ASYMMETRIC CONJUGATE ADDITION FOR THE SYNTHESIS OF α-CHIRAL HETEROCYCLES AND RHODIUM – CATALYZED NON –CARBONYL – STABILIZED CARBENOID CASCADE REACTIONS

A Dissertation Presented to

the Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

Phong Quang Le

August 2015

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Dean, College of Natural Sciences and Mathematics

Dedicated to my family

Mom, Dad, Sister Hang, Brother Quang, my wife Hang

and to many teachers in my life

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ABSTRACT

A method for the synthesis of compounds which have chiral centers on the carbon alpha to heterocyclic rings will be first discussed. Heterocyclic compounds are known for a wide range of applications and are of particular interest in medicinal chemistry and natural product synthesis. The presented development used an air-stable boronic acid as a nucleophile for conjugate addition to a β-heteroaryl enone. Therefore, different heterocycles with different connectivity attached to the stereocenters could be obtained. An improved BINOL catalyst also was synthesized in order to speed up the reaction rate and, consequently, prevented the racemization that occurred when electron-deficient heterocycles were used. Furthermore, a BINOL catalyzed propargylic substitution reaction was simultaneously developed. Preliminary results will also be mentioned.

The next project delivered the rhodium-catalyzed reactions of alkyne tethered alkyl tosylhydrazones. The novel cascade reaction generated bridged polycycles efficiently. This approach was also useful for acyclic hydrazones to form fused bicycles. Mechanistically, the reaction was found to go through a cyclopropene intermediate, which was isolated and characterized.

Finally, the rhodium-catalyzed cascade reaction using diazoketones and its application toward the synthesis of maoecrystal V's core structure will be discussed.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	acetyl, acetate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BHT	butylated hydroxytoluene
Cap	caprolactamate
Cod	cyclooctadiene
CI	chemical ionization
d	doublet
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
DBU	1,8-diazabicycloundec-7-ene
DMP	Dess–Martin periodinane
DIBAL	diisobutylaluminium hydride
DMDO	dimethyldioxirane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DMA	dimethylaniline
DIAD	diisopropyl azodicarboxylate
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DMF	*N*,*N*-dimethylformamide
Ee	enantiomeric excess
Er	enantiomeric ratio
Et	ethyl
Esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid

ESI	electrospray ionization
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HRMS	high resolution mass spectroscopy
HPLC	high performance liquid chromotography
IR	infrared (spectroscopy)
J	coupling constant
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m	multiplet or milli
m/z	mass to charge ratio
Me	methyl
MS	molecular sieves
mCPBA	*meta*-Chloroperoxybenzoic acid
Ms	methanesulfonyl (mesyl)
MOM	methoxymethyl
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear overhauser effect
NCS	*N*-chlorosuccinimide
pABSA	*p*-acetamidobenzenesulfonyl azide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Py	pyridine
Ph	phenyl
q	quartet
rt	room temperature

s	singlet
t	triplet
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
TBS	tert-butyldimethylsilyl
TIPS	triisopropylsilyl
TBAF	tetrabutylammonium fluoride
Ts	p-toluenesulfonyl
TMS	trimethylsilyl
TMP	2,2,6,6-Tetramethylpiperidine
TM	transition metal
TPA	triphenylacetate

CHAPTER 1

CONJUGATE ADDITION REACTIONS FOR THE SYNTHESIS OF α-CHIRAL HETEROCYCLES

1.1 Importance of heterocycles

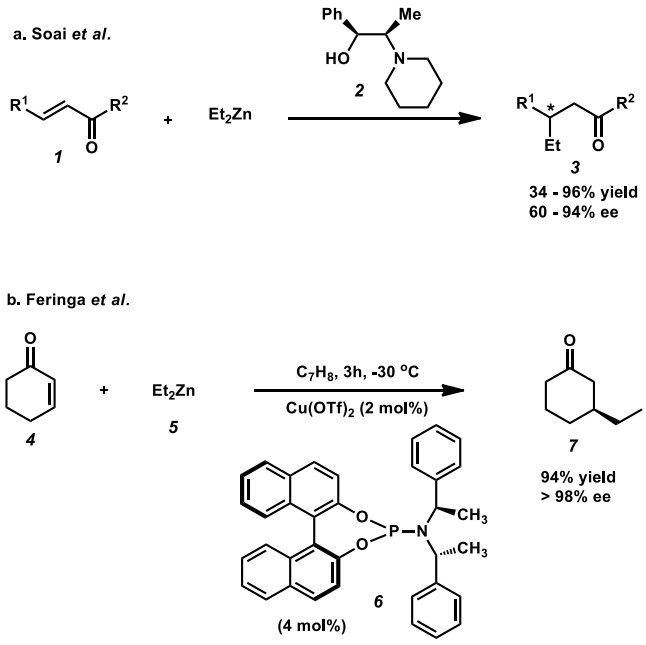
Heterocycles are structural motifs present in many natural products and pharmaceuticals. These structures, especially those that are chiral, usually have interesting biological activities. As a result, many researchers have worked to develop asymmetric methods for the synthesis of heterocyclic molecules.

A chiral center next to the heterocyclic ring has been one of the most challenging to generate. The reasons for the difficulty are the ease of epimerization at those stereocenters, the interaction of the heteroatom on the ring with reagents to negatively affect the new bond formation, and potentially deleterious side reactions with the heteroaryl ring in acidic, basic, oxidative and/or photochemical conditions.[1] An asymmetric conjugate addition has received extensive notice among methods to form such stereocenters. The following is our effort to highlight elegant work related to heterocycles in this 1,4-addition reaction.

1.2 Conjugate addition using organometallic reagents

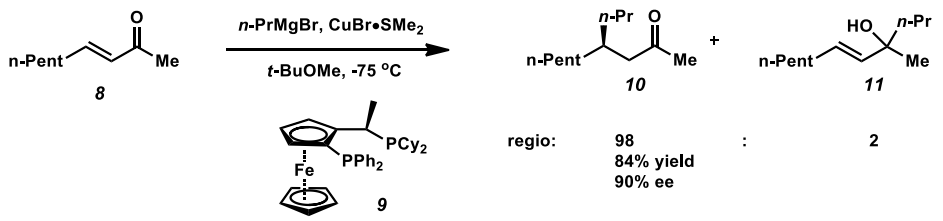
Transition metal reactions have been advanced significantly in recent decades. In 1991, Soai *et al.* reported an enantioselective conjugate addition of diethyl zinc to enones using a β-aminoalcohol as a chiral catalyst or ligand. Unlike previous methods that required stoichiometric amounts of chiral auxiliaries, the authors succeeded in

establishing a catalytic version of the reaction in high yield, although the selectivity was not great (Scheme 1.2.1a).[2] Later, this low selectivity was improved by Feringa and coworkers in the catalytic asymmetric l,4-addition reactions of organometallic reagents with complete stereocontrol. The 1997 report featured the use of binaphthol-derived phosphoramidites for the copper-catalyzed 1,4-addition of diethyl zinc to cyclic enones with excellent yield and ee (Scheme 1.2.1b).[3] Although ester and acetal functionalities were tolerated in the reaction conditions, the enantioselectivities for five- and seven-membered cyclic enones did not show satisfactory results.



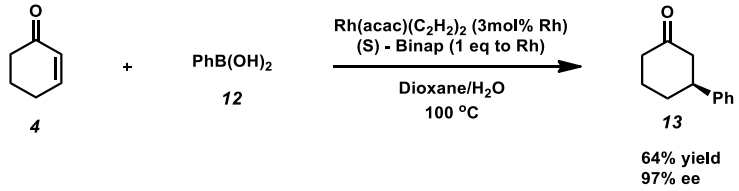
Scheme 1.2.1 Asymmetric conjugate addition with diethyl zinc

Several years later, Feringa and co-workers developed another copper-catalyzed transformation with high regio- and enantioselectivity to provide optically active β-substituted ketones, this time with Grignard reagents and acyclic enones (Scheme 1.2.2).[4]



Scheme 1.2.2 Asymmetric conjugate addition with Grignard reagents

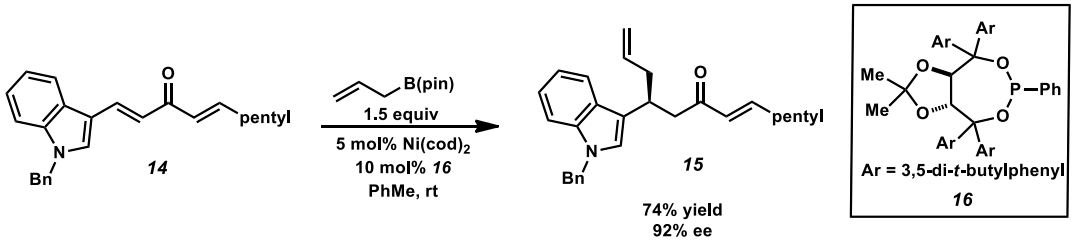
Both of the transformations above, however, could only afford the alkylation of the enones. The addition of an sp^2 carbon to the enone substrates was not successful until the Hayashi group introduced chiral phosphine ligands in the rhodium-catalyzed 1,4-addition of aryl and alkenylboronic acids (Scheme 1.2.3).[5] Because of the air and moisture stability of organoboronic acids, the reaction had a broad scope of nucleophiles. Both electron donating and withdrawing groups on the arylboronic acids worked effectively, as well as 1-alkenyl boronic acids. Notably, this catalytic asymmetric 1,4-addition proceeded with high enantioselectivity for both cyclic and linear α,β-unsaturated ketones.



Scheme 1.2.3 Rhodium-catalyzed conjugate addition using boronic acids

Nevertheless, in terms of heterocycles, Morken *et al.* reported one example of an indole in their nickel-catalyzed allylation using boronic esters as nucleophiles (Scheme 1.2.4).[6] The TADDOL-derived phosphoramidite catalyst system could selectively deliver

an allyl group to the benzylic position of a non-symmetric dialkylidene ketone, although the allylboronic acid pinacol ester normally undergoes 1,2-allylation reactions.



Scheme 1.2.4 Nickel-catalyzed conjugate addition with boronic ester and indole

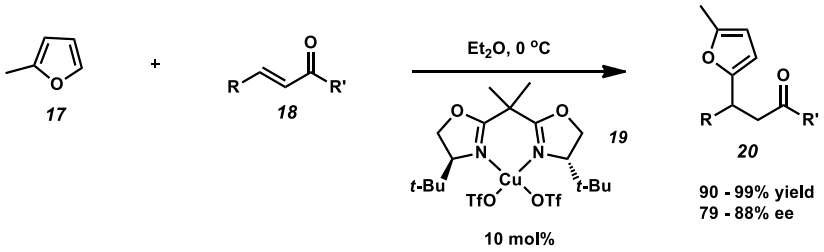
In spite of giving high regio- and enantioselectivity, transition metal-catalyzed conjugate additions still have limited compatibility with heterocycles. Friedel-Crafts reactions, in the other hand, are efficient methods to construct a chiral center next to a heterocyclic ring, especially for indoles. In the section below, we will cover these transformations.

1.3 Friedel-Crafts reactions

1.3.1 Catalyzed by organometallic complexes

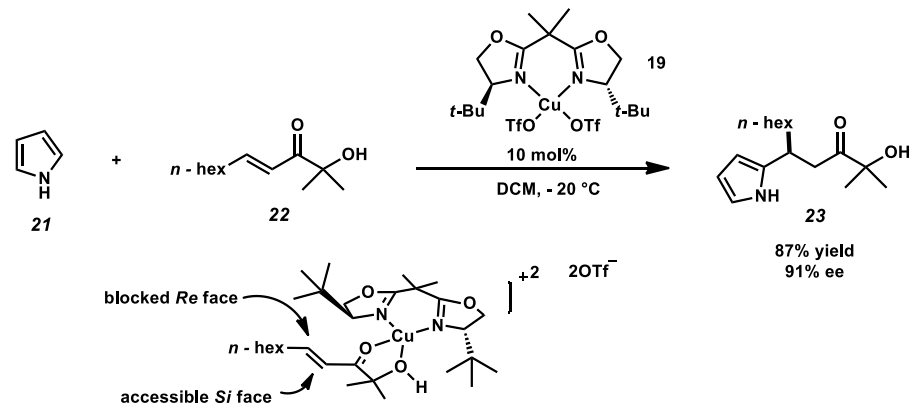
Lewis acids have been extensively used as catalysts in Friedel-Crafts reactions. Since the first non-asymmetric Friedel-Crafts reaction with indoles was reported in 1996 by Kerr and coworkers,[7] an ever-increasing number of mild, catalytic, and environmentally friendly Friedel-Crafts alkylations of indoles via Michael-type addition have been described.

In 2001, Jorgensen *et al.* reported the first catalytic enantioselective Friedel-Crafts alkylation to β,γ-unsaturated α-ketoesters catalyzed by chiral Lewis acids (Scheme 1.3.1.1).[8] A chiral bisoxazoline (BOX) copper complex promoted the reaction and gave the optically active products in very high yield, in some cases without chromatographic purification. The reaction proceeded smoothly with different substituents on indole along with 2-methylfuran. Two years later, more heteroaromatic substrates such as pyrroles were used by the same group when alkylidene malonates served as starting materials.[9]



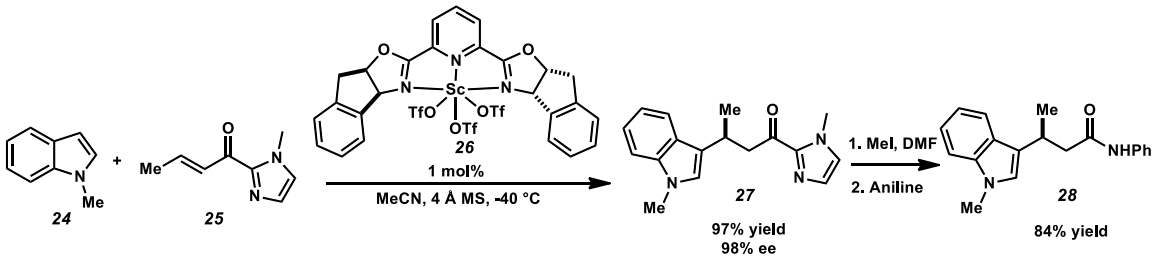
Scheme 1.3.1.1 Enantioselective Friedel-Crafts reaction with α-ketoester

Implementing another catalyst activating mode, Palomo and coworkers used α'-hydroxy enones as substrates in their copper-catalyzed Friedel-Crafts reactions. The hydroxyl group formed a 1,4-chelation with the catalyst for higher selectivity (Scheme 1.3.1.2).[10] Practically, the hydroxyl ketone products could be directly converted to aldehydes, carboxylic acids, or esters through oxidative cleavage processes.



Scheme 1.3.1.2 Copper-catalyzed Friedel-Crafts alkylation of hydroxylenones

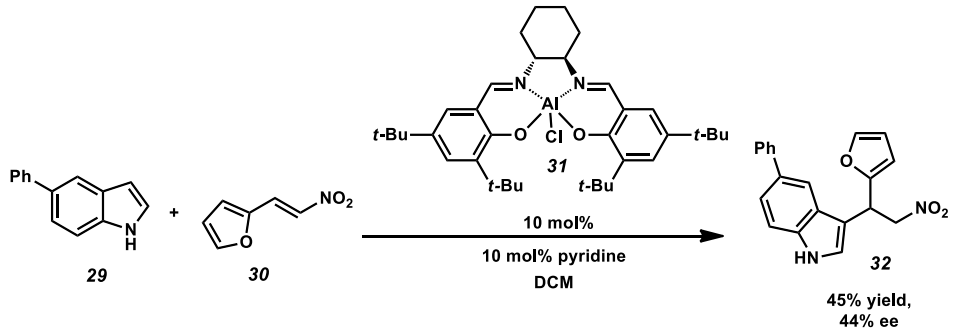
Other types of enone substrates could be utilized in Friedel-Crafts alkylations. In 2005, Evans *et al* described the Friedel-Crafts reactions of α,β-unsaturated 2-acyl *N*-methylimidazoles with electron-rich heterocycles catalyzed by the chiral bis(oxazolinyl) pyridine (PYBOX)-scandium(III) triflate complex (Scheme 1.3.1.3).[11] The authors were able to develop the reaction with high enantioselectivities (> 90% ee) and a broad scope of substrates. The 2-acyl *N*-methylimidazoles products could be transformed into synthetically useful amides, esters, carboxylic acids, ketones, and aldehydes.



Scheme 1.3.1.3 Friedel-Crafts reaction with 2-acyl N-methylimidazoles

Interestingly, the Umani-Ronchi group reported a Friedel-Crafts reaction with nitro olefins using a commercially available catalyst (Scheme 1.3.1.4).[12] The β-indolyl

nitroalkanes represent ideal precursors for numerous natural indole-based compounds, such as 1,2,3,4-tetrahydro-β-carbolines, tryptans, and melatonin analogues.



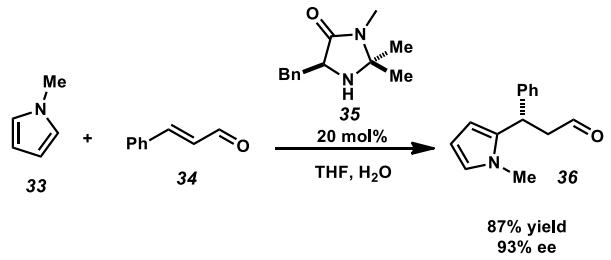
Scheme 1.3.1.4 Friedel-Craft reaction with nitroalkene

1.3.2 Catalyzed by organic molecules

Throughout the years, Friedel-Crafts reactions catalyzed by transition metals have received substantial consideration as we have shown above. However, these reactions often have critical drawbacks. Most of the transition metals are toxic to some extent, and removal of trace amounts of transition-metal residues from products is quite costly and challenging, especially in the pharmaceutical industry. Furthermore, many transition-metal catalysts are sensitive to oxygen and moisture; thus, very strict air-free manipulation is required. For these reasons, a metal-free operation is in demand; especially for Friedel-Crafts reactions containing heteroaromatic compounds.

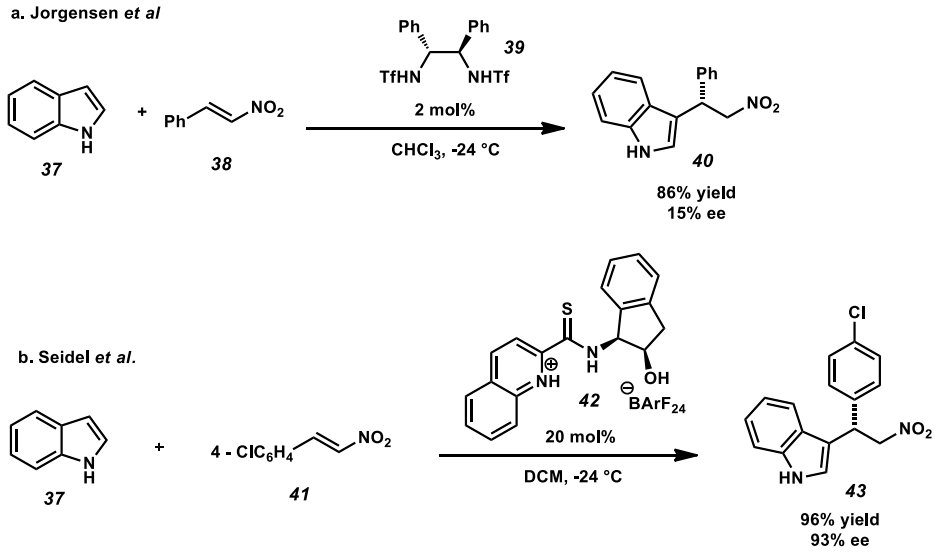
One of the important non-metal-activating reagents in organic chemistry is the secondary amine catalyst that MacMillan developed. His group reported in 2001 the enantioselective conjugate pyrrole addition to α,β-unsaturated aldehydes using a chiral imidazolidinone as a catalyst (Scheme 1.3.2.1).[13] Besides high selectivities and a broad

scope of aldehydes, the reaction was surprisingly performed under an aerobic atmosphere, using wet solvents and an inexpensive bench-stable catalyst. The indole version of the reaction was introduced later by the same group in 2002.[14]



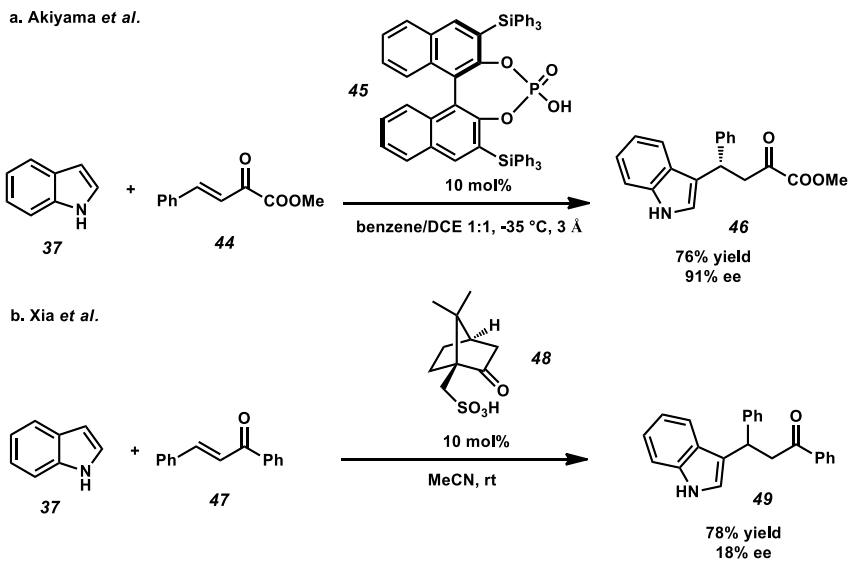
Scheme 1.3.2.1 Secondary amine catalyzed Friedel-Craft alkylation of enals

In 2005, Jorgensen introduced asymmetric hydrogen-bonding-catalyzed Friedel-Crafts reactions on nitro-olefins. A chiral bis-sulfonamide catalyst acts as a chiral hydrogen-bonding donor, potentially activating the oxygen atoms of the nitro-olefin (Scheme 1.3.2.2a).[15] However, the reaction suffered from moderate yields and low enantioselectivities. About 3 years later, this reaction was improved dramatically with a more active hydrogen-bonding catalyst developed by the Seidel group (Scheme 1.3.2.2b).[16] After screening dozens of pyrimidine- and benzothiazone-containing thiourea catalysts, the group was able to obtain nitro indolyl compounds in very high yields (80-96% yield) and enantioselectivities (90-98% ee).



Scheme 1.3.2.2 Friedel-Crafts reactions by hydrogen-bonding catalysts

Another metal-free catalyst that promotes Friedel-Crafts alkylation is a Bronsted acid. Both chiral binapthol based phosphoric acid and camphor sulfonic acid showed good catalytic activity for Friedel-Crafts reactions. The first was mentioned in 2008 by Akiyama and coworkers when unprotected indoles were used with α,β-unsaturated acyl phosphonates to afford Friedel-Crafts adducts with high enantioselectivities (Scheme 1.3.2.3a).[17] The latter was introduced by Xia *et al.* in 2006, although the selectivity was low (Scheme 1.3.2.3b).[18]

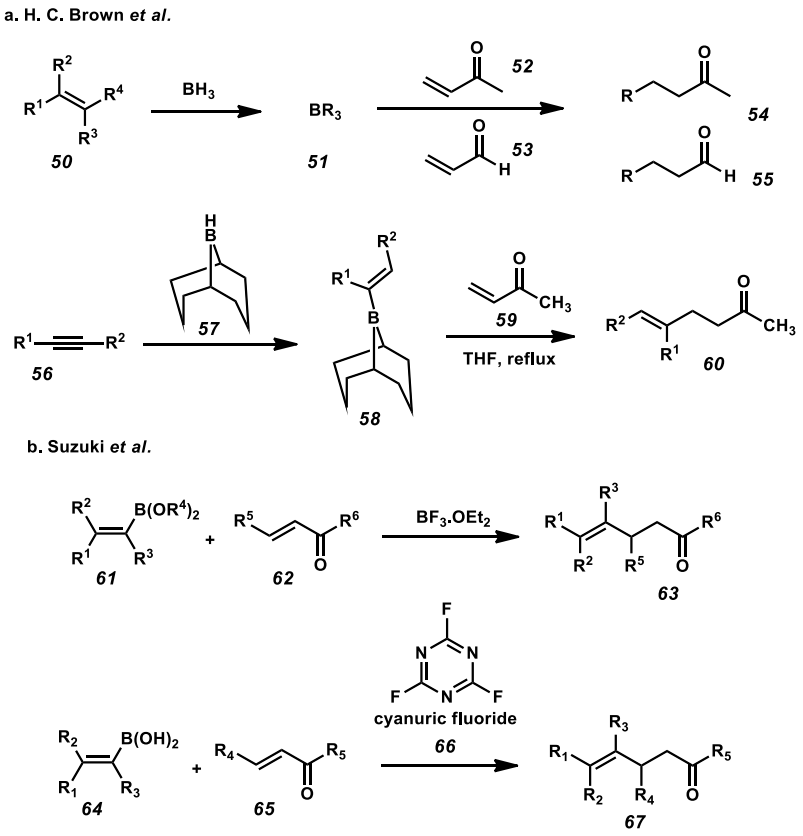


Scheme 1.3.2.3 Bronsted acid-catalyzed Friedel-Crafts alkylation

The Friedel-Crafts reactions in general are very efficient for the synthesis of chiral heterocyclic compounds. High yields and selectivities could usually be obtained. However, the major disadvantages of these reactions are that only electron-rich heteroaromatic compounds can be utilized as the nucleophiles and that the point of connection between nucleophiles to electrophiles is also restricted. In the next section, we will discuss conjugate additions using organoboronates, which will provide a solution to solve these problems.

1.4 Conjugate addition using organoboronates

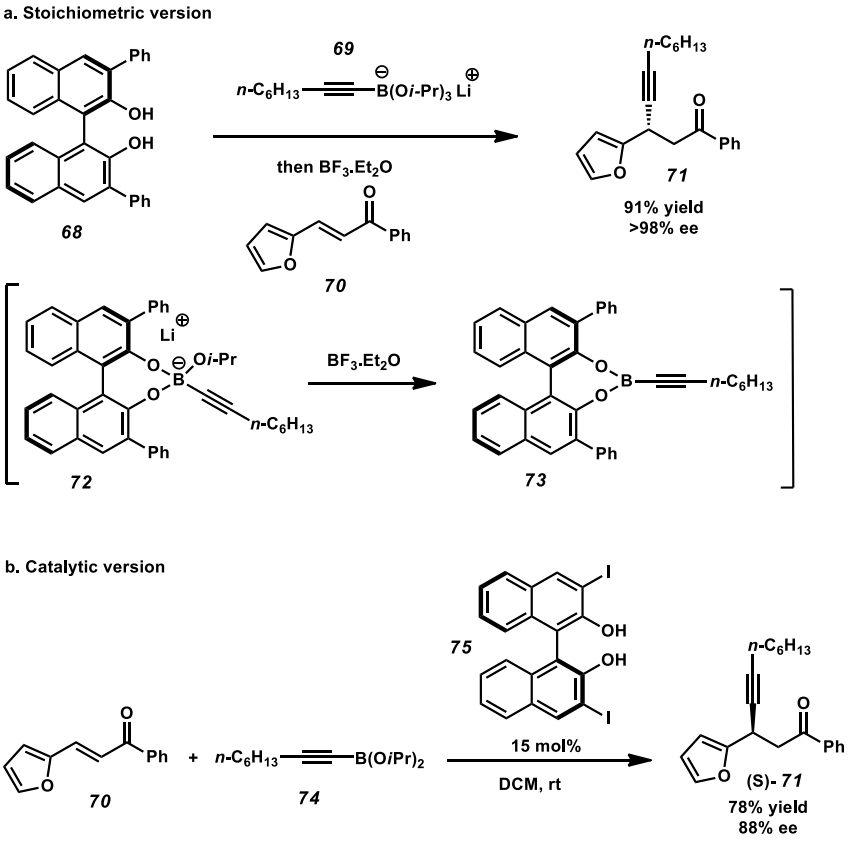
The pioneering works in this field were reported by Herbert C. Brown[19] and Akira Suzuki.[20] Their research in the non-asymmetric conjugate addition of alkyl boranes, alkenyl boranes, and boronic acids established a solid foundation for the 1,4-addition reactions using these organoboron reagents.



Scheme 1.4 Pioneer works in the conjugate addition reaction. a) H. C. Brown's work. b) Akira Suzuki's work.

1.4.1 Michael Chong's work

In 2000, Chong *et al.* introduced the enantioselective alkynylation of α,β-unsaturated ketones using a stoichiometric amount of binapthols as the asymmetric-inducing agents (Scheme 1.4.1a).[21] The reaction, which generated a 3,3'-diphenylBINOL alkynyl boronate complex **73** in situ, provides the conjugate addition products in high yield and selectivity. The authors also found that the tetravalent boron complex **72** was inert to the enones and that cyclic enones were unreactive in the reaction conditions.

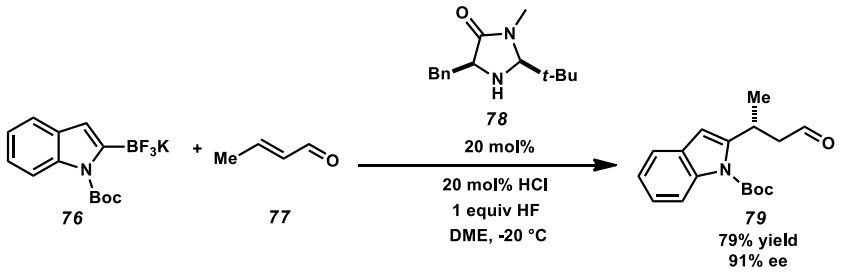


Scheme 1.4.1 BINOL-catalyzed conjugate addition of boronic esters to enones

Later, Chong developed a catalytic version of his alkynylation reaction (Scheme 1.4.1b).[22] He rationalized that a chiral BINOL actually can be used as an "exchangeable" ligand with the boronic esters to form a similar active intermediate to **73**. In fact, the conjugate addition adducts could be obtained with the same yields and selectivities. Asymmetric alkenylation and arylation were then investigated, and they successfully provided enantiopure β-substituted carbonyl compounds.[23]

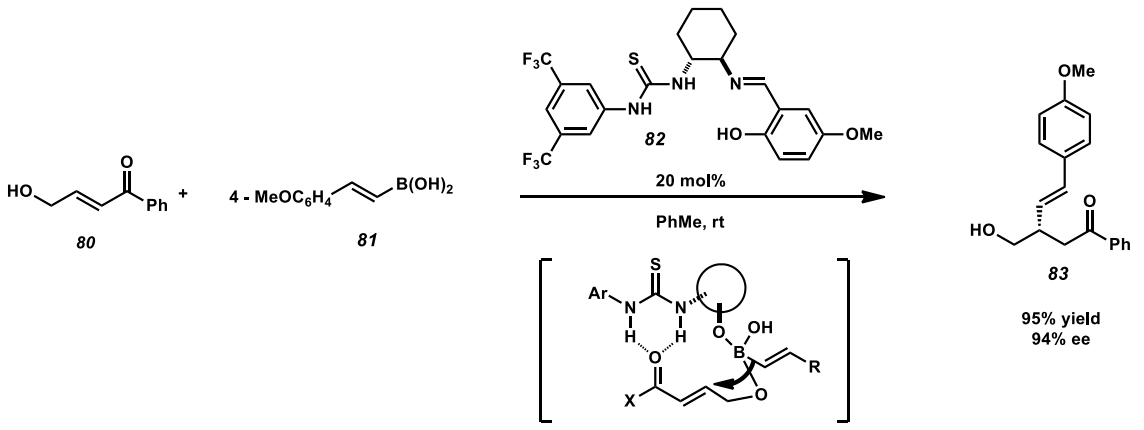
1.4.2 Other organocatalyzed conjugate additions

In 2007, MacMillan expanded his iminium catalysis into the conjugate addition of vinyl and heteroaryl triflouroborate salts (Scheme 1.4.2.1).[24] In this way, a site-specific alkylation of an electron-deficient indole at the 2-position could be obtained in high enantioselectivity. However, only enals were viable.



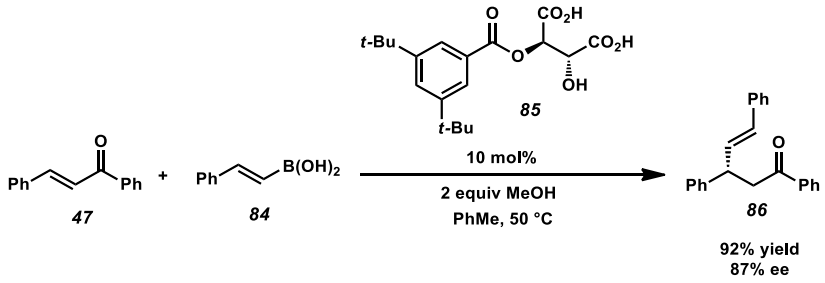
Scheme 1.4.2.1 Conjugate addition of boronate salts catalyzed by a secondary amine

Moreover, the Takemoto group reported an asymmetric Michael addition of α,β-unsaturated ketones with alkenylboronic acids using a chiral thiourea as the activating reagent. However, a hydroxyl group was needed at the γ position of the enones to establish dual coordination of the substrate and the catalyst to the organoboronic acid (Scheme 1.4.2.2).[25]



Scheme 1.4.2.2 Thiourea-catalyzed asymmetric conjugate addition using boronic acids

In 2010, Sugiura reported another enantioselective conjugate addition using boronic acids catalyzed by O-monoacyltartaric acids. However, the transformation showed only moderate yields and selectivities (Scheme 1.4.2.3).[26]



Scheme 1.4.2.3 Enantioselective conjugate addition catalyzed by tartaric acid

1.5 Conclusion

The number of asymmetric conjugate addition reactions we covered in this chapter are limited. Each of these methods has its own advantages, disadvantages, and/or limitations. In the next chapter, we will discuss our contributions to this field.

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CHAPTER 2

GENERAL METHOD FOR THE SYNTHESIS OF α-CHIRAL HETEROAROMATIC COMPOUNDS[1]

2.1 Introduction

As mentioned in the introduction of Chapter 1, chiral heterocycles, especially ones with a stereocenter next to the ring, are important structures in natural products and medicinal compounds. However, there has not been a general method that could be compatible with different varieties of heterocycles and that is flexible with the point of the ring substitution. Our goal was to develop such a method.

The conjugate addition reactions that we covered in Chapter 1 are excellent approaches to address the deficiency above. However, there are still limitations for these elegant methods. Organometallic reagents are often strong bases which give side products. The metal centers could also interact with unprotected heteroatoms, affecting new bond formation. On the other hand, Friedel-Crafts alkylation only proceeds with electron-rich heterocycles. The connection of the new bond also has to be at an electron-rich carbon and is restricted by steric interactions.

To this end, an organocatalysis approach using boronic acids and heterocyclic enones in neutral conditions seemed to be most suitable. MacMillan's strategy using boronate salts is excellent because the broad scope of nucleophiles that can be used. However, this method is limited to only enals. Moreover, Taketomo's thiourea approach

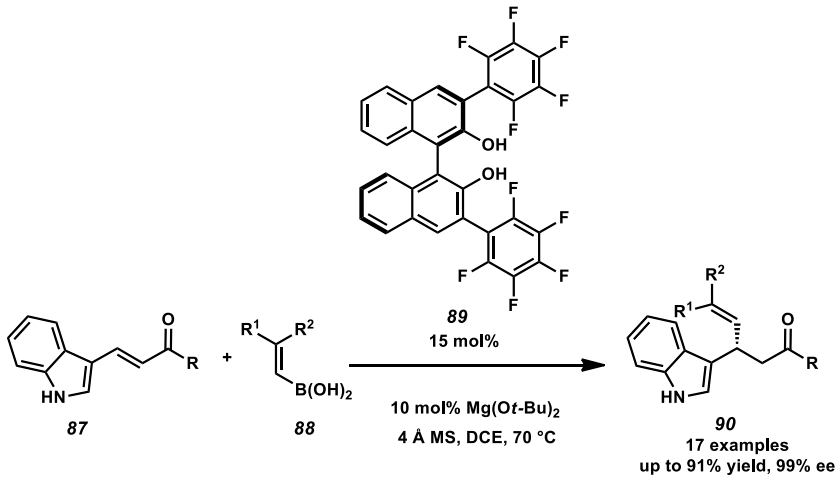
is dependent on a γ-hydroxyl group to enhance the nucleophile's activity, narrowing the scope of the enones. Sugiura's tartaric acid catalyst gave only low selectivity.

We realized that Michael Chong's BINOL chemistry would be the most advantageous starting point for our method development. Below will be a description of the research for fulfilling our goal.

2.2 The May group's preliminary research

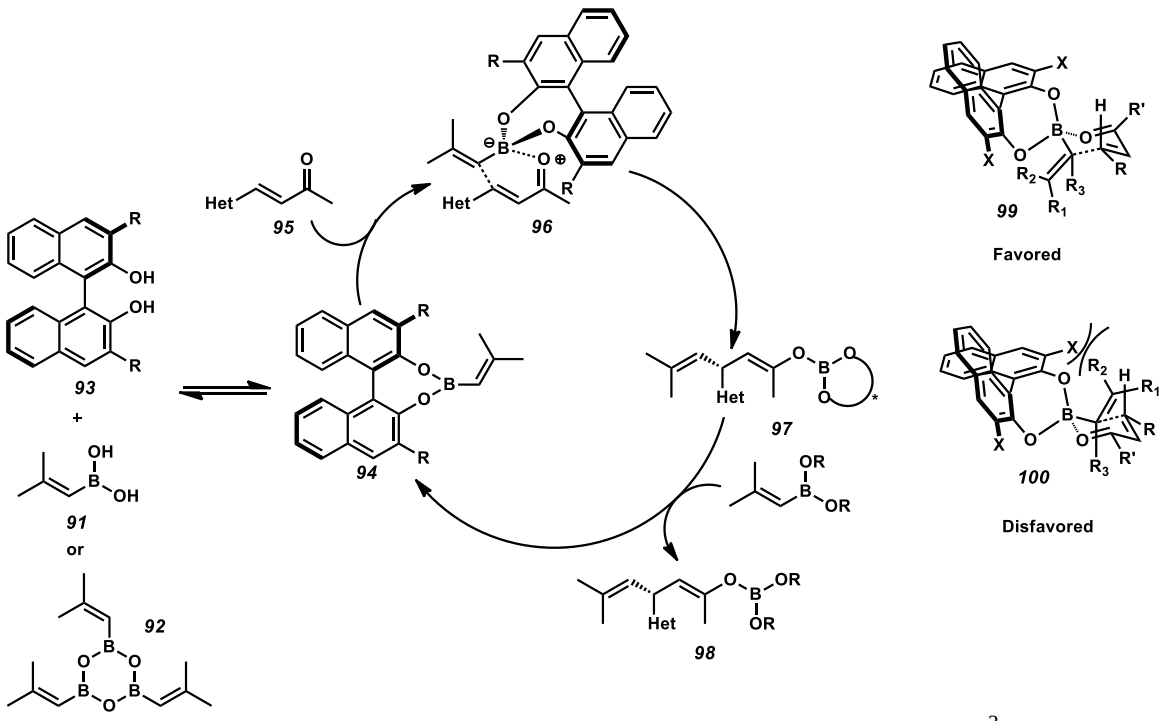
Our strategy started with the conjugate addition of a boron-based nucleophile to α,β-unsaturated carbonyls that have heterocycles attached to the beta position. Neutral organocatalytic conditions were expected to be compatible with unprotected heterocycles. Chong's work showed that a 3,3'-functionalized BINOL can promote the addition of an alkenyl or alkynyl boronate to β-arylenones .

In 2011, Dr. Brian Lundy and Dr. Jansone-Popova in the May lab developed a new 3,3'-perflourophenyl BINOL-catalyzed conjugate addition of a boronic acid to 3-indoloappended enones (Scheme 2.2a).[2] They hypothesized that instead of using a boronic ester, which is a volatile, hygroscopic, and hydrolytically unstable reagent, one could use the easy-to-handle, air-stable, and crystalline boronic acid. The acid can form a boroxine in the presence of molecular sieves and then act as the boronic ester.



Scheme 2.2a. Asymmetric conjugate addition with indole-appended enones

The mechanism of the transformation is shown in Scheme 2.2b. The reaction starts with the esterification of the boronic acid **91** or the boroxine **92** with the BINOL **93** to form boronic ester **94**. The coordination of this Lewis acidic boronic ester with the enone generates the ate complex **96**. The migration of the alkenyl group to the enone is proposed to occur in a chair-like transition state (like **99**) to form boron enolate **97**. Finally, the exchange of ligands regenerates chiral boronic ester **94** and delivers the alkylated product after the protonation.

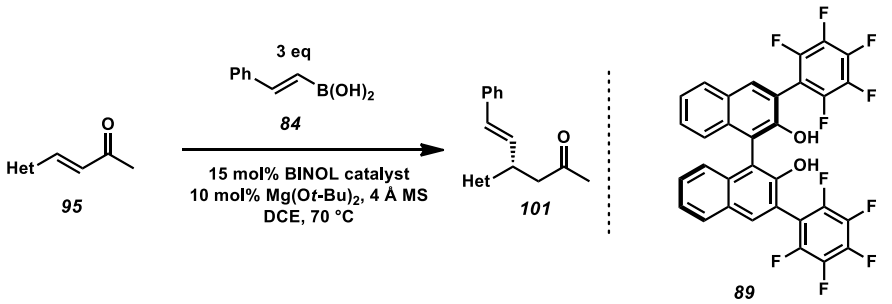


Scheme 2.2b. Reaction proposed mechanism and transition state[3]

The success of this methodology has inspired us to further develop the reaction for the synthesis of other chiral heterocycles.

2.3 Improvement of reaction conditions

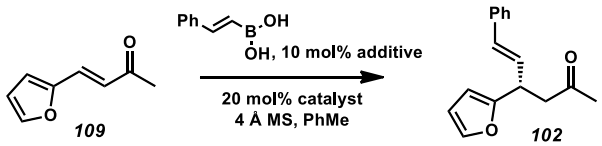
We initially applied Lundy's conditions to different heterocyclic enones. The reaction was carried out with 3 equivalents of styrenylboronic acid, 15 mol% of 3,3'-bis(perfluorophenyl) BINOL catalyst, 10 mol% $Mg(O\textit{t}\text{-}Bu)_2$, and 4 Å molecular sieves in dichloroethane at 70^{o}C. In most cases of the heterocyclic enones, unfortunately, the products were obtained in low yields, even when a 20 mol% loading of the catalyst was used (Table 2.3a).



Product Het=	 102	 103	 104	 105	 106	 107	 108
Yield	29%	46%	14%	Trace	Trace	13%	19%

Table 2.3a. Preliminary results in enantioselective conjugate addition with different heterocyclic enones

Both products and starting materials were stable in the reaction conditions, and no side reactions occurred. These observations made us think that we could carry out the reactions at a higher temperature. Doing so would help overcome the lack of reactivity of the substrates and accelerate the reaction (Table 2.3b). In fact, when the reaction was refluxed in toluene, 2-furanyl enone gave product in good yield and good enantioselectivity (entry 5, Table 2.3b). At this temperature, however, a background reaction was present that generated product in a significant yield with or without additives (entries 1 and 2). Hence, decreasing the boronic acid loading was proposed to slow down the background reaction and increase the pathway controlled by the catalyst. With 1.3 equivalents of boronic acid, the 2-furanyl product was in fact produced in very high yield and excellent er (entry 6). Either *t*-butanol or Mg(O*t*-Bu)$_2$ could be used to enhance the reaction, but the latter gave a slightly higher product yield and allowed the reaction to be carried out at a higher temperature (entries 7 and 8).



entry	catalyst	additive	time	temp	yield	er
1	none	none	24 h	reflux	15%	50:50
2	none	$Mg(Ot\text{-}Bu)_2$	24 h	reflux	28%	50:50
3	BINOL	none	24 h	reflux	40%	62:38
4	*89*	none	24 h	reflux	67%	95:5
5	*89*	$Mg(Ot\text{-}Bu)_2$	24 h	reflux	90%	91:9
6	*89*	$Mg(Ot\text{-}Bu)_2$	24 h	reflux	93%[a]	96:4
7	*89*	*t*-BuOH	48 h	80 °C	68%[a]	97:3
8	*89*	$Mg(Ot\text{-}Bu)_2$	48 h	80 °C	71%[a]	93:7

[a] with 1.3 eq boronic acid were used

Table 2.3b. Reaction optimization

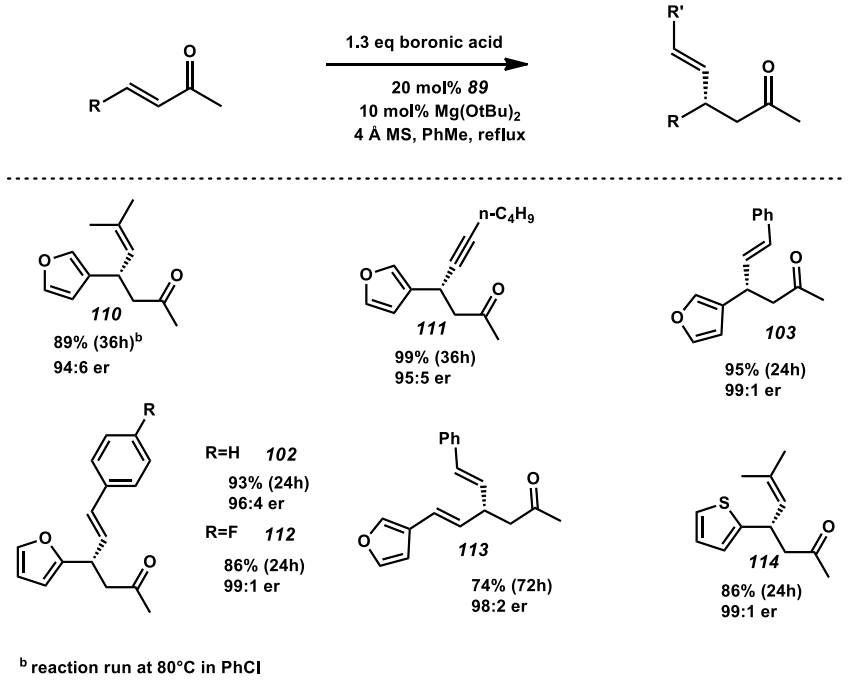
2.4 Reaction substrate scope

2.4.1 Furanyl and thiophenyl enones

With improved conditions in hand, we tried to expand the scope of the reaction with different boronic acids (Scheme 2.4.1). 2-Furanyl enone gave ketone **110** with a very good yield and er using dimethyl boronic acid. An electron-withdrawing group on styrenyl boronic acid is well tolerated, producing a small drop in reactivity relative to the unsubstituted compound **102**, but giving higher stereoselectivity in **112**. Due to unstability of alkynylboronic acids, the *n*-hexynylboronic ester was used and effectively gives the conjugate addition product in excellent yield and enantioselectivity (see **111**).

2-Substituted furan and thiophene enones have similar reactivity (compare **110** and **114**). 3-Substituted furans gave slightly higher stereoselectivity (see **103**). Meanwhile, when a furanyl dienone was used, only the product of selective 1,4-addition

was observed with no 1,6-addition (see **113**). This supports the proposed 6-membered ring transition state.



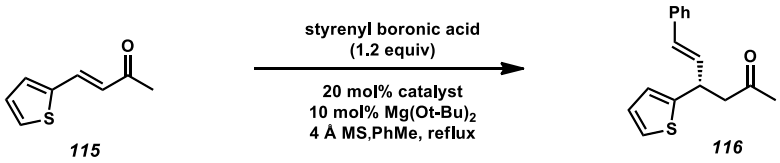
Scheme 2.4.1. Asymmetric conjugate addition with furanyl and thiophenyl enones

2.4.2 Pyridyl enones

2.4.2.1 Catalyst development

One of the difficulties of working with heterocyclic compounds, especially when forming a chiral center alpha to the heterocyclic ring, is the potential racemization at that carbon, resulting in poor enantioselectivity. This was obvious in the cases of electron-deficient pyridine-, quinoline-, and pyrazine-appended enones which gave products in low selectivity (see results shown in section 2.4.2.2). These substrates are very reactive in general and usually required a shorter reaction time than the furanyl and thiophenyl substrates. However, their electron-withdrawing character also caused racemization at the

benzylic stereocenter. To prevent racemization, one strategy would be shorten the time of the reaction, therefore minimizing the time for racemization to occur. Our focus was on developing a new catalyst with a stronger electron-withdrawing group at the 3 and 3' positions. As mentioned in the theoretical study of Pellegrinet,[4] a stronger electron-withdrawing group at the 3 and 3' positions on the catalyst should increase the Lewis acidity of **94** and stabilize the ate complex **96**. This will help to increase the rate of the reaction. The results of several 3,3'-substituted BINOL catalyst candidates with thiophenyl enone and styrenyl boronic acid are summarized in Table 2.4.2.1.



entry	catalyst	time	yield	er
1	none	6 h	<5%	50:50
2	*117*	6 h	15%	73:27
3	*118*	6 h	40%	96:4
4	*119*	6 h	44%	95:5
5	*89*	6 h	58%	97:3
6	*120*	4 h	87%	96:4
7	*121*	6h	53%	98:2

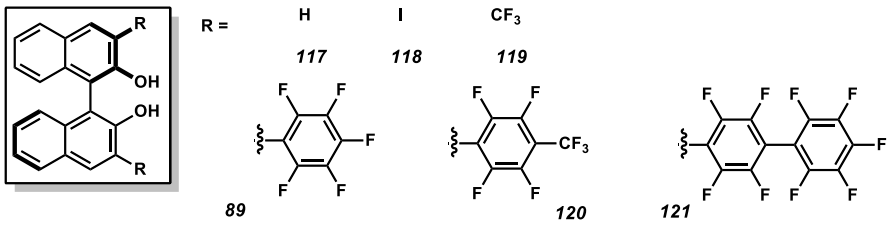


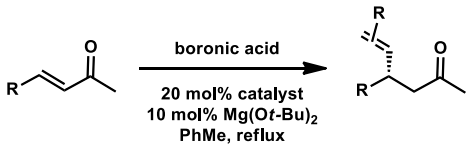
Table 2.4.2.1. Catalyst screening with thiophenyl enone

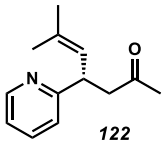
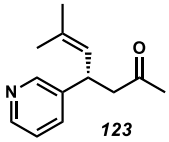
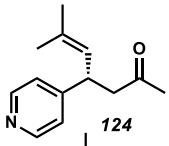
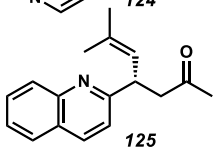
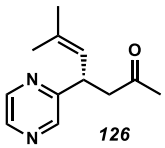
3,3'-Diiodo-BINOL **118** and the bistriflouromethyl-BINOL **119** did not show improvement in the performance or the enantiocontrol compared to our first generation

catalyst **89**. On the other hand, catalyst **120** gave an 87% yield of the product and 92% ee in only 4 hours, which was much faster than the other catalysts. This indicated that both the strength of the electron withdrawing groups and the size of the substituents play a role in the reactivity of the catalyst (compare entries 6 to 4, 5, and 7, Table 2.4.2.1).

2.4.2.2 Apply new catalyst to pyridyl substrates

With the new catalyst, we were able to obtain products in high yield and er for the problematic pyridine substrates as well as furanyl and thiophenyl substrates (see experimental section). Table 2.4.2.2 showed the conjugate addition adducts with both our first and second generation catalyst. There, 2- and 4-pyridyl products were obtained in higher enantioselectivities (entries 2,3 and 6). In the same way, quinoline and pyrazine rings also gave excellent yields and high er even at lower temperatures (entries 8 and 10). In most of the cases, the new catalyst showed much greater yields and selectivities compared to our first generation catalyst. The thiazolyl enones also provided products with great yield and selectivity. These results have been reported in Dr. Thien Nguyen's dissertation.[5]



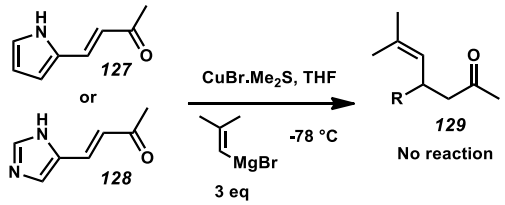
Entry	Product	catalyst	time	yield	er
1		*89*	3h	71%	86:14
2		*120*[c]	16h	95%	94:6
3	*122*	*120*	75 min	92%	93:7
4	 *123*	*89*	15h	87%	98:2
5	 *124*	*89*	21h	92%	91:9
6		*120*	22h	91%	95:5
7	 *125*	*89*	1h	85%	88:12
8		*120*[c]	5h	94%	96:4
9	 *126*	*89*	4h	95%	92:8
10		*120*[c]	8h	99%	95:5

[c] Reaction run at 70°C

Table 2.4.2.2. Pyridines, quinoline, and pyrazine substrates

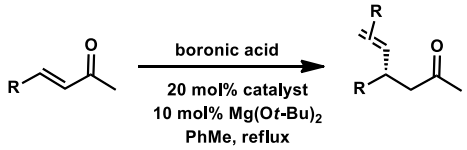
2.4.3 Imidazolyl and pyrolyl enones – unprotected heterocycles

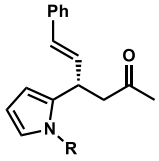
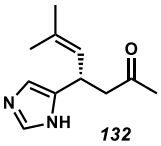
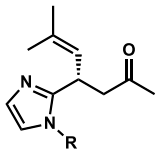
Unprotected heterocyclic compounds such as pyrroles and imidazoles are difficult substrates. As shown in Scheme 2.4.3, when these substrates were subjected to a copper-catalyzed conjugate addition reaction, no products were obtained.



Scheme 2.4.3. Copper-catalyzed conjugate addition with pyrolyl- and imidazolyl-enones

However, good results could be obtained by using our organocatalytic system (Table 2.4.3). Both free-NH 2- and 4-substituted imidazoles gave alkenylated products in good yields and useful enatioselectivities. Such compatibility has not been seen in other methods. The methyl-protected substrates, though, provided products more productively. Again, the new catalyst **120** accelerated the reactions and improved stereoselectivity (compare results of **89** and **120**, Table 2.4.3).



Entry	Product	catalyst	time	yield	er
		R= H, *130*			
1		*89*[c]	48h	23%	92:8
2		*120*[c]	24h	39%	96:4
		R= Me, *131*			
3		*89*	24h	63%	97:3
4		*120*	2h	90%	96:4
5		*89*	72h	83%	81:19
6	*132*	*120*	36h	88%	87:13
		R= H, *133*			
7		*89*	32h	76%	83:17
8		*120*	15h	83%	91:9
		R= Me, *134*			
9		*89*	12h	92%	96:4

[c] Reaction run at 70 °C

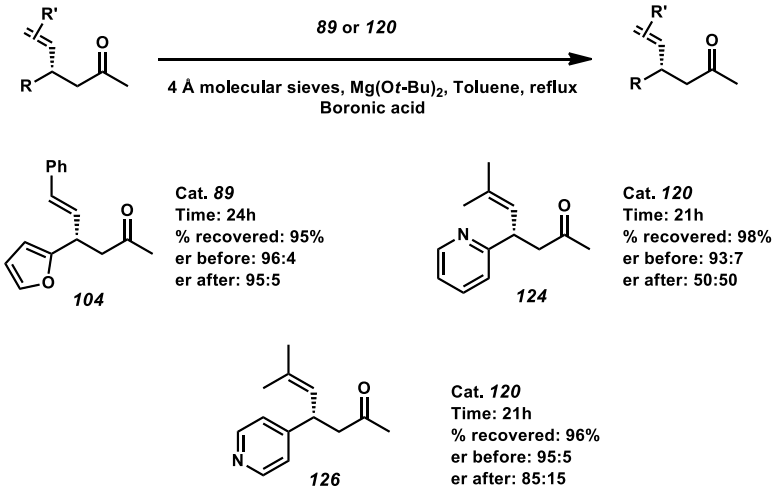
Table 2.4.3. Pyrroles and imidazoles substrates

2.5 Some mechanistic aspects

2.5.1 Racemization experiments

As mentioned in the section 2.4.2.1, we hypothesized that the low selectivity of the electron-deficient pyridyl substrates lay in the epimerization of the products. We performed an experiment to test our hypothesis. When the products of 2- and 4-substituted pyridines **124** and **126**, were resubjected to the reaction conditions, the enantiomeric excess noticeably dropped. The drop in er of 2-pyridyl ketone **124** was faster than that of 4-pyridyl ketone **126**, which only dropped slightly. The 2-Furanyl

products showed practically no racemization when performed with catalyst **89** (Scheme 2.5.1).



Scheme 2.5.1. Racemization experiments

2.5.2 Monomethylated BINOL experiment

In 2009, Schaus *et al.* reported their attempts to understand the mechanism of BINOL catalyzed asymmetric allylation reactions using boronic esters.[6] Through NMR and mass spectrometry methods, they could observe the formation of a monodentate compound **135** between 3,3'-bisbromophenylBINOL and the boronic ester (Figure 2.5.2a). This raised a question about whether both hydroxyl groups on the BINOL are required for its catalylic activity. Therefore, we decided to synthesize the monoalkylated BINOL **138** and utilize it in our conjugate addition reaction. The reaction of styrenylboronic acid with 2-furanyl enone in the presence of **138** showed almost same as background reaction (Scheme 2.5.2b). Although this result did not fully clarify whether the reaction follow the bidentate pathway (like **136**, Figure 2.5.2a) or the hydrogen-

bonded activation pathway (like 1**37**, Figure 2.5.2a), we confirmed the involvement of both BINOL hydroxyls in the catalytic reaction.

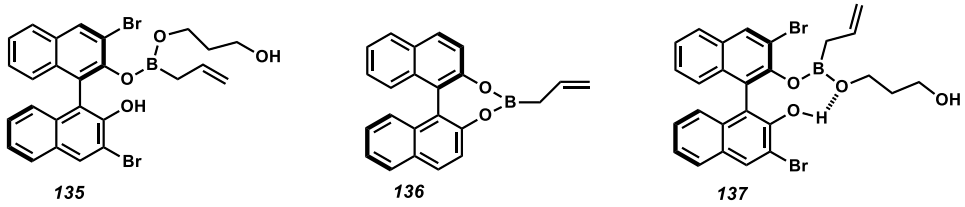
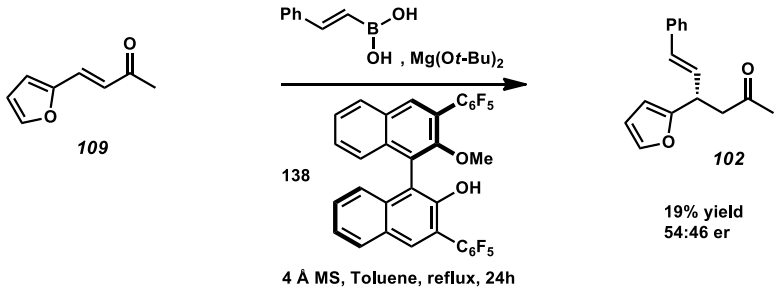


Figure 2.5.2a. BINOL-boronate complex. (a) Schaus's NMR-observed monodentate complex, **135**. (b) Bidentate complex, **136.** (c) hydrogen-bonding activation complex**, 137**

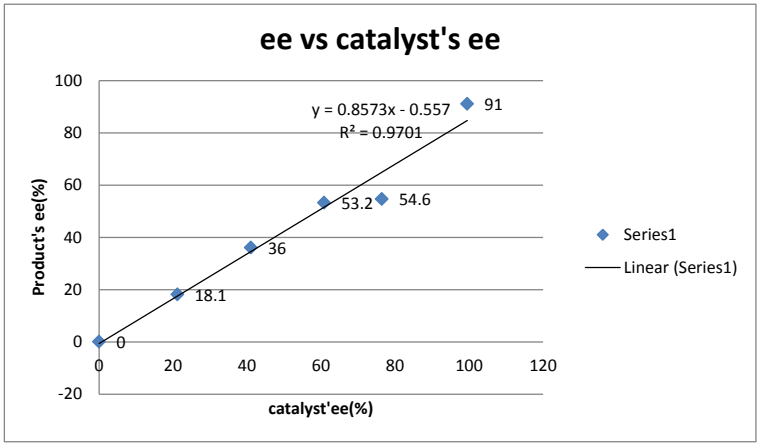


Scheme 2.5.2b. Conjugate addition with a monomethylated BINOL catalyst

2.5.3 Linear effect of catalyst's enantiomeric excess on product's selectivity

The correlation between the enantiomeric excess of the product and that of the chiral catalyst provides insights about reaction mechanism and the structure of the active catalytic species. In enantioselective catalysis, the correlation is usually linear; in other words, each of enantiomers of the catalyst acts independently in the reaction to give enantiopure products. However, it is possible to have a non-linear effect, either positive or negative, which suggests the involvement of more than one catalyst species in the reaction mechanism.

We conducted an experiment in which we mixed enantiopure and racemic BINOL catalysts in varying ratios, used the mixture in the conjugate addition reaction, and then measured the enantiomeric ratio of the products. We observed a linear relation between these two numbers, indicating that only one molecule of BINOL catalyst is involved in the enantio differentiating step of the catalytic cycle (Scheme 2.5.3).



Scheme 2.5.3. Linear correlation between product's ee vs catalyst's ee

2.6 Conclusion

We successfully developed a BINOL-catalyzed conjugate addition reaction to form a wide range of α-chiral heterocyclic compounds that may be functionalized at any position of the aryl ring. The key improvement is a new catalyst that can accelerate the reaction and allow less time for product epimerization. The organocatalytic reaction was also compatible with unprotected heterocycles to provide products with useful enantiopurity. The development of new generations of BINOL catalysts and their application to other methods is in progress in our lab.

2.7 Experimental

2.7.1 General consideration

All reactions were carried out in flame- or oven-dried glassware. THF, toluene, and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA- 500 or ECX-400P spectrometer using residual solvent peak as an internal standard ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an external standard in ^{19}F NMR spectra. NMR yields were determined by addition of 0.5 equivalent of methyl (4-nitrophenyl) carboxylate as an internal standard to the crude reaction mixture. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via ESI method and a US10252005 instrument.

2.7.2 HPLC columns for separation of enantiomers

Chiralpak AY-3: Amylose tris-(5-chloro-2-methylphenylcarbamate) coated on 3 µm silica gel

Chiralpak AD-H: Amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 µm silica gel

Chiralpak ID: Amylose tris-(3-chlorophenylcarbamate) immobilized on 5 µm silica gel

Chiralcel OJ-H: Cellulose tris-(4-methylbenzoate) coated on 5 µm silica gel

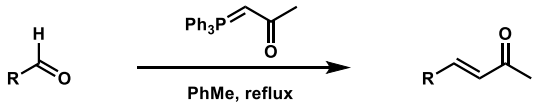
Chiralcel OD-H: Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5 µm silica gel

Chiralpak AS-H: Amylose tris-[(S)-α-methylbenzylcarbamate) coated on 5 µm silica gel

2.7.3 Materials

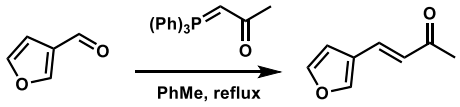
Commercially available compounds were purchased from Aldrich, Acros, and Alfa Aesar and were used without further purification.

2.7.4 General procedures for starting material synthesis



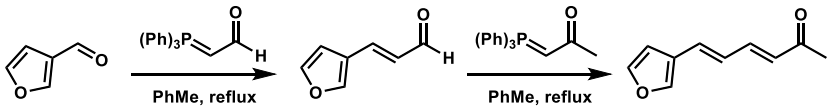
To a flask equipped with a stir bar and a condenser was added carboxaldehyde (4 mmol, 1.0 equiv), 1-(triphenylphosphoranylidene)-2-propanone (5 mmol, 1.25 equiv), and toluene (8 mL). The reaction mixture was refluxed overnight. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via flash column chromatography with an appropriate eluent on silica gel.

2.7.4.1 Synthesis of (*E*)-4-(furan-2-yl)-6-phenylhex-5-en-2-one, precursor to 103, 110, 111



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel to afford a white solid (539.2 mg, 3.96 mmol, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.41 (s, 1H), 7.39 (d, J= 16.5 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 6.41 (d, J= 16.0 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 198.3, 145.0, 144.6, 133.5, 127.3, 122.8, 107.5, 27.4. **LR-MS-EI** m/z: [M^+], calculated for $C_8H_8O_2$ 136.1479, found 136. **IR** (neat): 3115, 2924, 2861, 1666, 1629, 1268, 1158, 974, 869 cm^{-1}.

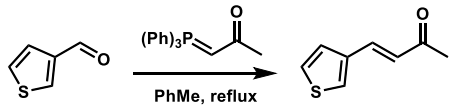
2.7.4.2 Synthesis of (3*E*,5*E*)-6-(furan-3-yl)hexa-3,5-dien-2-one, precursor to 113



To a flask equipped with a stir bar and a condenser was added furan-3-carbaldehyde (4 mmol, 1.0 equiv), (triphenylphosphoranylidene)acetaldehyde (5 mmol, 1.25 equiv), and toluene (8 mL). The reaction mixture was refluxed overnight. After completion, 1-(triphenylphosphoranylidene)-2-propanone (5 mmol, 1.25 equiv) was added to reaction mixture which was refluxed for another 12 hours. The reaction mixture was then concentrated via rotary evaporation. The crude mixture was purified via flash column chromatography with 5-10% ethyl acetate in hexane on silica gel to obtain a yellowish solid (486.6 mg, 3 mmol, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (s,

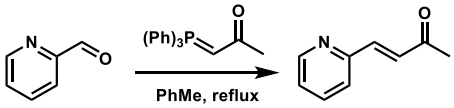
1H), 7.41 (s, 1H), 7.23 (dd, J= 16.0, 11.4 Hz, 1H), 6.83 (d, J= 15.6 Hz, 1H), 6.89 (m, 2H), 6.19 (d, J= 15.6 Hz, 1H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.6, 144.3, 143.5, 142.9, 131.1, 129.7, 126.6, 124.1, 107.4, 27.5. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{10}H_{10}NaO_2$ 185.0573, found 185.0570 **IR** (neat): 3122, 1625, 1254, 1163, 1086, 990, 868, 788, 638 cm^{-1}.

2.7.4.3 Synthesis of (*E*)-4-(thiophen-2-yl)-but-3-en-2-one (98), precursor to 114, 116



See the general procedure for enone formation above. 897.2 mg of 2-thiophenecarboxaldehyde was used. The crude reaction mixture was purified via flash column chromatography with a 5- 10% gradient of ethyl acetate in hexanes as eluent on silica gel to afford a yellow oil (1.205 g, 7.92 mmol, 99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.6 (d, J=15.7 Hz, 1H), 7.37 (d, J=4.5 Hz, 1H), 7.2 (d, J=3.4 Hz, 1H), 7.03 (dd, J= 4.5, 3.4 Hz, 1H), 6.49 (d, J = 15.7 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 197.8, 139.8, 135.8, 131.6, 129.0, 128.3, 125.8, 27.8. **IR** (neat): 1663, 1613, 1594, 1254, 966, 710 cm^{-1}.

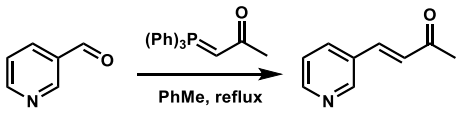
2.7.4.4 Synthesis of (*E*)-4-(pyridin-2-yl)but-3-en-2-one, precursor to 122



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 20-40% gradient of ethyl acetate in hexanes as eluent on silica gel to afford light yellow oil (582.8 mg, 3.96 mmol, 99%

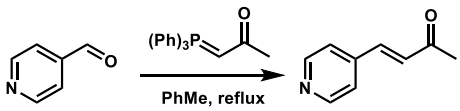
yield). The spectroscopic data for the compound was identical to that reported in the chemical literature.[7]

2.7.4.5 Synthesis of (*E*)-4-(pyridin-3-yl)but-3-en-2-one, precursor to 123



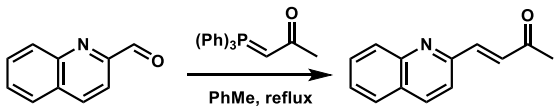
See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10-20% gradient of ethyl acetate in dichloromethane as eluent on silica gel to afford light yellow oil (541.6 mg, 3.68 mmol, 92% yield). The spectroscopic data for the compound was identical to that reported in the chemical literature.[4]

2.7.4.6 Synthesis of (*E*)-4-(pyridin-4-yl)but-3-en-2-one, precursor to 124



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10–20% gradient of ethyl acetate in chloroform as eluent on silica gel to afford a red brown solid (559.2 mg, 3.8 mmol, 95% yield). The spectroscopic data for the compounds was identical to that reported in the chemical literature.[4]

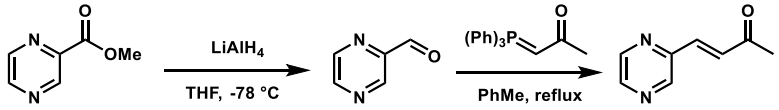
2.7.4.7 Synthesis of (*E*)-4-(quinolin-2-yl)but-3-en-2-one, precursor to 125



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10-20% gradient of ethyl acetate in

hexanes as eluent on silica gel to afford a brown solid (631.2 mg, 3.2 mmol, 80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.20 (d, J= 8.6 Hz, 1H), 8.11 (d, J=8.6 Hz, 1H), 7.83 (d, J= 8.0 Hz, 1H), 7.75 (m, 2H), 7.68 (d, J= 8.6 Hz, 1H), 7.59 (t, J= 6.9 Hz, 1H), 7.15 (d, J= 16.6 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 198.9, 148.2, 143.1, 137.0, 132.0, 130.3, 129.8, 128.2, 127.7, 127.6, 120.1, 27.7. **LR-MS-EI** m/z: [M+], calculated for $C_{13}H_{11}NO_2$ 197.2325, found 197. **IR** (neat): 1658, 1362, 1348, 1271, 1252, 985, 819, 760, 656 cm^{-1}.

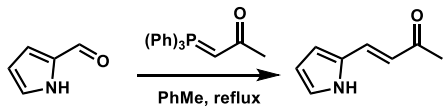
2.7.4.8 Synthesis of (*E*)-4-(pyrazin-2-yl)but-3-en-2-one, precursor to 126



To a flame-dried 100 ml round bottom flask was added methyl pyrazine-2-carboxylate (1.38 g, 10 mmol) and 20 ml THF. The mixture was then cooled to -78 ^{o}C followed by adding lithium aluminium hydride (189.8 mg, 5 mmol) in THF (5 ml). The reaction was stirred for another 20 minutes and quenched with acetic acid glacial (2 ml) at -78 ^{o}C. When the reaction was warmed up to room temperature, HCl 3N (3 ml) was added and organic layer was separated. The aqueous layer was then extracted with dichloromethane (3 times). The organic layers was combined and concentrated via rotary evaporation. The resulting mixture was purified via flash column chromatography with a 20-30% gradient of ethyl acetate in hexanes as eluent on silica gel to afford crude light yellow oil (235.0 mg, 22% yield). The carboxaldehyde was confirmed by 2,4-dinitrophenylhydrazine stain and was carried into the next reaction. The Wittig reaction was carried out following the general enone formation procedure above and was purified via flash column chromatography with a 10-40% gradient of ethyl acetate in hexanes as

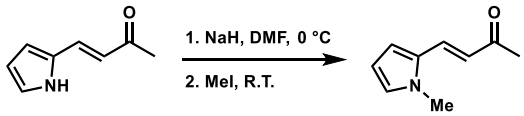
eluent on silica gel to afford a light yellow solid (222.2 mg, 1.5 mmol, 15% overall yield after 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.60 (s, 1H), 8.54 (s, 1H), 7.52 (d, J=16.0 Hz, 1H), 7.25 (d, J=16.0 Hz, 1H), 2.41 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 197.9, 148.9, 145.4, 145.3, 145.0 137.8, 132.0 28.5 **LR-MS-EI** m/z: [M+], calculated for $C_8H_8N_2O$ 148.1619, found 148. **IR** (neat): 1670, 1475, 1262, 1015, 984, 883, 640 cm^{-1}.

2.7.4.9 Synthesis of (*E*)-4-(1*H*-pyrrol-2-yl)-but-3-en-2-one, precursor to 130



See the general procedure for enone formation above. 1g of 2-pyrrolecarboxaldehyde was used. The crude reaction mixture was purified via flash column chromatography with a 10-40% gradient of ethyl acetate in hexanes as eluent on silica gel to afford a light yellow solid (1.3092 g, 7.69 mmol, 73% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.27(bs, 1H), 7.42 (d, J=16.0 Hz, 1H), 7.00 (m, 1H), 6.60 (m, 1H), 6.39 (d, J=16.0 Hz, 1H), 6.30 (m, 1H), 2.33 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3) δ 198.7, 133.8, 128.4, 123.6, 120.8, 115.8, 111.3, 26.9 IR (neat): 3300, 1629, 1617, 1265, 1008, 961, 737 cm^{-1}.

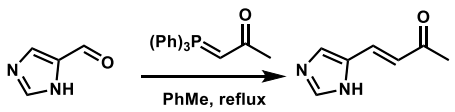
2.7.4.10 Synthesis of (*E*)-4-(1*H*-pyrrol-2-yl)-but-3-en-2-one, precursor to 131



To a flame-dried 25ml round bottom flask was added (E)-4-(1H-pyrrol-2-yl)-but-3-en-2-one (500mg, 3.7 mmol), NaH (177.6 mg, 4.4 mmol) and 7ml anhydrous DMF. The mixture was then cooled to 0°C and stirred in 20 minutes. After 20 minutes, methyl

iodide was added and the reaction was allowed to warm up to room temperature. After completion, reaction was quenched with water and extracted with dichloromethane (3 times). Organic layers were combined and washed with water and brine and dried over magnesium sulfate. The crude mixture was concentrated via rotary evaporation and purified via flash column chromatography using 10-20% gradient of ethyl acetate in hexanes as eluent. The product was obtained as a yellow liquid (353mg, 2.37 mmol, 64% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, J=15.57 Hz, 1H), 6.78 (m, 1H), 6.70 (m, 1H), 6.49 (d, J=15.57 Hz, 1H), 6.18 (m, 1H), 3.71 (s, 3H), 2.3 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$): δ 197.8, 130.7, 129.3, 127.8, 121.6, 112.6, 109.7, 34.5, 28.3. **IR** (neat): 1613, 1589, 1480, 1415, 1271, 1251, 1059, 967, 730 cm^{-1}.

2.7.4.11 Synthesis of (*E*)-4-(1*H*-imidazol-5-yl)but-3-en-2-one, precursor to 132

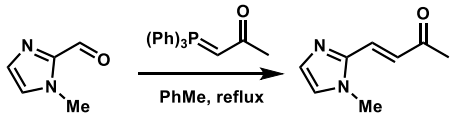


See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 2-5% gradient of methanol in dichloromethane as eluent on silica gel to afford a yellowish solid (381.2 mg, 2.8 mmol, 70% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.47 (d, J= 16.0 Hz, 1H), 7.33 (s, 1H), 2.33 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 199.0, 137.4, 134.6 (broad peak), 124.8, 119.1 (broad peak), 27.8. **LR-MS-EI** m/z: [M+], calculated for $C_7H_8N_2O$ 136.1512, found 136. **IR** (neat): 3140, 1609, 1362, 1270, 1159, 1099, 977, 621 cm^{-1}

2.7.4.12. Synthesis of (*E*)-4-(1H-imidazol-2-yl)but-3-en-2-one, precursor to 133

(E)-4-(1H-imidazol-2-yl)but-3-en-2-one was synthesized following the literature procedure.[8]

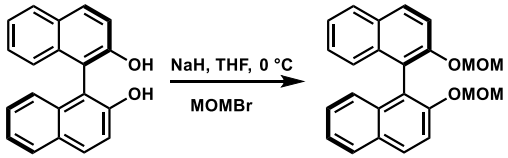
2.7.4.13. Synthesis of (*E*)-4-(1-methyl-1*H*-imidazol-5-yl)but-3-en-2-one, precursor to 134



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 40-100% gradient of ethyl acetate in hexanes as eluent on silica gel to get a yellowish solid (533.7 mg, 3.98 mmol, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, J= 15.5 Hz, 1H), 7.16 (s, 1H), 7.15 (d, J= 15.5 Hz, 1H), 6.99 (s, 1H), 3.75 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$): δ 197.7, 143.3, 130.6, 127.5, 126.1, 124.1, 33.2, 29.6 **LR-MS-EI** m/z: [M+], calculated for $C_8H_{10}N_2O$ 150.1778, found 150. **IR** (neat): 3137, 1650, 1632, 1481, 1429, 1263, 980, 789 cm^{-1}.

2.7.5 Procedures for catalyst synthesis

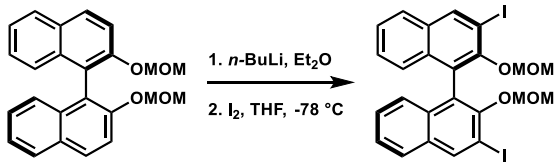
2.7.5.1 Synthesis of (R)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl



The title compound was prepared via modification of the literature procedure.[9] To a flame-dried flask fitted with a stir bar and addition funnel was added NaH (60% dispersion in mineral oil, 840 mg, 21 mmol, 3 equiv) and THF (30 mL). The reaction was cooled to 0 °C. R-(+)-BINOL (2.00 g, 7 mmol, 1.0 equiv) was then added as one portion. The reaction mixture was stirred at 0 °C for 1 h. MOM-Br (1.3 mL, 15.4 mmol, 2.2 equiv) was then added dropwise. The reaction was allowed to stir at 0 °C for 10 min.

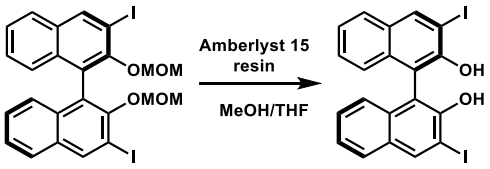
After completion, the reaction mixture was quenched with saturated aq. NH_4Cl, extracted with Et_2O, and washed with brine. The organic layer was dried with $MgSO_4$ and the solvent was removed via rotary evaporation. The crude product mixture was purified via column chromatography with a 10–20% gradient of ethyl acetate in hexanes as eluent on silica gel. (2.5162 g, 6.72 mmol, 96% yield).

2.7.5.2 Synthesis of (*R*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl



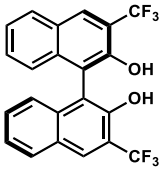
The title compound was prepared as previously described in the literature.[6] To a flame-dried flask equipped with a stir bar was added (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl obtained above (700 mg, 1.87 mmol 1.0 equiv), and then Et_2O (35 mL). 2.5 M n-BuLi (2.3 mL, 5.61 mmol, 3.0 equiv) was added to the reaction. The reaction mixture was allowed to stir for 4 hours at room temperature. The reaction mixture was then cooled to -78 °C and I_2 (1.424 g, 5.61 mmol, 3.0 equiv) was added as one portion. The reaction was allowed to slowly warm to R.T. and stir overnight. After completion, the reaction mixture was quenched with saturated aq. NH_4Cl, extracted with Et_2O, and washed with 10% aq. $Na_2S_2O_3$ followed by brine solution. The organic layer was dried with $MgSO_4$ and the solvent was removed via rotary evaporation. The crude product mixture was then purified via column chromatography with 5% ethyl acetate in hexanes as eluent on silica gel. (909.5 mg, 1.45 mmol, 78% yield).

2.7.5.3 Synthesis of (*R*)-3,3'-diiodo-1,1'-binaphthyl-2,2'-diol (118)



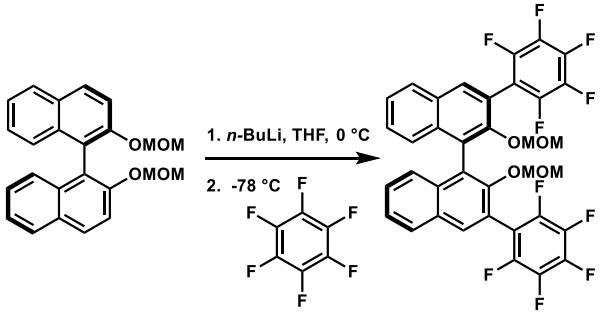
Compound **101** was prepared as previously described in the literature.[6] To (*R*)-3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (300 mg, 0.479 mmol) was added MeOH (2 mL) and THF (2 mL). Amberlyst 15 resin (600 mg) was then added, and reaction was allowed to reflux at 65 °C overnight. After completion, the resin was filtered off and the organic layer concentrated to reduce solvent amount. The organic layer was then passed through a silica plug with 5% ethyl acetate in hexanes as eluent to afford the hydrolyzed product. (214.8 mg, 0.399 mmol, 83% yield).

2.7.5.4 (*R*)-3,3'-bis(trifluoromethyl)-[1,1'-binaphthalene]-2,2'-diol (119)



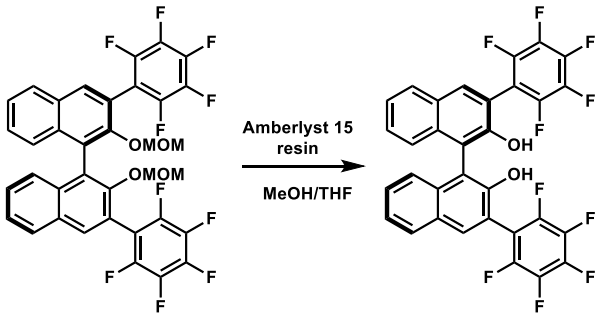
119 was prepared as previously reported.[10]

2.7.5.5 Synthesis of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(perfluorophenyl)-1,1'-binaphthyl



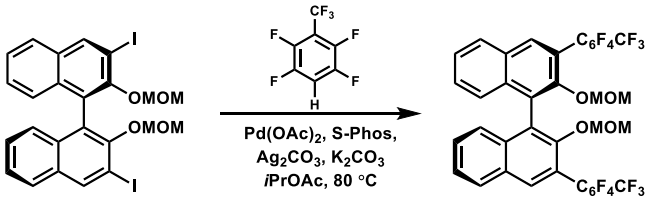
The title compound was prepared following the procedure previously described in the literature.[7] To a flame-dried flask equipped with a magnetic stir bar was added (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (1g, 2.67 mmol, 1 equiv) and 16ml THF. The reaction mixture was then cooled down to 0 °C followed by the addition of 2.5M n-BuLi (3.2 ml, 8 mmol, 3 equiv) and allowed to stir in 30 minutes. The reaction temperature was decreased to - 78 °C and hexafluorobenzene (2.2 ml, 18.7 mmol, 7 equiv) was added dropwise via syringe. The reaction mixture was then warmed up to R.T. and stirred at this temperature for 12h. After completion, the reaction was quenched with saturated aq. NH_4Cl, extracted with Et_2O, and washed with brine. After the removal of solvents via rotary evaporation, the reaction mixture was purified by column chromatography on silica gel using 5% ethyl acetate in hexanes as eluent. The product was obtained as a white solid (1.341 g, 1.9 mmol, 71% yield) and the spectral data agreed with the reported data.[7]

2.7.5.6 Synthesis of (*R*)-3,3'-bis(perfluorophenyl)-1,1'-binaphthyl-2,2'-diol (89)



Compound **89** was prepared following the procedure described for the preparation of compound **101** above. 649.5 mg of (R)-2,2'-bis(methoxymethoxy)-3,3'-bis(perfluorophenyl)-1,1'-binaphthyl was used. The product was obtained as a white solid (553.4 mg, 0.77 mmol, 96% yield) after column chromatography using 5% ethyl acetate in hexanes as eluent. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (s, 2H), 7.97 (d, J= 7.3 Hz, 2H), 7.48 (m, 4H), 7.26 (d, J= 8.2 Hz, 2H), 5.29 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.0, 134.0, 133.8, 129.4, 129.1, 128.9, 125.4, 124.0, 115.5, 111.4. **^{19}F NMR** (470.6 MHz, $CDCl_3$) δ -58.48 (t, J= 21.8 Hz, 6F), -140.0 (dd, J= 23.1, 12.2 Hz, 2F), - 140.3 (dd, J= 21.8, 12.2 Hz, 2F), -143.06- -143.33 (m, 4F). **HR-MS-ESI** m/z: [M+Na], calculated for $C_{34}H_{12}F_{14}NaO_2$ 741.0506, found 741.0506.

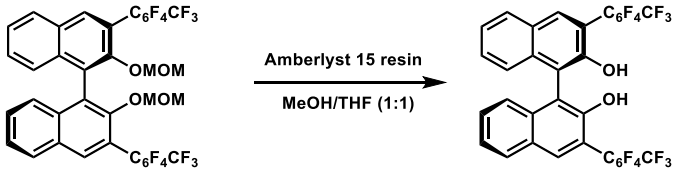
2.7.5.7 Synthesis of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,1'-binaphthyl



The title compound was prepared following the procedure previously described in the literature.[11] To a flame-dried sealable flask equipped with a magnetic stir bar was

added K_2CO_3 (737.7 mg, 5.33 mmol, 4.0 equiv), Ag_2CO_3 (367.7 mg, 1.33 mmol, 1.0 equiv), S-Phos (109.5 mg, 0.27 mmol, 0.2 equiv), and $Pd(OAc)_2$ (30 mg, 0.13 mmol, 0.1 equiv). To this mixture 2,3,5,6-tetrafluorobenzotrfluoride (0.73 mL, 5.33 mmol, 4.0 equiv) and i-PrOAc (1.5 mL) were added. The reaction mixture was allowed to stir for 2 min at R.T. before the addition of 3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (835.6 mg, 1.33 mmol, 1.0 equiv). The reaction temperature was increased to 80 °C and stirred at this temperature for 12h. The reaction mixture was then cooled to R.T. and passed through a plug of Celite washing with EtOAc. After the removal of solvents via rotary evaporation, the reaction mixture was purified by column chromatography on silica gel using 5% ethyl acetate in hexanes as eluent. The product was obtained as a white solid (649.5 mg, 0.805 mmol, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (s, 2H), 7.94 (d, J= 7.8 Hz, 2H), 7.52 (dt, J= 6.8, 1.3 Hz, 2H), 7.42 (dt, J= 6.8, 1.3 Hz, 2H), 7.32 (d, J= 8.7, 2H), 4.48 (d, J= 5.9 Hz, 2H), 4.42 (d, J= 6.4 Hz, 2H), 2.62 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.7, 134.7, 132.3, 130.3, 128.5, 128.3, 126.2, 125.8, 120.6, 99.5, 56.2.

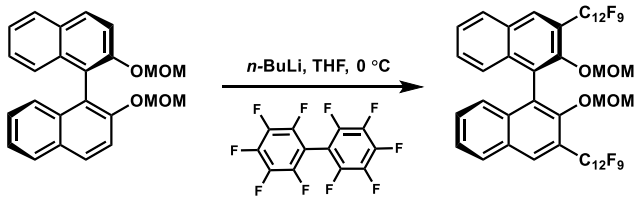
2.7.5.8 Synthesis of (*R*)-3,3'-bis(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,1'-binaphthyl-2,2'-diol (120)



Compound **120** was prepared following the procedure described for the preparation of compound **118** above. 649.5 mg of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,1'-binaphthyl was used. The product

was obtained as a white solid (553.4 mg, 0.77 mmol, 96% yield) after column chromatography using 5% ethyl acetate in hexanes as eluent. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.97 (d, J= 7.3 Hz, 2H), 7.48 (m, 4H), 7.26 (d, J= 8.2 Hz, 2H), 5.29 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.0, 134.0, 133.8, 129.4, 129.1, 128.9, 125.4, 124.0, 115.5, 111.4. **^{19}F NMR** (470.6 MHz, $CDCl_3$): δ -58.48 (t, J= 21.8 Hz, 6F), -140.0 (dd, J= 23.1, 12.2 Hz, 2F), - 140.3 (dd, J= 21.8, 12.2 Hz, 2F), -143.06- -143.33 (m, 4F). **HR-MS-ESI** m/z: [M+Na], calculated for $C_{34}H_{12}F_{14}NaO_2$ 741.0506, found 741.0506.

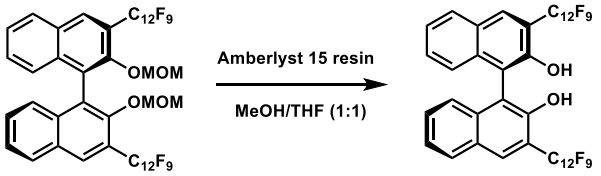
2.7.5.9 Synthesis of (*R*)-bis(methoxymethoxy)-3,3'-bis(perfluorobiphenyl-4-yl)-1,1'-binaphthyl



To a flame-dried flask equipped with a magnetic stir bar was added (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (500 mg, 1.33 mmol, 1 equiv) and 8 ml THF. The reaction mixture was then cooled down to 0 °C followed by the addition of 2.5M n-BuLi (2.7 ml, 6.7 mmol, 5 equiv) and allowed to stir in 30 minutes. The reaction temperature was decreased to -78 °C and decafluorobiphenyl (3.122 g, 9.34 mmol, 7 equiv) was added. The reaction mixture was then warmed up to R.T. and stirred at this temperature for 12h. After completion, the reaction was quenched with saturated aq. NH_4Cl, extracted with Et_2O, and washed with brine. After the removal of solvents via rotary evaporation, the reaction mixture was purified by column chromatography on silica gel using 5% ethyl acetate in hexanes as eluent. The product was obtained as a white solid (868 mg, 0.86

mmol, 65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (s, 2H), 7.96 (d, J= 8.2 Hz, 2H), 7.52 (app.t., J= 7.5 Hz, 2H), 7.42 (app.t., J= 7.5 Hz, 2H), 7.35 (d, J= 8.7, 2H), 4.56 (d, J= 5.04 Hz, 2H), 4.48 (d, J= 5.95 Hz, 2H), 2.68 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.1, 145.8, 143.4, 134.6, 132.4, 130.4, 128.4, 128.1, 126.2, 126.1, 125.9, 121.4, 99.7, 56.1.

2.7.5.10 Synthesis of (*R*)-3,3'-bis(perfluoro-[1,1'-biphenyl]-4-yl)-1,1'-binaphthalene-2,2'-diol (121)



Compound **121** was prepared following the procedure described for the preparation of compound **118** above. 868 mg of (*R*)-bis(methoxymethoxy)-3,3'-bis(perfluorobiphenyl-4-yl)-1,1'-binaphthyl was used. The product was obtained as a white solid (361.7 mg, 0.395 mmol, 46% yield) after column chromatography using 5% ethyl acetate in hexanes as eluent. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.13 (s, 2H), 7.98 (app.d., J= 7.4 Hz, 2H), 7.48 (m, 4H), 7.30 (app.d., J= 7.4 Hz, 2H), 5.33 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.3, 134.1, 133.8, 129.2, 129.1, 129.0, 125.2, 124.1, 116.2, 111.4. **^{19}F NMR** (376 MHz, CDCl3) δ -139.2 (d, J= 21.6 Hz, 2F), -139.6 (d, J= 22.5 Hz, 2F), -141.0- - 141.4 (m, 8F), -152.6 (t, J= 20.8 Hz, 2F), -162.7- -162.9 (m, 4F). **HR-MS-ESI** m/z: [M+Na], calculated for $C_{44}H_{12}F_{18}NaO_2$ 937.0442, found 937.0426.

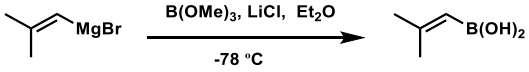
2.7.5.11 Synthesis of (3'r)-2'-methoxy-3,3'-bis(perfluorophenyl)-[1,1'-binaphthalen]-2-ol (138)

To a flame-dried flask fitted with a stir bar was added NaH (60% dispersion in mineral oil (20 mg, 0.49 mmol, 1.5 equiv) and THF (4 mL) and was cooled to 0 °C. BINOL **89** (200 mg, 0.32 mmol, 1.0 equiv) was then added in one portion. The reaction mixture was stirred at 0 °C for 1 hour and MeI (20 µm, 0.32 mmol, 1.0 equiv) was added. The reaction was allowed to warm up to room temperature for 2 hours. After completion, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, and washed with brine. The organic layer was dried with Na_2SO_4 and the solvent was removed via rotary evaporation. The crude product mixture was purified via column chromatography with a 1-2% gradient of ethyl acetate in hexanes as eluent on silica gel. (60.7 mg, 0.096 mmol, 30% yield, unoptimized). The BINOL **89** was recovered (108 mg, 55%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.96 (s, 1H), 7.96 (d, J= 7.8 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.33 – 7.44 (m, 4H), 7.21 (d, J = 7.8 Hz, 1H), 5.25 (s, -OH, 1H), 3.22 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.0, 149.0, 134.4, 134.1, 133.9, 133.0, 130.7, 128.8, 128.6, 128.2, 126.4, 125.2, 124.9, 124.6, 120.7, 120.5, 115.7, 115.6. **^{19}F NMR** (470.33 MHz, CDCl3) δ -142.17 (dd, J = 23.16, 8.17 Hz, 1F), -142.31 (dd, J = 23.16, 8.17 Hz, 1F), -142.39 (dd, J = 24.52, 9.54 Hz, 2F), -156.70 (t, J = 20.44 Hz, 1F), -157.40 (t, J = 20.44 Hz, 1F), -164.38 (qd, J = 21.80, 6.81 Hz, 2F), -165.0 (m, 2F)

2.7.6 Procedures for boronic acid/ester synthesis

2.7.6.1 Synthesis of 2-methylprop-1-enylboronic acid

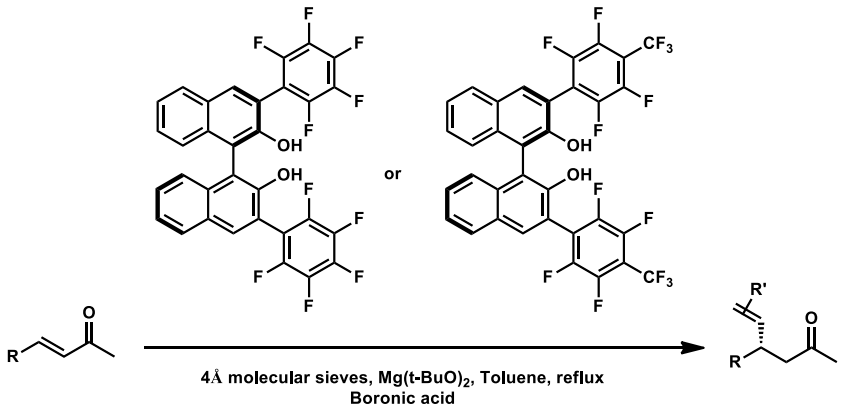


To a 250 ml-flask was added LiCl (1.008 g, 24 mmol, 1.2 equiv) and the flask was flamed-dried under high vacuum. The flask was then back-filled with Argon. 0.5 M 2-Methyl-1-propenyl magnesium bromide in THF (40 mL, 20 mmol, 1.0 equiv) and Et_2O (50ml) were added. The solution was cooled to -78 ºC. Trimethyl borate (2.5 mL, 22 mmol, 1.1 equiv) was added dropwise and the reaction was allowed to slowly warm to room temperature and stir overnight. The next day it was quenched with 1 M HCl (30 ml) until the reaction mixture became clear and then stirred for 1 hour. It was then extracted with Et_2O (3 times), and washed with saturated aqueous $NaHCO_3$, and brine solution. The organic layer was dried with Na_2SO_4 and then concentrated via rotary evaporation. The crude solid was purified via column chromatography with a 20-30% gradient of ethyl acetate in hexanes as eluent on silica gel to afford a white solid (1.105 g, 11.06 mmol, 55% yield). All spectral properties were identical to those reported in the literature.[12]

2.7.6.2 Diisopropyl hex-1-ynylboronate

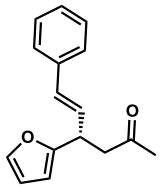
The title compound was prepared as previously reported.[13]

2.7.7 General procedure for conjugate addition



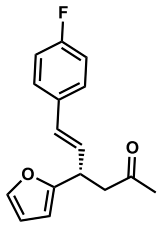
To a flask equipped with a stir bar and a condenser was added 4Å powdered molecular sieves (100mg) and the flask was flamed-dried under high vacuum. The flask was then back-filled with argon. The heterocycle-appended enone (0.2 mmol, 1.0 equiv), Mg(*t*-BuO)$_2$ (3.4 mg, 0.02 mmol, 0.1 equiv), boronic acid (1.2 to 3 equiv), and BINOL catalyst (0.04 mmol, 0.2 equiv) were then added. Freshly dried toluene (4 mL) was added and the reaction was heated to reflux in a 111^{0}C oil bath and allowed to stir at this temperature (see each product for specific reaction times). After completion, methanol was added and the reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with appropriate eluents. (See each product for specific eluent)

2.7.7.1 Synthesis of (*E*)-4-(furan-2-yl)-6-phenylhex-5-en-2-one (102)



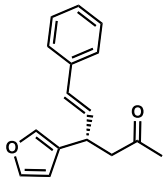
See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 30–60% gradient of dichloromethane in hexanes as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-254 detector). Trial 1: 47 mg, 0.195 mmol, 97% yield; 97:3 er (with catalyst **89**, 1.3 eq of boronic acid). Trial 2: 44.2 mg, 0.184 mmol, 92% yield; 95:5 er (with catalyst **89**, 1.3 eq of boronic acid). Trial 3: 47.6 mg, 0.198 mmol, 99% yield; 95:5 er (with catalyst **120**, 1.3 eq of boronic acid). Trial 4: 47.5 mg, 0.197 mmol, 98.8% yield, 96:4 (with catalyst **120**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.36 (m, 3H), 7.26-7.31 (m, 2H), 7.21 (tt, J = 7.3, 1.4 Hz, 1H), 6.45 (d, J = 15.6 Hz, 1H), 6.31 (app.dd, J = 1.8, 3.2 Hz, 1H), 6.25 (dd, J = 16.0, 7.8 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 4.17 (dd, J = 7.8, 14.6 Hz, 1H), 3.02 (dd, J= 6.4, 16.5 Hz, 1H), 2.85 (dd, J = 16.5, 7.3 Hz, 1H), 2.15 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.4, 155.8, 141.6, 136.9, 131.4, 129.2, 128.6, 127.6, 126.4, 110.3, 105.5, 47.3, 37.8, 30.6. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{16}H_{16}NaO_2$ 263.1042, found 263.1041. IR (neat): 3031, 2930, 1712, 1360, 967, 749, 696 cm^{-1}

2.7.7.2 Synthesis of (*E*)-6-(4-fluorophenyl)-4-(furan-2-yl)hex-5-en-2-one (112)



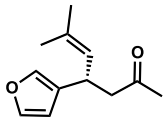
See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 30–60% gradient of dichloromethane in hexanes as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-254 detector). Trial 1: 44.9 mg, 0.174 mmol, 87% yield; 99.3:0.7 er (with cat. **89**, 1.3 eq of boronic acid). Trial 2: 43.1 mg, 0.167 mmol, 84% yield; 99.9:0.1 er (with cat. **89**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26-7.34 (m, 3H), 6.94-6.99 (dapp.t, J = 8.7 Hz, 2H), 6.39 (d, J = 16.0 Hz, 1H), 6.3 (dd, J = 3.2, 2.3 Hz, 1H), 6.14 (dd, J = 15.6, 7.8 Hz, 1H), 6.06 (d, J = 3.2 Hz, 1H), 4.15 (dd, J = 7.3, 14.2 Hz, 1H), 3.00 (dd, J = 16.5, 6.9 Hz, 1H), 2.84 (dd, J = 16.9, 7.3, 1H), 2.14 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.3, 163.2, 161.0, 155.7, 144.6, 133.4, 130.2, 129.0, 127.9, 115.5, 110.3, 105.5, 47.2, 37.7, 30.6. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{16}H_{15}FNaO_2$ 281.0948, found 281.0948. **IR** (neat): 2930, 1712, 1600, 1509, 1226, 970, 832, 603 cm^{-1}

2.7.7.3 Synthesis of (*E*)-4-(furan-3-yl)-6-phenylhex-5-en-2-one (103)



See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 30–60% gradient of dichloromethane in hexanes as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-254 detector). Trial 1: 44.2 mg, 0.184 mmol, 92% yield; 99:1 er (with cat. **89**, 1.3 eq of boronic acid). Trial 2: 90.1 mg, 0.375 mmol, 94% yield; 98:2 er (with cat. **89**, 0.4 mmol enone, 1.3 eq of boronic acid). Trial 3: 47.7 mg, 0.198 mmol, 98% yield; 98:2 er (with cat. **89**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (m, 7H), 6.41 (d, J=16.0Hz, 1H), 6.31 (s, 1H), 6.25 (dd, J = 16.0, 7.8, 1H), 4.05 (q, J = 14.2, 7.3, 1H), 2.84 (d, J=7.3, 2H), 2.14 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.9, 143.3, 138.9, 137.0, 131.5, 130.4, 128.6, 127.5, 126.3, 110.0, 49.1, 34.9, 30.8. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{16}H_{16}NaO_2$ 263.1042, found 263.1041. **IR** (neat): 3034, 2937, 1712, 1362, 1161, 969, 753, 697 cm^{-1}.

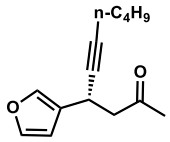
2.7.7.4 Synthesis of 4-(furan-3-yl)-6-methylhept-5-en-2-one (110)



See the general procedure for 1,4-conjugate addition reaction above, chlorobenzene was used as solvent at 80^{o}C. The crude reaction mixture was purified via flash column chromatography with a 30–60% gradient of dichloromethane in hexanes as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-

230 detector). Trial 1: 34.3 mg, 0.179 mmol, 89% yield; 93.9:6.1er (with cat. **120,** 1.3 eq of boronic acid). Trial 2: 34.4 mg, 0.179 mmol, 89% yield; 94:6 er (with cat. **120,** 1.3 eq of boronic acid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, J= 1.6 Hz, 1H), 7.17 (s, 1H), 6.24 (s, 1H), 5.11 (td, J= 9.7, 1.2 Hz, 1H), 3.98 (q, J= 16.6, 6.9, 1H), 2.71 (dd, J= 16.0, 6.9 Hz, 1H), 2.61 (dd, J= 16.0, 8.0 Hz, 1H), 2.10 (s, 3H), 1.69 (s, 3H), 1.55 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 207.5, 143.1, 138.4, 133.5, 133.0, 126.3, 109.7, 50.1, 30.9, 25.8, 18.1. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{12}H_{16}NaO_2$ 215.1042, found 215.1039. **IR** (neat): 2985, 2937, 1713, 1154, 1154, 1020, 971, 792 cm^{-1}

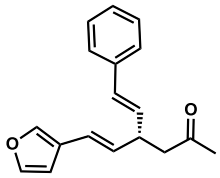
2.7.7.5 Synthesis of 4-(furan-3-yl)dec-5-yn-2-one (111)



See the general procedure for 1,4-conjugate addition reaction above. 3 equivalents of boronic ester were used. The crude reaction mixture was purified via flash column chromatography with a 30–60% gradient of dichloromethane in hexanes as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-190 detector). Trial 1: 43.4 mg, 0.199 mmol, 99% yield; 95:5 er (with cat. **120,** 3 equivalent of boronic ester). Trial 2: 43.3 mg, 0.198 mmol, 99% yield; 95:5 er (with cat. **120,** 3 equivalent of boronic ester**)**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (ss, 2H), 6.32 (s, 1H), 4.04 (tt, J = 9.0, 2.5 Hz, 1H), 2.86 (dd, J = 16.5, 7.8 Hz, 1H), 2.76 (dd, J = 16.5, 7.8 Hz, 1H), 2.15 (s, 3H), 1.40 (m, 6H), 0.89 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.3, 143.1, 139.5, 125.9, 109.7, 82.2, 80.1, 50.8, 31.0, 30.7, 23.8, 22.0, 18.4,

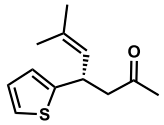
13.7. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{14}H_{18}NaO_2$ 241.1199, found 241.1198. **IR** (neat): 2939, 2879, 2348, 1715, 1359, 1163, 1033, 655 cm^{-1}.

2.7.7.6 Synthesis of (E)-6-(furan-3-yl)-4-((E)-styryl)hex-5-en-2-one (113)



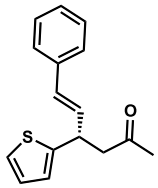
See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 30–60% gradient of dichloromethane in hexanes as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-254 detector). Trial 1: 39.3 mg, 0.147 mmol, 74% yield; 98:2 er (with cat. **89**, 1.3 eq of boronic acid). Trial 2: 39.4 mg, 0.147 mmol, 74% yield; 98:2 er (with cat. **89**, 1.3 eq of boronic acid). Trial 3: 39.9 mg, 0.15 mmol, 75% yield; 97:3 er (with cat. **120**, 1.3 eq of boronic acid). Trial 4: 40 mg, 0.15 mmol, 75% yield; 98:2 er (with cat. **120**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22-7.40 (m, 7H), 6.50 (s,1H), 6.42 (d, J=16.0 Hz, 1H), 6.30 (d, J= 16.0, 7.3 Hz, 1H), 6.16 (dd, J = 16.0, 7.3 Hz, 1H), 5.91 (dd, J= 16.0, 6.9 Hz,1H), 3.59 (m,1H), 2.67 (d, J= 6.9, 2H), 2.16 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.0, 143.5, 140.2, 137.1, 131.1, 130.7, 130.5, 128.6, 127.4, 120.3, 107.5, 48.7, 41.3, 30.8. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{18}H_{18}NaO_2$ 289.1199, found 289.1199. **IR** (neat): 2976, 1710, 1361, 1260, 1161, 1032, 752, 699 cm^{-1}

2.7.7.7 Synthesis of 6-methyl-4-(thiophen-2-yl)hept-5-en-2-one (114)



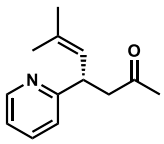
See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via column chromatography with a 30–50% gradient of dichloromethane in hexanes as eluent on silica gel. Trial 1: 30.7 mg, 0.147 mmol, 75% yield; 94:6 er (with 15 mol% catalyst **89,** 4 equiv of boronic acid, 17h, 29.7 mg of starting material). Trial 2: 26 mg, 0.125 mmol, 70% yield; 87:13 er (with 15 mol% catalyst **89,** 4 equiv of boronic acid, 17h, 27.2 mg of starting material). Trial 3: 44.7 mg, 0.214 mmol, 99% yield; 96:4 er (with cat. **120,** 2 equiv of boronic acid, 2h, 33 mg of starting material). Trial 4: 41.6 mg, 0.199 mmol, 99% yield; 96:4 er (with cat. **120,** 2 equiv of boronic acid, 2h, 29.6 mg of starting material). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (dd, J= 5.0, 1.3 Hz, 1H), 6.89 (dd, J= 5.0, 3.6 Hz, 1H), 6.78 (dd, J= 3.6, 1.3 Hz, 1H), 5.19 (td, J= 9.6, 1.3 Hz, 1H), 4.36 (ddd, J= 9.6, 7.5, 6.6 Hz, 1H), 2.87 (dd, J= 16.0, 6.6 Hz, 1H), 2.74 (dd, J= 16.0, 7.5 Hz, 1H), 2.10 (s, 3H), 1.71 (d, J= 1.3 Hz, 3H), 1.70 (d, J= 1.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.0, 148.7, 133.5, 126.7, 126.6, 123.2, 123.0, 51.3, 35.3, 30.8, 25.8, 18.1. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{12}H_{16}NaOS$ 231.08141, found 231.08126. **IR** (neat): 1716, 1357, 847, 696 cm^{-1}

2.7.7.8 Synthesis of (*E*)-6-phenyl-4-(thiophen-2-yl)hex-5-en-2-one (116)



See the general procedure for 1,4-conjugate addition reaction above. 3 equivalent of boronic acid was used. The crude reaction mixture was purified via column chromatography with a 30–50% gradient of dichloromethane in hexanes as eluent on silica gel. Trial 1: 50.3 mg, 0.196 mmol, 98% yield; 96:4 er (with catalyst **89,** 3 equiv of boronic acid, 24h). Trial 2: 47.5 mg, 0.185 mmol, 93% yield; 93:7 er (with catalyst **89,** 3 equiv of boronic acid, 24h). Trial 3: 52 mg, 0.203 mmol, 98% yield; 97:3 er (with cat. **120,** 3 equiv of boronic acid, 22h). Trial 4: 56 mg, 0.218 mmol, 99% yield, 97:3 er (with cat. **120,** 3 equiv of boronic acid, 22h). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (m, 6H), 6.94 (d, J= 5.5 Hz, 1H), 6.88 (d, J= 3.2 Hz, 1H), 6.46 (d, J= 16 Hz, 1H), 6.29 (dd, J= 16, 7.3 Hz, 1H), 4.38 (q, J= 7.3 Hz, 1H), 2.98 (m, 2H), 2.15 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 206.3, 146.8, 136.9, 131.6, 130.6, 128.6, 127.6, 126.9, 126.4, 124.1, 123.8, 50.3, 39.3, 30.8. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{16}H_{16}NaOS$ 279.08141, found 279.08139. **IR** (neat): 1715, 1357, 1163, 965 cm^{-1}

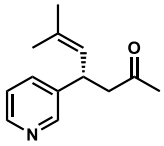
2.7.7.9 Synthesis of 6-methyl-4-(pyridine-2-yl)hept-5-en-2-one (122)



See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 10 - 20%

gradient of ethyl acetate in dichloromethane as eluent on silica gel. HPLC Chiralpak AY-3 (hexane/i-PrOH/Et_3N = 50:45.5:0.5, 1.0 mL/min, UV-254 detector). Trial 1: 34.7 mg, 0.174 mmol, 87% yield; 86:14 er (with cat. **89**, 1.3 eq of boronic acid, 115^{o}C, 3h). Trial 2: 36.2 mg, 0.180 mmol, 90% yield; 87:13 er (with cat. **89**, 1.3 eq of boronic acid, 115^{o}C, 3h). Trial 3: 38.9 mg, 0.191 mmol, 96% yield; 94:6 er (with cat. **120**, 1.3 eq of boronic acid, 70^{o}C, 16h). Trial 4: 39.5 mg, 0.194 mmol, 97% yield; 94:6 er (with cat. **120**, 1.3 eq of boronic acid, 70^{o}C, 16h). Trial 5: 37.4 mg, 92% yield; 93:7 er (with cat. **120**, 1.3 eq of boronic acid, 120^{o}C, 75min). Trial 6: 37.5 mg, 92% yield; 93:7 er (with cat. **120**, 1.3 eq of boronic acid, 120^{o}C, 75min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, J=4.1 Hz, 1H), 7.56 (t, J= 7.8 Hz, 1H), 7.18 (d, J= 7.8 Hz, 1H), 7.06 (t, J= 6.9 Hz,1H), 5.25 (d, J= 9.6 Hz,1H), 4.23 (q, J= 16.9, 8.7 Hz, 1H), 3.20 (dd, 16.5, 7.8 Hz, 1H), 2.70 (dd, J= 16.5, 6.4, 1H), 2.10 (s, 3H), 1.73 (s, 3H), 1.69 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.0, 163.2, 149.1, 136.5, 133.2, 126.1, 122.9, 121.3, 48.5, 41.8, 30.7, 25.9, 18.3. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{13}H_{17}NNaO$ 226.1202, found 226.1201. **IR** (neat): 2970, 2924, 1713, 1590, 1434, 992, 764, 603 cm^{-1}

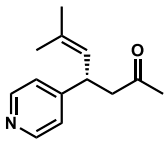
2.7.7.10 Synthesis of 6-methyl-4-(pyridine-3-yl)hept-5-en-2-one (123)



See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 2% of ethyl acetate in diethyl ether as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 50:50, 0.75 mL/min, UV-254 detector). Trial 1: 35.3 mg, 0.176 mmol, 88% yield; 98:2 er

(with cat. **89**, 1.3 eq of boronic acid). Trial 2: 34.8 mg, 0.174 mmol, 87% yield; 98:2 er (with cat. **89**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (d, J=2.3 Hz, 1H), 8.40 (dd,J= 1.8,5.0 Hz, 1H), 7.49 (td, J= 1.8, 7.8 Hz,1H), 7.18 (dd, J= 7.8, 4.6 Hz, 1H), 5.19 (td, J= 9.6, 1.4 Hz, 1H), 4.08 (dd, J= 7.3, 6.8 Hz, 1H), 2.78 (dd, 6.9, 3.2 Hz, 2H), 2.07 (s, 3H), 1.66 (d, J= 2.8 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.8, 149.1, 147.7, 140.2, 134.8, 133.9, 125.9, 123.5, 50.4, 37.3, 30.8, 25.9, 18.2. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{13}H_{17}NNaO$ 226.1202, found 226.1201. **IR** (neat): 2924, 1713, 1424, 1162, 1032, 807, 714, 621 cm^{-1}

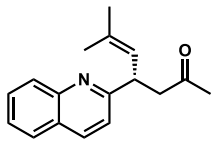
2.7.7.11 Synthesis of 6-methyl-4-(pyridine-4-yl)hept-5-en-2-one (124)



See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 5% of ethyl acetate in diethyl ether as eluent on silica gel. HPLC Chiralpak AY-3 (hexane/i-PrOH/Et_3N = 50:45.5:0.5, 1.5 mL/min, UV-254 detector). Trial 1: 37.5 mg, 0.184 mmol, 92% yield; 91:9 er (with cat. **89**, 1.3 eq of boronic acid). Trial 2: 37.3 mg, 0.184 mmol, 92% yield; 91:9 er (with cat. **89**, 1.3 eq of boronic acid). Trial 3: 36.6 mg, 0.180 mmol, 90% yield; 96:4 er (with cat. **120**, 1.3 eq of boronic acid). Trial 4: 37 mg, 0.182 mmol, 91% yield; 95:5 er (with cat. **120**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (dd, J=4.6, 2.3 Hz, 2H), 7.11 (dd, J= 4.6, 1.8 Hz, 2H), 5.15 (td, J= 9.2, 1.4 Hz, 1H), 4.05 (dd, J= 14.6, 7.3 Hz, 1H), 2.72-2.82 (ddd, J= 16.5, 7.3, 6.9 Hz, 2H), 2.08 (s, 3H), 1.67 (d, J= 7.3 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.6, 153.6, 150.1, 134.5,

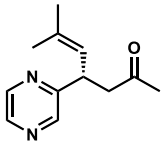
125.3, 122.7, 49.8, 39.0, 30.8, 25.9, 18.3. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{13}H_{17}NNaO$ 226.1202, found 226.1202. **IR** (neat): 2988, 1713, 1600, 1416, 1365, 1157, 1001, 814, 629 cm^{-1}.

2.7.7.12 Synthesis of 6-methyl-4-(quinolin-2-yl)hept-5-en-2-one (125)



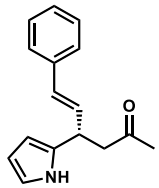
See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 5% gradient of ethyl acetate in hexanes as eluent on silica gel. HPLC Chiralcel OJ-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-254 detector). Trial 1: 43.0 mg, 0.170 mmol, 85% yield; 88:12 er (with cat. **89**, 1.3 eq of boronic acid). Trial 2: 43.2.5 mg, 0.170 mmol, 85% yield; 88:12 er (with cat. **89**, 1.3 eq of boronic acid). Trial 3: 48.5 mg, 0.191 mmol, 96% yield; 95:5 er (with cat. **120**, 1.3 eq of boronic acid). Trial 4: 46.6 mg, 0.186 mmol, 93% yield; 96:4 er (with cat. **120**, 1.3 eq of boronic acid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (dd, J=8.6, 13.2 Hz, 2H), 7.73 (dd, J= 8.0, 1.2 Hz, 1H), 7.65 (ddd, J= 8.6, 6.9, 1.8 Hz, 1H), 7.45 (dt, J= 6.9, 1.2 Hz, 1H), 7.28 (d, J=8.0, 1H), 5.26 (dm, J=9.7 Hz, 1H), 4.47 (ddd, J= 9.7, 8.6, 6.3 Hz, 1H), 3.44 (dd, J= 16.6, 8.6 Hz, 1H), 2.71 (dd, J= 16.6, 5.7 Hz, 1H), 2.24 (s, 3H), 1.83 (d, J=1.2 Hz, 3H), 1.71 (d, J= 1.7 Hz, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 208.3, 163.3, 147.7, 136.2, 133.5, 129.2, 127.5, 127.0, 126.1, 125.8, 121.7, 47.6, 42.6, 30.9, 25.9, 18.4. **HR-MS-ESI** m/z: [M+H], calculated for $C_{17}H_{20}NO$ 255.1572, found 255.1571. **IR** (neat): 3064, 2982, 1711, 1599, 1503, 1427, 1142, 827, 756, 622 cm^{-1}.

2.7.7.13 Synthesis of 6-methyl-4-(pyrazine-2-yl)hept-5-en-2-one (126)



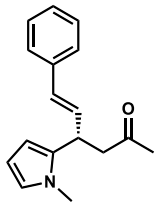
See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 5 - 10% gradient of ethyl acetate in hexanes as eluent on silica gel. HPLC Chiralcel OD-H (hexane/i-PrOH = 90:10 – 70-30, 0.75 mL/min, UV-254 detector). Trial 1: 38.6 mg, 0.188 mmol, 94% yield; 92:8 er (with cat. **89**, 1.3 eq of boronic acid, 120^{o}C, 4h). Trial 2: 39.0 mg, 0.190 mmol, 95% yield; 92:8 er (with cat. **89**, 1.3 eq of boronic acid, 120^{o}C, 4h). Trial 3: 42.4 mg, 0.198 mmol, 99% yield; 95:5 er (with cat. **120**, 1.3 eq of boronic acid, 70^{o}C, 8h). Trial 4: 42.2 mg, 0.198 mmol, 99% yield; 94:6 er (with cat. **120**, 1.3 eq of boronic acid, 70^{o}C, 8h). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (dd, J= 1.4 Hz, 1H), 8.38 (td, J= 2.7, 1.4 Hz, 1H), 8.32 (d, J=2.7 Hz, 1H), 5.17 (dt (J= 9.6, 1.8 Hz, 1H), 4.27 (ddd, J= 8.7, 8.2, 6.0 Hz, 1H), 3.19 (dd, J= 17.4, 8.2 Hz, 1H), 2.70 (dd, J=17.4, 8.2 Hz, 1H), 2.10 (s, 3H), 1.73 (d, J= 0.9 Hz, 3H), 1.67 (d, J=1.4Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.2, 158.9, 145.1, 143.7, 142.2, 134.2, 125.0, 47.6, 39.1, 30.5, 25.8, 18.3. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{12}H_{16}N_2NaO$ 227.1155, found 227.1153. **IR** (neat): 2937, 1711, 1405, 1159, 1019, 652 cm^{-1}.

2.7.7.14 Synthesis of (*E*)-6-phenyl-4-(1*H*-pyrrol-2-yl)hex-5-en-2-one (130)



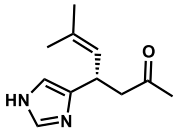
See the general procedure for 1,4-conjugate addition reaction above. 3 equivalent of boronic acid was used. The reaction was done at 70°C in 24h. The crude reaction mixture was purified via column chromatography with a 5-10% gradient of ethyl acetate in hexanes as eluent on silica gel. Trial 1: 9.4 mg, 0.039 mmol, 19% yield; 88:12 er (with catalyst **89,** 27.4 mg of starting material, 48h). Trial 2: 13.8 mg, 0.058 mmol, 28% yield; 96:4 er (with catalyst **89,** 27.4 mg of starting material, 48h). Trial 3: 20.4 mg, 0.085 mmol, 42% yield; 96:4 er (with cat. **120**, 27.5 mg of starting material). Trial 4: 17.7 mg, 0.074 mmol, 36% yield; 97:3 er (with cat. **120,** 27.5 mg of starting material). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 88.42 (s, 1H), 7.35 (d, J= 7.4 Hz, 2H), 7.31-7.28 (m, 2H), 7.24-7.20 (m, 1H), 6.70-6.69 (m, 1H), 6.47 (d, J=16.0, 1H), 6.32 (dd, J= 16.0, 8.0 Hz, 1H), 6.12 (q, J= 2.8 Hz, 1H), 5.94 (m, 1H), 4.09 (q, J= 7.4 Hz, 1H), 3.01 (dd, J= 17.5, 7.4 Hz, 1H), 2.92 (dd, J= 17.5, 5.7 Hz, 1H), 2.17 (s, 3H). **^{13}C NMR** (125.77 MHz, $CDCl_3$) δ 208.1, 136.9, 133.2, 130.7, 130.5, 128.6, 127.6, 126.3, 117.2, 108.1, 104.6, 49.0, 36.9, 30.7. **HR-MS-ESI** m/z: [M+H], calculated for $C_{16}H_{17}NNaO$ 262.12024, found 262.12010. **IR** (neat): 3284, 1695, 1355, 973, 761, 715, 692 cm^{-1}.

2.7.7.15 Synthesis of (*E*)-4-(1-methyl-1*H*-pyrrol-2-yl)-6-phenylhex-5-en-2-one (131)



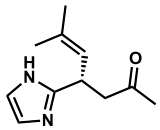
See the general procedure for 1,4-conjugate addition reaction above. 3 equivalent of boronic acid was used. The crude reaction mixture was purified via column chromatography with a 5-10% gradient of ethyl acatete in hexanes as eluent on silica gel. Trial 1: 35.1 mg, 0.138 mmol, 60% yield; 97:3 er (with catalyst **89,** 24h, 34.2 mg of starting material). Trial 2: 37.8 mg, 0.149 mmol, 66% yield; 97:3 er (with catalyst **89,** 24h, 33.8 mg of starting material). Trial 3: 48.1 mg, 0.190 mmol, 90% yield; 97:3 er (with cat. **120,** 2h, 31.4 mg of starting material). Trial 4: 51.8 mg, 0.204 mmol, 90% yield; 95:5 er (with cat. **120**, 2h, 33.9 mg of starting material). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 4H), 7.20-7.17 (m, 1H), 6.56 (appt, J= 2.0 Hz, 1H), 6.25 (d, J= 16.0 Hz, 1H), 6.18 (dd, J= 16.0, 6.4 Hz, 1H), 6.08 (t, J= 3.2 Hz, 1H), 5.95 (dd, J= 3.6, 1.8 Hz, 1H), 4.10 (q, J= 6.4 Hz, 1H), 3.56 (s, 3H), 3.00 (dd, J= 16.9, 6.4 Hz, 1H), 2.9 (dd, J= 16.9, 8.2 Hz, 1H), 2.16 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.8, 137.0, 133.5, 131.5, 130.4, 128.5, 127.4, 126.3, 122.0, 106.7, 105.1, 48.3, 35.4, 33.9, 30.9. **HR-MS-ESI** m/z: [M+Na], calculated for $C_{17}H_{19}NNaO$ 276.13589, found 276.13566. **IR** (neat): 1715, 1492, 1360, 1089, 968, 747, 710, 694 cm^{-1}

2.7.7.16 Synthesis of 4-(1*H*-imidazol-4-yl_-6-methylhept-5-en-2-one (132)



See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a mixture of 2% methanol, 5% triethyl amine, 46.5% dichloromethane and 46.5% ethyl acetate as eluent on silica gel. HPLC Chiralpak ID (hexane/i-PrOH/Et_3N = 70:29.5:0.5, 1.0 mL/min, UV-230 detector). Trial 1: 31.8 mg, 0.166 mmol, 83% yield; 81:19 er (with cat. **89**, 1.3 eq of bronic acid). Trial 2: 32 mg, 0.166 mmol, 83% yield; 81:19 er (with cat. **89**, 1.3 eq of boronic acid). Trial 3: 34.4 mg, 0.178 mmol, 89% yield; 87:13 er (with cat. **120**, 1.3 eq of boronic acid). Trial 4: 33.8 mg, 0.178 mmol, 88% yield; 88:12 er (with cat. **120**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 6.73 (bs, 1H), 5.25 (dt, J= 9.6, 1.4 Hz, 1H), 4.08 (dt, J= 9.6, 7.3 Hz, 1H), 2.94 (dd, J= 16.9, 7.3 Hz, 1H), 2.70 (dd, J= 16.9, 6.4 Hz, 1H), 2.11 (s, 3H), 1.69 (d, J= 0.9 Hz,3H), 1.66 (d, J= 1.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.9, 133.3, 125.1, 49.7, 32.3, 30.6, 25.8, 18.1. **HR-MS-ESI** m/z: [M+H], calculated for $C_{11}H_{17}N_2O$ 193.1335, found 193.1334. **IR** (neat): 3091, 2923, 2873, 1710, 1446, 1361, 1155, 1085, 988, 628 cm^{-1}

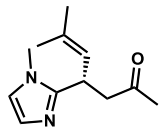
2.7.7.17 Synthesis of 4-(1*H*-imidazol-2-yl)-6-methylhept-5-en-2one (133)



See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 100% ethyl

acetate as eluent on silica gel. HPLC Chiralpak ID (hexane/i-PrOH/Et_3N = 70:29.5:0.5, 1.0 mL/min, UV-230 detector). Trial 1: 29.3 mg, 0.152 mmol, 76% yield; 83:17 er (with cat. **89**, 1.3 eq of boronic acid). Trial 2: 29.4 mg, 0.152 mmol, 76% yield; 84:16 er (with cat. **89**, 1.3 eq of boronic acid). Trial 3: 32 mg, 0.166 mmol, 83% yield; 91:9 er (with cat. **120**, 1.3 eq of boronic acid). Trial 4: 32 mg, 0.166 mmol, 83% yield; 91:9 er (with cat. **120**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.14 (bs, 1H), 6.92 (s, 2H), 5.36 (dm, J= 9.6 Hz, 1H), 4.18 (ddd, J= 9.6, 7.3, 5.9 Hz, 1H), 3.20 (dd, J= 17.8, 7.3 Hz, 1H), 2.76 (dd, 17.8, 5.5 Hz, 1H), 2.14 (s, 3H), 1.74 (d, J= 1.4 Hz, 3H), 1.70 (d, J= 1.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.2, 149.6, 134.8, 123.6, 48.3, 33.4, 30.6, 25.9, 18.2. **HR-MS-ESI** m/z: [M+H], calculated for $C_{11}H_{17}N_2O$ 193.1335, found 193.1332. **IR** (neat): 2967, 2888, 2654, 1720, 1566, 1449, 1360, 1097, 757, 732, 648 cm^{-1}

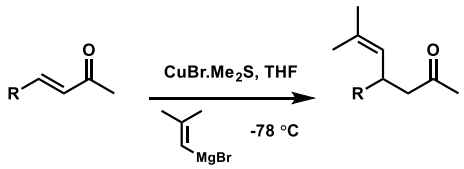
2.7.7.18 Synthesis of 6-methyl-4-(1-methyl-1*H*-imidazol-2-yl)hept-5-en-2-one (134)



See the general procedure for 1,4-conjugate addition reaction above. The crude reaction mixture was purified via flash column chromatography with a 100% ethyl acetate as eluent on silica gel. HPLC Chiralpak ID (hexane/EtOH/Et_3N = 70:29.5:0.5, 1.0 mL/min, UV-230 detector). Trial 1: 38.8 mg, 0.188 mmol, 94% yield; 96:4 er (with cat. **120**, 1.3 eq of boronic acid). Trial 2: 37 mg, 0.180 mmol, 90% yield; 96:4 er (with cat. **120**, 1.3 eq of boronic acid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.85 (d, J=0.92 Hz, 1H), 6.70 (d, J= 1.5 Hz, 1H), 5.08 (dm, J= 9.6, 1H), 4.14 (ddd, J= 10.0, 8.2, 5.9 Hz, 1H), 3.54 (s, 3H), 3.32 (dd, J= 17.4, 8.2 Hz, 1H), 2.69 (dd, J= 17.4, 5.5 Hz, 1H), 2.12 (s, 3H), 1.74 (d, J= 1.4 Hz, 3H), 1.65 (d, J= 1.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.6, 149.8,

132.8, 126.9, 124.5, 120.6, 47.6, 32.6, 31.7, 30.8, 25.7, 18.2. **HR-MS-ESI** m/z: [M+H], calculated for $C_{12}H_{19}N_2O$ 207.1492, found 207.1492. **IR** (neat) 2976, 2927, 1713, 1492, 1363, 1156, 1133, 726 cm^{-1}.

2.7.7.19 General procedure for cuprate conjugate addition (Scheme 2.4.3)



To a flame-dried flask equipped with stir bar was added $CuBr.Me_2S$ and 4 ml THF. The temperature was then cooled down to -78 °C. 2-Methyl-1-propenylmagnesium bromide was added dropwise and the rection mixture was then allowed to stir at that temperature for 30 minutes. A solution of enone (2 mmol in 5ml THF) was added via cannula and stirred for 30 minutes. After then, the reaction mixture was warmed up to room temperature, quenched with 2N HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated via rotary evaporation. The crude product was purified via flash column chromatography on silica gel with appropriate eluents.[14]

2.8 References and notes

1. Reproduced with permission from [Le, Phong Q.; Nguyen, Thien S.; May, Jeremy A. *Org. Lett.* ***2012****, 14*, 6104.] Copyright [2012] American Chemical Society.
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APPENDIX ONE

Spectra relevant to Chapter 2:

GENERAL METHOD FOR THE SYNTHESIS OF α-CHIRAL HETEROAROMATIC COMPOUNDS

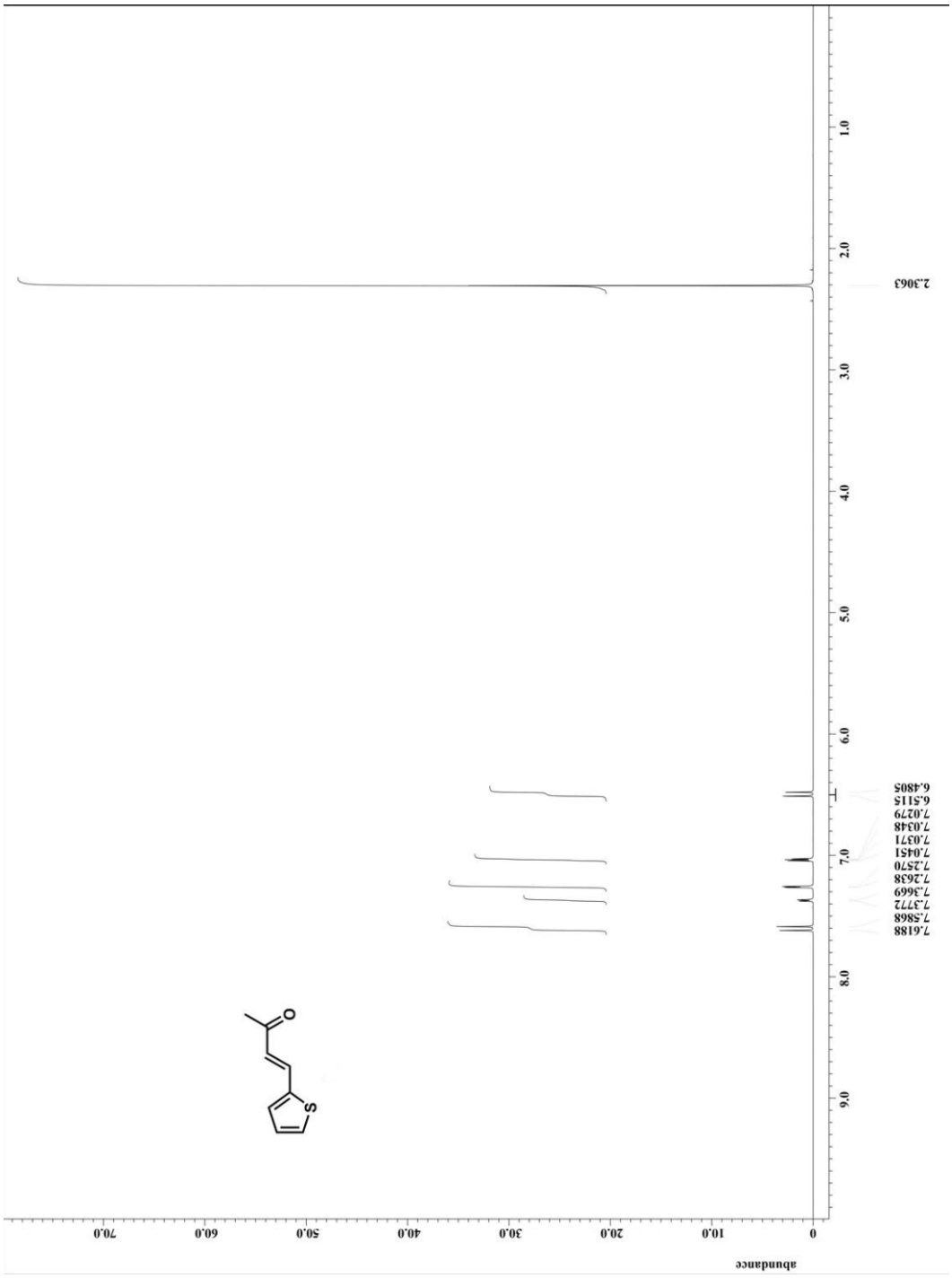


Figure A.1.1. ^{1}H NMR for compound **115**

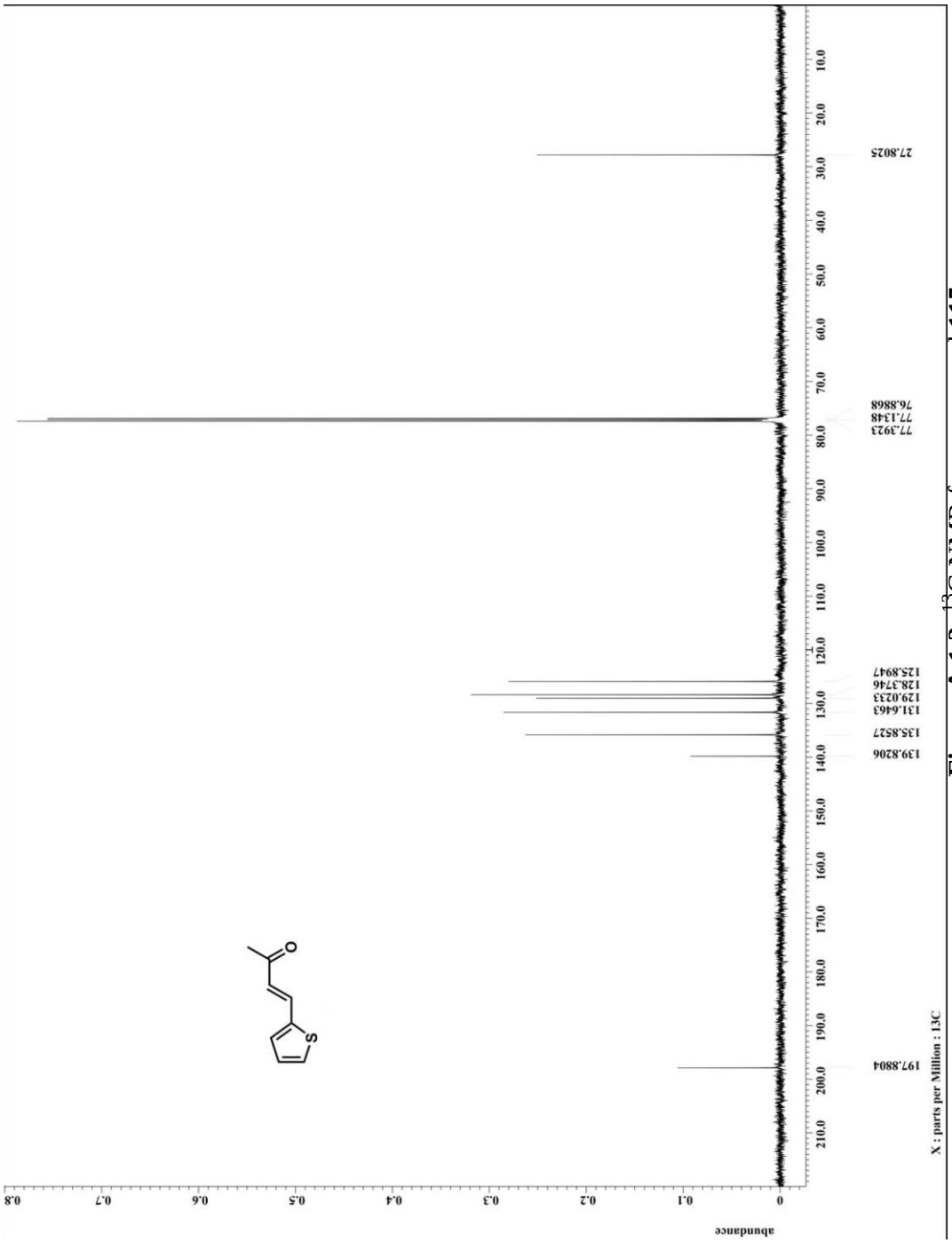


Figure A.1.2. ^{13}C NMR for compound **115**

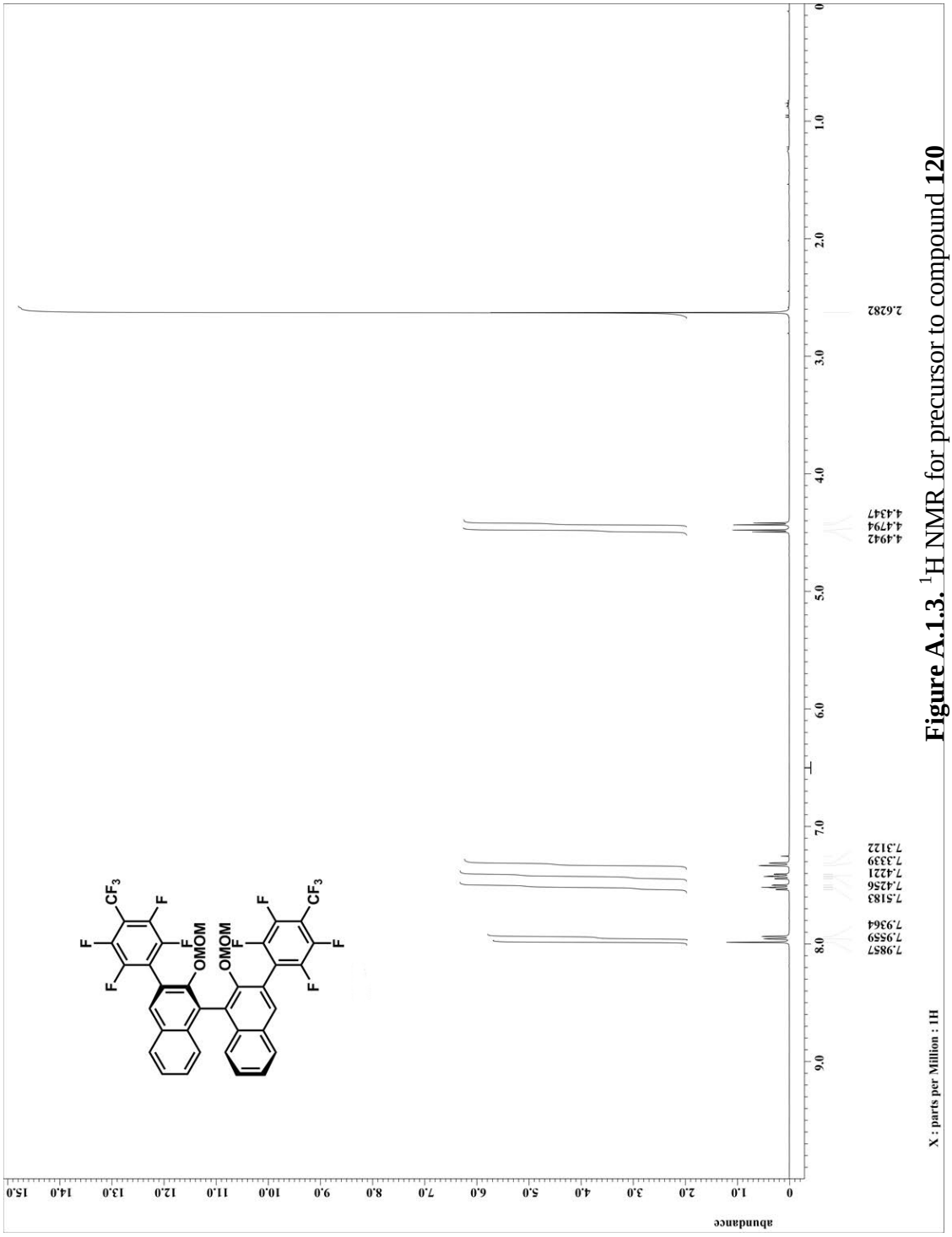


Figure A.1.3. ^{1}H NMR for precursor to compound **120**

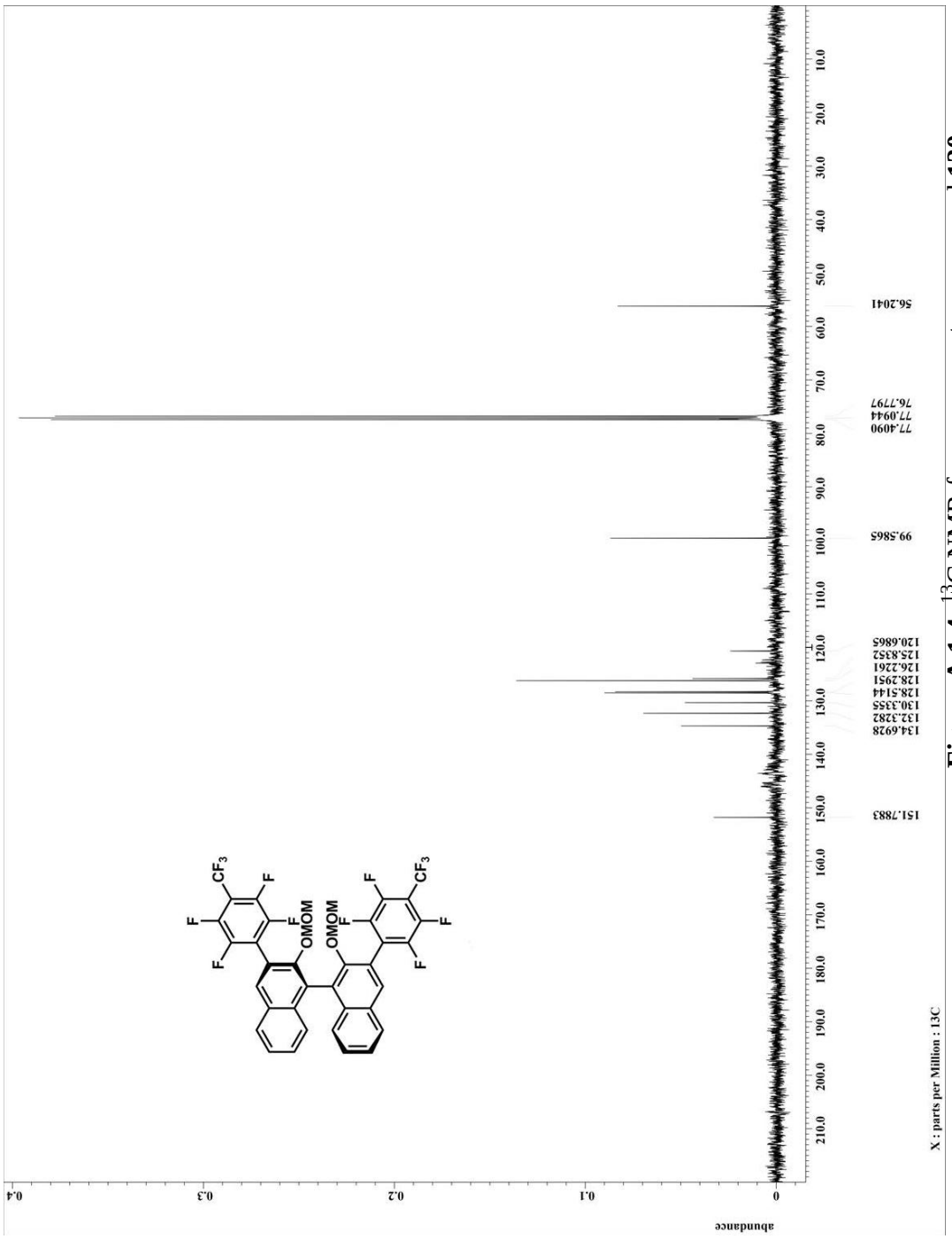


Figure A.1.4. ^{13}C NMR for precursor to compound **120**

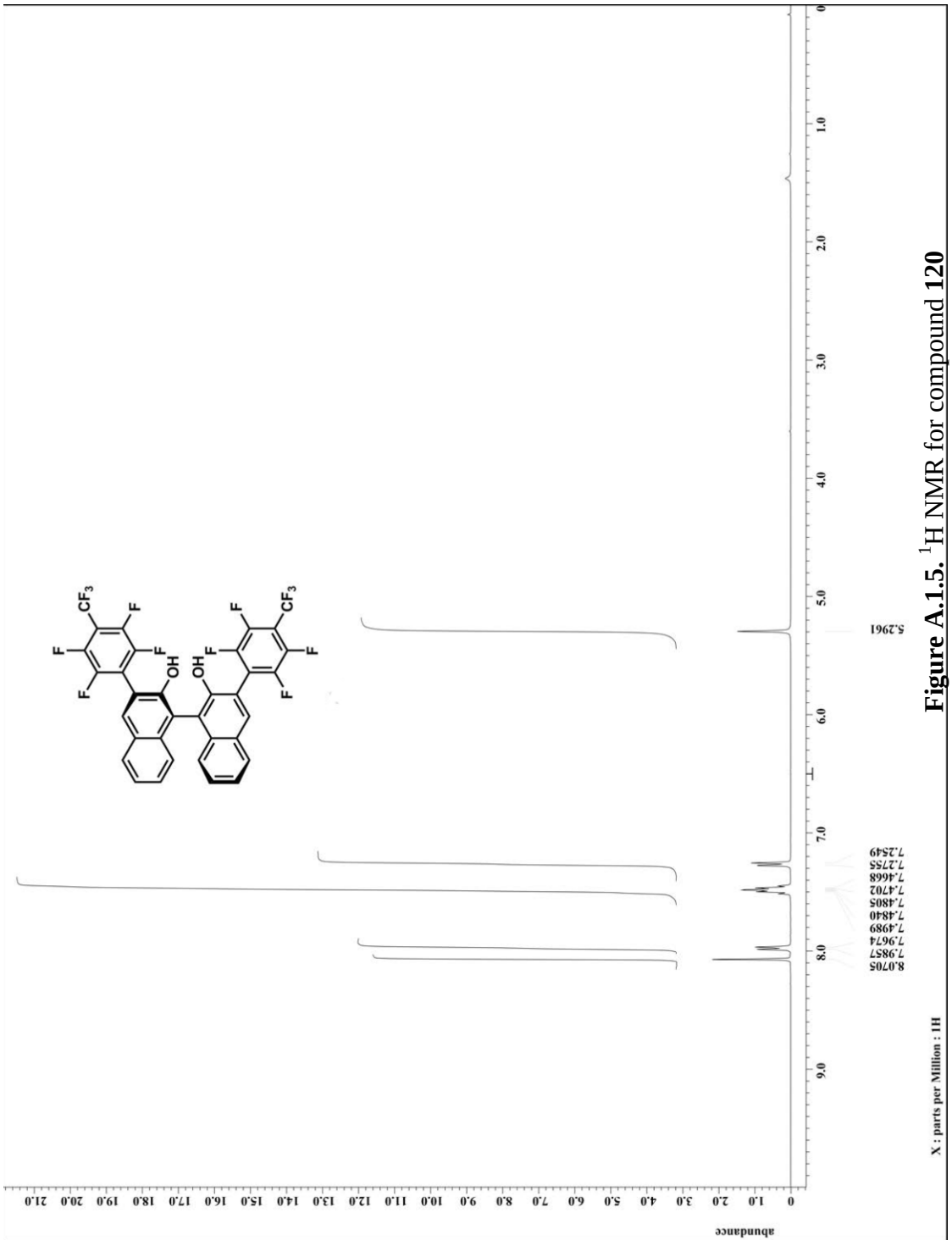


Figure A.1.5. ^{1}H NMR for compound **120**

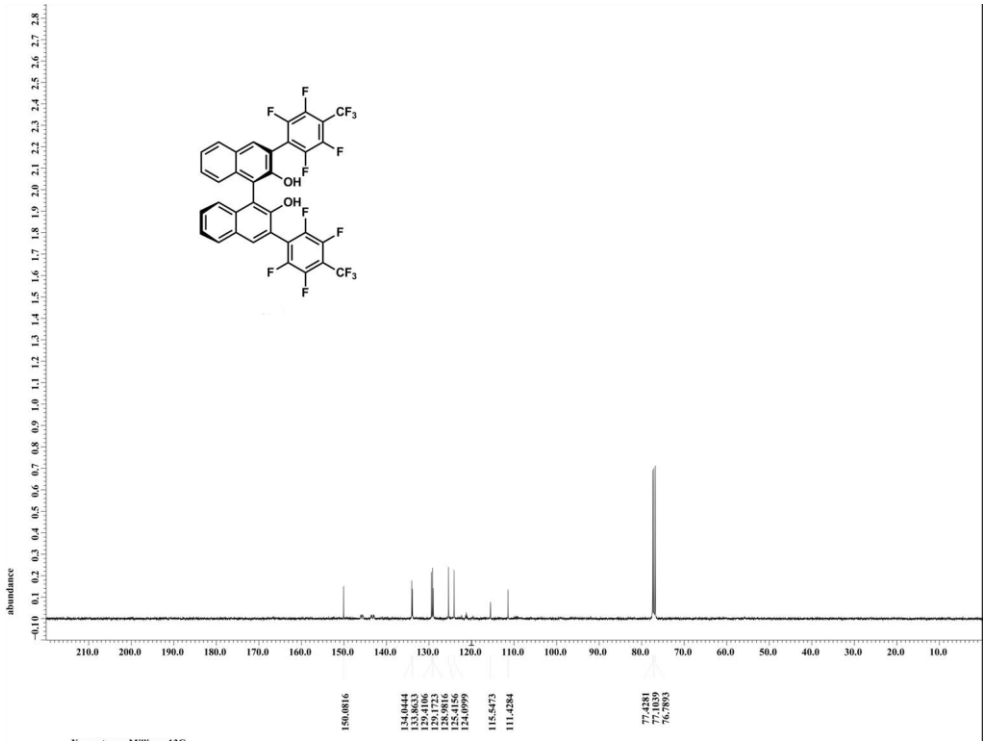


Figure A.1.6. ^{13}C NMR for compound **120**

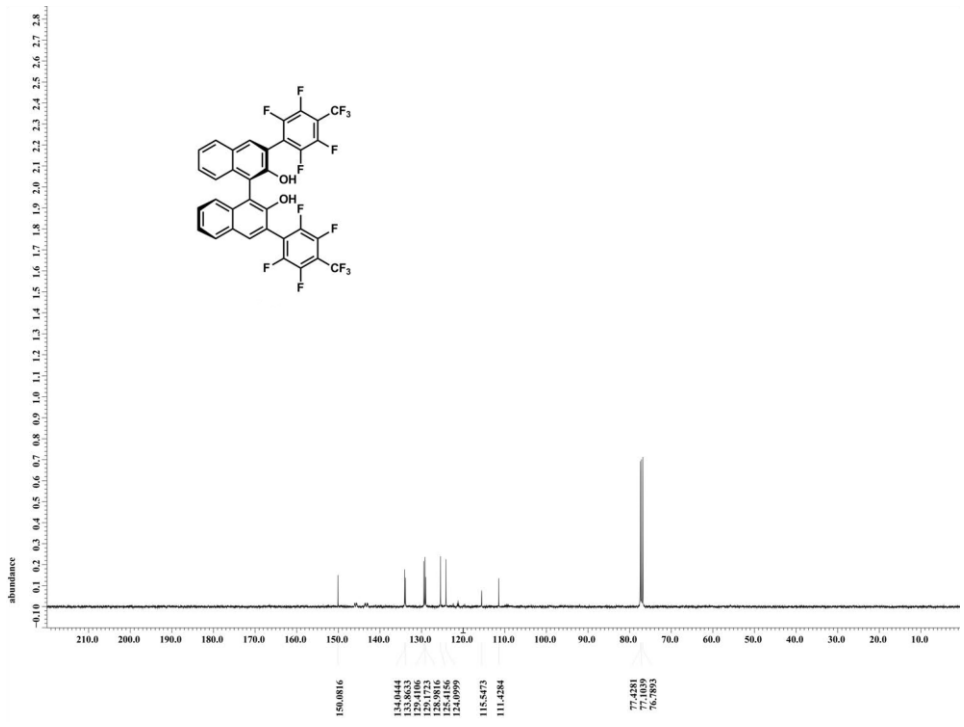


Figure A.1.7. ^{19}F NMR for compound **120**

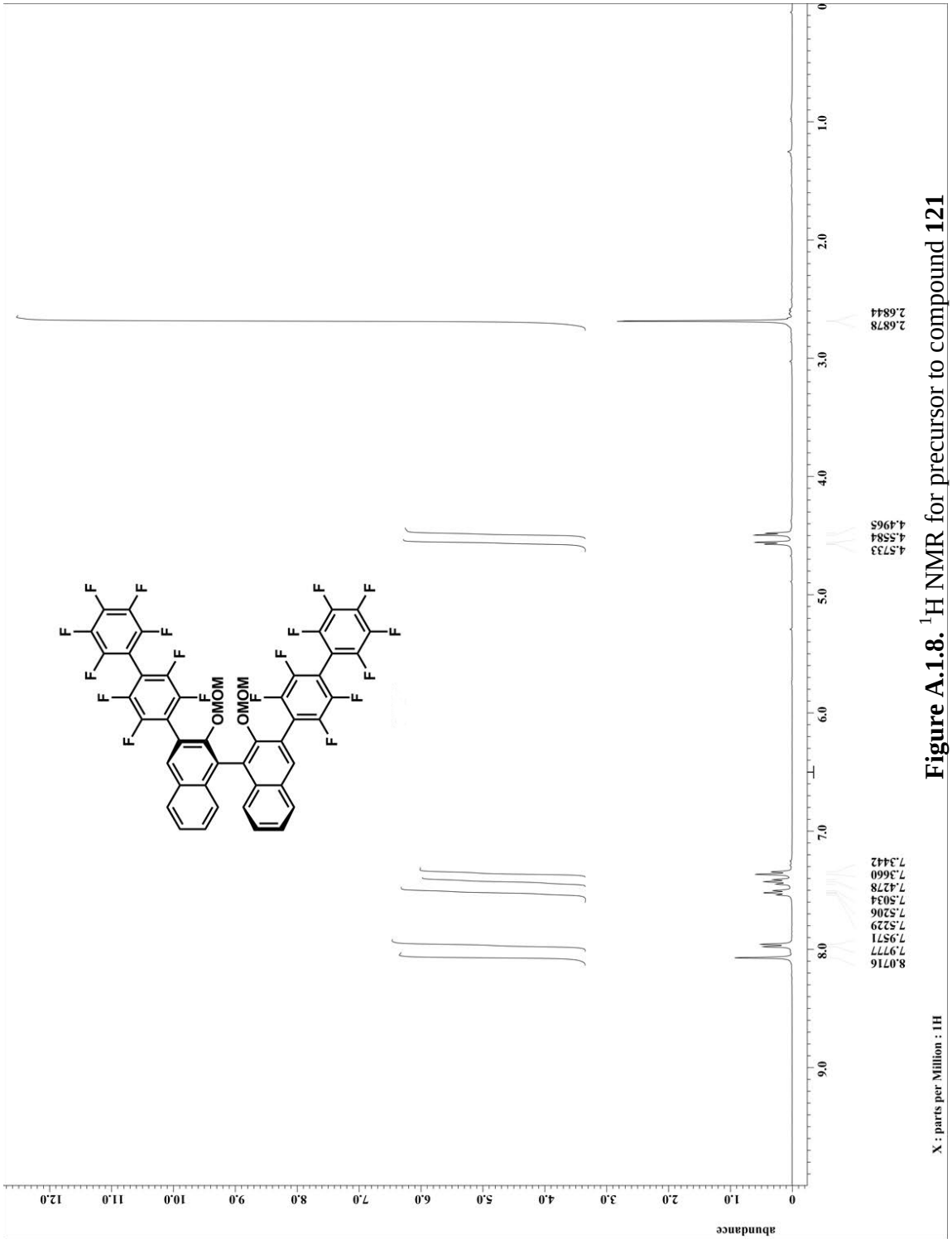


Figure A.1.8. ^{1}H NMR for precursor to compound **121**

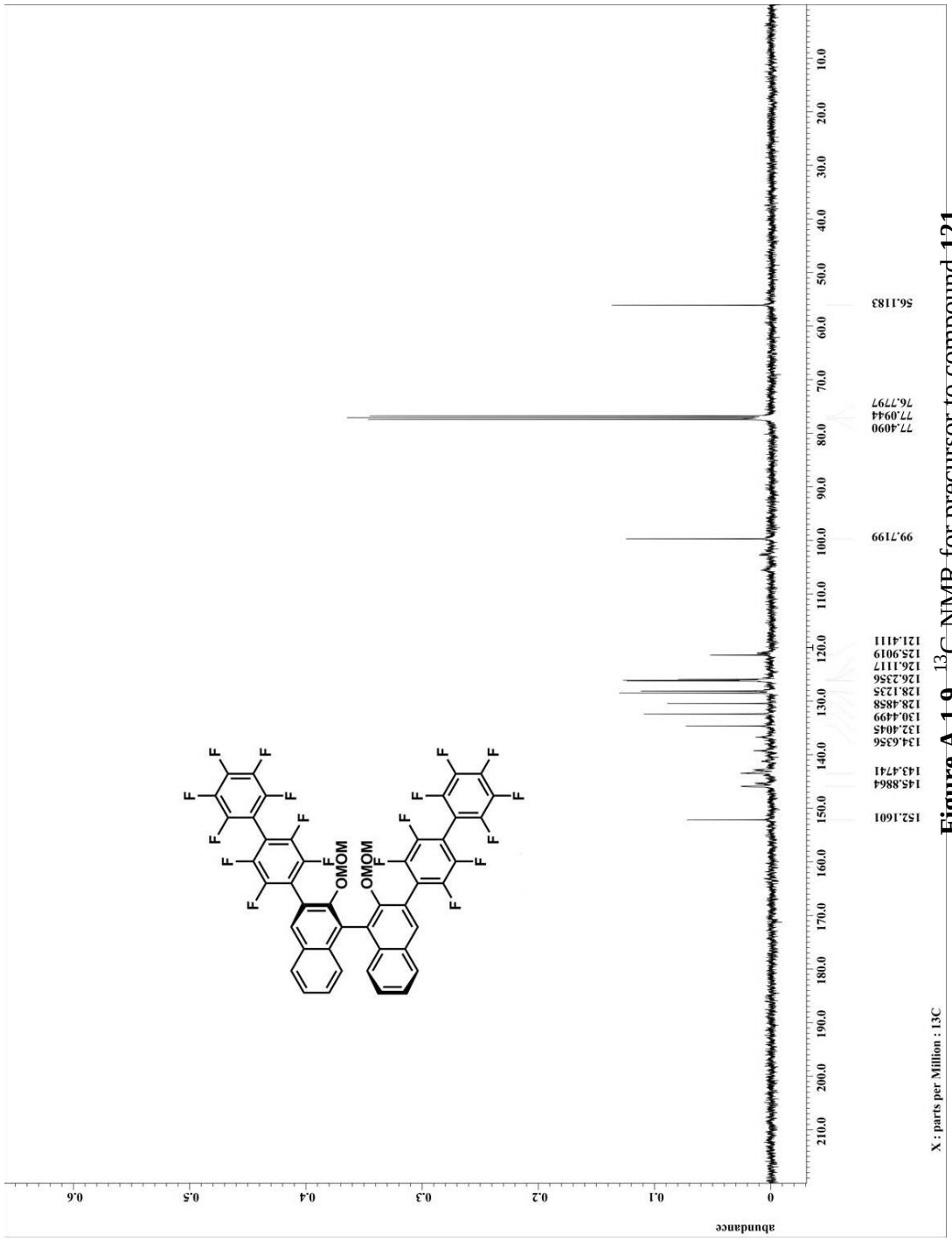


Figure A.1.9. ^{13}C NMR for precursor to compound **121**

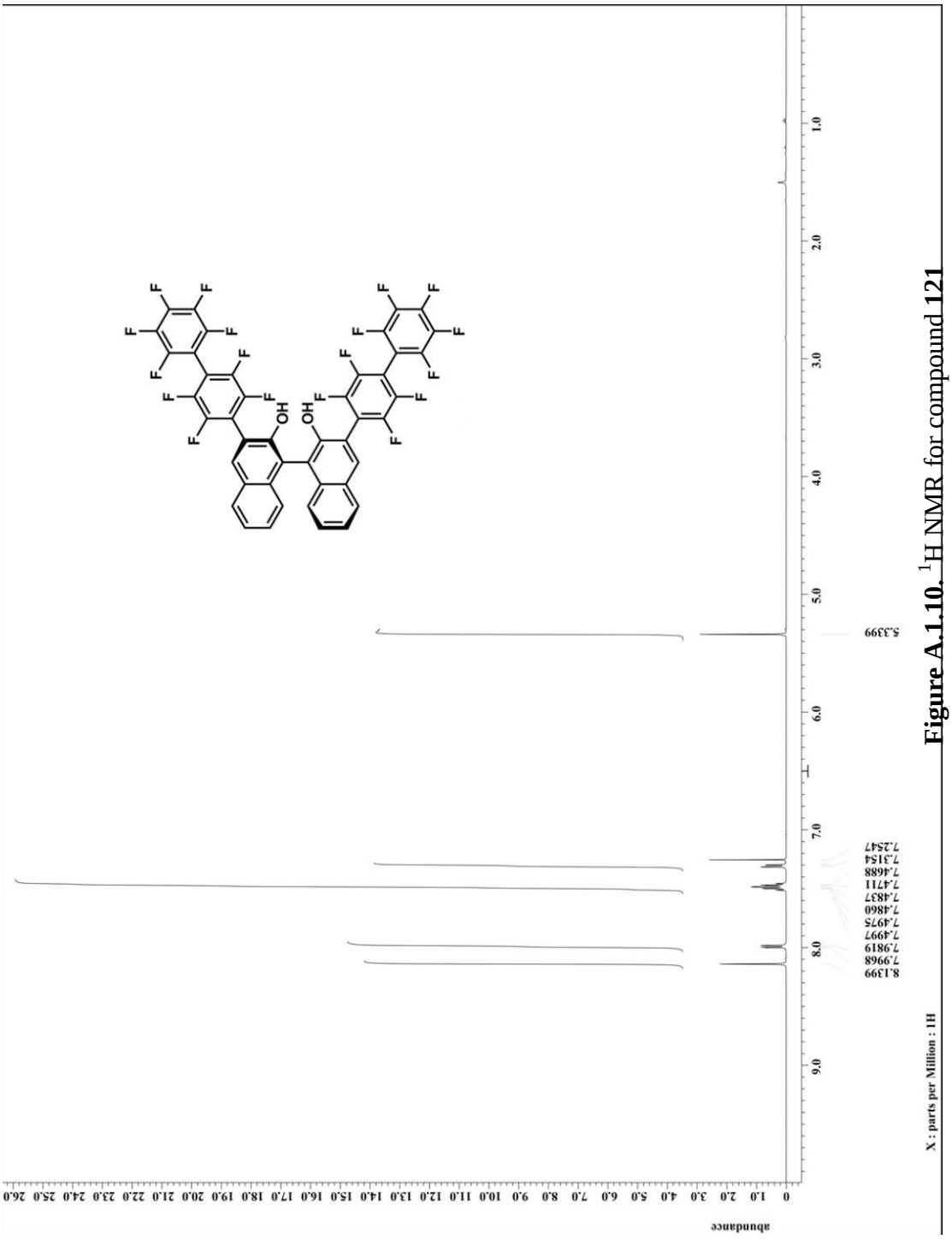


Figure A.1.10. ^{1}H NMR for compound **121**

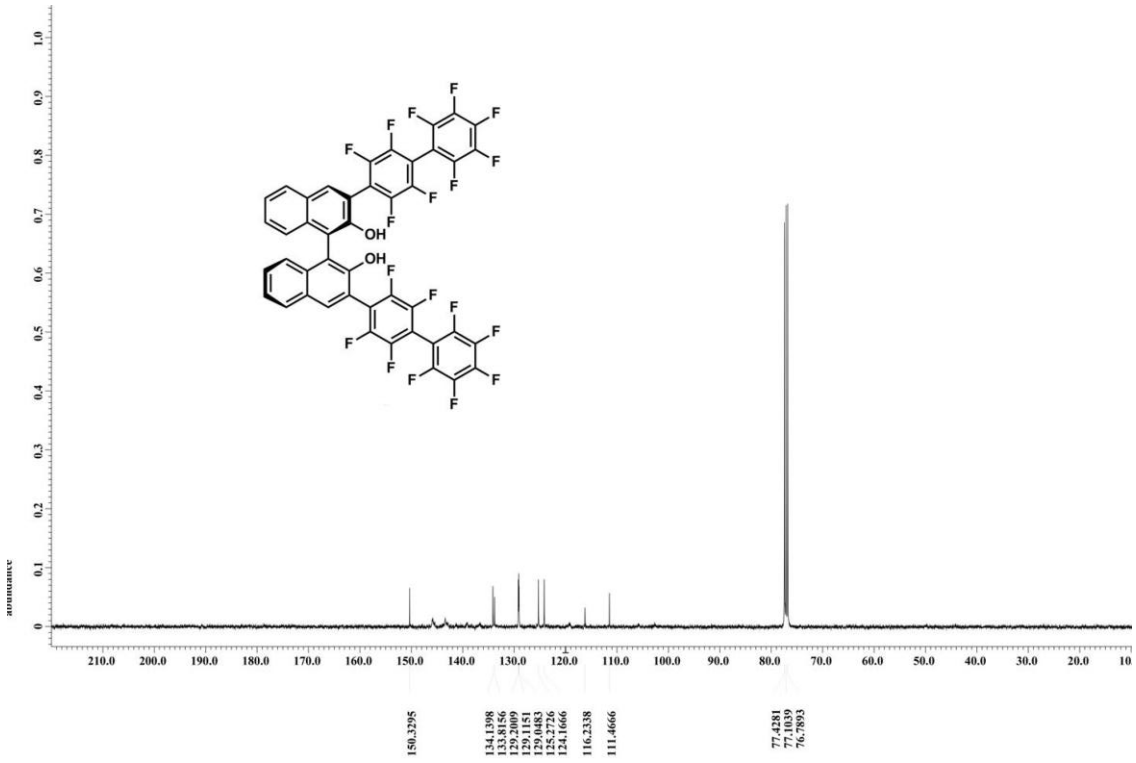


Figure A.1.11. ^{13}C NMR for compound **121**

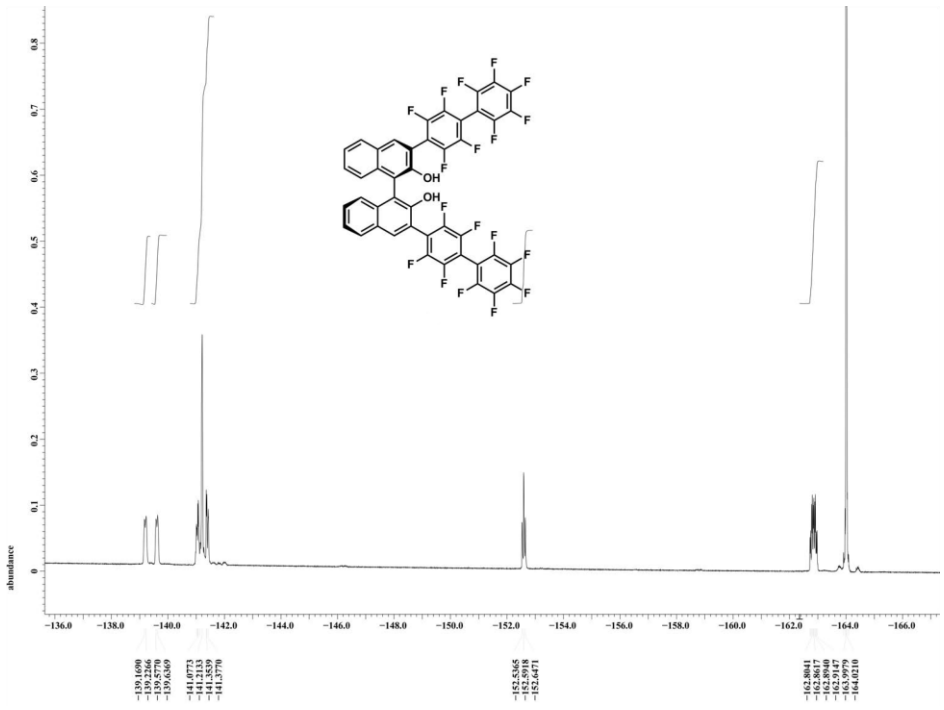


Figure A.1.12. ^{19}F NMR for compound **121**

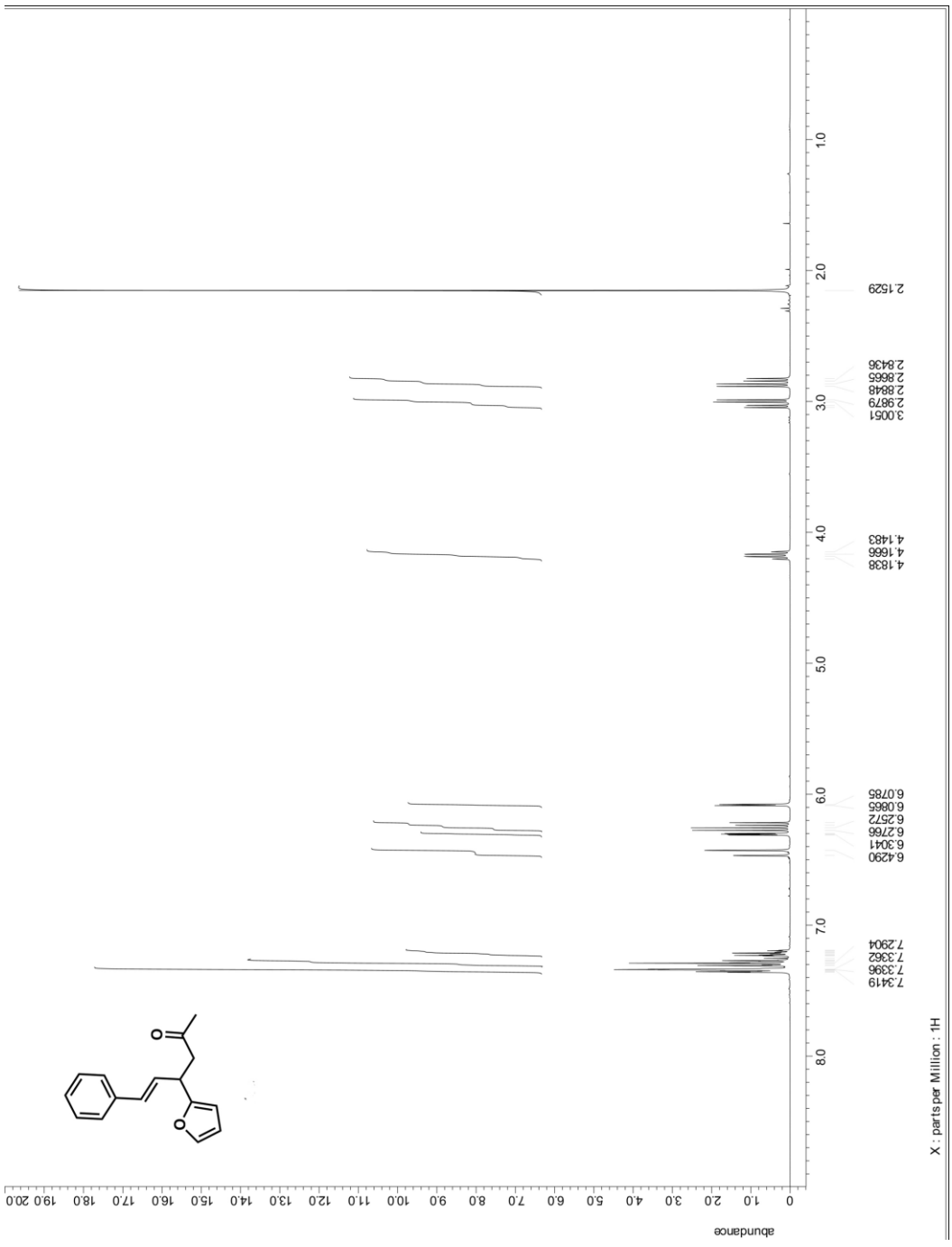


Figure A.1.13. ^{1}H NMR for compound **102**

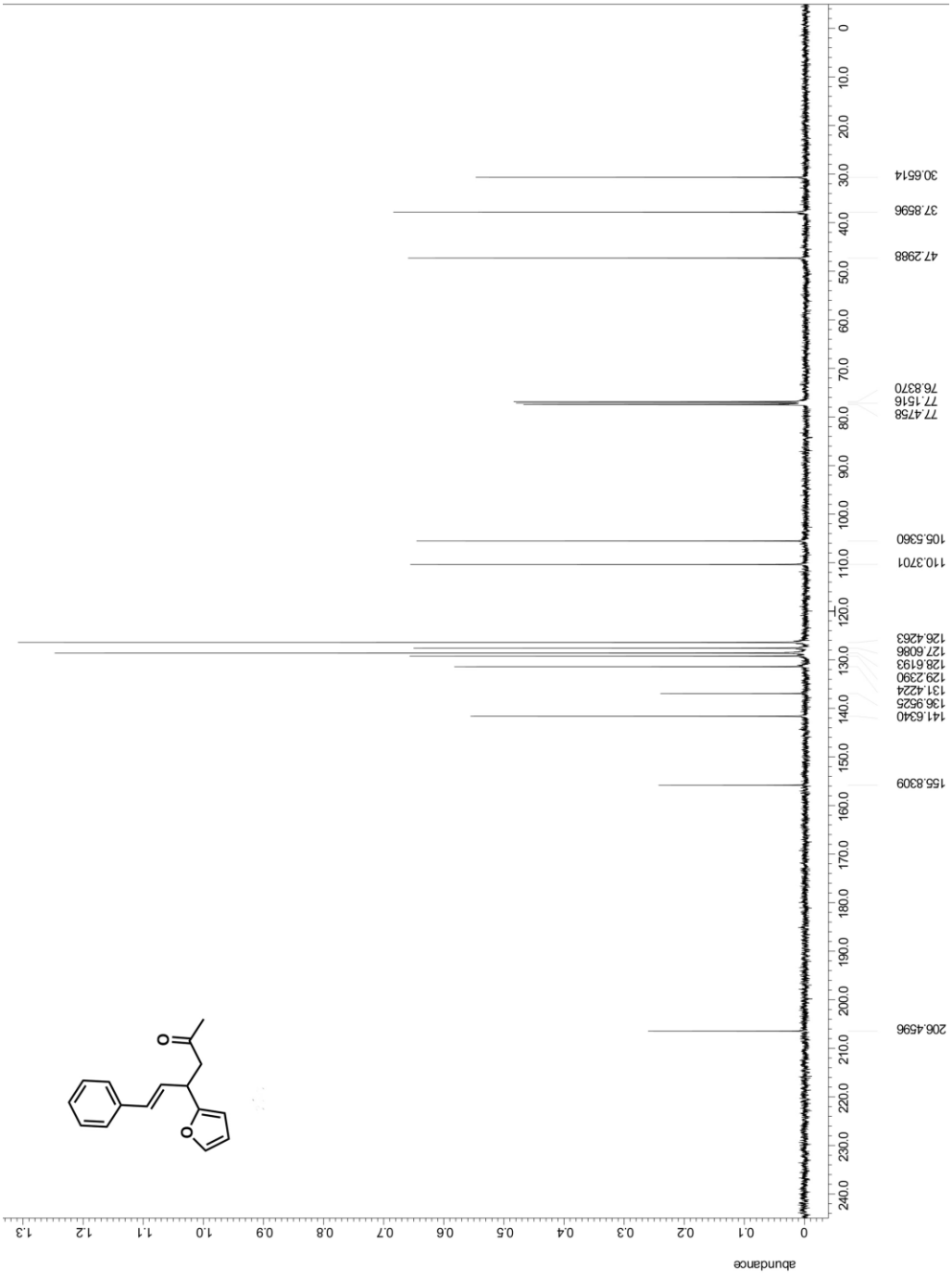
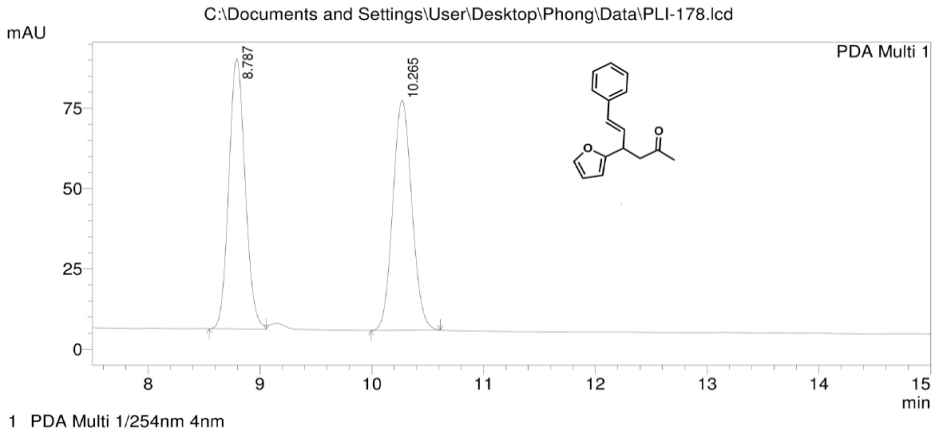


Figure A.1.14. ^{13}C NMR for compound **102**



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PeakTable

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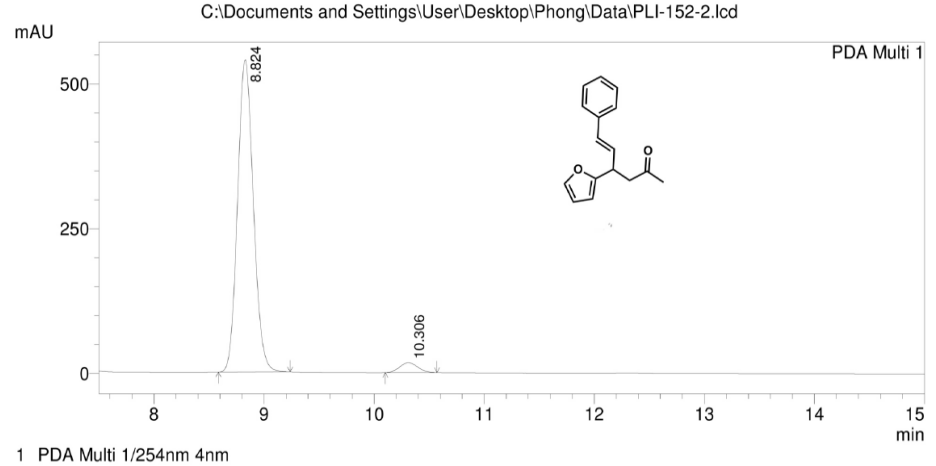
Total		1696759	155826	100.000	100.000



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PeakTable

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Peak#	Ret. Time	Area	Height	Area %	Height %
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2	10.306	192389	17012	3.445	3.060
Total		5584848	555904	100.000	100.000

Figure A.1.15. HPLC trace for compound **102**

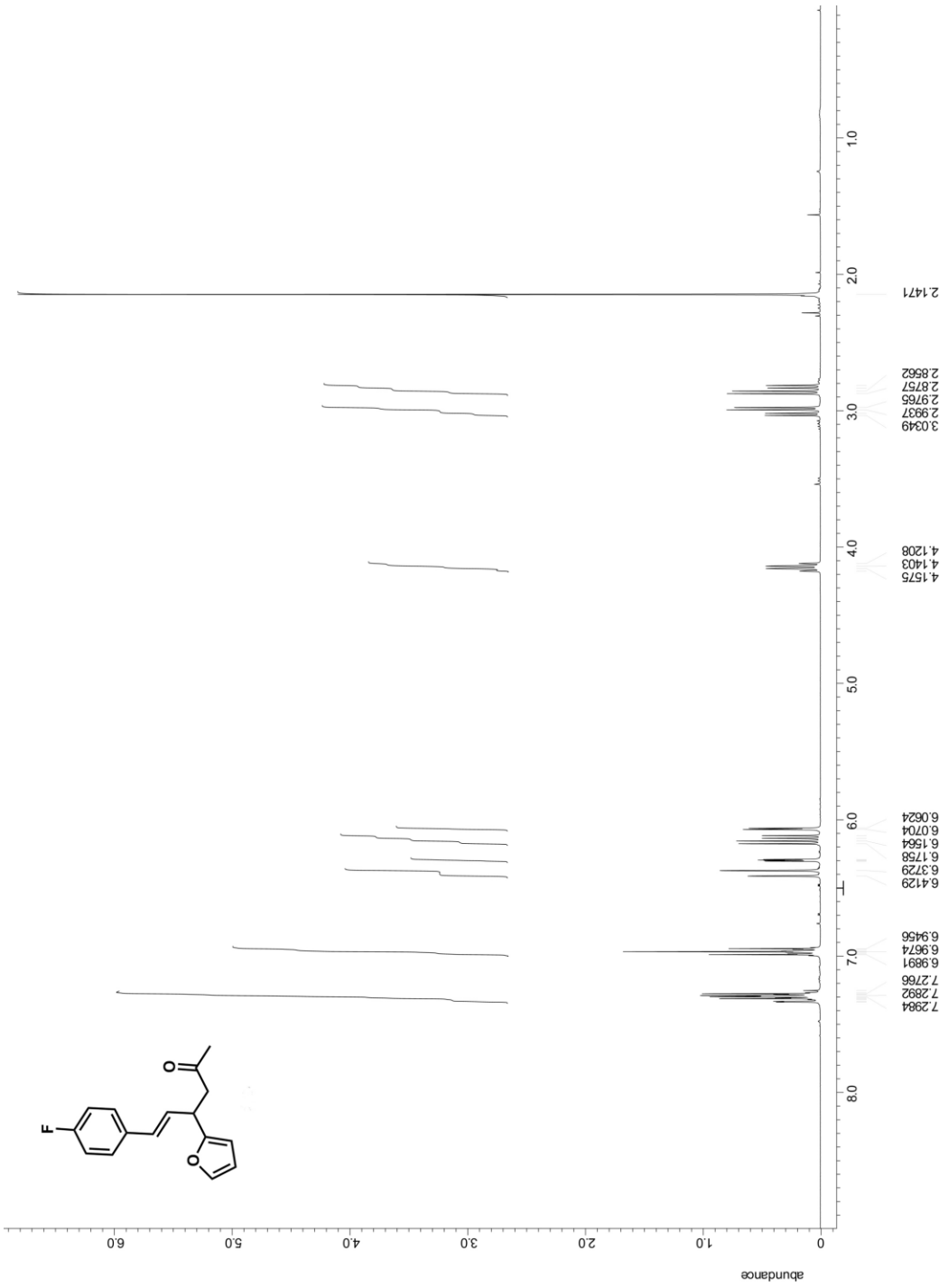


Figure A.1.16. ^{1}H NMR for compound **112**

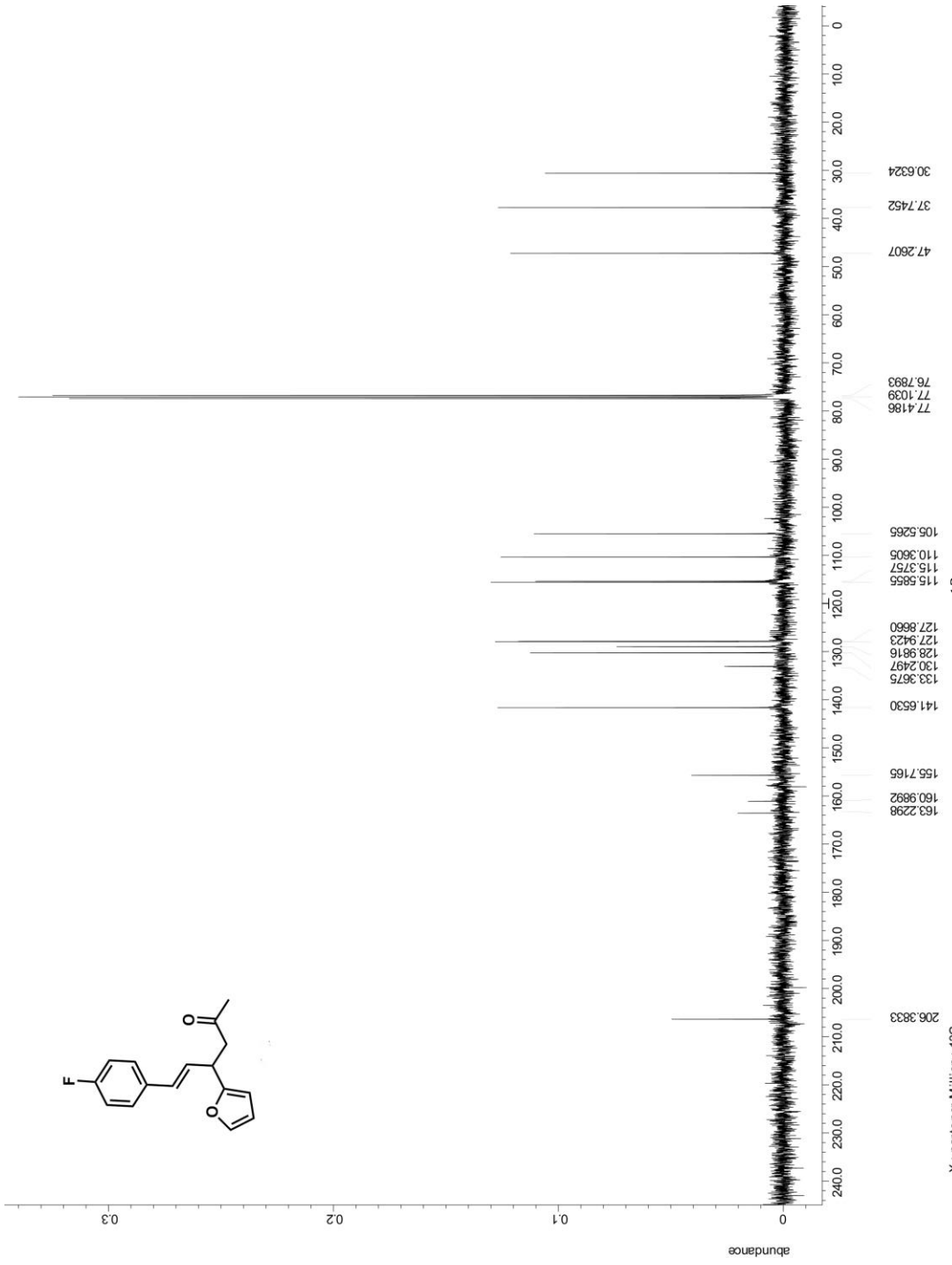
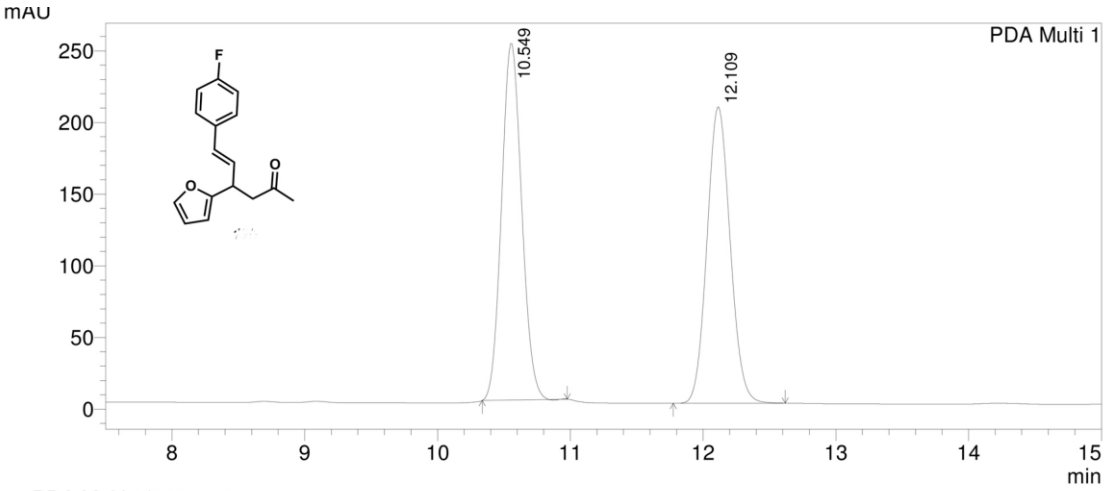


Figure A.1.17. ^{13}C NMR for compound **112**



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PeakTable

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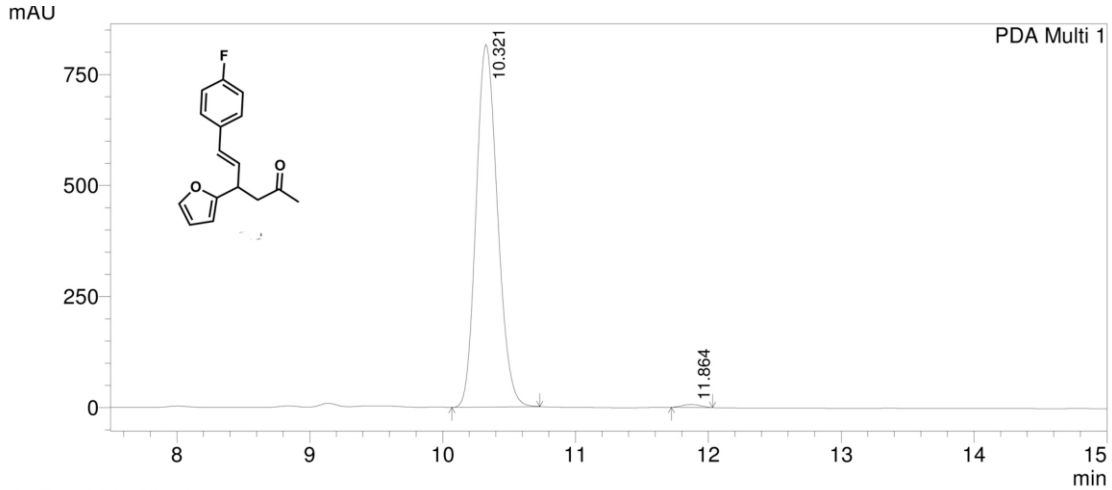
Total		5132314	455581	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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1	10.321	9134267	816771	99.314	99.197
2	11.864	63084	6609	0.686	0.803
Total		9197351	823380	100.000	100.000

