pale-yellow oil. Yield 63% over three steps (0.29g, 0.78 mmol); Rf = 0.42, 30% EtOAc in hexanes.

(±)-(2R,3S,4R)-1-benzyl 2-methyl 3-(2-methoxy-2-oxoethyl)-4-(prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate (3-25)

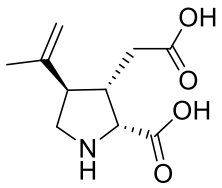


^{1}H NMR (600 MHz, $CDCl_3$) 1:1 mixture of rotamers; δ 7.37-7.27 (m, 10H), 5.19-5.02 (overlapped ABq, J_{AB} = 12.4 Hz, 4H), 4.19 (dt, J = 7.9, 1.3 Hz, 2H), 4.85 (br d, J = 3.9 Hz, 2H), 4.65 (d, J = 8.1 Hz, 1H), 4.61 (d, J = 8.3 Hz, 1H), 3.86-3.78 (m, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.58 (s, 3H), 3.36-3.26 (m, 2H), 2.92-2.82 (m, 2H), 2.79-2.67 (m, 2H), 2.47 (t, J = 3.5 Hz, 1H), 2.43 (t, J = 3.5 Hz, 1H), 2.08-1.98 (m, 2H), 1.70 (s, 3H), 1.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.88, 171.72, 171.66, 171.58, 154.60, 153.99, 140.82, 140.76, 136.44, 136.40, 128.45, 128.37, 128.03, 127.93, 127.77, 114.94, 114.90, 67.17, 67.05, 61.76, 61.49, 51.91, 51.86, 51.78, 51.77, 49.87, 49.54, 49.20, 48.26, 40.73, 39.95, 33.34, 33.26, 18.51; **IR** (cm^{-1}) 2952, 1738, 1702, 1412; **HRMS** (EI) *m/z* calc'd for $C_{20}H_{25}NO_6$ 375.1682 (M^+), found 375.1682.

Procedure for the synthesis of β-allokainic acid (**3-1d**)

Compound **3-25** (0.025g, 0.066 mmol) was dissolved in methanol (0.35ml) and 10M NaOH (0.6ml) and was heated to 100 °C for 14 hours. The reaction mixture was cooled to room temperature and washed with DCM. The aqueous layer was collected and Amberlite CG-50 (H^+ form) was periodically added with stirring until the aqueous layer was neutralized. The mixture was filtered and concentrated. The resulting compound was then purified using Dowex 50WX8 resin (100-200 mesh, H^+ form) eluting with 5% aqueous ammonia providing the final compound **3-1d** in a 60% yield (8mg, 0.04 mmol) as an off-white solid with characterization matching the following references[113,144].

(±)-β-allokainic acid (3-1d)



^{1}H NMR (600 MHz, D_2O) δ 5.13 (s, 1H), 5.06 (s, 1H), 4.72 (d, J = 8.8 Hz, 1H), 3.78 (dd, J = 11.9, 8.2 Hz, 1H), 3.39 (dd, J = 11.9, 10.5 Hz, 1H), 3.04 (dtd, J = 11.4, 9.2, 4.9 Hz, 1H), 2.88 (td), J = 10.9, 8.3 Hz, 1H), 2.77 (dd, J = 17.7, 5.1 Hz, 1H), 2.55 (dd, J = 17.7, 9.7 Hz, 1H), 1.82 (s, 3H); **^{13}C NMR** (D_2O, 100MHz) δ 175.7, 170.4, 139.7, 115.9, 61.5, 48.5, 47.9, 39.6, 33.1, 17.6; **HRMS** (ESI) *m/z* calc'd for $C_{10}H_{15}NO_4$ 213.1001 (M^+), found 214.1079 (M^+ + 1).

Chapter 4

4 Lewis Acid Assisted Rearrangement of Dihydrofurans to Cyclopentenes

This chapter is part of a manuscript that is in preparation:

Piotrowski, M. L.; Kerr, M. A. *Org Lett.*

4.1 Introduction

Five-membered carbocycles are commonly found within a variety of bioactive molecules.[47–51] Natural products (**4-1a-c**) and pharmaceuticals (**4-2a-c**) exemplify both the prevalence and importance of these scaffolds (Figure **4-1**). Synthesizing these five-membered rings has attracted the attention of the chemical community for many years.

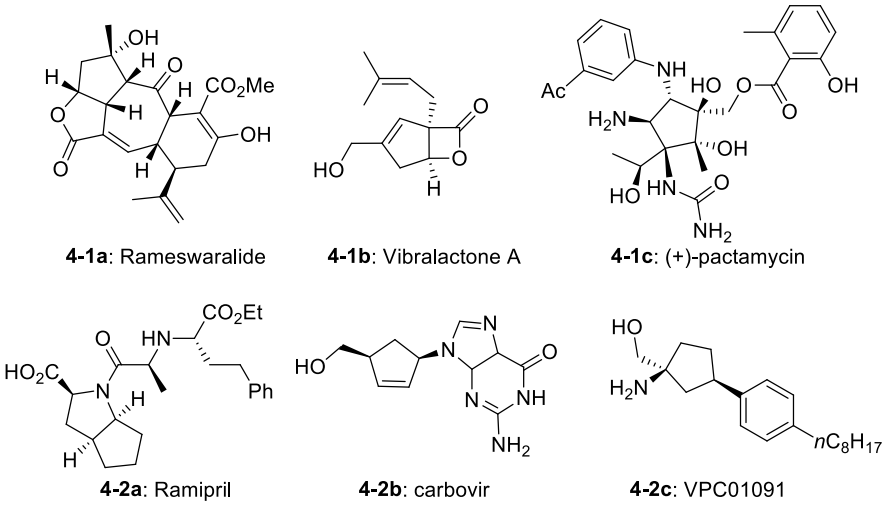
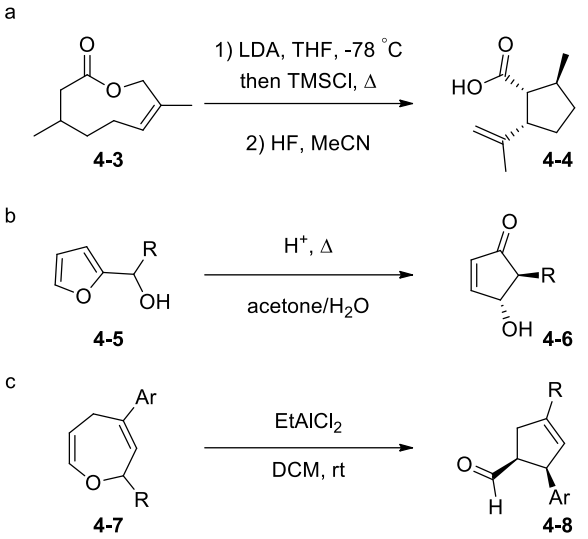


Figure 4-1. Bioactive natural products and pharmaceuticals containing a five-membered carbocycle

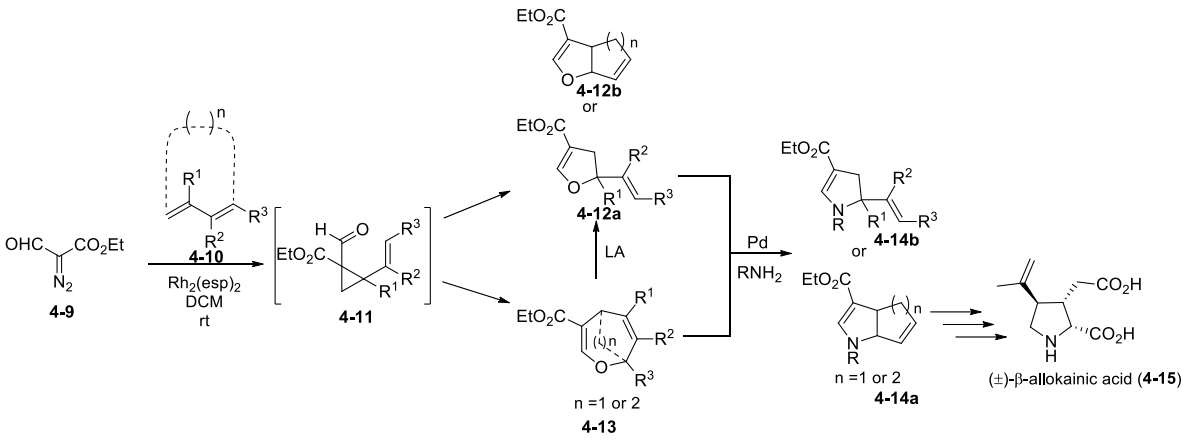
Although the prevalence of cyclopentene scaffolds in bioactive molecules is limited compared to examples containing cyclopentanes, cyclopentenes serve as key intermediates towards saturated counterparts. The most common ways of synthesizing functionalized cyclopentenes are cycloaddition/annulation reactions[148–151] and rearrangements.[92,152–156] Rearrangement reactions constitute an important class of reactivity since they provide easy access to cyclopentenes in an atom-economic fashion.

There are only a few examples in the literature where heterocycles were rearranged to five-membered carbocycles. Funk *et al.* showcased a Ireland-Claisen rearrangement of lactones (**4-3**) forming carbocyclic compounds of various ring sizes.[157] One example was the formation of a cyclopentane ring (**4-4**) (Scheme **4-1a**). The Piancatelli rearrangement is a useful reaction for the conversion of 2-furylcarbinols (**4-5**) to 4-hydroxycyclopentanones (**4-6**) under aqueous acid conditions (Scheme **4-1b**).[158,159] More recently, the work by Rovis showed a Lewis acid mediated [1,3]-ring contraction of 2,5-dihydrooxepines (**4-7**) towards substituted cyclopentenes (**4-8**) (Scheme **4-1c**).[160]



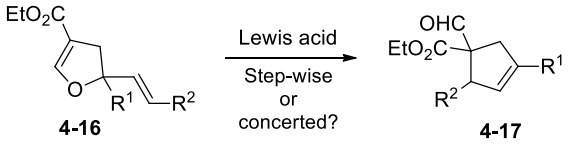
Scheme 4-1. Rearrangements of heterocycles to five-membered carbocycles

We recently reported the synthesis of a variety of dihydrofurans (**4-12a**) and 2,5-dihydrooxepines (**4-13**) through the tandem cyclopropanation/Cloke-Wilson rearrangement or vinylogous variant respectively.[133] Each of these heterocycles are easily manipulated to other useful compounds (**4-12a,b**), (**4-14a,b**) in a single transformation via Lewis acid or transition metal catalyzed reactions. We showcased these transformations in the synthesis of (±)-β-allokainic acid (see chapter 3) (**4-15**) (Scheme **4-2**).[161]



Scheme 4-2. Tandem cyclopropanation/(vinylogous)Cloke-Wilson rearrangement and subsequent transformations

We were interested to see whether we could continue to find ways of forming other heterocyclic, or even carbocyclic compounds, through single step manipulations of the heterocycles obtained via our previous methodologies. After examining the various heterocycles synthesized, we noticed that dihydrofurans (**4-12a**) contain a 1,5-diene system which could potentially be utilized in a Claisen rearrangement or through an allyl cation intermediate to generate cyclopentenes. Herein, we report the rearrangement of dihydrofurans (**4-16**) to cyclopentenes (**4-17**) under Lewis acid catalysis and propose a mechanism for the transformation (Scheme **4-3**).



Scheme 4-3. Rearrangement of dihydrofurans to cyclopentenes

4.2 Results and Discussion

The dihydrofurans used in this study (Figure **4-2**) were synthesized using our previously reported procedures. Dihydrofurans (**4-16a**, **d-f**, **h**) required an additional treatment with a Lewis acid to induce complete cyclization followed by filtration through a silica plug. Dihydrofuran (**4-16k**) was produced via a cross-metathesis reaction (see Experimental).

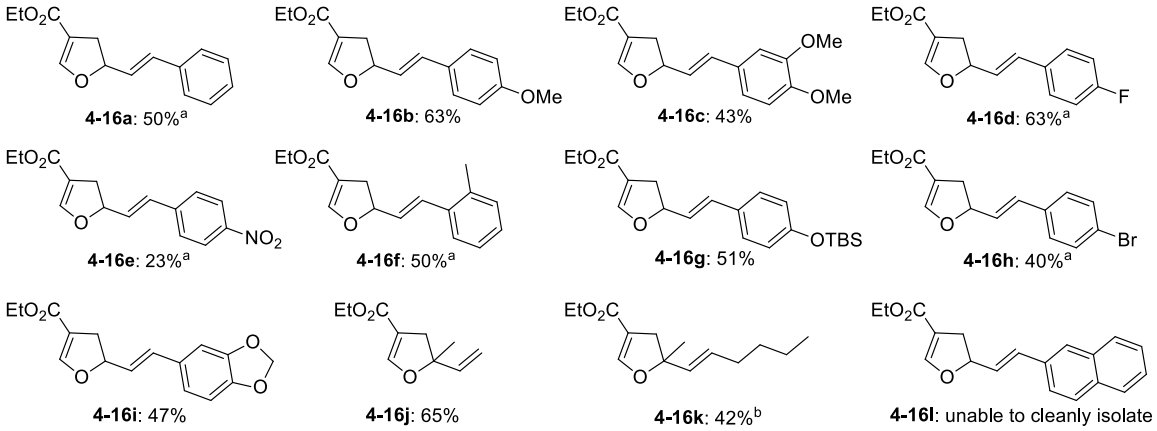
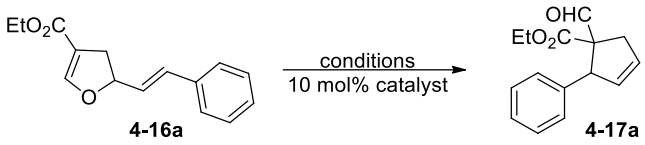


Figure 4-2. Dihydrofurans synthesized for cyclopentene formation. [a] additional treatment with a Lewis acid; overall yields as shown [b] formed via cross-metathesis

Our study commenced by treating dihydrofuran (**4-16b**) with $Sc(OTf)_3$ in DCM at 40 °C and to our delight we obtained cyclopentene (**4-17b**) in a quantitative yield with a 5:1 dr. However, when treating dihydrofuran (**4-16a**) under the exact same reaction conditions, a poor yield of cyclopentene (**4-17a**) was obtained due to a high amount of decomposition. Our optimization studies therefore commenced with dihydrofuran (**4-16a**) (Table **2**).

Table 2. Conditions tested for the rearrangement of dihydrofurans to cyclopentenes



Entry	Catalyst	Solvent	Temp (° C)	Yield %
1	$Sc(OTf)_3$	DCM	40	Trace
2	$Sc(OTf)_3$	DCM	25	No reaction
3	$Sc(OTf)_3$	DCE	60	Trace
4	$Sc(OTf)_3$	toluene	60	Trace
5	$Sc(OTf)_3$	toluene	110	Decomp.
6	$Sc(OTf)_3$	MeCN	60	Trace

7	$Yb(OTf)_3$	DCM	40	Trace
8	$Yb(OTf)_3$	DCE	60	Trace
9	$Yb(OTf)_3$	toluene	60	Trace
10	$TiCl_4$	DCM	40	Decomp.
11	BF_3OEt_2	DCM	40	Trace
12	BF_3OEt_2	toluene	60	Trace
13	$Cu(OTf)_2$	DCM	40	Decomp.
14	$Al(OTf)_3$	DCM	40	Trace
15	$Sn(OTf)_2$	DCM	40	Trace
16	$Sc(OTf)_3$	HFIP	65	50% (2:1 dr)
17	$Sc(OTf)_3$	EtOH	65	No reaction
18	BF_3OEt_2	HFIP	65	Decomp.
19	BF_3OEt_2	HFIP	25	39% (2:1 dr)
20	$Yb(OTf)_3$ (20mol%)	HFIP	65	50% (2:1 dr)
21	$In(OTf)_3$	HFIP	65	69% (2:1 dr)
22	$In(OTf)_3$	HFIP	25	55% (2:1 dr)
23	$Sn(OTf)_2$	HFIP	65	72% (2:1 dr)
24	**$Al(OTf)_3$**	**HFIP**	**65**	**83% (2:1 dr)**
25	$Zn(OTf)_2$	HFIP	65	trace
26	N/A	HFIP	80	No reaction

After screening a great deal of Lewis acids, solvents, and temperatures, the best conditions obtained in our hands was with the use of 10 mol% of $Al(OTf)_3$ in refluxing hexafluoroisopropanol (HFIP) (entry 24) (Figure **4-3**). Some key notes to mention: (1) except for the two electron rich examples (**4-17b**,**c**), the reaction gave poor results in any

solvent other than HFIP. (2) Cyclopentenes (**4-17b**,**c**) required milder conditions as mentioned in the experimental. (3) The mixture of cyclopropane/dihydrofuran that was obtained during the formation of (**4-16a**, **d-f**, **h**) can be treated under these optimized conditions to provide cyclopentenes (**4-17a**,**d**,**f**,**h**) with no change in yield. (4) Dihydrofuran (**4-16l**) was never isolated cleanly since both steps resulted in a mixture of inseparable products (note (3) was applied to cleanly obtain cyclopentene (**4-17l**)). (5) With the exception of cyclopentene (**4-17k**) the products are not stable to column chromatography as indications of regenerated starting material was seen implying that the reaction may be reversible.

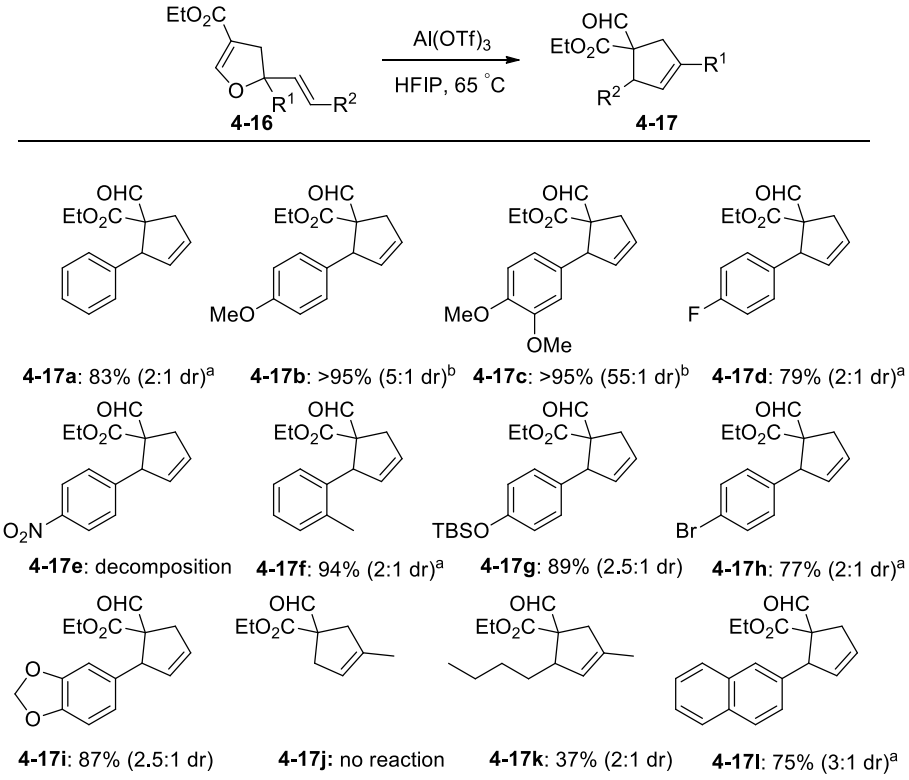
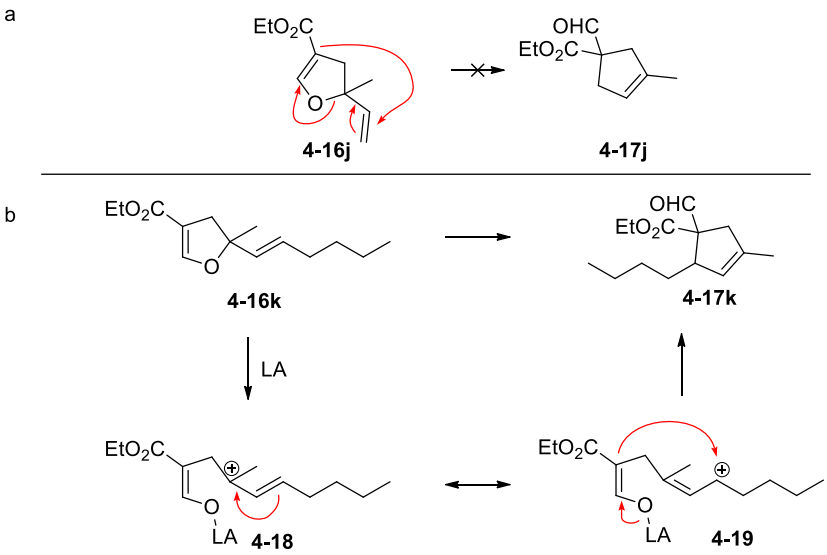


Figure 4-3. Formation of cyclopentenes. [a] the cyclopentenes can also be obtained from the cyclopropane/dihydrofuran mixture without going through pure dihydrofuran. [b] required milder conditions: DCM, 40 °C

Interestingly, in (Figure **4-3**), (**4-17j**) was not formed, however, extending the carbon chain resulted in cyclopentene (**4-17k**) albeit in low yield. Due to these reasons, we hypothesized that the rearrangement may be going through a step-wise mechanism

instead of a concerted [3+3] sigmatropic rearrangement (Scheme **4-4**). Upon treatment with a Lewis acid, an allyl cation intermediate (**4-18**) may be generated. The allyl cation would undergo resonance (**4-19**) followed by an enolate-type cyclization generating the final cyclopentene products. Based on the proposed mechanism, cyclopentene (**4-17j**) was not formed because the rearrangement would require going from a tertiary to a primary carbocation. This mechanism also explains why the cyclopentenes containing aromatic groups worked so well since benzylic carbocations would be generated. HFIP is known to stabilize carbocations and could have positively impacted the transition state energy of the intermediates of this reaction[162].



Scheme 4-4. Proposed mechanism for cyclopentene formation. [a] Ruled out concerted mechanism. [b] Proposed step-wise mechanism involving an allyl cation intermediate followed by enolate-type cyclization

With the completion of the rearrangements, we attempted improving the diastereoselectivity of the reaction and possibly provide kinetic resolution of the products. Both catalysts (Figure **4-4**) have been reported in a variety of enolate addition reactions.[163–167] Following literature procedures[168,169], we synthesized [Sn(pybox)](OTf)$_2$ (**4-20**), since Sn(OTf)$_2$ gave good results during the optimization process (see Table **2**).

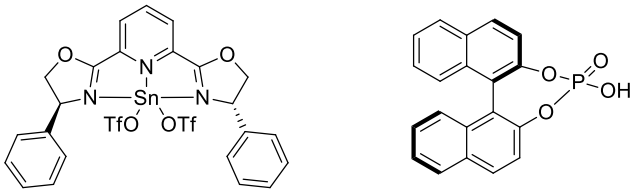
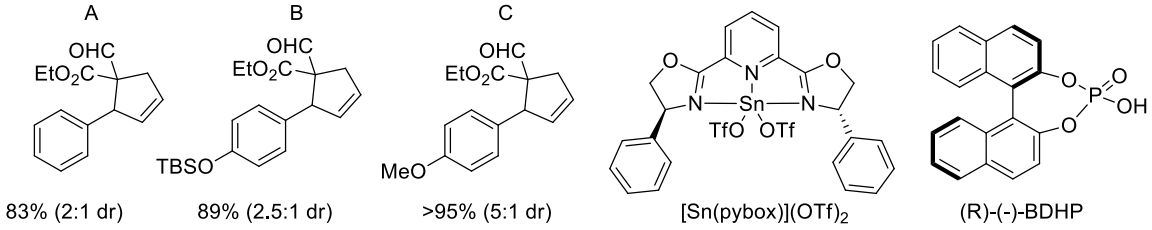


Figure 4-4. Chiral catalysts

We tested this chiral catalyst under a variety of conditions and unfortunately, only starting material was isolated (Table **3**). When using commercially available chiral phosphoric acid (R)-(-)-BDHP (**4-21**), we were excited to see the diastereoselectivity for cyclopentenes (**4-17b**,**g**) increase from 5:1 and 2.5:1 to 7:1 dr, but with a significant drop-in yield. Treating the less electron-rich dihydrofuran (**4-16a**) resulted in no change in dr with a decrease in yield. We tested this rearrangement with chiral catalyst (**4-21**) using a variety of solvents and solvent mixtures containing HFIP, all of which resulted in no improvement in dr and poor yields.

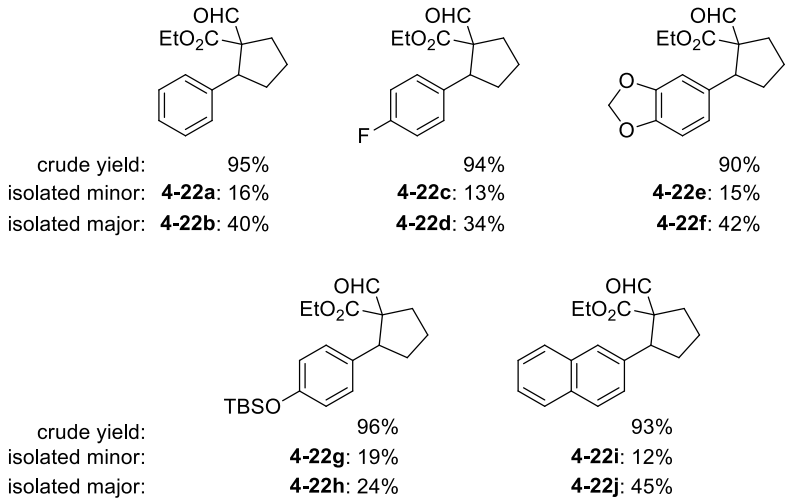
Table 3. Attempts at improving diastereoselectivity



Catalyst (30 mol%)	*Solvent*	*Temp (°C)*	*Product*	*Results*
[Sn(pybox)](OTf)₂	HFIP	65	B	No rxn
[Sn(pybox)](OTf)₂	DCM	40	B	No rxn
[Sn(pybox)](OTf)₂	DCM/HFIP	65	B	No rxn
(R)-(-)-BDHP	HFIP	65	B	50% (7:1dr)
(R)-(-)-BDHP	HFIP	65	C	50% (7:1dr)
(R)-(-)-BDHP	HFIP	65	A	35% (2:1dr)
(R)-(-)-BDHP	MeCN	65	A	Trace

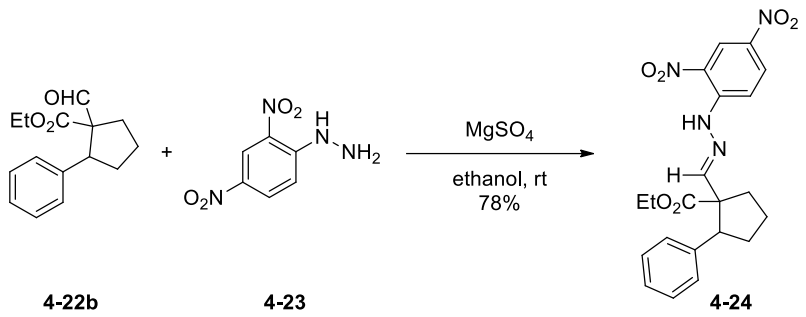
(R)-(-)-BDHP	DCM	40	A	Trace
(R)-(-)-BDHP	DCM/HFIP	65	A	Trace

To determine the relative stereochemistry of the major and minor diastereomers, we attempted to hydrogenate the sensitive cyclopentenes in the hopes of separating the diastereomers via column chromatography. Cyclopentenes (**4-17b**,**c**,**f**,**k**) were inseparable after hydrogenation and cyclopentene (**4-17h**) underwent dehalogenation under these conditions. However, a collection of separated diastereomers (**4-22a-j**) were isolated (Scheme **4-5**).



Scheme 4-5. Hydrogenation of cyclopentenes to cyclopentanes

To determine the relative structural configuration of these products, experiments with ^{1}H NMR such as NOE failed to yield conclusive results. However, reacting cyclopentane (**4-22b**) with 2,4-DNPH (**4-23**) formed hydrazone (**4-24**) that was isolated as a crystal for X-ray analysis (Scheme **4-6**).



Scheme 4-6. Hydrazone formation

Due to the similarities in ^{1}H NMR of each major diastereomer, the resulting stereochemistry is tentatively assigned to each cyclopentene product (Figure **4-5**).

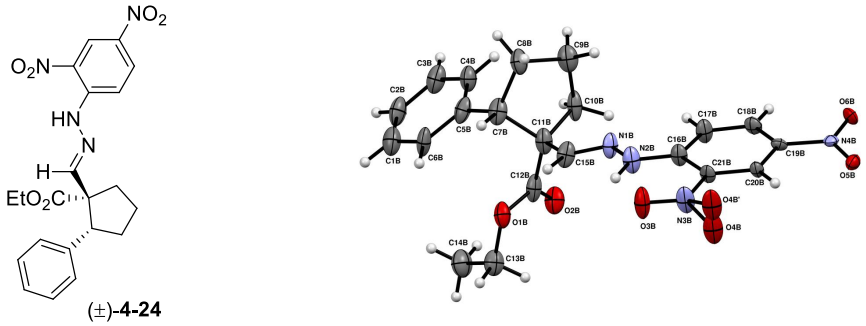


Figure 4-5. Determined stereochemistry for major diastereomer

4.3 Conclusion

In summary, we have synthesized functionalized cyclopentenes through the rearrangement of dihydrofurans in high yields and moderate diastereoselectivities. Based on the reaction yields and solvent studies, our proposed mechanism involves the formation of an ionic intermediate that undergoes an enolate type ring closure generating the desired cyclopentenes. The products obtained have useful functional handles that can provide access to more complex frameworks.

4.4 References

(148) López, E.; Lonzi, G.; López, L. A. *Synthesis* **2017**, *49* (19), 4461–4468.

(149) Sarabia, F. J.; Li, Q.; Ferreira, E. M. *Angew. Chem. Int. Ed.* **2018**, *57* (34), 11015–

11019.

(150) Scott, L.; Nakano, Y.; Zhang, C.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2018**, *57* (32), 10299–10303.

(151) Chen, Y.; Cui, B. D.; Bai, M.; Han, W. Y.; Wan, N. W.; Chen, Y. Z. *Tetrahedron* **2019**, *75* (21), 2971–2979.

(152) Chiang, P. C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129* (12), 3520–3521.

(153) Leemans, E.; D'Hooghe, M.; De Kimpe, N. *Chem. Rev.* **2011**, *111* (5), 3268–3333.

(154) Umland, K. D.; Kirsch, S. F. *Synlett* **2013**, *24* (12), 1471–1484.

(155) Catti, L.; Pöthig, A.; Tiefenbacher, K. *Adv. Synth. Catal.* **2017**, *359* (8), 1331–1338.

(156) Jana, N.; Driver, T. G. *Org. Biomol. Chem.* **2015**, *13* (38), 9720–9741.

(157) Abelman, M. M.; Funk, R. L.; Munger, J. D. *J. Am. Chem. Soc.* **1982**, *104* (14), 4030–4032.

(158) Piutti, C.; Quartieri, F. *Molecules* **2013**, *18* (10), 12290–12312.

(159) Cabrele, C.; Reiser, O. *J. Org. Chem.* **2016**, *81* (21), 10109–10125.

(160) Nasveschuk, C. G.; Rovis, T. *Angew. Chem. Int. Ed.* **2005**, *44* (21), 3264–3267.

(161) Piotrowski, M. L.; Kerr, M. A. *Eur. J. Org. Chem.* **2019**, *2019* (20), 3122–3126.

(162) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, *1* (11), 1–12.

(163) Poisson, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 7890–7892.

(164) Cichowicz, N. R.; Kaplan, W.; Khomutnyk, Y.; Bhattarai, B.; Sun, Z.; Nagorny, P. *J. Am. Chem. Soc.* **2015**, *137*, 14341–14348.

(165) Comelles, J.; Pericas, A.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledos, A.; Parella, T.; Roglans, A.; García-Granda, S.; Roces-Fernández, L. *J. Org. Chem.* **2007**, *72*, 2077–2087.

(166) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227–2256.

(167) Cano, R.; Zakarian, A.; McGlacken, G. P. *Angew. Chem. Int. Ed.* **2017**, *56*, 9278–9290.

(168) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860.

(169) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103* (8), 3119–3154.

4.5 Experimental

4.5.1 General Considerations

All reactions were conducted under an atmosphere of argon unless otherwise indicated. DCM, toluene, and acetonitrile were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other solvents and reagents were used as purchased from Sigma Aldrich, Alfa Aesar, Caledon, VWR or Oakwood Chemicals and used as received. Reaction progress was followed by thin layer chromatography (TLC) (Merck, TLC silica gel 60 F254) visualized with UV light, and the plates developed with p-anisaldehyde, vanillin, basic potassium permanganate or DMP stains. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc).

NMR experiments were performed on Varian Mercury 400, Bruker AvIII 400, Inova 400 and Inova 600 MHz instruments with 13C operating frequencies of 100, 100, 100, and 150 MHz respectively. Chemical shifts are reported in ppm relative to the residual solvent signal; CDCl3, referenced to residual CHCl3 at $\delta = 7.26$ for ^{1}H and $\delta = 77.1$ for

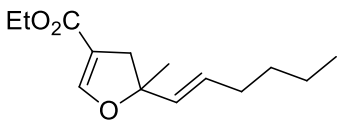
^{13}C; d^6-DMSO referenced at δ = 2.50 for ^{1}H and δ = 39.5 for ^{13}C. Coupling constants (J) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization. Melting points were determined using a Digimelt MPA160 melting point apparatus from Stanford Research Systems (SRS). Infrared spectra were obtained using a Bruker Alpha II Platinum ATR spectrometer or as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm-1). The synthetic procedures for dihydrofurans can be found in our previous published work[133] along with the following changes: 0.1 mol% of $Rh_2(esp)_2$ was used and a filtration through a silica plug eluting with EtOAc/Hexanes was required for the dihydrofurans (**4-16a**, **d-f**, **h**) that needed to be treated with $Sc(OTf)_3$ to complete the cyclization in order to obtain good results for cyclopentene rearrangement.

4.5.2 Experimental procedures and characterization data

Synthesis of dihydrofuran (**4-17k**)

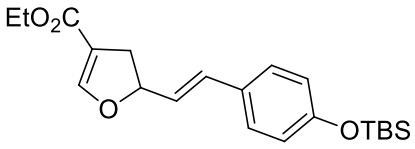
Dihydrofuran (**4-16j**) (1 equiv.) was placed in flask with stir bar under an atmosphere of argon. Deoxygenated DCM (0.088M) was added followed by deoxygenated 1-hexene (5 equiv.) that was distilled prior to use over CaH_2. Grubbs second generation catalyst (4 mol%) was added and the reaction was refluxed for 24 hours. The reaction was concentrated under reduced pressure and purified by column chromatography using 5 % EtOAc/Hexanes as the eluent providing dihydrofuran (**4-16k**) as an oil; yield 42% (0.12g, 0.5 mmol); Rf = 0.27, 5% EtOAc/Hexanes.

(E)-ethyl 5-(hex-1-en-1-yl)-5-methyl-4,5-dihydrofuran-3-carboxylate (4-16k)



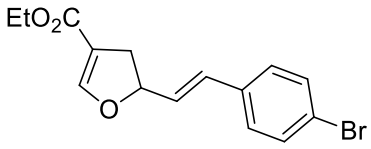
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 1.9 Hz, 1H), 5.69-5.57 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.80, 2.63 (AB_q, J_{AB} = 14.6 Hz, 2H); with each signal split into a doublet due to $^{4}J_{CH}$ = 1.9 Hz coupling with the methine proton), 2.03 (br q, J = 6.6 Hz, 2H), 1.45 (s, 3H), 1.39-1.28 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.6, 155.4, 132.8, 129.9, 107.8, 90.9, 59.7, 40.2, 31.9, 31.3, 26.7, 22.2, 14.5, 14.0; **IR** (cm^{-1}) 2928, 1702, 1623, 1155, 1100, 1053; **HRMS** (EI) *m/z* calc'd for $C_{14}H_{22}O_3$ 238.1569 (M^+), found 238.1571.

(E)-ethyl 5-(4-((tert-butyldimethylsilyl)oxy)styryl)-4,5-dihydrofuran-3-carboxylate (4-16g)



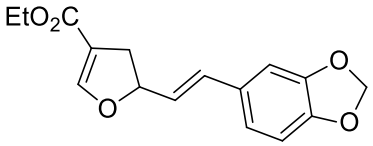
Reagents employed: (E)-(4-(buta-1,3-dien-1-yl)phenoxy)(tert-butyl)dimethylsilane (0.32g, 1.24 mmol), formyldiazoacetate (0.35g, 2.48 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (1mg, 0.00124 mmol), DCM (10.5ml): yield 51% (0.24g, 0.64 mmol) as a yellow oil; Rf = 0.37, 10% EtOAc/Hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 3H), 6.81-6.78 (AA'BB', 2H), 6.57 (d, J = 15.7 Hz, 1H), 6.14 (dd, J = 15.8, 7.5 Hz, 1H), 5.35 (dt, J = 11.1, 8.1 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.08 (ddd, J = 14.7, 10.5, 1.9 Hz, 1H), 2.72 (ddd, J = 14.7, 8.0, 1.8 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H), 0.20 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 156.4, 156.1, 132.5, 129.3, 128.0, 125.3, 120.4, 108.9, 86.2, 59.9, 34.2, 25.8, 18.3, 14.5, -4.2; **IR** (cm^{-1}) 2930, 1702, 1624, 1508, 1252, 1098; **HRMS** (EI) *m/z* calc'd for $C_{21}H_{30}O_4Si$ 374.1913 (M^+), found 374.1909.

(E)-ethyl 5-(4-bromostyryl)-4,5-dihydrofuran-3-carboxylate (4-16h)



Reagents employed: (E)-1-bromo-4-(buta-1,3-dien-1-yl)benzene (0.27g, 1.29 mmol), formyldiazoacetate (0.36g, 2.58 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (1mg, 0.00129 mmol), DCM (10.5ml): yield 45% (0.19g, 0.59 mmol) as an oil; Rf = 0.34, 10% EtOAc/Hexanes; **Reagents employed**: cyclopropane/dihydrofuran mixture (0.19g, 0.59 mmol), $Sc(OTf)_3$ (0.014g, 0.029 mmol), DCM (5ml): yield 87% (0.16g, 0.51 mmol) as a white solid; **Melting point**: 38.5-39.8 °C; Rf = 0.34, 10% EtOAc/Hexanes; **^{1}H NMR** (400 MHz, DMSO-d^6) δ 7.55-7.52 (m, 2H), 7.49-7.45 (m, 3H), 6.65 (d, J = 15.9 Hz, 1H), 6.48 (dd, J = 15.9, 6.9 Hz, 1H), 5.44 (dt, J = 9.9, 7.3 Hz, 1H), 4.10 (q, J = 7.1Hz, 2H), 3.02 (ddd, J = 14.6, 10.6, 1.9 Hz, 1H), 2.62 (ddd, J = 14.6, 7.9, 1.9 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d^6) δ 164.2, 156.6, 135.1, 131.5, 130.3, 128.9, 128.7, 121.1, 108.1, 84.8, 59.2, 33.3, 14.3; **IR** (cm^{-1}) 2979, 1699, 1618, 1127, 1097, 1071; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{15}BrO_3$ 322.0205 (M^+), found 322.0192.

(E)-ethyl 5-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dihydrofuran-3-carboxylate (4-16i)



Note: compound may be light sensitive

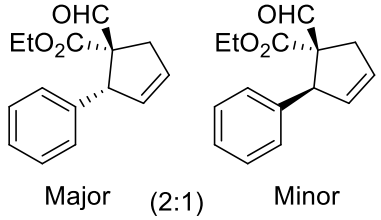
Reagents employed: (E)-5-(buta-1,3-dien-1-yl)benzo[d][1,3]dioxole (0.4g, 2.29 mmol), formyldiazoacetate (0.65g, 4.58 mmol), Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (2mg, 0.00229 mmol), DCM (19.5ml): yield 47% (0.31g, 1.07 mmol) as a yellow solid; Melting point 56.4-57.8 °C; Rf = 0.25, 25% EtOAc/Hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (t, J = 1.9 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.84-6.82 (m, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 15.7 Hz, 1H), 6.10 (dd, J = 15.7, 7.4 Hz, 1H), 5.96 (s, 2H), 5.34 (dddd, J = 10.5, 8.2, 7.4, 1.0 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.08 (ddd, J = 14.7, 10.5, 1.9 Hz, 1H), 2.71 (ddd, J = 14.7, 8.0, 1.9 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 165.2, 156.3, 148.2, 147.9, 132.5, 130.4, 125.6, 121.8, 108.9, 108.4, 106.0, 101.3, 86.0, 59.9, 34.2, 14.5; **IR** (cm^{-1}) 2985, 1690,

1626, 1442, 1243, 1097, 1036; **HRMS** (EI) *m/z* calc'd for $C_{16}H_{16}O_5$ 288.0998 (M^+), found 288.1002.

General procedure for the synthesis of cyclopentenes

The starting dihydrofuran (1 equiv.) was placed in a round bottom flask under an atmosphere of argon. Hexafluoroisopropanol (0.12M) was added followed by $Al(OTf)_3$ (10 mol%) and the reaction was heated to 65 °C under reflux; (For dihydrofurans (**4-16b,c**) mild conditions were required, DCM (0.12M) was used and heated to 40 °C for 30 minutes). Once the dihydrofuran was fully consumed, the reaction was cooled to room temperature and concentrated under reduced pressure. The crude material was filtered through a silica plug eluting with the indicated mixture of EtOAc/Hexanes and concentrated under reduced pressure.

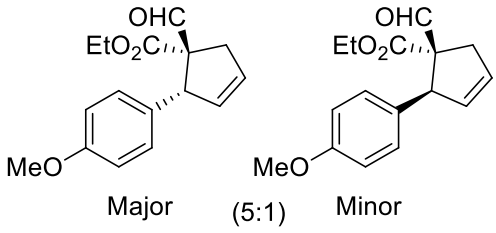
(±)-Ethyl 1-formyl-2-phenylcyclopent-3-enecarboxylate (4-17a)



Reagents employed: (E)-ethyl 5-styryl-4,5-dihydrofuran-3-carboxylate (**4-16a**) (0.32g, 1.34 mmol), $Al(OTf)_3$ (0.063g, 0.134 mmol), HFIP (11ml): yield 84% (0.28, 1.1 mmol) as a colourless oil; Rf = 0.52 and 0.44 for minor and major diastereomer respectively; filtered through silica plug using 10% EtOAc/Hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer δ 9.78 (s, 1H), 7.33-7.27 overlap (m, 3H), 7.25-7.20 overlap (m, 3H), 7.19-7.16 overlap (m, 3H), 5.93-5.90 (m, 1H), 5.70-5.64 overlap (m, 2H), 4.50-4.49 (m, 1H), 3.71 (dq, J = 10.7, 7.1 Hz, 1H), 3.60 (dq, J = 10.8, 7.1 Hz, 1H), 3.28-3.20 overlap (m, 2H), 2.88-2.85 overlap (m, 1H), 2.84-2.82 overlap (m, 1H), 0.86 (t, J = 7.1 Hz, 3H); minor diastereomer δ 9.02 (s, 1H), 5.97-5.94 (m, 1H), 4.82-4.80 (m, 1H), 4.32-4.26 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) mixture of diastereomers δ 197.0, 196.8, 172.1, 169.2, 138.5, 137.3, 131.2, 131.0, 130.3, 129.7, 129.1, 129.0, 128.9, 128.3, 127.8, 127.6, 69.4, 66.8, 62.1, 61.5, 58.6, 55.9, 36.1, 35.4, 14.3, 13.7; **IR** (cm^{-1})

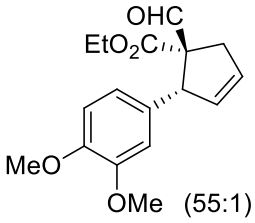
2982, 1742, 1715, 1231, 698; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ 244.1099 (M^+), found 244.1095.

(±)-Ethyl 1-formyl-2-(4-methoxyphenyl)cyclopent-3-enecarboxylate (4-17b)



Reagents employed: Dihydrofuran (**4-16b**) (0.1g, 0.36 mmol), $Al(OTf)_3$ (0.017g, 0.036 mmol), DCM (3ml): yield 100% (0.1g, 0.36 mmol) as a yellow oil; Rf = 0.48, 30% EtOAc/Hexanes; filtered through Celite plug; **^{1}H NMR** (600 MHz, $CDCl_3$) major diastereomer δ 9.78 (s, 1H), 7.09-7.07 overlap (AA'BB', 2H), 6.82-6.79 (AA'BB', 2H), 5.89-5.87 (m, 1H), 5.64-6.61 overlap (m, 1H), 4.45-4.44 (m, 1H), 3.77 (s, 3H), 3.74 (dq, J = 10.7, 7.1 Hz, 1H), 3.64 (dq, J = 10.7, 7.1 Hz, 1H), 3.22-3.17 overlap (m, 1H), 2.85-2.80 overlap (m, 1H), 0.91 (t, J = 7.1 Hz, 3H); minor diastereomer δ 9.04 (s, 1H), 6.84-6.83 (AA'BB', 2H), 5.93-5.91 (m, 1H), 4.76-4.75 (m, 1H), 4.33-4.25 (m, 2H), 3.78 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) mixture of diastereomers δ 197.2, 196.0, 172.2, 169.2, 159.2, 159.1, 131.3, 131.2, 130.3, 130.1, 130.0, 129.9, 129.4, 129.1, 114.3, 113.6, 69.3, 66.6, 62.0, 61.4, 58.0, 55.38, 55.36, 55.31, 35.9, 35.1, 14.2, 13.7; **IR** (cm^{-1}) 2957, 1741, 1716, 1510, 1241, 1032; **HRMS** (EI) *m/z* calc'd for $C_{16}H_{18}O_4$ 274.1205 (M^+), found 274.1200.

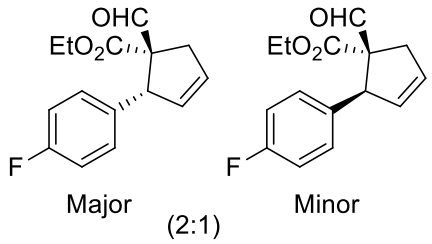
(±)-Ethyl 2-(3,4-dimethoxyphenyl)-1-formylcyclopent-3-enecarboxylate (4-17c)



Reagents employed: Dihydrofuran (**4-16c**) (0.1g, 0.33 mmol), $Al(OTf)_3$ (0.015g, 0.033 mmol), DCM (2.8ml): yield 100% (0.1g, 0.33 mmol) as a yellow oil; Rf = 0.35, 20%

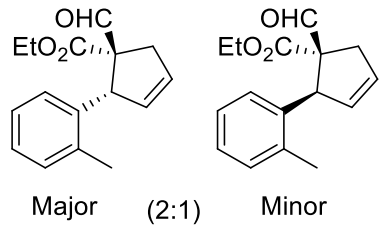
EtOAc/Hexanes; filtered through a Celite plug; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.78-6.66 (m, 3H), 5.88 (ddt, J = 5.8, 2.6, 1.9 Hz, 1H), 5.63 (dtd, J = 5.8, 2.5, 1.8 Hz, 1H), 4.45 (apparent q, J = 2.4 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.76 (dq, J = 10.8, 7.2 Hz, 1H), 3.66 (dq, J = 10.8, 7.1 Hz, 1H), 3.24-3.18 (m, 1H), 2.85-2.80 (m, 1H), 0.90 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.8, 169.2, 148.6, 148.4, 131.4, 130.9, 129.3, 121.3, 112.3, 110.8, 69.3, 61.4, 56.0, 55.9, 55.5, 35.3, 13.8; **IR** (cm^{-1}) 2935, 1742, 1715, 1590, 1232; **HRMS** (EI) *m/z* calc'd for $C_{17}H_{20}O_5$ 304.1311 (M^+), found 304.1314.

(±)-Ethyl 2-(4-fluorophenyl)-1-formylcyclopent-3-enecarboxylate (4-17d)



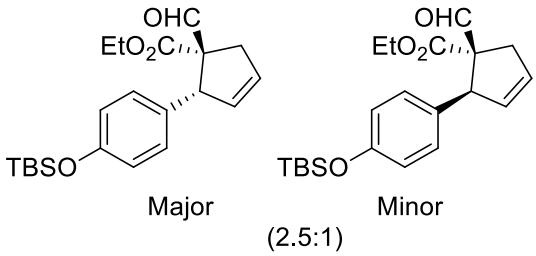
Reagents employed: (E)-ethyl 5-(4-fluorostyryl)-4,5-dihydrofuran-3-carboxylate (**4-16d**) (0.1g, 0.38 mmol), $Al(OTf)_3$ (0.018g, 0.038 mmol), HFIP (3.2ml): yield 79% (0.079g, 0.30 mmol) as a oil; Rf = 0.4, 0.33, 10% EtOAc/Hexanes; filtered through a silica plug eluting with 10% EtOAc/Hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) major diastereomer δ 9.74 (s, 1H), 7.16-7.12 overlap (m, 4H), 6.97-6.94 (m, 2H), 5.90 (ddt, J = 5.7, 2.6, 1.9 Hz, 1H), 5.64-5.61 overlap (m, 2H), 4.50 (apparent q, J = 2.4 Hz, 1H), 3.74 (dq, J = 10.7, 7.2 Hz, 1H), 3.65 (dq, J = 10.8, 7.1 Hz, 1H), 3.24-3.18 overlap (m, 2H), 2.85-2.81 overlap (m, 2H), 0.90 (t, J = 7.1 Hz, 3H); minor diastereomer δ 9.02 (s, 1H), 7.00-6.97 (m, 2H), 5.95-5.93 (m, 1H), 4.79 (apparent quin, J = 2.3 Hz, 1H), 4.28 (qd, J = 7.1, 4.8 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); **^{13}C NMR** mixture of diastereomers (150 MHz, $CDCl_3$) δ 196.8, 195.4, 171.9, 169.0, 163.2, 163.1, 161.5, 161.4, 134.25, 134.23, 133.1, 133.0, 131.1, 130.8, 130.7, 130.6, 130.52, 130.50, 130.4, 129.7, 115.8, 115.7, 115.1, 115.0, 69.2, 66.7, 62.1, 61.5, 57.7, 54.8, 36.0, 35.4, 14.2, 13.7; **^{19}F NMR** mixture of diastereomers (564 MHz, $CDCl_3$) δ -114.6, -115.0; **IR** (cm^{-1}) 2983, 1742, 1717, 1508, 1225; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{15}FO_3$ 262.1005 (M^+), found 262.0998.

(±)-Ethyl 1-formyl-2-(o-tolyl)cyclopent-3-enecarboxylate (4-17f)



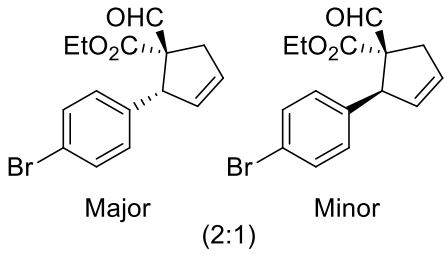
Reagents employed: (E)-ethyl 5-(2-methylstyryl)-4,5-dihydrofuran-3-carboxylate (**4-16f**) (0.03g, 0.12 mmol), $Al(OTf)_3$ (6mg, 0.012 mmol), HFIP (1ml): yield 94% (0.028g, 0.11 mmol) as a colourless oil; Rf = 0.52, 0.44 for minor and major diastereomer respectively; filtered through silica plug using 10% EtOAc/Hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) major diastereomer δ 9.81 (s, 1H), 7.18-7.10 overlap (m, 5H), 7.07-7.04 (m, 1H), 5.89 (ddt, J = 5.8, 2.7, 2.0 Hz, 1H), 5.89 (dtd, J = 5.7, 2.5, 1.8 Hz, 1H), 4.85 (apparent q, J = 2.3 Hz, 1H), 3.68 (dq, J = 10.7, 7.1 Hz, 1H), 3.55 (dq, J = 10.8, 7.2 Hz, 1H), 3.32-3.26 overlap (m, 2H), 2.85-2.84 overlap (m, 1H), 2.82-2.81 overlap (m, 1H), 2.41 (s, 3H), 0.84 (t, J = 7.1 Hz, 3H); minor diastereomer δ 8.97 (s, 1H), 5.99-5.97 (m, 1H), 5.62-5.60 (m, 1H), 5.04-5.03 (m, 1H), 4.29 (qd, J = 7.1, 1.8 Hz, 2H), 2.43 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) mixture of diastereomers δ 197.0, 196.6, 172.7, 169.4, 137.0, 136.9, 136.7, 135.4, 131.8, 131.5, 130.9, 130.3, 130.0, 129.0, 128.8, 128.6, 127.7, 127.4, 126.6, 126.0, 69.2, 66.1, 62.5, 61.5, 54.6, 51.0, 36.2, 36.1, 20.3, 20.1, 14.2, 13.5; **IR** (cm^{-1}) 2981, 1742, 1715, 1231; **HRMS** (EI) *m/z* calc'd for $C_{16}H_{18}O_3$ 258.1256 (M^+), found 258.1246.

(±)-Ethyl 2-(4-((tert-butyldimethylsilyl)oxy)phenyl)-1-formylcyclopent-3-enecarboxylate (4-17g)



Reagents employed: dihydrofuran (**4-16g**) (0.055g, 0.14 mmol), $Al(OTf)_3$ (7mg, 0.014 mmol), HFIP (1.2ml): yield 89% (0.049g, 0.13 mmol) as an oil; Rf = 0.45, 0.34 for minor and major diastereomer respectively, 10% EtOAc/Hexanes; filtered through silica plug eluting with 10% EtOAc/Hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) major diastereomer δ 9.78 (s, 1H), 7.03-7.00 overlap (m, 3H), 6.75-6.72 (AA'BB', 2H), 5.87 (ddt, J = 5.7, 2.5, 1.9 Hz, 1H), 5.64-5.61 overlap (m, 1H), 4.42 (apparent q, J = 2.4 Hz, 1H), 3.74 (dq, J = 10.8, 7.2 Hz, 1H), 3.64 (dq, J = 10.7, 7.2 Hz, 1H), 3.24-3.17 overlap (m, 2H), 2.85-2.79 overlap (m, 2H), 0.97 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H), 0.16 (s, 6H); minor diastereomer δ 9.03 (s, 1H), 6.78-6.76 (AA'BB', 2H), 5.93-5.90 (m, 1H), 4.74 (apparent quin, J = 2.2 Hz, 1H), 4.32-4.24 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H), 0.18 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) mixture of diastereomers δ 197.2, 196.0, 172.3, 169.2, 155.3, 155.2, 131.3, 131.2, 131.0, 130.1, 130.0, 129.9, 129.8, 129.3, 120.5, 119.8, 69.3, 66.6, 62.0, 61.4, 58.1, 55.4, 35.9, 35.1, 25.8, 25.7, 18.4, 18.3, 14.3, 13.8, -4.2, -4.3; **IR** (cm^{-1}) 2930, 1746, 1718, 1508, 1235; **HRMS** (EI) *m/z* calc'd for $C_{21}H_{30}O_4Si$ 374.1913 (M^+), found 374.1910.

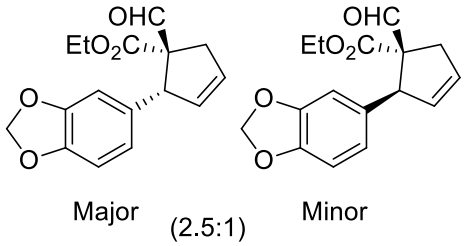
(±)-Ethyl 2-(4-bromophenyl)-1-formylcyclopent-3-enecarboxylate (4-17h)



Reagents employed: dihydrofuran (**4-16h**) (0.19g, 0.59 mmol) $Al(OTf)_3$ (0.028g, 0.059 mmol), HFIP (5ml): yield 77% (0.14g, 0.43 mmol) as a clear oil; Rf = 0.44, 0.37, 10% EtOAc/Hexanes, for minor and major diastereomer respectively; filtered through silica plug eluting with 10% EtOAc/Hexanes; **^{1}H NMR** (600 MHz, $CDCl_3$) major diastereomer δ 9.73 (s, 1H), 7.40-7.37 (AA'BB', 2H), 7.07-7.03 overlap (m, 3H), 5.90 (ddt, J = 5.8, 2.6, 1.9 Hz, 1H), 5.62-5.60 overlap (m, 2H), 4.48 (apparent q, J = 2.3 Hz, 1H), 3.76 (dq, J = 10.8, 7.1 Hz, 1H), 3.66 (dq, J = 10.8, 7.1 Hz, 1H), 3.24-3.18 overlap (m, 2H), 2.85-2.81 overlap (m, 2H), 0.90 (t, J = 7.1 Hz, 3H); minor diastereomer δ 9.02 (s, 1H), 7.43-7.41

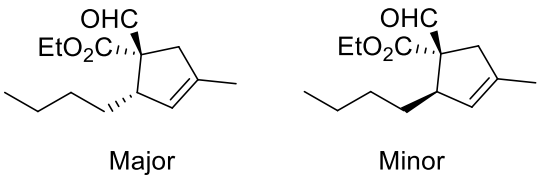
(AA'BB', 2H), 5.96-5.94 (m, 1H), 4.76 (apparent quin, J = 2.3 Hz, 1H), 4.28 (qd, J = 7.1, 4.9 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); **^{13}C NMR** mixture of diastereomers δ 196.5, 195.2, 171.8, 168.9, 137.6, 136.4, 132.0, 131.3, 130.9, 130.83, 130.81, 130.6, 130.5, 130.0, 121.8, 121.5, 69.2, 66.7, 62.1, 61.6, 57.8, 54.9, 36.1, 35.5, 14.2, 13.7; **IR** (cm^{-1}) 2981, 1742, 1715, 1487, 1230; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{15}BrO_3$ 322.0205 (M^+), found 322.0200.

(±)-Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-1-formylcyclopent-3-enecarboxylate (4-17i)



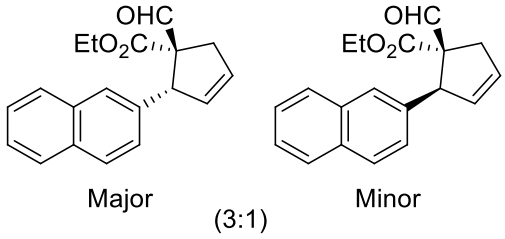
Reagents employed: dihydrofuran (**4-16i**) (0.21g, 0.71 mmol), $Al(OTf)_3$ (0.034g, 0.071 mmol), HFIP (6ml): yield 87% (0.18g, 0.62 mmol) as a dark yellow oil; Rf = 0.27, 0.2 for minor and major diastereomer respectively, 10% EtOAc/Hexanes; filtered through a silica plug eluting with 15% EtOAc/Hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer δ 9.75 (s, 1H), 6.76-6.70 overlap (m, 2H), 6.67-6.63 overlap (m, 3H), 5.92 (s, 2H), 5.90-5.87 (m, 1H), 5.63-5.60 overlap (m, 1H), 4.43 (apparent q, J = 2.4 Hz, 1H), 3.82 (dq, J = 10.7, 7.2 Hz, 1H), 3.74 (dq, J = 10.8, 7.1 Hz, 1H), 3.25-3.15 overlap (m, 2H), 2.85-2.79 overlap (m, 2H), 0.97 (t, J = 7.1 Hz, 3H); minor diastereomer δ 9.08 (s, 1H), 5.94 (s, 2H), 4.73 (apparent quin, J = 2.1 Hz, 1H), 4.32-4.24 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) mixture of diastereomers δ 197.0, 195.8, 172.1, 169.1, 148.2, 147.6, 147.2, 147.0, 132.1, 131.8, 131.3, 131.0, 130.3, 129.6, 122.4, 122.1, 109.5, 109.1, 108.6, 108.0, 101.2, 101.1, 69.3, 66.6, 62.1, 61.5, 58.3, 55.5, 36.0, 35.2, 14.3, 13.8; **IR** (cm^{-1}) 2982, 1739, 1715, 1484, 1227, 1035; **HRMS** (EI) *m/z* calc'd for $C_{16}H_{16}O_5$ 288.0998 (M^+), found 288.0998.

(±)-Ethyl 2-butyl-1-formyl-4-methylcyclopent-3-enecarboxylate (4-17k)



Reagents employed: dihydrofuran (**4-16k**) (0.03g, 0.12 mmol) $Al(OTf)_3$ (5mg, 0.012 mmol), HFIP (1ml): yield 37% (0.011g, 0.04 mmol) as an oil; Rf = 0.25, 5% EtOAc/Hexanes; required column purification eluting with 5% EtOAc/Hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer δ 9.73 (s, 1H), 5.25-5.22 overlap (m, 1H), 4.27-4.16 overlap (m, 3H), 3.38-3.33 (m, 1H), 2.95-2.84 overlap (m, 2H), 2.73-2.59 overlap (m, 2H), 1.74 (s, 3H), 1.74-1.55 overlap (m, 1H), 1.40-1.23 overlap (m, 14H), 0.93-0.86 overlap (m, 6H); minor diastereomer δ 9.67 (s, 1H), 3.09-3.05 (m, 1H), 1.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) mixture of diastereomers δ 199.0, 197.4, 172.5, 170.4, 138.7, 137.9, 125.5, 124.6, 67.8, 66.6, 61.6, 61.4, 53.8, 49.7, 40.2, 38.5, 31.4, 30.8, 29.8, 22.9, 22.8, 16.5, 16.4, 14.3, 14.2, 14.1, 14.0; **IR** (cm^{-1}) 2930, 1744, 1716, 1445, 1230; **HRMS** (EI) *m/z* calc'd for $C_{14}H_{22}O_3$ 238.1569 (M^+), found 238.1575.

(±)-Ethyl 1-formyl-2-(naphthalen-2-yl)cyclopent-3-enecarboxylate (4-17l)



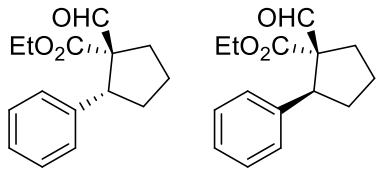
Reagents employed: dihydrofuran/cyclopropane mixture (0.13g, 0.44 mmol), $Al(OTf)_3$ (0.021g, 0.044 mmol), HFIP (3.6ml): yield 75% (0.098g, 0.33 mmol) as an oil; Rf = 0.45, 0.41 for minor and major diastereomer respectively, 10% EtOAc/Hexanes; filtered through a plug of silica eluting with 5% EtOAc/Hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer δ 9.83 (s, 1H), 7.80-7.74 overlap (m, 4H), 7.65-7.7.64 overlap (m, 1H), 7.48-7.42 overlap (m, 2H), 7.30-7.27 overlap (m, 1H), 5.98 (ddt, J = 5.7, 2.6, 1.9 Hz, 1H), 5.77-5.71 overlap (m, 1H), 4.68 (apparent q, J = 2.4 Hz, 1H), 3.61 (dq, J = 10.8, 7.1 Hz, 1H), 3.48 (dq, J = 10.8, 7.1 Hz, 1H), 3.35-3.28 overlap (m, 1H), 2.93-2.86

overlap (m, 1H), 0.70 (t, J = 7.1 Hz, 3H); minor diastereomer δ 6.03-6.01 (m, 1H), 4.98 (apparent quin, J = 1.9 Hz, 1H), 4.36-4.26 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) mixture of diastereomers δ 196.9, 195.7, 172.2, 169.1, 136.0, 134.9, 133.5, 133.3, 132.97, 132.90, 131.2, 131.0, 130.5, 129.9, 128.7, 128.0, 127.9, 127.88, 127.85, 127.81, 127.78, 127.70, 127.1, 126.8, 126.4, 126.2, 126.0, 125.7, 69.5, 66.9, 62.1, 61.5, 58.7, 55.9, 36.2, 35.5, 14.3, 13.5; **IR** (cm^{-1}) 2981, 1740, 1715, 1231; **HRMS** (EI) *m/z* calc'd for $C_{19}H_{18}O_3$ 294.1256 (M^+), found 294.1254.

General procedure for hydrogenation of cyclopentene

Palladium on carbon (1 equiv.) was placed in round bottom flask with stir bar under house vacuum. Methanol (0.12M) was added and the flask was purged with hydrogen gas. The starting cyclopentene (1 equiv.) was dissolved in methanol (0.12M) under an atmosphere of argon and was added to the Pd/C mixture. The reaction was stirred for three hours, filtered through Celite and concentrated under reduced pressure. The crude material was purified by column chromatography eluting with the indicated EtOAc/Hexanes mixture.

(±)-Ethyl 1-formyl-2-phenylcyclopentanecarboxylate (4-22a,b)

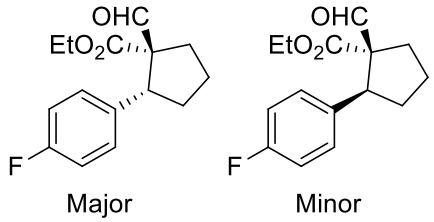


Reagents employed: Cyclopentene (**4-17a**) (0.1g, 0.41 mmol), Pd/C (0.044g, 0.41 mmol), methanol (7ml): crude yield (mixture of diastereomers) 95% (0.095g, 0.38 mmol), isolated yield minor 16% (0.016g, 0.06 mmol) as an oil; Rf = 0.52, 10% EtOAc/Hexanes; isolated yield major 40% (0.04g, 0.16 mmol) as an oil; Rf = 0.44, 10% EtOAc/Hexanes; purified by column chromatography eluting with 2.5% to 5% EtOAc/Hexanes.

