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Cycloaddition Chemistry for the Synthesis of Heterocyclic Compounds and Progress Towards the Total Synthesis of Grandilodine A

Andrew C. Stevens
The University of Western Ontario

Supervisor
Brian L. Pagnekopf
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

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by

Andrew Charles Stevens

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The University of Western Ontario
London, Ontario, Canada

Abstract and Key Words

This thesis describes three separate research projects within the broad topic of synthetic organic chemistry. The synthesis of alkyl-substituted siloles and their reactivity in Diels–Alder chemistry is reported. Furthermore, the cleavage of the bicyclic adducts by Tamao–Fleming oxidation has been achieved which reveals a highly substituted cyclohexene-1,4-diol structure.

The second chapter describes the cycloaddition chemistry of alkoxy-activated cyclobutane dicarboxylates with aldehydes, nitrones and nitrosoarenes. The cycloaddition occurs, in the case of aldehydes, with uniformly high diastereoselectivity to afford tetrahydropyrans in good to excellent yield. When nitrones were used as the dipolarophile the cycloaddition occurs in a rather unselective manner though the formed oxazepanes undergo equilibration to yield single diastereomers in most cases. The cycloaddition with nitrosoarenes, however, proved an exception as the regioselectivity of the reaction was dependant both on the nitrosoarenes and the catalyst employed.

Lastly, progress towards the synthesis of grandilodine A is reported. Several routes were developed in attempts to form the central 8-membered ring; however, successful ring closure has eluded this study.

Key Words: Diels–Alder, Dipolar Cycloaddition, Donor-Acceptor Cyclobutane, Grandilodine A, Methodology, Natural Product, Nitrone, Nitrosoarene, Total Synthesis, Tamao–Fleming Oxidation.

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For my family

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List of Abbreviations

10-CSA	10-camphorsulfonic acid
Å	angstrom
Ac	acetyl
acac	acetylacetone
Ar	aryl
ASG	anion stabilizing group
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
CAM	cerium ammonium molybdate
*m*CPBA	*meta*-chloroperbenzoic acid
DA	donor acceptor
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	dichlorodicyanobenzoquinone
DIBAL	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4- dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
E^+	electrophile
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbondiimide
EDG	electron donating group
ee	enantiomeric excess

EI	electron impact ionization
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group
HMBCAD	heteronuclear multiple bond correlation adibatic
HOMO	highest occupied molecular orbital
HWE	Horner–Wadsworth–Emmons
IBX	2-iodoxybenzoic acid
kJ	kilojoules
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
Me	methyl
Mes	mesityl
Mg*	Rieke magnesium
mol	mole(s)
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
nOe	nuclear Overhouser effect
Nu	nucleophile
PCC	pyridinium chlorochromate

PDMS	polydimethylsiloxane
Ph	phenyl
PMB	*para*-methoxylbenzyl
PMP	1,2,2,6,6-pentamethylpiperidine
RCM	ring-closing metathesis
Red-Al	sodium bis-(2-methoxyethoxy)aluminum hydride
TBAF	tetrabutylammonium flouride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyl diphenylsilyl
TBHP	*tert*-butylhydrogen peroxide
TBS	*tert*-butylsilyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
Tf	triflouromethylsulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl

Preface

The field of synthetic organic chemistry is a rich source of unsolved problems. It continually challenges and inspires practitioners to create innovative solutions, discover new processes, and apply these methods to the synthesis of complex target molecules. Furthermore, it provides us with pleasing challenges to test our understanding of fundamental principles and rewards our endeavors richly upon success. To this end, I have worked towards expanding our understanding of several fundamental concepts described within this thesis. Enclosed within are three projects which may seem, at first, to be disparate. However, the broad nature of synthetic organic chemistry encompasses all of these subjects. The synthetic methodologies of the first two chapters create intriguing new molecules which may possess biological activity, or can be used as platforms for the installation of further complexity. The last chapter explores the de novo synthesis of a complex natural product and, while the process does not use any of the methods developed in the first two chapters, serves as a lesson of current challenges in synthetic organic chemistry that still need to be addressed and possibly as a stimulus for further methodology development.

The first chapter demonstrates that siloles may engage productively in Diels–Alder chemistry with exceptionally high levels of stereocontrol. I have also displayed the value of the corresponding adducts in context by oxidatively cleaving the silicon-carbon bonds; creating the complex cyclohexene-1,4-diol core of the eudesmanolide natural products.

The second chapter of this thesis describes the investigation of donor-acceptor strained ring systems. I, along with coworkers, was able to show that alkoxy-activated

cyclobutane dicarboxylates could successfully undergo annulation events with two and three atom dipoles to form a variety of unique bicyclic hetereocycles. These new compounds have striking molecular architecture and may find application as novel scaffolds for biological studies.

Lastly, I directed efforts towards the total synthesis of the recently disclosed natural product grandilodine A. I explored multiple routes towards the total synthesis of grandilodine A, yet was continually stymied by unanticipated intricacies that revealed themselves through my studies. Despite the incomplete nature of the work, many lessons were learned that may assist in the successful synthesis in the future.

Though these projects appear to be quite disparate in scope and nature, they serve as a reminder of the wide breadth of the field of synthetic organic chemistry. I hope the reader will find the body of work as stimulation for further studies, or as a valuable resource of relevant background information.

-Andrew C. Stevens

Chapter 1. Diels–Alder Chemistry of Siloles and their Transformation into Cyclohex-2-ene-1,4-diols.

This chapter describes the synthesis of siloles with substitution patterns that are continuative toward natural product synthesis and their reactivity in Diels–Alder chemistry. The cleavage of the resulting bicyclic adducts reported reveals a highly functionalized cyclohexene-diol core. Relevant background information of silicon's role in organic synthesis is included. A portion of this work has been published in *Organic Letters*.[1] Portions of text and schemes have been reprinted in part with permission from Stevens, A. C.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 3658–3661. Copyright © 2010 American Chemical Society.

1.1 Introduction: Silicon in Organic Synthesis

Silicon is the second most abundant element in our planet's crust, after oxygen.[2] The unique reactivity of silicon has promoted its extensive use in organic chemistry over the past several decades.[3] Much of the chemistry associated with silicon is due to the strength of the silicon-carbon, silicon-oxygen, and silicon-fluorine bonds (290 kJ/mol, 368 kJ/mol and 582 kJ/mol respectively).[4] The silicon-carbon and silicon-oxygen bonds are strong enough to survive most organic transformations, but can be readily cleaved under mild conditions which has led to the extensive use of silicon-based protecting groups.[5] In addition, the ability of silicon to stabilize positive charges ß to the functional group has facilitated important carbon-carbon bond forming reactions such as the Hosomi–Sakurai[6] and Mukaiyama aldol[7] reactions. More recently, silicon has found use

as an activating group for cross-coupling chemistry where organosilicon reagents act as nucleophilic donors (i.e., the Hiyama coupling).[8] This reaction allows toxic, expensive and reactive organo-metallic reagents such as organozinc and organotin species to be replaced with benign organosilicon reagents. Though initial findings required fluoride sources to activate the silicon for cross-coupling, extensive investigations have found that mild bases can be used as an alternative when the organosilane is appropriately substituted.[9]

Silicon has also found use as a Lewis acid in a plethora of transformations when weakly coordinating anions are present (e.g, TMSOTf).[10] Recent reports from the Leighton group have described the use of strain-release from silacycles which has resulted in a new class of allylation reagents (**1-1**) which act as both an allylation source and a Lewis acid (Figure 1.1).[11,12] These reagents are important as allylations are one of the most used reactions for the generation of new stereocenters and append a vital synthetic handle for further chemical transformations. They have proven to be a viable alternative to the commonly used Brown allylation, as the Leighton allylation reagents are readily available from commodity chemicals (and are now commercially available), are stable solids that can be stored for extended periods of time, have good enantioselectivity and the products are easily separated from the reaction byproducts. This is in contrast to the Brown allylation reagents which must be prepared fresh (a time-intensive procedure), are exceedingly moisture sensitive and require extensive work-up conditions to remove the by-products from the reaction products. Additionally, derivatives of the silacycle have been synthesized and applied as the first enantioselective

silicon Lewis acids for a number of transformations including but not limited to Diels–Alder,[13] Mannich,[14] and Pictet–Spengler[15] reactions.

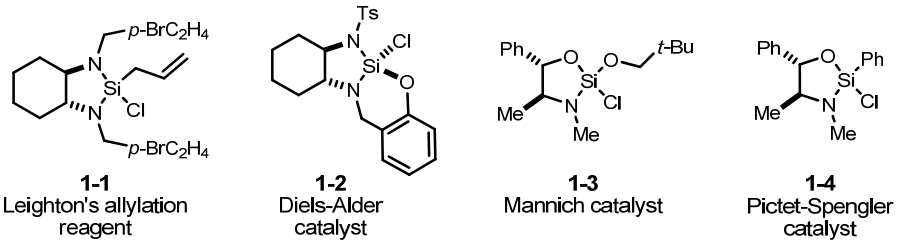
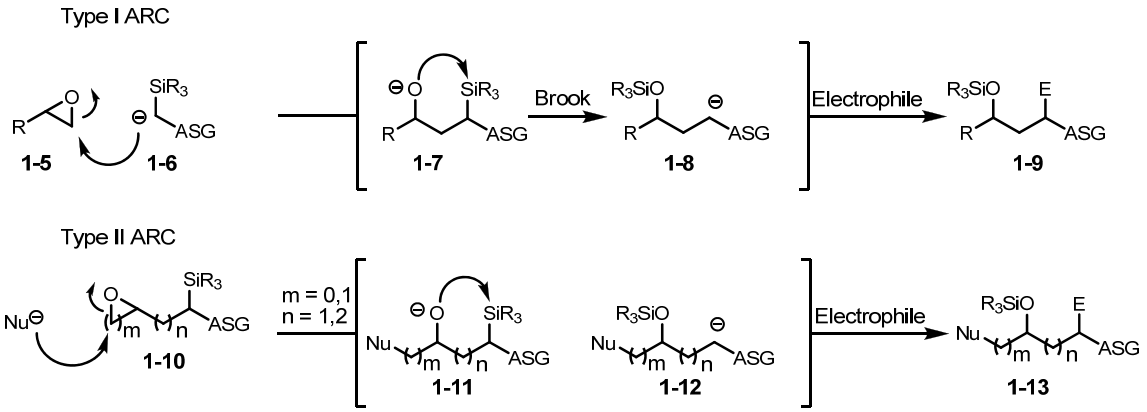


Figure 1.1. Enantioselective Silicon Based Lewis Acid Catalysts

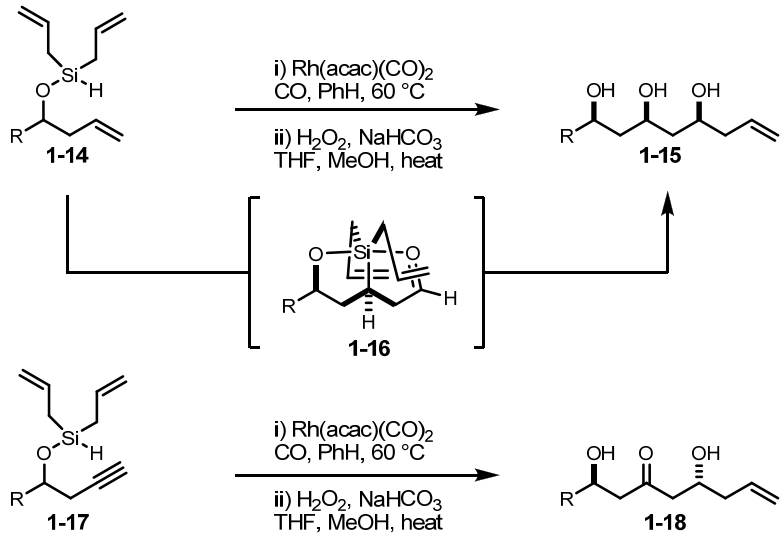
The use of silicon as a lynchpin for novel strategies in synthetic chemistry has also seen intense investigation. Application of the disparity between carbon-silicon and carbon-oxygen bond strength allows for the Brook rearrangement (**1-7** to **1-8** or **1-11** to **1-12**), where a carbon-silicon bond is cleaved and an oxygen-silicon bond is formed, creating a carbanion. Typically this carbanion is protolytically quenched; however, tandem reactions involving the Brook rearrangement have recently been explored, most notably by Smith and Takeda (Scheme 1.1). This strategy has been dubbed anionic relay chemistry and is capable of engaging a diverse array of reaction partners for rapid and efficient generation of libraries of compounds.[16]

Scheme 1.1. Type I and Type II Anion Relay Chemistry



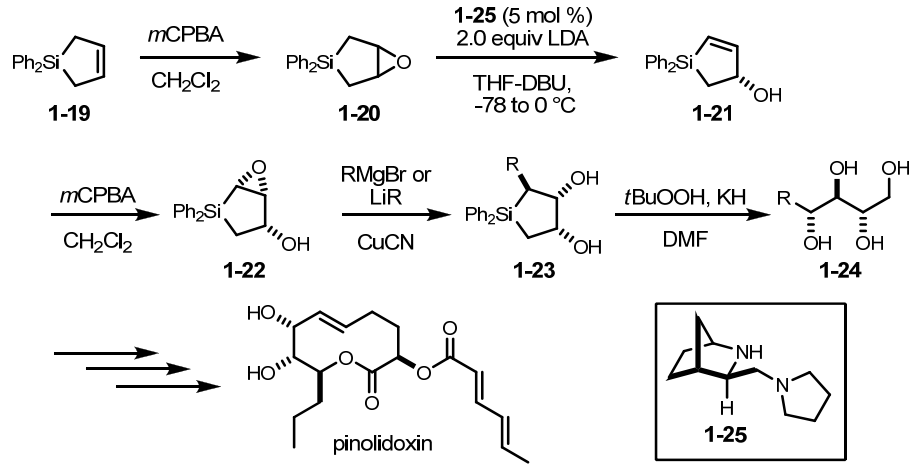
The widespread use of silicon as a protecting group has led to investigation of silicon as a temporary tether or as a template, strategies explored both by Leighton and Kozmin. Leighton has demonstrated this concept through a tandem silylformylation/allylsilation sequence.[17] Treatment of diallylsilyl ether (**1-14**) with Rh(acac) under carbon monoxide atmosphere followed by Tamao–Fleming oxidation afforded 1,3,5-triol **1-15** with high diastereoselectivity (Scheme 1.2). Extension of this methodology to pendant alkynes allowed for an alternative stereochemical outcome.[18] In both cases the proposed stereochemical model implicates allyl transfer through activation of the aldehyde (installed *via* silylformylation) in an intramolecular fashion and intramolecular allyl transfer.

Scheme 1.2. Tandem Silylformylation/Allylation of Pendant Alkenes and Alkynes



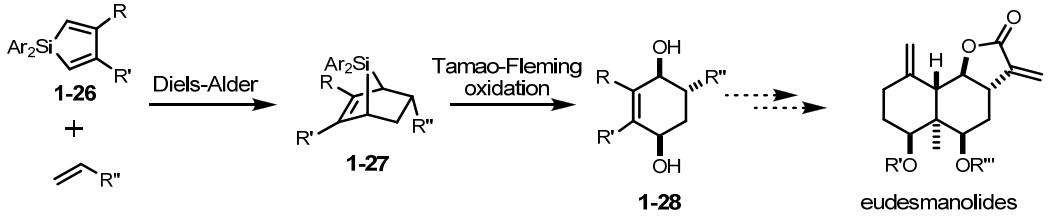
Kozmin has also developed chemistry whereby he uses silicon as a templating reagent, allowing for an asymmetric rearrangement to occur.[19] *meso*-Silacyclopentene oxide **1-20** was treated with a chiral amine base (**1-25**) to afford chiral allyl alcohol **1-21** (Scheme 1.3). Subsequent hydroxyl-directed epoxidation and epoxide opening allowed for the synthesis of highly substituted silacyclopentane **1-23**. Cleavage of the silicon-carbon bonds (once again *via* Fleming–Tamao oxidation) revealed the polyol structure, available with complete control over the stereochemical outcome at each stereogenic center. Importantly, the chiral amine base was found to be capable of acting in a catalytic fashion, allowing for application in large-scale reactions such as those required for total synthesis. Subsequently, this methodology was applied in the enantioselective synthesis of pinolidoxin.[20]

Scheme 1.3. Enantioselective Rearrangement of Silacyclopenteneoxide and Application for Total Synthesis



Though there has been significant exploration of silacycles in organic chemistry, there remain many opportunities that have not yet been realized. One such area of potential utility is that of siloles, which have previously been extensively investigated for their intriguing optoelectronic properties.[21] It is readily apparent that siloles may undergo Diels–Alder cycloadditions, as cyclopentadiene is a well explored diene for Diels–Alder chemistry. It was somewhat surprising that there have only been few reports of Diels–Alder chemistry of siloles, very limited in scope, and the adducts obtained have only had rudimentary explorations as to their potential usefulness.[22] At the onset of this work, it was believed that the bicyclic adduct of a silole Diels–Alder reaction could undergo silicon-carbon bond cleavage to form a highly functionalized cyclohex-2-ene-1,4-diol (Scheme 1.4). The structural features contained in **1-28** could facilitate rapid access to a diverse range of compounds, potentially leading to the synthesis of natural products such as the eudesmanolides.[23]

Scheme 1.4. Cyclohex-2-ene-1,4-diols from Siloles and Potential Applications

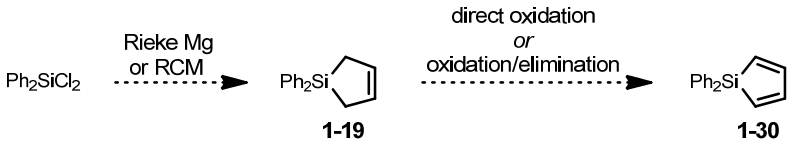


1.2 Results and Discussion

1.2.1 Synthesis of a *C*-Unsubstituted Silole

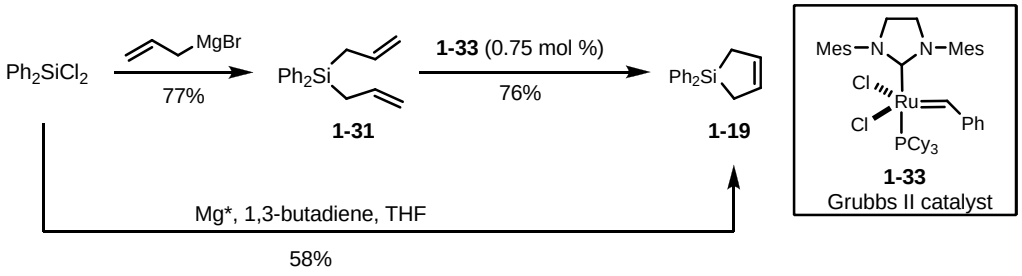
The initial target of study was 1,1-diphenylsilole (**1-30**) as the limited hindrance about the carbon ring would increase the likelihood of a successful Diels–Alder reaction[24] and the aromatic substituents on the silicon would enable the subsequent oxidative cleavage of the silicon-carbon bond (Scheme 1.5).[25] The majority of research regarding siloles has involved development for electrochemical purposes[26] resulting in synthetic strategies that are only suitable for siloles bearing aromatic substituents about the carbon ring.[27] Rapid preparation of siloles absent of an aromatic substituent has been reported using flash vacuum pyrolysis,[28] a process our lab was ill-equipped to perform. Additionally, this method has only been demonstrated successfully with siloles bearing small alkyl substituents on the silicon atom, which would prove ineffective for subsequent Tamao–Fleming oxidation and as such, an alternative synthesis was explored. It was believed that a direct oxidation or an oxidation-elimination sequence could provide an expedient route to access silole **1-30** from commercially available dichlorodiphenylsilane (Scheme 1.5).

Scheme 1.5. Proposed Synthetic Route to a *C*-unsubstituted Silole



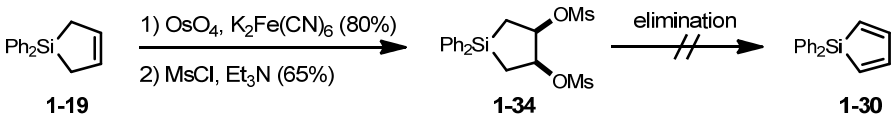
Synthetic efforts began with formation of dihydrosilole **1-19** (Scheme 1.6). The material was readily available through either a two-step process by reaction of dichlorodiphenylsilane with allylmagnesium bromide and subsequent RCM[29] or in a one-step reductive cyclization of dichlorodiphenylsilane with Rieke magnesium and 1,3-butadiene.[30] The single step process was preferred due to shorter reaction times and the potential to access tri- and tetrasubstituted olefins which would be problematic to form via RCM.[31]

Scheme 1.6. Synthesis of Silacyclopentene **1-19**



Unfortunately, direct oxidation of **1-19** with DDQ, MnO_2, Pd/C, and SeO_2 failed to deliver the silole, thus a stepwise dihydroxylation/elimination reaction sequence was explored (Scheme 1.7). Dihydrosilole **1-19** was dihydroxylated with OsO_4 and $K_2Fe(CN)_6$ and the diol was converted to a *bis*-mesylate. Unfortunately, base promoted elimination of the *bis*-mesylate (**1-34**) failed under a variety of reaction conditions.

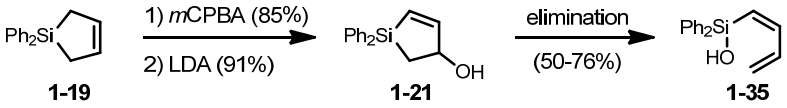
Scheme 1.7. Oxidation-Elimination of Dihydrosilole **1-19**



1-19 **1-34** **1-30**

As a double elimination was not possible, elimination of an allylic alcohol was investigated. Through a sequence similar to that employed by Kozmin,[19] allylic alcohol **1-21** was obtained through epoxidation of dihydrosilole **1-19** and epoxide rearrangement with LDA (Scheme 1.8). Unfortunately, derivatives of compound **1-21** were highly susceptible to silicon-carbon bond cleavage, as installation of relatively stable leaving groups (sulfonates) resulted in elimination *in situ* to form silanol **1-35**. This process also occurred even when mild elimination protocols of Burgess[32] or Grieco[33] were employed.

Scheme 1.8. Elimination *via* Allylic Alcohol



1-19 **1-21** **1-35**

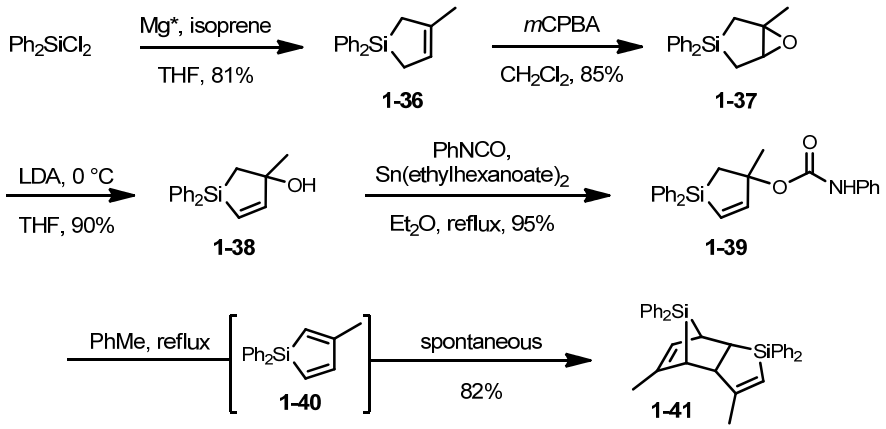
Faced with difficulties in the formation of a *C*-unsubstituted silole, research was directed towards the more stable *C*-substituted siloles (i.e, **1-40**, Scheme 1.9).[34] Additionally, since tertiary alcohols are more readily eliminated from dihydrosiloles than are secondary alcohols, milder reaction conditions were expected to be applicable.[34]

1.2.2 Synthesis of 1,1-Diphenyl-3-methylsilole

The same three-step protocol was used to prepare tertiary alcohol **1-38** (Scheme 1.9). Reductive cyclization between dichlorodiphenylsilane, isoprene and Rieke magnesium formed dihydrosilole **1-36**, which was epoxidized with *m*CPBA. Rearrangement of epoxide **1-37** with LDA occurred with complete regioselectivity to

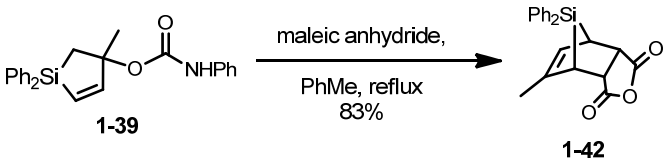
afford tertiary alcohol **1-38**. Dehydration of tertiary alcohol **1-38** was achieved through formation of the phenyl carbamate followed by thermolysis; however, only the dimeric product **1-41** was obtained and the monomeric silole **1-40** was not observed. Lower-temperature eliminations were examined *via* mesylates or tosylates but *in situ* elimination occurred and only the dimeric product was obtained.

Scheme 1.9. Preparation of an Alkyl Silole Dimer



Introduction of maleic anhydride as a dienophile during thermolysis of tertiary carbamate **1-39** was successful in trapping the silole and Diels–Alder adduct **1-42** was obtained in 83% yield (Scheme 1.10). Unfortunately, this interception strategy could not be extended to other dienophiles. Attempts to crack the silole dimer (**1-41**) and trap it with maleic anhydride were also unsuccessful and only slow decomposition of the dimer was observed even under prolonged times at high temperature (refluxing xylenes).

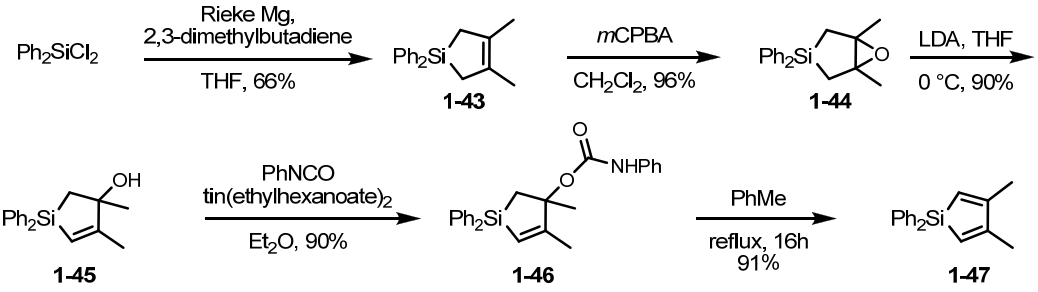
Scheme 1.10. Trapping of 1,1-Diphenyl-3-methylsilole with Maleic Anhydride



1.2.3 Synthesis of 3,4-Dimethyl-1,1-diphenylsilole

Buoyed by the successful formation of the Diels–Alder adduct, yet frustrated by the inability to isolate the monomeric silole, attention was turned towards synthesis of a *C*-disubstituted silole in hopes of isolating a monomeric compound whose reactivity could be fully explored. To this end, the same 3-step protocol used previously was applied to synthesize tertiary alcohol **1-45** (Scheme 1.11).

Scheme 1.11. Synthesis of 3,4-Dimethyl-1,1,-diphenylsilole (**1-47**)



Reductive cyclization of 2,3-dimethylbutadiene with diphenyldichlorosilane afforded dihydrosilole **1-43**. Epoxidation and subsequent rearrangement afforded allylic alcohol **1-45** in good yield, producing only the *endo*-alkene. Subsequent conversion of the allylic alcohol to carbamate **1-46** occurred readily and in high yield. Upon heating **1-46** in toluene thermal elimination occurred to produce 3,4-dimethylsilole **1-47** without formation of the dimer and only trace amounts of *exo*-elimination products (<5%). Single step eliminations of allylic alcohol **1-45** to form the silole through a mesylate or tosylate

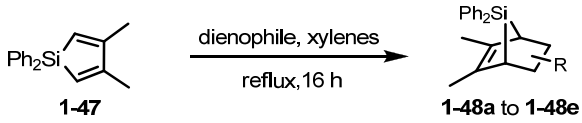
were found to be unsatisfactory due to substantial (25%) formation of the *exo* isomer which could not be separated from the silole. Investigation into the propensity of the silole to dimerize found that 3,4-dimethyl-1,1-diphenylsilole (**1-47**) was very resilient, as dimerization was not observed even over extended periods of time at elevated temperatures.

1.2.4 Diels–Alder Reactions of Siloles

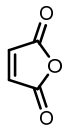
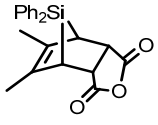
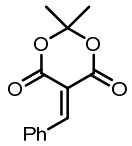
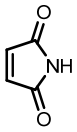
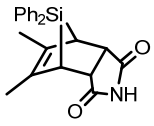
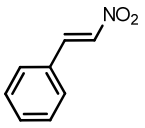
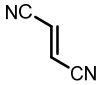
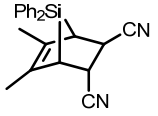
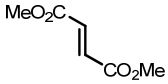
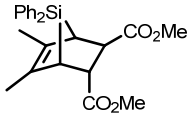
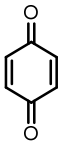
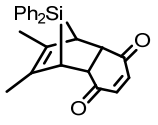
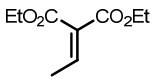
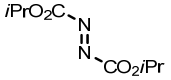
1.2.4.1 Thermal Diels–Alder Reaction

Having secured a reliable route to a monomeric silole, the breadth of the thermal Diels–Alder cycloaddition was investigated (Table 1.1). Cycloadditions with highly reactive dienophiles, such as maleic anhydride or maleimide (entries 1 and 2), were complete after 16 h at room temperature while less reactive dienophiles, such as fumarates and quinones (entries 3 - 5), required elevated temperatures to undergo cyclization. Trisubstituted dienophiles (entries 6 and 7) or those bearing only a single activating group (entries 8 - 10) did not react and only starting material was observed. Acetylenic species (entry 11) did not undergo the reaction, and hetero-Diels–Alder reactions did not occur (entry 12).

Table 1.1. Thermal Diels–Alder Reaction



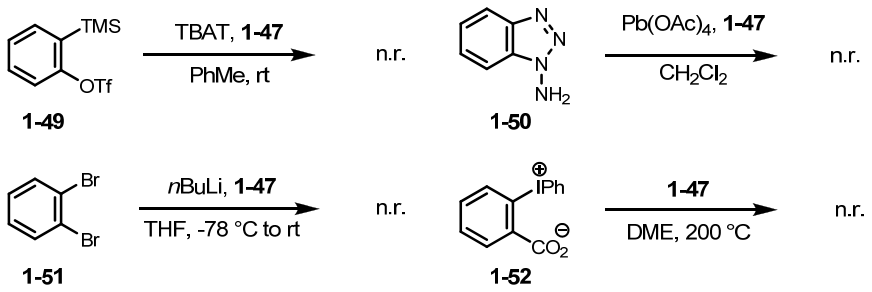
1-47 **1-48a** to **1-48e**

entry	dienophile	product, yield	entry	dienophile	product, yield
1[a]		 90%	7		n.r.[c]
2[a]		 85%	8		n.r.[c]
3[b]		 85%	9		n.r.[c]
4		 83%	10		n.r.[c]
5		 80%	11		n.r.[c]
6		n.r.[c]	12		n.r.[c]

[a] PhMe, 22 °C, 16 h. [b] PhMe, reflux, 16 h. [c] Silole starting material recovered.

The reaction of benzyne with 3,4-dimethylsilole was also investigated (Scheme 1.12). Benzyne was generated through four different methods; however, each case failed to provide the desired cycloadduct. Control tests were performed and, in the presence of cyclopentadiene, the expected cycloadducts were formed.

Scheme 1.12. Investigation of Benzyne Reactivity with Siloles



Due to the sluggish nature of these silole Diels–Alder reactions and the somewhat limited scope, methods for accelerating the reaction were investigated.

1.2.4.2 Lewis Acid Mediated and High Pressure Diels–Alder Reactions

Two known methods for the enhancement of Diels–Alder reaction, Lewis acid activation and high pressure conditions, were explored.[35] Though both accelerate Diels–Alder reactions, they do so through different mechanisms.

The Diels–Alder reaction is a $4\pi + 2\pi$ pericyclic reaction that forms two new σ-bonds at the expense of two π-bonds. The net result is a new 6-membered ring that forms in a strongly exergonic process ($\Delta H^{\ddagger} \sim 16$ to 18 kcal • mol^{-1} and $\Delta S^{\ddagger} \sim -30$ to - 40 cal • K^{-1} • mol^{-1}). The reaction occurs due to overlap between the HOMO of a diene and the LUMO of a dienophile (or vice-versa in the case of inverse demand Diels–Alder reactions) (Figure 1.2). The selectivity observed in Diels–Alder chemistry has, for many years, been attributed to secondary orbital overlap between the diene and the electron withdrawing groups on the dienophile. More recently, this rationale has fallen out of favor as calculations have shown that the atoms presumed to engage in secondary orbital interactions are situated relatively far (2.8 Å) apart in the transition state structures.[36] The currently prevailing view is that a combination of steric interactions, solvent effects and

electrostatic forces can successfully explain the typically high level of *endo* selectivity found in Diels–Alder reactions.[36]

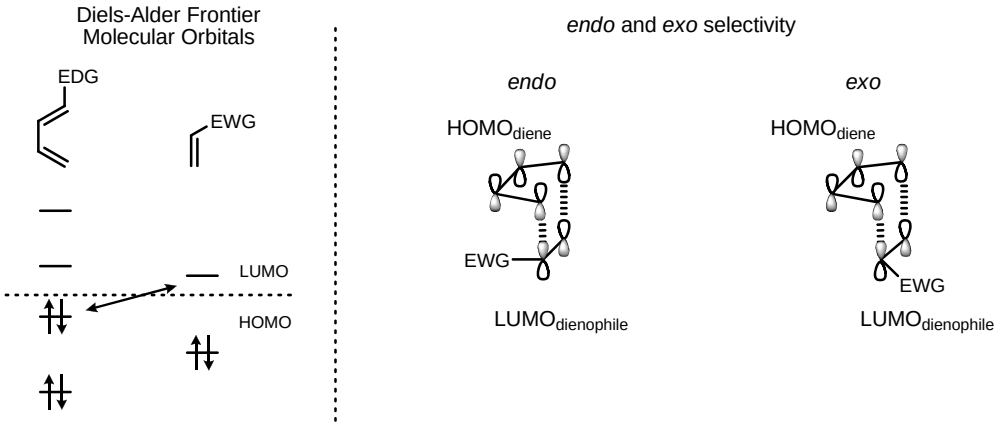


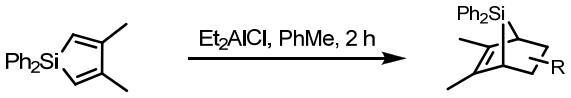
Figure 1.2. Frontier Molecular Orbitals of Diels–Alder Reactions and *Endo*/*Exo* Selectivity

Lewis acids serve as catalysts in Diels–Alder chemistry where they increase not only the speed of the reaction, but also the selectivity. This process occurs through coordination of the Lewis acid to the dienophile, lowering the energy of the LUMO and causing better overlap between the diene and the dienophile resulting in an increased rate of reaction.

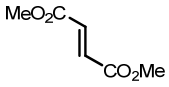
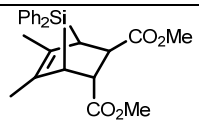
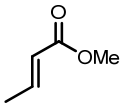
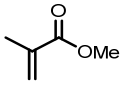
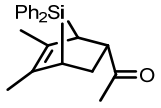
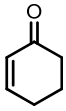
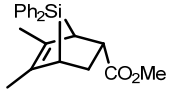
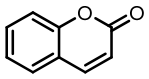
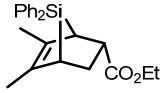
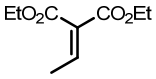
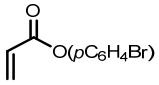
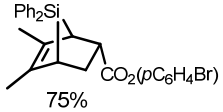
After screening several Lewis acids, it was found that diethylaluminium chloride mediated the reaction between the siloles and dienophiles, though one full equivalent of Lewis acid was required to promote full conversion of the starting material (Table 1.2). Lewis acidic conditions allowed for dienophiles bearing a single activating group (e.g., acrylates, methyl vinyl ketone, entries 3 - 6) to react at ambient temperature and reduced reaction times (from 16 h to 2 h). Despite the increased rate of reaction of singly-activated dienophiles, the Diels–Alder reaction was found to be quite limited as disubstituted alkenes (entries 1, 7 - 10) did not undergo the cycloaddition unless both

substituents on the dienophile were activating groups. Additionally, compounds prone to polymerization (entry 2) could not be accessed as they were found to undergo polymerization faster than the desired Diels–Alder reaction. Due to these limitations, additional modes of Diels–Alder enhancement were investigated.

Table 1.2. Lewis Acid Mediated Diels–Alder Reaction



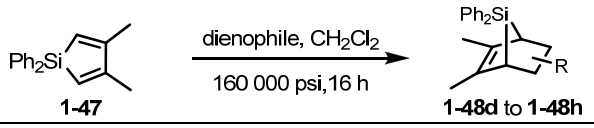
1-47 → **1-48d, 1-48g** to **1-48j**

entry	dienophile	product, yield	entry	dienophile	product, yield
1		 83%	7		n.r.
2		polymer	8		n.r.
3		 91%	9		n.r.
4		 90%	10		n.r.
5		 92%	11		n.r.
6		 75%			

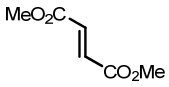
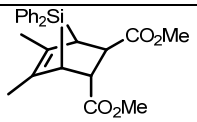
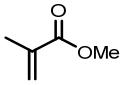
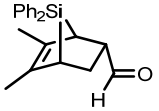
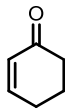
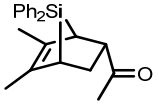
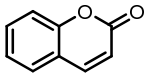
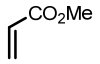
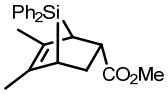
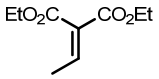
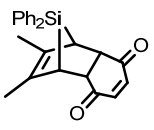
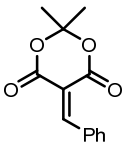
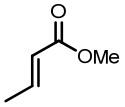
High pressure has also been explored for its effect on Diels–Alder chemistry. Diels–Alder reactions have large negative volumes of activation,[37] and as such high pressures accelerate the rate of reaction without necessitating high temperatures.[38] High

pressure reactions facilitated access to the same cycloadducts available using Lewis acid catalysis (Table 1.3); however, compounds which were previously found to readily polymerize preferentially underwent Diels–Alder cycloaddition (entry 4). Once again, disubstituted olefins were found to be beyond the scope of the reaction unless both of the substituents were activating groups (entries 1, 5 - 9) and trisubstituted olefins were found to be unreactive, even if two of the substituents were activating groups (entries 10 and 11).

Table 1.3. High Pressure Diels–Alder Reaction



1-47 **1-48d** to **1-48h**

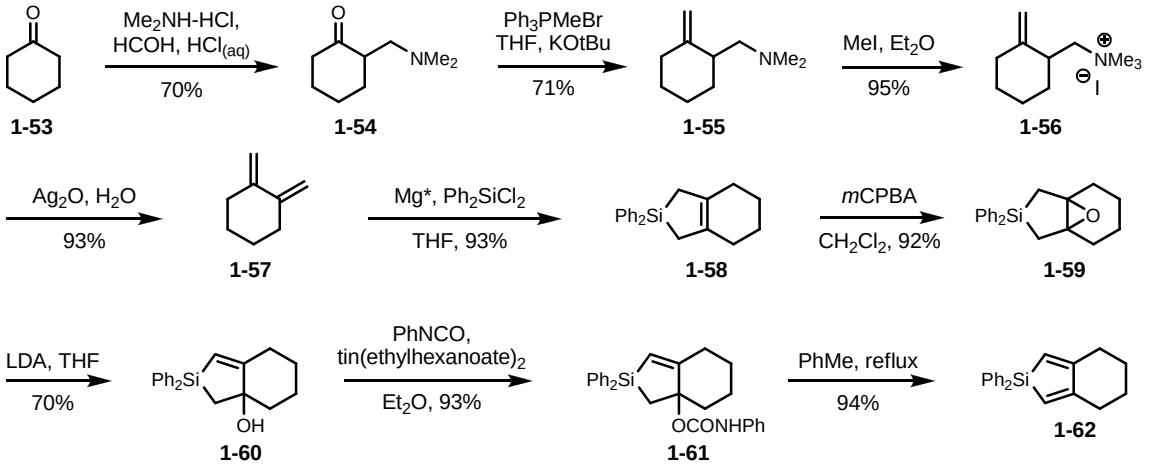
entry	dienophile	product, yield	entry	dienophile	product, yield
1		 89%	7		n.r.
2		 84%	8		n.r.
3		 90%	9		n.r.
4		 92%	10		n.r.
5		 87%	11		n.r.
6		n.r			

1.2.5 Synthesis of Alternative Silole Substitution Patterns

Having successfully discovered complementary reaction conditions for the Diels–Alder reaction with siloles, more interesting substrates with greater potential utility in natural product synthesis were prepared.

Cyclohexyl-fused silole **1-62** was prepared from cyclohexanone according to the route outlined in Scheme 1.13. Mannich reaction between cyclohexanone, dimethylamine and formaldehyde followed by Wittig olefination and Hoffmann elimination afforded the requisite diene (**1-57**). Reductive cyclization with Rieke magnesium and dichlorodiphenylsilane produced dihydrosilole **1-58**. Epoxidation with *m*CPBA, rearrangement with LDA and elimination *via* carbamate thermolysis yielded silole **1-62**.

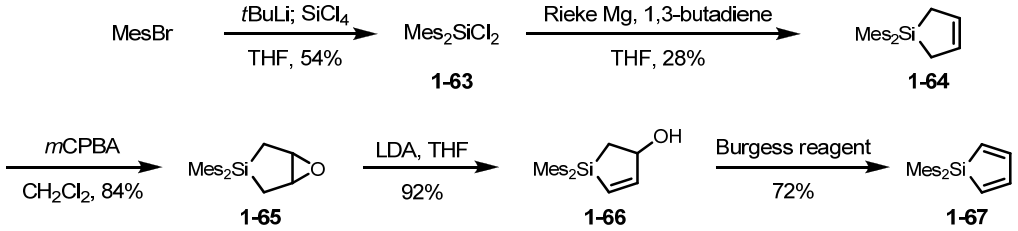
Scheme 1.13. Synthesis of a Cyclohexyl-Fused Silole



A previously reported *C*-unsubstituted silole was also synthesized;[22c] however it bore the very large mesityl groups about the silicon atom to prevent the previously described dimerization (see Scheme 1.9) and silicon-carbon bond cleavage (see Scheme 1.8). Lithiation of mesityl bromide and treatment with tetrachlorosilane afforded dichlorodimesitylsilane (Scheme 1.14). Reductive cyclization with 1,3-butadiene and

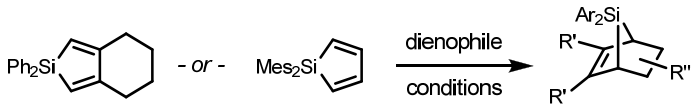
Rieke magnesium afforded dihydrosilole **1-64**. Epoxidation and epoxide rearrangement formed allylic alcohol **1-66**. The previous synthesis of silole **1-67** used a Chugaev elimination to form the silole; however, a very low yield was reported (23-36%). It was found that the Burgess reagent proved vastly superior, affording silole **1-67** in 72% yield.

Scheme 1.14. Synthesis of a *C*-unsubstituted Silole

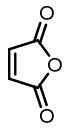
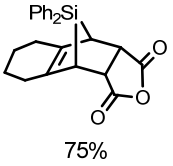
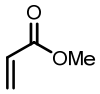
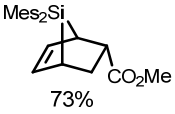
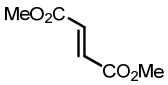
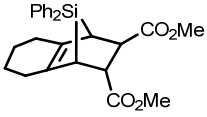
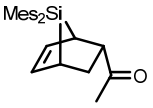
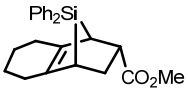
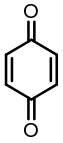
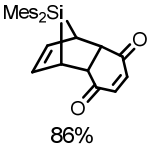
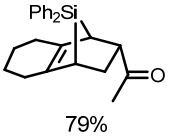


With siloles **1-62** and **1-67** in hand, the Diels–Alder reaction was explored using the previously developed conditions (Table 1.4). Cyclohexyl-fused silole **1-62** was found to undergo the cycloaddition with maleic anhydride, methyl fumarate, methylacrolein, and methylvinyl ketone (entries 1 - 4) in yields comparable to those found with silole **1-47**. Likewise, *C*-unsubstitued silole **1-67** formed the desired cycloadducts with methacrolein, methyl vinyl ketone, and benzoquinone (entries 5 - 7); however, there was a noticeable increase in reaction times due to increased steric bulk of the mesityl groups.[39]

Table 1.4. Additional Substituted Silole Substrates



1-62 **1-67** **1-68a** to **1-68d** **1-69a** to **1-69c**

entry	dienophile	product, yield	entry	dienophile	product, yield
1[a]		 75%	5[c]		 73%
2[b]		 72%	6[b]		 84%
3[b]		 82%	7[d]		 86%
4[b]		 79%			

[a] PhMe, 22 °C, 16 h. [b] PhMe, Et_2AlCl, 2 h. [c] PhMe, Et_2AlCl, 24 h. [d] CH_2Cl_2, 160 000 psi.

The relative stereochemistry of the Diels–Alder adducts was determined through NMR by observing nOe interactions between the methine proton α to the electron-withdrawing group and the aryl protons (Figure 1.3). Furthermore, the typically diagnostic chemical shift difference between the axial and equatorial positions of all-carbon [2.2.1] bicyclic systems suggests that the *exo* products were never formed in a quantity sufficient to be detected by NMR spectroscopy.[40]

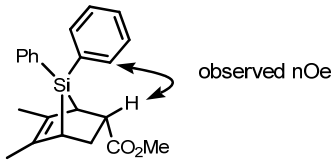
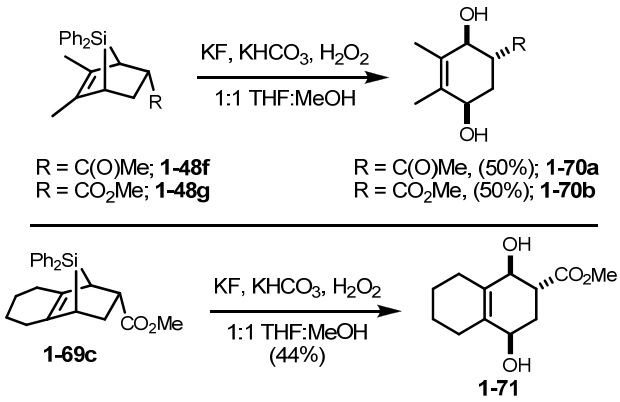


Figure 1.3. Key nOe Interaction for Structural Determination

1.2.6 Tamao–Fleming Oxidation

The 7-silabicyclo[2.2.1]hept-2-ene framework displays several functional groups that evoke opportunities for synthetic manipulation (Scheme 1.15). To illustrate this point, oxidation of the carbon-silicon bond by the Tamao–Fleming reaction successfully converted representative silole Diels–Alder adducts **1-48f**, **1-48g**, and **1-69c** diastereoselectively to their respective *cis*-diols in 44-50% isolated yield.

Scheme 1.15. Tamao–Fleming Oxidation of the Diels–Alder Adducts



1.3 Concluding Remarks

In summary, the reactivity of siloles in Diels–Alder chemistry has been explored. Various promoters, including elevated temperatures, Lewis acids, and high pressures were necessary to expand the reaction scope with less active dienophiles and in all cases

complete *endo* selectivity was observed. Furthermore, the resulting bicyclic adducts were successfully cleaved to reveal highly substituted cyclohex-2-ene-1,4-diols. Future research will focus on accessing alternate substitution patterns about the silole ring and application of the 1,4-diol species in natural product synthesis.

1.4 Experimental

The following section contains experimental procedures and characterization data for the compounds prepared in Chapter 1.

1.4.1 General Experimental Details

All reactions were run under an argon atmosphere unless otherwise indicated. Flasks were oven dried and cooled in a dessicator prior to use unless water was used in the reaction. Solvents and reagents were purified by standard methods.[41] Dichloromethane, diethyl ether, THF, and toluene were purified by passing the solvents through activated alumina columns. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions were monitored by TLC performed on F254 silica gel plates. The plates were visualized by UV light (254 nm) or by staining with ceric ammonium molybdate.[42] Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[43]

The ^{1}H and ^{13}C NMR data were obtained on 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and were referenced to residual chloroform at δ 7.25 ppm for ^{1}H spectra and the center peak of the triplet at δ 77.0 (t) for ^{13}C spectra. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. EI mass spectra were obtained on a Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV. Melting points were obtained in an Electrothermal Mel-Temp instrument and are uncorrected.

General Reductive Cyclization Procedure for the Preparation of Dihydrosiloles

To a mixture of Rieke magnesium (1.5 equiv), prepared according to literature procedures,[44] in THF was added the diene (1.0 equiv). After 30 min freshly distilled diphenyldichlorosilane (1.2 equiv) was added dropwise and the reaction mixture was stirred for an additional 16 h. The reaction mixture was diluted slowly with ½ saturated NH_4Cl and the mixture was extracted with hexanes (3 x). The combined organic layers were washed with water, brine, and dried ($MgSO_4$). After filtration through a pad of

celite the solvent was removed under reduced pressure. The resulting oil was then purified by flash chromatography (100% hexanes).

General Epoxidation Procedure

To a solution of dihydrosilole (1.0 equiv) in CH_2Cl_2 at 0 °C was added *m*CPBA (1.2 equiv) portion wise. The reaction was warmed to room temperature and stirred for 1 h. A half saturated solution of potassium carbonate was added and the reaction mixture was stirred for 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with half saturated $NaHCO_3$, water, brine, and dried ($MgSO_4$). After filtration through a pad of celite the solvent was removed under reduced pressure. The residue was subsequently purified by flash chromatography (10:1 hexanes/EtOAc).

General Epoxide Rearrangement Procedure

To a solution of lithium diisopropylamide (2.0 equiv) in THF at 0 °C was added a solution of epoxide (1.0 equiv) in THF. After the reaction was complete by TLC a half saturated NH_4Cl solution was added and the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with water, brine, and dried ($MgSO_4$). After filtration through a pad of celite the solvent was removed under reduced pressure. The residue was purified by flash chromatography (5:1 hexanes/EtOAc).

General Carbamate Formation Procedure

A solution of allylic alcohol (1.0 equiv), phenyl isocyanate (1.5 equiv), and tin(ethylhexanoate)$_2$ (2 mol %) in Et_2O was heated to reflux. After 4 h the solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography (10:1 hexanes/ EtOAc).

General Thermal Diels–Alder Procedure

A solution of silole (1.0 equiv) and dienophile (1.0 equiv) in toluene or xylene (mixture of *o,m,p* isomers) was heated to reflux. After 16 h the solution was allowed to cool to room temperature, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexanes/EtOAc).

General Lewis Acid Catalyzed Diels–Alder Procedure

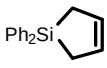
To a solution of silole (1.0 equiv) and dienophile (1.0 equiv) in toluene was added a solution of Et_2AlCl (1.8 M in toluene, 1.0 equiv) and stirred for 2 h. Water was added, followed by 1 M HCl to dissolve the aluminum salts, and the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were washed with half saturated $NaHCO_3$, brine, and dried ($MgSO_4$). After filtration through a pad of celite the solvent was removed under reduced pressure. The resulting residue was then purified by flash chromatography (hexanes/EtOAc).

General High Pressure Diels–Alder Procedure

A solution of silole (1.0 equiv) and dienophile (1.0 equiv) in CH_2Cl_2 was placed in a ~ 5 cm segment of heat shrinkable Teflon tubing which was pinched and sealed at one end with a brass screw clamp. Excess air was squeezed from the tube and the open end was sealed with a brass screw clamp. The vessel was then pressurized in a LECO Tempres HPC 200 system at 13 kbar for 16 h, after which time the solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc).

1.4.2 Experimental Details

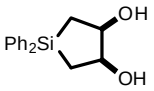
1,1-Diphenylsilacyclopent-3-ene (1-19)



The title compound was prepared according to the general reductive cyclization procedure to afford a colorless oil (1.66 g, 58%). R_f 0.66 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 4 H), 7.44-7.38 (m, 6 H), 6.07 (t, J = 1.1 Hz, 2 H), 1.89 (d, J = 1.0 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1,

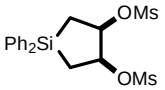
135.0, 129.8, 128.2, 17.1. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[45]

1,1-Diphenylsilacyclopentane-3,4-diol (1-70)



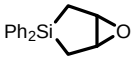
To a mixture of alkene **1-19** (1.41g, 5.96 mmol, 1.0 equiv), methanesulfonamide (0.57 g, 5.96 mmol, 1.0 equiv), $K_3Fe(CN)_6$ (5.89 g, 17.66 mmol, 3.0 equiv), and K_2CO_3 (2.47 g, 17.88 mmol, 3.1 equiv) in H_2O (4 mL) and CH_2Cl_2 (10 mL) was added OsO_4 (30 mg, 0.118 mmol) and stirred until reaction completion by TLC. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered through a pad of celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography (1:2 hexanes/EtOAc) to afford the title compound as a white foam (1.54 g, 80%). R_f 0.20 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.38 (m, 10 H), 4.04-3.97 (m, 2 H), 2.65 (s, 2 H), 1.77 (dd, J = 14.8, 5.7 Hz, 2 H), 1.21 (dd, J = 14.4, 10.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 134.6, 129.7, 128.1, 78.1, 18.8. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[46]

1,1-diphenylsilacylopentane-3,4-diyl dimethanesulfonate (1-34)



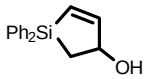
To a solution of diol **1-70** (232 mg, 0.86 mmol, 1.0 equiv) and triethylamine (0.74 mL, 5.4 mmol, 6.3 equiv) in THF (5 mL) at 0 °C was added methanesulfonyl chloride (0.17 mL, 2.1 mmol, 2.5 equiv). After 20 min the reaction mixture was diluted with a half saturated solution of $NaHCO_3$ and CH_2Cl_2, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). After filtration through a pad of celite the solvent was removed under reduced pressure and the residue was purified by flash chromatography (5:1 hexanes/EtOAc) to afford the title compound as a white solid (290 mg, 79%). R_f 0.36 (5:1 hexanes/EtOAc); mp 100 °C, decomposition; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.41 (m, 10 H), 5.14-5.06 (m, 2 H), 3.09 (s, 6 H), 2.10-2.05 (m, 2 H), 1.57-1.51 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 132.3, 130.7, 128.5, 83.8, 39.0, 17.0.

3,3-Diphenyl-6-oxa-3-silabicyclo[3.1.0]hexane (1-20)



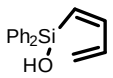
The title compound was prepared according to the general epoxidation procedure to afford a white solid (1.71 g, 85%). R_f 0.44 (5:1 hexanes/EtOAc); mp 75-76°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.53 (m, 4 H), 7.44-7.35 (m, 6 H), 3.64 (t, *J* = 1.0 Hz, 2 H), 1.78 (dt, *J* = 16.2, 1.1 Hz, 2 H), 1.49 (ddd, *J* = 16.2, 1.8, 0.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 134.8, 129.6, 129.4, 128.0, 127.8, 58.0, 15.2. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[47]

1,1-Diphenylsilacyclopent-2-en-4-ol (1-21)



The title compound was prepared according to the general epoxide rearrangement procedure to afford an orange oil (0.83 g, 91%). R_f 0.56 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.45 (m, 4 H), 7.45-7.36 (m, 6 H), 7.07 (dd, *J* = 10.0, 2.1 Hz, 1), 6.41 (dd, *J* = 10.1, 1.8 Hz, 1 H), 5.01 (t, *J* = 5.9, 1 H), 1.94 (dd, *J* = 14.9, 7.5 Hz, 1 H), 1.80 (s, 1 H), 1.15 (dd, *J* = 14.9, 5.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 134.9, 134.8, 130.0, 129.8, 129.7, 128.0, 76.0, 21.6. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.47

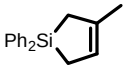
(Z)-buta-1,3-dienyldiphenylsilanol (1-35)



To a solution of **1-21** (60 mg, 0.24 mmol, 1.0 equiv) in pyridine (2.0 mL) at 0 °C was added *p*-toluenesulfonyl chloride (73 mg, 0.38 mmol, 1.6 equiv). After the reaction was complete by TLC, ½ $NaHCO_3$ and CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x) and the combined organic layers were washed with 1M HCl, water, brine and dried ($MgSO_4$). After filtration through a pad of celite the solvent was removed under reduced pressure and the residue was purified by flash chromatography (10:1 hexanes/EtOAc) to afford the product as a colorless oil (42 mg, 70%). R_f 0.35 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* =7.2 Hz, 4 H), 7.46-7.38 (m, 6 H), 7.11 (t, *J* = 11.9 Hz, 1 H), 6.71 (dt, *J* = 16.8, 10.6 Hz, 1 H), 6.00 (d, *J* = 14.3 Hz, 1 H), 5.34 (d, *J* = 16.6 Hz, 1 H), 5.23 (d, *J* = 10.0 Hz, 1 H), 2.39 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 137.0,

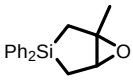
136.2, 134.4, 130.0, 128.0, 127.1, 121.5; HRMS *m/z* 252.0964 (calcd for $C_{16}H_{16}OSi$, 252.0970).

1,1-diphenyl-3-methyl-silacyclopent-3-ene (1-36)



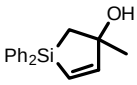
The title compound was prepared according to the general reductive cyclization procedure to afford a colorless oil (3.42 g, 81%). R_f 0.52 (5:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 4 H), 7.42-7.34 (m, 6 H), 5.64 (s, 1 H), 1.84 (s, 5 H), 1.77 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 136.4, 129.7, 128.1, 124.9, 22.8, 22.0, 17.8. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[44]

1-methyl-3,3-diphenyl-6-oxa-3-silabicyclo[3.1.0]hexane (1-37)



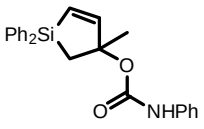
The title compound was prepared according to the general epoxidation procedure to afford a white solid (2.95 g, 85%). R_f 0.40 (5:1 Hex: EtOAc); mp 75-76°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.32 (m, 10 H), 3.42 (s, 1 H), 1.74 (t, *J* = 17.4 Hz, 1 H), 1.53 (d, *J* = 15.8 Hz, 1 H) 1.51 (s, 3 H), 1.44 (d, *J* = 15.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.4, 135.3, 134.8, 129.5, 129.4, 128.0, 127.7, 65.3, 64.9, 22.6, 20.2, 16.5; HRMS *m/z* 266.1135 (calcd for $C_{17}H_{18}OSi$, 266.1127).

1,1-diphenyl-4-methylsilacyclopent-2-en-4-ol (1-38)



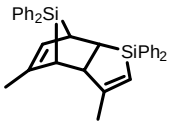
The title compound was prepared according to the general epoxide rearrangement procedure to afford an orange oil (2.34 g, 90%). R_f 0.20 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.60 (m, 4 H), 7.48-7.40 (m, 6 H), 6.97 (d, *J* = 9.9 Hz, 1 H), 6.31 (d, *J* = 9.9 Hz, 1 H), 2.19 (s, 1 H), 1.71 (d, *J* = 15.2 Hz, 1 H), 1.53 (d, *J* = 15.4 Hz, 1 H), 1.48 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 134.9, 129.7, 129.6, 128.0, 127.1, 81.4, 30.8, 27.4; HRMS *m/z* 266.1119 (calcd for $C_{17}H_{18}OSi$, 266.1127).

1,1-diphenyl-3-methylsilacyclopent-2-en-4-yl phenylcarbamate (1-39)



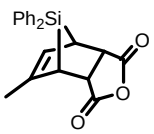
The title compound was prepared according to the general carbamate formation procedure to afford the title compound as a white foam (0.41 g, 95%). R_f 0.38 (5:1 hexanes/EtOAc); mp 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.44 (m, 4 H), 7.36-7.26 (m, 8 H), 7.23-7.18 (m, 2 H), 7.09 (d, *J* = 10.2 Hz, 1 H), 6.98-6.95 (m, 1 H), 6.41 (s, 1 H), 6.27 (d, *J* = 10.2 Hz, 1 H), 1.97 (s, 1 H), 1.96 (d, *J* = 9.4 Hz, 1 H), 1.96 (s, 1 H), 1.66 (d, *J* = 14.8 Hz, 1 H), 1.50 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.1, 135.1, 134.94, 134,87, 134.3, 129.8, 129.7, 128.9, 128.0, 127.9, 127.7, 123.1, 90.5, 28.6, 25.0; HRMS *m/z* 385.1489 (calcd for $C_{24}H_{23}NO_2Si$, 385.1498).

1,1-diphenyl-3-methylsilole dimer (1-41)



A solution of carbamate **1-39** (120 mg, 0.31 mmol) in toluene (2.0 mL) was heated to reflux. After 16 h, the reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography afforded the silole dimer as a white solid (63 mg, 82%). R_f 0.61 (5:1 hexanes/EtOAC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.06 (m, 20 H), 5.77 (t, *J* = 1.3 Hz, 1 H), 4.91 (dt, *J* = 5.7, 1.7 Hz, 1 H), 3.58 (d, *J* =8.8 Hz, 1 H), 2.54 (s, 1 H), 2.35 (ddd, *J* = 5.7, 2.0, 0.9 Hz, 1 H), 2.20 (dd, *J* = 8.8, 2.2 Hz, 1 H), 1.96 (s, 3 H), 1.58 (d, *J* = 1.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 138.7, 138.5, 137.1, 137.0, 135.8, 135.6, 134.9, 134.0, 133.7, 129.4, 129.3, 128.9, 128.8, 128.2, 127.6, 127.4, 127.3, 123.9, 56.5, 38.6, 30.9, 29.5, 22.2, 20.9; HRMS *m/z* 347.1110 (calcd for $C_{21}H_{18}O_3Si + H^+$, 347.1103).

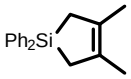
(±)-*endo*-2,3-maleicanhydro-5-methyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene (1-42)



A solution of carbamate **1-39** (80 mg, 0.21 mmol, 1.0 equiv) and maleic anhydride (23 mg, 0.23 mmol, 1.0 equiv) in toluene (2.0 mL) was heated to reflux and stirred for 16 h after which time the reaction mixture was allowed to cool to room temperature, filtered, and the solvent was removed under reduced pressure to afford the product as a orange solid (60 mg, 83%). R_f decomposition

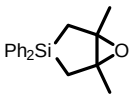
(SiO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.19 (m, 10 H), 6.03-6.01 (m, 1 H), 3.56 (dd, *J* = 5.1, 2.7 Hz, 1 H), 2.98 (ddd, *J* = 5.5, 2.8, 1.3 Hz, 1 H), 2.87-2.86 (m, 1 H), 1.83 (d, *J* = 1.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.2, 156.1, 150.6, 135.8, 134.9, 133.5, 130.8, 130.7, 128.8, 128.0, 127.1, 47.5, 46.8, 37.7, 33.2, 20.39.; HRMS *m/z* 347.1110 (calcd for $C_{21}H_{18}O_3Si + H^+$, 347.1103).

3,4-dimethyl-1,1-diphenyl-silacyclopent-3-ene (1-43)



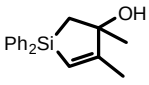
The title compound was prepared according to the general reductive cyclization procedure to afford a colorless oil (6.15 g, 66%). R_f 0.63 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.56 (m, 4 H), 7.43-7.35 (m, 6 H), 1.89 (d, *J* = 1.1 Hz, 4 H), 1.80 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 134.7, 130.7, 129.3, 127.9, 24.2, 19.3. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[44]

1,5-dimethyl-3,3-diphenyl-6-oxa-3-silabicyclo[3.1.0]hexane (1-44)



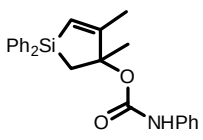
The title compound was prepared according to the general epoxidation procedure to afford a white solid (5.98 g, 96%). R_f 0.44 (5:1 hexanes/EtOAc); mp 77-78; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.56 (m, 4 H), 7.46-7.35 (m, 6 H), 1.84 (d, *J* = 15.8 Hz, 2 H), 1.56 (d, *J* = 15.8 Hz, 2 H), 1.52 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ135.8, 135.5, 135.4, 134.8, 129.4, 129.3, 128.0, 127.7, 68.9, 22.4, 20.3; HRMS *m/z* 280.1281 (calcd for $C_{18}H_{20}OSi$, 280.1283).

3,4-dimethyl-1,1-diphenylsilacyclopent-2-en-4-ol (1-45)



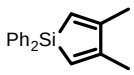
The title compound was prepared according to the general epoxide rearrangement procedure to afford an orange oil (5.69 g, 90%). R_f 0.25 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.56 (m, 4 H), 7.43-7.38 (m, 6 H), 5.92 (q, *J* = 1.2 Hz, 1 H), 2.08 (d, *J* = 1.2 Hz, 3 H), 1.78 (d, *J* = 15.2 Hz, 1 H), 1.74 (s, 1 H), 1.56 (d, *J* = 15.2 Hz, 1 H), 1.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 135.8, 135.1, 135.0, 134.9, 129.5, 129.5, 127.8, 122.8, 122.8, 82.3, 29.7, 29.7, 18.2; HRMS *m/z* 280.1275 (calcd for $C_{18}H_{20}OSi$, 280.1283).

3,4-dimethyl-1,1-diphenylsilacyclopent-2-en-4-yl phenylcarbamate (1-46)



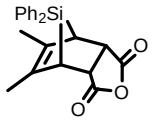
The title compound was prepared according to the general carbamate formation procedure to afford the title compound as a white foam (4.17 g, 95%). R_f 0.34 (5:1 hexanes/EtOAc); mp 108-111°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 4 H), 7.41-7.21 (m, 10 H), 7.03 (t, *J* = 7.2, 1 H), 6.56 (s, 1 H), 5.94 (d, *J* = 1.6, 1 H), 2.28 (d, *J* = 14.4 Hz, 1 H), 2.00 (d, *J* = 1.2 Hz, 1 H), 1.76 (d, *J* = 14.4 Hz, 1 H), 1.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 152.4, 138.1, 135.3, 135.1, 129.8, 129.6, 129.5, 129.0, 128.9, 127.8, 123.2, 122.6, 118.6, 91.3, 28.3, 25.6, 18.3; HRMS *m/z* 399.1655 (calcd for $C_{25}H_{25}NO_2Si$, 399.1655).

3,4-dimethyl-1,1-diphenylsilole (1-47)



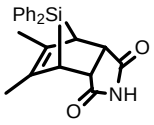
A solution of carbamate **1-46** (3.78 g, 9.46 mmol, 1.0 equiv) in toluene (20 mL) was heated to reflux. After 16 h the solution was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash chromatography (10:1 hexanes/EtOAc) to afford the title compound as an opaque solid (2.26 g, 91%). R_f 0.64 (5:1 hexanes/EtOAc); mp 37-38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.58 (m, 4 H), 7.40-7.34 (m, 6 H), 6.00 (d, *J* = 1.2 Hz, 2 H), 2.11 (d, *J* = 1.2 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 135.4, 133.2, 129.7, 127.9, 123.8, 21.0; HRMS *m/z* 266.1189, (calcd for $C_{18}H_{18}OSi$, 262.1178).

(±)-*endo*-2,3-maleicanhydro-5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene (1-48a)



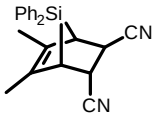
To a solution of silole **1-46** (55 mg, 0.21 mmol, 1.0 equiv)**,** in toluene was added maleic anhydride (21 mg, 0.21 mmol, 1.0 equiv). After 16 h the solvent was removed under reduced pressure and the residue was purified by flash chromatography to afford the title compound as a white solid (75 mg, 90%). R_f 0.14 (5:1 hexanes/EtOAc); mp 165-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.28 (m, 10 H), 3.64 (dd, *J* = 1.8 Hz, 2 H), 2.88 (dd, *J* = 1.8 Hz, 2 H), 1.84 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 135.5, 133.6, 133.5, 132.8, 130.8, 130.6, 129.4, 128.8, 128.1, 47.5, 38.8, 16.7; HRMS *m/z* 360.1186 (calcd for $C_{22}H_{20}O_3Si$, 360.1182).

(±)-*endo*-2,3-maleimido-5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene (1-48b)



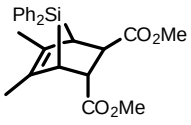
To a solution of silole **1-46 (**55 mg, 0.21 mmol, 1.0 equiv) in toluene was added maleimide (21 mg, 0.21 mmol, 1.0 equiv). After 16 h the solvent was removed under reduced pressure and the residue was purified by flash chromatography to afford the title compound as a white solid a white solid (70 mg, 85%). R_f 0.10 (5:1 hexanes/EtOAc); mp 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.46-7.19 (m, 10 H), 3.32 (dd, *J* = 1.6 Hz, 2 H), 2.71 (dd, *J* = 1.6 Hz, 2 H), 1.71 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 135.5, 133.7, 131.7, 130.4, 130.3, 128.6, 128.0, 110.8, 47.9, 37.9, 16.7; HRMS *m/z* 359.1229 (calcd for $C_{22}H_{21}NO_2Si$, 359.1342).

(2*R,3*S**)-5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2,3-dicarbonitrile (1-48c)**



The title compound was prepared according to the general thermal Diels–Alder procedure to afford a colorless oil (67 mg, 85%). R_f 0.11 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.31 (m, 10 H), 3.56 (dd, *J* = 5.9, 2.3 Hz, 1 H), 2.83 (dd, *J* = 5.9, 1.8 Hz, 1 H), 2.72 (s, 1 H), 2.64 (s, 1 H), 1.94 (s, 3 H), 1.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.6, 134.2, 132.3, 131.1, 130.8, 128.8, 128.7, 128.2, 120.9, 118.9, 39.8, 39.4, 35.3, 35.1, 16.8, 15.6; HRMS *m/z* 340.1388 (calcd for $C_{22}H_{20}N_2Si$, 340.1396).

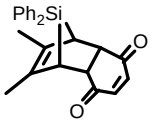
(2*R,3*S**)-dimethyl 5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (1-48d)**



The title compound was prepared according to the general thermal Diels–Alder procedure, the general Lewis acid Diels–Alder procedure or the general high pressure Diels–Alder procedure to afford a pale yellow oil. R_f 0.30 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.50 (m, 2 H), 7.40-7.33 (m, 6 H), 7.26-7.23 (m, 2 H), 3.78-3.76 (m, 1 H), 3.70 (s, 3 H), 3.26 (s, 3 H), 3.24-3.23 (m, 1 H), 2.73 (m, 1 H), 2.69 (m, 1 H), 1.86 (s, 3 H), 1.9 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 173.2, 135.5, 134.8, 134.4, 134.2, 131.9, 131.7, 129.8, 129.7,

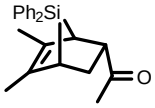
128.0, 127.7, 51.9, 51.5, 48.3, 47.4, 39.2, 38.4, 16.4, 15.6; HRMS *m/z* 406.1590 (calcd for $C_{24}H_{26}O_4Si$, 406.1600).

(±)-*endo*-5,6-(5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-en-2-yl)dihydrobenzoquinone (1-48e)



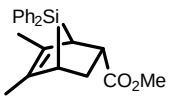
The title compound was prepared according to the general thermal Diels–Alder procedure or the general high pressure Diels–Alder procedure to afford an orange oil. R_f decomposition (SiO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.45 (m, 2 H), 7.34-7.29 (m, 8 H), 7.20-7.16 (m, 2 H), 6.62 (s, 2 H), 3.33 (s, 2 H), 1.60 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 142.9, 135.6, 134.9,134.3, 133.8, 132.8, 130.2, 128.6, 127.9, 49.3, 43.3, 16.7; HRMS *m/z* 370.1406 (calcd for $C_{22}H_{24}O_2Si$, 370.1389).

(±)-*endo*-1-(5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-en-2-yl)ethanone (1-48g)



The title compound was prepared according to the general Lewis acid Diels–Alder procedure or the general high pressure Diels–Alder procedure to afford a pale yellow oil. R_f 0.38 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2 H), 7.43-7.33 (m, 6 H), 7.27-7.23 (m, 2 H), 3.19 (ddd, *J* = 9.6, 5.6, 2.0 Hz, 1 H), 2.56 (t, *J* = 1.8 Hz, 1 H), 2.16 (s, 3 H), 2.08-1.96 (m, 2 H), 1.77 (d, *J* = 0.9 Hz, 3 H), 1.71 (d, *J* = 0.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 136.2, 135.6, 134.9, 133.9, 132.5, 129.8, 129.7, 129.6, 128.3, 127.6, 52.4, 39.9, 35.2, 28.7, 16.9, 15.7; HRMS *m/z* 332.1592 (calcd for $C_{22}H_{24}OSi$, 332.1596).

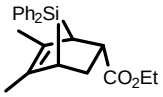
(±)-*endo*-methyl 5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2-carboxylate (1-48h)



The title compound was prepared according to the general Lewis acid Diels–Alder procedure or the general high pressure Diels–Alder procedure to afford a pale yellow oil. R_f 0.44 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2 H), 7.45 (m, 6 H), 7.28 (m, 2 H), 3.64 (d, 3 H), 3.15 (ddd, *J* = 10.2, 5.2, 2.4 Hz, 1 H), 2.21-2.15 (m, 2 H), 1.99 (ddd, *J* = 13.0, 5.7, 2.4 Hz, 1 H), 1.79 (d, *J* = 1.1

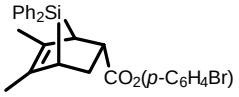
Hz, 3 H), 1.74 (d, *J* = 1.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 136.0, 135.6, 134.9, 133.9, 132.4, 130.5, 129.7, 129.6, 128.2, 127.6, 51.5, 43.6, 39.6, 35.1, 29.7, 16.6, 15.9; HRMS *m/z* 348.1531 (calcd for $C_{22}H_{24}O_2Si$, 348.1546).

(±)-*endo*-ethyl 5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2-carboxylate (1-48i)



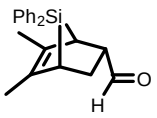
The title compound was prepared according to the general Lewis acid Diels–Alder procedure to afford a pale yellow oil (100 mg, 92%). R_f 0.45 (5:1 Hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.24 (m, 10 H), 4.12-4.04 (m, 2 H), 3.13 (ddd, *J* = 9.8, 4.7, 2.0 Hz, 1 H), 2.57 (dd, *J* = 2.3, 1.7 Hz, 1 H), 2.20-2.14 (m, 2 H), 1.99 (ddd, *J* = 12.9, 5.9, 2.3 Hz, 1 H), 1.78 (d, *J* = 1.7 Hz, 3 H), 1.74 (d, *J* = 1.7 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 136.1, 135.6, 134.8, 133.9, 132.5, 130.5, 129.61, 129.57, 128.2, 127.6, 60.2, 43.8, 39.6, 35.1, 29.6, 16.7, 15.7, 14.3; HRMS *m/z* 362.1708 (calcd for $C_{23}H_{26}O_2Si$, 362.1702).

(±)-*endo*-*p*-bromophenyl 5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2-carboxylate (1-48j)



The title compound was prepared according to the general Lewis acid Diels–Alder procedure to afford a pale yellow oil (100 mg, 75%). R_f 0.50 (5:1 Hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.60 (m, 1 H), 7.50-7.27 (m, 10 H), 6.98 (m, 2 H), 3.41 (ddd, *J* = 10.0, 5.3, 2.3 Hz, 1 H), 2.77 (t, *J* = 1.8 Hz, 1 H), 2.33-2.29 (m, 2 H), 2.10 (ddd, *J* = 12.3, 4.1, 1.8 Hz, 1 H), 1.84 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 150.1, 135.8, 135.6, 135.4, 133.9, 132.3, 132.0, 130.1, 129.8, 129.7, 128.3,127.7, 123.3, 118.5, 44.0, 39.9,35.1, 29.7, 16.9, 15.7; HRMS *m/z* 488.0799 (calcd for $C_{27}H_{25}BrO_2Si$, 488.0807).

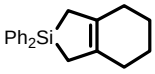
(±)-*endo*-5,6-dimethyl-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2-carbaldehyde (1-48f)



The title compound was prepared according to the general high pressure Diels–Alder procedure to afford a yellow oil (50 mg, 84%). R_f 0.42 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, *J* = 2.3 Hz, 1 H),

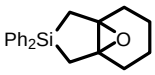
7.45 (m, 2 H), 7.36-7.26 (m, 6 H), 7.19-7.17 (m, 2 H), 3.02 (m, 1 H), 2.51 (t, *J* = 1.8 Hz, 1 H), 2.19 (d, *J* = 1.8 Hz, 1 H), 2.02 (ddd, *J* = 12.3, 9.4, 2.3 Hz, 1 H), 1.90 (ddd, *J* = 12.7, 5.1, 2.1 Hz, 1 H), 1.71 (s,3 H), 1.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 137.9, 135.8, 135.6, 133.9, 131.9, 130.0, 129.8, 129.8, 128.3, 127.7, 52.5, 37.7, 35.2, 26.9, 17.2, 15.7; HRMS *m/z* 318.1441(calcd for $C_{21}H_{22}OSi$, 318,1440).

2,2-diphenyl-1,3,4,5,6,7-hexahydrobenzo[c]silole (1-58)



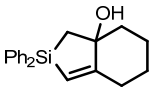
The title compound was prepared according to the general reductive cyclization procedure to afford a colorless oil (2.70 g, 93%). R_f 0.29 (100% hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 4 H), 7.46-7.41 (m, 6 H), 2.13 (br s, 4 H), 1.88 (br s, 4 H), 1.70 (p, *J* = 3.3 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.8, 133.2, 129.3, 127.8, 31.1, 23.5, 22.5; HRMS *m/z* 290.1505 (calcd for $C_{20}H_{22}Si$, 290.1491).

2,2-diphenyl-1,3,4,5,6,7-hexahydro-7a-oxo-benzo[c]silole (1-59)



The title compound was prepared according to the general epoxidation procedure to afford a colorless oil (0.774 g, 92%). R_f 0.59 (5:1 hexanes/EA) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.58 (m, 4 H), 7.47-7.36 (m, 6 H), 2.15 (dt, *J* = 14.9, 7.0 Hz, 2 H), 1.91 (dt, *J* = 15.6, 6.3 Hz, 2 H), 1.88 (d, *J* = 15.6 Hz, 2 H), 1.56-1.49 (m, 2 H), 1.50 (d, *J* = 15.6 Hz, 2 H), 1.37-1.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.7, 135.3, 134.9, 129.4, 129.2, 127.9, 127.7, 68.5, 30.9, 21.8, 20.6; HRMS *m/z* 306.1441 (calcd for $C_{20}H_{22}OSi$, 306.1440).

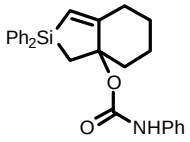
2,2-diphenyl-1,4,5,6,7,-hexahydro-benzo[c]silol-7a-ol (1-60)



The title compound was prepared according to the general epoxide rearrangement procedure to afford an orange oil (1.52 g, 90%). R_f 0.36 (5:1 hexanes/EA) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, 4 H), 7.42-7.36 (m, 6 H), 5.86 (d, *J* = 1.2 Hz, 1 H), 2.62-2.50 (m, 2 H), 2.17 (dq, *J* = 13.7, 2.6 Hz, 1 H), 1.92-1.80 (m, 2 H), 1.64-1.62 (m, 1 H), 1.59 (br s, 1 H), 1.55 (s, 2 H), 1.51-1.48 (m, 1 H), 1.41-1.28 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 136.1, 135.7, 134.9, 139.5,

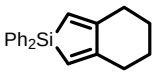
137.93, 127.90, 120.7, 81.1, 43.3, 32.7, 28.0, 27.8, 22.3; HRMS *m/z* 306.1461 (calcd for $C_{20}H_{22}OSi$, 306.1440).

2,2-diphenyl-1,4,5,6,7-hexahydro-benzo[c]silol-7a-yl phenylcarbamate (1-61)



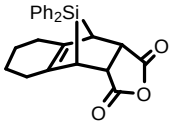
The title compound was prepared according to the general carbamate formation procedure to afford an orange oil (0.625 g, 93%). R_f 0.58 (5:1 hexanes/EA) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.59 (m, 4 H), 7.43 (m, 10 H), 7.07 (t, *J* = 7.2 Hz, 1 H), 6.62 (br s, 1 H), 6.01 (d, *J* = 0.8 Hz, 1 H), 2.73 (d, *J* = 14.1 Hz, 1 H), 2.62 (d, *J* = 12.9 Hz, 1 H), 2.49 (td, *J* = 13.0, 4.1 Hz, 1 H), 2.12 (d, *J* = 15.6 Hz, 1 H), 1.94-1.90 (m, 1 H), 1.80 (tt, *J* = 13.7, 3.9 Hz, 1 H), 1.72 (d, *J* = 16.0 Hz, 1 H), 1.61 (d, *J* = 14.1 Hz, 1 H), 1.43-1.36 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 152.3, 138.2, 135.4, 135.2, 135.0, 129.52, 129.48, 129.0, 128.0, 127.9, 127.8, 123.1, 121.3, 118.5, 90.9, 41.2, 33.0, 28.3, 24.0, 22.2; Low res. mass spec. *m/z* 425.1 (calcd for $C_{27}H_{27}NO_2Si$, 425.1).

2,2-diphenyl-4,5,6,7-tetrahydro-benzo[c]silole (1-62)



A solution of carbamate **1-61** (327 mg, 0.77 mmol, 1 equiv) in toluene (7 mL) was heated to reflux. After 16 h the solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (10:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (204 mg, 94%). R_f 0.58 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 4 H), 7.43-7.34 (m, 6H), 5.93 (t, *J* = 1.4 Hz, 2 H), 2.64 (br s, 4 H), 1.67 (p, *J* = 3.3 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 135.4, 133.5, 129.6, 127.9,121.5,32.1, 23.9; HRMS *m/z* 288.1326 (calcd for $C_{20}H_{20}Si$, 288.1334).

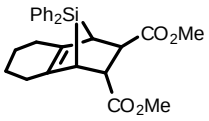
(±)-*endo*-2,3-maleicanhydro-tetrahydrobenzo[c]-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene (1-68a)



The title compound was prepared according to the general thermal Diels–Alder procedure to afford a colorless oil (65 mg, 75%). R_f 0.21 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.26 (m, 10 H), 3.65 (t, *J* = 1.6 Hz, 2 H), 2.85 (t, *J* = 1.6 Hz, 2 H), 2.12 (br s, 4 H), 1.57 (br s, 4 H); ^{13}C NMR

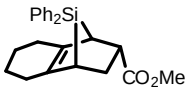
(100 MHz, $CDCl_3$) δ 173.6, 135.8, 135.5, 133.7, 133.6, 130.7, 130.6, 129.5, 128.8,47.6, 36.9, 27.7, 22.8; HRMS *m/z* 386.1344 (calcd for $C_{24}H_{22}O_3Si$, 386.1338).

(2*R,3*S**)-dimethyl tetrahydrobenzo[c]-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (1-68b)**



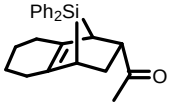
The title compound was prepared according to the general Lewis acid Diels–Alder procedure to afford a pale yellow oil (49 mg, 72%). R_f 0.21 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.24 (m, 10 H), 3.79 (dd, *J* = 5.5, 2.3 Hz, 1 H), 3.70 (s, 3 H), 3.26 (s, 3 H), 3.24 (dd, *J* = 5.7, 2.2 Hz, 1 H), 2.72 (t, *J* = 1.8, Hz, 1 H), 2.66 (t, *J* = 2.0 Hz, 1 H), 2.29-2.24 (m, 1 H), 2.15-2.08 (m, 1 H), 1.95-1.94 (m, 2 H), 1.60-1.47 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, `73.3, 137.4, 135.5, 135.1, 134.9, 134.2, 132.0, 129.8, 128.0,127.8, 127.6, 51.9, 51.5, 48.4,47.6, 37.3, 36.4, 27.7, 26.7,23.1, 23.0; Low res. mass spec. *m/z* 432.1 (calcd for $C_{26}H_{28}O_4Si$, 432.1).

(±)-*endo*-methyl tetrahydrobenzo[c]-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-ene-2-carboxylate (1-68c)



The title compound was prepared according to the general Lewis acid Diels–Alder procedure to afford a yellow oil (78 mg, 82%). R_f 0.29 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.16 (m, 10 H), 3.55 (s, 3 H), 3.09 (ddd, *J* = 9.9, 5.2, 2.2 Hz, 1 H), 2.46 (dd, *J* = 2.0, 1.2 Hz, 1 H), 2.14-2.07 (m, 3 H), 1.94-1.89 (m, 4 H), 1.50-1.40 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 137.7, 136.2, 135.6, 133.9, 133.5, 132.6, 129.60,129.56, 128.2, 127.5, 51.5, 43.7, 37.8, 33.0, 29.8, 27.9, 26.8, 23.3; HRMS *m/z* 374.1699 (calcd for $C_{24}H_{26}O_2Si$, 374.1702).

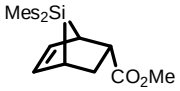
(±)-*endo*-1-(tetrahydrobenzo[c]-7,7-diphenyl-7-silabicyclo[2.2.1]hept-5-en-2-yl)ethanone (1-68d)



The title compound was prepared according to the general Lewis acid Diels–Alder procedure to afford a yellow oil (90 mg, 79%). R_f 0.30 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.24 (m, 10 H), 3.23 (ddd, *J* = 9.4, 5.3, 2.2 Hz, 1 H), 2.54 (t, *J* = 1.2 Hz, 1 H), 2.24-2.18 (m, 2 H), 2.16 (s, 3

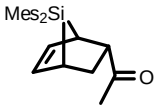
H), 2.08 (ddd, *J* = 12.5, 5.1, 2.0 Hz, 1 H), 2.03-1.97 (m, 3 H), 1.56-1.43 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 137.8, 136.3, 135.5, 133.9, 132.7, 132.6, 129.6, 128.7, 127.5, 52.3, 38.0, 33.2, 28.7, 28.2, 27.4, 26.8, 23.1; HRMS *m/z* 358.1759 (calcd for $C_{24}H_{26}OSi$, 358.1753).

(±)-*endo*-methyl 7,7-dimesityl-7-silabicyclo[2.2.1]hept-5-ene-2-carboxylate (1-69a)



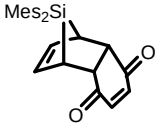
The title compound was prepared according to the general Lewis acid Diels–Alder procedure to afford a yellow oil (18 mg, 73%). R_f 0.26 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1 H), 6.78 (s, 3H), 6.45 (t, *J* = 5.9 Hz, 1 H), 6.24 (t, *J* = 5.7 Hz, 1 H), 3.63 (s, 3 H), 3.14 (ddd, *J* = 10.0, 5.4, 2.0 Hz, 1 H), 2.88 (d, *J* = 4.3 Hz, 1 H), 2.52(s, 3 H), 2.49 (s, 12 H), 2.29 (ddd, *J* = 12.5, 10.2, 2.3 Hz, 1 H), 2.23 (s, 3 H), 2.22 (s, 3 H), 1.82 (ddd, *J* = 12.5, 5.5, 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 144.8, 143.8, 143.7, 139.1, 139.0, 135.5, 131.4, 130.2, 129.1, 121.0, 128.9, 128.4, 51.6, 42.4, 38.0, 37.9, 34.2, 29.4, 24.1, 22.9, 22.8, 20.9; HRMS *m/z* 404.2161 (calcd for $C_{26}H_{32}O_2Si$, 404.2172).

(±)-*endo*-1-(7,7-dimesityl-7-silabicyclo[2.2.1]hept-5-en-2-yl)ethanone (1-69b)



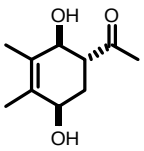
The title compound was prepared according to the general Lewis acid Diels–Alder procedure to afford a yellow oil (26 mg, 84%). R_f 0.25 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 11.7 Hz, 2 H), 6.78 (s, 2 H), 6.41 (t, *J* = 5.9 Hz, 1 H), 6.17 (t, *J* = 5.7 Hz, 1 H), 3.18 (ddd, *J* = 9.8, 5.5, 2.0 Hz, 1 H), 2.86 (d, *J* = 3.5 Hz, 1 H), 2.54 (s, 3 H), 2.52 (s, 3 H), 2.49 (s, 6 H), 2.25 (s, 3 H), 2.22 (s, 3 H), 2.14 (ddd, *J* = 12.5, 9.8, 2.3Hz, 1 H), 2.13 (s, 3 H), 1.89 (ddd, *J* = 12.4, 5.6, 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 144.7, 143.9, 139.1, 139.0, 135.6, 131.5, 129.5, 129.2, 129.0, 128.9, 128.4, 51.1, 37.9, 34.4, 28.8, 27.6, 24.1, 23.0, 22.9, 22.8; HRMS *m/z* 388.2230 (calcd for $C_{26}H_{32}OSi$, 388.2222).

(±)-*endo*-5,6-(7,7-dimesityl-7-silabicyclo[2.2.1]hept-5-en-2-yl)dihydrobenzoquinone (1-69c)



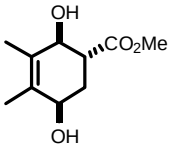
The title compound was prepared according to the general high pressure Diels–Alder procedure to afford an orange oil (20 mg, 86%). R_f 0.26 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2 H), 6.80 (s, 2 H), 6.68 (s, 2 H), 6.31 (dd, *J* = 3.9, 3.1 Hz, 2 H), 3.43 (s, 2 H), 3.22 (s, 2 H), 2.56 (s, 6 H), 2.48 (s, 6 H), 2.24 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 144.9, 143.8, 143.1, 139.7, 139.6, 136.5,132.8, 130.0, 129.3, 129.1, 126.9, 126.6, 48.2, 41.5, 29.7, 24.1, 23.0, 20.9; HRMS *m/z* 426.2016 (calcd for $C_{28}H_{30}O_2Si$, 426.2015).

1-((1*R,2*S**,5*R**)-2,5-dihydroxy-3,4-dimethylcyclohex-3-enyl)ethanone (1-70a)**



To a mixture of Diels–Alder adduct **1-48f** (60 mg, 0.18 mmol, 1.0 equiv), $KHCO_3$ (107 mg, 1.07 mmol, 6.0 equiv), KF (62 mg, 1.07 mmol, 6.0 equiv) in methanol (1.0 mL) and THF (1.0 mL) was added H_2O_2 (30% in H_2O, 24 μL, 0.21 mmol, 1.2 equiv). After 16 h a half saturated solution of $Na_2S_2O_3$ (2 mL) was added and, after 30 min, CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered through a pad of celite. After the solvent was removed under reduced pressure the residue was purified by flash chromatography (1:1 hexanes/EtOAc) to afford the title compound as a white solid (16 mg, 50%). R_f 0.22 (1:1 hexanes/EtOAc); mp 115-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3 H), 2.91-2.83 (m, 1 H), 2.20 (s, 3 H), 2.11 (d, *J* = 8.8 Hz, 2 H), 2.07 (dt, *J* = 13.8, 3.1 Hz, 1 H), 1.77 (s, 3 H), 1.72 (s, 1 H), 1.67 (s, 3 H), 1.58 (td, *J* = 13.3, 3.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 129.8, 126.8, 69.1, 42.8, 33.8, 33.3, 28.2, 19.2, 16.7; HRMS *m/z* 185.1179 (calcd for $C_{10}H_{16}O_3 + H^+$, 185.1178).

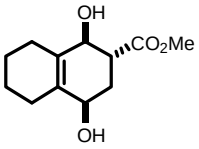
(1*R,2*S**,5*R**)-methyl 2,5-dihydroxy-3,4-dimethylcyclohex-3-enecarboxylate (1-70b)**



To a mixture of Diels–Alder adduct **1-48g** (62 mg, 0.18 mmol, 1.0 equiv), $KHCO_3$ (107 mg, 1.07 mmol, 6 equiv), KF (62 mg, 1.07 mmol, 6.0 equiv) in methanol (1 mL) and THF (1 mL) was added H_2O_2 (30% in H_2O, 24 μL, 0.21 mmol, 1.2 equiv). After 16 h a half saturated solution of $Na_2S_2O_3$

(2 mL) was added and, after 30 min, CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered through a pad of celite. After the solvent was removed under reduced pressure the residue was purified by flash chromatography (1:1 hexanes/EtOAc) to afford the title compound as a white solid (17 mg, 50%). R_f 0.16 (1:1 hexanes/EtOAc); mp 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (d, *J* = 8.2 Hz, 1 H), 4.01(s, 1 H), 3.76 (s, 3 H), 2.84 (ddd, *J* = 12.9, 9.4, 2.9 Hz, 1 H), 2.71 (d, *J* = 4.7, 1 H), 2.15 (dt, *J* = 13.5, 2.9 Hz, 1 H), 1.80 (dt, *J* = 12.5, 4.1 Hz, 1 H), 1.79 (s, 3 H), 1.77 (s, 3 H), 1.55 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 132.5,130.0, 71.3, 68.4, 52.0, 43.5, 32.2, 17.1, 14.4; HRMS *m/z* 200.1056 (calcd for $C_{10}H_{16}O_4$, 200.1049).

(1*S,2*R**,4*R**)-methyl 1,4-dihydroxy-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carboxylate (1-71)**



To a mixture of Diels–Alder adduct **1-69c** (150 mg, 0.40 mmol, 1.0 equiv), $KHCO_3$ (240 mg, 2.40 mmol, 6.0 equiv), KF (133 mg, 2.40 mmol, 6.0 equiv) in methanol (2.0 mL) and THF (2.0 mL) was added H_2O_2 (30% in H_2O, 54 μL, 0.48 mmol, 1.2 equiv). After 16 h a half saturated solution of $Na_2S_2O_3$ (2 mL) was added and, after 30 min, CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered through a pad of celite. After the solvent was removed under reduced pressure the residue was purified by flash chromatography (1:1 hexanes/EtOAc) to yield the title compound as a white solid (16 mg, 50%). R_f 0.25 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (d, *J* = 9.4 Hz, 1 H), 3.92 (s, 1 H), 3.75 (s, 3 H), 2.90 (br s, 1 H), 2.85 (ddd, *J* = 12.8, 9.5, 3.1 Hz, 1 H), 2.33 (br d, *J* = 15.2 Hz, 2 H), 2.13 (dt, *J* = 13.8, 2.9 Hz, 1 H), 1.94 (br s, 2 H), 1.90 (br s, 1 H), 1.82 (dd, *J* = 13.5, 3.7 Hz, 1 H), 1.77-1.71 (m, 2 H), 1.56-1.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 134.2, 131.9, 71.0, 67.4, 52.0,43.5, 32.4, 27.6, 25.3, 22.42, 22.38; HRMS *m/z* 226.1203 (calcd for $C_{10}H_{16}O_3$, 226.1205).

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Chapter 2. Alkoxy-Activated Cyclobutane Dicarboxylates and their Application in Cycloaddition Chemistry

This chapter describes the recently discovered annulation chemistry of alkoxy-activated cyclobutane dicarboxylates with aldehydes, nitrones and nitrosoarenes. Relevant background information regarding the reactivity of donor-accepter cyclobutanes and the currently reported annulations of donor acceptor cyclobutanes with dipolar reagents will be presented. The research in this chapter was carried out in collaboration with colleagues Mahmoud Abd Rabo Moustafa (Ph.D.), Mr. Ben P. Machin, Mr. Cory Palmer, Mr. Naresh Vemula, and Mr. Tyler Schon. Results are those generated by the author unless otherwise attributed, which can be found below the presented examples. Portions of this work has been published in peer reviewed journals.[1,2] Portions of text and schemes have been reprinted in part with permission from Moustafa, M. M. A. R.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4736–4738 and Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 1528–1531.

2.1 Introduction

2.1.1 Structure and Reactivity of Donor Acceptor Cyclobutanes

The prevalence of polycyclic frameworks containing heteroatoms in biological, pharmaceutical, and other industrially relevant molecules (i.e., pesticides, herbicides, etc.) necessitates efficient routes for their formation. Ideally, this should be accomplished through a minimum number of steps and occur in high yield with control over diastereoselectivity and regioselectivity. In this regard, dipolar annulations of donor

acceptor (DA) cyclopropanes have been extensively developed as effective partners for the rapid assembly of highly functionalized molecules,[3] including precursors in natural product total syntheses.[4] In contrast, DA cyclobutanes have only recently been explored for application in dipolar annulations despite their preparation being known for a number of years[5] and the similar magnitude of ring strain when compared to cyclopropanes (110 kJ/mol for cyclobutanes vs 115 kJ/mol for cyclopropanes).[6]

The strain present in the cyclobutane ring system originates from the constrained bond angles which, for a planar cyclobutane, are 90°. This is a significant deviation from the ideal 109.8° for a sp^3 hybridized center, imparting a large degree of Baeyer strain. In a planar cyclobutane, the methylene groups would be in an eclipsed position, resulting in high levels of torsional strain. Puckering of the cyclobutane ring occurs to decrease the torsional strain, but this reduces the C-C-C bond angles leading to an increase in angle strain. Experimentally, cyclobutanes have been determined to deviate from planarity by approximately 35° resulting in C-C-C bond angles of 88° (Figure 2.1).[7]

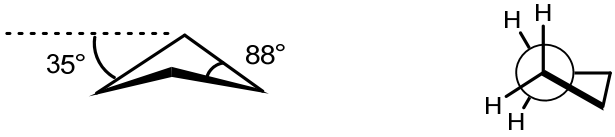
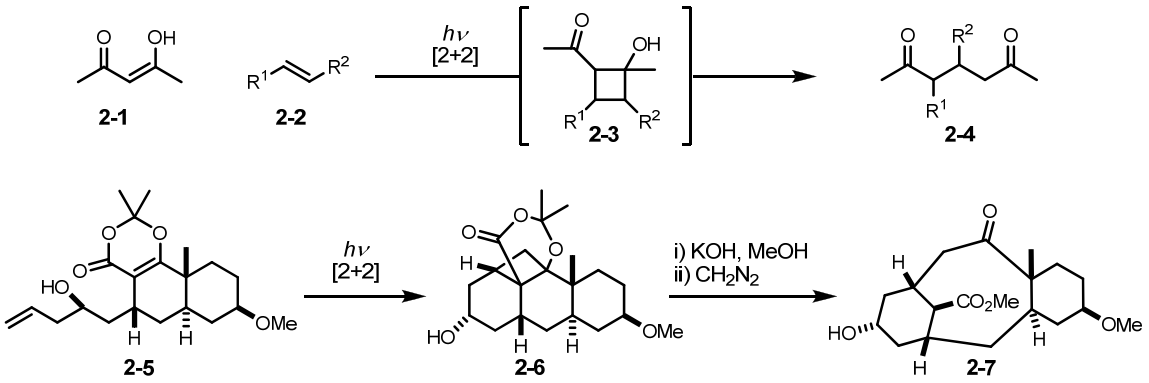


Figure 2.1. Geometry of the Cyclobutane Ring

While the cyclobutane ring system has a high level of strain, forcing conditions are required to induce ring cleavage. Installation of vicinal electron-donating and electron-accepting functionalities allows for facile bond cleavage through maximizing bond polarization. A prominent example of successful application of this strategy can be seen in the de Mayo reaction where a transient cyclobutane is formed that rapidly

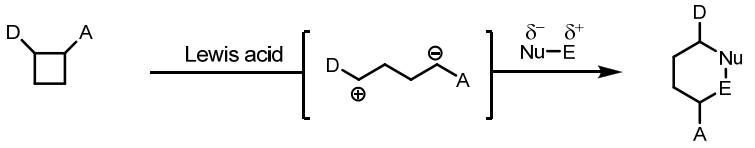
undergoes fragmentation to afford 1,5-dicarbonyl species (Scheme 2.1).[8] This has been extensively applied for the formation of medium-sized rings, such as in the synthesis of taxol analogs.[9]

Scheme 2.1. Reactivity of the Cyclobutane Ring System *via* the de Mayo Reaction



If, however, the electron donating group is not capable of terminating the reaction sequence through formation of a neutral species, a stabilized zwitterionic intermediate can be formed. This intermediate can be considered a 1,4-dipole equivalent which can be quenched by nucleophilic or electrophilic sources to afford ring-opened products. The pinnacle of this principle can be seen when a nucleophilic and electrophilic component are tethered, such as in dipolar reagents, creating the opportunity for annulation events to occur and leading to the formation of a new ring system (Scheme 2.2). This mode of activation has been extensively developed for DA cyclopropanes;[4] however, the analogous reactivity pattern in DA cyclobutanes has only recently been investigated.

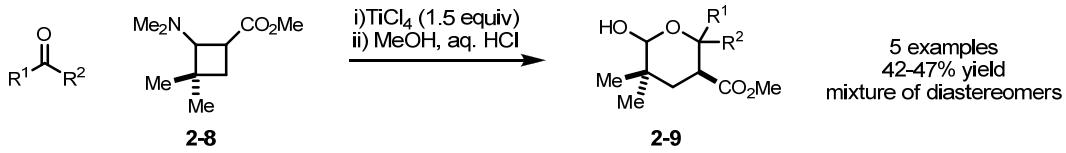
Scheme 2.2. Annulation of DA Cyclobutanes with Dipolar Reagents



2.1.2 **Dipolar Cycloadditions of DA Cyclobutanes**

The first intermolecular cycloaddition of a DA cyclobutane was reported by Saigo in 1991.[10] It was disclosed that an amino-activated cyclobutane underwent an annulation event with both aldehydes and ketones to generate tetrahydropyrans. This transformation required stoichiometric $TiCl_4$ for the reaction to proceed in modest yield, affording a diastereomeric mixture of hemiketals after acidic hydrolysis of the intermediate aminal.

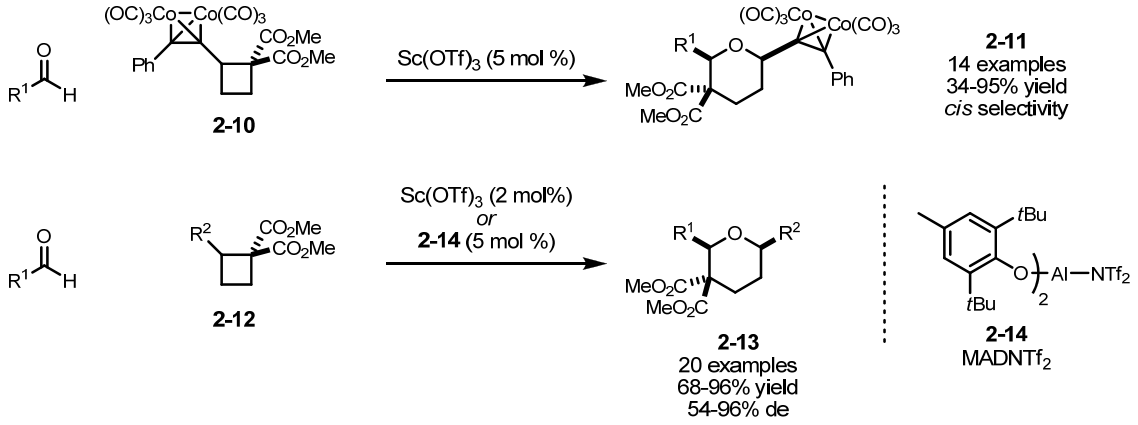
Scheme 2.3. (4 + 2) Cycloaddition Between Amino-Activated Cyclobutanes and Aldehydes or Ketones



2-8 **2-9**

Reactivity of this kind was seemingly abandoned until recently, with a number of contributions occurring in rapid succession. In 2009 near simultaneous reports by Johnson[11] and Christie and Pritchard[12] disclosed the reactivity of DA cyclobutanes with carbon-based activating groups undergoing annulation events with aldehydes (Scheme 2.4). Both reports describe the process as being incredibly facile, requiring low catalytic loadings of $Sc(OTf)_3$ and affording tetrahydropyran products in high yield with excellent diastereoselectivity.

Scheme 2.4. (4 + 2) Cycloaddition Between DA Cyclobutanes and Aldehydes

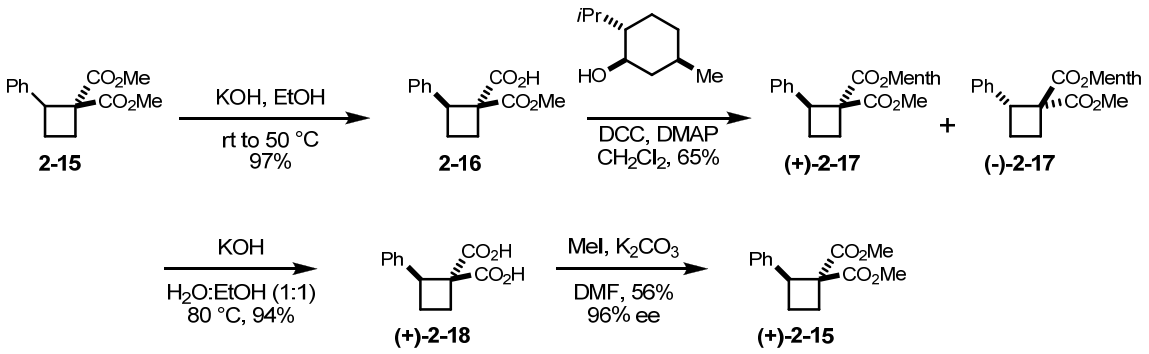


While the report by Christie and Prichard demonstrated the feasibility of a highly diastereoselective (4 + 2) cycloaddition of DA cyclobutanes, the scope of the reaction was limited as only a single cyclobutane (**2-10**) was investigated and only electron-rich aldehydes underwent the reaction in good yield. Electron-poor aldehydes suffered from low yields and aliphatic aldehydes were found to not participate in the reaction. In contrast, the report by Johnson explored a number of carbon-based cyclobutane activating groups. They found that the annulation would occur between cyclobutanes and aromatic aldehydes with $Sc(OTf)_3$ in good yield and high diastereoselectivity; however, a different catalyst ($MADNTf_2$, **2-14**) was required to facilitate the reaction between DA cyclobutanes and aliphatic aldehydes. Additionally, and more importantly, preliminary studies were undertaken to determine the mechanism of the reaction.

In efforts to elucidate the mechanism of the cycloaddition, an enantiomerically enriched DA cyclobutane was prepared through a circuitous route (Scheme 2.5). The racemic DA cyclobutane **2-15** was monosaponified and esterified with (–)-menthol. The resulting diastereomers were separated and saponification of the pure (+)-diastereomer

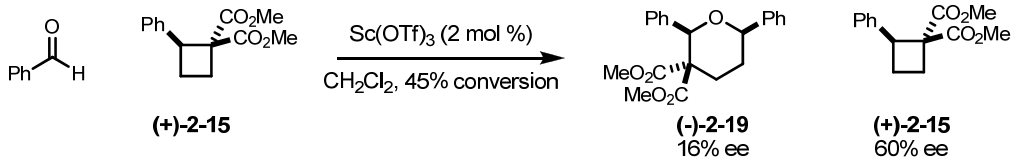
provided diacid **2-18**. Subsequent esterification with MeI afforded enantiomerically enriched DA cyclobutane (+)-**2-15**.

Scheme 2.5. Synthesis of an Enantiomerically Enriched DA Cyclobutane



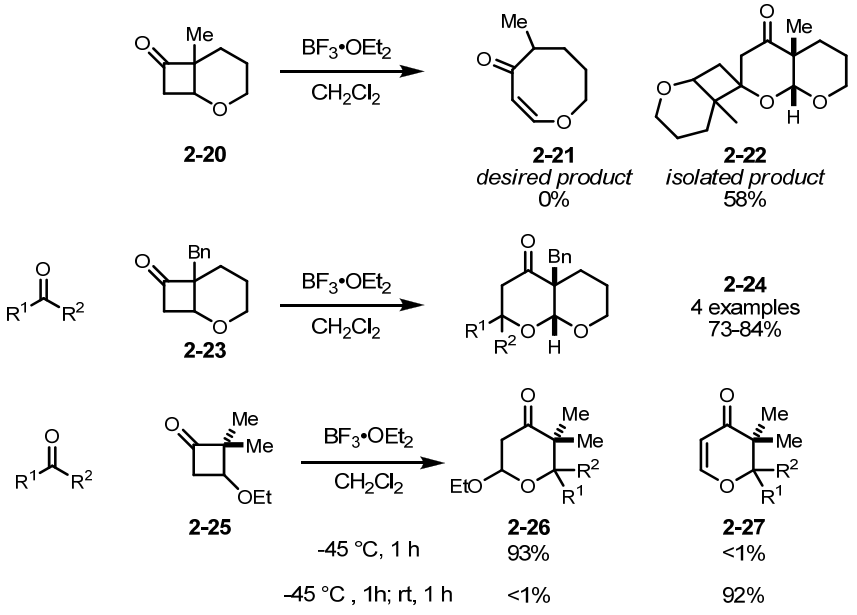
Treatment of the enantiomerically enriched DA cyclobutane **2-15** to the cycloaddition conditions afforded surprising results (Scheme 2.6). Johnson found that at low reaction conversions, despite having enantiomerically enriched cyclobutane, the tetrahydropyran product was almost racemic. In addition, the enantiomeric purity of the DA cyclobutane slowly degraded throughout the reaction; at 45% conversion the enantiomeric excess of the DA cyclobutane was only 60%. This study demonstrated that, unlike the case of DA cyclopropanes,[13] the analogous reaction with DA cyclobutanes may be mechanistically more complex.

Scheme 2.6. (4 + 2) Cycloaddition Between Enantioenriched DA Cyclobutane **2-15** and Benzaldehyde



Other major reports in the field of DA cyclobutane annulation chemistry investigate the reactivity of cyclobutanones. The first example of an intermolecular annulation of cyclobutanones with a dipolar species was reported in 2008.[14] While attempting to form ring-expansion products from cyclobutanone **2-20**, a dimeric product (**2-22**) was isolated (Scheme 2.7). Realizing that the dimer had occurred through a (4 + 2) cycloaddition and cognizant of the potential of a (4 + 2) cycloaddition between cyclobutanones and carbonyl compounds, they quickly realigned their objectives and explored the annulation event.

Scheme 2.7. (4 + 2) Cycloaddition of Cyclobutanones with Carbonyl Species

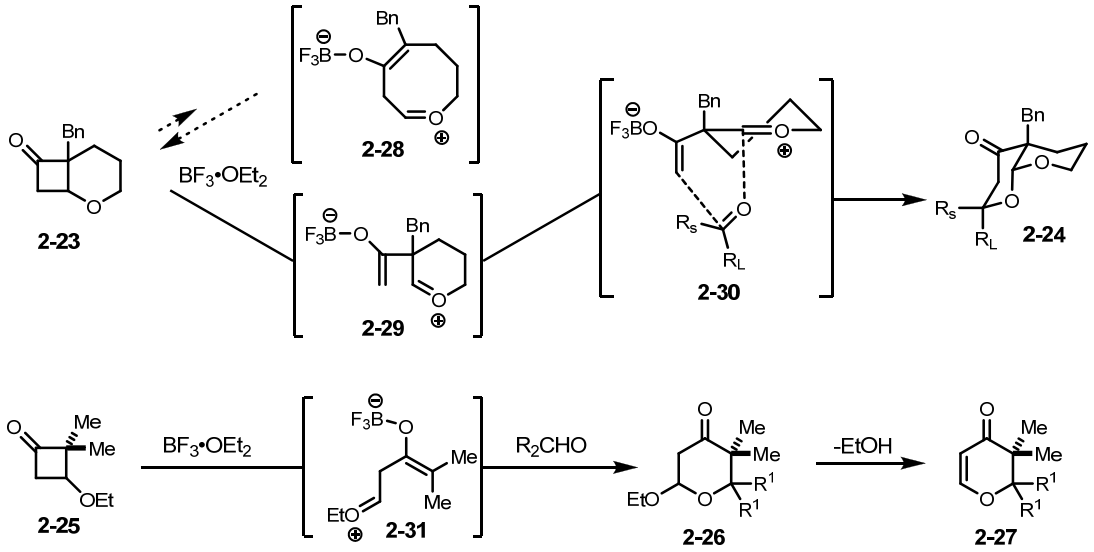


The fused cyclobutane **2-23** underwent smooth cycloaddition with benzaldehyde, pivaldehyde, and acetophenone to afford the desired adducts in good yield and high diastereoselectivity (Scheme 2.7). However, when non-fused cyclobutanone **2-25** was subjected to the reaction conditions, the process was revealed to be stereorandom, and the regioselectivity was opposite to that of cyclobutanone **2-23**. The poor diastereoselectivity

of the cycloaddition with ethoxy-substituted cyclobutanone **2-25** could be compensated for by allowing the reaction to warm to room temperature, facilitating elimination of ethanol and resulting in formation of dihydropyrone **2-27**.

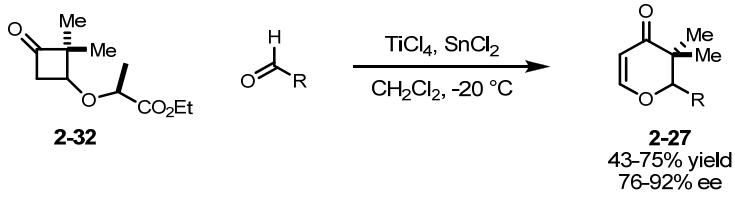
With regards to the opposite regioselectivity observed between the two cyclobutanones, both steric and electronic factors were believed to be responsible. The regioselectivity of the reaction, in the case of the fused cyclobutanone (**2-23**), was due to high levels of ring strain that would be present if an eight-membered ring bearing two double bonds were formed (**2-28**), while the high diastereoselectivity was believed to be due to pseudo-equatorial approach of the carbonyl species (Scheme 2.8). In contrast, the ethoxy-substituted cyclobutanone **2-25** cleaved at the more substituted carbon. Matsuo attributed this reversal as cleaving at the bond more able to stabilize the developing positive charge (following Lewis acid coordination of the cyclobutanone). This rationale is likely incorrect, and cleavage at the more substituted carbon occured to form the more substituted (and thermodynamically favored) enolate. The low diastereoselectivity observed with cyclobutanone **2-25** was attributed to the reaction occurring through the open zwitterionic intermediate **2-31**.

Scheme 2.8. Mechanistic Rationale for Observed Selectivity with Cyclobutanone Cycloadditions



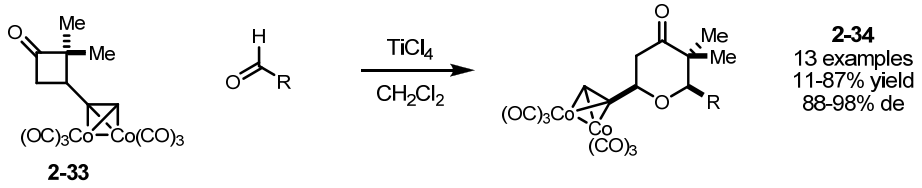
Following their initial disclosure, Matsuo explored the potential of the (4 + 2) cycloaddition to afford products in an enantioselective manner. This was realized through appendage of an inexpensive auxiliary via an ether linkage. In this case, the auxiliary would serve two purposes, to act as an activating group for the cyclobutanone and to facilitate chirality transfer (Scheme 2.9).[15] After exploration of a number of candidates, it was shown that the L-ethyl lactate auxiliary (**2-32**) could afford dihydropyrone products with moderate to high levels of enantiopurity. Interestingly, the addition of a second metal chloride to the reaction mixture proved vital to achieving good levels of chirality transfer, the most successful combination being $TiCl_4$ and $SnCl_2$, both in super-stoichiometric quantities.

Scheme 2.9. Asymmetric Annulation of Cyclobutanones and Aldehydes



Matsuo has also demonstrated that the activating group required for cyclobutanone cleavage and subsequent annulation does not need to be an ether linkage, as cobalt-alkyne complexes could also facilitate the cycloaddition, though alkynes would not (Scheme 2.10).[16] This is a similar finding to that of DA cyclopropanes where alkyne-activated cyclopropanes dicarboxylates would react with nitrones to afford only trace quantities of products; however, upon cobalt-complexation of the alkyne, the yield dramatically increased to 90%.[17] Surprisingly, the reaction between the cyclobutanone bearing the alkyne-cobalt complex (**2-32**) and aldehydes occurred in high diastereoselectivity, in sharp contrast to when an ether linkage was used where the diastereoselectivity was almost non-existent.

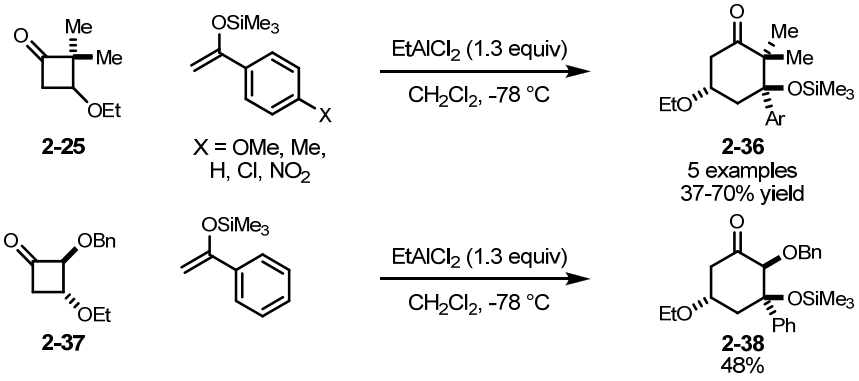
Scheme 2.10. (4 + 2) Cycloaddition Between Cyclobutanones Bearing an Alkyne-Cobalt Complex and Aldehydes



A number of alternative dipolarophile partners were also investigated by Matsuo with varying degrees of success. Electron-rich olefins were explored though the scope and selectivity of the processes were found to be somewhat limited.[18] Electron-rich silyl enol ethers participated in (4 + 2) cycloadditions with cyclobutanone **2-25** to afford

cyclohexanone products (Scheme 2.11). A number of Lewis acids were explored and it was found that $EtAlCl_2$ facilitated the reaction in the highest yield. The selectivity of the reaction with a number of acetophenone-derived silyl enol ethers was found to be high, however extension of the reaction to silyl enol ethers derived from propiophenone resulted in diastereomeric mixtures. Interesting the diastereomerically pure cyclobutanone **2-37** underwent the (4 + 2) cycloaddition with a silyl enol ether to afford a highly substituted cyclohexanone (**2-38**) with good control over the diastereoselectivity at all three stereocenters.

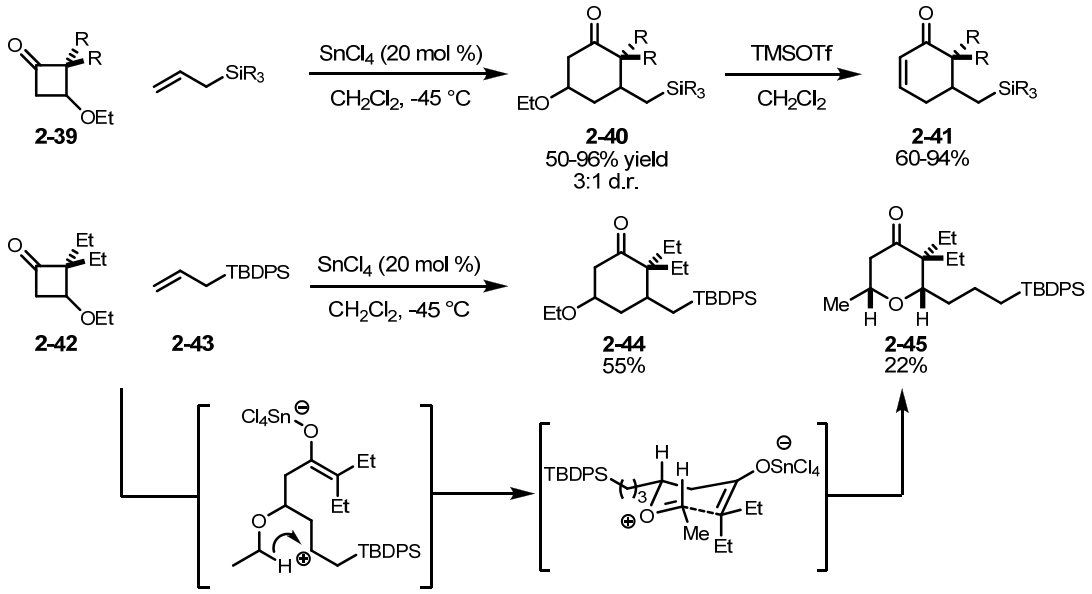
Scheme 2.11. Cycloadditions Between Silyl Enol Ethers and Cyclobutanones



The reactivity of allylsilanes with cyclobutanones was also investigated (Scheme 2.12).[19] In contrast to previously reported reactions with cyclobutanones, the reaction of allylsilanes was found to proceed with only catalytic amounts of Lewis acid. A number of Lewis acids were examined and $SnCl_4$ was found to afford the products in the highest yield, though the diastereoselectivity was only 3:1. The diastereoselectivity issue could once again be solved though elimination of ethanol by treating the isolated product with TMSOTf. A number of symmetrically substituted cyclobutanones were examined, providing comparable yields and diastereoselectivities throughout. Substitution about the

silicon atom of the allyl silanes was also investigated and, upon examining allylsilane **2-43**, a peculiar rearrangement process occurred and a mixture of cyclohexanone **2-44** and tetrahydropyrone **2-45** was obtained. The rearrangement was believed to occur through a 1,5-hydride shift followed by ring closure of the pendant enolate.

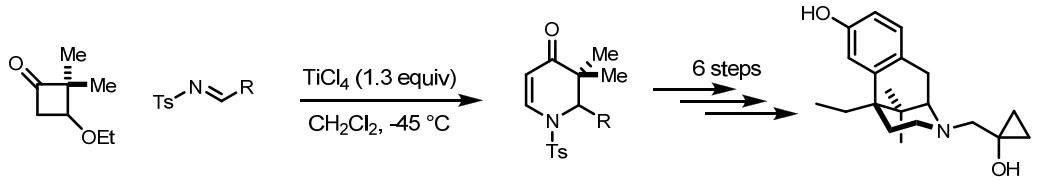
Scheme 2.12. Cycloaddition Between Allylsilanes and Cyclobutanones



Subsequently, the reactivity of DA cyclobutanones and *N*-sulfonyl imines was investigated and found to be a facile and useful process.[20] As in previous cases, $TiCl_4$ was found to be the Lewis acid of choice for the cycloaddition, mediating the reaction at –45 °C within 1 h (Scheme 2.13). Fortuitously, the ethoxy-activating group was eliminated *in situ* to afford dihydropyridones directly. The reaction scope was quite broad, as substitution about the carbon portion of the imine was tolerant of electron-rich or poor aryl rings, as well as conjugated and aliphatic substituents. The effects of nitrogen substitution were not explored but *N*-tosyl groups can easily be cleaved, rendering alternative nitrogen substitution patterns a non-issue. Exploration of the stereochemical

outcome of the reaction with non-symmetrical cyclobutanones revealed that the process occurred with almost no stereoselectivity. However, they were able to demonstrate the applicability of this methodology by utilizing it in a rather rapid synthesis of the alkaloid (±)-bremazocine.

Scheme 2.13. Cycloaddition Between *N*-Sulfonyl Imines and Cyclobutanones



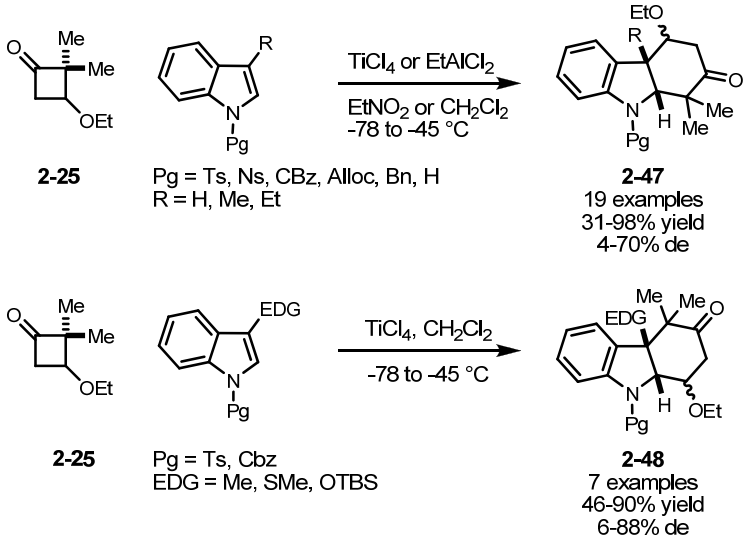
2-25

2-46
13 examples
31-78% yield

(±)-bremazocine

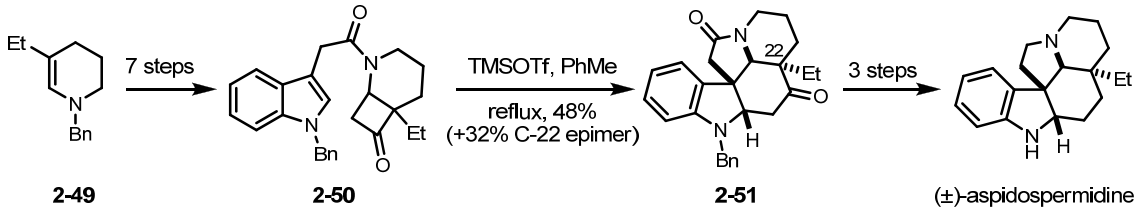
The most recent, and possibly most impressive, example to date of the utility of dipolar cycloaddition chemistry with cyclobutanones is the reactivity of cyclobutanones and indoles for the generation of hydrocarbazoles (Scheme 2.14).[21] The reaction proceeded with high *cis* selectivity about the ring fusion; however, the relative stereochemistry between the ring fusion and the ethoxy substitutent was moderate to poor. The yield was moderate to excellent and once again they were able to remove the ethoxy activating group to install an α,β-unsaturated ketone, circumventing the poor diastereoselectivity of the reaction. Additionally, with proper substitution about the indole nucleus, the cycloaddition could be influenced to occur with opposite regioselectivity, revealing the strong influence that electronics play in the reaction.

Scheme 2.14. (4 + 2) Dipolar Cycloaddition Between Cyclobutanones and Indoles



The utility of this process was demonstrated through the synthesis of (±)-aspidospermidine (Scheme 2.15). An amino-activated cyclobutanone was synthesized over seven steps to afford **2-50**. An extensive Lewis acid screen was required to identify that TMSOTf was capable of mediating the desired (4 + 2) intramolecular cycloaddition, though once again a mixture of two diastereomers was formed. Another three steps were required to complete the synthesis.

Scheme 2.15. Synthesis of **(±)**-Aspidospermidine from the (4 + 2) Cycloaddition of Indoles and Cyclobutanones



While a number of DA cyclobutanes have been employed in dipolar cycloaddition chemistry, the bulk of the examples explore chemistry of cyclobutanones. Additionally, the reactions typically lack control over the diastereoselectivity of the process and require

super-stoichiometric amounts of Lewis acid activators. It would therefore be useful to investigate DA cyclobutanes bearing alternative donating and accepting groups and explore their reactivity in cycloaddition chemistry.

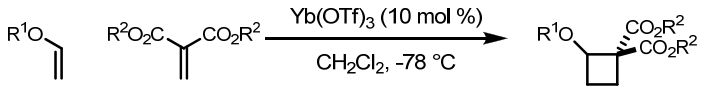
The Pagenkopf group has previously explored the dipolar cycloaddition chemistry of DA cyclopropanes activated by alkoxy donating groups and ester withdrawing groups.[3c,4c,22] It was believed, based the precedent set by Saigo,[10] Matsuo[14] and Johnson,[11] that alkoxy-activated cyclobutane dicarboxylates could undergo cycloaddition chemistry with a number of dipolarophiles to afford diverse and unique molecular scaffolds.

2.2 Cycloadditions of Alkoxy-Activated Donor-Acceptor Cyclobutanes and Dipolar Reagents

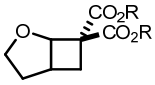
2.2.1 Synthesis of Alkoxy-Substituted Donor-Acceptor Cyclobutanes

At the outset of this work, Mahmoud Moustafa (Ph.D.) had developed a modified procedure for the synthesis of alkoxy-activated DA cyclobutanes based upon the method of Roberts (Table 2.1).[23] The original procedure required stoichiometric zinc bromide to form the cyclobutanes; however, this proved to be too aggressive of a Lewis acid, as only cyclobutanes bearing the bulky *t*-butyl esters were stable enough under the reaction conditions to be successfully isolated in appreciable quantities. Much weaker Lewis acids were necessary to produce cyclobutanes bearing the less protective and more reactive ethyl and methyl esters. This was readily accomplished using $Yb(OTf)_3$, which was only required in catalytic amounts (10 mol %). It should be noted that prior to our report Johnson had also observed this phenomenon and utilized $Sc(OTf)_3$ as a catalyst for the formation of a carbon-activated cyclobutane dicarboxylate through this method.[11]

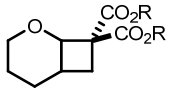
Table 2.1. Synthesis of Alkoxy-Activated Cyclobutane Dicarboxylates



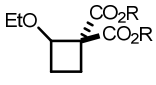
2-52 **2-53** **2-54** to **2-64**



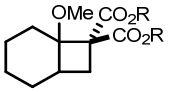
2-54; R = Et, 93%;
2-55; R = *i*Pr, 61%;
2-56; R = *t*Bu, 72%;



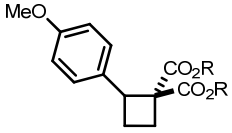
2-57; R = Et, 84%



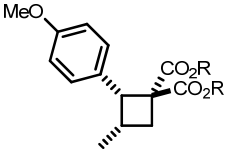
2-58; R = Me, 56%
2-59; R = Et, 80%



2-60; R = Et, 70%



2-61; R = Et, 81%



2-62; R = Me, 51%
2-63; R = Et, 71%
2-64; R = *t*Bu, 59%

2.3 Results and Discussion

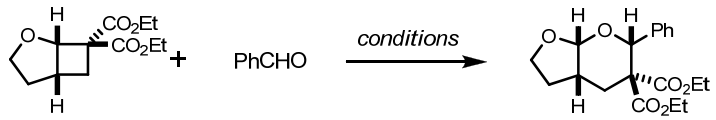
2.3.1 Annulation of Alkoxy-activated Cyclobutane Dicarboxylates and Aldehydes

With access to DA cyclobutanes bearing a variety of alkoxy-activating groups and ester substitutions, we examined possible dipolar reagents for feasibility in cycloaddition chemistry. Aldehydes were selected among the first dipolarophiles to be evaluated as potential annulation partners with alkoxy-activated cyclobutane dicarboxylates.[24]

Our studies in this area began by examining the cycloaddition between cyclobutane **2-54** and benzaldehyde (Table 2.2). After a brief Lewis acid screen, $Yb(OTf)_3$ was found to be the optimal choice, affording fused acetal **2-65a** as a single diastereomer in 70% yield.[25] Screening of the reaction conditions revealed that temperature had little effect on the yield or diastereoselectivity (entries 1 – 3), and that catalyst loadings as low as 0.5 mol % (entry 7) could be used, though prolonged reaction times were necessary. At 2 mol % catalyst loadings, the reactions were complete in 2 min

when quickly heated in the microwave reactor and allowed to cool (entry 8). For convenience, however, 10 mol % of $Yb(OTf)_3$ (entry 4) was used throughout this study as the reactions were complete in 15 min at 0 °C. It is important to note that only a single diastereomer was observed by NMR spectroscopy in this case, and in all subsequent examples.

Table 2.2. Optimization of the (4 + 2) Cycloaddition Between DA Cyclobutane **2-54** and Benzaldehyde



2-54 **2-65a**

	conditions[a]				
entry	$Yb(OTf)_3$ (mol %)	PhCHO (equiv)	temp (°C)	time (min)	yield[b] (%)
1	10	3.0	-40	120	70
2	10	3.0	0	15	84
3	10	3.0	20	15	78
4	10	1.1	0	15	78
5	10	0.9	0	15	68
6	2	1.1	0	45	74
7[a]	0.5	1.1	25	18 h	79
8[b]	2	1.1	60	2	76

[a] No reaction was observed at 0 °C. [b] Reaction was conducted in a microwave reactor. Optimization studies were conducted in conjunction with Ben Machin.

Having identified suitable reaction conditions, the scope of the transformation was explored (Figure 2.2). Aromatic aldehydes were found to be excellent reaction partners regardless of whether they were electron rich (**2-65b**), halogenated (**2-65c**), electron poor (**2-65d, 2-65e**), or conjugated (**2-65g** to **2-65i**). Heteroaromatic aldehydes also underwent the cycloaddition (2-furfural, 2-thiofurfural, and indole-2-carboxaldehyde, **2-65j** to **2-65l**).

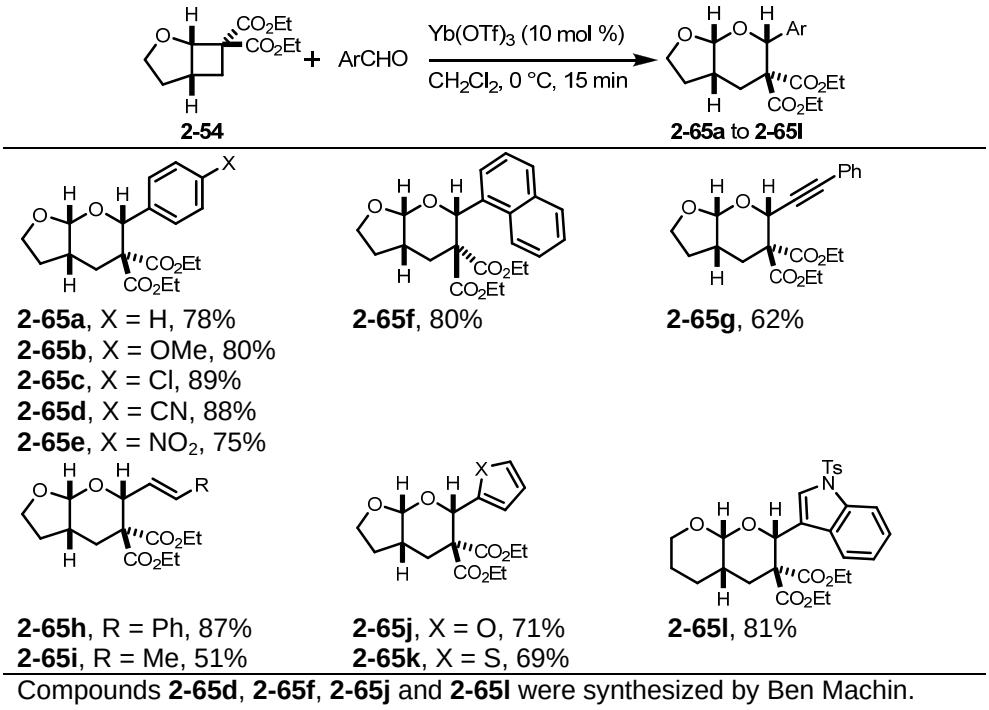


Figure 2.2. Scope of the (4 + 2) Cycloaddition of DA Cyclobutanes and Aromatic and Heteroaromatic Aldehydes

Related studies indicated that aliphatic aldehydes may require stronger Lewis acids;[11] however, in this study it was observed that the same Lewis acid, $Yb(OTf)_3$, could effectively catalyze the (4 + 2) cycloaddition between the alkoxy-substituted cyclobutane dicarboxylates and aliphatic aldehydes (Figure 2.3). Examination of the reaction scope revealed that linear (**2-65m**, **2-65n**), branched (**2-65o**), acetaldehyde (**2-65p**), and cyclopropyl aldehydes (**2-65q**) all underwent the cycloaddition to provide exclusively the *cis* bicyclic acetals.

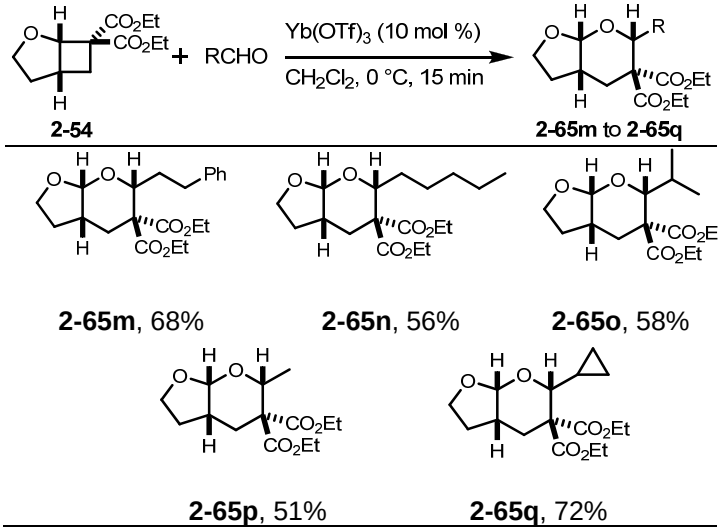
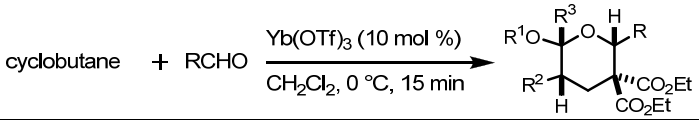
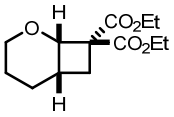
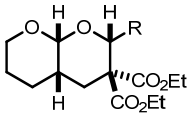
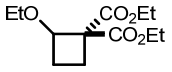
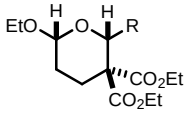
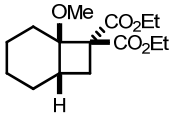
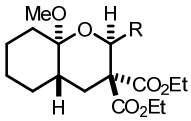


Figure 2.3. (4 + 2) Cycloaddition of DA Cyclobutanes and Aliphatic Aldehydes

Lastly, several additional DA cyclobutanes were investigated (Table 2.3). Pyran-fused cyclobutane **2-57** underwent successful cycloaddition with both aromatic and aliphatic aldehydes to afford the all *cis*-products (**2-66a**, **2-66b**). The ethoxy-substituted cyclobutane **2-59** also participated in the cycloaddition with aromatic and aliphatic aldehydes (**2-67a**, **2-65b**). Furthermore, the cyclohexyl-fused cyclobutane **2-60** underwent cycloadditions with aromatic aldehydes to afford the fused ring systems **2-68a** to **2-68e**, each as a single diastereomer.

Table 2.3. Additional DA Cyclobutanes for the (4 + 2) Cycloaddition with Aldehydes



cyclobutane	tetrahydropyran
 **2-57**	 **2-66a**, R = Ph, 60% **2-66b**, R = $(CH_2)_2Ph$, 62%
 **2-59**	 **2-67a**, R = Ph, 72% **2-67b**, R = $(CH_2)_2Ph$, 70%
 **2-60**	 **2-68a**, R = *p*-C_6H_4OMe, 76% **2-68b**, R = *p*-C_6H_4Cl, 69% **2-68c**, R = *m*-$C_6H_4NO_2$, 60% **2-68d**, R = *trans*-C_2H_2Ph, 71% **2-68e**, R = 2-thiophene, 56%

Compounds **2-68a** to **2-68e** were synthesized by Mahmoud Moustafa.

The assignment of stereochemistry of the cycloadducts was based on NMR analysis (Figure 2.4). Observed nOe interactions between protons H_A and H_B indicated a *cis* relationship in all adducts. Additionally, the small ^3J_H coupling constant between the ring fusion protons (H_A and H_C) of furan-fused (**2-65**) and pyran-fused (**2-66**) cycloadducts indicated *cis*-ring fusions in both cases. The cyclohexyl-fused adducts (**2-68**) were believed to bear *trans*-ring fusions based upon the lack of observed nOe between the methoxy substituent and ring fusion proton, as well as other coupling experiments.

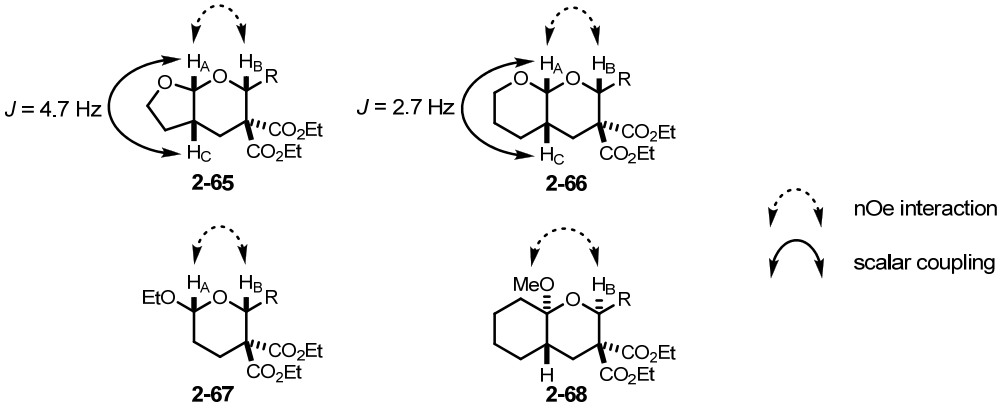
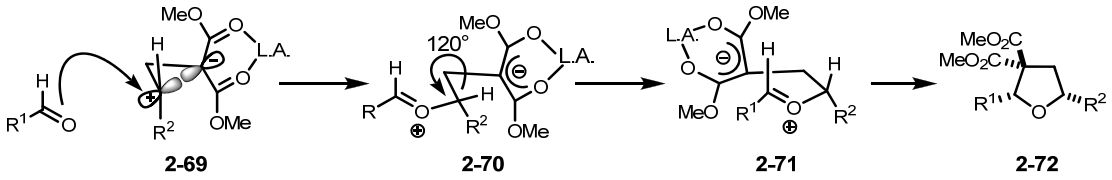


Figure 2.4. Selected NMR Interactions

The mechanism of (3 + 2) cycloadditions of carbon-activated cyclopropane dicarboxylates has been the subject of study.[13] The reaction is believed to occur through an intimate ion-pair (**2-69**) as seen in Scheme 2.16. The aldehyde acts as a nucleophile and, following addition, a 120° rotation about the C-2/C-3 bond occurs to allow nucleophilic ring closure *via* envelope-shaped intermediate **2-71**. Overall, a net inversion occurs at C-3 as if a S_N2 reaction had taken place. Due to the formation of an ion-pair, and the potential for the cyclopropane starting material to undergo racemization, this mechanism has been exploited for use in dynamic kinetic asymmetric transformations.[26]

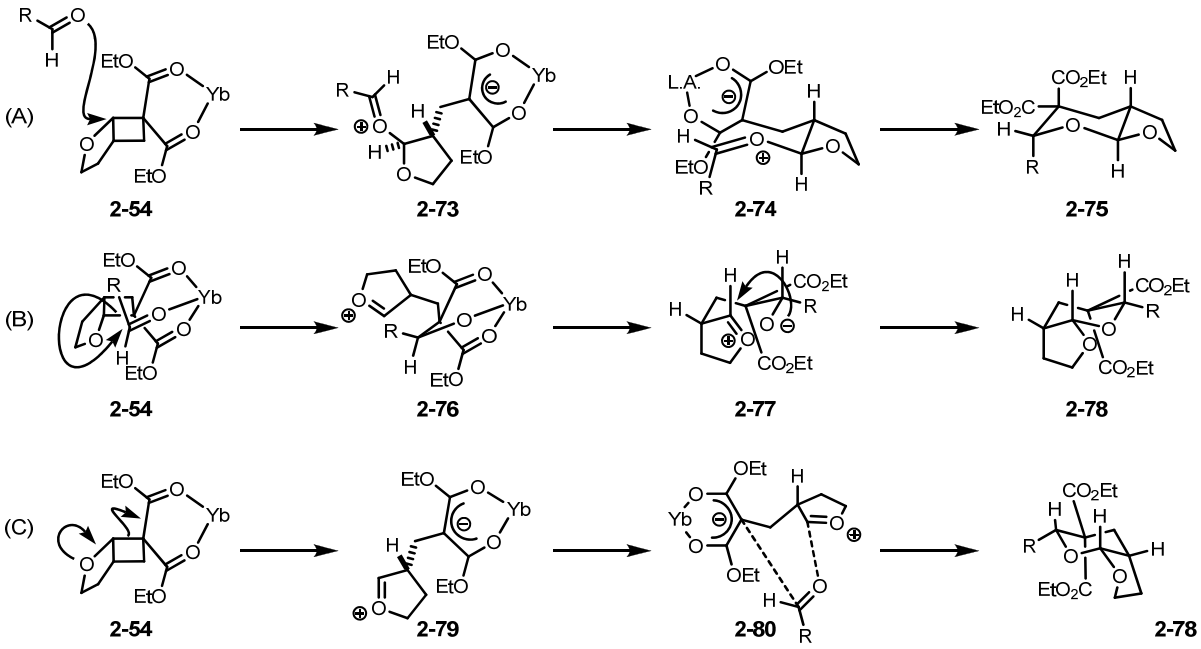
Scheme 2.16. Mechanism of the (3 + 2) Cycloadiditon Between DA Cycloproanes and Aldehydes



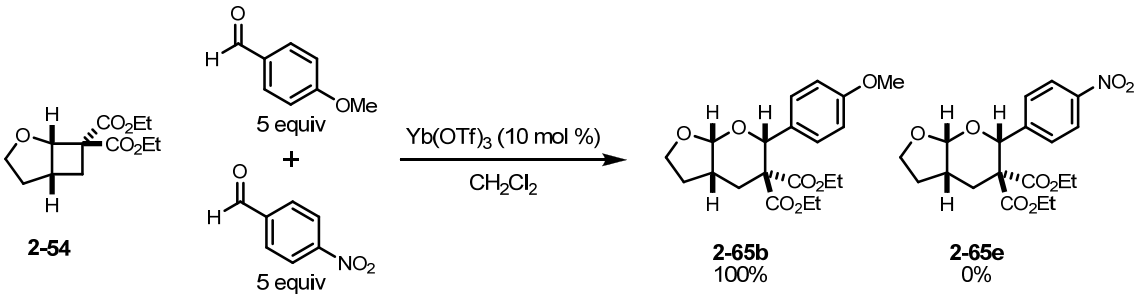
When the (4 + 2) cycloaddition between alkoxy-activated cyclobutane dicarboxylates and aldehydes is compared to the above (3 + 2) cycloaddition of cyclopropanes, it is immediately evident that a similar mechanism is not operating

(Scheme 2.17). Overall a net retention occurs at the carbon center bearing the activating group, ruling out a direct S_N2 type reaction which would lead to a net inversion (mechanism A). Alkylation of the aldehyde by the cyclobutane ring (mechanism B) would lead to the observed stereochemistry; however, this mechanism is not believed to be operating due to preliminary competition experiments between electron-rich anisaldehyde and electron-deficient *para*-nitrobenzaldehyde (Scheme 2.18). The reaction showed complete preference for the electron-rich aldehyde, indicating that the most likely mechanism involves a nucleophilic, rather than electrophilic component. The remaining pathway is similar to that proposed by Matsuo,[14] where cleavage of the cyclobutane occurs to form a zwitterionic intermediate (**2-79**), followed by annulation with an aldehyde to afford the tetrahydropyran (**2-78**, mechanism C). Currently, the favored pathway for the above reasons is that of mechanism C.

Scheme 2.17. Plausible Mechanisms for the (4 + 2) Cycloaddition of DA Cyclobutanes and Aldehydes



Scheme 2.18. Competition Experiment Between Electron-Rich and Deficient Aldehydes



In conclusion, we have developed an efficient $Yb(OTf)_3$ catalyzed (4 + 2) dipolar cycloaddition between alkoxy-activated DA cyclobutanes and aldehydes. This process occurs in high diastereoselectivity and yield to afford fused acetals under mild conditions.

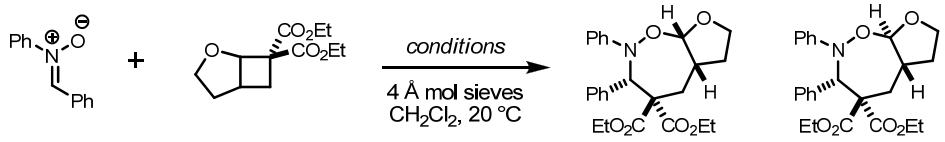
2.3.2 Annulation of Alkoxy-Activated Cyclobutane Dicarboxylates and Nitrones

Having successfully demonstrated that alkoxy-activated DA cyclobutanes can undergo annulations with aldehydes[1] and imines,[24] alternative dipolarophiles were investigated. The abundance of cycloaddition chemistry with nitrones,[27] combined with the lack of exploration of 3-atom dipolarophiles in cyclobutane annulation chemistry, led us to investigate their feasibility as annulation partners. A successful (4 + 3) cycloaddition would result in a unique oxazepane structure. This intriguing structural motif, though not naturally occurring, has been shown to be relevant as oxazepane analogs of eudistomin natural products display antiviral[28] and antiproliferative[29] activity.

$Yb(OTf)_3$ has previously been shown to be an effective catalyst for the reaction between nitrones and DA cyclopropanes,[30,31] as well as in the previous section where it catalyzed the cyclization of DA cyclobutanes with aldehydes, and thus was selected initially for optimization studies (Table 2.4). Much to our delight, upon addition of cyclobutane **2-54** to a solution of nitrone and 10 mol % $Yb(OTf)_3$ in CH_2Cl_2 the

anticipated cycloadduct **2-81a** was formed as a single diastereomer in 60% isolated yield (entry 1).[32] Control tests demonstrated that a metal catalyst was not required for the reaction to occur; however, extended reaction times were necessary and a mixture of two apparently non-equilibrating diastereomers resulted (entry 2). A modest increase in yield was observed when the nitrone, rather than the cyclobutane, was used as the limiting reagent (compare entries 1 and 3). When the catalytic loading was decreased from 10 mol % to 5 mol %, a mixture of two diastereomers was found if the reaction was stopped after 10 minutes (entry 4), and the diastereomeric ratio reversed when the reaction was conducted at 0 °C (entry 5). In all cases, increasing the reaction time or catalyst loading led ultimately to the single diastereomer **2-81a** (entry 6) and, as expected, exposure of **2-82a** to $Yb(OTf)_3$ resulted in isomerization to **2-81a**. Further decreasing the reaction temperature resulted in a complex mixture of diastereomers, and thus was not explored as a viable option. Additionally, decreasing the catalytic loading of $Yb(OTf)_3$ to 1 mol % resulted in the formation of three diastereomers.[33] To date conditions have not been identified that allow for exclusive formation of the *trans* diastereomer (**2-82a**).

Table 2.4. Optimization of the (4 + 3) Cycloaddition of DA Cyclobutanes and Nitrones



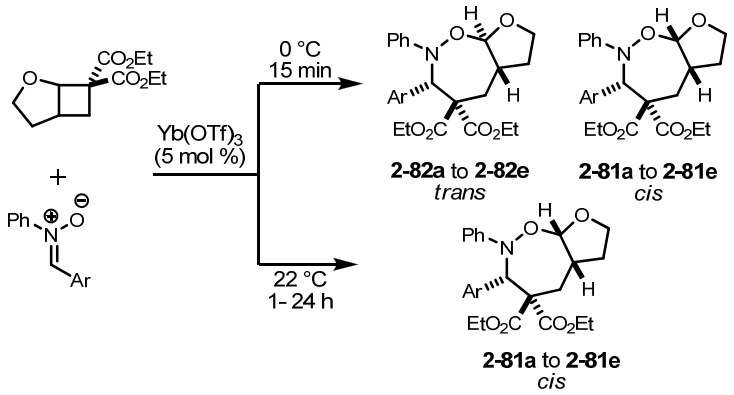
2-54 **2-81a** *cis* **2-82a** *trans*

entry	nitrone (equiv)	**2-54** (equiv)	$Yb(OTf)_3$ (mol %)	time (min)	**2-81a : 2-82a**	yield (%)
1	1.5	1.0	10	10	1.0:0.0	60
2	1.5	1.0	0	60	1.3:1.0	87[a]
3	1.0	1.2	10	10	1.0:0.0	81
4	1.0	1.2	5	10	1.7:1.0	78
5	1.0	1.2	5	10	1.0:2.2	91[b]
6	1.0	1.2	5	60	1.0:0.0	76

[a]Reaction conducted in the presence of 4 Å molecular sieves. In the absence of both molecular sieves and Lewis acids, no reaction occurs. [b]Reaction conducted at 0 °C.

The breadth of the cycloaddition reaction was then examined, and separate experiments were conducted to obtain both diastereomeric mixtures and a single diastereomer. The length of time required for single diastereomer formation was dependent upon the electronic nature of the nitrone (Table 2.5). While electron-rich nitrones required less than an hour to afford a single diastereomer (entries 1 – 3), electron-deficient nitrones required extended reaction times (up to 24 h) to allow for full conversion (entries 4 and 5). Additionally, when electron-deficient nitrones (entries 4 and 5) were subjected to the reaction condititions a third inseparable diastereomer (not shown) was observed with short reaction times. The yields were found to be consistent regardless of the electronic nature of the nitrone, though the extended times required for equilibrating the diastereomeric mixtures resulted in lower yields due to competing background decomposition of the product.

Table 2.5. Effect of *C*-Substitution on the Cyclobutane/Nitrone Cycloaddition



entry	nitrone	diastereomeric mixture[a]		single *cis* diastereomer[b]
		yield (%)	d.r. (*trans*:*cis*:3rd)	yield (%)
1	Ar = C_6H_5	91	69:31	76[c]
2	Ar = *p*-$C_6H_4OCH_3$	88	63:37	74[c]
3	Ar = *p*-C_6H_4Cl	82	71:29	73[c]
4	Ar = *p*-C_6H_4CN	95	57:15:27	76[d]
5	Ar = *p*-$C_6H_4NO_2$	90	63:11:26	73[d]

[a]Conditions: 0 °C, 15 min. [b]Conditions: 22 °C, reaction allowed to proceed until only a single product was observable by TLC. [c]Reactions required less than 1 hour to form single diastereomers. [d]Reactions required 24 h to form single diastereomers.

The stereochemistry of the *cis* and *trans* diastereomers were assigned based on nOe interactions. In the case of entry 3, the stereochemistry of both diastereomers was unambiguously confirmed by single crystal X-ray analysis (Figure 2.5).

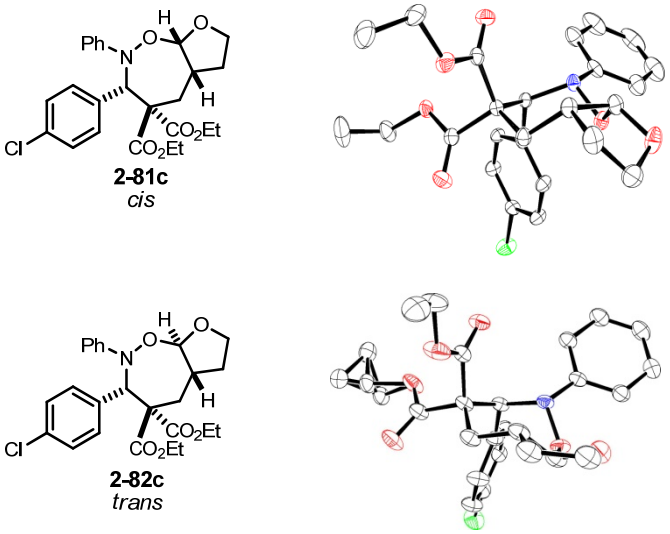
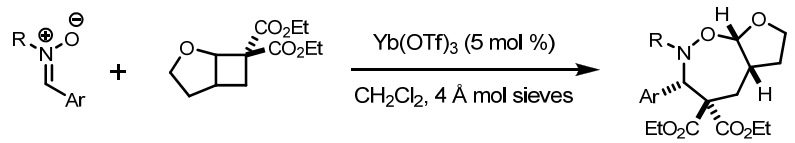


Figure 2.5. X-ray Structures of the *cis* and *trans* Diastereomers (**2-81c** and **2-82c**)

Next, the effect of *N*-substitution on the nitrone was examined (Table 2.6). Nitrones bearing an electron-deficient *N*-aryl group were found to be viable reaction partners (entries 2 and 3), as were electron-rich *N*-PMP (entries 4 - 6). An *N*-aliphatic nitrone (*N*-benzyl) was also found to undergo the reaction; however, only a single diastereomer was observed even under short reaction times (entry 7).

