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The syntheses of methyl jasmonate and analogs of alpha-methylene-gamma-butyrolactone utilizing titanium medicated cyclocarbonylation

Steve O. Lawrence
Louisiana State University and Agricultural and Mechanical College

THE SYNTHESES OF METHYL JASMONATE AND ANALOGS OF ALPHA–METHYLENE–GAMMA–BUTYROLACTONE UTILIZING TITANIUM MEDIATED CYCLOCARBONYLATION

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Steve O. Lawrence
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DEDICATION

Family life is full of major and minor crises -- the ups and downs of health, success and failure in career, marriage, and divorce -- and all kinds of characters. It is tied to places and events and histories. With all of these felt details, life etches itself into memory and personality. It's difficult to imagine anything more nourishing to the soul.

-Thomas Moore

The family. We were a strange little band of characters trudging through life sharing diseases and toothpaste, coveting one another's desserts, hiding shampoo, borrowing money, locking each other out of our rooms, inflicting pain and kissing to heal it in the same instant, loving, laughing, defending, and trying to figure out the common thread that bound us all together.

~Erma Bombeck

"Good family life is never an accident but always an achievement by those who share it." - **~James H.S. Bossard**

I'd like to dedicate this manuscript to my mother, Mevilyn M. Williams; good food, infinite wisdom, and priceless advice, what more could a son ask for? To my brother Roland and my sister Jacklyn thanks for your listening ears and the everlasting friendship. To Nishawn, thanks for the laughter (remember the Pizza Mare incident?) and for helping to add joy (your three precious daughters) to the family. To my nieces Yvonilyn, Yvonisha and Jadalyn, just stay cute and thanks for showing me there's still hope for the next generation.

To my late father Ohenio Lawrence Jr., I'll miss the phone calls and the car advice and the political discussions. Unfortunately, God saw it fit to take you home now. Rest in peace.

Each of you adds value to my life in some way or the other and without their guidance and support I wouldn't be the person that I am today.

ACKNOWLEDGEMENTS

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For paving the path and helping me to be an inspiration to others I'd also like to thank the current and former members of the Crowe group. There are a number of other people who have helped support and encourage me along the way. I'd like to acknowledge and thank several special friends who have made this journey quite the ride both in and out of the classroom. Specifically, I want to acknowledge Algernon Kelley and Mr. Roya Hughes for giving me good advice when I needed to hear it and for helping me to "stay the course" when I wanted to go astray. There's also Veronica Holmes and Maria Appeaning who both took me under their wings and helped me to achieve my goals. I'd also like to acknowledge Janet Manono for all of her help while at Louisiana State University. I'd also like to thank Ms. Sheridan Wilkes for all of her help in the department throughout my time here. Finally, I wish to also acknowledge all of the friends that I have made while at Louisiana State University who weren't specifically mentioned by name.

Last, but not least, there is my family who gave me words of encouragement, love and support throughout my ups and downs. Without you I wouldn't be here today.

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

9–BBN	9–borabicyclo[3.3.1]nonane
Al_2O_3	aluminum oxide
aq.	aqueous
BINAP	2,2–bis(diphenylphosphino)–1,1–binaphthyl
n–BuLi	n–butylithium
C	carbon
^0C	degrees Celsius
C_6D_6	benzene–*d*
$CDCl_3$	chloroform–*d*
^{13}C NMR	Carbon–13 Nuclear Magnetic Resonance
CO	carbon monoxide
Cp	cyclopentadienyl
$Cp_2Ti(PMe_3)_2$	bis(trimethylphosphine) titanocene
CrO_3	chromium (VI) oxide
$CuBr{\bullet}SMe_2$	copper (I) bromide–dimethyl sulfide complex
$CyNH_2$	cyclohexyl amine
δ	chemical shift in ppm downfield from Me_4Si
Δ	heat to reflux
d	doublet (NMR)
dd	double of doublet (NMR)
DIBAL–H	diisobutylaluminum hydride
DBU	1,8–diazabicyclo[5.4.0]undec–7–ene
DCM	dichloromethane, methylene chloride
DMAP	4–(dimethylamino)pyridine
DME	1,2–dimethoxyethane
DMF	dimethyl formamide
DMPU	1,3–dimethyl–3,4,5,6–tetrahydro–2(1*H*)–pyrimidinone
Et	ethyl
EtOAc	ethyl acetate
eq	equivalence
g	gram(s)
h	hour(s)
HBr	hydrobromic acid
HCl	hydrochloric acid
H	hydrogen
H_2O_2	hydrogen peroxide
H_2SO_4	sulfuric acid
Hz	hertz
^1H NMR	Proton Nuclear Magnetic Resonance
HPK	hetero Pauson–Khand
HPKR	hetero Pauson–Khand Reaction
J	coupling constant
K(DB18C6)	dibenzo–18–crown–6–Potassium
KH_2PO_4	potassium phosphate, monobasic
L	liter(s), ligand(s)
LAH	lithium aluminum hydride