Data analysis for minor diastereomer (**4-22a**): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.31-7.28 (m, 2H), 7.25-7.20 (m, 3H), 4.25 (qd, J = 7.1, 1.8 Hz, 2H), 3.88 (dd, J = 11.5, 6.5 Hz, 1H), 2.58-2.53 (m, 1H), 2.10-2.05 (m, 1H), 2.01-1.94 (m, 3H), 1.87-1.81 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.0, 173.2, 137.5, 128.7, 128.5, 127.4, 66.3, 61.7, 53.8, 31.3, 30.5, 24.0, 14.3; **IR** (cm^{-1}) 2958, 1739, 1712, 1248; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{18}O_3$ 246.1256 (M^+), found 246.1257.

Data analysis for major diastereomer (**4-22b**): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.27-7.23 (m, 2H), 7.22-7.18 (m, 3H), 3.86 (dd, J = 10.7, 7.0 Hz, 1H), 3.76 (dq, J = 10.7, 7.1 Hz, 1H), 3.64 (dq, J = 10.7, 7.2 Hz, 1H), 2.43 (ddd, J = 13.7, 10.6, 7.9 Hz, 1H), 2.19-2.12 (m, 3H), 2.05-2.00 (m, 1H), 1.65-1.56 (m, 1H), 0.82 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.9, 171.1, 140.1, 128.6, 128.2, 127.0, 69.2, 61.2, 49.9, 32.6, 31.4, 24.6, 13.6; **IR** (cm^{-1}) 2959, 1711, 1223; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{18}O_3$ 246.1256 (M^+), found 246.1249.

(±)-Ethyl 2-(4-fluorophenyl)-1-formylcyclopentanecarboxylate (4-22c,d)



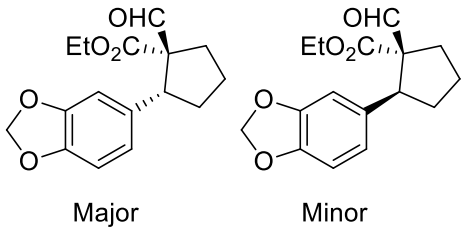
Reagents employed: Cyclopentene (**4-17d**) (0.14g, 0.54 mmol), Pd/C (0.057g, 0.54 mmol), methanol (9ml): crude yield (mixture of diastereomers) 94% (0.13g, 0.49 mmol), isolated yield minor 13% (0.019g, 0.07 mmol) as an oil; Rf = 0.44, 10% EtOAc/Hexanes; isolated yield major 24% (0.035g, 0.13 mmol) as an oil; Rf = 0.37, 10% EtOAc/Hexanes; purified by column chromatography eluting with 5% EtOAc/Hexanes.

Data analysis for minor diastereomer (**4-22c**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.21-7.15 (m, 2H), 7.01-6.95 (m, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.85 (dd, J = 11.4, 6.5 Hz, 1H), 2.54 (dt, J = 14.0, 8.0 Hz, 1H), 2.10-1.77 (m, 5H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.9, 173.0, 162.1 (d, $^{1}J_{CF}$ = 246.1 Hz), 133.2 (d, $^{4}J_{CF}$ = 3.4 Hz), 130.0 (d, $^{3}J_{CF}$ = 7.9 Hz), 115.5 (d, $^{2}J_{CF}$ = 21.1 Hz), 66.3, 61.8, 52.9, 31.5, 30.6,

23.9, 14.3; **^{19}F{^{1}H}** (376 MHz, $CDCl_3$) δ -115.2; **IR** (cm^{-1}) 2960, 1740, 1712, 1510, 1224; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{17}FO_3$ 264.1162 (M^+), found 264.1149.

Data analysis for major diastereomer (**4-22d**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80, 7.20-7.15 (m, 2H), 6.97-6.91 (m, 2H), 3.87 (dd, J = 10.3, 7.5 Hz, 1H), 3.79 (dq, J = 10.7, 7.1 Hz, 1H), 3.68 (dq, J = 10.7, 7.1 Hz, 1H), 2.42 (ddd, J = 13.8, 10.7, 7.7 Hz, 1H), 2.17-2.08 (m, 3H), 2.05-1.97 (m, 1H), 1.65-1.52 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.5, 171.1, 161.9 (d, $^{1}J_{CF}$ = 245.2 Hz), 135.7 (d, $^{4}J_{CF}$ = 3.3 Hz), 130.1 (d, $^{3}J_{CF}$ = 7.9 Hz), 114.9 (d, $^{2}J_{CF}$ = 21.2 Hz), 69.1, 61.3, 48.7, 32.7, 31.6, 24.5, 13.7; **^{19}F{^{1}H}** (376 MHz, $CDCl_3$) δ -115.9; **IR** (cm^{-1}) 2960, 1712, 1510, 1220; **HRMS** (EI) *m/z* calc'd for $C_{15}H_{17}FO_3$ 264.1162 (M^+), found 264.1152.

(±)-Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-1-formylcyclopentanecarboxylate (4-22e,f)

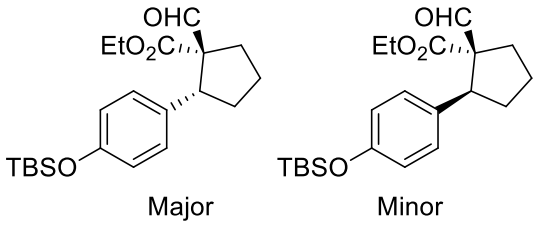


Reagents employed: cyclopentene (**4-17i**) (0.071g, 0.24 mmol), Pd/C (0.025g, 0.24 mmol), methanol (4ml): crude yield (mixture of diastereomers) 90% (0.064g, 0.22 mmol); isolated yield minor 15% (0.011g, 0.04 mmol) as an oil; Rf = 0.37, 5% EtOAc/Hexanes; isolated yield major 42% (0.03g, 0.1 mmol) as an oil; Rf = 0. 31, 5% EtOAc/Hexanes; purified by column chromatography eluting with 5% EtOAc/Hexanes.

Data analysis for minor diastereomer (**4-22e**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 6.75-6.66 (m, 3H), 5.93 (s, 2H), 4.25 (qd, J = 7.1, 0.8 Hz, 2H), 3.81 (dd, J = 11.3, 6.5 Hz, 1H), 2.53 (dt, J = 13.9, 8.0 Hz, 1H), 2.07-1.76 (m, 5H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.1, 173.2, 147.9, 146.8, 131.2, 121.5, 108.8, 108.3, 101.9, 66.2, 61.7, 53.5, 31.5, 30.4, 23.9, 14.3; **IR** (cm^{-1}) 2958, 1737, 1711, 1488, 1233; **HRMS** (EI) *m/z* calc'd for $C_{16}H_{18}O_5$ 290.1154 (M^+), found 290.1147.

Data analysis for major diastereomer (**4-22f**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.71-6.67 (m, 3H), 5.89 (s, 2H), 3.89-3.74 (m, 3H), 2.39 (ddd, J = 13.7, 10.4, 7.8 Hz, 1H), 2.15-2.05 (m, 3H), 2.03-1.95 (m, 1H), 1.63-1.51 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.9, 171.2, 147.4, 146.5, 133.7, 121.7, 109.1, 107.9, 101.0, 69.0, 61.3, 49.7, 32.7, 31.3, 24.3, 13.8; **IR** (cm^{-1}) 2959, 1711, 1487, 1225; **HRMS** (EI) *m/z* calc'd for $C_{16}H_{18}O_5$ 290.1154 (M^+), found 290.1150.

(±)-Ethyl 2-(4-((tert-butyldimethylsilyl)oxy)phenyl)-1-formylcyclopentanecarboxylate (4-22g,h)



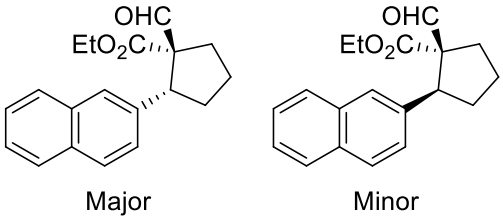
Reagents employed: cyclopentene (**4-17g**) (0.093g, 0.25 mmol), Pd/C (0.027g, 0.25 mmol), methanol (4ml): crude yield (mixture of diastereomers) 96% (0.09g, 0.24 mmol); isolated yield minor 19% (0.018g, 0.05 mmol) as an oil; Rf = 0.34, 5% EtOAc/Hexanes; isolated yield major 24% (0.023g, 0.06 mmol) as an oil; Rf = 0.28, 5% EtOAc/Hexanes; purified by column chromatography eluting with 5% EtOAc/Hexanes.

Data analysis for minor diastereomer (**4-22g**): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.06-7.04 (AA'BB', 2H), 6.77-6.74 (AA'BB', 2H), 4.24 (qd, J = 7.2, 5.9 Hz, 2H), 3.81 (dd, J = 11.7, 6.6 Hz, 1H), 2.53 (dt, J = 13.8, 8.2 Hz, 1H), 2.06-2.01 (m, 1H), 2.00-1.78 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H), 0.18 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.4, 173.3, 154.9, 129.9, 129.4, 120.1, 66.2, 61.6, 53.3, 31.4, 30.3, 25.7, 23.9, 18.3, 14.3, -4.2; **IR** (cm^{-1}) 2955, 1741, 1715, 1509, 1226; **HRMS** (EI) *m/z* calc'd for $C_{21}H_{32}O_4Si$ 376.2070 (M^+), found 376.2061.

Data analysis for major diastereomer (**4-22h**): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.83, 7.07-7.04 (AA'BB', 2H), 6.73-6.71 (AA'BB', 2H), 3.81-3.77 (m, 2H), 3.66 (dq, J = 10.7, 7.2 Hz, 1H), 2.39 (ddd, J = 13.7, 10.6, 7.9 Hz, 1H), 2.16-2.07 (m, 3H), 2.03-1.98 (m, 1H), 1.62-1.53 (m, 1H), 0.96 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H), 0.16 (s, 6H); **^{13}C NMR** (150

MHz, $CDCl_3$) δ 198.1, 171.3, 154.7, 132.6, 129.5, 119.7, 69.1, 61.2, 49.5, 32.8, 31.3, 25.8, 24.5, 18.3, 13.8, -4.3; **IR** (cm^{-1}) 2931, 1741, 1714, 1510, 1252; **HRMS** (EI) *m/z* calc'd for $C_{21}H_{32}O_4Si$ 376.2070 (M^+), found 376.2063.

(±)-Ethyl 1-formyl-2-(naphthalen-2-yl)cyclopentanecarboxylate (4-22i,j)



Reagents employed: cyclopentene (**4-17l**) (0.09g, 0.31 mmol), Pd/C (0.032g, 0.31 mmol), methanol (5ml): crude yield (mixture of diastereomers) 93% (0.085g, 0.28 mmol); isolated yield minor 12% (0.011g, 0.04 mmol) as an oil; Rf = 0.45, 10% EtOAc/Hexanes; isolated yield major 45% (0.041g, 0.14 mmol) as an oil; Rf = 0.41, 10% EtOAc/Hexanes; purified by column chromatography eluting with 5% EtOAc/Hexanes.

Data analysis for minor diastereomer (**4-22i**): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.82-7.77 (m, 3H), 7.67 (br s, 1H), 7.49-7.44 (m, 2H), 7.34 (dd, J = 8.5, 1.9 Hz, 1H), 4.27 (qd, J = 7.1, 1.9 Hz, 2H), 4.06 (dd, J = 11.6, 6.6 Hz, 1H), 2.62 (dt, J = 14.1, 8.4 Hz, 1H), 2.19-2.13 (m, 1H), 2.11-2.02 (m, 3H), 1.93-1.85 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 199.9, 173.2, 135.1, 133.4, 132.7, 128.3, 127.9, 127.7, 127.2, 126.6, 126.4, 126.0, 66.5, 61.8, 53.9, 31.4, 30.7, 24.1, 14.3 **IR** (cm^{-1}) 2957, 1738, 1717, 1245; **HRMS** (EI) *m/z* calc'd for $C_{19}H_{20}O_3$ 296.1412 (M^+), found 296.1411.

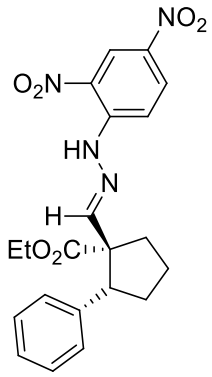
Data analysis for major diastereomer (**4-22j**) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.79-7.77 (m, 2H), 7.74 (d, J = 8.5 Hz, 1H), 7.67 (br s, 1H), 7.46-7.41 (m, 2H), 7.34 (dd, J = 8.5, 1.8 Hz, 1H), 4.04 (dd, J = 10.8, 6.8 Hz, 1H), 3.68 (dq, J = 10.7, 7.1 Hz, 1H), 3.54 (dq, J = 10.8, 7.2 Hz, 1H), 2.50 (ddd, J = 13.9, 10.5, 7.9 Hz, 1H), 2.33 (dtd, J = 12.5, 10.8, 7.2 Hz, 1H), 2.23-2.18 (m, 2H), 2.10 (dddt, J = 12.7, 7.6, 5.3, 2.4 Hz, 1H), 0.64 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 197.9, 171.1, 137.5, 133.3, 132.6, 127.8, 127.7, 127.6, 127.1, 127.0, 126.1, 125.7, 69.3, 61.2, 50.0 32.7, 31.65, 31.64, 24.6, 13.5;

IR (cm^{-1}) 2958, 1711, 1225; **HRMS** (EI) *m/z* calc'd for $C_{19}H_{20}O_3$ 296.1412 (M^+), found 296.1409.

Procedure for the formation of hydrazone derivative

Cyclopentane (**4-22b**) (0.11g, 0.45 mmol) was placed in a round bottom flask under an argon gas atmosphere. Absolute ethanol (7ml) was added followed by $MgSO_4$ (0.13g, 1.1 mmol) and the mixture was stirred. To the mixture was added 2,4-dinitophenylhydrazine (0.13g, 0.58 mmol) and the reaction was stirred for five hours. The reaction was concentrated under reduced pressure, re-dissolved in DCM, pre-absorbed onto silica and purified by column chromatography eluting with 10% EtOAc/Hexanes providing hydrazone (**4-24**) as a bright yellow solid; yield = 78% (0.15g, 0.35 mmol); Rf = 0.32, 10% EtOAc/Hexanes; melting point = 133.5-134.8 °C.

(±)-(1R,2R)-ethyl 1-((E)-(2-(2,4-dinitrophenyl)hydrazono)methyl)-2-phenylcyclopentanecarboxylate (4-24)



^{1}H NMR (600 MHz, $CDCl_3$) δ 11.15 (s, 1H), 9.15 (d, J = 2.5 Hz, 1H), 8.35 (dd, J = 9.6, 2.6, 0.7 Hz, 1H), 7.98 (d, J = 9.5 Hz, 1H), 7.89 (br s, 1H), 7.30-7.27 (m, 2H), 7.25-7.22 (m, 3H), 3.82-3.72 (m, 3H), 2.55 (ddd, J = 13.5, 9.3, 8.3 Hz, 1H), 2.41-2.35 (m, 1H), 2.34-2.29 (m, 1H), 2.22-2.12 (m, 2H), 1.90-1.82 (m, 1H), 0.91 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 153.1, 145.3, 139.9, 138.3, 130.2, 129.3, 128.4, 128.3, 127.3, 123.6, 116.6, 61.6, 61.3, 54.5, 34.1, 32.0, 24.3, 13.8; **IR** (cm^{-1}) 3277, 2954, 1716, 1615, 1585, 1496, 1136; **HRMS** (EI) *m/z* calc'd for $C_{21}H_{22}N_4O_6$ 426.1539 (M^+), found 426.1544.

4.5.3 X-ray analysis data

Experimental for C21H22N4O6 (b20024)

Data Collection and Processing. The sample (b20024) was submitted by Mathew Piotrowski of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of 9904 reflections with $4.96° < 2\theta < 59.34°$. The data collection strategy was a number of ω and φ scans which collected data up to 64.12° (2θ). The frame integration was performed using SAINT. The resulting raw data was scaled and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.

Structure Solution and Refinement. The structure was solved by using a dual space methodology using the SHELXT program. All non-hydrogen atoms were obtained from the initial solution. The hydrogen atoms were introduced at idealized positions. The carbon bound hydrogen atoms were allowed to ride on their parent carbon while the nitrogen bound hydrogen atoms were allowed to refine isotropically.

Pseudo-symmetry. The structure exhibits a high degree of pseudo-symmetry. The structure was solved and refined as primitive monoclinic with a space group of P 21 containing two symmetry independent molecules in the asymmetric unit (designated as A and B). The structure can also be reasonably refined as primitive orthorhombic with a space group assignment of P na21 with one molecule in the asymmetric unit. However, the systematic absences for the n and a glide planes exhibit numerous and significant violations. There were 253 out of 1715 and 117 out of 416 reflections which had intensities above $3\sigma(I)/I$ for the n and a glide planes absences respectively. For this reason, the lower symmetry structure was chosen. It is necessary to note that the ADDSYM (missing symmetry) routine in PLATON gives a 100% match for a P na21 structure.

The structural model was fit to the data using full matrix least-squares based on F2. The refinement model included twinning by pseudo-merohedry. The twin law, a mirror plane across the (100), was derived by the COSET program. One of the nitro groups on each of the symmetry independent molecules exhibits a disorder which leads to two distinct positions for one of the oxygen atoms. For the A molecule the occupancy of the predominant conformer was 0.62(8) while for the B molecule the predominant conformer had an occupancy of 0.532(15). The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELX suite of crystallographic software. Graphic plots were produced using the Mercury program suite. Additional information and other relevant literature references can be found in the reference section of this website (http://xray.chem.uwo.ca).

1 . Bruker-AXS, SAINT version 2013.8, **2013**, Bruker-AXS, Madison, WI 53711, USA

2 . Bruker-AXS, SADABS version 2012.1, **2012**, Bruker-AXS, Madison, WI 53711, USA

3 . Sheldrick, G. M., *Acta Cryst.* **2015**, *A71*, 3-8

4 . Spek, A. L., *J. Appl. Cryst*., **2003**, *36*, 7-13

5 Boyle, P. D. *J. Appl. Cryst*., **2014**, *47*, 467-470

6 . Sheldrick, G. M., *Acta Cryst.* **2015**, *C71*, 3-8

7 . Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J. and Wood, P. A. *J. Appl. Cryst.*, **2008**, *41*, 466-470

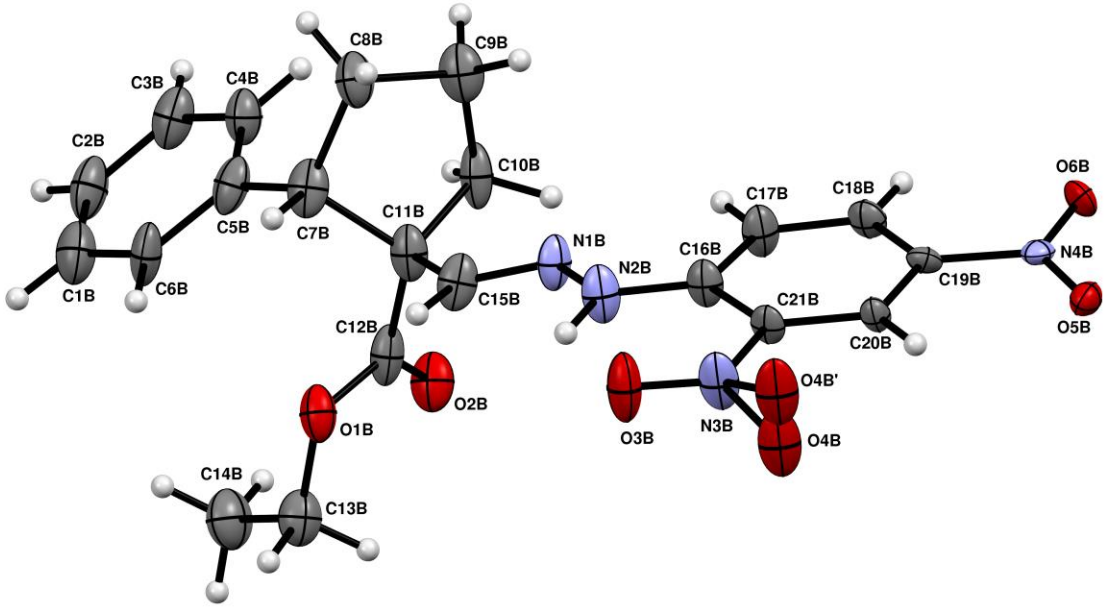


Figure 4-6. ORTEP drawing of *b20024 molecule B* showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity. The disordered oxygen position is designated as O4B'.

Table 4. Summary of crystal data for *b20024*

Formula	$C_{21}H_{22}N_4O_6$
Formula Weight (*g/mol*)	426.42
Crystal Dimensions (*mm*)	0.423 × 0.268 × 0.043
Crystal Color and Habit	yellow plate
Crystal System	monoclinic
Space Group	P 2_1
Temperature, K	110
a, Å	9.2001(19)
b, Å	6.1392(14)
c, Å	36.280(9)
a,°	90

b,°	90.137(11)
g,°	90
V, $Å^3$	2049.1(8)
Number of reflections to determine final unit cell	9904
Min and Max 2q for cell determination, °	4.96, 59.34
Z	4
F(000)	896
r (*g/cm*)	1.382
l, Å, (MoKa)	0.71073
m, (cm^{-1})	0.103
Diffractometer Type	Bruker Kappa Axis Apex2
Scan Type(s)	phi and omega scans
Max 2q for data collection, °	64.12
Measured fraction of data	0.999
Number of reflections measured	55522
Unique reflections measured	12633
R_{merge}	0.0566
Number of reflections included in refinement	12633
Cut off Threshold Expression	I > 2sigma(I)
Structure refined using	full matrix least-squares using F^2
Weighting Scheme	$w=1/[sigma^2(Fo^2)+(0.0471P)^2+0.8526P]$ where $P=(Fo^2+2Fc^2)/3$
Number of parameters in least-squares	582
R_1	0.0548
wR_2	0.1154

R_1 (all data)	0.0722
wR_2 (all data)	0.1239
GOF	1.034
Maximum shift/error	0.000
Min & Max peak heights on final DF Map (e^-/Å)	-0.325, 0.278

Where:

R1 = □(|Fo| - |Fc|) / □ Fo

wR2 = [□(w(Fo2 - Fc2)2) / □(w Fo4)]½

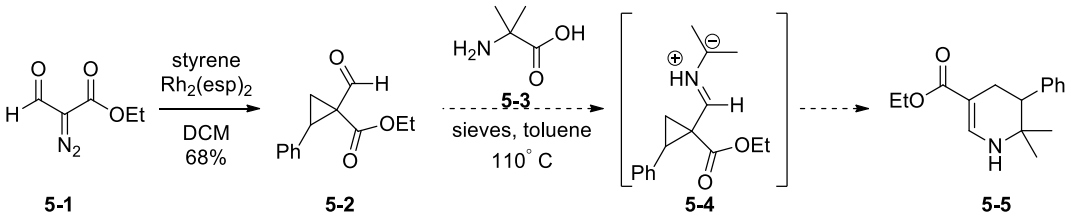
GOF = [□(w(Fo2 - Fc2)2) / (No. of reflns. - No. of params.)]½

Chapter 5

5 Future Work and Summary

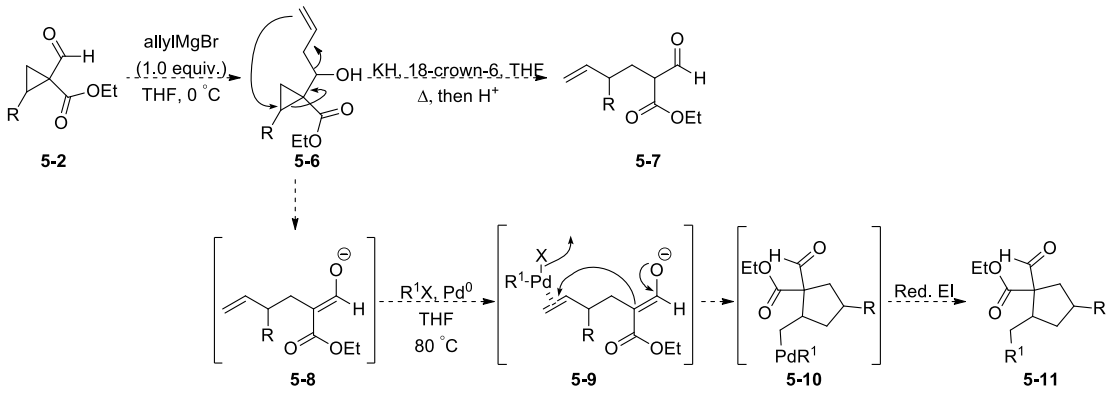
5.1 Future work

The use of formyldiazoacetate (**5-1**) towards the synthesis of DA cyclopropane (**5-2**) can offer novel and underexplored reactivity that can generate compounds of high synthetic interest. DA cyclopropane (**5-2**) can be obtained in modest yields under metal carbenoid conditions. Azomethine ylides could be formed via condensation between the aldehyde on the cyclopropane (**5-2**) and an amine (**5-3**). Upon heating, this would result in a decarboxylation generating the desired ylide (**5-4**) followed by ring-opening of the cyclopropane forming various tetrahydropyridine derivatives (**5-5**) (Scheme **5-1**)[170].



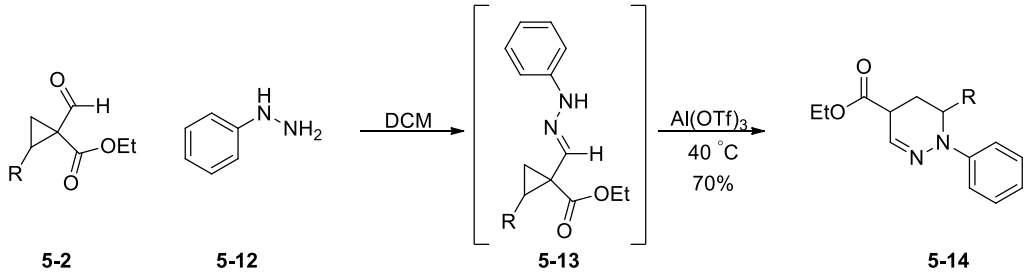
Scheme 5-1. Generation of aldehyde/ester DA cyclopropane and subjecting it to azomethine ylide formation/ring-opening forming tetrahydropyridine derivatives

Anionic oxy-Cope rearrangements could also be explored with DA cyclopropane (**5-2**). Reacting cyclopropane (**5-2**) with allylmagnesium bromide would generate allyl alcohol (**5-6**). Deprotonating the alcohol with KH in the presence of 18-crown-6, an oxy-Cope rearrangement would occur, resulting in ring-opened products such as (**5-7**). A one-pot procedure to functionalized cyclopentanes could be possible as well. Instead of isolating the ring-opened product (**5-8**), a palladium mediated cyclization (**5-9**) in the presence of aryl or alkenyl halides followed by a reductive elimination (**5-10**) would furnish cyclopentane compounds (**5-11**) (Scheme **5-2**)[171,172].



Scheme 5-2. Anionic oxy-Cope rearrangement of DA cyclopropane and possible one-pot procedure to functionalized cyclopentanes

Recently, treatment of DA cyclopropane (**5-2**) with phenylhydrazine (**5-12**) forming hydrazone derivatives (**5-13**) has been shown to provide tetrahydropyridazines (**5-14**) in moderate to good yields[173,174] (Scheme **5-3**). The conditions that provided the best results thus far is with the use of 10 mol% of $Al(OTf)_3$ in refluxing DCM. Further conditions need to be tested in order to improve the yields, more examples need to be synthesized, and the stereochemistry around the tetrahydropyridazine ring needs to be determined.



Scheme 5-3. Intramolecular ring-opening of hydrazone derived cyclopropanes to tetrahydropyridazines

5.2 Summary

The work presented within this thesis describes new ways of synthesizing sought after heterocycles and carbocycles such as pyrrolidines, dihydropyrroles, dihydrofurans, cyclopentenes, and dihydrooxepines. Beginning with the (vinylogous) Cloke-Wilson rearrangement, the required vinylcyclopropyl aldehyde (**5-16**) was obtained in a single step which underwent spontaneous rearrangement *in situ* to either dihydrofurans (**5-17**) or

2,5-dihydrooxepines (**5-18**) depending on the 1,3-diene system used (**5-15**). Each of the heterocycles synthesized were capable of being transformed to other dihydrofuran derivatives (**5-17**, **5-19**), dihydropyrroles (**5-20**, **5-21**) or cyclopentenes (**5-22**) with careful choice of solvent, temperature, and catalyst (Figure **5-1**).

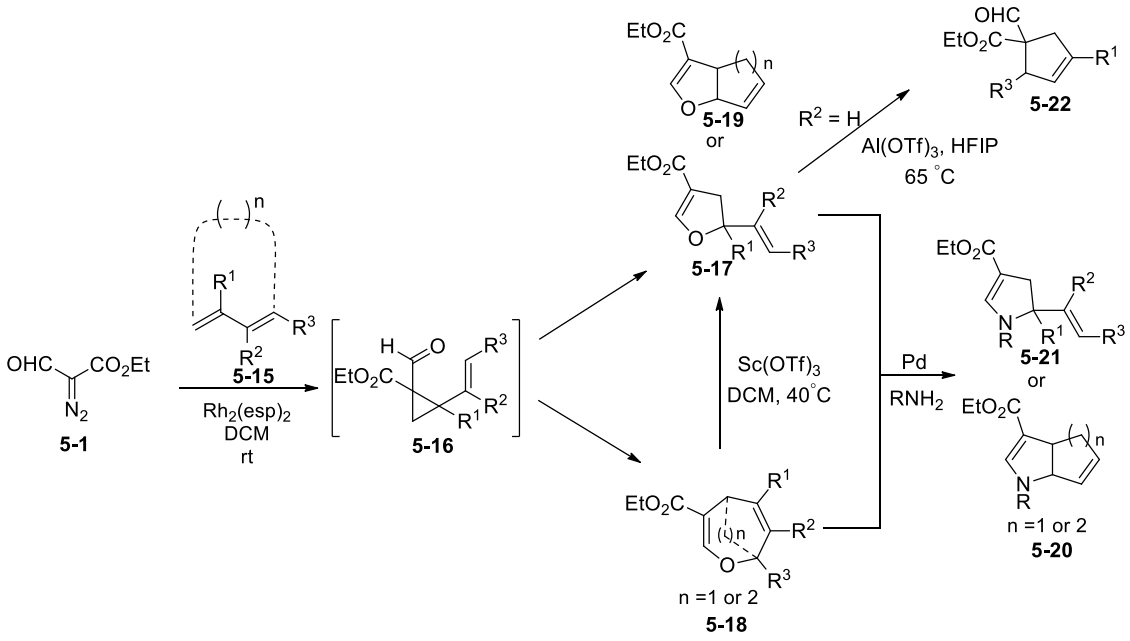


Figure 5-1. Synthesis of dihydrofurans and 2,5-dihydrooxepines via (vinylogous)-Cloke-Wilson rearrangement and subsequent transformations to dihydrofurans, dihydropyrroles and cyclopentenes

With the successful formation of dihydropyrroles, one of the scaffolds (**5-23**) caught our attention as it was deemed a viable synthetic precursor to target kainic acid. This natural molecule possesses important biological properties such as neuroexcitatory and excitotoxic activities that were used to create model conditions for the better understanding of common human neurological disorders. However, due to stereochemical constraints, one of the less active isomers of kainic acid, β-allokainic acid (**5-27**) was synthesized instead (Figure **5-2**).

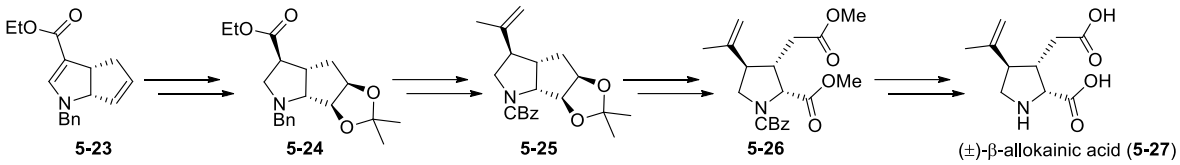


Figure 5-2. Synthetic route towards (±)-β-allokainic acid

The synthesis of cyclic systems will always dominate organic chemistry literature. Numerous bioactive natural products and pharmaceuticals contain the abovementioned cyclic systems as well as many others not mentioned within this dissertation. Therefore, discovering new methodologies towards carbocycles and heterocycles is of value in the synthetic community. The reader may ask themselves who cares about this "random" heterocyclic or carbocyclic compound and why is it important? The ability to easily synthesize sought after structural motifs, such as pyrrolidines and cyclopentenes, but also new and underexplored heterocycles or carbocycles can have great potential in pharmaceutical industries. Unknowingly, these types of academic discoveries can potentially result in new lead compounds to combat various diseases.

5.3 References

(170) Mazzoni, M.; Franco, L.; Corvaja, C. *ChemPhysChem* **2002**, No. 6, 527–531.

(171) Bouyssi, D.; Balme, G.; Fournet, G.; Monteiro, N.; Gore, J. *Tetrahedron Lett.* **1991**, *32* (13), 1641–1644.

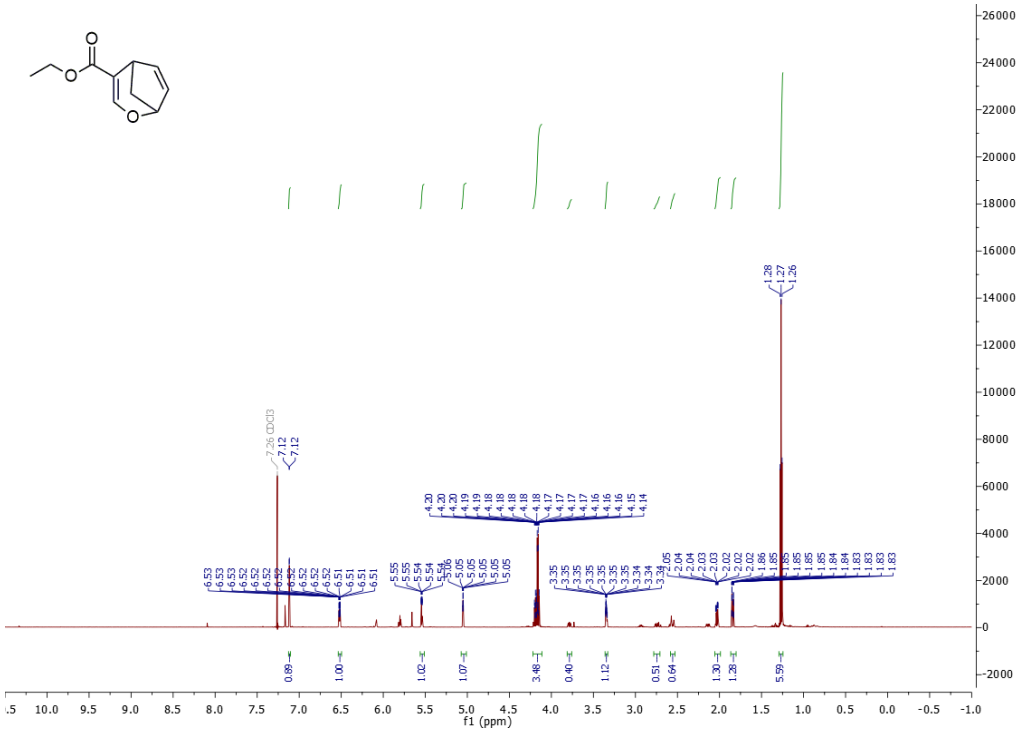
(172) Nicolai, S.; Swallow, P.; Waser, J. *Tetrahedron* **2015**, *71* (35), 5959–5964.

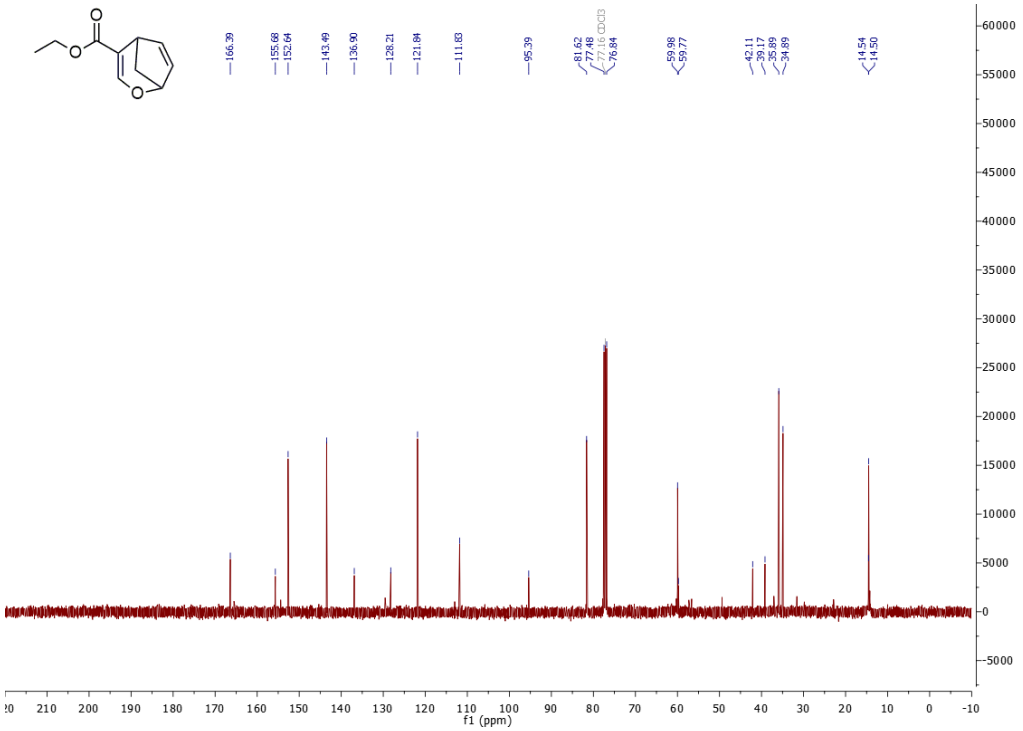
(173) Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2016**, *18* (3), 564–567.

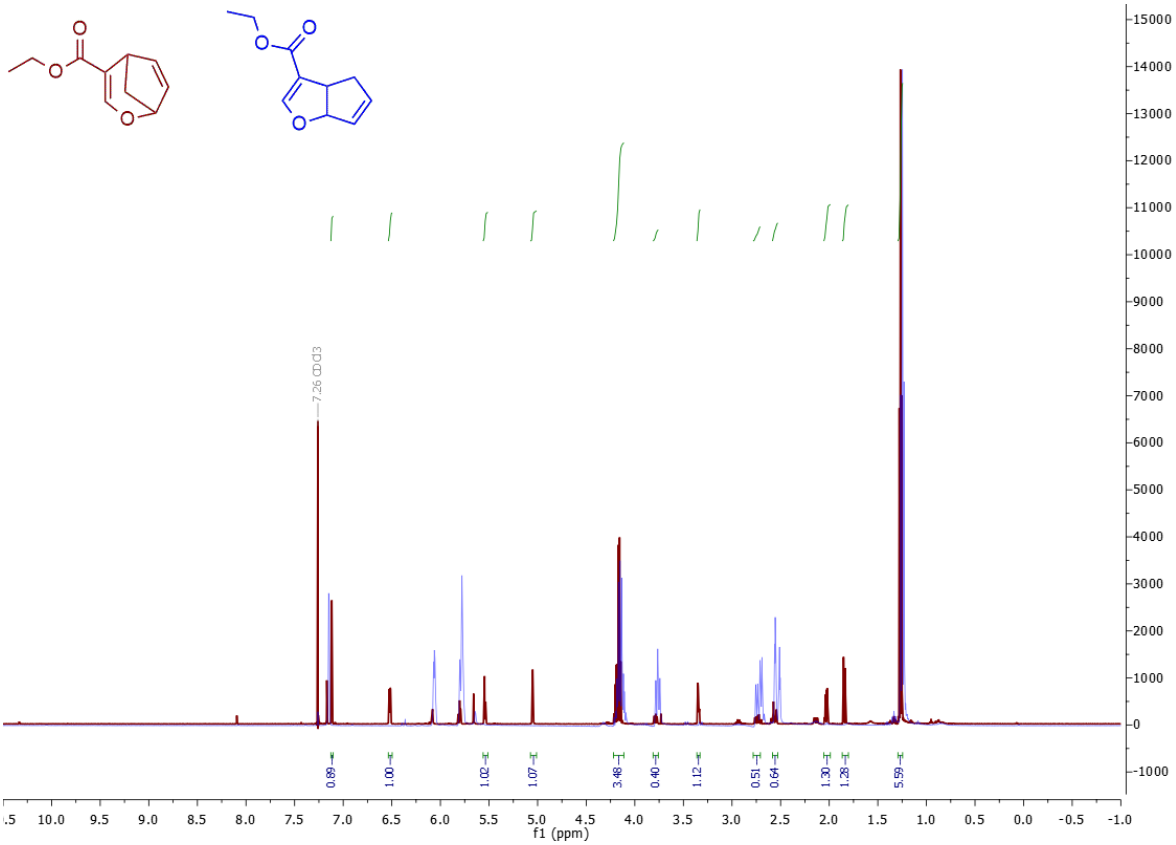
(174) Dey, R.; Kumar, P.; Banerjee, P. *J. Org. Chem.* **2018**, *83*, 5438–5449.

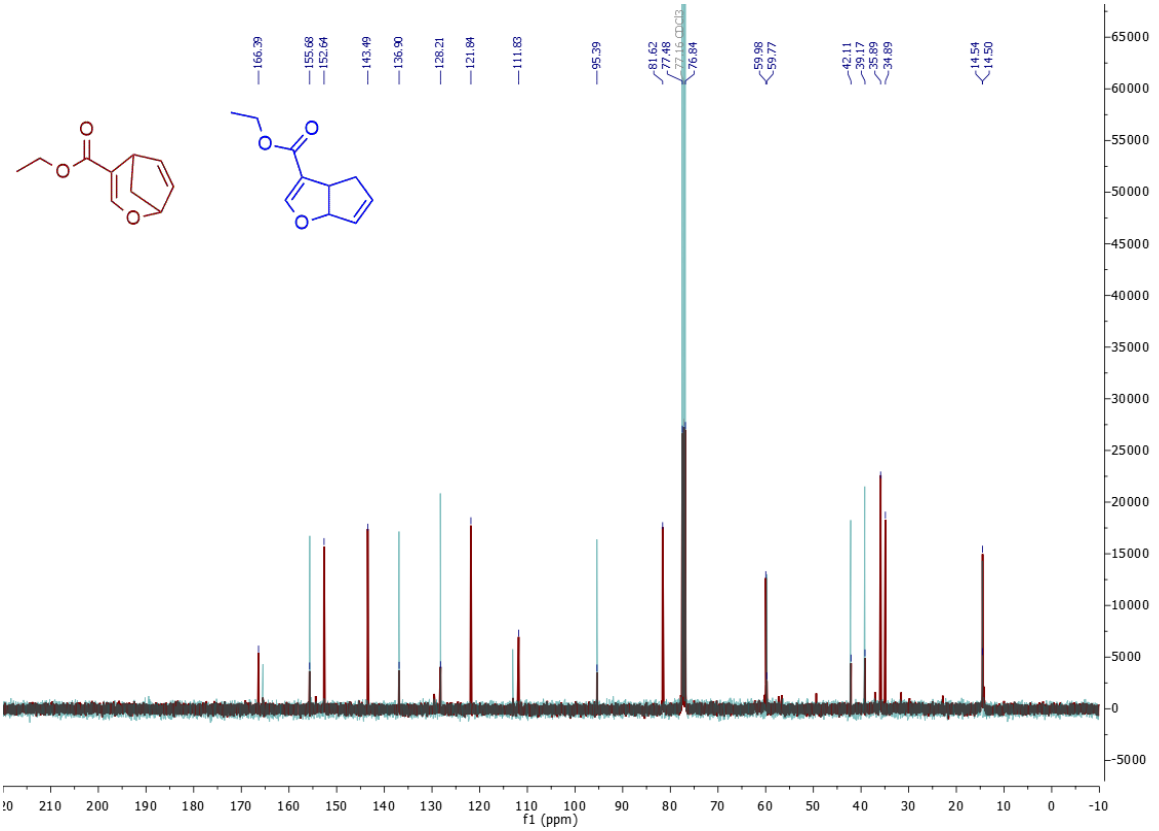
Appendices

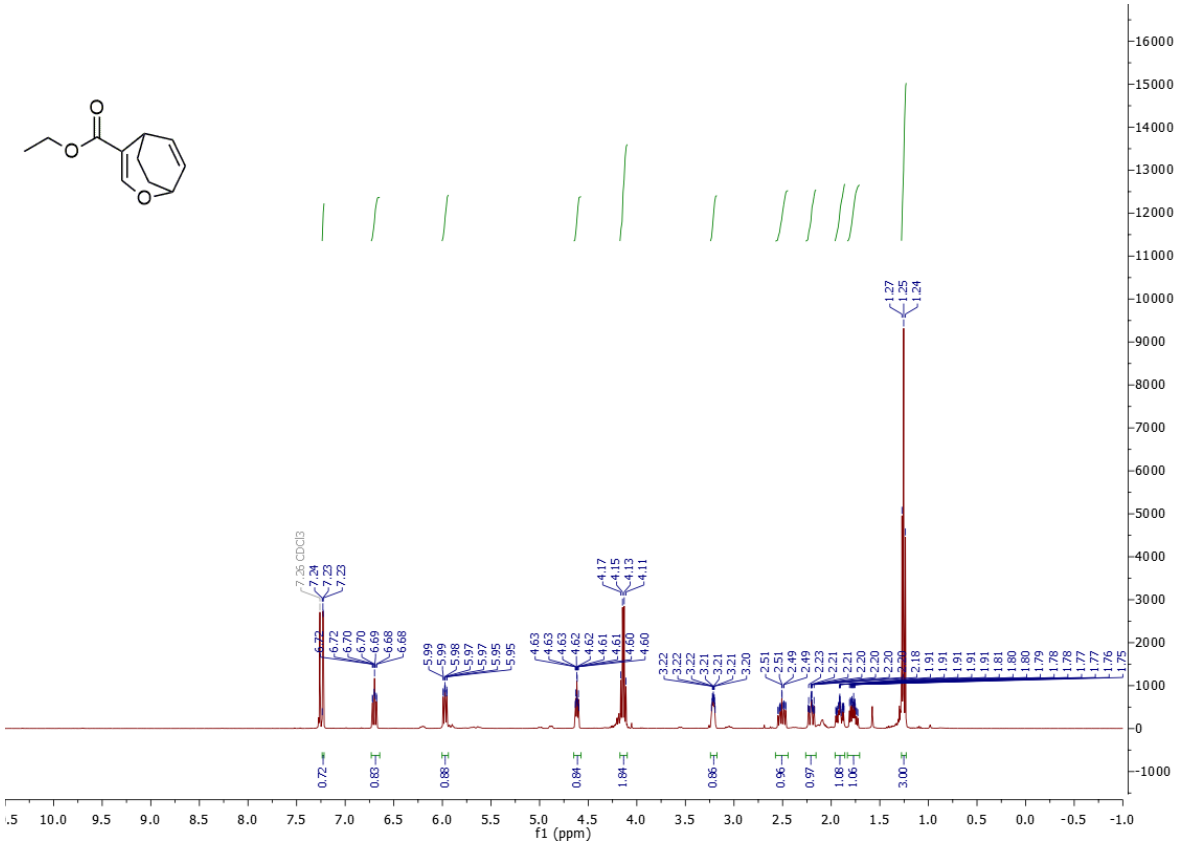
Appendix 1- Supporting Information for Chapter 2

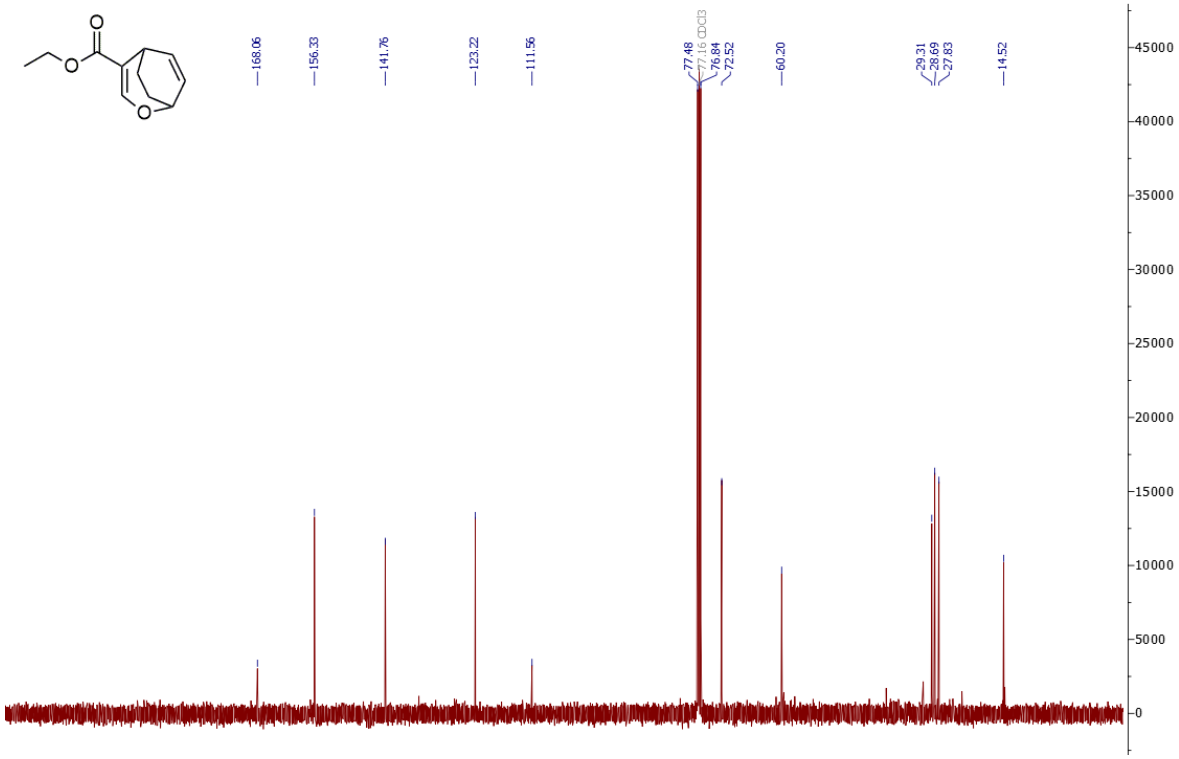


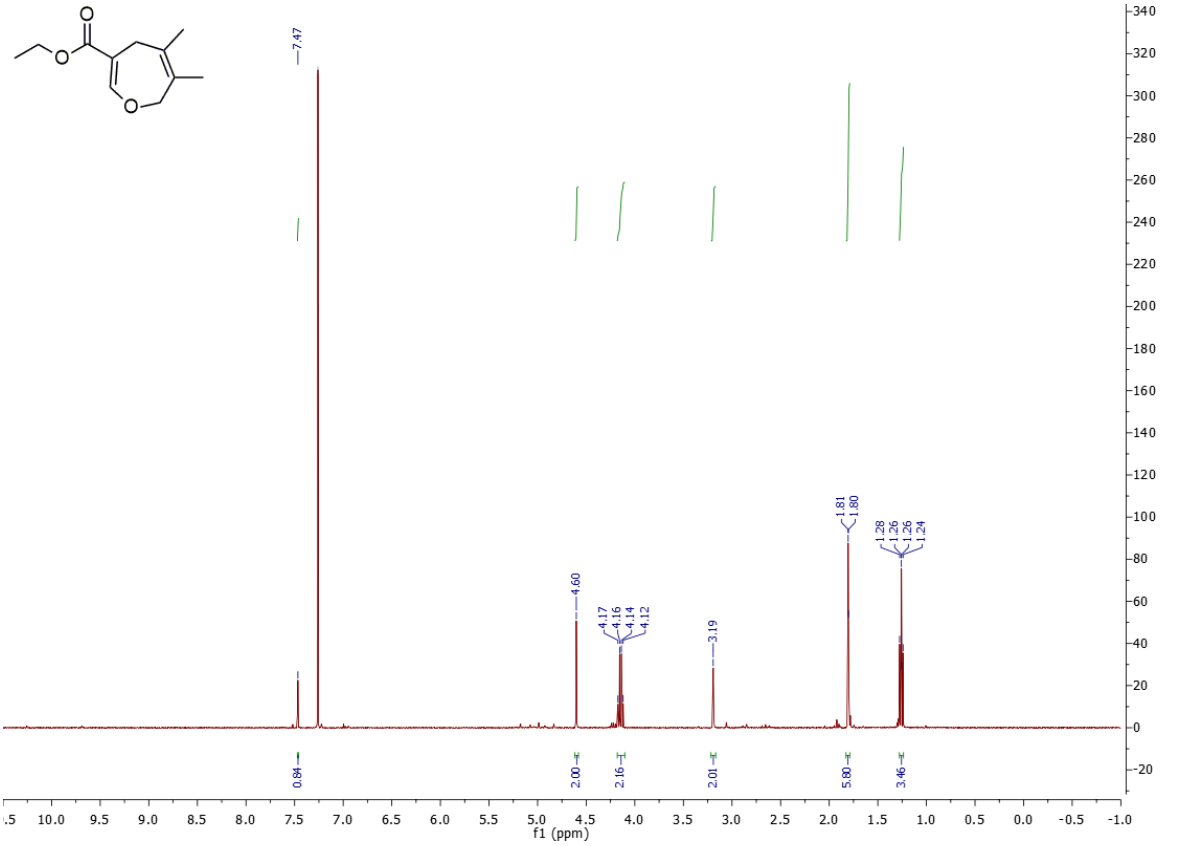


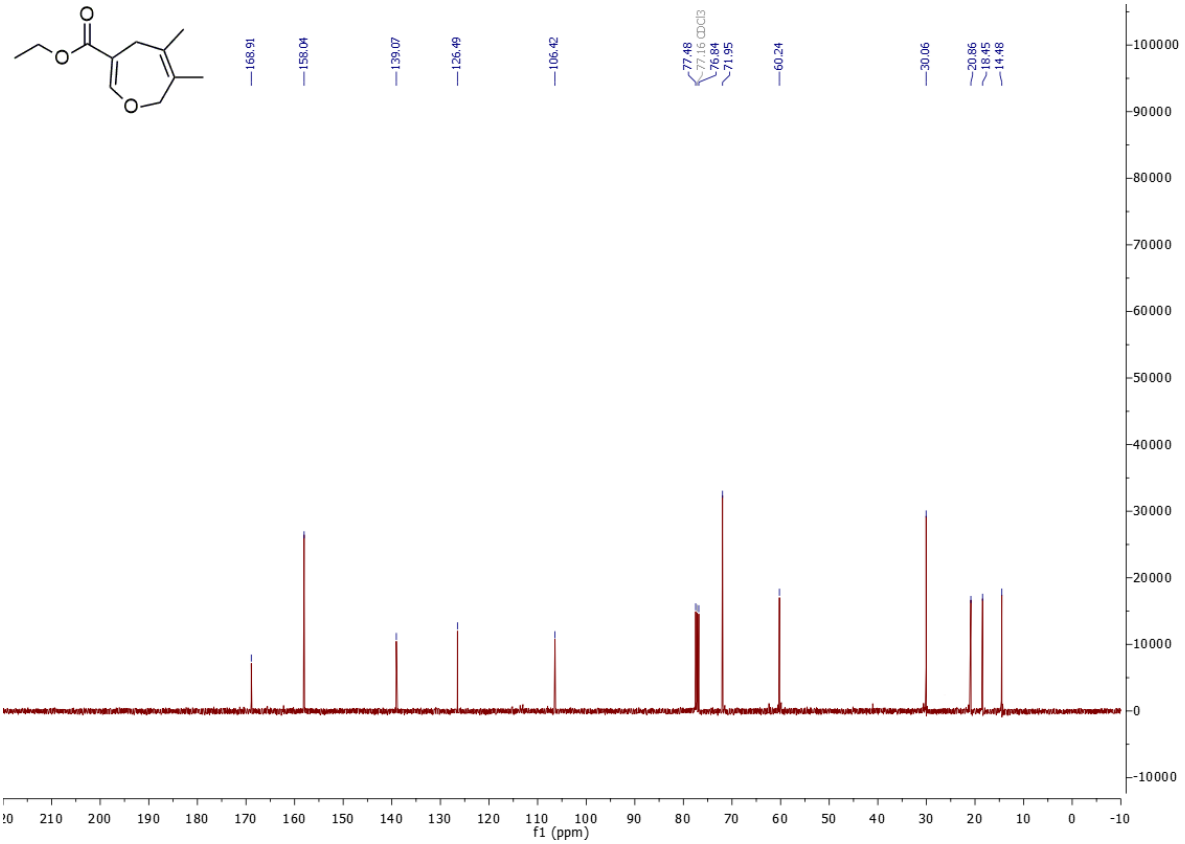

7.26 CDCl3
0.89
1.00
1.02
1.07
3.48
0.40
1.12
0.51
0.64
1.30
1.28
5.59
f1 (ppm)

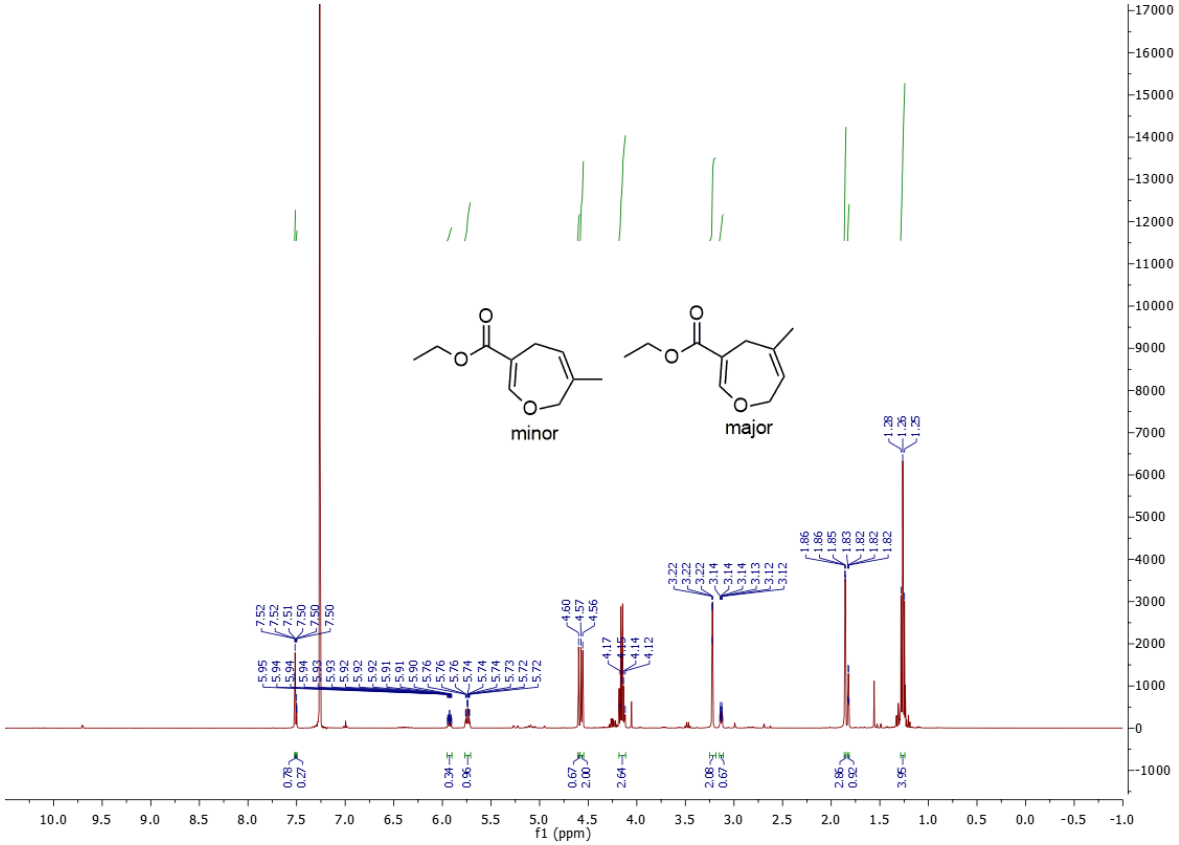

166.39
155.68
152.64
143.49
136.90
128.21
121.84
111.83
95.39
81.62
77.48
77.16 CDCl3
76.84
59.98
59.77
42.11
39.17
35.89
34.89
14.54
14.50
f1 (ppm)

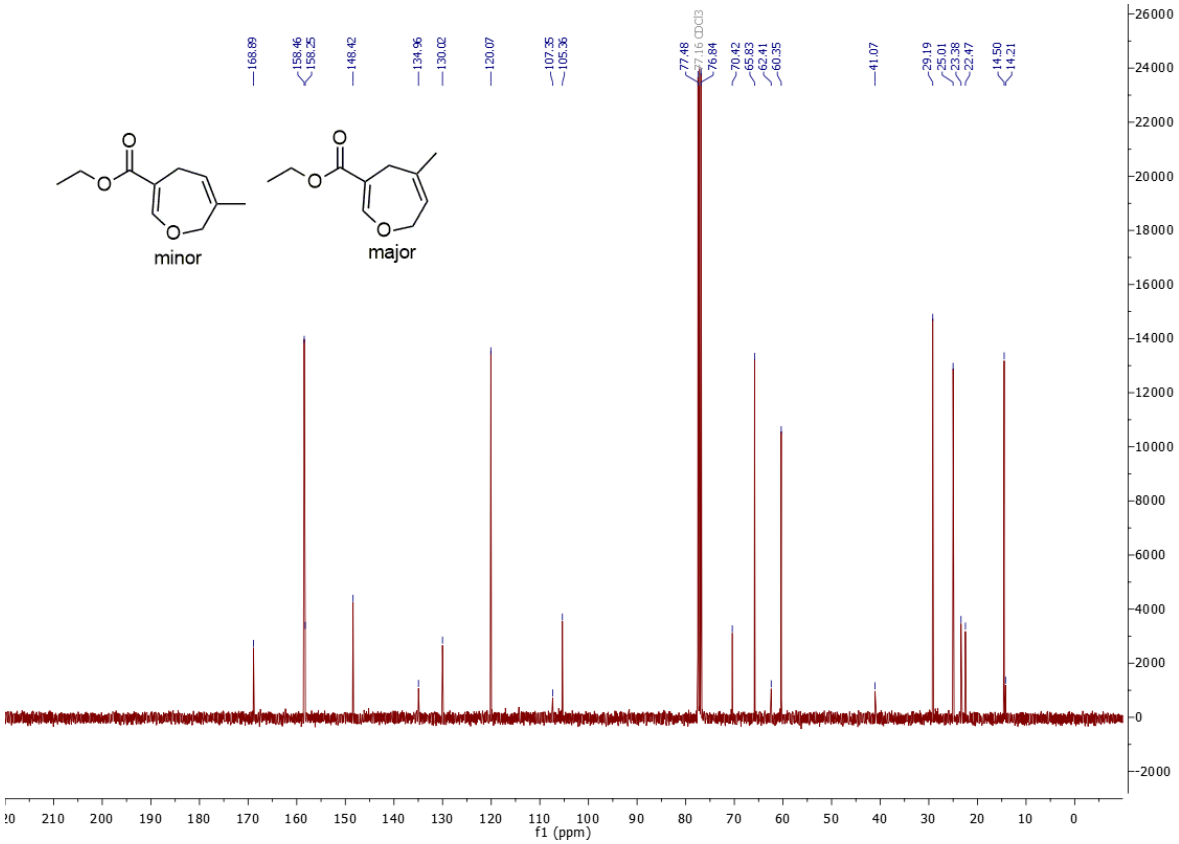

7.26 CDCl3
7.24
7.23
7.23
6.72
6.72
6.70
6.70
6.69
6.68
6.68
5.99
5.99
5.98
5.97
5.97
5.95
5.95
4.63
4.63
4.62
4.62
4.61
4.61
4.60
4.60
4.17
4.15
4.13
4.11
3.22
3.22
3.22
3.21
3.21
3.21
3.20
2.51
2.51
2.49
2.49
2.23
2.21
2.21
2.20
2.20
2.20
2.20
2.18
1.91
1.91
1.91
1.91
1.91
1.91
1.81
1.80
1.80
1.79
1.78
1.78
1.77
1.77
1.76
1.75
1.27
1.25
1.24
0.72
0.83
0.88
0.84
1.84
0.86
0.96
0.97
1.08
1.06
3.00
f1 (ppm)