Figure A.1.18. HPLC trace for compound **112**

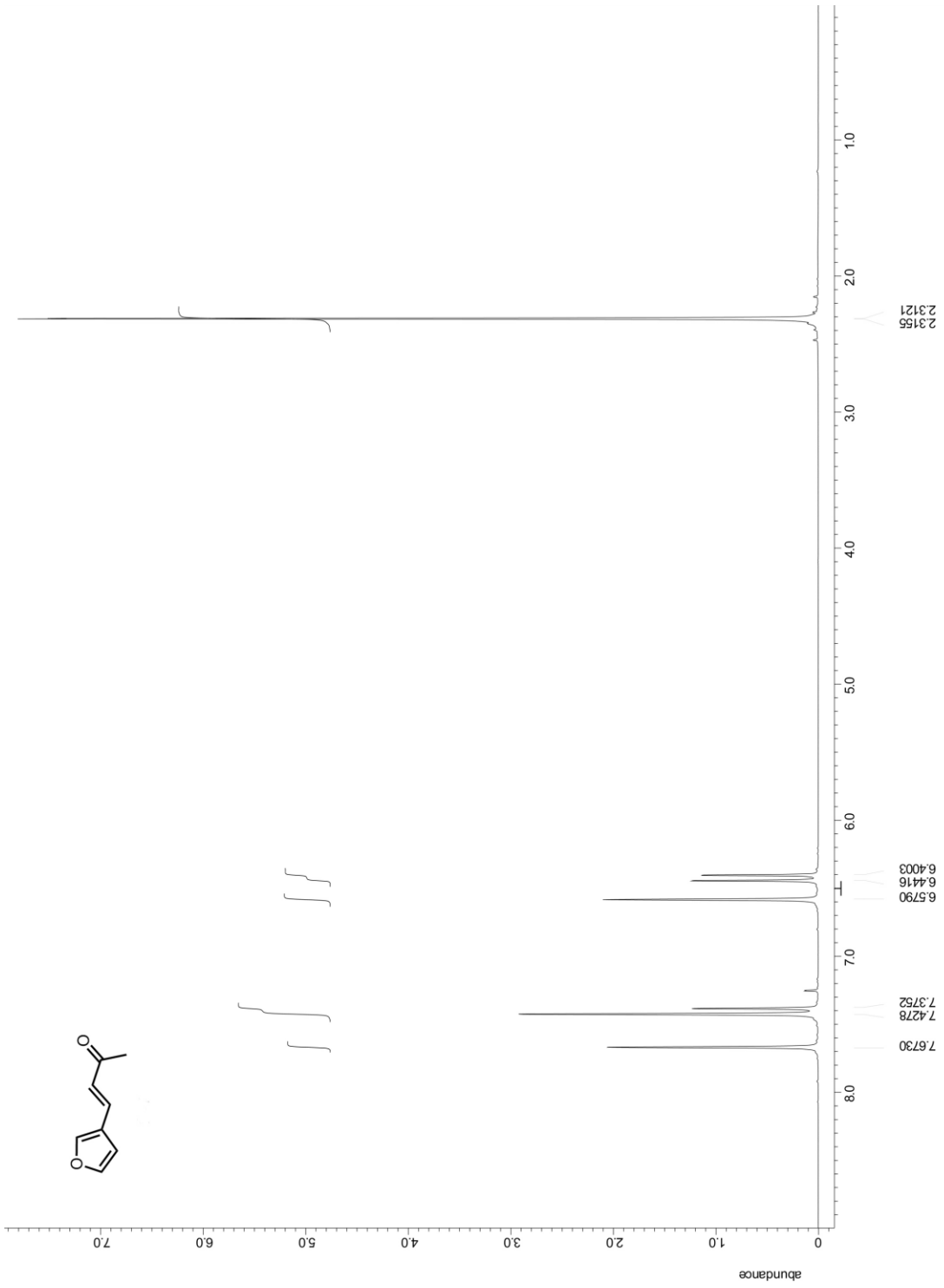


Figure A.1.19. ^{1}H NMR for precursor to compound **103**

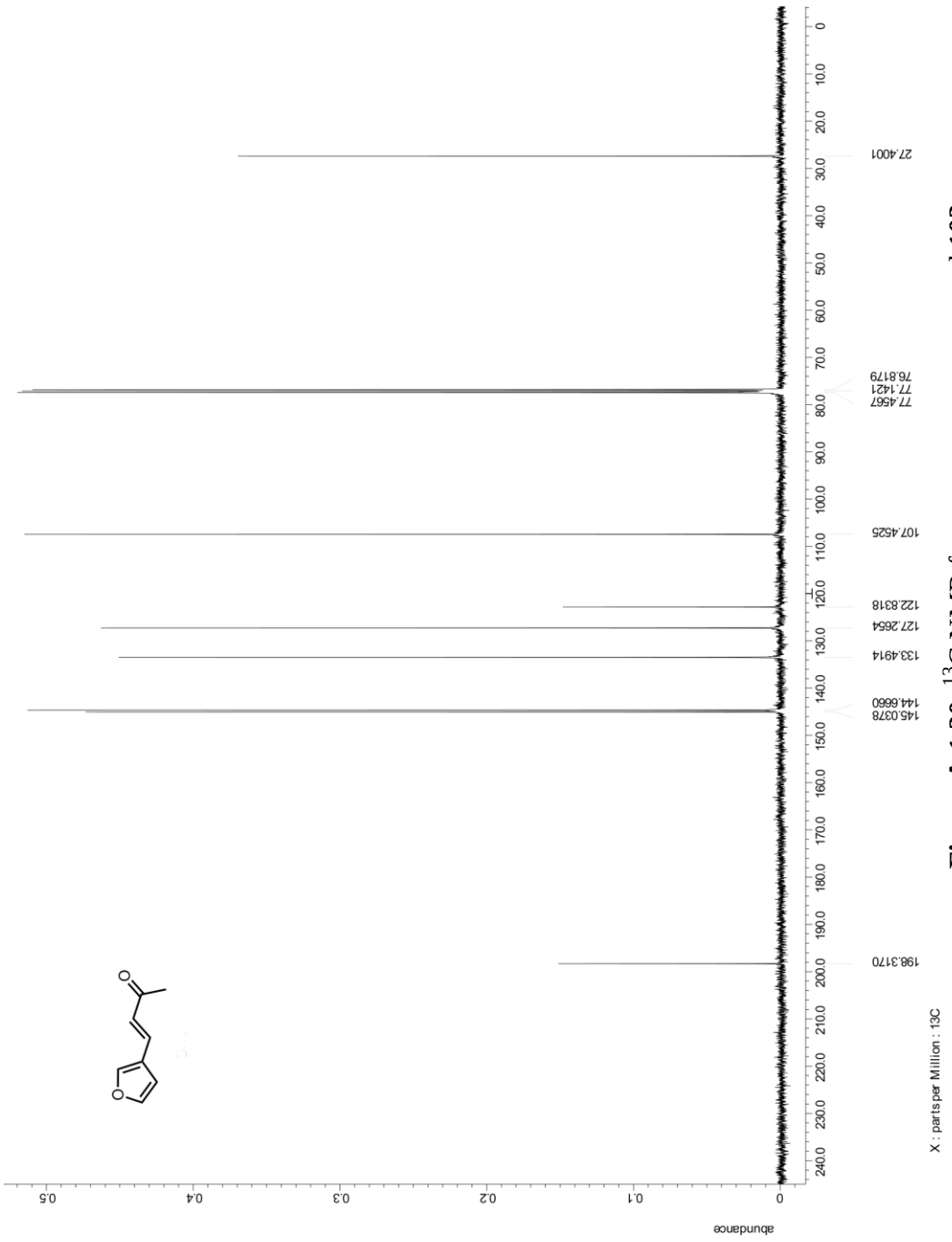


Figure A.1.20. ^{13}C NMR for precursor to compound **103**

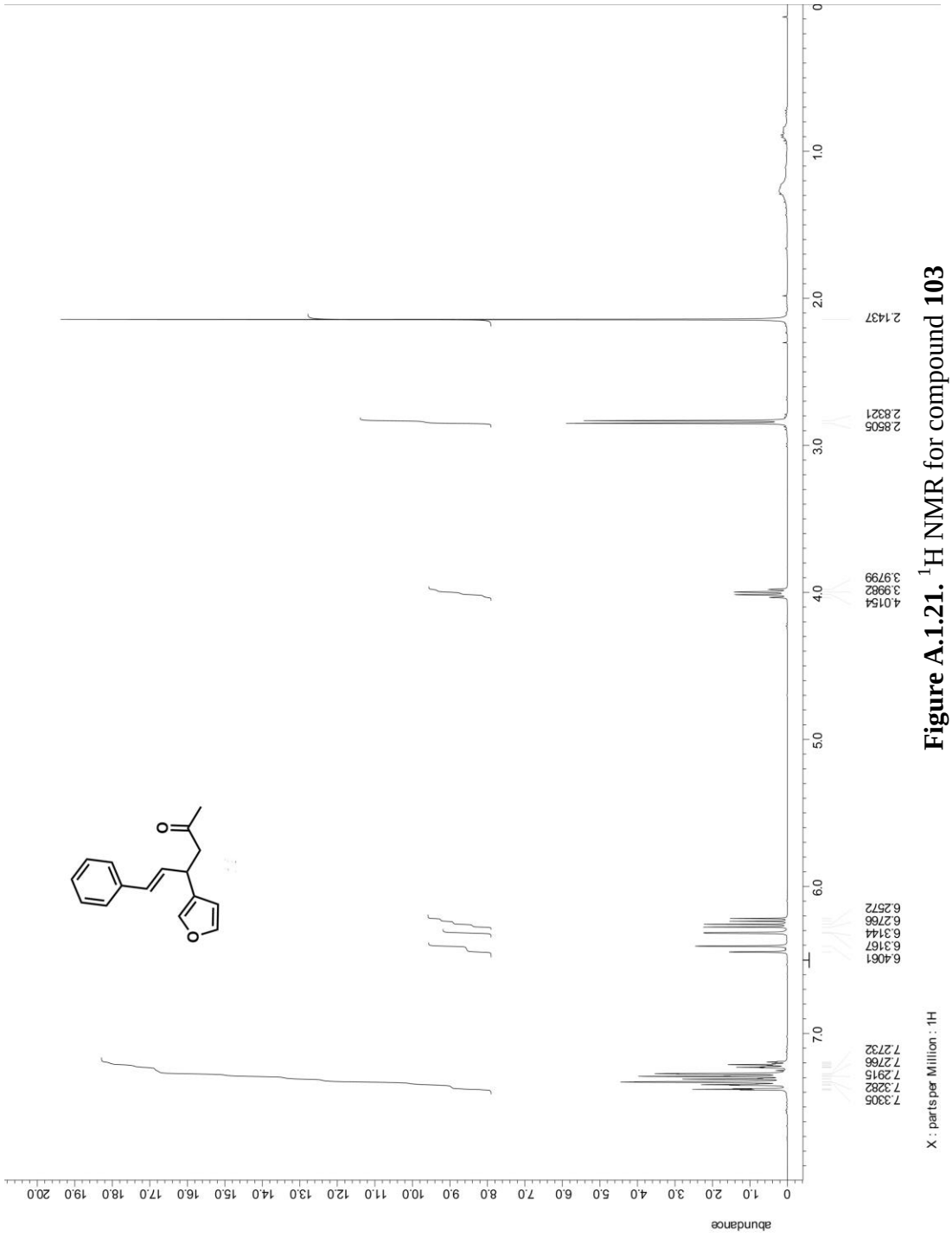


Figure A.1.21. ^{1}H NMR for compound **103**

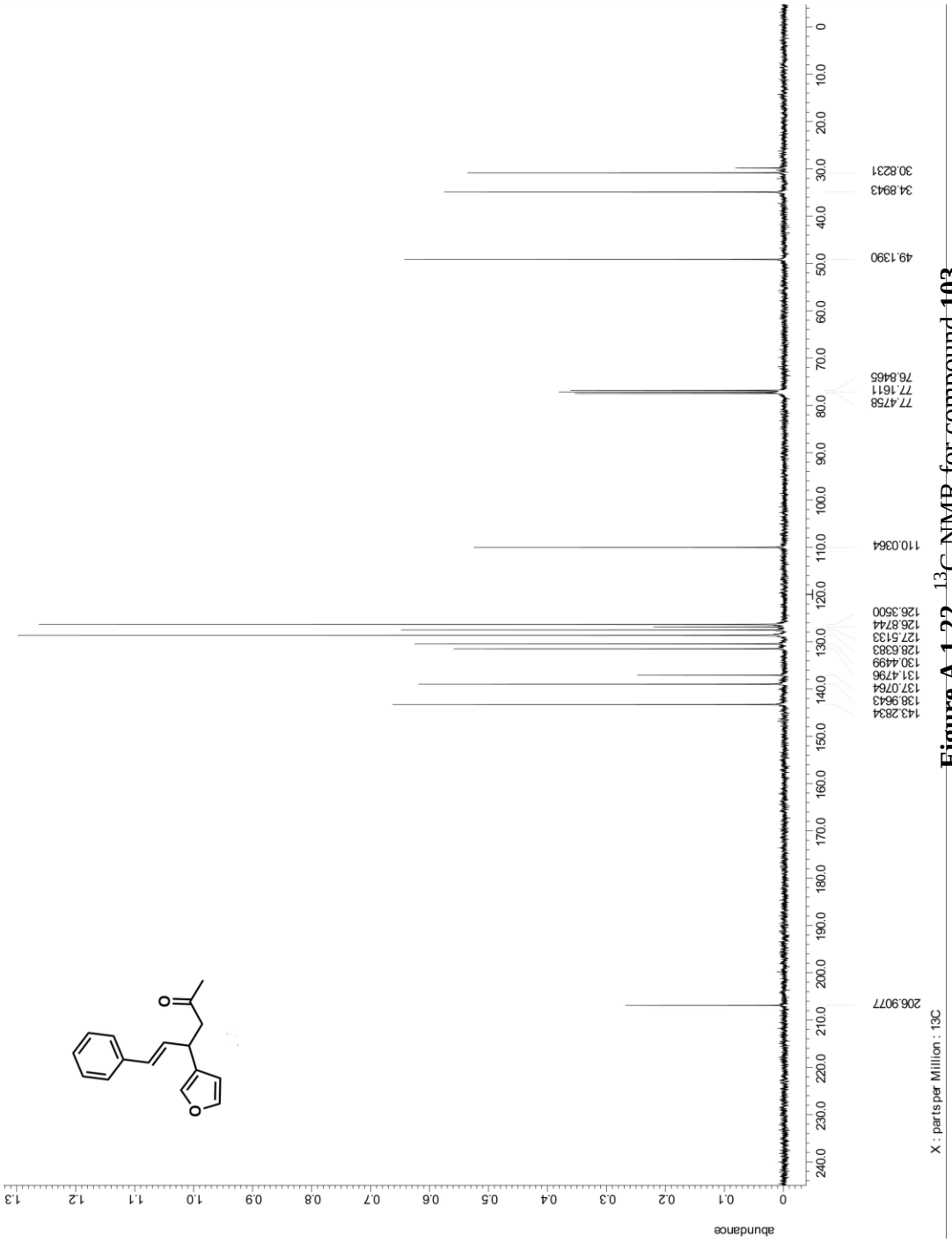
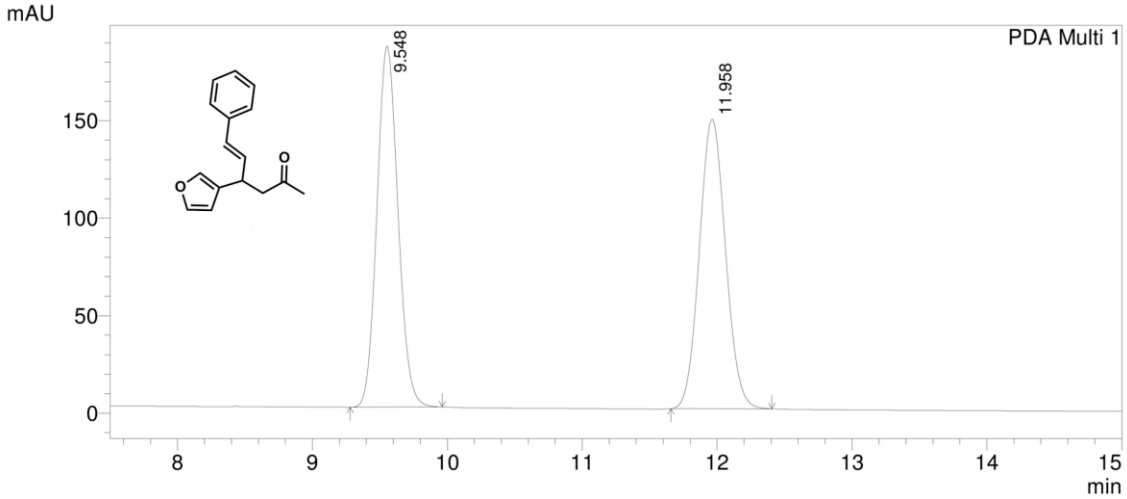


Figure A.1.22. ^{13}C NMR for compound **103**

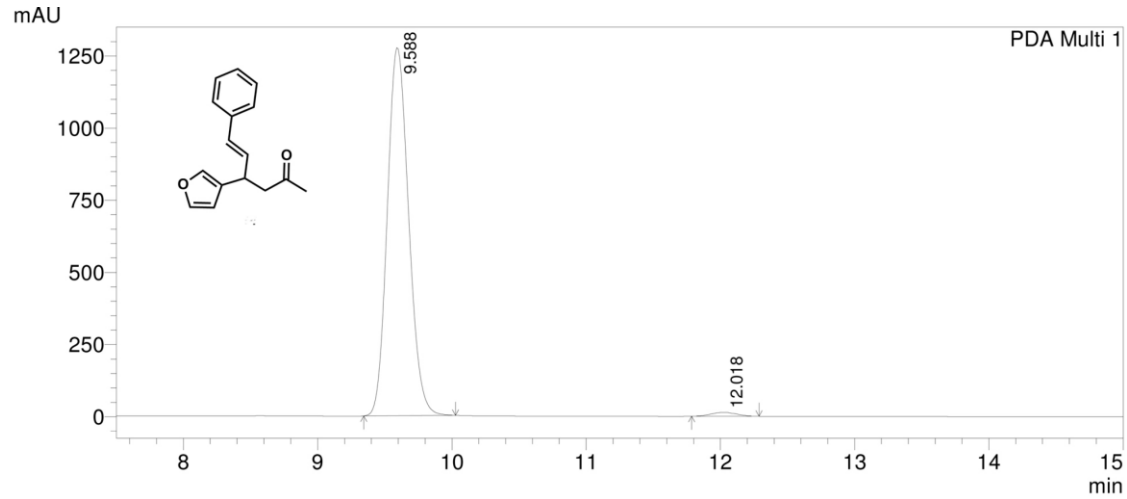


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.548	2005872	185246	50.054	55.508
2	11.958	2001537	148482	49.946	44.492
Total		4007409	333728	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.588	14092530	1274742	98.753	98.933
2	12.018	178013	13750	1.247	1.067
Total		14270543	1288492	100.000	100.000

Figure A.1.23. HPLC trace for compound **103**

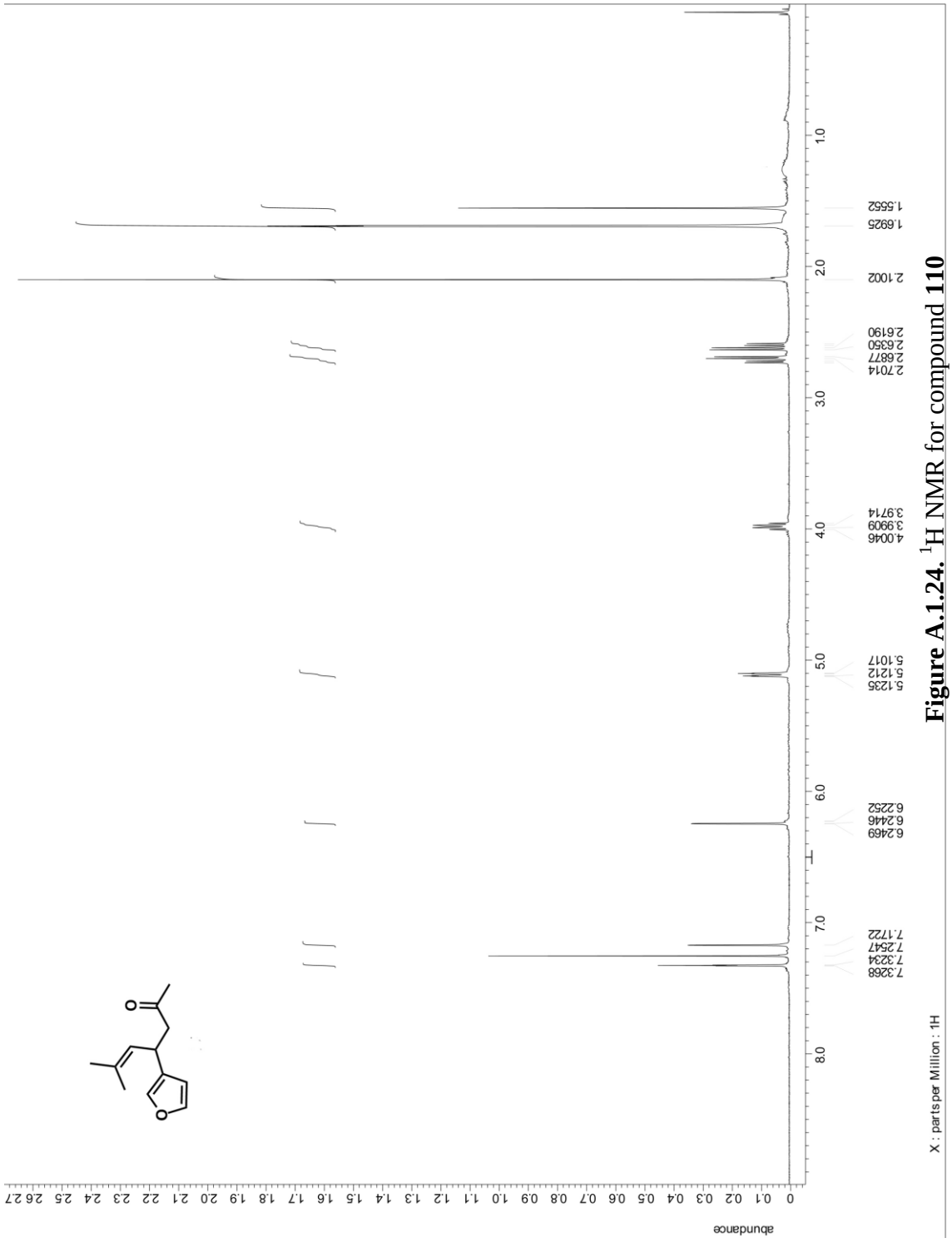


Figure A.1.24. ^{1}H NMR for compound **110**

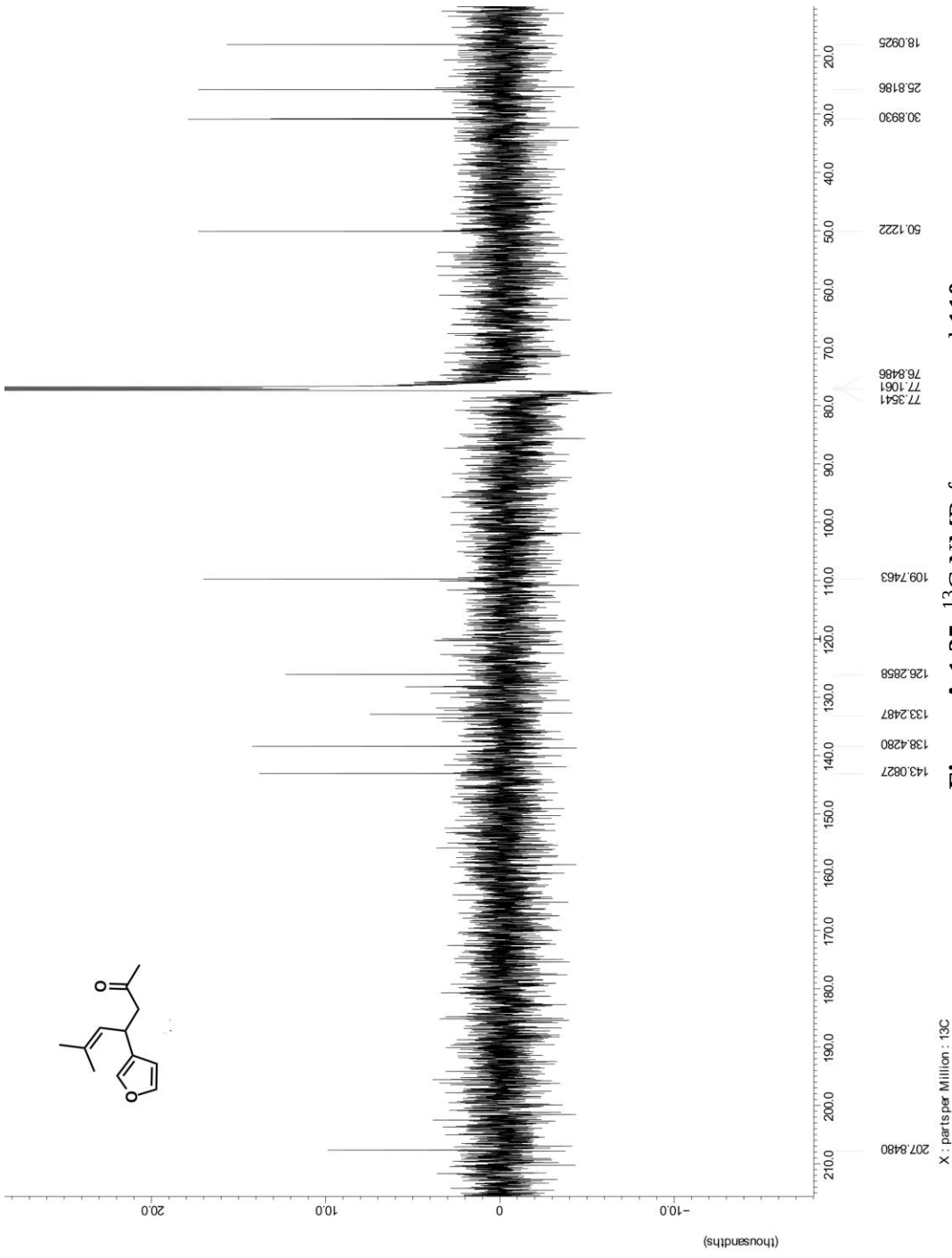
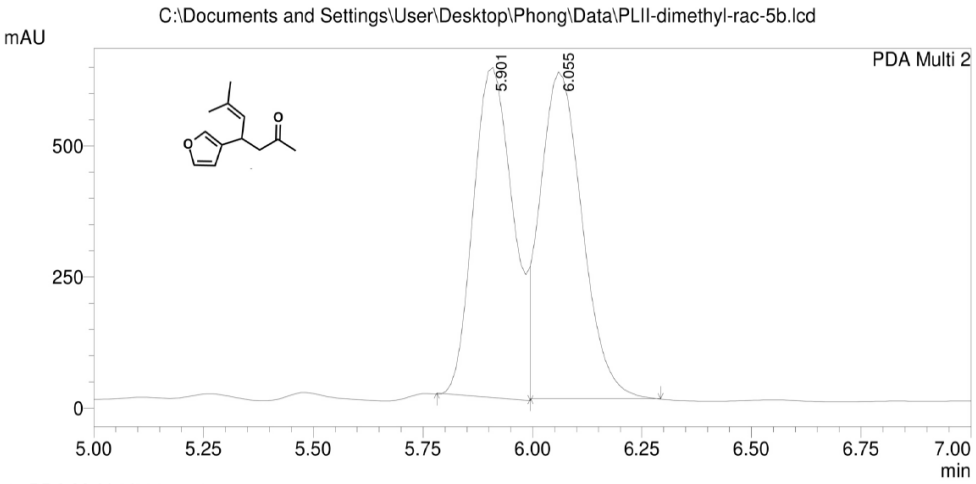


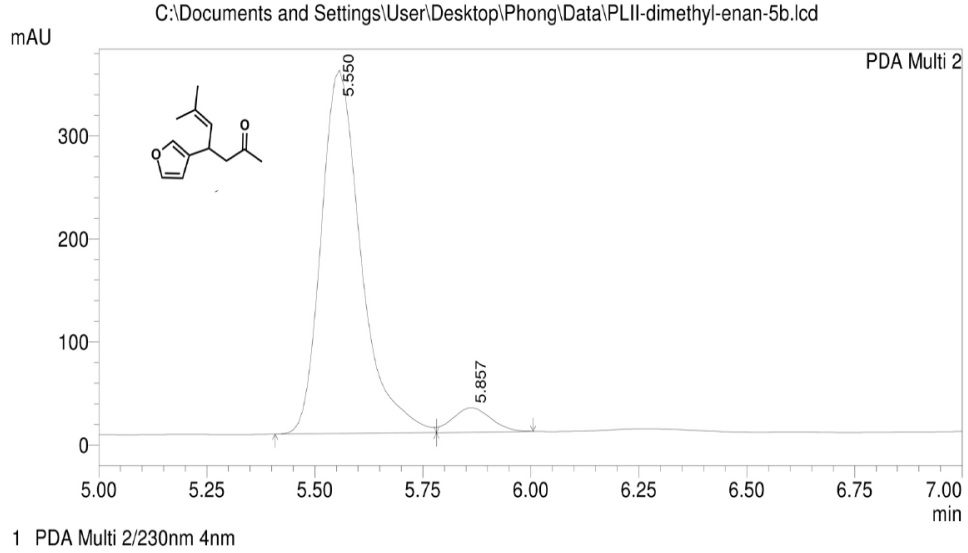
Figure A.1.25. ^{13}C NMR for compound **110**



PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.901	4065896	629375	50.001	50.236
2	6.055	4065661	623456	49.999	49.764
Total		8131557	1252831	100.000	100.000



PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.550	2268350	352799	93.917	93.680
2	5.857	146920	23801	6.083	6.320
Total		2415270	376600	100.000	100.000

Figure A.1.26. HPLC trace for compound **110**

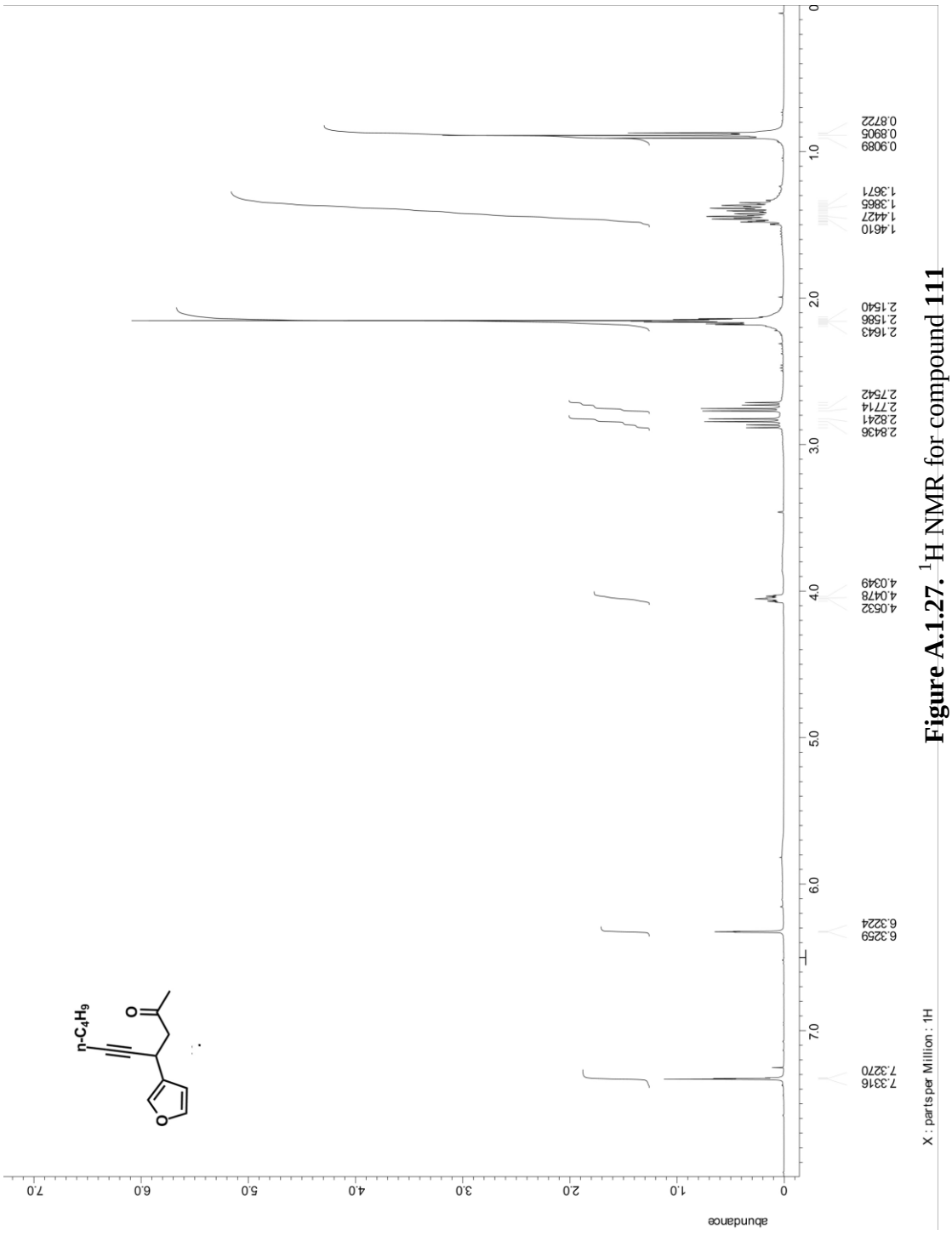


Figure A.1.27. ^{1}H NMR for compound **111**

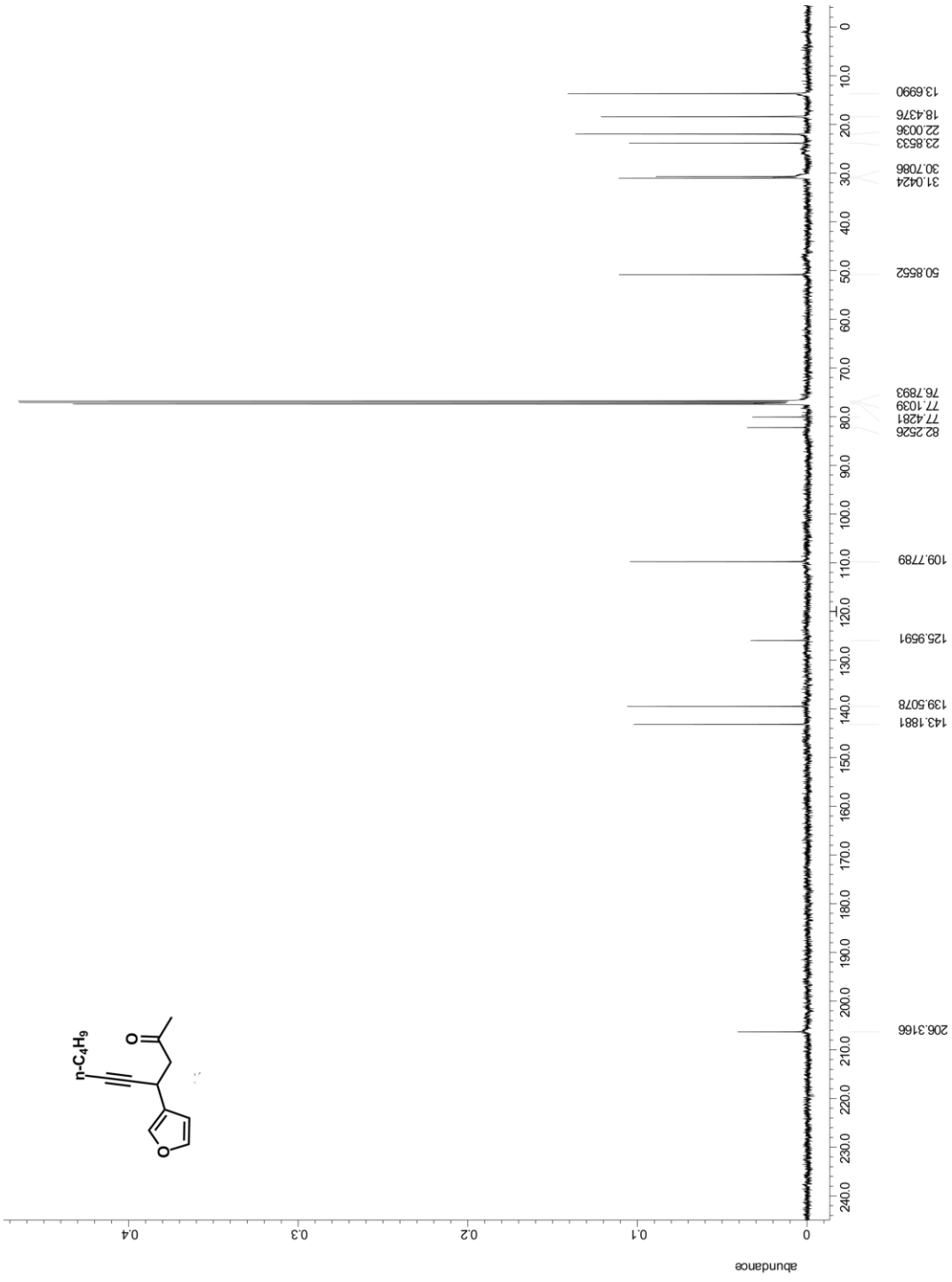
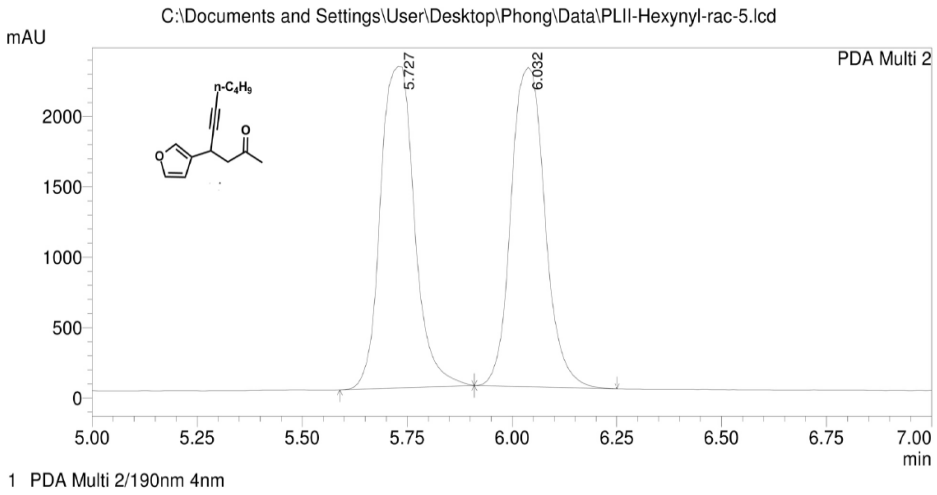


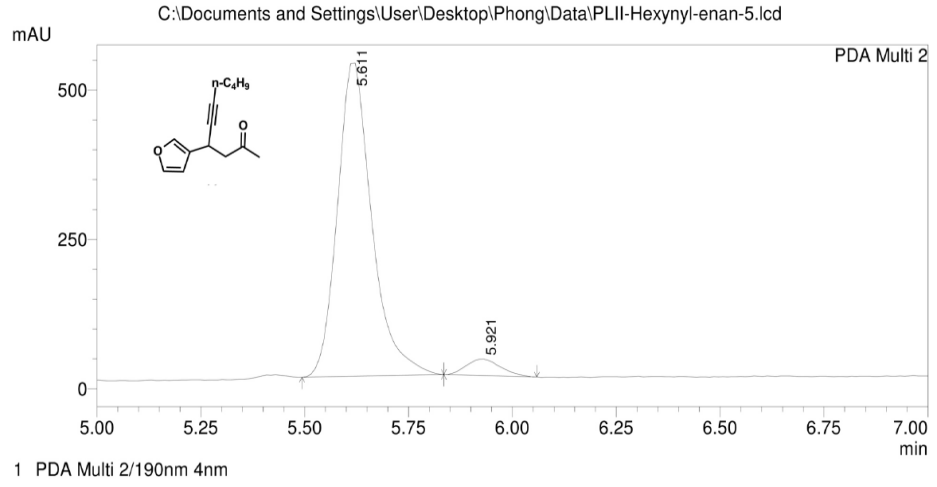
Figure A.1.28. ^{13}C NMR for compound **111**



PeakTable

PDA Ch2 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.727	12923414	2285599	50.380	50.172
2	6.032	12728306	2269949	49.620	49.828
Total		25651720	4555548	100.000	100.000



PeakTable

PDA Ch2 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.611	3025046	523365	95.099	95.044
2	5.921	155901	27293	4.901	4.956
Total		3180947	550658	100.000	100.000

Figure A.1.29. HPLC trace for compound **111**

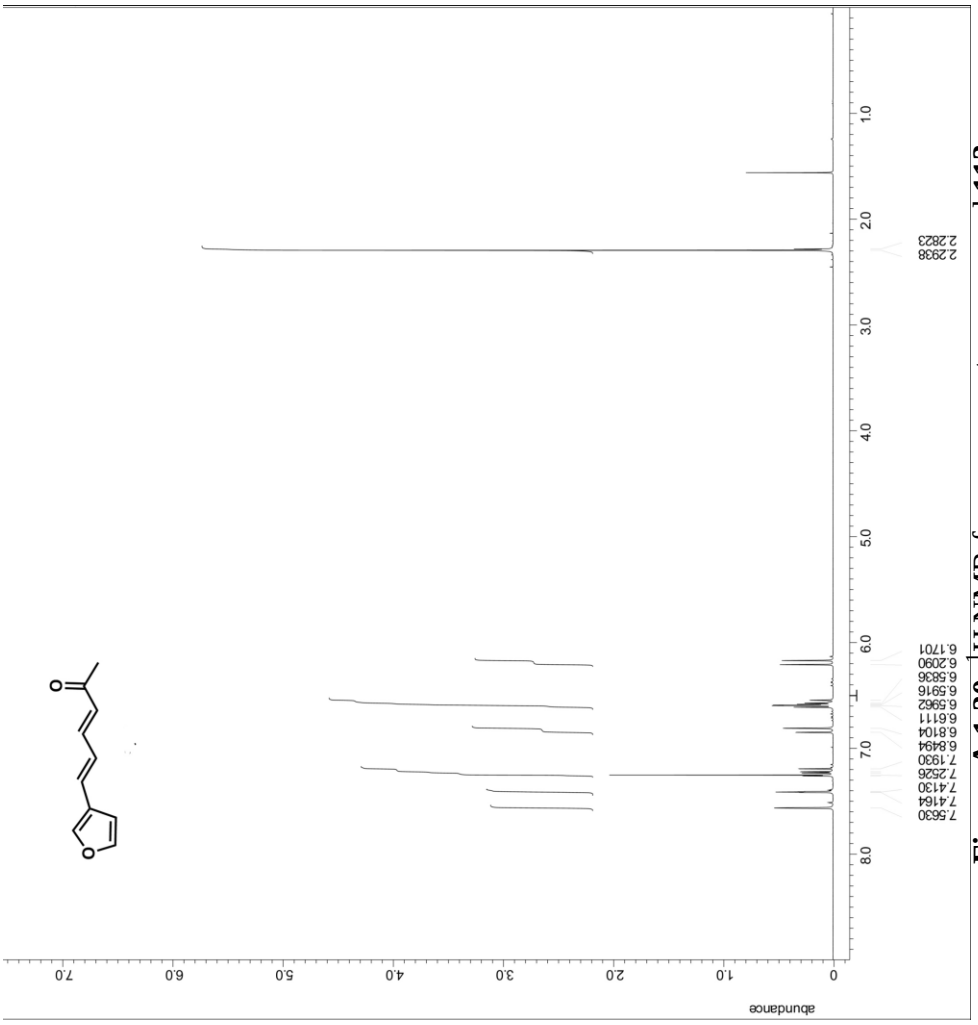


Figure A.1.30. ^{1}H NMR for precursor to compound **113**

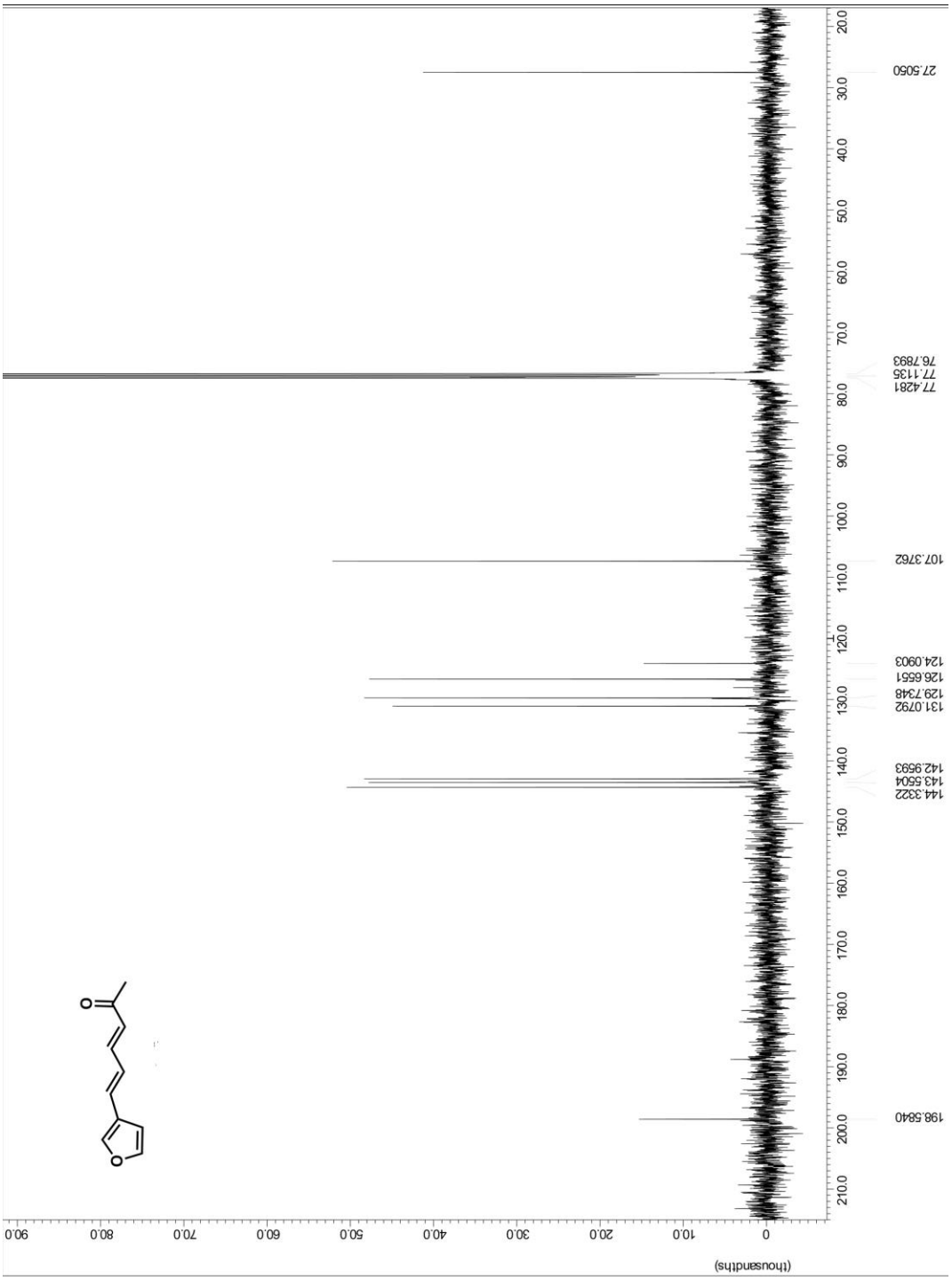


Figure A.1.31. ^{13}C NMR for precursor to compound **113**

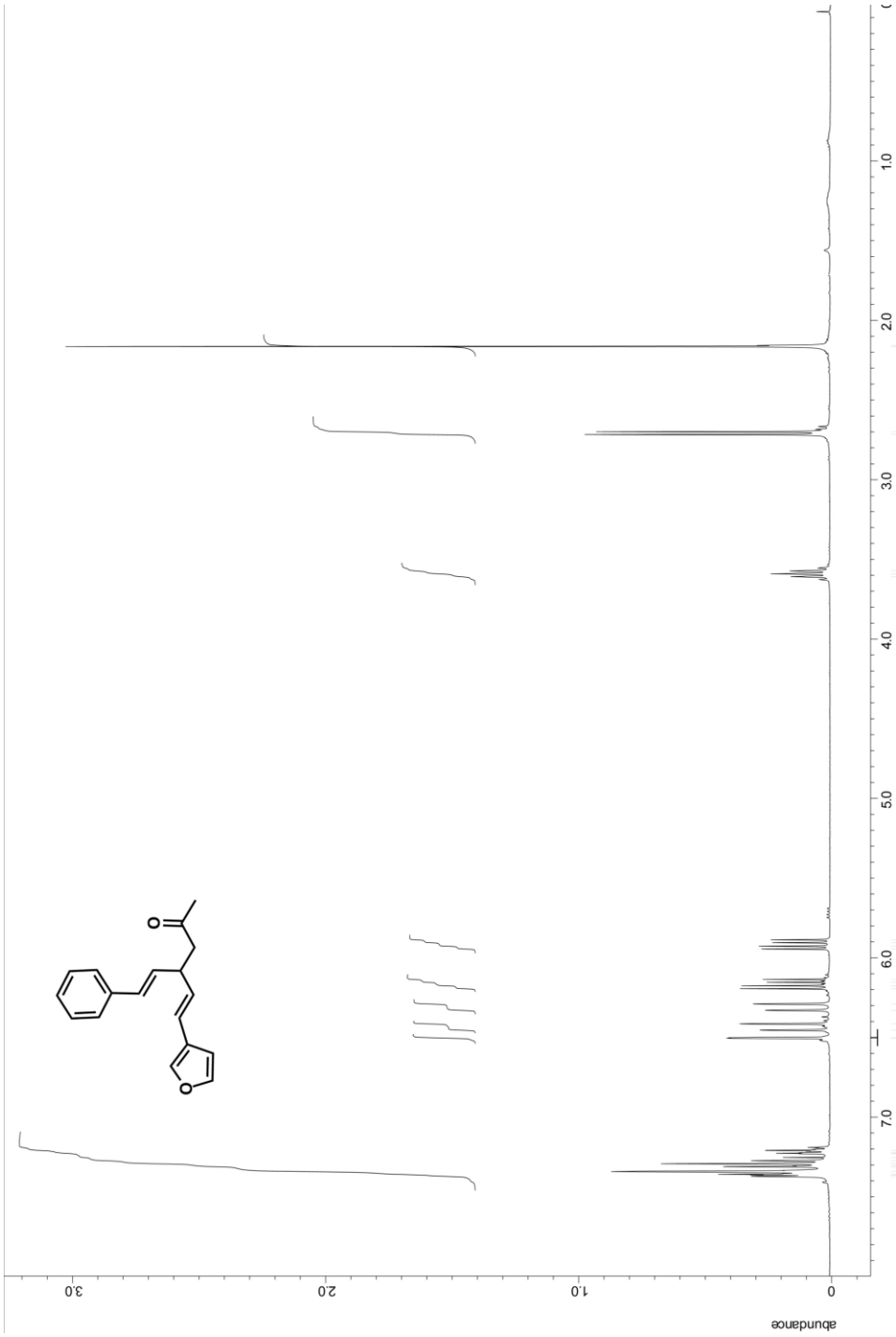


Figure A.1.32. ^{1}H NMR for compound **113**

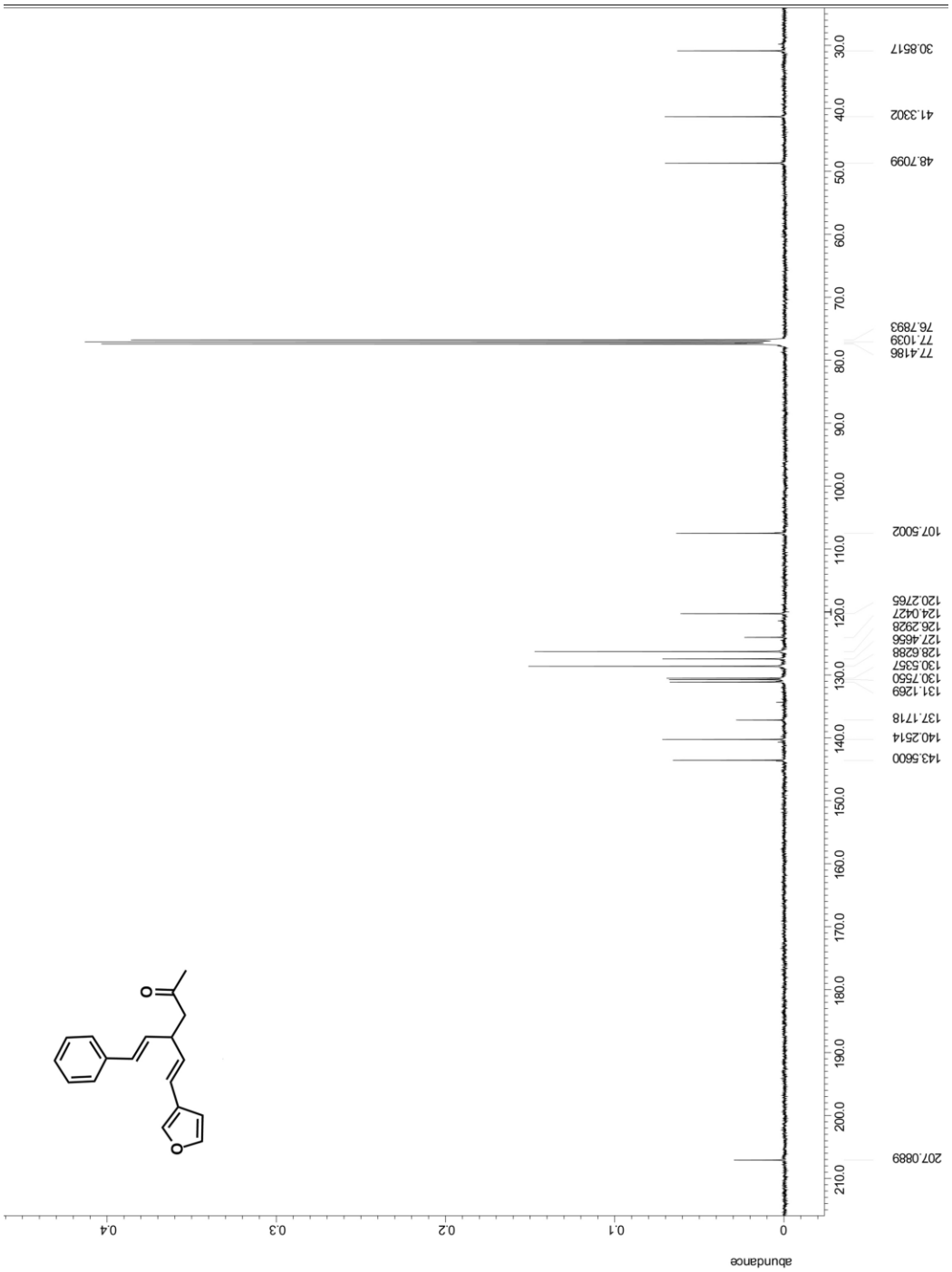
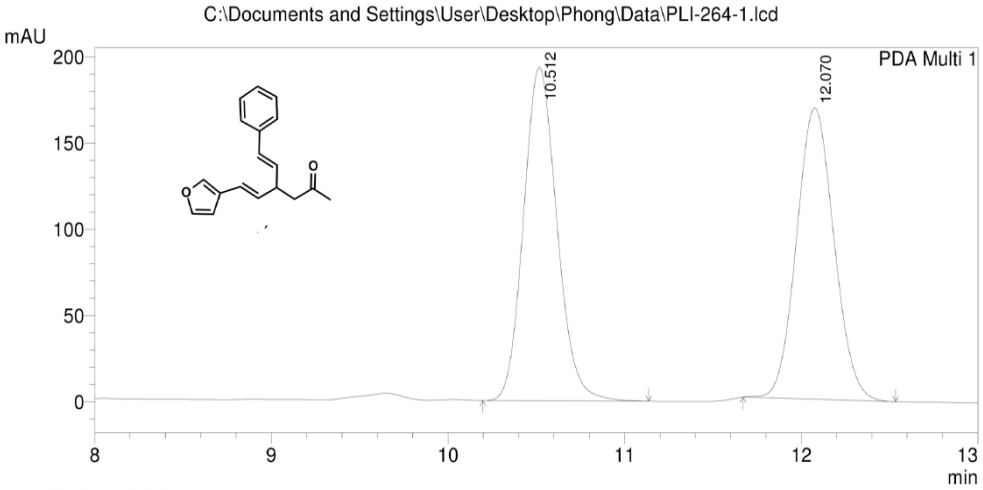


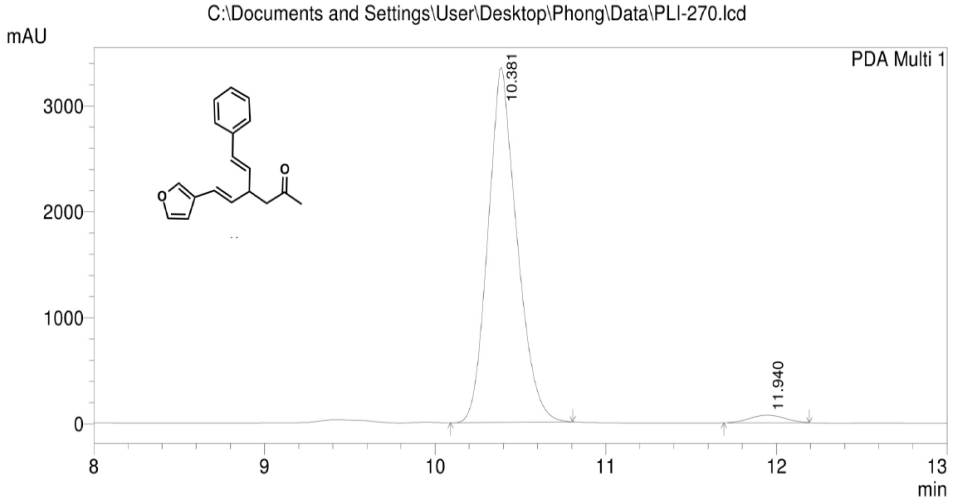
Figure A.1.33. ^{13}C NMR for compound **113**



PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.512	2543982	193595	50.508	53.381
2	12.070	2492857	169069	49.492	46.619
Total		5036839	362665	100.000	100.000



PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.381	39464596	3351167	97.489	97.870
2	11.940	1016274	72935	2.511	2.130
Total		40480871	3424103	100.000	100.000

Figure A.1.34. HPLC trace for compound **113**

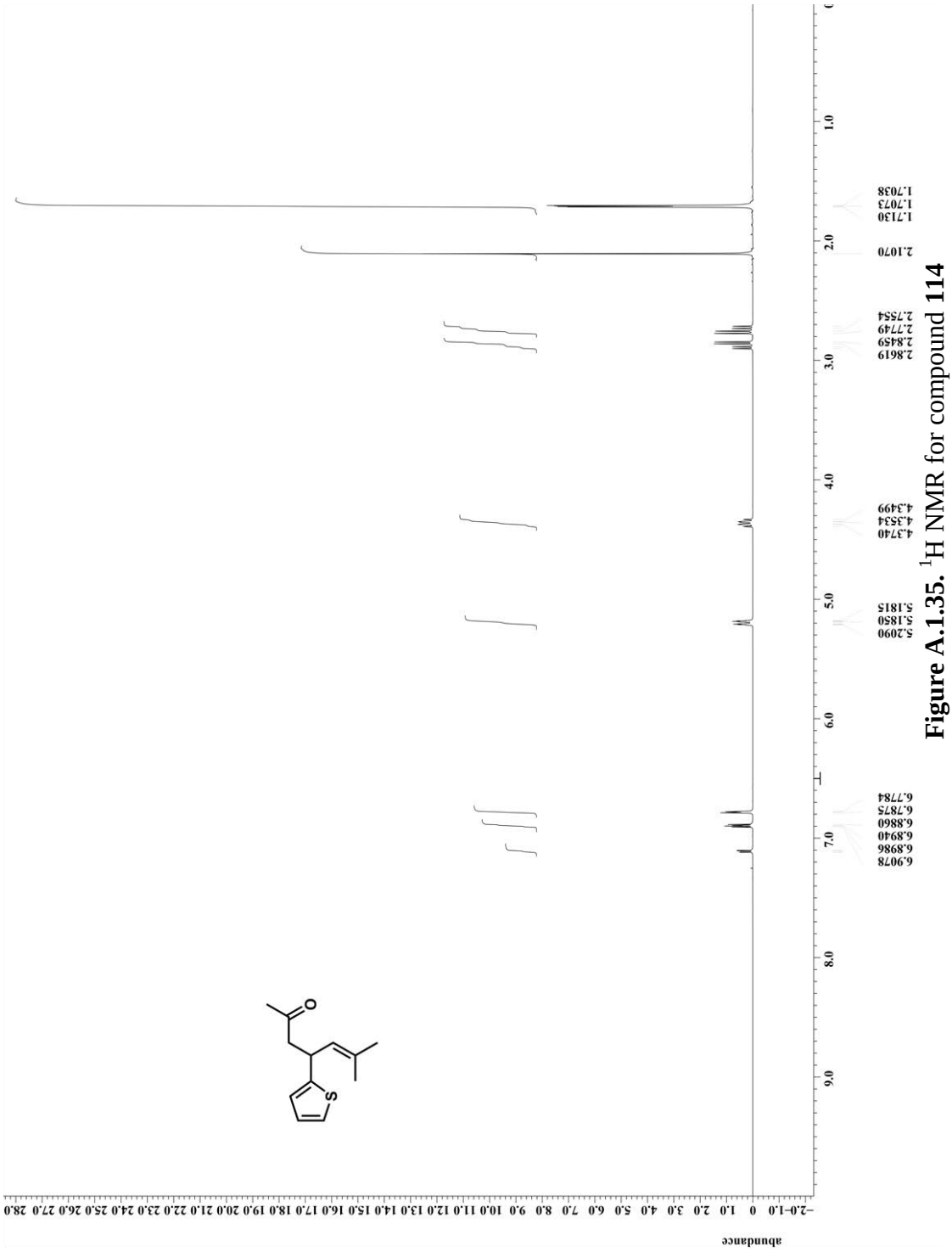


Figure A.1.35. ^{1}H NMR for compound **114**

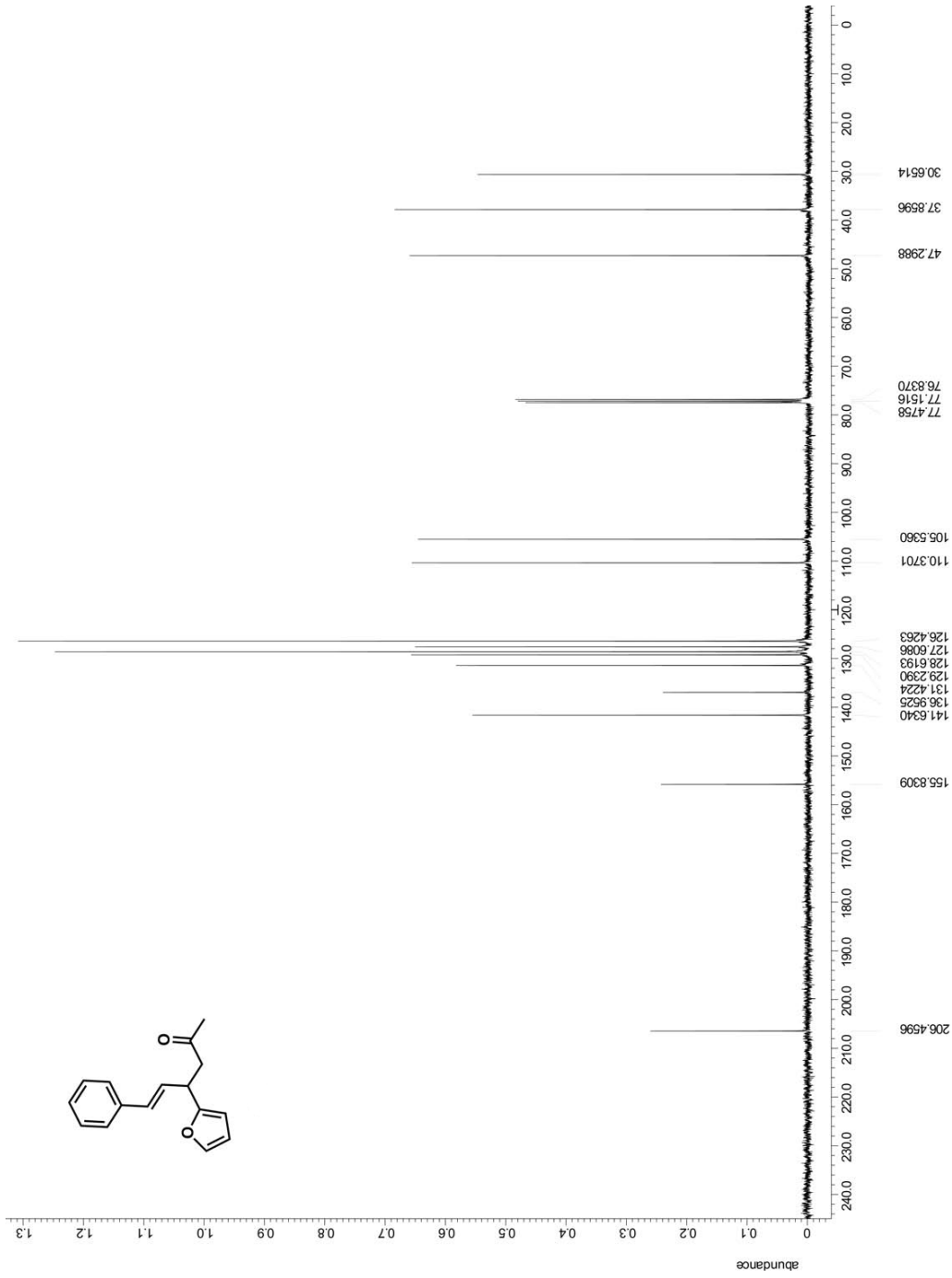
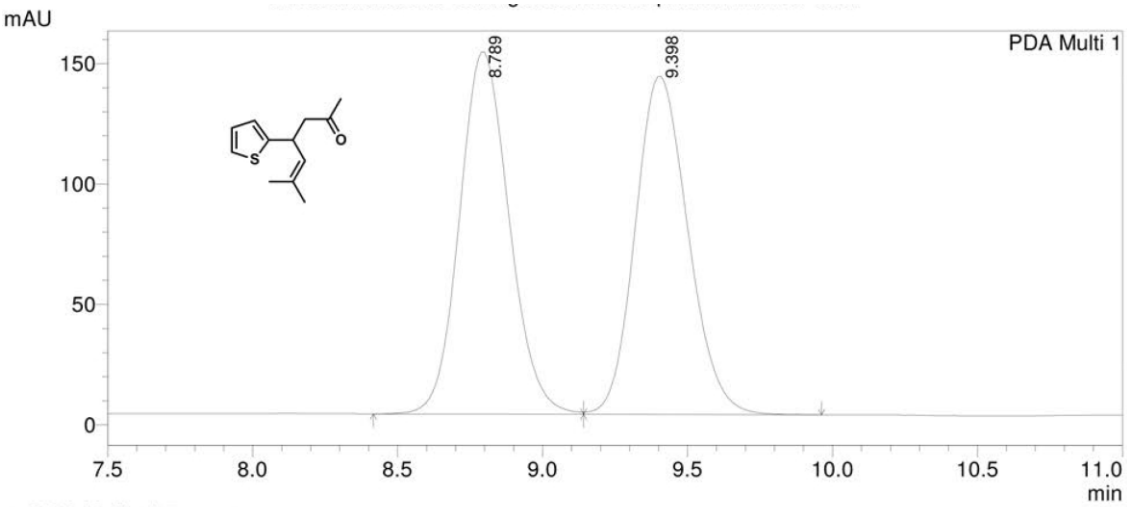


Figure A.1.36. ^{13}C NMR for compound **114**

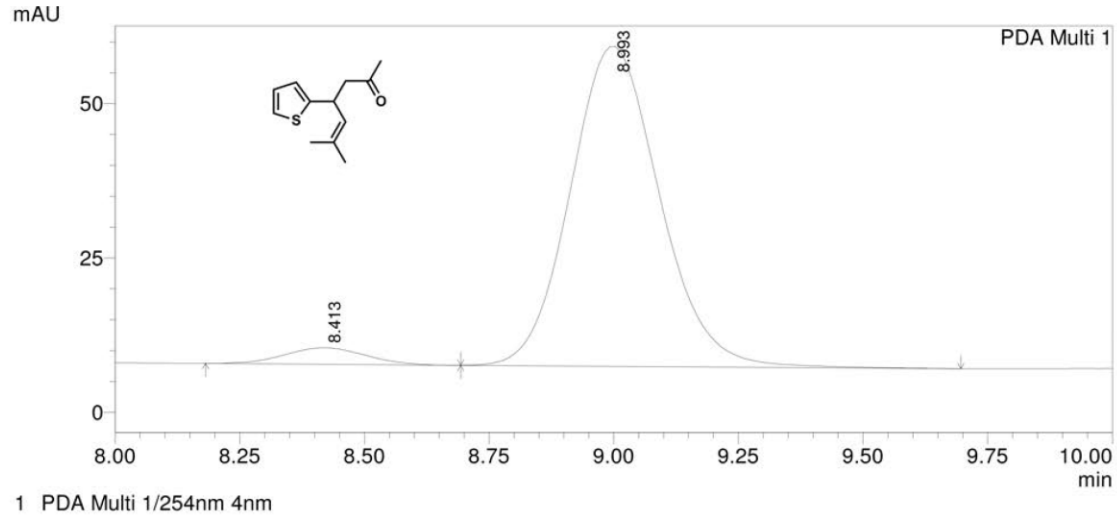


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.789	1792053	150475	50.236	51.720
2	9.398	1775195	140465	49.764	48.280
Total		3567248	290940	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.413	29748	2653	4.400	4.871
2	8.993	646319	51824	95.600	95.129
Total		676066	54478	100.000	100.000

Figure A.1.37. HPLC trace for compound **114**

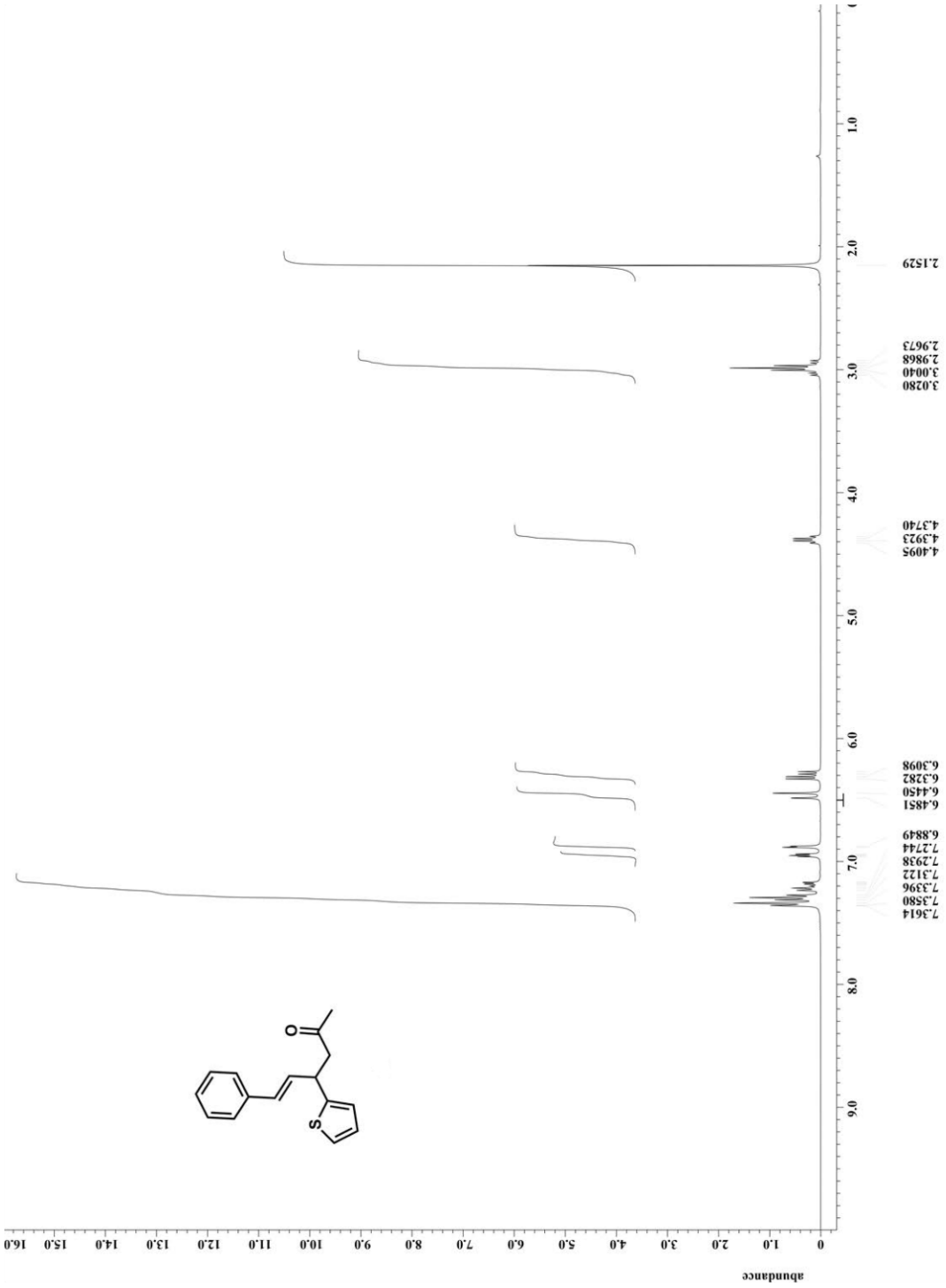


Figure A.1.38. ^{1}H NMR for compound **116**

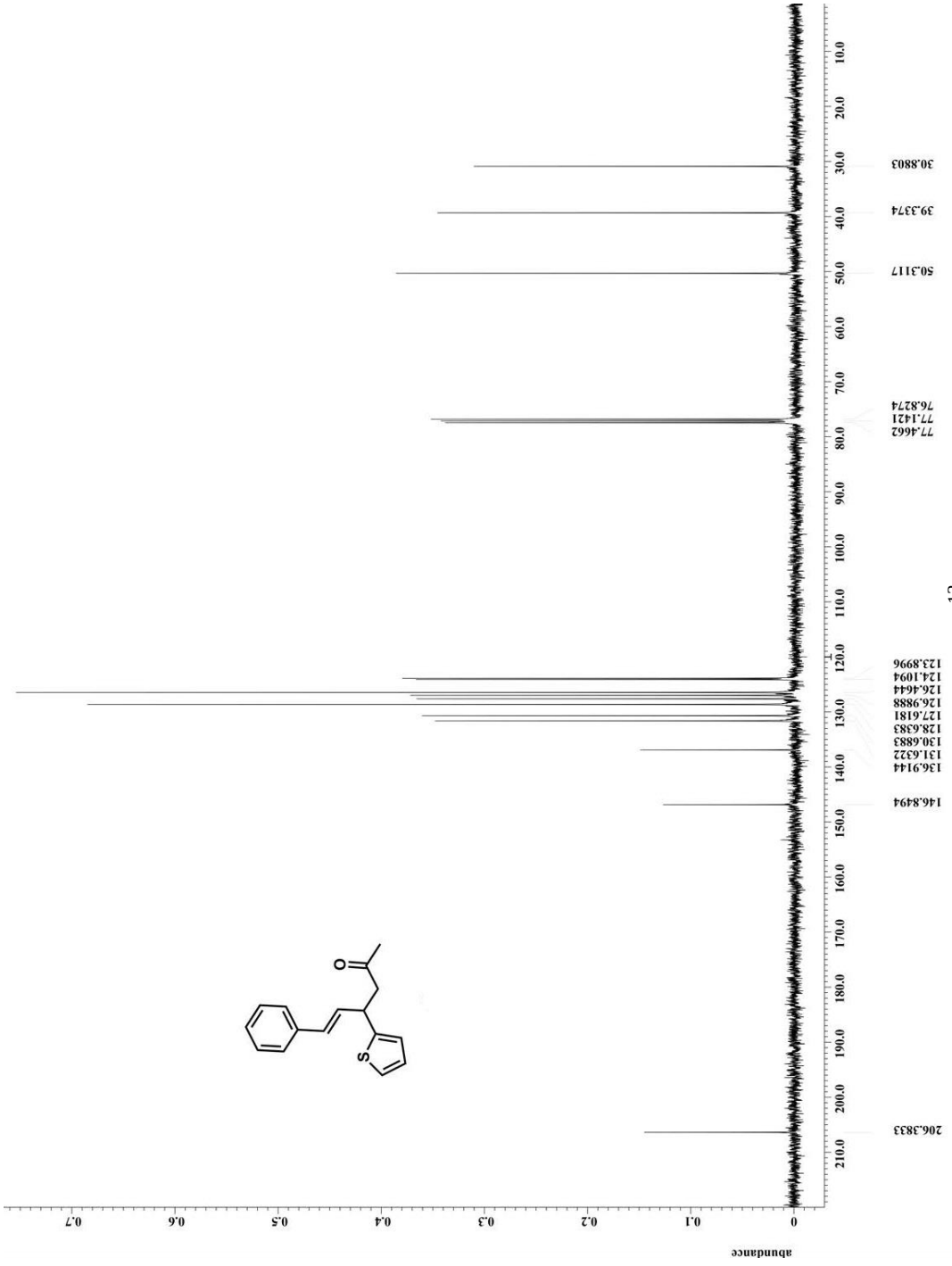
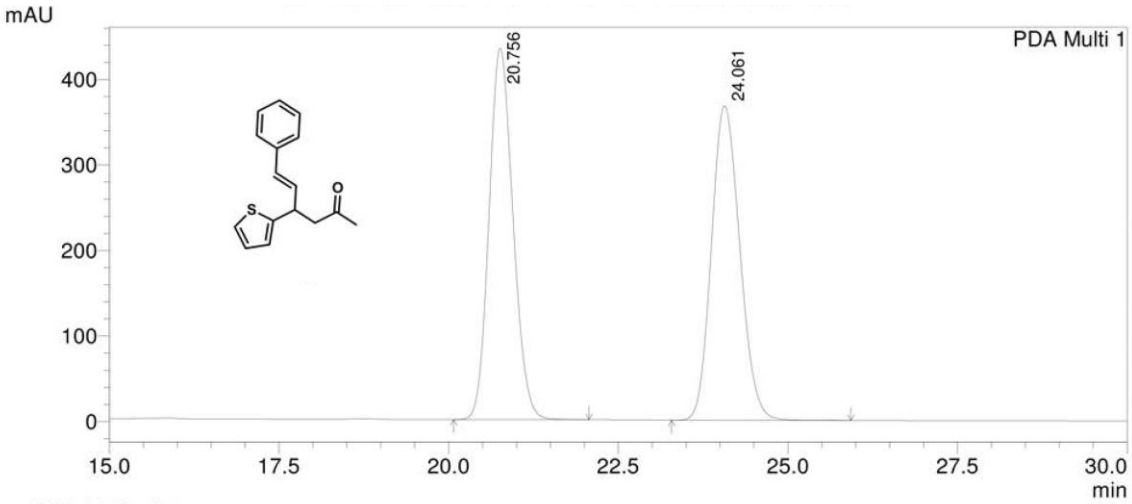


Figure A.1.39. ^{13}C NMR for compound **116**

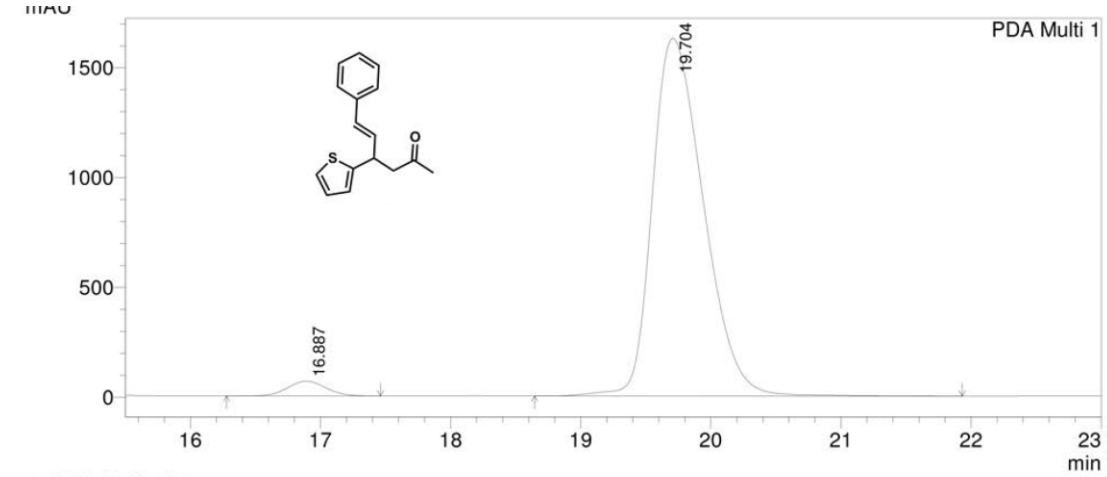


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.756	10669071	434446	49.946	54.160
2	24.061	10692160	367704	50.054	45.840
Total		21361231	802151	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.887	1376592	67452	2.996	3.975
2	19.704	44566510	1629240	97.004	96.025
Total		45943102	1696692	100.000	100.000

Figure A.1.40. HPLC trace for compound **116**

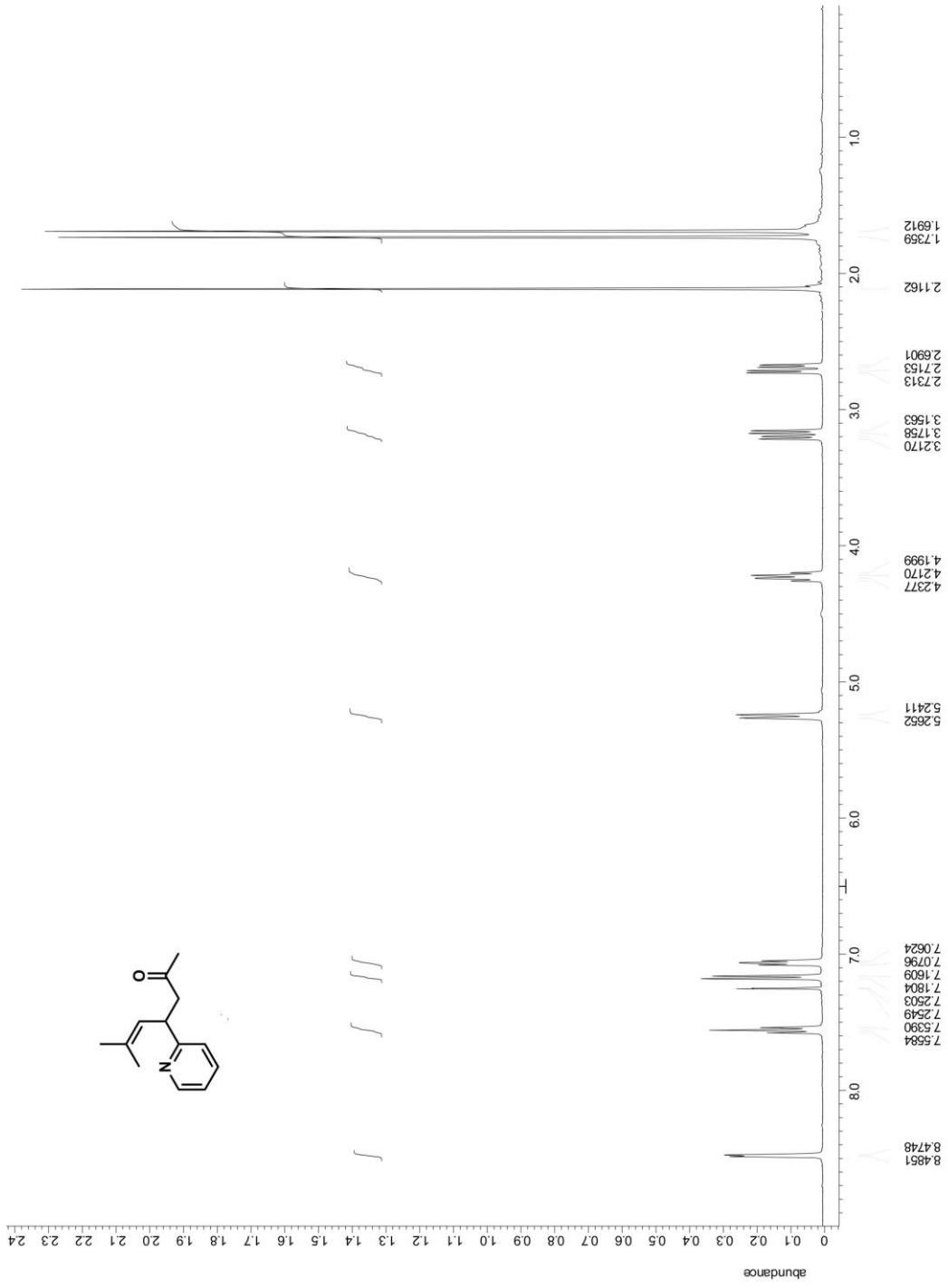


Figure A.1.41. ^{1}H NMR for compound **122**

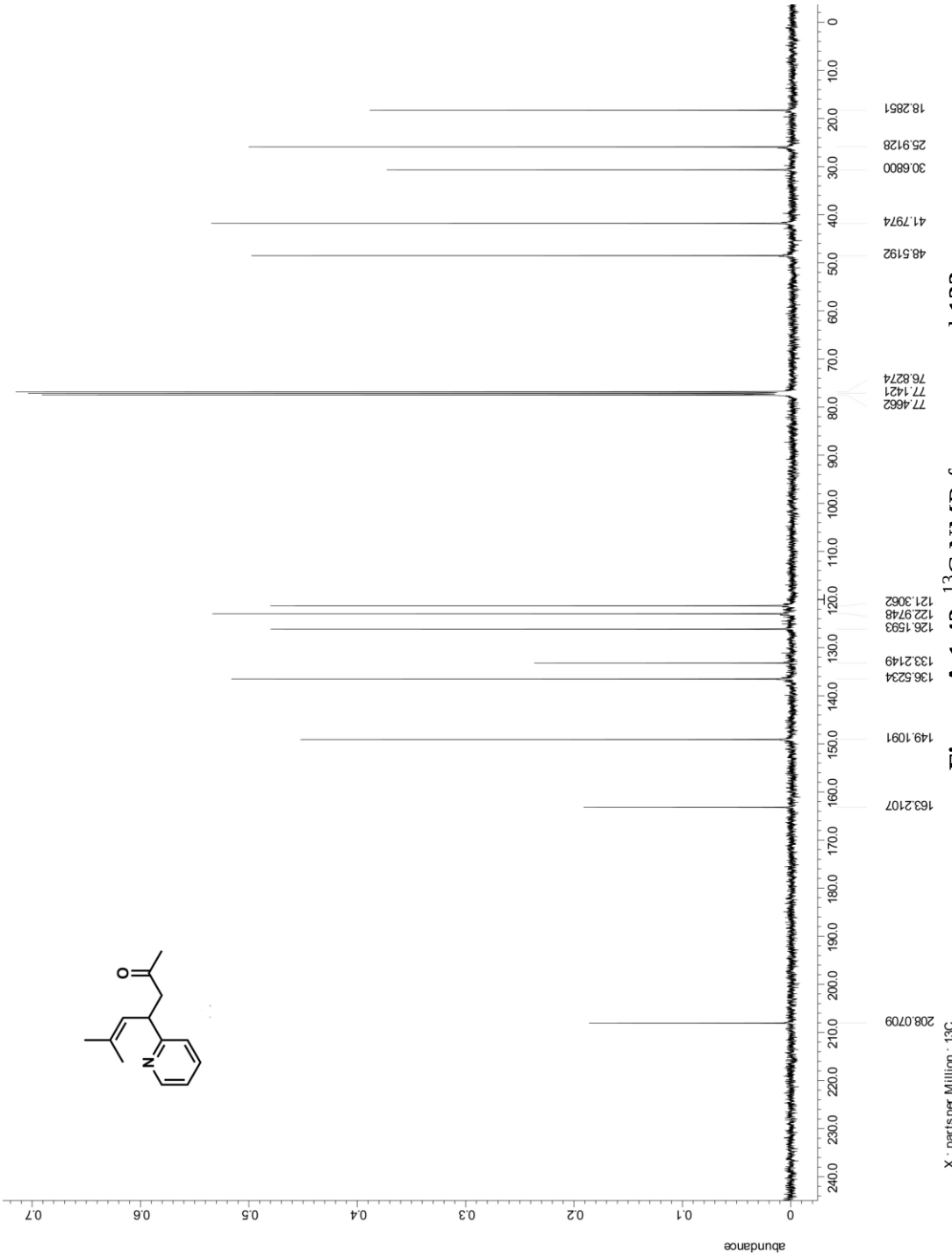
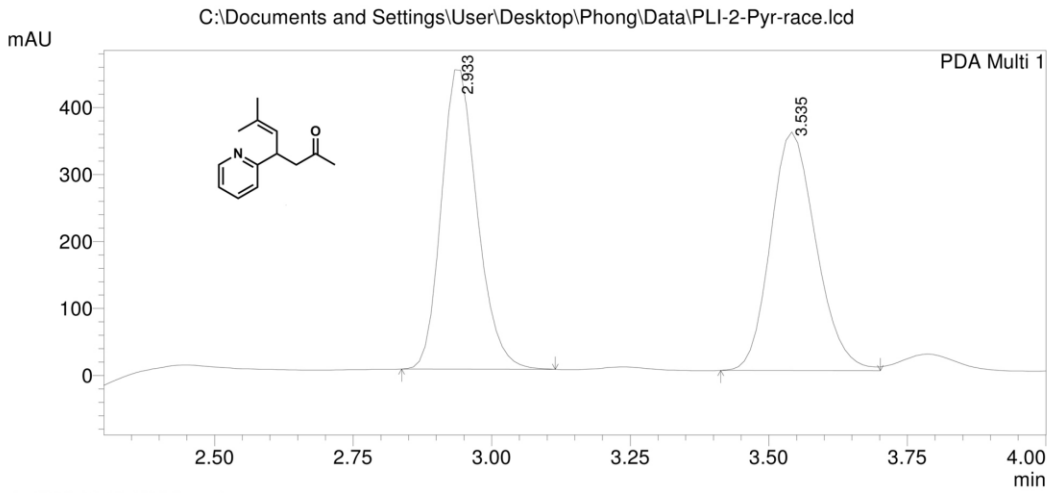


Figure A.1.42. ^{13}C NMR for compound **122**

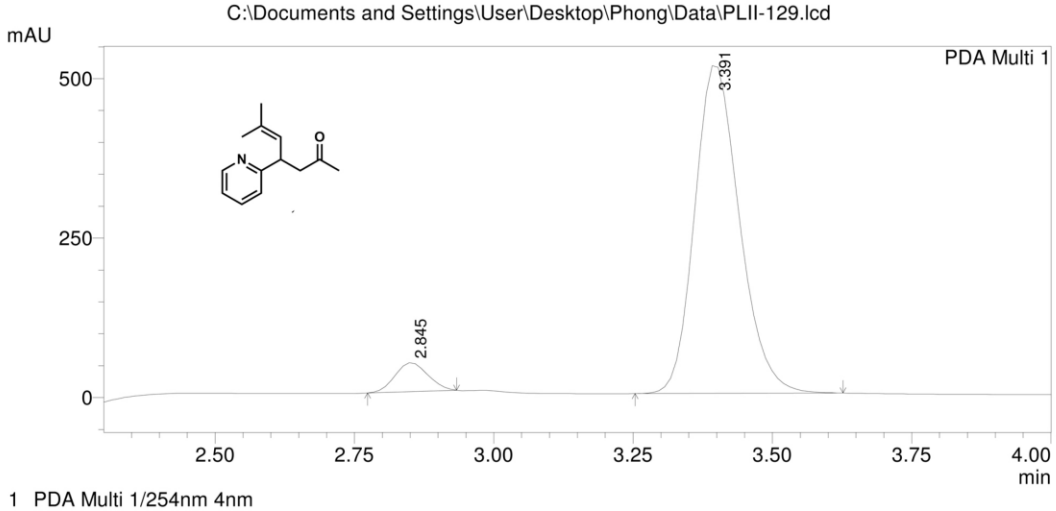


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.933	2022257	447091	49.855	55.675
2	3.535	2034011	355949	50.145	44.325
Total		4056268	803041	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.845	188720	45688	6.132	8.168
2	3.391	2889147	513637	93.868	91.832
Total		3077867	559325	100.000	100.000

Figure A.1.43. HPLC trace for compound **122**

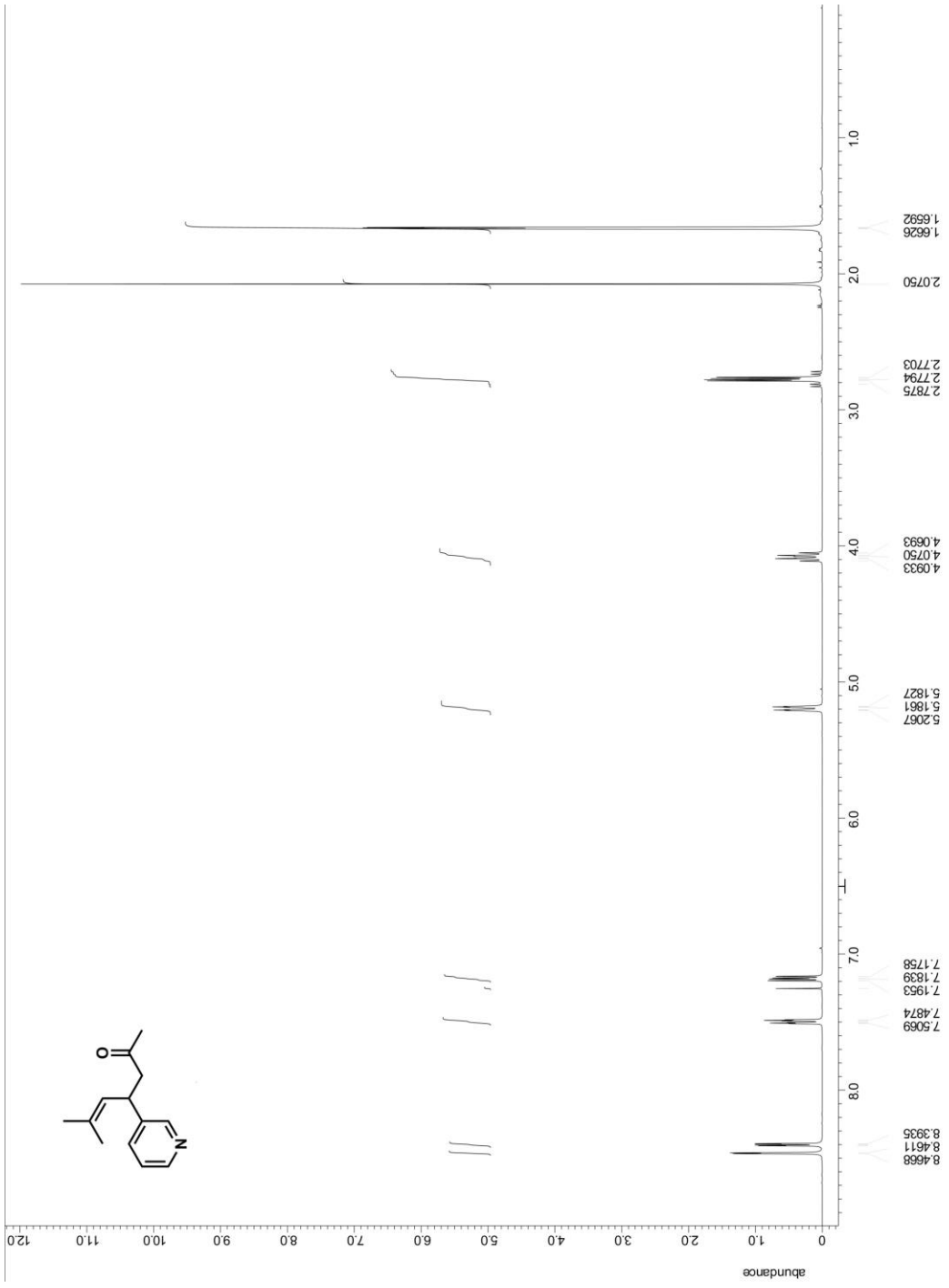


Figure A.1.44. ^{1}H NMR for compound **123**

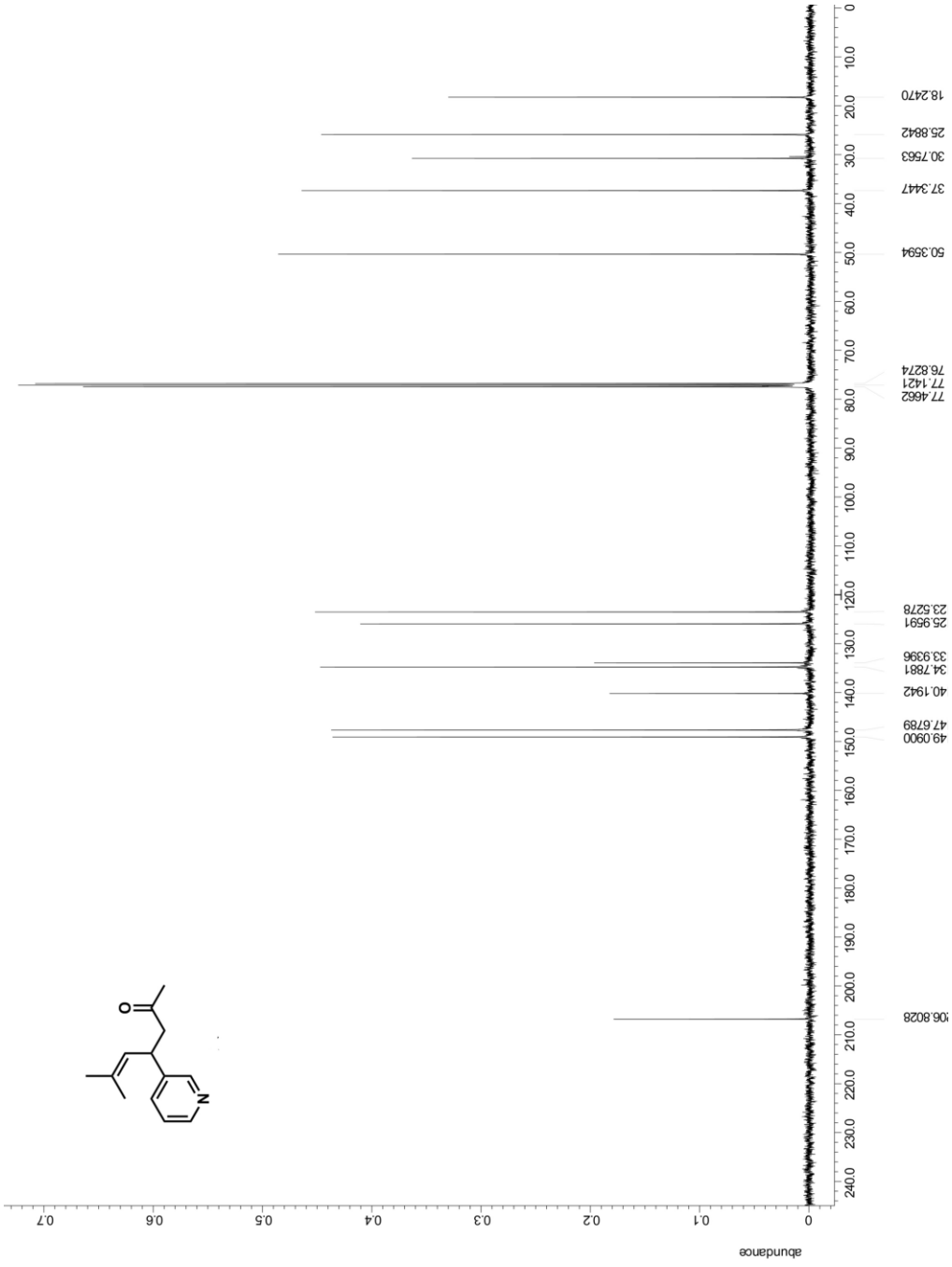
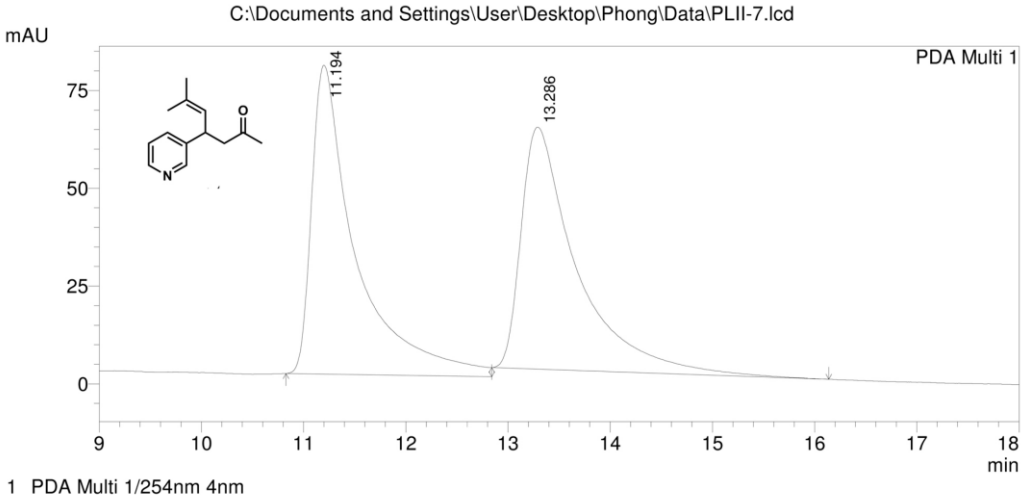


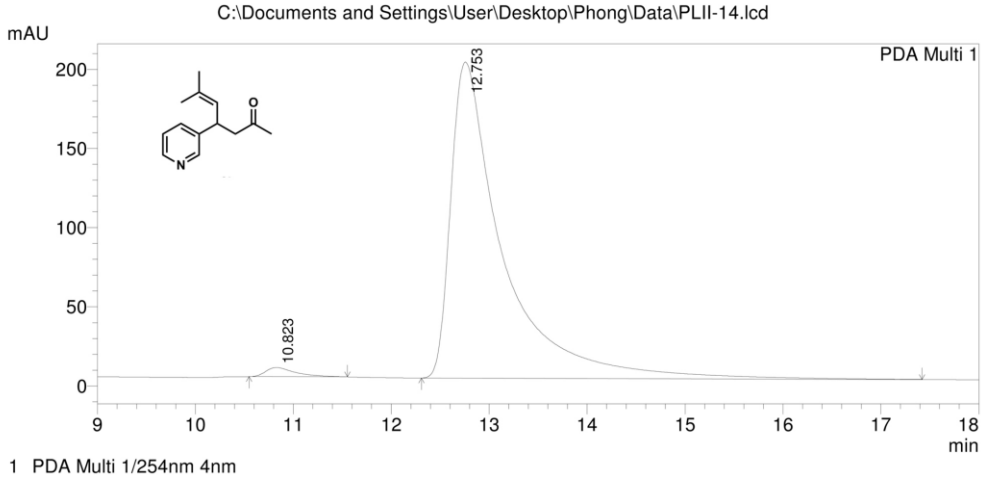
Figure A.1.45. ^{13}C NMR for compound **123**



PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.194	2349716	78928	50.241	56.079
2	13.286	2327219	61818	49.759	43.921
Total		4676935	140746	100.000	100.000



PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.823	123044	5831	1.639	2.838
2	12.753	7386276	199657	98.361	97.162
Total		7509319	205487	100.000	100.000

Figure A.1.46. HPLC trace for compound **123**

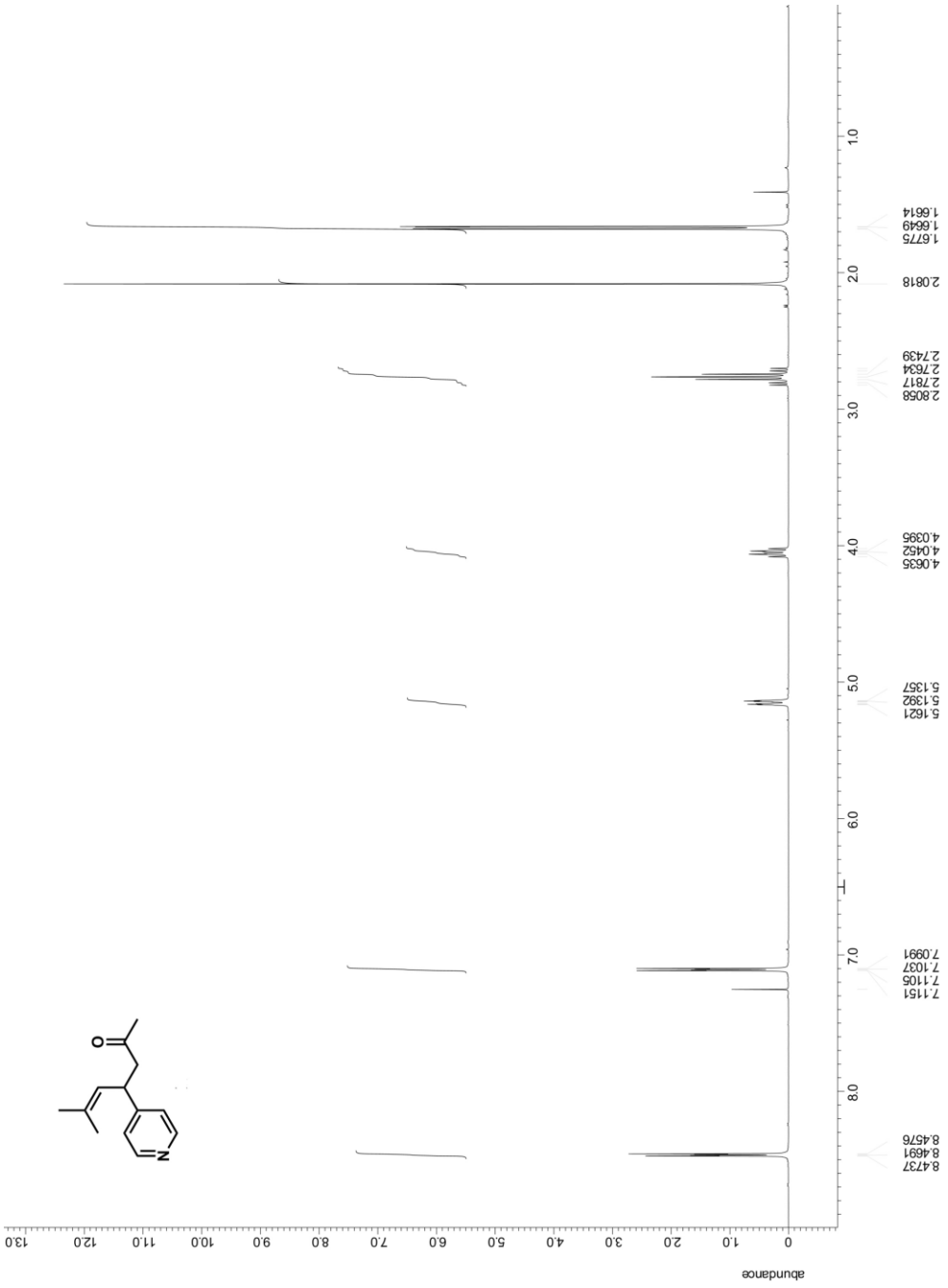


Figure A.1.47. ^{1}H NMR for compound **124**

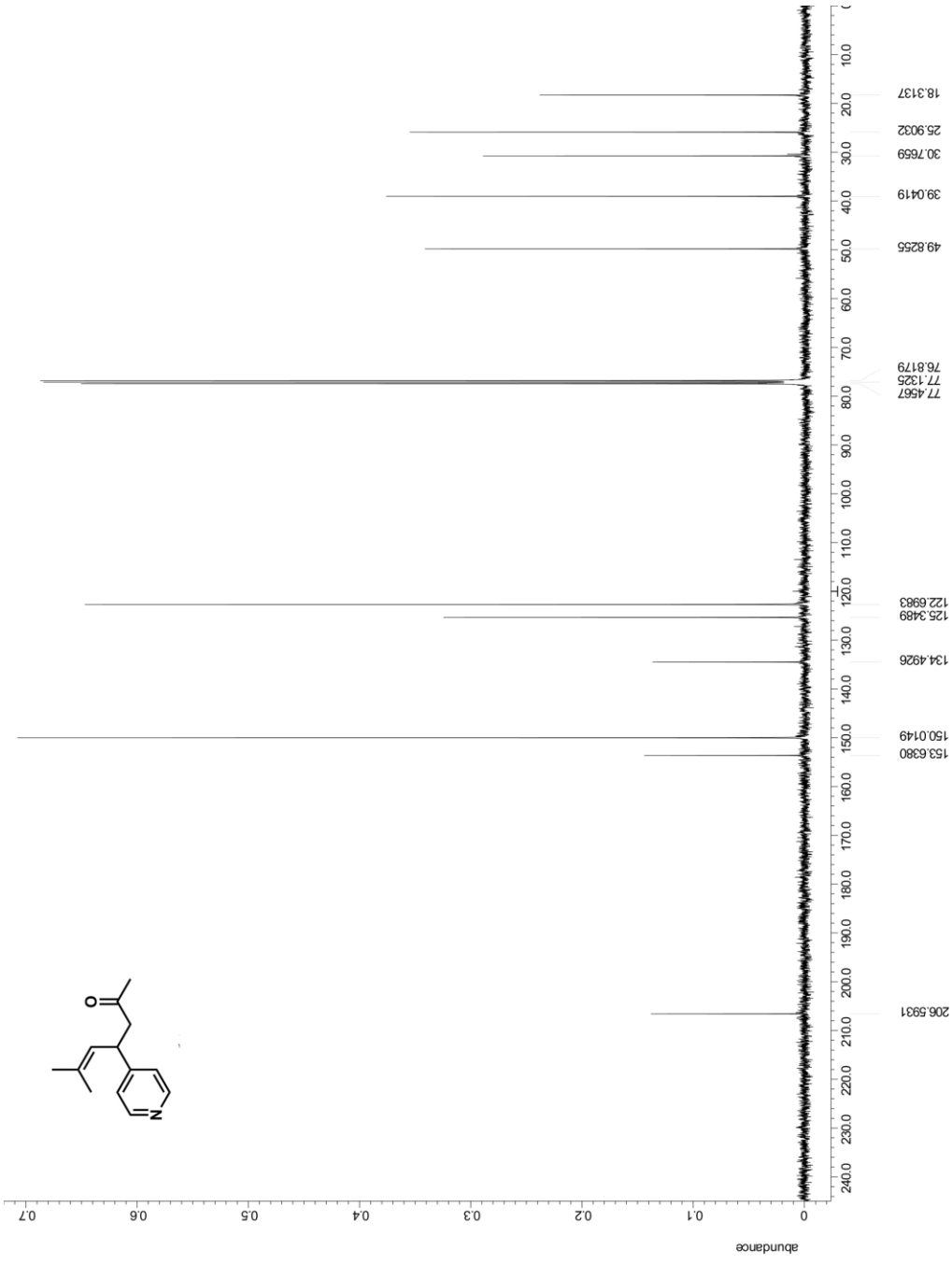
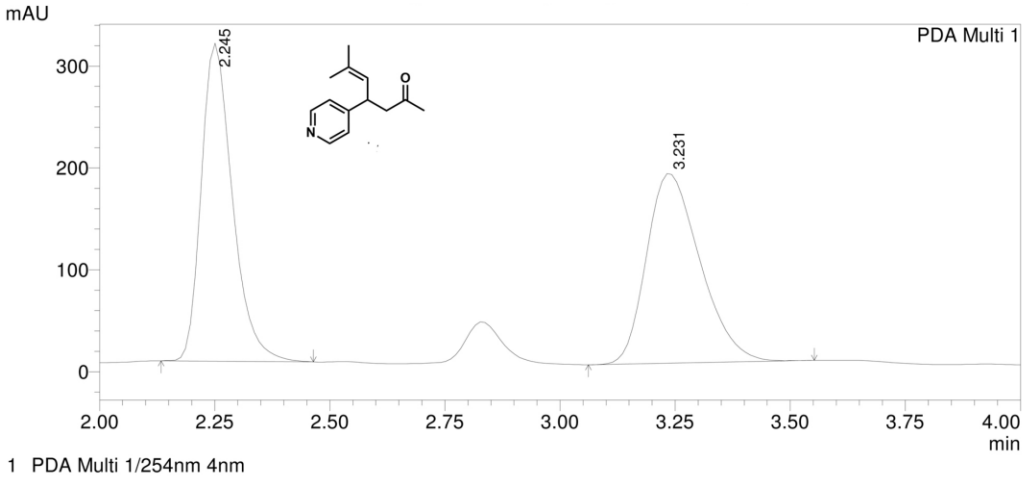


Figure A.1.48. ^{13}C NMR for compound **124**

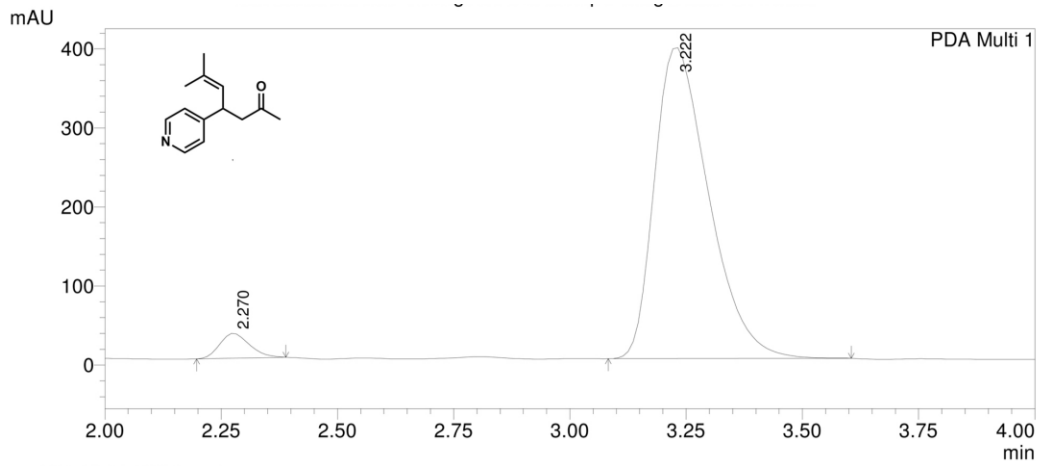


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.245	1471231	312075	49.401	62.653
2	3.231	1506900	186028	50.599	37.347
Total		2978131	498103	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.270	140357	31342	4.209	7.382
2	3.222	3194561	393231	95.791	92.618
Total		3334918	424573	100.000	100.000

Figure A.1.49. HPLC trace for compound **124**

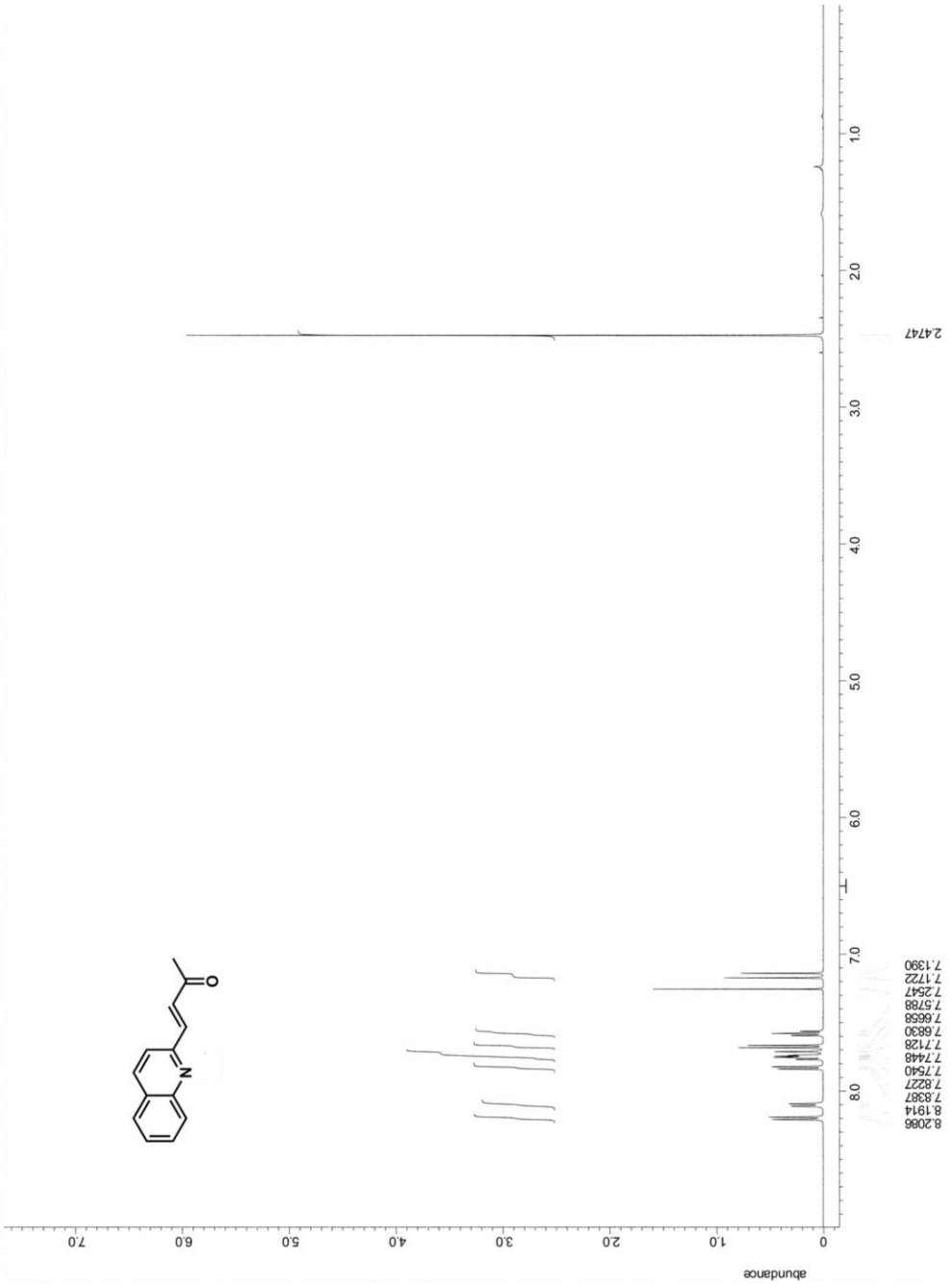


Figure A.1.50. ^{1}H NMR for precursor to compound **125**

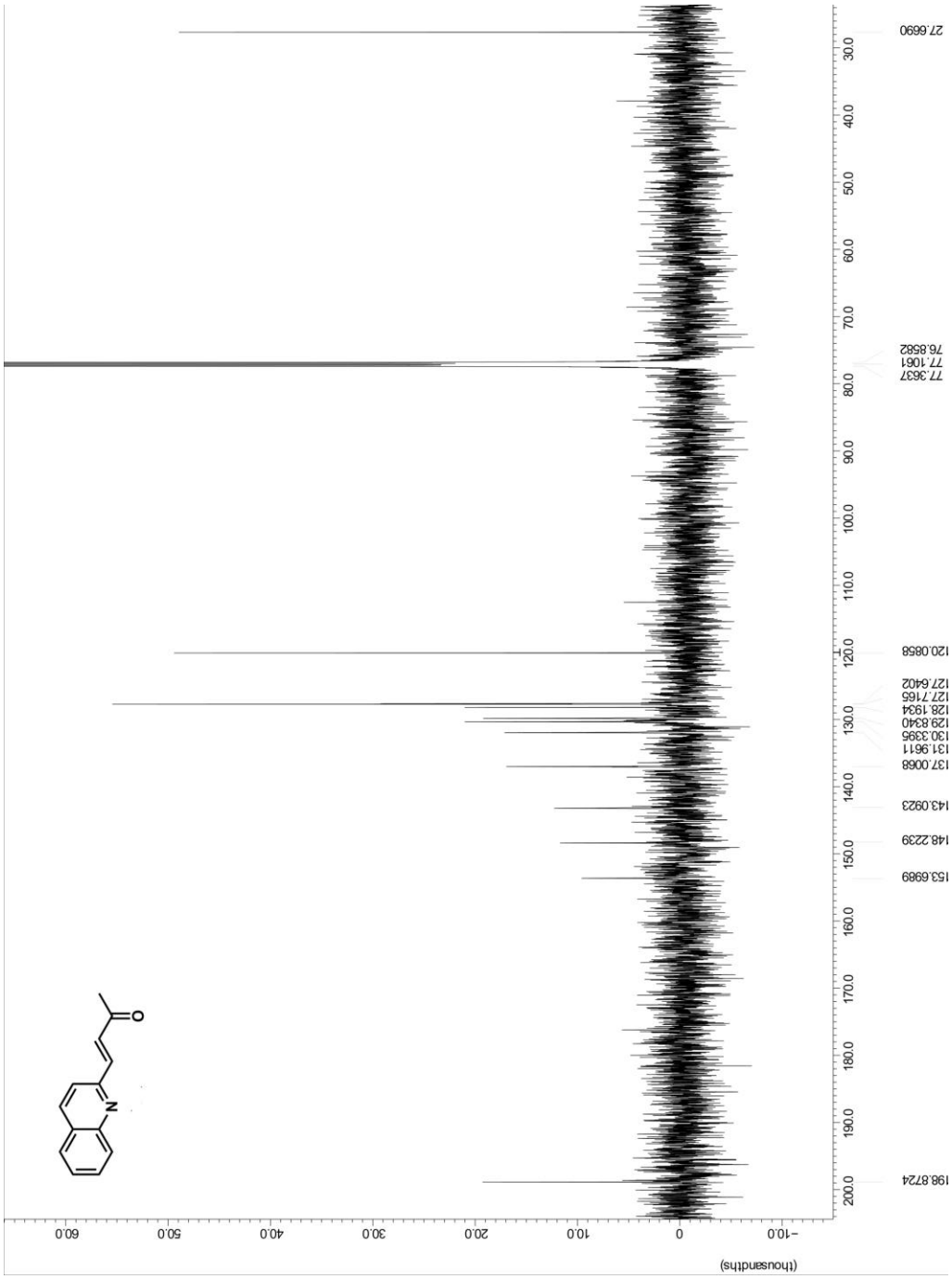


Figure A.1.51. ^{13}C NMR for precursor to compound **125**

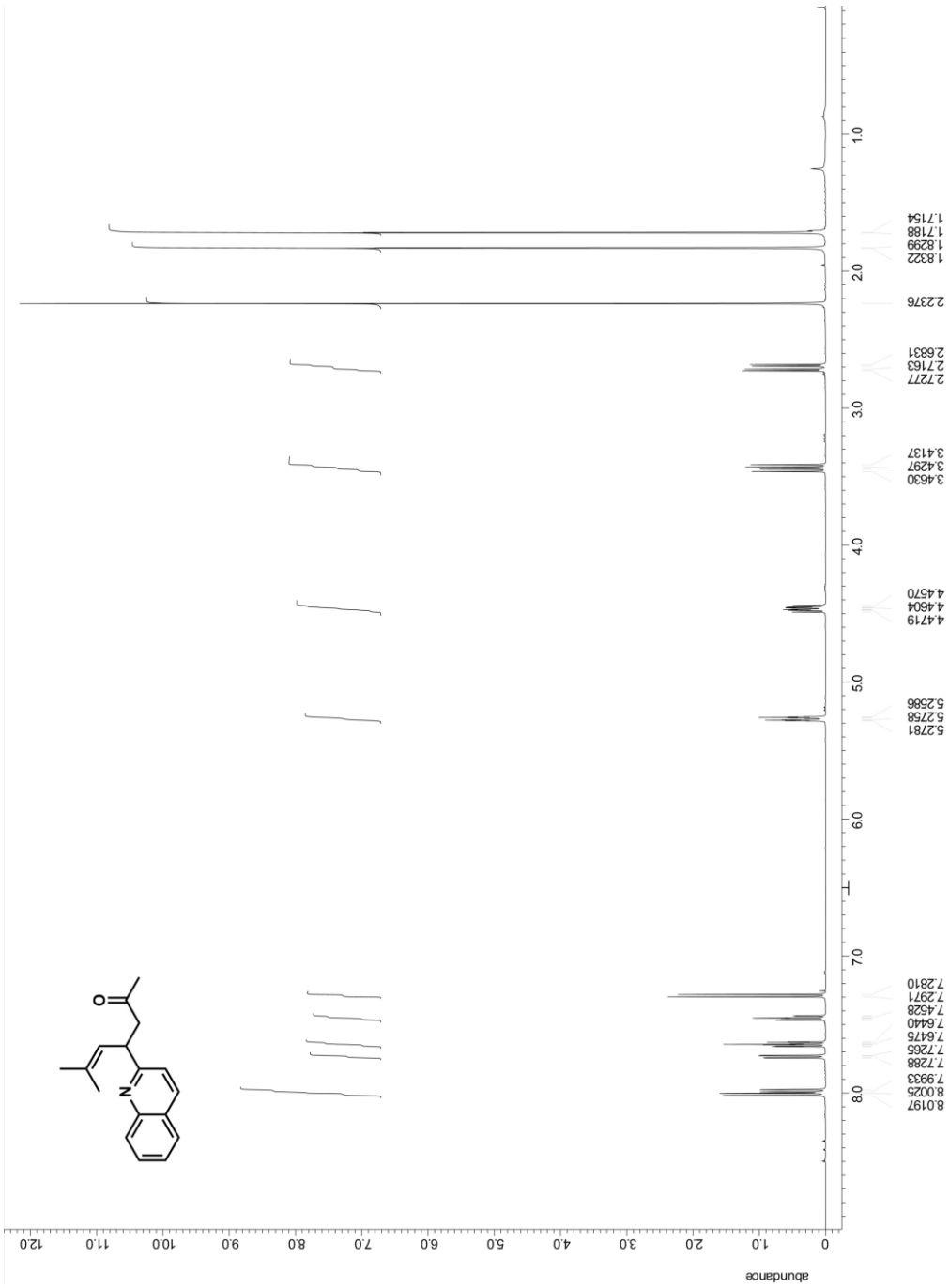


Figure A.1.52. ^{1}H NMR for compound **125**

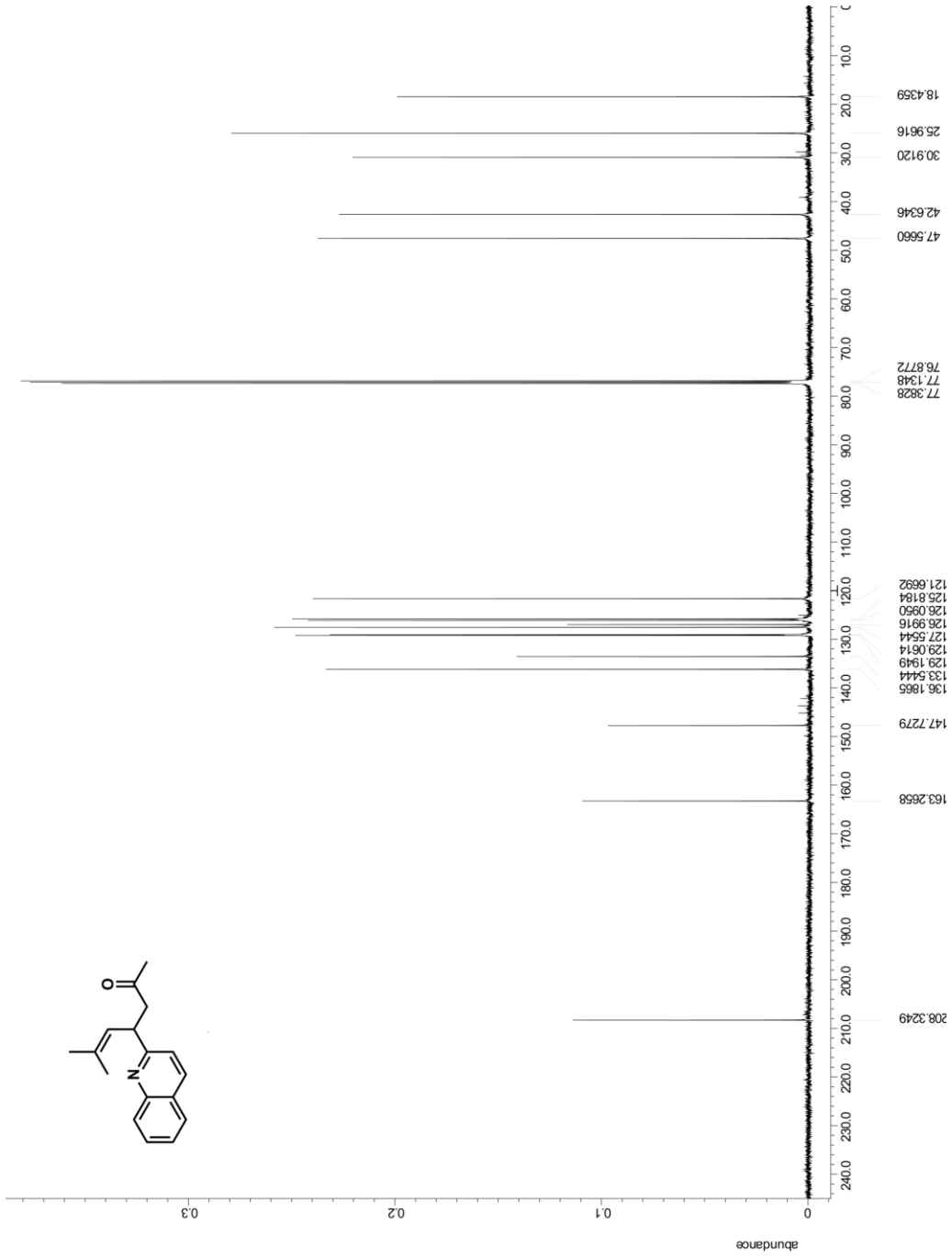
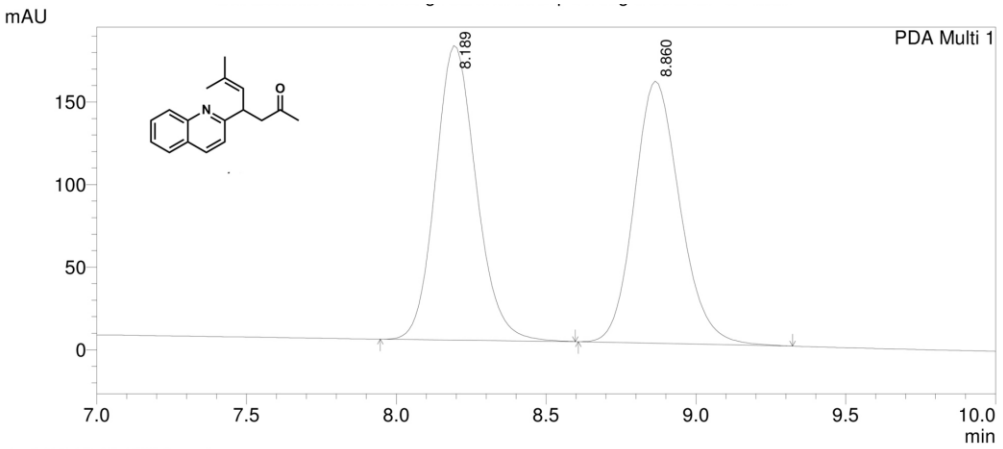


Figure A.1.53. ^{13}C NMR for compound **125**

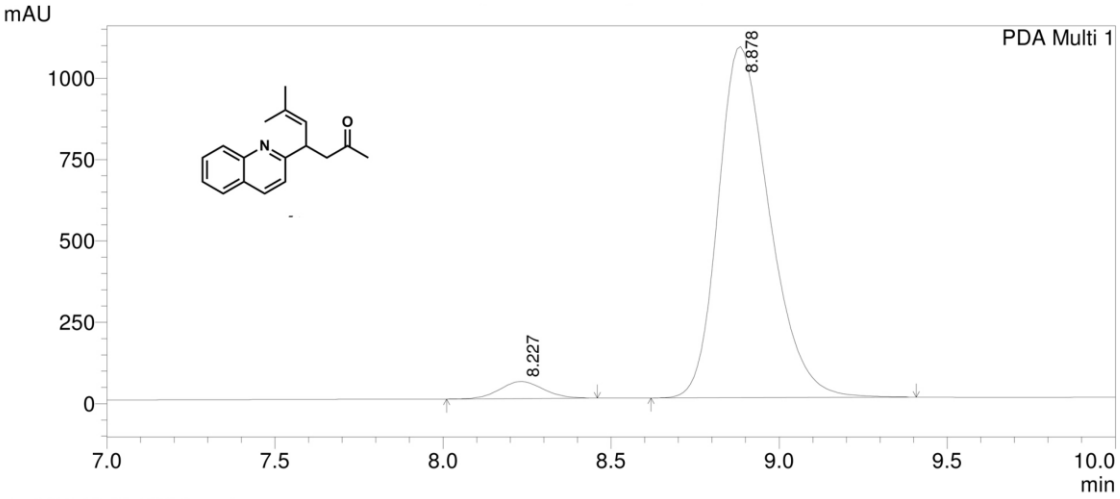


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.189	1688952	178304	50.045	52.915
2	8.860	1685933	158656	49.955	47.085
Total		3374885	336959	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.227	472476	52538	3.964	4.644
2	8.878	11448049	1078880	96.036	95.356
Total		11920525	1131418	100.000	100.000

Figure A.1.54. HPLC trace for compound **125**

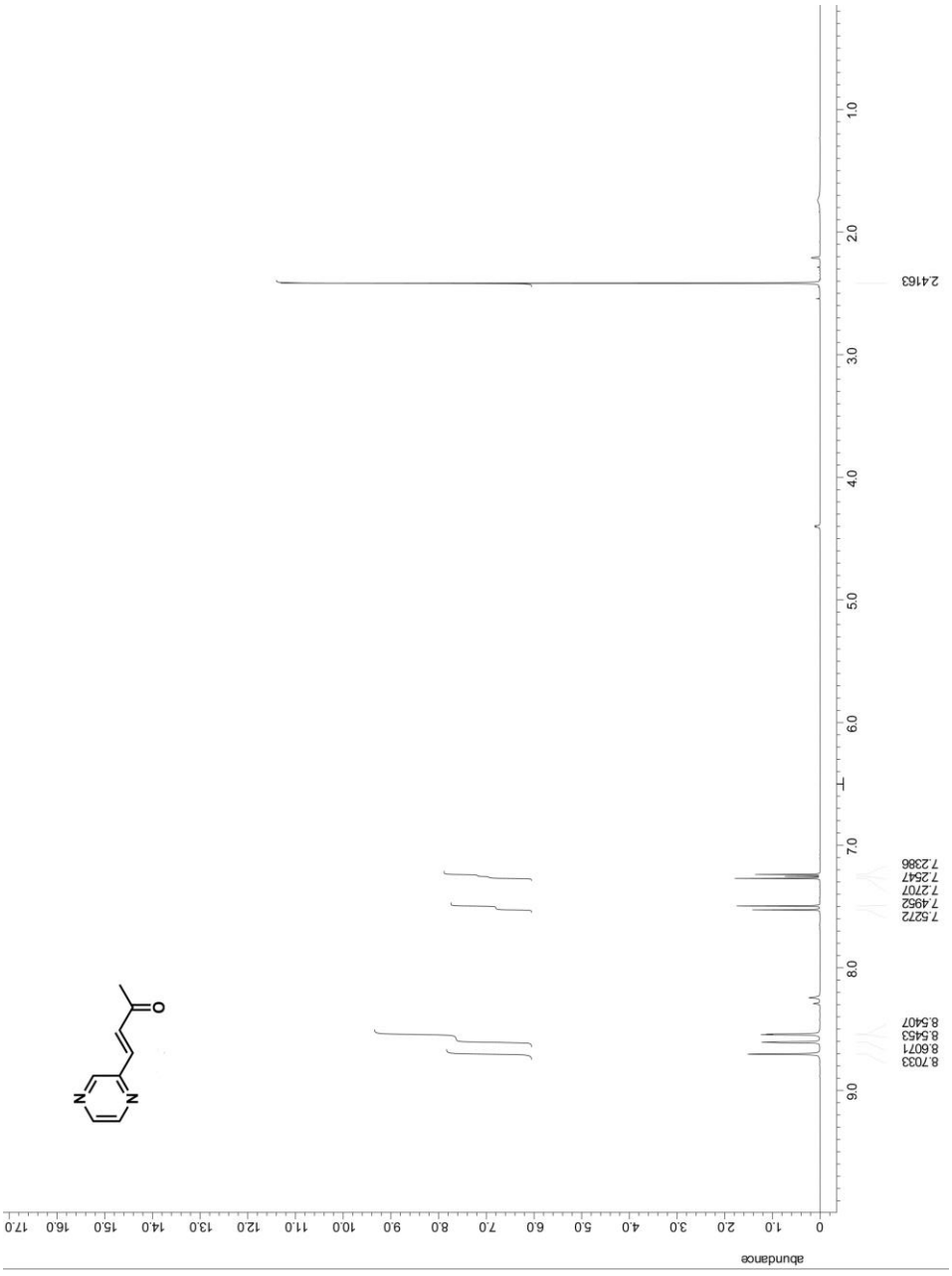


Figure A.1.55. ^{1}H NMR for precursor to compound **126**

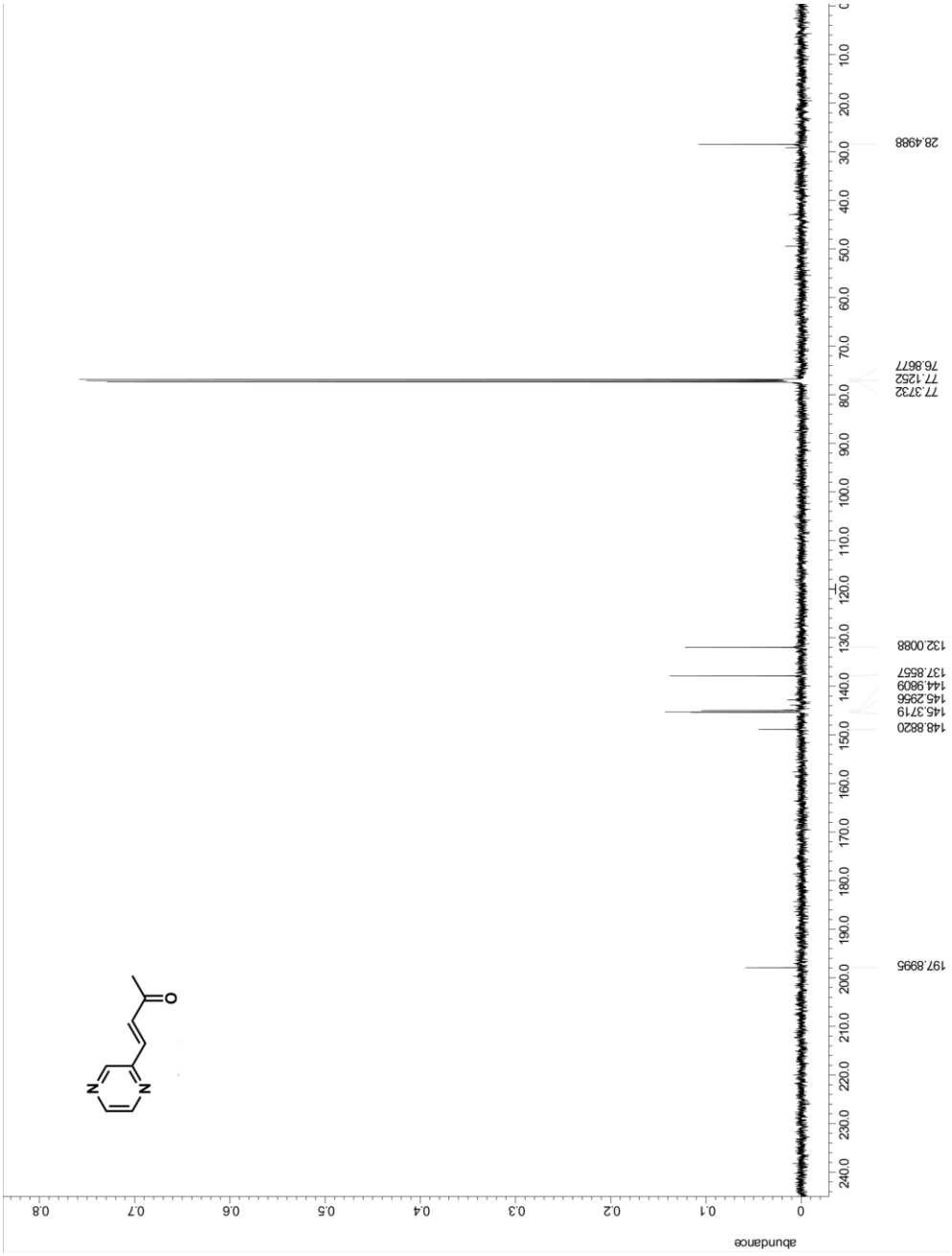


Figure A.1.56. ^{13}C NMR for precursor to compound **126**

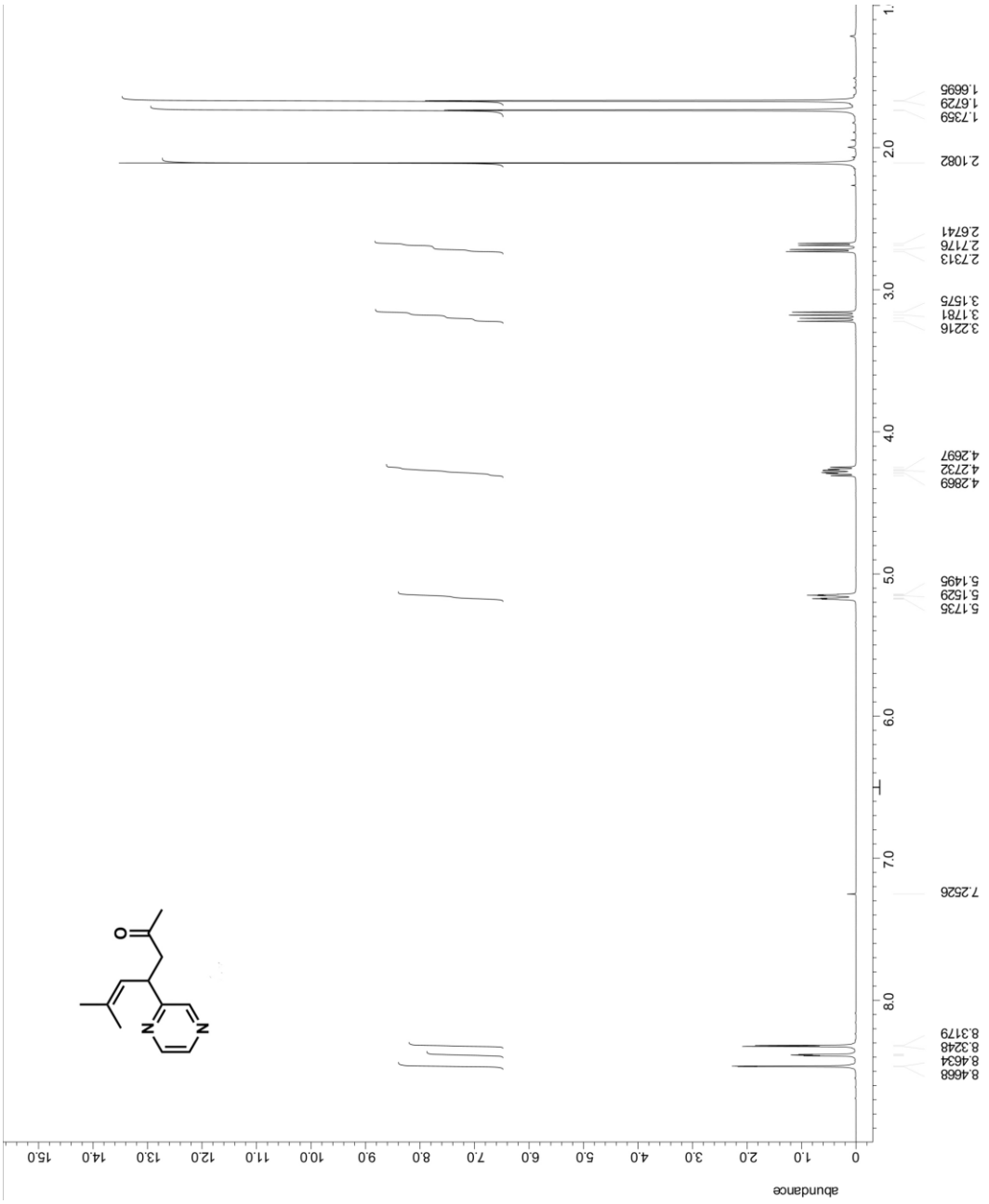


Figure A.1.57. ^{1}H NMR for compound **126**

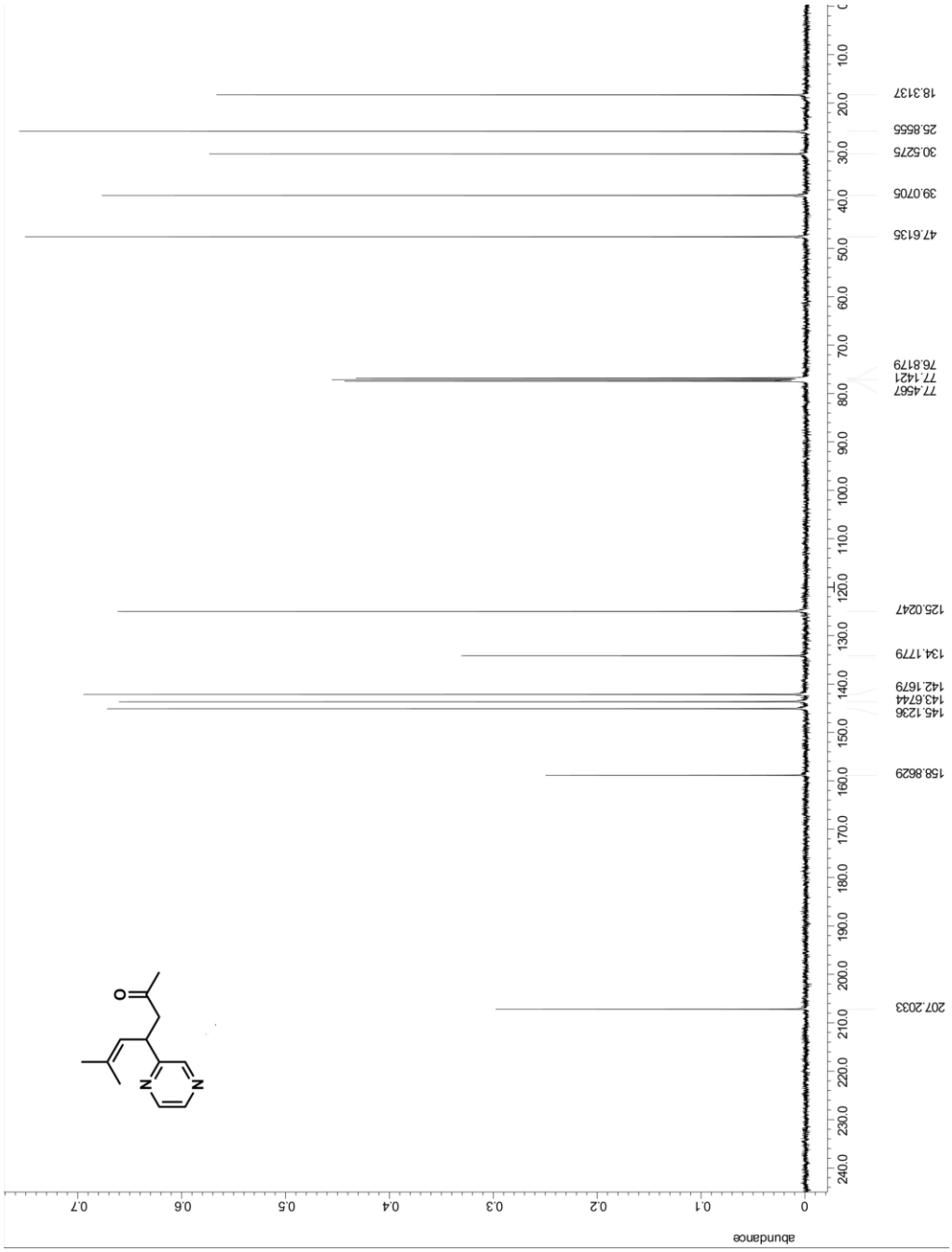
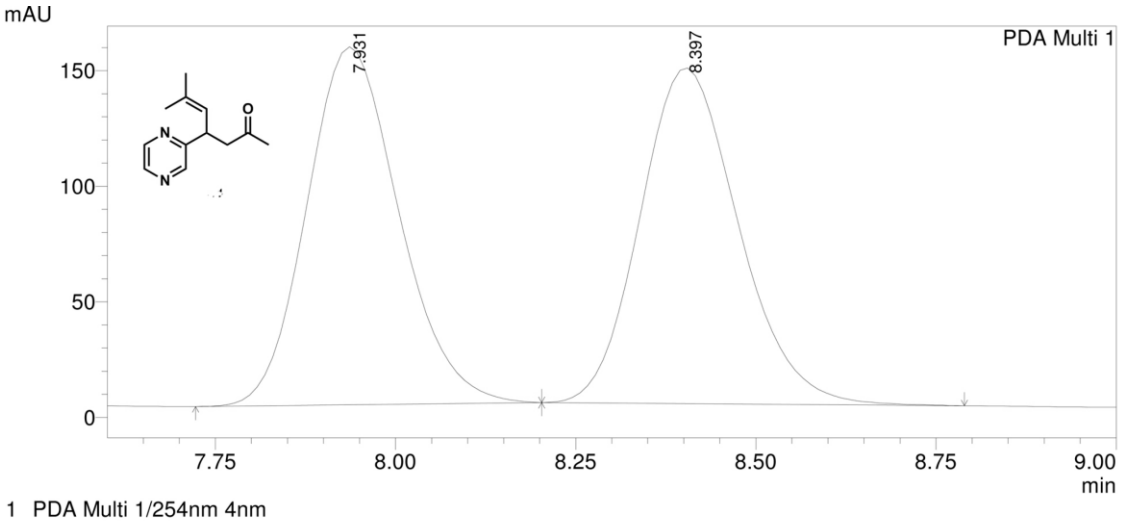


Figure A.1.58. ^{13}C NMR for compound **126**

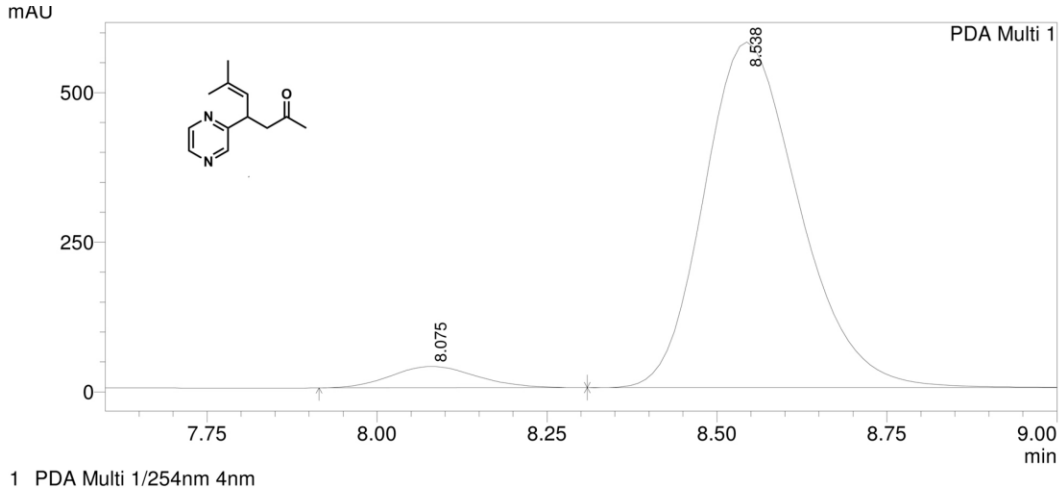


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.931	1376121	154841	50.010	51.622
2	8.397	1375565	145113	49.990	48.378
Total		2751686	299954	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.075	313935	35725	5.271	5.827
2	8.538	5641998	577402	94.729	94.173
Total		5955932	613127	100.000	100.000

Figure A.1.59. HPLC trace for compound **126**

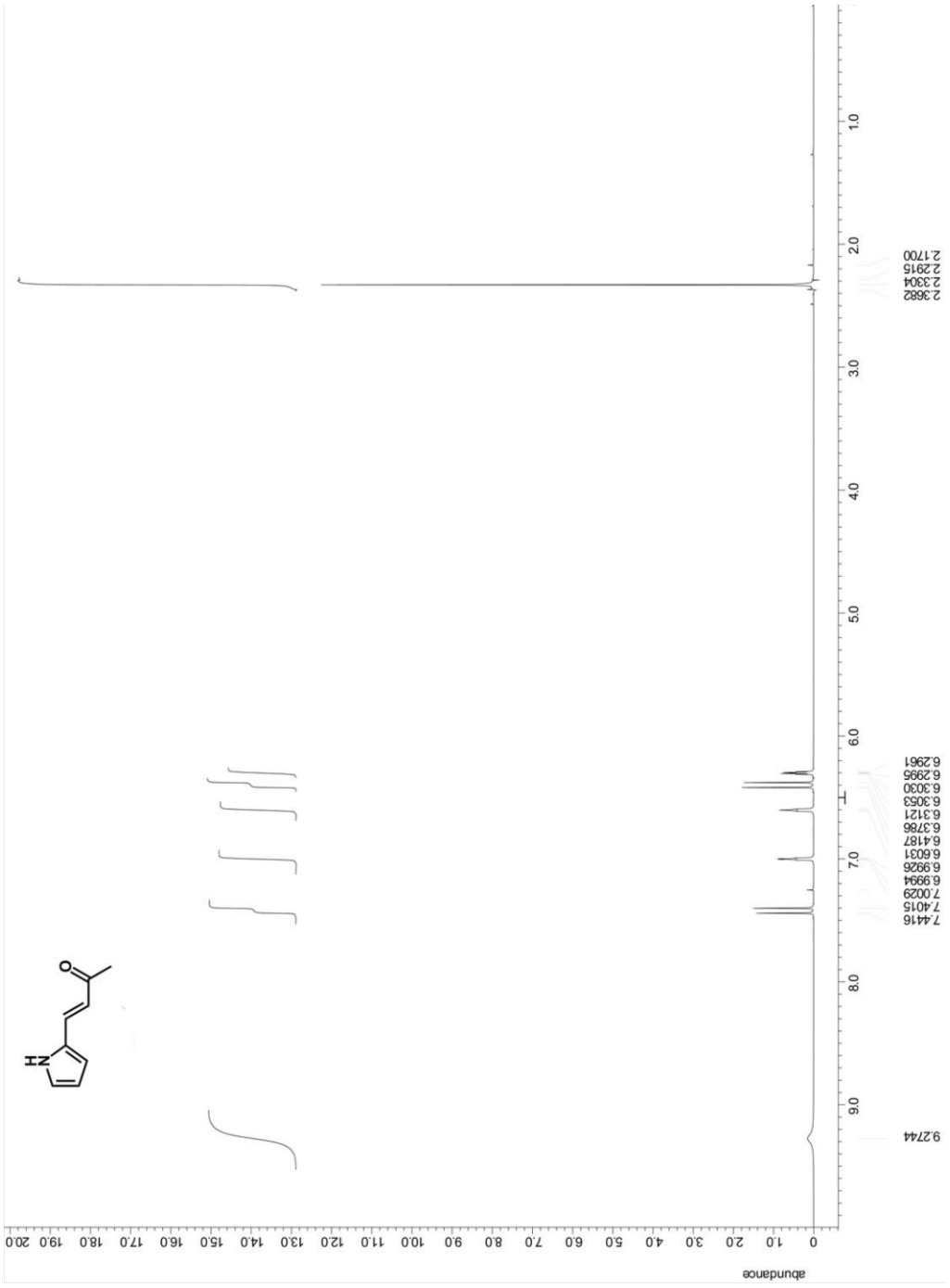


Figure A.1.60. ^{1}H NMR for precursor to compound **130**

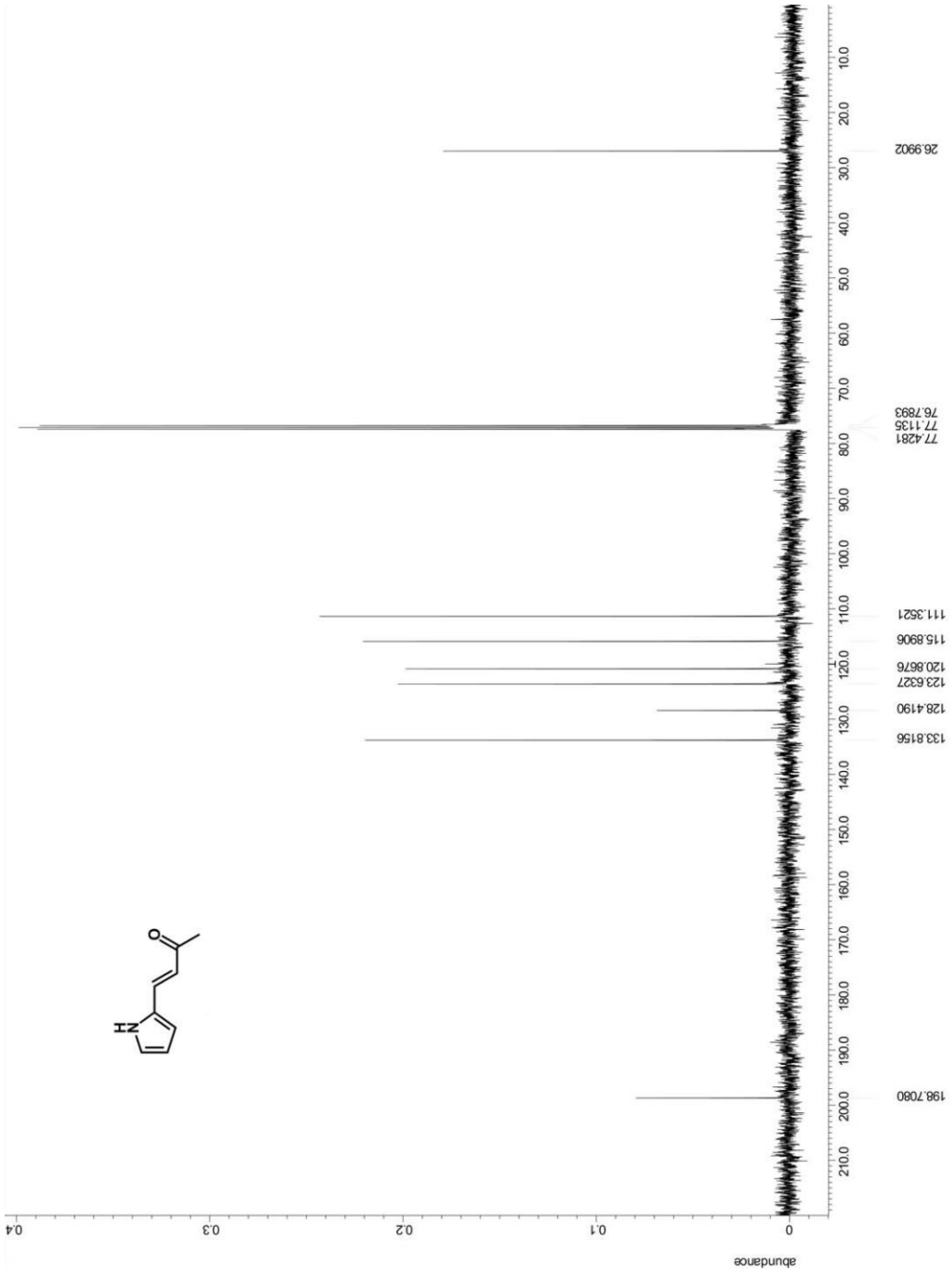


Figure A.1.61. ^{13}C NMR for precursor to compound **130**

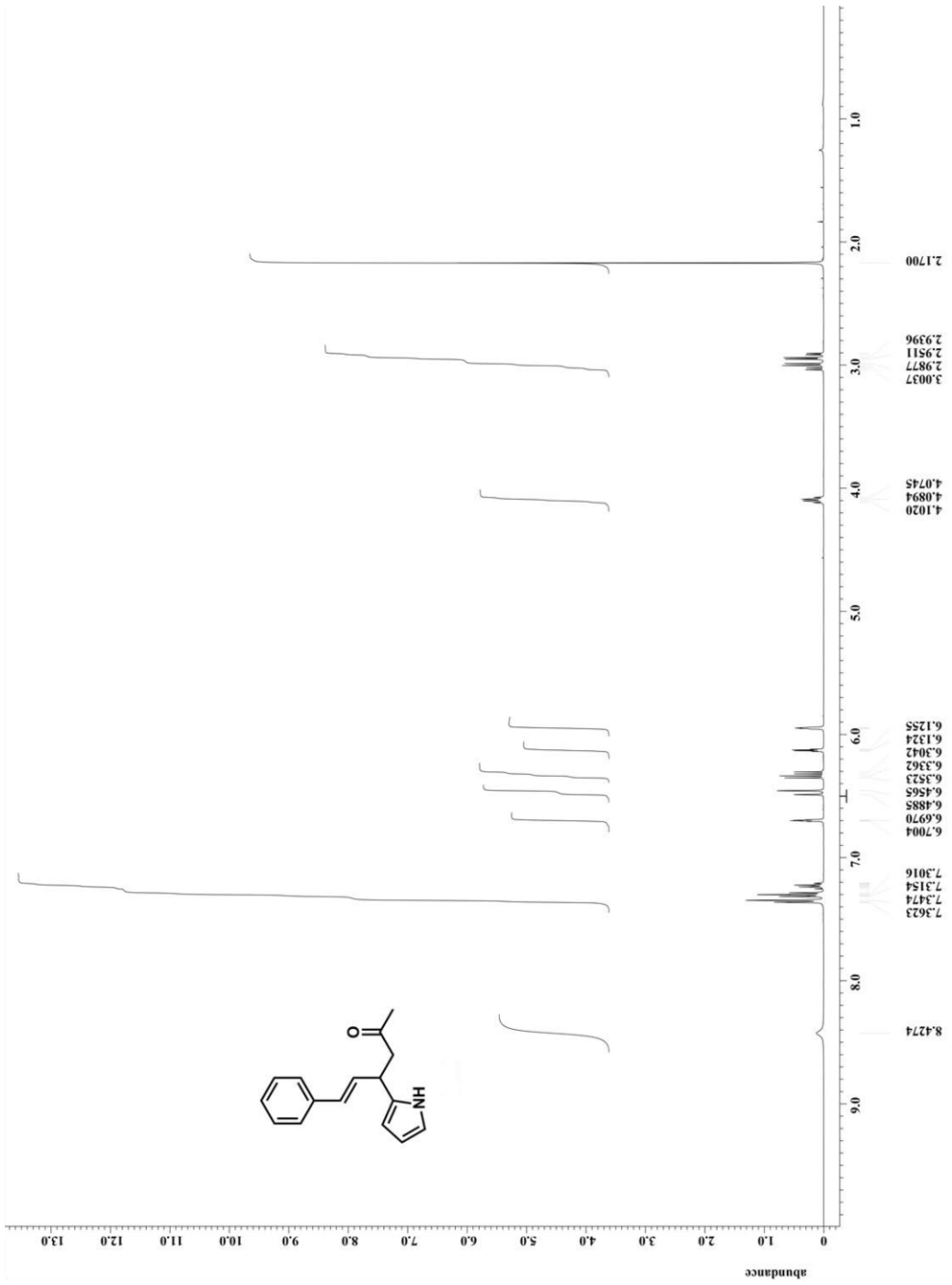


Figure A.1.62. ^{1}H NMR for compound **130**

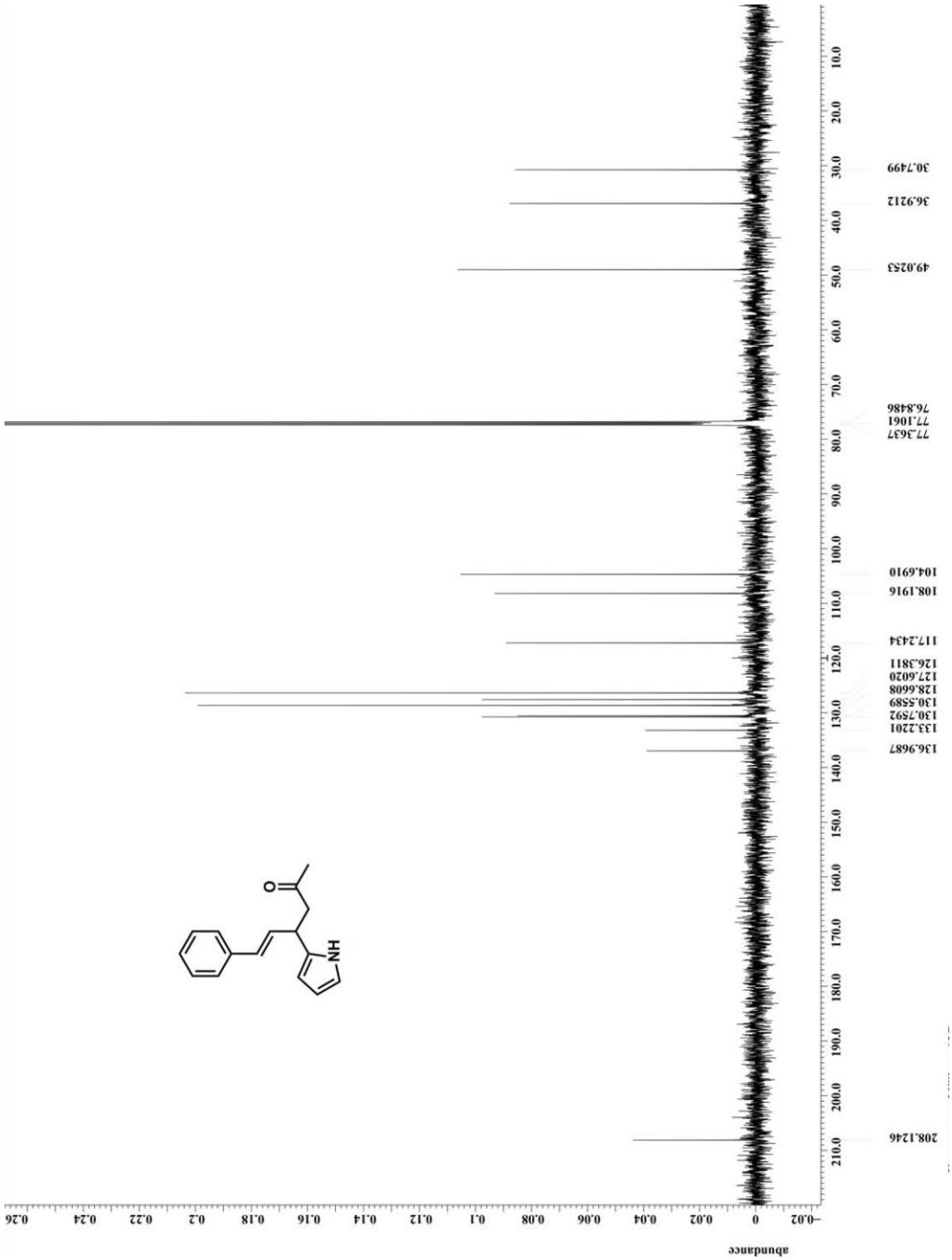
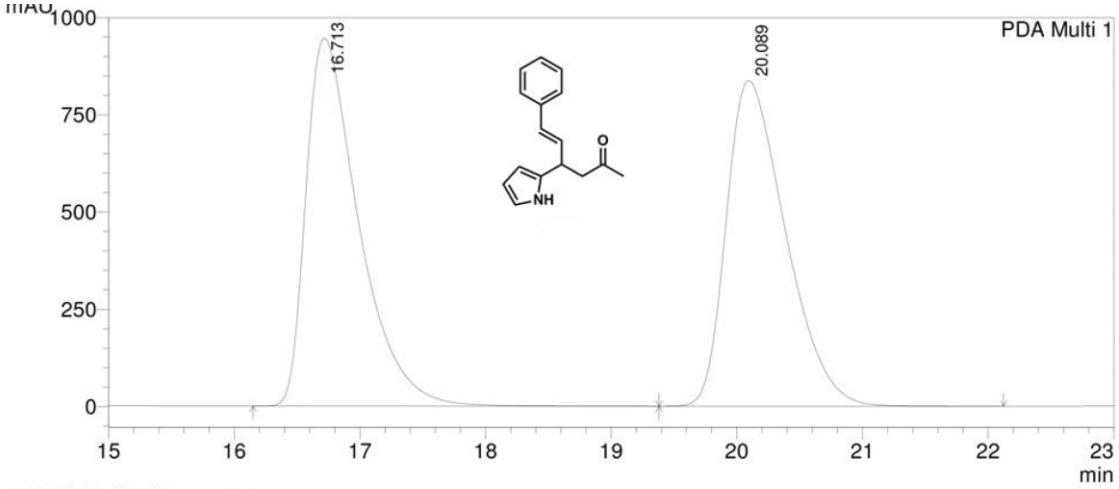


Figure A.1.63. ^{13}C NMR for compound **130**

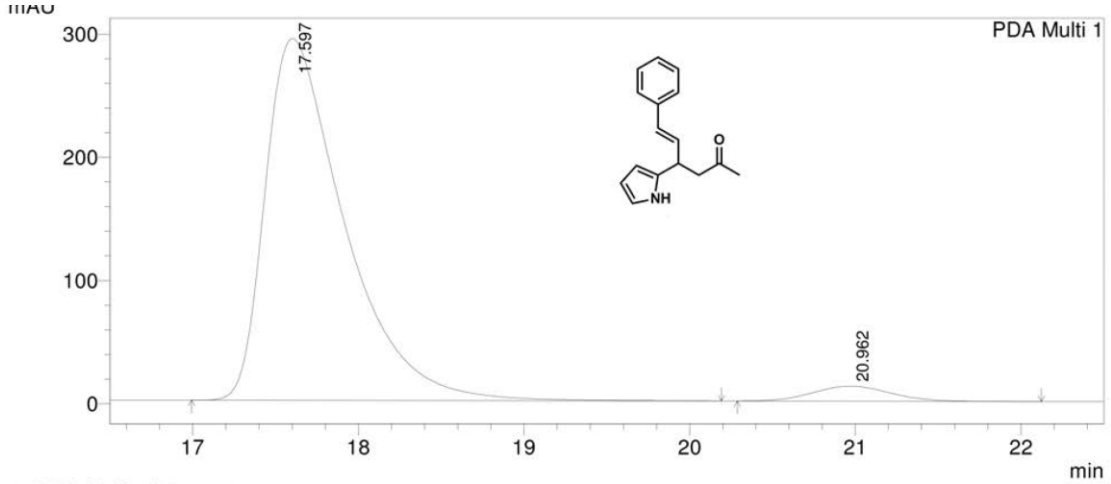


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.713	27603593	945629	50.093	53.022
2	20.089	27501630	837848	49.907	46.978
Total		55105223	1783477	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.597	9780860	293753	96.121	96.039
2	20.962	394660	12116	3.879	3.961
Total		10175520	305868	100.000	100.000

Figure A.1.64. HPLC trace for compound **130**

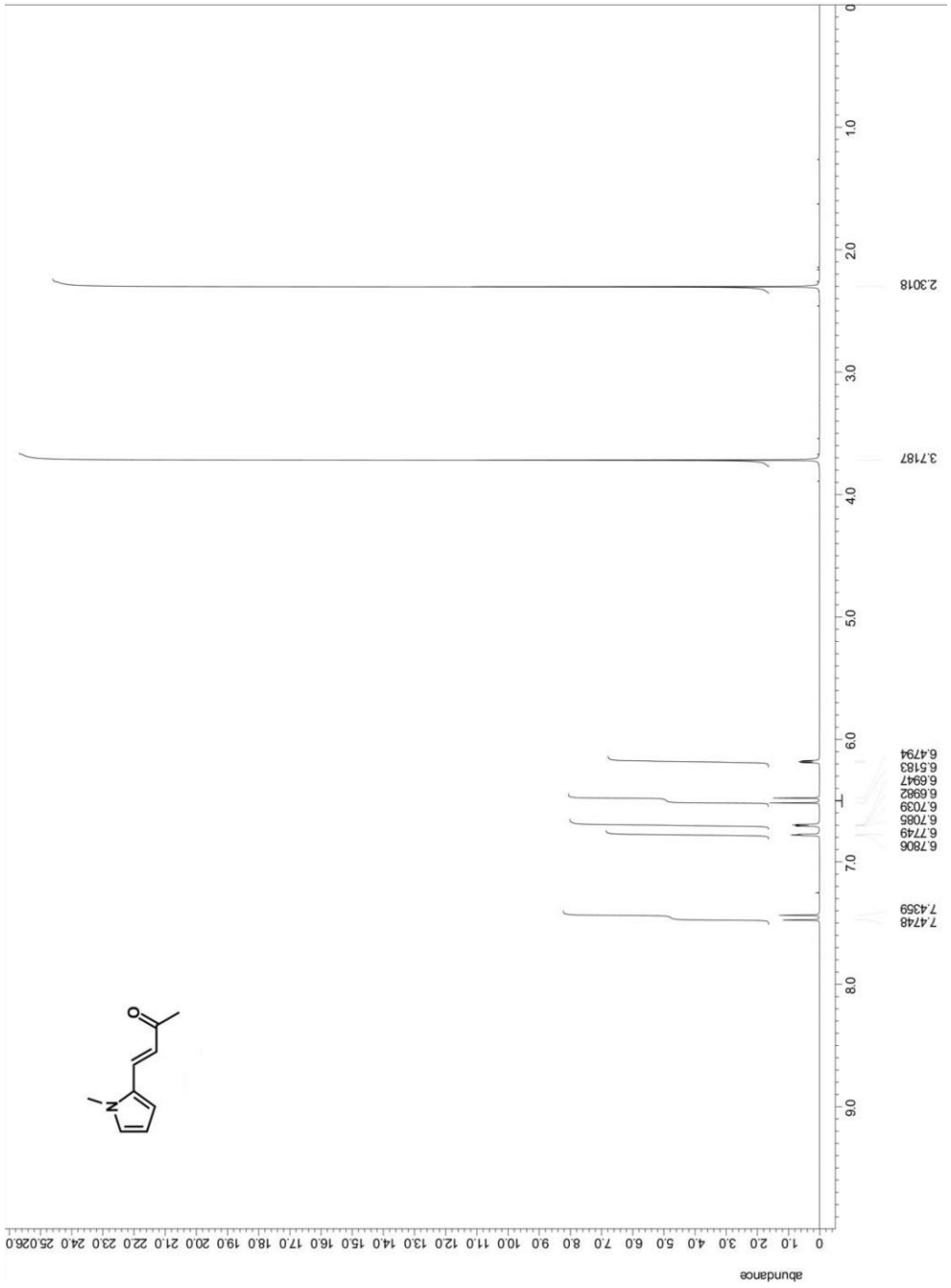


Figure A.1.65. ^{1}H NMR for precursor to compound **131**

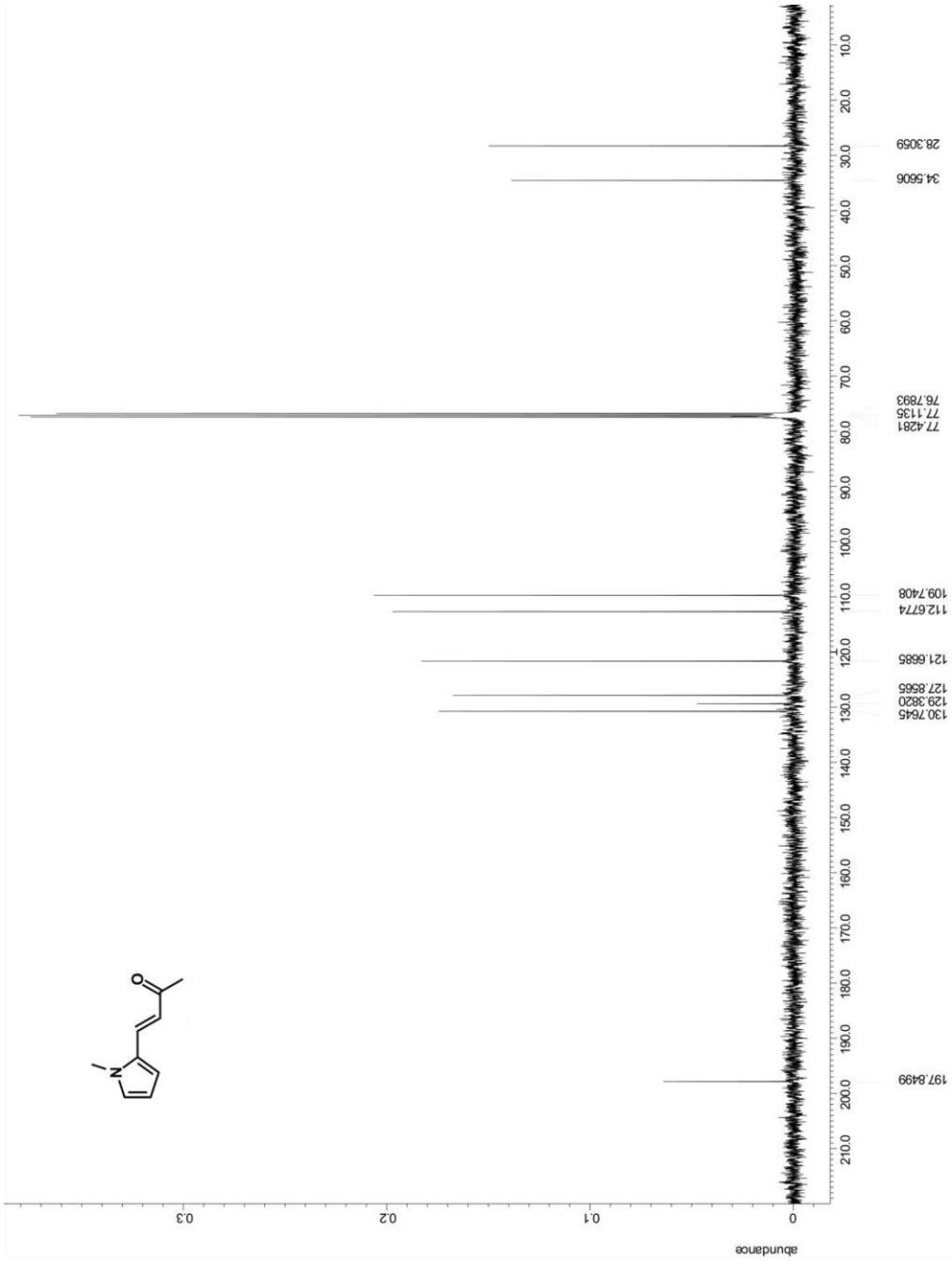


Figure A.1.66. ^{13}C NMR for precursor to compound **131**

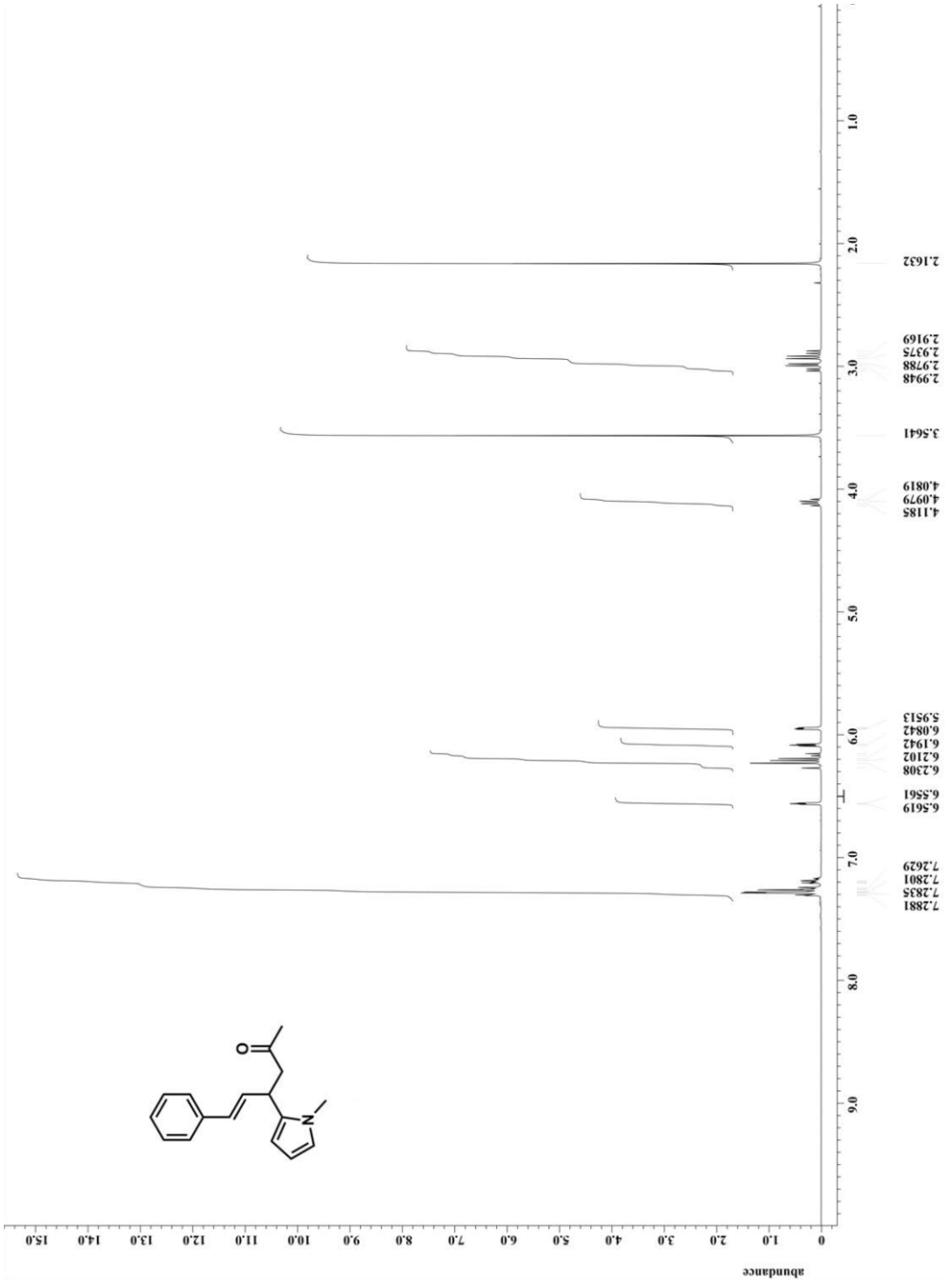


Figure A.1.67. ^{1}H NMR for compound **131**

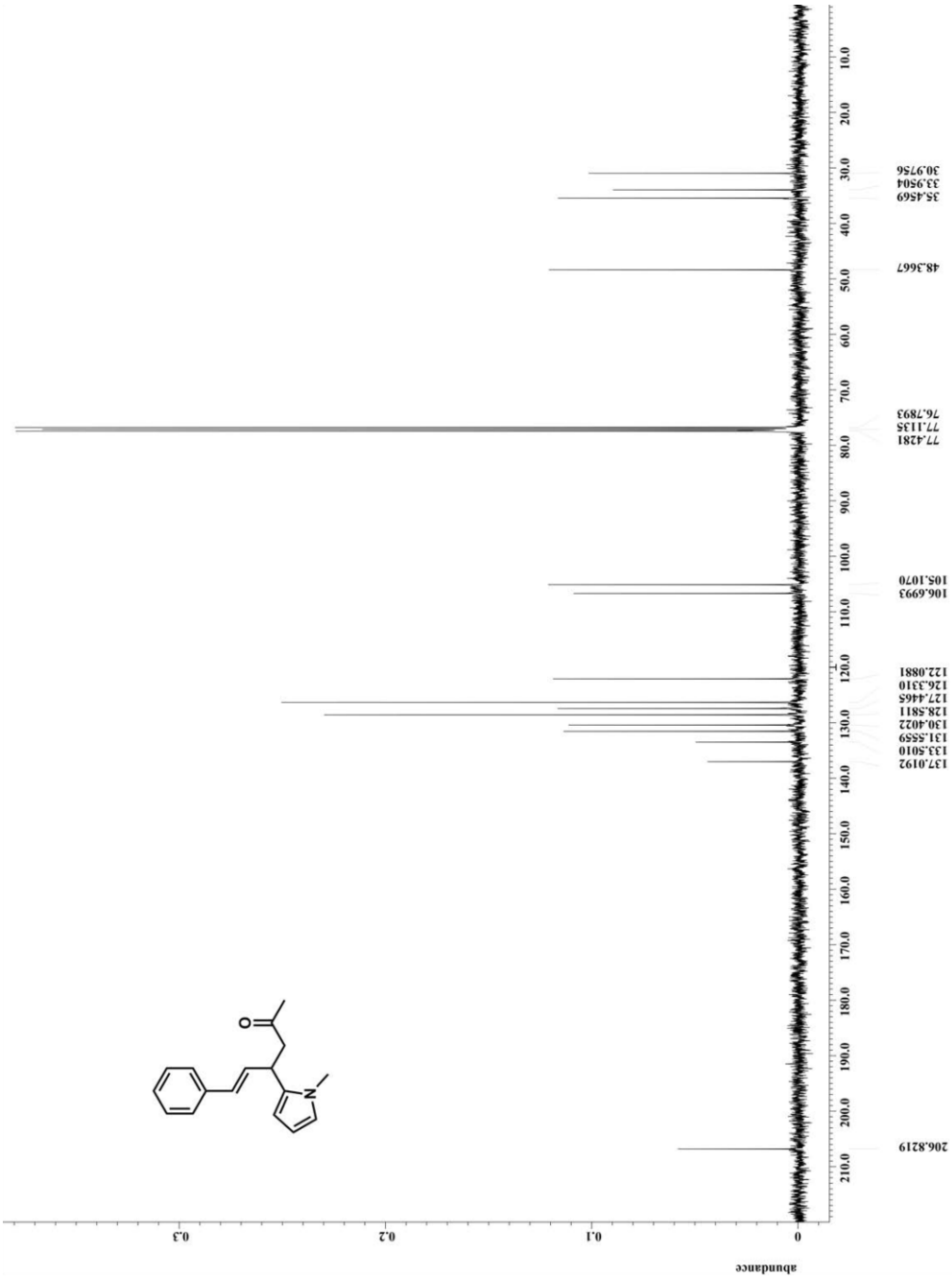
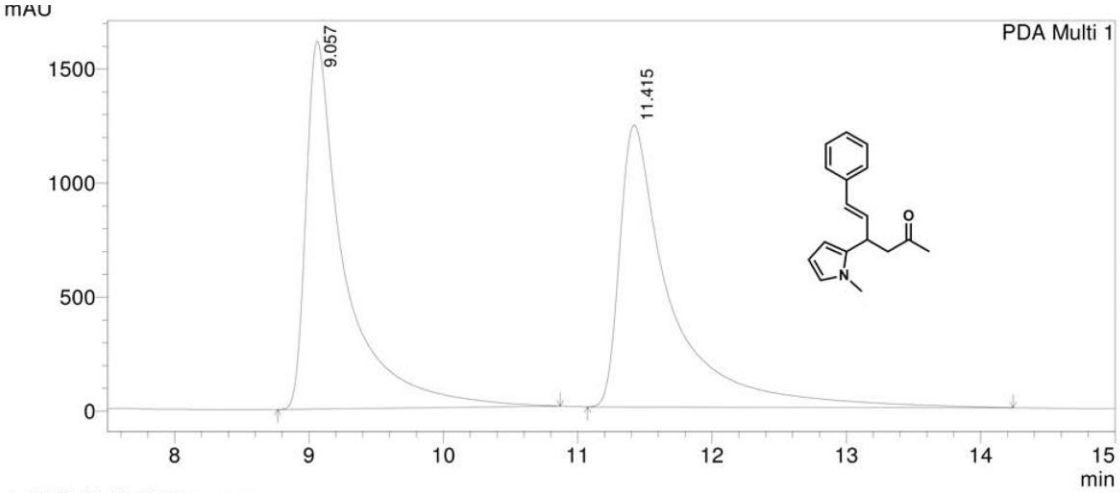


Figure A.1.68. ^{13}C NMR for compound **131**

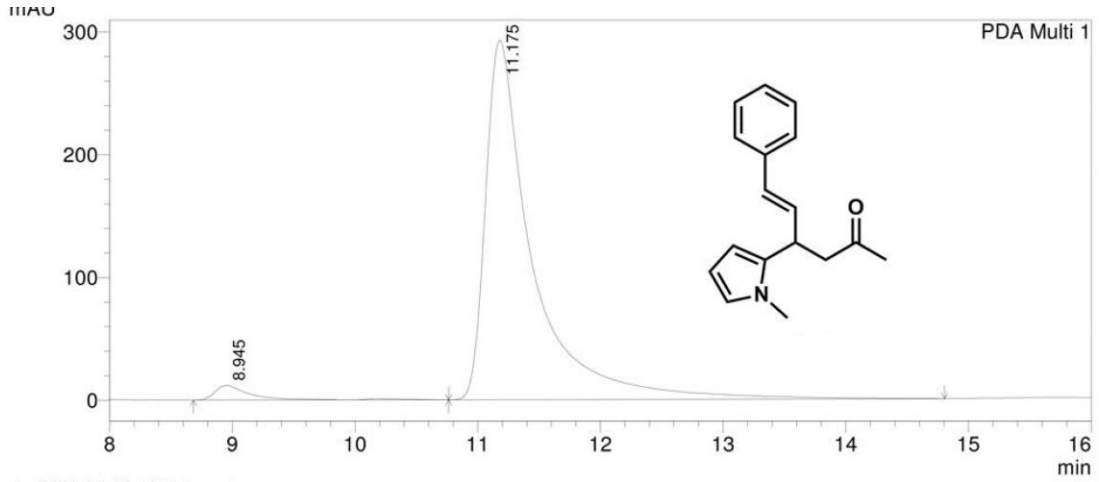


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.057	32338256	1612769	49.480	56.608
2	11.415	33017688	1236240	50.520	43.392
Total		65355944	2849009	100.000	100.000



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.945	237026	12026	2.949	3.944
2	11.175	7799758	292861	97.051	96.056
Total		8036784	304887	100.000	100.000

Figure A.1.69. HPLC trace for compound **131**

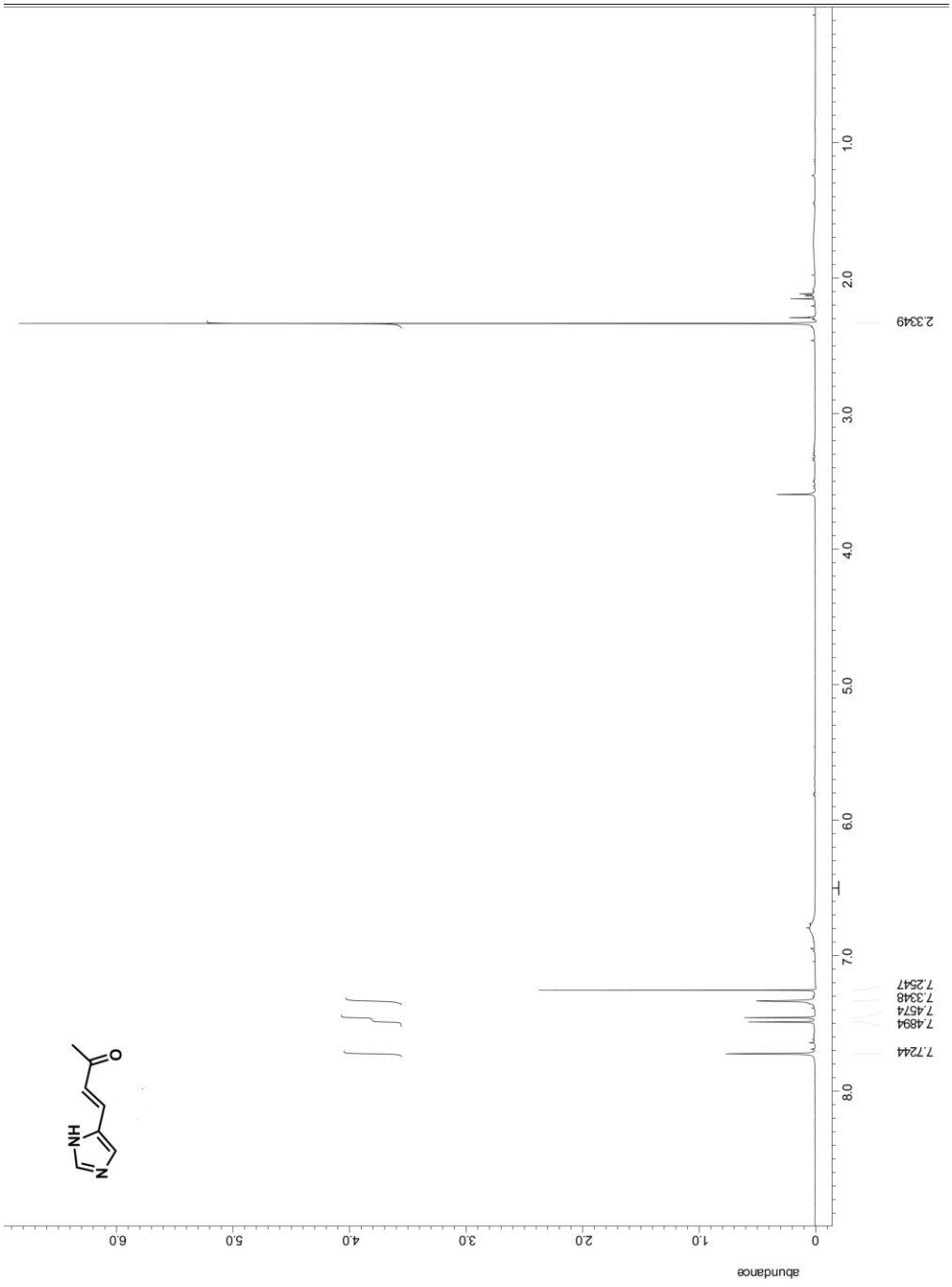


Figure A.1.70. ^{1}H NMR for precursor to compound **132**

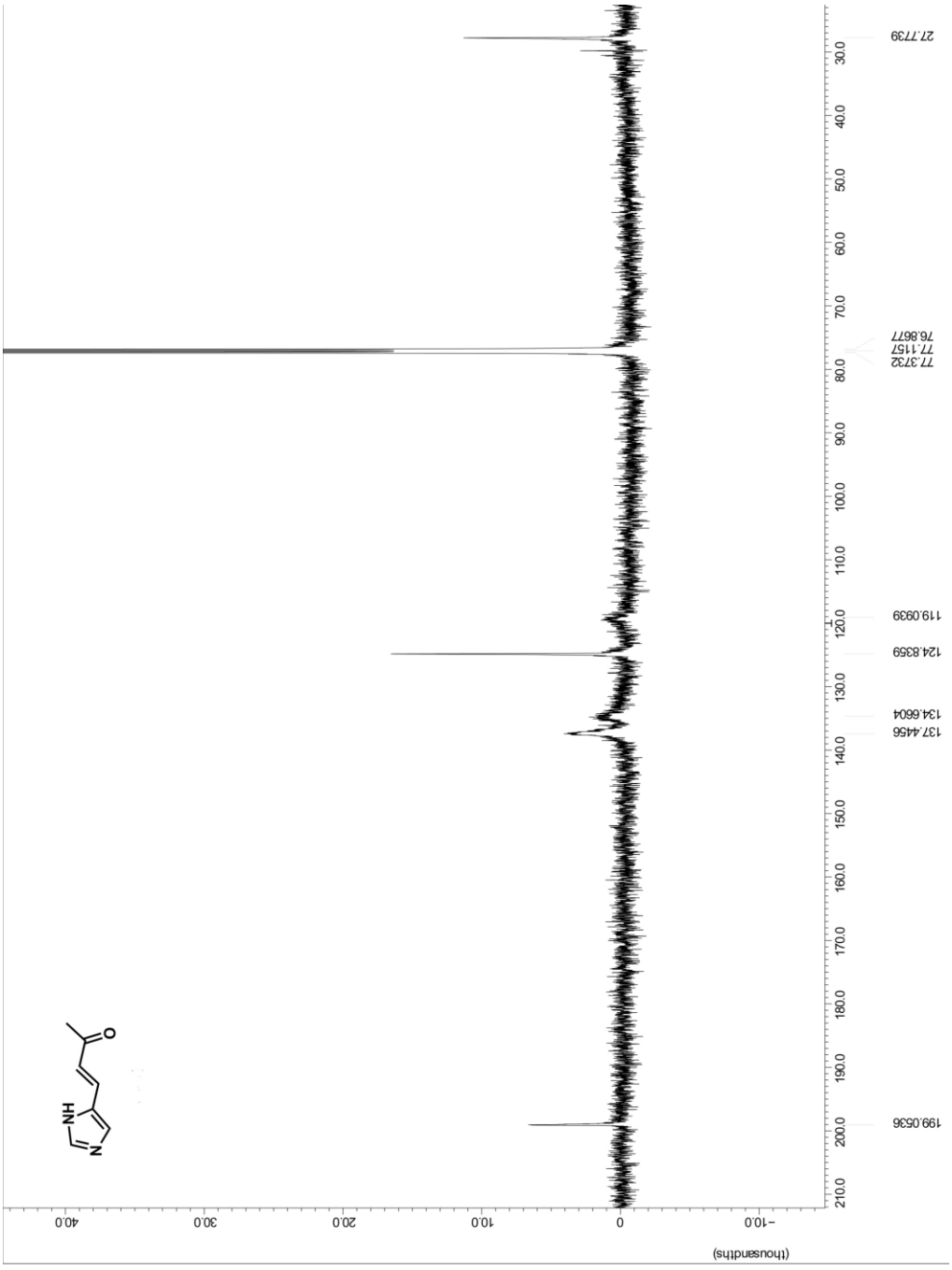


Figure A.1.71. ^{13}C NMR for precursor to compound **132**

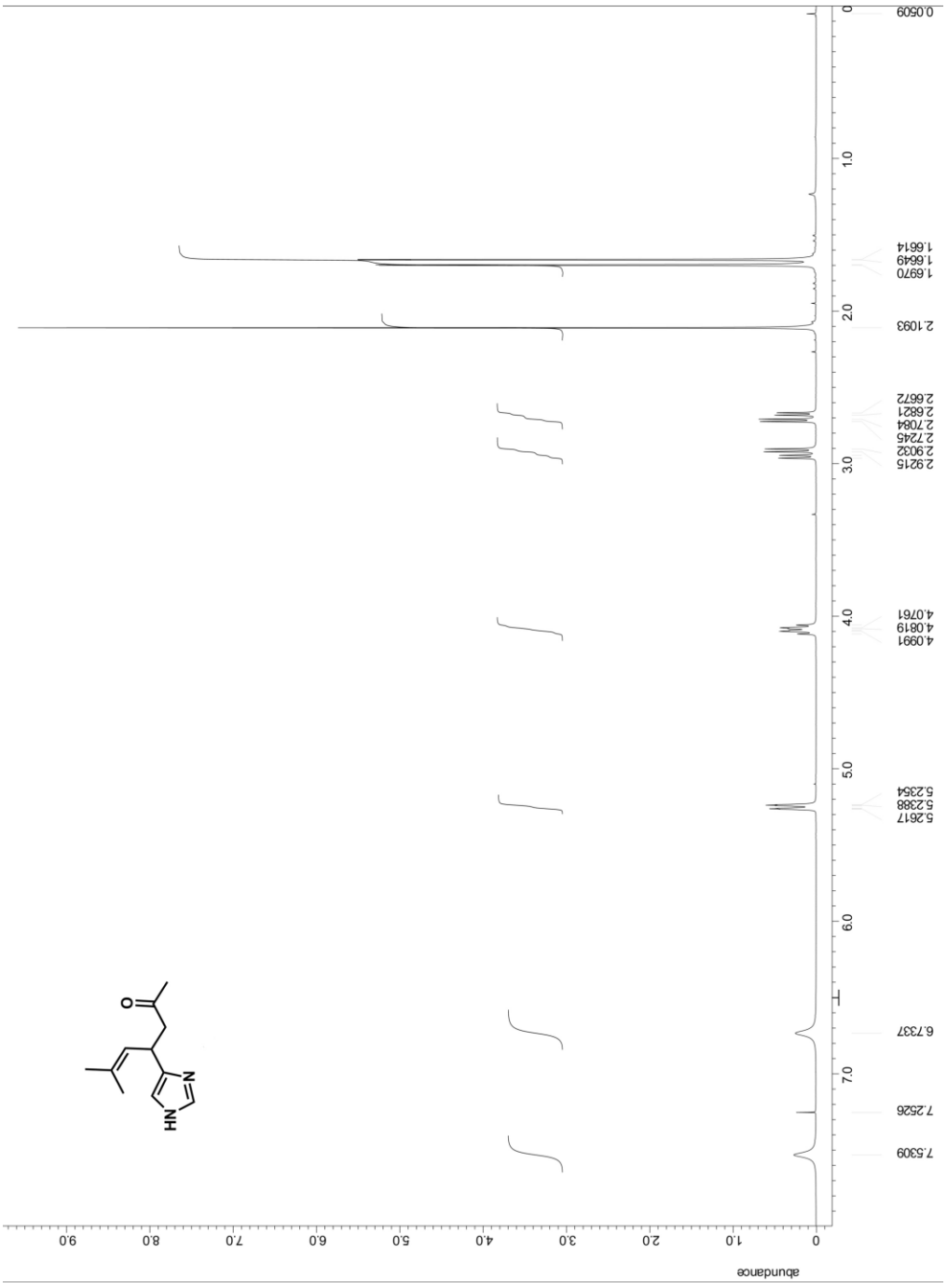


Figure A.1.72. ^{1}H NMR for compound **132**

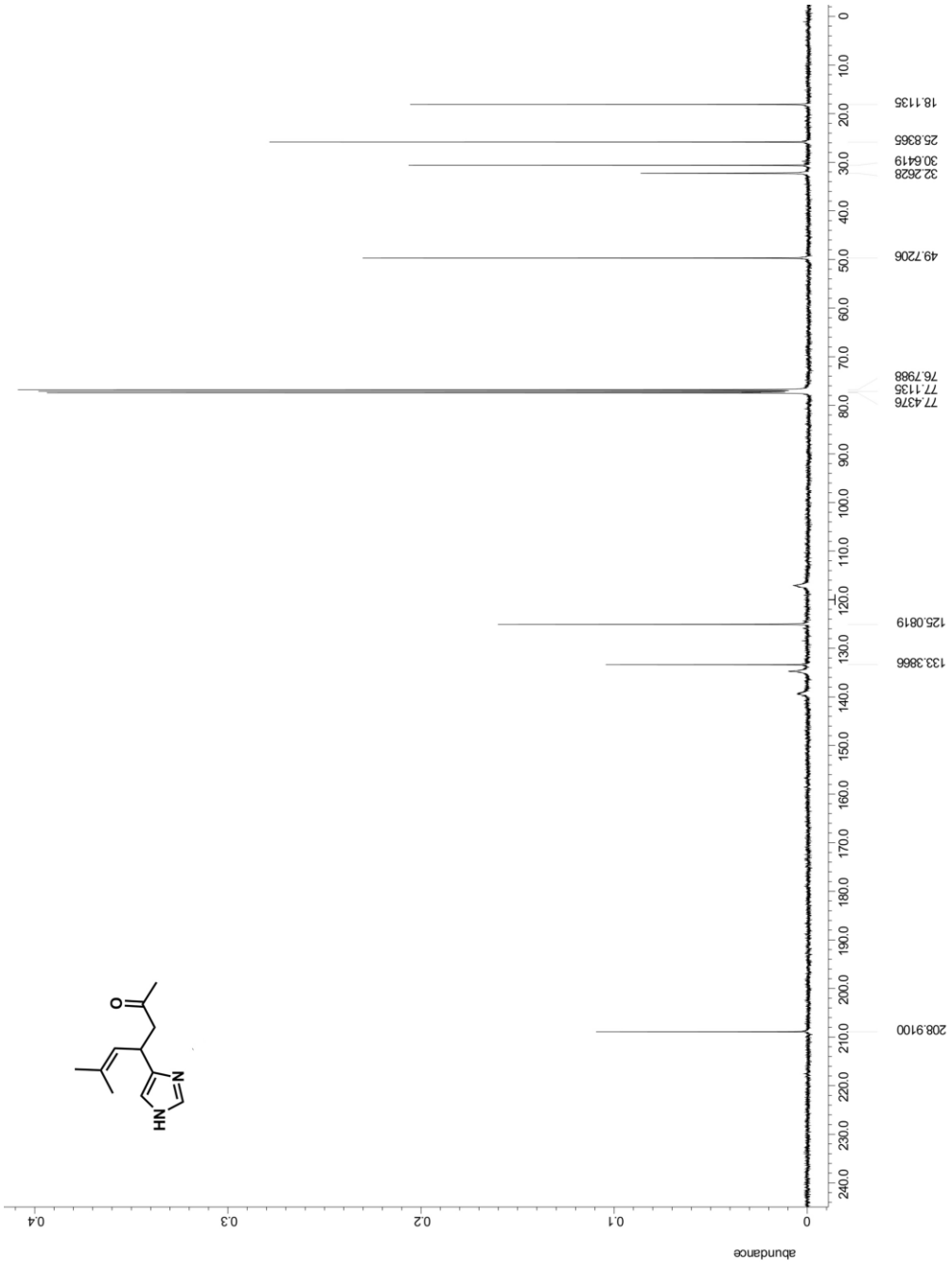
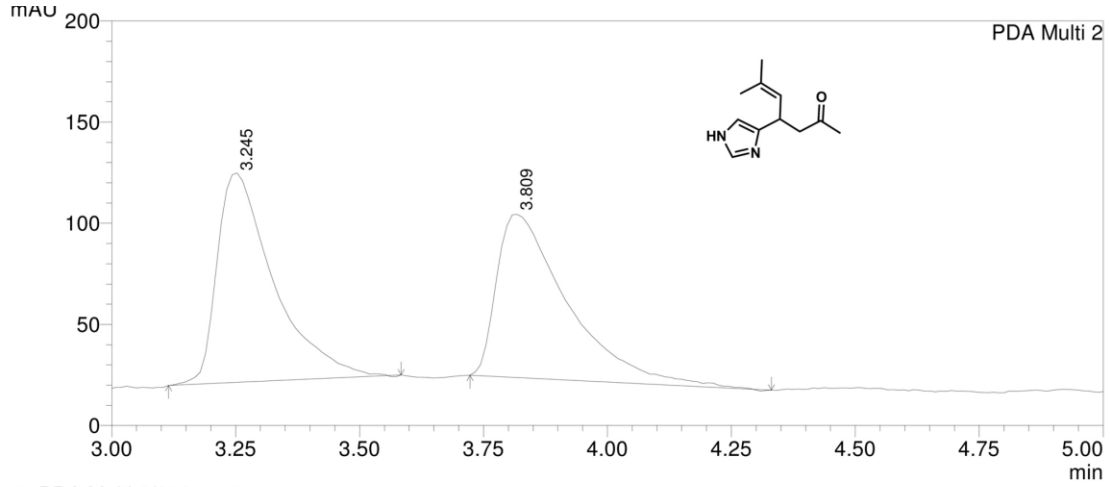