Table 2.6. Effect of *N*-substitution on the Cycloaddition of DA Cyclobutanes and Nitrones



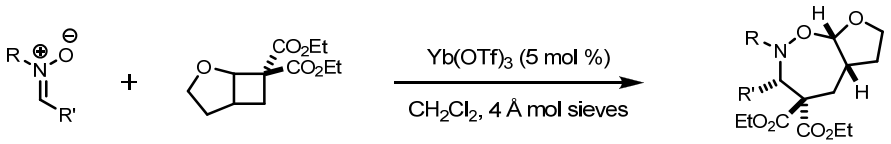
2-54 **2-81a**, **2-81f** to **2-81k**

entry	nitrone	diastereomeric mixture[a]		single *cis* diastereomer[b]
		yield (%)	dr (*cis*:*trans*:3rd)	yield (%)
1	R = C_6H_5 Ar = C_6H_5	91	31:69	76
2	R = *p*-$C_6H_4CO_2Me$ Ar = C_6H_5	68	16:40:44	52[c]
3	R = *p*-$C_6H_4CO_2Me$ Ar = *p*-$C_6H_4NO_2$	74	7:58:35	68
4	R = *p*-C_6H_4OMe Ar = C_6H_5	69	34:66	43
5	R = *p*-C_6H_4OMe Ar = *p*-C_6H_4CN	66	32:68	55
6	R = *p*-C_6H_4OMe Ar = *p*-C_6H_4OMe	70	56:44	54
7	R = Bn Ar = C_6H_5	-	-	60

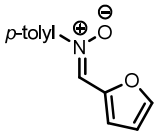
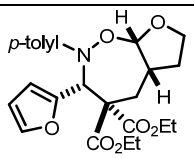
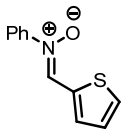
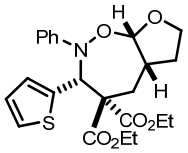
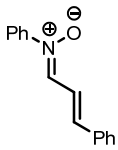
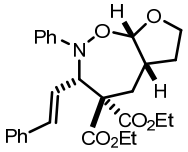
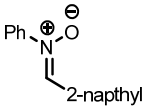
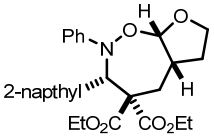
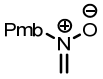
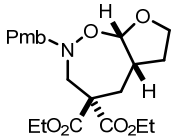
[a]Conditions: 0 °C, 15 min. [b]Conditions: 22 °C, reaction allowed to proceed until only a single product was observable by TLC. [c]Incomplete conversion, 72:28 *cis*:*trans* after 24 h and 10 mol % $Yb(OTf)_3$. Entry 7 was conducted by Cory Palmer.

Having found the reaction to be compatible with a variety of nitrones, additional functionalities of the *C*-substituents were explored (Table 2.7). It was discovered that heteroaromatic nitrone substituents worked well in the cycloaddition (entries 1 and 2). Surprisingly, when naphthyl- or cinnamyl-substituted nitrones were subjected to the reaction conditions, only single diastereomers were observed rather than diastereomeric mixtures, similar to the results obtained with *N*-alkyl substitution (Table 2.7, entries 3 and 4 vs Table 2.6, entry 7). It was found that *C*-substitution was not necessary for the reaction as a *C*-unsubstituted benzyl nitrone underwent the reaction to form exclusively the *cis* adduct (entry 5).

Table 2.7. Exploration of Nitrone Functionality Tolerance in the Cycloaddition



2-54 **2-81l** to **2-81p** (dr *cis*:*trans*)

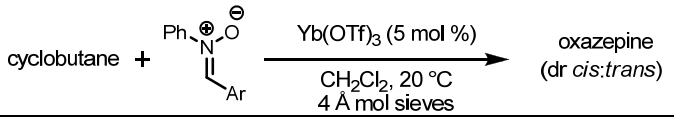
entry	nitrone	oxazepane	diastereomeric mixture[a] yield (*cis*:*trans*)	single *cis* diastereomer[b] yield
1			85% (55:45)	75%
2			77% (55:45)	67%
3			N/A	70%
4			N/A	74%
5			N/A	78%

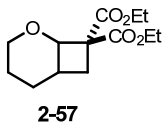
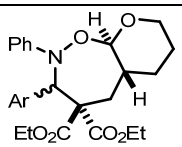
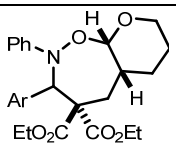
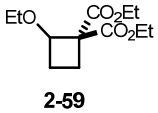
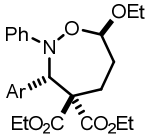
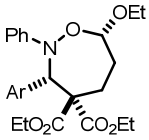
[a]Conditions: 0 °C, 15 min. [b]Conditions: 22 °C, reaction allowed to proceed until only a single product was observable by TLC. Entries 1, 2 and 5 were conducted by Cory Palmer.

Lastly, two additional cyclobutanes were subjected to the reaction conditions with several nitrones (Table 2.8). Pyran-fused cyclobutane **2-57** was found to react with nitrones to produce diastereomeric cycloadducts (Table 2.8, entries 1-3). Unlike the furan-fused examples, a mixture of three diastereomers was obtained that failed to coalesce to a single product. Ethoxy-substituted cyclobutane **2-59** also successfully formed the oxazepanes in good yield (entries 4 and 5), though a mixture of two

diastereomers was formed. The highly crystalline material of entry 5 allowed for the collection of single crystal X-ray data which permitted unambiguous assignment of the two diastereomers formed during the reaction.

Table 2.8. Alternative Cyclobutane Substitution for the (4 + 3) Cycloaddition



entry	cyclobutane	oxazepane (ratio)		yield
	 **2-57**	 **2-83a** to **2-83c**	 **2-84a** to **2-84c**	
1	Ar = C_6H_5	76:21	3	65%
2	Ar = *p*-C_6H_4OMe	56:21	23	51%
3	Ar = *p*-C_6H_4Cl	46:46	8	60%
	 **2-59**	 **2-85a**, **2-85b**	 **2-85a**, **2-85b**	
4	Ar = C_6H_5	79	21	85%
5	Ar = *p*-C_6H_4OMe	69	31	82%

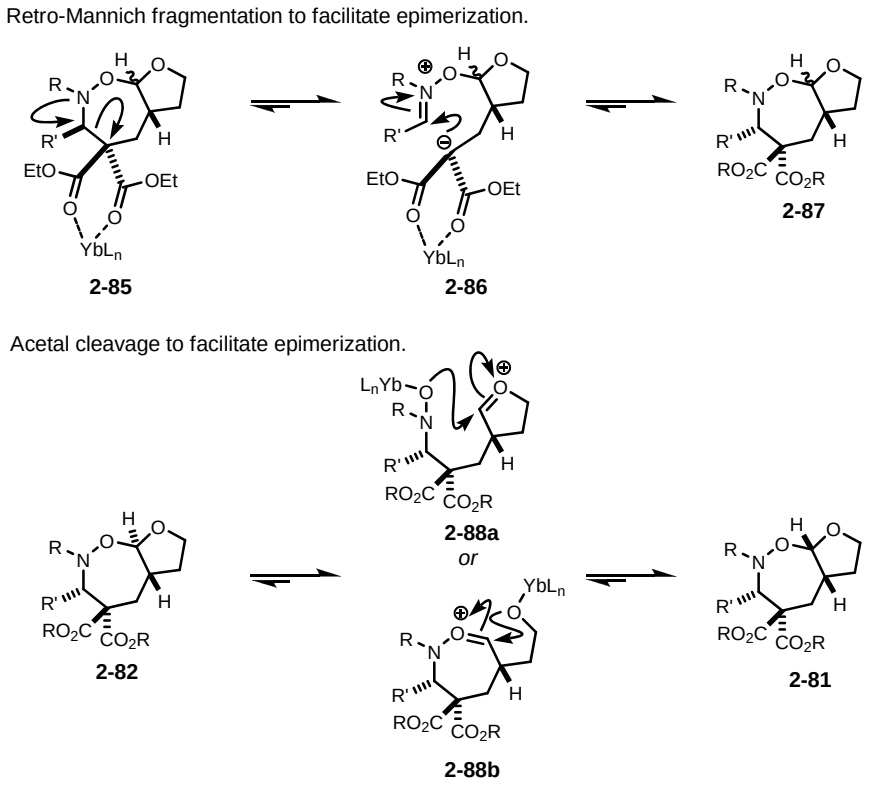
Entries 1-5 were conducted by Cory Palmer

Unlike the case of the (4 + 2) cycloaddition between DA cyclobutane and aldehydes, the (4 + 3) cycloaddition between DA cyclobutanes and nitrones occurs initially with poor selectivity. This result may indicate that a different mechanism is in operation, or that interception of the zwitterionic intermediate proposed in Scheme 2.17, mechanism C occurs with poor selectivity. Currently, it is believed that the nitrone intercepts zwitterion **2-80** with poor selectivity.

The mixture of diastereomers obtained during this study coalesced into a single *cis* diastereomer when fused with a tetrahydrofuran ring system. The mechanism for

epimerization at two of the chiral centers is presented in Scheme 2.19. The epimerization adjacent to the quaternary center occurs in a retro-Mannich fashion following coordination of the esters by the Yb catalyst. It can therefore easily be rationalized why electron-deficient substrates would require extended reaction times for complete conversion to a single diastereomer. Epimerization about the acetal position occurs through acetal cleavage facilitated by either of the two acetal oxygen atoms.

Scheme 2.19. Equilibration of Diastereomers



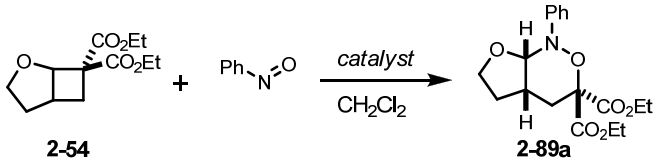
In conclusion, we have developed a formal (4 + 3) cycloaddition between alkoxy-activated cyclobutane dicarboxylates and nitrones to afford structurally unique 2,3,4,6,7-substituted oxazepanes. The reaction, in most cases, initially affords a diastereomeric mixture which equilibrates to a single diastereomer. To date, all nitrones examined successfully participated in the cycloaddition reaction.

2.3.3 Annulation of Alkoxy-Activated Donor-Acceptor Cyclobutanes and Nitrosoarenes

Having investigated nitrones, imines and aldehydes, further dipolarophiles candidates were sought after. Nitroso compounds have been utilized in a variety of transformations,[34] such as dienes in hetero-Diels–Alder cycloadditions[35] and enophiles in nitroso-ene chemistry.[36] The most intriguing reports originate in their dichotomous capacity to act as either nitrogen or oxygen transfer reagents in nitroso-aldol chemistry, which can be controlled by judicious catalyst choice.[37] Surprisingly, nitrosoarenens have yet to see application in dipolar cycloaddition chemistry with strained ring systems such as DA cyclopropanes or cyclobutanes.

Investigations into the reactivity of nitrosoarenes and DA cyclobutanes began with examination of the reaction between cyclobutane **2-54** and nitrosobenzene (Table 2.9). While a variety of Lewis acids were found to catalyze the reaction, maximal yields were obtained with $Yb(OTf)_3$. Additionally, decreasing the catalytic loading from 10 to 2 mol % dramatically increased product yield (compare entries 1 and 8).

Table 2.9. Catalyst Screening for the Cycloaddition Between DA Cyclobutanes and Nitrosoarenes



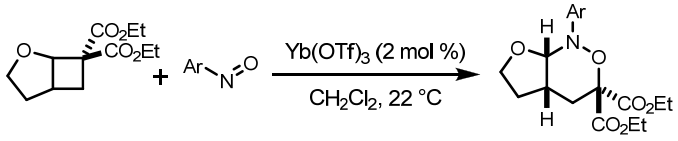
2-54 **2-89a**

entry	catalyst	mol %	yield (%)
1	$Yb(OTf)_3$	10	60
2	$Sc(OTf)_3$	10	55
3	$La(OTf)_3$	10	22
4	$Zn(OTf)_2$	10	61
5	$Pr(OTf)_3$	10	63
6	$Yb(OTf)_3$	5	72
7	$Sc(OTf)_3$	5	61
8	$Yb(OTf)_3$	2	92

Optimization conducted in conjunction with Tyler Schon.

With optimal conditions at hand, the scope of the cycloaddition was examined (Table 2.10). It was discovered that aryl halogen,[38] ester, or ketone substituents were tolerated (entries 2 – 5). Strong electron-withdrawing groups afforded moderate yields (entries 6 and 7); however, a second, inseparable compound was detected comprising up to 33% of the isolated mixture. Substrates with weakly electron-donating substituents resulted in a substantially decreased yield (entry 8) and upon addition of a strongly electron-donating group (entry 9), only trace quantities of product were detected. Substrates that could sequester the Lewis acid did not react (entry 12), and hydroxamic acid–derived nitroso compounds did not participate in the reaction, and only cyclobutane decomposition was observed (entry 13).

Table 2.10. Examination of Nitrosoarene Compatibility in the (4 + 2) Cycloaddition



2-54 **2-89a** to **2-89h**

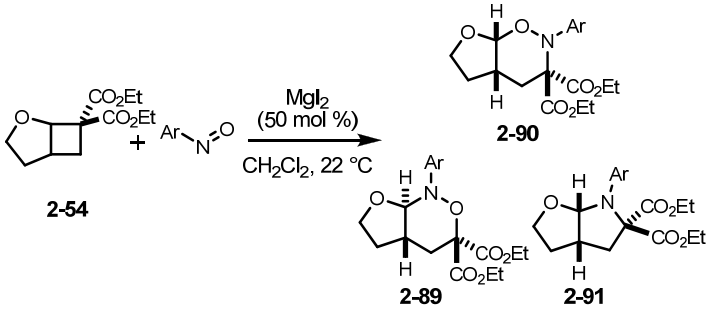
entry	nitrosoarene	regioselectivity	yield (%)
1	Ar = C_6H_5	>20:1	92
2	Ar = *p*-C_6H_4Br	>20:1	89
3	Ar = 2,4-$C_6H_3Br_2$	>20:1	47
4	Ar = *p*-$C_6H_4C(O)Me$	>20:1	69
5	Ar = *p*-$C_6H_4CO_2Et$	13:1	82
6	Ar = *p*-C_6H_4CN	3:1	61
7	Ar = *p*-$C_6H_4NO_2$	4:1	59
8	Ar = *p*-$C_6H_4CH_3$	>20:1	29
9	Ar = *p*-$C_6H_4OCH_3$	–	trace
10	Ar = *p*-$C_6H_4N(CH_3)_2$	–	–[a]
12	Ar = *o*-pyridine	–	–[a]
13	Ar = $C(O)C_6H_5$	–	–[b]

[a]No reaction. [b]Cyclobutane decomposition observed. Entries 4,7,8,9 were conducted by Tyler Schon.

A second Lewis acid catalyst screen was undertaken to improve reactivity with electron-rich nitrosoarenes and MgI_2 was found to facilitate the reaction of *para*-methoxy nitrosobenzene (Table 2.11, entry 1), though a complete reversal of regiochemistry

occurred (*vide infra*). Interestingly, when prolonged reaction times were used or when the isolated compound **2-90a** was exposed to MgI_2, deoxygenation occurred to afford pyrrolidine **2-91a**. The more electron-rich *para*-dimethylaminonitroso benzene (entry 2) afforded the pyrrolidine **2-91b** directly, and isolation of the tetrahydrooxazine was not possible. It was also found that MgI_2 could catalyze the reaction with 2-nitrosopyridine (entry 3) or electron-deficient nitrosoarenes (compare Table 2.11, entry 4 and Table 2.10, entry 6); however, only the tetrahydrooxazines with electron donating groups (i.e., Table 2.11, entry 1 and 2) could be converted to the corresponding pyrrolidines with MgI_2.

Table 2.11. MgI_2 Catalyzed (4 + 2) Cycloadditon of DA Cyclobutanes and Nitrosoarenes

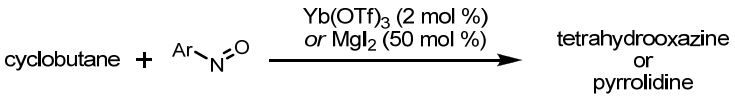


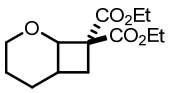
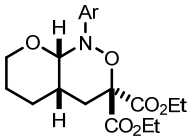
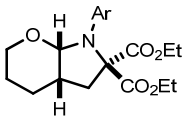
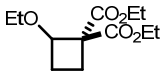
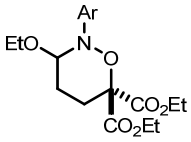
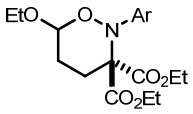
entry	nitrosoarene	product	yield (%)
1	Ar = $C_6H_4OCH_3$	**2-90a**	26
2	Ar = *p*-$C_6H_4N(Me)_2$	**2-91b**	21
3	Ar = *o*-pyridine	**2-90b**	28
4	Ar = *p*-C_6H_4CN	**2-90b**, **2-89i**	13, 22

Entries 1-4 conducted by Naresh Vemula.

Two additional alkoxy-activated cyclobutane dicarboxylates were investigated and found to display analogous reactivity with nitrosoarenes under $Yb(OTf)_3$ or MgI_2 conditions, though the reaction yields were rather poor (Table 2.12).

Table 2.12. Alternative Cyclobutanes in the (4 + 2) Cycloaddition with Nitrosoarenes



entry	cyclobutane	product yield	
		$Yb(OTf)_3$	MgI_2
	 **2-57**		
1	Ar = C_6H_5	**2-92**, 45%	-
2	Ar = *p*-C_6H_4OMe	-	**2-93**, 35%
3	Ar = *p*-$C_6H_4NMe_2$	-	**2-94**, 15%
	 **2-59**		
4	Ar = C_6H_5	**2-95**, 21%	-
5	Ar = *p*-C_6H_4OMe	-	**2-96**, 38%

Entries 1-5 conducted by Naresh Vemula.

The stereo- and regiochemistry of the tetrahydrooxazines and pyrrolidines were established by a combination of single crystal X-ray and NMR analyses. X-ray quality crystals of compound **2-89b** (Table 2.10, entry 2) and **2-93b** (Table 2.12, entry 2) were obtained and the ORTEP structures are depicted in Figure 2.6. The structures unambiguously establish both the regiochemistry of the cyclization and the relative stereochemistry at the ring fusion.

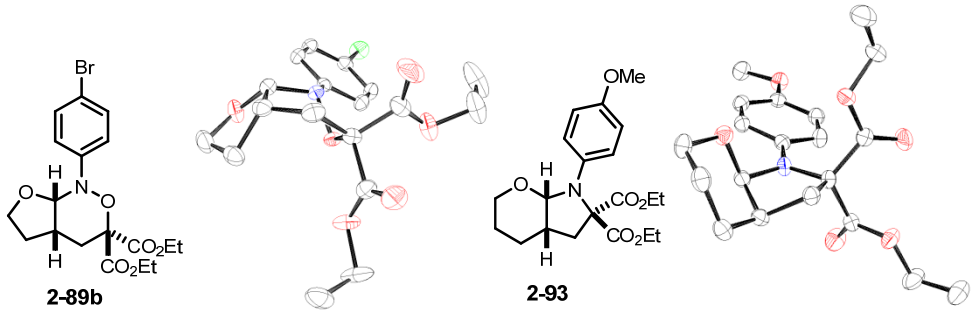


Figure 2.6. X-ray Crystal Structures of **2-89b** and **2-93**

While the structure of **2-89b** was firmly established by single crystal X-ray diffraction, we set out to identify the structures of the product mixtures formed with electron-deficient nitrosoarenes (Table 2.10, entries 5–7). The major product in each of the cases was found to have nOe and ^{15}N-^{1}H HMBCAD interactions that were consistent with those observed for **2-89b** (Figure 2.7). The minor component of the mixtures showed nOe interactions suggesting a *cis* ring fusion, and ^{15}N-^{1}H HMBCAD data indicated that a regioisomer, rather than a diastereomer, was formed.

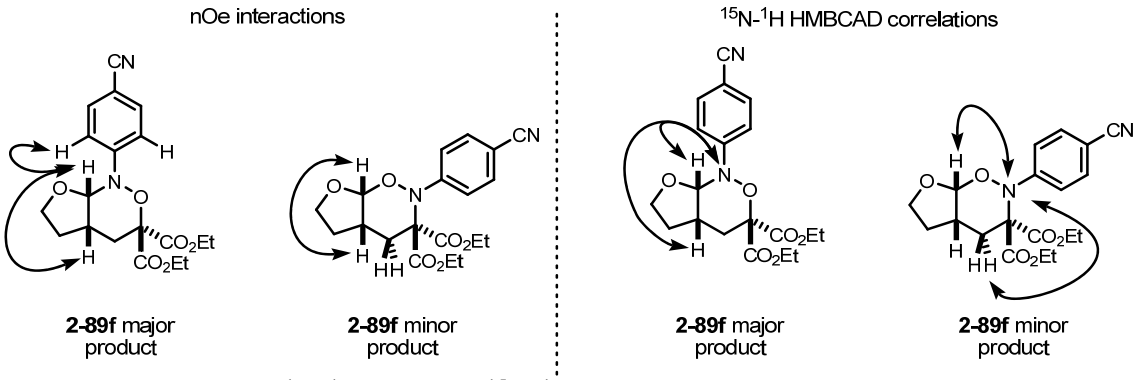
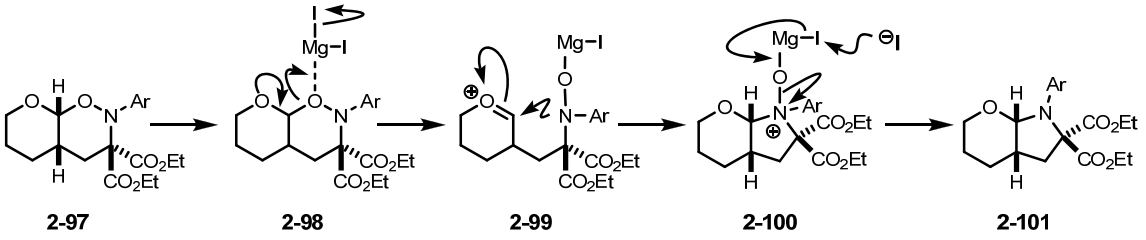


Figure 2.7. Key ^{1}H-^{1}H nOe and ^{15}N-^{1}H HMBCAD Correlations for Structural Determination of **2-89**

Once again, the mechanism of the transformation has not yet been intensively investigated, though it is currently believed to occur through a zwitterionic intermediate.

With regards to the formation of pyrrolidine products from the tetrahydrooxazines, a plausible mechanism is proposed in Scheme 2.20. A net reduction is occurring, and it is believed that MgI_2 is acting as the reductant in this case, as 50 mol % was required to effect the transformation. Following formation of the tetrahydrooxazine, coordination of oxygen by MgI_2 occurs (**2-98**). The acetal is cleaved and the resulting oxacarbenium ion is attacked by the pendant nitrogen atom (**2-99**). Finally, the initially displaced iodide reacts with the attached Lewis acid, causing the N-O bond reduction and producing I_2, MgO, and the pyrrolidine (**2-101**). Theoretically, one full equivalent of MgI_2 is required for the transformation; however, maximum yields were observed only for 50 mol % of MgI_2. Additionally, the fate of the I_2 in this reaction was not determined, as attempts to detect I_2 were not successful. The low yield of the process also proved troublesome, as decomposition occurs which convolutes the process of determining the operational mechanism.

Scheme 2.20. Mechanism of Pyrrolidine Formation



In conclusion, we have developed the first example of a dipolar cycloaddition between DA cyclobutanes and nitrosoarenes. The regiochemistry and stereochemistry of the cycloadducts has been determined by a combination of NMR and X-ray diffraction analyses. The reaction proceeds well with electron-deficient or neutral nitrosoarenes to form tetrahydrooxazines; however, other nitroso reagents are currently outside the scope

of this reaction. Though the cycloaddition of DA cyclobutanes and nitrosoarenes is a fascinating process, the poor yields even after extensive optimization studies leave much to be desired.

2.4 Conclusions

In summary, cycloadditions of alkoxy-activated cyclobutane dicarboxylates with aldehydes, nitrones, and nitrosoarenes have been developed. These processes facilitate rapid access to structurally intriguing heterocyclic frameworks in moderate to excellent yield. While a range of dipolarophile partners for annulation events have been reported, this reactivity pattern with cyclobutanes is only in its infancy and further exploration will surely prove a rich source of study. The mechanism for the high diastereoselectivity of the cycloadditions with aldehydes and nitrosoarenes has not yet been extensively investigated. Revelation of the mechanism will surely bring about new and intriguing opportunities for this field of chemistry. In addition, elaboration of these cycloaddition adducts remains to be explored which could prove invaluable in the synthesis of complex natural products.

2.5 Experimental

2.5.1 General Experimental Details

All reactions were run under an argon atmosphere. Flasks were oven dried and cooled in a dessicator prior to use. Solvents and reagents were purified by standard methods.[39] Dichloromethane and toluene were purified by passing the solvent through activated alumina columns. Aldehydes were distilled immediately prior to use. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions was monitored by thin layer chromatography performed on F254 silica gel plates. The plates were visualized by UV light (254 nm) or by staining with ceric ammonium molybdate,[40] or $KMnO_4$. Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[41]

The ^1H and ^{13}C NMR data were obtained on 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and were referenced to the residual chloroform at δ 7.25 ppm for ^1H spectra and the center peak of the triplet at δ 77.0 for ^{13}C spectra. EI mass spectra were obtained on a Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV.

Compounds **2-65d**, **2-65f**, **2-65j**, **2-65l** and **2-68a** to **2-68e** were prepared by others and are not included below.

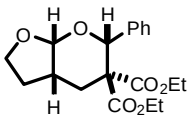
2.5.2 Experimental Details

2.5.2.1 Cycloadditions of Aldehydes and Cyclobutanes

General Procedure for the $Yb(OTf)_3$ Catalyzed Cycloaddition of Aldehydes and Cyclobutanes

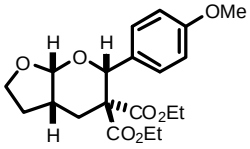
To a solution of $Yb(OTf)_3$ (26 mg, 0.042 mmol, 10 mol %) in CH_2Cl_2 (2 mL) at 0 °C was added aldehyde (0.45 mmol, 1.1 equiv) followed by cyclobutane (0.41 mmol, 1 equiv). After 15 min the reaction was flushed through a plug of SiO_2 and the solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc).

(3a*R,6*R**,7a*R**)-diethyl 6-phenyltetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65a)**



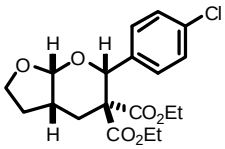
The title compound was prepared according to the general cycloaddition procedure to afford a pale yellow oil (111 mg, 78%). R_f 0.14 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.0 Hz, 2 H), 7.14 - 7.21 (m, 3 H), 5.41 (s, 1 H), 5.23 (d, *J* = 4.7 Hz, 1 H), 4.24 (dq, *J* = 7.1, 10.8 Hz, 1 H), 4.17 (dq, *J* = 7.2, 10.6 Hz, 1 H), 4.09 (td, *J* = 6.4, 8.5 Hz, 1 H), 3.91 (td, *J* = 3.5, 7.9 Hz, 1 H), 3.59 (dq, *J* = 7.2, 10.6 Hz, 1 H), 3.31 (dq, *J* = 7.1, 10.8 Hz, 1 H), 2.37 (dd, *J* = 11.7, 13.5 Hz, 1 H), 2.30 (dd, *J* = 5.9, 13.5 Hz, 1 H), 2.10 - 2.17 (m, 1 H), 2.03 - 2.10 (m, 1 H), 1.70 - 1.75 (m, 1 H), 1.20 (t, *J* = 7.3 Hz, 3 H), 0.77 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 169.2, 138.2, 128.0, 127.6, 127.4, 102.3, 75.6, 67.5, 61.9, 61.1, 59.3, 36.0, 31.4, 30.2, 14.0, 13.4; HRMS *m/z* 348.1583 (calcd for $C_{19}H_{24}O_6$, 348.1573).

(3a*R,6*R**,7a*R**)-diethyl 6-(4-methoxyphenyl)tetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65b)**



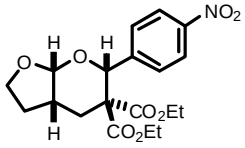
The title compound was prepared according to the general cycloaddition procedure to afford a viscous colorless oil (150 mg, 80%). R_f 0.14 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 5.44 (s, 1 H), 5.28 (d, *J* = 4.7 Hz, 1 H), 4.19 - 4.36 (m, 2 H), 4.11 - 4.19 (m, 1 H), 3.96 (td, *J* = 3.9, 8.0 Hz, 1 H), 3.76 (s, 3 H), 3.70 (dq, *J* = 7.1, 10.8 Hz, 1 H), 3.44 (dq, *J* = 7.3, 10.6 Hz, 1 H), 2.33 - 2.45 (m, 2 H), 2.09 - 2.24 (m, 2 H), 1.74 - 1.84 (m, 1 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 169.2, 159.2, 130.4, 128.5, 112.9, 102.2, 75.2, 67.4, 61.8, 61.1, 59.2, 55.2, 36.0, 31.3, 30.1, 14.0, 13.5; HRMS *m/z* 378.1689 (calcd for $C_{20}H_{26}O_7$, 378.1679).

(3a*R,6*R**,7a*R**)-diethyl 6-(4-chlorophenyl)tetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65c)**



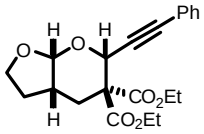
The title compound was prepared according to the general cycloaddition procedure to afford a colorless oil (140 mg, 89%). R_f 0.14 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 5.42 (s, 1 H), 5.28 (d, *J* = 4.7 Hz, 1 H), 4.31 (dq, *J* = 10.5, 7.6 Hz, 1 H), 4.224 (dq, *J* = 10.5, 7.3 Hz, 1 H), 4.15 (td, *J* = 8.5, 6.4 Hz, 1 H), 3.98 (ddd, *J* = 7.6, 7.6, 3.8 Hz, 1 H), 3.73 (dq, *J* = 11.1, 7.6 Hz, 1 H), 3.49 (dq, *J* = 10.5, 7.0 Hz, 1 H), 2.40 (dq, *J* = 11.1, 13.5 Hz, 2 H), 2.17 - 2.24 (m, 1 H), 2.11 - 2.17 (m, 1 H), 1.78 - 1.83 (m, 1 H), 1.27 (t, *J* = 7.3 Hz, 3 H), 0.90 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 169.0, 136.8, 133.7, 128.8, 127.7, 102.4, 75.0, 67.5, 62.0, 61.3, 59.2, 36.0, 31.2, 30.2, 14.0, 13.5; HRMS *m/z* 382.1171 (calcd for $C_{19}H_{23}ClO_6$, 382.1183).

(3a*R,6*R**,7a*R**)-diethyl 6-(4-nitrophenyl)tetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65e)**



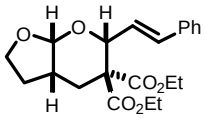
The title compound was prepared according to the general cycloaddition procedure to afford a white solid (121 mg, 75%). R_f 0.21 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.0 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 2 H), 5.48 (s, 1 H), 5.30 (d, *J* = 5.1 Hz, 1 H), 4.23 - 4.37 (m, 2 H), 4.14 - 4.23 (m, 1 H), 4.01 (ddd, *J* = 7.8, 7.8, 4.3 Hz, 1 H), 3.74 (dq, *J* = 7.1, 10.8 Hz, 1 H), 3.51 (dq, *J* = 7.2, 10.8 Hz, 1 H), 2.39 - 2.54 (m, 2 H), 2.21 - 2.32 (m, 1 H), 2.08 - 2.20 (m, 1 H), 1.79 - 1.89 (m, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 168.7, 147.5, 145.6, 128.3, 122.7, 102.7, 74.9, 67.7, 62.2, 61.4, 59.1, 35.9, 30.8, 30.4, 14.0, 13.5; HRMS *m/z* 393.1419 (calcd for $C_{19}H_{23}NO_8$, 393.1424).

(3a*R,6*R**,7a*R**)-diethyl 6-(phenylethynyl)tetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65g)**



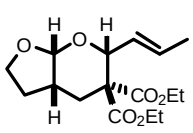
The title compound was prepared according to the general cycloaddition procedure to afford a pale yellow oil (80 mg, 62%). R_f 0.14 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.6, 1.8 Hz, 2 H), 7.22 - 7.24 (m, 2 H), 7.19 - 7.22 (m, 1 H), 5.31 (s, 1 H), 5.24 (d, *J* = 4.7 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 4.16 (qd, *J* = 7.2, 1.8 Hz, 2 H), 4.07 (td, *J* = 8.6, 6.7 Hz, 1 H), 3.83 (td, *J* = 8.2, 3.5 Hz, 1 H), 2.41 (dd, *J* = 14.1, 6.4 Hz, 1 H), 2.28 (dd, *J* = 13.8, 10.2 Hz, 1 H), 2.15 - 2.22 (m, 1 H), 1.99 - 2.09 (m, 1 H), 1.71 - 1.76 (m, 1 H), 1.22 (t, *J* = 7.3 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 168.0, 131.7, 128.4, 128.2, 122.4, 101.2, 86.0, 85.0, 66.3, 64.4, 62.1, 61.9, 56.9, 33.6, 30.6, 27.1, 14.0, 13.9; HRMS *m/z* 372.1570 (calcd for $C_{21}H_{24}O_6$, 372.1573).

(3a*R,6*R**,7a*R**)-diethyl 6-styryltetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65h)**



The title compound was prepared according to the general cycloaddition procedure to afford a viscous colorless oil (133 mg, 87%). R_f 0.20 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 - 7.38 (m, 5 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.47 (dd, *J* = 16.0, 7.4 Hz, 1 H), 5.25 (d, *J* = 4.3 Hz, 1 H), 4.71 (dd, *J* = 7.0, 0.8 Hz, 1 H), 4.09 - 4.26 (m, 5 H), 3.86 - 3.94 (m, 1 H), 2.50 (dq, *J* = 7.0, 14.5 Hz, 2 H), 2.17 - 2.27 (m, 1 H), 1.96 - 2.06 (m, 1 H), 1.87 (dq, *J* =12.1, 7.8 Hz, 1 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.3, 136.6, 132.6, 128.4, 127.7, 126.6, 125.8, 102.0, 76.5, 67.7, 61.8, 61.4, 57.1, 36.0, 29.8, 28.8, 14.0, 14.0; HRMS *m/z* 374.1727 (calcd for $C_{21}H_{26}O_6$, 374.1729).

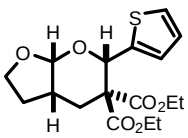
(3a*R,6*R**,7a*R**)-diethyl 6-((*E*)-prop-1-enyl)tetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65i)**



The title compound was prepared according to the general cycloaddition procedure to afford a colorless oil (65 mg, 51%). R_f 0.14 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 - 5.83 (m, 2 H),

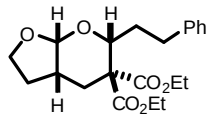
5.18 (d, *J* = 4.3 Hz, 1 H), 4.51 (d, *J* = 7.4 Hz, 1 H), 4.12 - 4.28 (m, 4 H), 4.08 (td, *J* = 8.0, 5.9 Hz, 1 H), 3.86 (td, *J* = 7.9, 6.4 Hz, 1 H), 2.40 (dd, *J* = 6.8, 4.1 Hz, 2 H), 2.09 - 2.19 (m, 1 H), 1.93 - 2.05 (m, 1 H), 1.73 - 1.83 (m, 1 H), 1.67 (d, *J* = 5.5 Hz, 3 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.3, 130.1, 127.3, 101.7, 76.5, 67.4, 61.7, 61.2, 56.8, 35.8, 29.5, 29.0, 17.7, 14.02, 13.99; LRMS 312.1 (calcd for $C_{16}H_{24}O_6$, 312.1).

(3a*R,6*S**,7a*R**)-diethyl 6-(thiophen-2-yl)tetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65k)**



The title compound was prepared according to the general cycloaddition procedure to afford a yellow oil (100 mg, 69%). R_f 0.15 (4:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.3, 1.2 Hz, 1 H), 6.99 (d, *J* = 3.5 Hz, 1 H), 6.90 (dd, *J* = 5.3, 3.5 Hz, 1 H), 5.75 (s, 1 H), 5.30 (d, *J* = 5.3 Hz, 1 H), 4.31 (dq, *J* = 7.0, 10.5 Hz, 1 H), 4.24 (dd, *J* = 7.0, 10.5 Hz, 1 H), 4.12 - 4.18 (m, 1 H), 3.95 (td, *J* = 4.7, 8.2 Hz, 1 H), 3.86 (dq, *J* = 7.1, 10.8 Hz, 1 H), 3.71 (dq, *J* = 7.2, 10.6 Hz, 1 H), 2.44 (d, *J* = 8.2 Hz, 2 H), 2.18 - 2.25 (m, 1 H), 2.08 - 2.16 (m, 1 H), 1.84 (ddt *J* = 11.9, 7.0, 4.9 Hz, 1 H), 1.28 (t, *J* = 7.6 Hz, 4 H), 1.00 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 168.7, 140.8, 125.8, 125.7, 125.0, 101.9, 72.8, 67.6, 62.0, 61.4, 59.0, 36.3, 30.7, 29.7, 14.0, 13.6; HRMS *m/z* 354.1145 (calcd for $C_{17}H_{22}O_6S$, 354.1137).

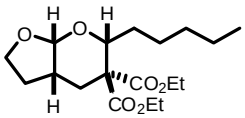
(3a*R,6*R**,7a*R**)-diethyl 6-phenethyltetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65m)**



The title compound was prepared according to the general cycloaddition procedure to afford a colorless oil (105 mg, 68%). R_f 0.25 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 - 7.23 (m, 2 H), 7.08 - 7.14 (m, 3 H), 5.02 (d, *J* = 4.3 Hz, 1 H), 4.00 - 4.16 (m, 5 H), 3.74 - 3.82 (m, 2 H), 2.89 (ddd, *J* = 13.8, 9.5, 4.5 Hz, 1 H), 2.57 (ddd, *J* = 13.7, 9.0, 7.8 Hz, 1 H), 2.42 (dd, *J* = 14.1, 6.6 Hz, 1 H), 2.13 - 2.27 (m, 2 H), 2.04 - 2.12 (m, 1 H), 1.77 - 1.93 (m, 2 H), 1.67 - 1.77 (m, 1 H), 1.18 (t, *J* = 7.0 Hz, 3 H), 1.14 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 169.7, 141.7, 128.6, 128.2, 125.7, 102.6, 74.7, 67.6,

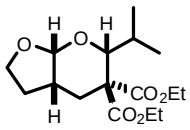
61.6, 61.3, 56.2, 35.9, 33.2, 32.7, 30.3, 28.8, 13.94, 13.93; HRMS *m/z* 376.1880 (calcd for $C_{21}H_{28}O_6$, 376.1886).

(3a*R,6*R**,7a*R**)-diethyl 6-pentyltetrahydro-2*H*-furo[2,3-*b*]pyran-5,5(3*H*)-dicarboxylate (2-65n)**



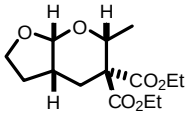
The title compound was prepared according to the general cycloaddition procedure to afford a pale yellow oil (68 mg, 56%). R_f 0.28 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.11 (d, *J* = 4.1 Hz, 1 H), 4.17 - 4.26 (m, 4 H), 4.08 (td, *J* = 7.9, 5.9 Hz, 1 H), 3.82 - 3.89 (m, 2 H), 2.49 (dd, *J* = 14.1, 7.0 Hz, 1 H), 2.32 (dd, *J* = 14.1, 5.9 Hz, 1 H), 2.12 - 2.18 (m, 1 H), 1.91 - 1.98 (m, 1 H), 1.83 - 1.90 (m, 2 H), 1.58 - 1.66 (m, 1 H), 1.44 - 1.51 (m, 1 H), 1.23 - 1.34 (m, 11 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 169.9, 102.6, 75.8, 67.6, 61.6, 61.3, 56.4, 36.0, 31.8, 31.6, 30.5, 28.9, 26.6, 22.6, 14.1, 13.99, 13.98; HRMS *m/z* 342.2042 (calcd for $C_{18}H_{30}O_6$, 342.2042).

(3a*R,6*R**,7a*R**)-diethyl 6-isopropyltetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65o)**



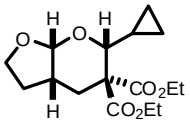
The title compound was prepared according to the general cycloaddition procedure to afford a yellow oil (85 mg, 58%). R_f 0.29 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.10 (d, *J* = 4.7 Hz, 1 H), 4.14 - 4.29 (m, 5 H), 4.07 (dd, *J* = 14.6, 7.6 Hz, 1 H), 3.83 - 3.88 (m, 2 H), 2.46 (dd, *J* = 13.5, 7.6 Hz, 1 H), 2.30 (dd, *J* = 13.8, 6.1 Hz, 1 H), 2.19 (sxt, *J* = 6.4 Hz, 1 H), 2.08 - 2.14 (m, 1 H), 1.93 - 2.00 (m, 1 H), 1.78 - 1.85 (m, 1 H), 1.29 (t, *J* = 7.4 Hz, 3 H), 1.27 (t, *J* = 7.4 Hz, 3 H), 0.97 (d, *J* = 5.3 Hz, 3 H), 0.98 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.1, 102.6, 79.8, 67.8, 61.7, 61.4, 56.3, 36.3, 31.9, 30.9, 29.5, 20.6, 18.3, 13.92, 13.90; HRMS *m/z* 314.1730 (calcd for $C_{15}H_{24}O_6$, 314.1729).

(3a*R,6*R**,7a*R**)-diethyl 6-methyltetrahydro-2*H*-furo[2,3-*b*]pyran-5,5(3*H*)-dicarboxylate (2-65p)**



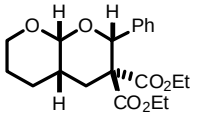
The title compound was prepared according to the general cycloaddition procedure to afford a yellow oil (61 mg, 51%). R_f 0.20 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (d, *J* = 4.3 Hz, 1 H), 4.15 - 4.25 (m, 5 H), 4.05 (q, *J* = 7.8 Hz, 1 H), 3.84 (q, *J* = 7.4 Hz, 1 H), 2.38 (dd, *J* = 14.1, 7.4 Hz, 1 H), 2.30 (dd, *J* = 14.1, 6.2 Hz, 1 H), 2.07 - 2.16 (m, 1 H), 1.91 - 2.00 (m, 1 H), 1.78 - 1.86 (m, 1 H), 1.34 (d, *J* = 6.6, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 169.7, 102.0, 71.0, 67.5, 61.7, 61.3, 56.3, 35.9, 29.9, 29.7, 29.2, 17.8, 14.0; HRMS *m/z* 287.1503 (calcd for $C_{14}H_{22}O_6$ + H^+, 287.1489).

(3a*R,6*R**,7a*R**)-diethyl 6-cyclopropyltetrahydro-2*H*-furo[2,3-b]pyran-5,5(3*H*)-dicarboxylate (2-65q)**



The title compound was prepared according to the general cycloaddition procedure to afford a yellow oil (107, 72%). R_f 0.21 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, *J* = 4.3 Hz, 1 H), 4.14 - 4.28 (m, 4 H), 4.09 (td, *J* = 8.0, 6.6 Hz, 1 H), 3.86 (td, *J* = 8.0, 5.9 Hz, 1 H), 3.29 (d, *J* = 9.8 Hz, 1 H), 2.40 (d, *J* = 7.0 Hz, 2 H), 2.05 - 2.14 (m, 1 H), 1.94 - 2.04 (m, 1 H), 1.69 - 1.79 (m, 1 H), 1.35 - 1.45 (m, 1 H), 1.28 (t, *J* = 7.2 Hz, 6 H), 0.57 - 0.65 (m, 1 H), 0.37 - 0.48 (m, 2 H), 0.21 - 0.28 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 169.7, 101.9, 79.5, 67.3, 61.7, 61.2, 56.7, 35.9, 30.0, 29.3, 14.0, 14.0, 12.7, 3.8, 3.7; HRMS *m/z* 312.1581 (calcd for $C_{16}H_{24}O_6$, 312.1573).

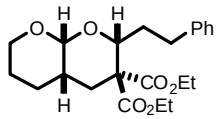
(2*R,4a*S**,8a*R**)-diethyl 2-phenylhexahydropyrano[2,3-b]pyran-3,3(2*H*)-dicarboxylate (2-66a)**



The title compound was prepared according to the general cycloaddition procedure to afford a colorless oil (92 mg, 60%). R_f 0.33 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.42 (m, 2 H), 7.16 - 7.26 (m, 3 H), 5.00 (d, *J* = 2.3 Hz, 1 H), 5.00 (s, 1 H), 4.09 - 4.20 (m, 1 H), 4.01 - 4.09 (m, 1 H), 3.88 - 4.01 (m, 3 H), 3.64 - 3.70 (m, 1 H), 2.57 (dd, *J* = 14.2, 3.7 Hz, 1 H),

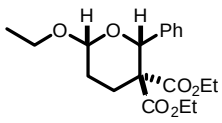
2.47 (dd, *J* = 14.4, 5.1 Hz, 1 H), 1.90 - 1.98 (m, 1 H), 1.69 - 1.81 (m, 1 H), 1.50 - 1.63 (m, 3 H), 1.10 (t, *J* = 7.0 Hz, 3 H), 1.02 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 169.4, 138.5, 127.5, 127.4, 127.1, 99.2, 80.8, 62.5, 61.8, 60.7, 56.9, 35.2, 33.0, 24.9, 24.0, 13.8, 13.7; HRMS *m/z* 362.1729 (calcd for $C_{20}H_{26}O_6$, 362.1729).

(2*R,4a*S**,8a*R**)-diethyl 2-phenethylhexahydropyrano[2,3-b]pyran-3,3(2*H*)-dicarboxylate (2-66b)**



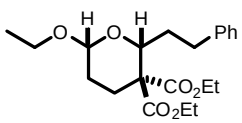
The title compound was prepared according to the general cycloaddition procedure to afford a colorless oil (94 mg, 62%). R_f 0.31 (4:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 - 7.29 (m, 2 H), 7.15 - 7.21 (m, 3 H), 4.83 (d, *J* = 2.9 Hz, 1 H), 4.13 - 4.21 (m, 5 H), 3.94 - 3.98 (m, 1 H), 3.51 - 3.55 (m, 1 H), 3.05 (ddd, *J* = 13.6, 9.5, 4.4 Hz, 1 H), 2.63 (ddd, *J* = 13.6, 9.5, 6.7 Hz, 1 H), 2.52 - 2.57 (m, 1 H), 2.50 (dd, *J* = 14.1, 8.8 Hz, 1 H), 2.11 (dd, *J* = 13.8, 4.4 Hz, 1 H), 1.73 - 1.78 (m, 1 H), 1.62 - 1.70 (m, 3 H), 1.58 (br. s., 1 H), 1.45 - 1.52 (m, 1 H), 1.40 - 1.45 (m, 1 H), 1.25 - 1.30 (m, 1 H), 1.22 (t, *J* = 7.3 Hz, 3 H), 1.23 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.4, 142.3, 128.6, 128.2, 125.6, 98.4, 75.7, 64.9, 61.7, 61.2, 56.9, 33.8, 32.7, 32.3, 28.7, 26.0, 22.5, 14.0, 13.9; HRMS *m/z* 390.2037 (calcd for $C_{22}H_{30}O_6$ 390.2042).

(2*R,6*R**)-diethyl 6-ethoxy-2-phenyldihydro-2*H*-pyran-3,3(4*H*)-dicarboxylate (2-67a)**



The title compound was prepared according to the general cycloaddition procedure to afford a colorless oil (75 mg, 72%). R_f 0.33 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.47 (m, 2 H), 7.24 - 7.31 (m, 3 H), 5.10 (s, 1 H), 4.70 (dd, *J* = 9.4, 2.3 Hz, 1 H), 4.11 - 4.19 (m, 2 H), 4.00 - 4.08 (m, 1 H), 3.87 - 3.98 (m, 2 H), 3.53 (dq, *J* = 9.7, 7.1 Hz, 1 H), 2.62 (dt, *J* = 13.7, 4.3 Hz, 1 H), 2.15 (td, *J* = 13.4, 4.5 Hz, 1 H), 1.97 (tdd, *J* = 13.2, 9.2, 4.3 Hz, 1 H), 1.82 - 1.89 (m, 1 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.16 (t, *J* = 7.0 Hz, 3 H), 0.96 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 168.3, 139.2, 127.4, 127.3, 127.2, 102.5, 79.4, 64.4, 61.4, 60.7, 58.5, 31.1, 27.9, 15.1, 13.9, 13.5; HRMS *m/z* 350.1654 (calcd for $C_{19}H_{26}O_6$ 350.1729).

(2*R,6*R**)-diethyl 6-ethoxy-2-phenethyldihydro-2*H*-pyran-3,3(4*H*)-dicarboxylate (2-67b)**



The title compound was prepared according to the general cycloaddition procedure to afford a colorless oil (79 mg, 70%). R_f 0.30 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 - 7.28 (m, 5 H), 4.41 (d, *J* = 9.4 Hz, 1 H), 4.03 - 4.27 (m, 4 H), 3.90 - 4.01 (m, 1 H), 3.74 (d, *J* = 10.2 Hz, 1 H), 3.40 - 3.54 (m, 1 H), 2.83 - 2.97 (m, 1 H), 2.49 - 2.70 (m, 1 H), 2.42 - 2.49 (m, 1 H), 2.10 - 2.33 (m, 1 H), 1.91 - 2.03 (m, 1 H), 1.67 - 1.91 (m, 2 H), 1.44 - 1.67 (m, 2 H), 1.11 - 1.28 (m, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 168.7, 141.8, 128.5, 128.3, 125.8, 102.4, 78.0, 70.7, 64.5, 61.3, 61.1, 56.2, 33.7, 33.5, 33.4, 33.1, 30.7, 28.1, 15.1, 14.0, 13.9; HRMS *m/z* 377.1962 (calcd for $C_{21}H_{30}O_6$-H 377.1964).

2.5.2.2 Cycloadditions of Nitrones and Cyclobutanes

All nitrones were prepared according to the following methods: a) Gautheron-Chapoulaud, V.; Pandya, S. U.; Cividino, P.; Masson, G.; Py, S.; Vallee, Y. *Synlett,* **2001**, 1281. b) Lo, M. M.-C.;Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572-4573.

Compounds **2-81k**, **2-81l**, **2-81m**, **2-81p**, **2-83a** to **2-83c**, **2-85a** and **2-85b** were prepared by Cory Palmer and are not included below.

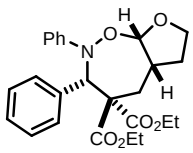
General Cycloaddition Procedure for the Formation of a Single Diastereomer:

To a mixture of nitrone (0.30 mmol, 1.0 equiv), $Yb(OTf)_3$ (9.0 mg, 0.015 mmol, 0.05 equiv) and 4 Å molecular sieves (1.0 g) in CH_2Cl_2 (2 mL) at room temperature was added cyclobutane (0.36 mmol, 1.2 equiv). Following convergence of the products to a single diastereomer (as indicated by TLC) the reaction mixture was layered directly onto a SiO_2 column and eluted with EtOAc/hexanes to afford the *cis* oxazepane compounds.

General Cycloaddition Procedure for the Formation of a Diastereomeric Mixture:

To a mixture of nitrone (0.30 mmol, 1.0 equiv), $Yb(OTf)_3$ (9.0 mg, 0.015 mmol, 0.05 equiv) and 4 Å molecular sieves (1.0 g) in CH_2Cl_2 (2 mL) at 0 °C was added cyclobutane (0.36 mmol, 1.2 equiv). Following consumption of the cyclobutane the reaction mixture was layered directly onto a SiO_2 column and eluted with hexanes/EtOAc to afford the oxazepane product as a mixture of *cis* and *trans* isomers.

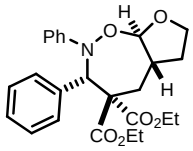
Compound 2-81a, *cis* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a pale yellow oil (100 mg, 76%). R_f 0.60 (33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 5.9 Hz, 2 H), 7.08 - 7.22 (m, 7 H), 6.85 (t, *J* = 6.7 Hz, 1 H), 5.58 (s, 1 H), 5.36 (d, *J* = 5.3 Hz, 1 H), 4.35 - 4.41 (m, 1 H), 4.29 - 4.35 (m, 1 H), 4.21 - 4.27 (m, 1 H), 3.99 (td, *J* = 2.3, 7.9 Hz, 1 H), 3.83 (dq, *J* = 7.1, 11.1 Hz, 1 H), 3.72 (dq, *J* = 7.2, 10.6 Hz, 1 H), 2.94 - 3.00 (m, 1 H), 2.60 - 2.66 (m, 1 H), 2.46 (dd, *J* = 2.9, 14.6 Hz, 1 H), 2.23 - 2.32 (m, 1 H), 1.81 - 1.87 (m, 1 H), 1.32 (t, *J* = 7.3 Hz, 3 H), 0.94 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.8,

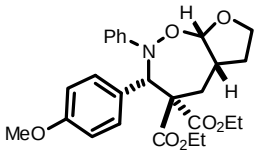
149.2, 134.5, 130.7, 128.6, 128.2, 127.8, 122.0, 116.8, 108.5, 70.4, 68.1, 62.0, 61.9, 61.6, 40.4, 34.2, 31.8, 14.2, 13.6; HRMS *m/z* 439.1993(calcd for $C_{25}H_{29}NO_6$, 439.1995).

Compound 2-81a, *trans* diastereomer



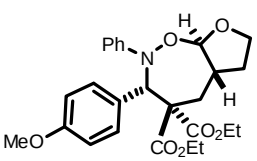
The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture, affording an inseparable mixture of *cis* and *trans* isomers (120 mg, 91%, *cis*:*trans* 31:61). R_f 0.60 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) Identifiable, distinguishable, and diagnostic peaks for the *trans* diastereomer: 5.90 (s, 1 H), 5.17 (d, *J* = 7.8 Hz, 1 H). See spectra.

Compound 2-81b, *cis* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a white solid (100 mg, 74%). R_f 0.24 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.36 (m, 2 H), 7.13 - 7.22 (m, 4 H), 6.83 - 6.89 (m, 1 H), 6.63 - 6.69 (m, 2 H), 5.52 (s, 1 H), 5.36 (d, *J* = 5.1 Hz, 1 H), 4.27 - 4.43 (m, 2 H), 4.18 - 4.27 (m, 1 H), 3.99 (td, *J* = 2.3, 8.2 Hz, 1 H), 3.82 - 3.91 (m, 1 H), 3.70 - 3.78 (m, 1 H), 3.69 (s, 3 H), 2.95 (dd, *J* = 14.1, 14.1 Hz, 1 H), 2.56 - 2.66 (m, 1 H), 2.43 (dd, *J* = 2.7, 14.5 Hz, 1 H), 2.20 - 2.32 (m, 1 H), 1.81 - 1.81 (m, 1 H), 1.32 (t, *J* = 7.0 Hz, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.9, 159.2, 149.3, 131.8, 128.6, 126.6, 122.0, 116.8, 113.1, 108.4, 69.9, 68.0, 62.1, 61.8, 61.6, 55.0, 40.4, 34.2, 31.7, 14.2, 13.7; HRMS *m/z* 469.2107 (calcd for $C_{26}H_{31}NO_7$, 469.2101).

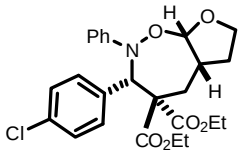
Compound 2-81b, *trans* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture to afford a mixture of separable *cis* and *trans* isomers (124 mg, 88%, *cis*:*trans* 37:63). R_f 0.21 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.8 Hz, 2 H), 7.16 - 7.25 (m, 2 H), 7.03 - 7.10 (m, 2 H),

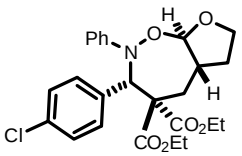
6.91 (t, *J* = 7.2 Hz, 1 H), 6.65 - 6.71 (m, 2 H), 5.83 (s, 1 H), 5.17 (d, *J* = 7.8 Hz, 1 H), 4.33 (qq, *J* = 7.0, 10.6 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.73 - 3.84 (m, 2 H), 3.71 (s, 3 H), 2.84 (d, *J* = 14.9 Hz, 1 H), 2.74 - 2.83 (m, 1 H), 2.66 (dd, *J* = 10.9, 14.9 Hz, 1 H), 1.85 - 2.03 (m, 2 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 0.83 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 168.4, 159.2, 150.4, 131.5, 128.5, 125.6, 121.9, 116.8, 112.8, 111.7, 73.4, 66.0, 62.2, 61.6, 61.5, 55.0, 37.2, 29.0, 28.1, 14.1, 13.5.

Compound 2-81c, *cis* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a highly crystalline colorless solid (104 mg, 73%), R_f 0.40 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.6 Hz, 2 H), 7.16 - 7.21 (m, 4 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 6.86 - 6.92 (m, 1 H), 5.55 (s, 1 H), 5.36 (d, *J* = 5.5 Hz, 1 H), 4.36 - 4.44 (m, 1 H), 4.29 - 4.36 (m, 1 H), 4.18 - 4.25 (m, 1 H), 4.03 (dt, *J* = 2.2, 8.1 Hz, 1 H), 3.89 (dq, *J* = 7.2, 10.8 Hz, 1 H), 3.75 (dq, *J* = 7.1, 10.8 Hz, 1 H), 2.91 (dd, *J* = 12.9, 14.5 Hz, 1 H), 2.58 - 2.69 (m, 1 H), 2.46 (dd, *J* = 2.7, 14.8 Hz, 1 H), 2.23 - 2.34 (m, 1 H), 1.88 - 1.83 (m,1 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.7, 149.0, 134.2, 133.0, 131.9, 128.7, 128.0, 122.3, 116.9, 108.5, 70.0, 68.1, 62.0, 61.9, 61.8, 40.4, 34.1, 31.7, 14.2, 13.7; HRMS *m/z* 473.1607 (calcd for $C_{25}H_{28}ClNO_6$, 473.1605).

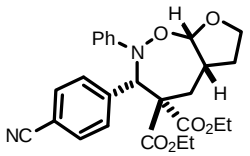
Compound 2-81c, *trans* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture to afford a mixture of separable *cis* and *trans* isomers (117 mg, 82%, *cis*:*trans* 29:71). R_f 0.36 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.4 Hz, 2 H), 7.19 - 7.25 (m, 2 H), 7.08 - 7.17 (m, 2 H), 7.01 - 7.06 (m, 2 H), 6.92 (t, *J* = 7.4 Hz, 1 H), 5.83 (s, 1 H), 5.13 (d, *J* = 7.8 Hz, 1 H), 4.25 - 4.39 (m, 2 H), 3.95 - 4.11 (m, 2 H), 3.70 - 3.85 (m, 2 H), 2.88 (d, *J* = 14.8 Hz, 1 H), 2.75 - 2.84 (m, 1 H), 2.64 (dd, *J* = 11.3, 14.9 Hz, 1 H), 1.82 - 1.99 (m, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 0.82 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.2,

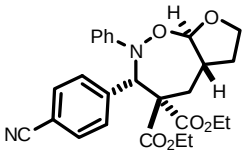
150.1, 134.1, 131.8, 131.5, 128.6, 127.7, 122.3, 116.9, 111.6, 73.5, 66.1, 62.4, 61.7, 61.2, 37.1, 29.1, 28.0, 14.1, 13.5.

Compound 2-81d, *cis* diastereomer



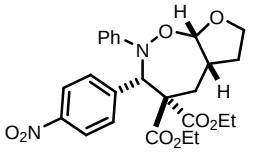
The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a white solid (106 mg, 76%). R_f 0.42 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.52 (m, 2 H), 7.42 - 7.47 (m, 2 H), 7.12 - 7.21 (m, 4 H), 6.87 - 6.92 (m, 1 H), 5.61 (s, 1 H), 5.36 (d, *J* = 5.5 Hz, 1 H), 4.28 - 4.44 (m, 2 H), 4.22 (ddd, *J* = 5.3, 8.4, 10.6 Hz, 1 H), 4.01 (td, *J* = 2.1, 8.1 Hz, 1 H), 3.86 (dq, *J* = 7.2, 10.8 Hz, 1 H), 3.74 (dq, *J* = 7.1, 10.9 Hz, 1 H), 2.88 (dd, *J* = 12.9, 14.5 Hz, 1 H), 2.57 - 2.68 (m, 1 H), 2.48 (dd, *J* = 2.7, 14.5 Hz, 1 H), 2.22 - 2.34 (m, 1 H), 1.82 - 186 (m, , 1 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 0.94 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.4, 148.7, 139.8, 131.5, 131.3, 128.8, 122.7, 118.5, 116.9, 112.1, 108.6, 70.4, 68.1, 62.2, 61.9, 61.6, 40.3, 34.1, 31.9, 14.1, 13.6; HRMS *m/z* 464.1929 (calcd for $C_{26}H_{28}N_2O_6$, 464.1947).

Compound 2-81d, *trans* diastereomer



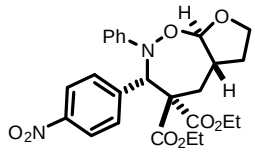
The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture to afford a mixture of separable *cis*, *trans*, and a third isomer (132 mg, 95%, *cis*:*trans*:*3rd* 15:57:27). R_f 0.30 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 6.95 (t, *J* = 7.2 Hz, 1 H), 5.91 (s, 1 H), 5.12 (d, *J* = 8.2 Hz, 1 H), 4.30 - 4.40 (m, 2 H), 4.19 - 4.28 (m, 1 H), 3.98 - 4.10 (m, 2 H), 3.74 - 3.83 (m, 2 H), 2.94 (d, *J* = 15.2 Hz, 3 H), 2.79 - 2.89 (m, 1 H), 2.65 (dd, *J* = 11.3, 15.2 Hz, 3 H), 1.32 (t, *J* = 7.0 Hz, 3 H), 0.80 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 168.0, 149.8, 138.7, 131.2, 130.7, 128.7, 122.6, 118.4, 116.8, 112.0, 111.6, , 73.9, 66.1, 62.6, 61.9, 60.8, 37.0, 29.4, 28.0, 14.1, 13.4.

Compound 2-81e, *cis* diastereomer



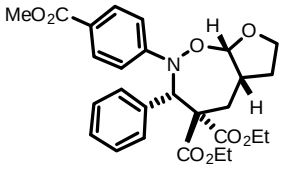
The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford bright yellow solid (106 mg, 73%). R_f 0.39 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2 H), 7.7 (d, *J* = 9.0 Hz, 2 H), 7.14 - 7.21 (m, 4 H), 6.87 - 6.93 (m, 1 H), 5.68 (s, 1 H), 5.37 (d, *J* = 5.5 Hz, 1 H), 4.29 - 4.45 (m, 2 H), 4.24 (ddd, *J* = 5.5, 8.6, 10.6 Hz, 1 H), 4.01 (dt, *J* = 2.3, 8.2 Hz, 1 H), 3.87 (dq, *J* = 7.2, 10.8 Hz, 1 H), 3.74 (dq, *J* = 7.2, 10.8 Hz, 1 H), 2.89 (dd, *J* = 12.9, 14.5 Hz, 1 H), 2.59 - 2.69 (m, 1 H), 2.50 (dd, *J* = 2.7, 14.8 Hz, 1 H), 2.23 - 2.36 (m, 1 H), 1.84 - 1.87 (m, 1 H), 1.34 (t, *J* = 7.0 Hz, 3 H), 0.96 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.4, 148.7, 147.6, 141.9, 131.5, 128.8, 122.8, 122.8, 116.9, 108.6, 70.1, 68.2, 62.3, 62.0, 61.6, 40.3, 34.1, 31.9, 14.2, 13.6.

Compound 2-81e, *trans* diastereomer



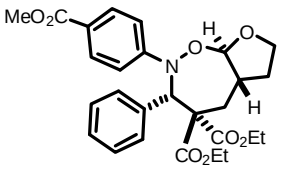
The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture to afford a mixture of separable *cis*, *trans*, and a third isomer (131 mg, 90%, *cis*:*trans*:*3*rd 11:63:26). R_f 0.27 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 2 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 7.22 - 7.28 (m, 3 H), 7.15 - 7.22 (m, 3 H), 6.96 (t, *J* = 7.2 Hz, 1 H), 6.31 (s, 1 H), 5.18 (d, *J* = 7.4 Hz, 1 H), 4.16 - 4.28 (m, 2 H), 3.96 - 4.13 (m, 4 H), 3.85 (dq, *J* = 7.1, 10.8 Hz, 1 H), 2.71 (dd, *J* = 5.1, 14.5 Hz, 1 H), 2.61 (dd, *J* = 11.3, 14.5 Hz, 1 H), 2.45 - 2.56 (m, 1 H), 2.10 - 2.20 (m, 1 H), 1.81 - 1.97 (m, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 169.8, 149.2, 147.0, 143.3, 130.2, 129.0, 122.9, 122.3, 116.0, 111.0, 71.3, 68.3, 62.8, 62.3, 62.0, 43.1, 30.9, 30.0, 13.9, 13.6; HRMS *m/z* 484.1845 (calcd for $C_{25}H_{28}N_2O_8$, 484.1846).

Compound 2-81f, *cis* diastereomer



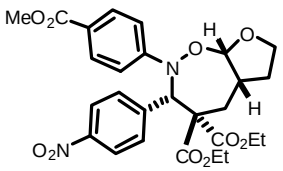
The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a white solid (78 mg, 52%). R_f 0.32 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 9.0 Hz, 2 H), 7.41 (dd, *J* = 2.3, 7.4 Hz, 2 H), 7.21 (d, *J* = 9.0 Hz, 2 H), 7.12 - 7.18 (m, 3 H), 5.71 (s, 1 H), 5.34 (d, *J* = 5.5 Hz, 1 H), 4.20 - 4.41 (m, 3 H), 4.00 (td, *J* = 2.9, 8.1 Hz, 1 H), 3.82 - 3.91 (m, 2 H), 3.81 (s, 3 H), 3.71 - 3.80 (m, 1 H), 2.94 (dd, *J* = 12.5, 14.5 Hz, 1 H), 2.56 - 2.65 (m, 1 H), 2.49 (dd, *J* = 3.1, 14.5 Hz, 1 H), 2.22 - 2.34 (m, 1 H), 1.81 - 1.89 (m, 1 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 0.96 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.5, 166.9, 153.0, 134.3, 130.7, 130.3, 128.4, 128.0, 123.0, 115.2, 108.8, 69.0, 68.3, 62.0, 61.9, 61.8, 51.7, 40.5, 34.0, 31.6, 14.1, 13.6; HRMS *m/z* 497.2043 (calcd for $C_{27}H_{31}NO_8$, 497.2043).

Compound 2-81f, *trans* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture, affording an inseparable mixture of three diastereomers (101 mg, 68%, *cis*:*trans*:*3rd* 16:40:44). R_f 0.32 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) Identifiable, distinguishable, and diagnostic peaks of the *trans* diastereomer: 6.05 (s, 1 H), 5.19 (d, *J* = 7.4 Hz, 1 H); See spectra.

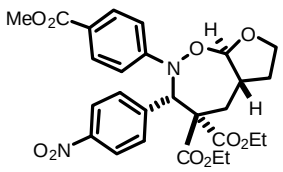
Compound 2-81g, *cis* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford bright yellow solid (111 mg, 68%). R_f 0.29 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 2 H), 7.93 (d, *J* = 9.0 Hz, 2 H), 7.39 (d, *J* = 9.0 Hz, 2 H), 7.30 (d, *J* = 9.0 Hz, 2 H), 6.12 (s, 1 H), 5.15 (d, *J* = 7.8 Hz, 1 H), 4.28 - 4.41 (m, 2 H), 4.13 - 4.21 (m, 1 H), 3.99 - 4.10 (m, 3 H), 3.86 (s, 3 H), 3.77 - 3.82 (m, 2 H), 2.97 (d, *J* = 14.5 Hz, 1 H), 2.65 -

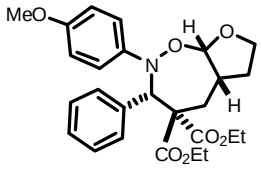
2.81 (m, 2 H), 1.87 - 2.02 (m, 3 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 0.83 (t, *J* = 7.2 Hz, 3 H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 167.7, 166.8, 153.4, 147.6, 140.6, 130.7, 130.5, 123.8, 122.9, 115.6, 111.9, 72.4, 66.3, 62.8, 62.1, 60.6, 51.8, 37.0, 29.3, 27.9, 14.1, 13.5; HRMS *m/z* 542.1895 (calcd for $C_{26}H_{31}NO_7$, 542.1900).

Compound 2-81g, *trans* diastereomer



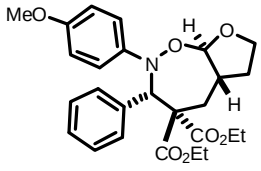
The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture, affording a separable mixture of three diastereomers (120 mg, 74%, *cis*:*trans*:*3rd* 7:58:35). R_f 0.27 (33% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.0 Hz, 2 H), 7.95 (d, *J* = 9.0 Hz, 2 H), 7.29 (d, *J* = 9.0 Hz, 2 H), 7.23 (d, *J* = 9.0 Hz, 2 H), 6.47 (s, 1 H), 5.19 (d, *J* = 7.4 Hz, 1 H), 4.19 - 4.27 (m, 1 H), 4.06 - 4.17 (m, 2 H), 3.93 - 4.06 (m, 3 H), 3.87 (s, 3 H), 2.70 (d, *J* = 8.6 Hz, 2 H), 2.30 - 2.43 (m, 1 H), 2.09 - 2.17 (m, 1 H), 1.83 - 1.96 (m, 1 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.08 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.6, 166.7, 152.6, 147.1, 143.1, 131.1, 129.5, 123.2, 123.2, 114.1, 111.0, 69.6, 68.6, 63.0, 62.3, 62.2, 51.9, 43.3, 31.3, 29.6, 13.9, 13.7.

Compound 2-81h, *cis* diastereomer



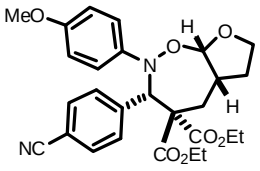
The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a white solid (61, 43%). R_f 0.37 (33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.0 Hz, 2 H), 7.12 - 7.19 (m, 3 H), 7.08 (d, *J* = 8.8 Hz, 2 H), 6.69 (d, *J* = 9.4 Hz, 2 H), 5.36 (d, *J* = 5.3 Hz, 1 H), 5.36 (s, 1H), 4.39 (dq, *J* = 7.2, 10.6 Hz, 1 H), 4.32 (dq, *J* = 7.1, 10.8 Hz, 1 H), 4.20 - 4.26 (m, 1 H), 3.95 - 4.01 (m, 1 H), 3.80 (dq, *J* = 7.0, 10.5 Hz, 1 H), 3.69 (s, 3 H), 2.97 (t, *J* = 13.8 Hz, 1 H), 2.60 - 2.67 (m, 1 H), 2.44 (d, *J* = 14.6 Hz, 1 H), 2.22 - 2.30 (m, 1 H), 1.79 - 1.88 (m, 1 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 0.91 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.9, 142.9, 130.9, 128.1, 127.7, 119.3, 119.3, 113.6, 108.3, 71.7, 68.0, 62.0, 61.8, 61.6, 55.3, 40.4, 34.3, 31.8, 14.2, 13.5; HRMS *m/z* 469.2102 (calcd for $C_{26}H_{31}NO_7$, 469.2101).

Compound 2-81h, *trans* diastereomer



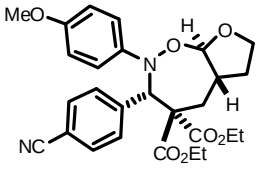
The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture to afford a mixture of separable *cis* and *trans* isomers (97 mg, 69%, *cis*:*trans* 34:66). R_f 0.33 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 - 7.24 (m, 5 H), 7.08 (d, *J* = 7.0 Hz, 2 H), 6.75 (d, *J* = 9.4 Hz, 2 H), 5.66 (s, 1 H), 5.15 (d, *J* = 7.8 Hz, 1 H), 4.27 - 4.42 (m, 2 H), 4.03 - 4.15 (m, 1 H), 3.99 (td, 2.3, 9.0 Hz, 1 H), 3.73 (s, 3 H), 3.69 - 3.77 (m, 2 H), 2.80 - 2.92 (m, 2 H), 2.66 - 2.75 (m, 1 H), 1.80 - 2.02 (m, 2 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 0.76 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 168.4, 155.2, 144.2, 133.1, 130.5, 128.0, 127.4, 119.1, 113.6, 111.5, 75.2, 66.0, 62.2, 61.5, 61.4, 55.4, 37.2, 29.2, 28.2, 14.1, 13.3.

Compound 2-81i, *cis* diastereomer



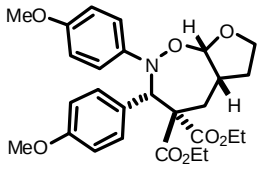
The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a white solid (82 mg, 55%). R_f 0.26 (33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 - 7.48 (m, 4 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 6.69 (d, *J* = 9.4 Hz, 2 H), 5.40 (br. s., 1 H), 5.35 (d, *J* = 5.3 Hz, 1 H), 4.39 (dq, *J* = 7.1, 10.8 Hz, 1 H), 4.33 (dq, *J* = 7.0, 10.5 Hz, 1 H), 4.18 - 4.24 (m, 1 H), 3.99 (td, *J* = 2.3, 8.2 Hz, 1 H), 3.83 (dq, *J* = 7.1, 11.1 Hz, 1 H), 3.70 (s, 3 H), 3.67 - 3.74 (m, 1 H), 2.87 (dd, *J* = 13.5, 13.5 Hz, 1 H), 2.60 - 2.67 (m, 1 H), 2.47 (dd, *J* = 2.3, 14.6 Hz, 1 H), 2.24 - 2.31 (m, 1 H), 1.83 (br. d, *J* = 8.8 Hz, 1 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.5, 155.7, 142.3, 139.8, 131.4, 131.4, 119.2, 118.5, 113.8, 112.0, 108.4, 71.6, 68.0, 62.2, 61.8, 61.6, 55.3, 40.3, 34.1, 31.9, 14.2, 13.6; HRMS *m/z* 494.2063 (calcd for $C_{27}H_{30}N_2O_7$, 494.2053).

Compound 2-81i, *trans* diastereomer



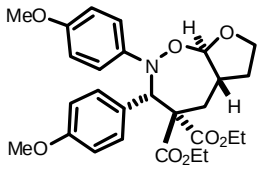
The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture to afford a mixture of separable *cis* and *trans* isomers (98 mg, 66%, *cis*:*trans* 32:68). R_f 0.23 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.6 Hz, 2 H), 7.15 (d, *J* = 9.0 Hz, 4 H), 6.76 (d, *J* = 9.4 Hz, 2 H), 5.69 (s, 1 H), 5.09 (d, *J* = 8.2 Hz, 1 H), 4.29 - 4.42 (m, 2 H), 3.99 (dt, *J* = 2.0, 9.0 Hz, 2 H), 3.73 (s, 3 H), 3.67 - 3.81 (m, 2 H), 2.91 (d, *J* = 14.9 Hz, 1 H), 2.79 - 2.91 (m, 1 H), 2.63 (dd, *J* = 11.3, 15.2 Hz, 1 H), 1.82 - 2.03 (m, 2 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 0.78 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 168.0, 155.6, 143.5, 138.4, 131.1, 131.0, 119.0, 118.5, 113.8, 111.9, 111.5, 75.0, 66.1, 62.5, 61.8, 60.9, 55.4, 37.0, 29.3, 28.0, 14.1, 13.4).

Compound 2-81j, *cis* diastereomer



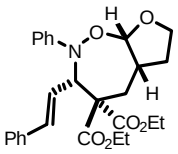
The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford white solid (81 mg, 54%). R_f 0.29 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz , 2 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 6.63 - 6.71 (m, 4 H), 5.35 (d, *J* = 5.5 Hz, 1 H), 5.31 (s, 1 H), 4.34 - 4.42 (m, 1 H), 4.28 - 4.34 (m, 1 H), 4.24 - 4.18 (m, 1 H), 3.97 (td, *J* = 2.3, 8.2 Hz, 1 H), 3.79 - 3.88 (m, 1 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.68 - 3.73 (m, 1 H), 2.94 (app. t, *J* = 1.33 Hz, 1 H), 2.56 - 2.70 (m, 1 H), 2.42 (br. d, *J* = 12.5 Hz, 1 H), 2.20 - 2.33 (m, 1 H), 1.82 (br. d, *J* = 10.9 Hz, 1 H), 1.32 (t, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 168.9, 159.2, 143.1, 132.0, 131.9, 126.5, 119.2, 113.6, 113.0, 108.2, 71.1, 67.9, 62.1, 61.8, 61.5, 55.3, 55.0, 40.4, 34.3, 31.7, 14.2, 13.7; HRMS *m/z* 499.2206 (calcd for $C_{27}H_{33}NO_8$, 499.2206).

Compound 2-81j, *trans* diastereomer



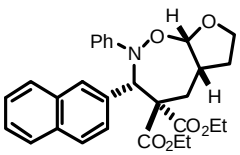
The title compound was prepared according to the general cycloaddition procedure for the formation of a diastereomeric mixture, affording an inseparable mixture of *cis* and *trans* isomers (105 mg, 70%, *cis*:*trans* d.r. 56:44). R_f 0.29 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) Identifiable, distinguishable, and diagnostic peaks for the *trans* diastereomer: 5.60 (s, 1 H), 5.13 (d, J = 8.2 Hz, 1 H); See spectra.

Compound 2-81n, *cis* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a bright yellow solid (98 mg, 70%). R_f 0.37 (33% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 - 7.34 (m, 5 H), 7.27 (m, 4 H), 7.19 - 7.25 (m, 1 H), 6.98 (t, J = 7.0 Hz, 1 H), 6.52 (dd, J = 9.4, 15.8 Hz, 1 H), 6.29 (d, J = 15.8 Hz, 1 H), 5.38 (d, J = 5.3 Hz, 1 H), 5.01 (d, J = 9.4 Hz, 1 H), 4.39 - 4.45 (m, 1 H), 4.33 - 4.39 (m, 1 H), 4.23 (ddd, J = 5.3, 8.2, 10.5 Hz, 1 H), 4.07 - 4.14 (m, 2 H), 4.00 (dt, J = 2.6, 8.1 Hz, 1 H), 2.71 (dd, J = 12.3, 14.1 Hz, 1 H), 2.62 - 2.68 (m, 1 H), 2.44 (dd, J = 1.2, 14.1 Hz, 1 H), 2.31 (tdd, J = 7.8, 10.7, 12.5 Hz, 1H), 1.87 (pd, J = 2.9, 12.3 Hz, 1 H), 1.38 (t, J = 7.0 Hz, 3 H), 1.19 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.0, 149.5, 136.2, 136.1, 128.7, 128.4, 127.8, 126.7, 122.3, 120.5, 116.9, 108.2, 70.5, 68.0, 61.9, 61.7, 61.7, 40.3, 34.4, 30.9, 14.2, 14.1; HRMS *m/z* 465.2143 (calcd for $C_{27}H_{31}NO_6$, 465.2151).

Compound 2-81o, *cis* diastereomer



The title compound was prepared according to the general cycloaddition procedure for the formation of a single diastereomer to afford a colorless crystalline solid (109 mg, 74%). R_f 0.38 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br. s., 1 H), 7.78 (d, J = 7.0 Hz, 1 H), 7.48 (d, J = 8.2 Hz, 1 H), 7.45 (d, J = 9.4 Hz, 1 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.08 - 7.15 (m, 2 H), 7.03 - 7.05 (m, 3 H), 6.83 (t, J = 7.6 Hz, 2 H), 6.49 - 6.58 (m, 2 H), 5.22 (d, J = 5.1 Hz, 1 H), 4.05 - 4.29 (m, 3 H), 3.82 (td, J = 2.1, 8.1 Hz, 1 H), 3.12 - 3.27 (m, 1 H), 2.95 (t, J = 13.3 Hz, 1 H), 2.79 (br. t, J = 7.42 Hz, 1 H), 2.52 (br.

s, 1 H), 2.26 (dd, *J* = 2.3, 14.5 Hz, 1 H), 2.02 - 2.17 (m, 1 H), 1.68 (br. d, *J* = 7.8 Hz, 1 H), 1.15 (t, *J* = 7.2 Hz, 3 H), 0.27 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.6, 149.2, 133.4, 132.6, 131.0, 128.7, 128.7, 128.5, 128.4, 125.6, 125.1, 124.8, 123.5, 122.3, 117.2, 108.7, 68.1, 62.3, 62.0, 61.6, 61.2, 40.6, 34.2, 32.2, 14.2, 12.9; HRMS *m/z* 489.2150 (calcd for $C_{29}H_{31}NO_6$, 489.2151).

2.5.2.3 (4 + 2) Cycloaddition of Donor-Acceptor Cyclobutanes and Nitrosoarenes

Scalar coupling was eliminated from nOe experiments by using acquisition delays of 500 ms. Signal intensity in ^{1}H- ^{15}N HMBCAD experiments is proportional to ^{1}H-^{15}N *J*-value, thus observed $^{2}J_{1H\text{-}15N}$ signals are significantly more intense than $^{3}J_{1H\text{-}15N}$ signals. EI mass spectra were obtained on a Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV.

All nitrosoarenes not available commercially were prepared from the corresponding anilines according to literature methods.[42]

Compounds **2-89d**, **2-89g** and **2-89h** were prepared in collaboration with Tyler Schon and are included below, compounds **2-89i**, **2-90a**, **2-90b**, **2-91a**, **2-91b** and **2-92** to **2-96** were prepared by Naresh Vemula and the data is not included below.

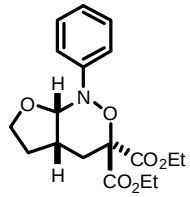
General Procedure for the $Yb(OTf)_3$ Catalyzed Cycloaddition of Nitrosoarenes and Cyclobutanes

To a mixture of nitrosoarene (0.30 mmol, 1.0 equiv) and $Yb(OTf)_3$ (4 mg, 0.006 mmol, 2 mol %) in CH_2Cl_2 (3 mL) was added the cyclobutane (0.36 mmol, 1.2 equiv). After complete consumption of the cyclobutane (as indicated by TLC) the reaction mixture was layered directly onto a silica gel column and purified by flash chromatography.

General Procedure for the MgI_2 Catalyzed Cycloaddition of Nitrosoarenes and Cyclobutanes

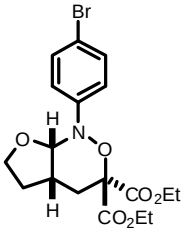
To a mixture of nitrosoarene (0.30 mmol, 1.0 equiv) and MgI_2 (42 mg, 0.15 mmol, 50 mol %) in CH_2Cl_2 (3 mL) was added the cyclobutane (0.36 mmol, 1.2 equiv). After complete consumption of the cyclobutane (as indicated by TLC) the reaction mixture was layered directly onto a silica gel column and purified by flash chromatography.

(4a*R,7a*R**)-diethyl 1-phenyltetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89a)**



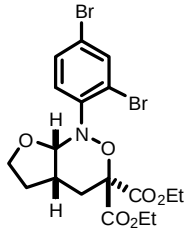
The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford a pale yellow oil (96 mg, 92%). R_f 0.27 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.35 (m, 4 H), 6.97 - 7.02 (m, 1 H), 5.44 (d, *J* = 5.9 Hz, 1 H), 4.25 - 4.33 (m, 2 H), 4.15 - 4.24 (m, 2 H), 4.09 (td, *J* = 6.8, 8.5 Hz, 1 H), 3.93 (td, *J* = 3.9, 8.2 Hz, 1 H), 2.80 - 2.90 (m, 1 H), 2.60 (dd, *J* = 6.6, 14.1 Hz, 1 H), 2.16 (dq, *J* = 8.2, 12.7 Hz, 1 H), 2.04 (dd, *J* = 8.6, 14.1 Hz, 1 H), 1.83 - 1.92 (m, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.6, 146.7, 128.5, 123.0, 117.5, 88.6, 83.6, 67.0, 62.2, 62.0, 33.3, 30.6, 29.6, 14.0, 13.9; HRMS *m*/*z* 349.1525 (calcd for $C_{18}H_{23}NO_6$, 349.1525).

(4a*R,7a*R**)-diethyl 1-(4-bromophenyl)tetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89b)**



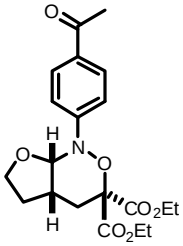
The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford a cream colored solid (114 mg, 89%). R_f 0.27 (2:1 hexanes /EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.40 (m, 2 H), 7.18 - 7.23 (m, 2 H), 5.37 (d, *J* = 5.9 Hz, 1 H), 4.24 - 4.33 (m, 2 H), 4.16 - 4.24 (m, 3 H), 4.08 (td, *J* = 7.0, 8.4 Hz, 1 H), 3.92 (td, *J* = 3.9, 8.2 Hz, 1 H), 2.79 - 2.89 (m, 1 H), 2.59 (dd, *J* = 6.6, 14.1 Hz, 1 H), 2.15 (dq, *J* = 8.1, 12.5 Hz, 1 H), 2.07 (dd, *J* = 7.8, 14.1 Hz, 1 H), 1.84 - 1.92 (m, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.5, 145.9, 131.4, 119.2, 115.8, 88.7, 83.6, 67.1, 62.3, 62.1, 33.4, 30.6, 29.4, 14.0, 14.0; HRMS *m*/*z* 427.0614 (calcd for $C_{18}H_{22}BrNO_6$, 427.0631).

(4a*R,7a*R**)-diethyl 1-(2,4-dibromophenyl)tetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89c)**



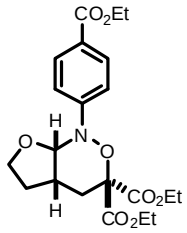
The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford an orange oil (72 mg, 47%). R_f 0.37 (2:1 hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, 1 H), 7.64 (d, *J* = 2.3 Hz, 1 H), 7.38 (dd, *J* = 2.3, 8.8 Hz, 1 H), 5.59 (d, *J* = 4.7 Hz, 1 H), 4.21 - 4.24 (m, 2 H), 4.13 - 4.18 (m, 2 H), 4.06 - 4.11 (m, 1 H), 4.00 - 4.06 (m, 1 H), 3.87 (q, *J* = 7.8 Hz, 1 H), 2.73 - 2.80 (m, 2 H), 2.52 - 2.56 (m, 1 H), 1.95 - 2.06 (m, 3 H), 1.19 (t, *J* = 7.3 Hz, 3 H), 1.04 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 166.7, 143.9, 134.3, 130.2, 129.8, 123.4, 120.2, 104.2, 69.0, 62.2, 62.0, 61.5, 36.1, 32.4, 27.4, 13.8, 13.6; HRMS *m*/*z* 504.9750 (calcd for $C_{18}H_{21}Br_2NO_6$, 504.9736).

(4a*R,7a*R**)-diethyl 1-(4-acetylphenyl)tetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89d)**



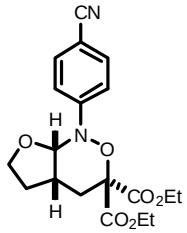
The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford a cream colored solid (81 mg, 69%). R_f 0.16 (2:1 hexanes /EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 2.0 Hz, 1 H), 7.55 - 7.61 (m, 2 H), 7.34 - 7.41 (m, 1 H), 5.49 (d, *J* = 6.3 Hz, 1 H), 4.25 - 4.36 (m, 2 H), 4.20 (qd, *J* = 1.0, 7.1 Hz, 3 H), 4.04 - 4.13 (m, 1 H), 3.94 (td, *J* = 3.9, 8.2 Hz, 1 H), 2.82 - 2.92 (m, 1 H), 2.60 (dd, *J* = 7.8, 14.1 Hz, 1 H), 2.58 (s, 3 H), 2.17 (dq, *J* = 8.0, 12.7 Hz, 1 H), 2.09 (dd, *J* = 8.2, 14.1 Hz, 1 H), 1.85 - 1.95 (m, 1 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 167.8, 167.5, 147.2, 137.6, 128.8, 123.0, 122.2, 117.1, 88.6, 83.7, 67.2, 62.3, 62.1, 33.4, 30.6, 29.4, 26.7, 14.0, 13.9; HRMS *m*/*z* 391.1623 (calcd for $C_{20}H_{25}NO_7$, 391.1631).

(4a*R,7a*R**)-diethyl 1-(4-(ethoxycarbonyl)phenyl)tetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89e)**



The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford a pale yellow oil (104 mg, 82%) as a 13:1 mixture of regioisomers (major regioisomer shown). R_f 0.21 (2:1 hexanes /EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 - 7.98 (m, 2 H), 7.30 - 7.35 (m, 2 H), 5.54 (d, *J* = 5.9 Hz, 1 H), 4.26 - 4.36 (m, 4 H), 4.13 - 4.22 (m, 3 H), 4.06 - 4.13 (m, 1 H), 3.93 (td, *J* = 3.9, 8.2 Hz, 1 H), 2.82 - 2.91 (m, 1 H), 2.62 (dd, *J* = 6.4, 14.3 Hz, 1 H), 2.06 - 2.22 (m, 2 H), 1.90 (tdd, *J* = 4.2, 6.8, 12.5 Hz, 1 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.6, 167.3, 166.4, 150.5, 130.3, 124.2, 115.8, 88.1, 83.7, 67.2, 62.3, 62.2, 60.5, 33.2, 30.5, 29.2, 14.3, 14.0, 13.9; HRMS *m*/*z* 421.1742 (calcd for $C_{18}H_{23}NO_6$, 421.1737).

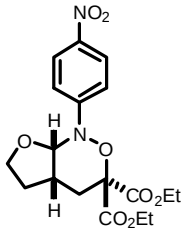
(4a*R,7a*R**)-diethyl 1-(4-cyanophenyl)tetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89f)**



The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford a cream colored solid (89 mg, 61%) as a 3:1 mixture of regioisomers (major regioisomer shown). R_f 0.22 (2:1 hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 - 7.59 (m, 2 H), 7.36 - 7.41 (m, 2 H), 5.52 (d, *J* = 6.4 Hz, 1 H), 4.25 - 4.34 (m, 3 H), 4.16 - 4.23 (m, 3 H), 4.05 - 4.12 (m, 1 H), 3.93 (td, *J* = 4.7, 8.2 Hz, 1 H), 2.84 - 2.91 (m, 1 H), 2.61 (dd, *J* = 6.4, 14.1 Hz, 1 H), 2.14 - 2.21 (m, 2 H), 1.87 - 1.94 (m, 2 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.17 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) see spectra; HRMS *m*/*z* 374.1482 (calcd for $C_{19}H_{22}N_2O_6$, 374.1478).

Minor Regioisomer: Identifiable, distinguishable, and diagnostic peaks of the minor diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 - 808 (m, 2 H), 7.08 - 7.05 (m, 2 H), 5.59 (d, *J* = 4 Hz, 1 H), 1.15 (t, *J* = 7.03 Hz, 3 H); See spectra.

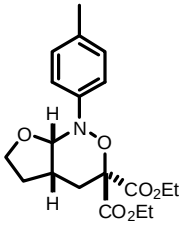
(4a*R*,7a*R***)-diethyl 1-(4-nitrophenyl)tetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89g)**



The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford a yellow solid (70 mg, 59%) as a 4:1 mixture of regioisomers (major regioisomer shown). R_f 0.19 (2:1 hexanes /EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 - 8.20 (m, 2 H), 7.37 - 7.42 (m, 2 H), 5.58 (d, *J* = 6.3 Hz, 1 H), 4.27 - 4.36 (m, 2 H), 4.15 - 4.24 (m, 2 H), 4.07 - 4.14 (m, 2 H), 3.95 (td, *J* = 4.3, 8.2 Hz, 1 H), 2.85 - 2.94 (m, 1 H), 2.62 (dd, *J* = 6.3, 14.5 Hz, 1 H), 2.15 - 2.24 (m, 2 H), 1.94 (td, *J* = 4.7, 11.9 Hz, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4, 167.0, 152.0, 142.3, 124.7, 115.9, 88.0, 83.7, 67.5, 62.6, 62.4, 33.4, 30.3, 28.9, 14.0, 13.9; HRMS *m*/*z* 394.1377 (calcd for $C_{18}H_{22}N_2O_8$, 394.1376).

Minor Regioisomer: Identifiable, distinguishable, and diagnostic peaks of the minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-808 (m, 2 H), 7.08-7.05 (m, 2 H), 5.59 (d, *J* = 4 Hz, 1 H), 1.15 (t, *J* = 7.03 Hz, 3 H); See spectra.

(4a*R*,7a*R***)-diethyl 1-p-tolyltetrahydro-1H-furo[2,3-c][1,2]oxazine-3,3(7aH)-dicarboxylate (2-89h)**



The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure to afford a pale yellow oil (32 mg, 29%). R_f 0.29 (2:1 hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 - 7.21 (m, 2 H), 7.04 - 7.08 (m, 2 H), 5.34 (d, *J* = 5.9 Hz, 1 H), 4.22 - 4.33 (m, 2 H), 4.14 - 4.22 (m, 3 H), 4.06 (q, *J* = 8.8 Hz, 1 H), 3.90 (td, *J* = 3.8, 8.3 Hz, 1 H), 2.78 - 2.85 (m, 1 H), 2.57 (dd, *J* = 6.4, 14.1 Hz, 1 H), 2.25 (s, 3 H), 2.12 (dq, *J* = 8.1, 12.6 Hz, 1 H), 2.02 (dd, *J* = 8.2, 14.1 Hz, 2 H), 1.83 - 1.89 (m, 1 H), 1.26 (t, *J* = 7.0 Hz, 3 H), 1.17 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 167.8, 144.3, 132.7, 129.1, 118.0, 89.0, 83.6, 66.9, 62.1, 62.0, 33.3, 30.6, 29.6, 20.7, 20.6, 14.0, 14.0, 13.9; HRMS *m*/*z* 363.1686 (calcd for $C_{19}H_{25}NO_6$ 363.1682).

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32. 4 Å molecular sieves were needed to prevent hydrolysis of the nitrone.

33. A mixture of three diastereomers was formed, *cis*:*trans*:3rd 1.0:1.4:1.4, 95% yield.

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Chapter 3. Studies Towards the Synthesis of Grandilodine A

This chapter describes studies towards the synthesis of grandilodine A. Relevant background information regarding the alkaloid, as well as previous reported studies directed towards the synthesis of the grandilodines and related alkaloids is presented.

3.1 Introduction

3.1.1 Grandilodine A

Complex natural products provide a unique opportunity for the chemical and medicinal community, as many compounds isolated from natural sources have been found to possess potent biological activity. Indeed, from the development of chemotherapy for cancer treatment, greater than 48% of the small molecules used in the treatment of cancer are either natural products or natural product derived.[1] New and intriguing compounds continue to be isolated, often times in such limited quantities to allow only a cursory examination of their potential biological activity. One such series of compounds isolated in 2011 are the grandilodines (Figure 3.1).[2] Preliminary examination of the biological properties of the grandilodines revealed that both grandilodine A and C restored vincristine activity in multidrug resistant KB cells (IC_{50} 4.35 and 4.11 μg/mL respectively, in the presence of 0.1 μg/mL of vincristine) without showing cytotoxicity against both drug-sensitive and drug-resistant cells in the absence of vincristine. While this was a promising preliminary result, the sparse availability of these compounds has hindered further studies from being undertaken.

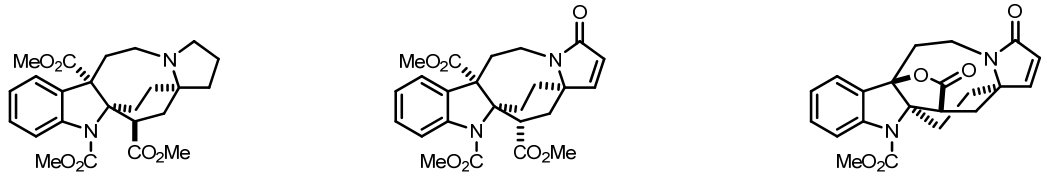


Figure 3.1. Grandilodines A-C

Synthetic organic chemistry provides a unique opportunity in this regard, as an efficient synthesis of the grandilodines would allow for sufficient material to facilitate full elucidation of the medicinal utility of this series of compounds. Additionally it would allow for potential enhancement of their biological properties through structure-activity relationship studies. The potential utility of these compounds aside, the grandilodines possess a rare carbon framework. The central [4.2.2] bicyclic system poses a significant synthetic challenge. Moreover, the adjacent quaternary and tertiary centers present in the indoline core create additional impediment as the high steric requirements of the centers would prove challenging to form.

3.1.2 Synthetic Efforts Towards the Grandilodines and Related Alkaloids

To date there have only been two reports of synthetic efforts towards the synthesis of any of the grandilodine natural products. There are, however, two series of compounds with closely related structures, the lapidilectines[3] and the lundurines[4] (Figure 3.2). Once again there have only been a few reports of efforts towards their synthesis, which have been summarized below. These studies can assist in illustrating some of the challenges faced when constructing molecules with the peculiar [4.2.2] framework.

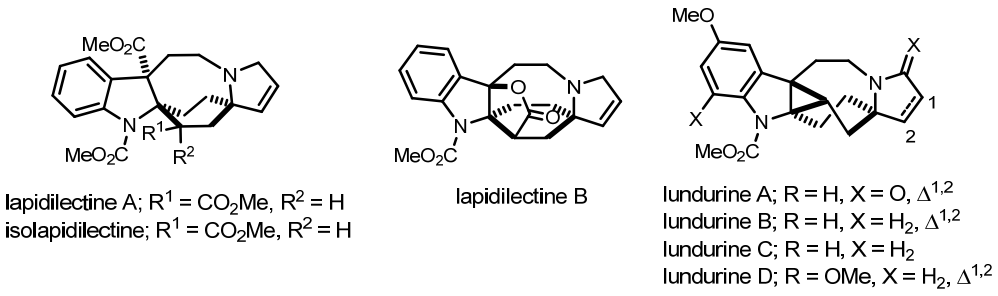
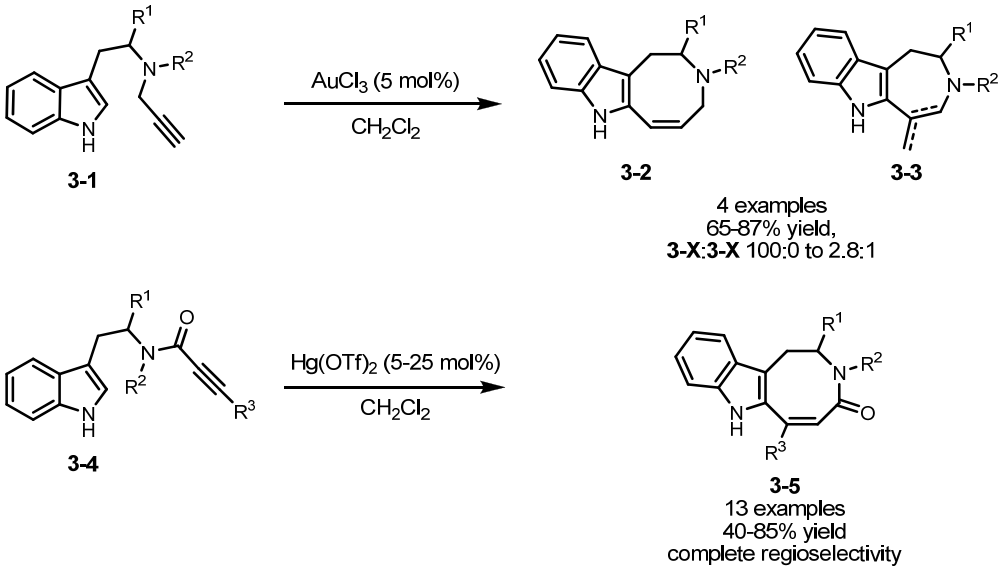


Figure 3.2. The Lapidilectine and Lundurine Natural Products

3.1.2.1 Synthesis of the Indoloazocine Ring *via* Intramolecular Alkyne Cyclization

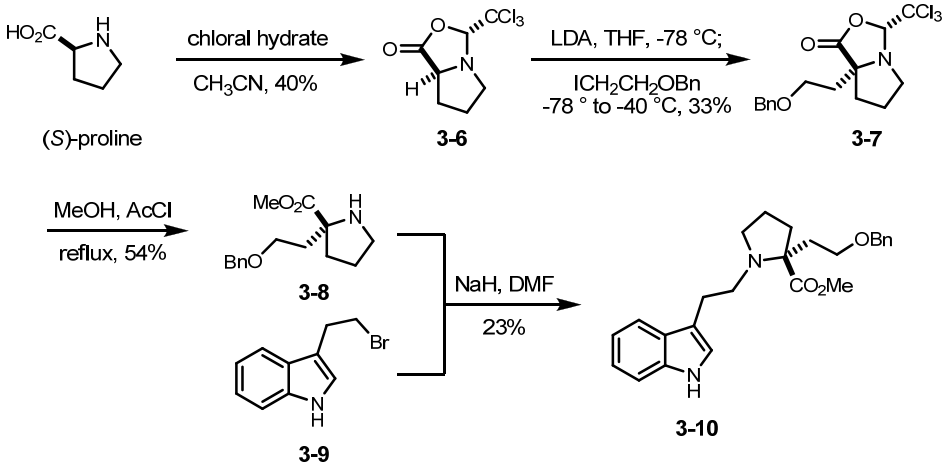
Echavarren and Van der Eycken have both developed methodologies for the synthesis of the central indoloazocine ring of the grandilodine, lapidilectine, and lundurine alkaloids, which utilize intramolecular alkyne cyclizations. Echavarren and coworkers described a method that employs a gold catalyst and terminal alkynes; however, the selectivity for the desired 8-*endo*-dig vs. the undesired 7-*exo*-dig processes appears to be highly substrate dependent, though it is difficult to draw conclusions as only four compounds were investigated (Scheme 3.1).[5] Subsequently, Van der Eycken and coworkers developed a methodology using a propargyl amide as a cyclization precursor, as opposed to a propargyl amine substrate.[6] This proved to be an advantageous and most likely crucial alteration as complete selectivity for the 8-*endo*-dig pathway was observed, affording the 8-membered ring products in good yield. Unfortunately, they found that internal alkynes were required, as terminal alkynes afforded extremely slow reactions (2 days) with low yield (21–25%) and extensive decomposition.

Scheme 3.1. Indole-Alkyne Cyclizations for the Formation of Indoloazocines



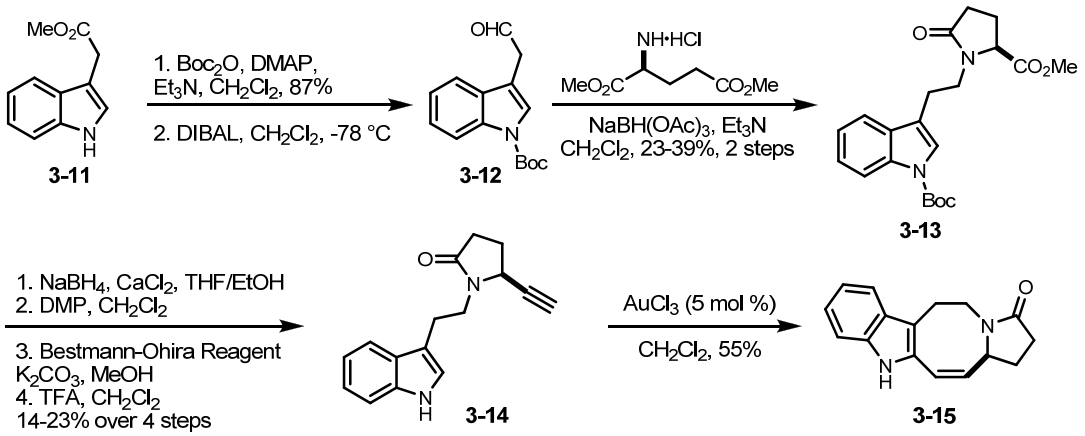
Though the initial scope was limited, Echavarren and coworkers believed that their gold-catalyzed cyclization would facilitate synthesis of the lundurines, and thus embarked on the synthesis of the tetracyclic core (Scheme 3.2).[7] Desiring an enantioselective route, they first studied the synthesis of the pyrrolidine portion of the molecule. Following a procedure developed by Germans and coworkers,[8] chloral (trichloroacetaldehyde) and (*S*)-proline were condensed to form oxazolidinone **3-6** which was alkylated with ((2-iodoethoxy)methyl)benzene, affording **3-7** in low yield. Subsequent acidic cleavage of the oxazolidinone afforded the desired pyrrolidine. The indole moiety was appended through an S_N2 reaction with indole derivative **3-9** to afford **3-10**. The poor yields obtained throughout (1.6% over 4 steps) necessitated abandoning this route and an alternative synthesis with a less complicated substrate was investigated.

Scheme 3.2. Echavarren's Synthetic Efforts Towards the Lundurines



The second route investigated by Echavarren began with Boc protection and DIBAL reduction of commercially available indole-3-acetic acid methyl ester to afford aldehyde **3-12** (Scheme 3.3). A pendant pyrrolidinone was then installed *via* reductive amination and lactam formation with dimethyl (*S*)-glutamate. The synthesis of the cyclization precursor was completed through ester reduction, oxidation with DMP, alkyne formation with the Bestmann–Ohira reagent and Boc cleavage to afford alkyne **3-14**. Treatment of alkyne **3-14** with $AuCl_3$ afforded the cyclized product (**3-15**) in 55% yield. Despite the poor overall efficiency (5% yield over 7 steps), the study demonstrated the feasibility of this methodology for the synthesis of the indoloazocine skeleton.

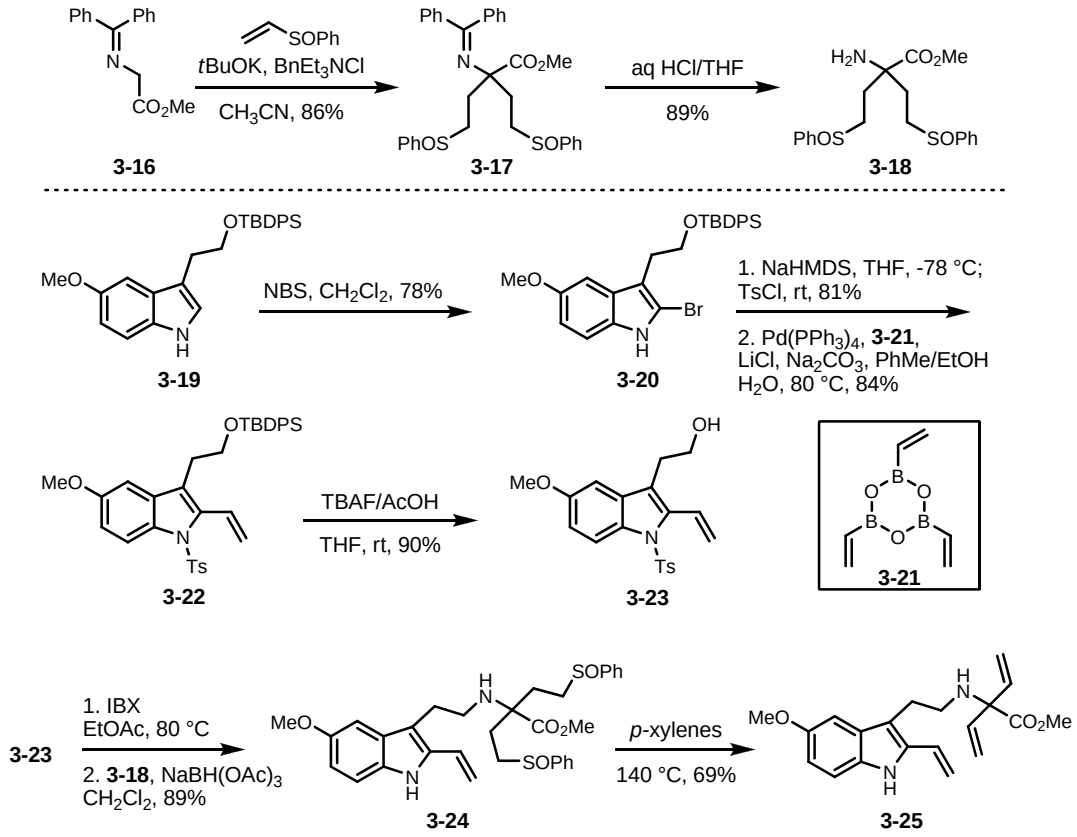
Scheme 3.3. Echavarren's Synthesis of the Tetracyclic Core



3.1.2.2 Martin's Approach Towards Lundurine A

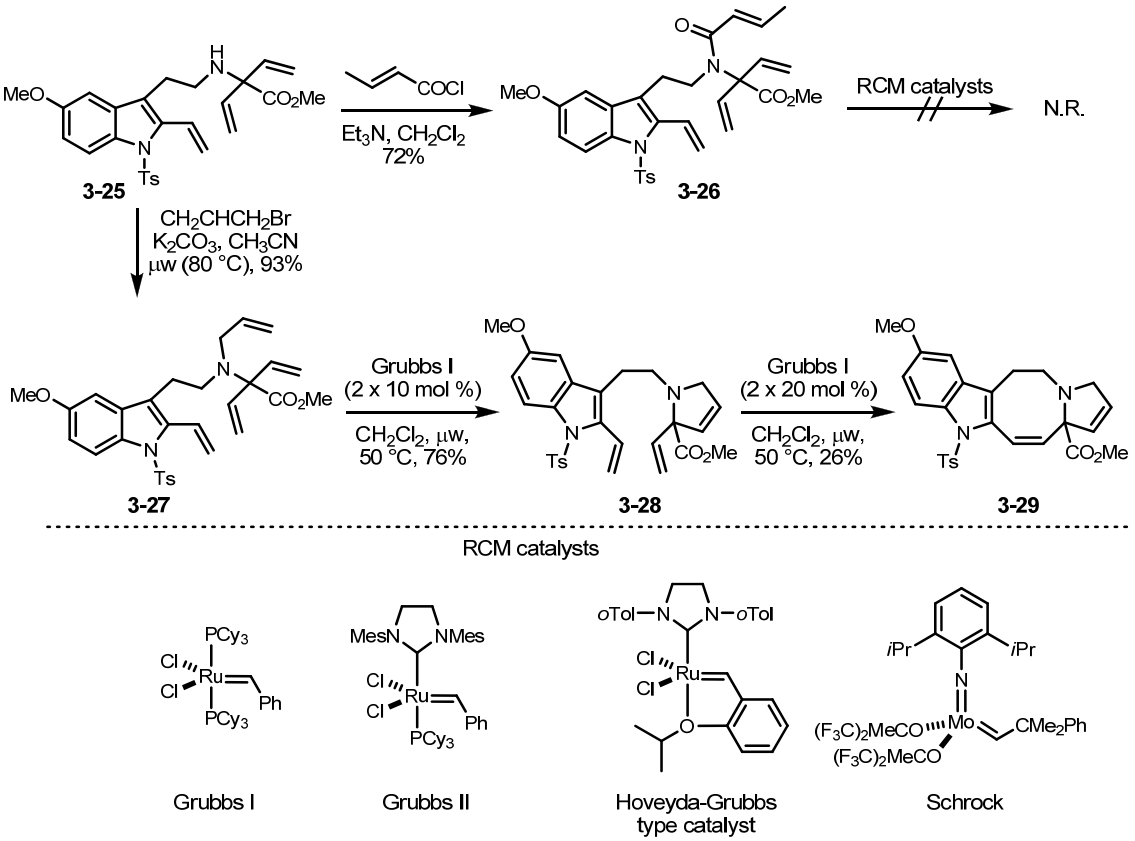
The Martin group has disclosed studies towards the synthesis of the lundurine alkaloids based on a double RCM approach.[9] They began the synthesis by formation of amine partner **3-18** through bisalkylation of **3-16** with phenyl vinyl sulfoxide followed by acidic hydrolysis of the Schiff base. The indole portion was created through electrophilic bromination of indole derivative **3-19**, *N*-tosylation and Suzuki cross-coupling to afford vinyl indole **3-22**. Silyl-group deprotection with TBAF gave alcohol **3-23**. Oxidation of the newly released alcohol with IBX and reductive amination with amine **3-23** afforded **3-24**. Lastly, pyrolytic elimination of the two phenyl sulfoxides afforded key triene **3-25**.

Scheme 3.4. Preparation of the RCM Precursor



Installation of the fourth and final olefin was accomplished through alkylation of **3-25** with either crotonyl chloride or allyl bromide to afford tetraenes **3-26** and **3-27** (Scheme 3.5). It was found that amide **3-26** would not undergo RCM with a variety of different RCM catalysts. In contrast, amine **3-27** underwent RCM with all catalysts surveyed to afford **3-28**; however, Grubbs I provided the superior yield. They subsequently described that the next RCM event could also be catalyzed by Grubbs I, Grubbs II, or Schrock catalysts to afford tetracycle **3-29**. Regrettably, this process was found to be irreproducible approximately one year after being reported and the publication was retracted.[10]

Scheme 3.5. RCM for Formation of the Indoloazocine Skeleton of Lundurine A

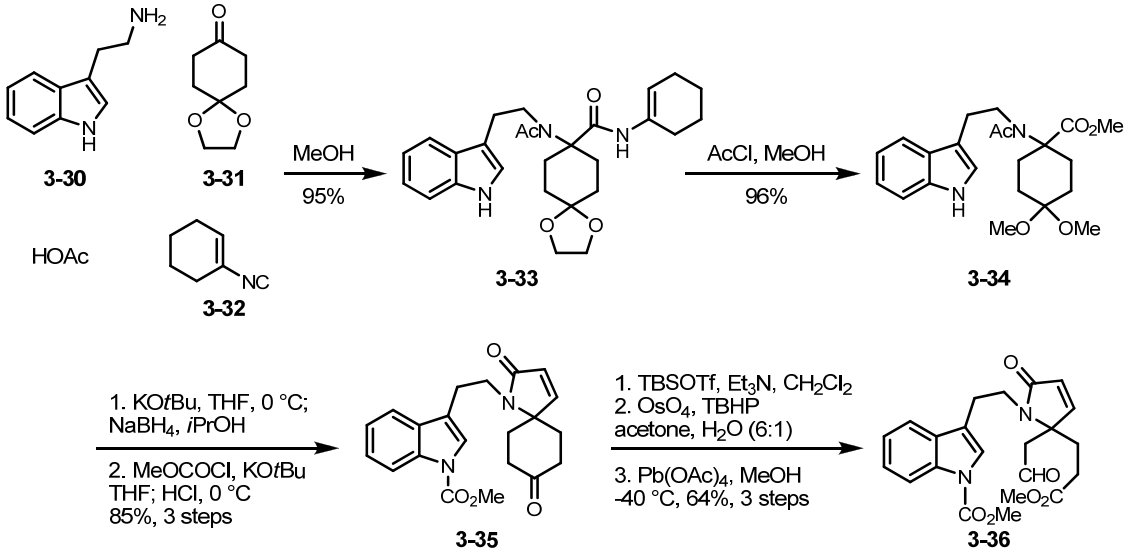


3.1.2.3 Studies towards Grandilodine C

Sarpong recently disclosed studies towards the synthesis of lapidilectine-type alkaloids, including grandilodine C and the lapidilectine and lundurine natural products.[11] Key steps in his strategy include a four component Ugi coupling and three methods for formation of the indoloazocine ring system. The synthesis began with a four-component Ugi coupling leading to adduct **3-33**. The undesired enamide artifact of the Ugi reaction was cleaved through acidic methanolysis to afford a methyl ester, which underwent subsequent Dieckmann condensation, dehydration and protection of the indole nitrogen through methyl carbamate formation, to afford **3-35**. Fission of the cyclohexanone ring

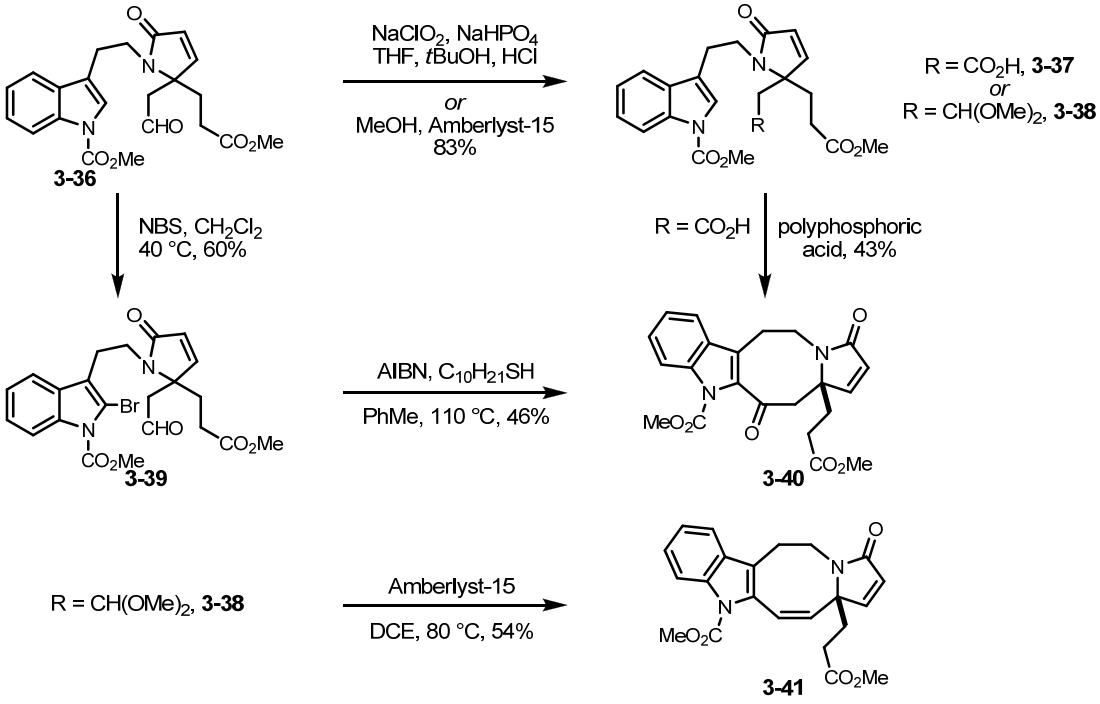
was accomplished through silyl enol ether formation, dihydroxylation with OsO_4 and oxidative cleavage with $Pb(OAc)_4$ to afford **3-36** in 64% yield over the three steps.

Scheme 3.6. Sarpong's Synthesis of the Cyclization Precursor



With efficient access to **3-36**, a number of methods to form the indoloazocine ring were investigated (Scheme 3.7). Conversion of **3-36** to aryl bromide **3-39**, carboxcylic acid **3-37** or dimethyl acetal **3-38** was achieved efficiently through standard procedures. Friedel–Crafts reactions could be accomplished through carboxylic acid **3-37** or dimethyl acetal **3-38** to afford **3-40** or **3-41** respectively. The indoloazocine ring could also be formed through a radical cyclization by subjection of aryl bromide **3-39** to AIBN and dodecane thiol, affording ketone **3-40**. This study represents the most efficient route to form the indoloazocine ring system to date and includes adequate functionality for further studies.

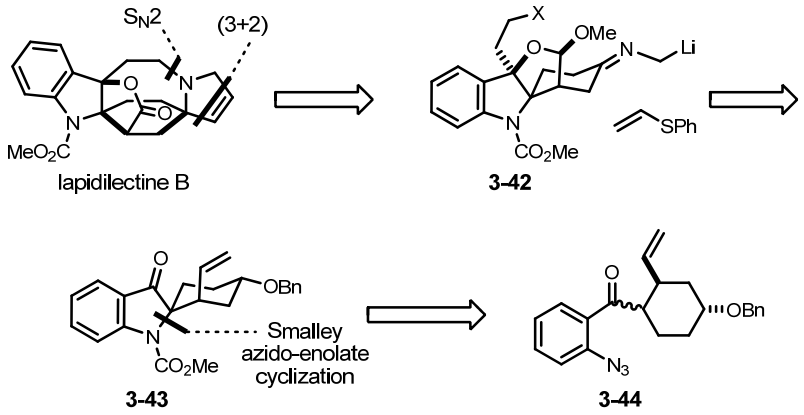
Scheme 3.7. Sarpong's Synthesis of the Indoloazocine Ring



3.1.2.4 Pearson's Total synthesis of Lapidilectine B

To date, the only completed synthesis of the lapidilectine, lundurine, or grandilodine natural products has been that of Pearson and coworkers who have successfully synthesized lapidilectine B.[12] The successful route relied on construction of the [4.2.2] ring system at a late stage, preceded by a (3 + 2) cycloaddition between azaallyllithium **3-42** and vinylsulfide (Scheme 3.8). The cycloaddition precursor was synthesized from 3-oxindole **3-43**, which was made available through a Smalley azido-enolate cyclization of **3-44**.

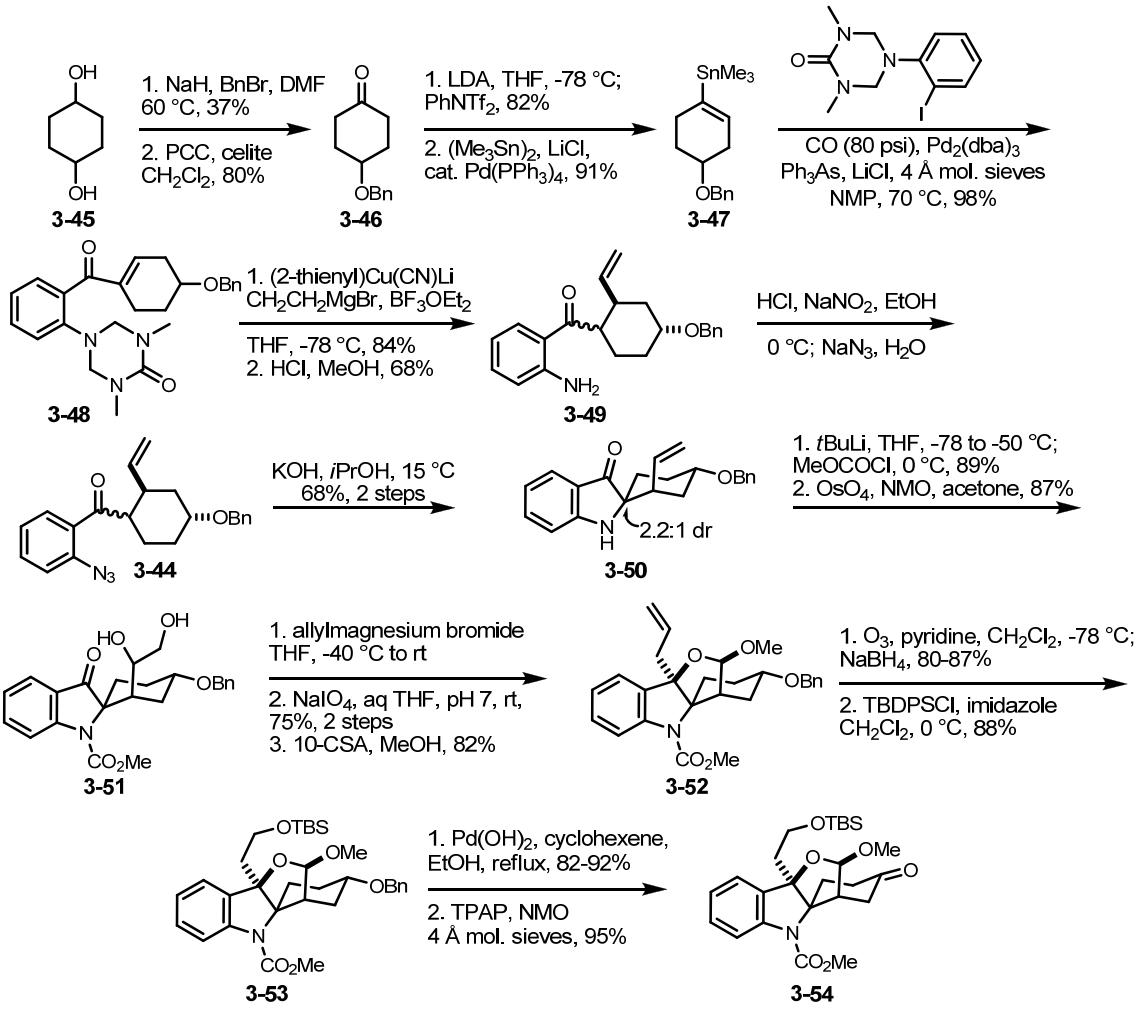
Scheme 3.8. Pearson's Retrosynthesis of Lapidilectine B



The synthesis began with monobenzylation and oxidation of *cis/trans*-cyclohexane-1,4-diol to give ketone **3-45** (Scheme 3.9). Enol-triflate formation and stannylation afforded stannane **3-47** which underwent a Stille carbonylative cross-coupling to afford **3-48**. Conjugate addition of vinylmagnesium bromide and cleavage of the nitrogen protecting group produced amine **3-49**. Installation of an azide was accomplished by conversion of the amine to a diazonium salt with sodium nitrite and HCl, followed by displacement with sodium azide. Subsequent Smalley azido-enolate cyclization afforded **3-50** as a 2.2:1 mixture of separable diastereomers. *N*-Acylation with methylchloroformate and dihydroxylation of the terminal olefin afforded **3-51**. Allylation of the ketone with allylmagnesium bromide and subsequent periodate cleavage afforded an aldehyde which was ketalized in acidic methanol to afford methyl acetal **3-52** as a single diastereomer whose stereochemistry was confirmed through X-ray crystallography. Ozonolysis of the newly installed terminal olefin with a reductive workup afforded a primary alcohol which was immediately protected as a TBDPS ether (**3-53**). Completion of the (3 + 2) cycloaddition precursor was accomplished through

reductive removal of the benzyl protective group with Pearlman's catalyst followed by Ley oxidation to afford ketone **3-54**.

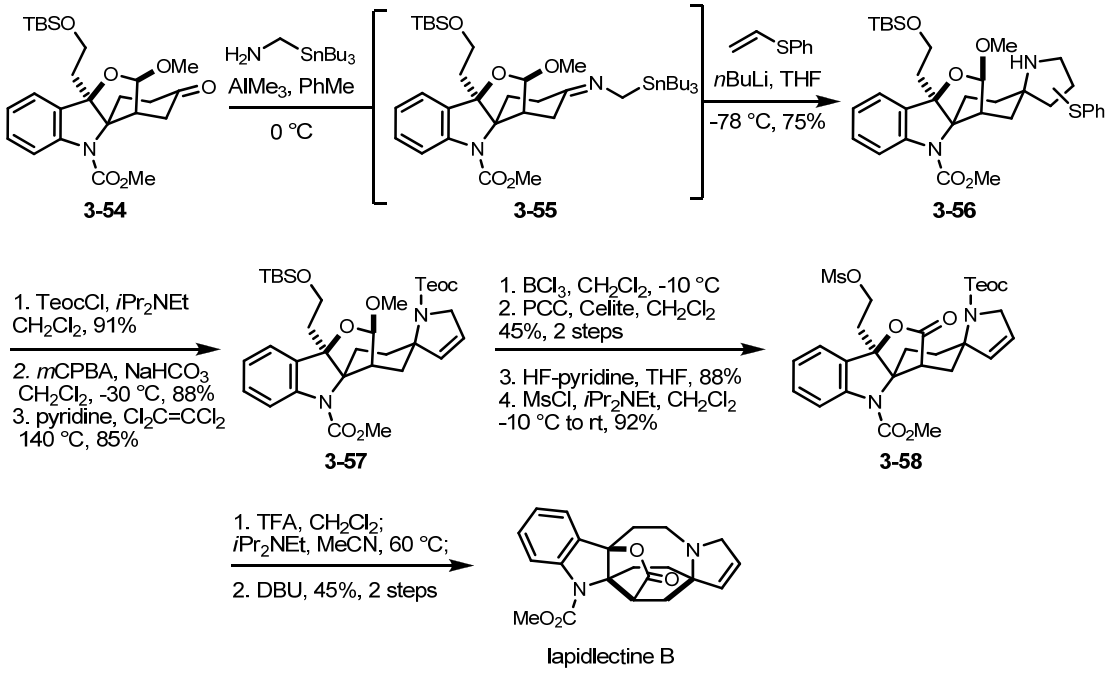
Scheme 3.9. Synthesis of the Cycloaddition Precursor



With ketone **3-54** in hand, the stage was set for the key (3 + 2) cycloaddition (Scheme 3.10). Condensation of aminomethyltributylstannane with ketone **3-54** afforded intermediate **3-55** which, upon treatment with phenylvinyl sulfide and *n*-butyllithium, underwent the (3 + 2) cycloaddition to produce pyrrolidine **3-56** in 75% yield as an undetermined mixture of carbamate rotamers or regio- and stereoisomers. Protection of

the free secondary amine as a Teoc carbamate and oxidation of the sulfide to the sulfoxide followed by thermolysis coalesced the mixture of compounds into a single product, **3-57**, in good overall yield. Demethylation of the methylacetal with BCl_3 followed by PCC oxidation installed the required lactone functionality, and deprotection of the TBDPS ether and mesylation afforded mesylate **3-58**. The synthesis was completed by TFA deprotection of the Teoc-protected nitrogen and intramolecular ring closure, facilitated by heat and Hunig's base, to afford (±)-lapidilectine B. Overall, the synthesis required 28 steps and provided the natural product in 0.14% yield from commercially available cyclohexane-1,4-diol.

Scheme 3.10. Cycloaddition and Completion of the Total Synthesis of Lapidilectine B



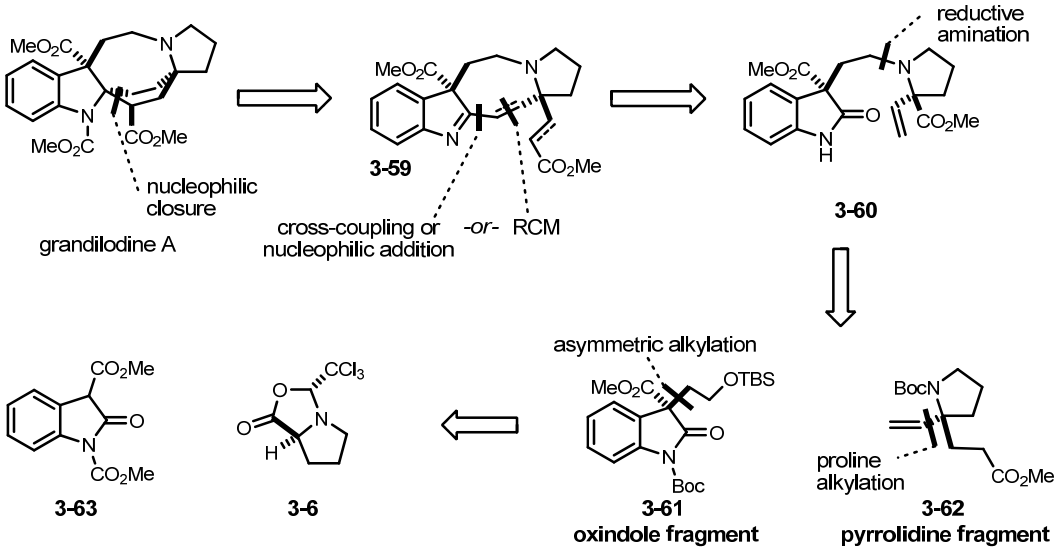
3.2 Studies Towards the Synthesis of Grandilodine A

3.2.1 Retrosynthetic Analysis

Our original retrosynthesis of grandilodine A is outlined in Scheme 3.11. Formation of the azabicyclo[4.2.2]becane system could occur *via* nucleophilic addition to

an imine species, creating the last quaternary center. It was believed that this could be accomplished through an aza-Baylis–Hillman reaction, similar to the procedure developed by Andrade and coworkers for the synthesis of the *Strychnos* alkaloids[13] and subsequently applied by Andrew and Kwon for the synthesis of (+)-ibophyllidine.[14] The central 8-membered ring (**3-59**), difficult to form due to increased strain from trans-annular interactions, would rely on RCM, nucleophilic addition, or cross-coupling chemistry. Formation of the 8-membered ring precursor (**3-60**) would be achieved through reductive amination of pyrrolidine fragment **3-62** with oxindole fragment **3-61**. The requisite oxindole (**3-61**) and pyrrolidine fragments (**3-62**), each in enantioenriched form, would arise from an asymmetric-organocatalytic aldol reaction and proline oxazolidinone-alkylation/homologation respectively.

Scheme 3.11. Retrosynthetic Analysis of Grandilodine A

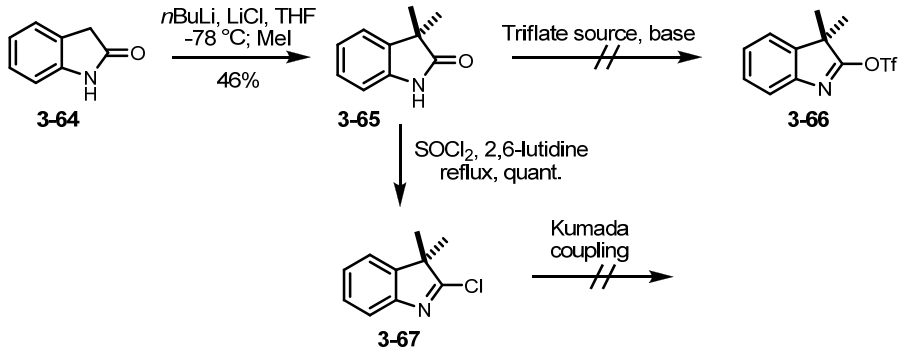


3.2.2 Synthesis of the Oxindole Fragment

3.2.2.1 Model Study for Cross-Coupling or RCM Formation of the 8-Membered Ring

It was deemed prudent to assess the viability of the cross-coupling chemistry necessary for the 8-membered ring formation prior to exploration with more complex substrates. There are examples of cross-coupling of both iminotriflates[15] and iminochlorides,[16] though the reports are relatively few. Test substrate **3-65** was synthesized through alkylation of commercially available 2-oxindole with methyl iodide to afford 3,3-dimethyl-2-oxindole (Scheme 3.12). Attempts to form the iminotriflate through treatment of oxindole **3-65** with triflation sources, such as Tf_2O, *N*-phenyl triflamide or Comins reagent and a variety of bases all failed to provide the iminotriflate and thus cross-coupling chemistry though the iminotriflate was abandoned. Iminochloride **3-67** was also synthesized through treatment of oxindole **3-65** with thionyl chloride and 2,6-lutidine; however, subsequent Kumada couplings did not occur.

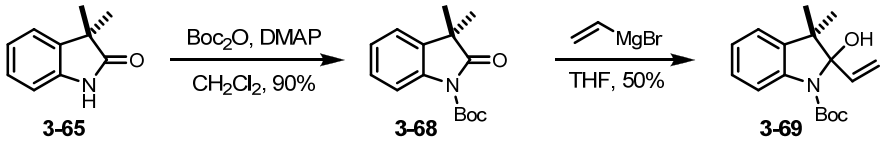
Scheme 3.12. Model Study for Ring Closure *via* Cross-coupling Chemistry



We next explored nucleophilic addition as a means of introducing either the pyrrolidine portion directly, or to introduce an olefin for subsequent RCM (Scheme 3.13). Protection of the nitrogen was necessary and was accomplished by introduction of a Boc

group. It was found that, similar to what has been described by Weinreb and coworkers,[17] nucleophilic addition of vinylmagnesium bromide afforded the desired product (**3-69**) in 60% yield. With a means of introducing the functionality necessary for 8-membered ring formation, attention was focused on the synthesis of the oxindole and pyrrolidine fragments.

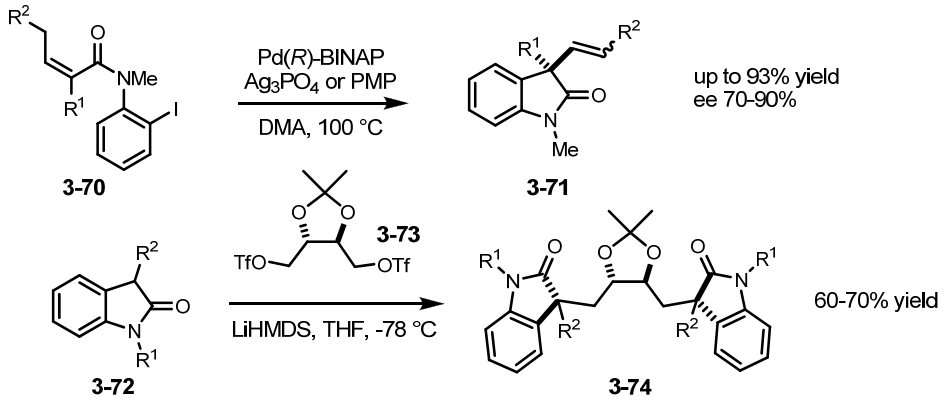
Scheme 3.13. Nucleophilic Addition to Oxindole



3.2.2.2 Quaternary Center Formation *via* Alkyation

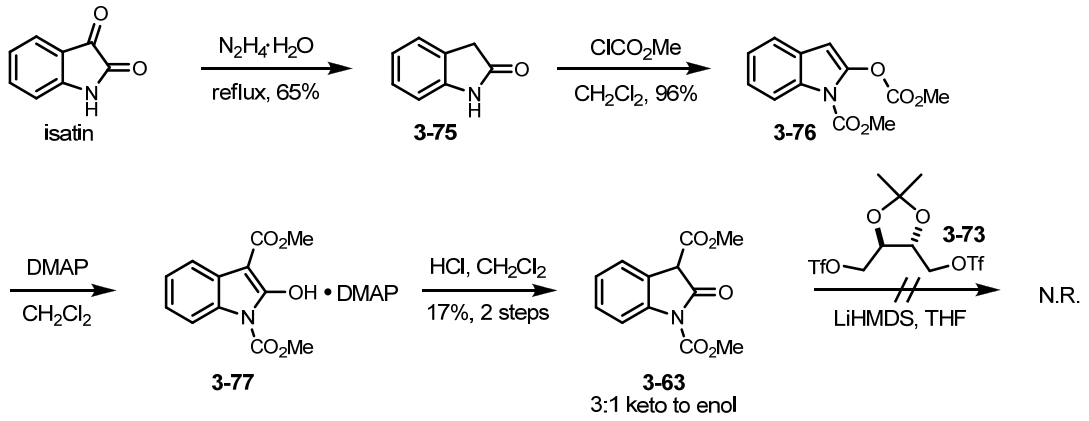
Several routes existed for the formation of the quaternary center present in oxindole fragment **3-61**, two of which were developed by Overman and coworkers (Scheme 3.14). The first method was an asymmetric Heck reaction of iodoanilide **3-70** to afford oxindoles in high yield and acceptable enantioselectivity.[18] The enantiomeric purity of the oxindole could be subsequently increased through recrystallization. Unfortunately, the preparation of the Heck precursor was non-trivial, utilized expensive reagents, and the enantioselectivity of the process was substrate-dependent. To avoid these pitfalls, they developed a second route that relied on alkylation with tartrate-derived electrophile **3-73**.[19] Unlike the Heck route, the alkylation substrates were readily available in few steps and afforded the product in good yield. Notably, the minor products in this transformation are diastereomers of the desired C_2-symmetric product, allowing for facile isolation of the desired compound in very high ee.

Scheme 3.14. Overman's Routes for Synthesis of Quaternary Oxindiole Substrates



It was determined that alkylation with tartrate-derived bis-triflate **3-73** was the most promising route, and thus was elected as the first candidate to be explored (Scheme 3.15). The oxindole substrate was prepared by Wolff–Kishner reduction of isatin, followed by attempted Boc protection of the nitrogen. Unfortunately, a mixture of *N*-Boc, *O*-Boc and *C*-3-Boc compounds were formed, requiring an alternative approach. To that end, treatment of 2-oxindole (**3-75**) with an excess of methyl chloroformate formed enol-formate **3-76** which underwent *O* to *C* acyl transfer mediated by DMAP to affording the DMAP-enolate salt **3-77**. Acidic workup produced the desired oxindole (**3-63**) as a 3:1 keto to enol mixture. The unoptimized yield of this sequence is poor; however, it afforded the requisite starting material necessary for alkylation and could likely be optimized to increase efficiency. Unfortunately, the desired alkylation did not occur, as treatment of the enolate with bistriflate **3-73** afforded only starting material, even after extended reaction times at high temperatures.

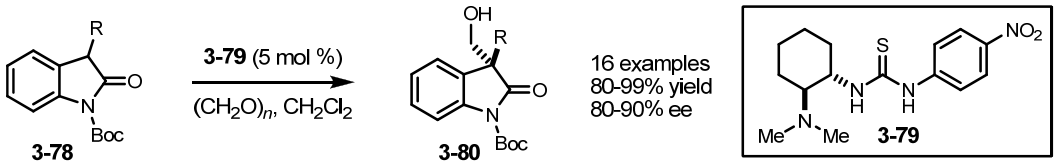
Scheme 3.15. Asymmetric Alkylation with Tartarate-Derived Electrophile



3.2.2.3 Organocatalytic Formation of the Quaternary Center

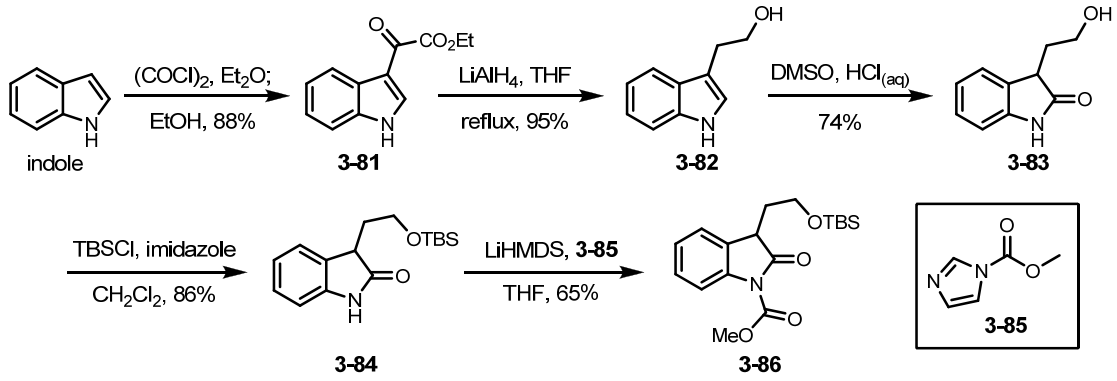
When the alkylation route failed to produce the desired substrate, it occurred to us that an asymmetric aldol between an oxindole and formaldehyde would install the requisite functionality (Scheme 3.16). Fortunately, a recent report describing such a transformation was disclosed by Yuan and coworkers.[20] Many asymmetric organocatalytic transformations for the synthesis of 3,3-disubstituted oxindoles are known; however, the number of direct aldol reactions involving formaldehyde are limited. The report described by Yuan makes use of bifunctional thiourea catalyst **3-79**, paraformaldehyde and an oxindole bearing an *N*-Boc protecting group. It was demonstrated that the *N*-Boc protection was crucial in achieving good enantioselectivity. As this reaction would install the requisite functionality, the organocatalytic transformation was explored for inclusion into the total synthesis.

Scheme 3.16. Organocatalytic Aldol with Thiourea Catalyst **3-79**



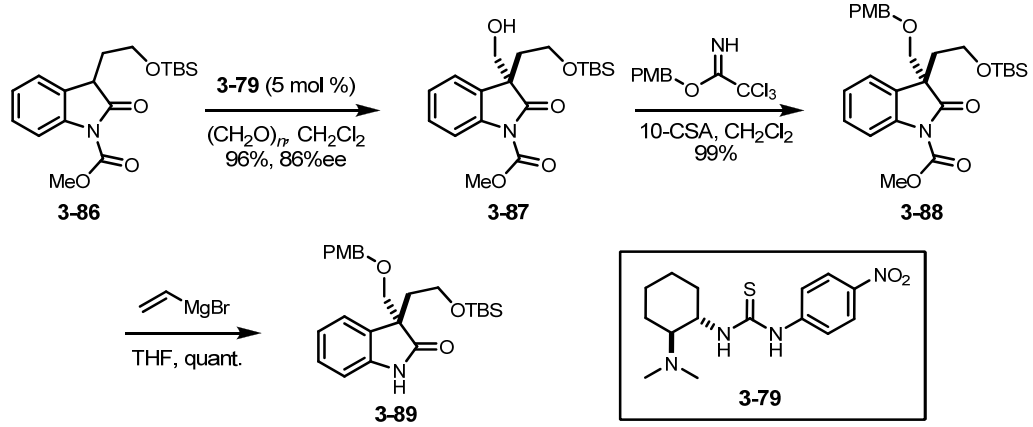
To synthesize the requisite oxindole substrate, attention was turned towards older chemistry (Scheme 3.17). Indole was treated with oxalyl chloride followed by ethanol to form **3-81**, which was subsequently reduced with $LiAlH_4$ to afford tryptophol (**3-82**).[21] Oxidation of the indole ring with DMSO in concentrated hydrochloric acid gave oxindole **3-83**[22] whose primary alcohol was protected as a TBS ether (**3-84**). As previously discussed, the very acidic 3-position proved problematic when attempting to Boc protect the amide nitrogen, forming mixtures of *N*-, *O*- and *C*-bound Boc groups under standard Boc protection conditions. This phenomenon has been noted by others, and Trost[23] has developed an elegant solution whereby attenuation of the electrophilicity of the acylating reagent allowed for selective installation of the methoxylcarbonyl group. Following the procedure of Trost, *N*-methoxycarbonyl protection was readily accomplished using imidazole carboxylate **3-85**, setting the stage for the organocatalytic transformation.

Scheme 3.17. Synthesis of the Organocatalytic Aldol Precursor



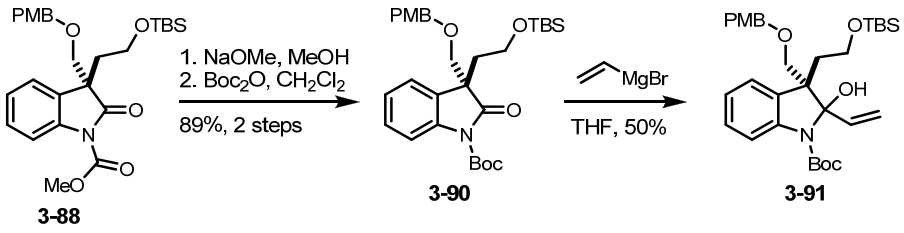
Having synthesized the requisite starting material (**3-86**), the organocatalytic transformation was explored (Scheme 3.18). Fortunately, the reaction proceeded exactly as described to afford primary alcohol **3-87** in excellent yield and acceptable enantioselectivity (86% ee as confirmed by Mosher's ester analysis). To control the reactivity of the newly generated primary alcohol, it was protected as a PMB ether (**3-88**) under standard conditions. At this stage it we elected to explore the potential for nucleophilic addition to the carbonyl. As such, oxindole **3-88** was treated with vinylmagnesium bromide which resulted in *N*-methoxylcarbonyl removal rather than installation of a vinyl group.

Scheme 3.18. Organocatalytic Aldol Reaction



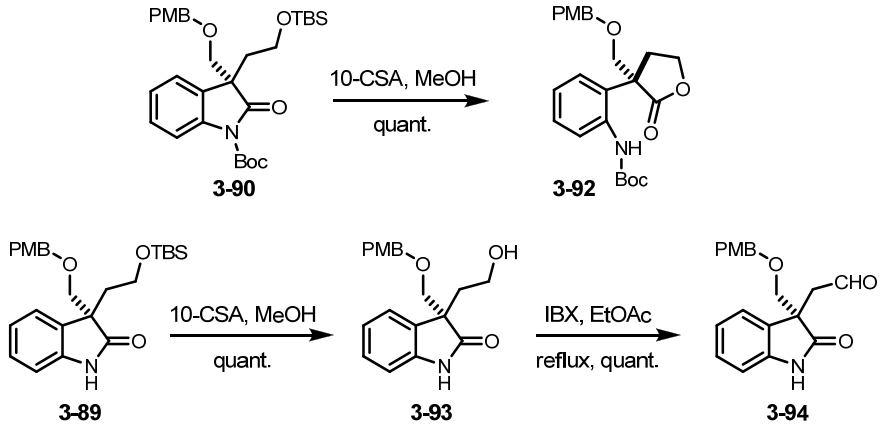
It was clear that the *N*-methoxylcarbonyl group was not robust enough to allow for nucleophilic addition, and thus it was removed and replaced with a Boc protecting group (Scheme 3.19). The addition was found to proceed well to afford the desired addition product (**3-91**) in 50% yield as a 1:1.2 mixture of two diastereomers. Ultimately, the stereochemistry at the newly generated center would be eliminated at a later stage, rendering the poor selectivity inconsequential and as such, the synthesis was carried forward.

Scheme 3.19. Nucleophilic Addition to Oxindole



With a viable coupling route in hand, the oxindole substrate was brought forward to a suitable point for coupling with an amine fragment (Scheme 3.20). To this end, the TBS group of compound **3-90** was removed with 10-CSA. Unfortunately, the newly released alcohol lactonized, resulting in Boc-protected aniline species **3-92**. Deprotection under basic conditions (TBAF) induced similar lactonization, and thus it was necessary to cleave the TBS group prior to installation of the Boc protecting group. Subsequent oxidation of the primary alcohol with IBX afforded the requisite aldehyde (**3-95**) for reductive amination in good yield over the three steps.

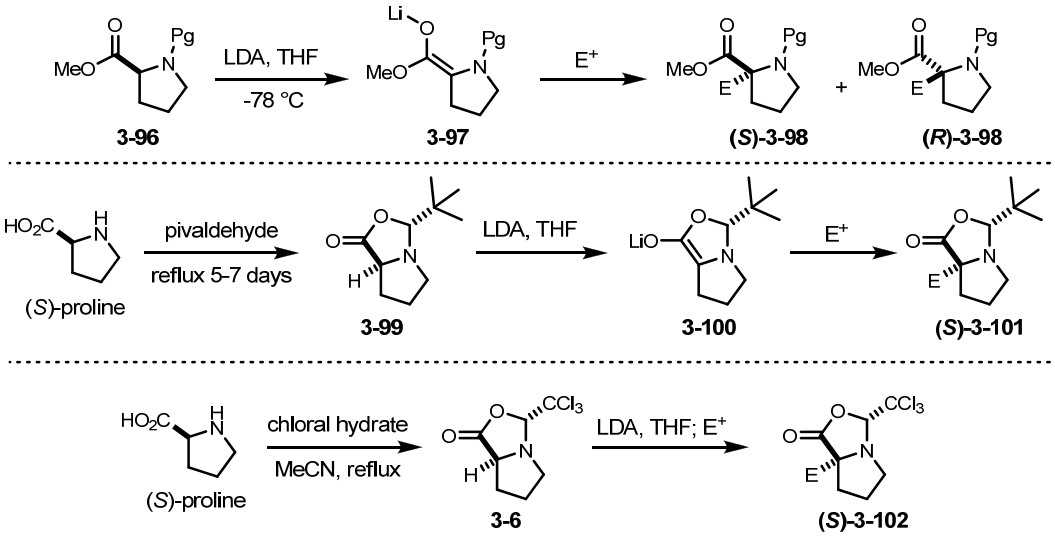
Scheme 3.20. Preparation of the Oxindole Fragment for Coupling



3.2.3 Synthesis of the Pyrrolidine Fragment

In contrast to the multiple routes available for synthesis of the oxindole fragment, the route for the formation of the quaternary center on the pyrrolidine fragment was easily identified. The most obvious choice for a starting material, if one is looking for an enantiopure and readily available substance, is proline. In order to alkylate adjacent to the nitrogen, however, it is necessary to destroy the only chiral center present in the starting material (**3-97**), thus causing the product to be formed in a racemic sense (Scheme 3.21). This problem was addressed by Seebach[24] and coworkers as they demonstrated that condensation of proline with pivaldehyde forms an oxazolidinone (**3-99**) whose stereochemistry is dictated by the concave nature of the newly-formed bicyclic ring system. Enolate formation destroys one of the stereocenters (**3-100**); however, the stereochemical information is preserved in the oxazolidinone ring and, upon treatment with an electrophile, the desired product can be formed with high diastereoselectivity. Following cleavage of the oxazolidinone ring, pyrrolidines of high enantiomeric purity can be obtained.

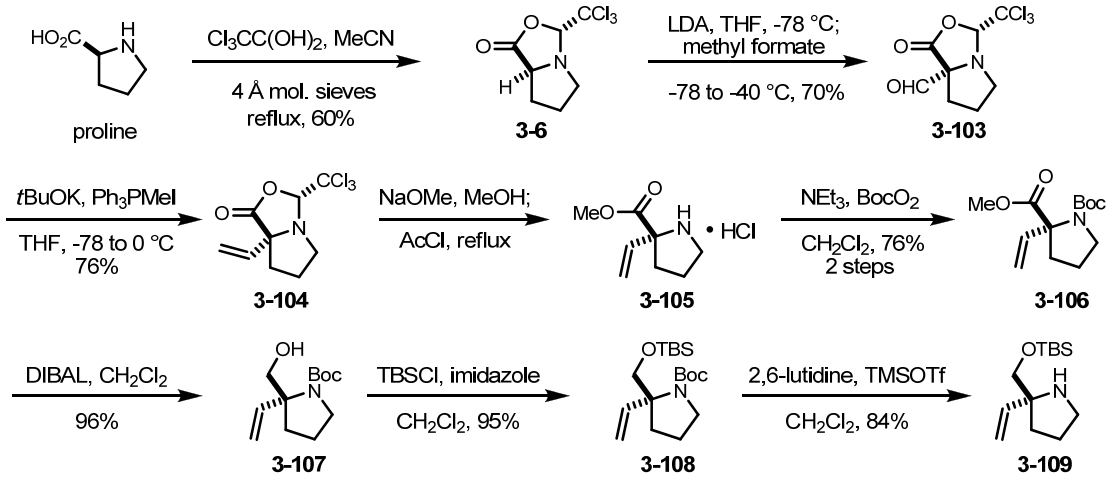
Scheme 3.21. Asymmetric Alkylation of Proline



Despite this method's historic successes, there are multiple drawbacks with which it is associated. The method relies upon using pivaldehyde as the condensation partner which is expensive ($535 for 100 g), must be used in large excess (> 7 equiv), and the condensation requires extended reaction times (5 – 7 days). In addition, the formed oxazolidinone is extremely moisture sensitive and must be isolated under inert atmosphere and used immediately. More recently, chloral has been identified as a superior alternative.[7,8,25] Though chloral is a controlled substance, it is comparably inexpensive ($55 for 500 g) and readily forms the desired condensation product (**3-6**), which is a moisture stable and highly crystalline solid. Additionally, though the auxiliary is moisture stable and can be purified *via* column chromatography, as can the alkylation products, the auxiliary can be readily cleaved through basic hydrolysis. Despite the superior nature of the chloral-derived auxiliary, it has seen only sparse use in the literature.[26] It was decided that this method would provide the most facile route to an enantiopure pyrrolidine fragment.