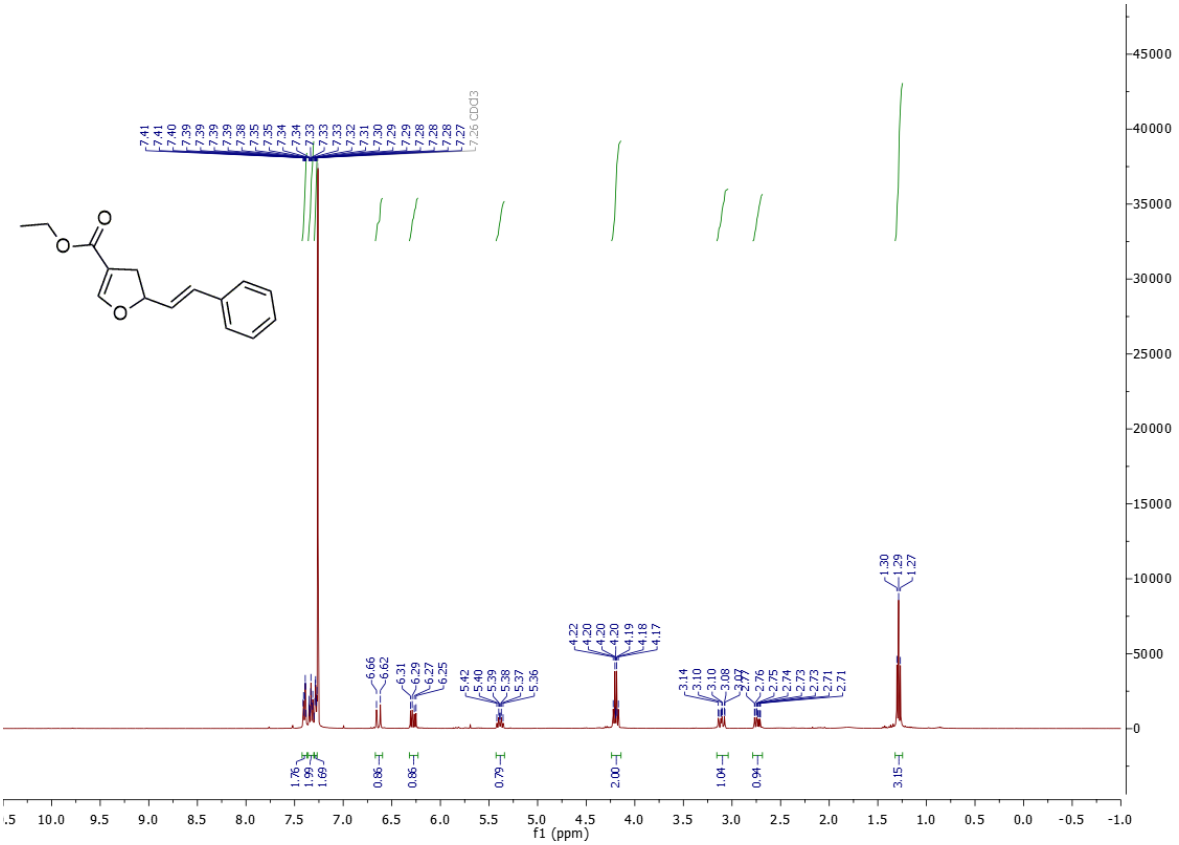

168.06
156.33
141.76
123.22
111.56
77.48
77.16 CDCl3
76.84
72.52
60.20
29.31
28.69
27.83
14.52

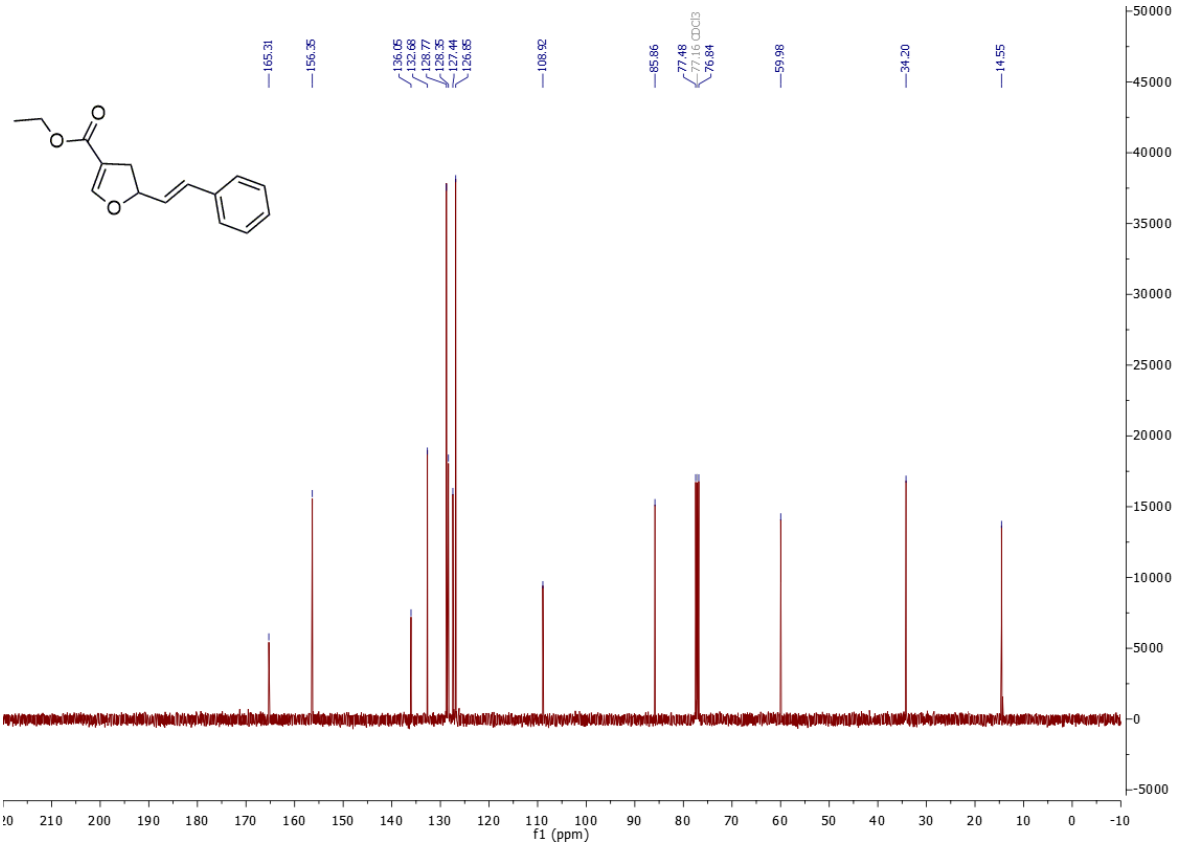

7.47
4.60
4.17
4.16
4.14
4.12
3.19
1.81
1.80
1.28
1.26
1.26
1.24
0.84
2.00
2.16
2.01
5.80
3.46
f1 (ppm)

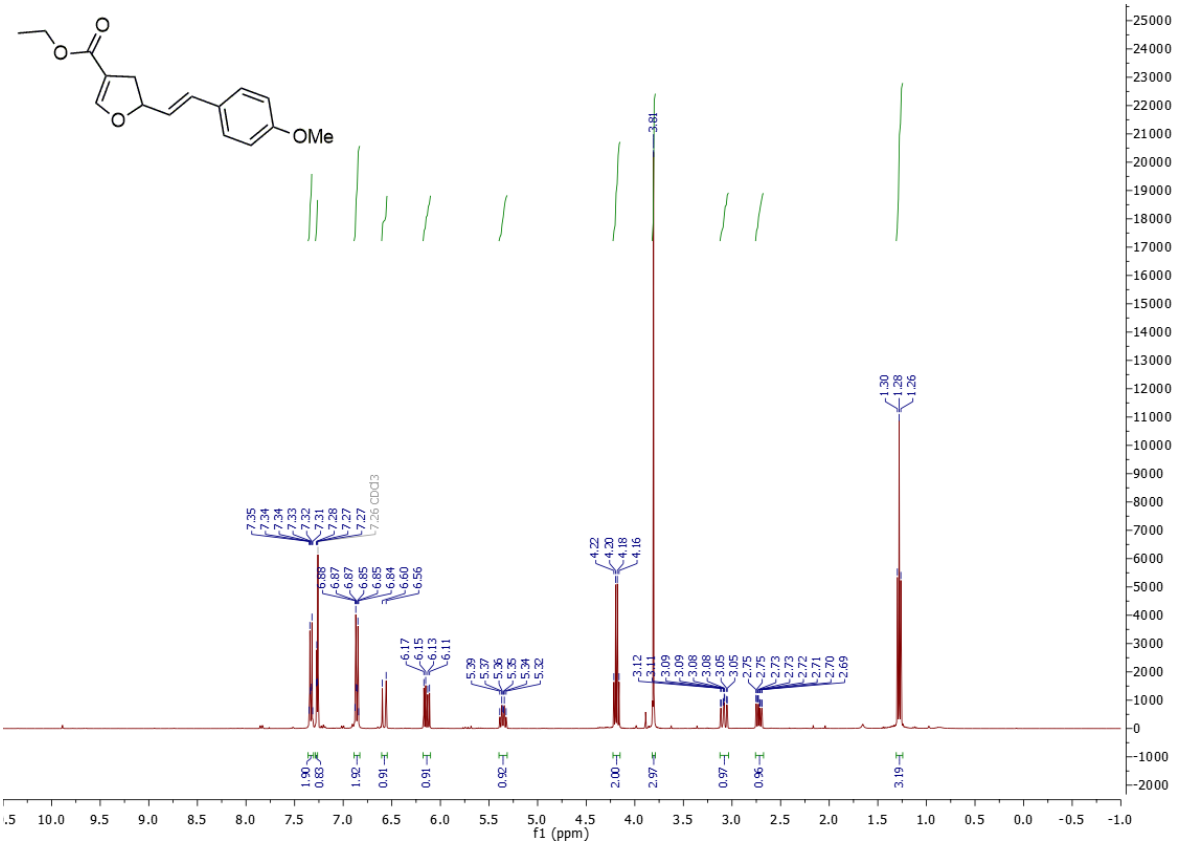

168.91
158.04
139.07
126.49
106.42
77.48
77.16 CDCl3
76.84
71.95
60.24
30.06
20.86
18.45
14.48
f1 (ppm)

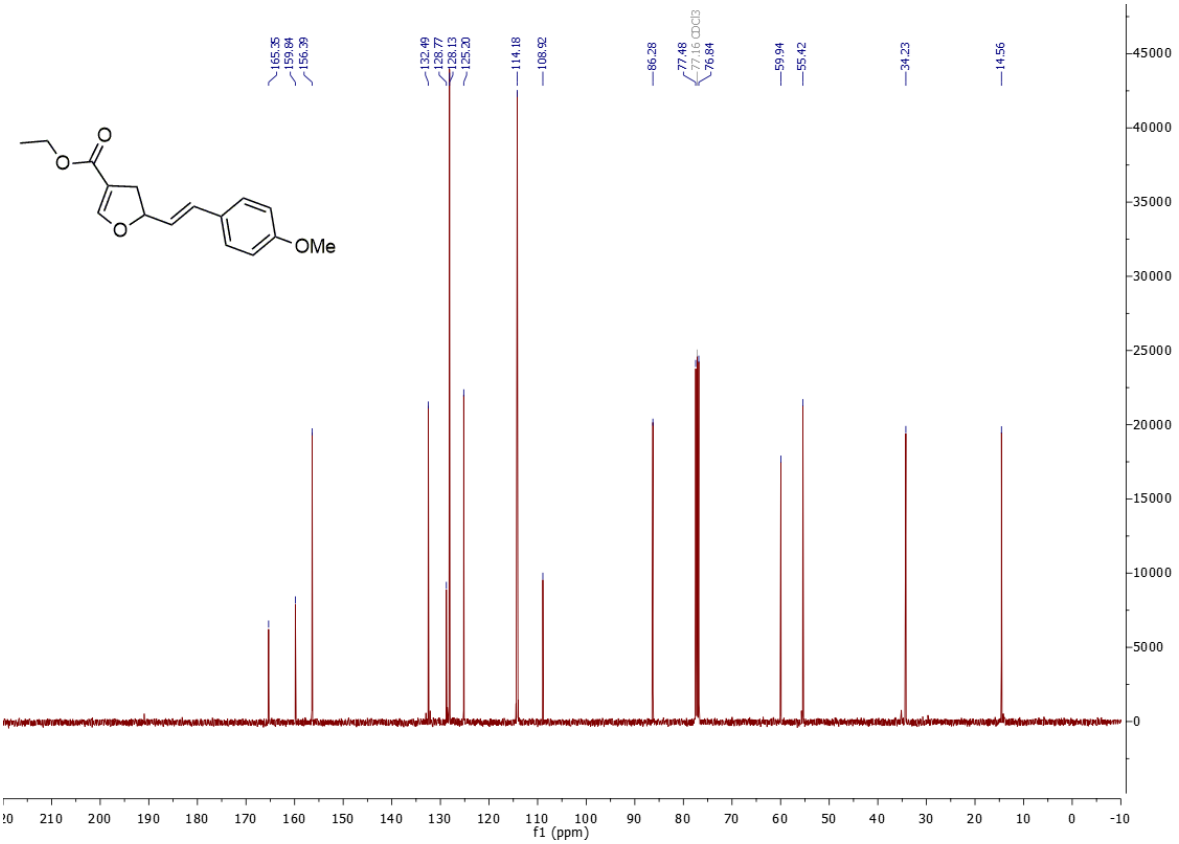

minor
major
f1 (ppm)

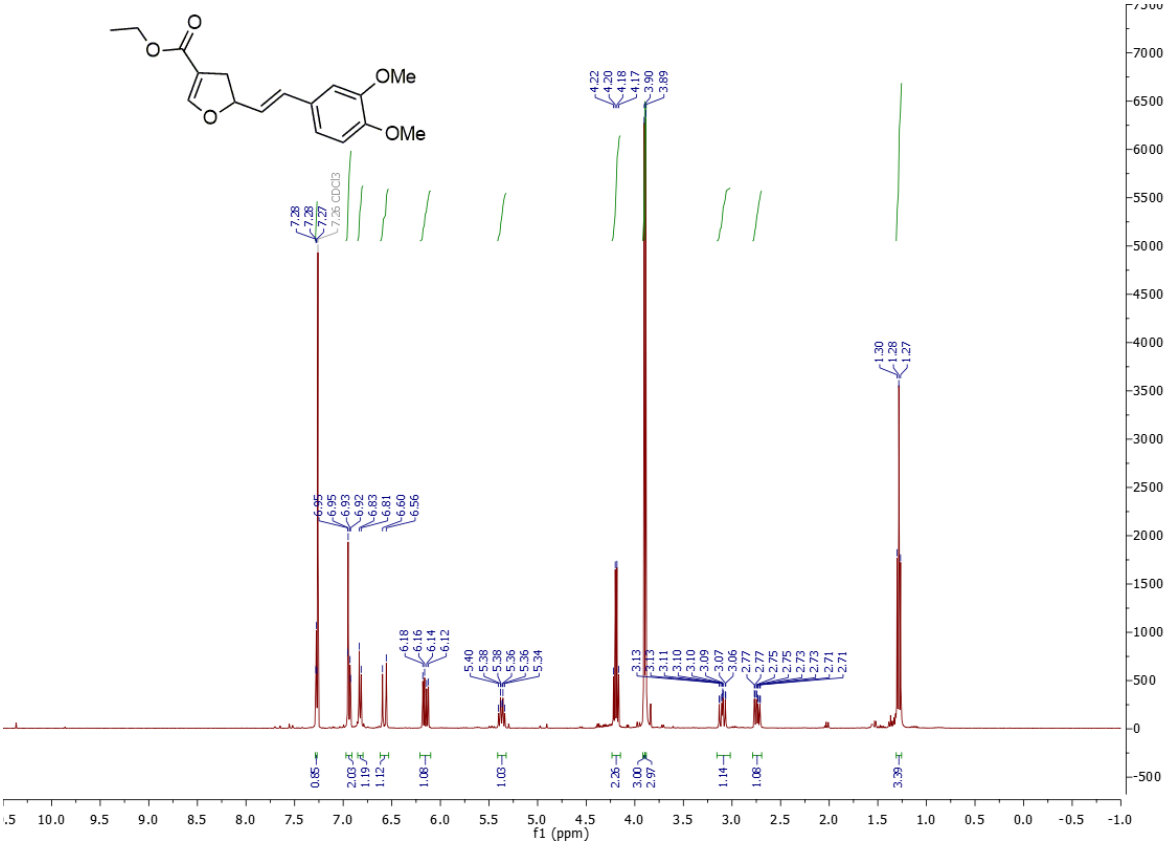

minor
major
f1 (ppm)

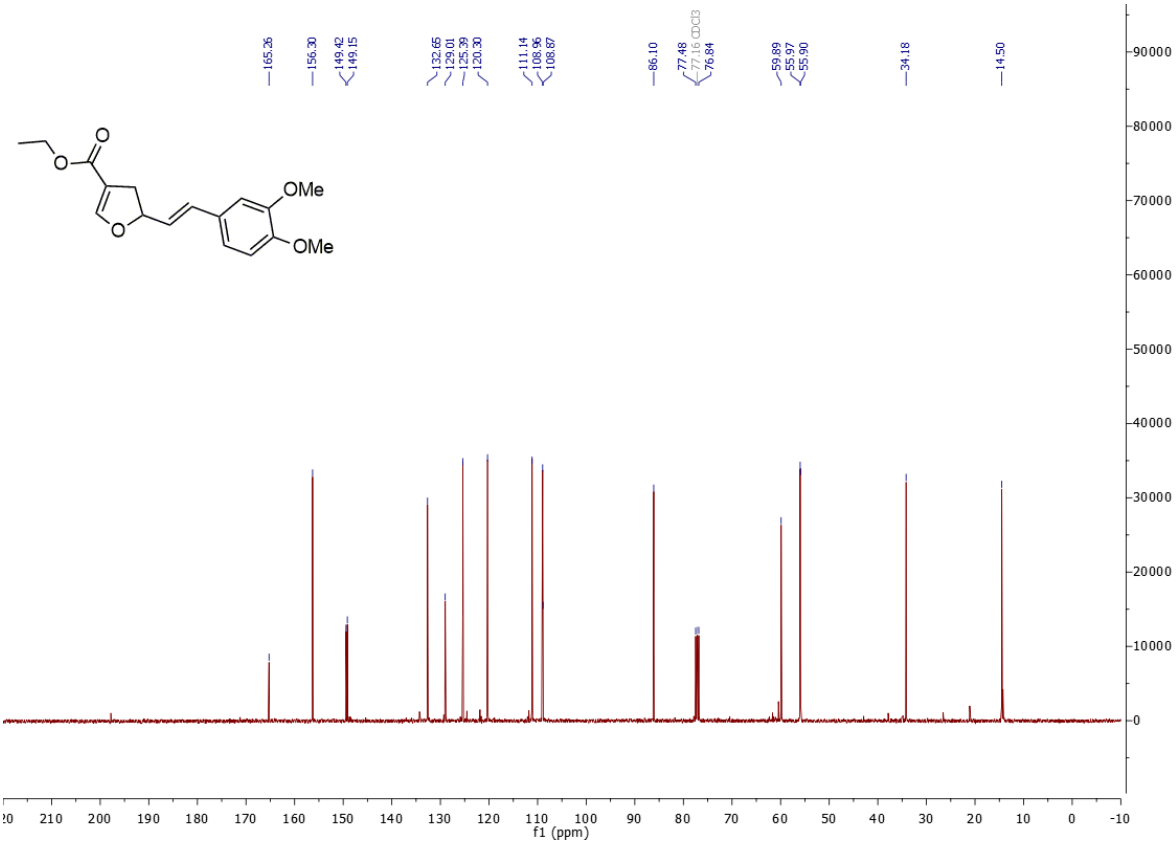

7.41
7.41
7.40
7.39
7.39
7.39
7.38
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.30
7.29
7.29
7.28
7.28
7.27
7.26 CDCl3
6.66
6.62
6.31
6.29
6.27
6.25
5.42
5.40
5.39
5.38
5.37
5.36
4.22
4.20
4.20
4.20
4.19
4.18
4.17
3.14
3.10
3.10
3.08
2.77
2.76
2.75
2.74
2.73
2.71
2.71
1.30
1.29
1.27
1.76
1.99
1.69
0.86
0.86
0.79
2.00
1.04
0.94
3.15
f1 (ppm)

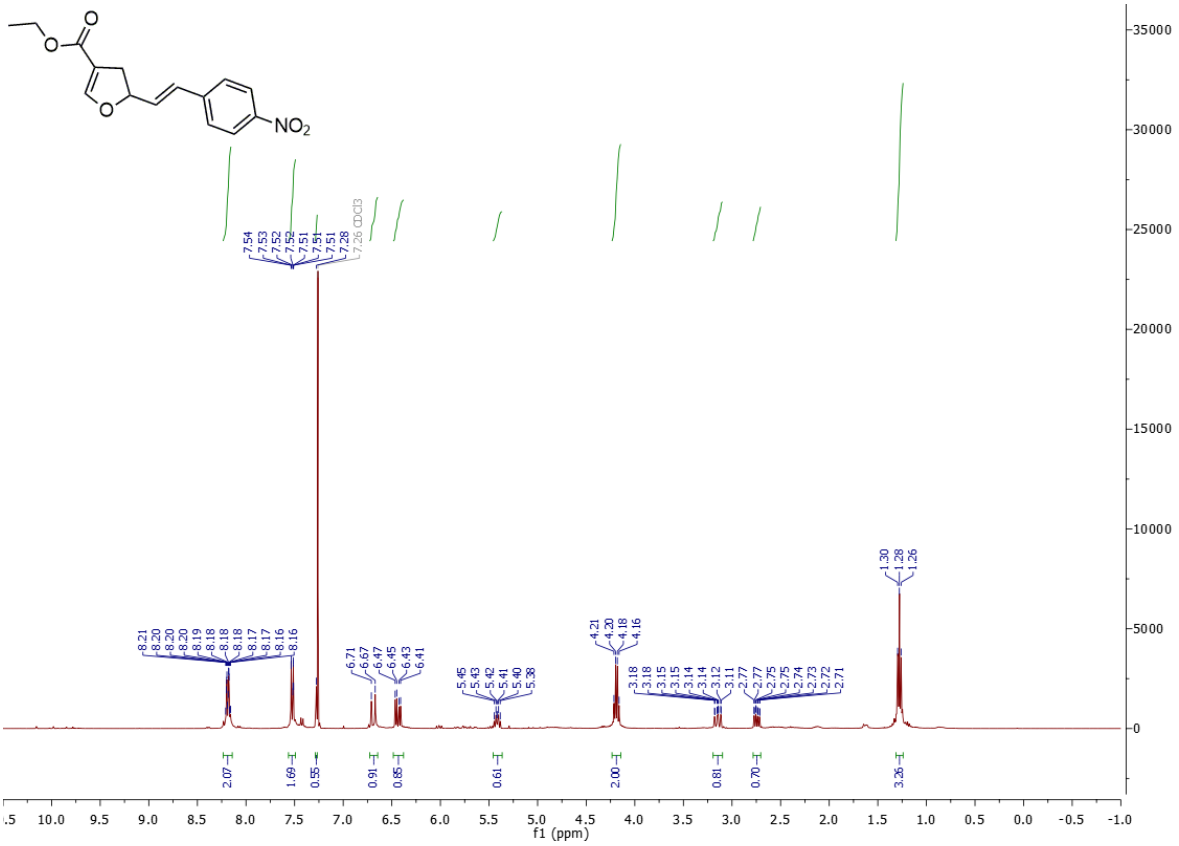

165.31
156.35
136.05
132.68
128.77
128.35
127.44
126.85
108.92
85.86
77.48
77.16 CDCl3
76.84
59.98
34.20
14.55
f1 (ppm)

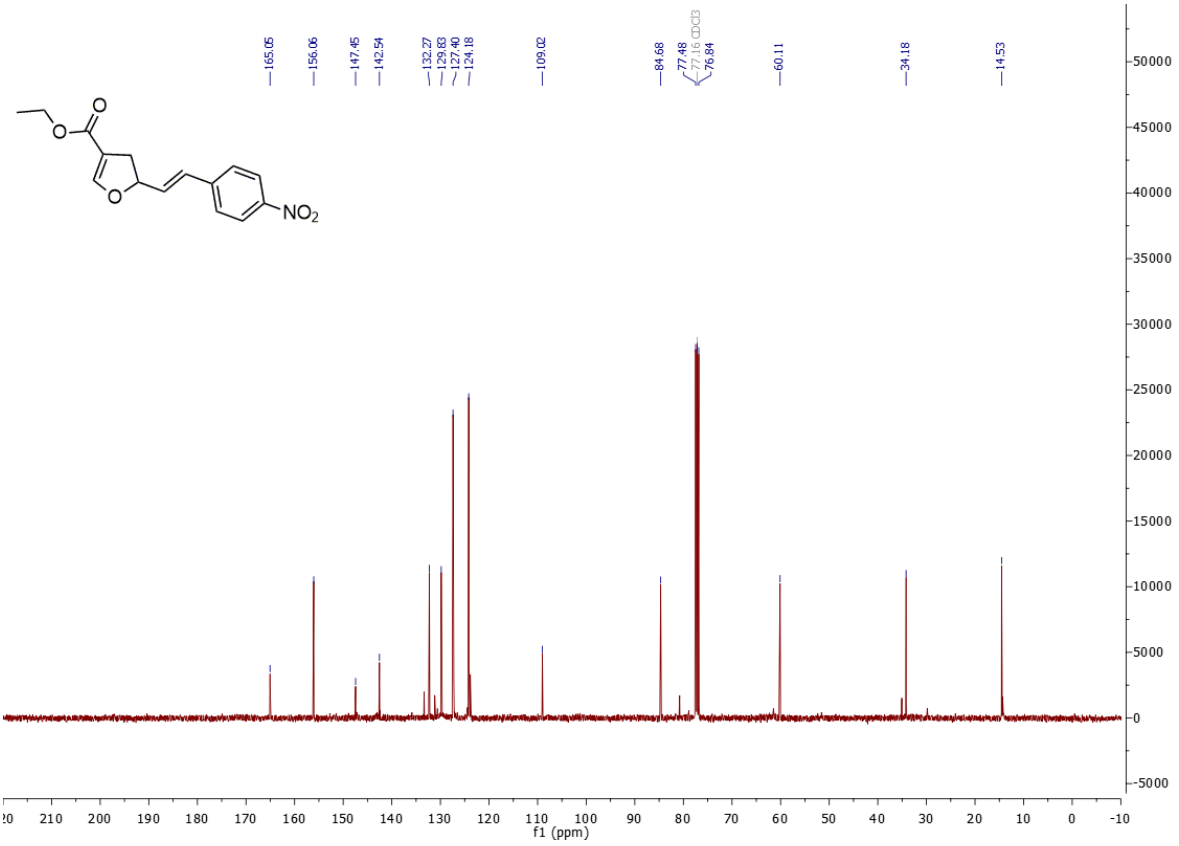

OMe
7.35
7.34
7.34
7.33
7.32
7.31
7.28
7.27
7.27
7.26 CDCl3
6.88
6.87
6.87
6.85
6.85
6.84
6.60
6.56
6.17
6.15
6.13
6.11
5.39
5.37
5.36
5.35
5.34
5.32
4.22
4.20
4.18
4.16
3.81
3.12
3.11
3.09
3.09
3.08
3.08
3.05
3.05
2.75
2.75
2.73
2.73
2.72
2.71
2.70
2.69
1.30
1.28
1.26
1.90
0.83
1.92
0.91
0.91
0.92
2.00
2.97
0.97
0.96
3.19
f1 (ppm)

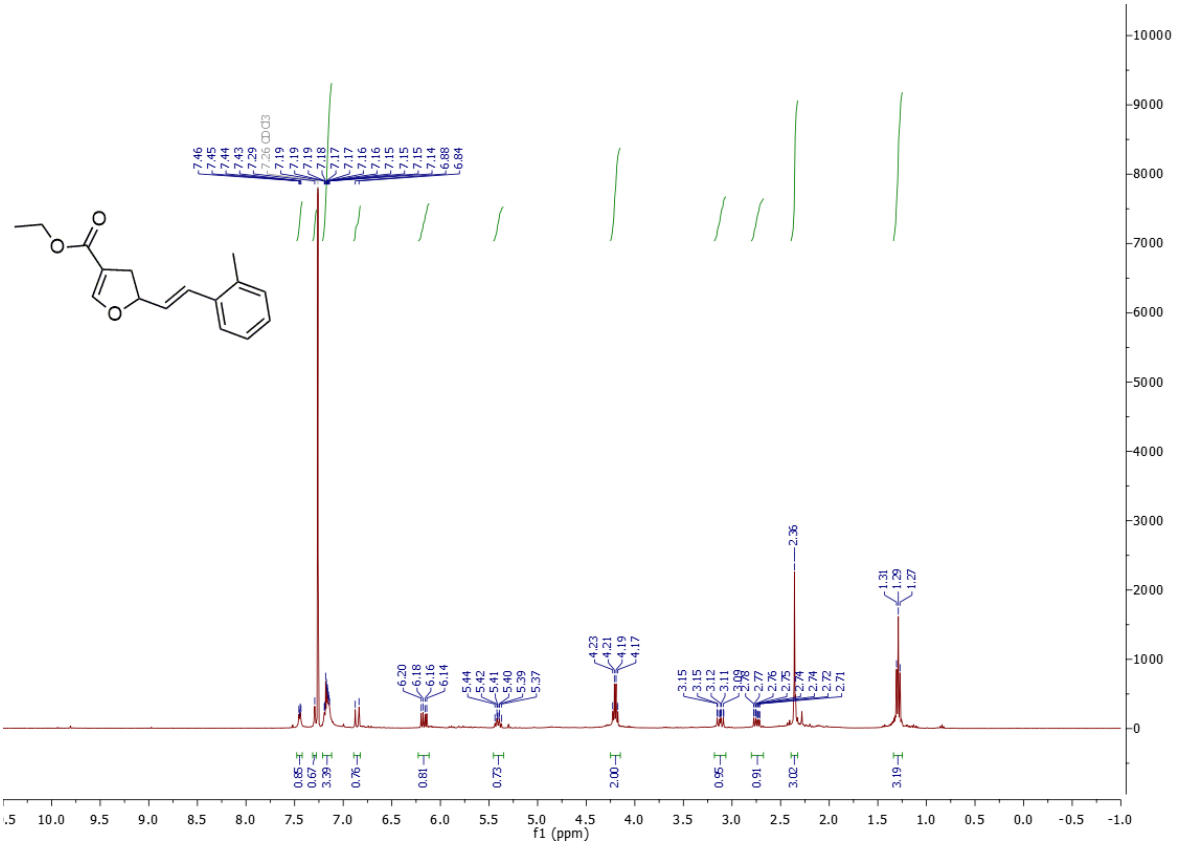

OMe
165.35
159.04
156.39
132.49
128.77
128.13
125.20
114.18
108.92
86.28
77.48
77.16 CDCl3
76.84
59.94
55.42
34.23
14.56
f1 (ppm)

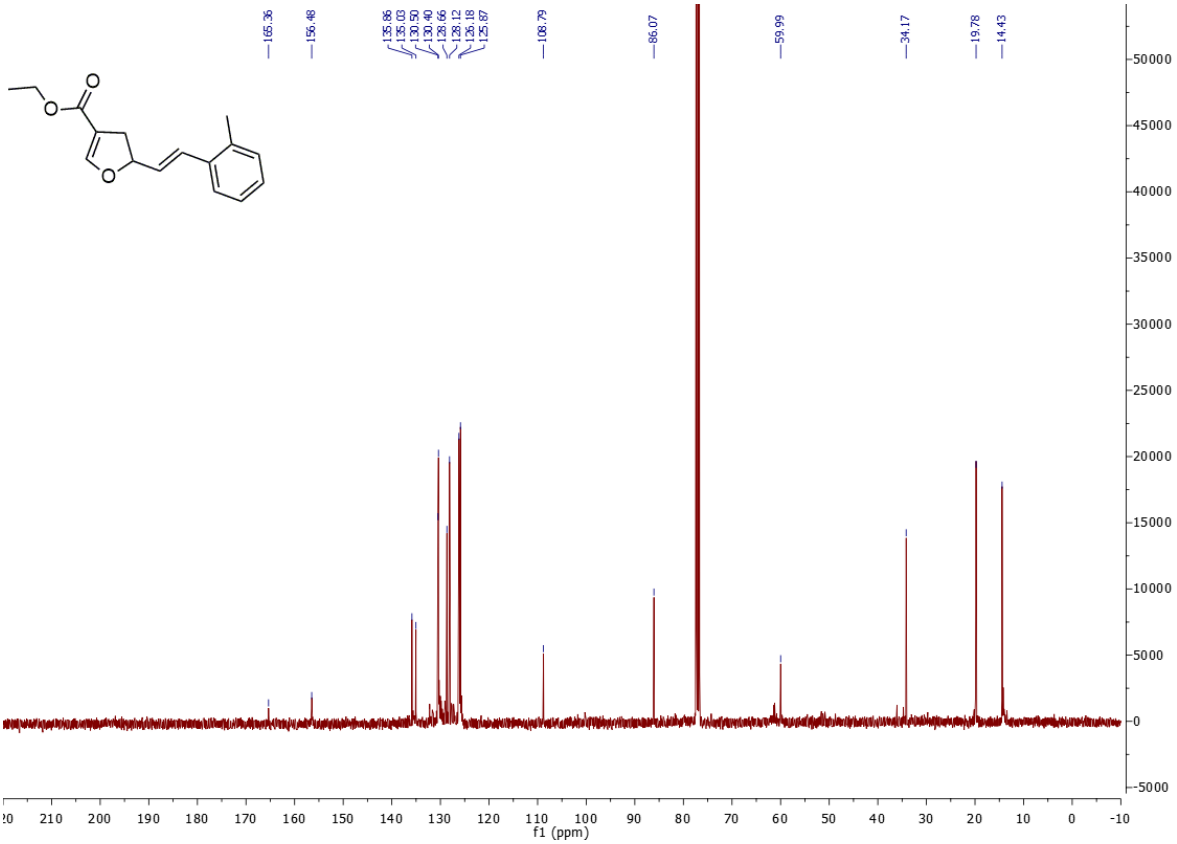

OMe
OMe
f1 (ppm)

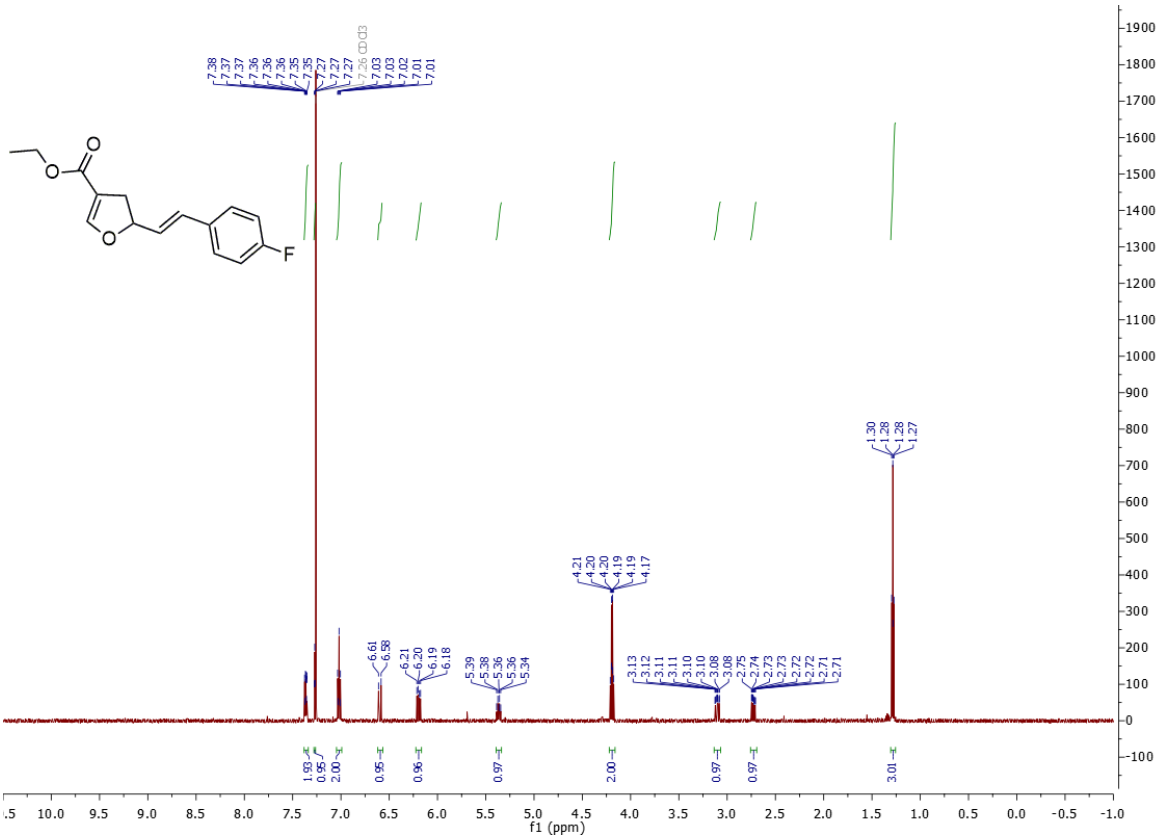

OMe
OMe
f1 (ppm)

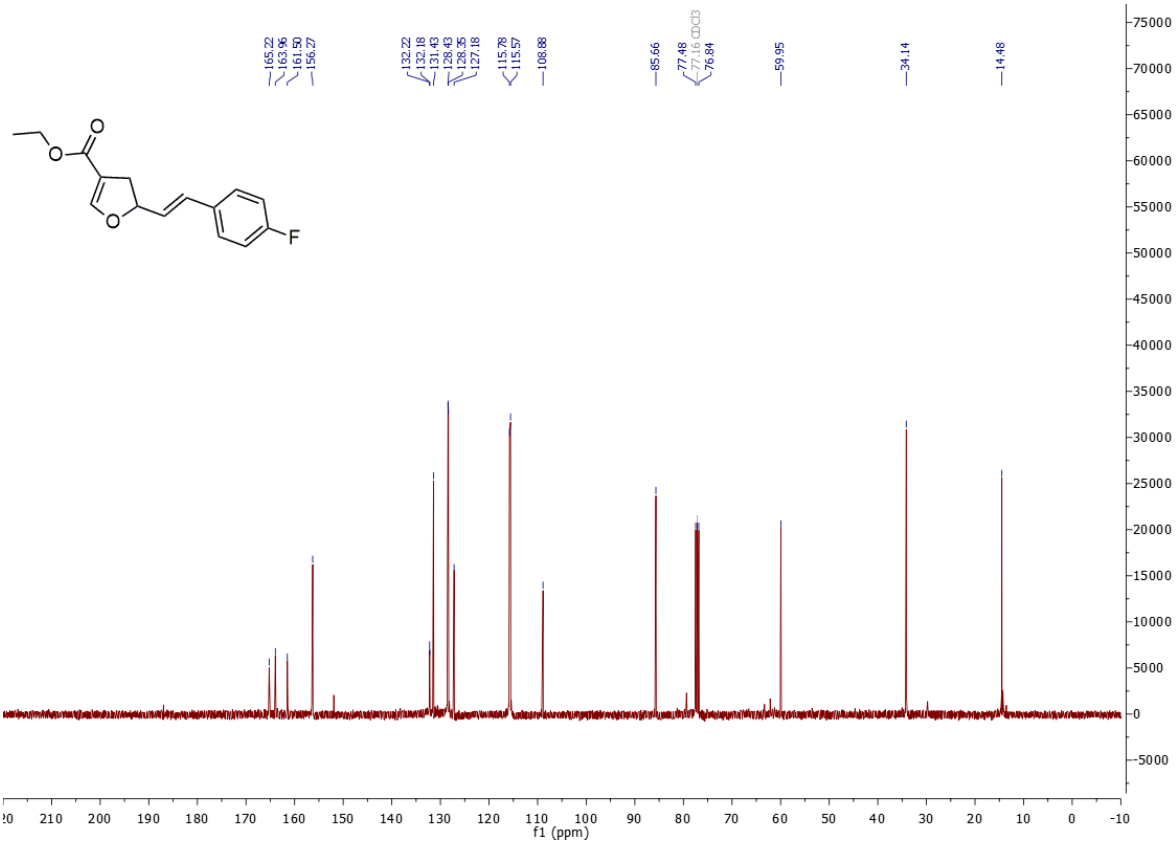

NO2
7.54
7.53
7.52
7.52
7.51
7.51
7.51
7.51
7.26 CDCl3
8.21
8.20
8.20
8.20
8.19
8.18
8.18
8.18
8.17
8.17
8.16
8.16
6.71
6.67
6.47
6.45
6.43
6.41
5.45
5.43
5.42
5.41
5.40
5.38
4.21
4.20
4.18
4.16
3.18
3.18
3.15
3.15
3.14
3.14
3.12
3.11
2.77
2.77
2.75
2.75
2.74
2.73
2.72
2.71
1.30
1.28
1.26
2.07
1.69
0.55
0.91
0.85
0.61
2.00
0.81
0.70
3.26
f1 (ppm)

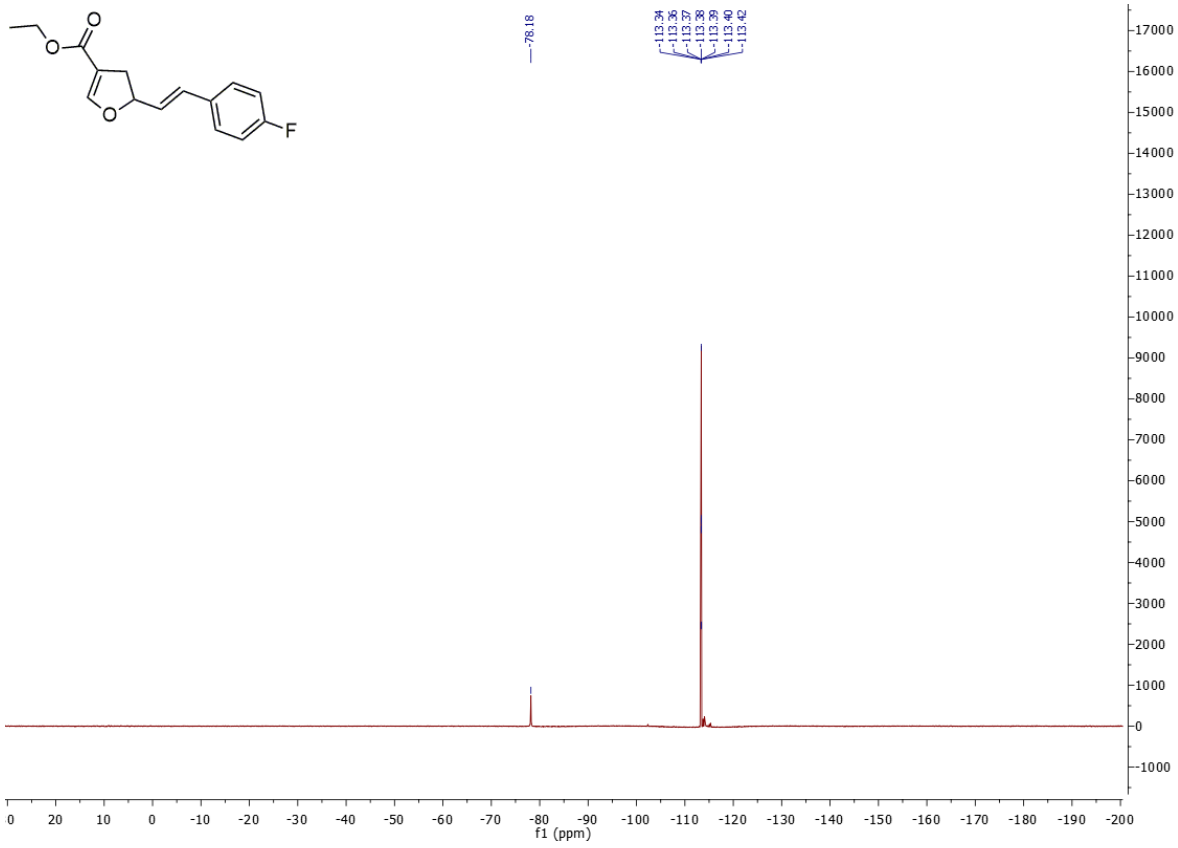

NO2
165.05
156.06
147.45
142.54
132.27
129.83
127.40
124.18
109.02
84.68
77.48
77.16 CDCl3
76.84
60.11
34.18
14.53
f1 (ppm)

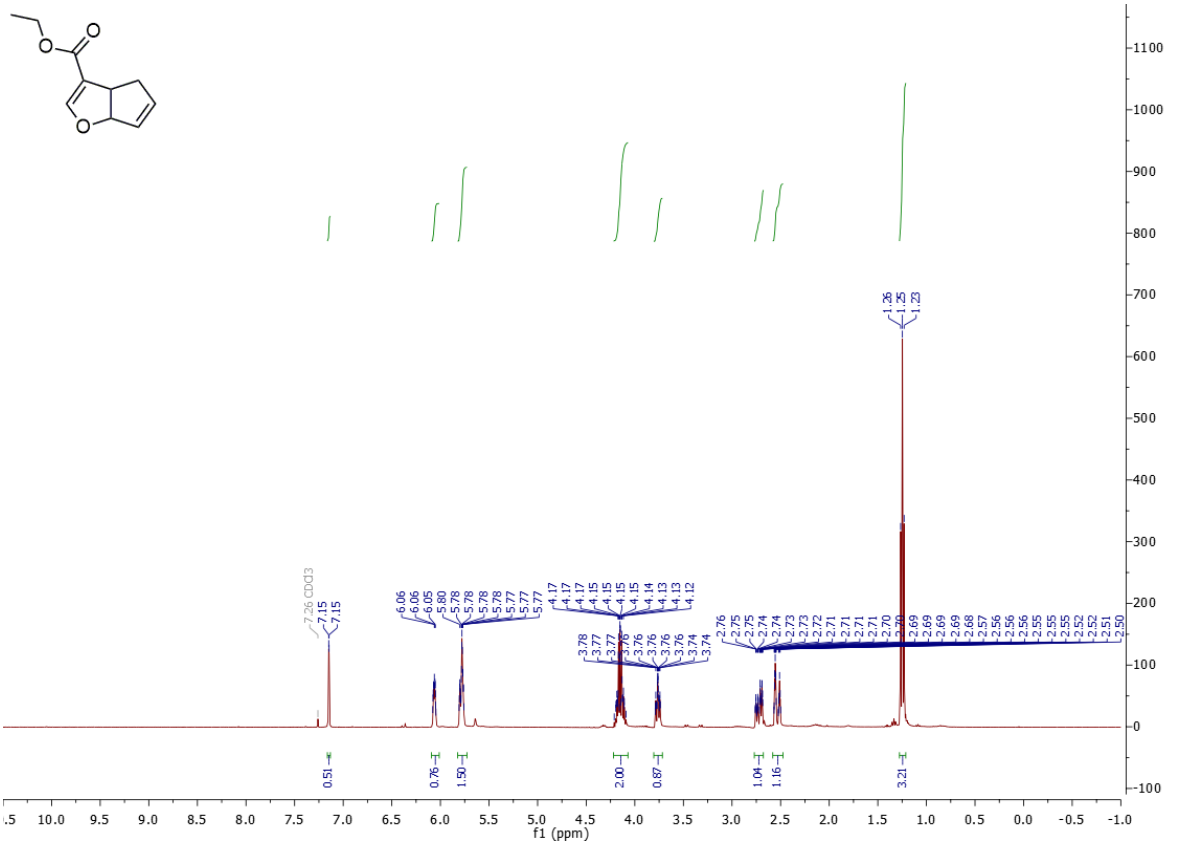

7.46
7.45
7.44
7.43
7.29
7.26 CDCl3
7.19
7.19
7.19
7.18
7.17
7.17
7.16
7.16
7.15
7.15
7.15
7.14
6.88
6.84
6.20
6.18
6.16
6.14
5.44
5.42
5.41
5.40
5.39
5.37
4.23
4.21
4.19
4.17
3.15
3.15
3.12
3.11
2.77
2.76
2.75
2.74
2.74
2.72
2.71
2.36
1.31
1.29
1.27
0.85
0.67
3.39
0.76
0.81
0.73
2.00
0.95
0.91
3.02
3.19
f1 (ppm)

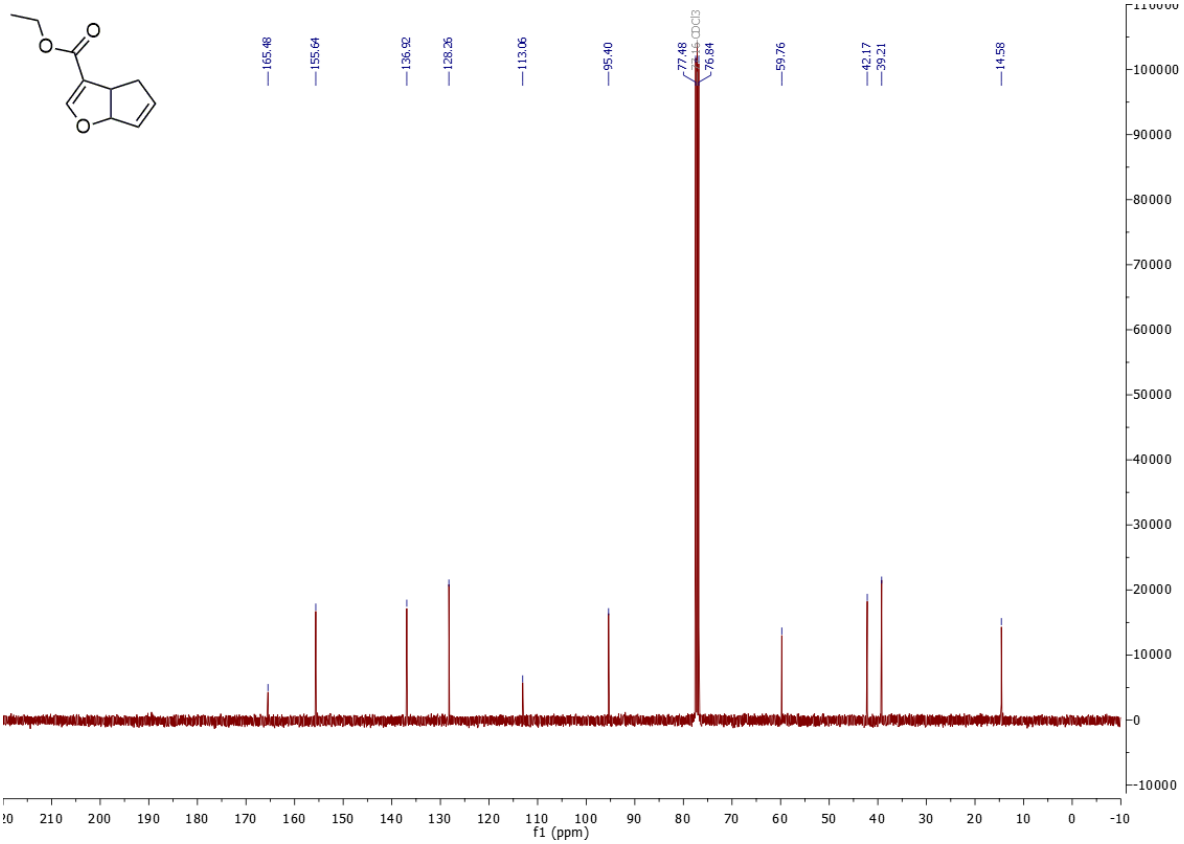

165.36
156.48
135.86
135.03
130.50
130.40
128.66
128.12
126.18
125.87
108.79
86.07
59.99
34.17
19.78
14.43
f1 (ppm)

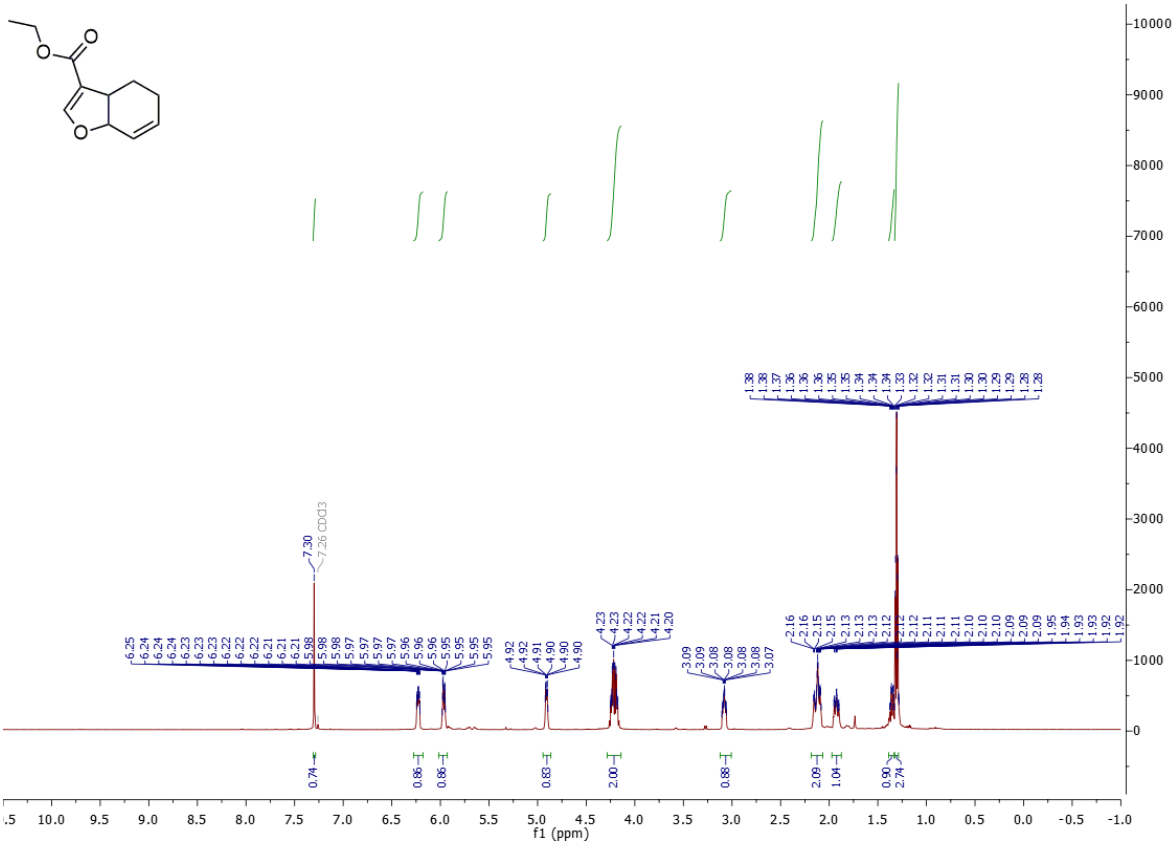

7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.27
7.27
7.27
7.26 CDCl3
7.03
7.03
7.02
7.01
7.01
6.61
6.58
6.21
6.20
6.19
6.18
5.39
5.38
5.36
5.36
5.34
4.21
4.20
4.20
4.19
4.19
4.17
3.13
3.12
3.11
3.11
3.10
3.10
3.08
3.08
2.75
2.74
2.73
2.73
2.72
2.72
2.71
2.71
1.30
1.28
1.28
1.27
1.93
0.95
2.00
0.95
0.96
0.97
2.00
0.97
0.97
3.01
f1 (ppm)

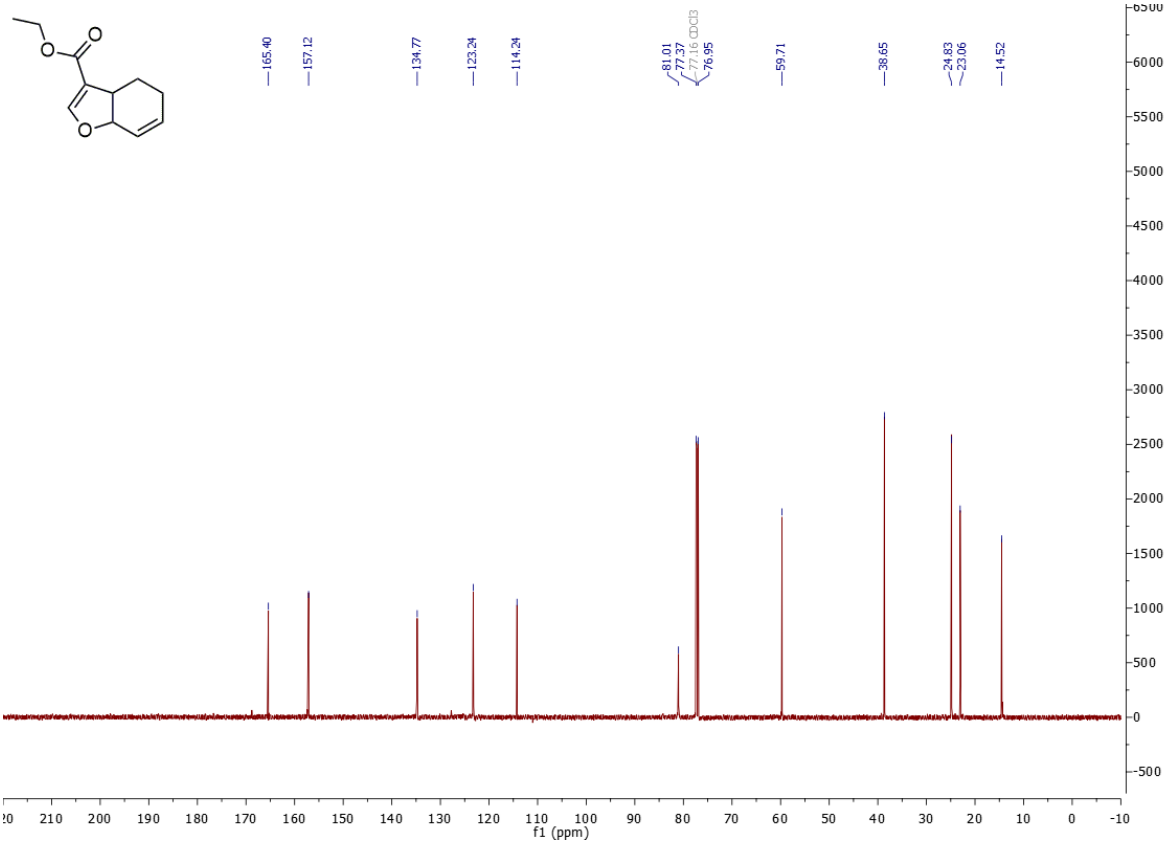

165.22
163.96
161.50
156.27
132.22
132.18
131.43
128.43
128.35
127.18
115.78
115.57
108.88
85.66
77.48
77.16 CDCl3
76.84
59.95
34.14
14.48
f1 (ppm)

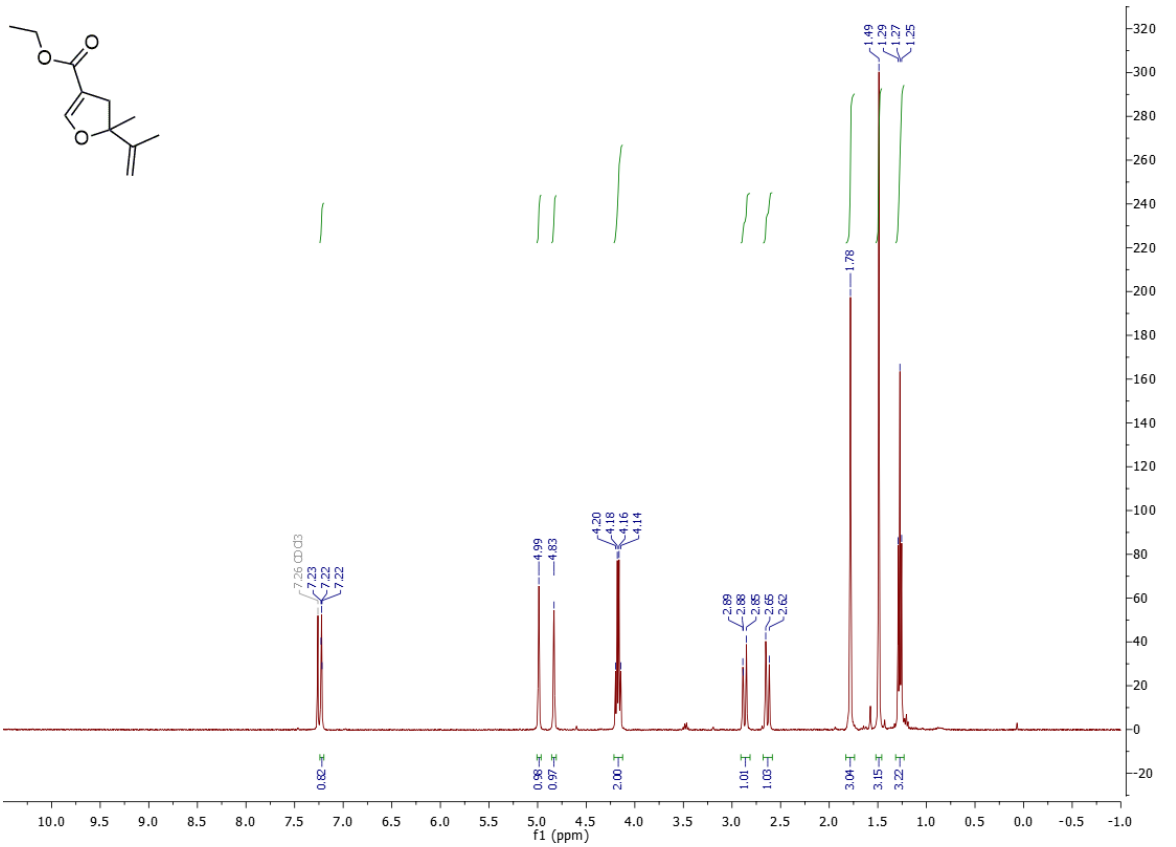

-78.18
-113.34
-113.36
-113.37
-113.38
-113.39
-113.40
-113.42
F
O
O
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

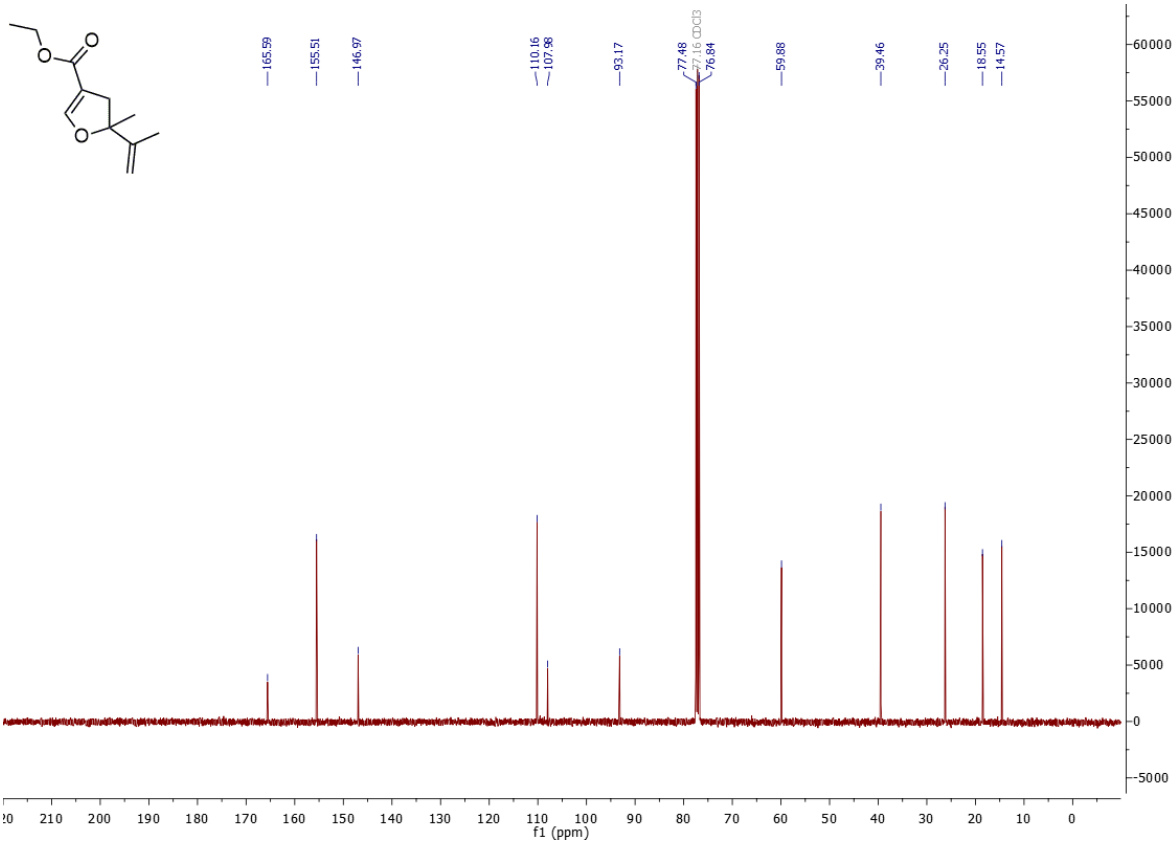

7.26 CDCl3
7.15
7.15
6.06
6.06
6.05
5.80
5.78
5.78
5.78
5.78
5.77
5.77
5.77
4.17
4.17
4.15
4.15
4.15
4.14
4.13
4.13
4.12
3.78
3.77
3.77
3.76
3.76
3.76
3.76
3.74
3.74
2.76
2.75
2.75
2.74
2.74
2.73
2.73
2.72
2.71
2.71
2.71
2.71
2.70
1.26
1.25
1.23
0.51
0.76
1.50
2.00
0.87
1.04
1.16
3.21
f1 (ppm)