LDA	lithium diisopropylamide
µ	micro
µg	microgram
m	milli, multiplet (NMR)
mg	milligram(s)
mL	milliliter(s)
M	moles per liter, mega
Me	methyl
$Me_3N\bullet HCl$	propylamine hydrochloride, 1–aminopropane
$MgSO_4$	magnesium sulfate anhydrous
MHz	megahertz
min	minute(s)
mol	mole(s)
mmol	milli moles
Ms	methanesulfonyl
MsCl	methanesulfonyl chloride
N	normal
NaHCO	sodium bicarbonate
$NaNH_2$	sodium amine
NaOH	sodium hydroxide
$Na_2Cr_2O_7$	sodium dichromate
Na_2SO_4	sodium sulfate
NEt_3	triethyl amine
NMR	nuclear magnetic resonance
O	oxygen
OAc	acetate
ORTEP	Oak Ridge Thermal Ellipsoid Plot
P	para
PCC	pyridinium chlorochromate
PK	Pauson–Khand
PKR	Pauson–Khand Reaction
ppm	parts per million
psig	pounds per square inch
qd	quartet of doublet (NMR)
quin	quintet (NMR)
rt	room temperature
s	singlet (NMR)
sat	saturated
t	triplet (NMR)
t–Bu	*tert*–butyl
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*–butyldimethylsilyl
TBS	*tert*–butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane
Ts	*p*–toluenesulfonyl

ABSTRACT

From its humble beginnings as a novel carbon–carbon bond forming reaction, the Pauson–Khand reaction has lead to the synthetic development of a variety of natural products. One particular variation of the Pauson–Khand reaction was called the hetero Pauson–Khand. This reaction differs from the normal Pauson–Khand reaction because the reaction employs an intramolecular titanium mediated cycloaddition using enal and enones instead of alkenes and alkynes functional groups to prepare a variety of natural products. These natural products usually contain a bicyclic cyclopentenone core. Because the new ring contains a hetero atom, the name hetero Pauson–Khand was coined.

α–Methylene–γ–Butyrolactones posses a wide range of biological activities. These activities range from antibacterial to anti–inflammatory and make these lactones interesting targets for synthetic groups to produce in labs. In an attempt to expand our knowledge of titanium chemistry, α–methylene–γ–butyrolactones syntheses were investigated using titanium catalyzed hetero Pauson–Khand reaction. Several substituted titanacene metallacycles were produced in good to excellent yields since the carbon monoxide insertion under pressure proved problematic.

Because of its importance to the perfume industry; many synthetic groups have synthesized methyl jasmonate. Methyl jasmonate was synthesized from 3–(*tert*–Butyl–dimethyl–silanyloxy)–propionaldehyde and 5–Bromo–penta–1,3–diene using the hetero Pauson–Khand reaction in twelve steps. Methyl jasmonate was converted from jasmonic acid in 60 % yield as clear oil.

In an effort to circumvent the problems associated with synthesizing α–methylene–γ–butyrolactones from the hetero Pauson–Khand reaction; isonitrile insertions into allenals and allenones were investigated. If successful, these iminocyclopentanones would have been

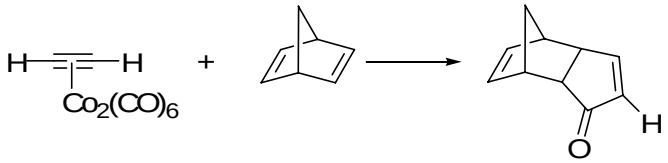
hydrolyzed to the corresponding α–methylene–γ–butyrolactones. Initial titanacene macrocycles formed, but the desired iminocyclopentanones intermediates were never produced.