To this end, (*S*)-proline was condensed with chloral hydrate to form bicyclic oxazolidinone **3-6** (Scheme 3.22). Subsequent alkylation with methyl formate allowed for installation of a formyl group; however, the reaction had to be acidified at –40 °C as the methoxide byproduct quickly cleaved the auxiliary at temperatures above –40 °C. Wittig olefination of the aldehyde installed the desired olefin, and removal of the auxiliary by basic, then acidic conditions afforded alkylated proline fragment **3-105**. Protection of the pyrrolidine nitrogen was necessary,[27] thus a Boc protecting group was installed (**3-106**). The ester was then reduced with DIBAL and protected as the TBS ether (**3-108**). Finally, efficient removal of the Boc protecting group was achieved with TMSOTf and 2,6-lutidine to afford pyrrolidine fragment **3-109** ready for reductive amination with the oxindole fragment.

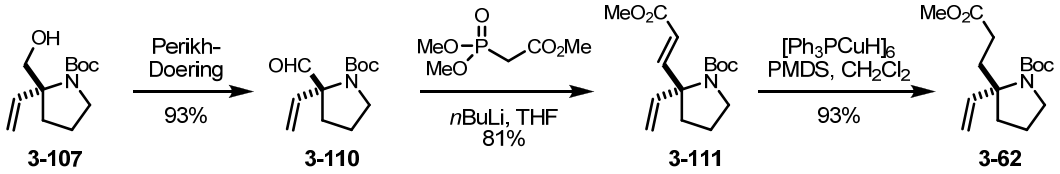
Scheme 3.22. Synthesis of Pyrrolidine Fragment



At this point, the viability of the ester homologation procedure required for installation of the necessary enone for closure of the azabicyclo[4.2.2]decane system was explored. Starting from primary alcohol **3-107**, oxidation under Parikh–Doering conditions and homologation with trimethyl phosphonoacetate afforded the required α,β-

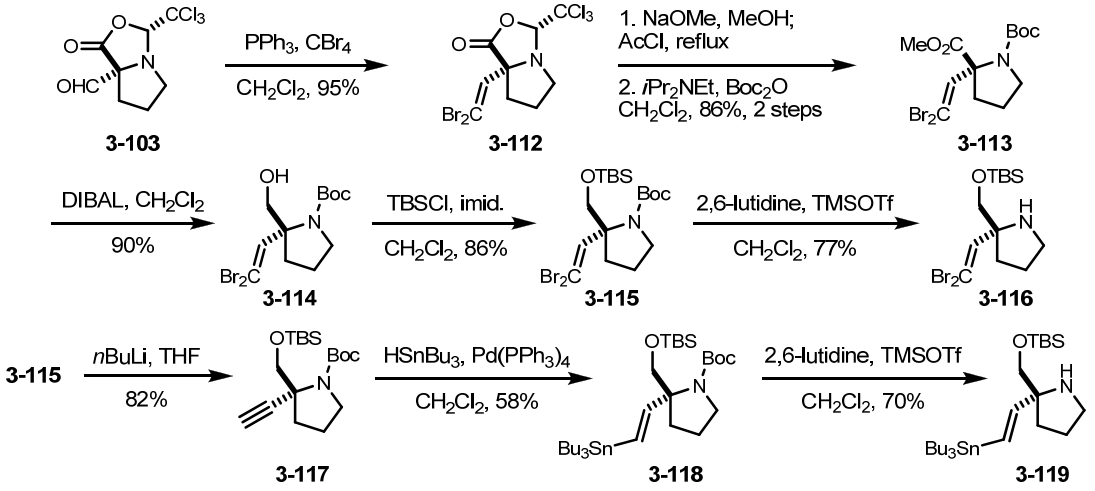
unsaturated ester (Scheme 3.23). The conjugated double bond of **3-111** would eventually need to be hydrogenated, possibly in the presence of other olefins, and as such the reduction was explored. Unfortunately, $NaBH_4$, $LiBH_4$, and $NiBH_4$ were all incapable of reducing the enoate. However, treatment of **3-111** with Stryker's reagent and PDMS successfully effected the reduction with complete selectively for the conjugated olefin, affording saturated ester **3-62** in high yield.

Scheme 3.23. Ester Homologation and Reduction



Following completion of the pyrrolidine fragment, it was deemed prudent to explore alternative options for closure of the eight-membered ring. Thus, several related substrates were synthesized, particularly those which could act as nucleophiles (Scheme 3.24). A pyrrolidine fragment with a latent alkyne was synthesized by homologation of aldehyde **3-103** with PPh_3 and CBr_4. The substrate was carried forward through the same sequence of reactions found in Scheme 3.22 to afford pyrrolidine **3-116**. Alternatively, dibromoolefin **3-115** was converted to the alkyne prior to Boc deprotection by exposure to *n*-BuLi, affording alkynyl-pyrrolidine **3-117**. Subsequent hydrostannylation of the alkyne was performed and, following Boc deprotection, stannyl-pyrrolidine **3-119** was obtained.

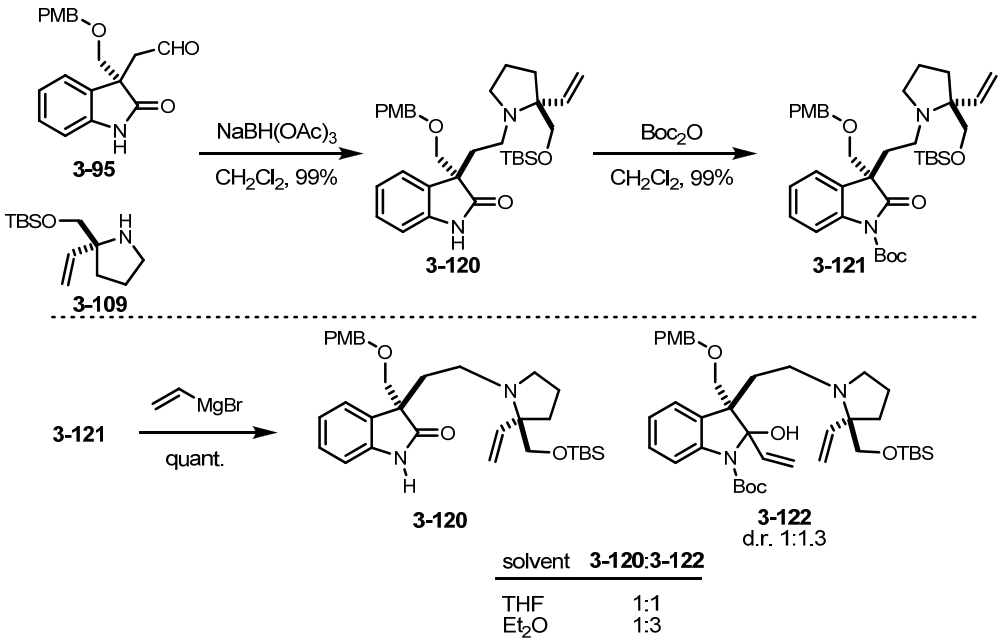
Scheme 3.24. Alternative Pyrrolidine Fragment Synthesis



3.2.4 Fragment Coupling and Attempted Ring Closure

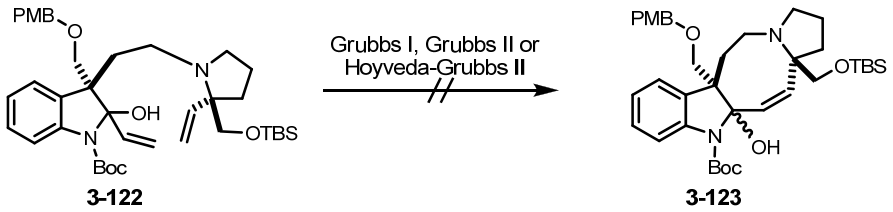
Pyrrolidine **3-109** and oxindole **3-95** were coupled smoothly via reductive amination and the product was subsequently *N*-Boc protected to afford **3-121** in good yield (Scheme 3.25). Analysis of the crude reaction mixture confirmed the previously determined enantiomeric purity of the oxindole substrate, as 7% of a separable diastereomer was observed by ^{1}H NMR. Addition of vinylmagnesium bromide afforded the desired product **3-122** in 50% yield as a 1:1.3 mixture of diastereomers with the mass balance being Boc deprotected material (**3-120**). It was possible to suppress the formation of the Boc deprotection by using diethyl ether, as opposed to THF, as the reaction solvent.

Scheme 3.25. Installation of the Pyrrolidine *via* Reductive Amination



With compound **3-122** in hand, formation of the 8-membered ring by RCM was investigated (Scheme 3.26). Unfortunately, despite attempting multiple different catalysts and forcing conditions, only starting material was obtained and no RCM product was detected by NMR.

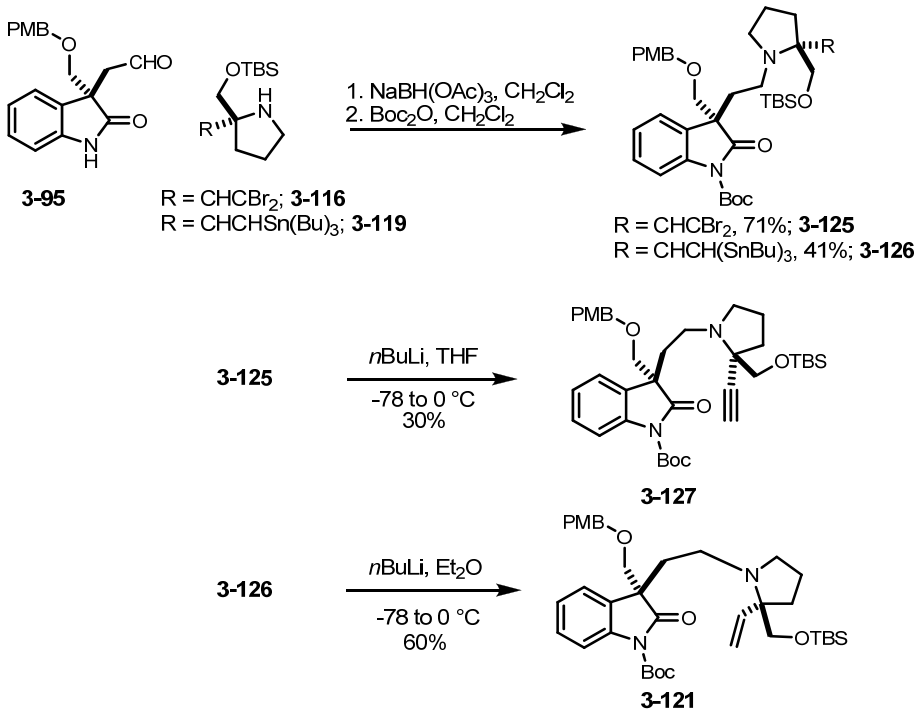
Scheme 3.26. Attempted RCM for 8-Membered Ring Formation



Due to the failure of the RCM event, the previously synthesized alternative pyrrolidine fragments (Scheme 3.24) were investigated. Dibromoolefin **3-116** and vinylstannane **3-119** were reductively aminated with oxindole **3-95** and subsequently *N*-

Boc protected to afford substrates **3-125** and **3-126** (Scheme 3.27). Treatment of dibromoolefin **3-125** with *n*-BuLi afforded alkyne **3-127**, though in moderate yield. Unfortunately, alkyne **3-127** would not undergo nucleophilic addition to the oxindole carbonyl upon treatment with base, most likely due to the inability of the alkyne nucleophile to approach the carbonyl in the correct geometry. The vinyl stannane **3-126** was transmetallated with *n*-BuLi; however, once again no nucleophilic addition was observed and only destannylated product **3-121** was recovered.

Scheme 3.27. Alternative Nucleophilic Addition Attempts

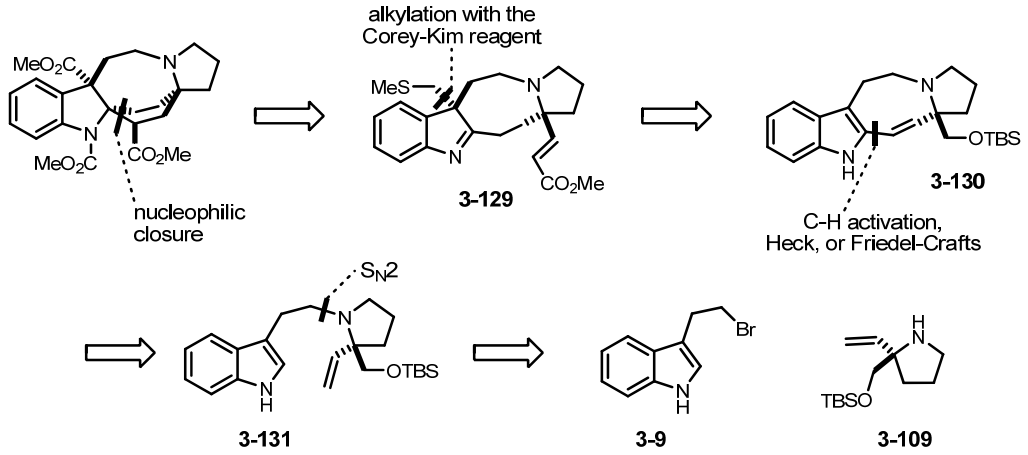


3.2.5 Revision of the 8-Membered Ring Closure

Due to the difficulties encountered with formation of the 8-membered ring, the retrosynthetic disconnections were revised (Scheme 3.28). The final ring closure was not altered; however, the use of an oxindole substrate was eliminated. Instead, it was believed

that a late-stage alkylation with the Corey–Kim reagent would be capable of installing the necessary quaternary center at the 3-position.[28] It was believed that, though 8-membered rings are very flexible, the geometry of the indoloazocine would dictate the correct facial selectivity of the alkylation event. Alternatively, allylation of the 3-position could be accomplished through direct allylation as shown by Rawal,[29] though lengthy subsequent transformations would be necessary to afford the ester. The indoloazocine ring system of **3-130** could arise through C-H activation or Heck reaction in an intramolecular fashion, and the pyrrolidine fragment could be appended to the indole by an S_N2 reaction.

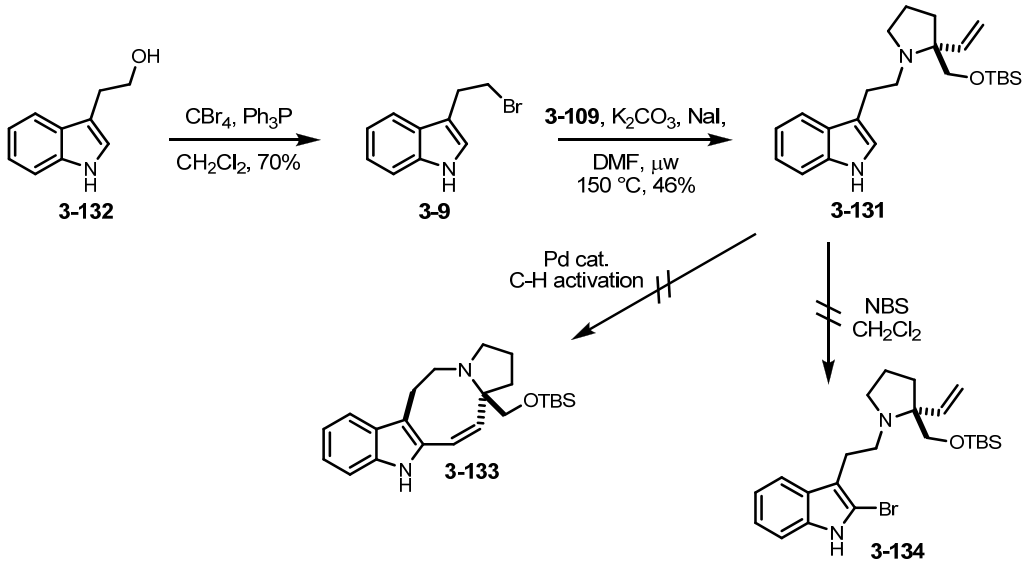
Scheme 3.28. Revised Retrosynthetic Plan



To this end, tryptophol (**3-132**) was converted to primary bromide **3-9** with CBr_4 and PPh_3. Microwave heating of a mixture of bromide **3-9**, pyrrolidine **3-109**, NaI, K_2CO_3 and DMF facilitated the S_N2 reaction to afford **3-131**. Despite encouraging literature precedent for the C-H activation/Heck reaction,[30] the desired product was not formed and only starting material was obtained. It was believed that the lack of reactivity may be due to a failure of the C-H activation event, and thus the indole substrate (**3-131**)

was exposed to bromination conditions to install an activating group. Unfortunately, rapid decomposition was observed and thus the route was abandoned.

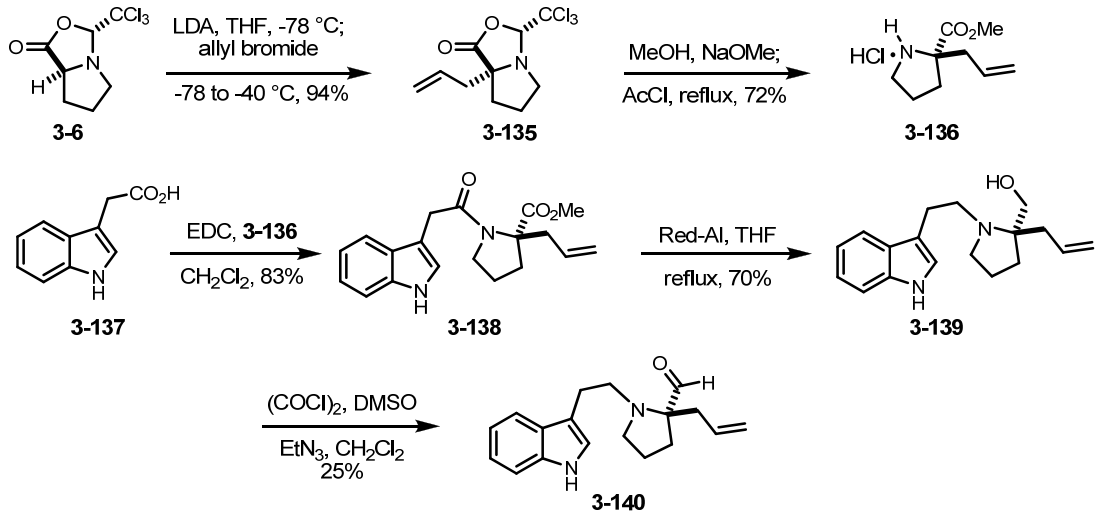
Scheme 3.29. Attempted Heck Coupling



With the failure of the Heck route, a Friedel–Crafts reaction was investigated. A similar route was recently described by Sarpong and coworkers for the synthesis of related alkaloids (see Section 3.1.2.3).[11] Accordingly, pyrrolidine **3-136** was synthesized in a similar manner as the previously described pyrrolidine fragments (Scheme 3.30). Pyrrolidine fragment **3-136** was then coupled with indole-3-acetic acid (**3-137**) and, following exhaustive reduction with Red-Al, primary alcohol **3-139** was obtained. Attempts at oxidation of the primary alcohol were met with frustration, as a variety of oxidation conditions failed to facilitate aldehyde formation. Protection of the indole nitrogen as a methyl carbamate failed to improve the situation; however, Swern oxidation conditions were found to afford the desired aldehyde (**3-140**), albeit in low yield. The difficulties associated with this oxidation most likely lie with the tertiary amine, as ring-

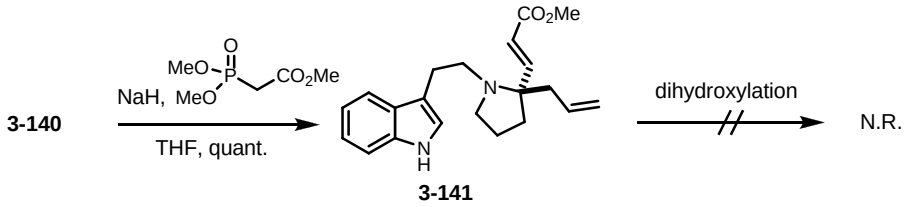
expansion chemistry of pyrrolidines to piperidines *via* an aziridinium can be a facile process.[31]

Scheme 3.30. Synthesis of Friedel-Crafts Precursor



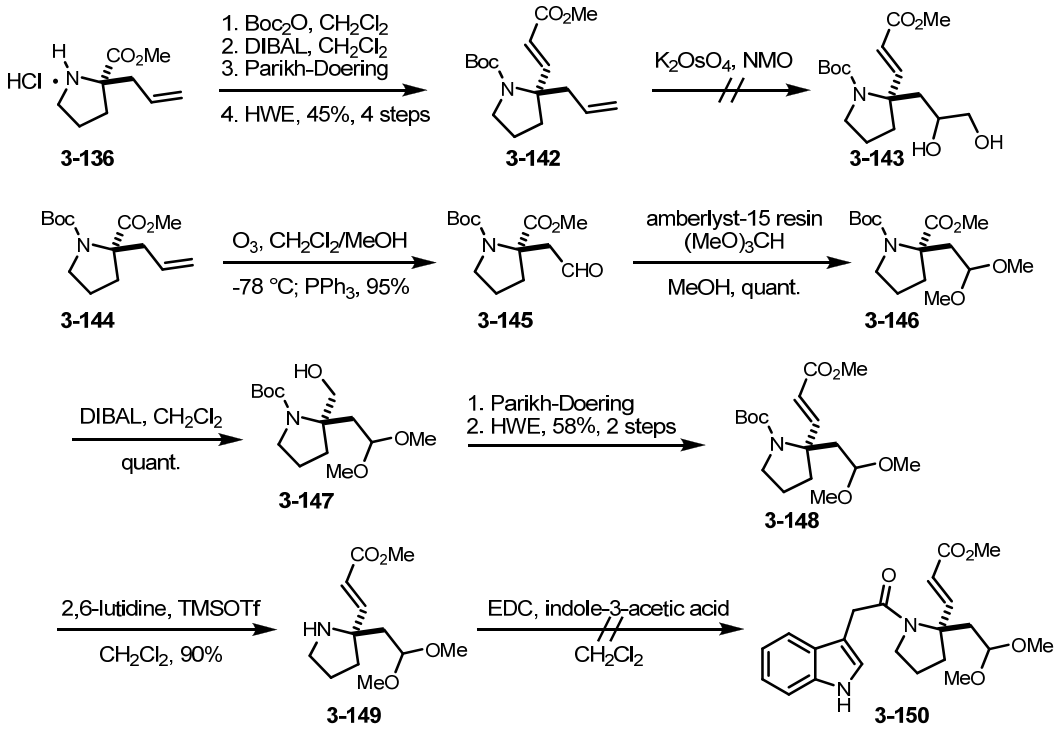
Though the Swern oxidation occurred in low yield, enough material was available for further study. Thus, HWE homologation of aldehyde **3-140** afforded enoate **3-141** (Scheme 3.31). The next step was to oxidatively cleave the terminal olefin; however, it proved exceptionally resilient to oxidation as dihydroxylation with K_2OsO_4 failed to deliver the diol under a number of reaction conditions and only starting material was obtained.

Scheme 3.31. Attempted Olefin Cleavage



To circumvent the poor yield of the oxidation of the primary alcohol (**3-139** to **3-140**) and to effect cleavage of the terminal olefin, studies were conducted on the pyrrolidine fragment prior to indole installation (Scheme 3.32). It was discovered that oxidative cleavage of the terminal olefin could be accomplished by ozonolysis. Following ozonolysis, the aldehyde **3-145** was protected as the dimethylacetal and the ester was reduced with DIBAL. Oxidation and HWE homologation afforded **3-148**. Removal of the Boc group formed secondary amine **3-149**, ready for appendage to the indole fragment. Unfortunately, it was discovered that amine **3-149** would not undergo amide coupling with indole-3-acetic acid due to the increased steric bulk associated with installation of the α,β-unsaturated ester moiety. Hindered amines are known to be problematic when attempting to form amide bonds.[32]

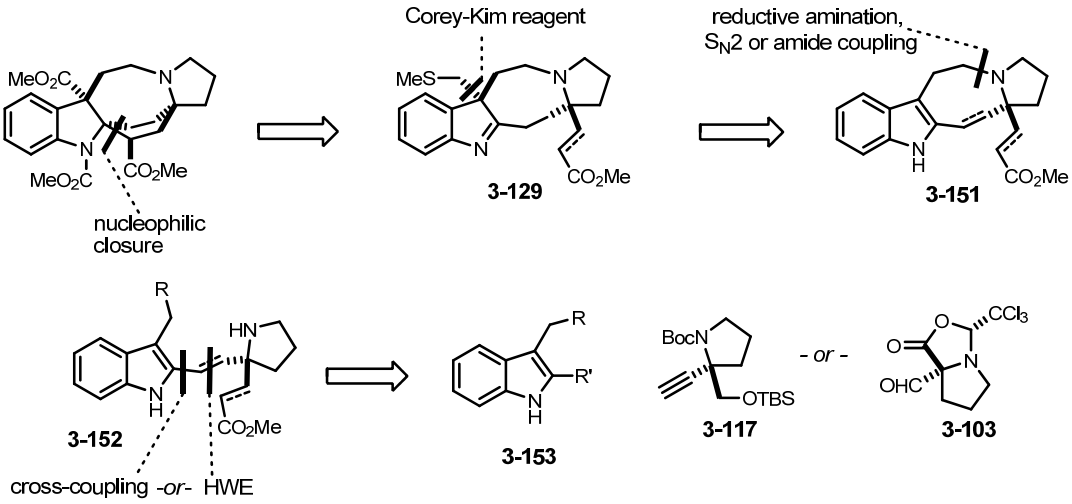
Scheme 3.32. Elaboration of the Pyrrolidine Prior to Coupling



3.2.6 Retrosynthesis dealing with C-2 bond formation prior to C-3

Having encountered difficulties in forming the C-2 attachment, the retrosynthesis of grandilodine A was once again revisited (Scheme 3.33). As before, the late stage nucleophilic closure through aza-Baylis–Hillmann chemistry would be investigated and installation of the quaternary center at the indoline 3-position would be through indole addition to the Corey–Kim reagent followed by Pummerer rearrangement. Closure of the indoloazocine ring would originate from an intramolecular reductive amination, S_N2 displacement, or amide coupling (**3-151**). Accordingly, introduction of the pyrrolidine portion would be afforded through coupling at the 2-position of indole, rather than the 3 position.

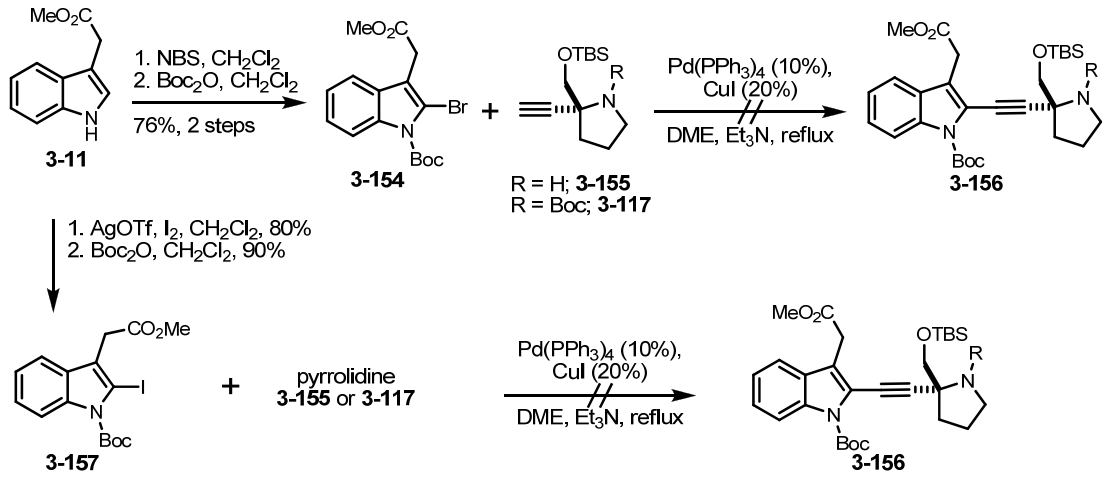
Scheme 3.33. Revised Grandilodine A Retrosynthesis



Installation of the pyrrolidine fragment at the 2-position of indole was investigated first through cross-coupling chemistry. The Sonogashira reaction has been successfully applied for the cross-coupling of 2-haloindoles with complex alkyne substrates by Fukuyama for the synthesis of aspidophytine[33] and by Baran for the

synthesis of chartelline C.[34] Similarly, it was believed that 2-bromoindole **3-154** would undergo Sonogashira coupling with alkyne **3-155** or **3-117** to afford the desired product. The requisite 2-bromo and 2-iodoindole substrates **3-154**[35] and **3-157**[36] were synthesized according to literature procedures. Unfortunately, the Sonogashira reaction was unsuccessful as treatment of alkyne **3-155** and indole **3-154** afforded only starting material and traces of alkyne dimer. Similar results were obtained whether the pyrrolidine nitrogen was protected (**3-117**) or not (**3-155**), as well as when the more reactive 2-iodoindole **3-157** was used as the cross-coupling partner.

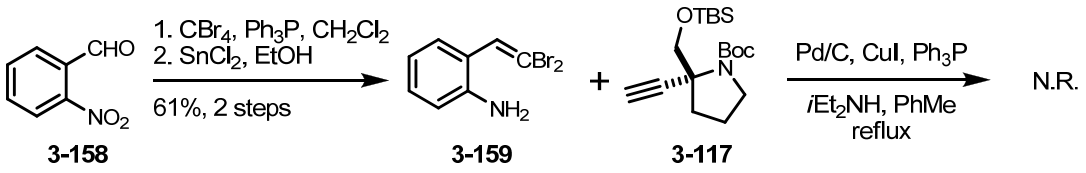
Scheme 3.34. Sonogashira Cross-Coupling for Installation of the Pyrrolidine Fragment



Alternatively, a tandem Ullman/Sonsogashira reaction was investigated (Scheme 3.35). This tandem reaction has been shown to be an effective method for the synthesis of 2-alkynyl indoles by Lautens.[37] To this end, 2-nitrobenzaldehyde (**3-158**) was treated with PPh_3 and CBr_4 followed by nitro group reduction with $SnCl_2$ to afford anilide **3-159**. Under the conditions of Lautens, subjection of anilide **3-159** and alkyne **3-117** to the reaction conditions resulted only in isolation of starting material, without the observance

of any cross-coupled product. A control test was performed with 1-hexyne and the reaction was found to proceed as described, affording the alkynylindole in excellent yield, indicating that the reaction was substrate specific, rather than suffering from irreproducibility.

Scheme 3.35. Tandem Ullman/Sonogashira Cross Coupling

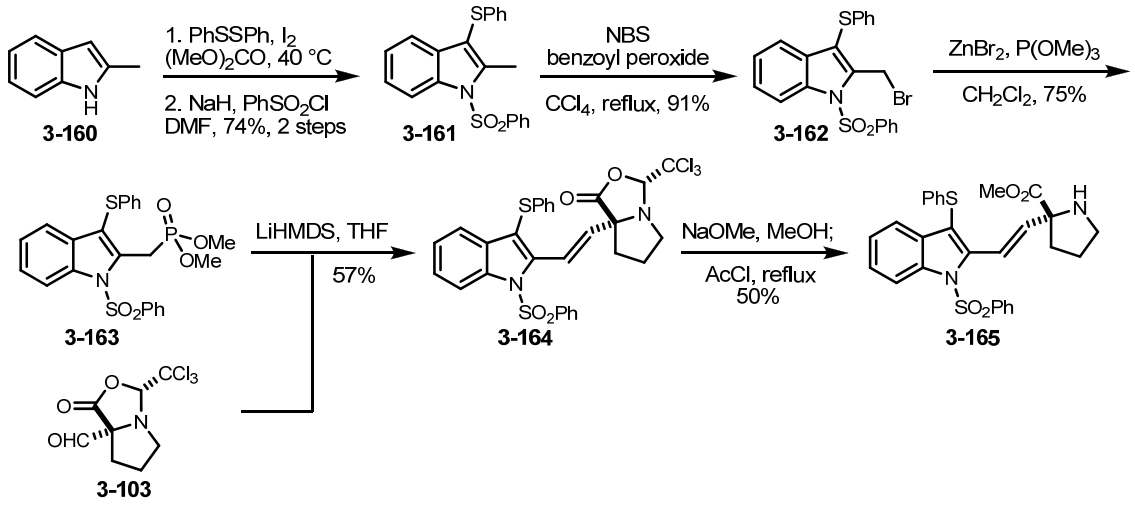


3-158 **3-159** **3-117**

3.2.7 Horner–Wadsworth–Emmons Route

A new strategy was devised, whereby the indole C-2 position would first be joined to the pyrrolidine fragment through HWE chemistry, followed by ring closure at the 3-position (See Scheme 3.33). To this end, the 3-position of 2-methyl indole was thiolated and the nitrogen was protected as the benzenesulfonamide (Scheme 3.36). Next, the phosphonate was installed *via* radical bromination and subsequent $ZnBr_2$-catalyzed Arbuzov reaction. With phosphonate **3-163** in hand, we were delighted to discover that the HWE reaction worked as planned, as treatment of a mixture of **3-163** and aldehyde **3-103** with LiHMDS afforded the desired product (**3-164**) in 83% yield. Unfortunately, as the scale of the reaction was increased, a significant decrease in yield was observed (83% at 0.64 mmol scale, 57% at 2.8 mmol scale). Attempts to increase the yield through use of modified conditions (LiCl/DBU[38] or NaI/DBU[39]) were unsuccessful and resulted in only decomposition of the aldehyde. Cleavage of the oxazolidinone could be achieved as previously described through basic, then acidic conditions. Unfortunately, due to time constraints, the project was suspended.

Scheme 3.36. HWE Route Towards Grandilodine A

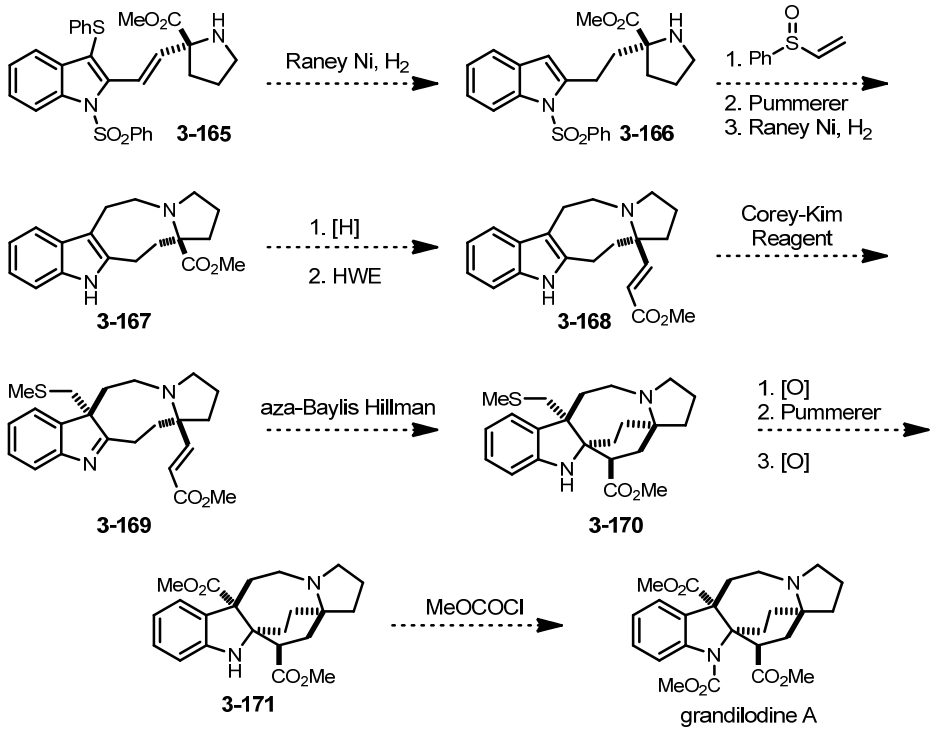


The current route bears promise, as effective coupling of indole and pyrrolidine fragments has been achieved. Further study is required to successfully elaborate **3-165** and determine if the route is viable for the total synthesis of grandilodine A.

In a forward-looking scence, the current route being investigated has been summarized below in **Scheme 3.37**. The benzenethiol protecting group and the internal olefin in HWE product **3-165** would be reduced using Ranney nickel and hydrogen to afford **3-166**. Subsequent Michael addition of the secondary amine in **3-166** to phenyl vinyl sulfoxide followed by Pummerer rearrangement and reduction would afford the necessary 2-carbon bridge, forming the 8-membered ring in **3-167**. A partial reduction of the ester present in **3-167**, followed by HWE homologation would afford **3-168** which, upon treatment with the Corey–Kim reagent, would yield the necessary quaternary stereocenter. An aza-Baylis–Hillman reaction would then close on the generated imine, generating the azabicyclo[2.2.4]decane ring system (**3-170**). All that would remain would be functional group manipulations: oxidation of the thioether, Pummerer rearrangement and further oxidation to afford the methyl ester present in **3-171** and installation of the

carbamate on the indoline nitrogen using methyl chloroformate, affording grandilodine A.

Scheme 3.37. Future Work Towards Grandilodine A



3.3 Summary and Outlook

The grandilodines are structurally and biologically fascinating natural products that will continue to provide inspiration for chemists to develop new strategies and methods for their effective formation. Enclosed herein we have described multiple routes toward the synthesis of the grandilodine A. We have developed an effective procedure for formation of a variety of pyrrolidine fragments, which may be of use for future synthesis of the natural product. The most recently explored route bears promise; however, many synthetic transformations remain to be completed.

3.4 Experimental

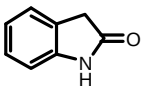
3.4.1 General Experimental Details

All reactions were run under an argon atmosphere. Flasks were oven dried and cooled in a dessicator prior to use. Solvents and reagents were purified by standard methods.[40] Dichloromethane and toluene were purified by passing the solvent through activated alumina columns. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions was monitored by thin layer chromatography performed on F254 silica gel plates. The plates were visualized by UV light (254 nm) or by staining with ceric ammonium molybdate,[41] or $KMnO_4$. Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[42]

The ^1H and ^{13}C NMR data were obtained on 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and were referenced to the residual chloroform at δ 7.25 ppm for ^1H spectra and the center peak of the triplet at δ 77.0 for ^{13}C spectra. EI mass spectra were obtained on a Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV.

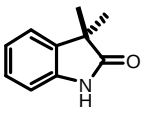
3.4.2 Experimental Details

2-oxindole (3-64)



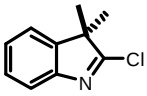
Isatin (15 g, 102 mmol, 1 equiv) was added to hydrazine hydrate (60 mL) and the solution was heated to reflux. After 4 h the reaction mixture was cooled to room temperature, poured into an ice/water mixture and acidified with 6 M HCl. After sitting at room temperature for 2 days the resulting brown-orange solids were collected by vacuum filtration, washed with water, and dried under vacuum to afford 2-oxindole as a brown-orange solid (8.85 g, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (br. s., 1 H), 7.16 - 7.25 (m, 2 H), 6.96 - 7.05 (m, 1 H), 6.88 (d, J = 8.2 Hz, 1 H), 3.54 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.33, 139.87, 136.24, 127.60, 122.53, 122.39, 109.94, 44.70, 24.27 . ^1H and ^{13}C NMR spectra were in agreement with previously reported data.[43]

3,3-dimethyl-2-oxindole (3-65)



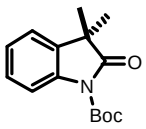
To a solution of 2-oxindole (1.5 g, 11.3 mmol, 1 equiv) and LiCl (1.18 g, 27.9 mmol, 2.47 equiv) in THF (50 mL) at 0 °C was added *n*BuLi (2.35 M, 10 mL, 23.7 mmol, 2.1 equiv). After 20 min MeI (1.40 mL, 22.5 mmol, 2 equiv) was added and the reaction mixture was allowed to warm to room temperature. After 16 h the reaction mixture was diluted with ½ saturated NH_4Cl and Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (2:1 hexanes/EtOAc) to afford the title compound as a waxy white solid (830 mg, 46%). R_f 0.37 (2:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (br. s., 1 H), 7.15 - 7.23 (m, 2 H), 7.04 (t, *J* = 7.9 Hz, 1 H), 7.00 (d, *J* = 7.6 Hz, 1 H), 1.43 (s, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.7, 140.0, 136.2, 127.6, 122.4, 122.3, 110.1, 44.7, 24.2; LRMS *m/z* 161.2 (calcd for $C_{10}H_{11}NO$, 161.0841).

Compound 3-67



To a solution of oxindole **2-65** (65 mg, 0.5 mmol, 1.0 equiv) and 2,6-lutidine (93 μL, 0.80 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) at 0 °C was added oxalyl chloride (43 μL, 0.5 mmol, 1 equiv). After 15 min the reaction mixture was diluted with Et_2O and filtered and concentrated *in vacuo* to afford the iminochloride as a moisture sensitive yellow oil (90 mg, quant.) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 1 H), 7.29 - 7.43 (m, 3 H), 1.53 (s, 6 H.

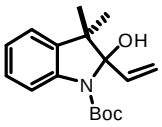
Compound 3-68



To a solution of 3,3-dimethyl-2-oxindole (**3-65**, 559 mg, 3.47 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL)was added Boc_2O (0.957 mL, 4.2 mmol, 1.3 equiv). After 18 h the solvent was removed *in vacuo* and the residue was purified by column chromatography to afford compound **3-68** as a waxy white solid (816 mg, 90%). R_f 0.38 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 1 H), 7.27 - 7.31 (m, 1 H), 7.14 - 7.24 (m, 2 H), 1.66 (s, 9 H), 1.43 (s, 6 H); ^{13}C NMR

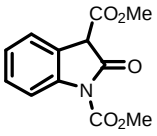
(101 MHz, $CDCl_3$) δ 179.8, 149.5, 138.3, 134.6, 127.9, 124.5, 122.2, 115.0, 84.2, 44.5, 28.1, 25.3; HRMS *m/z* 261.1369 (calcd for $C_{15}H_{19}NO_3$, 261.1365).

Compound 3-69



To a solution of **3-68** (125 mg, 0.47 mmol, 1.0 equiv) in THF (5 mL) was added vinyl magnesium bromide (0.72 M in Et_2O, 2 mL, 1.42 mmol, 3.0 equiv). After 30 min the reaction mixture was diluted with ½ saturated NH_4Cl and Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (10:1hexanes/EtOAc) to afford the title compound as a colorless oil (68 mg, 50%). R_f 0.63 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (br. s., 1 H), 7.15 - 7.22 (m, 1 H), 7.10 - 7.15 (m, 1 H), 6.98 - 7.06 (m, 1 H), 5.98 (dd, *J* = 10.6, 17.2 Hz, 1 H), 5.40 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.25 (dd, *J* = 1.0, 10.7 Hz, 1 H), 1.60 (s, 9 H), 1.30 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 139.2, 138.6, 138.4, 127.6, 123.1, 122.1, 114.5, 114.4, 97.5, 82.6, 47.4, 28.4, 24.4, 23.8; HRMS *m/z* 289.1683 (calcd for $C_{15}H_{19}NO_3$, 289.1678).

Compound 3-63



To a solution of 2-oxindole (6.66 g, 50 mmol, 1.0 equiv) and Et_3N (18.2 mL, 130 mmol, 3.0 equiv) in THF (100 mL) at 0 °C was added methyl chloroformate (9.6 mL, 125 mmol, 2.5 equiv) dropwise. The reaction mixture was allowed to warm to room temperature and after 30 min the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with ½ saturated $NaHCO_3$ (50 mL), the aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite and the solvent was removed *in vacuo* to afford the *N,O*-bismethylformate product (**3-76**, 12.0 g, 96%) that was used without further purification. To the *N,O*-bismethyl formate (10.88 g, 43.7 mmol, 1.0 equiv) in PhMe (150 mL) was added DMAP (5.33 g, 43.6 mmol, 1.0 equiv). After 30 min CH_2Cl_2 (50 mL) was added, followed by 1 M HCl (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the

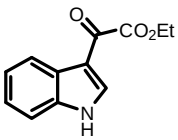
organic layers were combined, dried over $MgSO_4$, filtered through celite and the solvent was removed *in vacuo*. The residue was purified by column chromatography (2:1 hexanes/EtOAc) to afford the title compound (1.88 g, 17%) as a waxy blue solid as a 1.2:1 mixture of keto and enol forms. R_f 0.34 (1:1 hexanes/EtOAc);

Keto form: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1 H), 7.36 - 7.40 (m, 1 H), 0 7.19 - 7.24 (m, 2 H), 4.57 (s, 1 H), 4.02 (s, 3 H), 3.78 (s, 3 H);

Enol form: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.6 Hz, 1 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.36 - 7.40 (m, 1 H), 7.26 - 7.29 (m, 1 H), 4.10 (s, 3 H), 3.99 (s, 3 H).

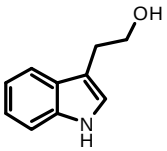
Due to the interconverison of the two compounds, ^{13}C spectra could not be correlated to either of the specific compounds.^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 168.2, 166.4, 160.0, 151.0, 140.1, 129.9, 129.4, 128.1, 124.9, 124.4, 124.2, 124.0, 123.0, 122.0, 119.2, 115.4, 115.1, 114.6, 88.0, 54.3, 54.0, 53.2, 52.7, 51.6; HRMS *m/z* 249.0634 (calcd for $C_{12}H_{11}NO_5$, 249.0637).

Compound 3-81



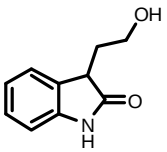
To a solution of indole (11.7 g, 100 mmol, 1.0 equiv) in Et_2O (200 mL) at 0 °C was added oxalyl chloride (10.3 mL, 120 mmol, 1.2 equiv) dropwise and the reaction was warmed to room temperature. After 1 h ethanol (19.1 mL, 500 mmol, 5.0 equiv) was added to the reaction mixture. After 16 h the reaction mixture was diluted with H_2O (100 mL) and the solids were isolated by vacuum filtration. The solids were washed with H_2O (50 mL), cold Et_2O (50 mL) and then dried under vacuum to afford the product as a tan to pale pink powder (19.2 g, 88%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.40 (br. s., 1 H), 8.42 (d, *J* = 3.1 Hz, 1 H), 8.13 - 8.17 (m, 1 H), 7.46 - 7.58 (m, 1 H), 7.15 - 7.32 (m, 2 H), 4.34 (q, *J* = 7.0 Hz, 2 H), 1.31 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 179.5, 164.0, 138.7, 137.1, 125.9, 124.3, 123.3, 121.6, 113.2, 112.8, 62.0, 14.4.

Compound 3-82



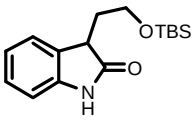
To a slurry of $LiAlH_4$ (2.62 g, 69 mmol, 3.0 equiv) in THF (50 mL) at 0 °C was added the glyoxylate (5.0 g, 23 mmol, 1.0 equiv) portionwise. Upon completion of the glyoxylate addition, the reaction mixture was warmed to room temperature for 1 h, then heated to reflux. After 2 h at reflux the reaction mixture was cooled to 0 °C and diluted with diethyl ether (100 mL) and H_2O (2.62 mL) was added dropwise, followed by 15% aqueous NaOH (2.62 mL), and H_2O (7.86 mL). The reaction mixture was warmed to room temperature and after 15 min the solids were removed by filtration. After concentration *in vacuo* the product was obtained as a colorless oil that slowly solidified on standing (3.52 g, 95%) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br. s., 1 H), 7.63 (d, *J* = 7.8 Hz, 1 H), 7.31 - 7.37 (m, 1 H), 7.23 (t, *J* = 6.8 Hz, 1 H), 7.13 - 7.19 (m, 1 H), 6.97 (d, *J* = 2.3 Hz, 1 H), 3.89 (t, *J* = 6.1 Hz, 2 H), 3.02 (t, *J* = 6.4 Hz, 2 H), 2.18 (br. s., 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 127.2, 122.6, 121.9, 119.2, 118.6, 111.9, 111.2, 62.4, 28.5. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[44]

Compound 3-83



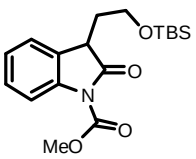
To a solution of the indole (2.54 g, 15.8 mmol, 1.0 equiv) in DMSO (8 mL) in a room temperature water bath was added conc. HCl (11 mL) dropwise. After 3 h the dark mixture was poured into an ice/water mixture (80 mL) and the pH was adjusted to ~7 by addition of a conc. NaOH solution. The aqueous solution was extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a orange semisolid (2.06 g, 74%) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (br. s., 1 H), 7.19 - 7.25 (m, 2 H), 7.03 - 7.08 (m, 1 H), 6.91 (d, *J* = 7.4 Hz, 1 H), 3.91 (q, *J* = 5.1 Hz, 2 H), 3.63 (dd, *J* = 4.9, 8.4 Hz, 1 H), 3.28 (br. s., 1 H), 2.21 - 2.31 (m, 1 H), 2.06 - 2.14 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.3, 141.2, 129.4, 128.1, 124.0, 122.6, 109.9, 60.8, 44.8, 33.1; ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[45]

Compound 3-84



To a solution of alcohol **3-83** (16.7 g, 94.4 mmol, 1.0 equiv) and imidazole (12.6 g, 188.8 mmol, 2.0 equiv) in CH_2Cl_2 (100 mL) was added TBSCl (17.07 g, 113.3 mmol, 1.2 equiv). After complete consumption of the starting material (as indicated by TLC) H_2O (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 hex/EtOAc) to afford the title compound as a pale yellow oil (23.6 g, 86%). R_f 0.30 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1 H), 7.24 (d, *J* = 7.4 Hz, 1 H), 7.16 - 7.23 (m, 1 H), 6.98 - 7.04 (m, 1 H), 6.91 (d, *J* = 7.4 Hz, 1 H), 3.74 - 3.87 (m, 2 H), 3.62 (t, *J* = 6.6 Hz, 1 H), 2.17 - 2.28 (m, 1 H), 2.10 (dq, *J* = 6.7, 13.6 Hz, 1 H), 0.86 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.2, 141.7, 129.5, 127.7, 124.3, 122.0, 109.8, 59.7, 42.9, 33.2, 25.9, 18.2, -5.5, -5.5; LRMS *m/z* 291.3 (calc'd for $C_{16}H_{25}NO_2Si$, 291.1655).

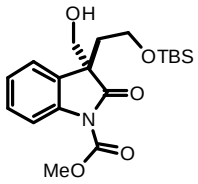
Compound 3-86



To a solution of oxindole **3-84** (2.55 g, 8.75 mmol, 1.0 equiv) in THF (25 mL) at - 20 °C was added LiHMDS (1.0 M in THF, 9.62 mL, 9.62 mmol, 1.1 equiv). After 20 min acyl imidazole **3-85** (1.21 g, 9.62 mmol, 1.1 equiv) in THF (8 mL) was added dropwise and the reaction mixture was allowed to warm to 0 °C. After 3 h at 0 °C acetic acid (2.2 mL) in THF (8 mL) was added, the reaction mixture was diluted with water (15 mL), EtOAc (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by flash column chromatography (5:1 hex/EtOAc) to afford the title compound as a pale yellow oil (2.00 g, 65%). R_f 0.27 (5:1 hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1 H), 7.29 - 7.35 (td, *J* = 0.8, 7.4 Hz, 1 H), 7.25 (d, *J* = 6.6 Hz, 1 H), 7.15 - 7.21 (td, *J* = 0.8, 7.4 Hz, 1 H), 4.00 (s, 3 H), 3.67 - 3.78 (m, 3 H), 2.23 - 2.33 (m, 1 H), 2.13 - 2.23 (m, 1 H), 0.82 (s, 9 H), -0.04 (s, 3 H), -0.07 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 151.7, 139.9, 128.1, 127.5,

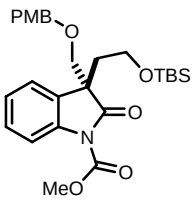
124.4, 123.8, 115.1, 59.2, 53.6, 42.8, 33.6, 25.8, 18.2, -5.7, -5.7; HRMS *m/z* 349.1654 (calc'd for $C_{18}H_{27}NO_4Si$, 349.1709).

Compound 3-87



To a solution of oxindole **3-86** (1.09 g, 3.1 mmol, 1.0 equiv), organocatalyst **3-79** (50 mg, 0.155 mmol, 5 mol %) in CH_2Cl_2 (25 mL) was added paraformaldehyde (280 mg, 9.3 mmol, 3.0 equiv). After 18 h the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (1:1 hex/EtOAc) to afford the title compound as a white foam (1.11 g, 96%, 86% ee by Mosher's ester). R_f 0.34 (1:1 hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1 H), 7.36 (ddd, *J* = 1.8, 7.0, 8.4 Hz, 1 H), 7.19 - 7.27 (m, 2 H), 3.97 (s, 3 H), 3.77 - 3.88 (m, 2 H), 3.57 (ddd, *J* = 3.7, 5.2, 10.3 Hz, 1 H), 3.43 (td, *J* = 3.9, 10.4 Hz, 1 H), 2.39 - 2.49 (m, 2 H), 1.95 (dt, *J* = 3.9, 14.2 Hz, 1 H), 0.75 (s, 9 H), -0.14 (s, 3 H), -0.17 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 151.5, 140.0, 128.7, 128.6, 124.6, 123.2, 115.3, 68.4, 58.9, 53.6, 53.1, 36.0, 25.7, 18.1, -6.0 (x 2); HRMS *m/z* 380.1891 (calc'd for $C_{19}H_{29}NO_5Si+H^+$, 380.1888).

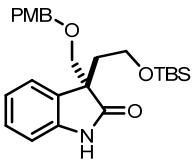
Compound 3-88



To a solution of oxindole **3-87** (200 mg, 0.527 mmol, 1.0 equiv) and *para*methoxybenzyl (300 mg, 1.05 mmol, 2.0 equiv) in CH_2Cl_2 (5 mL) was added 10•CSA (6.1 mg, 0.026 mmol, 5 mol %). Following complete consumption of the starting material as indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and ½ saturated $NaHCO_3$ (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was then purified by flash column chromatography (5:1 hex/EtOAc) to afford the title compound as a pale yellow oil (263 mg, 99%). R_f 0.29 (3:1 hex/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1 H), 7.32 - 7.36 (m, 1 H), 7.15 - 7.21 (m, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 4.37 (d, *J* = 12.3 Hz, 1 H), 4.27 (d, *J* = 11.7 Hz, 1 H), 3.99 (s, 3 H), 3.80 (s, 3 H), 3.61 - 3.67 (m, 2 H), 3.48 (ddd, *J* = 3.5, 6.0, 9.8 Hz, 1 H), 3.28 (td, *J* = 4.7, 10.2 Hz, 1 H), 2.28 (ddd, *J* =

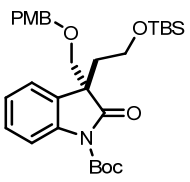
5.9, 10.2, 13.8 Hz, 1 H), 1.98 (dt, *J* = 4.1, 14.1 Hz, 1 H), 0.72 (s, 9 H), -0.19 (s, 3 H), -0.22 (s, 3 H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 176.7, 159.0, 151.7, 140.2, 129.8, 129.2, 128.9, 128.2, 124.2, 123.4, 115.1, 113.6, 74.9, 72.9, 59.0, 55.2, 53.5, 52.4, 36.1, 25.7, 18.1, -6.0, -6.1; HRMS *m/z* 499.2378 (calc'd for $C_{27}H_{37}NO_6Si$, 499.2390).

Compound 3-89



To a solution of Moc protected oxindole **3-88** (131 mg, 0.262 mmol, 1.0 equiv) in MeOH (2 mL) was added NaOMe (25 wt % in MeOH, 0.29 mL, 0.29 mmol, 1.1 equiv). After 30 min, the reaction mixture was diluted with ½ sat NH_4Cl (2 mL), EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the free N-H oxindole (116 mg, 99%) as a colorless syrup that was used without further purification. R_f 0.26 (3:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (br. s., 1 H), 7.20 - 7.24 (m, 2 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 7.03 (t, *J* = 7.0 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 6.78 - 6.83 (m, 2 H), 4.40 (d, *J* = 11.7 Hz, 1 H), 4.33 (d, *J* = 11.7 Hz, 1 H), 3.77 (s, 3 H), 3.70 (d, *J* = 9.4 Hz, 1 H), 3.64 (d, *J* = 8.8 Hz, 1 H), 3.43 (dd, *J* = 5.9, 7.0 Hz, 2 H), 2.14 - 2.22 (m, 1 H), 2.06 - 2.12 (m, 1 H), 0.78 (s, 9 H), -0.12 (s, 2 H), -0.13 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.6, 159.0, 141.4, 131.1, 130.1, 128.9, 127.8, 124.1, 122.0, 113.6, 109.6, 74.2, 73.0, 59.1, 55.2, 52.6, 35.8, 25.8, 18.1, -5.7, -5.8; HRMS *m/z* 441.2331 (calc'd for $C_{25}H_{35}NO_4Si$, 441.2335).

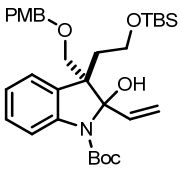
Compound 3-90



To a solution of oxindole **3-89** (53 mg, 0.120 mmol, 1.0 equiv) in THF () 3 mL) at -78 °C was added LiHMDS (0.91 M, 198 μL, 0.18 mmol, 1.5 equiv). After 30 min Boc_2O (55 μL, 0.24 mmol, 2.0 equiv) and the reaction mixture was allowed to warm to room temperature. After 1 h at room temperature the reaction mixture was diluted with a ½ saturated NH_4Cl solution (3 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified

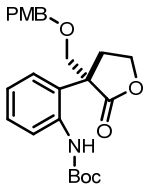
by column chromatography (5:1 hexanes/EtOAc) to afford the title compound as a colorless oil (45 mg, 90%). R_f 0.18 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 8.08 (d, *J* = 8.2 Hz, 1 H), 7.51 (td, *J* = 1.6, 7.8 Hz, 1 H), 7.38 - 7.43 (m, 1 H), 7.32 - 7.38 (m, 1 H), 7.23 - 7.28 (m, 2 H), 6.99 - 7.04 (m, 2 H), 4.58 (d, *J* = 12.1 Hz, 1 H), 4.49 (d, *J* = 12.1 Hz, 1 H), 3.99 (s, 3 H), 3.79 - 3.86 (m, 2 H), 3.68 (ddd, *J* = 3.5, 6.2, 10.3 Hz, 1 H), 3.50 (td, *J* = 4.9, 10.1 Hz, 1 H), 2.47 (ddd, *J* = 6.1, 9.8, 13.9 Hz, 1 H), 2.22 (dt, *J* = 4.2, 13.8 Hz, 1 H), 1.84 (s, 9 H), 0.93 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 159.0, 149.4, 140.4, 130.0, 129.2, 128.9, 128.0, 123.7, 123.6, 114.9, 113.6, 83.6, 75.0, 72.9, 59.0, 55.2, 52.3, 35.9, 28.1, 25.8, 18.2, -5.9, -5.9.

Compound 3-91



To a solution of oxindole **3-90** (45 mg, 0.083 mmol, 1.0 equiv) in THF (3 mL) at -78 °C was added vinyl magnesium bromide (0.72 M solution in Et_2O, 0.35 mL, 0.25 mmol, 3.0 equiv) and, after 15 min, the reaction mixture was allowed to warm to room temperature. After 2 h at room temperature the reaction mixture was diluted with ½ saturated NH_4Cl (3 mL) and Et_2O (5 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite and the solvent was removed *in vacuo*. The residue was purified by column chromatography (7:1 hexanes/EtOAc) to afford the product as a pale yellow oil (18 mg, 50%) as an inseparable mixture of two diastereomers. R_f 0.46 (6:1 hexanes/EtOAc); See spectra for ^{1}H NMR and ^{13}C NMR; LRMS *m/z* 569 (calc'd for $C_{32}H_{47}NO_6Si$, 569.3173).

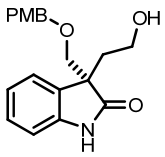
Compound 3-92



To a solution of **3-90** (50 mg, 0.092 mmol, 1.0 equiv) in EtOH (1.5 mL) was added 10•CSA. After 1 h the reaction mixture was diluted with ½ saturated $NaHCO_3$ (2 mL) and CH_2Cl_2 (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the organic layers were combined and dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to afford the title compound as a sticky syrup (39 mg, quant.); R_f 0.52

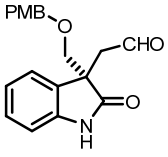
(1:2 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (br. s., 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.28 - 7.35 (m, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 6.87 - 6.93 (m, 2 H), 4.49 - 4.57 (m, 2 H), 4.35 (td, *J* = 4.7, 8.5 Hz, 1 H), 4.08 - 4.16 (m, 1 H), 3.88 - 3.96 (m, 2 H), 3.82 (s, 3 H), 2.85 (ddd, *J* = 4.1, 7.0, 13.5 Hz, 1 H), 2.60 (dt, *J* = 8.2, 12.9 Hz, 1 H), 1.48 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 159.5, 153.8, 136.6, 129.6, 128.9, 128.8, 127.5, 126.6, 124.9, 113.9, 80.0, 74.7, 73.6, 66.5, 55.2, 52.3, 33.3, 28.4, 28.2; HRMS *m/z* 427.1990 (calc'd for $C_{24}H_{29}NO_6$, 427.1995).

Compound 3-93



To a solution of free N-H oxindole **3-89** (2.018 g, 4.57 mmol, 1.0 equiv) in EtOH (10 mL) was added 10•CSA (106 mg, 0.457 mmol, 10 mol %). After 1 h the reaction mixture was diluted with CH_2Cl_2 (20 mL) and a ½ saturated solution of $NaHCO_3$ (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by flash column chromatography (100% EtOAc) to afford the title compound as a sticky syrup (1.49 g, quant.); R_f 0.35 (100% EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 - 7.26 (m, 2 H), 7.08 - 7.12 (m, 2 H), 7.03 - 7.08 (m, 1 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 6.79 - 6.86 (m, 2 H), 4.42 (d, *J* = 12.3 Hz, 1 H), 4.35 (d, *J* = 11.7 Hz, 1 H), 3.79 (s, 3 H), 3.73 (d, *J* = 8.8 Hz, 1 H), 3.65 (d, *J* = 8.8 Hz, 1 H), 3.61 (br. s., 1 H), 3.49 (br. s., 1 H), 2.17 - 2.23 (m, 1 H), 2.10 (dt, *J* = 5.9, 14.1 Hz, 1 H), 1.58 - 1.67 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.9, 159.1, 140.8, 131.3, 129.8, 129.0, 128.2, 124.2, 122.4, 113.7, 109.8, 73.5, 73.1, 59.0, 55.2, 52.6, 36.1; HRMS *m/z* 327.1474 (calc'd for $C_{19}H_{21}NO_4$, 327.1471).

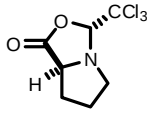
Compound 3-94



To a solution of alcohol **3-93** (423 mg, 1.3 mmol, 1.0 equiv) in EtOAc (10 mL) was added IBX (1.09 g, 3.9 mmol, 3.0 equiv) and the resulting reaction mixture was heated to reflux for 3 h. The reaction mixture was then cooled to 0 °C, filtered, and the solids were rinsed with cold EtOAc (10 mL). The filtrates were combined and concentrated *in vacuo* to afford the aldehyde as

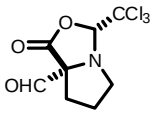
an orange gum (423 mg, quant.) that was used without further purification. R_f 0.35 (1:2 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J* = 0.8 Hz, 1 H), 8.11 (s, 1 H), 7.20 - 7.27 (m, 2 H), 7.08 - 7.14 (m, 2 H), 6.98 - 7.05 (m, 1 H), 6.91 (d, *J* = 7.4 Hz, 1 H), 6.80 - 6.87 (m, 2 H), 4.33 - 4.46 (m, 2 H), 3.79 (s, 3 H), 3.70 (d, *J* = 8.6 Hz, 1 H), 3.53 (d, *J* = 9.0 Hz, 1 H), 3.17 (dd, *J* = 18.0, 1.6 Hz, 1 H), 2.9 (dd, *J* = 18.0, 0.8 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 178.8, 159.2, 140.8, 130.5, 129.6, 129.1, 128.5, 124.1, 122.5, 113.7, 109.8, 73.3, 73.2, 55.2, 50.4, 46.8; LRMS *m/z* 326.2 (calc'd for $C_{19}H_{19}NO_4$, 325.1314).

Compound 3-6



A mixture of L-(-) *S*-proline (11.52 g, 100 mmol, 1.0 equiv), chloral hydrate (19.84 g, 120 mmol, 1.2 equiv) and 4 Å molecular sieves in acetonitrile (200 mL) was heated to 90 °C. After 2.5 h the mixture was cooled to room temperature, filtered through a celite pad and the celite pad was rinsed with CH_2Cl_2 (100 mL). The solution was concentrated *in vacuo* and the residue was taken up in diethyl ether (125 mL) and filtered through a celite pad. The solution was concentrated *in vacuo* until solids began to form, at which point diethyl ether was added until the solids remained in solution at 40 °C. The orange solution was cooled to room temperature, then 0 °C to fully precipitate the product. The crystals were collected by vacuum filtration, washed with cold diethyl ether, and dried under vacuum to afford the title compound (15.15 g, 60%) as pale orange crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 1 H), 4.12 (dd, *J* = 4.7, 8.6 Hz, 1 H), 3.43 (ddd, *J* = 5.9, 7.8, 10.9 Hz, 1 H), 3.13 (dt, *J* = 5.9, 11.2 Hz, 1 H), 2.18 - 2.29 (m, 1 H), 2.07 - 2.16 (m, 1 H), 1.89 - 1.99 (m, 1 H), 1.69 - 1.81 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 103.6, 62.4, 57.9, 41.8, 29.9, 25.3. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[46]

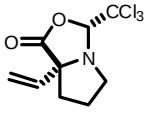
Compound 3-103



To a freshly prepared solution of LDA (15 mmol, 1.5 equiv) in THF (50 mL) at -78 °C was added oxazolidine **3-6** (2.55 g, 10 mmol, 1.0 equiv) as a solid. After 30 min at -78 °C methyl formate (2.45 mL, 40 mmol, 4.0 equiv) was added over 5 min and after 20 min the reaction mixture was warmed to -40 °C. After

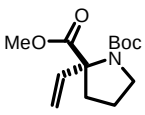
30 min at -40 °C a ½ saturated solution of NH_4Cl (30 mL) was quickly added and the reaction mixture was warmed to room temperature. The aqueous layer was extracted with Et_2O (3 x 30 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The residue was then purified by flash column chromatography (6:1 to 3:1 hex/EtOAc) to afford the title compound as a waxy white solid (1.90 g, 70%). R_f 0.24 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 5.20 (s, 1 H), 3.54 (ddd, *J* = 6.3, 7.8, 11.3 Hz, 1 H), 3.34 (dt, *J* = 6.0, 11.5 Hz, 1 H), 2.26 - 2.43 (m, 2 H), 1.92 - 2.02 (m, 1 H), 1.79 - 1.92 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 169.3, 102.3, 99.9, 78.1, 58.9, 33.9, 25.4. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[47]

Compound 3-104



To a solution of *t*BuOK (247 mg, 2.2 mmol, 1.2 equiv) in THF (15 mL) was added Ph_3PMeI (890 mg, 2.2 mmol, 1.2 equiv). After 30 min the bright yellow mixture was cooled to -78 °C and aldehyde **3-103** (500 mg, 1.83 mmol, 1.0 equiv) was added as a solid. After 30 min the reaction mixture was slowly warmed to 0 °C and, after 1 h, was filtered through a SiO_2/celite bilayer pad, rinsed with Et_2O (50 mL) and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (5:1 hex/EtOAc) to afford the title compound as a pale yellow to orange oil (379 mg, 76%). R_f 0.59 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 10.4, 17.0 Hz, 1 H), 5.51 (dd, *J* = 1.2, 16.8 Hz, 1 H), 5.22 (dd, *J* = 1.2, 10.6 Hz, 1 H), 5.07 (s, 1 H), 3.46 (dt, *J* = 6.4, 11.0 Hz, 1 H), 3.19 (dt, *J* = 6.3, 11.2 Hz, 1 H), 2.17 (dt, *J* = 7.8, 12.5 Hz, 1 H), 1.97 - 2.07 (m, 1 H), 1.88 - 1.97 (m, 1 H), 1.80 - 1.88 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 135.7, 116.1, 102.6, 73.5, 58.3, 41.8, 38.3, 24.8. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[47]

Compound 3-106



A solution of NaOMe in MeOH (25 wt %, 2 mL, 8.8 mmol, 0.5 equiv) was added dropwise to a solution of oxazolidinone **3-104** (4.173 g, 15.4 mmol, 1.0 equiv) in MeOH (40 mL) at room temperature. After 30 min and

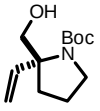
complete consumption of the starting material by TLC (R_f 0.48, 5:1 hexanes/EtOAc) the solution was cooled to 0 °C and acetyl chloride (22 mL, 308 mmol, 20 equiv) was added dropwise. The solution was heated to reflux until only baseline material was observed by TLC (1:1 hexanes/EtOAc) at which time the solution was cooled to room temperature and the solvent was removed *in vacuo*. The residue was diluted with anhydrous CH_2Cl_2 (50 mL) and *i*Pr_2NEt (8.06 mL, 46.2 mmol, 3 equiv) and Boc_2O (10.6 mL, 46.2 mmol, 3 equiv) were added sequentially. After 16 h the volatiles were removed *in vacuo* and the residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to afford the title compound as a colorless oil (1.44 g, 76%) as a 2.4:1 mixture of two rotamers. R_f 0.32 (3:1 hexanes/EtOAc).

Major Rotamer: H NMR (400 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 10.6, 17.2 Hz, 1 H), 5.15 (dd, *J* = 10.6, 0.8, 1H), 5.03 (dd, *J* = 0.8, 17.2, 1 H), 3.73 (s, 3 H), 3.62 - 3.68 (m, 1 H), 3.52 - 3.60 (m, 1 H), 2.12 - 2.25 (m, 1 H), 1.95 - 2.03 (m, 1 H), 1.76 - 1.92 (m, 2 H), 1.35 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 153.4, 137.1, 113.0, 79.9, 69.3, 52.2, 47.8, 39.1, 28.1, 21.8.

Minor Rotamer: H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 10.6, 17.2 Hz, 1 H), 5.16 (dd, *J* = 10.6, 0.8, 1 H), 5.05 (dd, *J* = 0.8, 17.2, 1 H), 3.74 (s, 3H), 3.62 - 3.68 (m, 1 H), 3.52 - 3.60 (m, 1 H), 2.12 - 2.25 (m, 1 H), 1.95 - 2.03 (m, 1 H), 1.76 - 1.92 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 153.5, 136.3, 113.1, 79.7, 69.4, 52.4, 48.0, 37.9, 28.4, 22.7.

HRMS *m/z* 255.1471 (calcd for $C_{13}H_{21}NO_4$, 255.1471).

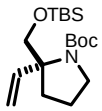
Compound 3-107



A solution of DIBAL (1.0 M in hexanes, 3.43 mL, 3.43 mmol, 2.5 equiv) was added to a solution of ester **3-106** (350 mg, 1.37 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) and, after 1 h, 1 M HCl (5 mL) was added. The reaction mixture was diluted with H_2O (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo* to afford the product as a colorless oil (300 mg, 96%) that was used without further purification. R_f 0.33 (1:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 10.6, 17.2 Hz, 1 H), 5.51 (dd, *J* = 1.6, 10.6

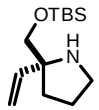
Hz, 1 H), 5.22 (d, *J* = 10.6 Hz, 1 H), 4.97 (d, *J* = 17.2 Hz, 1 H), 3.77 - 3.84 (m, 1 H), 3.68 - 3.74 (m, 1 H), 3.52 - 3.61 (m, 1 H), 3.33 - 3.43 (m, 1 H), 1.61 - 1.84 (m, 4 H), 1.47 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 138.0, 114.0, 80.2, 70.1, 68.9, 49.0, 36.1, 28.4, 20.7; HRMS *m/z* 228.1608 (calcd for $C_{12}H_{21}NO_3$+H^+, 228.1594).

Compound 3-108



To a solution of alcohol **3-107** (1.86 g, 8.19 mmol, 1.0 equiv) and imidazole (1.115 g, 16.38 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL) was added TBSCl (1.48 g, 9.82 mmol, 1.2 equiv). After complete consumption of the starting material as indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and a ½ saturated $NaHCO_3$ solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by flash column chromatography (10:1 hexanes/EtOAc) to afford the product as a colorless oil (2.66 g, 95%) as a mixture of greater than two rotamers. R_f 0.52 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 - 5.70 (m, 1 H), 4.53 - 4.76 (m, 2 H), 3.77 (d, *J* = 9.4 Hz, 1 H), 3.47 (d, *J* = 9.4 Hz, 1 H), 3.25 - 3.37 (m, 1 H), 3.19 - 3.25 (m, 1 H), 3.10 - 3.17 (m, 1 H), 2.88 - 3.05 (m, 1 H), 1.78 - 1.88 (m, 1 H), 1.23 - 1.47 (m, 3 H), 1.04 (d, *J* = 5.9 Hz, 9 H), 0.47 - 0.54 (m, 9 H), -0.29 (s, 1 H), -0.37 - -0.32 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 153.4, 140.1, 139.4, 112.7, 112.4, 79.3, 78.6, 68.1, 67.4, 66.2, 64.9, 49.2, 49.0, 37.0, 35.3, 28.5, 28.5, 25.8, 25.7, 21.7, 21.2, 18.1, 18.1, -3.6, -5.4, -5.5, -5.6; HRMS *m/z* 341.2386 (calcd for $C_{18}H_{35}NO_3Si$, 341.2386).

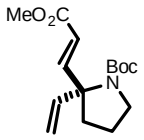
Compound 3-109



To a solution of protected alcohol **3-108** (1.544 g, 4.5 mmol, 1.0 equiv) and 2,6-lutidine (2.63 mL, 22.5 mmol, 5.0 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added TMSOTf (3.27 mL, 18.1 mmol, 4.0 equiv). Following complete consumption of the starting material by TLC, a ½ saturated solution of NH_4Cl (5 mL) was added. Once gas evolution had ceased, a ½ saturated $NaHCO_3$ solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite, and

concentrated *in vacuo*. Residual 2,6-lutidine was removed under vacuum to afford the free secondary amine as a pale brown oil (0.911 g, 84%) that was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.83 (dd, *J* = 10.8, 17.3 Hz, 1 H), 5.20 (d, *J* = 17.6 Hz, 1 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 3.47 (s, 2 H), 2.99 (d, *J* = 7.0 Hz, 1 H), 2.84 - 2.95 (m, 1 H), 2.18 (br. s., 1 H), 1.75 (br. d, *J* = 6.4 Hz, 2 H), 1.57 - 1.70 (m, 1 H), 1.26 (br. s., 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 113.0, 67.5, 67.4, 46.1, 32.3, 25.9, 25.6, 18.3, -5.5; HRMS *m/z* 241.1859 (calcd for $C_{13}H_{27}NOSi$, 241.1862).

Compound 3-111



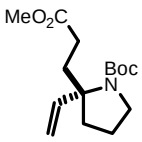
To a solution of alcohol **3-107** (300 mg, 1.32 mmol, 1.0 equiv), diisopropylethylamine (1.61 mL, 9.24 mmol, 7.0 equiv), and DMSO (468 μL, 6.60 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C was added SO_3•pyridine complex (632 mg, 3.97 mmol, 3.0 equiv) as a solid. After complete consumption of the starting material as indicated by TLC (2 h) the reaction mixture was diluted with CH_2Cl_2 (10 mL) and a ½ saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the product as a pale yellow oil (276 mg, 93%) that was used without further purification. To a solution of trimethyl phosphonoacetate (314 μL, 2.18 mmol, 1.5 equiv) in THF (10 mL) at 0 °C was added *n*BuLi (2.35 M, 0.86 mL, 2.03 mmol, 1.4 equiv). After 10 min at 0 °C the above synthesized aldehyde **3-110** (326 mg, 1.45 mmol, 1.0 equiv) in THF (5 mL) was added and the reaction was warmed to room temperature. After 16 h the reaction mixture was diluted with a ½ saturated solution of NH_4Cl (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was then purified by flash column chromatography (4:1 hexanes/EtOAc) to afford the product as a pale yellow oil (330 mg, 81%) as a 1.8 to 1 mixture of rotamers. R_f 0.56(5:1 hexanes/EtOAc). Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 16.0 Hz, 1 H), 5.95 (dd, *J* = 10.7, 17.4 Hz, 1 H), 5.79 (dd, *J* = 15.6 Hz, 1 H), 5.14 - 5.25 (m, 1 H), 5.01 - 5.14 (m, 1

H), 3.75 (s, 3 H), 3.42 - 3.60 (m, 2 H), 1.88 - 2.03 (m, 2 H), 1.74 - 1.86 (m, 2 H), 1.36 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 153.9, 151.8, 138.9, 119.0, 114.1, 80.1, 66.8, 51.6, 47.8, 39.9, 28.3, 21.5.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 16.0 Hz, 1 H), 6.08 (dd, *J* = 10.7, 17.4 Hz, 1 H), 5.80 (d, *J* = 15.6 Hz, 1 H), 5.14 - 5.25 (m, 1 H), 5.01 - 5.14 (m, 1 H), 3.72 (s, 3 H), 3.42 - 3.60 (m, 2 H), 1.88 - 2.03 (m, 2 H), 1.74 - 1.86 (m, 2 H), 1.45 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 153.9, 150.8, 138.7, 119.3, 114.1, 79.5, 67.1, 51.6, 47.9, 38.9, 28.5, 22.2.

HRMS *m/z* 282.1693 (calcd for $C_{15}H_{23}NO_4$+H^+, 282.1705).

Compound 3-62



To a solution of α,β unsaturated ester **3-111** (20 mg, 0.071 mmol, 1.0 equiv) and poly(methylhydrogensiloxane) (60 μL, 1.065 mmol, 15 equiv) in THF (2 mL) at 0 ° C was added a solution of Stryker's reagent (7 mg, 0.004 mmol, 5 mol %) in THF (1 mL) and the reaction mixture was warmed to room temperature. After 18 h the reaction mixture the septum and argon balloon was removed and H_2O (5 mL) was added. After 30 min the reaction mixture was filtered through celite, diluted with EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was then purified by flash column chromatography (4:1 hexanes/EtOAc) to afford the product as a pale yellow oil (18.5 mg, 93%) as a 1.4:1 mixture of two rotamers. R_f 0.36 (3:1 hexanes/EtOAc).

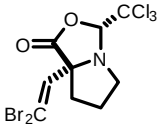
Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 10.6, 17.2 Hz, 1 H), 5.02 (d, *J* = 10.9 Hz, 1 H), 4.94 (d, *J* = 17.2 Hz, 1 H), 3.68 (s, 3 H), 3.63 - 3.66 (m, 1 H), 3.25 - 3.39 (m, 1 H), 2.32 - 2.46 (m, 1 H), 2.16 - 2.32 (m, 2 H), 1.97 - 2.06 (m, 1 H), 1.78 - 1.97 (m, 2 H), 1.64 - 1.78 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 141.7, 111.7, 79.7, 65.7, 48.7, 37.3, 32.1, 31.4, 29.0, 28.4, 20.8.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 10.6, 17.2 Hz, 1 H), 5.06 (d, *J* = 10.9 Hz, 1 H), 4.96 (d, *J* = 17.2 Hz, 1 H), 3.66 (s, 3 H), 3. 49 - 3.56 (m, 1 H), 3.25 - 3.39 (m, 1 H), 2.32 - 2.46 (m, 1 H), 2.16 - 2.32 (m, 3 H), 1.78 - 1.97 (m, 2 H), 1.64 - 1.78

(m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 140.7, 112.0, 79.7, 66.2, 65.7, 51.6, 36.0, 32.1, 31.4, 29.4, 28.5, 21.4.

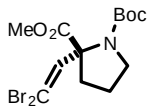
HRMS *m/z* 283.1775 (calcd for $C_{15}H_{25}NO_4$, 283.1784).

Compound 3-112



To a solution of PPh_3 (6.86 g, 26.2 mmol, 4 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added CBr_4 (4.34 g, 13.08 mmol, 2 equiv) portion-wise. After 30 min a solution of aldehyde **3-103** (1.782 g, 6.54 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added slowly and the reaction mixture was allowed to warm to room temperature. After 1 h the reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (9:1 hexanes/EtOAc) to afford the title compound as a brown oil (2.65 g, 95%). R_f 0.46 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1 H), 5.14 (s, 1 H), 3.64 (ddd, *J* = 6.1, 8.6, 11.5 Hz, 1 H), 3.25 (ddd, *J* = 4.5, 6.6, 11.5 Hz, 1 H), 2.35 - 2.44 (m, 1 H), 2.22 - 2.33 (m, 1 H), 1.99 - 2.09 (m, 1 H), 1.70 - 1.83 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 135.9, 103.1, 99.9, 90.5, 74.2, 59.0, 39.0, 25.5; HRMS *m/z* 425.8055 (calcd for $C_9H_8Br_2Cl_3NO_2$+H^+, 425.8066).

Compound 3-113



A solution of NaOMe in MeOH (25 wt %, 1 mL, 4.4 mmol, 1.0 equiv) was added dropwise to a solution of oxazolidinone **3-112** (1.9 g, 4.4 mmol, 1.0 equiv) in MeOH (20 mL) at room temperature. After 30 min and complete consumption of the starting material by TLC (R_f 0.30, 3:1 hexanes/EtOAc) the solution was cooled to 0 °C and acetyl chloride (6.97 mL, 88.7 mmol, 20 equiv) was added dropwise. The solution was heated to reflux until only baseline material was observed by TLC (1:1 hexanes/EtOAc) at which time the solution was cooled to room temperature and the solvent was removed *in vacuo*. The residue was diluted with anhydrous CH_2Cl_2 (50 mL) and *i*Pr_2NEt (2.30 mL, 13.2 mmol, 3 equiv) and Boc_2O (2.60 mL, 13.2 mmol, 3 equiv) were added sequentially. After 16 h the volatiles were removed *in vacuo* and the

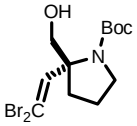
residue was purified by flash column chromatography (7:1 hexanes/EtOAc) to afford the title compound as a colorless oil (1.56 g, 86%) as a 3:1 mixture of two rotamers. R_f 0.32 (3:1 hexanes/EtOAc).

Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1 H), 3.76 (s, 3 H), 3.71 - 3.76 (m, 1 H), 3.51 - 3.65 (m, 1 H), 2.29 - 2.40 (m, 1 H), 2.18 - 2.26 (m, 1 H), 1.93 - 2.02 (m, 2 H), 1.40 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 152.6, 137.2, 87.4, 80.4, 69.6, 52.9, 47.8, 39.2, 28.2, 23.1.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1 H), 3.77 (s, 3 H), 3.71 - 3.76 (m, 1 H), 3.51 - 3.65 (m, 1 H), 2.29 - 2.40 (m, 1 H), 2.18 - 2.26 (m, 1 H), 1.93 - 2.02 (m, 2 H), 1.46 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 152.6, 136.6, 87.3, 80.1, 69.7, 52.9, 48.0, 38.2, 28.3, 23.8.

HRMS *m/z* 411.9753 (calcd for $C_{13}H_{19}Br_2NO_4$+H^+, 411.9759).

Compound 3-114



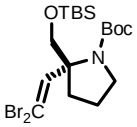
A solution of DIBAL (1.0 M in hexanes, 7.1 mL, 7.1 mmol, 3.5 equiv) was added to a solution of ester **3-113** (869 mg, 2.03 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) and, after 1 h, the reaction mixture was diluted with Et_2O (30 mL). Water (0.28 mL) was added dropwise, followed by a 10% $NaOH_{(aq)}$ solution (0.28 mL) followed by additional water (0.7 mL). $MgSO_4$ was added and the reaction mixture was filtered through celite and the solvent was removed *in vacuo* to afford the title compound as a colorless oil as a 2.7:1 mixture of two rotamers that was used without further purification (704 mg, 90%). R_f 0.33 (1:1 hexanes/EtOAc).

Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1 H), 5.19 (dd, *J* = 2.0, 9.4 Hz, 1 H), 3.65 - 3.83 (m, 2 H), 3.49 - 3.62 (m, 1 H), 3.36 - 3.46 (m, 1 H), 2.78 (br. s, 1 H), 2.08 - 2.17 (m, 1 H), 1.72 - 1.95 (m, 3 H), 1.46 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 138.7, 87.4, 80.7, 69.8, 66.1, 49.0, 36.2, 28.4, 22.5.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1 H), 5.19 (dd, *J* = 2.0, 9.4 Hz, 1 H), 3.65 - 3.83 (m, 2 H), 3.49 - 3.62 (m, 1 H), 3.36 - 3.46 (m, 1 H), 2.78 (br. s, 1 H), 2.18 - 2.26 (m, 1 H), 1.72 - 1.95 (m, 3 H), 1.49 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 139.4, 87.7, 80.3, 69.8, 67.6, 48.5, 35.2, 28.4, 22.2.

HRMS *m/z* 383.9816 (calcd for $C_{12}H_{19}Br_2NO_3$+H^+, 383.9810).

Compound 3-115



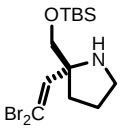
To a solution of alcohol **3-114** (704 mg, 1.83 mmol, 1.0 equiv) and imidazole (276 mg, 4.06 mmol, 2.2 equiv) in CH_2Cl_2 (5 mL) was added TBSCl (367 mg, 2.44 mmol, 1.3 equiv). After complete consumption of the starting material as indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and a ½ saturated $NaHCO_3$ solution (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by flash column chromatography (10:1 hexanes/EtOAc) to afford the product as a colorless oil (784 mg, 86%) as a 2:1 mixture of two rotamers.

Major Rotamer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.79 (s, 1 H), 3.71 - 3.75 (m, 1 H), 3.49 - 3.57 (m, 2 H), 3.48 (d, J = 8.8 Hz, 1 H), 3.40 - 3.46 (m, 1 H), 2.24 - 2.30 (m, 1 H), 2.06 - 2.18 (m, 1 H), 1.83 - 1.91 (m, 2 H), 1.47 (s, 0 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 153.2, 139.8, 87.2, 79.7, 67.4, 65.2, 48.4, 34.8, 28.5, 25.8, 22.0, 18.2, -5.4, -5.5.

Minor Rotamer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (s, 1 H), 3.77 - 3.81 (m, 2 H), 3.49 - 3.52 (m, 2 H), 3.40 - 3.46 (m, 1 H), 2.24 - 2.30 (m, 1 H), 2.06 - 2.18 (m, 1 H), 1.83 - 1.91 (m, 1 H), 1.78 - 1.83 (m, 1 H), 1.44 (s, 9 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 152.8, 139.2, 86.3, 79.1, 68.2, 64.3, 48.6, 34.6, 28.5, 25.8, 22.9, 18.1, -5.4, -5.5.

HRMS *m/z* 398.0140 (calcd for $C_{13}H_{25}Br_2NOSi+H^+$, 398.0140)

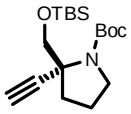
Compound 3-116



To a solution of protected alcohol **3-115** (210 mg, 0.42 mmol, 1.0 equiv) and 2,6-lutidine (243 μL, 2.1 mmol, 5.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added TMSOTf (304 μL, 1.68 mmol, 4.0 equiv). Following complete consumption of the starting material by TLC, a ½ saturated solution of NH_4Cl (5 mL) was added. Once gas evolution had ceased, a ½ saturated $NaHCO_3$ solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite,

and concentrated *in vacuo*. Residual 2,6-lutidine was removed under vacuum to afford the free secondary amine as a pale brown oil (130 mg, 77%) that was used without further purification. ^{1}H NMR (599 MHz, $CDCl_3$) δ 6.76 (s, 1 H), 3.63 - 3.65 (m, 2 H), 2.95 - 3.00 (m, 1 H), 2.89 - 2.95 (m, 1 H), 2.19 (br. s., 1 H), 1.96 - 2.03 (m, 1 H), 1.86 - 1.93 (m, 1 H), 1.79 - 1.86 (m, 1 H), 1.69 - 1.79 (m, 1 H), 0.87 - 0.95 (m, 10 H), 0.04 - 0.11 (m, 6 H); HRMS *m/z* 398.0140 (calcd for $C_{13}H_{25}Br_2NOSi+H^+$, 398.0140).

Compound 3-117

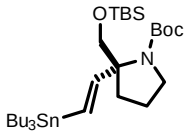


To a solution of dibromoolefin **3-115** (2.34 g, 4.69 mmol, 1.0 equiv) in THF (50 mL) at -78 °C was added *n*BuLi (1.88 M in hexanes, 5.5 mL, 10.3 mmol, 2.2 equiv). After 15 min a ½ saturated solution of NH_4Cl (20 mL) was added and the reaction mixture was warmed to room temperature. The reaction mixture was diluted with Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered through celite and the solvent was removed *in vacuo*. The residue was purified by column chromatography (10:1 hexanes/EtOAc) to afford the title compound as a colorless oil (1.31 g, 82%) as a 1.1:1 mixture of two rotamers. R_f 0.43 (10:1 hexanes/EtOAc).

Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (d, J = 9.4 Hz, 1 H) 3.73 (d, J = 9.8 Hz, 1 H), 3.58 - 3.69 (m, 1 H), 3.23 - 3.38 (m, 1 H), 2.35 - 2.45 (m, 1 H), 2.27 (s, 1 H), 2.04 - 2.20 (m, 1 H), 1.80 - 1.92 (m, 2 H), 1.49 (s, 9 H), 0.88 (br. s., 9 H), 0.02 - 0.08 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 85.3, 80.0, 70.4, 66.4, 60.5, 48.3, 38.7, 28.5, 25.8, 22.5, 18.2, -5.4, -5.5.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, J = 9.8 Hz, 1 H), 3.65 (d, J = 9.8 Hz, 1 H) 3.49 - 3.58 (m, 1 H), 3.23 - 3.38 (m, 1 H), 2.35 - 2.45 (m, 1 H), 2.33 (s, 1 H), 2.04 - 2.20 (m, 1 H), 1.80 - 1.92 (m, 2 H), 1.46 (s, 9 H), 0.88 (br. s., 9 H), 0.02 - 0.08 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 84.7, 79.2, 70.7, 65.0, 60.7, 48.6, 37.5, 28.5, 25.8, 23.1, 18.2, -5.3, -5.4.

Compound 3-118

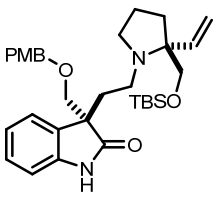


To a a solution of alkyne **3-117** (177 mg, 0.52 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 5 mol %) in THF (3 mL) was added *n*Bu_3SnH (154 μL, 0.57 mmol, 1.1 equiv). After 40 min the solvent was removed *in vacuo* and the residue was purified by column chromatography (20:1 hexanes/EtOAc) to afford the title compound as a colorless oil (187 mg, 58%) as a 2.2:1 mixture of two rotamers. R_f 0.66 (10:1 hexanes/EtOAc).

Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (d, *J* = 19.3 Hz, 1 H), 5.87 (d, 19.3 Hz, 1 H), 3.84 (d, *J* = 9.4 Hz, 1 H), 3.76 (d, *J* = 9.4 Hz, 1 H), 3.63 (td, *J* = 3.7, 7.1 Hz, 1 H), 3.34 - 3.42 (m, 1 H), 2.20 (ddd, *J* = 6.8, 10.3, 12.2 Hz, 1 H), 1.78 - 1.86 (m, 1 H), 1.69 - 1.78 (m, 1 H), 1.59 - 1.68 (m, 1 H), 1.46 - 1.54 (m, 6 H), 1.42 (s, 9 H), 1.25 - 1.37 (m, 6 H), 0.93 - 0.99 (m, 6 H), 0.90 (s, 9 H), 0.84 - 0.89 (m, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 149.2, 124.4, 79.1, 69.6, 66.5, 49.2, 37.2, 30.6, 29.1, 28.5, 27.5, 27.3, 25.8, 21.1, 13.7, 10.0, 9.4, -5.4, -5.5.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (d, *J* = 19.3 Hz, 1 H), 5.87 (d, *J* = 19.3 Hz, 1 H), 4.17 (d, *J* = 9.8 Hz, 1 H), 3.68 (d, *J* = 9.8 Hz, 1 H), 3.50 - 3.57 (m, 1 H), 3.27 - 3.33 (m, 1 H), 2.20 (ddd, *J* = 6.8, 10.3, 12.2 Hz, 1 H), 1.78 - 1.86 (m, 1 H), 1.69 - 1.78 (m, 1 H), 1.59 - 1.68 (m, 1 H), 1.46 - 1.54 (m, 6 H), 1.44 (s, 9 H), 1.25 - 1.37 (m, 6 H), 0.93 - 0.99 (m, 6 H), 0.92 (s, 9 H), 0.84 - 0.89 (m, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 148.3, 124.7, 78.3, 70.3, 65.1, 49.2, 35.2, 30.6, 29.1, 28.5, 27.5, 27.2, 25.8, 21.7, 13.7, 10.0, 9.5, -5.4, -5.5.

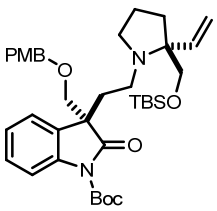
Compound 3-120



To a solution of aldehyde **3-95** (423 mg, 1.3 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added amine **3-109** (314 mg, 1.3 mmol, 1.0 equiv). After 10 min $NaBH(OAc)_3$ (551 mg, 2.6 mmol, 2.0 equiv) was added in one portion. After 2 h the reaction mixture was diluted with ½ saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo* to afford the title compound as a pale brown oil (716 mg, 99%) that was used without further

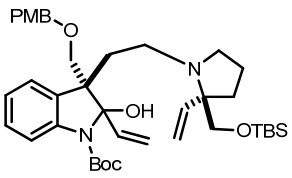
purification. R_f 0.46 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.17 - 7.24 (m, 2 H), 7.04 - 7.09 (m, 2 H), 6.99 - 7.04 (m, 1 H), 6.87 (d, *J* = 7.8 Hz, 1 H), 6.78 - 6.82 (m, 2 H), 5.36 (dd, *J* = 10.9, 17.6 Hz, 1 H), 4.88 (dd, *J* = 1.6, 18.0 Hz, 1 H), 4.82 (dd, *J* = 1.6, 10.9 Hz, 1 H), 4.39 (d, *J* = 12.1 Hz, 1 H), 4.31 (d, *J* = 12.1 Hz, 1 H), 3.78 (s, 3 H), 3.60 - 3.66 (m, 2 H), 3.33 - 3.40 (m, 2 H), 2.88 - 2.96 (m, 1 H), 2.60 - 2.68 (m, 1 H), 2.36 - 2.45 (m, 1 H), 2.15 - 2.24 (m, 1 H), 2.07 - 2.14 (m, 1 H), 1.98 - 2.07 (m, 1 H), 1.77 - 1.86 (m, 1 H), 1.57 - 1.74 (m, 3 H), 0.80 (s, 9 H), -0.07 (s, 3 H), -0.10 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 159.0, 141.4, 141.0, 131.3, 130.1, 128.9, 127.7, 123.9, 122.1, 113.6, 113.2, 109.5, 74.5, 72.9, 67.3, 66.1, 55.2, 53.2, 51.6, 43.9, 34.5, 32.7, 25.8, 21.8, 18.0, -5.7; HRMS *m/z* 551.3327 (calcd for $C_{32}H_{46}N_2O_4Si+H^+$, 551.3305).

Compound 3-121



To a solution of oxindole **3-120** (716 mg, 1.3 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added Boc_2O (448 µL, 1.95 mmol, 1.3 equiv) and DMAP (16 mg, 0.13 mmol, 10 mol %) sequentially. After 16 h the reaction mixture was concentrated *in vacuo* and residue was purified by flash column chromatography (5:1 hex/EtOAc) to afford the title compound as a pale yellow oil (814 g, 99%). R_f 0.26 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 1 H), 7.30 (td, *J* = 1.8, 7.7 Hz, 1 H), 7.10 - 7.19 (m, 2 H), 7.02 - 7.07 (m, 2 H), 6.78 - 6.83 (m, 2 H), 4.90 (dd, *J* = 10.9, 17.6 Hz, 1 H), 4.66 (dd, *J* = 1.6, 17.6 Hz, 1 H), 4.57 (dd, *J* = 1.6, 10.9 Hz, 1 H), 4.37 (d, *J* = 12.1 Hz, 1 H), 4.27 (d, *J* = 12.1 Hz, 1 H), 3.79 (s, 3 H), 3.57 (s, 2 H), 3.28 - 3.41 (m, 2 H), 2.99 - 3.06 (m, 1 H), 2.42 (q, *J* = 7.8 Hz, 1 H), 2.34 (dd, *J* = 6.1, 11.9 Hz, 1 H), 2.15 - 2.28 (m, 2 H), 1.92 - 2.00 (m, 1 H), 1.75 - 1.85 (m, 1 H), 1.65 - 1.74 (m, 2 H), 1.64 (s, 9 H), 1.49 - 1.59 (m, 1 H), 0.81 (s, 9 H), -0.06 (s, 3 H), -0.07 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 159.0, 149.5, 141.4, 141.0, 130.1, 129.4, 128.9, 127.8, 123.7, 123.5, 115.1, 113.6, 112.6, 83.3, 75.5, 72.9, 67.0, 64.7, 55.2, 52.7, 50.4, 43.6, 33.9, 32.5, 28.1, 25.8, 21.8, 18.0, -5.7; HRMS *m/z* 651.3853 (calcd for $C_{37}H_{54}N_2O_6Si+H^+$, 651.3825).

Compound 3-123

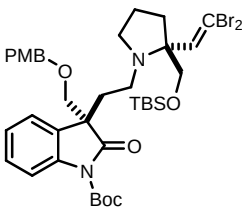


To a solution of oxindole **3-121** (538 mg, 0.827 mmol, 1.0 equiv) in Et_2O (10 mL) was added vinyl magnesium bromide (1.0 M in Et_2O, 1.65 mL, 1.65 mmol, 2.0 equiv). After 30 min the reaction mixture was diluted with ½ saturated NH_4Cl (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 10 mL) and the organic layers were combined, weashed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by column chromatography (3:1 hexanes/EtOAc to 100% EtOAc) to afford the title compound as a pale yellow oil (414 mg, 74%) as a 1.2:1 mixture of two diastereomers. R_f 0.23 (3:1 hexanes/EtOAc).

Isolated pure diastereomer (for diastereomeric mixture, see ^{1}H spectrum).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br. s., 1 H), 7.17 - 7.26 (m, 2 H), 7.11 - 7.17 (m, 2 H), 6.96 - 7.03 (m, 1 H), 6.80 - 6.85 (m, 2 H), 5.94 (dd, *J* = 10.4, 17.0 Hz, 1 H), 5.77 (dd, *J* = 10.9, 17.6 Hz, 1 H), 5.43 (d, *J* = 17.2 Hz, 1 H), 5.25 (d, *J* = 11.3 Hz, 1 H), 5.11 (dd, *J* = 1.6, 17.6 Hz, 1 H), 5.07 (dd, *J* = 1.6, 10.9 Hz, 1 H), 4.27 - 4.38 (m, 2 H), 3.87 (d, *J* = 9.4 Hz, 1 H), 3.76 - 3.82 (m, 1 H), 3.80 (s, 3 H), 3.50 - 3.59 (m, 2 H), 3.48 (d, *J* = 9.8 Hz, 1 H), 2.83 - 2.91 (m, 1 H), 2.75 - 2.83 (m, 1 H), 2.51 - 2.67 (m, 2 H), 2.16 - 2.27 (m, 1 H), 1.87 - 1.98 (m, 1 H), 1.72 - 1.81 (m, 3 H), 1.64 - 1.72 (m, 1 H), 1.58 (s, 9 H), 0.89 (s, 9 H), 0.02 - 0.09 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 141.1, 136.7, 133.9, 130.8, 128.8, 127.8, 125.4, 122.6, 115.3, 114.2, 113.6, 113.5, 98.1, 82.6, 72.9, 70.1, 67.9, 66.6, 55.2, 53.1, 52.1, 43.6, 34.6, 30.7, 28.5, 25.9, 21.8, 18.2, -5.5, -5.6; HRMS *m/z* 679.4147 (calcd for $C_{39}H_{58}N_2O_6Si+H^+$, 679.4142).

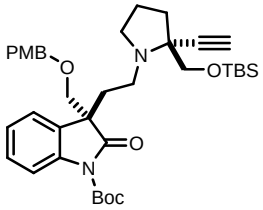
Compound 3-125



To a solution of aldehyde **3-95** (170 mg, 0.52 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added amine **3-116** (201 mg, 0.504 mmol, 1.0 equiv). After 10 min $NaBH(OAc)_3$ (221 mg, 1.05 mmol, 2.0 equiv) was added in one portion. After 2 h the reaction mixture was diluted with ½ saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers

were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo* to a pale brown oil. CH_2Cl_2 (5 mL), Boc_2O (179 μL, 0.78 mmol, 1.5 equiv), and DMAP (6 mg, 0.05 mmol, 0.1 equiv) were added and, after 16 h the solvent was removed *in vacuo* and the reside was purified by column chromatography (5:1 hexanes/EtOAc) to afford the title compound as a light yellow oil (300 mg, 71%). R_f 0.46 (5:1 hexanes/EtOAc) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 1 H), 7.30 - 7.38 (m, 1 H), 7.14 - 7.24 (m, 2 H), 7.06 (d, *J* = 8.6 Hz, 2 H), 6.78 - 6.87 (m, 2 H), 5.48 (s, 1 H), 4.25 - 4.40 (m, 2 H), 3.75 - 3.82 (m, 3 H), 3.57 (s, 2 H), 3.47 - 3.56 (m, 2 H), 3.07 (td, *J* = 2.1, 8.1 Hz, 1 H), 2.33 - 2.48 (m, 2 H), 2.19 - 2.33 (m, 2 H), 1.88 - 2.04 (m, 3 H), 1.66 (s, 9 H), 0.79 (s, 9 H), -0.05 (s, 3 H), -0.06 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 159.0, 149.1, 143.0, 140.4, 130.0, 128.9, 128.9, 128.8, 123.9, 123.4, 115.8, 113.6, 85.9, 83.5, 75.5, 73.0, 69.9, 63.3, 55.2, 52.5, 49.3, 44.4, 33.4, 32.0, 28.1, 25.7, 21.8, 17.9, -5.7; HRMS *m/z* 807.2080 (calcd for $C_{37}H_{52}Br_2N_2O_6Si+H^+$, 807.2040).

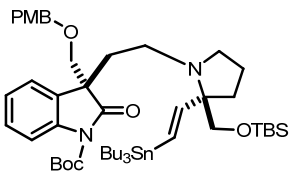
Compound 3-127



To a solution of dibromoolefin **3-125** (42 mg, 0.052 mmol, 1.0 equiv) in THF (5 mL) at -78 °C was added *n*BuLi (2.45 M in hexanes, 43 μL, 0.104 mmol, 2.0 equiv). After 30 min the reaction mixture was diluted with ½ saturated NH_4Cl (5 mL) and Et_2O (10 mL) warmed to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The reside was purified by column chromatography (5:1 hexanes/EtOAc) to afford the title compound as a light yellow oil (10 mg, 30%). R_f 0.36 (4:1 hexanes/EtOAc) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 1 H), 7.29 - 7.32 (m, 1 H), 7.20 - 7.23 (m, 1 H), 7.11 - 7.17 (m, 1 H), 7.02 - 7.07 (m, 2 H), 6.78 - 6.83 (m, 2 H), 4.38 (d, *J* = 12.1 Hz, 1 H), 4.28 (d, *J* = 12.1 Hz, 1 H), 3.79 (s, 3 H), 3.64 (s, 2 H), 3.42 (d, *J* = 10.2 Hz, 1 H), 3.35 (d, *J* = 9.8 Hz, 1 H), 2.68 (td, *J* = 4.5, 8.5 Hz, 1 H), 2.47 - 2.55 (m, 1 H), 2.40 - 2.47 (m, 1 H), 2.13 - 2.29 (m, 2 H), 2.03 (s, 1 H), 1.93 - 2.01 (m, 1 H), 1.86 - 1.93 (m, 1 H), 1.79 - 1.86 (m, 1 H), 1.68 - 1.77 (m, 1 H), 1.65 (m, 9 H), 0.84 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 159.0, 149.4, 140.5, 130.0, 129.7, 128.9,

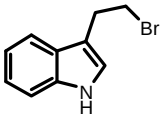
128.0, 123.9, 123.3, 115.0, 113.6, 84.0, 83.6, 75.1, 72.9, 72.3, 67.8, 64.3, 55.2, 53.1, 51.8, 45.2, 36.2, 33.6, 29.7, 28.2, 25.9, 25.7, 21.0, 18.2, -5.4; HRMS *m/z* 649.3684 (calcd for $C_{37}H_{52}N_2O_6Si+H^+$, 649.3595).

Compound 3-126



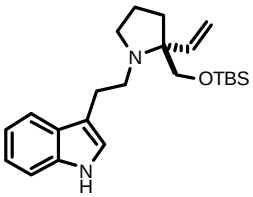
To a solution of aldehyde **3-95** (85 mg, 0.26 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added amine **3-119** (138 mg, 0.26 mmol, 1.0 equiv). After 10 min $NaBH(OAc)_3$ (110 mg, 0.52 mmol, 2.0 equiv) was added in one portion. After 2 h the reaction mixture was diluted with ½ saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo* to a pale brown oil. CH_2Cl_2 (5 mL), Boc_2O (90 μL, 0.39 mmol, 1.5 equiv), and DMAP (5 mg, 0.04 mmol, 0.15 equiv) were added and, after 16 h the solvent was removed *in vacuo* and the reside was purified by column chromatography (5:1 hexanes/EtOAc) to afford the title compound as a light yellow oil (100 mg, 41%). R_f 0.30 (5:1 hexanes/EtOAc); ^1H NMR (599 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 1 H), 7.27 - 7.31 (m, 1 H), 7.19 (d, *J* = 6.5 Hz, 1 H), 7.10 - 7.14 (m, 1 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 5.80 (d, *J* = 19.4 Hz, 1 H), 5.62 (d, *J* = 19.4 Hz, 1 H), 4.35 (d, *J* = 12.3 Hz, 1 H), 4.25 (d, *J* = 12.3 Hz, 1 H), 3.79 - 3.82 (m, 1 H), 3.76 - 3.79 (m, 3 H), 3.58 - 3.67 (m, 3 H), 3.42 (d, *J* = 10.0 Hz, 1 H), 3.36 (d, *J* = 10.0 Hz, 1 H), 2.73 (d, *J* = 8.8 Hz, 1 H), 2.57 - 2.62 (m, 1 H), 2.30 - 2.36 (m, 1 H), 2.22 - 2.30 (m, 1 H), 2.05 - 2.12 (m, 1 H), 1.91 - 2.00 (m, 1 H), 1.72 - 1.79 (m, 1 H), 1.60 - 1.63 (m, 2 H), 1.62 (s, 9 H), 1.39 - 1.50 (m, 6 H), 1.27 (dq, *J* = 7.4, 14.9 Hz, 6 H), 0.87 (t, *J* = 7.6 Hz, 9 H), 0.80 - 0.82 (m, 5 H) 0.79 (s, 9 H), -0.05 (s, 3 H), -0.08 (s, 3 H); HRMS *m/z* 941.4839 (calcd for $C_{49}H_{80}N_2O_6SiSn+H^+$, 941.4886).

Compound 3-9



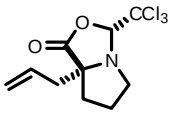
To a solution of tryptophol (**3-132**, 200 mg, 1.24 mmol, 1.0 equiv) and Ph_3P (655 mg, 2.5 mmol, 2 equiv) in CH_2Cl_2 (5 mL) was added CBr_4 (824 mg, 2.5 mmol, 2 equiv). After 1 h the reaction mixture was diluted with water (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by column chromatography to afford the title compound as a pale yellow oil (193 mg, 70%). R_f 0.57 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br. s., 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.23 (t, *J* = 7.0 Hz, 1 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 7.11 (d, *J* = 2.3 Hz, 1 H), 3.66 (t, *J* = 7.6 Hz, 2 H), 3.36 (t, *J* = 7.8 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 126.9, 122.2, 122.2, 119.6, 118.5, 113.6, 111.3, 32.8, 29.3; ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[48]

Compound 3-131



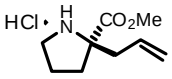
A mixture of indole **3-9** (50 mg, 0.22 mmol, 1.5 equiv), amine **X3-109** (36 mg, 0.15 mmol, 1.0 equiv), K_2CO_3 (207 mg, 1.5 mmol, 5.0 equiv) and NaI (45 mg, 0.3 mmol, 0.5 equiv) in DMF (1 mL) was heated to 150 °C in a microwave reaction. After 3 h the reaction mixture was cooled to 0 °C and diluted with H_2O (5 mL) and EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (53 mg, 46%). R_f 0.33 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br. s., 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.12 (t, *J* = 7.4 Hz, 1 H), 7.04 (d, *J* = 2.3 Hz, 1 H), 5.87 (dd, *J* = 10.9, 18.0 Hz, 1 H), 5.08 - 5.19 (m, 2 H), 3.61 (s, 2 H), 3.03 - 3.10 (m, 2 H), 2.85 - 3.00 (m, 4 H), 1.96 - 2.05 (m, 1 H), 1.76 - 1.92 (m, 3 H), 0.83 - 0.93 (m, 9 H), 0.02 - 0.06 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 136.2, 127.6, 121.8, 121.3, 119.1, 119.0, 115.1, 113.7, 111.0, 67.7, 66.6, 52.3, 50.3, 34.5, 26.0, 25.9, 21.9, 18.2, -5.5; HRMS *m/z* 384.2609 (calcd for $C_{23}H_{36}N_2OSi$, 384.2597).

Compound 3-135



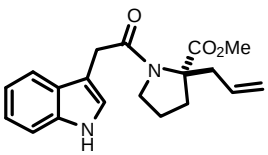
To a freshly prepared solution of LDA (81.6 mmol, 1.5 equiv) in THF (100 mL) at -78 °C was added oxazolidine **3-6** (13.9 g, 54 mmol, 1.0 equiv) as a solid. After 30 min at -78 °C allyl bromide (8.41 mL, 97.2 mmol, 1.8 equiv) was added over 5 min and after 20 min the reaction mixture was warmed to -40 °C. After 30 min at -40 °C a ½ saturated solution of NH_4Cl (40 mL) was quickly added and the reaction mixture was warmed to room temperature. The aqueous layer was extracted with $CHCl_3$ (3 x 100 mL), the combined organic layers were dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo* to afford the title compound that was used without further purification (14.5 g, 94%). R_f 0.50 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 - 5.96 (m, 1 H), 5.21 (s, 1 H), 5.15 - 5.20 (m, 1 H), 4.99 (s, 1 H), 3.13 - 3.26 (m, 2 H), 2.52 - 2.68 (m, 2 H), 2.11 - 2.19 (m, 1 H), 1.98 - 2.09 (m, 1 H), 1.82 - 1.95 (m, 1 H), 1.58 - 1.73 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) 176.2, 131.9, 119.9, 102.3, 100.4, 71.3, 58.3, 41.5, 35.2, 25.2. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[46b]

Compound 3-136



To a solution of allylated oxazolidinone **3-135** (13.9 g, 48.8 mmol, 1.0 equiv) in MeOH (100 mL) at 0 °C was added sodium metal (600 mg, 26 mmol, 0.53 equiv). After 30 min AcCl (67 mL, 947 mmol, 19 equiv) was added dropwise and the reaction mixture was heated to reflux. After complete consumption of the intermediate formate (R_f 0.29, 2:1 EtOAc/hexanes) the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by column chromatography (20:1 to 10:1 CH_2Cl_2/MeOH) to afford the title compound (7.2 g, 72%). ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[46b]

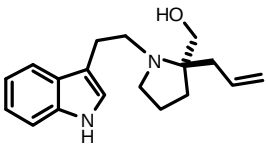
Compound 3-138



To a solution of indole-3-acetic acid (964 mg, 5.5 mmol, 1.1 equiv) in CH_2Cl_2 (25 mL) was added EDCl (1.05 g, 5.5 mmol, 1.0 equiv). After 5 min amine hydrochloride **3-136** (1.0g, 5.0 mmol, 1.0 equiv) was added, followed by Hunig's base (2.6 mmol, 15 mmol, 3.0 equiv). After

16 h at room temperature the reaction mixture was diluted with 1 M HCl (10 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo* to afford the title compound as a pale brown oil (1.36 g, 83%) that was used without further purification. R_f 0.25 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br. s., 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.15 - 7.22 (m, 1 H), 7.08 - 7.15 (m, 2 H), 5.59 - 5.73 (m, 1 H), 5.01 - 5.12 (m, 2 H), 3.77 (s, 2 H), 3.71 - 3.77 (m, 2 H), 3.68 (s, 3 H), 3.49 (dt, *J* = 7.2, 9.9 Hz, 1 H), 3.21 (dd, *J* = 6.6, 14.1 Hz, 1 H), 2.67 (dd, *J* = 8.0, 14.3 Hz, 1 H), 2.00 - 2.13 (m, 2 H), 1.83 - 2.00 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 169.9, 136.1, 133.4, 127.3, 122.9, 121.9, 119.3, 119.0, 118.5, 111.2, 108.5, 68.2, 52.3, 49.1, 37.8, 35.1, 32.8, 23.8; HRMS *m/z* 326.1636 (calcd for $C_{19}H_{22}N_2O_3$, 326.1630).

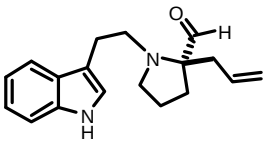
Compound 3-139



To a solution of **3-138** (1.36 g, 4.17 mmol, 1.0 equiv) in THF (20 mL) at 0 °C was added RED-Al (65 wt% in PhMe, 8.9 mL, 29.2 mmol, 7.0 equiv) dropwise. After 2 h, the reaction mixture was heated to reflux. After 16 h the reaction mixture was cooled to room temperature and excess RED-Al was quenched by slowly pouring the reaction mixture into a vigorously stirred ½ saturated solution of Rochelle's salt (50 mL). After 2 h the layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a colorless syrup (0.84 g, 70%) that was used without further purification. R_f 0.27 (1:2 hexanes/EtOAc, 5% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br. s., 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.21 (td, *J* = 1.4, 7.5 Hz, 1 H), 7.11 - 7.17 (m, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 5.62 - 5.75 (m, 1 H), 5.07 - 5.11 (m, 1 H), 5.06 (s, 1 H), 3.46 - 3.57 (m, 1 H), 3.39 (d, *J* = 10.9 Hz, 1 H), 3.28 (d, *J* = 10.9 Hz, 1 H), 2.94 - 3.12 (m, 3 H), 2.74 - 2.83 (m, 1 H), 2.69 (d, *J* = 8.2 Hz, 1 H), 2.14 - 2.23 (m, 1 H), 2.05 - 2.14 (m, 1 H), 1.76 - 1.92 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 133.5, 127.3, 122.0, 121.8, 119.4, 118.6, 118.5, 113.7, 111.3, 67.6, 63.6,

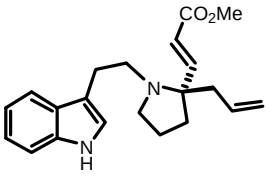
51.7, 48.9, 36.2, 31.4, 24.9, 22.0; HRMS *m/z* 285.1972 (calcd for $C_{18}H_{24}N_2O+H^+$, 285.1961).

Compound 3-140



To a solution of oxalyl chloride (61 µ:, 0.71 mmol. 1.2 equiv) in CH_2Cl_2 (5 mL) at -78 °C was added DMSO (101 µL, 1.42 mmol, 2.4 equiv) dropwise. After 30 min alcohol **3-139** (168 mg, 0.59 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added and, after 1 h, Et_3N (411 µL, 2.95 mmol, 5 equiv) was added. After 15 min at -78 °C the reaction mixture was allowed to warm to 0 °C. After 30 min at 0 °C the reaction mixture was diluted with ½ saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5mL), the organic layers were combined, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 hexanes/EtOAc, 5 % Et_3N) to afford the title compound as an impure pale yellow oil (42 mg, 25%) that was used immediately in the next step. R_f 0.33 (2:1 hexanes/EtOAc, 5 % Et_3N); ^{1}H NMR (599 MHz, $CDCl_3$) δ 9.34 (s, 1 H), 7.98 (br. s., 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.10 - 7.15 (m, 1 H), 7.01 (d, *J* = 2.3 Hz, 1 H), 5.73 - 5.82 (m, 1 H), 5.04 - 5.13 (m, 2 H), 3.20 - 3.27 (m, 1 H), 2.87 - 3.05 (m, 6 H), 2.47 (dd, *J* = 7.0, 14.1 Hz, 1 H), 2.24 (dd, *J* = 7.6, 14.1 Hz, 1 H), 1.89 - 1.99 (m, 4 H), 1.83 - 1.89 (m, 1 H).

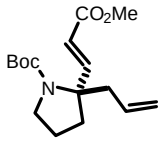
Compound 3-141



To a mixture of NaH (60 % in mineral oil, 63 mg, 1.6 mmol, 2.5 equiv) in THF (10 mL) was added trimethyl phosphonoacetate (135 µL, 0.94 mmol, 1.5 equiv). After 15 min a solution of aldehyde **3-140** (176 mg, 0.625 mmol, 1.0 equiv) in THF (5 mL) was added and after 2 h the reaction mixture was diluted with ½ saturated NH_4Cl (2 mL) and, after 10 min, the reaction mixture was diluted with ½ saturated $NaHCO_3$ (10 mL) and EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The residue was purified by

column chromatography (2:1 hexanes/EtOAc, 5% Et_3N) to afford the title compound as a pale yellow oil (211 mg, quant.). R_f 0.26 (2:1 hexanes/EtOAc, 5% Et_3N); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (br. s., 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.09 - 7.15 (m, 1 H), 7.03 (d, *J* = 2.3 Hz, 1 H), 6.95 (d, *J* = 16.0 Hz, 1 H), 5.85 (d, *J* = 16.0 Hz, 1 H), 5.73 - 5.82 (m, 1 H), 5.08 - 5.12 (m, 1 H), 5.06 (s, 1 H), 3.72 (s, 3 H), 3.16 (ddd, *J* = 5.5, 7.5, 9.3 Hz, 1 H), 2.81 - 2.98 (m, 4 H), 2.60 - 2.74 (m, 1 H), 2.38 (dd, *J* = 7.4, 14.0 Hz, 1 H), 2.29 (dd, *J* = 6.8, 13.8 Hz, 1 H), 1.81 - 1.98 (m, 3 H), 1.72 - 1.81 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 151.4, 136.2, 134.4, 127.5, 121.9, 121.4, 119.6, 119.2, 118.8, 117.8, 114.6, 111.1, 66.1, 51.5, 51.0, 49.6, 39.0, 34.8, 25.8, 21.2, 21.1; HRMS *m/z* 338.1986 (calcd for $C_{21}H_{26}N_2O_2$, 338.1994).

Compound 3-142



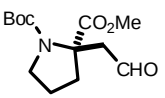
To a solution of amine hydrochloride **3-136** (1.44 g, 7.0 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added DMAP (10 mg), *i*Pr_2NEt (2.4 mL, 14 mmol, 2.0 equiv) and Boc_2O (1.77 mL, 7.7 mmol, 1.1 equiv) sequentially. After 16 h the solvent was removed *in vacuo* and the residue was purified by column chromatography (5:1 hexanes/EtOAc) to afford Boc protected amine (1.44 g, 77%). To the above prepared amine (108 mg, 0.40 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added DIBAL (1.0 M in hexanes, 1.0 mL, 1.0 mmol, 2.5 equiv) dropwise. After 30 min the reaction mixture was poured into a ½ saturated solution of Rochelle's salt (10 mL). The mixture was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the organic layers were combined, drived over $MgSO_4$, filtered through celite and concentrated *in vacuo* to afford an alcohol (97 mg, quant.) that was used without further purification. To a solution of the above prepared alcohol (97 mg, 0.40 mmol, 1.0 equiv), diisopropylethylamine (660 μL, 2.8 mmol, 7.0 equiv), and DMSO (142 μL, 2.0 mmol, 5.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C was added SO_3•pyridine complex (191 mg, 1.2 mmol, 3.0 equiv) as a solid. After complete consumption of the starting material as indicated by TLC the reaction mixture was diluted with CH_2Cl_2 (10 mL) and a ½ saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to

afford the product as a pale yellow oil that was used without further purification. To a slurry of NaH (60% in mineral oil, 24 mg, 06 mmol, 1.5 equiv) in THF (5 mL) at 0 °C was added trimethyl phosphonoacetate (64 μL, 0.44 mmol, 1.1 equiv). After 10 min at 0 °C the above synthesized aldehyde in THF (5 mL) was added and the reaction was warmed to room temperature. After 16 h the reaction mixture was diluted with a ½ saturated solution of NH_4Cl (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was then purified by flash column chromatography (5:1 hexanes/EtOAc) to afford the product as a pale yellow oil (70 mg, 59% over 2 steps) as a 1.3 to 1 mixture of two rotamers. R_f 0.30 (5:1 hexanes/EtOAc).

Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 15.6 Hz, 1 H), 5.63 - 5.80 (m, 2 H), 5.10 - 5.20 (m, 2 H), 3.74 (s, 3 H), 3.61 - 3.69 (m, 1 H), 3.23 - 3.38 (m, 1 H), 2.83 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.44 (dd, *J* = 8.2, 13.7 Hz, 1 H), 1.99 - 2.15 (m, 1 H), 1.78 - 1.86 (m, 1 H), 1.62 - 1.78 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 153.8, 152.2, 132.8, 119.3, 118.2, 80.0, 64.9, 51.6, 48.7, 41.1, 37.7, 28.4, 21.1.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 15.6 Hz, 1 H), 5.63 - 5.80 (m, 2 H), 5.10 - 5.20 (m, 2 H), 3.71 (s, 3 H), 3.54 (ddd, *J* = 3.1, 7.5, 10.5 Hz, 1 H), 3.23 - 3.38 (m, 1 H), 3.00 (dd, *J* = 6.3, 13.7 Hz, 1 H), 2.53 (dd, *J* = 8.2, 13.7 Hz, 1 H), 1.99 - 2.15 (m, 1 H), 1.78 - 1.86 (m, 1 H), 1.62 - 1.78 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 153.2, 151.3, 133.0, 119.3, 118.4, 79.2, 65.7, 51.5, 48.8, 40.0, 36.4, 28.5, 21.5.

Compound 3-145



A solution of alkene **3-144** (1.35 g, 5.0 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (1:1, 100 mL) at -78 °C was degassed with O_2 for 5 min, then O_3 was bubbled through the reaction mixture. Once a blue-grey color was observed O_2 was bubbled through the reaction mixture for 15 min then Ph_3P (2.32 g, 8.5 mmol, 1.5 equiv) was added and the reaction mixture was allowed to warm to room temperature. Once the reaction mixture obtained room temperature the solvent was removed *in vacuo* and the residue was purified by column chromatography (2:1 hexanes/EtOAc) to afford the title

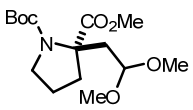
compound as a colorless oil (1.29 g, 95%) as a 1:1 mixture of two rotamers. R_f 0.43 (1:1 hexanes/EtOAc).

Rotamer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 - 9.84 (m, 1 H), 3.75 (s, 3 H), 3.67 (dt, *J* = 7.0, 10.6 Hz, 1 H), 3.41 - 3.53 (m, 1 H), 3.07 (dd, *J* = 3.1, 15.2 Hz, 1 H) 2.99 (dd, 3.1, 11.7 Hz, 1 H), 2.21 - 2.33 (m, 1 H), 2.16 (td, *J* = 6.8, 13.6 Hz, 1 H), 1.98 (dt, *J* = 6.5, 17.4 Hz, 1 H), 1.81 - 1.92 (m, 1 H), 1.42 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 174.0, 154.2, 81.0, 66.2, 52.5, 48.6, 38.1, 28.3, 23.2.

Rotamer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 - 9.84 (m, 1 H), 3.74 (sz, 3 H), 3.57 (dt, *J* = 7.0, 10.6 Hz, 1 H), 3.41 - 3.53 (m, 1 H), 2.99 (dd, 3.1, 11.7 Hz, 1 H), 2.77 (dd, *J* = 1.6, 15.2 Hz, 1 H), 2.21 - 2.33 (m, 1 H), 2.16 (td, *J* = 6.8, 13.6 Hz, 1 H), 1.98 (dt, *J* = 6.5, 17.4 Hz, 1 H), 1.81 - 1.92 (m, 1 H), 1.41 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 173.7, 153.0, 80.3, 65.7, 49.2, 47.9, 37.1, 28.2, 22.6.

HRMS *m/z* 271.1413 (calcd for $C_{13}H_{21}NO_5$, 271.1420).

Compound 3-146



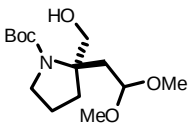
To a solution of aldehyde **3-145** (1.4 g, 5.0 mmol, 1.0 equiv) and trimethyl orthoformate (1.7 mL, 15.0 mmol, 3.0 equiv) in MeOH (15 mL) was added amberlyst acidic resin (28 mg, 2 wt %). After 16 h at room temperature the reaction mixture was filtered through celite, the celite pad was washed with MeOH and the combined filtrates were concentrated *in vacuo* to afford the title compound as a colorless oil (1.59 g, quant.) as a 2:1 mixture of two rotamers that was used without further purification. R_f 0.38 (2:1 hexanes/EtOAc).

Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (dd, *J* = 3.9, 6.6 Hz, 1 H), 3.70 - 3.75 (m, 1 H), 3.69 (s, 3 H), 3.35 - 3.43 (m, 1 H), 3.32 (s, 3 H), 3.29 (s, 3 H), 2.35 - 2.46 (m, 2 H), 2.17 - 2.25 (m, 1 H), 1.96 - 2.07 (m, 1 H), 1.75 - 1.94 (m, 2 H), 1.39 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 153.6, 102.6, 80.2, 65.7, 53.5, 52.6, 52.1, 48.3, 37.4, 36.3, 28.2, 22.5.

Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 3.5, 6.6 Hz, 1 H), 1 3.68 (s, 3 H), 3.53 - 3.60 (m, 1 H), 3.35 - 3.43 (m, 1 H), 3.32 (s, 3 H), 3.28 (s, 3 H), 2.50 (dd, *J* = 3.5, 14.5 Hz, 1 H), 2.25 - 2.33 (m, 1 H), 2.17 - 2.25 (m, 1 H), 1.96 - 2.07 (m, 1 H), 1.75 -

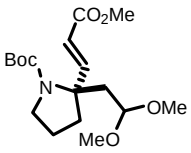
1.94 (m, 2 H), 1.43 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 154.1, 102.9, 79.5, 66.1, 53.9, 52.5, 52.1, 48.3, 36.9, 36.3, 28.3, 23.1.
HRMS *m/z* 316.1767 (calcd for $C_{15}H_{27}NO_6$-H^+, 316.1760).

Compound 3-147



To a solution of ester **3-146** (1.59 g, 5.0 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) was added DIBAL (1.0 M in hexanes, 12.5 mL, 12.5 mmol, 2.5 equiv) dropwise. After 30 min at room temperature the reaction mixture was slowly poured into a ½ saturated solution of Rochelle's salt (100 mL). After 1 h the mixture was diluted with CH2Cl2 (25 mL) and the layers were seperatted. The aqueous layer was extracted with Ch2Cl2 (2 x 50 mL) and the organic layers were combined, drived over MgSO4, filtered through celite, and concentrated *in vacuo* to afford the title compound as a colorless oil (1.45 g, quant.) as a 10:1 mixture of two rotamers that was used without further purification. R_f 0.33 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (dd, *J* = 2.0, 9.8 Hz, 1 H), 4.58 (dd, *J* = 4.1, 6.8 Hz, 1 H), 3.56 - 3.74 (m, 2 H), 3.37 - 3.47 (m, 1 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 2.21 - 2.30 (m, 1 H), 2.13 - 2.21 (m, 1 H), 2.03 (dd, *J* = 6.6, 14.5 Hz, 1 H), 1.67 - 1.87 (m, 3 H), 1.46 - 1.52 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 102.8, 80.1, 69.4, 65.8, 53.4, 53.3, 48.5, 35.0, 34.4, 28.4, 21.8; HRMS *m/z* 290.1960 (calcd for $C_{14}H_{27}NO_5$+H^+, 290.1962).

Compound 3-148



To a solution of alcohol **3-147** (173 mg, 0.60 mmol, 1.0 equiv), *i*Pr_2NEt_2 (729 µL, 4.18 mmol, 7 equiv) and DMSO (211 µL, 3.0 mmol, 5.0 equiv) in CH_2Cl_2 (6 mL) was added pyridine•SO_3 complex (286 mg, 1.8 mmol, 3.0 equiv). After 30 min the reaction mixture was diluted with a ½ saturated solution of $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the organic layers were combined, dried over $MgSO_4$, filtered through celite and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with water (2 x 10 mL), brine, dried over $MgSO_4$, filtered through celite and the solvent was removed *in vacuo* to afford the aldehyde that was used without further purification. To a mixture of NaH (60 % in

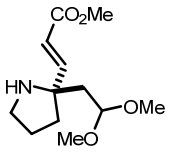
mineral oil, 36 mg, 0.9 mmol, 1.5 equiv) in THF (5 mL) was added trimethyl phosphonoacetate (95 μL, 0.66 mmol, 1.1 equiv). After 15 min a solution of the above prepared aldehyde (172 mg, 0.6 mmol, 1.0 equiv) in THF (5 mL) was added and after 2 h the reaction mixture was diluted with ½ saturated NH_4Cl (2 mL) and, after 10 min, the reaction mixture was diluted with ½ saturated $NaHCO_3$ (10 mL) and EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (211 mg, 58% over 2 steps) as a mixture of two rotamers. R_f 0.28 (2:1 hexanes/EtOAc).

Rotamer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 16.0 Hz, 1 H), 5.69 (d, *J* = 15.6 Hz, 1 H), 4.34 - 4.44 (m, 1 H), 3.73 (s, 3 H), 3.61 - 3.68 (m, 1 H), 3.32 - 3.41 (m, 1 H), 3.24 - 3.32 (m, 6 H), 2.31 - 2.41 (m, 1 H), 2.20 - 2.31 (m, 1 H), 2.12 - 2.20 (m, 1 H), 1.78 - 1.88 (s, 1 H), 1.61 - 1.78 (m, 2 H), 1.41 (m, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 153.8, 152.2, 117.8, 102.2, 80.2, 63.7, 53.3, 52.6, 51.6, 48.4, 39.0, 37.8, 28.3, 21.1.

Rotamer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9 7.02 (d, *J* = 16.0 Hz, 1 H), 5.69 (d, *J* = 15.6 Hz, 1 H), 4.34 - 4.44 (m, 1 H), 3.70 (s, 3 H), 3.50 - 3.55 (m, 1 H), 3.32 - 3.41 (m, 1 H), 3.24 - 3.32 (m, 6 H), 2.31 - 2.41 (m, 1 H), 2.20 - 2.31 (m, 2 H), 1.78 - 1.88 (m, 1 H), 1.61 - 1.78 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 153.2, 151.3, 118.1, 102.7, 79.3, 64.2, 53.3, 52.9, 51.5, 48.4, 38.3, 37.0, 28.4, 21.6.

HRMS *m/z* 343.1991 (calcd for $C_{17}H_{29}NO_6$, 313.1995).

Compound 3-149



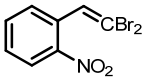
To a solution of protected amine **3-148** (200 mg, 0.58 mmol, 1.0 equiv) and 2,6-lutidine (337 μL, 2.91 mmol, 5.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added TMSOTf (421 μL, 2.32 mmol, 4.0 equiv). Following complete consumption of the starting material by TLC, a ½ saturated solution of NH_4Cl (5 mL) was added. Once gas evolution had ceased, a ½ saturated $NaHCO_3$ solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. Residual 2,6-lutidine was removed under vacuum to afford

the free secondary amine as a pale brown oil (128 mg, 90%) that was used without further purification as a 2.3:1 mixture of two rotamers.

Major Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 15.2 Hz, 1 H), 5.88 (d, *J* = 15.6 Hz, 1 H), 4.99 (dd, *J* = 3.1, 10.2 Hz, 1 H), 3.76 (s, 3 H), 3.55 - 3.73 (m, 3 H), 3.54 (s, 3 H), 2.52 (s, 1 H), 2.43 (dd, *J* = 3.1, 13.3 Hz, 1 H), 2.08 - 2.15 (m, 1 H), 1.87 - 1.98 (m, 2 H), 1.77 - 1.83 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 148.6, 122.8, 100.3, 62.8, 57.0, 51.9, 46.7, 38.5, 38.0, 20.8.

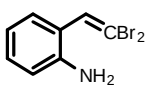
Minor Rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 15.6 Hz, 1 H), 6.76 (d, *J* = 15.2 Hz, 1 H), 5.88 (d, *J* = 15.6 Hz, 1 H), 5.75 (d, *J* = 15.2 Hz, 1 H), 5.20 (dd, *J* = 1.0, 3.7 Hz, 1 H), 3.74 (s, 3 H), 3.55 - 3.73 (m, 3 H), 3.40 (s, 3 H), 2.52 (s, 1 H), 2.48 (d, *J* = 12.9 Hz, 1 H), 2.08 - 2.15 (m, 1 H), 1.87 - 1.98 (m, 2 H), 1.77 - 1.83 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 150.7, 120.1, 100.2, 62.8, 56.4, 51.9, 47.3, 39.4, 37.6, 20.0.

Compound 3-166



To a solution of 2-nitrobenzaldehyde (**3-158**, 1.17 g, 7.7 mmol, 1.0 equiv) and CBr_4 (3.8 g, 11.6 mmol, 1.5 equiv) in CH_2Cl_2 (100 mL) at 0 °C was added PPh_3 (6.10 g, 23.2 mmol, 3.0 equiv) and the reaction mixture was allowed to warm to room temperature. After 30 min the reaction mixture was filtered through a SiO_2/celite bilayer pad and the pad was rinsed with CH_2Cl_2 (100 mL). The filtrates were combined and the solvent was removed *in vacuo*. The residue was purified by column chromatography (2:1 hexanes/EtOAc) to afford the title compound as a yellow solid (2.10 g, 89%). R_f 0.58 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) d 8.14 (dd, *J* = 1.4, 8.4 Hz, 1 H), 7.79 (s, 1 H), 7.66 - 7.72 (m, 1 H), 7.59 - 7.64 (m, 1 H), 7.53 - 7.59 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 134.0, 133.5, 131.6, 131.4, 129.4, 124.8, 93.2. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[49]

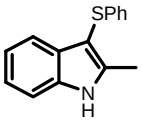
Compound 3-159



To solution of dibromide **3-166** (306 mg, 1.0 mmol, 1.0 equiv) in EtOH (5 mL) was added $SnCl_2$•$2H_2O$ (903 mg, 4.0 mmol, 4.0 equiv) and the reaction mixture was heated to reflux. After 2 h the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was diluted with H_2O (10

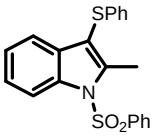
mL) and EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered through celite and the solvent was removed *in vacuo*. The residue was purified by column chromatography (3:1 hexanes/EtOAc) to afford the title compound as a orange oil (190 mg, 69%). R_f 0.58 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1 H), 7.30 (d, J = 7.4 Hz, 1 H), 7.14 - 7.21 (m, 1 H), 6.76 - 6.83 (m, 1 H), 6.67 - 6.75 (m, 1 H), 3.71 (br. s., 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 134.0, 129.7, 129.2, 121.7, 118.4, 115.7, 92.8. ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[49]

Compound 3-167



To a solution of 2-methylindole (5.25 g, 40 mmol, 2.0 equiv), phenyldisulfide (4.36 g, 20 mmol, 1.0 equiv) and DMSO (4.25 mL, 60 mmol, 3.0 equiv) in methyl carbonate (40 mL) at 40 °C open to atmosphere was added and I_2 (254 mg, 5 mol %). After 4 hours at 40 °C the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to afford the title compound as a pale pink solid (8.2 g, 86%). R_f 0.28 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br. s., 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H), 7.11 - 7.26 (m, 4 H), 7.02 - 7.11 (m, 3 H), 2.51 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 139.3, 135.4, 130.2, 128.6, 125.4, 124.5, 122.1, 120.6, 118.9, 110.6, 99.2, 12.1; ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[50]

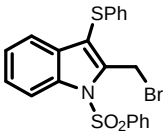
Compound 3-161



To a solution of **3-167** (3.0 g, 12.5 mmol, 1.0 equiv) in DMF (50 mL) at 0 °C was added NaH (60% in mineral oil, 602 mg, 15 mmol, 1.2 equiv) and the reaction mixture was warmed to room temperature. After 1h the reaction mixture was cooled to 0 °C and phenylsulfonyl chloride (1.76 mL, 13.75 mmol,

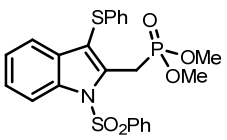
1.1 equiv) was added dropwise. After 2 h the reaction mixture was added to a 1 M HCl solution (50 mL) and diluted with EtOAc (100 mL). The aqueous layer was removed and the organic layer was washed with water (3 x 25 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (8:1 hexanes/EtOAc) to afford the title compound as an orange syrup (4.07 g, 86%). R_f 0.44 (5:1 hexanes/EtOAc); ^{1}H NMR (599 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.8 Hz, 1 H), 7.78 - 7.83 (m, 2 H), 7.55 - 7.59 (m, 1 H), 7.41 - 7.48 (m, 3 H), 7.30 - 7.36 (m, 1 H), 7.20 - 7.24 (m, 1 H), 7.12 (t, *J* = 7.6 Hz, 2 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 6.90 - 6.94 (m, 2 H), 2.74 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 135.7, 134.0, 129.4, 129.0, 129.0, 128.9, 127.5, 126.4, 126.1, 125.2, 125.0, 124.1, 119.6, 119.2, 114.5, 29.7; ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[51]

Compound 3-162



To a solution of **3-161** (573 mg, 1.46 mmol, 1.0 equiv) and NBS (259 mg, 1.46 mmol, 1.0 equiv) in CCl_4 (10 mL) was added benzoyl peroxide (20 mg, 0.07 mmol, 5 mol %) and the mixture was heated to 90 °C. After 8 h the reaction mixture was cooled to room temperature and filtered through a SiO_2/celite bilayer pad and the pad was rinsed flushed with EtOAc/hexanes (50 mL). The filtrate was concentrated *in vacuo* to afford the title compound (690 mg, 91%) that was used without further purification. R_f 0.36 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1 H), 7.96 - 8.02 (m, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 3 H), 7.35 - 7.45 (m, 3 H), 7.20 - 7.25 (m, 1 H), 7.13 - 7.20 (m, 3 H), 7.06 - 7.11 (m, 2 H), 5.29 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 134.9, 134.3, 129.8, 129.3, 129.3, 129.0, 127.5, 127.0, 126.6, 126.1, 126.1, 124.5, 120.7, 115.7, 115.0, 29.7; ^{1}H and ^{13}C NMR spectra were in agreement with previously reported data.[51]

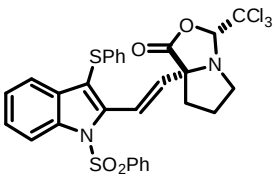
Compound 3-163



To a solution of bromide **3-162** (290 mg, 0.614 mmol, 1.0 equiv) and $P(OMe)_3$ (87 μL, 0.74 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL) was added $ZnBr_2$ (27 mg, 0.12 mmol, 20 mol %). After 18 h the reaction mixture was diluted with CH_2Cl_2 (10 mL) and 1 M HCl (10 mL), the layers were separated and

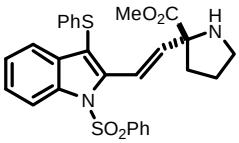
the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered through celite, concentrated *in vacuo* and purified by column chromatography (4:1 hexanes/EtOAc to 100% EtOAc) to afford the title compound as a colorless syrup (230 mg, 75%). R_f 0.49 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1 H), 7.76 (d, *J* = 7.4 Hz, 2 H), 7.51 - 7.56 (m, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.39 - 7.44 (m, 2 H), 7.27 - 7.32 (m, 1 H), 7.20 - 7.26 (m, 1 H), 6.83 (d, *J* = 3.5 Hz, 1 H), 3.79 (d, *J* = 22.3 Hz, 2 H), 3.77 (d, *J* = 10.9 Hz, 8 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 137.0, 133.8, 130.7, 130.7, 129.5, 129.2, 126.3, 124.6, 123.9, 120.7, 115.0, 112.8, 112.7, 53.1 (d, *J* = 6.1 Hz, 1 C), 25.3 (d, *J* = 142.6 Hz, 1 C); LRMS *m/z* 487.1 (calcd for $C_{23}H_{22}NO_5PS_2$, 271.1420

Compound 3-164



To a mixture of phosphonate **3-163** (1.38 g, 2.83 mmol, 1.0 equiv) and aldehyde **3-103** (926 mg, 3.40 mmol, 1.0 equiv) at 0 °C in THF (20 mL) was added LiHMDS (1.0 M in THF, 3.40 mL, 3.40 mmol, 1.1 equiv) dropwise. After 30 min the reaction mixture was diluted with ½ saturated NH_4Cl (10 mL) and Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The residue was purified by column chromatography (3:1 hexanes/EtOAc) to afford the title compound as a bright yellow solid (1.02 g, 57%). R_f 0.25 (5;1 hexanes/EtOAc); ^{1}H NMR (599 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.2 Hz, 1 H), 7.68 (d, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.36 - 7.41 (m, 2 H), 7.31 - 7.36 (m, 1 H), 7.23 (d, *J* = 15.3 Hz, 1 H), 7.17 - 7.20 (m, 1 H), 7.06 - 7.10 (m, 1 H), 7.02 - 7.06 (m, 1 H), 6.83 (d, *J* = 7.0 Hz, 1 H), 6.39 (d, *J* = 15.3 Hz, 1 H), 5.12 (s, 1 H), 3.57 - 3.63 (m, 1 H), 3.23 (dt, *J* = 6.9, 10.9 Hz, 1 H), 2.18 - 2.25 (m, 1 H), 2.14 (dt, *J* = 5.9, 12.2 Hz, 1 H), 2.04 - 2.11 (m, 1 H), 1.91 (dq, *J* = 6.1, 12.1 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 140.5, 137.9, 136.4, 136.3, 136.2, 134.0, 131.4, 129.2, 128.9, 126.5, 125.9, 125.5, 124.5, 120.4, 119.7, 115.2, 112.8, 103.6, 102.5, 100.2, 73.6, 58.3, 38.6, 25.0; HRMS *m/z* 632.0162 (calcd for $C_{29}H_{23}Cl_3N_2O_5S_2$, 632.0165.

Compound 3-165



To a solution of oxazolidinone **3-164** (300 mg, 0.47 mmol, 1.0 equiv) in MeOH/MeOAc (1:1, 5 mL) was added sodium metal (12 mg, 0.5 mmol, 1.0 equiv). After 30 min AcCl (780 μL, 9.0 mmol, 19 equiv) was added dropwise and the reaction mixture was heated to reflux. Following disappearance of the intermediate *N*-formate by TLC, the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by column chromatography (2:1 hexanes/EtOAc to 100% EtOAc) to afford the title compound as a white solid (54 mg, 50%) .R_f 0.39 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.2 Hz, 1 H), 7.69 - 7.78 (m, 2 H), 7.48 - 7.56 (m, 1 H), 7.30 - 7.41 (m, 4 H), 7.14 - 7.22 (m, 2 H), 7.01 - 7.14 (m, 3 H), 6.84 - 6.91 (m, 2 H), 6.36 (d, *J* = 15.6 Hz, 1 H), 3.72 (s, 3 H), 3.09 - 3.15 (m, 2 H), 2.21 - 2.31 (m, 1 H), 1.93 - 2.03 (m, 1 H), 1.71 - 1.91 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 141.2, 140.8, 138.1, 136.5, 136.4, 133.9, 129.0, 128.8, 126.9, 126.6, 125.7, 125.4, 124.4, 120.3, 118.1, 115.3, 111.8, 89.8, 70.7, 52.7, 46.4, 36.8, 24.7; HRMS *m/z* 518.1324 (calcd for $C_{28}H_{26}N_2O_4S_2$, 518.1334).

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Chapter 4. Conclusions

Presented herein has been the culmination of a number of projects which disclosed the development of novel strategies and methodologies, and progress towards the natural product grandilodine A. These projects, though disparate in nature, are all encompassed within the broad field that is synthetic organic chemistry.

I have demonstrated that siloles may engage productively in Diels–Alder chemistry with exceptionally high levels of stereocontrol. These silanorbornene adducts have been shown to be valuable substrates as oxidative cleavage of the bridging silicon atom reveals a complex cyclohexene-1,4-diol. This complex core is found in numerous natural products, including the eudesmanolides; however, further studies were not conducted as we deemed the 5-step protocol for the synthesis of the silole to be excessively lengthy. Despite its shortcomings, the disclosed study represents the first systematic investigation of the Diels–Alder chemistry of siloles in the 85 year history of this venerable reaction.

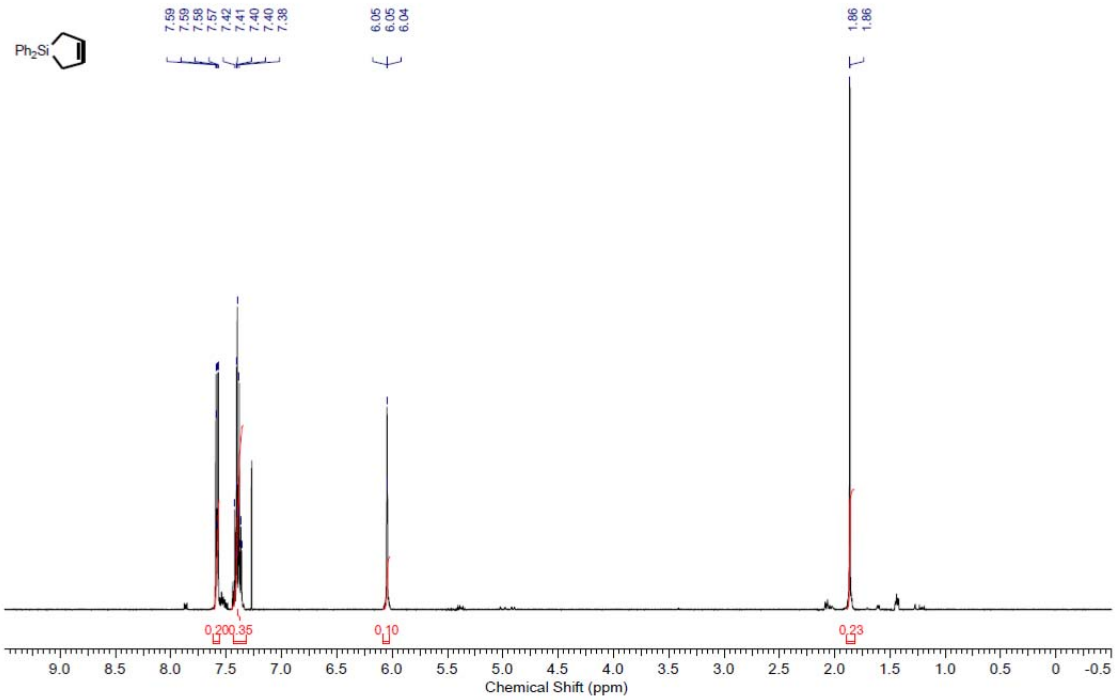
Following the termination of the silole project, I turned my attention towards exploration of the cycloaddition chemistry of donor-acceptor strained ring systems. I, along with coworkers, was able to show that alkoxy-activated cyclobutane dicarboxylates could successfully undergo annulation events with two and three atom dipoles to form a variety of unique bicyclic hetereocycles. Currently, there are no known natural products which bear these *cis*-fused acetal systems but the striking molecular architecture these compounds posses may lead to their application as novel scaffolds for biological studies. We have also conducted preliminary studies towards functionalization of the cycloadducts and are optimistic that they may become valuable synthons in the near

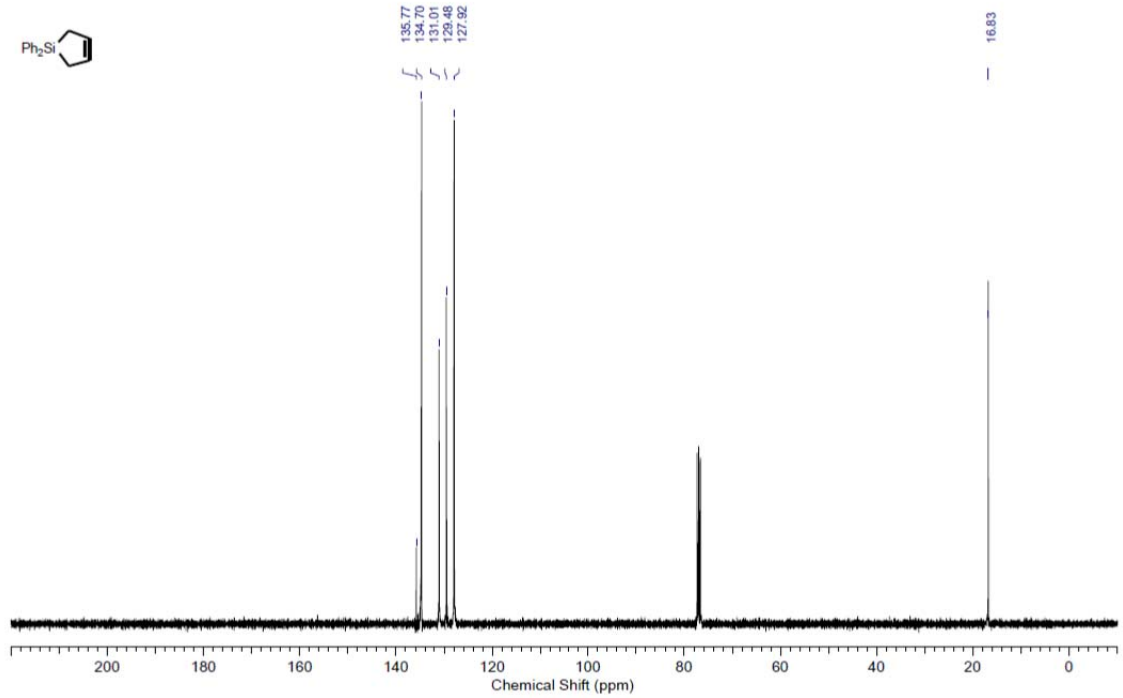
future. These newly developed methods greatly expand the current paradigm of herteroatom-activated strained ring systems, demonstrating that exceptional levels of regio- and stereo-control can be obtained during a variety of annulation events.

Upon the completion of the cycloaddition projects, I directed efforts towards the total synthesis of the recently disclosed natural product grandilodine A. The methods which I had developed in the earlier chapters were not tenable for the synthesis of an alkaloid of this nature, and thus alternative chemistry was explored. Multiple routes towards the total synthesis of grandilodine A were examined, yet I was continually stymied by unanticipated intricacies that revealed themselves through my studies. Despite the incomplete nature of the work, many lessons were learned that may assist in a successful synthesis in the future.