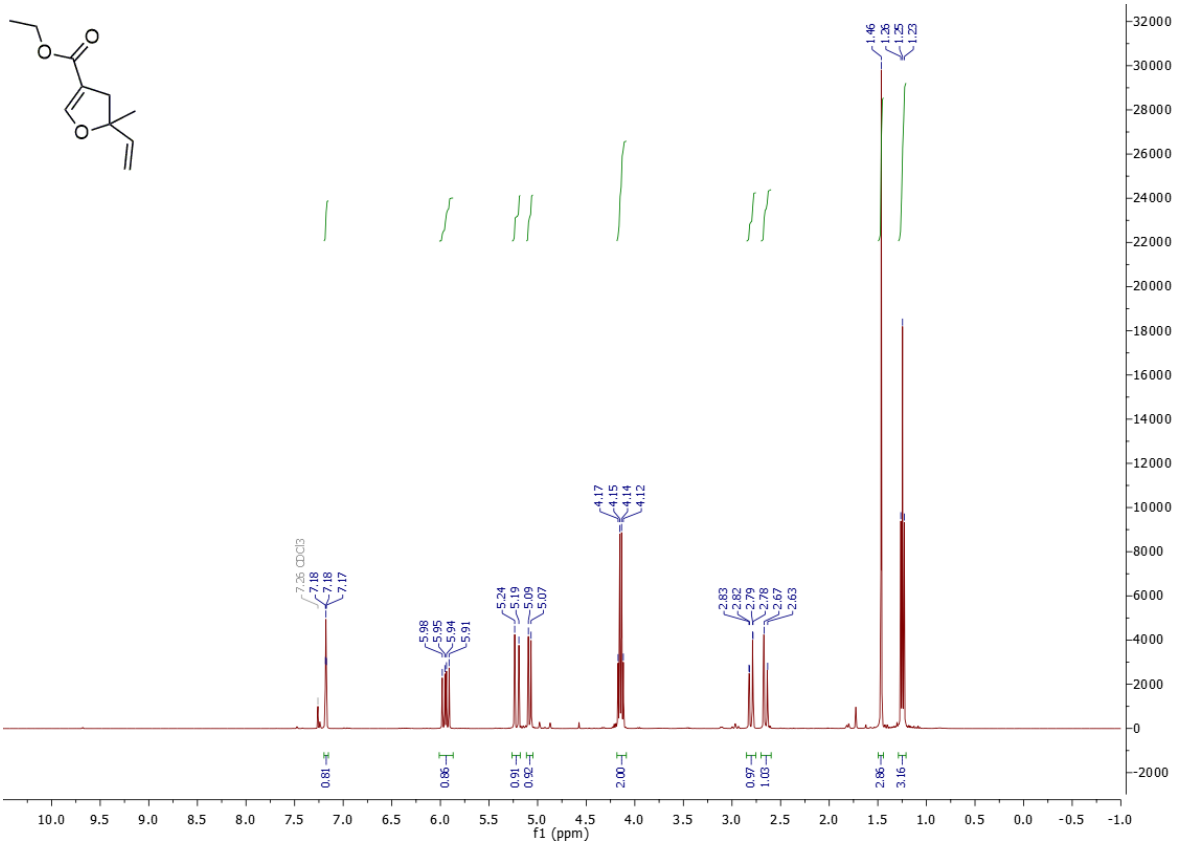

165.48
155.64
136.92
128.26
113.06
95.40
77.48
77.16
76.84
59.76
42.17
39.21
14.58
f1 (ppm)

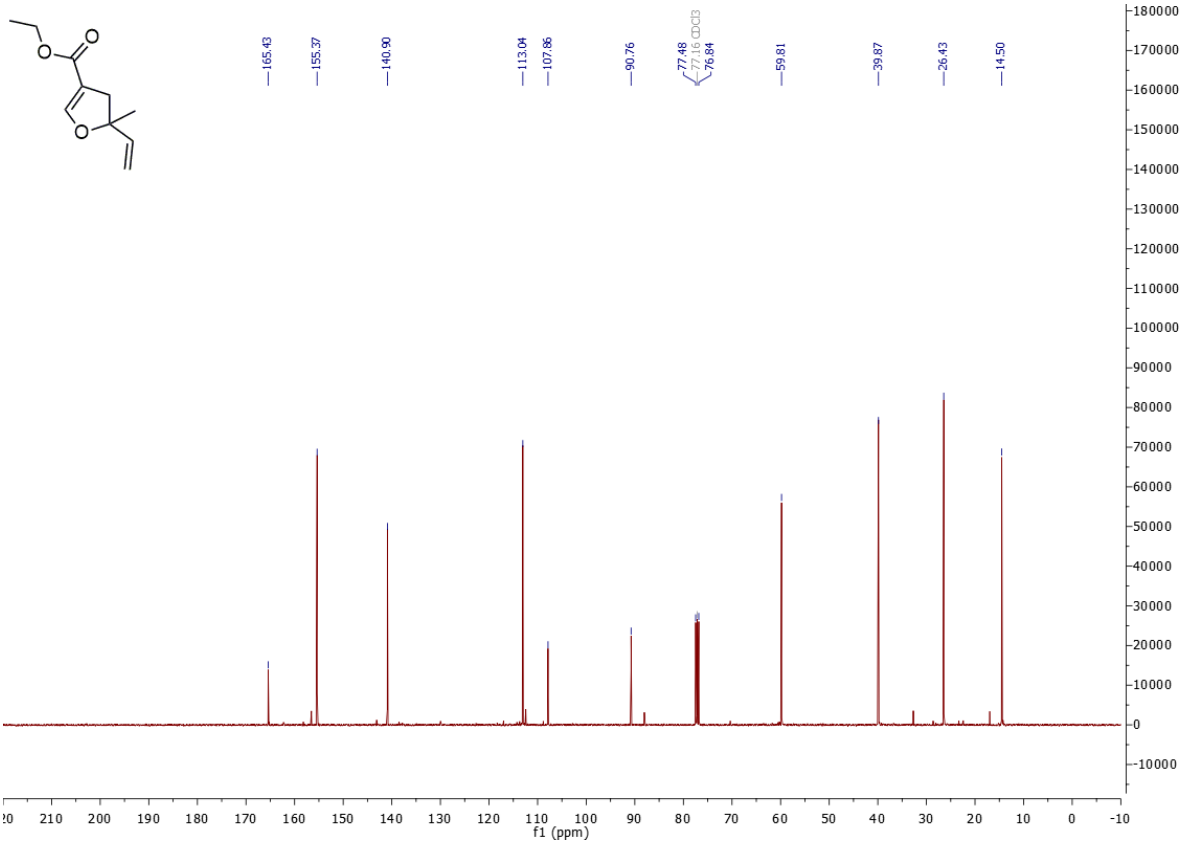

7.30
7.26 CDCl3
f1 (ppm)

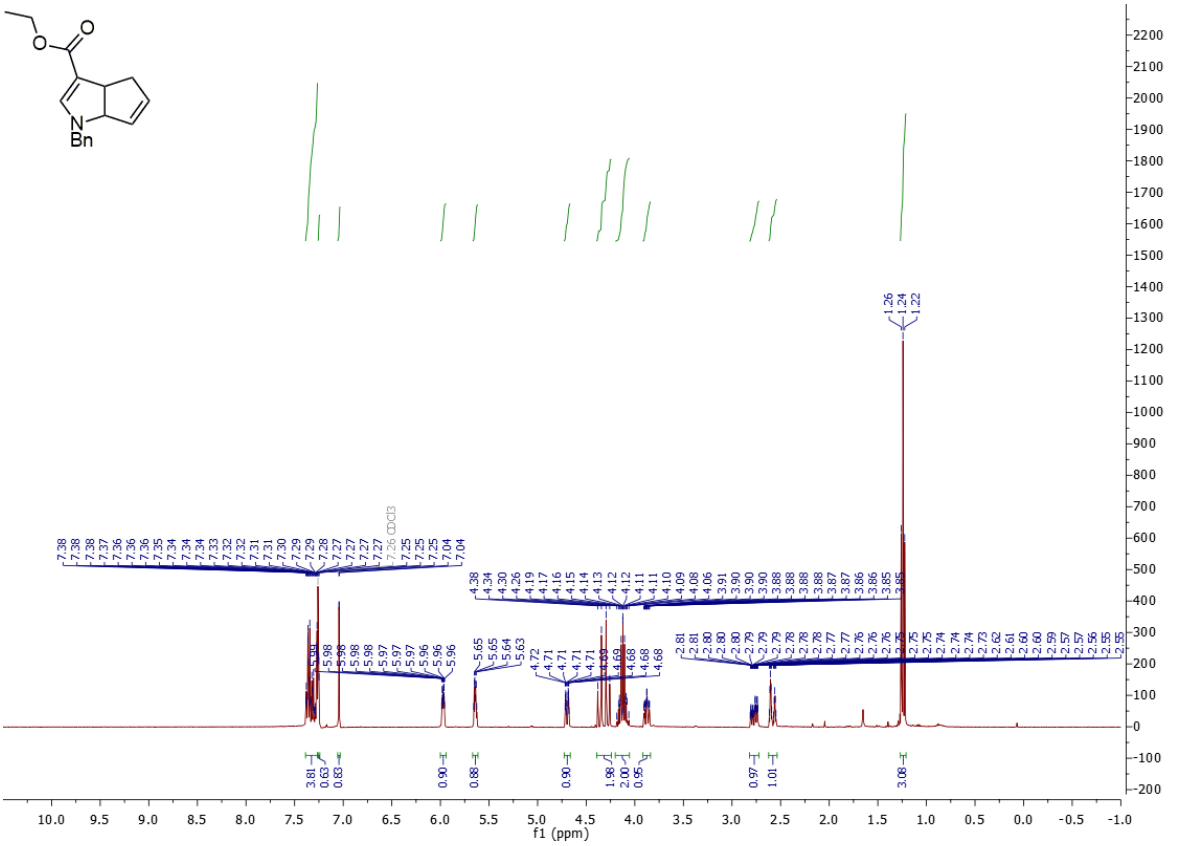

165.40
157.12
134.77
123.24
114.24
81.01
77.37
77.16 CDCl3
76.95
59.71
38.65
24.83
23.06
14.52
f1 (ppm)

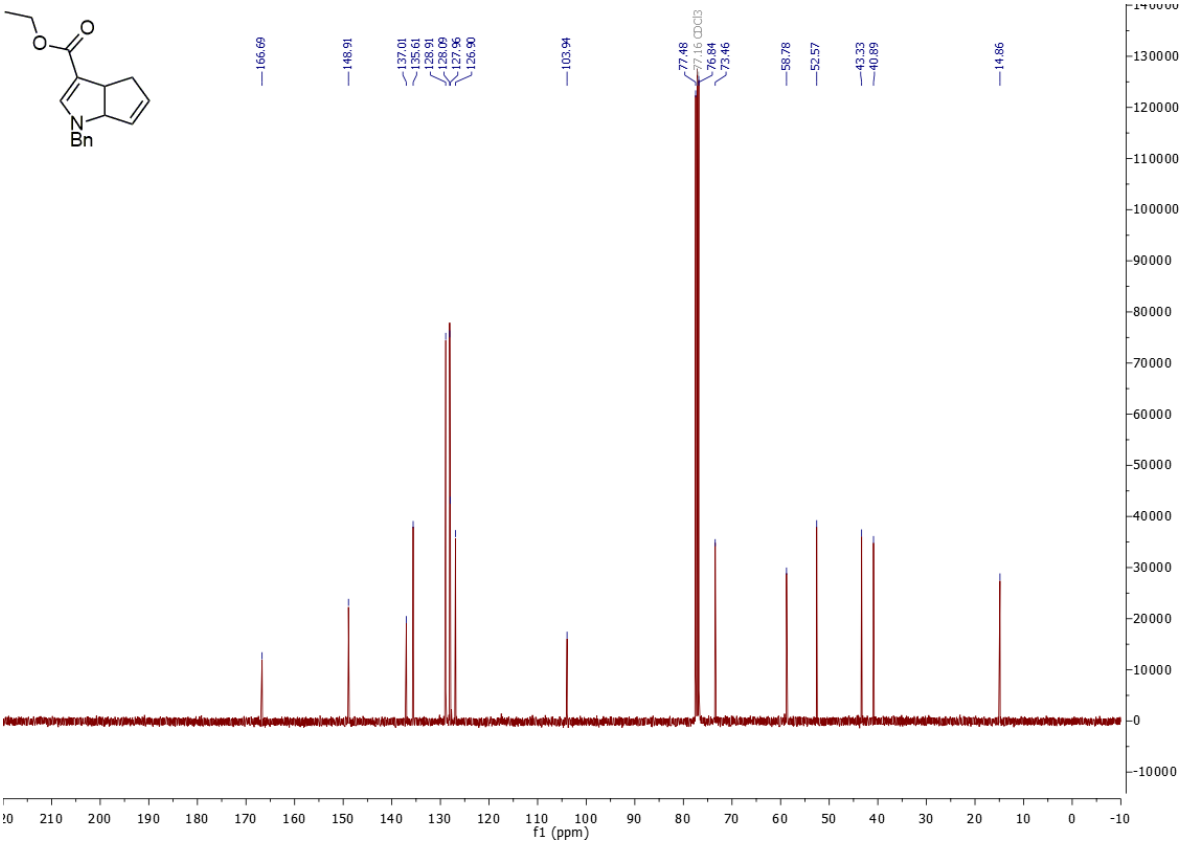

7.26 CDCl3
7.23
7.22
7.22
7.22
4.99
4.83
4.20
4.18
4.16
4.14
2.89
2.88
2.85
2.65
2.62
1.78
1.49
1.29
1.27
1.25
0.82
0.98
0.97
2.00
1.01
1.03
3.04
3.15
3.22
f1 (ppm)

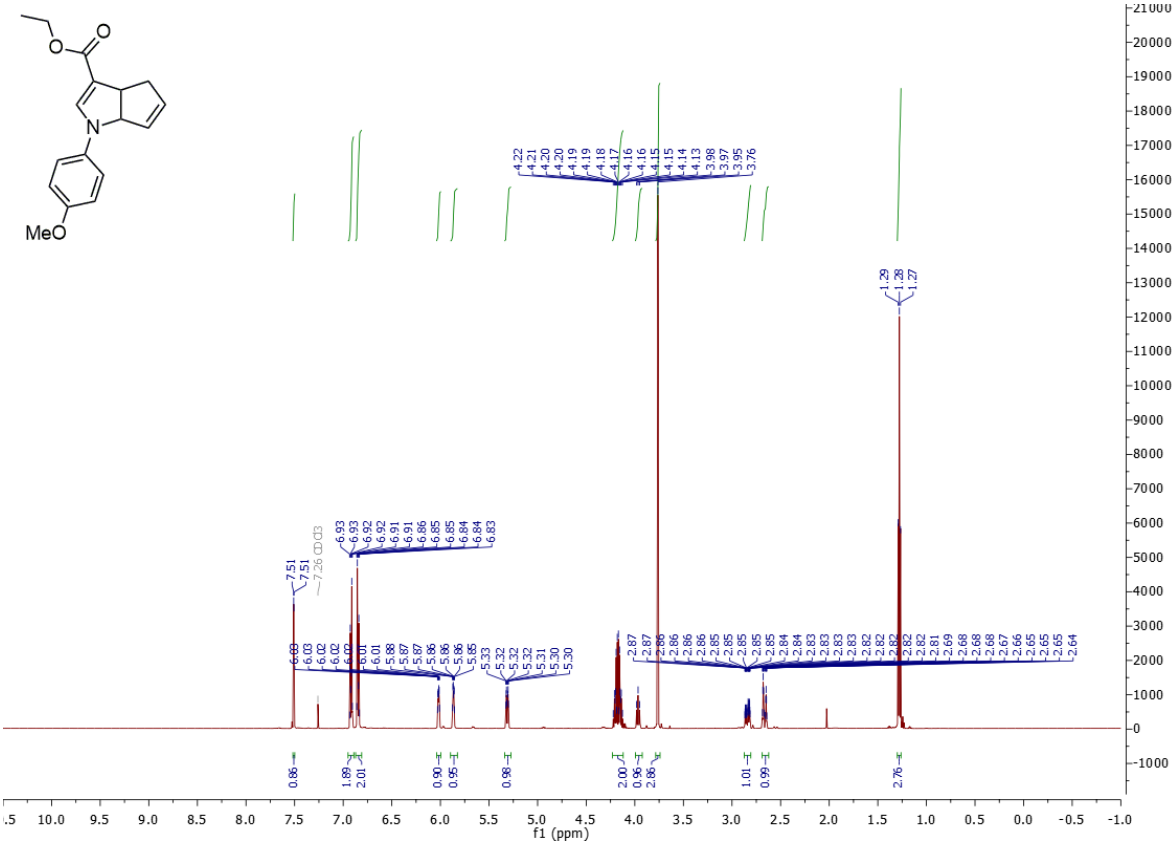

165.59
155.51
146.97
110.16
107.98
93.17
77.48
77.16 CDCl3
76.84
59.88
39.46
26.25
18.55
14.57
f1 (ppm)

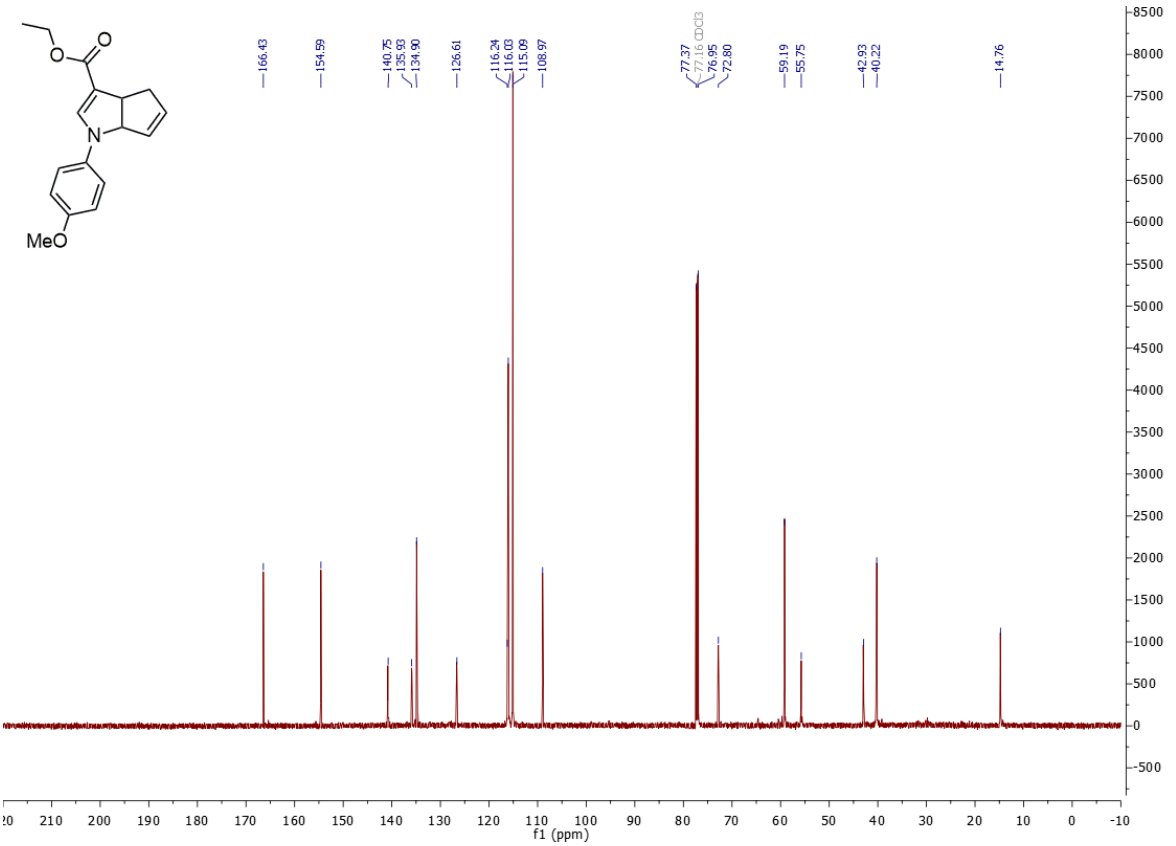

7.26 CDCl3
7.18
7.18
7.17
5.98
5.95
5.94
5.91
5.24
5.19
5.09
5.07
4.17
4.15
4.14
4.12
2.83
2.82
2.79
2.78
2.67
2.63
1.46
1.26
1.25
1.23
0.81
0.86
0.91
0.92
2.00
0.97
1.03
2.86
3.16
f1 (ppm)

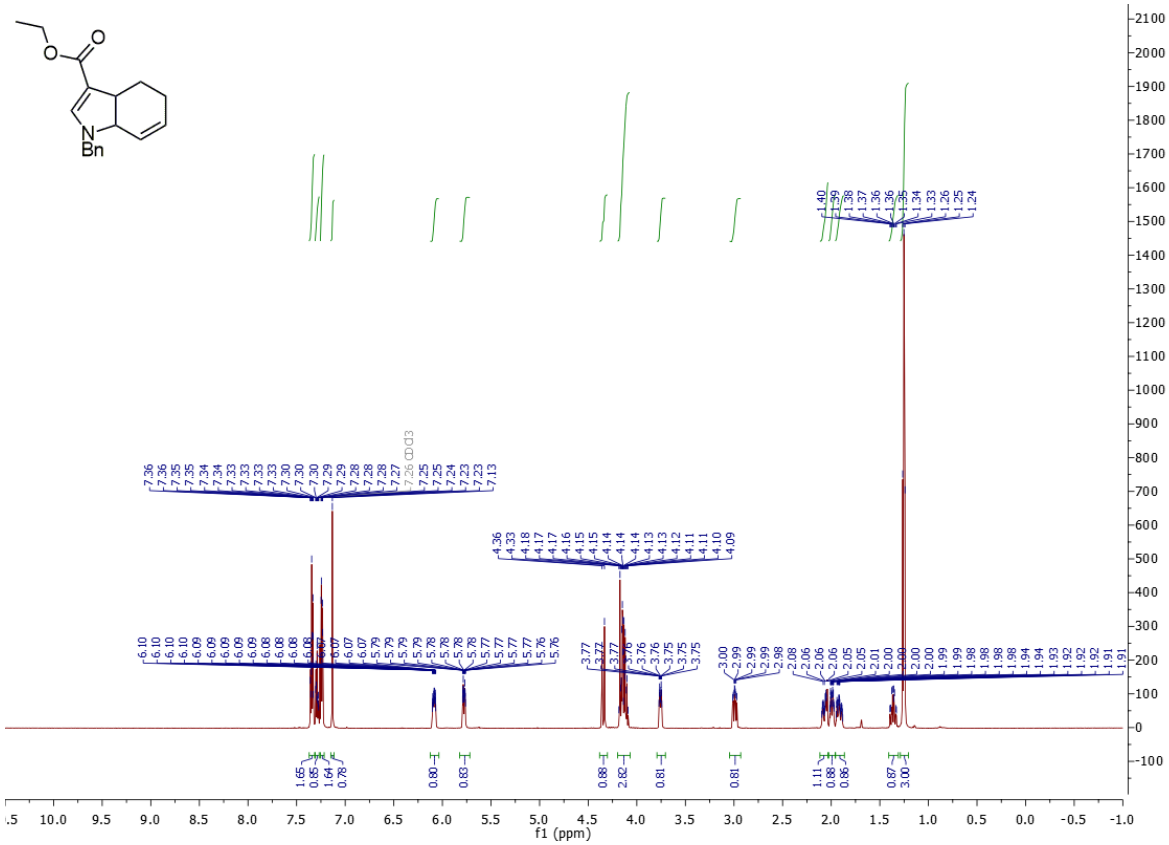

165.43
155.37
140.90
113.04
107.86
90.76
77.48
77.16 CDCl3
76.84
59.81
39.87
26.43
14.50
f1 (ppm)

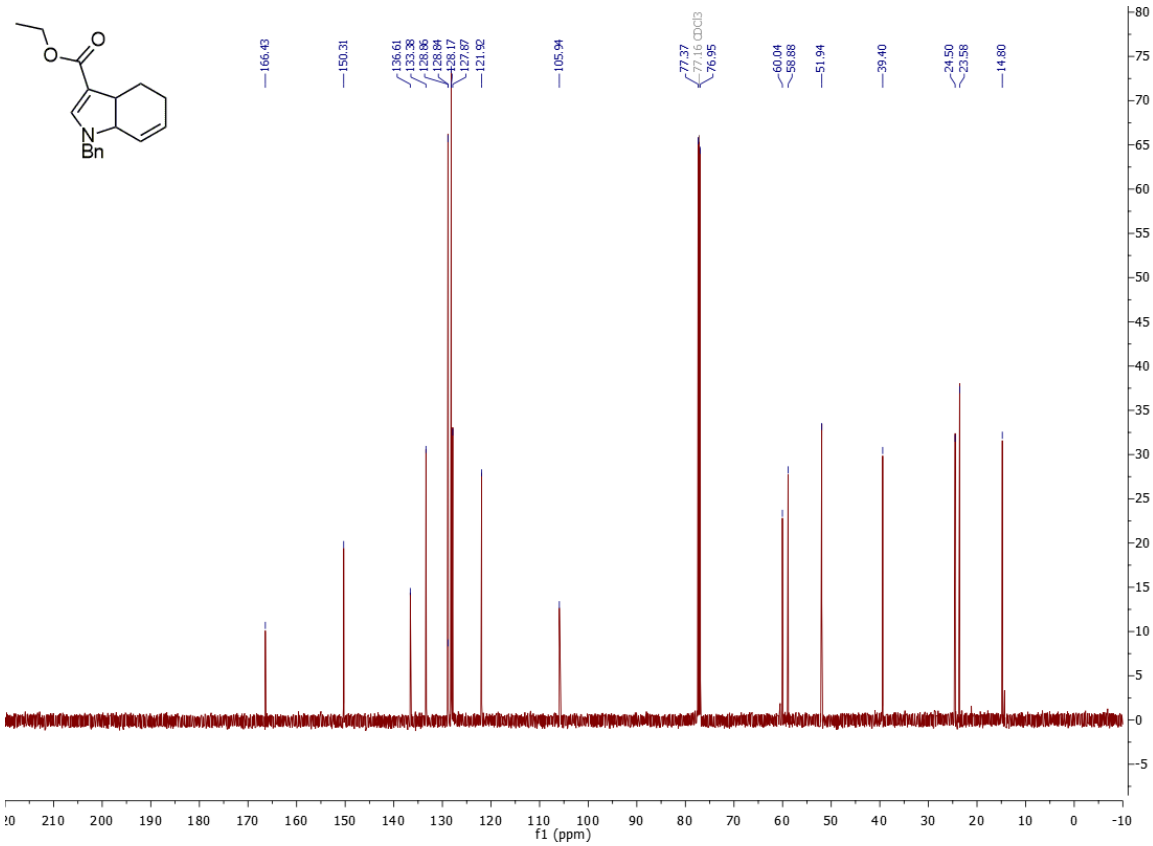

O
O
N
Bn
f1 (ppm)

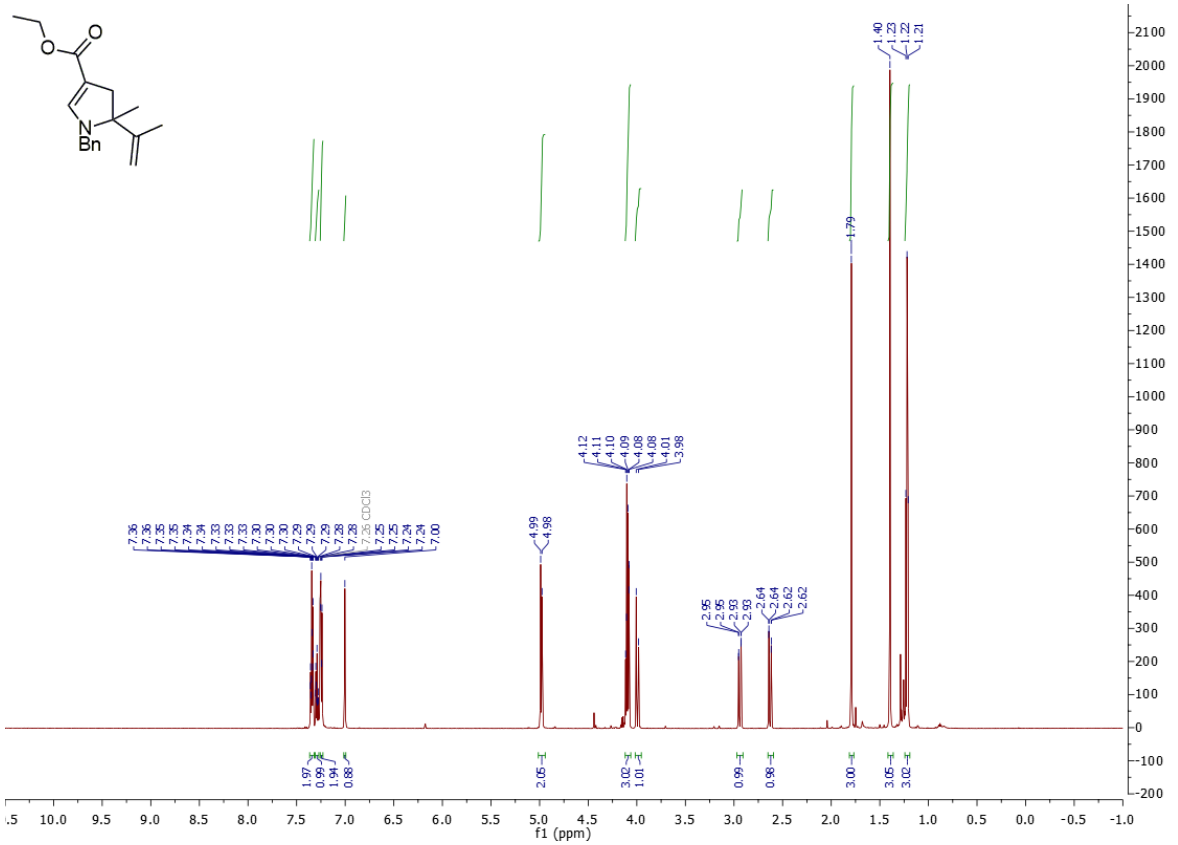

O
O
N
Bn
166.69
148.91
137.01
135.61
128.91
128.09
127.96
126.90
103.94
77.48
77.16 CDCl3
76.84
73.46
58.78
52.57
43.33
40.89
14.86
f1 (ppm)

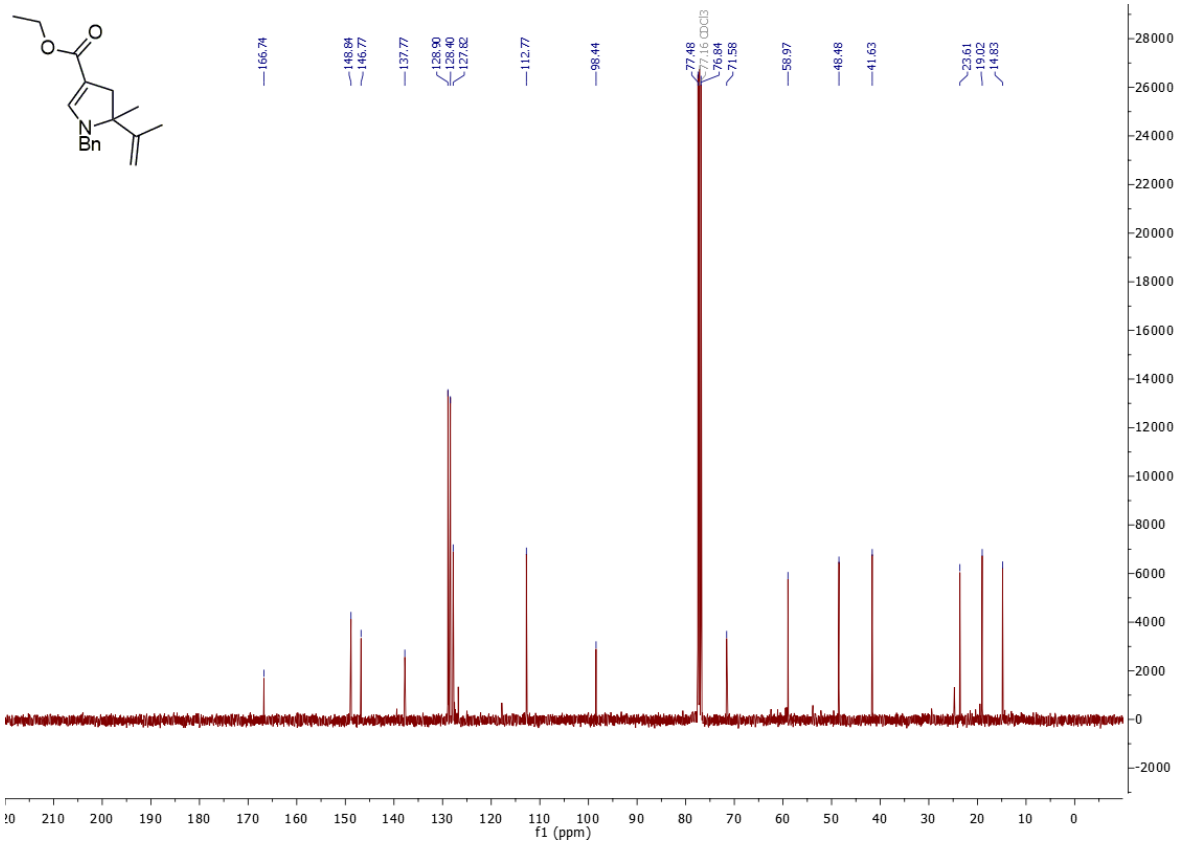

MeO
f1 (ppm)

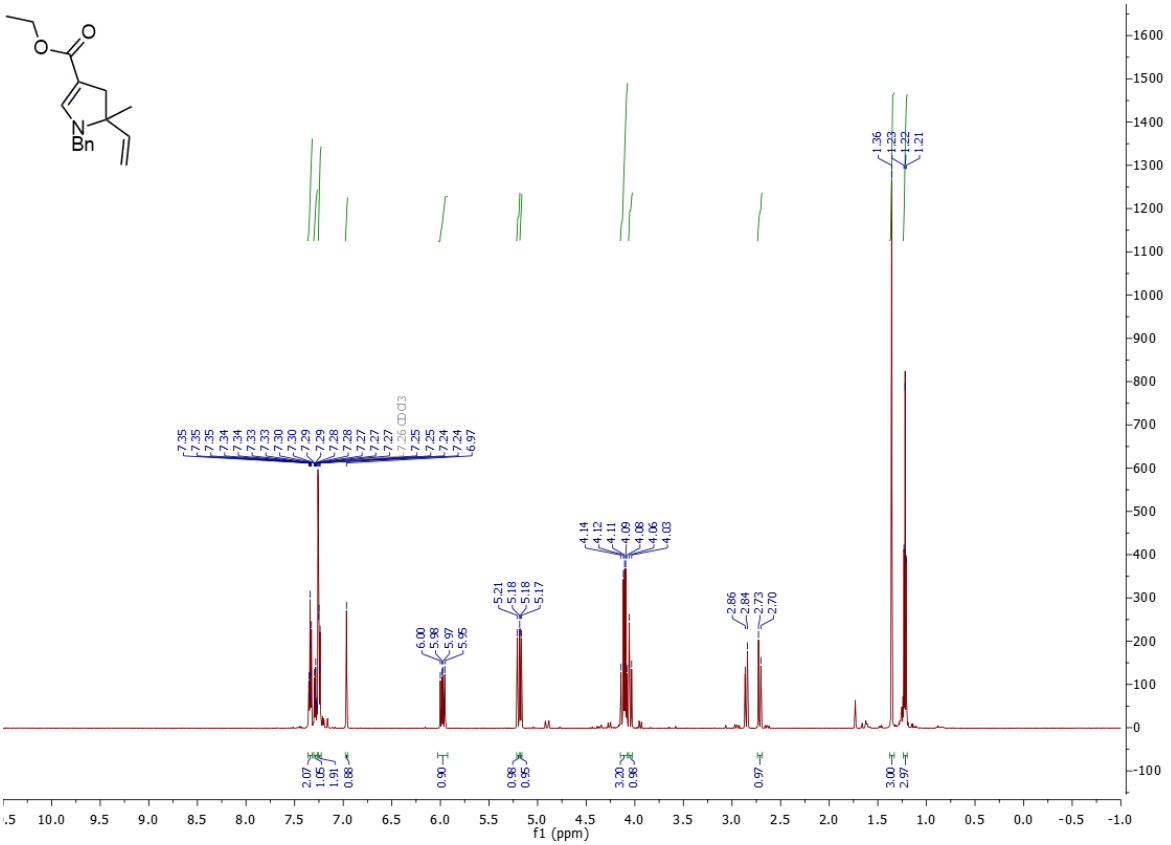

MeO
f1 (ppm)

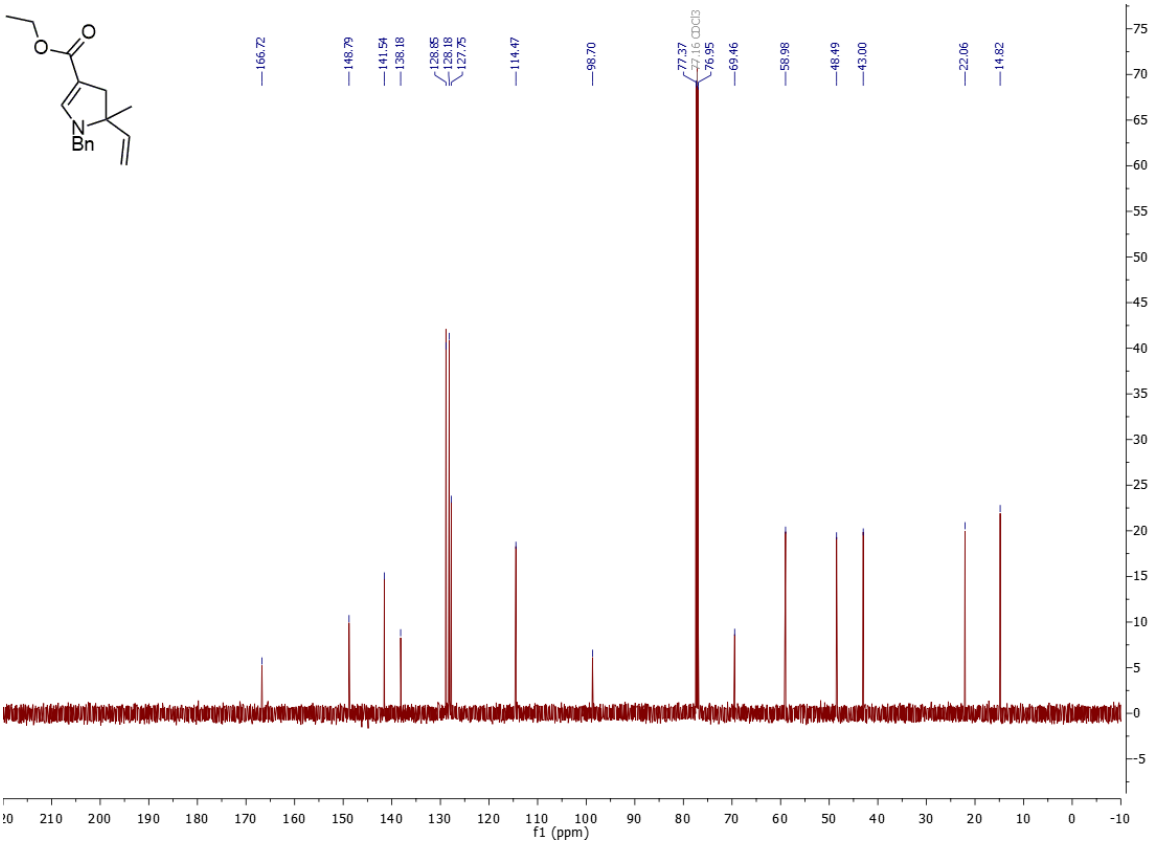

f1 (ppm)

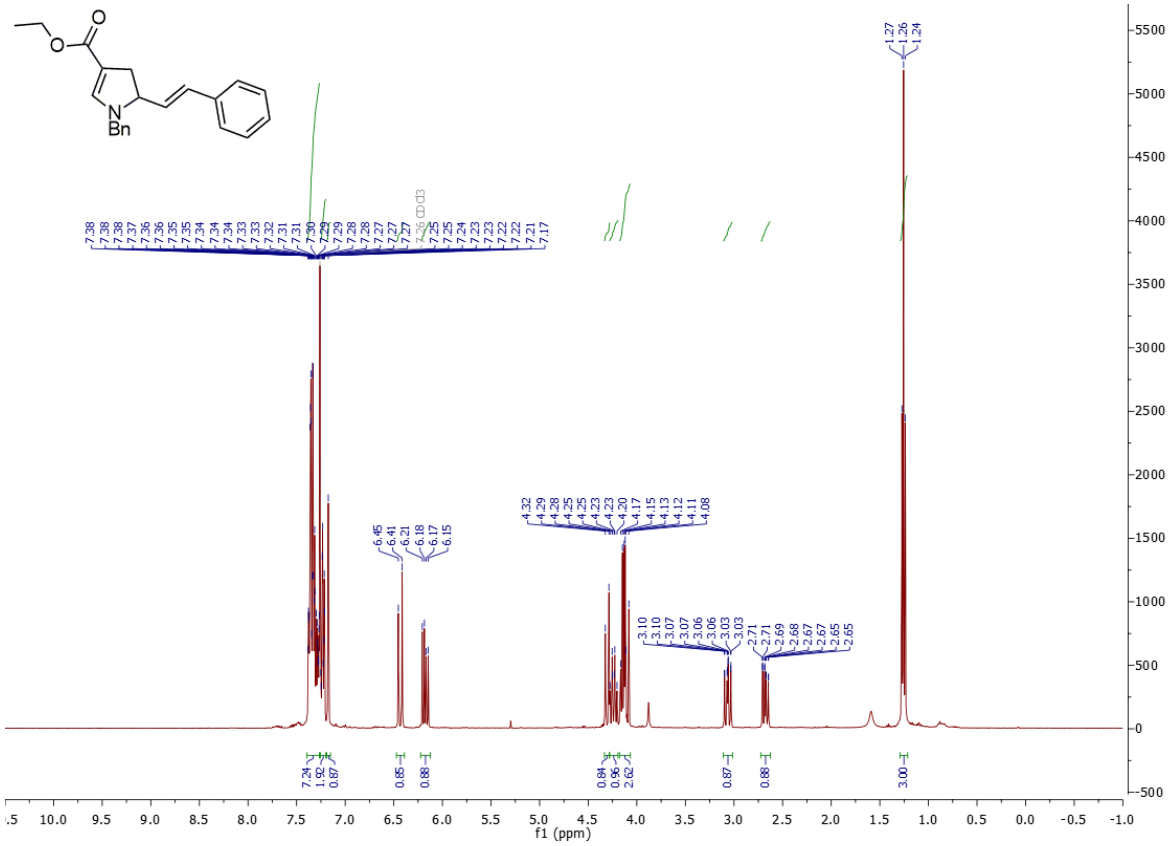

f1 (ppm)

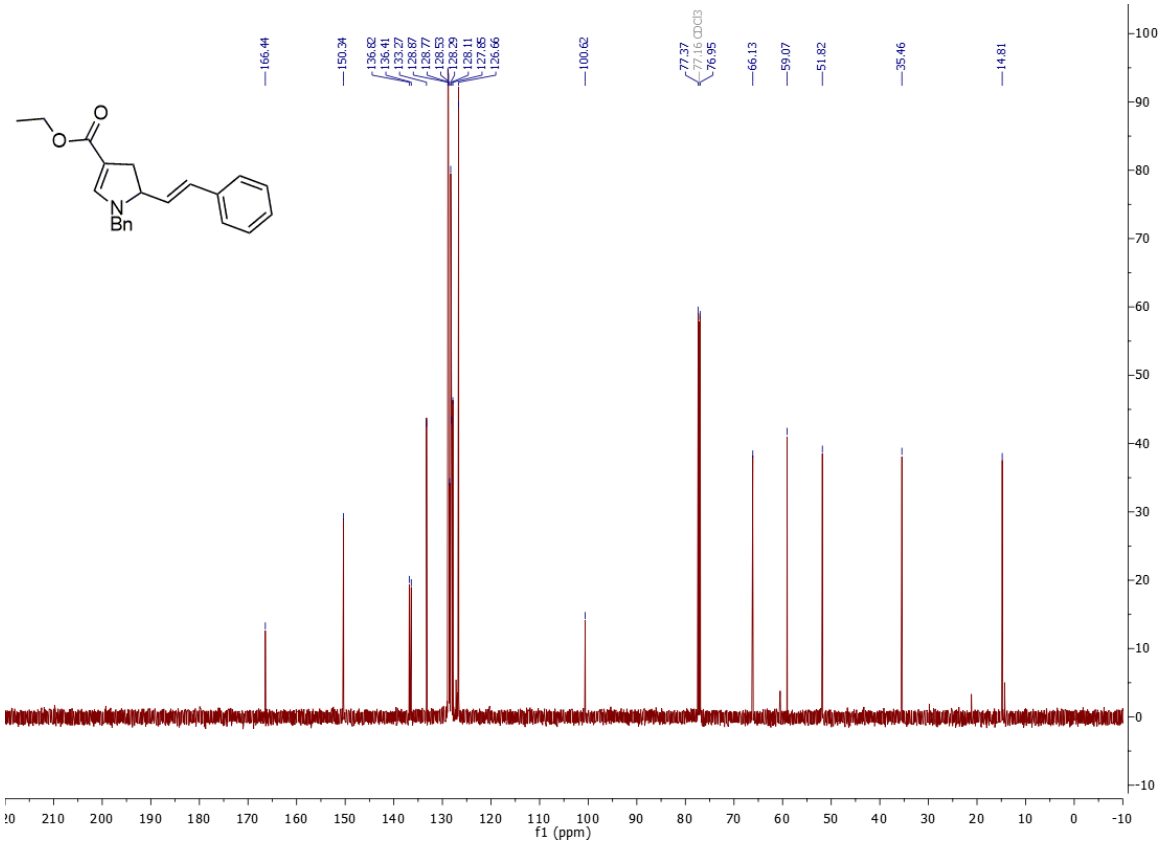

O
O
N
Bn
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.33
7.30
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.25 CDCl3
7.25
7.24
7.24
7.00
4.99
4.98
4.12
4.11
4.10
4.09
4.08
4.08
4.01
3.98
2.95
2.95
2.93
2.93
2.64
2.64
2.62
2.62
1.79
1.40
1.23
1.22
1.21
1.97
0.99
1.94
0.88
2.05
3.02
1.01
0.99
0.98
3.00
3.05
3.02
f1 (ppm)

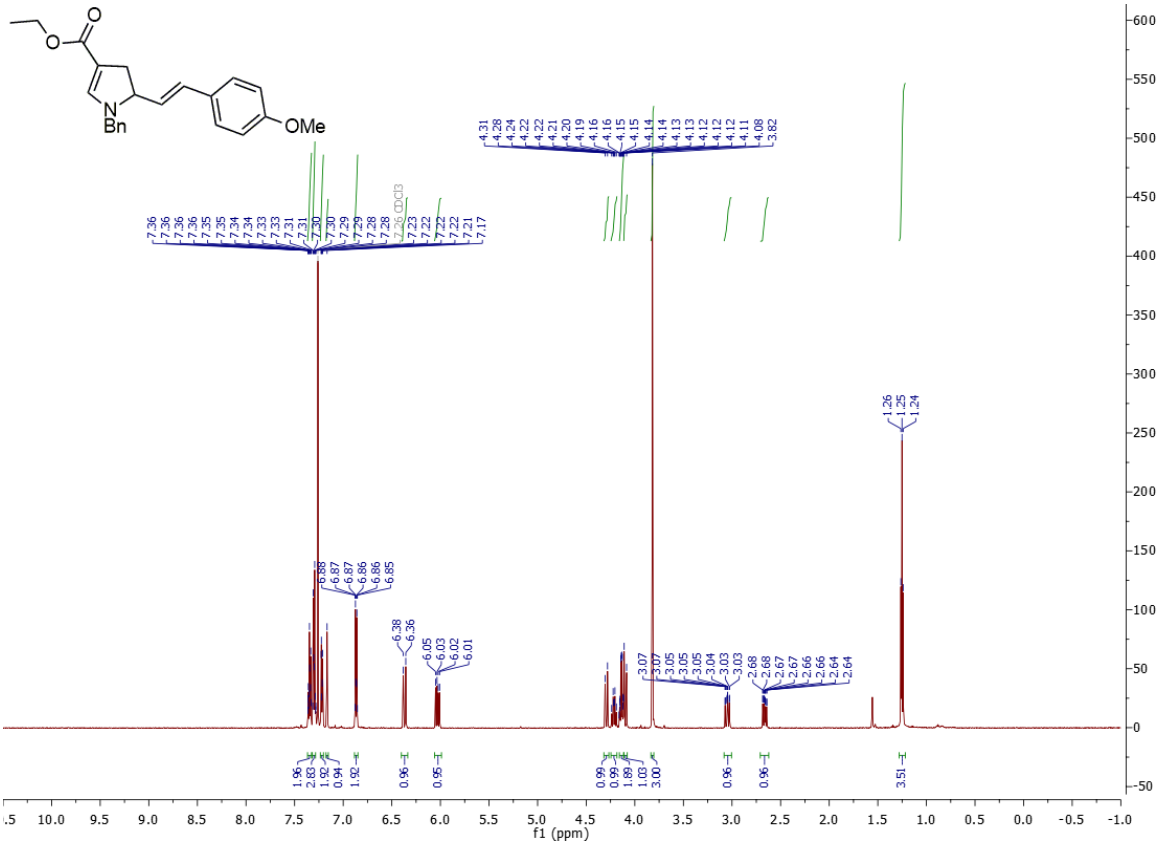

O
O
N
Bn
166.74
148.84
146.77
137.77
128.90
128.40
127.82
112.77
98.44
77.48
77.16 CDCl3
76.84
71.58
58.97
48.48
41.63
23.61
19.02
14.83
f1 (ppm)

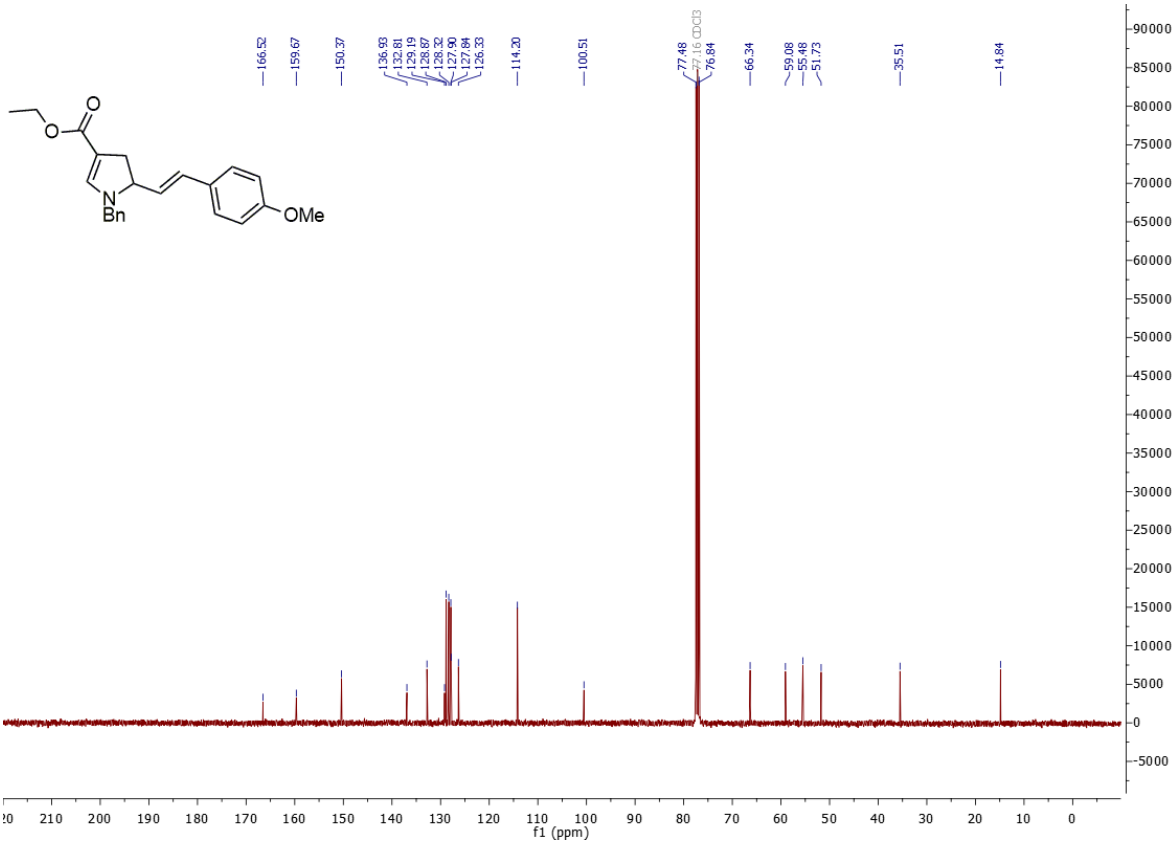

O
O
N
Bn
7.35
7.35
7.35
7.34
7.34
7.33
7.33
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26 CDCl3
7.25
7.25
7.24
7.24
6.97
6.00
5.98
5.97
5.95
5.21
5.18
5.18
5.17
4.14
4.12
4.11
4.09
4.08
4.06
4.03
2.86
2.84
2.73
2.70
1.36
1.23
1.22
1.21
2.07
1.05
1.91
0.88
0.90
0.98
0.95
3.20
0.98
0.97
3.00
2.97
f1 (ppm)

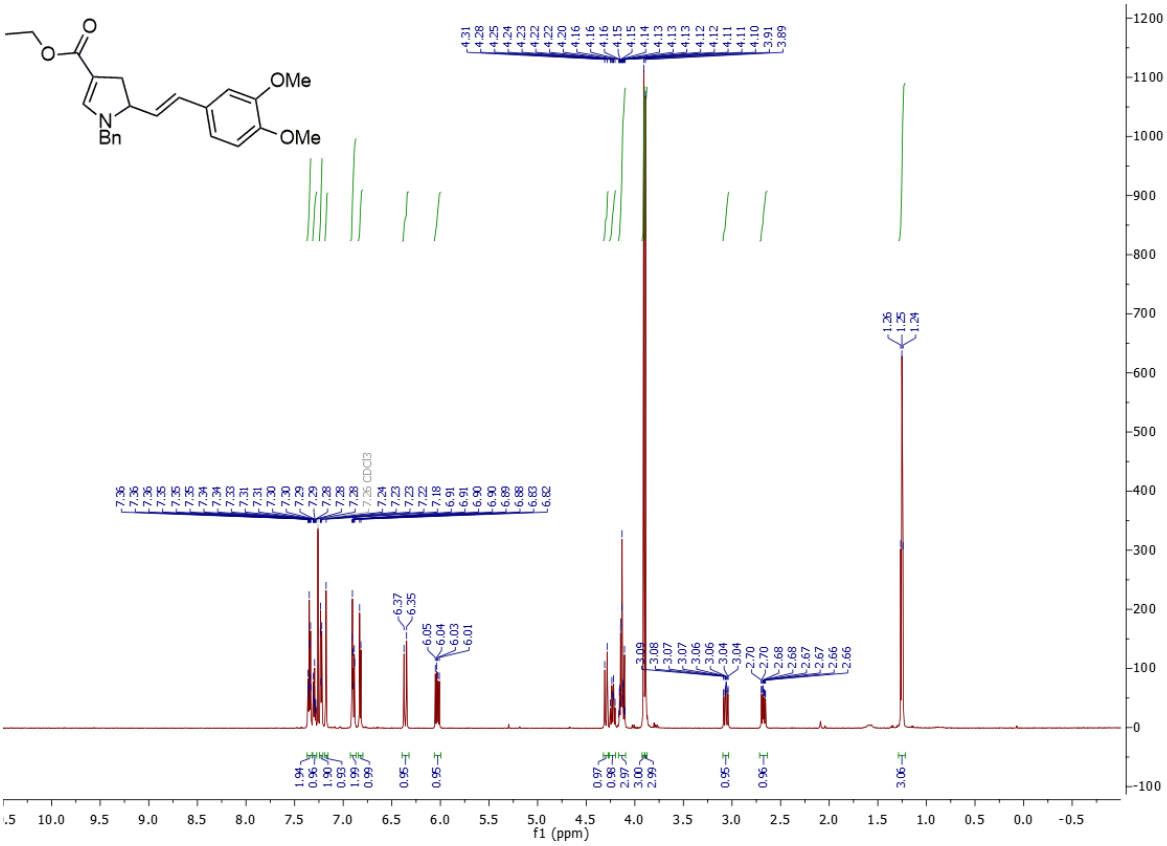

O
O
N
Bn
166.72
148.79
141.54
138.18
128.85
128.18
127.75
114.47
98.70
77.37
77.16 CDCl3
76.95
69.46
58.98
48.49
43.00
22.06
14.82
f1 (ppm)

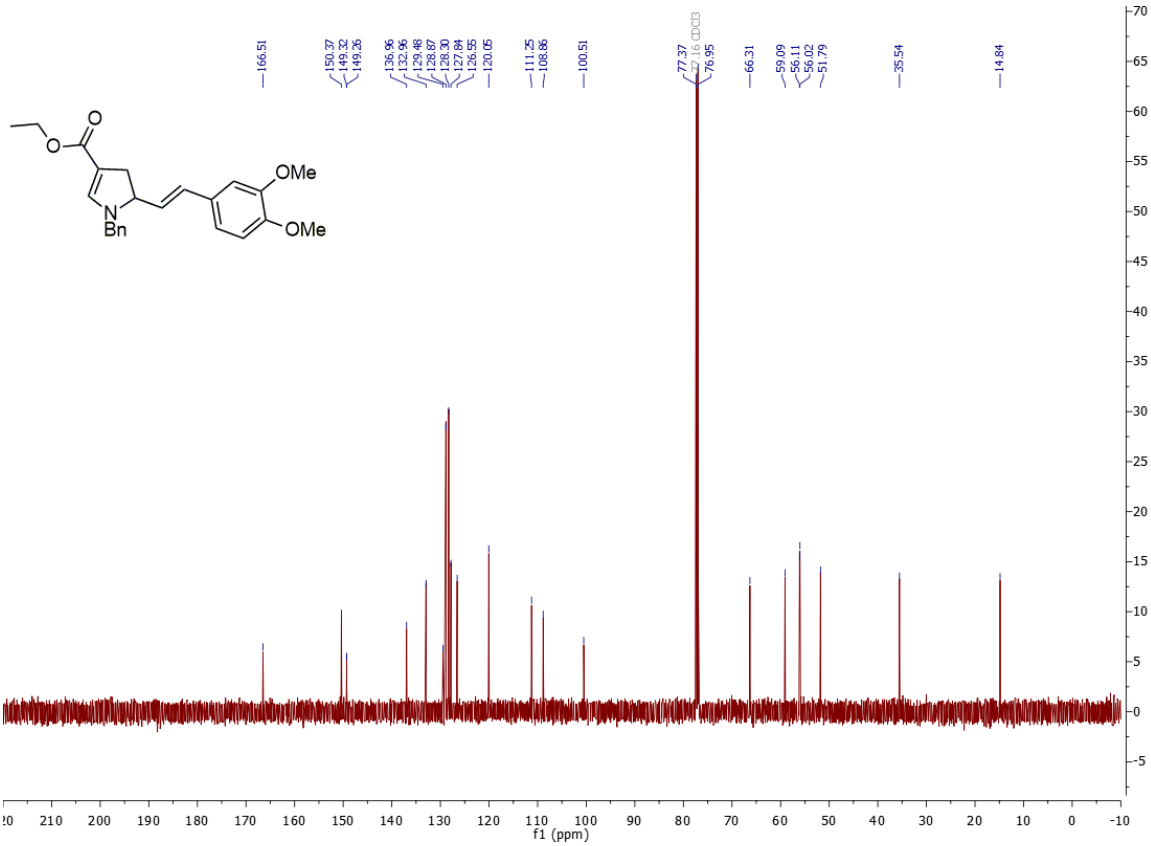

O
O
N
Bn
7.38
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.27
CDCl3
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.21
7.17
6.45
6.41
6.21
6.18
6.17
6.15
4.32
4.29
4.28
4.25
4.25
4.23
4.23
4.20
4.17
4.15
4.13
4.12
4.11
4.08
3.10
3.10
3.07
3.07
3.06
3.06
3.03
3.03
2.71
2.71
2.69
2.68
2.67
2.67
2.65
2.65
1.27
1.26
1.24
7.24
1.92
0.87
0.85
0.88
0.84
0.96
2.62
0.87
0.88
3.00
f1 (ppm)

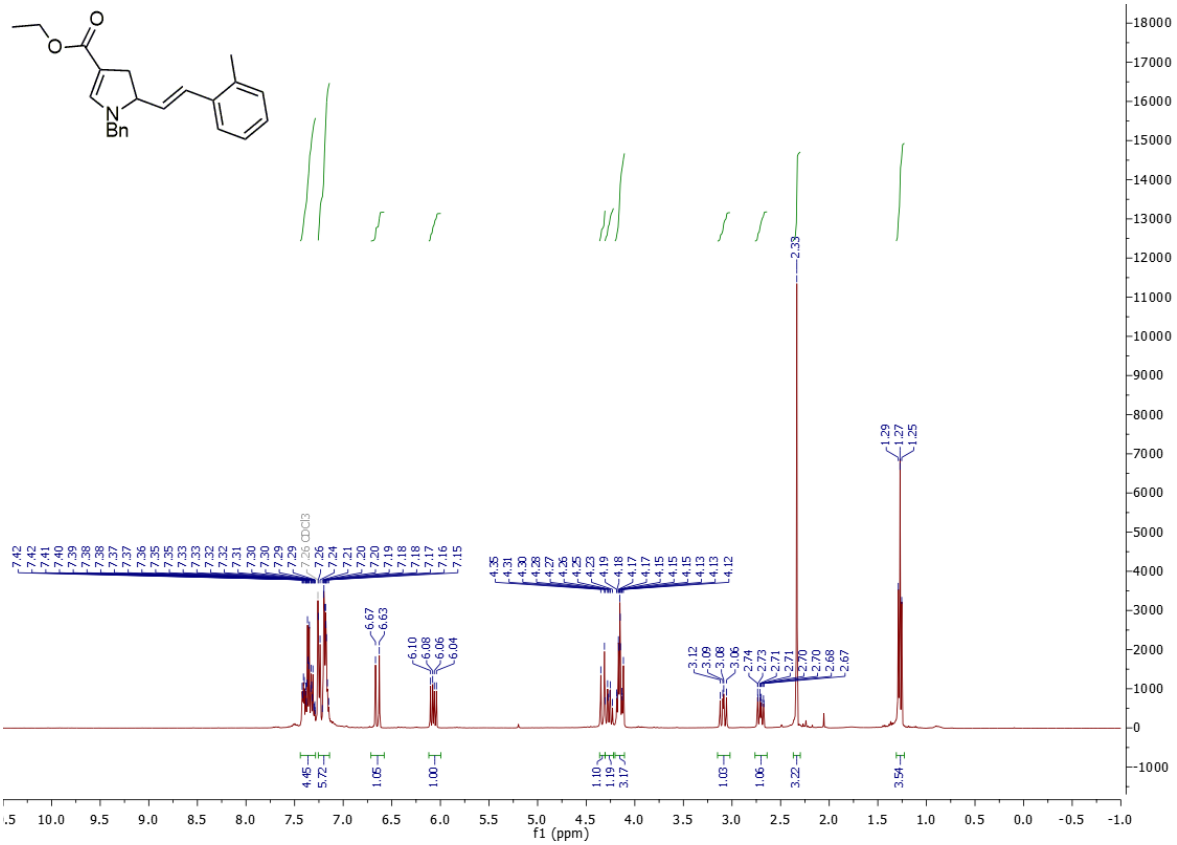

O
O
N
Bn
166.44
150.34
136.82
136.41
133.27
128.87
128.77
128.53
128.29
128.11
127.85
126.66
100.62
77.37
77.16
CDCl3
76.95
66.13
59.07
51.82
35.46
14.81
f1 (ppm)