Figure A.1.73. ^{13}C NMR for compound **132**

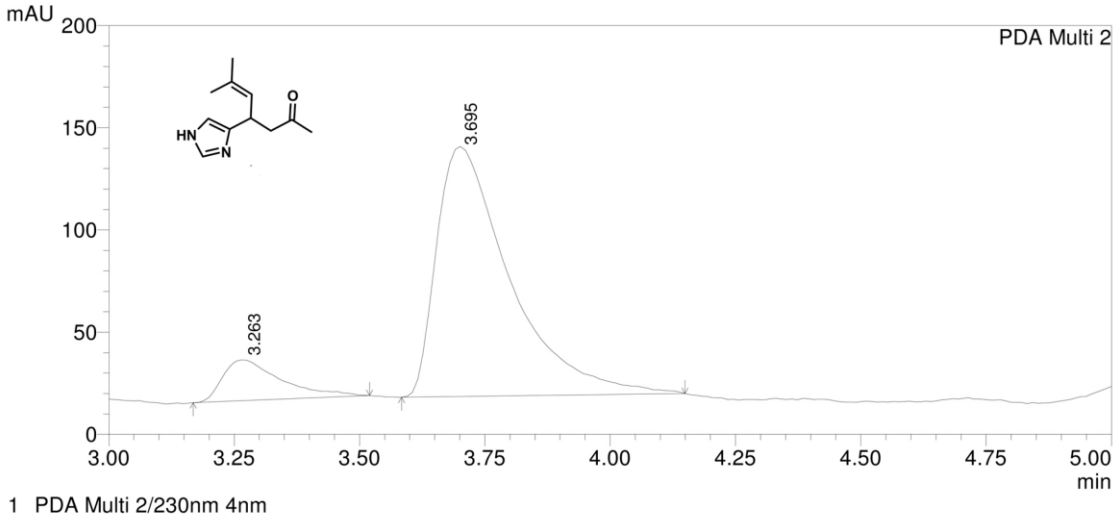


1 PDA Multi 2/230nm 4nm

PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.245	822398	103584	50.694	56.237
2	3.809	799880	80608	49.306	43.763
Total		1622278	184192	100.000	100.000



1 PDA Multi 2/230nm 4nm

PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.263	162714	19952	11.582	14.014
2	3.695	1242206	122421	88.418	85.986
Total		1404920	142373	100.000	100.000

Figure A.1.74. HPLC trace for compound **132**

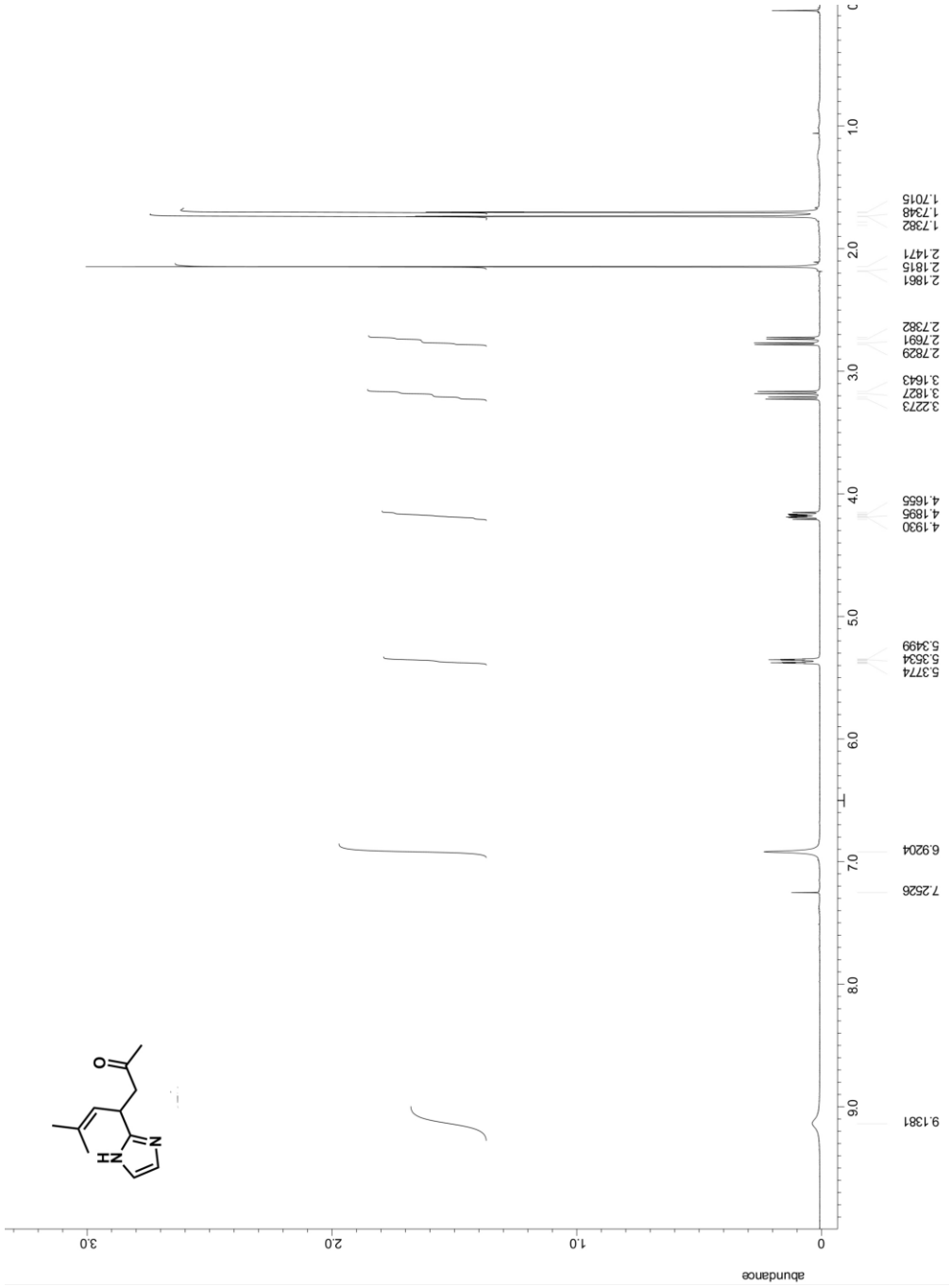


Figure A.1.75. ^{1}H NMR for compound **133**

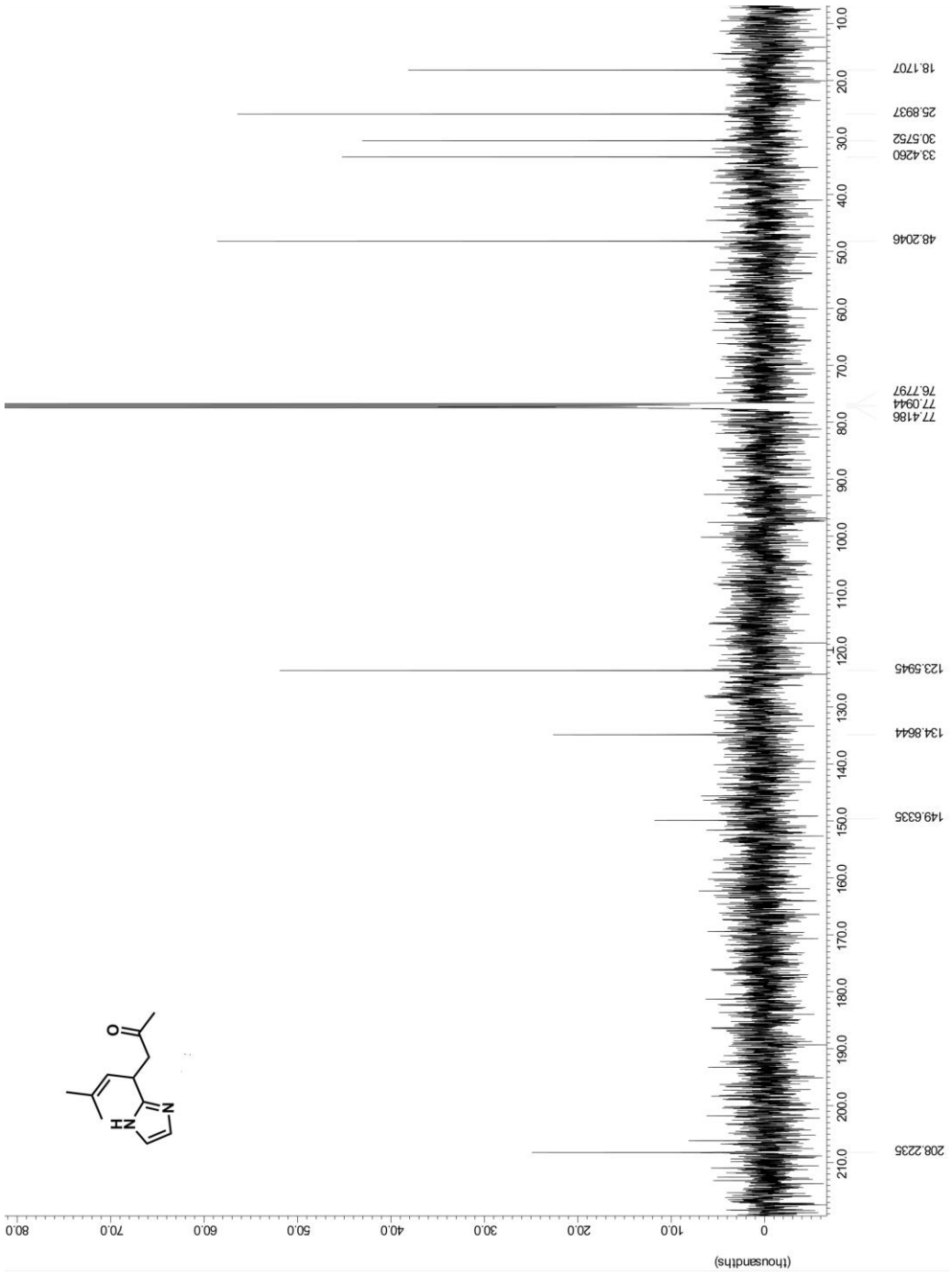
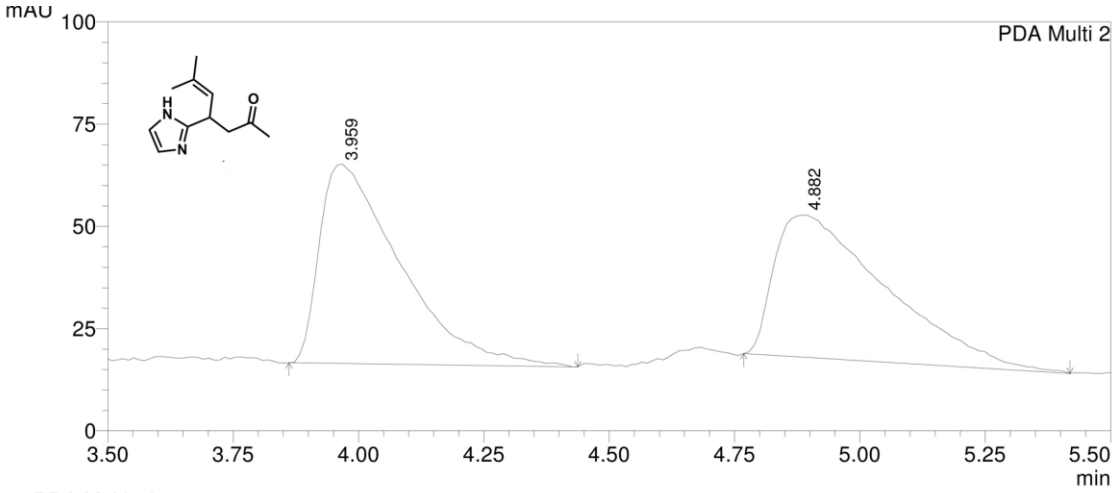


Figure A.1.76. ^{13}C NMR for compound **133**

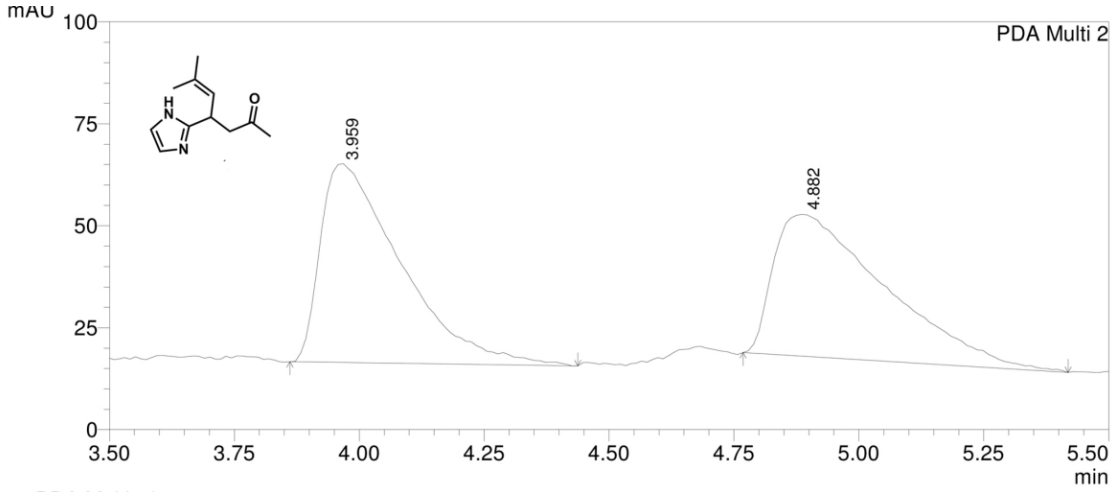


1 PDA Multi 2/230nm 4nm

PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.959	543131	48678	50.203	58.358
2	4.882	538748	34735	49.797	41.642
Total		1081879	83413	100.000	100.000



1 PDA Multi 2/230nm 4nm

PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.959	543131	48678	50.203	58.358
2	4.882	538748	34735	49.797	41.642
Total		1081879	83413	100.000	100.000

Figure A.1.77. HPLC trace for compound **133**

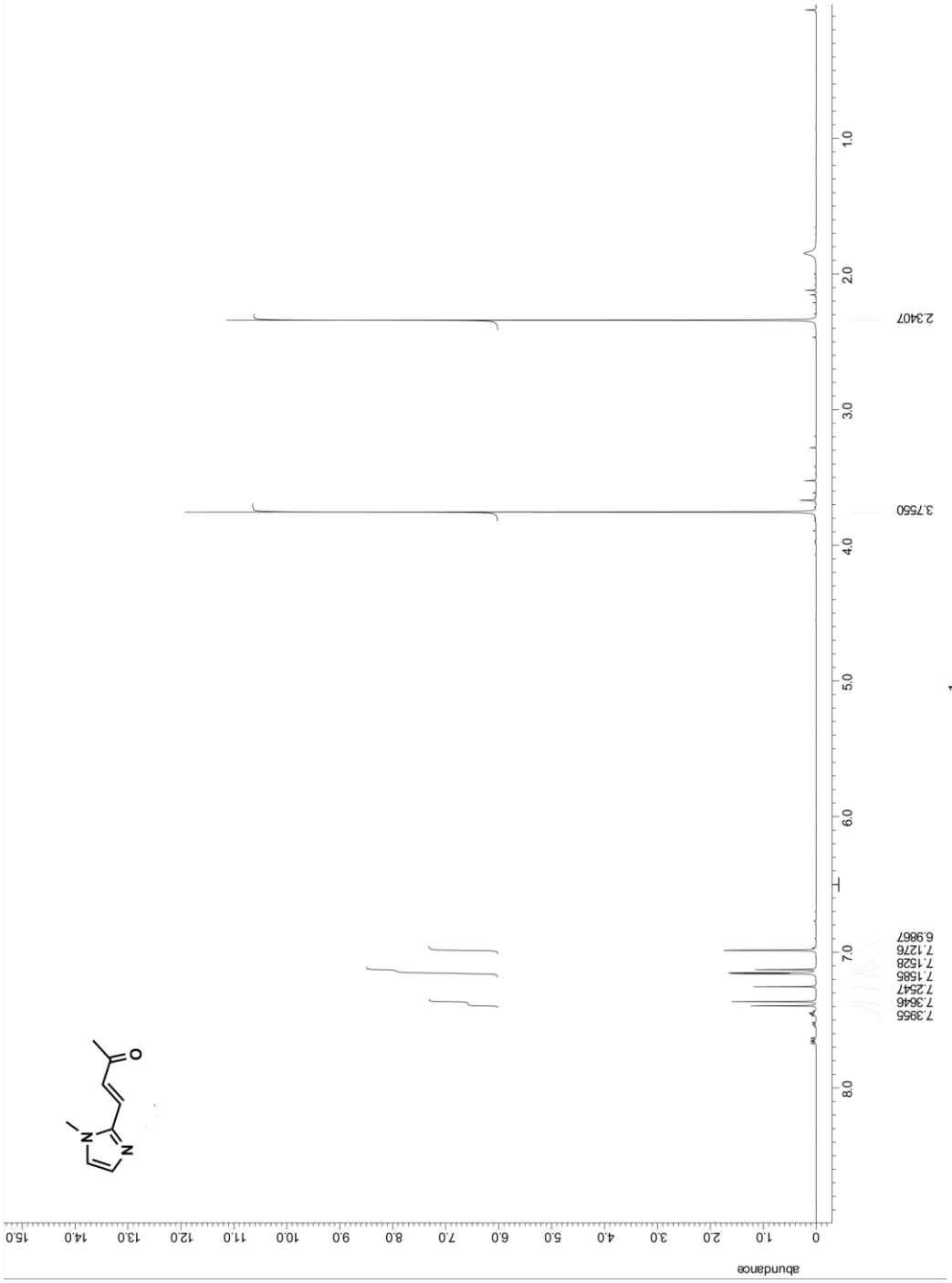


Figure A.1.78. ^{1}H NMR for precursor to compound **134**

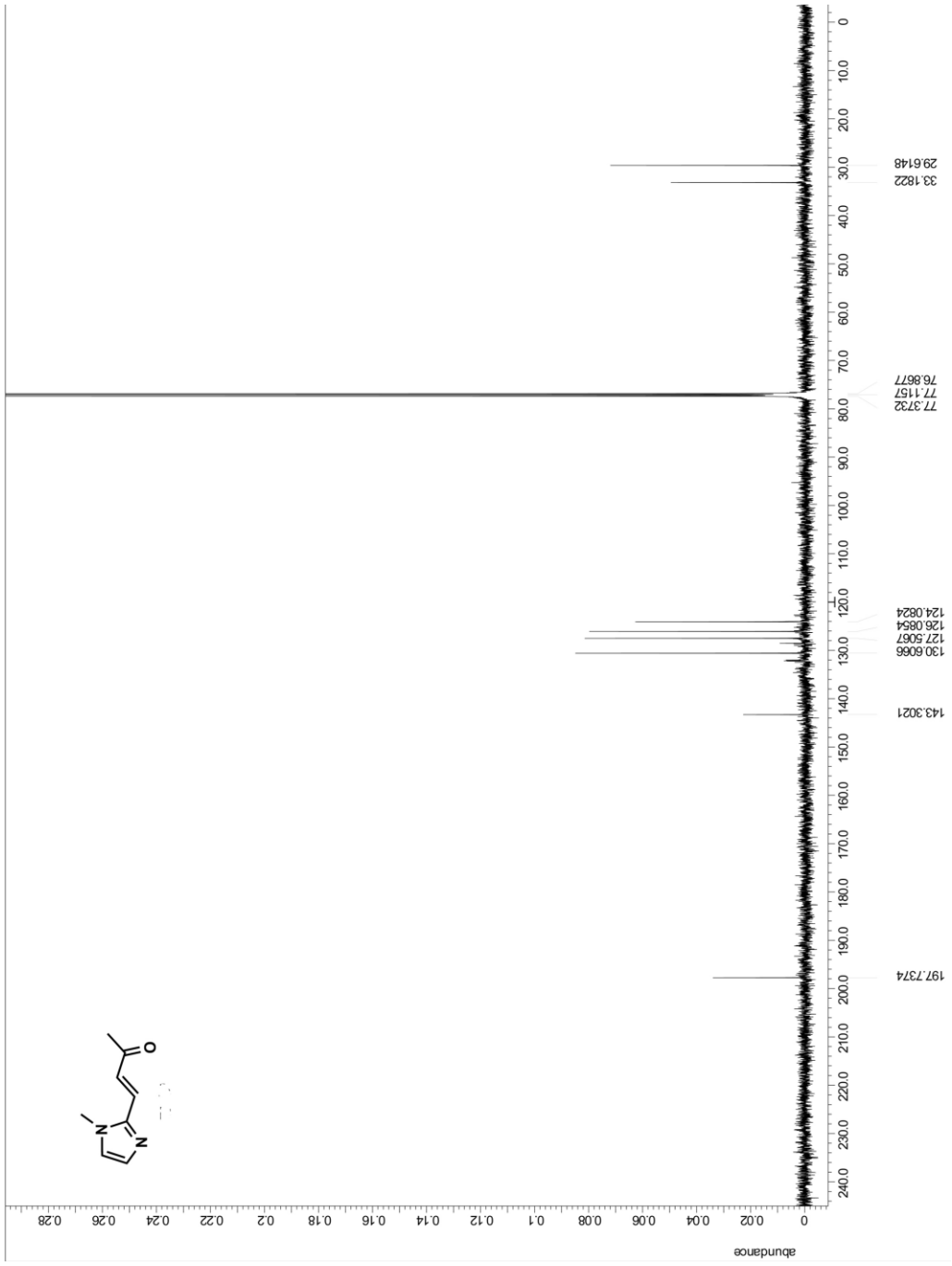


Figure A.1.79. ^{13}C NMR for precursor to compound **134**

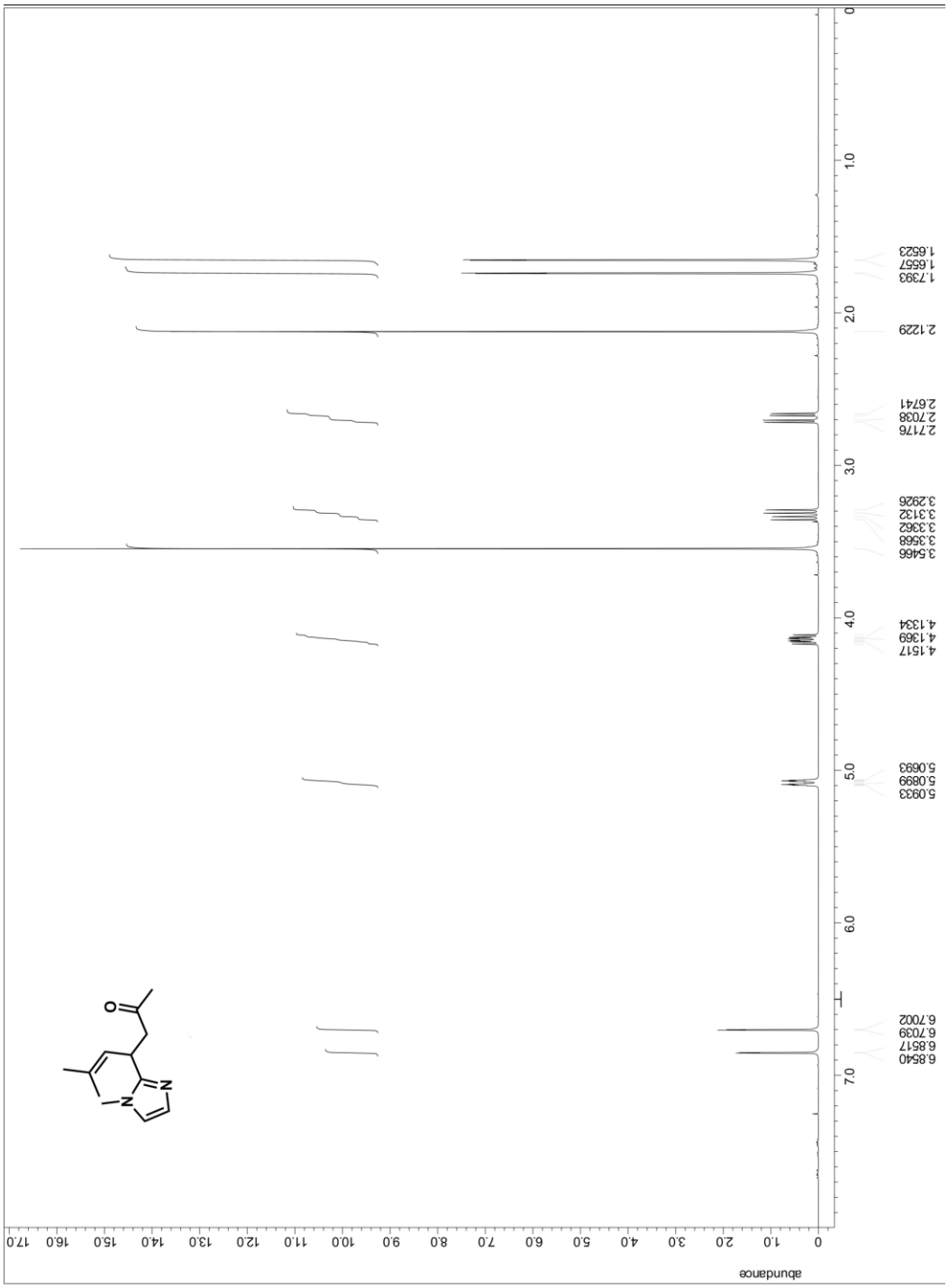


Figure A.1.80. ^{1}H NMR for compound **134**

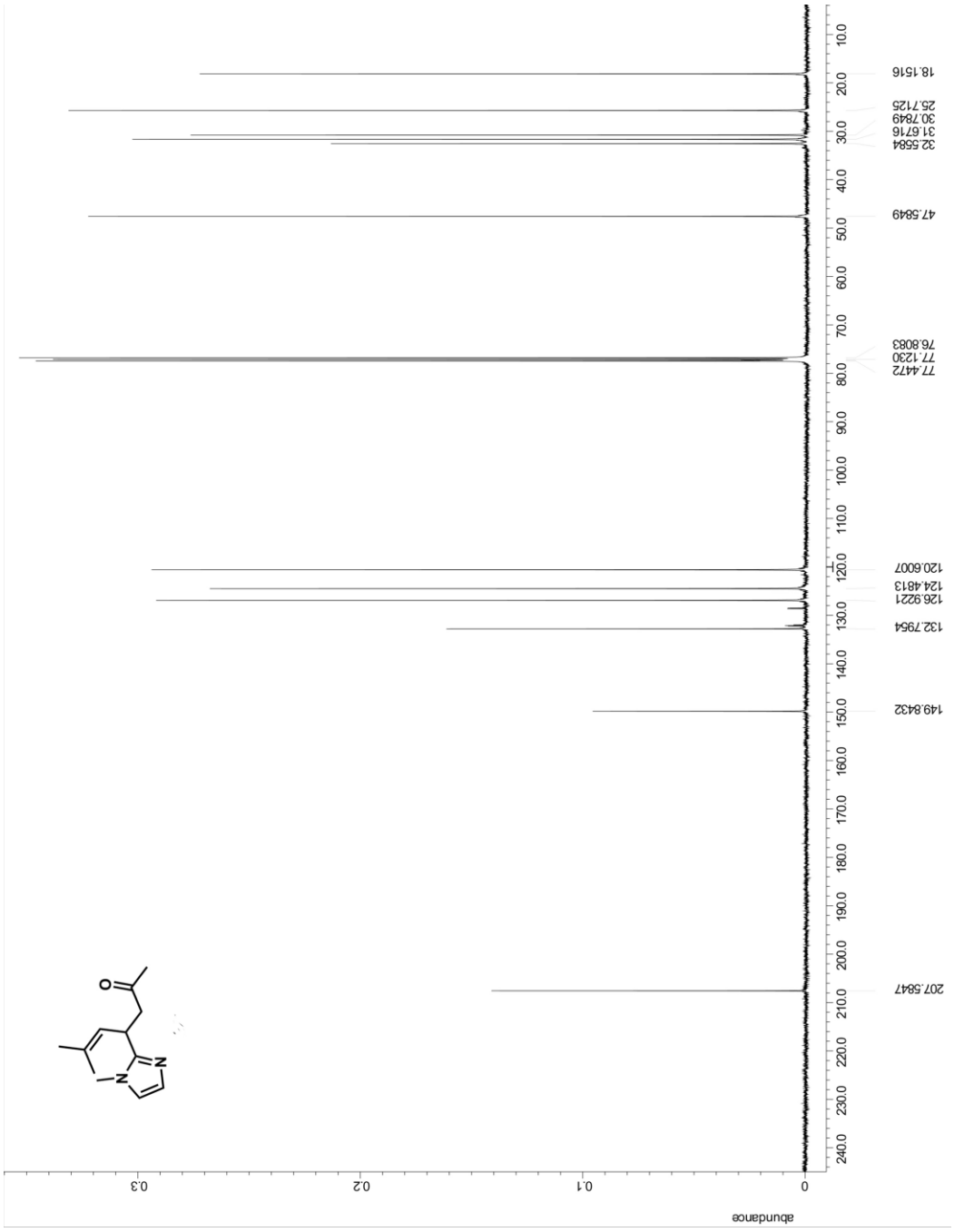
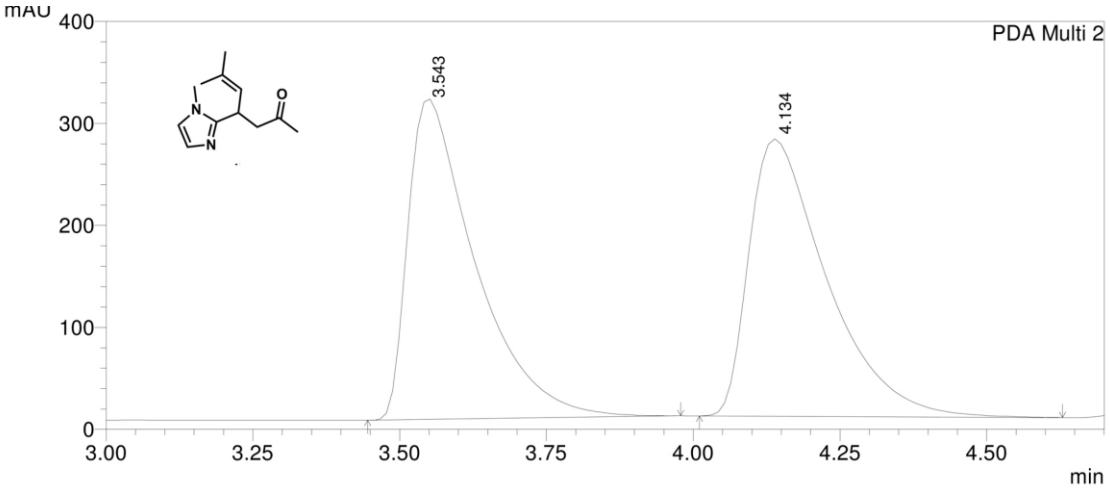


Figure A.1.81. ^{13}C NMR for compound **134**

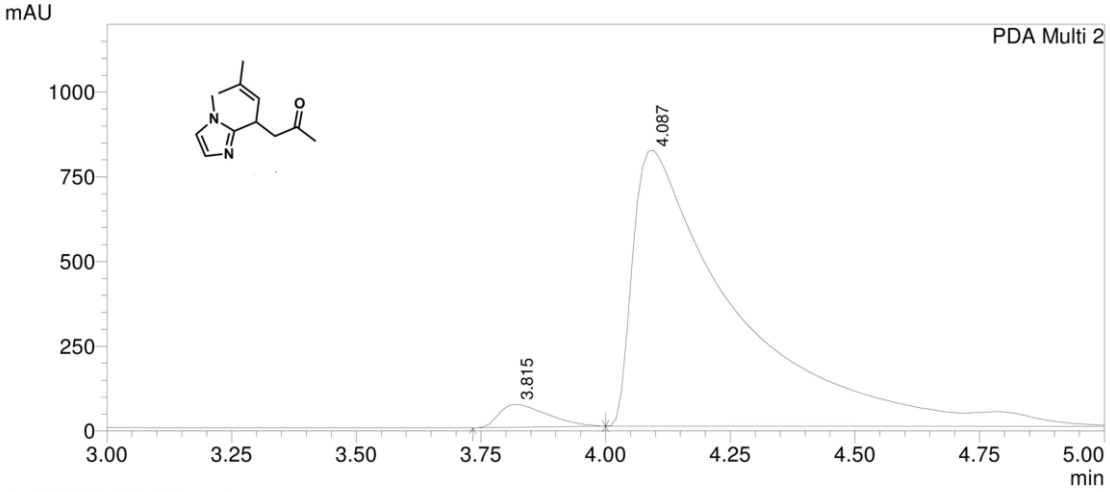


1 PDA Multi 2/230nm 4nm

PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.543	2507726	314225	50.134	53.601
2	4.134	2494341	272001	49.866	46.399
Total		5002067	586227	100.000	100.000



1 PDA Multi 2/230nm 4nm

PeakTable

PDA Ch2 230nm 4nm

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1	3.815	455913	67851	3.687	7.693
2	4.087	11910445	814159	96.313	92.307
Total		12366357	882010	100.000	100.000

Figure A.1.82. HPLC trace for compound **134**

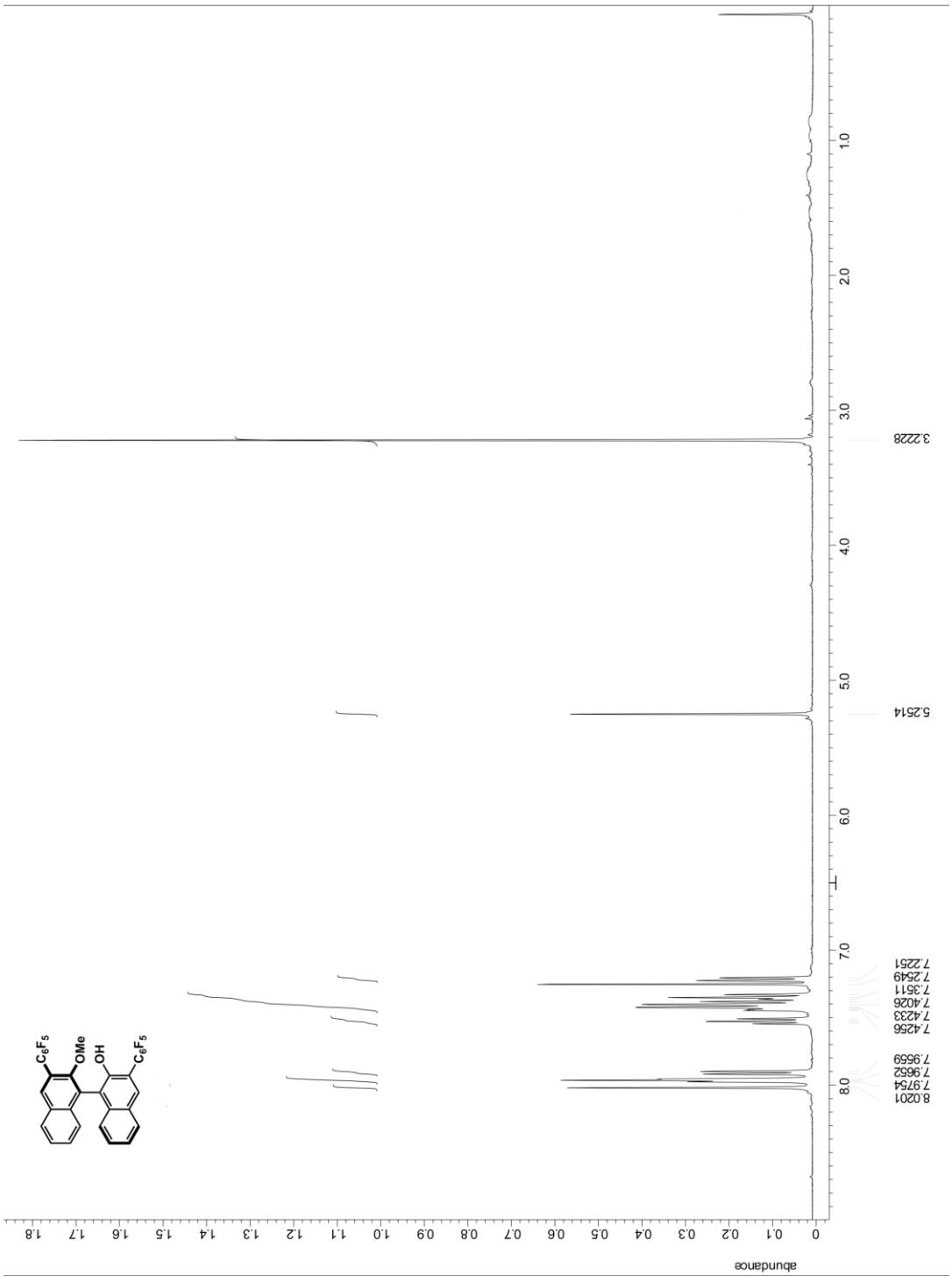


Figure A.1.83. ^{1}H NMR for compound **138**

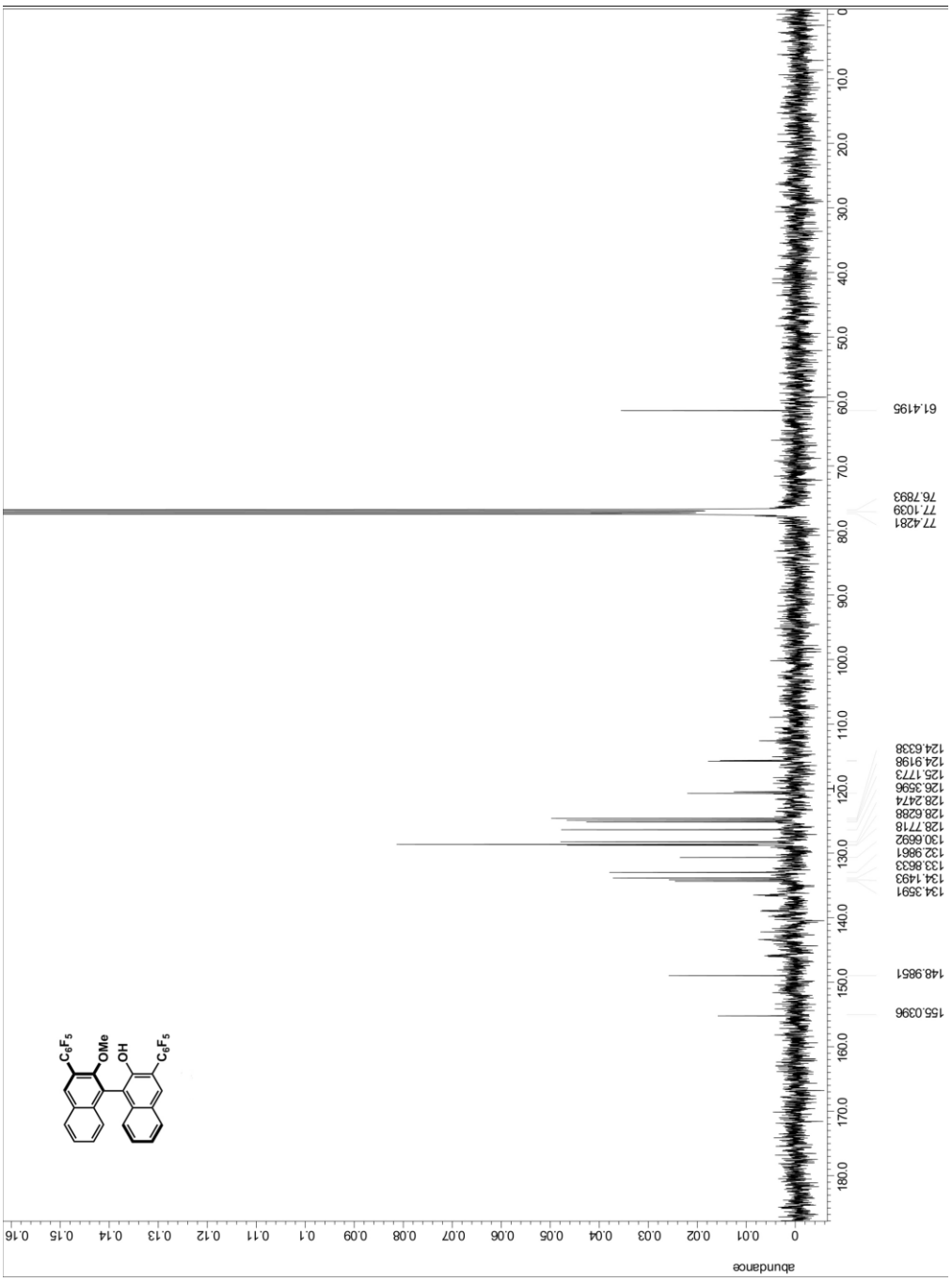


Figure A.1.84. ^{13}C NMR for compound **138**

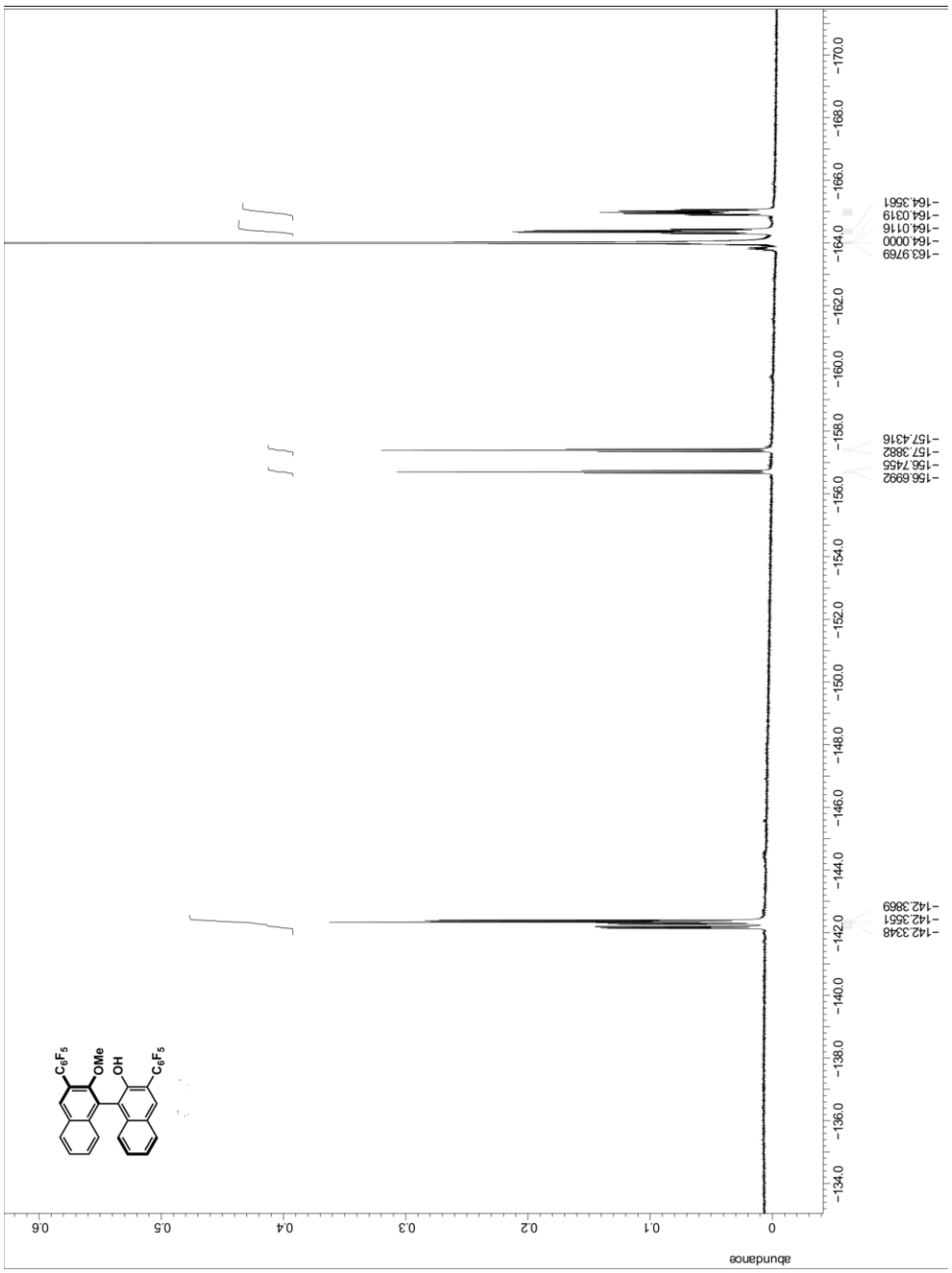


Figure A.1.85. ^{19}F NMR for compound **138**

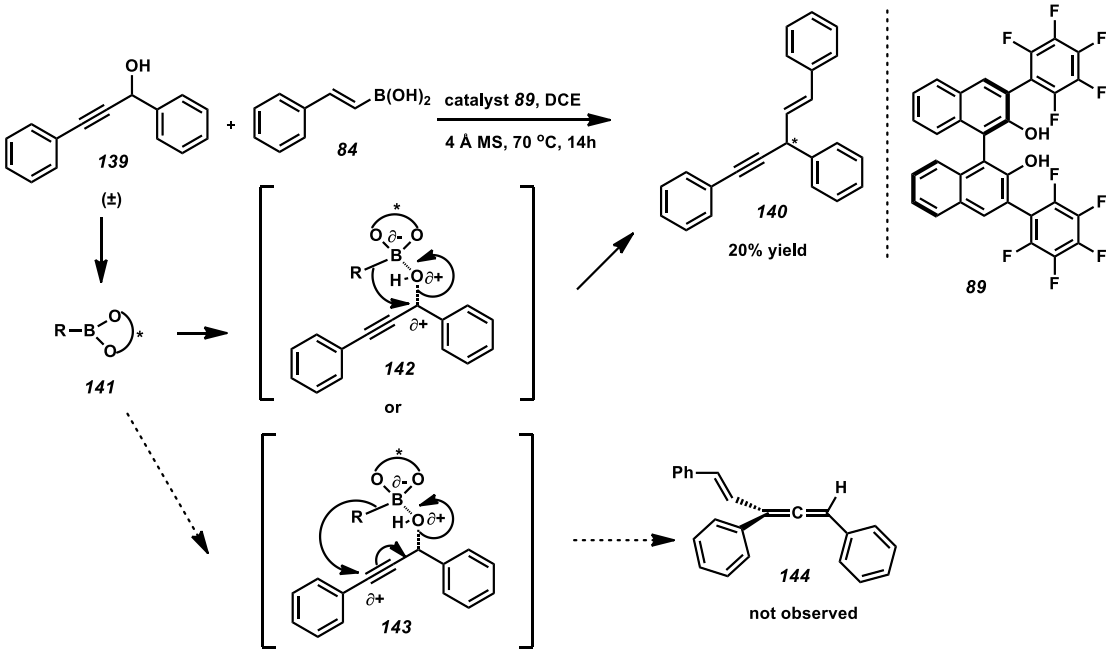
CHAPTER 3

ATTEMPTS TOWARD ENANTIOSELECTIVE PROPARGYLIC SUBSTITUTION USING BORONIC ACIDS AND A BINOL CATALYST

3.1 Introduction

During the time developing the conjugate addition reaction, we also wanted to apply our BINOL catalysis to the discovery of other useful transformations. In our opinion, the boronic acids together with BINOL catalysts could create excellent Lewis acidic nucleophiles. These Lewis acidic boronate complexes were already known to have good functional group tolerance. If appropriate electrophiles were used, we could have a transformation with a very broad scope of nucleophiles, since there are many commercially available boronic acids. Furthermore, the ability to synthesize different chiral BINOL derivatives will help develop an asymmetric transformation.

Due to the broad application of allenes in organic synthesis,[1] we proposed the reaction shown in Scheme 3.1 with the purpose of making allene **144**.



Scheme 3.1. Reaction of styrenyl boronic acid and propargyl alcohol

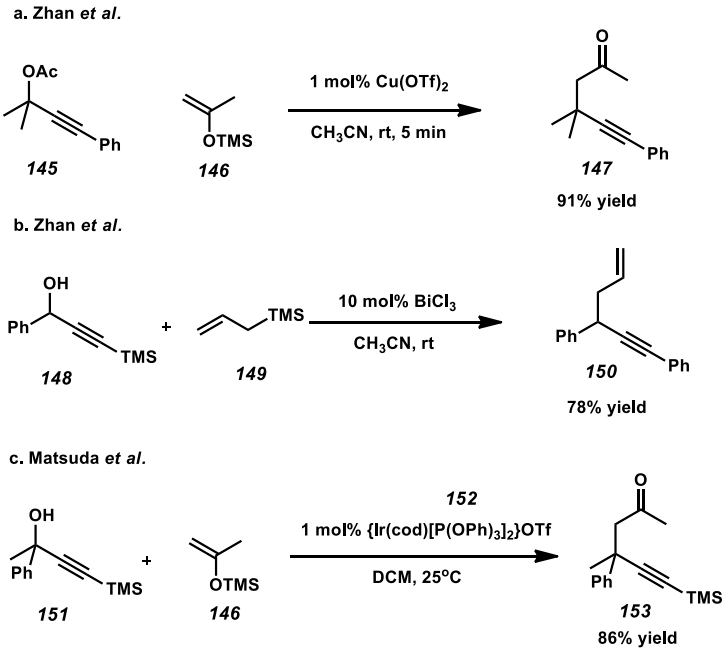
We rationalized that as in the conjugate addition the boronate **141**, generated from boronic acid **84** and BINOL **89**, could coordinate to the oxygen of a propargyl alcohol, making the hydroxyl a better leaving group. This coordination would then facilitate the R group's migration from the boron atom to the γ-position of the propargyl alcohol to form the allene **144**. However, when we ran the reaction with our best conditions at the time, we did not observe any allene **144**; instead the alkyne **140** was isolated as the sole product. Presumably, this product was formed by a propargylic substitution where the R group has attacked at the α position, but not the γ, possibly via a cationic intermediate.

Although we could not obtain the allene products, the propargylated product also had potential applications. Many natural products, fine chemicals, and synthetic pharmaceuticals have the propargylic subunit as part of their structure or as part of a

synthetic intermediate.[2] Also, the π-nucleophilic character of the triple bond is a common functionality in chemical reactions.[3] These reasons, together with the fact that there are not many established methods of asymmetric propargylic substitution, have inspired us to develop an enantioselective version of this interesting transformation.

3.2 Background

Propargylic substitution is an important topic in organic chemistry.[4] However, research in enantioselective reactions has been underdeveloped and reports are limited. The racemic propargylic substitution of internal alkynes mainly relies on the use of Lewis acids. A variety of Lewis acids could be used: copper,[5] iron,[6] bismuth,[7] and iridium[8] (Scheme 3.2a). Normally, the starting material of this approach will be a propargyl alcohol or a derivative in which the hydroxyl group has been converted to a better leaving group. Mechanistically, the reaction proceeds through a stabilized carbocation and then a nucleophilic attack to generate a new carbon-nucleophile bond.

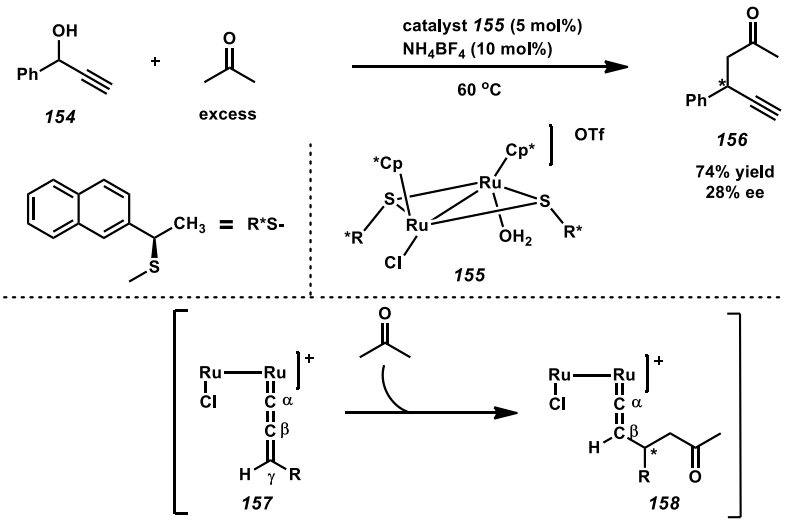


Scheme 3.2a. Propargylic substitution by Lewis acids

However, the use of a strong Lewis acid has limited the functional group tolerance of the reaction. Furthermore, the carbocation does not form a tight complex with the Lewis acid, making it difficult to have enantiocontrol and develop an enantioselective method, although a diasteroselective approach could be possible.[9]

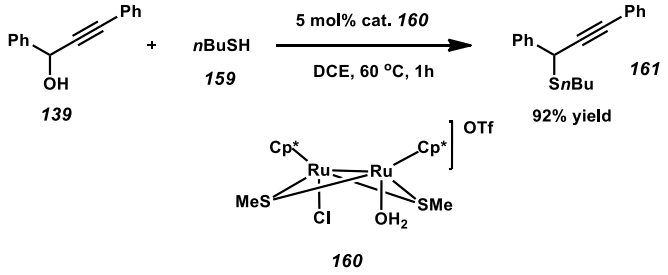
In contrast to Lewis acids, palladium could provide enantioenriched propargylic substitution products, but the starting material must be a pure enantiomer.[10]

An enantioselective transformation, however, could be achieved using other chiral transitional-metal-catalysts, mostly ruthenium and copper for terminal alkynes.[11] Notable work in the field is the research of the Nishibayashi group. In 2003 they reported the first enantioselective propargylic substitution using ruthenium (Scheme 3.2b).[12] The reaction was believed to proceed through a metal-allenylidene complex (**157**, Scheme 3.2b).



Scheme 3.2b Nishibayashi's enantioselective propargylic substitution

Later, Nishibayashi introduced another ruthenium catalyst applicable for internal alkynes, although a chiral version of this catalyst has not been reported for an asymmetric transformation (Scheme 3.2c).[13]



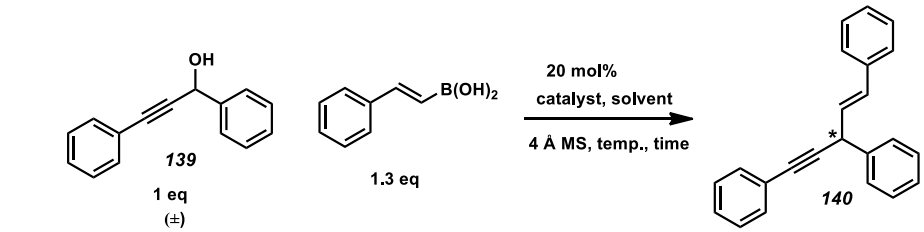
Scheme 3.2c Ruthenium-catalyzed propargylic substitution with terminal alkynes

Despite that ruthenium and copper being good catalysts for enantioselective propargylic substitution, they are only limited to terminal alkynes to form enantioenriched products. To date, we could not find an enantioselective propargylic substitution that can apply effectively to internal alkynes with metal-free, mild, and

neutral conditions. In this context, we will report our first attempts in developing the BINOL catalyzed asymmetric propargylic substitution using racemic internal alkynes.

3.3 Preliminary results

We started out screening different conditions by changing catalysts, solvents, and temperature in the reaction between propargyl alcohol **139** and styrenyl boronic acid (Table 3.3). At that time, our best conditions for the conjugate addition were 20 mol% of the BINOL catalyst in dichloroethane (DCE) at 70^{o}C, and we applied this condition to the new transformation (entry 2).



Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield	er	Note
1	None	DCE	70	14h	trace	50:50	
2	*117*	DCE	70	14h	trace	51:49	
3	*118*	DCE	70	14h	68%	53:47	
4	*89*	DCE	70	14h	20%	50:50	
5	*118*	Toluene	70	14h	0%	ND	
6	*118*	THF	70	14h	0%	ND	
7	*118*	MeCN	70	14h	trace	52:48	
8	*118*	DCE	70	5.5h	57%	56:44	1 eq of boronic acid was used
9	*118*	DCE	70	2.5h	70%	57:43	1 eq of boronic acid and catalyst was used

All yields are isolated yields.

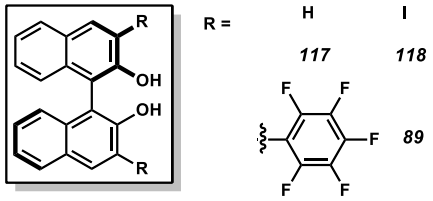


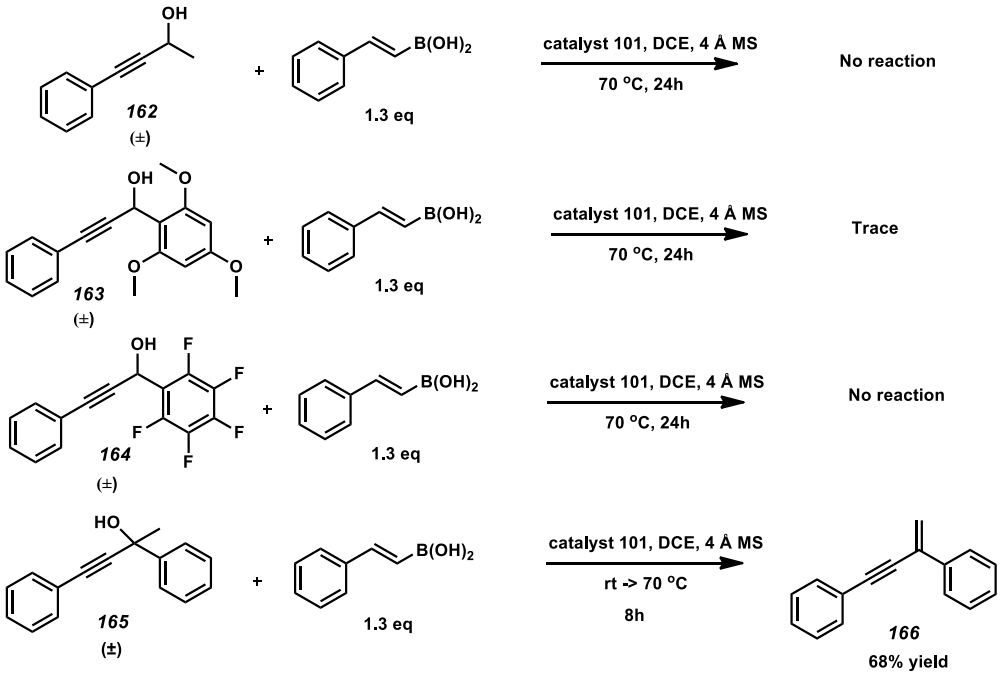
Table 3.3. Preliminary results of enantioselective propargylic substitution

The preliminary results are summarized in Table 3.3**.** The background reaction gave only trace amounts of product (entry 1). We then tried different BINOL catalysts. BINOL **117**, which has no substituents at the 3 and 3' positions, also gave negligible amounts of product (entry 2). When the bispentaflourobenzene catalyst **89** was used, a 20% yield of the product could be obtained; however, no enantioselectivity was observed (entry 4). Surprisingly, diiodo catalyst **118**, which was less reactive in the conjugate addition, gave us a better yield of the alkenylated product and some enantioselectivity

(68% yield and 53:47 er, entry 3). We next examined the effects of other solvents on the reaction outcome. However, none of them were as good as DCE (entries 5-7). The number of equivalents of the boronic acid was also shown in the conjugate addition to affect the reaction outcome. In fact, we lowered the amount of boronic acid to one equivalent and obtained the product with higher enantioselectivity, 56:44 er (entry 8). Finally, using a full equivalent of catalyst, we could isolate the product in higher yield and improve the selectivity to 57:43 er (entry 9).

3.4 Other substrates

We also tested the compatibility of the reaction with other substrates (Scheme 3.4). They were the propargyl alcohol **162** with no aromatic resonance stabilization, propargyl alcohol **163** with electron donating groups to stabilize the carbocation, and propargyl alcohol **164** with electron withdrawing groups to destabilize the carbocation. Although we were not surprised when substrates **162** and **164** gave no sign of the substitution products, alcohol **163** with strong stabilization for an intermediate carbocation reacted sluggishly, presumably due to the steric hindrance of two methoxy groups. Moreover, the substrate **165**, which could form a quaternary carbon, only provided the dehydration product **166**.



Scheme 3.4 Propargylic substitution with other substrates

3.5 Conclusion

The enantioselective propargylic substitution reaction is still in early stages of development. Preliminary results show good yields of product formation and low stereoselectivity. Once the reaction has been improved, we are confident that it will be a great method for generating new carbon-carbon bonds with a wide scope of nucleophiles and have a broad functional group tolerance.

3.5 Experimental section

3.5.1 General consideration

All reactions were carried out in flame- or oven-dried glassware. THF, toluene, and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash

chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using residual solvent peak as an internal standard ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an external standard in ^{19}F NMR spectra. NMR yields were determined by addition of 1.0 equivalent of methyl (4-nitrophenyl) carboxylate as an internal standard to the crude reaction mixture. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via ESI method and a US10252005 instrument.

3.5.2 HPLC columns for separation of enantiomers

Chiralpak AY-3: Amylose tris-(5-chloro-2-methylphenylcarbamate) coated on 3 µm silica gel

Chiralpak AD-H: Amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 µm silica gel

Chiralpak ID: Amylose tris-(3-chlorophenylcarbamate) immobilized on 5 µm silica gel

Chiralcel OJ-H: Cellulose tris-(4-methylbenzoate) coated on 5 µm silica gel

Chiralcel OD-H: Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel

Chiralpak AS-H: Amylose tris-[(S)-α-methylbenzylcarbamate) coated on 5 μm silica gel

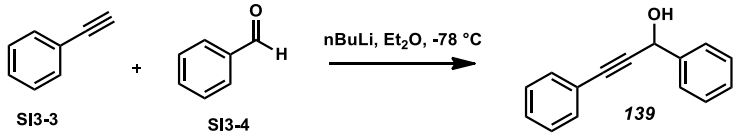
3.5.3 Materials

Commercially available compounds were purchased from Aldrich, Acros, and Alfa Aesar and were used without further purification.

3.5.4 Synthesis of Propargyl Alcohols

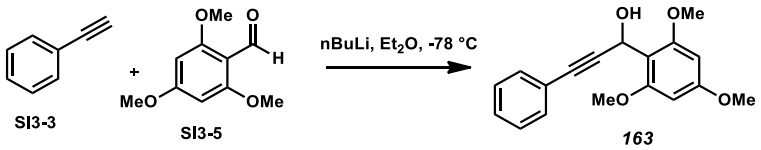
General Procedure: A flame-dried round-bottom flask was charged with anhydrous diethyl ether (0.5 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. The terminal acetylene **SI3-A** (1.0 eq) was then added under an argon atmosphere. *n*BuLi (1.0 eq, 2.5 M) was added dropwise to the flask while maintaining the reaction temperature at -78˚C . After 30 minutes at -78 ˚C, the aldehyde/ketone **SI3-1** (1.1 eq) was added dropwise (if a solid, prior to addition it was dissolved in anhydrous ether). The reaction mixture was allowed to warm to room temperature and stir for 2 hours. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.

3.5.4.1 Synthesis of 1,3-diphenylprop-2-yn-1-ol 139



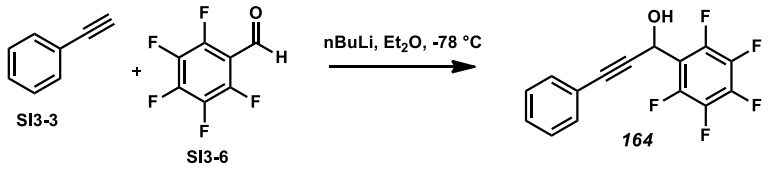
This compound was synthesized from benzaldehyde (0.56 ml, 5.5 mmol) and phenylacetylene (0.55ml, 5.0 mmol) following the general procedure. The crude product was purified by column chromatography on silica gel using a 10-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as light yellow oil that solidifies on standing (0.85 g, 82% yield), and the spectral data agreed with the reported data.[14]

3.5.4.2 Synthesis of 3-phenyl-1-(2,4,6-trimethoxyphenyl)prop-2-yn-1-ol 1963



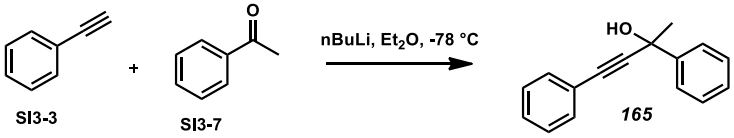
This compound was synthesized from 1,3,5-trimethoxybenzaldehyde (1.08g, 5.5 mmol) and phenylacetylene (0.55 ml, 5.0 mmol) following the general procedure. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as bright yellow solid (0.92 g, 62% yield), and the spectral data agreed with the reported data.[15]

3.5.4.3 Synthesis of 1-(perfluorophenyl)-3-phenylprop-2-yn-1-ol 133



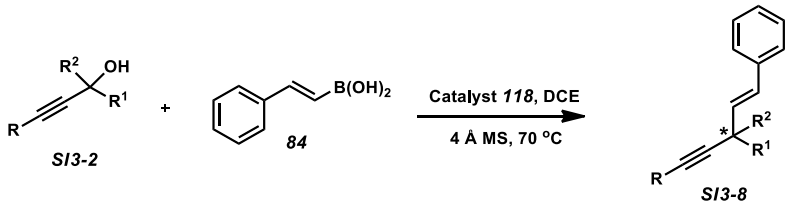
This compound was synthesized from pentaflourobenzaldehyde (0.68 ml, 5.5 mmol) and phenylacetylene (0.55 ml, 5.0 mmol) following the general procedure. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as white solid (1.09 g, 73% yield), and the spectral data agreed with the reported data.[16]

3.5.4.4 Synthesis of 2,4-diphenylbut-3-yn-2-ol 135



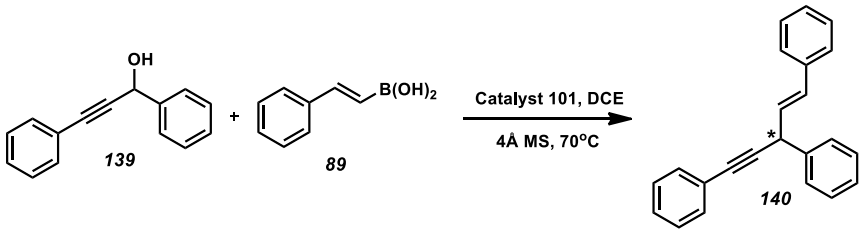
This compound was synthesized from acetophenone (0.64 ml, 5.5 mmol) and phenylacetylene (0.55ml, 5.0 mmol) following the general procedure. The crude product was purified by column chromatography on silica gel using a 5-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as white solid (1.11 g, 99% yield), and the spectral data agreed with the reported data[17]

3.5.5 Synthesis of enantioenriched propargylic substitution product



General procedure: To a 10ml flask equipped with a stir bar was added 4 Å powdered molecular sieves (100mg), and the flask was flamed-dried under high vacuum. The flask was then back-filled with Argon. After the flask was cooled to room temperature, propargyl alcohol **SI3-C** (0.2 mmol, 1 eq), boronic acid **84** (0.26 mmol, 1.3 eq), and catalyst **118** (0.04 mmol, 0.2 eq) were added. Anhydrous dichloroethane (4ml) was then added and the flask was heated to 70 ^{o}C and allowed to stir at this temperature (see each product for specific reaction times). After completion, the reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with appropriate eluents.

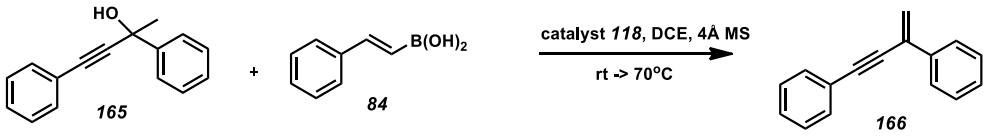
3.5.5.1 Synthesis of (E)-pent-1-en-4-yne-1,3,5-triyltribenzene 113



See general procedure for propargylic substitution above. The crude reaction mixture was purified via flash column chromatography with a 2–5% gradient of EtOAc in hexanes as eluent on silica gel. The product was obtained as pale yellow oil, and the

spectral data agreed with the reported data (see table 3.3 for yield and er).[18] HPLC Chiralcel OJ-H (hexane/*i*-PrOH = 95:5, 0.75 mL/min, UV-254 detector)

3.5.5.2 Synthesis of but-3-en-1-yne-1,3-diyldibenzene 136



See general procedure for propargylic substitution above. The crude reaction mixture was purified via flash column chromatography with a 1–3% gradient of EtOAc in hexanes as eluent on silica gel. The product was obtained as yellow oil (27.8 mg, 0.13 mmol, 68% yield), and the spectral data agreed with the reported data.[19]

3.6 References and notes

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APPENDIX TWO

HPLC data relevant to Chapter 3:

ATTEMPTS TOWARD ENANTIOSELECTIVE PROPARGYLIC SUBSTITUTION USING BORONIC ACIDS AND A BINOL CATALYST

==== Shimadzu LCsolution Analysis Report ====

C:\Documents and Settings\User\Desktop\Phong\PLI-98-3.lcd

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Sample ID	: 98
Tray#	: 1
Vail #	: 16
Injection Volume	: 10 uL
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Method File Name	: pos4_95%_30min.lcm
Batch File Name	: Batch_table_4-95%_30min_PLI-98-3.lcb
Report File Name	: Default.lcr
Data Acquired	: 6/15/2011 7:27:09 PM
Data Processed	: 6/16/2011 10:07:39 AM

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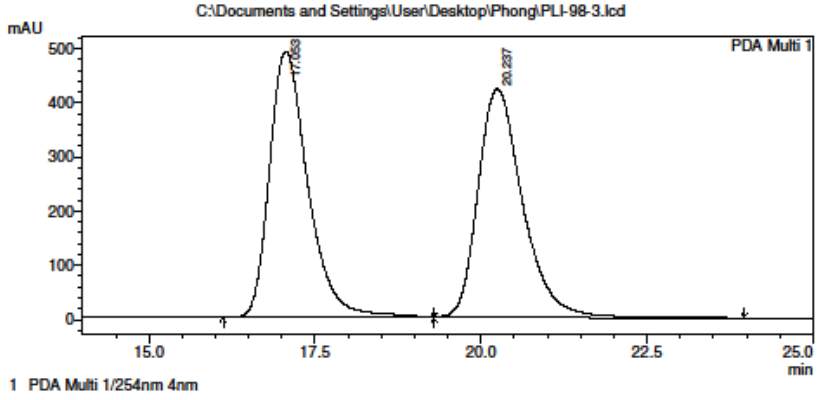
C:\Documents and Settings\User\Desktop\Phong\PLI-98-3.lcd



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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1	17.053	19836383	490747	50.074	53.733
2	20.237	19777461	422551	49.926	46.267
Total		39613845	913298	100.000	100.000

Figure A.2.1. HPLC trace for racemic compound **140**

==== Shimadzu LCsolution Analysis Report ====

C:\Documents and Settings\User\Desktop\Phong\Data\II-66B.lcd

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Sample Name	: II-66b
Sample ID	: 9
Tray#	: 1
Vail #	: 92
Injection Volume	: 10 uL
Data File Name	: II-66B.lcd
Method File Name	: pos4_95%_30min.lcm
Batch File Name	: Batch_table_4-95%_30min_PLII-46-2sample.lcb
Report File Name	: Default.lcr
Data Acquired	: 2/25/2012 5:41:49 PM
Data Processed	: 2/25/2012 6:11:53 PM

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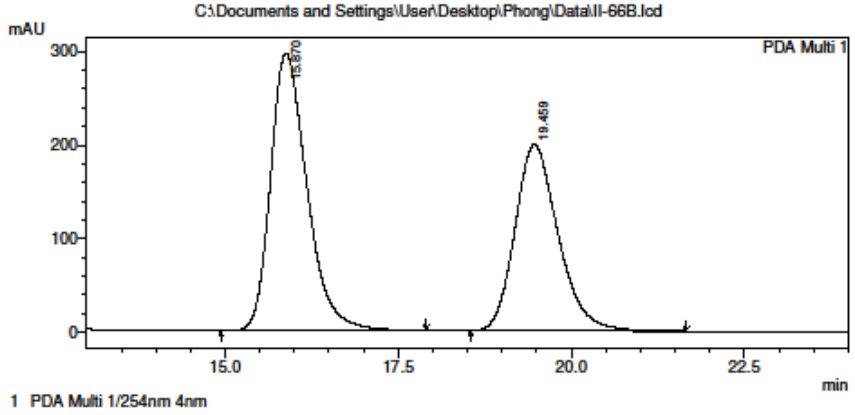

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.870	10803521	296247	55.670	59.786
2	19.459	8602823	199265	44.330	40.214
Total		19406344	495512	100.000	100.000

C:\Documents and Settings\User\Desktop\Phong\Data\II-66B.lcd

Figure A.2.2. HPLC trace for enantioenriched compound **140,** entry 8 Table 3.3

==== Shimadzu LCsolution Analysis Report ====

C:\Documents and Settings\User\Desktop\Phong\Data\II-58.lcd

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Sample ID	: 58
Tray#	: 1
Vail #	: 7
Injection Volume	: 10 uL
Data File Name	: II-58.lcd
Method File Name	: pos4_95%_30min.lcm
Batch File Name	: Batch_table_4-95%_30min_PLII-56.lcb
Report File Name	: Default.lcr
Data Acquired	: 2/15/2012 12:08:50 PM
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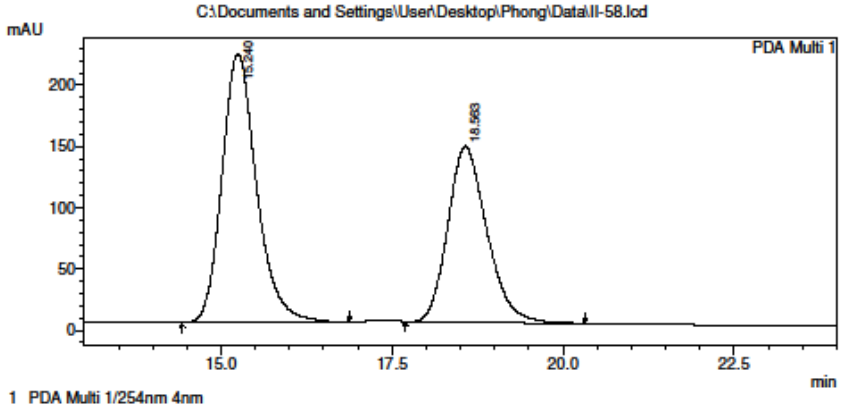


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.240	7687620	219354	57.447	60.411
2	18.563	5694400	143746	42.553	39.589
Total		13382020	363099	100.000	100.000

Figure A.2.2. HPLC trace for enantioenriched compound **140,** entry 9 Table 3.3

CHAPTER 4

RHODIUM – CATALYZED NON – CARBONYL – STABILIZED CARBENE ALKYNE CASCADE REACTIONS TO FORM BRIDGED POLYCYCLIC COMPOUNDS

4.1 Importance of bridged polycyclic systems

Bridged polycycles and bicycles are common structures present in many natural products, many of which possess great biological activities (examples in Figure 4.2). They are also challenging targets for synthetic chemists, who are interested in complex molecules.[1] Consequently, they drive innovation in organic syntheses and method development.

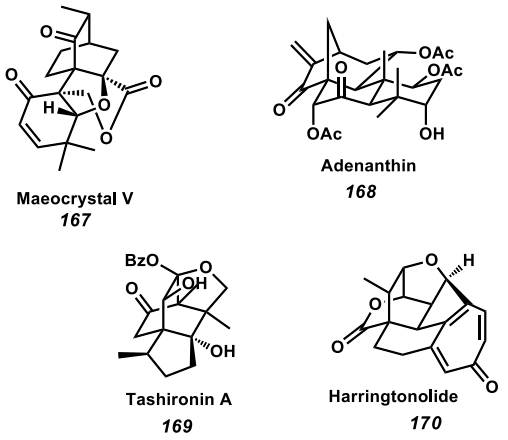


Figure 4.1. Bridged polycyclic structures in natural products

4.2 Carbene alkyne metathesis and C-H bond insertion in cascade reactions

Taking into account the significance of bridged polycycles, we desired to develop a transformation in which bridged polycycles were generated; such a method could be

efficiently applied in natural product syntheses. A carbene alkyne metathesis cascade reaction and carbene C-H bond functionalization have been two productive approaches in organic chemistry to construct complex molecules. Utilizing them in this method development would be powerful.

4.2.1 Cascade reaction

Tandem or cascade reactions play an important role in organic chemistry and are powerful tools in building molecular complexity.[2] Cascade reactions are defined as a multistep process where multiple carbon-carbon bonds can be formed in a single chemical operation. The benefits from a cascade reaction include atom economy, as well as economy of time, labor, and waste management. Normally, in total syntheses of natural products, cascade reactions will increase synthetic efficiency, achieving a more convergent strategy with easier access to more robust intermediates.

4.2.2 Introduction to carbenes and rhodium carbenes

Carbenes are neutral, divalent carbon compounds. The carbene moiety consists of a carbon with two ligands and two electrons, resulting in a six-electron carbon species. If the electrons are paired in a single orbital, the carbene is a singlet carbene. However, some carbene species have been generated where the electrons are in different orbitals with parallel spins. These carbenes are triplet carbenes and react like diradicals (Figure 4.2.2**)**.[3]

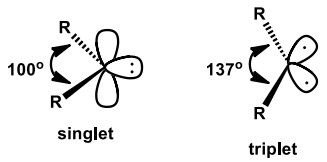
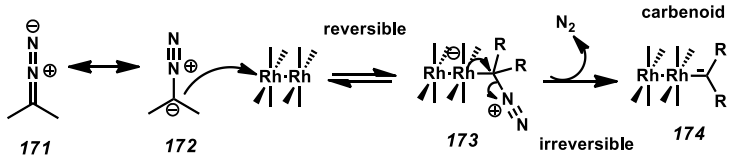


Figure 4.2.2 States of free carbenes

Carbenes are very reactive electrophiles, so they often have undesired and non-selective reactions. Therefore, metallocarbenes are used to control the reactivity. Formally, these carbenoids are carbenes directly bonded to a metal. The *d*-orbital electrons on the metal reduce the electron deficiency on the carbon, making the carbene more stable and easier to work with. When this electron donation is moderate, as in low oxidation state middle and late *d*-series metals, the carbenoids still behave electrophilically and are known as Fischer-type carbenoids. When the electron donation from the metal to the carbenic carbon is extreme, as in the early transition metals, the carbenes become nucleophilic in their reactivity and are known as Schrock-type carbenoids.[4]

There are a variety of ways to make Fischer-type carbenoids. The most common method involves transition metal-catalyzed decomposition of diazo compounds (see the example with rhodium in Scheme 4.2.2). Carbenoids (and also called metallocarbenes) are usually generated using one of these types of catalysts: rhodium, copper, palladium, ruthenium, and molybdenum complexes.[5] The most common metallocarbenes found in organic synthesis are dirhodium (II) carboxylate complexes.[6] The mild reaction conditions achievable using these catalysts increases the synthetic utility of carbene chemistry. Rhodium carbenes, like carbenes, will electrophilically add to alkenes and

aromatics, undergo Wolff rearrangements, and perform R-H bond insertion [R=C, N, O, Si, S]. [6]



Scheme 4.2.2 Rhodium catalyzed decomposition of diazo compounds

4.2.3 Stabilized carbenes and non-carbonyl-stabilized carbenes

As mentioned above, diazo compounds are useful precursors to generate metallocarbenes. The driving force for the formation lies in the extrusion of nitrogen gas (demonstrated in Scheme 4.2.2 above). However, despite their excellent reactivity, the instability of these diazo compounds is a significant problem. Diazoalkanes are challenging to prepare, inherently unstable, and even explosive in pure form. α-Diazo carbonyl compounds, on the other hand, derive resonance stabilization from the adjacent carbonyl, and consequently they are resistant to uncatalyzed decomposition for longer periods of time.[7] Diazo compounds adjacent to an aromatic ring gain same resonance stabilization, though they cannot be stored as long. In addition to the stabilization to the diazo compounds, these adjacent groups also tend to enhance the reactivity of the metallocarbenoid once it is formed, mainly because their electron-withdrawing character increases the carbene electrophilicity (Figure 4.2.3a).[8]

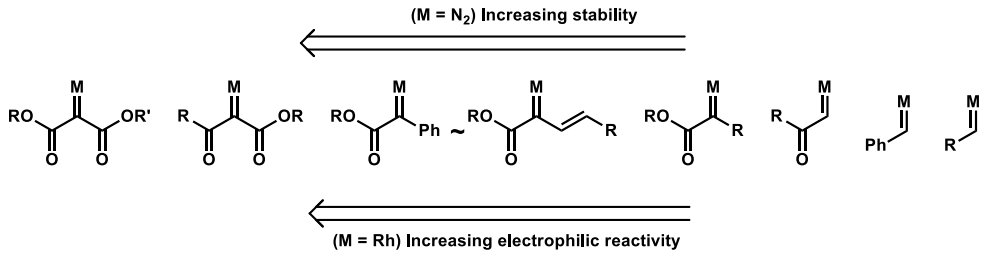
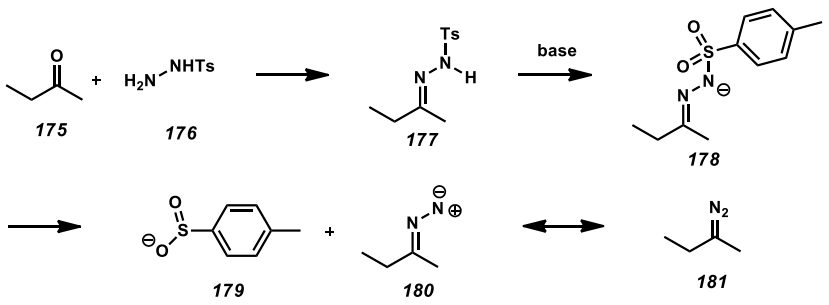


Figure 4.2.3a Stability and reactivity of diazo compounds and corresponding rhodium carbenes.

Unfortunately, the carbonyl groups required for the stabilization of diazo compounds limit their synthetic applications. A non-stabilized diazo equivalent, therefore, is in demand. Such diazo equivalents will enable the carbene generation to occur at any desired carbon and any position in the molecule in which carbenes are required for a chemical transformation.

In this scenario, tosyl hydrazones[9] and Eschenmoser hydrazones (also called *N*-aziridinyl imines)[10] have been extensively used as alternative methods for generating alkyl carbenes. May *et al.*, for example, reported the use of Eschenmoser hydrazones in tandem Bamford-Steven/Claisen reactions.[11] An Eschenmoser hydrazone can generate a diazo group thermally or photolytically. Meanwhile, the generation of a diazoalkane from a tosylhydrazone takes place in the presence of a base with thermal induction. The transformation occurs by initial deprotonation with base and subsequent spontaneous loss of the tosyl group as a sulfinate (Scheme 4.2.3b).

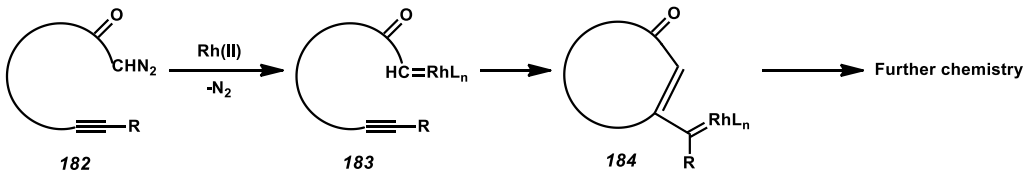


Scheme 4.2.3b Diazo formation from tosyl hydrazone

Due to its safe handling and ease of generating reactive alkyl carbenes, we pursued the use of tosyl hydrazone as a masked diazo compound in an efficient rhodium carbene alkyne metathesis cascade reaction.

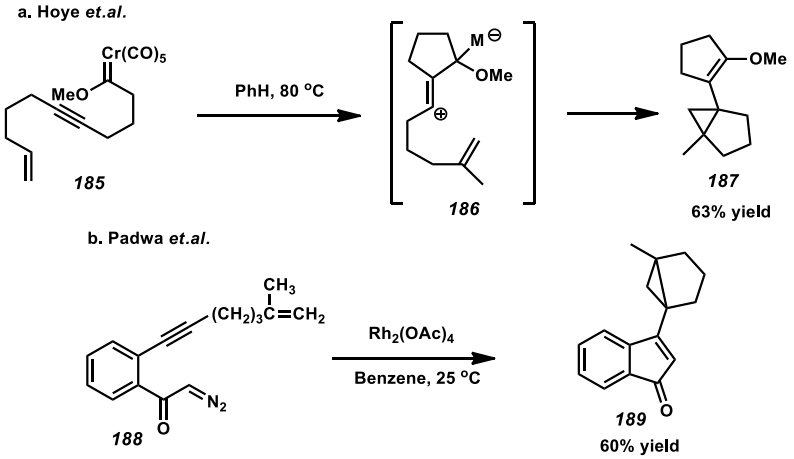
4.3 Carbene alkyne metathesis reactions

The reaction of a metal carbene with a tethered alkyne group has been previously explored. Because of the stability of their precursor diazo compounds, diazo ketones and diazo esters have been most prominently used in this reaction. Mechanistically, the transformation initially proceeds via decomposition of the α-diazo carbonyl **182** to generate a rhodium carbene like **183**. Attack of the carbenoid carbon on the π-bond alkyne generates the new vinyl carbene **184** in which carbene-like character has been transferred to the beta-carbon of the alkyne. This new vinyl carbenoid then reacts further to give novel products (Scheme 4.3a)[12]



Scheme 4.3a. The generalized rhodium carbene alkyne metathesis

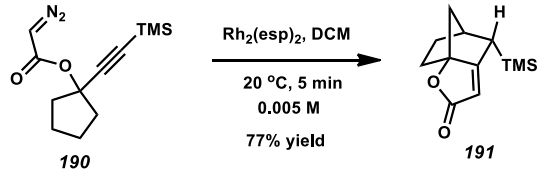
The first examples of this elegant transformation were introduced by Hoye[13] and Padwa[14] in 1988 and 1989, respectively (Scheme 4.3b). In these examples, the new vinyl carbene was trapped by a tethered alkene to form cascade products. Due to its great diversity and potential application, this carbene alkyne metathesis was then applied significantly by these two groups and others.[15]



Scheme 4.3b. Introduction of carbene alkyne metathesis

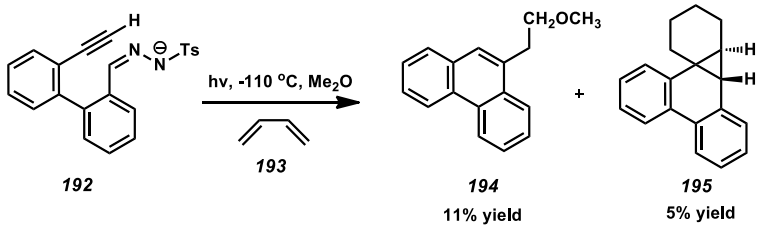
The new allylic carbene **184** could undergo variety of further transformations such as cyclopropanation, [2+3]-cycloaddition, and 1,2-hydride or alkyl migration. However, the incorporation of C-H bond functionalization in this cascade has been rare. This strategy, interestingly, was discovered by Dr. Jansone-Popova in our group in 2012

where different bridged polycycles were formed from an alkyne-tethered diazo ester like **190** (Scheme 4.3c).[16]



Scheme 4.3c. Rhodium carbene alkyne cascade forming bridged polycyclic compounds

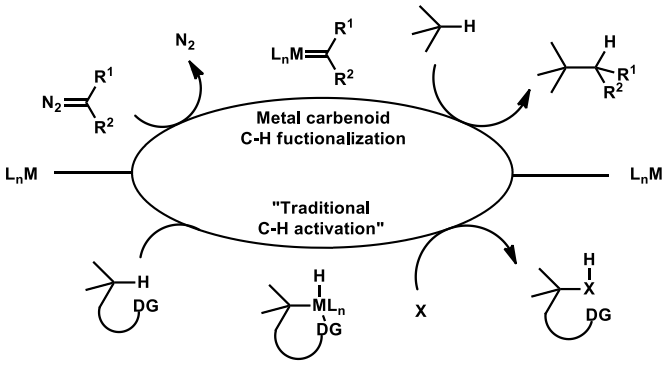
Interestingly, in 1975, Mykytka *et al.* reported a reaction of an aromatic-stabilized diazo compound generated from tosyl hydrazone with a tethered alkyne (Scheme 4.3d).[17] The research showed different pathways for a free carbene alkyne metathesis reaction.



Scheme 4.3d Free carbene alkyne metathesis

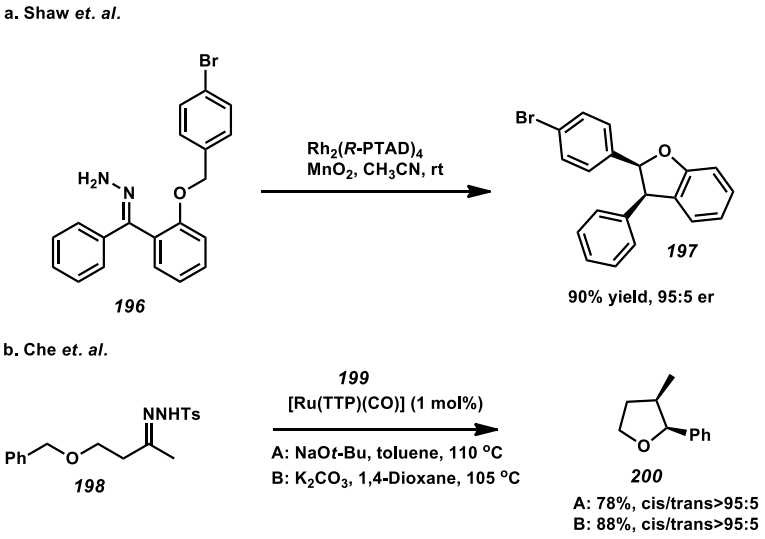
4.4 C-H functionalization by alkyl carbenes

In recent years, insertions into an unreactive C-H bond by metal carbenes are rapidly becoming general strategic reactions for the synthesis of natural products and pharmaceutical targets. Unlike C-H activation using highly reactive transition metal complexes in which a directing group usually needed, the C-H insertion by a metallocarbene has achieved high chemoselectivity, regioselectivity and stereoselectivity without requirement of directing groups (Scheme 4.4a).[18]



Scheme 4.4a C-H activation by metal complexes vs carbene C-H bond insertion

In contrast to the substantial number of publications related to C-H bond functionalization using carbonyl-stabilized metallocarbenes, C-H bond insertions with metal carbenes produced from a tosylhydrazone have been less explored. Recently, Shaw *et al.* reported the highly enantioselective intramolecular C−H insertion reactions of donor−donor metal carbenes.[19] In his report, a chiral metallocarbene generated from the decomposition of an aromatic hydrazones provides a variety of ethers with high efficiency and stereoselectivity (Scheme 4.3.4b). The same year, Che and coworkers introduced a diastereoselective intramolecular alkyl carbene insertion into C-H bonds of alkyl diazomethanes generated in situ from *N*-tosylhydrazones (Scheme 4.4b).[20]

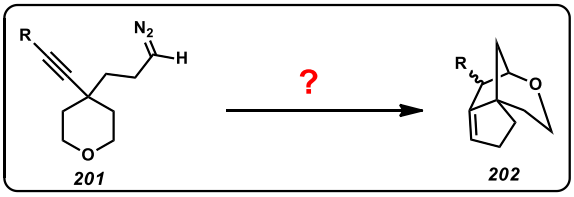


Scheme 4.4b Metal carbene C-H functionalization from tosylhydrazones.

The great success in the development of highly efficient methods in both carbene alkyne metathesis reactions and C-H bond functionalization by metal carbenes has inspired an approach that could apply to the synthesis of polycycles. This approach will be presented in the next section.

4.5 Our approach

We realized that Jansone-Popova's method is an excellent strategy to synthesize bridged polycyclic compounds. If a diazo ester could initiate the rhodium-catalyzed carbene alkyne cascade reaction, an alkyl diazo (**201** in Scheme 4.5), thermally generated from tosyl hydrazone and base, should provide the polycyclic products in the same manner.



Scheme 4.5. New strategy for the alkyl carbene alkyne cascade reaction

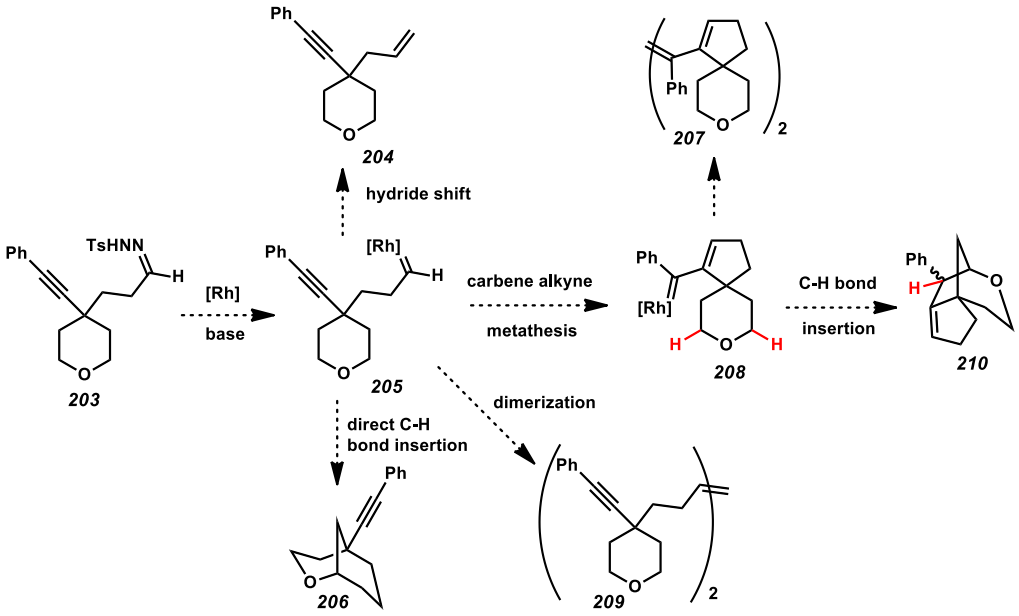
We envisioned that an alkyl metal carbene would have different reactivity relative to the carbonyl-stabilized carbene. However, its precursor, a diazoalkane, is unstable and could be explosive. Furthermore, the lack of an electron-withdrawing group could decrease the electrophilicity of the metal carbene toward an electron-rich alkyne π-system.

However, there are other factors that we can count on to enable the reaction. Firstly, the diazoalkane will be formed gradually in the reaction conditions, giving it less time to exist in the solution before the rhodium catalyst reacts with it, consequently preventing by-product formation. Secondly, although the alkyl metal carbenes are less electrophilic than the carbonyl-stabilized metallocarbenes, we think that with an appropriate rhodium catalyst, we could have sufficient electrophilicity on the alkyl carbenoid and have a better selectivity for the cascade reaction. Furthermore, the high temperature we use to generate the diazo compound from the tosyl hydrazone could compensate for the lack of reactivity of the alkyl carbenoid.

4.6 Concerns

As shown in Scheme 4.6, the cascade reaction could go through several other pathways to give undesired products. The first step would be the rhodium-catalyzed diazo

decomposition to give rhodium alkyl carbenoid **205**. From here, the carbenoid could form a dimer product **209**, the olefin **204** from a 1,2-hydrogen shift (known as a Bamford-Stevens reaction), or undergo direct C-H bond functionalization at the methylene next to the oxygen (product **206**). Even when the metathesis intermediate **208** is generated, dimerization could also occur and diminish formation of **210** (product **207**). Bicycle **210** from the insertion of the carbene to the highlighted C-H bond is the desired product.

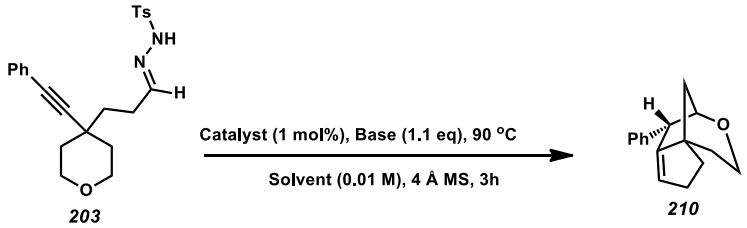


Scheme 4.6 Possible pathways in the rhodium alkyl carbene alkyne cascade reaction

4.7 Improvement of reaction conditions

The hydrazone **203** was quickly synthesized. To start examining the feasibility of the transformation, we utilized the conditions that are wildly used to generate alkyl diazo compounds from tosyl hydrazones.[21] This tosylhydrazone was added at 90^{o}C together with 1.1 equivalents of *tert*-butoxide as a base, 4 Å molecular sieves (MS), descicant to

prevent insertion into water's O-H bond, and 1 mol% of $Rh_2(esp)_2$, the most effective catalyst in carbene/alkyne metathesis and C-H insertion (Table 4.7).



203 *210*

Entry	catalyst	base	solvent	conc.	yield (%)
1	$Rh_2(esp)_2$	LiOtBu	Dioxane	0.01 M	78%
2	$Rh_2(esp)_2$	NaOtBu	Dioxane	0.01 M	76%
3	$Rh_2(esp)_2$	KOtBu	Dioxane	0.01 M	70%
4	$Rh_2(esp)_2$	NaOtBu	DCE	0.01 M	23%
6	$Rh_2(esp)_2$	NaOtBu	Toluene	0.01 M	45%
7	$Rh_2(esp)_2$	NaOtBu	MeCN	0.01 M	trace
8	$Rh_2(esp)_2$	NaOtBu	DME	0.01 M	none
9	$Rh_2(esp)_2$	NaOtPent	Dioxane	0.01 M	81%
10	$Rh_2(esp)_2$	NaOTMS	Dioxane	0.01 M	85%
11	$Rh_2(esp)_2$	NaOTMS	Dioxane	0.02 M	69%
12	$Rh_2(esp)_2$	NaOTMS	Dioxane	0.05 M	72%
13	$Rh_2(OAc)_4$	NaOTMS	Dioxane	0.01 M	52%
14	$Rh_2(cap)_2$	NaOTMS	Dioxane	0.01 M	34%
15	$Rh_2(TFA)_4$	NaOTMS	Dioxane	0.01 M	30%
16	$Rh_2(piv)_4$	NaOTMS	Dioxane	0.01 M	88%
17	$Rh_2(piv)_4$ (0.5 mol%)	NaOTMS	Dioxane	0.01 M	82%
18	$(CuOTf)_2.PhH$ (10 mol%)	NaOTMS	Dioxane	0.01 M	none
19	CuI (10 mol%)	NaOTMS	Dioxane	0.01 M	none
20	None	NaOTMS	Dioxane	0.01 M	none

Table 4.7 Optimization of the reaction

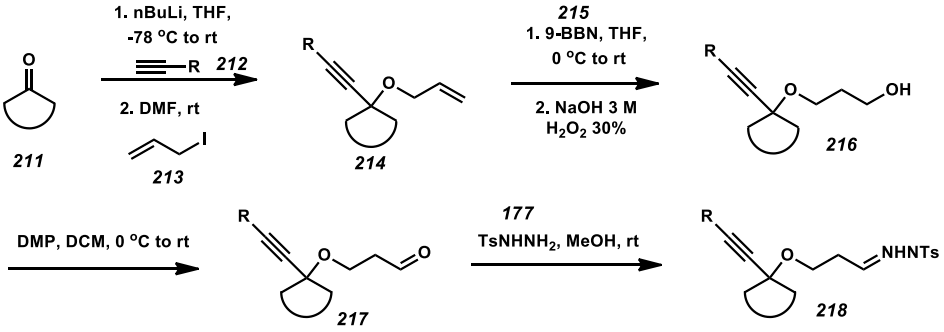
The first parameter we wanted to evaluate is the counter ion of the tosylhydrazone salts, as it is an important factor.[9a] To our delight, potassium, sodium, and lithium *tert*-butoxide provide the bridged oxabicyclo[3.2.1]octane **210** in good yield in just 3 hours. Lithium and sodium were better counter ions than potassium (entries 1-3, Table 4.7). More excitingly, only one diastereomer of the cascade product was obtained. We choose sodium *tert*-butoxide as the base for exploration of the other reaction parameters because it afforded a cleaner reaction while giving a similar yield (76% to 78% isolated yield). Dioxane was found to be the superior solvent, and no insertion into the C-H bond of the solvent was observed (entries 4-8). In looking at a milder base, we were excited to find that sodium trimethylsilanolate give a greater yield, and the reaction was even cleaner than when using NaO*t*Bu (entry 10). Trying a more concentrated reaction was less successful, although the product was still formed in moderate yield (entries 11-12).

Other catalytic systems were also tested. Copper (I) is an effective catalyst in other tosylhydrazone-diazo decompositions;[22] however it was unproductive here (entries 18-19). Other rhodium catalysts, with an electron-donating ligand or with an electron-withdrawing ligand, were also not as good (entries 13-15). To our surprise, $Rh_2(piv)_4$, a simpler version of $Rh_2(esp)_2$, also generated the polycyclic product in similar yield as $Rh_2(esp)_2$ (88% to 85%, compare entry 16 to entry 10), although $Rh_2(piv)_4$ has been shown to be less effective than $Rh_2(esp)_2$ in nitrene C-H insertion.[23] $Rh_2(piv)_4$ is much cheaper and much easier to synthesize than $Rh_2(esp)_2$. To examine the scope of this method, we will use both of these as catalysts.

4.8 Synthesis of starting materials

4.8.1 Starting materials for 6-exo-dig cyclization

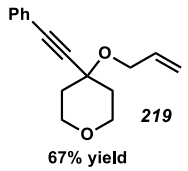
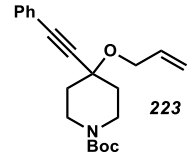
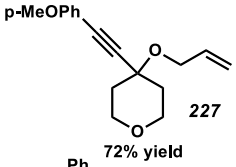
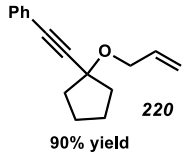
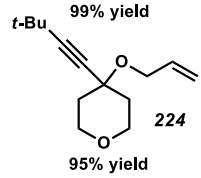
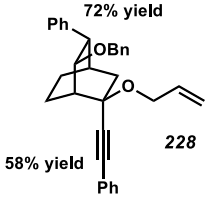
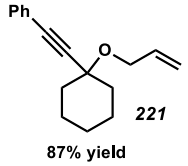
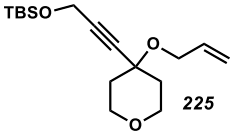
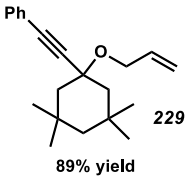
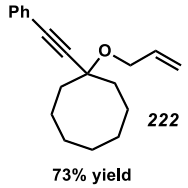
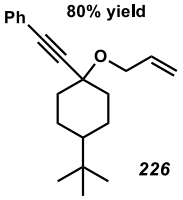
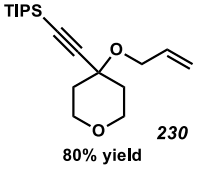
The polycyclic product **210** was generated from a 5-exo-dig carbene alkyne cyclization. We would like to see if a 6-exo-dig cyclization would work in the same manner to give other types of polycycles. The results of the cascade reaction will be shown later; in this section, we want to report how the starting materials were synthesized.



Scheme 4.8.1 General scheme for the synthesis of tosyl hydrazones

We started with nucleophilic addition of lithium acetylides (like **212)** to different cyclic ketones (like **211**) and obtained varieties of tertiary alcohols (Scheme 4.8.1). These propargylic alcohols then underwent allylic substitution with allyl iodide to give the allylated products. These reactions initially took two steps. However, we could shorten the sequence to only one operational step by omitting the alcohol isolation. After the acetylide addition, instead of quenching the reaction with a proton source, we added the allyl iodide and DMF directly to the reaction mixture with the alkoxide intermediate. The

allylated products **214** also were obtained in high to excellent yield by this method (Table 4.8.1a).

Entry	Product	Entry	Product	Entry	Product
1	 **219** 67% yield	5	 **223** 99% yield	9	 **227** 72% yield
2	 **220** 90% yield	6	 **224** 95% yield	10	 **228** 58% yield
3	 **221** 87% yield	7	 **225** 80% yield	11	 **229** 89% yield
4	 **222** 73% yield	8	 **226** 81% yield dr 3.3:1	12	 **230** 80% yield

Scheme 4.8.1a Synthesis of allylated compounds

Hydroboration with 9-BBN was used to convert the allylic groups (as in **214**, Scheme 4.8.1) into primary alcohols (like **216**), which were then were oxidized by Dess-Martin periodinane (DMP) to give aldehydes (like **217**). It is worth mentioning that the Swern oxidation was used at first; however, DMP oxidation was later employed because it is much simpler and faster (see Table 4.8.1b for hydroboration products).

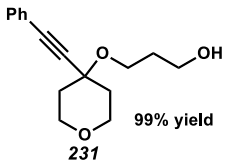
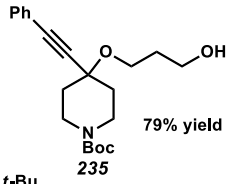
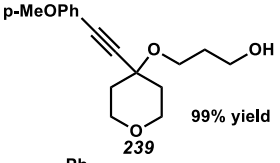
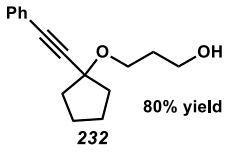
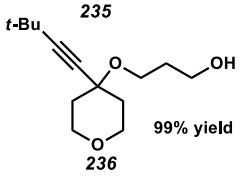
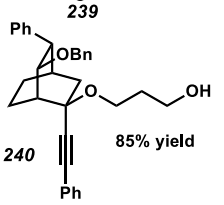
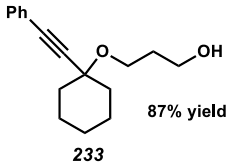
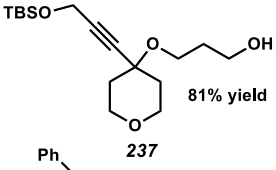
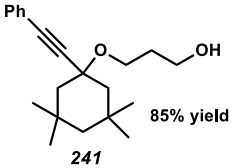
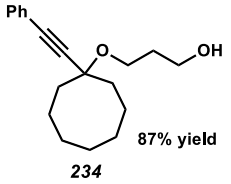
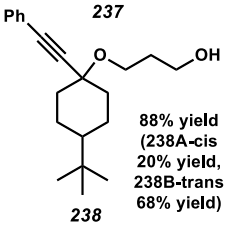
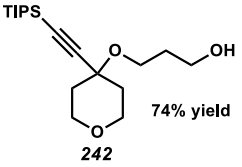
Entry	Product	Entry	Product	Entry	Product
1	 99% yield *231*	5	 79% yield *235*	9	 99% yield *239*
2	 80% yield *232*	6	 99% yield *236*	10	 85% yield *240*
3	 87% yield *233*	7	 81% yield *237*	11	 85% yield *241*
4	 87% yield *234*	8	 88% yield (238A-cis 20% yield, 238B-trans 68% yield) *238*	12	 74% yield *242*

Table 4.8.1b Hydroboration of allyl ethers

Due to the alkyl aldehydes tending to be oxidized and decompose over time, we immediately converted the aldehydes to the hydrazones with tosylhydrazide (**177**) in methanol after the confirmation of the aldehydes' structure by ^{1}H NMR (Table 4.8.1c). The tosylhydrazones are white solids and could be stored for a long period of time at low temperature. However, if trace amounts of solvent were present in the products, the hydrazones were prone to hydrolysis back to the aldehydes.

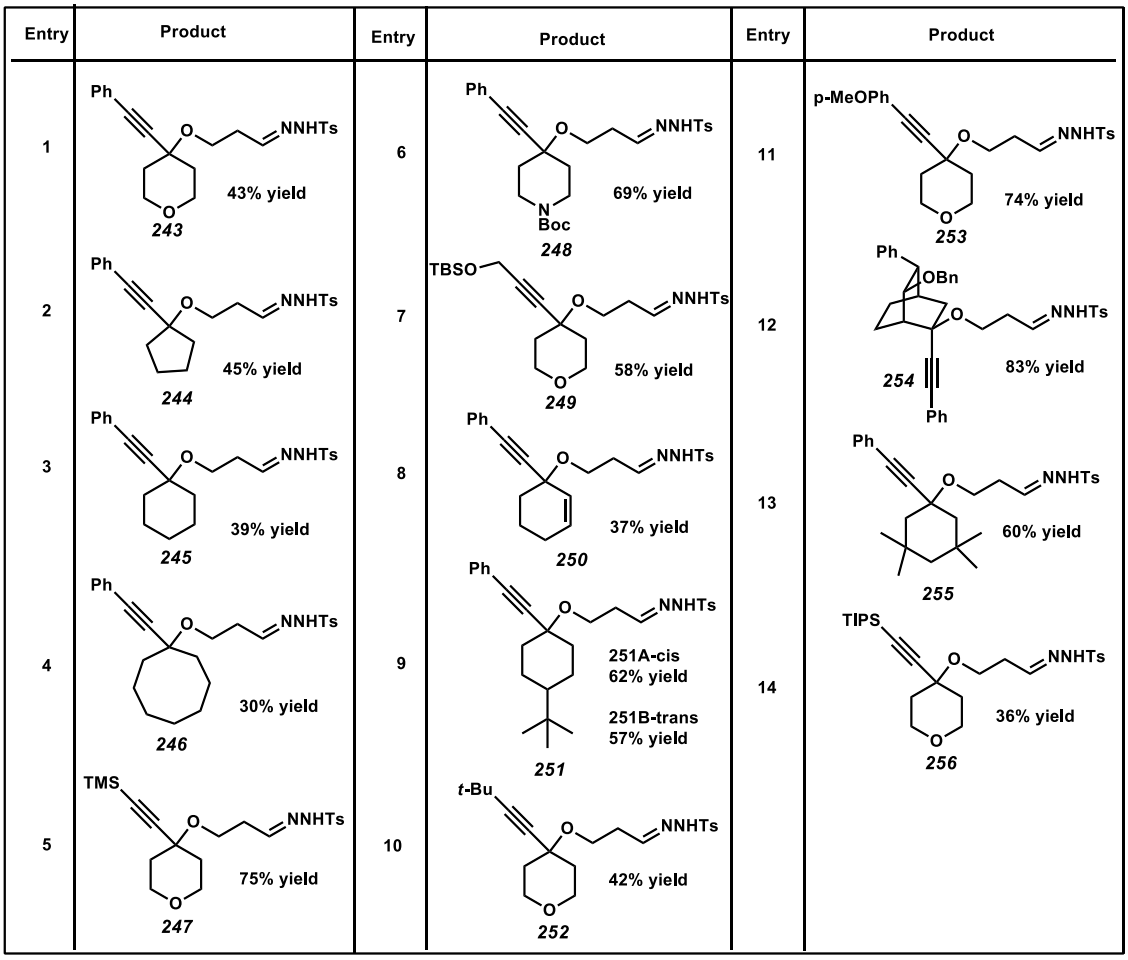
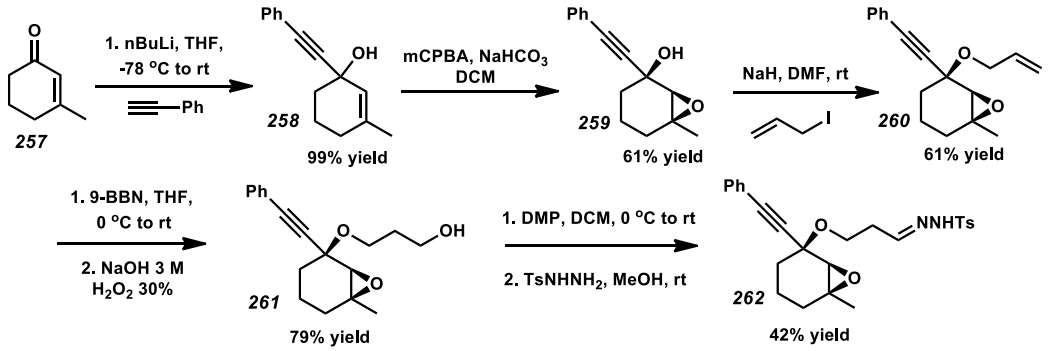


Table 4.8.1c Tosylhydrazone formation

4.8.2 Synthesis of a tosyl hydrazone with an epoxide group

This substrate was synthesized similarly to the general procedure above. After the formation of the propargyl alcohol **258** through lithium acetylide nucleophilic addition, hydroxyl-directed epoxidation with mCPPA gave epoxide **259** in good yield (Scheme 4.8.2). The alcoholic epoxide **259** then underwent allylic substitution with allyl iodide and sodium hydride to provide ether **260** in good yield. To obtain the primary alcohol

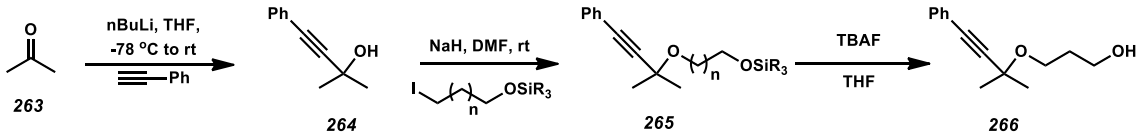
261, we performed hydroboration on **260** with 9-BBN. Finally, DMP oxidation and tosylhydrazone formation on **261** gave hydrazone **262** in acceptable yield.



Schem 4.8.2 Synthesis of epoxide **262**.

4.8.3 Other primary alcohols

For synthesizing the substrates where we could not use hydroboration to form the primary alcohols, we followed the general procedure in Scheme 4.8.3. The tertiary alcohol **264** was alkylated with a silyloxy iodoalkane to form propargyl ether **265**. Next, silyl deprotection using TBAF on the ether **265** provided the primary alcohol **266** (see experimental section for more details).

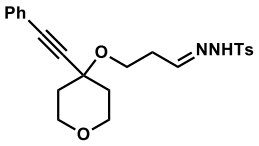
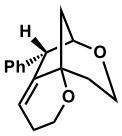
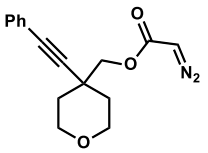
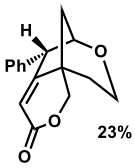
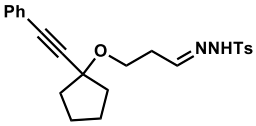
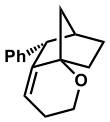
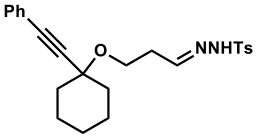
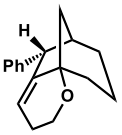
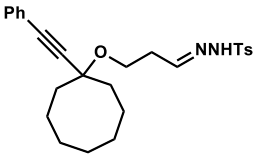
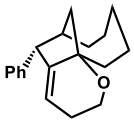
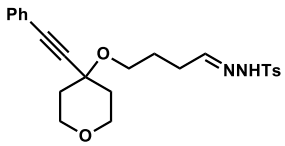
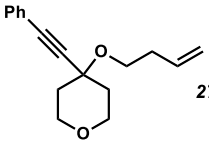


Scheme 4.8.3 General procedure for syntheses of other primary alcohols

4.9 Substrate scope of the rhodium-catalyzed cascade reaction

4.9.1 Variants of ring size

We first focused on testing the feasibility of forming different ring sizes (Table 4.9.1). We were very surprised but excited when the oxabicyclo[3.2.1]octane **268** was obtained in 82% yield, a similar yield to the bicycle **210** (entry 1). **268** is generated from 6-exo-dig cyclization of the metallocarbene to the alkyne. Generally, 6-exo-dig cyclization is more difficult than a 5-exo-dig cyclization. For example, the cascade reaction using a diazoester gave the oxabicyclo[3.2.1]octane product similar to **268** in just around 23% yield (entry 2).[24] The 7-exo-dig cyclization substrate (**267**), however, did not provide any cascade product. Instead, when hydrazone **267** was subjected to the reaction condition, a 1,2-hydrogen shift occurred in the major product (entry 6).

Entry	Starting material	Product
1	 *243*	 *268* 82% yield
2		 23% yield*
3	 *244*	 *269* 51% yield
4	 *245*	 *270* 72% yield (dr 7:1)**
5	 *246*	 *271* 69% yield (4:1 dr)
6	 *267*	 *272* 60% yield

* The reaction with $Rh_2(esp)_2$, DCM at reflux

** The reaction was run at 140 °C in sealed tube

Table 4.9.1 Bridged polycycles with various ring size

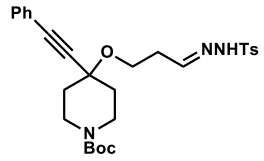
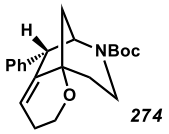
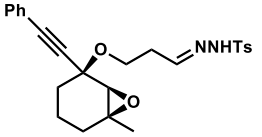
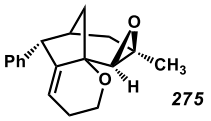
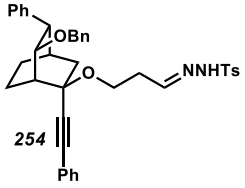
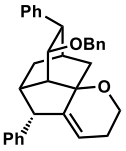
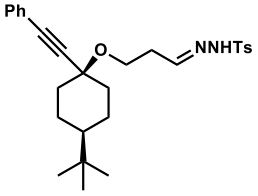
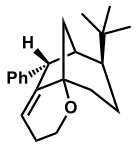
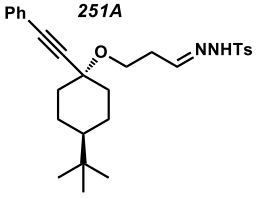
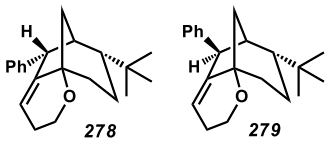
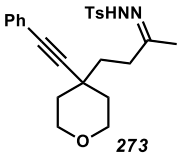
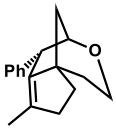
Due to the ease of synthesis, we chose the 6-exo-dig cyclization substrates with different ring patterns to explore the compatibility of our method. As shown in Table 4.9.1, the bicyclo[2.2.1]heptane **269** was formed in only 27% yield with $Rh_2(piv)_4$. However, the product's formation could be improved to 51% yield when $Rh_2(esp)_2$ was

used (entry 3). On the other hand, the bicyclo[5.2.1]decane **271** was obtained as the major product, and no product from insertions into the other methylenes was observed (entry 5).

When the hydrazone **245** was used, the reaction went slowly, with only trace amounts of the cascade product. The outcome of the reaction, however, was predictable. When comparing the compounds **243** and **245**, the only difference is the C-H bond that reacts. The C-H bond in **243** is activated by the adjacent oxygen atom. The C-H bond insertion in **245**, consequently, was more difficult because of the lack of activation. One solution could be the use of more electrophilic rhodium catalyst to facilitate the C-H bond functionalization. Unfortunately, when we employed $Rh_2(TFA)_4$, more by-products were formed due to an unknown decomposition. At this time, we realized that the reaction was just slow; therefore, a higher temperature could speed up the reaction and provide more energy to the C-H bond insertion step. In fact, when we heated the reaction to 140^{o}C in a sealed tube, the product **270** was generated in 71% yield (entry 4). Because of the higher temperature, the diastereoselectivity of the reaction decreased and we observed the other diastereomer.

4.9.2 Variants of the groups on the ring.

We next put our efforts toward generating more useful bridged bicycles (Table 4.9.2). The Boc-protected pyrolidine **248** provided exclusively the cascade product **274** in high yield (entry 1). The bridged bicycle **274** is highly practical as it could serve as a core structure for alkaloid natural products.[25] Furthermore, the epoxide **275** was obtained in excellent yield. Since the reaction occurs under basic conditions, the epoxide tolerance is surprising (entry 2).

Entry	Starting material	Product
1	 248	 274 82% yield
2	 262	 275 97% yield
3	 254	 276 54% yield (1.5:1 dr)
4	 251A	 277 83% yield*
5	 251B	 278 279 71% yield (dr 3:1)*
6	 273	 280 52% yield*

* The reaction was run at 140 °C in a sealed tube

Table 4.9.2 Other bridged polycyclic products

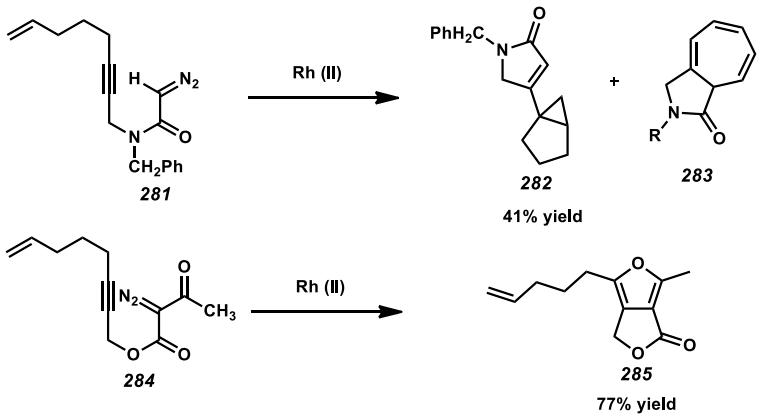
The caged polycycles increase the complexity in the molecules. As shown in our Table 4.9.2, the caged polycyclic compound **276** was obtained in good yield (entry 3). This product is similar to the core of Palhinine A, one of the natural product targets in our laboratory.

Interestingly, we were able to synthesize two sterically hindered-cis/trans t-butyl hydrazone isomers **251A** and **251B** to evaluate the steric effects on the reaction outcome. Unsurprisingly, both of the starting materials **251A** and **251B** gave no sign of cascade products when the reaction was run at 90^{o}C. However, at 140^{o}C, we observed different results. Although the bicyclo[3.2.1]octanes were still the only products to be isolated, the trans hydrazone **251B** gave two diastereomers while the cis hydrazone **251A** produce only one (entries 5 and 4, respectively).

Finally, we were delighted when the ketone hydrazone **273** afforded the bridged bicycle **280,** in which the olefin is tetrasubstituted, in moderate yield (entry 6). This is in contrast to alkyl substituted carbonyl-stabilized metallocarbenes in which a 1,2-hydrogen shift usually occurs.

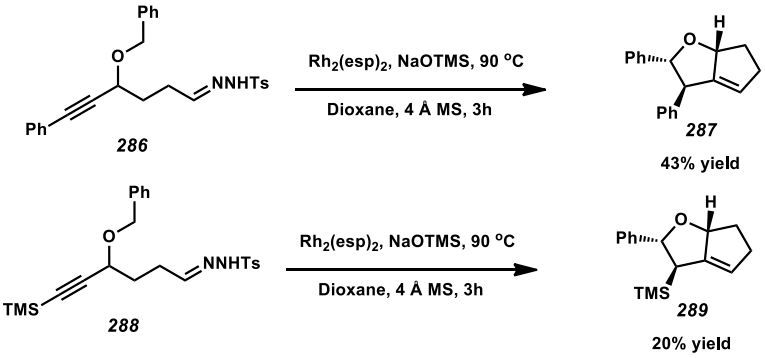
4.9.3 Cascade reaction on acyclic system

The fused bicycle products have been shown difficult to obtain using acyclic systems in rhodium carbene cascade reactions. The reason lies in the flexibility of the system, as more than one rotamer of the structure could be present making the metathesis transformation more difficult.[26] The problems usually could be overcome when a distabilized diazo ketoester was employed (Scheme 4.9.3a).[27]



Scheme 4.9.3a Carbonyl-stabilized carbene alkyne cascade reactions with acyclic system

We were able to obtain the fused bicycle **287** and **289** in single diastereomer, although the yields were low. The low yield of **289** could be from purification process since we observed **289** as the major component in crude ^{1}H NMR.

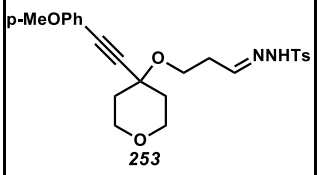
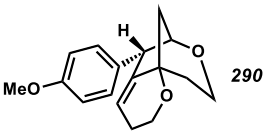
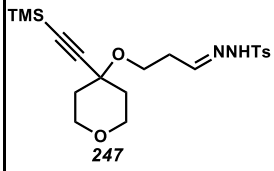
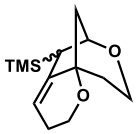


Scheme 4.9.3b Non-carbonyl-stabilized carbene cascade reactions with acyclic systems

4.9.4 Substituents on the alkyne

We were also concerned about electronic effects on the reaction, so we put different substituents on the alkyne (Table 4.9.4). When a hydrazone with an electron-donating group on the phenyl substituent was used (**253**), the reaction proceeded

sluggishly. The product **290** was isolated in only 31% yield at 90°C. However, the formation of the product could be increased to 68% yield when we ran the reaction at 140°C (entry 1).

Entry	Starting material	Product
1	 *253*	 *290* 68% yield*
2	 *247*	 *291* 8% yield

* The reaction was run at 140 °C in a sealed tube

Table 4.9.4 Other substituents on the alkyne of tosylhydrazone substrates

A silyl substituent on the alkyne, on the other hand, was not as effective as the phenyl (entry 2). This is different the cascade reaction with diazoesters, where silyl groups normally give good yields of the bridged bicyclic products. In addition to an unexpected product, we could also obtain the trimethylsilyl **291** in low yield. Furthermore, a *tert*-butyl group on the alkyne gave only another unexpected compound, but not a bridged bicyclic. These two unexpected products will be mentioned in the mechanistic study section of this chapter.

4.10 Competition of other mechanism with the metathesis reaction

While the reaction of an alkyl metallocarbene with an alkyne is rare, its reaction with other reactive centers such as in C-H bond functionalization, cyclopropanation, and

1,2-hydrogen migration, etc…is better known, Therefore, it will be important to know how well the metathesis reaction occurs when other reactions can compete.

When we operated the cascade reaction with compounds **203** and **243** in which C-H bonds are activated by the adjacent oxygen atom, we observed only trace amounts of the olefin coming from the 1,2-hydrogen shift or Bamford-Stevens reaction (as in **204** in Scheme 4.6). Obviously in this case, the 1,2-hydrogen shift was slower than the carbene alkyne metathesis and C-H bond insertion. However, as we explored other substrates with a less reactive C-H bond (like **244** and **245**, Figure 4.10), relatively more of the olefin was generated. Presumably, the C-H insertion step was slower, therefore giving more time for the Bamford-Stevens reaction to occur.

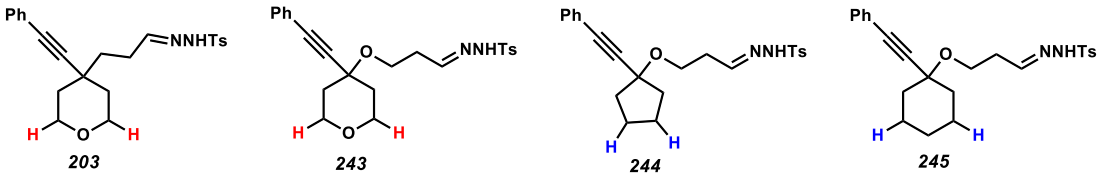


Figure 4.10 Hydrazone starting materials with different C-H bond for insertion

The 1,2-hydrogen migration happened even in larger magnitude with hydrazone **292** since we obtained the vinyl ether **293** as the only product (entry 1, Table 4.10). Obviously, the oxygen atom has activated the migration of the hydrogen to the electrophilic carbene. This argument can be applied in the case of TBS-protected propagyl ether **249** as well. With this substrate, the carbene alkyne metathesis took place very fast, but the oxygen at the propargylic position facilitated the migration of hydrogen to the newly-formed vinyl carbene and provided the diene **294** in high yield.

Interestingly, we could observe a small amount of the C-H bond insertion product **295** (entry 2).

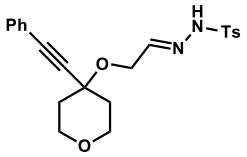
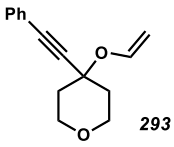
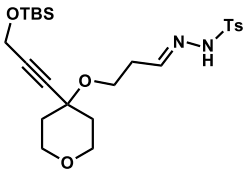
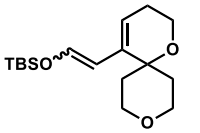
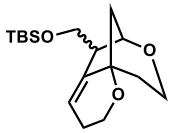
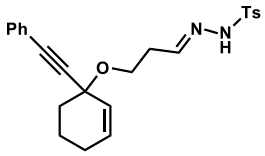
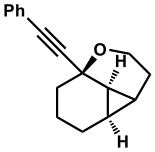
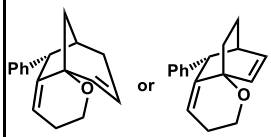
Entry	Starting material	Product
1	 *292*	 *293* 78% yield
2	 *249*	 *294* 70% yield  *295* trace
3	 *250*	 *296* 54% yield  *297A* or *297B* 24% yield

Table 4.10 Competition experiments

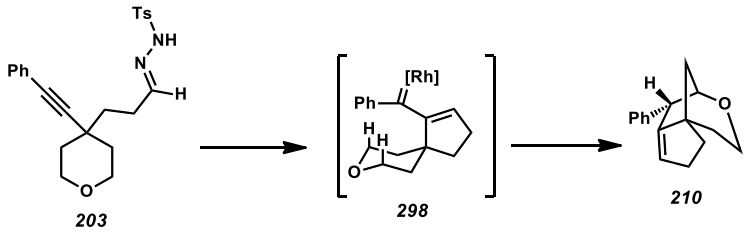
Moreover, when we carried out the reaction with cyclohexenyl hydrazone **250**, we obtained cyclopropane **296** as the major product, and the bridged bicycle **297A** or **297B** as the minor product. This is reasonable, as the double bond is a better nucleophile than

triple bond toward the electrophilic carbene. Determination of the structure of the minor product is ongoing.

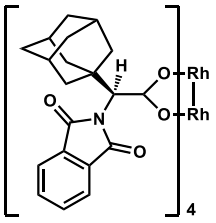
4.11 Asymmetric cascade reactions for enantiopure bridged polycycles

From the beginning of this chapter, we have emphasized how important the bridged polycycles are and how a method that could generate those polycycles productively is valuable. The method that we successfully developed could shorten the length of a natural product synthesis, save time, and save chemical expenses. However, the ability to generate the products in an asymmetric manner is also important since most of the target compounds are present in nature in their enantiopure form. Therefore, we looked to transform the method that we developed into an enantioselective cascade reaction. Such a reaction could increase its application to the synthesis of enantioenriched natural products.

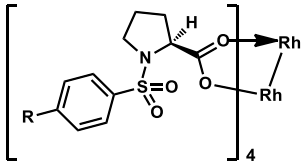
As shown in Table 4.11, the hydrazone **203** is a meso structure. After the carbene alkyne metathesis reaction, the new vinyl carbene in **298** has two choices for the C-H bond insertion. Each of these C-H bond insertions will give a different enantiomer of the bridged polycyclic product. A chiral ligand on the rhodium catalyst will be needed for the metallocarbene to differentiate the site for the C-H bond functionalization.



Entry	Catalyst	Base	Solvent	Tempt	Yield (%)	er
1	$Rh_2(esp)_2$	NaOTMS	Dioxane	90 °C	85%	50:50
2	Rh_2(S-PTAD)$_2$	NaOTMS	Dioxane	90 °C	86%	77:23
3	Rh_2(S-PTAD)$_2$	NaOTMS	Dioxane	60 °C	68%	86:14
4	Rh_2(S-DOSP)$_4$	NaOTMS	Dioxane	90 °C	14%	>99:1
5	Rh_2(S-TBSP)$_4$ (5 mol%)	NaOTMS	Dioxane	90 °C	38%	>99:1



Rh_2(S-PTAD)$_4$



R = $CH_2(CH_2)_{9\text{-}11}CH_3$: Rh_2(S-DOSP)$_4$
R = *tert*-butyl : RH_2(S-TBSP)$_4$

Table 4.11 Catalyst screening for an enantioselective cascade reaction

Table 4.11 showed the results of different chiral rhodium catalysts in the cascade reaction. These catalysts have been found effective in many enantioselective reactions. The Rh_2(S-PTAD)$_4$ gave hope of an successful transformation when it provided product **210** in 85% yield and an enantiomeric ratio of 77:23 (entry 2). Lower temperature could be a solution to have a better selectivity. In fact, at 60^{o}C Rh_2(S-PTAD)$_4$ gave **210** in higher enantioselectivity (86:14 er, entry 3); however, the yield of the reaction dropped to 68%. To our delight, Rh_2(S-DOSP)$_4$ gave products in almost enantiopure form with larger than 99:1 er, although the yield of the reaction was only 14% (entry 4). When

using with 5 mol% of Rh_2(S-TBSP)$_4$, a similar catalyst to Rh_2(S-DOSP)$_4$, the selectivity was still excellent and the product could be obtained in higher yield, 38% (entry 5).

We are now in the process of developing a new chiral rhodium catalyst for this cascade reaction. These preliminary results for an enantioselective transformation are promising.

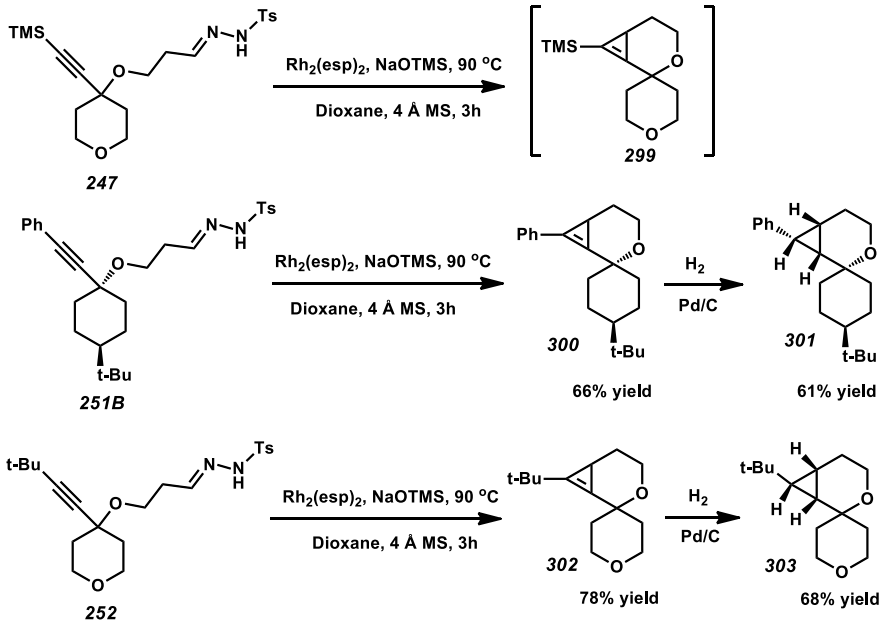
4.12 Mechanistic study

4.12.1 Cyclopropene formation

As mentioned in the Section 4.9.4, when hydrazones with trimethylsilyl and *tert*-butyl on the alkyne (**257** and **252**, Scheme 4.12.1) were employed in the reaction at 90^{o}C, we observed unexpected products in the crude reaction mixture. At the same time, the trans 4-*tert*-butylcyclohexyl hydrazone **251B** at 90^{o}C also gave a product with a similar pattern of peaks in the NMR spectrometry. At this point, we could not figure out what the products were.

We rationalized that the triple bond has similar electronic properties as a double bond. Therefore, cyclopropenation between metal carbenes and a triple bond could also happen similarly to cyclopropanation between carbenes and a double bond. In fact, Padwa has proposed the cyclopropene as the first intermediate of the metathesis step.[14,15,28] He and Hoye also proposed another reaction mechanism that goes through a Zwitterionic intermediate.[29] However, they could not confirm the existence of a cyclopropene since it was never isolated. The cyclopropene could only be observed when it was trapped or reacted with other internal or external reactive species.

From the above information, we were able to assign the NMR peaks for the products that we isolated and confirm that they were cyclopropenes. The confirmation was strongly supported by the hydrogenation of these products to provide the more stable cyclopropanes (Scheme 4.12.1).



Scheme 4.12.1 Formation of cyclopropenes and structural confirmation by hydrogenation

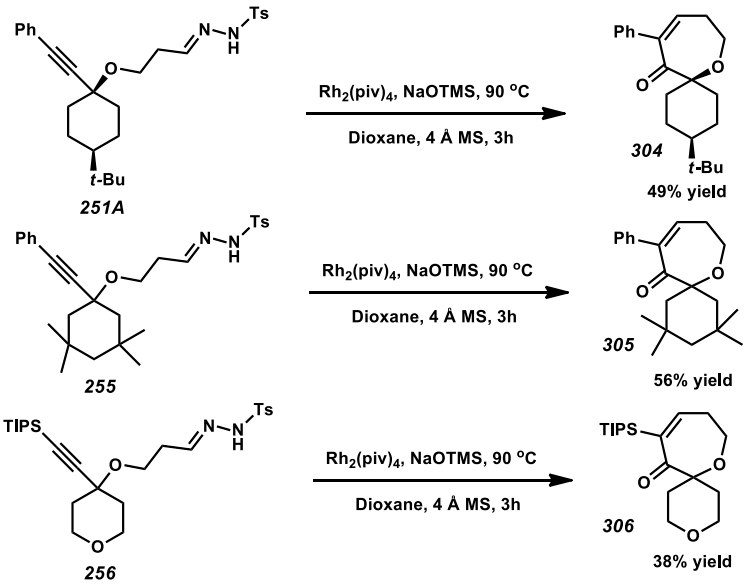
We were very surprised by these results. First, as we discussed above, the isolation of the cyclopropene intermediate after the metathesis step in this cascade reaction is unprecedented. Second, although many cyclopropenes are stable and cyclopropene chemistry has been well developed,[30] the cyclopropenes **300** and **302** that we obtained are very strained as they are fused three- and six-membered rings with two sp^2 carbons. Such a structure should be very reactive. One explanation could be due to the sterics since trimethylsilyl and *tert*-butyl are big groups. The electronics of the cyclopropene in the case of trimethylsilyl and *tert*-butyl substituents could be another

reason since having no resonance group adjacent to the ring makes it much less reactive. Furthermore, if the vinyl carbene could be formed, it may not be reactive enough for C-H bond insertion. Nevertheless, the cyclopropene **300** decomposed over time, even when stored at low temperature.

While we know the cyclopropene is the product of the reaction with the alkyne, there are more questions that need to be answered. Is the cyclopropene really an intermediate of the cascade reaction, followed by the C-H bond insertion or is it a dead-end side reaction? What happens before the C-H bond insertion step? Is the rhodium necessary to promote the cyclopropenation? We would like to go further to answer these questions.

4.12.2 Oxygen insertion of carbenes

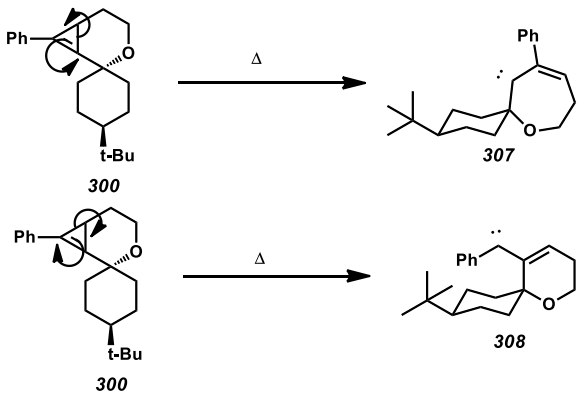
When running the cascade reaction at 90^{o}C with hydrazones **251A**, **255** and **256**, we isolated the cycloheptenones **304-306** instead of the desired products (Scheme 4.12.2a). This result was confusing since we didn't know where the oxygen atoms of the ketones came from. There is no oxygen in the reaction since we carry out the reaction under an inert atmosphere. There is no water as well, as it was absorbed by molecular sieves.



Scheme 4.12.2a Cycloheptenone formation in the rhodium-catalyzed cascade reactions

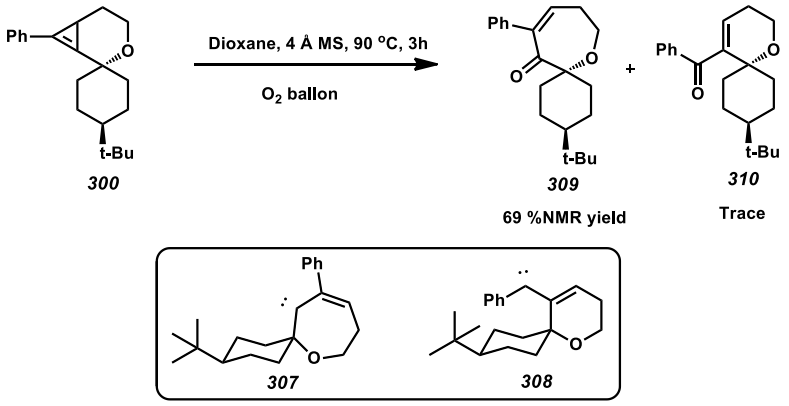
When we first looked at the crude ^{1}H NMR of these reactions, we did not see the cycloheptenones. Therefore, we proposed that the ketones were generated during the exposure of the reaction mixture to the environment, during the work-up process and/or during flash chromatography.

Cyclopropenes have been known to rearrange to vinyl carbenes (like **307** and **308**, Scheme 4.12.2b).[31] We rationalized that this process occurred in our products and the vinyl carbene produced by the rearrangement reacted with the oxygen in the atmosphere to give corresponding ketones. This reaction was reported by Enders *et al*. in the reaction of an NHC carbene with oxygen to give a triazolinone,[32] and Padwa also showed a similar outcome when a cyclopropene was exposed to oxygen.[15f]



Scheme 4.12.2b Rearrangement of cyclopropenes to vinyl carbenes

To test this hypothesis, we subjected the isolated cyclopropene **300** to an oxygen atmosphere without base at 90°C (Scheme 4.12.2c). We observed the formation of enones **309** and **310**. The cycloheptenone **309**, which was generated from the vinyl carbene **307** reacting with oxygen, was isolated as the major product. Meanwhile, the vinyl ketone **310,** which was from the vinyl carbene **308**, was observed in only trace amounts. We could confirm the structure of **310** by synthesizing this ketone using another method.[33]

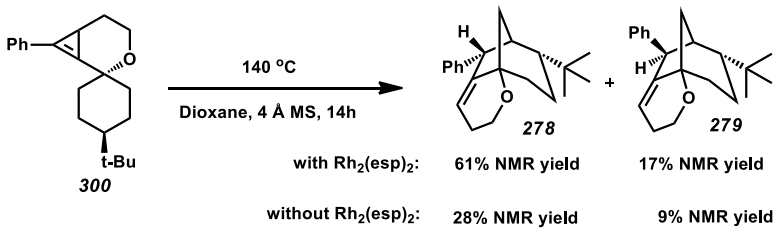


Scheme 4.12.2c Exposure of cyclopropenes to an oxygen atmosphere

At this stage, we have circumstantial support for the assumption that the cyclopropene could have rearranged to the vinyl carbene, which then would be followed by a C-H bond insertion to formed bridged bicyclic products. Nevertheless, more data need to be collected to conclude whether the cyclopropene is a mechanistic intermediate between the hydrazones and bridged bicyclic products. These data will be provided in the next section.

4.12.3 Cyclopropene to C-H bond insertion products

As shown in entry 5 of Table 4.9.2, the products **278** and **279** were obtained from tosylhydrazone **251B** only when the reaction was run at 140^{o}C. On the other hand, **251B** provided the cyclopropene **300** exclusively at 90^{o}C. This is an advantage since we could isolate the cyclopropene **300**, and then resubject it to the reaction conditions with or without the rhodium catalyst to see whether the cascade products were formed (Scheme 4.12.3a).

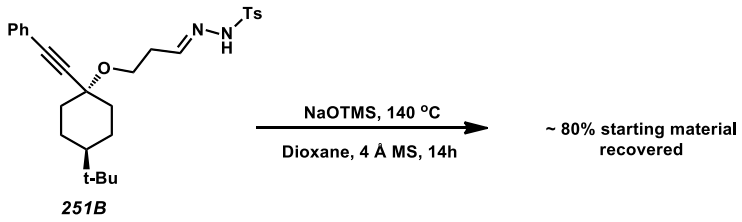


Scheme 4.12.3a Experiment to form bridged polycycles from the cyclopropene

As we predicted, the bicycles **278** and **279** could be obtained when cyclopropene **300** was heated at 140^{o}C in the presence of the rhodium catalyst, providing the evidence that cyclopropene is a competent intermediate in this cascade reaction. Notably, the

reaction proceeded to form bridged bicyclic products even without the presence of a rhodium catalyst, although the yield was lower.

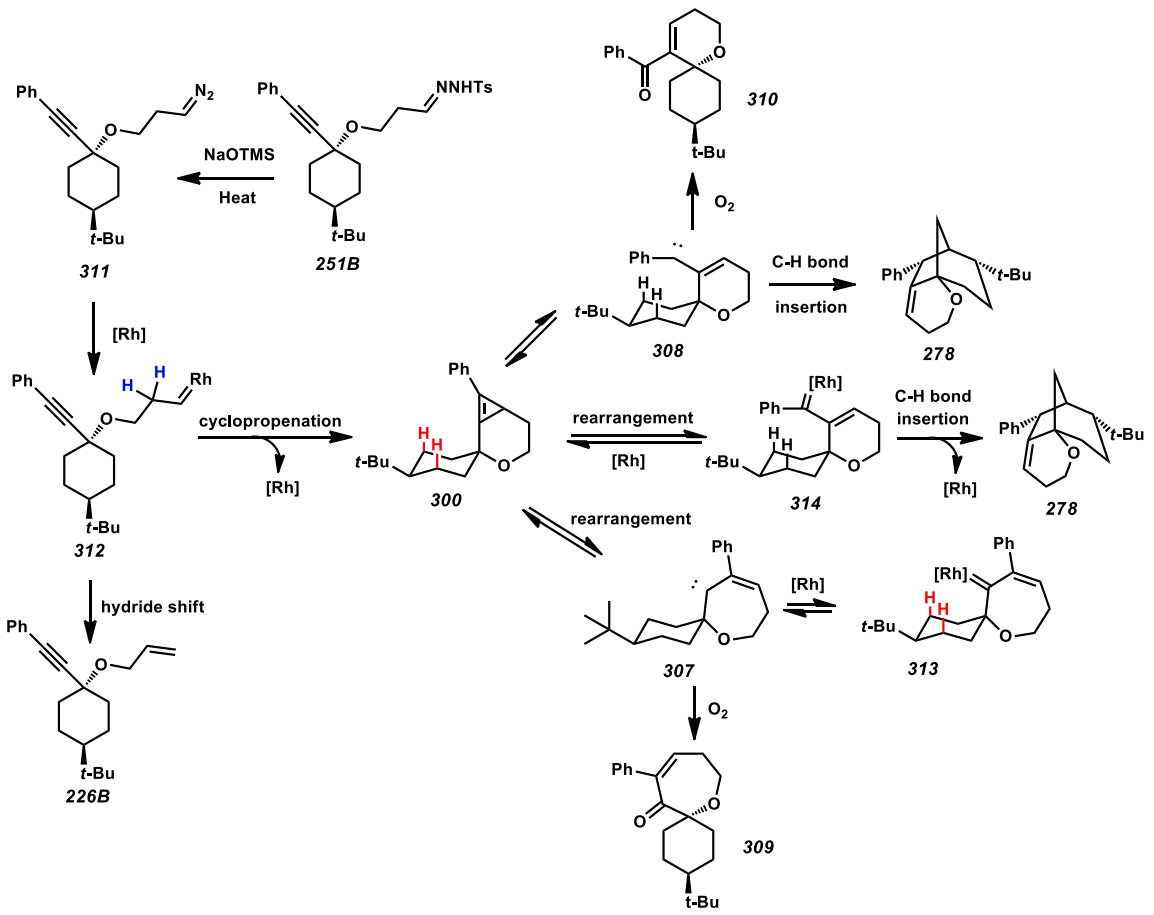
The ability of the free carbene to follow C-H bond insertion in the above experiment urged us to evaluate the necessity of the rhodium catalyst in the cyclopropenation step. **251B** was heated at 90^{o}C and 140^{o}C in the presence of base without the catalyst (Scheme 4.12.3b). In both cases, a majority of the starting material was recovered with no observation of the cyclopropene. Therefore, the rhodium catalyst promotes the diazo decomposition and the cyclopropenation.



Scheme 4.12.3b Cascade reaction without rhodium catalyst

4.12.4 Proposed reaction pathway

With all the information in hand, we propose that the mechanism for the rhodium-catalyzed alkyl carbene alkyne cascade reaction is as shown in Scheme 4.12.4.



Scheme 4.12.4 Proposed reaction mechanism

The N-H on the tosyl hydrazone **251B** would be deprotonated by sodium trimethylsilanolate first to form the tosylhydrazone salt. Upon the release of the sulfinic acid, the alkyl diazo **311** would be generated. The diazo decomposition reaction would be catalyzed by rhodium to give the rhodium carbene **312,** which would react with the π-bond on the tethered-alkyne to provide the cyclopropene intermediate **300**, releasing the rhodium back to the catalytic cycle. Cyclopropene formation would be followed by the rearrangement to vinyl carbenes **307** and **308**. It is unclear whether the catalyst would be involved in the rearrangement to form **313** and **314**, although it has been shown that this

has happened at lower temperatures.[34] At 90 ^{o}C and 140 ^{o}C, the metallocarbene **314** performs the C-H bond insertion to give the bicyclic product and again release the catalyst. At 140 ^{o}C, the product **278** could be obtained through the C-H bond insertion of the vinyl carbene **308**.

4.13 Conclusion

The rhodium-catalyzed alkyl carbene alkyne cascade reaction provides a rapid and efficient method to access different fused, bridged and caged polycyclic compounds. The method is highly diastereoselective, predictable, and tolerant of sterically hindered products. An enantioselective version of the reaction is being investigated, promising to provide enantiopure bridged bicyclic compounds, which are the core structures of many natural products. It was also found that a cyclopropene is a reaction intermediate. More experiments are being performed to have a deeper understanding of the reaction mechanism.

4.14 Experimental section

4.14.1 General consideration

All reactions were carried out in flame- or oven-dried glassware. THF, toluene, and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB)

equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA- 500 or ECX-400P spectrometer using residual solvent peak as an internal standard ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an external standard in ^{19}F NMR spectra. NMR yields were determined by the addition of 1.0 equivalent of methyl (4-nitrophenyl) carboxylate as an internal standard to the crude reaction mixture. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via ESI method and a US10252005 instrument.

4.14.2 HPLC columns for separation of enantiomers

Chiralpak AY-3: Amylose tris-(5-chloro-2-methylphenylcarbamate) coated on 3 μm silica gel

Chiralpak AD-H: Amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel

Chiralpak ID: Amylose tris-(3-chlorophenylcarbamate) immobilized on 5 μm silica gel

Chiralcel OJ-H: Cellulose tris-(4-methylbenzoate) coated on 5 μm silica gel

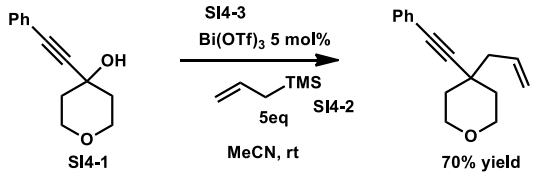
Chiralcel OD-H: Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel

Chiralpak AS-H: Amylose tris-[(S)-α-methylbenzylcarbamate) coated on 5 μm silica gel

4.14.3 Materials

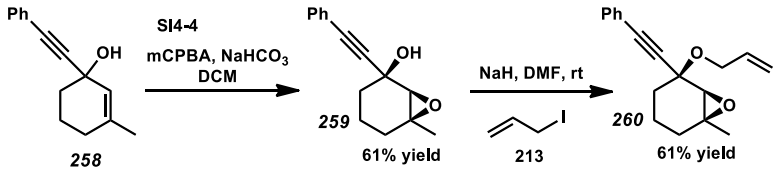
Commercially available compounds were purchased from Aldrich, Acros, and Alfa Aesar and were used without further purification.

4.14.4 Synthesis of 4-allyl-4-(phenylethynyl)tetrahydro-2H-pyran (204)



To a solution of the propargylic alcohol **SI4-1** (4.04 g, 1.0 equiv), allyltrimethylsilane (9.6 ml, 3.0 equiv) and CH_3CN (0.5 M) in a flame-dried flask was added $Bi(OTf)_3$ (0.66 g, 5 mol%) in three small portions at 0 °C. After 10 min the reaction mixture was warmed to room temperature. The solvent was removed under reduced pressure, and the crude reaction mixture was purified by flash column chromatography using a 0.5-2% gradient of EtOAc in hexanes as an eluent. The product was obtained as clear oil (3.17 g, 70% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 2H), 7.35 – 7.27 (m, 3H), 6.08 – 5.93 (m, 1H), 5.18 – 5.09 (m, 2H), 3.92 – 3.78 (m, 4H), 2.30 (d, *J* = 7.3 Hz, 2H), 1.71 (dd, *J* = 13.2, 1.8 Hz, 2H), 1.59 (ddd, *J* = 13.2, 9.5, 5.1 Hz, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 133.94, 131.70, 128.34, 127.92, 123.66, 118.12, 93.07, 84.51, 65.15, 47.42, 37.64, 34.97.

4.14.5 Synthesis of (±) (1S,5S,6S)-5-(allyloxy)-1-methyl-5-(phenylethynyl)-7-oxabicyclo[4.1.0]heptane (260)



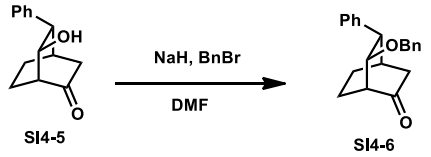
(±) (1R,2S,6S)-6-methyl-2-(phenylethynyl)-7-oxabicyclo[4.1.0]heptan-2-ol (259)

To a solution of **258** (1.10 g, 5.2 mmol) in CH_2Cl_2 (30 mL) in a flame-dried round-bottom flask, $NaHCO_3$ (1.09 g, 13 mmol) was added. The resulting mixture was cooled to 0 °C, and mCPBA (1.75 g, 7.8 mmol, wet 70%) was added slowly. The mixture was allowed to warm to room temperature and was stirred 14h. The reaction was quenched with aquaous Na_2SO_3 (sat.), and then extracted with EtOAc. The combined organic phase was washed with aquaous $NaHCO_3$ (sat.), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product **259** (0.73 g, 3.17 mmol, 61% yield) was obtained as a colorless oil. It was directly used for the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 2H), 7.35 – 7.28 (m, 3H), 3.30 (s, 1H), 2.57 (s, 1H), 1.97 – 1.69 (m, 4H), 1.63 – 1.50 (m, 2H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.96, 128.74, 128.39, 122.33, 89.89, 85.33, 67.57, 65.17, 62.24, 34.96, 28.22, 23.85, 17.94.

(±) (1S,5S,6S)-5-(allyloxy)-1-methyl-5-(phenylethynyl)-7-oxabicyclo[4.1.0]heptane (260)

A flame-dried round-bottom flask was charged with NaH (60% in oil) (0.163g, 1.3 eq). The NaH was then washed three times with anhydrous hexanes using an oven-dried needle to remove the solvent. The hexanes residue was removed by high vacuum and the flask was back-filled with Argon. To the fine powder NaH was added anhydrous DMF (10 ml) and the flask was cooled to 0 ˚C in an ice bath. The alcohol **259** (0.72g, 3.15 mmol, 1.0 eq) was dissolved in anhydrous DMF (2 ml) in a separate vial and then was added dropwise to the NaH solution. After 30 minutes at 0 °C, allyl iodide **213** (0.60 ml, 2 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After the reaction was completed, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a light yellow oil (0.52 g, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.33 (dd, *J* = 5.2, 1.9 Hz, 3H), 6.02 (ddt, *J* = 17.0, 10.3, 5.6 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (ddd, *J* = 10.2, 2.9, 1.3 Hz, 1H), 4.32 (dt, *J* = 5.5, 1.4 Hz, 2H), 3.28 (s, 1H), 1.94 – 1.69 (m, 4H), 1.67 – 1.55 (m, 2H), 1.38 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 135.32, 131.94, 128.75, 128.45, 122.41, 116.81, 88.20, 87.25, 73.84, 65.63, 62.78, 60.65, 31.66, 28.15, 24.19, 18.64.

4.14.6 Synthesis of (1R,4R,5S,6S)-6-(benzyloxy)-5-phenylbicyclo[2.2.2]octan-2-one (SI4-7), precursor of 228

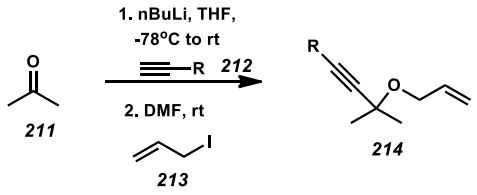


(1R,4R,5S,6S)-6-hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (SI4-6) was synthesized following a previously reported procedure.[35]

A flame-dried round-bottom flask was charged with NaH (60% in oil) (0.52g, 1.3 eq). The NaH was then washed 3 times with anhydrous hexanes using an oven-dried needle to remove the solvent. The hexanes residue was removed by high vacuum and the flask was back-filled with Argon. To the fine powder NaH was added anhydrous DMF (20 ml) and the flask was cooled to 0 ˚C in an ice bath. The alcohol **SI4-5** (2.16 g, 1.0 eq) was dissolved in anhydrous DMF (5 ml) in a separate vial and then was added dropwise to the NaH solution. After 30 minutes at 0 °C, benzyl bromide (2.40 ml, 2.0 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After the reaction was completed, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as white amorphous solid (2.76 g, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.30 – 7.20 (m, 6H), 7.20 – 7.13 (m, 2H), 4.54

(d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.15 (t, *J* = 3.7 Hz, 1H), 3.10 (s, 1H), 2.83 (dd, *J* = 6.3, 3.1 Hz, 1H), 2.53 (dt, *J* = 18.9, 2.8 Hz, 1H), 2.37 (dd, *J* = 18.9, 3.0 Hz, 1H), 2.28 (dd, *J* = 5.7, 2.8 Hz, 1H), 1.97 – 1.75 (m, 2H), 1.70 (tdd, *J* = 11.1, 5.8, 2.3 Hz, 1H), 1.40 (dd, *J* = 13.7, 11.5 Hz, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 214.02, 142.69, 137.83, 128.68, 128.38, 127.85, 127.68, 127.66, 126.62, 80.17, 70.13, 51.61, 47.49, 45.59, 35.11, 20.30, 18.67.

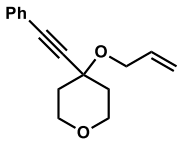
4.14.7 Synthesis of propargyl allyl ethers



General procedure: A flame-dried round-bottom flask was charged with anhydrous THF (0.5 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. The terminal acetylene **212** (1.35 eq) was then added under an argon atmosphere. *n*BuLi (1.3 eq, 2.5 M) was added dropwise to the flask while maintaining the reaction temperature at -78 °C . After 30 minutes at -78 °C, the ketone **211** (1.0 eq) was added dropwise (if a solid, prior to addition it was dissolved in 3-5 ml anhydrous THF). The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After the disappearance of ketone as confirmed by TLC, allyl iodide **213** and DMF (0.5M) were added. The reaction mixture was then stirred overnight at room temperature after which a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), and brine,

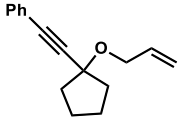
dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.

4.14.7.1 Synthesis of 4-(allyloxy)-4-(phenylethynyl)tetrahydro-2H-pyran (219)



This compound was synthesized from tetrahydro-4-pyranone (1.00 ml, 10.83 mmol, 1 eq) and phenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.76 g, 67% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (dt, J = 5.2, 2.2 Hz, 2H), 7.36 – 7.28 (m, 3H), 6.06 – 5.95 (m, 1H), 5.34 (ddd, J = 17.2, 3.1, 1.5 Hz, 1H), 5.18 (ddd, J = 10.4, 2.9, 1.4 Hz, 1H), 4.22 (dt, J = 2.7, 1.1 Hz, 2H), 3.94 (dt, J = 11.7, 4.3 Hz, 3H), 3.73 (ddd, J = 11.9, 9.4, 2.7 Hz, 2H), 2.10 – 2.01 (m, 2H), 1.91 (ddd, J = 13.2, 9.5, 4.0 Hz, 2H).. **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.26, 131.83, 128.62, 128.44, 122.55, 116.73, 89.00, 87.17, 71.83, 64.92, 64.70, 37.86.

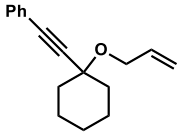
4.14.7.2 Synthesis of ((1-(allyloxy)cyclopentyl)ethynyl)benzene (220)



This compound was synthesized from cyclopentanone (0.89 ml, 10 mmol) and phenylacetylene following the general procedure above. The crude product was purified

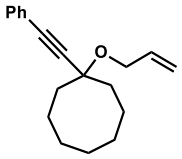
by column chromatography on silica gel using a 1-2% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (2.04 g, 90% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 2H), 7.33 – 7.26 (m, 3H), 5.99 (ddd, *J* = 22.7, 10.7, 5.6 Hz, 1H), 5.32 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.16 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.16 (dd, *J* = 4.3, 1.3 Hz, 2H), 2.15 – 2.06 (m, 2H), 2.06 – 1.93 (m, 3H), 1.90 – 1.69 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.60, 131.75, 128.34, 128.21, 123.13, 116.44, 90.94, 84.95, 80.90, 66.25, 39.79, 23.52.

4.14.7.3 Synthesis of ((1-(allyloxy)cyclohexyl)ethynyl)benzene (221)



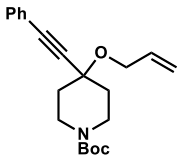
This compound was synthesized from cyclohexanone (2.10 ml, 20 mmol) and phenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 1-2% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (4.17 g, 87% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.40 (m, 2H), 7.31 (dq, *J* = 4.3, 1.5 Hz, 3H), 6.01 (ddt, *J* = 17.1, 10.5, 5.6 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (ddd, *J* = 10.3, 3.1, 1.3 Hz, 1H), 4.21 (dt, *J* = 5.6, 1.5 Hz, 2H), 2.02 (d, *J* = 9.8 Hz, 2H), 1.77 – 1.66 (m, 4H), 1.66 – 1.52 (m, 3H), 1.33 (ddd, *J* = 19.1, 11.2, 7.7 Hz, 1H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.81, 131.80, 128.35, 128.24, 123.14, 116.36, 90.70, 86.24, 74.39, 64.75, 37.50, 25.63, 23.09.

4.14.7.4 Synthesis of 1-(allyloxy)-1-(phenylethynyl)cyclooctane (222)



This compound was synthesized from cyclooctanone (1.32 ml, 10 mmol) and phenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 1-2% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.97 g, 73% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.31 (dd, *J* = 6.3, 2.7 Hz, 3H), 6.00 (ddt, *J* = 17.1, 10.7, 5.5 Hz, 1H), 5.33 (ddd, *J* = 17.3, 3.4, 1.7 Hz, 1H), 5.20 – 5.12 (m, 1H), 4.17 (dt, *J* = 5.5, 1.3 Hz, 2H), 2.10 (ddd, *J* = 14.7, 8.8, 2.6 Hz, 2H), 2.04 – 1.95 (m, 2H), 1.81 – 1.48 (m, 10H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 135.90, 131.81, 128.35, 128.21, 123.17, 116.19, 91.66, 85.24, 65.02, 35.02, 28.20, 24.69, 21.82.

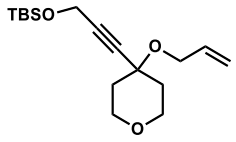
4.14.7.5 Synthesis of tert-butyl 4-(allyloxy)-4-(phenylethynyl)piperidine-1-carboxylate (223)



This compound was synthesized from *tert*-butyl-4-oxopiperidine-1-carboxylate (2.00 g, 10 mmol) and phenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 5-10% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (3.41 g, 99%

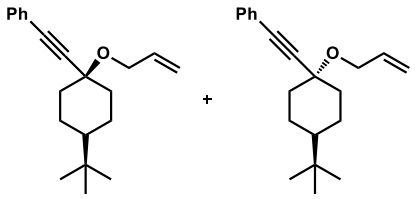
yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.34 – 7.27 (m, 3H), 6.04 – 5.91 (m, 1H), 5.36 – 5.27 (m, 1H), 5.16 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.24 – 4.16 (m, 2H), 3.77 (s,br, 2H), 3.39 – 3.28 (m, 2H), 1.98 (s, 2H), 1.88 – 1.75 (m, 2H), 1.45 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 154.80, 135.21, 131.83, 128.64, 128.43, 122.46, 116.67, 88.75, 87.25, 79.68, 72.65, 64.94, 28.54.

4.14.7.6 Synthesis of ((3-(4-(allyloxy)tetrahydro-2H-pyran-4-yl)prop-2-yn-1-yl)oxy)(tert-butyl)dimethylsilane (225)



This compound was synthesized from tetrahydro-4-pyranone (0.92 ml, 10 mmol) and *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane following the general procedure above. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (2.48 g, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.15 (ddd, *J* = 10.4, 3.0, 1.4 Hz, 1H), 4.39 – 4.35 (m, 2H), 4.11 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.92 – 3.80 (m, 2H), 3.64 (ddd, *J* = 11.8, 9.0, 2.9 Hz, 2H), 1.98 – 1.86 (m, 2H), 1.81 (ddd, *J* = 13.0, 9.1, 4.0 Hz, 2H), 0.90 (s, 9H), 0.11 (s, 6H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 135.16, 116.69, 85.67, 84.53, 71.23, 64.68, 64.54, 51.76, 37.57, 25.85, 18.35, -4.97.

4.14.7.7 Synthesis of (((1r,4r)-1-(allyloxy)-4-(tert-butyl)cyclohexyl)ethynyl)benzene (226A) and (((1s,4s)-1-(allyloxy)-4-(tert-butyl)cyclohexyl)ethynyl)benzene (226B)

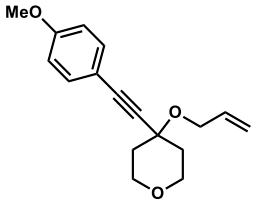


226A *226B*

This compound was synthesized from 4-tertbutylcyclohexanone (1.54 g, 10 mmol) and phenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 1-3% gradient of EtOAc in hexanes as an eluent. The product was obtained as a clear oil which solidifies on standing (2.39 g, 81% yield, dr 1:3.3). Spectra for minor diastereomer **226A ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 2H), 7.36 – 7.22 (m, 3H), 6.00 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.41 – 5.28 (m, 1H), 5.22 – 5.07 (m, 1H), 4.12 (d, *J* = 1.5 Hz, 2H), 2.27 (dd, *J* = 9.7, 7.5 Hz, 2H), 1.65 (td, *J* = 13.8, 3.9 Hz, 2H), 1.56 (d, *J* = 7.5 Hz, 2H), 1.54 (s, 1H), 1.46 – 1.26 (m, 2H), 1.12 – 0.96 (m, 1H), 0.86 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 135.71, 131.78, 128.31, 128.16, 123.12, 115.95, 92.11, 84.01, 71.45, 64.51, 47.19, 36.77, 32.56, 27.62, 21.91.

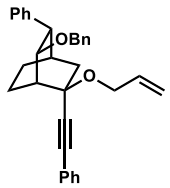
Spectra for major diastereomer **226B ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 2H), 7.35 – 7.27 (m, 3H), 6.05 – 5.94 (m, 1H), 5.34 (s, 1H), 5.20 – 5.09 (m, 1H), 4.24 (s, 2H), 2.27 – 2.13 (m, 2H), 1.87 – 1.72 (m, 2H), 1.58 – 1.39 (m, 4H), 1.11 – 0.97 (m, 1H), 0.88 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.83, 131.69, 128.39, 128.22, 123.18, 116.55, 90.03, 87.35, 75.59, 65.10, 47.43, 38.01, 32.42, 27.73, 24.69.

4.14.7.8 Synthesis of 4-(allyloxy)-4-((4-methoxyphenyl)ethynyl)tetrahydro-2H-pyran (227)



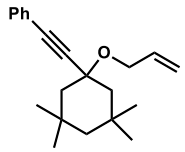
This compound was synthesized from tetrahydro-4-pyranone (0.65 ml, 7 mmol) and 4-methoxyphenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 5-10% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.37 g, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 2H), 6.87 – 6.81 (m, 2H), 5.99 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.18 (dt, *J* = 7.3, 3.6 Hz, 1H), 5.16 – 5.13 (m, 1H), 4.20 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.92 (dt, *J* = 11.7, 4.4 Hz, 2H), 3.81 (s, 3H), 3.72 (ddd, *J* = 11.8, 9.4, 2.8 Hz, 3H), 2.08 – 1.99 (m, 2H), 1.89 (ddd, *J* = 13.1, 9.5, 4.0 Hz, 2H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 159.78, 135.33, 133.21, 116.66, 114.53, 114.15, 87.50, 86.97, 71.79, 64.96, 64.56, 55.40, 37.93.

4.14.7.9 Synthesis of (1R,2R,4R,5S,6S)-2-(allyloxy)-6-(benzyloxy)-5-phenyl-2-(phenylethynyl)bicyclo[2.2.2]octane (228)



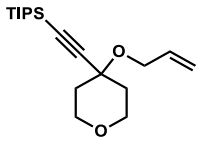
This compound was synthesized from **SI4-7** (1.22 g, 3.98 mmol) and phenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.04 g, 58% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.36 – 7.16 (m, 13H), 5.97 (ddt, *J* = 17.1, 10.8, 5.4 Hz, 1H), 5.23 (ddd, *J* = 17.2, 3.3, 1.6 Hz, 1H), 5.07 (ddd, *J* = 10.3, 3.0, 1.1 Hz, 1H), 4.45 (dd, *J* = 27.6, 12.0 Hz, 2H), 4.27 (ddd, *J* = 5.1, 3.4, 1.7 Hz, 2H), 4.00 (dd, *J* = 7.5, 1.6 Hz, 1H), 3.26 (d, *J* = 7.4 Hz, 1H), 2.64 (s, 1H), 2.39 – 2.31 (m, 1H), 2.27 (dd, *J* = 14.1, 2.4 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.92 (d, *J* = 1.4 Hz, 1H), 1.91 – 1.88 (m, 1H), 1.69 – 1.53 (m, 2H), 1.32 (t, *J* = 16.3, 7.8 Hz, 1H). **^{13}C NMR** (125.76 MHz, $CDCl_3$)) δ 144.12, 138.75, 135.86, 131.77, 128.41, 128.38, 128.24, 128.17, 127.79, 127.72, 127.31, 126.14, 123.13, 116.32, 92.33, 84.29, 80.62, 74.87, 71.03, 65.61, 49.32, 45.52, 37.26, 33.47, 22.61, 19.18.

4.14.7.10 Synthesis of ((1-(allyloxy)-3,3,5,5-tetramethylcyclohexyl)ethynyl)benzene (229)



This compound was synthesized from 3,3,5,5-tetramethylcyclohexanone (0.88 ml, 5 mmol) and phenylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 1-3% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.32 g, 89% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.33 – 7.27 (m, 3H), 5.98 (ddt, *J* = 17.1, 10.4, 5.3 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 – 5.11 (m, 1H), 4.20 (dt, *J* = 5.5, 1.6 Hz, 2H), 1.78 (d, *J* = 3.3 Hz, 4H), 1.27 (s, 2H), 1.11 (s, 6H), 1.09 (s, 6H).**^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.57, 131.55, 128.36, 128.20, 123.19, 115.94, 92.44, 85.30, 73.89, 64.53, 51.82, 48.07, 32.29, 31.92, 31.77.

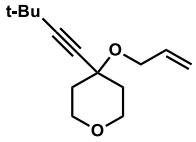
4.14.7.11 Synthesis of ((4-(allyloxy)tetrahydro-2H-pyran-4-yl)ethynyl)triisopropylsilane (230)



This compound was synthesized from tetrahydro-4-pyranone (0.46ml, 5 mmol) and triisopropylsilylacetylene following the general procedure above. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in

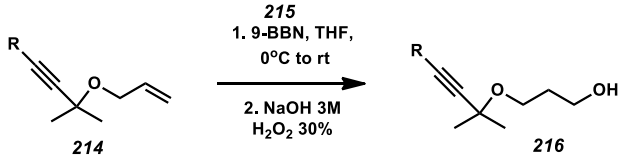
hexanes as an eluent. The product was obtained as a colorless oil (1.29 g, 80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 22.6, 10.8, 5.6 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.15 (dd, *J* = 10.3, 1.1 Hz, 1H), 4.16 (d, *J* = 5.7 Hz, 2H), 3.90 (dt, *J* = 11.7, 3.9 Hz, 2H), 3.73 – 3.59 (m, 2H), 1.94 (d, *J* = 12.7 Hz, 2H), 1.87 – 1.74 (m, 2H), 1.15 – 0.97 (m, 1H), 1.15 – 0.97 (s, 18H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.25, 116.80, 107.40, 88.10, 72.09, 65.08, 64.67, 38.04, 18.71, 11.19.

4.14.7.12 Synthesis of 4-(allyloxy)-4-(3,3-dimethylbut-1-yn-1-yl)tetrahydro-2H-pyran (224)



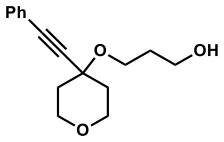
This compound was synthesized from tetrahydro-4-pyranone (0.46ml, 5 mmol) and 3,3-dimethyl-1-butyne following the general procedure above. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.06 g, 95% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.00 – 5.86 (m, 1H), 5.27 (dq, J = 17.1, 1.6 Hz, 1H), 5.15 – 5.08 (m, 1H), 4.08 (dt, J = 5.7, 1.4 Hz, 2H), 3.85 (dt, J = 11.7, 4.2 Hz, 2H), 3.66 – 3.53 (m, 2H), 1.90 – 1.80 (m, 2H), 1.80 – 1.68 (m, 2H), 1.21 (s, 9H).**^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 135.51, 116.46, 96.56, 78.14, 71.46, 65.08, 64.27, 38.19, 31.18, 27.51.

4.14.8 Synthesis of primary alcohols via hydroboration



General procedure: To a flame-dried round-bottom flask, allyl ether **214** (1 eq) and THF (0.5 M) were added under an argon atmosphere and the flask was cooled to 0 ˚C in an ice bath. 9-BBN **215** (1.5 eq, 0.5M) was then added dropwise. The reaction mixture was allowed to warm to room temperature and stir overnight. The flask was then cooled back to 0 ˚C and NaOH 3M (15 ml for each 10 mmol of **214**), H_2O_2 30% (15 ml for each 10 mmol of **214**) were successively added dropwise. The reaction mixture was allowed to warm to room temperature and stir for additional 3h. After completion, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, was filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.

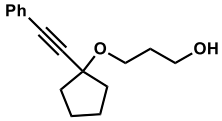
4.14.8.1 Synthesis of 3-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (231)



This compound was synthesized from **219** (1.76 g, 7.26 mmol) following the general procedure above. The crude product was purified by column chromatography on

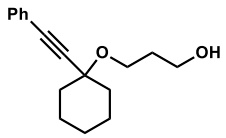
silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.87g, 99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.36 – 7.28 (m, 3H), 3.91 (dt, *J* = 11.7, 4.4 Hz, 2H), 3.86 (t, *J* = 5.7 Hz, 2H), 3.82 (t, *J* = 5.4 Hz, 2H), 3.72 (ddd, *J* = 11.8, 9.3, 2.7 Hz, 2H), 2.25 (s,br, 1H), 2.05 (ddd, *J* = 5.9, 3.5, 1.4 Hz, 2H), 1.92 – 1.81 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.83, 128.70, 128.48, 122.37, 88.88, 87.13, 77.37, 77.12, 76.87, 71.91, 64.84, 62.24, 62.00, 37.70, 32.40.

4.14.8.2 Synthesis of 3-((1-(phenylethynyl)cyclopentyl)oxy)propan-1-ol (232)



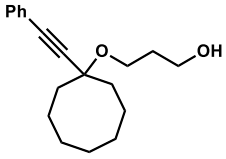
This compound was synthesized from **220** (2.04 g, 9 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.76 g, 80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (ddd, *J* = 5.4, 2.8, 1.5 Hz, 2H), 7.32 – 7.26 (m, 3H), 3.83 – 3.73 (m, 4H), 2.55 (s, br, 1H), 2.13 – 2.02 (m, 2H), 2.02 – 1.91 (m, 2H), 1.88 – 1.81 (m, 2H), 1.81 – 1.69 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.74, 128.37, 128.30, 122.94, 90.59, 85.03, 80.93, 63.90, 62.21, 39.58, 32.42, 23.41.

4.14.8.3 Synthesis of 3-((1-(phenylethynyl)cyclohexyl)oxy)propan-1-ol (233)



This compound was synthesized from **221** (4.17 g, 17.3 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (3.90 g, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.33 – 7.26 (m, 3H), 3.84 (t, *J* = 5.7 Hz, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 2.68 (s, br, 1H), 2.07 – 1.92 (m, 2H), 1.91 – 1.80 (m, 2H), 1.74 – 1.46 (m, 7H), 1.41 – 1.24 (m, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.78, 128.38, 128.34, 122.91, 90.55, 86.14, 74.39, 62.63, 62.35, 37.28, 32.41, 25.52, 22.92.

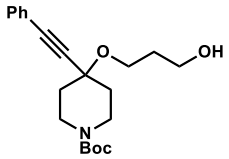
4.14.8.4 Synthesis of 3-((1-(phenylethynyl)cyclooctyl)oxy)propan-1-ol (234)



This compound was synthesized from **222** (1.97 ml, 7.3 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.82 g, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.33 – 7.26 (m, 3H), 3.81 (t, *J* = 5.6 Hz, 4H), 2.62 (s, br, 1H), 2.12 – 1.91 (m, 4H), 1.90 – 1.78 (m, 2H), 1.74 – 1.43 (m, 10H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ

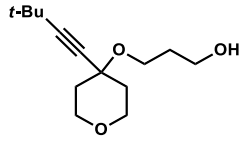
131.80, 128.38, 128.32, 122.92, 91.34, 85.33, 63.17, 62.69, 34.84, 32.32, 28.10, 24.58, 21.69.

4.14.8.5 Synthesis of tert-butyl 4-(3-hydroxypropoxy)-4-(phenylethynyl)piperidine-1-carboxylate (235)



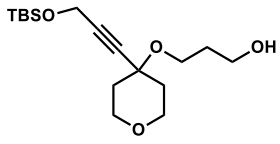
This compound was synthesized from **223** (3.38 g, 9.9 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (2.81 g, 79% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.35 – 7.28 (m, 3H), 3.84 (t, *J* = 5.7 Hz, 2H), 3.80 (t, *J* = 5.7 Hz, 2H), 3.74 (s,br, 1H), 3.39 – 3.30 (m, 2H), 1.98 (s, 2H), 1.91 – 1.83 (m, 2H), 1.83 – 1.73 (m, 2H), 1.46 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 154.77, 131.83, 128.71, 128.46, 122.30, 88.65, 87.22, 79.77, 72.75, 62.45, 61.92, 32.42, 28.53.

4.14.8.6 Synthesis of 3-((4-(3,3-dimethylbut-1-yn-1-yl)tetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (236)



This compound was synthesized from **224** (1.06 g, 4.75 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 15-25% gradient of EtOAc in hexanes as an eluent. The product was obtained as a a colorless oil which solidifies on standing (1.01 g, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.84 (dt, *J* = 11.7, 4.2 Hz, 2H), 3.80 – 3.68 (m, 4H), 3.65 – 3.52 (m, 2H), 2.44 (s, 1H), 1.92 – 1.77 (m, 4H), 1.77 – 1.64 (m, 2H), 1.22 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 96.62, 78.12, 71.57, 65.02, 62.03, 61.83, 38.03, 32.28, 31.18, 27.52.

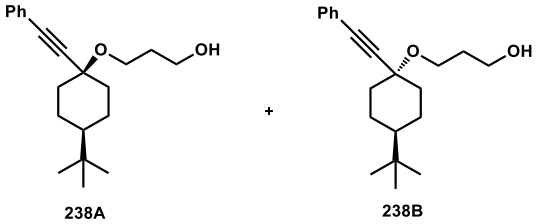
4.14.8.7 Synthesis of 3-((4-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)tetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (237)



This compound was synthesized from **225** (1.32 g, 4.24 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.13 g, 81% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.38 (s,

2H), 3.88 – 3.80 (m, 2H), 3.76 (t, *J* = 5.7 Hz, 4H), 3.64 (ddd, *J* = 11.7, 8.9, 2.9 Hz, 2H), 2.26 (s, 1H), 1.98 – 1.89 (m, 2H), 1.88 – 1.74 (m, 4H), 0.91 (s, 9H), 0.12 (s, 6H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 85.50, 84.55, 71.33, 64.61, 61.98, 61.73, 51.76, 37.42, 32.37, 25.86, 18.38.

4.14.8.8 Synthesis of 3-(((1s,4s)-4-(tert-butyl)-1-(phenylethynyl)cyclohexyl)oxy)propan-1-ol (238A) and 3-(((1r,4r)-4-(tert-butyl)-1-(phenylethynyl)cyclohexyl)oxy)propan-1-ol (238B)

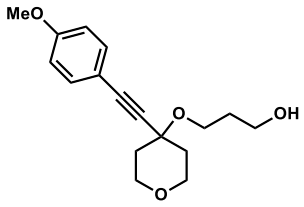


238A 238B

This compound was synthesized from mixture of **226A and 226B** (2.39 g, 8.07 mmol, ratio 1:3) following the general procedure above. The crude products were purified by column chromatography on silica gel using a 5-10% gradient of EtOAc in hexanes as an eluent. The products **238A** and **238B** were obtained in 88% total yield for hydroboration. The product **238A** was obtained as white amorphous solid (0.51 g, 81% yield). Spectra for **238A, ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.32 – 7.26 (m, 3H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.77 (t, *J* = 5.5 Hz, 2H), 2.54 (s, br, 1H), 2.23 (dd, *J* = 14.8, 2.4 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.65 (td, *J* = 13.8, 3.8 Hz, 2H), 1.57 (d, *J* = 13.1 Hz, 2H), 1.30 (qd, *J* = 13.2, 3.1 Hz, 2H), 1.05 (tt, *J* = 12.1, 3.2 Hz, 1H), 0.86 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.78, 128.35, 128.28, 122.91, 91.79, 84.23, 71.79, 62.71, 62.62, 47.02, 36.55, 32.55, 32.32, 27.57, 21.91.

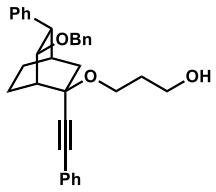
The product **238B** was obtained as a white amorphous solid (1.72 g, 91% yield). Spectra for **238A, ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 2H), 7.35 – 7.27 (m, 3H), 3.89 (t, *J* = 5.7 Hz, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 2.58 (s, 1H), 2.25 – 2.14 (m, 2H), 1.90 – 1.81 (m, 2H), 1.81 – 1.71 (m, 2H), 1.53 – 1.35 (m, 4H), 1.11 – 0.98 (m, 1H), 0.88 (s, 9H). **^{13}C NMR** (100.56 MHz, $CDCl_3$δ 131.68, 128.42, 128.33, 122.96, 89.81, 87.34, 75.66, 62.98, 62.43, 47.41, 37.93, 32.41, 27.72, 24.63.

4.14.8.10 Synthesis of 3-((4-((4-methoxyphenyl)ethynyl)tetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (239)



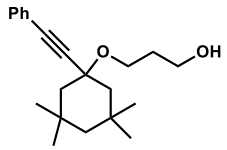
This compound was synthesized from **227** (1.11 g, 4.09 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.17 g, 99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 6.86 – 6.82 (m, 2H), 3.90 (dt, *J* = 11.6, 4.3 Hz, 2H), 3.84 (dd, *J* = 7.8, 3.6 Hz, 2H), 3.82 – 3.78 (m, 2H), 3.81 (s, 3H), 3.71 (ddd, *J* = 11.9, 9.4, 2.7 Hz, 2H), 2.31 (s, br, 1H), 2.06 – 1.97 (m, 2H), 1.91 – 1.81 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 159.89, 133.29, 114.43, 114.07, 87.46, 87.02, 71.95, 64.86, 62.14, 61.99, 55.42, 37.78, 32.39.

4.14.8.11 Synthesis of 3-(((1R,2R,4R,5S,6S)-6-(benzyloxy)-5-phenyl-2-(phenylethynyl)bicyclo[2.2.2]octan-2-yl)oxy)propan-1-ol (240)



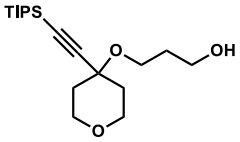
This compound was synthesized from **228** (1.04 g, 2.31 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (0.92 g, 85% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.36 – 7.30 (m, 3H), 7.29 – 7.10 (m, 10H), 4.47 (q, *J* = 12.6 Hz, 2H), 3.94 (pd, *J* = 8.8, 6.0 Hz, 3H), 3.75 (d, br, *J* = 46.0 Hz, 3H), 3.16 (d, *J* = 7.4 Hz, 1H), 2.55 (s, 1H), 2.33 (d, *J* = 13.5 Hz, 1H), 2.20 (dd, *J* = 14.1, 2.3 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.88 (d, *J* = 25.0 Hz, 3H), 1.64 (s, br, 1H), 1.61 – 1.50 (m, 2H), 1.29 (td, *J* = 13.9, 6.9 Hz, 1H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 143.59, 137.98, 131.78, 128.41, 128.27, 127.79, 127.63, 126.27, 122.92, 91.75, 85.08, 79.88, 75.04, 70.89, 63.12, 61.96, 49.74, 44.75, 38.11, 33.48, 32.48, 22.63, 19.16.

4.14.8.12 Synthesis of 3-((3,3,5,5-tetramethyl-1-(phenylethynyl)cyclohexyl)oxy)propan-1-ol (241)



This compound was synthesized from **229** (1.32 g, 4.45 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.19 g, 85% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H), 7.33 – 7.27 (m, 3H), 3.86 (t, *J* = 5.6 Hz, 2H), 3.81 (s, br, 2H), 2.51 (s, 1H), 1.90 – 1.81 (m, 2H), 1.74 (dd, *J* = 37.1, 13.6 Hz, 4H), 1.25 (s, 2H), 1.10 (s, 6H), 1.07 (s, 6H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.52, 128.41, 128.31, 122.98, 92.35, 85.37, 74.24, 62.69, 62.54, 51.66, 48.13, 32.37, 32.18, 31.95, 31.76.

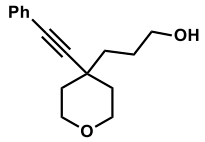
4.14.8.13 Synthesis of 3-((4-((triisopropylsilyl)ethynyl)tetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (242)



This compound was synthesized from **230** (1.54 g, 4.78 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 15-25% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.21 g, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.89 (dt, *J*

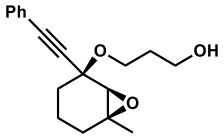
= 11.8, 4.0 Hz, 2H), 3.85 – 3.74 (m, 4H), 3.72 – 3.61 (m, 2H), 2.33 – 2.19 (m, 1H), 1.98 – 1.89 (m, 2H), 1.89 – 1.81 (m, 2H), 1.81 – 1.72 (m, 2H), 1.1 – 0.95 (m, 1H), 1.07 (s, 18H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 107.26, 88.24, 72.15, 65.03, 62.34, 62.16, 37.88, 32.32, 18.62, 11.02.

4.14.8.14 Synthesis of 3-(4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)propan-1-ol (SI4-7), precursor of 203



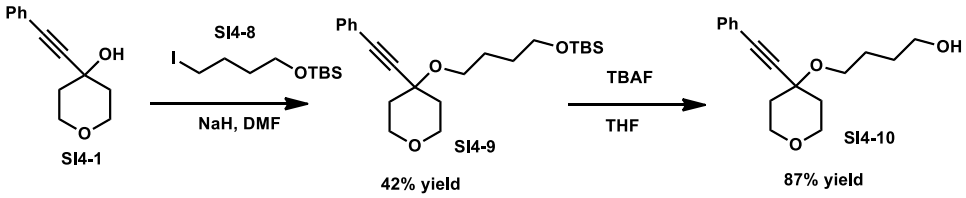
This compound was synthesized from **204** (1.68 g, 7.4 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.34 g, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 2H), 7.27 – 7.14 (m, 3H), 3.86 (dt, *J* = 11.4, 4.2 Hz, 2H), 3.72 – 3.55 (m, 2H), 3.11 (s, 1H), 1.93 (d, *J* = 13.1 Hz, 2H), 1.86 – 1.72 (m, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.68, 128.55, 128.37, 122.38, 91.43, 85.03, 66.07, 64.96, 40.05.

4.14.8.15 Synthesis of 3-(((1S,2S,6S)-6-methyl-2-(phenylethynyl)-7-oxabicyclo[4.1.0]heptan-2-yl)oxy)propan-1-ol (261)



This compound was synthesized from **260** (1.28 g, 4.77 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.34 g, 98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ δ 7.49 – 7.43 (m, 1H), 7.37 – 7.28 (m, 1H), 4.01 – 3.88 (m, 2H), 3.81 (ddd, *J* = 20.3, 10.8, 5.4 Hz, 2H), 3.29 (s, 1H), 2.60 (s, br, 1H), 1.98 – 1.78 (m, 4H), 1.77 – 1.68 (m, 2H), 1.64 – 1.47 (m, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.93, 128.81, 128.47, 122.25, 88.37, 87.05, 72.85, 62.84, 62.54, 61.62, 60.76, 32.74, 32.29, 28.62, 23.92.

4.14.9 Synthesis of 4-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)butan-1-ol (SI4-10), precursor of 267



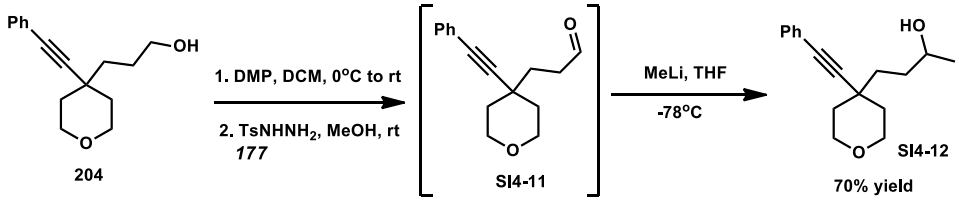
tert-butyldimethyl(4-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)butoxy)silane (SI4-9) A flame-dried round-bottom flask was charged with NaH (60% in oil) (0.21 g, 5.25 mmol, 1.5 eq). The NaH was then washed 3 times with anhydrous hexanes using an oven-dried needle to remove the solvent. The hexanes

residue was removed by high vacuum and the flask was back-filled with Argon. To the fine powder NaH was added anhydrous DMF (12 ml) and the flask was cooled to 0 ˚C in an ice bath. The alcohol **SI4-1** (0.71 g, 3.5 mmol, 1 eq) was dissolved in anhydrous DMF (2 ml) in a separate vial and then was added dropwise to the NaH solution. After 30 minutes at 0 °C, **SI4-8** (2.49 g, 2 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After completion, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using a 5-10% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (0.58 g, 42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.34 – 7.27 (m, 3H), 3.91 (dt, *J* = 9.1, 4.3 Hz, 2H), 3.72 (ddd, *J* = 11.8, 9.2, 2.8 Hz, 2H), 3.65 (td, *J* = 6.1, 3.9 Hz, 4H), 2.07 – 1.98 (m, 2H), 1.86 (ddd, *J* = 13.1, 9.2, 3.9 Hz, 2H), 1.70 – 1.57 (m, 4H), 0.88 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.80, 128.50, 128.41, 122.69, 89.51, 86.66, 71.30, 64.88, 63.12, 63.07, 37.78, 29.81, 26.65, 26.08, 18.47.

4-((4-(Phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)butan-1-ol (SI4-10) To a flame-dried round-bottom flask, **SI4-9** (0.58 g, 1 eq), AcOH (0.17 ml, 2 eq) and THF (14 ml, 0.1M) were added under an argon atmosphere and the flask was cooled to 0 ˚C in an ice bath. TBAF (1.6 ml, 1.1 eq, 0.5M) was then added dropwise. The reaction mixture was allowed to warm to room temperature and stir for 30 minutes. After completion, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the

organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as colorless oil (0.36 g, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ δ 7.48 – 7.39 (m, 2H), 7.32 (dd, *J* = 5.0, 1.9 Hz, 3H), 3.91 (dt, *J* = 11.7, 4.4 Hz, 2H), 3.71 (ddt, *J* = 6.2, 5.2, 3.1 Hz, 6H), 2.04 (ddd, *J* = 9.7, 4.3, 2.3 Hz, 2H), 1.87 (ddd, *J* = 13.1, 9.3, 4.0 Hz, 2H), 1.78 – 1.66 (m, 4H), 1.62 (s, br, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.81, 128.62, 128.45, 122.52, 122.50, 89.05, 87.02, 71.68, 64.87, 63.11, 62.82, 37.73, 30.26, 26.88.

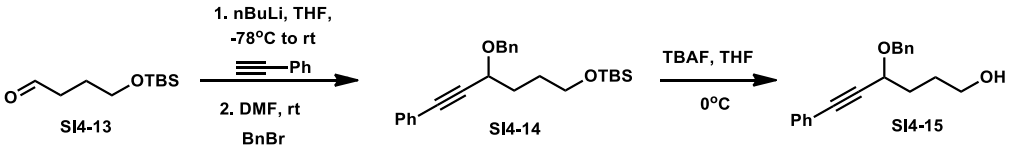
4.14.10 Synthesis of 4-(4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)butan-2-ol (SI4-12), precursor of 273



To a solution of the primary alcohol **204** (0.40 g, 1.65 mmol, 1.0 eq) and DCM (3.3 ml, 0.5M) in a flame-dried flask, DMP (1.2 eq) was added in five small equal portions at 0 °C. The reaction mixture was allowed to warm to room temperature within 1 hour and stirred for additional 2 hours. After the disappearance of alcohol was confirmed by TLC, $NaHCO_3$ (1.2 eq) was added and the reaction was filtered through a celite pad, the solid was washed 3 times with DCM. The combined DCM was quickly removed under reduced pressure to give a crude product.

To a flame-dried round-bottom flask containing the above crude product, THF (3.2 ml, 0.5M) were added under an argon atmosphere and the flask was cooled to -78 ˚C in dry ice/acetone bath. MeLi (1.1 ml, 1.3eq, 0.5M) was then added dropwise. The reaction mixture was allowed to warm to room temperature and stir overnight. After completion, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as colorless oil (0.30 g, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.33 – 7.26 (m, 3H), 3.92 – 3.78 (m, 5H), 1.77 – 1.46 (m, 8H), 1.24 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.68, 128.36, 127.94, 123.62, 93.15, 84.61, 68.49, 65.22, 39.28, 38.12, 37.90, 34.97, 33.74, 23.79.

4.14.11 Synthesis of 4-(benzyloxy)-6-phenylhex-5-yn-1-ol (SI4-15), precursor of 286



((4-(benzyloxy)-6-phenylhex-5-yn-1-yl)oxy)(tert-butyl)dimethylsilane (SI-14)

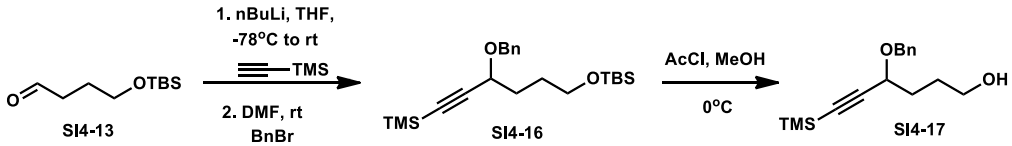
A flame-dried round-bottom flask was charged with anhydrous THF (10ml, 0.5 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. Phenyl acetylene (0.74 ml, 1.35 eq) was then added under an argon atmosphere. *n*BuLi (2.6 ml, 1.3 eq, 2.5 M) was added dropwise to the flask while maintaining the reaction temperature at -78 °C. After 30

minutes at -78 °C, **SI4-13**[36] (1.01 g, 1.0 eq) was added dropwise (prior to addition it was dissolved in 3 ml anhydrous THF). The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After the disappearance of aldehyde **SI-13** as confirmed by TLC, benzyl bromide (1.2 ml, 2.0 eq) and DMF (5 ml) were added. The reaction mixture was then stirred overnight at 60 °C after which a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 1-2% gradient of EtOAc in hexanes as an eluent. The product was obtained as colorless oil (1.56 g, 79% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.27 (m, 10H), 4.86 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.34 (t, *J* = 6.5 Hz, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 1.97 – 1.83 (m, 2H), 1.81 – 1.69 (m, 2H), 0.88 (s, 9H), 0.05 (d, *J* = 11.3 Hz, 12H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 138.47, 132.17, 128.47, 128.37, 128.12, 127.75, 123.09, 88.59, 86.51, 71.09, 69.22, 62.94, 32.71, 31.08, 29.81, 29.06, 26.19, 18.34, 1.36.