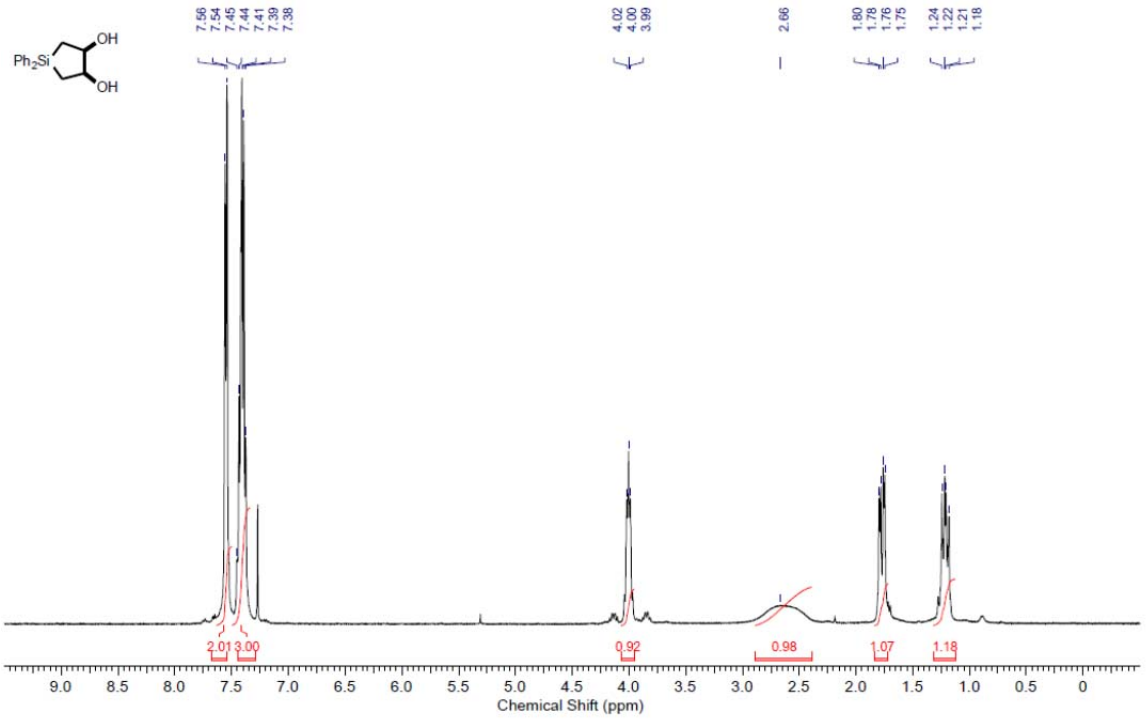
Appendix 1 – NMR Spectral Data for Chapter 1

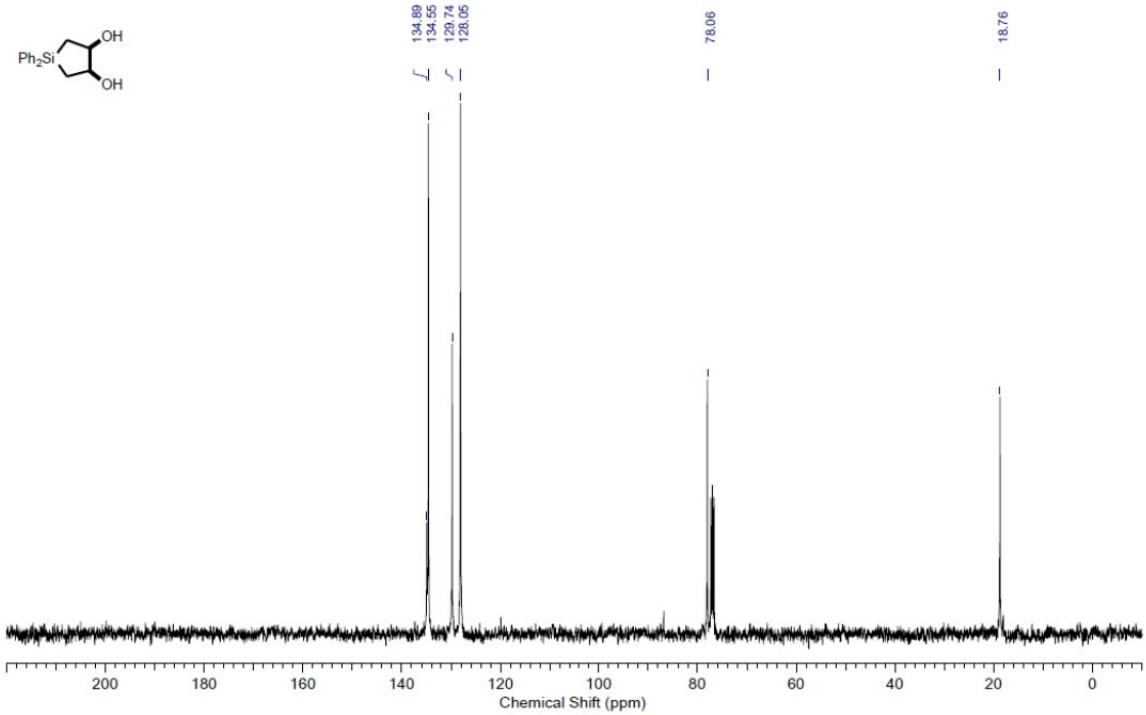
^{1}H and ^{13}C NMR of compound **1-19**



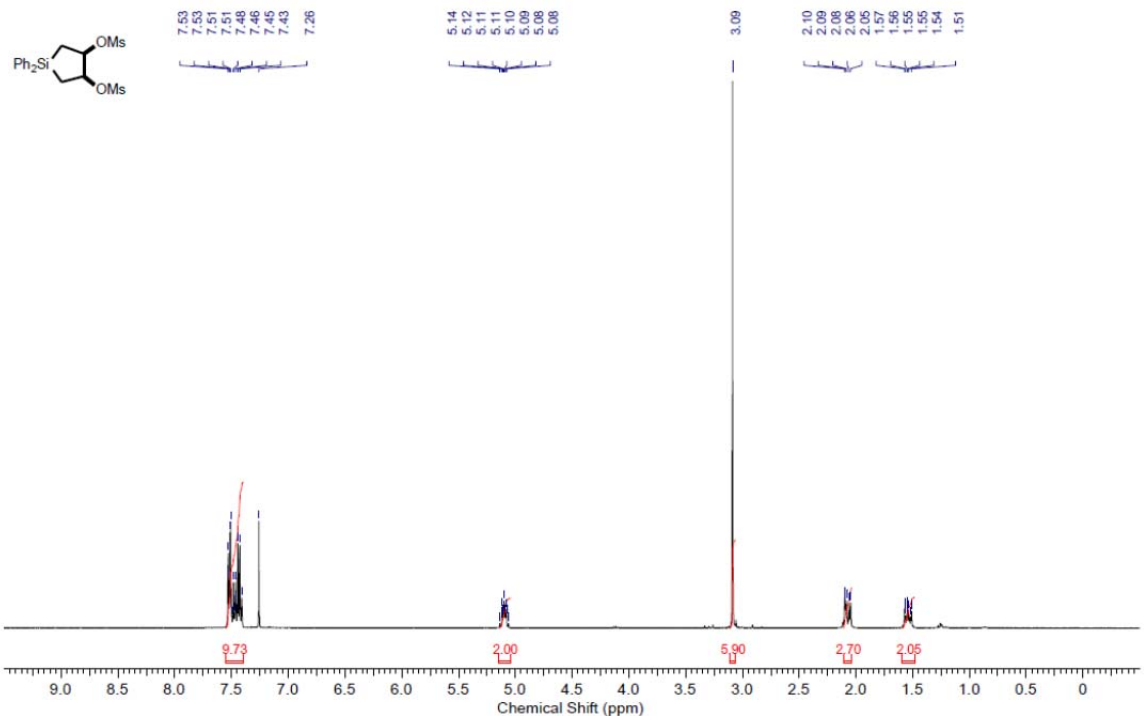


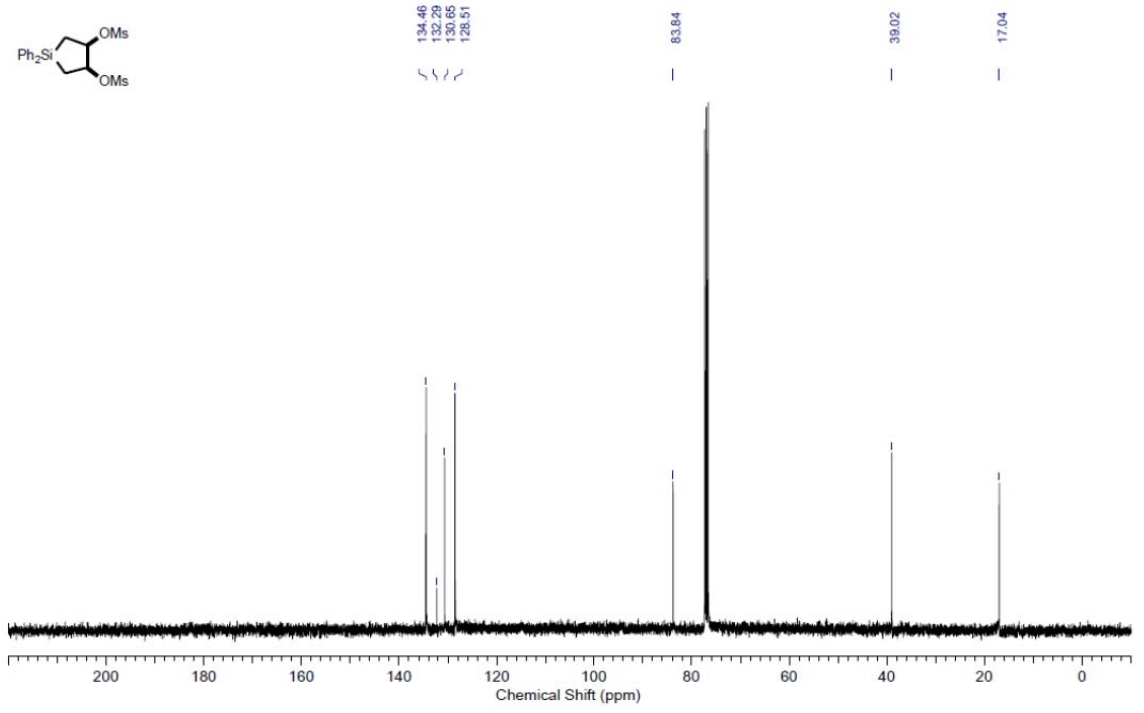
^{1}H and ^{13}C NMR of compound **1-70**



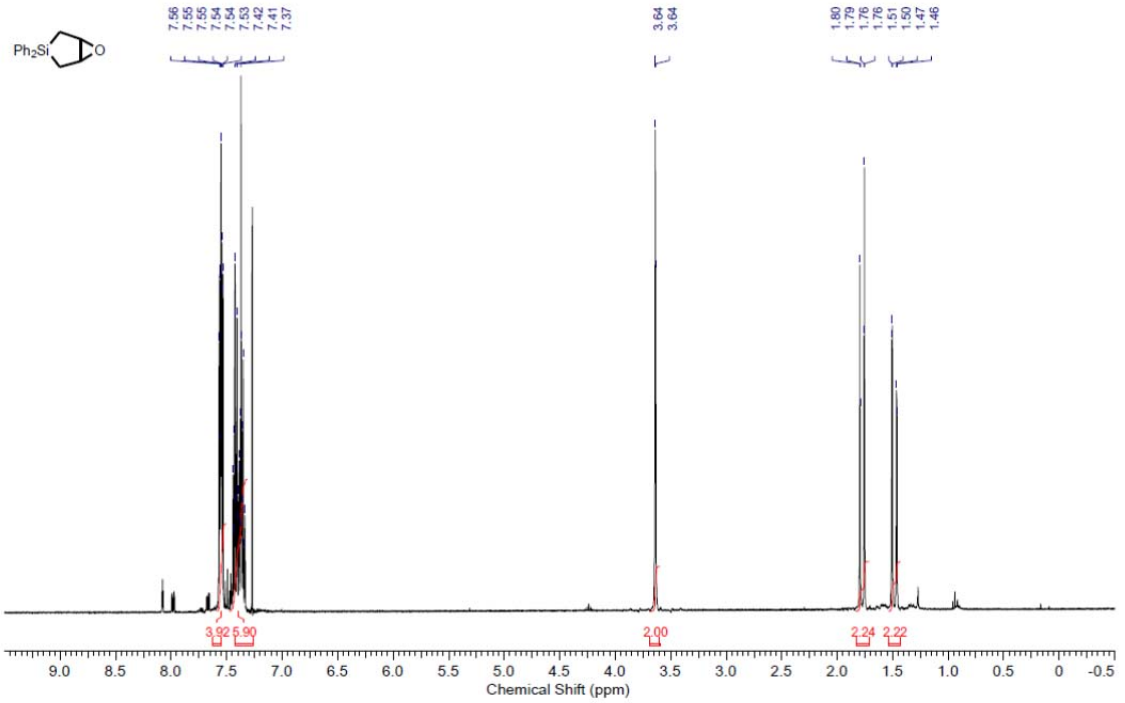


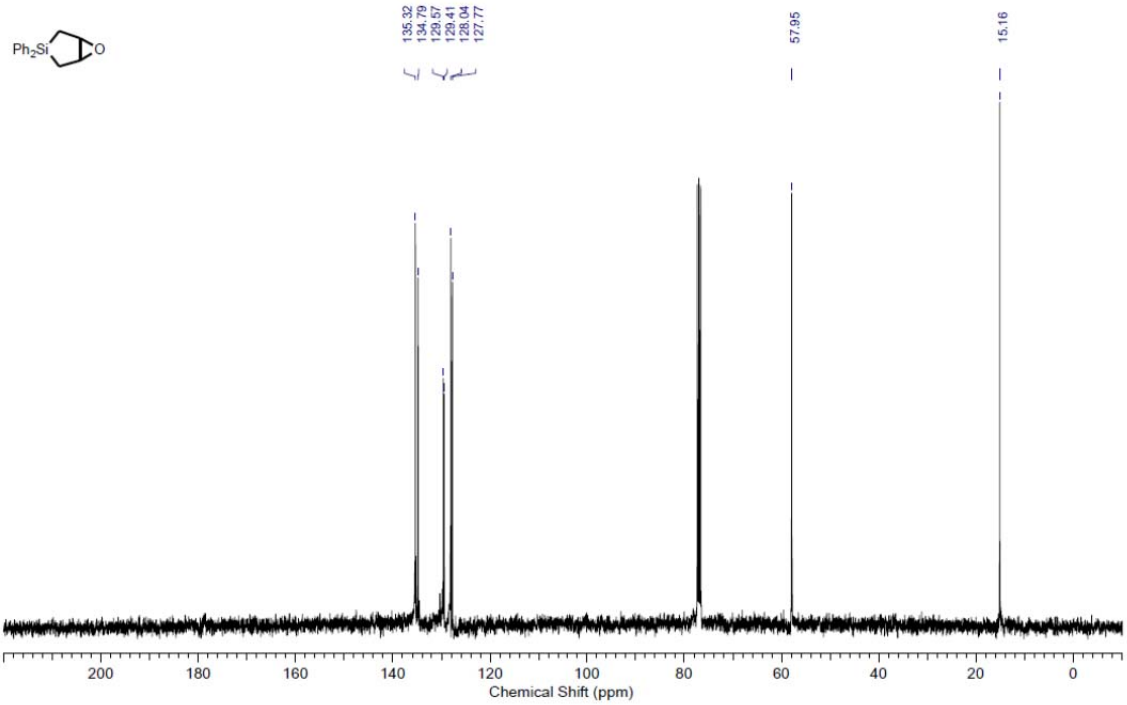
^{1}H and ^{13}C NMR of compound **1-34**



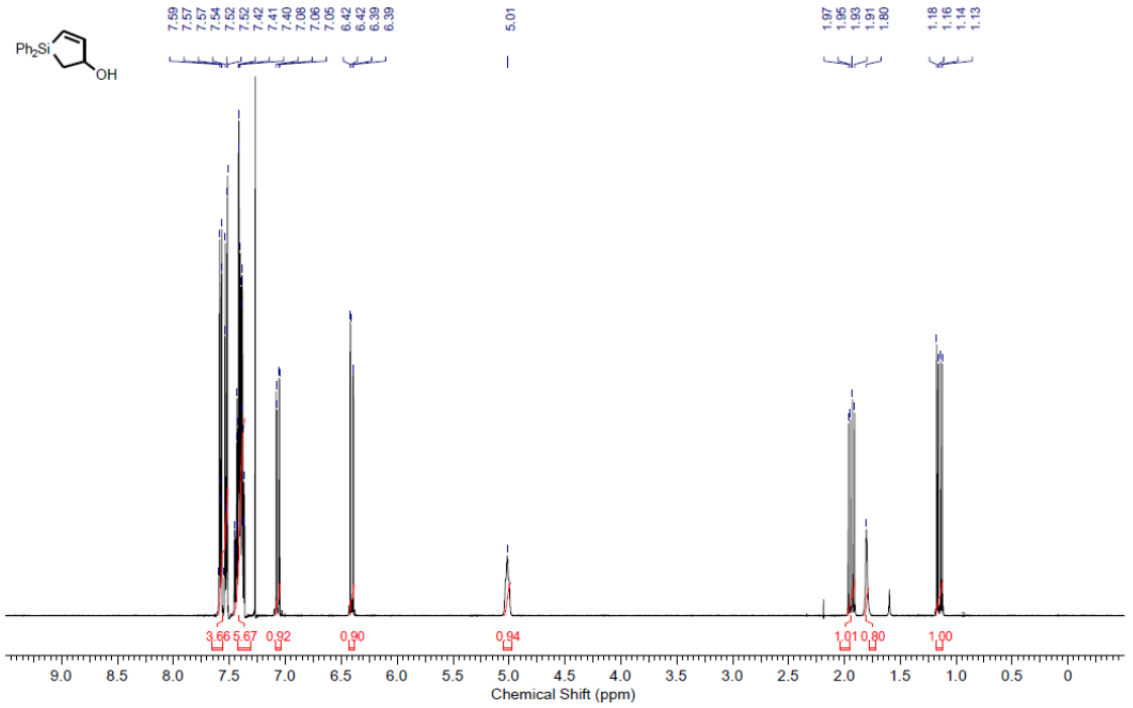


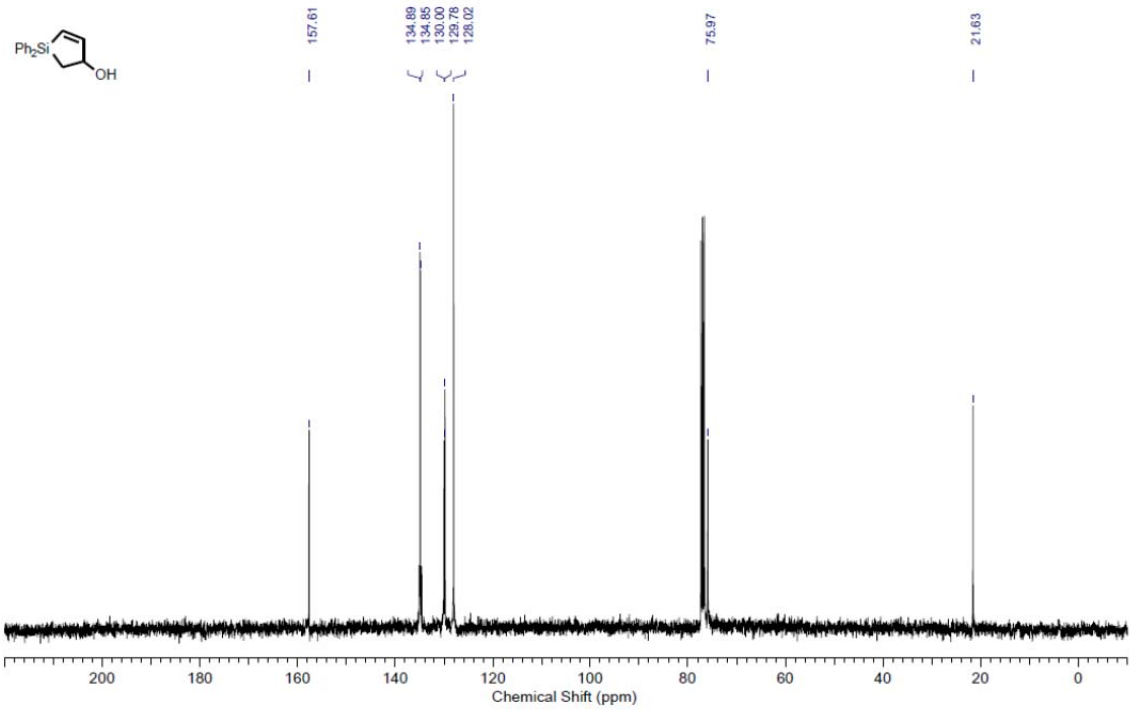
^{1}H and ^{13}C NMR of compound **1-20**



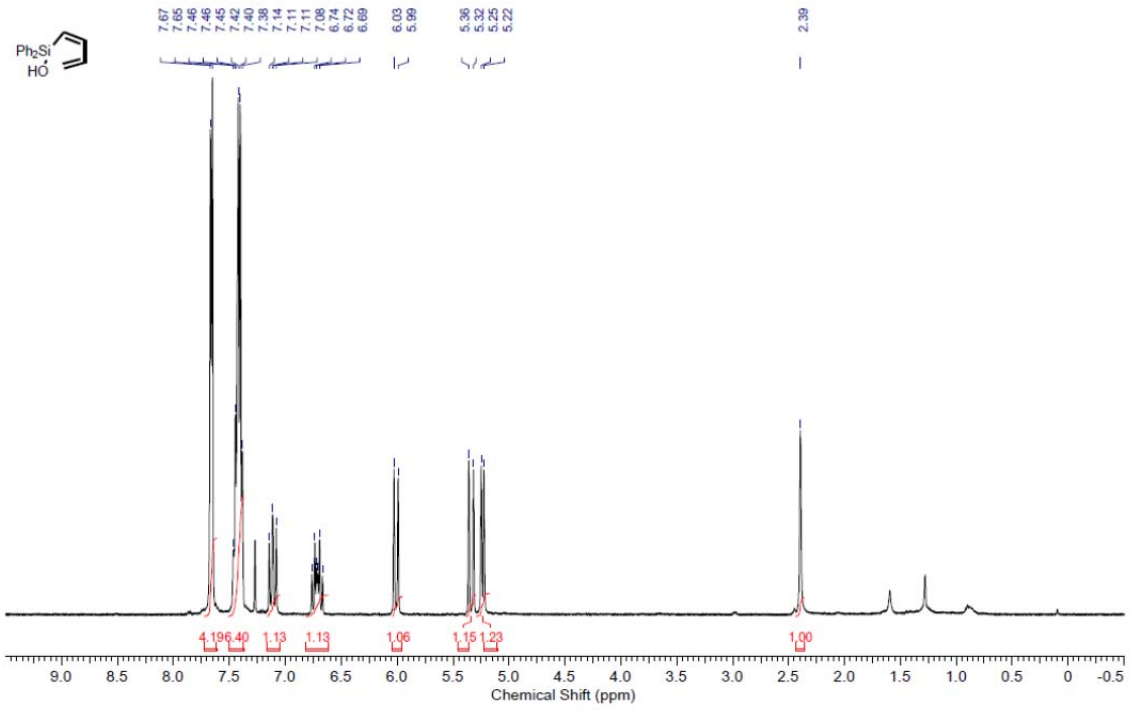


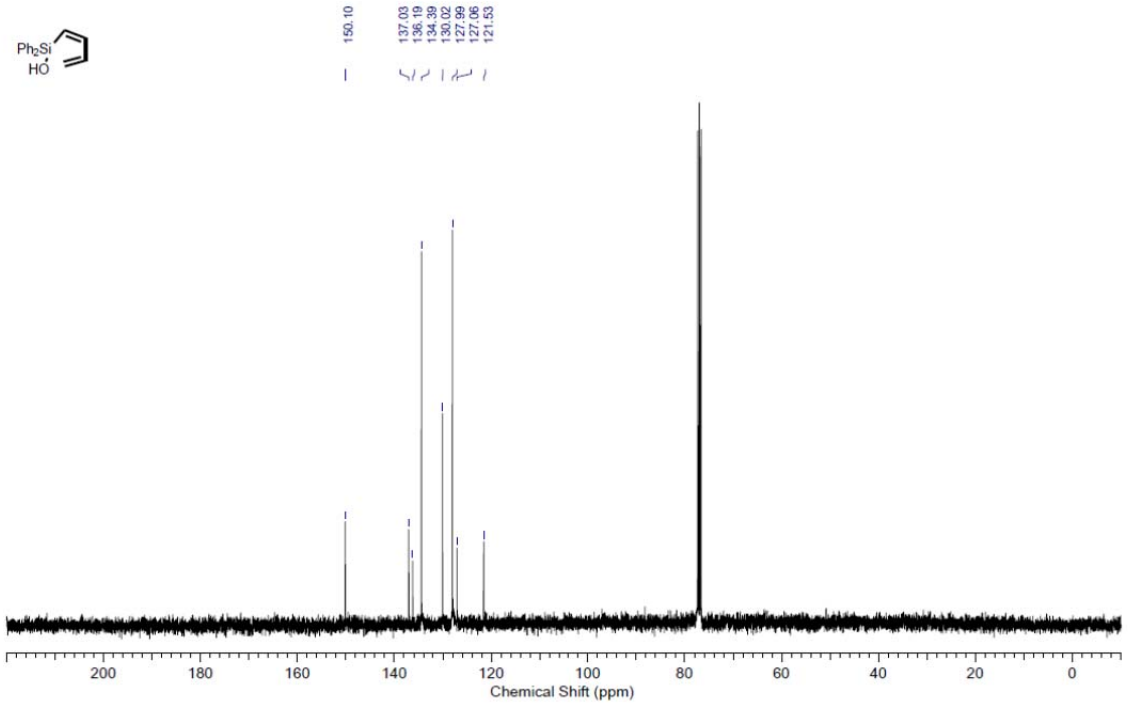
^{1}H and ^{13}C NMR of compound **1-21**



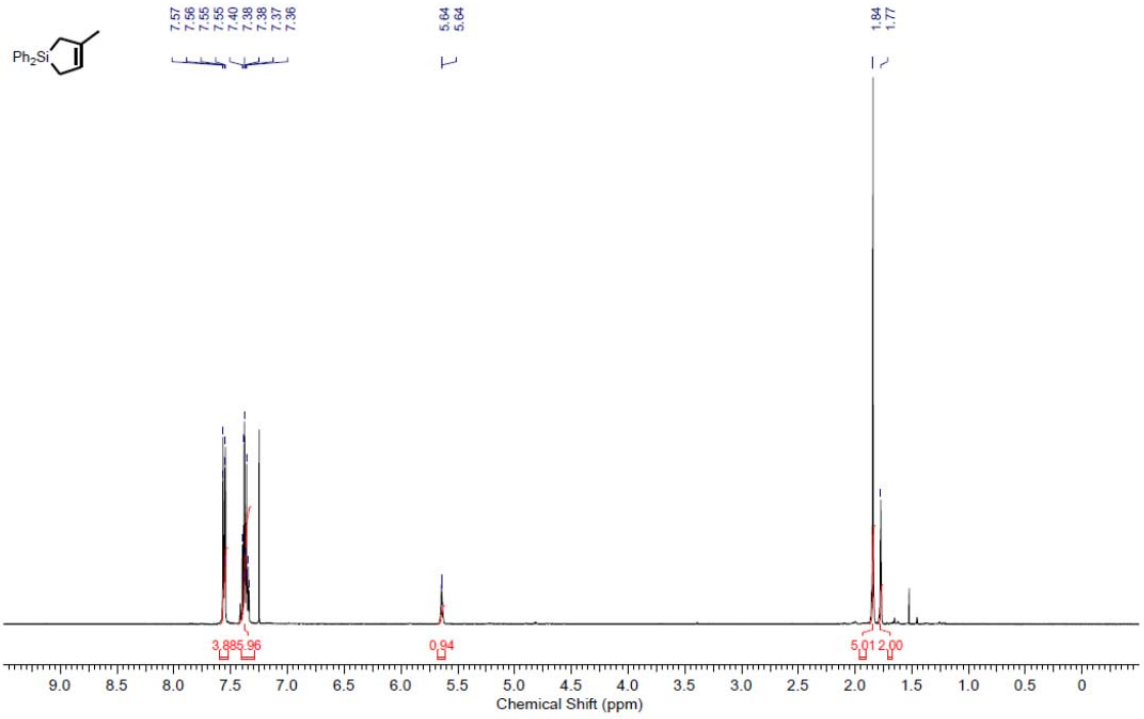


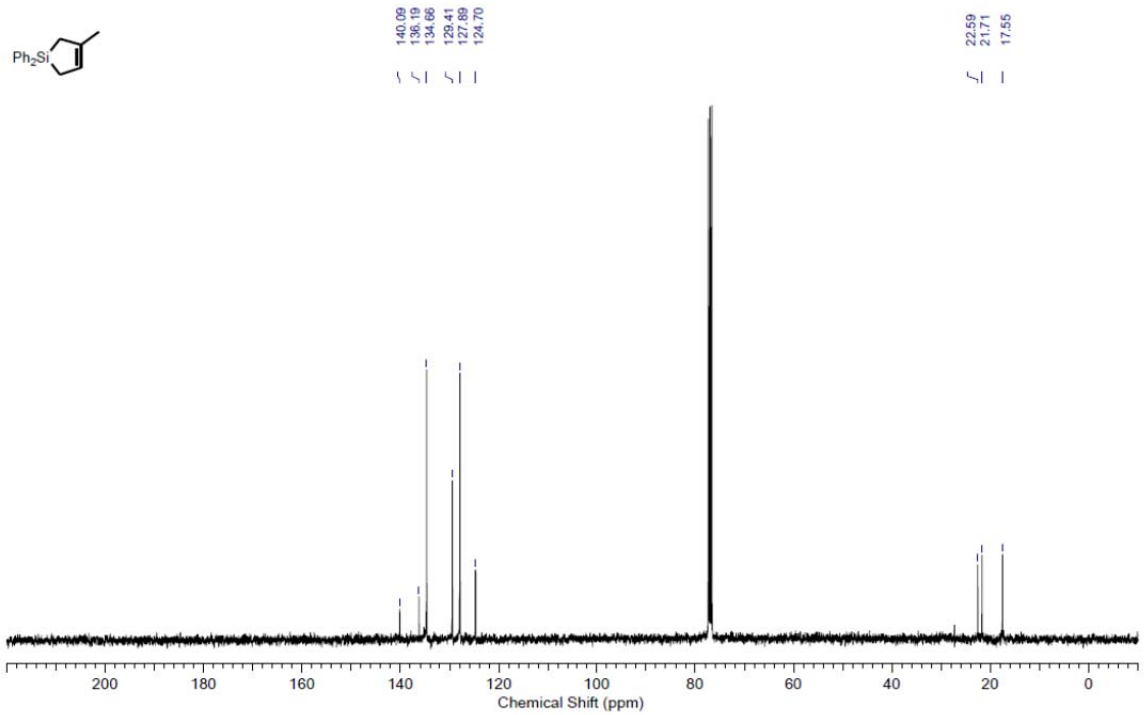
^{1}H and ^{13}C NMR of compound **1-35**



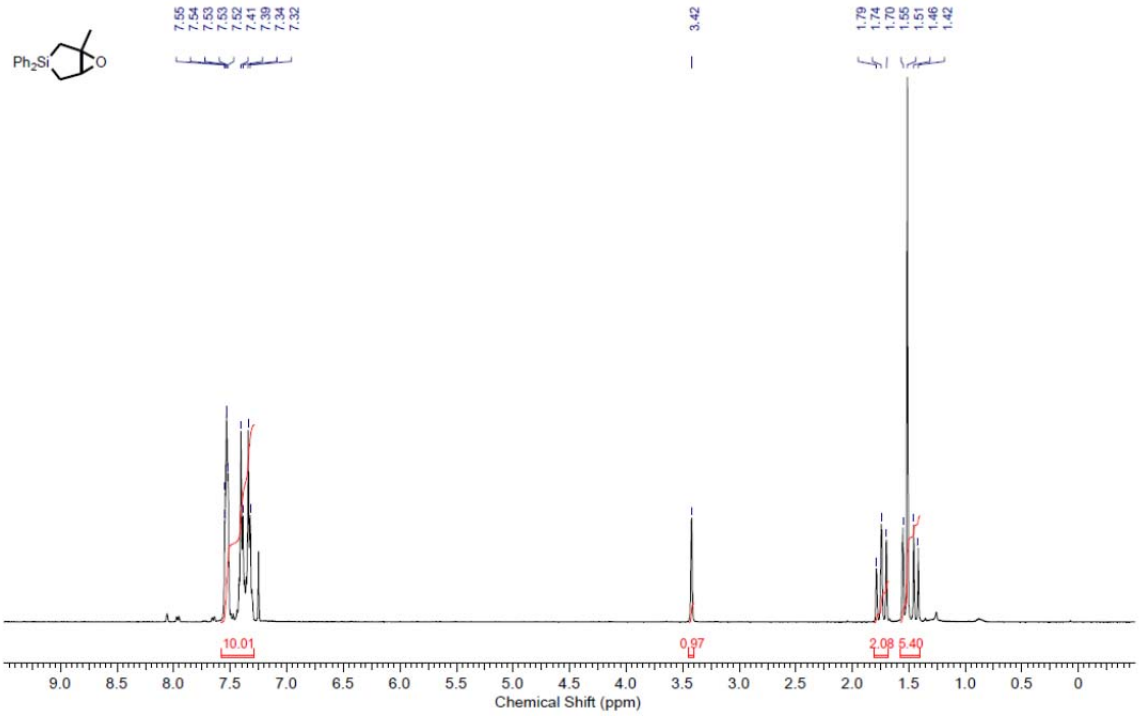


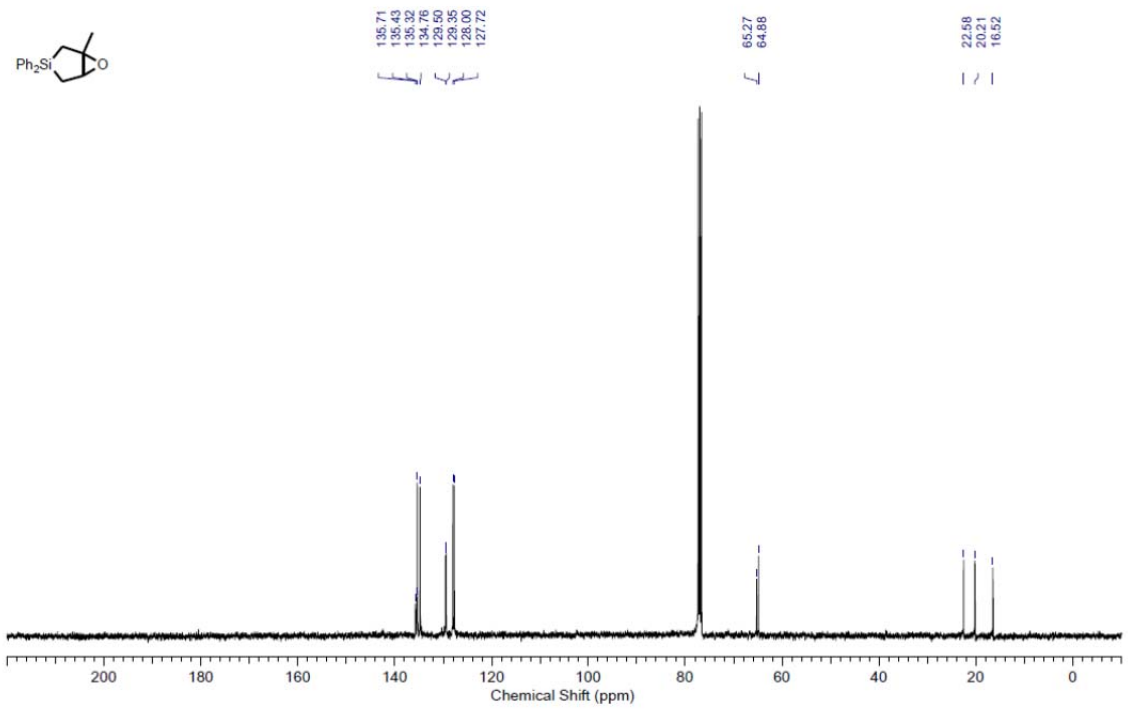
^{1}H and ^{13}C NMR of compound **1-36**



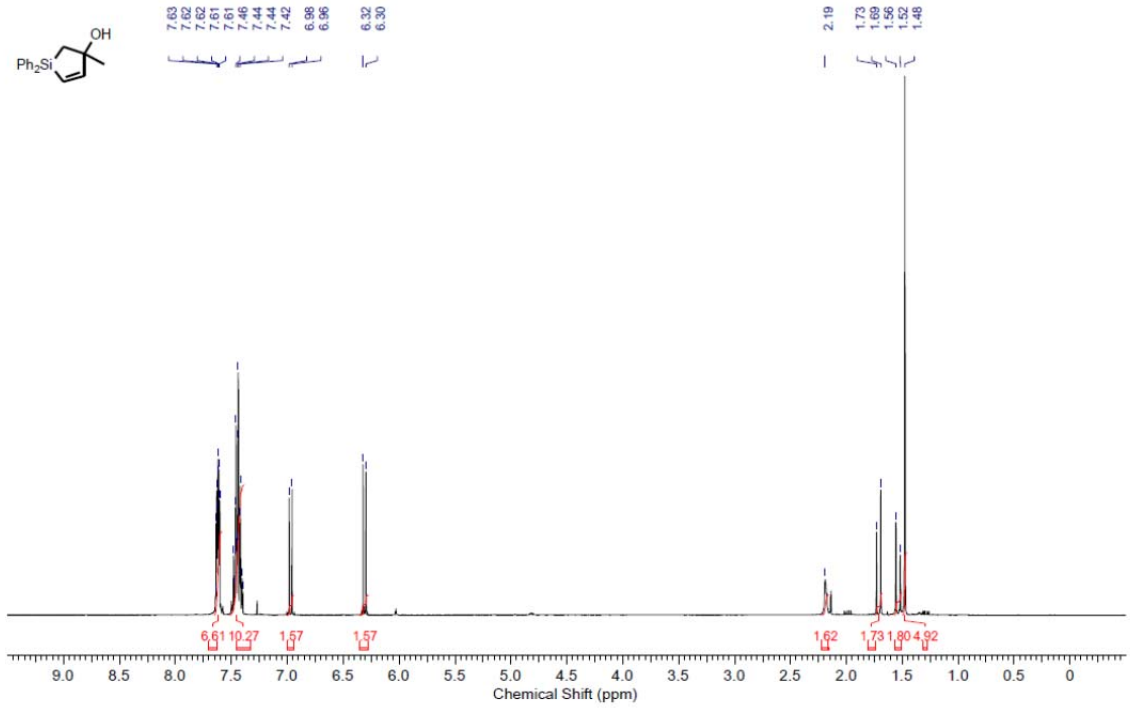


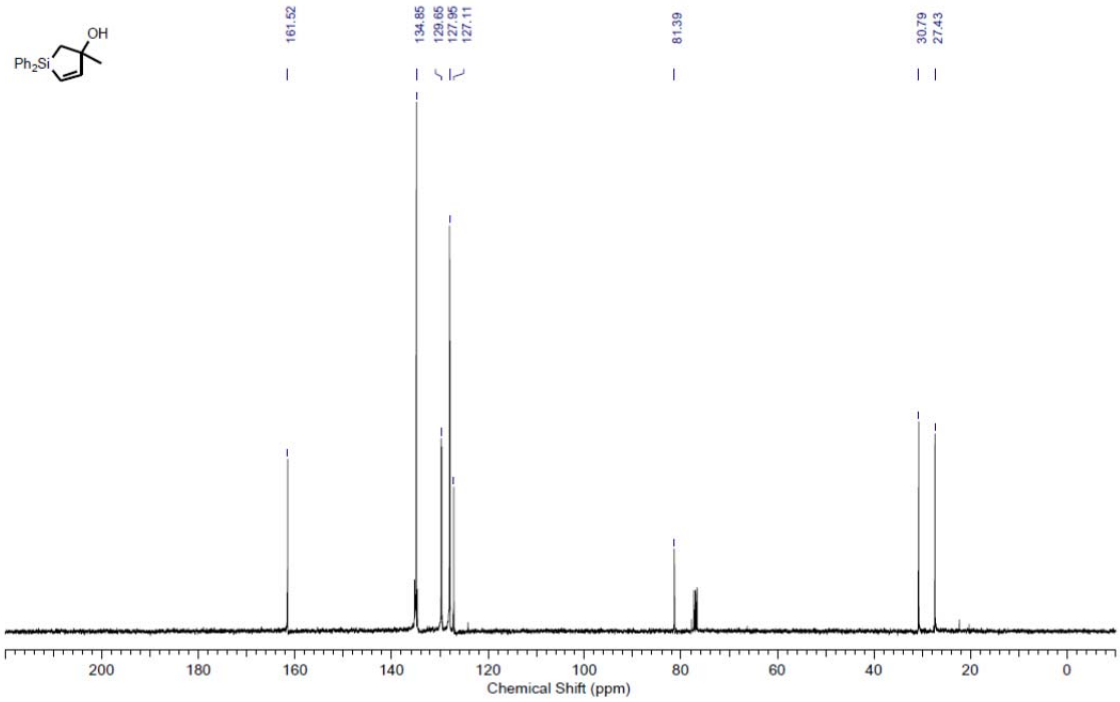
^{1}H and ^{13}C NMR of compound **1-37**



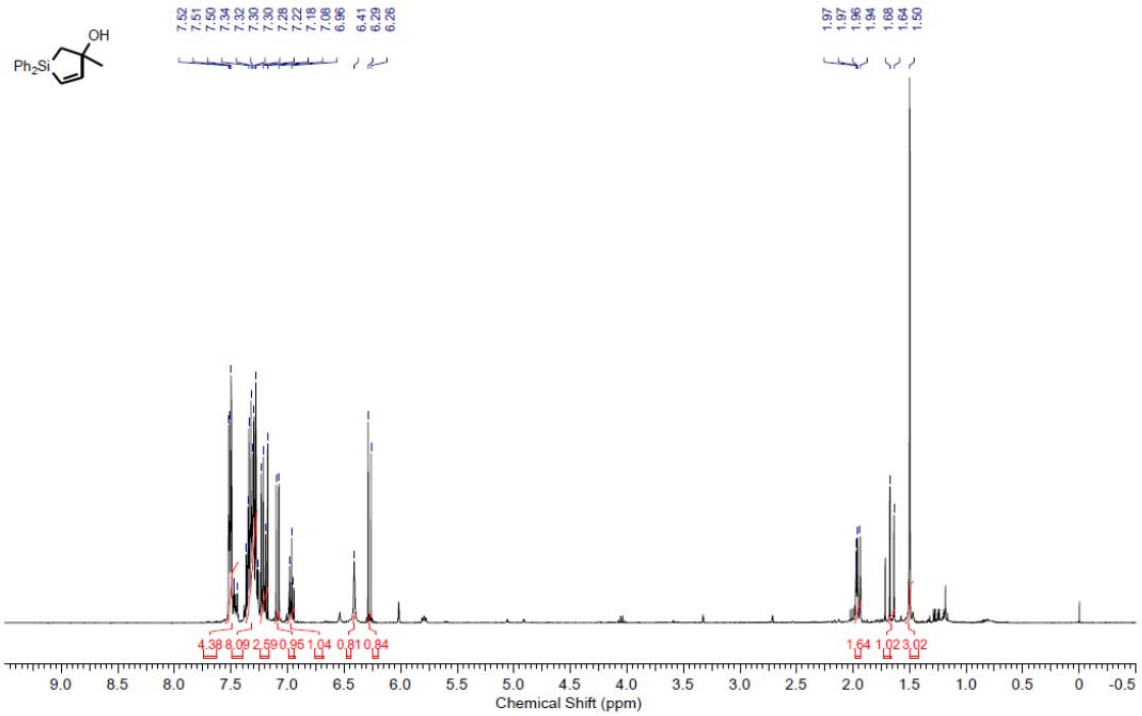


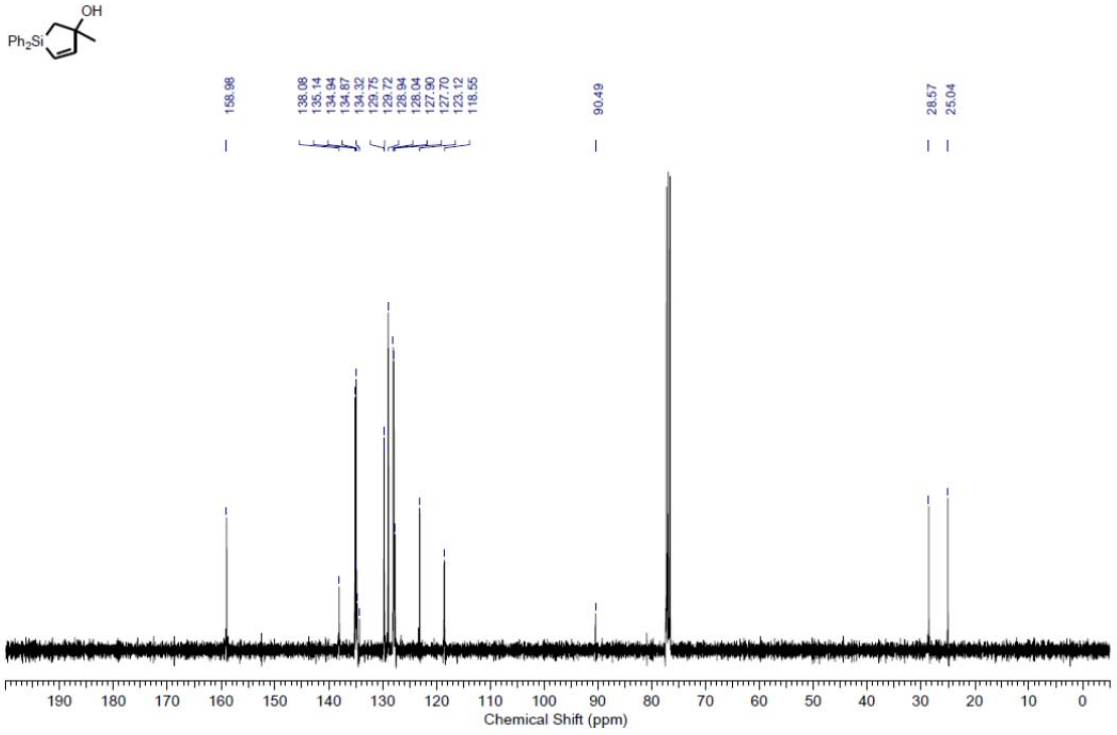
^{1}H and ^{13}C NMR of compound **1-38**



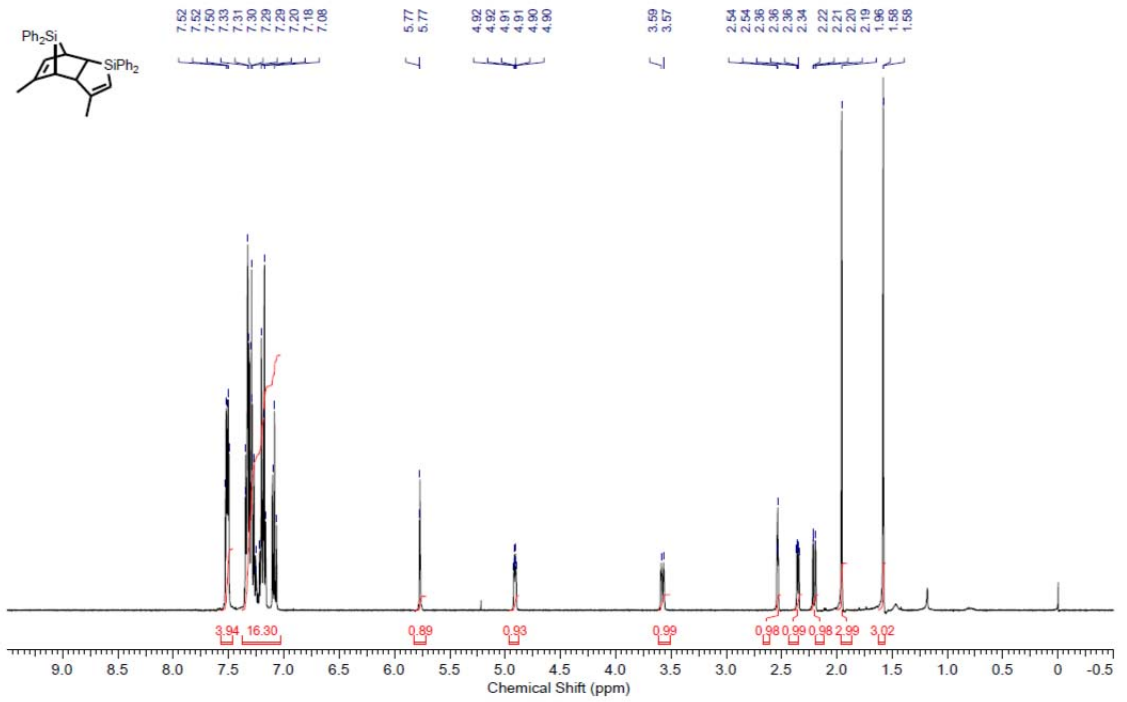


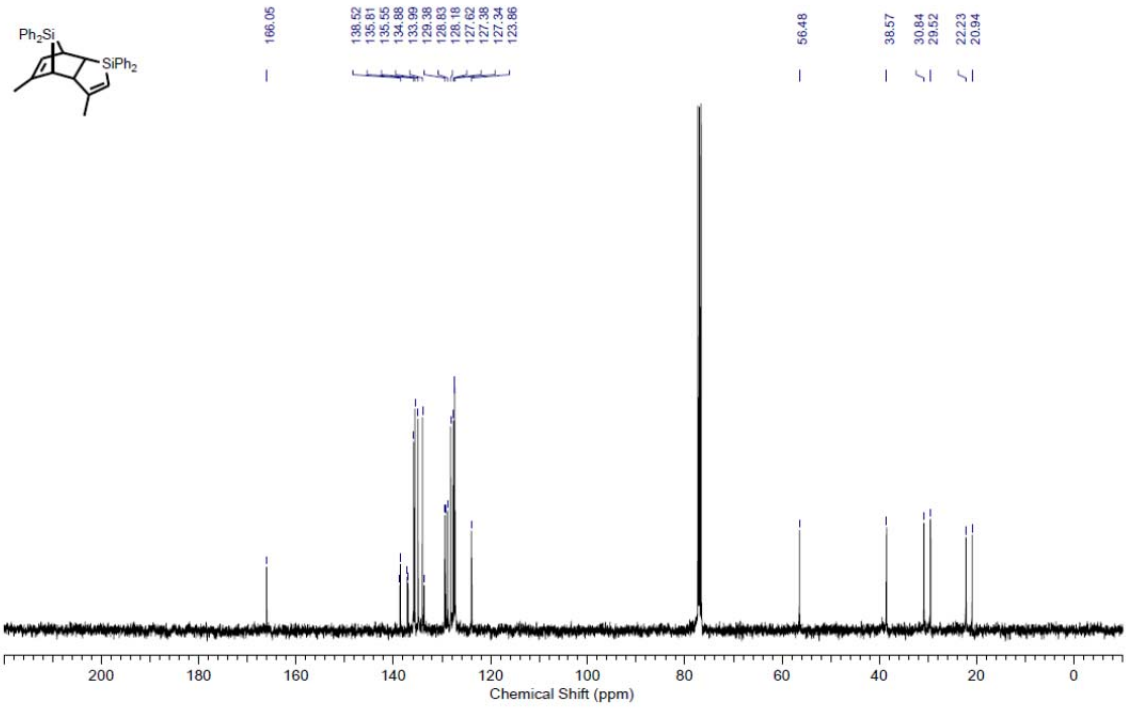
^{1}H and ^{13}C NMR of compound **1-39**



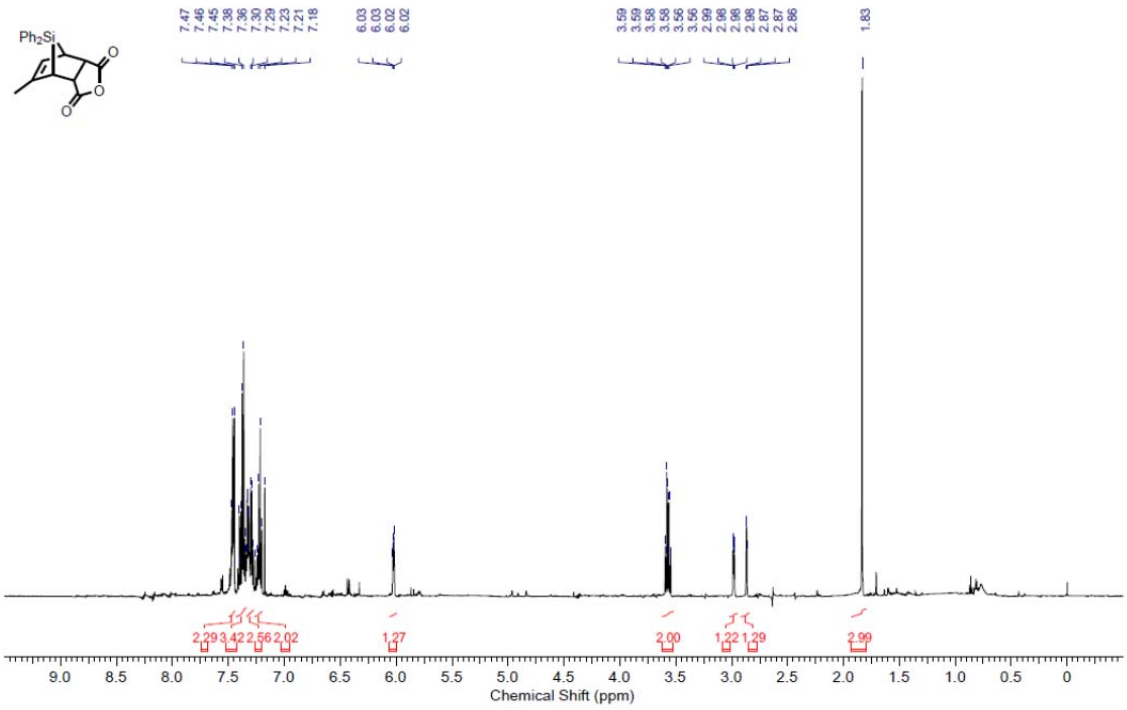


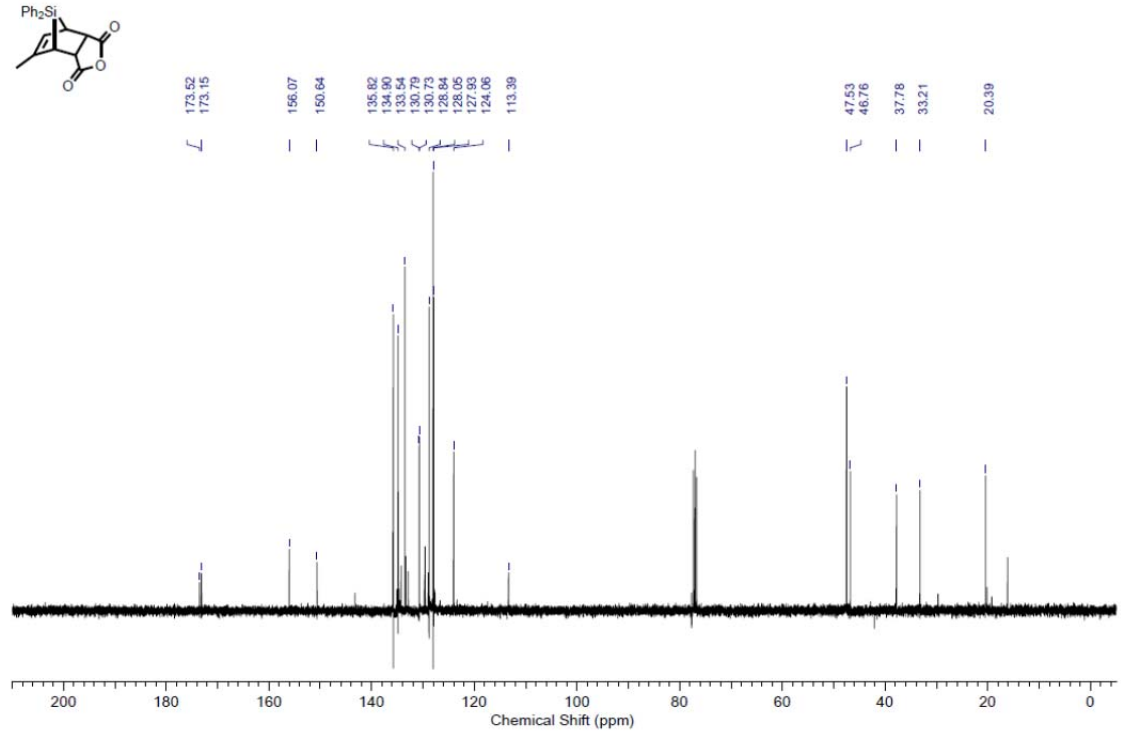
^{1}H and ^{13}C NMR of compound **1-41**



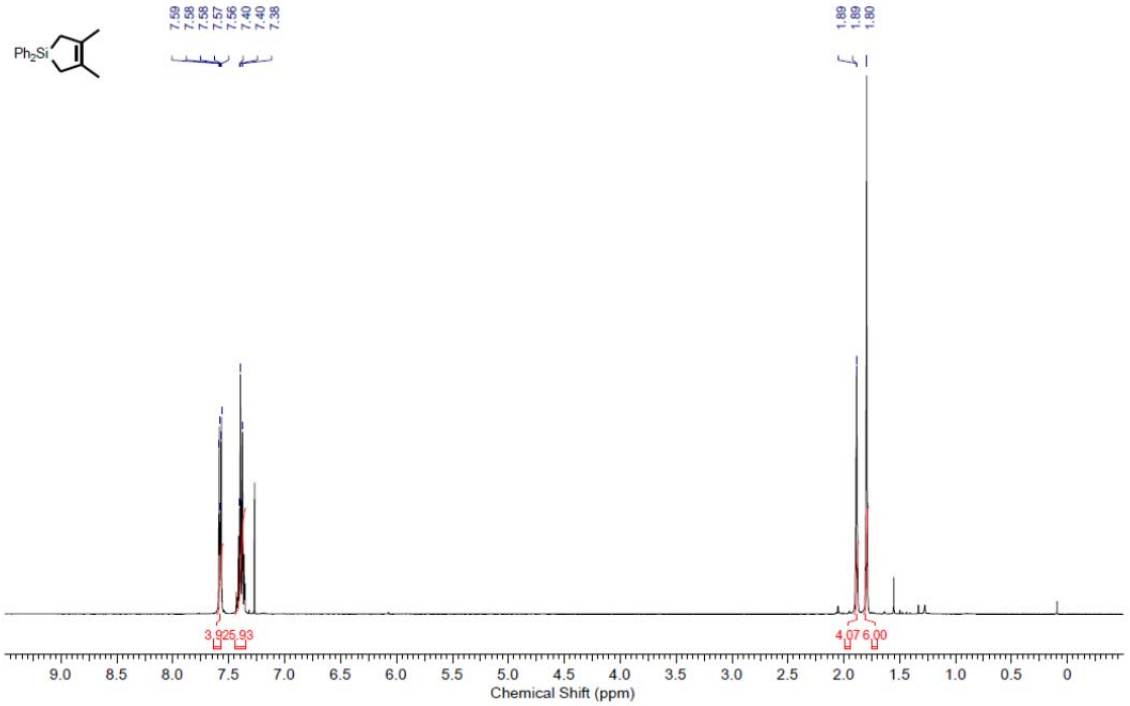


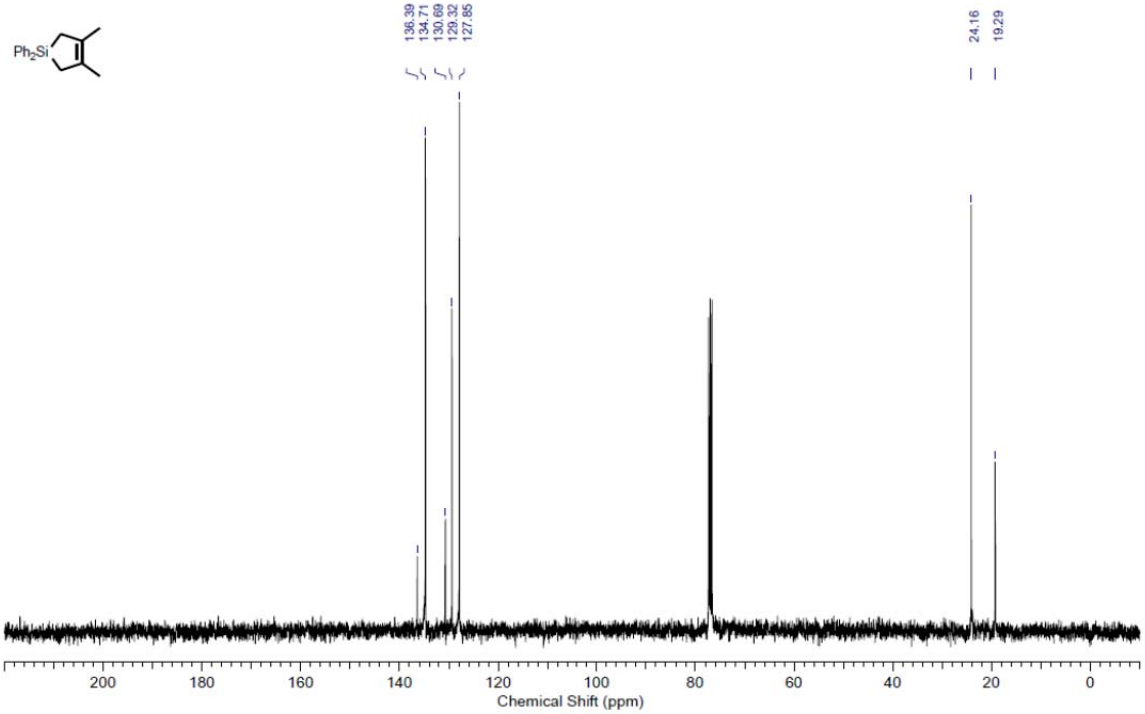
^{1}H and ^{13}C NMR of compound **1-42**



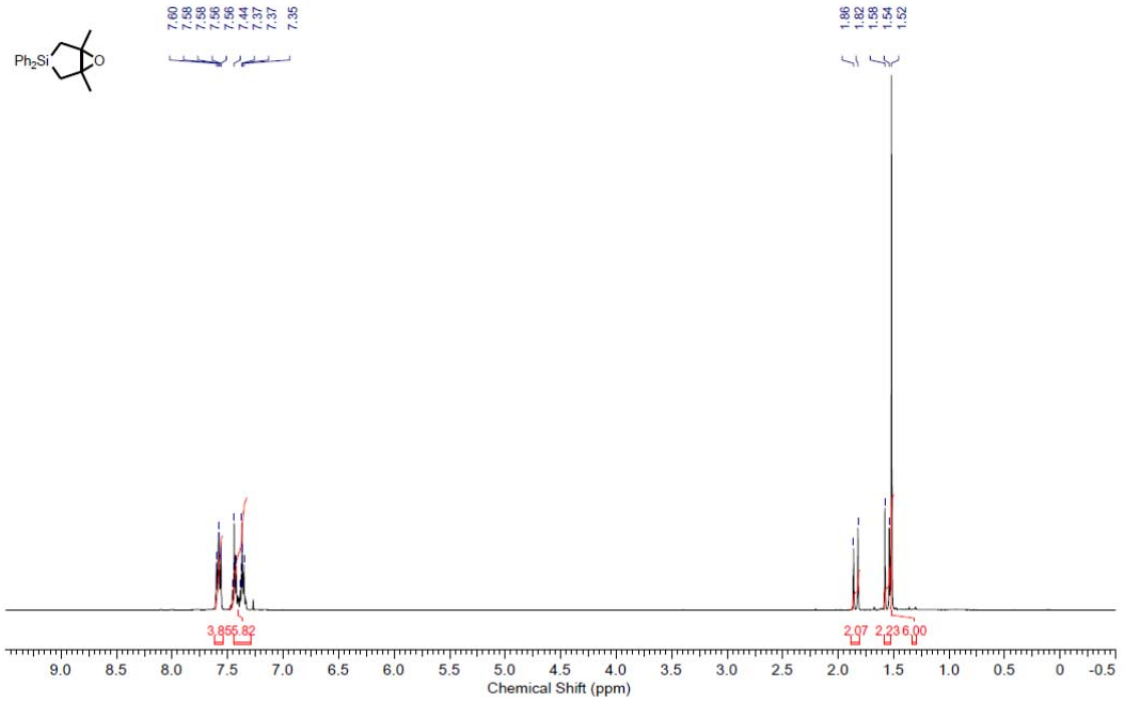


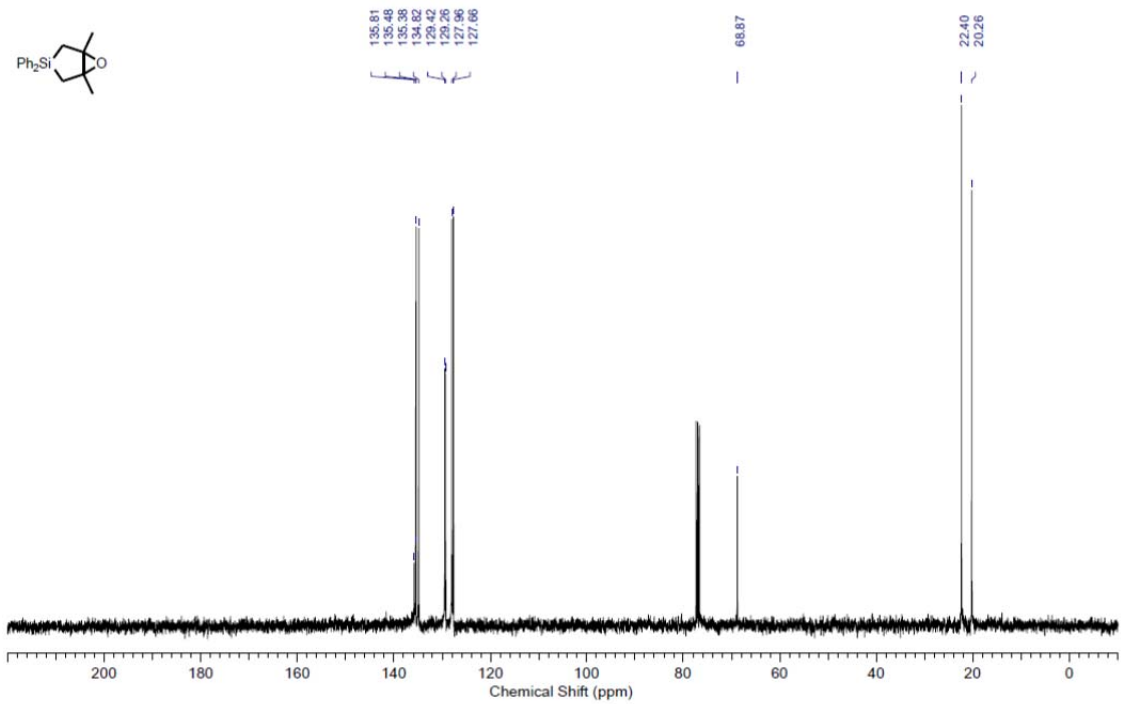
^{1}H and ^{13}C NMR of compound **1-43**



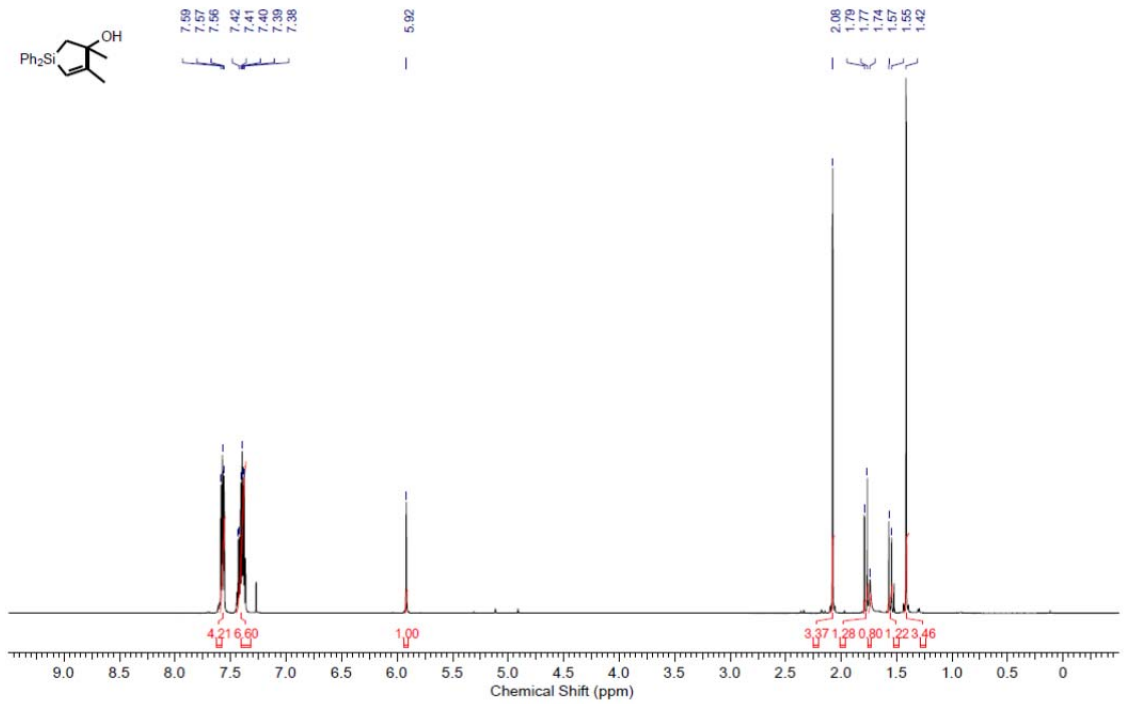


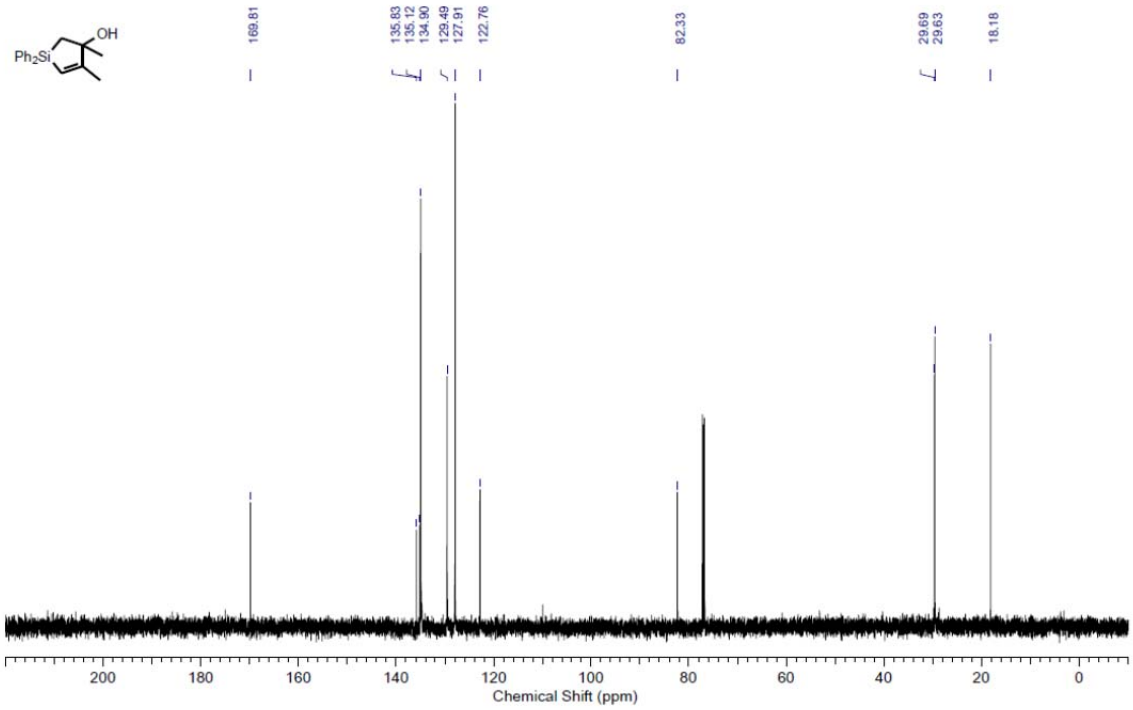
^{1}H and ^{13}C NMR of compound **1-44**



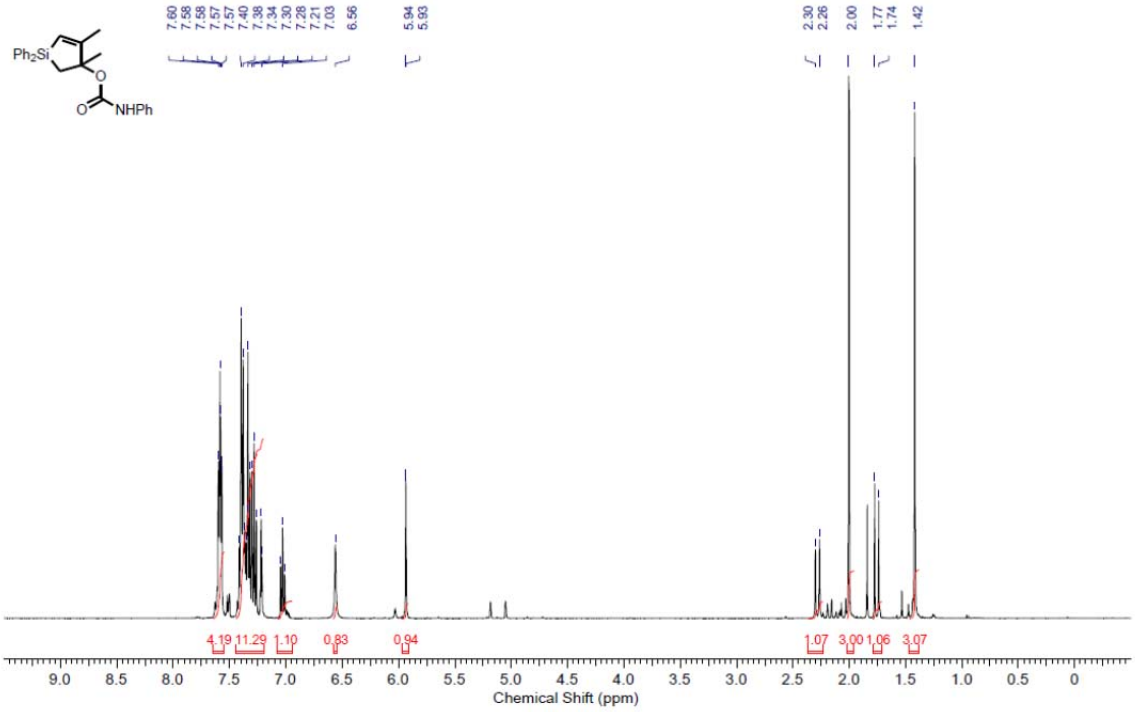


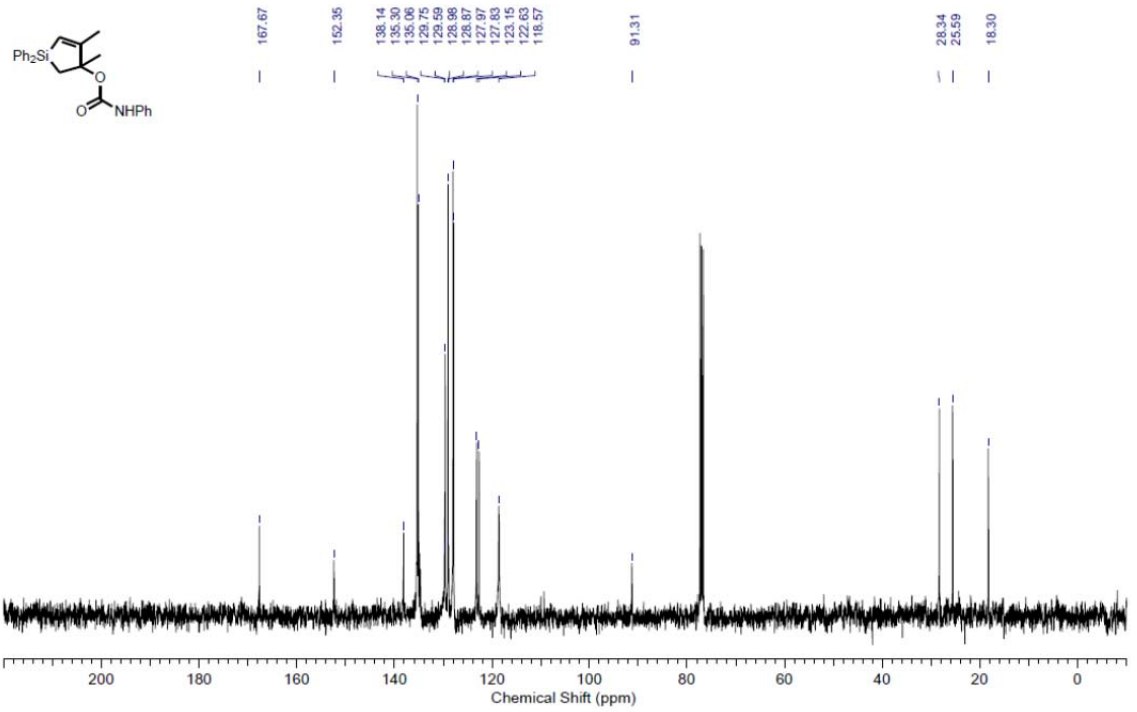
^{1}H and ^{13}C NMR of compound **1-45**



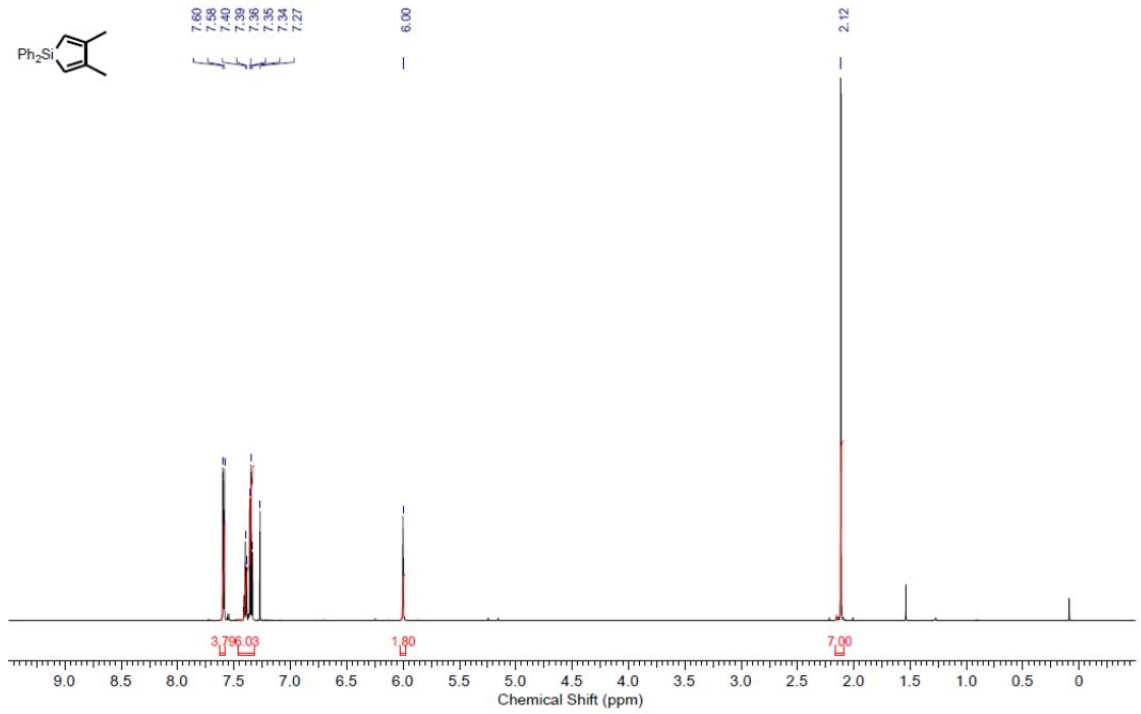


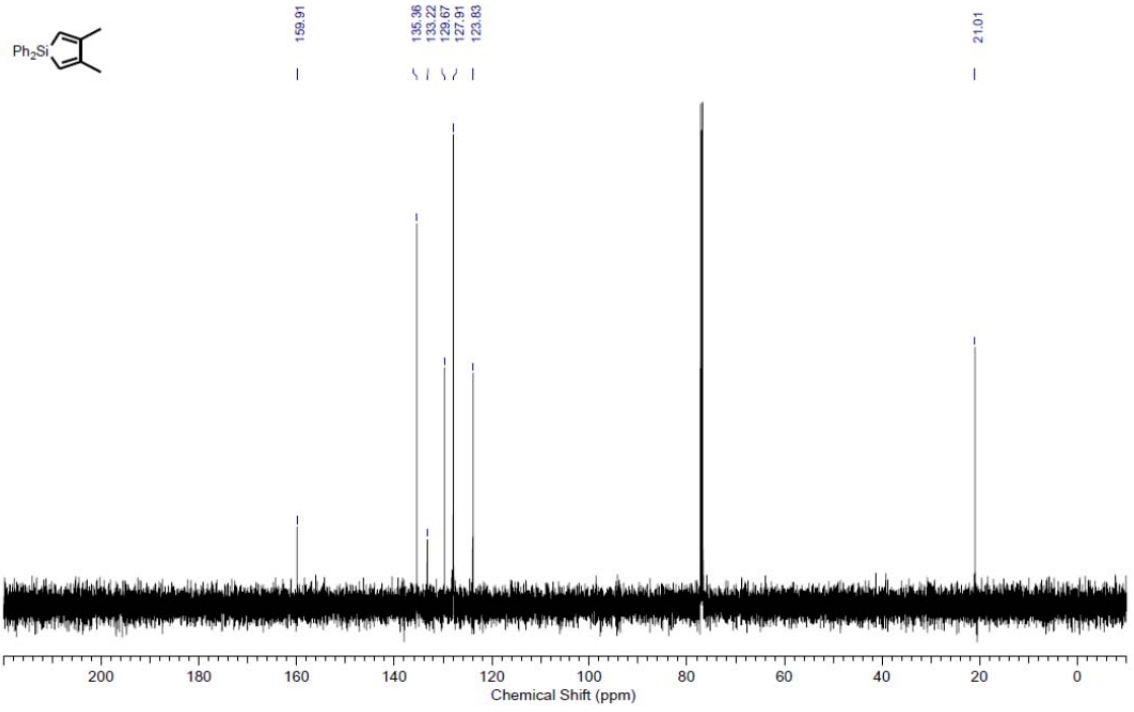
^{1}H and ^{13}C NMR of compound **1-46**



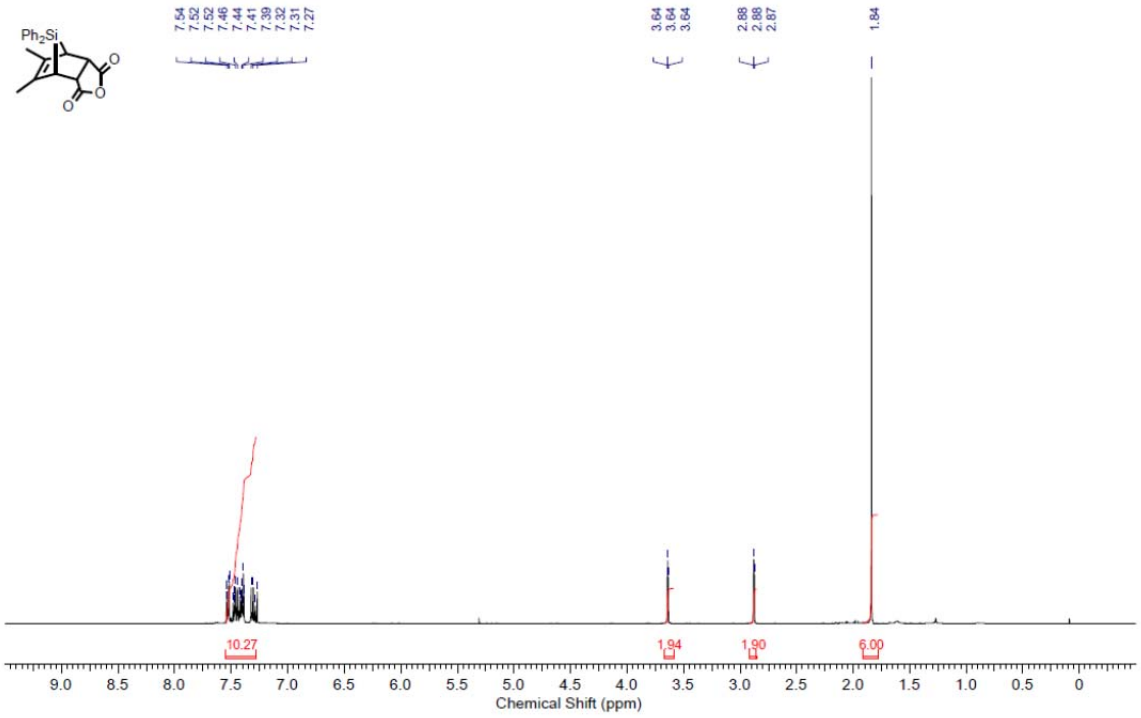


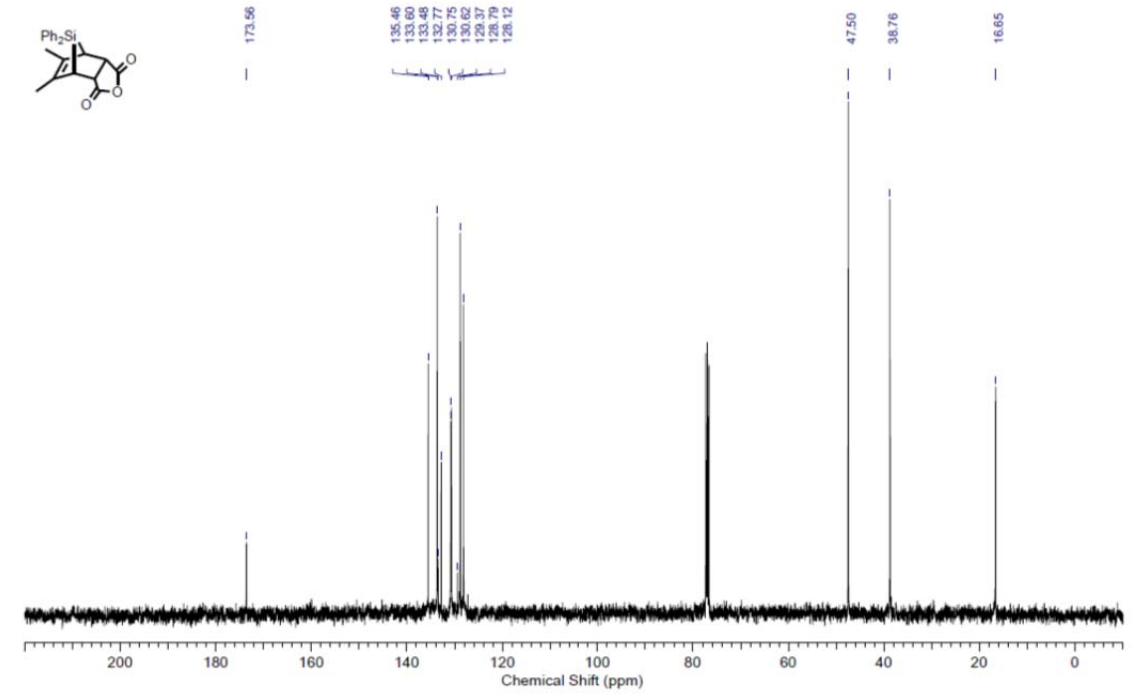
^{1}H and ^{13}C NMR of compound **1-47**



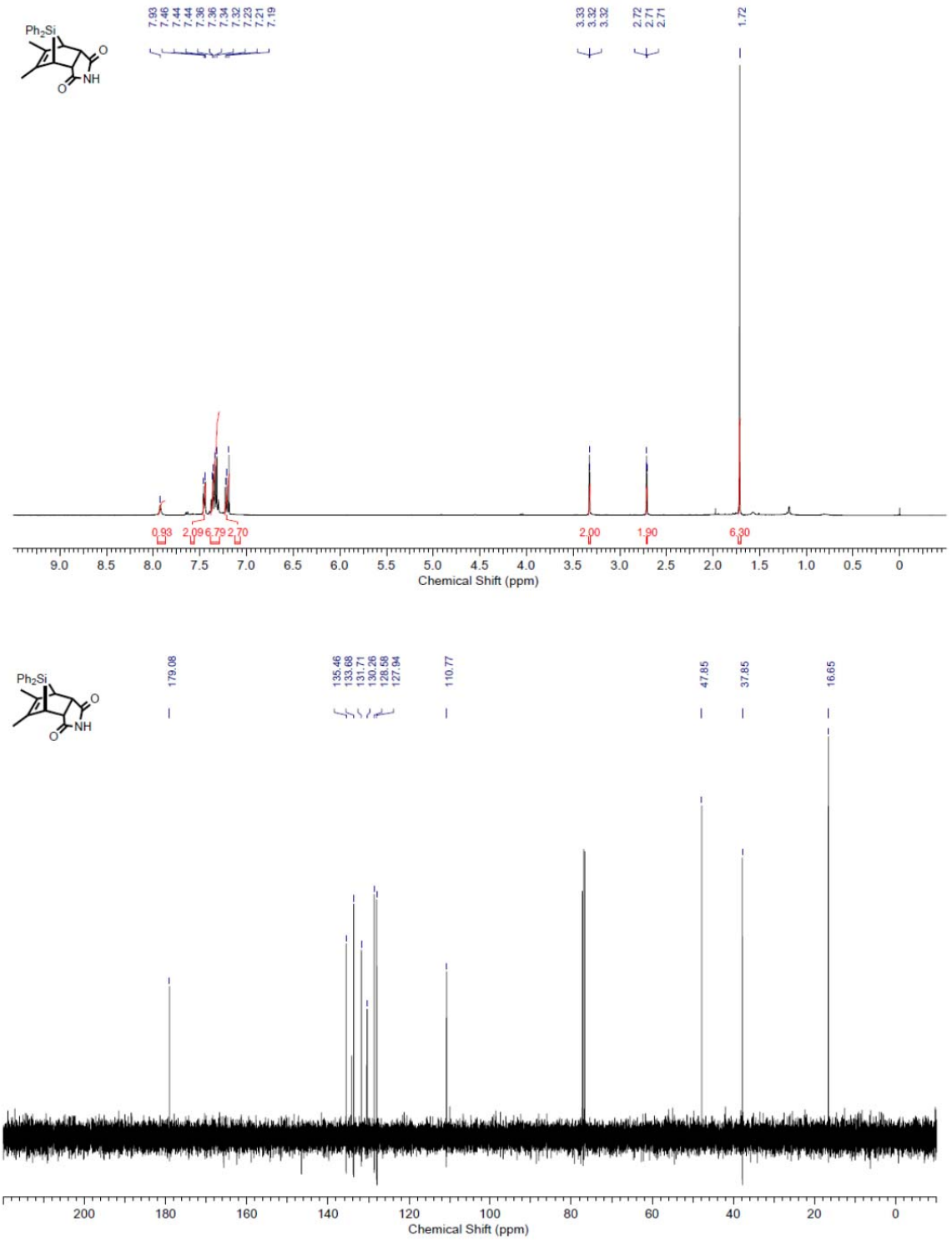


^{1}H and ^{13}C NMR of compound **1-48a**

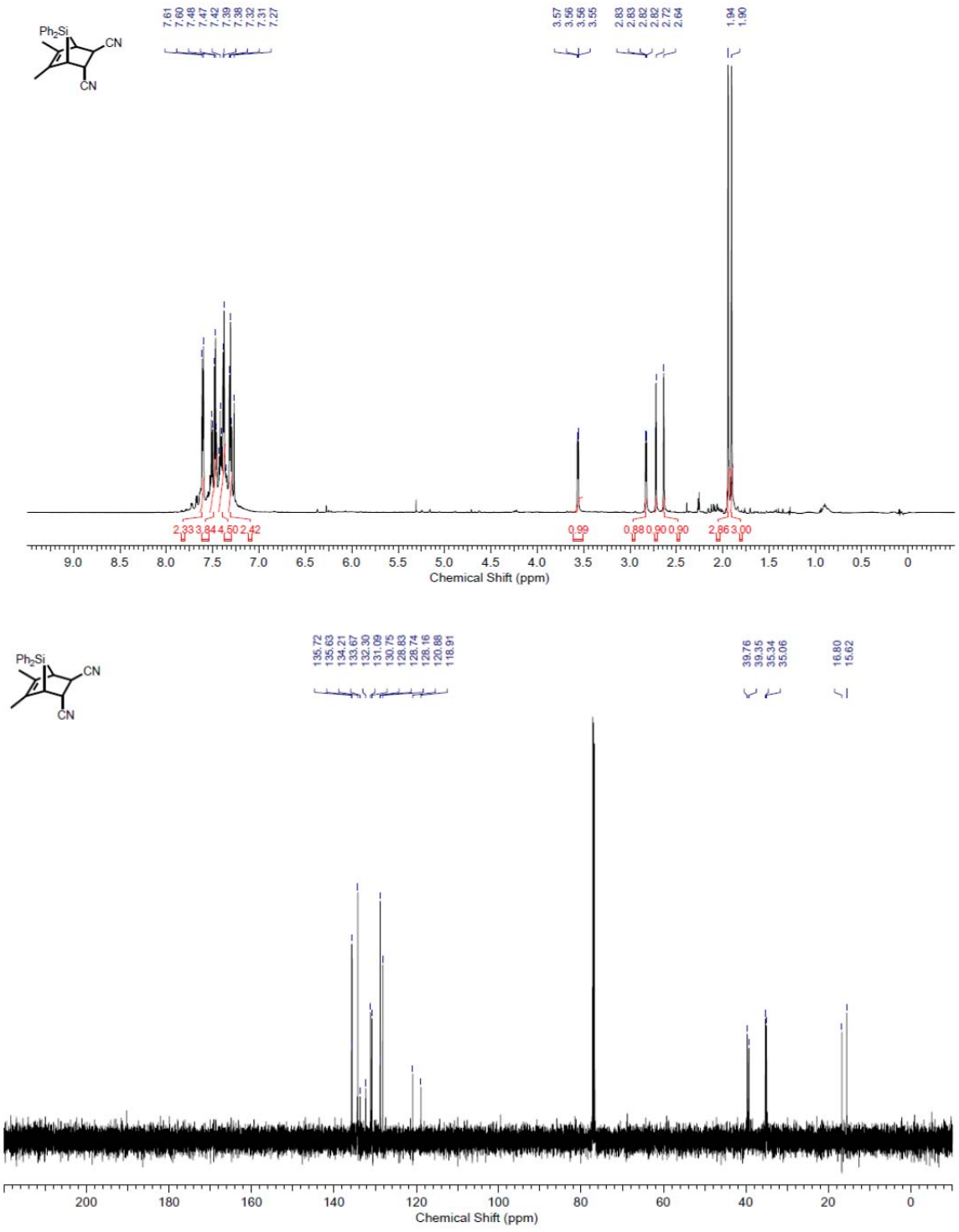




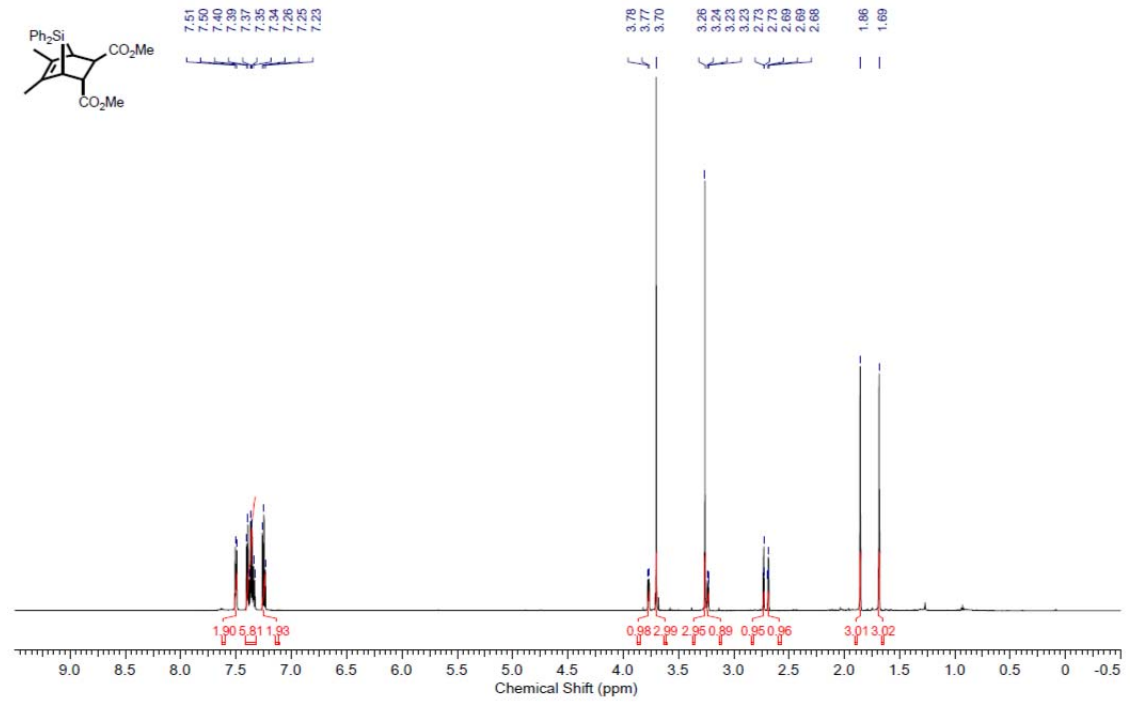
^{1}H and ^{13}C NMR of compound **1-48b**

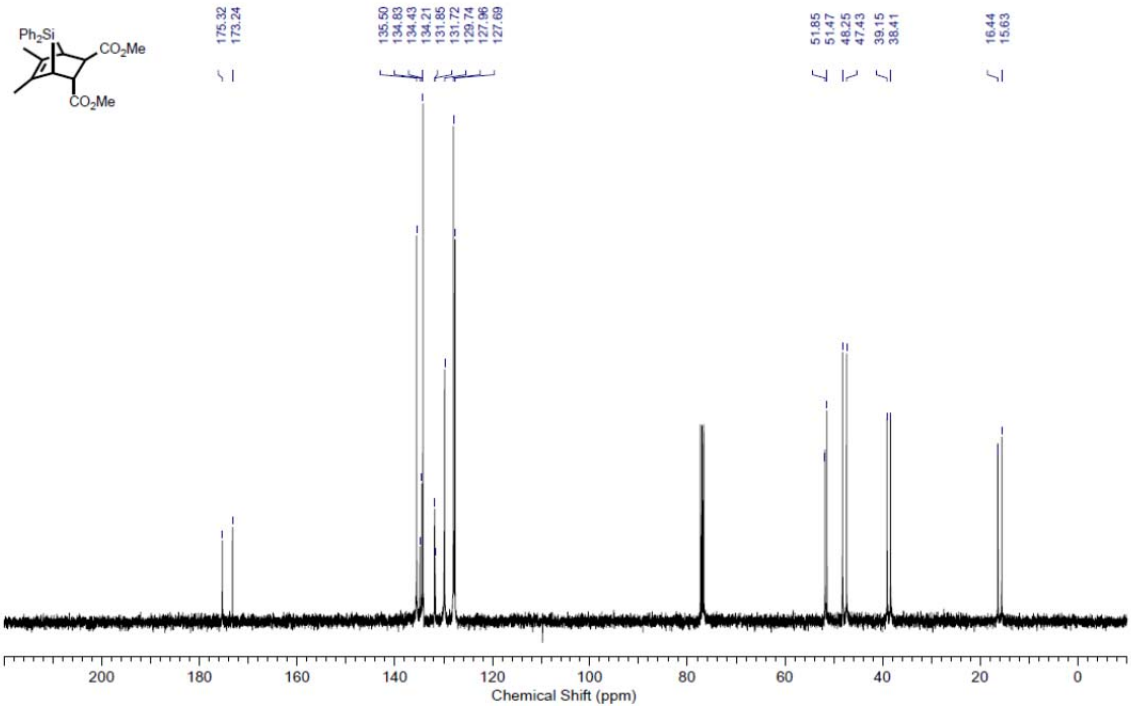


^{1}H and ^{13}C NMR of compound **1-48c**

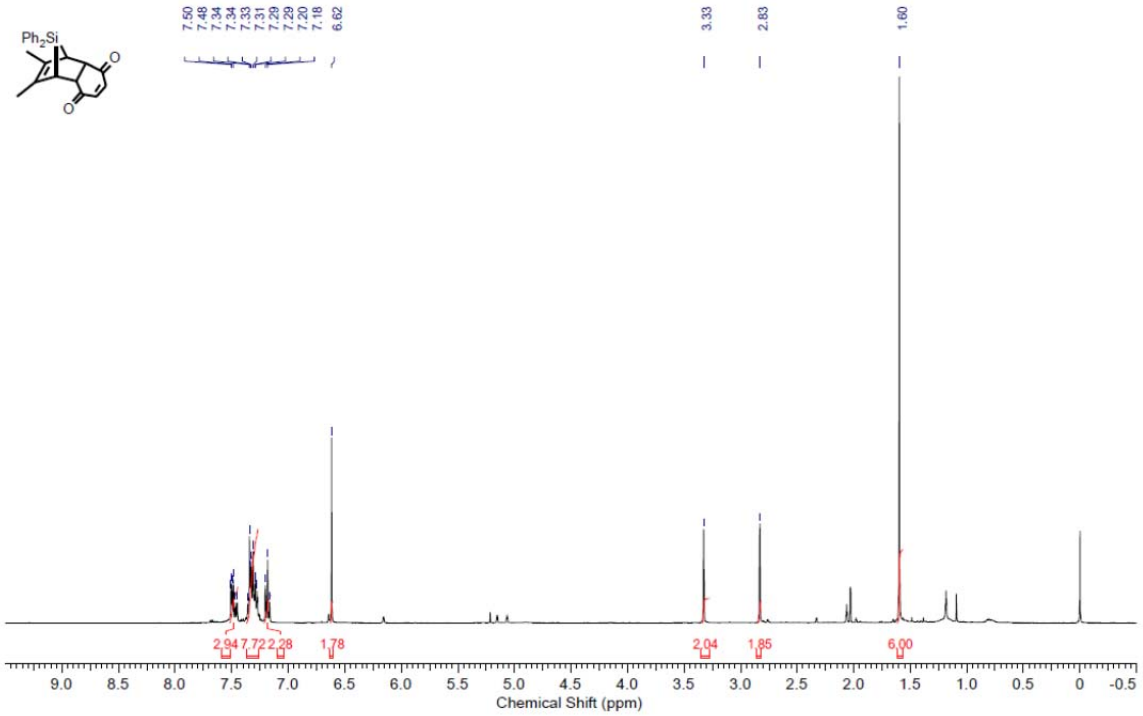


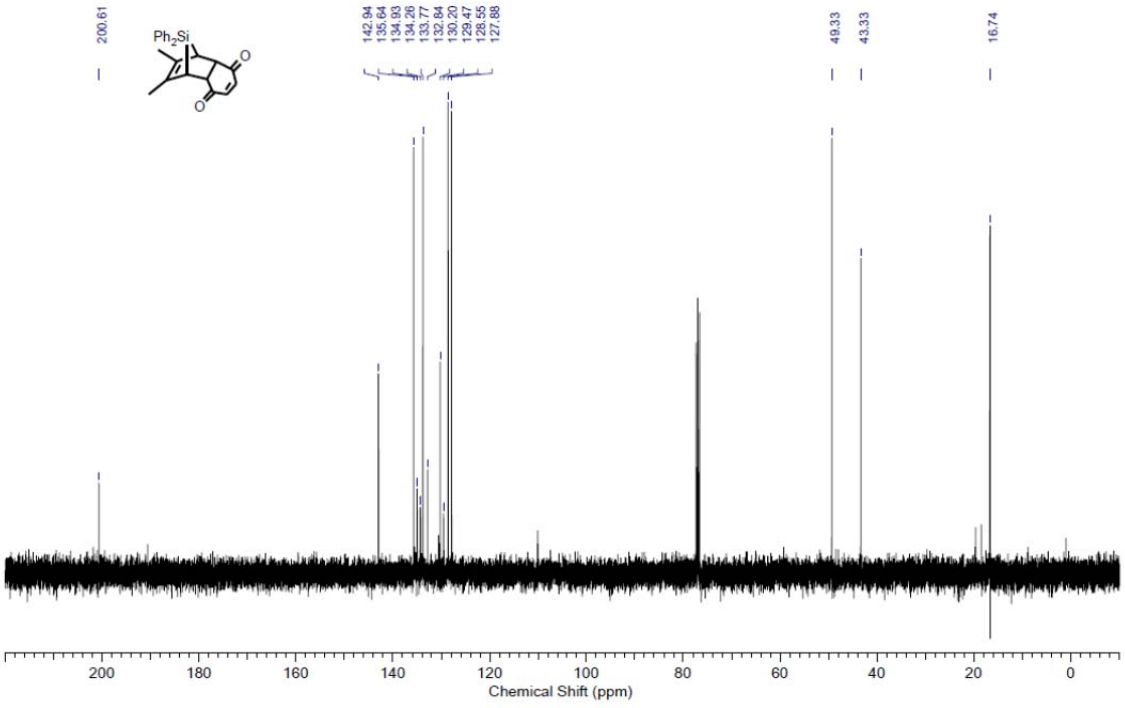
^{1}H and ^{13}C NMR of compound **1-48d**



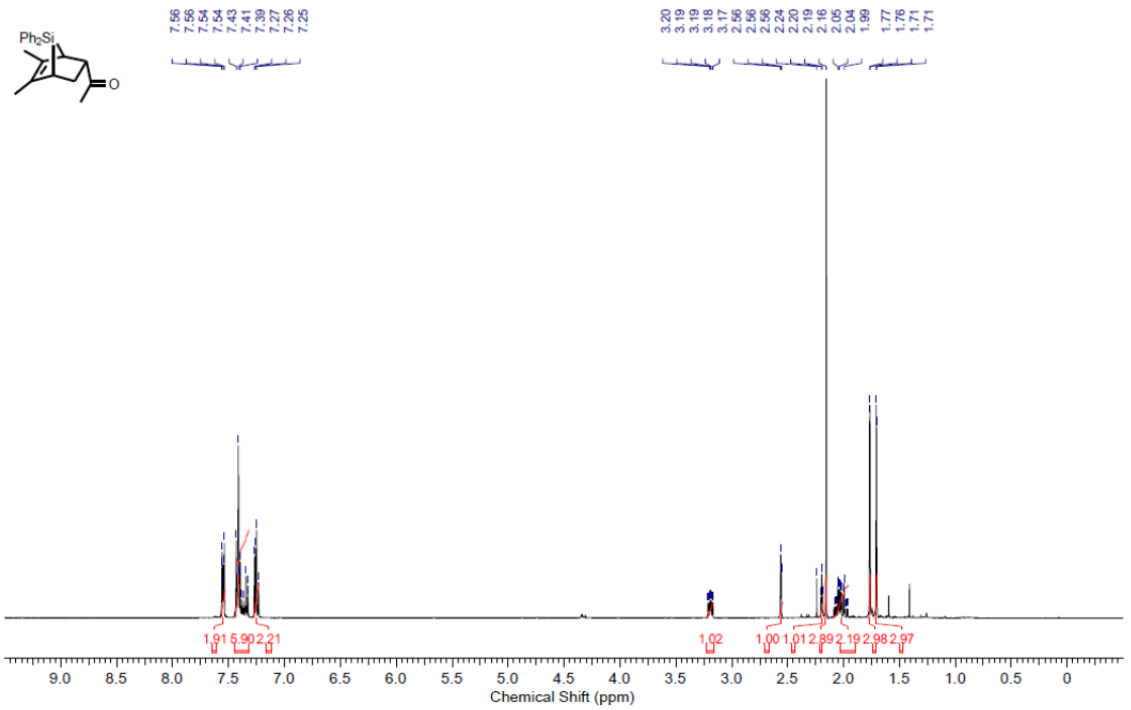


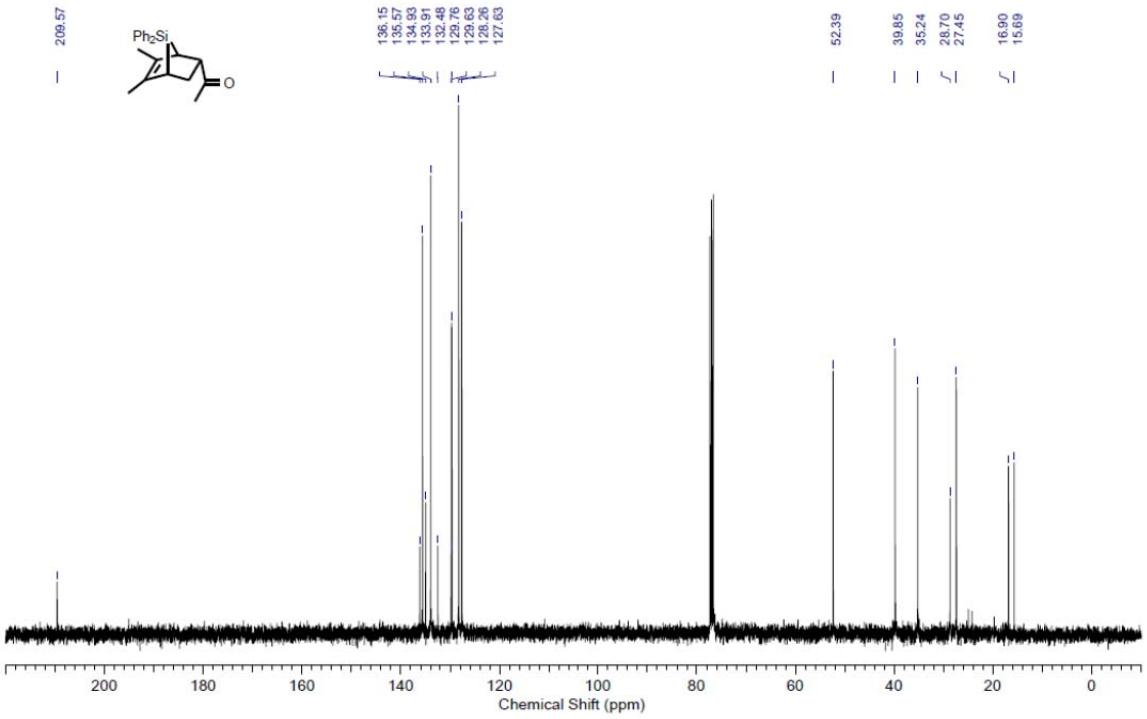
^{1}H and ^{13}C NMR of compound **1-48e**



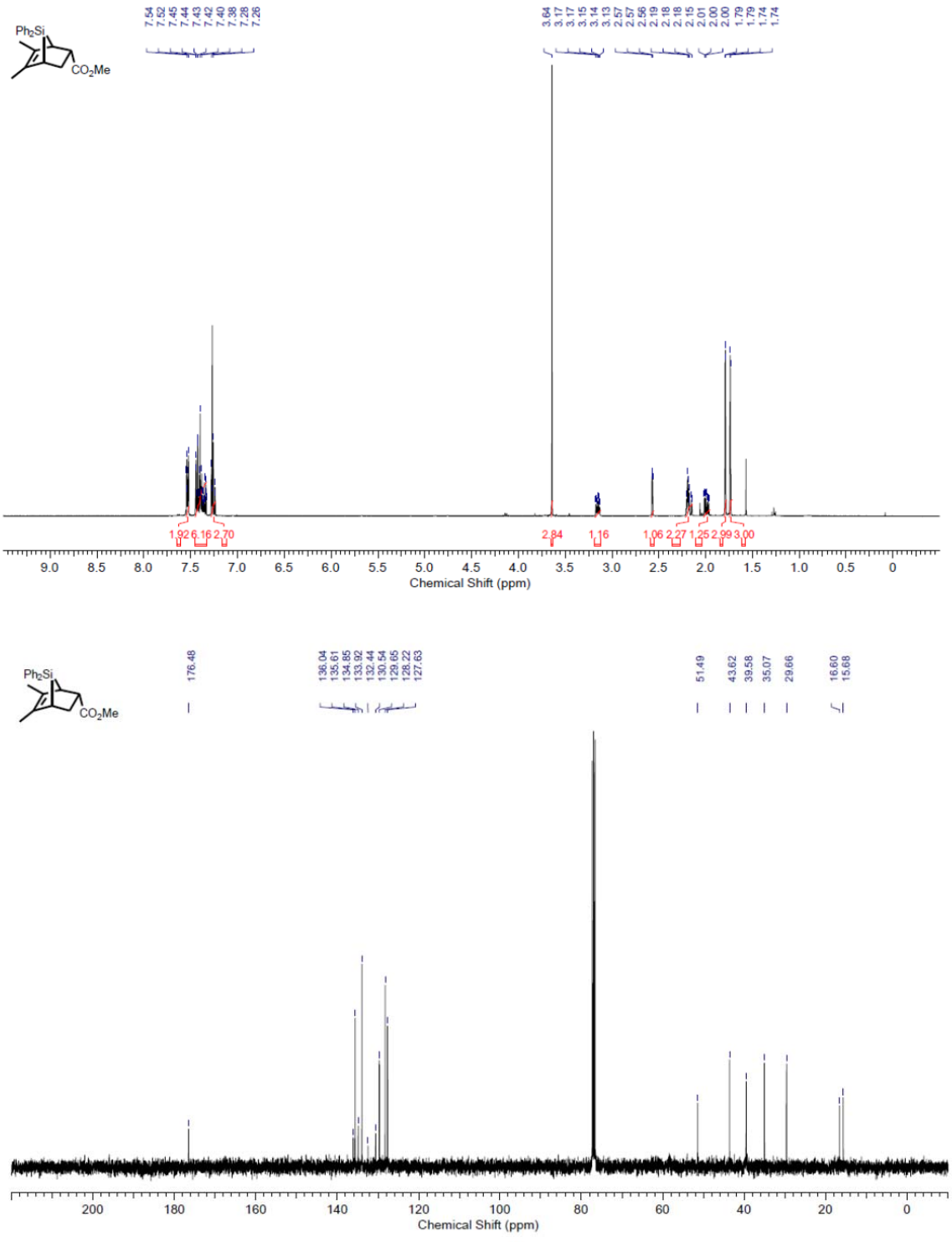


^{1}H and ^{13}C NMR of compound **1-48g**

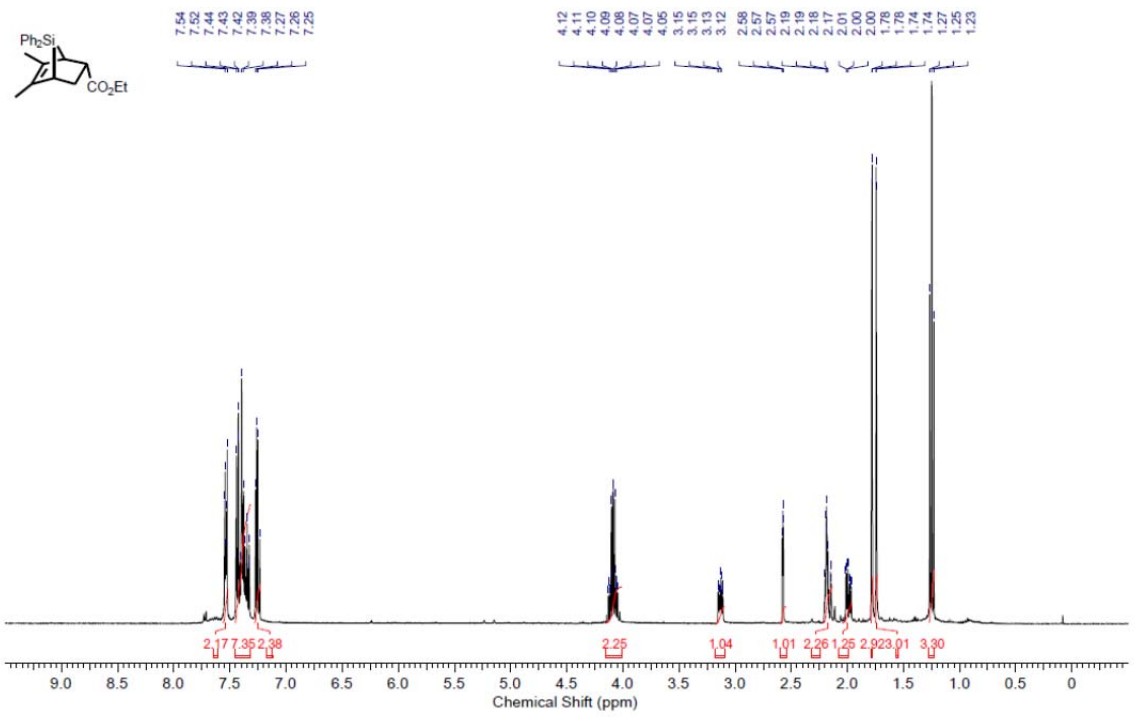


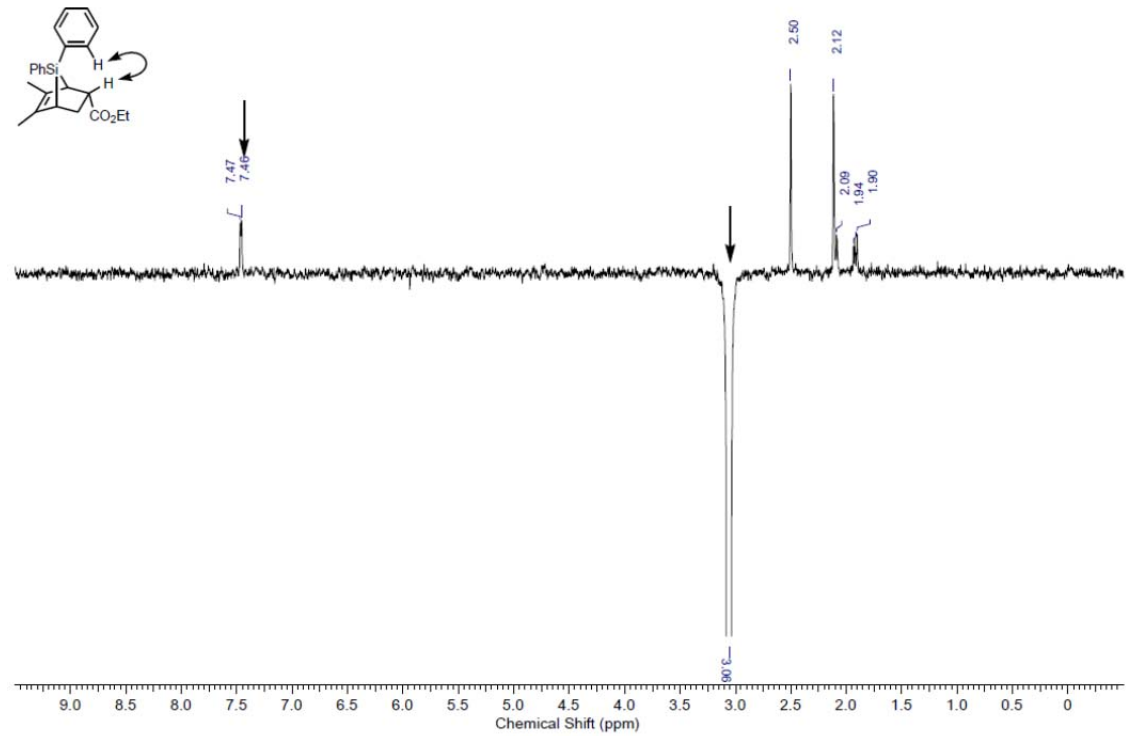


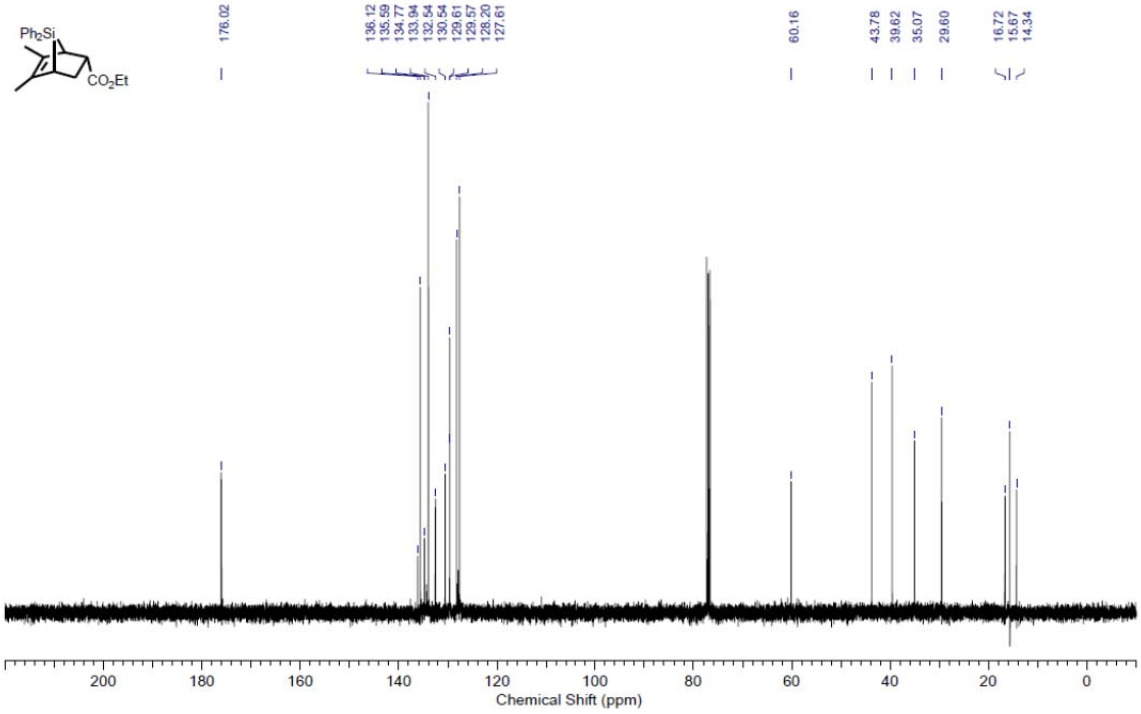
^{1}H and ^{13}C NMR of compound **1-48h**



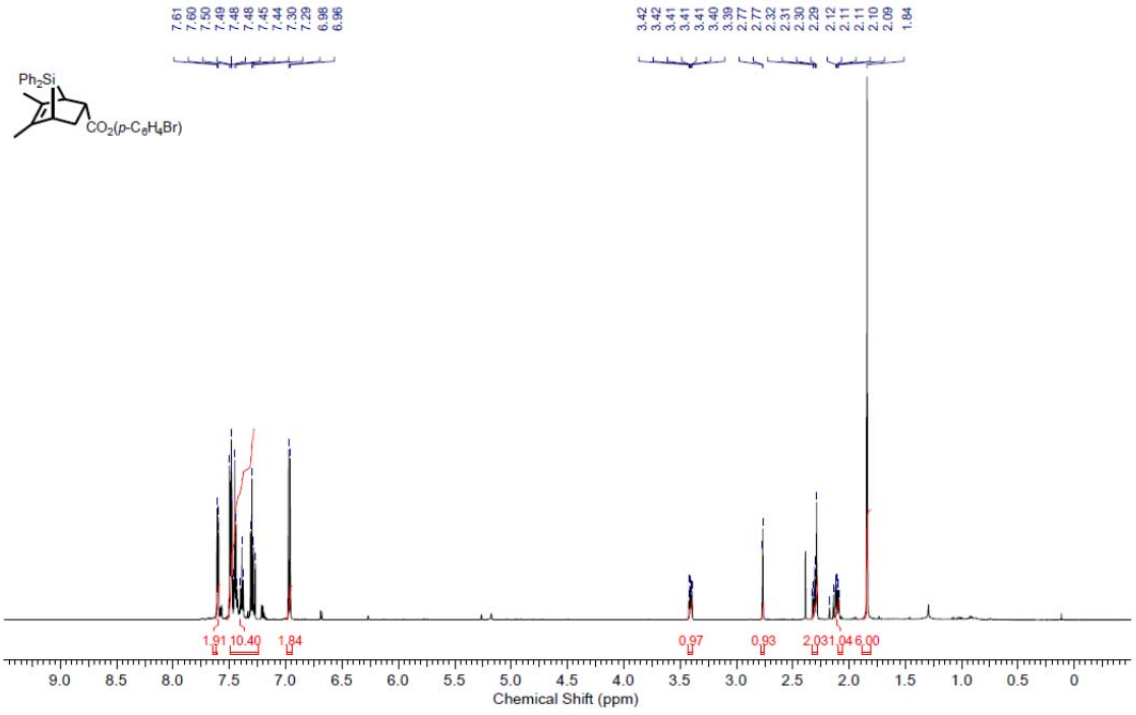
^{1}H, 1D nOe, and ^{13}C NMR of compound **1-48i**

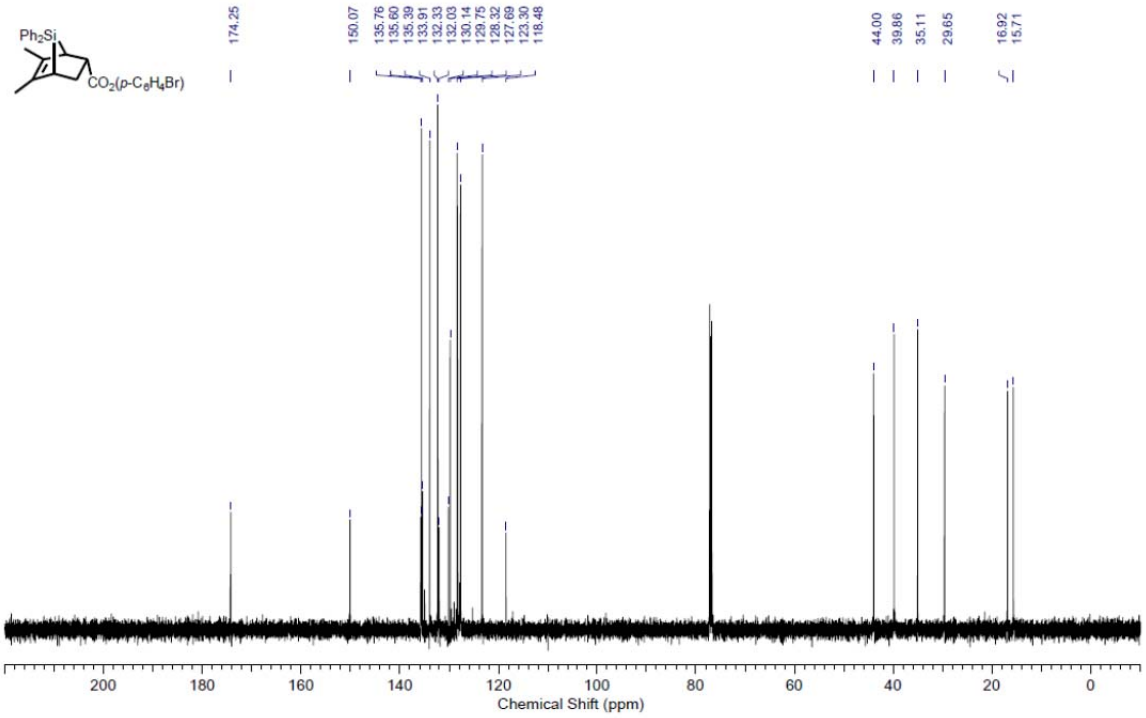

Ph2Si
CO2Et
7.54 7.52 7.44 7.43 7.42 7.39 7.38 7.27 7.26 7.25
4.12 4.11 4.10 4.09 4.08 4.07 4.07 4.05 3.15 3.15 3.13 3.12 2.58 2.57 2.57 2.19 2.19 2.18 2.17 2.01 2.00 2.00 1.78 1.78 1.74 1.74 1.27 1.25 1.23
2.17 7.35 2.38 2.25 1.04 1.01 2.26 1.25 2.02 3.01 3.30
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


PhSi
H
H
CO2Et
7.47
7.46
2.50
2.12
2.09
1.94
1.90
3.06
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

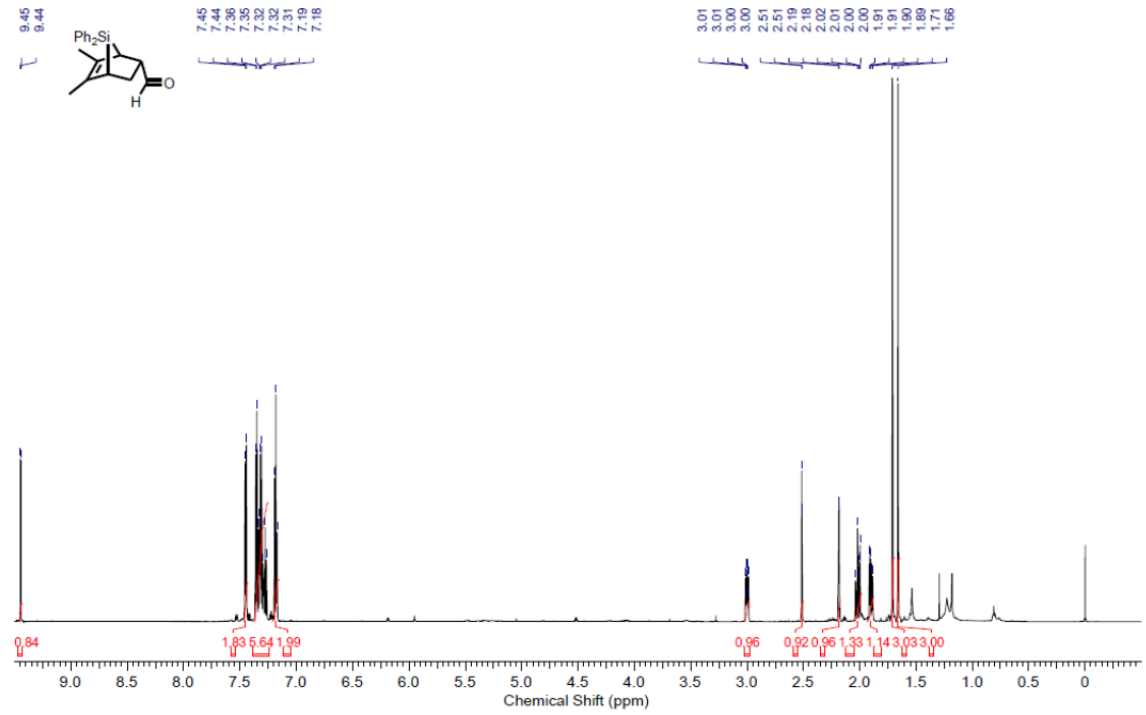


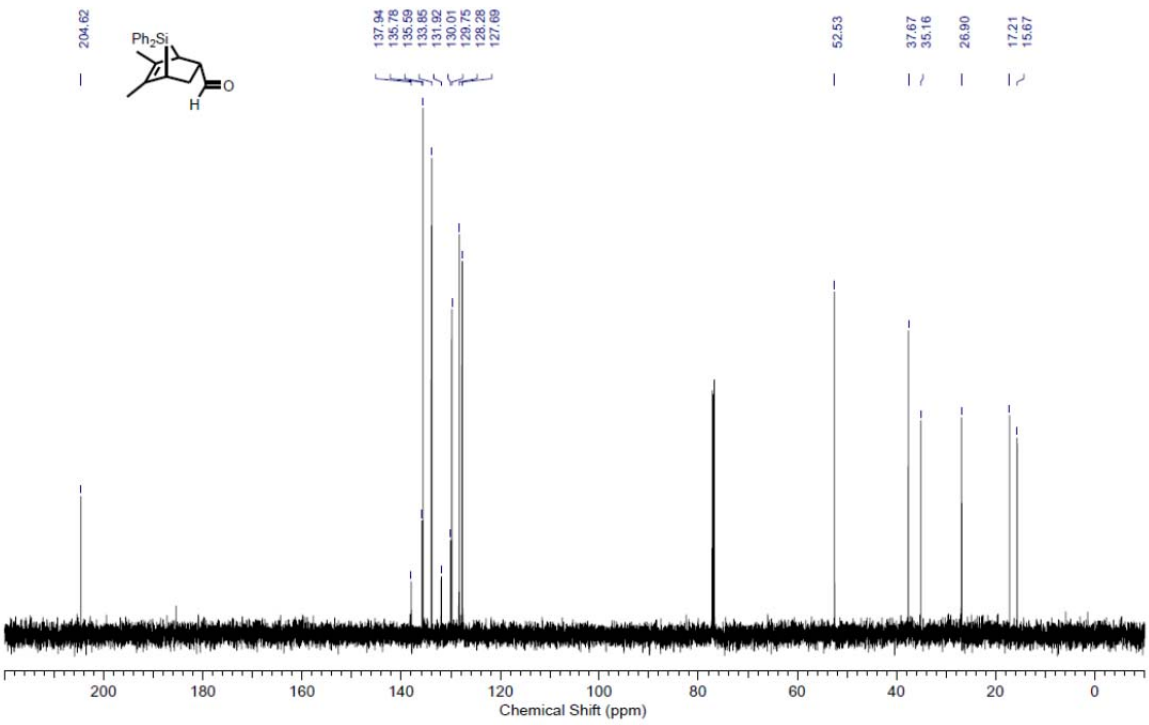
^{1}H and ^{13}C NMR of compound **1-48j**



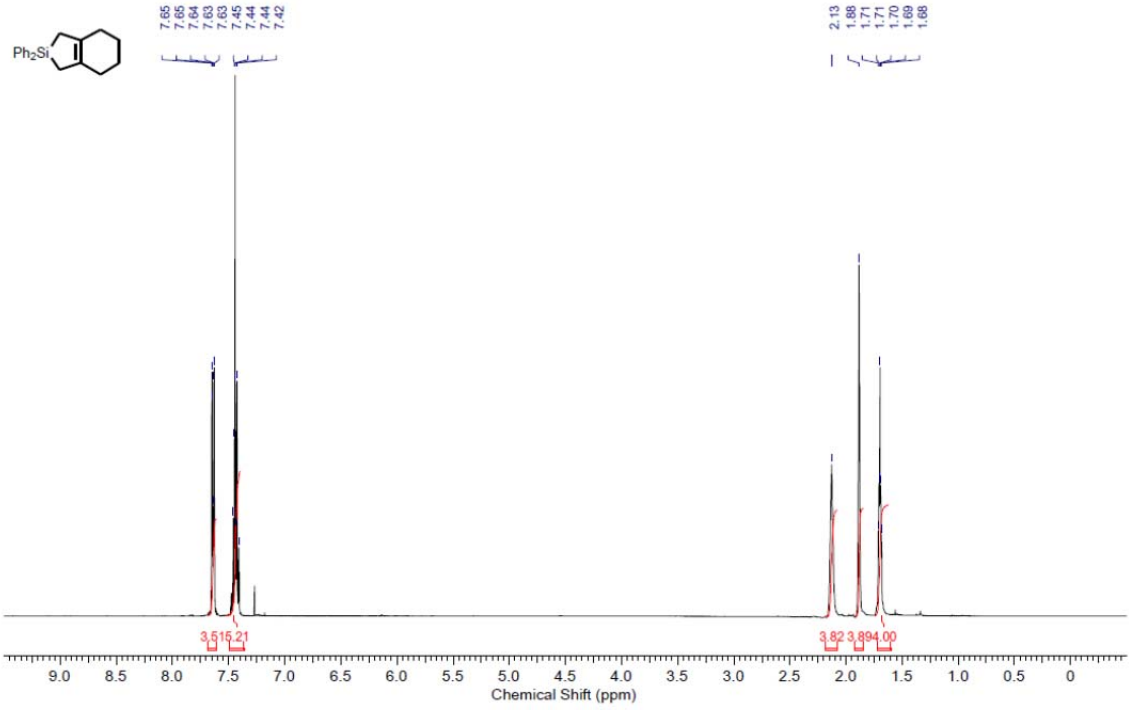


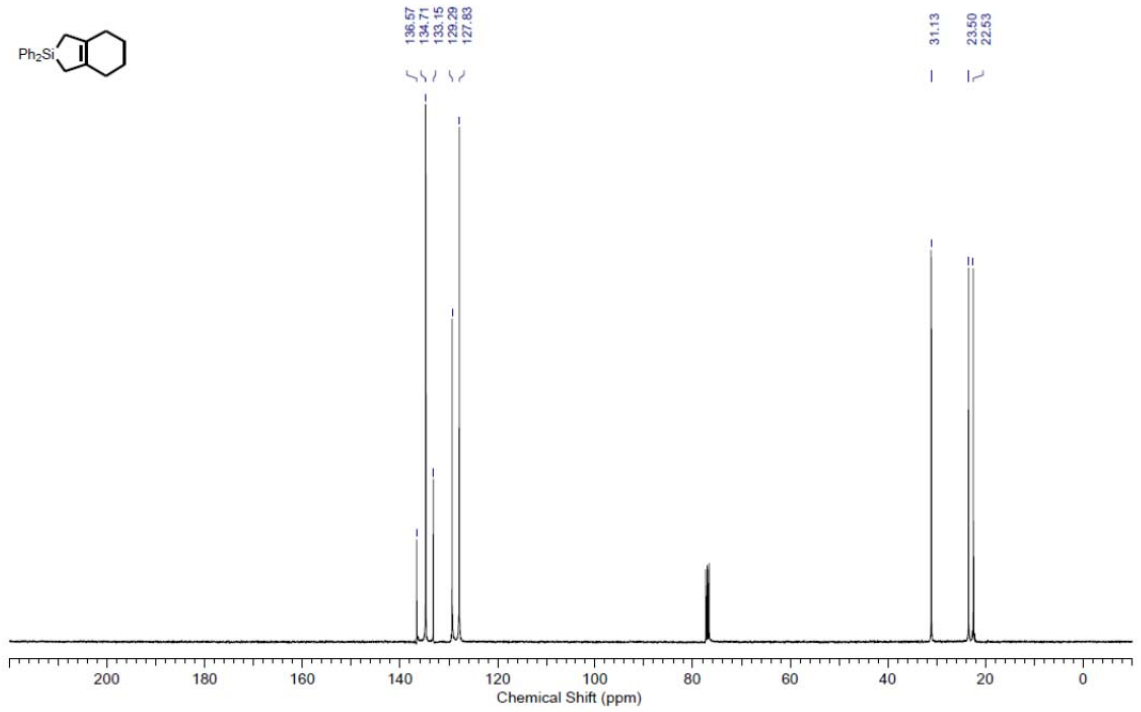
^{1}H and ^{13}C NMR of compound **1-48f**



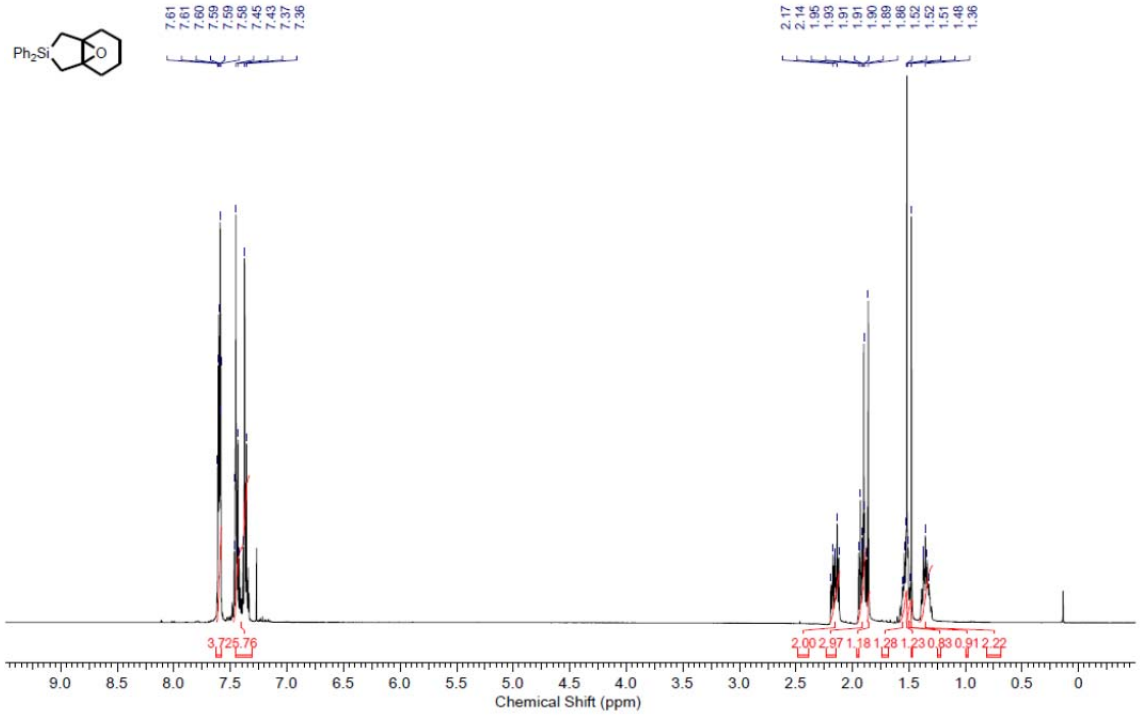


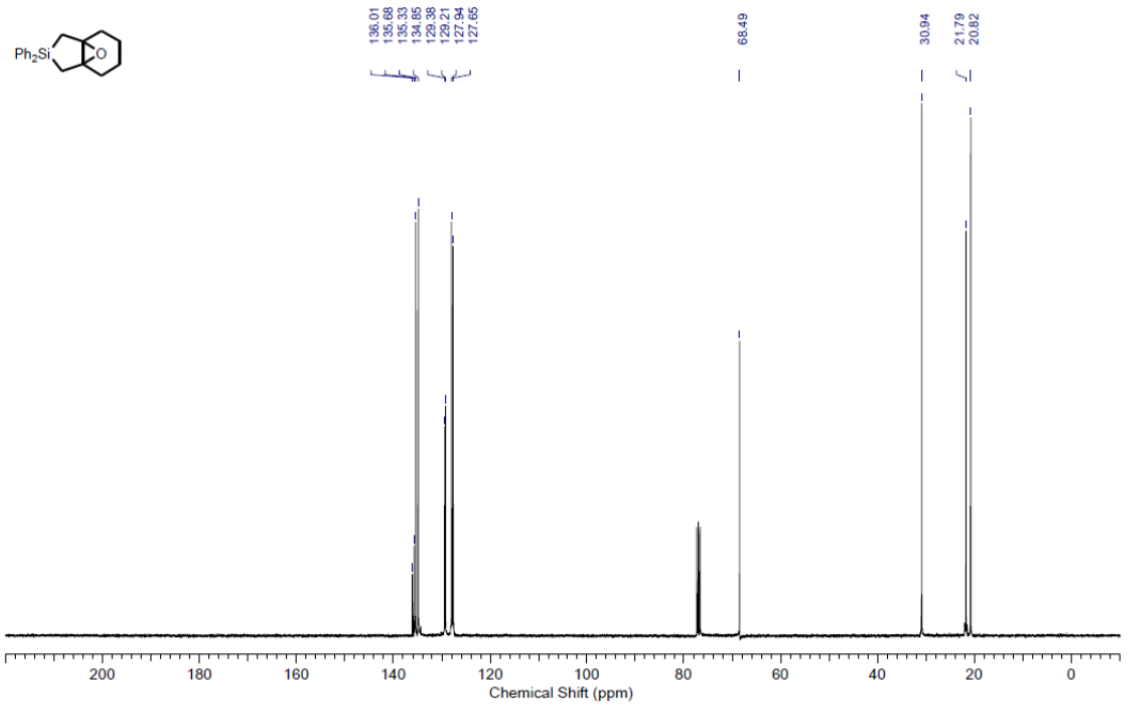
^{1}H and ^{13}C NMR of compound **1-58**



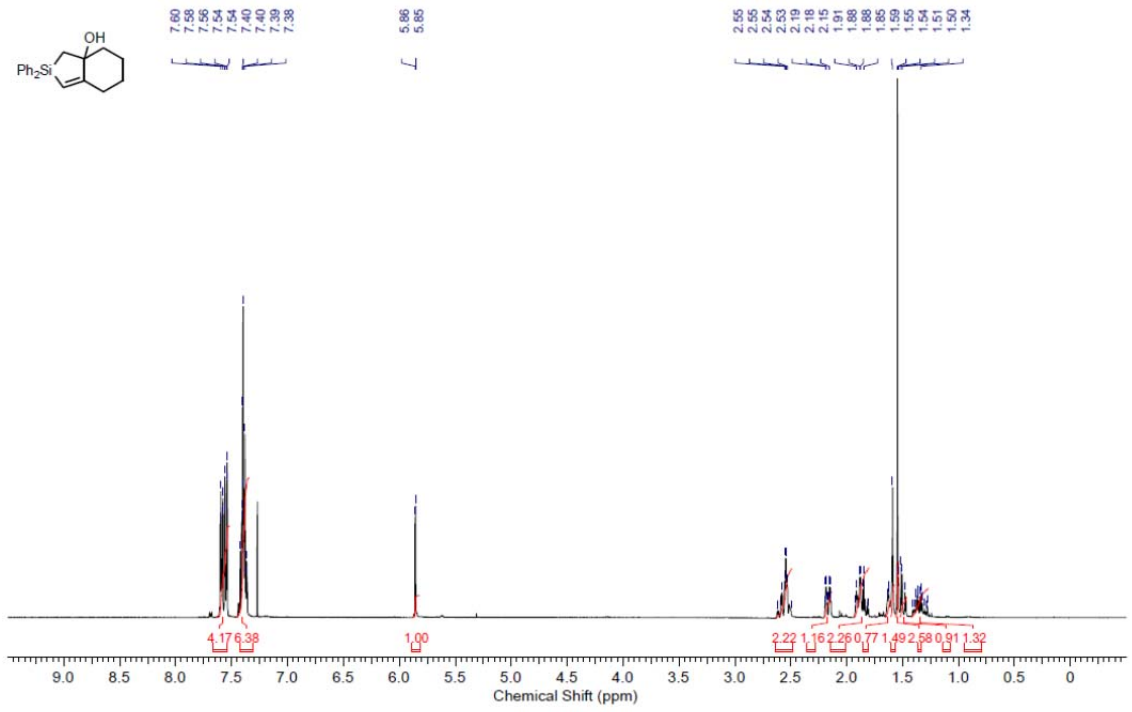


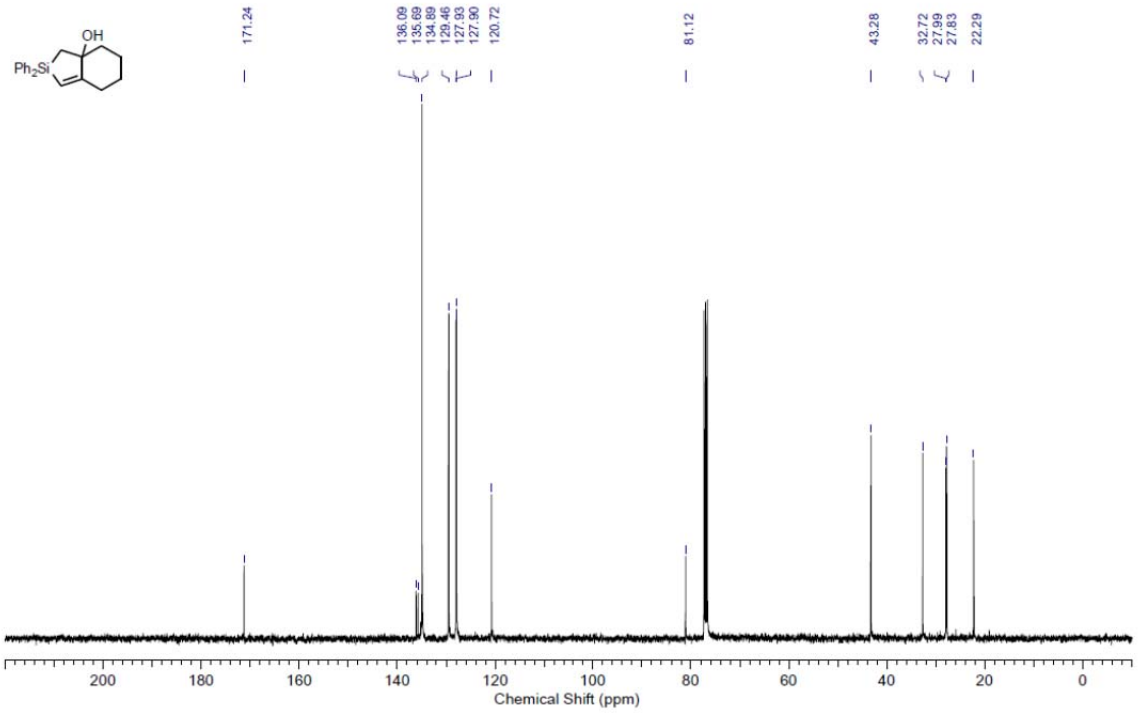
^{1}H and ^{13}C NMR of compound **1-59**



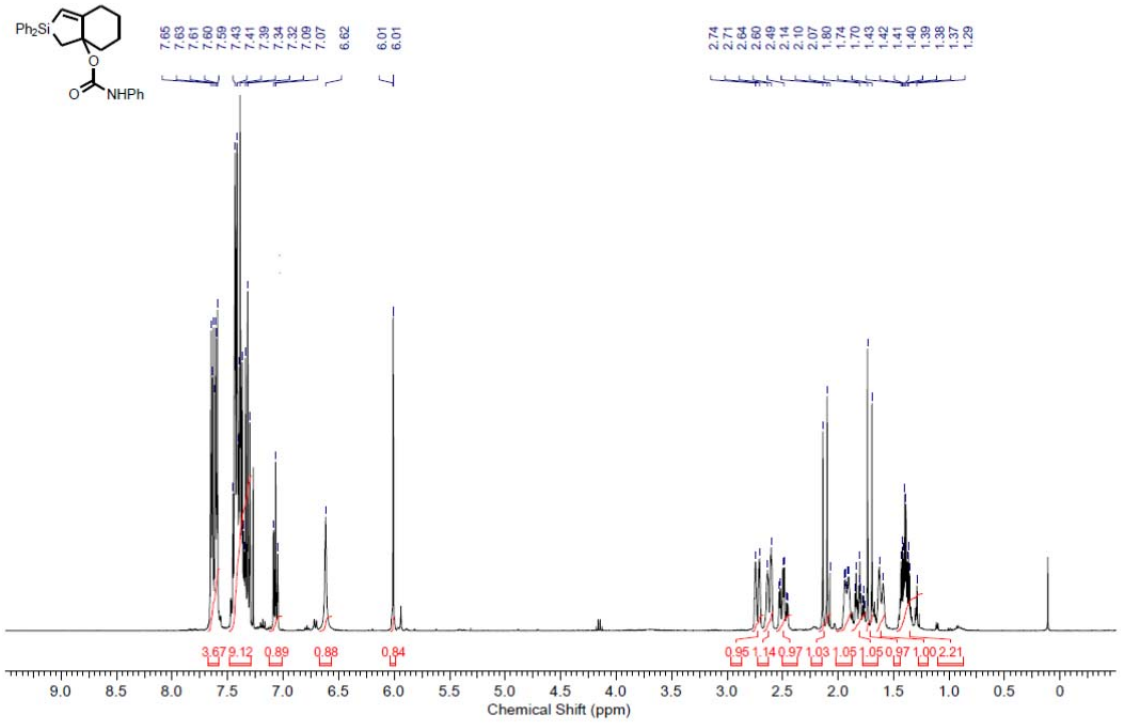


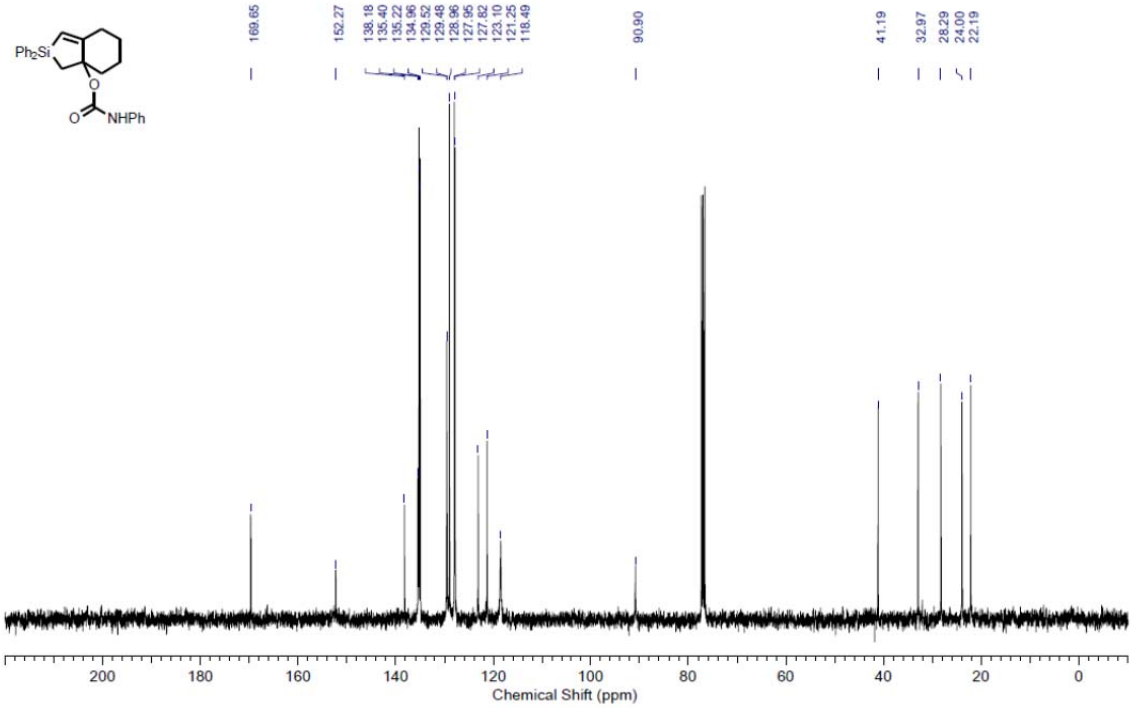
^{1}H and ^{13}C NMR of compound **1-60**



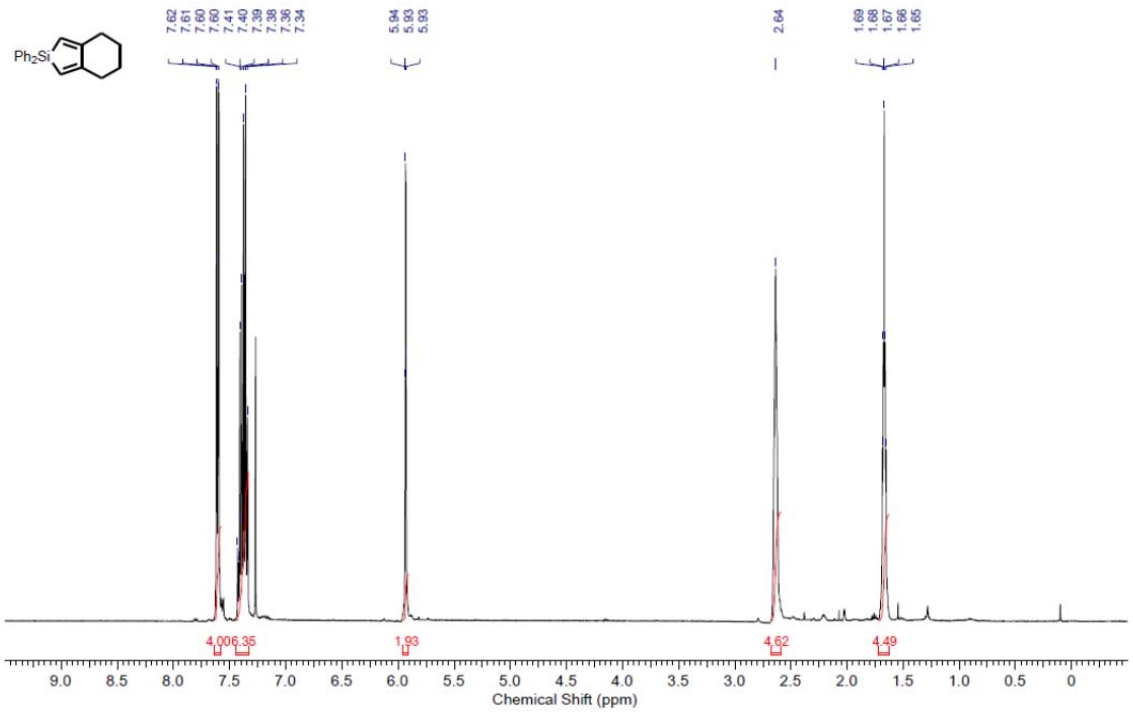


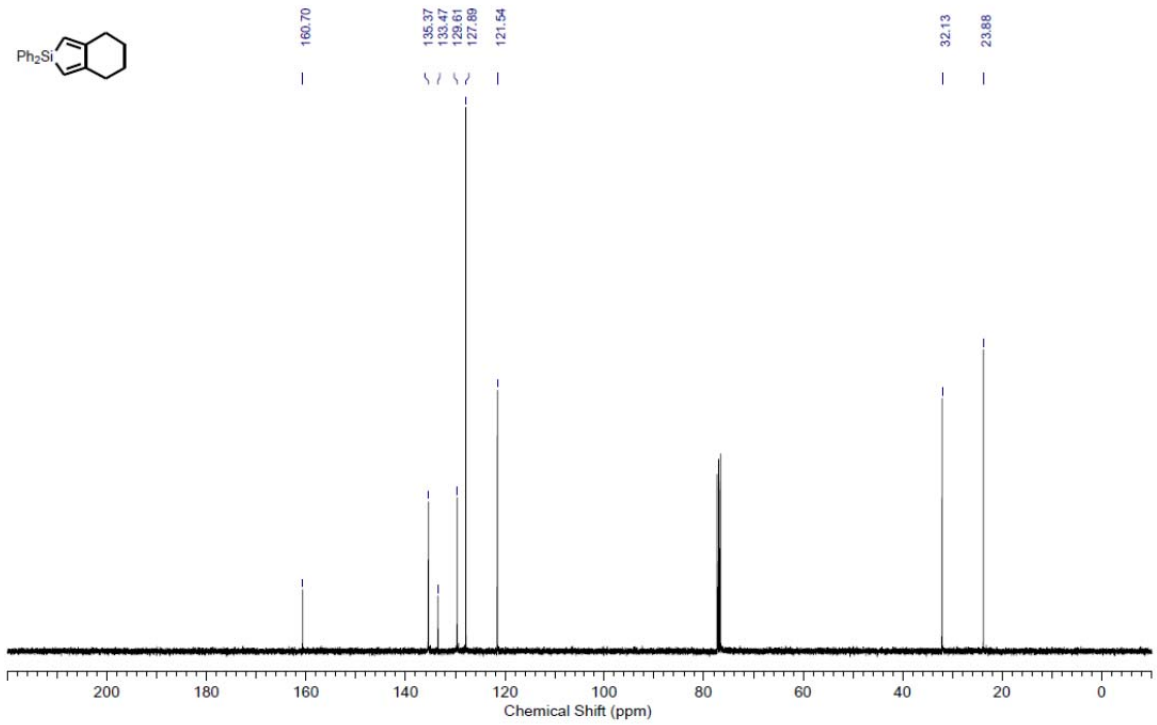
^{1}H and ^{13}C NMR of compound **1-61**