CHAPTER 1

THE HISTORY OF THE PAUSON–KHAND REACTION FROM ITS INTRODUCTION TO SYNTHETIC UTILITY

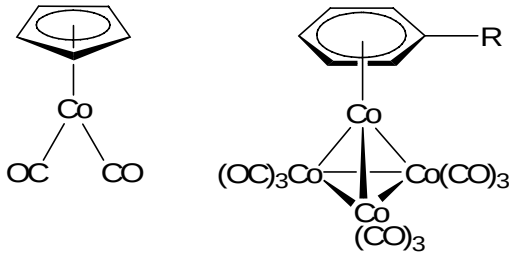
1.1. Introduction

The first Pauson–Khand reaction was done by Peter L. Pauson, Ishan U. Khand and co–workers in 1973.[1,2] The Pauson–Khand reaction is a [2+2+1] cycloaddition. The first reaction used an alkyne–dicobalt hexacarbonyl complex and norbornadiene to produce a cyclopentenone which is illustrated in Scheme **1.1**.



Scheme **1.1.** The first Pauson–Khand reaction.

They also produced several "arenecobalt complexes" shown in Figure **1.1**.



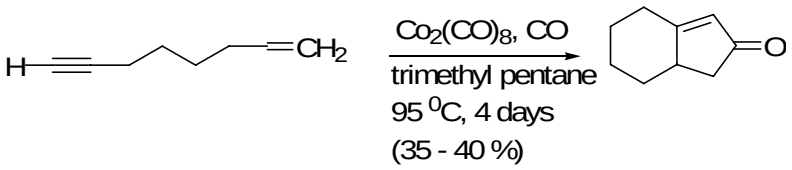
1 2
R = H or Me

Figure **1.1.** Other products made from the reaction.

Several reviews for the Pauson-Khand reaction have been published.[3-6]

1.2. Intramolecular Pauson–Khand Reaction

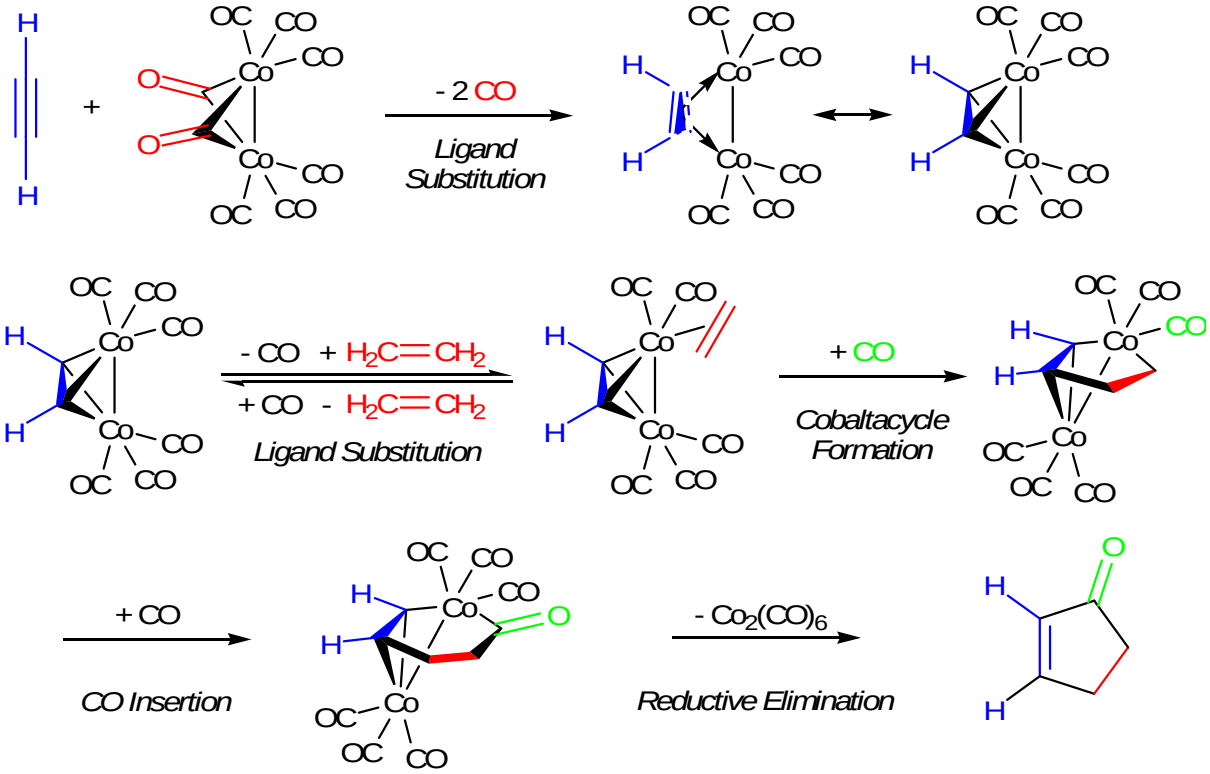
The intramolecular PK reaction was done by Schore and coworkers.[7] This reaction used an α, ω–enynes with $Co_2(CO)_8$ in trimethyl pentane to produce the desired bicyclic–cyclopentenone. Scheme **1.2** shows the first intramolecular reaction.