4-(benzyloxy)-6-phenylhex-5-yn-1-ol (SI4-15) To a flame-dried round-bottom flask, **SI4-14** (1.56 g, 1.0 eq), THF (8 ml, 0.5M) were successively added under an argon atmosphere and the flask was cooled to 0 ˚C in an ice bath. TBAF (4.8 ml, 1.2 eq, 1M) was then added dropwise and the reaction mixture was stirred at same temperature, and monitored periodically by TLC. After 30 min, the reaction was completed, and the solvent was concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using a 20% of EtOAc in hexanes as an eluent to

afford product as a white amorphous solid (0.99 g, 89% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 – 7.43 (m, 2H), 7.43 – 7.27 (m, 8H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.38 (t, *J* = 6.1 Hz, 1H), 3.70 (t, *J* = 9.3, 3.2 Hz, 2H), 2.77 (s, 1H), 2.03 – 1.90 (m, 2H), 1.84 (qd, *J* = 14.0, 7.5 Hz, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 137.83, 131.87, 128.55, 128.42, 128.23, 127.92, 122.73, 87.81, 86.49, 70.87, 69.04, 62.69, 32.55, 28.77.

4.14.12 Synthesis of 4-(benzyloxy)-6-(trimethylsilyl)hex-5-yn-1-ol (SI4-17), precursor of 288

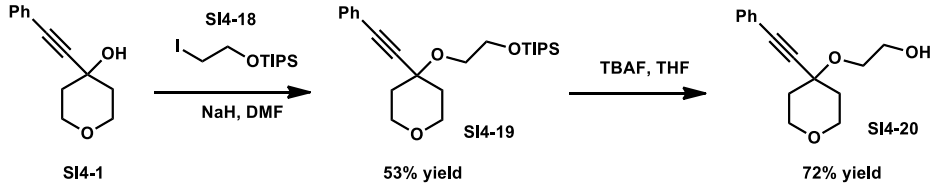


(3-(benzyloxy)-6-((tert-butyldimethylsilyl)oxy)hex-1-yn-1-yl)trimethylsilane (SI-16) A flame-dried round-bottom flask was charged with anhydrous THF (12 ml, 0.5 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. Trimethylsilylacetylene (1.2 ml, 1.35 eq) was then added under an argon atmosphere. *n*BuLi (3.1 ml, 1.3 eq, 2.5 M) was added dropwise to the flask while maintaining the reaction temperature at -78 °C . After 30 minutes at -78 °C, **SI4-13** (0.96 g, 1.0 eq) was added dropwise (prior to addition it was dissolved in 3 ml anhydrous THF). The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After the disappearance of aldehyde **SI-13** as confirmed by TLC, benzyl bromide and DMF (0.5M) were added. The reaction mixture was then stirred overnight at 60 °C after which a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined

and washed with sodium thiosulfate ($Na_2S_2O_3$), brine, dried over anhydrous $MgSO_4$, was filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 1-2% gradient of EtOAc in hexanes as an eluent. The product was obtained as colorless oil (2.0 g, 86% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.28 (m, 1H).4.79 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 1H), 3.67 – 3.59 (m, 2H), 1.85 – 1.75 (m, 2H), 1.75 – 1.61 (m, 2H), 0.89 (s, 9H), 0.19 (s, 6H), 0.16 (d, *J* = 7.0 Hz, 6H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 138.22, 128.47, 128.12, 127.69, 104.84, 90.80, 70.56, 69.08, 62.91, 35.07, 32.27, 28.76, 26.07, 18.42, 0.08, -5.22.

4-(benzyloxy)-6-(trimethylsilyl)hex-5-yn-1-ol (SI4-17) To a flame-dried round-bottom flask, **SI4-16** (1.96 g, 1.0 eq), methanol (17 ml, 0.3M) were successively added under an argon atmosphere and the flask was cooled to 0 ˚C in an ice bath. Acetyl chloride (0.08 ml, 0.2 eq) was then added dropwise and the reaction mixture was stirred at the same temperature, and monitored periodically by TLC. After 5 min, the reaction was completed and the solvent was concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using a 20% of EtOAc in hexanes as an eluent to afford product as a colorless oil (0.67 g, 49% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.13 (t, *J* = 6.0 Hz, 1H), 3.65 (t, *J* = 6.1 Hz, 2H), 1.89 – 1.80 (m, 2H), 1.80 – 1.68 (m, 2H), 0.19 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 137.80, 128.51, 128.23, 127.88, 104.28, 91.28, 70.70, 68.92, 62.65, 32.34, 28.70, 0.06.

4.14.13 Synthesis of 2-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)ethanol (SI4-20), precursor of 292

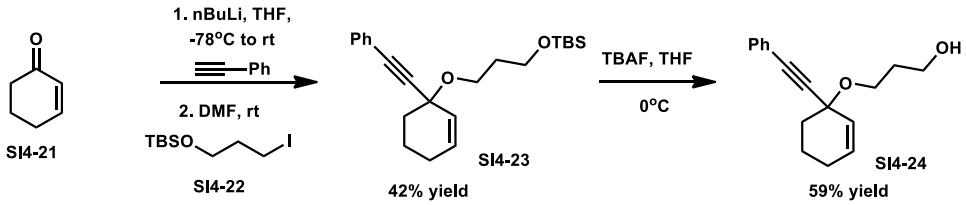


Triisopropyl(2-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)ethoxy)silane (SI4-19) A flame-dried round-bottom flask was charged with NaH (60% in oil) (0.3 g, 7.5 mmol, 1.5 eq). The NaH was then washed 3 times with anhydrous hexanes using an oven-dried needle to remove the solvent. The hexanes residue was removed by high vacuum and the flask was back-filled with Argon. To the fine powder NaH was added anhydrous DMF (16 ml) and the flask was cooled to 0 ˚C in an ice bath. The alcohol **SI4-1** (1.01 g, 5.0 mmol, 1 eq) was dissolved in anhydrous DMF (3 ml) in a separate vial and then was added dropwise to the NaH solution. After 30 minutes at 0 °C, **SI4-18** (3.28 g, 2 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After completion, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.07 g, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 2H), 7.36 – 7.26 (m, 3H), 3.91 (ddd, *J* = 20.6, 10.4, 4.8 Hz, 4H), 3.72 (ddd, *J* = 11.8, 10.1, 4.3 Hz, 4H), 2.11 – 1.97 (m, 2H), 1.89 (ddd, *J* = 13.0, 9.0,

3.9 Hz, 2H), 1.17 – 0.99 (m, 3H), 1.17 – 0.99 (s, 18H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.82, 128.52, 128.39, 122.65, 89.29, 86.77, 71.44, 64.97, 64.79, 63.04, 37.68, 18.09, 12.08.

2-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)ethanol (SI4-20), precursor of 292 To a flame-dried round-bottom flask, **SI4-19** (1.07 g, 1 eq) and THF (25 ml, 0.1M) were added under an argon atmosphere and the flask was cooled to 0 ˚C in an ice bath. TBAF (2.65 ml, 1 eq, 1.0M) was then added dropwise. The reaction mixture was allowed to warm to room temperature and stir for 30 minutes. After completion, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as colorless oil (0.47 g, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 2H), 7.38 – 7.28 (m, 3H), 3.93 (dt, *J* = 11.7, 4.3 Hz, 2H), 3.79 (s, 4H), 3.73 (ddd, *J* = 12.0, 9.5, 2.7 Hz, 2H), 2.10 – 1.97 (m, 2H), 1.88 (ddd, *J* = 13.2, 9.5, 4.0 Hz, 2H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.82, 128.72, 128.46, 122.34, 88.74, 87.37, 71.93, 64.90, 64.46, 62.24, 37.77.

4.14.14 Synthesis of 3-((1-(phenylethynyl)cyclohex-2-en-1-yl)oxy)propan-1-ol (SI4-24), precursor of 250

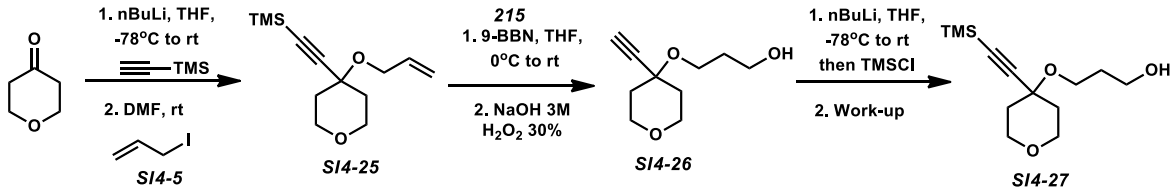


Tert-butyldimethyl(3-((1-(phenylethynyl)cyclohex-2-en-1-yl)oxy)propoxy)silane (SI4-23) A flame-dried round-bottom flask was charged with anhydrous THF (10 ml, 0.3 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. Phenyl acetylene (0.38 ml, 1.15 eq) was then added under an argon atmosphere. *n*BuLi (1.3 ml, 1.1 eq, 2.5 M) was added dropwise to the flask while maintaining the reaction temperature at -78 °C . After 30 minutes at -78 °C, the enone **SI4-21** (0.29 ml, 1.0 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After the disappearance of enone as confirmed by TLC, **SI4-22** (1.35 g, 2 eq) and DMF (5 ml) were added. The reaction mixture was then stirred overnight at room temperature after which a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 1-3% gradient of EtOAc in hexanes as an eluent. The product was obtained as colorless oil (0.47 g, 42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.32 – 7.26 (m, 3H), 5.87 (s, 1H), 3.78 – 3.68 (m, 4H), 2.10 – 1.96 (m, 4H), 1.87 – 1.72 (m, 4H), 0.87

(s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.83, 130.23, 129.06, 128.26, 128.23, 123.05, 90.95, 85.27, 70.54, 60.50, 60.29, 34.97, 33.64, 26.05, 25.11, 18.99, 18.42.

3-((1-(Phenylethynyl)cyclohex-2-en-1-yl)oxy)propan-1-ol (SI4-24) To a flame-dried round-bottom flask, **SI4-23** (0.34 g, 1 eq) and THF (13 ml, 0.1M) were added under an argon atmosphere and the flask was cooled to 0 ˚C in an ice bath. TBAF (1.3 ml, 1.0 eq, 1.0 M) was then added dropwise. The reaction mixture was allowed to warm to room temperature and stir for 105 minutes. After completion, a saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as colorless oil (0.19 g, 59% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 2H), 7.30 (d, *J* = 2.0 Hz, 3H), 5.96 – 5.81 (m, 2H), 3.88 (t, *J* = 5.6 Hz, 2H), 3.80 (s, 2H), 2.38 (s, 1H), 2.14 – 1.96 (m, 4H), 1.95 – 1.71 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.82, 130.75, 128.44, 128.36, 122.85, 90.46, 85.65, 70.97, 62.93, 62.23, 35.03, 32.43, 25.03, 18.88.

4.14.15 Synthesis of 3-((4-((trimethylsilyl)ethynyl)tetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (SI4-27), precursor of 247



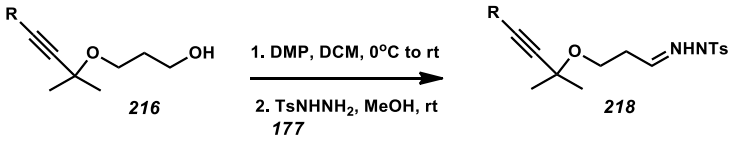
((4-(Allyloxy)tetrahydro-2H-pyran-4-yl)ethynyl)trimethylsilane (SI4-25) This compound was synthesized from tetrahydro-4-pyranone (1.90 ml, 20 mmol) and trimethylsilylacetylene following the general procedure to form propargyl allyl ether above. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a light yellow oil (3.76 g, 79% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.01 – 5.88 (m, 1H), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.18 – 5.11 (m, 1H), 4.13 – 4.05 (m, 2H), 3.86 (dt, *J* = 11.7, 4.3 Hz, 2H), 3.68 – 3.58 (m, 2H), 1.96 – 1.87 (m, 2H), 1.78 (ddd, *J* = 13.2, 9.6, 4.0 Hz, 2H), 0.17 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.25, 116.66, 105.46, 91.86, 71.67, 64.84, 64.55, 37.69, 0.06.

3-((4-ethynyltetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (SI4-26) This compound was synthesized from **SI4-25** (1.90 g, 8.0 mmol) following the general procedure for hydroboration above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (1.40 g, 95% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.86 (dt, *J*

= 11.7, 4.4 Hz, 2H), 3.82 – 3.75 (m, 4H), 3.66 (ddd, *J* = 11.8, 9.2, 2.8 Hz, 2H), 2.55 (s, 1H), 2.11 (t, *J* = 5.6 Hz, 1H), 1.99 – 1.92 (m, 2H), 1.89 – 1.76 (m, 3H).

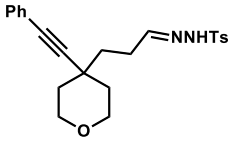
3-((4-((Trimethylsilyl)ethynyl)tetrahydro-2H-pyran-4-yl)oxy)propan-1-ol (SI4-27) A flame-dried round-bottom flask was charged with anhydrous THF (0.5 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. The terminal acetylene **SI4-26** (1.10 g, 6.0 mmol, 1.0 eq) was then added under an argon atmosphere. *n*BuLi (6.0 ml, 2.5 eq, 2.5 M) was added dropwise to the flask while maintaining the reaction temperature at -78 °C . After 30 minutes at -78 °C, trimethylsilyl chloride (2.0 ml, 2.6 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After the disappearance of **SI4-26** as confirmed by TLC, a saturated NH_4Cl solution was added and the reaction mixture was allowed to stir for 1 hour. The mixture was then extracted with Et_2O (3x), and the organic phases were combined and washed with sodium thiosulfate ($Na_2S_2O_3$), brine, dried over anhydrous $MgSO_4$, was filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (0.77 g, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.85 (dt, *J* = 11.7, 4.3 Hz, 2H), 3.82 – 3.72 (m, 4H), 3.63 (ddd, *J* = 11.9, 9.4, 2.7 Hz, 2H), 2.22 (t, *J* = 5.4 Hz, 1H), 1.96 – 1.87 (m, 2H), 1.87 – 1.80 (m, 2H), 1.76 (ddd, *J* = 13.2, 9.5, 4.0 Hz, 2H).**^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 105.54, 91.75, 71.80, 64.77, 61.94, 61.80, 37.53, 32.31, 0.05.

4.14.16 Synthesis of tosylhydrazones



General procedure: To a solution of the primary alcohol **216** (1.0 eq) and DCM (0.5M) in a flame-dried flask, DMP (1.2 eq) was added in five small equal portions at 0 °C. The reaction mixture was allowed to warm to room temperature within 1 hour and stirred for additional 2 hours. After the disappearance of alcohol was confirmed by TLC, $NaHCO_3$ (1.2 eq) was added and the reaction was filtered through a celite pad, the solid was washed 3 times with DCM. The combined DCM was quickly removed under reduced pressure to give a crude product, which was then transferred to a small vial. MeOH (1M) and tosylhydrazide **177** were successively added to the vial and the reaction mixture was stirred for 1 hour. The solvent was then removed under reduced pressure to yield a crude solid. The crude solid was then dissolved in minimum amount of benzene and quickly purified by column chromatography on silica gel.

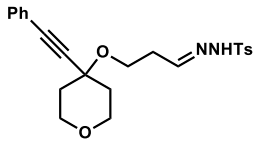
4.14.16.1 Synthesis of 4-methyl-N'-(3-(4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)propylidene)benzenesulfonohydrazide (203)



This compound was synthesized from **SI4-7** (0.65 g, 2.65 mmol) following the general procedure above. The crude product was purified by column chromatography on

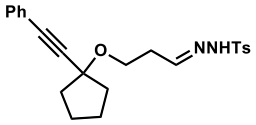
silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.22 g, 20% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 2H), 7.57 (s, 1H), 7.43 – 7.20 (m, 7H), 3.89 – 3.71 (m, 4H), 2.54 – 2.29 (m, 2H), 2.41 (s, 6H), 1.72 – 1.45 (m, 8H). **^{13}C NMR** (100.52 MHz, $CDCl_3$)) δ 153.19, 144.13, 135.38, 131.73, 131.62, 129.76, 129.69, 128.31, 128.09, 128.01, 127.89, 127.72, 123.92, 94.48, 84.03, 39.09, 37.86, 37.80, 36.99, 28.16, 26.21, 26.13, 23.24, 22.94, 21.73.

4.14.16.2 Synthesis of 4-methyl-N'-(3-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)propylidene)benzenesulfonohydrazide (243)



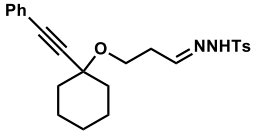
This compound was synthesized from **231** (0.41 g, 1.59 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 30-50% gradient of EtOAc in hexanes as an eluent. The product was obtained as an amorphous solid (0.29 g, 43% yield, mixture of 2 isomers, 1.1:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.87 – 7.81 (m, 2H), 7.81 – 7.76 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.28 (m, 8H), 7.28 – 7.22 (m, 5H), 6.95 (t, *J* = 6.1 Hz, 1H), 3.91 – 3.79 (m, 6H), 3.76 (t, *J* = 6.3 Hz, 2H), 3.71 – 3.62 (m, 4H), 2.55 – 2.47 (m, 4H), 2.37 (2s, *J* = 14.9 Hz, 6H), 2.00 – 1.92 (m, 4H), 1.80 – 1.68 (m, 4H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 150.34, 148.37, 144.19, 144.04, 135.76, 135.40, 131.82, 129.69, 129.63, 128.93, 128.76, 128.52, 128.49, 128.11, 128.00, 122.32, 121.95, 88.72, 88.00, 87.51, 72.98, 71.70, 64.81, 64.73, 60.84, 60.27, 37.60, 37.52, 33.23, 28.96, 21.66.

4.14.16.3 Synthesis of 4-methyl-N'-(3-((1-(phenylethynyl)cyclopentyl)oxy)propylidene)benzenesulfonohydrazide (244)



This compound was synthesized from **244** (1.76 g, 7.2 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 15-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as an amorphous solid (1.33 g, 45% yield, mixture of 2 isomers, 1.9:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.47 – 7.35 (m, 2H), 7.35 – 7.16 (m, 14H), 6.95 (t, *J* = 6.2 Hz, 1H), 3.76 – 3.70 (m, 2H), 3.67 (t, *J* = 6.4 Hz, 1H), 2.46 (dt, *J* = 27.2, 7.1 Hz, 4H), 2.34 (2s, 6H), 2.06 – 1.84 (m, 9H), 1.84 – 1.59 (m, 10H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 150.63, 148.80, 144.08, 143.87, 135.82, 135.43, 131.73, 131.68, 129.66, 129.57, 128.48, 128.41, 128.35, 128.12, 127.99, 126.98, 126.52, 122.91, 122.53, 122.49, 90.58, 89.42, 85.66, 85.01, 81.74, 80.75, 62.37, 61.70, 42.63, 39.54, 33.32, 29.18, 23.39, 23.38, 21.67, 21.61.

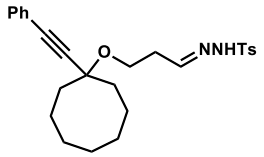
4.14.16.4 Synthesis of 4-methyl-N'-(3-((1-(phenylethynyl)cyclohexyl)oxy)propylidene)benzenesulfonohydrazide (245)



This compound was synthesized from **245** (1.55 g, 6.0 mmol) following the general procedure above. The crude product was purified by column chromatography on

silica gel using a 15-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as white thick viscous solid (0.99g, 39% yield, mixture of 2 isomers, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$)) δ 9.30 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.37 – 7.17 (m, 13H), 6.96 (t, *J* = 6.2 Hz, 1H), 3.80 – 3.74 (m, 2H), 3.72 (t, *J* = 6.4 Hz, 1H), 2.47 (dt, *J* = 18.5, 9.9 Hz, 4H), 2.35 (2s, *J* = 13.0 Hz, 6H), 2.01 – 1.81 (m, 4H), 1.73 – 1.38 (m, 14H), 1.35 – 1.12 (m, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 150.81, 149.05, 144.06, 143.89, 135.91, 135.43, 131.76, 129.74, 129.67, 129.55, 128.54, 128.43, 128.39, 128.12, 127.98, 122.90, 122.53, 122.49, 90.49, 89.14, 86.96, 75.54, 74.22, 60.97, 60.28, 37.26, 37.17, 33.45, 29.25, 25.52, 25.32.

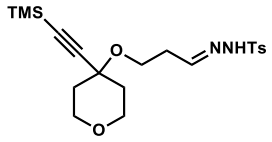
4.14.16.5 Synthesis of 4-methyl-N'-(3-((1-(phenylethynyl)cyclooctyl)oxy)propylidene)benzenesulfonohydrazide (246)



This compound was synthesized from **246** (0.51 g, 1.76 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 15-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.24 g, 30% yield, mixture of 2 isomers, 1.6:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.04 (s, 1H), 7.82 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 7.3 Hz, 2H), 7.35 (s, 2H), 7.31 – 7.10 (m, 14H), 6.92 (t, *J* = 5.5 Hz, 1H), 3.72 – 3.56 (m, 4H), 2.50 – 2.21 (m, 11H), 2.02 – 1.72 (m, 9H), 1.48 (2s,br, *J* = 44.8 Hz, 23H). **^{13}C NMR** (125.76 MHz, $CDCl_3$δ 150.80, 149.13, 143.96, 143.78, 135.94, 135.44, 131.71,

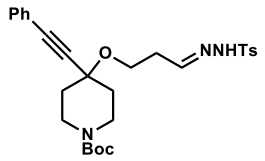
129.69, 129.59, 129.48, 128.43, 128.35, 128.30, 128.04, 127.92, 122.88, 122.50, 91.31, 89.99, 85.91, 85.25, 78.54, 61.08, 60.48, 34.76, 34.55, 33.42, 29.18, 28.03, 27.86, 24.55, 24.47, 21.62, 21.56.

4.14.16.6 Synthesis of 4-methyl-N'-(3-((4-((trimethylsilyl)ethynyl)tetrahydro-2H-pyran-4-yl)oxy)propylidene)benzenesulfonohydrazide (247)



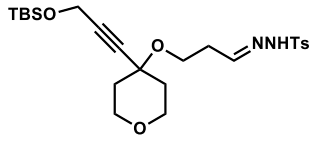
This compound was synthesized from **SI4-27** (0.78 g, 3.05 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.97 g, 75% yield, mixture of 2 isomers, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.87 – 7.64 (m, 10H), 7.39 – 7.27 (m, 10H), 7.24 – 7.16 (m, 3H), 6.92 (t, *J* = 6.1 Hz, 1H), 3.95 – 3.47 (m, 44H), 2.50 – 2.36 (m, 21H), 2.00 – 1.51 (m, 34H), 0.17 (s, 61H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 129.77, 129.68, 128.09, 127.98, 126.50, 65.02, 64.76, 64.63, 60.54, 58.57, 39.97, 37.38, 35.15, 21.68, 21.16, 20.80, 14.28, 0.04, 0.01.

4.14.16.7 Synthesis of tert-butyl 4-(phenylethynyl)-4-(3-(2-tosylhydrazono)propoxy)piperidine-1-carboxylate (248)



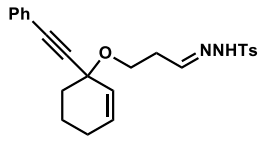
This compound was synthesized from **235** (1.19 g, 3.30 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.20 g, 69% yield, mixture of 2 isomers, 2.2:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 7.7 Hz, 4H), 7.41 – 7.34 (m, 3H), 7.34 – 7.24 (m, 10H), 7.24 – 7.17 (m, 7H), 6.90 (t, *J* = 6.0 Hz, 1H), 3.82 – 3.54 (m, 11H), 3.32 – 3.10 (m, 5H), 2.51 – 2.41 (m, 5H), 2.33 (d, *J* = 16.9 Hz, 7H), 1.93 – 1.80 (m, 5H), 1.68 – 1.59 (m, 4H), 1.42 (2s, 24H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 154.74, 154.61, 150.19, 148.29, 144.13, 144.03, 135.68, 135.37, 131.79, 129.64, 129.57, 128.91, 128.73, 128.47, 128.44, 128.07, 127.95, 126.50, 122.21, 121.83, 88.46, 88.20, 87.24, 87.14, 79.93, 79.77, 73.94, 72.51, 61.10, 60.49, 33.22, 28.90, 28.50, 21.62.

4.14.16.8 Synthesis of N'-(3-((4-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)tetrahydro-2H-pyran-4-yl)oxy)propylidene)-4-methylbenzenesulfonohydrazide (249)



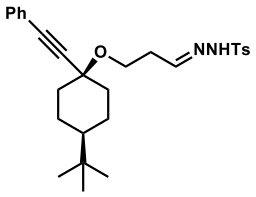
This compound was synthesized from **237** (0.66 g, 2.0 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.57 g, 58% yield, mixture of 2 isomers, 1.1:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.24 (s, 1H), 7.80 (m , 5H), 7.35 – 7.19 (m, 9H), 6.90 (t, J = 6.0 Hz, 1H), 4.31 (d, J = 1.8 Hz, 5H), 3.84 – 3.67 (m, 8H), 3.64 (t, J = 6.1 Hz, 3H), 3.60 – 3.48 (m, 6H), 2.50 – 2.32 (m, 14H), 1.81 (t, J = 14.1 Hz, 6H), 1.72 – 1.54 (m, 6H), 0.88 (2s, J = 4.0 Hz, 24H), 0.08 (2s, J = 7.9 Hz, 14H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 150.26, 148.57, 144.05, 135.74, 135.57, 129.76, 129.67, 129.63, 128.08, 127.97, 126.47, 86.68, 85.48, 84.53, 83.21, 72.26, 71.07, 64.57, 64.43, 60.54, 60.21, 51.70, 51.61, 37.27, 33.26, 28.82, 25.86, 25.82, 21.68, 18.36, 18.32, -4.98.

4.14.16.9 Synthesis of 4-methyl-N'-(3-((1-(phenylethynyl)cyclohex-2-en-1-yl)oxy)propylidene)benzenesulfonohydrazide (250)



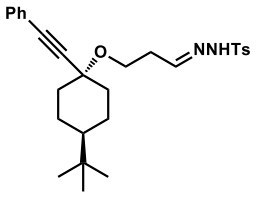
This compound was synthesized from **SI4-24** (1.96 g, 7.64 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.2 g, 37% yield, mixture of 2 isomers, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 3H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.18 (m, 14H), 6.95 (t, *J* = 6.2 Hz, 1H), 5.89 (ddt, *J* = 24.1, 10.0, 3.6 Hz, 2H), 5.76 (d, *J* = 9.9 Hz, 2H), 3.87 – 3.70 (m, 4H), 2.56 – 2.42 (m, 4H), 2.35 (2s, *J* = 14.1 Hz, 6H), 2.09 – 1.84 (m, 8H), 1.80 – 1.64 (m, 4H). **^{13}C NMR** (100.52 MHz, $CDCl_3$δ 150.56, 149.00, 144.10, 143.83, 135.83, 135.40, 131.80, 131.54, 130.68, 129.67, 129.52, 128.64, 128.52, 128.49, 128.41, 128.38, 128.17, 127.99, 127.69, 122.70, 122.37, 90.36, 89.26, 86.22, 85.59, 71.82, 70.87, 61.43, 60.77, 34.91, 34.75, 33.40, 29.27, 25.02, 24.95, 21.66, 18.85, 18.80.

4.14.16.10 Synthesis of N'-(3-(((1s,4s)-4-(tert-butyl)-1-(phenylethynyl)cyclohexyl)oxy)propylidene)-4-methylbenzenesulfonohydrazide (251A)



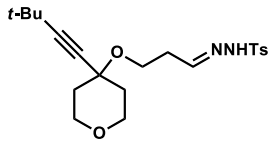
This compound was synthesized from **238A** (0.45 g, 1.43 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.43 g, 62% yield, mixture of 2 isomers, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.82 – 7.74 (m, 1H), 7.42 – 7.34 (m, 2H), 7.34 – 7.22 (m, 8H), 7.22 – 7.15 (m, 2H), 6.99 (td, *J* = 6.1, 1.0 Hz, 1H), 3.75 – 3.67 (m, 2H), 3.65 (t, *J* = 6.3 Hz, 1H), 2.56 – 2.48 (m, 3H), 2.39 (s, 1H), 2.30 (s, 3H), 2.20 – 2.07 (m, 3H), 1.69 – 1.44 (m, 7H), 1.13 (ddd, *J* = 16.2, 13.7, 2.8 Hz, 3H), 1.06 – 0.94 (m, 2H), 0.81 (2s, 13H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 150.81, 149.09, 131.74, 129.67, 129.57, 128.41, 128.31, 128.16, 128.01, 92.09, 90.69, 84.33, 72.79, 71.46, 60.79, 60.25, 47.02, 36.52, 36.43, 33.36, 32.49, 29.23, 27.56, 27.47, 21.93, 21.79, 21.61.

4.14.16.11 Synthesis of N'-(3-(((1r,4r)-4-(tert-butyl)-1-(phenylethynyl)cyclohexyl)oxy)propylidene)-4-methylbenzenesulfonohydrazide (251B)



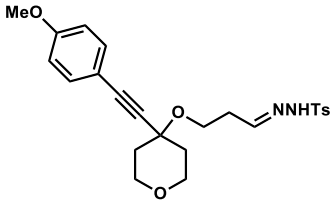
This compound was synthesized from **238B** (1.72, 5.48 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.51 g, 57% yield, mixture of 2 isomers, 1.6:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.43 – 7.36 (m, 1H), 7.36 – 7.20 (m, 11H), 6.96 (td, *J* = 6.3, 0.9 Hz, 1H), 3.85 – 3.73 (m, 3H), 2.54 – 2.43 (m, 3H), 2.38 (s, 2H), 2.35 (s, 3H), 2.14 – 2.03 (m, 3H), 1.81 – 1.70 (m, 3H), 1.46 – 1.24 (m, 7H), 1.05 – 0.91 (m, 2H), 0.87 (2s, *J* = 1.8 Hz, 14H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 150.80, 148.74, 144.11, 143.79, 136.02, 135.40, 131.65, 129.67, 129.52, 128.53, 128.46, 128.42, 128.38, 128.14, 128.02, 122.92, 122.56, 89.74, 88.45, 87.97, 87.36, 76.48, 75.50, 61.38, 60.57, 47.40, 47.20, 37.85, 37.64, 33.43, 32.40, 32.37, 29.33, 27.69, 24.60, 24.50, 21.67.

4.14.16.12 Synthesis of N'-(3-((4-(3,3-dimethylbut-1-yn-1-yl)tetrahydro-2H-pyran-4-yl)oxy)propylidene)-4-methylbenzenesulfonohydrazide (252)



This compound was synthesized from **236** (0.48 ml, 2.0 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.34 g, 42% yield, mixture of 2 isomers, 1.1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.78 (4d, 6H), 7.40 – 7.28 (m, 5H), 7.23 – 7.15 (m, 1H), 6.93 (t, *J* = 6.2 Hz, 1H), 4.01 – 3.74 (m, 6H), 3.74 – 3.48 (m, 8H), 2.52 – 2.35 (m, 10H), 1.94 – 1.45 (m, 17H), 1.21 (4s, *J* = 10.1, 3.4 Hz, 18H).

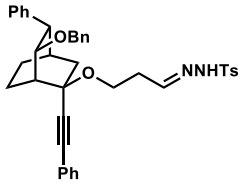
4.14.16.13 Synthesis of N'-(3-((4-((4-methoxyphenyl)ethynyl)tetrahydro-2H-pyran-4-yl)oxy)propylidene)-4-methylbenzenesulfonohydrazide (253)



This compound was synthesized from **239** (1.22 ml, 4.18 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-40% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.41 g, 74% yield, mixture of 2 isomers, 2.9:1). **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 9.08 (s,br , 1H), 7.82 (d, *J* = 8.3 Hz, 3H), 7.80 – 7.73 (m, 11H), 7.37 – 7.27 (m, 10H), 7.27 – 7.20 (m, 12H), 6.93 (t, *J* = 6.0 Hz, 1H), 6.82 (ddd, *J* = 8.6, 6.0, 2.8 Hz, 7H), 6.67 (s,br , 2H), 5.97 (s,br , 2H), 3.88 – 3.69 (m, 25H), 3.63 (tdd, *J* = 8.5, 7.1, 4.2 Hz, 11H), 2.48 (dd, *J* = 5.1, 1.9 Hz, 5H), 2.42 (s, 7H), 2.38 (s, 6H), 2.37 (s, 4H), 2.35 (s, 4H), 1.96 – 1.87 (m, 5H), 1.87 – 1.79 (m, 2H), 1.79 – 1.61 (m, 10H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 160.09, 160.04, 159.90, 150.38, 148.67, 144.65, 144.09, 144.05, 135.73, 135.45, 135.03, 133.32, 133.28, 133.26, 133.23, 130.03, 129.77, 129.67, 129.64, 128.35, 128.07, 128.04, 127.95, 114.15, 114.10, 114.08, 87.92, 87.44, 87.33, 87.05, 86.89, 86.15, 74.84, 72.96, 72.12, 71.68, 64.83, 64.75, 64.68, 60.69, 60.54, 60.48, 60.20, 55.45, 37.66, 37.60, 33.26, 29.59, 28.96, 21.71, 21.67, 14.30.

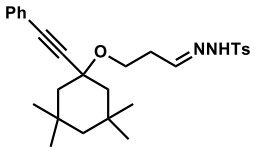
4.14.16.14 Synthesis of N'-(3-(((1R,2R,4R,5S,6S)-6-(benzyloxy)-5-phenyl-2-(phenylethynyl)bicyclo[2.2.2]octan-2-yl)oxy)propylidene)-4-methylbenzenesulfonohydrazide (254)



This compound was synthesized from **240** (0.92 g, 1.96 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.04 g, 83% yield, mixture of 2 isomers, 1.3:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.38 (s, br , 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.51 – 7.06 (m, 43H), 7.00 (s, 2H), 6.92 – 6.77 (m, 2H), 4.48 (d, *J* = 11.7 Hz, 1H),

4.44 – 4.24 (m, 4H), 4.05 – 3.83 (m, 4H), 3.83 – 3.70 (m, 4H), 3.48 (q, *J* = 7.0 Hz, 1H), 3.18 (d, *J* = 6.6 Hz, 1H), 3.04 (d, *J* = 7.2 Hz, 1H), 2.56 (d, *J* = 14.2 Hz, 2H), 2.51 – 1.95 (m, 21H), 1.89 (d, *J* = 14.0 Hz, 3H), 1.64 (dd, *J* = 26.6, 14.3 Hz, 6H), 1.31 (d, *J* = 11.4 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 151.71, 149.07, 144.01, 143.82, 143.69, 138.61, 138.31, 136.22, 135.58, 131.77, 131.72, 129.56, 129.52, 128.56, 128.53, 128.46, 128.40, 128.31, 128.12, 128.10, 128.02, 127.96, 127.85, 127.79, 127.60, 126.32, 122.85, 122.57, 91.80, 90.92, 85.13, 84.78, 81.23, 80.48, 75.24, 74.78, 71.49, 71.23, 65.98, 61.64, 60.84, 49.59, 49.21, 45.96, 45.08, 36.93, 33.30, 33.15, 32.99, 28.78, 22.47, 22.28, 21.65, 21.62, 19.25, 19.02, 15.40.

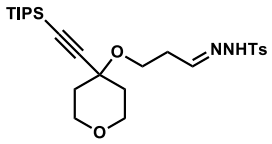
4.14.16.15 Synthesis of 4-methyl-N'-(3-((3,3,5,5-tetramethyl-1-(phenylethynyl)cyclohexyl)oxy)propylidene)benzenesulfonohydrazide (255)



This compound was synthesized from **241** (1.19 g, 3.78 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.09 g, 60% yield, mixture of 2 isomers, 1.1:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.22 (s,br , 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.37 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.34 – 7.22 (m, 11H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.96 (t, *J* = 6.1 Hz, 1H), 3.81 – 3.76 (m, 2H), 3.73 (t, *J* = 6.4 Hz, 1H), 2.51 – 2.43 (m, 4H), 2.37 (s, 2H), 2.30 (s, 3H), 1.78 (d, *J* = 13.3 Hz, 2H), 1.66 (q, *J* = 13.6 Hz, 3H), 1.45 (d, *J*

= 13.4 Hz, 2H), 1.27 (d, *J* = 14.2 Hz, 2H), 1.22 (s, 2H), 1.18 – 1.08 (m, 8H), 1.06 (2s, 5H), 1.00 (2s, 11H), 0.82 (d, *J* = 5.7 Hz, 1H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 150.77, 148.96, 144.07, 143.78, 136.04, 135.45, 131.52, 131.38, 129.67, 129.57, 128.49, 128.45, 128.38, 128.35, 128.14, 127.99, 122.94, 122.60, 92.24, 91.20, 86.30, 85.28, 74.79, 74.08, 60.67, 60.32, 51.64, 51.49, 48.26, 47.97, 33.54, 33.39, 32.24, 31.94, 31.87, 31.68, 30.29, 29.21, 21.69, 21.61.

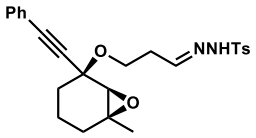
4.14.16.16 Synthesis of 4-methyl-N'-(3-((4-((triisopropylsilyl)ethynyl)tetrahydro-2H-pyran-4-yl)oxy)propylidene)benzenesulfonohydrazide (256)



This compound was synthesized from **242** (0.68, 2.0 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.36 g, 36% yield, mixture of 2 isomers, 2.3:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.89 (s, br, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 4H), 7.66 (s, br, 2H), 7.30 (d, *J* = 8.1 Hz, 6H), 7.21 (t, *J* = 5.3 Hz, 2H), 6.91 (dt, *J* = 6.2, 3.1 Hz, 1H), 3.88 – 3.78 (m, 6H), 3.78 – 3.74 (m, 2H), 3.71 (t, *J* = 6.2 Hz, 4H), 3.65 – 3.55 (m, 6H), 2.48 (dt, *J* = 7.7, 3.7 Hz, 6H), 2.41 (2s, 9H), 1.82 (t, *J* = 12.1 Hz, 6H), 1.68 – 1.55 (m, 7H), 1.09 – 0.93 (m, 62H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 150.23, 148.46, 144.17, 144.02, 135.79, 135.46, 129.69, 129.60, 128.09, 128.01, 107.15, 105.77, 89.51,

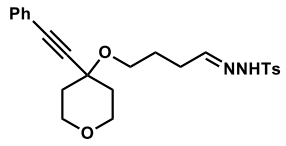
88.20, 73.13, 71.93, 64.96, 64.92, 60.73, 60.20, 37.80, 37.70, 33.24, 28.92, 21.69, 18.71, 11.15, 11.12.

4.14.16.17 Synthesis of 4-methyl-N'-(3-(((1S,2S,6S)-6-methyl-2-(phenylethynyl)-7-oxabicyclo[4.1.0]heptan-2-yl)oxy)propylidene)benzenesulfonohydrazide (262)



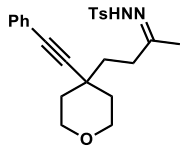
This compound was synthesized from **261** (1.34 g, 4.66 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.77 g, 42% yield, mixture of 2 isomers, 1.2:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.00 (s,br, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.46 – 7.37 (m, 3H), 7.37 – 7.18 (m, 10H), 6.96 (dd, *J* = 9.1, 3.6 Hz, 1H), 3.95 – 3.87 (m, 2H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.16 (2s, *J* = 14.8 Hz, 2H), 2.51 (ddd, *J* = 9.3, 7.2, 2.9 Hz, 4H), 2.36 (2s, 6H), 1.93 – 1.78 (m, 3H), 1.78 – 1.60 (m, 7H), 1.59 – 1.47 (m, 4H), 1.36 (2s, 6H).**^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 150.61, 148.89, 144.02, 143.75, 135.89, 135.48, 131.94, 129.65, 129.49, 129.03, 128.89, 128.52, 128.49, 128.28, 128.00, 122.16, 121.86, 87.84, 87.77, 87.33, 87.10, 74.30, 73.67, 62.61, 62.08, 61.69, 61.28, 60.83, 33.24, 31.76, 31.58, 29.17, 28.19, 28.15, 24.10, 23.97, 21.66, 18.45, 18.15, 14.30.

4.14.16.18 Synthesis of 4-methyl-N'-(4-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)butylidene)benzenesulfonohydrazide (267)



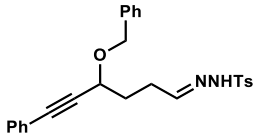
This compound was synthesized from **SI4-10** (0.35 g, 1.29 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.32 g, 57% yield, mixture of 2 isomers, 2.2:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 (s, br, 1H), 7.83 (d, *J* = 8.2 Hz, 3H), 7.79 (d, *J* = 8.2 Hz, 5H), 7.45 – 7.37 (m, 7H), 7.37 – 7.18 (m, 23H), 6.80 (t, *J* = 5.9 Hz, 1H), 3.96 – 3.80 (m, 8H), 3.74 – 3.63 (m, 8H), 3.60 (t, *J* = 6.1 Hz, 8H), 2.44 – 2.26 (m, 21H), 1.99 (dd, *J* = 35.6, 13.1 Hz, 9H), 1.91 – 1.82 (m, 3H), 1.77 (tdd, *J* = 16.4, 11.4, 5.2 Hz, 15H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 152.47, 150.80, 144.12, 135.44, 131.85, 131.79, 129.72, 128.80, 128.68, 128.51, 128.06, 127.96, 122.47, 122.28, 89.19, 88.67, 87.34, 86.84, 72.26, 71.42, 64.87, 64.79, 62.19, 61.64, 37.66, 29.62, 26.67, 26.18, 24.17, 21.71.

4.14.16.19 Synthesis of 4-methyl-N'-(4-(4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)butan-2-ylidene)benzenesulfonohydrazide (273)



This compound was synthesized from **SI4-12** (0.30, 1.15 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.38 g, 77% yield). **^{1}H NMR** (500 MHz, $CDCl_3$δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.30 (dt, *J* = 11.2, 4.6 Hz, 4H), 7.02 (s, 1H), 3.88 – 3.72 (m, 4H), 2.47 (dd, *J* = 9.3, 6.9 Hz, 2H), 2.42 (s, 3H), 1.79 (s, 3H), 1.73 – 1.62 (m, 4H), 1.51 (dd, *J* = 13.0, 4.6 Hz, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 144.11, 135.44, 131.83, 131.63, 129.61, 129.53, 128.47, 128.41, 128.22, 128.08, 123.40, 92.58, 84.94, 65.10, 65.04, 38.65, 37.79, 37.63, 34.85, 33.80, 21.72, 16.21.

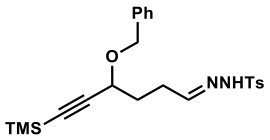
4.14.16.20 Synthesis of N'-(4-(benzyloxy)-6-phenylhex-5-yn-1-ylidene)-4-methylbenzenesulfonohydrazide (286)



This compound was synthesized from **SI4-15** (0.84 g, 3.0 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was

obtained as a white amorphous solid (0.38 g, 28% yield, mixture of 2 isomers, 2:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.83 – 7.77 (m, 5H), 7.43 (ddd, *J* = 7.0, 3.8, 2.0 Hz, 8H), 7.39 – 7.22 (m, 34H), 7.18 (t, *J* = 5.0 Hz, 2H), 4.85 (d, *J* = 11.9 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 3H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 2H), 4.28 (m , 3H), 2.51 – 2.42 (m, 5H), 2.39 (2s, 8H), 1.99 (dd, *J* = 14.0, 7.2 Hz, 5H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 151.86, 149.92, 144.22, 137.87, 135.31, 131.84, 129.72, 128.65, 128.54, 128.46, 128.35, 128.10, 128.05, 127.91, 122.50, 87.35, 86.70, 70.83, 68.21, 67.48, 32.11, 28.51, 22.94, 21.71.

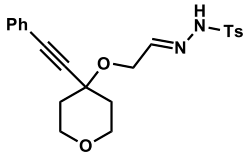
4.14.16.21 Synthesis of N'-(4-(benzyloxy)-6-(trimethylsilyl)hex-5-yn-1-ylidene)-4-methylbenzenesulfonohydrazide (288)



This compound was synthesized from **SI4-17** (0.64 g, 2.32 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.77 g, 75% yield, mixture of 2 isomers, 2:1). **^{1}H NMR** (500 MHz, $CDCl_3$)) δ 7.83 – 7.75 (m, 5H), 7.57 (s, br, 2H), 7.37 – 7.22 (m, 21H), 7.15 (t, *J* = 5.0 Hz, 2H), 4.73 (2d, *J* = 11.7 Hz, 3H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 2H), 4.02 (t, *J* = 6.1 Hz, 3H), 2.46 – 2.33 (m, 13H), 1.93 – 1.82 (m, 6H), 0.19 (d, *J* = 5.1 Hz, 24H). **^{13}C NMR** (125.76 MHz, $CDCl_3$)) δ 151.86, 149.87, 144.21,

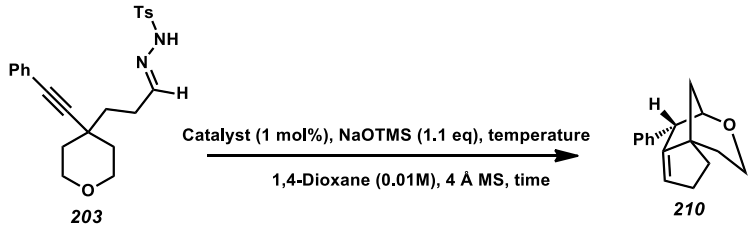
137.84, 135.27, 129.72, 128.60, 128.50, 128.35, 128.12, 128.08, 128.04, 127.88, 103.83, 91.51, 70.67, 68.11, 31.91, 28.30, 21.73, 0.06, -0.03.

4.14.16.22 Synthesis of (E)-4-methyl-N'-(2-((4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)oxy)ethylidene)benzenesulfonohydrazide (292)



This compound was synthesized from **SI4-20** (0.47 g, 1.90 mmol) following the general procedure above. The crude product was purified by column chromatography on silica gel using a 20-30% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (0.16 g, 20% yield, mixture of 2 isomers, 1.6:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.40 (s, br, 1H), 7.80 (dd, *J* = 8.3, 2.7 Hz, 5H), 7.46 – 7.16 (m, 17H), 6.81 (t, *J* = 3.4 Hz, 1H), 4.37 (d, *J* = 3.4 Hz, 2H), 4.30 (d, *J* = 5.1 Hz, 2H), 3.87 (ddd, *J* = 11.5, 10.2, 4.2 Hz, 5H), 3.75 – 3.60 (m, 4H), 2.40 (2s, 6H), 2.12 – 1.86 (m, 8H), 1.86 – 1.68 (m, 5H).**^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 148.04, 131.92, 131.84, 129.78, 129.43, 129.19, 128.91, 128.52, 128.02, 127.92, 88.07, 87.95, 72.62, 64.79, 64.51, 63.11, 60.70, 37.69, 37.47, 21.73.

4.14.17 Formation of cascade products

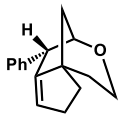


General procedure A (Synthesis of 210 as an example): A round-bottom flask containing 4Å molecule sieves (bead, 350 mg for 10 ml solvent) was flame-dried under high vacuum. The flask was back-filled with Argon 3 times and allowed to cool down to room temperature. Hydrazone **203** (1 eq), the rhodium catalyst (1 mol%) and 1,4-dioxane (0.01M) were successively added and the reaction mixture was stirred for 1 minute after which NaOTMS (1.1 eq) were added in one portion. The reaction was then heated to 90 °C for 3 hours. When the reaction was completed, the reaction mixture was allowed to reach room temperature and filtered through a celite pad using ethyl acetate to rinse the reaction residue. The solvent was removed under reduced pressure, and the crude mixture was purified by flash chromatography. (See each product for details of catalyst used and reaction time).

General procedure B: A schlenk flask containing 4Å molecule sieves (bead, 350 mg for 10 ml solvent) was flame-dried under high vacuum. The flask was back-filled with Argon 3 times and allowed to cool down to room temperature. Hydrazone **203** (1 eq), the rhodium catalyst (1 mol%), NaOTMS (1.1 eq) and 1,4-dioxane (0.01M) were successively added and the reaction mixture was sealed and heated to 140 °C. When the reaction was completed, the reaction mixture was allowed to reach room temperature and

filtered through a celite pad using ethyl acetate to rinse the reaction residue. The solvent was removed under reduced pressure, and the crude reaction mixture was purified by flash chromatography. (See each product for details of catalyst used and reaction time).

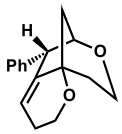
4.14.17.1 Synthesis of (1S,2R,5aS)-1-phenyl-1,2,4,5,6,7-hexahydro-2,5a-methanocyclopenta[d]oxepine (210)



This compound was synthesized from **203** (41 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (19.9 mg, 88% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.38 – 7.30 (m, 2H), 7.27 – 7.18 (m, 1H), 5.67 – 5.61 (m, 1H), 4.99 (t, *J* = 3.2 Hz, 1H), 3.89 (s, 1H), 3.45 (dd, *J* = 11.8, 6.6 Hz, 1H), 3.29 (td, *J* = 12.1, 4.4 Hz, 1H), 2.99 – 2.85 (m, 1H), 2.65 – 2.54 (m, 1H), 1.93 (d, *J* = 10.8 Hz, 1H), 1.85 – 1.67 (m, 3H), 1.63 – 1.48 (m, 2H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 152.79, 137.78, 128.31, 128.04, 126.08, 121.13, 83.00, 61.48, 57.25, 47.03, 44.56, 36.79, 36.20, 35.84.

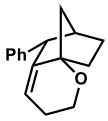
A similar reaction was conducted using a 5 mol% of Rh_2(S-TBSP)$_4$ also gave **210** (8.6 mg, 38% yield, >99:1 er). HPLC Chiralpak ID (hexane/i-PrOH = 99:1, 0.75 mL/min, UV-254 detector)

4.14.17.2 Synthesis of (5S,6R,9aS)-5-phenyl-2,3,5,6,8,9-hexahydro-6,9a-methanopyrano[2,3-d]oxepine (268)



This compound was synthesized from **243** (42.7 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (19.9 mg, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$ δ 7.53 – 7.46 (m, 2H), 7.35 (dd, *J* = 10.4, 4.9 Hz, 2H), 7.22 (d, *J* = 7.0 Hz, 1H), 5.89 (dd, *J* = 5.9, 3.4 Hz, 1H), 4.77 – 4.71 (m, 1H), 4.13 – 4.03 (m, 2H), 3.95 (dd, *J* = 11.9, 6.9 Hz, 1H), 3.55 (dd, *J* = 11.9, 6.7 Hz, 1H), 3.37 (td, *J* = 12.3, 4.4 Hz, 1H), 2.53 – 2.41 (m, 1H), 2.16 (ddd, *J* = 17.9, 7.3, 3.2 Hz, 1H), 2.10 – 1.98 (m, 2H), 1.88 – 1.78 (m, 2H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 140.84, 137.63, 128.38, 127.88, 126.29, 121.69, 78.43, 76.02, 60.79, 59.00, 49.94, 44.81, 36.02, 25.55.

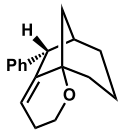
4.14.17.3 Synthesis of (6R,8aR)-5-phenyl-2,3,5,6,7,8-hexahydro-6,8a-methanochromene (269)



This compound was synthesized from **244** (41.1 mg, 0.1 mmol, 1 eq), $Rh_2(esp)_2$ (0.8 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 1-4% gradient of EtOAc in

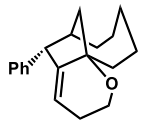
hexanes as an eluent. The product was obtained as a white amorphous solid (11.5 mg, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.16 (m, 3H), 5.52 (t, *J* = 4.8 Hz, 1H), 3.98 – 3.85 (m, 3H), 2.37 – 2.24 (m, 2H), 2.10 – 2.00 (m, 1H), 1.90 – 1.78 (m, 2H), 1.71 – 1.48 (m, 3H), 1.30 – 1.20 (m, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 144.45, 141.71, 128.31, 128.20, 126.24, 116.01, 84.86, 62.13, 51.11, 43.61, 39.43, 29.83, 25.17, 23.39.

4.14.17.4 Synthesis of (5S,6R,9aS)-5-phenyl-3,5,6,7,8,9-hexahydro-2H-6,9a-methanocyclohepta[b]pyran (270)



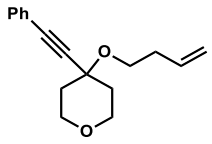
This compound was synthesized from **245** (64.8 mg, 0.15 mmol, 1 eq), $Rh_2(esp)_2$ (1.0 mg, 1 mol%) in 14 hours following the general procedure B. The crude product was purified by column chromatography on silica gel using a 0.5-1% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (25.9 mg, 71% yield, dr 7:1). **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.35 – 7.24 (m, 2H), 7.23 – 7.15 (m, 1H), 5.73 (dd, *J* = 5.8, 3.4 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.90 (dd, *J* = 11.6, 7.0 Hz, 1H), 2.67 (s, 1H), 2.47 – 2.34 (m, 1H), 2.25 – 2.03 (m, 2H), 1.95 – 1.85 (m, 1H), 1.77 (d, *J* = 10.2 Hz, 1H), 1.61 – 1.45 (m, 2H), 1.41 – 1.19 (m, 5H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 143.02, 140.12, 128.32, 128.06, 125.74, 120.40, 79.46, 59.00, 49.21, 45.29, 37.78, 35.14, 27.15, 25.48, 19.37.

4.14.17.5 Synthesis of (6R,11aR)-5-phenyl-3,5,6,7,8,9,10,11-octahydro-2H-6,11a-methanocyclonona[b]pyran (271)



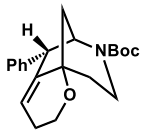
This compound was synthesized from **246** (45.3 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (18.5 mg, 69% yield, dr). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 2H), 7.24 – 7.14 (m, 3H), 5.54 (td, *J* = 3.8, 2.1 Hz, 1H), 4.92 (dd, *J* = 6.4, 3.6 Hz, 0.26H, minor diastereomer), 4.36 (d, *J* = 6.9 Hz, 1H), 4.05 (ddd, *J* = 11.9, 9.7, 5.3 Hz, 1H), 3.82 (ddd, *J* = 11.9, 7.3, 1.8 Hz, 1H), 2.64 – 2.51 (m, 1H), 2.43 (d, *J* = 12.3 Hz, 1H), 2.39 – 2.23 (m, 2H), 2.13 – 2.06 (m, 2H), 1.79 – 1.62 (m, 2H), 1.62 – 1.48 (m, 2H), 1.35 (ddd, *J* = 32.4, 16.5, 9.8 Hz, 3H), 1.07 – 0.91 (m, 1H), 0.72 (dt, *J* = 15.3, 10.0 Hz, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 146.96, 142.02, 128.90, 128.07, 125.79, 118.86, 80.25, 58.37, 51.18, 36.96, 34.89, 31.68, 31.07, 29.23, 25.02, 24.64, 23.51.

4.14.17.6 Synthesis of 4-(but-3-en-1-yloxy)-4-(phenylethynyl)tetrahydro-2H-pyran (272)



This compound was synthesized from **267** (45 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 2.5 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 5-10% gradient of EtOAc in hexanes as an eluent. The product was obtained as a light yellow oil (15.8 mg, 60% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.35 – 7.29 (m, 3H), 5.88 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.09 (ddd, *J* = 13.8, 11.7, 1.6 Hz, 2H), 3.91 (dt, *J* = 9.1, 4.3 Hz, 2H), 3.72 (ddd, *J* = 13.6, 8.0, 3.5 Hz, 4H), 2.41 – 2.35 (m, 2H), 2.07 – 1.99 (m, 3H), 1.88 (ddd, *J* = 13.0, 9.2, 3.9 Hz, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 135.52, 131.80, 128.54, 128.42, 122.65, 116.38, 89.32, 86.80, 71.41, 64.84, 62.71, 37.76, 34.66.

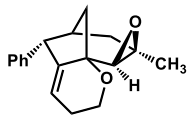
4.14.17.7 Synthesis of (5S,6R,9aS)-tert-butyl 5-phenyl-5,6,8,9-tetrahydro-2H-6,9a-methanopyrano[2,3-d]azepine-7(3H)-carboxylate (274)



This compound was synthesized from **248** (52.6 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 14 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 15-25% gradient of EtOAc in

hexanes as an eluent. The product was obtained as a white amorphous solid (28.1 mg, 82% yield, mixture of two rotamers, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.24 (m, 4H), 7.17 (td, *J* = 6.8, 1.2 Hz, 2H), 5.85 (m , 2H), 5.20 (dd, *J* = 5.8, 4.7 Hz, 1H), 5.03 – 4.97 (m, 1H), 4.18 (dd, *J* = 17.5, 3.0 Hz, 2H), 4.13 – 4.00 (m, 2H), 3.94 (dd, *J* = 11.8, 7.1 Hz, 2H), 3.77 (dd, *J* = 13.8, 7.2 Hz, 1H), 3.57 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.61 – 2.37 (m, 4H), 2.21 – 2.08 (m, 3H), 2.06 – 1.97 (m, 1H), 1.95 – 1.80 (m, 3H), 1.67 (ddd, *J* = 18.8, 10.0, 6.5 Hz, 1H), 1.41 (s, 9H), 1.23 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 155.03, 154.35, 128.25, 128.11, 128.05, 126.56, 126.19, 122.26, 122.06, 79.65, 79.28, 78.96, 59.36, 59.22, 54.92, 53.75, 50.49, 50.24, 44.06, 43.92, 39.25, 38.16, 33.43, 33.27, 28.54, 28.32, 25.53, 25.43.

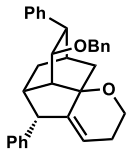
4.14.17.8 Synthesis of (1aR,3R,4S,8aR,8bS)-1a-methyl-4-phenyl-2,3,4,6,7,8b-hexahydro-1aH-3,8a-methanooxireno[2',3':6,7]cyclohepta[1,2-b]pyran (275)



This compound was synthesized from **262** (45.3 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 5 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 5-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (26 mg, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.21 (m , 3H), 5.75 (dd, *J* = 5.9, 3.8 Hz, 1H), 4.21 (ddd, *J* = 11.9, 9.9, 4.4 Hz, 1H), 4.16 – 4.10 (m, 1H), 3.97 (ddd, *J* = 11.9, 6.4, 2.2 Hz, 1H), 3.27 (s, 1H), 2.46 – 2.32 (m, 2H), 2.21 – 2.08 (m, 2H), 1.68 (dd, *J* = 15.3, 4.9 Hz, 1H), 1.51 (ddt, *J* = 10.4, 5.9, 1.8 Hz, 1H), 1.05 (dt, *J* = 15.3, 1.8 Hz,

1H), 0.97 (s, 3H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 141.85, 141.45, 128.62, 128.48, 126.45, 120.95, 78.84, 61.32, 60.28, 57.78, 49.28, 36.67, 35.30, 30.88, 25.08, 23.68.

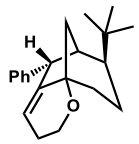
4.14.17.9 Synthesis of (5S)-9-(benzyloxy)-5,8-diphenyl-3,5,5a,6,7,8,9,9a-octahydro-2H-7,9b-methanoindeno[1,2-b]pyran (276)



This compound was synthesized from **254** (126.6 mg, 0.2 mmol, 1 eq), $Rh_2(piv)_4$ (1.2 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (49 mg, 54% yield, dr 1.5:1). Spectra for major diastereomer, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.06 (m, 15H), 5.57 (m , 1H), 4.55 (dd, *J* = 31.2, 12.8 Hz, 2H), 4.23 – 4.16 (m, 1H), 4.16 – 3.98 (m, 3H), 3.01 (d, *J* = 5.8 Hz, 1H), 2.49 – 2.35 (m, 3H), 2.19 (d, *J* = 2.7 Hz, 2H), 2.04 (dd, *J* = 17.6, 3.9 Hz, 1H), 1.70 (s, 1H), 1.21 (dd, *J* = 22.8, 8.6 Hz, 1H), 0.76 – 0.65 (m, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 147.29, 144.29, 140.93, 138.63, 128.98, 128.37, 128.29, 128.12, 127.74, 127.31, 126.14, 126.07, 117.75, 69.99, 59.66, 51.61, 49.58, 45.80, 43.90, 37.83, 32.07, 24.79, 20.94.

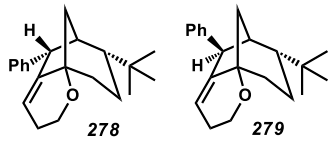
The allyl ether **228** was obtained as by-product (20 mg, 22% yield)

4.14.17.10 Synthesis of (5S,6S,7S,9aS)-7-(tert-butyl)-5-phenyl-3,5,6,7,8,9-hexahydro-2H-6,9a-methanocyclohepta[b]pyran (277)



This compound was synthesized from **251A** (48.1 mg, 0.1 mmol, 1 eq), $Rh_2(esp)_2$ (0.8 mg, 1 mol%) in 14 hours following the general procedure B. The crude product was purified by column chromatography on silica gel using a 0.5-1.5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (24.6 mg, 83% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.13 (m, 5H), 5.51 (dd, *J* = 6.1, 3.4 Hz, 1H), 4.14 (dd, *J* = 6.8, 3.1 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.89 (dd, *J* = 11.8, 7.1 Hz, 1H), 2.55 – 2.48 (m, 1H), 2.42 – 2.28 (m, 1H), 2.09 – 1.97 (m, 3H), 1.89 (ddd, *J* = 12.9, 7.0, 5.6 Hz, 1H), 1.55 – 1.50 (m, 1H), 1.48 – 1.36 (m, 1H), 1.36 – 1.23 (m, 1H), 0.89 – 0.81 (m, 1H), 0.67 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 146.70, 140.93, 129.42, 128.02, 126.02, 117.09, 78.48, 59.42, 51.81, 41.43, 38.58, 37.30, 34.87, 33.49, 27.95, 25.02, 19.11.

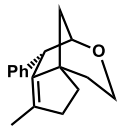
4.14.17.11 Synthesis of (5S,6S,7R,9aS)-7-(tert-butyl)-5-phenyl-3,5,6,7,8,9-hexahydro-2H-6,9a-methanocyclohepta[b]pyran (278) and (5R,6S,7R,9aS)-7-(tert-butyl)-5-phenyl-3,5,6,7,8,9-hexahydro-2H-6,9a-methanocyclohepta[b]pyran (279)



278 279

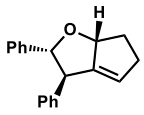
This compound was synthesized from **251B** (48.1 mg, 0.1 mmol, 1 eq), $Rh_2(esp)_2$ (0.8 mg, 1 mol%) in 14 hours following the general procedure B. The crude product was purified by column chromatography on silica gel using a 0.5-1.5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (20.9 mg, 71% yield, dr 3:1). Spectra for minor diastereomer (**279**), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.23 – 7.14 (m, 3H), 5.09 (m , 1H), 3.99 – 3.89 (m, 1H), 3.82 (dd, *J* = 11.8, 6.1 Hz, 1H), 3.65 (s,br, 1H), 2.38 (d, *J* = 6.1 Hz, 1H), 2.29 – 2.15 (m, 3H), 1.91 – 1.78 (m, 2H), 1.65 – 1.51 (m, 3H), 1.42 – 1.33 (m, 1H), 0.91 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 148.92, 146.38, 128.44, 128.28, 125.98, 117.64, 79.65, 59.42, 53.02, 47.47, 46.15, 42.61, 34.40, 33.40, 29.01, 25.34, 21.34.). Spectra for major diastereomer (**278**), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.09 (m, 5H), 5.59 (dd, *J* = 6.5, 3.7 Hz, 1H), 4.22 – 4.16 (m, 1H), 4.13 (ddd, *J* = 11.6, 9.9, 5.2 Hz, 1H), 3.90 – 3.85 (m, 1H), 2.84 (t, *J* = 5.9 Hz, 1H), 2.37 – 2.26 (m, 2H), 2.15 – 2.06 (m, 1H), 2.03 (ddd, *J* = 9.9, 5.4, 3.0 Hz, 1H), 1.72 (d, *J* = 10.1 Hz, 1H), 1.65 – 1.56 (m, 2H), 1.52 – 1.43 (m, 2H), 0.35 (s, 9H).

4.14.17.12 Synthesis of (1S,2R,5aS)-8-methyl-1-phenyl-1,2,4,5,6,7-hexahydro-2,5a-methanocyclopenta[d]oxepine (280)



This compound was synthesized from **273** (42.5 mg, 0.1 mmol, 1 eq), $Rh_2(esp)_2$ (3.0 mg, 5 mol%) in 14 hours following the general procedure B. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (13.2 mg, 55% yield). Start with 1 mol% $Rh_2(esp)_2$, the product also was obtained (12.5 mg, 52% yield) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 5.0, 4.3 Hz, 2H), 7.33 (dd, *J* = 10.4, 4.9 Hz, 2H), 7.21 (dd, *J* = 10.7, 4.0 Hz, 1H), 4.94 – 4.86 (m, 1H), 3.90 (s, 1H), 3.48 – 3.39 (m, 2H), 2.99 (dddd, *J* = 13.1, 9.7, 6.2, 2.0 Hz, 1H), 2.43 – 2.31 (m, 1H), 1.86 (d, *J* = 11.0 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.80 – 1.74 (m, 3H), 1.70 (s, 3H), 1.63 (d, *J* = 12.1 Hz, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 143.34, 138.33, 130.63, 128.71, 128.16, 125.91, 83.71, 61.49, 57.71, 47.19, 45.28, 41.07, 36.74, 36.10, 16.13.

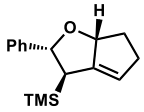
4.14.17.13 Synthesis of (2R,3R,6aR)-2,3-diphenyl-3,5,6,6a-tetrahydro-2H-cyclopenta[b]furan (287)



This compound was synthesized from **286** (46.8 mg, 0.105 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was

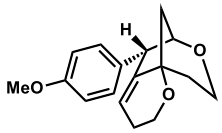
purified by column chromatography on silica gel using a 1-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (11.8 mg, 43% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 – 6.93 (m, 8H), 6.87 – 6.78 (m, 2H), 5.63 (d, *J* = 8.9 Hz, 1H), 5.39 (dt, *J* = 4.6, 2.2 Hz, 1H), 5.24 – 5.14 (m, 1H), 4.31 – 4.24 (m, 1H), 2.83 – 2.70 (m, 2H), 2.48 (tdd, *J* = 7.0, 5.6, 1.8 Hz, 1H), 2.15 (dtd, *J* = 12.4, 9.3, 7.6 Hz, 1H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 151.17, 139.78, 138.99, 129.89, 127.53, 127.38, 126.74, 126.60, 126.22, 123.23, 89.41, 89.22, 49.98, 36.22, 32.96.

4.14.17.14 Synthesis of trimethyl((2S,3R,6aR)-2-phenyl-3,5,6,6a-tetrahydro-2H-cyclopenta[b]furan-3-yl)silane (289)



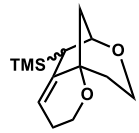
This compound was synthesized from **203** (41 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (19.9 mg, 88% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.18 (m, 5H), 5.50 (d, *J* = 9.4 Hz, 1H), 5.45 (s, 1H), 5.02 – 4.92 (m, 1H), 2.77 – 2.67 (m, 2H), 2.42 (ddd, *J* = 4.5, 3.8, 1.9 Hz, 1H), 2.39 – 2.30 (m, 1H), 1.97 – 1.84 (m, 1H), -0.29 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 149.37, 142.94, 127.98, 127.69, 127.46, 120.18, 90.60, 88.33, 36.34, 34.80, 32.78, -1.45.

4.14.17.15 Synthesis of (5S,6R,9aS)-5-(4-methoxyphenyl)-2,3,5,6,8,9-hexahydro-6,9a-methanopyrano[2,3-d]oxepine (290)



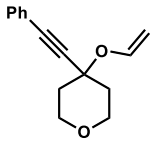
This compound was synthesized from **253** (45.7 mg, 0.1 mmol, 1 eq), $Rh_2(esp)_2$ (0.6 mg, 1 mol%) in 14 hours following the general procedure B. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (18.6 mg, 68% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.87 (dd, *J* = 6.0, 3.4 Hz, 1H), 4.70 – 4.64 (m, 1H), 4.11 – 4.03 (m, 1H), 3.99 (s, 1H), 3.94 (dd, *J* = 12.0, 6.9 Hz, 1H), 3.89 (dd, *J* = 5.7, 1.8 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.80 (s, 3H), 3.56 (dd, *J* = 11.9, 6.7 Hz, 1H), 3.38 (td, *J* = 12.3, 4.3 Hz, 1H), 2.51 – 2.41 (m, 1H), 2.18 – 2.09 (m, 1H), 2.05 (dt, *J* = 11.6, 3.7 Hz, 1H), 2.03 – 1.98 (m, 1H), 1.87 – 1.78 (m, 2H).**^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 158.00, 141.34, 129.52, 128.79, 121.36, 113.80, 78.43, 76.01, 60.75, 58.98, 55.35, 49.22, 44.79, 36.07, 25.52.

4.14.17.16 Synthesis of ((5S,6R,9aS)-2,3,5,6,8,9-hexahydro-6,9a-methanopyrano[2,3-d]oxepin-5-yl)trimethylsilane (291)



This compound was synthesized from **247** (42.3 mg, 0.1 mmol, 1 eq), $Rh_2(esp)_2$ (3.8 mg, 5 mol%) in 14 hours following the general procedure B. The crude product was purified by column chromatography on silica gel using a 1-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.9 mg, 8% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.53 (dd, *J* = 6.2, 3.7 Hz, 1H), 4.33 (d, *J* = 2.8 Hz, 1H), 3.97 (m , 1H), 3.81 (m , 4H), 2.33 (m , 1H), 2.15 – 2.09 (m, 1H), 2.00 – 1.91 (m, 2H), 1.83 – 1.72 (m, 2H), 1.61 – 1.51 (m, 2H), 0.08 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 142.66, 114.36, 77.80, 76.44, 60.04, 59.18, 44.57, 36.64, 34.92, 25.02, -1.53.

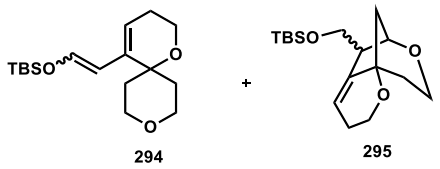
4.14.17.17 Synthesis of 4-(phenylethynyl)-4-(vinyloxy)tetrahydro-2H-pyran (293)



This compound was synthesized from **292** (41.3 mg, 0.1 mmol, 1 eq), $Rh_2(esp)_2$ (0.8 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (17.7 mg, 78% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.33 (m , 3H), 6.76 (dd, *J* = 13.8, 6.3

Hz, 1H), 4.60 (dd, *J* = 13.8, 0.8 Hz, 1H), 4.22 (d, *J* = 6.3 Hz, 1H), 3.97 – 3.88 (m, 2H), 3.74 (m , 2H), 2.13 – 2.02 (m, 2H), 2.02 – 1.92 (m, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 146.45, 131.91, 128.89, 128.46, 122.09, 92.66, 88.10, 87.75, 77.38, 77.12, 76.87, 73.10, 64.43, 37.92.

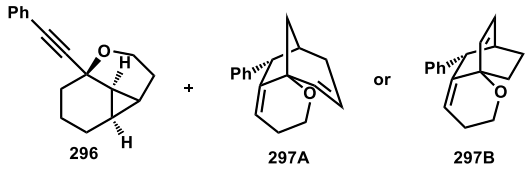
4.14.17.18 Synthesis of ((2-(1,9-dioxaspiro[5.5]undec-4-en-5-yl)vinyl)oxy)(tert-butyl)dimethylsilane (294) and tert-butyl(((6R,9aS)-2,3,5,6,8,9-hexahydro-6,9a-methanopyrano[2,3-d]oxepin-5-yl)methoxy)dimethylsilane (295)



This compound was synthesized from **249** (53.8 mg, 0.11 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 1-4% gradient of EtOAc in hexanes as an eluent. The product **294** was obtained as a white amorphous solid (23.63 mg, 70% yield, mixture of Z/E isomers with Z/E ratio 2.6:1). **^{1}H NMR** (400 MHz, $CDCl_3$ δ 6.51 (td, *J* = 10.4, 6.3 Hz, 1H, Z isomer), 6.31 (d, *J* = 6.8 Hz, 1H, Z isomer), 5.69 (td, *J* = 4.1, 1.0 Hz, 0.39H, E isomer), 5.51 (dd, *J* = 11.6, 1.4 Hz, 0.39H, E isomer), 4.62 (d, *J* = 6.7 Hz, 1H, Z isomer), 3.83 – 3.66 (m, 9H), 2.20 (q, *J* = 5.4 Hz, 2H), 2.15 – 2.06 (m, 0.84H, E isomer), 1.93 (ddd, *J* = 25.6, 13.2, 5.9 Hz, 3H), 1.52 (dd, *J* = 13.5, 7.8 Hz, 3H), 0.94 – 0.87 (m, 14H), 0.15 (d, *J* = 2.9 Hz, 8H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 141.80, 140.78, 139.42, 136.84, 123.90, 118.73, 110.90, 104.96, 72.23, 72.02, 63.53, 63.39, 58.31, 58.21, 33.63, 33.49, 26.00, 25.74, 25.66, 18.44, 18.28.

The product **295** was observed in trace amounts.

4.14.17.19 Synthesis of (3a1R,3bR,6aR)-6a-(phenylethynyl)octahydro-2H-cyclopropa[de]chromene (296) and (5S,6R,9aS)-5-phenyl-3,5,6,7-tetrahydro-2H-6,9a-methanocyclohepta[b]pyran (297A) or (5S,6R,8aR)-5-phenyl-2,3,5,6-tetrahydro-6,8a-ethanochromene (297B)

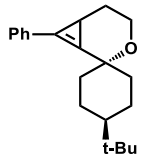


This compound was synthesized from **250** (65.6 mg, 0.15 mmol, 1 eq), $Rh_2(esp)_2$ (1.2 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product **296** was obtained as a white amorphous solid (19.8 mg, 54% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 7.34 – 7.26 (m, 3H), 3.61 – 3.47 (m, 2H), 2.01 – 1.92 (m, 1H), 1.87 – 1.67 (m, 3H), 1.67 – 1.47 (m, 3H), 1.44 – 1.33 (m, 1H), 1.31 – 1.18 (m, 1H), 1.10 (t, *J* = 8.8 Hz, 1H), 1.00 – 0.91 (m, 1H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.88, 128.26, 128.08, 123.27, 93.87, 81.62, 67.01, 60.73, 33.63, 18.19, 17.60, 13.98, 13.12, 11.36, 10.93.

The product **297A** or **297B** was obtained as a white amorphous solid (9 mg, 24% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 – 7.14 (m, 5H), 6.03 (d, *J* = 9.8 Hz, 1H), 5.40 (s, 1H), 5.33 (d, *J* = 9.8 Hz, 1H), 4.16 (d, *J* = 6.5 Hz, 1H), 4.05 (td, *J* = 11.3, 4.1 Hz, 1H), 3.95 (dd, *J* = 11.8, 6.5 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.39 – 2.27 (m, 1H), 2.09 – 2.01 (m, 2H), 2.00 – 1.90 (m, 2H), 1.39 (d, *J* = 18.1 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ

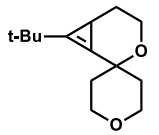
146.81, 141.80, 133.45, 128.54, 128.09, 126.12, 124.93, 124.88, 115.69, 115.66, 78.57, 59.99, 59.95, 50.63, 50.57, 40.84, 37.18, 30.03, 24.56.

4.14.17.20 Synthesis of (1'r,4'r)-4'-(tert-butyl)-7-phenyl-3-oxaspiro[bicyclo[4.1.0]hept[1(7)]ene-2,1'-cyclohexane] (300)



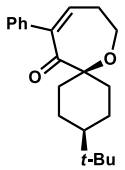
This compound was synthesized from **251B** (48.1 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 1-4% gradient of EtOAc in hexanes as an eluent. The product was obtained as light yellow oil (19.5 mg, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 3.68 – 3.57 (m, 1H), 3.41 – 3.30 (m, 1H), 2.49 (ddd, *J* = 12.2, 6.0, 3.0 Hz, 1H), 2.38 – 2.29 (m, 1H), 2.04 – 1.94 (m, 2H), 1.81 (m , 2H), 1.69 – 1.46 (m, 4H), 1.20 – 0.98 (m, 2H), 0.88 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 130.07, 129.20, 128.88, 128.60, 122.33, 121.17, 78.78, 60.09, 47.93, 35.68, 35.34, 32.46, 27.89, 27.78, 25.48, 25.33, 12.64.

4.14.17.21 Synthesis of 7-(tert-butyl)-2',3',5',6'-tetrahydro-3-oxaspiro[bicyclo[4.1.0]hept[1(7)]ene-2,4'-pyran] (302)



This compound was synthesized from **252** (82.2 mg, 0.2 mmol, 1 eq), $Rh_2(esp)_2$ (1.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (35.0 mg, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.96 – 3.85 (m, 2H), 3.73 – 3.61 (m, 2H), 3.46 (dddd, *J* = 17.9, 12.3, 8.8, 3.4 Hz, 2H), 2.12 – 1.89 (m, 3H), 1.88 – 1.79 (m, 1H), 1.67 (ddd, *J* = 18.5, 9.3, 4.8 Hz, 1H), 1.54 (dd, *J* = 4.4, 2.1 Hz, 1H), 1.38 – 1.29 (m, 1H), 1.19 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 131.71, 111.25, 73.25, 65.14, 59.91, 36.58, 34.61, 32.59, 28.83, 28.41, 11.31.

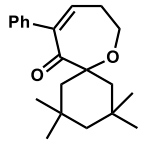
4.14.17.22 Synthesis of (3s,6s)-3-(tert-butyl)-11-phenyl-7-oxaspiro[5.6]dodec-10-en-12-one (304)



This compound was synthesized from **251A** (48.1 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 14 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 1-2% gradient of EtOAc in

hexanes as an eluent. The product was obtained as a white amorphous solid (15.2 mg, 49% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 5H), 6.48 (t, *J* = 4.3 Hz, 1H), 3.81 (t, *J* = 5.4 Hz, 2H), 2.71 (dd, *J* = 9.8, 5.3 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.74 – 1.60 (m, 4H), 1.39 (ddd, *J* = 15.9, 13.4, 3.3 Hz, 2H), 1.08 – 0.98 (m, 1H), 0.87 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 210.61, 141.20, 140.57, 136.49, 128.34, 127.90, 127.48, 87.94, 62.90, 47.34, 34.66, 32.56, 32.40, 27.66, 22.06.

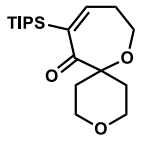
4.14.17.23 Synthesis of 2,2,4,4-tetramethyl-11-phenyl-7-oxaspiro[5.6]dodec-10-en-12-one (305)



This compound was synthesized from **255** (58.9 mg, 0.123 mmol, 1 eq), $Rh_2(esp)_2$ (0.9 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (17.5 mg, 56% yield). **^{1}H NMR** (600 MHz, $CDCl_3$δ 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 3H), 6.46 (t, *J* = 4.1 Hz, 1H), 3.73 (t, *J* = 5.3 Hz, 2H), 2.68 (dd, *J* = 9.6, 5.1 Hz, 2H), 1.74 (d, *J* = 14.8 Hz, 2H), 1.46 (d, *J* = 13.7 Hz, 2H), 1.39 (d, *J* = 13.8 Hz, 1H), 1.21 (s, 6H), 1.15 (d, *J* = 13.9 Hz, 1H), 0.92 (s, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 210.44, 140.93, 137.00, 128.31, 127.93, 127.41, 91.61, 63.12, 51.71, 42.27, 36.44, 34.87, 31.44, 28.32.

The allyl ether **229** was also obtained (11 mg, 37% yield).

4.14.17.24 Synthesis of 11-(triisopropylsilyl)-3,7-dioxaspiro[5.6]dodec-10-en-12-one (306)

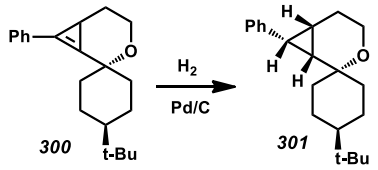


This compound was synthesized from **256** (50.7 mg, 0.1 mmol, 1 eq), $Rh_2(piv)_4$ (0.6 mg, 1 mol%) in 3 hours following the general procedure A. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (12.9 mg, 38% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.58 (t, *J* = 4.1 Hz, 1H), 3.85 – 3.67 (m, 6H), 2.67 (dd, *J* = 9.5, 5.3 Hz, 2H), 2.06 – 1.95 (m, 2H), 1.66 – 1.59 (m, 2H), 1.24 (dt, *J* = 14.7, 7.4 Hz, 3H), 1.04 (d, *J* = 7.3 Hz, 18H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 210.96, 149.65, 139.23, 85.34, 63.26, 62.87, 36.91, 33.00, 18.88, 11.32.

The allyl ether **230** was also obtained (13.4 mg, 42% yield).

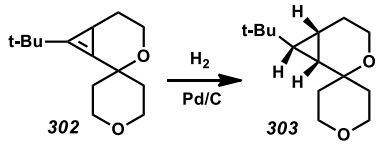
4.14.18 Cyclopropane formation via hydrogenation cyclopropenes

4.14.18.1 Synthesis of (1S,1'r,4'S,6S,7R)-4'-(tert-butyl)-7-phenyl-3-oxaspiro[bicyclo[4.1.0]heptane-2,1'-cyclohexane] (301)



To a flame-dried and septum-equipped vial was added cyclopropene **300** (30 mg) and palladium 10% on activated carbon (10.6 mg). MeOH (1 ml) was then added and the reaction was put under a hydrogen atmosphere using a balloon of hydrogen gas and stirred for 30 minutes. After the completion, the reaction was filtered through a celite pad and solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (18.1 mg, 61% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 2H), 7.29 – 7.22 (m, 2H), 7.18 – 7.11 (m, 1H), 3.75 – 3.65 (m, 1H), 3.61 – 3.53 (m, 1H), 2.40 (ddd, *J* = 12.3, 6.5, 3.3 Hz, 1H), 2.14 (t, *J* = 8.9 Hz, 1H), 1.95 – 1.88 (m, 1H), 1.86 – 1.70 (m, 2H), 1.69 – 1.59 (m, 2H), 1.59 – 1.55 (m, 1H), 1.40 – 1.27 (m, 2H), 1.28 – 1.13 (m, 3H), 1.11 – 0.99 (m, 1H), 0.85 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$δ 138.65, 131.06, 127.58, 125.16, 71.89, 57.42, 47.71, 37.32, 36.69, 32.39, 27.72, 26.36, 25.05, 23.62, 18.76, 17.09, 13.05.

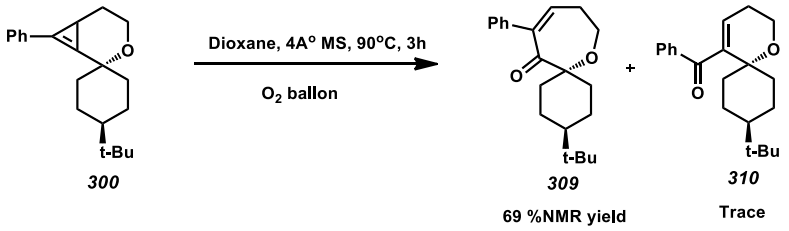
4.14.18.2 Synthesis of (1S,6S,7R)-7-(tert-butyl)tetrahydro-3-oxaspiro[bicyclo[4.1.0]heptane-2,4'-pyran] (303)



This compound was synthesized similarly to the compound **301**. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a light yellow oil (15.3 mg, 68% yield, from 23mg **302**). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.88 – 3.80 (m, 1H), 3.79 – 3.62 (m, 3H), 3.48 (dd, *J* = 10.0, 2.7 Hz, 2H), 2.15 – 2.02 (m, 2H), 1.95 (ddd, *J* = 13.8, 9.7, 4.1 Hz, 1H), 1.83 (tdd, *J* = 7.4, 6.2, 1.8 Hz, 1H), 1.69 (ddd, *J* = 13.7, 9.5, 4.0 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.27 – 1.15 (m, 1H), 1.13 (s, 9H), 0.64 – 0.55 (m, 2H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 68.25, 64.37, 63.63, 56.03, 39.57, 35.12, 32.69, 32.10, 31.24, 20.23, 17.20, 8.40.

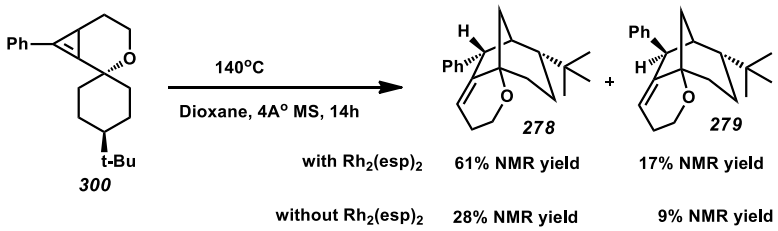
4.14.19 Mechanistic study reactions

4.14.19.1 Reactions under oxygen atmosphere: synthesis of (3r,6r)-3-(tert-butyl)-11-phenyl-7-oxaspiro[5.6]dodec-10-en-12-one (309) and ((6r,9r)-9-(tert-butyl)-1-oxaspiro[5.5]undec-4-en-5-yl)(phenyl)methanone (310)



A round-bottom flask containing 4Å molecule sieves (bead, 350 mg for 10 ml solvent) was flame-dried under high vacuum. The flask was back-filled with Argon 3 times and allowed to cool down to room temperature. Cyclopropene **300** (21.7 mg) and 1,4-dioxane (0.01M) were successively added and the reaction mixture was stirred for 14 hours at 90˚. When the reaction was completed, the reaction mixture was allowed to cool to room temperature and filtered through a celite pad using ethyl acetate to rinse the reaction residue. The solvent was removed under reduced pressure. The crude NMR of the reaction mixture showed a 69% yield of cycloheptenone **309** and trace amount of **310** (see below for synthesis of **310** using another method). Spectra for **309**, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 6.34 (t, *J* = 4.0 Hz, 1H), 3.84 (t, *J* = 5.4 Hz, 2H), 2.65 (dt, *J* = 9.6, 4.8 Hz, 2H), 2.31 (dd, *J* = 12.3, 1.3 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.47 (td, *J* = 13.5, 4.0 Hz, 2H), 1.34 – 1.23 (m, 2H), 1.03 (tt, *J* = 12.1, 3.2 Hz, 1H), 0.82 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 209.05, 141.03, 139.97, 134.70, 128.48, 127.53, 127.43, 87.55, 62.86, 47.39, 34.64, 34.45, 32.43, 27.73, 24.23.

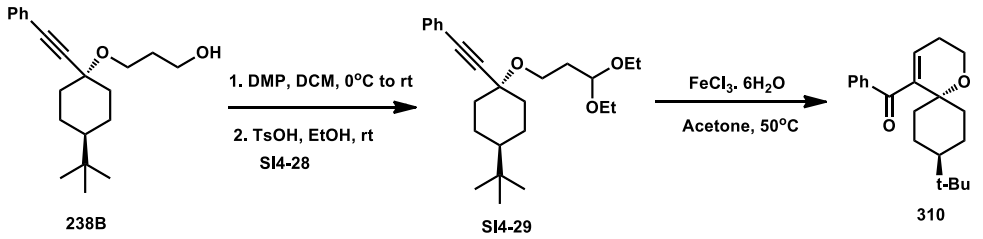
4.14.19.2 Reactions using cyclopropenes



A vial containing 4Å molecule sieves (bead, 350 mg for 10 ml solvent) was flame-dried under high vacuum. The vial was back-filled with Argon 3 times and allowed to cool down to room temperature. Cyclopropene **300** (1 eq), $Rh_2(esp)_2$ (0.05 eq) and 1,4-dioxane (0.01M) were successively added. The vial was then sealed and the reaction mixture was stirred at 140 °C for 14 hours. When the reaction was completed, the reaction mixture was allowed to cool to room temperature and filtered through a celite pad using ethyl acetate to rinse the reaction residue. The solvent was removed under reduced pressure. Crude NMR of the reaction mixture showed 61% yield of **278** and 17% yield of **279** (ratio 3.6:1).

A similar reaction was conducted without rhodium catalyst showed 28% yield of **278** and 9% yield of **279** (ratio 3:1)

4.14.20 Synthesis of ((6r,9r)-9-(tert-butyl)-1-oxaspiro[5.5]undec-4-en-5-yl)(phenyl)methanone (310)



(((1r,4r)-4-(Tert-butyl)-1-(3,3-diethoxypropoxy)cyclohexyl)ethynyl)benzene (SI4-29)

To a solution of the primary alcohol **238B** (0.63 g, 1.0 eq) and DCM (4 ml, 0.5M) in a flame-dried flask, DMP (1.02 g, 1.2 eq) was added in five small equal portions at 0 °C. The reaction mixture was allowed to warm to room temperature within 1 hour and stirred for additional 2 hours. After the disappearance of alcohol was confirmed by TLC, $NaHCO_3$ (1.2 eq) was added and the reaction was filtered through a celite pad, the solid residue was washed 3 times with DCM. The DCM was quickly removed under reduced pressure to give a crude product, which was then transferred to a small vial. EtOH (7 ml, 0.3M) and TsOH (19 mg, 0.05 eq) were successively added to the vial and the reaction mixture was stirred at room temperature for 30 minutes. The solvent was then removed under reduced pressure to yield a crude mixture. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (0.62 g, 80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.33 – 7.27 (m, 3H), 4.69 (t, *J* = 5.8 Hz, 1H), 3.75 (t, *J* = 6.3 Hz, 2H), 3.66 (dq, *J* = 9.4, 7.2 Hz, 2H), 3.52 (dq, *J* = 9.4, 7.2 Hz, 2H), 2.19 (dd, *J* = 6.7, 2.2 Hz, 2H), 1.91 (q, *J* = 6.2 Hz, 2H), 1.77 (s, br, 2H), 1.48 – 1.37 (m, 4H),

1.18 (t, *J* = 7.1 Hz, 6H), 1.08 – 0.98 (m, 1H), 0.88 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 131.68, 128.33, 128.14, 123.26, 100.90, 90.26, 87.11, 75.10, 61.58, 59.60, 47.49, 37.96, 34.84, 32.41, 27.73, 24.65, 15.50.

((6r,9r)-9-(tert-butyl)-1-oxaspiro[5.5]undec-4-en-5-yl)(phenyl)methanone (310) To a flame-dried and septum-equipped vial was added **SI4-29** (0.23 g, 0.6 mmol, 1 eq). Acetone (6 ml) and $FeCl_3.6H_2O$ was then successively added and the reaction was stirred at 50 ˚C for 1 hour. After completion, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel using a 2-5% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (18.7 mg, 10% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.9, 1.0 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.42 (dd, *J* = 10.6, 4.8 Hz, 2H), 6.17 (t, *J* = 4.0 Hz, 1H), 3.87 (t, *J* = 5.7 Hz, 2H), 2.33 – 2.20 (m, 4H), 1.68 – 1.55 (m, 4H), 1.41 – 1.27 (m, 3H), 0.82 (s, 9H). **^{13}C NMR** (125.76 MHz, $CDCl_3$) δ 198.08, 145.65, 138.72, 134.66, 132.48, 129.82, 128.32, 75.11, 57.34, 42.72, 33.41, 33.11, 27.71, 25.32, 21.23

4.15 References and notes

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APPENDIX THREE

Spectra relevant to Chapter 4:

RHODIUM – CATALYZED NON – CARBONYL – STABILIZED CARBENE ALKYNE CASCADE REACTIONS TO FORM BRIDGED POLYCYCLIC COMPOUNDS

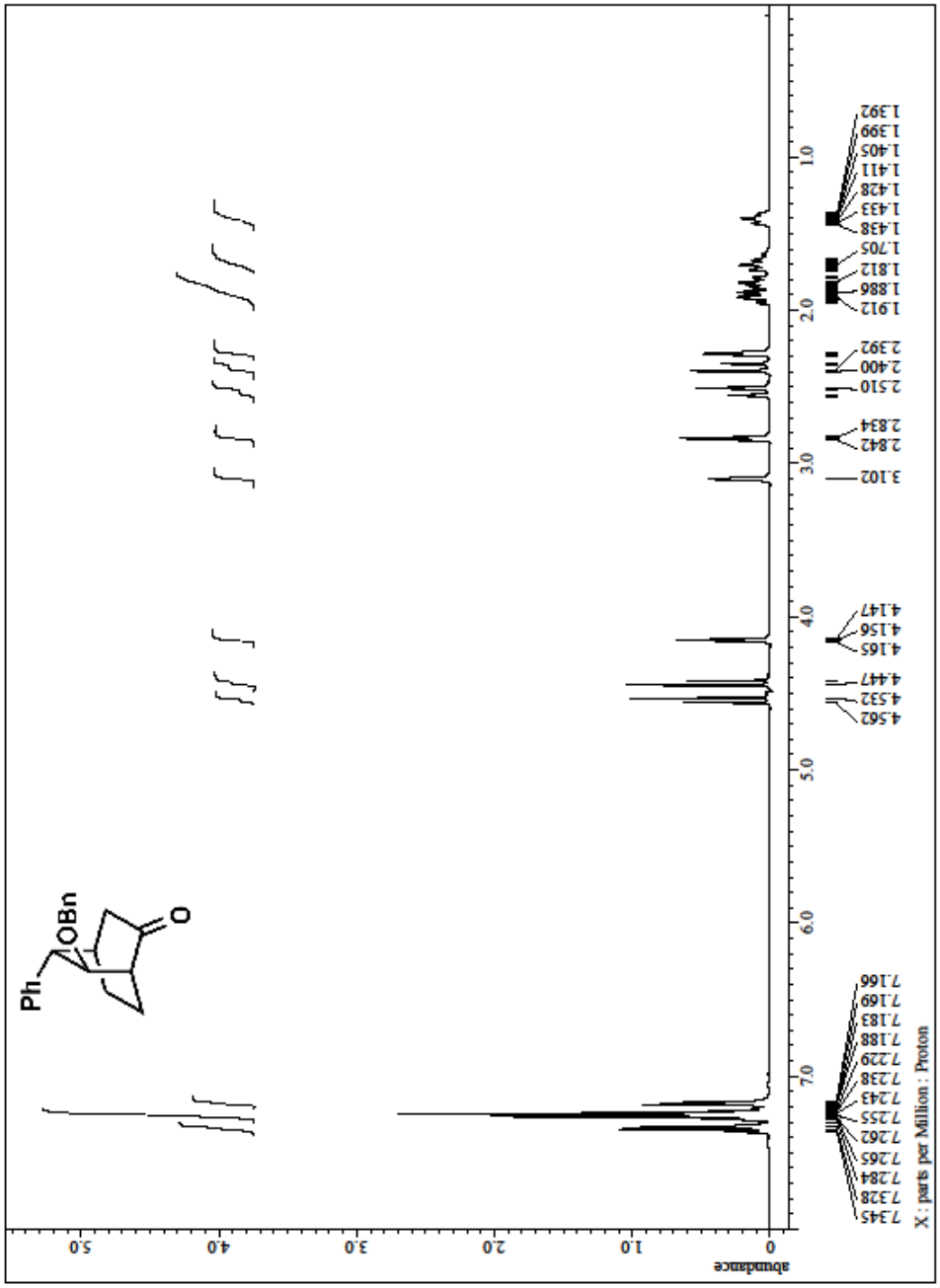

Figure A.3.1. ^{1}H NMR for compound **SI4-6**

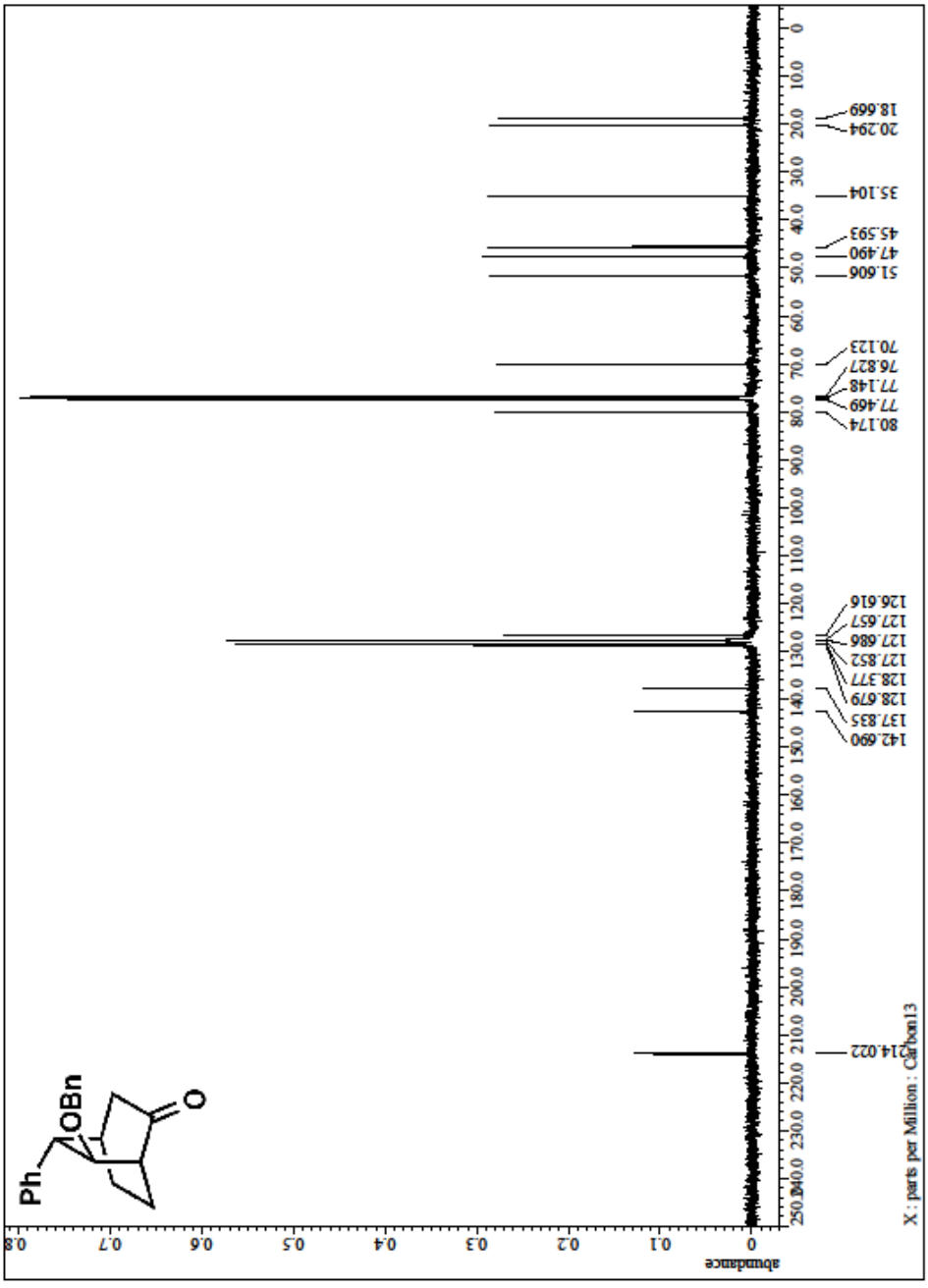

Figure A.3.2. ^{13}C NMR for compound **SI4-6**

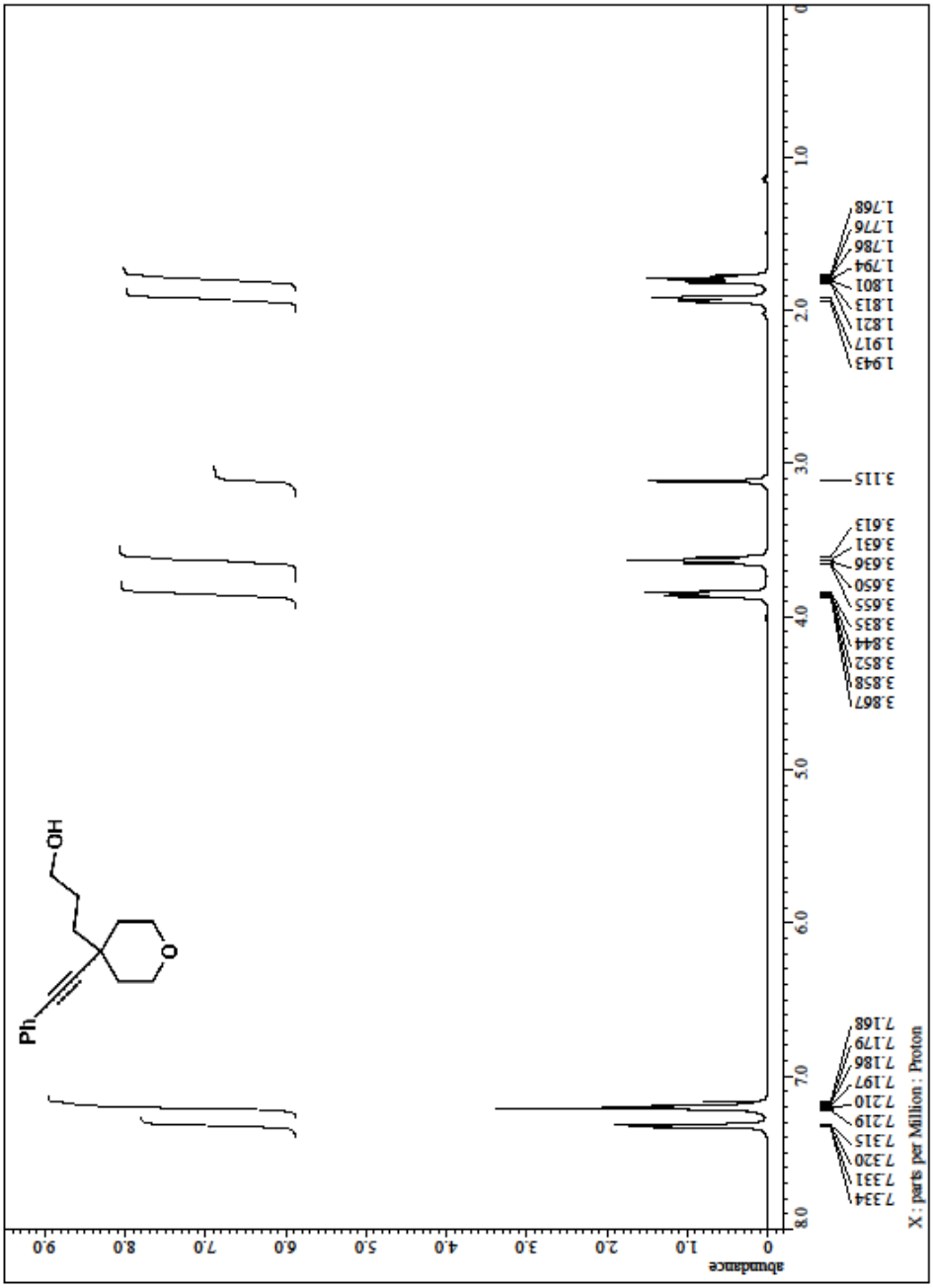

Figure A.3.3. ^{1}H NMR for compound **SI4-7**

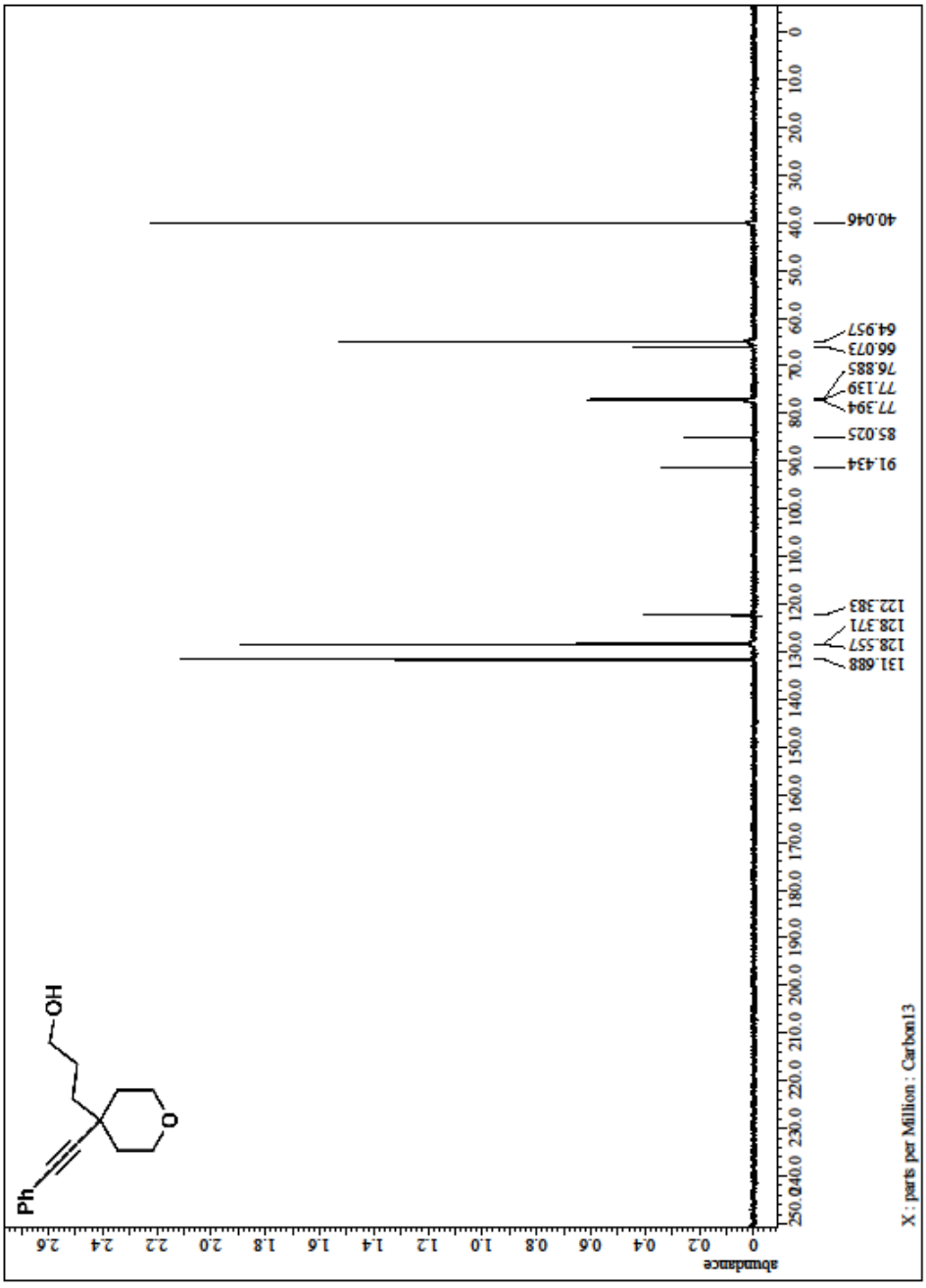

Figure A.3.4. ^{13}C NMR for compound **SI4-7**

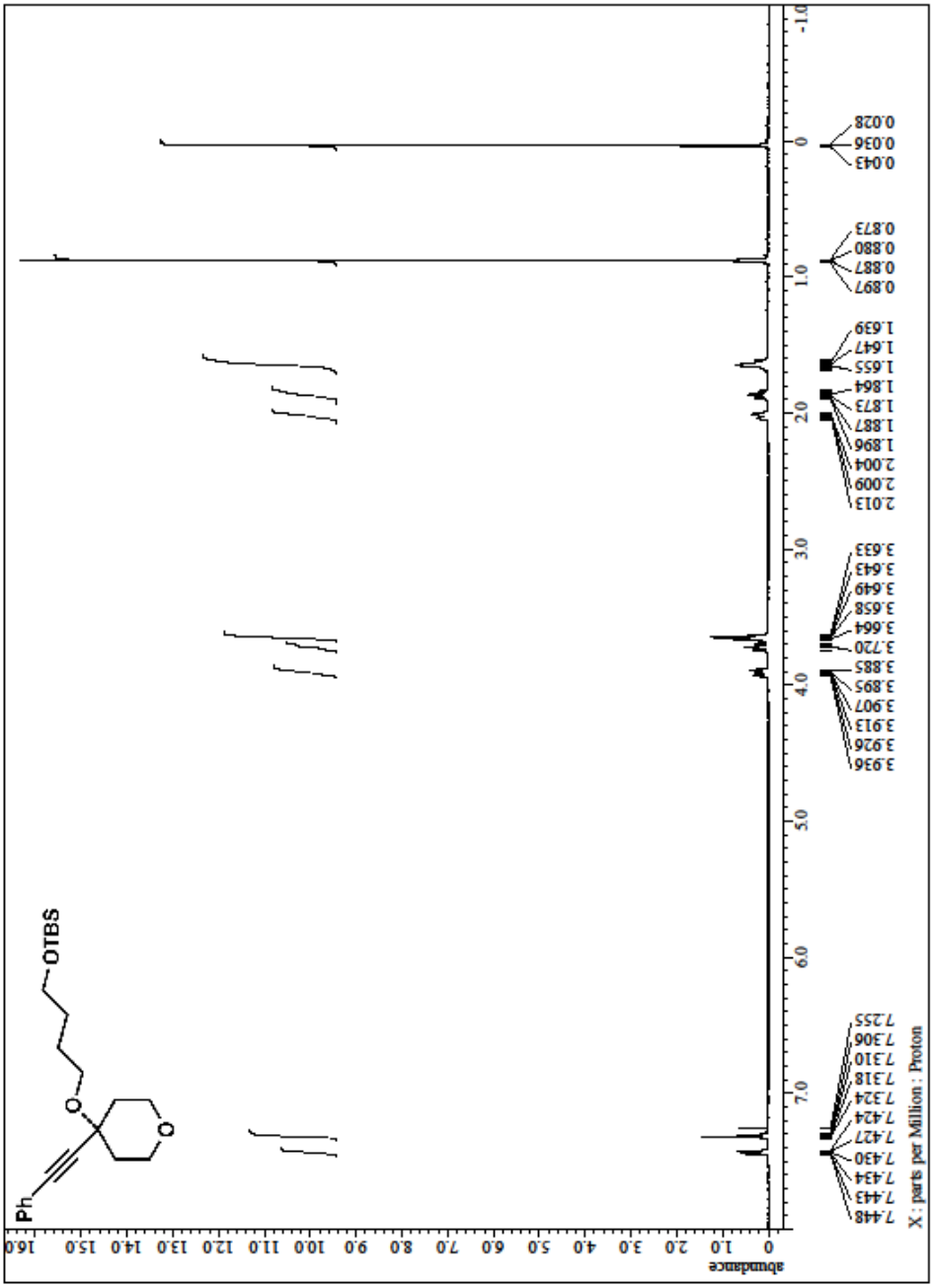

Figure A.3.5. ^{1}H NMR for compound **SI4-9**

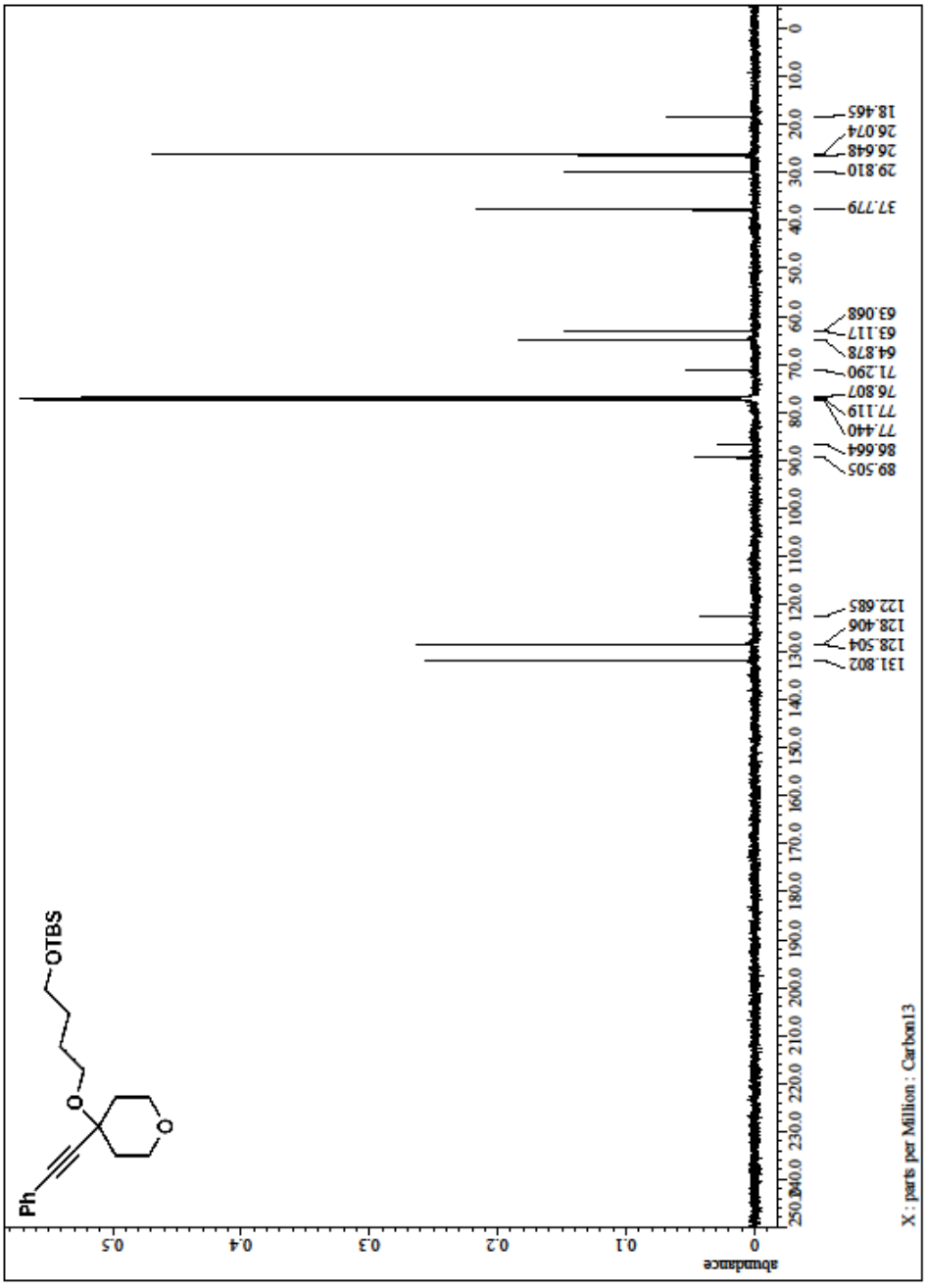

Figure A.3.6. ^{13}C NMR for compound **SI4-9**

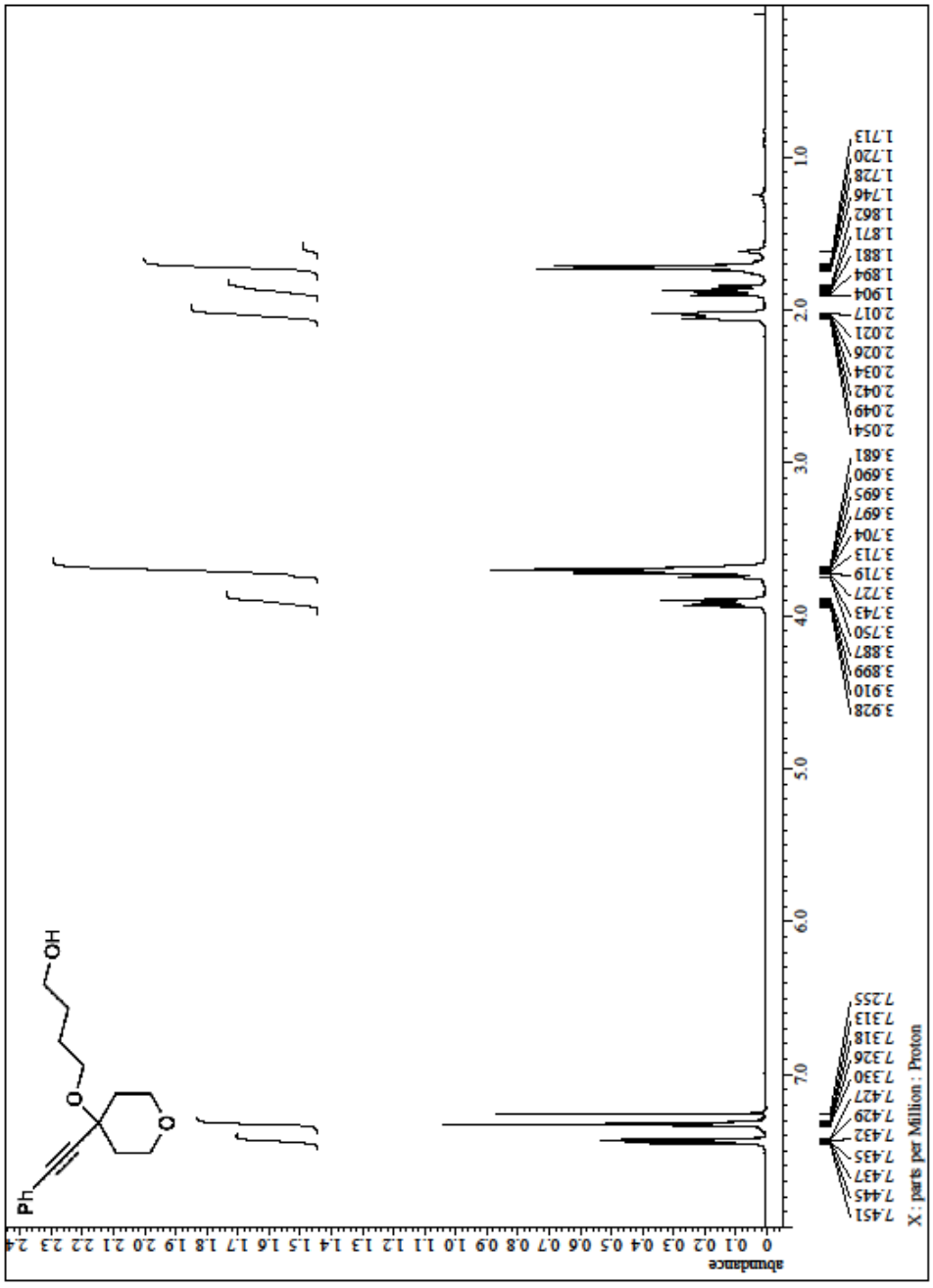

Figure A.3.7. ^{1}H NMR for compound **SI4-10**

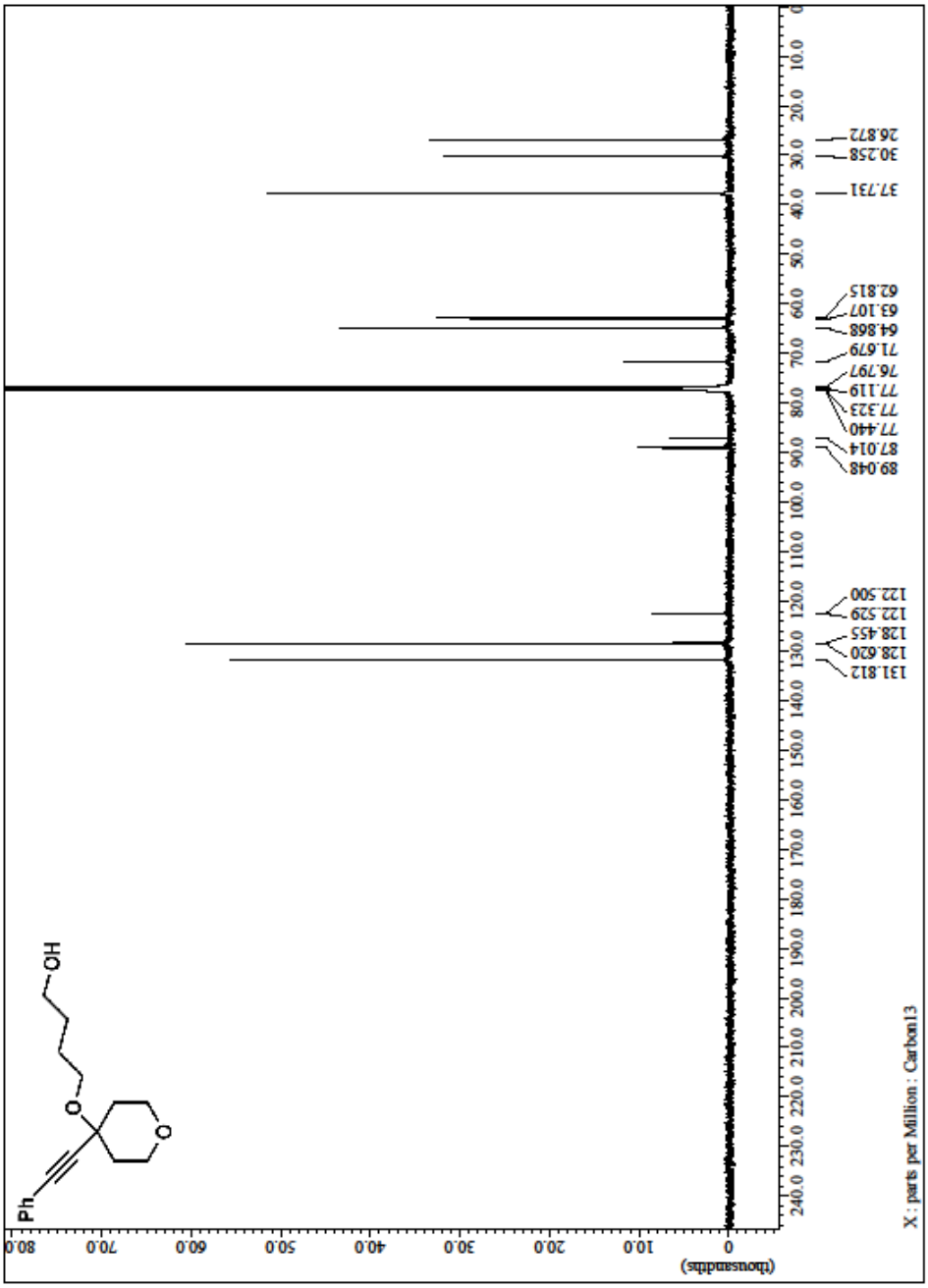

Figure A.3.8. ^{13}C NMR for compound **SI4-10**

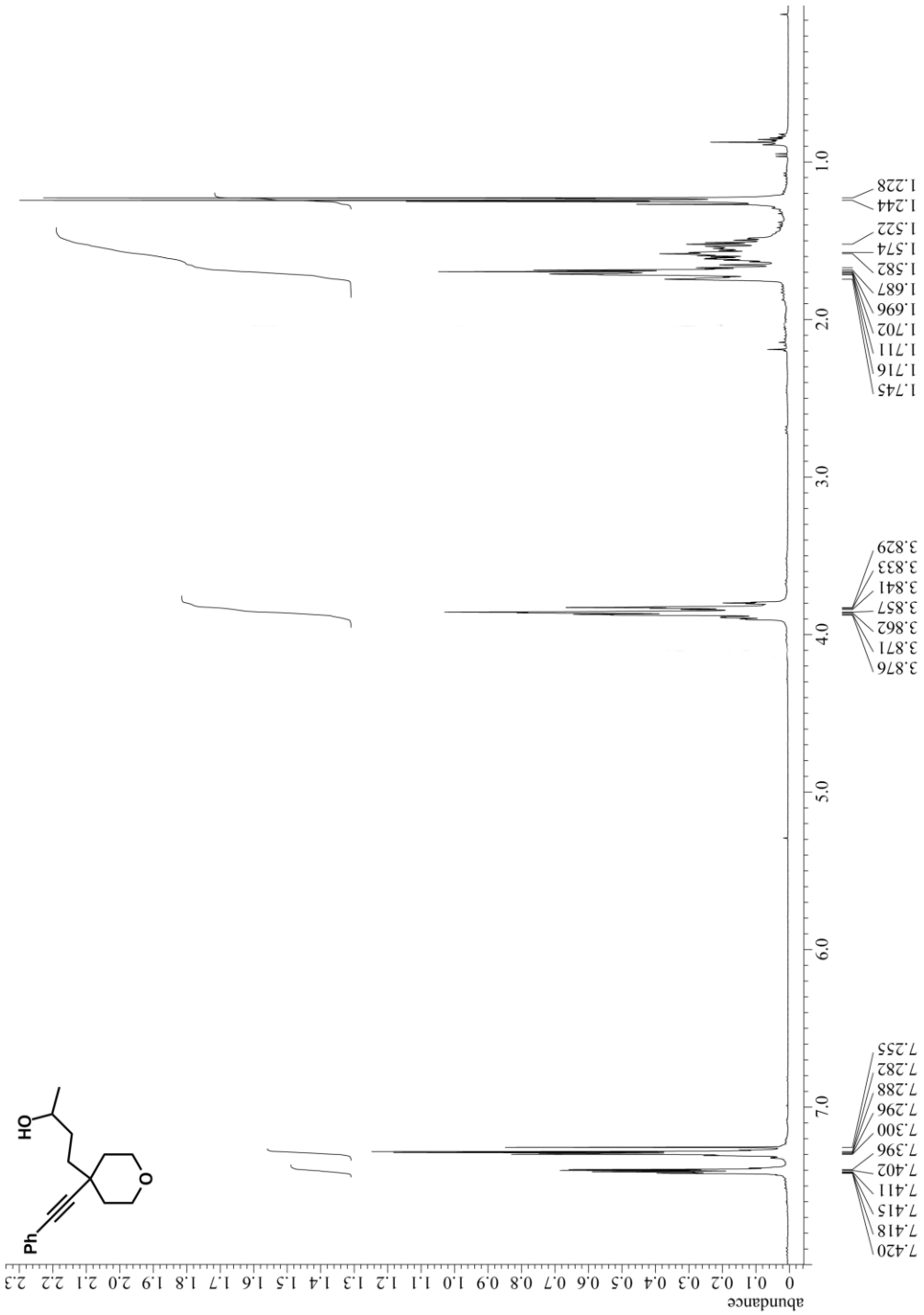

Figure A.3.9. ^{1}H NMR for compound **SI4-12**

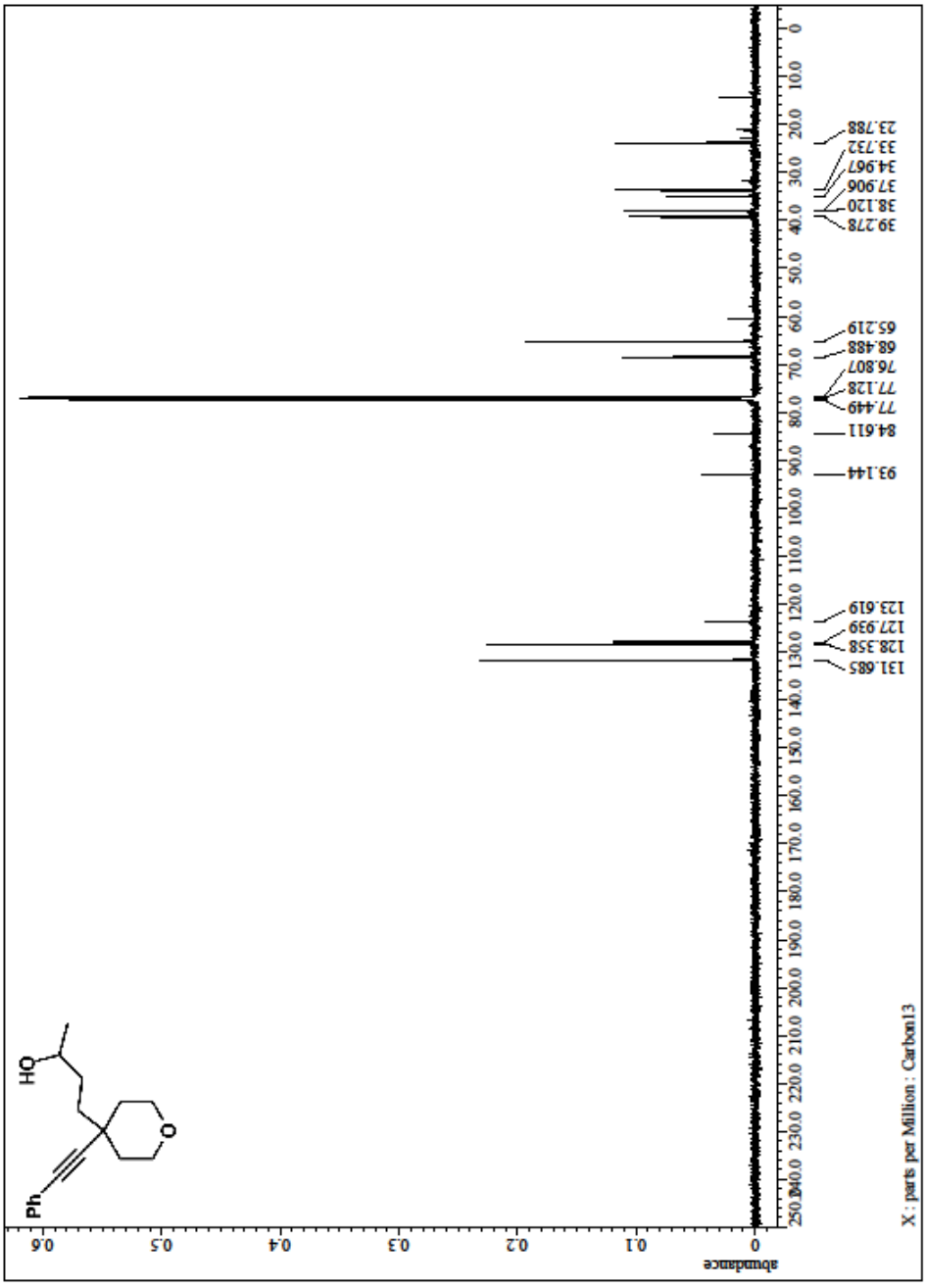

Figure A.3.10. ^{13}C NMR for compound **SI4-12**

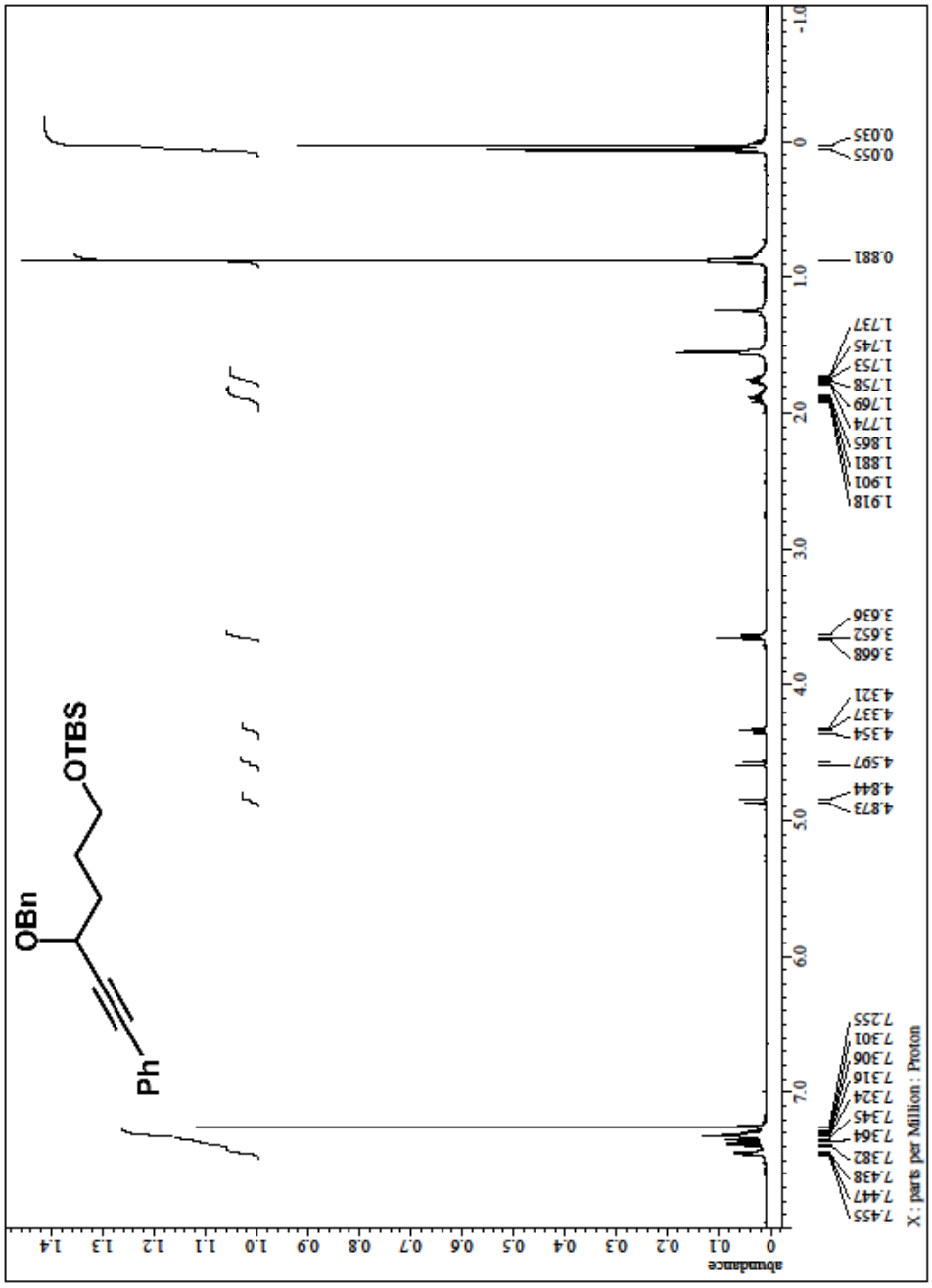

Figure A.3.11. ^{1}H NMR for compound **SI4-14**

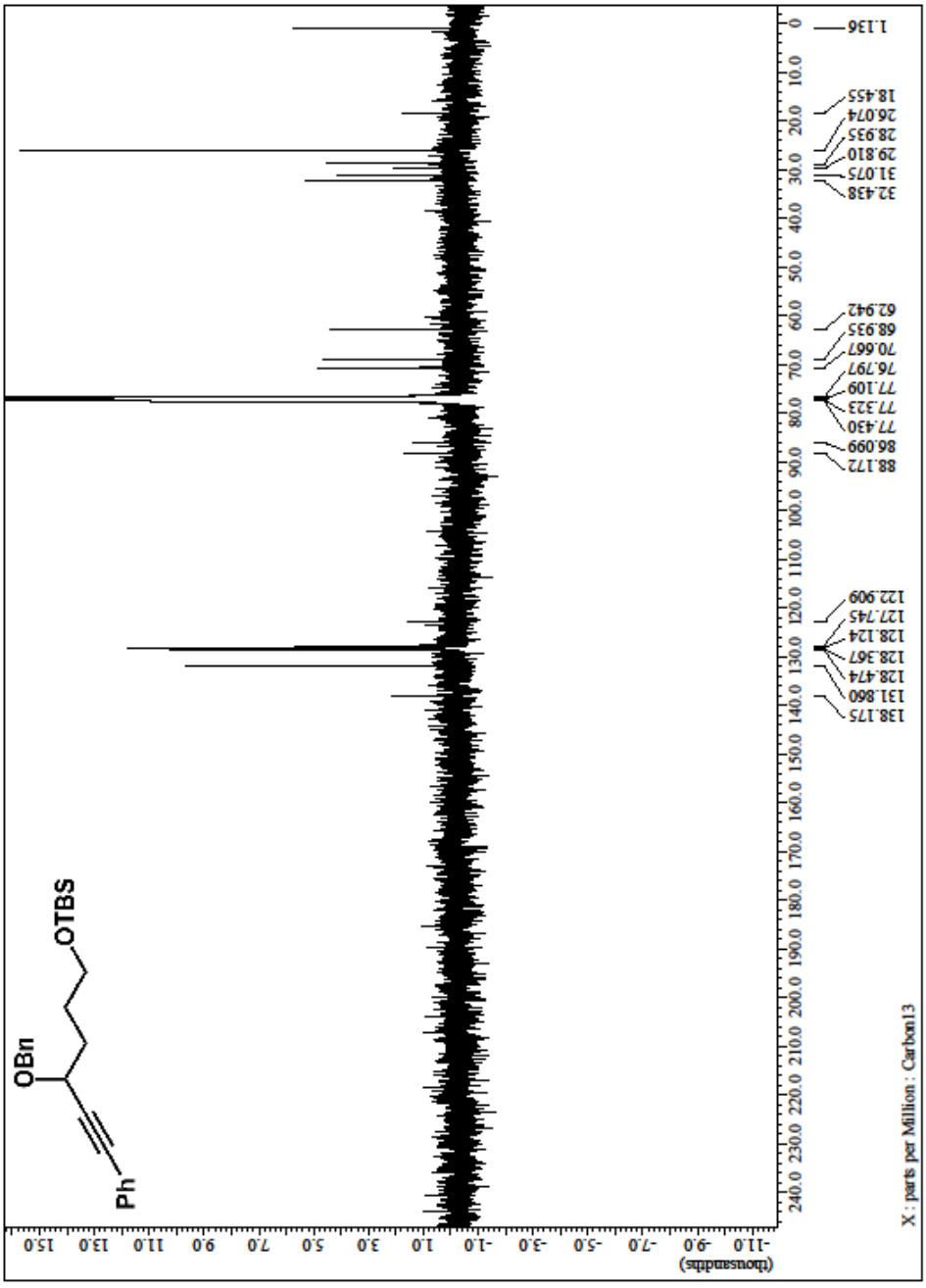

Figure A.3.12. ^{13}C NMR for compound **SI4-14**

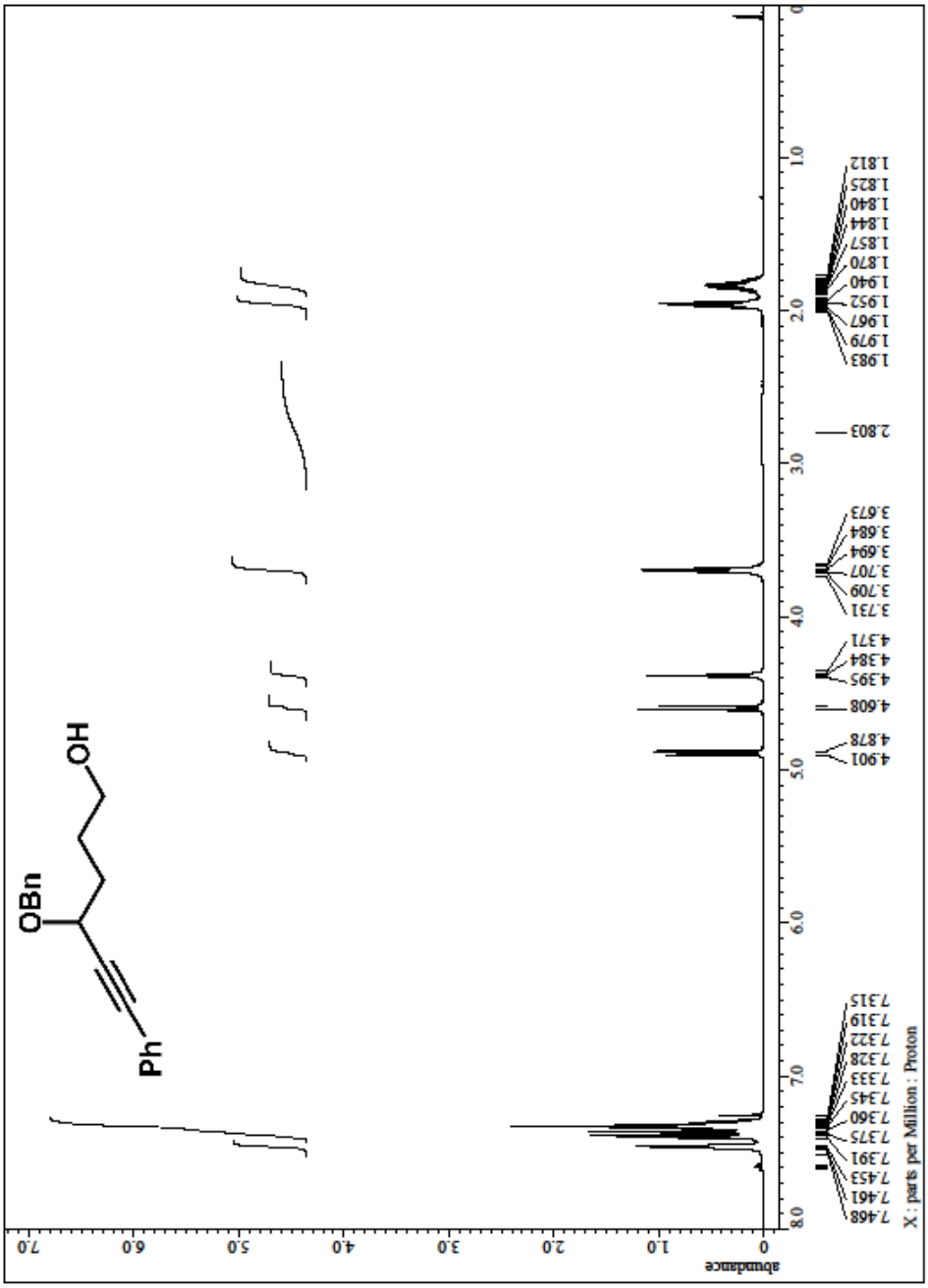

Figure A.3.13. ^{1}H NMR for compound **SI4-15**

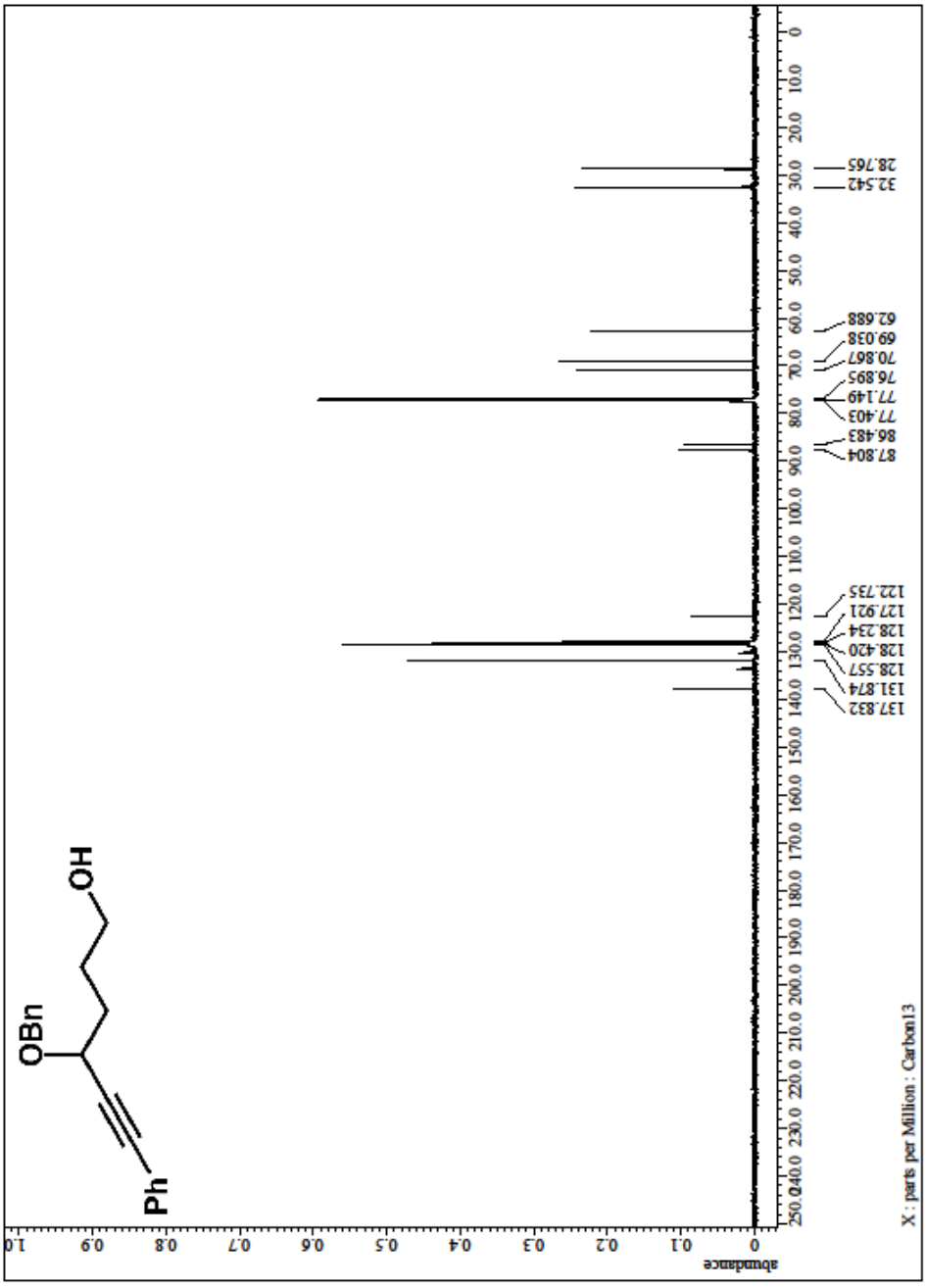

Figure A.3.14. ^{13}C NMR for compound **SI4-15**

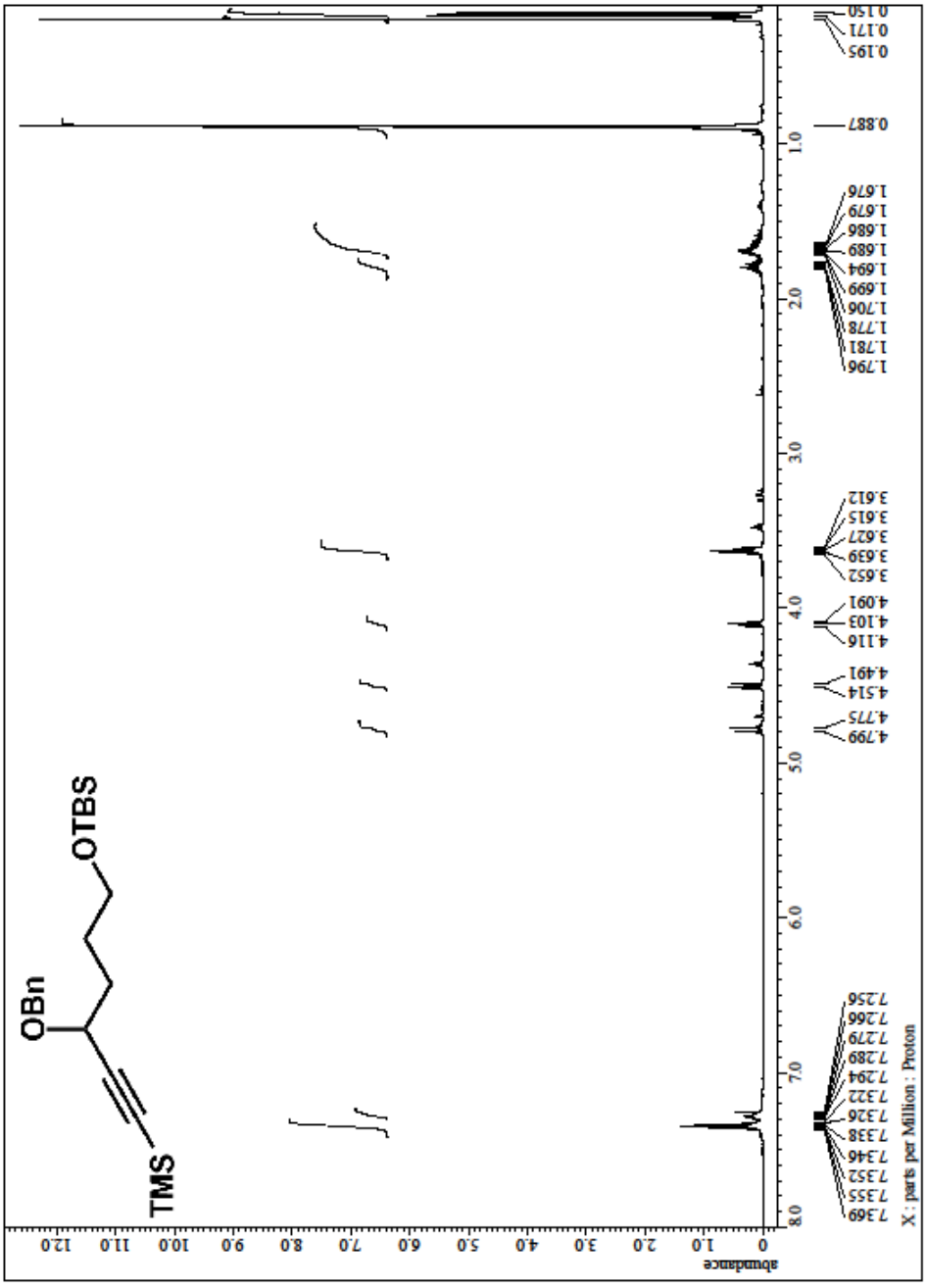

Figure A.3.15. ^{1}H NMR for compound **SI4-16**

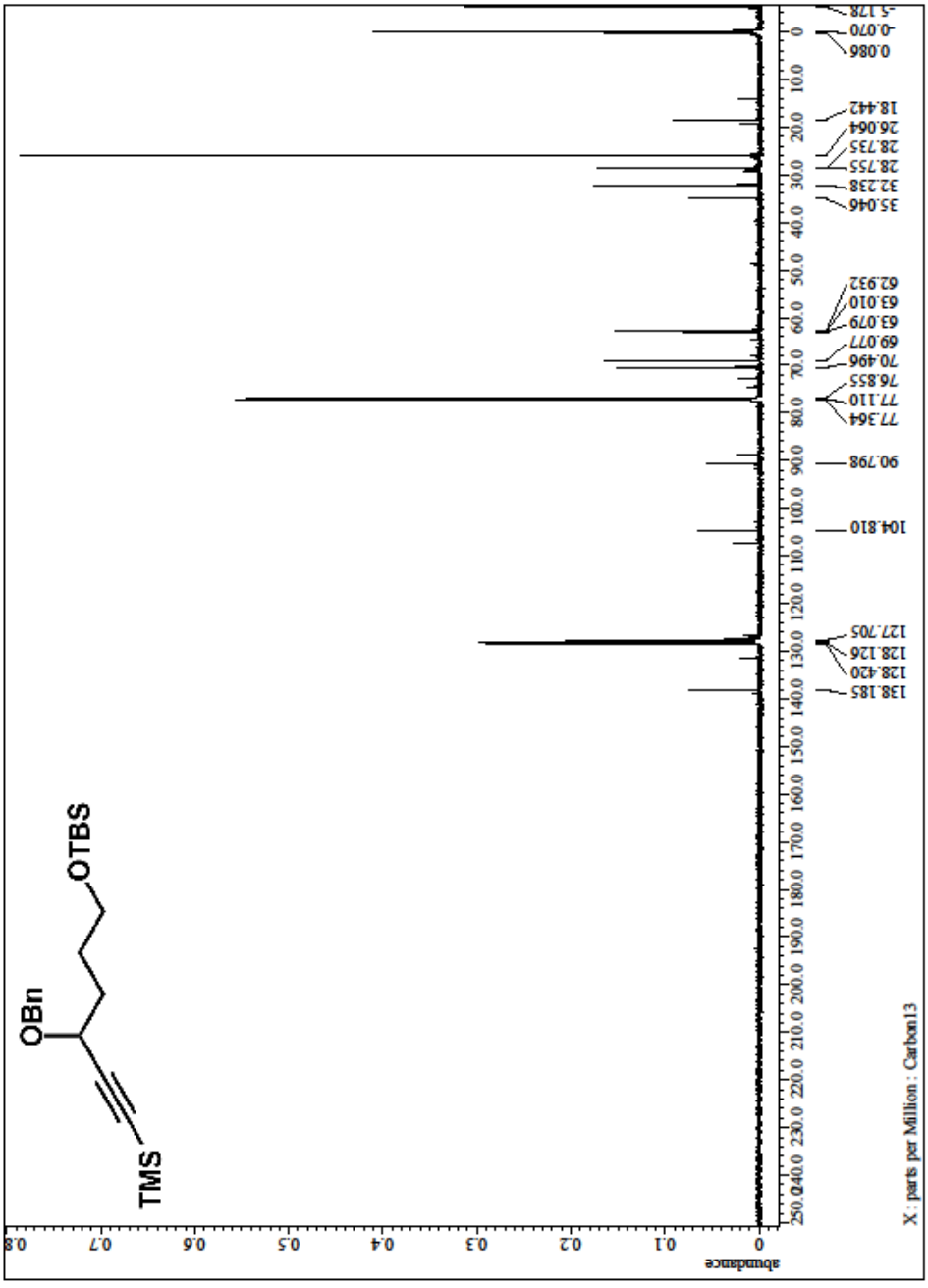

Figure A.3.16. ^{13}C NMR for compound **SI4-16**

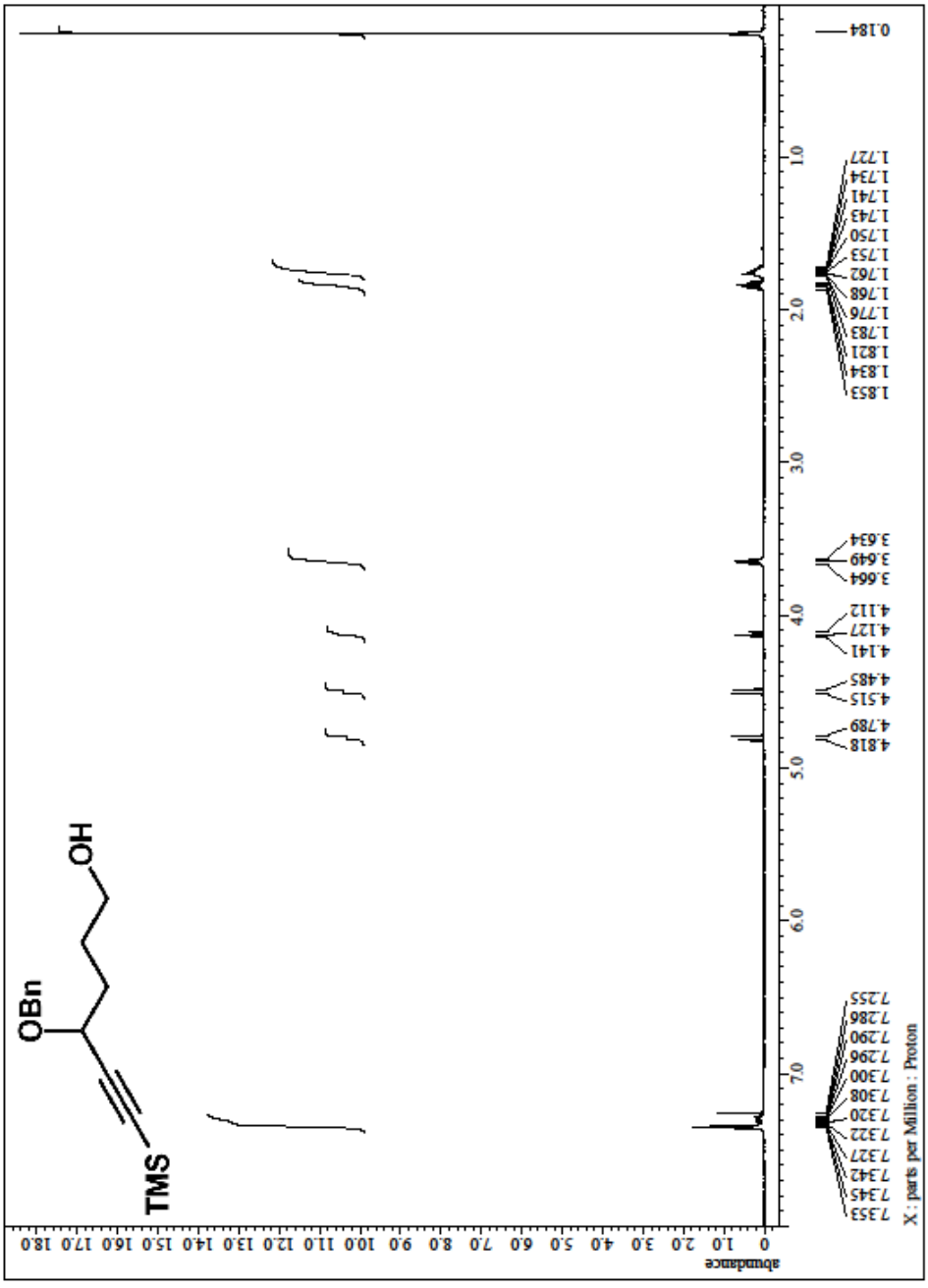

Figure A.3.17. ^{1}H NMR for compound **SI4-17**

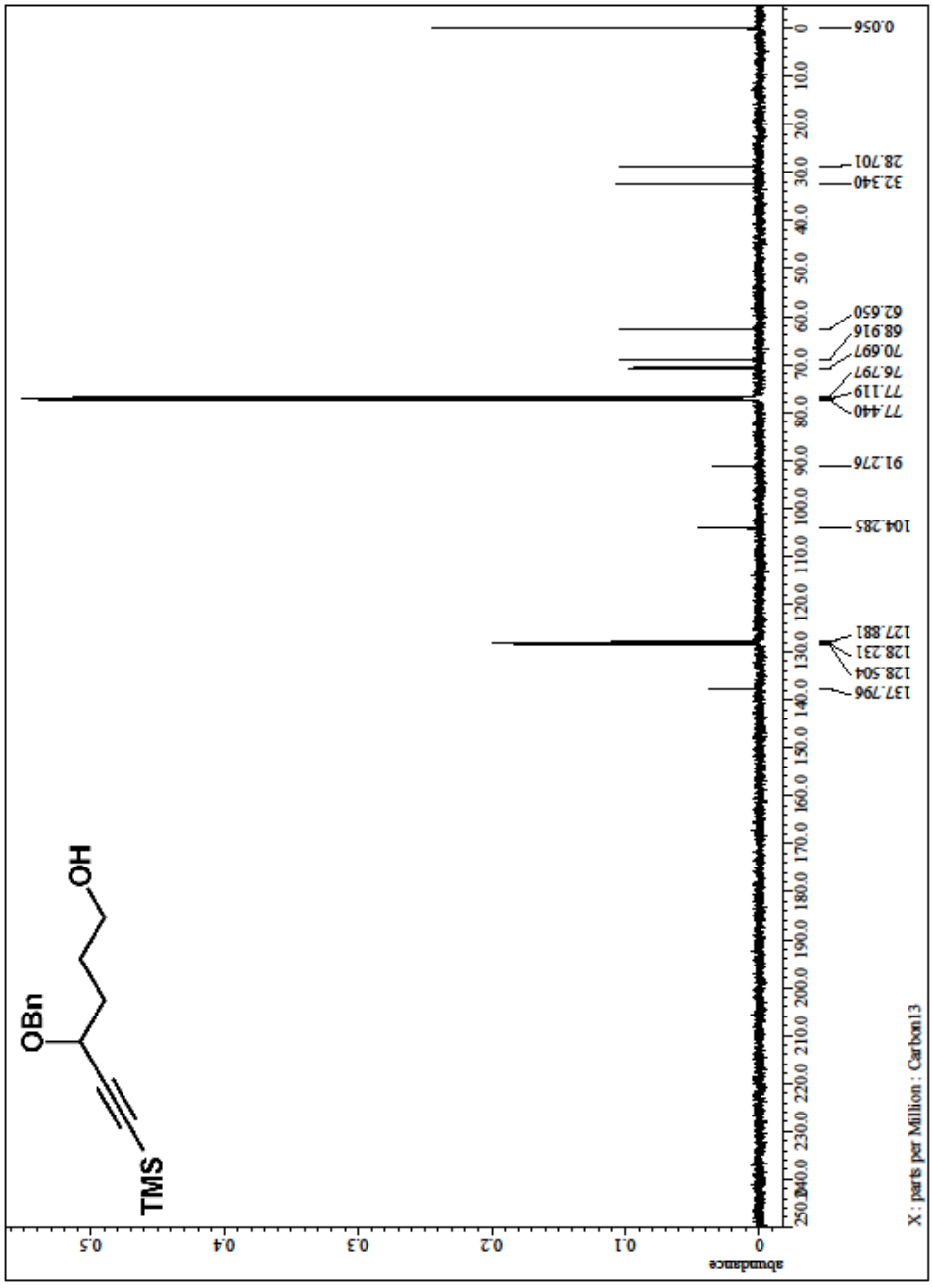

Figure A.3.18. ^{13}C NMR for compound **SI4-17**

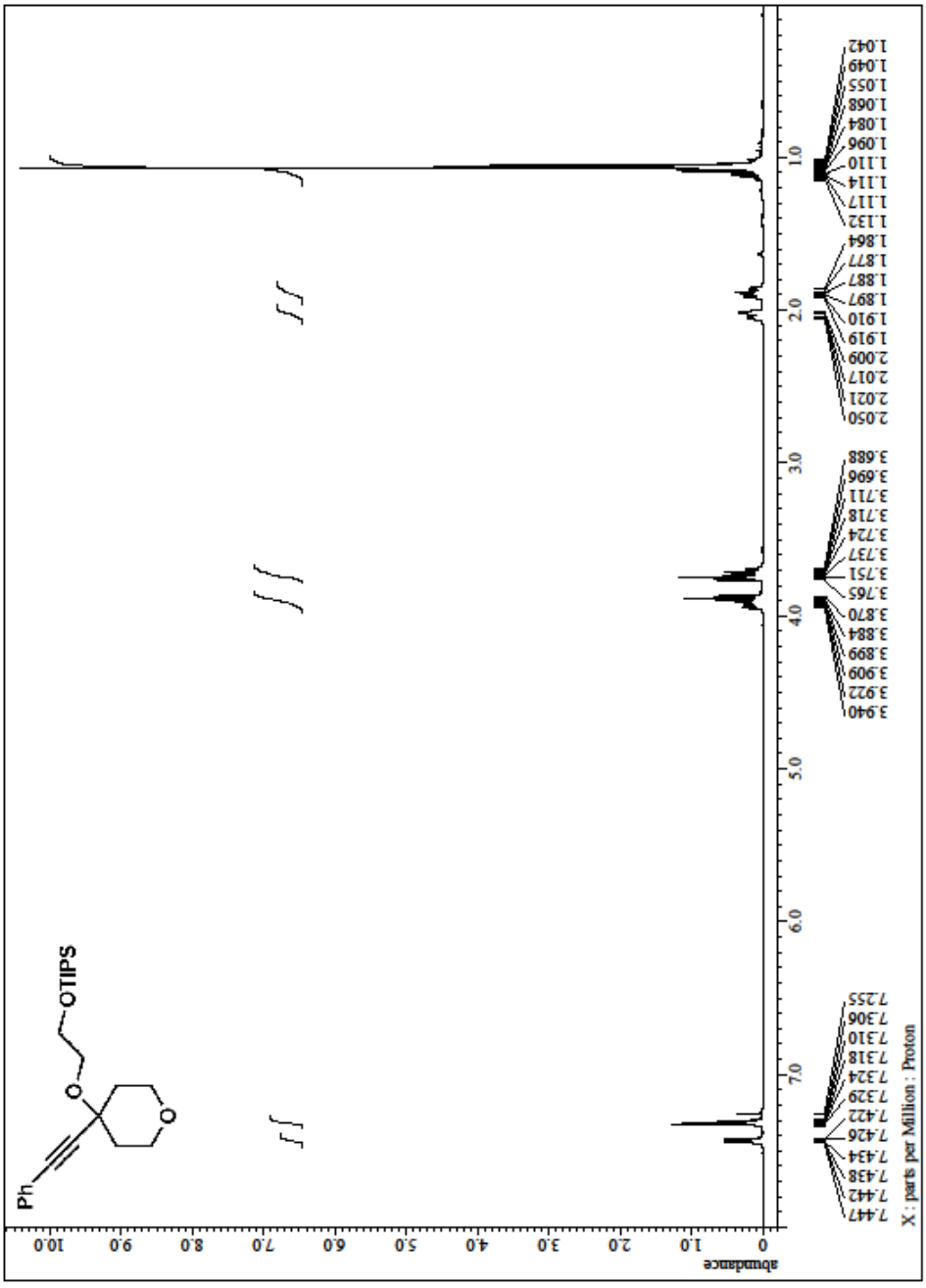

Figure A.3.19. ^{1}H NMR for compound **SI4-19**

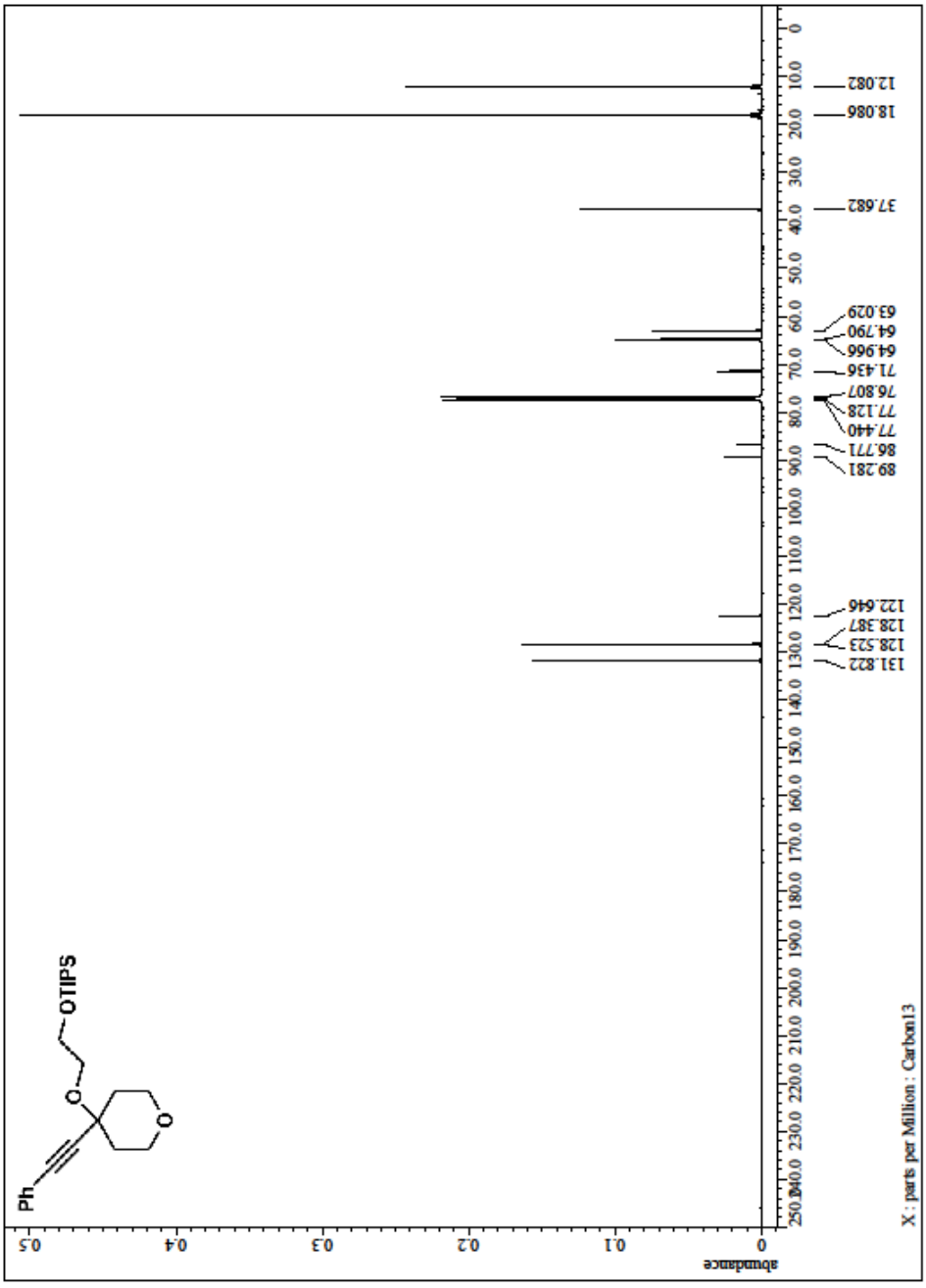

Figure A.3.20. ^{13}C NMR for compound **SI4-19**

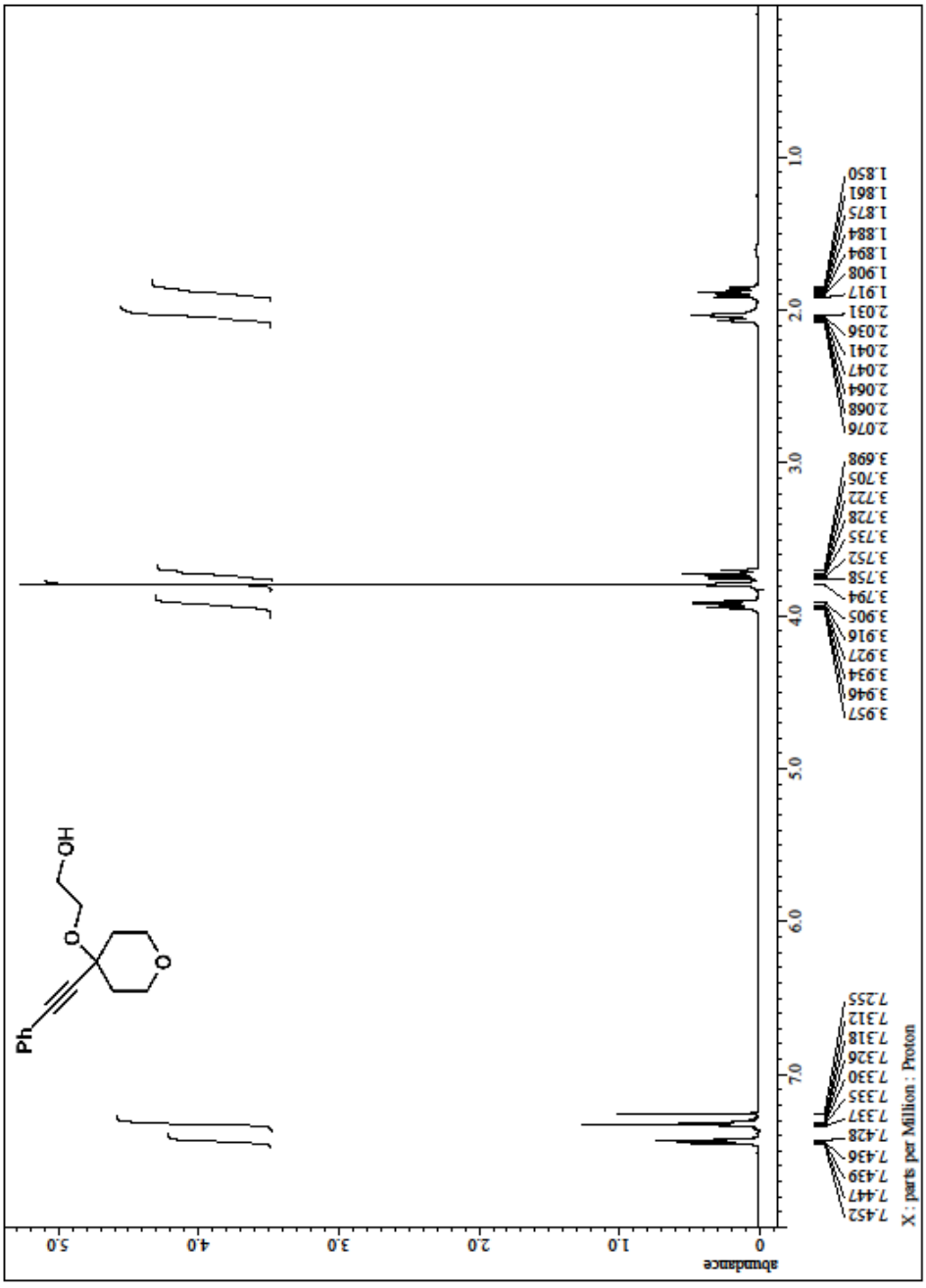

Figure A.3.21. ^{1}H NMR for compound **SI4-20**

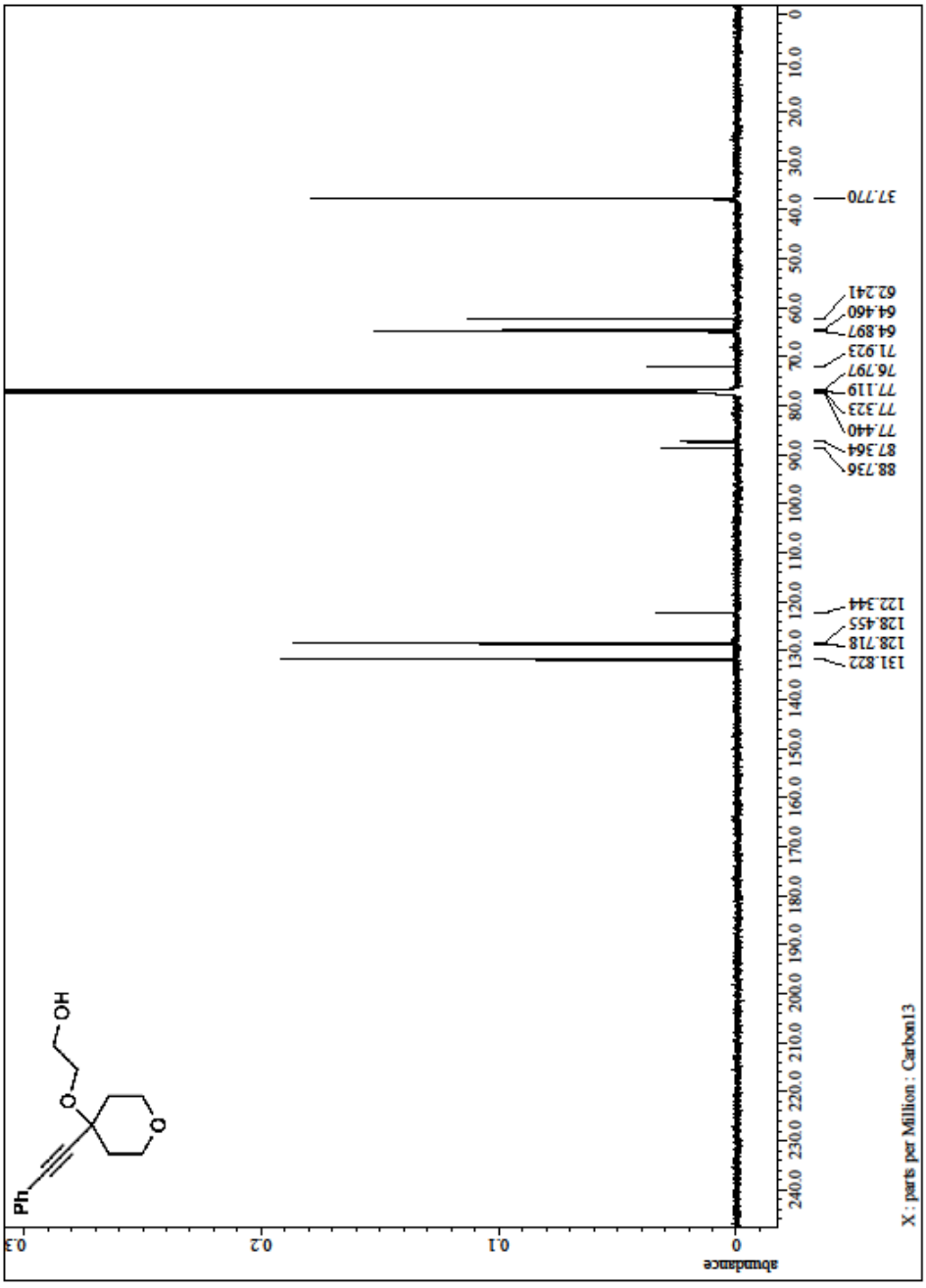

Figure A.3.22. ^{13}C NMR for compound **SI4-20**

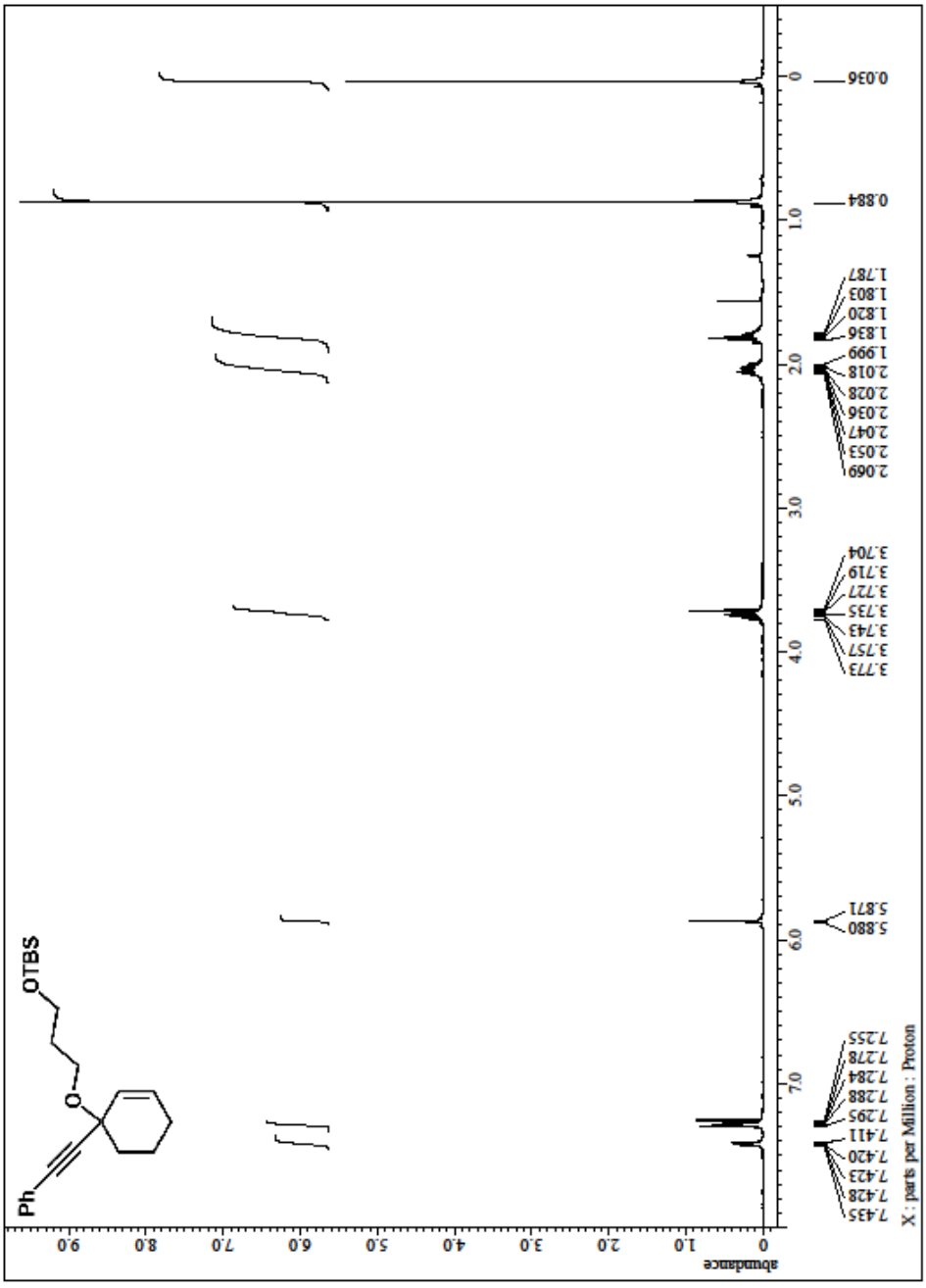

Figure A.3.23. ^{1}H NMR for compound **SI4-23**

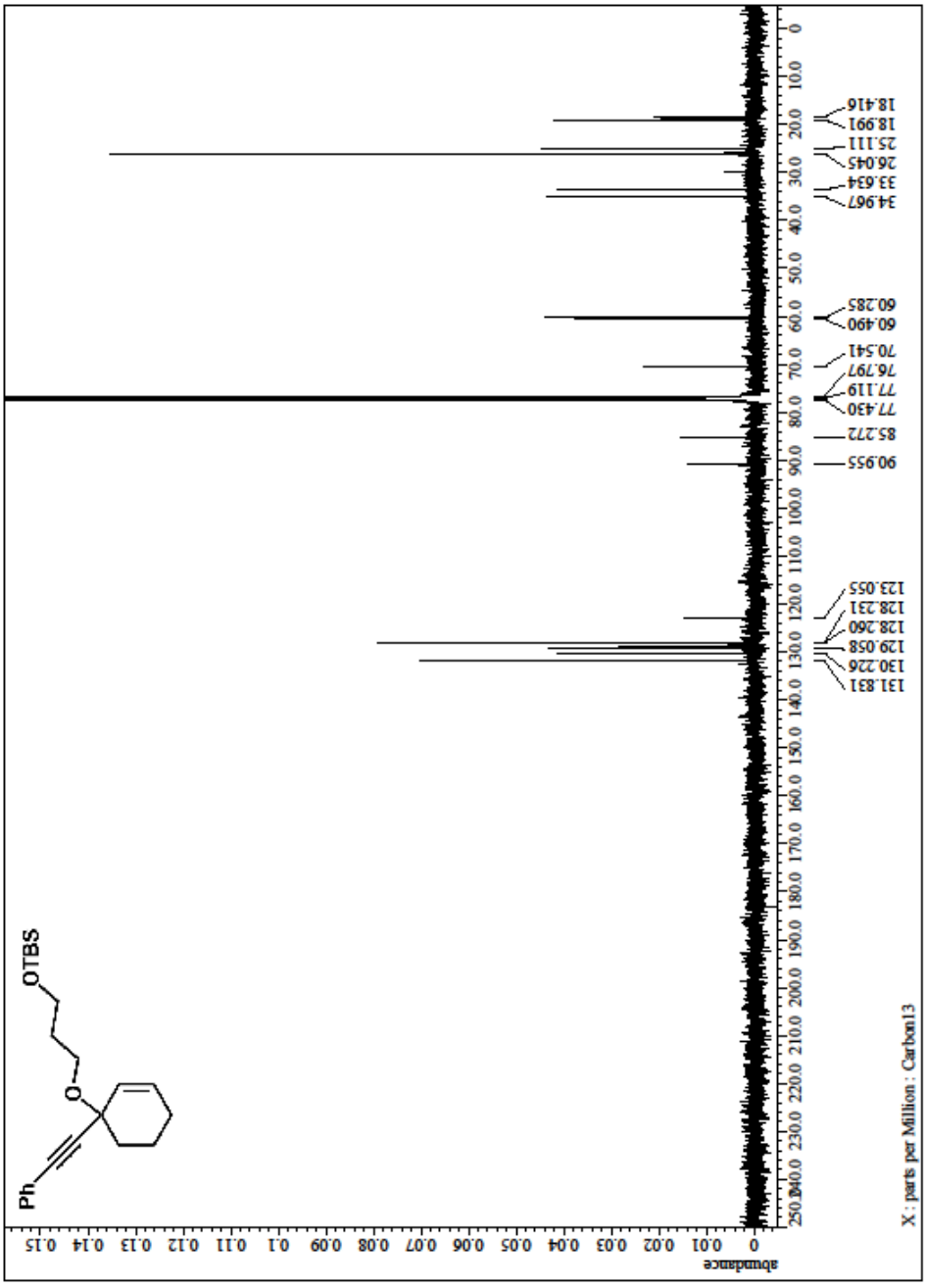

Figure A.3.24. ^{13}C NMR for compound **SI4-23**

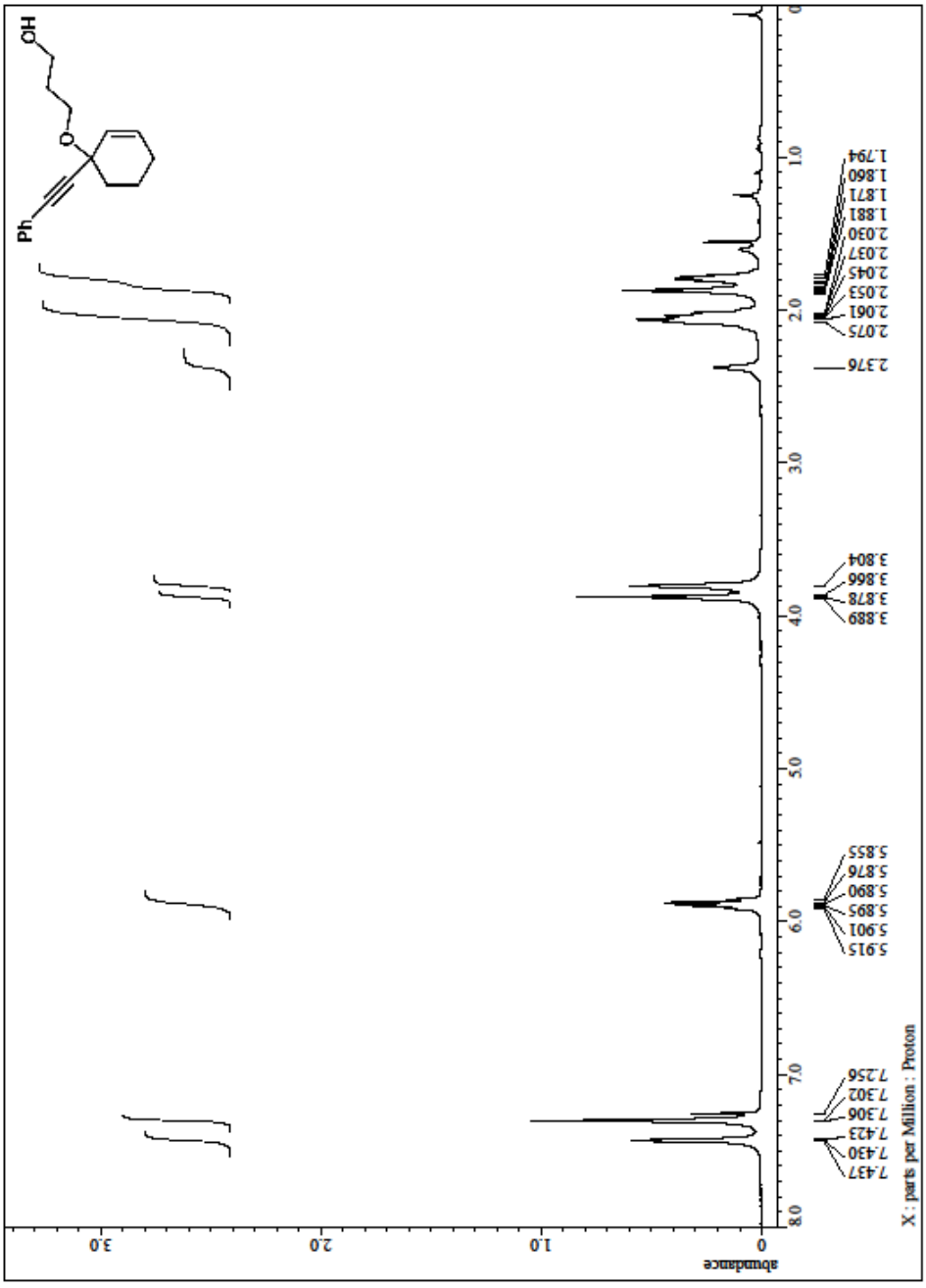

Figure A.3.25. ^{1}H NMR for compound **SI4-24**

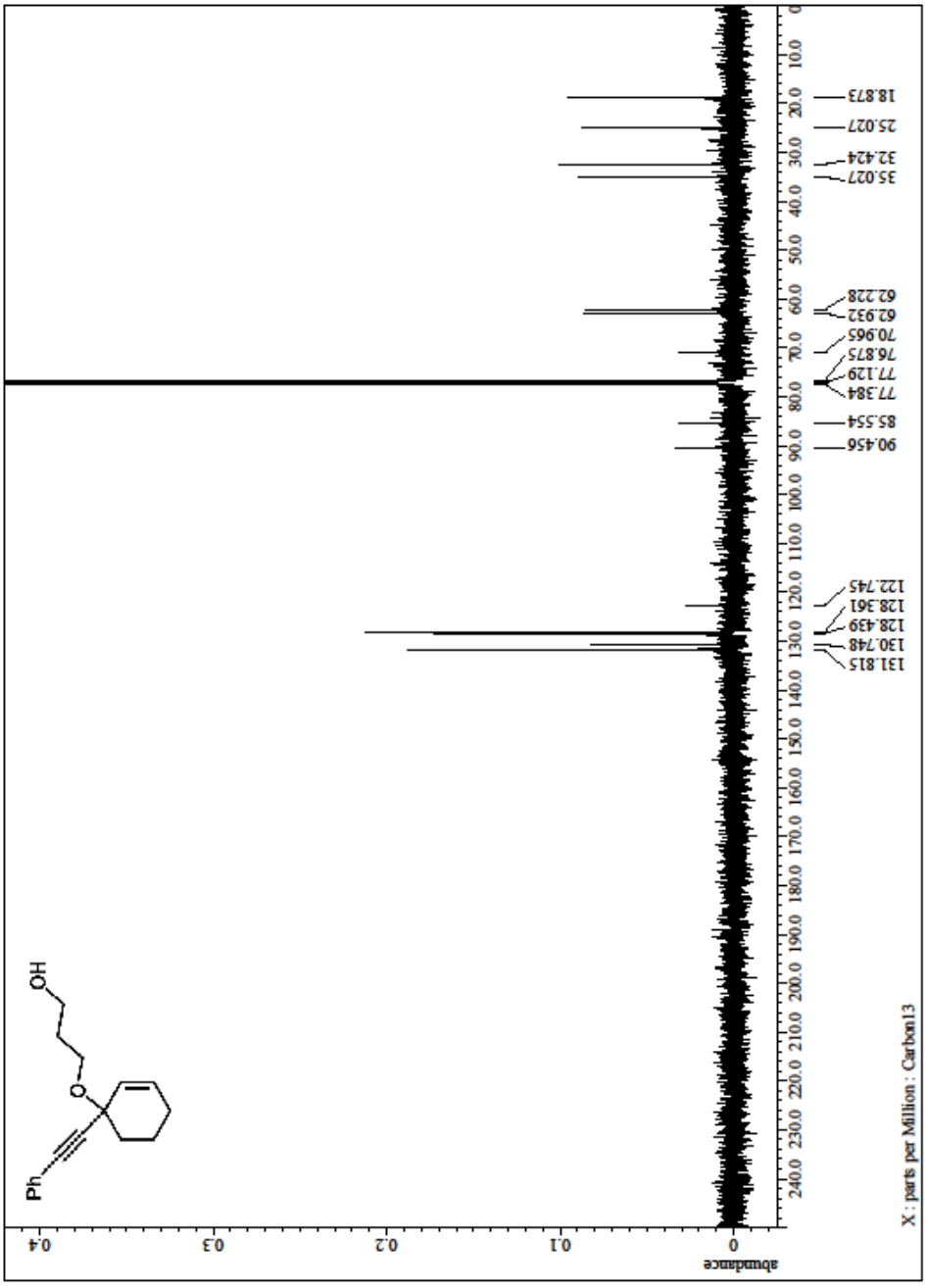

Figure A.3.26. ^{13}C NMR for compound **SI4-24**

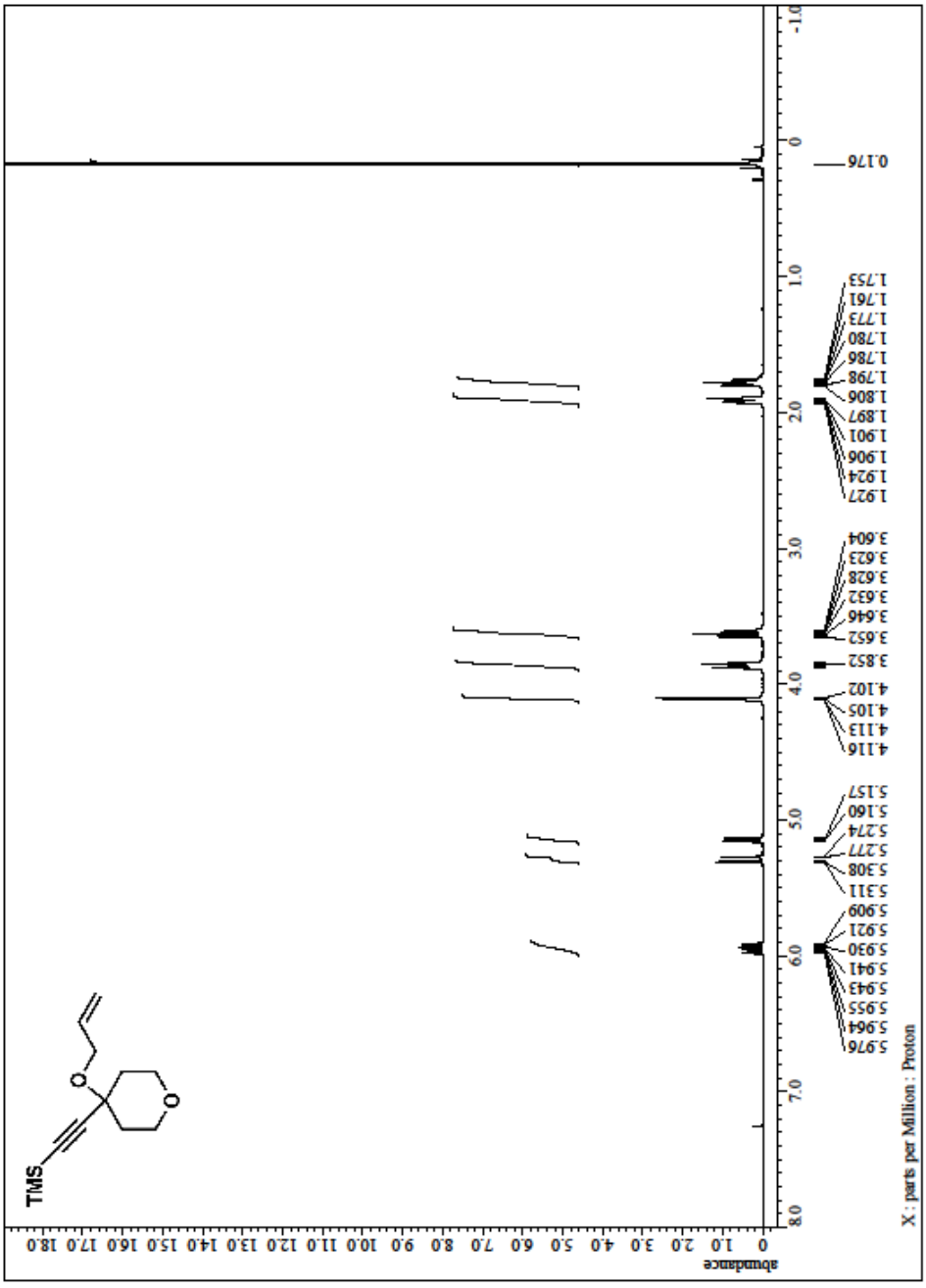

Figure A.3.27. ^{1}H NMR for compound **SI4-25**

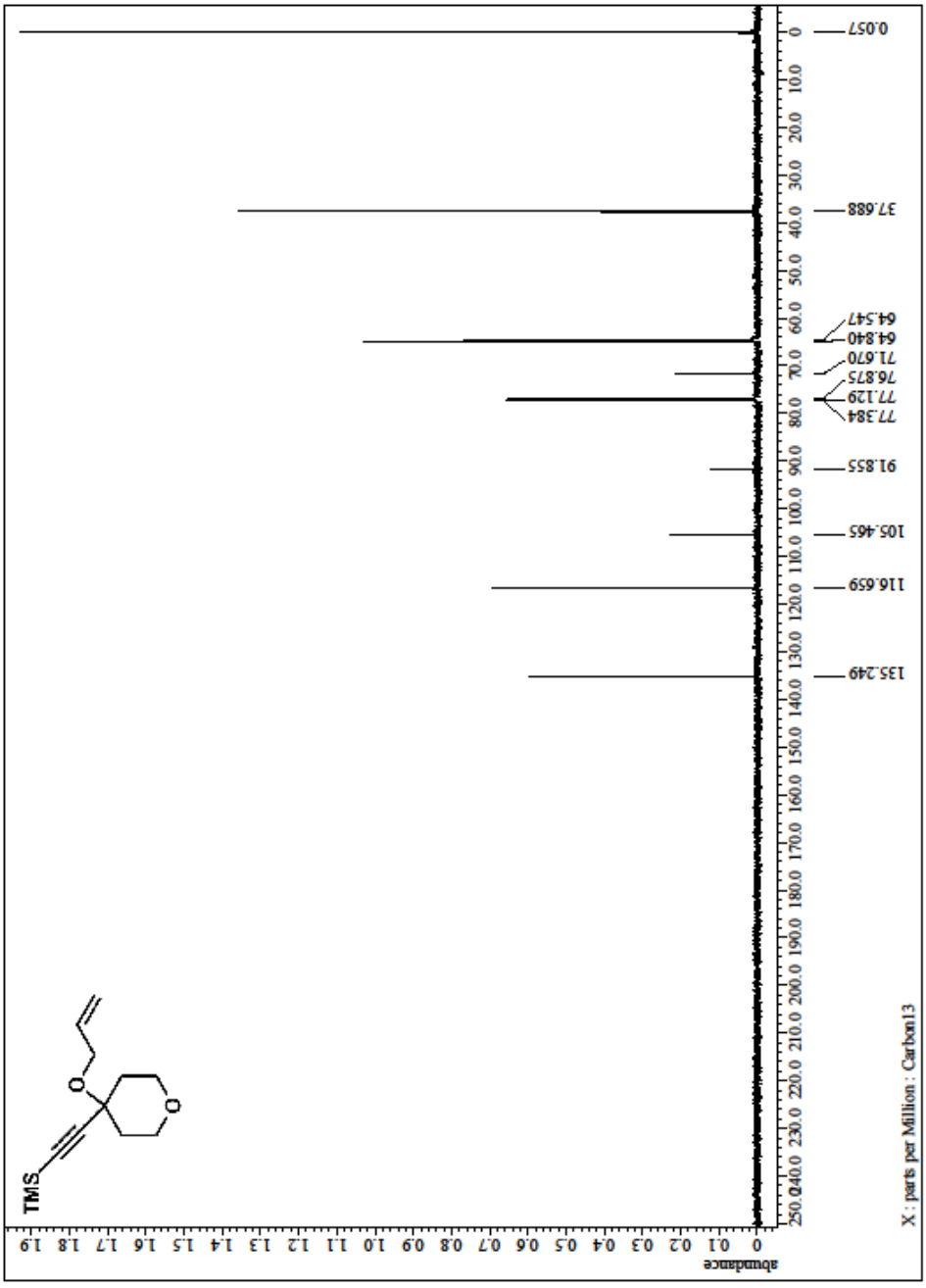

Figure A.3.28. ^{13}C NMR for compound **SI4-25**

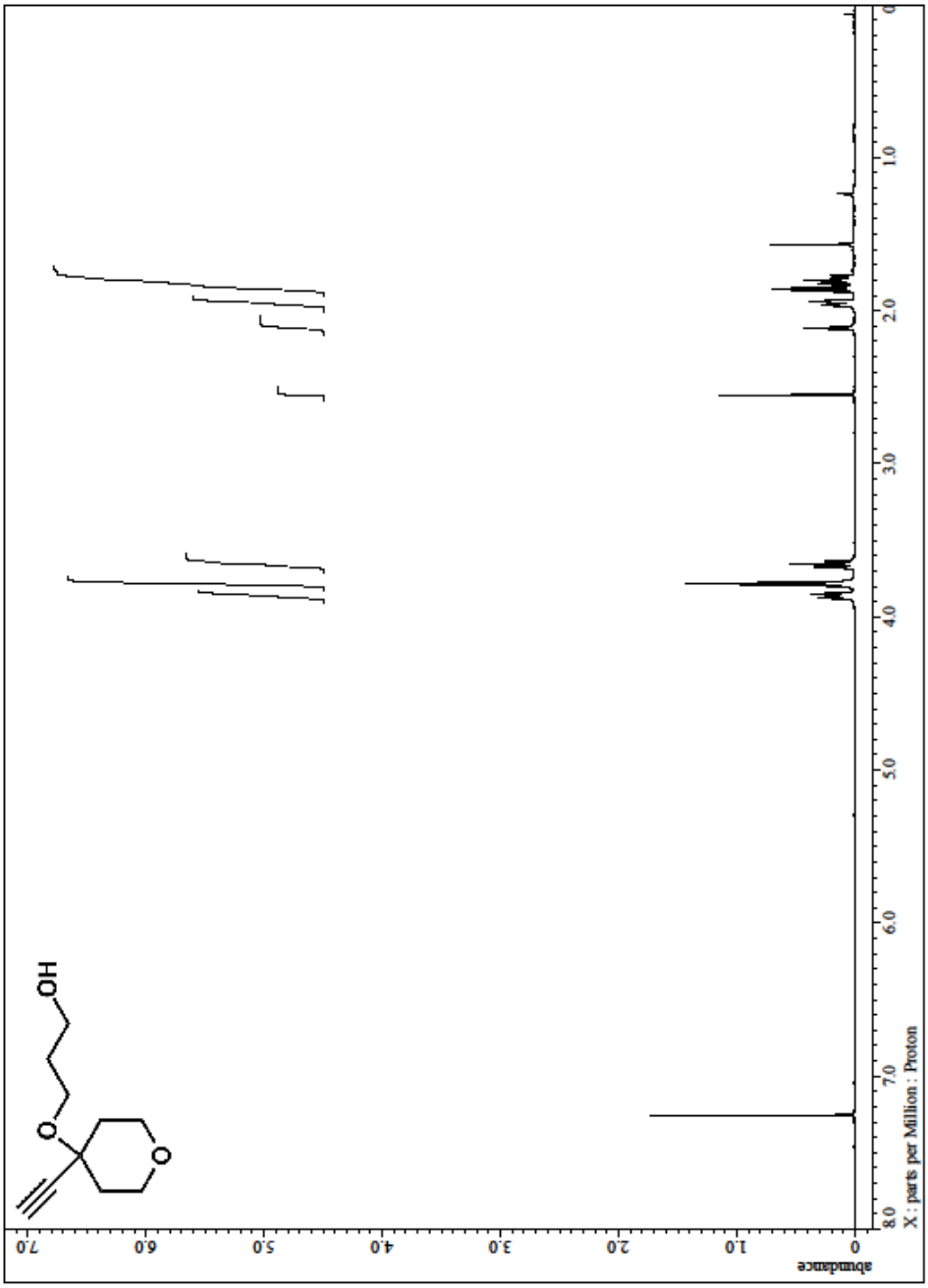

Figure A.3.29. ^{1}H NMR for compound **SI4-26**

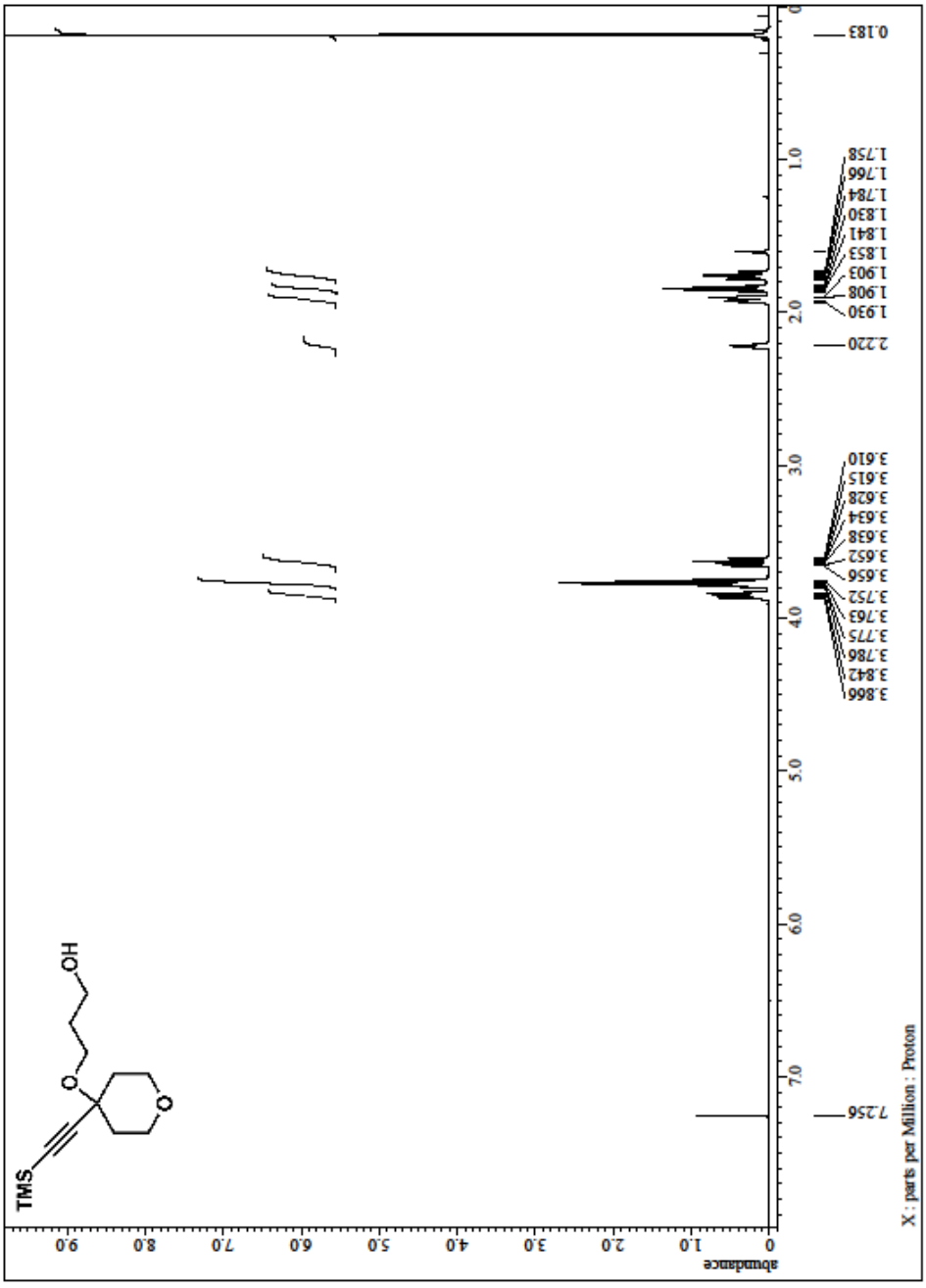

Figure A.3.30. ^{1}H NMR for compound **SI4-27**

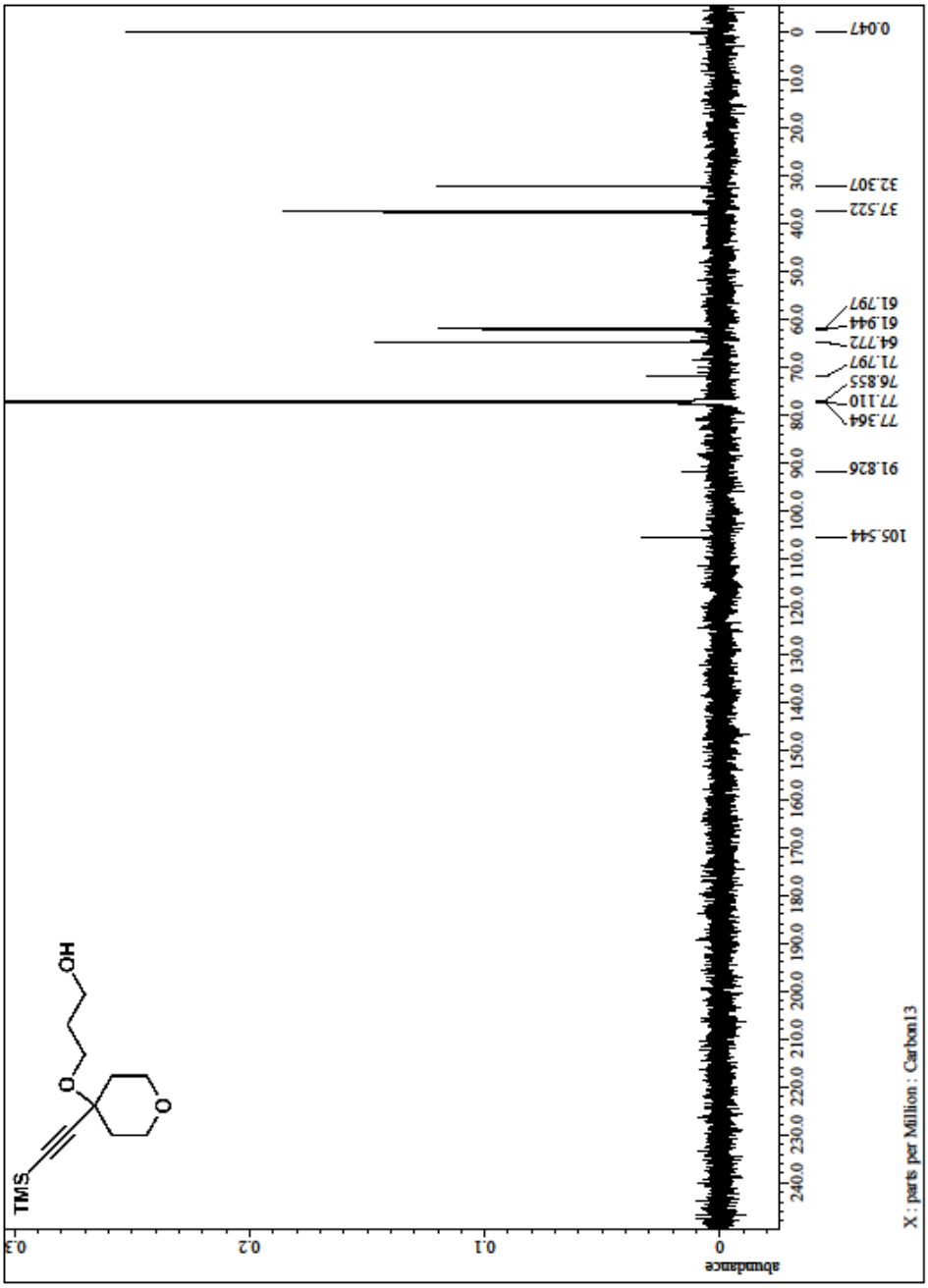

Figure A.3.31. ^{13}C NMR for compound **SI4-27**

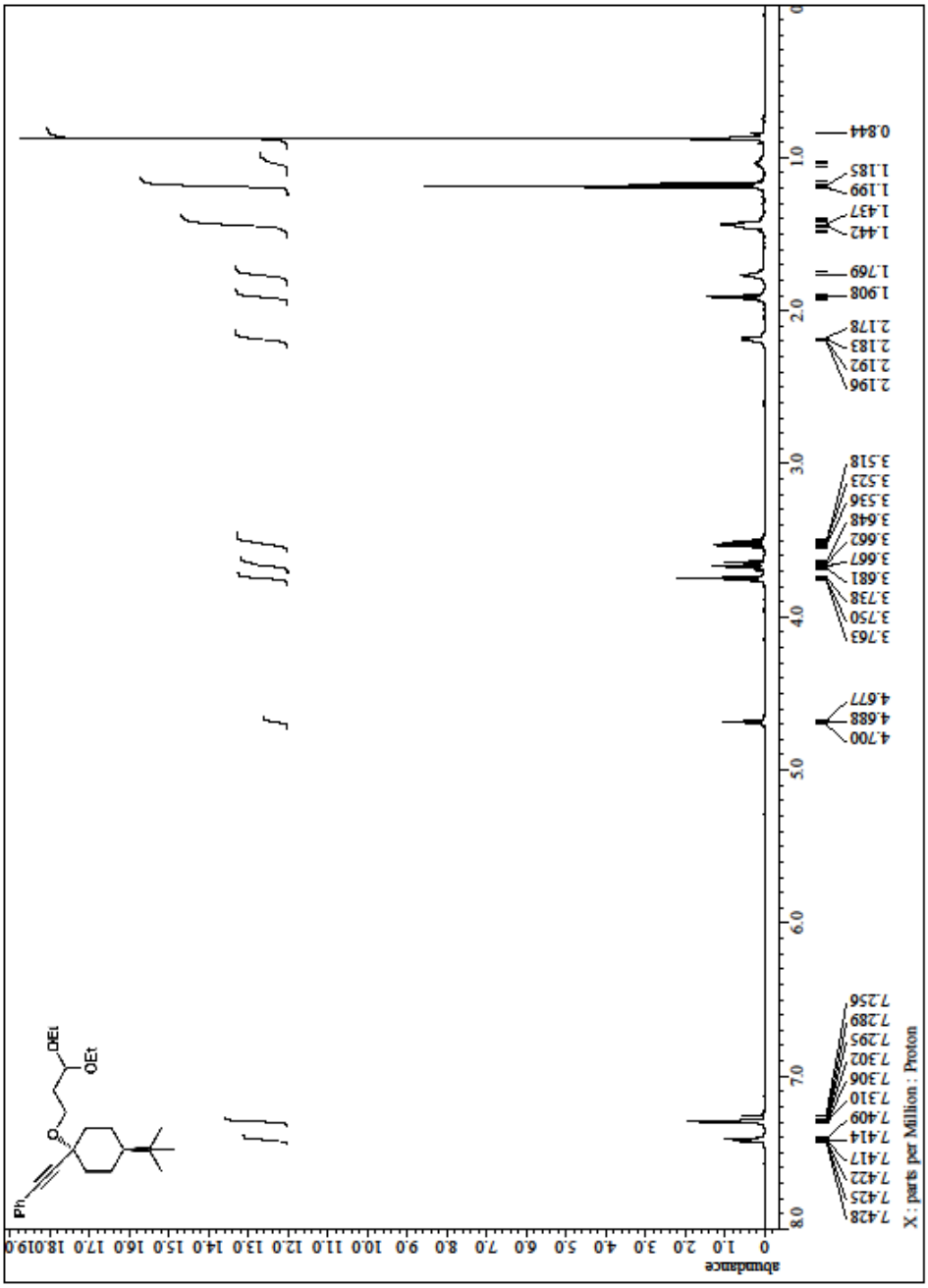

Figure A.3.32. ^{1}H NMR for compound **SI4-29**

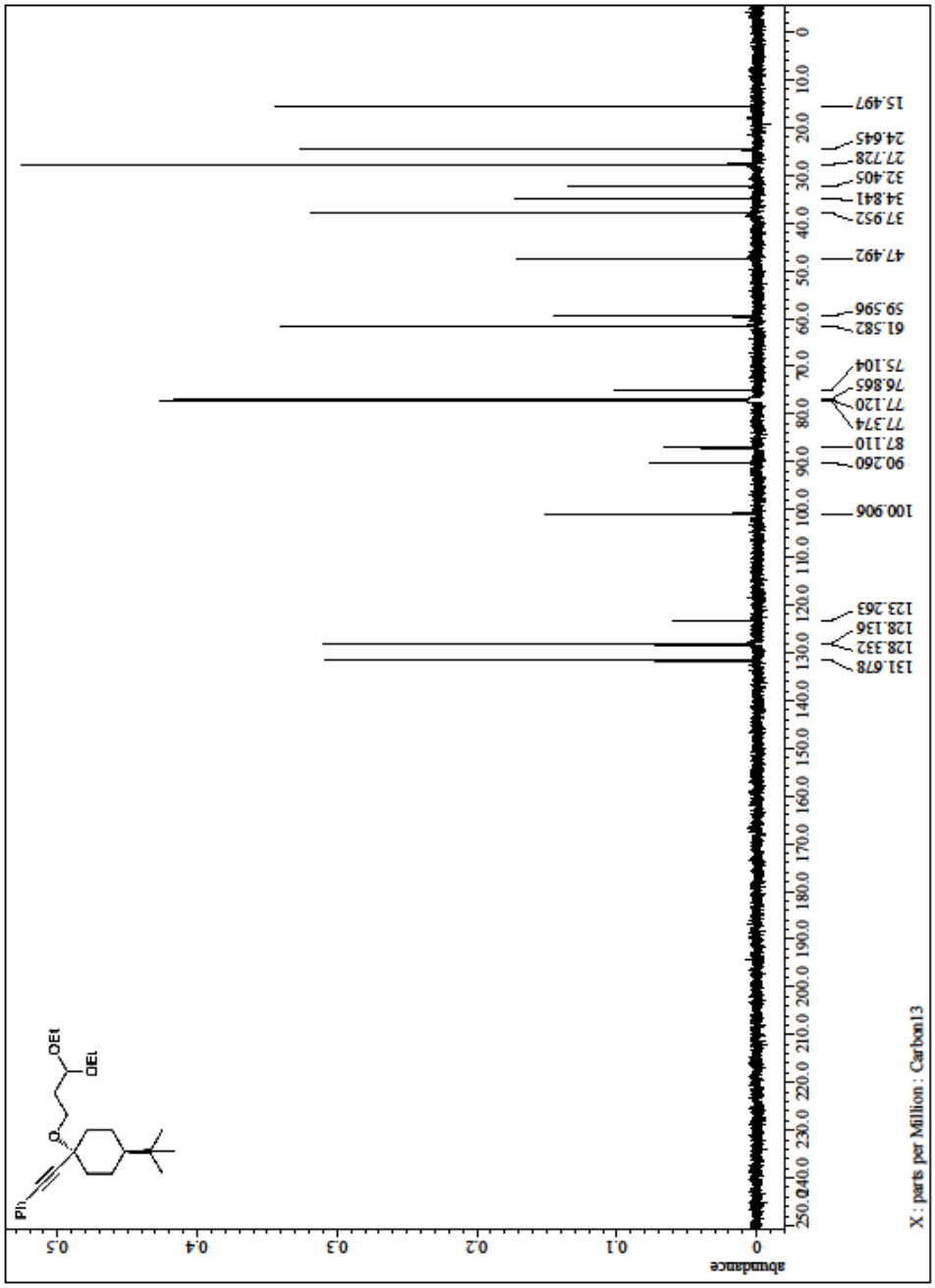

Figure A.3.33. ^{13}C NMR for compound **SI4-29**

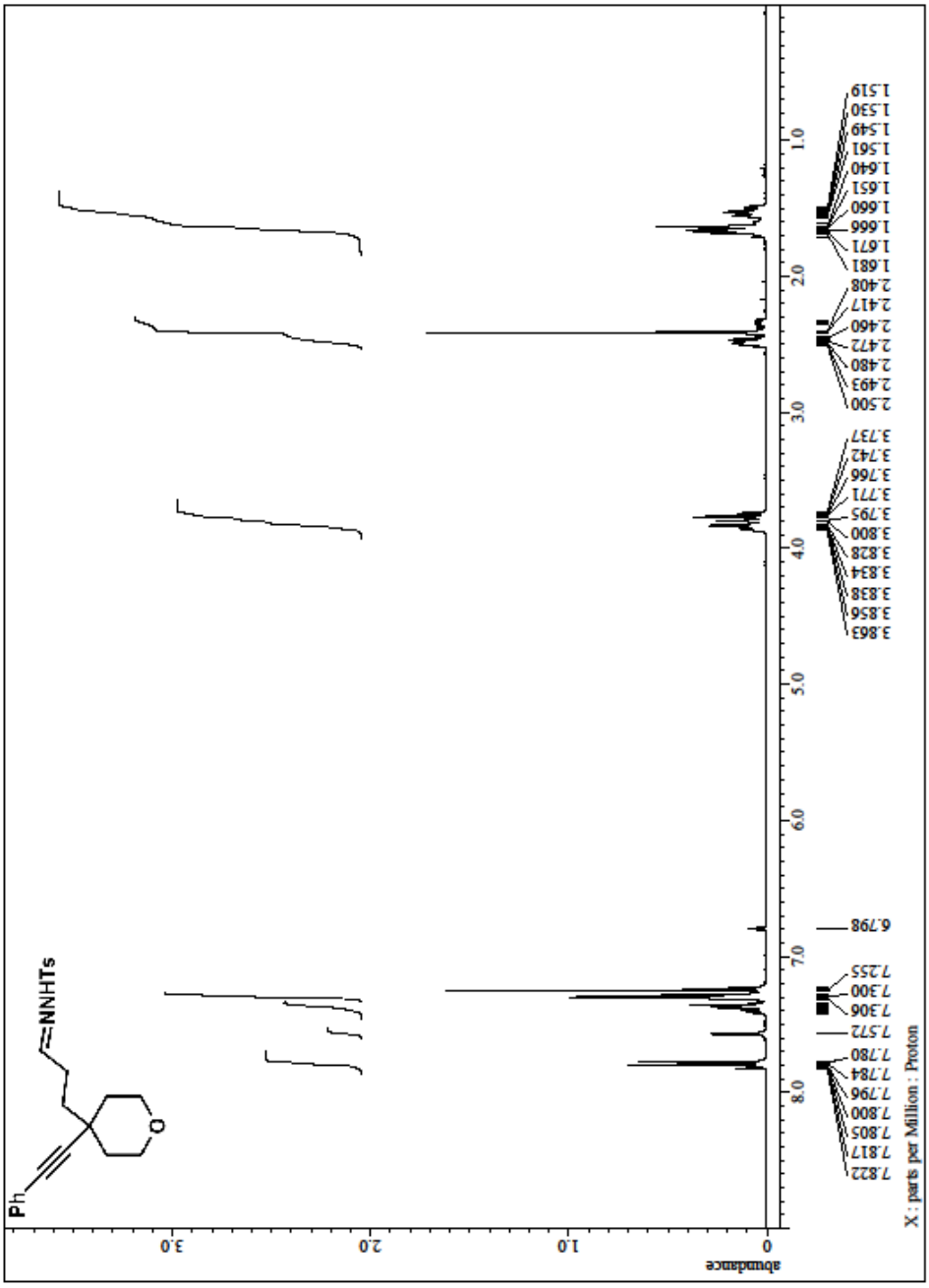

Figure A.3.34. ^{1}H NMR for compound **203**

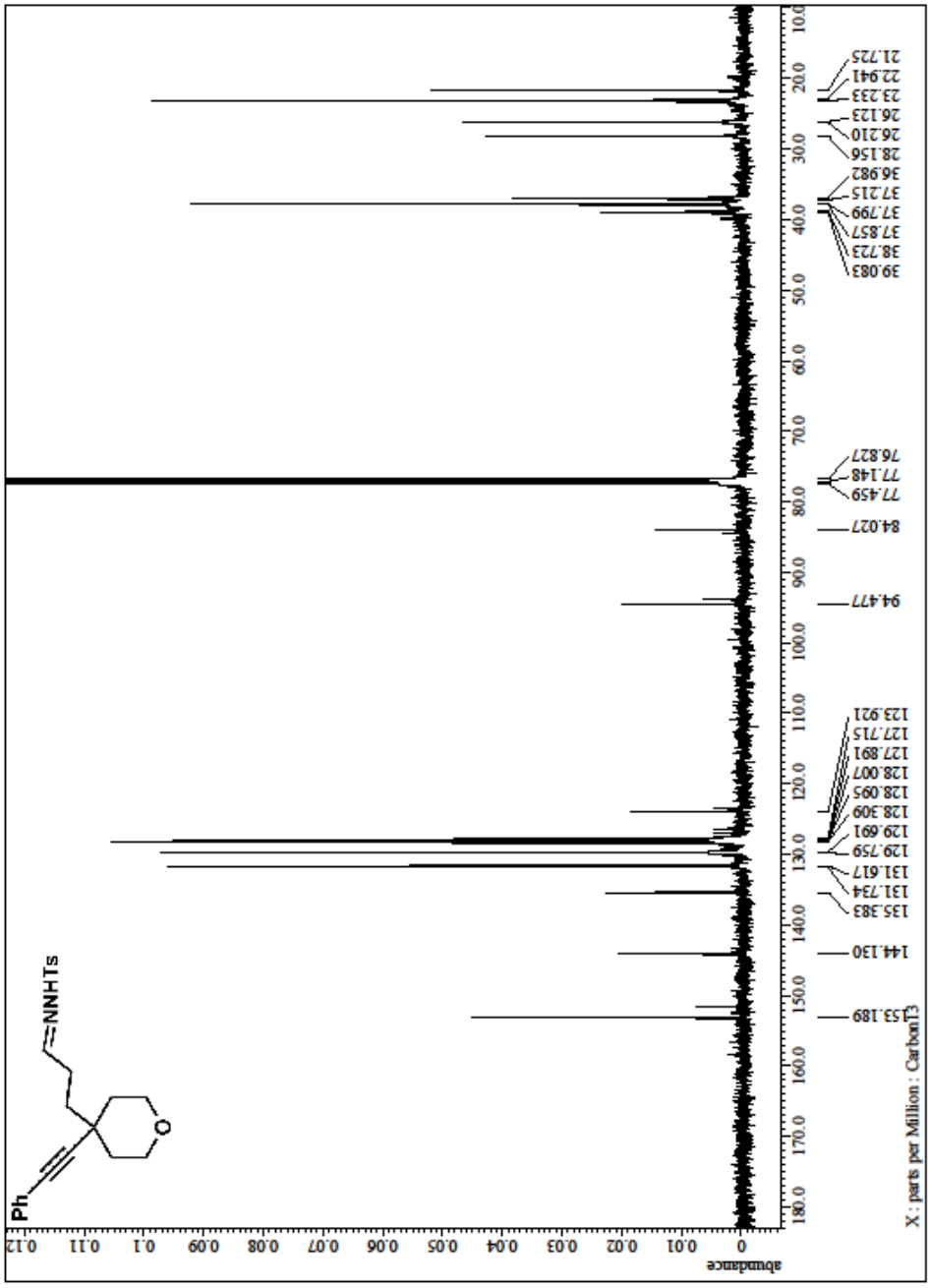

Figure A.3.35. ^{13}C NMR for compound **203**

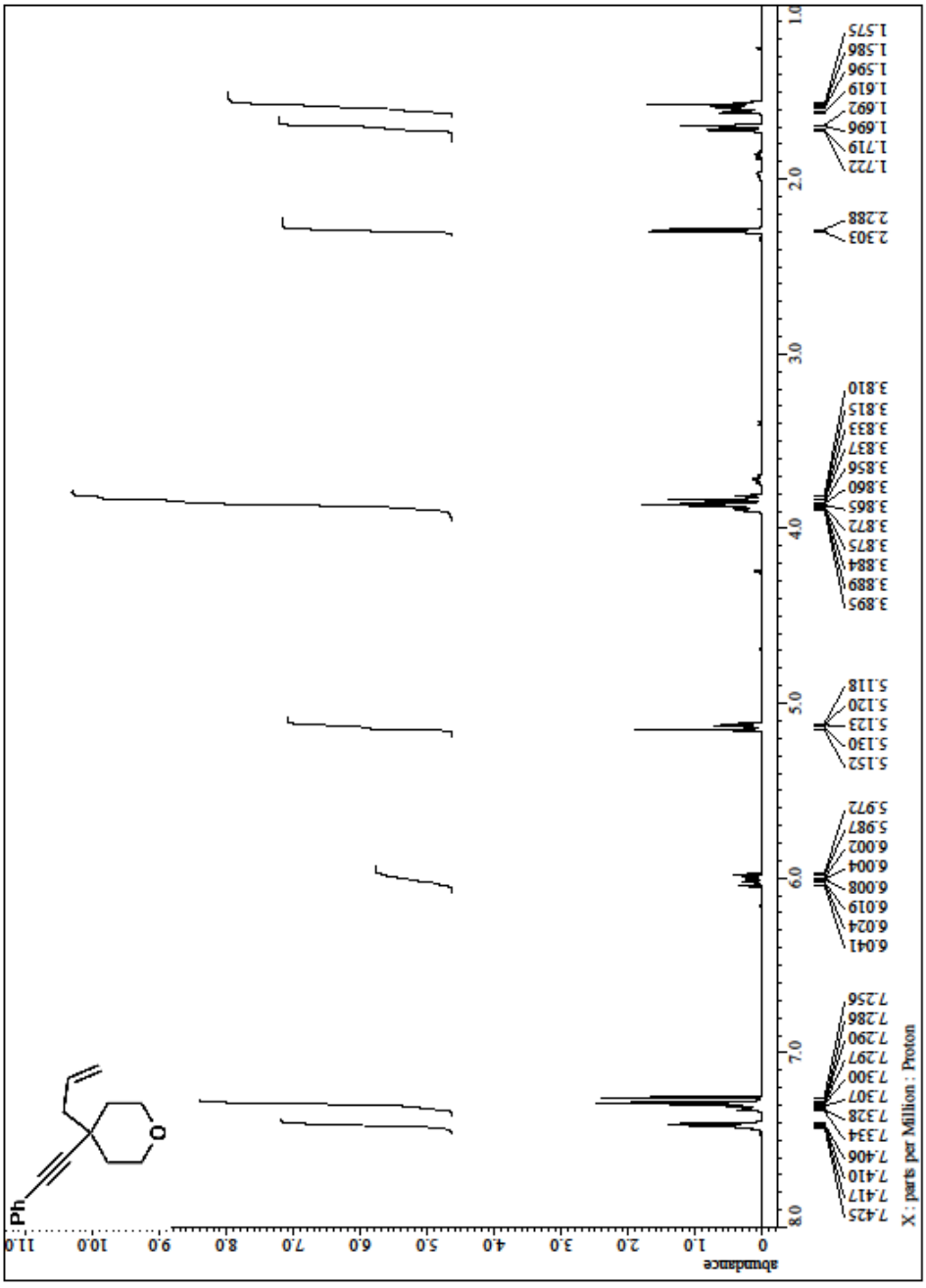

Figure A.3.36. ^{1}H NMR for compound **204**

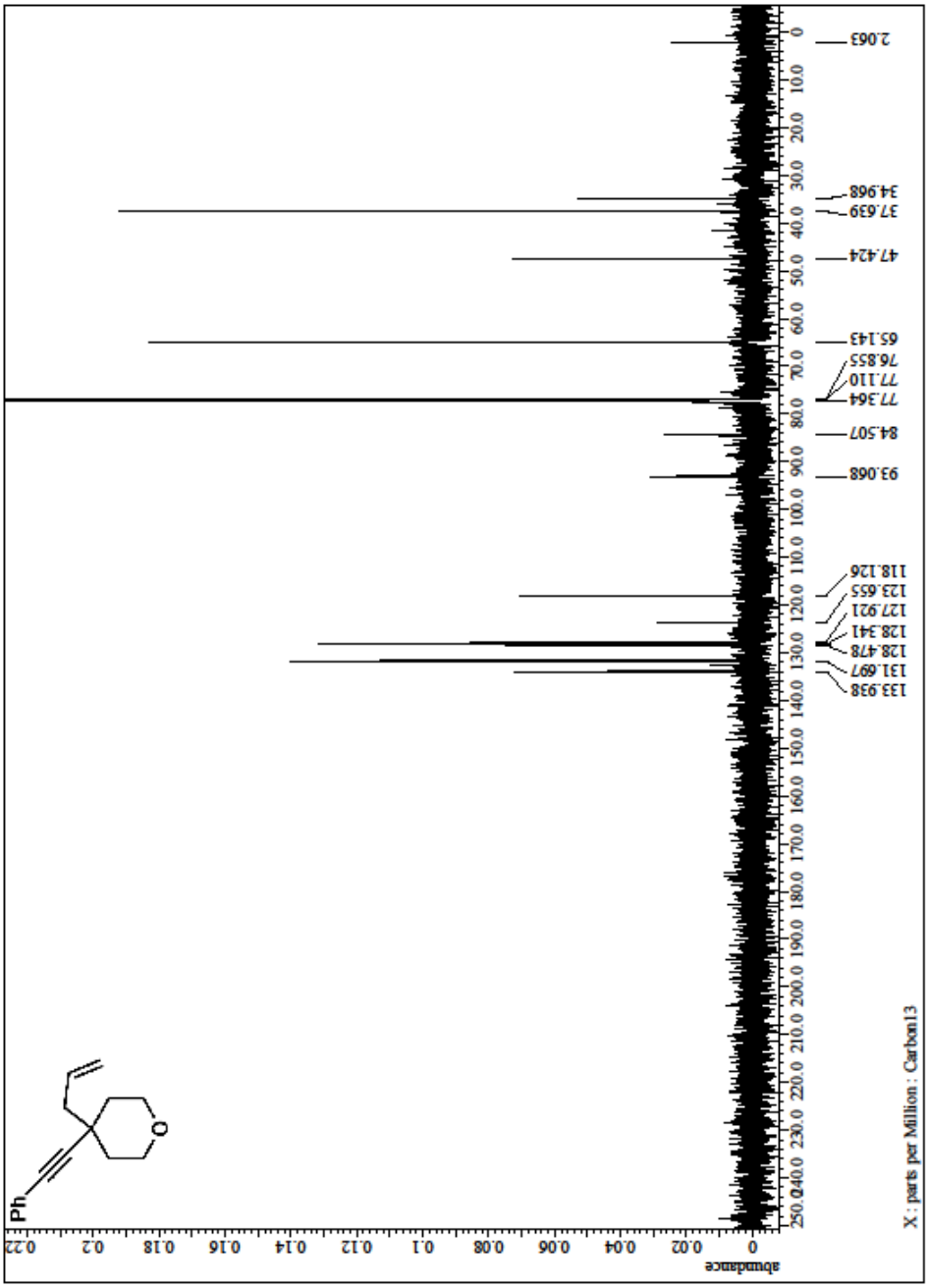

Figure A.3.37. ^{13}C NMR for compound **204**

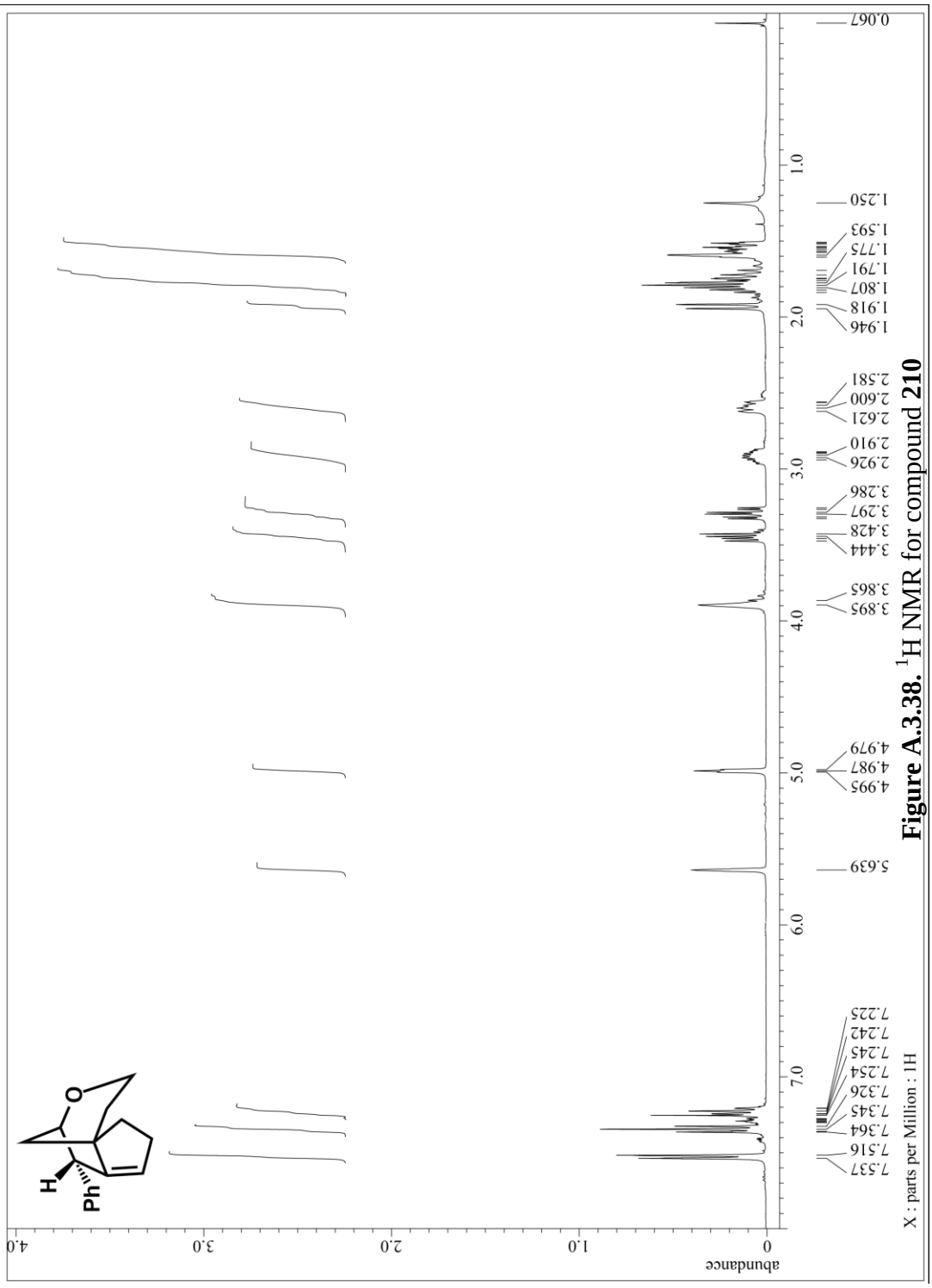

Figure A.3.38. ^{1}H NMR for compound **210**

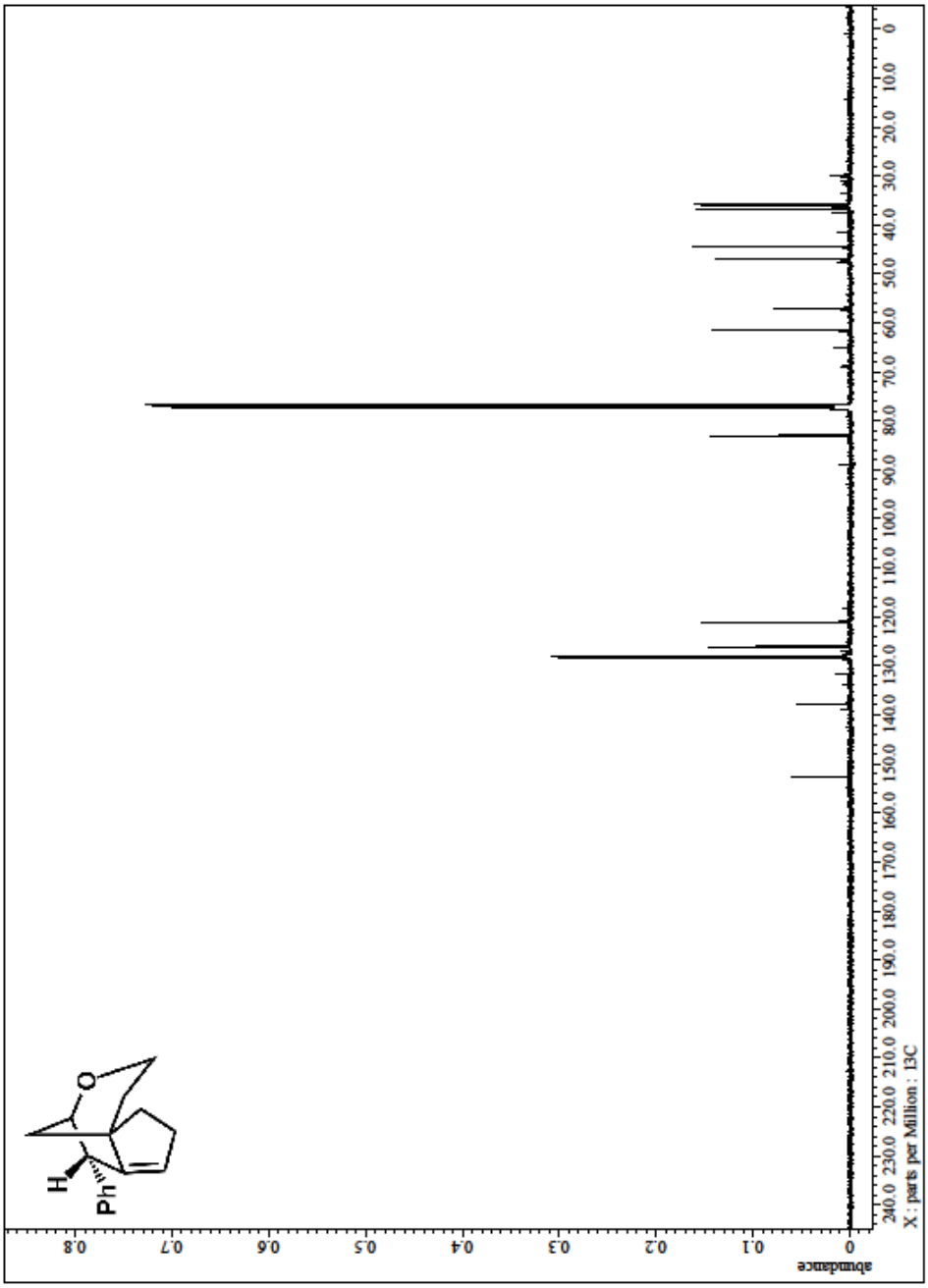

Figure A.3.39. ^{13}C NMR for compound **210**

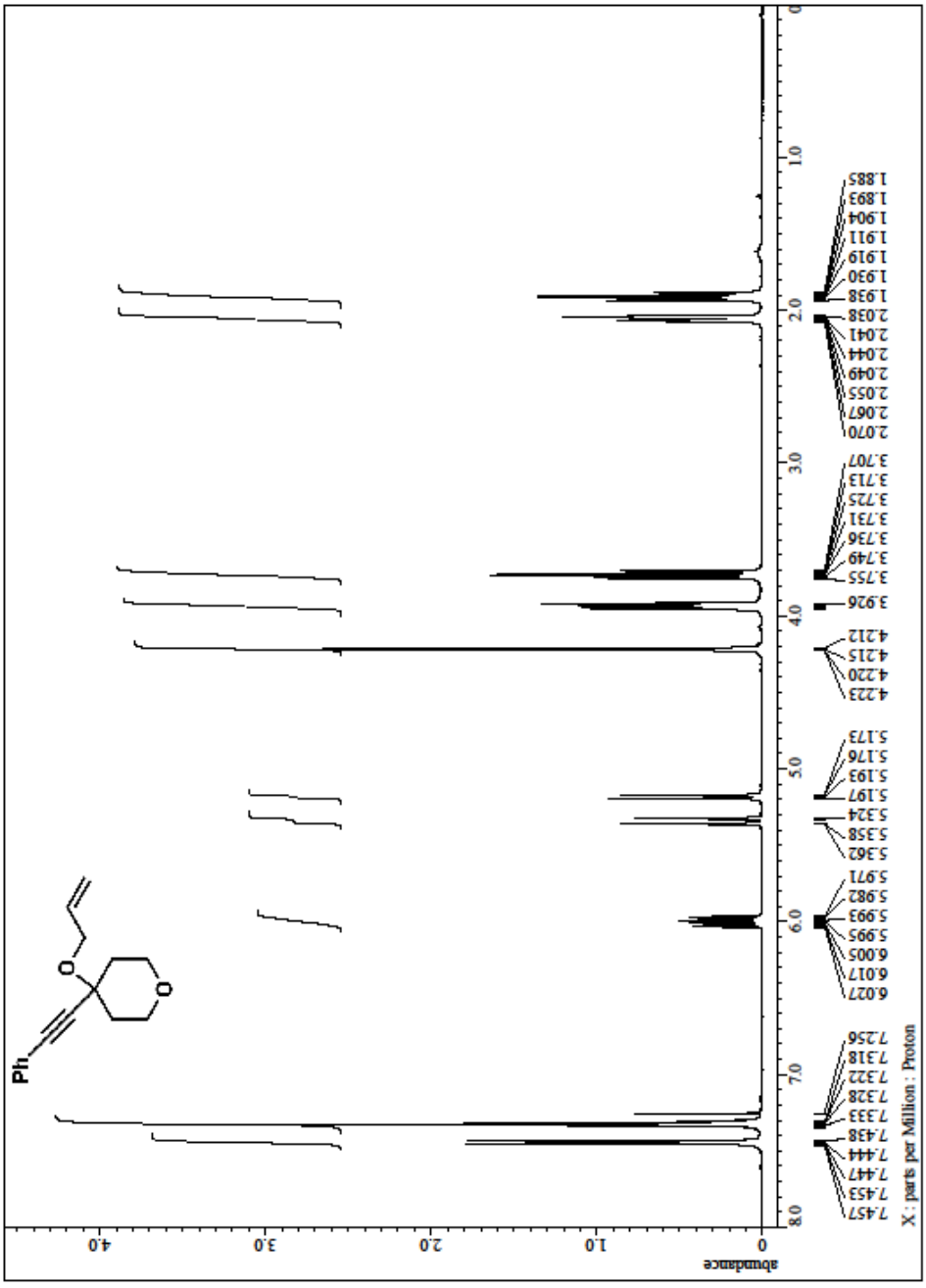

Figure A.3.40. ^{1}H NMR for compound **219**

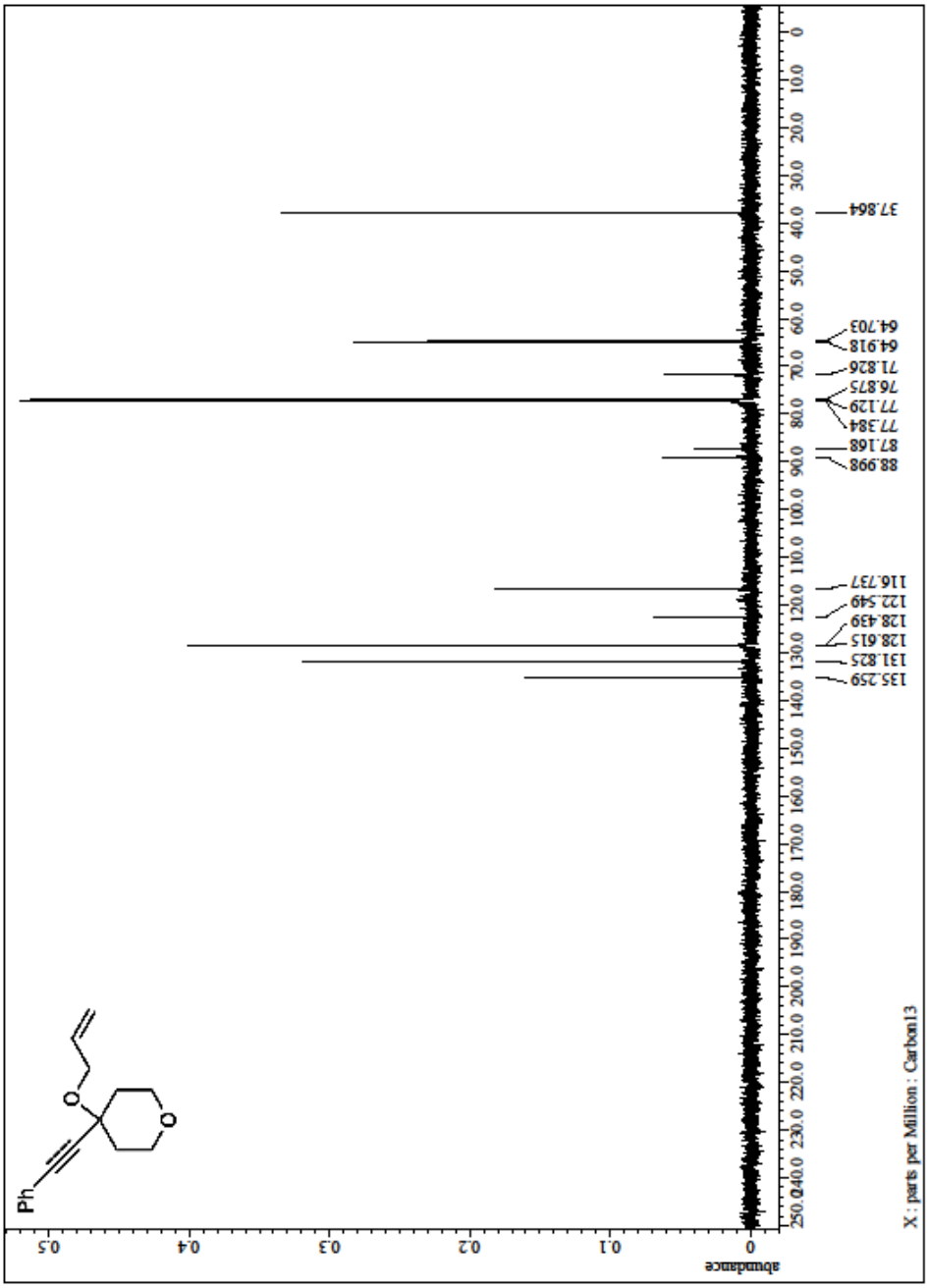

Figure A.3.41. ^{13}C NMR for compound **219**

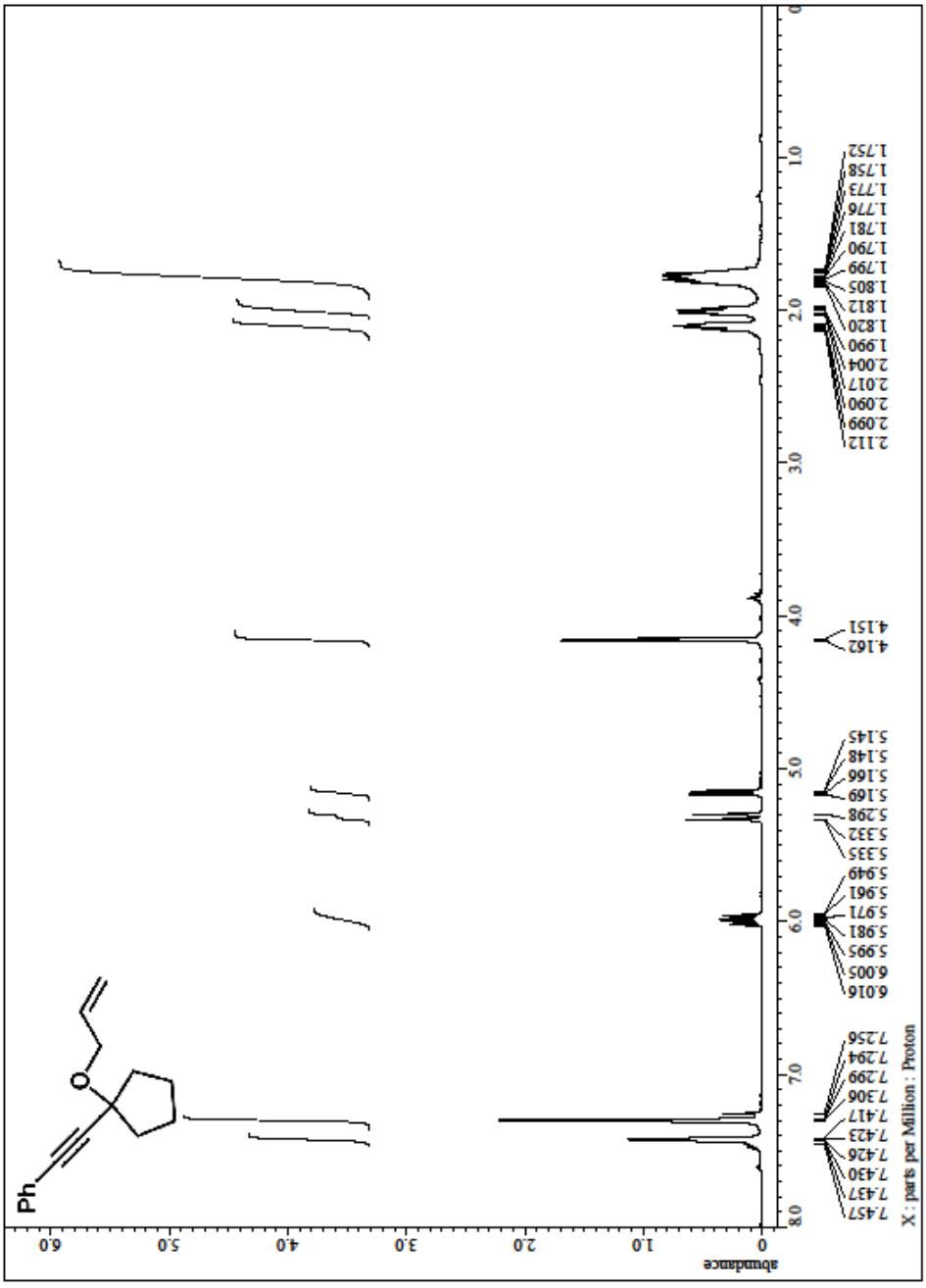

Figure A.3.42. ^{1}H NMR for compound **220**

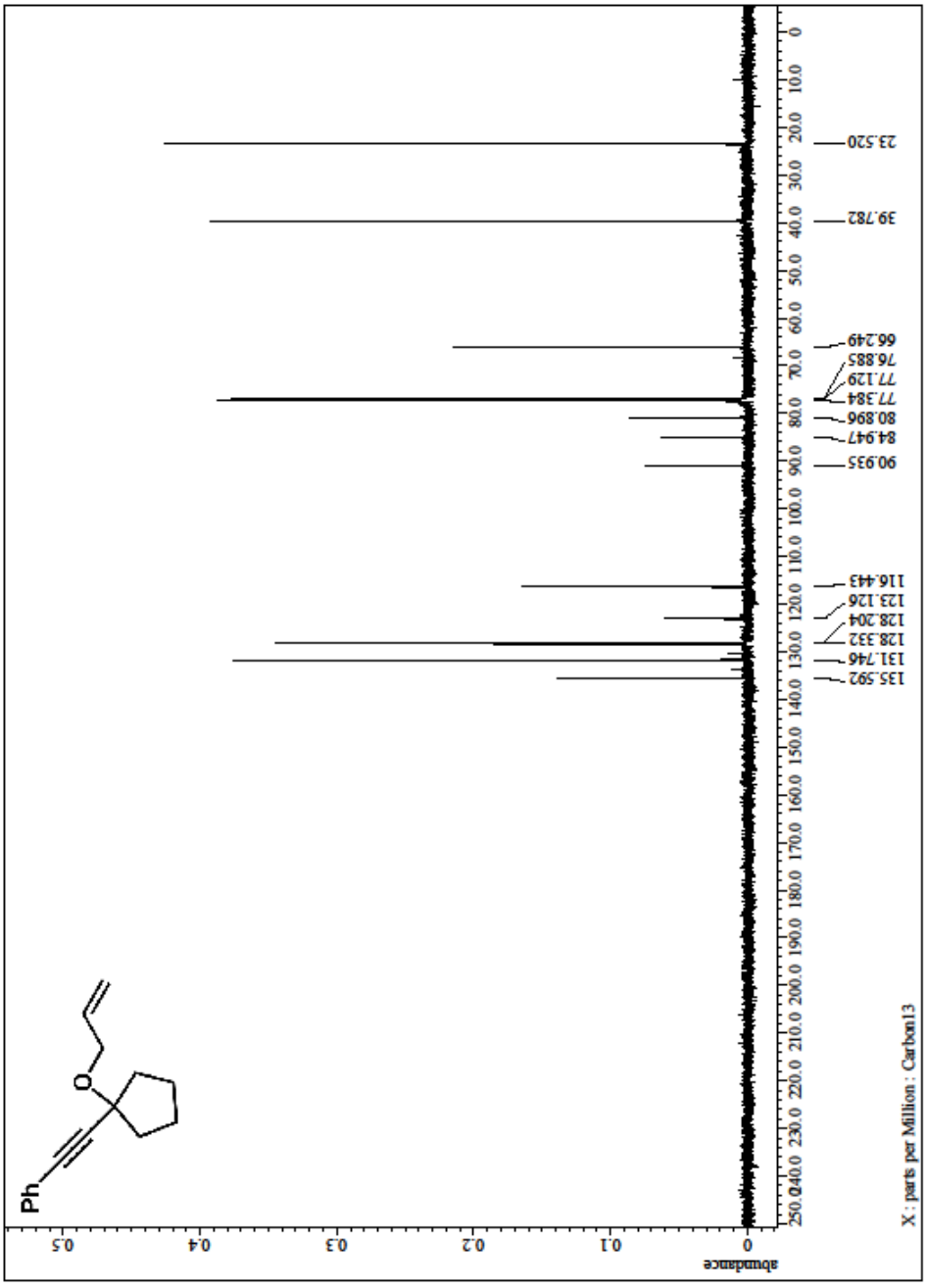

Figure A.3.43. ^{13}C NMR for compound **220**

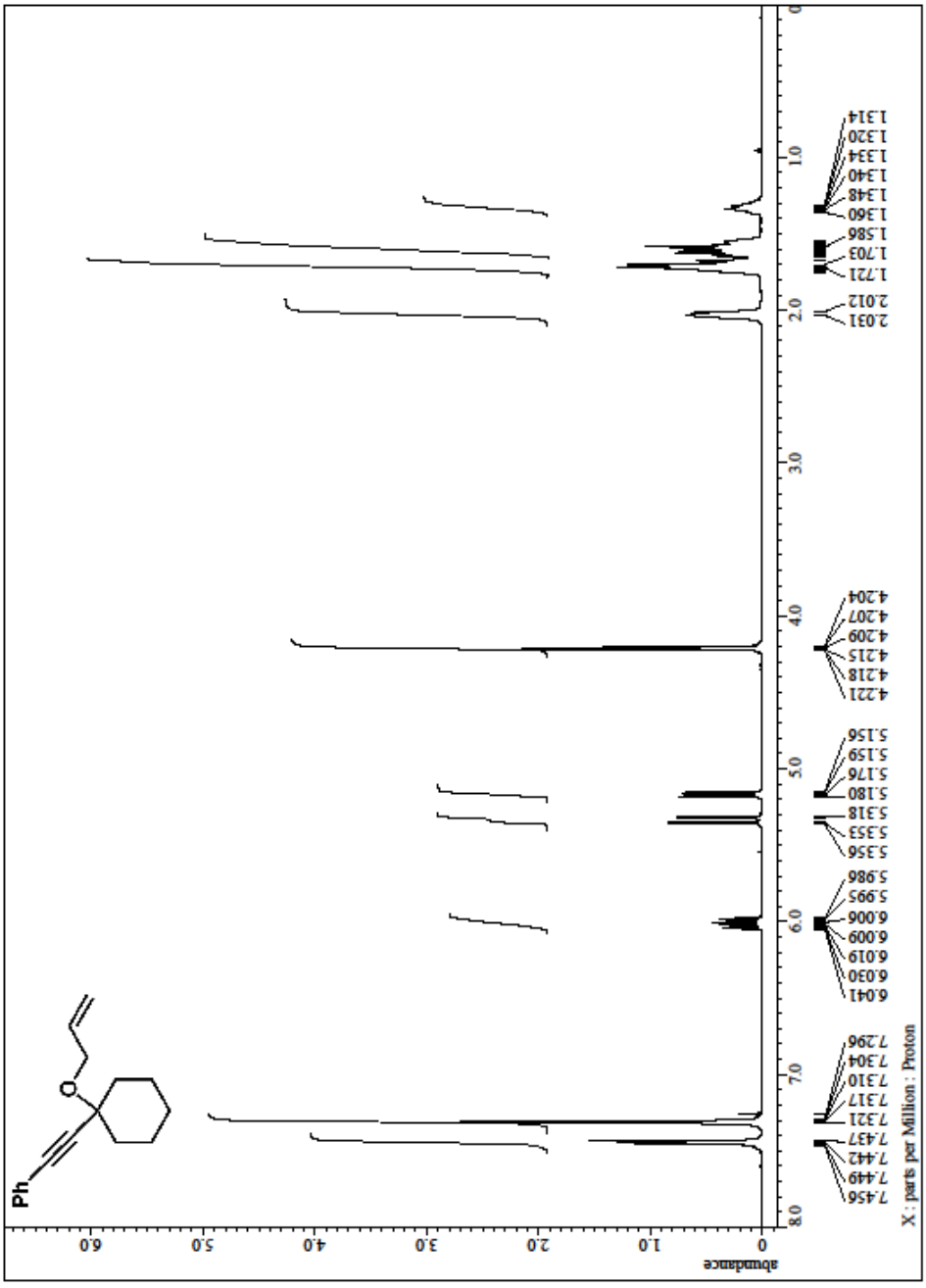

Figure A.3.44. ^{1}H NMR for compound **221**

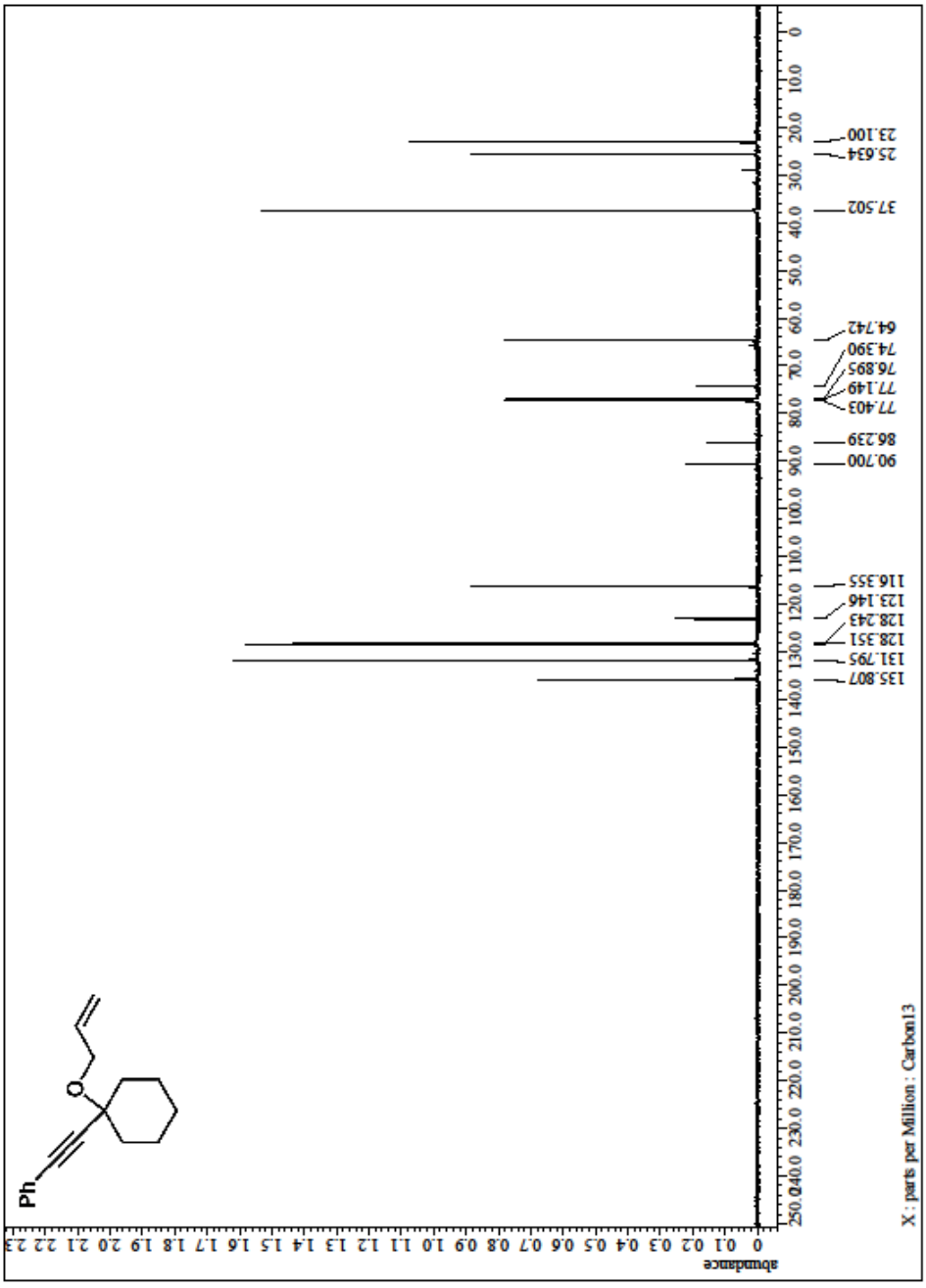

Figure A.3.45. ^{13}C NMR for compound **221**

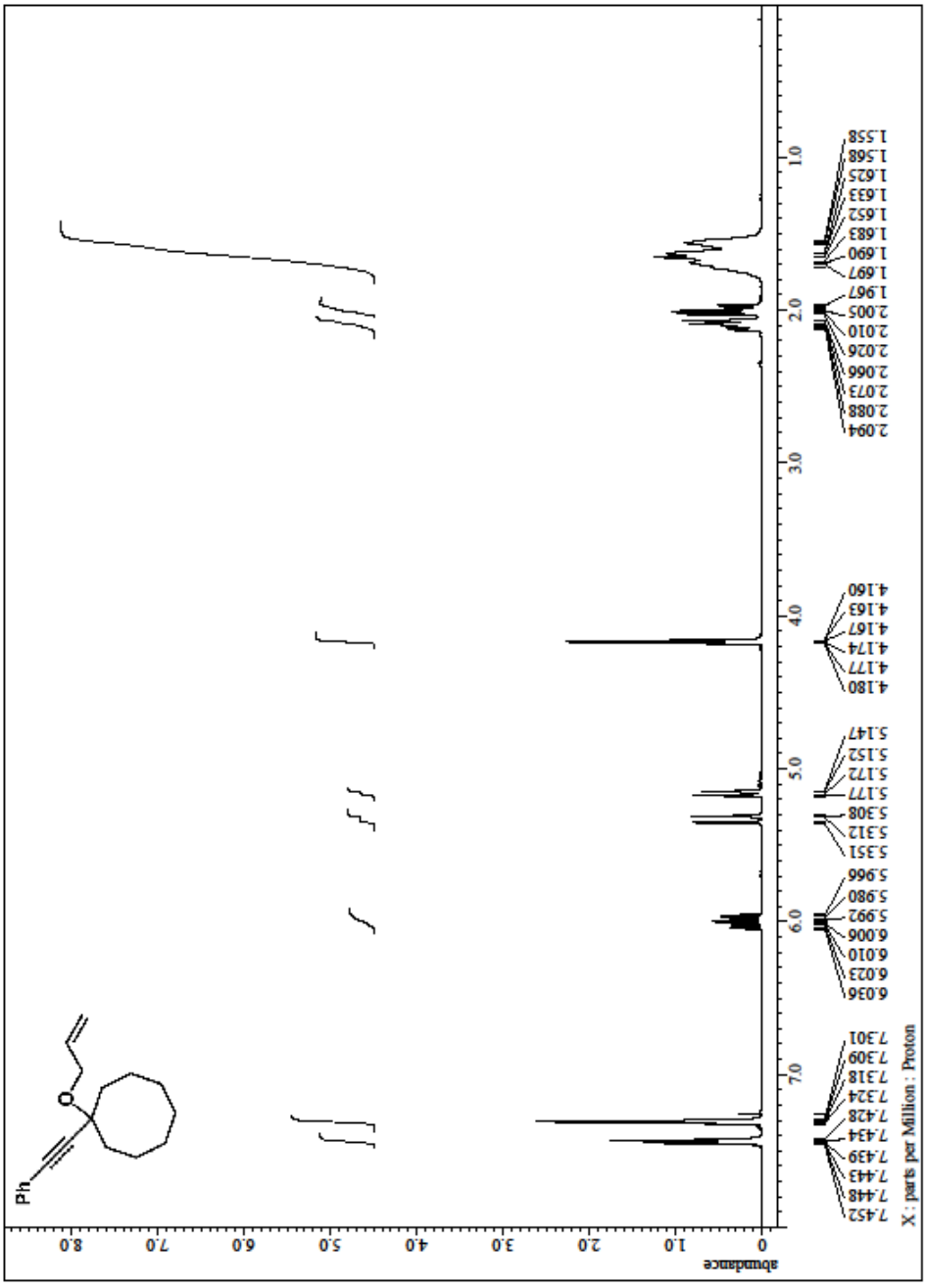

Figure A.3.46. ^{1}H NMR for compound **222**

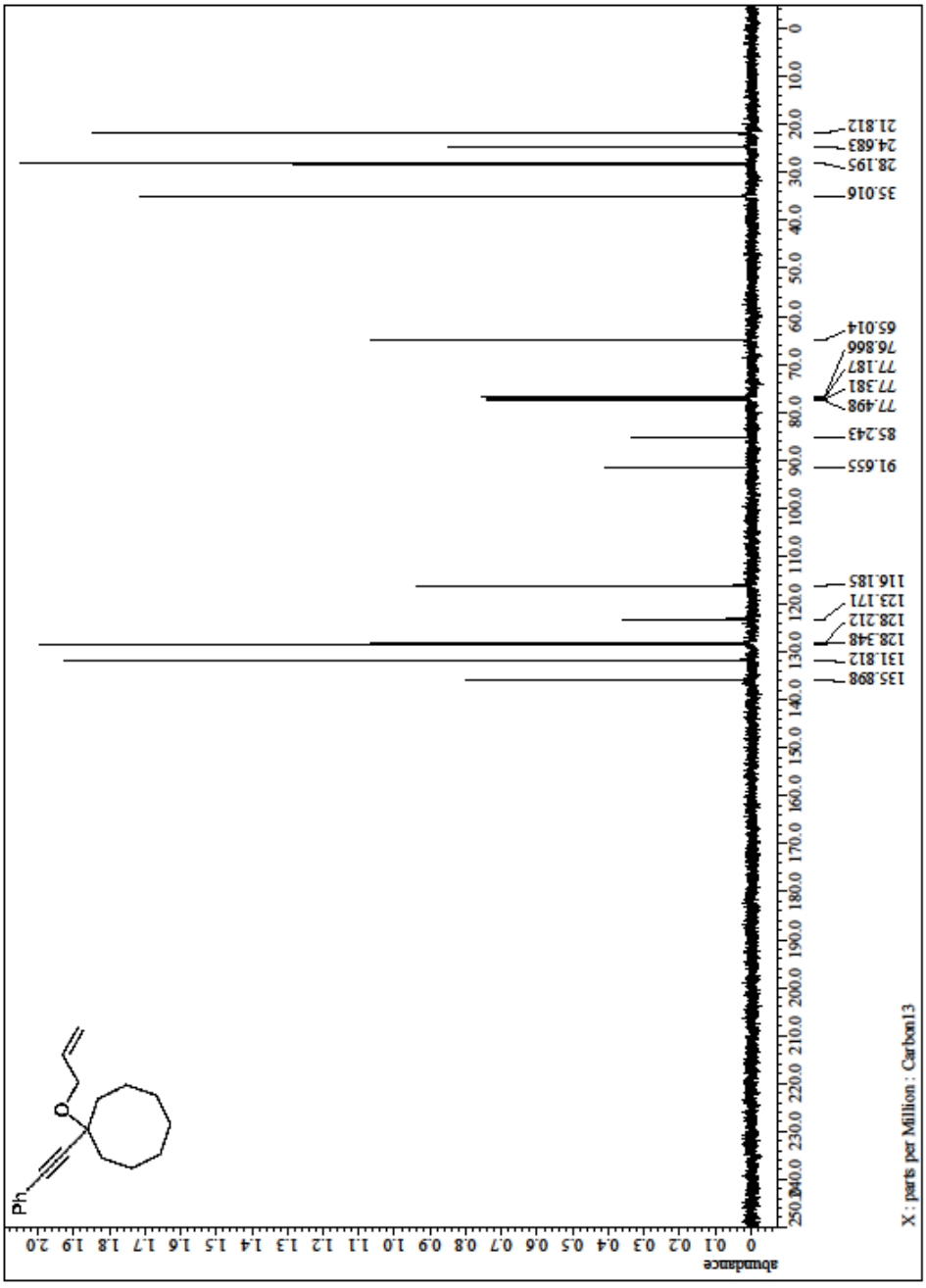

Figure A.3.47. ^{13}C NMR for compound **222**

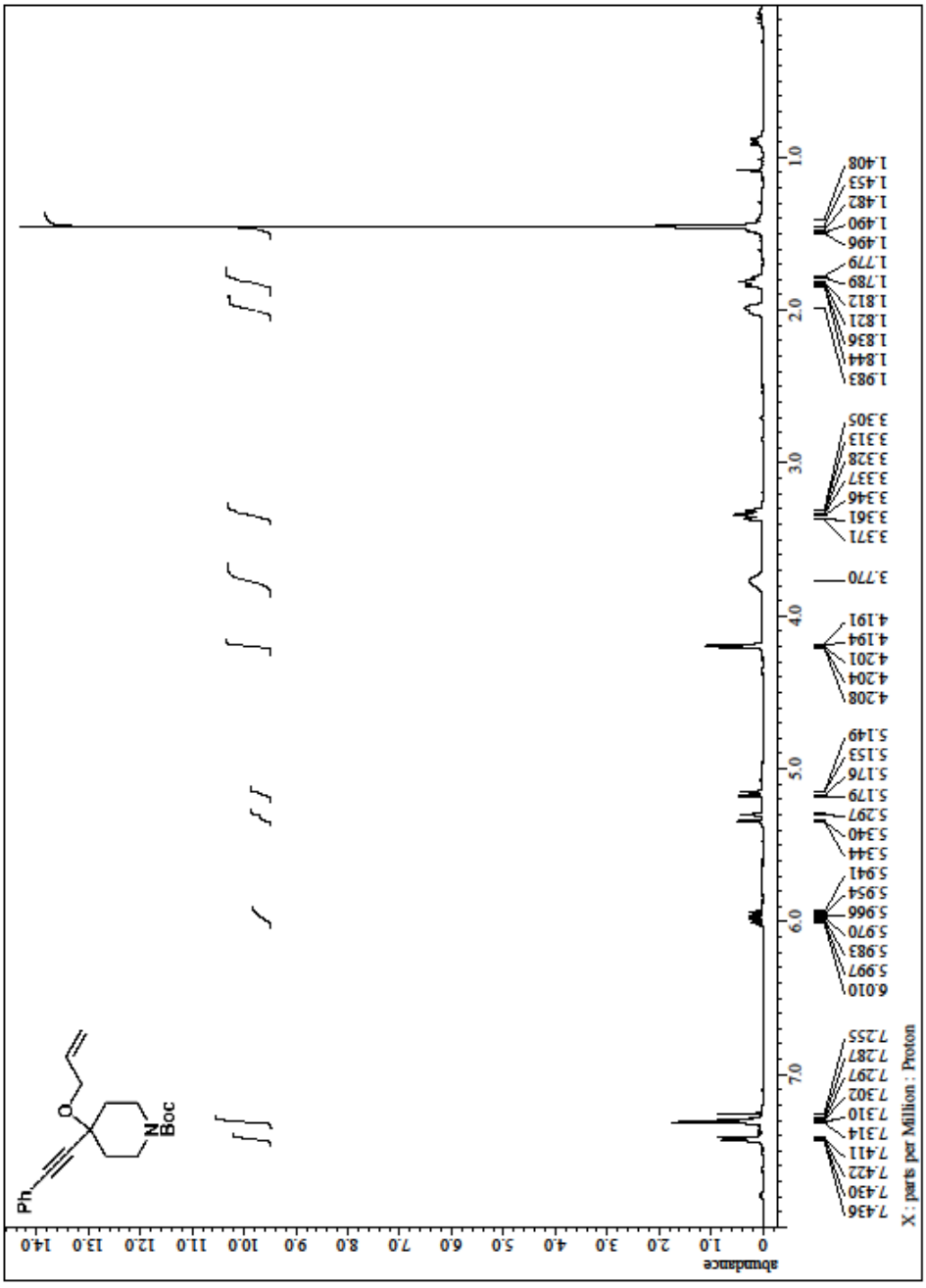

Figure A.3.48. ^{1}H NMR for compound **223**

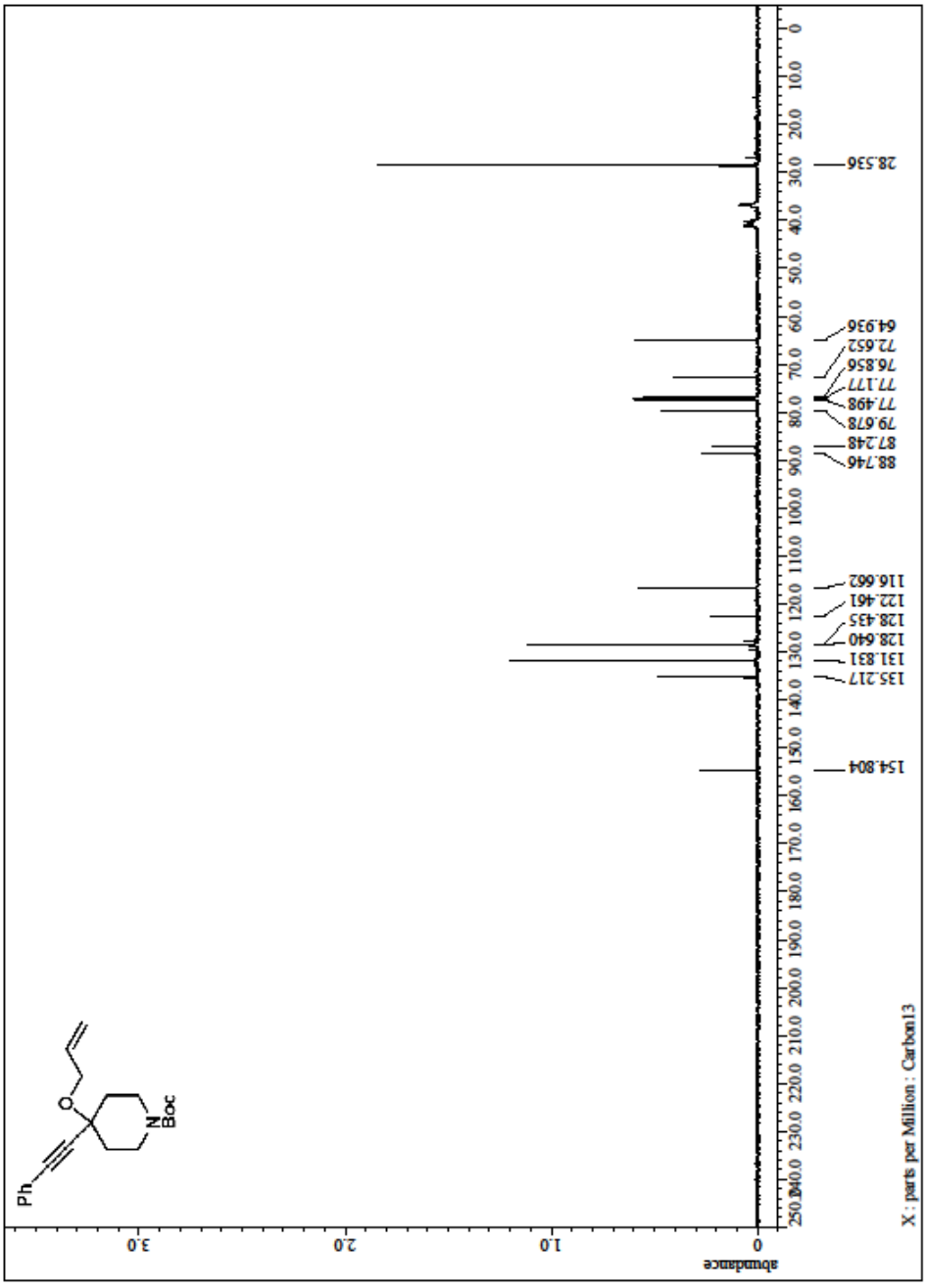

Figure A.3.49. ^{13}C NMR for compound **223**

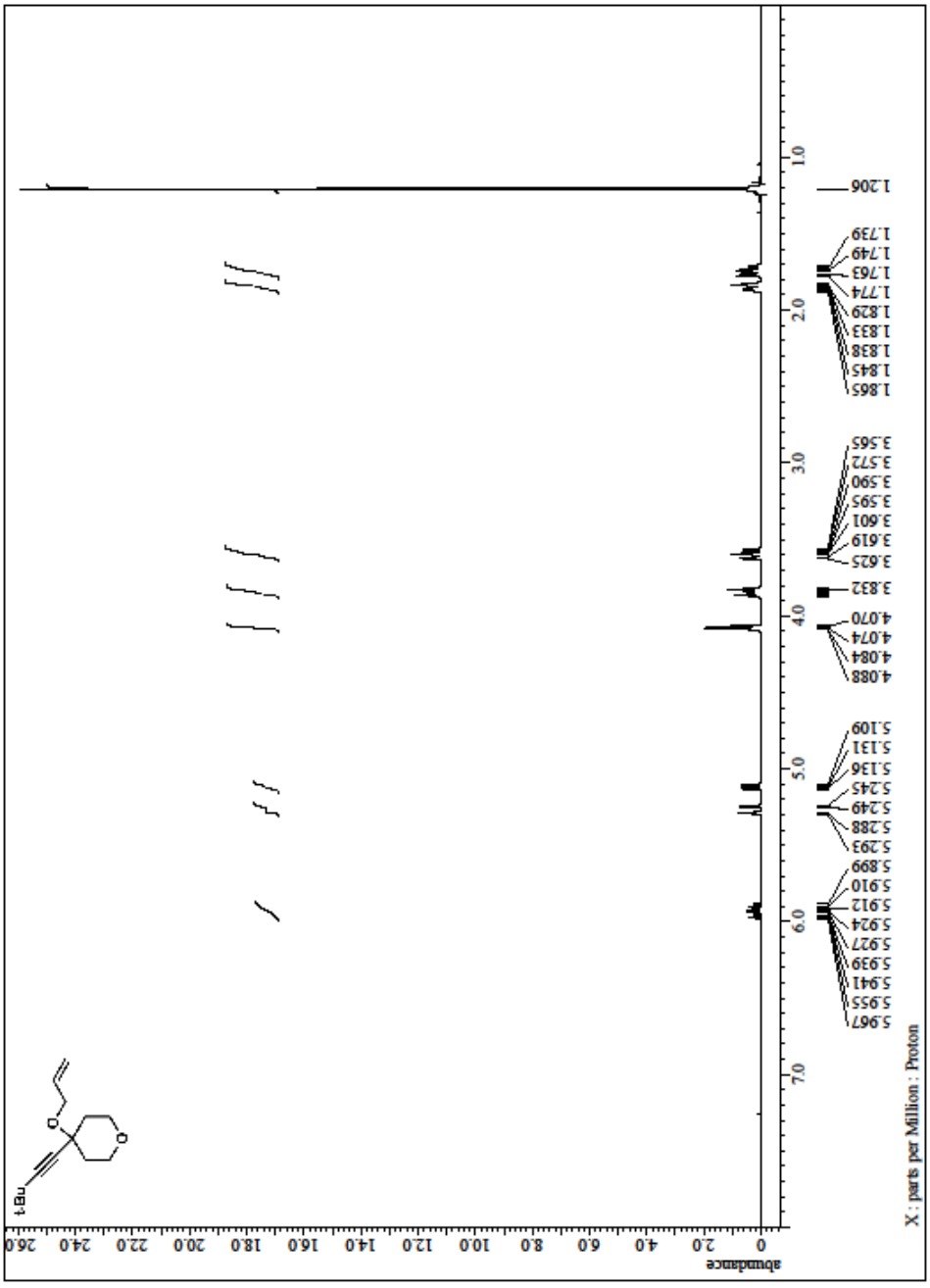

Figure A.3.50. ^{1}H NMR for compound **224**

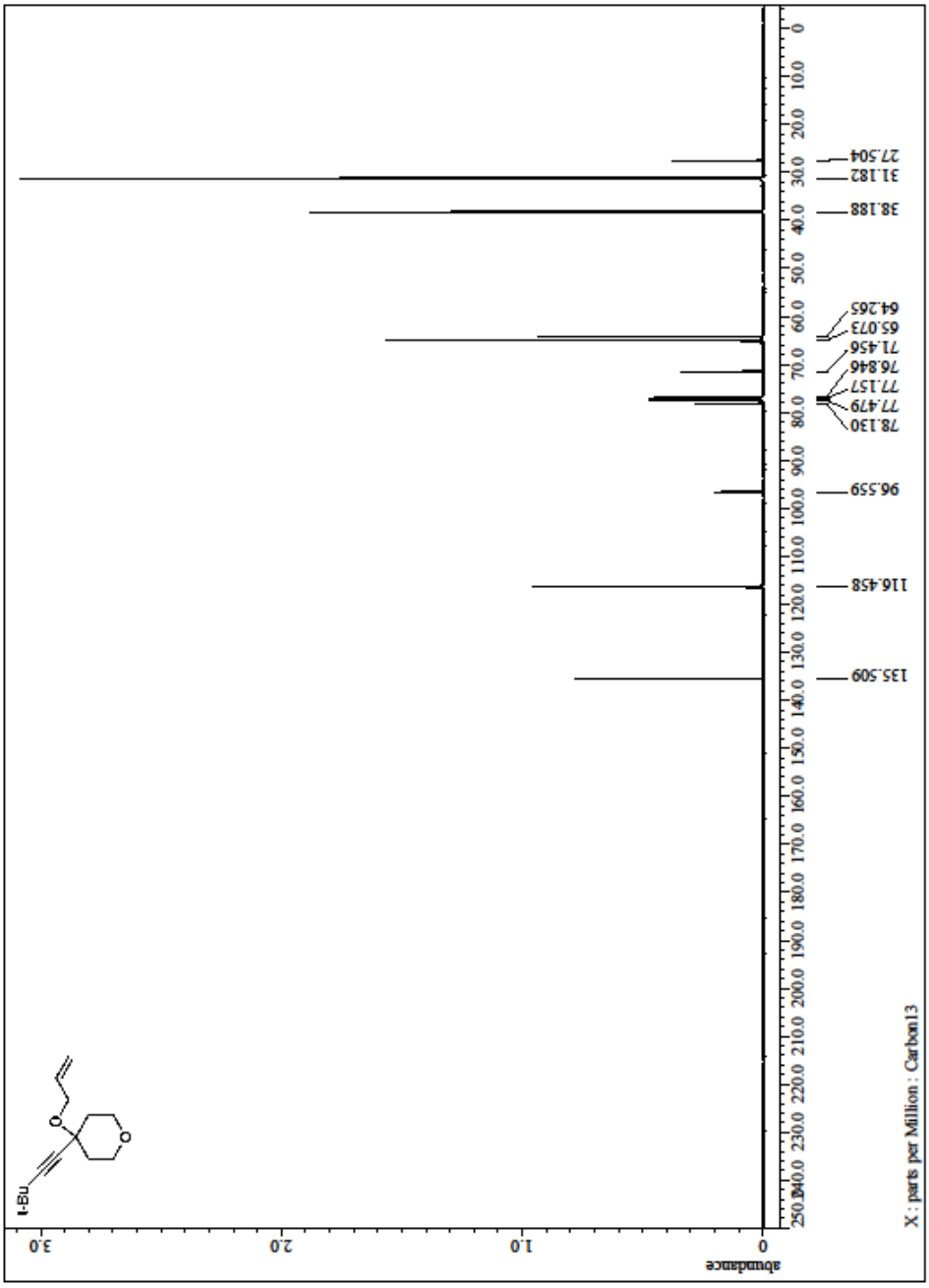

Figure A.3.51. ^{1}H NMR for compound **224**

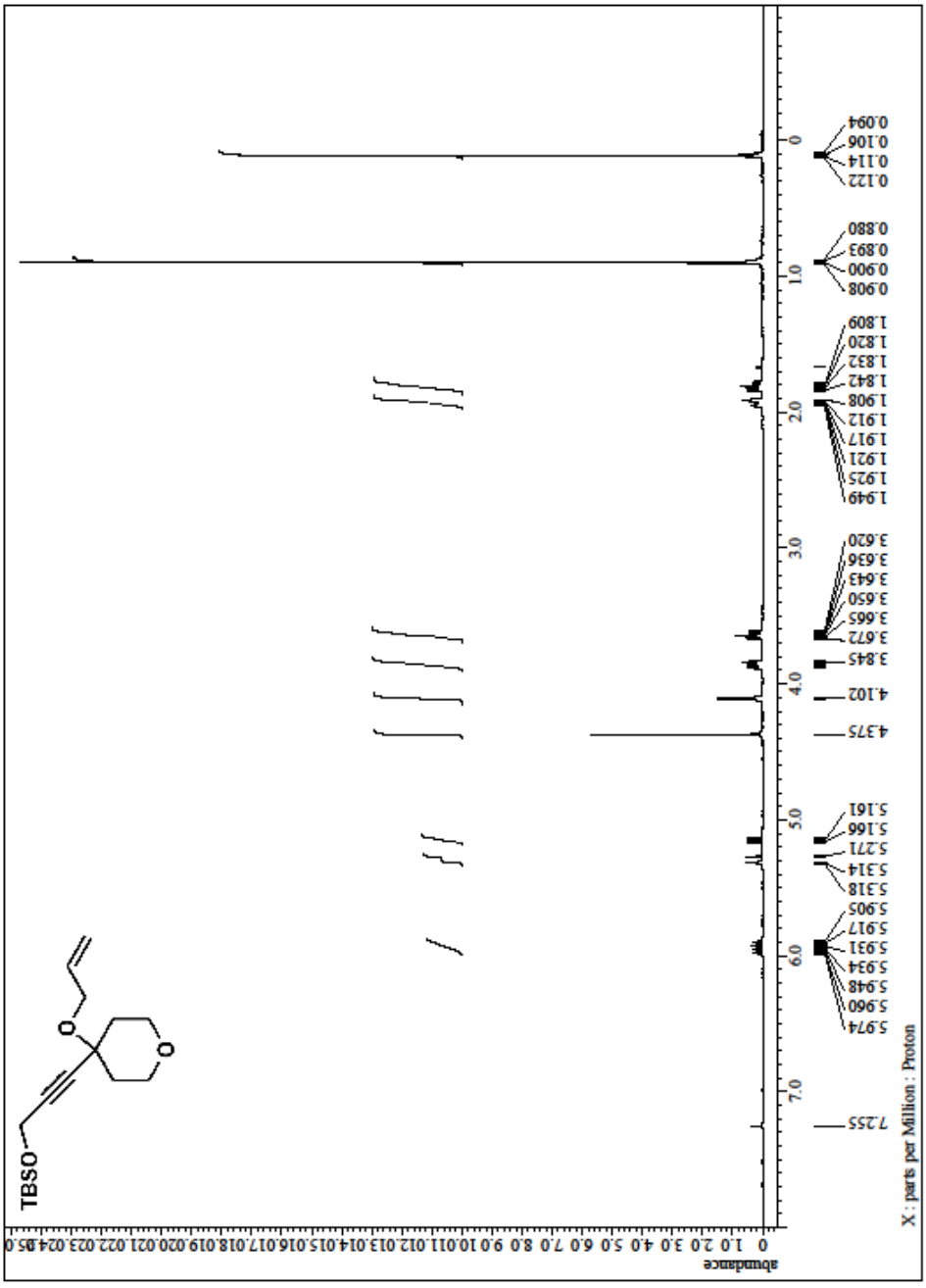

Figure A.3.52. ^{1}H NMR for compound **225**

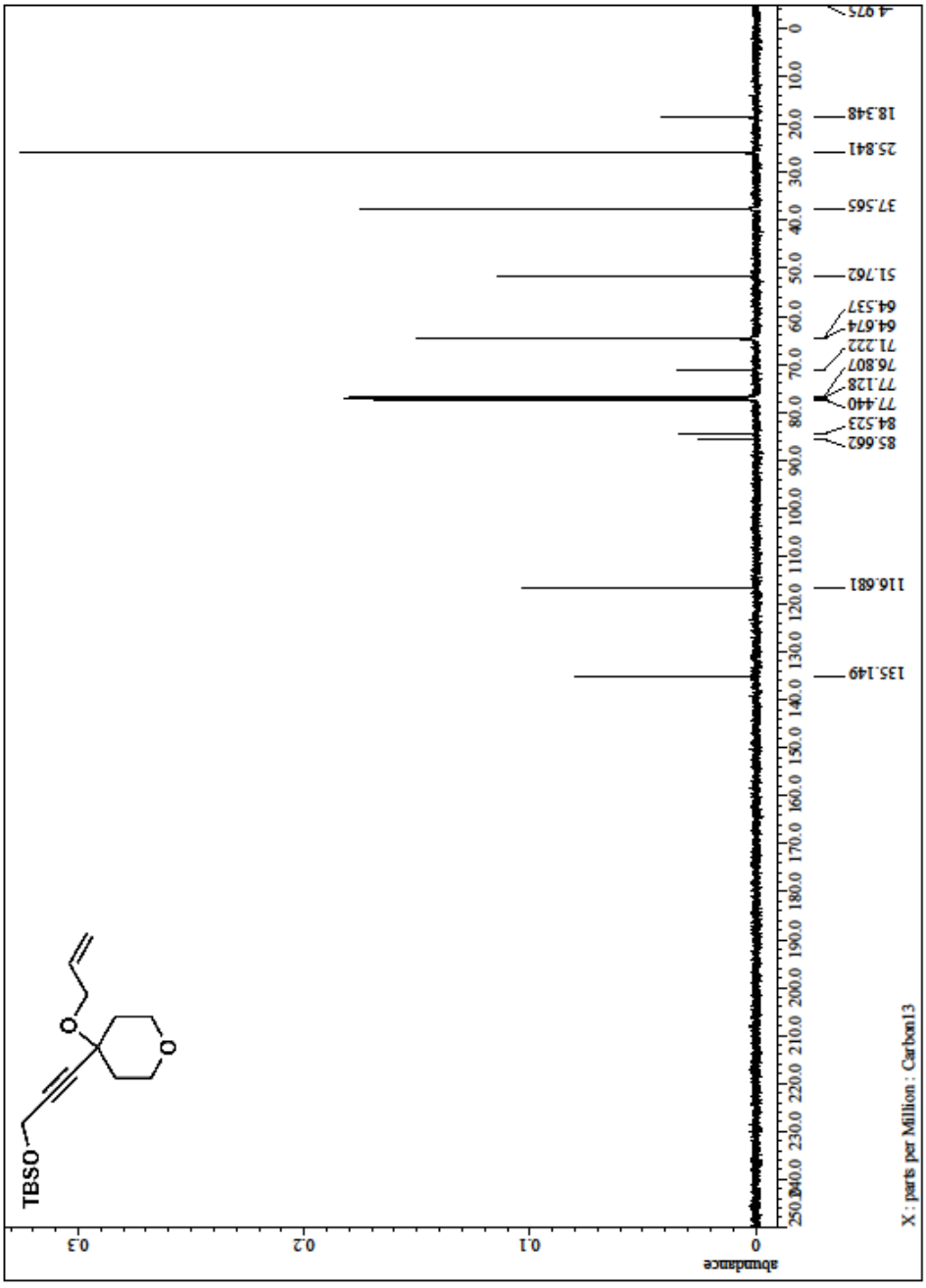

Figure A.3.53. ^{13}C NMR for compound **225**

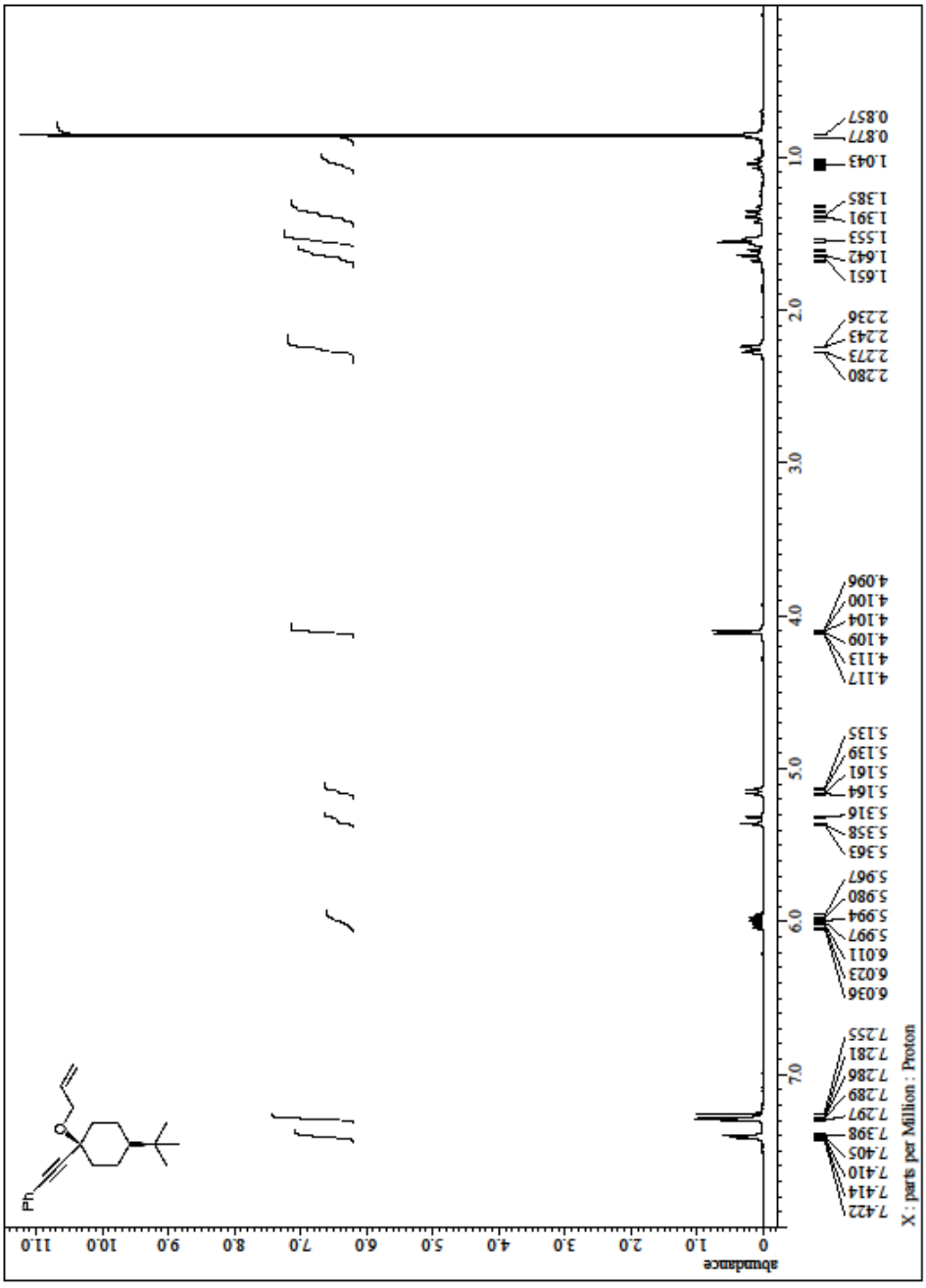

Figure A.3.54. ^{1}H NMR for compound **226A**

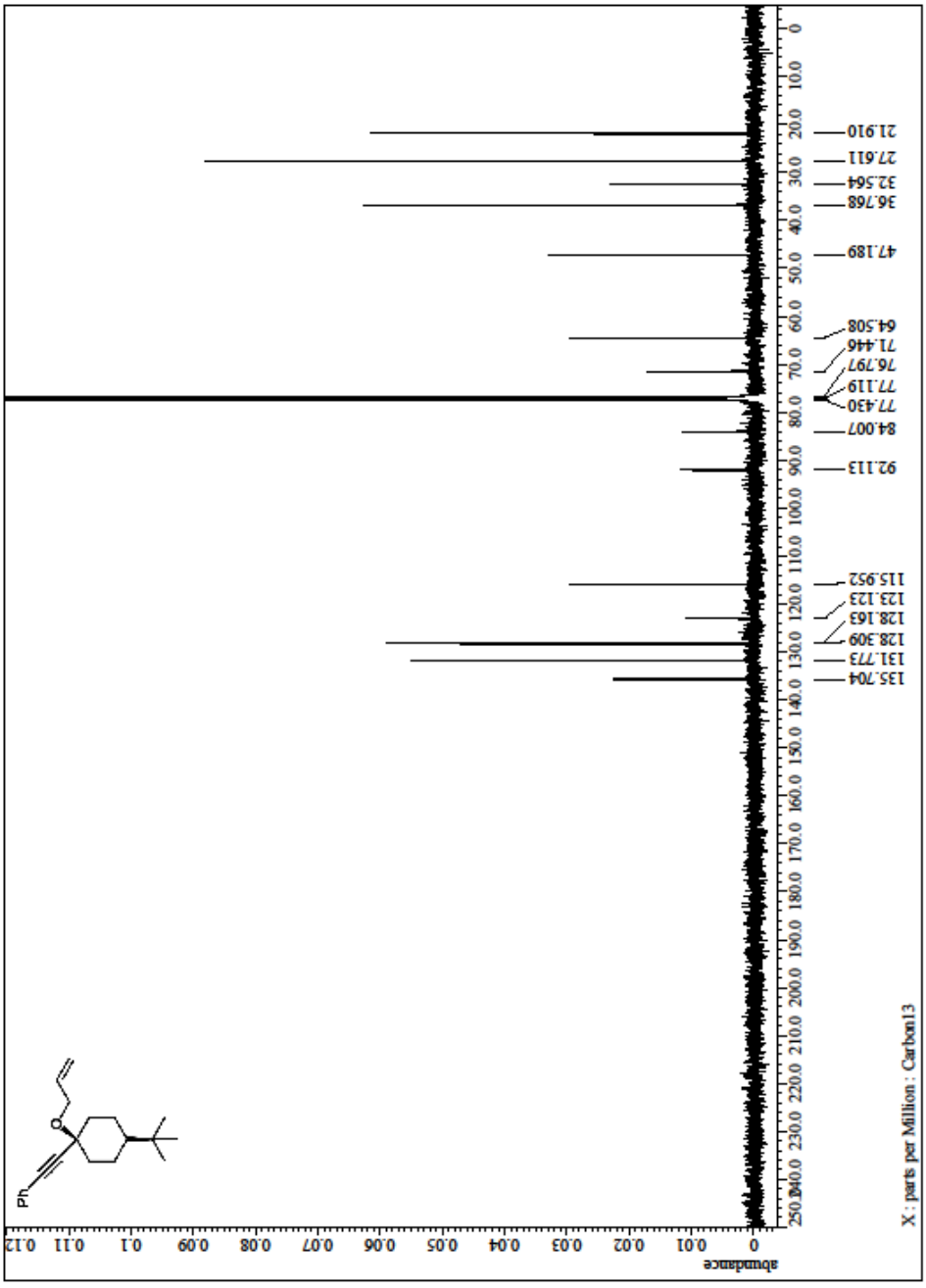