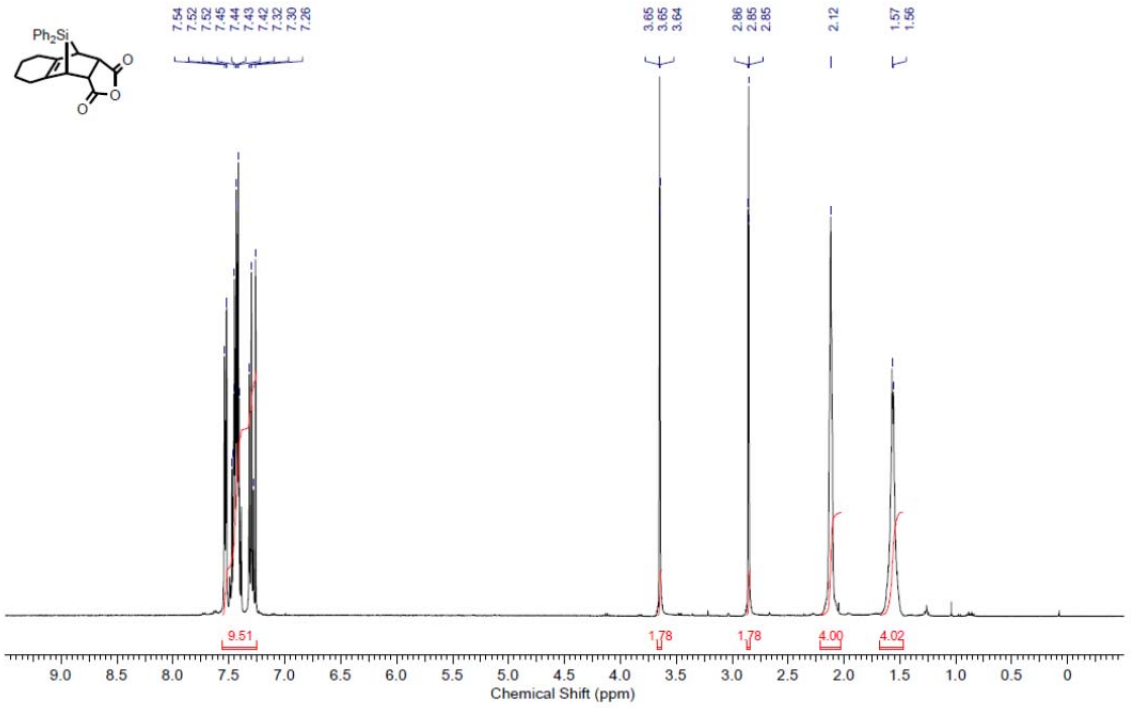


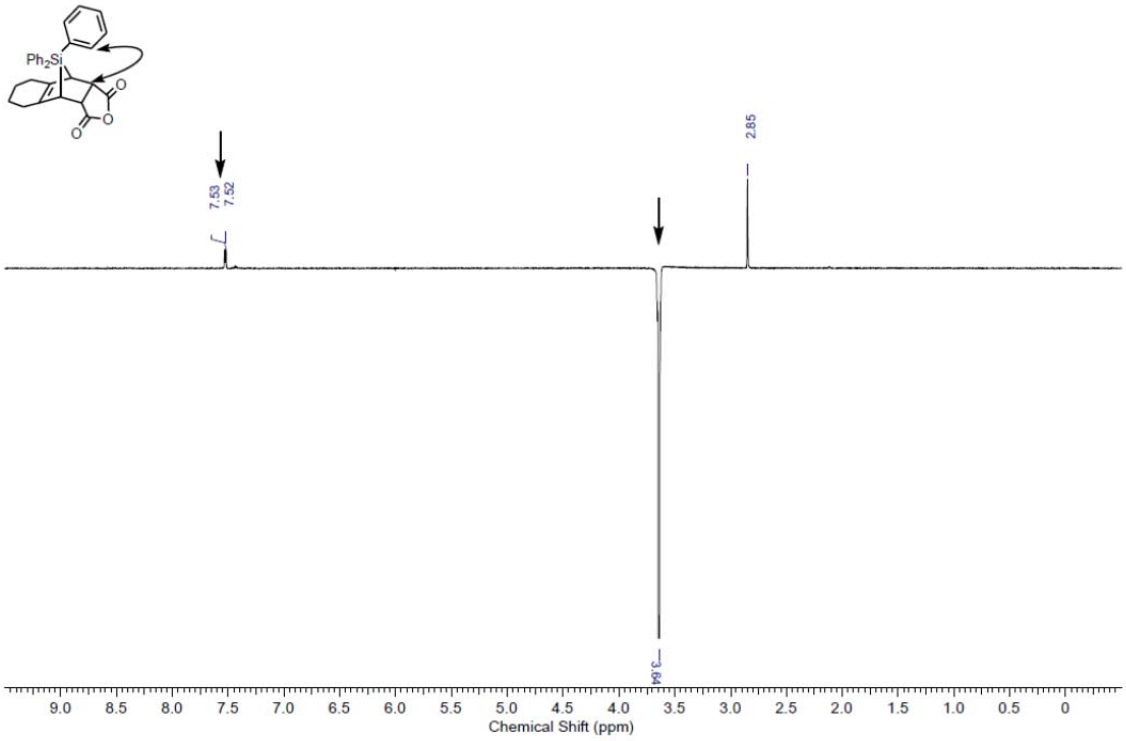
^{1}H and ^{13}C NMR of compound **1-62**

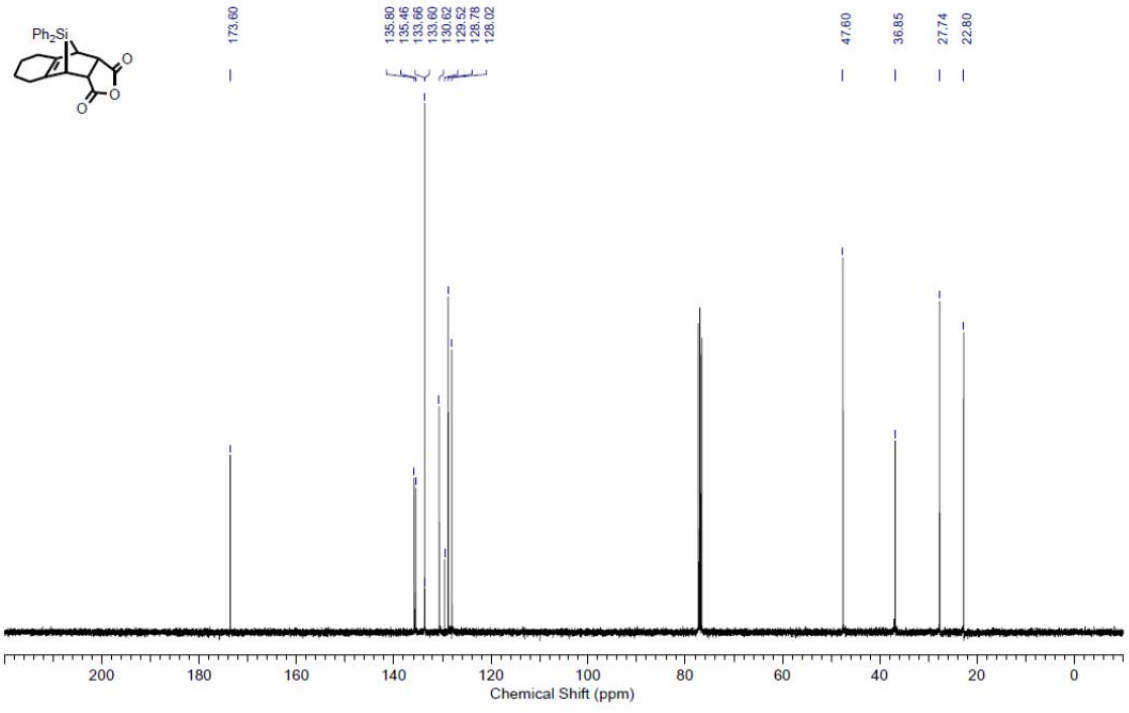




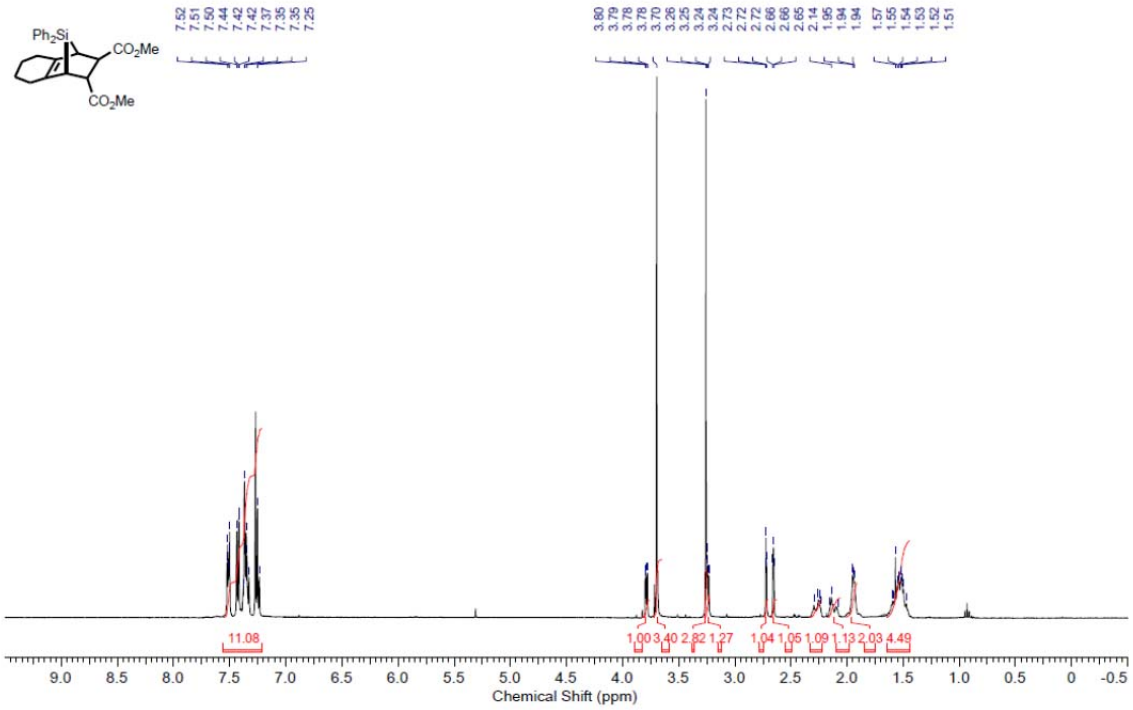
^{1}H, 1D nOe and ^{13}C NMR of compound **1-68a**

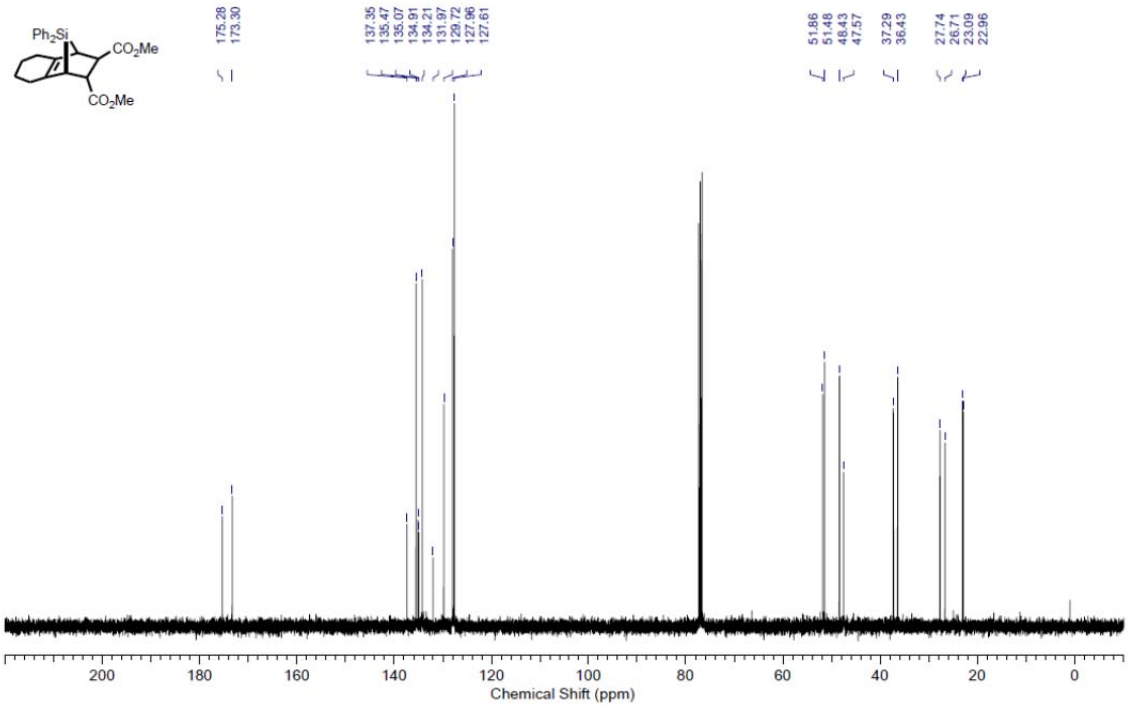



Ph2Si
7.53
7.52
2.85
3.64
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

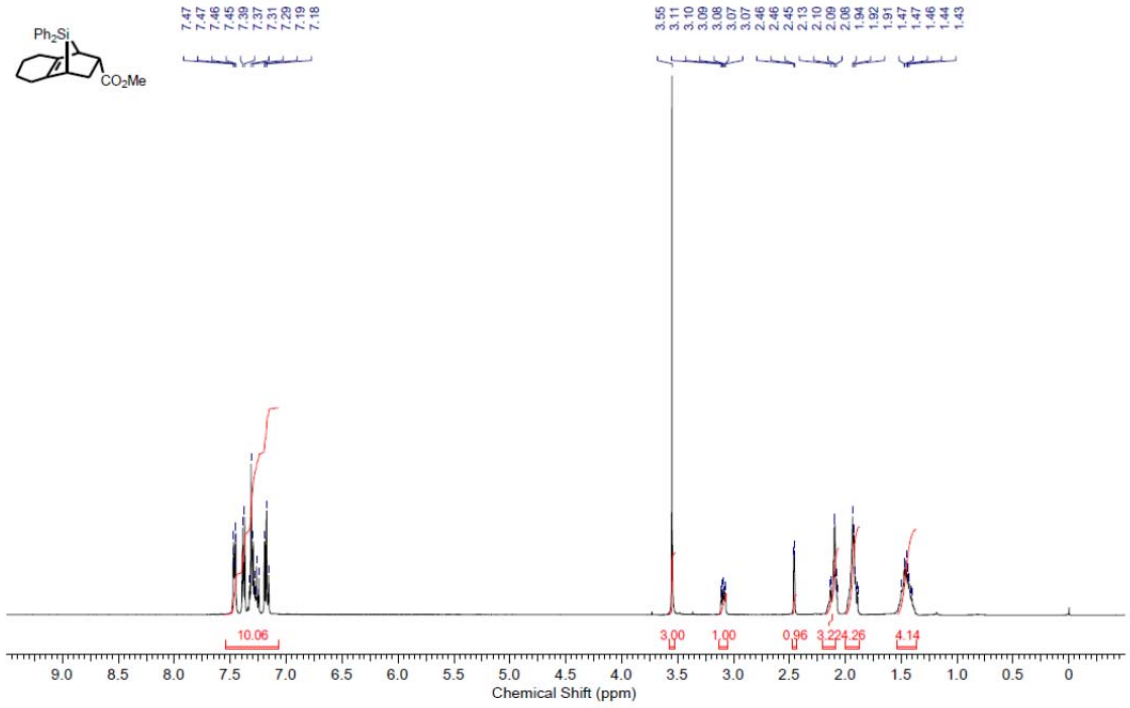

Ph2Si
173.60
135.80
135.46
133.66
133.60
130.62
129.52
128.78
128.02
47.60
36.85
27.74
22.80
200 180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)

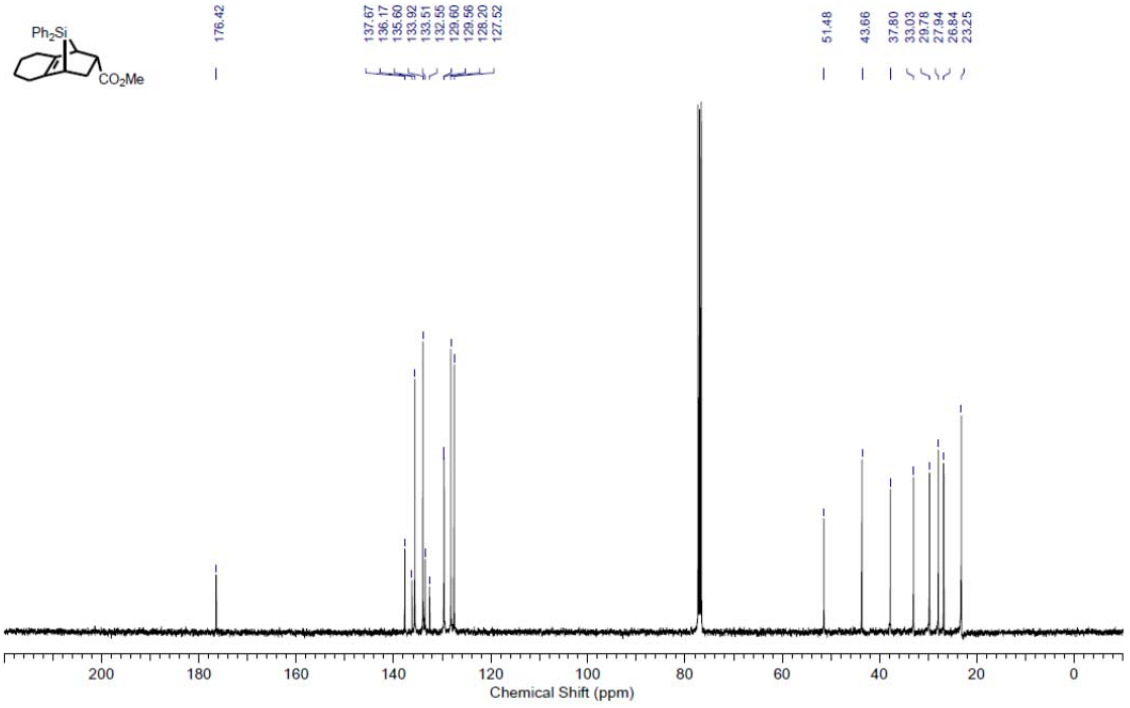
^{1}H and ^{13}C NMR of compound **1-68b**



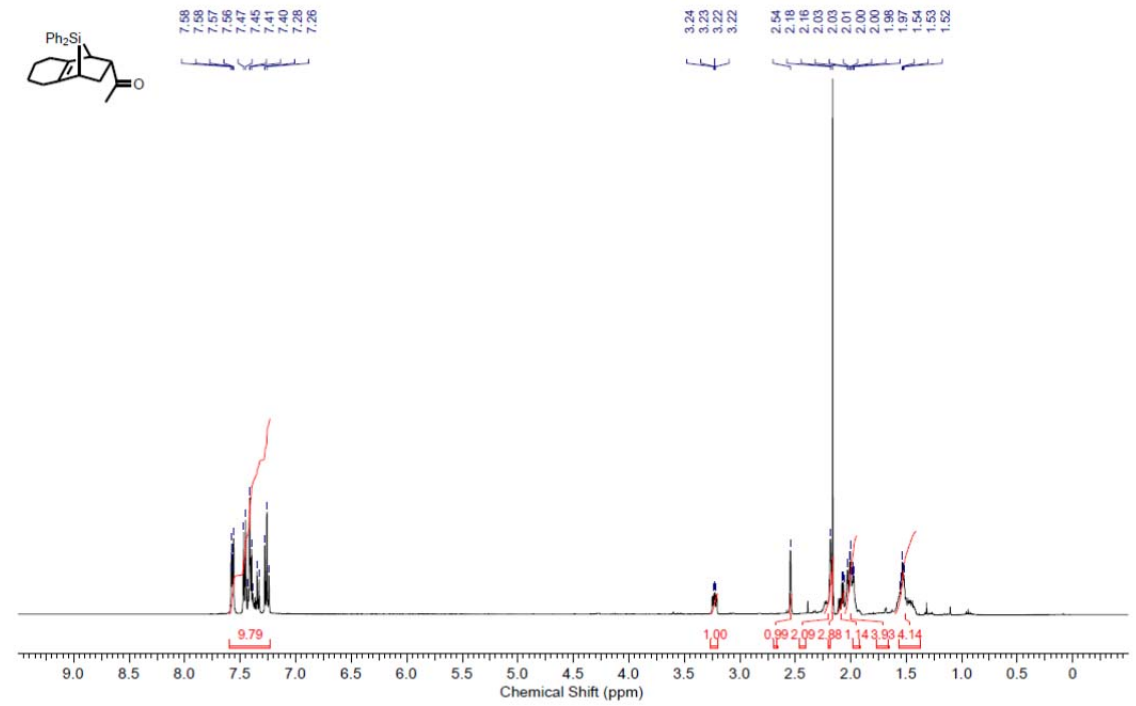


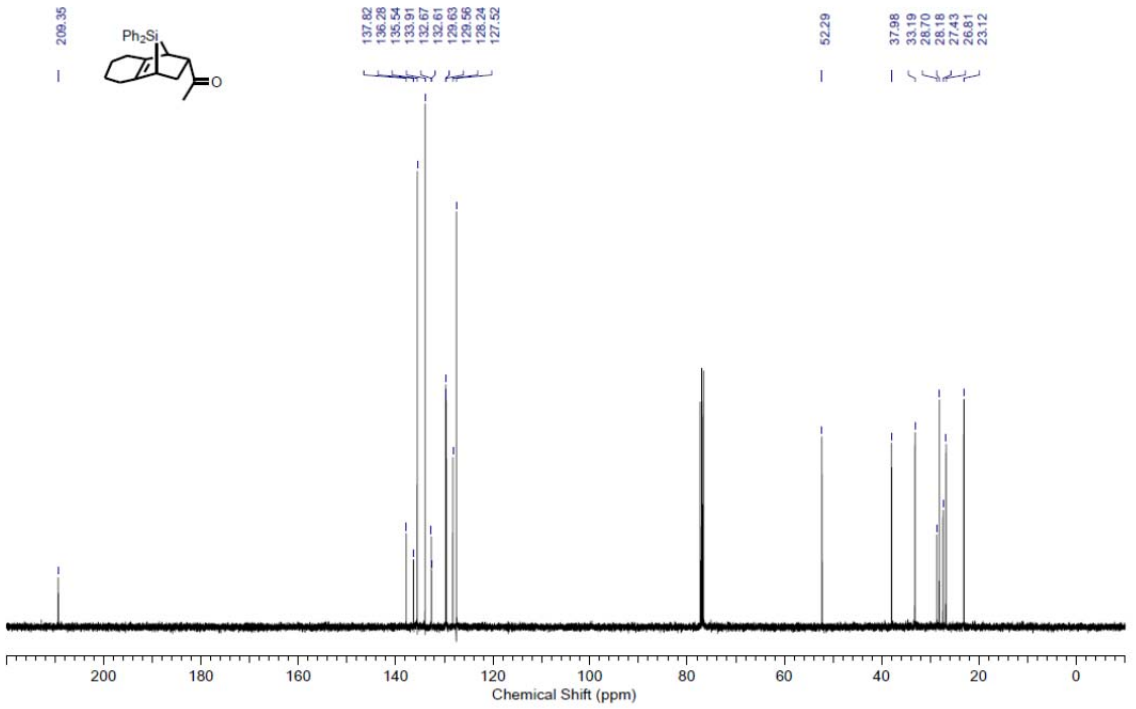
^{1}H and ^{13}C NMR of compound **1-68c**



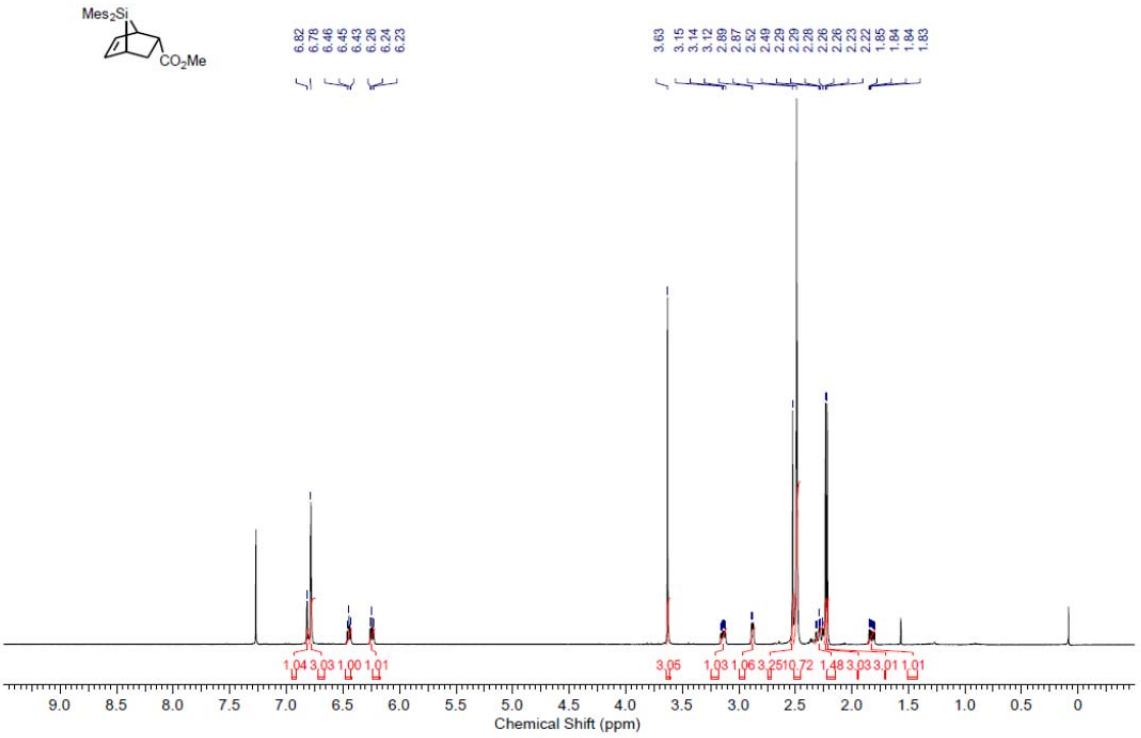


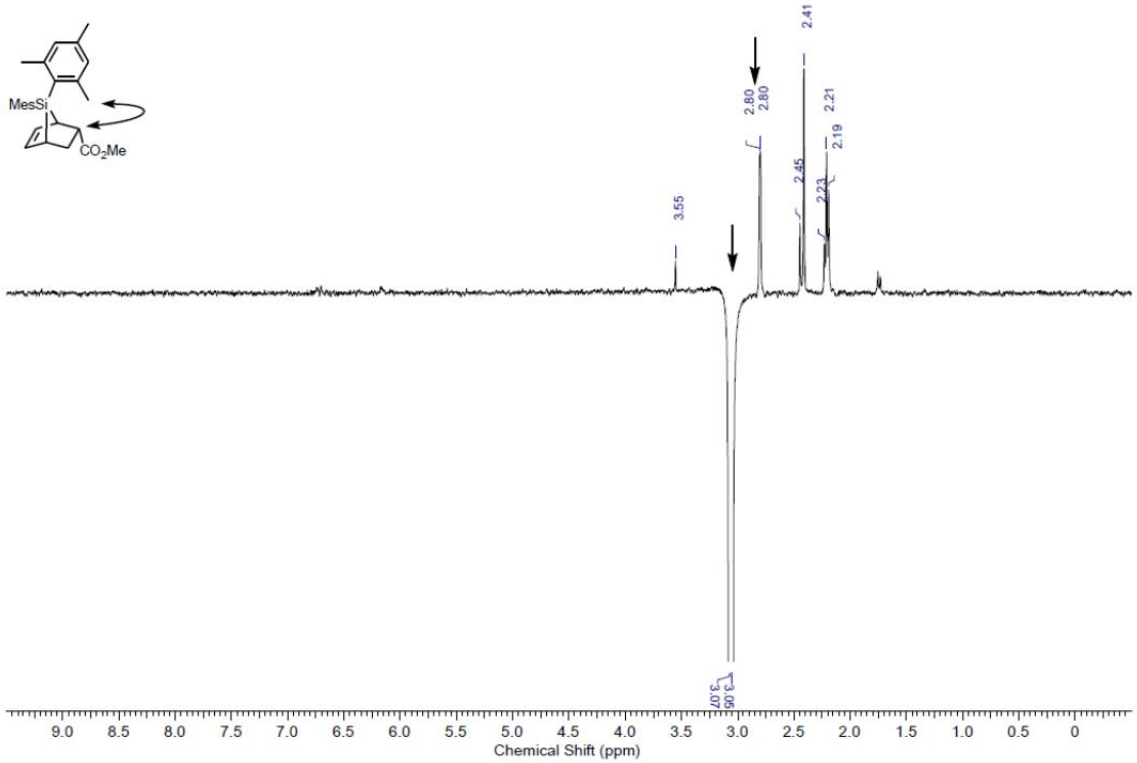
^{1}H and ^{13}C NMR of compound **1-68d**

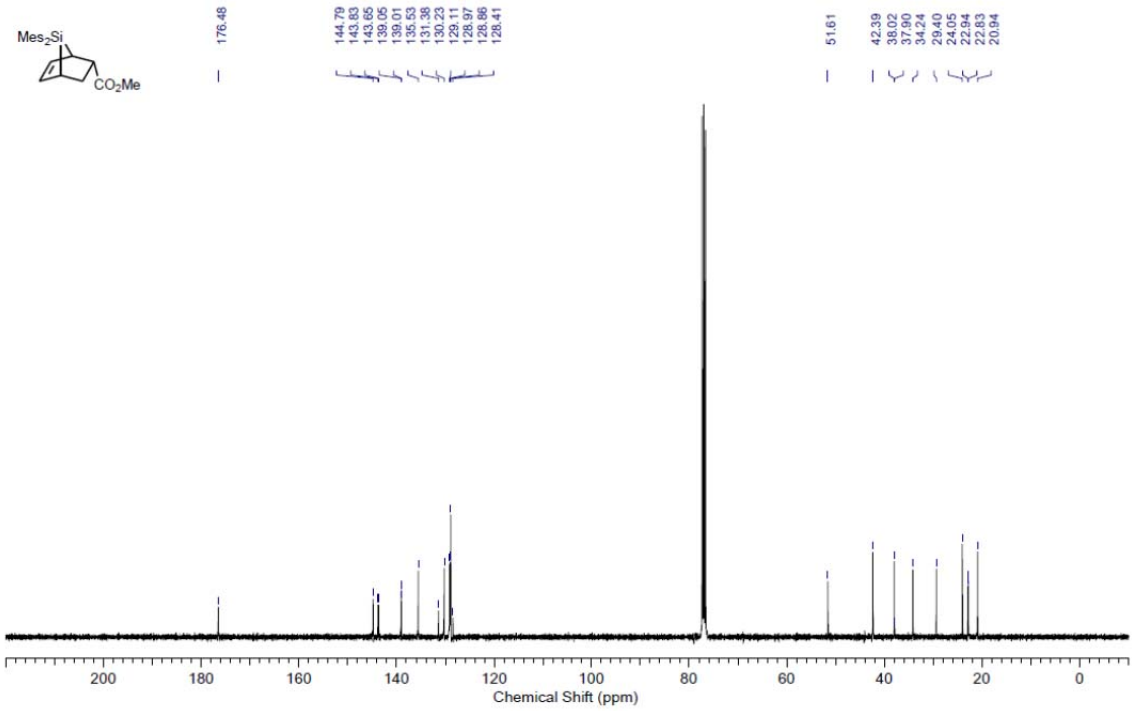




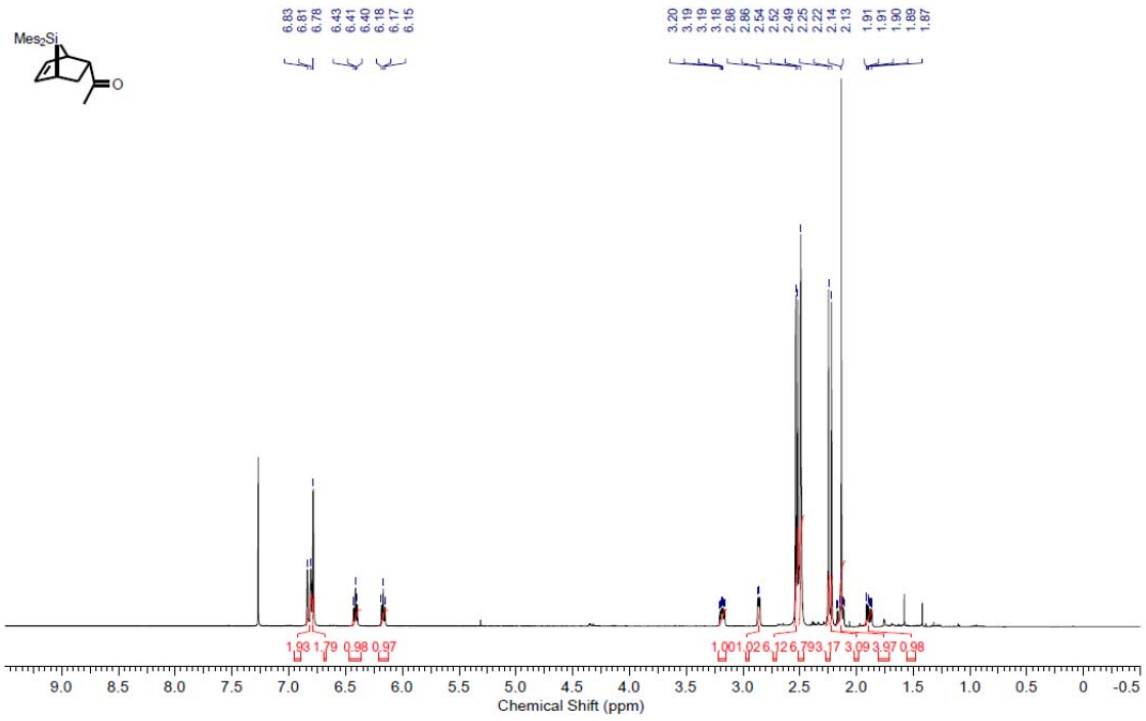
^{1}H, 1D nOe, and ^{13}C NMR of compound **1-69a**

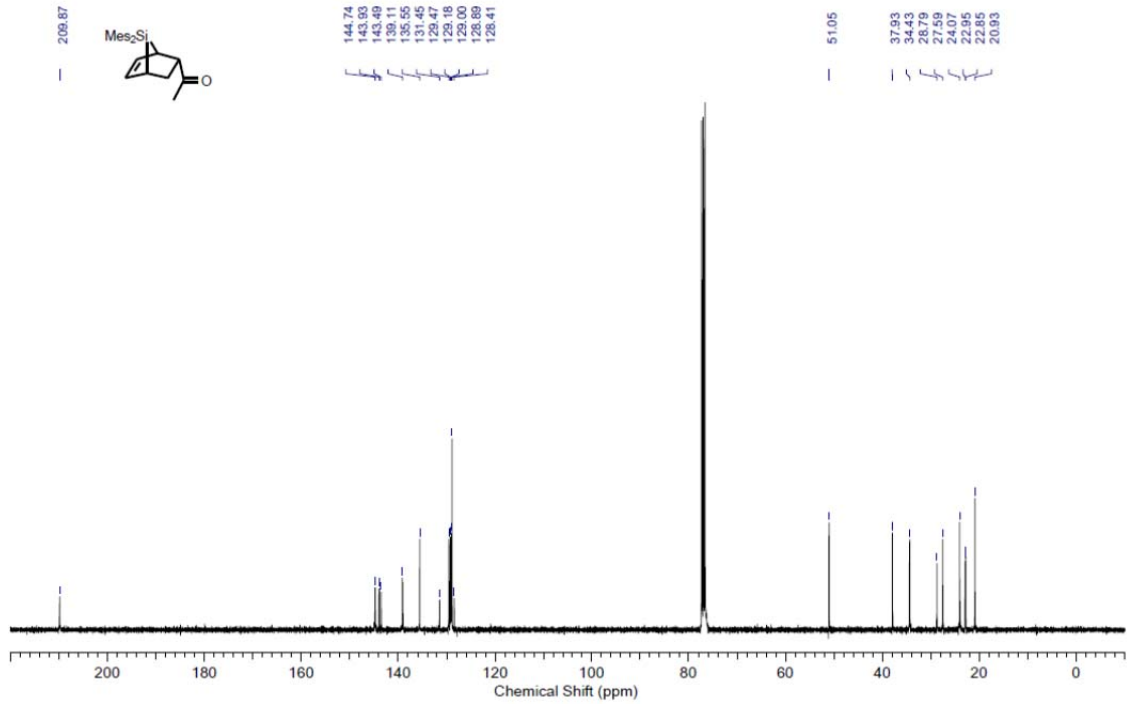




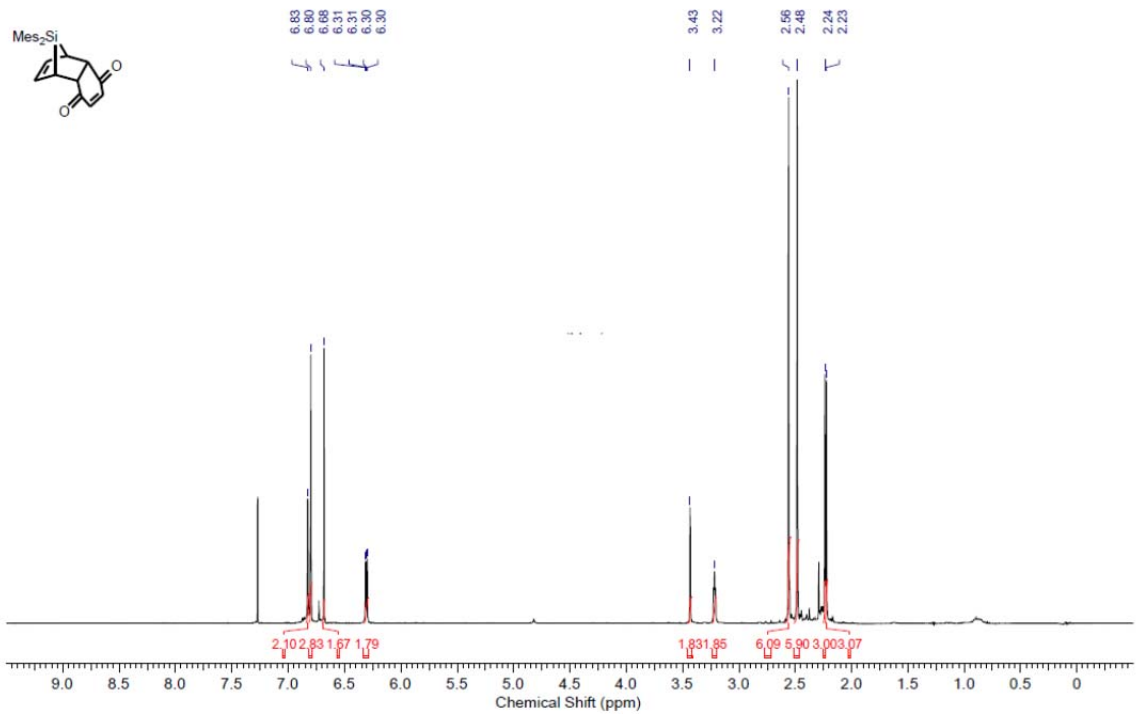


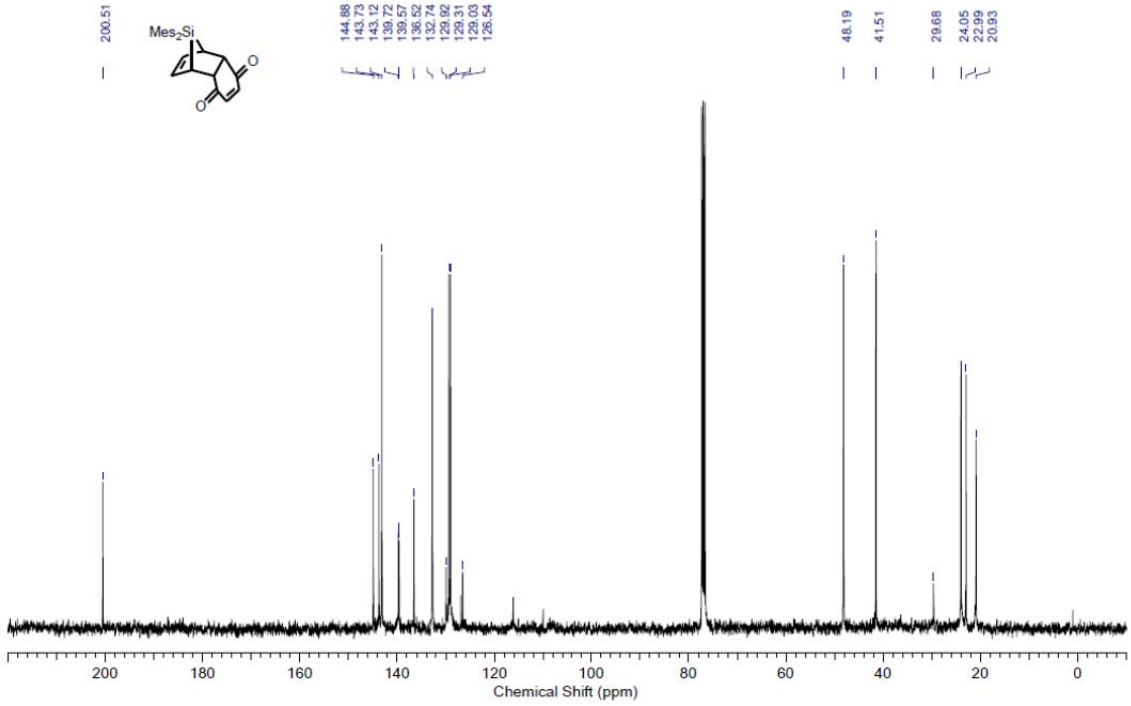
^{1}H and ^{13}C NMR of compound **1-69b**



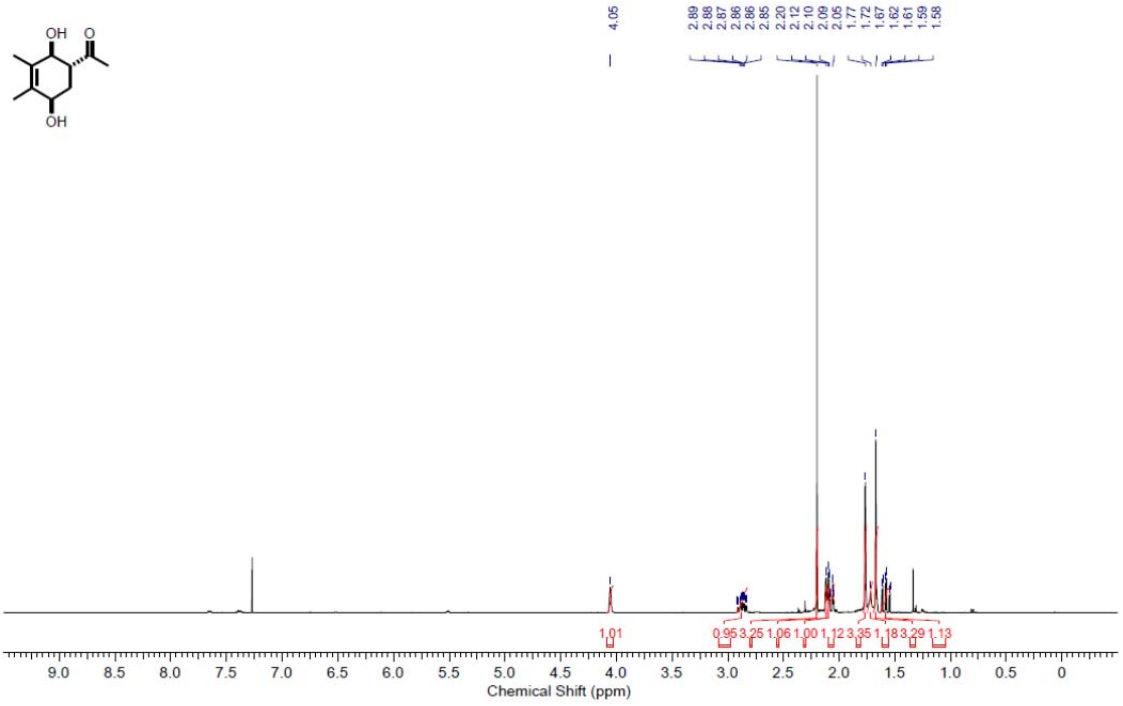


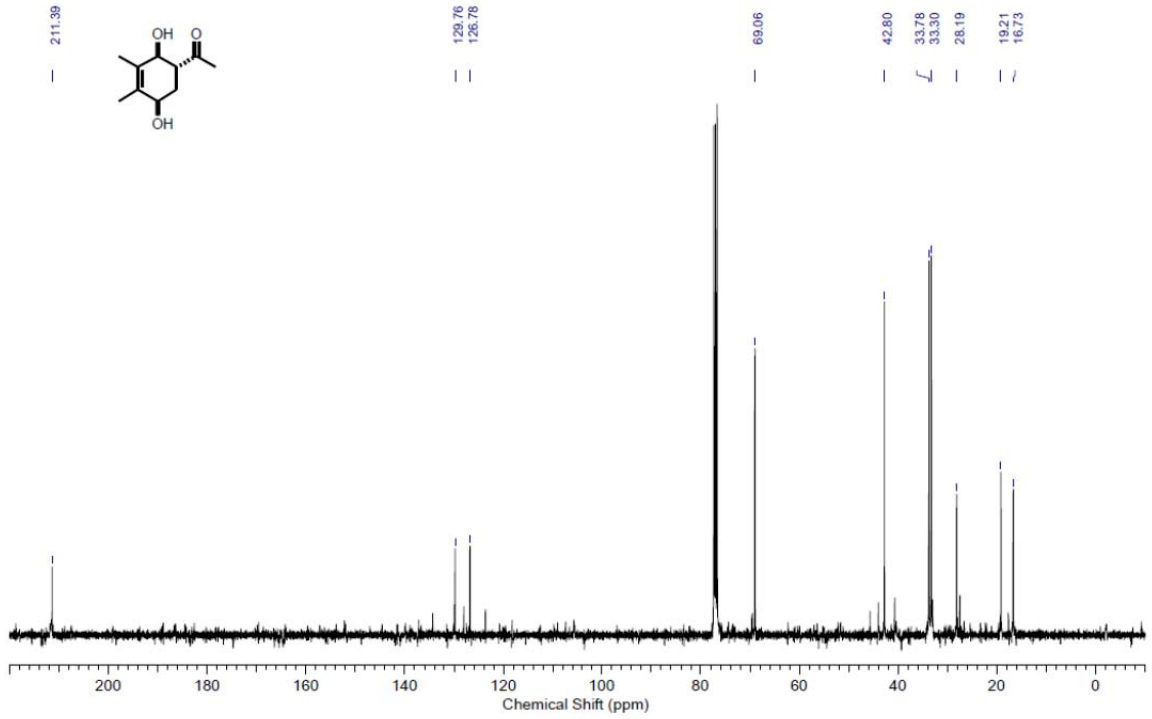
^{1}H and ^{13}C NMR of compound **1-69c**



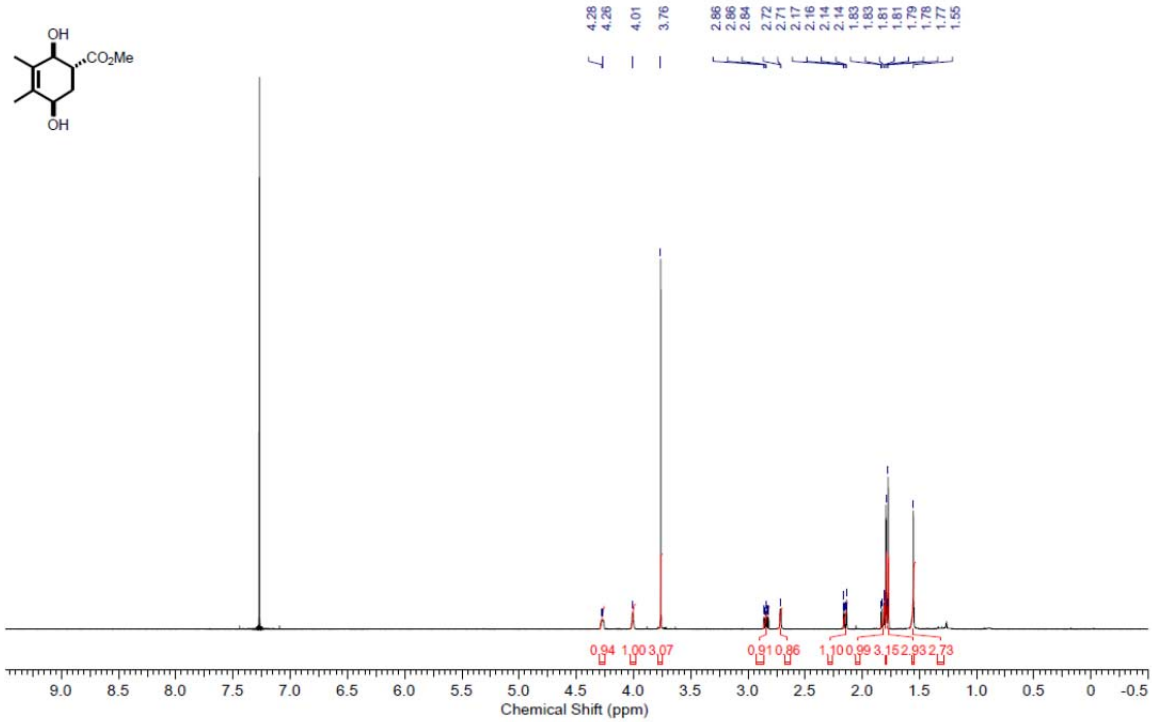


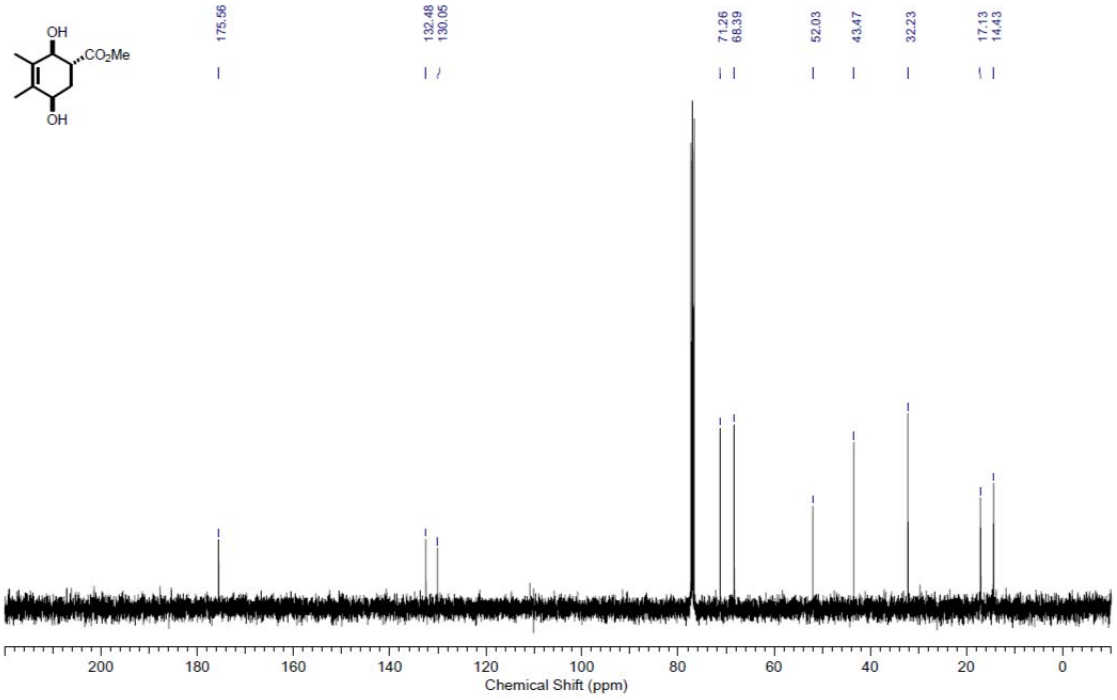
^{1}H and ^{13}C NMR of compound **1-70a**



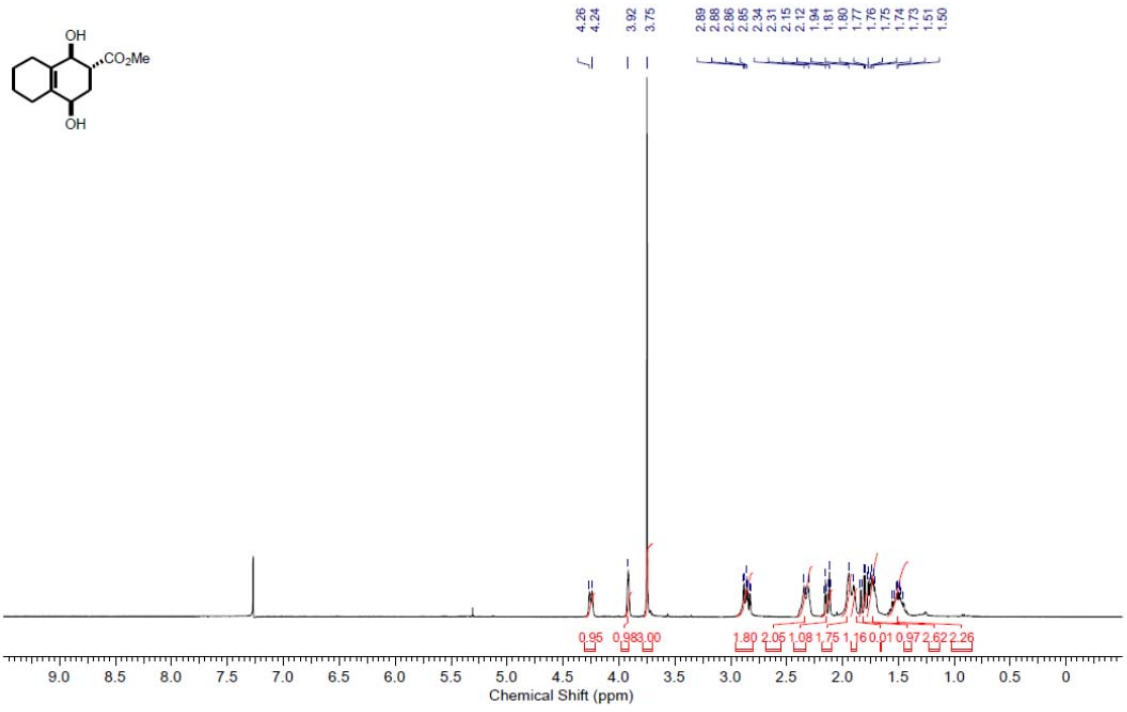


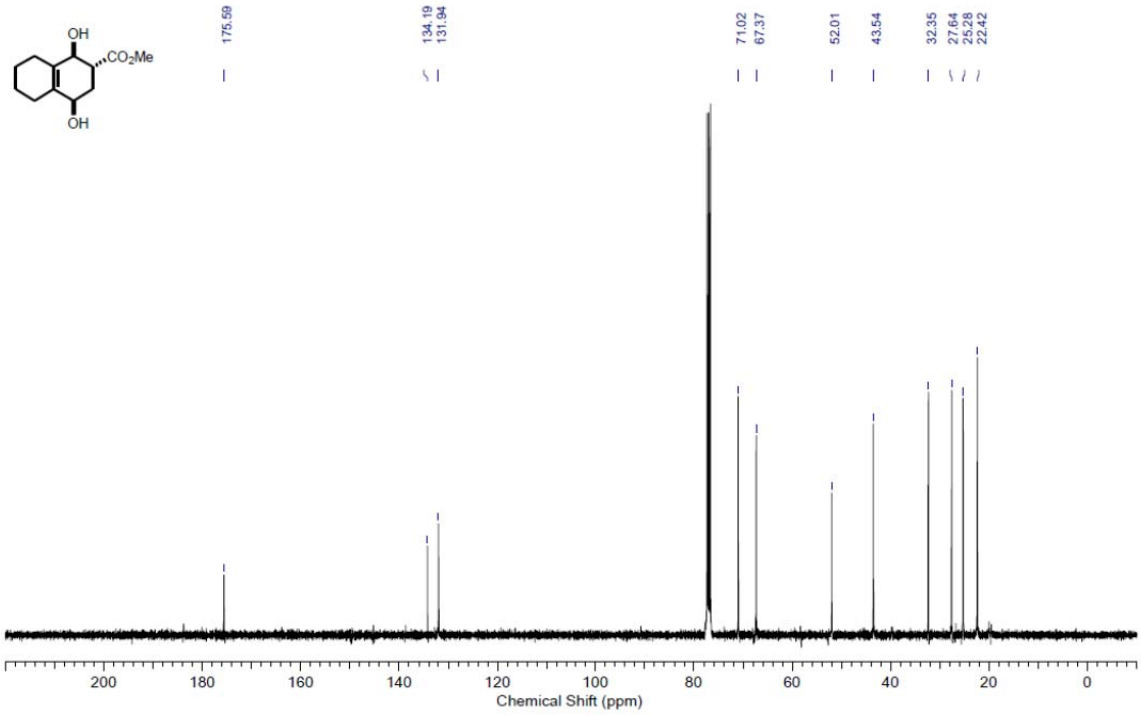
^{1}H and ^{13}C NMR of compound **1-70b**





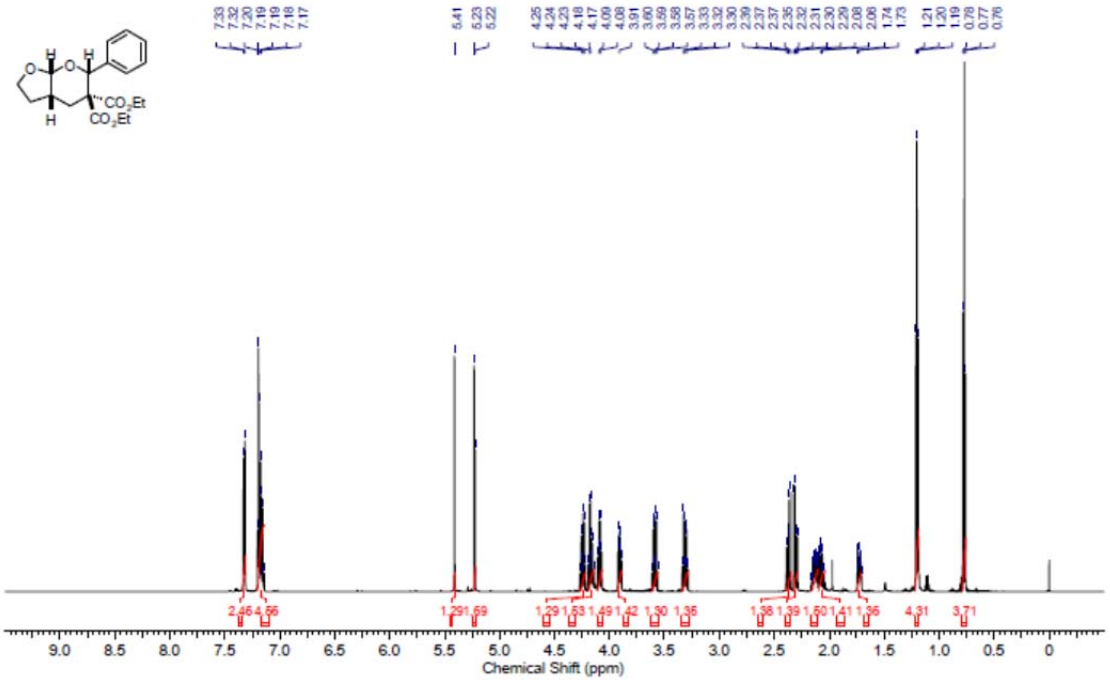
^{1}H and ^{13}C NMR of compound **1-71**

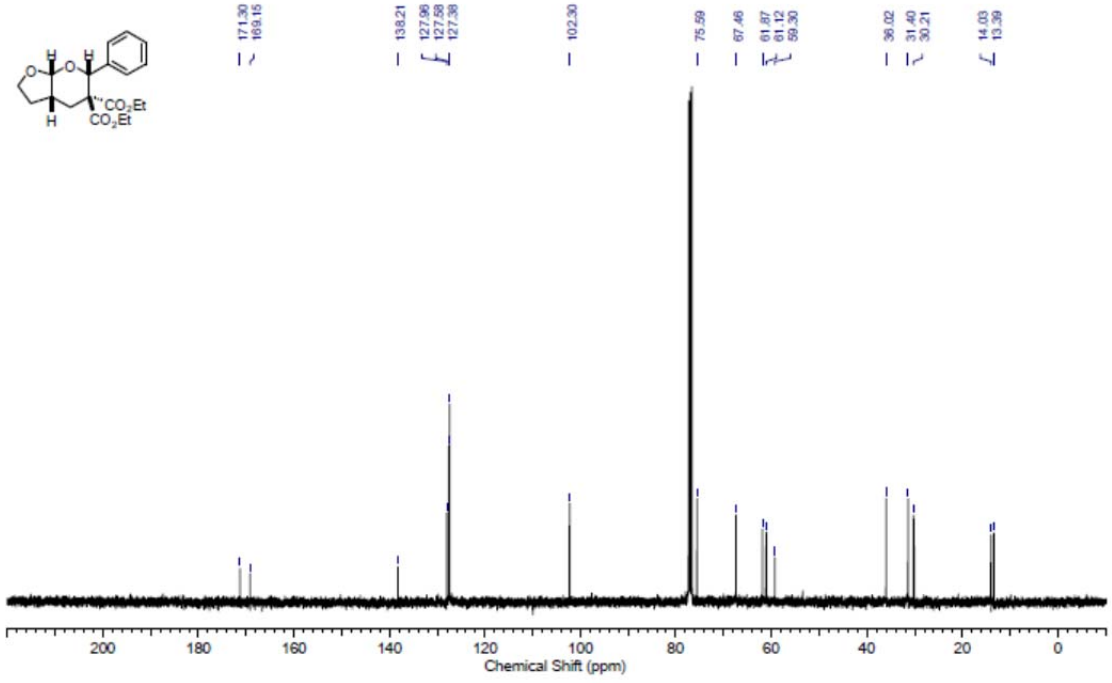


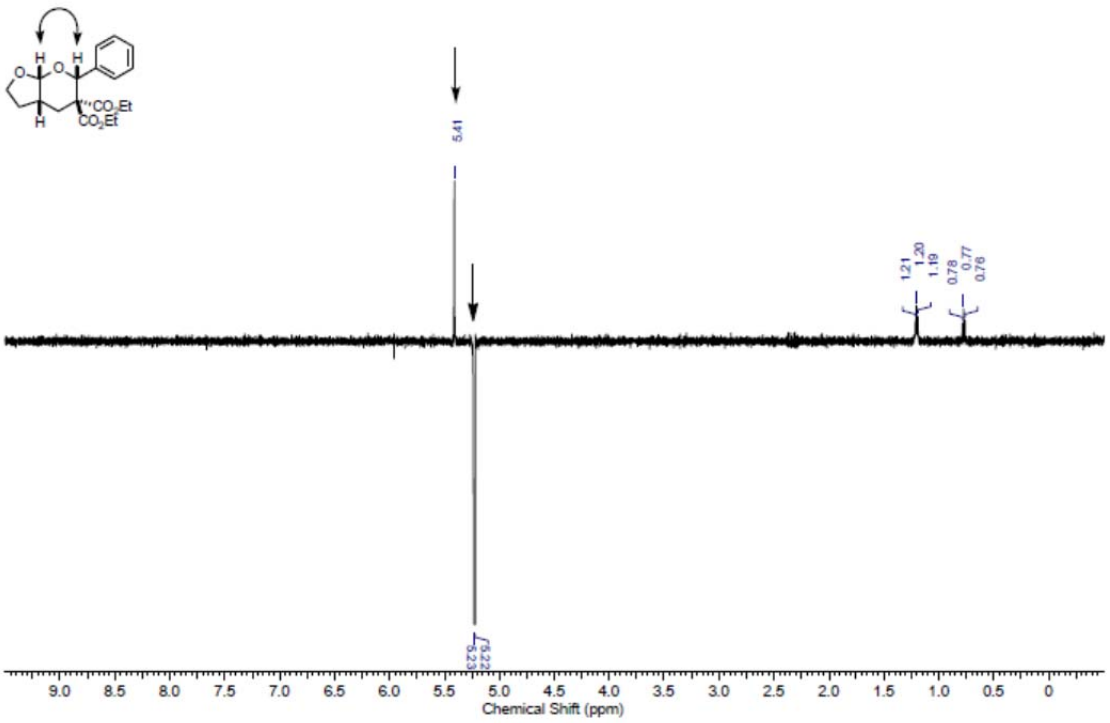

OH
CO2Me
OH
175.59
134.19
131.94
71.02
67.37
52.01
43.54
32.35
27.64
25.28
22.42
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

Appendix 2 – NMR Spectra Data for Chapter 2

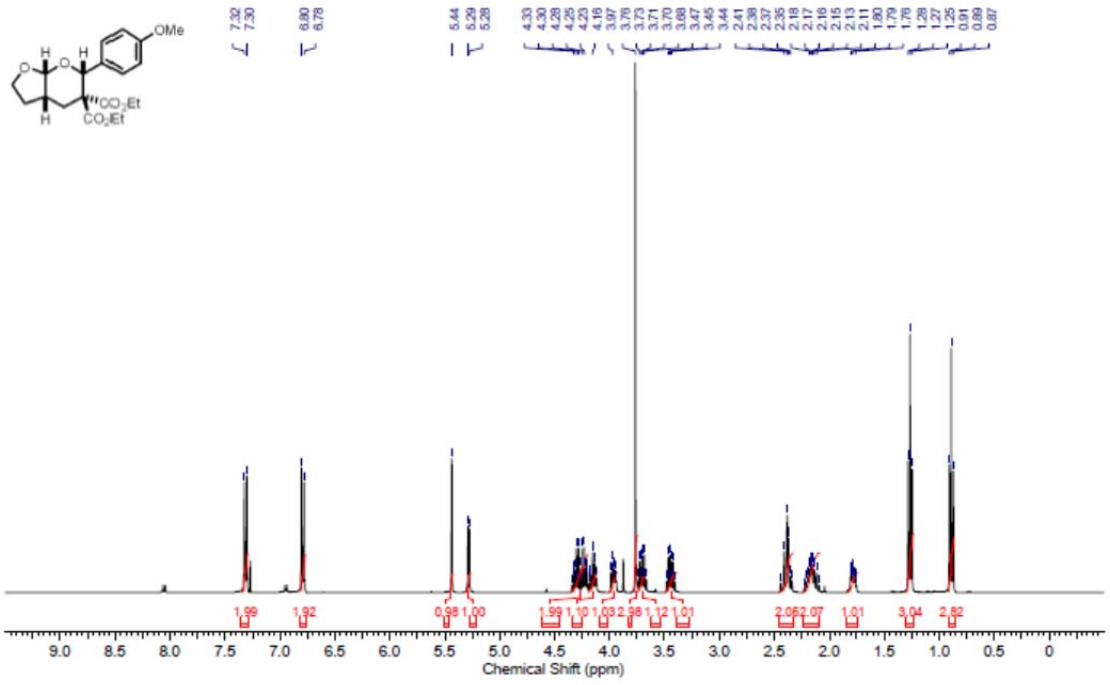
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65a**

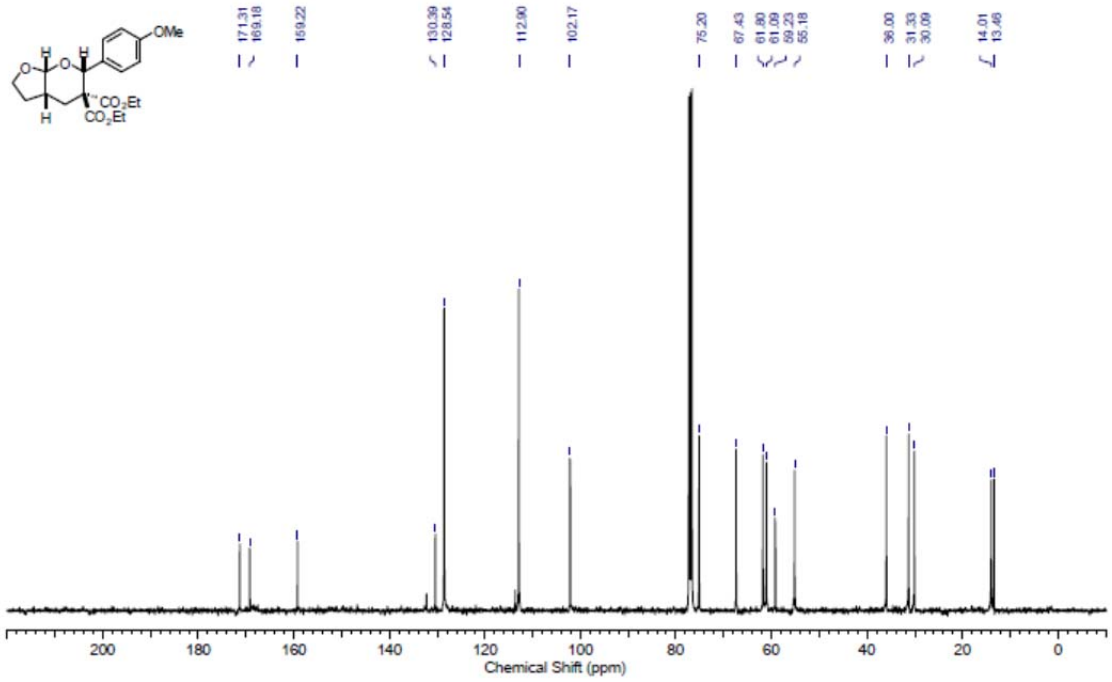


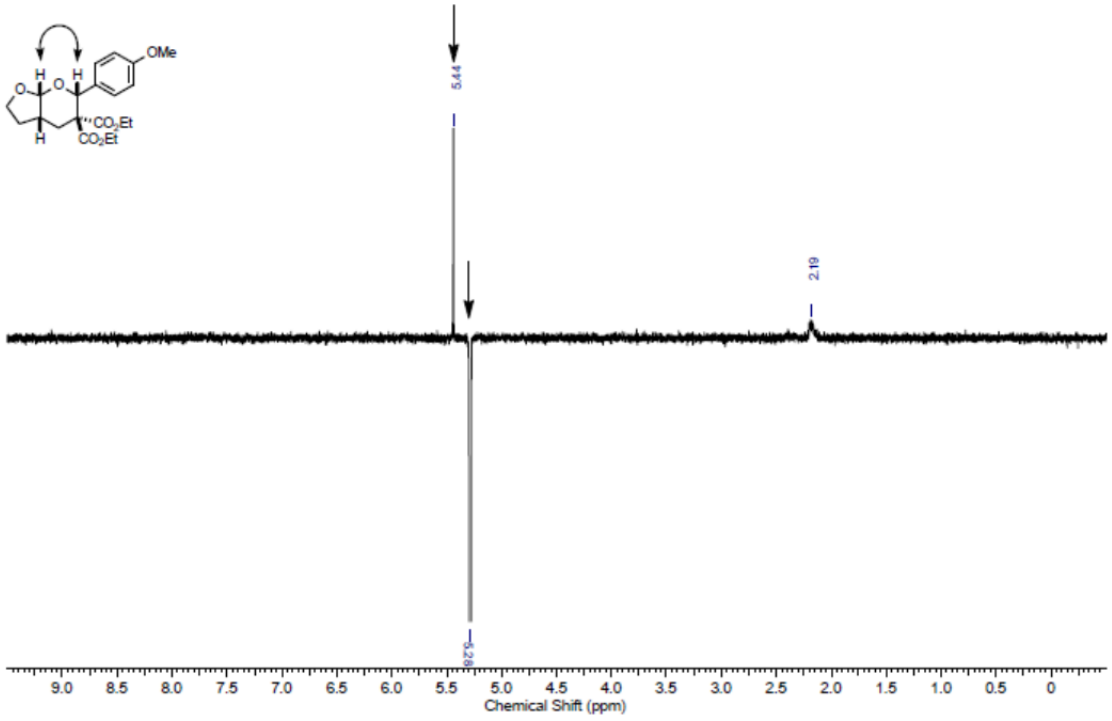




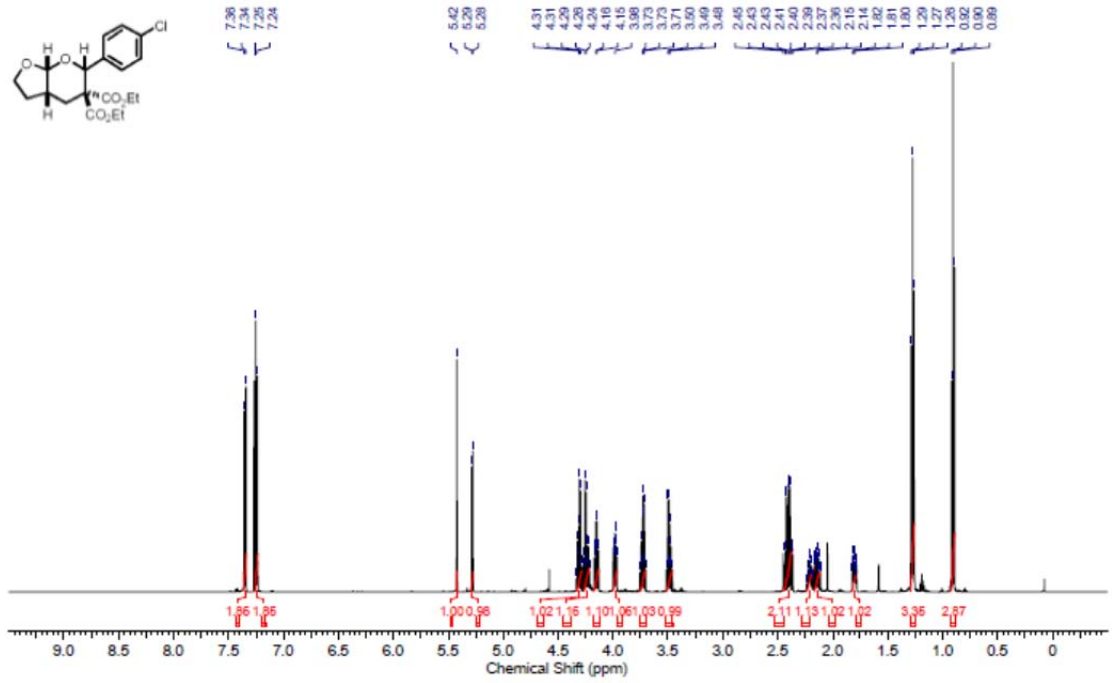
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65b**

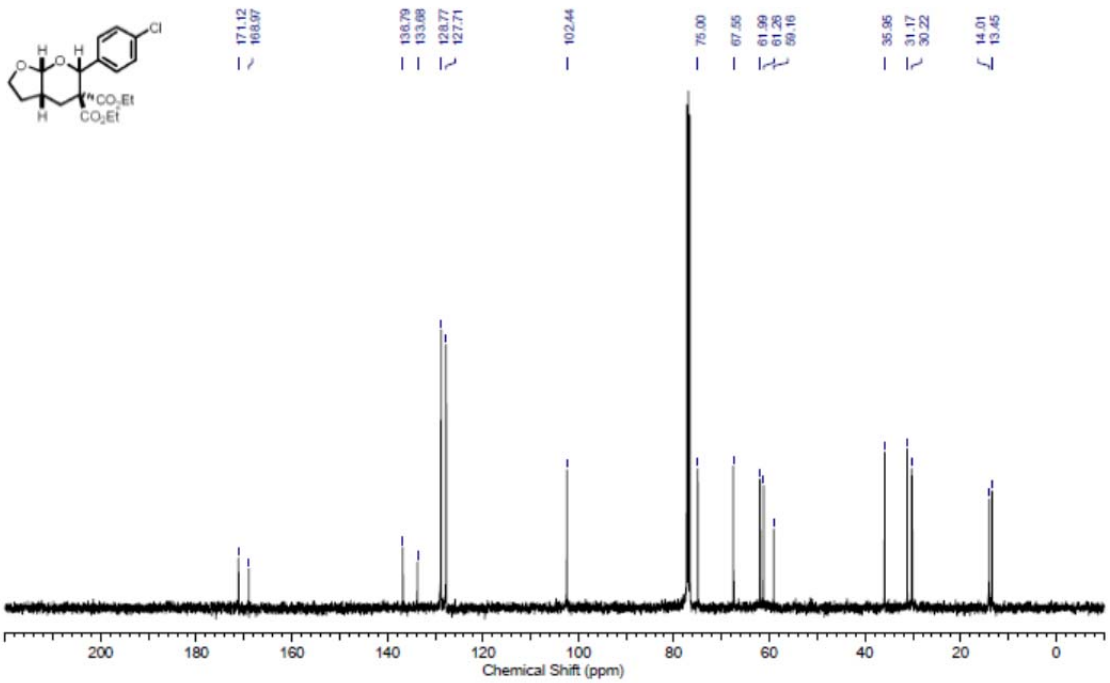


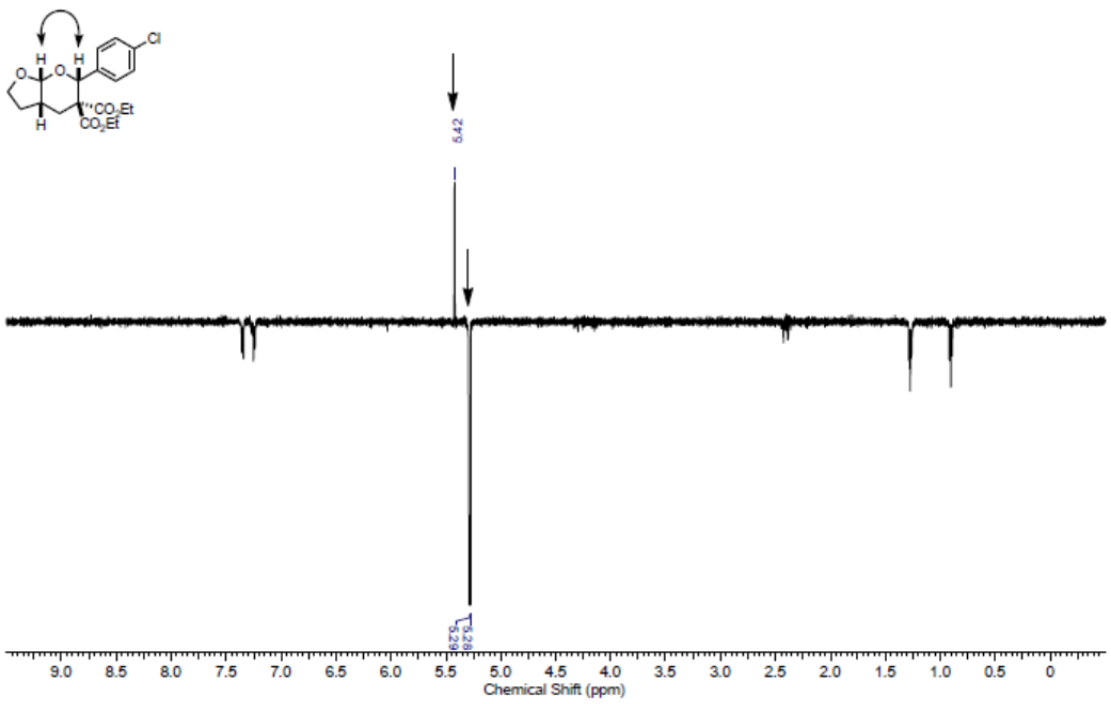

OMe
CO2Et
CO2Et
171.31
169.18
159.22
130.39
128.54
112.90
102.17
75.20
67.43
61.80
61.09
59.23
55.18
36.00
31.33
30.09
14.01
13.46
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


OMe
CO2Et
CO2Et
5.44
2.19
-5.26
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

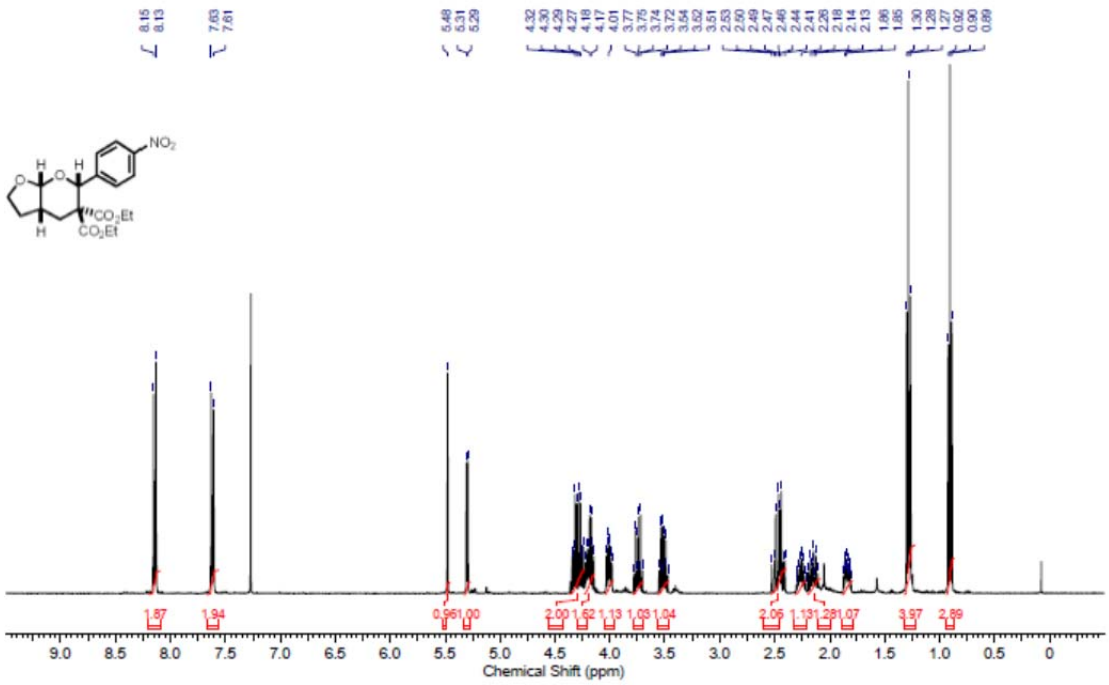
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65c**

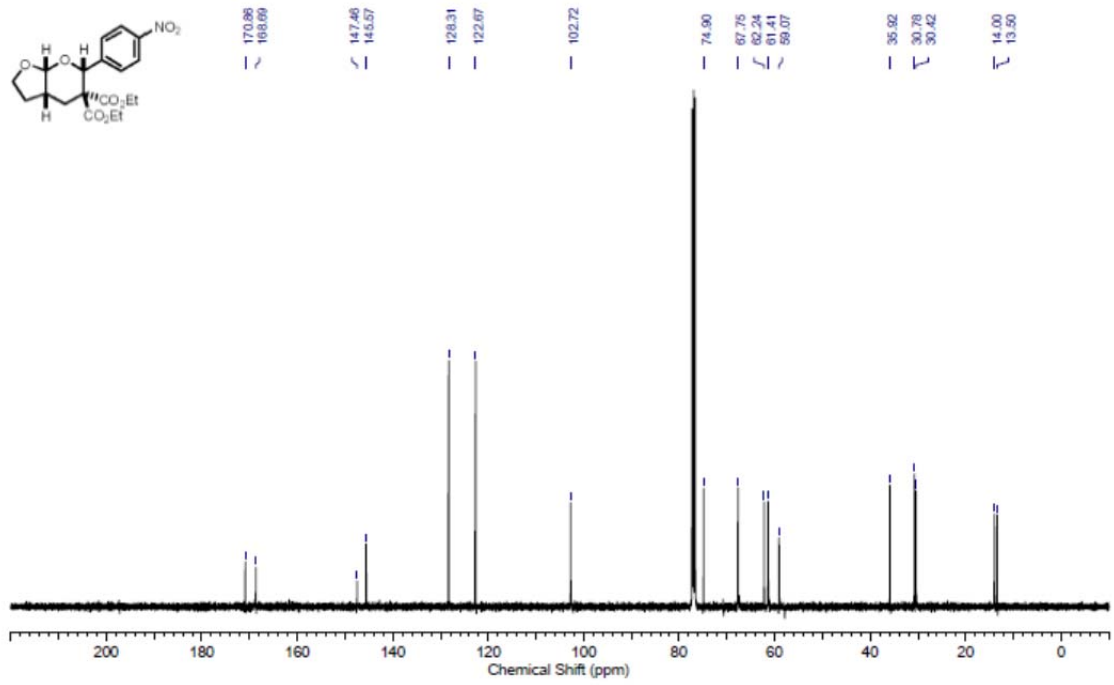


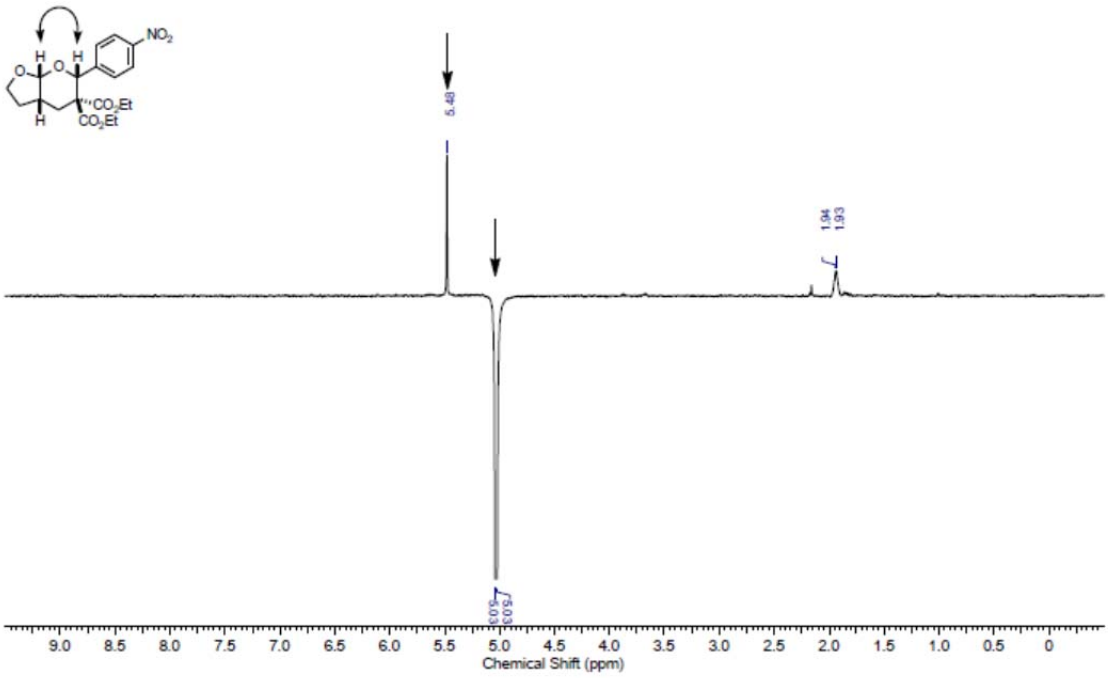




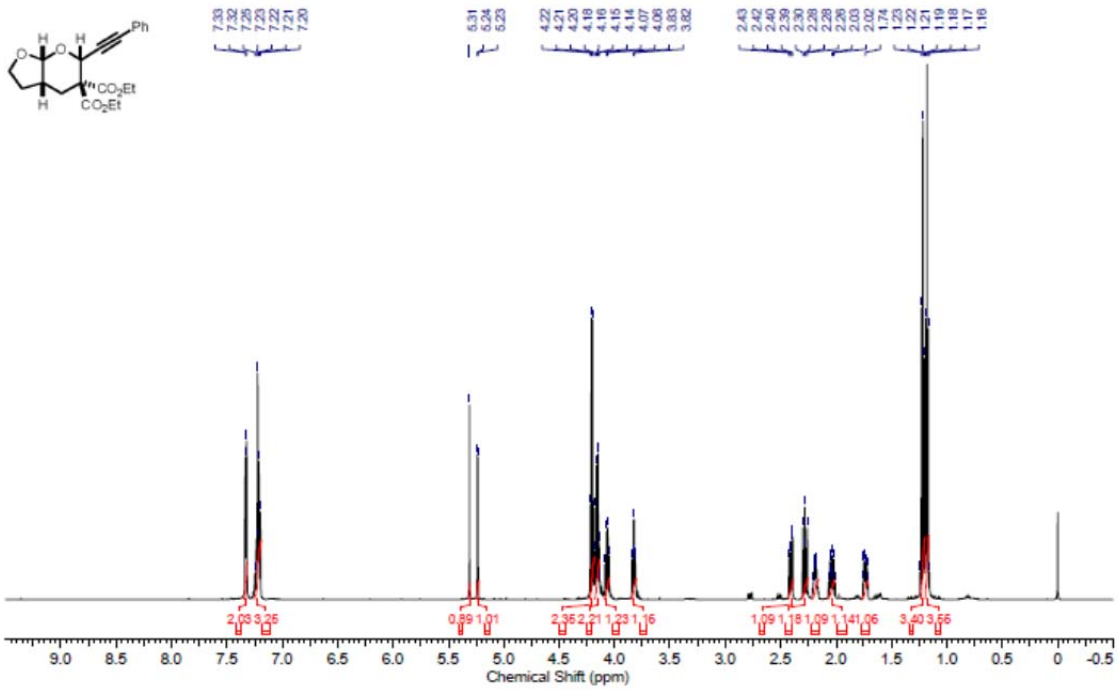
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65e**

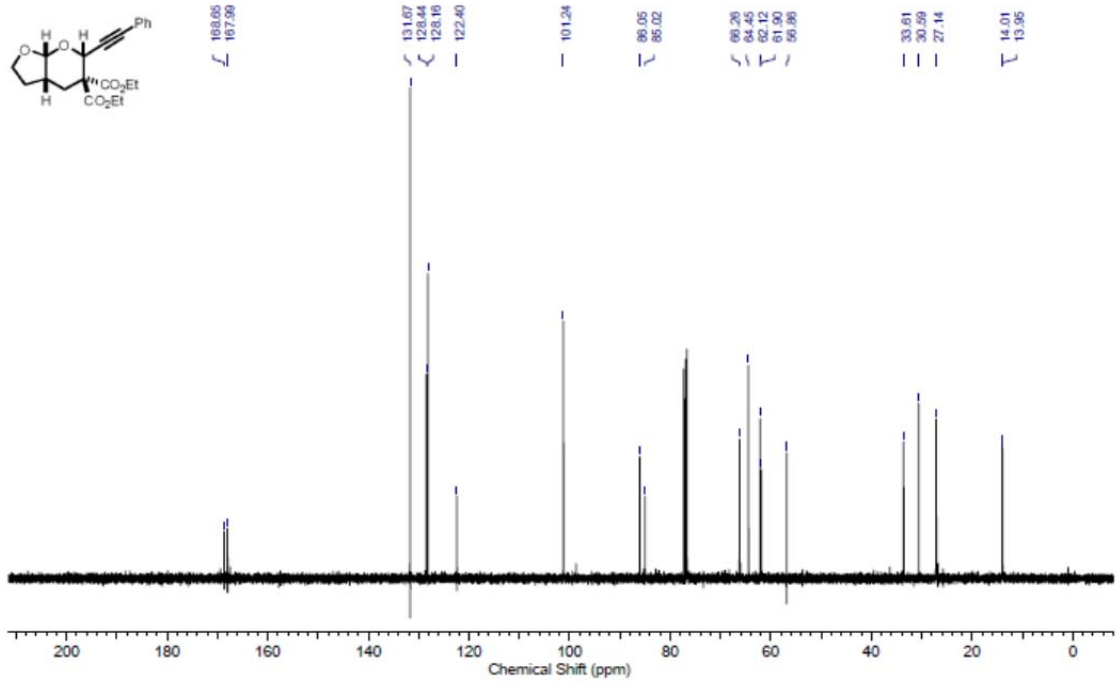


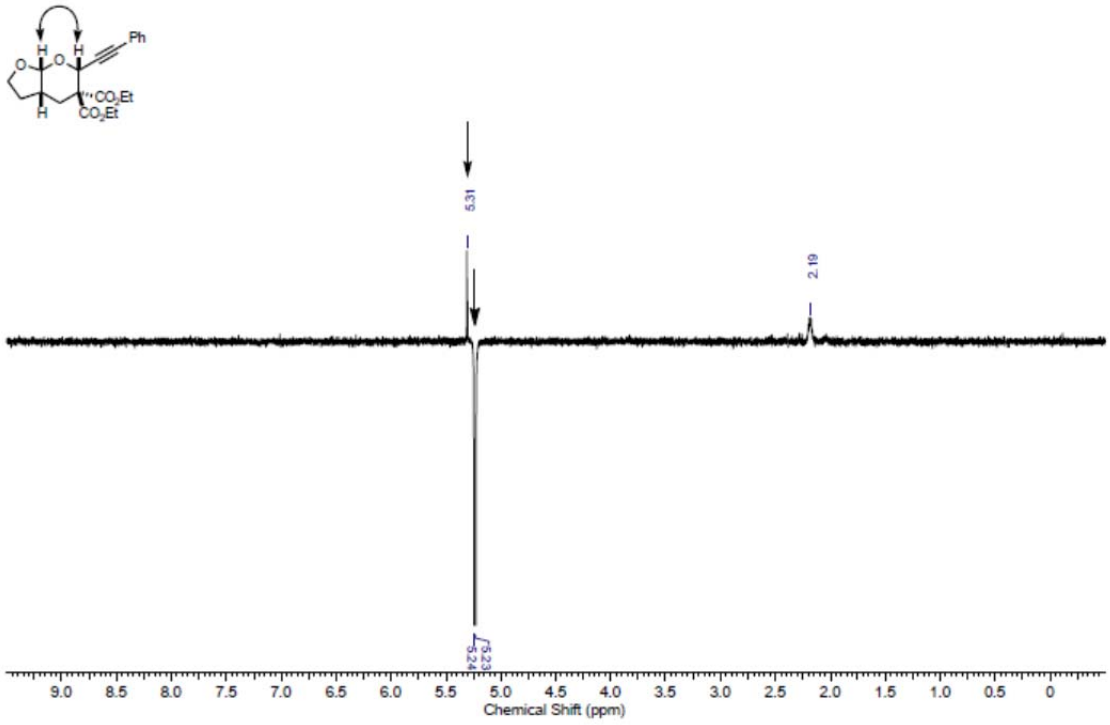

170.86
168.69
147.46
145.57
128.31
122.67
102.72
74.90
67.75
62.24
61.41
59.07
35.92
30.78
30.42
14.00
13.50
NO2
CO2Et
CO2Et
Chemical Shift (ppm)


5.48
1.94
1.93
7.03
7.03
NO2
CO2Et
CO2Et
Chemical Shift (ppm)

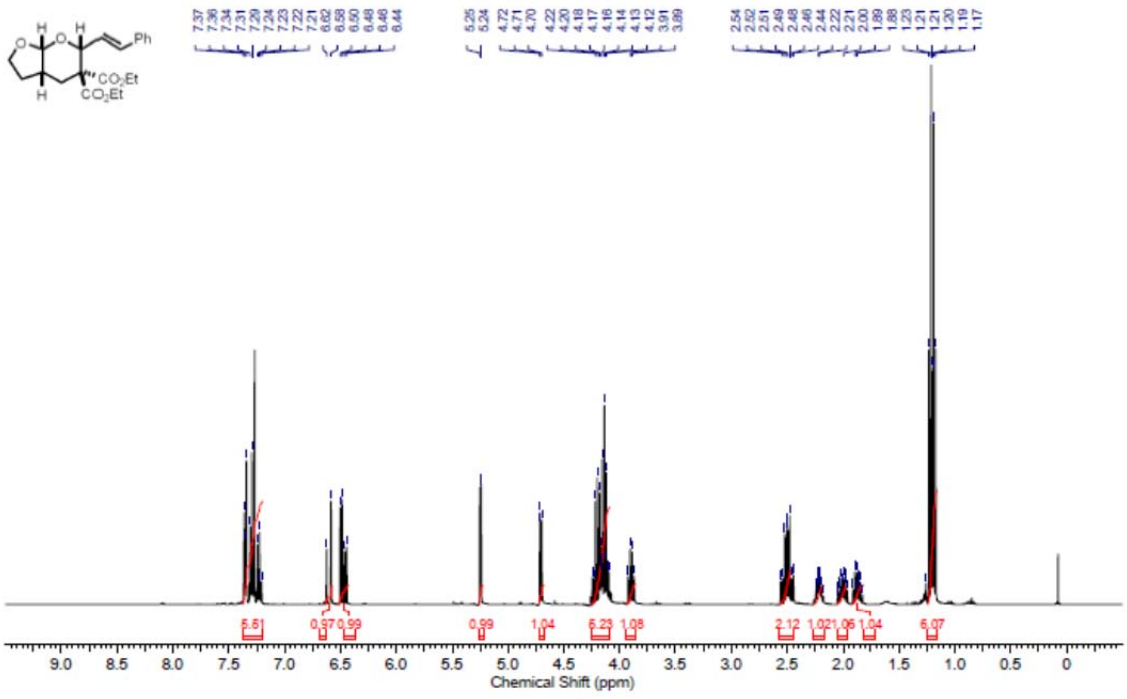
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65g**

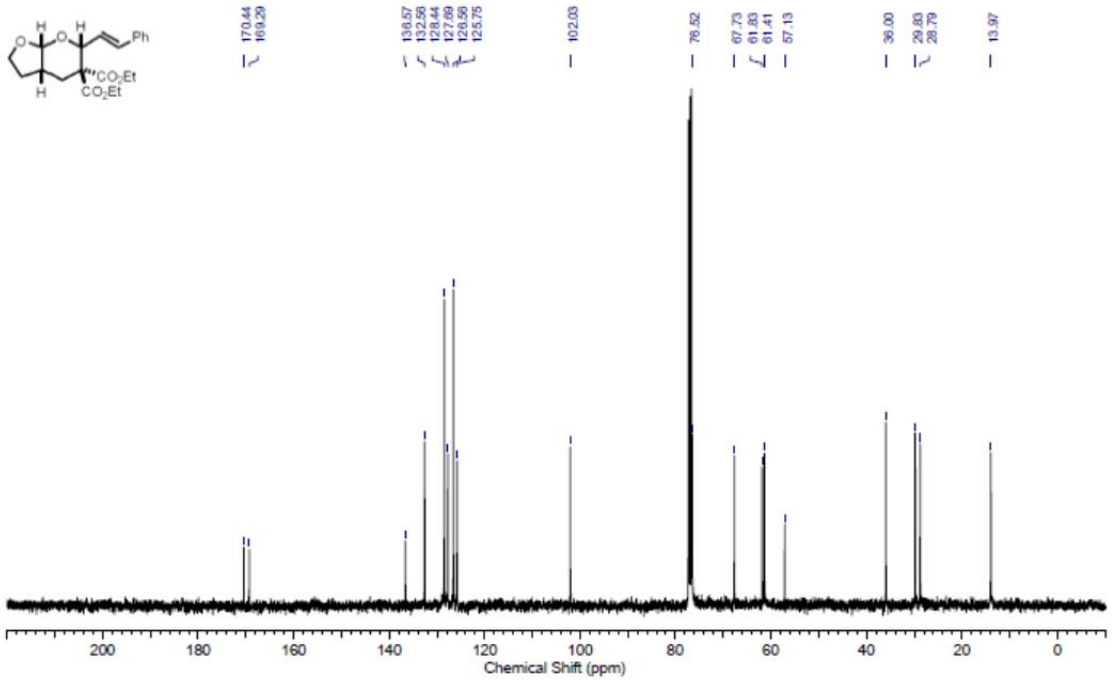


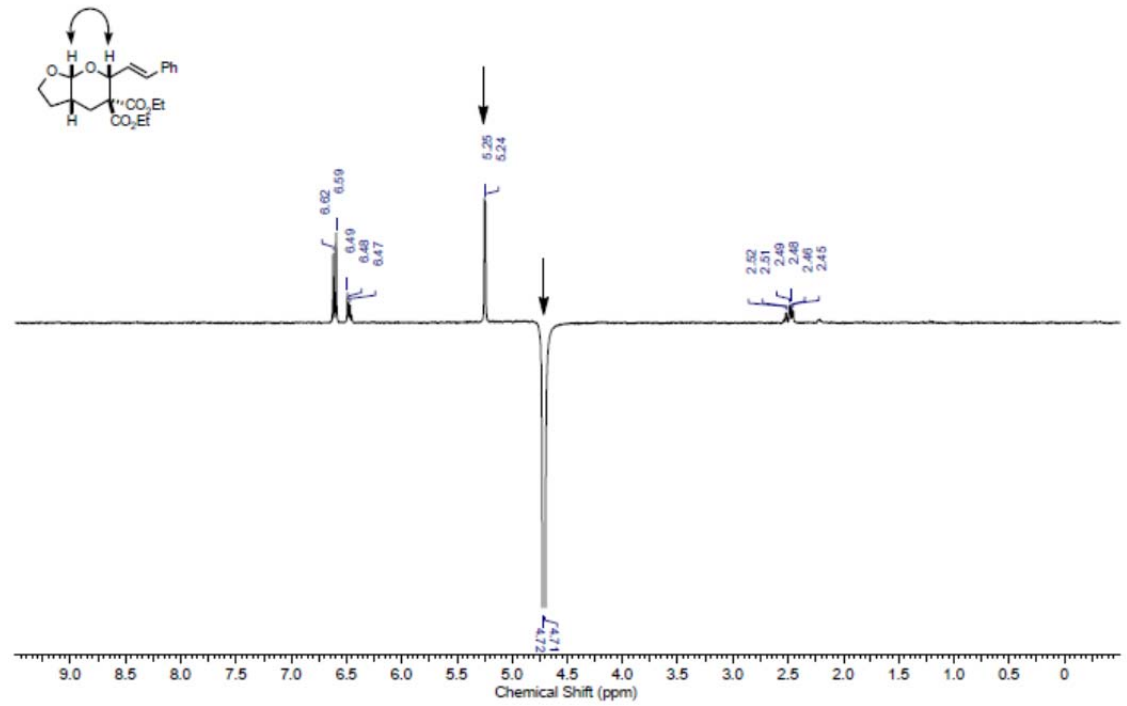




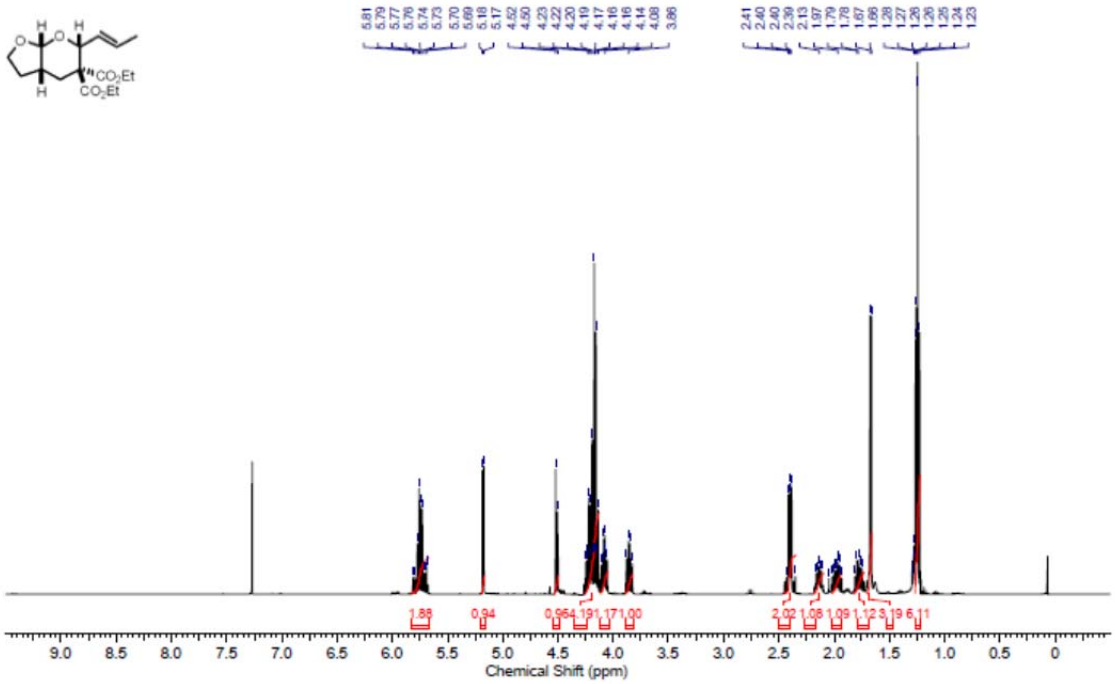
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65h**

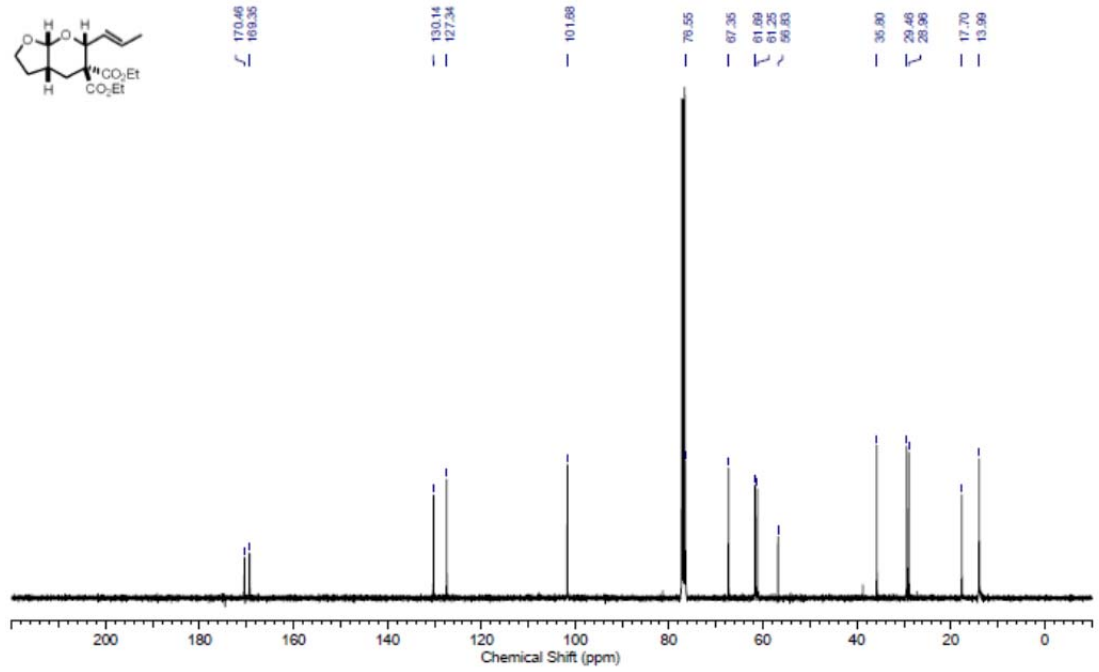


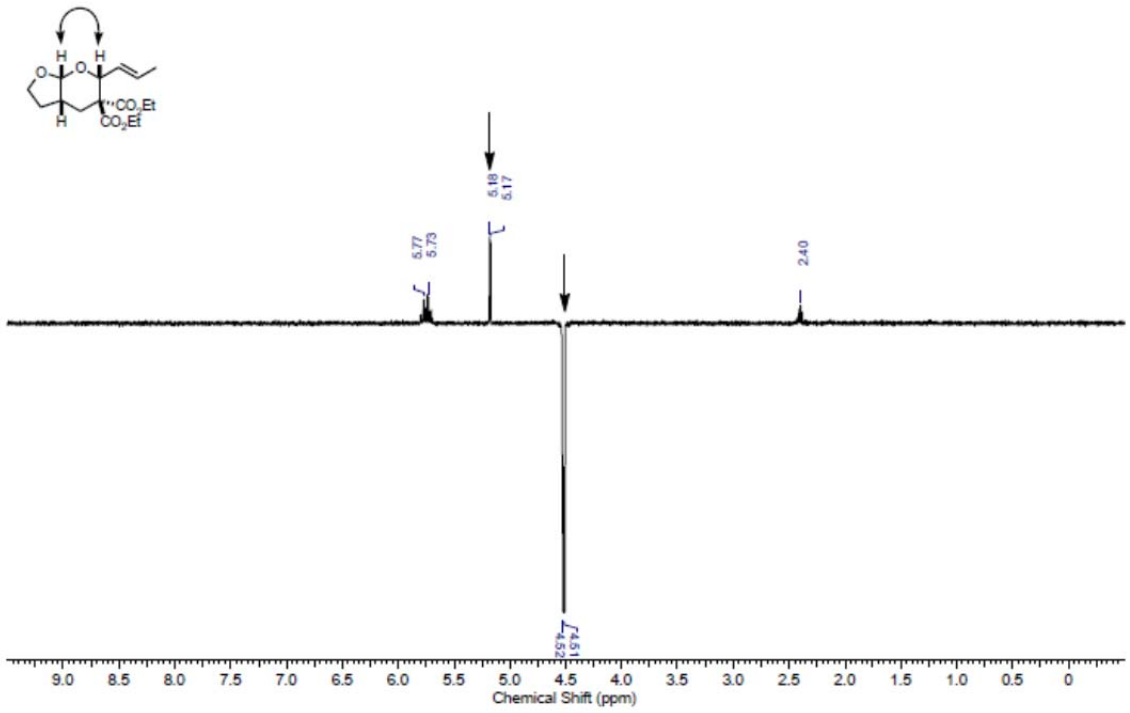

170.44
169.29
136.57
132.56
128.44
127.69
126.56
125.75
102.03
76.52
67.73
61.83
61.41
57.13
36.00
29.83
28.79
13.97
Ph
CO2Et
CO2Et
Chemical Shift (ppm)


Ph
CO2Et
CO2Et
6.62
6.59
6.49
6.48
6.47
5.26
5.24
2.52
2.51
2.49
2.48
2.46
2.45
4.17
Chemical Shift (ppm)

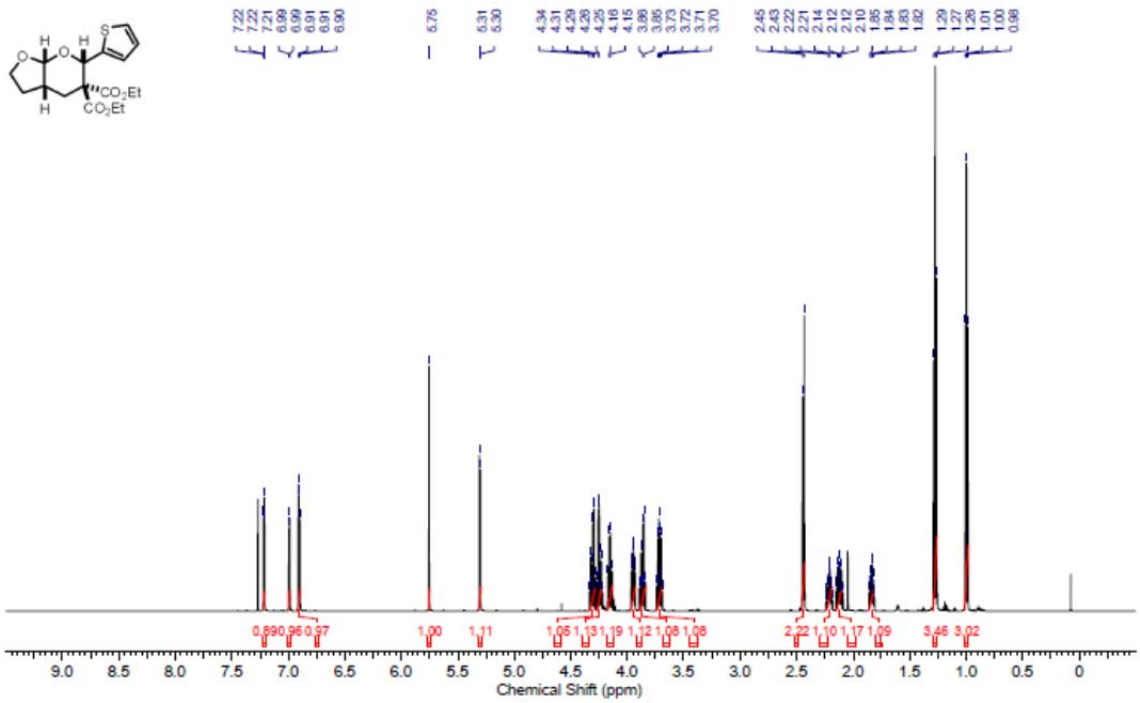
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65i**

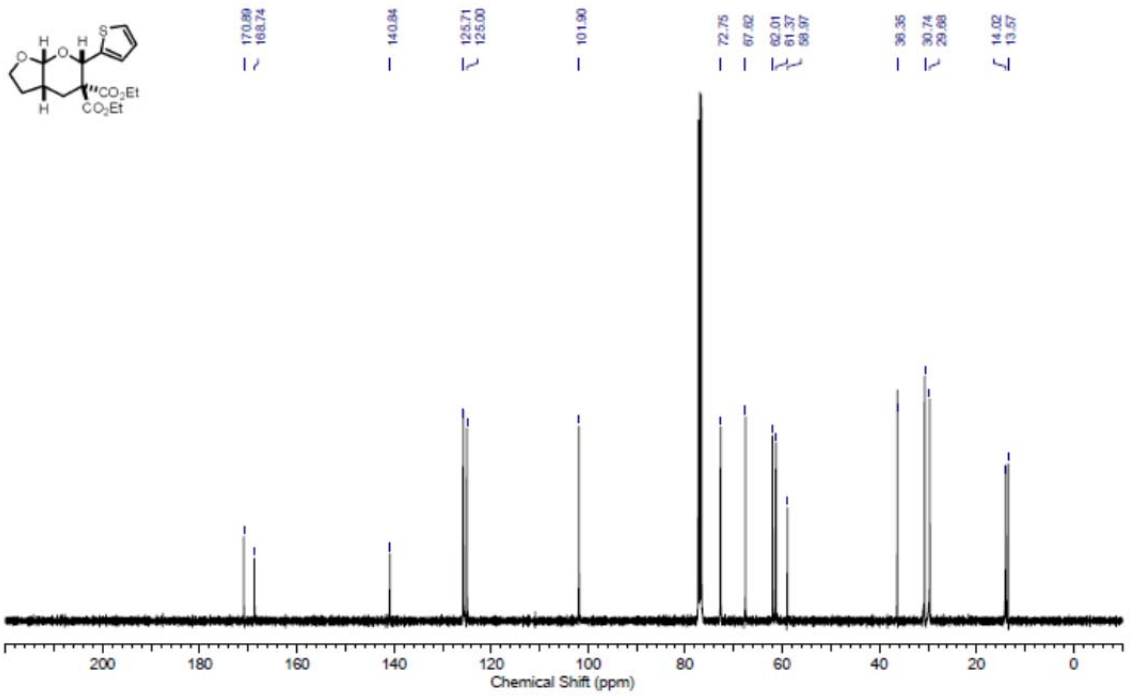


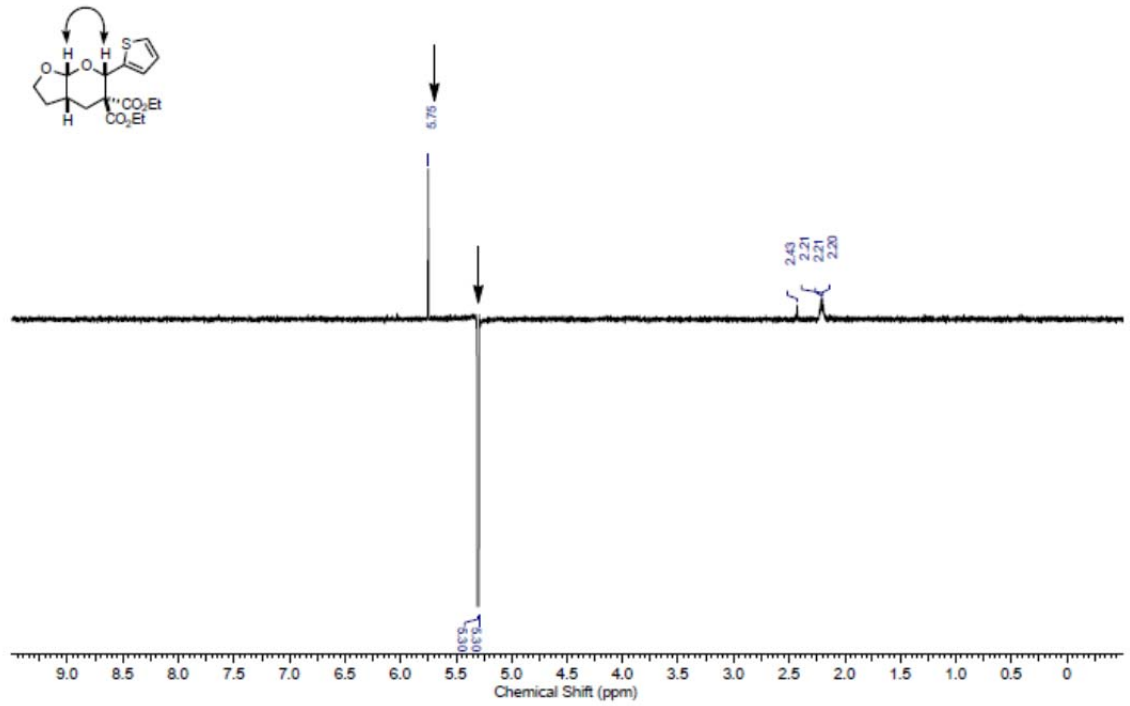




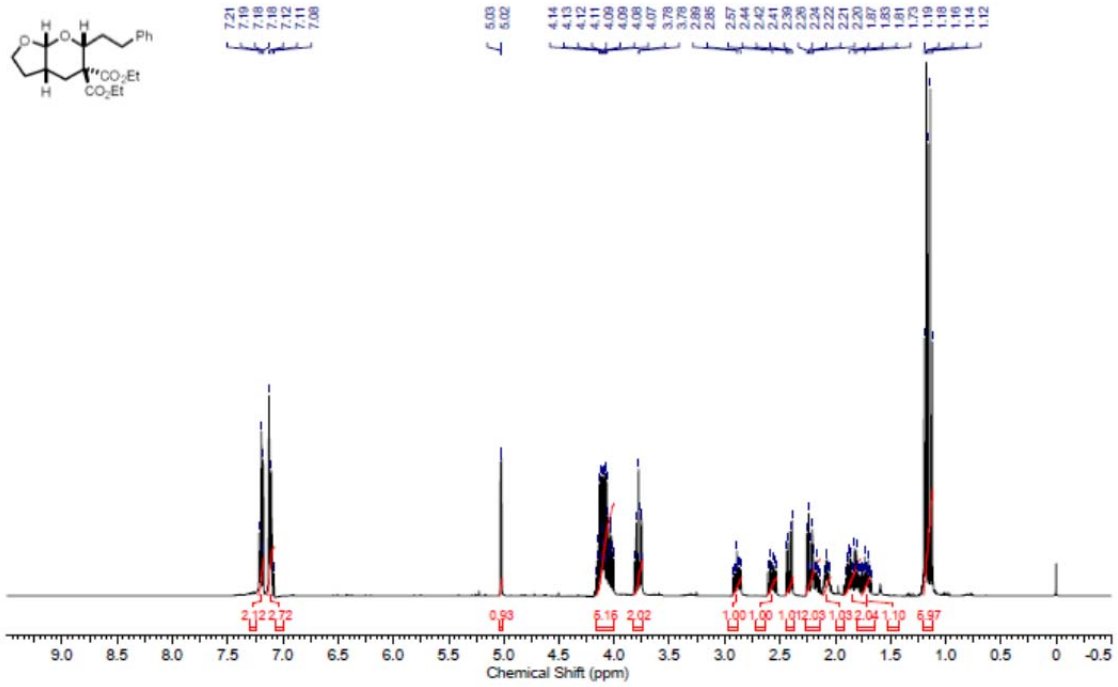
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65k**

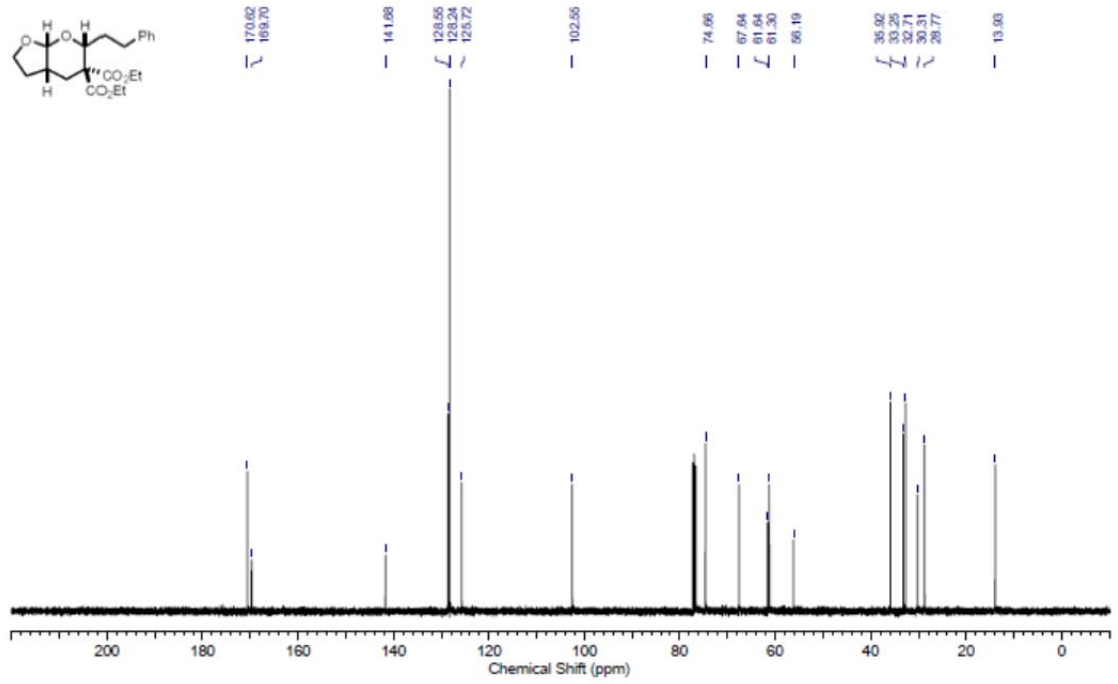


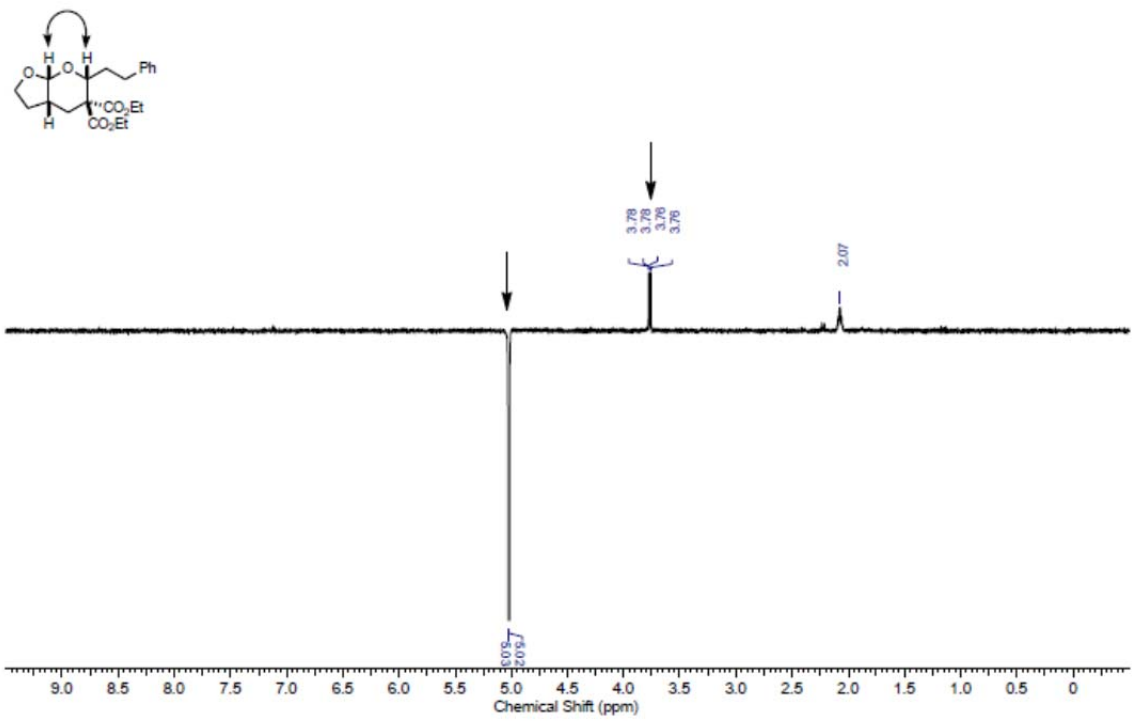

170.89
168.74
140.84
125.71
125.00
101.90
72.75
67.62
62.01
61.37
58.97
36.35
30.74
29.98
14.02
13.57
Chemical Shift (ppm)


5.75
2.43
2.21
2.21
2.20
5.30
5.30
Chemical Shift (ppm)

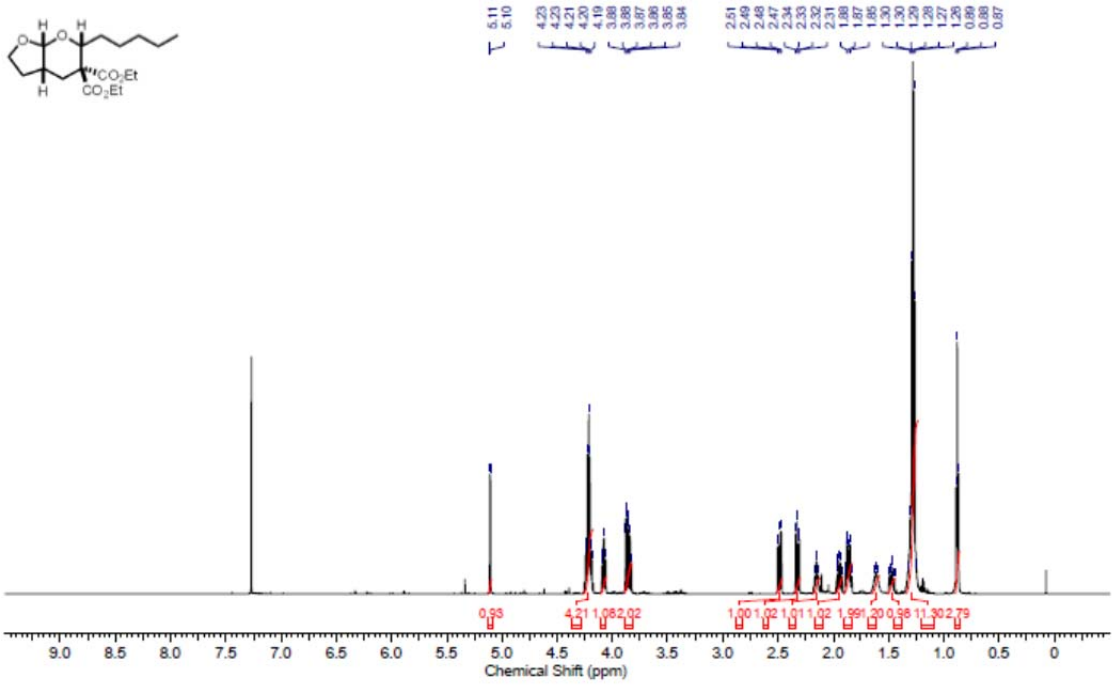
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65m**

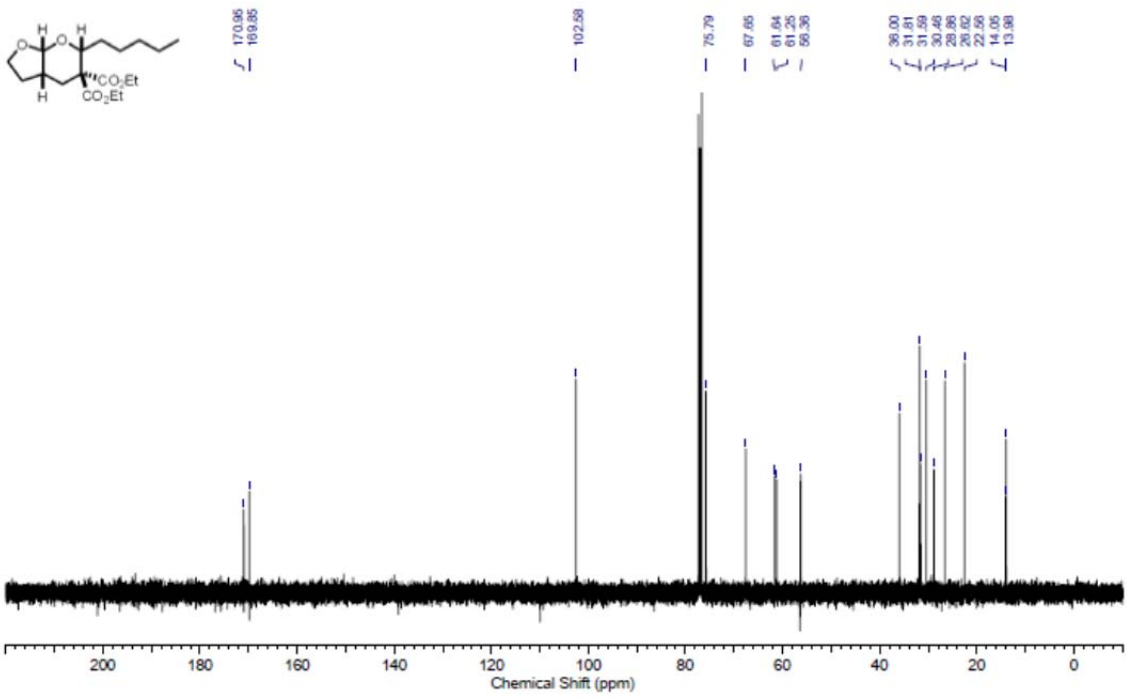


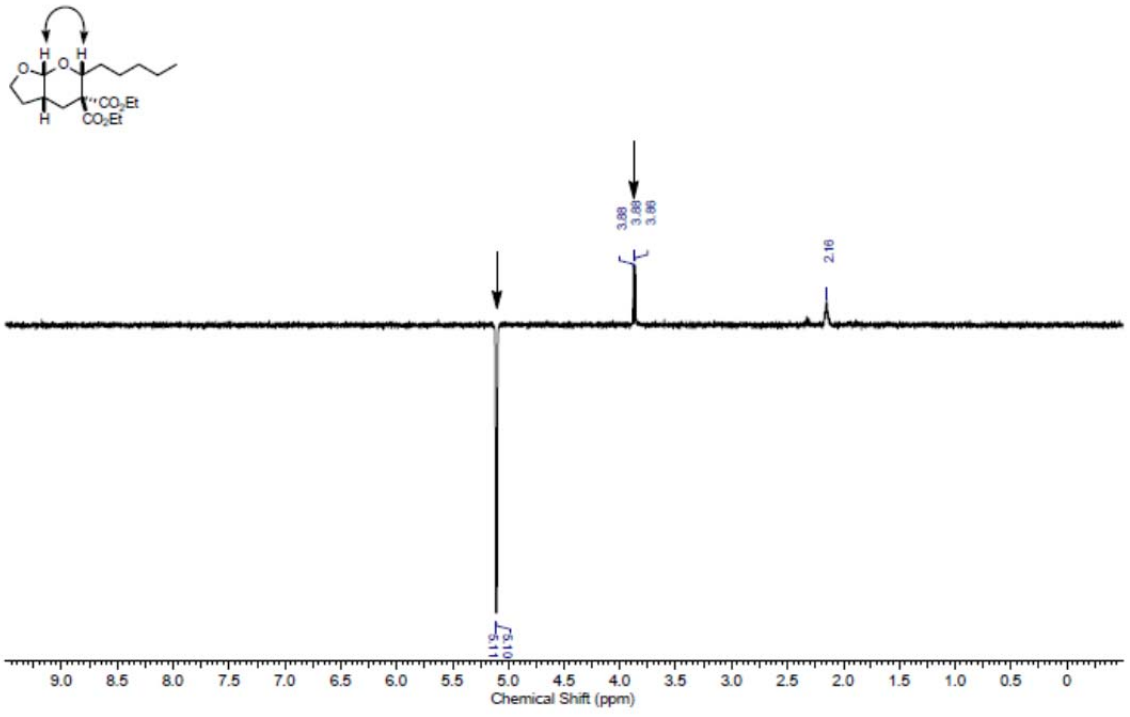




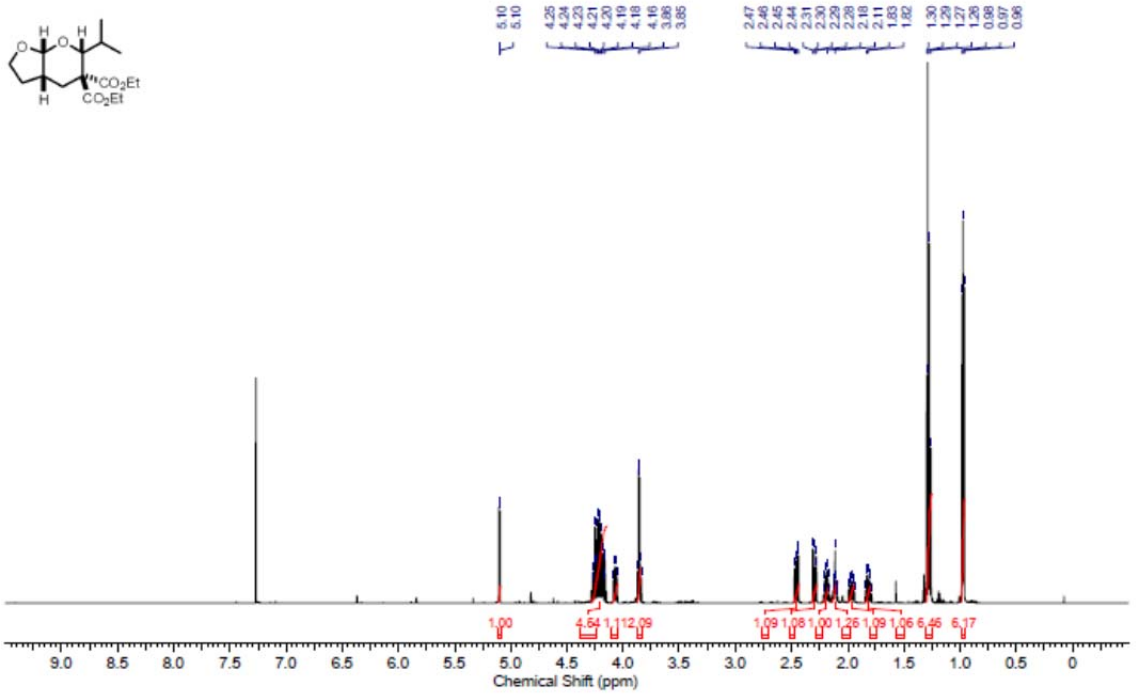
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65n**

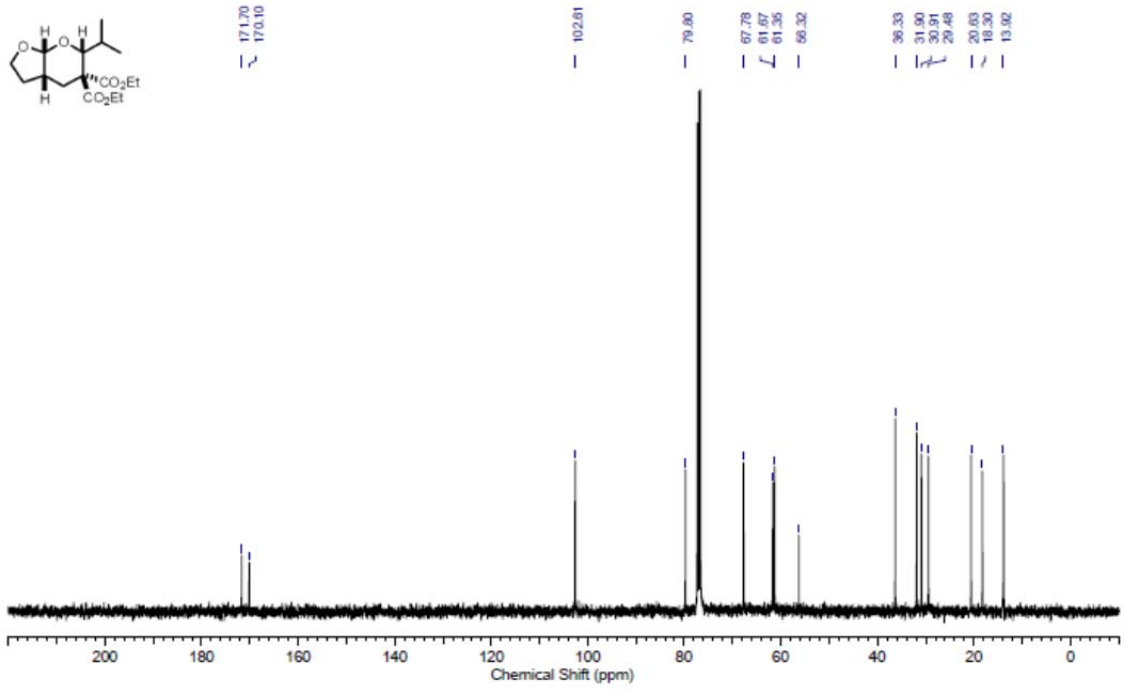


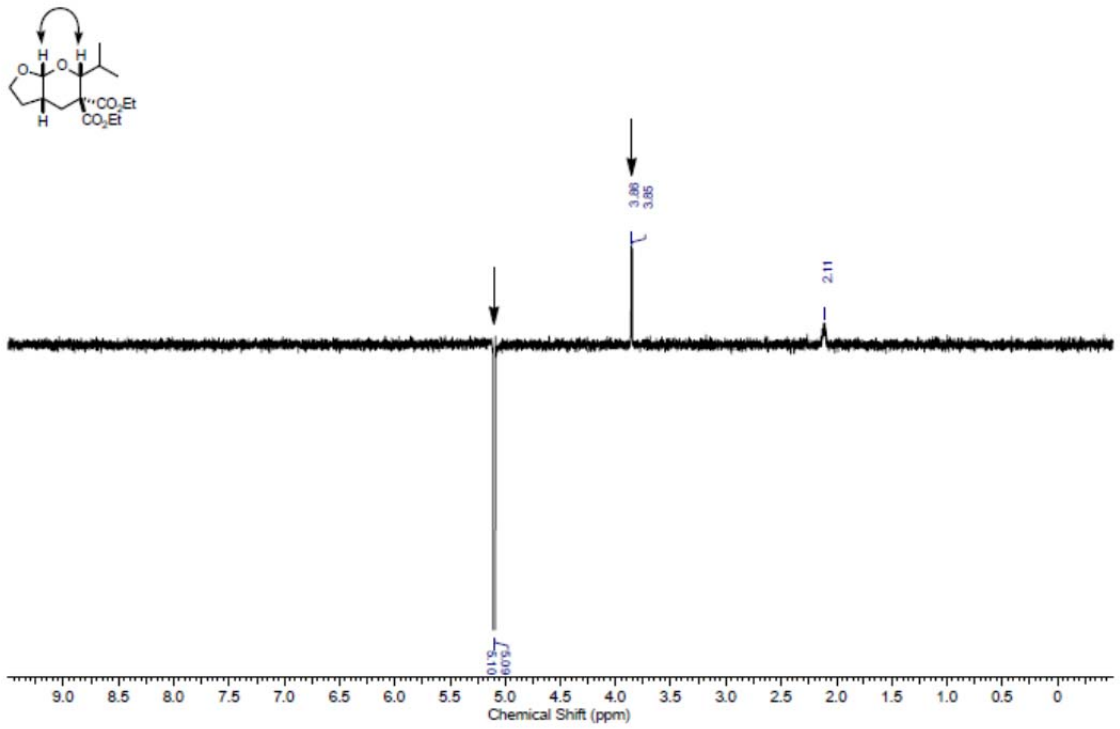

170.96
169.85
102.58
75.79
67.65
61.64
61.25
56.36
36.00
31.81
31.59
30.48
28.86
26.62
22.56
14.05
13.98
CO2Et
CO2Et
Chemical Shift (ppm)


3.88
3.88
3.86
2.16
5.11
5.10
CO2Et
CO2Et
Chemical Shift (ppm)

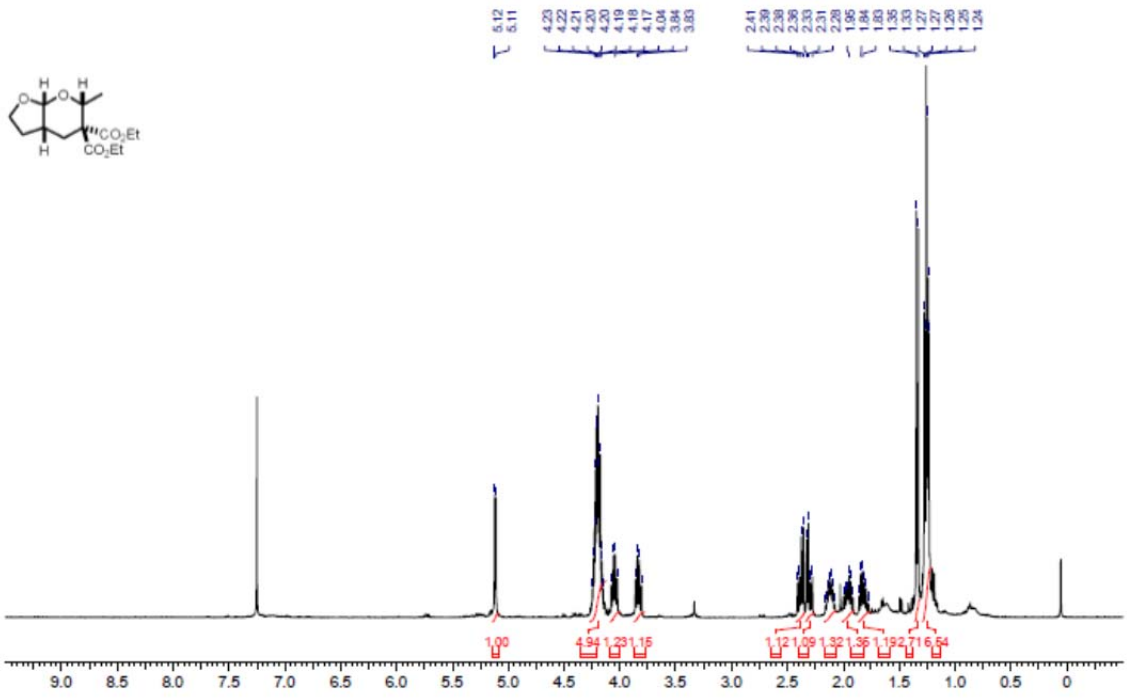
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65o**

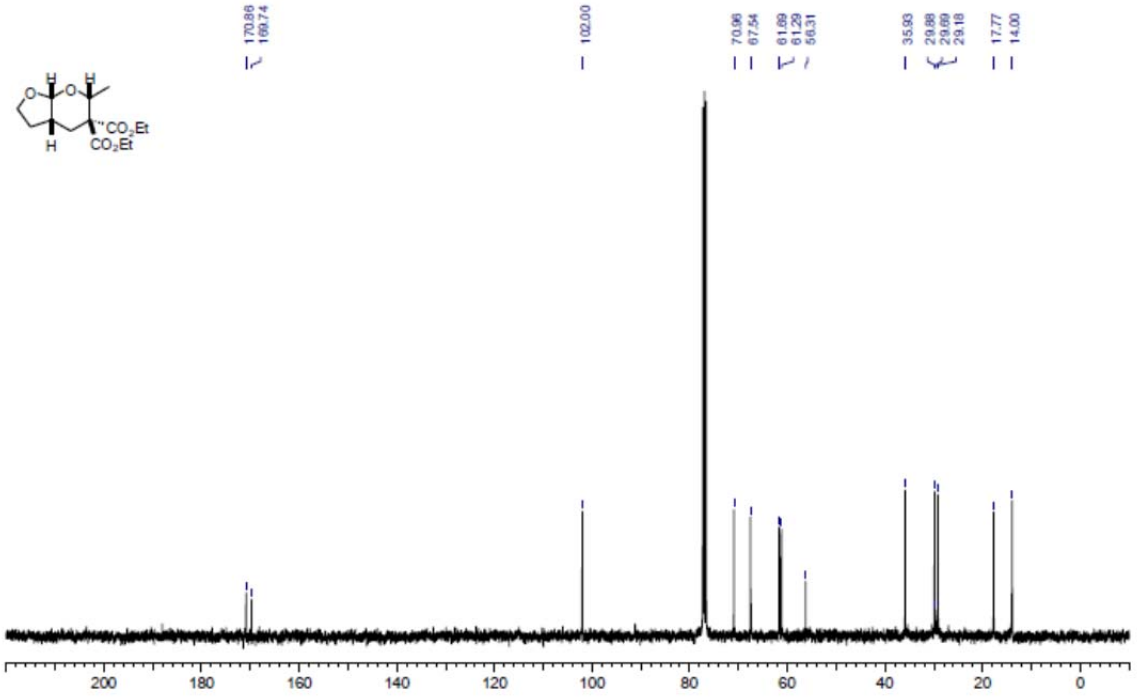


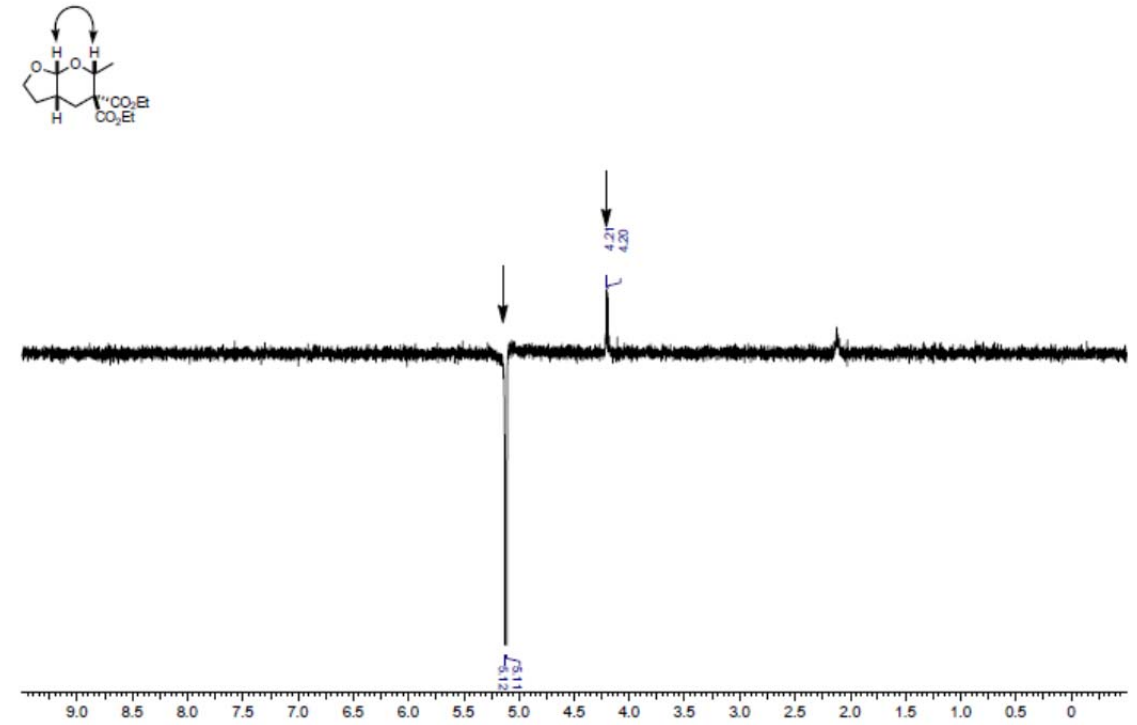




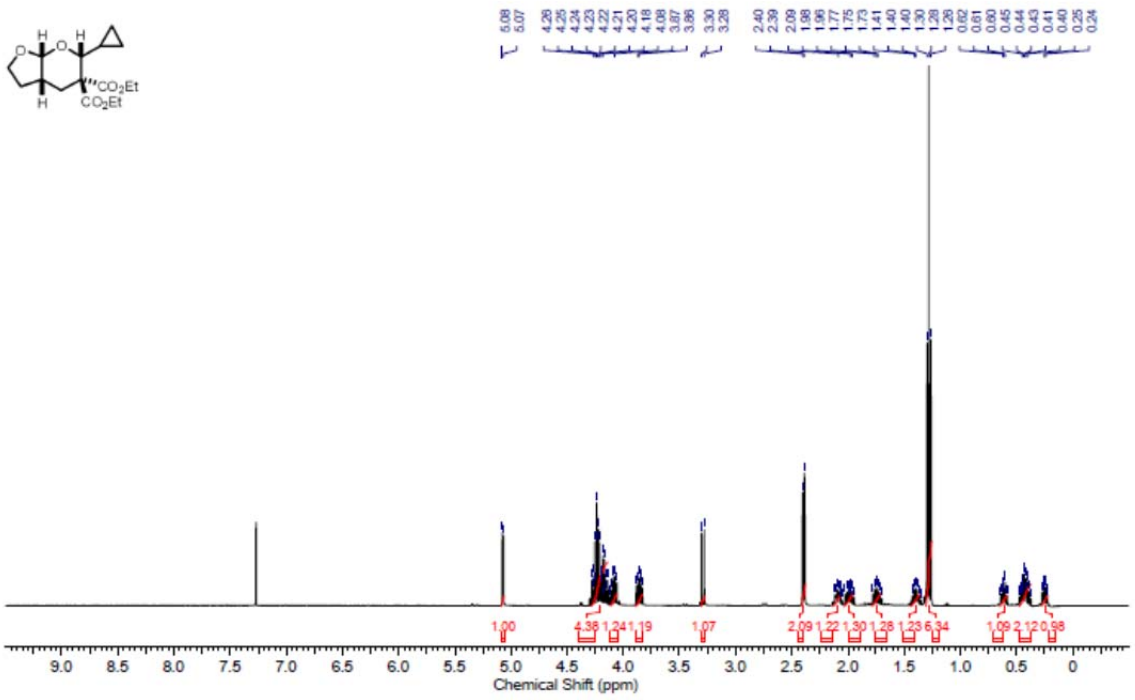
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65p**

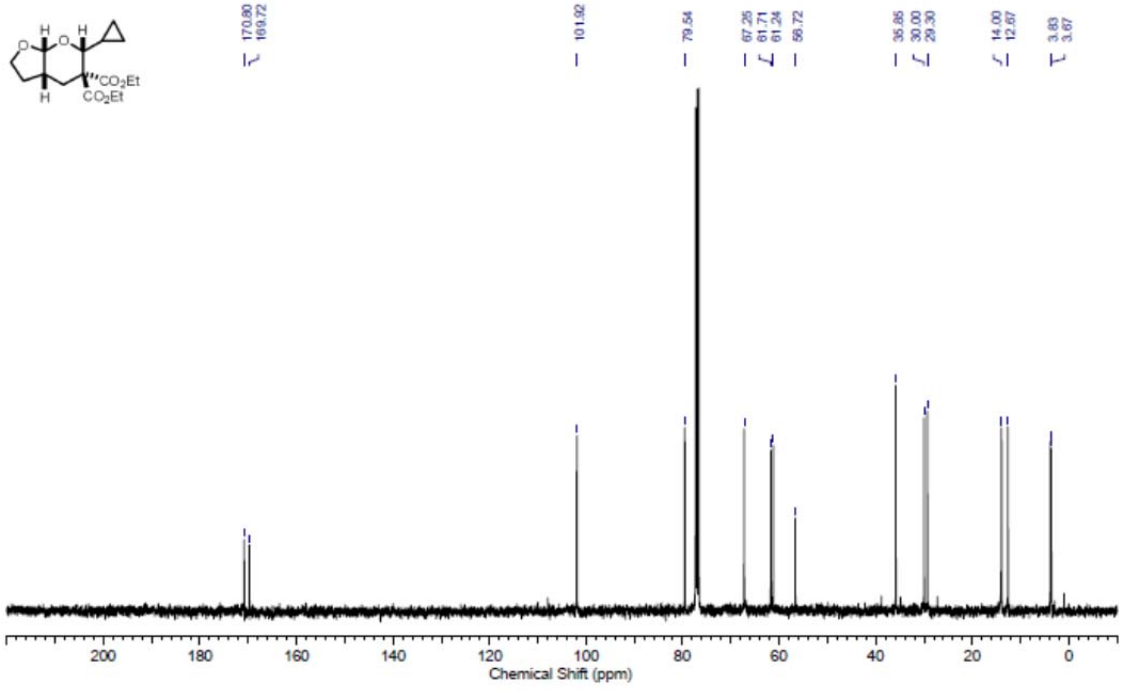


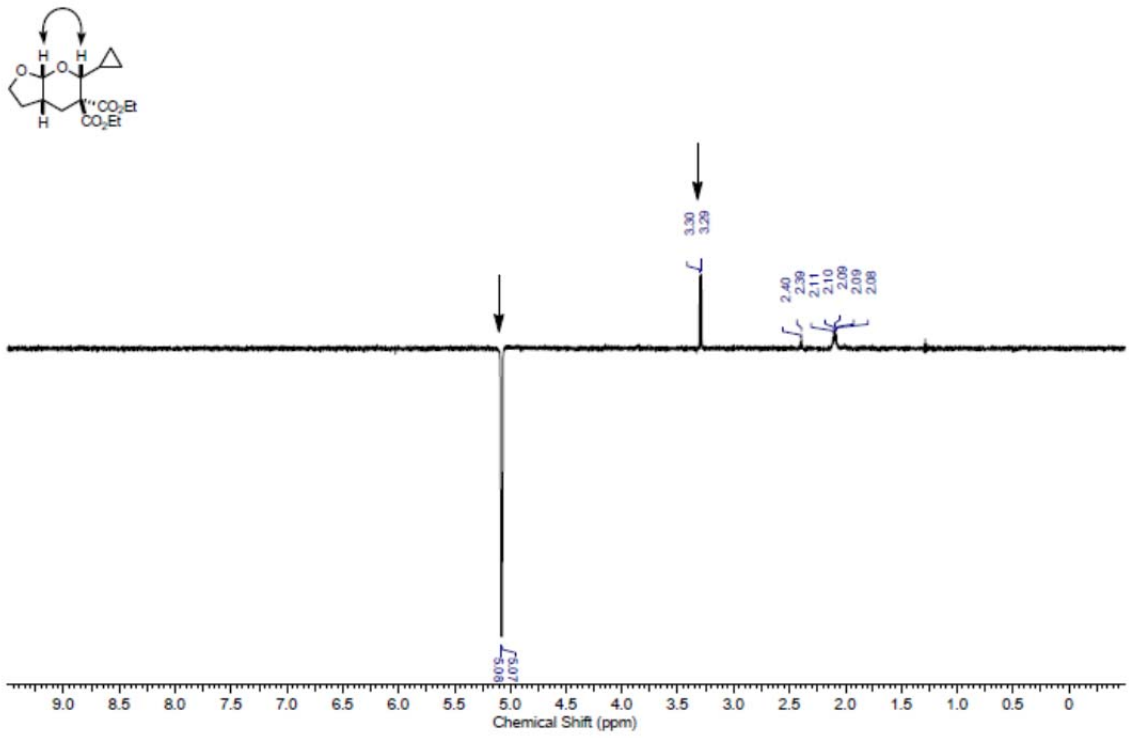

170.86
169.74
102.00
70.96
67.54
61.89
61.29
56.31
35.93
29.88
29.69
29.18
17.77
14.00
CO2Et
CO2Et