Scheme **1.2.** An intramolecular Pauson–Khand reaction.

1.3. Proposed Pauson–Khand Reaction Mechanism

Since it is difficult to isolate intermediates in the Pauson–Khand reaction; the mechanism of the Pauson–Khand reaction is not clearly known, but a mechanism was proposed.[8] The loss of two carbonyl ligands, CO, from dicobalt octacarbonyl complex, Co_2CO_8, is followed by the complexation of the alkyne to the vacant sites on the dicobalt hexacarbonyl complex.



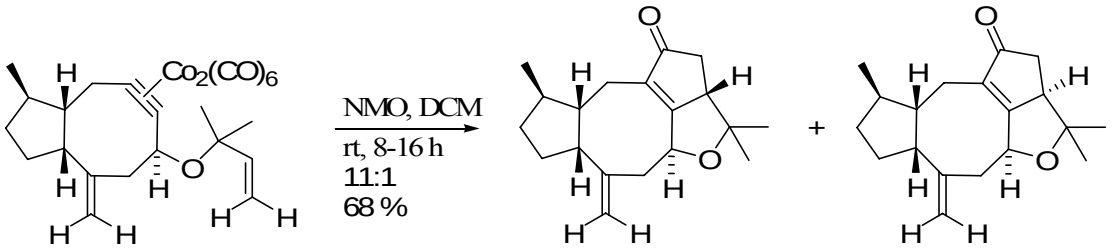
Scheme **1.3.** Proposed mechanism for the Pauson–Khand reaction.

One more carbonyl ligand, CO, is disassociated from the complex and an alkene is added. Another CO ligand adds to the complex after the alkene insertion which opens a vacant site. Then another CO adds to the complex after a CO is inserted to open up an empty site for the addition. The subsequent reductive elimination to produce the cyclopentenone and the

generation of the dicobalt hexacarbonyl complex illustrates a possible mechanism for the Pauson–Khand reaction (Scheme **1.3**). What is of interest here is that without the migratory insertion from the alkene; there would be no addition of CO ligands.

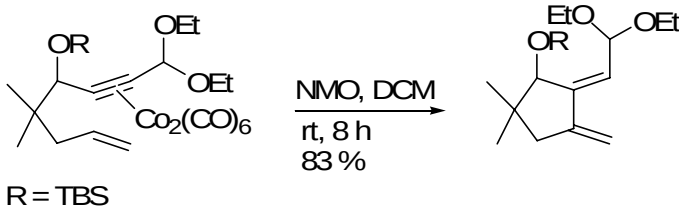
1.4. N–Oxide Promoters

It was discovered that N–methylmorpholine–N–oxide, NMO, can be used to accelerate intramolecular PK reactions at room temperature under argon or nitrogen.[9] Scheme **1.4** shows the NMO promoted PK reaction using enynes.



Scheme **1.4.** NMO promoted Pauson–Khand reaction.

The only limitation to this procedure is that electron deficient alkyne substrates on the enyne failed to cyclize and produced the desired bicyclic cyclopentenone. Instead, it produced a diene. Scheme **1.5** shows the diene product made when using electron deficient alkynes.