Figure A.3.55. ^{13}C NMR for compound **226A**

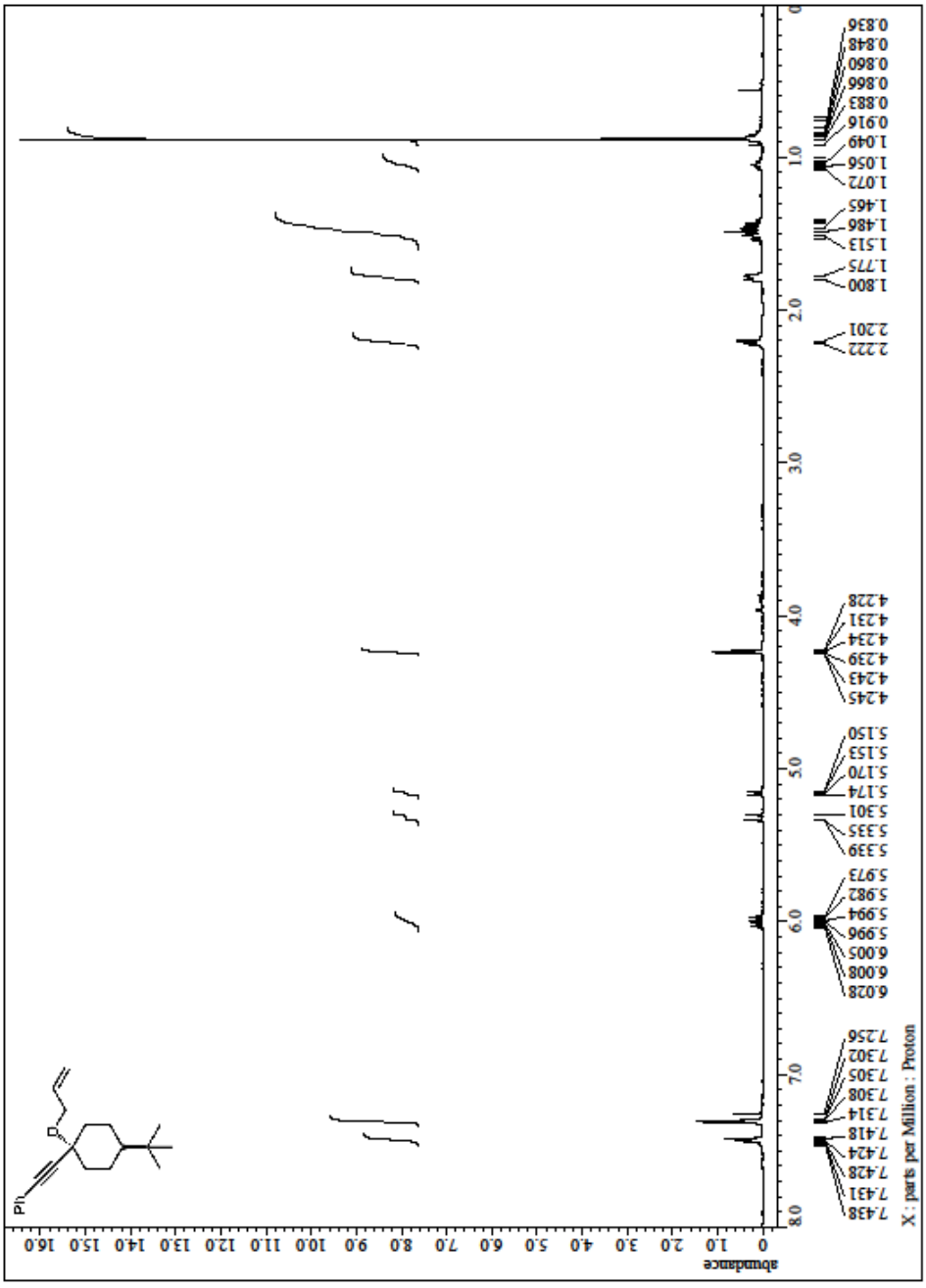

Figure A.3.56a. ^{1}H NMR for compound **226B**

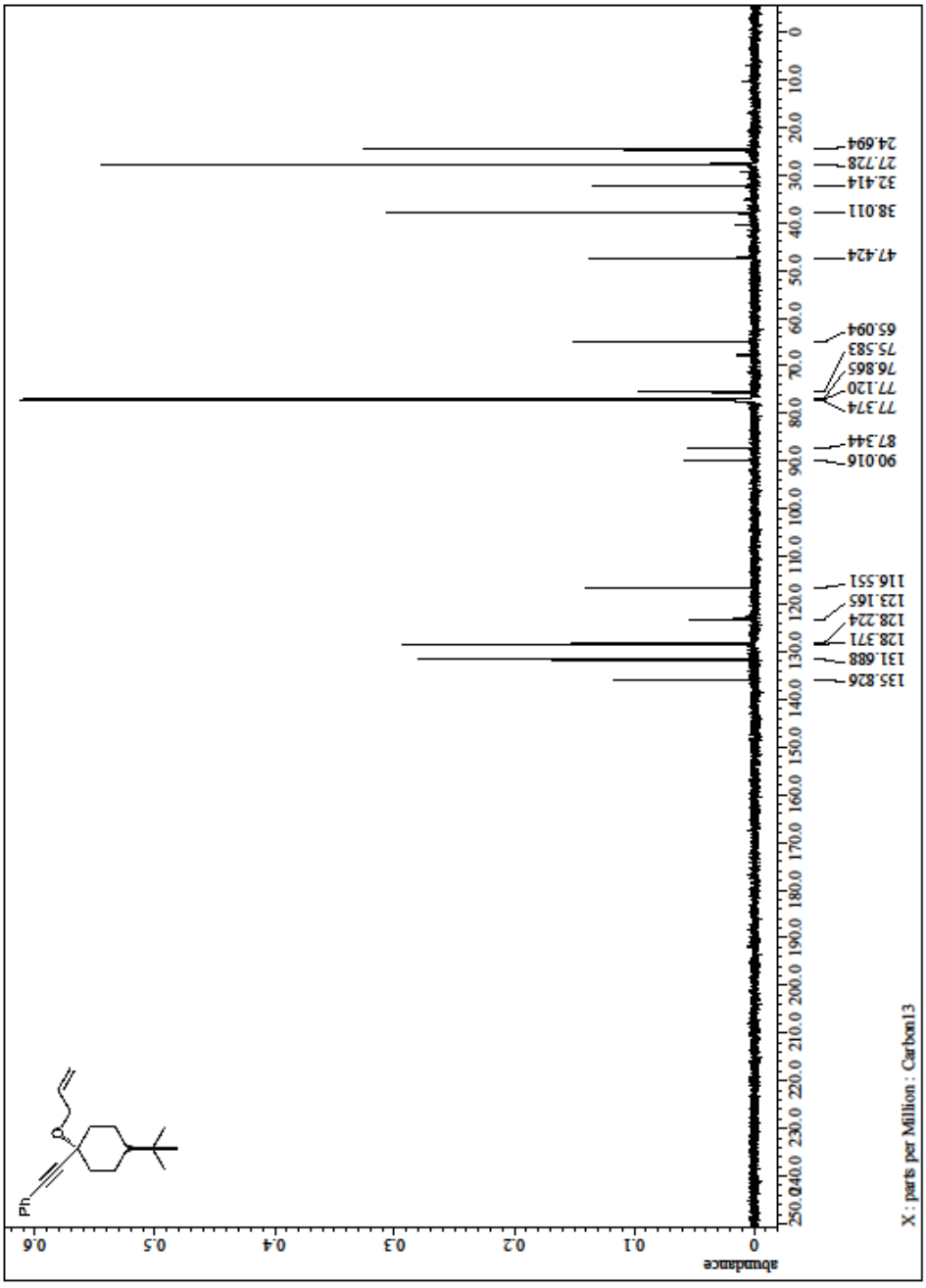

Figure A.3.56b. ^{13}C NMR for compound **226B**

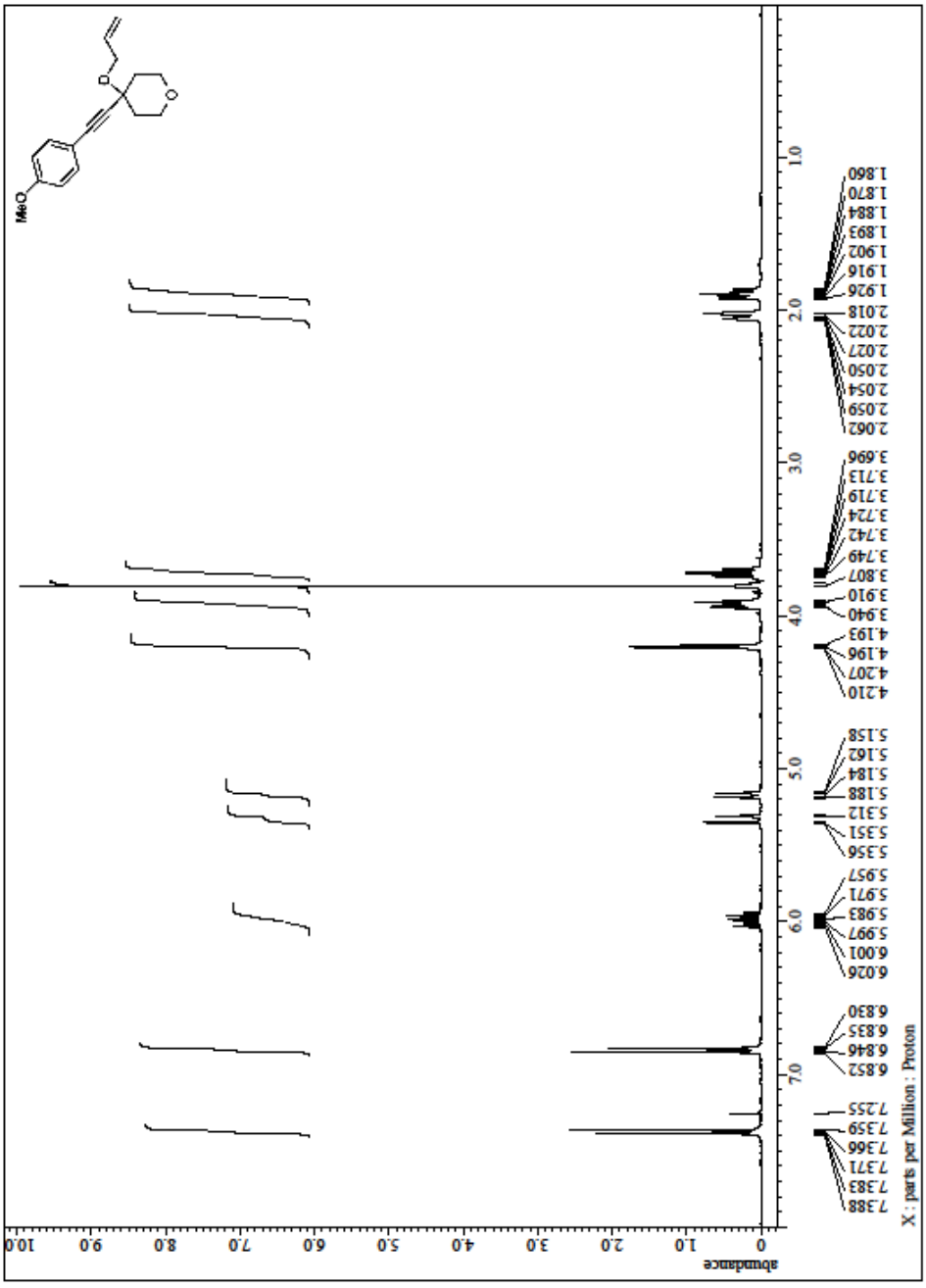

Figure A.3.57a. ^{1}H NMR for compound **227**

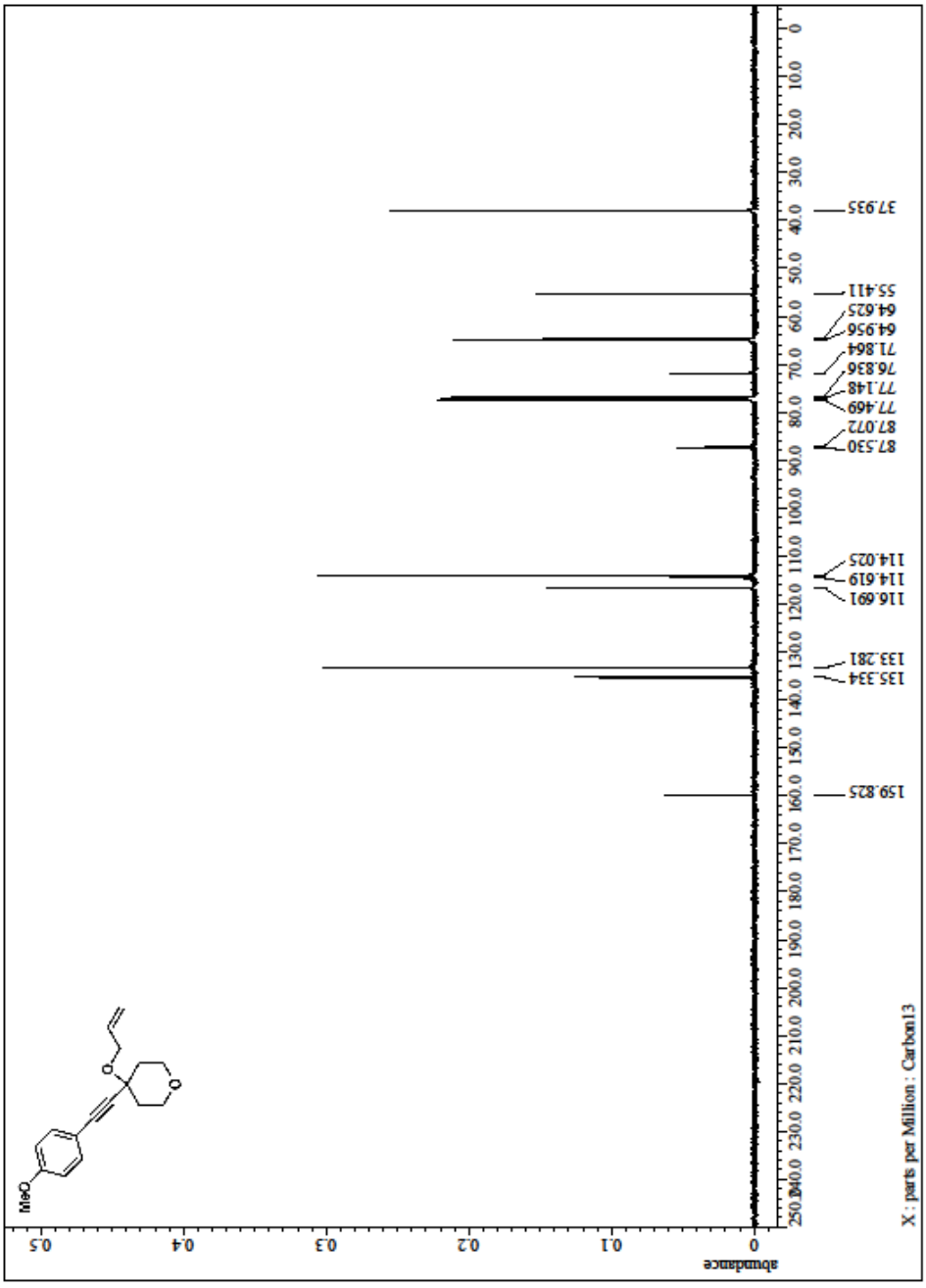

Figure A.3.57b. ^{13}C NMR for compound **227**

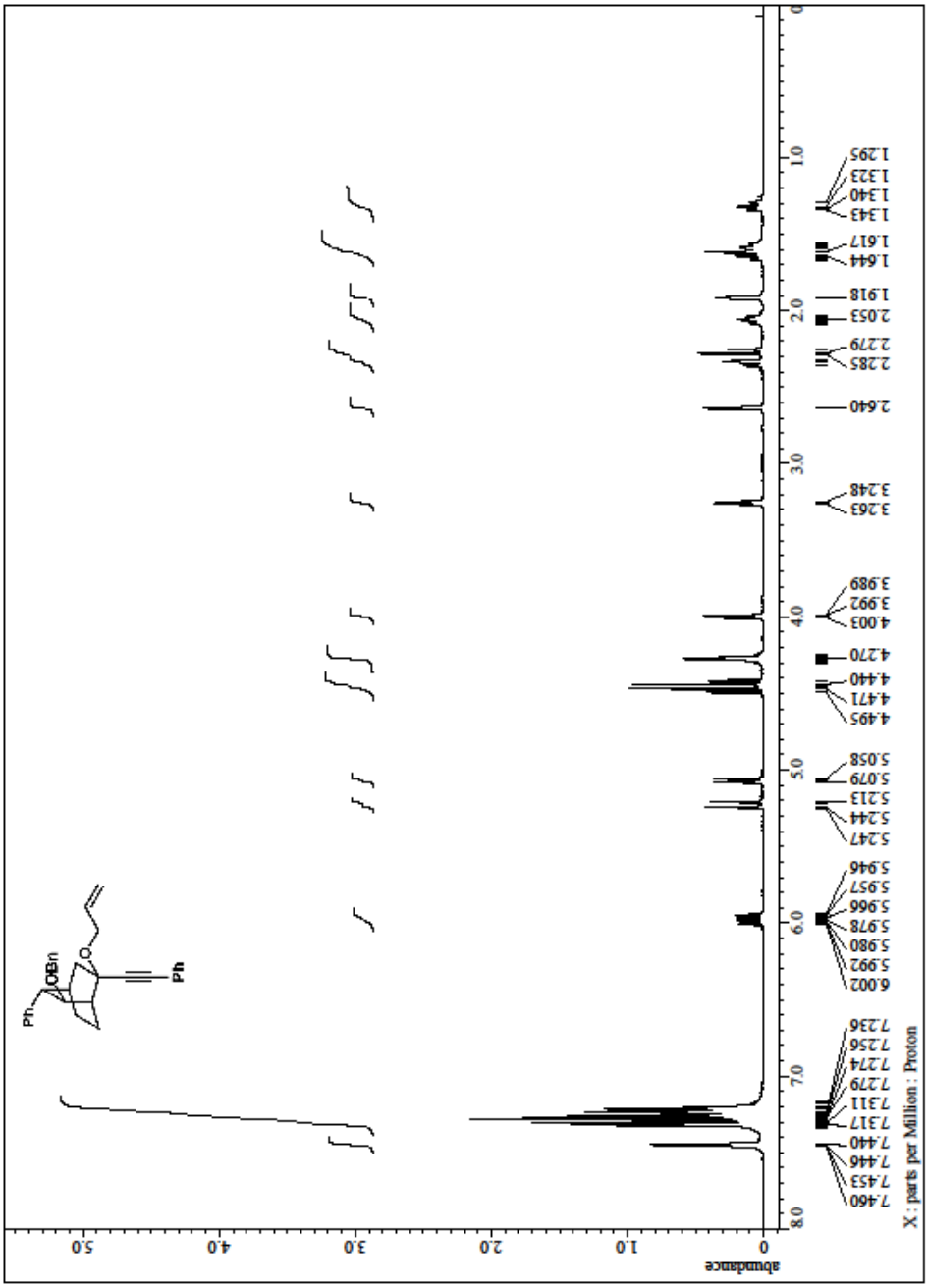

Figure A.3.58. ^{1}H NMR for compound **228**

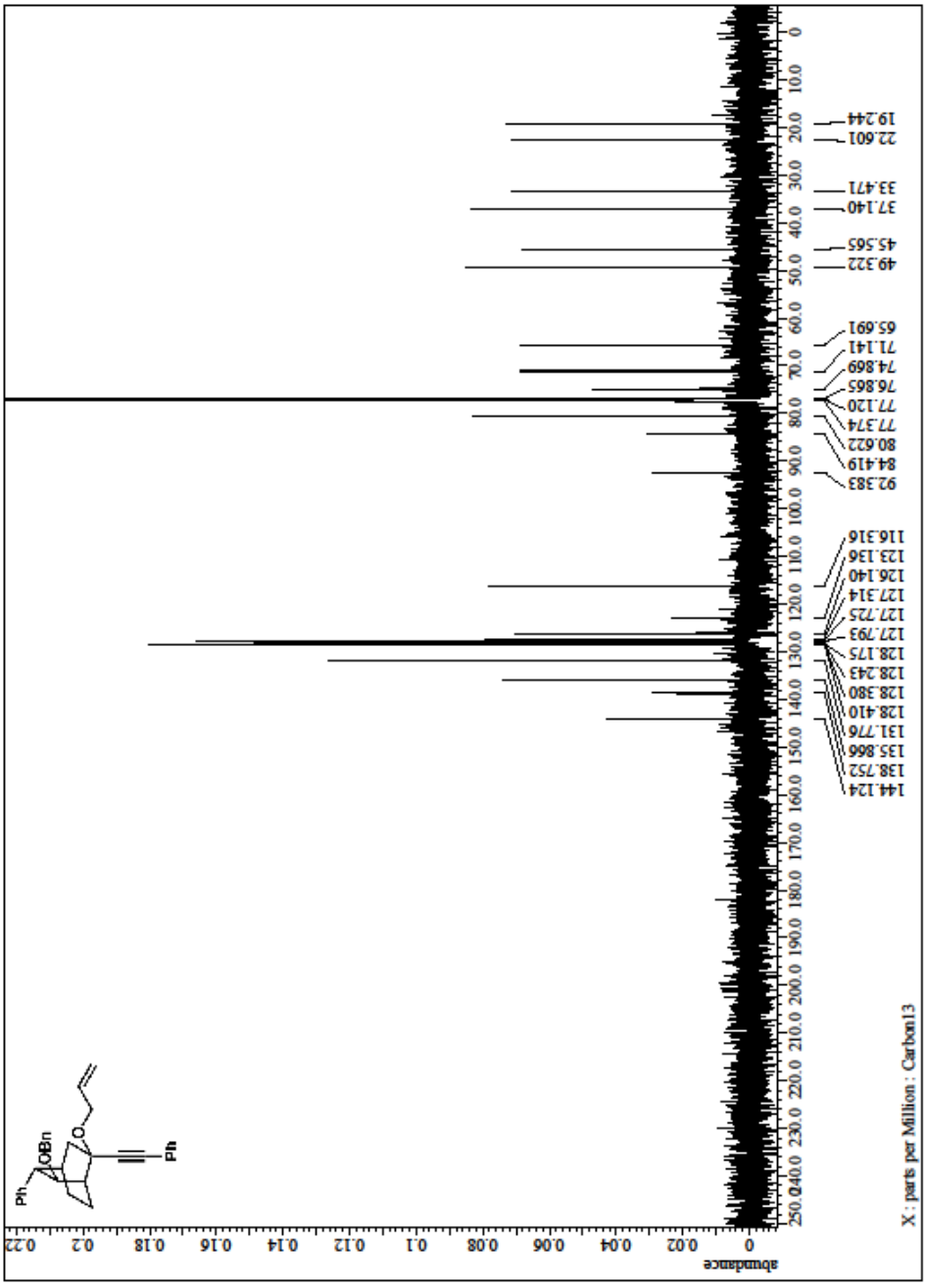

Figure A.3.59. ^{1}H NMR for compound **228**

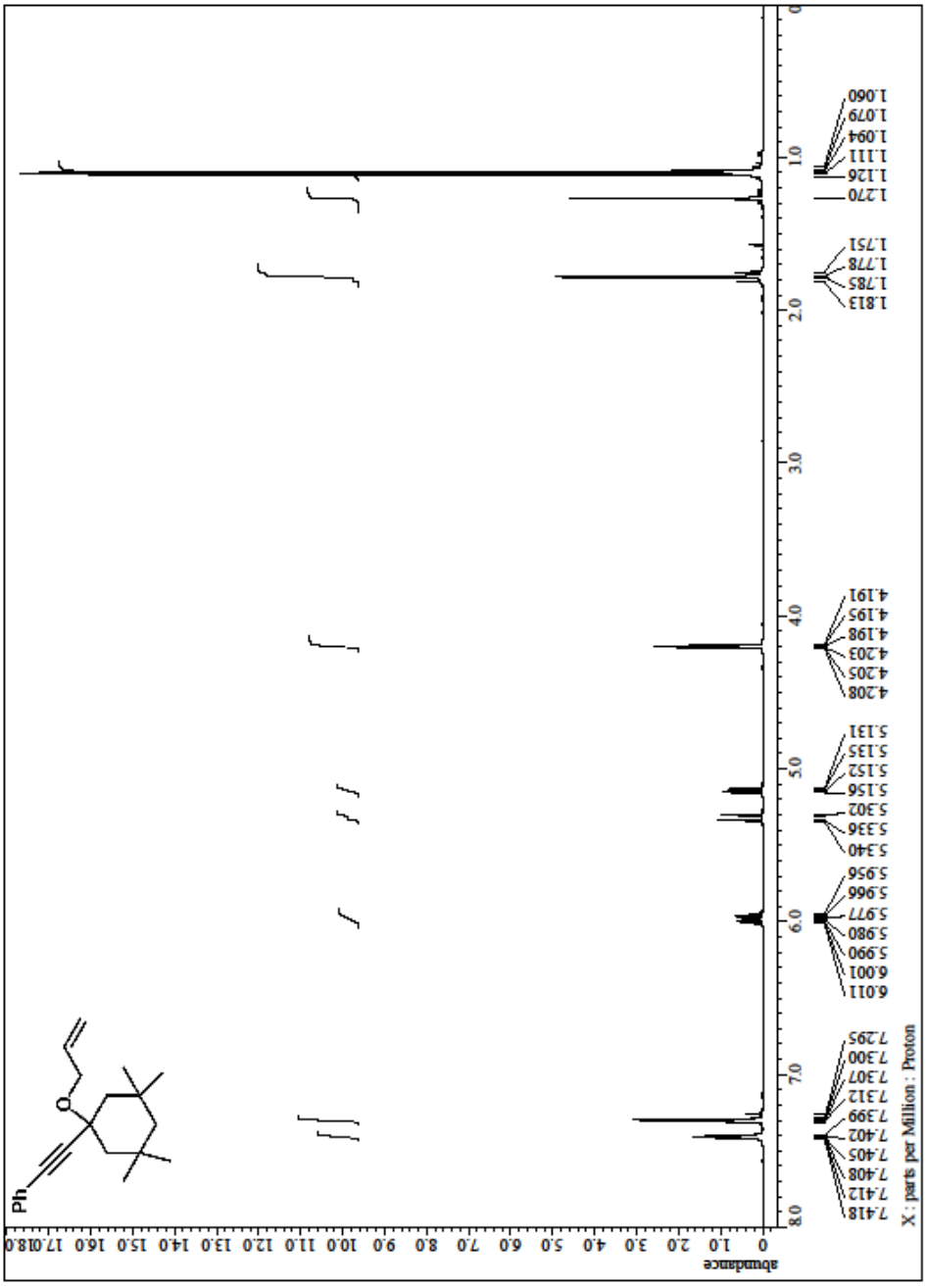

Figure A.3.60. ^{1}H NMR for compound **SI4-229**

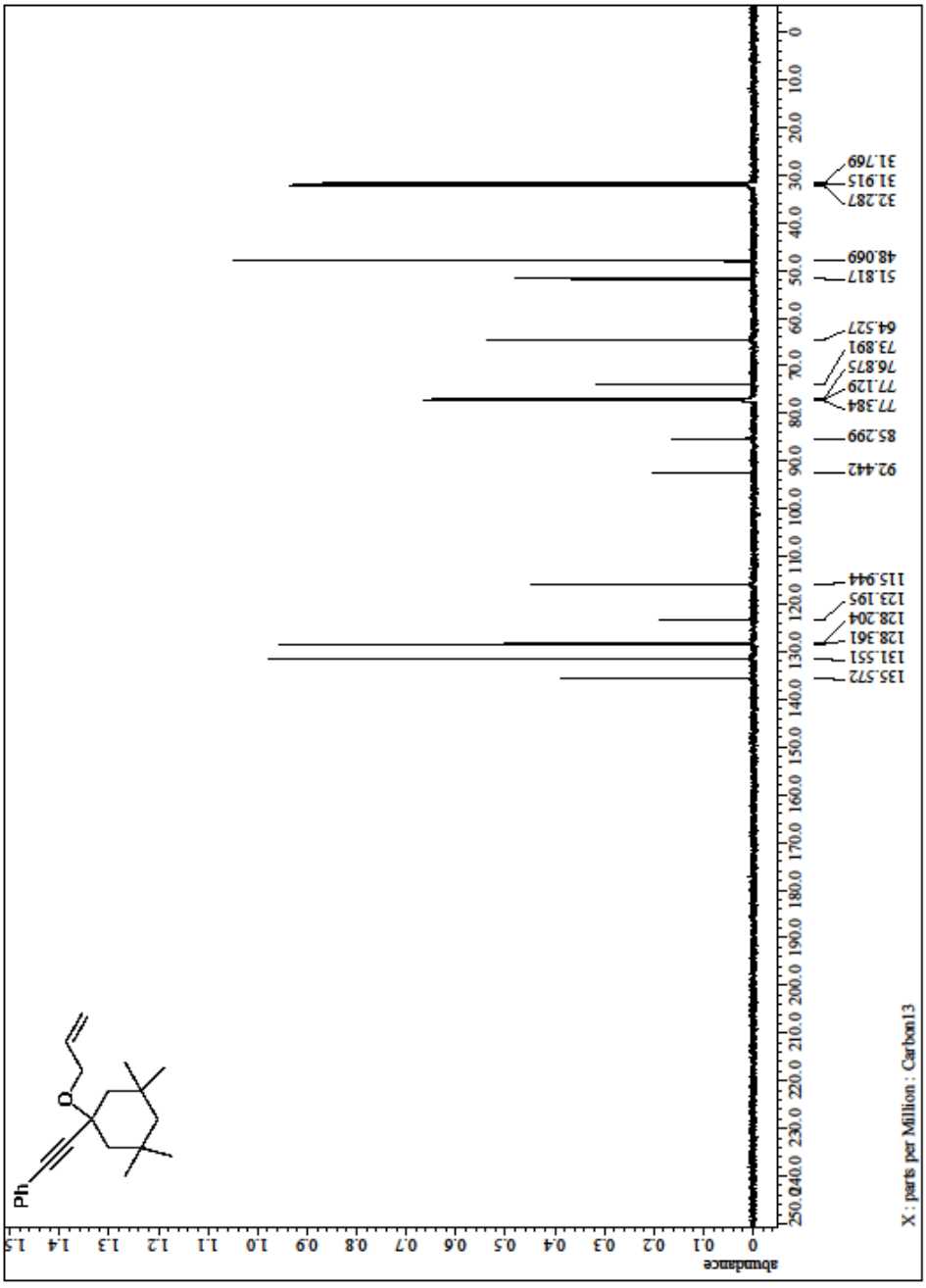

Figure A.3.61. ^{13}C NMR for compound **SI4-229**

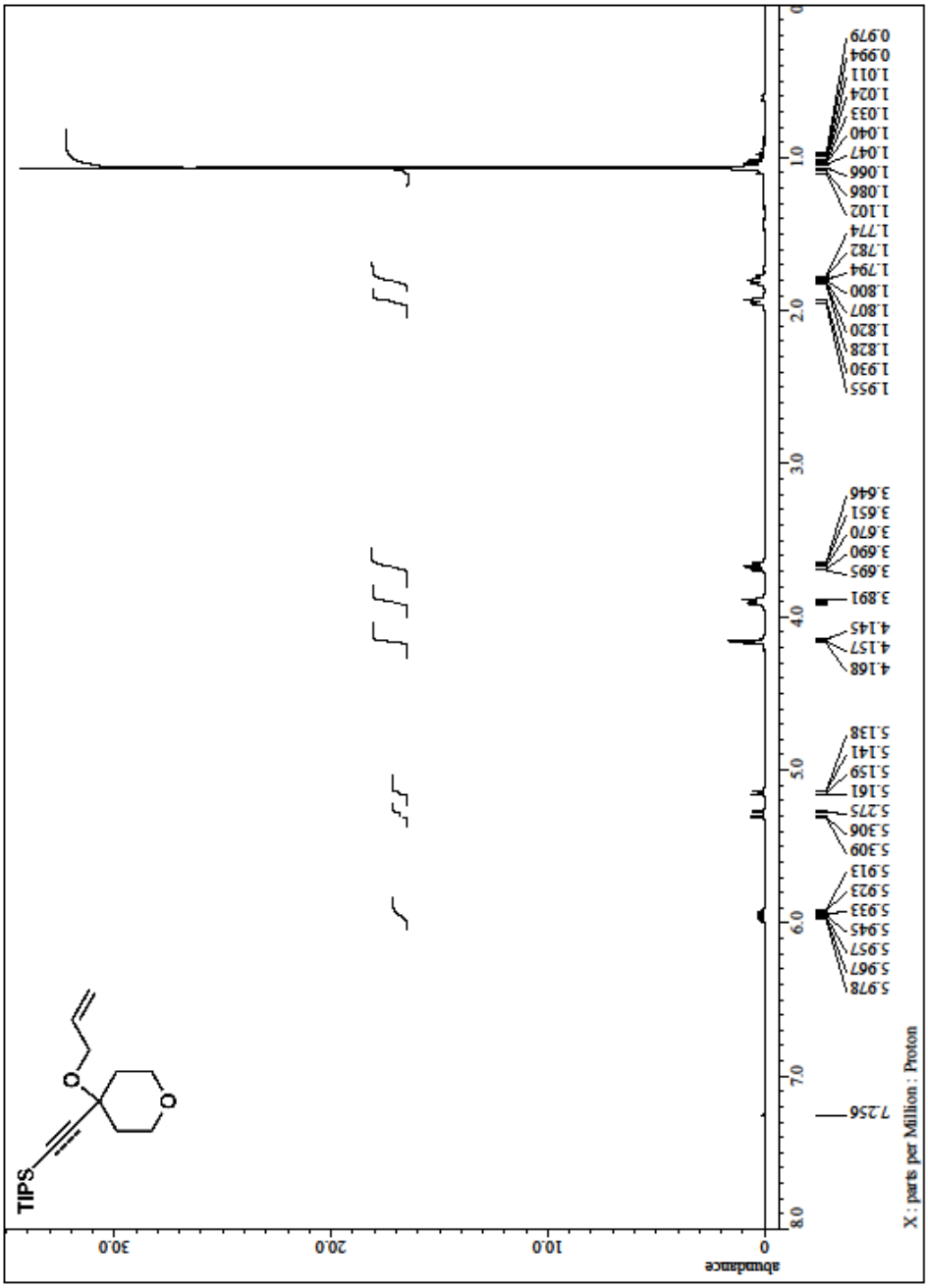

Figure A.3.62. ^{1}H NMR for compound **230**

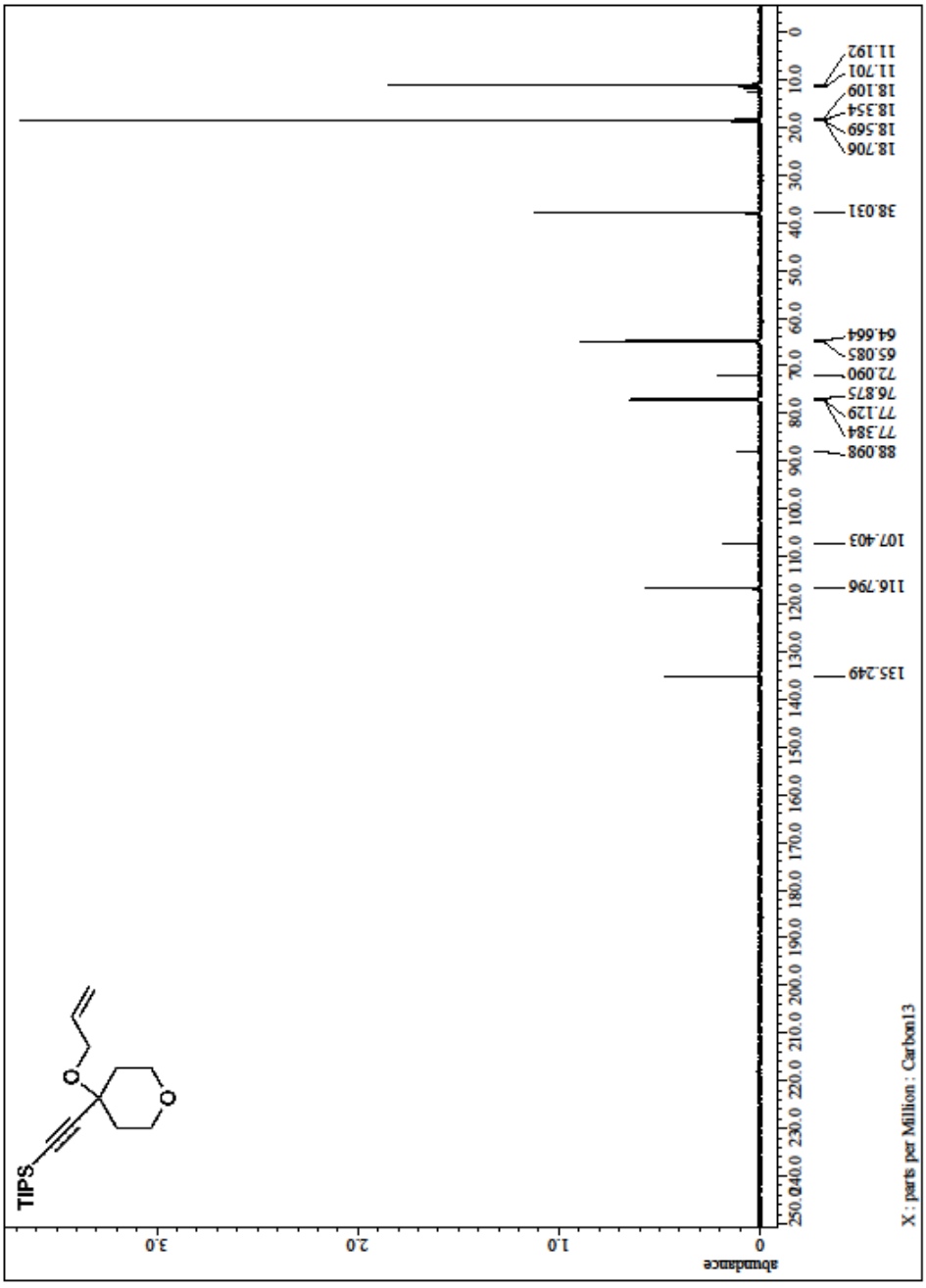

Figure A.3.63. ^{13}C NMR for compound **230**

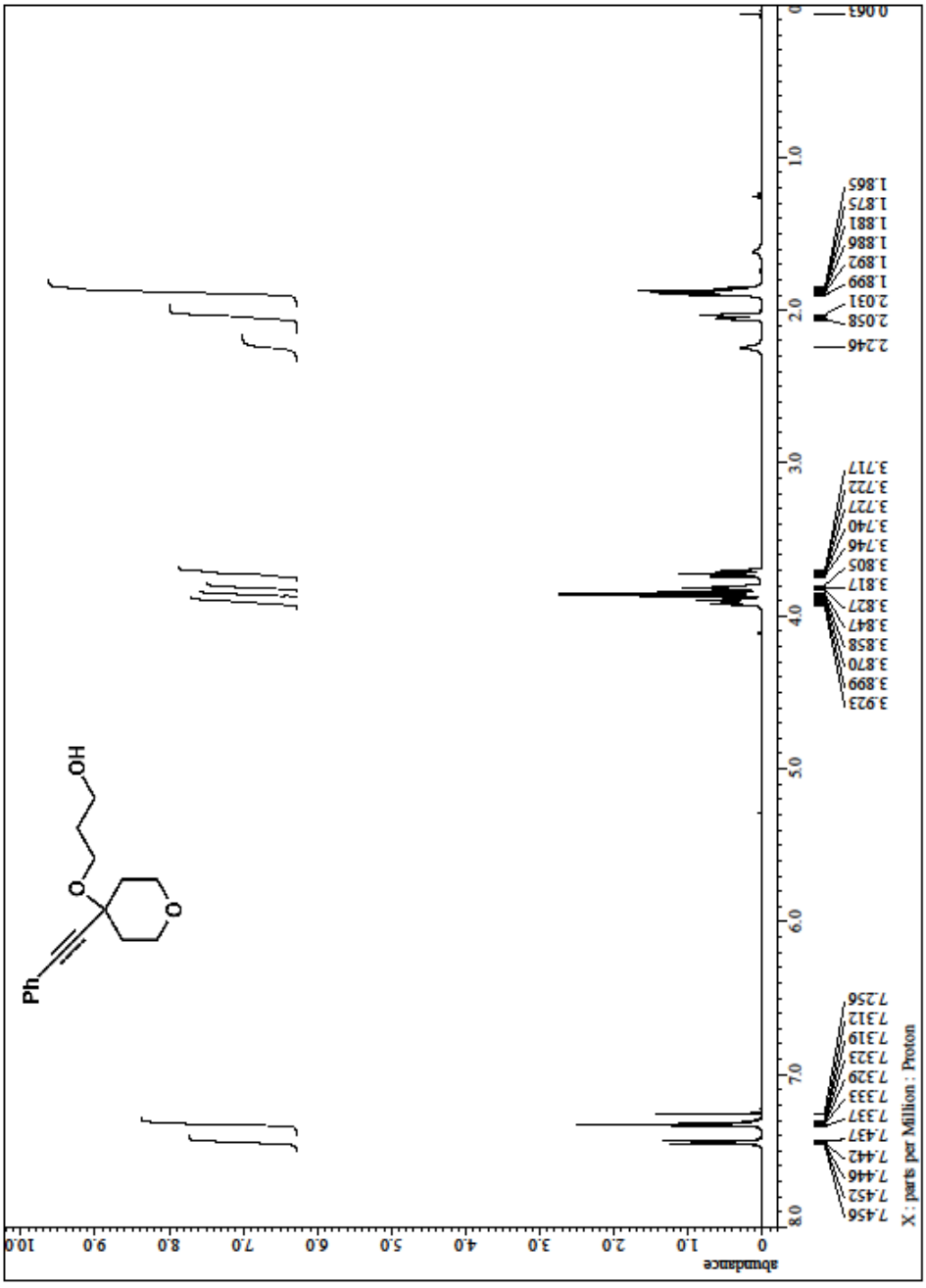

Figure A.3.64. ^{1}H NMR for compound **231**

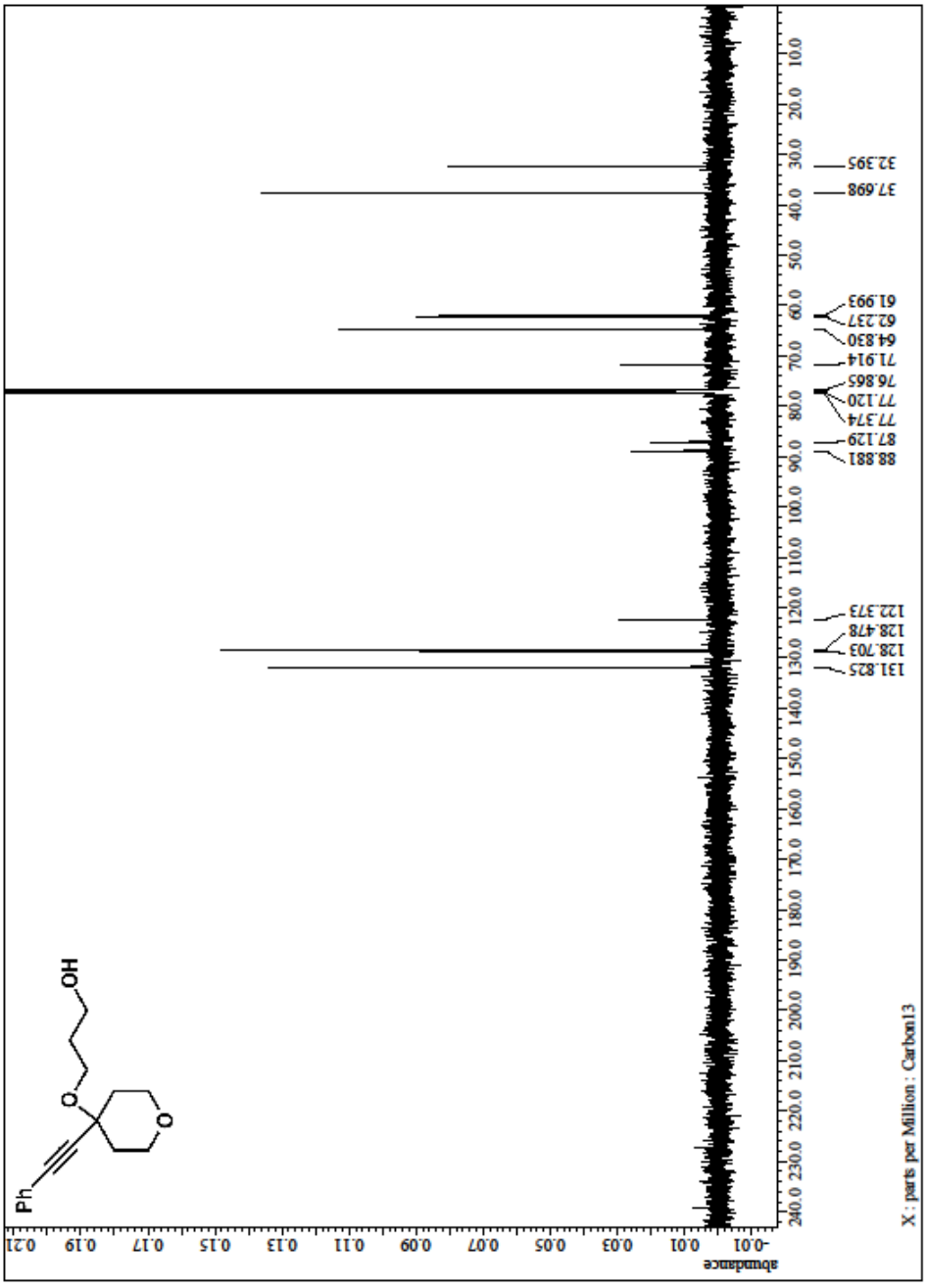

Figure A.3.65. ^{13}C NMR for compound **231**

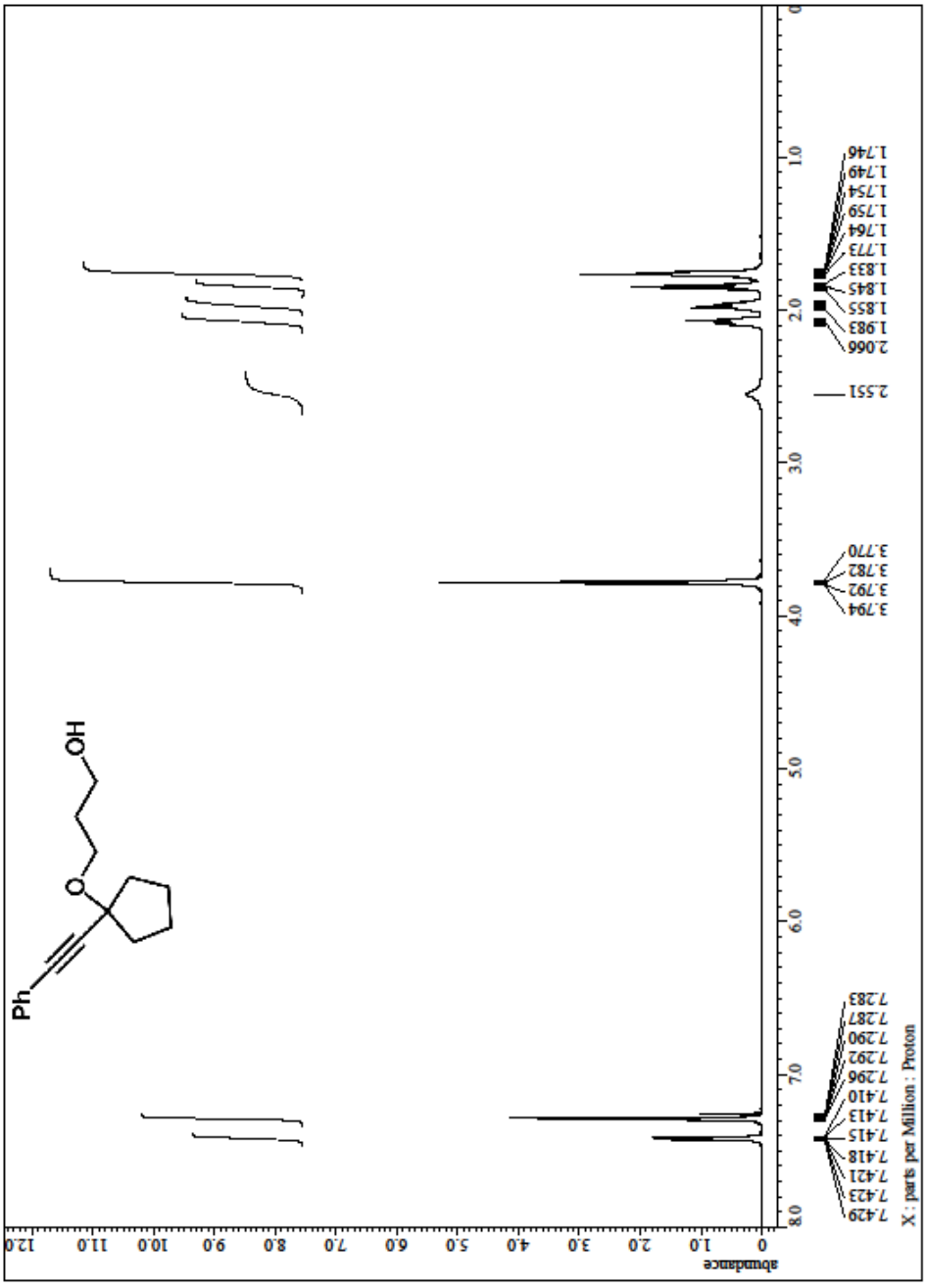

Figure A.3.66. ^{1}H NMR for compound **232**

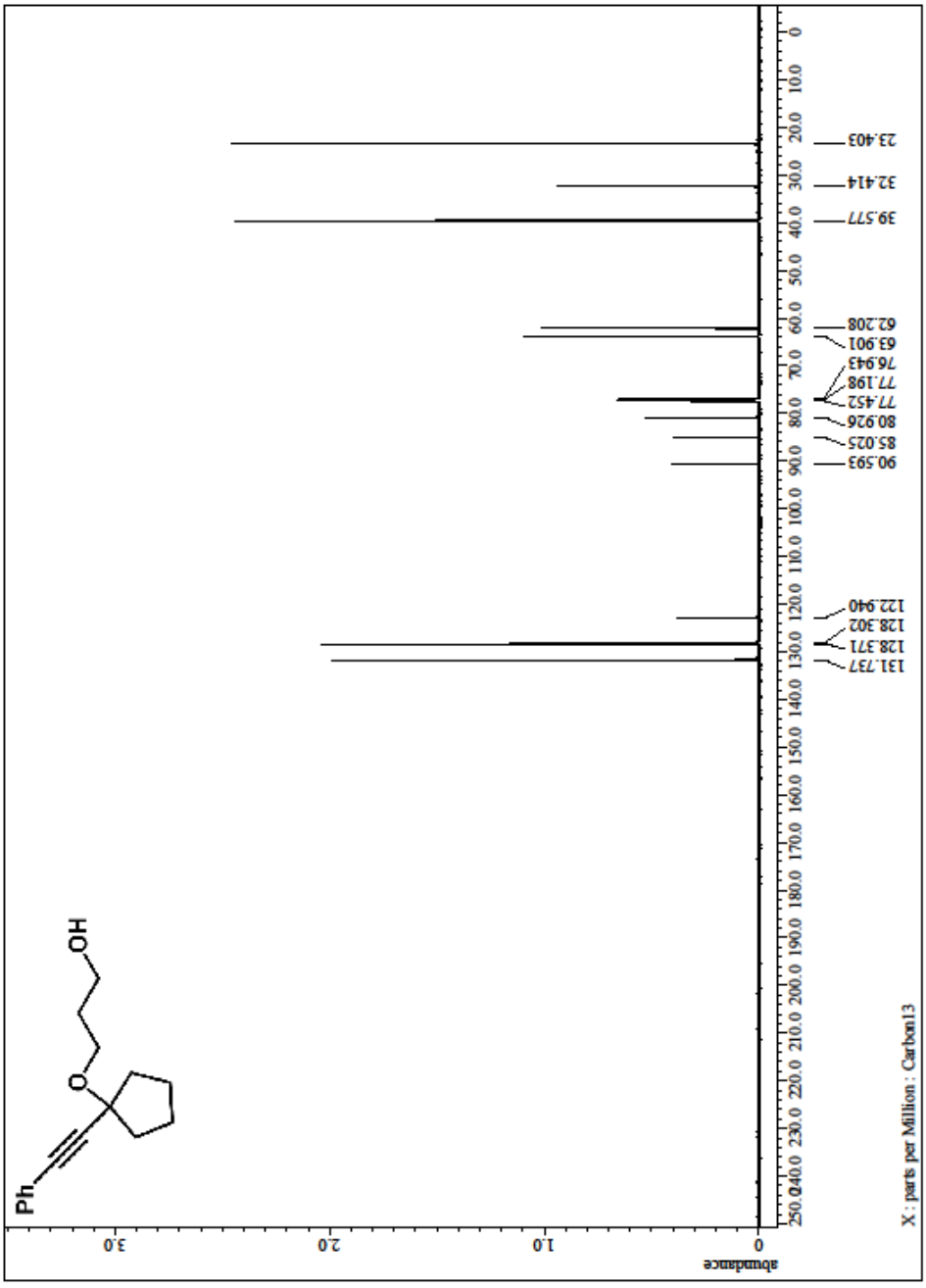

Figure A.3.67. ^{13}C NMR for compound **232**

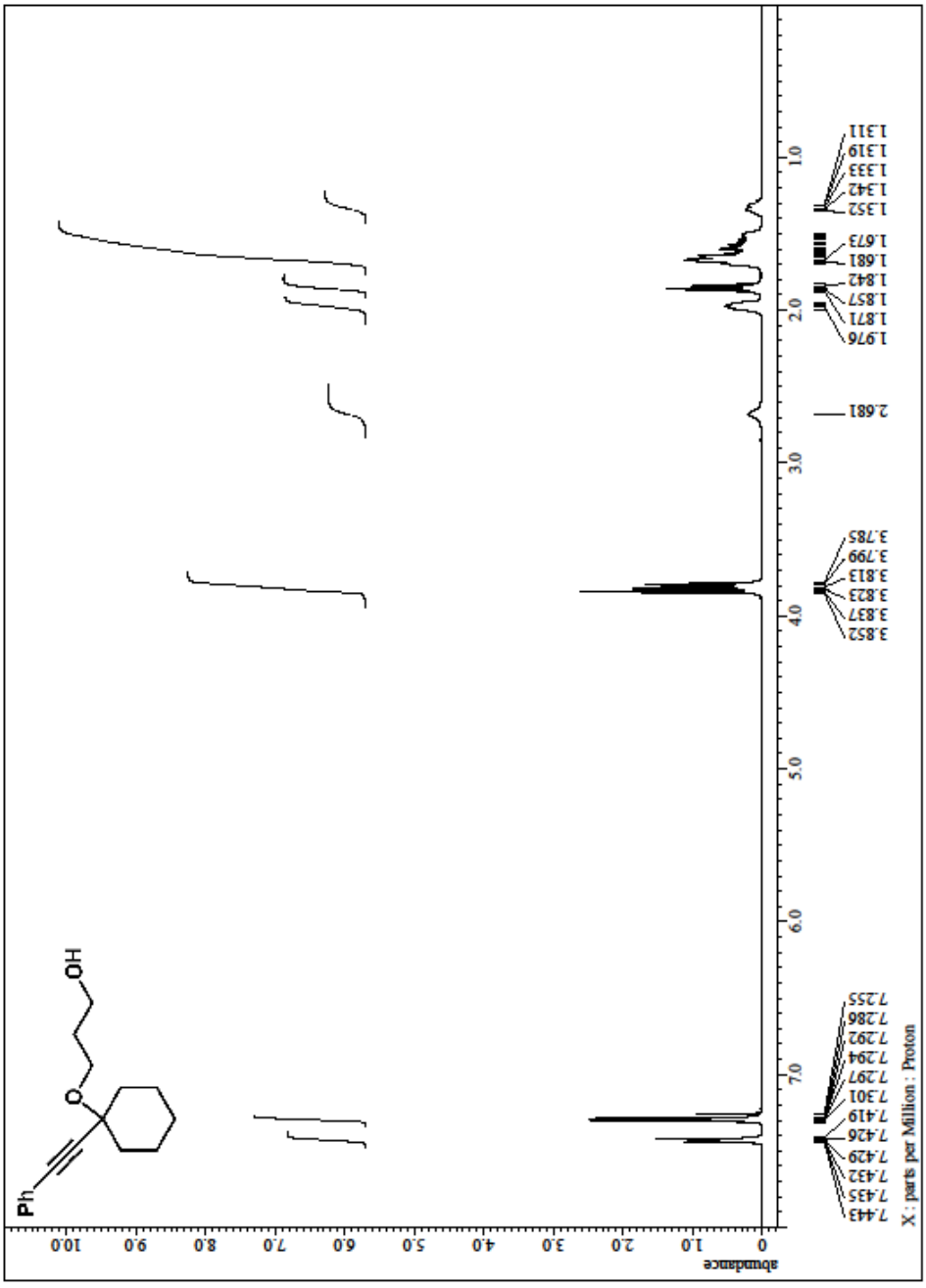

Figure A.3.68. ^{1}H NMR for compound **233**

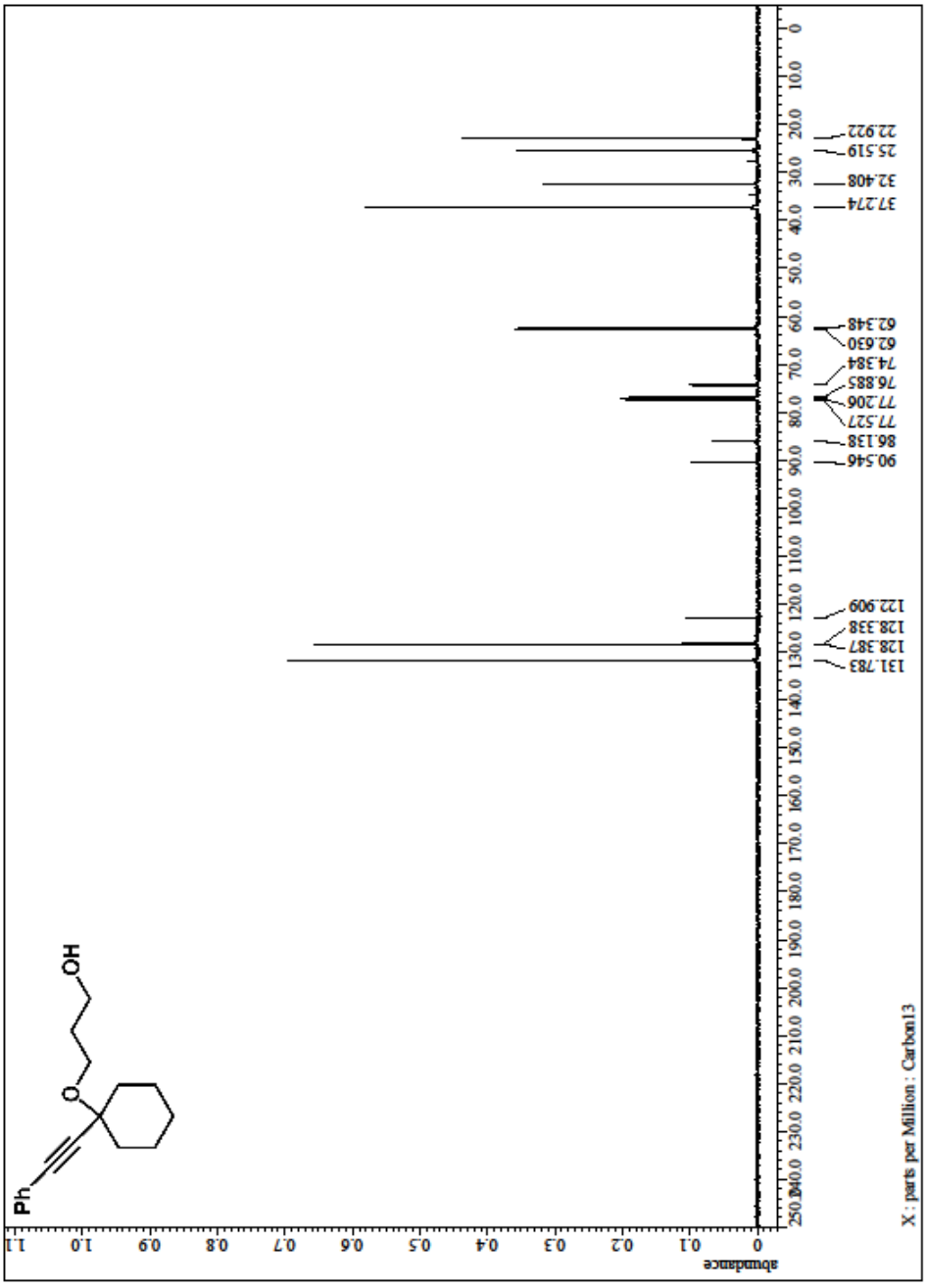

Figure A.3.69. ^{13}C NMR for compound **233**

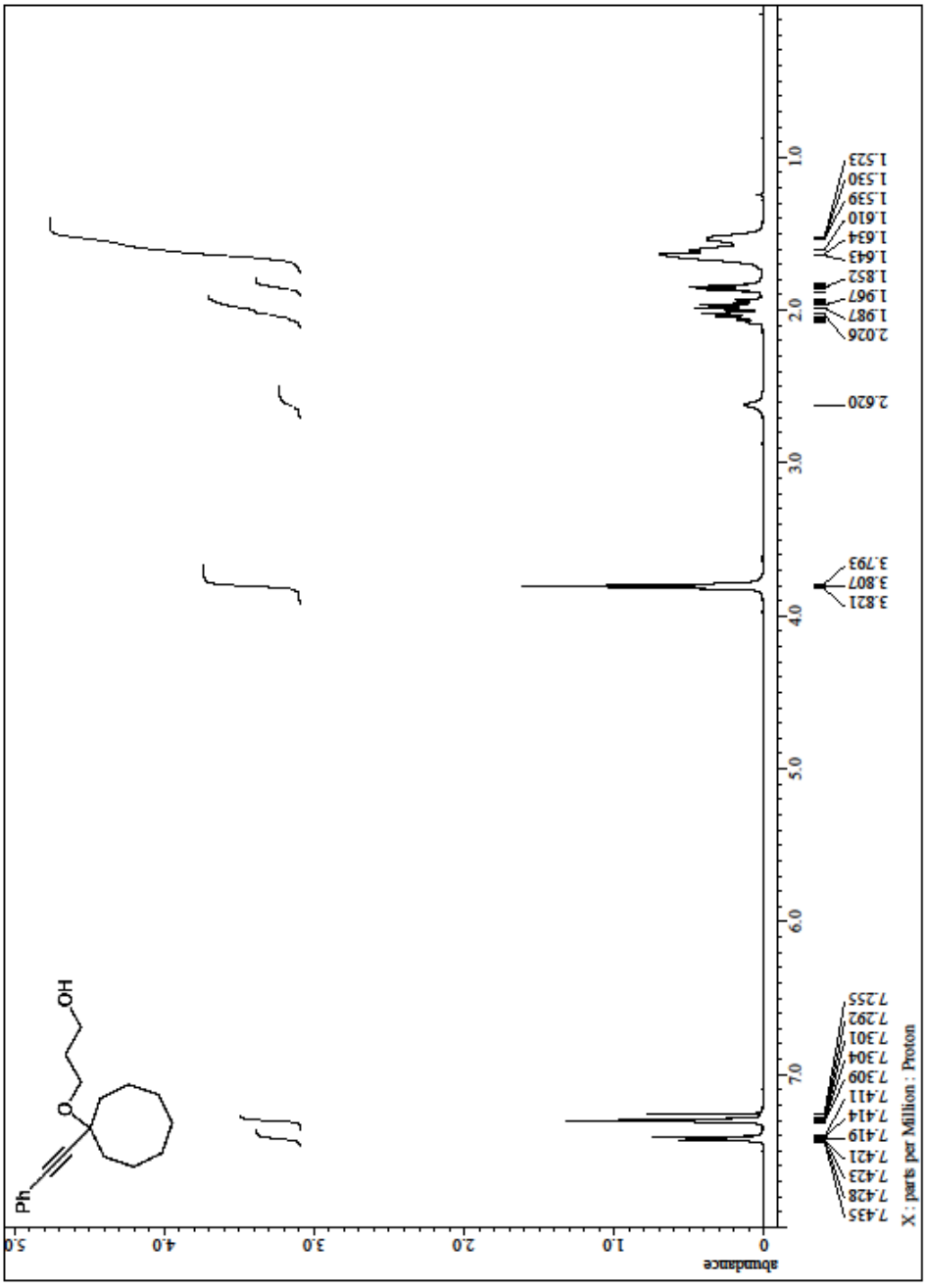

Figure A.3.70. ^{1}H NMR for compound **234**

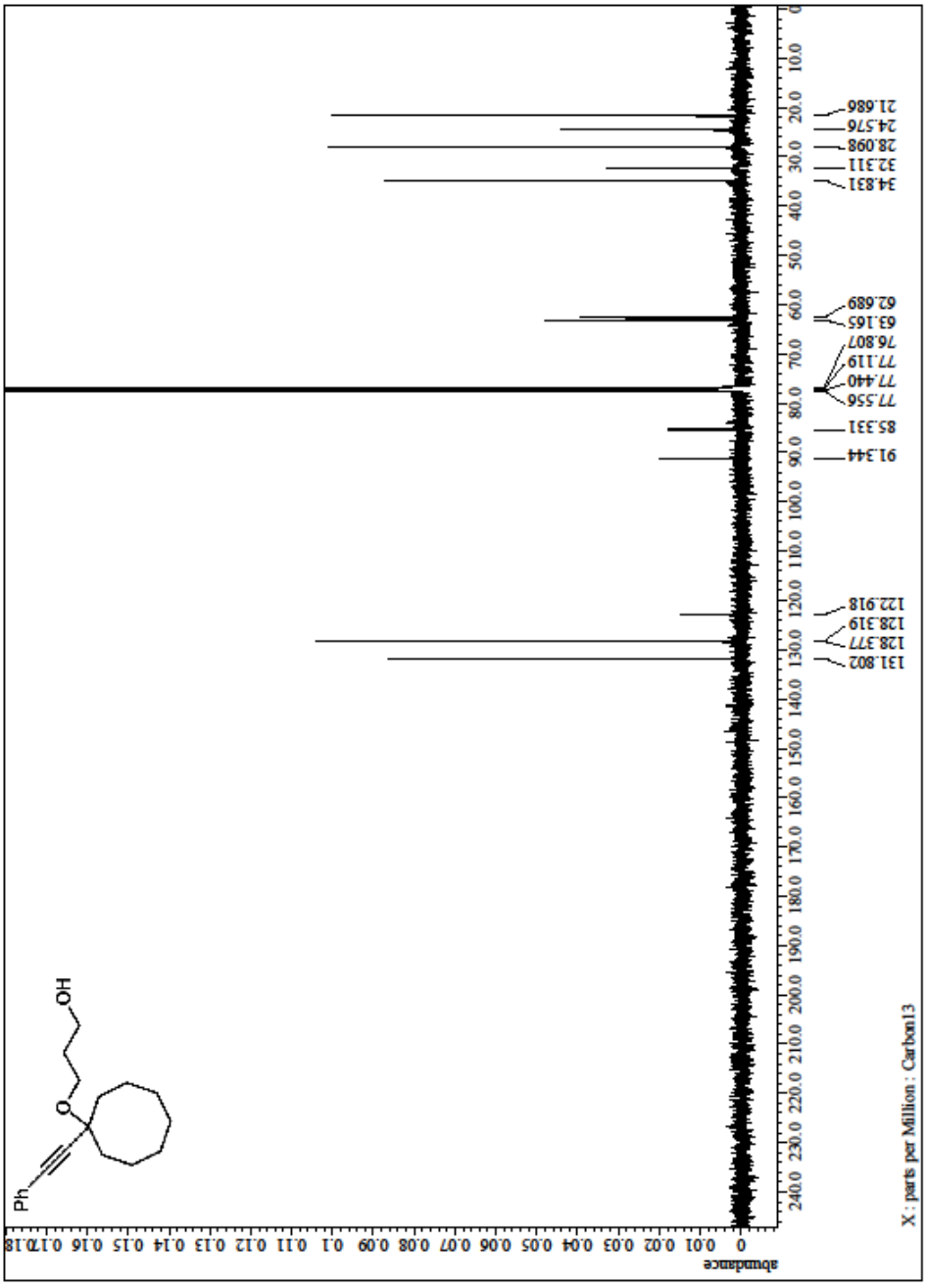

Figure A.3.71. ^{13}C NMR for compound **234**

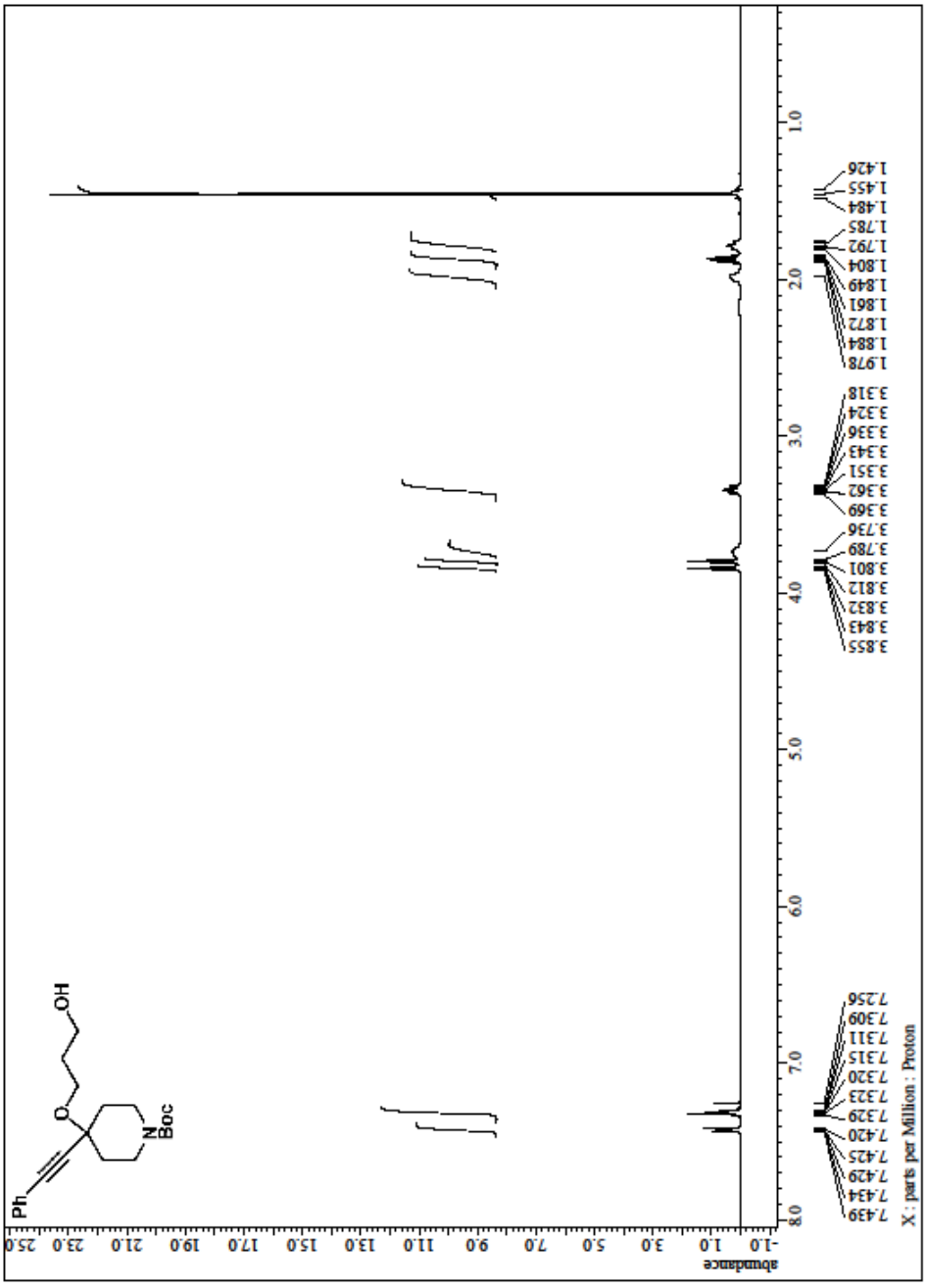

Figure A.3.72. ^{1}H NMR for compound **235**

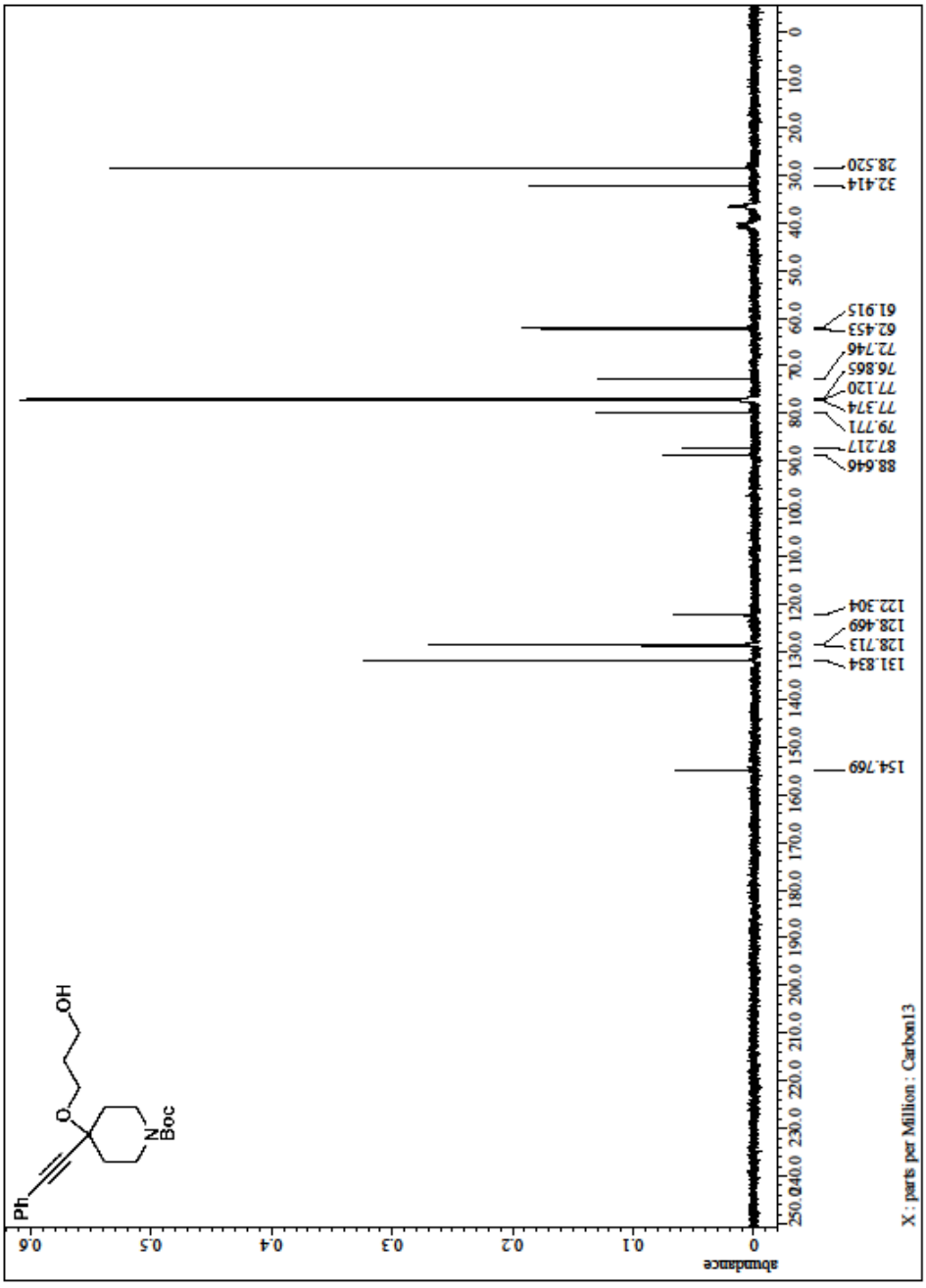

Figure A.3.73. ^{13}C NMR for compound **235**

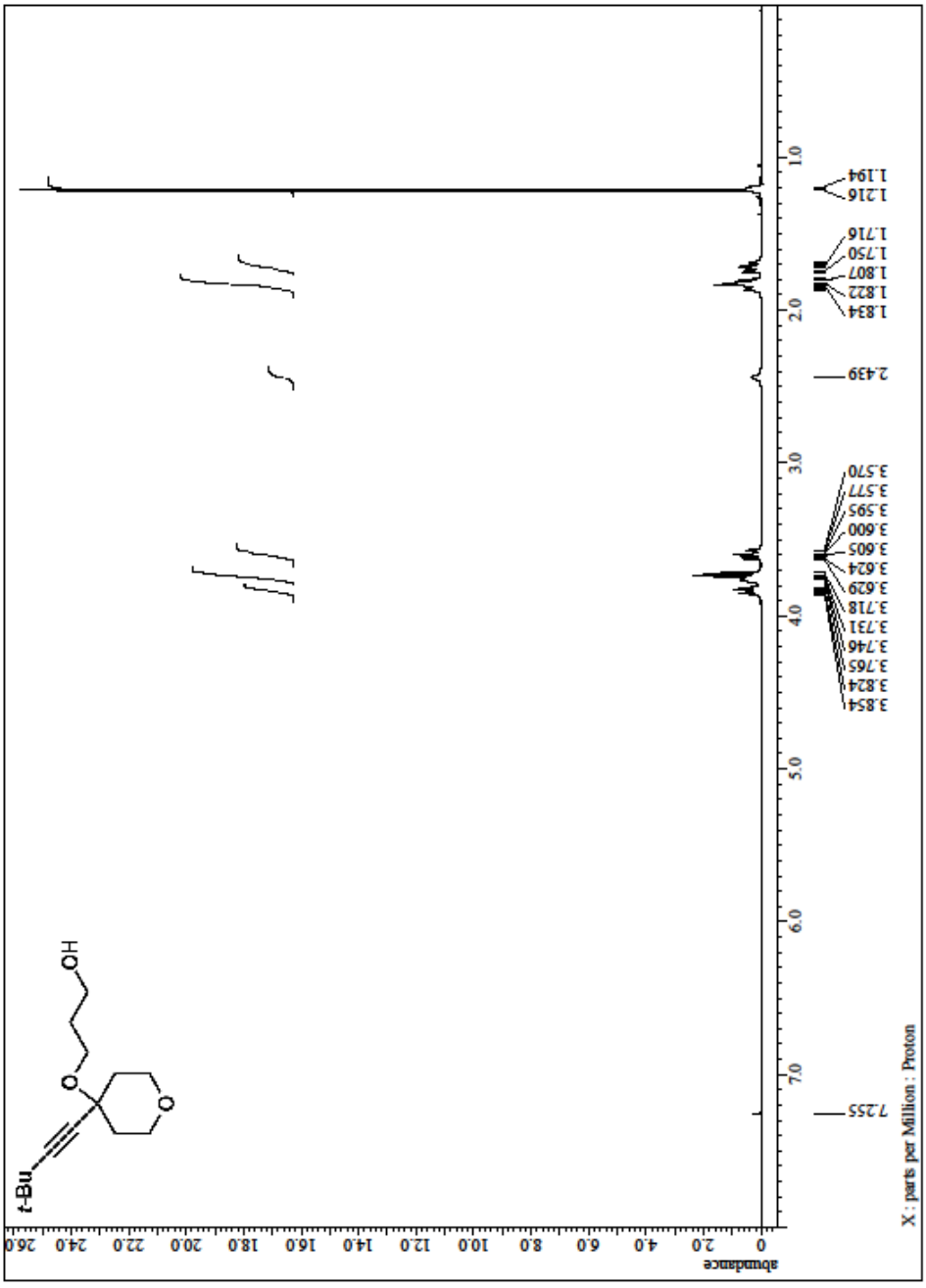

Figure A.3.74. ^{1}H NMR for compound **236**

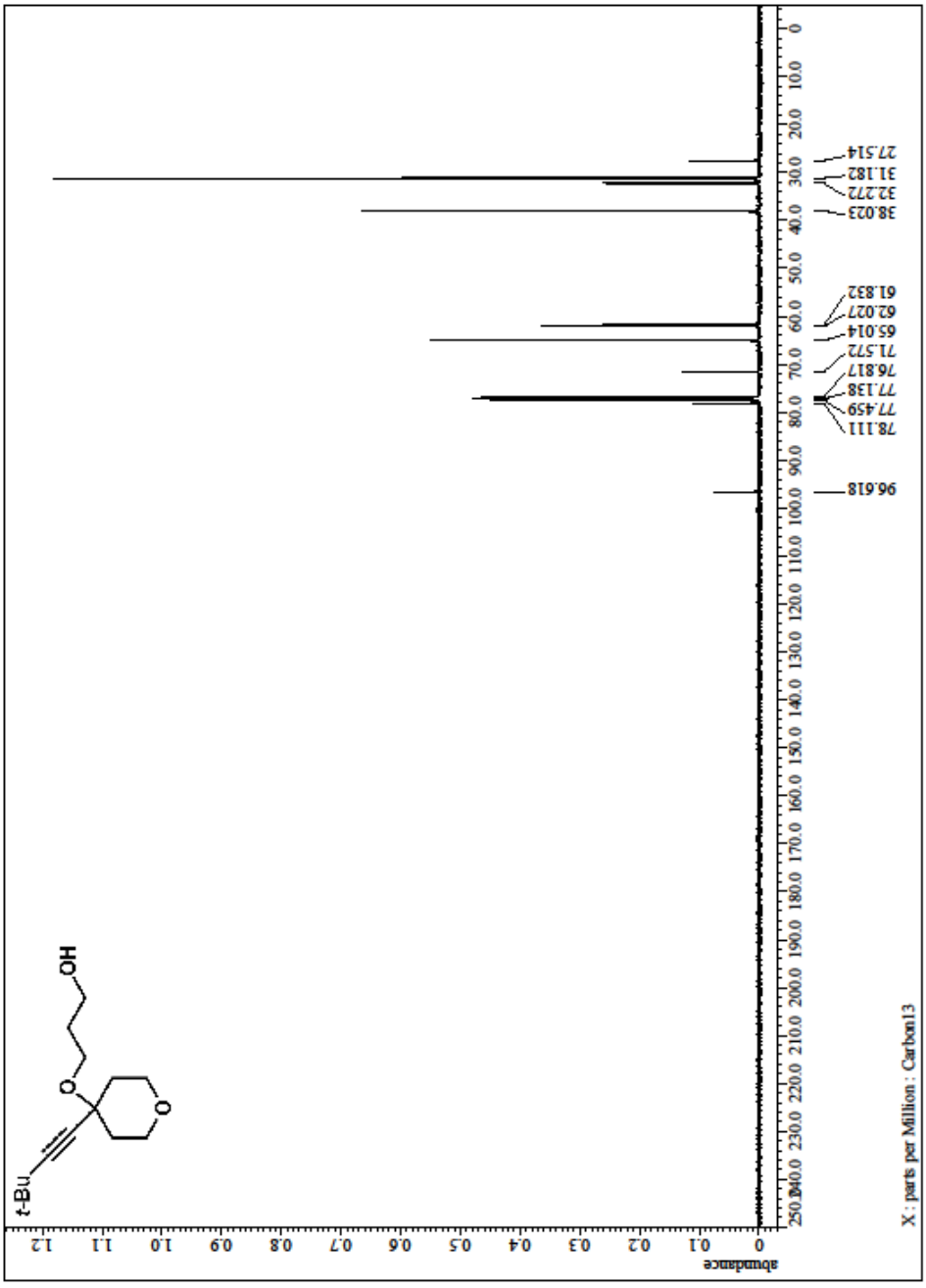

Figure A.3.75. ^{13}C NMR for compound **236**

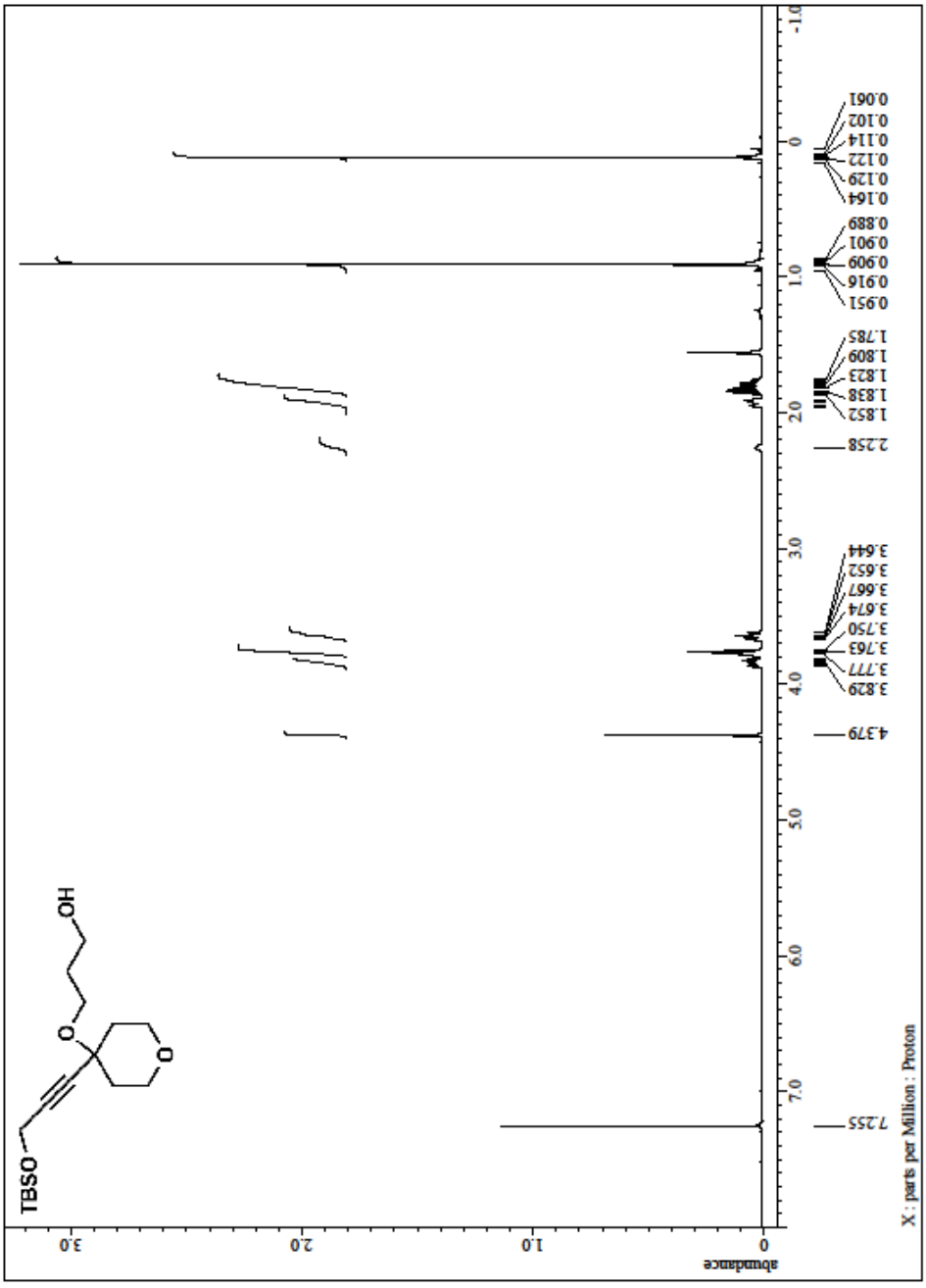

Figure A.3.76. ^{1}H NMR for compound **237**

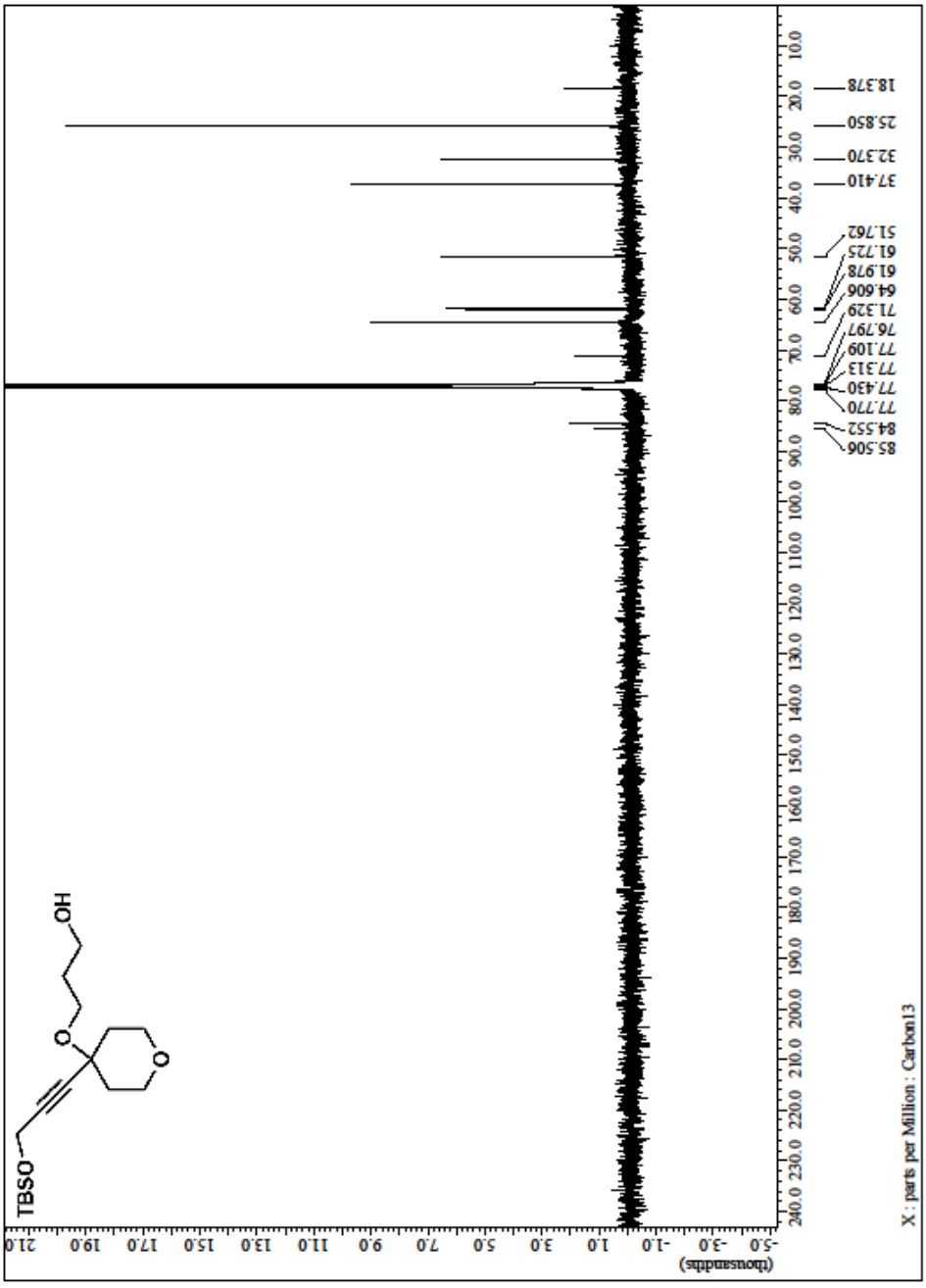

Figure A.3.77. ^{13}C NMR for compound **237**

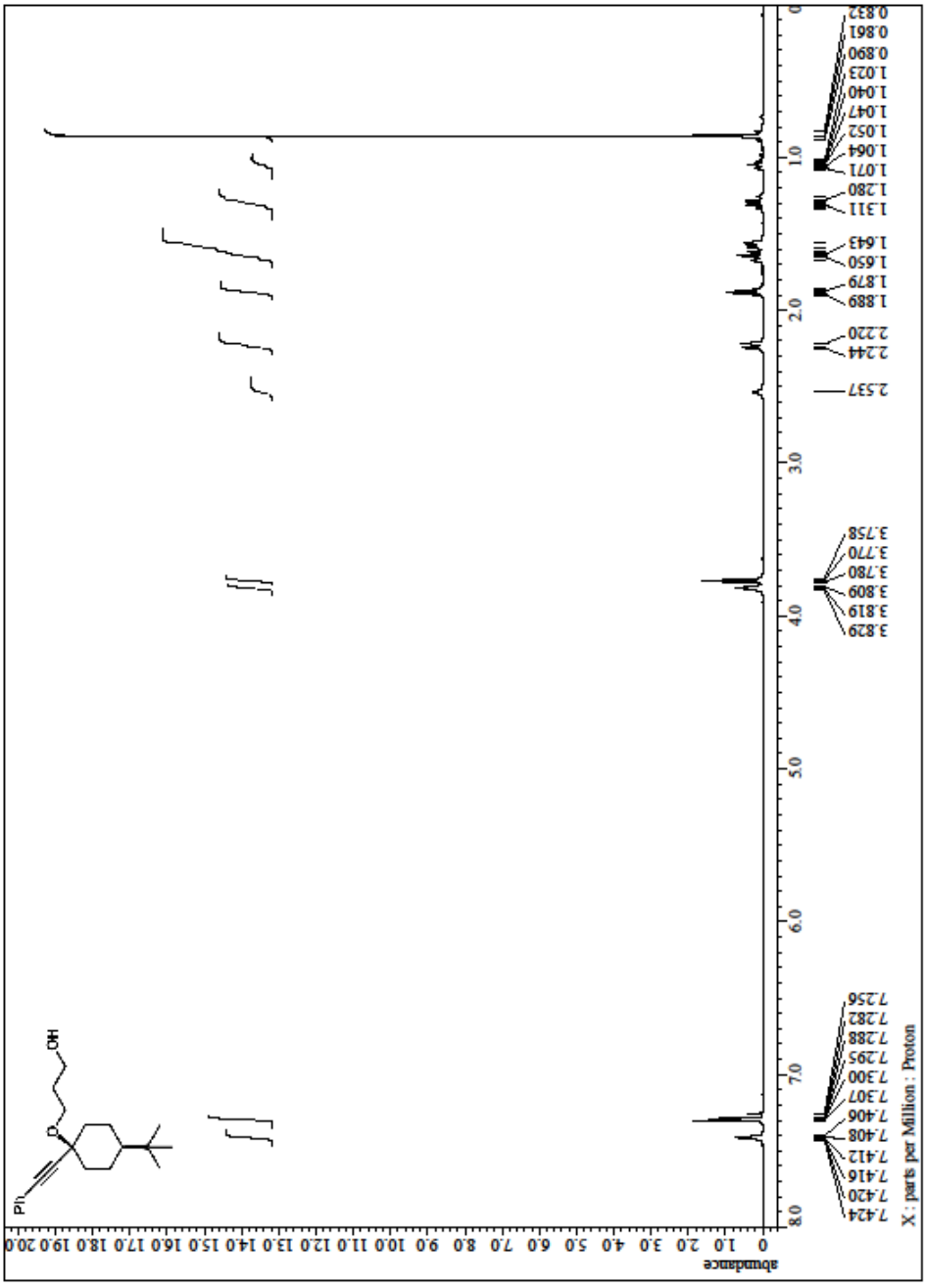

Figure A.3.78. ^{1}H NMR for compound **238A**

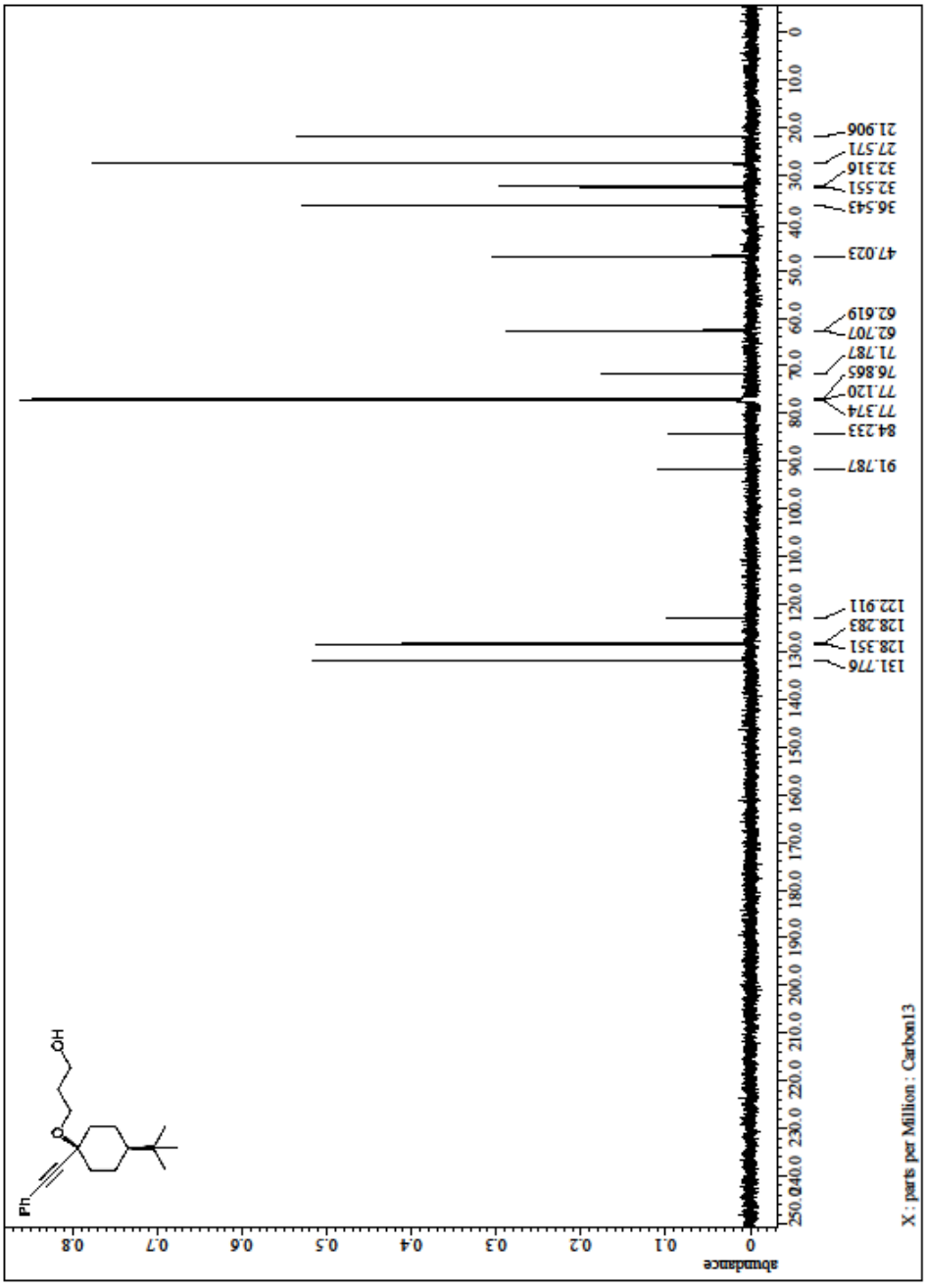

Figure A.3.79. ^{13}C NMR for compound **238A**

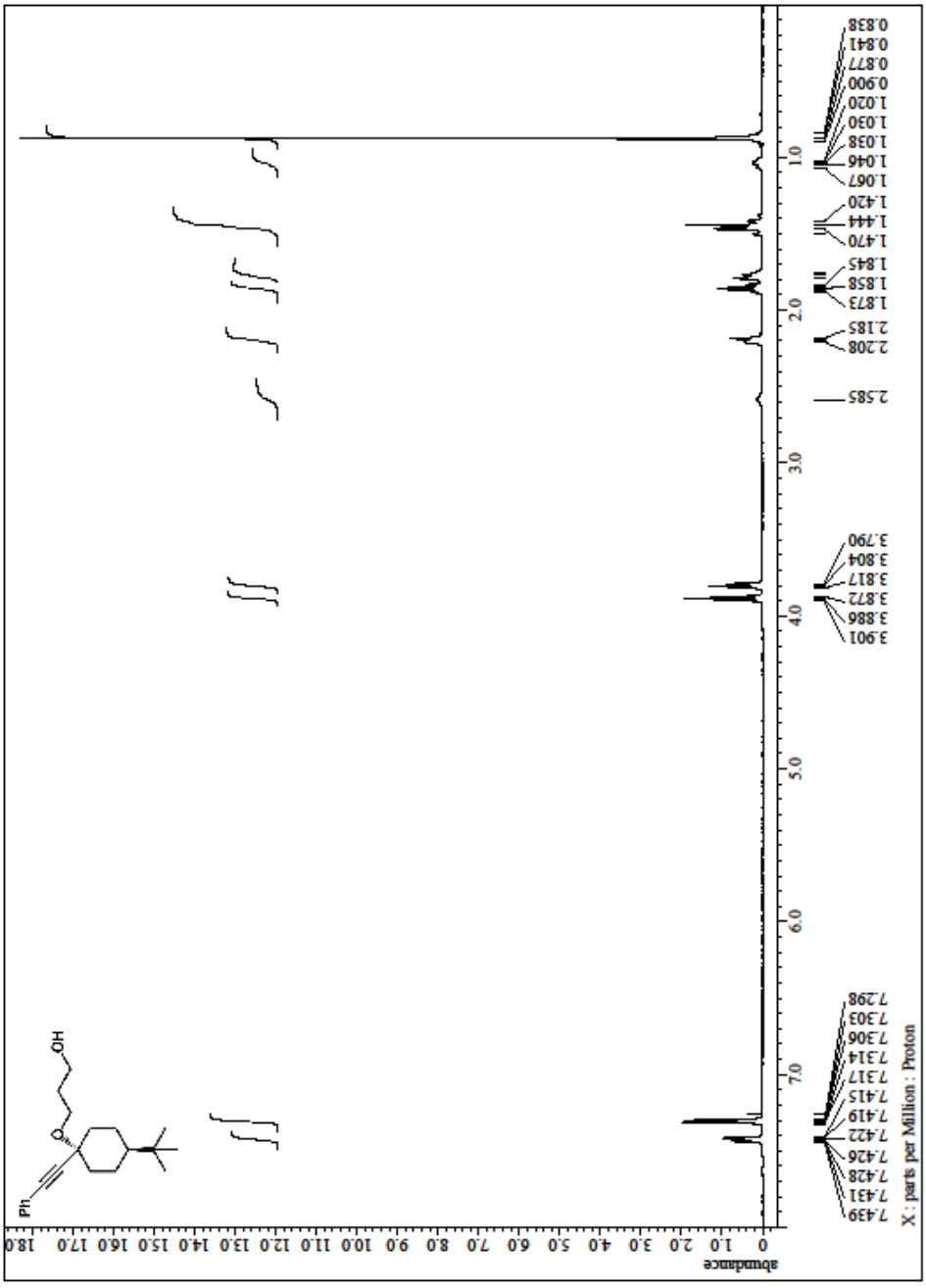

Figure A.3.80. ^{1}H NMR for compound **238B**

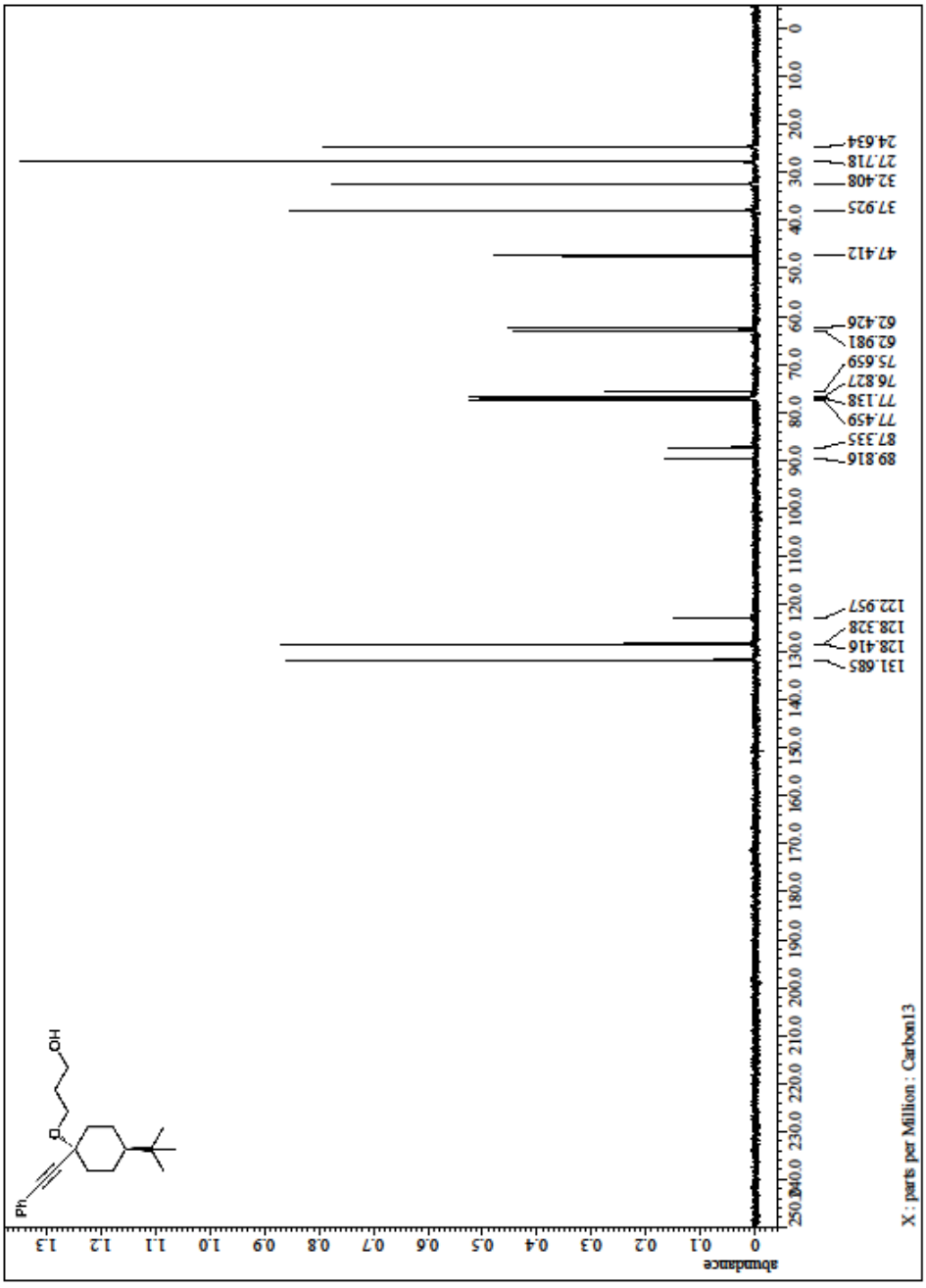

Figure A.3.81. ^{13}C NMR for compound **238B**

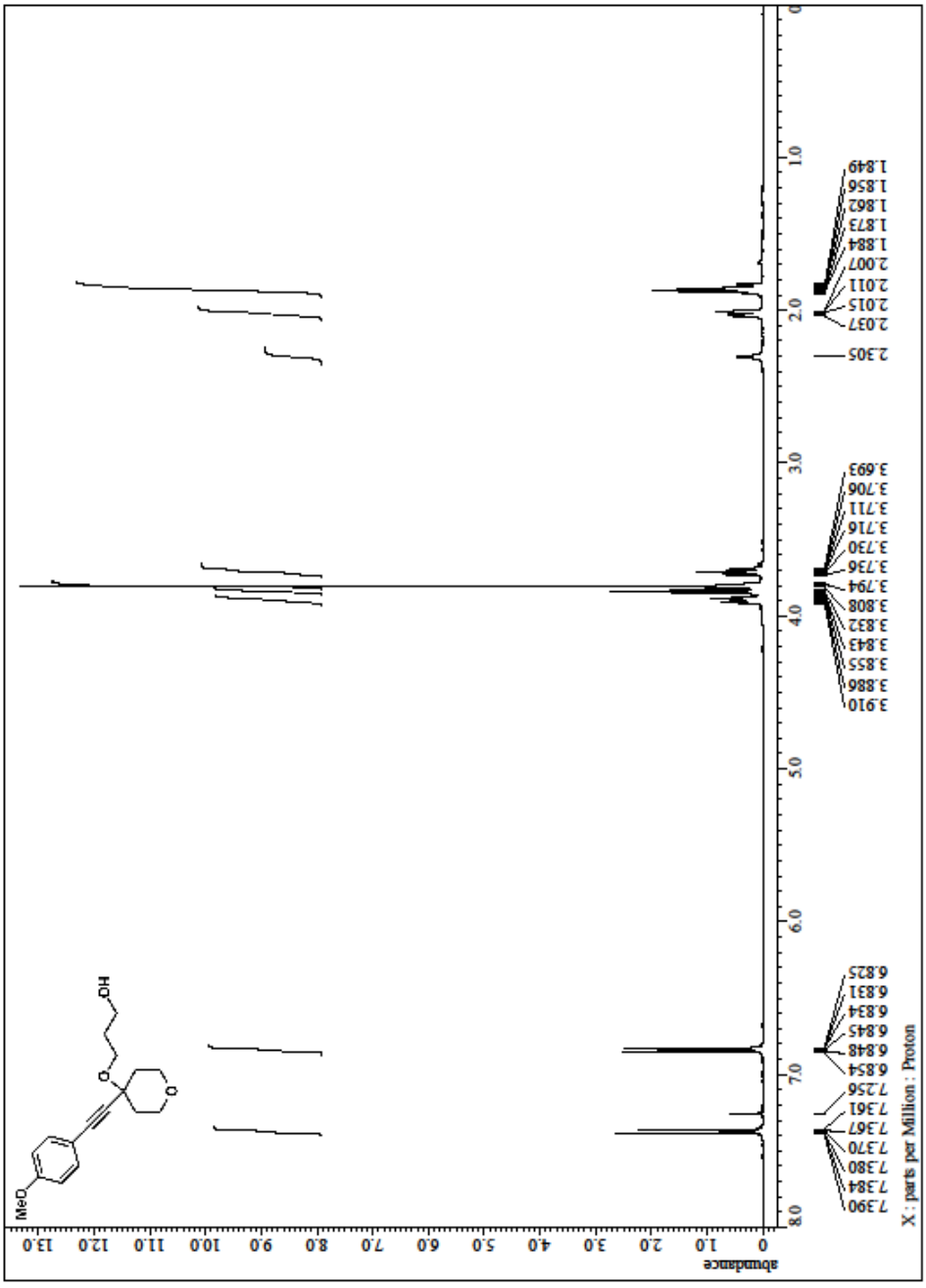

Figure A.3.82. ^{1}H NMR for compound **239**

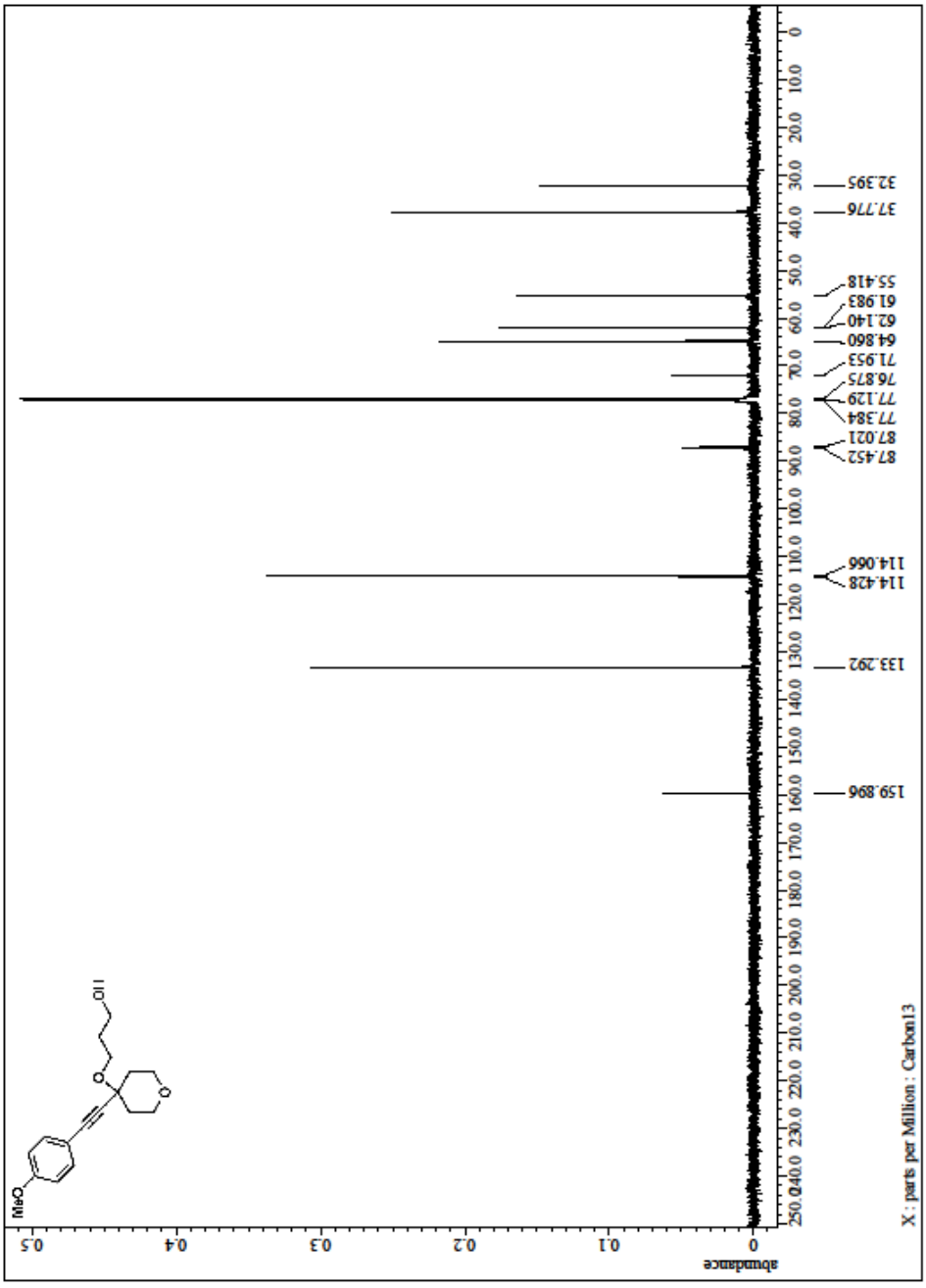

Figure A.3.83. ^{13}C NMR for compound **239**

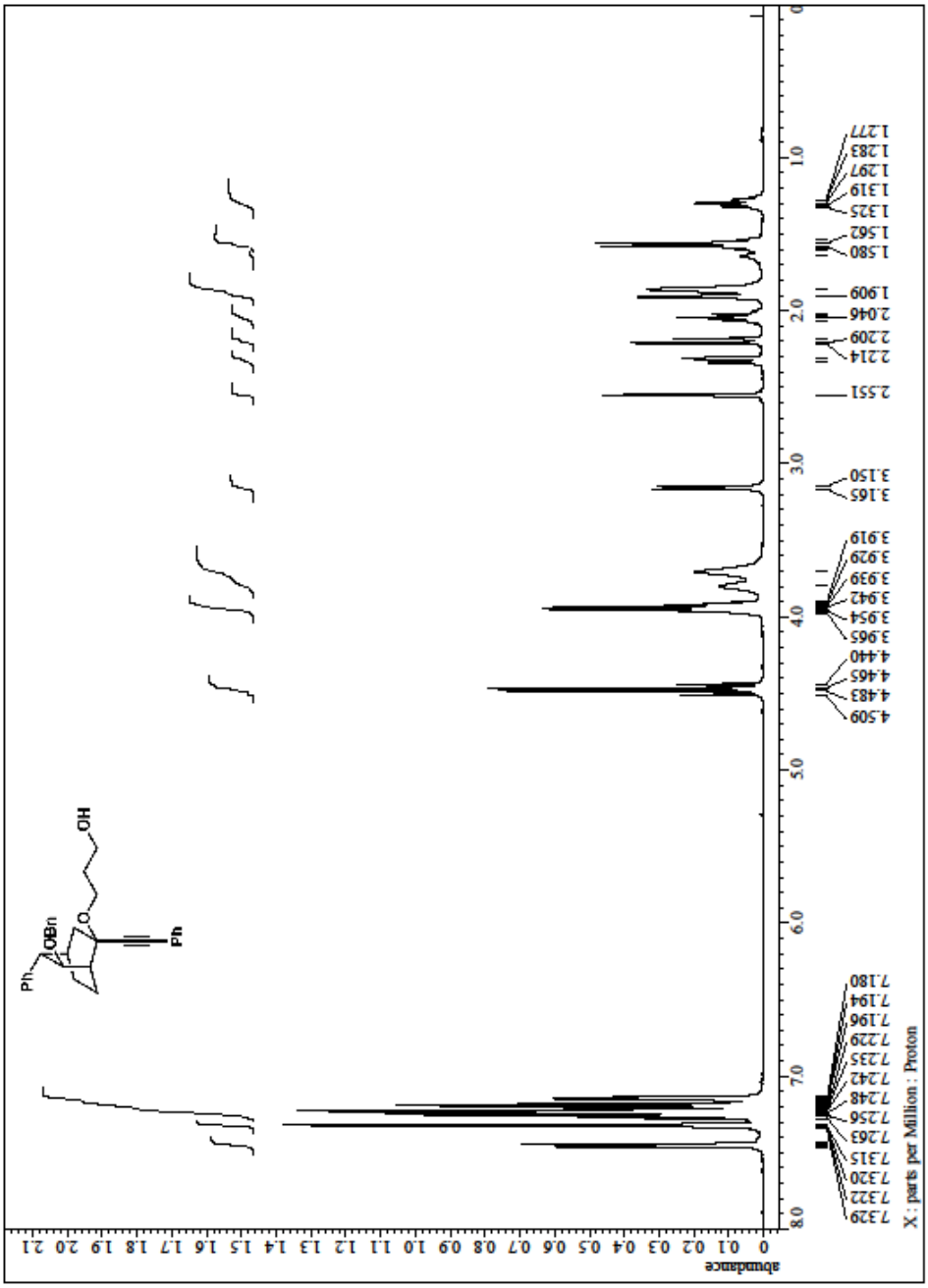

Figure A.3.84. ^{1}H NMR for compound **240**

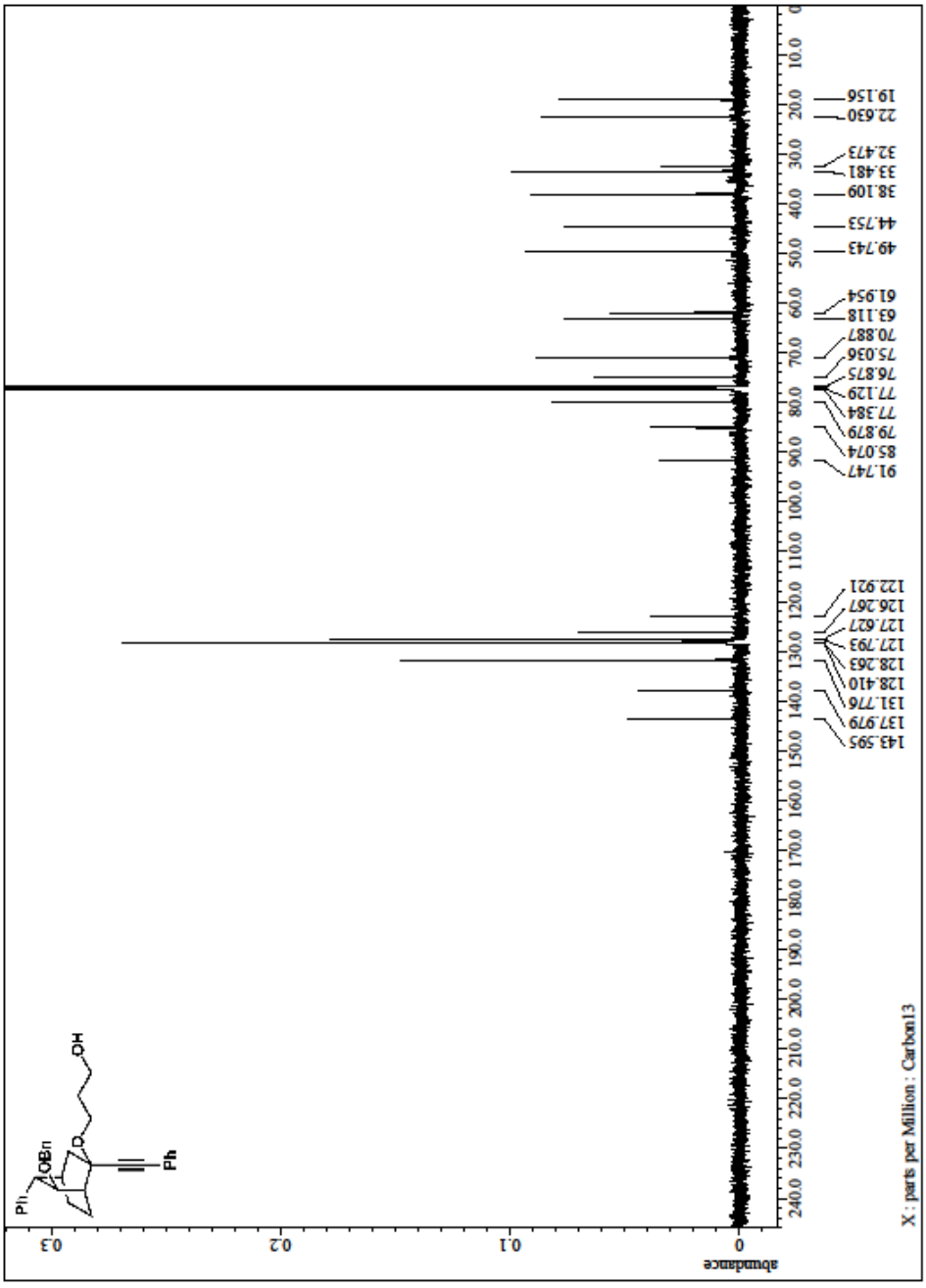

Figure A.3.85. ^{13}C NMR for compound **240**

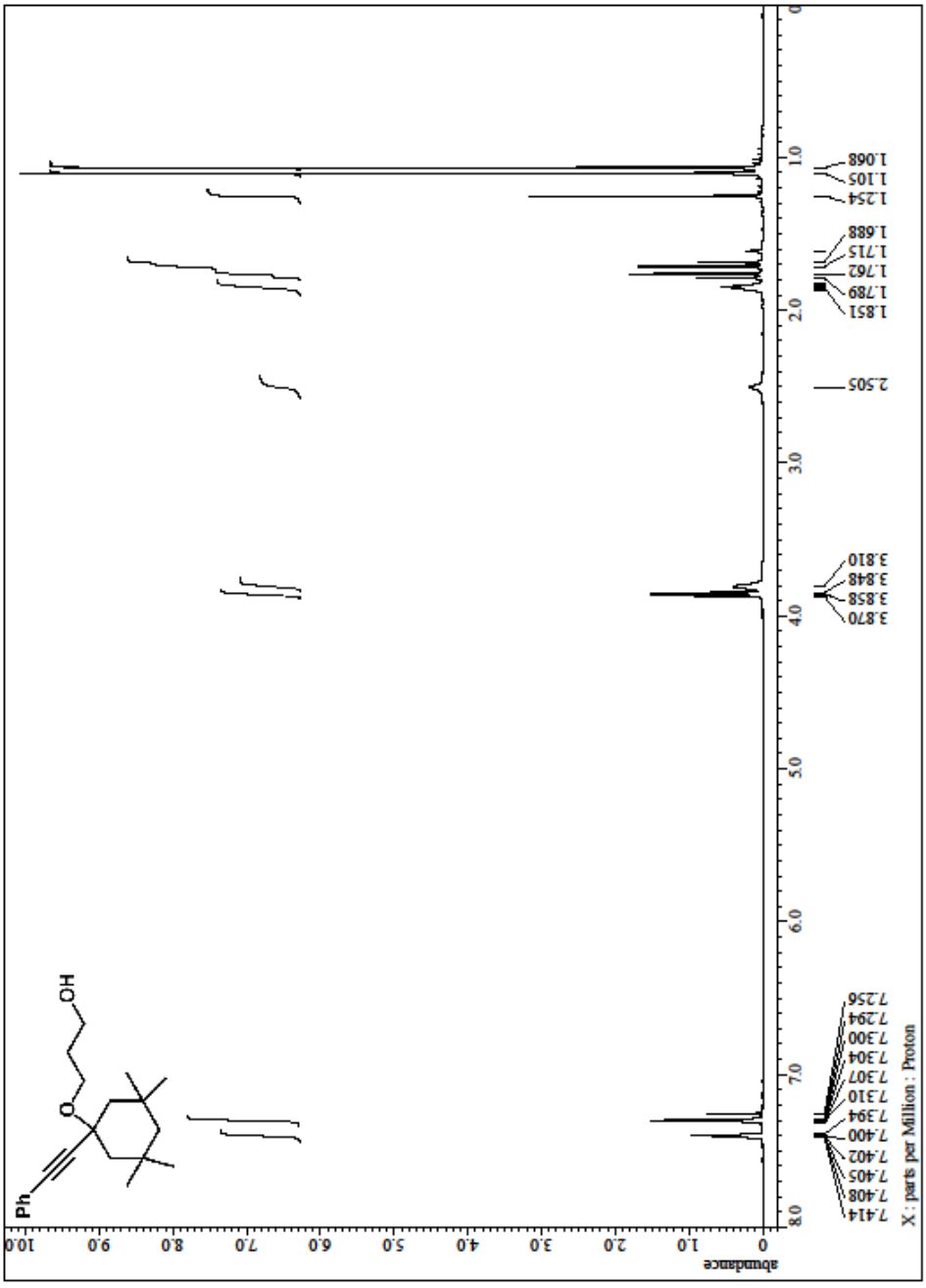

Figure A.3.86. ^{1}H NMR for compound **241**

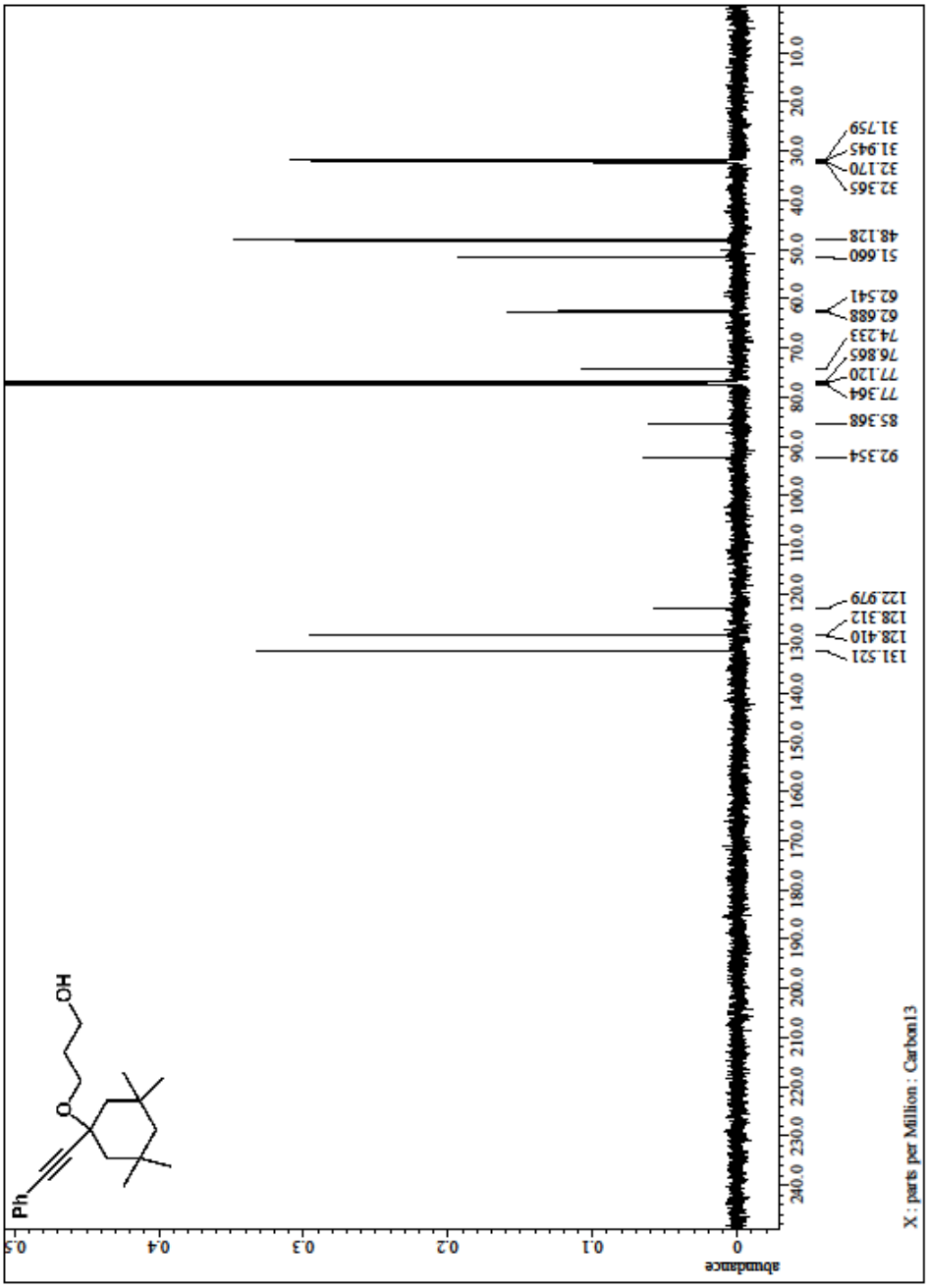

Figure A.3.87. ^{13}C NMR for compound **241**

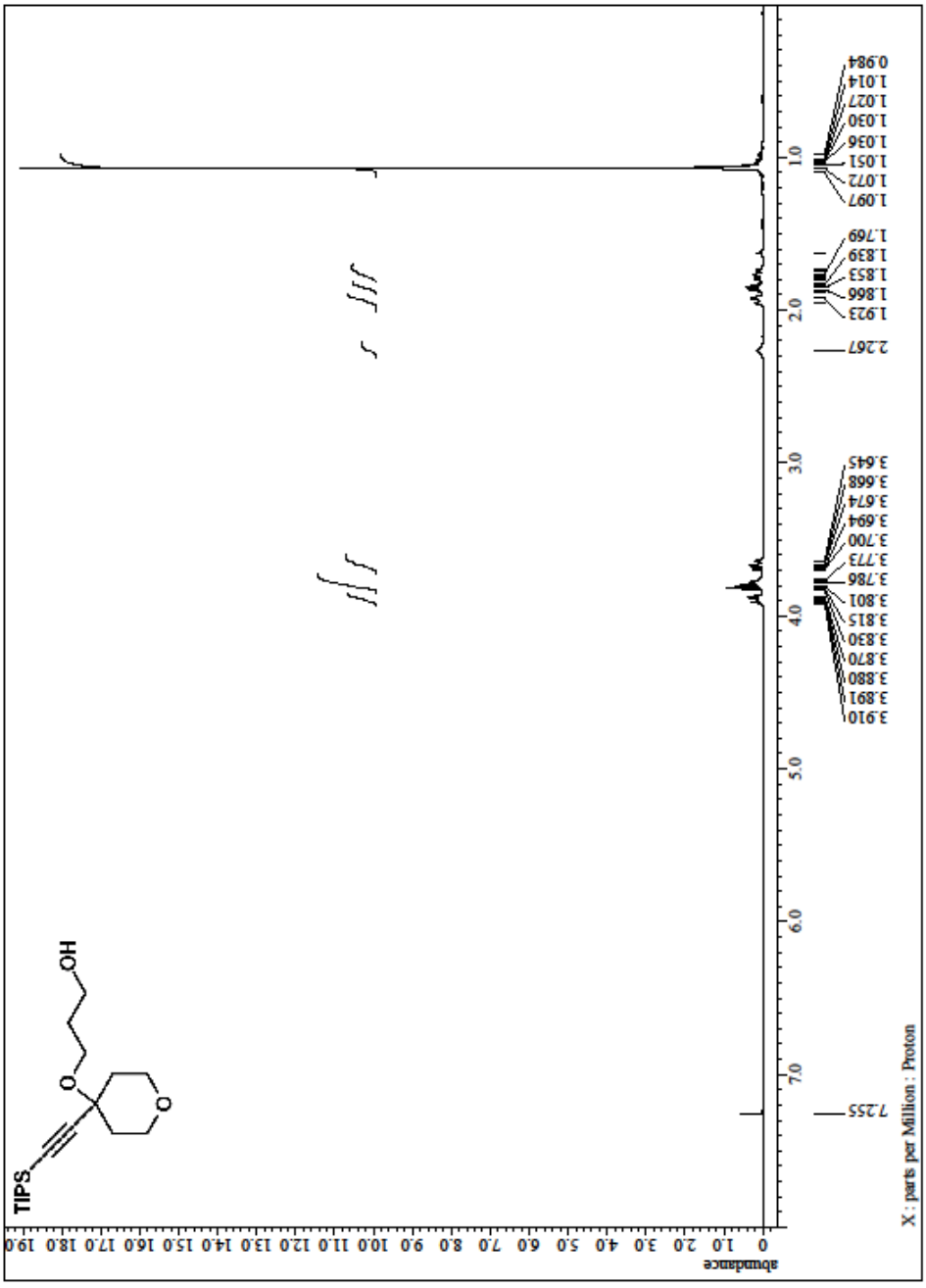

Figure A.3.88. ^{1}H NMR for compound **242**

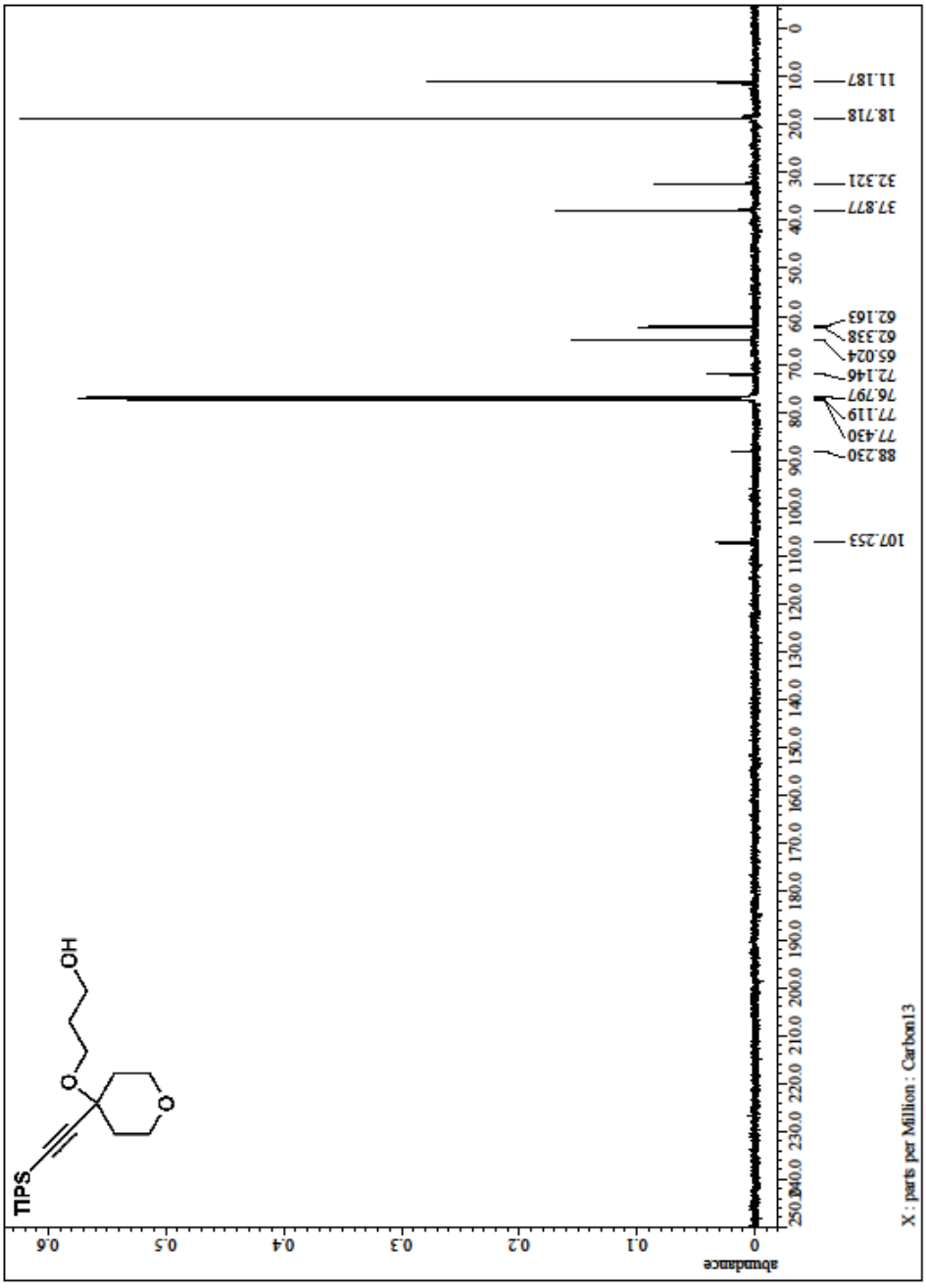

Figure A.3.89. ^{13}C NMR for compound **242**

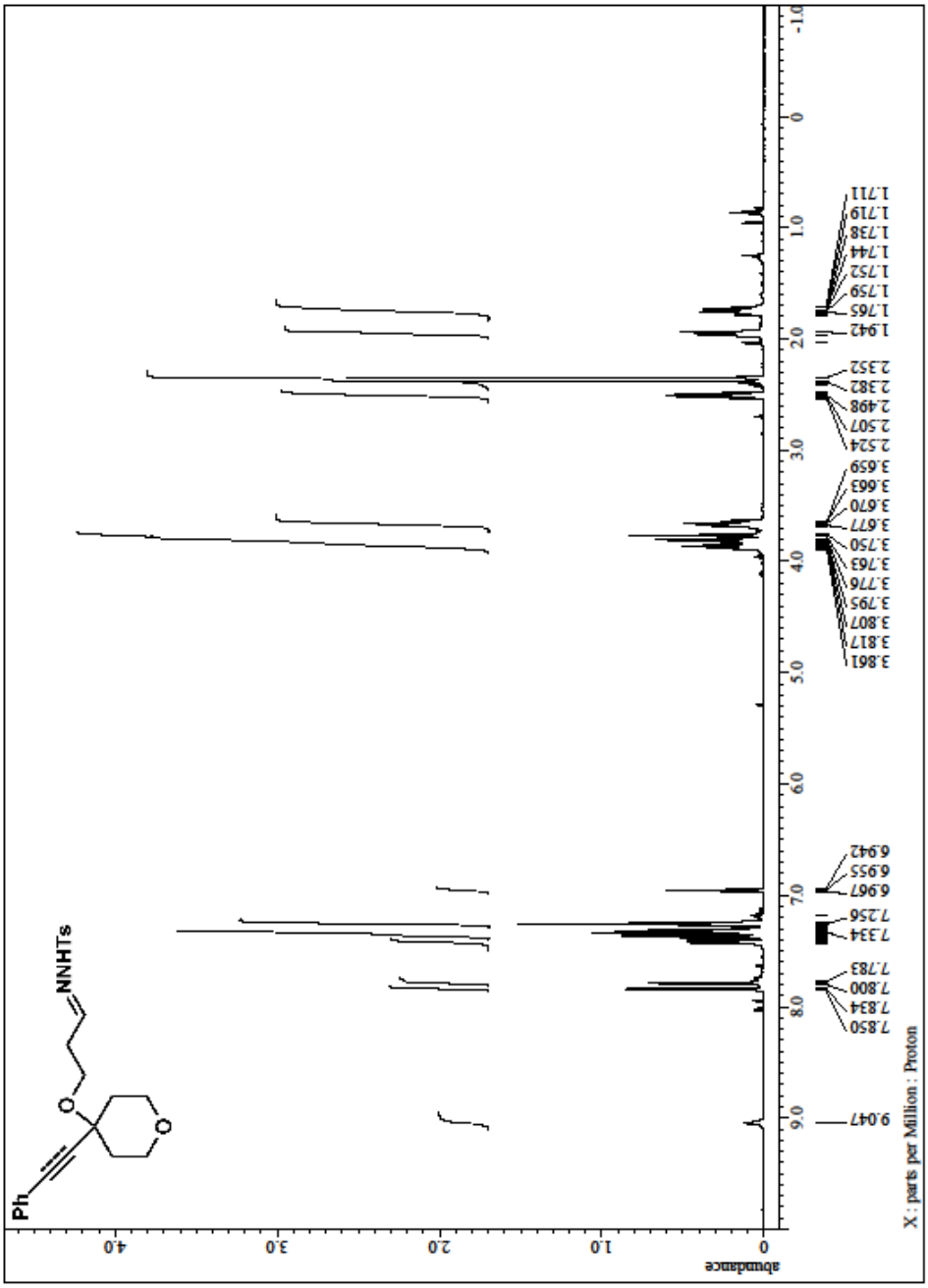

Figure A.3.90. ^{1}H NMR for compound **243**

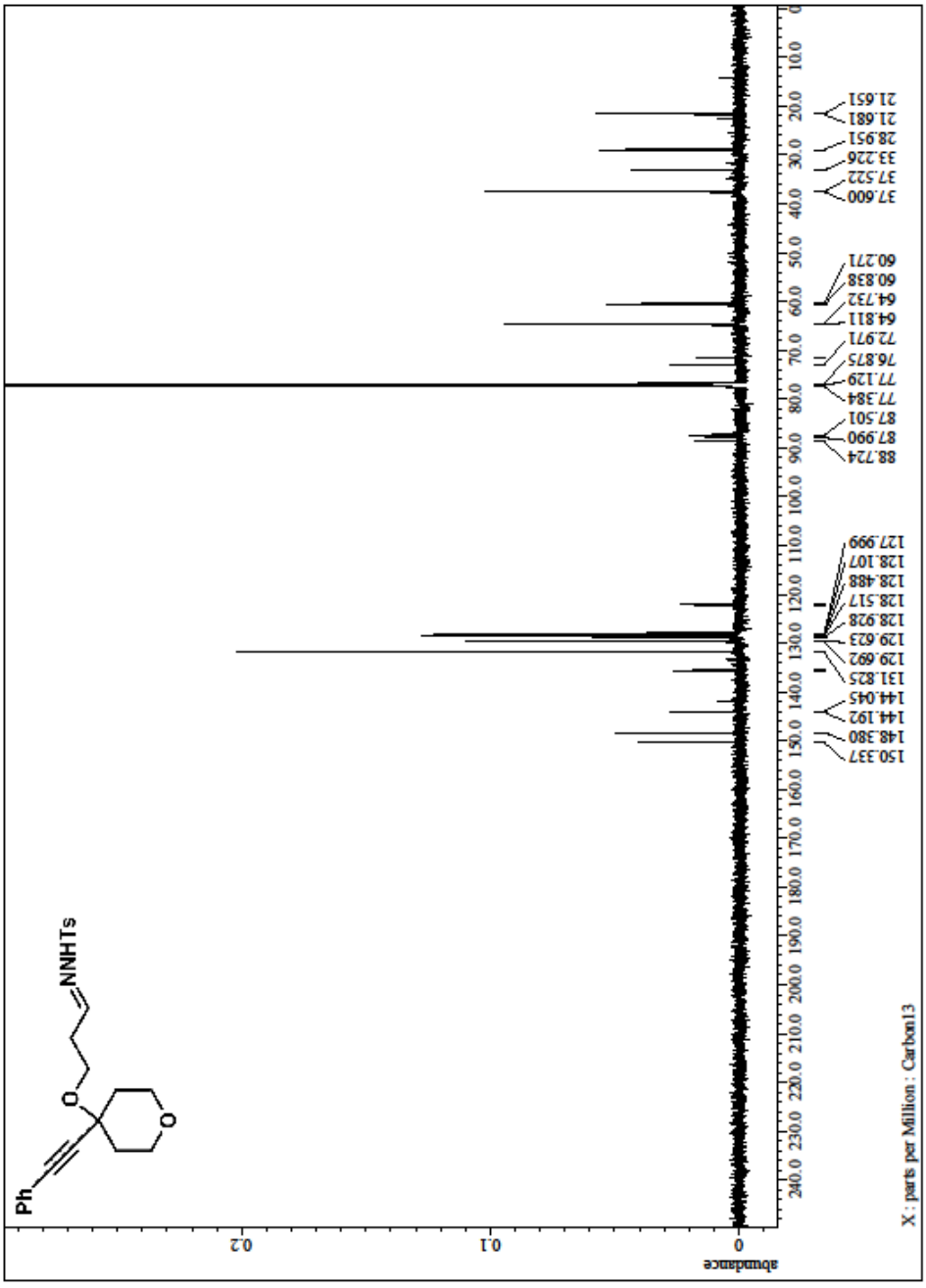

Figure A.3.91. ^{13}C NMR for compound **243**

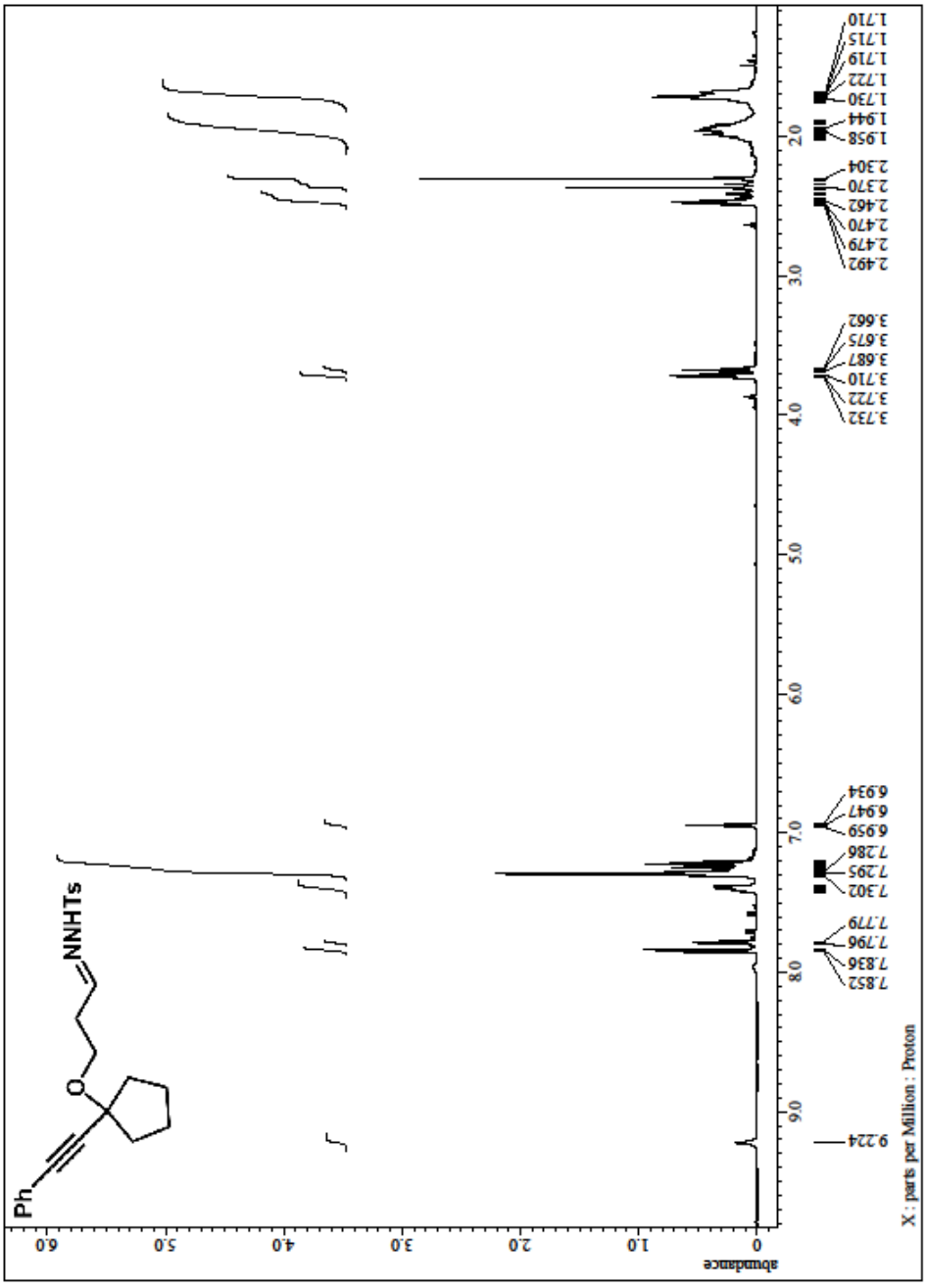

Figure A.3.92. ^{1}H NMR for compound **244**

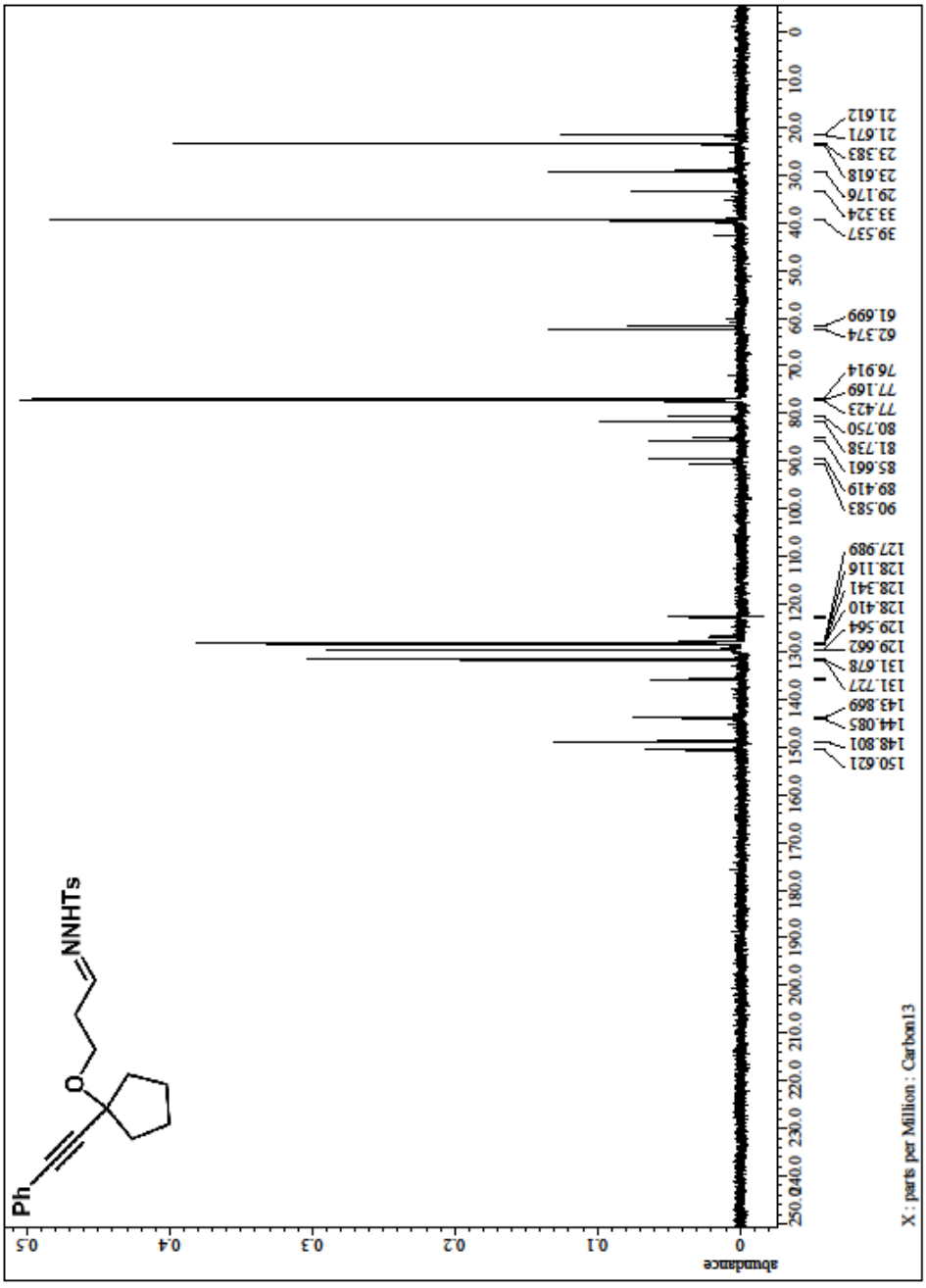

Figure A.3.93. ^{13}C NMR for compound **244**

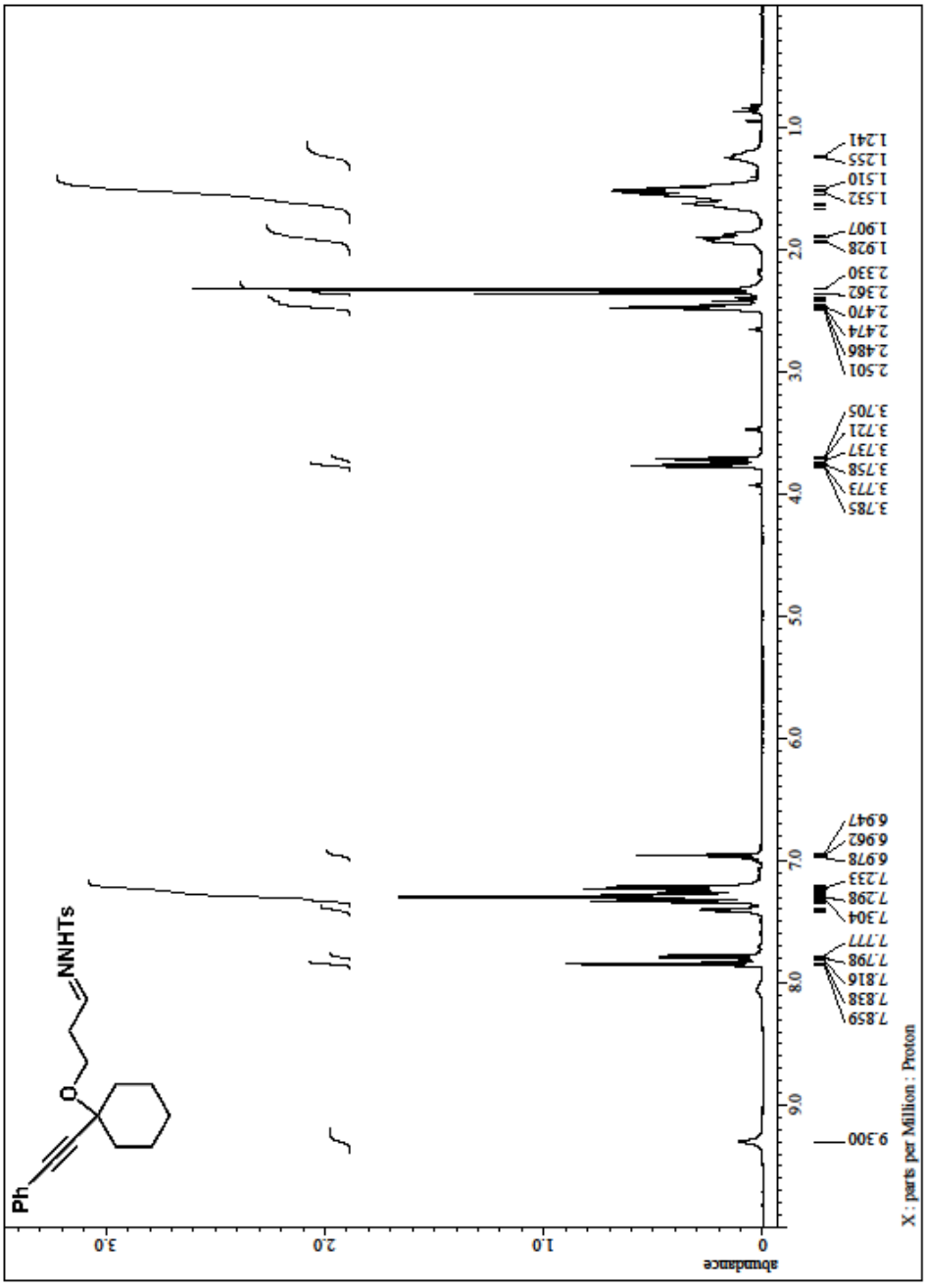

Figure A.3.94. ^{1}H NMR for compound **245**

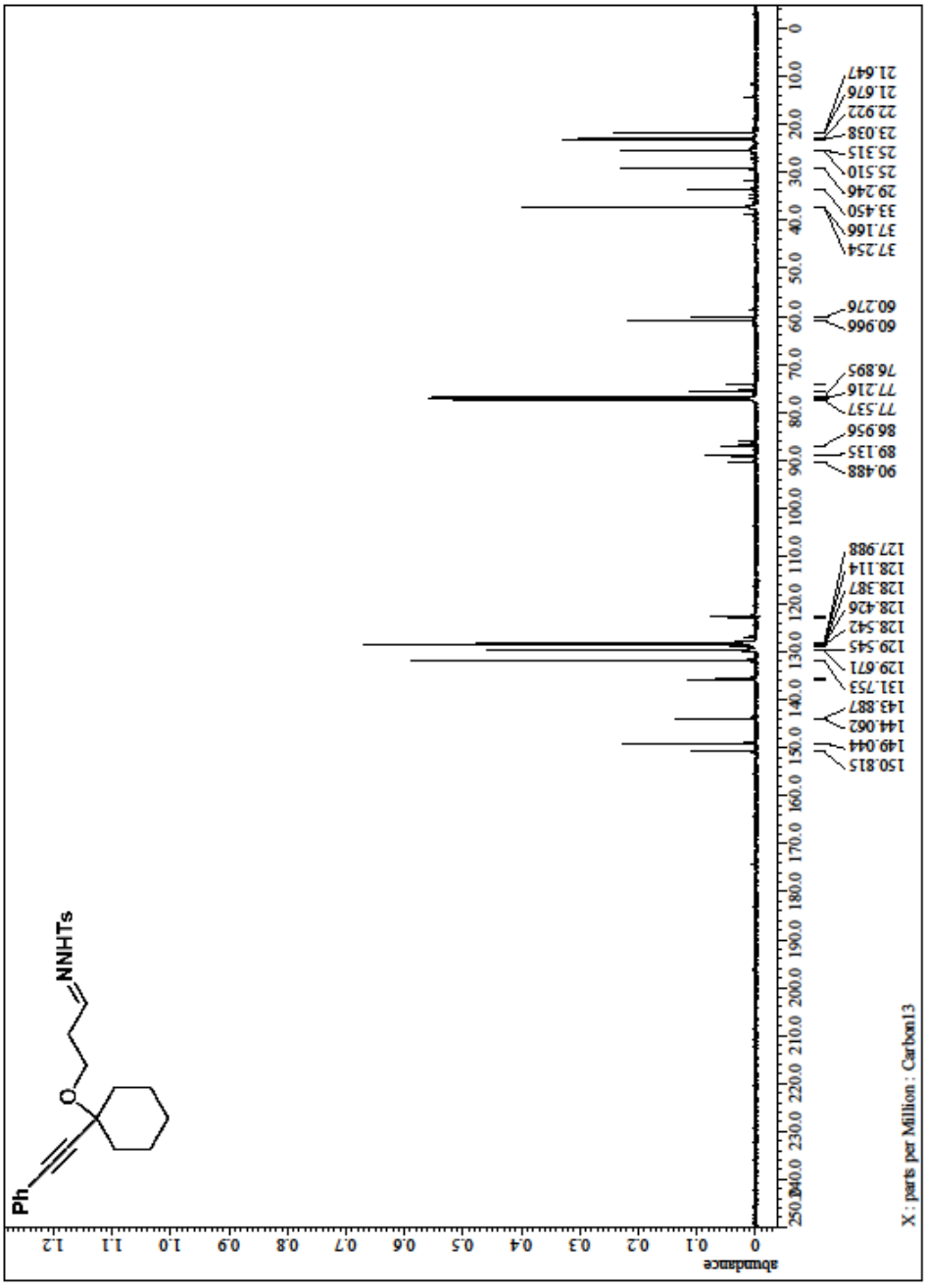

Figure A.3.95. ^{13}C NMR for compound **245**

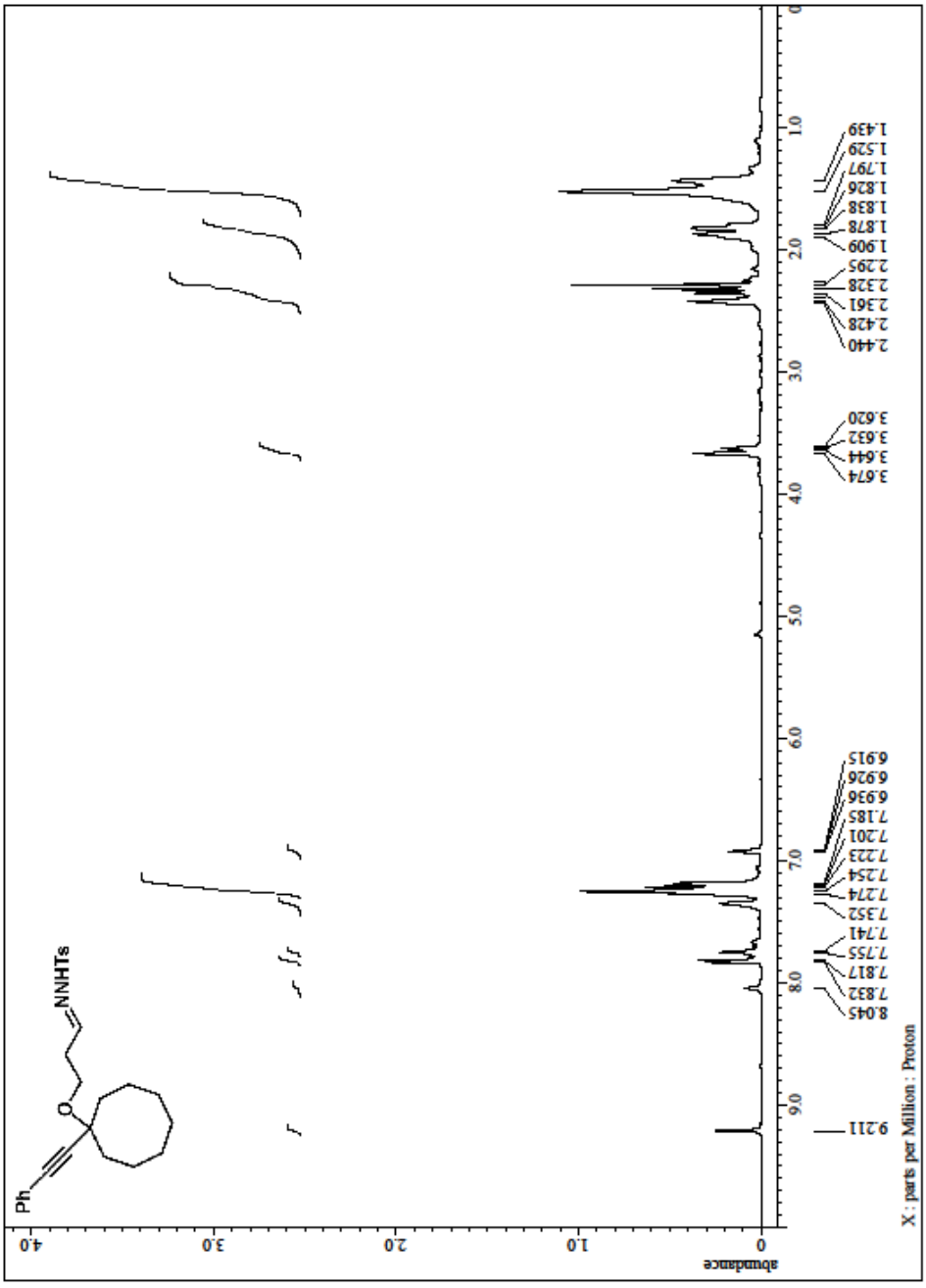

Figure A.3.96. ^{1}H NMR for compound **246**

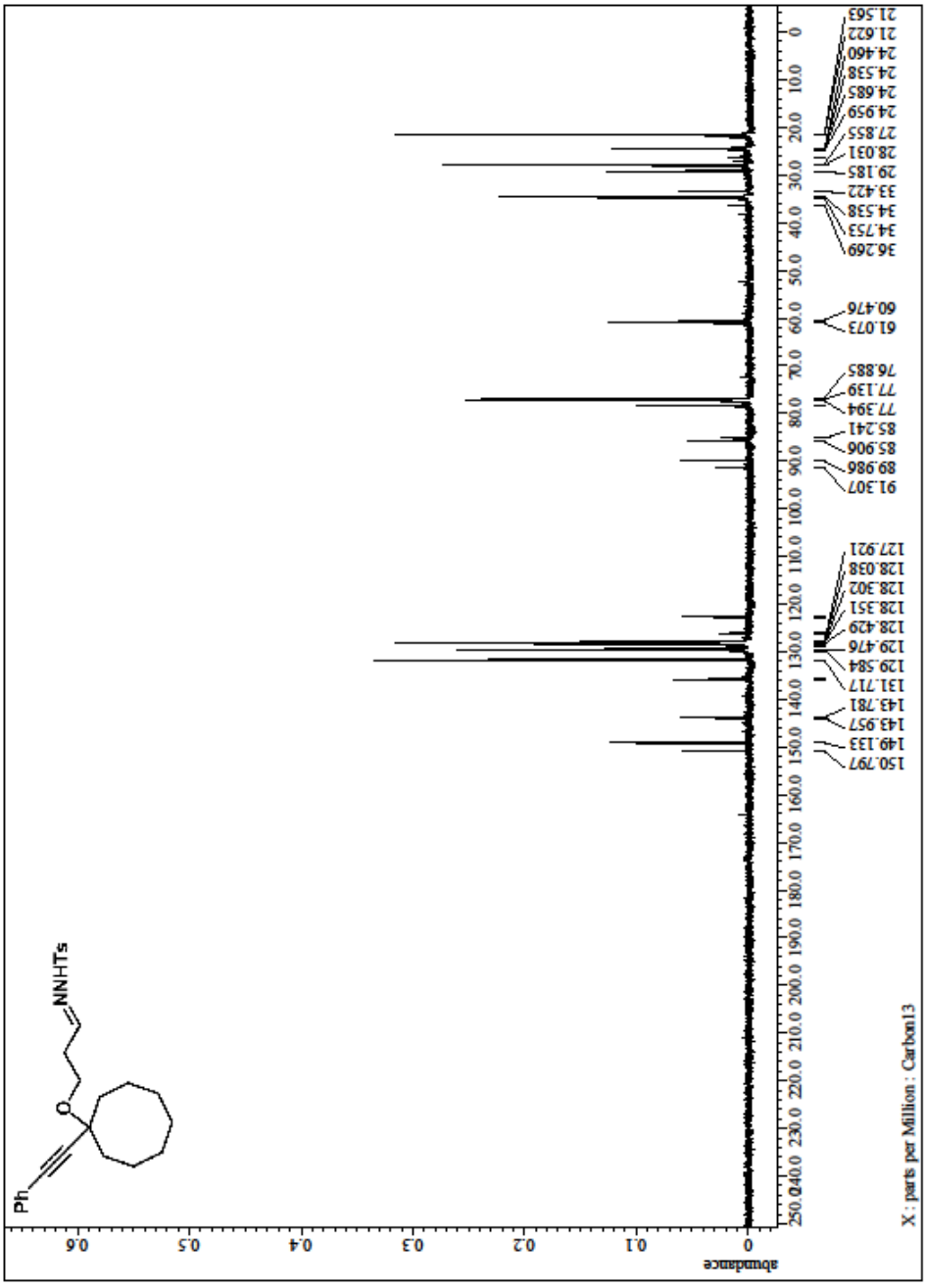

Figure A.3.97. ^{13}C NMR for compound **246**

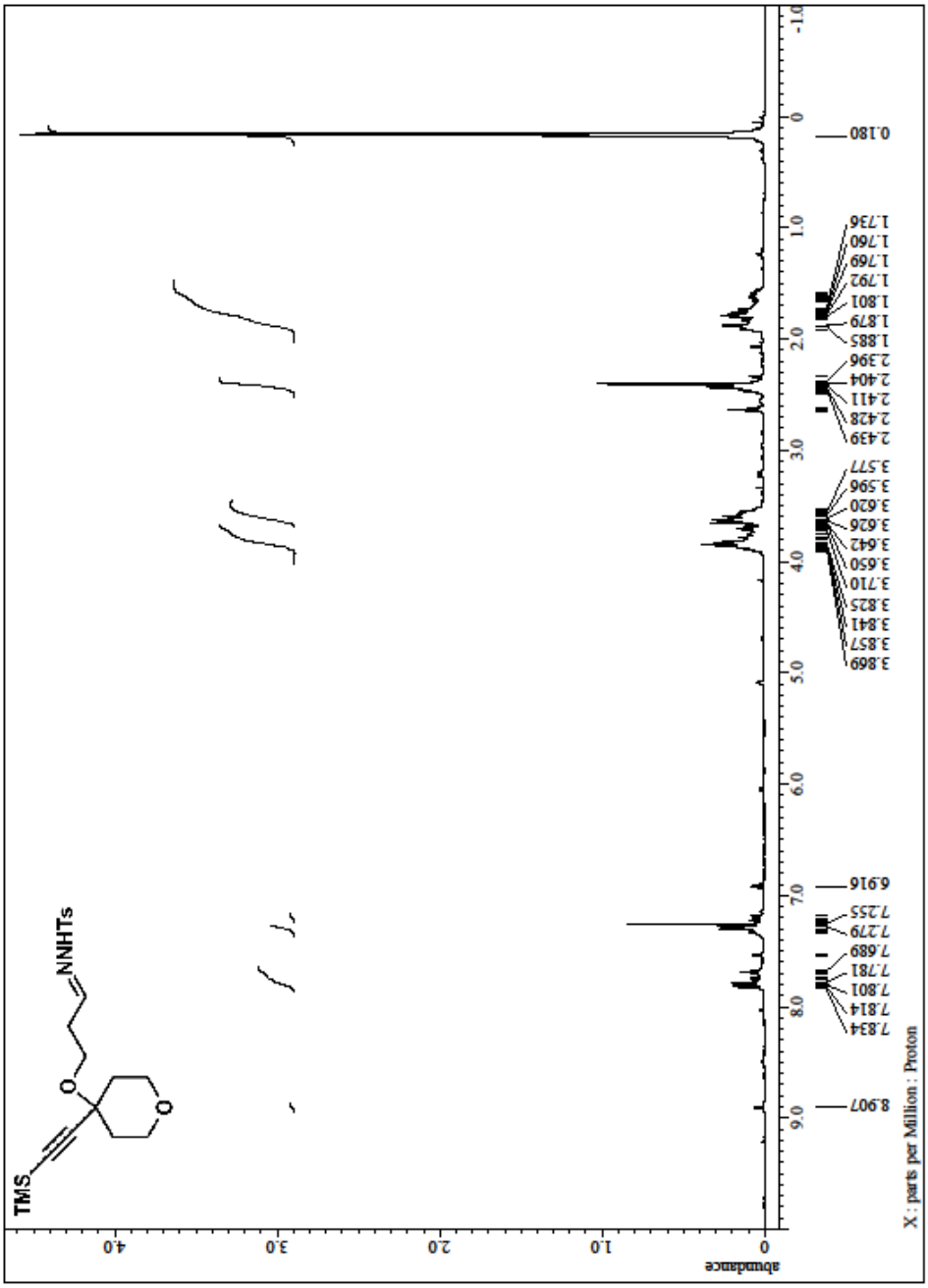

Figure A.3.98. ^{1}H NMR for compound **247**

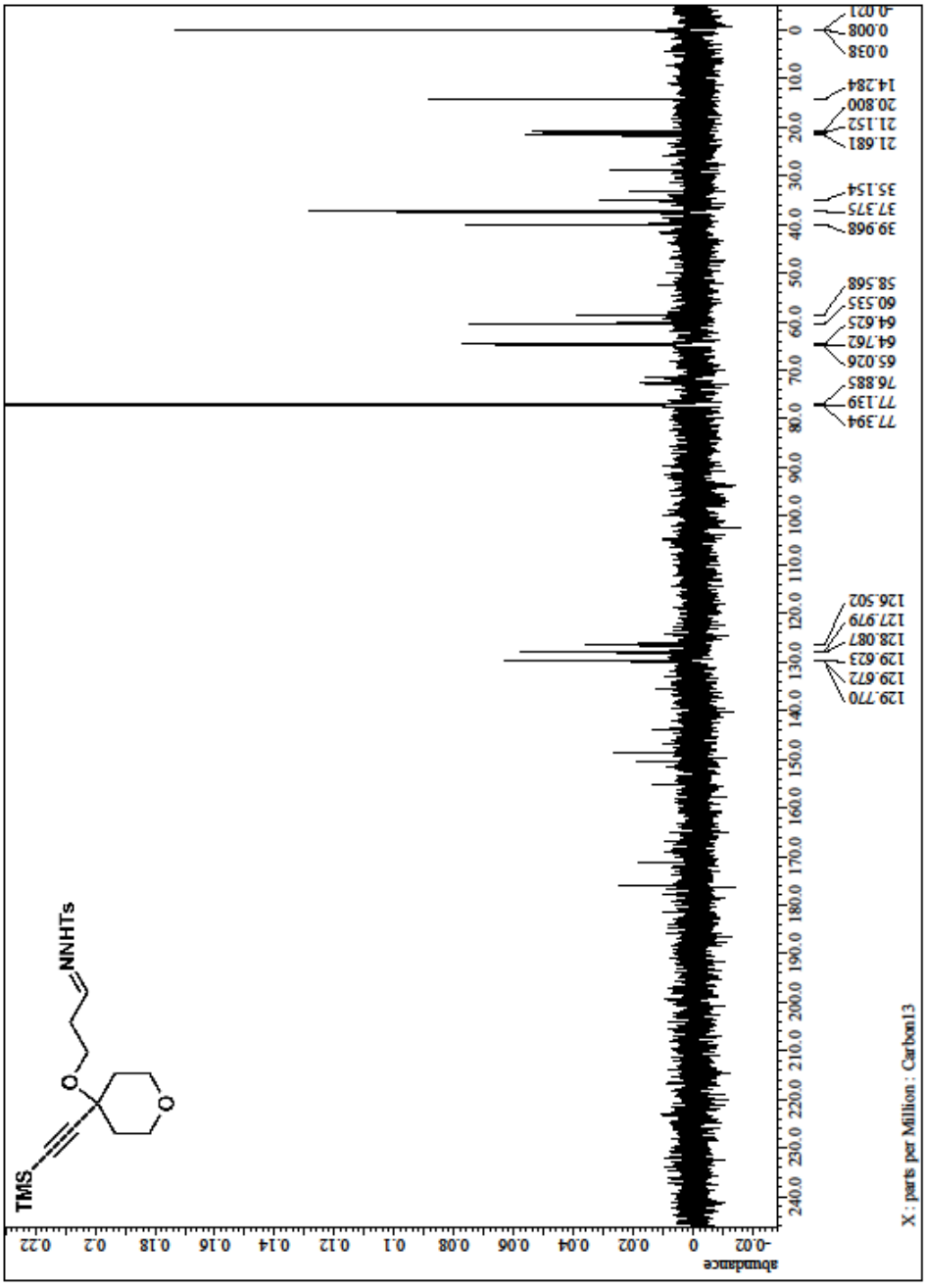

Figure A.3.99. ^{13}C NMR for compound **247**

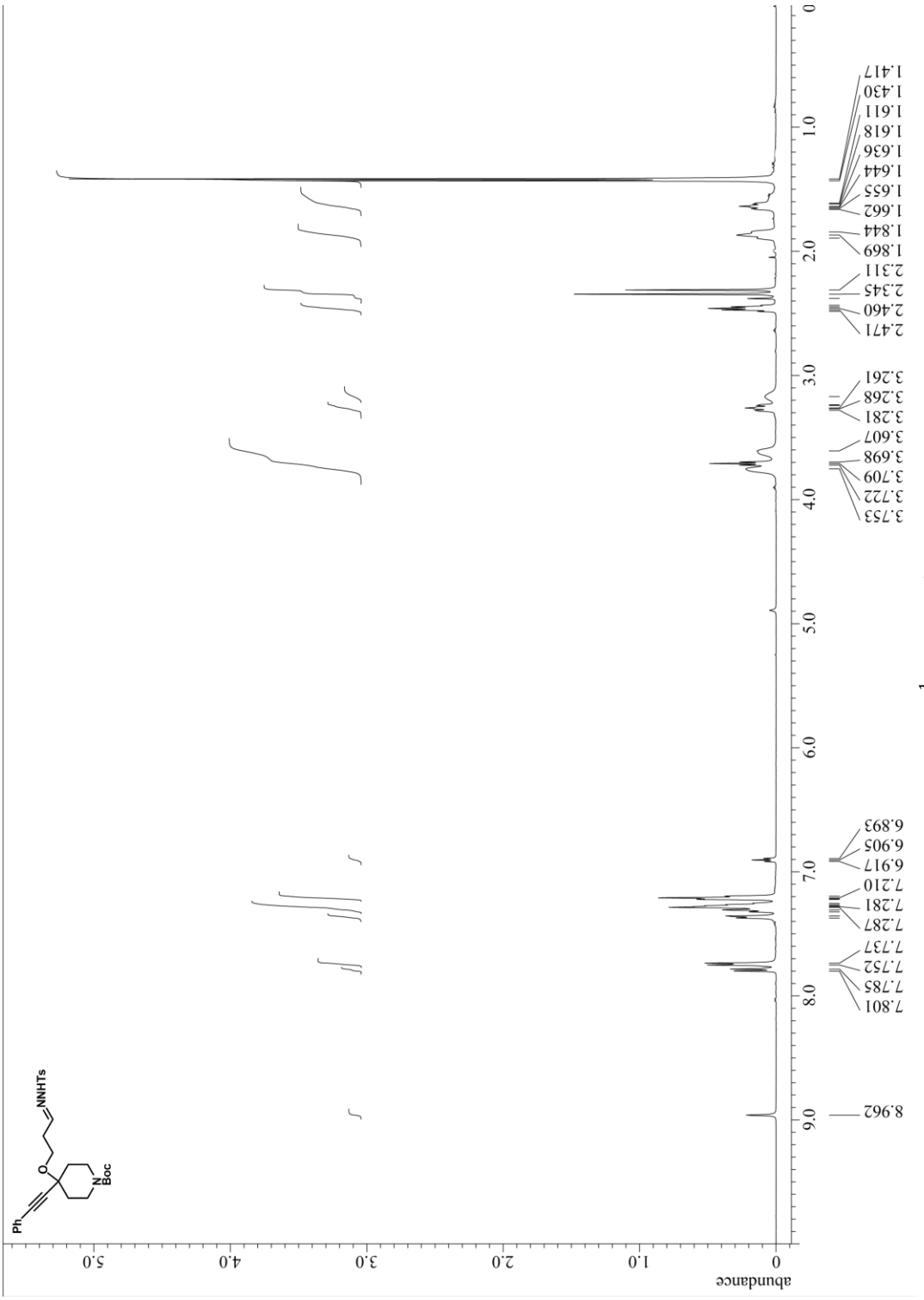

Figure A.3.100. ^{1}H NMR for compound **248**

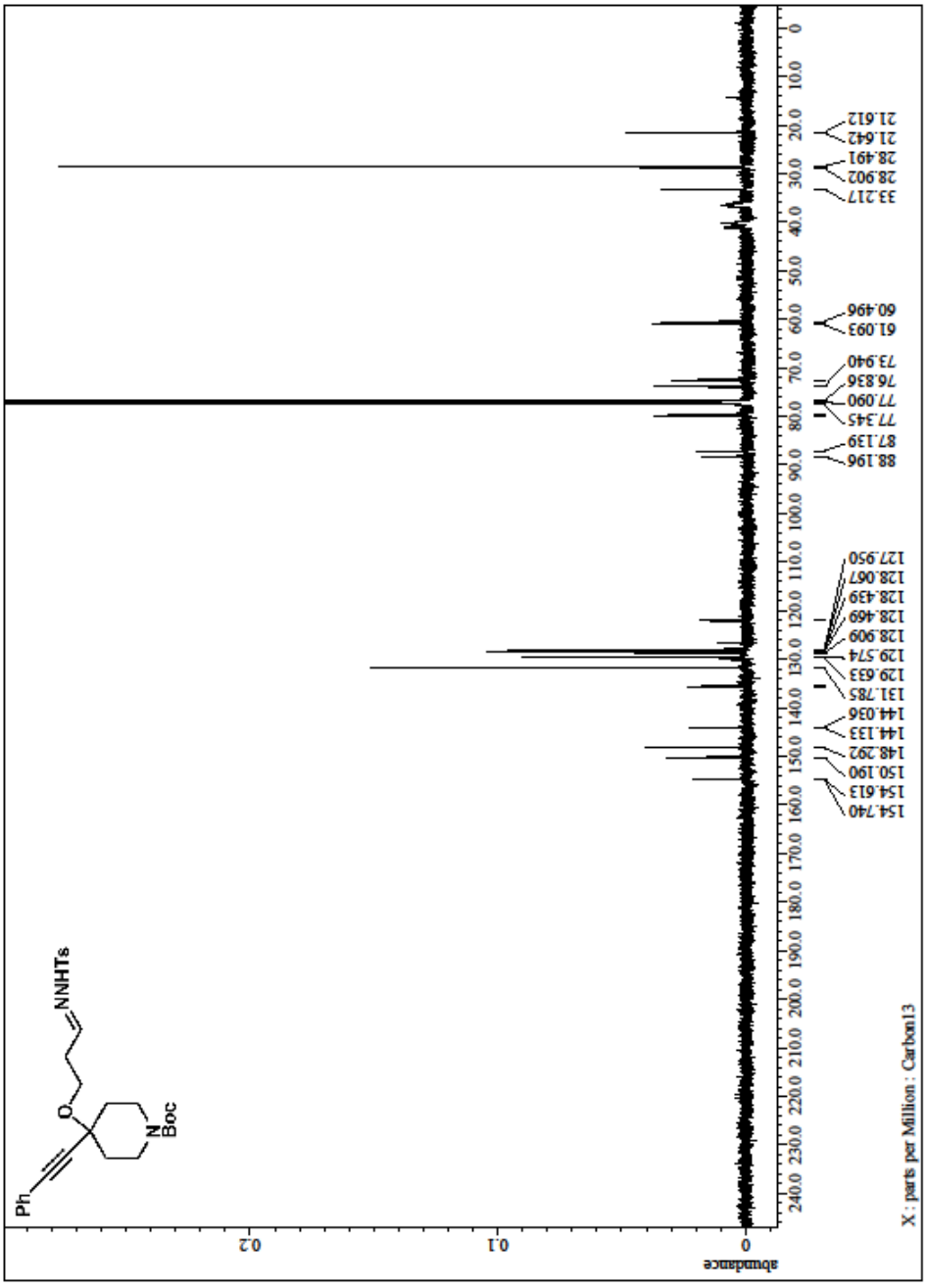

Figure A.3.101. ^{13}C NMR for compound **248**

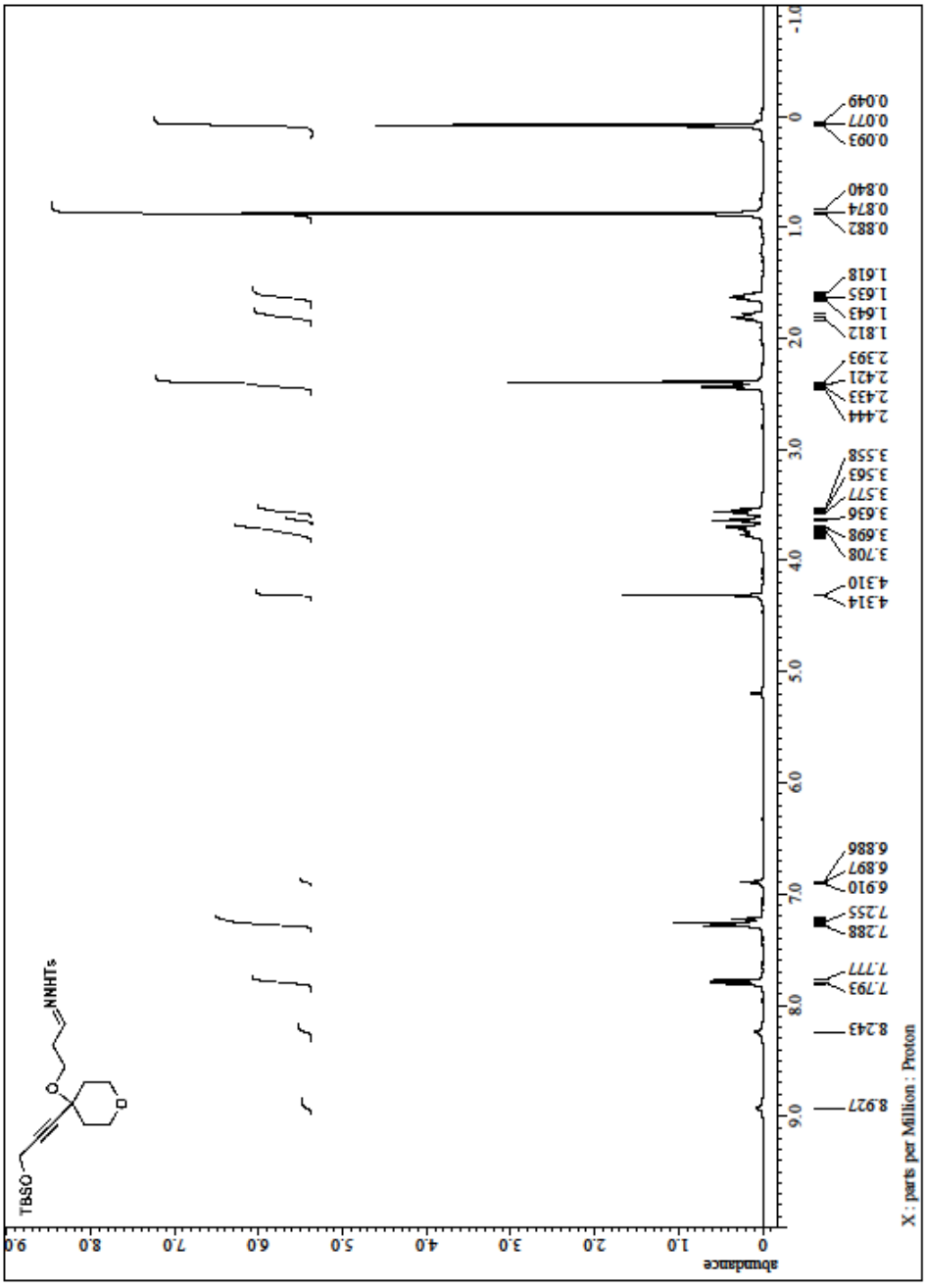

Figure A.3.102a. ^{1}H NMR for compound **249**

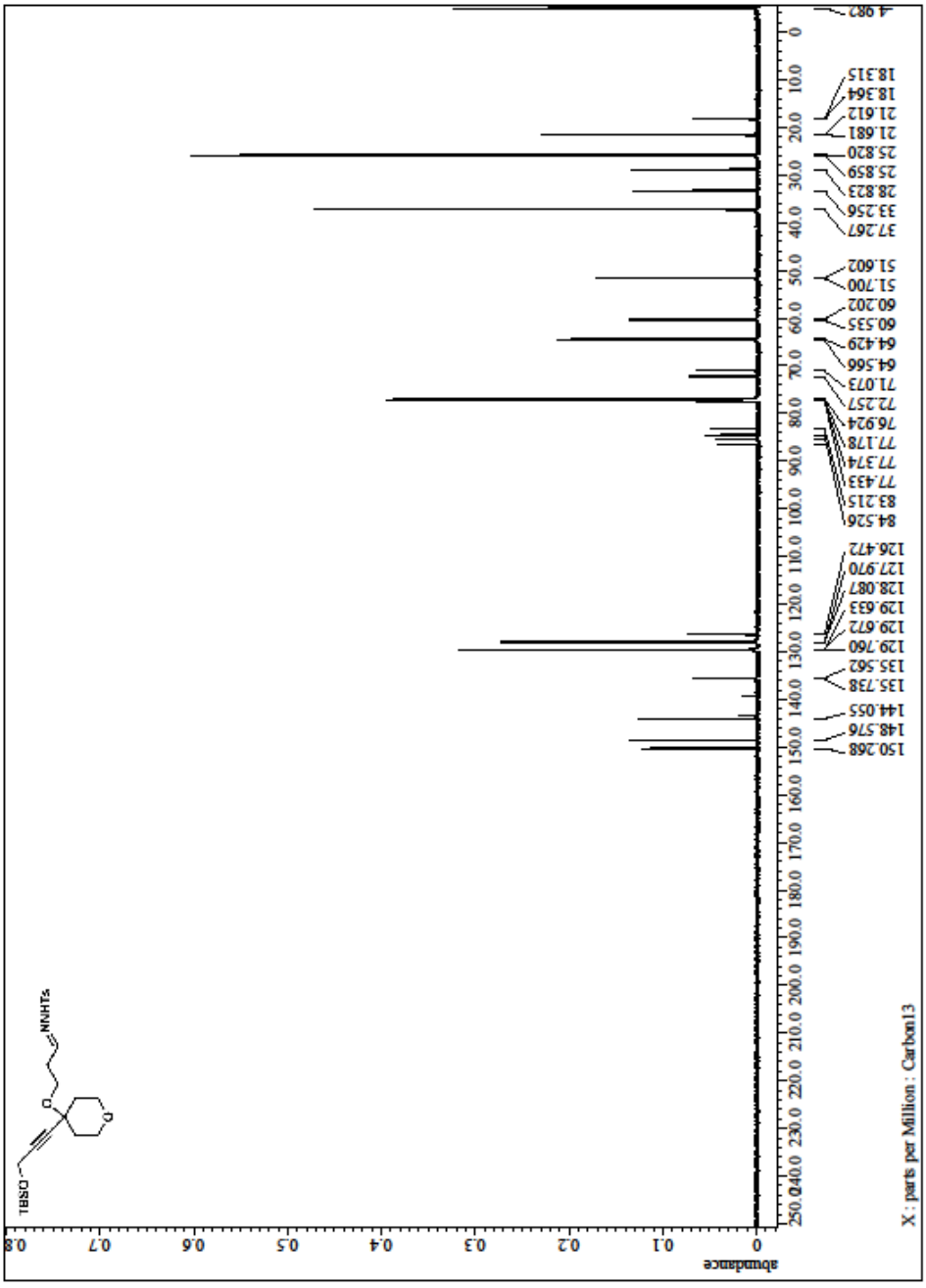

Figure A.3.102b. ^{13}C NMR for compound **249**

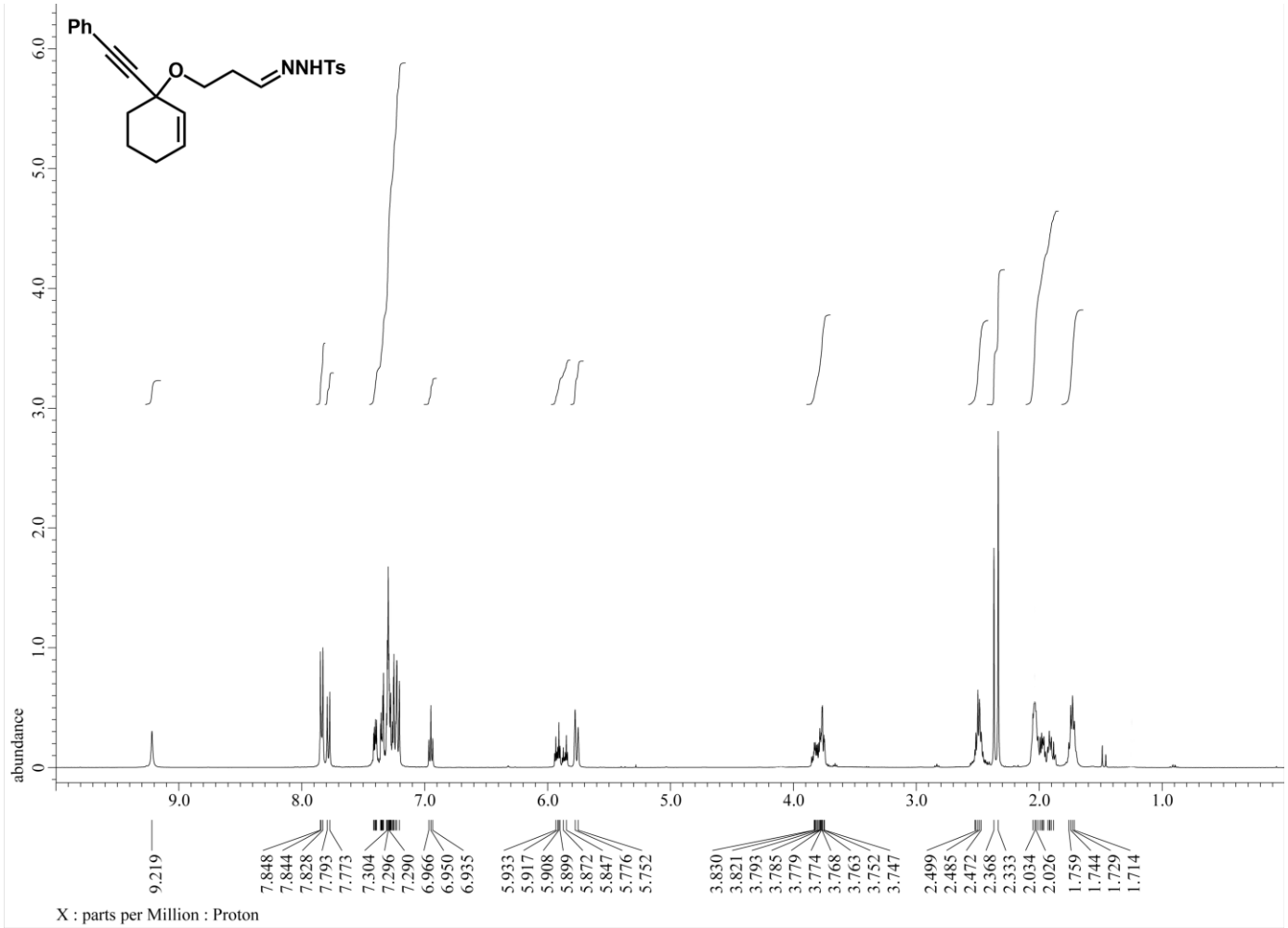

Figure A.3.103. ^{1}H NMR for compound **250**

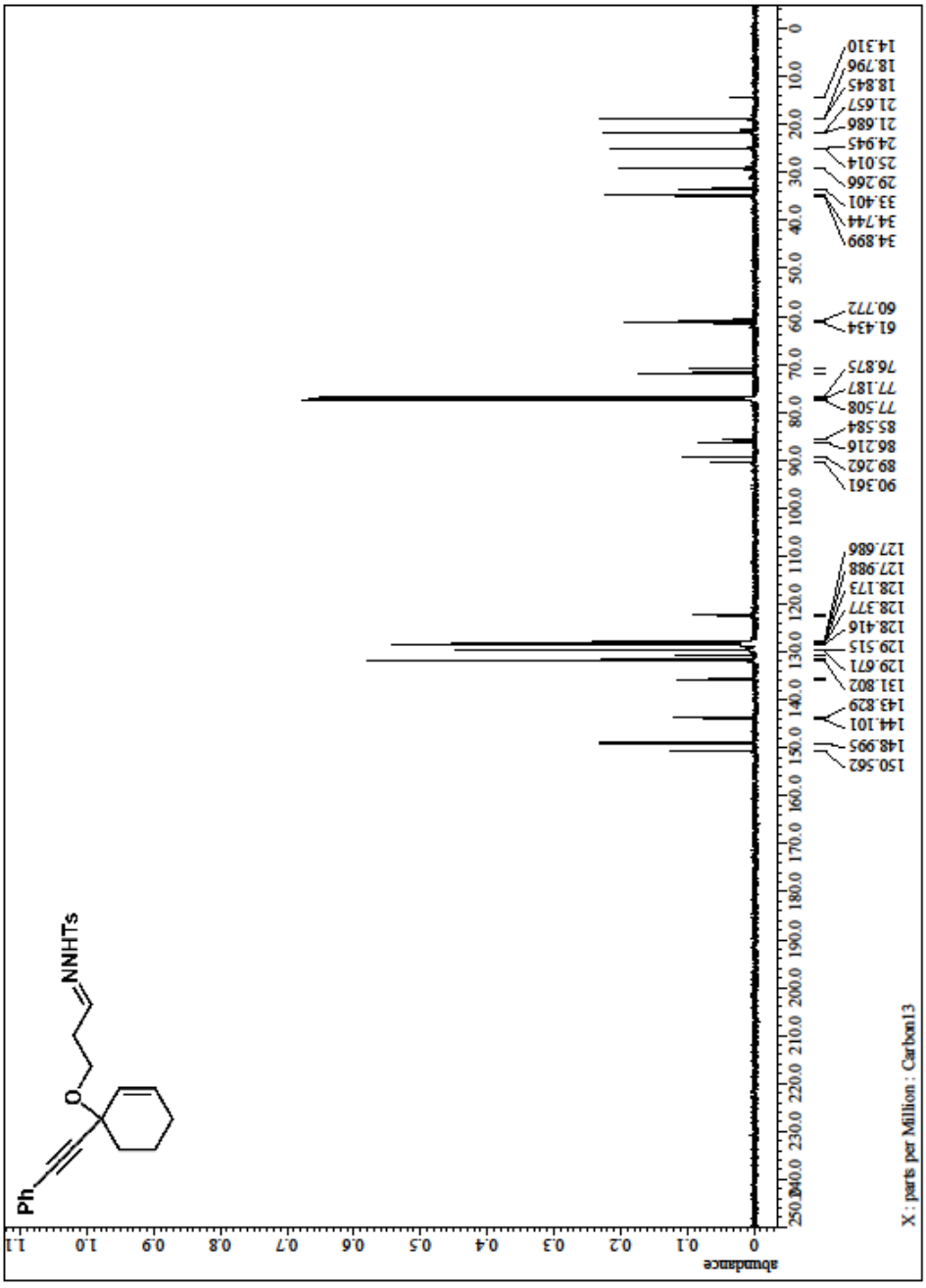

Figure A.3.104. ^{13}C NMR for compound **250**

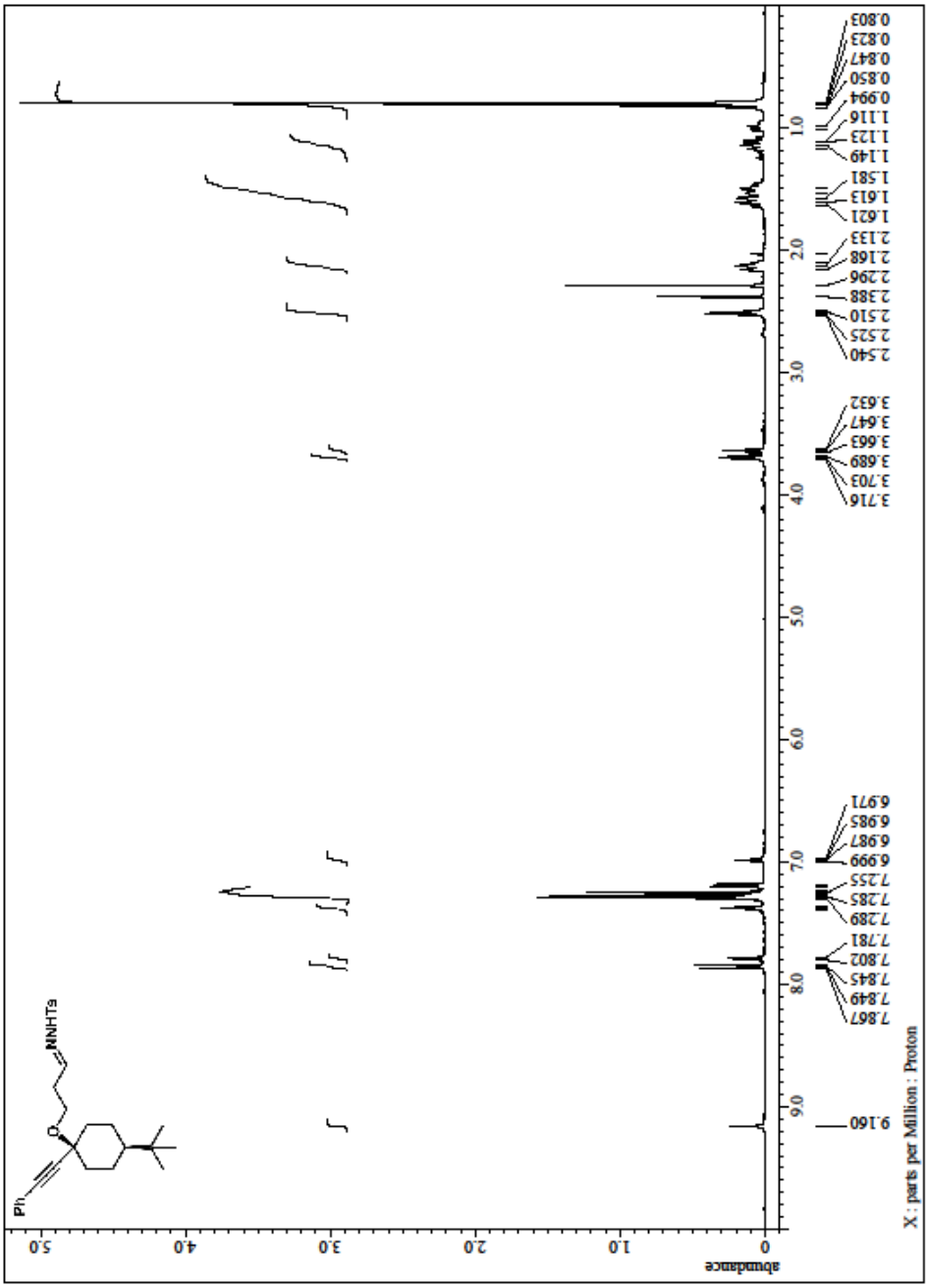

Figure A.3.105. ^{1}H NMR for compound **251A**

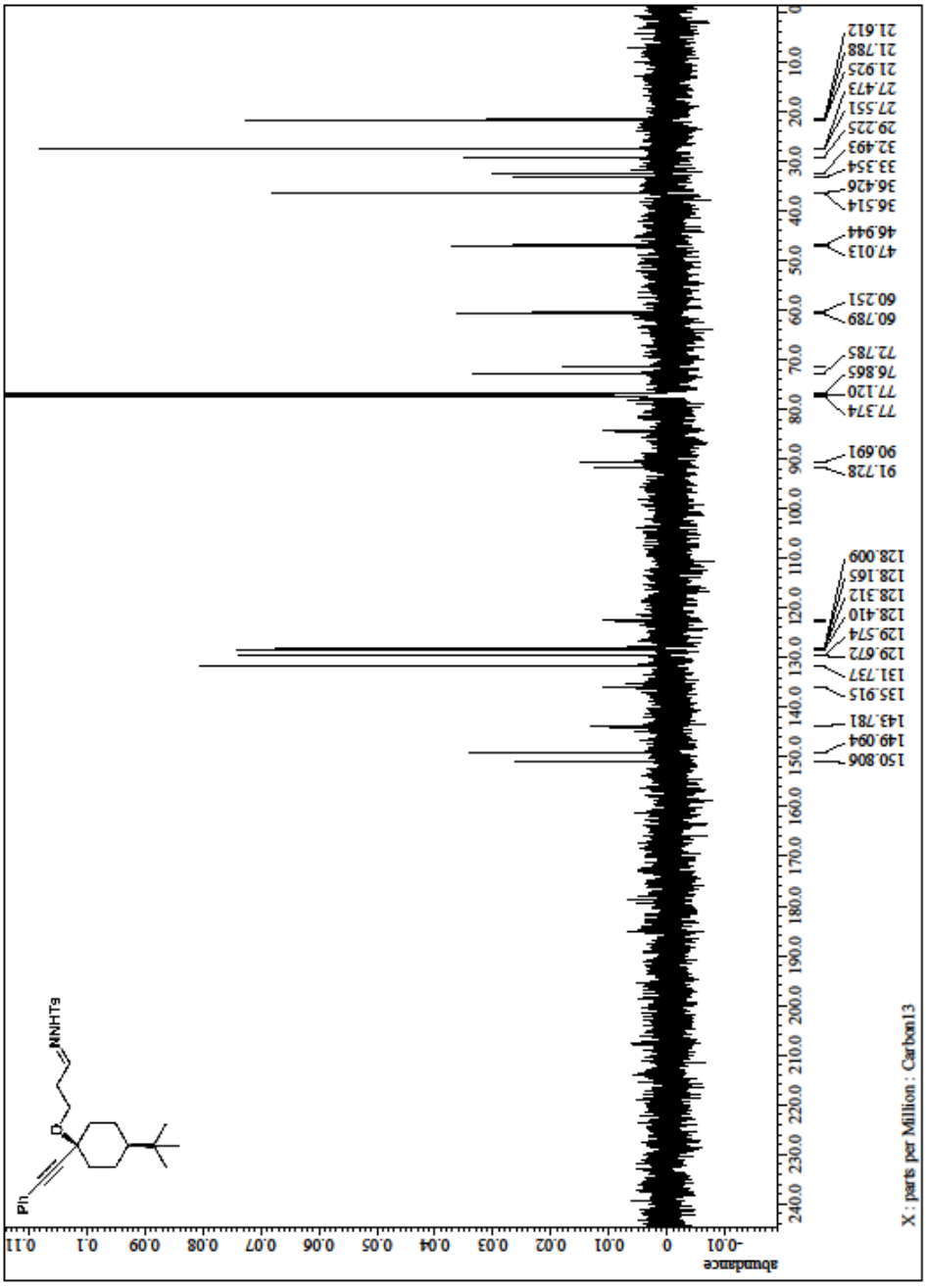

Figure A.3.106. ^{13}C NMR for compound **251A**

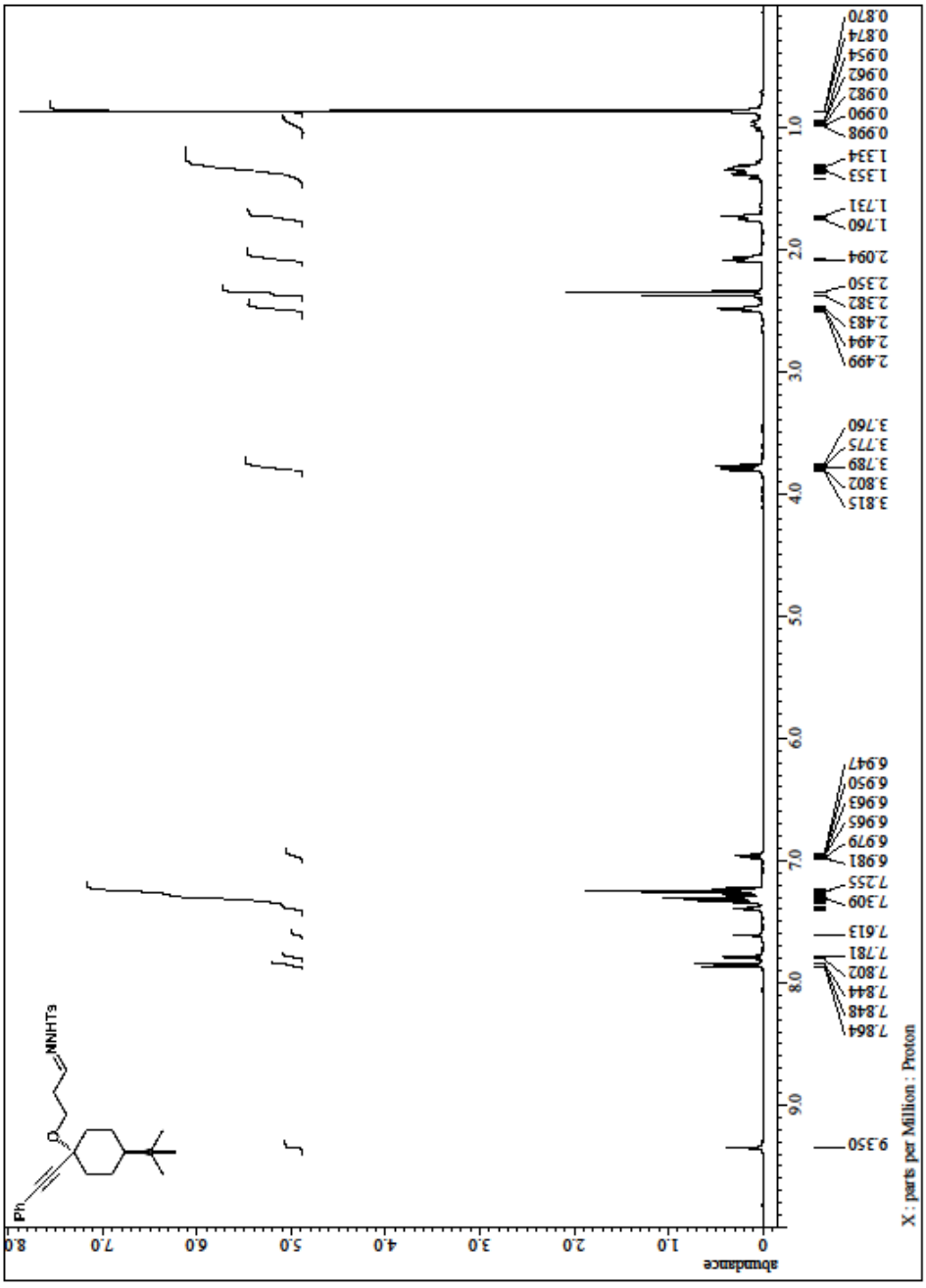

Figure A.3.107. ^{1}H NMR for compound **251B**

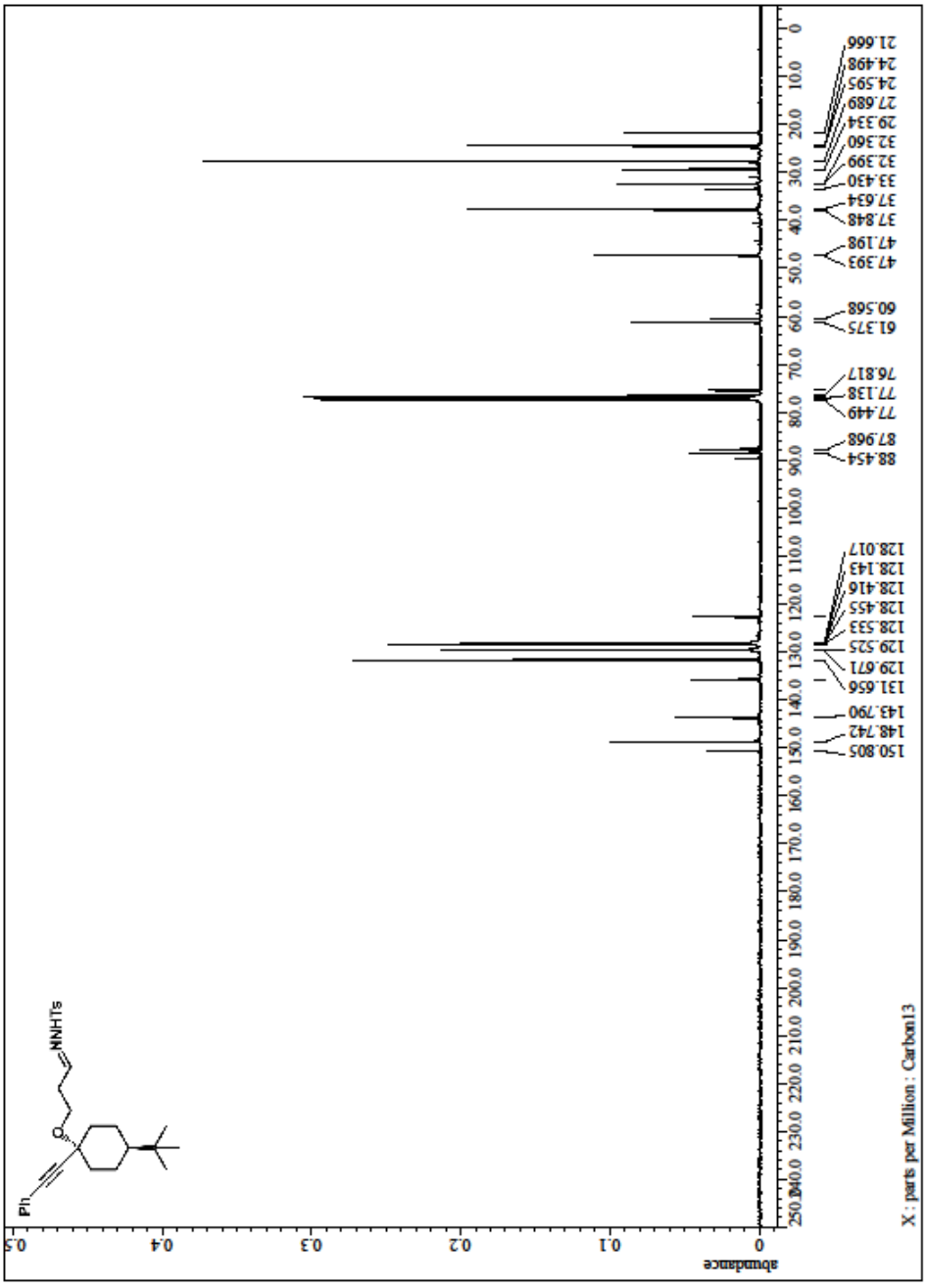