4.21
4.20
5.11
5.12
CO2Et
CO2Et

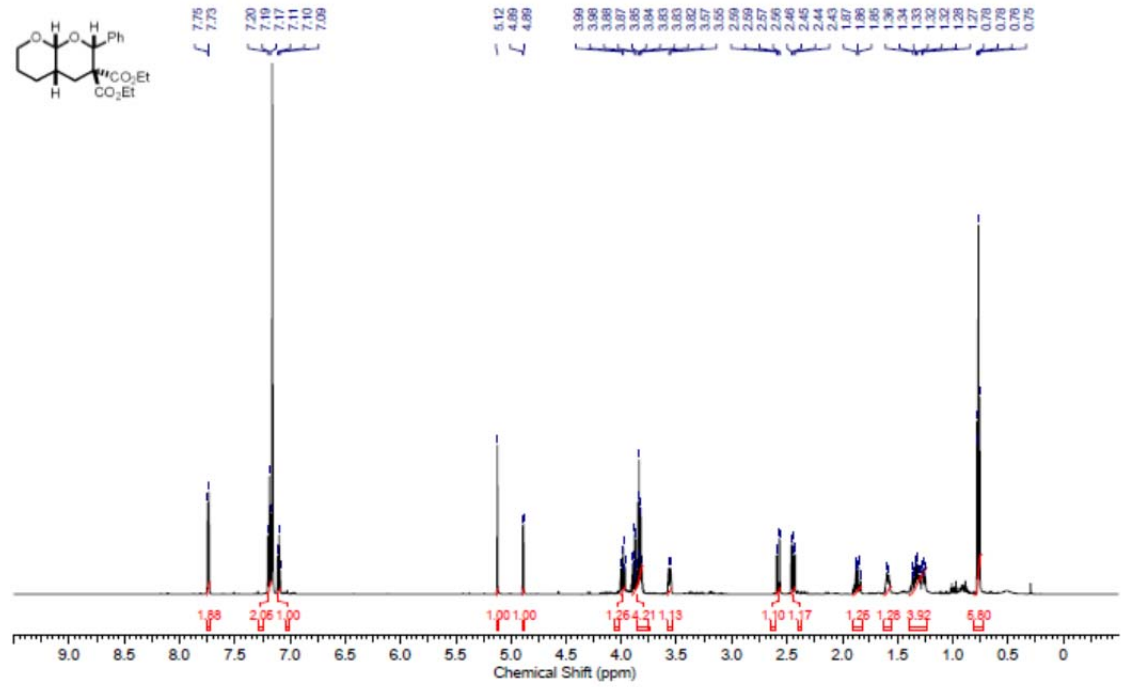
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-65q**

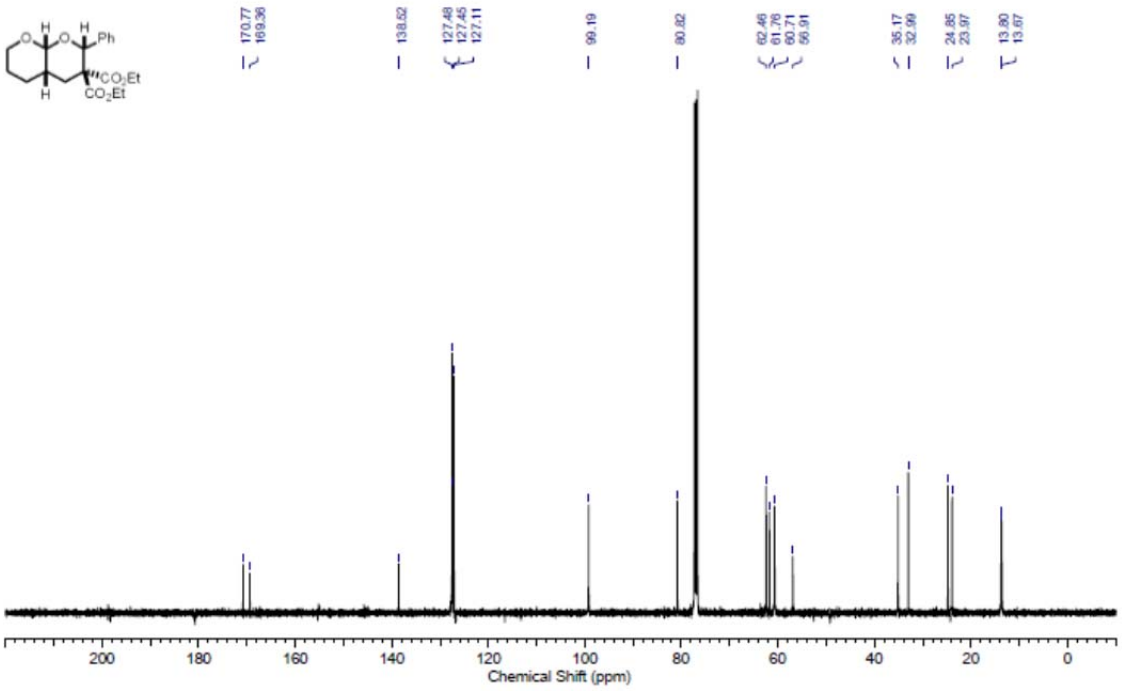


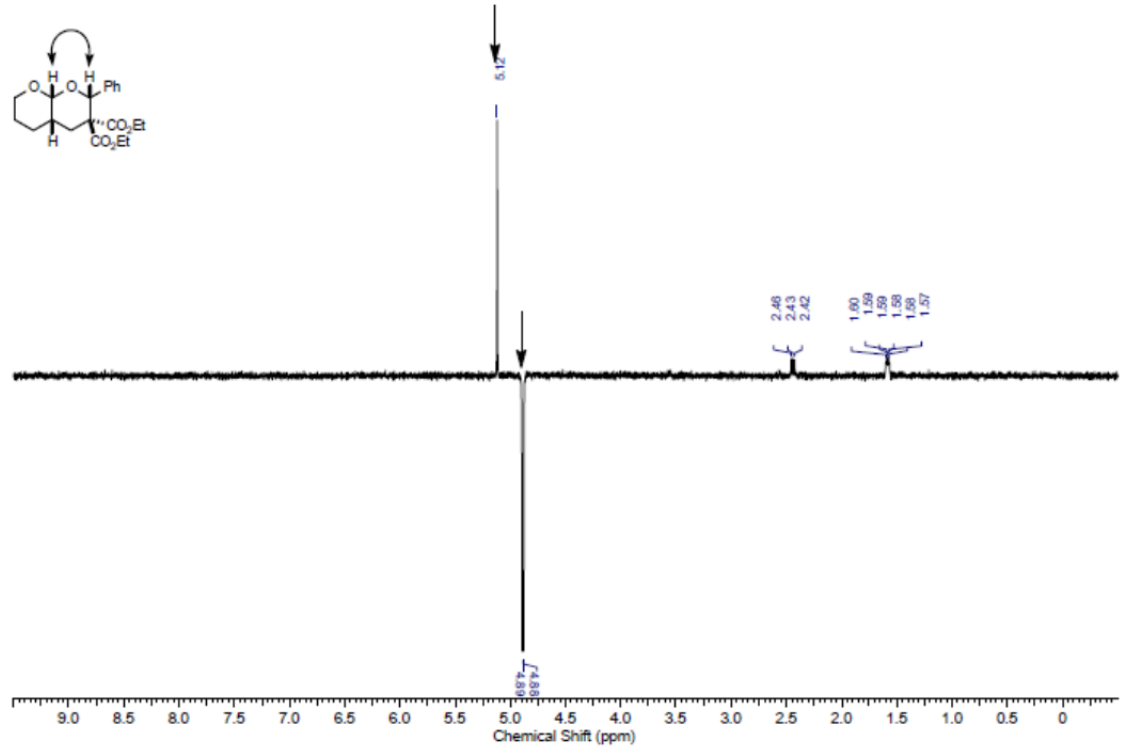




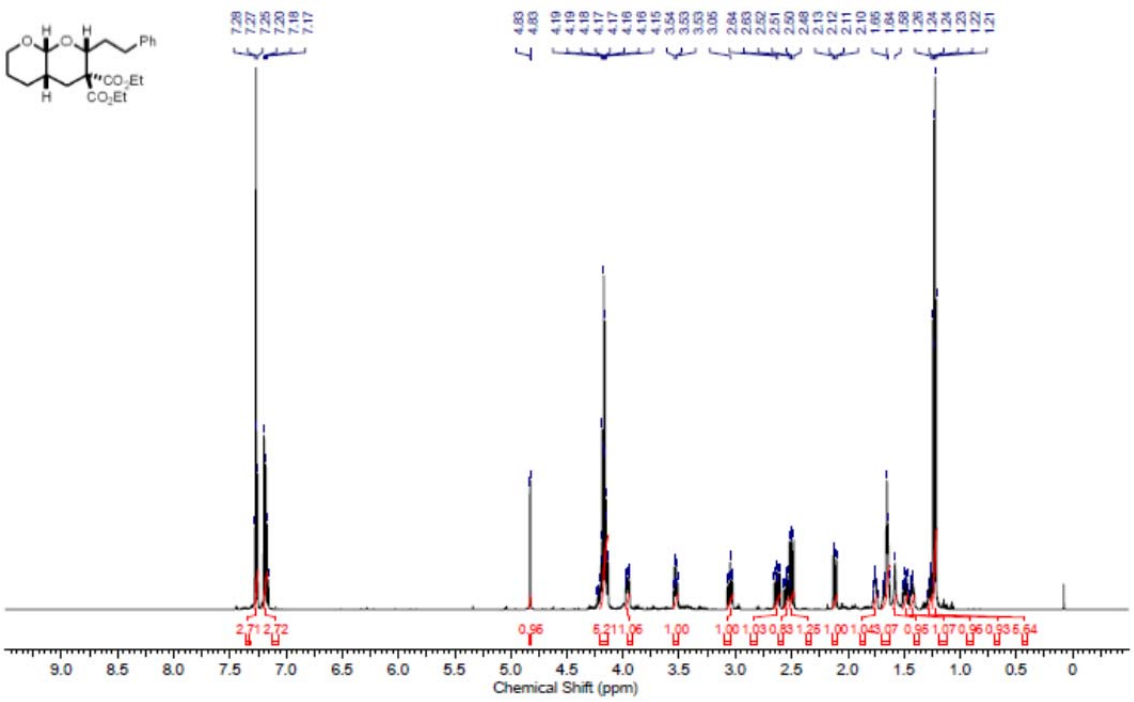
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-66a**

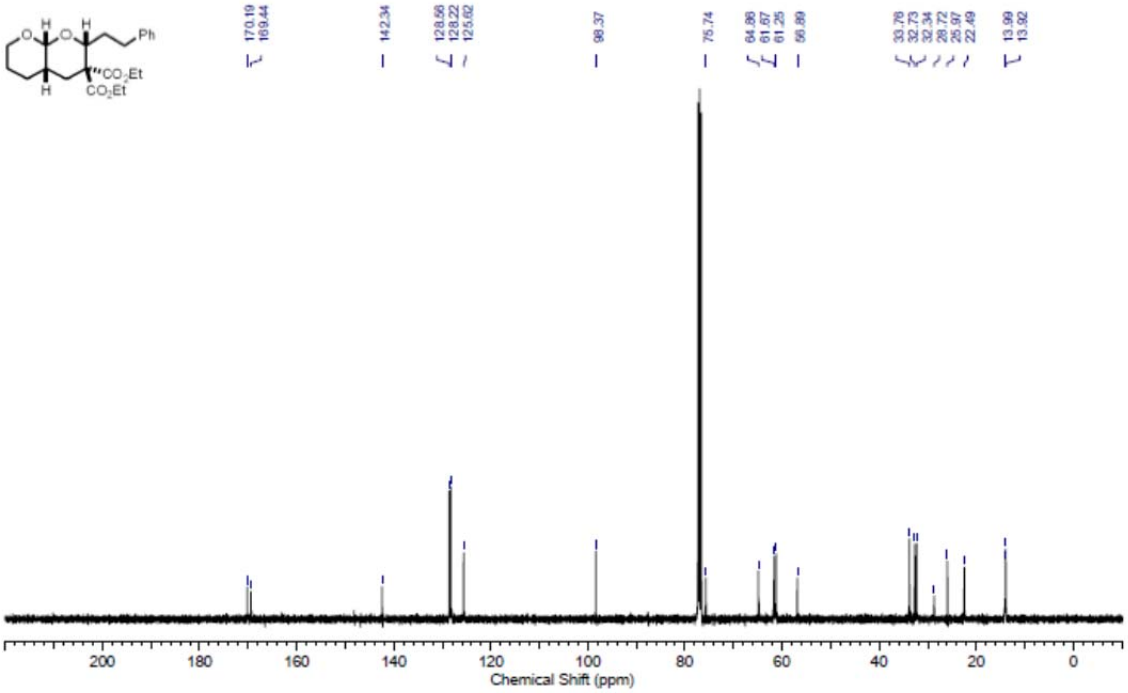


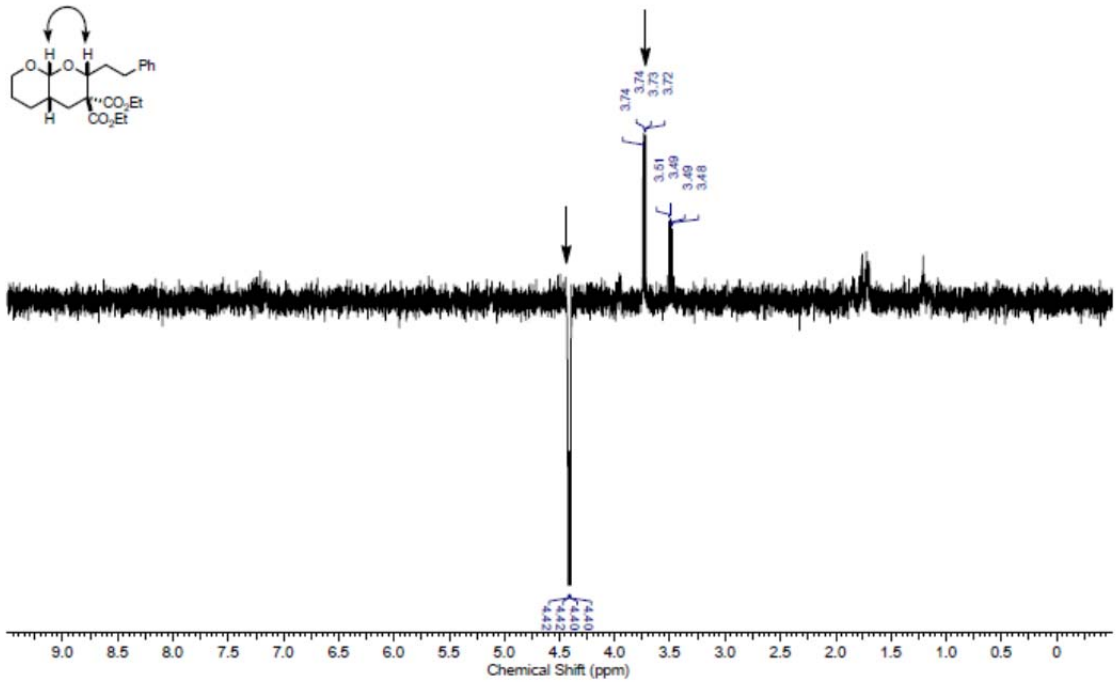

170.77
169.36
138.52
127.48
127.45
127.11
99.19
80.82
62.46
61.76
60.71
56.91
35.17
32.99
24.85
23.97
13.80
13.67
Ph
CO2Et
CO2Et
Chemical Shift (ppm)


5.12
2.46
2.43
2.42
1.60
1.59
1.59
1.58
1.58
1.57
4.89
Ph
CO2Et
CO2Et
Chemical Shift (ppm)

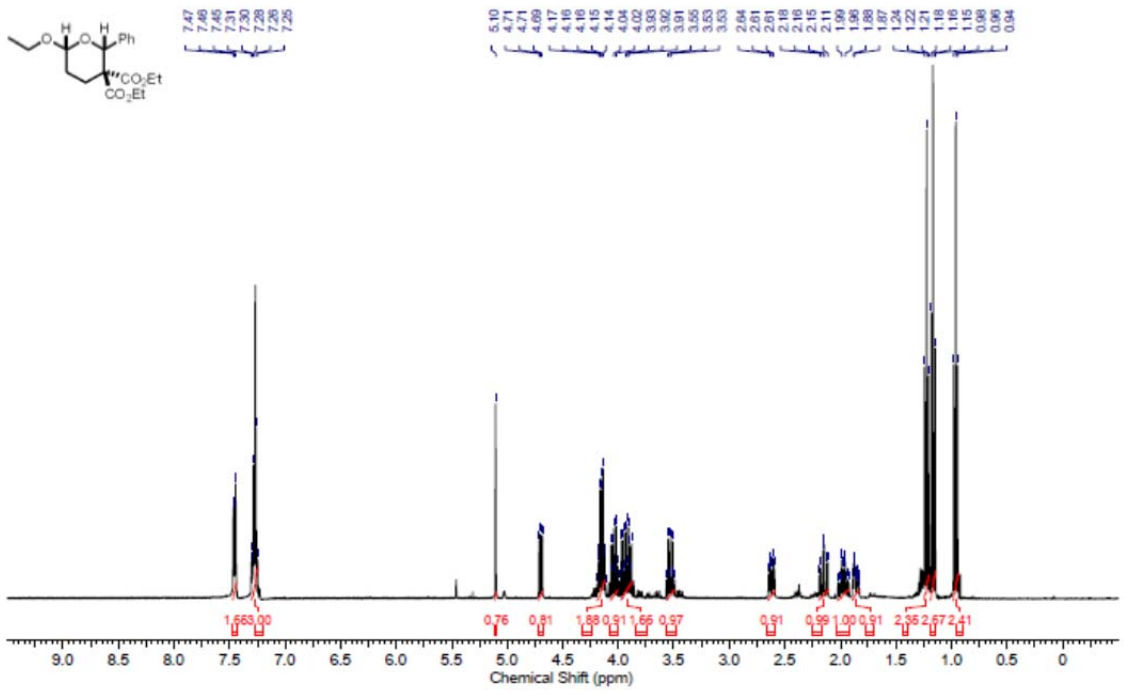
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-66b**

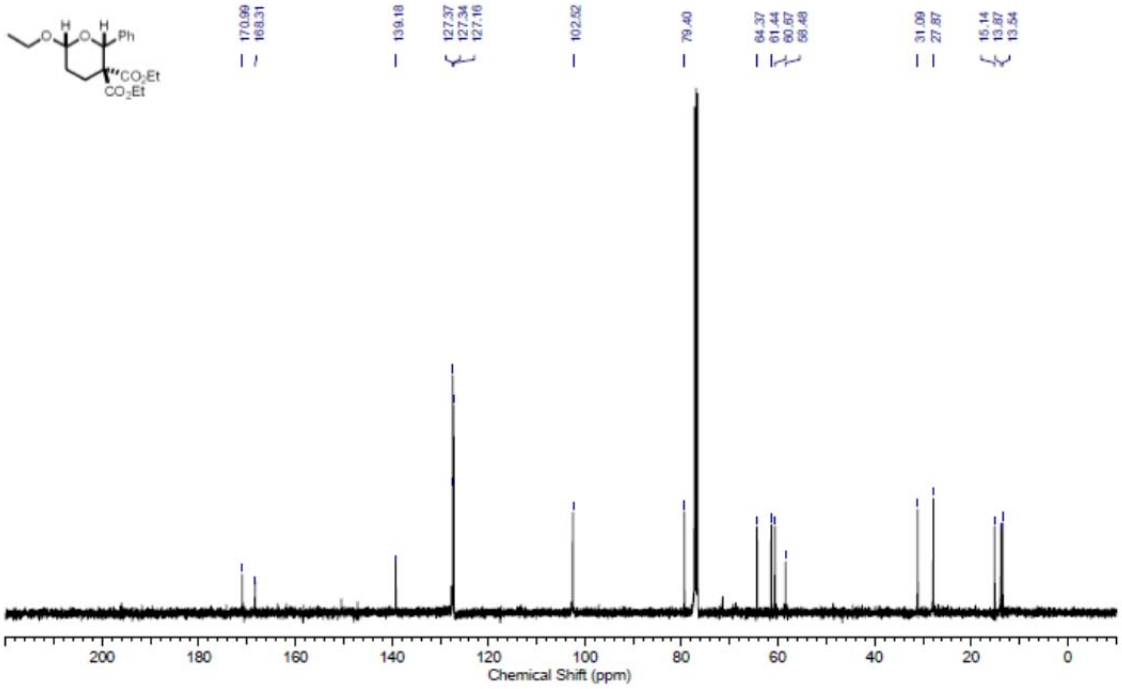


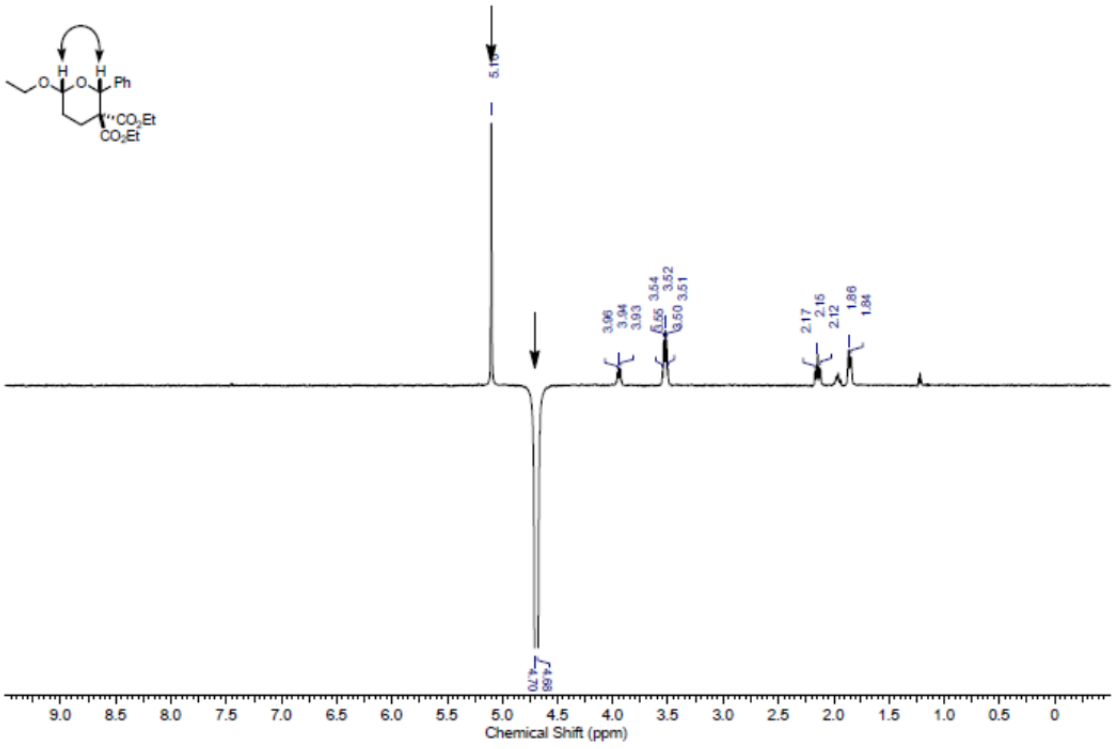




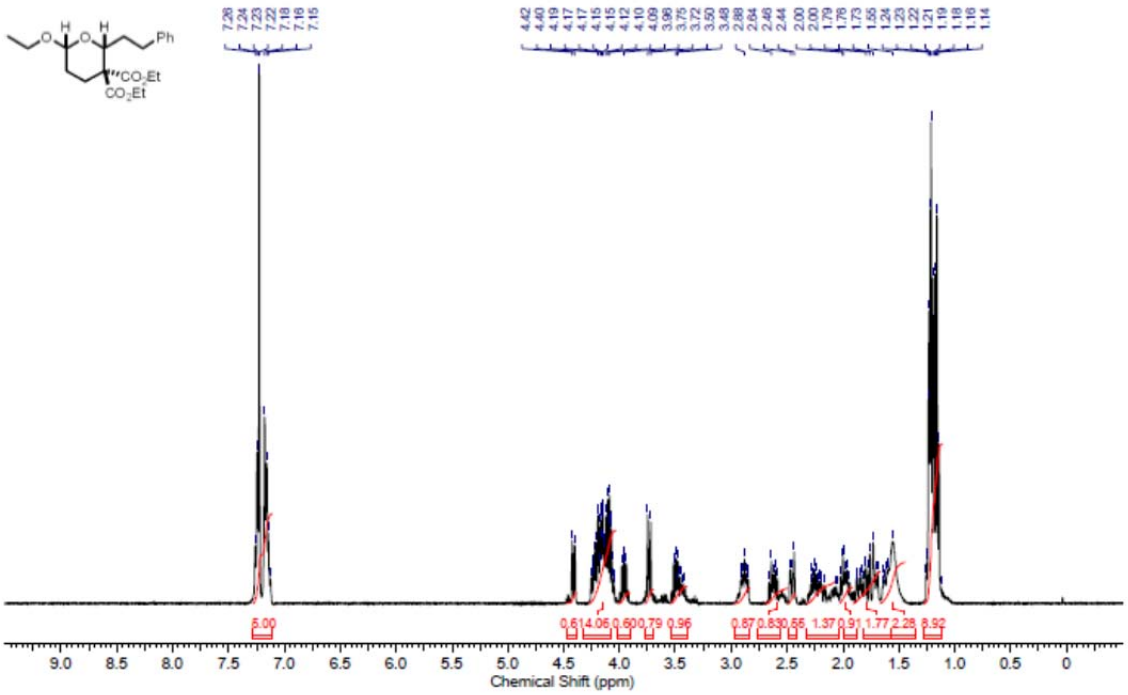
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-67a**

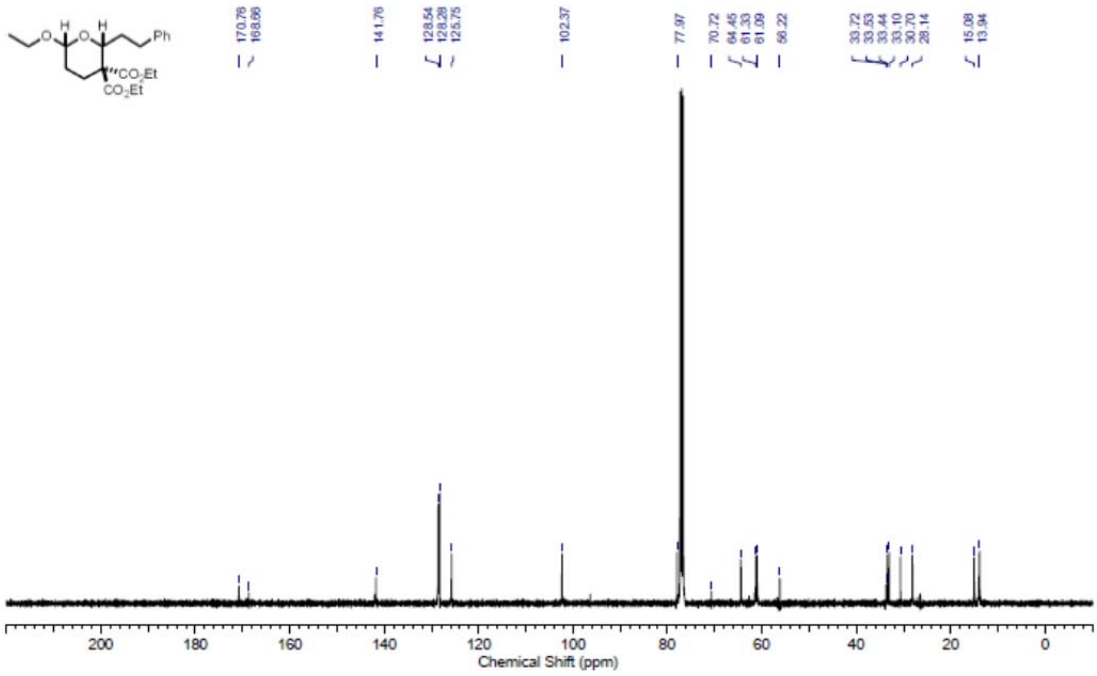


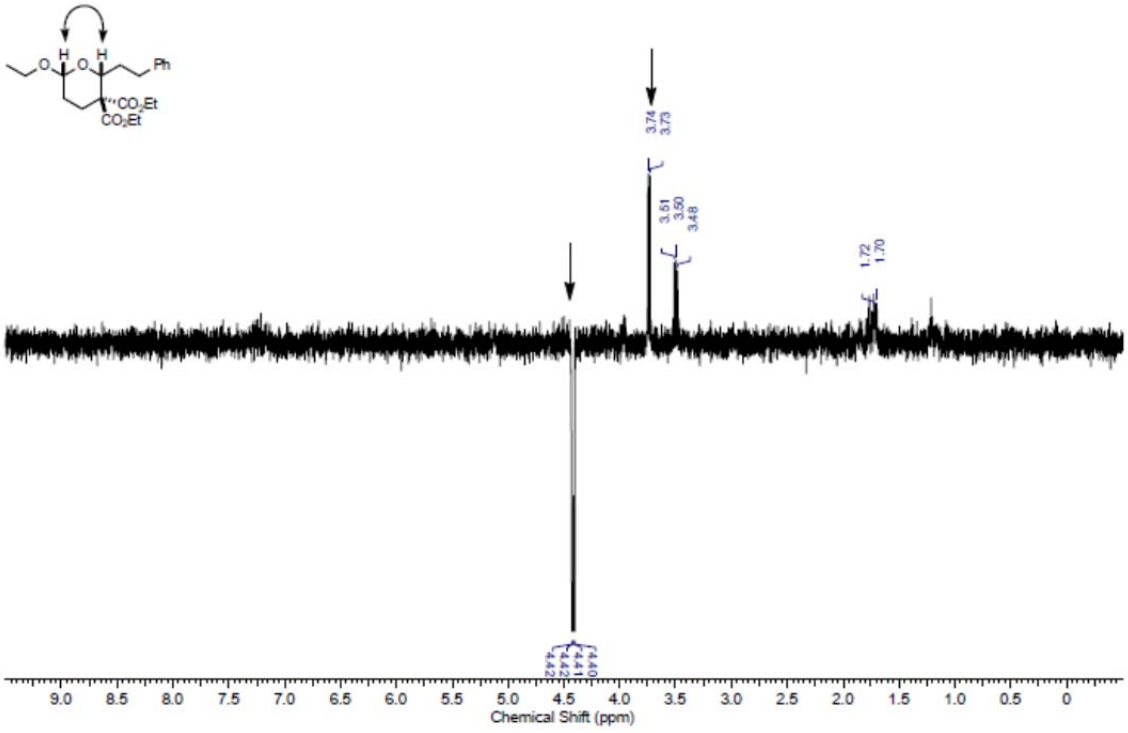

170.99
168.31
139.18
127.37
127.34
127.16
102.52
79.40
64.37
61.44
60.67
58.49
31.09
27.87
15.14
13.87
13.54
Chemical Shift (ppm)


5.19
3.96
3.94
3.93
3.54
3.52
3.51
2.17
2.15
2.12
1.86
1.84
4.70
4.68
Chemical Shift (ppm)

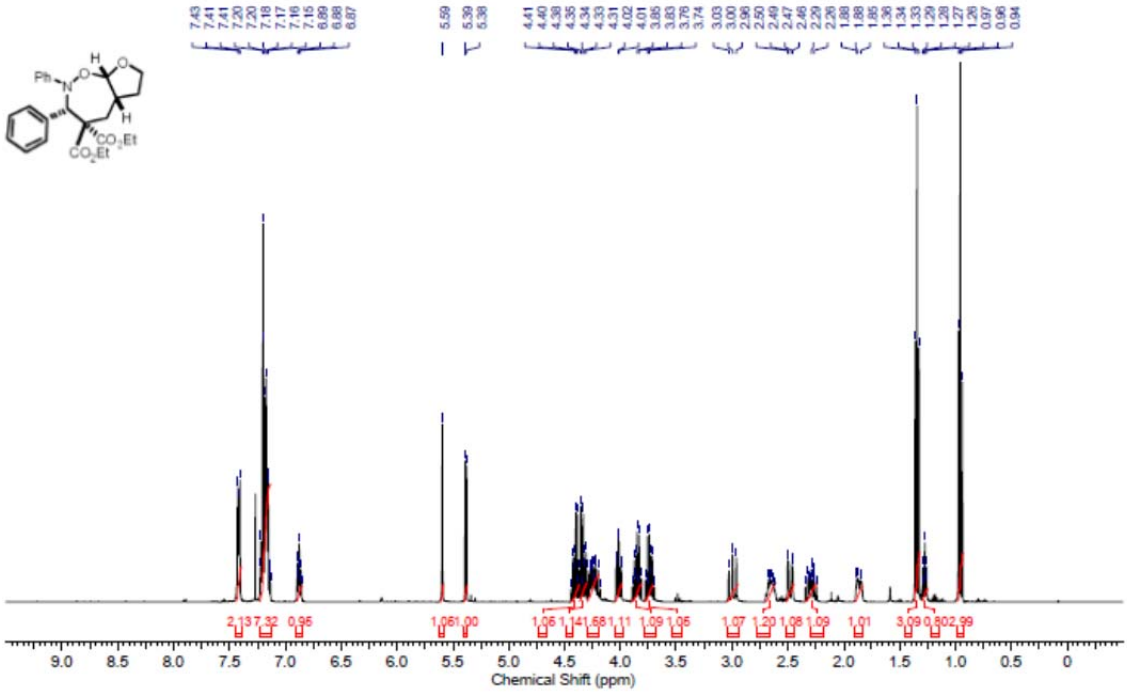
^{1}H, ^{13}C NMR, and 1D nOe of compound **2-67b**

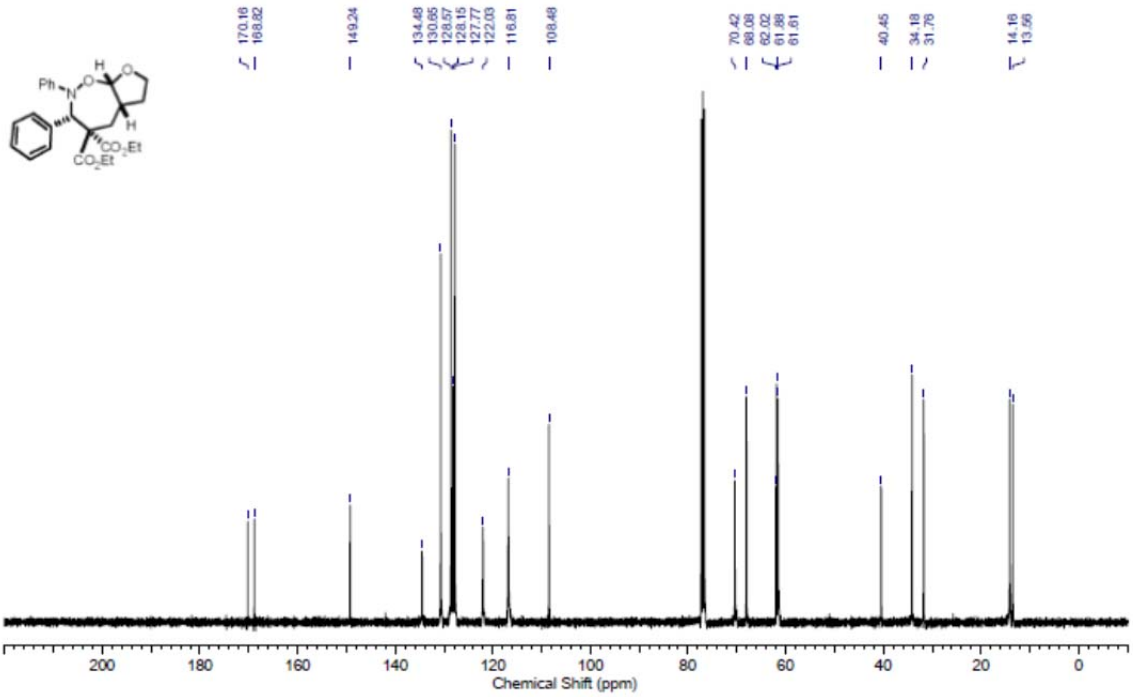


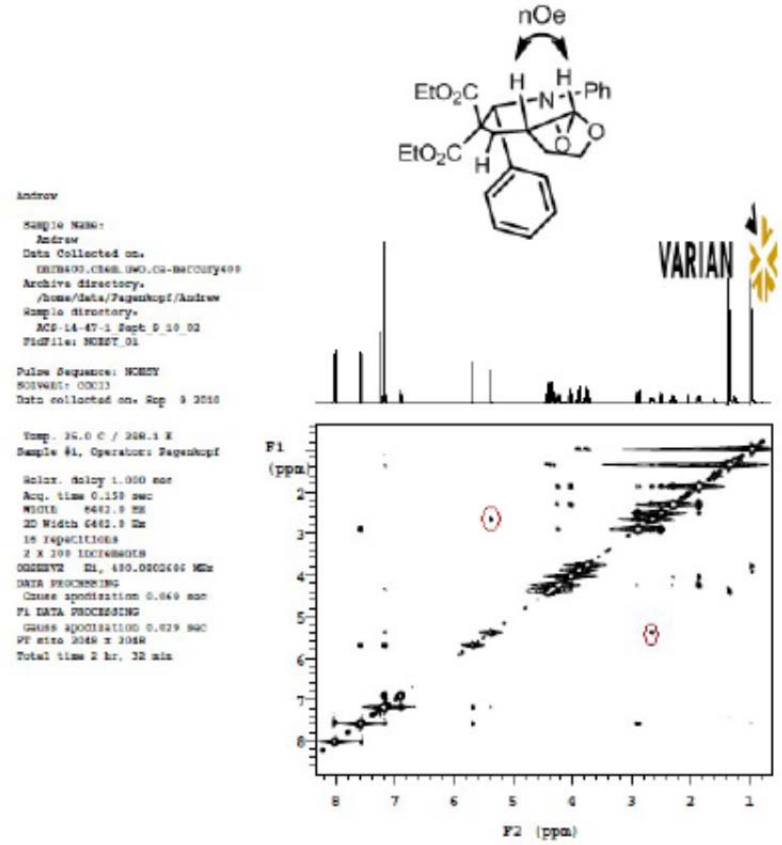




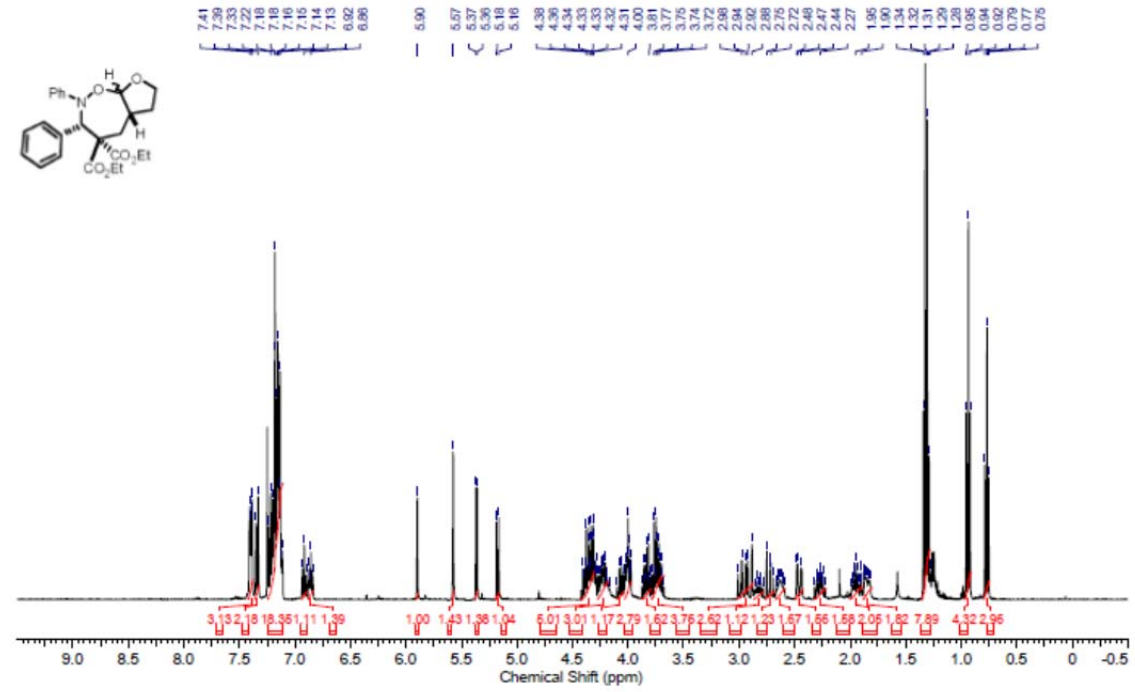
^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81a, *cis* diastereomer**

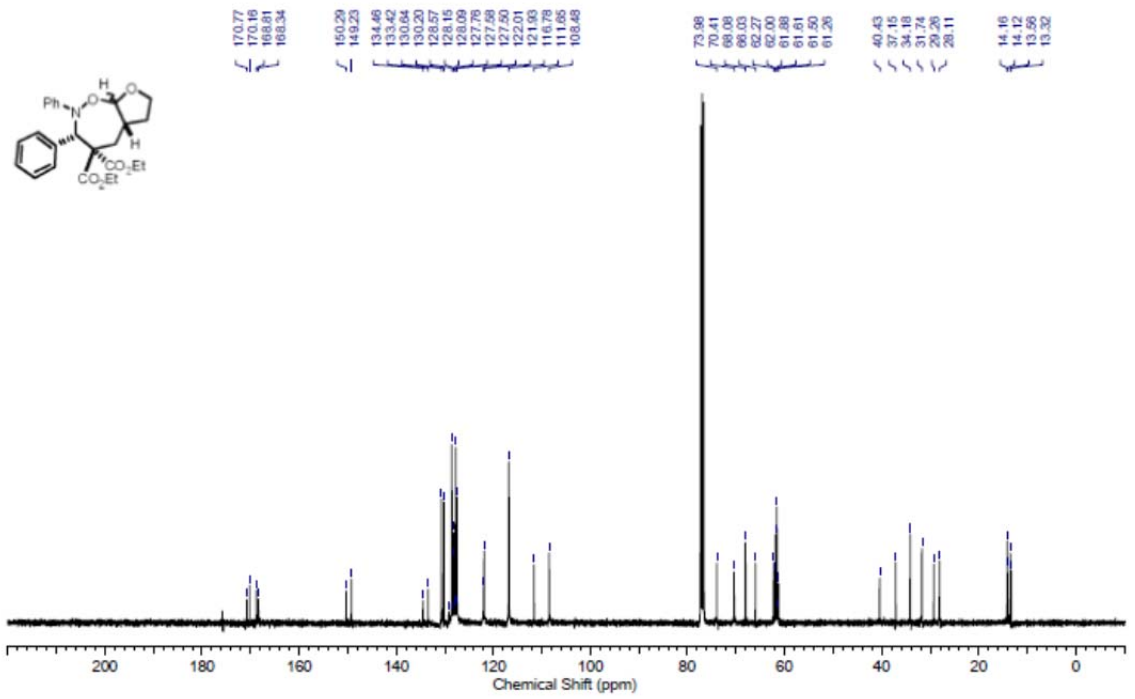



170.16
168.82
149.24
134.48
130.66
128.57
128.15
127.77
122.03
116.81
108.48
70.42
68.08
62.02
61.88
61.61
40.45
34.18
31.76
14.16
13.56
Ph
N
O
H
CO2Et
CO2Et
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

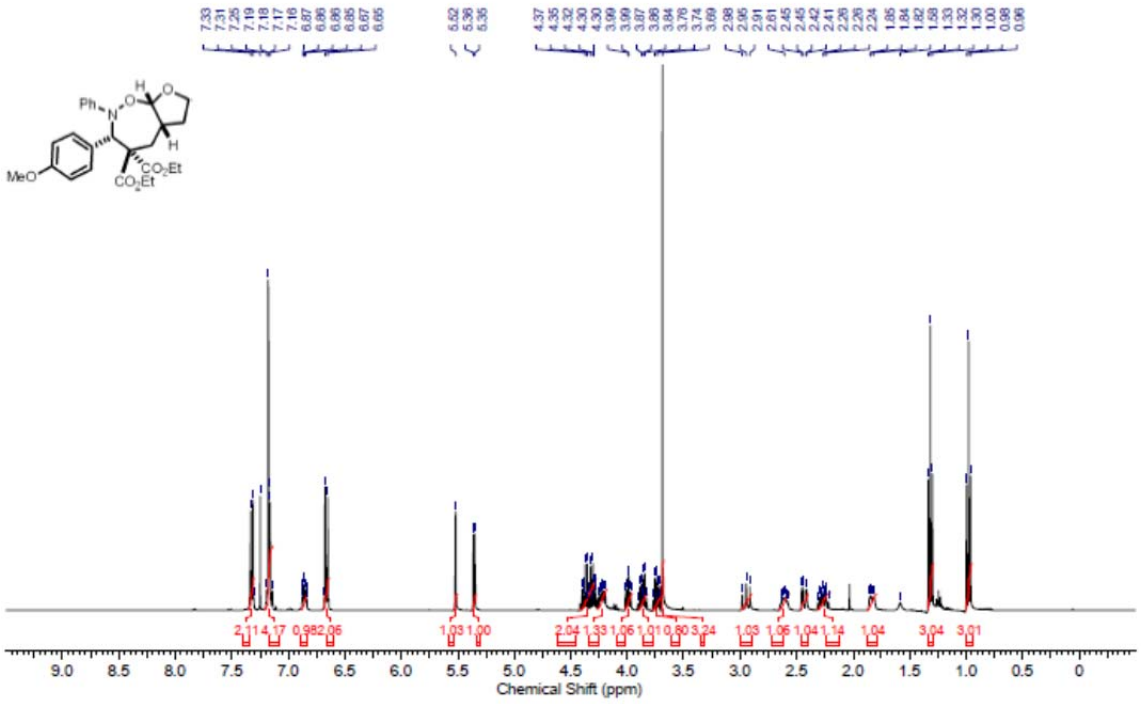

nOe
EtO2C
EtO2C
H
N
Ph
O
O
H
Andrew
Sample Name:
Andrew
Data Collected on:
Archive directory:
/home/data/Pagenkopf/Andrew
Sample directory:
ACE-14-47-1 Sept 9 10_02
FidFile: NOESY_01
Pulse Sequence: NOESY
Data collected on: Sep 9 2010
Temp. 25.0 C / 298.1 K
Sample #1, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
WIDTH 6402.8 Hz
2D Width 6402.8 Hz
16 repetitions
2 X 200 increments
SFRQ 400.0802600 MHz
Cosine apodization 0.049 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 32 min
VARIAN
F1 (ppm)
F2 (ppm)

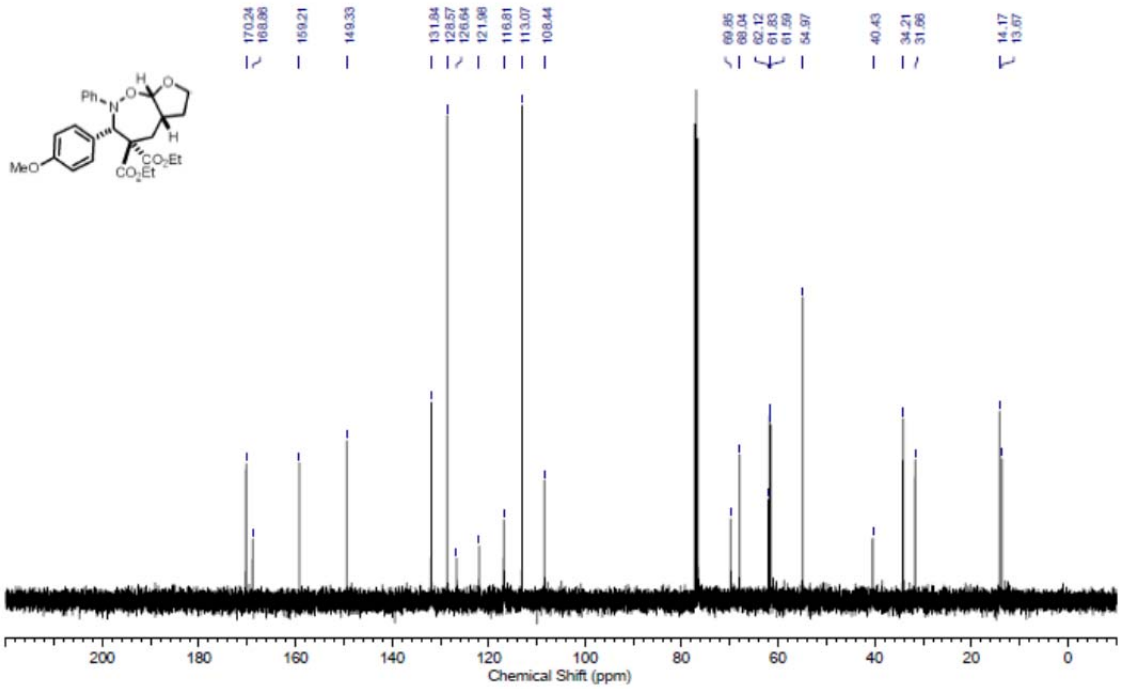
^{1}H and ^{13}C NMR of compound **2-81a, diastereomeric mixture**

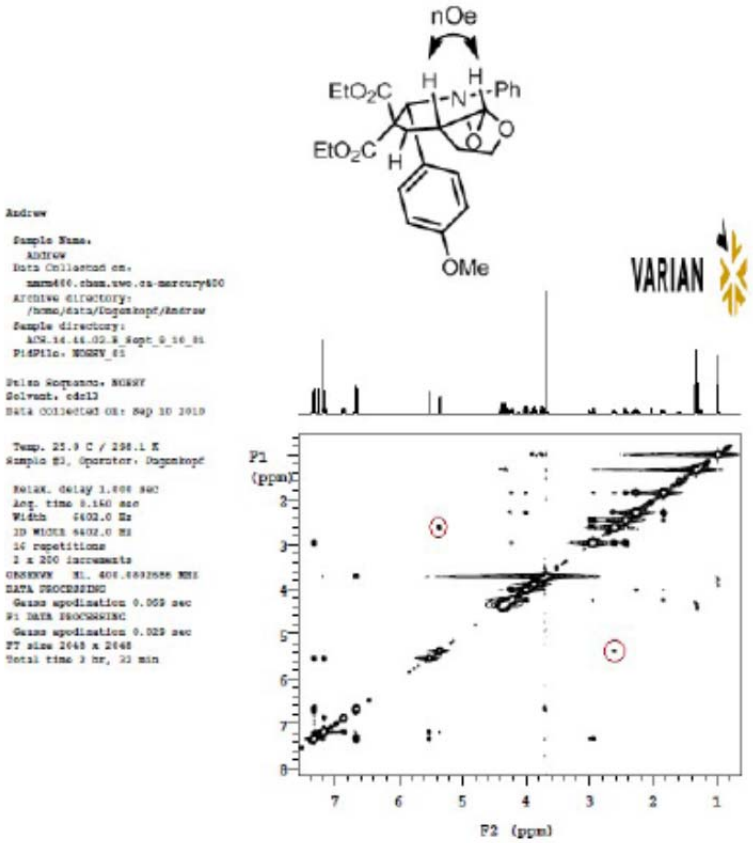




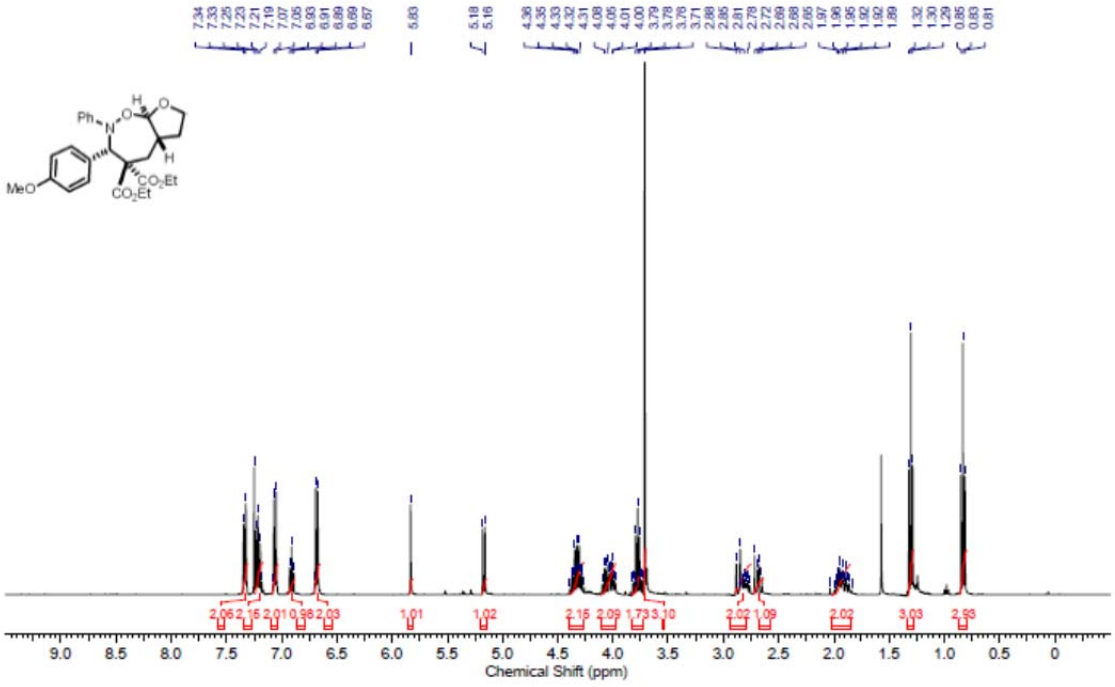
^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81b, *cis* diastereomer**

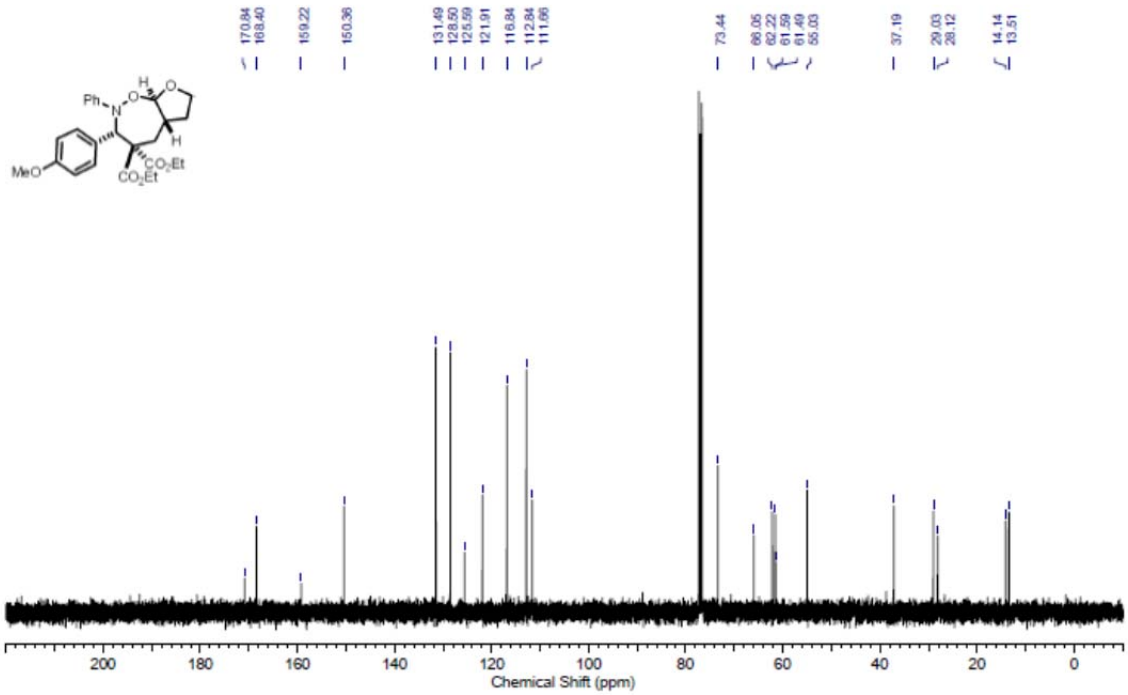






^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81b, *trans* diastereomer**

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168.40
159.22
150.36
131.49
128.50
125.59
121.91
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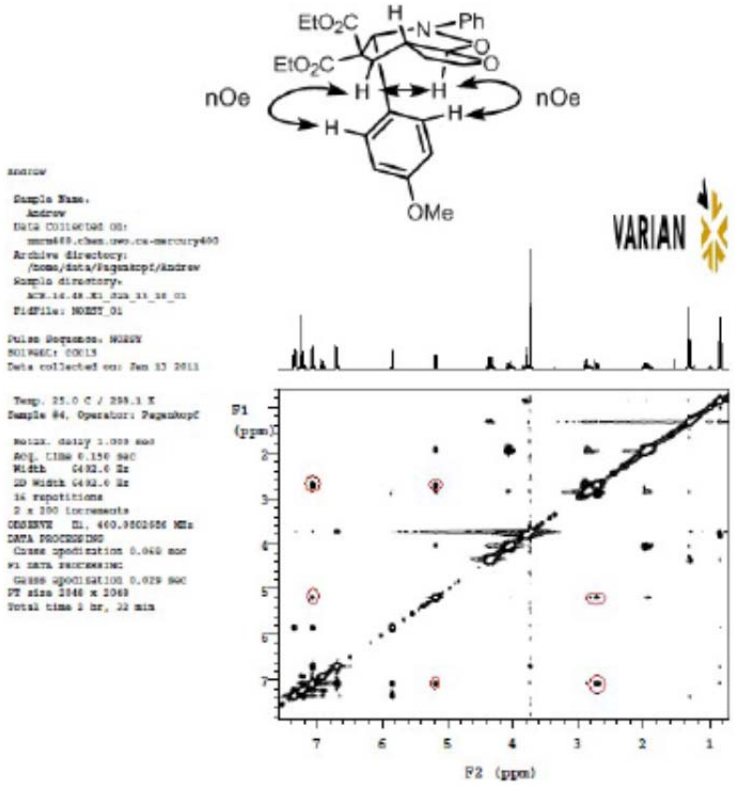
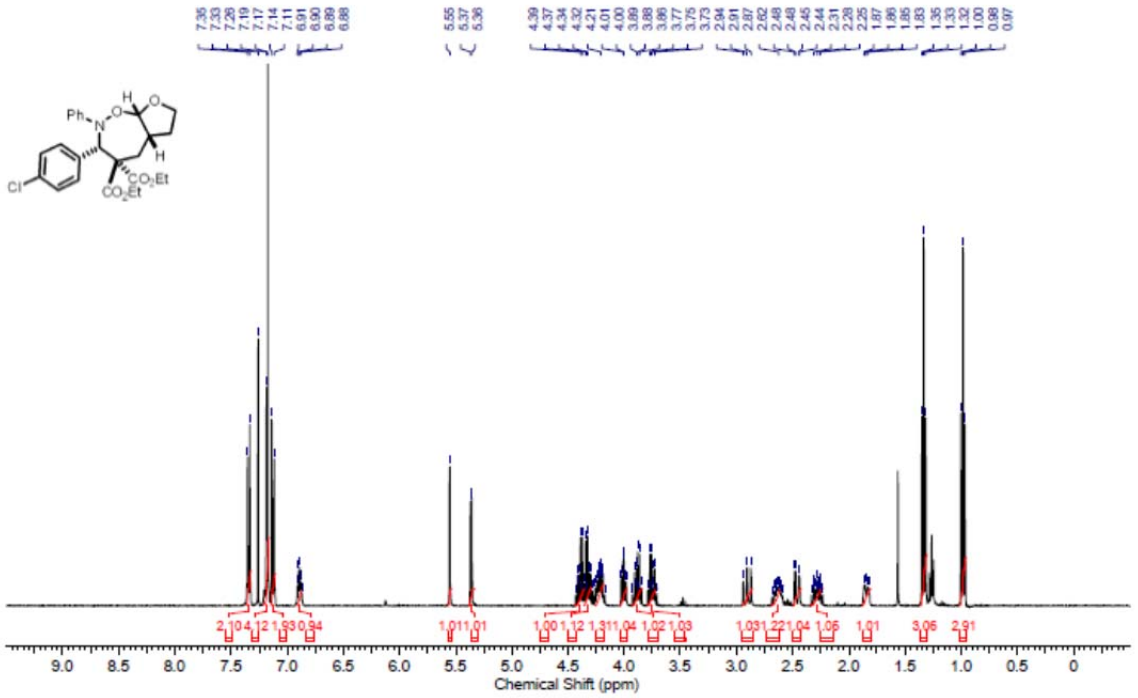
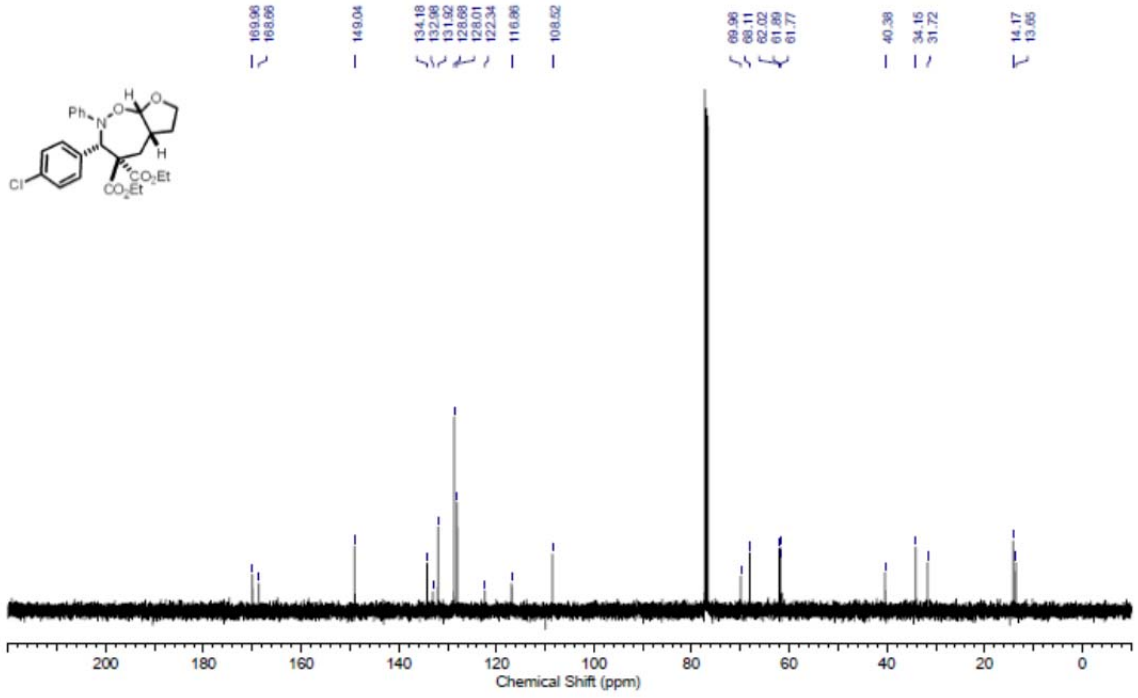
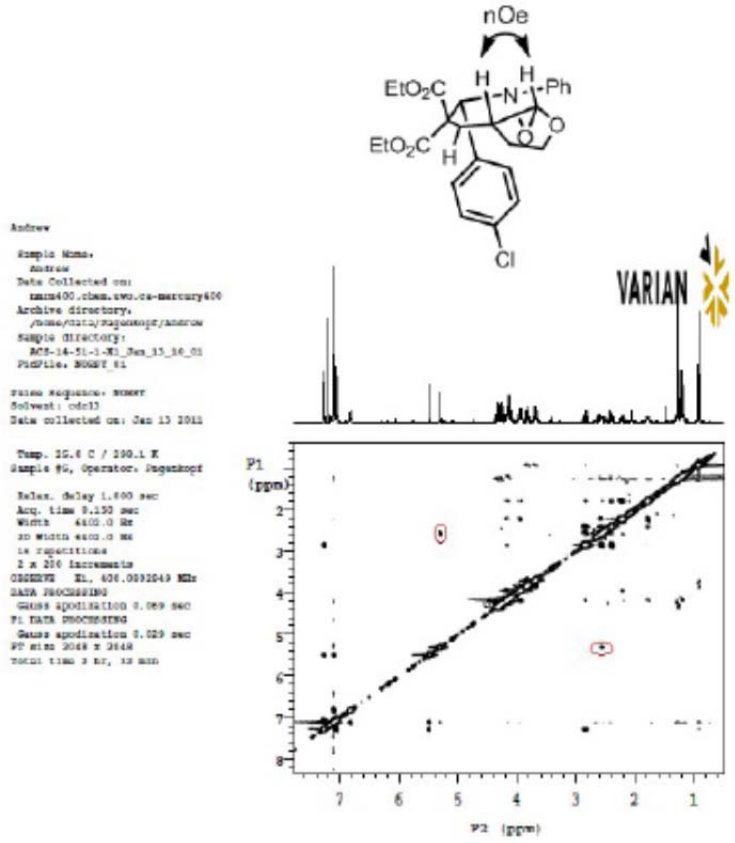
112.84
111.66
73.44
66.06
62.22
61.59
61.49
55.03
37.19
29.03
28.12
14.14
13.51
Ph
N
O
H
MeO
CO2Et
CO2Et
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


EtO2C
EtO2C
H
N
Ph
O
O
nOe
nOe
OMe
VARIAN
F1 (ppm)
F2 (ppm)

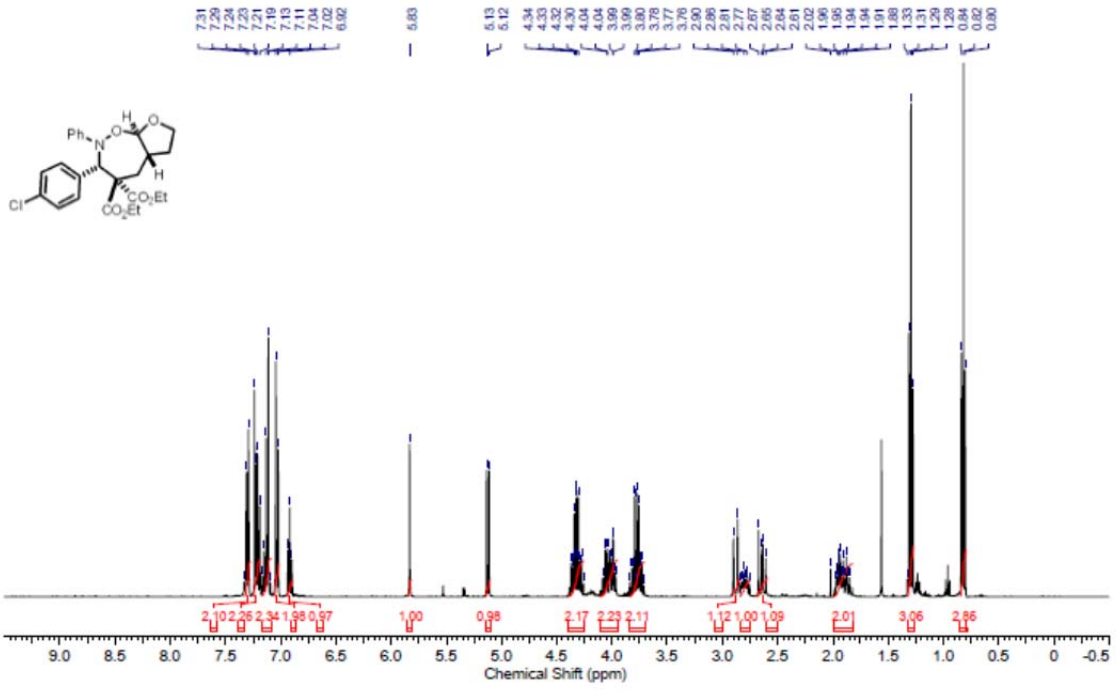
^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81c, *cis* diastereomer**

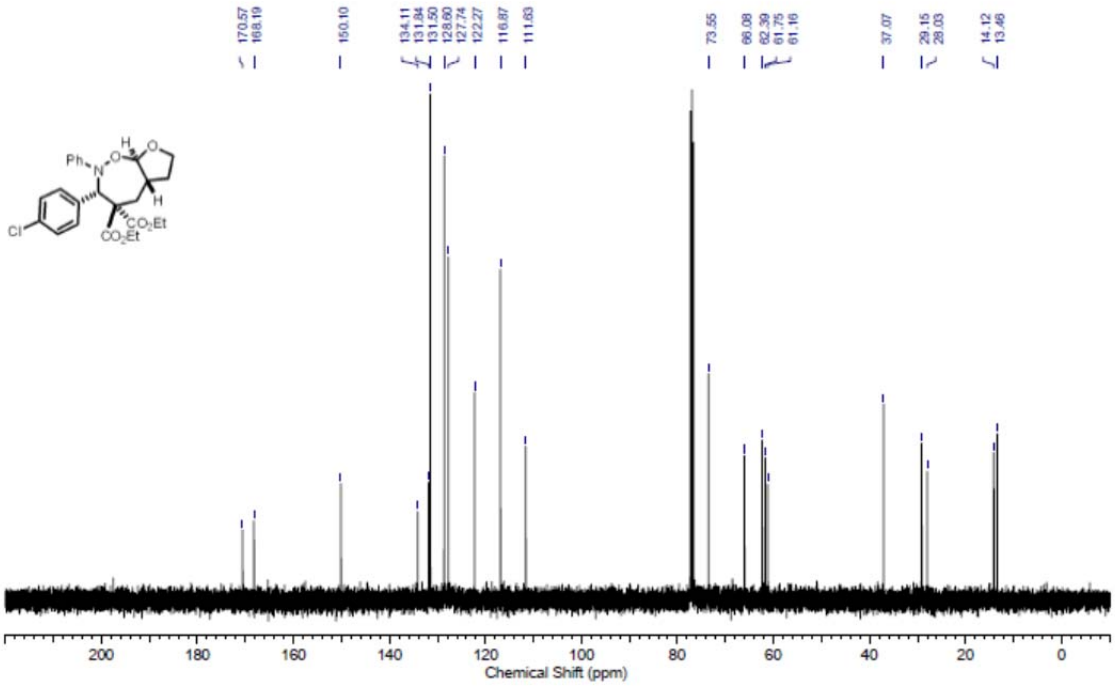






^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81c, *trans* diastereomer**

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168.19
150.10
134.11
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131.50
128.60
127.74
122.27
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111.63
73.55
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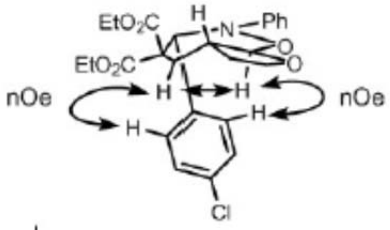
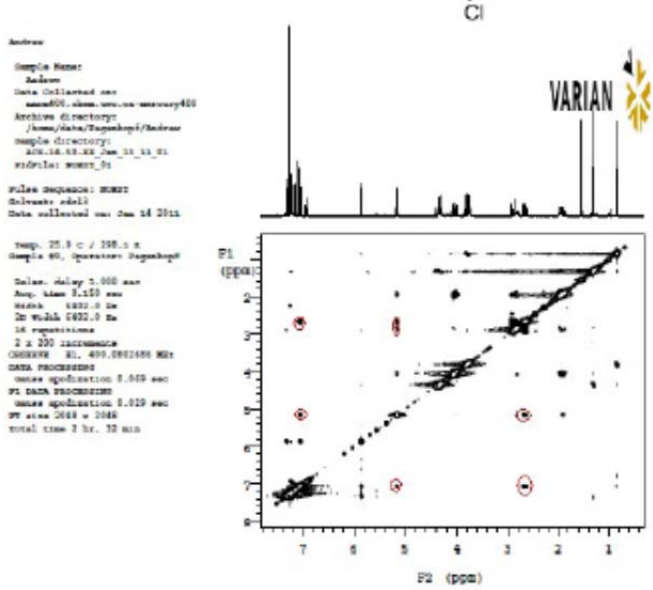
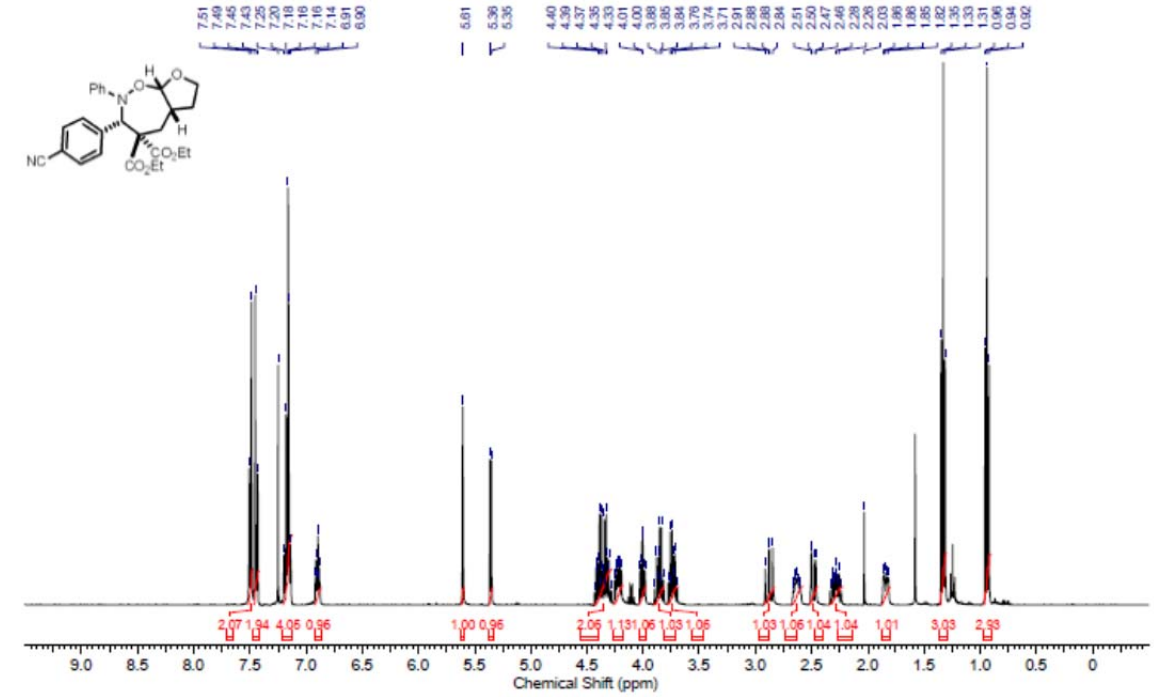
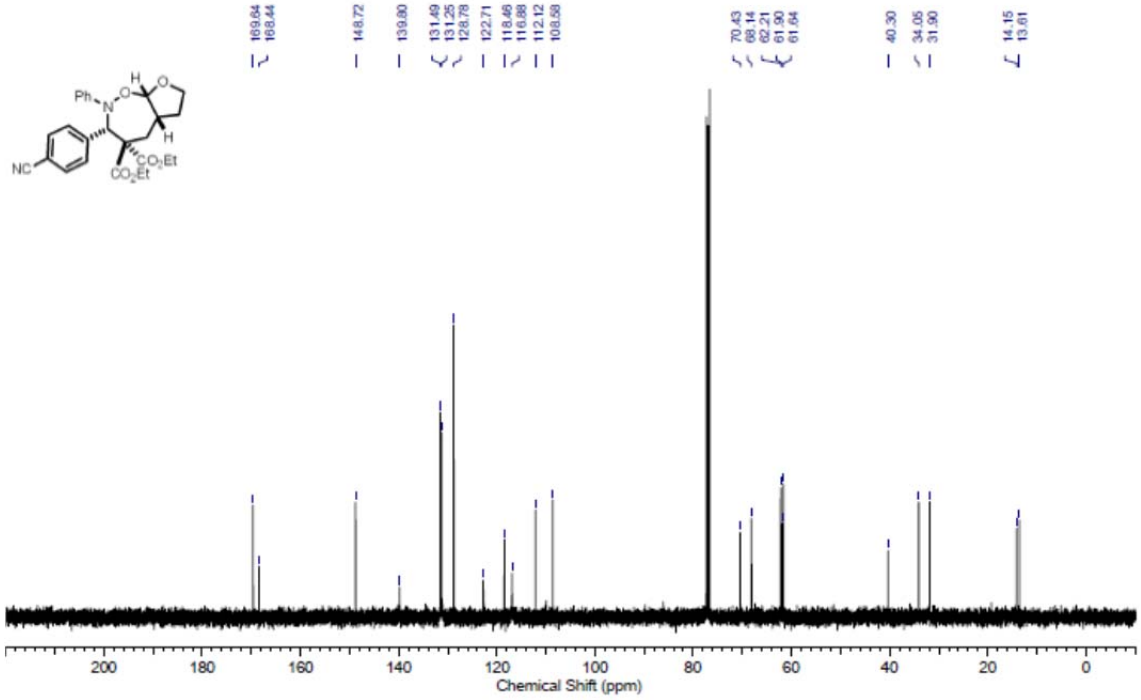
62.39
61.75
61.16
37.07
29.15
28.03
14.12
13.46
Ph
N
O
H
Cl
CO2Et
CO2Et
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

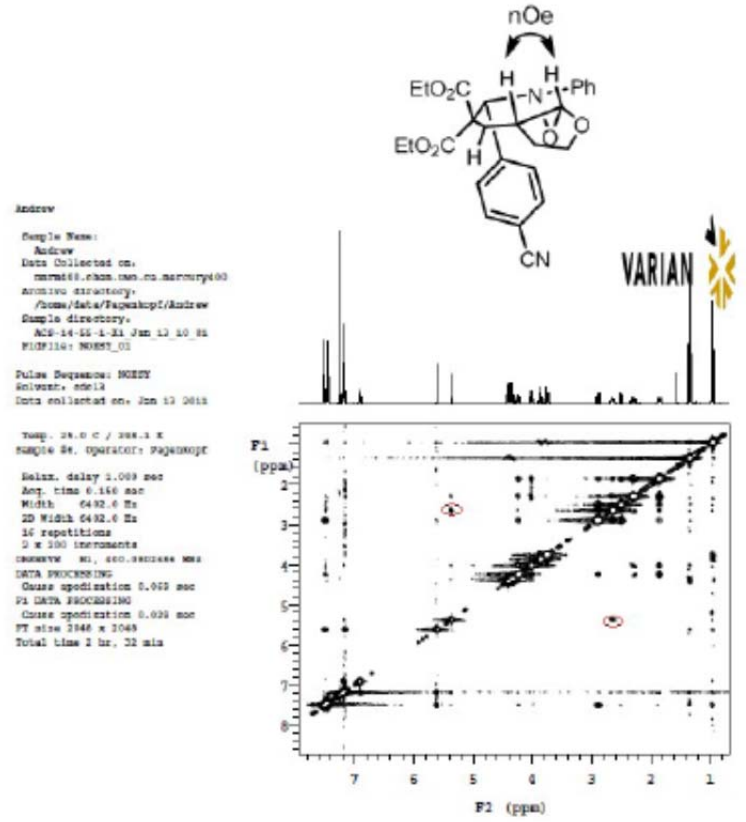

EtO2C
EtO2C
H
N
Ph
O
O
nOe
nOe
H
H
H
H
Cl


VARIAN
F1
(ppm)
F2 (ppm)

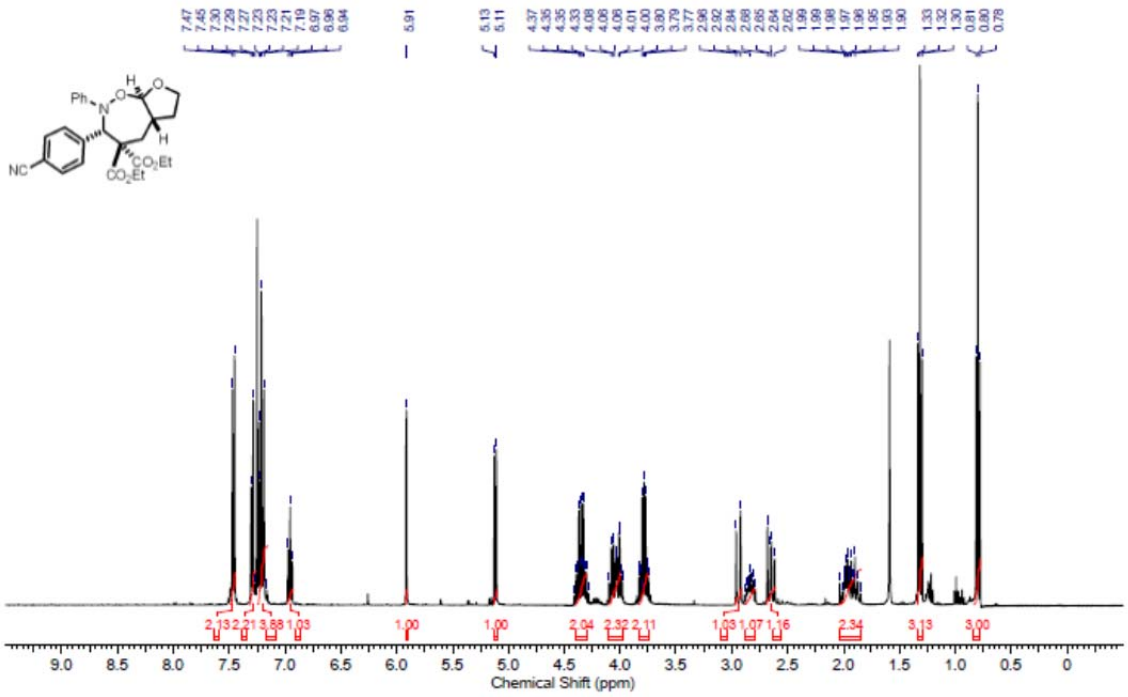
^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81d, *cis* diastereomer**

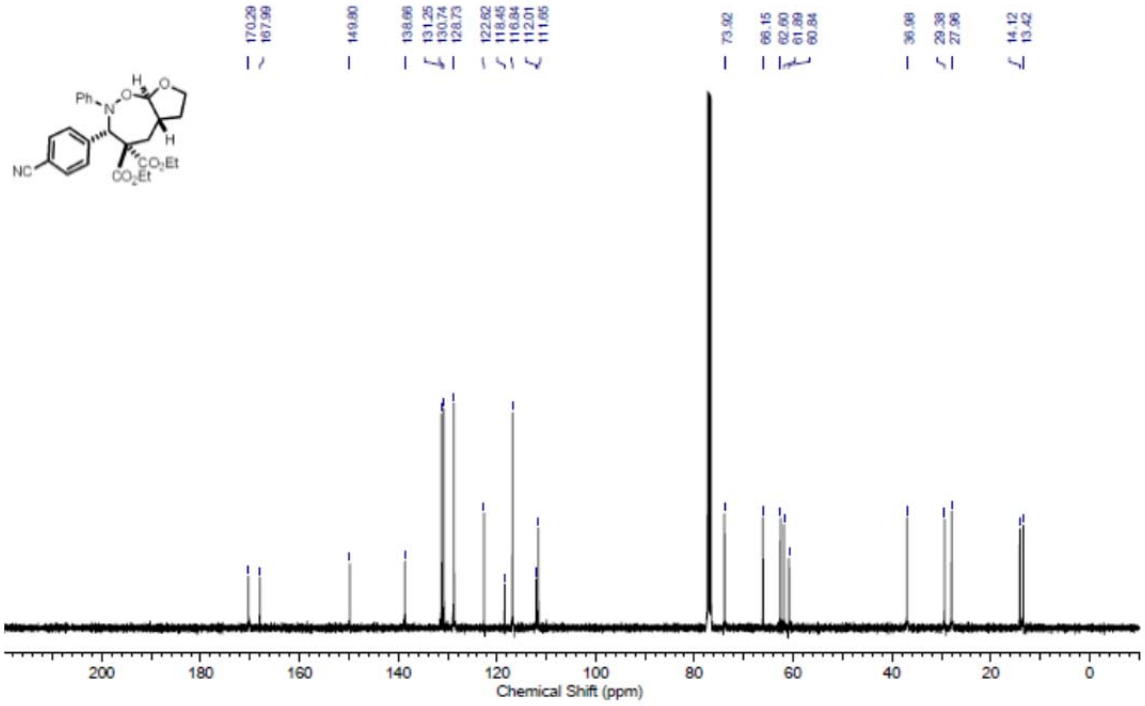


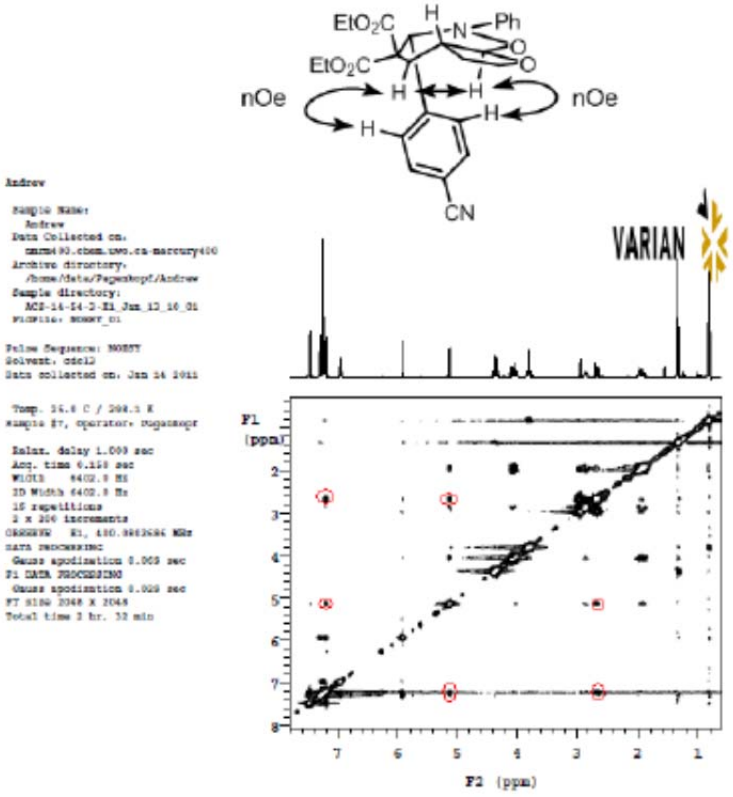




^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81d, *trans* diastereomer**







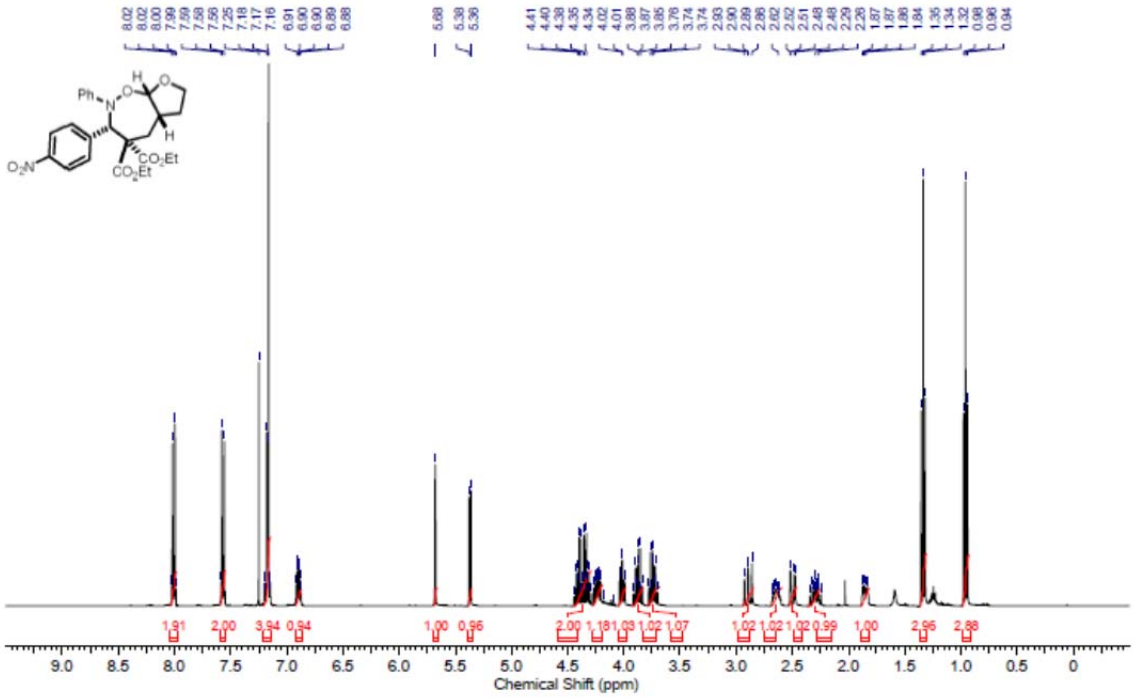
Andrew

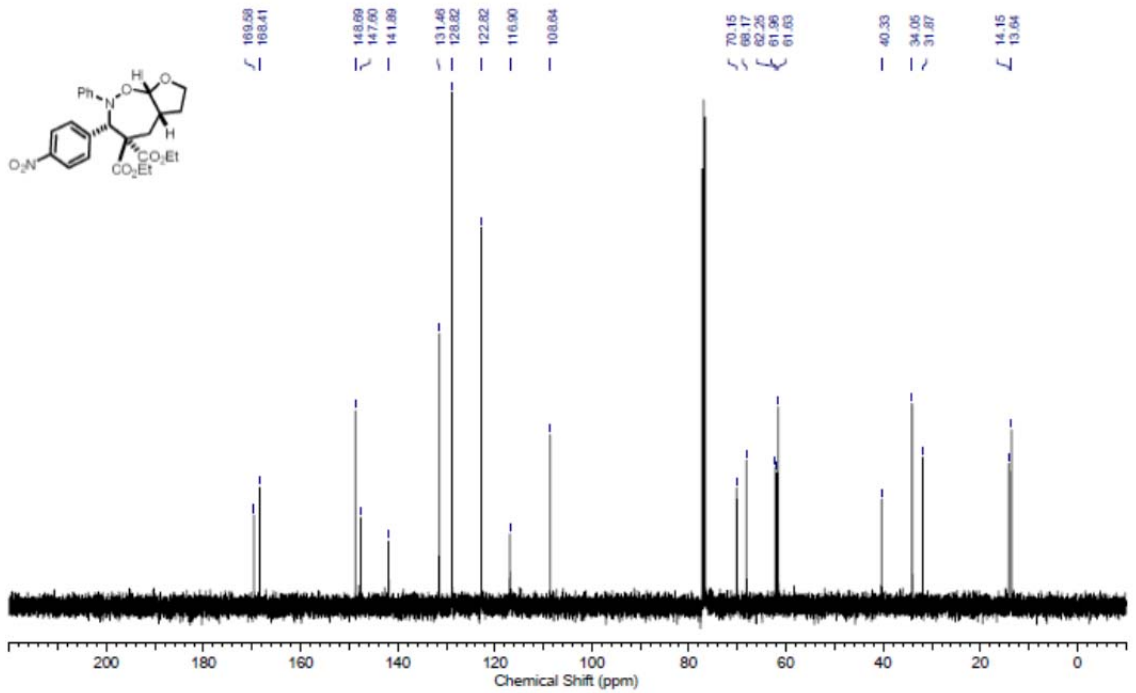
Sample Name:
Andrew
Data Collected on:
nmr400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/Andrew
Sample directory:
ACE-14-14-2-E1_Jan_12_16_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: Jan 16 2011

Temp. 16.0 C / 289.1 K
Sample 87, operator: Pagenkopf

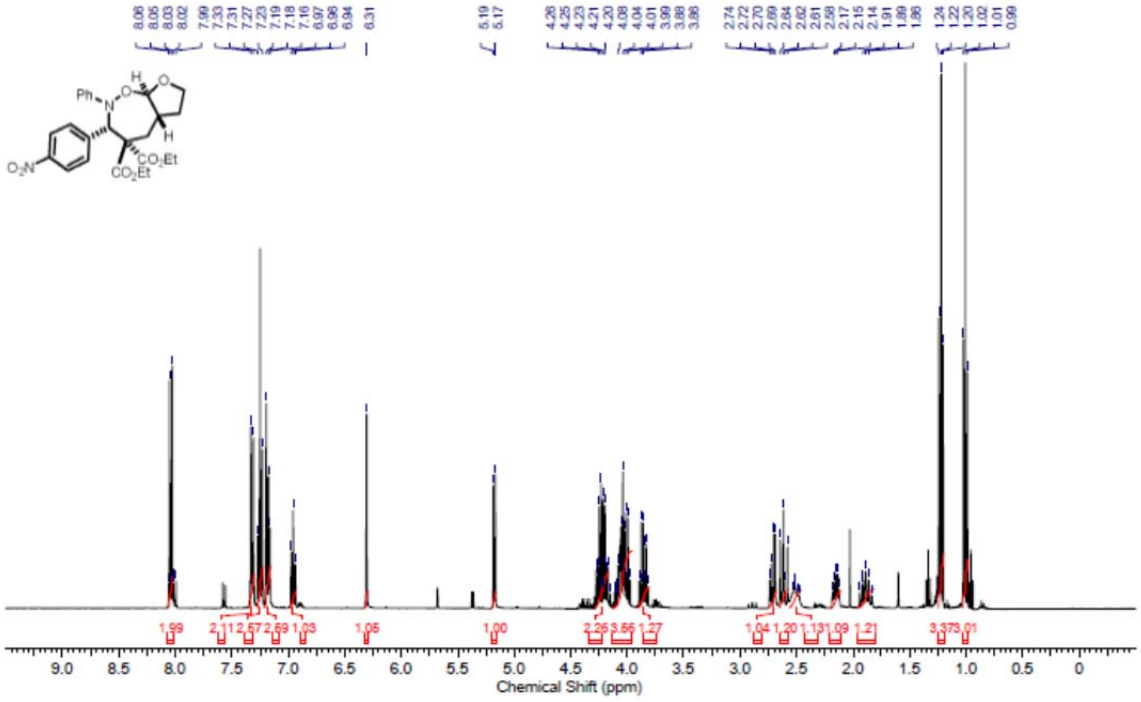
Relax. delay 1.000 sec
Acq. time 0.159 sec
W1(H1) 6402.9 Hz
2D Width 6402.9 Hz
16 repetitions
2 x 256 increments
OBSERVE H1, 400.0882586 MHz
DATA PROCESSING
Gauss apodization 0.000 sec
F1 DATA PROCESSING
Gauss apodization 0.020 sec
FT SIZE 2048 X 2048
Total time 3 hr, 32 min

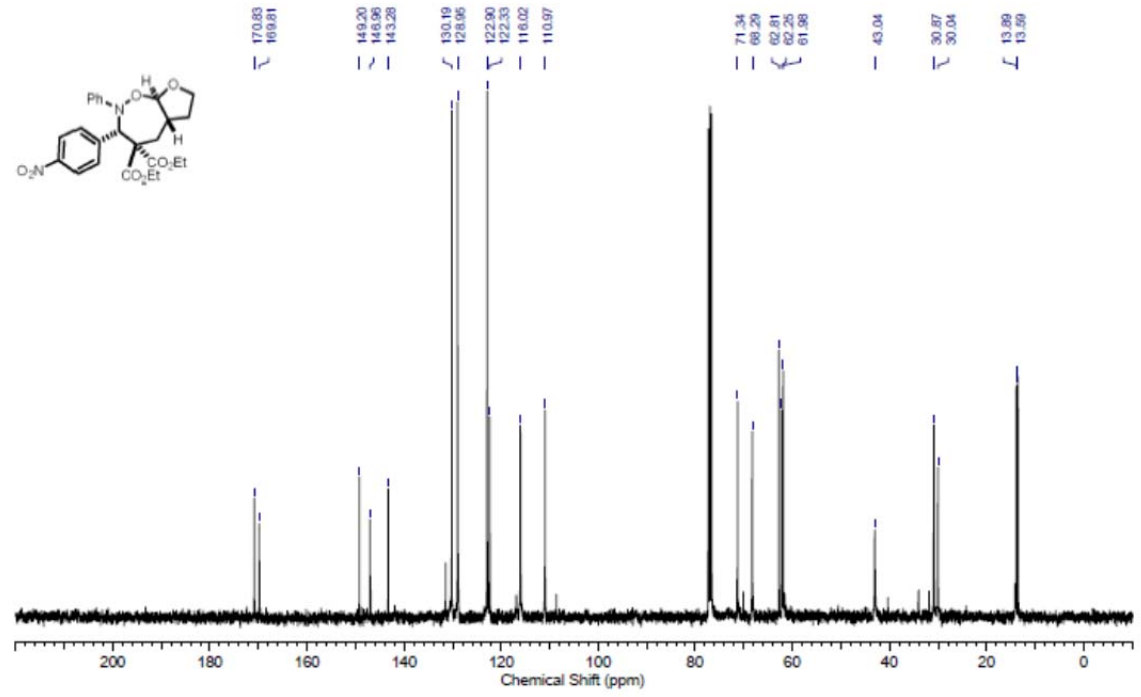
^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81f, *cis* diasteromer**

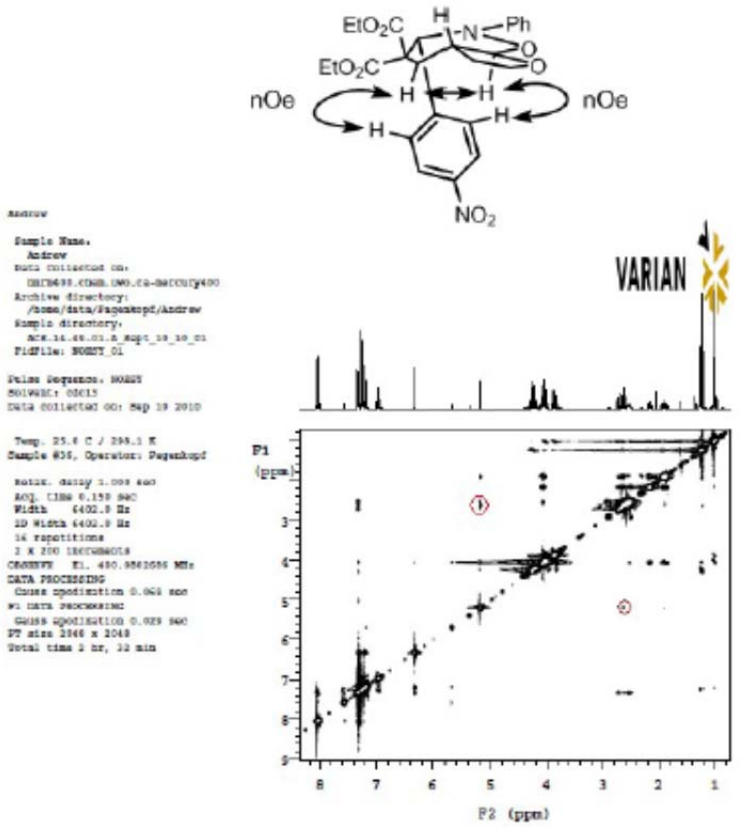




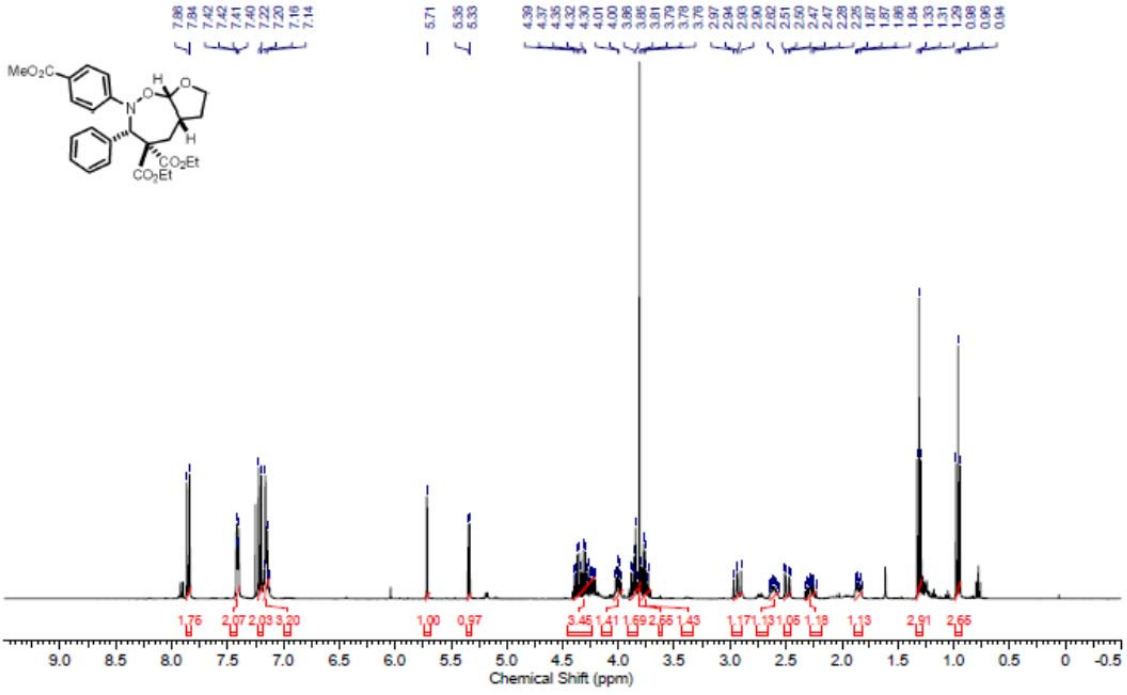
^{1}H, ^{13}C NMR, and 2D nOe of compound **2-81e, *trans* diastereomer**

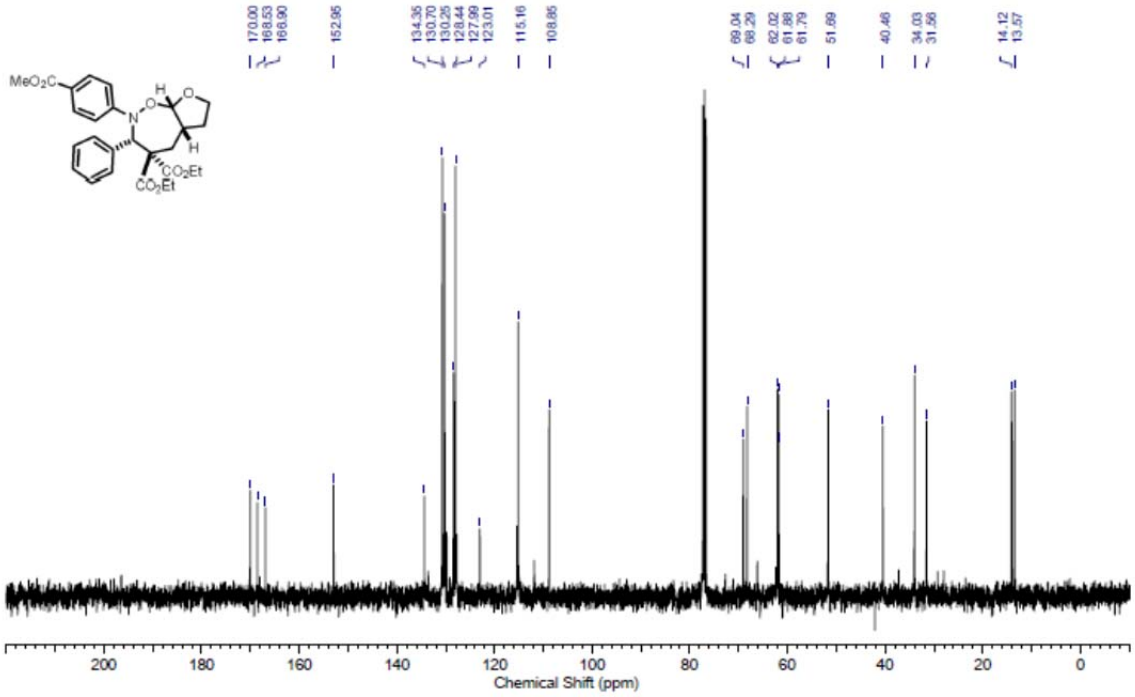




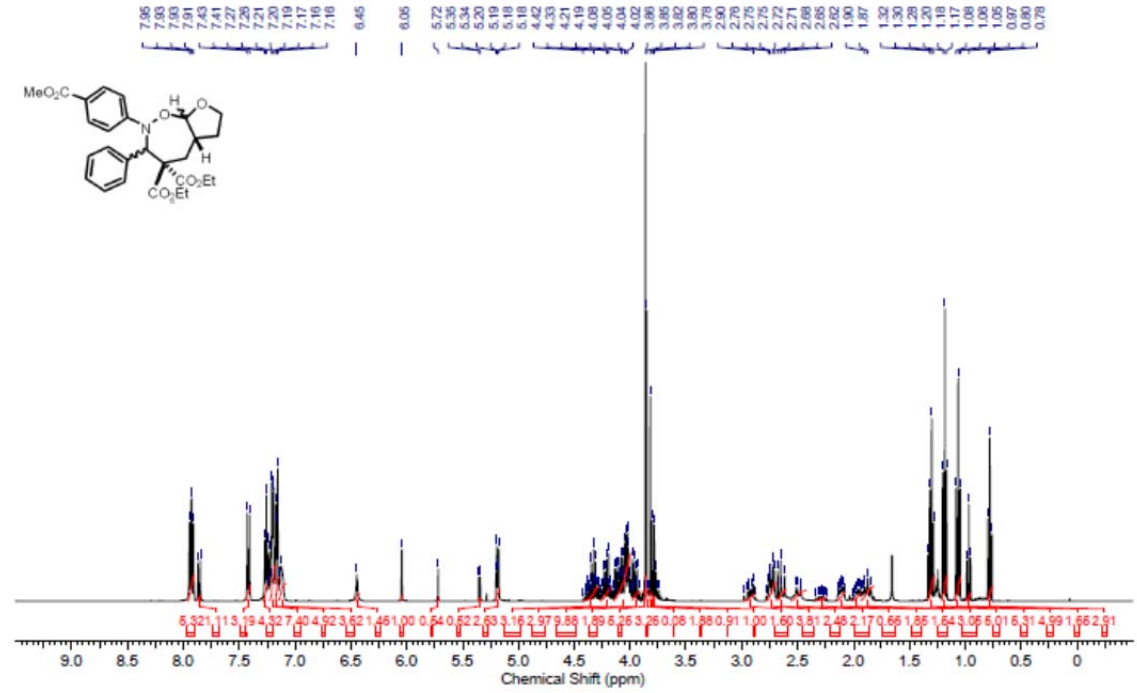


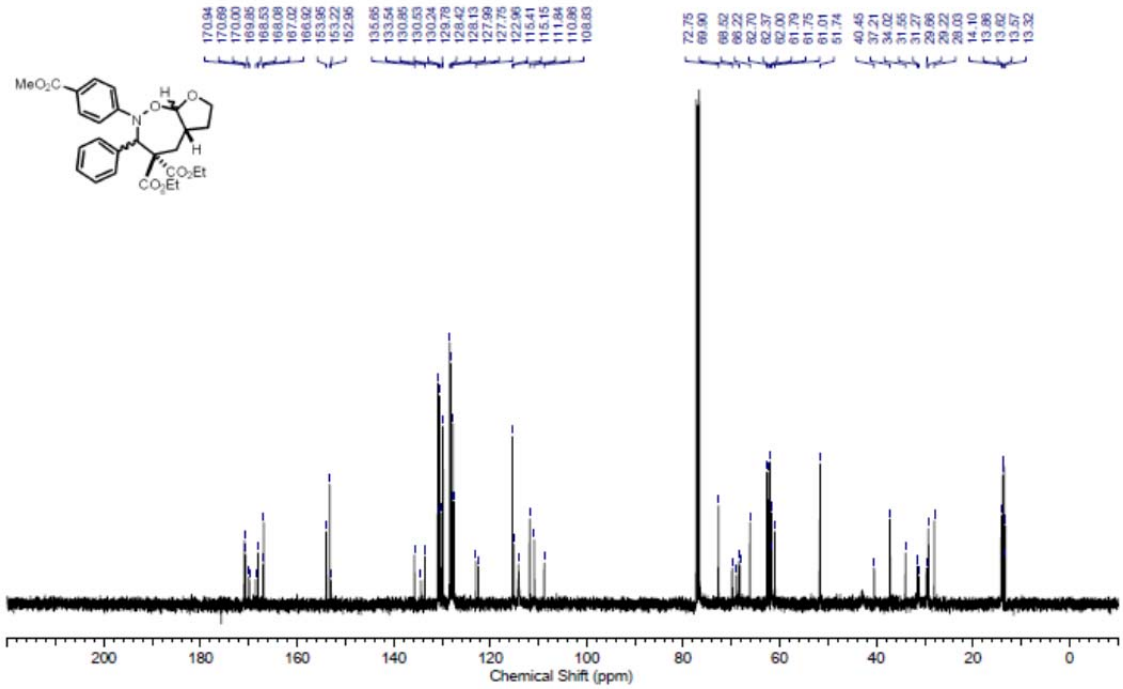
^{1}H and ^{13}C NMR of compound **2-81f, *cis* diastereomer**



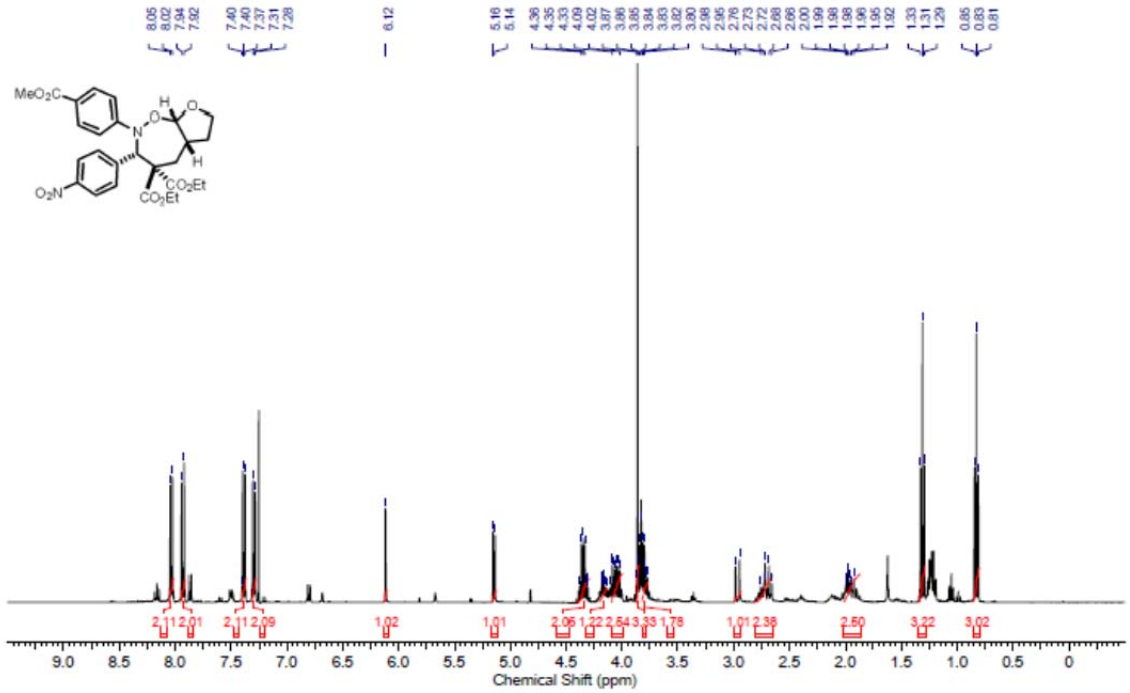


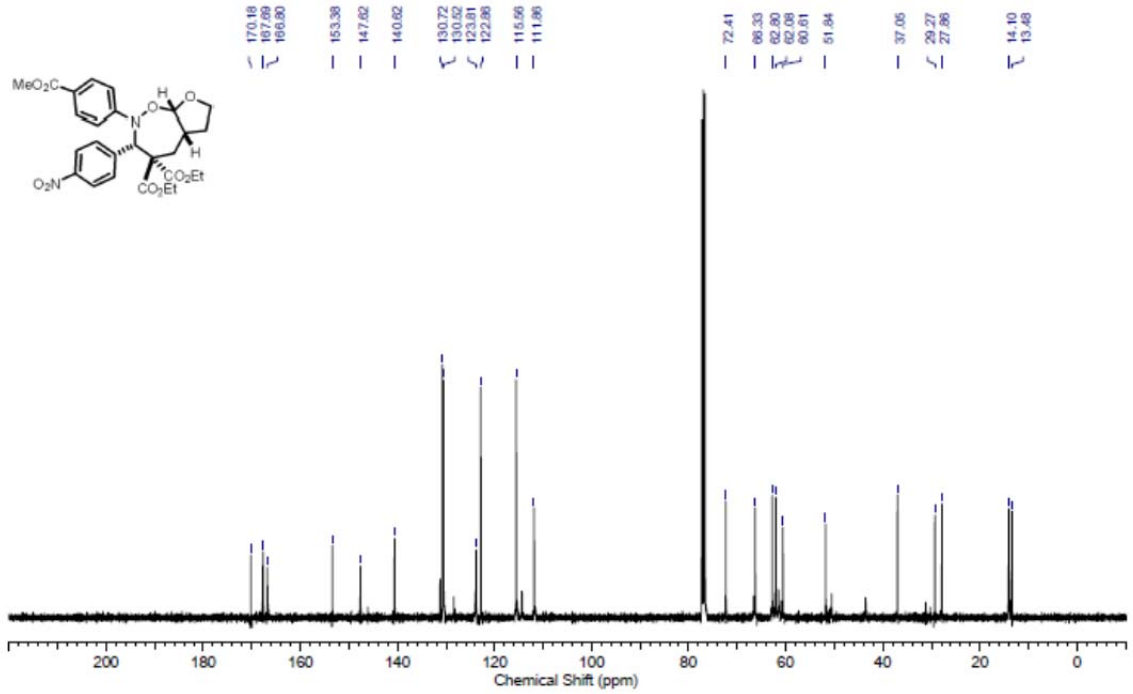
^{1}H and ^{13}C NMR of compound **2-81f, diastereomeric mixture**



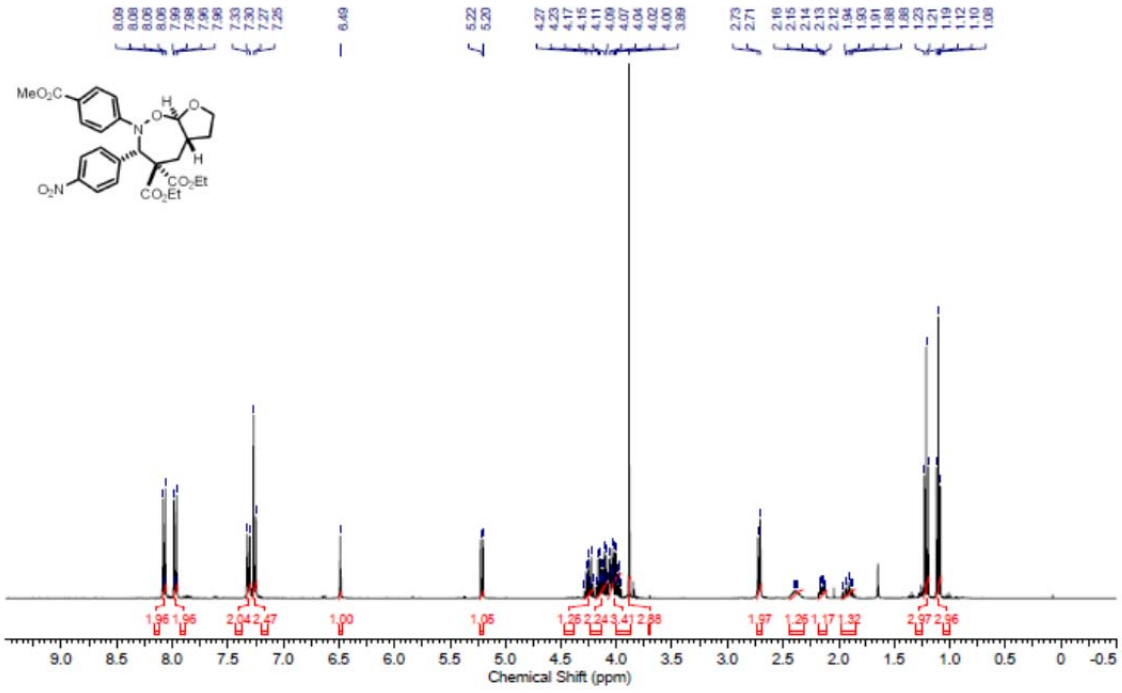


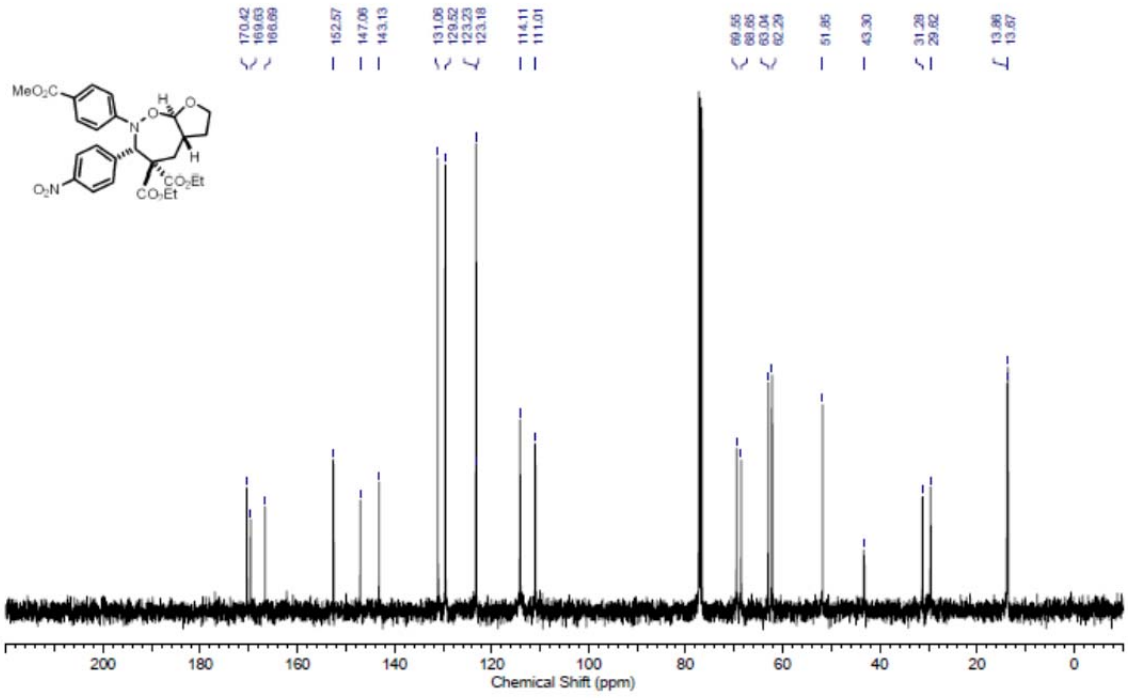
^{1}H and ^{13}C NMR of compound **2-81g, *cis* diastereomer**



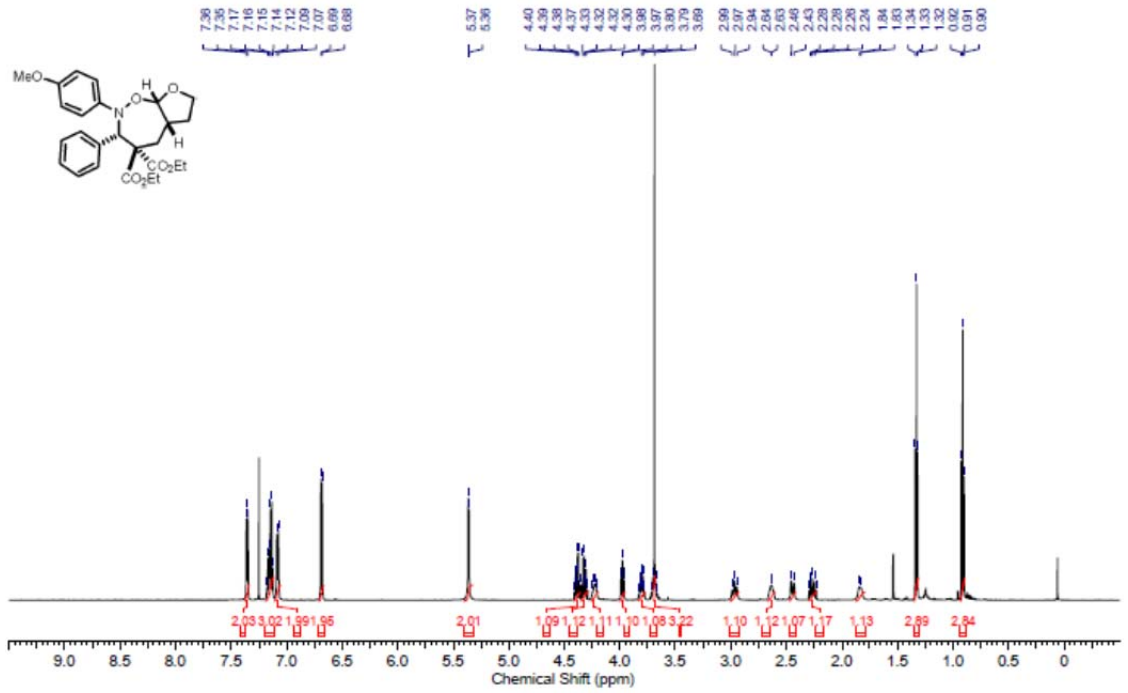


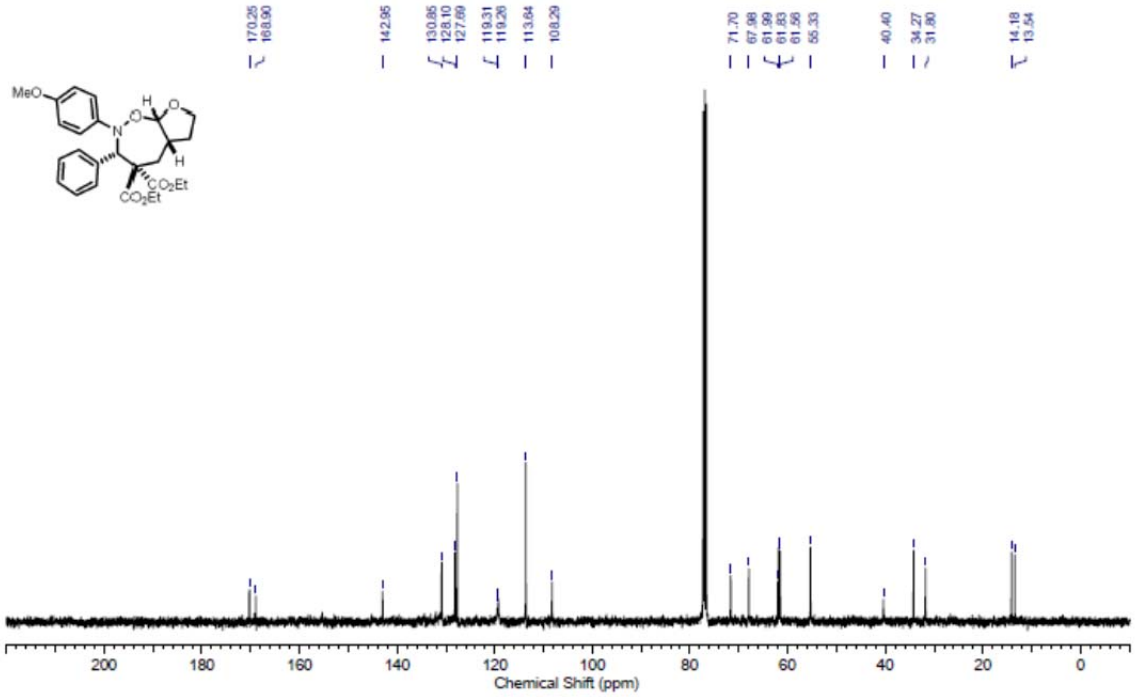
^{1}H and ^{13}C NMR of compound **2-81g, *trans* diastereomer**



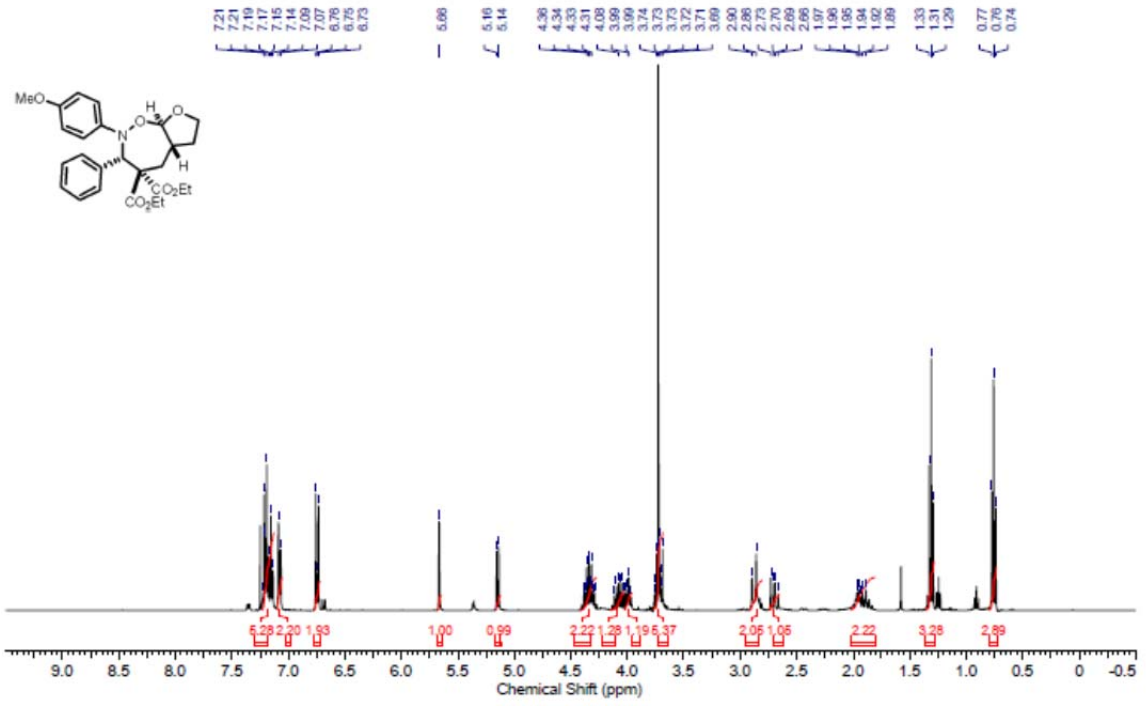


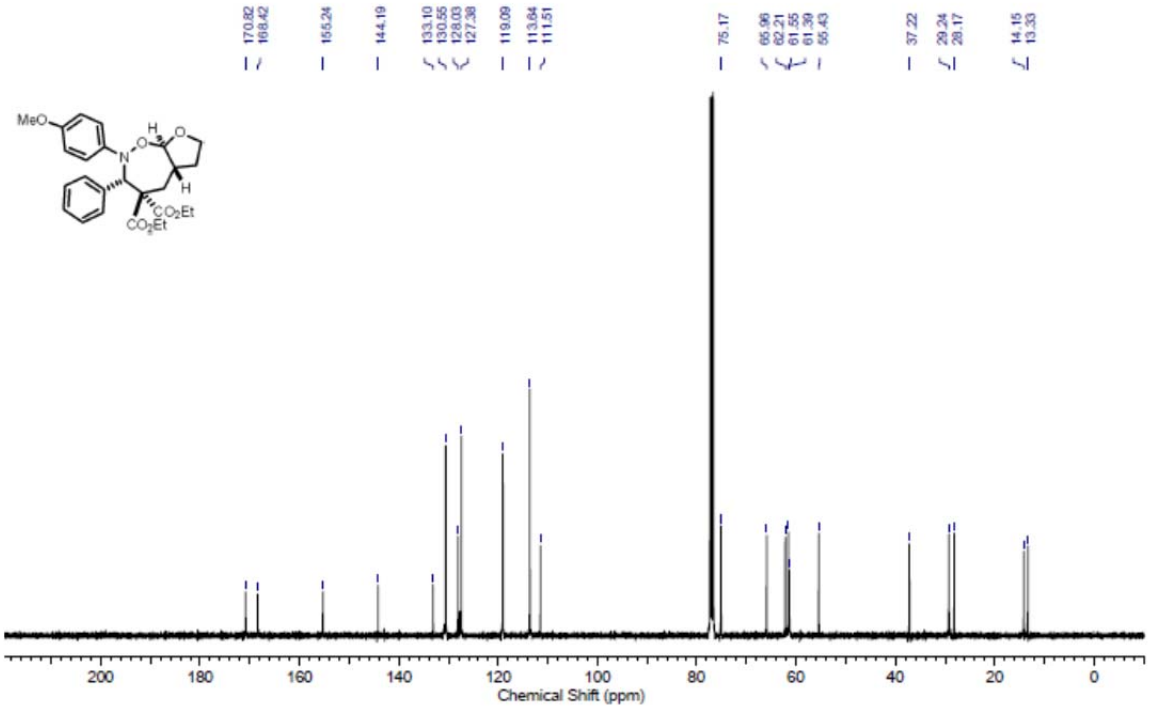
^{1}H and ^{13}C NMR of compound **2-81h, *cis* diastereomer**



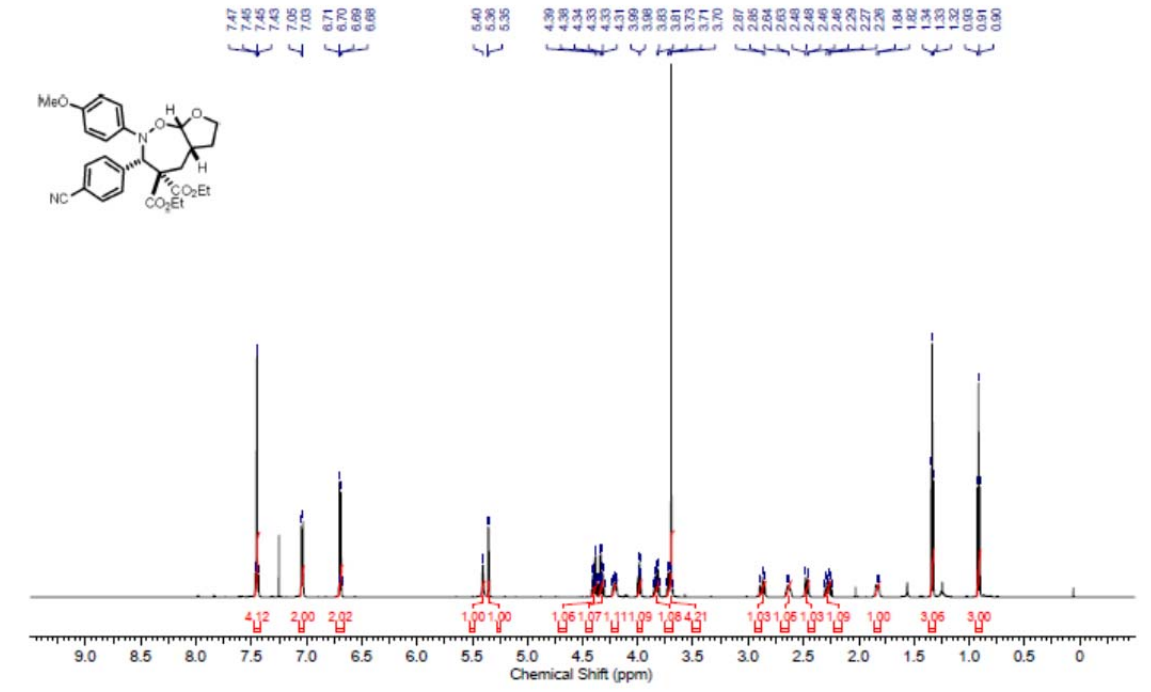


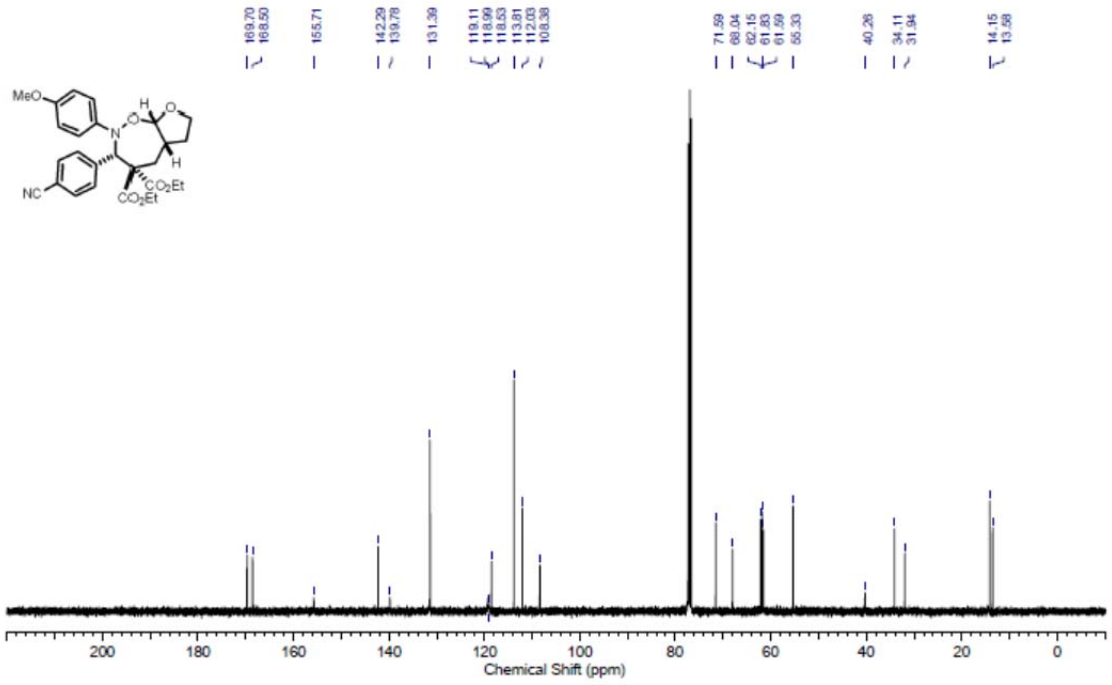
^{1}H and ^{13}C NMR of compound **2-81h, *trans* diastereomer**



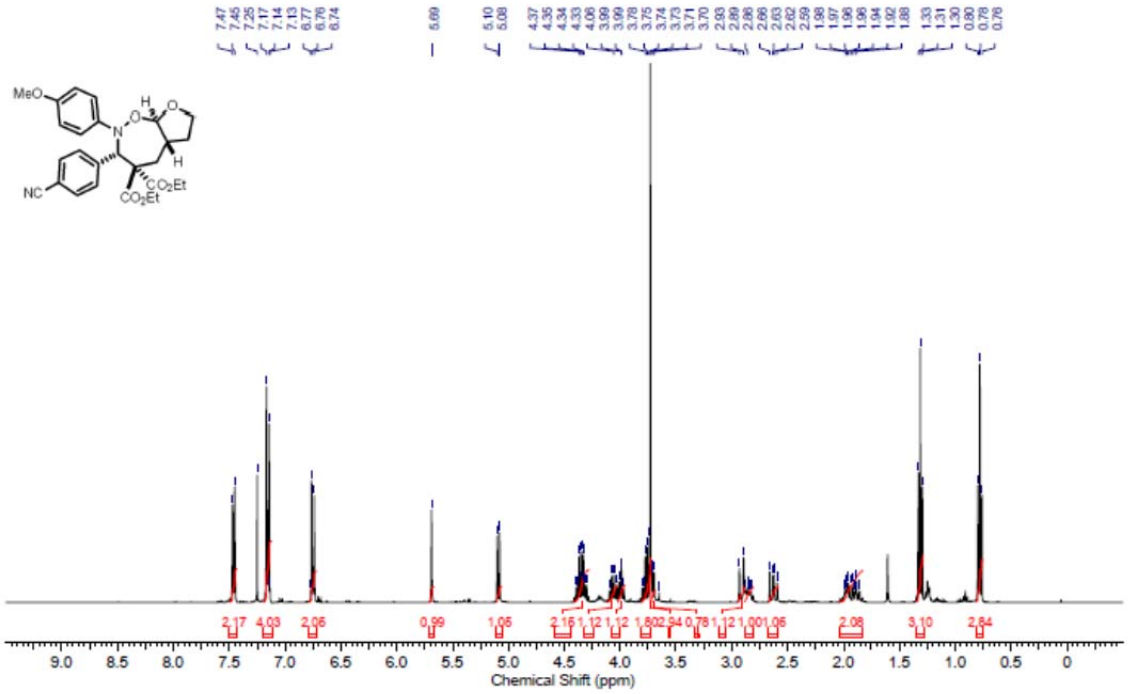


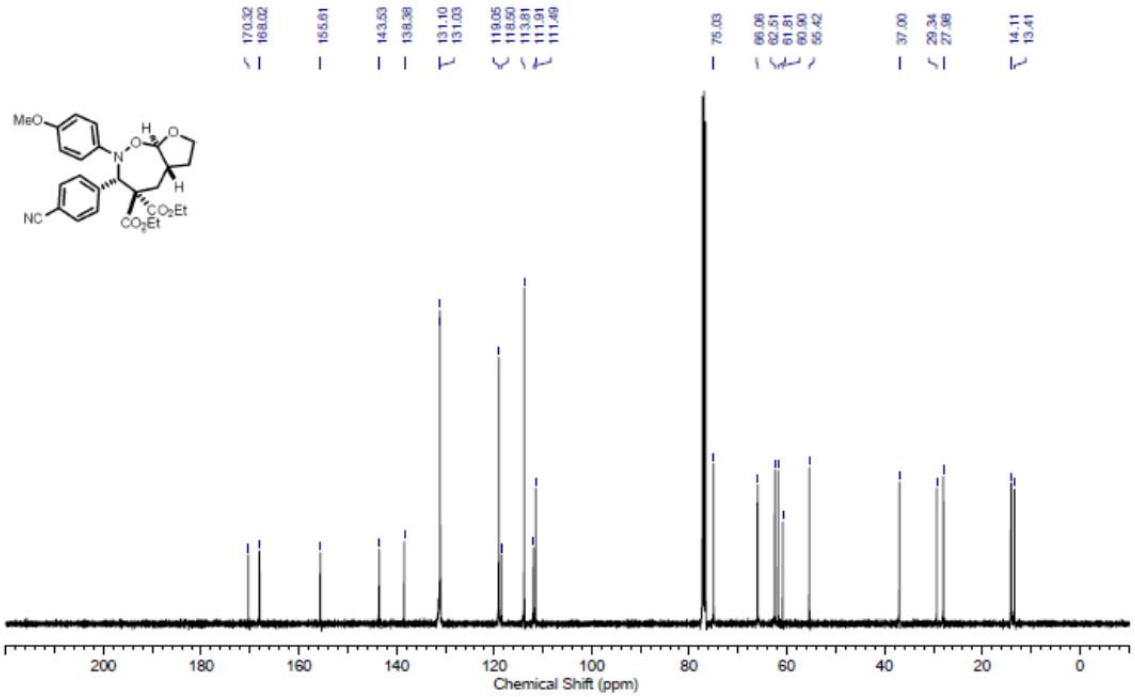
^{1}H and ^{13}C NMR of compound **2-81i, *cis* diastereomer**



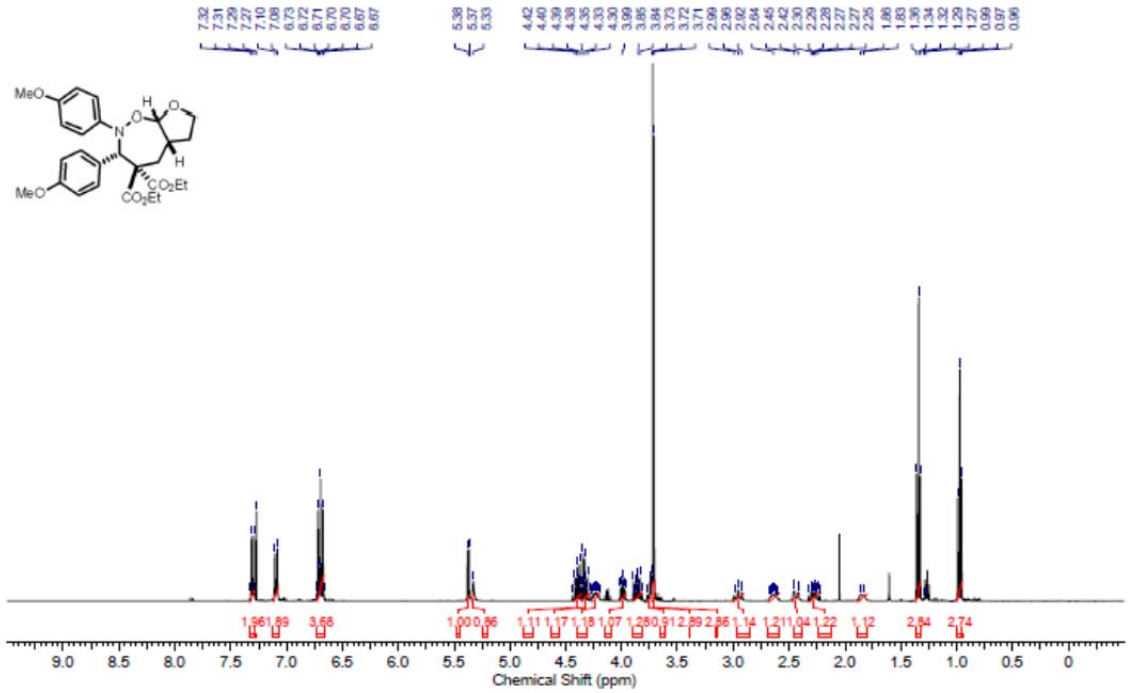


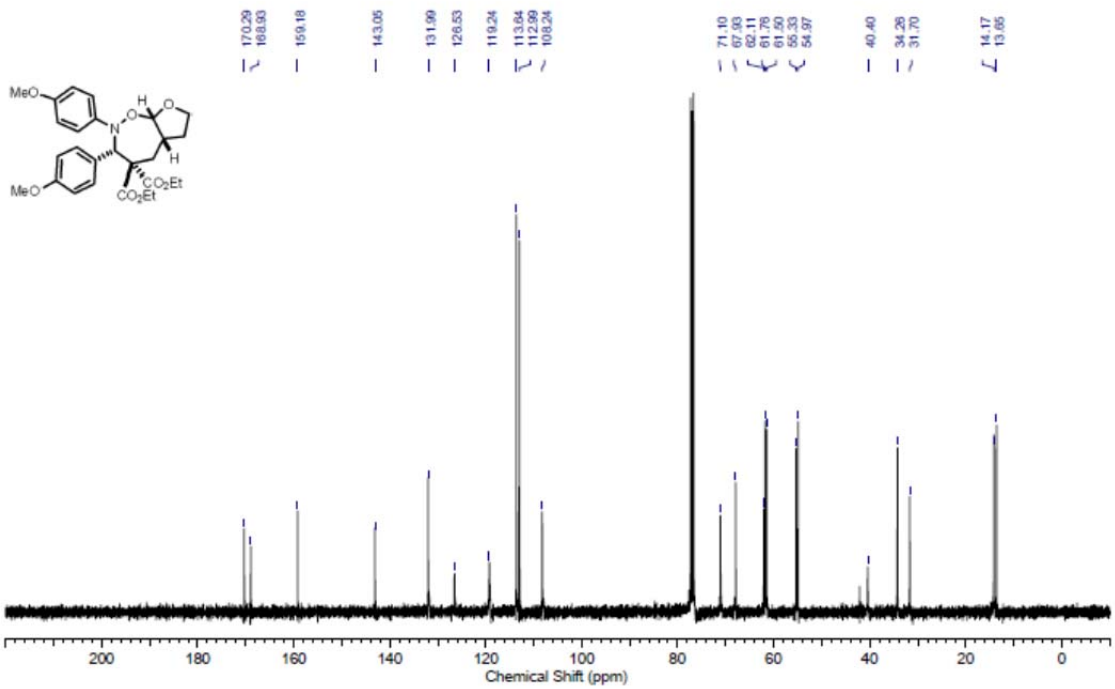
^{1}H and ^{13}C NMR of compound **2-81i, *trans* diastereomer**



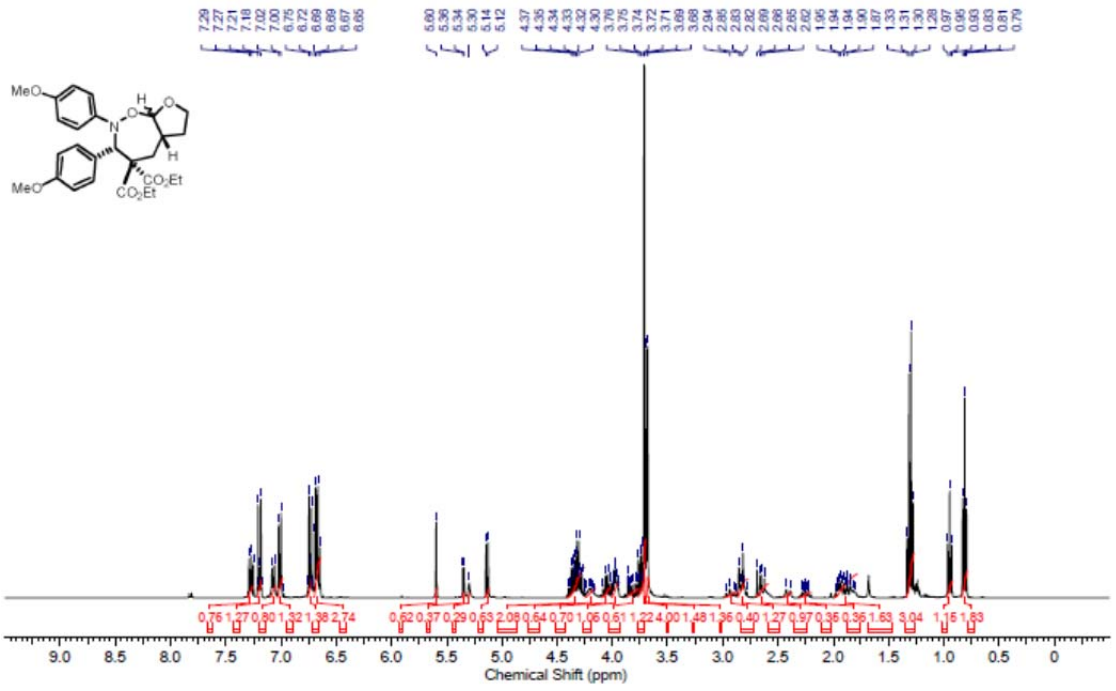


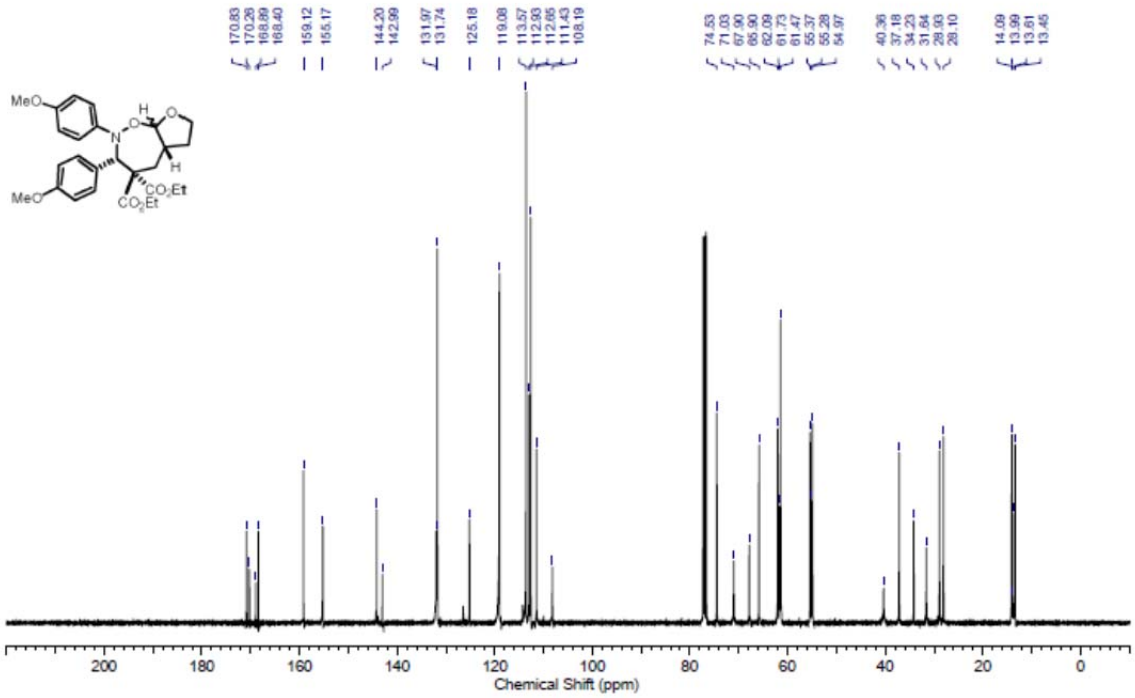
^{1}H and ^{13}C NMR of compound **2-81j, *cis* diastereomer**



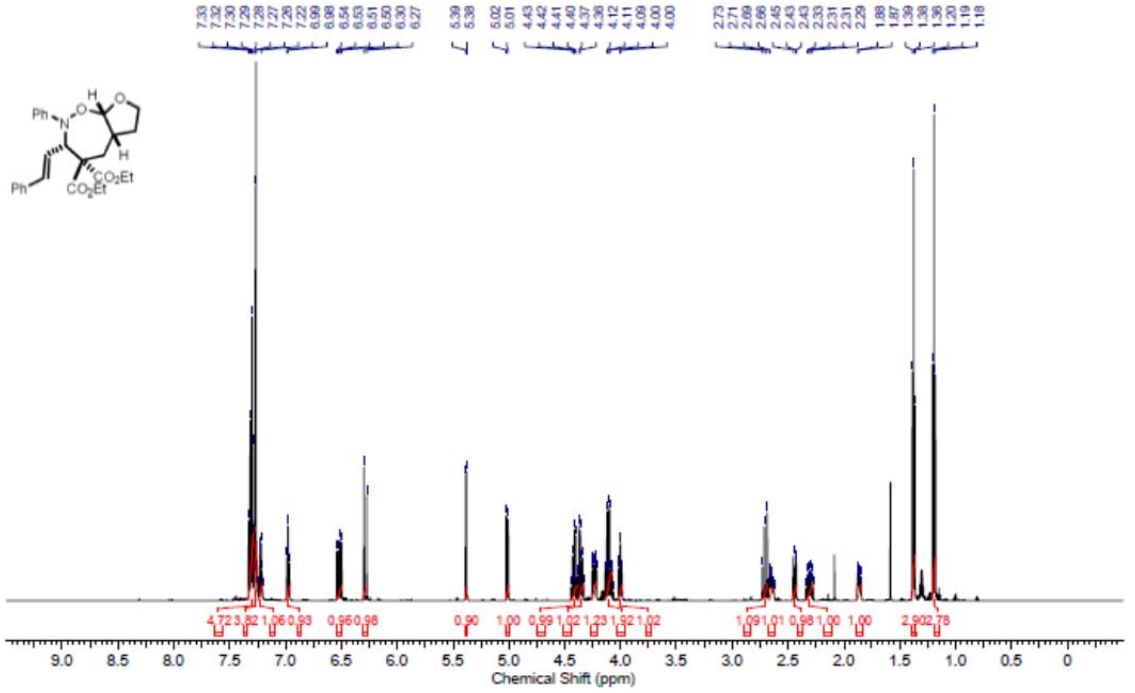


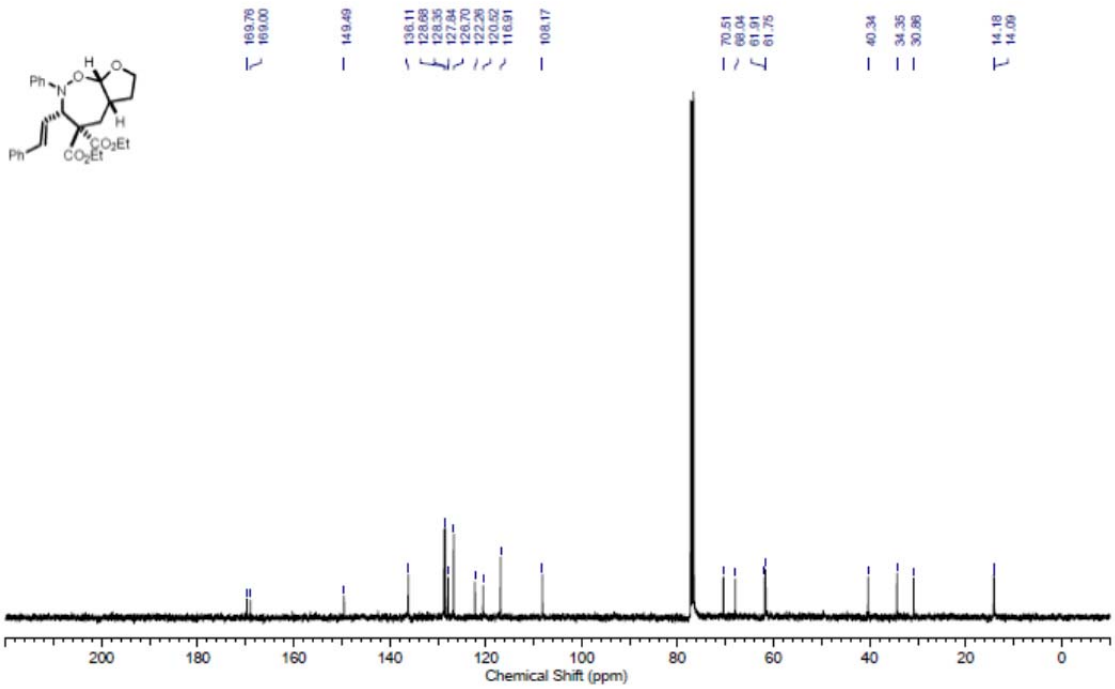
^{1}H and ^{13}C NMR compound **2-81j, diastereomeric mixture**