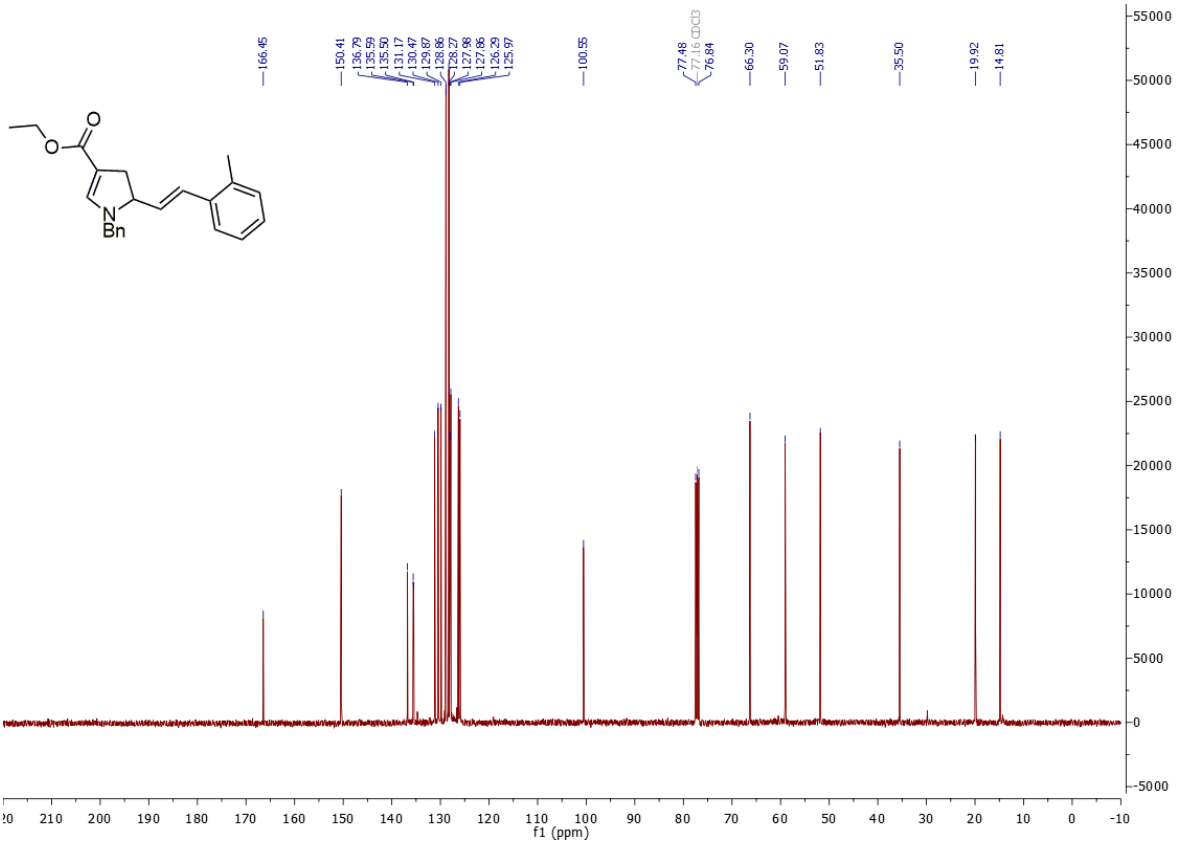

OMe
Bn
f1 (ppm)

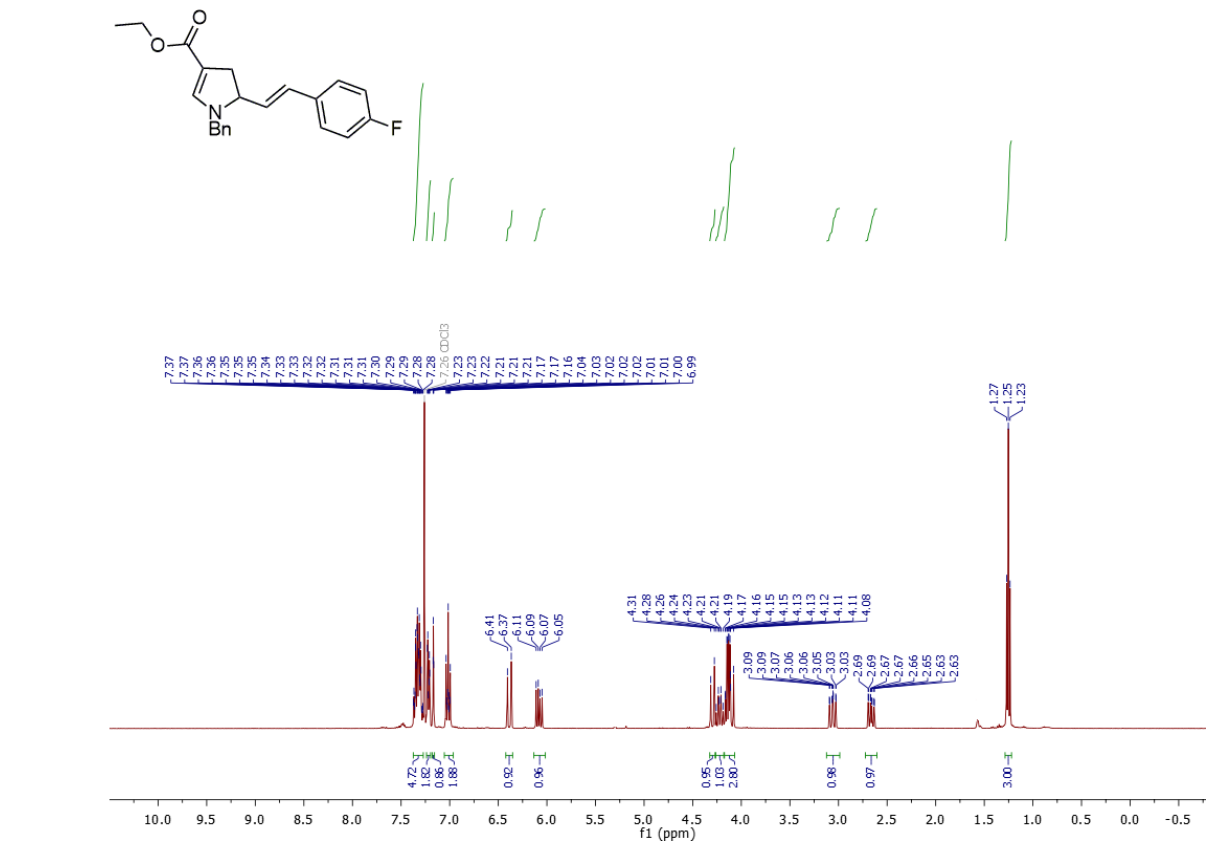

OMe
Bn
f1 (ppm)

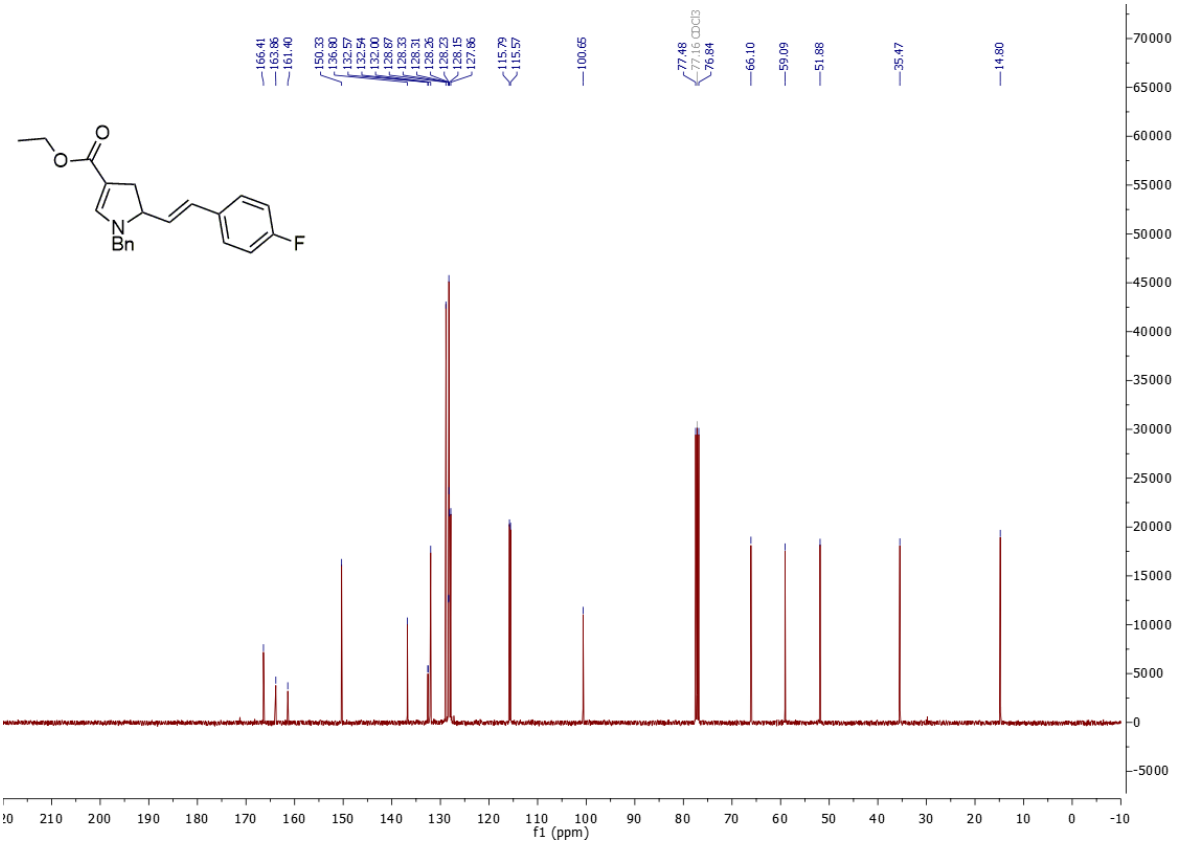

OMe
OMe
N
Bn
f1 (ppm)

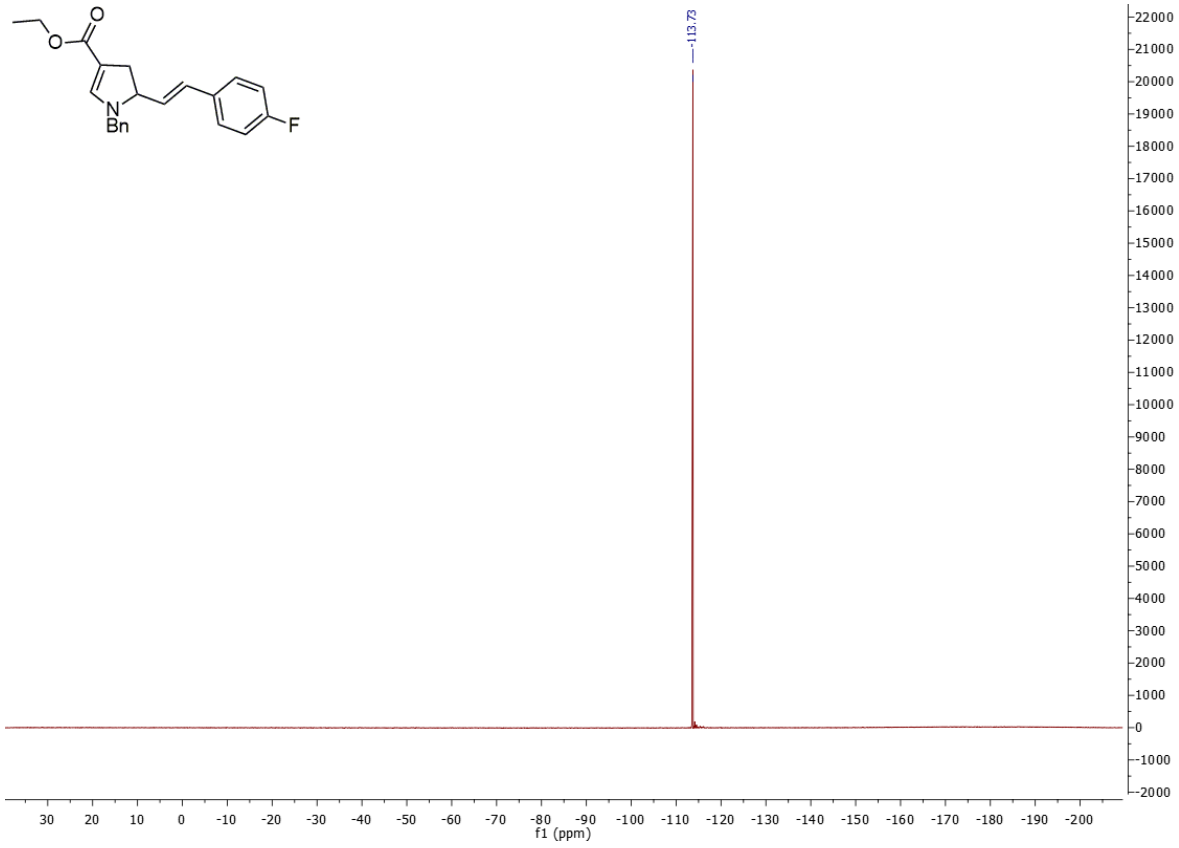

OMe
OMe
N
Bn
f1 (ppm)


O
O
N
Bn
7.42
7.42
7.41
7.40
7.39
7.38
7.38
7.37
7.37
7.36
7.35
7.35
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.29
7.26 CDCl3
7.26
7.24
7.21
7.20
7.20
7.19
7.18
7.18
7.17
7.16
7.15
6.67
6.63
6.10
6.08
6.06
6.04
4.35
4.31
4.30
4.28
4.27
4.26
4.25
4.23
4.19
4.18
4.17
4.17
4.15
4.15
4.15
4.13
4.13
4.12
3.12
3.09
3.08
3.06
2.74
2.73
2.71
2.71
2.70
2.70
2.68
2.67
2.33
1.29
1.27
1.25
4.45
5.72
1.05
1.00
1.10
1.19
3.17
1.03
1.06
3.22
3.54
f1 (ppm)

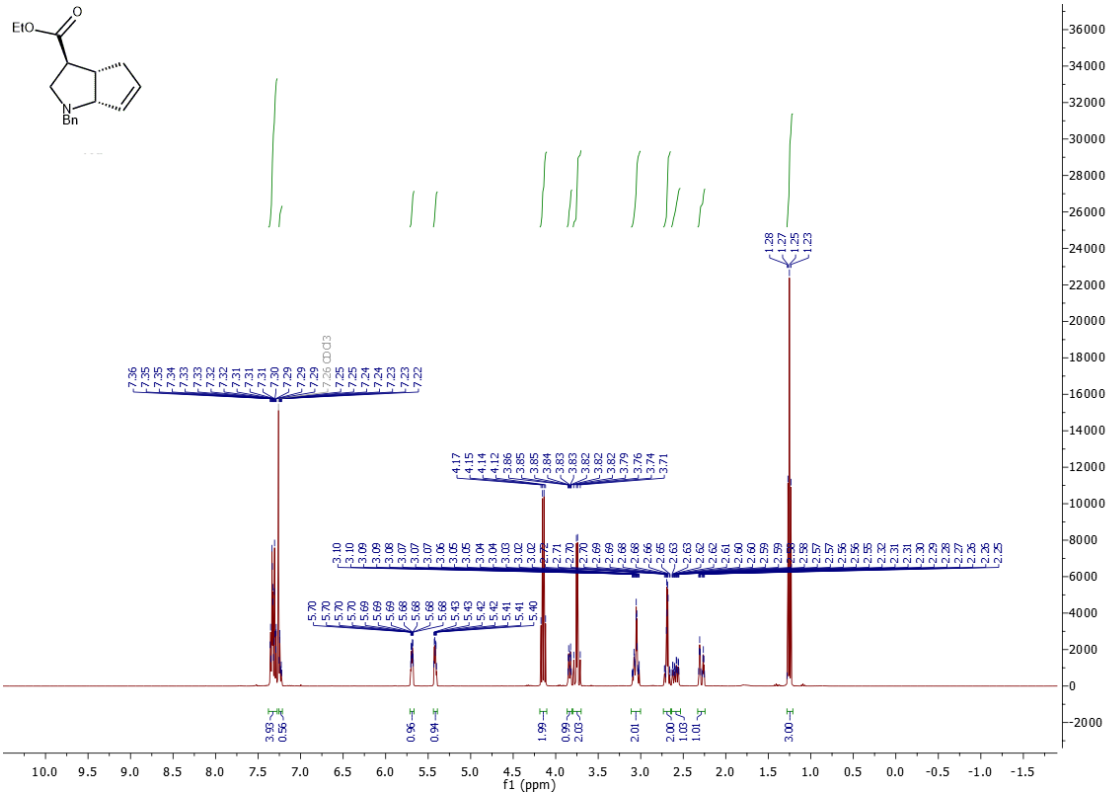

O
O
N
Bn
166.45
150.41
136.79
135.59
135.50
131.17
130.47
129.87
128.86
128.27
127.98
127.86
126.29
125.97
100.55
77.48
77.16 CDCl3
76.84
66.30
59.07
51.83
35.50
19.92
14.81
f1 (ppm)

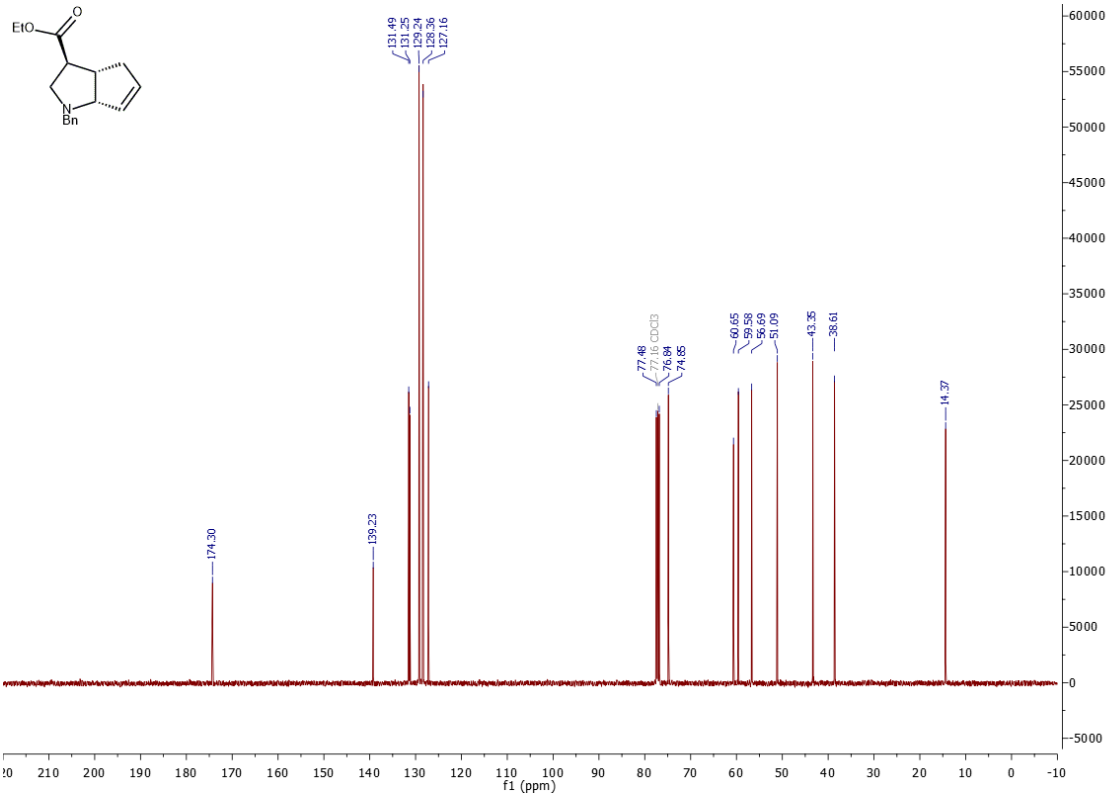

O
O
N
Bn
F
7.37
7.26 CDCl3
6.99
1.27
1.25
1.23
6.41
6.37
6.11
6.09
6.07
6.05
4.31
4.28
4.26
4.24
4.23
4.21
4.19
4.17
4.16
4.15
4.13
4.12
4.11
4.08
3.09
3.07
3.06
3.05
3.03
2.69
2.67
2.66
2.65
2.63
4.72
1.82
0.86
1.88
0.92
0.96
0.95
1.03
2.80
0.98
0.97
3.00
f1 (ppm)

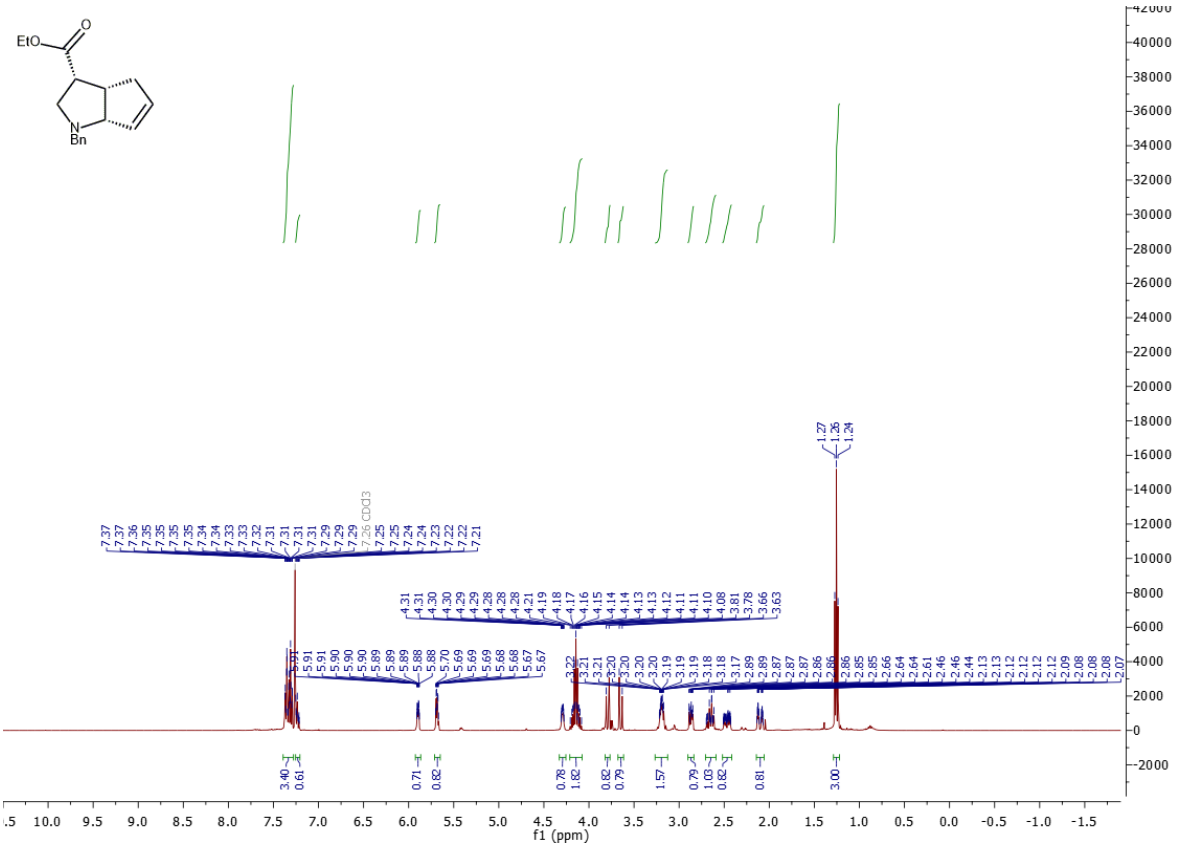

O
O
N
Bn
F
166.41
163.96
161.40
150.33
136.80
132.57
132.54
132.00
128.67
128.33
128.31
128.26
128.23
128.15
127.86
115.79
115.57
100.65
77.48
77.16 CDCl3
76.84
66.10
59.09
51.88
35.47
14.80
f1 (ppm)

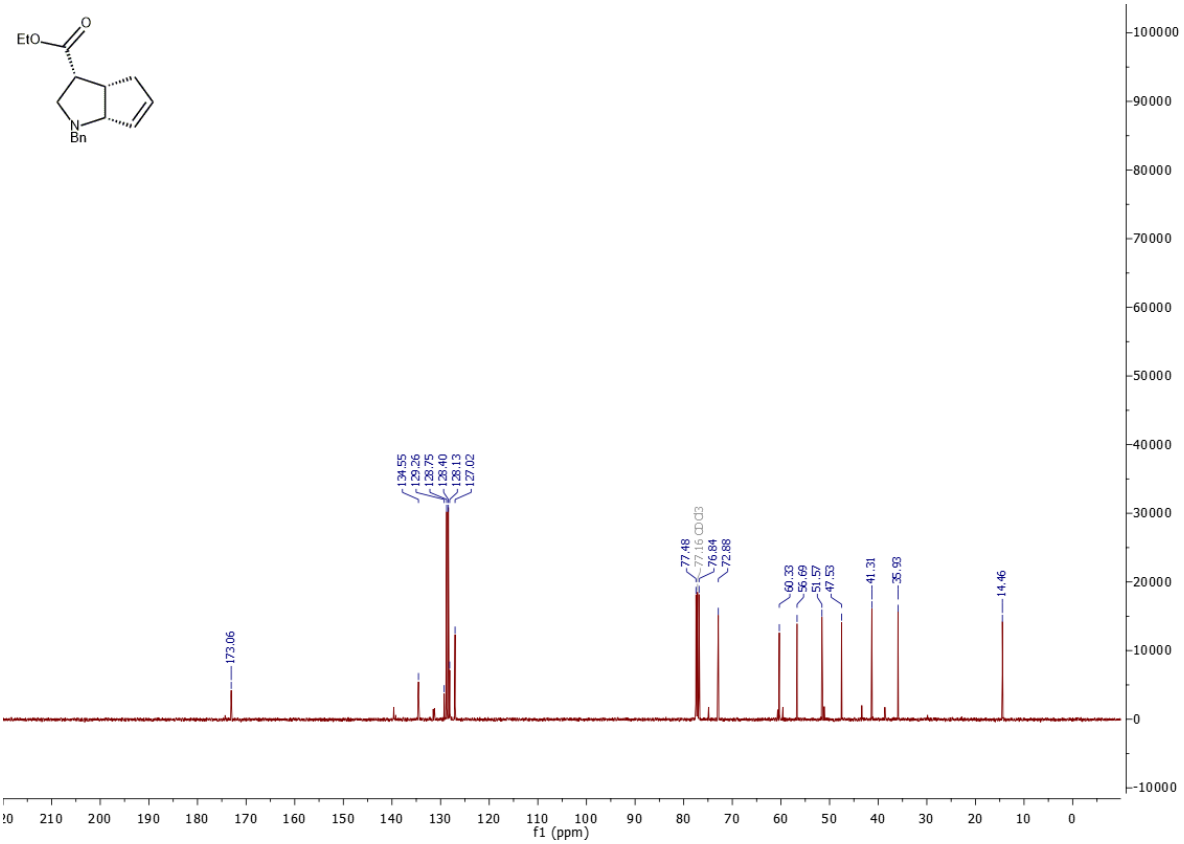

O
O
N
Bn
F
-113.73
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

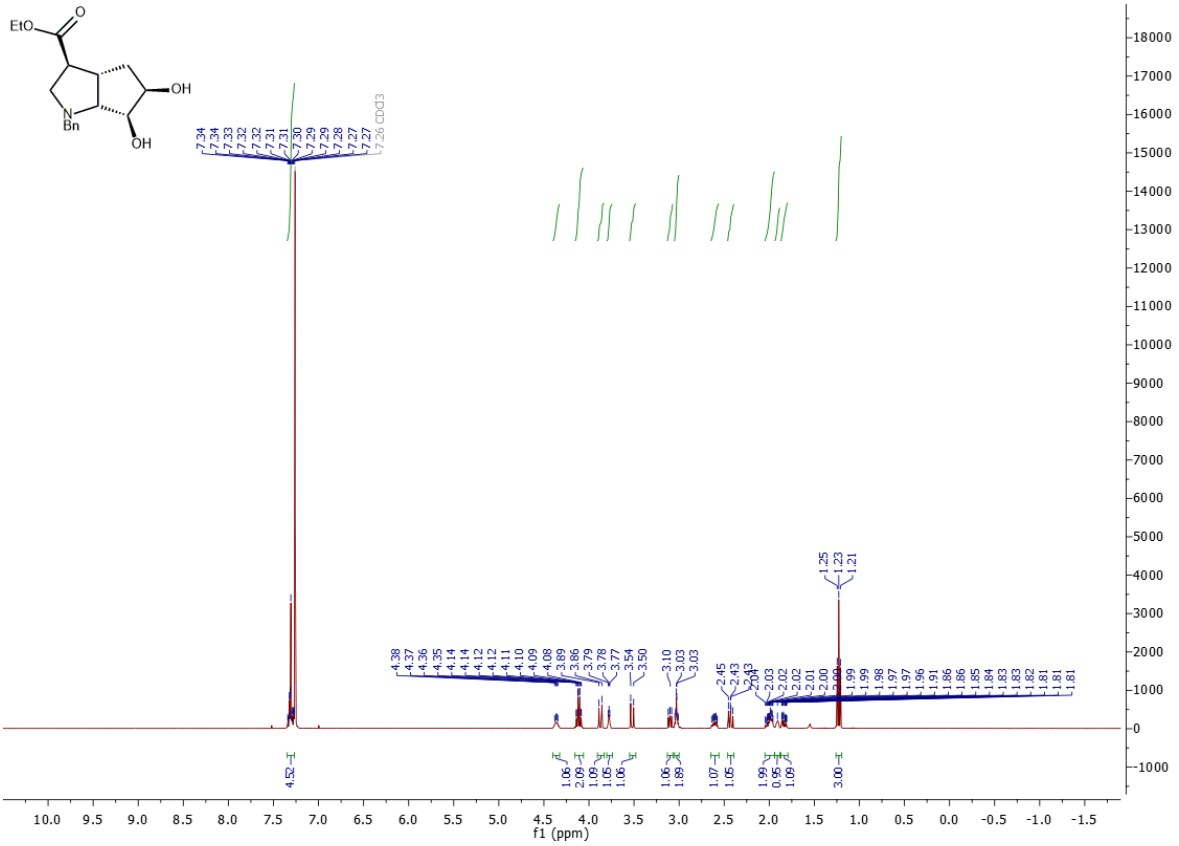
Appendix 2- Supporting Information for Chapter 3

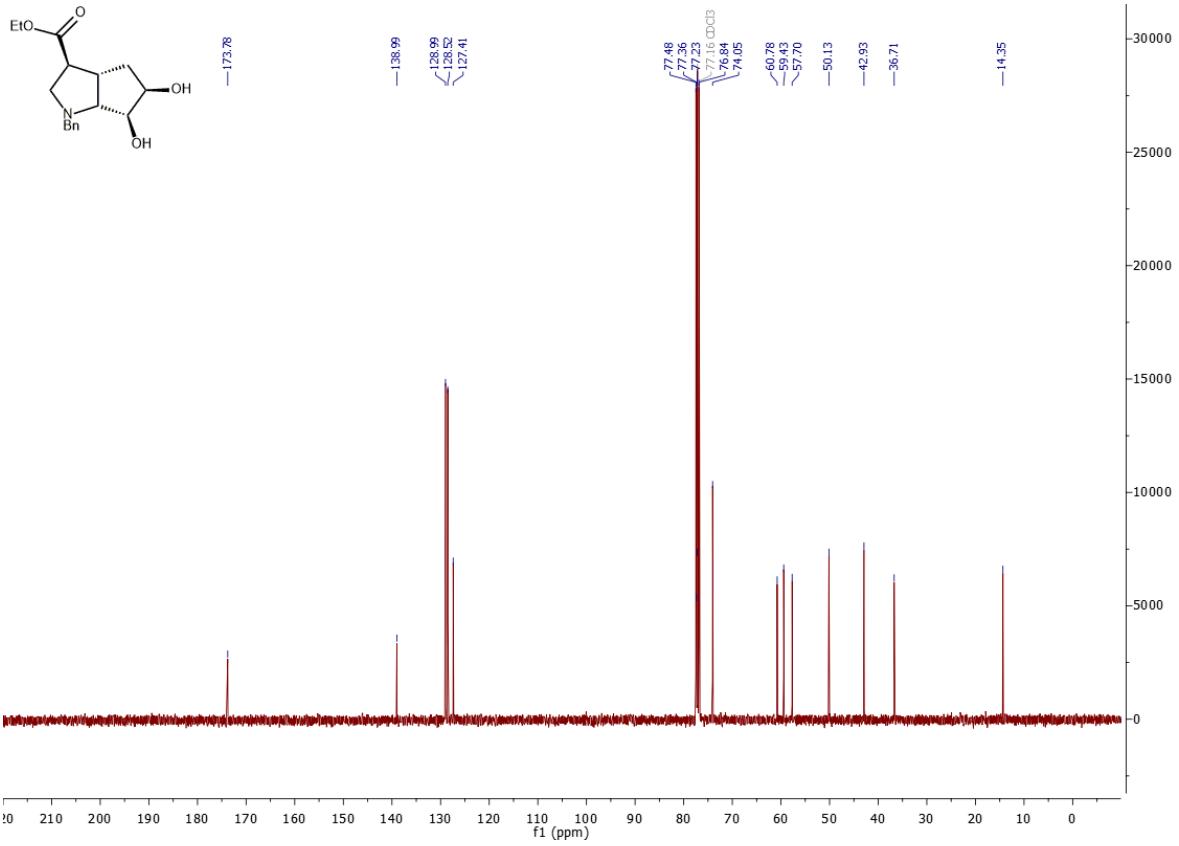


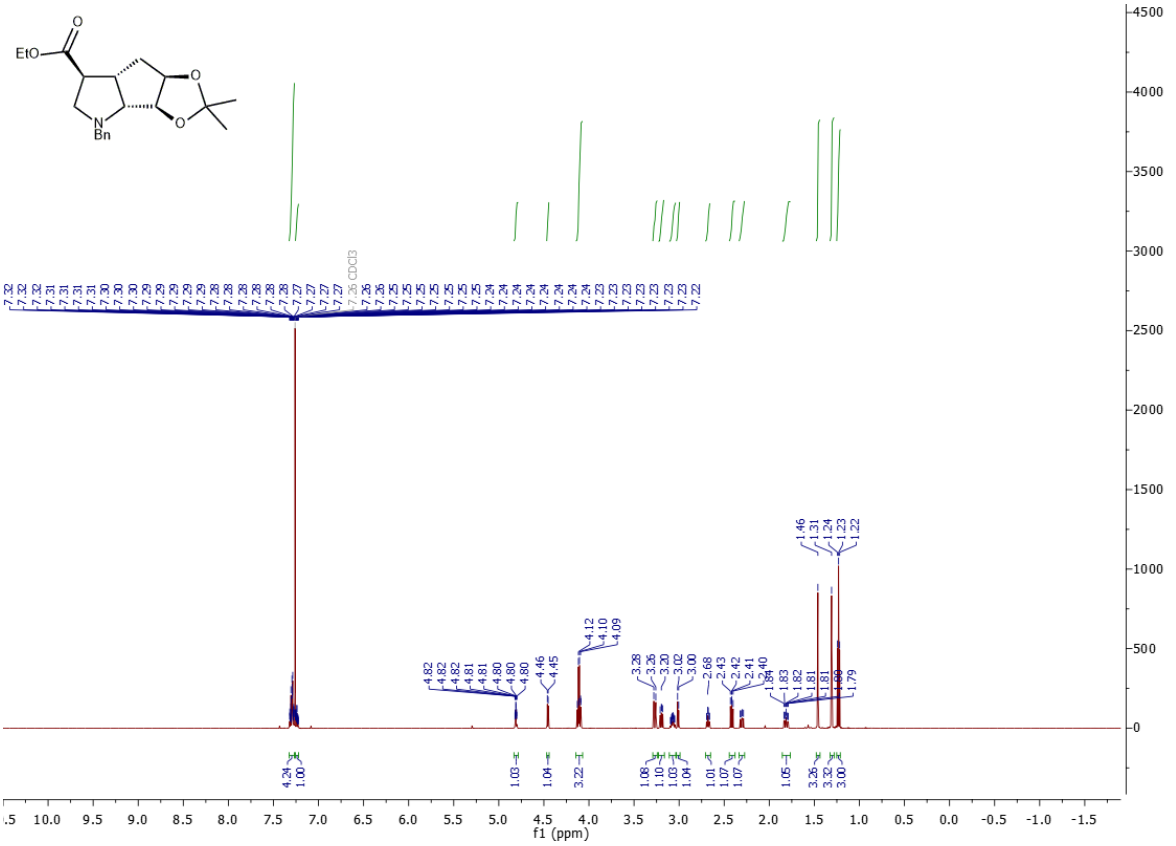


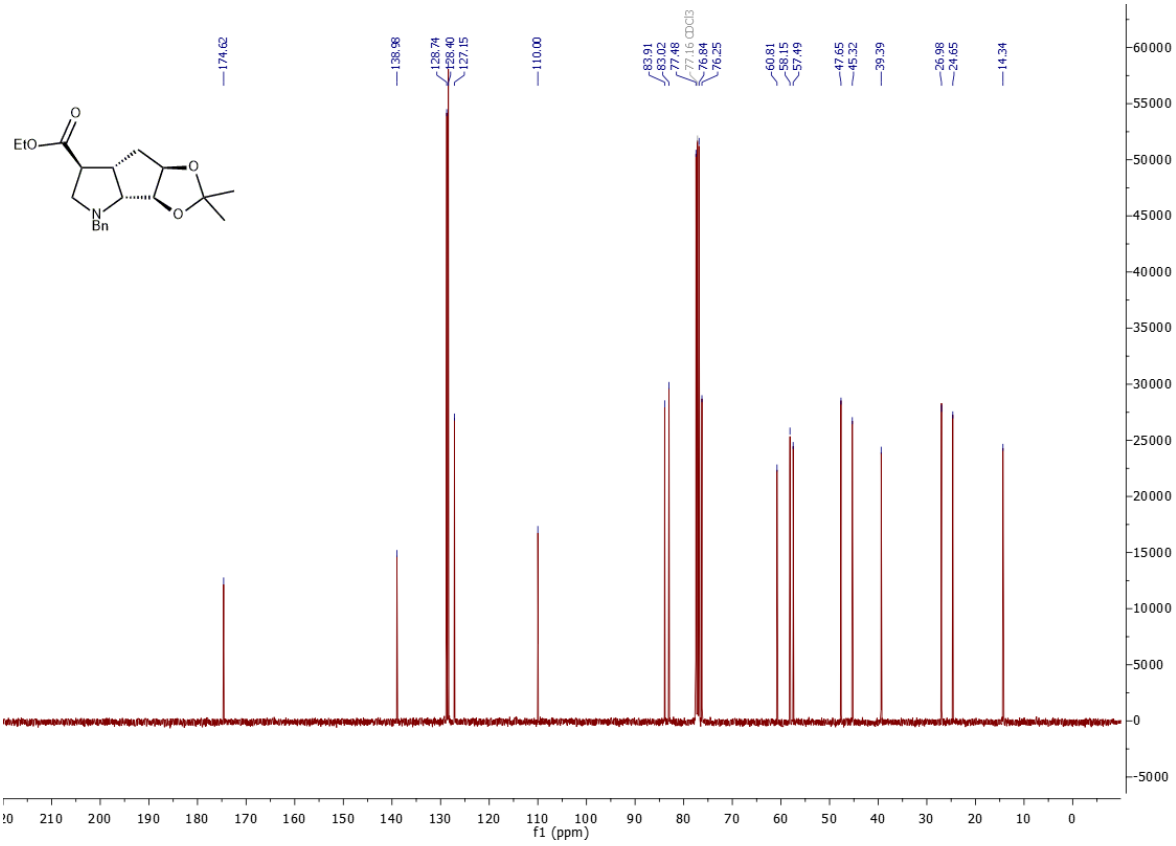

EtO
O
N
Bn
f1 (ppm)

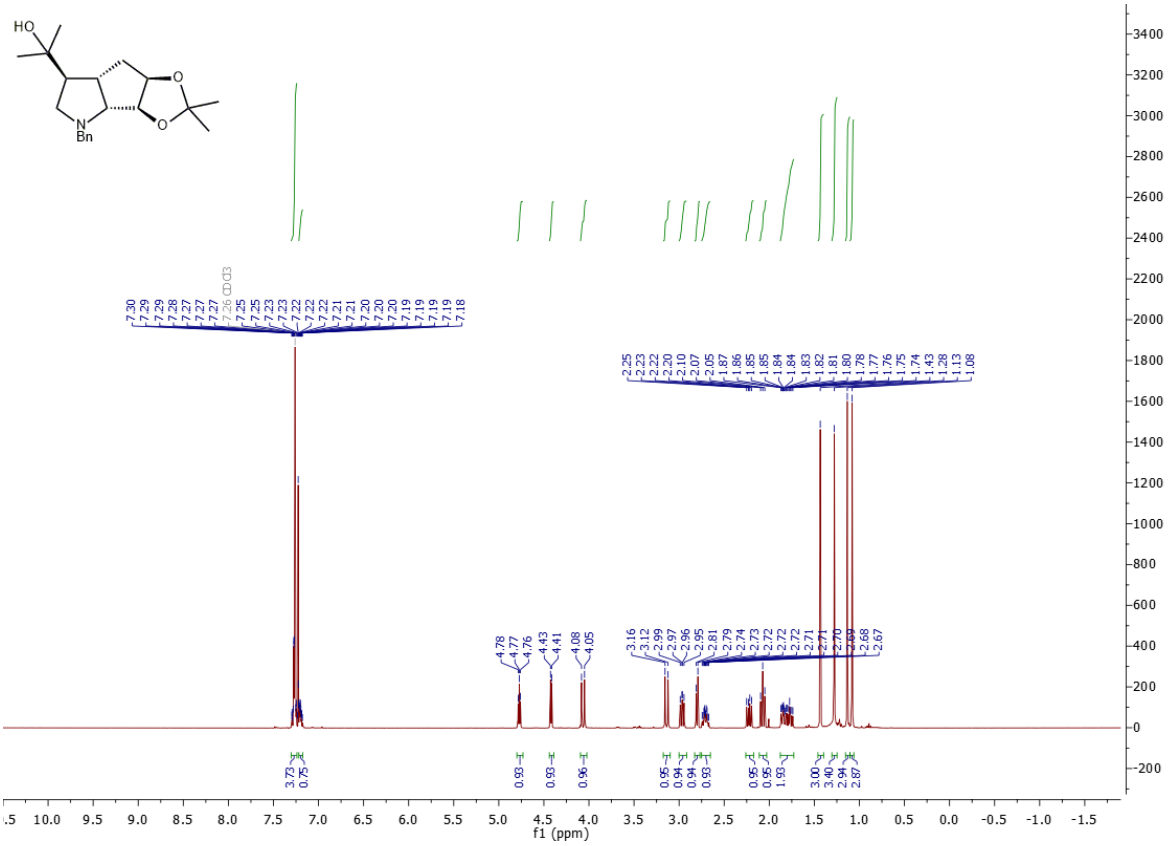

EtO
O
N
Bn
173.06
134.55
129.26
128.75
128.49
128.13
127.02
77.48
77.16
76.84
72.88
60.33
56.69
51.57
47.53
41.31
35.93
14.46
f1 (ppm)

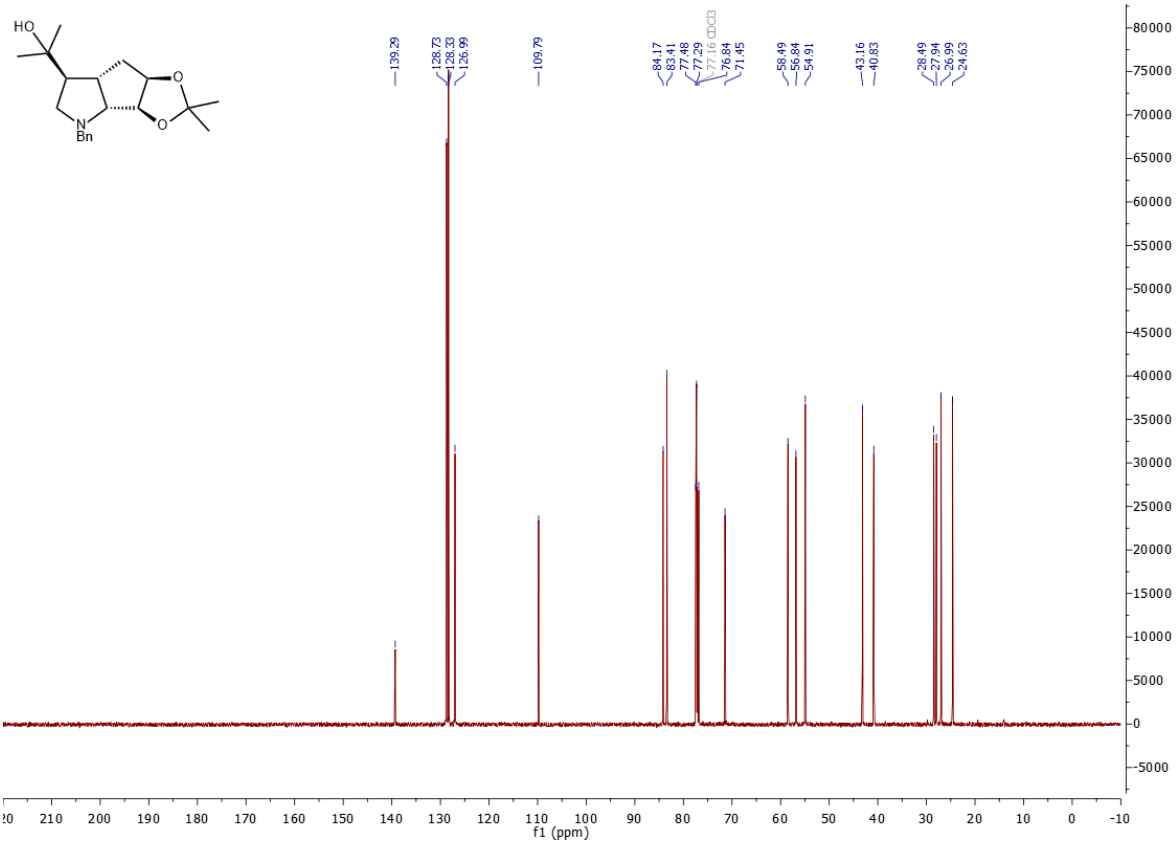

EtO
O
OH
N
Bn
OH
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.27
7.27
7.26 CDCl3
4.38
4.37
4.36
4.35
4.14
4.14
4.12
4.12
4.11
4.10
4.09
4.08
3.89
3.86
3.79
3.78
3.77
3.54
3.50
3.10
3.03
3.03
2.45
2.43
2.43
2.04
2.03
2.02
2.02
2.01
2.00
1.99
1.99
1.98
1.97
1.97
1.96
1.91
1.86
1.86
1.85
1.84
1.83
1.82
1.81
1.81
1.81
1.25
1.23
1.21
4.52
1.06
2.09
1.09
1.05
1.06
1.06
1.89
1.07
1.05
1.99
0.95
1.09
3.00
f1 (ppm)

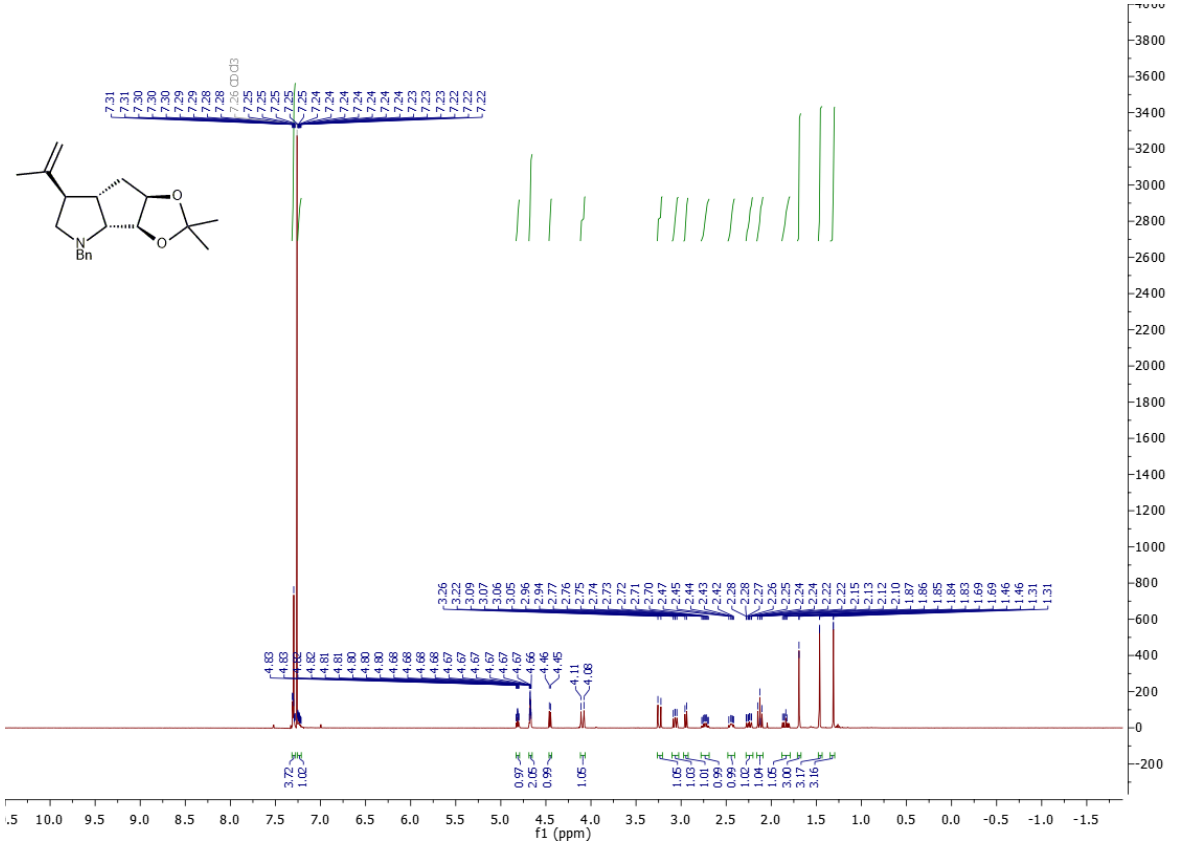

EtO
O
OH
N
Bn
OH
173.78
138.99
128.99
128.52
127.41
77.48
77.36
77.23
77.16 CDCl3
76.84
74.05
60.78
59.43
57.70
50.13
42.93
36.71
14.35
f1 (ppm)

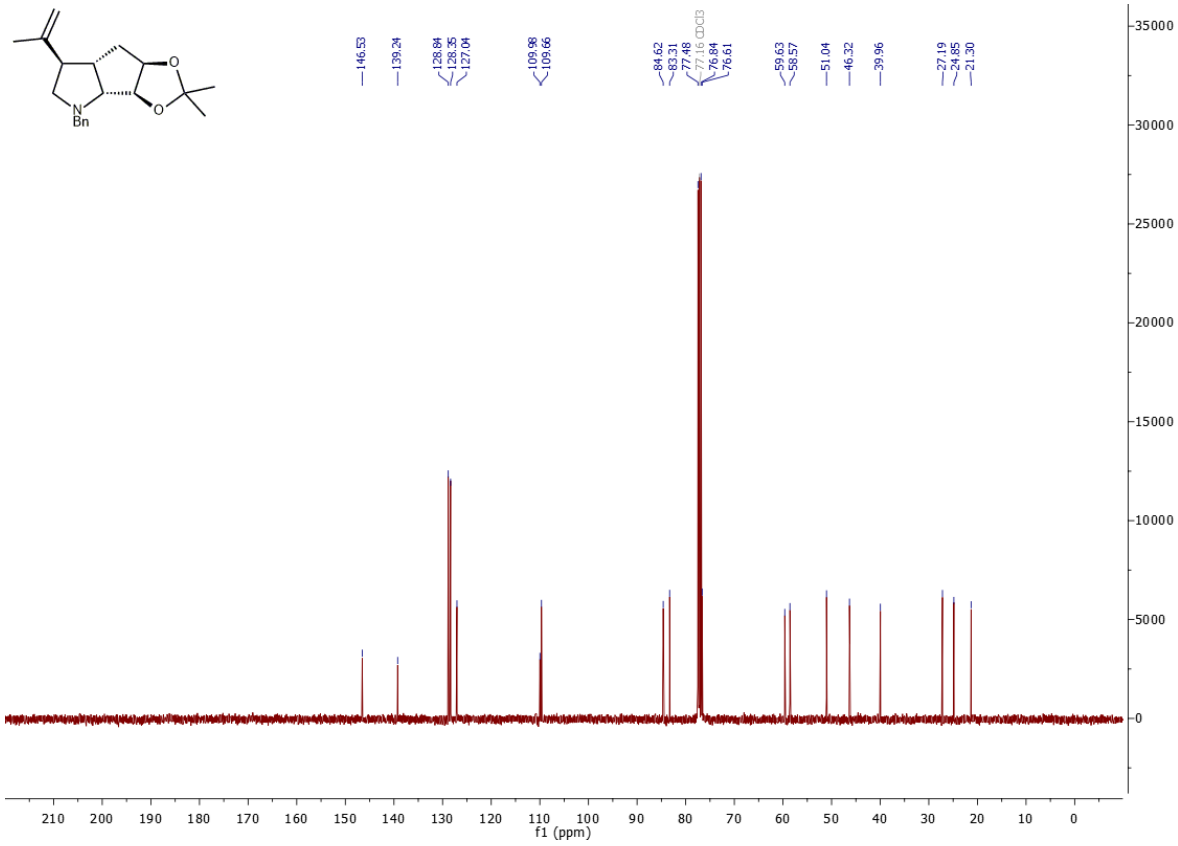

EtO
O
N
Bn
f1 (ppm)

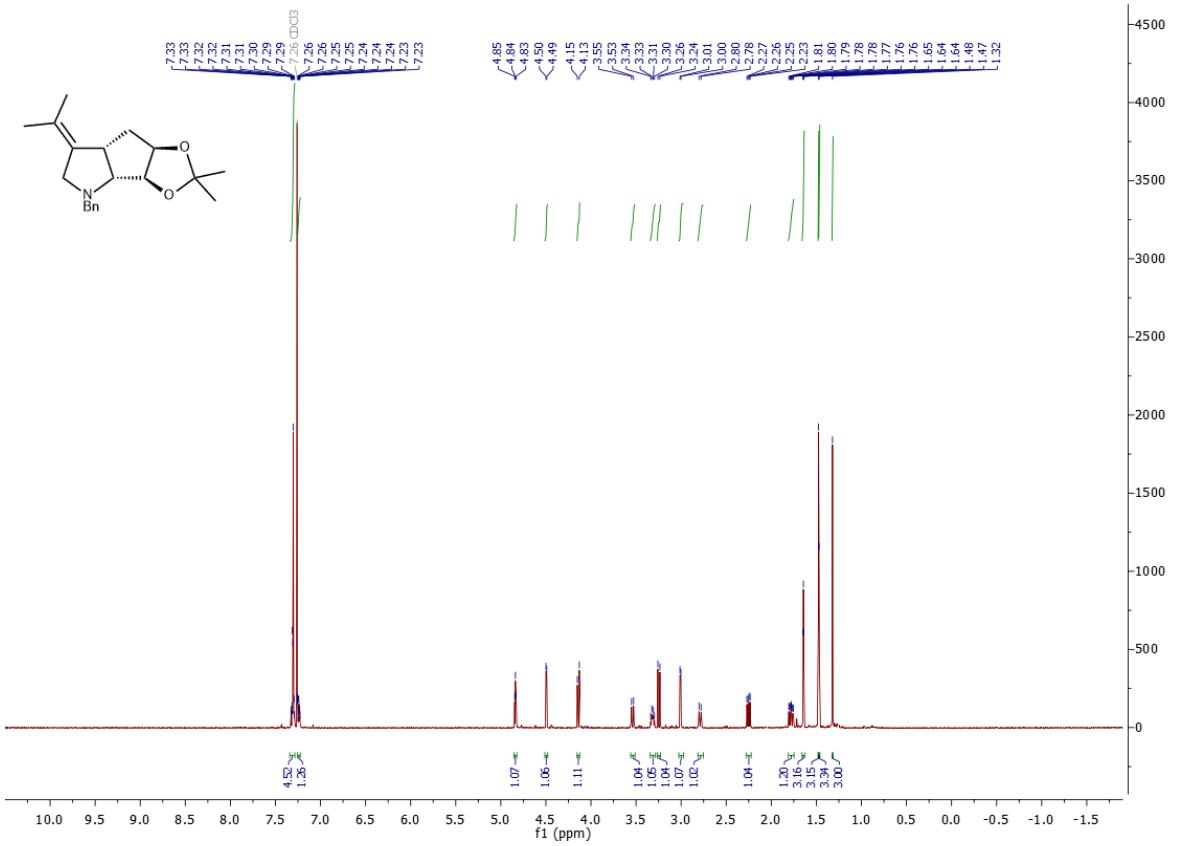

EtO
O
N
Bn
f1 (ppm)

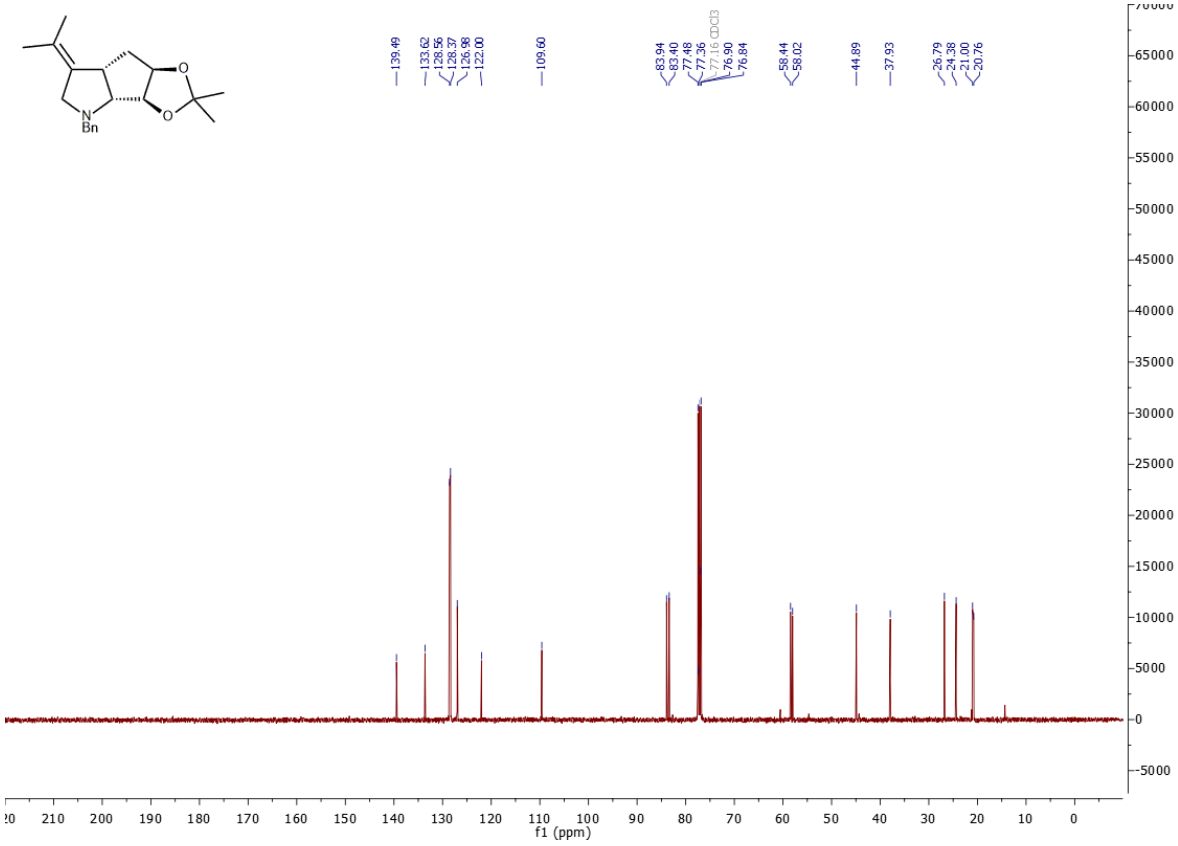

HO
N
Bn
O
O
f1 (ppm)

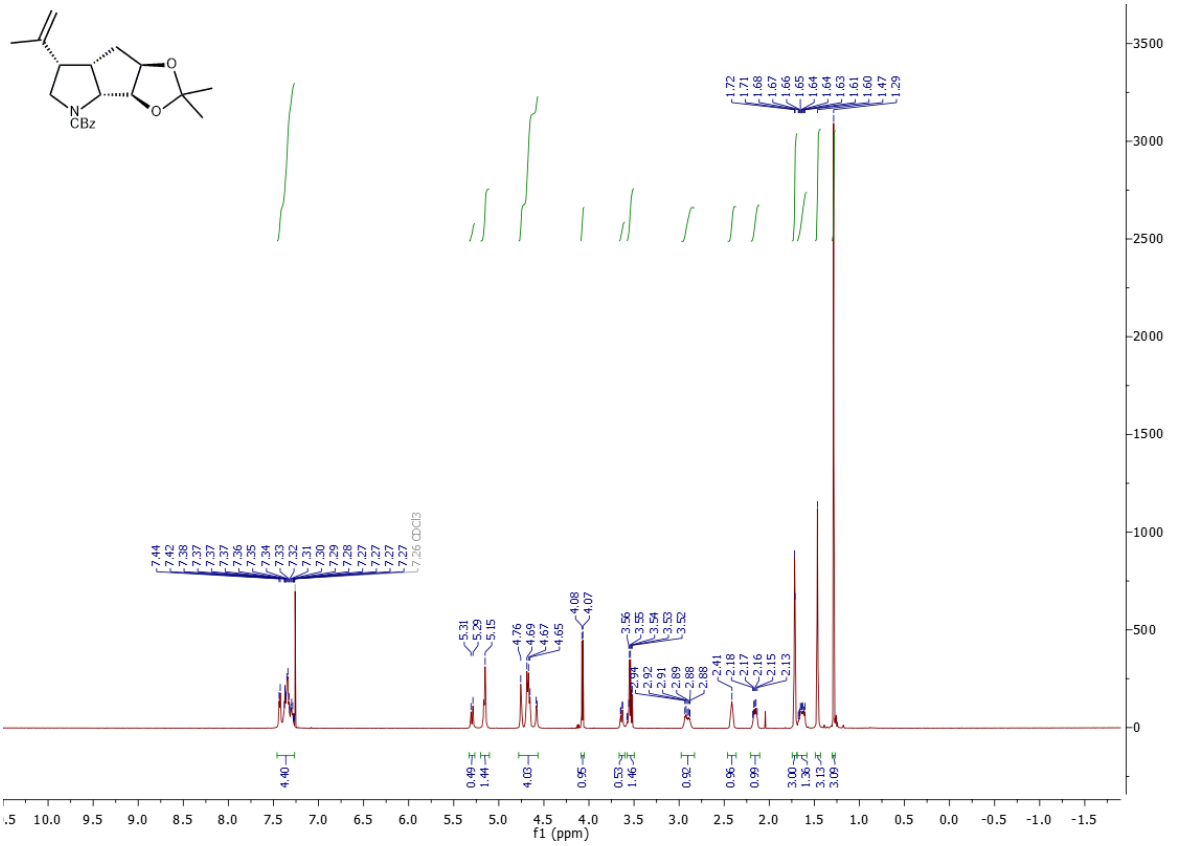

HO
N
Bn
O
O
f1 (ppm)

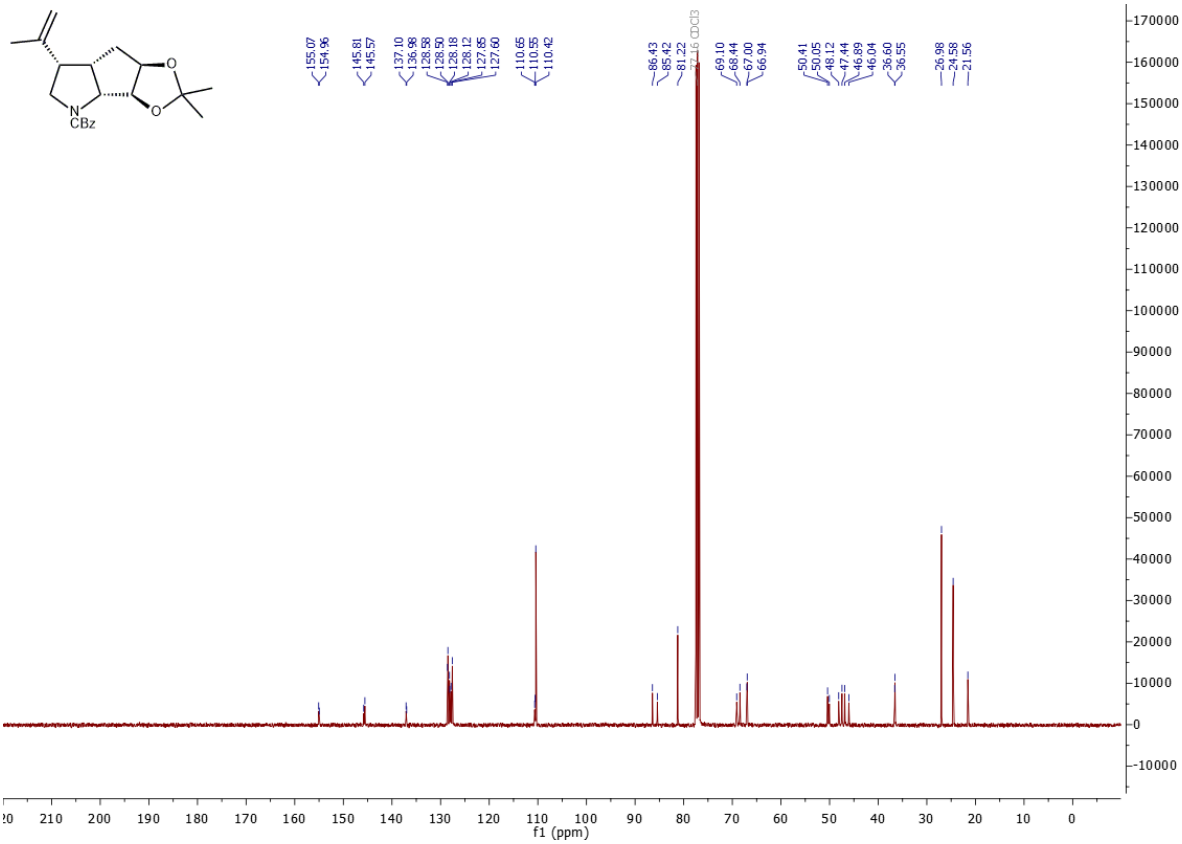

f1 (ppm)