Figure A.3.108. ^{13}C NMR for compound **251B**

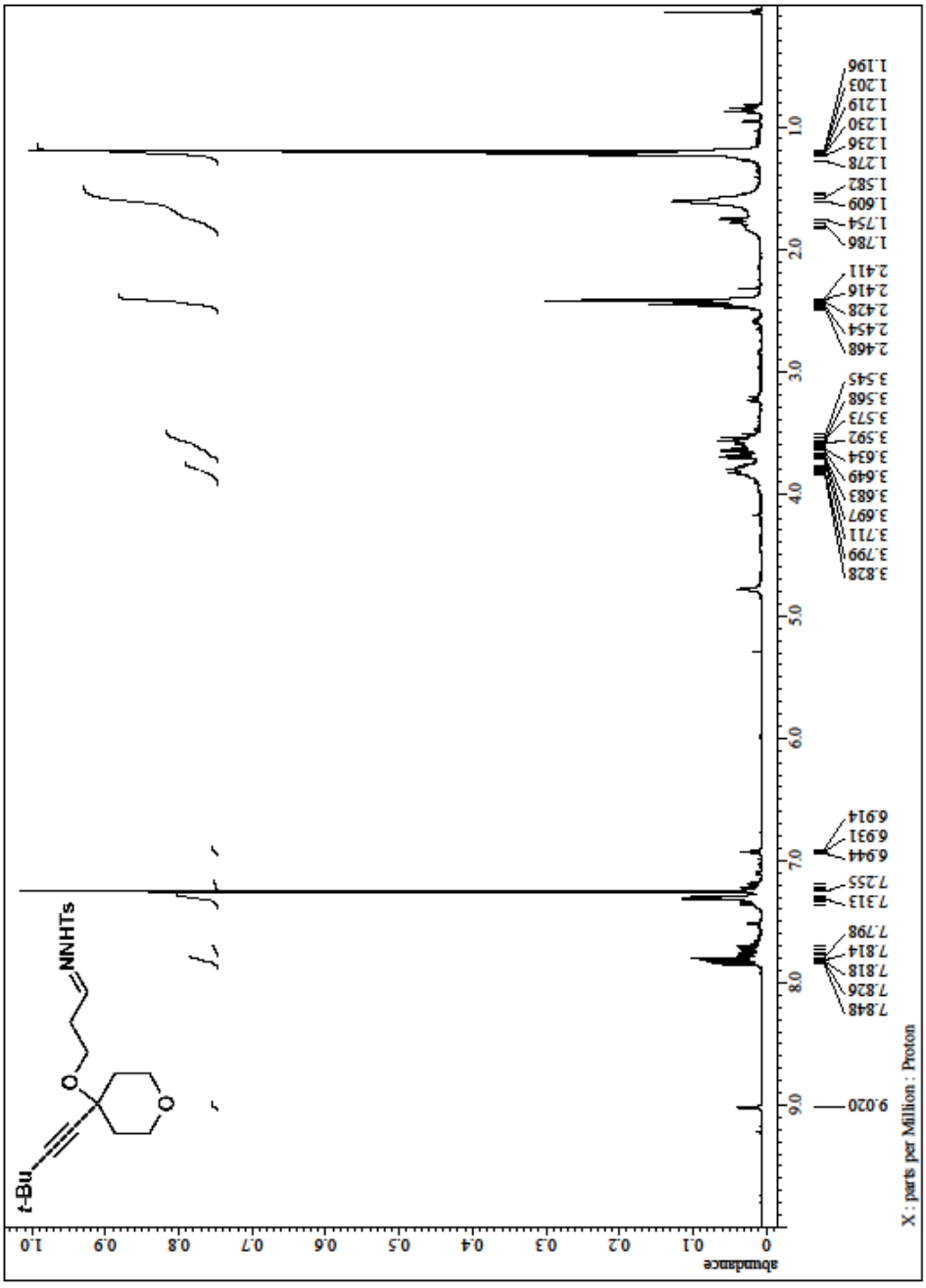

Figure A.3.109. ^{1}H NMR for compound **252**

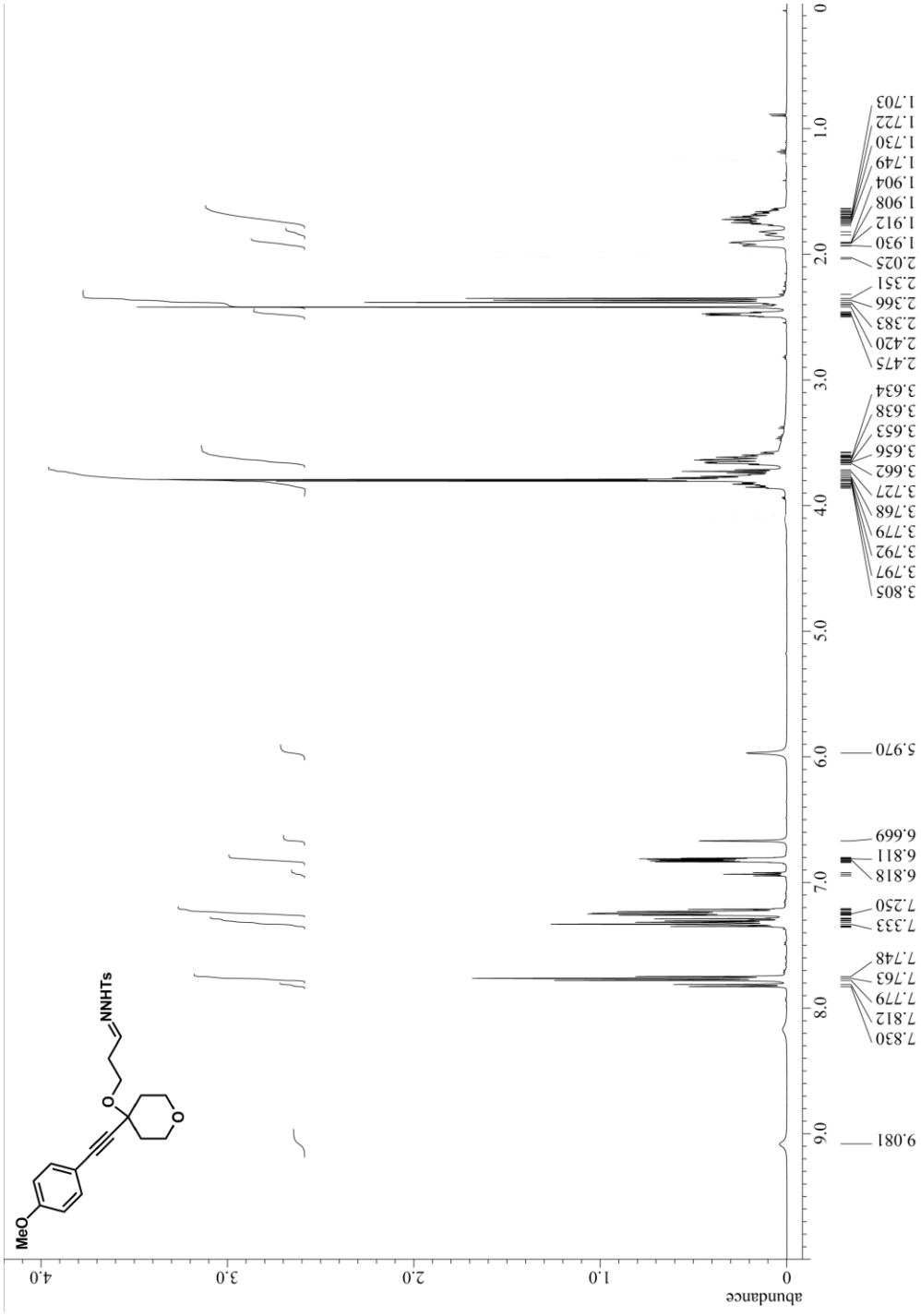

Figure A.3.110. ^{1}H NMR for compound **253**

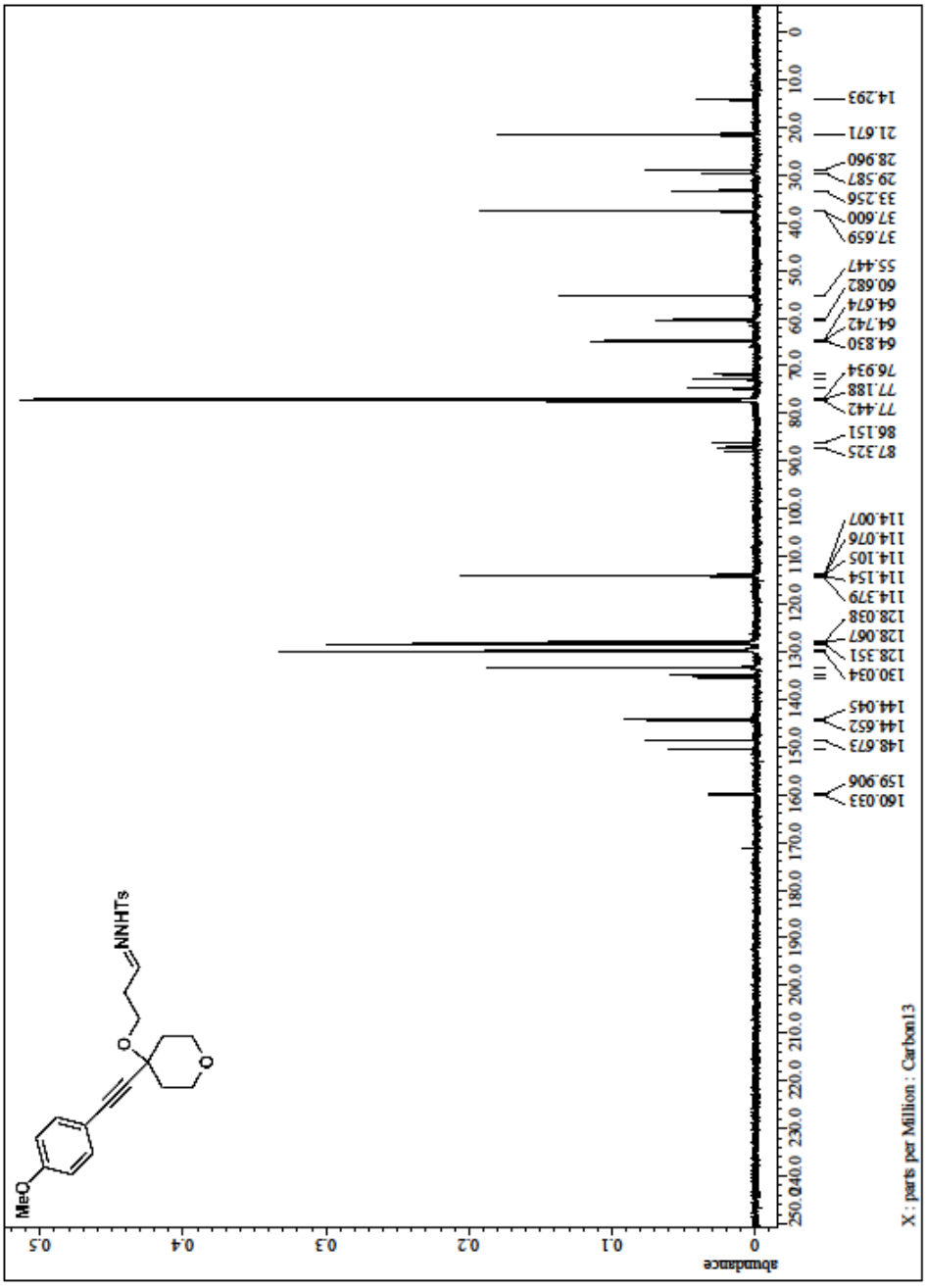

Figure A.3.111. ^{13}C NMR for compound **253**

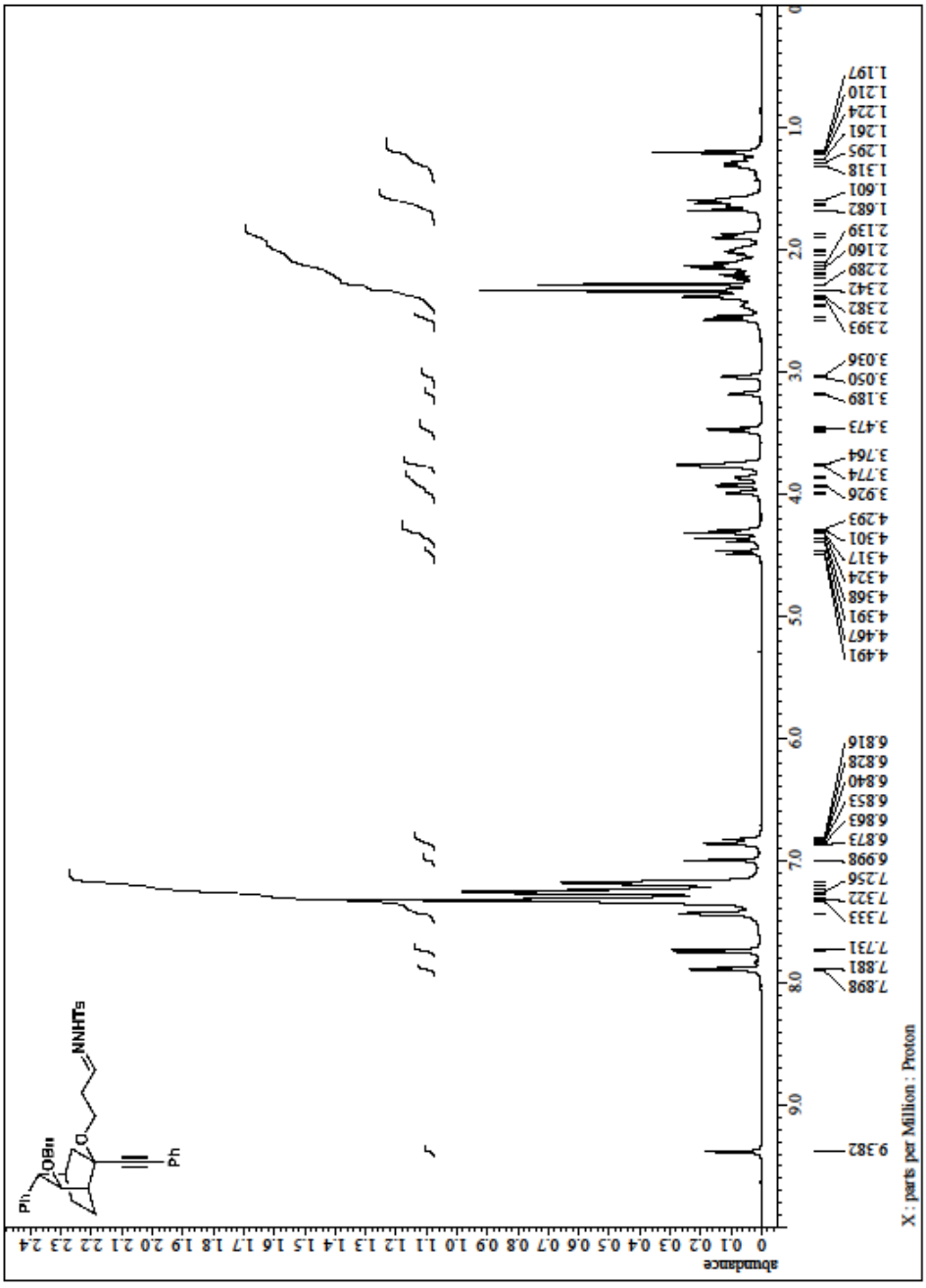

Figure A.3.112. ^{1}H NMR for compound **254**

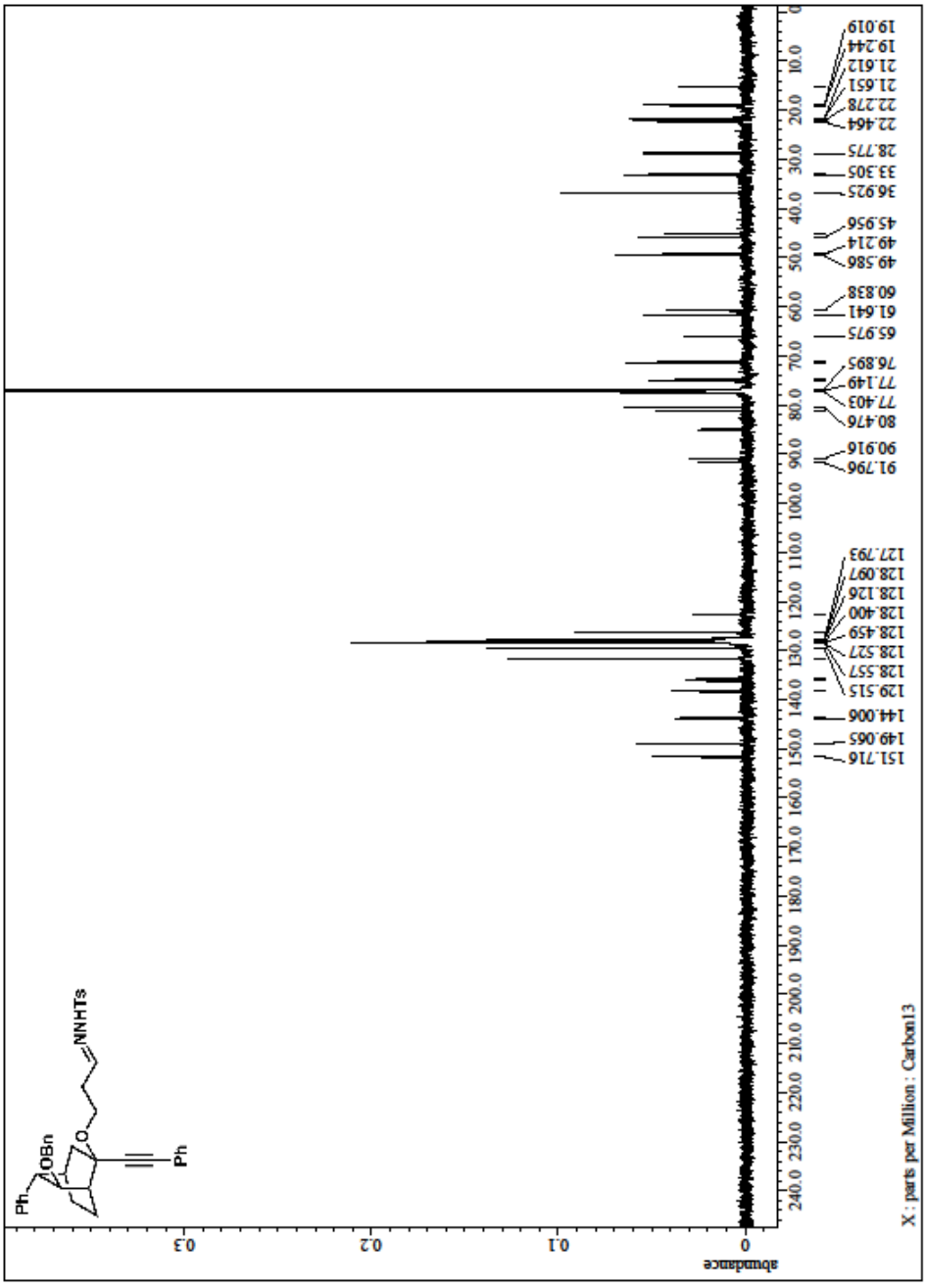

Figure A.3.113. ^{13}C NMR for compound **254**

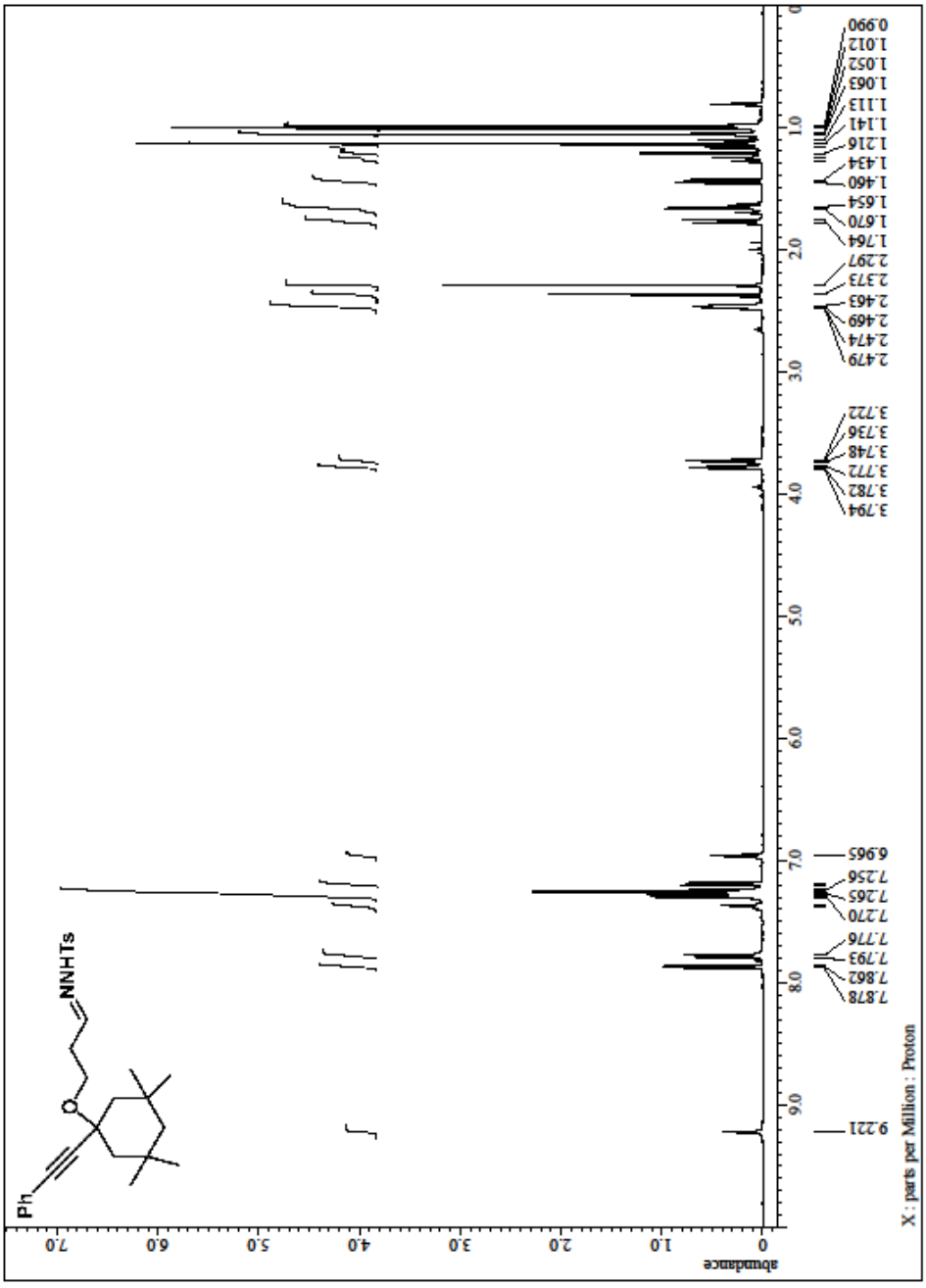

Figure A.3.114. ^{1}H NMR for compound **255**

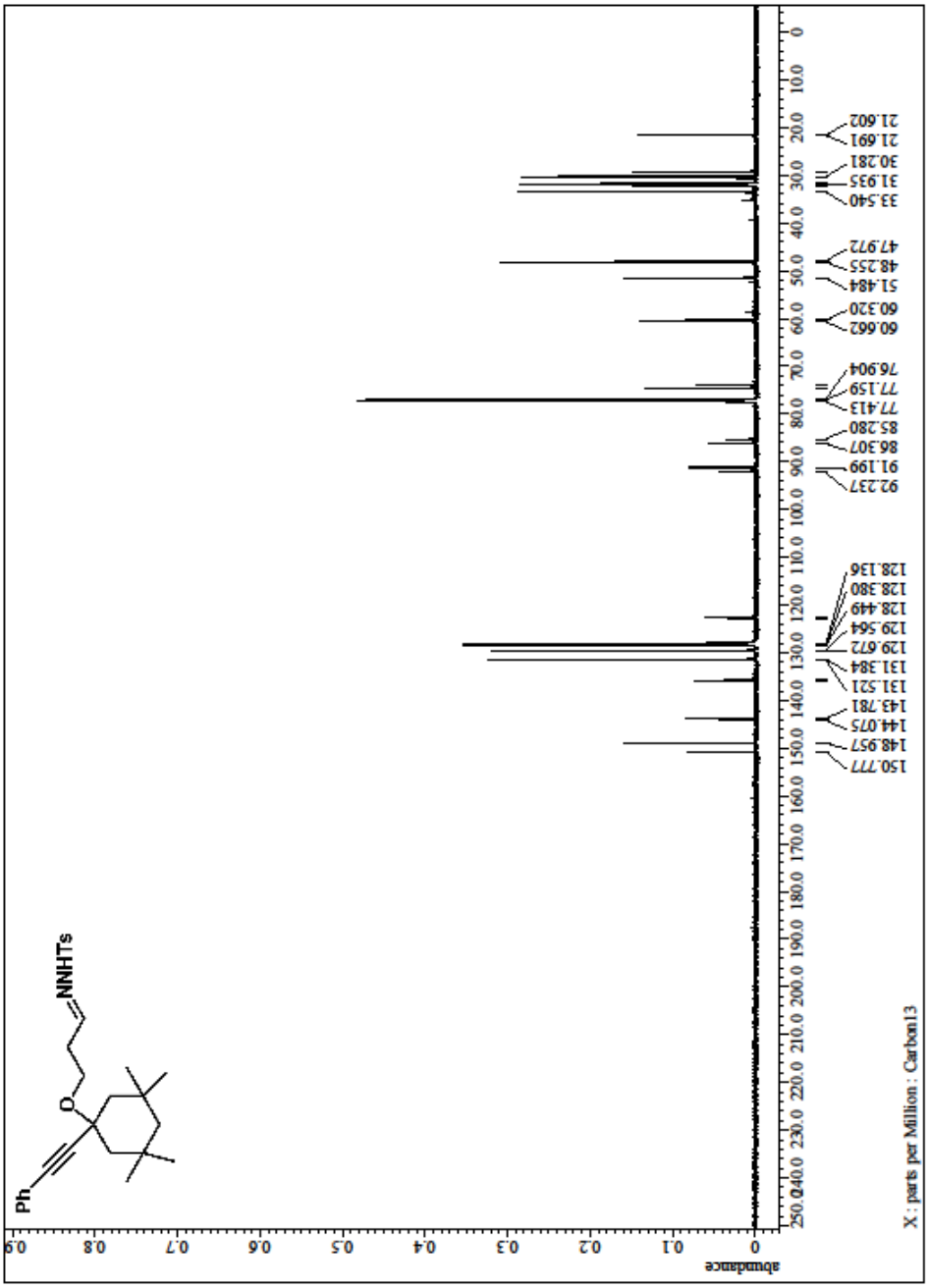

Figure A.3.115. ^{13}C NMR for compound **255**

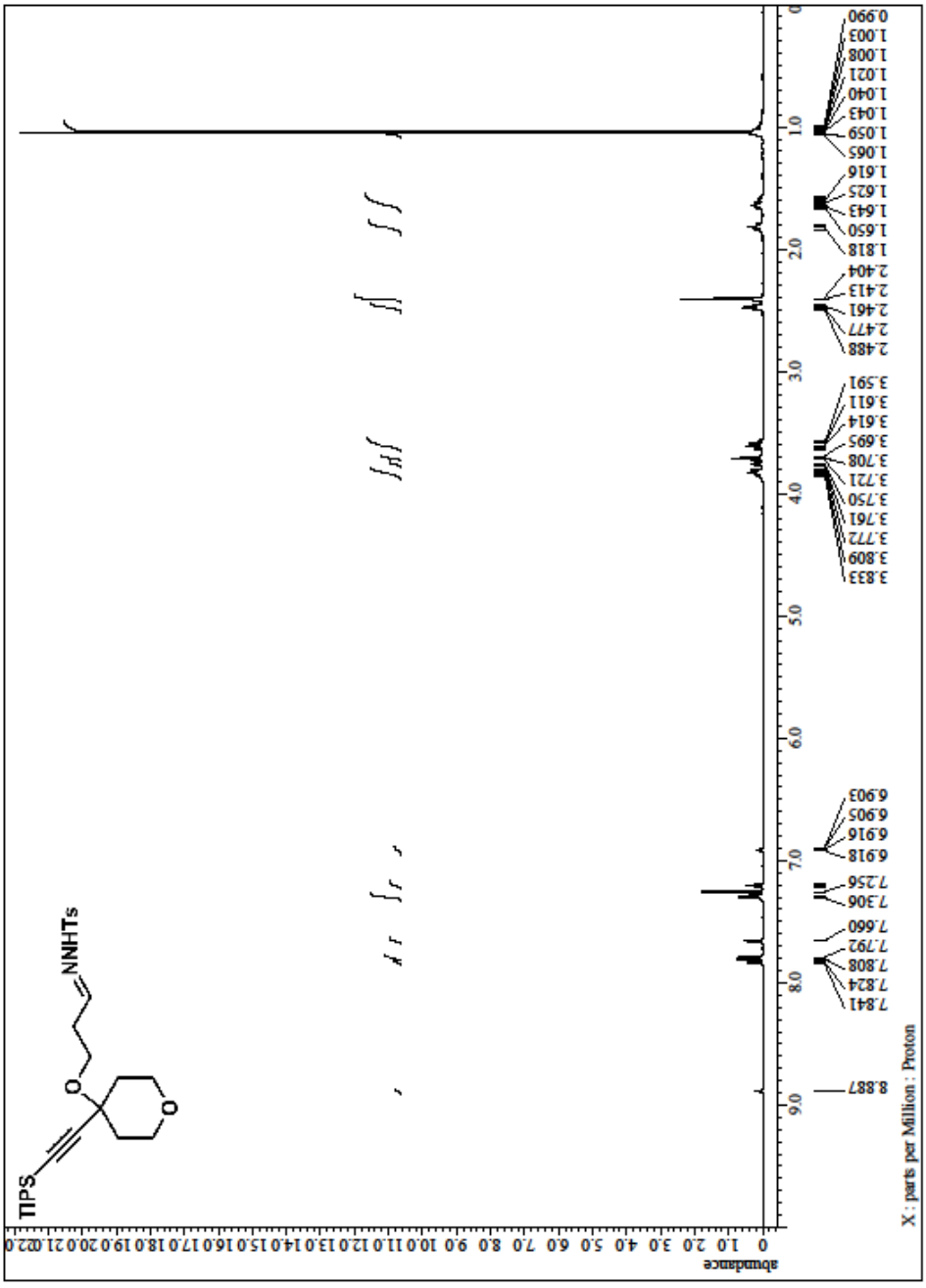

Figure A.3.116. ^{1}H NMR for compound **256**

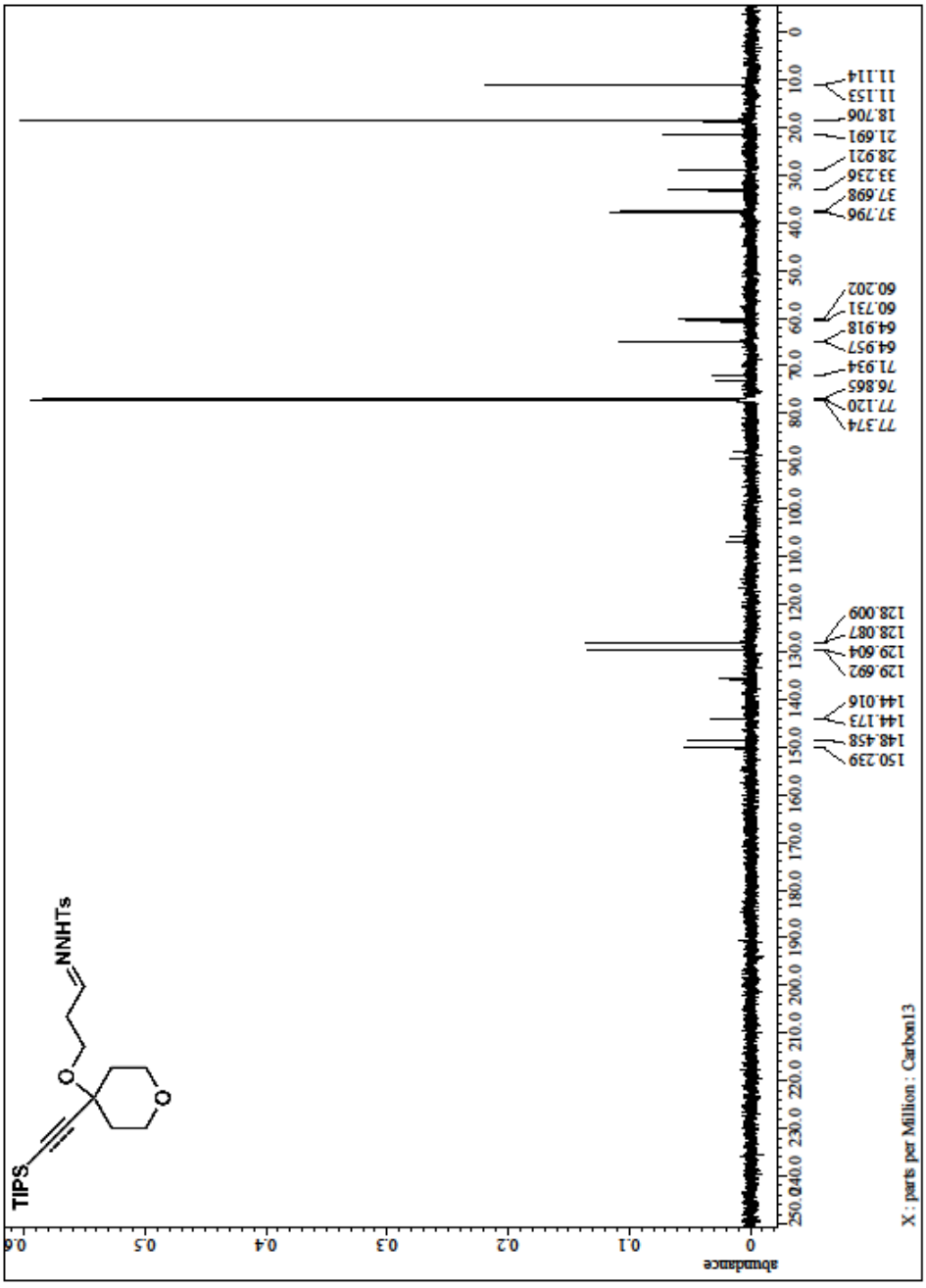

Figure A.3.117. ^{13}C NMR for compound **256**

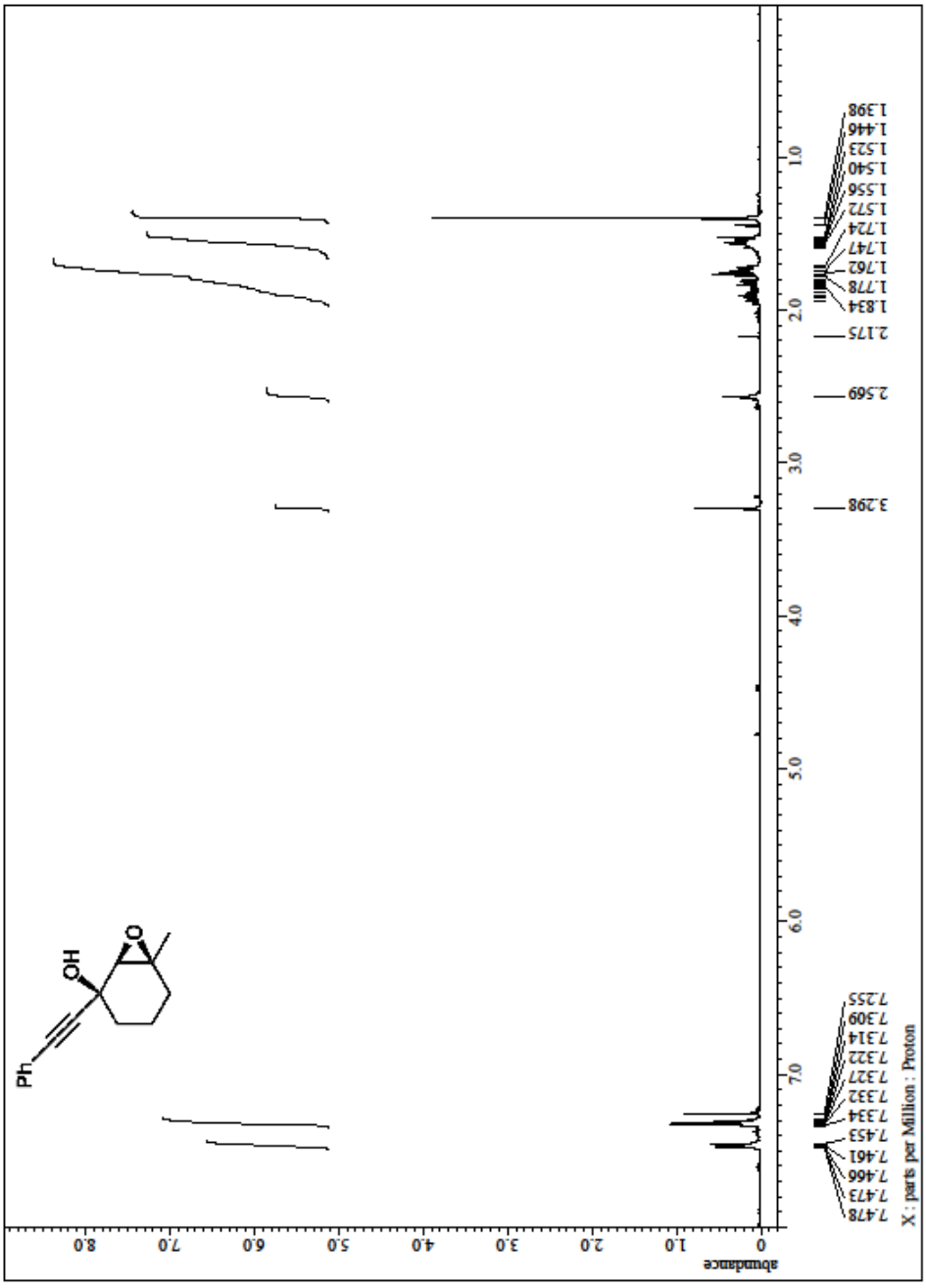

Figure A.3.118. ^{1}H NMR for compound **259**

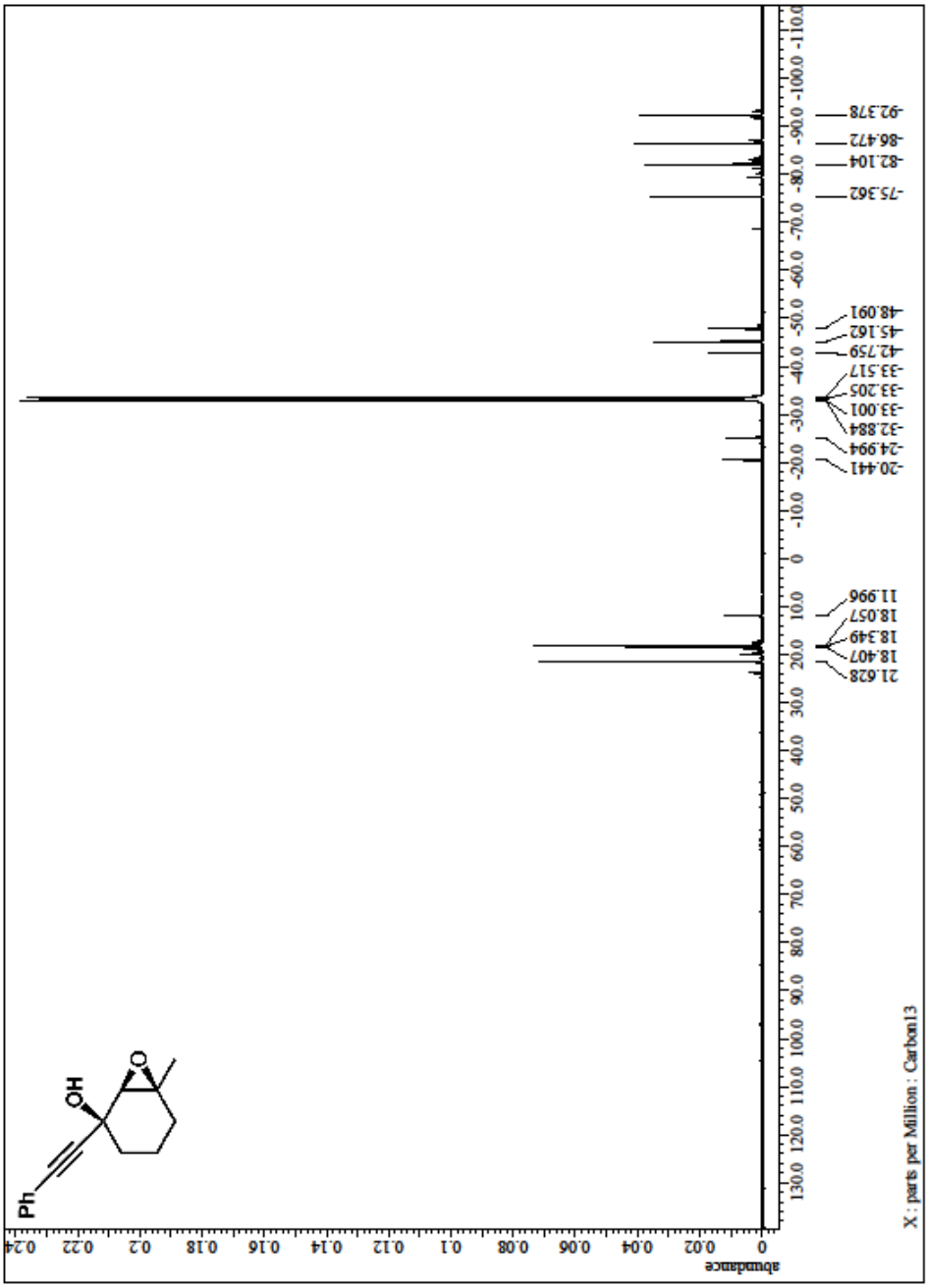

Figure A.3.119. ^{13}C NMR for compound **259**

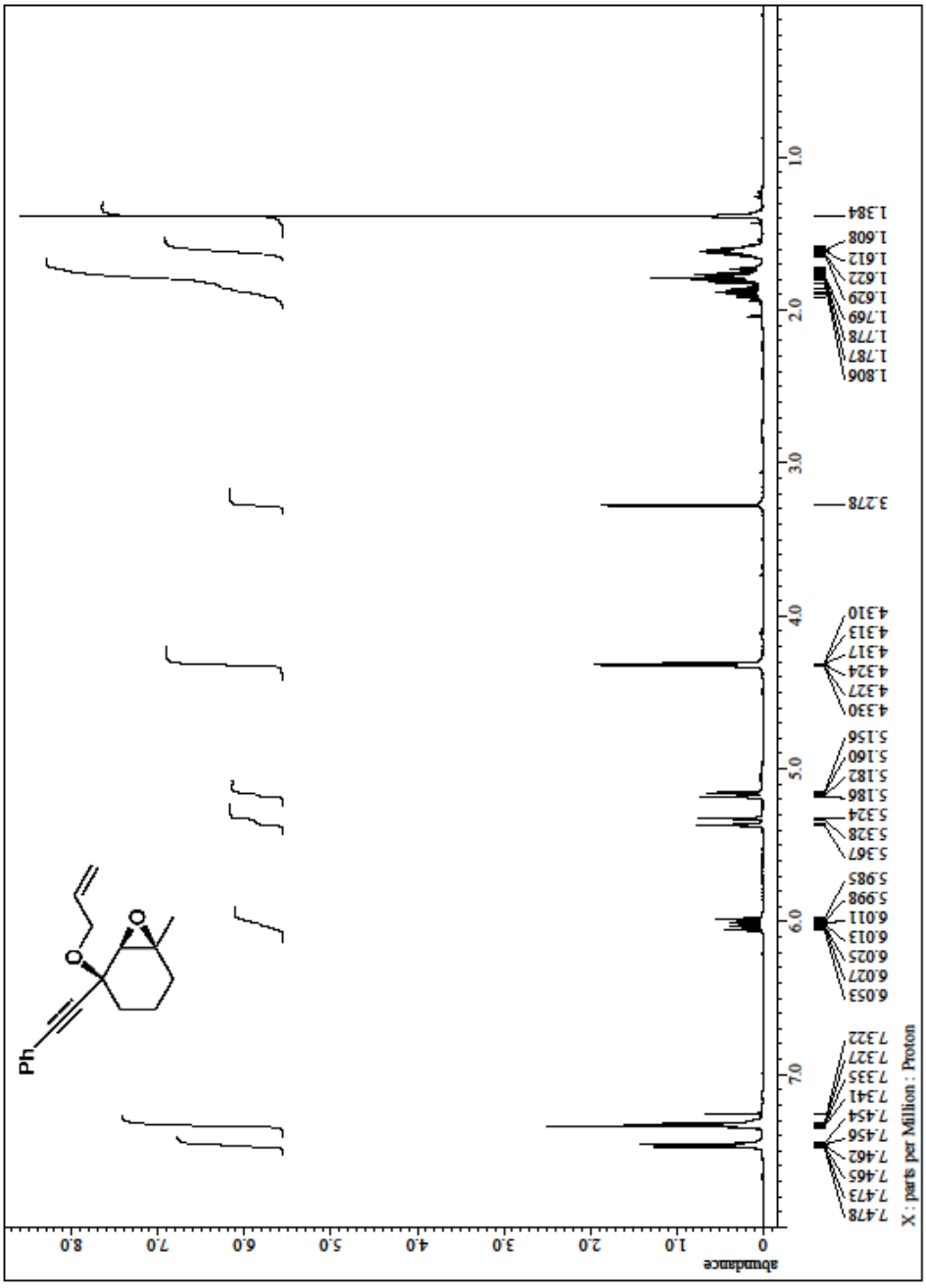

Figure A.3.120. ^{1}H NMR for compound **260**

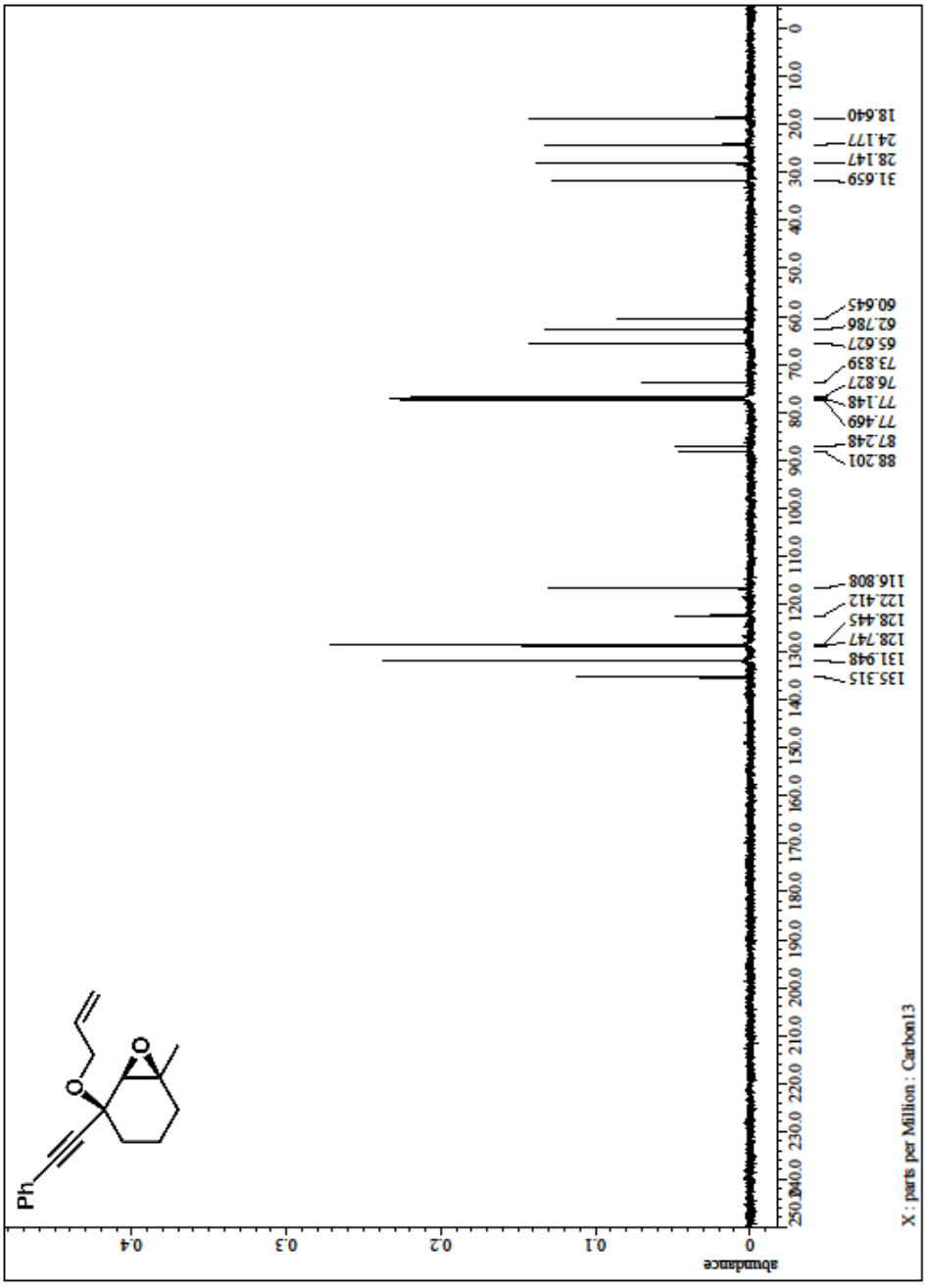

Figure A.3.121. ^{13}C NMR for compound **260**

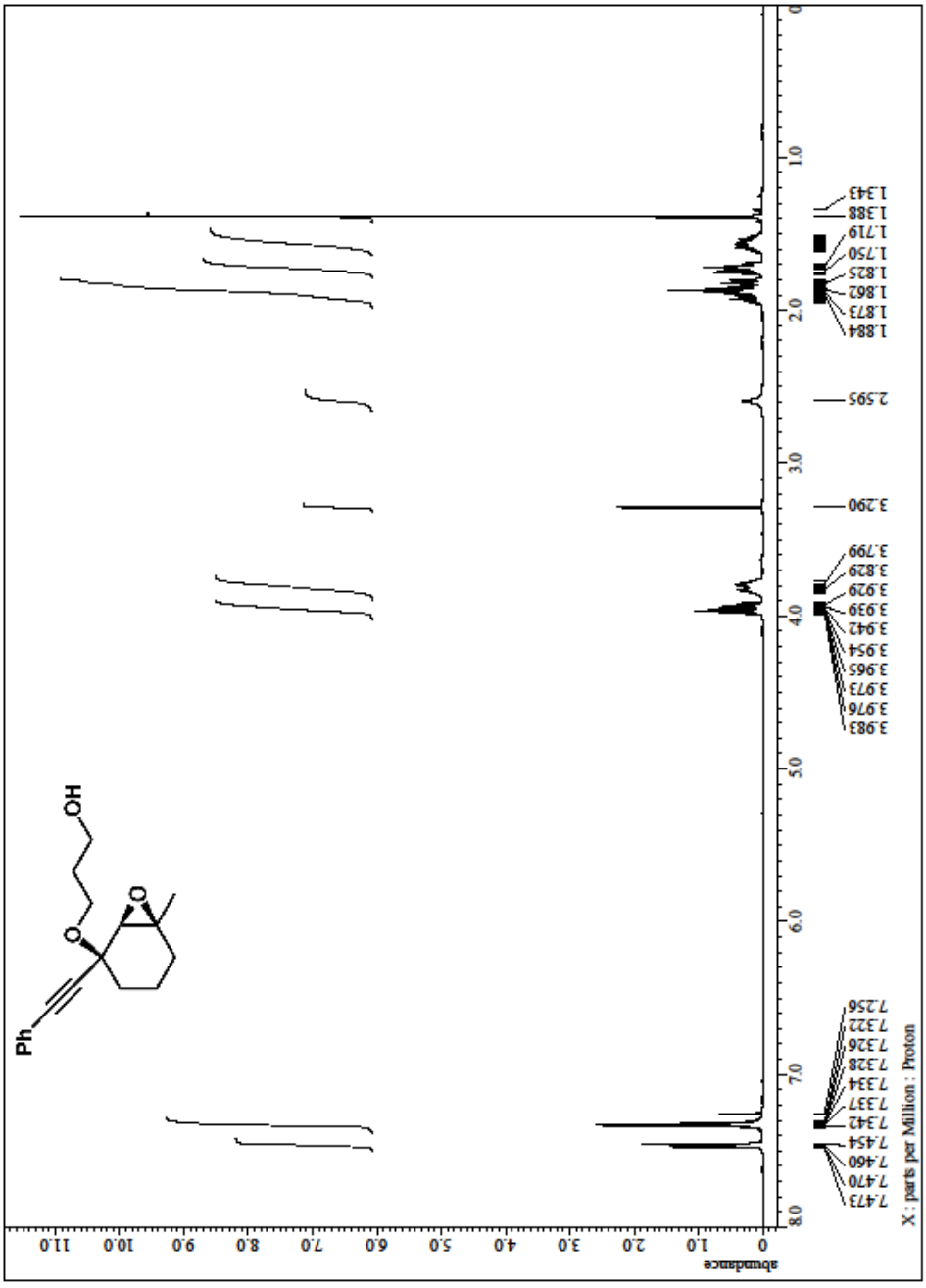

Figure A.3.122. ^{1}H NMR for compound **261**

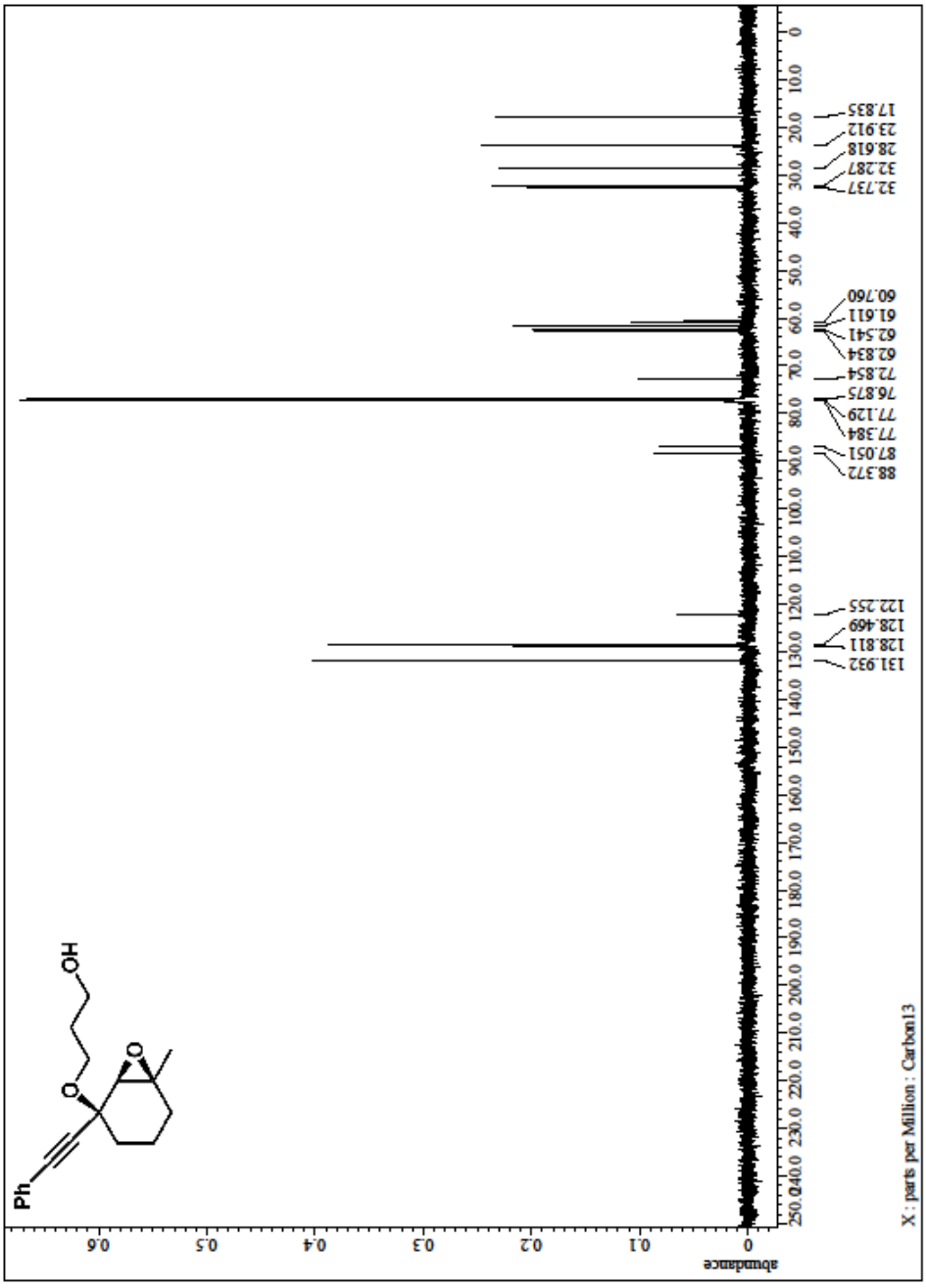

Figure A.3.123. ^{13}C NMR for compound **261**

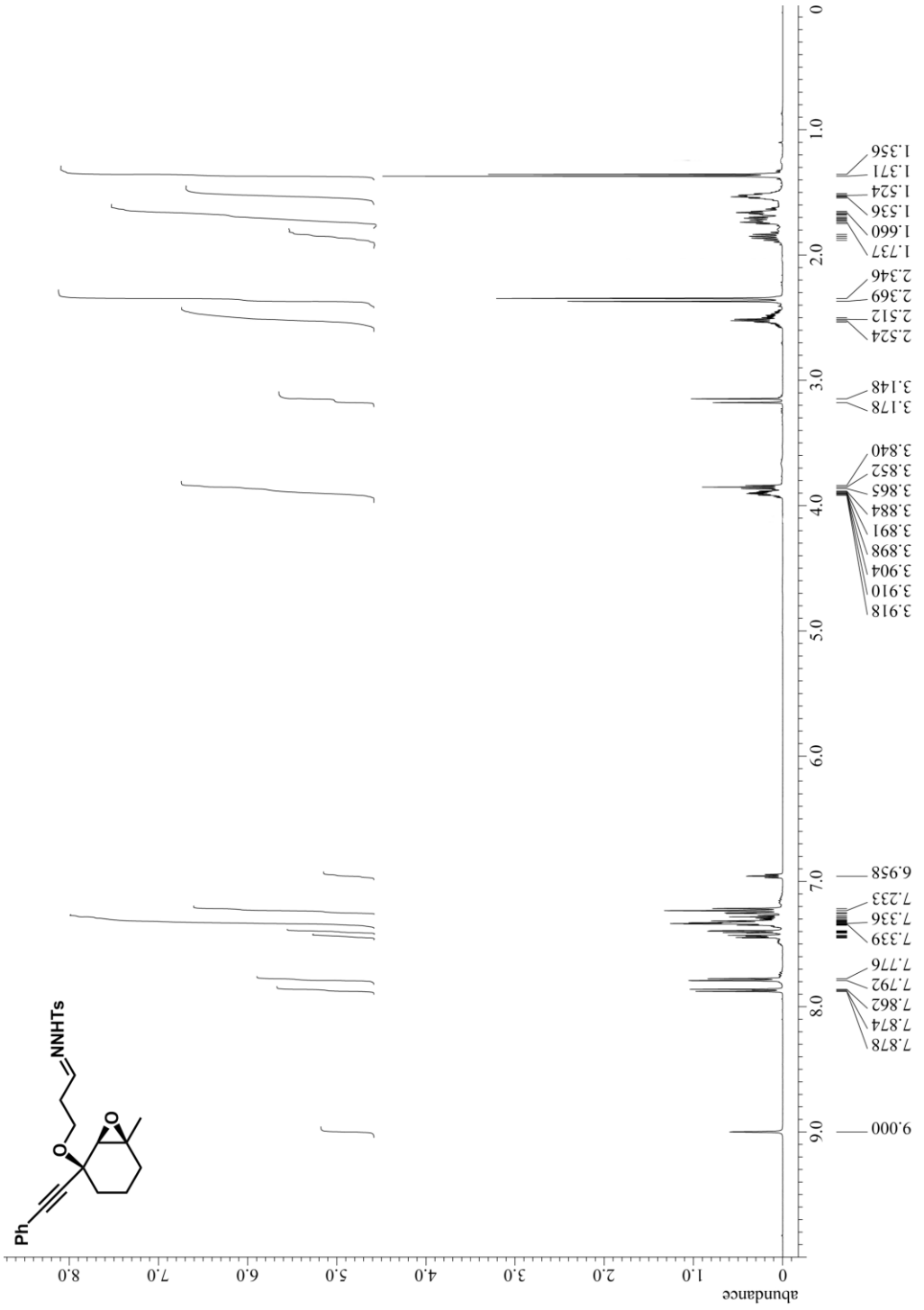

Figure A.3.124. ^{1}H NMR for compound **262**

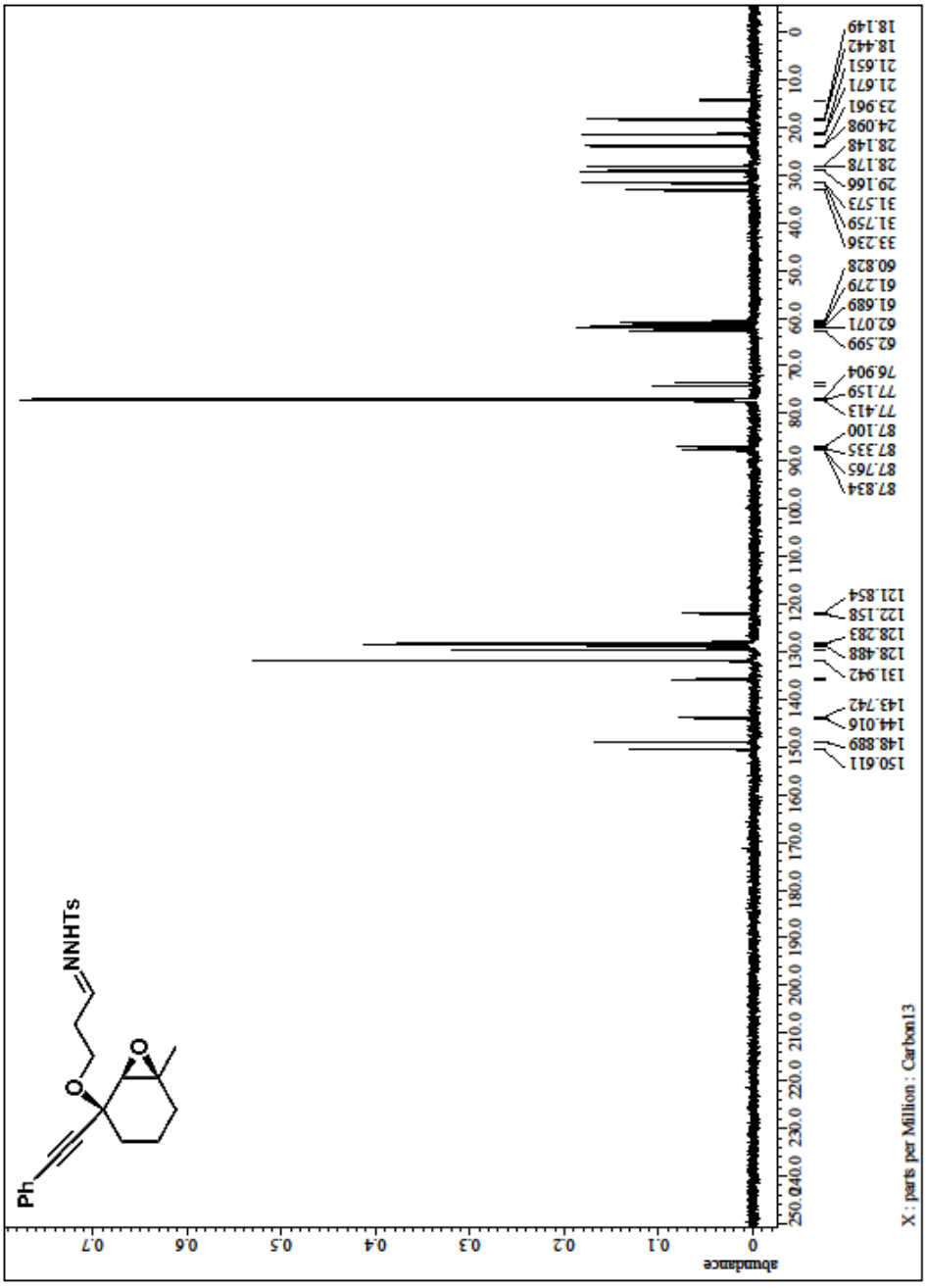

Figure A.3.125. ^{13}C NMR for compound **262**

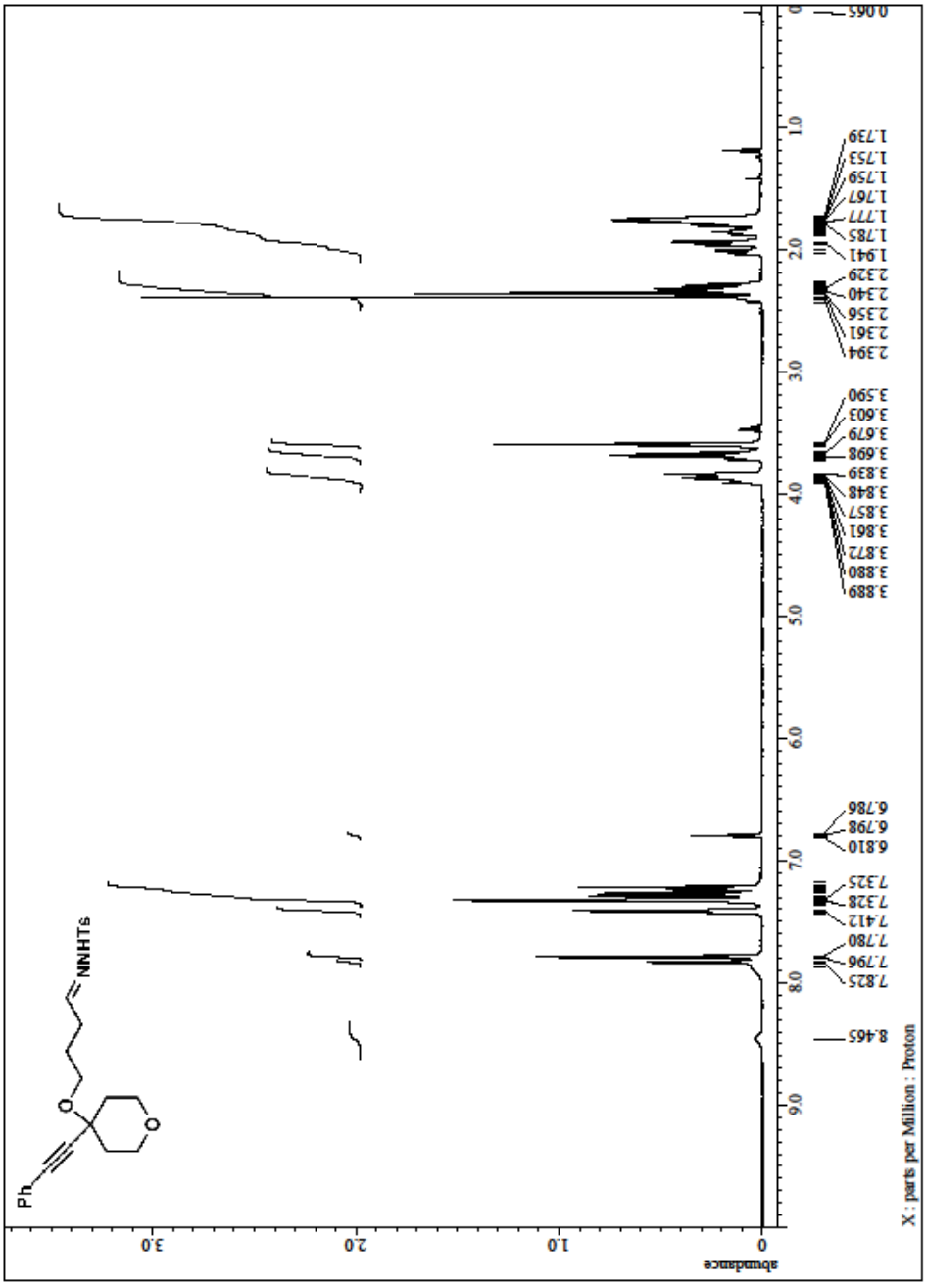

Figure A.3.126. ^{1}H NMR for compound **267**

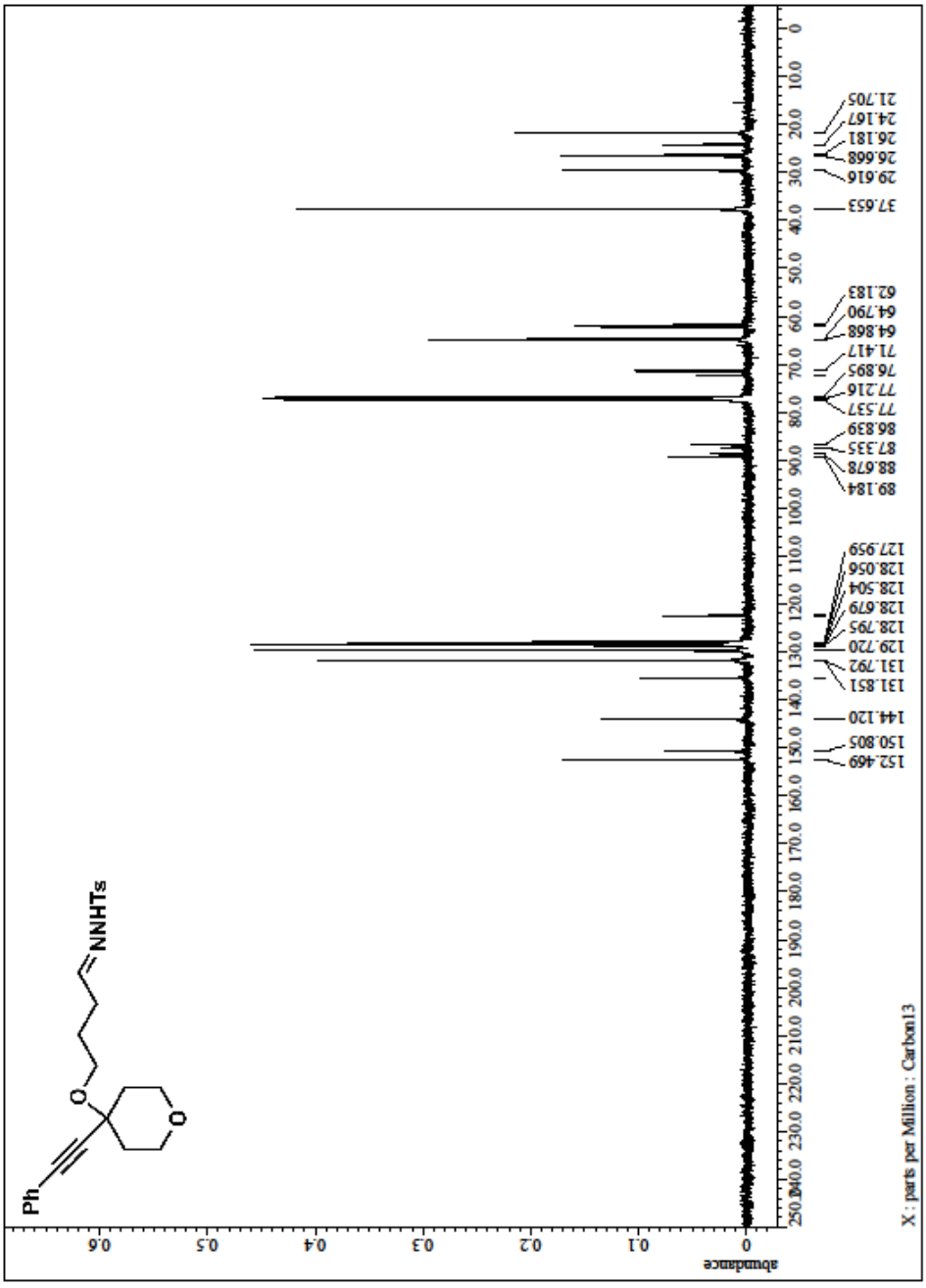

Figure A.3.127. ^{13}C NMR for compound **267**

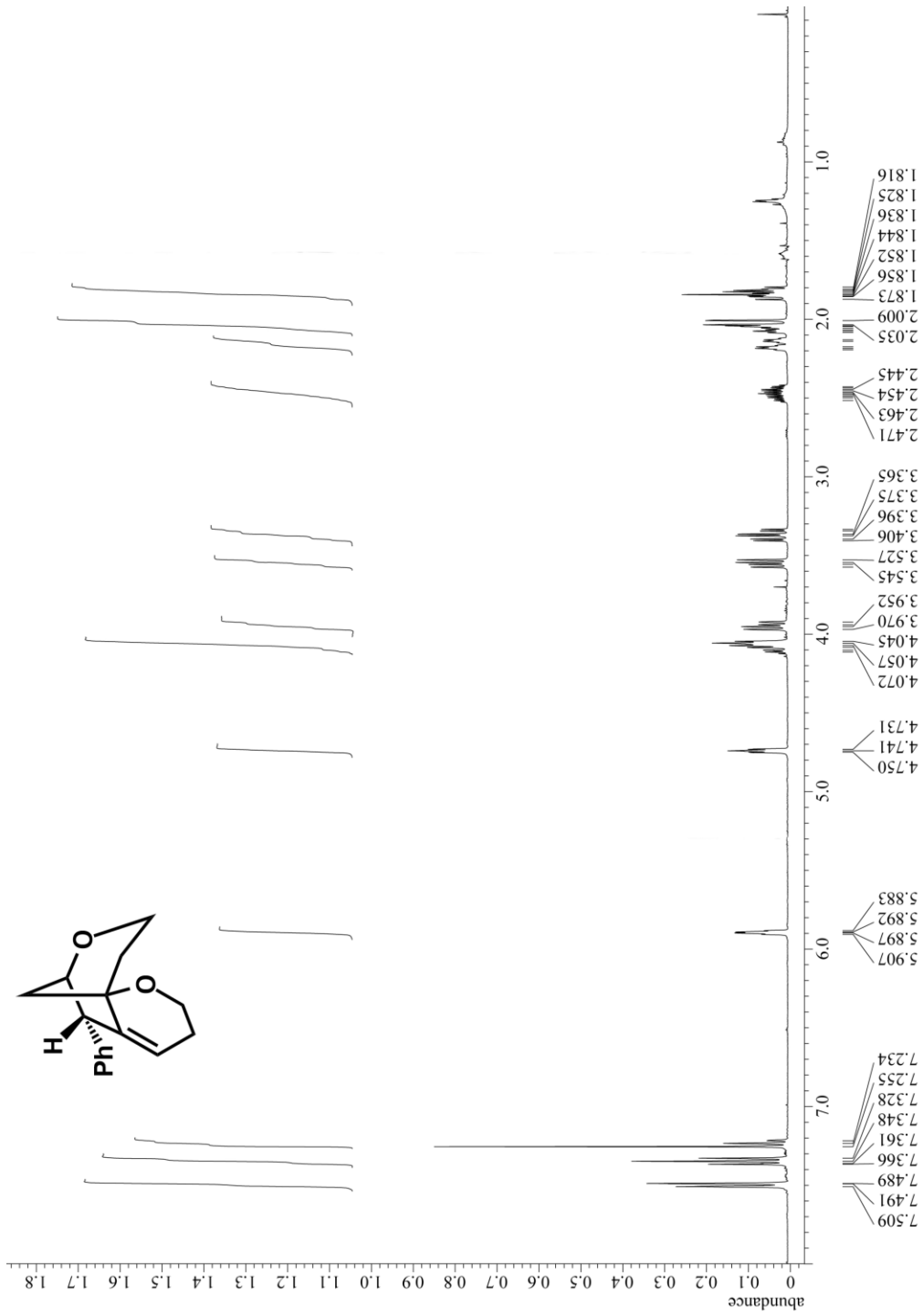

Figure A.3.128. ^{1}H NMR for compound **268**

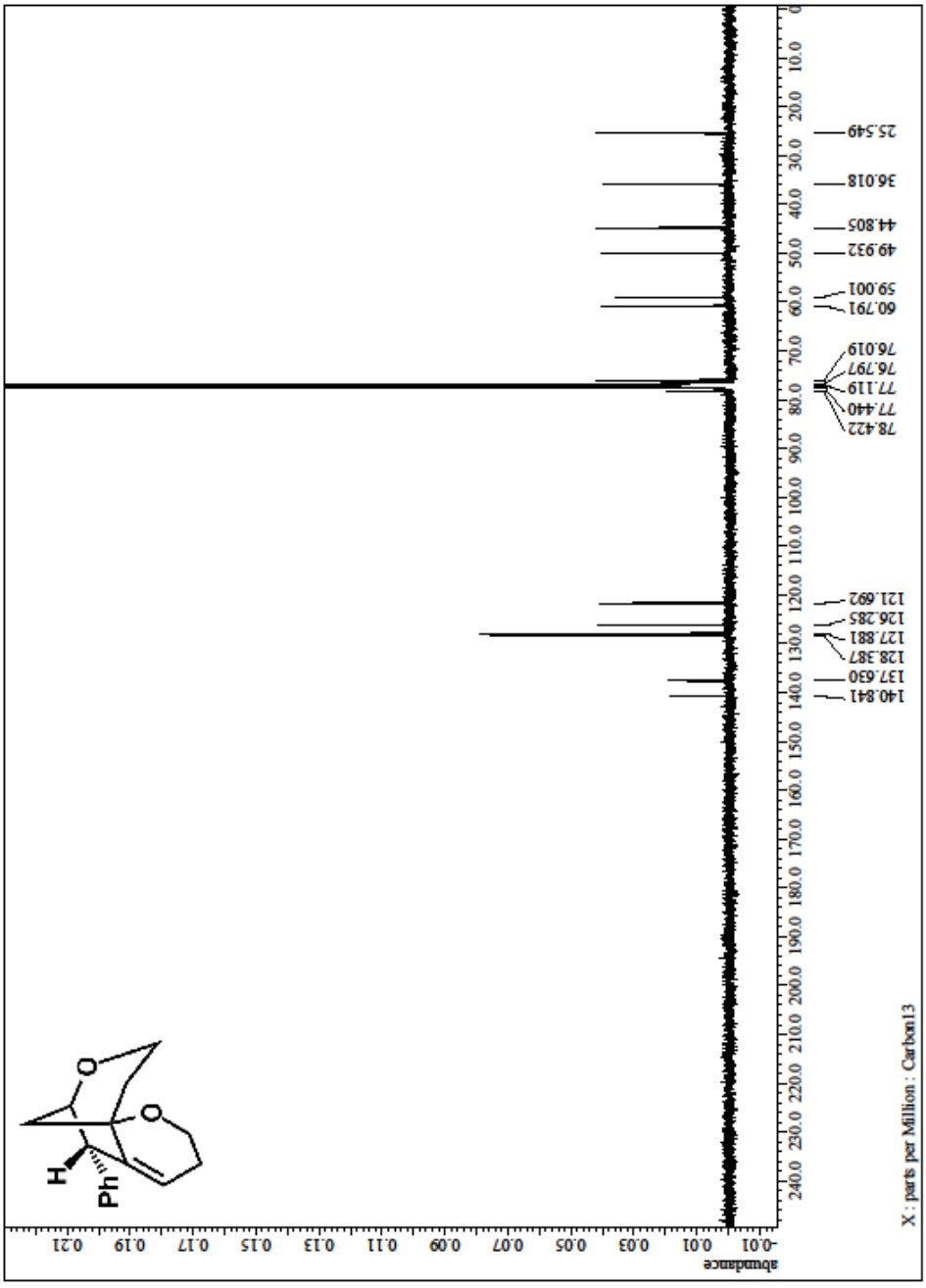

Figure A.3.129. ^{13}C NMR for compound **268**

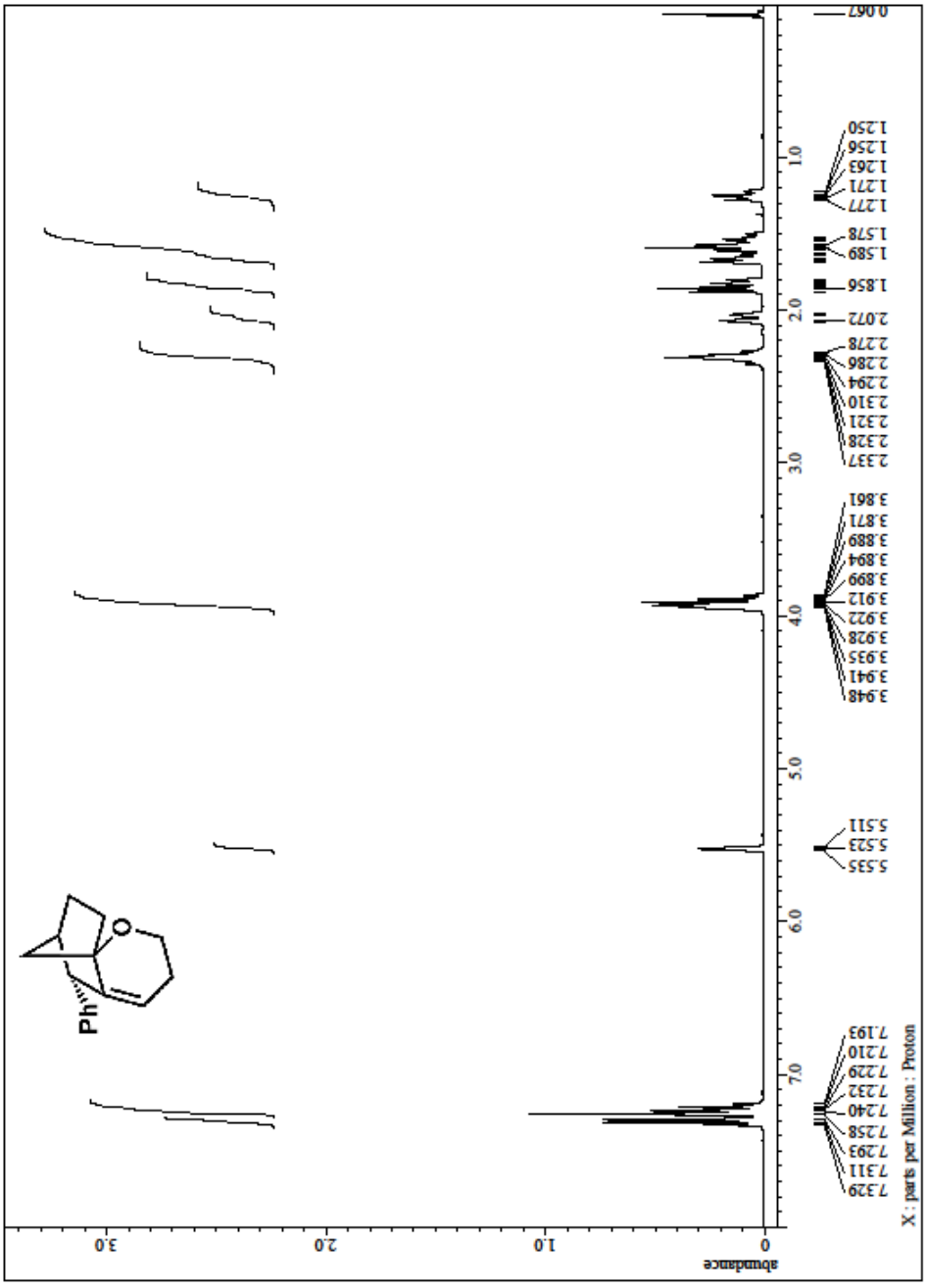

Figure A.3.130. ^{1}H NMR for compound **269**

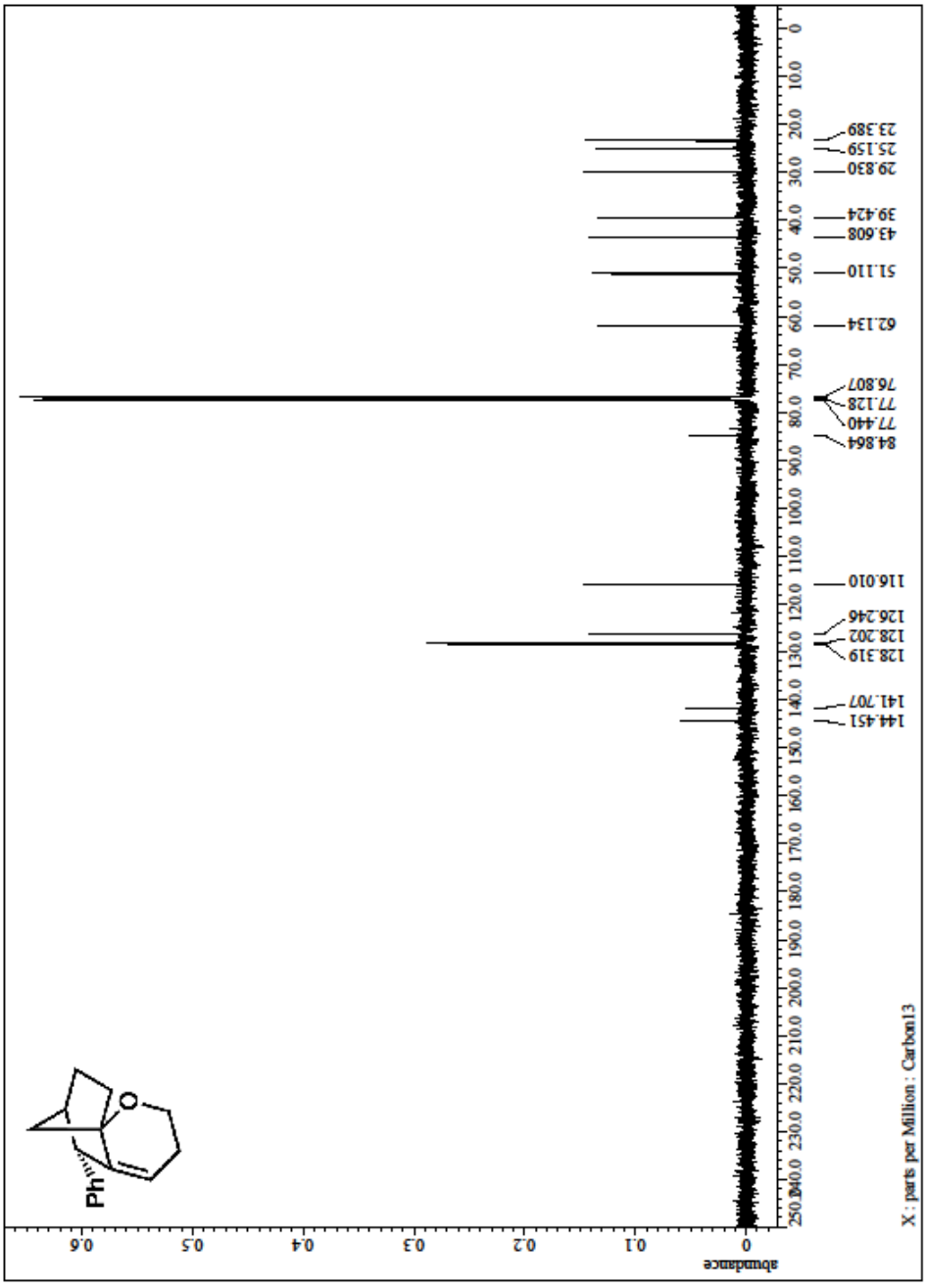

Figure A.3.131. ^{13}C NMR for compound **269**

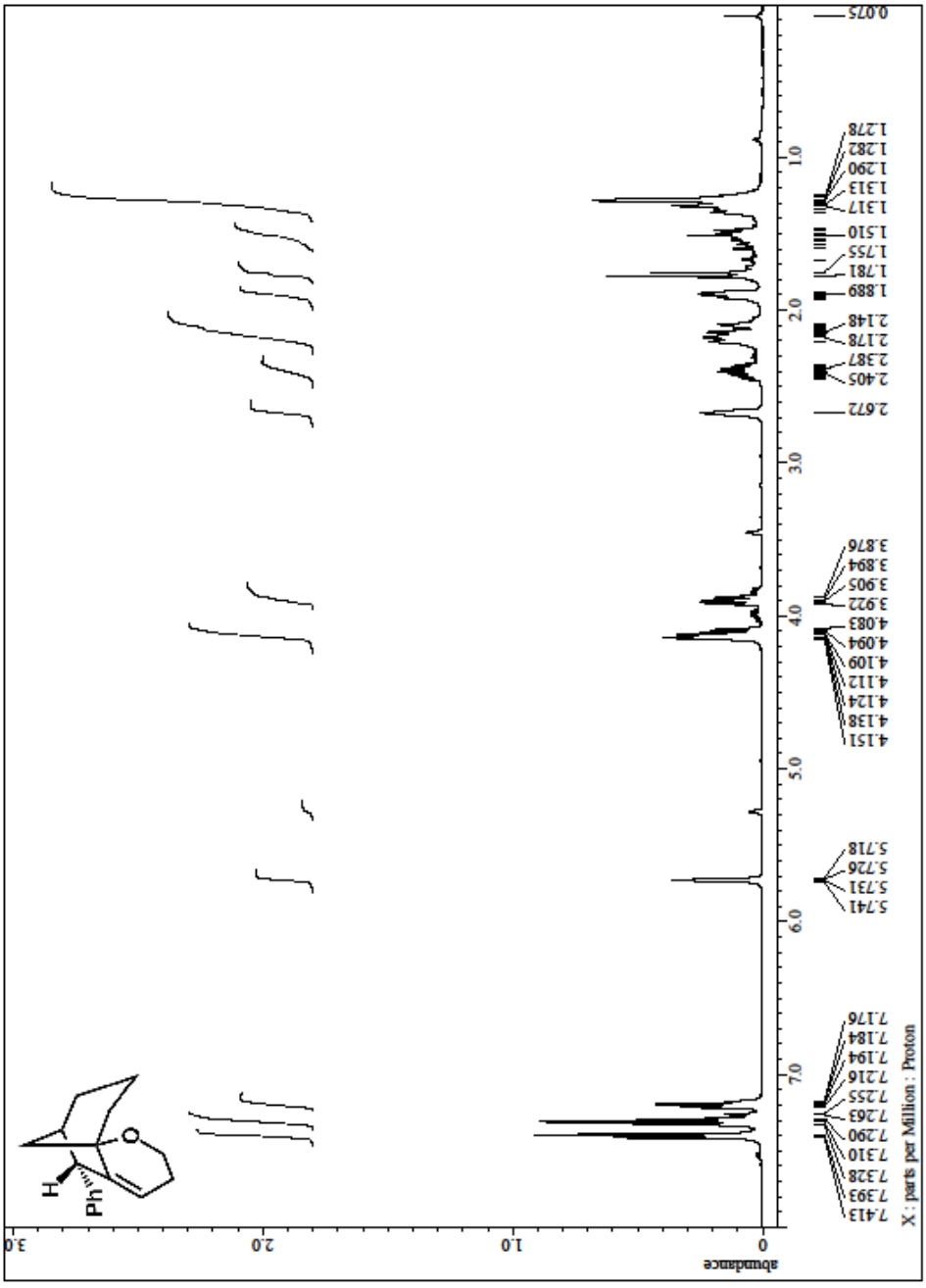

Figure A.3.132. ^{1}H NMR for compound **270**

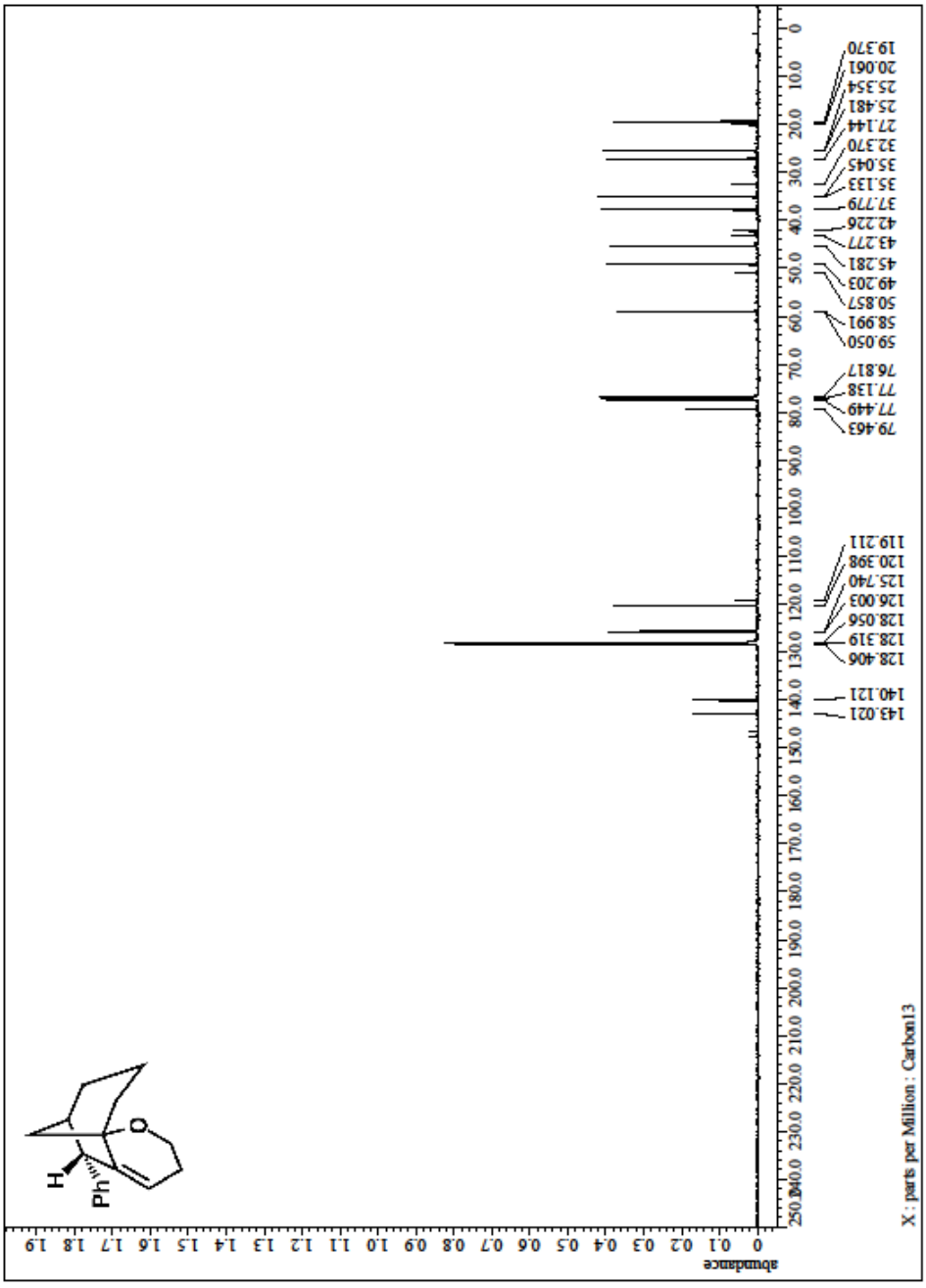

Figure A.3.133. ^{13}C NMR for compound **270**

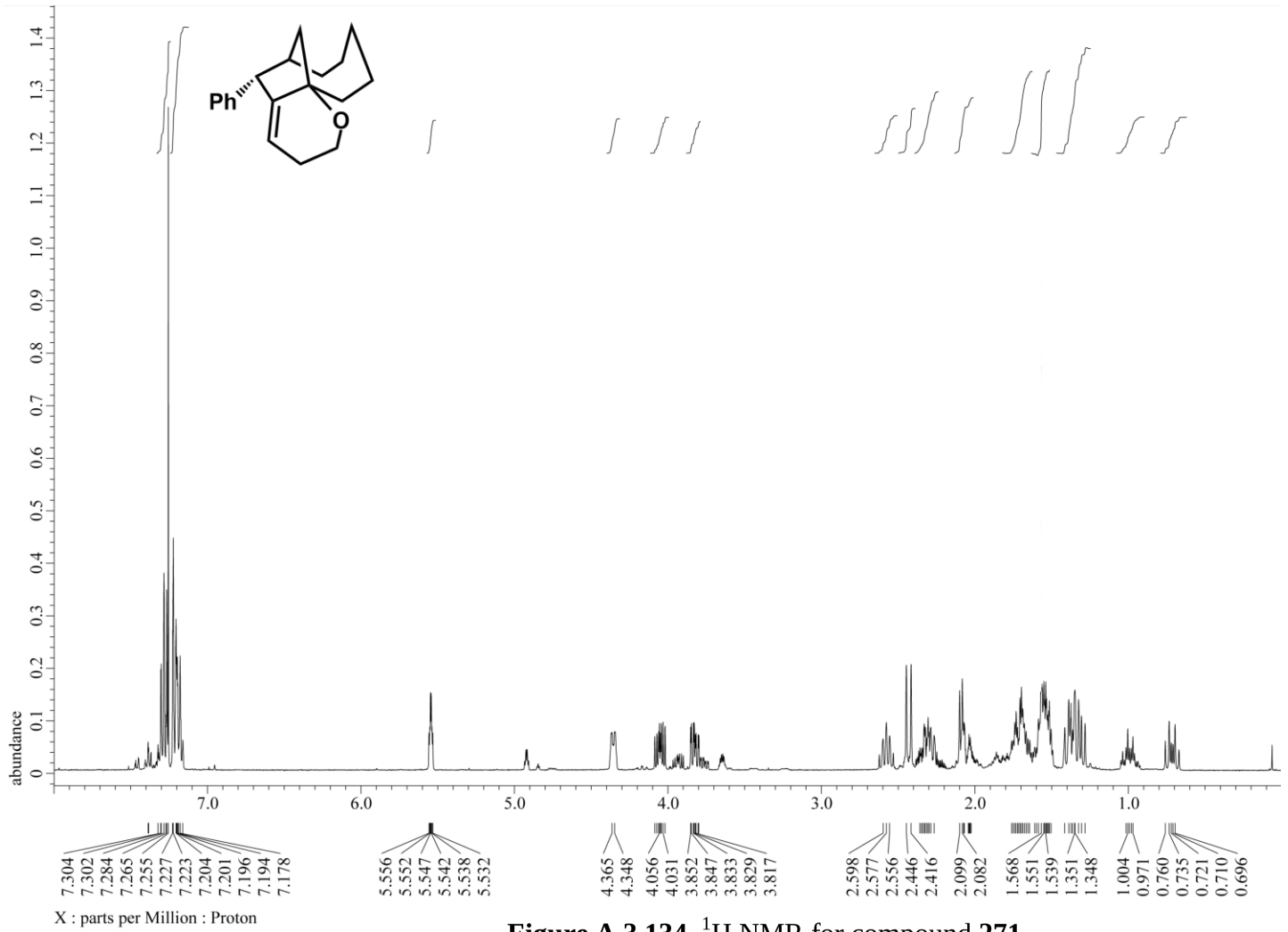

Figure A.3.134. ^{1}H NMR for compound **271**

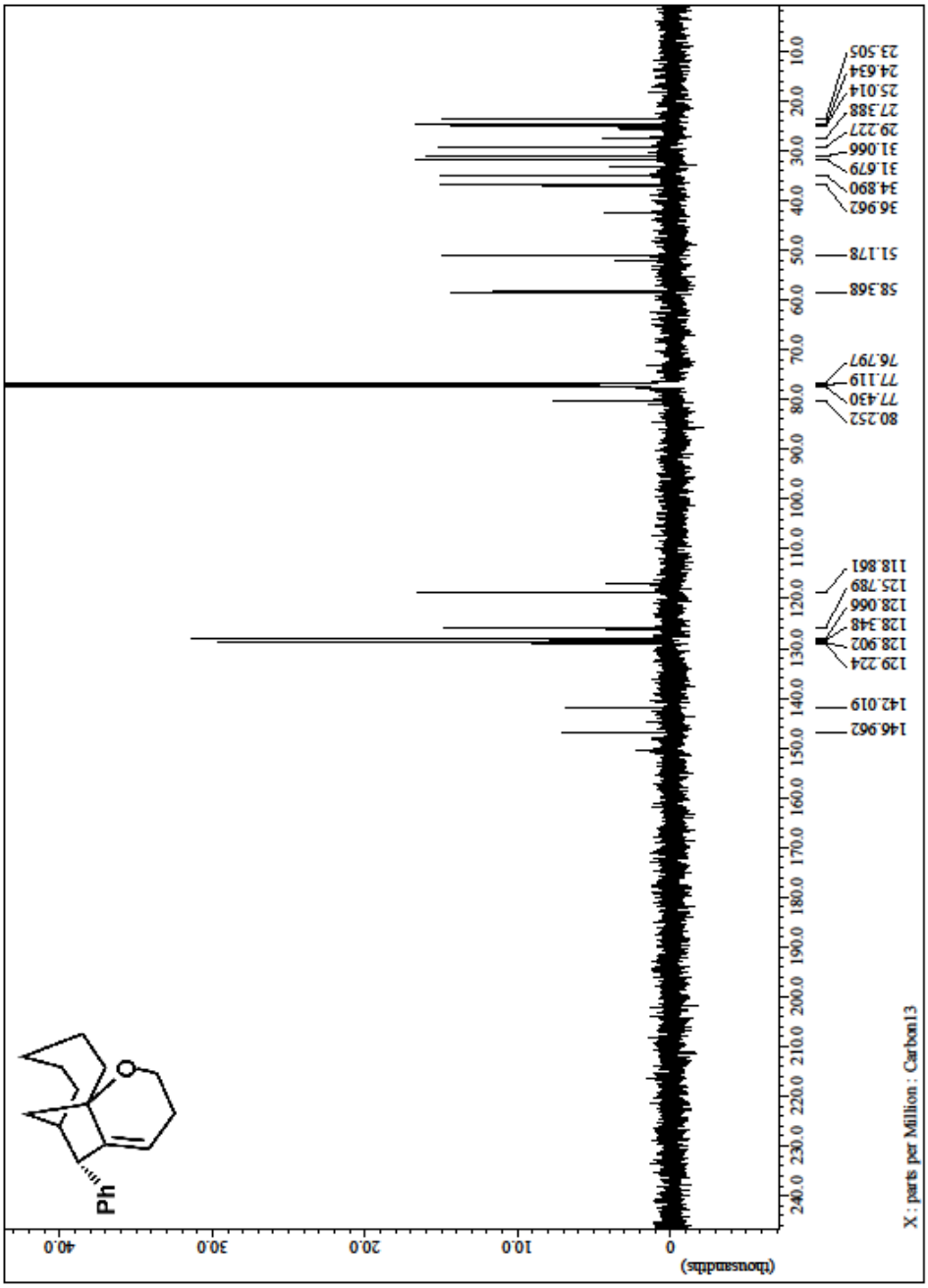

Figure A.3.135. ^{13}C NMR for compound **271**

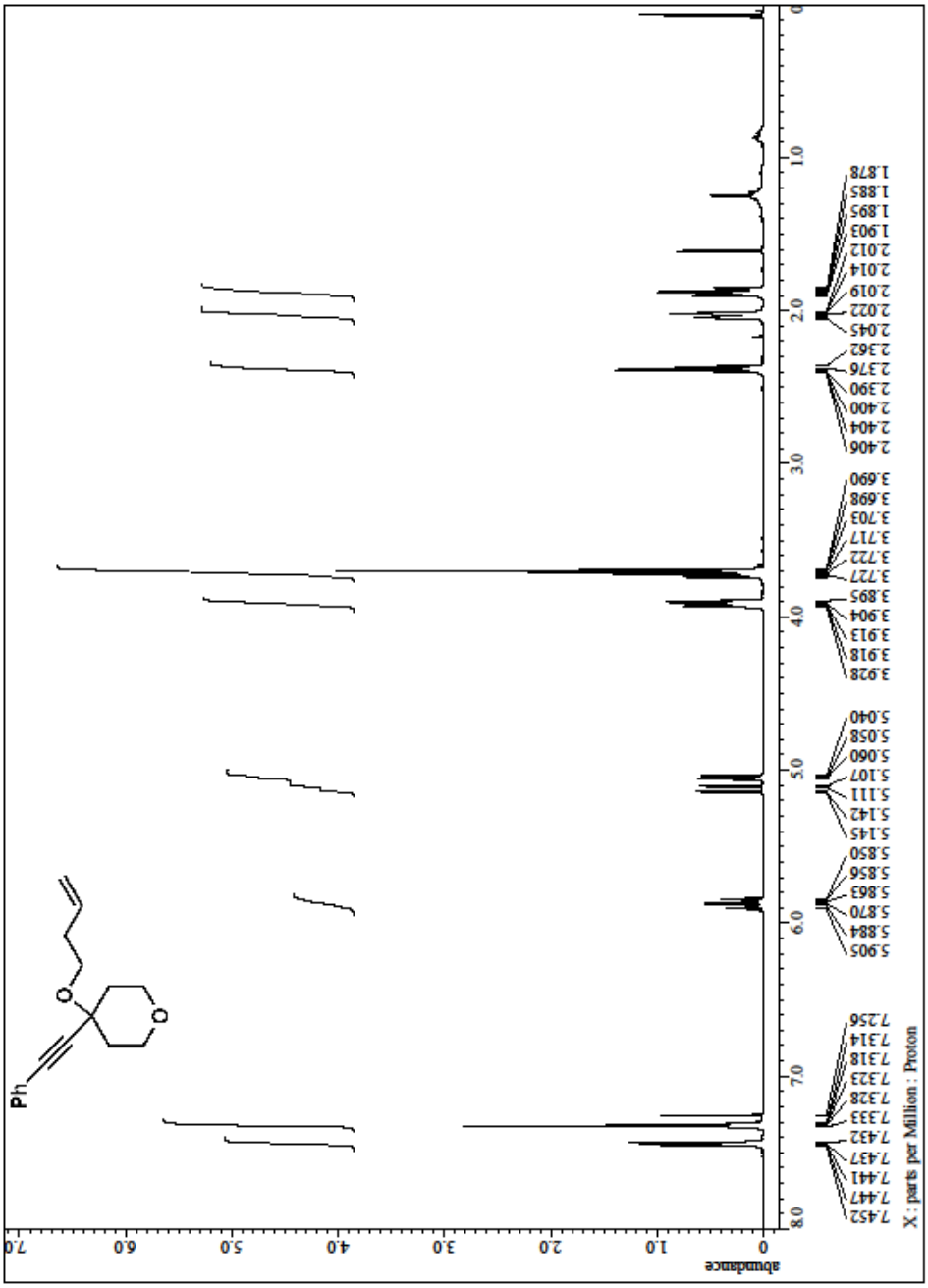

Figure A.3.136. ^{1}H NMR for compound **272**

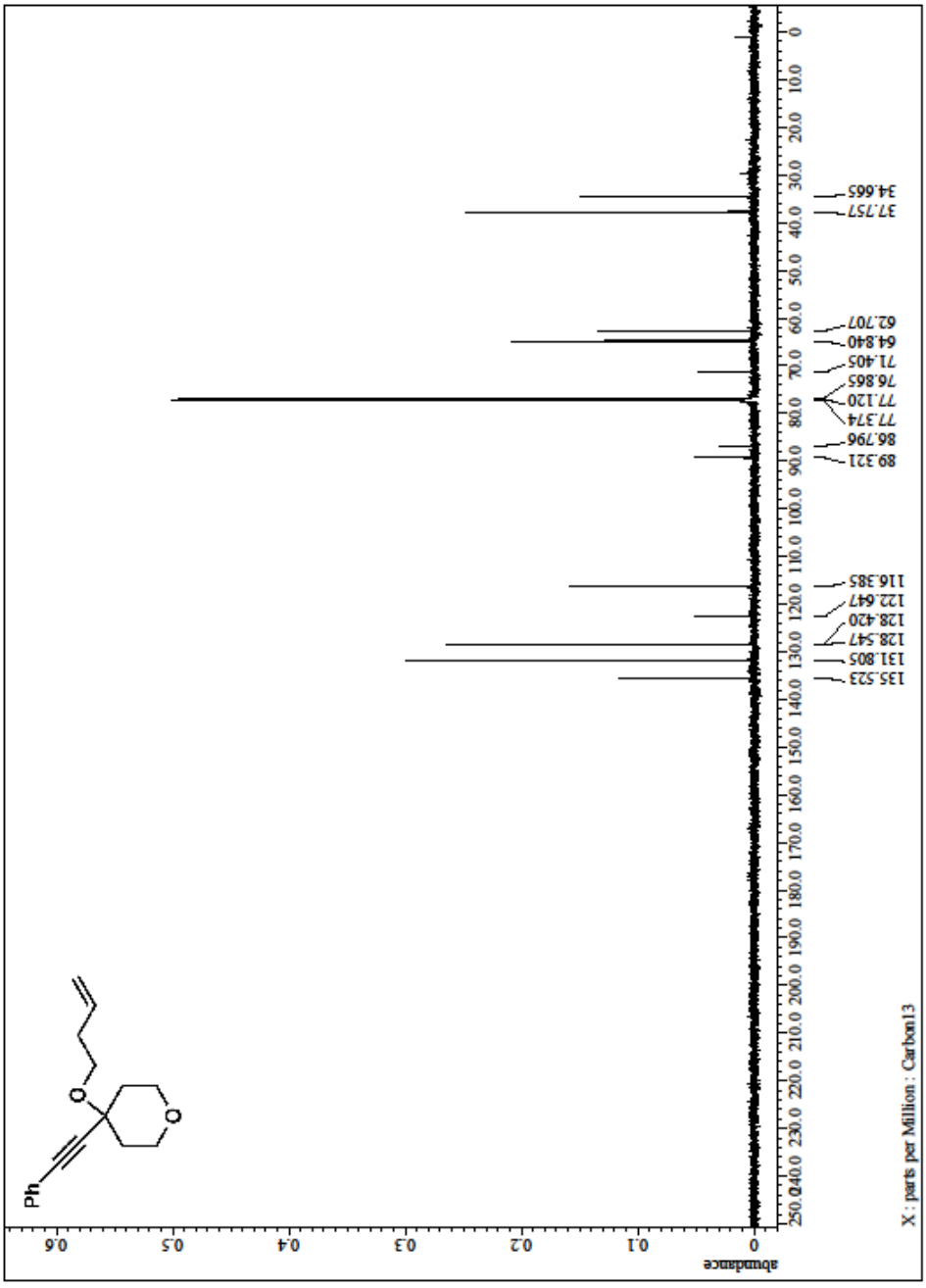

Figure A.3.137. ^{13}C NMR for compound **272**

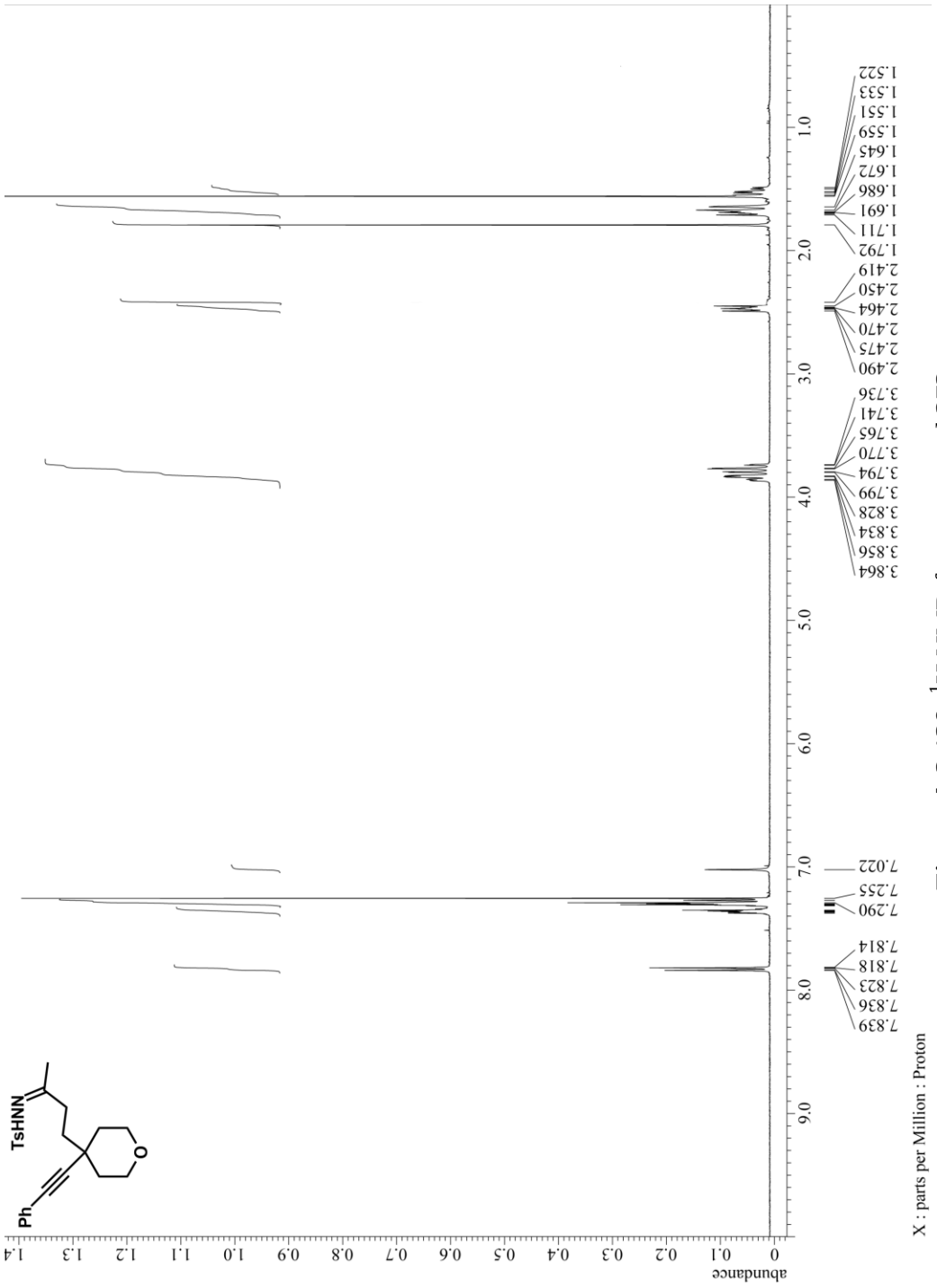

Figure A.3.138. ^{1}H NMR for compound **273**

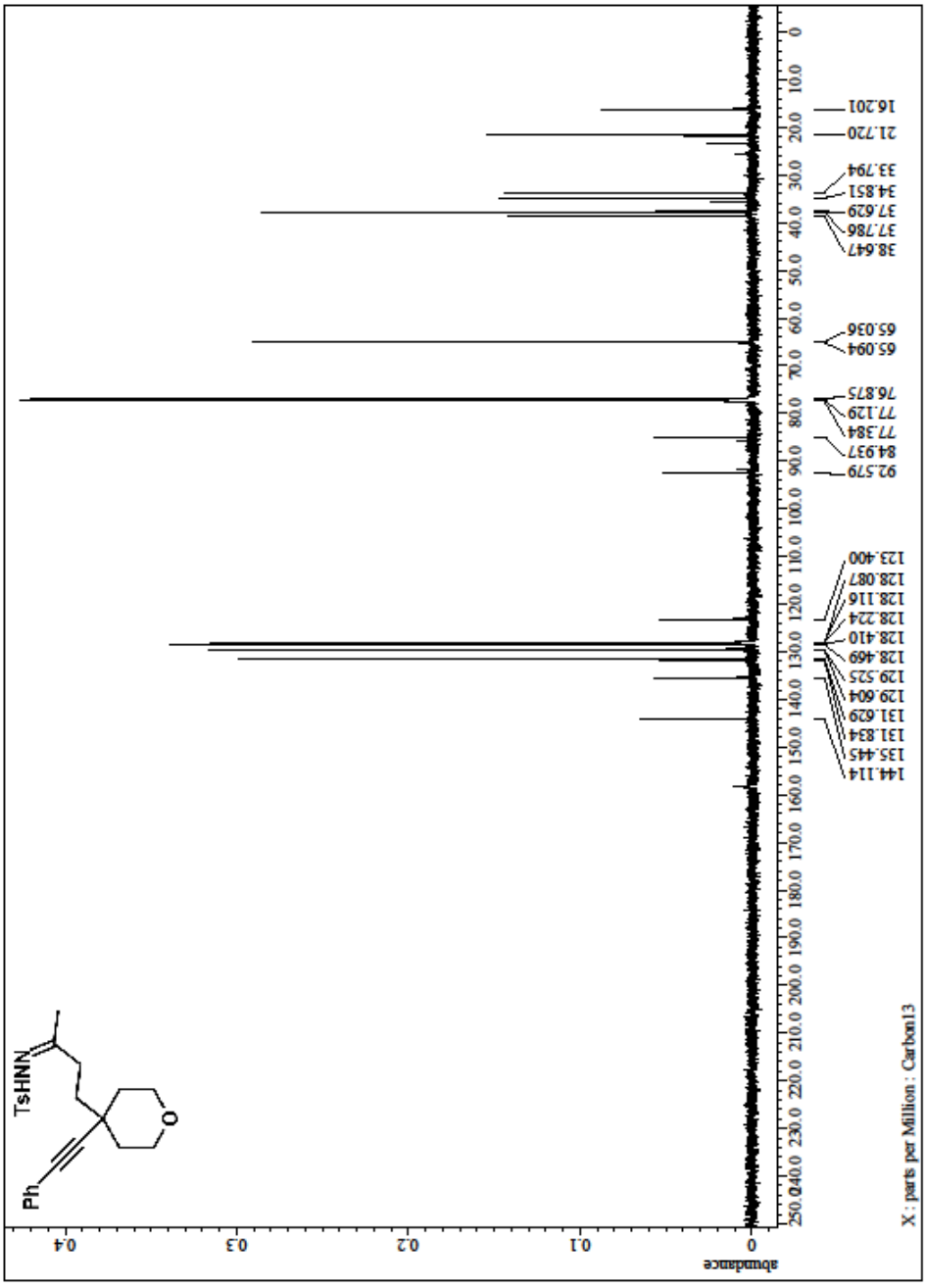

Figure A.3.139. ^{13}C NMR for compound **273**

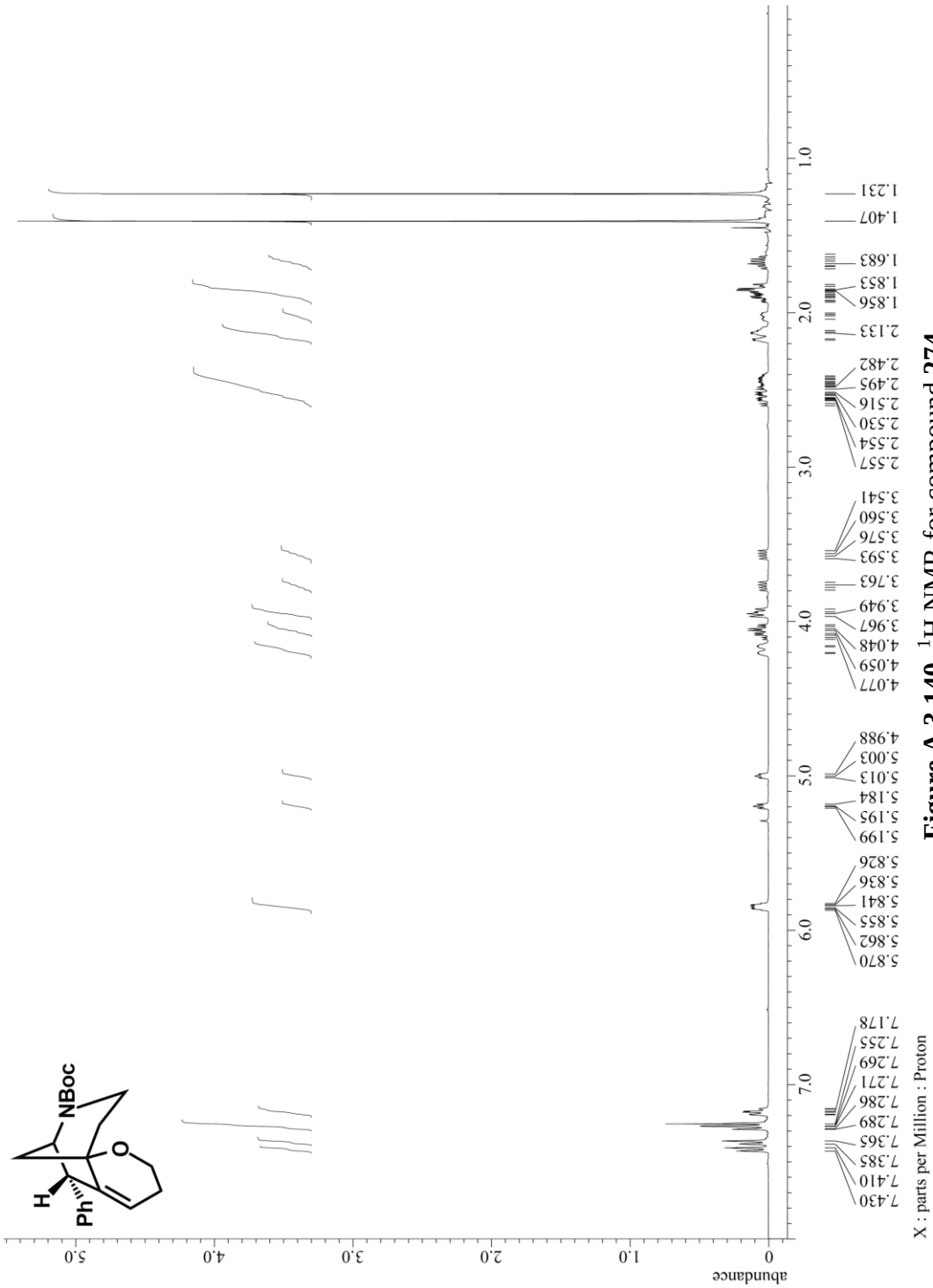

Figure A.3.140. ^{1}H NMR for compound **274**

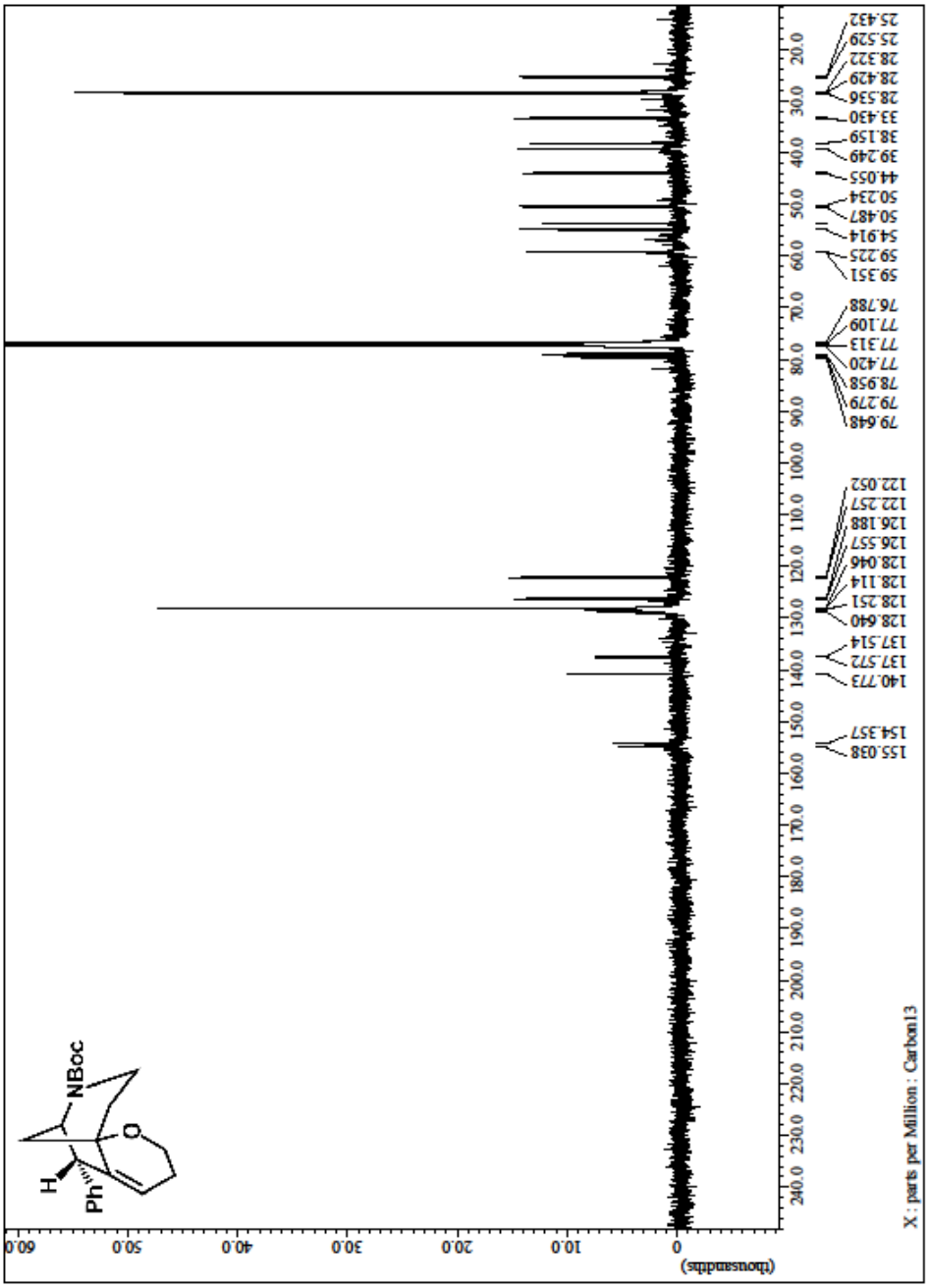

Figure A.3.141. ^{13}C NMR for compound **274**

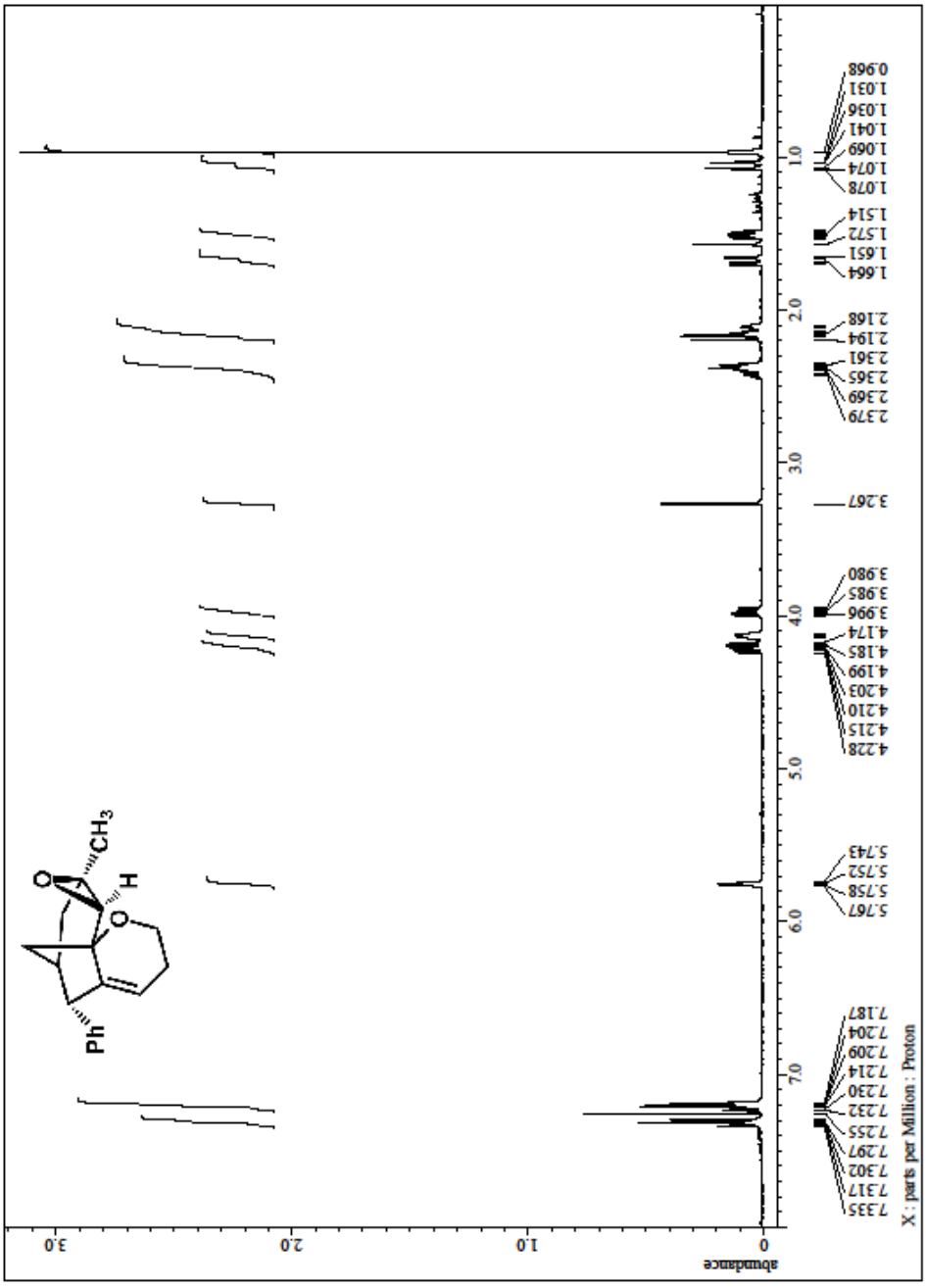

Figure A.3.142. ^{1}H NMR for compound **275**

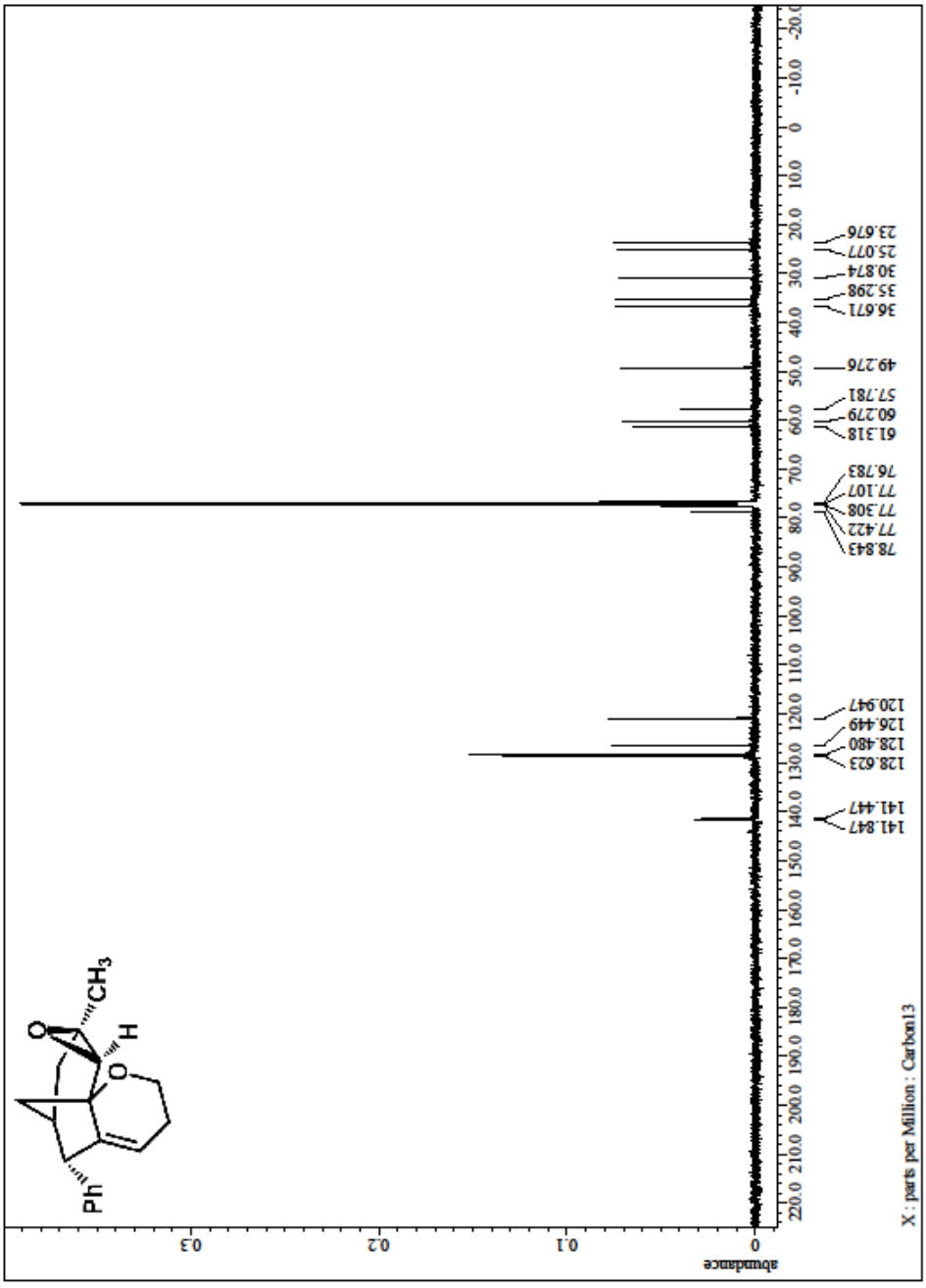

Figure A.3.143. ^{13}C NMR for compound **275**

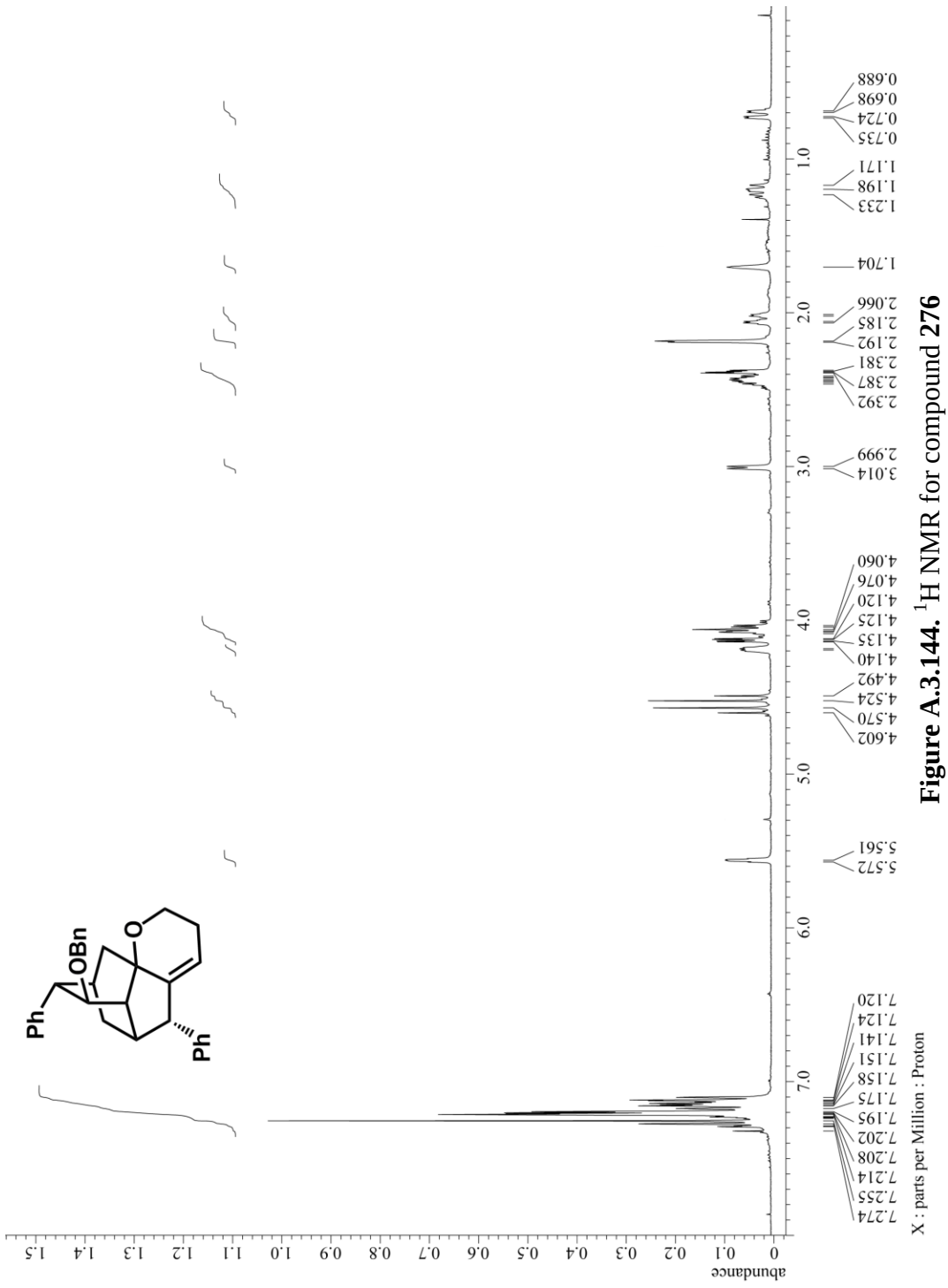

Figure A.3.144. ^{1}H NMR for compound **276**

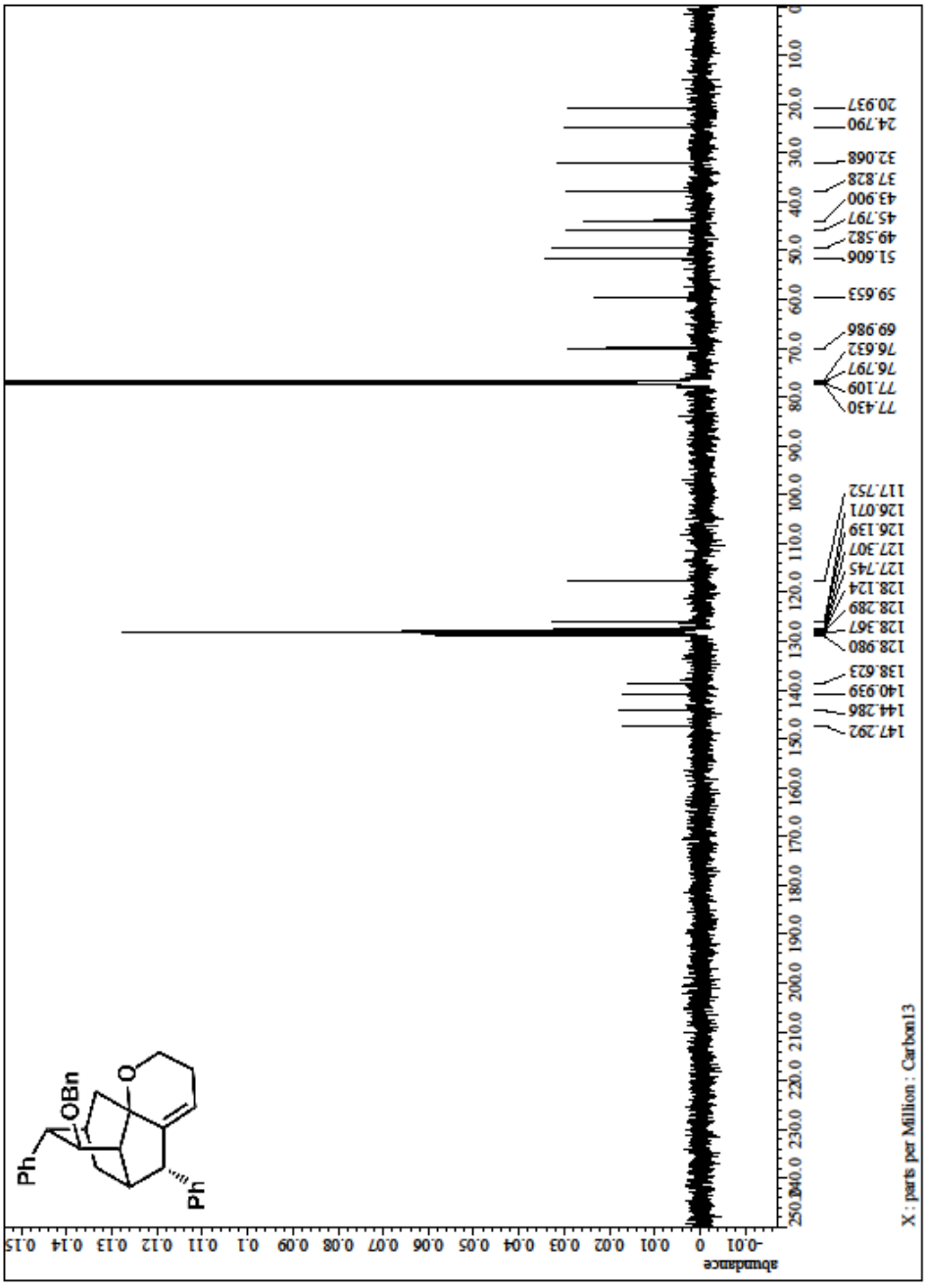

Figure A.3.145. ^{13}C NMR for compound **276**

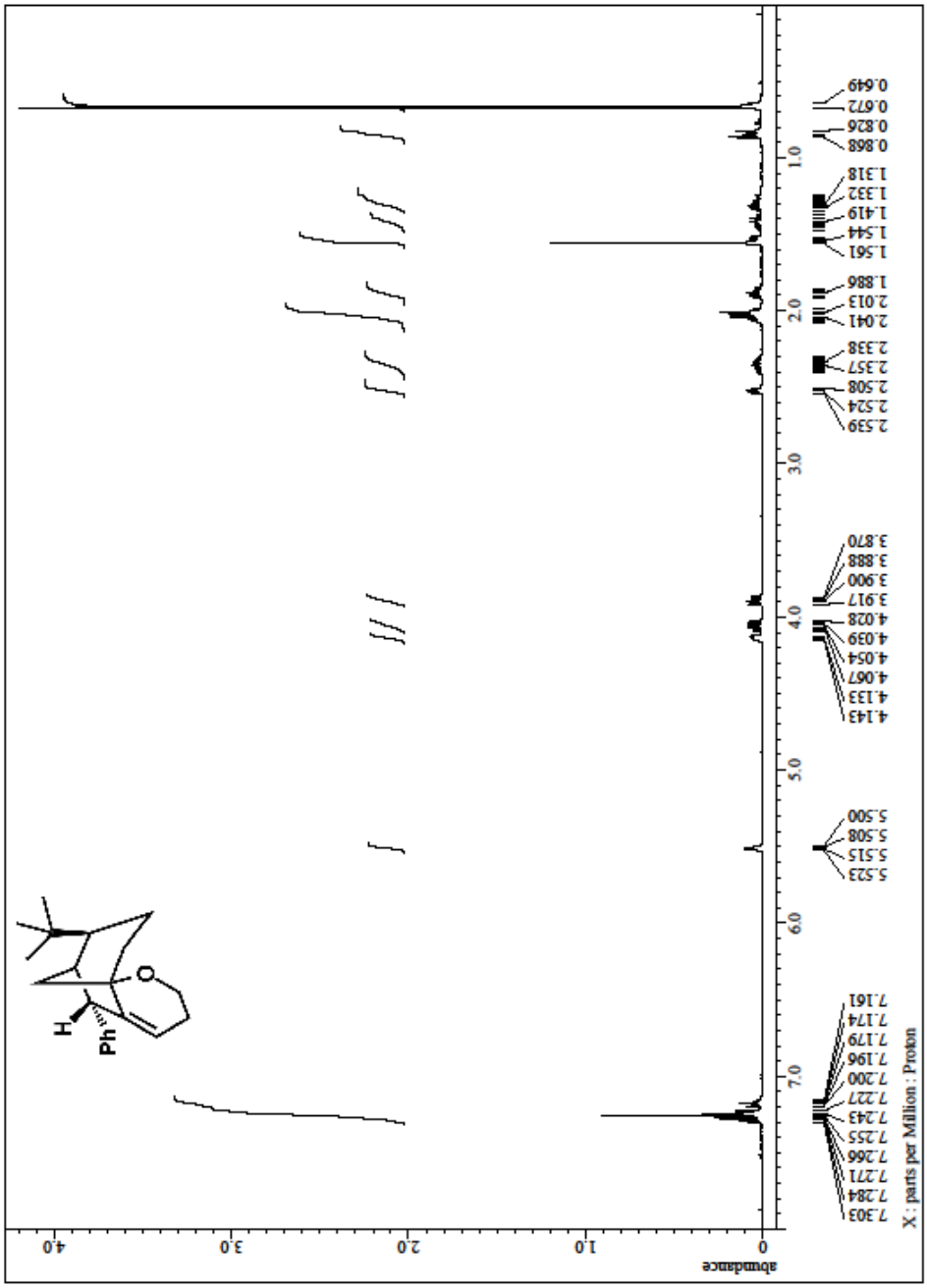

Figure A.3.146. ^{1}H NMR for compound **277**

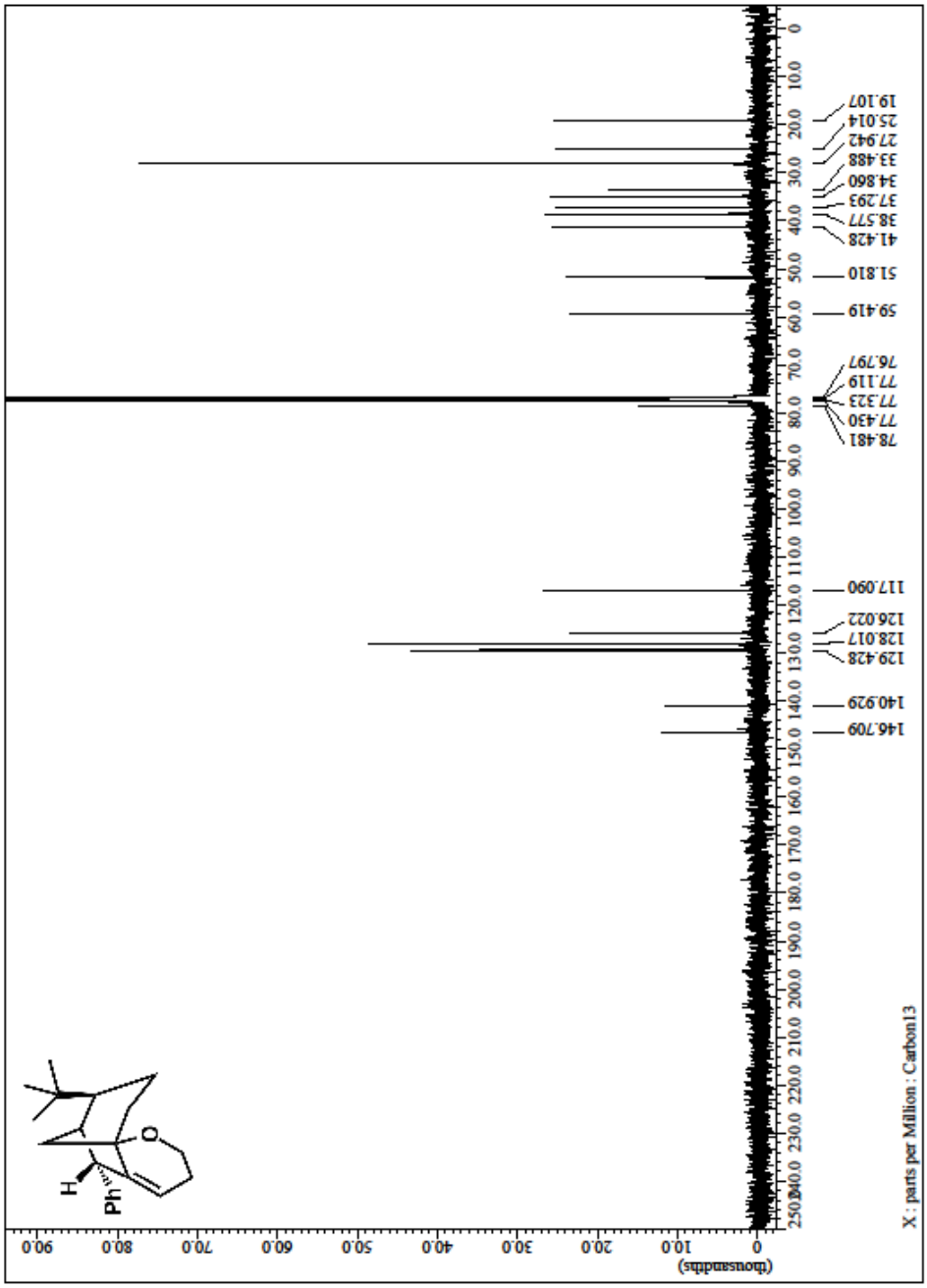

Figure A.3.147. ^{13}C NMR for compound **277**

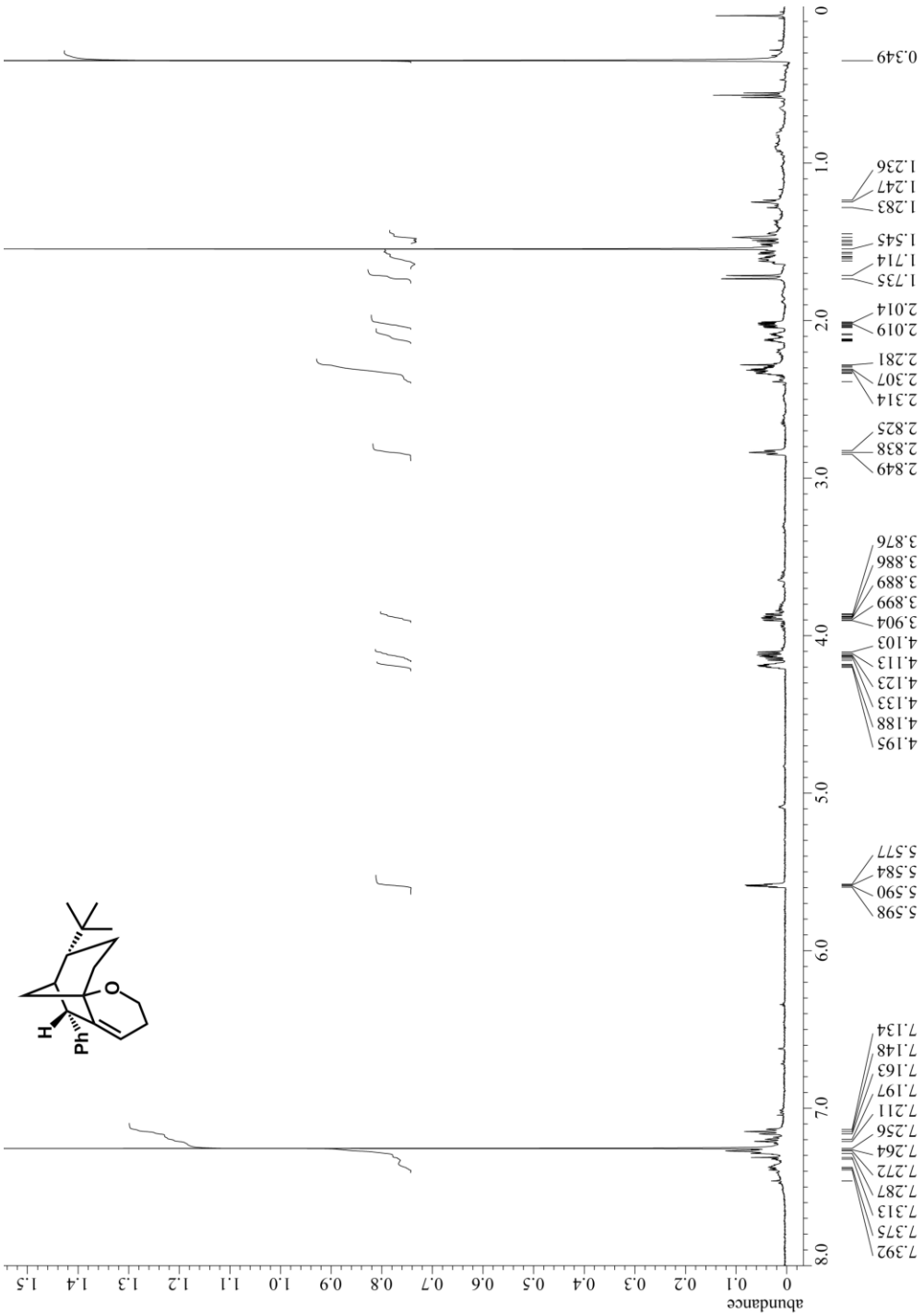

Figure A.3.148. ^{1}H NMR for compound **278**

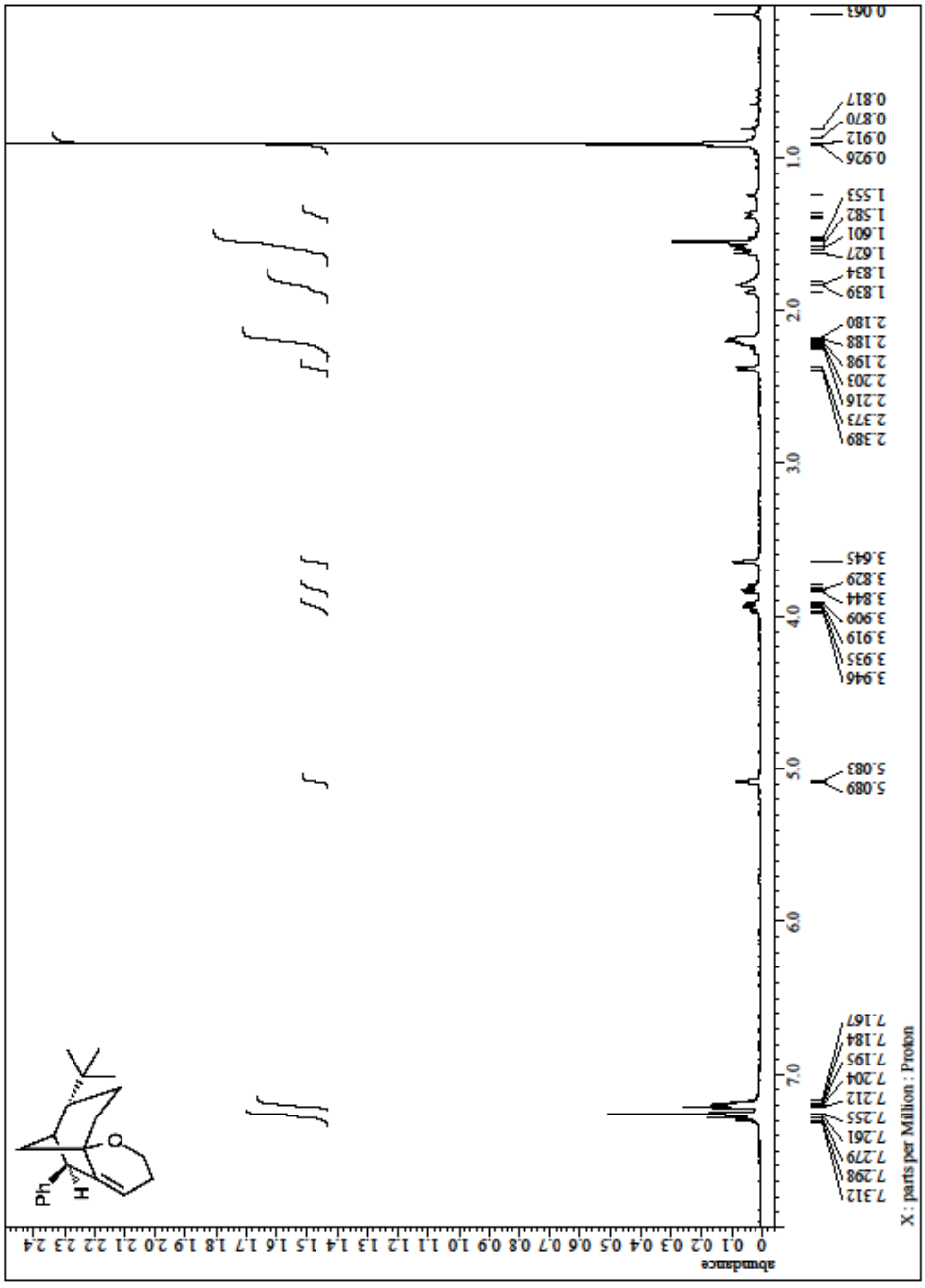

Figure A.3.149. ^{1}H NMR for compound **279**

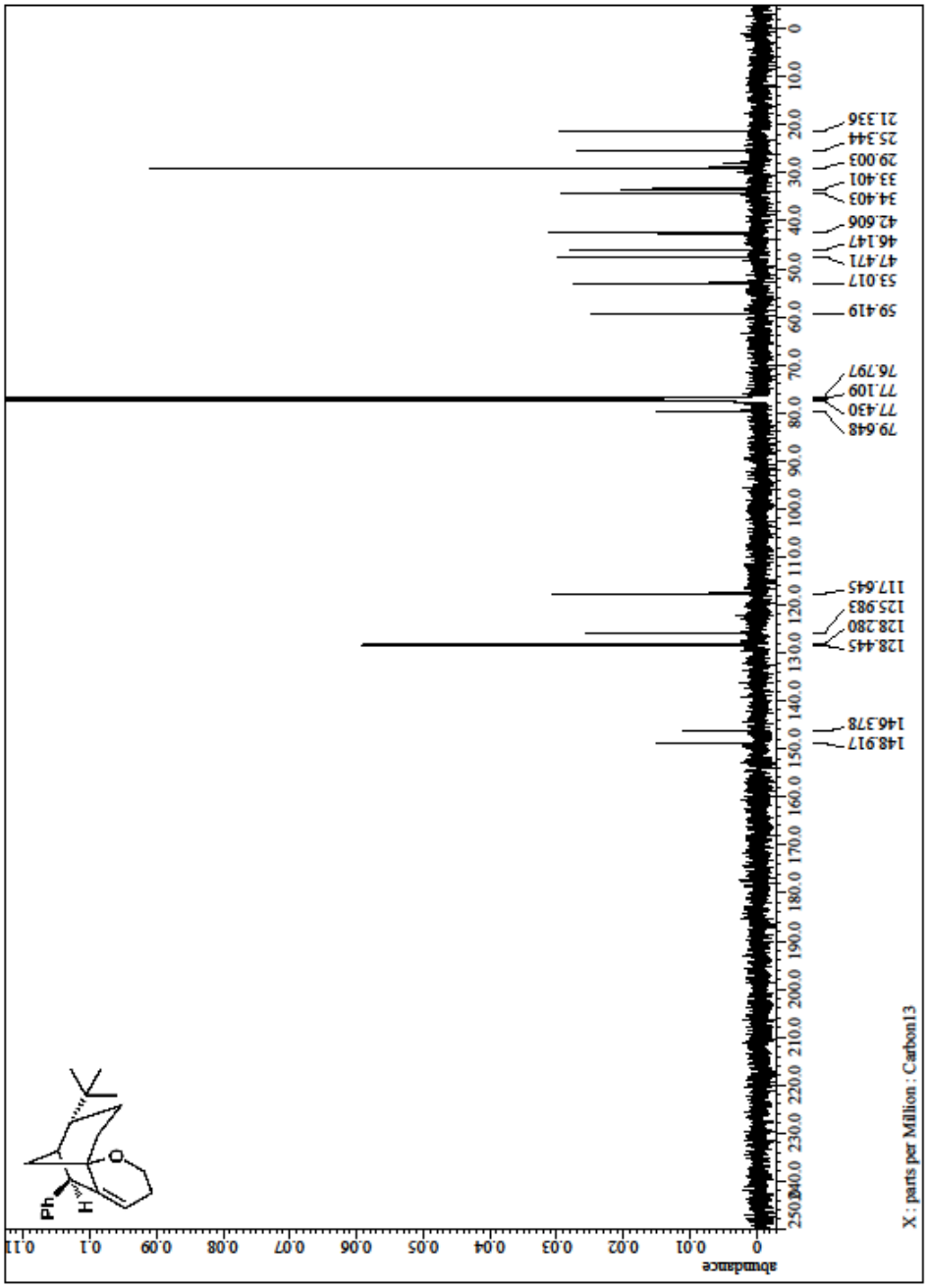

Figure A.3.150. ^{13}C NMR for compound **279**

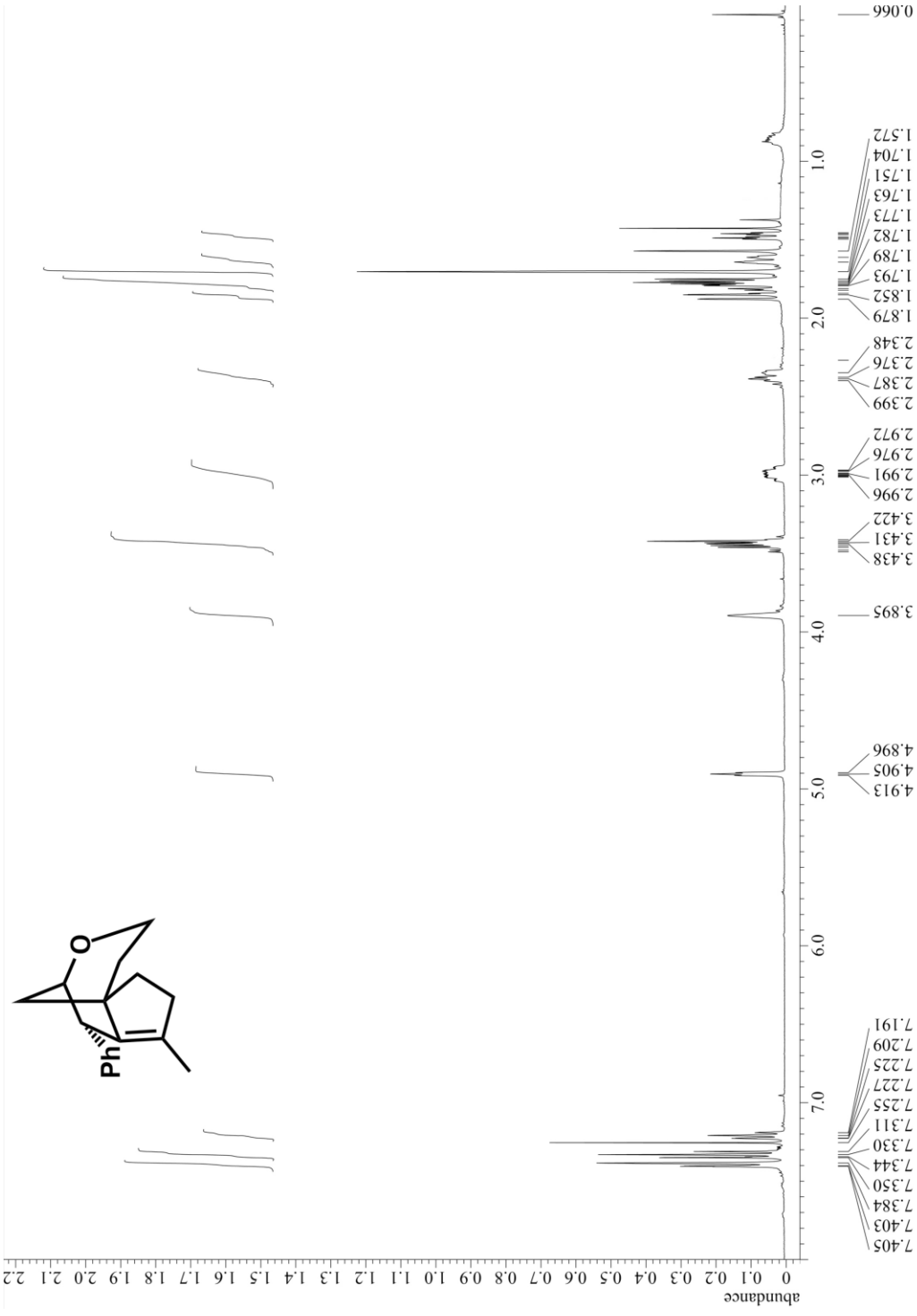

Figure A.3.151. ^{1}H NMR for compound **280**

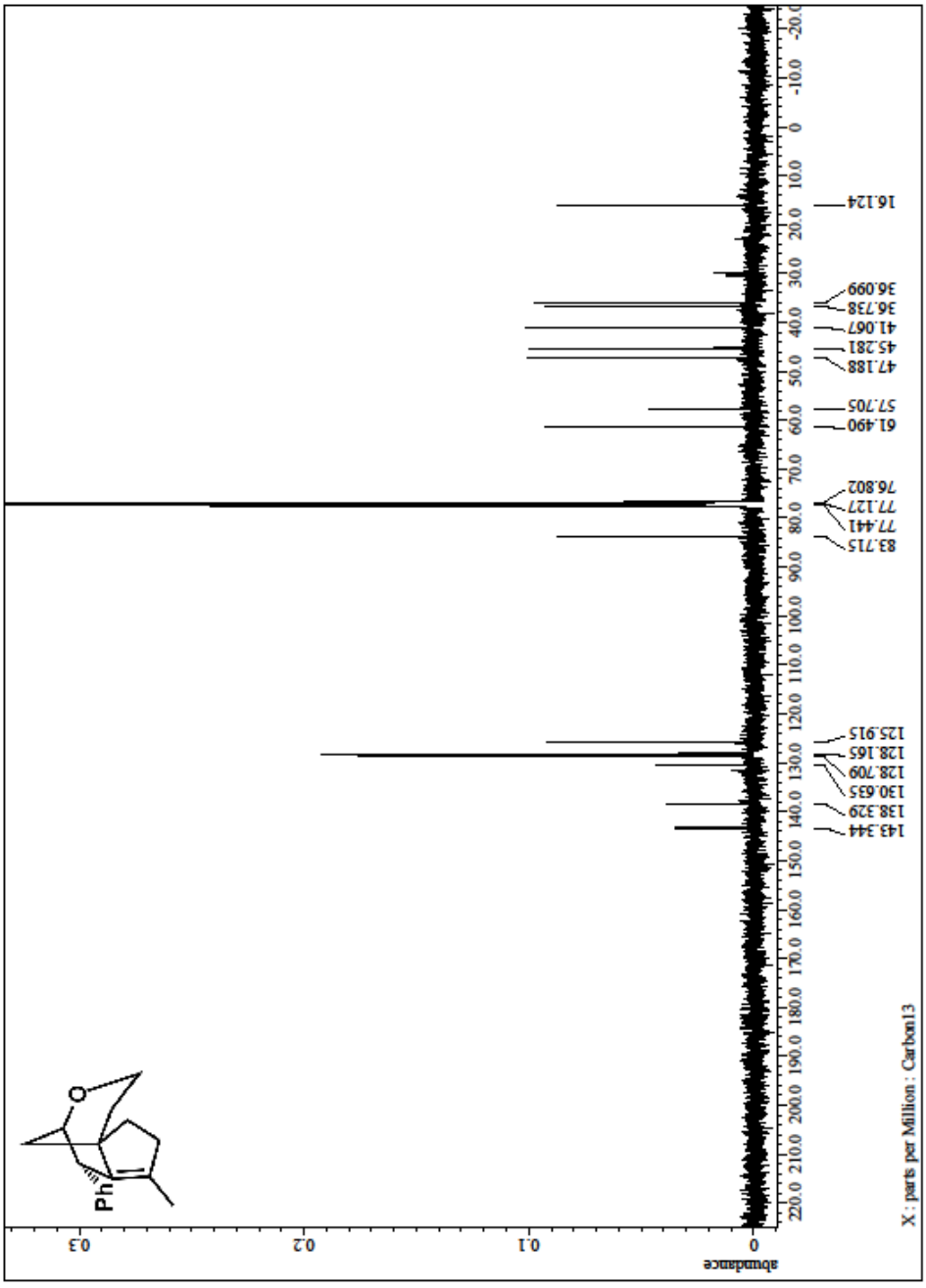

Figure A.3.152. ^{13}C NMR for compound **280**

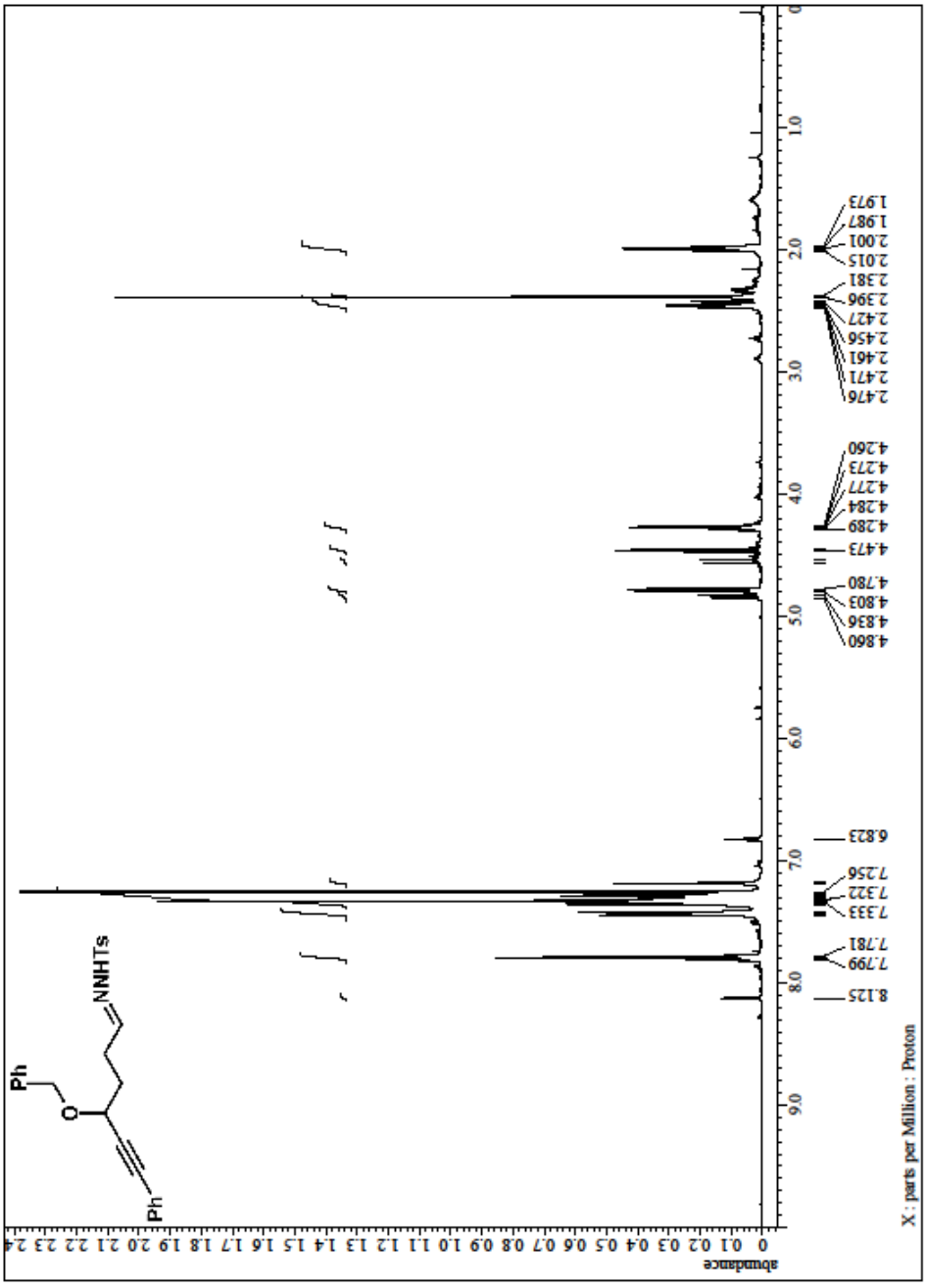

Figure A.3.153. ^{1}H NMR for compound **287**

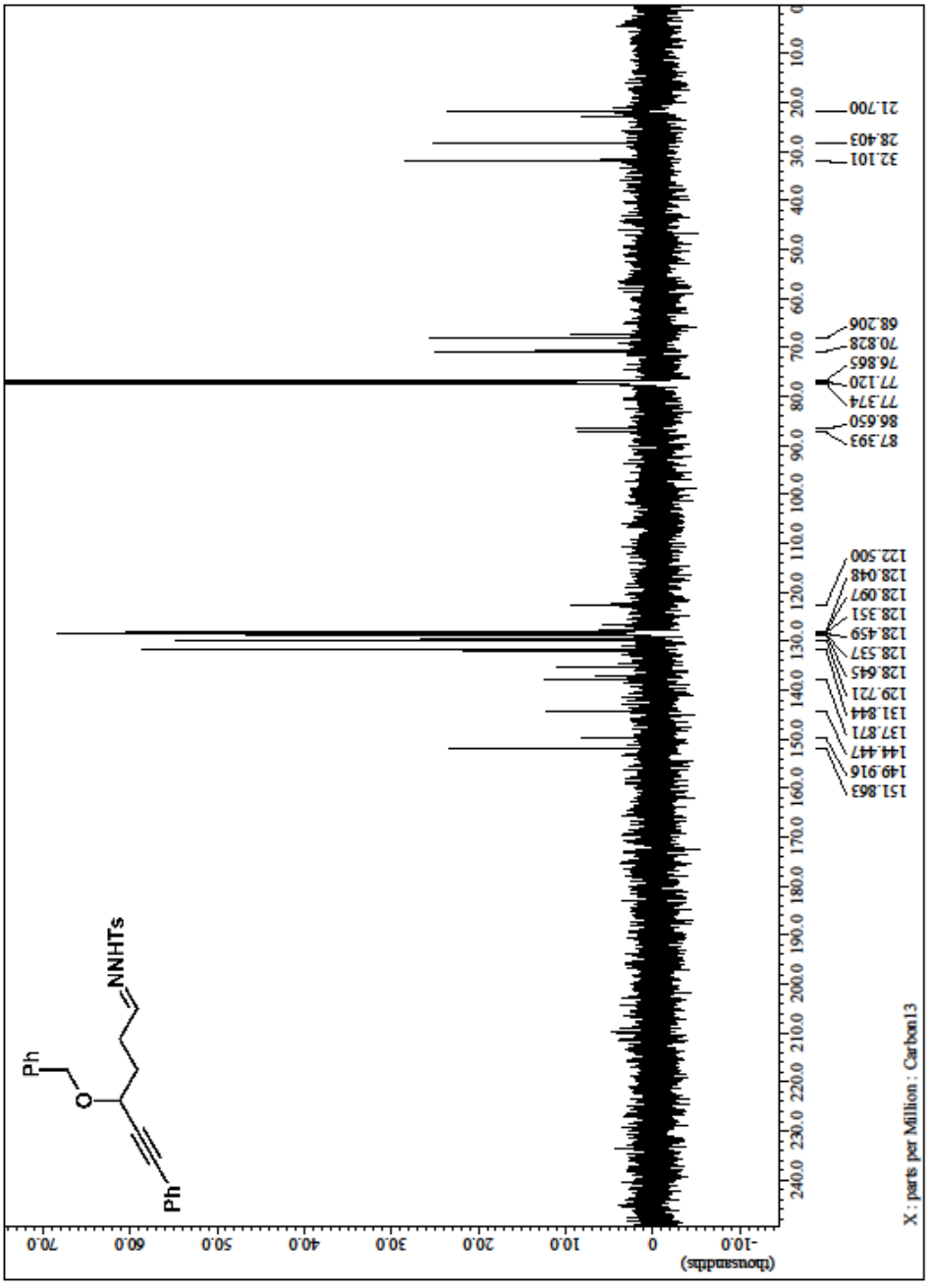

Figure A.3.154. ^{13}C NMR for compound **286**

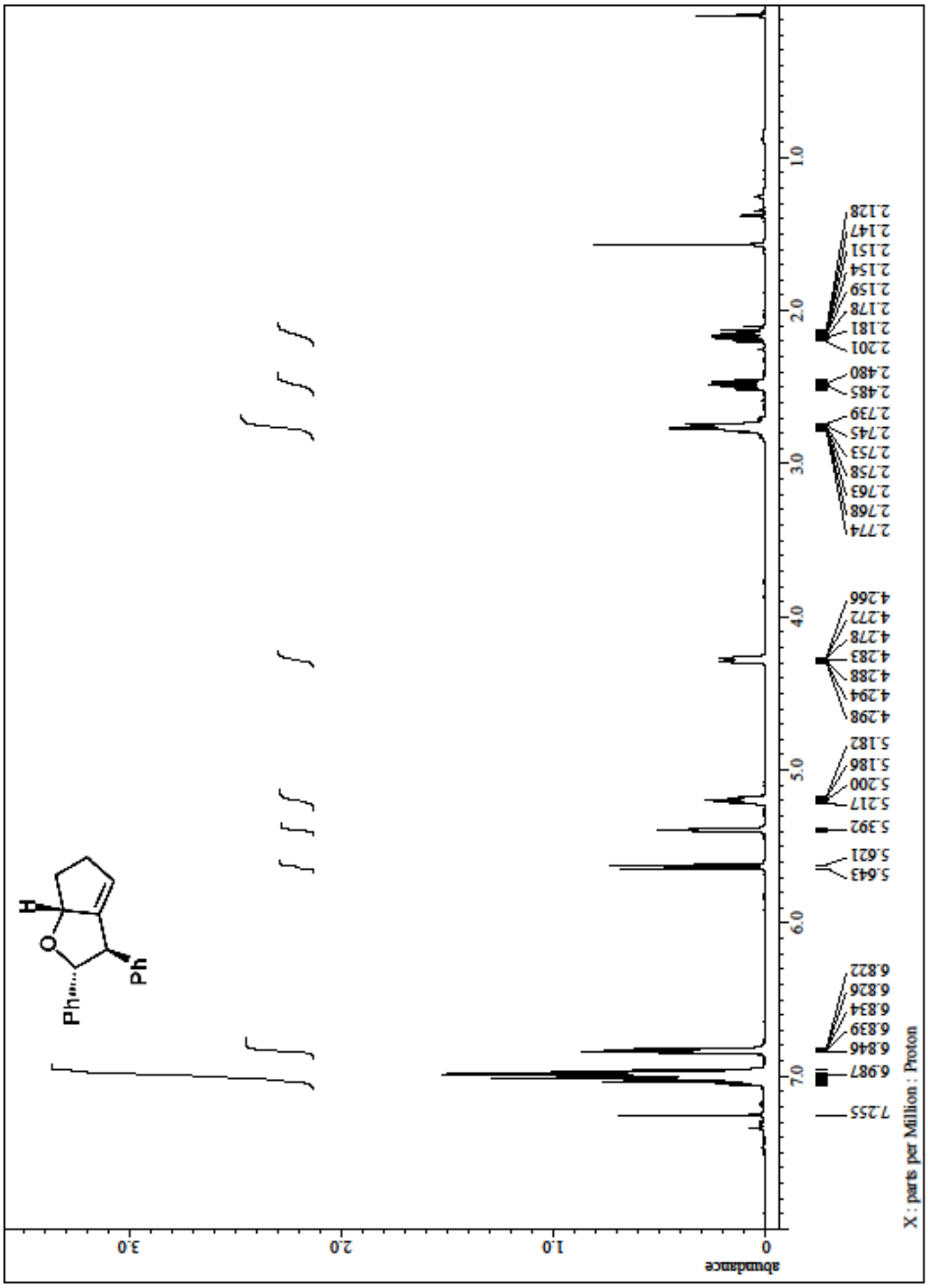

Figure A.3.155. ^{1}H NMR for compound **287**

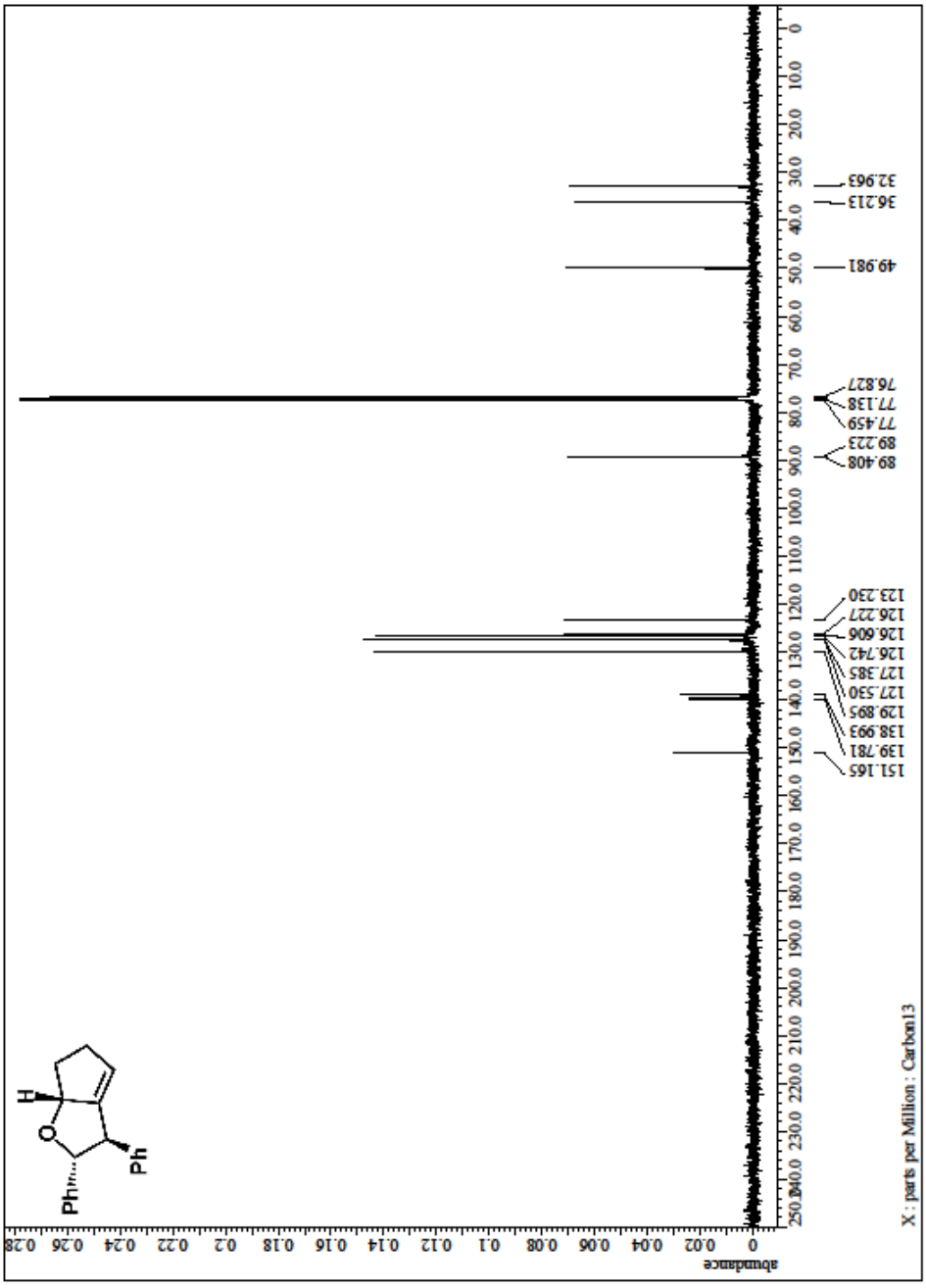

Figure A.3.156. ^{13}C NMR for compound **287**

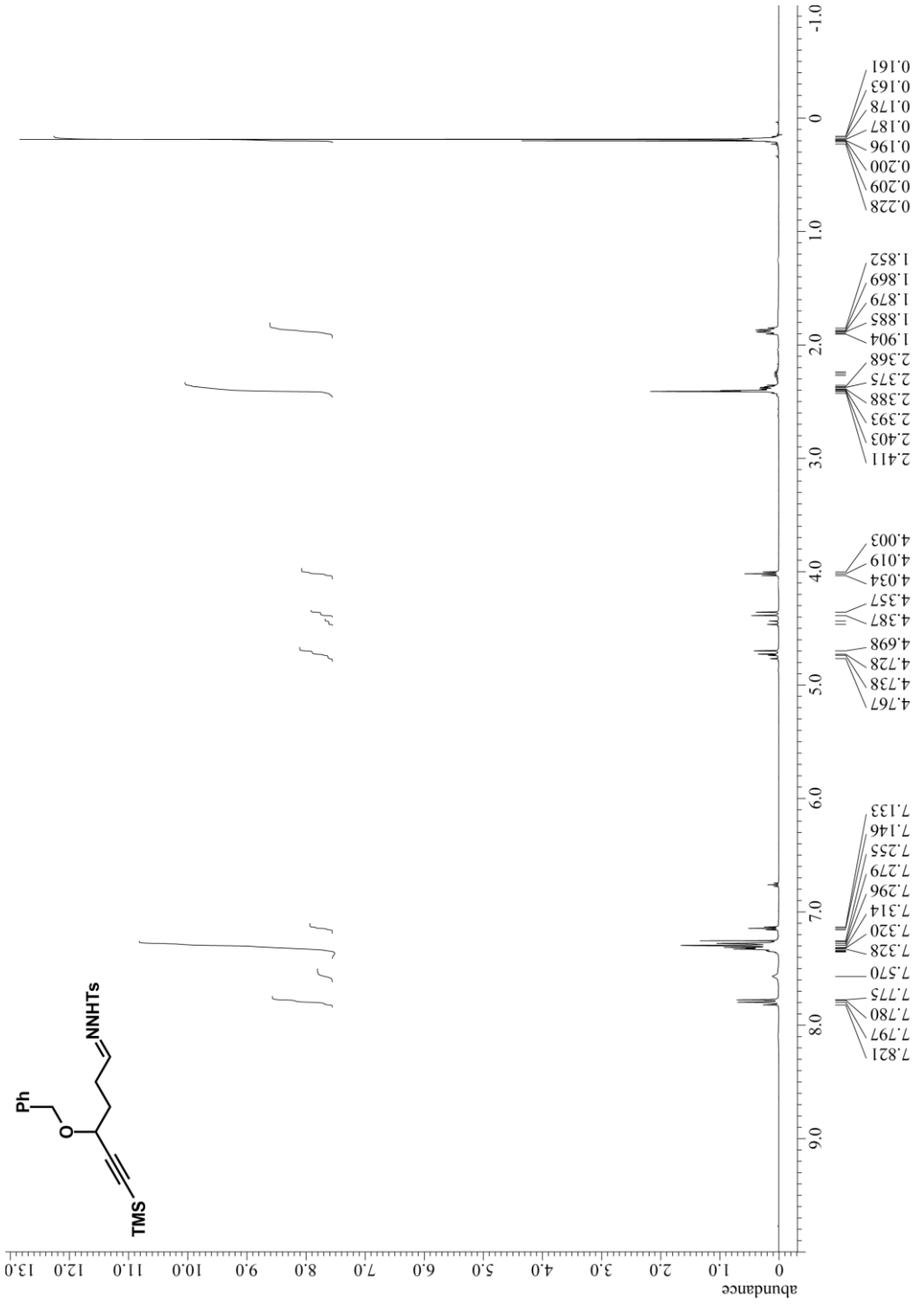

Figure A.3.157. ^{1}H NMR for compound **288**

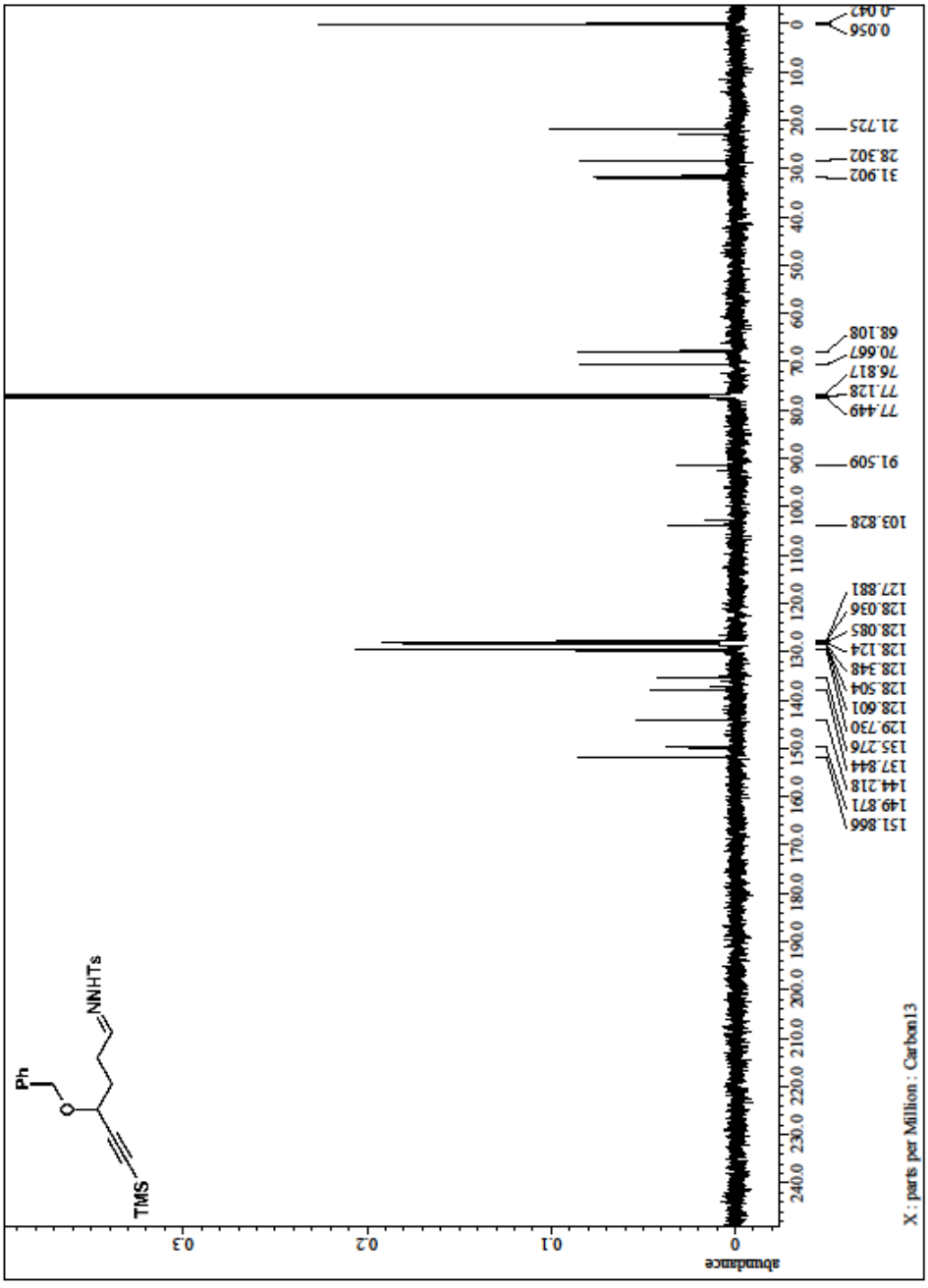

Figure A.3.158. ^{13}C NMR for compound **288**

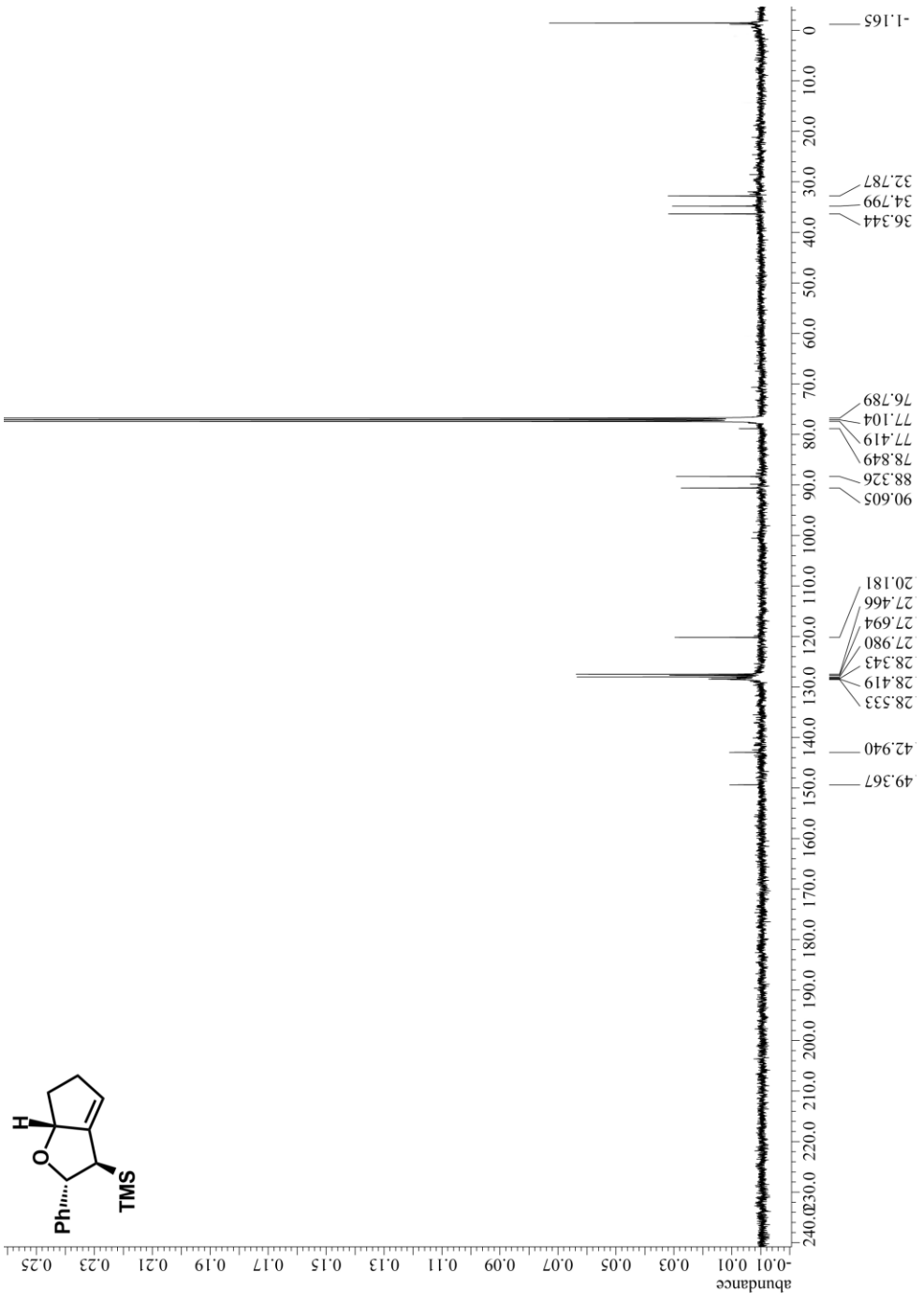

Figure A.3.159. ^{13}C NMR for compound **289**

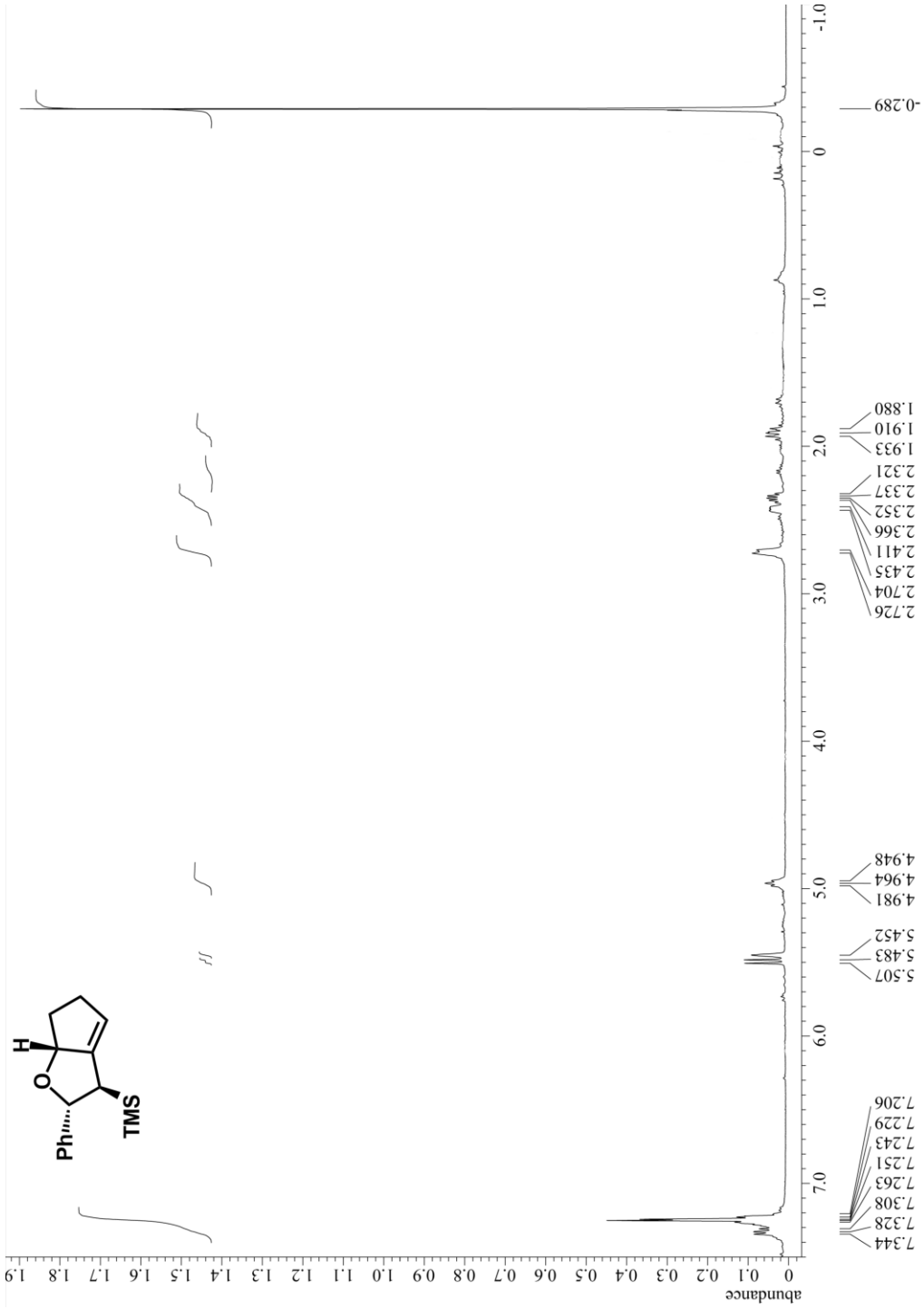

Figure A.3.160. ^{1}H NMR for compound **289**

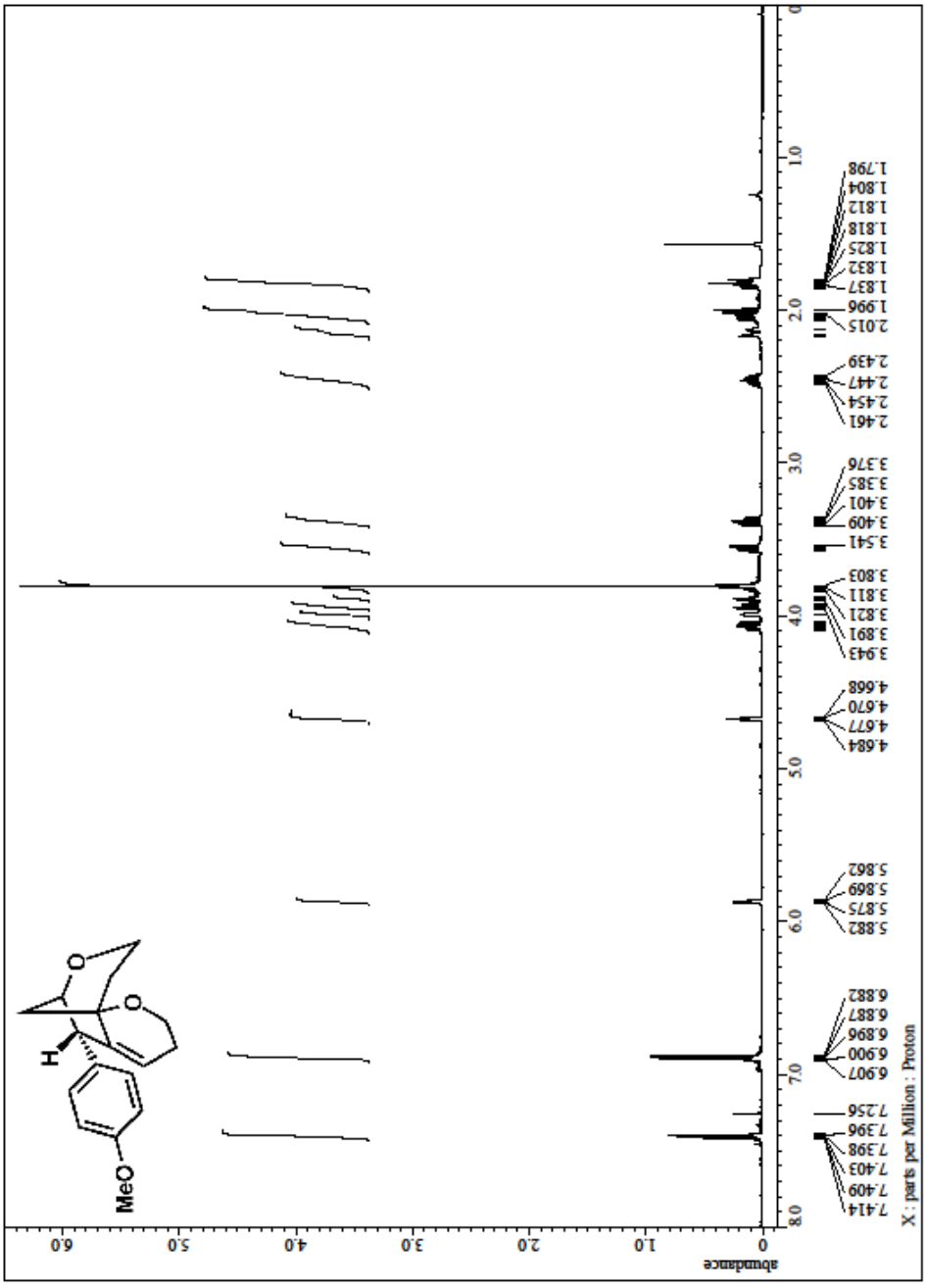

Figure A.3.161. ^{1}H NMR for compound **290**

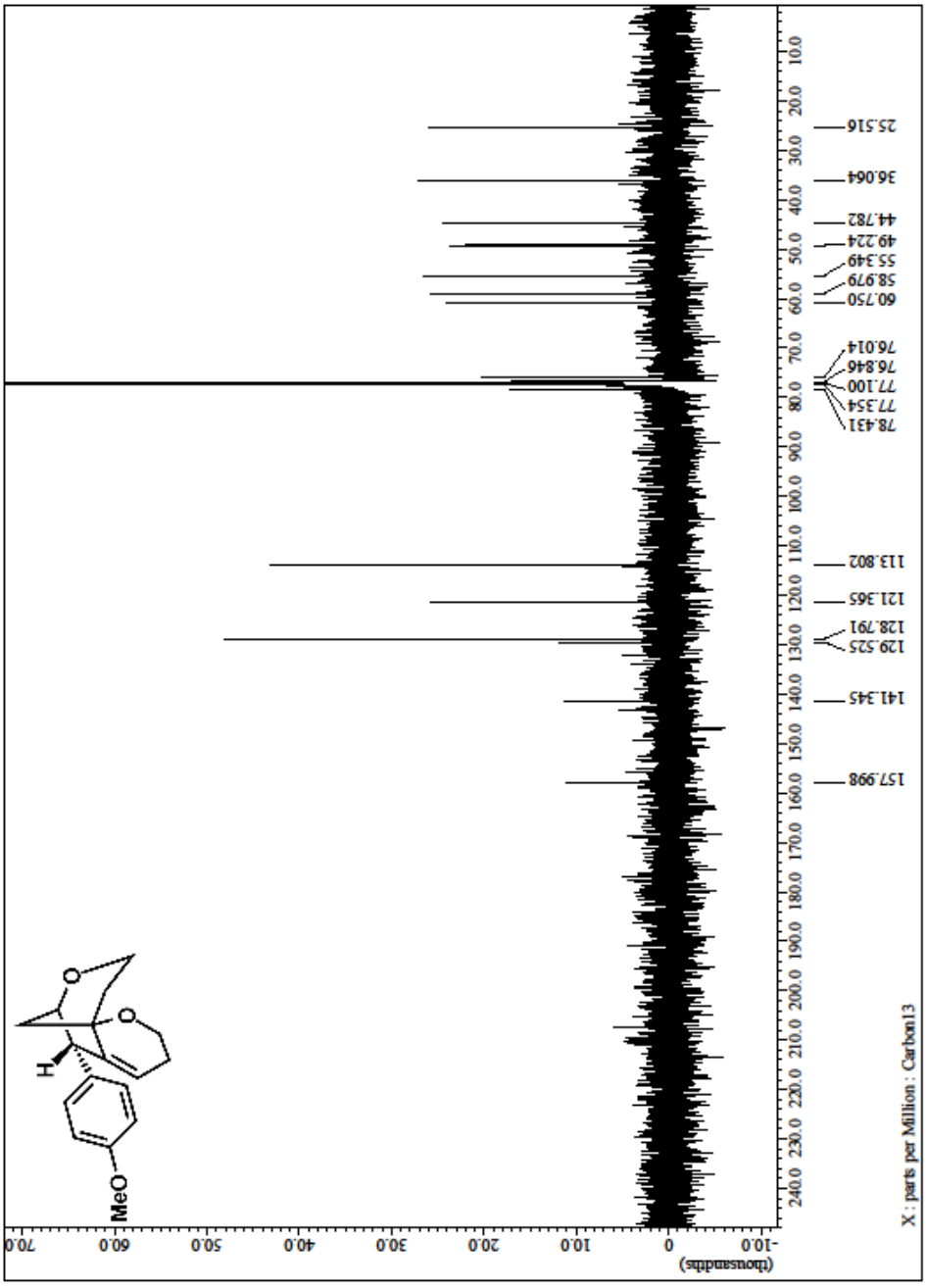

Figure A.3.162. ^{13}C NMR for compound **290**

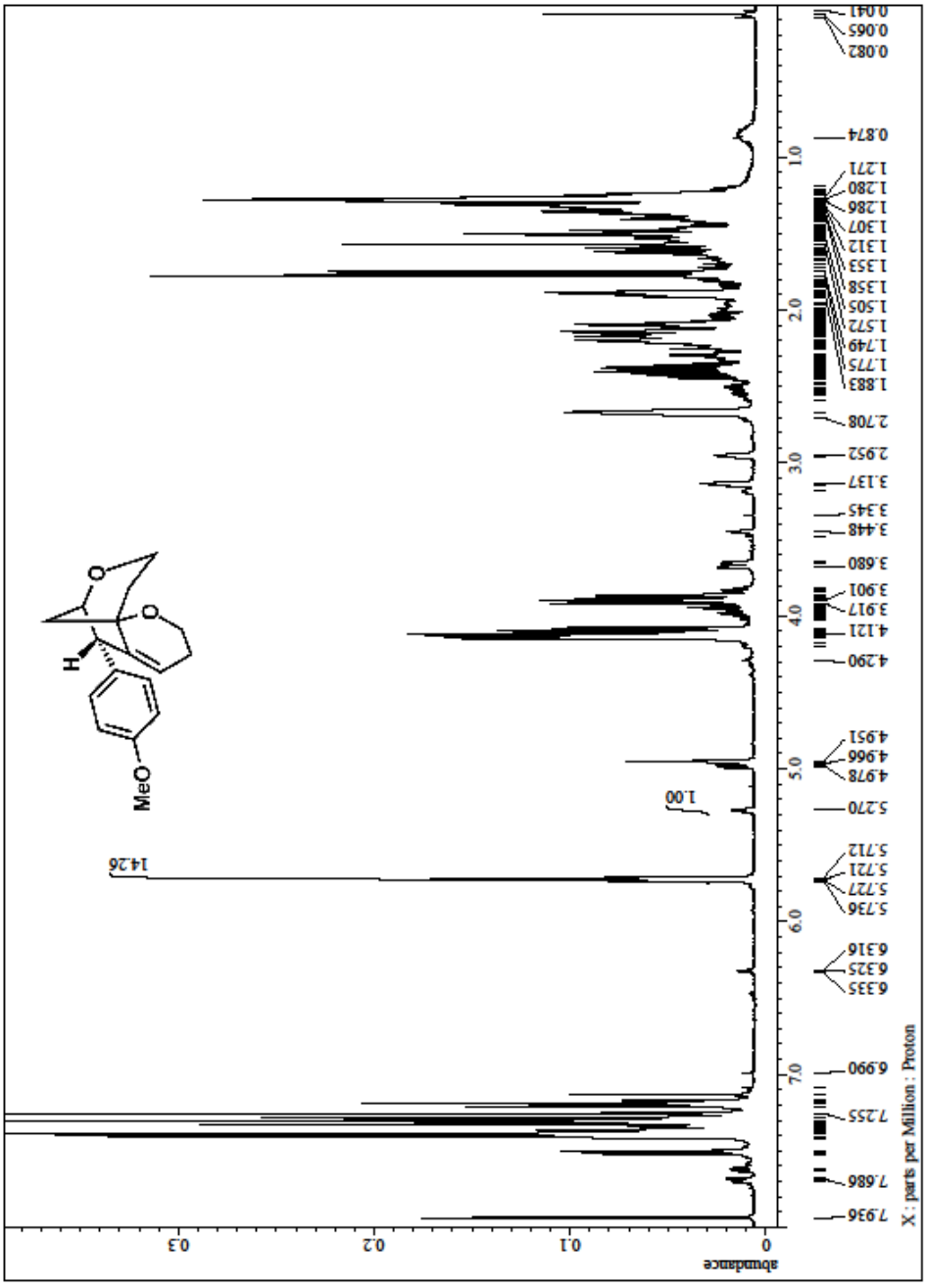

Figure A.3.163. Crude ^{1}H NMR of mixture of two diastereomers for compound **290**