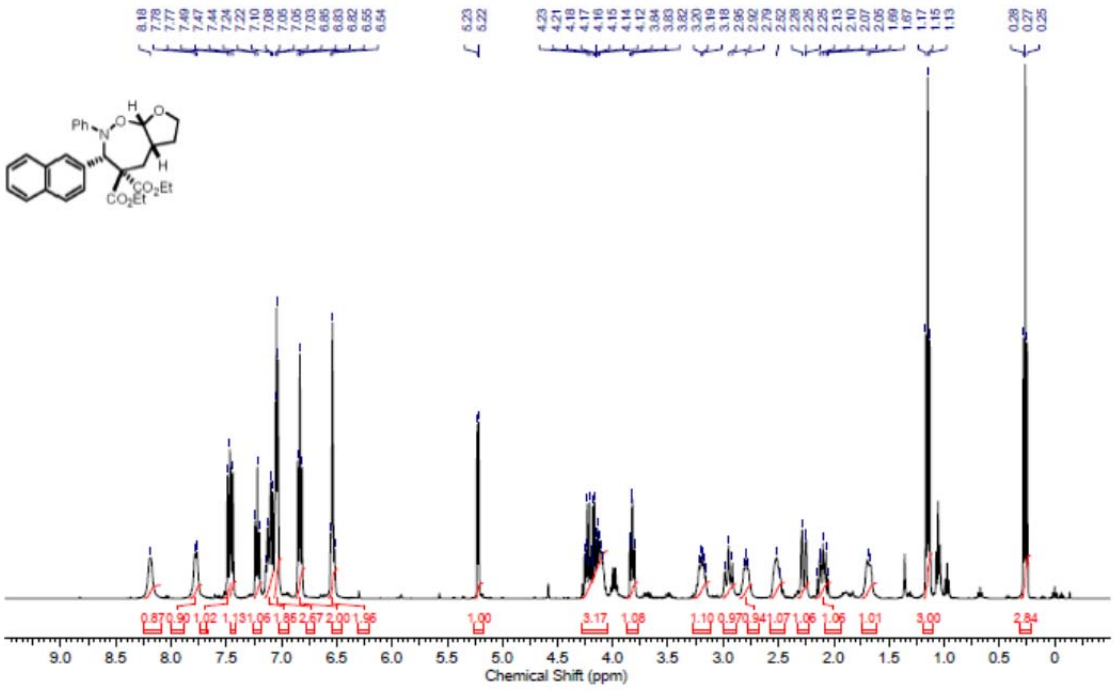


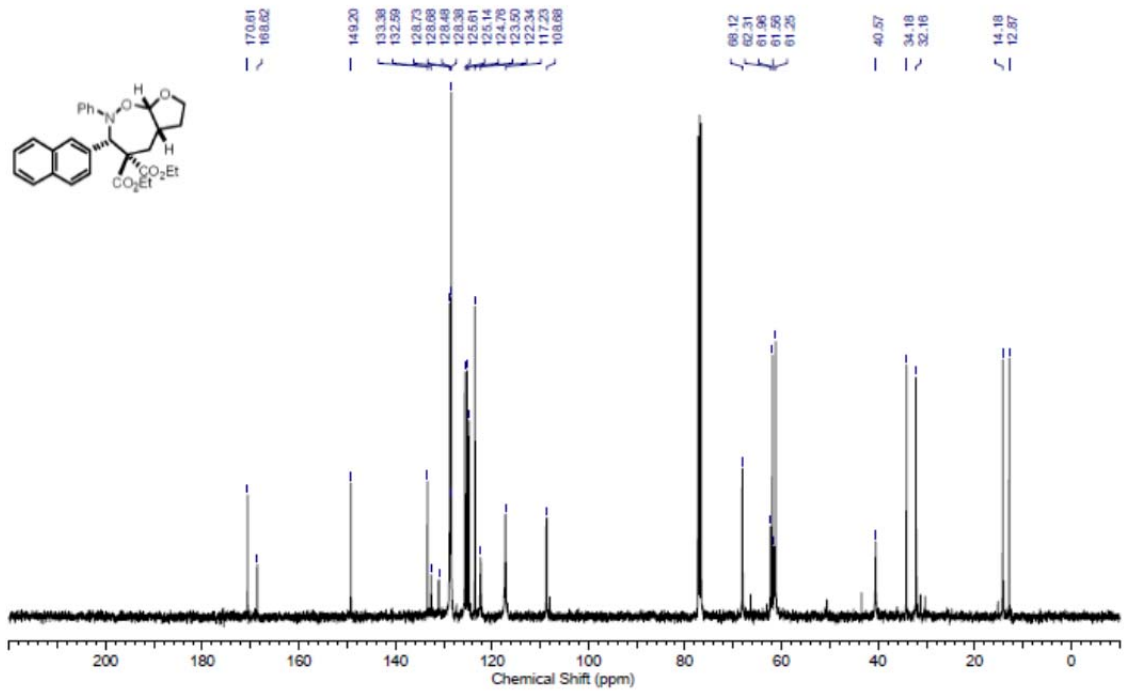
^{1}H and ^{13}C NMR of compound **2-81n, *cis* diastereomer**



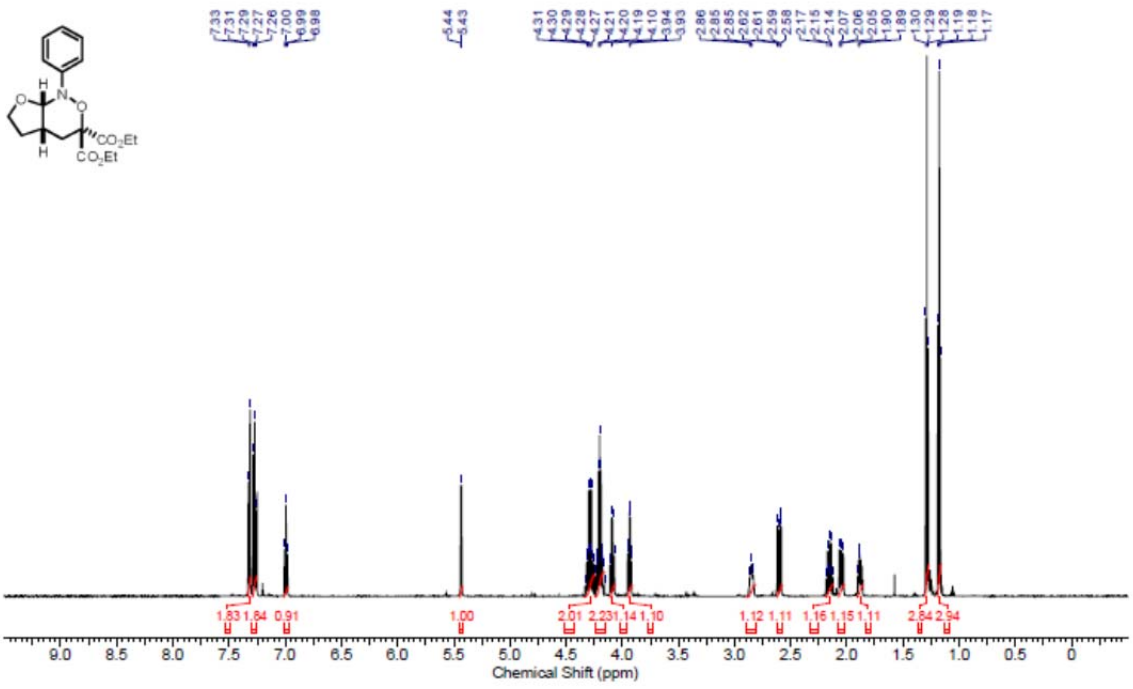


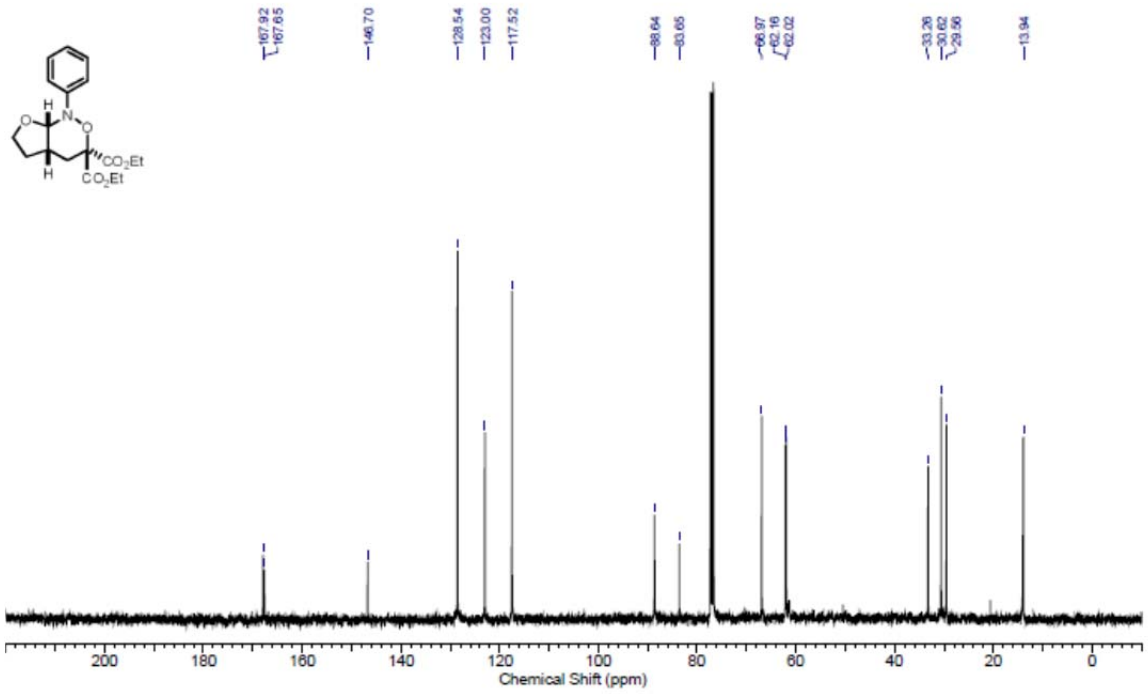
^{1}H and ^{13}C NMR of compound **2-81o, *cis* diastereomer**

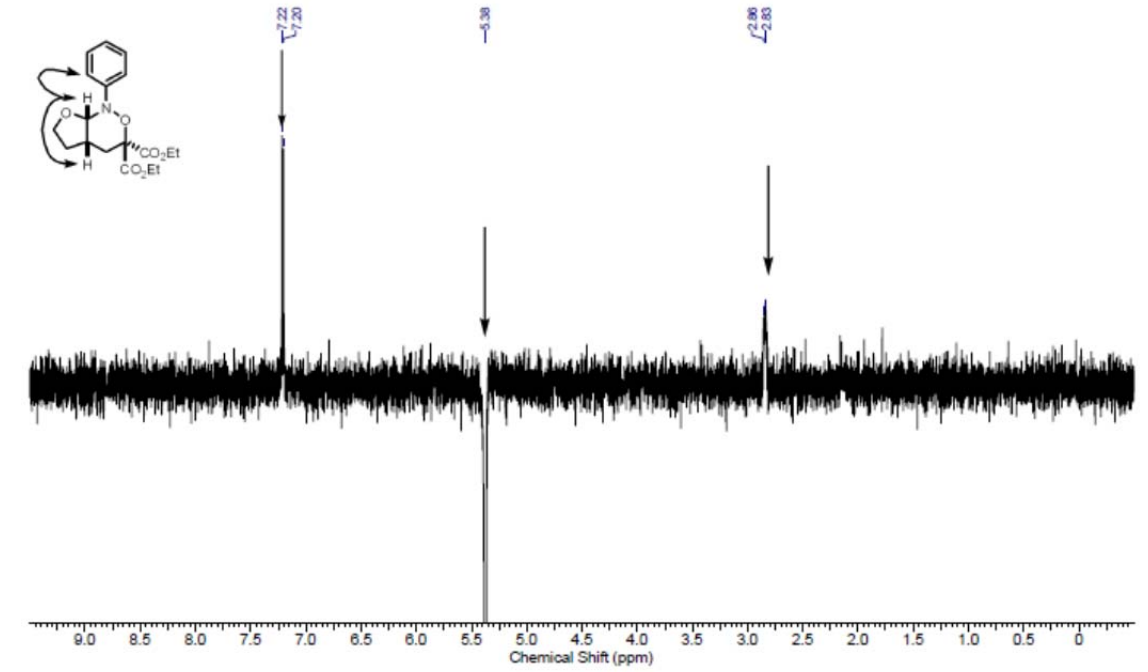




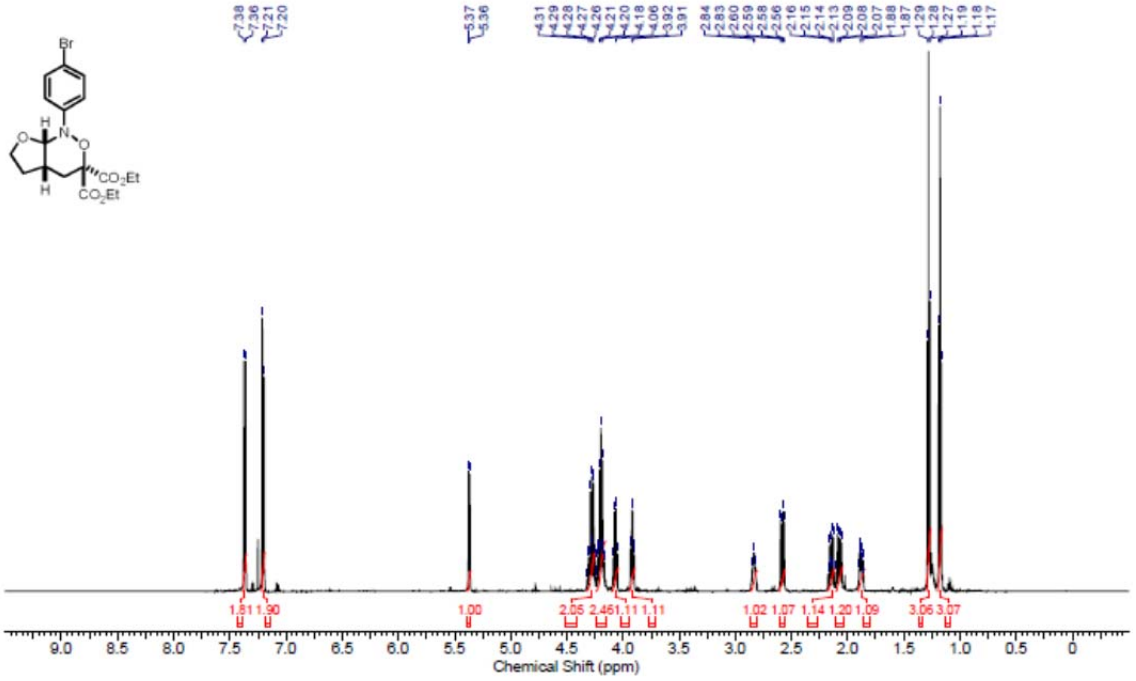
^{1}H, ^{13}C and 1D nOe NMR of compound **2-89a**

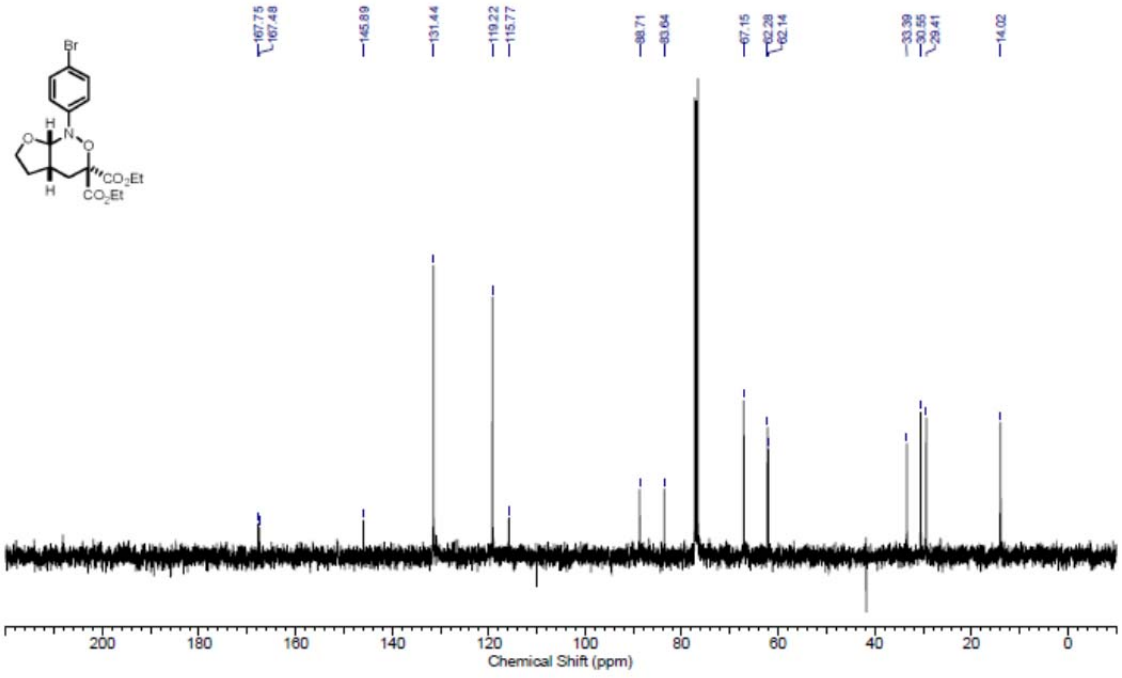


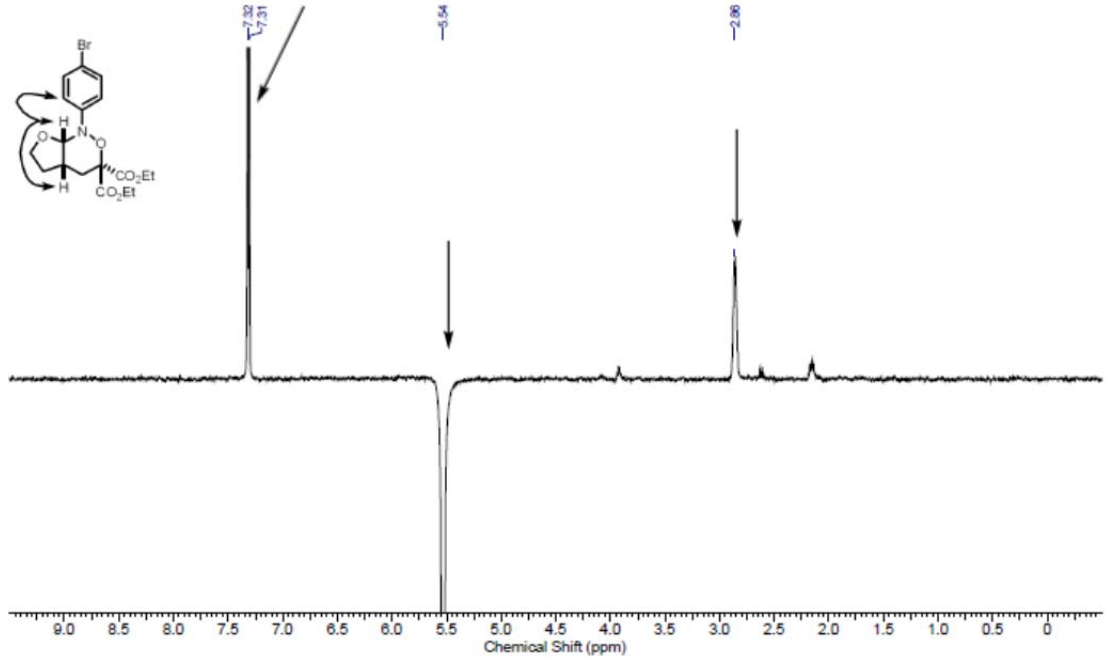

167.92
167.65
146.70
128.54
123.00
117.52
88.64
83.65
66.97
62.16
62.02
33.26
30.62
29.56
13.94
CO2Et
CO2Et
Chemical Shift (ppm)

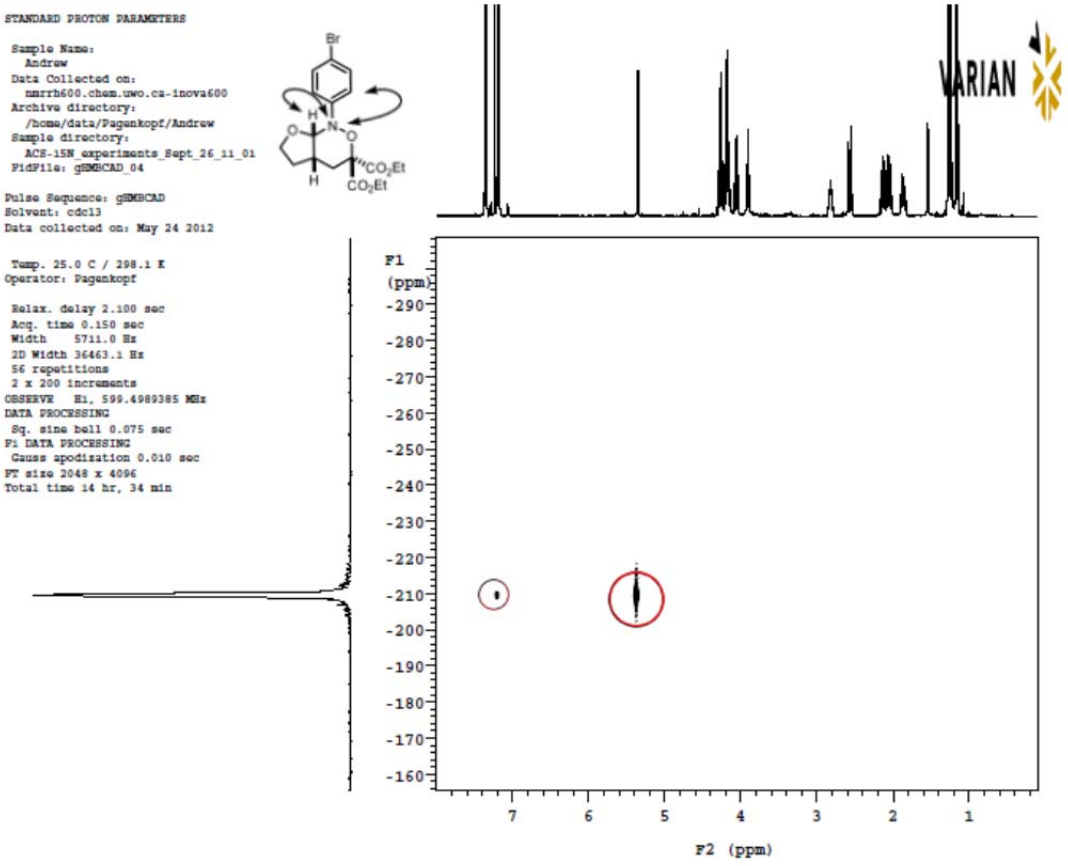

7.22
7.20
5.38
2.86
2.83
CO2Et
CO2Et
Chemical Shift (ppm)

^{1}H, ^{13}C, 1D nOe and 2D HMBCAD NMR of compound **2-89b**

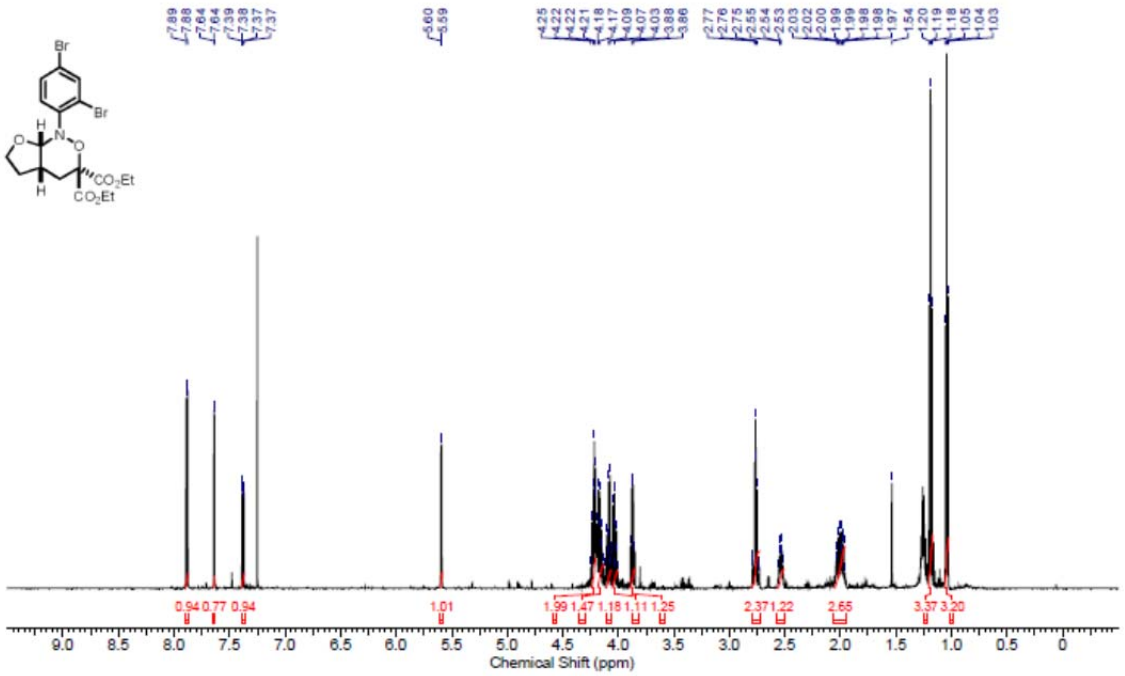


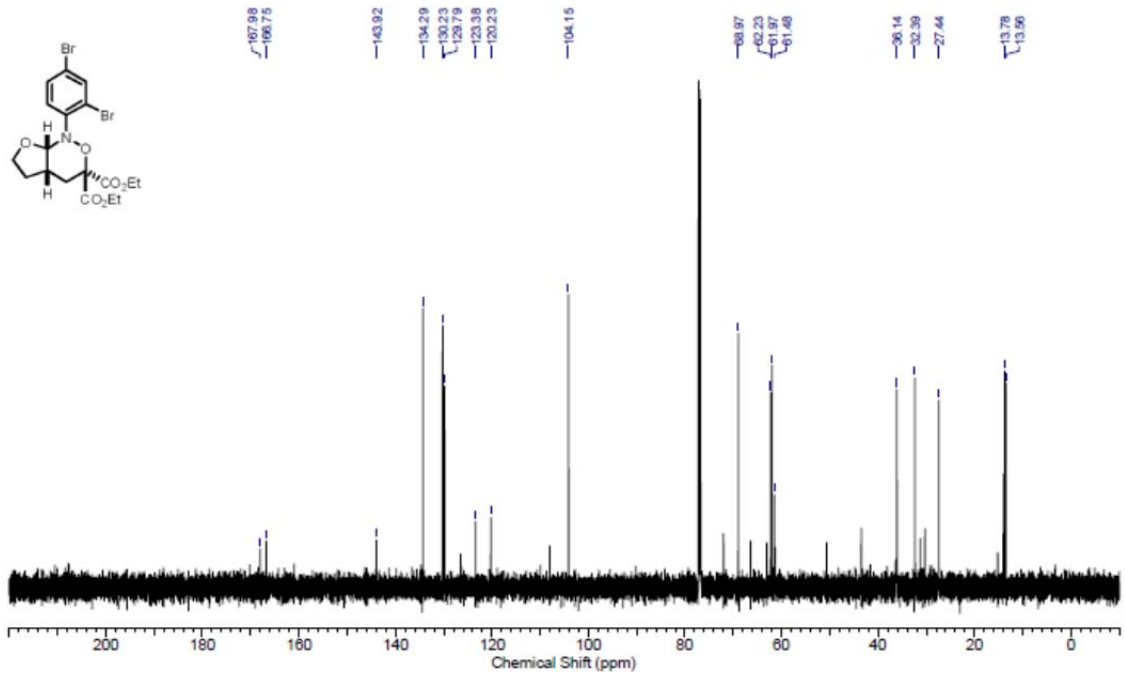



7.32
7.31
5.54
2.86
Br
H
N
O
O
H
CO2Et
CO2Et
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

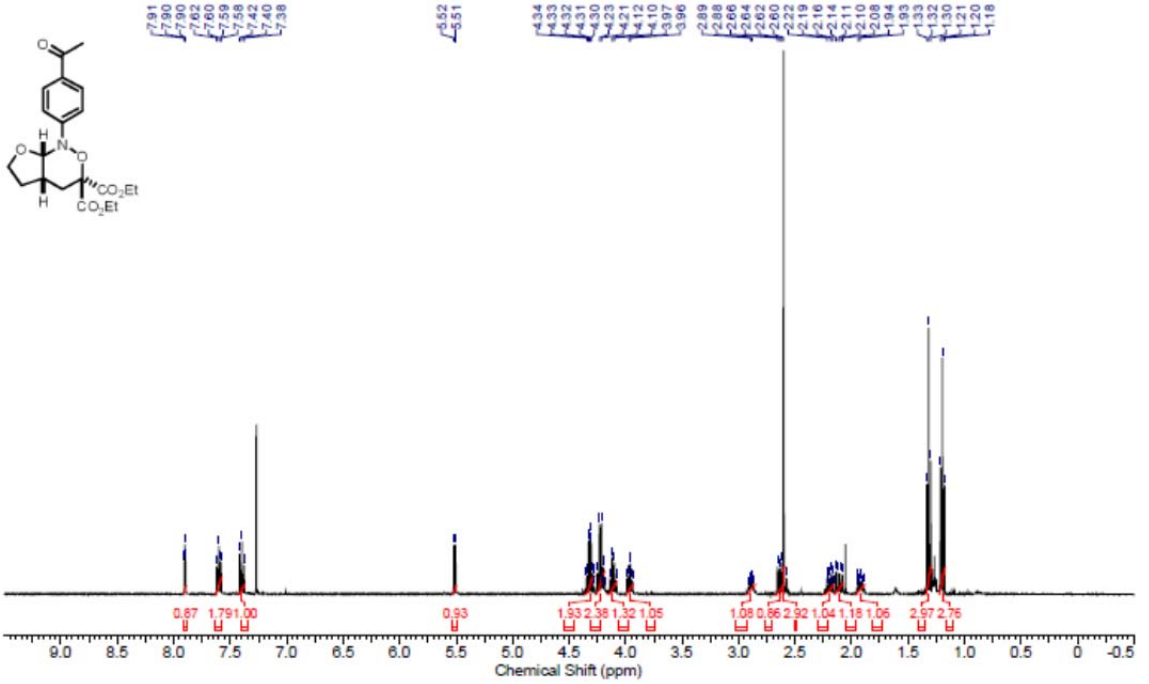

STANDARD PROTON PARAMETERS
Sample Name:
Andrew
Data Collected on:
nmrrh600.chem.uwo.ca-inova600
Archive directory:
/home/data/Pagenkopf/Andrew
Sample directory:
ACS-15N_experiments_Sept_26_11_01
PidFile: gHMBCAD_04
Pulse Sequence: gHMBCAD
Solvent: cdcl3
Data collected on: May 24 2012
Temp. 25.0 C / 298.1 K
Operator: Pagenkopf
Relax. delay 2.100 sec
Acq. time 0.150 sec
Width 5711.0 Hz
2D Width 36463.1 Hz
56 repetitions
2 x 200 increments
OBSERVE H1, 599.4989385 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Gauss apodization 0.010 sec
FT size 2048 x 4096
Total time 14 hr, 34 min
Br
H
N
O
O
H
CO2Et
CO2Et
VARIAN
F1
(ppm)
-290
-280
-270
-260
-250
-240
-230
-220
-210
-200
-190
-180
-170
-160
7 6 5 4 3 2 1
F2 (ppm)

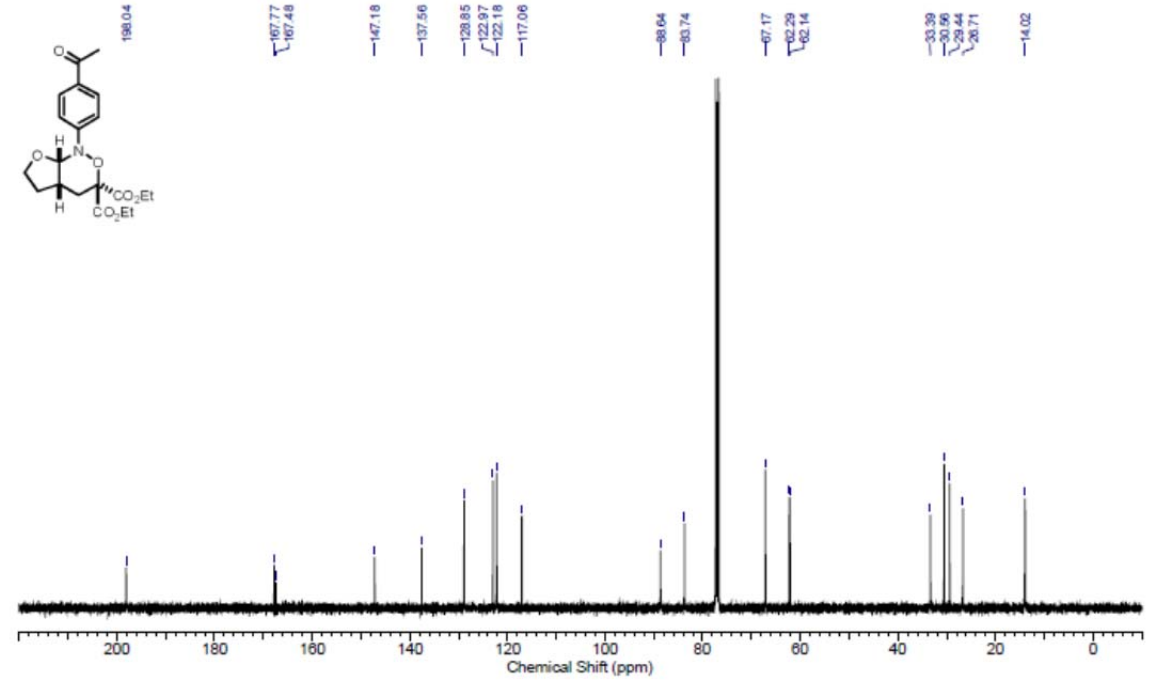
^{1}H and ^{13}C NMR of compound **2-89c**

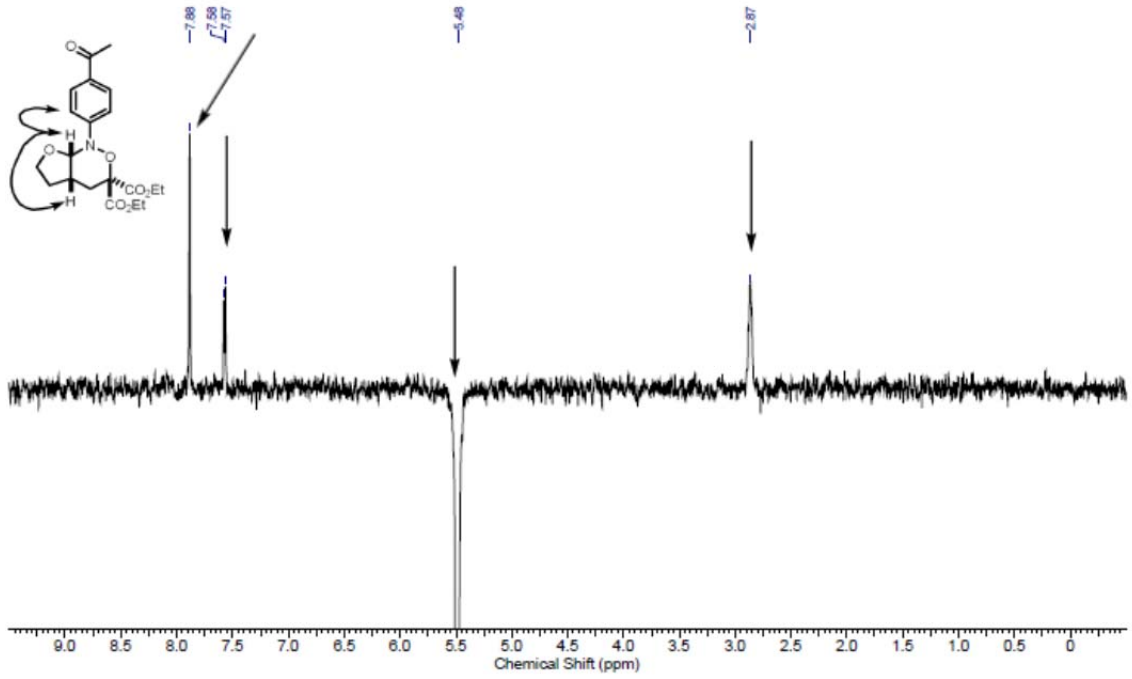




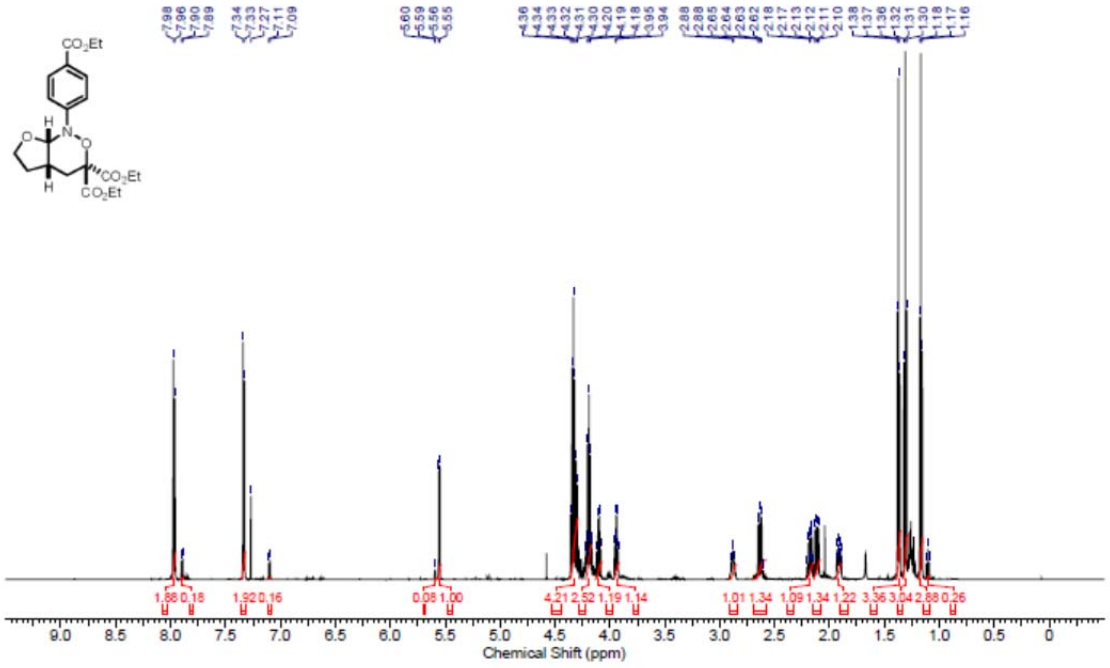
^{1}H, ^{13}C and 1 D nOe NMR of compound **2-89d**

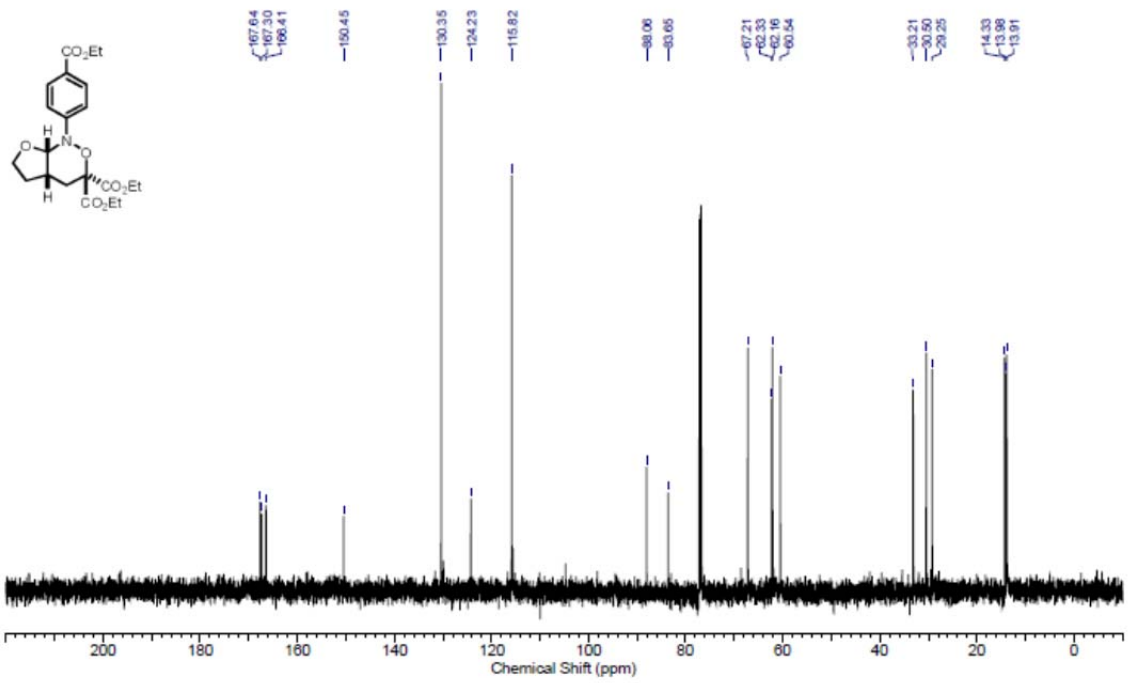


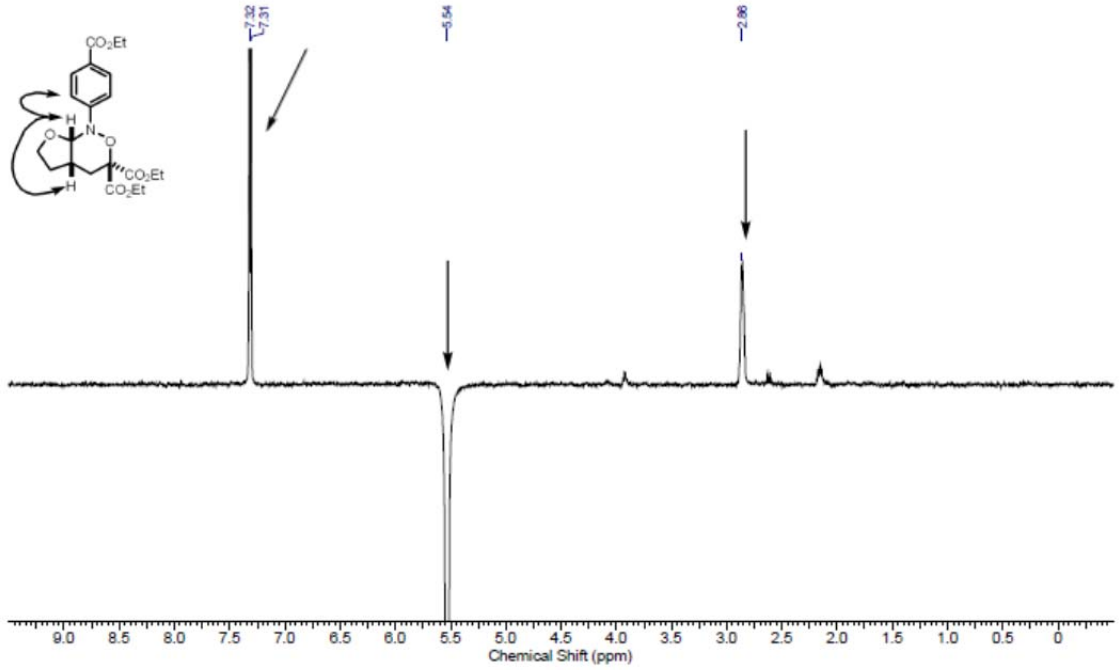




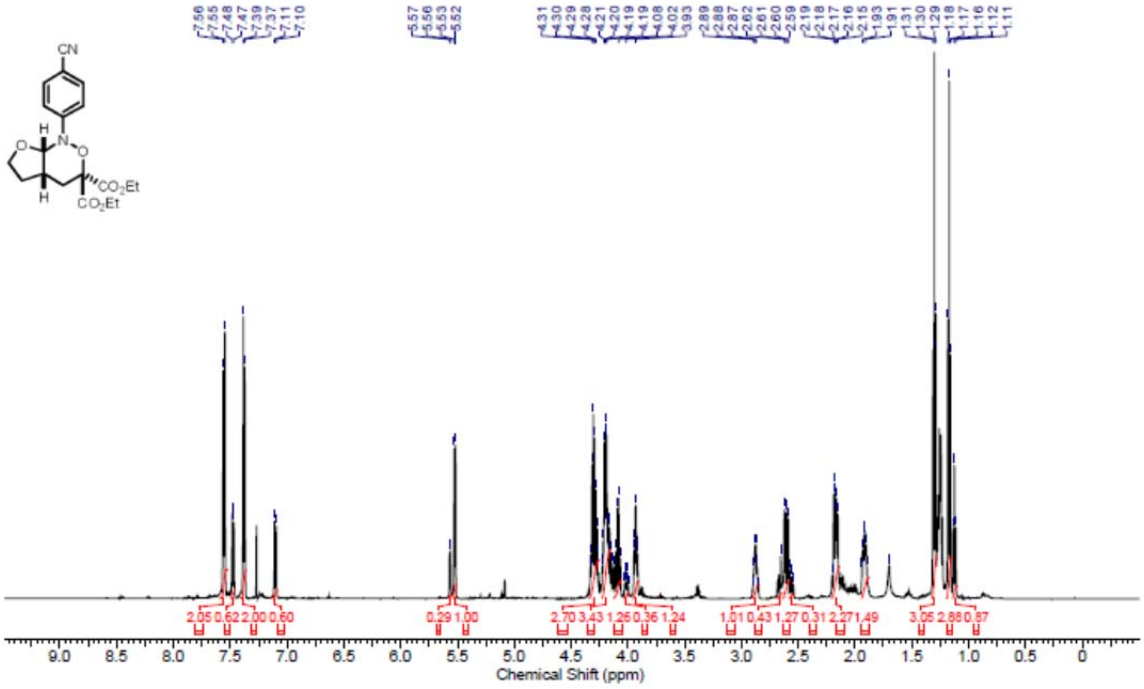
^{1}H, ^{13}C and 1 D nOe NMR of compound **2-89e**

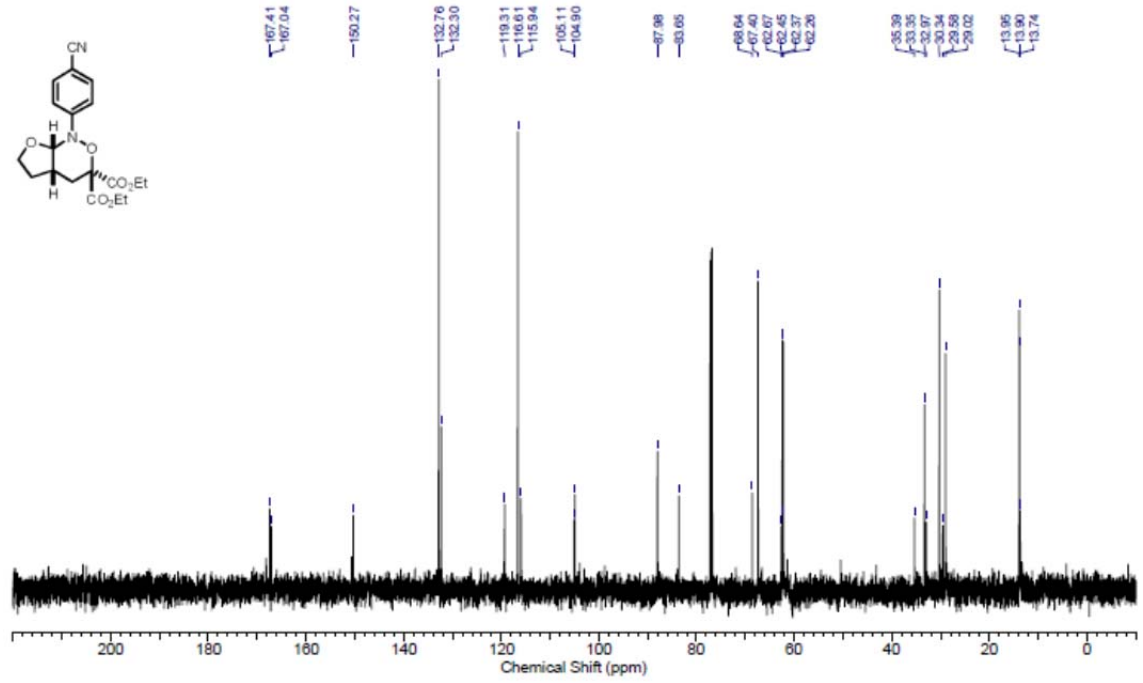


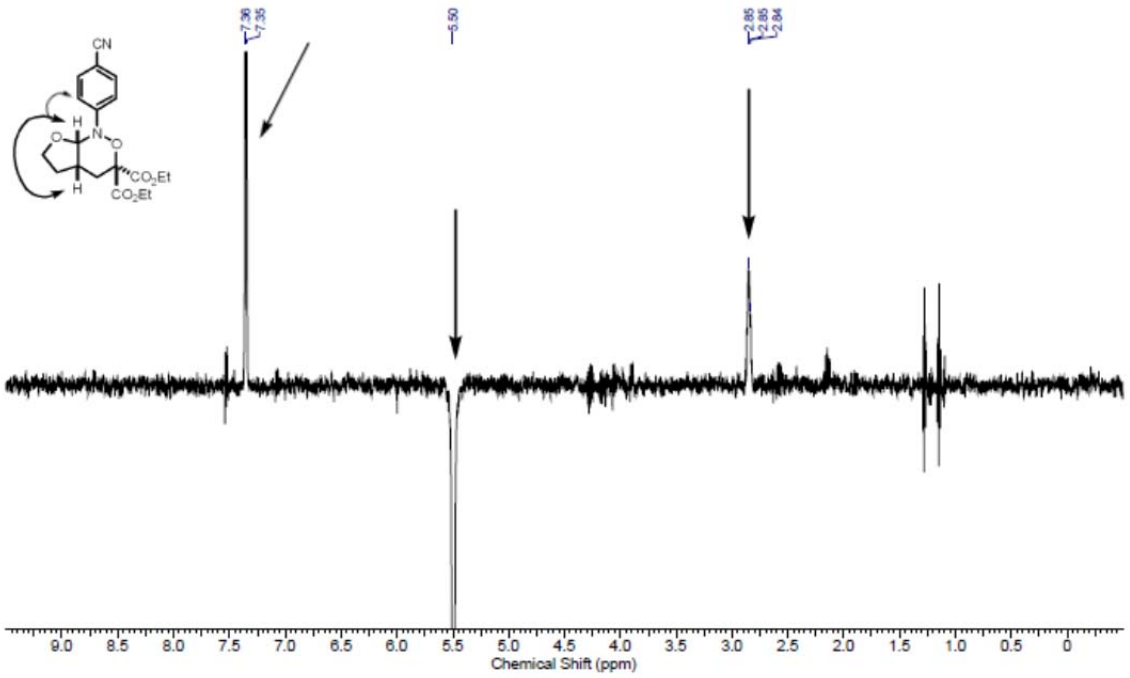

167.64
167.30
166.41
150.45
130.35
124.23
115.82
88.06
83.65
67.21
62.33
62.16
60.54
33.21
30.50
29.25
14.33
13.98
13.91
CO2Et
CO2Et
CO2Et
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

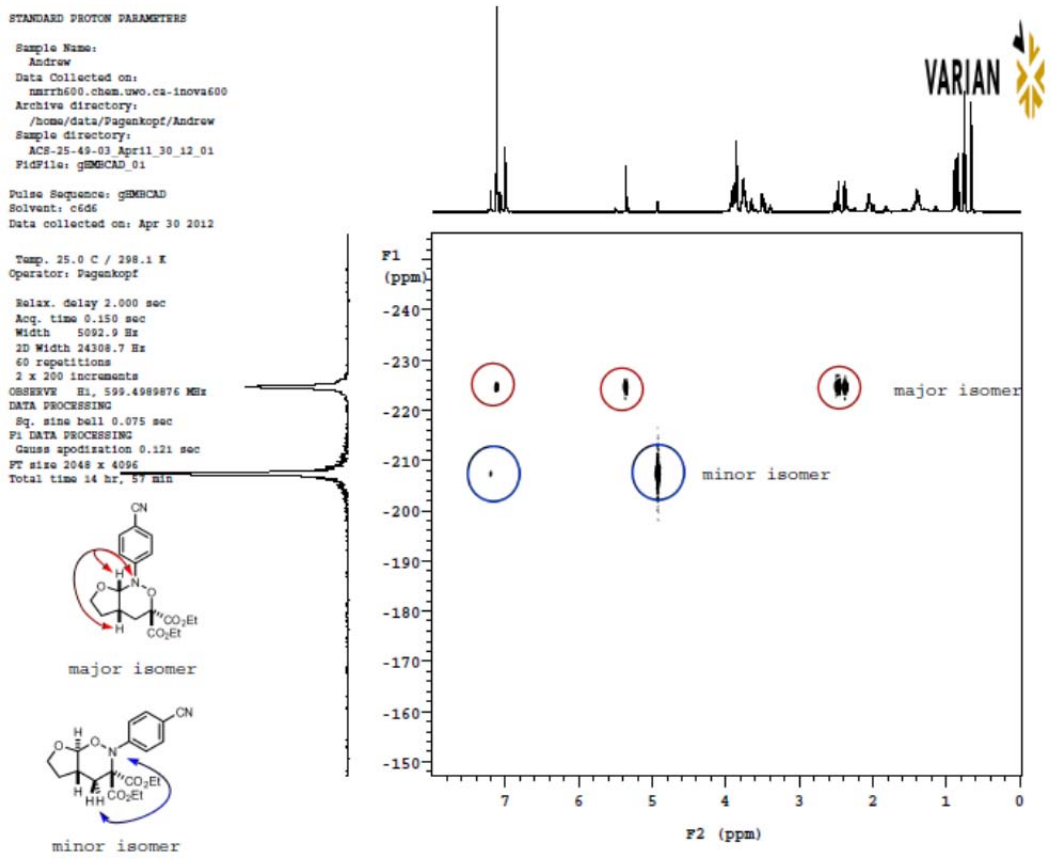

7.32
7.31
5.54
2.86
CO2Et
CO2Et
CO2Et
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

^{1}H, ^{13}C, 1D nOe, 2D HMBCAD NMR of compound **2-89f**

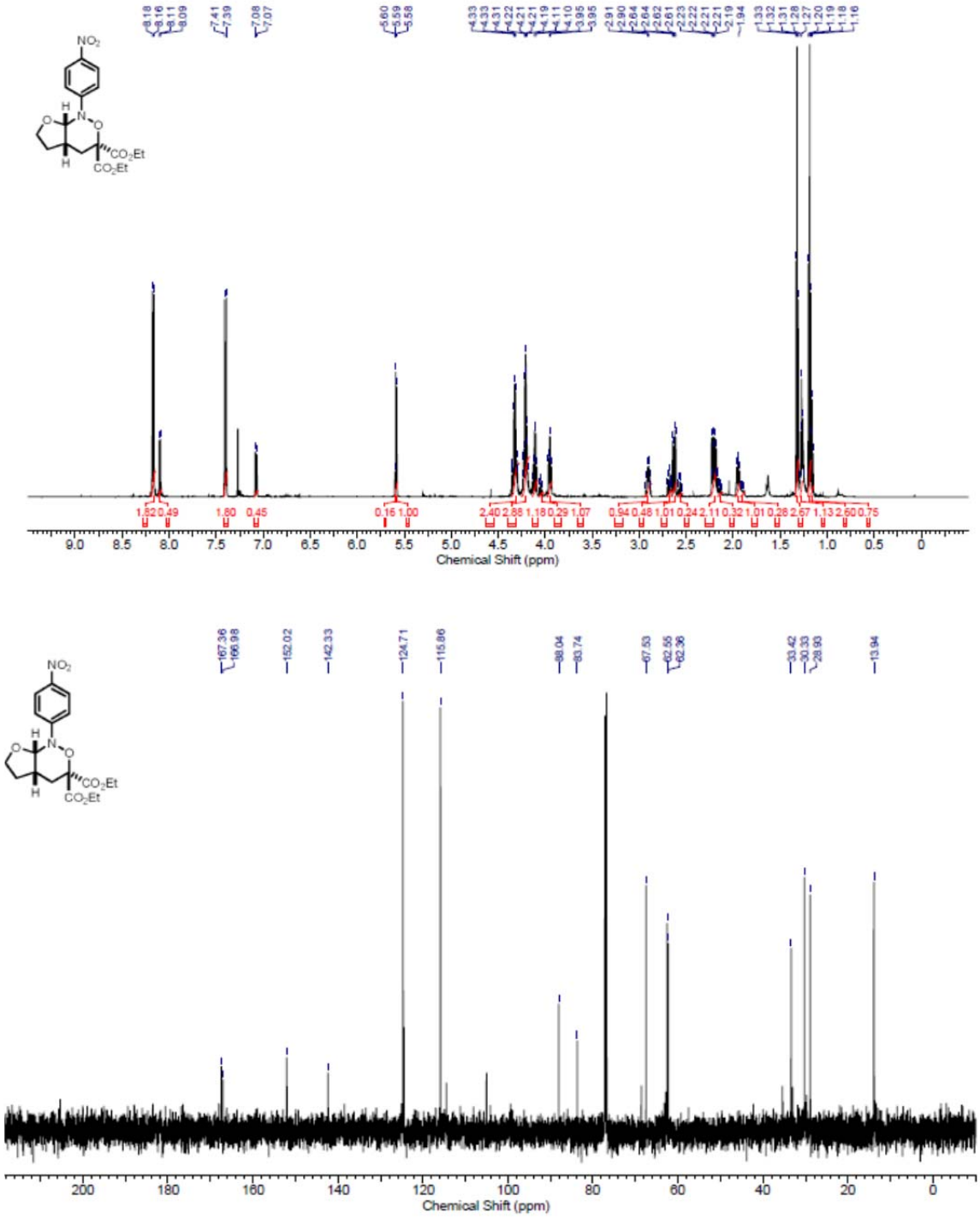


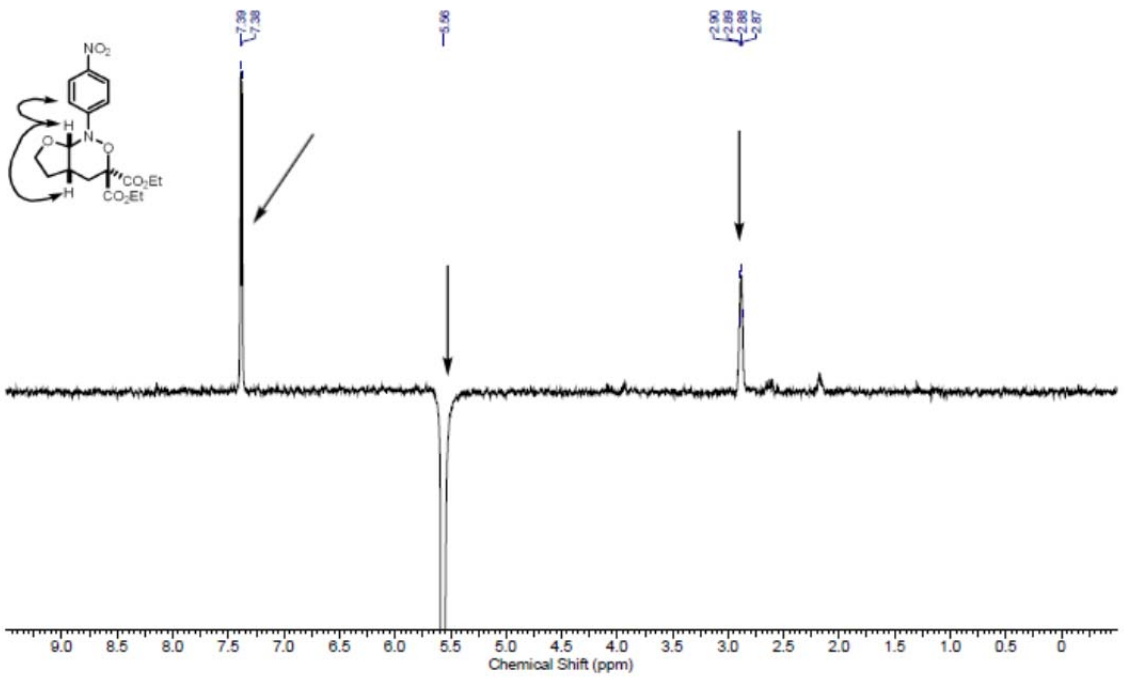



7.36
7.35
5.50
2.85
2.85
2.84
CN
H
N
O
O
H
CO2Et
CO2Et
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

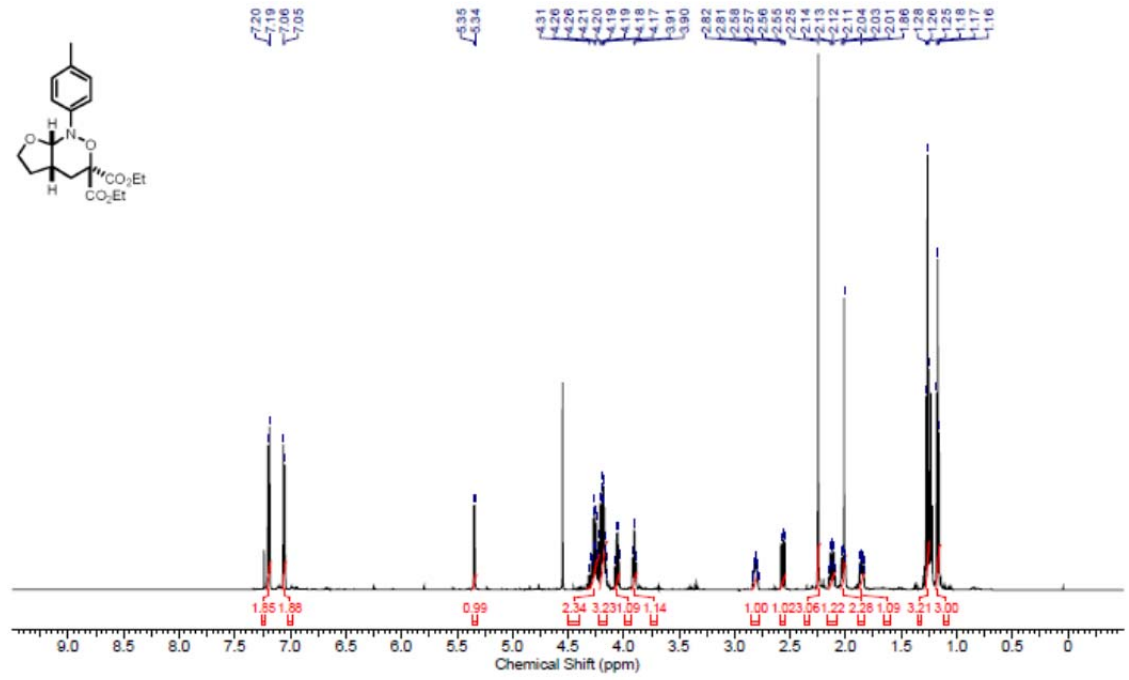

STANDARD PROTON PARAMETERS
Sample Name:
Andrew
Data Collected on:
nmrrh600.chem.uwo.ca-inova600
Archive directory:
/home/data/Pagenkopf/Andrew
Sample directory:
ACS-25-49-03_April_30_12_01
FidFile: gHMBCAD_01
Pulse Sequence: gHMBCAD
Solvent: c6d6
Data collected on: Apr 30 2012
Temp. 25.0 C / 298.1 K
Operator: Pagenkopf
Relax. delay 2.000 sec
Acq. time 0.150 sec
Width 5092.9 Hz
2D Width 24308.7 Hz
60 repetitions
2 x 200 increments
OBSERVE H1, 599.4989876 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Gauss apodization 0.121 sec
FT size 2048 x 4096
Total time 14 hr, 57 min
VARIAN
F1
(ppm)
-240
-230
-220
-210
-200
-190
-180
-170
-160
-150
major isomer
minor isomer
7
6
5
4
3
2
1
0
F2 (ppm)
CN
H
N
O
O
CO2Et
CO2Et
major isomer
minor isomer

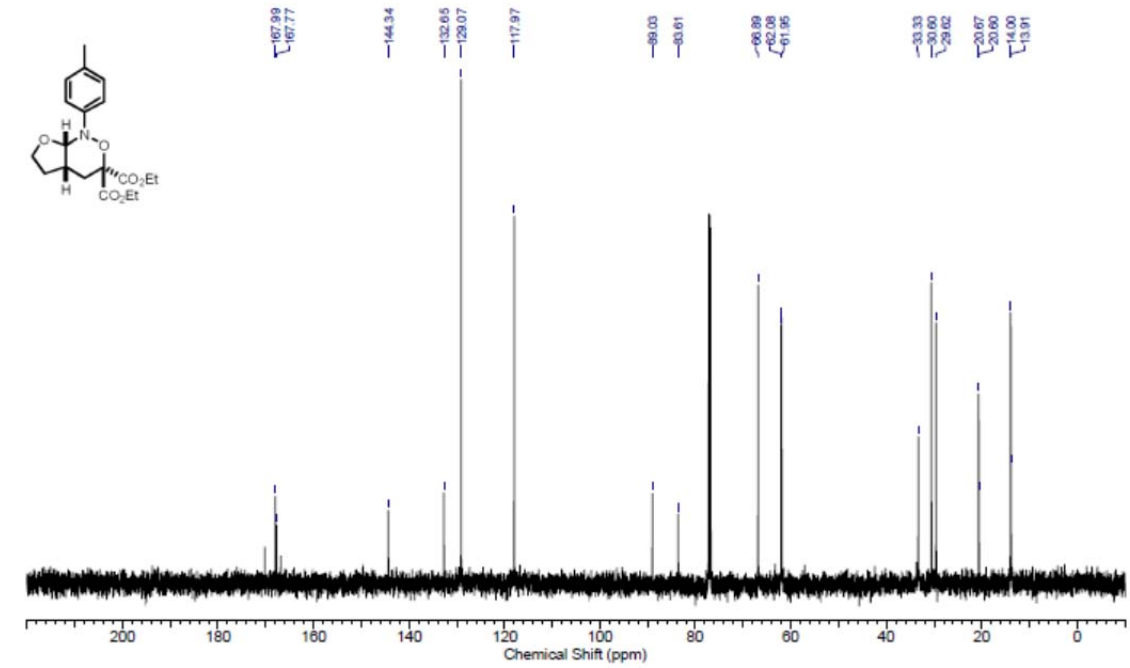
^{1}H, ^{13}C, 1D nOe NMR of compound **2-89g**

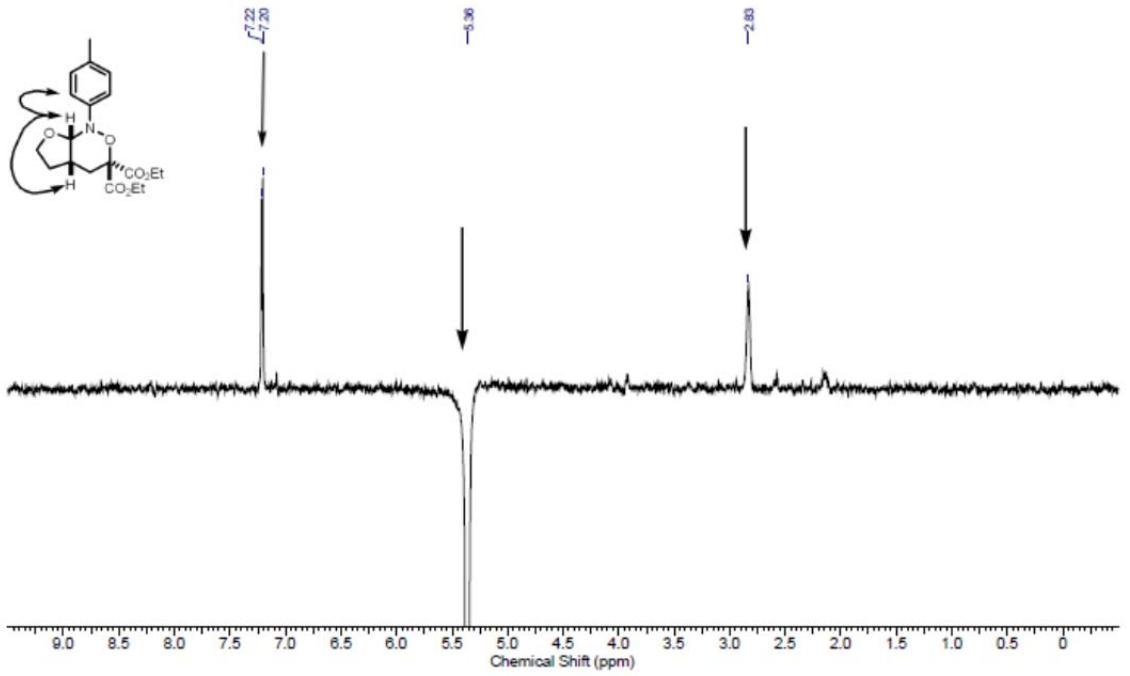


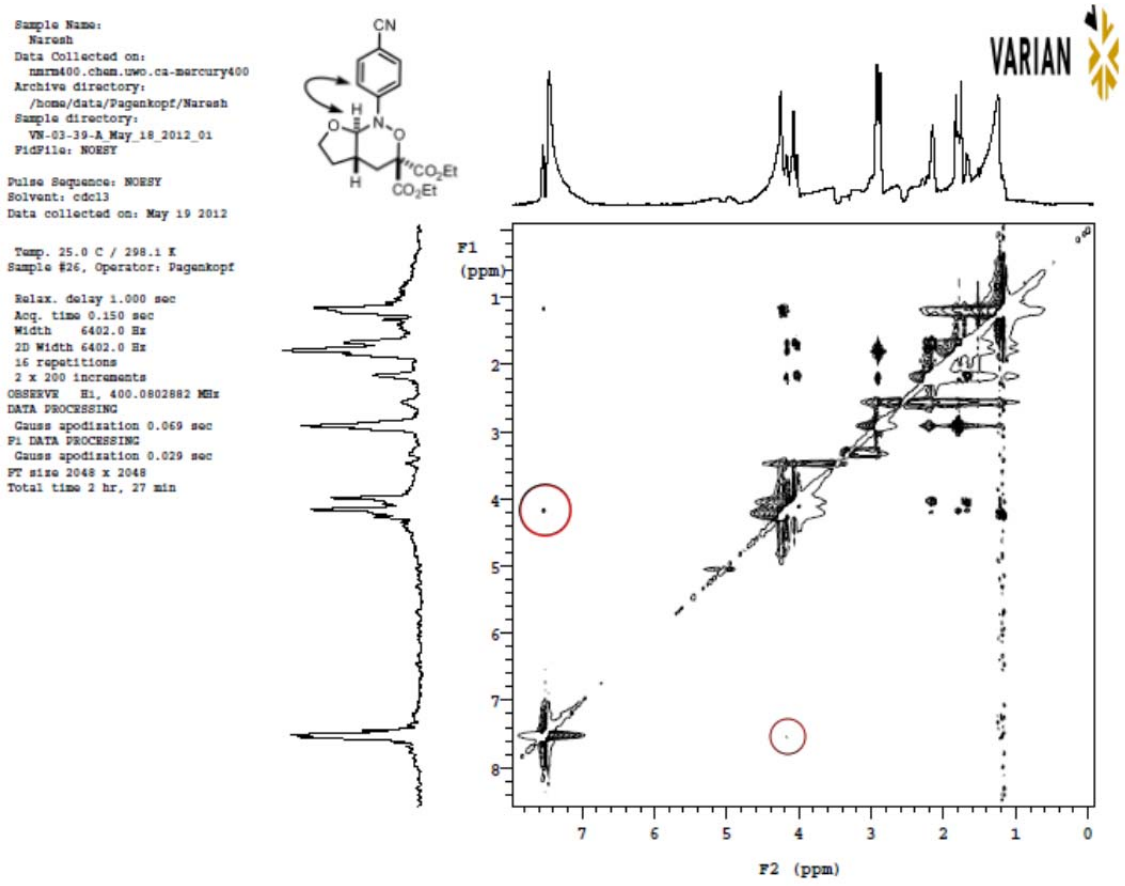


^{1}H, ^{13}C and 1D nOe NMR of compound **2-89h**



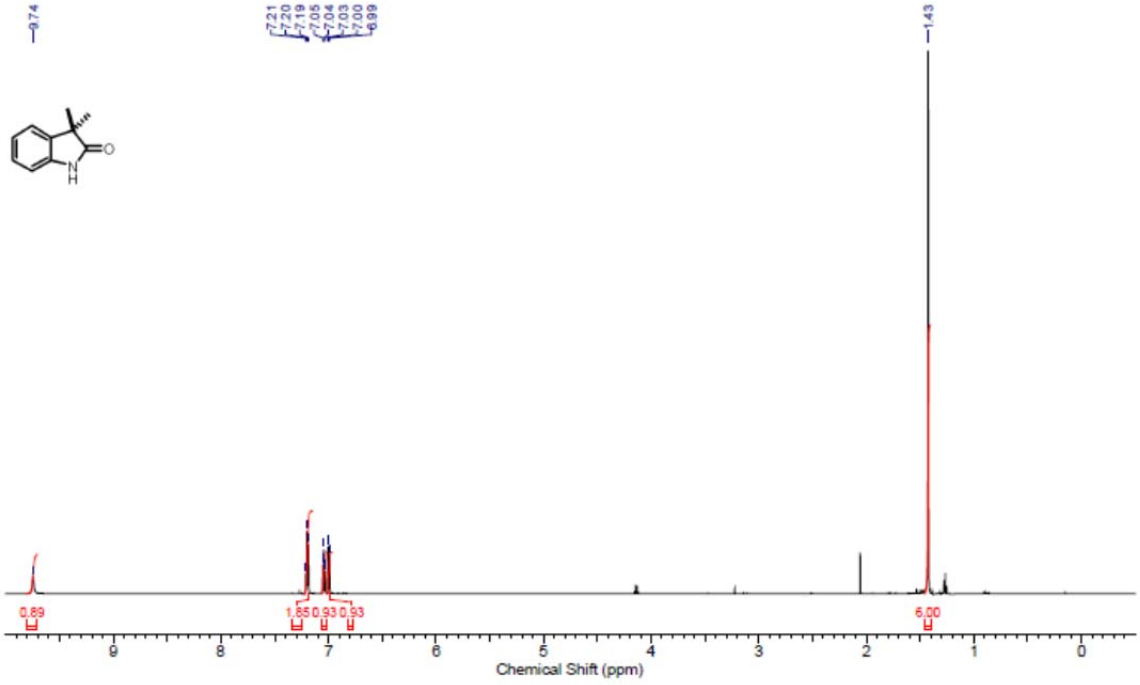

167.99
167.77
144.34
132.65
129.07
117.97
89.03
83.61
66.89
62.08
61.95
33.33
30.60
29.62
20.67
20.60
14.00
13.91
CO2Et
CO2Et
Chemical Shift (ppm)

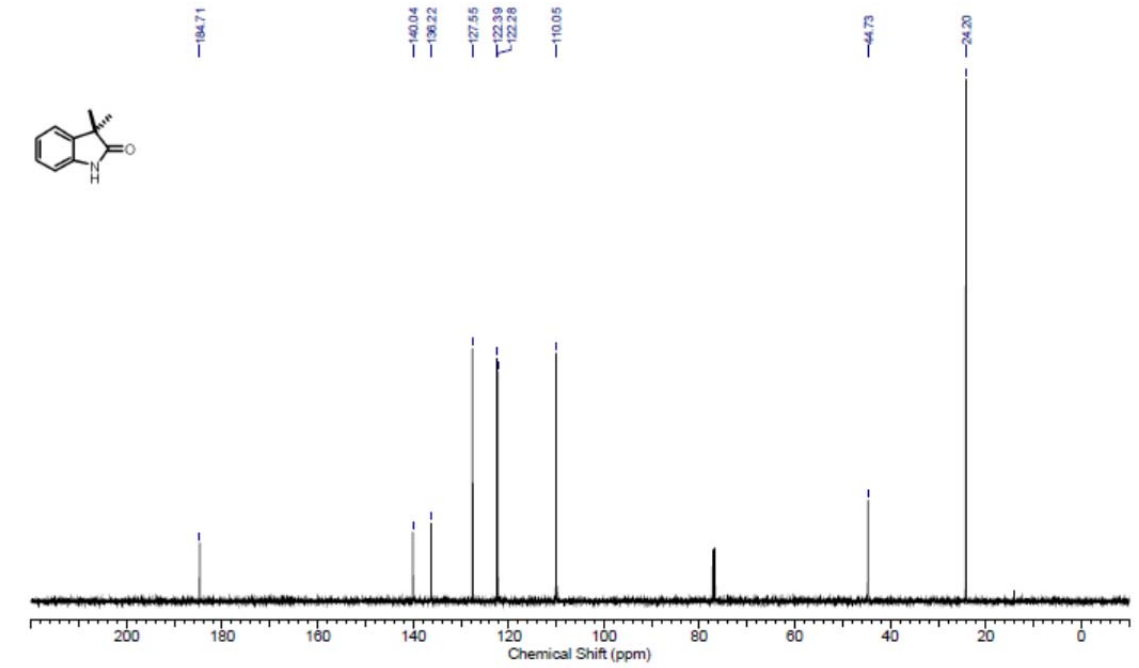

7.22
7.20
5.36
2.83
CO2Et
CO2Et
Chemical Shift (ppm)


Sample Name:
Naresh
Data Collected on:
nmrm400.chem.uwo.ca-mercury400
Archive directory:
/home/data/Pagenkopf/Naresh
Sample directory:
VN-03-39-A_May_18_2012_01
FidFile: NOESY
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: May 19 2012
Temp. 25.0 C / 298.1 K
Sample #26, Operator: Pagenkopf
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 6402.0 Hz
2D Width 6402.0 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.0802882 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.029 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
CN
H
N
O
O
H
CO2Et
CO2Et
VARIAN
F1
(ppm)
F2 (ppm)

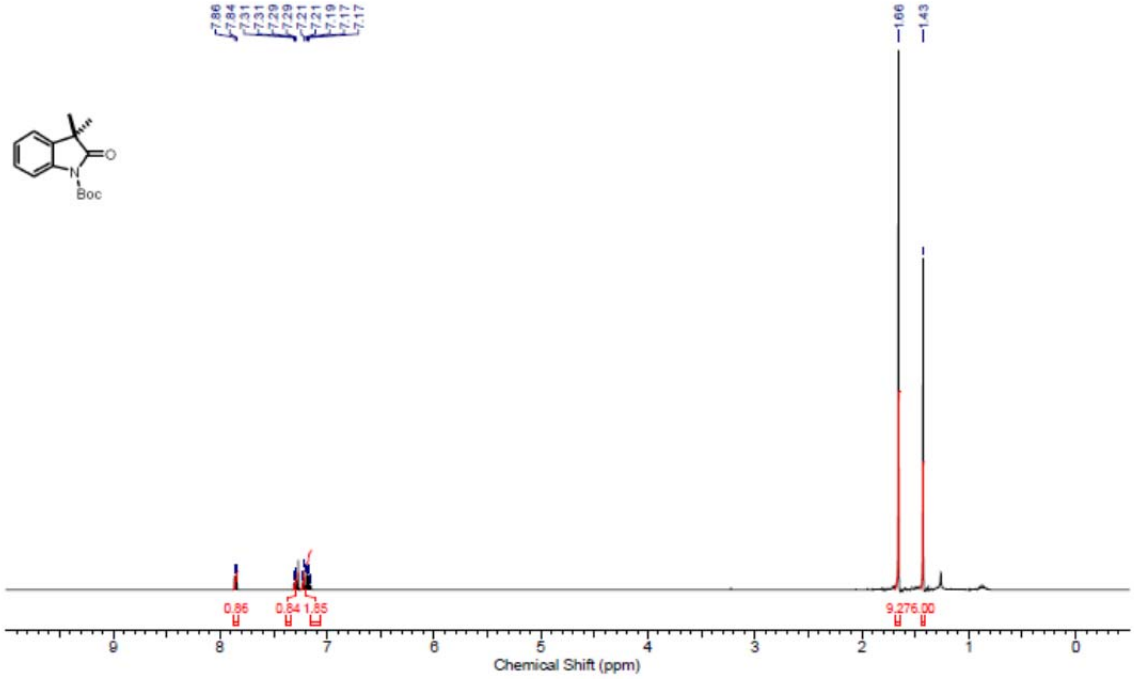
Appendix 3 – NMR Spectral Data for Chapter 3

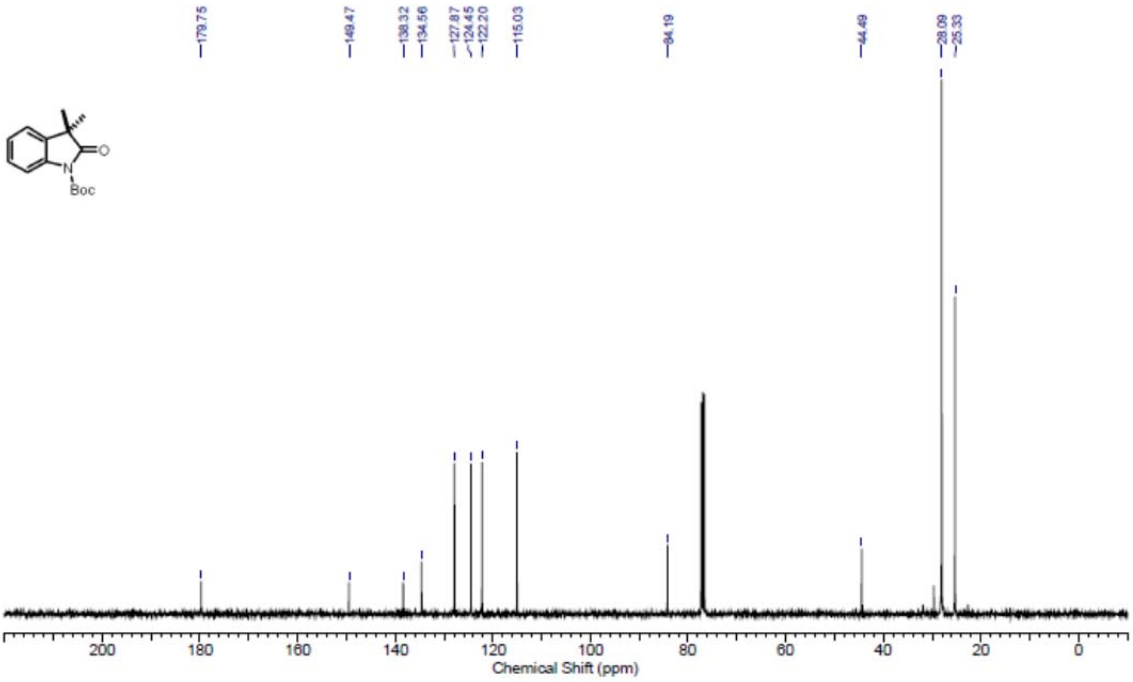
^{1}H and ^{13}C NMR of compound **3-65**



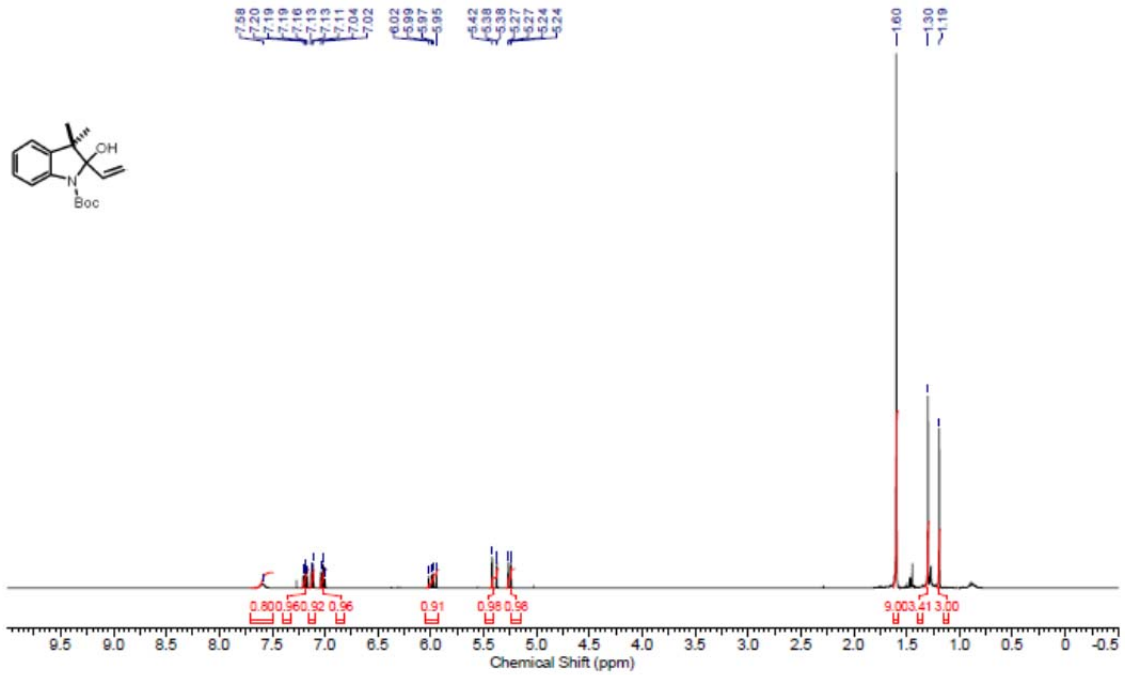


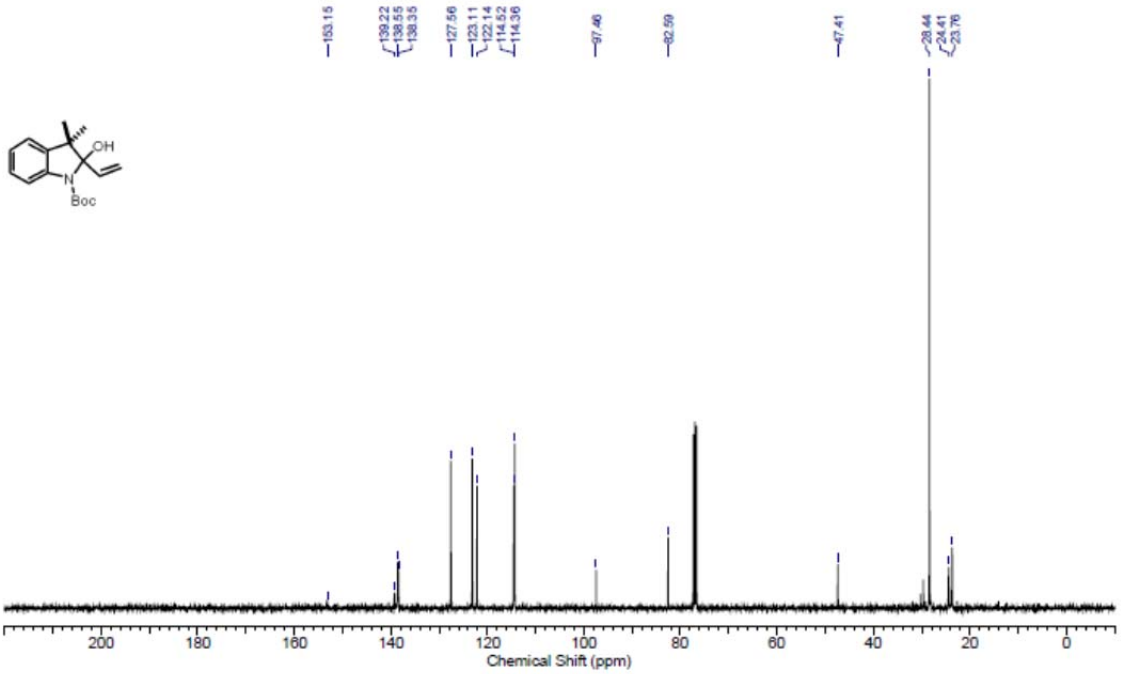
^{1}H and ^{13}C NMR of compound **3-68**



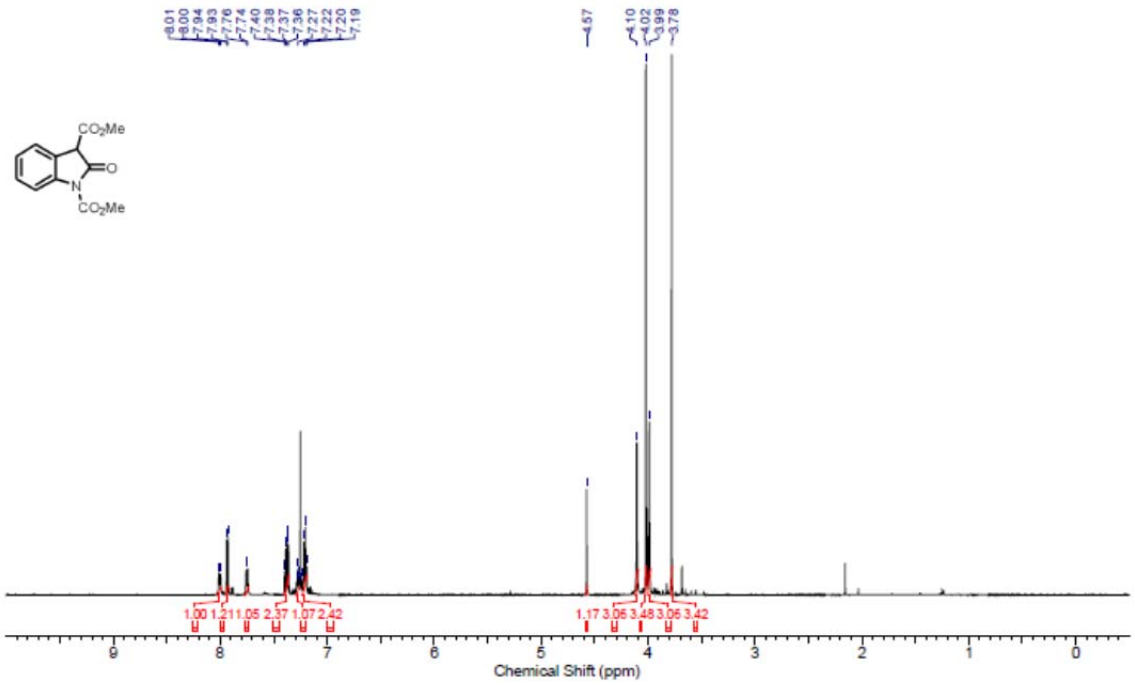


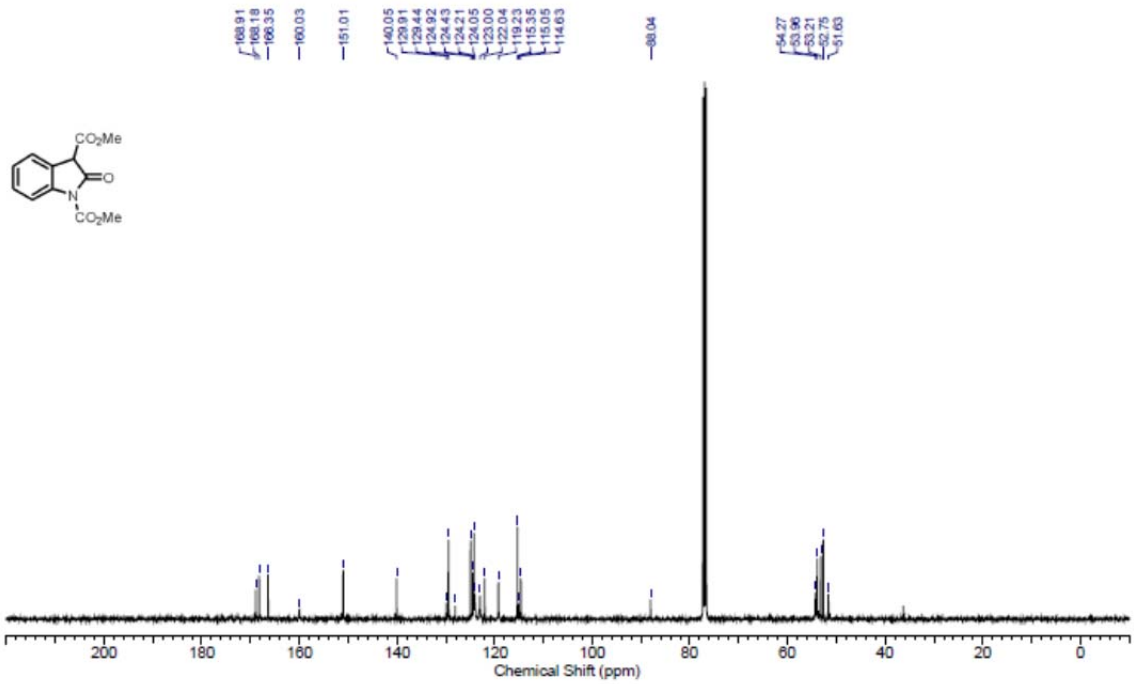
^{1}H and ^{13}C NMR of compound **3-69**



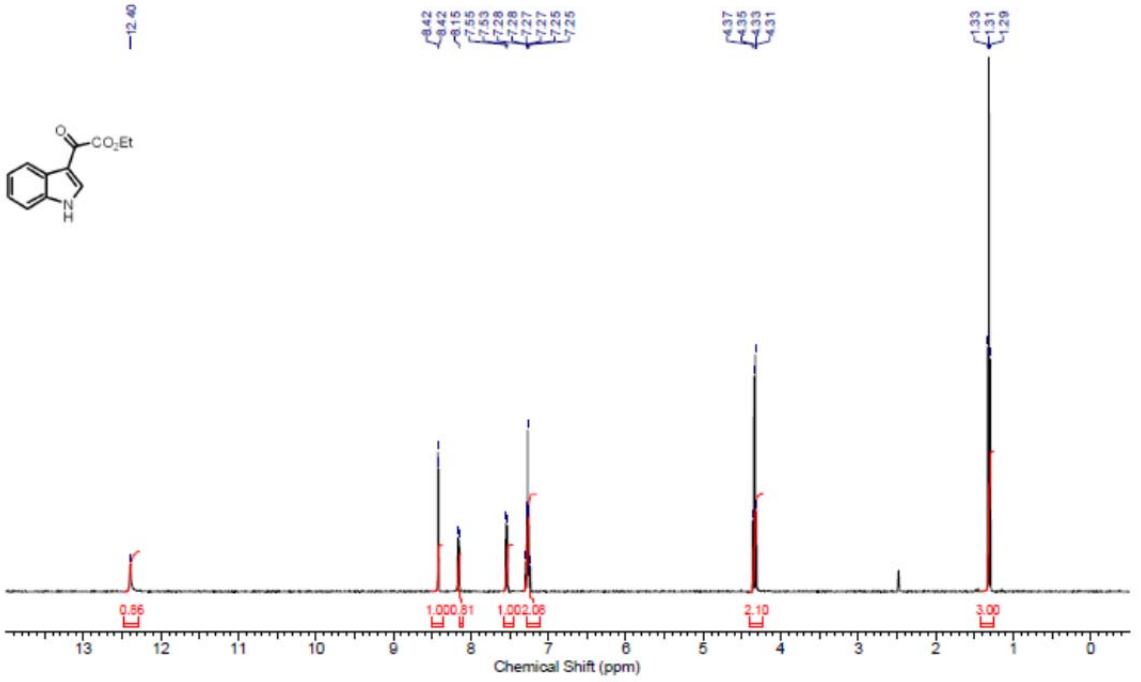


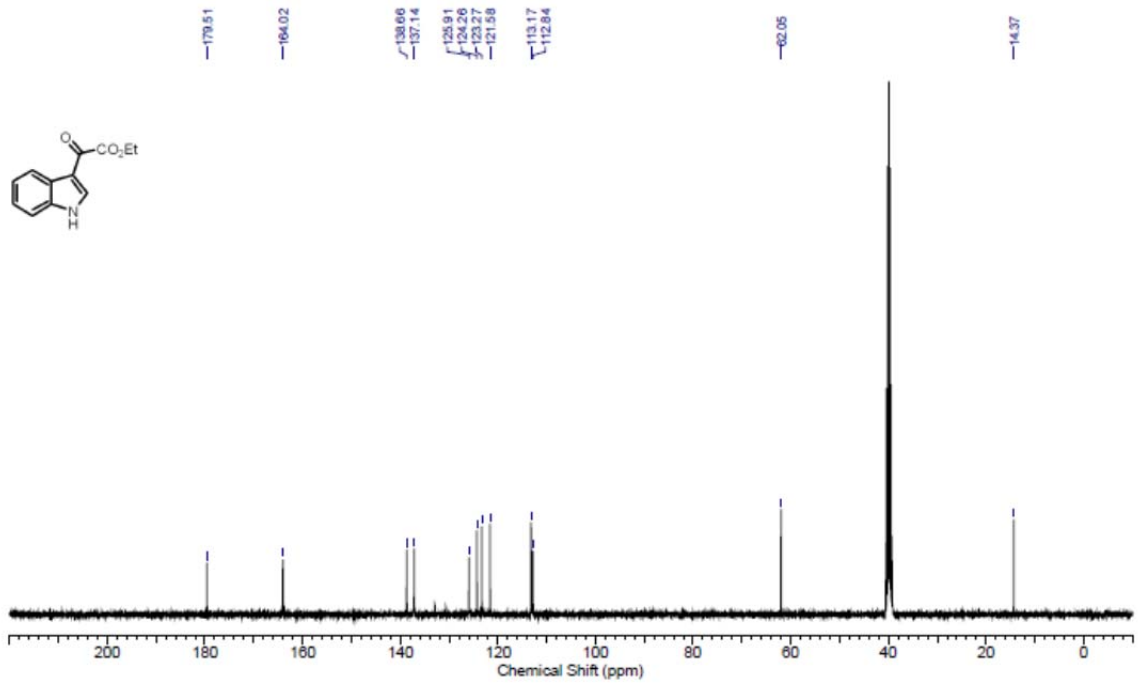
^{1}H and ^{13}C NMR of compound **3-63**



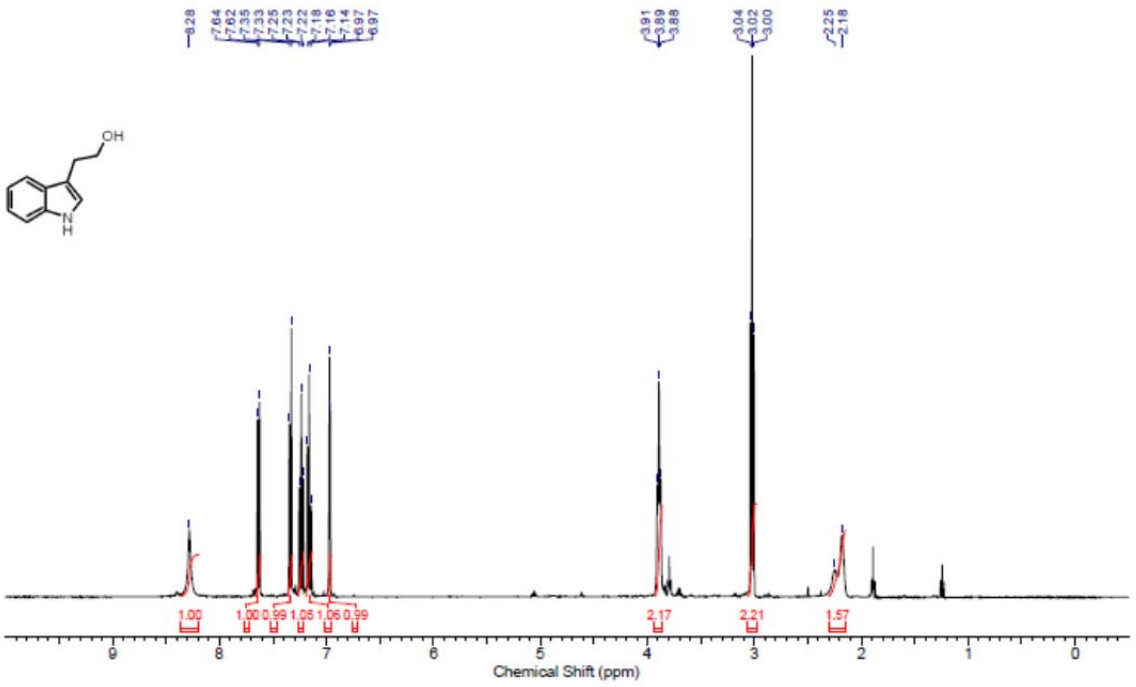


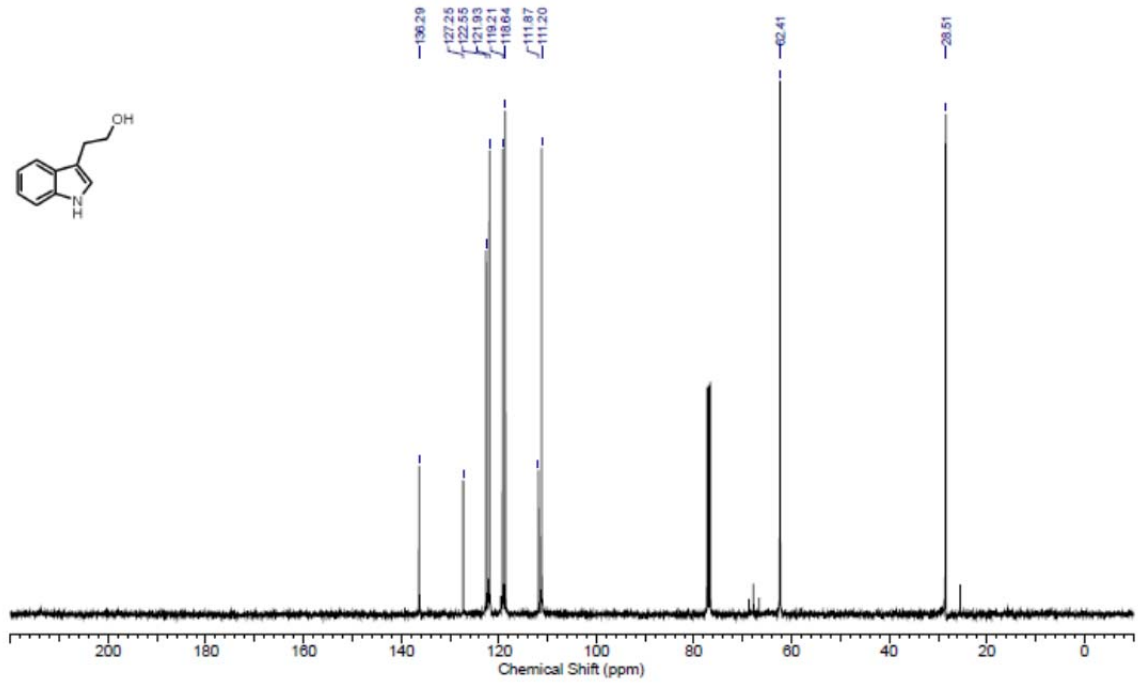
^{1}H and ^{13}C NMR of compound **3-81**



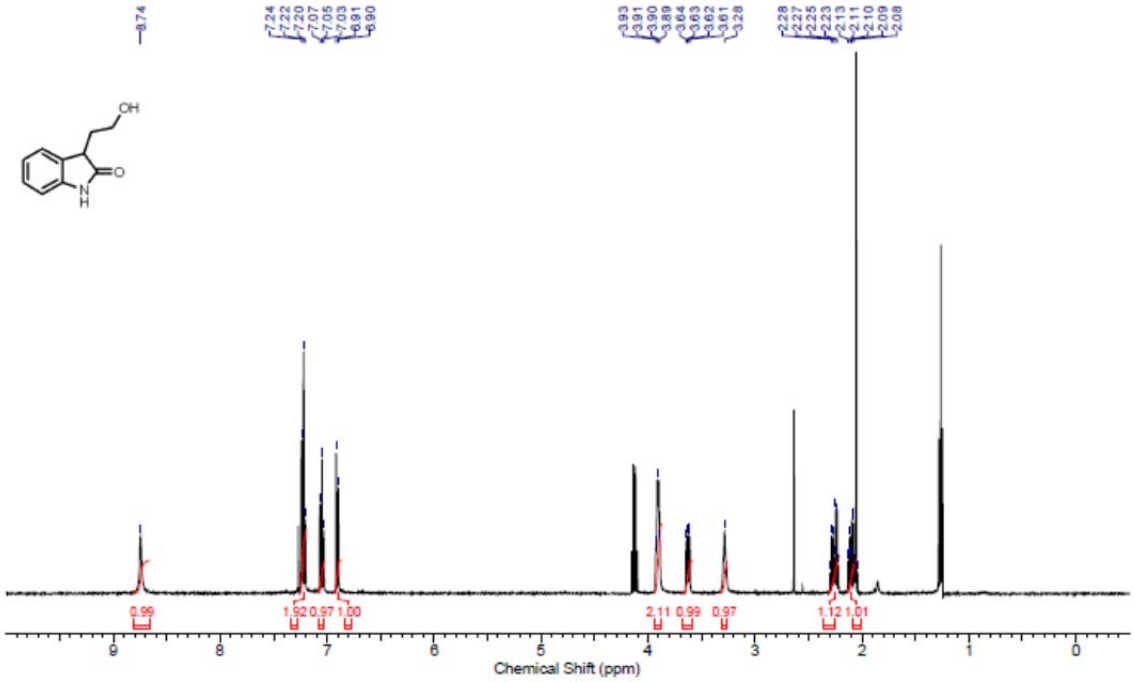


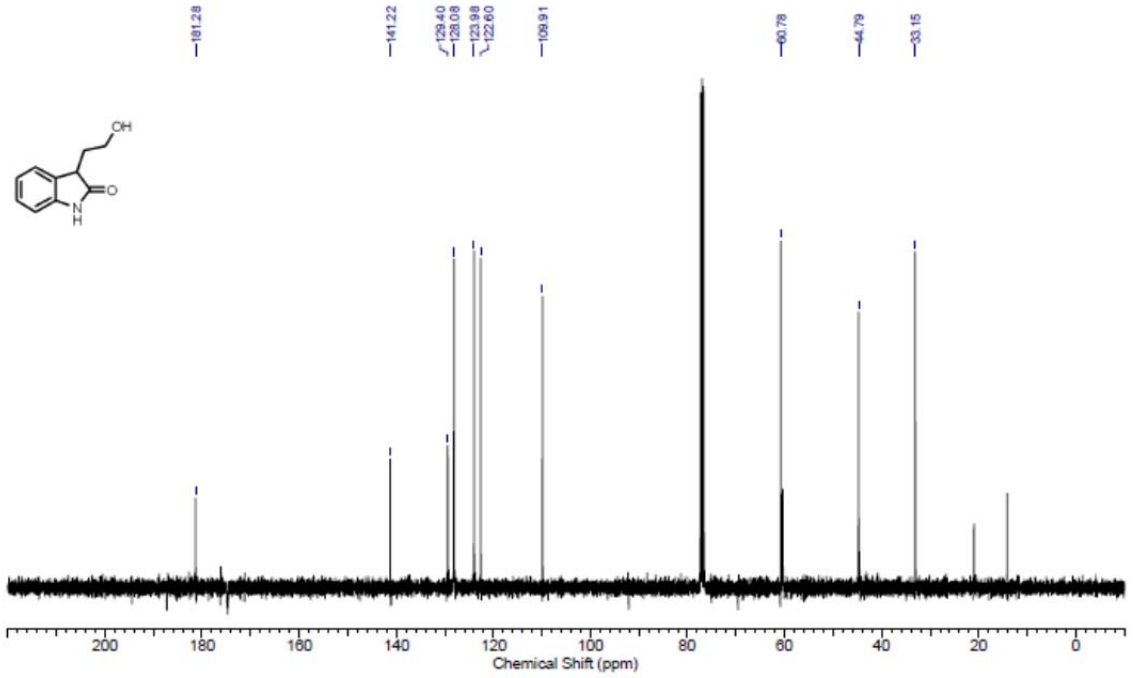
^{1}H and ^{13}C NMR of compound **3-82**



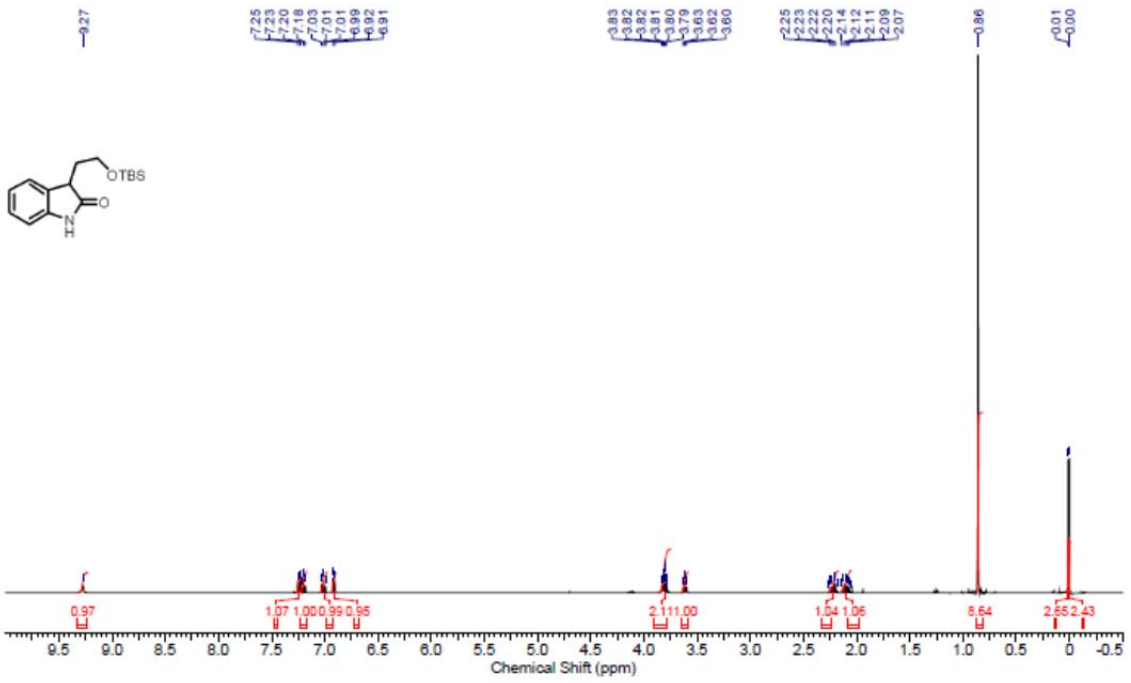


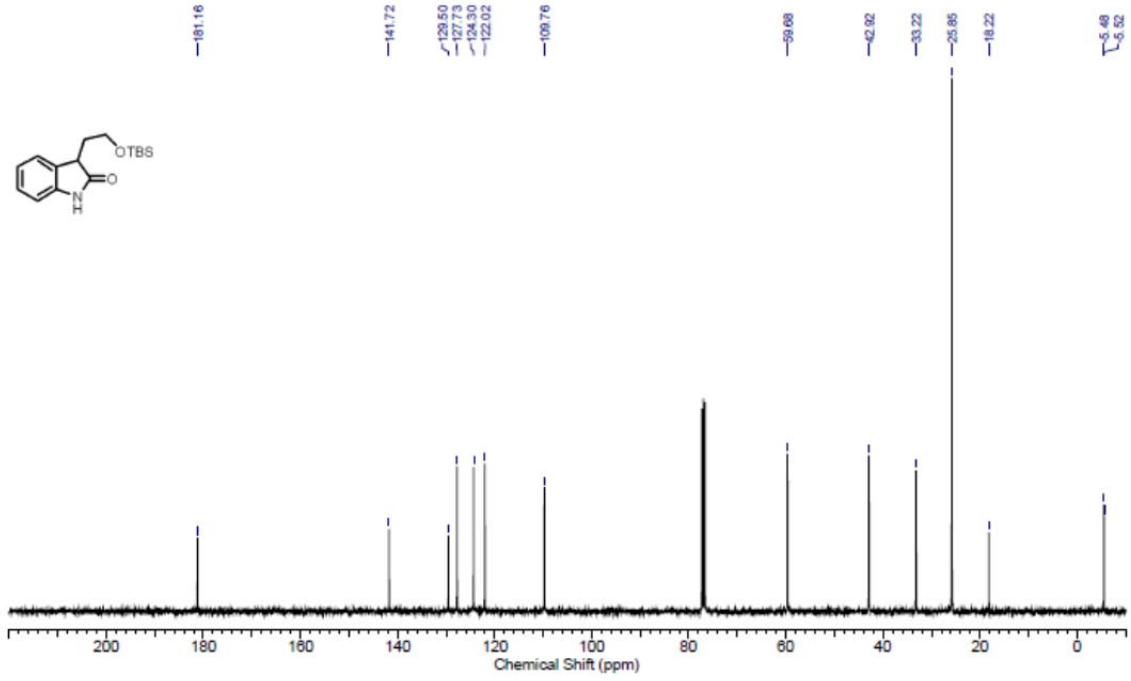
^{1}H and ^{13}C NMR of compound **3-83**



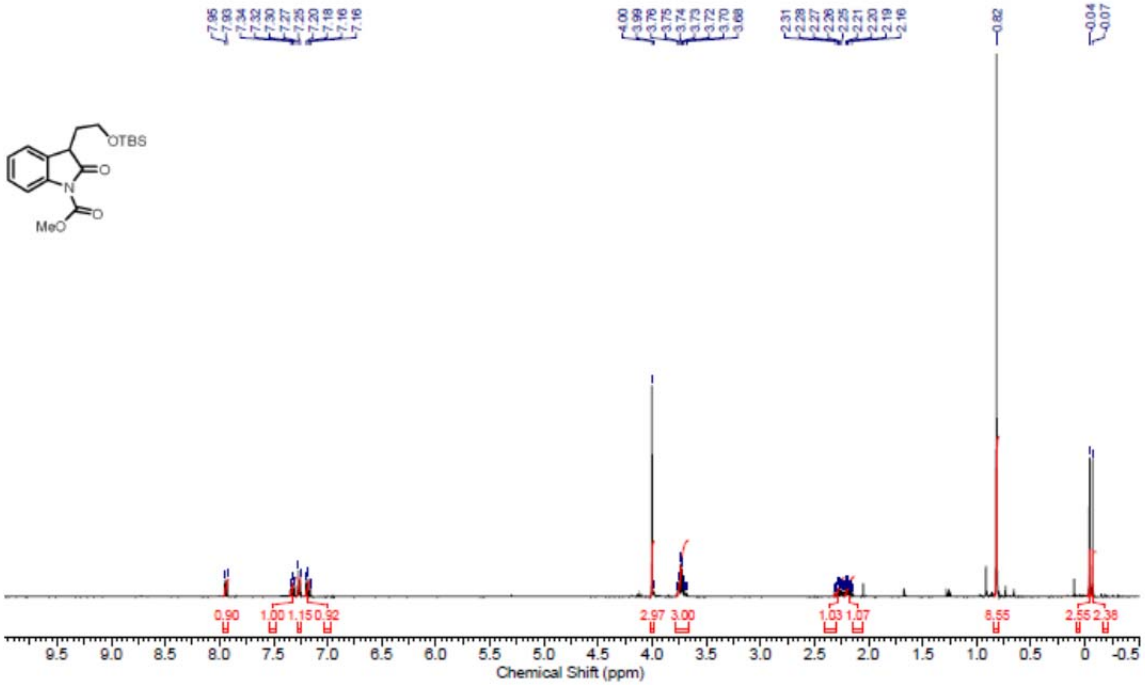


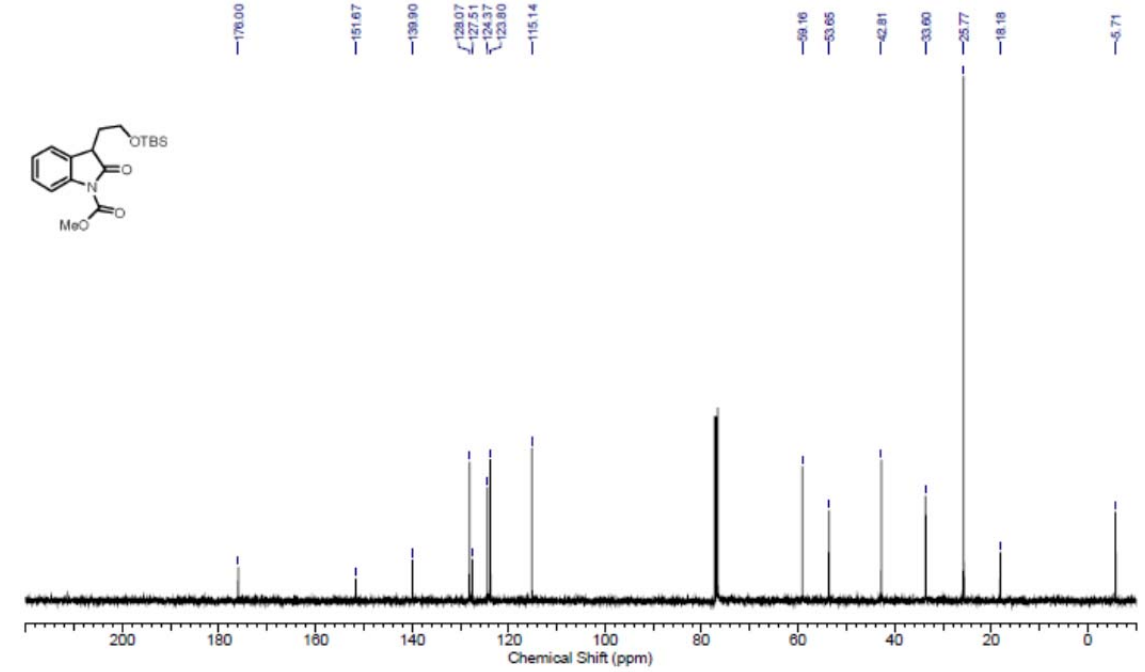
^{1}H and ^{13}C NMR of compound **3-84**



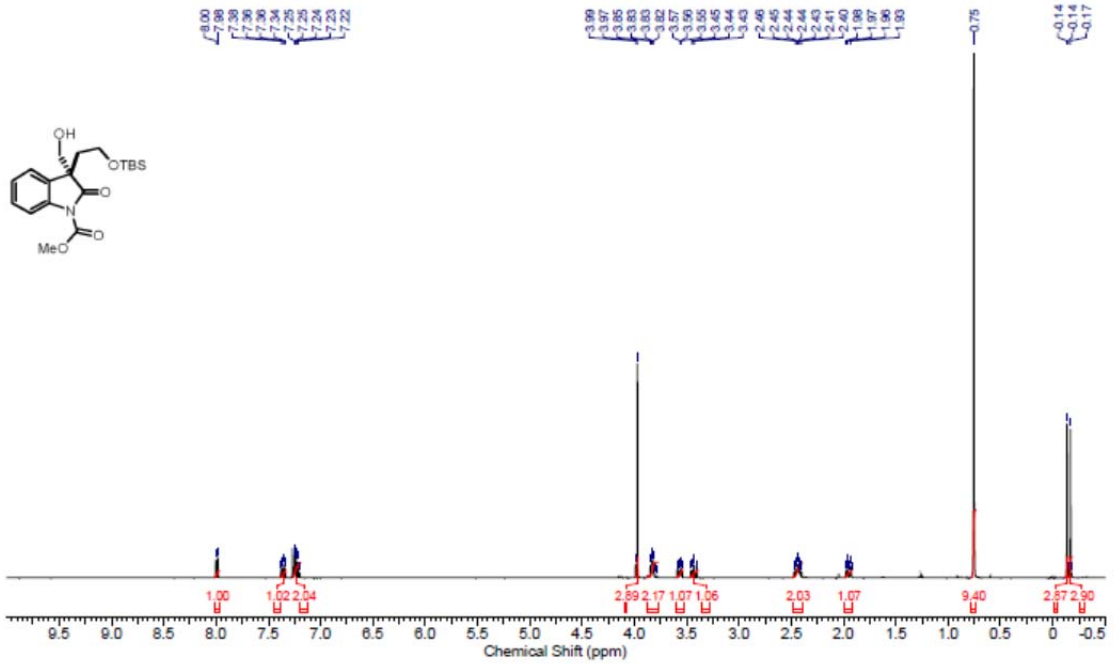


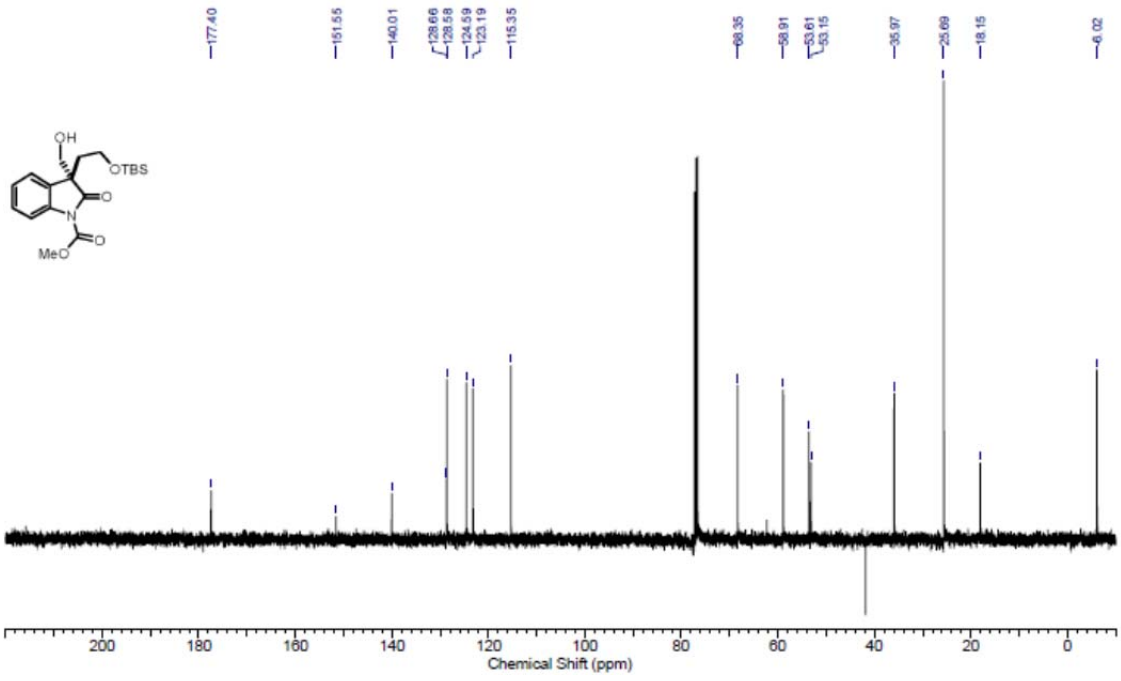
^{1}H and ^{13}C NMR of compound **3-86**



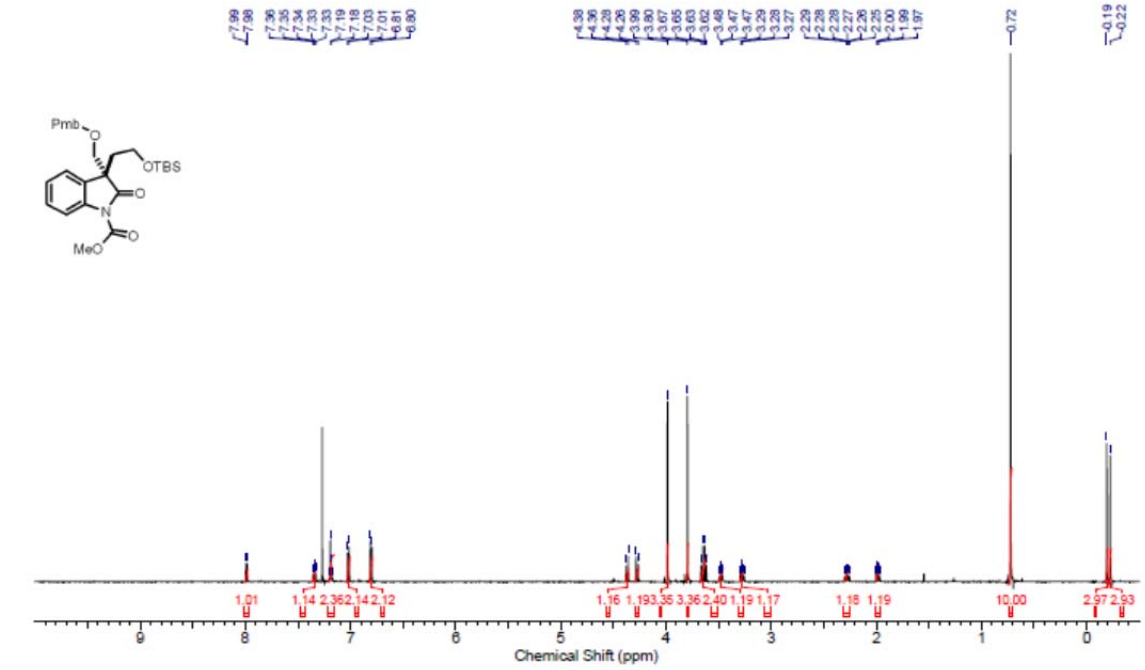


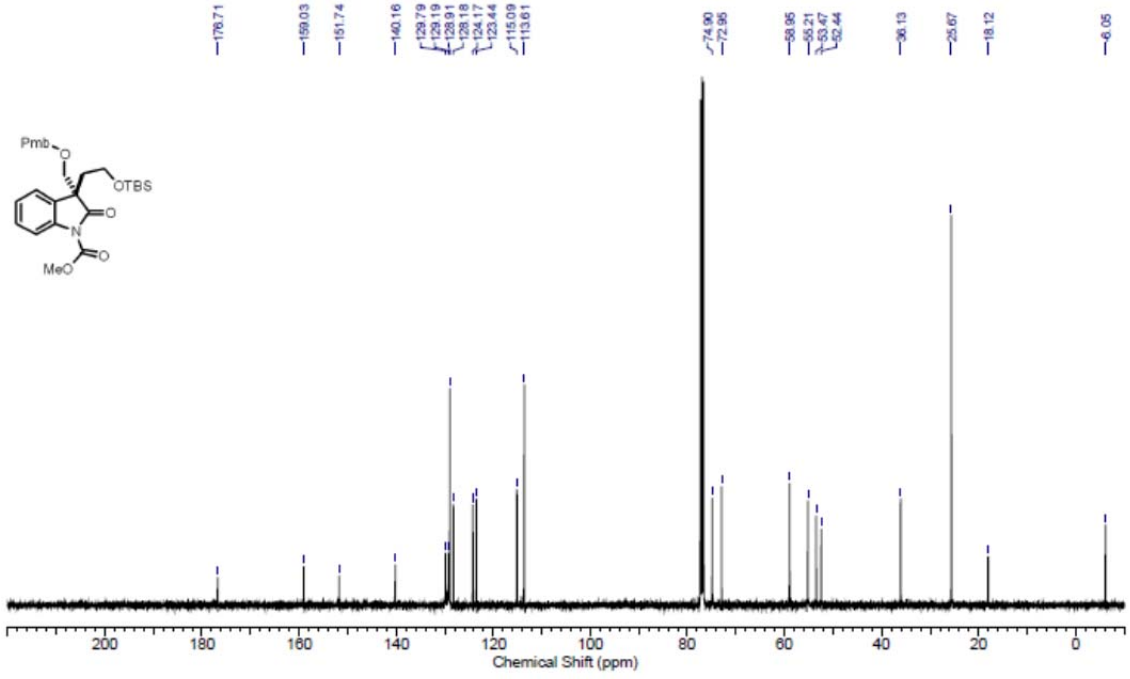
^{1}H and ^{13}C NMR of compound **3-87**



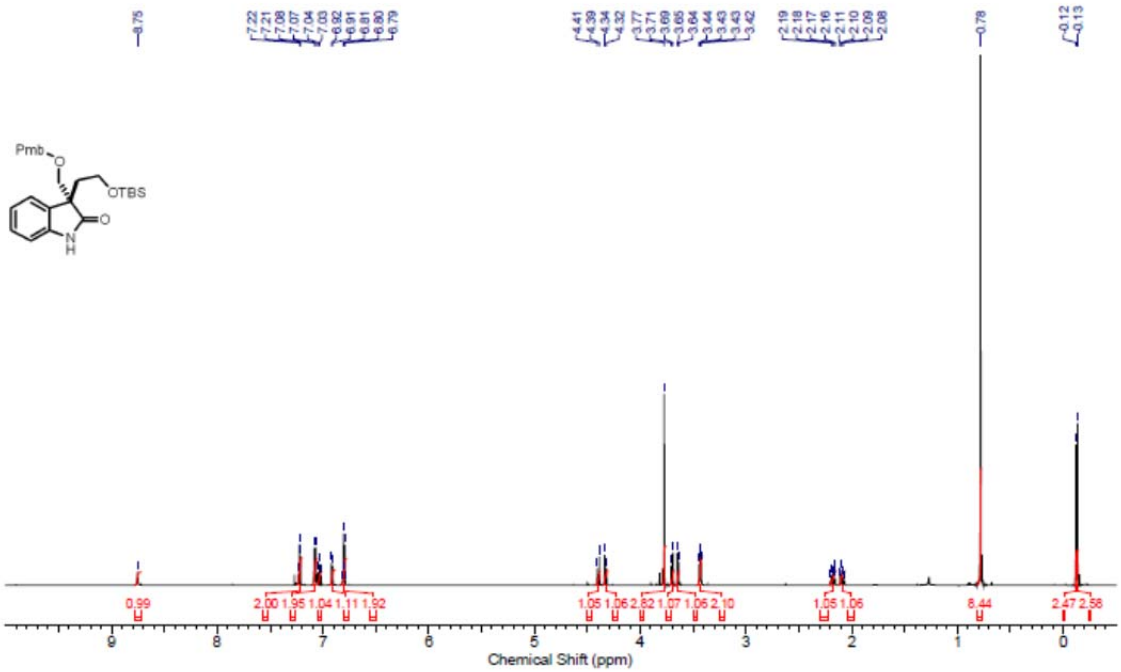


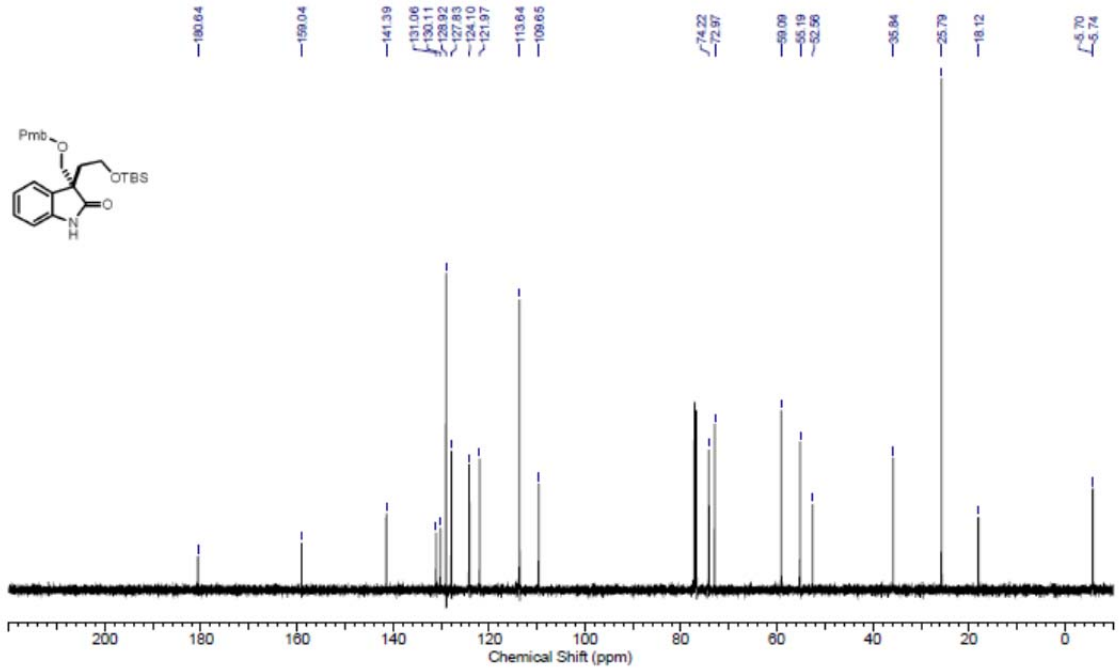
^{1}H and ^{13}C NMR of compound **3-88**



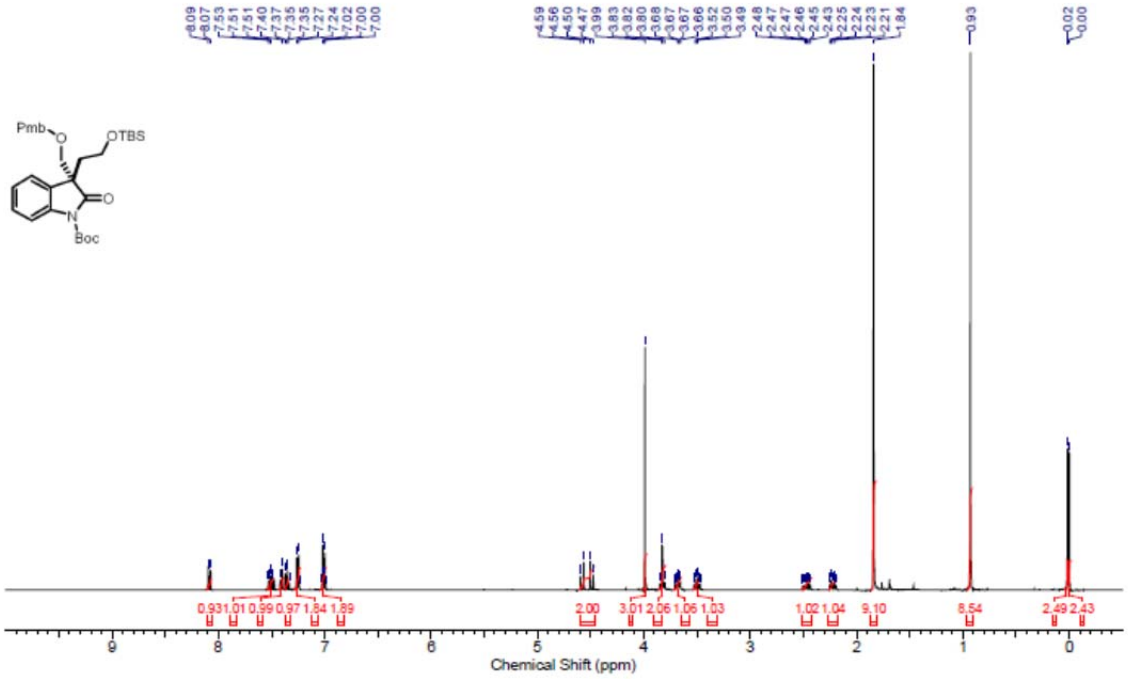


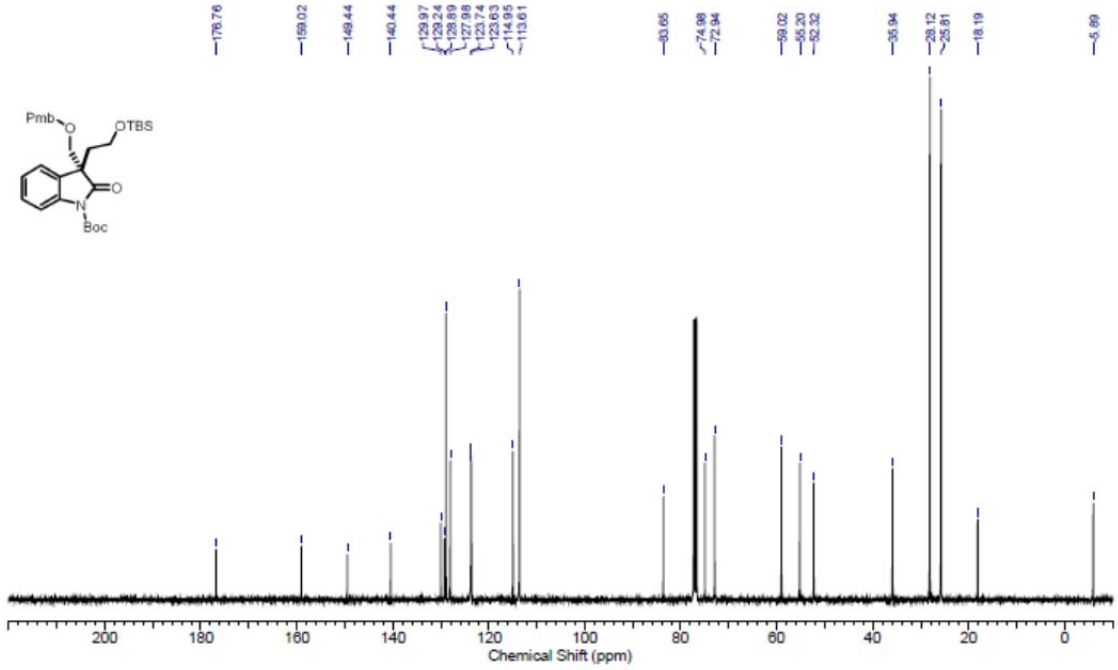
^{1}H and ^{13}C NMR of compound **3-89**



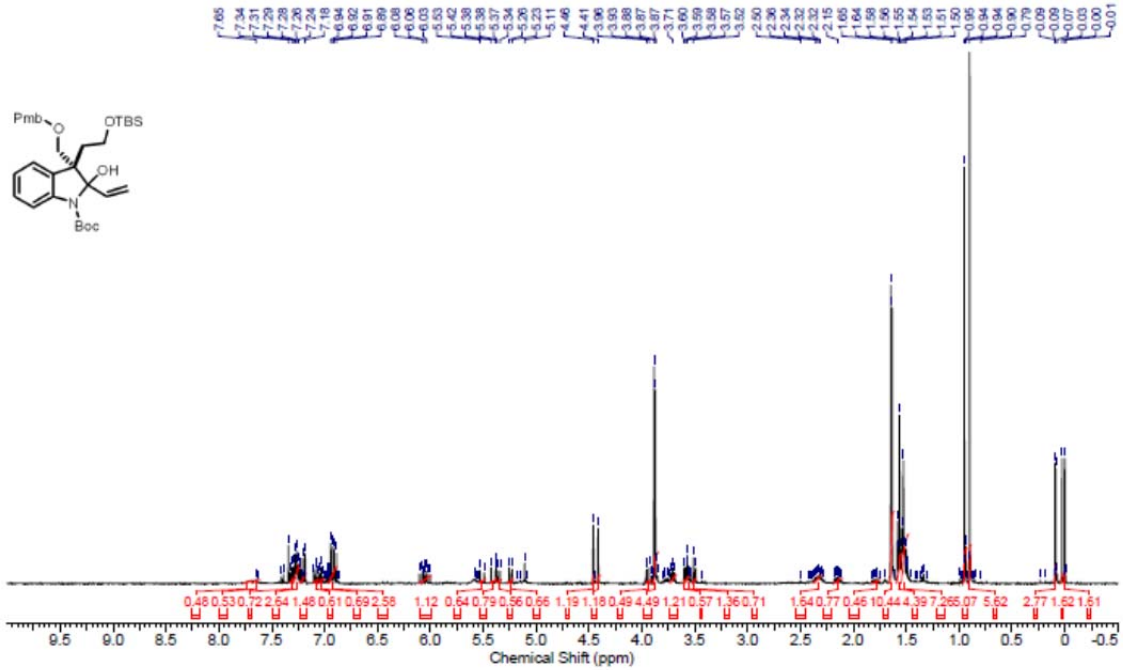


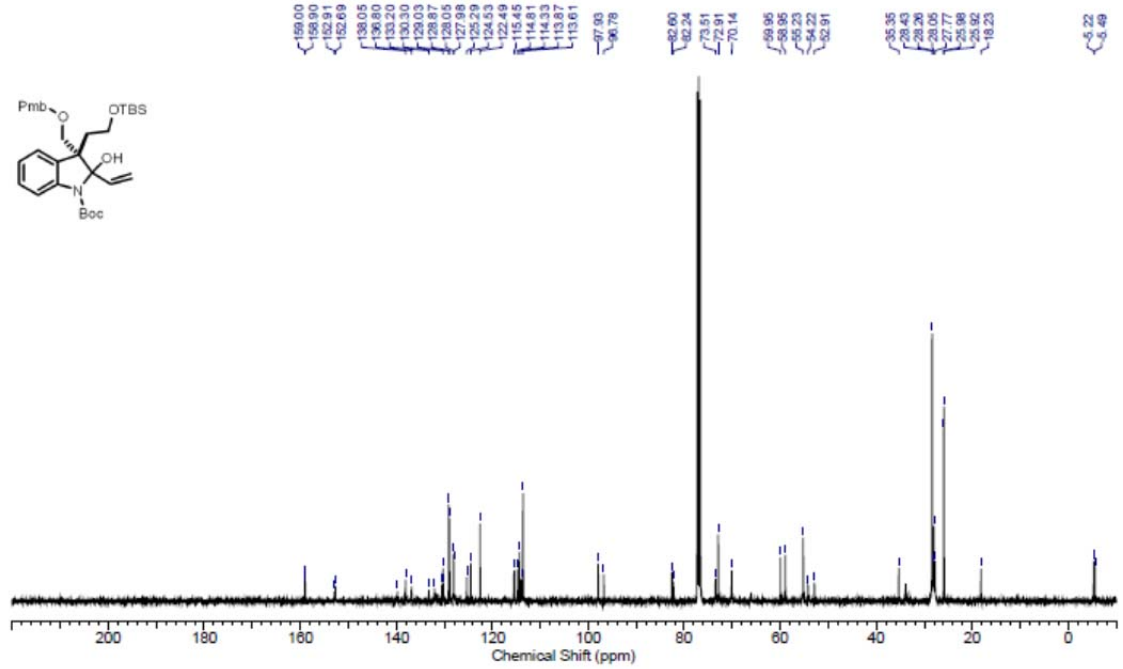
^{1}H and ^{13}C NMR of compound **3-90**



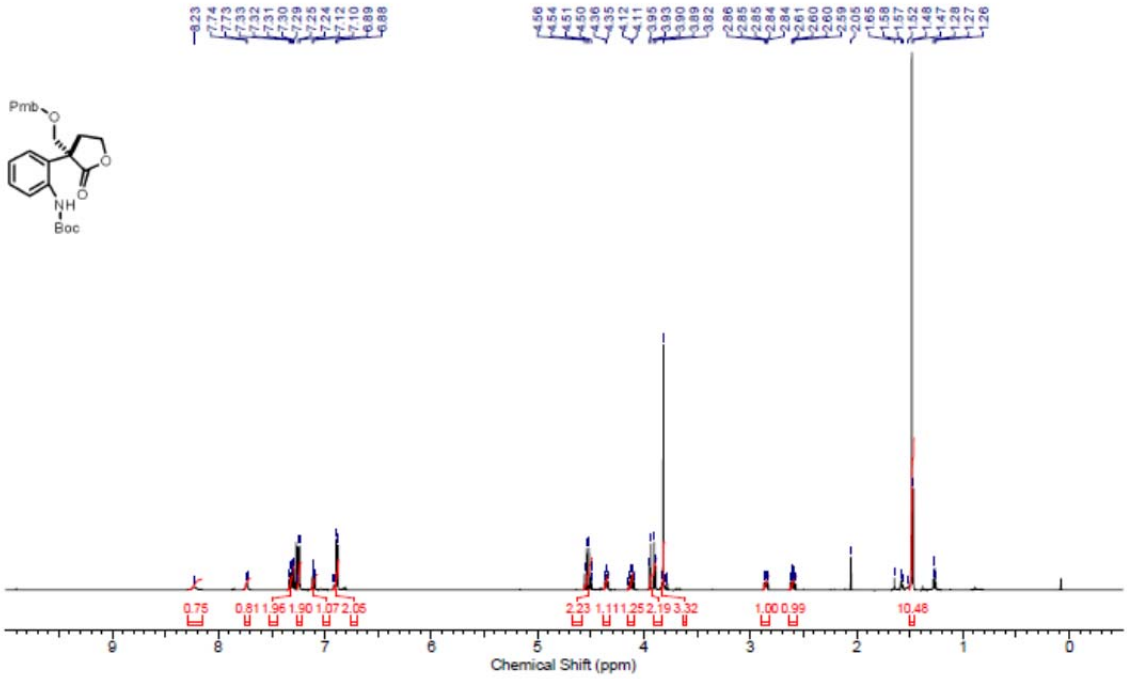


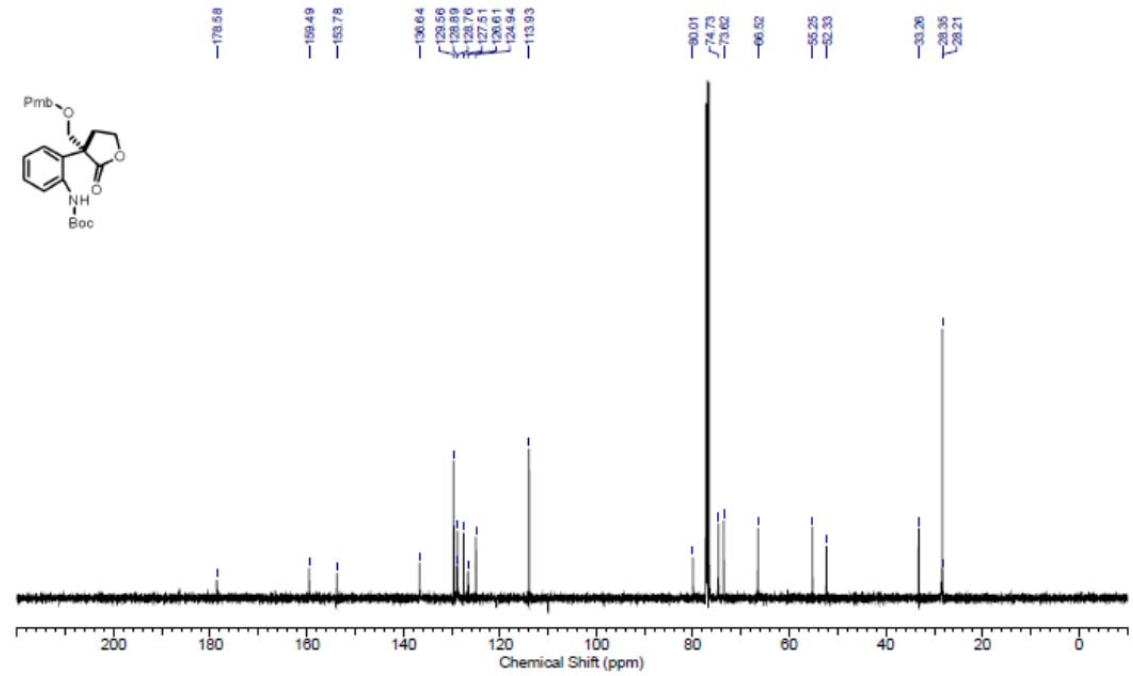
^{1}H and ^{13}C NMR of compound **3-91**



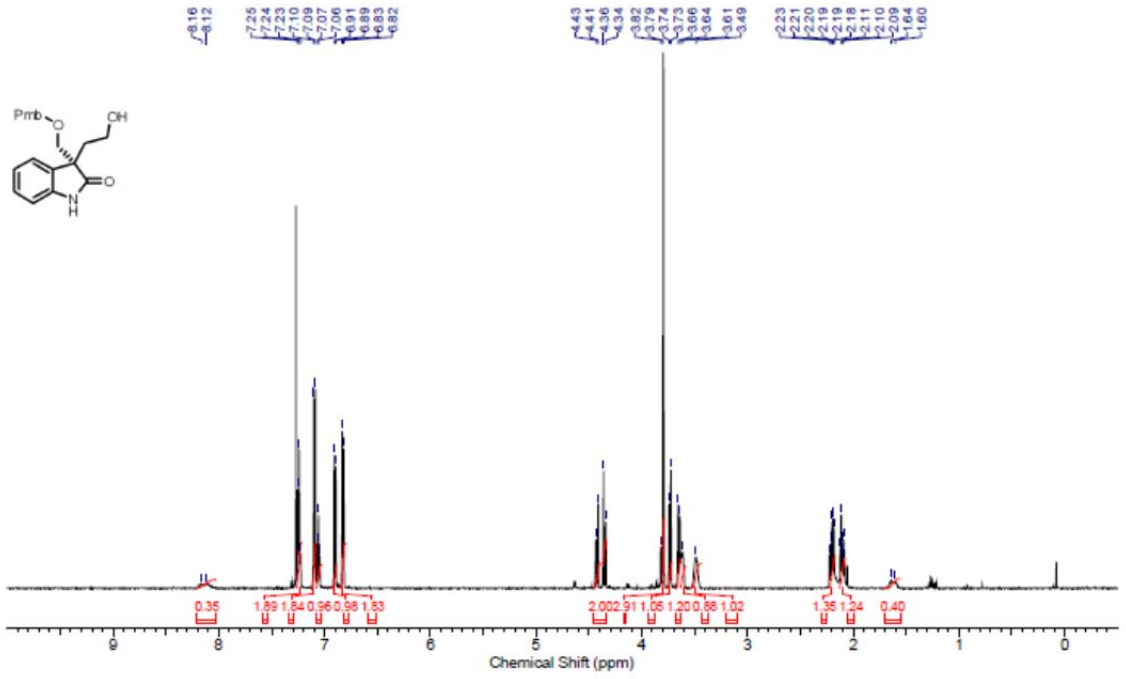


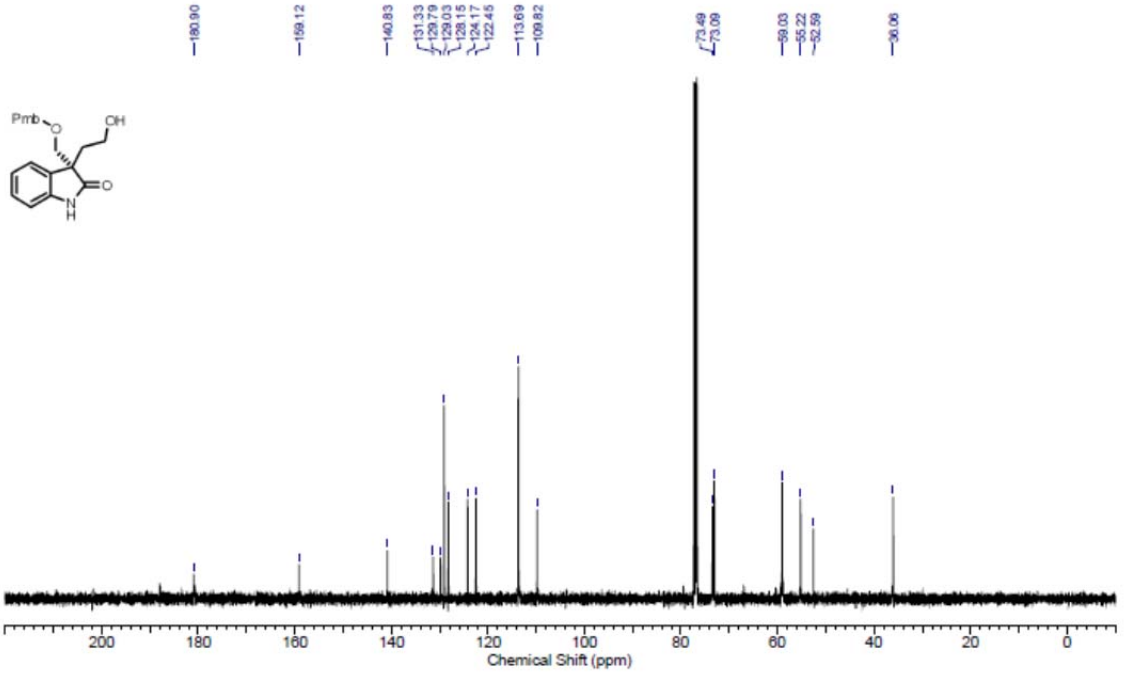
^{1}H and ^{13}C NMR of compound **3-92**



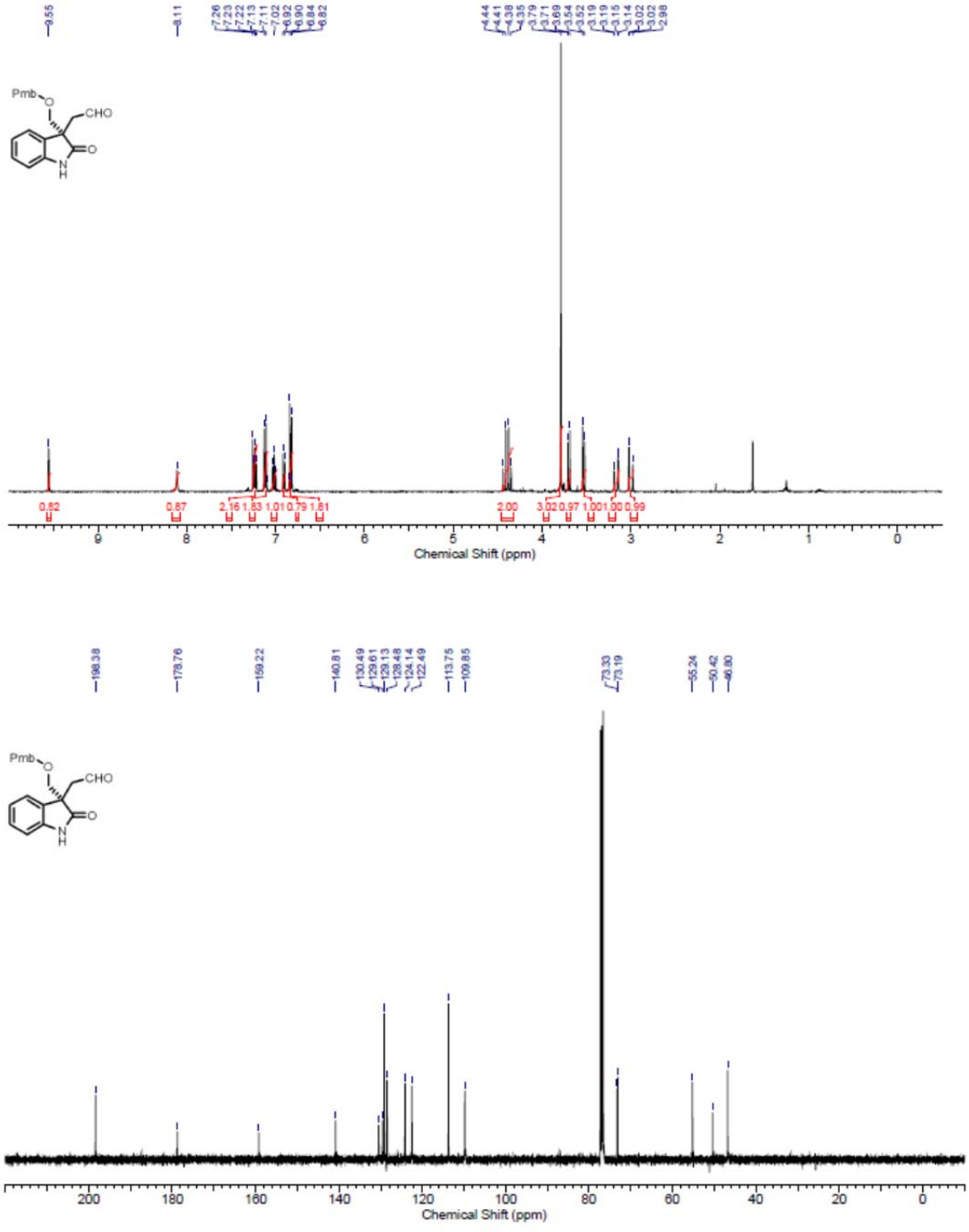


^{1}H and ^{13}C NMR of compound **3-93**

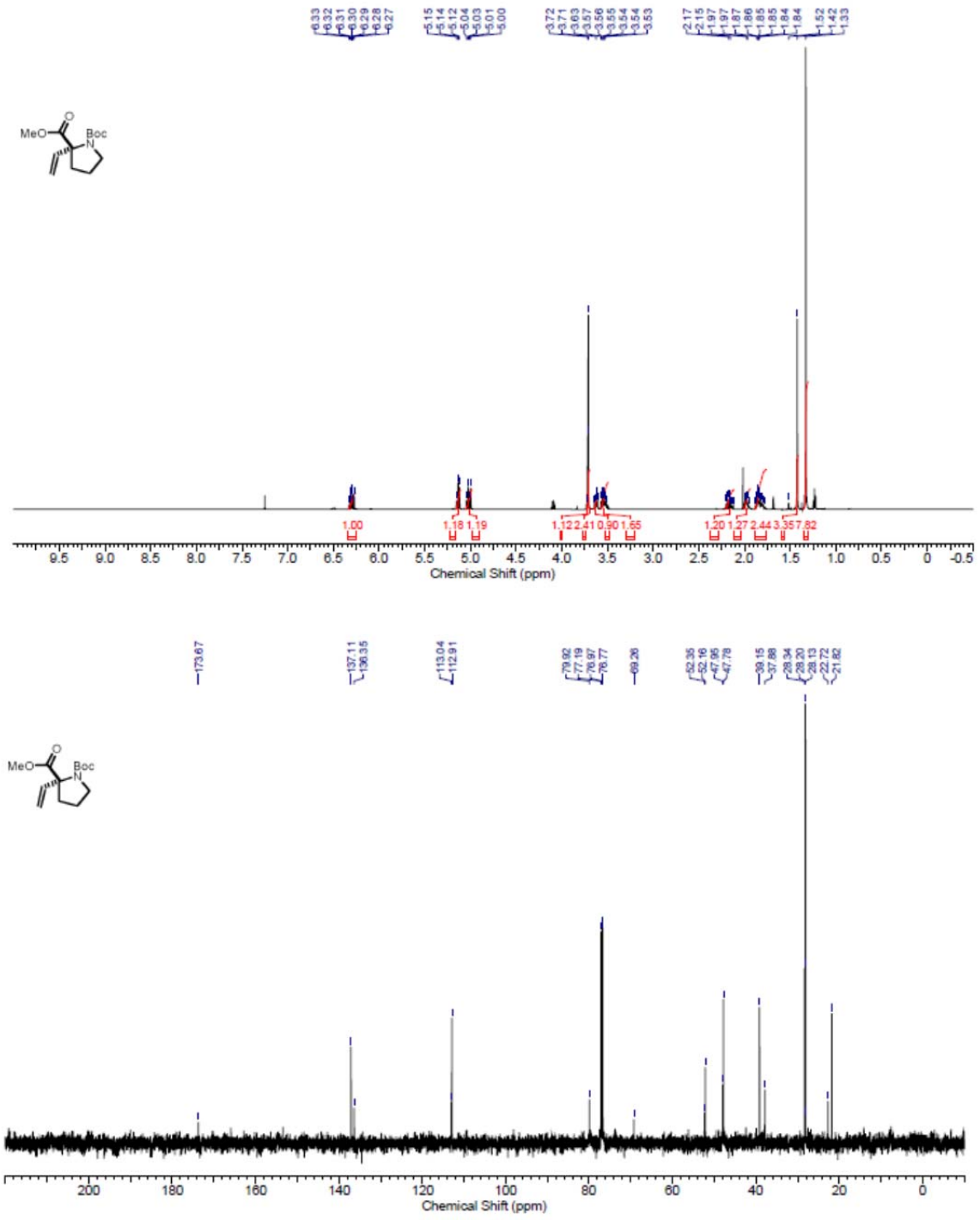




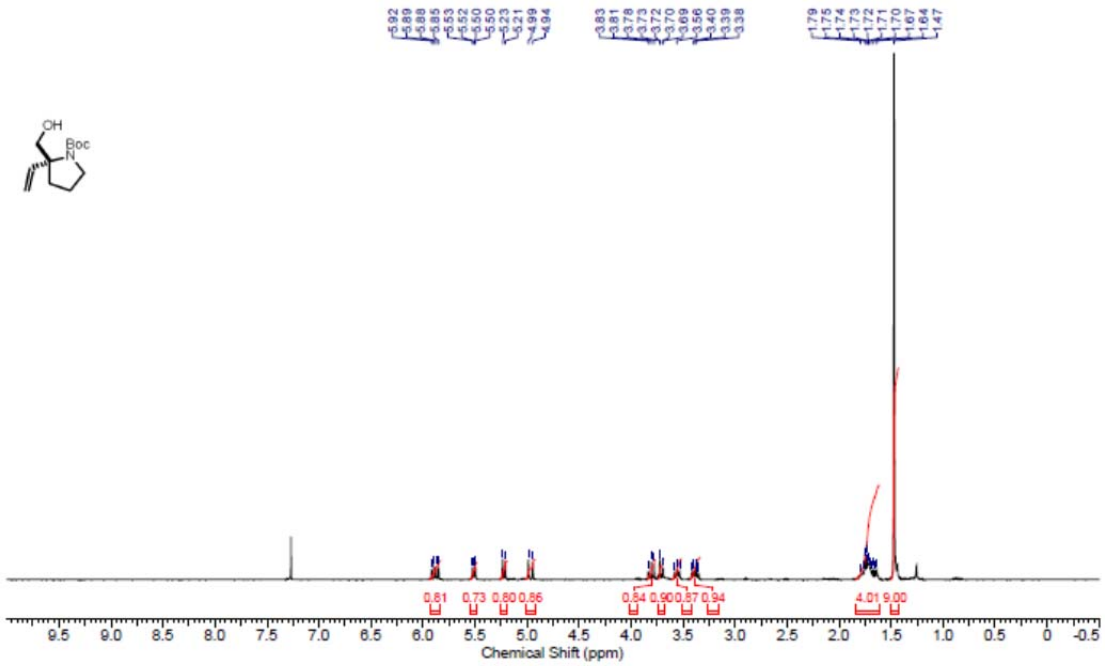
^{1}H and ^{13}C NMR of compound **3-94**