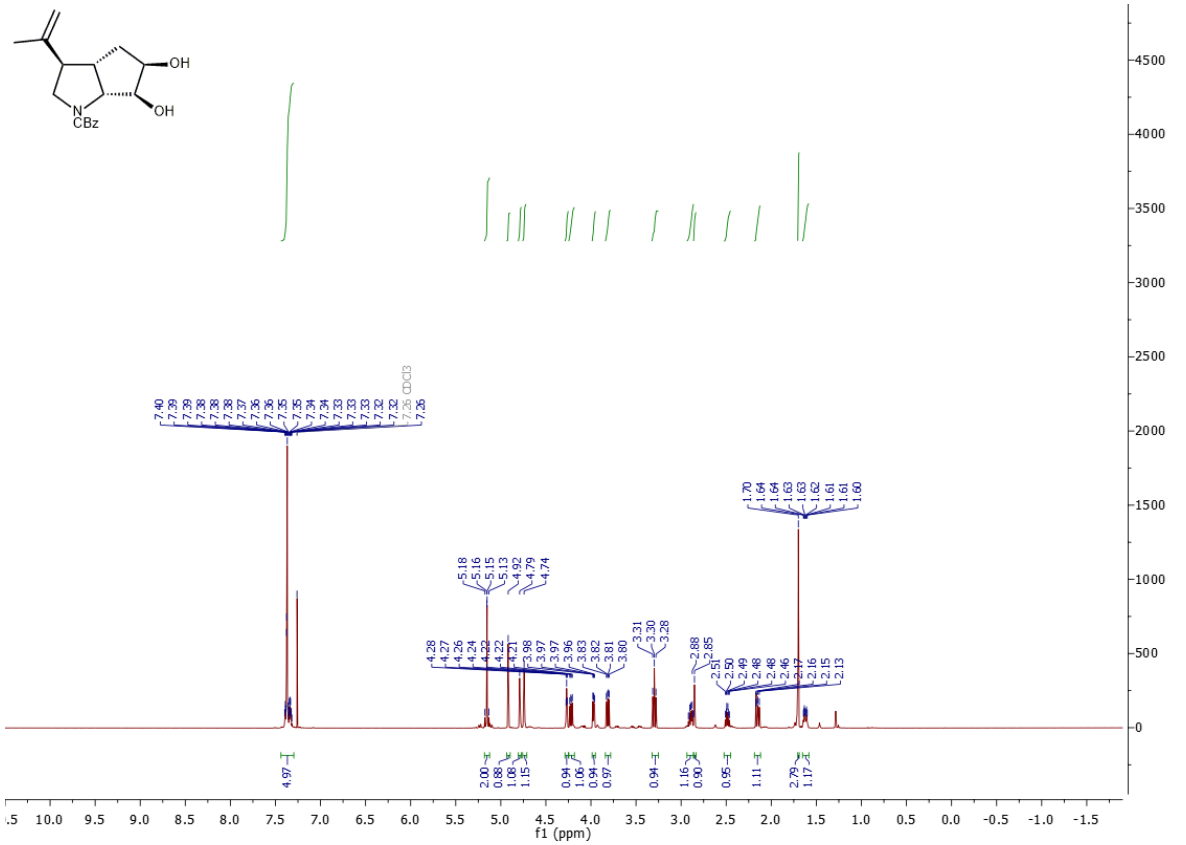

f1 (ppm)

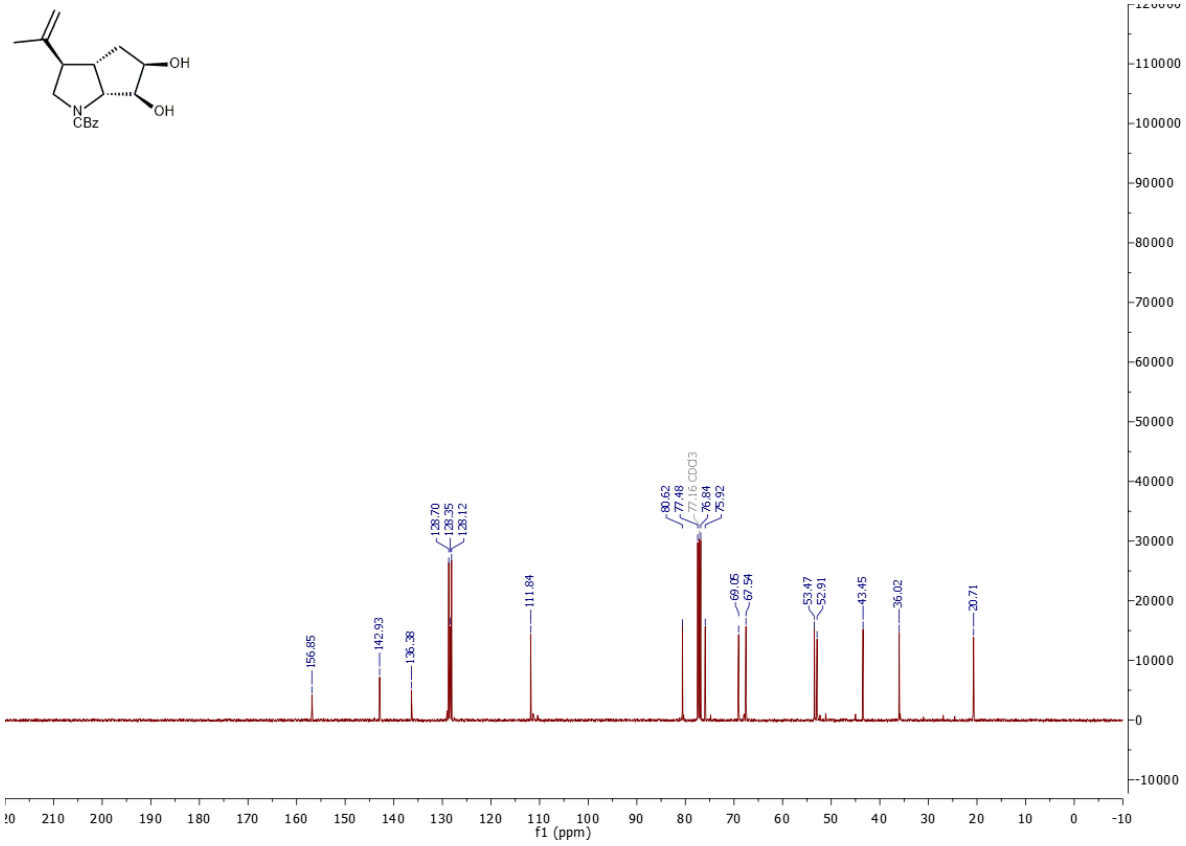

7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.26 CDCl3
7.26
7.26
7.25
7.25
7.24
7.24
7.24
7.23
7.23
4.85
4.84
4.83
4.50
4.49
4.15
4.13
3.55
3.53
3.34
3.33
3.31
3.30
3.26
3.24
3.01
3.00
2.80
2.78
2.27
2.26
2.25
2.23
1.81
1.80
1.79
1.78
1.78
1.77
1.76
1.76
1.65
1.64
1.64
1.48
1.47
1.32
N
Bn
O
O
4.52
1.26
1.07
1.06
1.11
1.04
1.05
1.04
1.07
1.02
1.04
1.20
3.16
3.15
3.34
3.00
f1 (ppm)

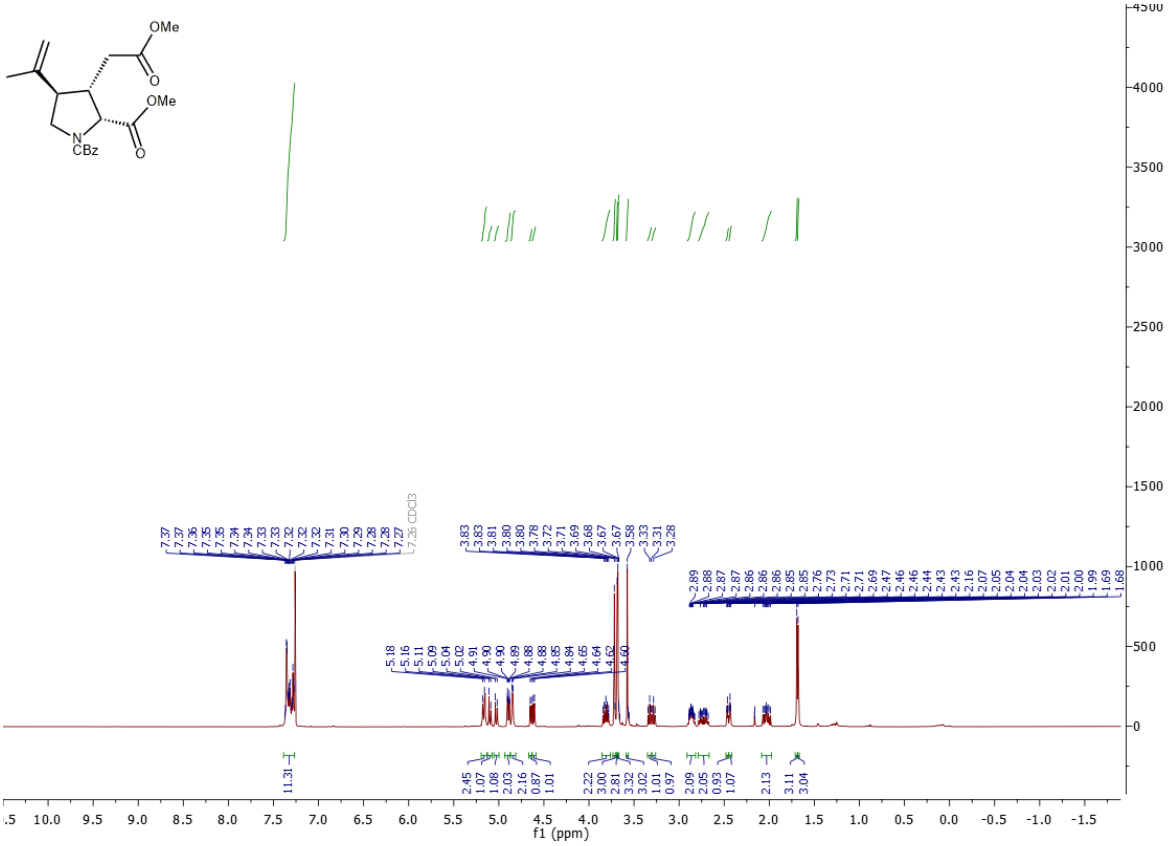

N
Bn
O
O
139.49
133.62
128.56
128.37
126.98
122.00
109.60
83.94
83.40
77.48
77.36
77.16 CDCl3
76.90
76.84
58.44
58.02
44.89
37.93
26.79
24.38
21.00
20.76
f1 (ppm)

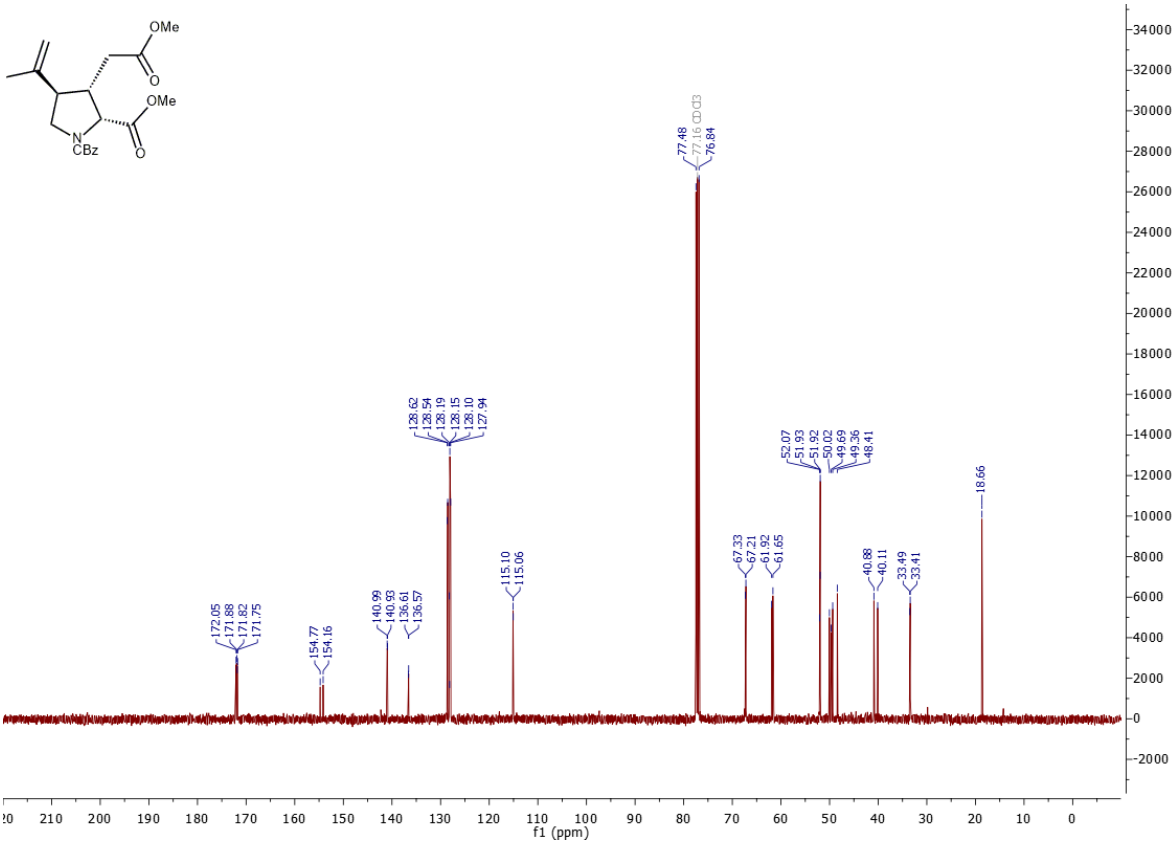

CBz
7.44
7.42
7.38
7.37
7.37
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.27
7.27
7.27
7.26 CDCl3
5.31
5.29
5.15
4.76
4.69
4.67
4.65
4.08
4.07
3.56
3.55
3.54
3.53
3.52
2.94
2.92
2.91
2.89
2.88
2.88
2.41
2.18
2.17
2.16
2.15
2.13
1.72
1.71
1.68
1.67
1.66
1.65
1.64
1.64
1.63
1.61
1.60
1.47
1.29
4.40
0.49
1.44
4.03
0.95
0.53
1.46
0.92
0.96
0.99
3.00
1.36
3.13
3.09
f1 (ppm)

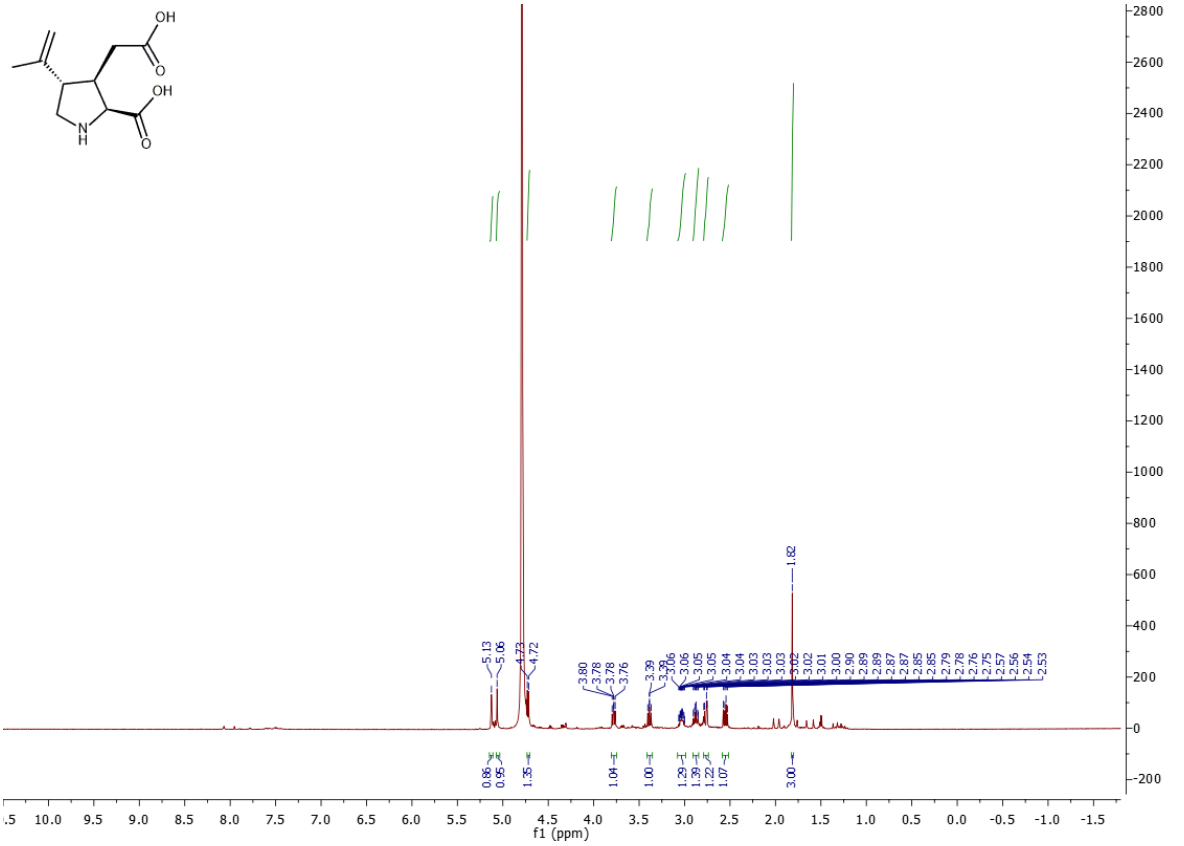

CBz
155.07
154.96
145.81
145.57
137.10
136.98
128.58
128.50
128.18
128.12
127.85
127.60
110.65
110.55
110.42
86.43
85.42
81.22
77.10 CDCl3
69.10
68.44
67.00
66.94
50.41
50.05
48.12
47.44
46.89
46.04
36.60
36.55
26.98
24.58
21.56
f1 (ppm)

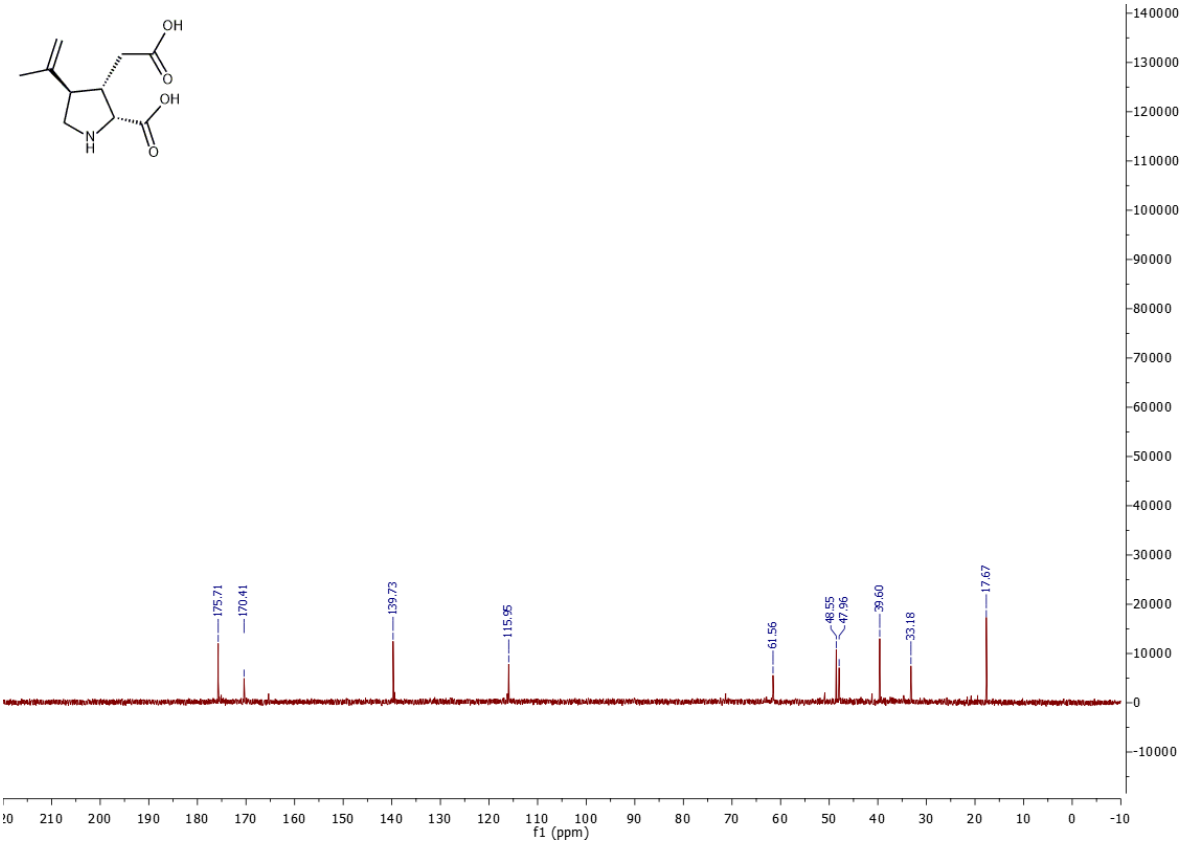

OH
OH
N
CBz
7.40
7.39
7.39
7.39
7.38
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.28 CDCl3
7.26
5.18
5.16
5.15
5.13
4.92
4.79
4.74
4.28
4.27
4.26
4.24
4.22
4.21
3.98
3.97
3.97
3.96
3.83
3.82
3.81
3.80
3.31
3.30
3.28
2.88
2.85
2.51
2.50
2.49
2.48
2.48
2.46
2.17
2.16
2.15
2.13
1.70
1.64
1.64
1.63
1.63
1.62
1.61
1.61
1.60
4.97
2.00
0.88
1.06
1.15
0.94
1.06
0.94
0.97
0.94
1.16
0.90
0.95
1.11
2.79
1.17
f1 (ppm)


OH
OH
N
CBz
156.85
142.93
136.38
128.70
128.35
128.12
111.84
80.62
77.48
77.16 CDCl3
76.84
75.92
69.05
67.54
53.47
52.91
43.45
36.02
20.71
f1 (ppm)

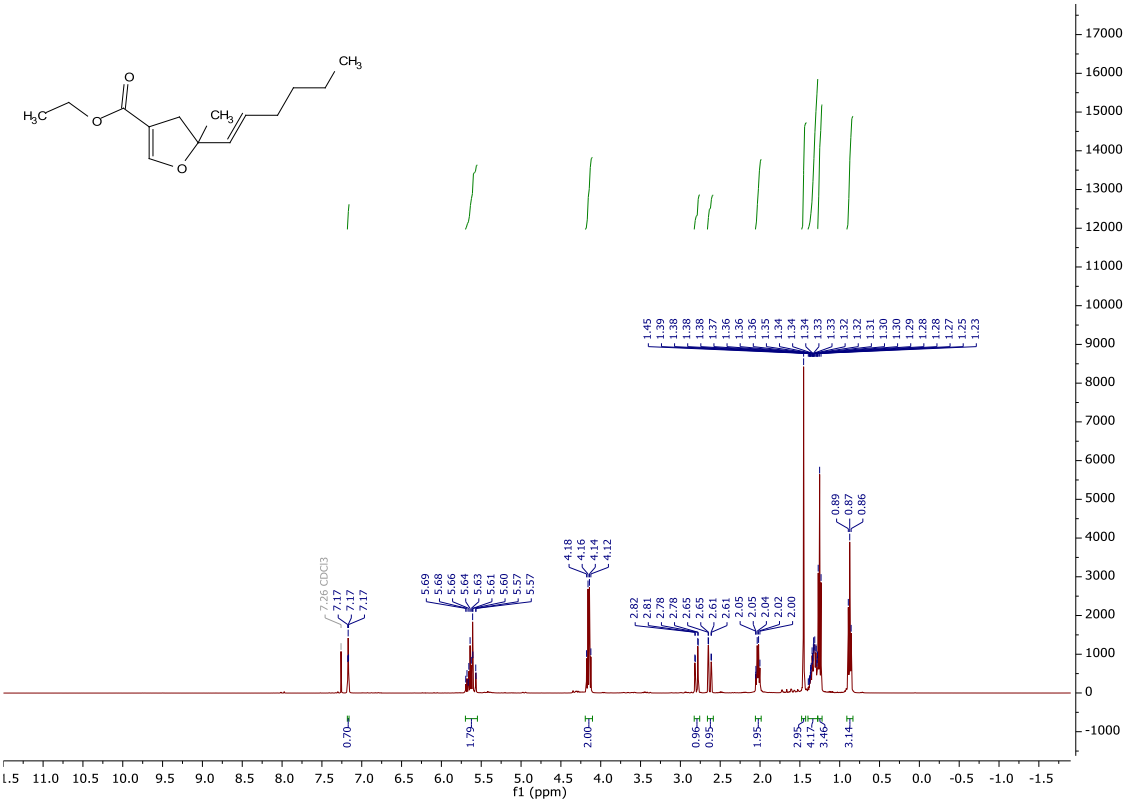

OMe
O
OMe
N
CBz
O
f1 (ppm)

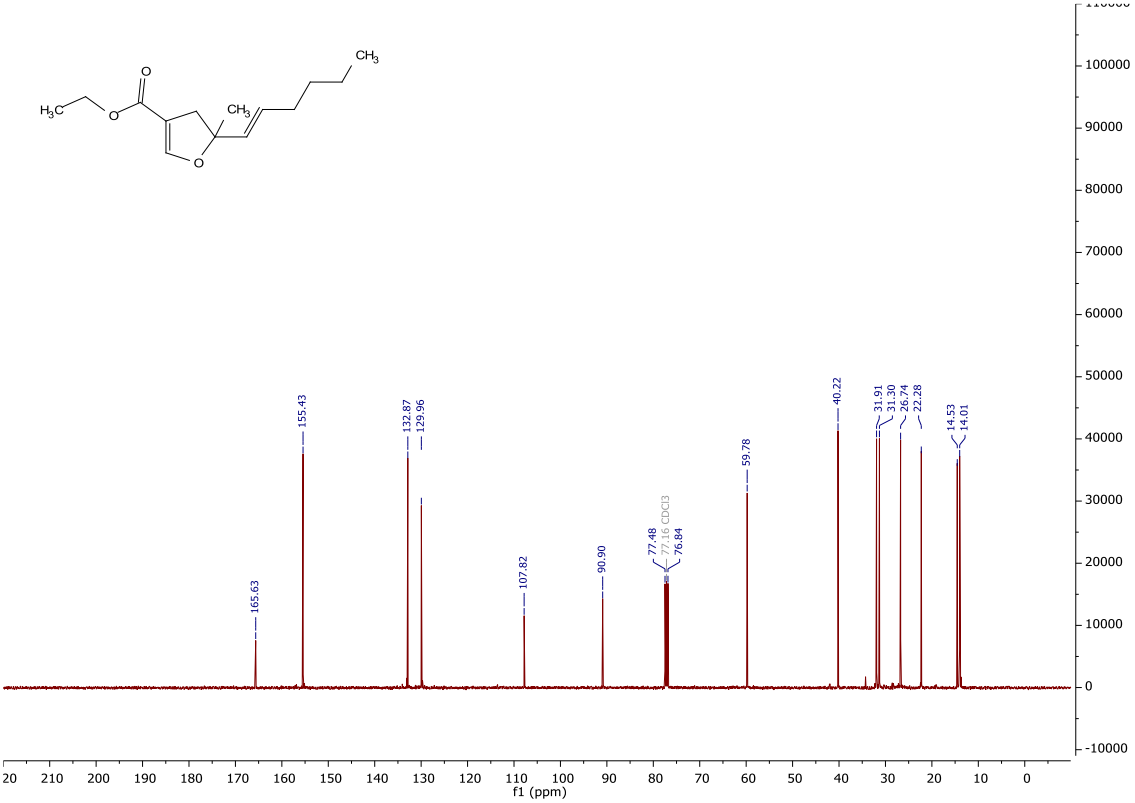

OMe
O
OMe
N
CBz
O
f1 (ppm)

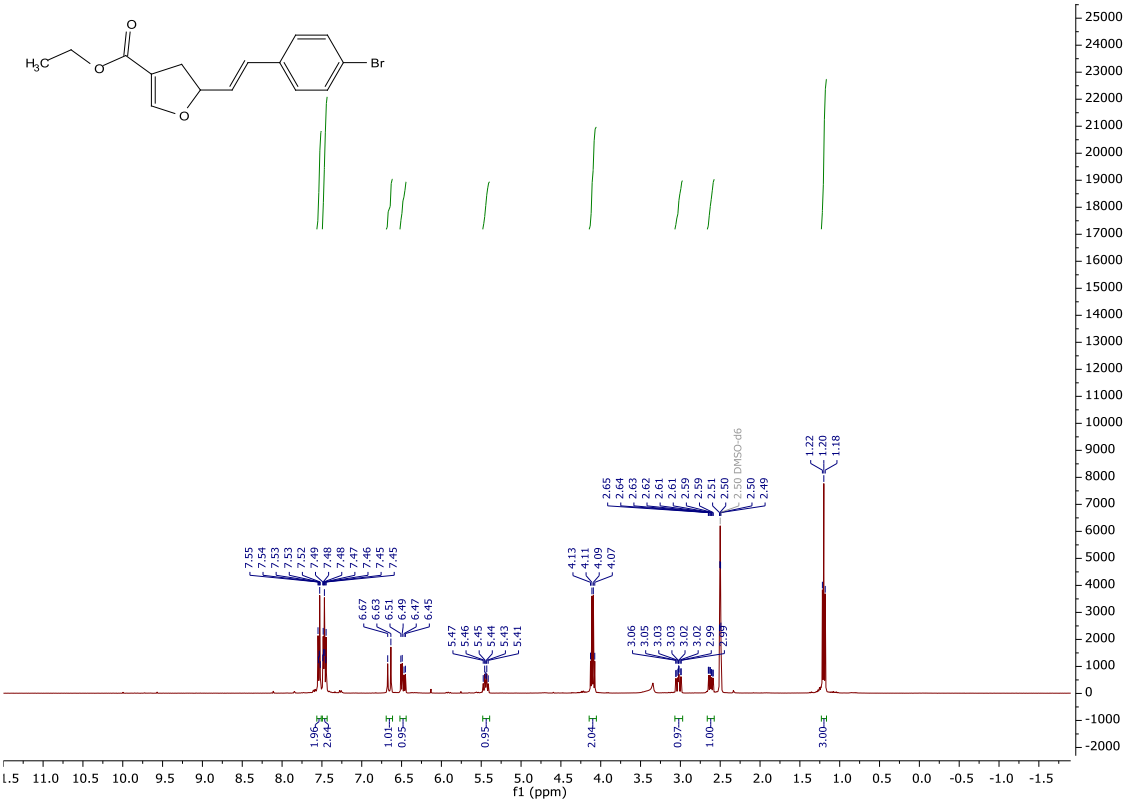

OH
O
OH
O
N
H
5.13
5.06
4.73
4.72
3.80
3.78
3.78
3.76
3.39
3.38
3.06
3.06
3.05
3.05
3.04
3.04
3.03
3.03
3.03
3.02
3.02
3.01
3.00
2.90
2.89
2.89
2.87
2.85
2.85
2.79
2.78
2.76
2.75
2.57
2.56
2.54
2.53
1.82
0.86
0.95
1.35
1.04
1.00
1.29
1.39
1.22
1.07
3.00
f1 (ppm)

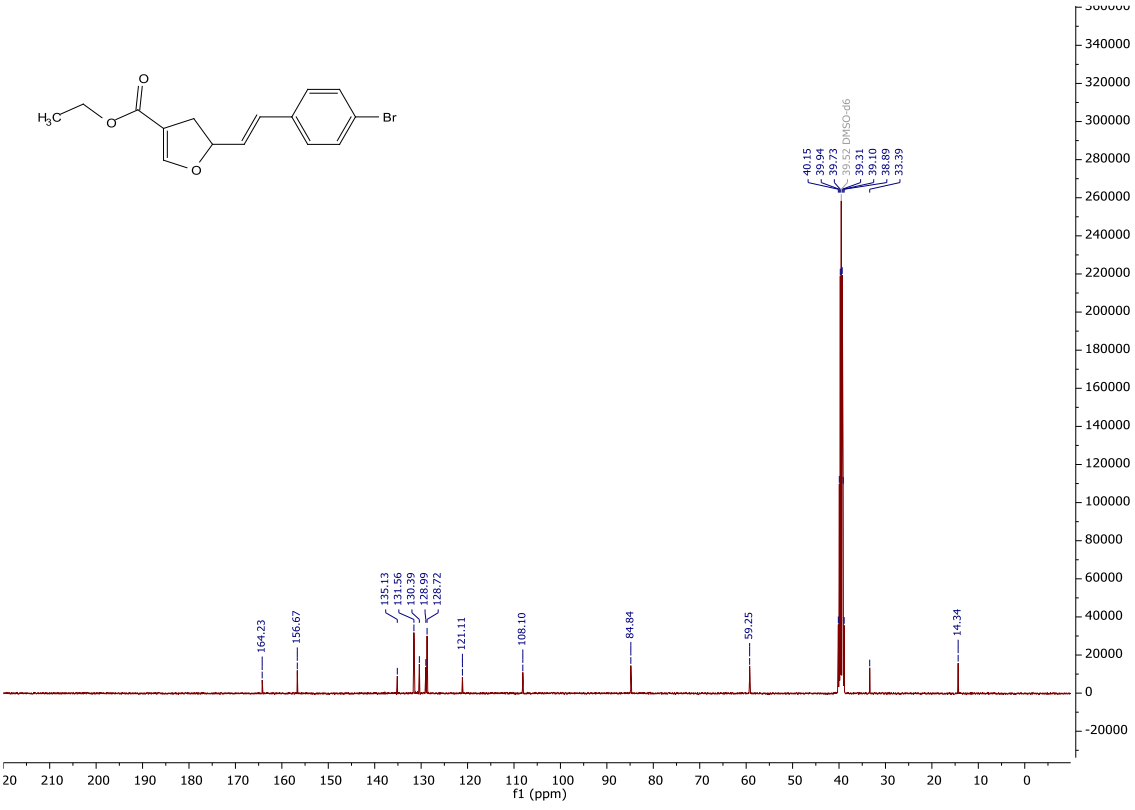

OH
O
OH
O
N
H
175.71
170.41
139.73
115.95
61.56
48.55
47.96
39.60
33.18
17.67
f1 (ppm)

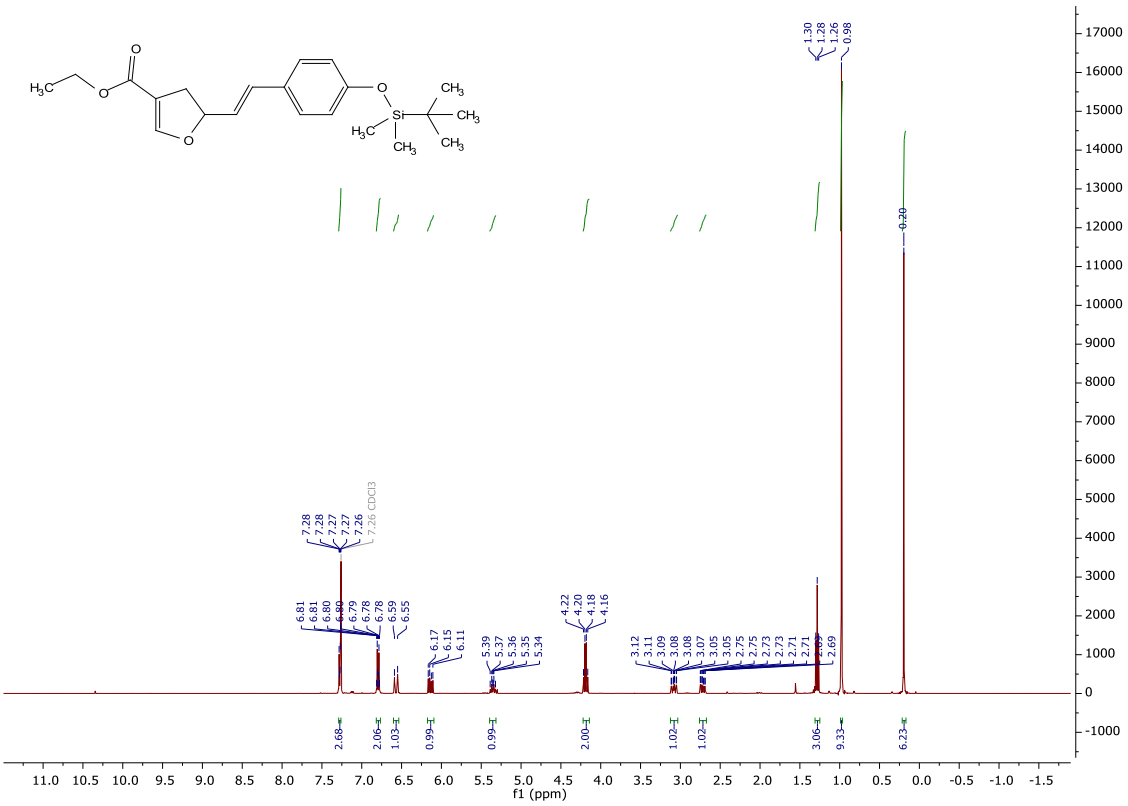
Appendix 3- Supporting Information for Chapter 4

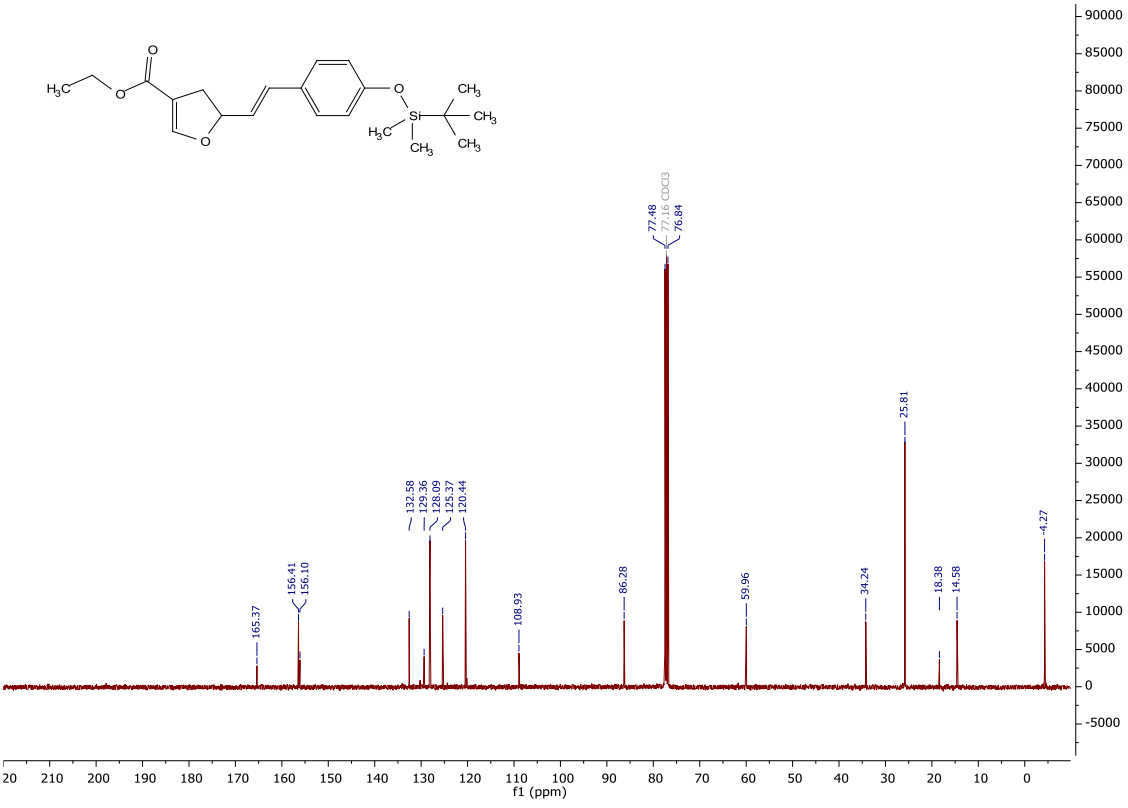


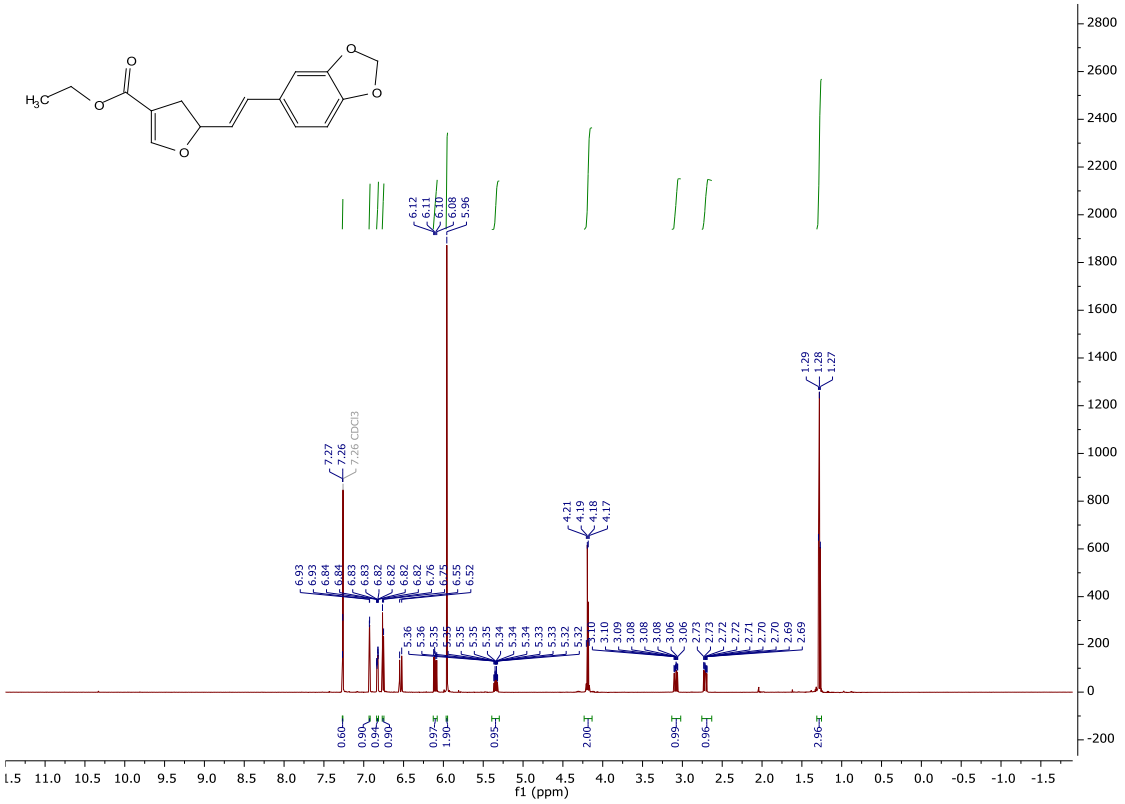


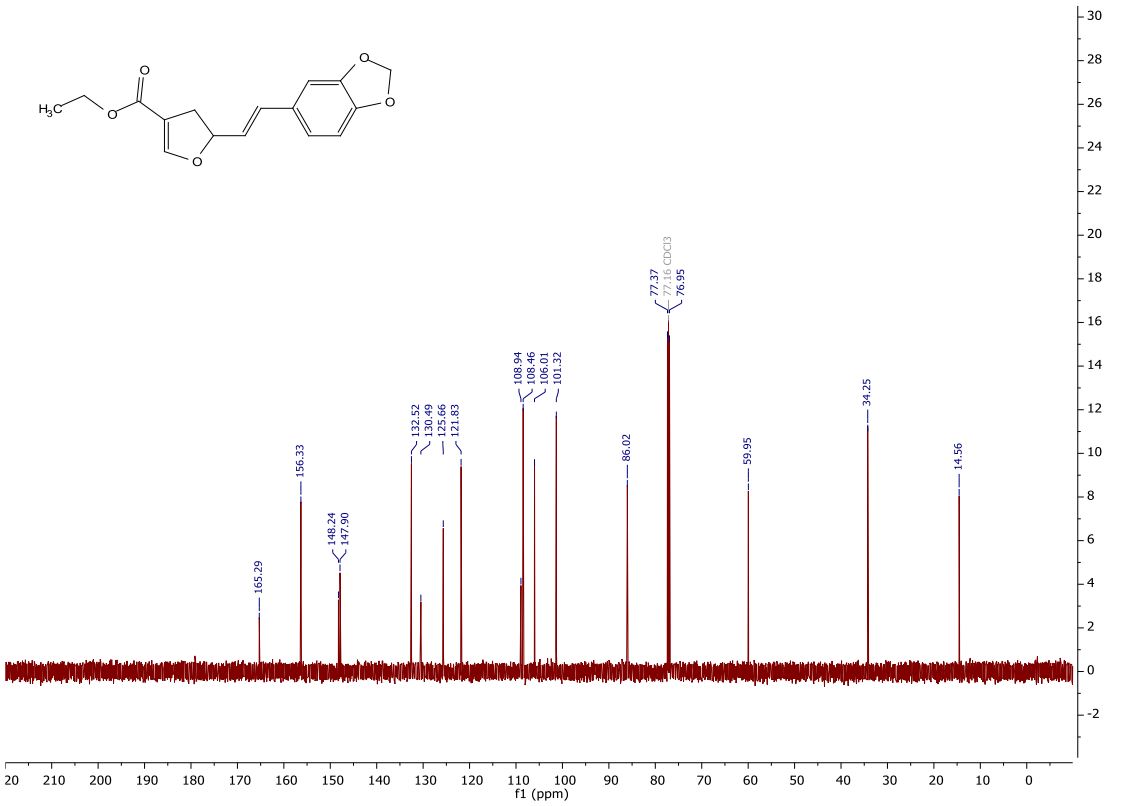

O
H3C
O
Br
O
7.55
7.54
7.53
7.53
7.52
7.49
7.48
7.48
7.47
7.46
7.45
7.45
6.67
6.63
6.51
6.49
6.47
6.45
5.47
5.46
5.45
5.44
5.43
5.41
4.13
4.11
4.09
4.07
3.06
3.05
3.03
3.03
3.02
3.02
2.99
2.99
2.65
2.64
2.63
2.62
2.61
2.61
2.59
2.59
2.51
2.50
2.50 DMSO-d6
2.49
1.22
1.20
1.18
1.96
2.64
1.01
0.95
0.95
2.04
0.97
1.00
3.00
f1 (ppm)

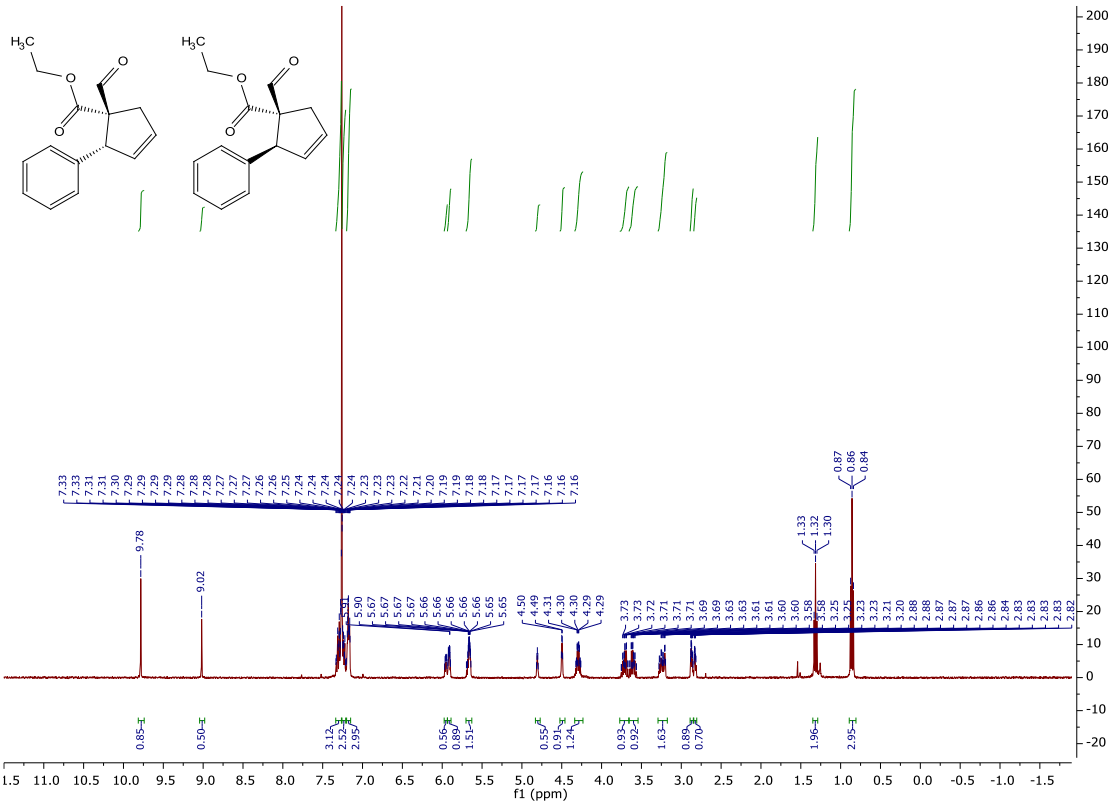

O
H3C
O
Br
O
164.23
156.67
135.13
131.56
130.39
128.99
128.72
121.11
108.10
84.84
59.25
40.15
39.94
39.73
39.52 DMSO-d6
39.31
39.10
38.89
33.39
14.34
f1 (ppm)

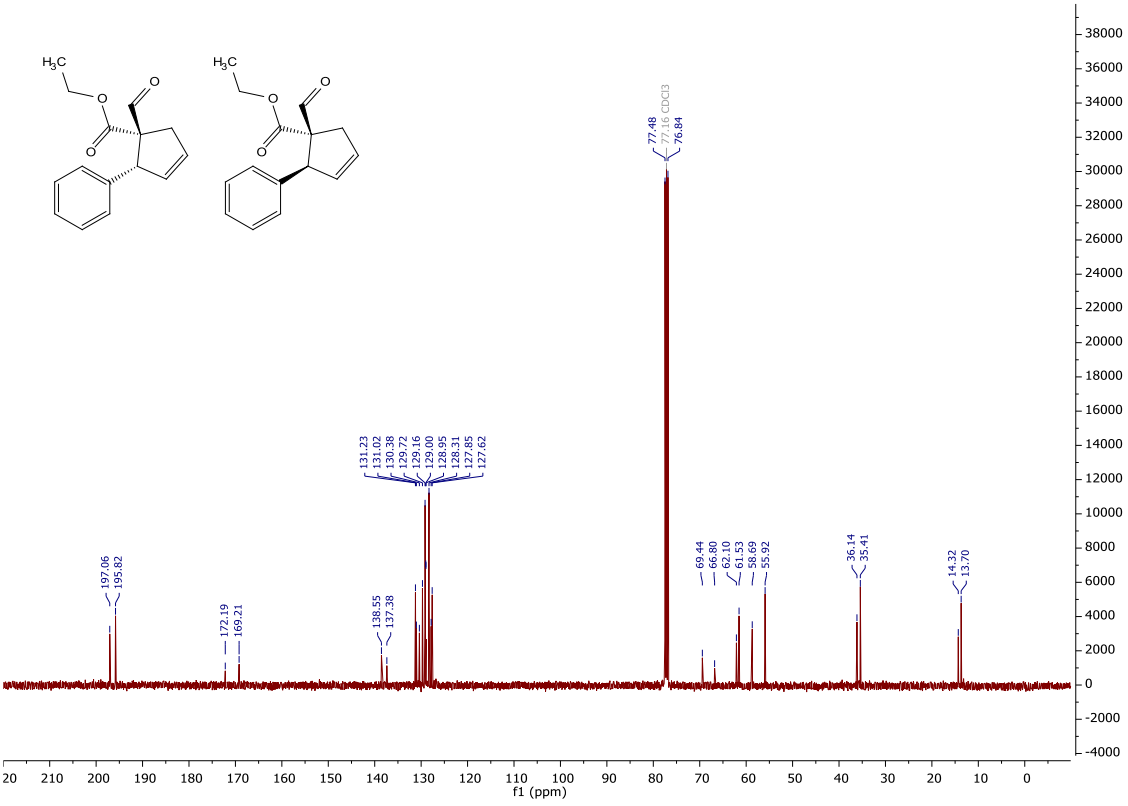

1.30
1.28
1.26
0.98
9.20
7.28
7.28
7.28
7.27
7.27
7.26
7.26 CDCl3
6.81
6.81
6.80
6.80
6.79
6.78
6.78
6.59
6.55
6.17
6.15
6.11
5.39
5.37
5.36
5.35
5.34
4.22
4.20
4.18
4.16
3.12
3.11
3.09
3.08
3.08
3.07
3.05
3.05
2.75
2.75
2.73
2.73
2.71
2.71
2.69
2.68
2.06
1.03
0.99
0.99
2.00
1.02
1.02
3.06
9.33
6.23
f1 (ppm)

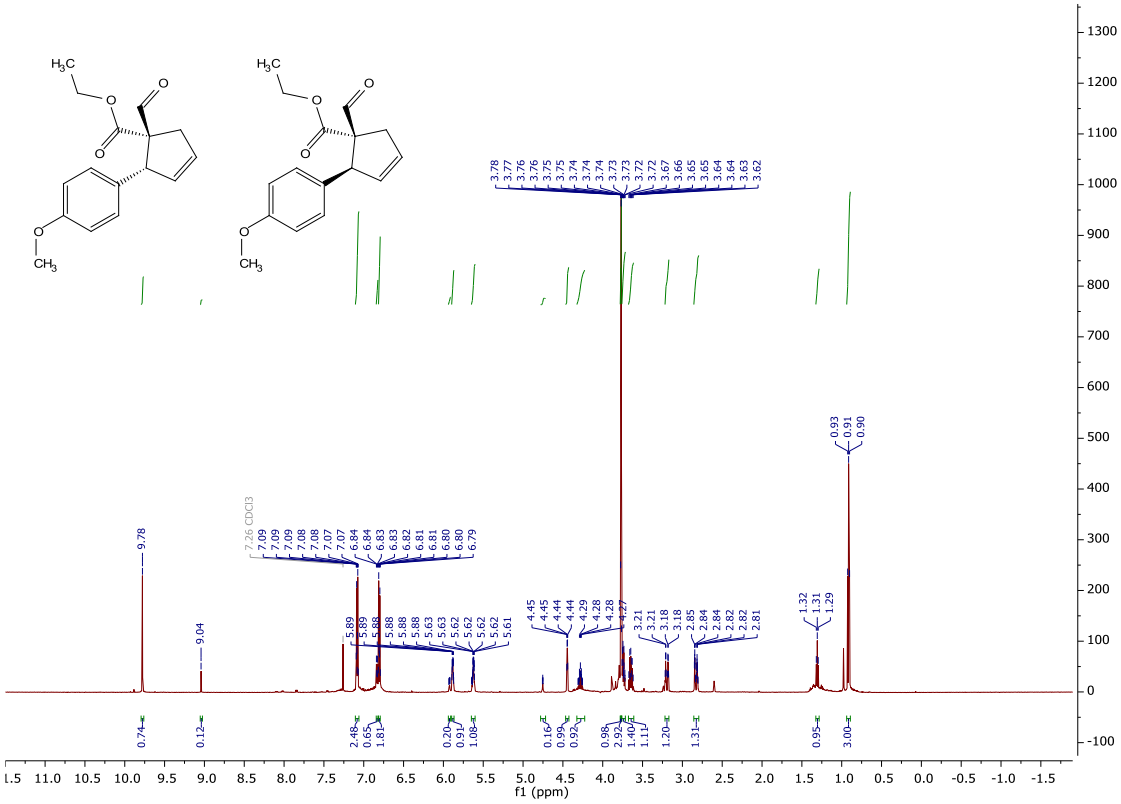

77.48
77.16 CDCl3
76.84
132.58
129.36
128.09
125.37
120.44
165.37
156.41
156.10
108.93
86.28
59.96
34.24
25.81
18.38
14.58
14.27
f1 (ppm)

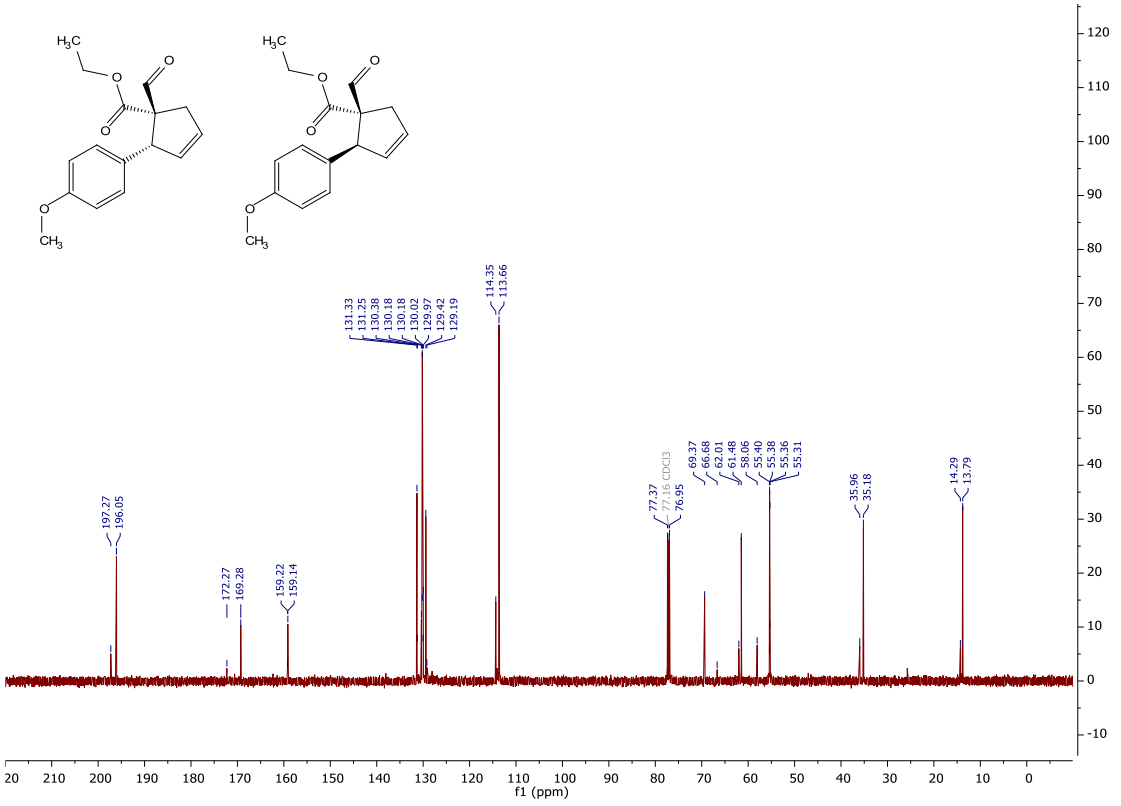

f1 (ppm)

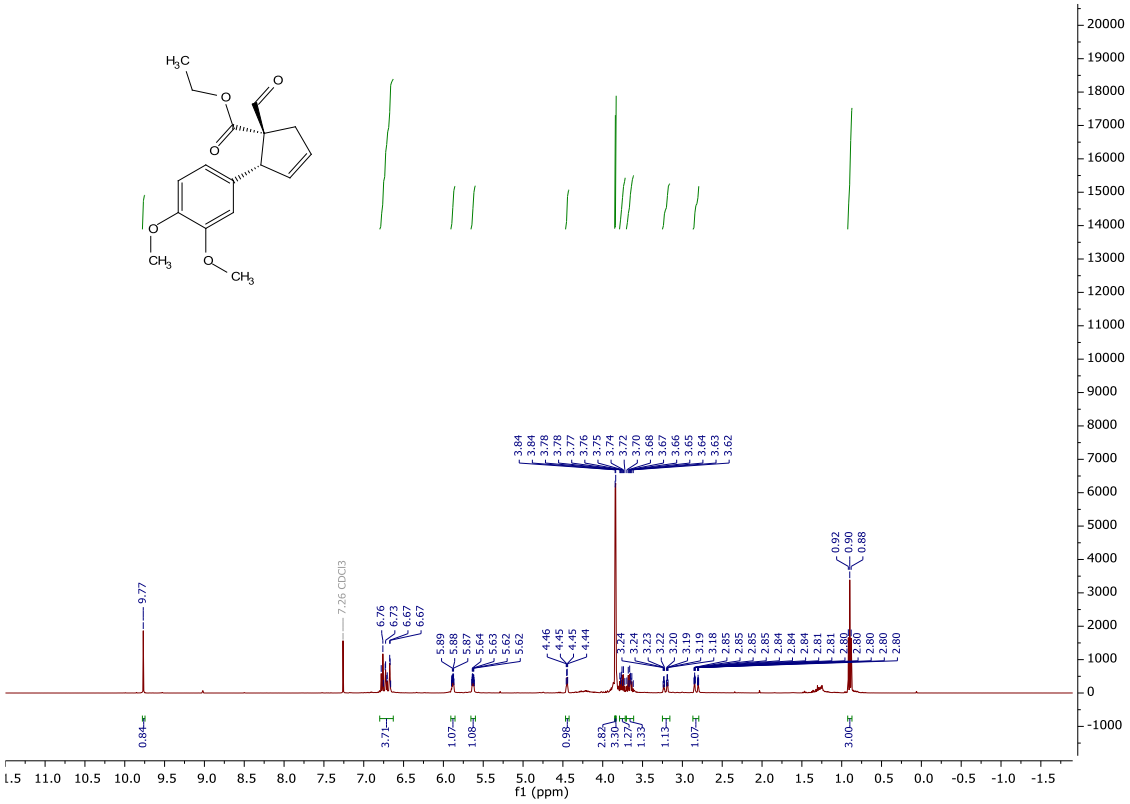

f1 (ppm)

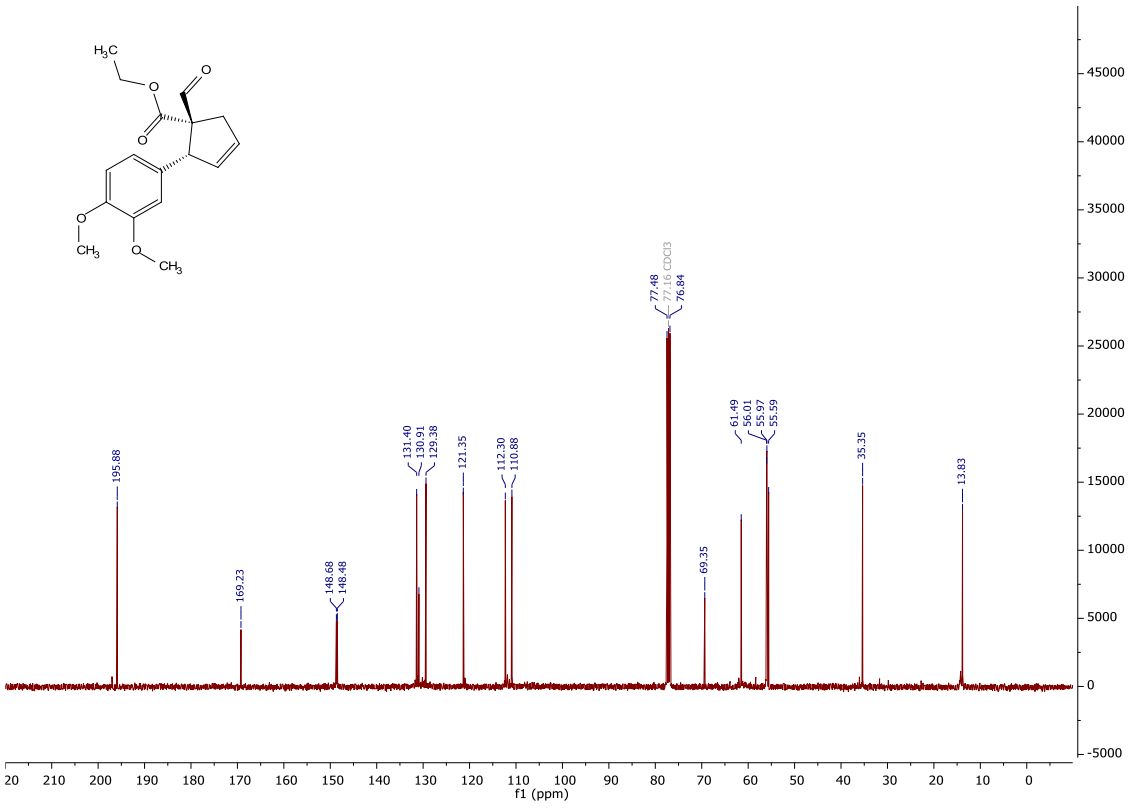

f1 (ppm)