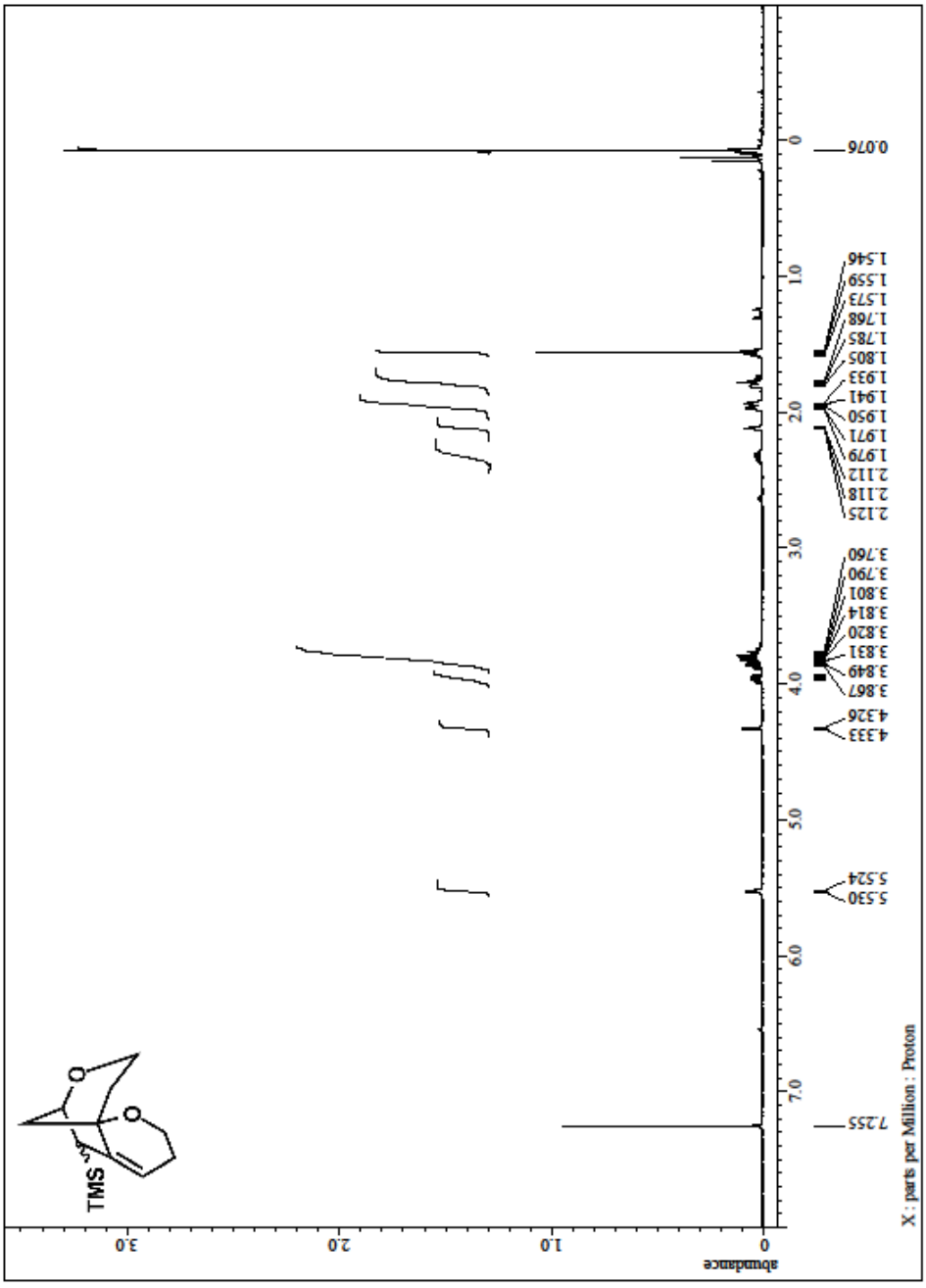

Figure A.3.164. ^{1}H NMR for compound **291**

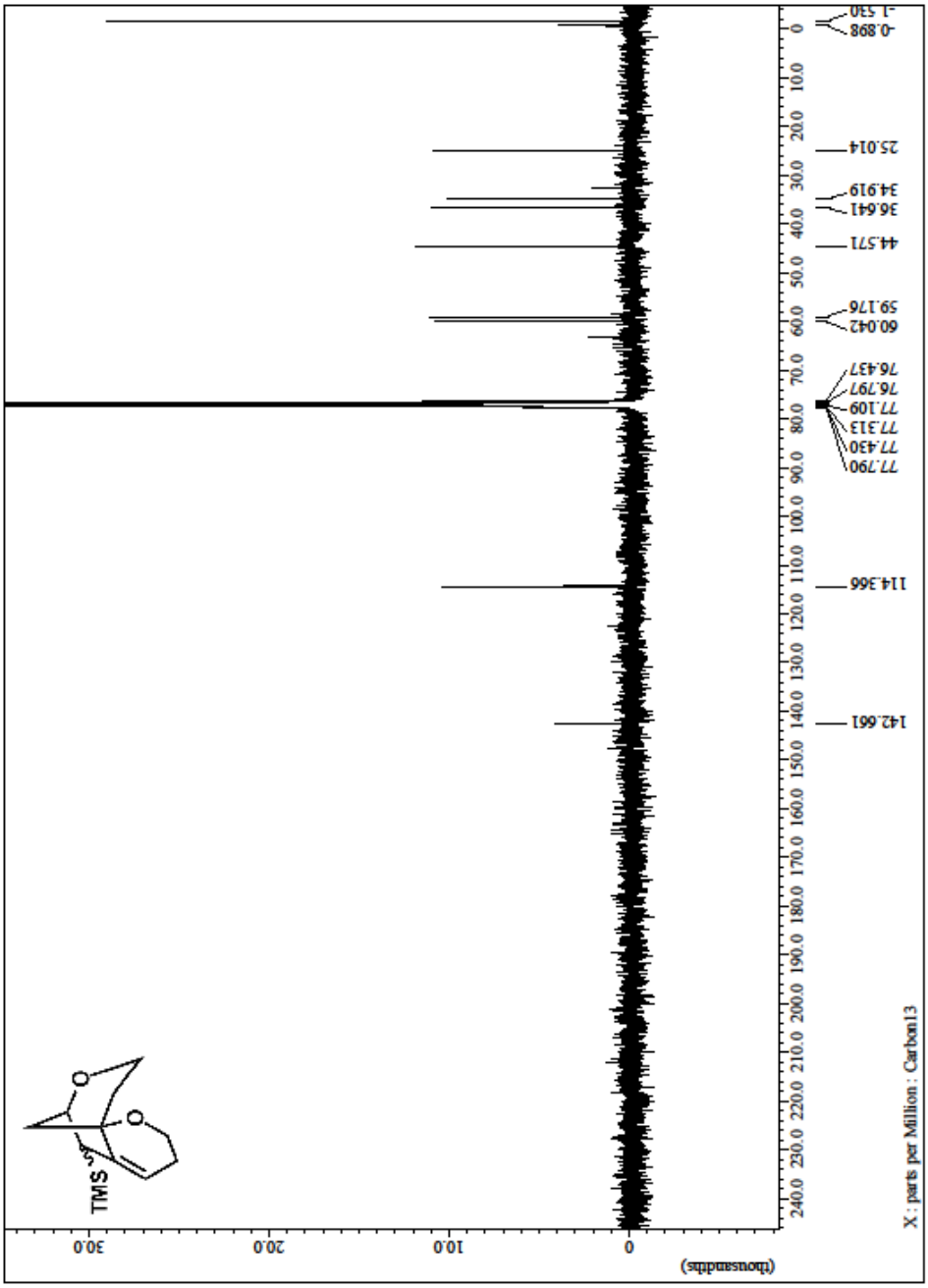

Figure A.3.165. ^{13}C NMR for compound **291**

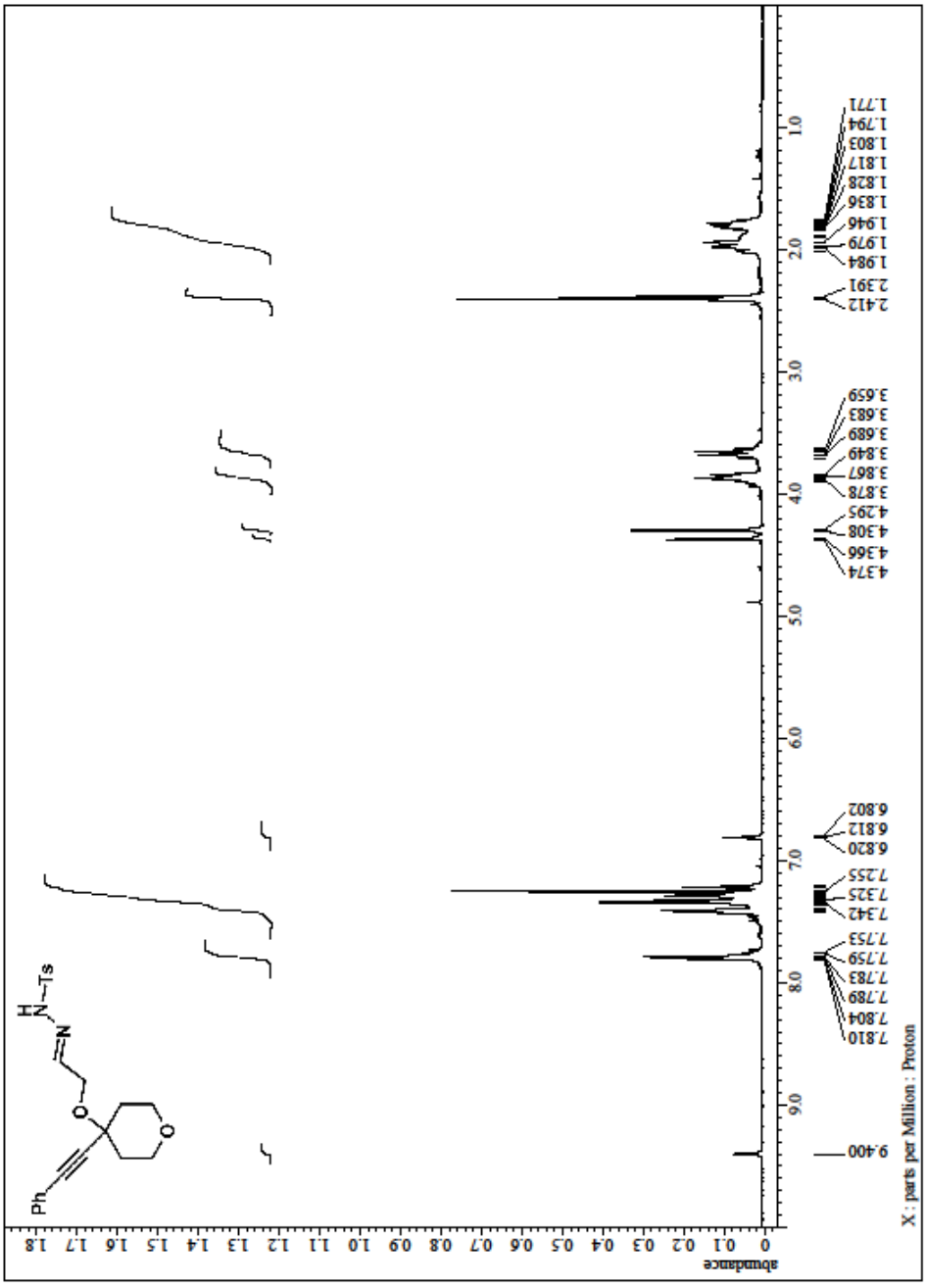

Figure A.3.166. ^{1}H NMR for compound **292**

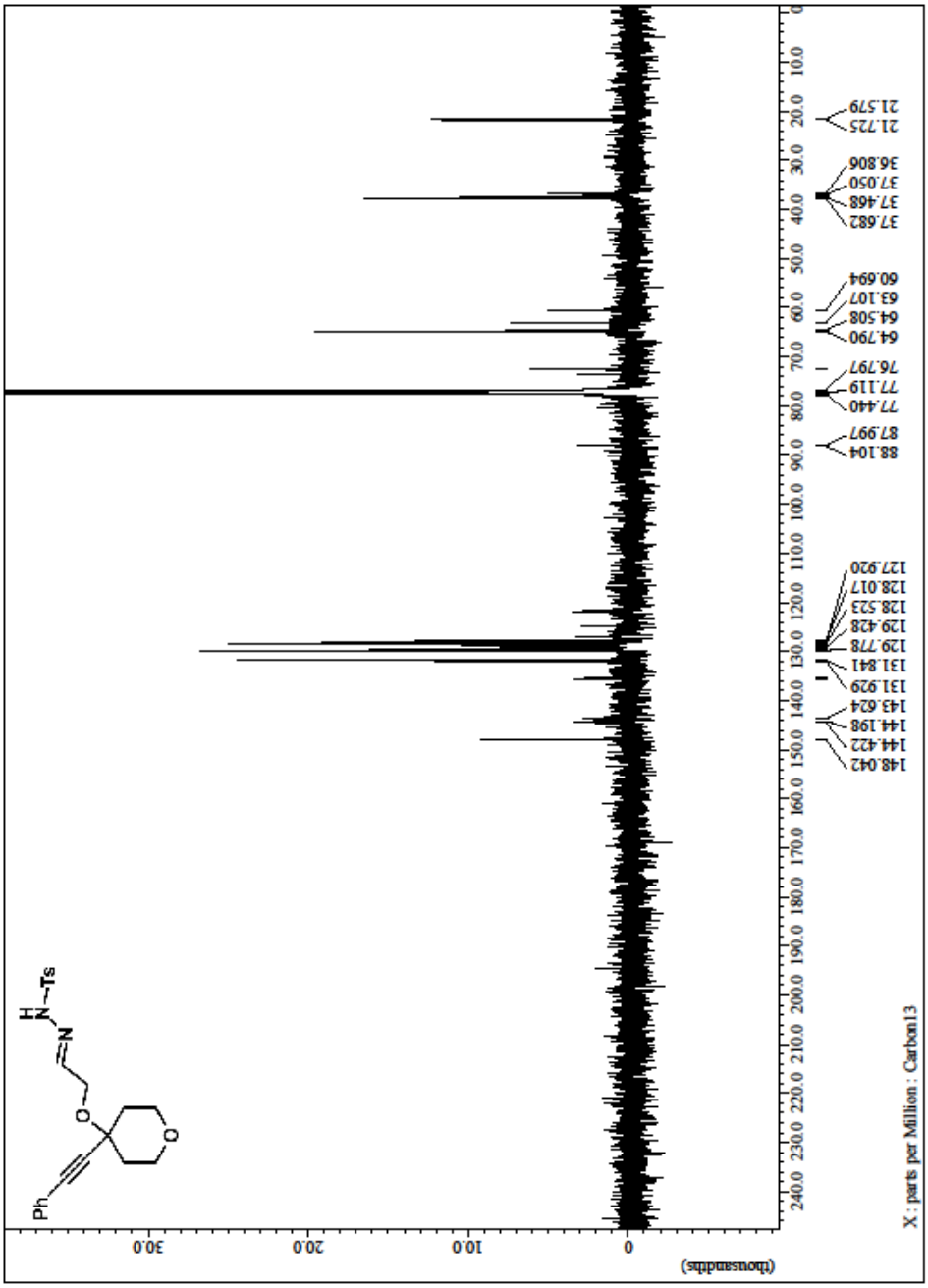

Figure A.3.167. ^{13}C NMR for compound **292**

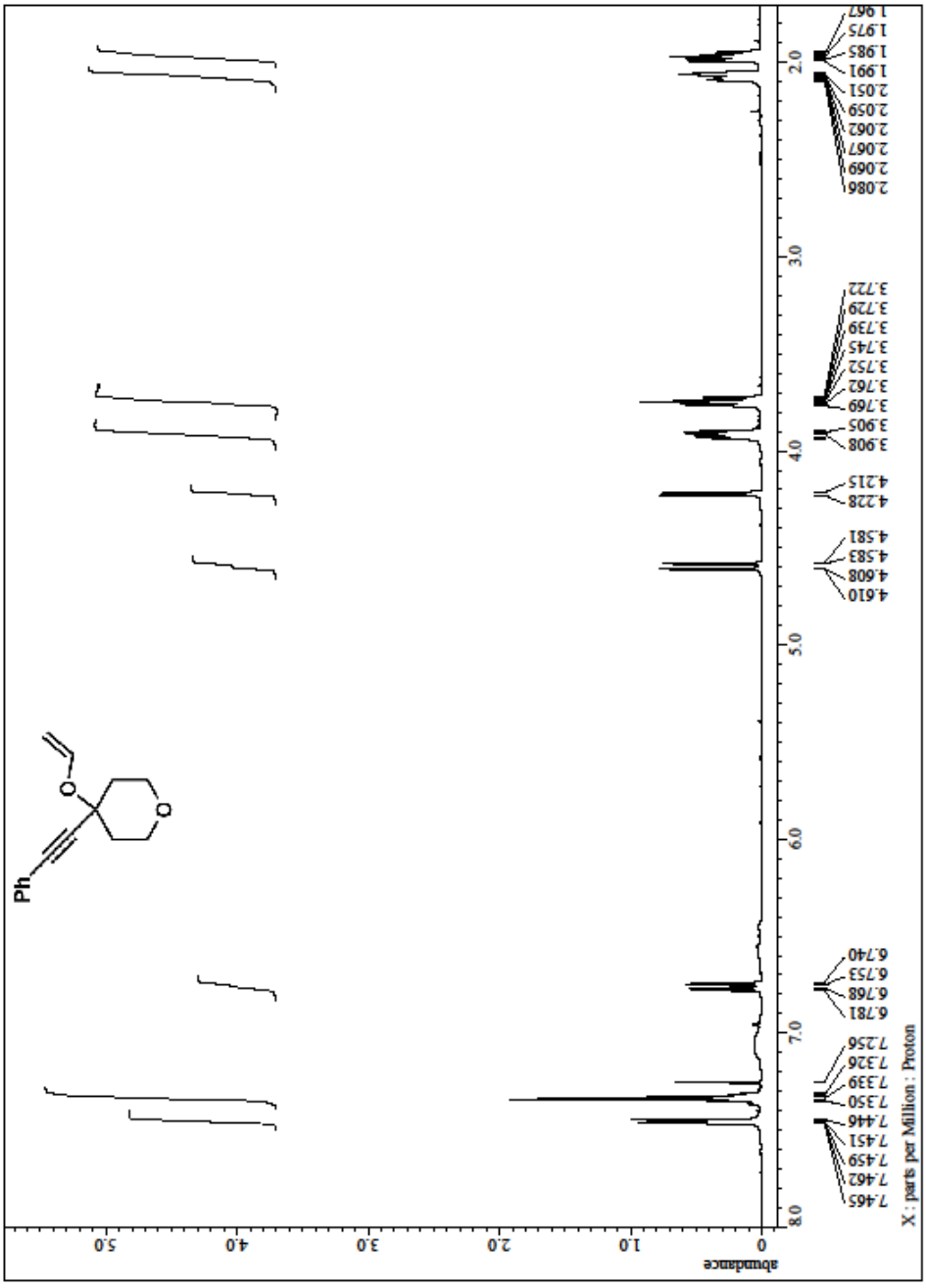

Figure A.3.168. ^{1}H NMR for compound **293**

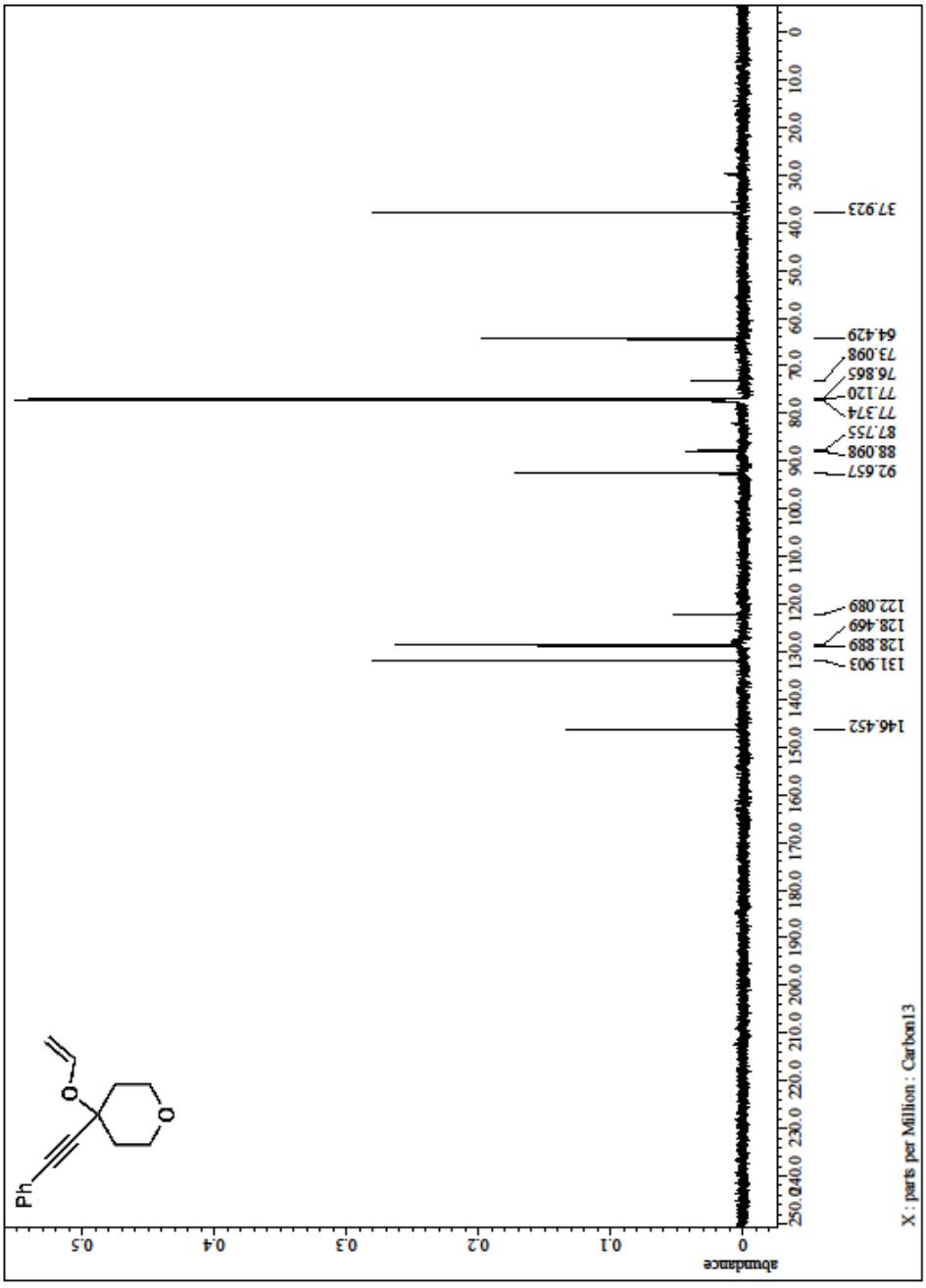

Figure A.3.169. ^{13}C NMR for compound **293**

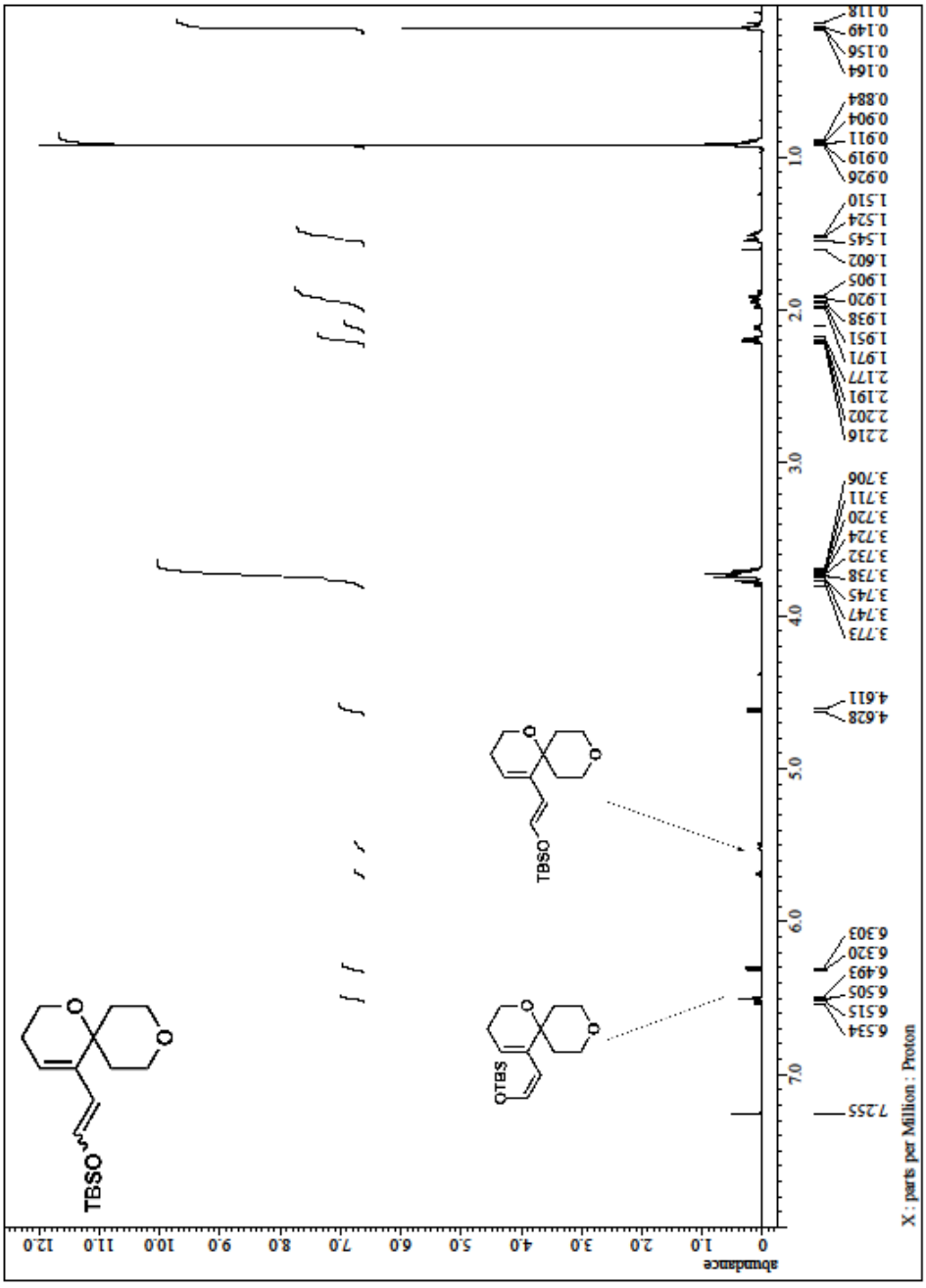

Figure A.3.170. ^{1}H NMR for compound **294**

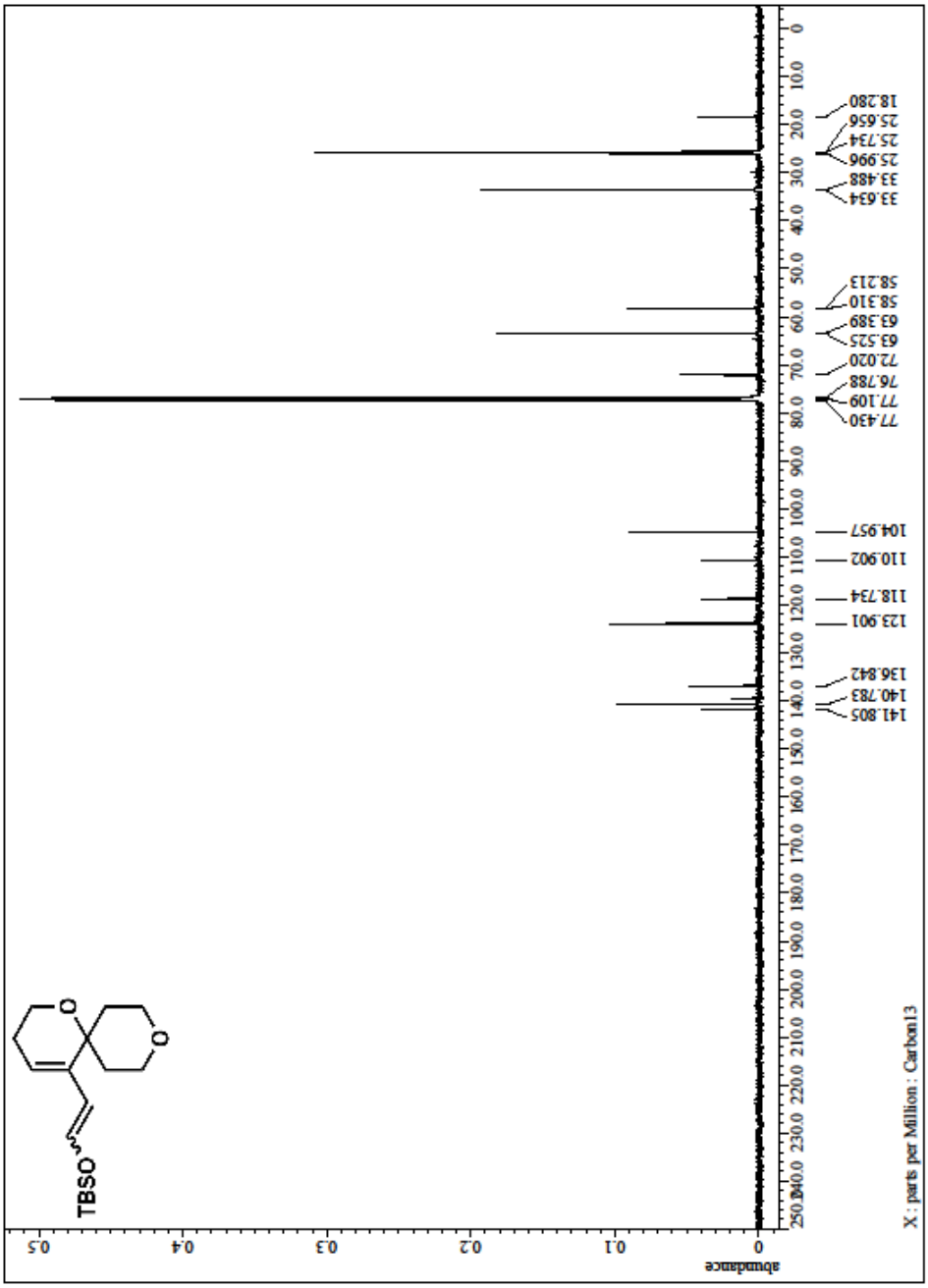

Figure A.3.171. ^{13}C NMR for compound **294**

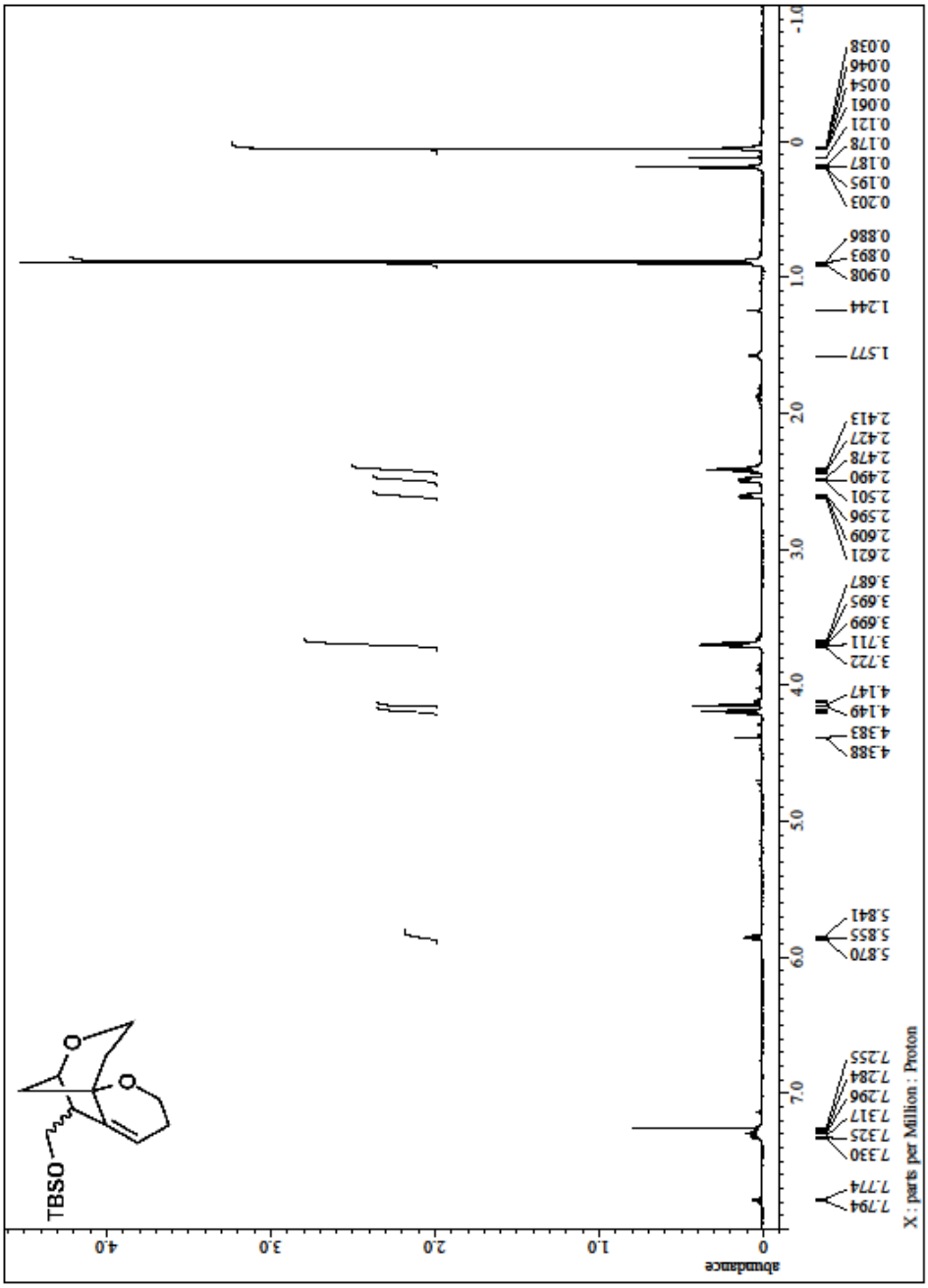

Figure A.3.172. ^{1}H NMR for compound **295**

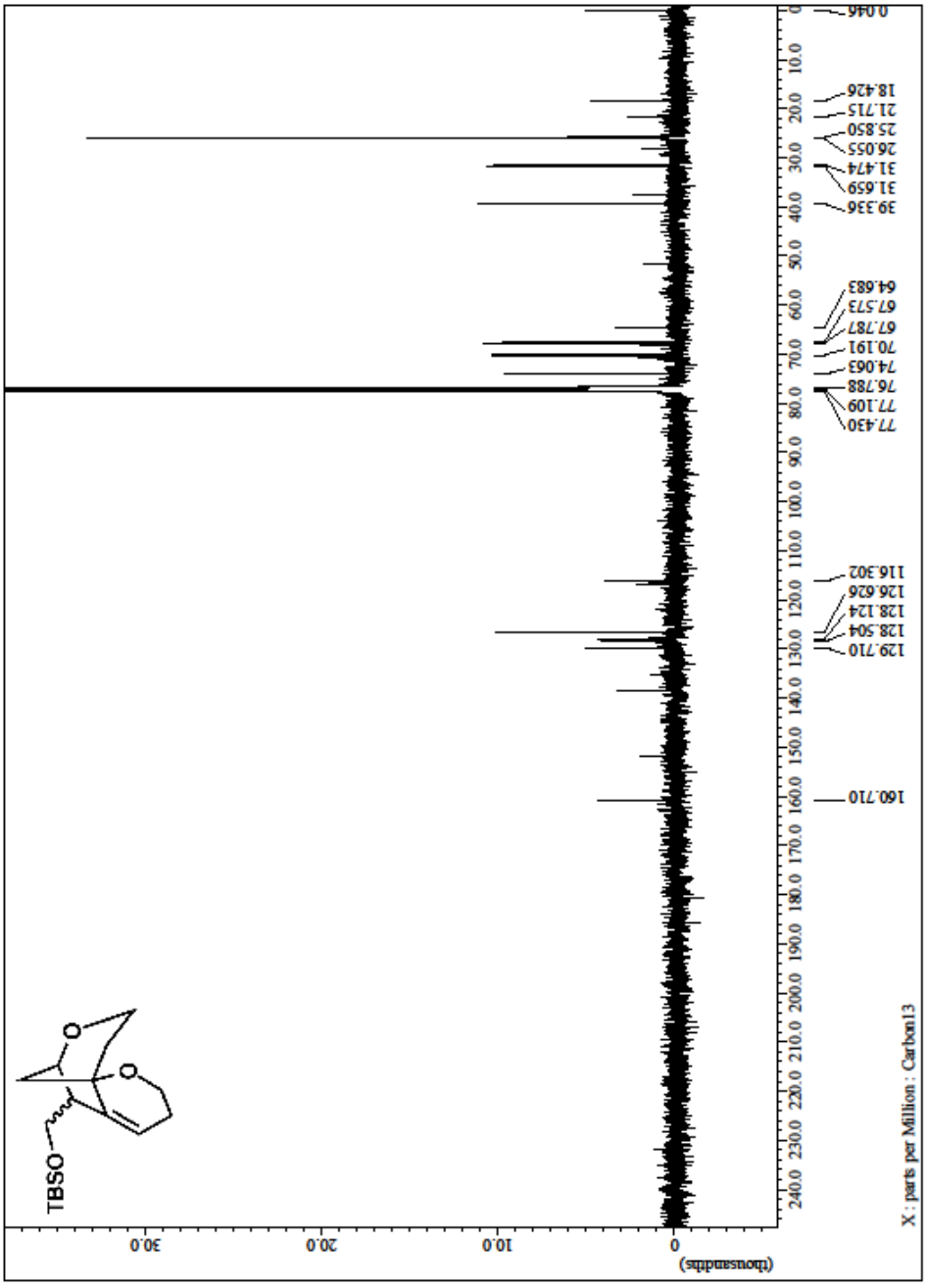

Figure A.3.173. ^{13}C NMR for compound **295**

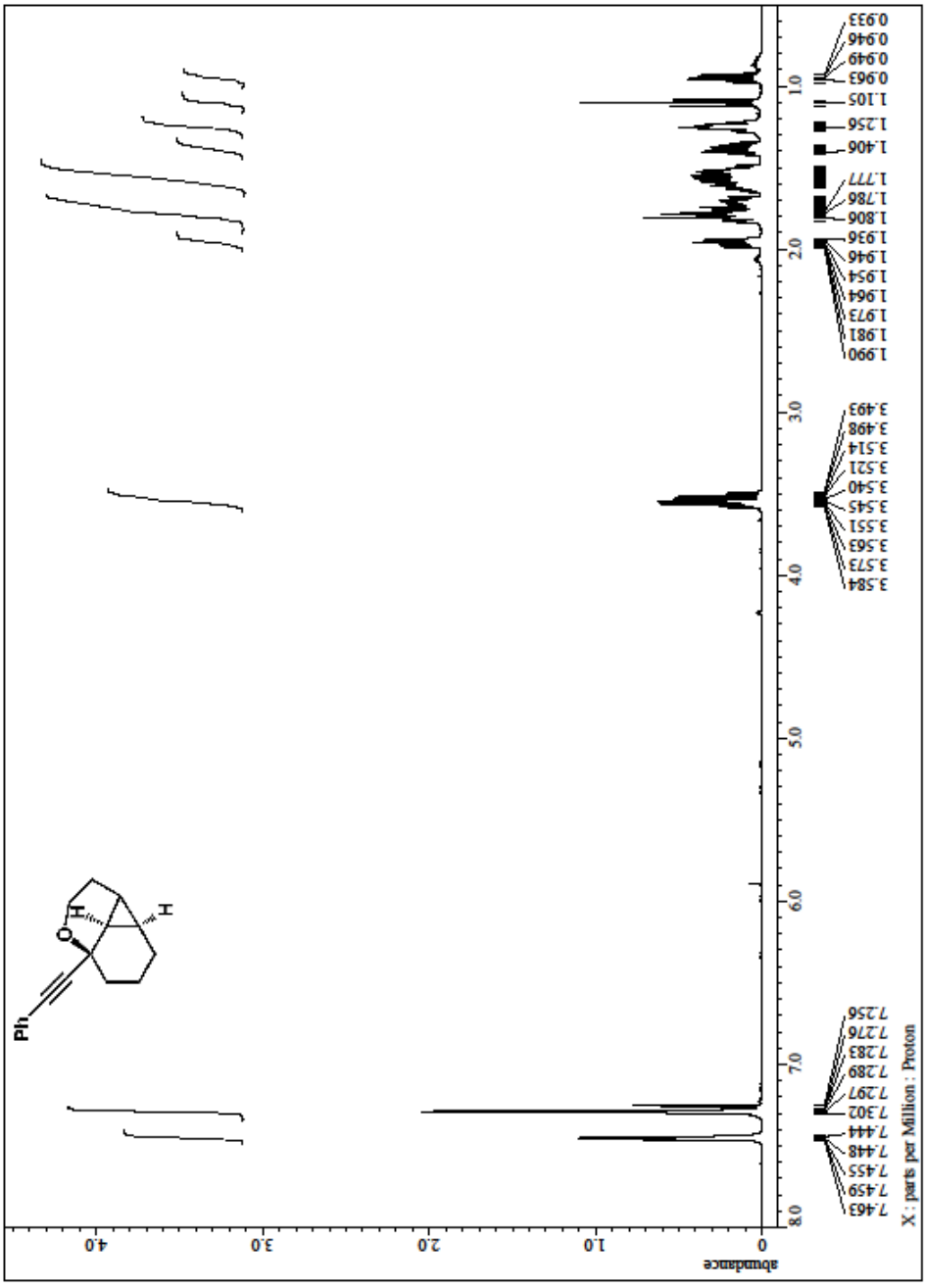

Figure A.3.174. ^{1}H NMR for compound **296**

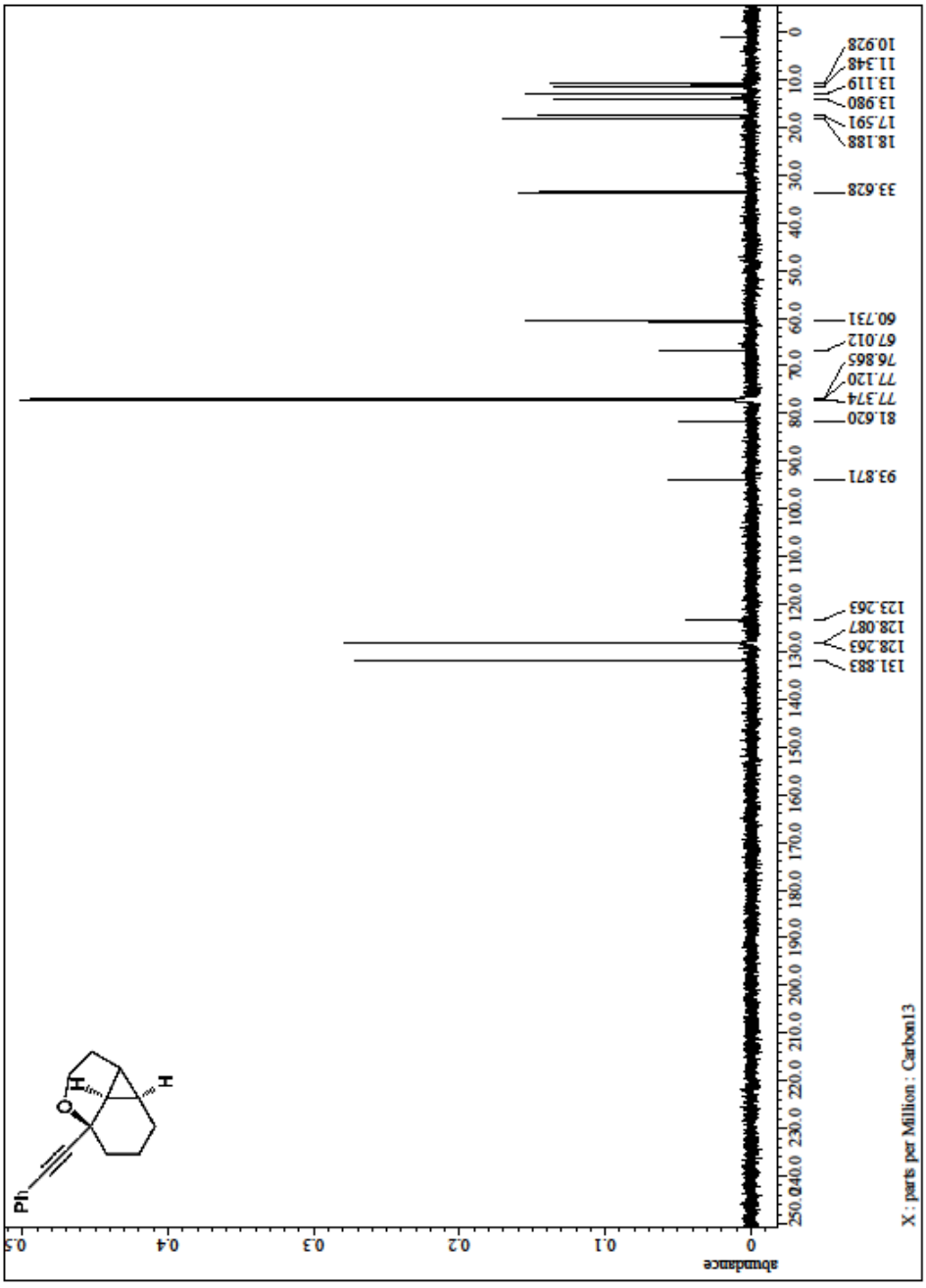

Figure A.3.175. ^{13}C NMR for compound **296**

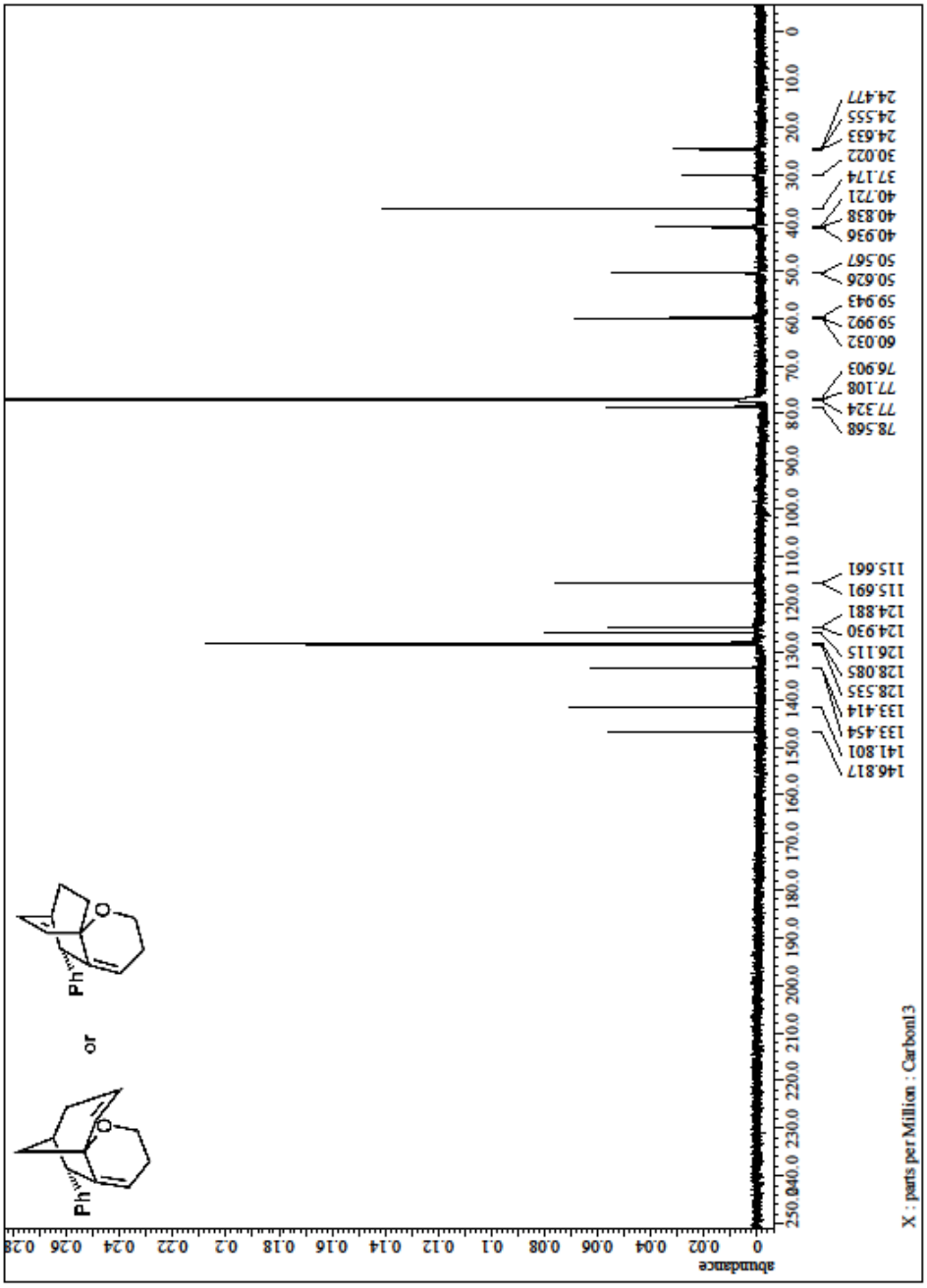

Figure A.3.176. ^{13}C NMR for compound **297A or 297B**

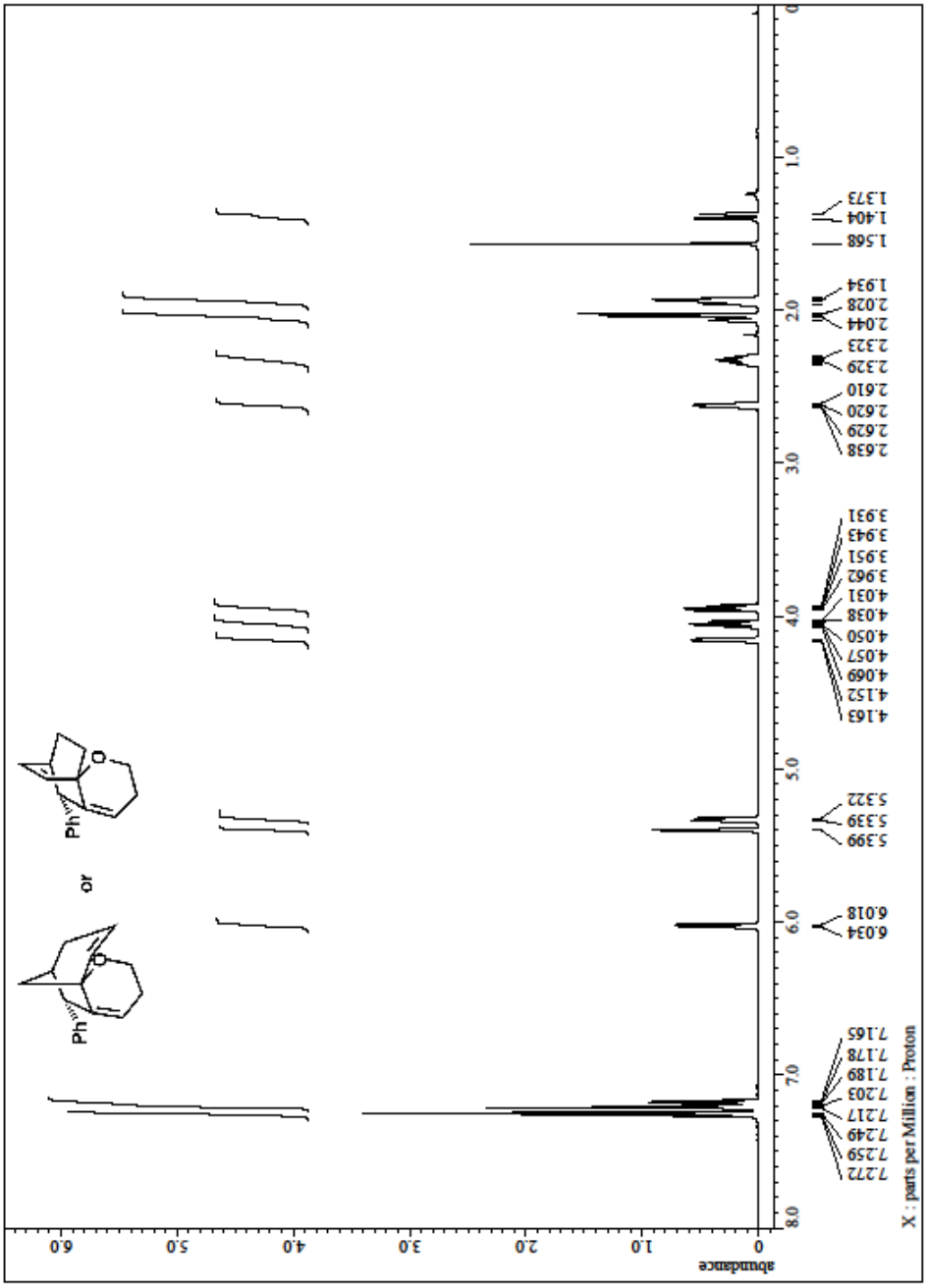

Figure A.3.177. ^{1}H NMR for compound **297A or 297B**

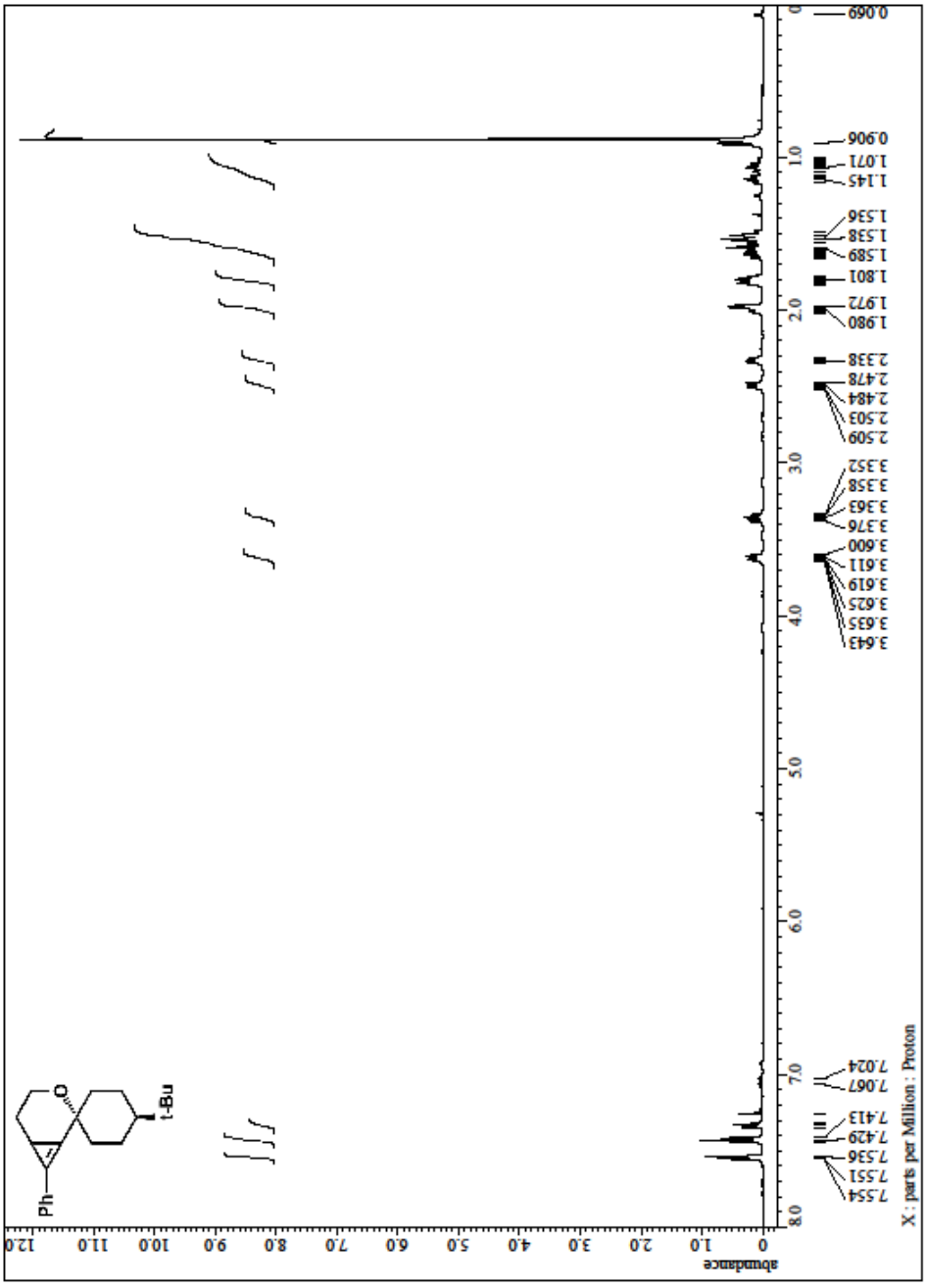

Figure A.3.178. ^{1}H NMR for compound **300**

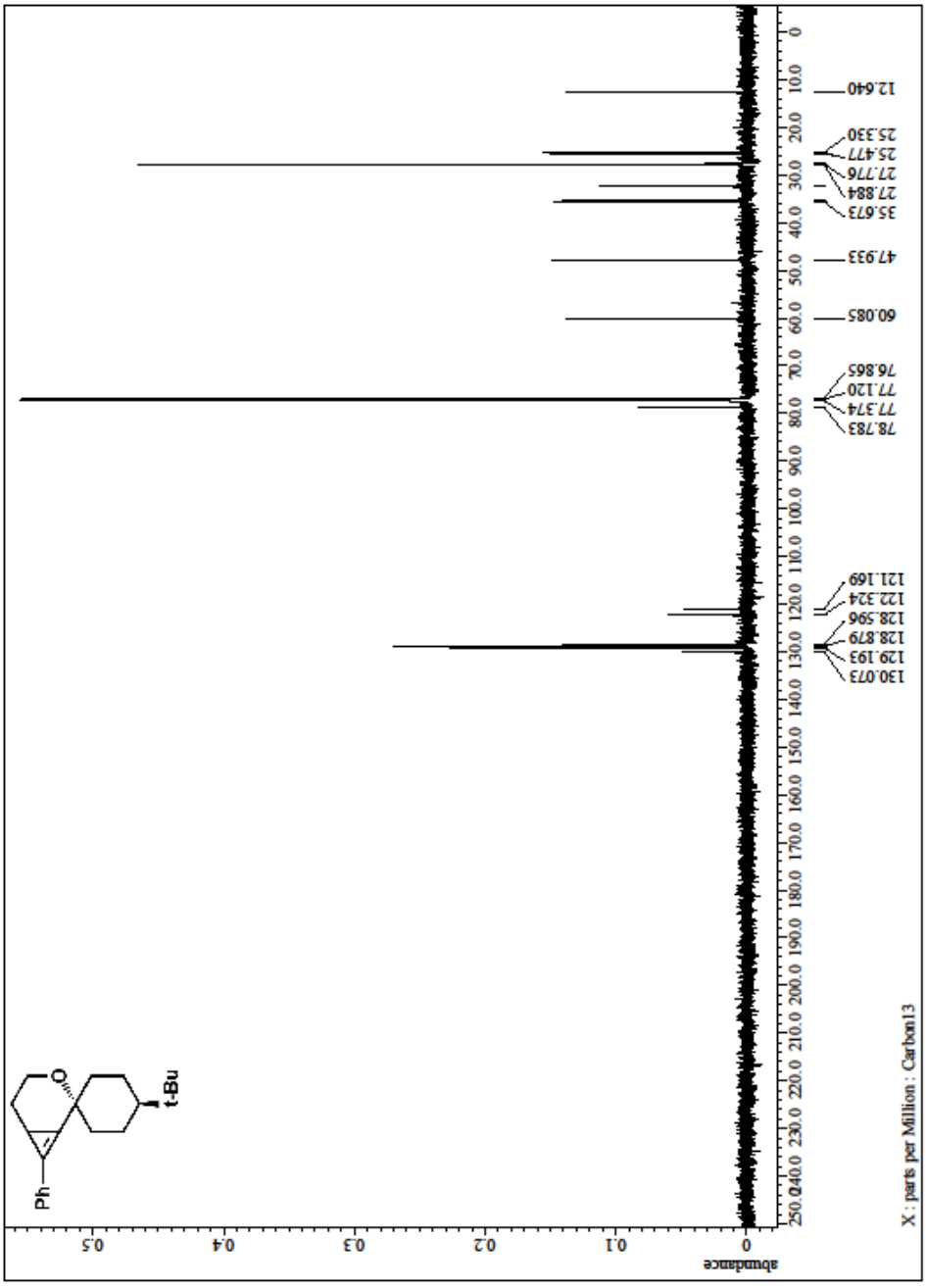

Figure A.3.179. ^{13}C NMR for compound **300**

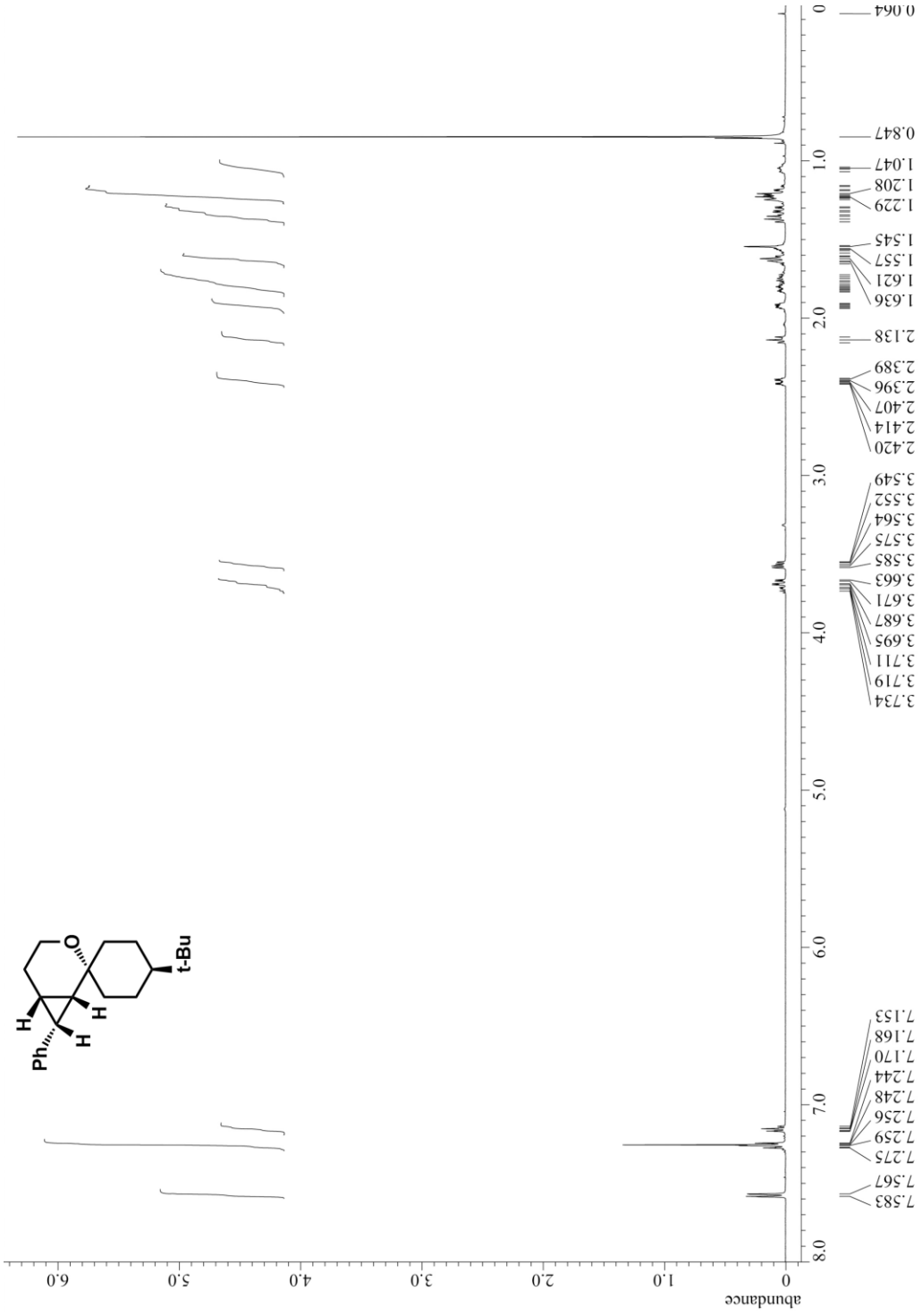

Figure A.3.180. ^{1}H NMR for compound **301**

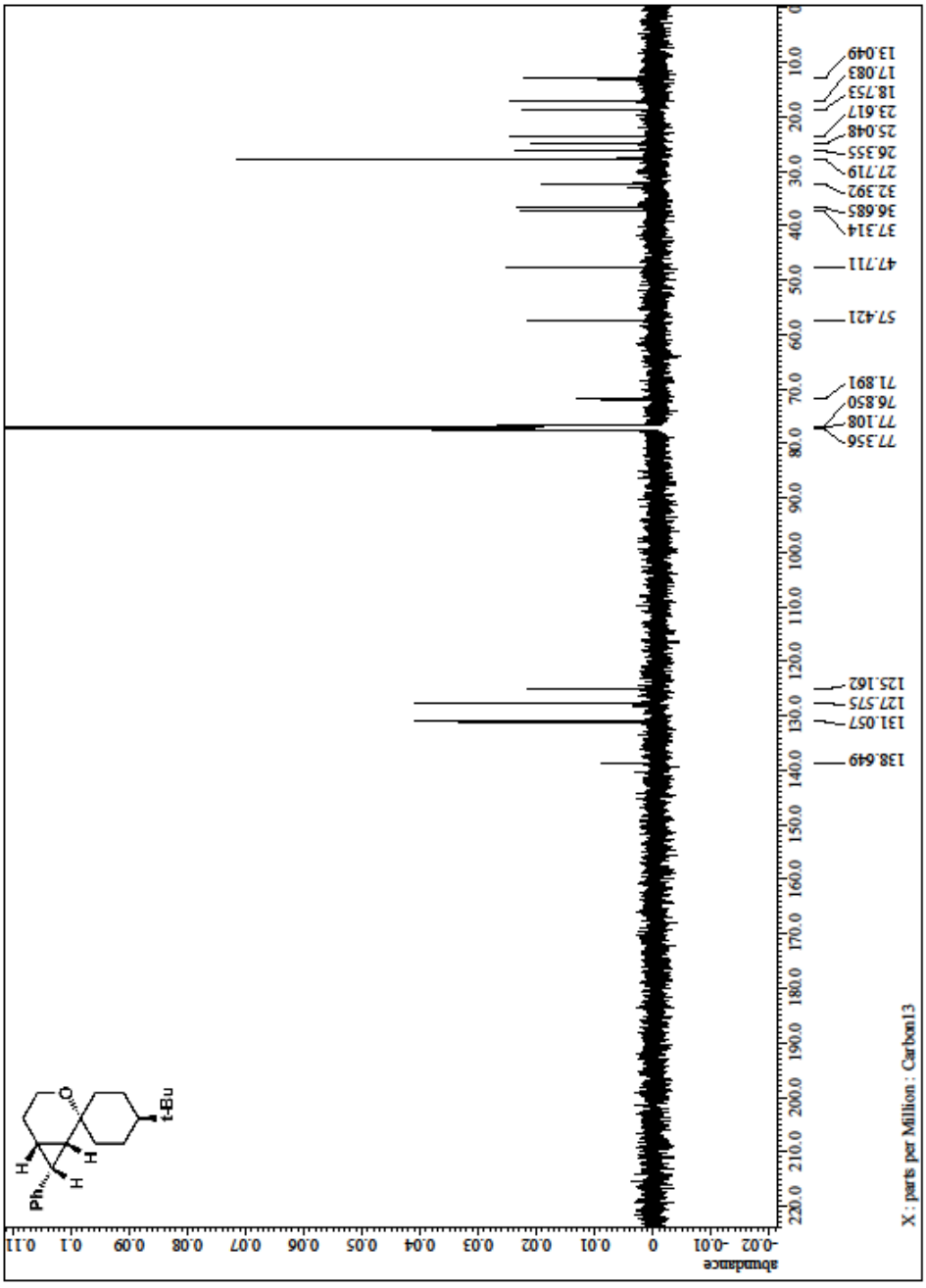

Figure A.3.181. ^{13}C NMR for compound **301**

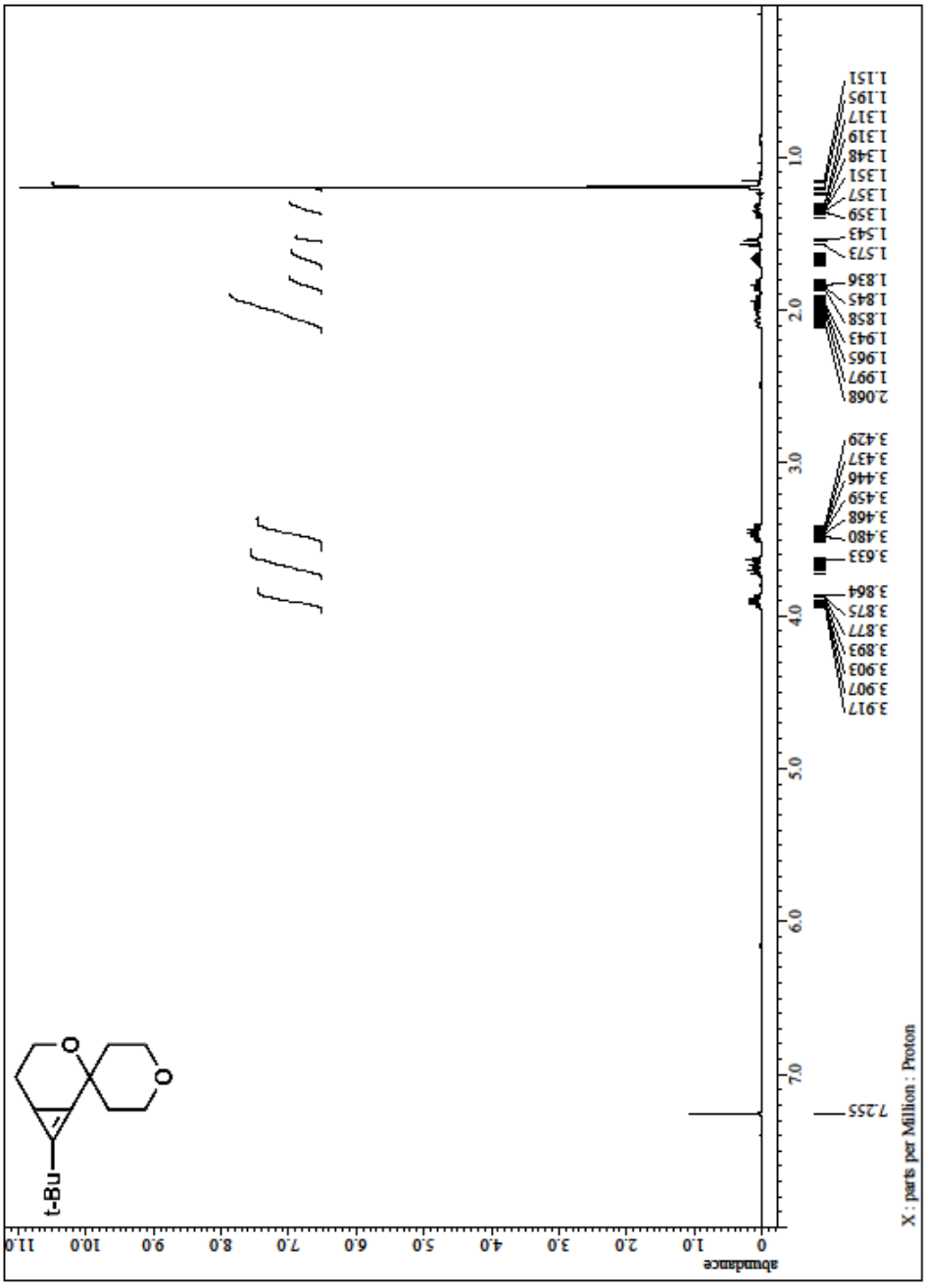

Figure A.3.182. ^{1}H NMR for compound **302**

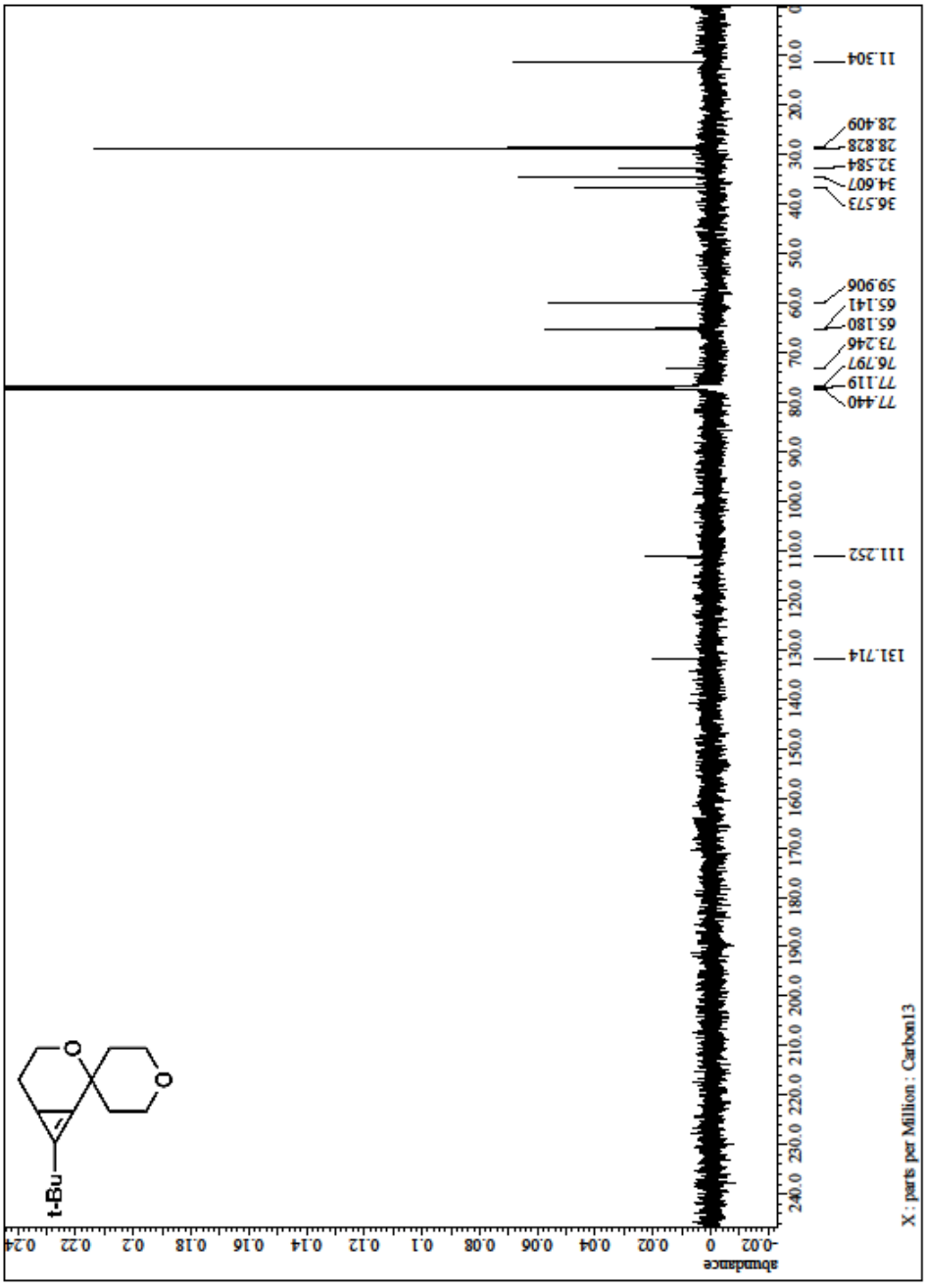

Figure A.3.183. ^{13}C NMR for compound **302**

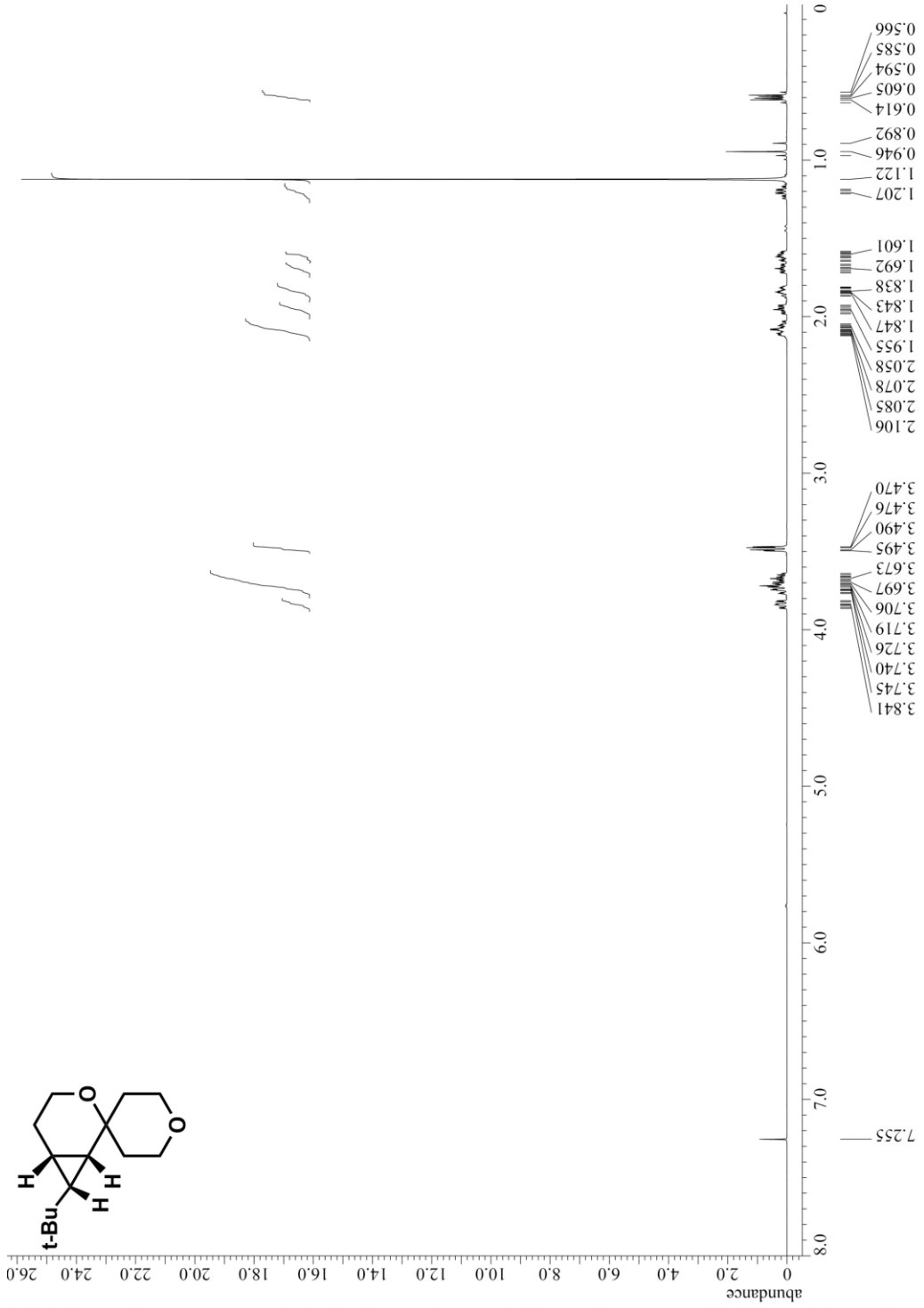

Figure A.3.184. ^{1}H NMR for compound **303**

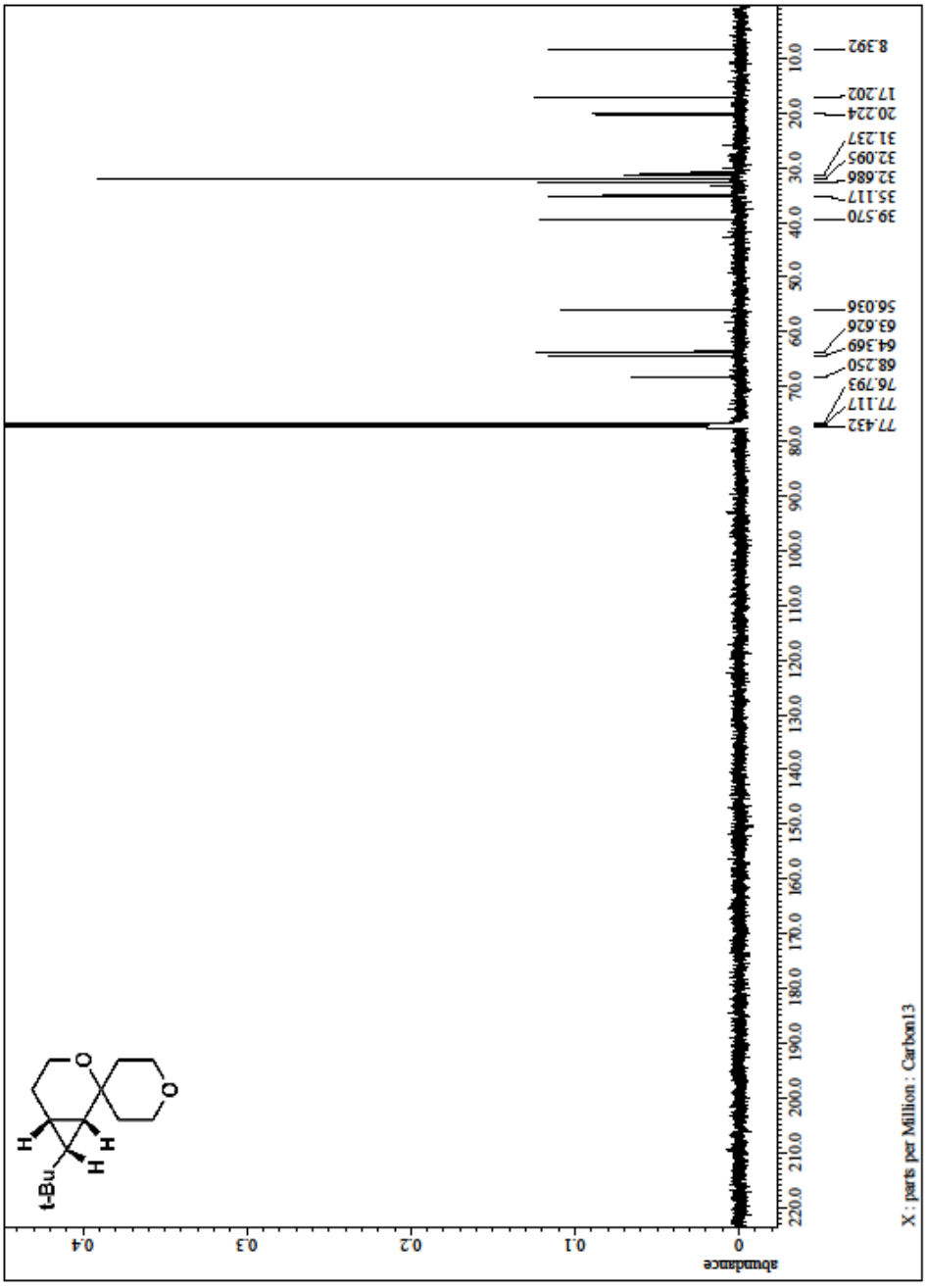

Figure A.3.185. ^{13}C NMR for compound **303**

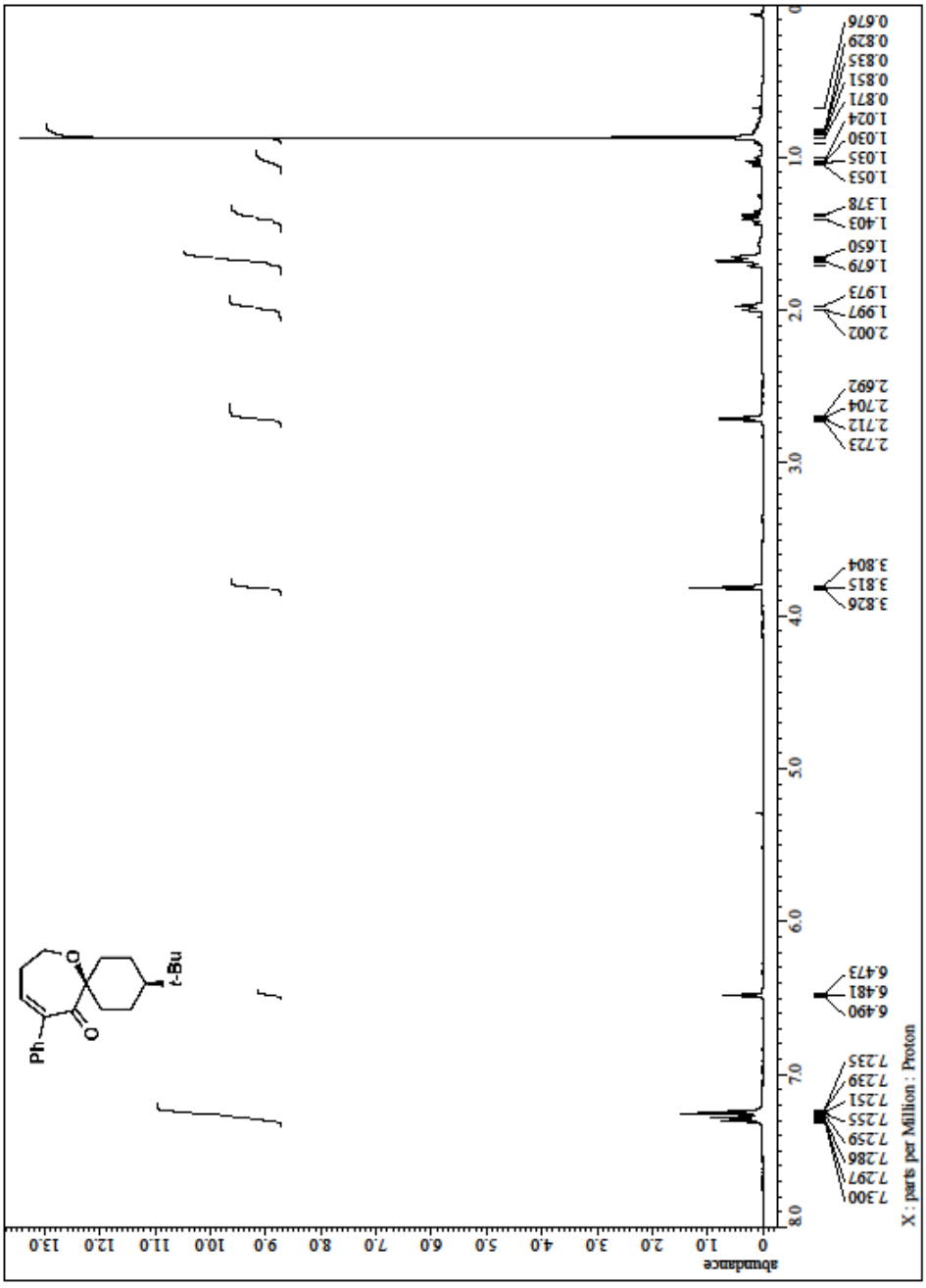

Figure A.3.186. ^{1}H NMR for compound **304**

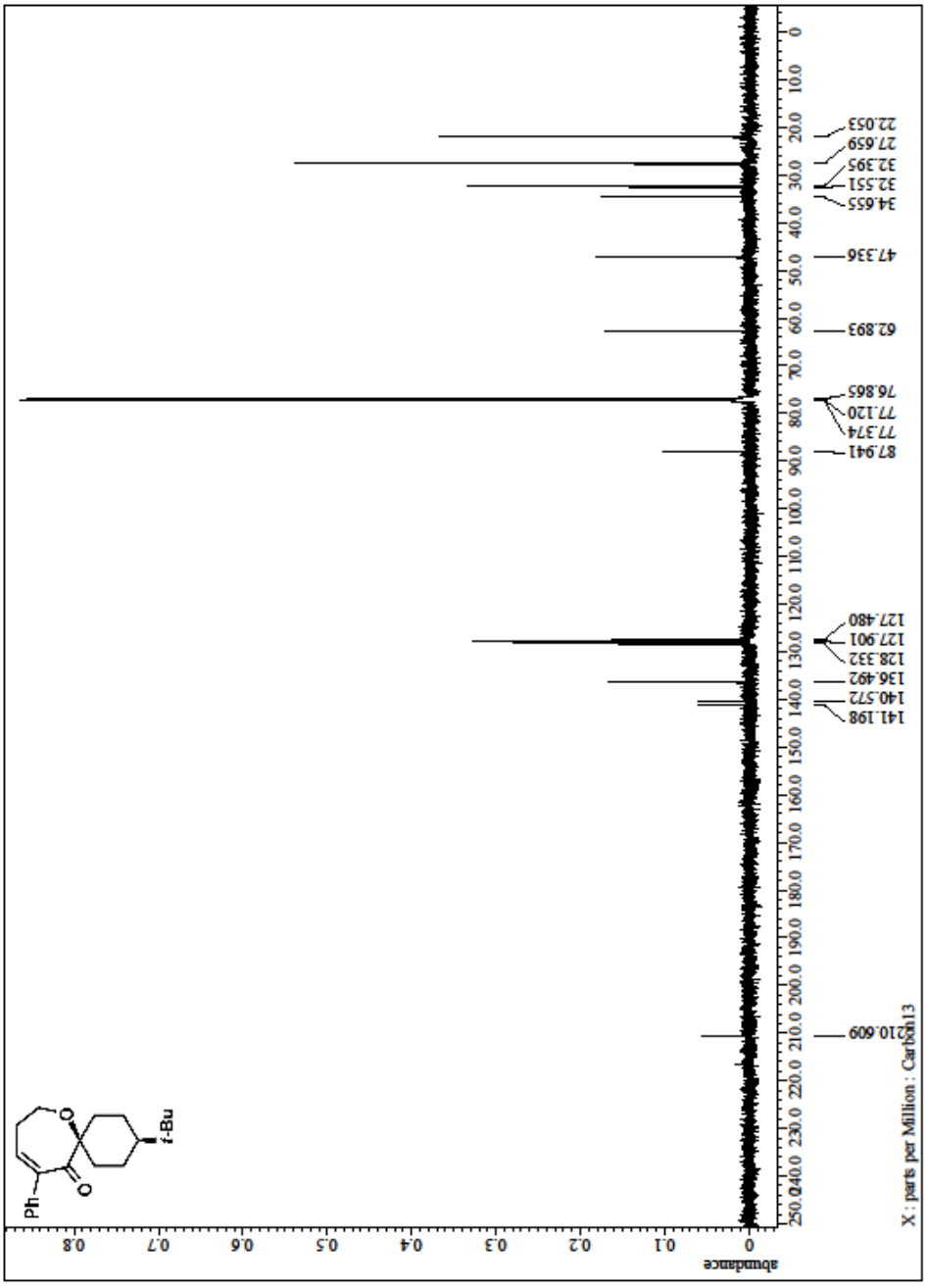

Figure A.3.187. ^{13}C NMR for compound **304**

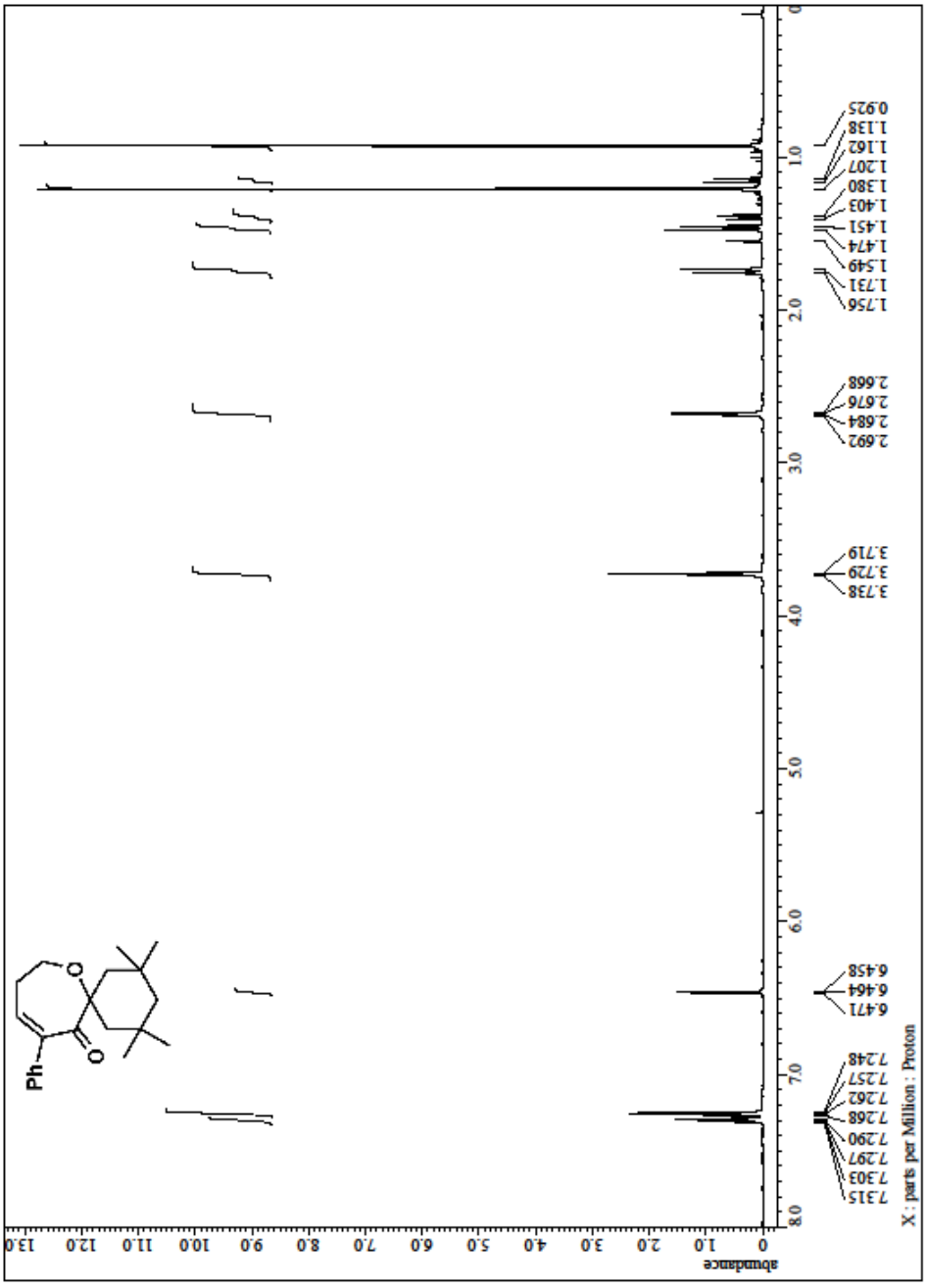

Figure A.3.188. ^{1}H NMR for compound **305**

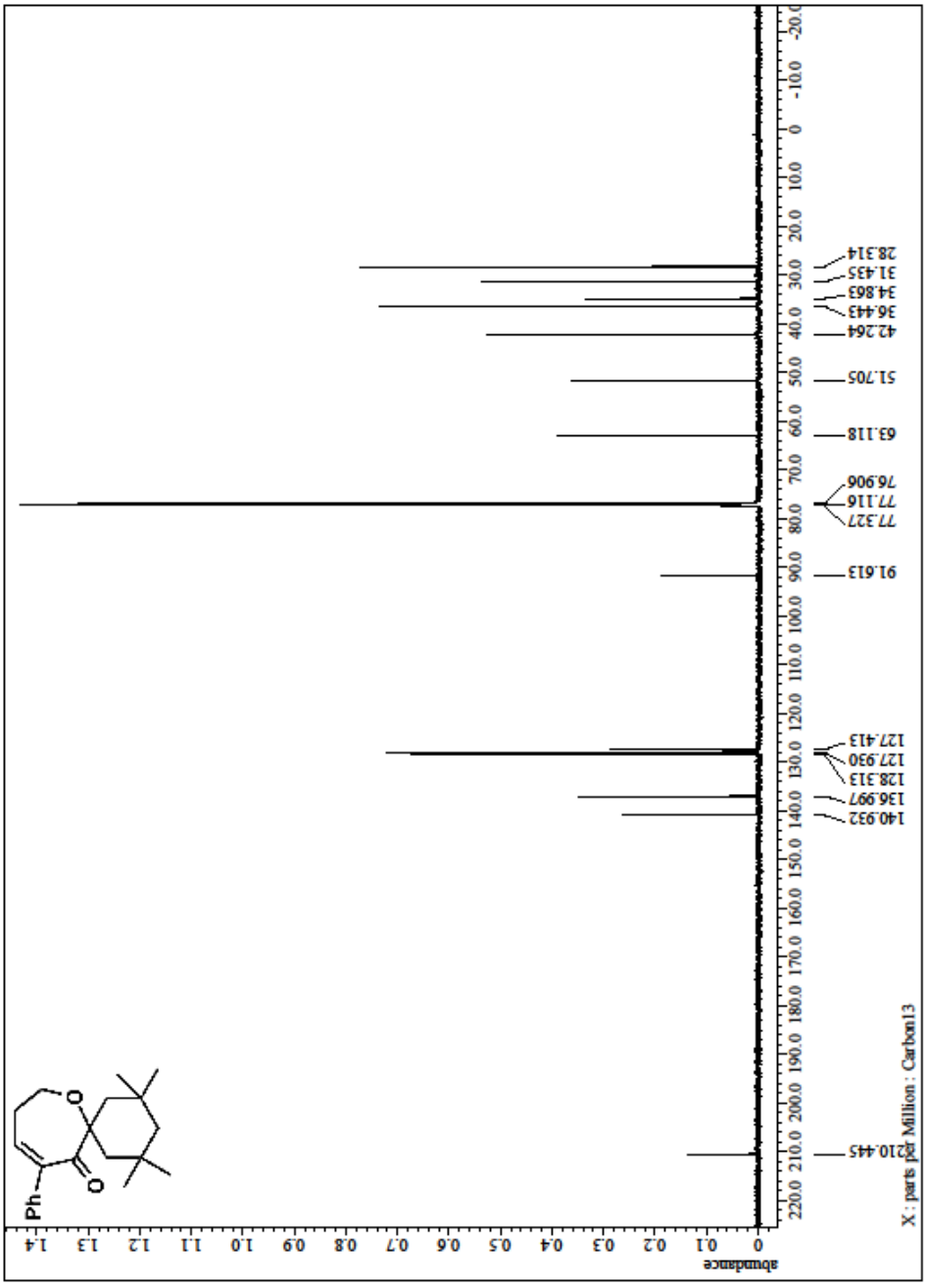

Figure A.3.189. ^{13}C NMR for compound **305**

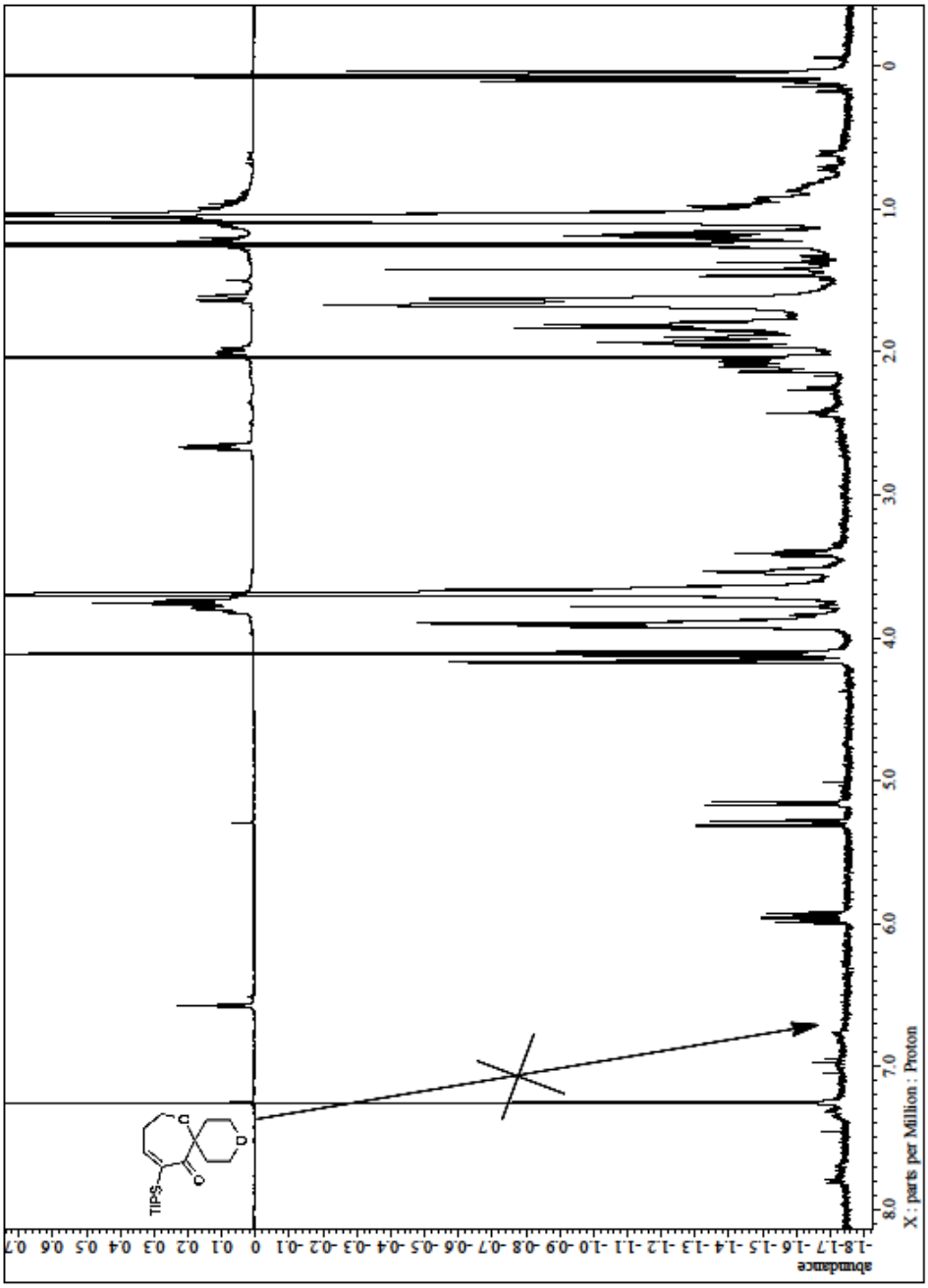

Figure A.3.190. Crude ^{1}H NMR for reaction in Section **4.14.17.24**

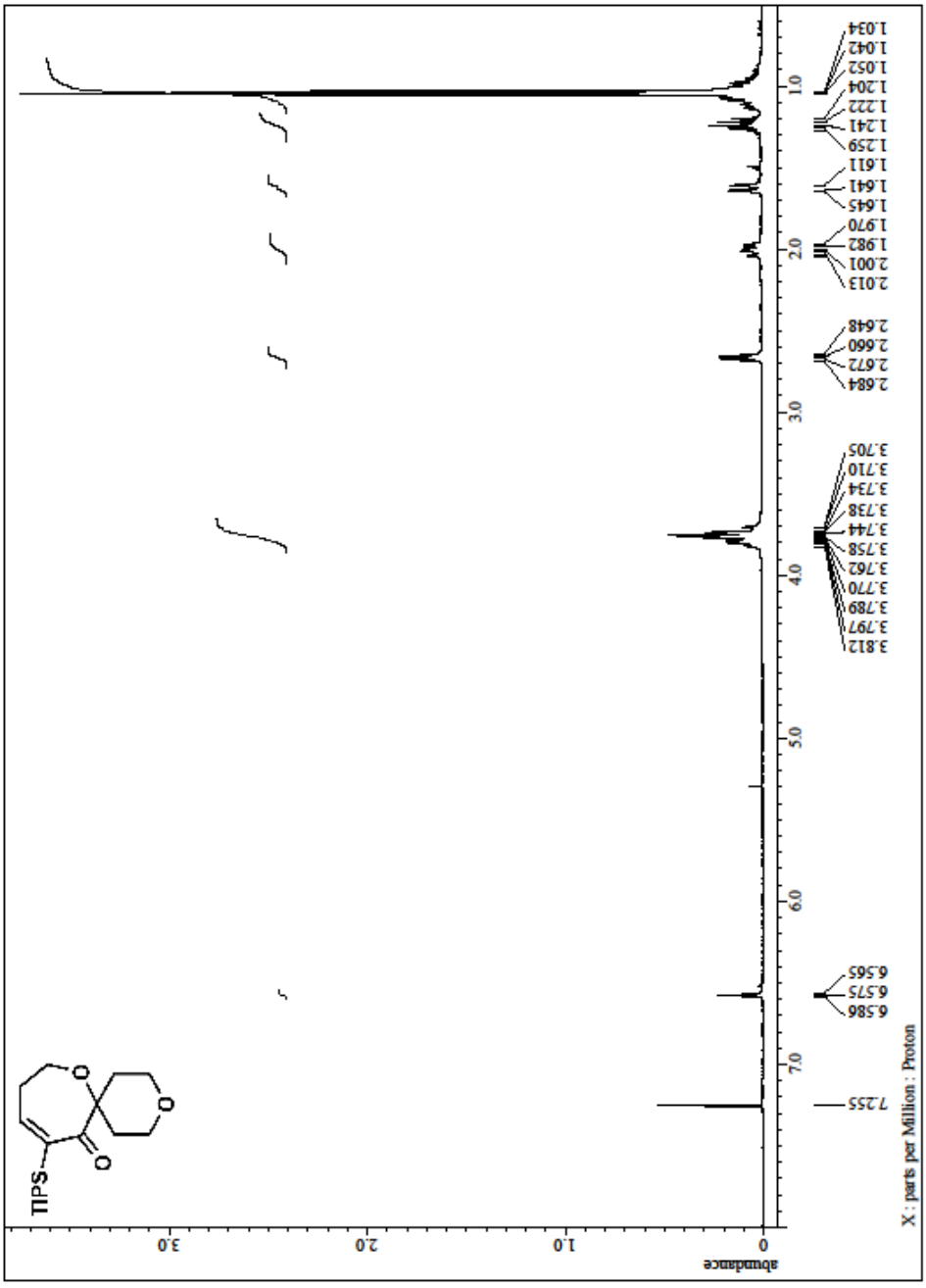

Figure A.3.191. ^{1}H NMR for compound **306**

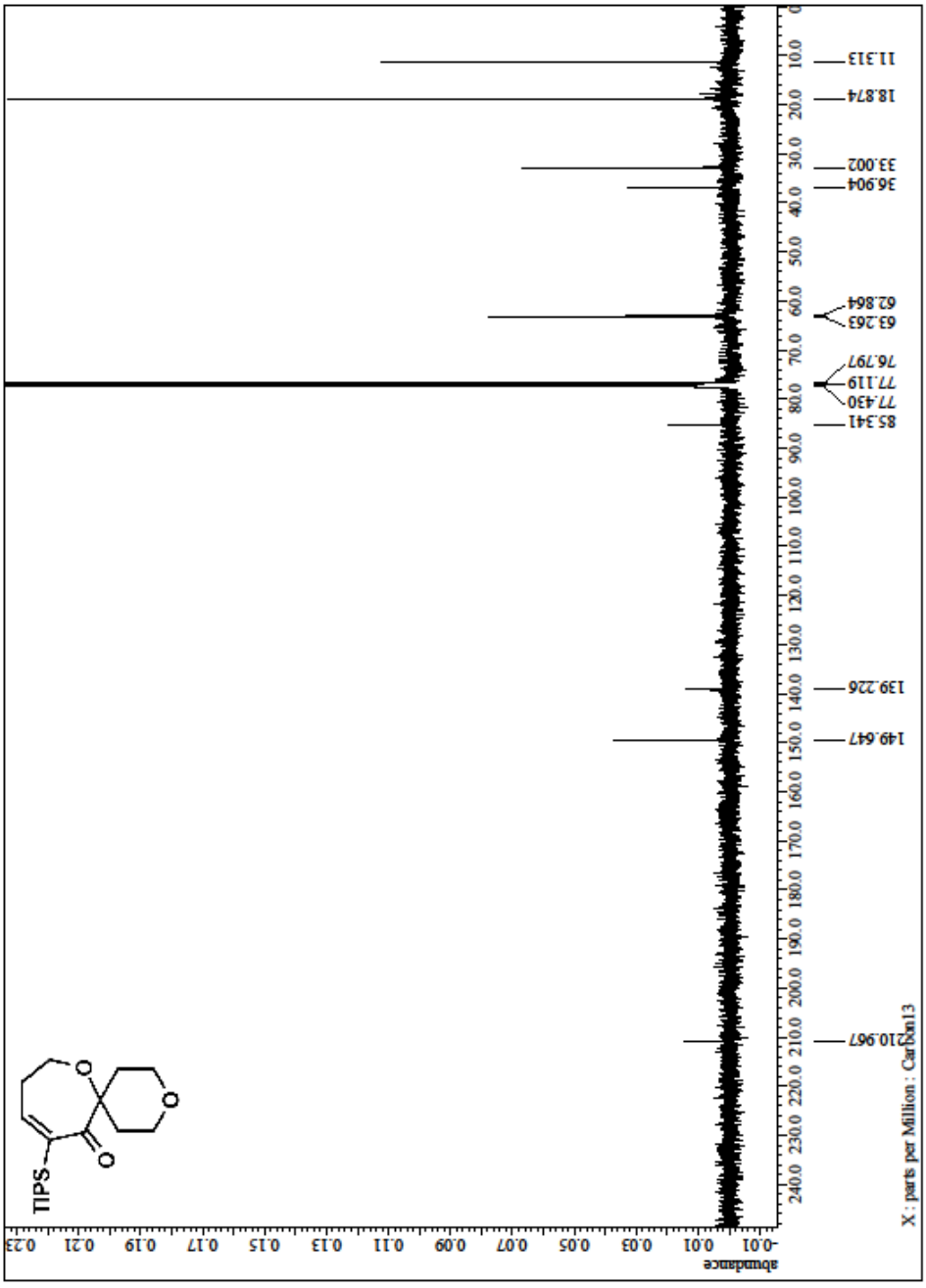

Figure A.3.192. ^{13}C NMR for compound **306**

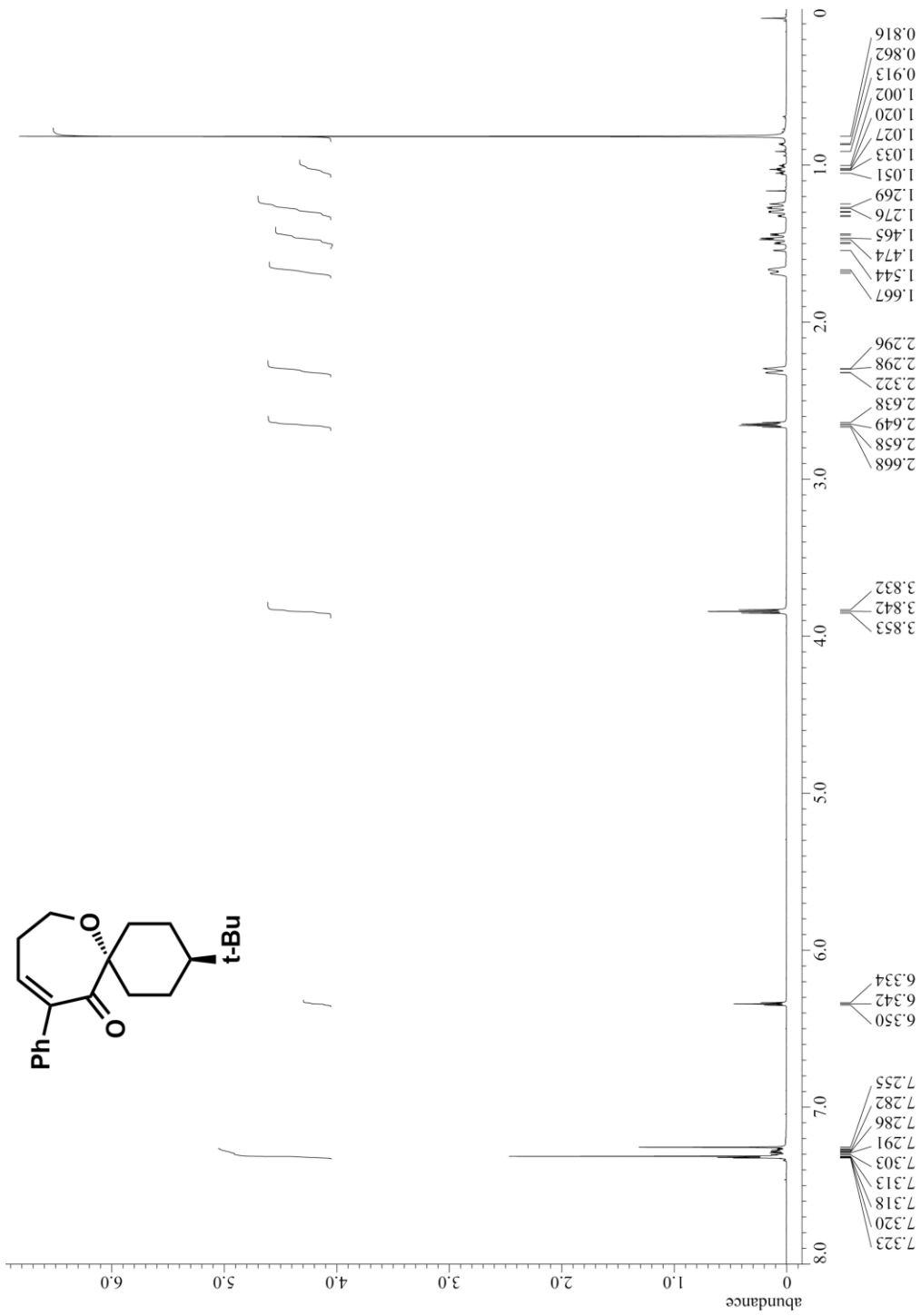

Figure A.3.193. ^{1}H NMR for compound **309**

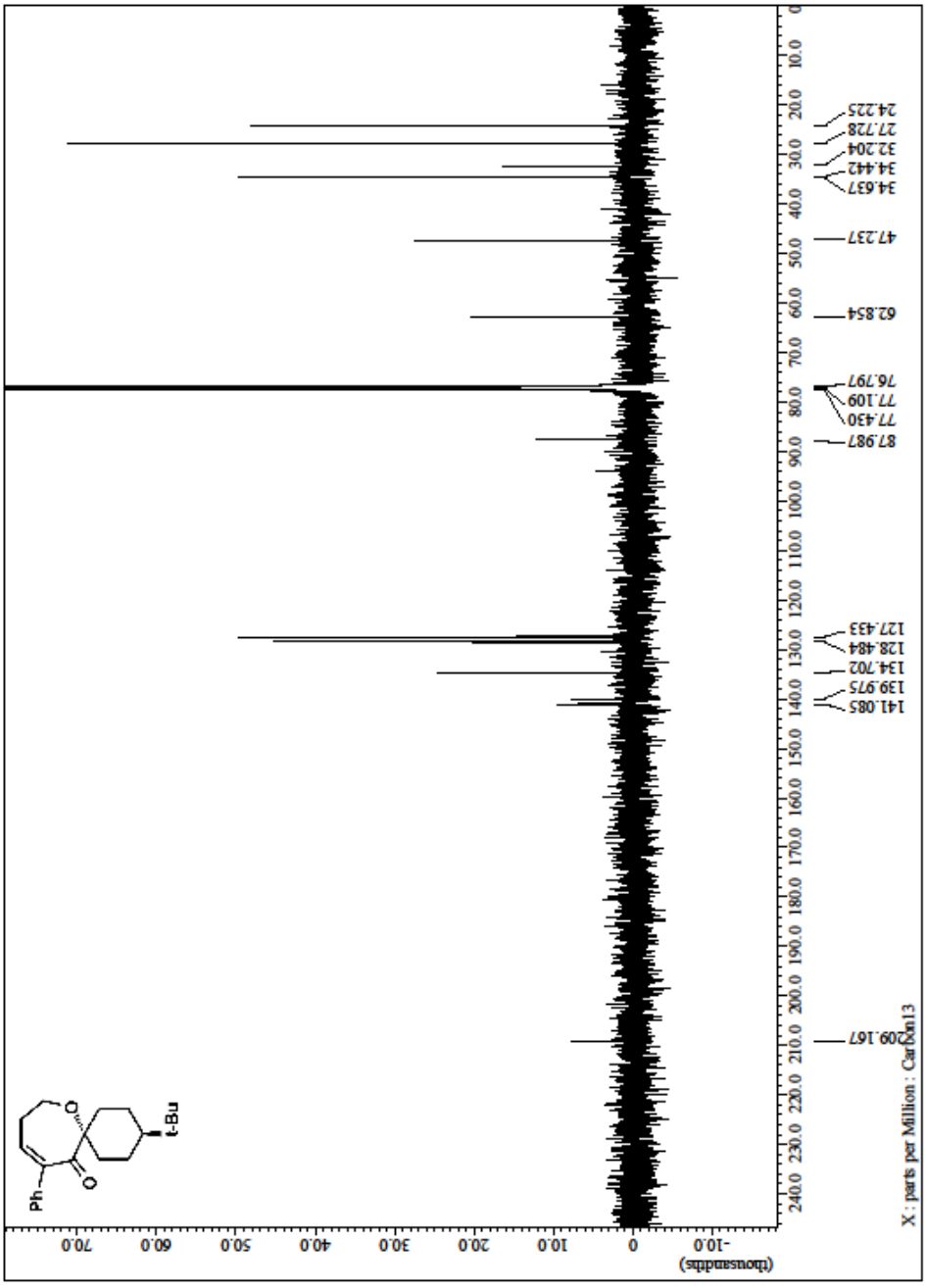

Figure A.3.194. ^{13}C NMR for compound **309**

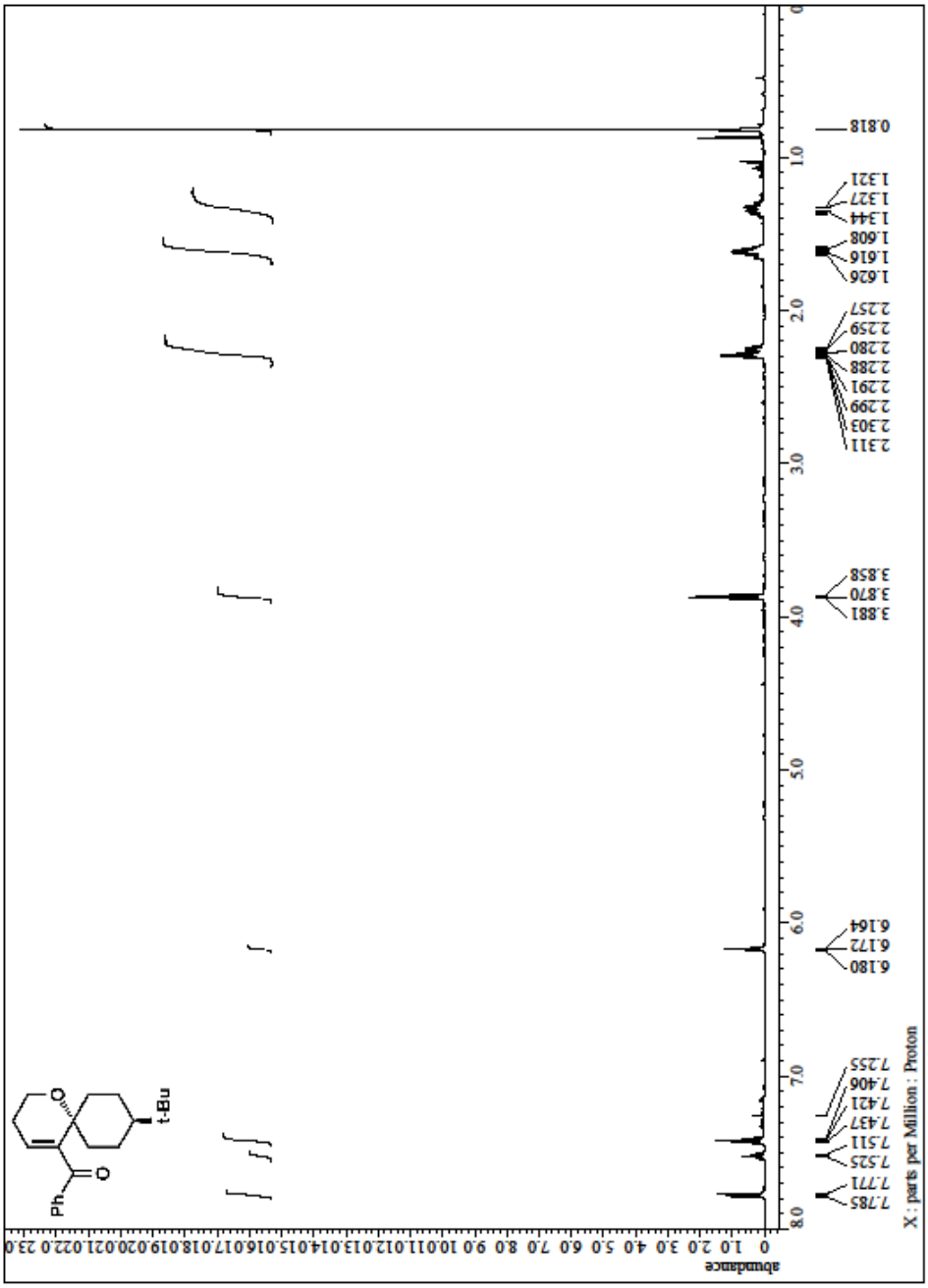

Figure A.3.195. ^{1}H NMR for compound **310**

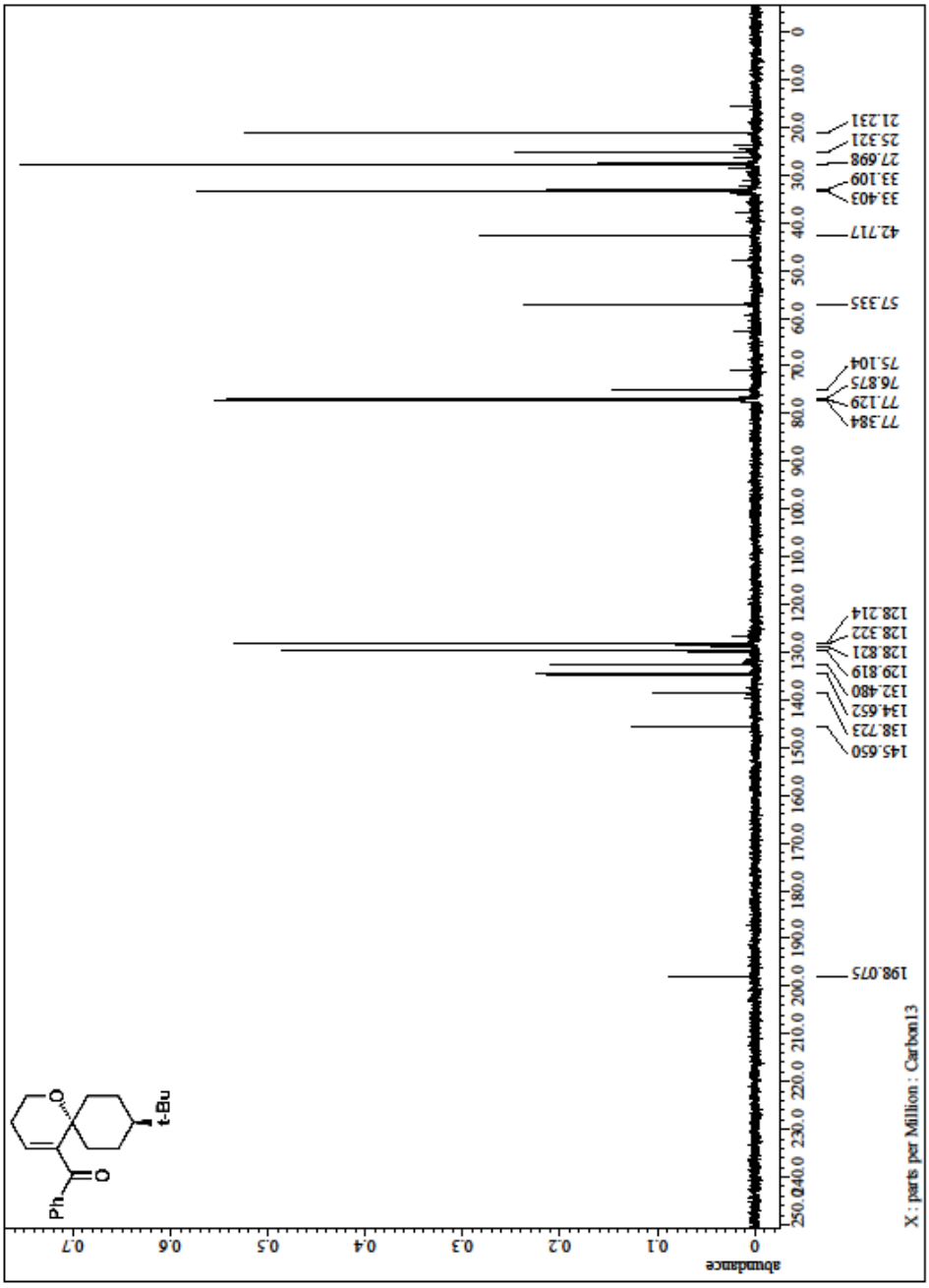

Figure A.3.196. ^{13}C NMR for compound **310**

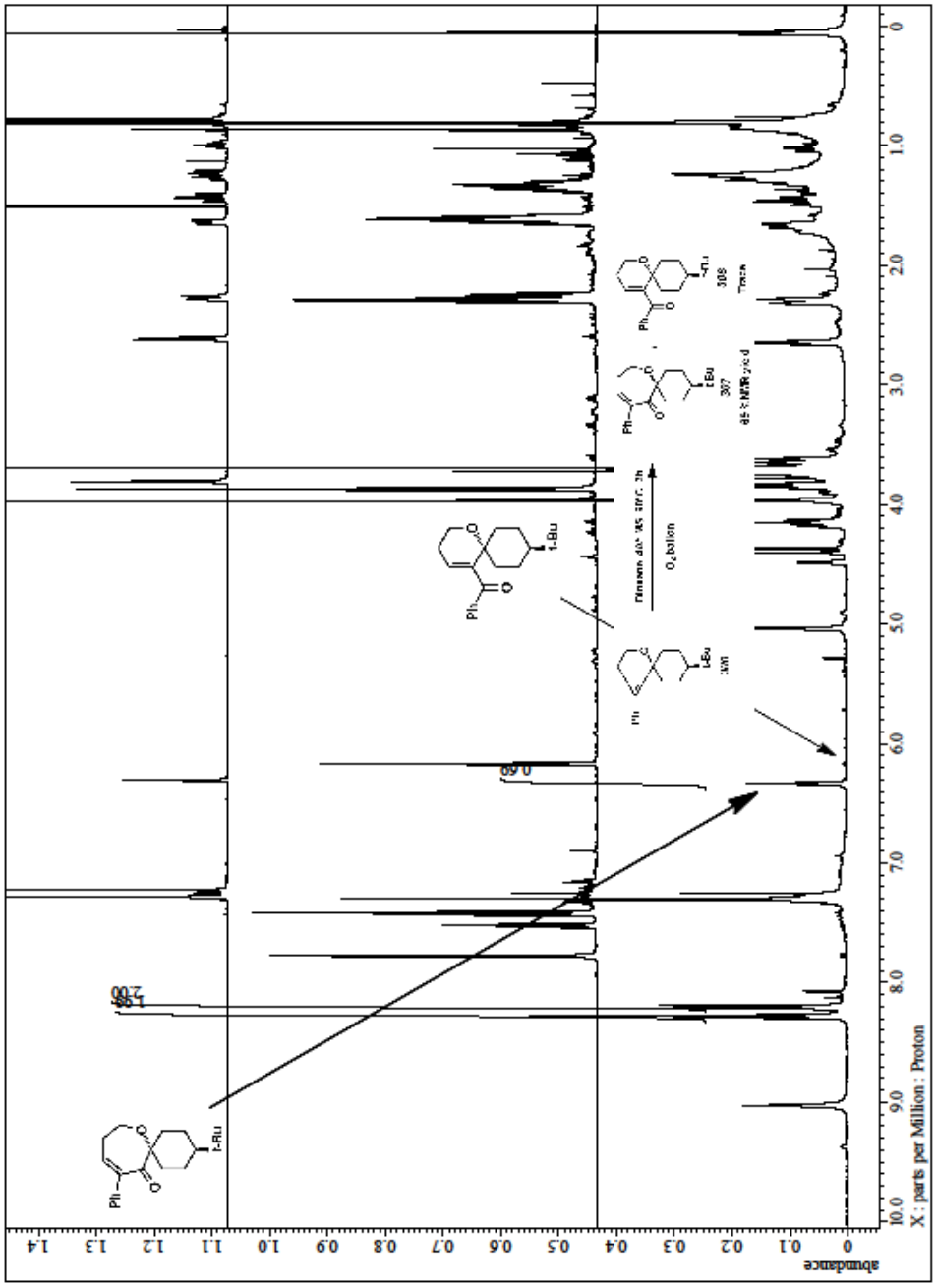

Figure A.3.197. Crude ^{1}H NMR of reaction in Section **4.14.19.1**

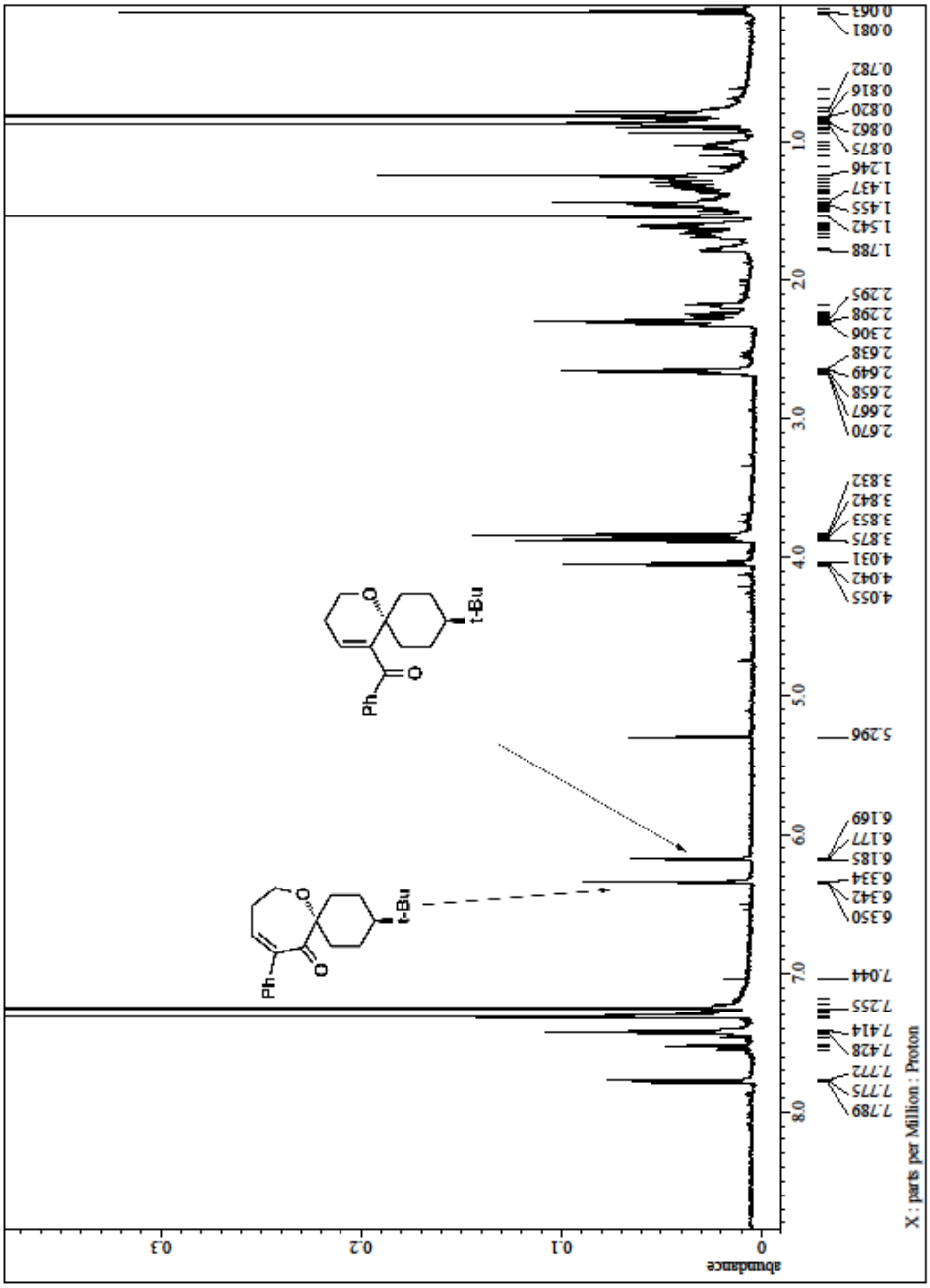

Figure A.3.198. Crude ^{1}H NMR of mixture of **309** and **310** of reaction in Section **4.14.19.1**

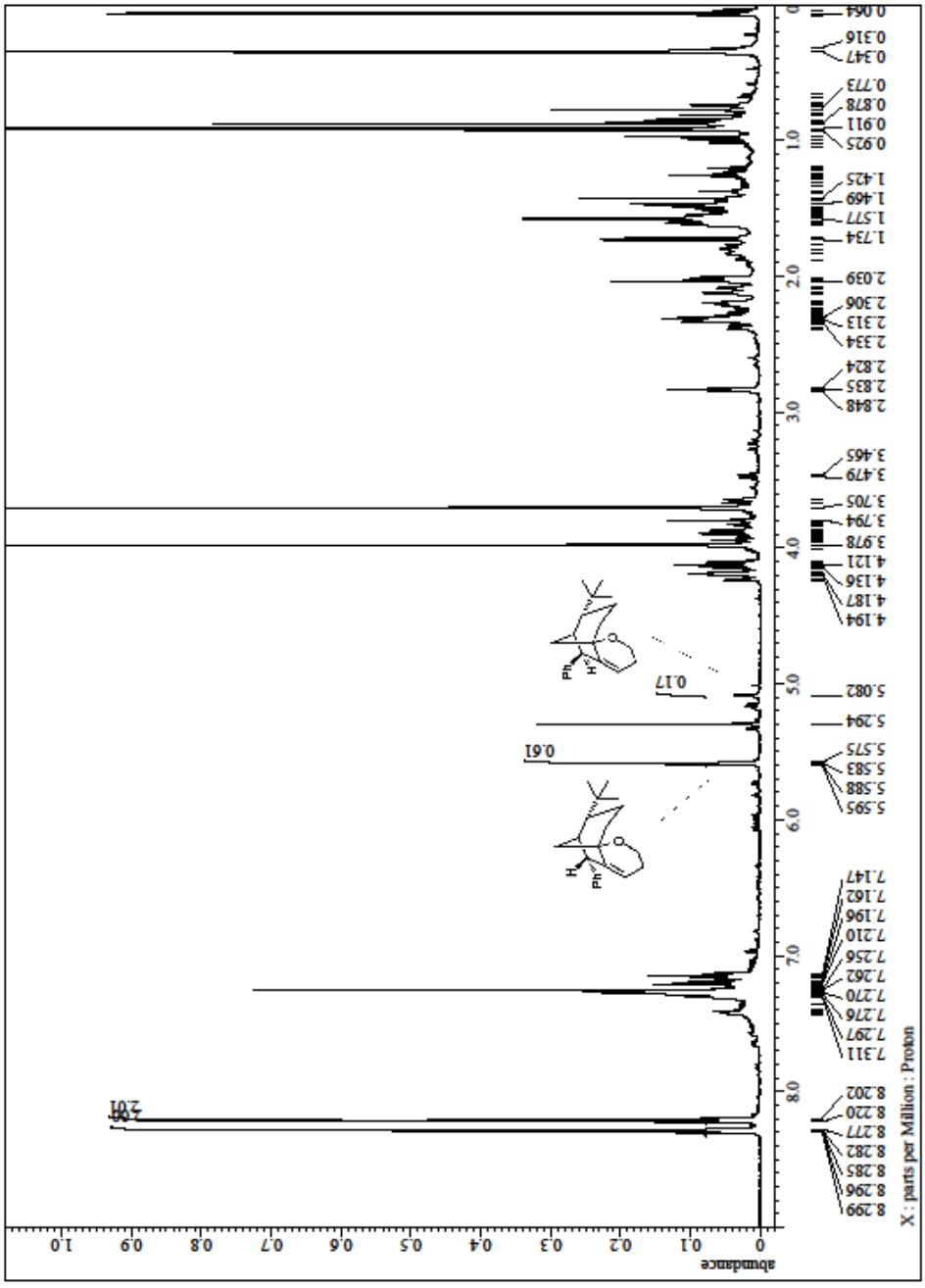

Figure A.3.199. Crude ^{1}H NMR of reaction in Section **4.14.19.2** with $Rh_2(esp)_2$

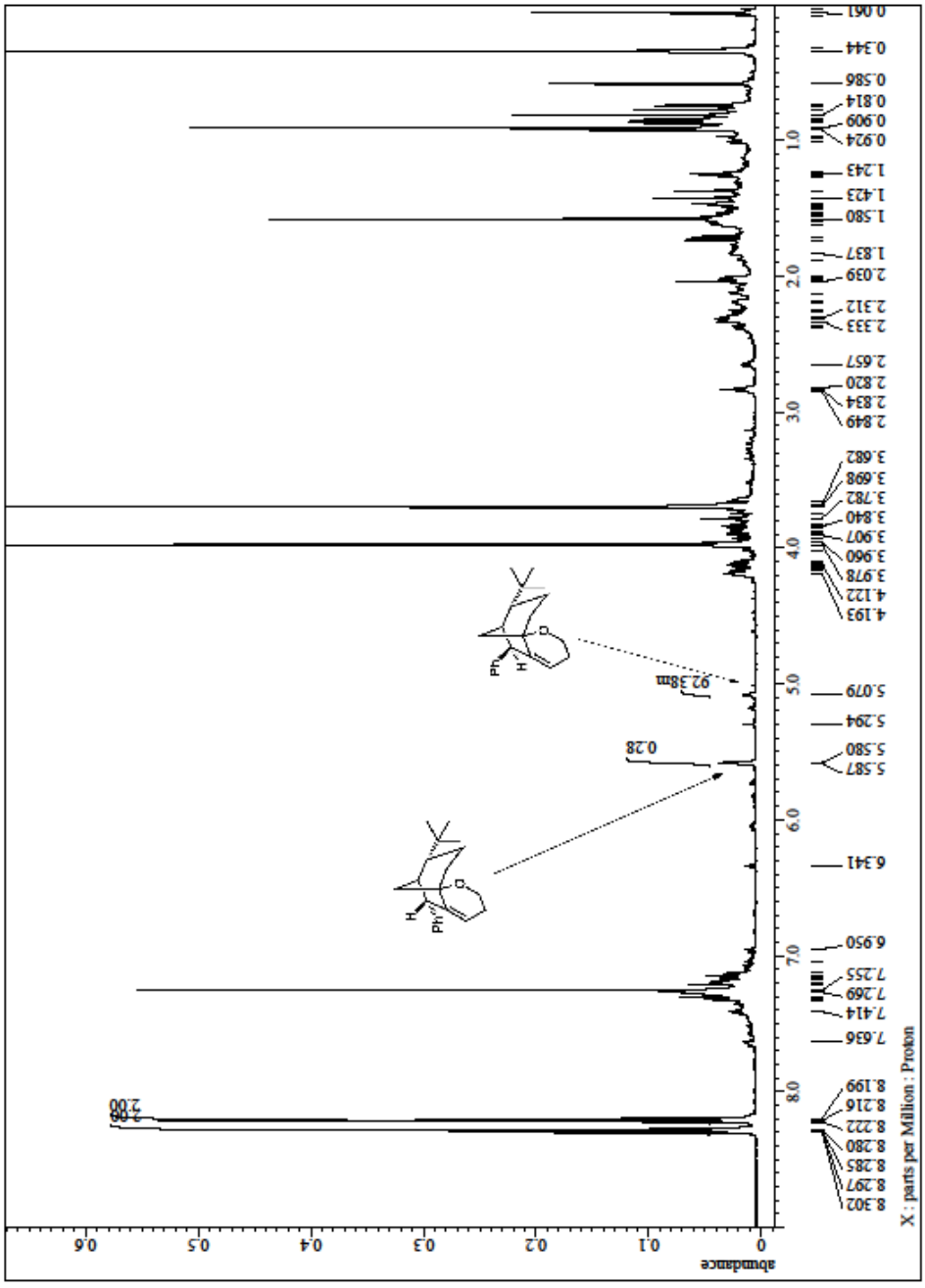

Figure A.3.200. Crude ^{1}H NMR of reaction in Section **4.14.19.2** without $Rh_2(esp)_2$

==== Shimadzu LCsolution Analysis Report ====

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Sample Name	: PLIV-72-2-rac
Sample ID	: PLIV-72-2-rac
Tray#	: 1
Vail #	: 46
Injection Volume	: 10 uL
Data File Name	: PLIV-72-2-rac-pos3-99%.lcd
Method File Name	: pos3-99%_30min.lcm
Batch File Name	: Batch_table_3-99%_30min_PLIV-72-2-rac.lcb
Report File Name	: Default.lcr
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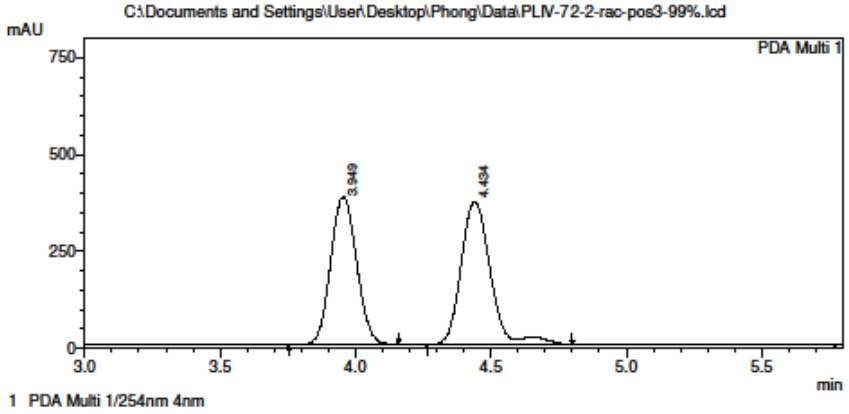

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	4.434	2763185	369102	52.337	49.279
Total		5279588	749006	100.000	100.000

Figure A.3.201. HPLC trace for compound **210**, entry 1 Table 4.11

==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: PLIV-72K-enan
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Vail #	: 46
Injection Volume	: 10 uL
Data File Name	: PLIV-72K-enan-pos3-99%.lcd
Method File Name	: pos3-99%_30min.lcm
Batch File Name	: Batch_table_3-99%_30min_PLIV-72-2-rac.lcb
Report File Name	: Default.lcr
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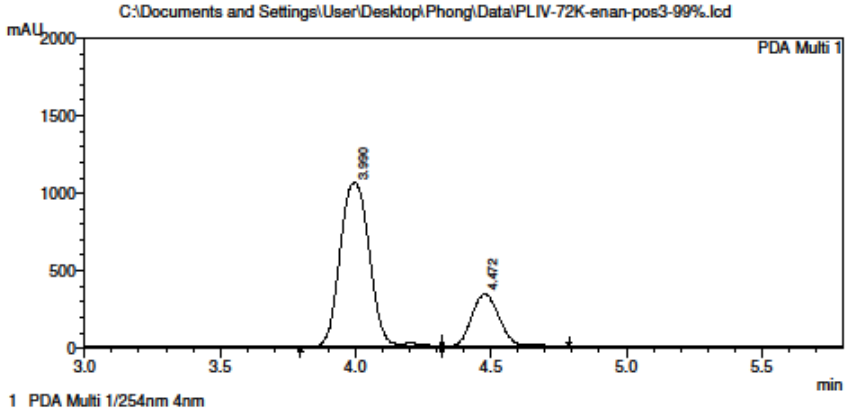

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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2	4.472	2390343	337729	23.133	24.229
Total		10333173	1393915	100.000	100.000

Figure A.3.202. HPLC trace for compound **210**, entry 2 Table 4.11

==== Shimadzu LCsolution Analysis Report ====

C:\Documents and Settings\User\Desktop\Phong\Data\PLIV-72L-enan-pos3-99%.lcd

Acquired by	: Admin
Sample Name	: PLIV-72L-enan
Sample ID	: PLIV-72L-enan
Tray#	: 1
Vail #	: 46
Injection Volume	: 10 uL
Data File Name	: PLIV-72L-enan-pos3-99%.lcd
Method File Name	: pos3-99%_30min.lcm
Batch File Name	: Batch_table_3-99%_30min_PLIV-72-2-rac.lcb
Report File Name	: Default.lcr
Data Acquired	: 11/10/2014 2:37:38 PM
Data Processed	: 11/10/2014 3:07:41 PM

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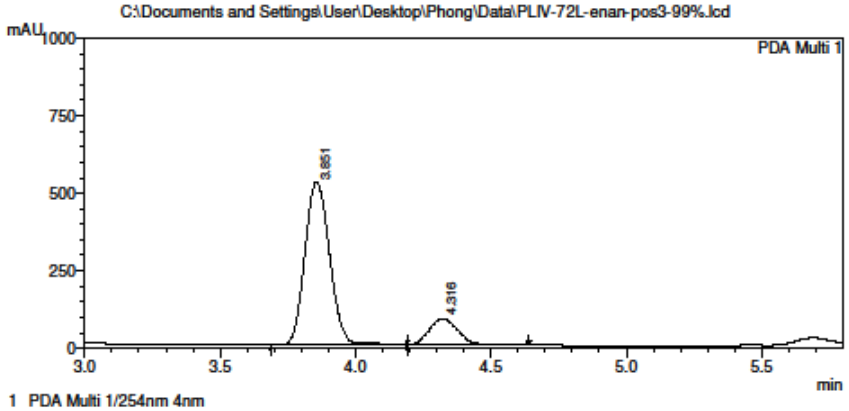
C:\Documents and Settings\User\Desktop\Phong\Data\PLIV-72L-enan-pos3-99%.lcd



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.851	3327527	522256	84.152	85.987
2	4.316	626671	85108	15.848	14.013
Total		3954198	607365	100.000	100.000

Figure A.3.203. HPLC trace for compound **210**, entry 3 Table 4.11

==== Shimadzu LCsolution Analysis Report ====

C:\Documents and Settings\User\Desktop\Phong\Data\PLIV-72O-enan-pos3-99%-.lcd

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Sample ID	: PLIV-72O-enan
Tray#	: 1
Vail #	: 31
Injection Volume	: 8 uL
Data File Name	: PLIV-72O-enan-pos3-99%-.lcd
Method File Name	: pos3-99%_30min.lcm
Batch File Name	: Batch_table_3-99%_30min_PLIV-72M-enan.lcb
Report File Name	: Default.lcr
Data Acquired	: 2/13/2015 3:33:06 PM
Data Processed	: 2/13/2015 5:24:48 PM

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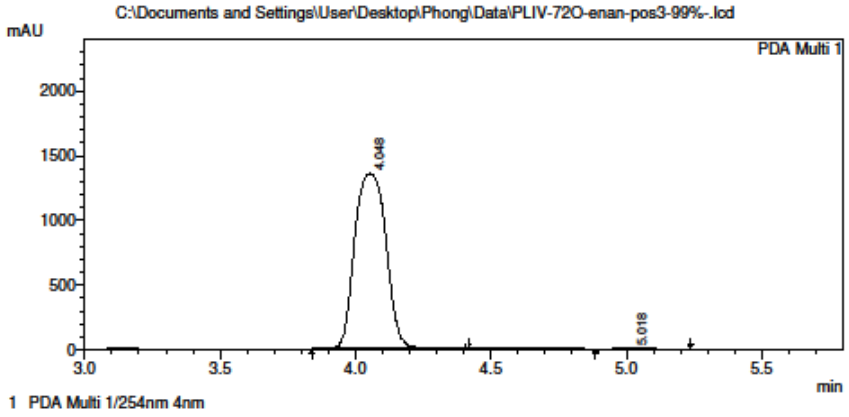


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.048	10855060	1355892	99.759	99.780
2	5.018	26186	2985	0.241	0.220
Total		10881246	1358877	100.000	100.000

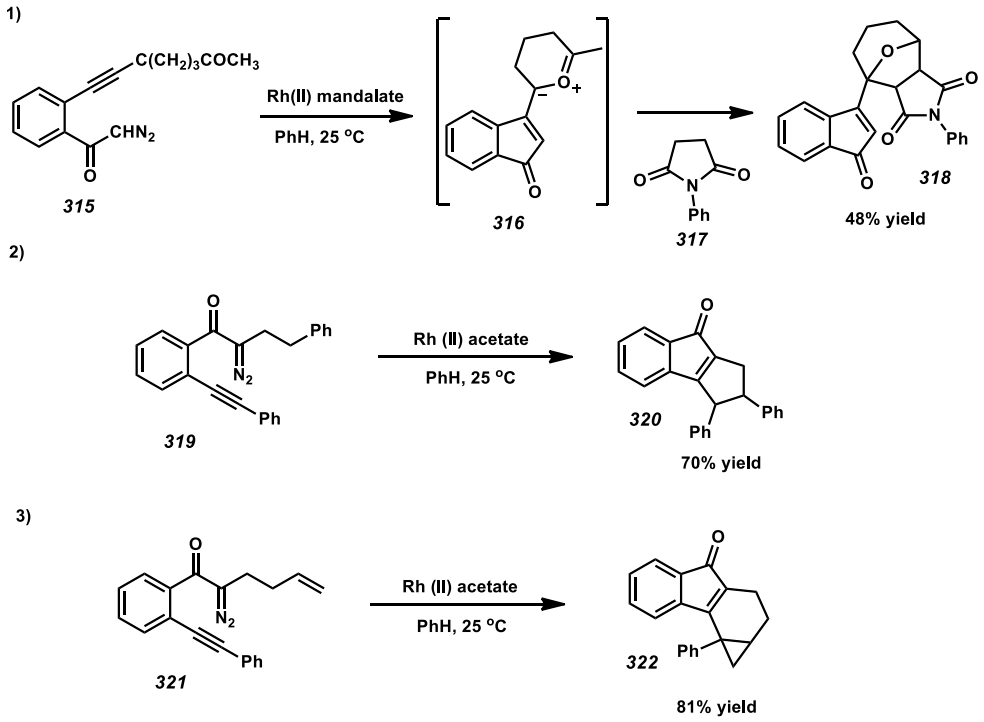
Figure A.3.204. HPLC trace for compound **210**, entry 5 Table 4.11

CHAPTER 5

RHODIUM – CATALYZED CARBENE ALKYNE CASCADE REACTIONS OF DIAZOKETONES

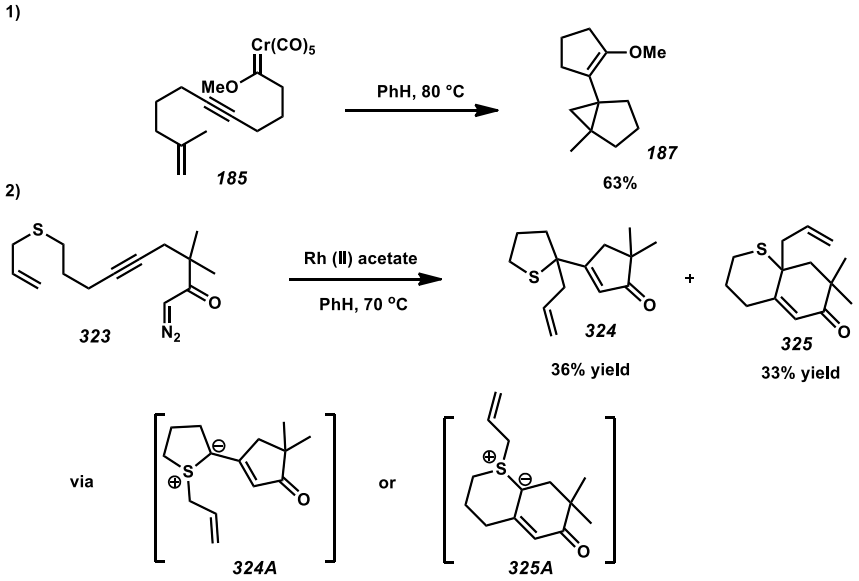
5.1 Introduction to carbene alkyne cascade reactions

In the previous chapter, we discussed rhodium (II)-catalyzed carbene alkyne metathesis reactions. The reaction in general has very broad applications. Padwa *et al.* has shown that a carbene alkyne metathesis could be followed by [3+2] cycloaddition, C-H bond insertion, cyclopropanation, etc… (Scheme 5.1a).[1]



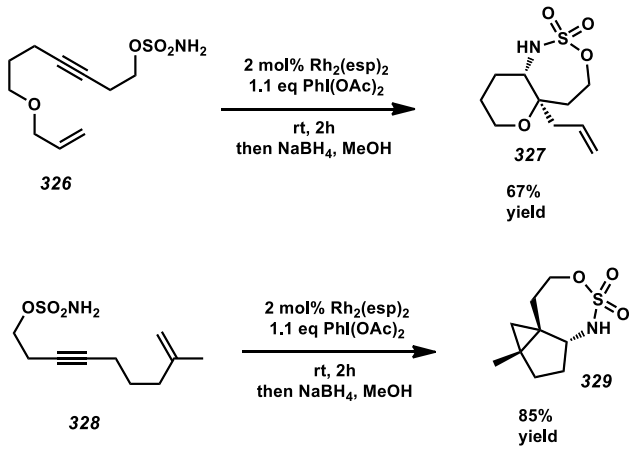
Scheme 5.1a Transformations by the Padwa group in rhodium carbene alkyne metathesis. 1) terminated in 1,3 dipolar cycloaddition. 2) terminated in C-H bond insertion. 3) terminated in cyclopropanation

On the other hand, the Hoye group performed a chromium Fisher carbene alkyne cascade reaction, as well as ylide formation with rhodium carbenes (Scheme 5.1b).[2]



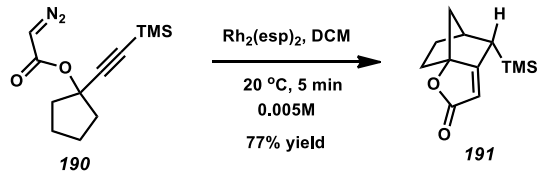
Scheme 5.1b Transformations by the Hoye group. 1) Chromium Fisher carbene alkyne metathesis. 2) Rhodium carbene alkyne metathesis with sulfonium ylide formation

Interestingly, the rhodium catalysts also show great reactivity in the nitrene alkyne metathesis reaction. The Blakey group has demonstrated that the cascade reaction using nitrene could follow the same transformation as the carbene in rhodium-catalyzed conditions (Scheme 5.1c).[3]



Scheme 5.1c Transformations by the Blakey group in rhodium nitrene alkyne metathesis

The carbene alkyne cascade reactions are excellent methods to construct complex molecules, especially biologically active compounds. In 2012, our group successfully developed a generalized strategy for the synthesis of bridged polycycles, which are core structures in many natural products (Scheme 5.1d).[4] In this approach, the rhodium complex initially catalyzed the diazo decomposition of α-diazoesters to form a metal carbene, followed by carbene alkyne metathesis and termination with a C-H bond insertion.



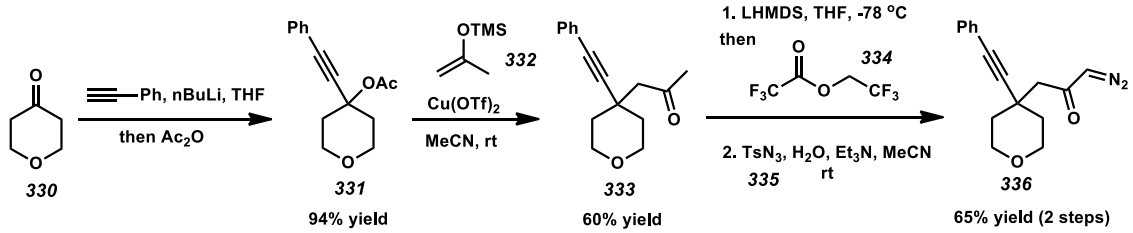
Scheme 5.1d Work by the May group in a cascade reaction with diazo esters

To expand the versatility of this methodology with other carbonyl-stabilized carbenes, we examined the reactivity of the diazoketones in the cascade reaction. In the

next sections, we will report examples of this type of substrate in the cascade as well as the efforts to apply it to the synthesis of a natural product's core structure.

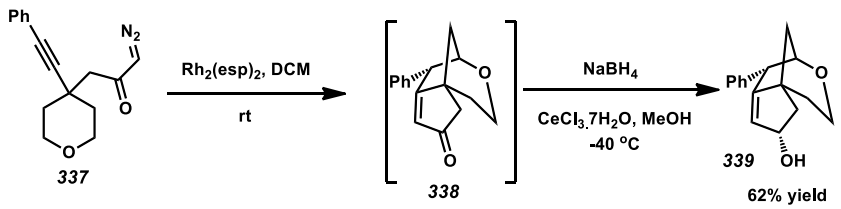
5.2 Diazoketones in rhodium carbene alkyne cascade reaction[5]

The diazoketone starting material that we will employ in the metathesis cascade reaction was synthesized in four steps (Scheme 5.2a). First, we performed a phenyl acetylide addition to the pyranone **330**, trapping with acetic anhydride to form the propargyl acetate **331**. Lewis-assisted propargylic substitution of **331** with TMS enol ether **332** provided ketone **333** in good yield.[6] We next employed Danheiser's diazotization method to convert ketone **333** to diazoketone **336** in 65% yield in 2 steps.[7]



Scheme 5.2a Synthesis of diazoketone

We then exposed this ketone to the conditions for the cascade reaction with 0.5 mol% $Rh_2(esp)_2$ in dichloromethane (Scheme 5.2b). To our delight, the bridged bicycle **338** could be observed in the reaction mixture. Since this oxacycle was prone to subsequent rearrangement during the reaction work-up and purification process, we carried out a Luche reduction on the crude product and obtained the allylic alcohol **339** in 62% yield.

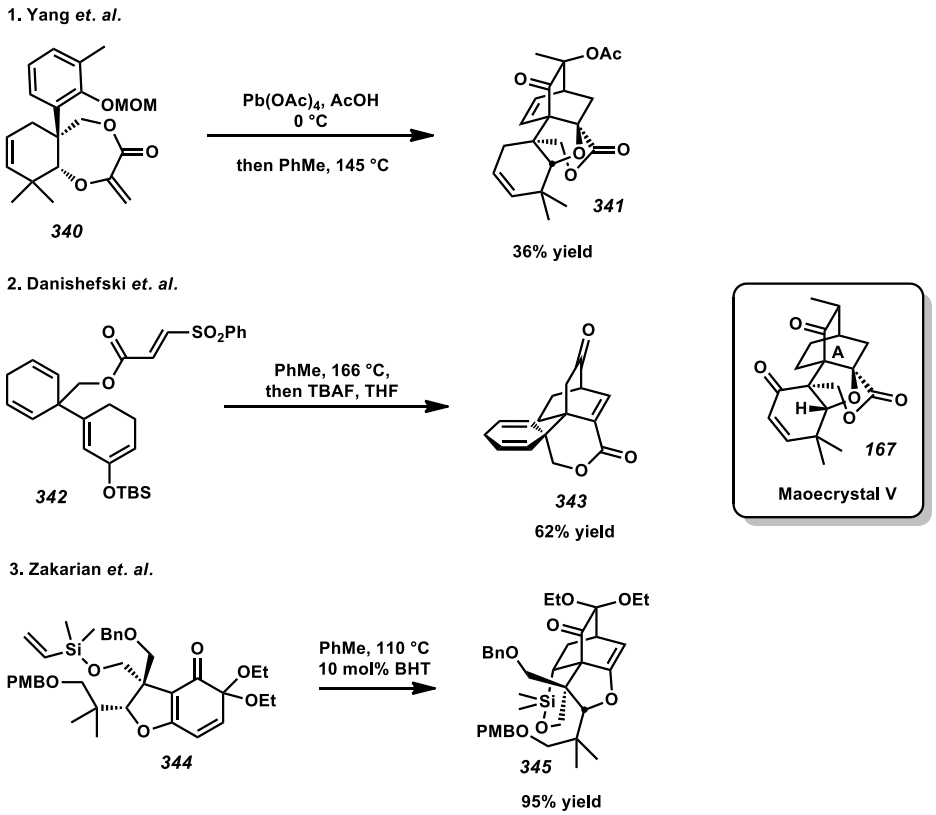


Scheme 5.2b Cascade reaction using a diazoketone

5.3 Toward the synthesis of maoecrystal V's core structure

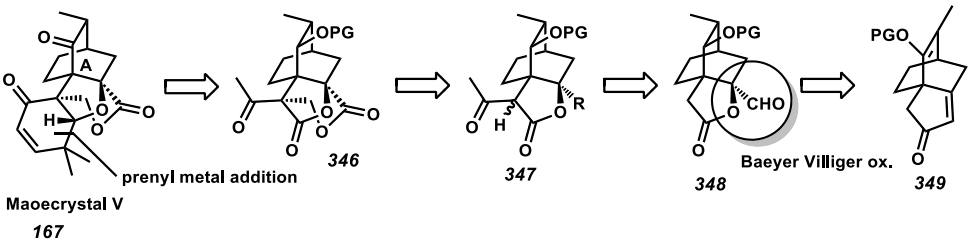
5.3.1 Introduction

The great ability of the cascade reaction to synthesize bridged polycycles has inspired us to apply it to natural product syntheses. Maoecrystal V is one of the targets in our laboratory. This natural product received significant attention from synthetic organic chemists worldwide because it possess potent and selective cytotoxic activity against HeLa cells (IC_{50} = 60 nM).[8] Different approaches have been reported for the syntheses of Maoecrystal V,[9] in which one of the challenges is to construct the bicyclo[2.2.2]octane **A** (**367**), mostly using an intramolecular Diels-Alder reaction (IMDA) (Scheme 5.3.1a). For example, Yang *et al.* reported an oxidative dearomatization reaction and subsequent IMDA to construct the highly strained core of maoecrystal V (**340** to **341**).[8m] On the other hand, the Danishefsky group applied this intramolecular Diels-Alder reaction to build the bicyclo[2.2.2]octane **343** for their maoecrystal V synthesis,[8n] as similar to the Zakarian group for **345**.[8o]



Scheme 5.3.1a Different approaches in synthesis of maoecrystal V

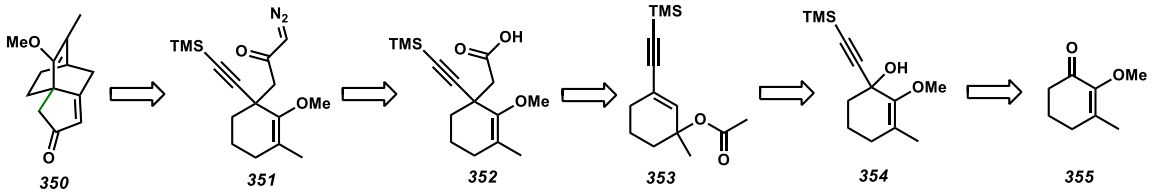
We realized that this bicyclic structure could be obtained from the enone **349** as shown in our retrosynthetic scheme (Scheme 5.3.1b). The enone **349** could undergo hydrolysis of the enol ether and a Baeyer Villiger oxidation of the enone to give the lactone **348**.[10] Reported herein is our attempt to synthesize the core structure **349** using the rhodium-catalyzed diazoketone cascade reaction.



Scheme 5.3.1b Retrosynthetic scheme for the synthesis of maoecrystal V

5.3.2 The approach

Scheme 5.3.2 illustrates our retrosynthetic approach for a model system, bicyclic enone **350**. In this case, we used a methyl protecting group. The enone **350** would come from a rhodium-catalyzed carbene alkyne cascade reaction of diazoketone **351**. We anticipated that the C-H bond insertion would occur at the activated allylic C-H bond. The diazoketone **351** would be derived from carboxylic acid **352** using diazotization by diazomethane. An Ireland/Claisen rearrangement could give the acid **352** from acetate **353**, which could be synthesized from tertiary alcohol **354** via 1,3-rearrangement. To obtain tertiary alcohol **354**, we could perform acetylide addition to ketone **355**.

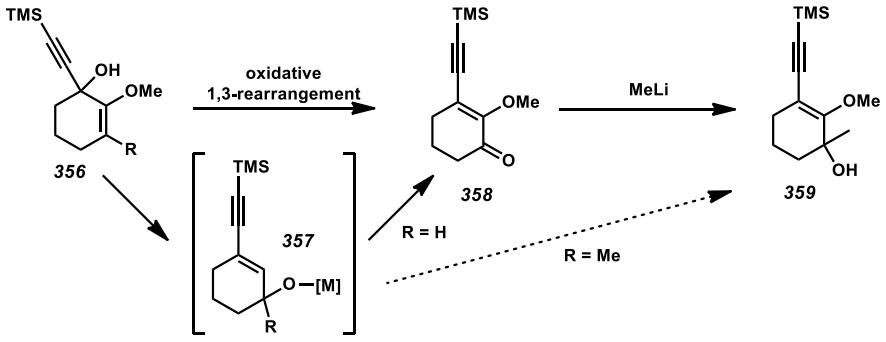


Scheme 5.3.2 Retrosynthesis for the bicyclic compound **350**

5.3.3 Forward synthesis

5.3.3.1 Synthesis of enyne acetate 353

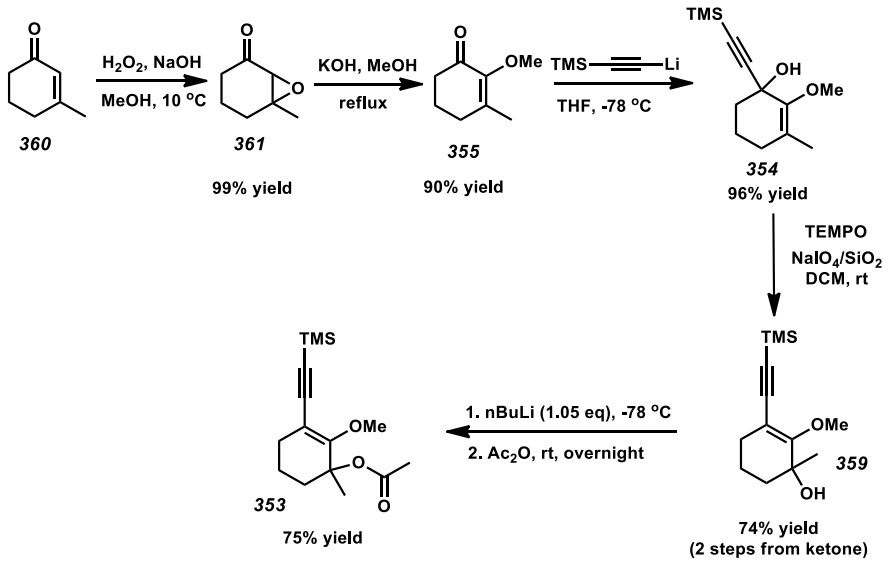
A possible pathway to synthesize the enynol **359**, the precursor of **353**, is through an oxidative 1,3-rearrangement of the allylic alcohol **356** to the enone **358**, followed by methyl lithium addition (Scheme 5.3.3.1a). The oxidative 1,3-rearrangement is a two-step process, starting with the 1,3-migration of the oxygen atom to form intermediate **357** (R = H), and then oxidation of the alcohol to ketone finishes the sequence (see Scheme 5.3.3.1a). However, we envisioned that if we have a methyl substituent at the olefin (R = Me, **357**), then after the 1,3-migration step, an oxidation could not take place on the tertiary alcohol, and would therefore give the desired tertiary alcohol **359** in just one step. Although an equilibrium between the two tertiary alcohols **356** and **359** could exist, the alkyne-alkene conjugation in **359** would make it more thermodynamically stable than **356**.



Scheme 5.3.3.1a General pathway for synthesis alcohol **359**

We started our synthesis by generating enone **355,** which could be obtained in two steps from commercially available 3-methyl-2-cyclohexanone (Scheme 5.3.3.1b).

Acetylide addition to the enone **355** provided the propargyl alcohol **354** in excellent yield.

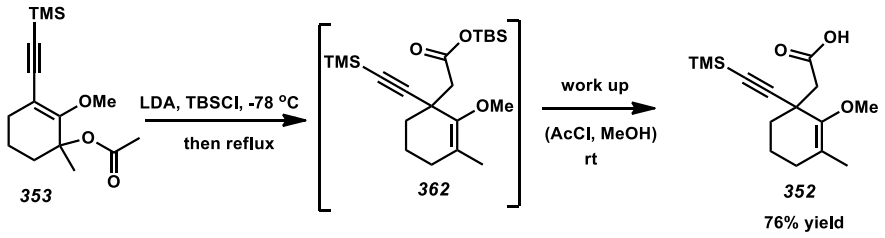


Scheme 5.3.3.1b Synthesis of allylic alcohol

With this tertiary alcohol in hand, we performed the 1,3-rearrangement with PDC, a popular reagent used in this rearrangement reaction, and SiO_2 in dichloromethane.[11] However, the conditions were too harsh as we observed the formation of many unidentified products. Later, we found that TEMPO combined with silica gel-supported sodium metaperiodate, which was developed by the Iwabuchi group, are mild and efficient conditions for 1,3-rearrangement.[12] As we hypothesized, the alcohol **359** was obtained in 74% isolated yield after 2 steps from ketone **355**. Next, the acetate **353** could be generated by exposing the propargyl alcohol **359** to acetic anhydride. This intermediate was ready for the Ireland/Claisen rearrangement reaction.

5.3.3.2 The Ireland/Claisen rearrangement

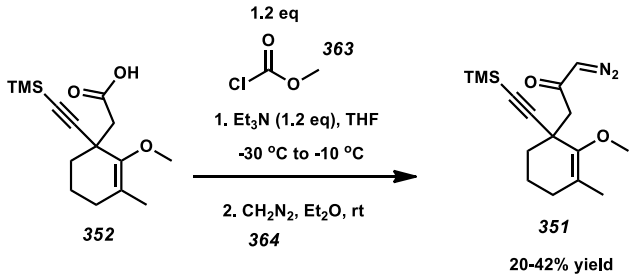
The next key reaction in the synthesis is the Ireland/Claisen rearrangement to synthesize the quaternary centers in the carboxylic acid **352** (Scheme 5.3.3.2). The rearrangement requires the formation of an enol ether in situ. After considerable screening of the reaction conditions, we realized that treatment with TBSCl and LDA, which would form an intermediate silyl enol ether, and then refluxing in THF gave the ester **362**. Upon work up with AcCl and MeOH, the carboxylic acid **352** was obtained in 76% yield. It is worthy to note that for a successful Ireland/Claisen rearrangement, the TBSCl needed to be redistilled in low pressure to avoid any contaminants affecting reaction outcome.



Scheme 5.3.3.2 Synthesis of carboxylic acid **352** via Ireland/Claisen rearrangement

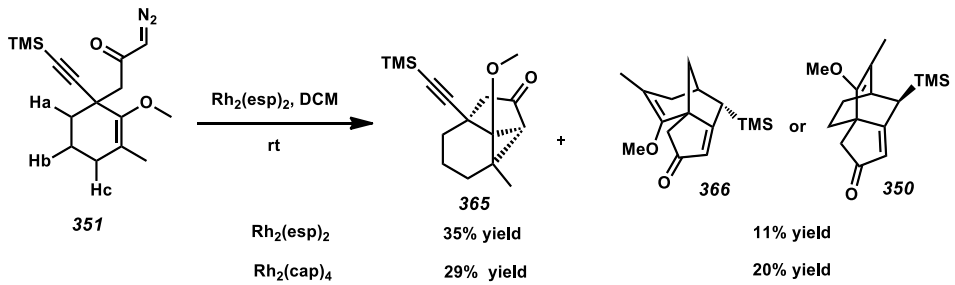
5.3.3.3 Diazotization and cascade reaction

We next transformed the acid **352** into an α-diazoketone **351** via a mixed anhydride and treatment with ethereal diazomethane (Scheme 5.3.3.3a).[13] The yield of the reaction, however, was low and irreproducible, ranging from 20% to 42%. This diazoketone was ready for the rhodium-catalyzed cascade reaction.



Scheme 5.3.3.3a Diazoketone formation

Let's take a closer look at different possible pathways of the cascade reaction. First, a direct C-H bond insertion of the rhodium carbene to C-H_a (**351**, Scheme 3.5.3.3b) could occur as well as cyclopropanation on the proximal olefin. Second, the new vinyl carbene would also have two options for the terminating C-H bond insertion, insertion into C-H_b or into C-H_c. The C-H_c bond was predicted to be preferred over C-H_b due to its activation as the allylic position. When exposed to 0.5 mol% $Rh_2(esp)_2$ in dichloromethane, the diazoketone **351** produced the cyclopropane **365** as the major product, and the minor was the cascade product **366A** or **350**. Due to unclear signals in the NMR spectra, we are still in the process of determining which cascade product we isolated.



Scheme 3.5.3.3b Cascade reactions for formation of bridged bicycle **350**

5.4 Conclusion

We successfully showed that a diazoketone also efficiently participates in a rhodium carbene alkyne metathesis, terminated in C-H bond insertion. The method was shown to be general for synthesizing useful bridged polycycles. The findings further strengthen the application of the approach to natural product syntheses. Our attempt to synthesize maoecrystal V's core structure is an example of this application. Although cyclopropanation was found to be slightly preferred over the cascade sequence with $Rh_2(esp)_2$ in our model substrate, recent developments in the selectivity of other rhodium (II) catalysts has expanded our efforts for improvement.

5.5 Experimental section

5.5.1 General consideration

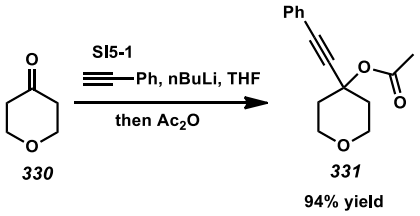
All reactions were carried out in flame- or oven-dried glassware. THF, toluene, and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA- 500 or ECX-400P spectrometer

using residual solvent peak as an internal standard ($CDCl_3$: 7.25 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an external standard in ^{19}F NMR spectra. NMR yields were determined by an addition of 0.5 equivalent of methyl (4-nitrophenyl) carboxylate as an internal standard to the crude reaction mixture. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by UT Austin's mass spectrometric facility via ESI method and a US10252005 instrument.

5.5.2 Materials

Commercially available compounds were purchased from Aldrich, Acros, and Alfa Aesar and were used without further purification. *tert*-Butyldimethylsilyl chloride was vacuum distilled prior use. Diazomethane was synthesized following *Org. Synth.* **1956**, *36*, 16.

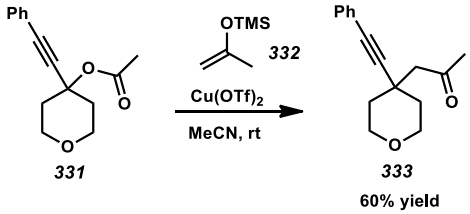
5.5.3 Synthesis of 4-(phenylethynyl)tetrahydro-2H-pyran-4-yl acetate (331)



A flame-dried round-bottom flask was charged with *n*BuLi (6 ml, 1.5 eq, 2.5M) under an argon atmosphere. Anhydrous THF (0.5 M) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. Phenyl acetylene **SI5-1** (1.65 ml, 1.5 eq) was then added dropwise. After 30 minutes at -78 ˚C, dihydro-2H-pyran-4(3H)-one **330** (0.92 ml, 1.0 eq) was added dropwise. The reaction mixture was allowed to warm to room

temperature and stir for 3h. Acetic anhydride (2.84 ml, 3.0 eq) was then added dropwise and the reaction mixture was allowed to stir overnight. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 5-10% gradient of EtOAc in hexanes as an eluent to afford a white amorphous solid (2.305 g, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.46-7.41 (m, 2H), 7.32-7.27 (m, 3H), 3.95-3.80 (m, 2H), 3.80-3.74 (m, 2H), 2.33-2.28 (m, 2H), 2.12-2.04 (m, 5H) **^{13}C NMR** (100.52 MHz, $CDCl_3$) 169.3, 132.0, 128.7, 128.3, 122.2, 87.6, 87.1, 73.0, 64.8, 37.8, 22.0. **HRMS**-CI m/z: [M+], calculated for $C_{15}H_{16}O_3$, 244.1099; found 244.1101.

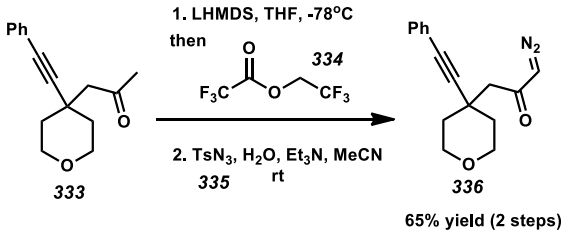
5.5.4 Synthesis of 1-(4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)propan-2-one (333)



To a flame-dried round-bottom flask, propargylic acetate **331** (488.6 mg, 1 eq), enoxysilane **332** (390.8 mg, 3 eq), CH_3CN (8 mL, 0.25M), and $Cu(OTf)_2$ (36.2 mg, 0.05 eq) were successively added under an argon atmosphere, the reaction mixture was stirred at room temperature, and monitored periodically by TLC. After 5 min, the reaction was completed and the solvent was concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using a 5-10% gradient of EtOAc

in hexanes as an eluent to afford product as a light yellow oil (290.8 mg, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.43-7.38 (m, 2H), 7.32-7.26 (m, 3H), 3.90-3.82 (m, 4H), 2.63 (s, 2H), 2.29 (s, 3H), 1.87-1.80 (m, 2H), 1.74-1.64 (m, 2H) **^{13}C NMR** (100.52 MHz, $CDCl_3$) 206.5, 131.7, 128.4, 123.1, 91.8, 85.2, 64.8, 55.3, 37.9, 33.4, 32.3. **HRMS**-CI m/z: [M+H], calculated for $C_{16}H_{19}O_2$, 243.1385; found 243.1383.

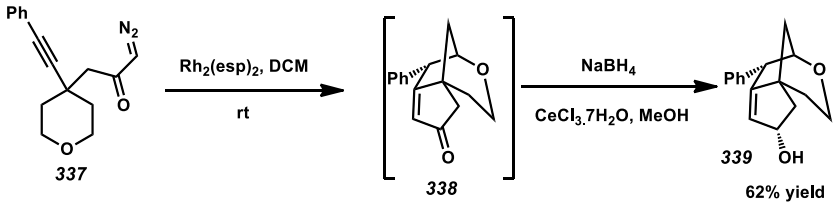
5.5.5 Synthesis of 1-diazo-3-(4-(phenylethynyl)tetrahydro-2H-pyran-4-yl)propan-2-one (336)



A flame-dried round-bottom flask was charged with LHMDS (0.22 ml, 1.1 eq, 1M in THF) and 1 ml of THF under an argon atmosphere, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. A solution of ketone **333** (48.5 mg, 1 eq) in 1 ml THF was then added dropwise over 10 min and the reaction mixture was allowed to stirred at –78 °C for 1h after which 2,2,2-trifluoroethyl trifluoroacetate **334** (0.054 ml, 2eq) was added rapidly by syringe in one portion. After 45 min, the reaction mixture was poured into a separatory funnel containing 5 mL of 5% aq HCl solution and 3 mL of Et_2O. The organic phase was washed with 5 mL of water, the combined aqueous phases were extracted with two 3-mL portions of Et_2O, and then the combined organic phases were washed with 10 mL of a saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated at reduced pressure in a round-bottom flask to give brown oil. The flask was then put in high

vacuum and back-filled with argon 3 times after which was diluted with 1 mL of CH_3CN. Water (3.6 mg, 1 eq) and Et_3N (0.056 ml, 2 eq) were added via syringe, and then a solution of p-toluenesulfonyl azide **335** (78.9 mg, 2 eq) in 1 mL of CH_3CN was added dropwise over 2 min. The resulting solution was stirred at room temperature for 3 h and then concentrated to a volume of ca. 1.5 mL. The residue was diluted with 5 mL of Et_2O and washed with four 3-mL portions of 10% aq NaOH solution and three 2.5-mL portions of water, and then the combined aqueous phases were extracted with 5 mL of Et_2O (3x). The combined organic layers were washed with 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford crude yellow oil. The crude product was purified by column chromatography on silica gel using a 3-5% gradient of EtOAc in hexanes as an eluent to afford a yellow amorphous solid (34.9 mg, 65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.43-7.39 (m, 2H), 7.33-7.29 (m, 3H), 5.54 (s, 1H), 3.89-3.79 (m, 4H), 2.51 (s, 2H), 1.85-1.71 (m, 4H) **^{13}C NMR** (100.52 MHz, $CDCl_3$) 191.7, 131.7, 128.5, 123.0, 91.8, 85.6, 64.8, 56.3, 53.2, 37.9, 34.3.

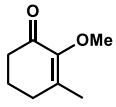
5.5.6 Synthesis of 1-phenyl-1,2,4,5,6,7-hexahydro-2,5a-methanocyclopenta[d]oxepin-7-ol (339)



A flame-dried round-bottom flask was charged with diazoketone **337** (26.8mg, 1.0 eq) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M) was added. The

reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (0.5 mol%) in one portion. After 10 minutes, the solvent was removed under reduced pressure, MeOH was added, and the reaction mixture was cooled down to -40 ^oC in an acetone bath. $CeCl_3.7H_2O$ (18.6 mg, 0.5 eq) was then added to the reaction mixture, followed by $NaBH_4$ (3.8mg, 1.0eq). After stirring for an additional 4 hours at -40 ^oC, the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using a 10-20% gradient of EtOAc in hexanes as an eluent to afford product as a white amorphous solid (14.9mg, 62% yield). **^{1}H NMR** (400 MHz, CDCl3) 7.59-7.27 (m, 2H), 7.35-7.31 (m, 2H), 7.26-7.24 (m, 1H), 6.22 (t, *J*=2.75 Hz, 1H), 4.02-3.97 (m, 1H), 3.77-3.71 (m, 1H), 2.90-2.85 (dd, *J*= 19.23, 1.83 Hz, 1H), 2.81-2.76 (dd, *J*= 17.86, 2.75 Hz, 1H), 2.69-2.53 (m, 5H), 2.15-2.10 (m,1H), 2.00-1.93 (m, 1H). **^{13}C NMR** (100.52 MHz, CDCl3) 217.1, 142.7, 133.6, 128.6, 127.7, 126.6, 100.6, 67.4, 55.1, 52.6, 49.7, 46.0, 42.5. **HRMS**-CI m/z: [M+H], calculated for C16H19O2, 243.1385; found 243.1390.

5.5.7 Synthesis of 2-methoxy-3-methylcyclohex-2-enone (355)

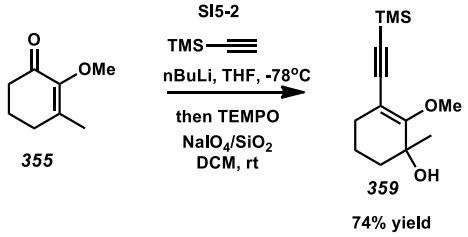


This compound was synthesized following the procedure which has been previously reported.[14]

5.5.8 Preparation of Silica Gel-Supported $NaIO_4$ Reagent.

The $NaIO_4/SiO_2$ reagent was prepared following the procedure which has been previously reported.[15]

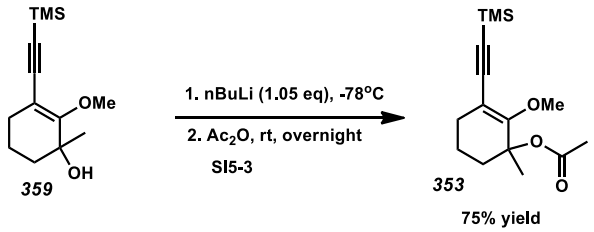
5.5.9 Synthesis of 1-methyl-3-((trimethylsilyl)ethynyl)cyclohex-2-enol (359)



A flame-dried round-bottom flask was charged with anhydrous THF (0.2 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. The trimethylsilyl acetylene **SI5-2** (1.72 ml, 11.79 mmol, 1.31 eq) was then added under an argon atmosphere. *n*BuLi (1.3 eq, 2.5 M) was added dropwise to the flask while maintaining the reaction temperature at -78˚C . After 30 minutes at -78˚C, the ketone **355** (1.26 g, 9.0 mmol, 1.0 eq), which was dissolved in 5 ml THF prior to addition, was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Upon completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield a white solid. The white solid was then placed in a round-bottom flask that has been charged with a stir bar. Dichloromethane (90 ml, 0.1M), TEMPO (0.028 g, 0.18 mmol, 0.02 eq), and $NaIO_4/SiO_2$ (3.85 g, 18 mmol, 2 eq), were successively added to the flask and the reaction mixture was stirred at room temperature for 36 hours. After completion, the reaction mixture was concentrated to yield a fine

powder which was purified by dry loading on silica gel and column chromatography using 5-10% gradient of EtOAc in hexanes as an eluent. The product was obtained as a white amorphous solid (1.58 g, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.04 (s, 3H), 2.32 – 2.21 (m, 1H), 2.21 – 2.11 (m, 1H), 1.82 – 1.72 (m, 1H), 1.72 – 1.61 (m, 2H), 1.60 – 1.47 (m, 1H), 1.33 (s, 3H), 0.16 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 163.44, 103.88, 99.49, 98.93, 71.14, 60.86, 37.60, 31.01, 27.18, 19.54, -0.02.

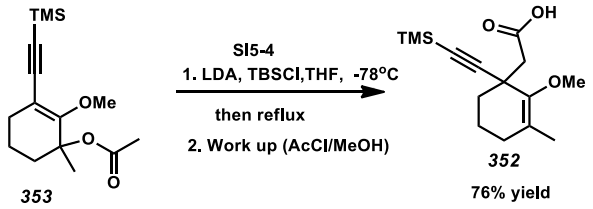
5.5.10 Synthesis of 2-methoxy-1-methyl-3-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl acetate (353)



A flame-dried round-bottom flask was charged with alcohol **359** (1.19 g, 5.0 mmol, 1.0 eq) and anhydrous THF (50 ml, 0.1 M), and the flask was cooled to -78 ˚C in a dry ice/acetone bath. *n*BuLi (1.05 eq, 2.5 M) was then added dropwise to the flask while maintaining the reaction temperature at -78 ˚C . After 30 minutes at -78˚C, acetic anhydride (**SI5-3)** (0.86 ml, 15.0 mmol, 2.0 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Upon completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel using 5-10% gradient of EtOAc in

hexanes as an eluent. The product was obtained as a light yellow oil (1.05 g, 75% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.96 (s, 3H), 2.45 (dd, J = 16.6, 6.4 Hz, 1H), 2.33 (ddd, J = 16.1, 8.3, 4.9 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.98 (s, 3H), 1.76 – 1.61 (m, 2H), 1.60 – 1.53 (m, 1H), 1.49 (s, 3H), 0.15 (s, 9H).

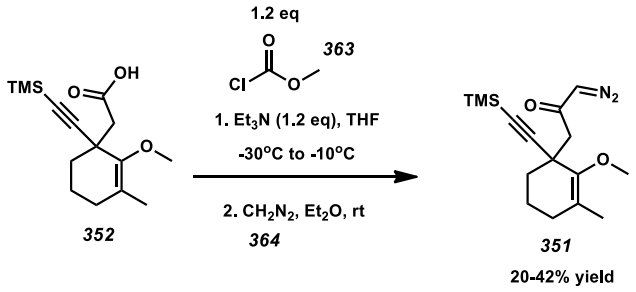
5.5.11 Synthesis of 2-(2-methoxy-3-methyl-1-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)acetic acid (352)



A flame-dried round-bottom flask was charged with diisopropylamine (1.09 ml, 1.55 eq) under an argon atmosphere. Anhydrous THF (25 ml, 0.2 M) was added, and the flask was cooled to -78 ˚C in a dry ice/acetone bath. *n*BuLi (3.0 ml, 1.5 eq, 2.5M) was then added dropwise. After 30 minutes at -78 ˚C, acetate **353** (1.40 g, 1.0 eq), which was dissolved in THF prior to addition, was added dropwise. The reaction mixture was allowed to stir for an additional 45 minutes at -78 ˚C. TBSCl **SI5-4** (1.13 g, 1.5 eq), which was dissolved in THF prior to addition, was added dropwise and the reaction mixture was allowed to warm up to room temperature within 1h and then was refluxed overnight. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude product.

To a flame-dried round-bottom flask, the crude product **362** (0.395 g, 1.0 eq), and methanol (4 ml, 0.3M) were successively added under an argon atmosphere and the flask was cooled to -0 ˚C in an ice bath. Acetyl chloride (0.015 ml, 0.2 eq) was then added dropwise, and the reaction mixture was stirred at same temperature and monitored periodically by TLC. After 5 min, the reaction was complete, and the solvent was concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using 20% of EtOAc and 0.5% of AcOH in hexanes as an eluent to afford product as a white amorphous solid (0.254 g, 91% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.79 (d, J = 14.4 Hz, 1H), 2.67 (d, J = 14.5 Hz, 1H), 2.00 (dd, J = 9.4, 4.8 Hz, 3H), 1.84 – 1.69 (m, 2H), 1.69 – 1.56 (m, 1H), 1.69 – 1.56 (s, 3H), 0.11 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) 175.8, 149.0, 120.5, 110.1, 86.7, 61.9, 43.3, 38.3, 36.4, 30.7, 19.6, 16.7, 0.04.

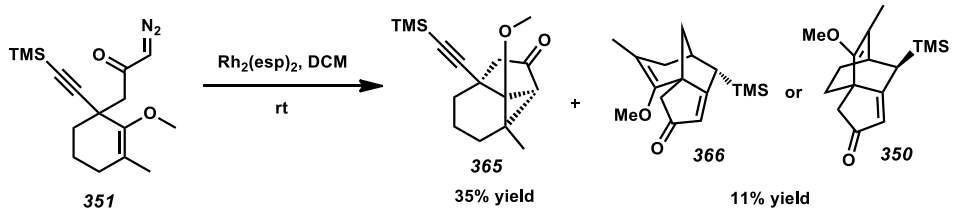
5.5.12 Synthesis of 1-diazo-3-(2-methoxy-3-methyl-1-((trimethylsilyl)ethynyl)cyclohex-2-en-1-yl)propan-2-one (351)



To a flame-dried round-bottom flask, acid **352** (0.14 g, 1 eq), anhydrous diethyl ether (1.3 ml), and THF (1.3 mL) were added under an argon atmosphere and the flask was cooled to -25 ˚C in a dry ice/acetone bath. Triethylamine (0.084 ml, 1.2 eq) and then

methyl chloroformate **363** (0.047 ml, 1.2 eq) were added dropwise. After 30 minutes at -25 ˚C, the reaction mixture was allowed to reach -10 ˚C and a diazomethane solution in ether (ca. 7 ml, 2–3 eq) was added dropwise. The suspension was stirred for an additional 3 hours and allowed to reach ambient temperature. The triethylamine hydrochloride was then filtered off and the filtrate was evaporated to half of its original volume. The resulting solution was washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried and evaporated to give a crude product. The crude product was purified by column chromatography on silica gel using 5-10% gradient of EtOAc in hexanes as an eluent to afford a yellow amorphous solid. Trial 1: 0.031 g, 20% yield. Trial 2: 0.064 g, 42% yield . **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.59 (s, 1H), 3.75 (s, 3H), 2.81 – 2.54 (m, 2H), 2.16 – 1.82 (m, 3H), 1.80 – 1.69 (m, 2H), 1.67 – 1.57 (m, 1H), 1.67 – 1.57 (s, 3H), 0.13 (s, 9H). **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 193.10, 149.38, 120.39, 111.14, 86.37, 61.82, 55.58, 49.30, 39.24, 35.85, 30.73, 19.49, 16.80, 0.08.

5.5.13 Synthesis of (2aS,2a1R,2bR,5aR)-2a1-methoxy-2b-methyl-5a-((trimethylsilyl)ethynyl)hexahydro-1H-cyclopropa[cd]inden-2(2aH)-one (365) and (3aR,7S)-4-methoxy-5-methyl-8-(trimethylsilyl)-3,6,7,8-tetrahydro-2H-3a,7-methanoazulen-2-one (366) or (3aR,6S,7R)-4-methoxy-5-methyl-7-(trimethylsilyl)-6,7-dihydro-3a,6-ethanoinden-2(3H)-one (350)



A flame-dried round-bottom flask was charged with $Rh_2(esp)_2$ catalyst (0.4 mg, 0.5 mol%) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.005 M) was added. The reaction mixture was vigorously stirred at room temperature while adding diazoketone **351** (27.3 mg, 1.0 eq), which was previously dissolved in 5 ml CH_2Cl_2, dropwise in 10 minutes. After an additional 10 minutes, the solvent was removed under reduced pressure to yield the crude product. The crude product was purified by column chromatography on silica gel using 3-5% gradient of EtOAc in hexanes as an eluent. Cyclopropane **365** was obtained as a white amorphous solid (8.7 mg, 35% yield). **^{1}H NMR** (400 MHz, CDCl3) δ 3.56 (s, 3H), 2.99 (d, *J* = 17.8 Hz, 1H), 2.35 (d, *J* = 17.7 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.89 – 1.66 (m, 2H), 1.59 (m, 1H), 1.27 (s, 3H), 1.01 (m, 1H), 0.85 (m, 1H), 0.18 (s, 9H)..**^{13}C NMR** (100.52 MHz, CDCl3) δ 210.00, 109.02, 87.29, 81.01, 57.90, 56.23, 45.43, 39.85, 37.79, 36.35, 29.71, 28.90, 22.87, 17.67, 0.09.

The enone **366** or **350** was obtained as a white amorphous solid (2.8 mg, 11% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ δ 5.57 (d, *J* = 1.5 Hz, 1H), 3.45 (s, 3H), 3.03 (dd, *J* = 17.0, 0.8 Hz, 1H), 2.80 – 2.63 (m, 1H), 2.42 (dd, *J* = 17.6, 4.0 Hz, 1H), 2.36 (d, *J* = 6.3 Hz, 1H), 2.09 (m, 2H), 2.03 (d, *J* = 17.6 Hz, 1H), 1.60 (m, 4H), 0.13 (s, 9H).. **^{13}C NMR** (100.52 MHz, $CDCl_3$) δ 211.10, 198.40, 150.17, 118.65, 115.79, 60.75, 57.07, 43.81, 42.67, 38.94, 38.26, 37.21, 15.98, -0.90.

5.6 References and notes

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5. The research was reported in Jansone-Popova, Santa; Le, Phong Q.; May, Jeremy A. *Tetrahedron* **2014**, *70*, 4118.

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APPENDIX FOUR

Spectra relevant to Chapter 5:

RHODIUM – CATALYZED CARBENE ALKYNE CASCADE REACTIONS OF DIAZO KETONES

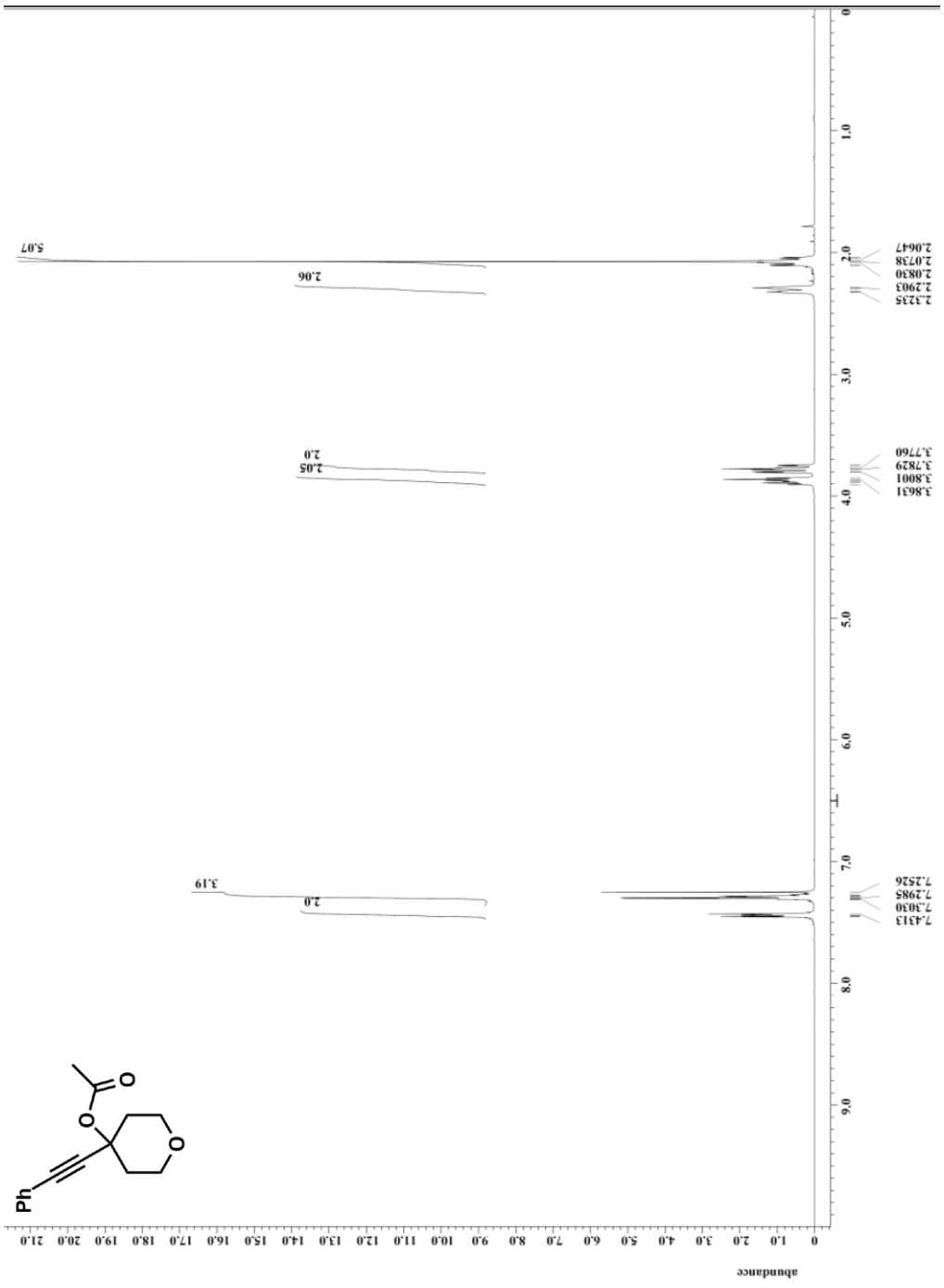

Figure A.4.1. ^{1}H NMR for compound **331**

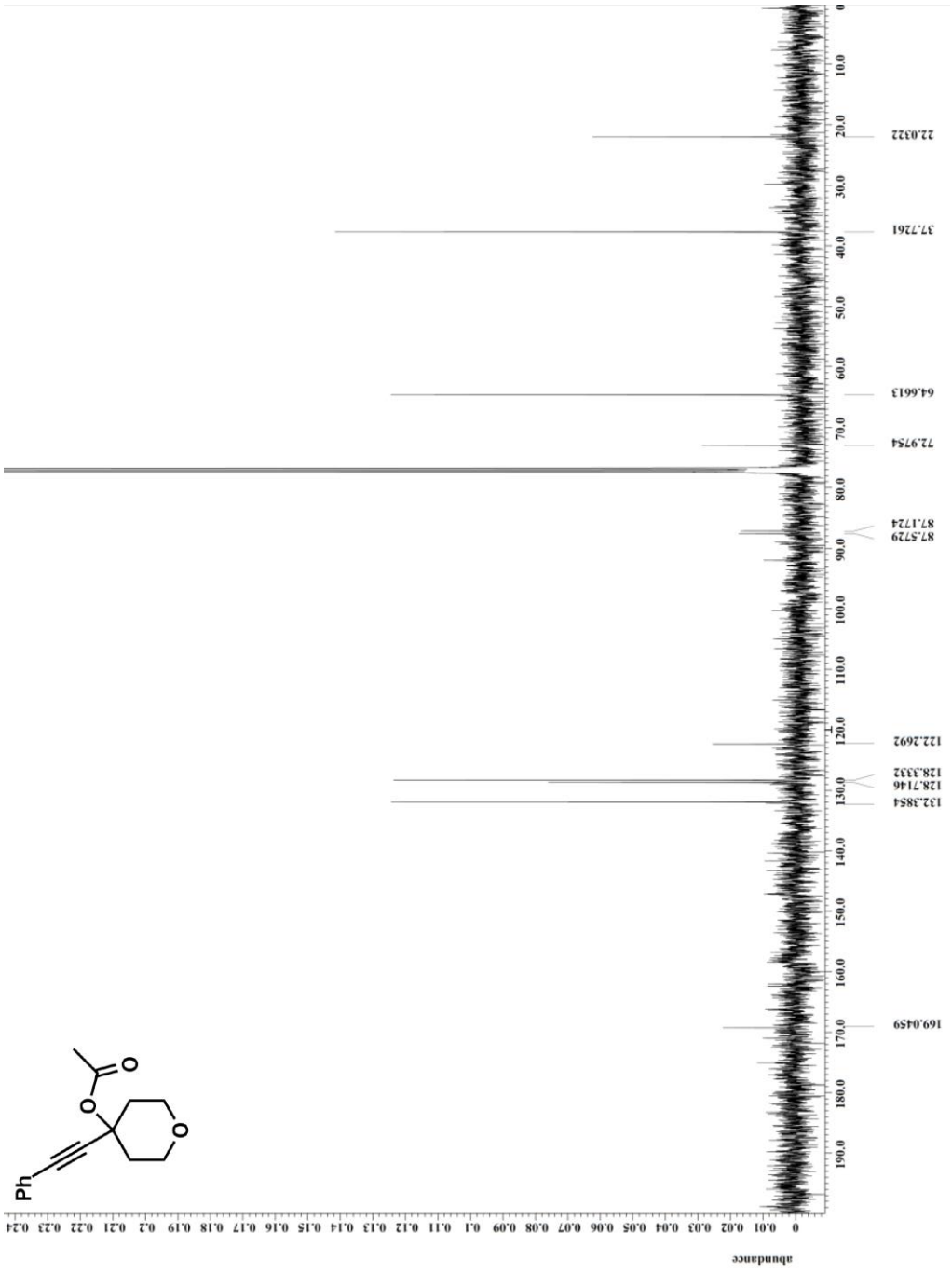

Figure A.4.2. ^{13}C NMR for compound **331**

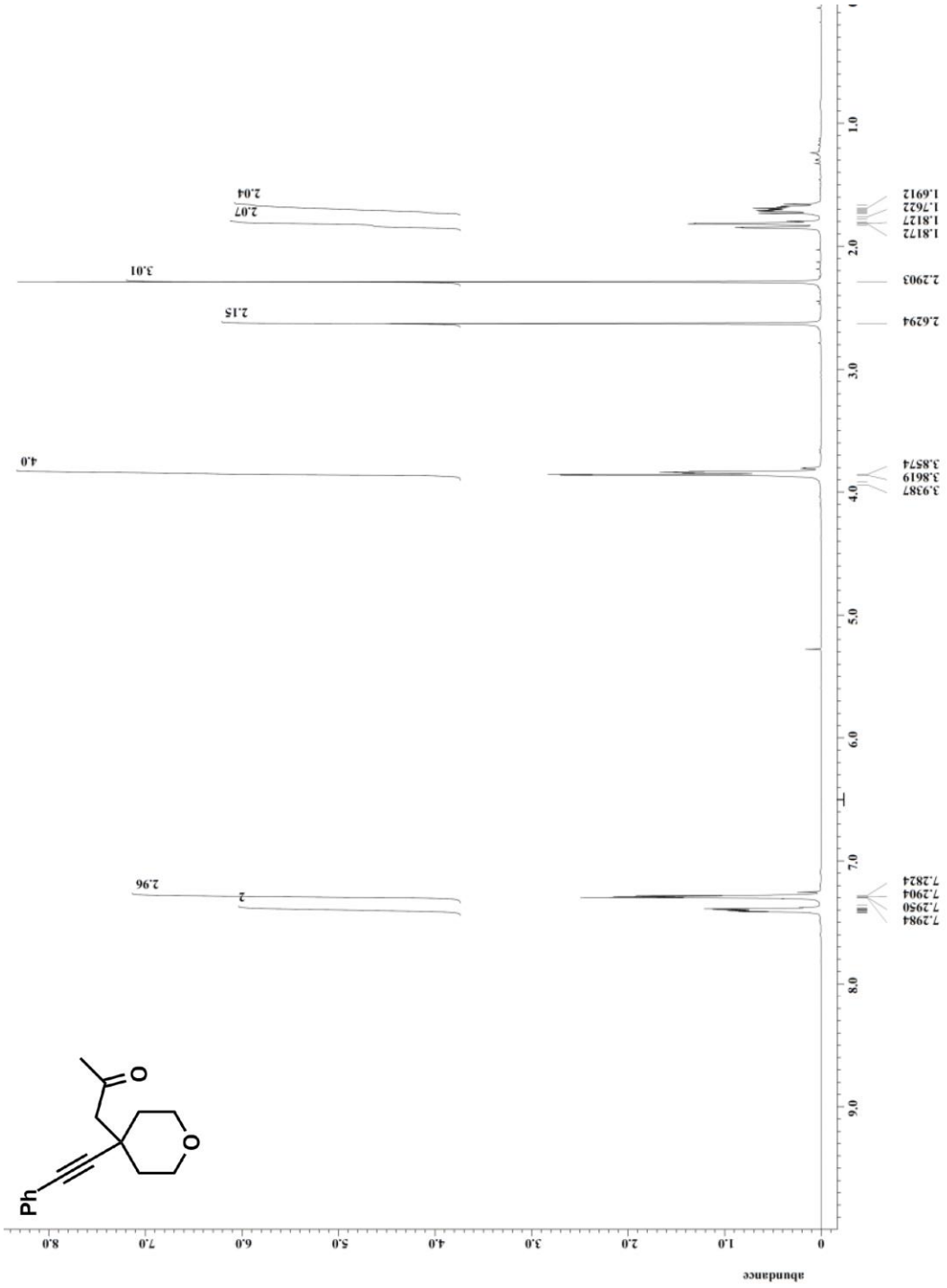

Figure A.4.3. ^{1}H NMR for compound **333**

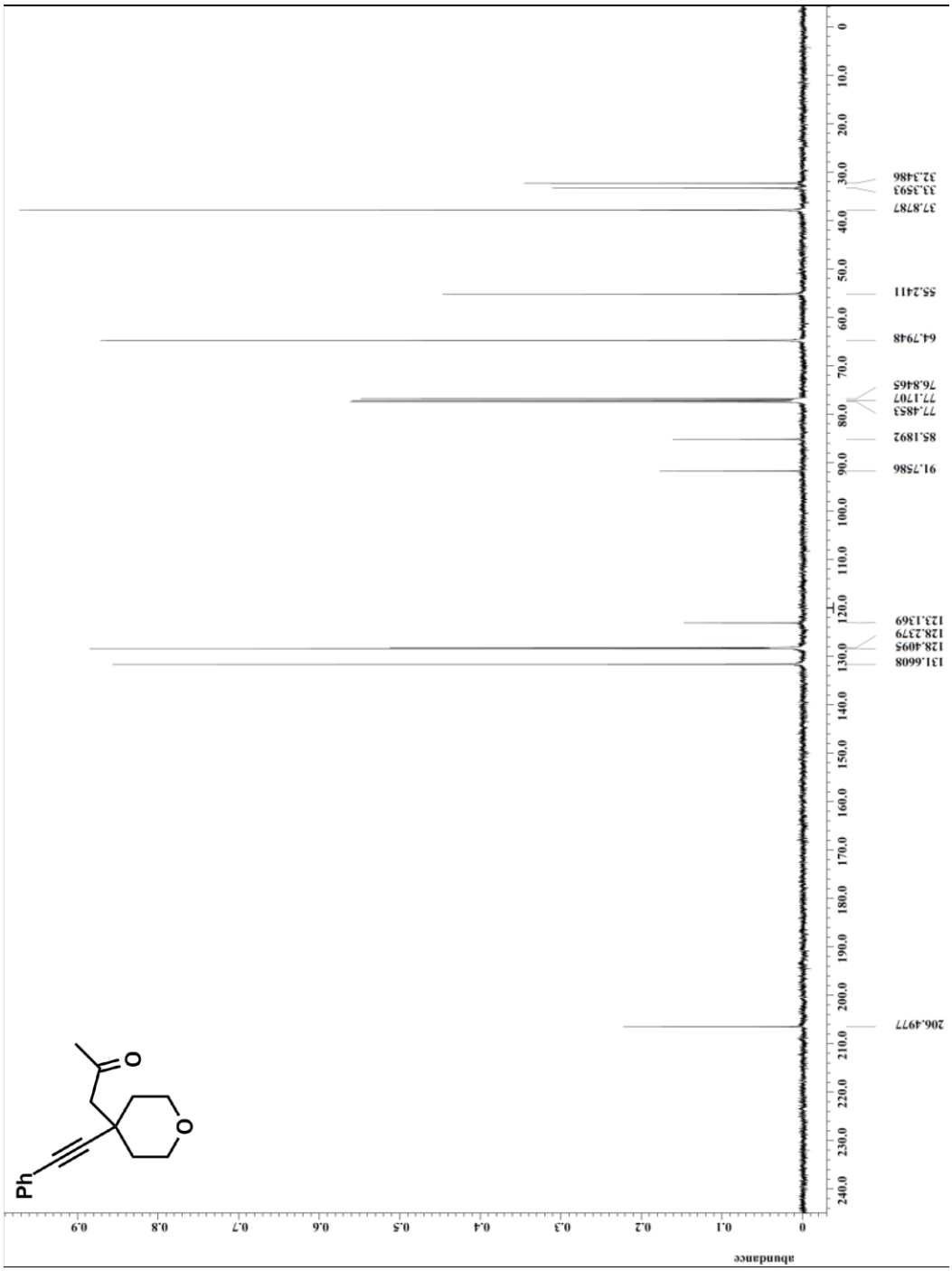

Figure A.4.4. ^{13}C NMR for compound **333**

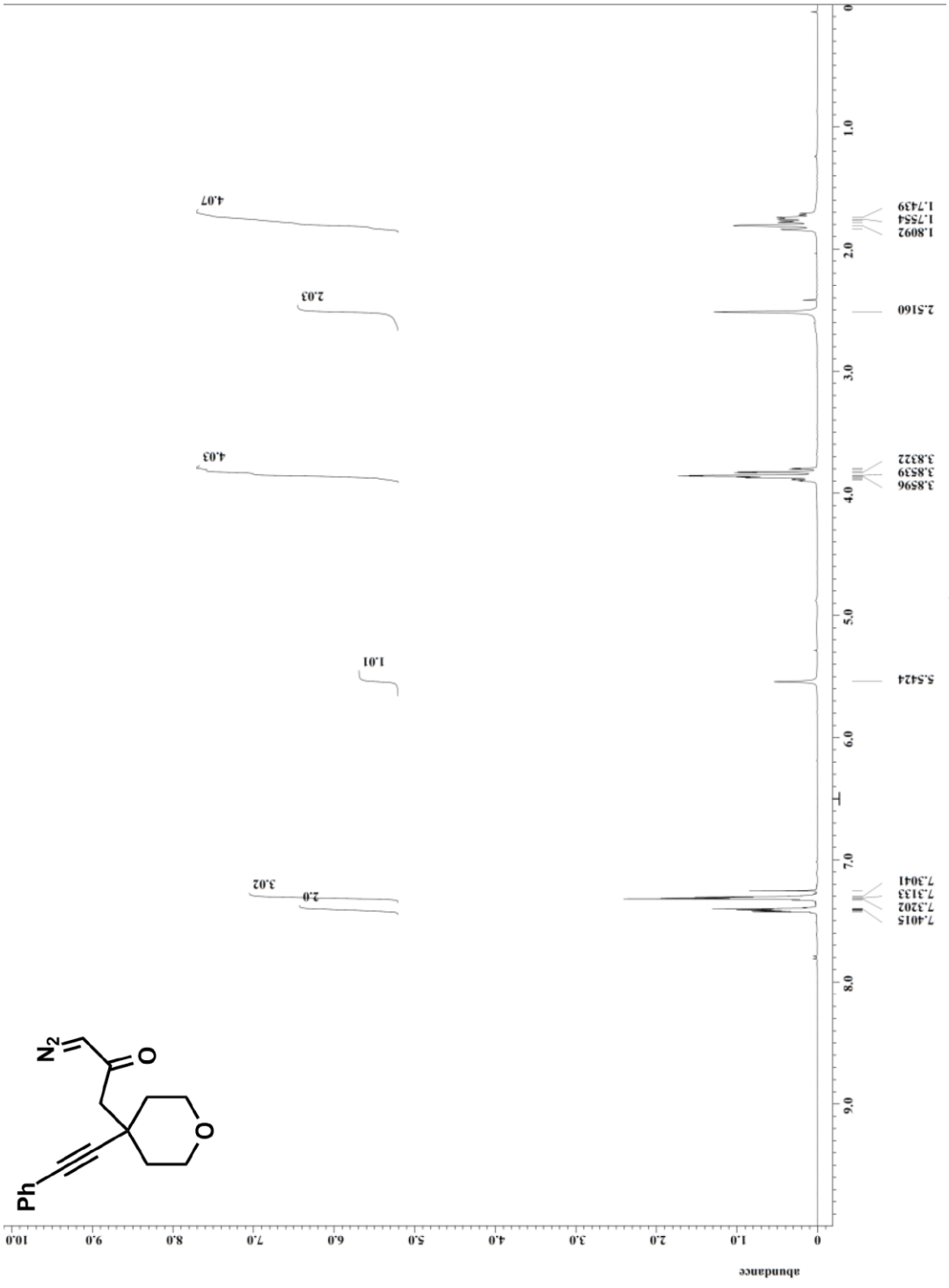

Figure A.4.5. ^{1}H NMR for compound **336**

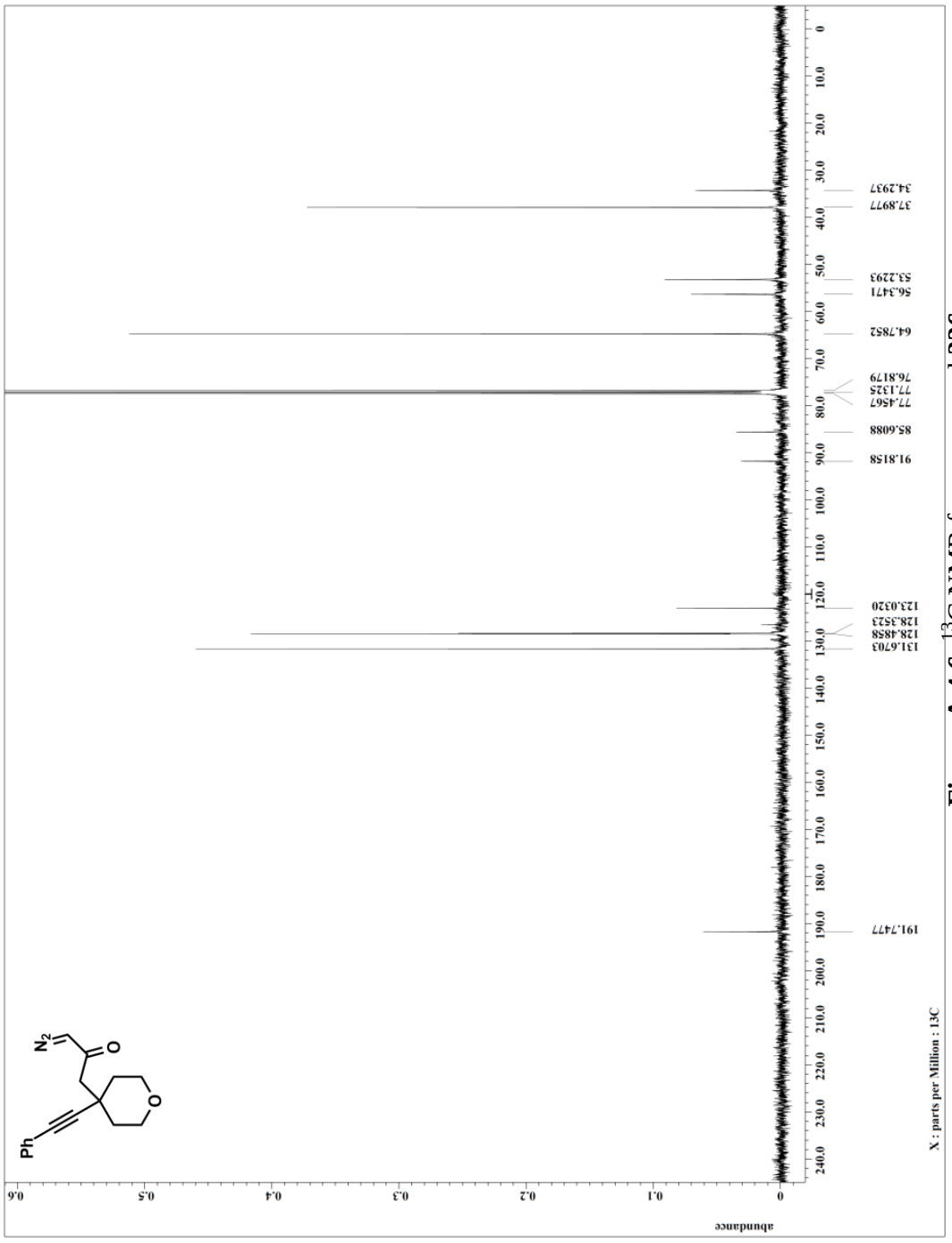

Figure A.4.6. ^{13}C NMR for compound **336**

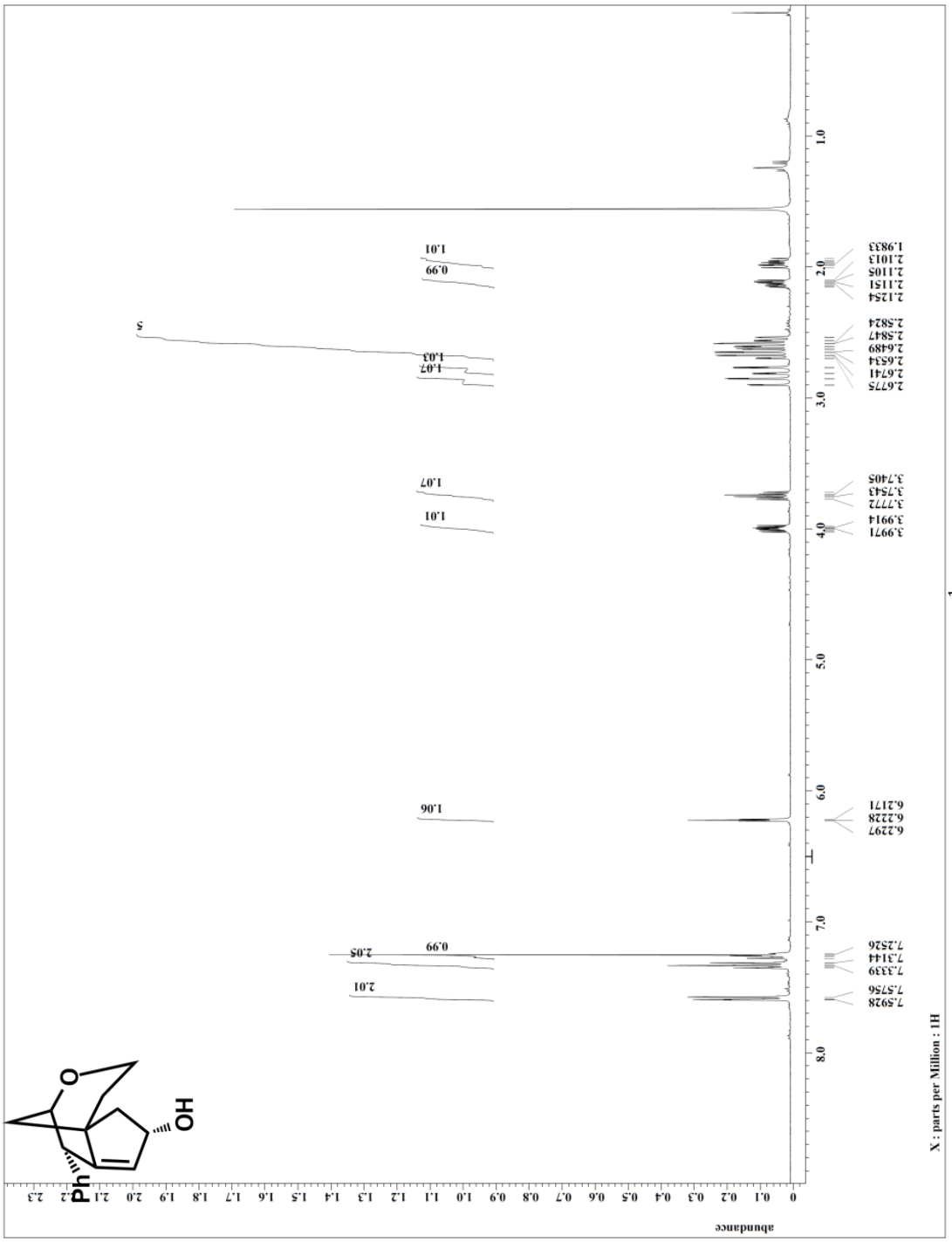

Figure A.4.7. ^{1}H NMR for compound **339**

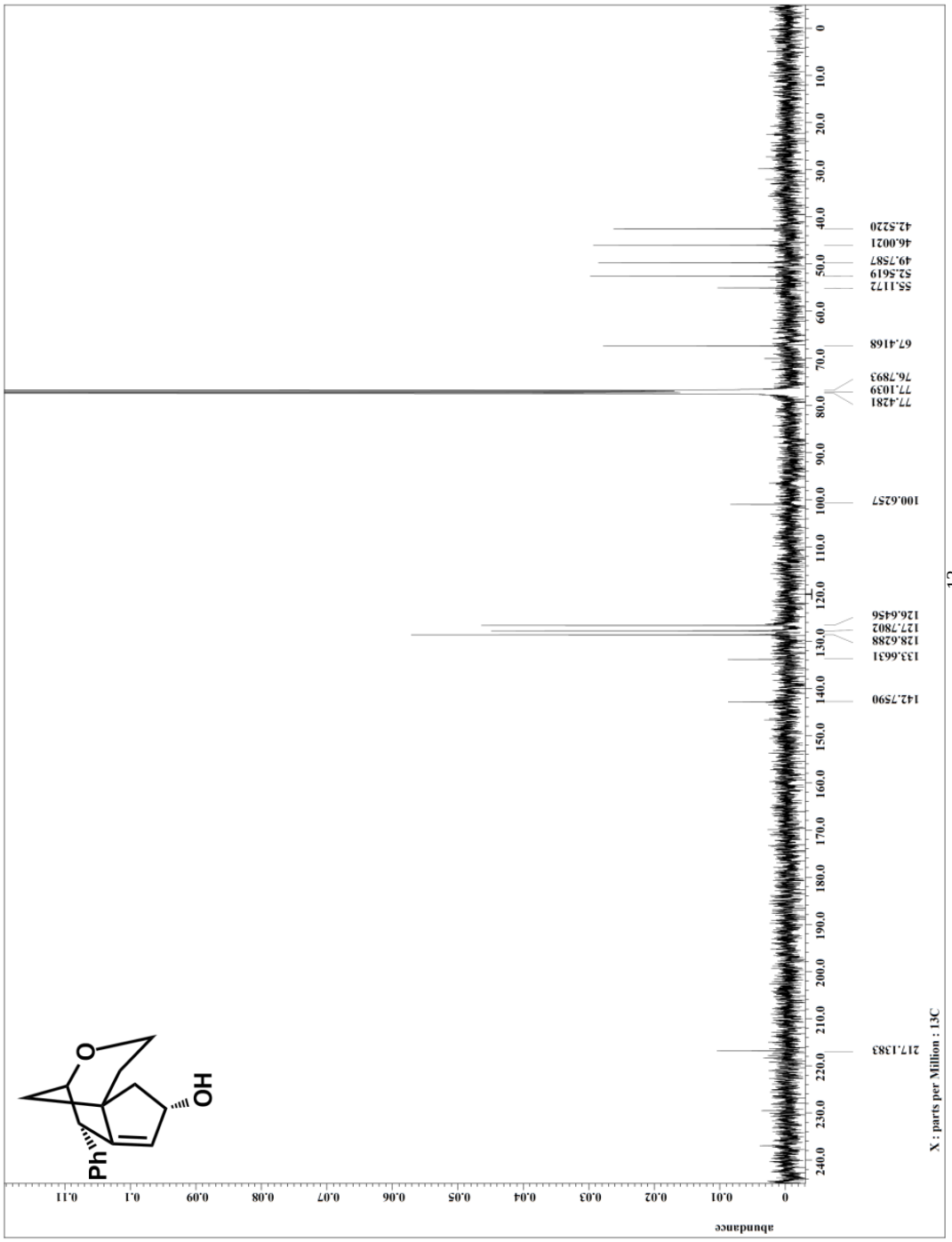

Figure A.4.8. ^{13}C NMR for compound **339**

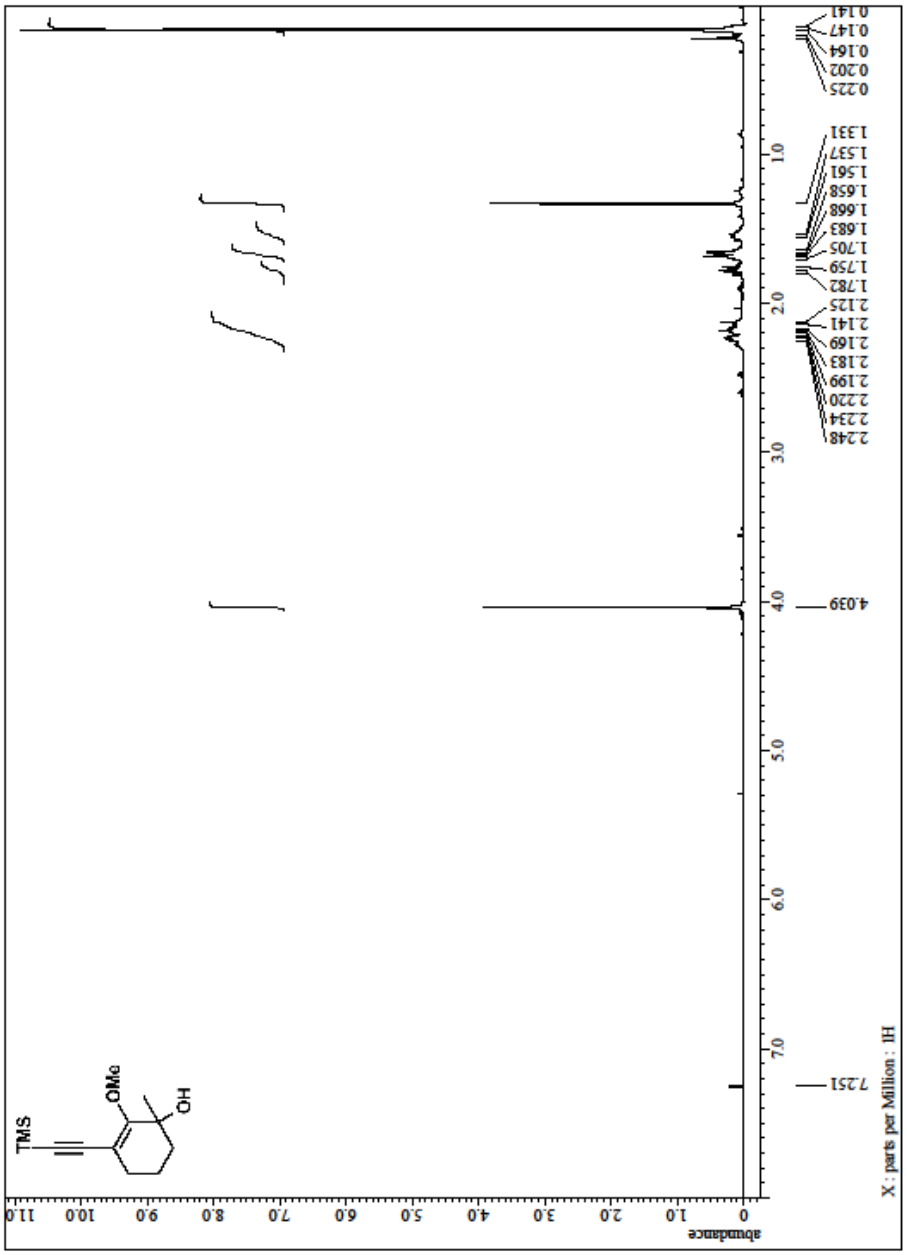

Figure A.4.9. ^{1}H NMR for compound **359**

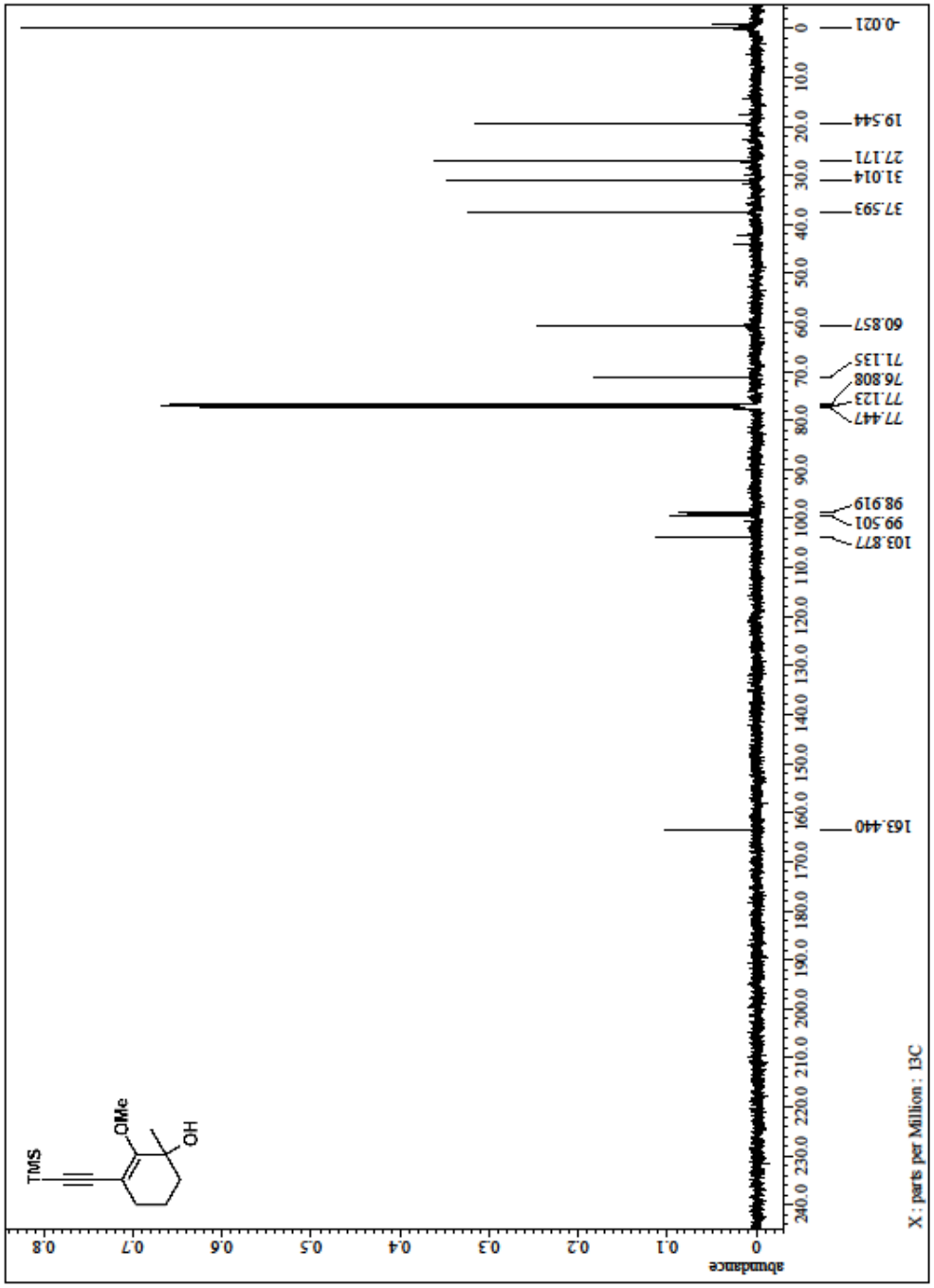

Figure A.4.10. ^{13}C NMR for compound **359**

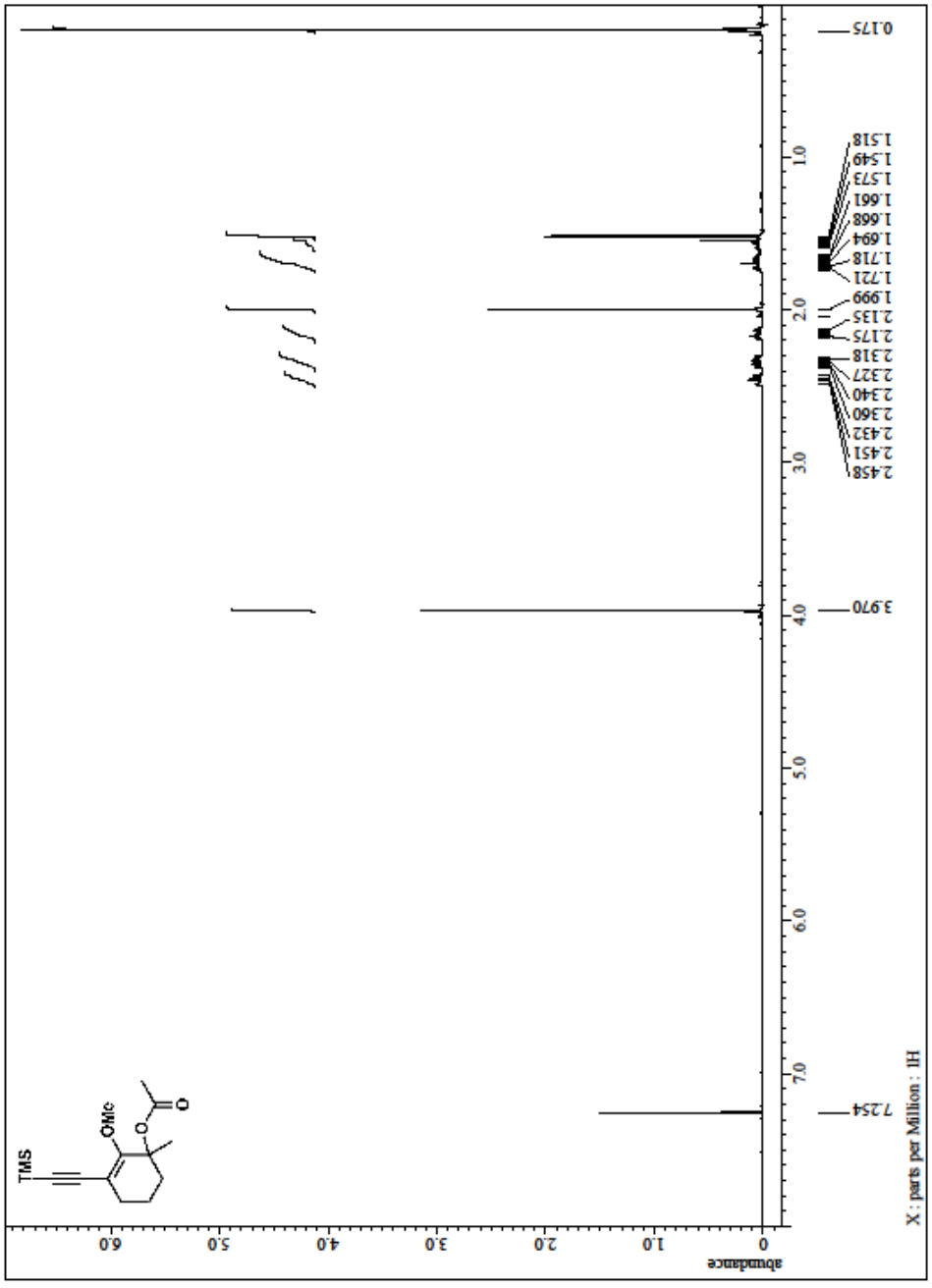

Figure A.4.11. ^{1}H NMR for compound **353**

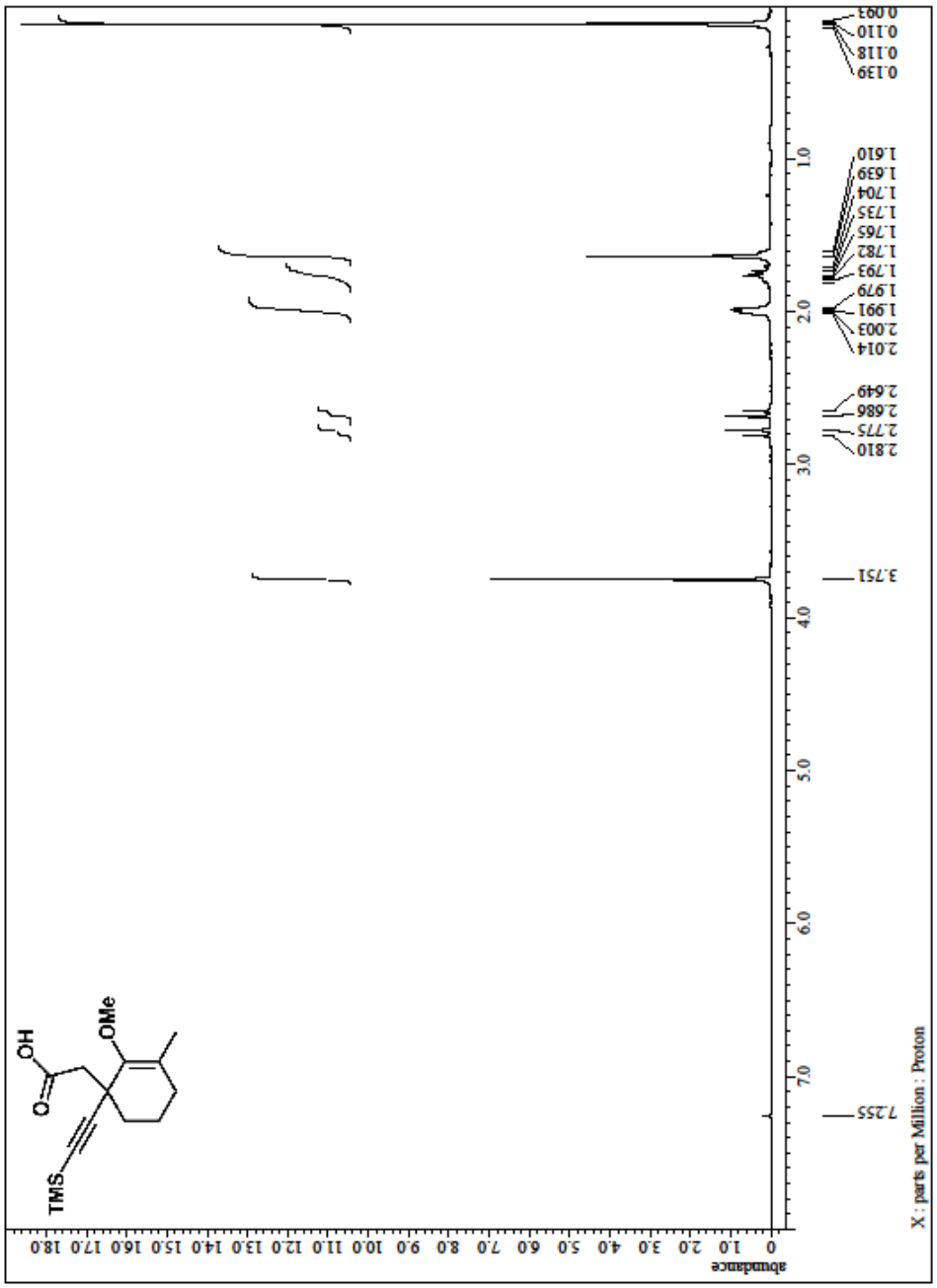

Figure A.4.12. ^{1}H NMR for compound **352**

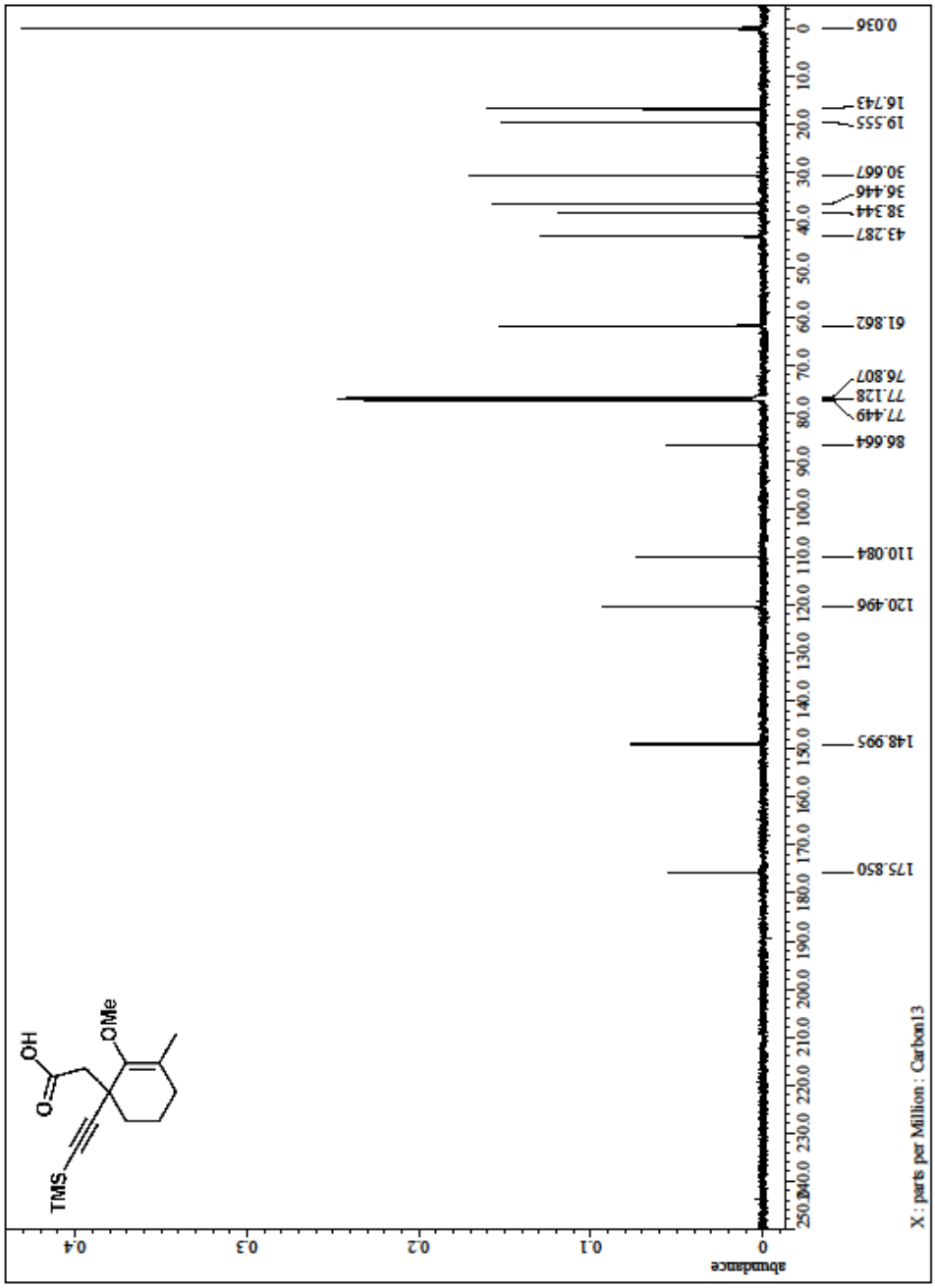

Figure A.4.13. ^{13}C NMR for compound **352**

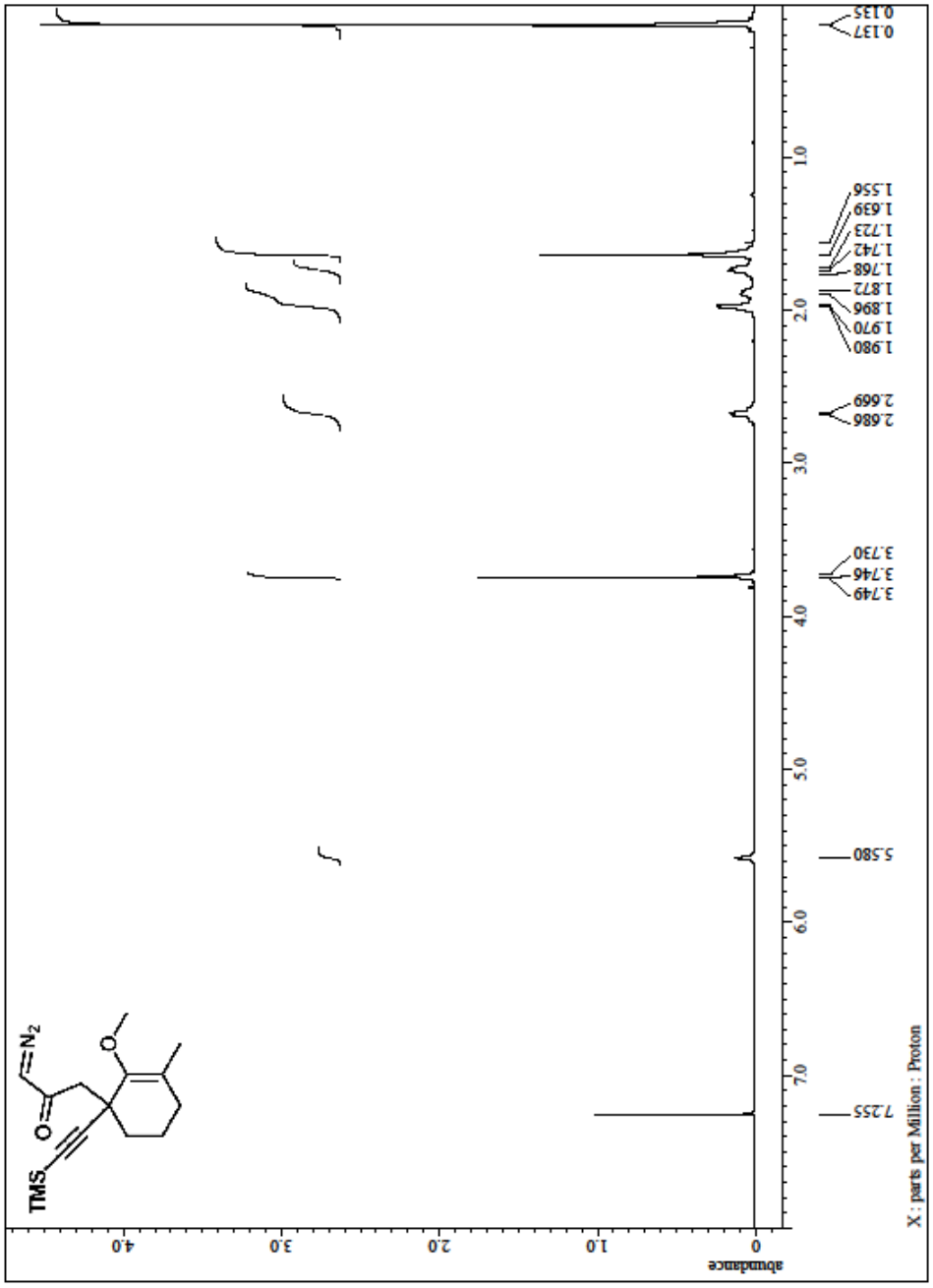

Figure A.4.14. ^{1}H NMR for compound **351**

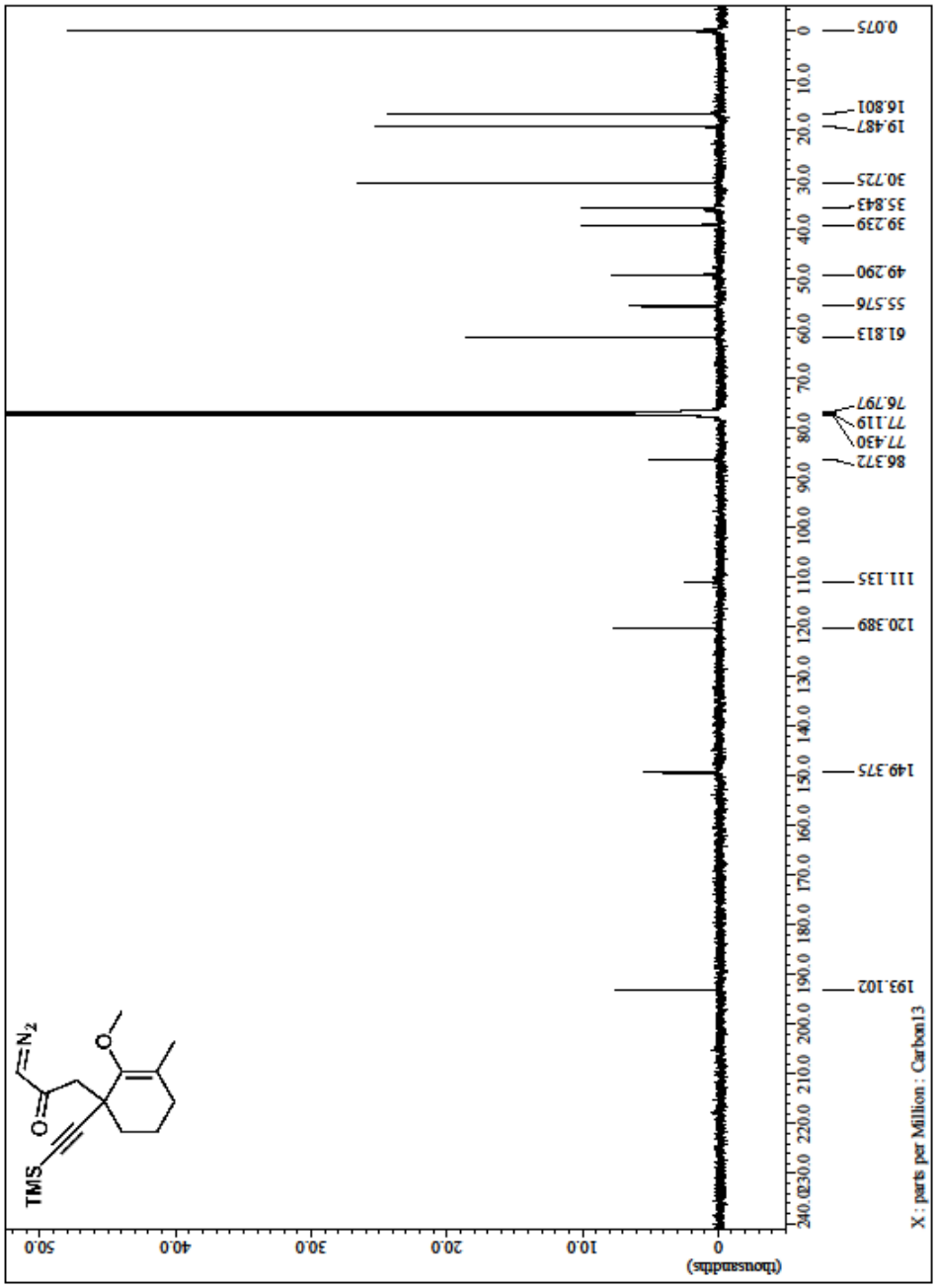

Figure A.4.15. ^{13}C NMR for compound **351**

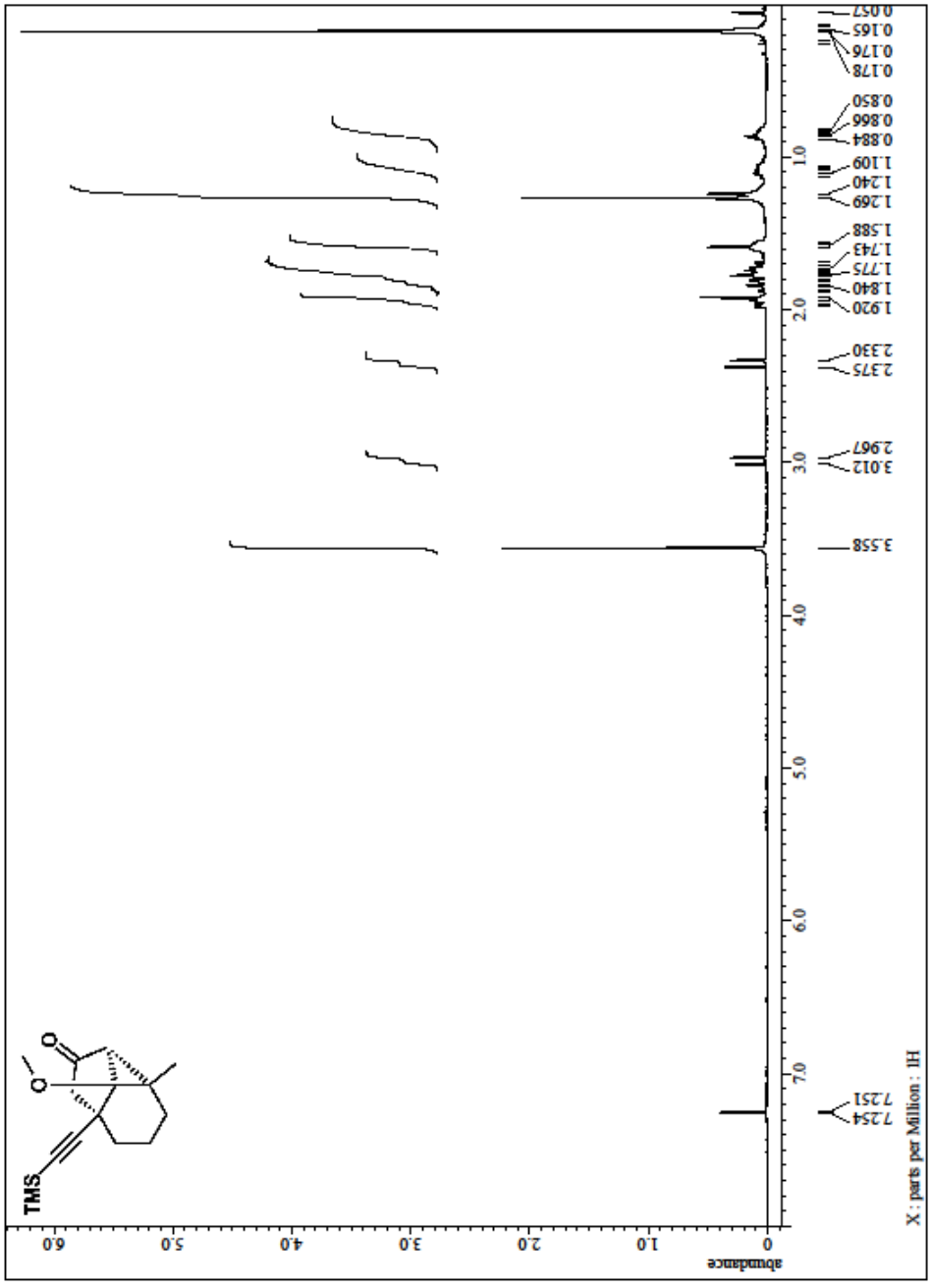

Figure A.4.16. ^{1}H NMR for compound **365**

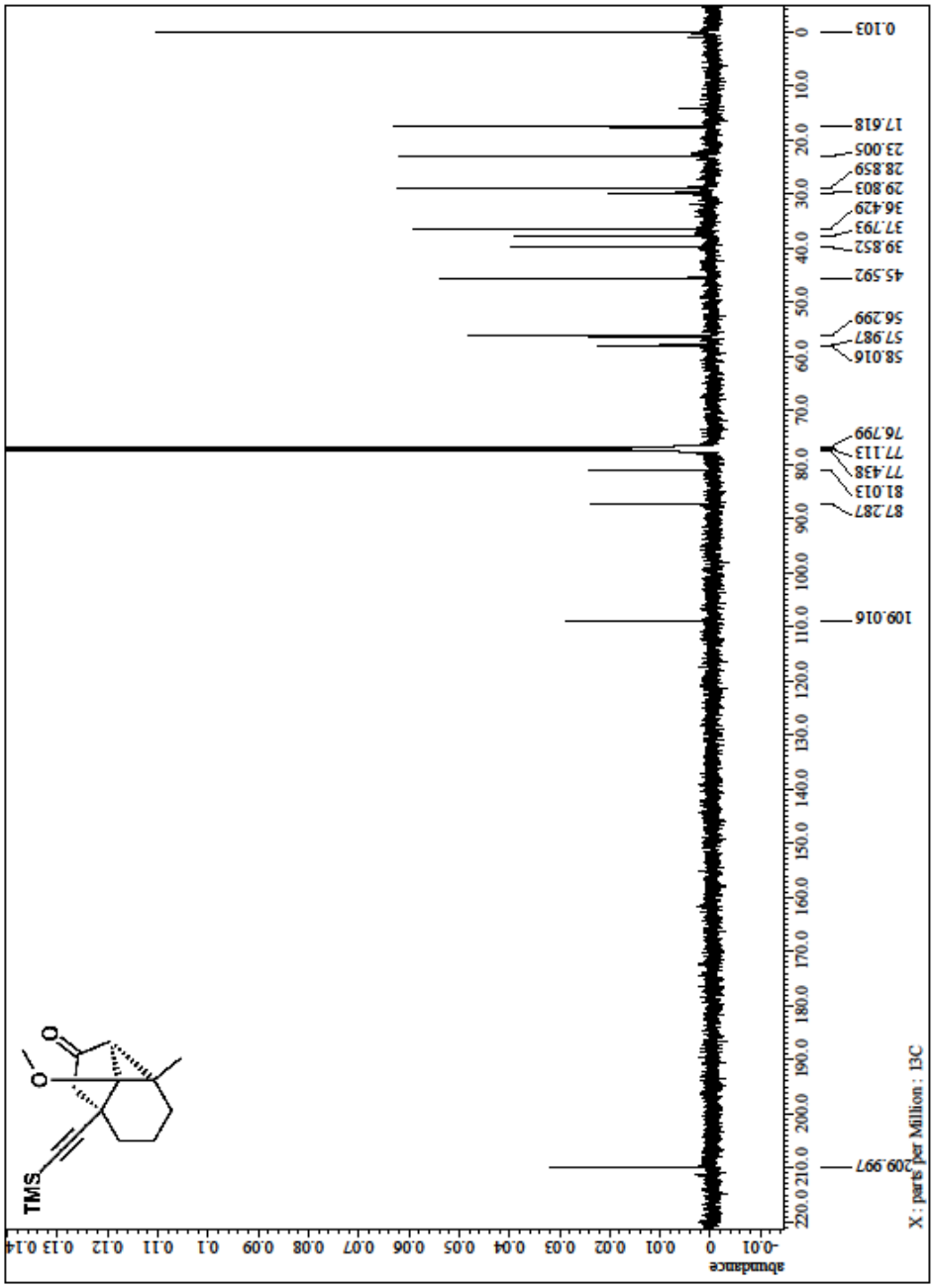

Figure A.4.17. ^{13}C NMR for compound **365**

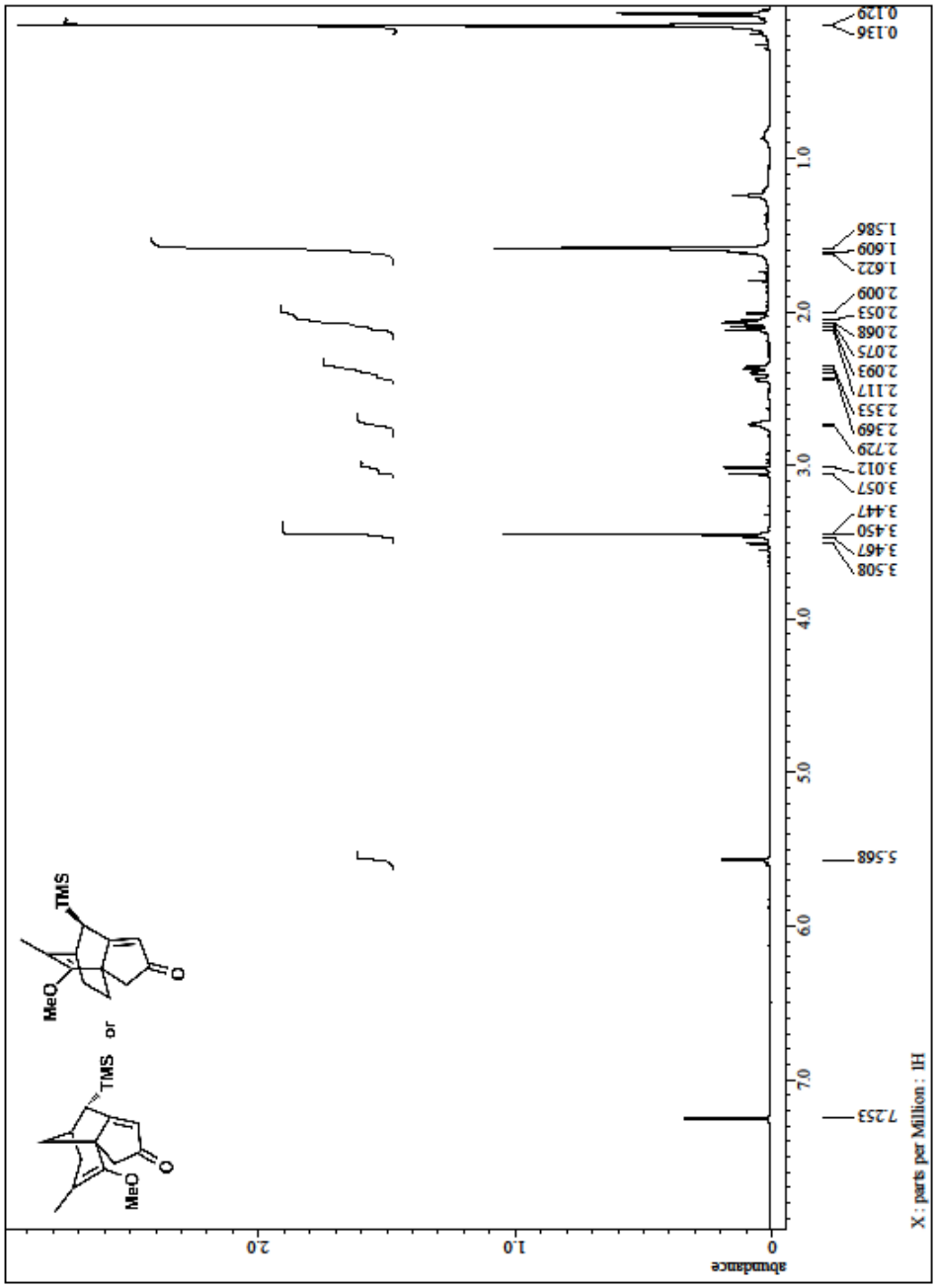

Figure A.4.18. ^{1}H NMR for compound **366 or 350**

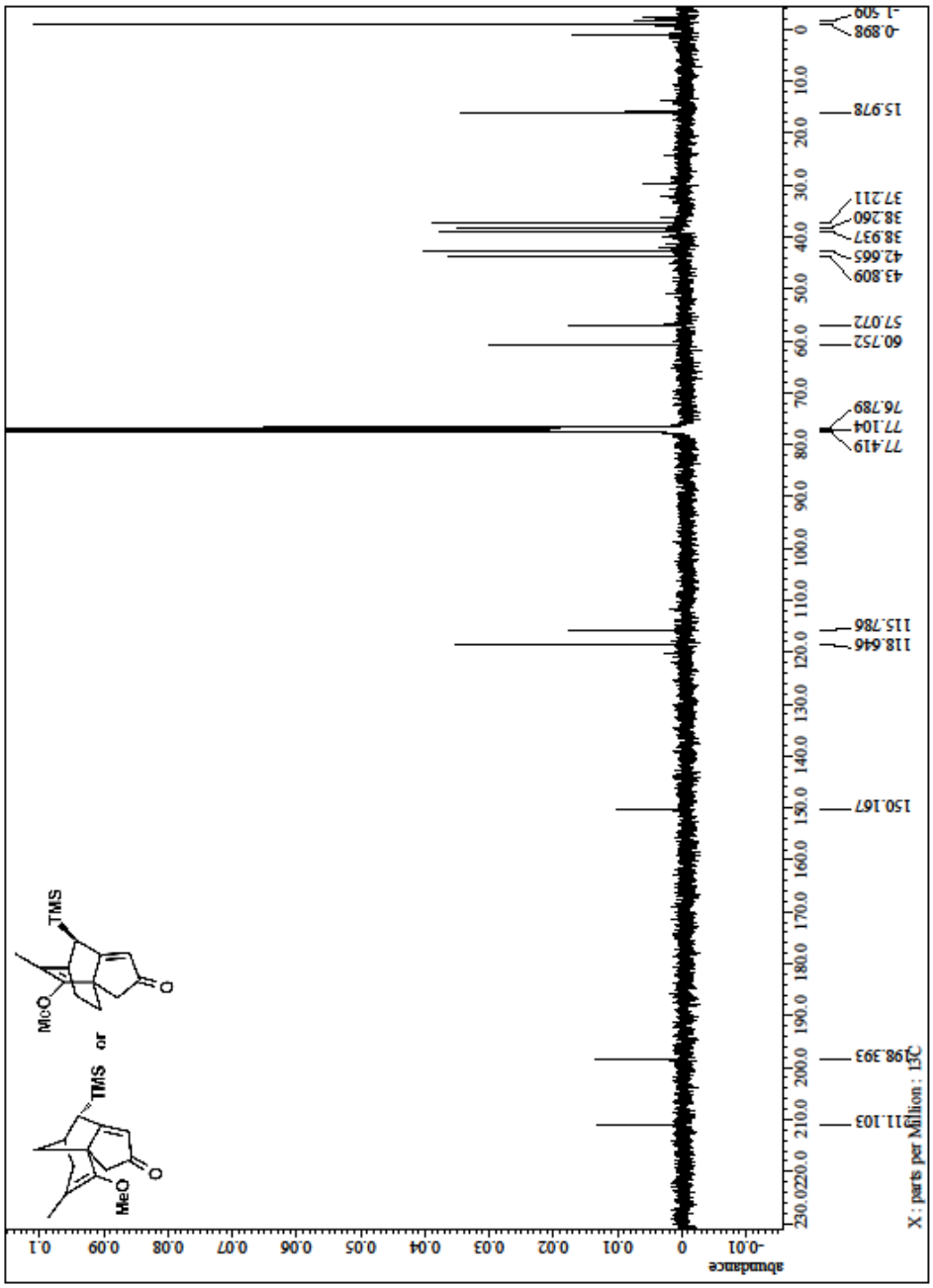

Figure A.4.19. ^{13}C NMR for compound **366**