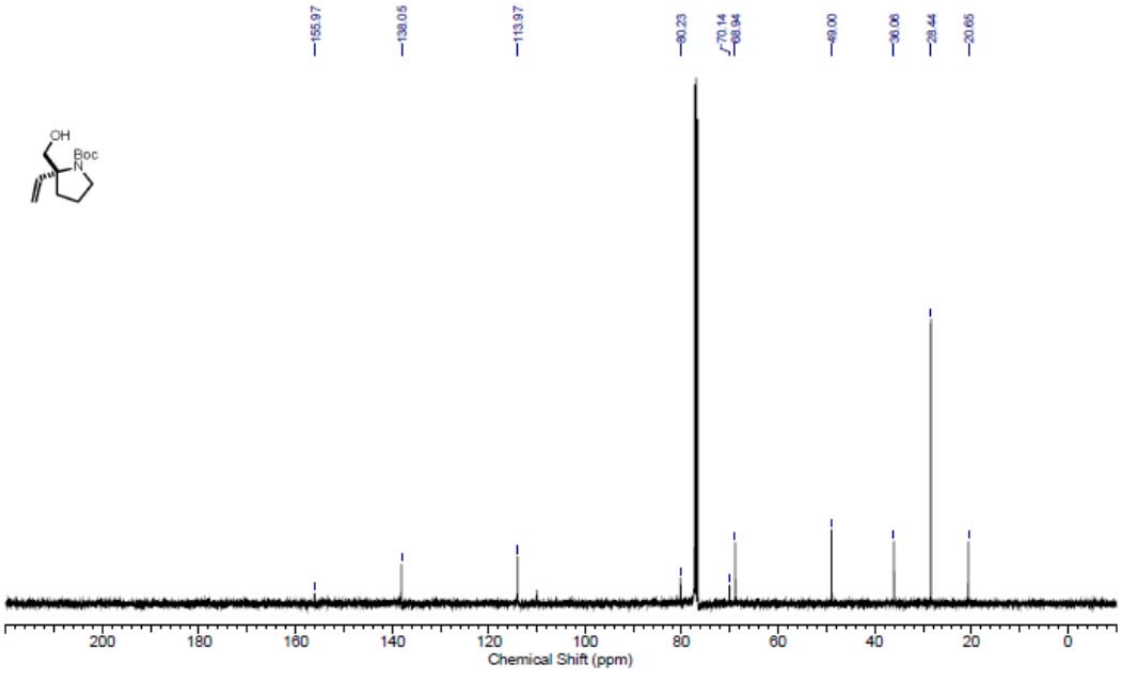


^{1}H and ^{13}C NMR of compound **3-106**

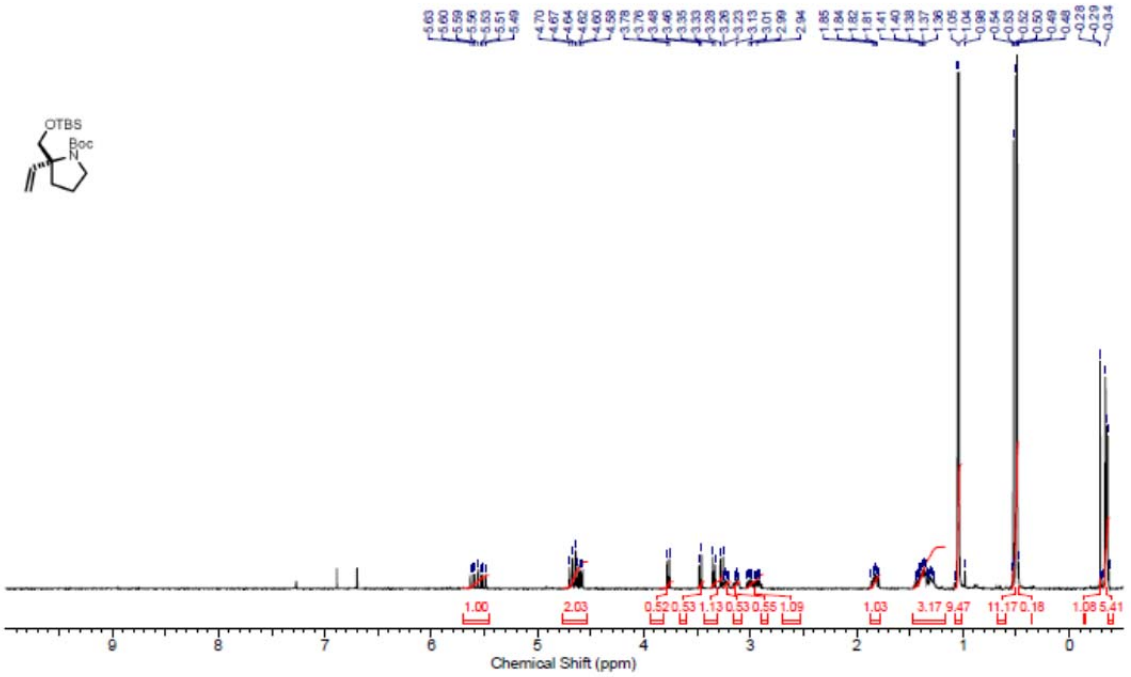


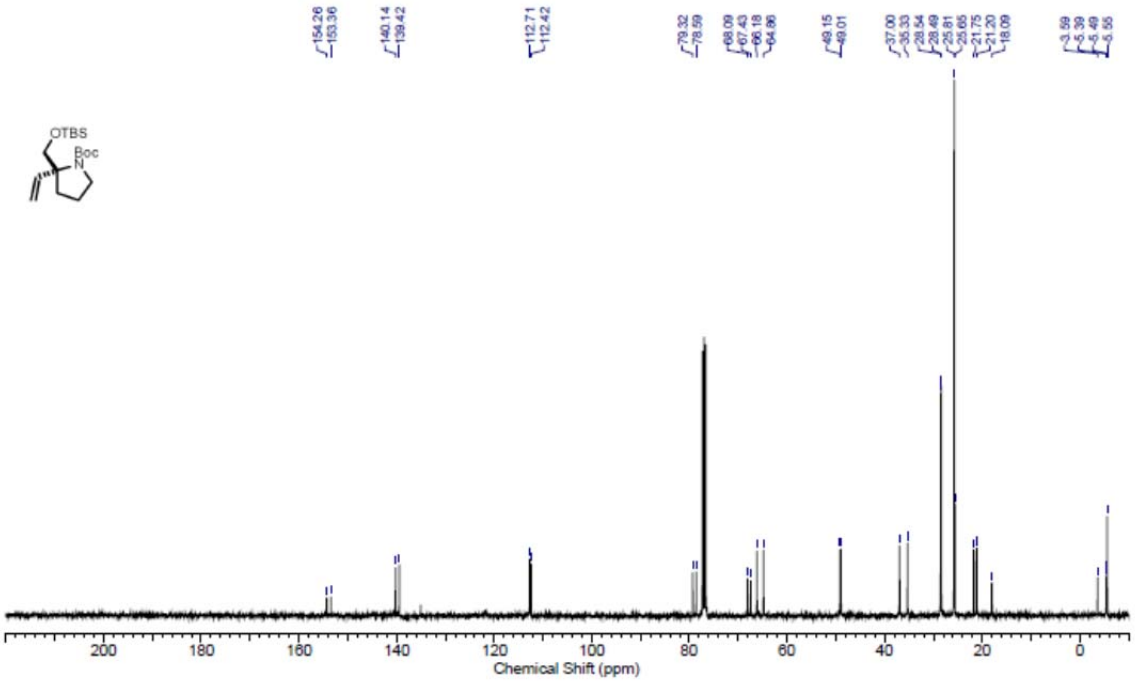
^{1}H and ^{13}C NMR of compound **3-107**



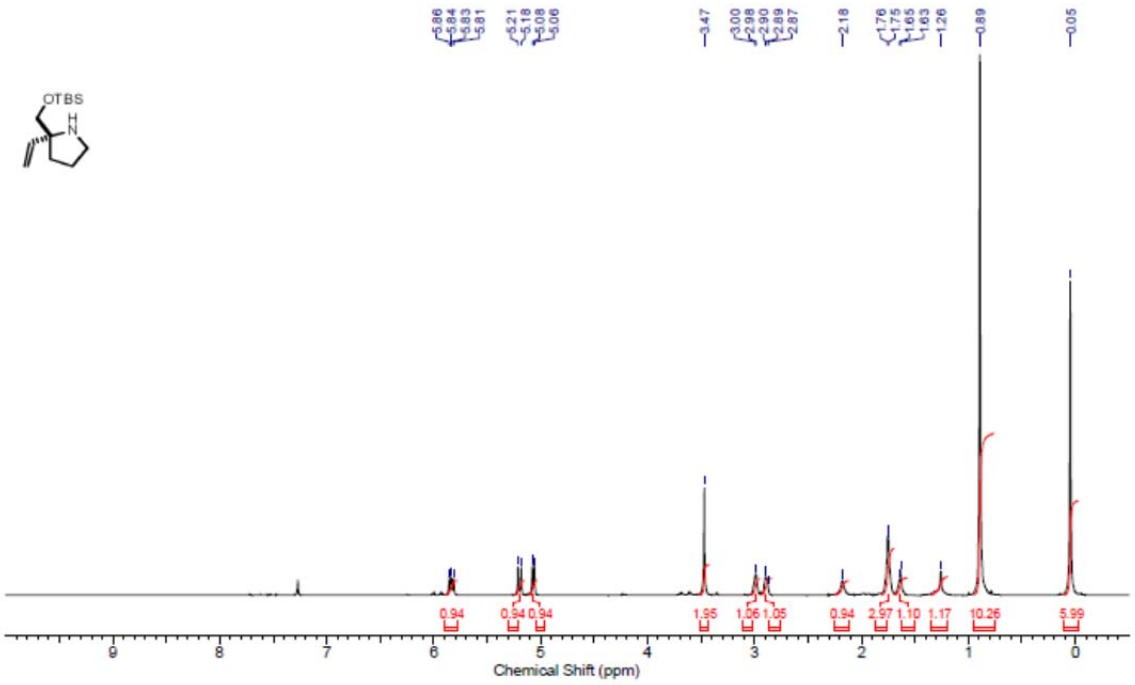


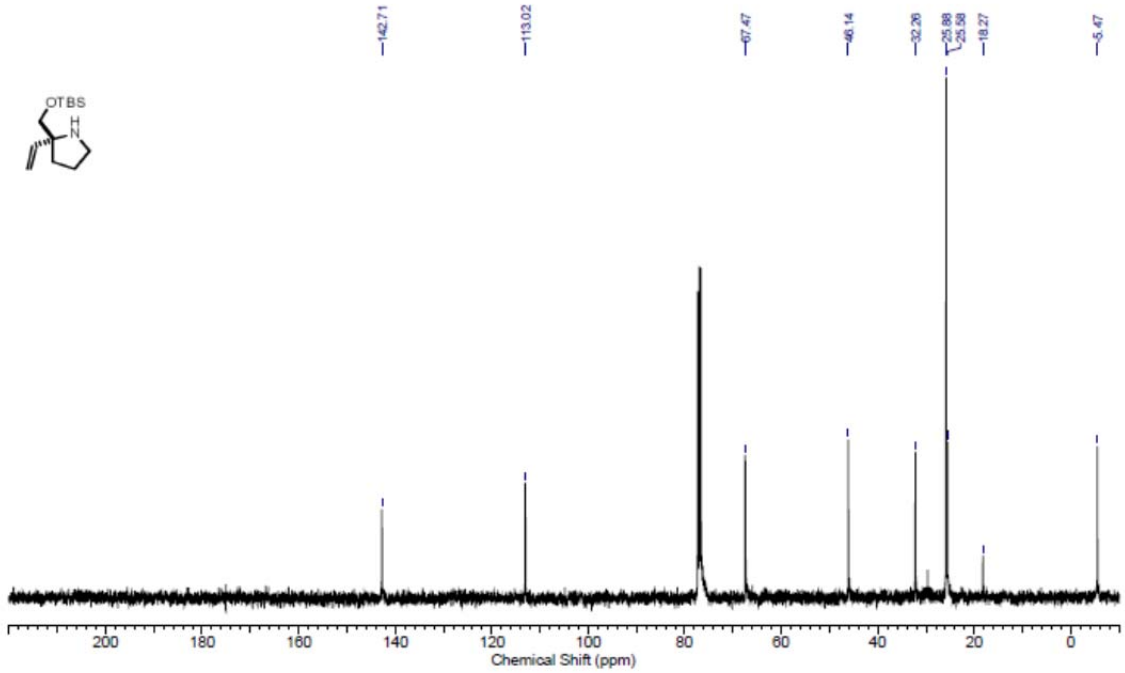
^{1}H and ^{13}C NMR of compound **3-108**



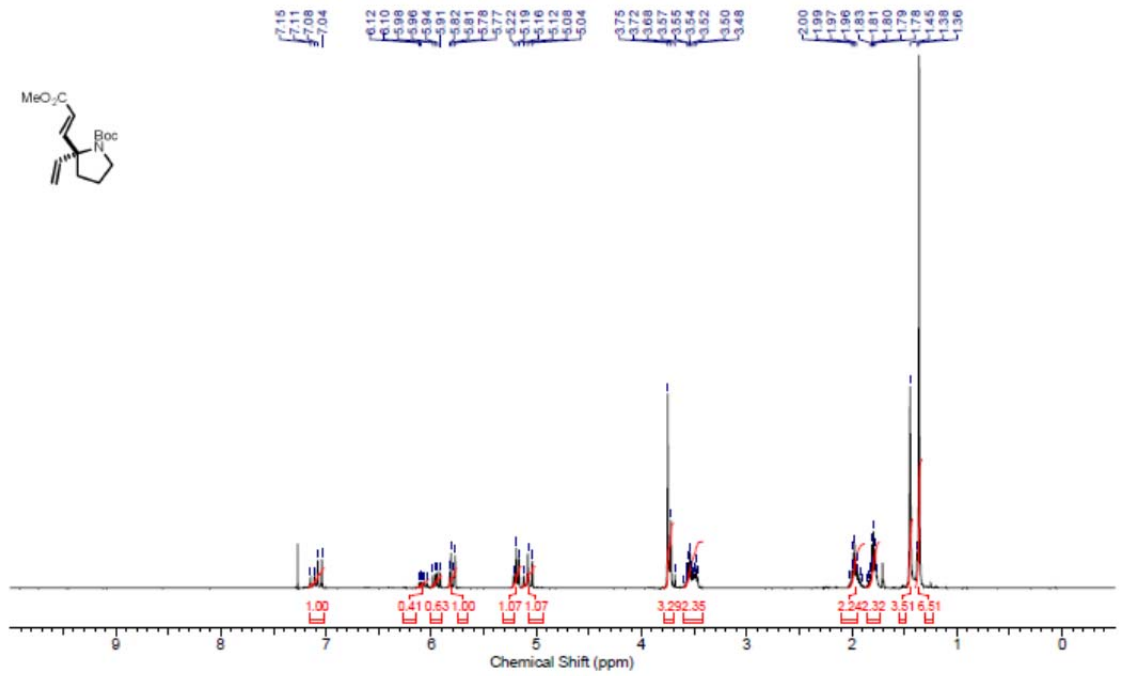


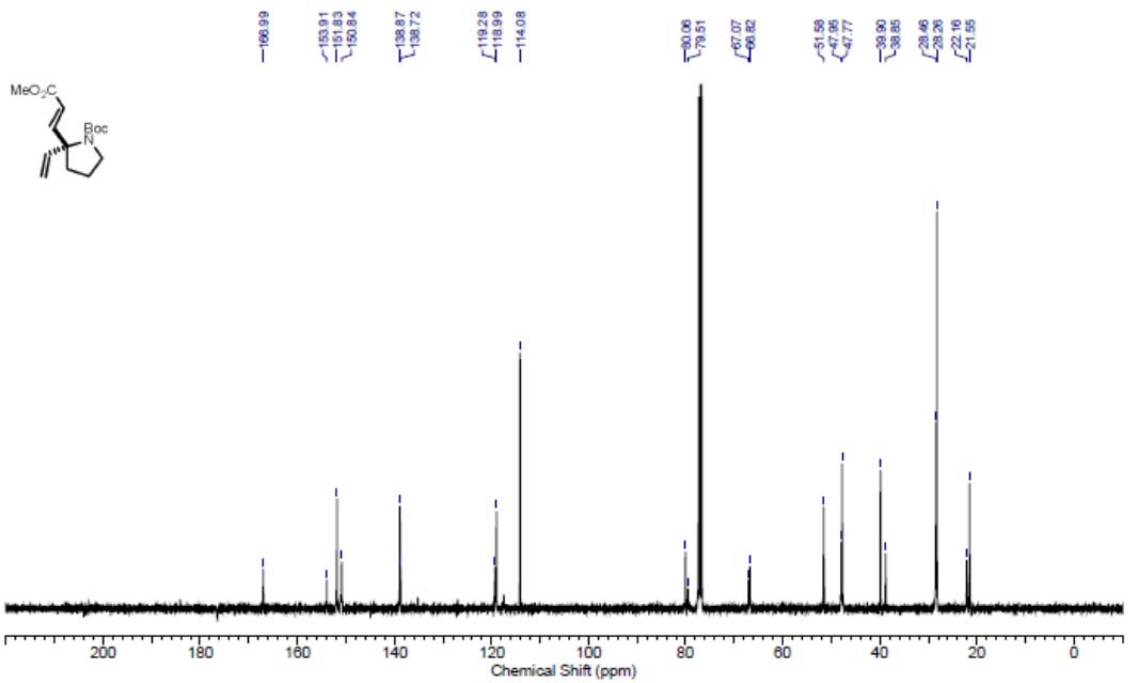
^{1}H and ^{13}C NMR of compound **3-109**



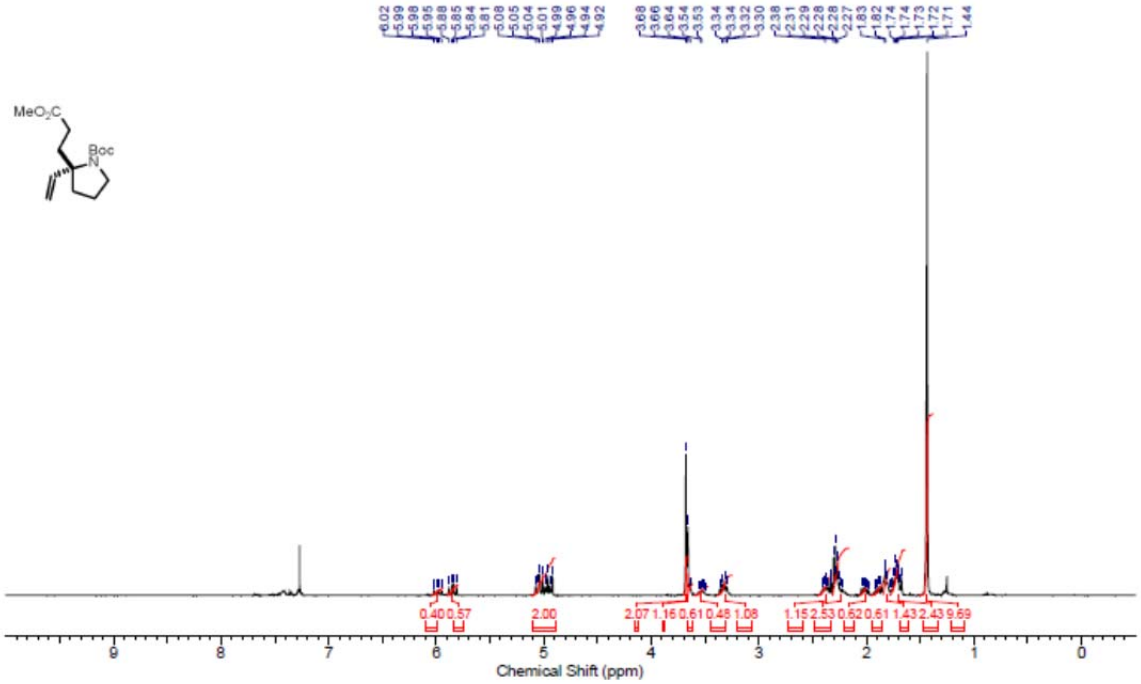


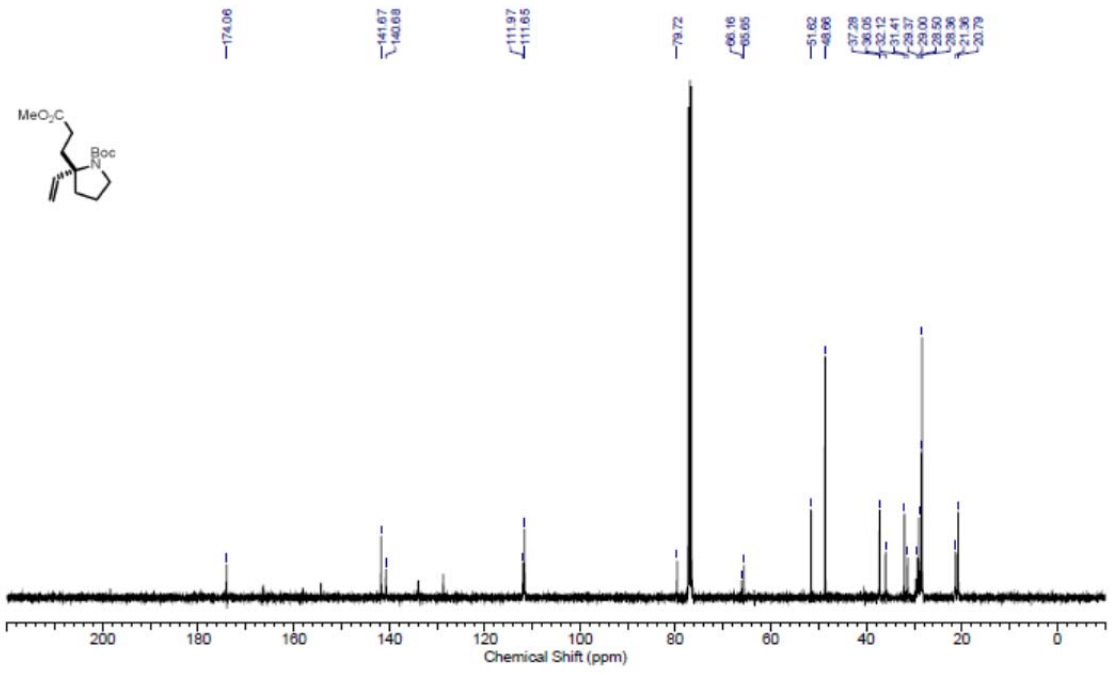
^{1}H and ^{13}C NMR of compound **3-111**



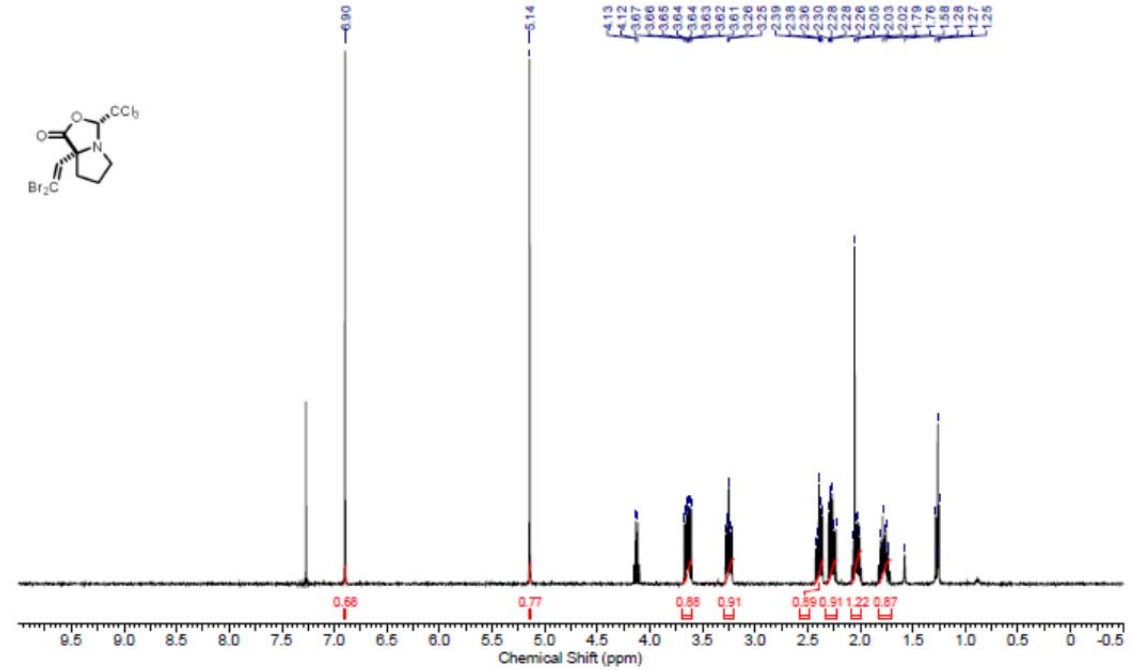


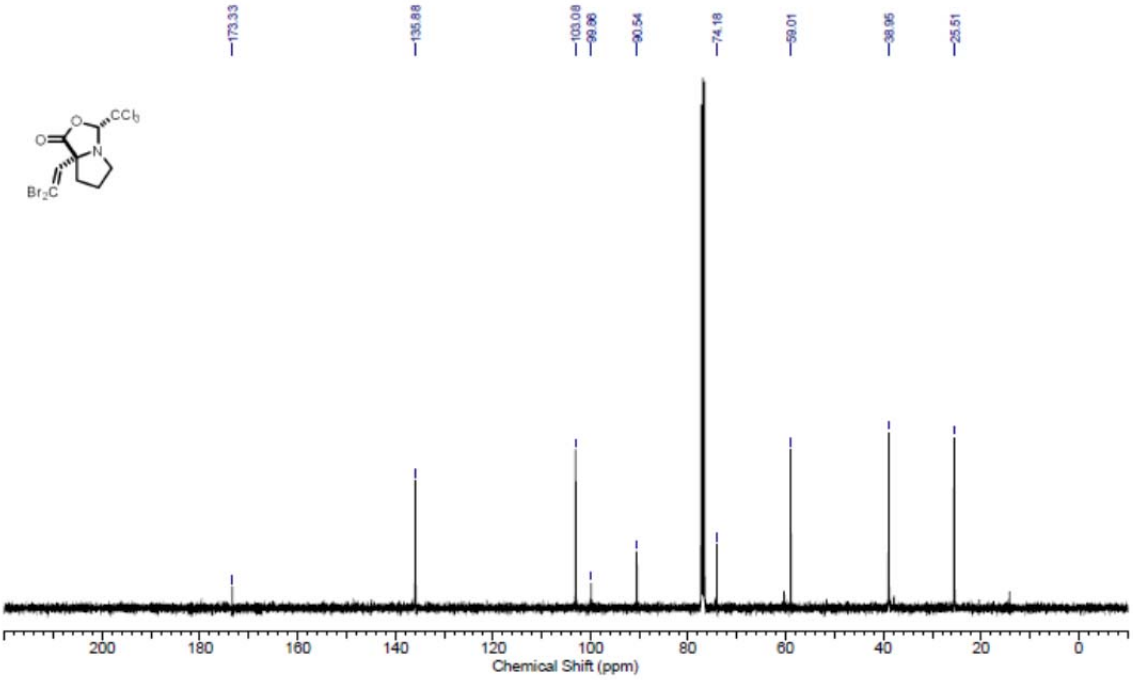
^{1}H and ^{13}C NMR of compound **3-62**



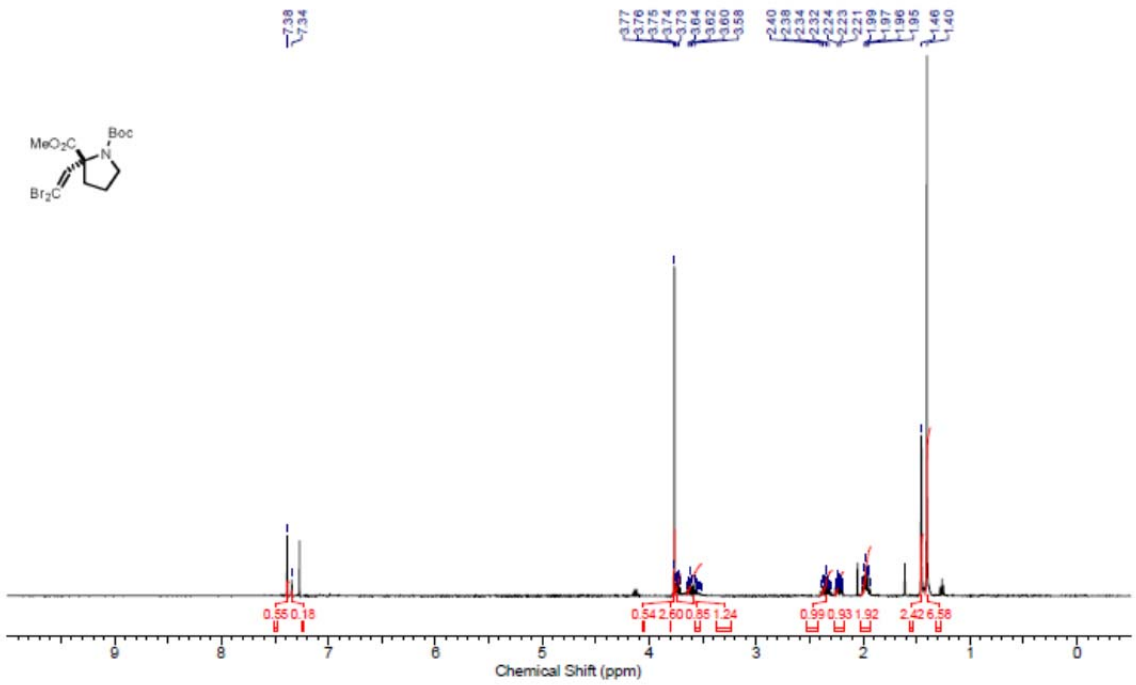


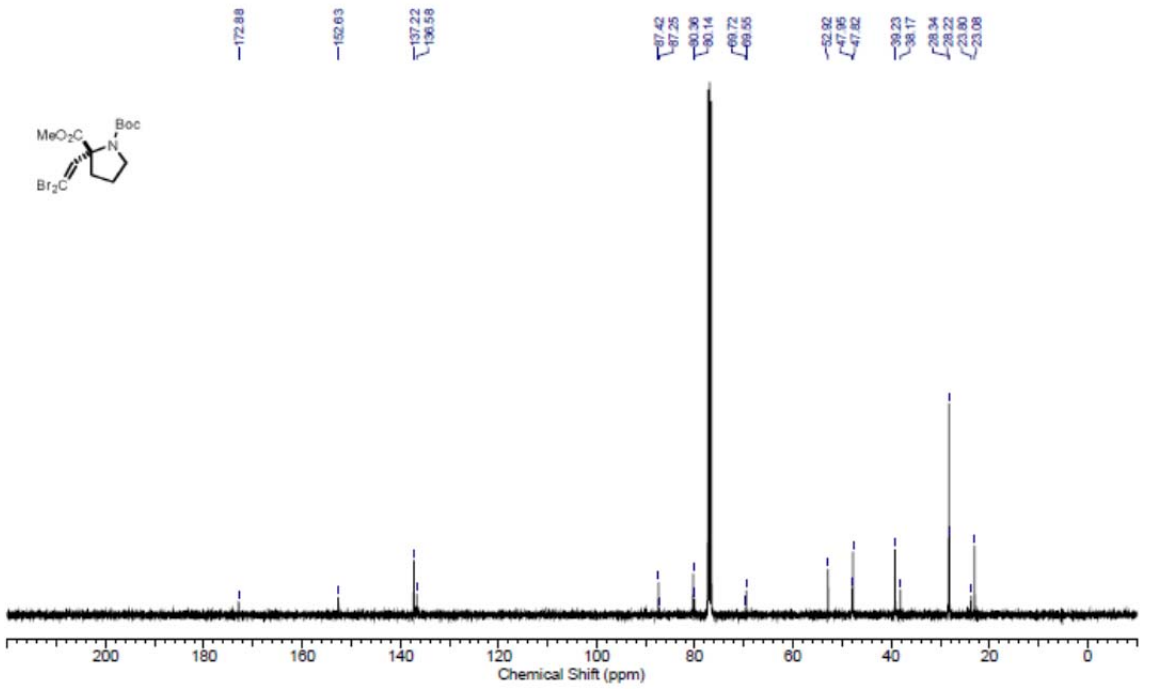
^{1}H and ^{13}C NMR of compound **3-112**



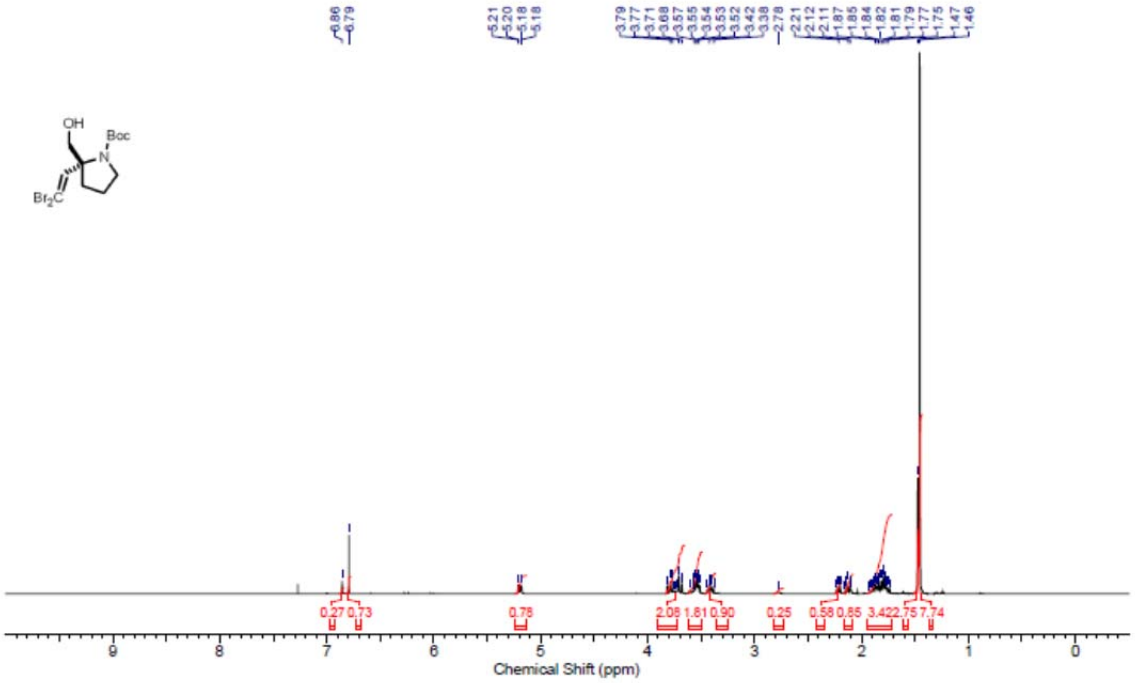


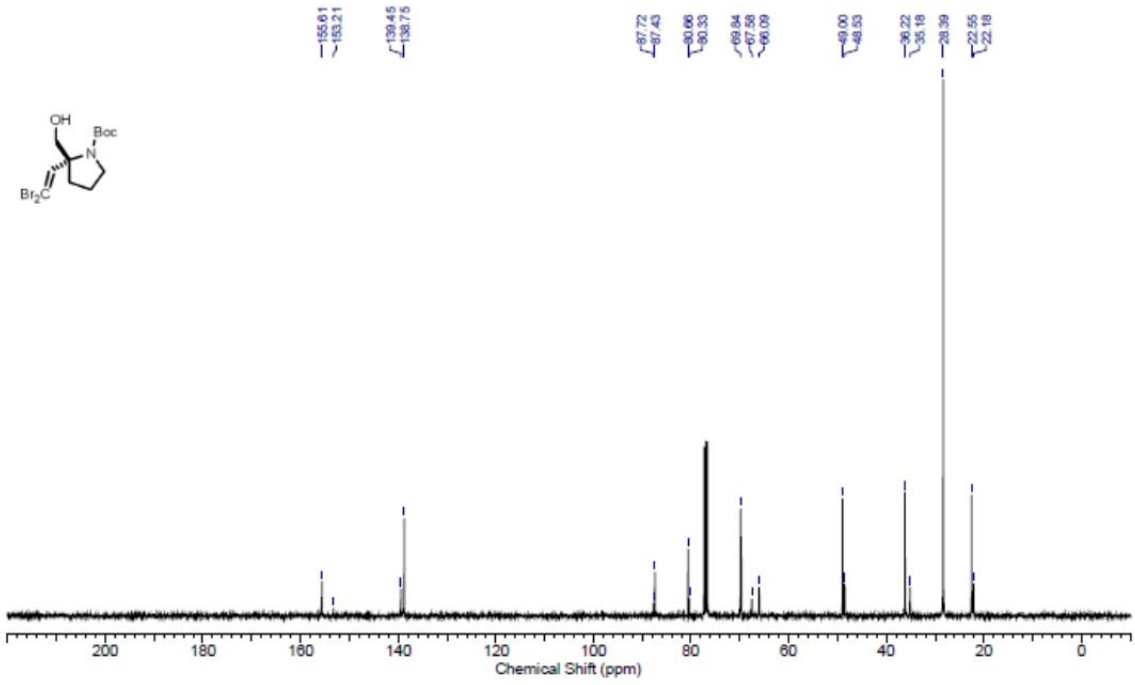
^{1}H and ^{13}C NMR of compound **3-113**



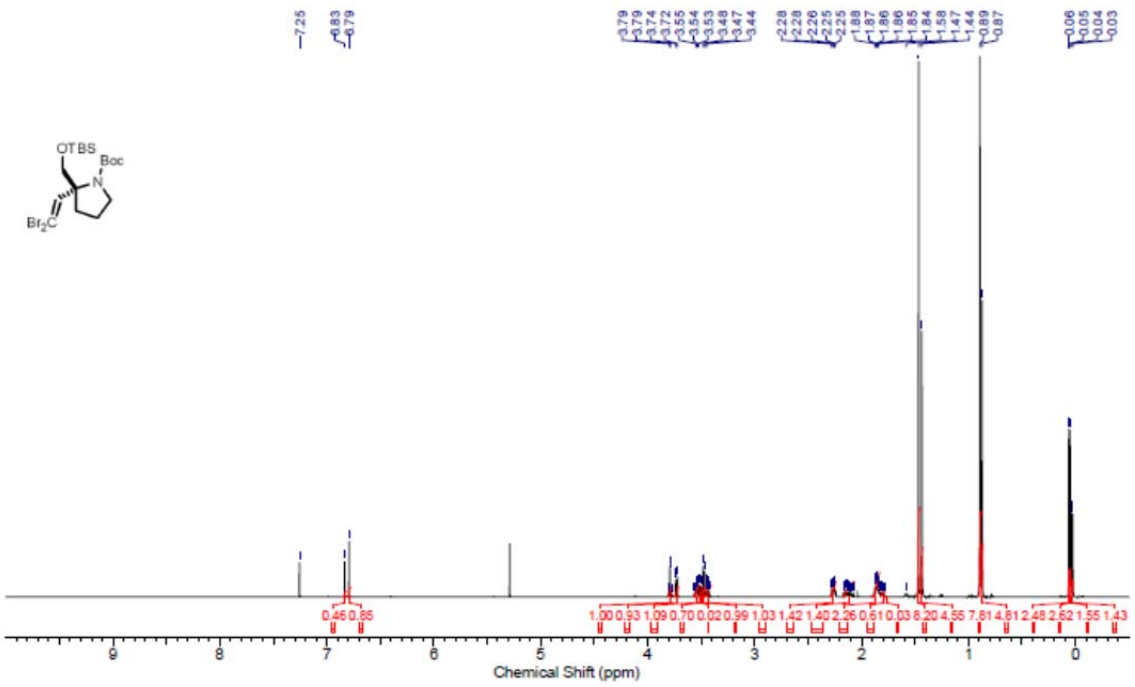


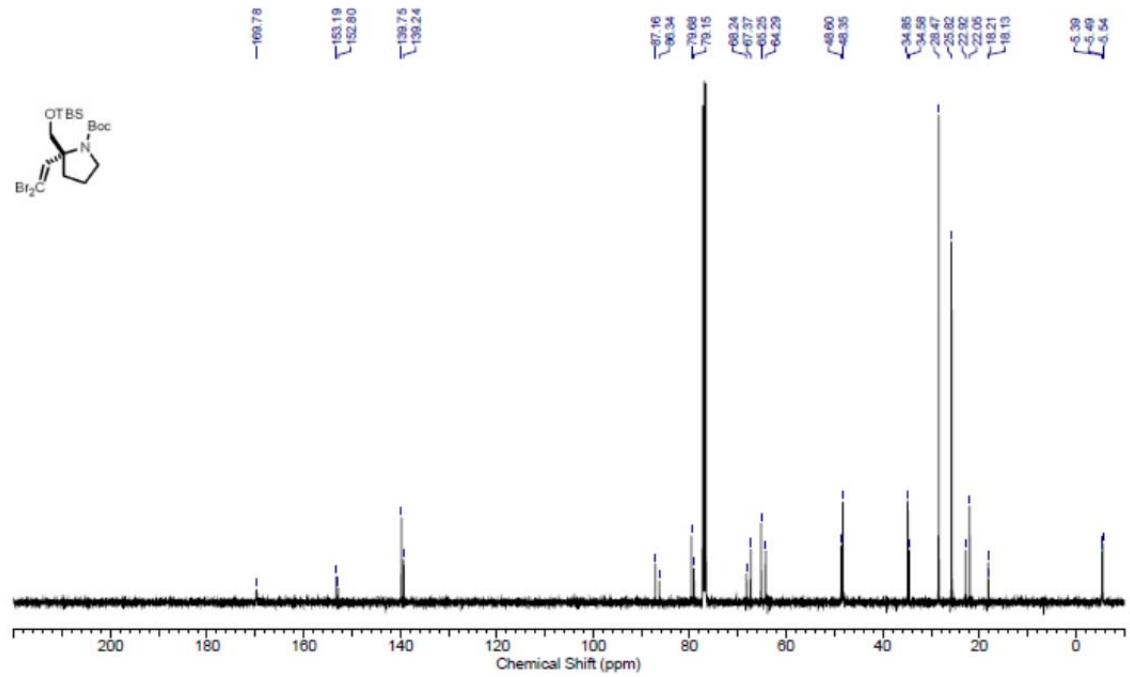
^{1}H and ^{13}C NMR of compound **3-114**



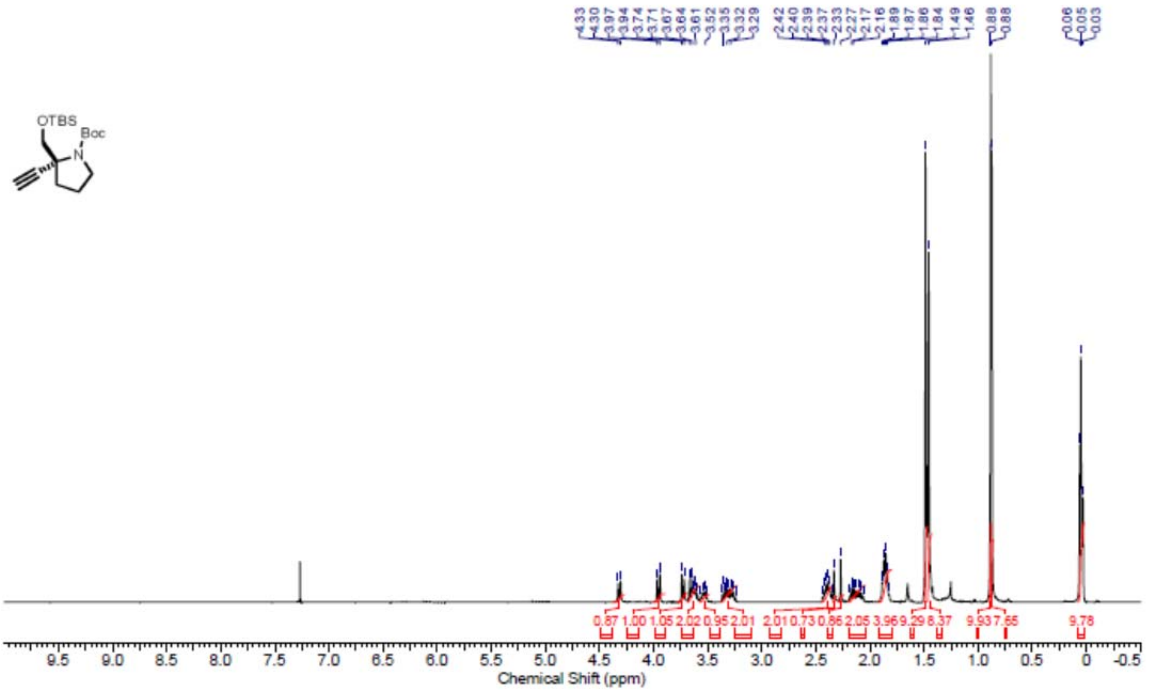


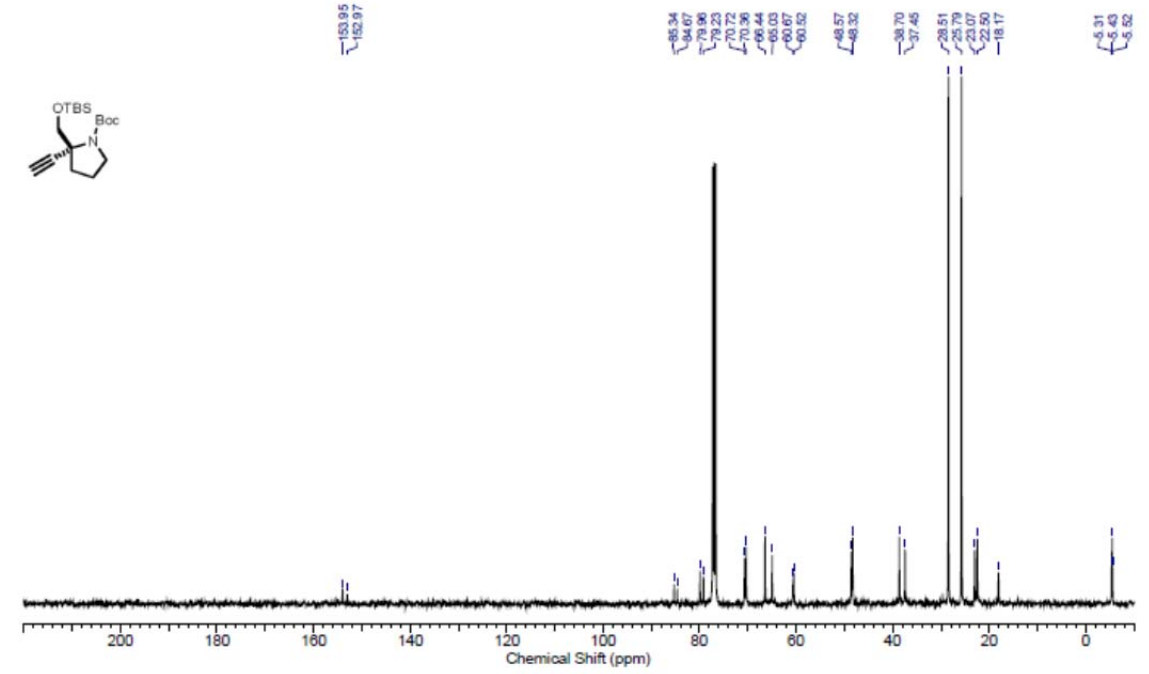
^{1}H and ^{13}C NMR of compound **3-115**



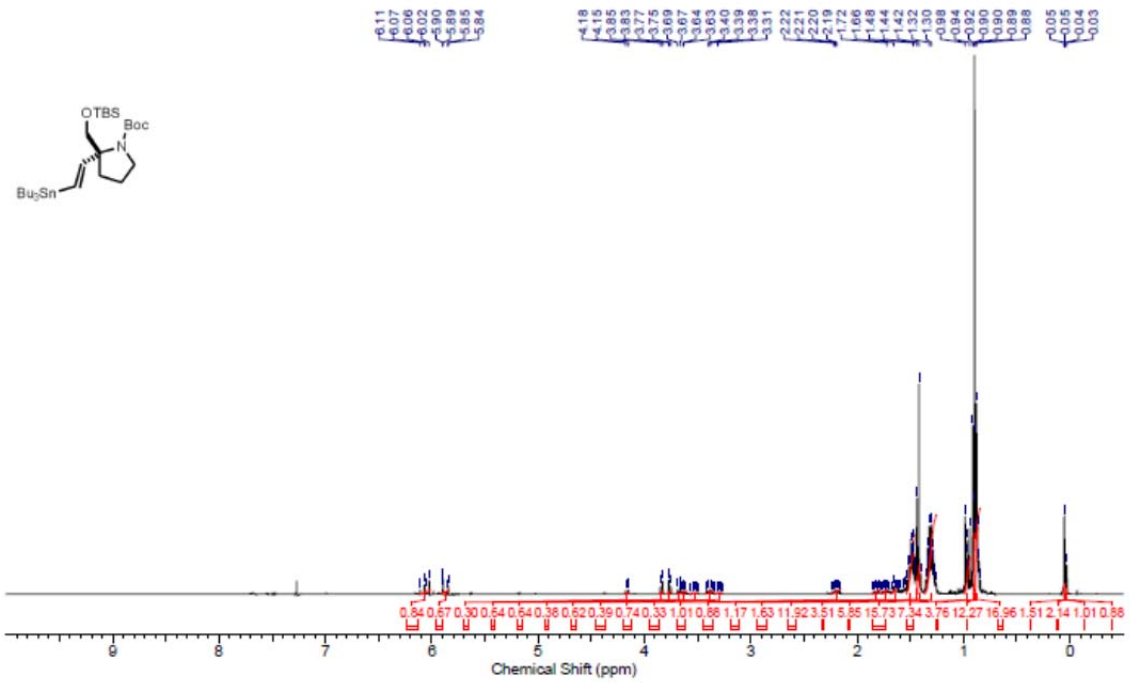


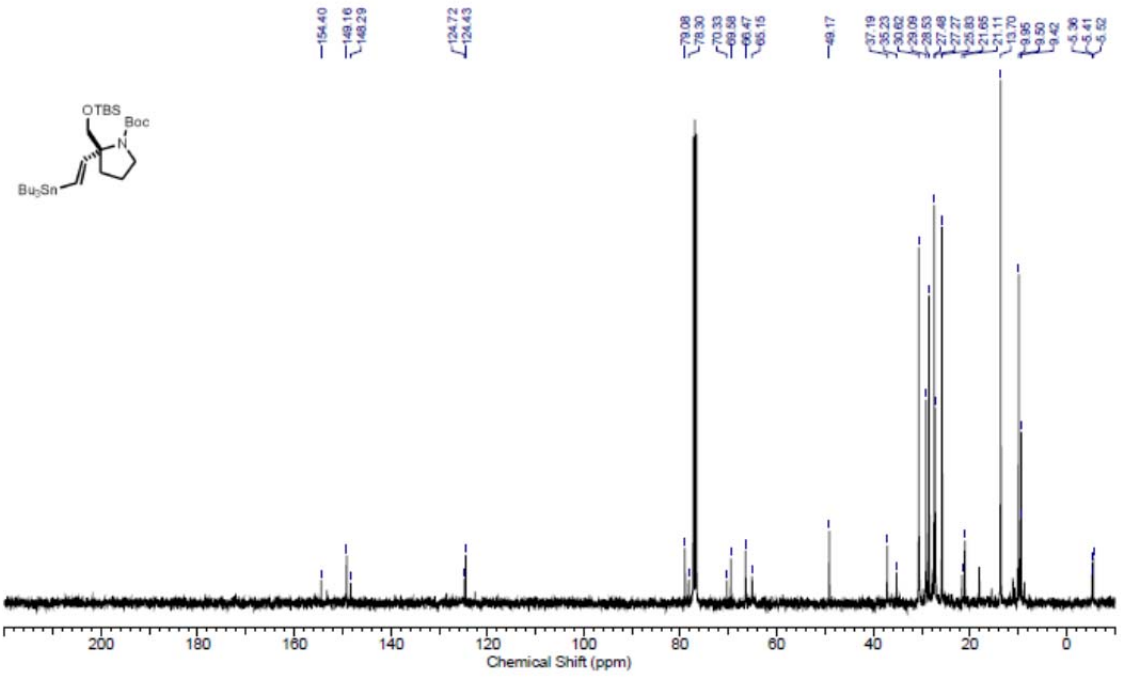
^{1}H and ^{13}C NMR of compound **3-117**



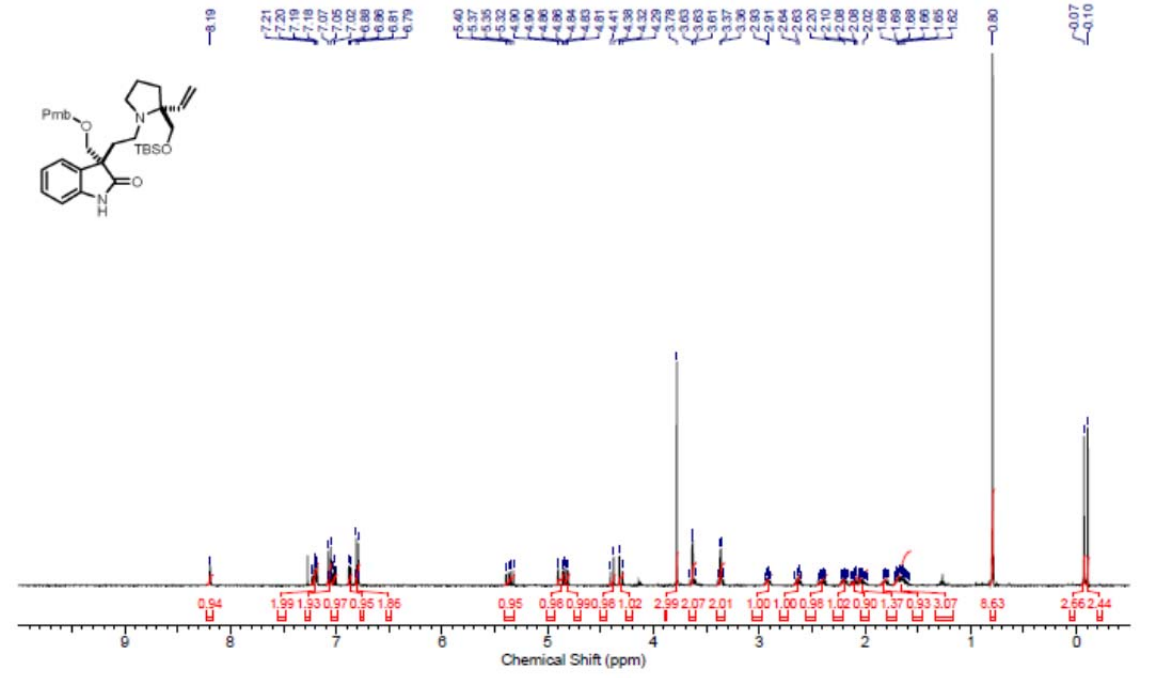


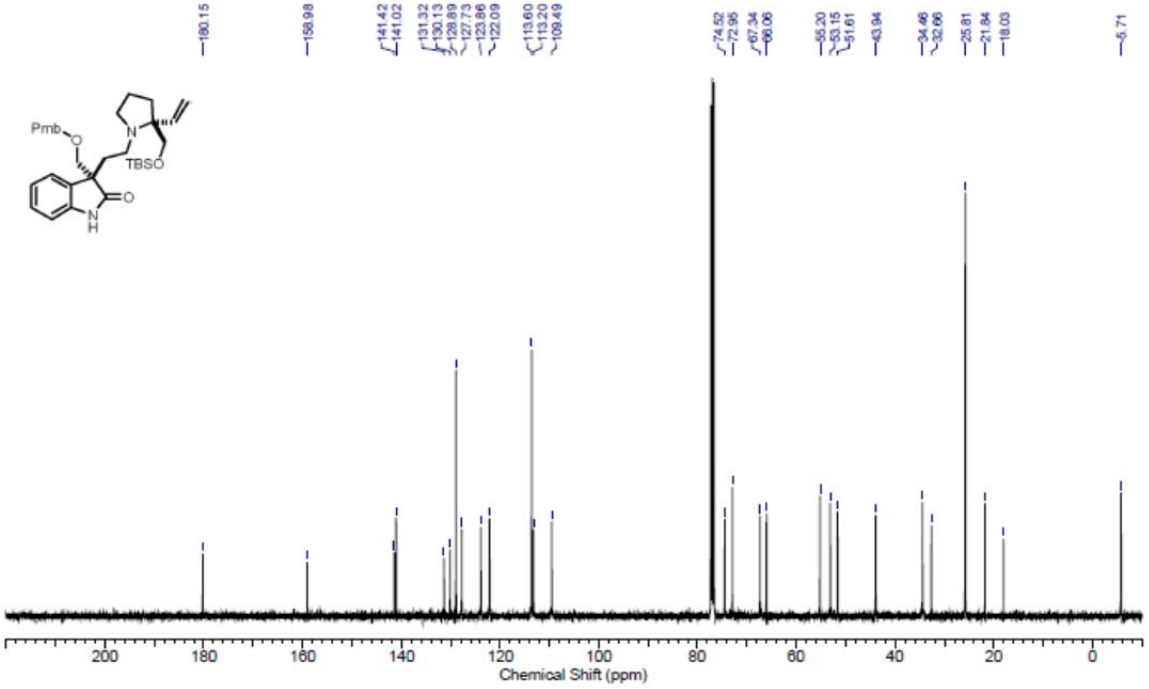
^{1}H and ^{13}C NMR of compound **3-118**



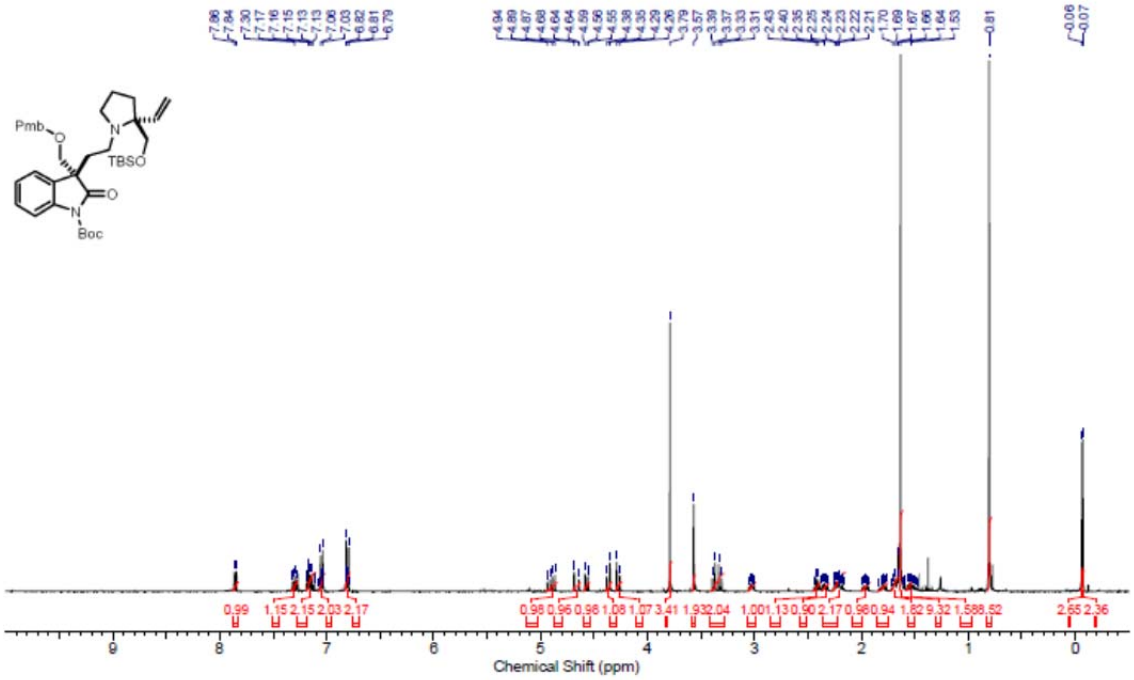


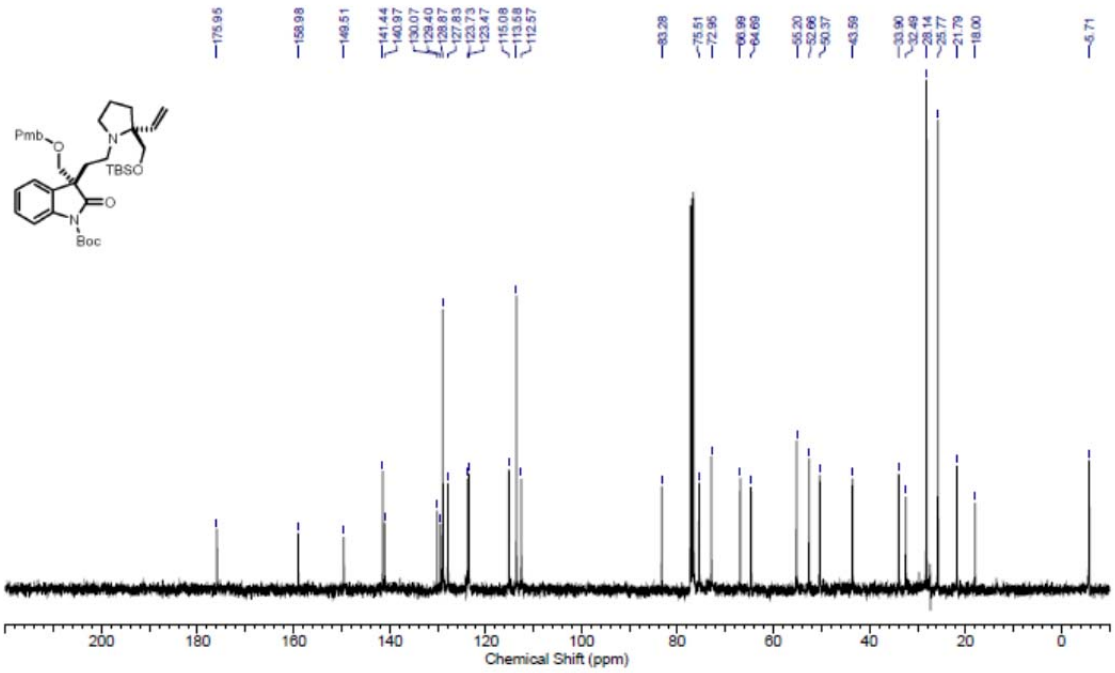
^{1}H and ^{13}C NMR of compound **3-120**



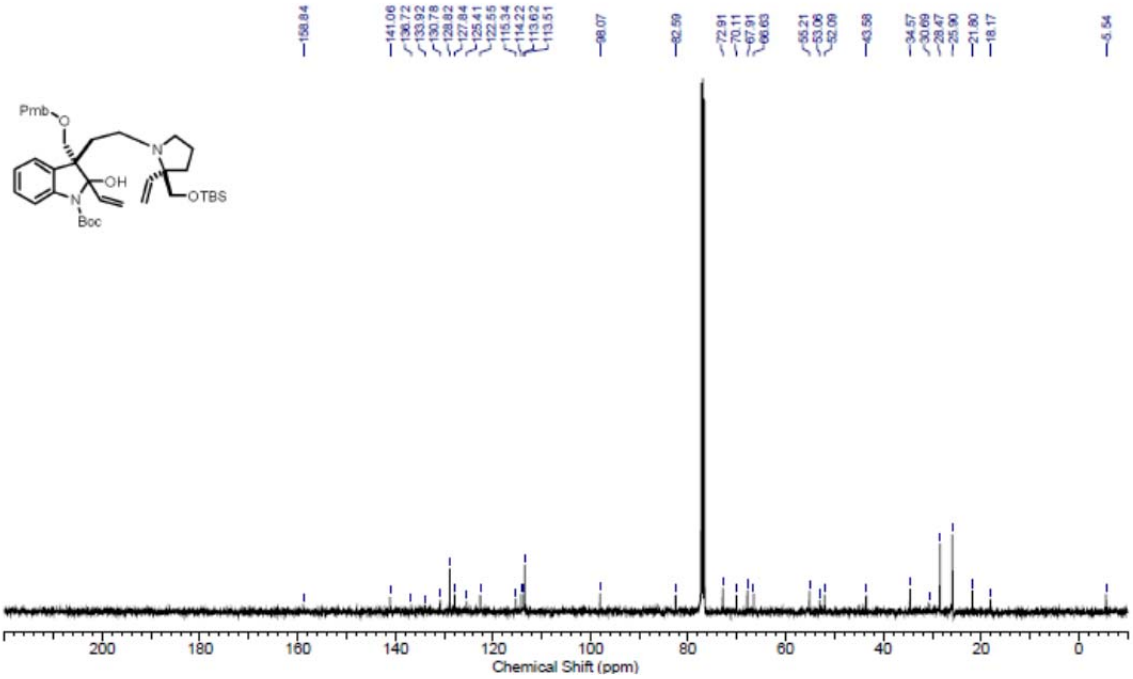


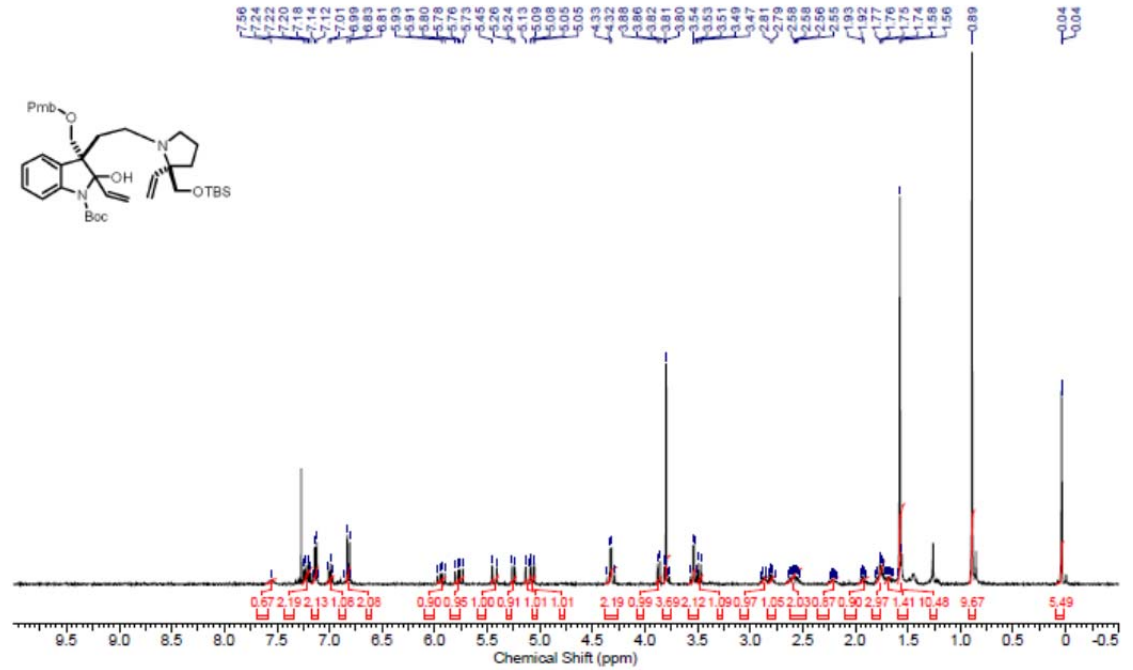
^{1}H and ^{13}C NMR of compound **3-121**



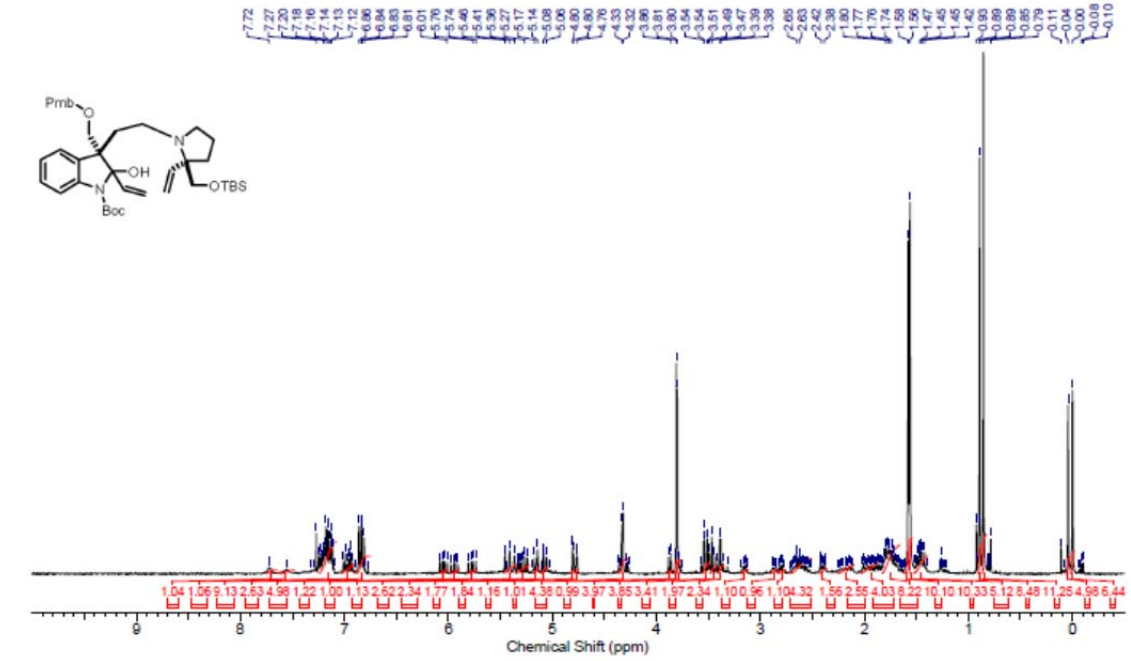


^{1}H and ^{13}C NMR of compound **3-122**

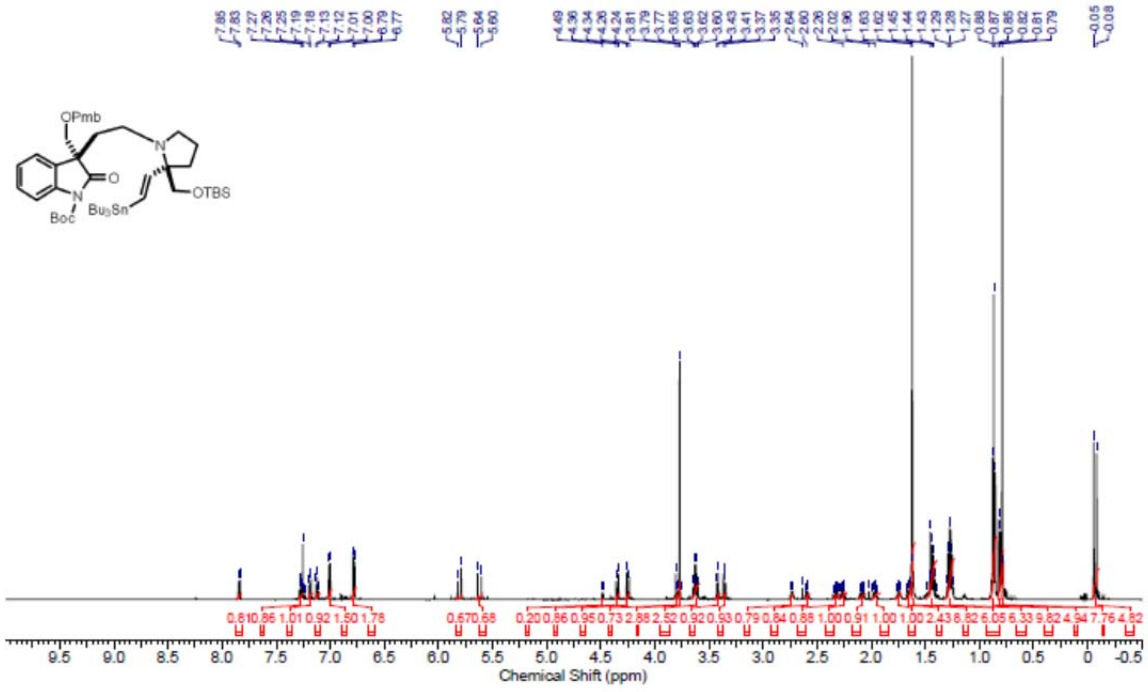




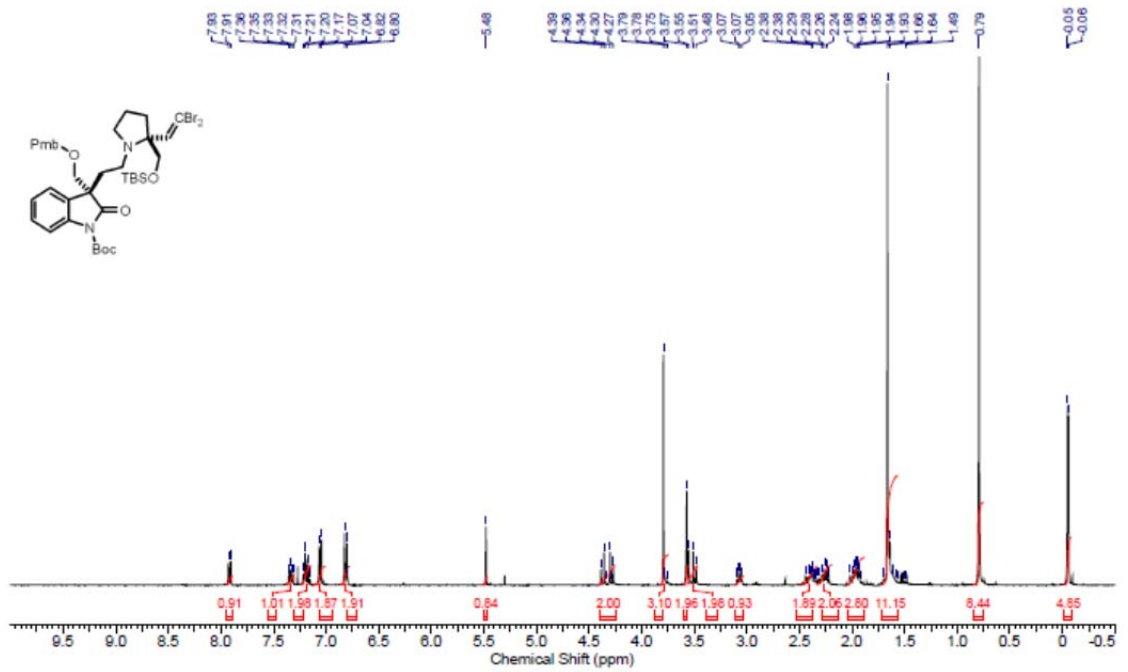
^{1}H of the diastereomeric mixture of compound **3-122**

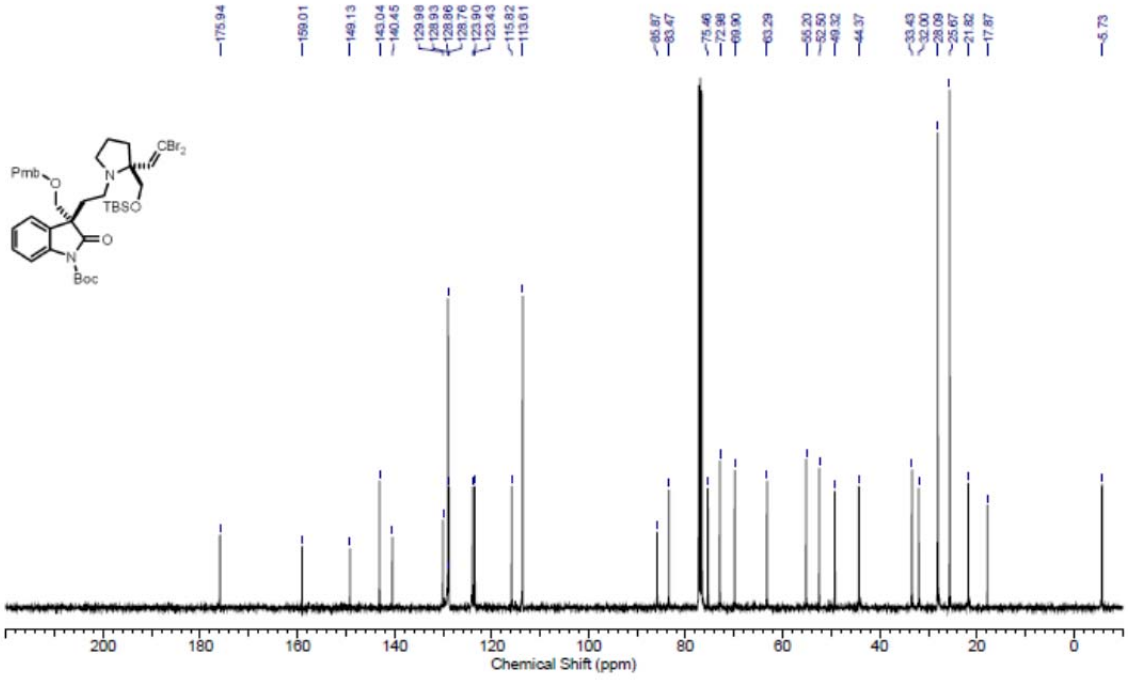


^{1}H of tim containing compound compound **3-126**

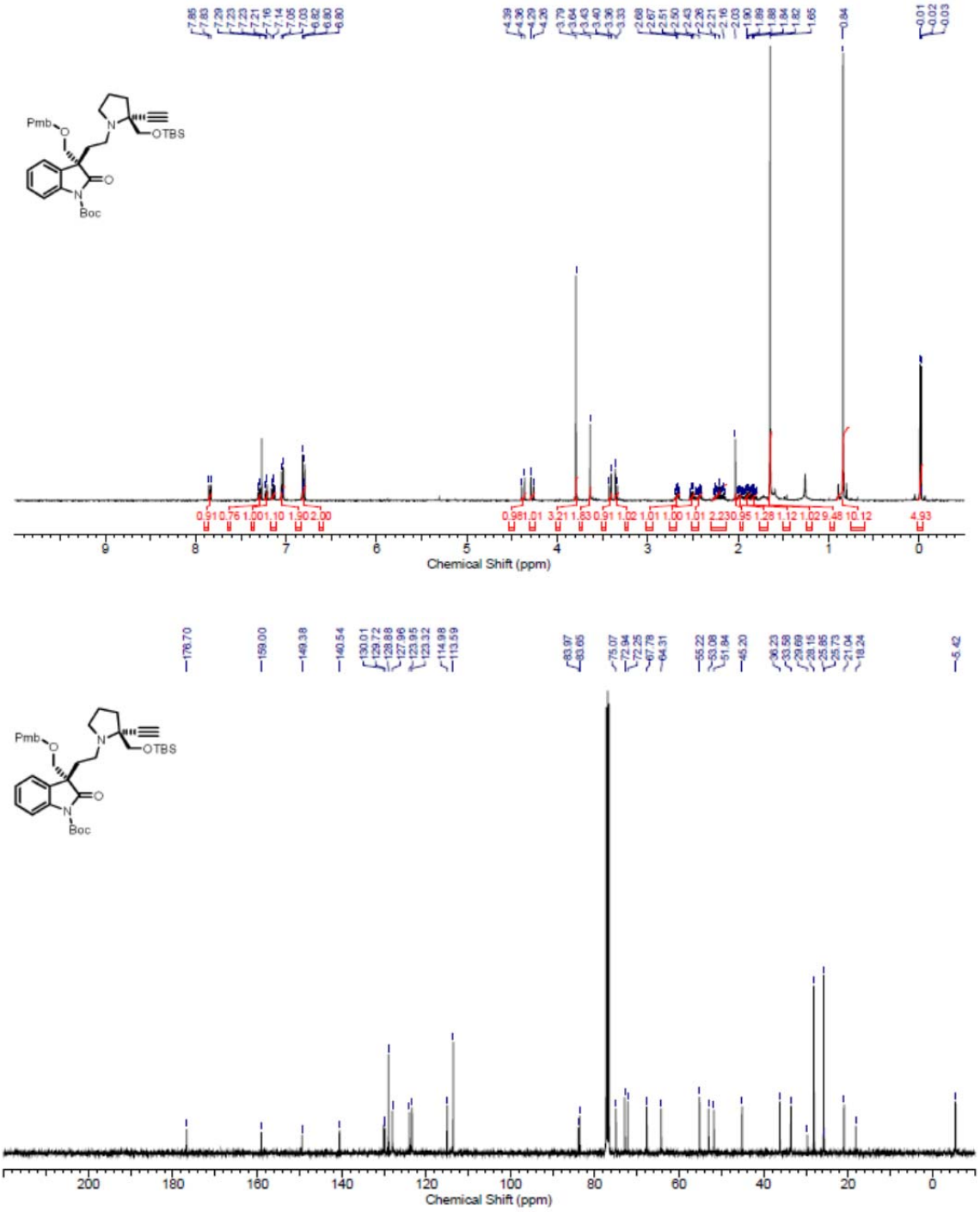


^{1}H and ^{13}C NMR of compound **3-125**

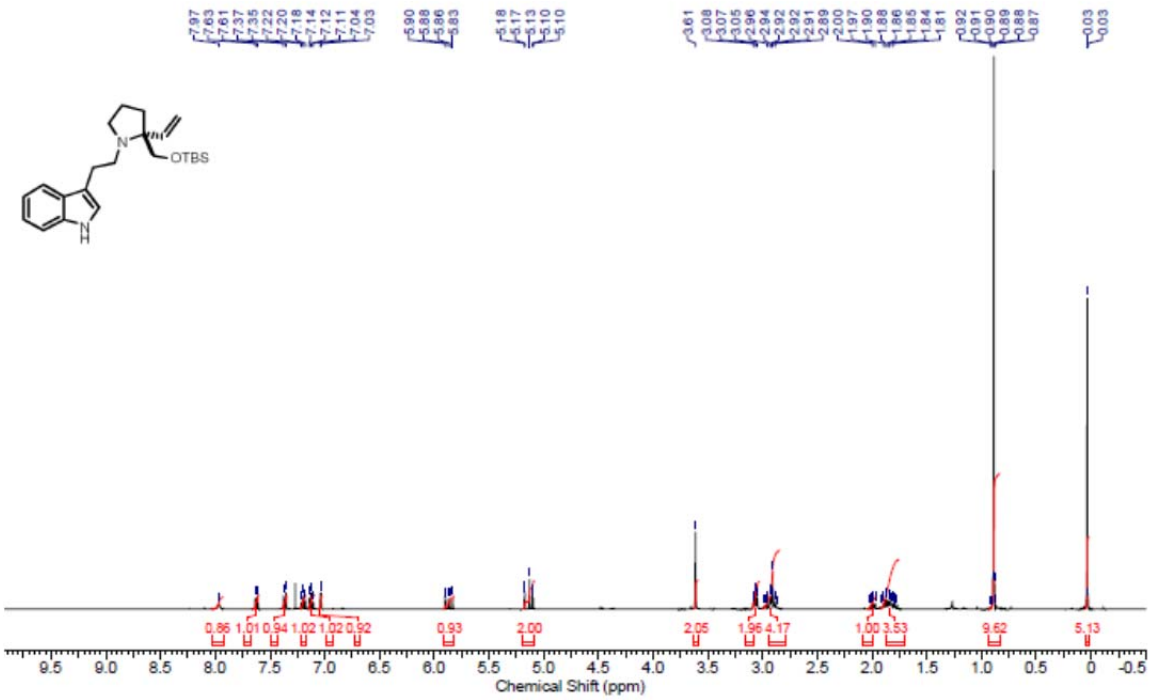


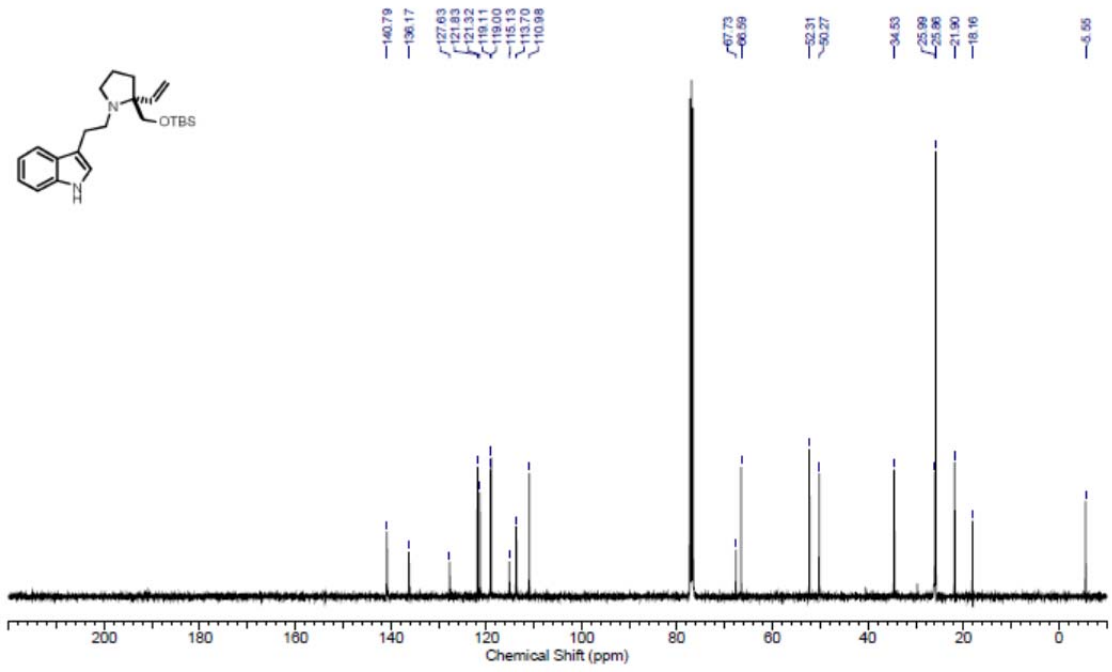


^{1}H and ^{13}C NMR of compound **3-127**

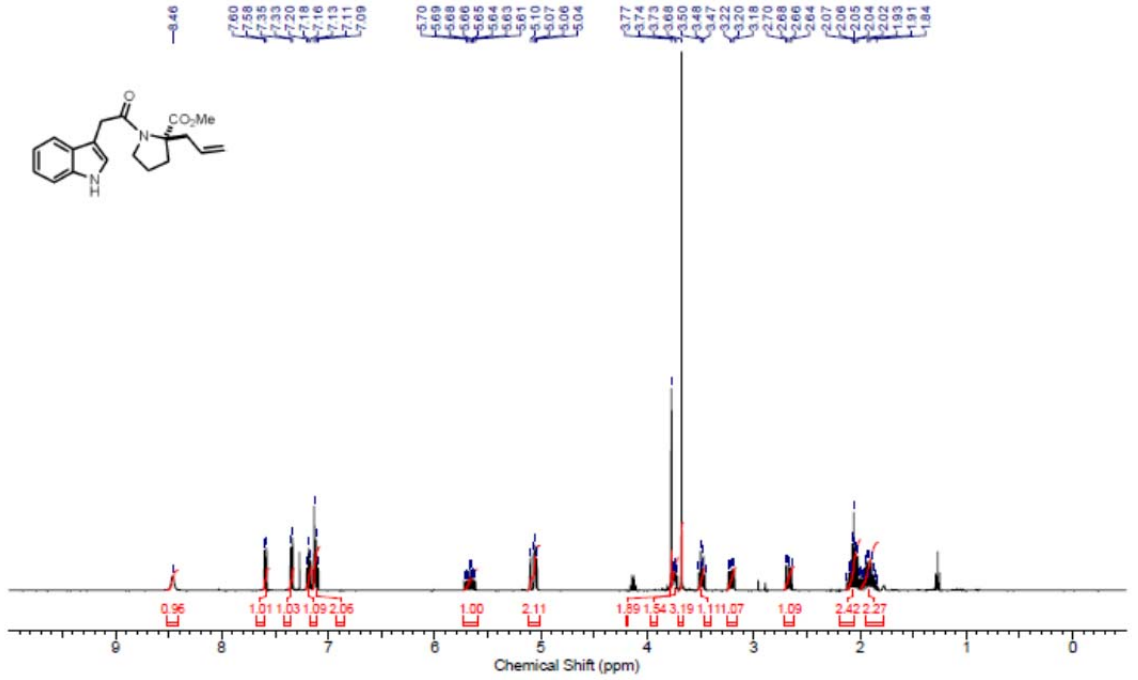


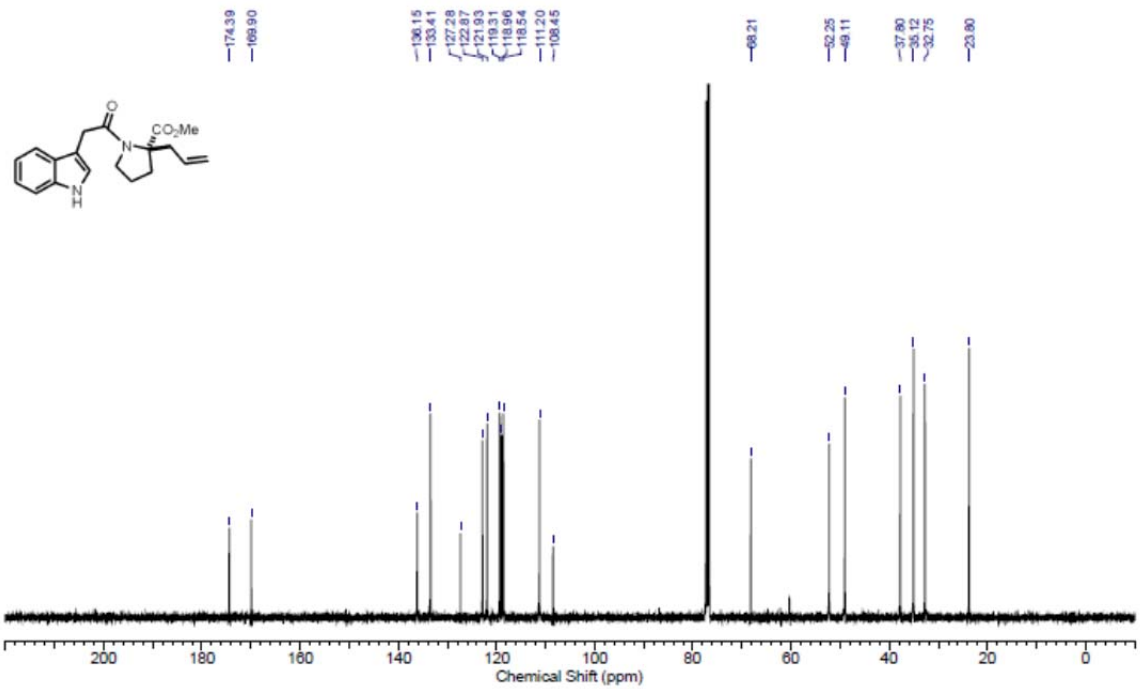
^{1}H and ^{13}C NMR of compound **3-131**



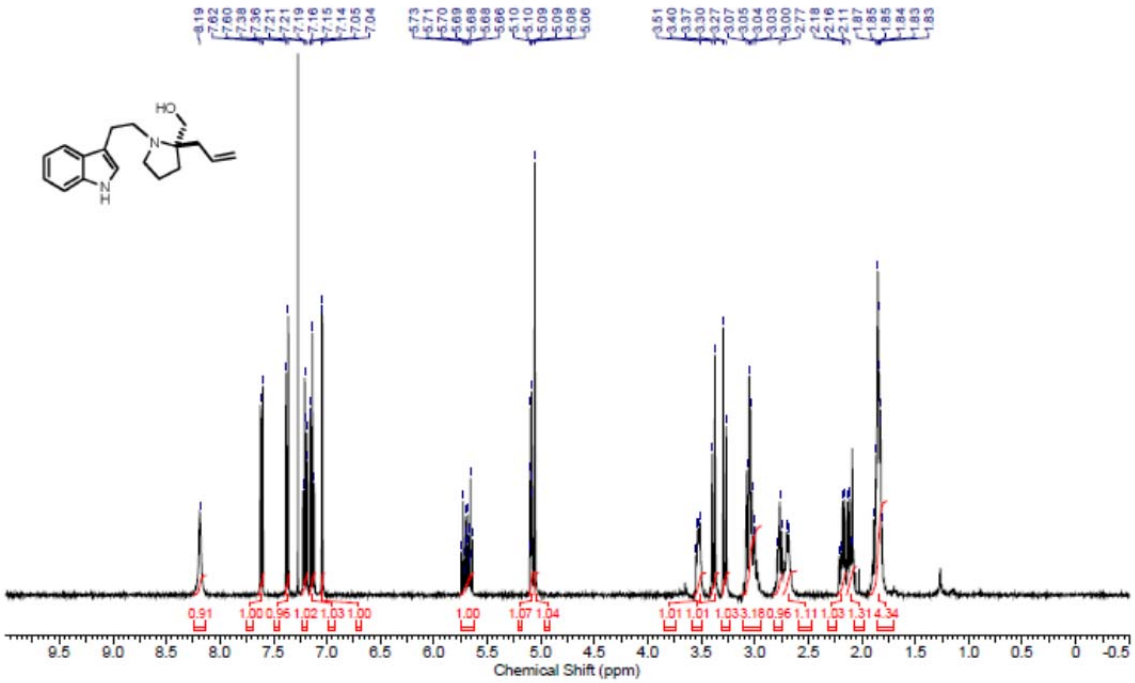


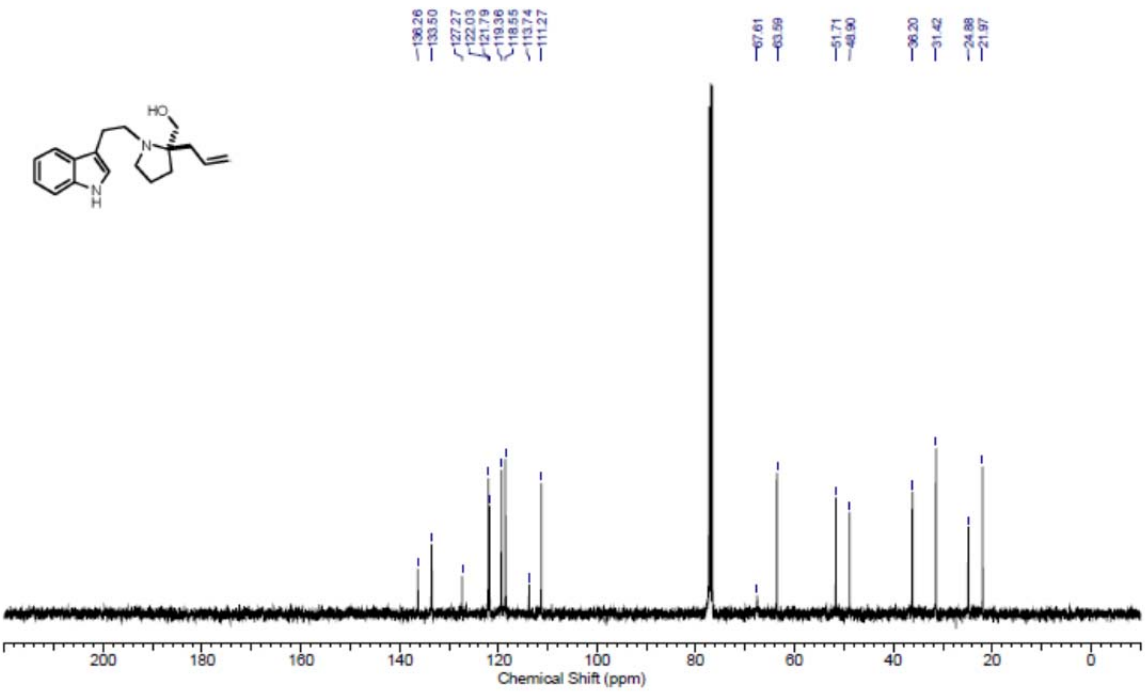
^{1}H and ^{13}C NMR of compound **3-138**



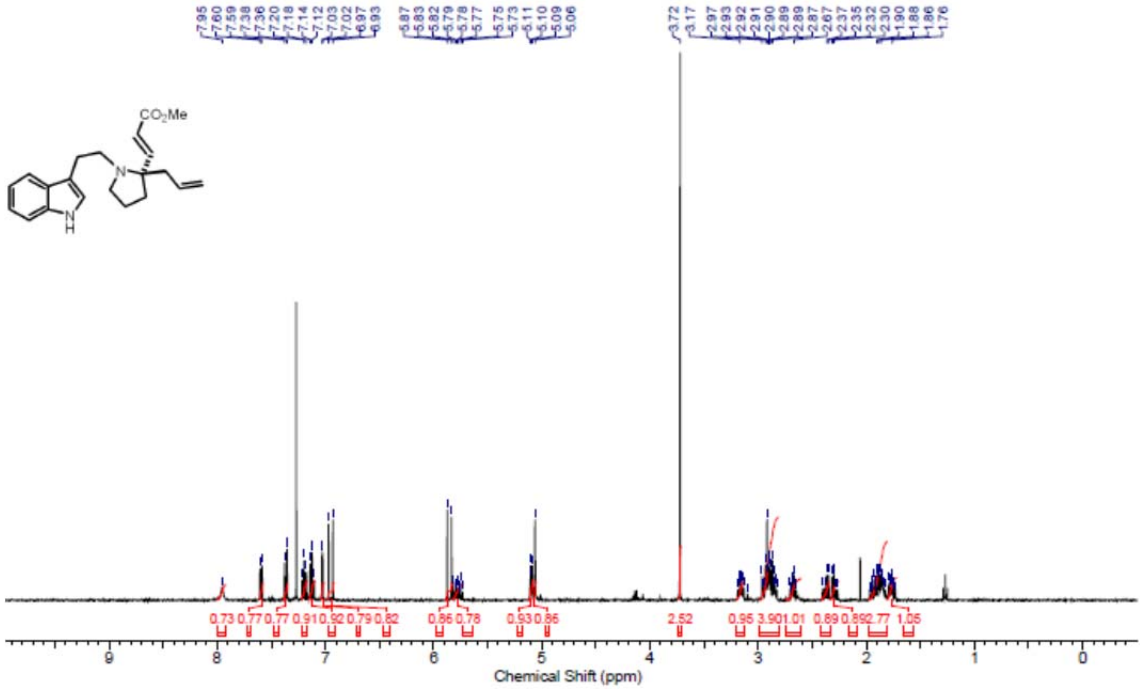


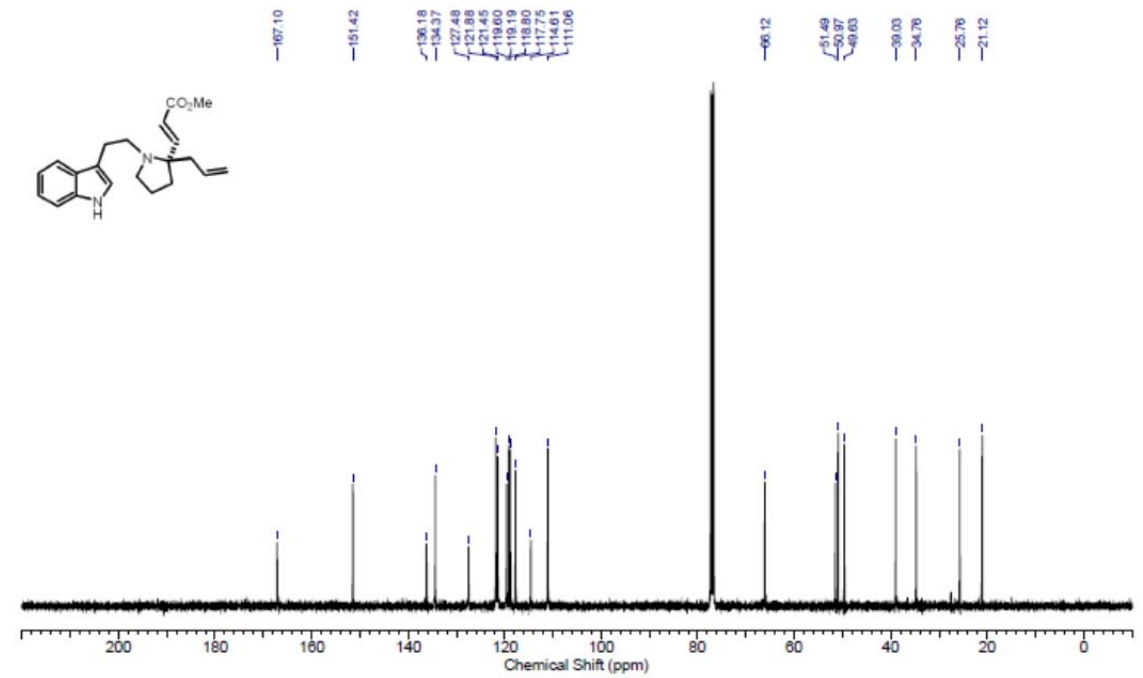
^{1}H and ^{13}C NMR of compound **3-139**



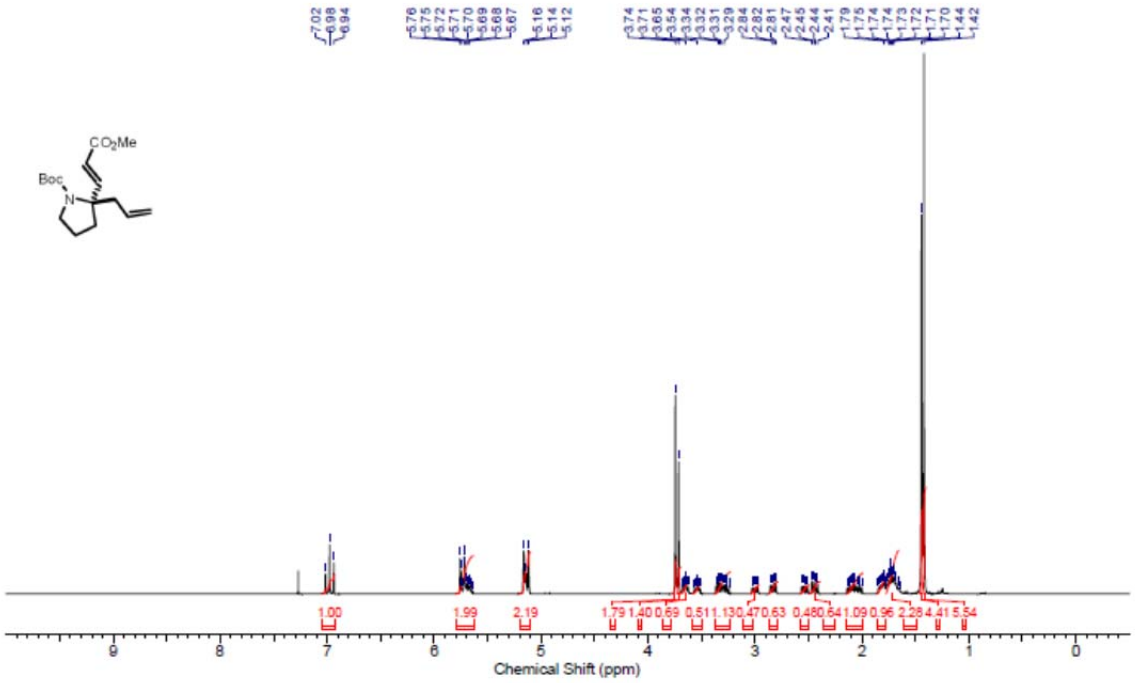


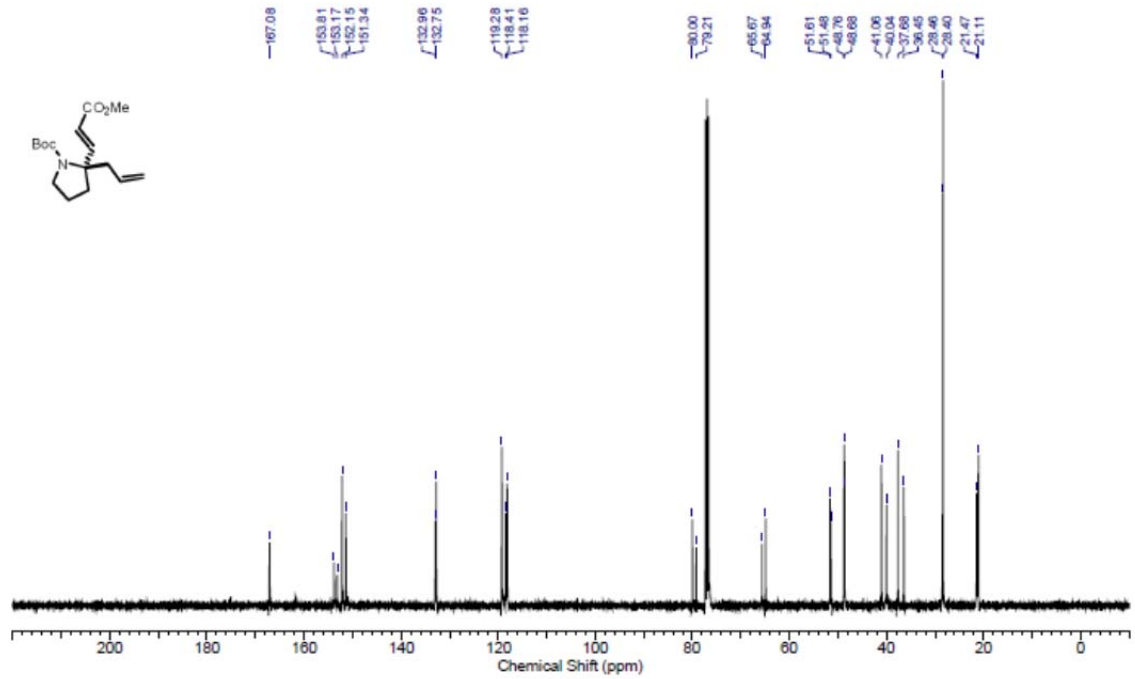
^{1}H and ^{13}C NMR of compound **3-141**



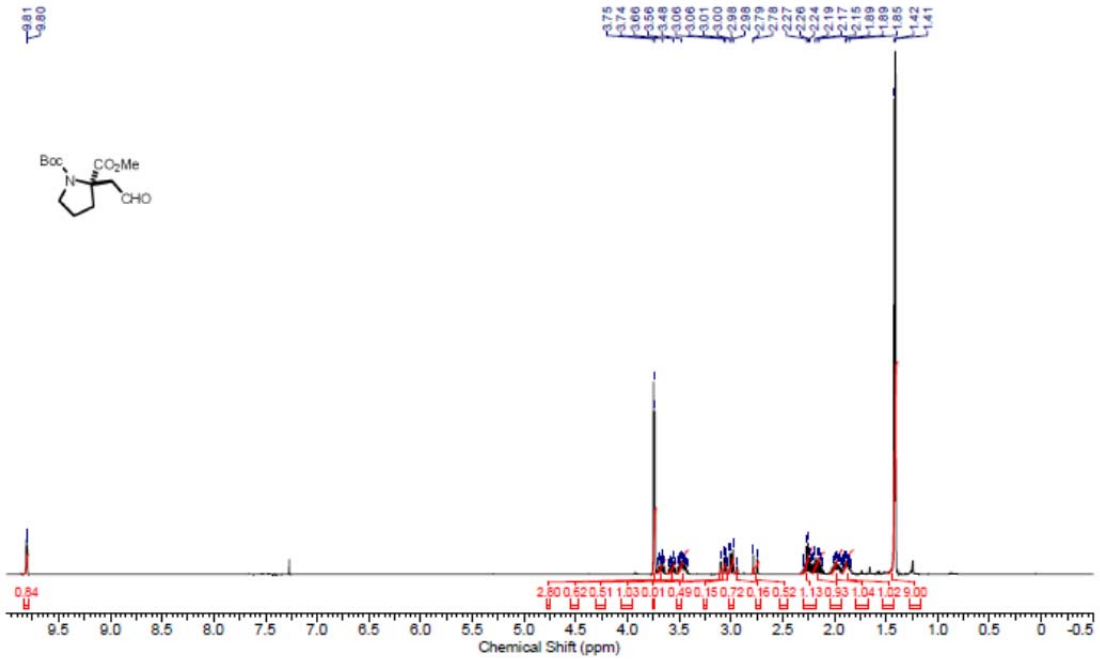


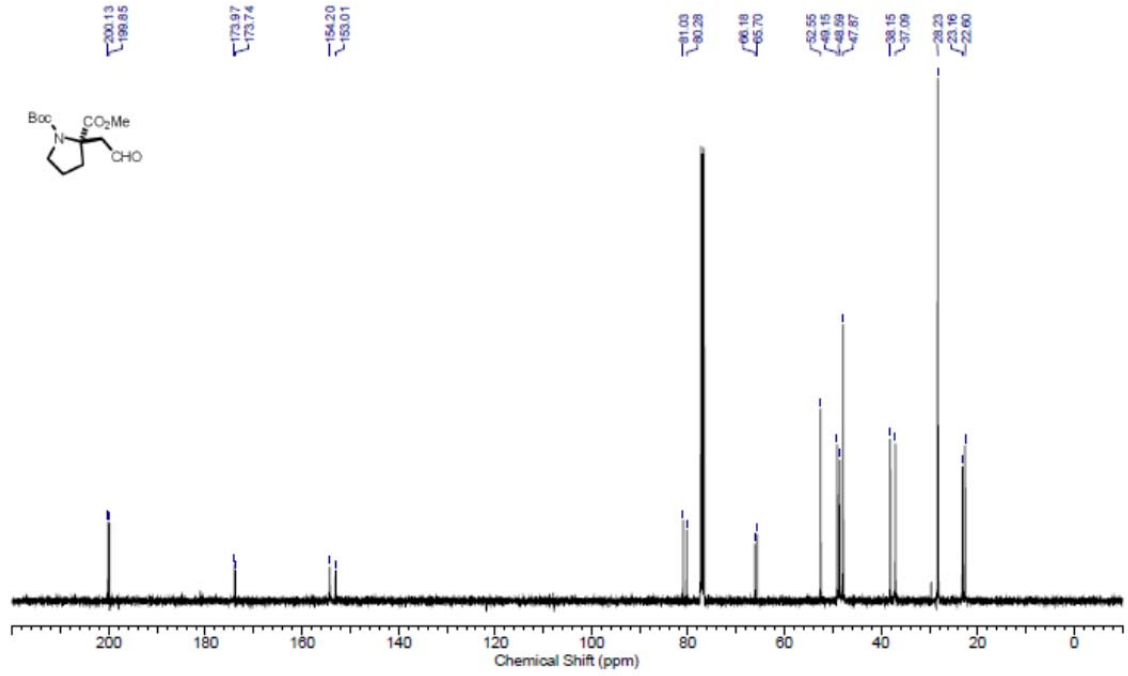
^{1}H and ^{13}C NMR of compound **3-142**



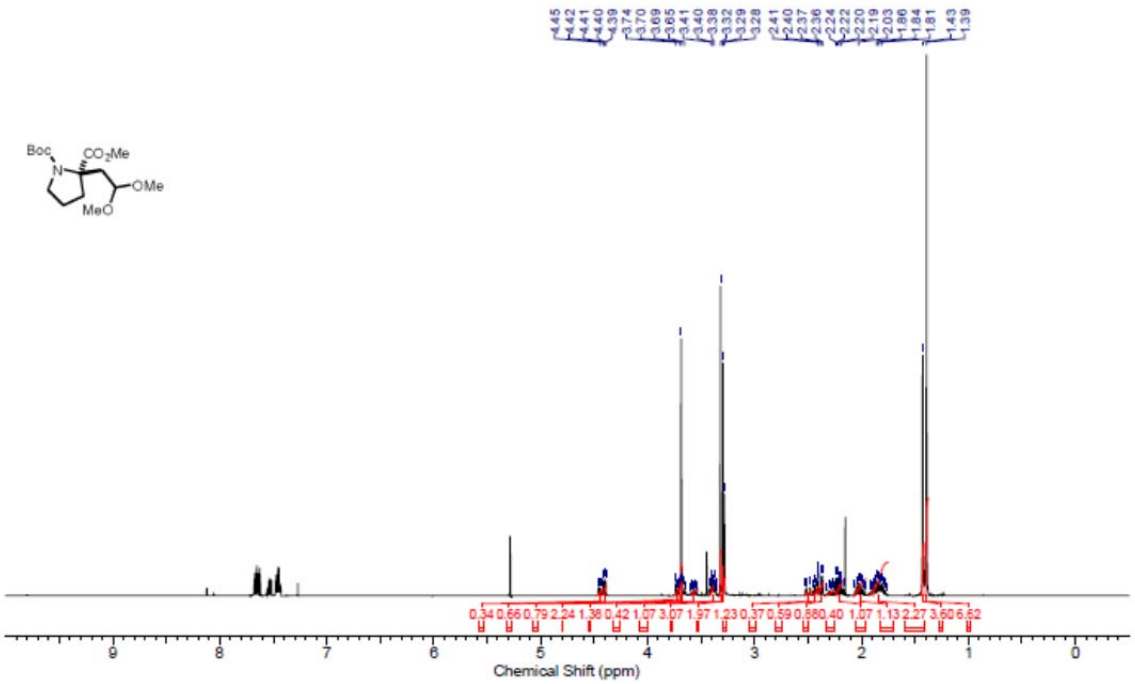


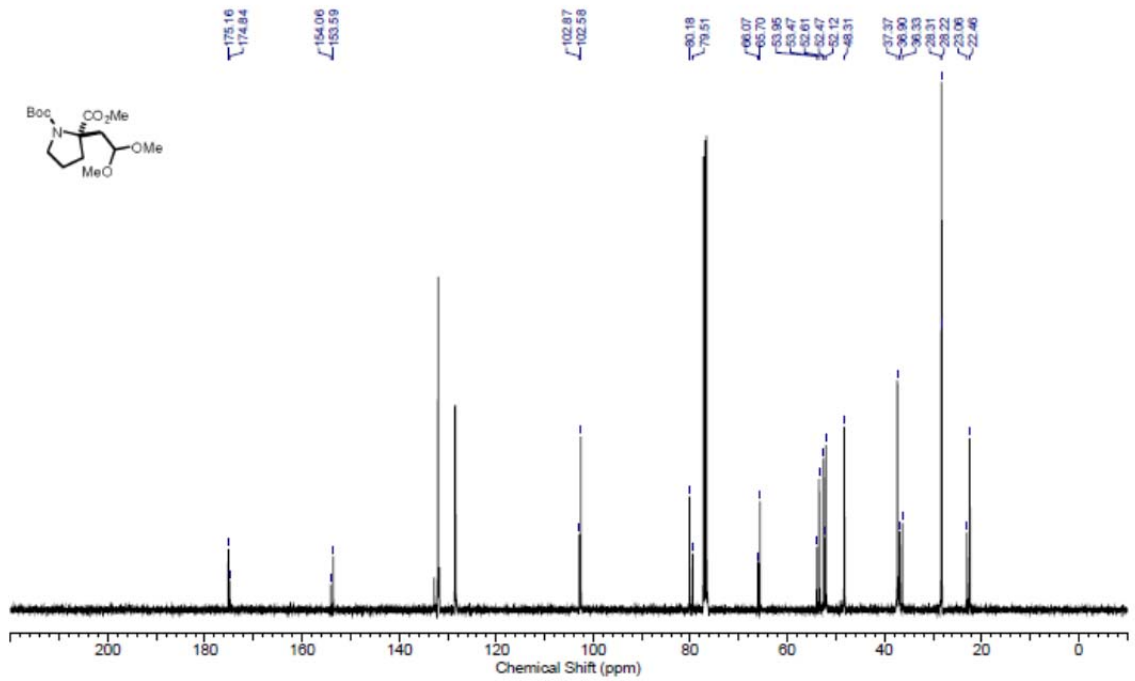
^{1}H and ^{13}C NMR of compound **3-145**



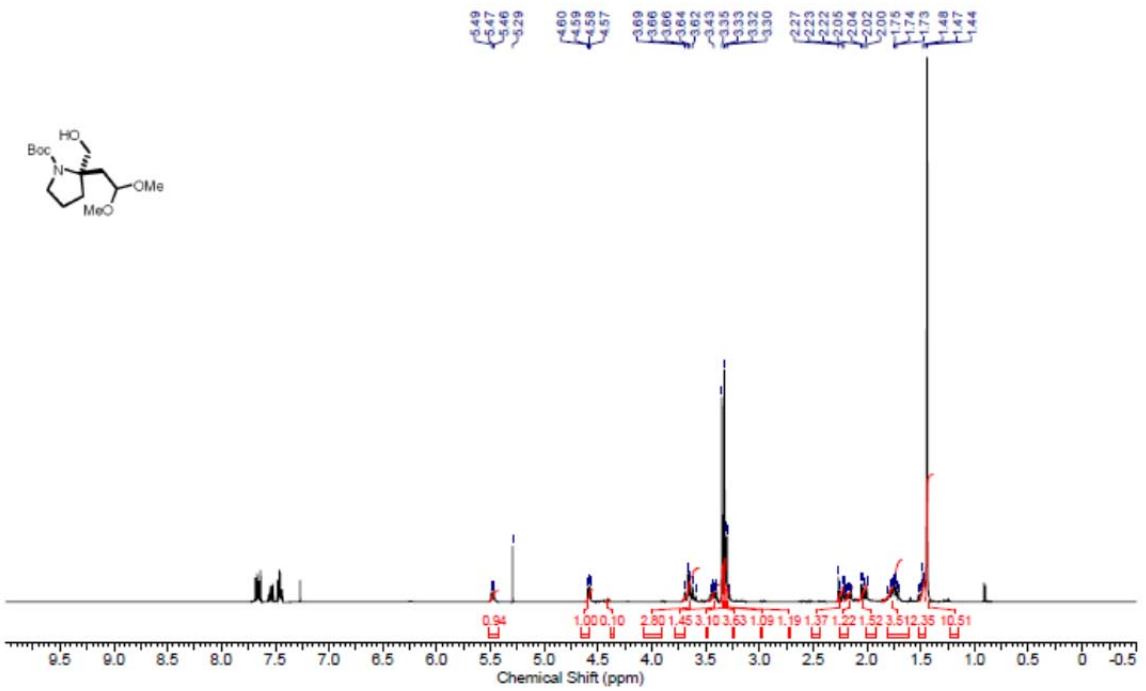


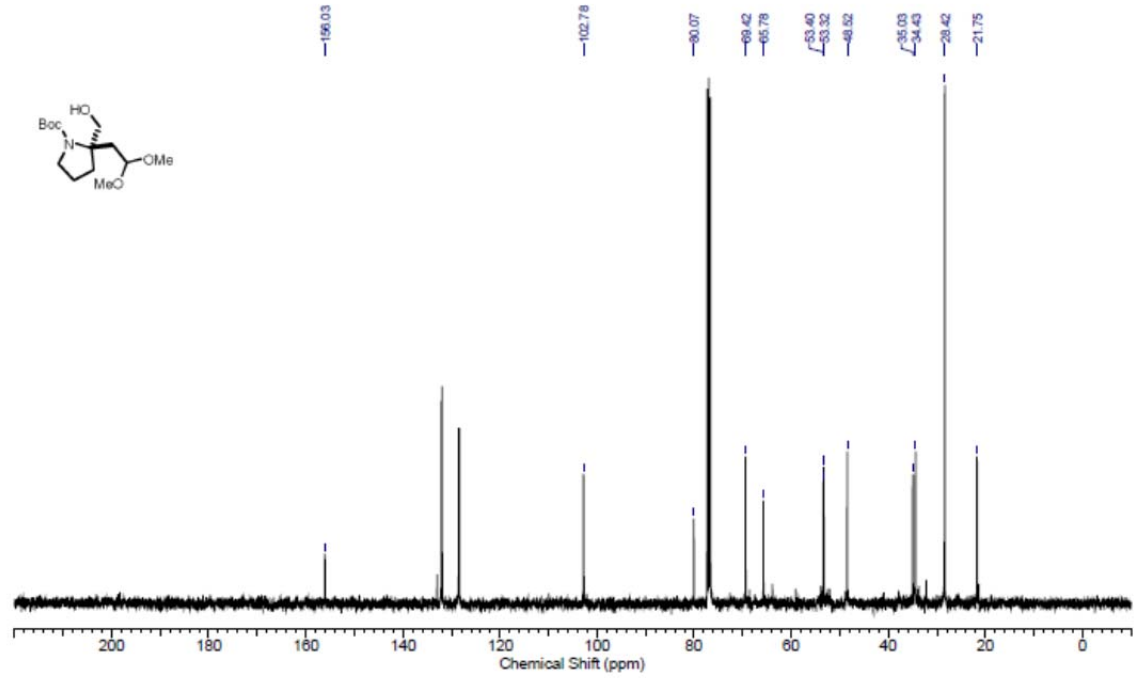
^{1}H and ^{13}C NMR of compound **3-146**



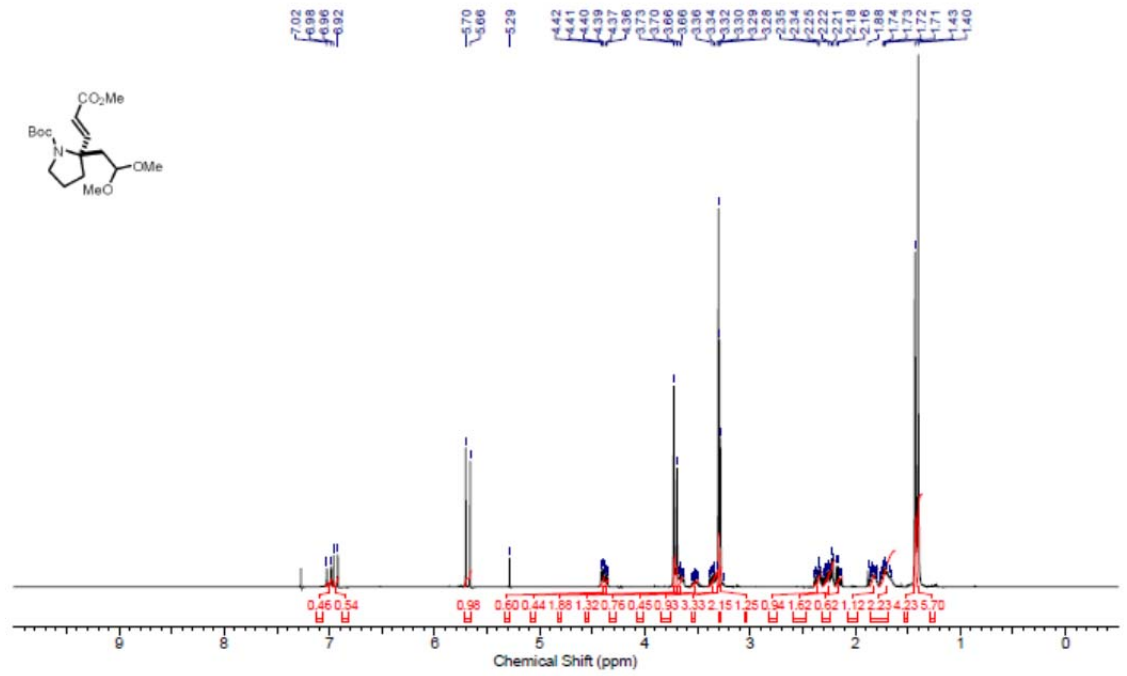


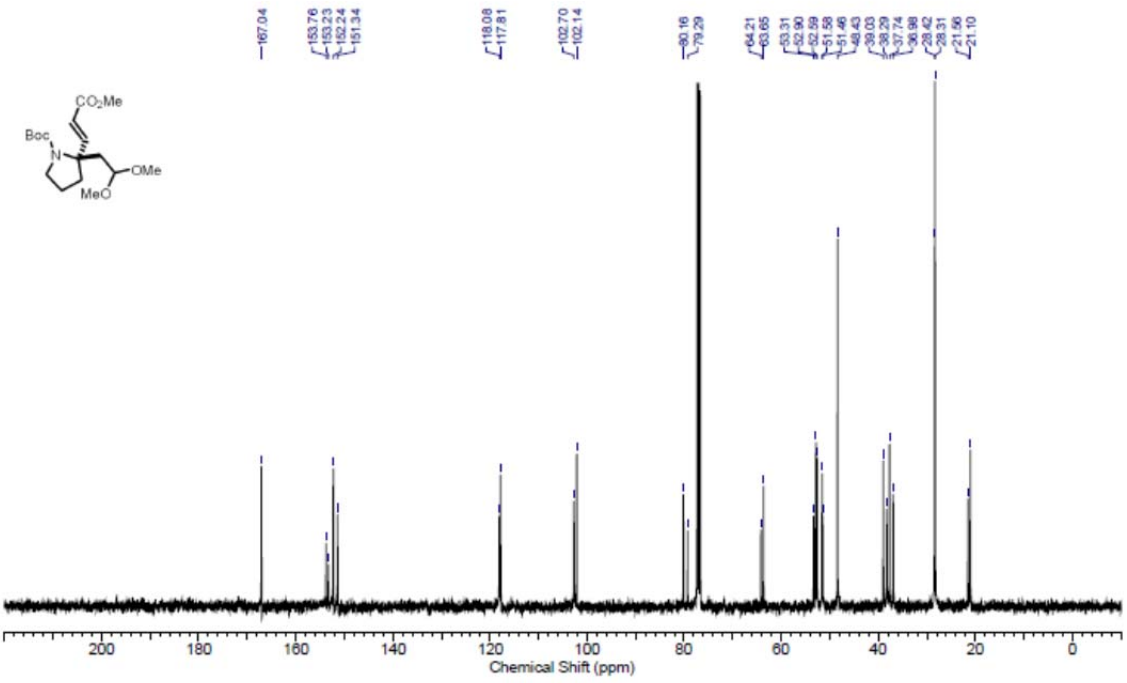
^{1}H and ^{13}C NMR of compound **3-147**



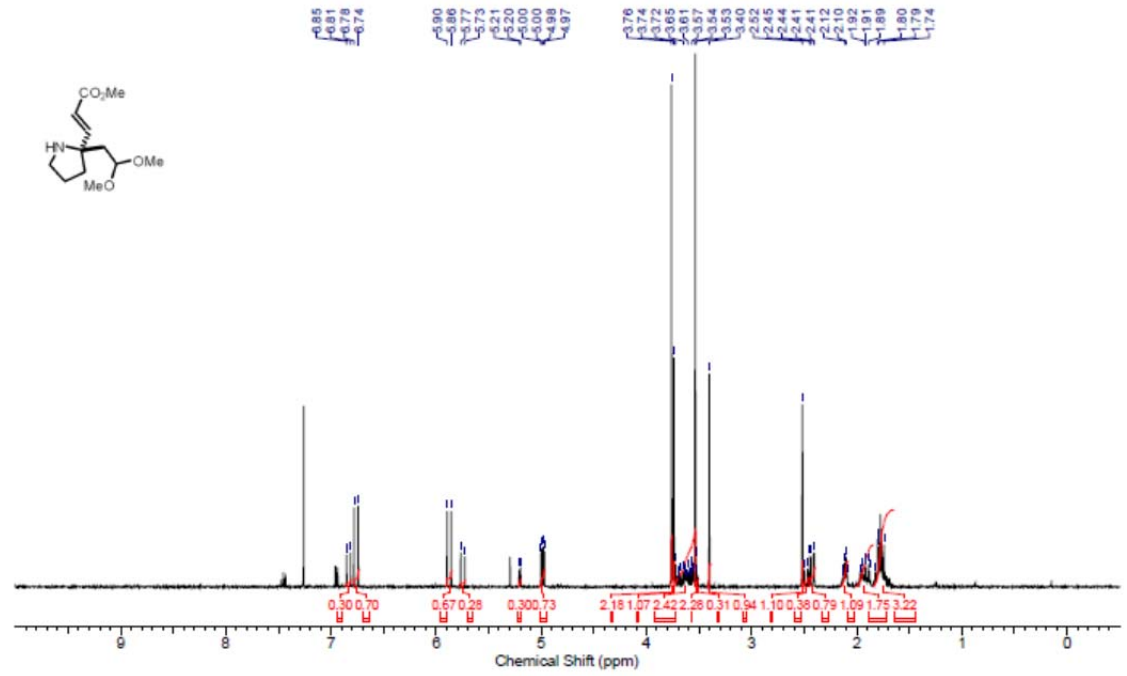


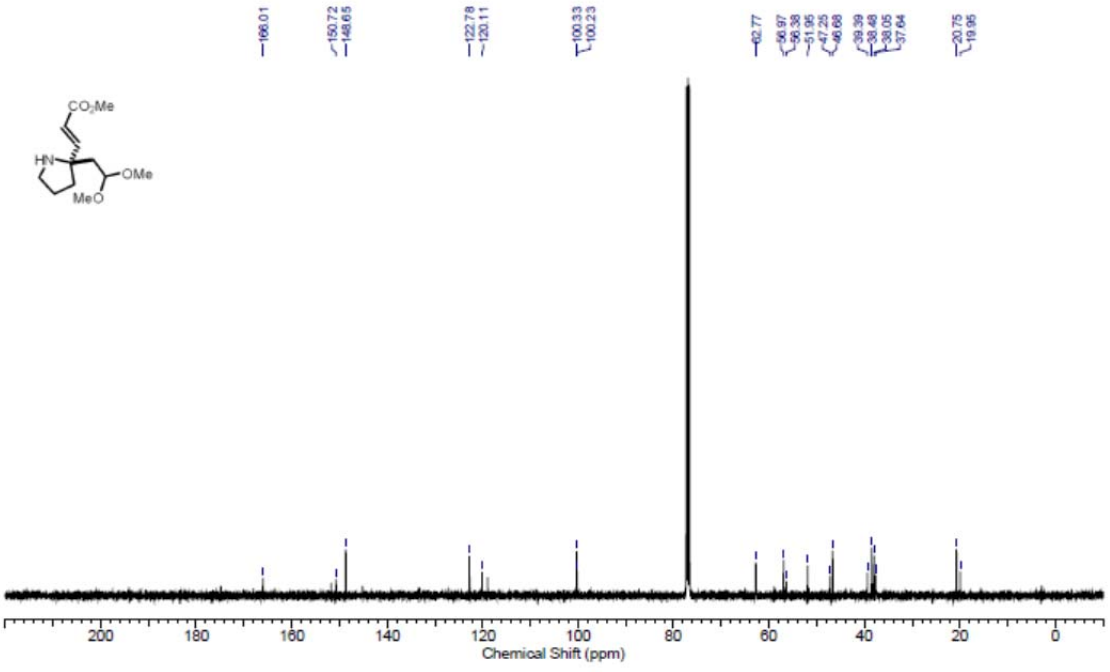
^{1}H and ^{13}C NMR of compound **3-148**



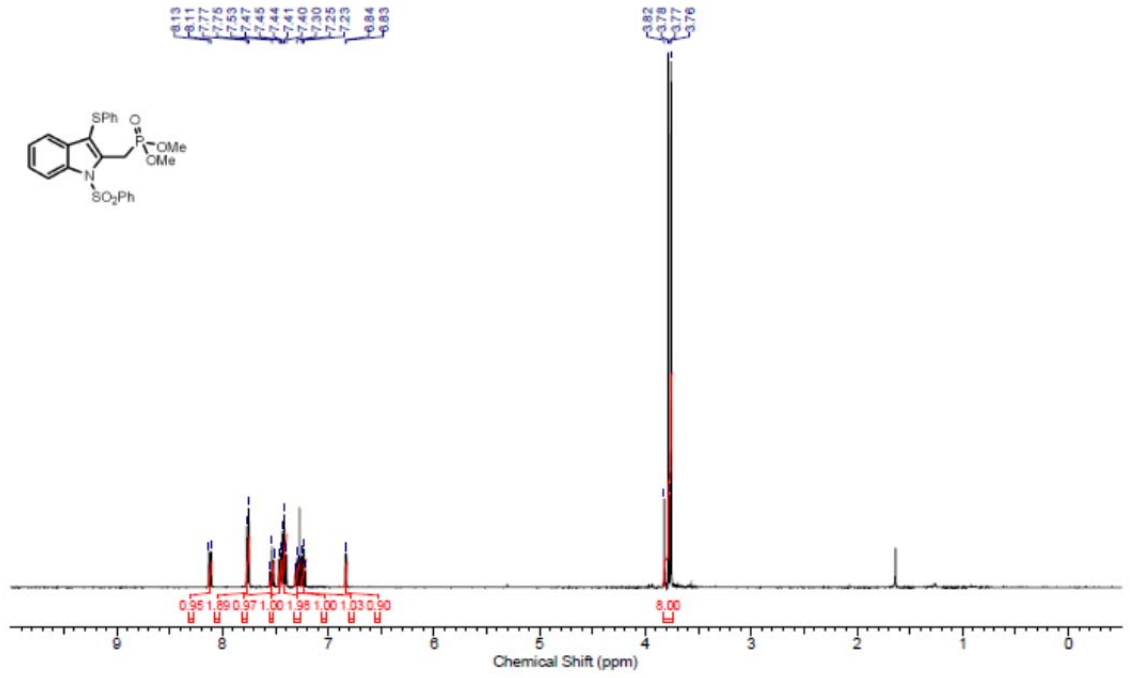


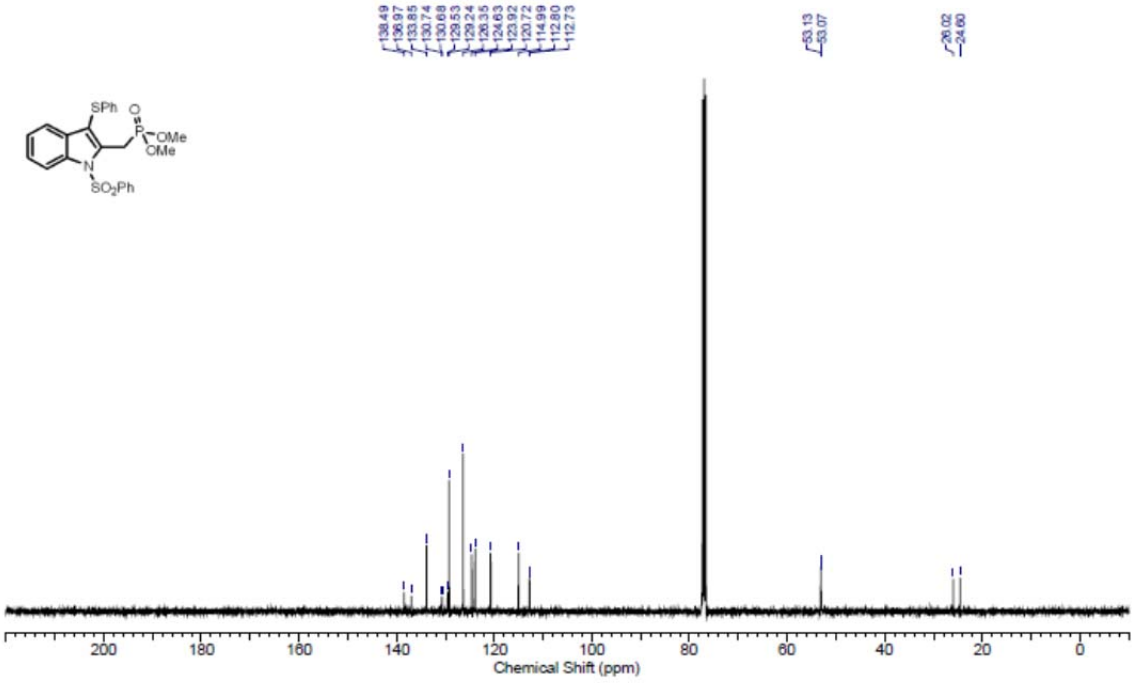
^{1}H and ^{13}C NMR of compound **3-149**



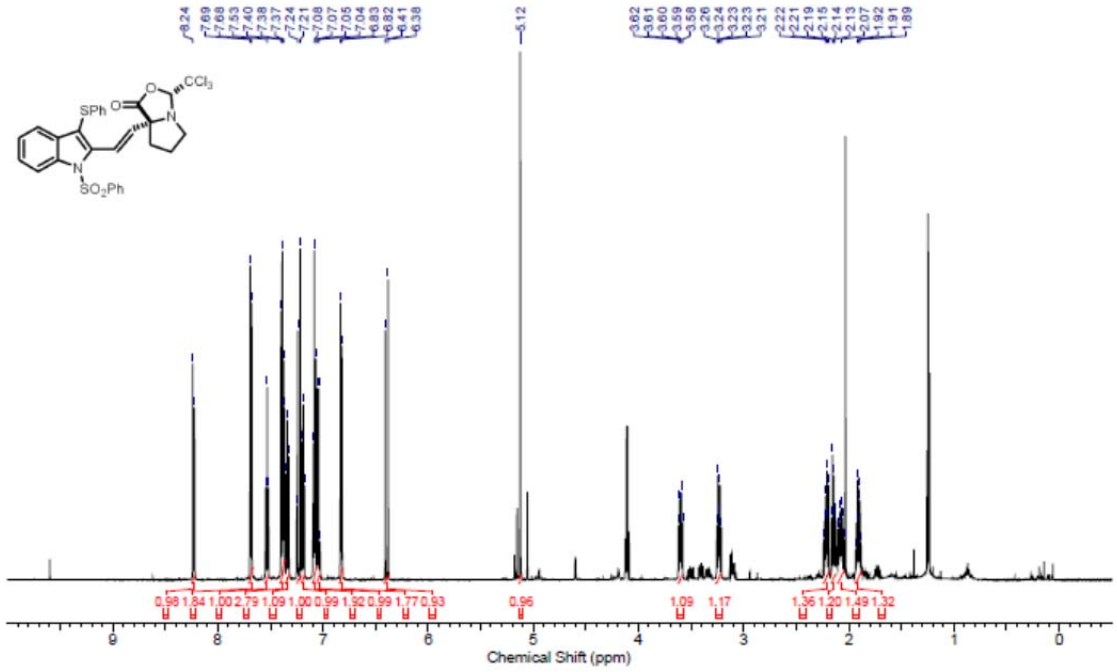


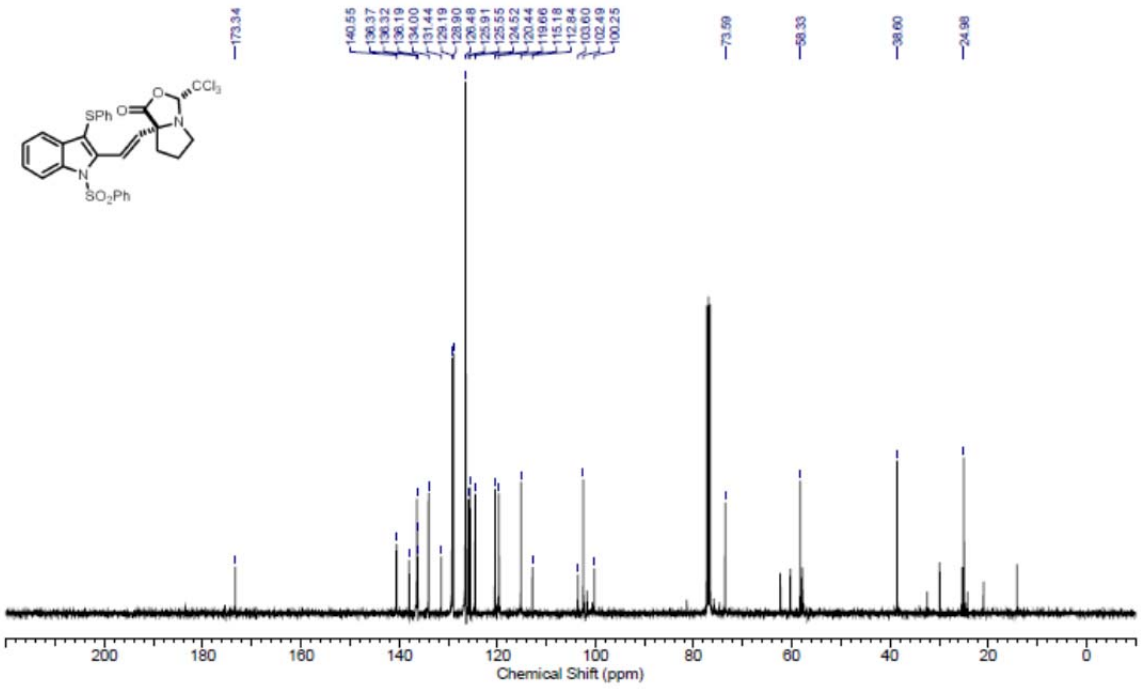
^{1}H and ^{13}C NMR of compound **3-163**



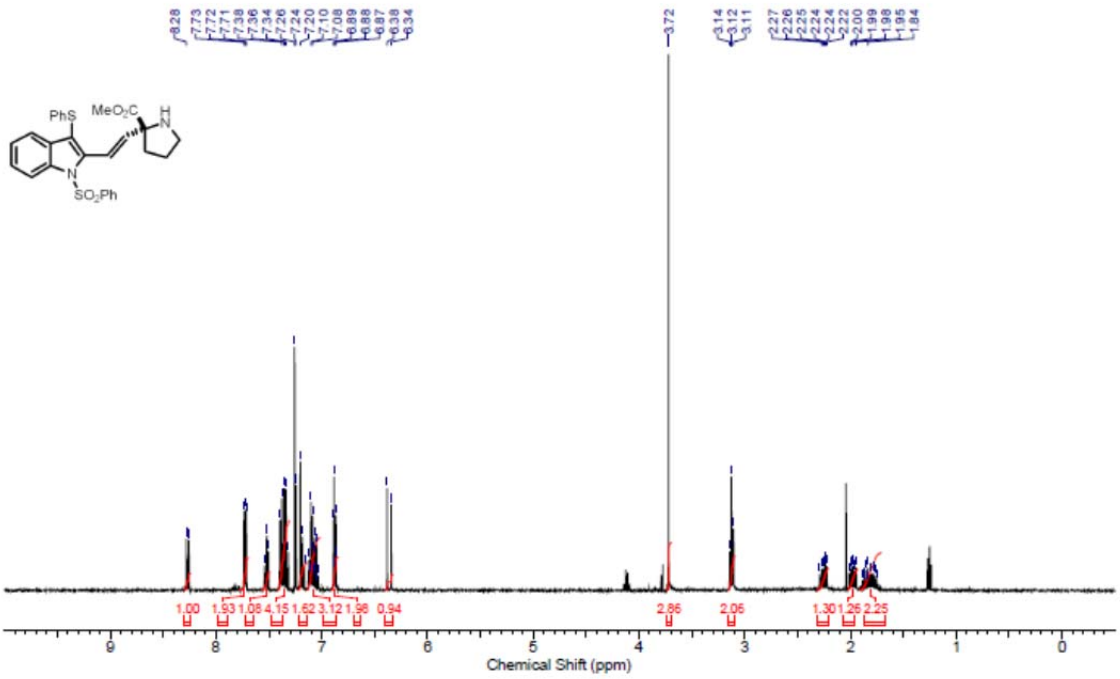


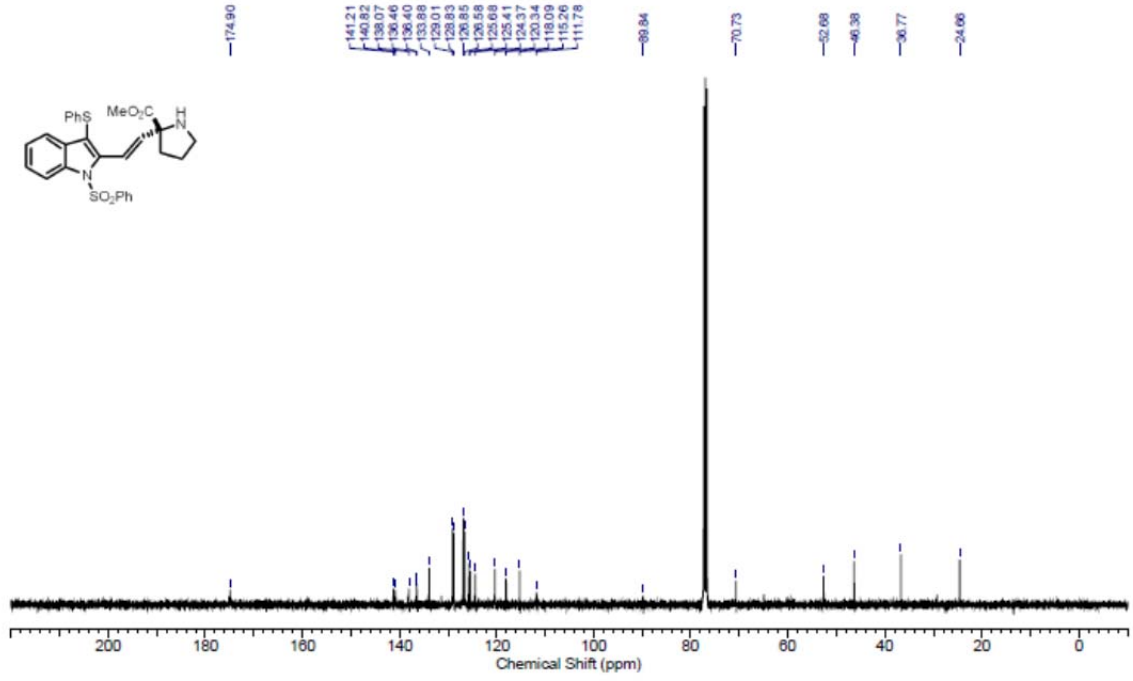
^{1}H and ^{13}C NMR of compound **3-164**





^{1}H and ^{13}C NMR of compound **3-165**





Curriculum Vitae

Andrew C. Stevens

Education

Doctor of Philosophy Candidate (2013)
Synthetic Organic Chemistry
The University *of* Western Ontario, London, Ontario
Research Advisor: Professor Brian L. Pagenkopf

Bachelor of Science (2008)
Honors in Chemistry, Industrial Internship Program
University of Alberta, Edmonton Alberta
Research Advisor: Professor Todd L. Lowary

Research and Relevant Work Experience

Graduate Student Researcher September 2008 – July 2013
The University *of* Western Ontario, London, Ontario
Research Advisor: Professor Brian L. Pagenkopf
Project: Progress Towards the Total Synthesis of Grandilodine A and New Methods for the Synthesis of Hetereocyclic Compounds.

Teaching Assistant September 2008 – July 2013
The University *of* Western Ontario, London, Ontario

Undergraduate Thesis Student September 2007 – April 2008
University of Alberta, Edmonton, Alberta
Research Advisor: Professor Todd L. Lowary
Project: The Stereoselective Introduction of 1,2-*cis*-Glycosidic Linkages in Furanose Systems.

Research Assistant May 2007 – August 2007
Johannes Gotenberg Universität Mainz, Mainz, Germany
Research Advisor: Professor Bernhard Witulski
Project: The Total Synthesis of Perlolyrine and Isoperlolyrine

Research Associate II May 2006 – April 2007
Gilead Sciences, Edmonton, Alberta
Process Research and Development

Publications

(4) The Formal [4+3] Cycloaddition Between Donor-Acceptor Cyclobutanes and Nitrones. Andrew C. Stevens, Cory Palmer, and Brian L. Pagenkopf,* *Organic Letters* **2011**, *13*, 1528 – 1531.
(3) Formal [4+2] Cycloaddition of Alkoxy-Substituted Donor-Acceptor Cyclobutanes and Aldehydes Catalyzed by $Yb(OTf)_3$. Mahmoud M. Abd Rabo Moustafa, Andrew C. Stevens, Ben P. Machin, and Brian L. Pagenkopf,* *Organic Letters* **2010**, *12*, 4736 – 4738.
(2) Diels–Alder Chemistry of Siloles and Their Transformation into Cyclohex-2-ene-1,4-*cis*-diols. Andrew C. Stevens and Brian L. Pagenkopf,* *Organic Letters* **2010**, *12*, 3658 – 3661.
(1) Improved Yields and Simplified Purification with a Second Generation Cobalt Catalyst for the Oxidative Formation of *trans*-THF Rings. Cory Palmer, Nicholas A. Morra, Andrew C. Stevens, Barbora Bajtos, Ben P. Machin and Brian L. Pagenkopf,* *Organic Letters* **2009**, *11*, 5614 – 5617.

Oral Presentations

(3) Formal Cycloadditions of Alkoxy-Substituted Donor-Acceptor Cyclopropanes and Cyclobutanes. Andrew C. Stevens and Brian L. Pagenkopf.* The 244th American Chemical Society National Meeting, Philadelphia, Pennsylvania, USA, 2013
(2) Formal Cycloadditions of Alkoxy-Substituted Donor-Acceptor Cyclopropanes and Cyclobutanes. Andrew C. Stevens and Brian L. Pagenkopf.* The 243rd American Chemical Society National Meeting, San Diego, California, USA, 2012.
(1) Formal Cycloadditions of Donor-Accpetor Cyclobutanes. Andrew C. Stevens and Brian L. Pagenkopf.* 94th Canadian Chemistry Conference, Montreal, QC, 2011

Poster Presentations

(7) Exploration of Siloles as Intermediates in Organic Synthesis. Andrew C. Stevens and Brian L. Pagenkopf.* The 244th American Chemical Society National Meeting, Philadelphia, Pennsylvania, USA, 2013
(6) Exploration of Siloles as Intermediates in Organic Synthesis. Andrew C. Stevens and Brian L. Pagenkopf.* The 243rd American Chemical Society National Meeting, San Diego, California, USA, 2012.
(5) Formal [4+2] Cycloaddition of Alkoxy-Substituted Donor-Acceptor Cyclobutanes and Aldehydes Catalyzed by $Yb(OTf)_3$. Andrew C. Stevens, Mahmoud M.Abd Rabo Moustafa, Ben P. Machin, and Brian L. Pagenkopf.* Latest Trends in Organic Synthesis, St. Catherines, ON, 2010.
(4) Exploration of Siloles as Intermediates in Organic Synthesis. Andrew C. Stevens, Brian L. Pagenkopf.* Keith Fagnou Organic Symposium, Ottawa, ON. 2010.
(3) Exploration of Siloles as Intermediates in Organic Synthesis. Andrew C. Stevens, Brian L. Pagenkopf.* 93rd Canadian Chemistry Conference, Toronto, ON. 2010

(2) The Synthesis and Electronic Properties of New Silole-Based Lumiphors and a Second Generation Catalyst for the Oxidative Formation of *trans*-THF Rings. Andrew C. Stevens, Barbora Bajtos, Benjamin P. Machin, Nicholas A. Morra, Mahmoud M. Abd Rabo Moustafa, Cory Palmer, and Brian L. Pagenkopf*. WORLDiscoveries Research Showcase, London, ON, 2010.

(1) Development of Siloles as Useful Intermediates in Natural Product Synthesis. Andrew C. Stevens and Brian L. Pagenkopf.* 92nd Canadian Chemistry Conference, Hamilton, ON, 2009.

Awards and Scholarships

2011 – 2013	Ontario Graduate Scholarship *Provincial Competition*, $15 000/yr
2012	Roberta and Ruth Lumsden Graduate Fellowship *University Competition,* $1 000
2012	Graduate Thesis Research Award *University Competition* $1 250
2007	DAAD Academic Research Award
2006	NSERC Industrial Undergraduate Student Research Award
2003	University of Alberta Academic Excellence Scholarship