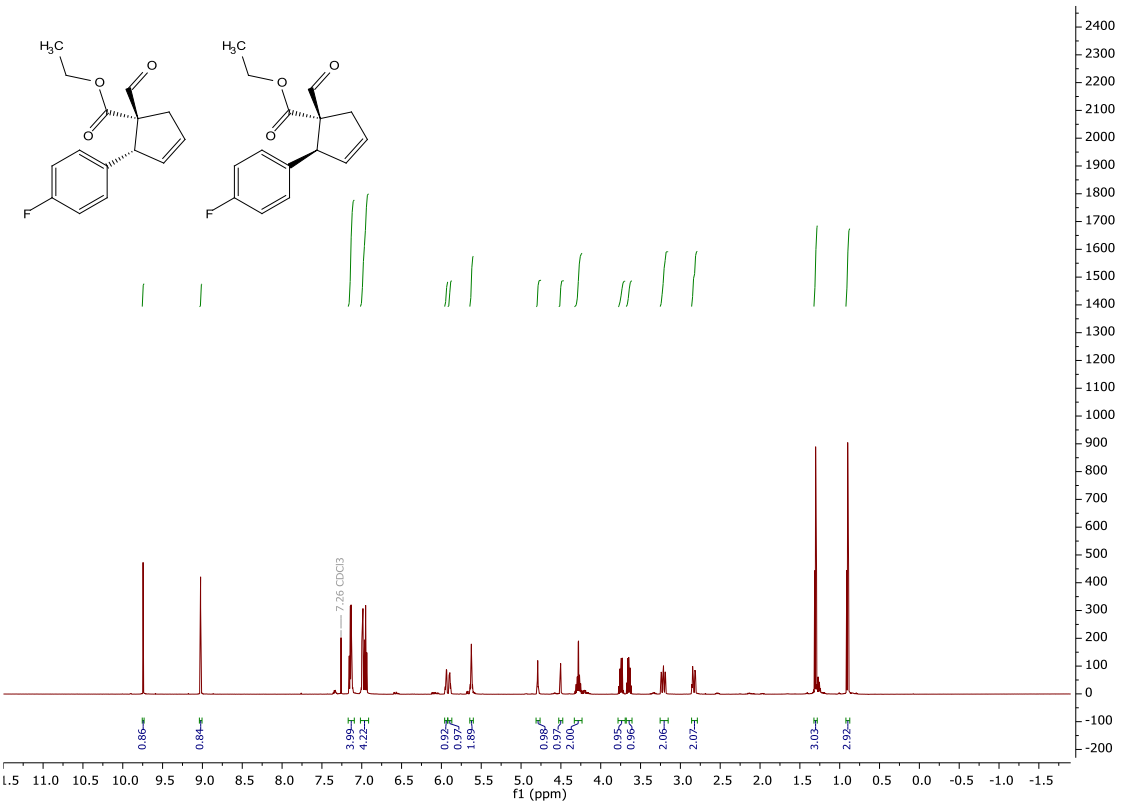

f1 (ppm)

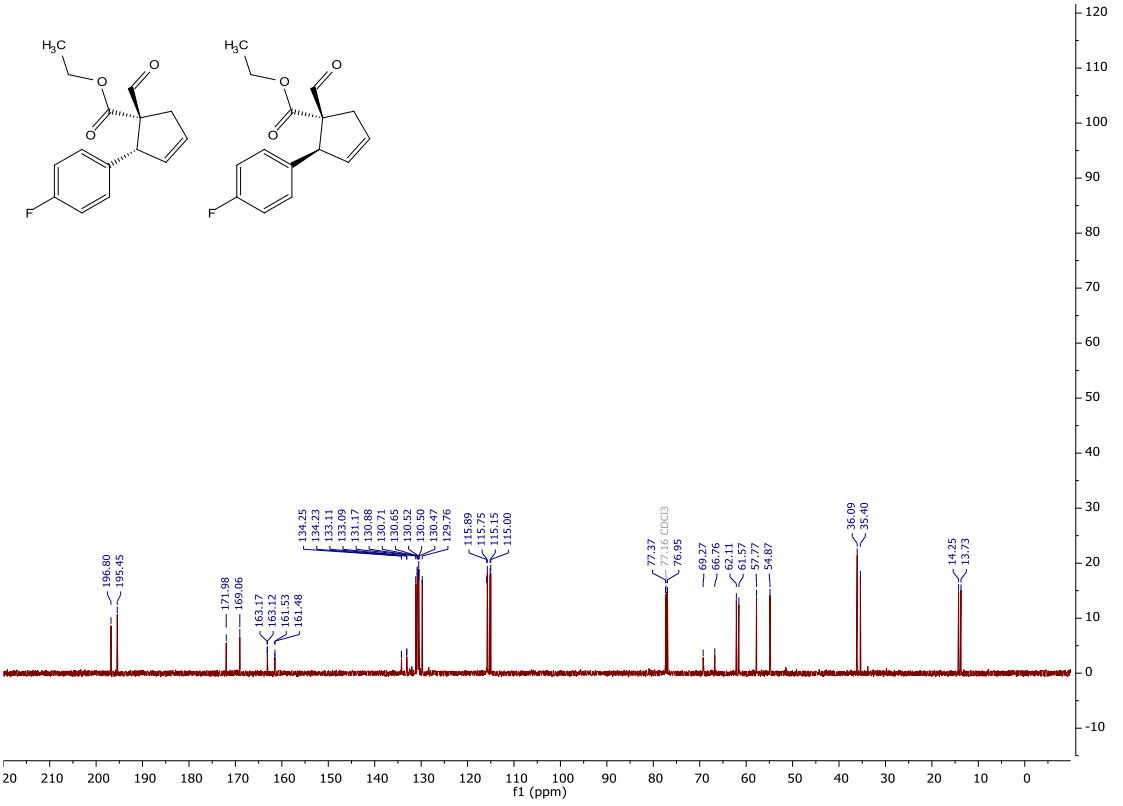

f1 (ppm)

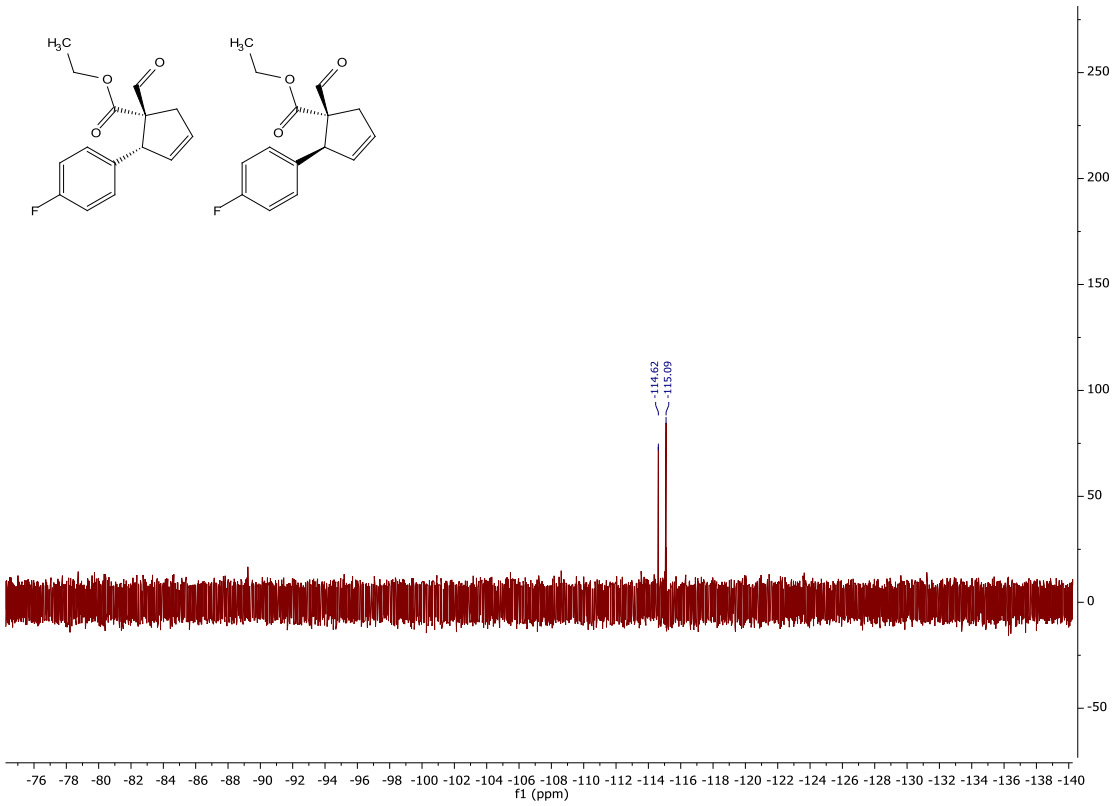

f1 (ppm)

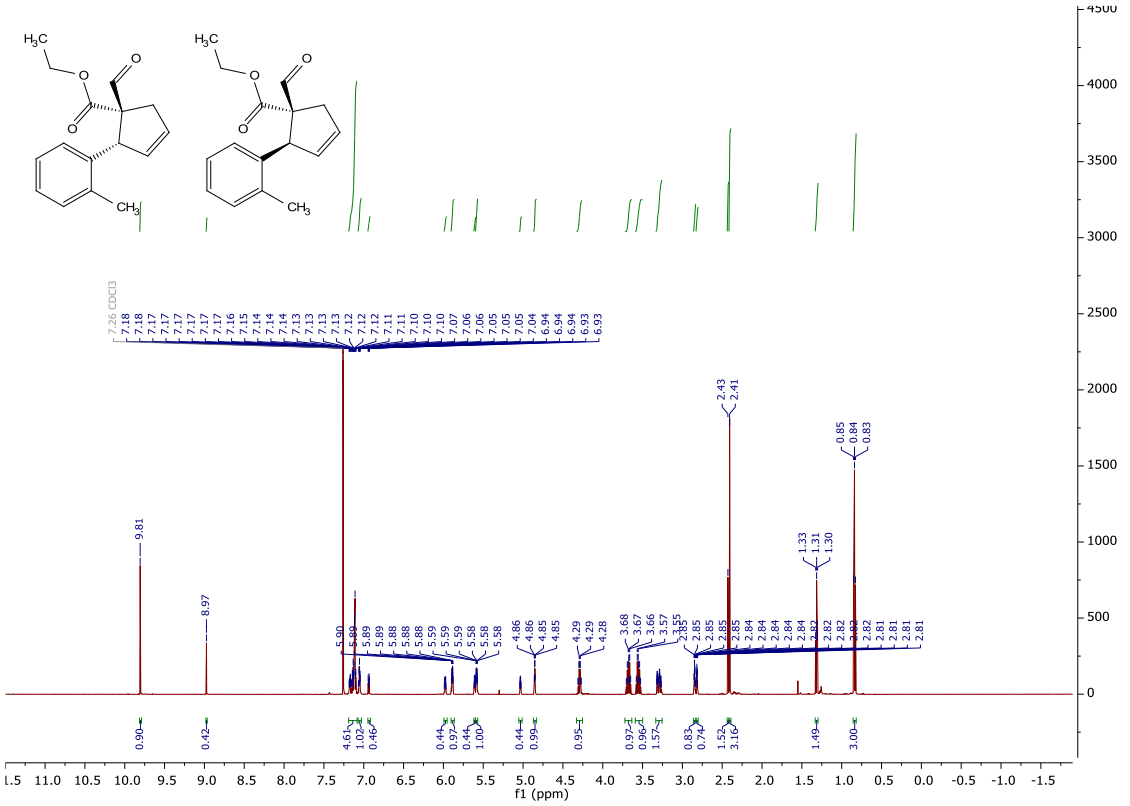

9.77
7.26 CDCl3
6.76
6.73
6.67
6.67
5.89
5.88
5.87
5.64
5.63
5.62
5.62
4.46
4.45
4.45
4.44
3.84
3.84
3.78
3.78
3.77
3.76
3.75
3.74
3.72
3.70
3.68
3.67
3.66
3.65
3.64
3.63
3.62
3.24
3.24
3.23
3.22
3.20
3.19
3.19
3.18
2.85
2.85
2.85
2.85
2.84
2.84
2.84
2.81
2.81
2.80
2.80
2.80
2.80
2.80
0.92
0.90
0.88
0.84
3.71
1.07
1.08
0.98
2.82
3.30
1.27
1.39
1.13
1.07
3.00
f1 (ppm)

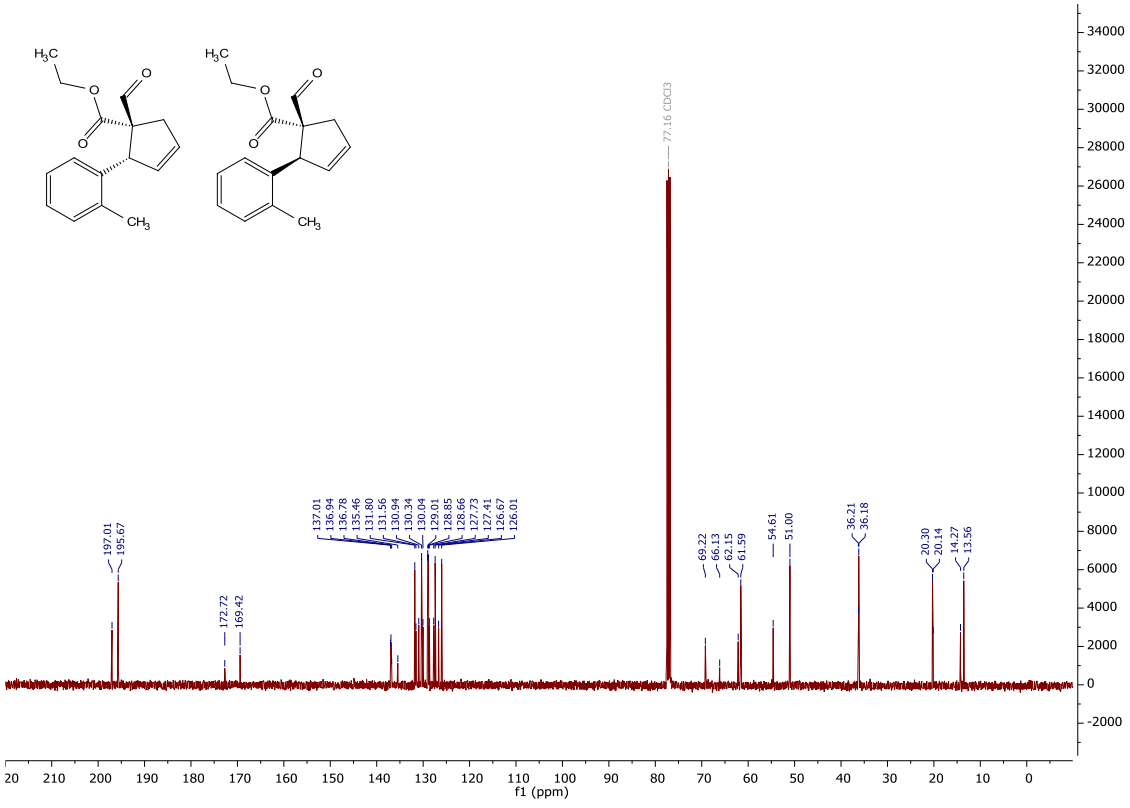

195.88
169.23
148.68
148.48
131.40
130.91
129.38
121.35
112.30
110.88
77.48
77.16 CDCl3
76.84
69.35
61.49
56.01
55.97
55.59
35.35
13.83
f1 (ppm)

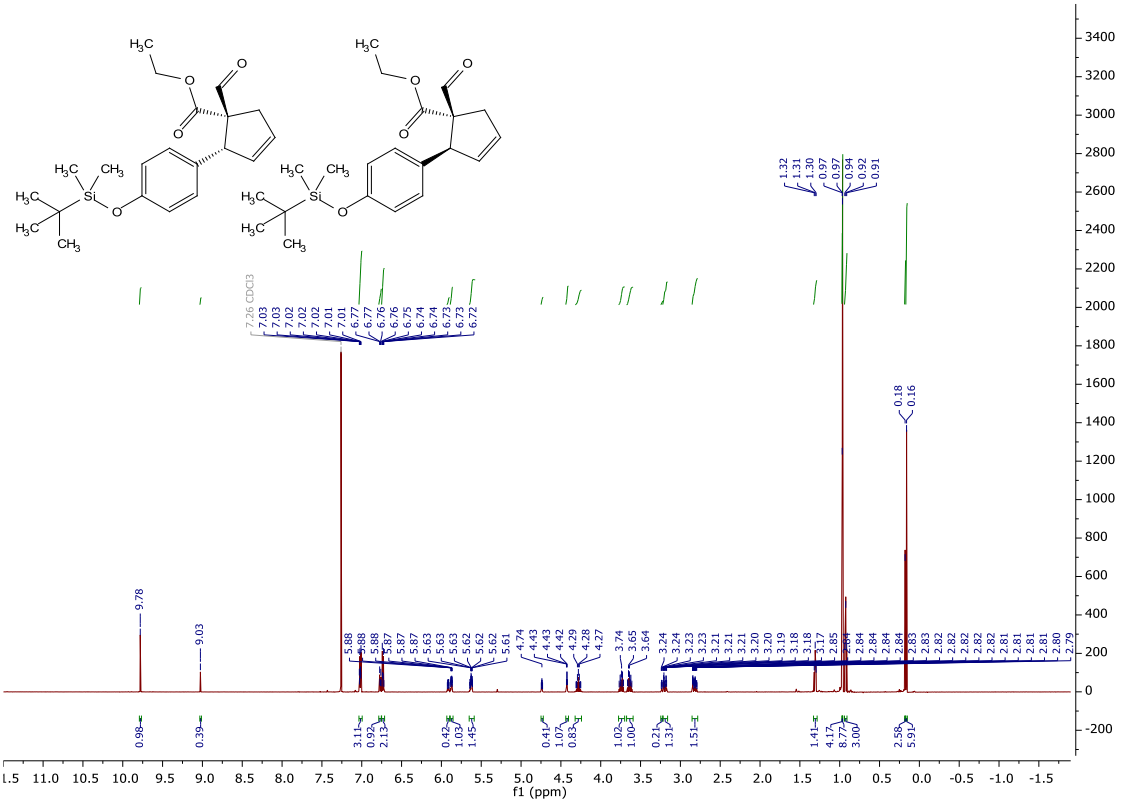

H3C
O
O
O
F
7.26 CDCl3
0.86
0.84
3.99
4.22
0.92
0.97
1.89
0.98
0.97
2.00
0.95
0.96
2.06
2.07
3.03
2.92
f1 (ppm)

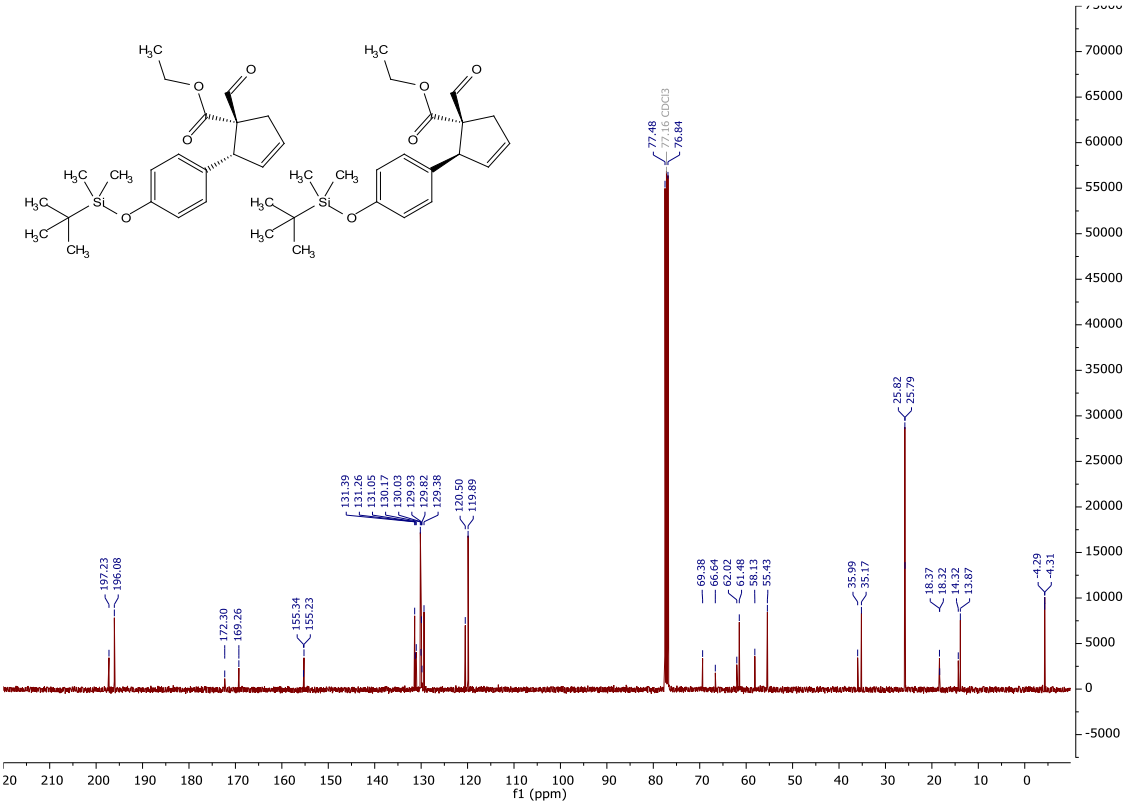

H3C
O
O
O
F
196.80
195.45
171.98
169.06
163.17
163.12
161.53
161.48
134.25
134.23
133.11
133.09
131.17
130.88
130.71
130.65
130.52
130.50
130.47
129.76
115.89
115.75
115.15
115.00
77.37
77.16 CDCl3
76.95
69.27
66.76
62.11
61.57
57.77
54.87
36.09
35.40
14.25
13.73
f1 (ppm)

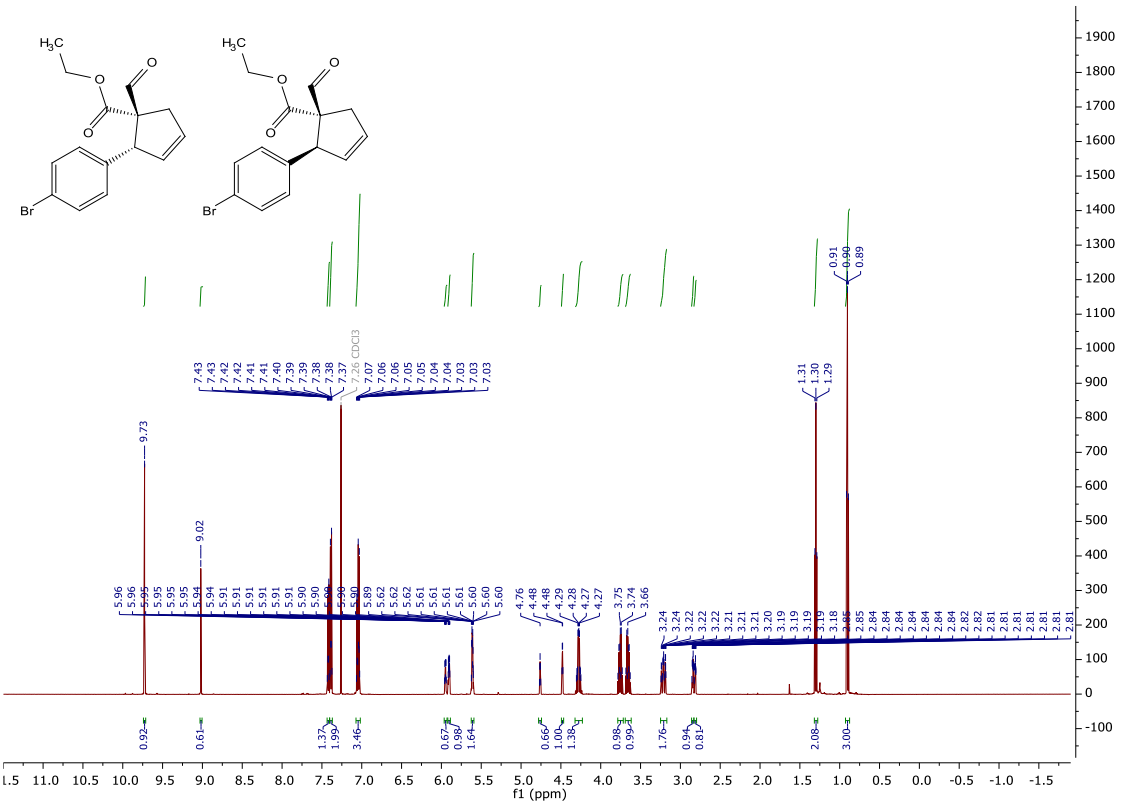

H3C
O
O
O
F
H3C
O
O
O
F
-114.62
-115.09
250
200
150
100
50
0
-50
-76 -78 -80 -82 -84 -86 -88 -90 -92 -94 -96 -98 -100 -102 -104 -106 -108 -110 -112 -114 -116 -118 -120 -122 -124 -126 -128 -130 -132 -134 -136 -138 -140
f1 (ppm)

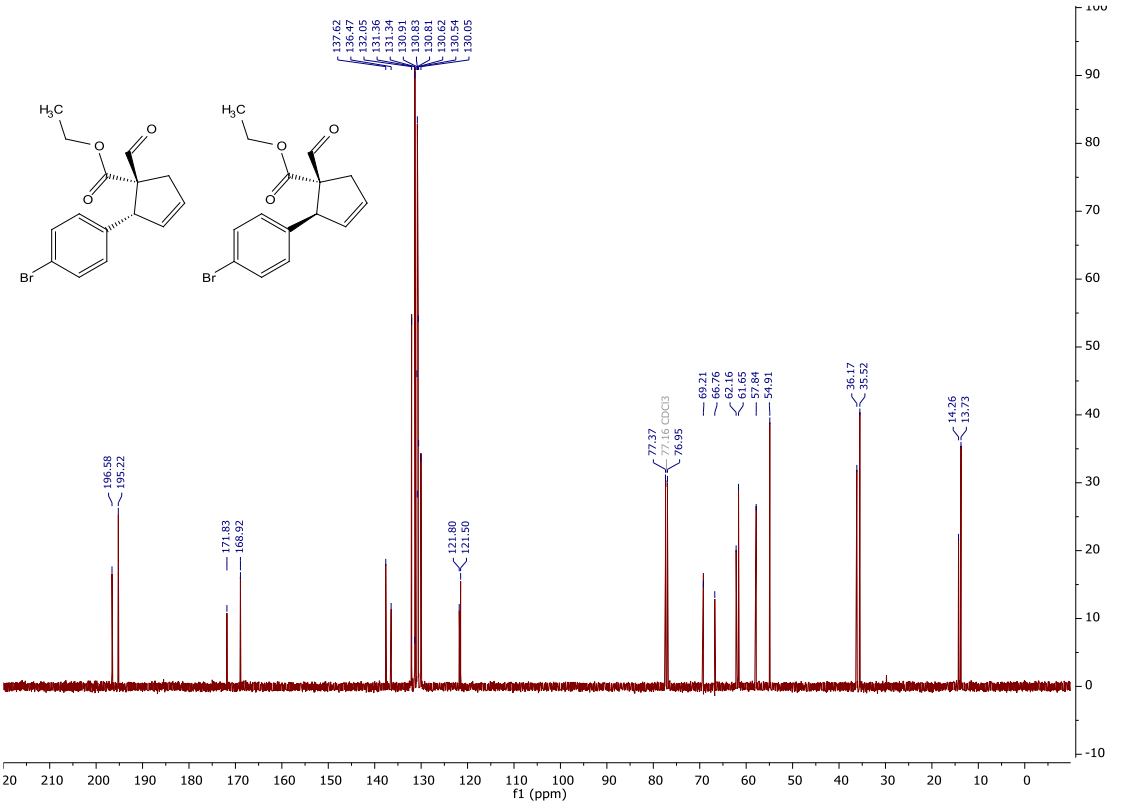

H3C
O
O
O
CH3
7.26 CDCl3
9.81
8.97
5.90
5.89
5.88
5.59
5.58
4.86
4.85
4.29
4.28
3.68
3.67
3.66
3.57
2.85
2.84
2.82
2.81
2.43
2.41
1.33
1.31
1.30
0.85
0.84
0.83
0.90
0.42
4.61
1.02
0.46
0.44
0.97
0.44
1.00
0.44
0.99
0.95
0.97
0.96
1.57
0.83
0.74
1.52
3.16
1.49
3.00
f1 (ppm)

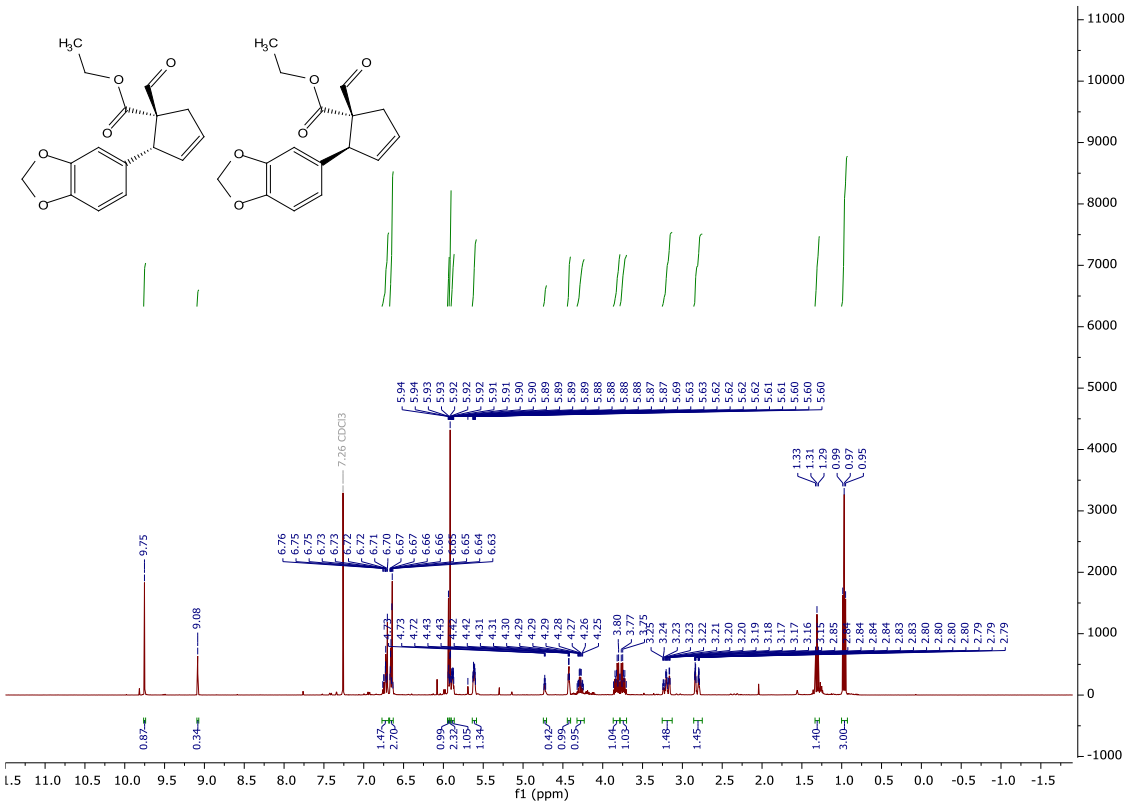

H3C
O
O
O
CH3
77.16 CDCl3
197.01
195.67
172.72
169.42
137.01
136.94
136.78
135.46
131.80
131.56
130.94
130.34
130.04
129.01
128.85
128.66
127.73
127.41
126.67
126.01
69.22
66.13
62.15
61.59
54.61
51.00
36.21
36.18
20.30
20.14
14.27
13.56
f1 (ppm)

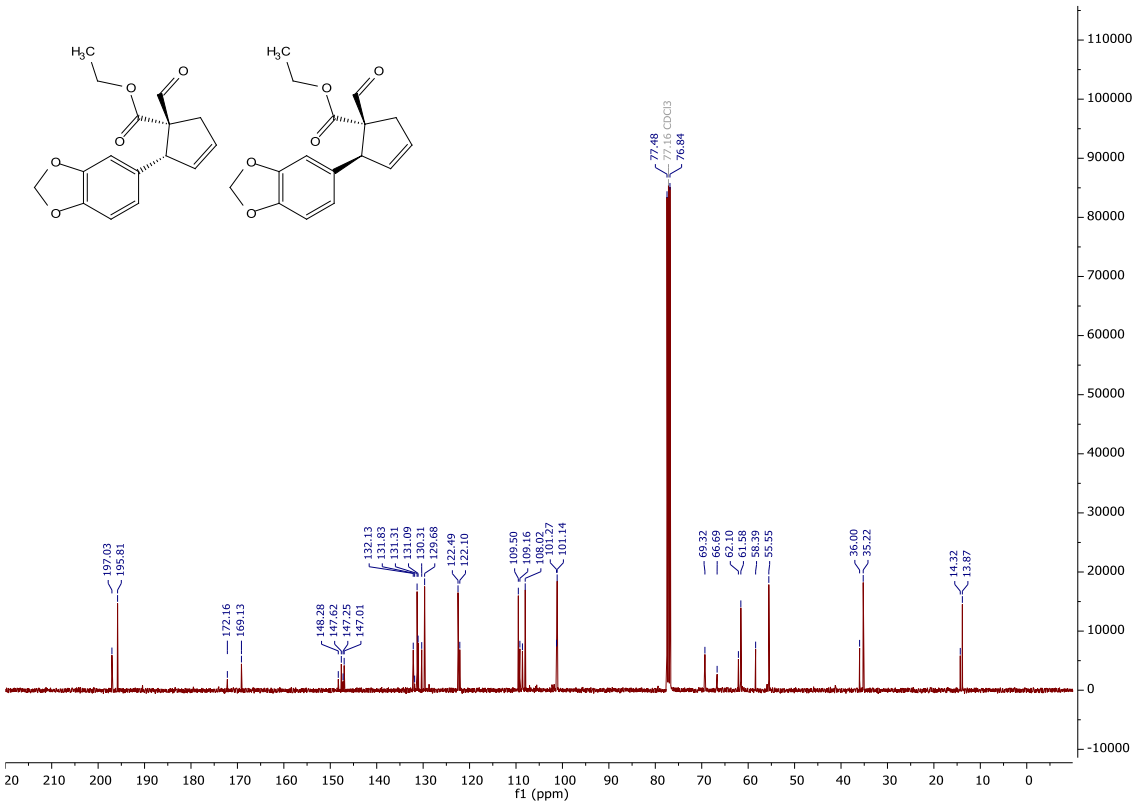

f1 (ppm)

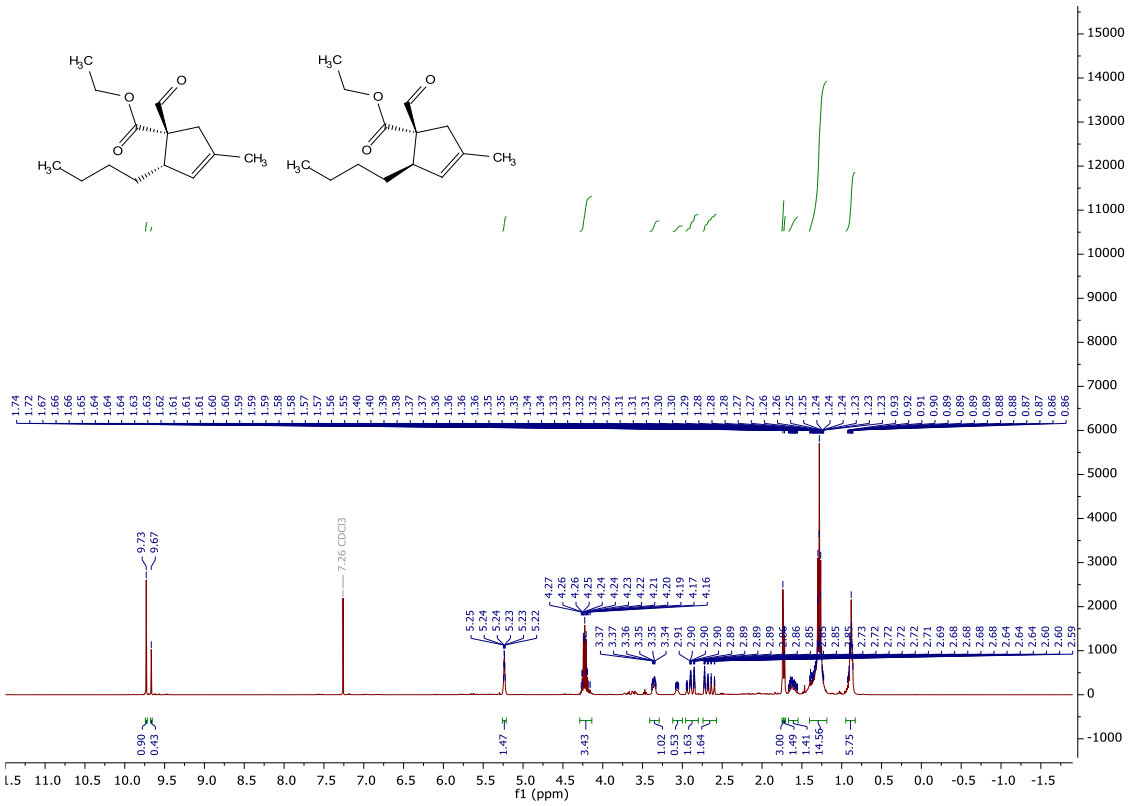

f1 (ppm)

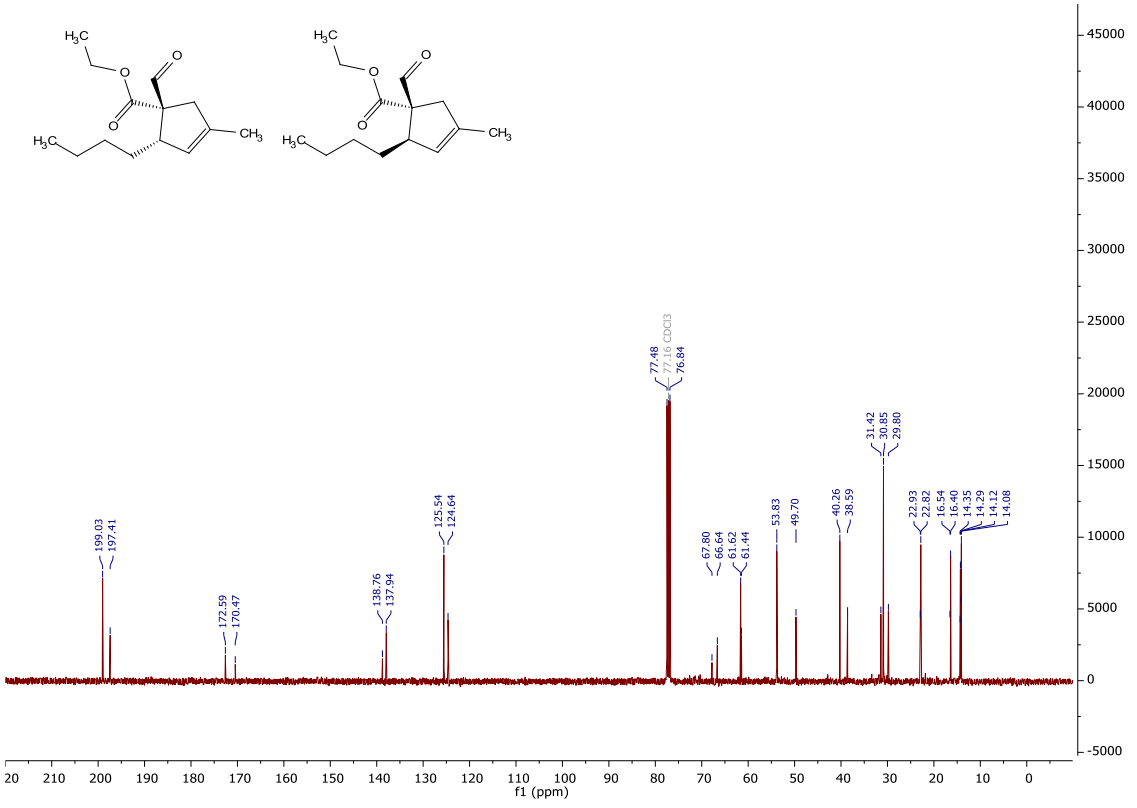

f1 (ppm)

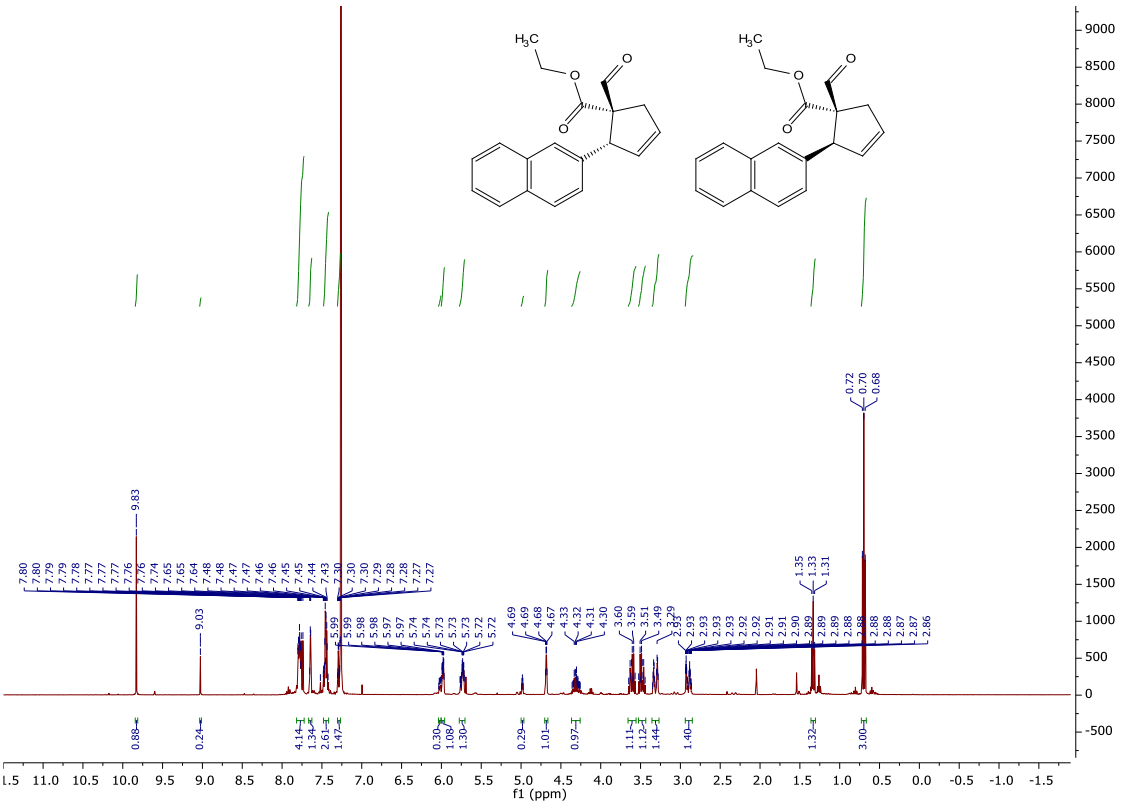

f1 (ppm)

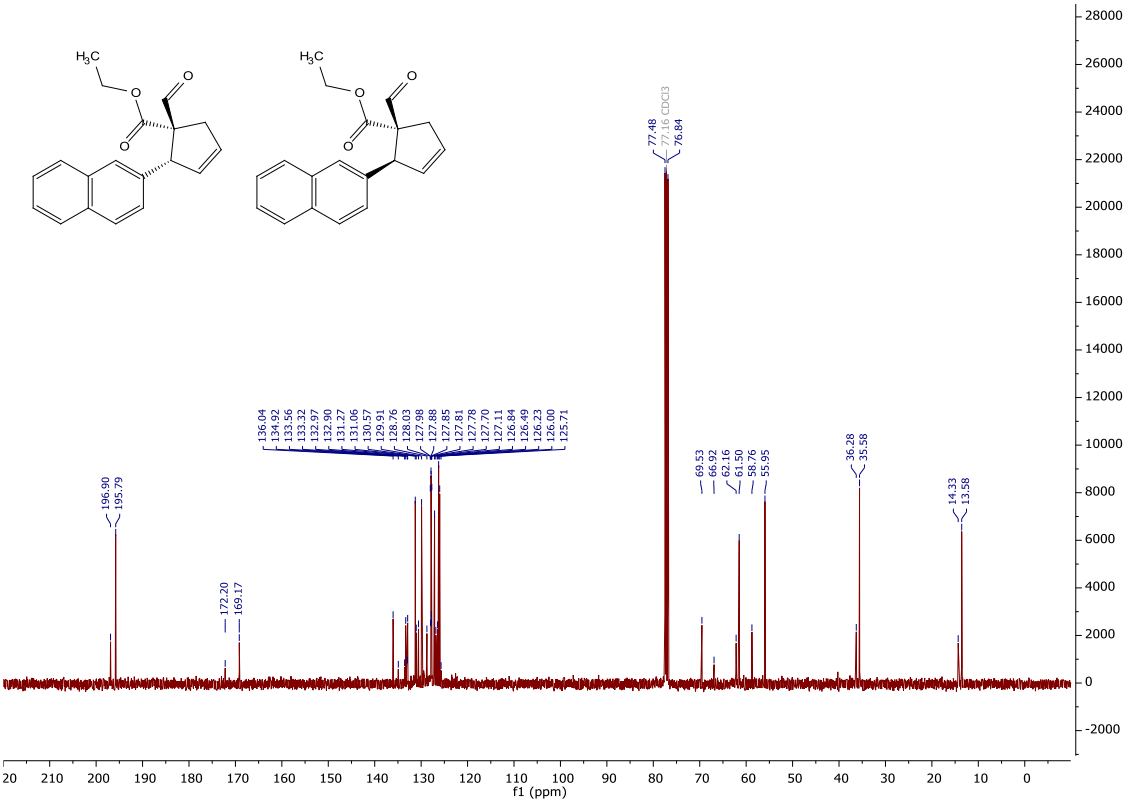

H3C
O
O
O
O
O
O
H3C
O
O
O
O
O
O
7.26 CDCl3
9.75
9.08
6.76
6.75
6.75
6.73
6.73
6.72
6.72
6.71
6.70
6.67
6.67
6.66
6.66
6.65
6.64
6.63
5.94
5.94
5.93
5.93
5.92
5.92
5.92
5.91
5.91
5.90
5.90
5.89
5.89
5.89
5.88
5.88
5.88
5.88
5.87
5.87
5.69
5.63
5.63
5.62
5.62
5.62
5.62
5.61
5.61
5.60
5.60
5.60
4.73
4.73
4.72
4.72
4.43
4.43
4.42
4.42
4.31
4.31
4.30
4.29
4.29
4.29
4.28
4.27
4.26
4.25
3.80
3.77
3.75
3.24
3.23
3.23
3.22
3.21
3.20
3.20
3.19
3.18
3.17
3.17
3.16
3.15
2.85
2.84
2.84
2.84
2.83
2.83
2.80
2.80
2.80
2.79
2.79
2.79
1.33
1.31
1.31
1.29
0.99
0.97
0.95
0.87
0.34
1.47
2.70
0.99
2.32
1.05
1.34
0.42
0.99
0.95
1.04
1.03
1.48
1.45
1.40
3.00
f1 (ppm)

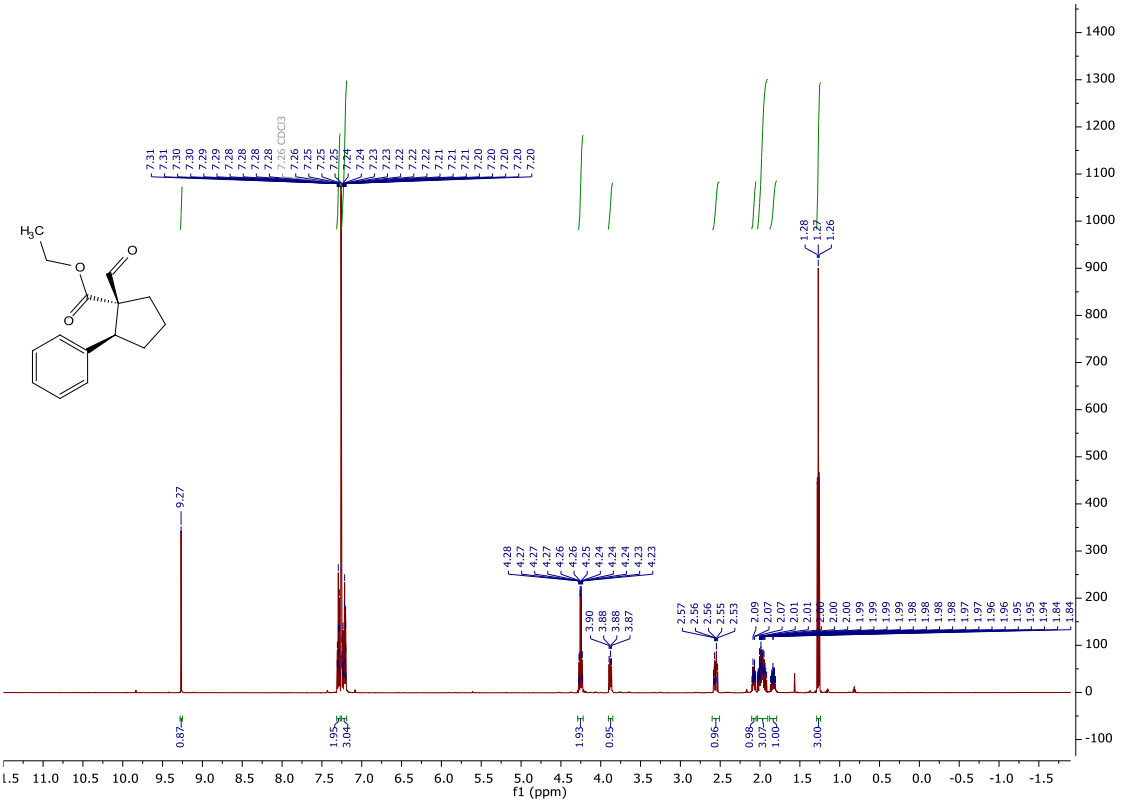

H3C
O
O
O
O
O
O
H3C
O
O
O
O
O
O
77.48
77.16 CDCl3
76.84
197.03
195.81
172.16
169.13
148.28
147.62
147.35
147.01
132.13
131.83
131.31
131.09
130.31
129.68
122.49
122.10
109.50
109.16
108.02
101.27
101.14
69.32
66.69
62.10
61.58
58.39
55.55
36.00
35.22
14.32
13.87
f1 (ppm)

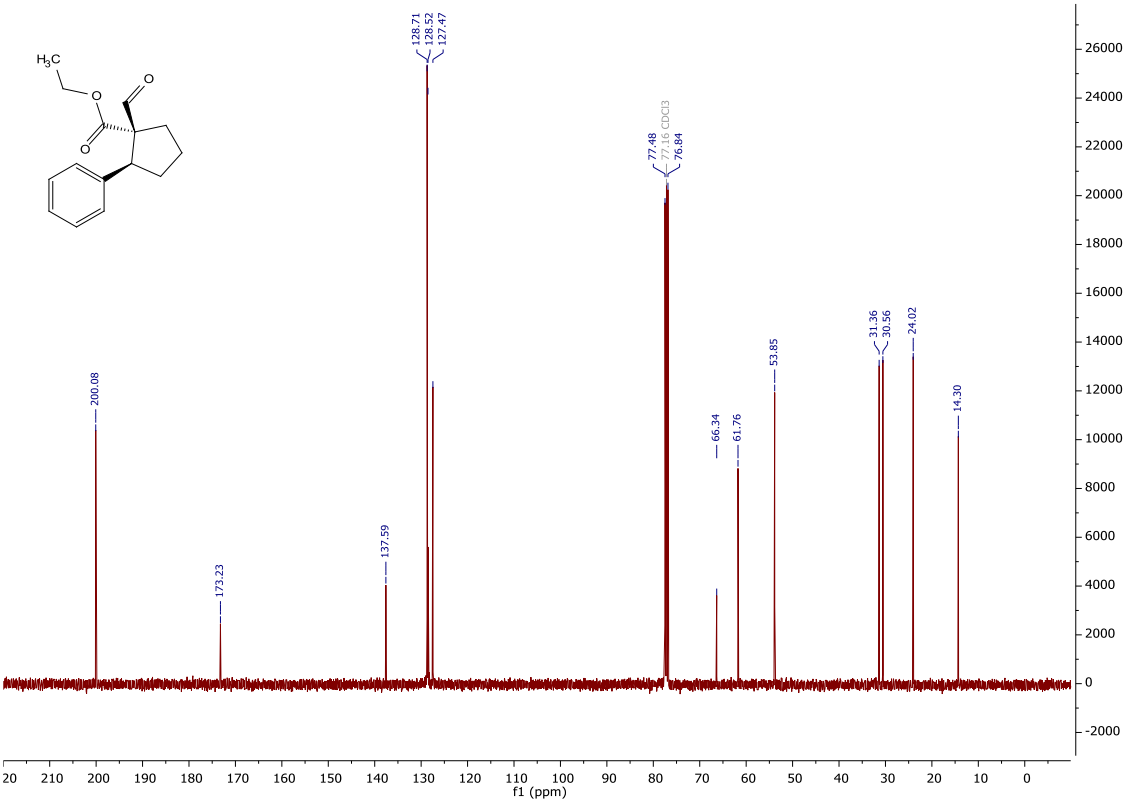

f1 (ppm)

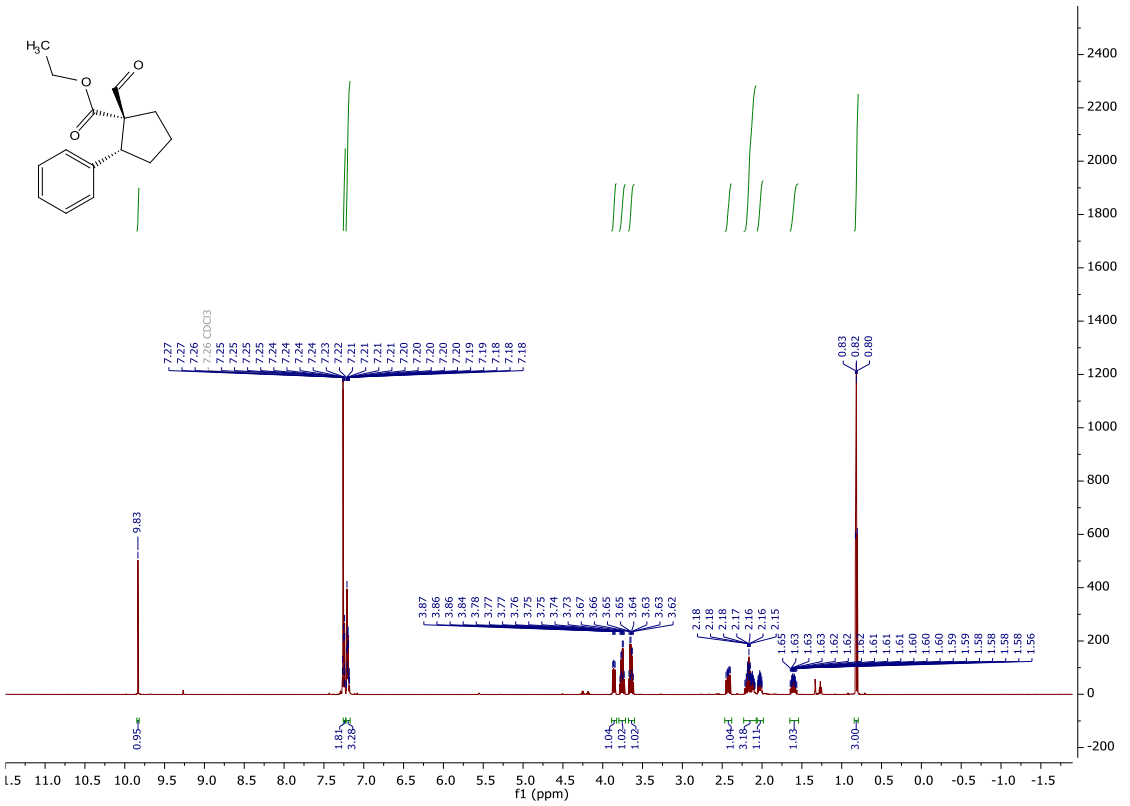

f1 (ppm)

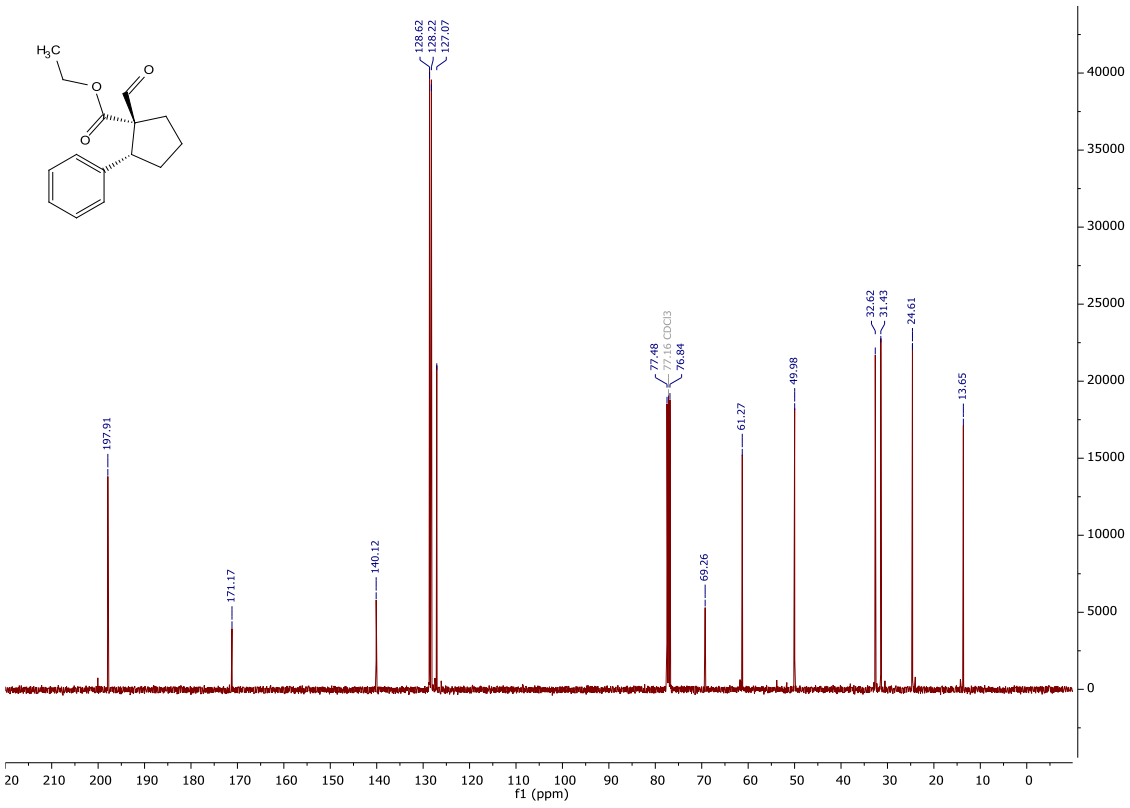

H3C
O
O
O
O
H3C
O
O
O
O
f1 (ppm)

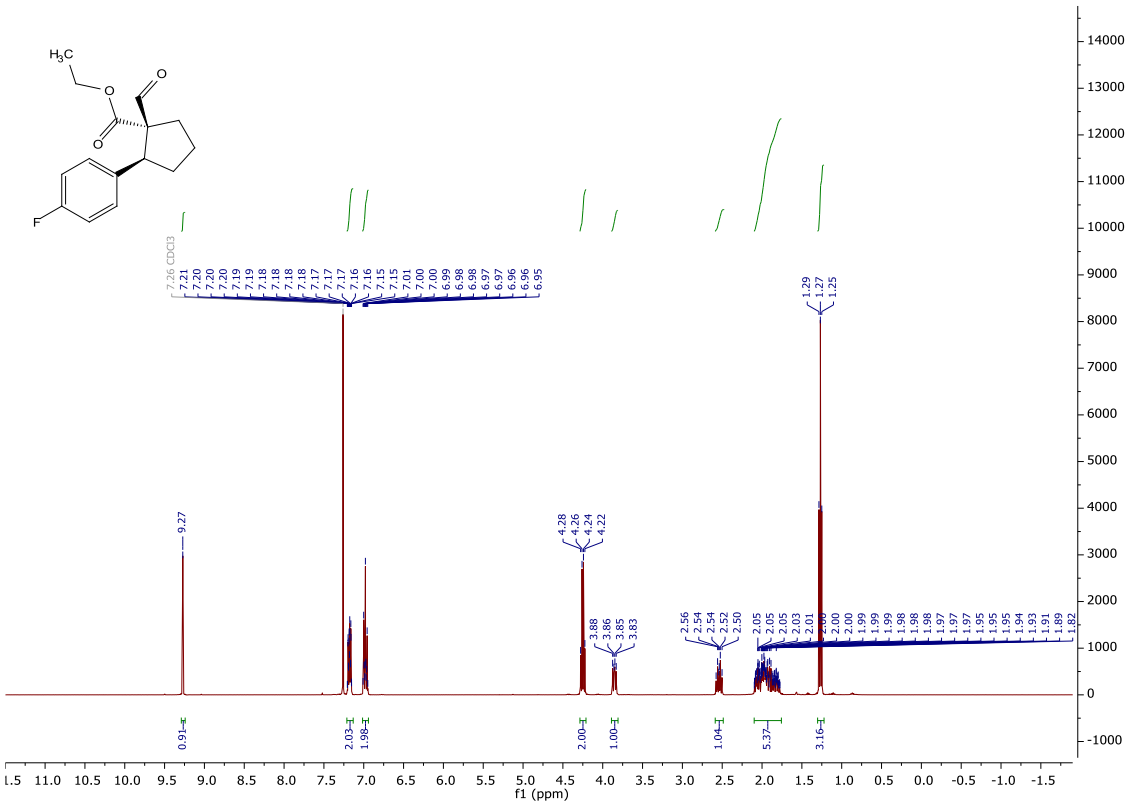

H3C
O
O
O
O
H3C
O
O
O
O
77.48
77.16 CDCl3
76.84
f1 (ppm)

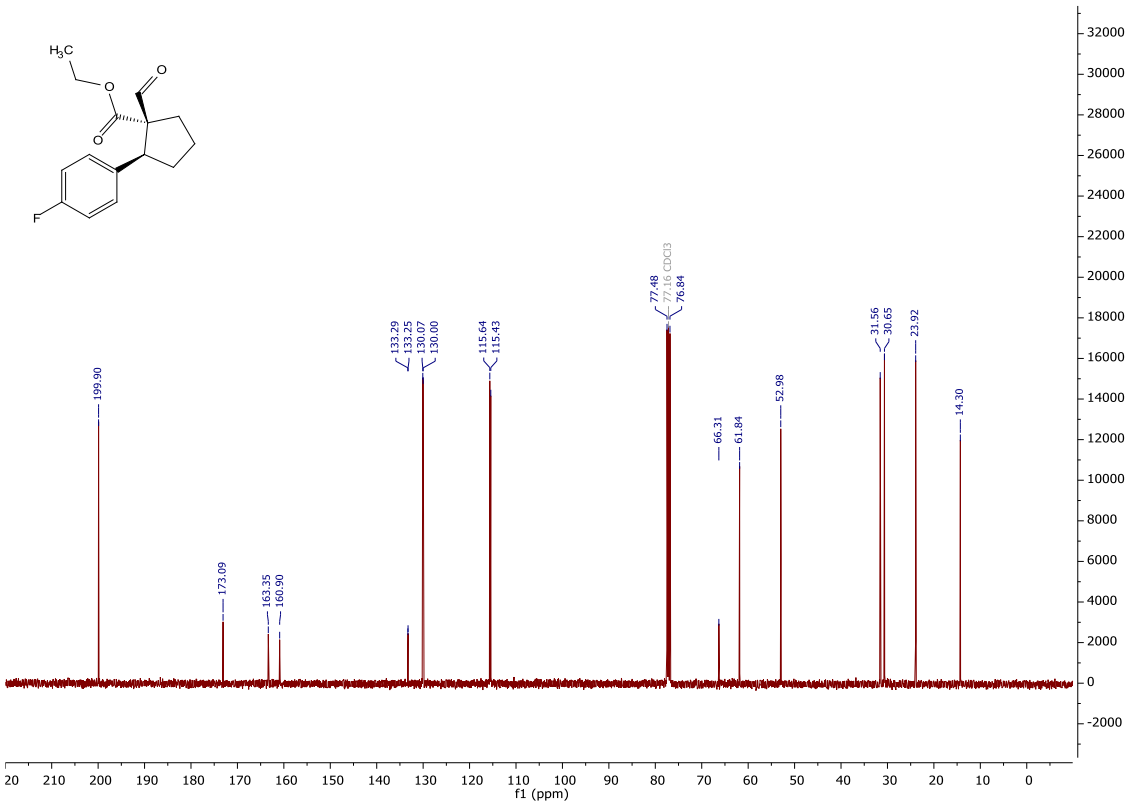

H3C
O
O
O
9.27
7.31
7.30
7.29
7.28
7.26 CDCl3
7.25
7.24
7.23
7.22
7.21
7.20
4.28
4.27
4.26
4.25
4.24
4.23
3.90
3.88
3.87
2.57
2.56
2.55
2.53
2.09
2.07
2.01
2.00
1.99
1.98
1.97
1.96
1.95
1.94
1.84
1.28
1.27
1.26
0.87
1.95
3.04
1.93
0.95
0.96
0.98
3.07
1.00
3.00
f1 (ppm)