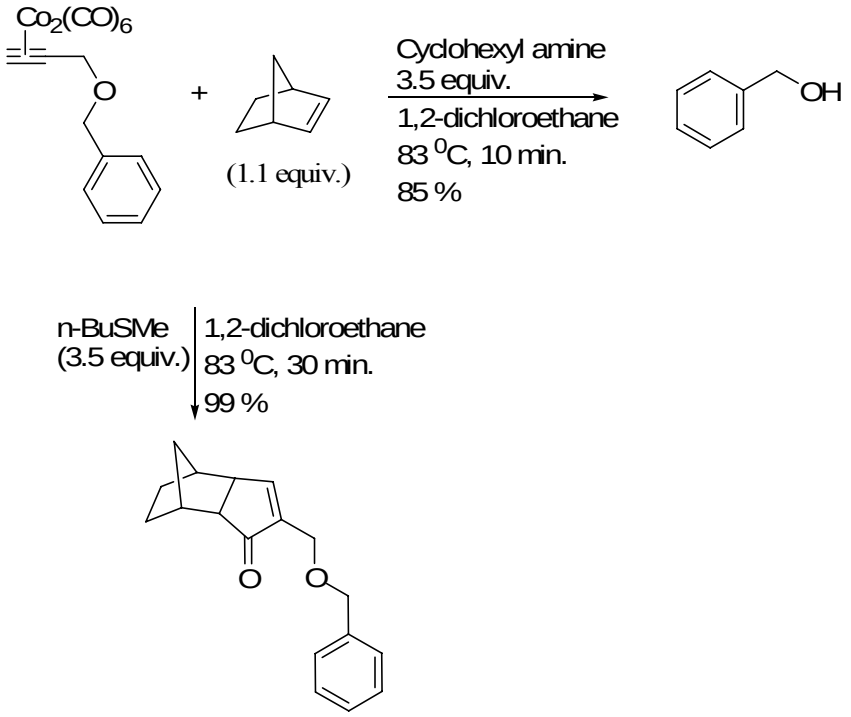
Scheme **1.5.** NMO promoted intramolecular Pauson–Khand reaction using electron deficient alkynes.

The likely mechanism for the NMO accelerated reaction used the initial oxidation of the CO ligand to CO_2. This process creates a vacant site on the cobalt complex.

1.5. Sulfide Promoters of PK Reaction

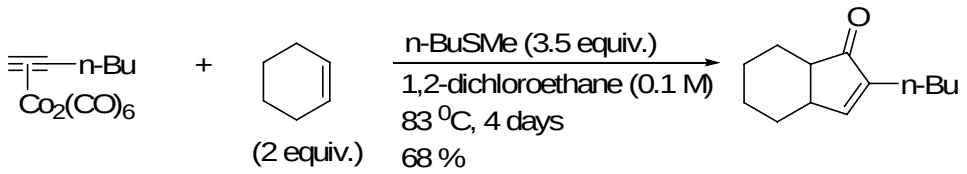
A variety of alkyl methyl sulfides were used to promote the PK reactions. n–Butyl methyl sulfides, n–BuSMe, were discovered to accelerate the stoiciometric PK reaction the

best.[10] When n–BuSMe used instead of an amine promoted Pauson–Khand reaction; cleavage of the "carbon–heteroatom" bond was not observed. The advantages of using a dialkyl sulfide promoted PK reaction as opposed to an amine promoted one is shown in Scheme **1.6**.



Scheme **1.6.** Advantages of utilizing a sulfide promoted Pauson–Khand reaction over a NMO reaction.

They discovered that n–BuSMe promote the intramolecular cyclization of the PK reaction using simple alkenes, alkynes, and cobalt catalyst (Scheme **1.7**).



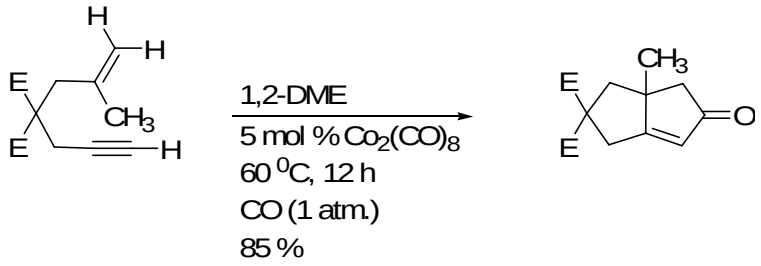
Scheme **1.7.** Sulfide promoted Pauson–Khand reaction.