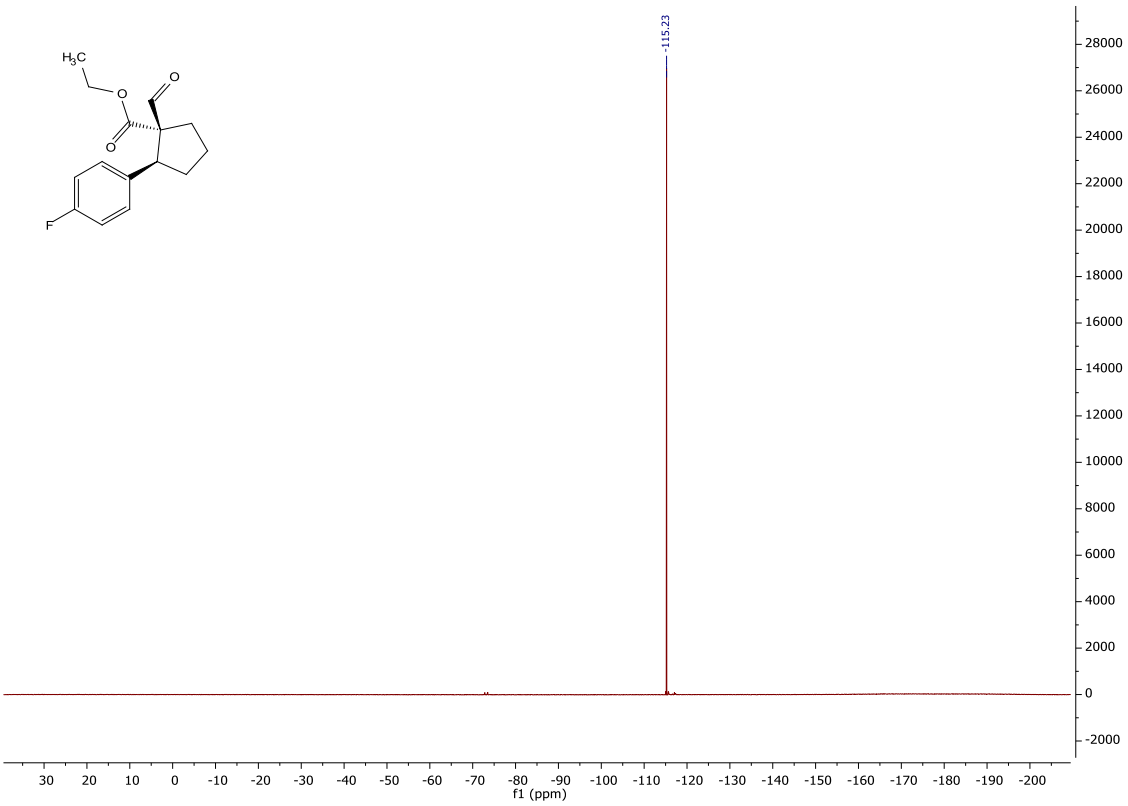

H3C
O
O
O
200.08
173.23
137.59
128.71
128.52
127.47
77.48
77.16 CDCl3
76.84
66.34
61.76
53.85
31.36
30.56
24.02
14.30
f1 (ppm)

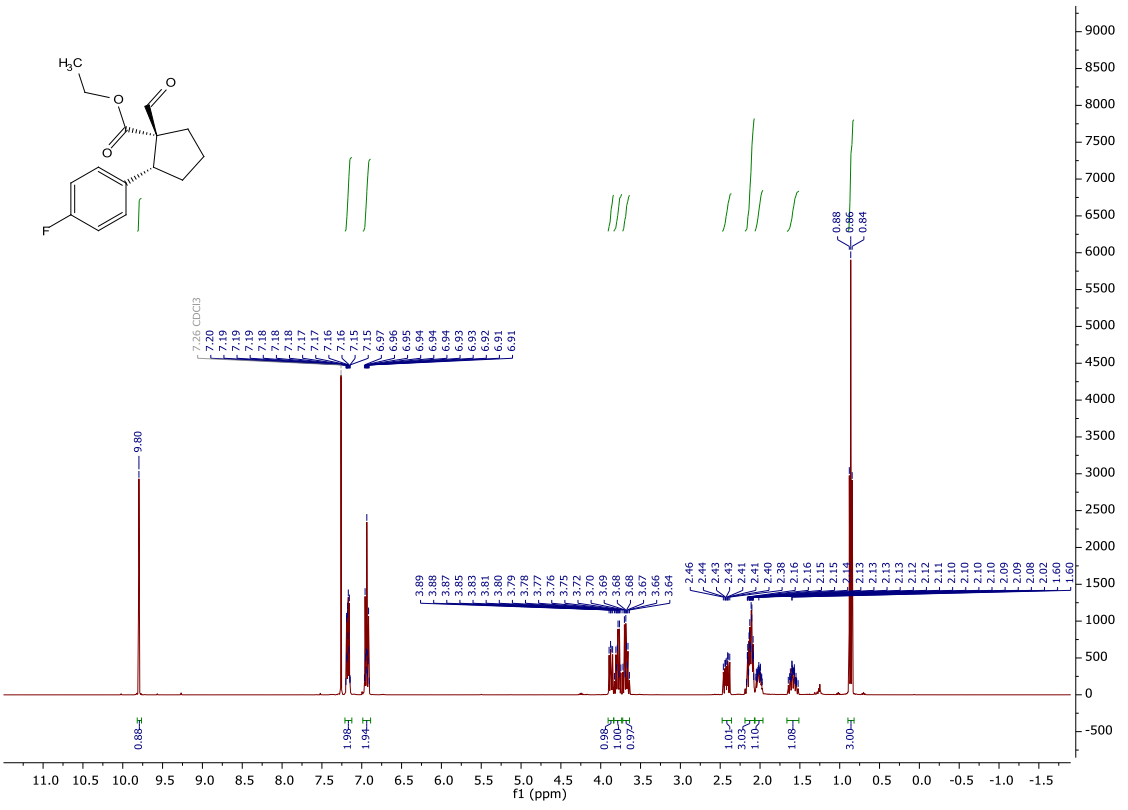

H3C
O
O
O
9.83
7.27
7.26 CDCl3
7.25
7.24
7.23
7.22
7.21
7.20
7.19
7.18
3.87
3.86
3.84
3.78
3.77
3.76
3.75
3.74
3.73
3.67
3.66
3.65
3.64
3.63
3.62
2.18
2.17
2.16
2.15
1.65
1.63
1.62
1.61
1.60
1.59
1.58
1.56
0.83
0.82
0.80
0.95
1.81
3.28
1.04
1.02
1.02
1.04
3.18
1.11
1.03
3.00
f1 (ppm)

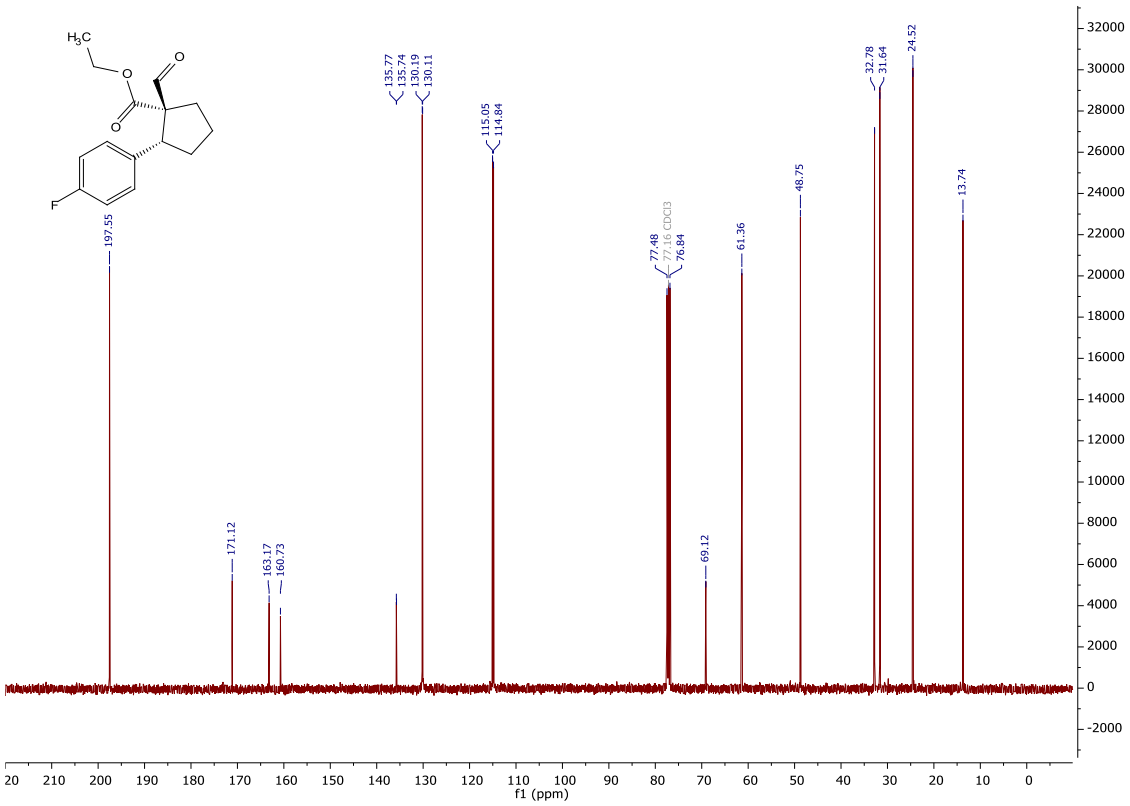

H3C
O
O
O
128.62
128.22
127.07
77.48
77.16 CDCl3
76.84
197.91
171.17
140.12
69.26
61.27
49.98
32.62
31.43
24.61
13.65
f1 (ppm)

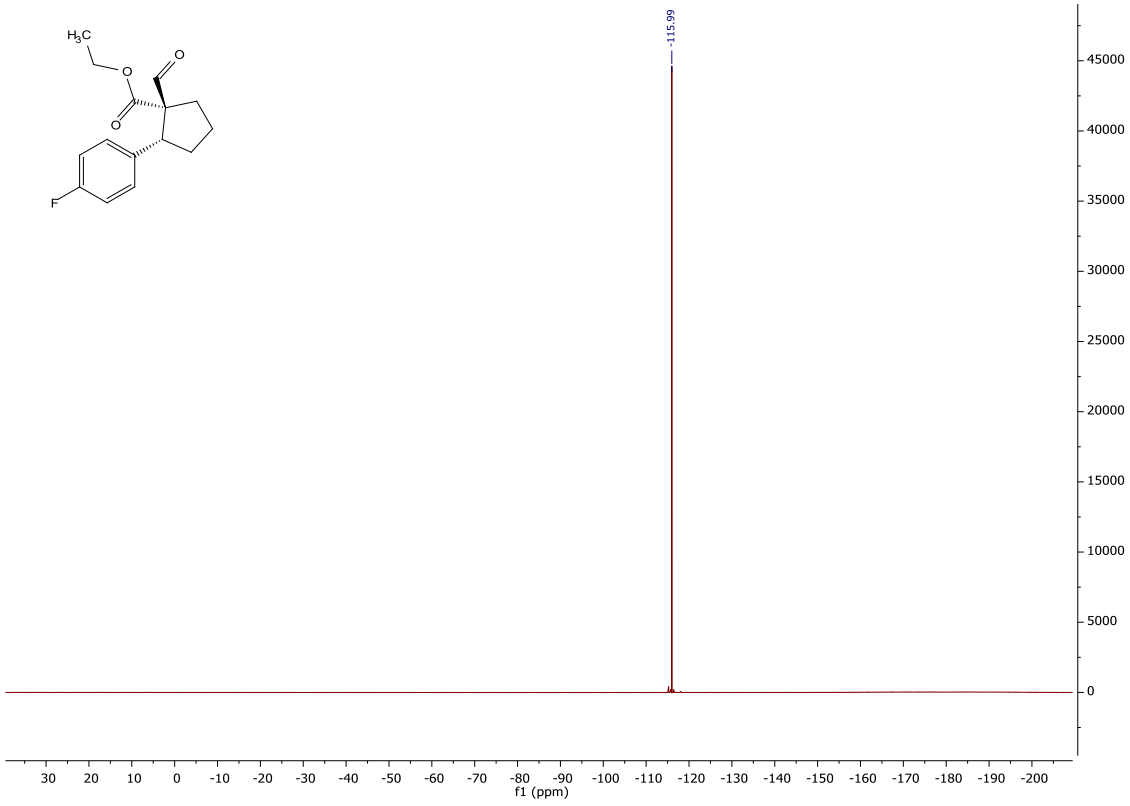

H3C
O
O
O
F
7.26 CDCl3
9.27
4.28
4.26
4.24
4.22
3.88
3.86
3.85
3.83
2.56
2.54
2.54
2.53
2.50
1.29
1.27
1.25
0.91
2.03
1.98
2.00
1.00
1.04
5.37
3.16
f1 (ppm)

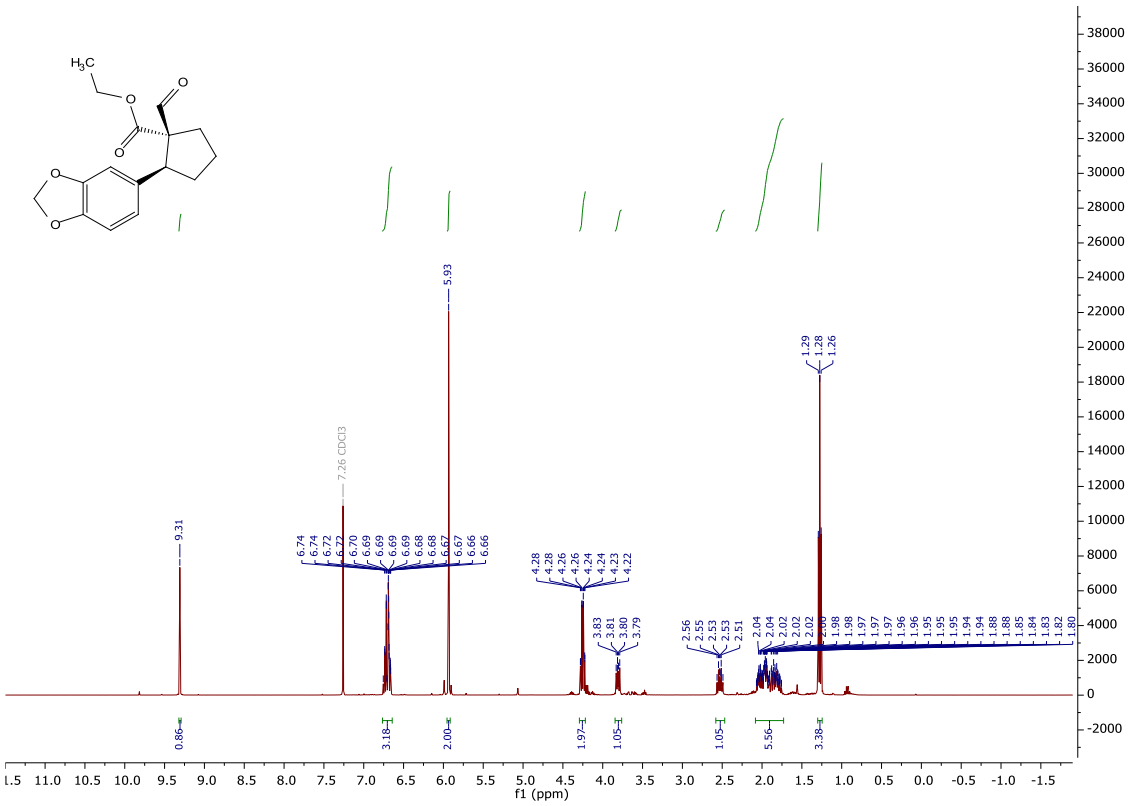

H3C
O
O
O
F
199.90
173.09
163.35
160.90
133.29
133.25
130.07
130.00
115.64
115.43
77.48
77.16 CDCl3
76.84
66.31
61.84
52.98
31.56
30.65
23.92
14.30
f1 (ppm)

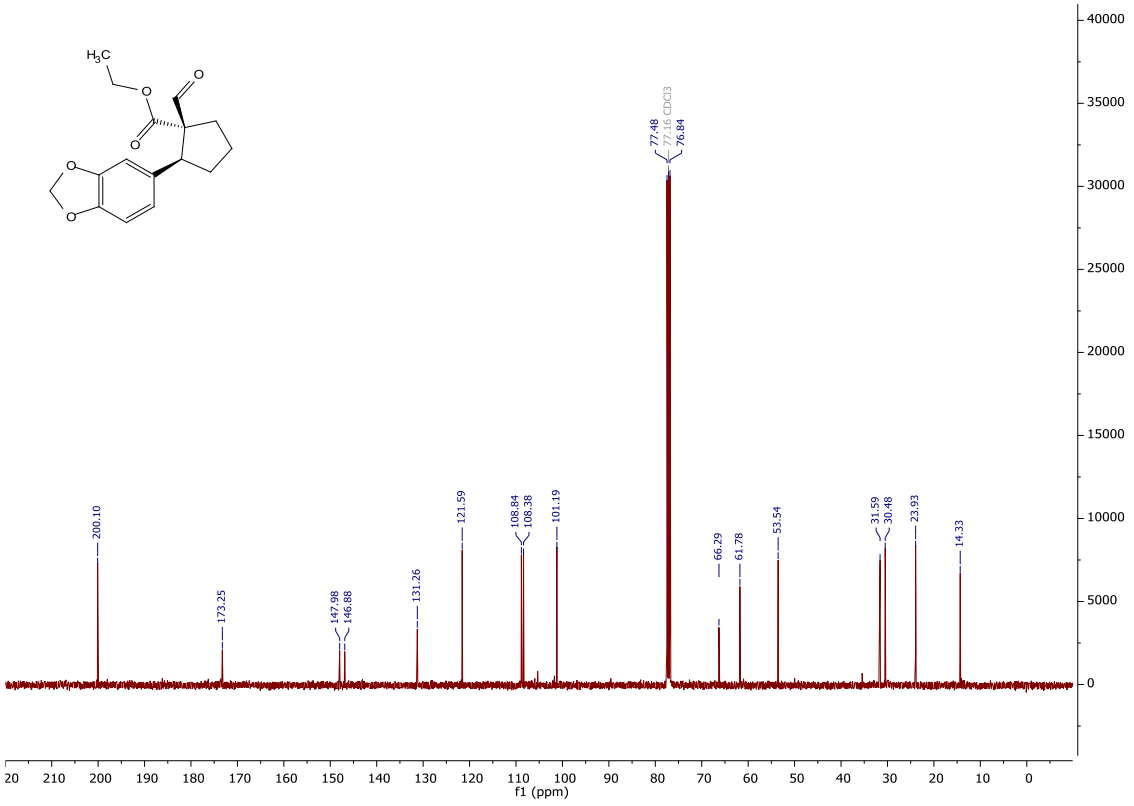

-115.23
f1 (ppm)

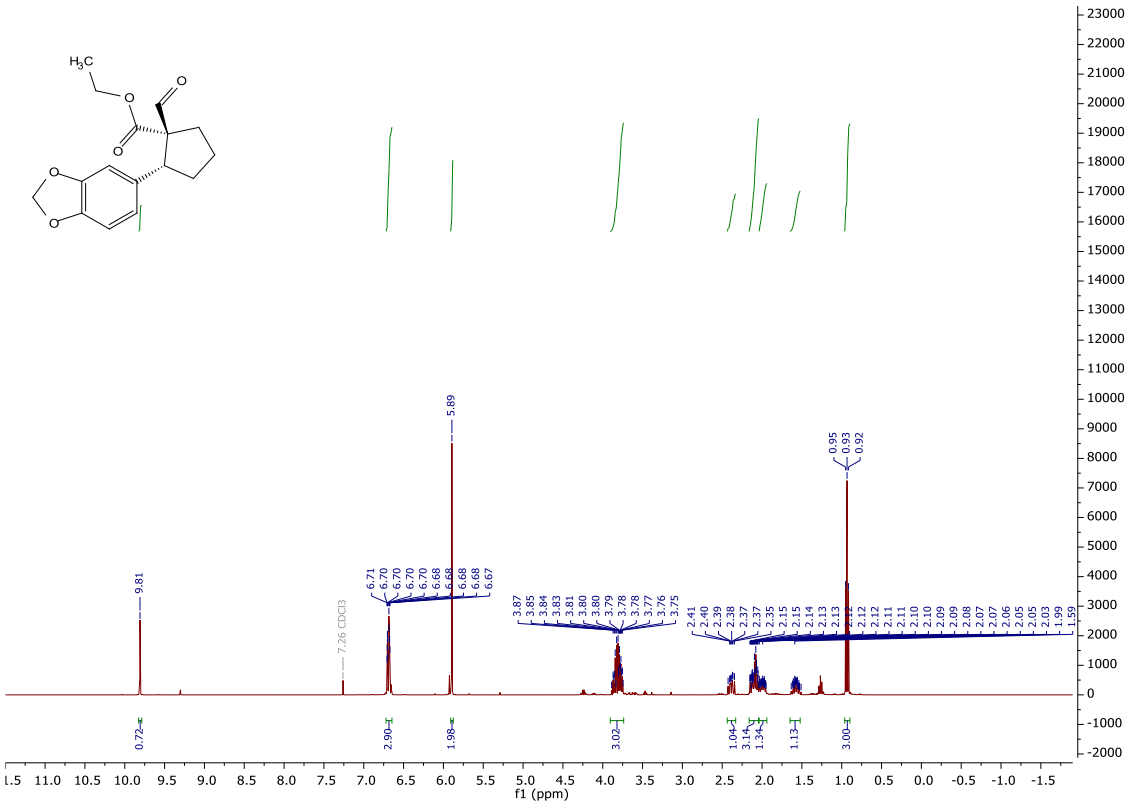

9.80
7.26 CDCl3
0.88
0.86
0.84
f1 (ppm)

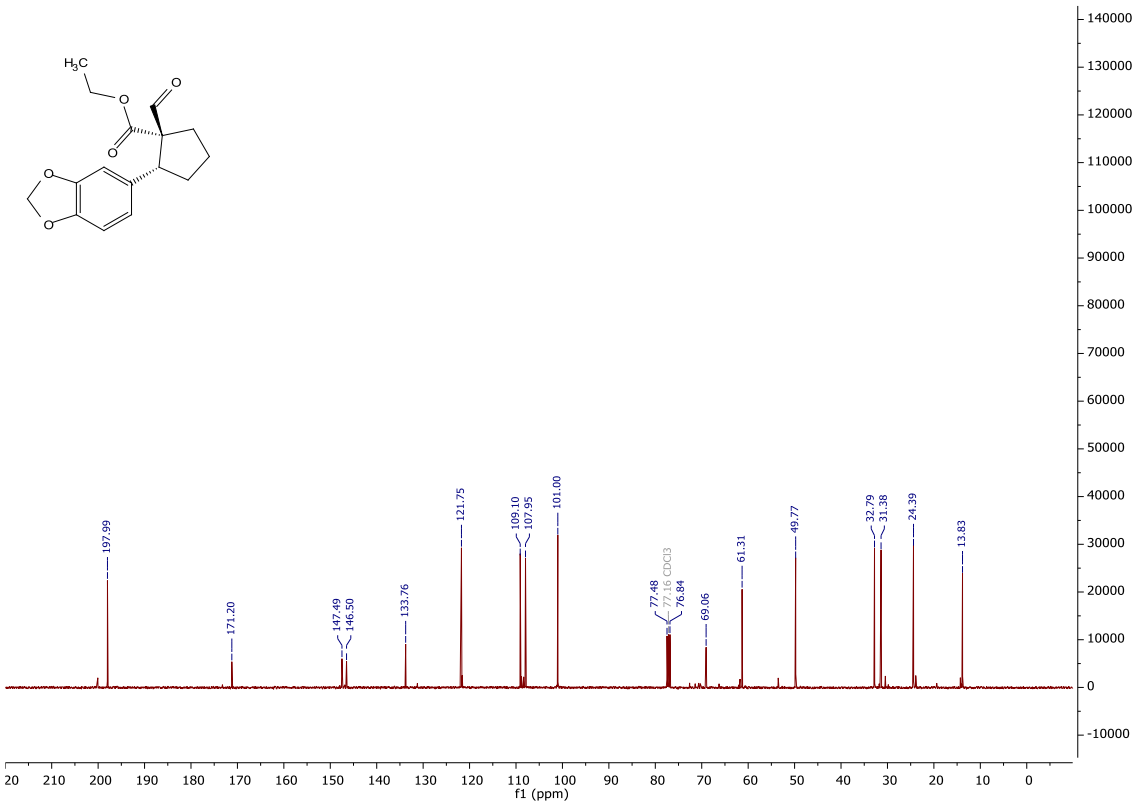

H3C
O
O
O
F
197.55
171.12
163.17
160.73
135.77
135.74
130.19
130.11
115.05
114.84
77.48
77.16 CDCl3
76.84
69.12
61.36
48.75
32.78
31.64
24.52
13.74
f1 (ppm)

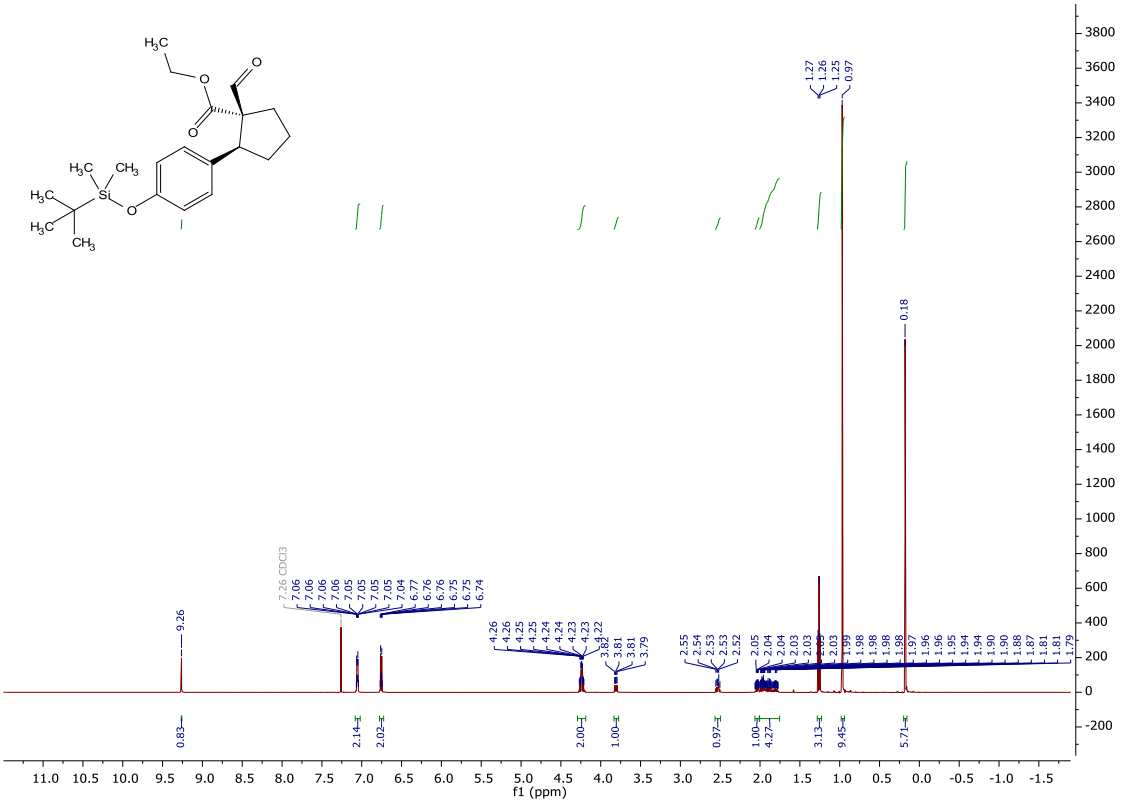

H3C
O
O
O
F
-115.99
f1 (ppm)

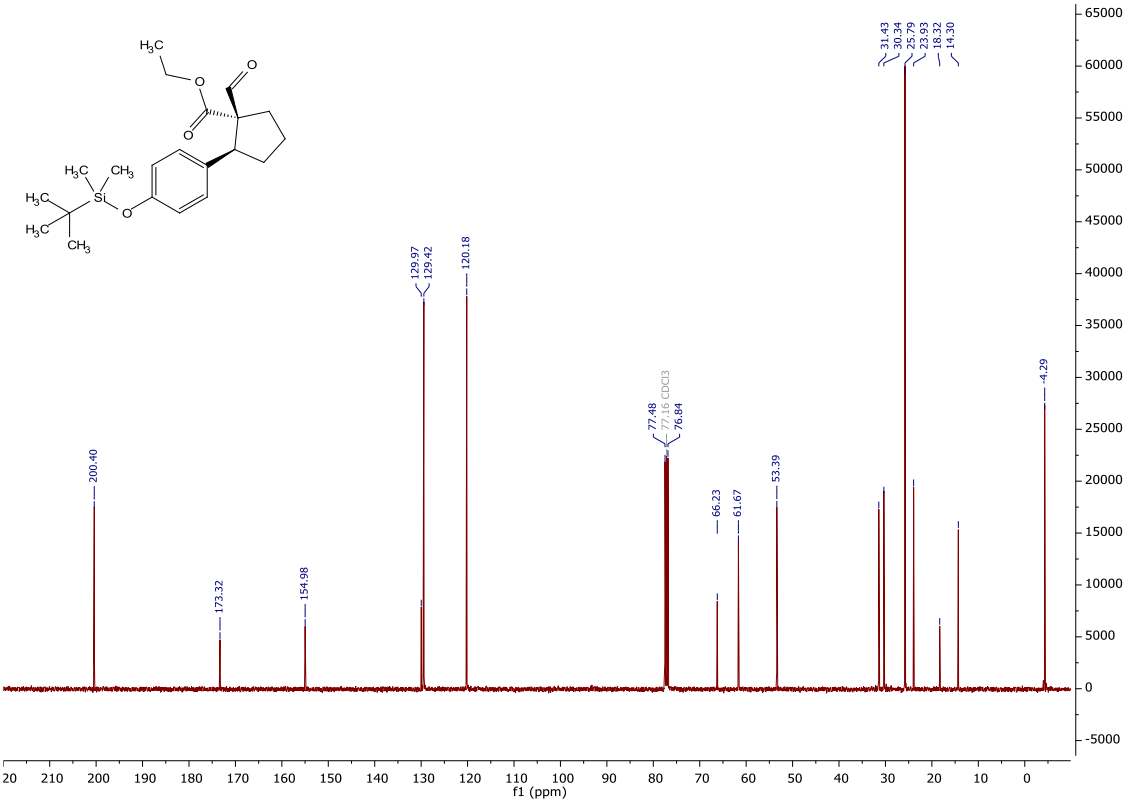

H3C
O
O
O
O
O
9.31
7.26 CDCl3
6.74
6.74
6.72
6.72
6.70
6.69
6.69
6.69
6.69
6.68
6.68
6.67
6.66
6.66
5.93
4.28
4.28
4.26
4.26
4.24
4.24
4.23
4.22
3.83
3.81
3.80
3.79
2.56
2.55
2.53
2.53
2.51
2.04
2.04
2.02
2.02
2.02
2.00
1.98
1.98
1.97
1.97
1.97
1.96
1.96
1.95
1.95
1.95
1.94
1.94
1.88
1.88
1.85
1.84
1.83
1.82
1.80
1.29
1.28
1.26
0.86
3.18
2.00
1.97
1.05
1.05
5.56
3.38
f1 (ppm)

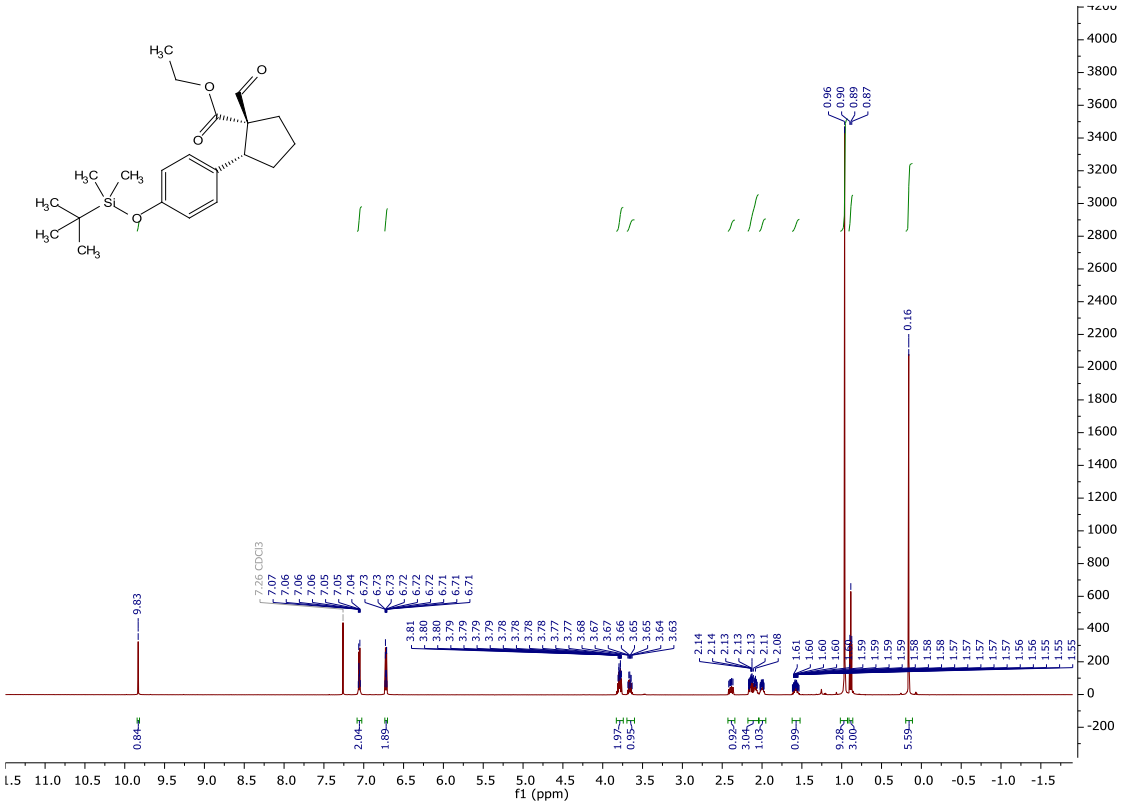

H3C
O
O
O
O
O
77.48
77.16 CDCl3
76.84
200.10
173.25
147.98
146.88
131.26
121.59
108.84
108.38
101.19
66.29
61.78
53.54
31.59
30.48
23.93
14.33
f1 (ppm)

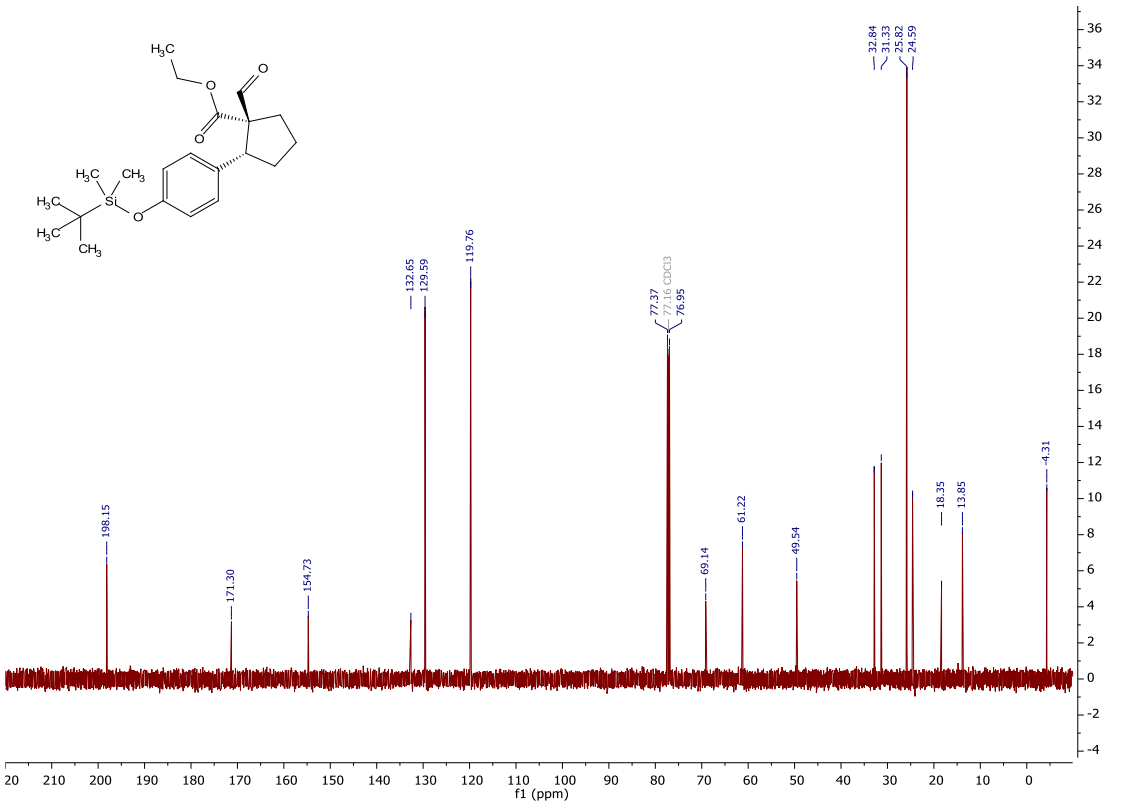

9.81
7.26 CDCl3
6.71
6.70
6.70
6.70
6.68
5.89
6.68
6.68
6.67
3.87
3.85
3.84
3.83
3.81
3.80
3.79
3.78
3.78
3.77
3.76
3.75
2.41
2.40
2.39
2.38
2.37
2.37
2.35
2.15
2.15
2.14
2.13
2.13
0.95
0.93
0.92
0.72
2.90
1.98
3.02
1.04
3.14
1.34
1.13
3.00
f1 (ppm)

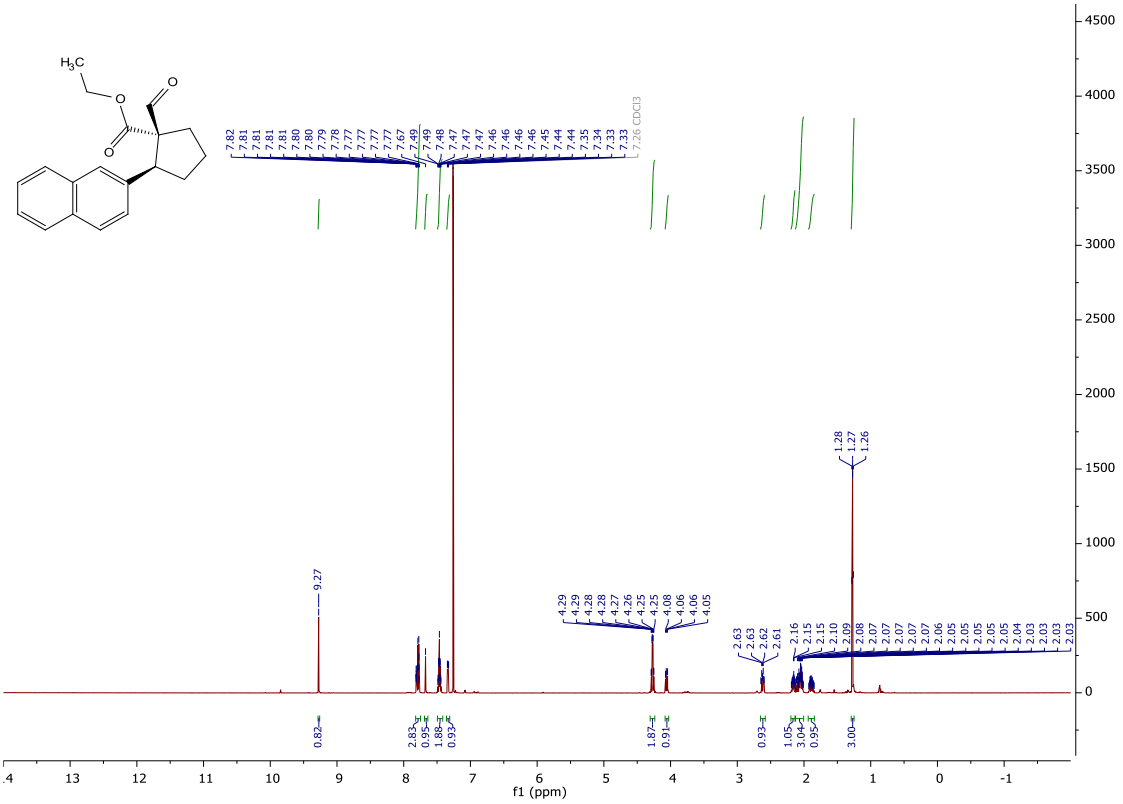

197.99
171.20
147.49
146.50
133.76
121.75
109.10
107.95
101.00
77.48
77.16 CDCl3
76.84
69.06
61.31
49.77
32.79
31.38
24.39
13.83
f1 (ppm)

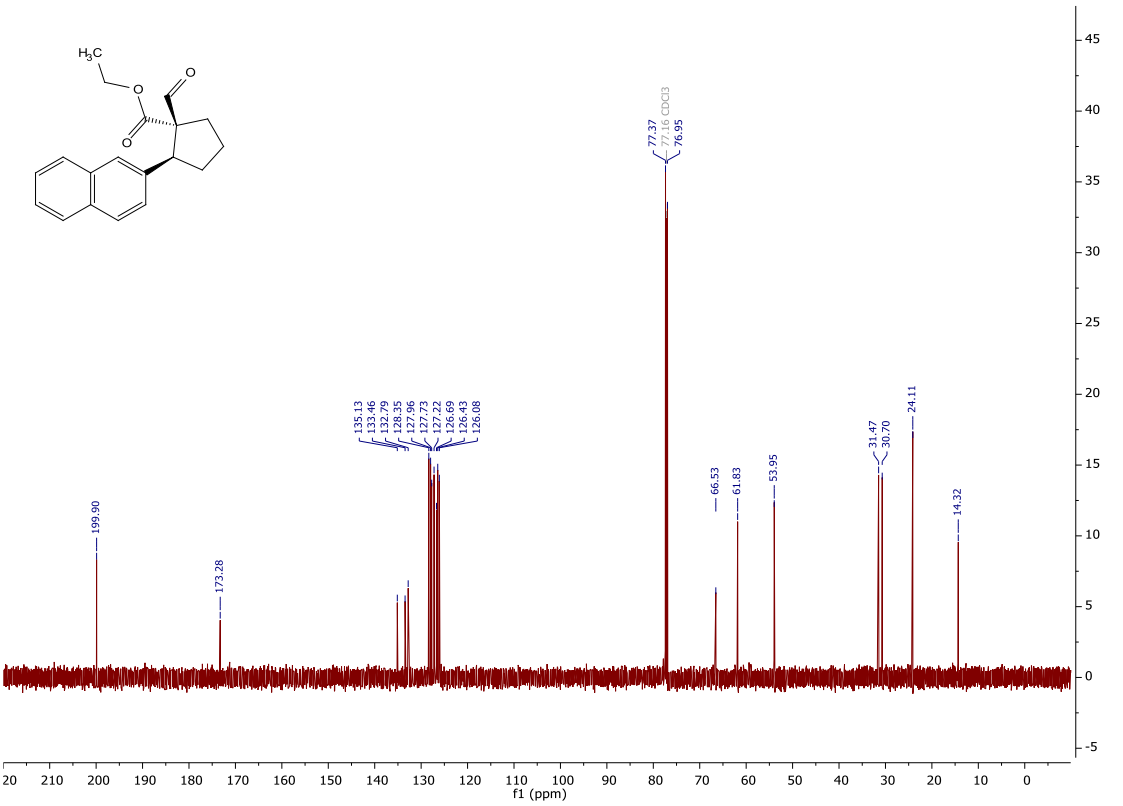

1.27
1.26
1.25
0.97
0.18
9.26
7.26 CDCl3
7.06
7.05
6.77
6.76
6.75
6.74
4.26
4.25
4.24
4.23
4.22
3.82
3.81
3.79
2.55
2.54
2.53
2.52
2.05
2.04
2.03
2.02
2.01
2.00
1.99
1.98
1.97
1.96
1.95
1.94
1.90
1.88
1.87
1.81
1.79
0.83
2.14
2.02
2.00
1.00
0.97
1.00
4.27
3.13
9.45
5.71
f1 (ppm)

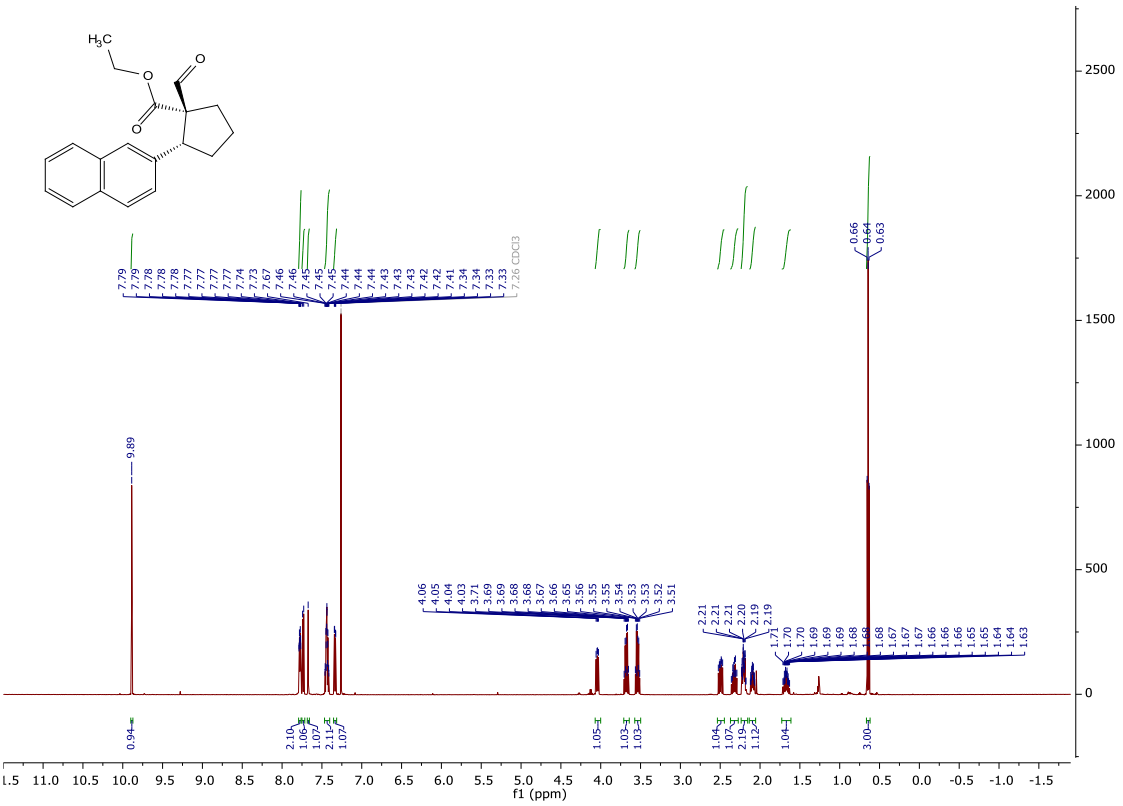

31.43
30.34
25.79
23.93
18.32
14.30
129.97
129.42
120.18
77.48
77.16 CDCl3
76.84
66.23
61.67
53.39
-4.29
200.40
173.32
154.98
f1 (ppm)

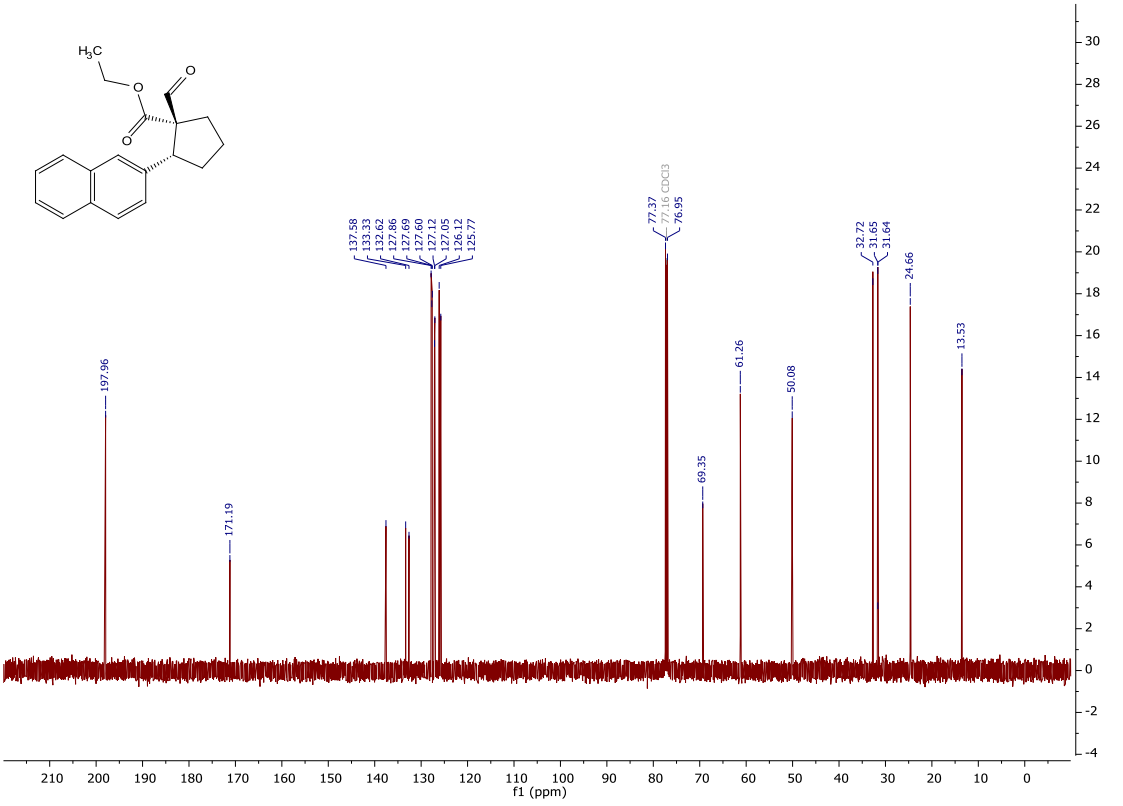

f1 (ppm)

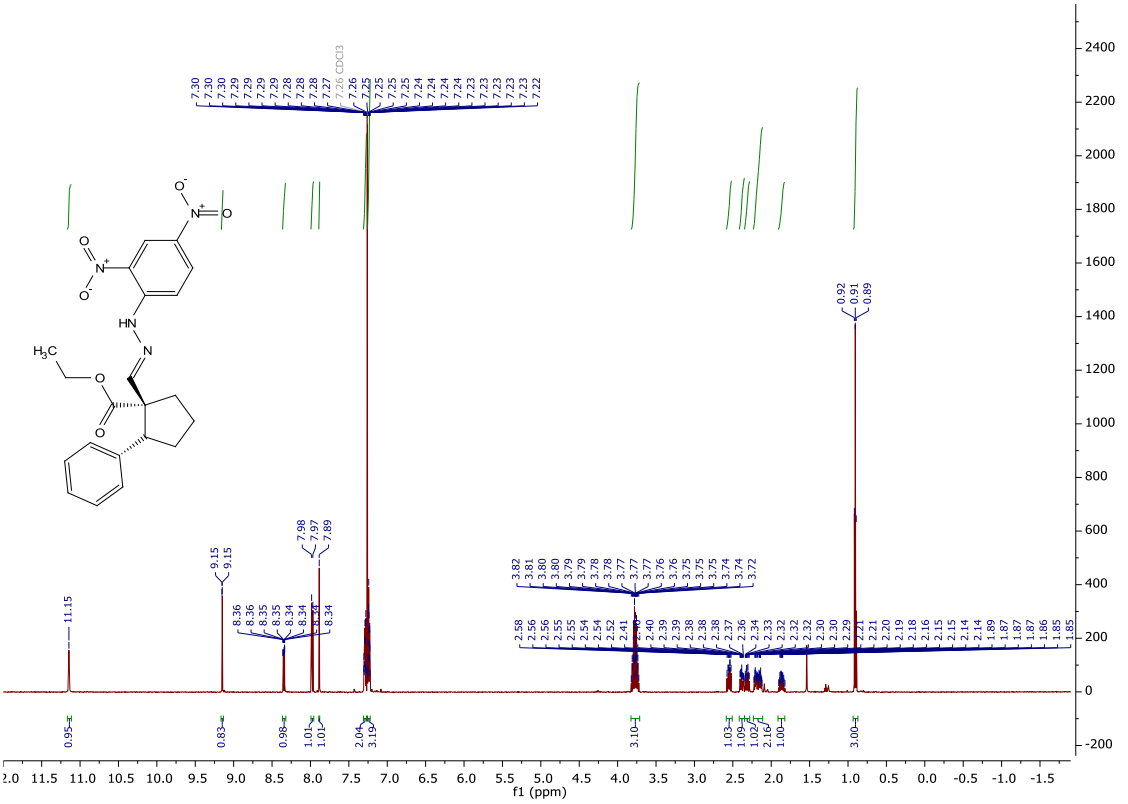

f1 (ppm)

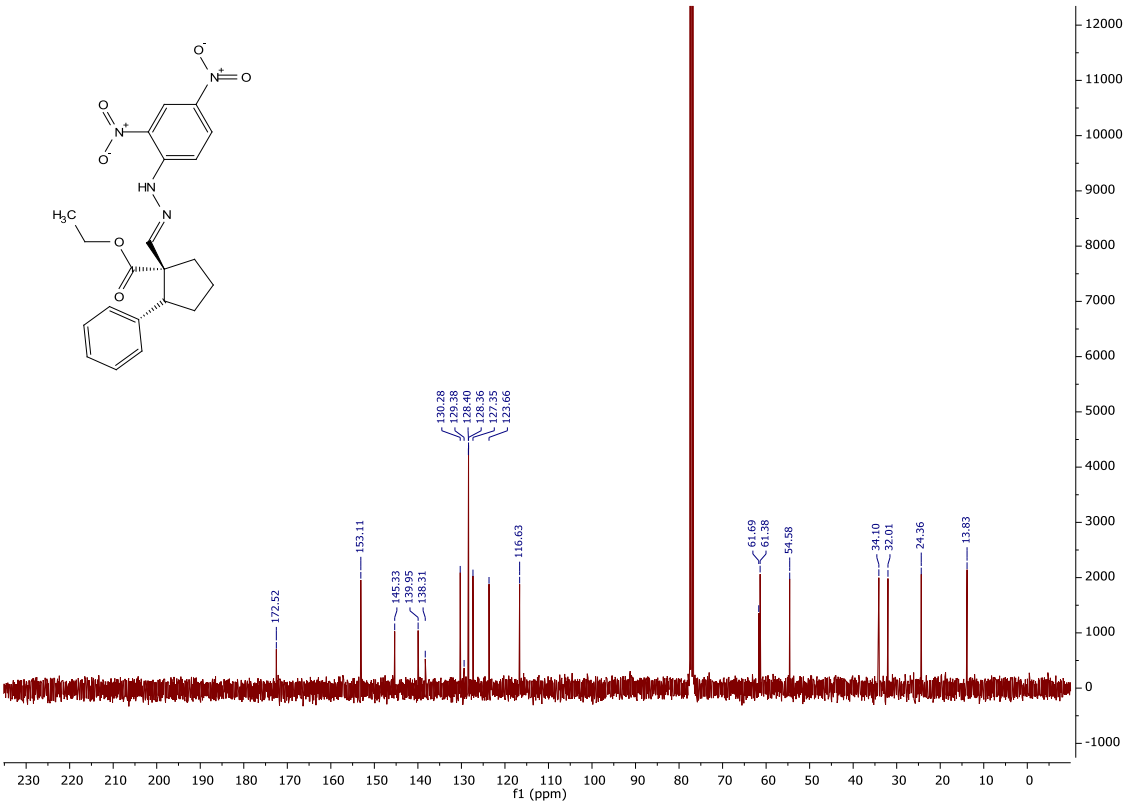

H3C
O
O
O
7.82
7.81
7.81
7.81
7.81
7.80
7.80
7.79
7.78
7.77
7.77
7.77
7.77
7.77
7.69
7.49
7.48
7.47
7.47
7.47
7.46
7.46
7.46
7.46
7.45
7.44
7.44
7.35
7.34
7.33
7.26 CDCl3
9.27
4.29
4.29
4.28
4.28
4.27
4.26
4.25
4.25
4.08
4.06
4.06
4.05
2.63
2.63
2.62
2.61
2.16
2.15
2.15
2.10
2.09
2.08
2.07
2.07
2.07
2.07
2.07
2.06
2.05
2.05
2.05
2.05
2.05
2.04
2.03
2.03
2.03
1.28
1.27
1.26
0.82
2.83
0.95
1.88
0.93
1.87
0.91
0.93
1.05
3.04
0.95
3.00
f1 (ppm)


H3C
O
O
O
77.37
77.16 CDCl3
76.95
135.13
133.46
132.79
128.35
127.96
127.73
127.22
126.69
126.43
126.08
199.90
173.28
66.53
61.83
53.95
31.47
30.70
24.11
14.32
f1 (ppm)


H3C
O
O
O
f1 (ppm)


H3C
O
O
O
f1 (ppm)


7.30
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.28
7.27
7.26 CDCl3
7.26
7.25
7.25
7.25
7.24
7.24
7.24
7.24
7.23
7.23
7.23
7.23
7.22
11.15
9.15
9.15
8.36
8.36
8.35
8.35
8.34
8.34
8.34
8.34
7.98
7.97
7.89
3.82
3.81
3.80
3.80
3.79
3.79
3.78
3.78
3.77
3.77
3.77
3.76
3.76
3.75
3.75
3.75
3.74
3.74
3.72
2.58
2.56
2.56
2.55
2.55
2.54
2.54
2.52
2.41
2.40
2.39
2.39
2.38
2.38
2.38
2.37
2.36
2.34
2.33
2.32
2.32
2.32
2.30
2.30
2.29
2.21
2.21
2.20
2.19
2.18
2.16
2.15
2.15
2.14
2.14
1.89
1.87
1.87
1.87
1.86
1.85
1.85
1.85
0.92
0.91
0.89
0.95
0.83
0.98
1.01
1.01
2.04
3.19
3.10
1.03
1.09
1.02
2.16
1.00
3.00
f1 (ppm)


172.52
153.11
145.33
139.95
138.31
130.28
129.38
128.40
128.36
127.35
123.66
116.63
61.69
61.38
54.58
34.10
32.01
24.36
13.83
f1 (ppm)

Curriculum Vitae

Mathew L. Piotrowski

EDUCATION

Ph. D. Synthetic Organic Chemistry September 2015-2019
The University of Western Ontario, London, Ontario
Research focus: Studies towards cyclopropane chemistry and natural molecule synthesis
Supervisor: Dr. Michael A. Kerr

B. Sc. Honors Specialization in Chemistry September 2011-2015
The University of Western Ontario, London, Ontario
Honors Thesis: The Tandem Cyclopropane Ring-Opening/Click Reaction as a Route to New Fluorescent Compounds
Supervisor: Dr. Michael A. Kerr

Awards and Scholarships

Dean's honor list of 2015

Publications

Phillips, G. A.; Palmer, C. Stevens, A. C. **Piotrowski, M. L.**; Dekruyf, D. S. R.; Pagenkopf, B. L. Oxidative cyclization of tertiary pentenols derivatives forming 2,5,5-trisubstituted THF rings and the total synthesis of cyclocapitelline. *Tetrahedron Lett.* **2015**, *56*, 6052-6055.

Piotrowski, M. L.; Kerr, M. A. Tandem Cyclopropanation/Vinylogous Cloke–Wilson Rearrangement for the Synthesis of Heterocyclic Scaffolds. *Org. Lett.* **2018**, *20*, 7624-7627.

Piotrowski, M. L.; Kerr, M. A. Synthesis of (±)-β-allokainic acid. *Eur. J. Org. Chem.* **2019**, 3122-3126.

Piotrowski, M. L.; Kerr, M. A. Lewis Acid Assisted Rearrangement of Dihydrofurans to Cyclopentenes. *Manuscript in Preparation.*

Oral Presentations

Piotrowski, M. L.; Kerr, M. A. The Synthesis of Carbo- and Hetero-cyclic Scaffolds Through the use of Sigmatropic Rearrangements. 102nd Chemistry Chemical Conference and Exhibition, Quebec City Convention Centre, Quebec City, Quebec.

Piotrowski, M. L.; Kerr, M. A. Synthetic Efforts Towards Alstofolinine A. 101st Chemistry Chemical Conference and Exhibition, Shaw Conference Center, Edmonton, Alberta.

Piotrowski, M. L.; Kerr, M. A. New Methodology Towards the Synthesis of Oxepines and Tetrahydropyridazines Involving DA-Cyclopropanes. 100th Chemistry Chemical Conference and Exhibition, Metro Toronto Convention Center, Toronto, Ontario.

Piotrowski, M. L.; Flisar, M. E.; Kerr, M. A. The Determination of Fluorescent Properties of Triazole Compounds obtained through the One Pot Ring-Opening/Click Reaction of Cyclopropane Hemimalonates. 43rd Southern Ontario Undergraduate Student Chemistry Conference. University of Toronto, Mississauga, Ontario.

Poster Presentations

Piotrowski, M. L., Kerr, M. A. Synthesis of Oxepines through Rhodium Catalyzed Cyclopropanation of 1,3-dienes and progress towards Kainic acid. 99th Chemistry Chemical Conference and Exhibition, Halifax, Nova Scotia.

Piotrowski, M. L., Kerr, M. A. Synthesis of Oxepines through Rhodium Catalyzed Cyclopropanation of 1,3-dienes and progress towards Kainic Acid and Cyclowaraterpols. QOMSBOC, University of Waterloo, Waterloo, Ontario.

Languages

Fluent in Polish

WORK EXPERIENCE

Management of Solvent Purification System (SPS) 2015-2019

The University of Western Ontario, London, Ontario

- Ensures proper working order of SPS instruments and maintains solvent levels for users
- Trains new users how to properly use the instruments
- Maintains and organizes proper billing of solvents
- Maintains cleanliness of room

Teaching assistant September 2015-2019

Department of Chemistry, The University of Western Ontario, London, Ontario
Courses: 3373 Organic Chemistry II: Mechanisms and Strategies for Synthesis

- Responsible for imparting pre-lab discussions in safety, proper laboratory techniques, and experiment information
- Evaluated laboratory reports, mid-terms, and final exams
- Assisted students with answering questions about course material and experiments

Research Assistant May 2014-August 2014

Department of Chemistry, The University of Western Ontario, London, Ontario
Supervisor: Dr. Brian L. Pagenkopf

- Assisted M.Sc. candidate towards his research studies
- Maintained cleanliness of laboratory equipment

Stock Room (Produce Department) 2012-2015

Food Basics, London, Ontario

- Filled fruits and vegetables onto shelves and bins for customers to purchase
- Maintained the overall appearance of the department

- Organized produce cooler when new shipments arrived
- Assisted fellow workers and supervisor when needed

Cashier 2010-2012
Food Basics, London, Ontario
- Dealt with customers in a professional and disciplined manner
- Created interpersonal relationships with customers
- Performed with great time management upon scanning the customers products for sale

VOLUNTEER EXPERIENCE

Chemistry with a bang show 2015, 2016, 2017, 2018, 2019
The University of Western Ontario, London, Ontario
- Prepared chemicals needed for various reactions
- Assisted in setting up space for performance
- Assisted in putting away all chemicals in proper locations once performance was finished

Laboratory Volunteer October 2013-April 2014
Department of Chemistry, University of Western Ontario, London, Ontario
Supervisor: Dr. Brian L. Pagenkopf
- Assisted Ph.D. candidates by synthesizing various starting materials and purifying compounds by column chromatography
- Became familiar with various laboratory instruments
- Maintained cleanliness of laboratory equipment

Chemistry Club 2011
The University of Western Ontario, London, Ontario
- Participated in presenting various chemical reactions for children explaining the technical principles behind them
- Assisted in setting up the space for performance