1.6. Catalytic PK Reactions

Rautenstrauch and coworkers accomplished a catalytic intermolecular PK reaction using $Co_2(CO)_8$, an unstrained alkene, an alkyne and CO.[11] A catalytic intramolecular version was previously reported by Pauson and co-workers.[2] Rautenstrauch's experiment involved utilizing

a 0.80 M toluene solution of 1-heptyne, 0.22 mol % of [$Co_2(CO)_8$], 40 bar of ethylene and 100 bar CO. The reaction mixture was heated to 150 ^{0}C and stirred for 16 h and produced 2-pentylcyclopent-2-en-1-one in a 47–49 % yield.

Livinghouse and coworkers discovered that they could use heat to promote an intramolecular PK reaction using $Co_2(CO)_8$ (Scheme **1.8**). The reaction involved using an enyne substrate, 5 mol % $Co_2(CO)_8$, stirring for 12 h at 60 ^{0}C and CO at 1 atm.[12]



Scheme **1.8.** The first PK reaction done using catalytic amounts of $Co_2(CO)_8$.

Livinghouse discovered that $Co_2(CO)_6$–alkyne complexes are generated from $Co_2(CO)_8$ and 2–methyl–3–butyn–2–ol or phenyl–ethyne (Scheme **1.9**). Livinghouse reported that $Co_2(CO)_6$–alkyne complexes can replace $Co_2(CO)_8$ in thermal catalytic PK reactions and they observed"significant" increase in the percent yield when $CyNH_2$ was present in the PK reactions.[13]

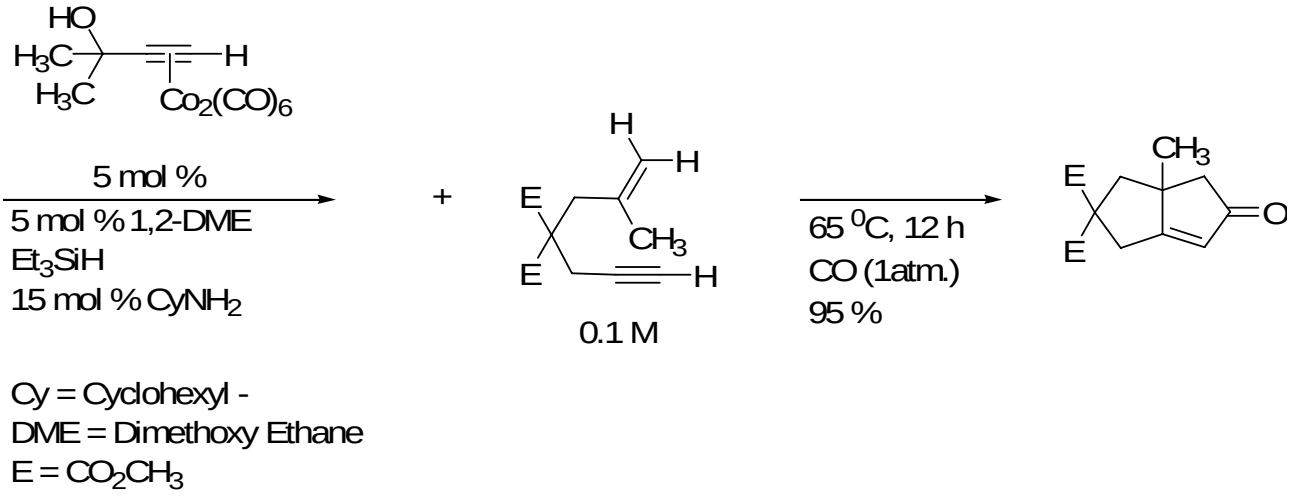
1.7. Metals Other Than Cobalt Used in PK Reaction

Besides cobalt, many other transition metals can be used to facilitate the Pauson–Khand reaction. These other transition metals were the first to be employed toward the Pauson–Khand reaction.

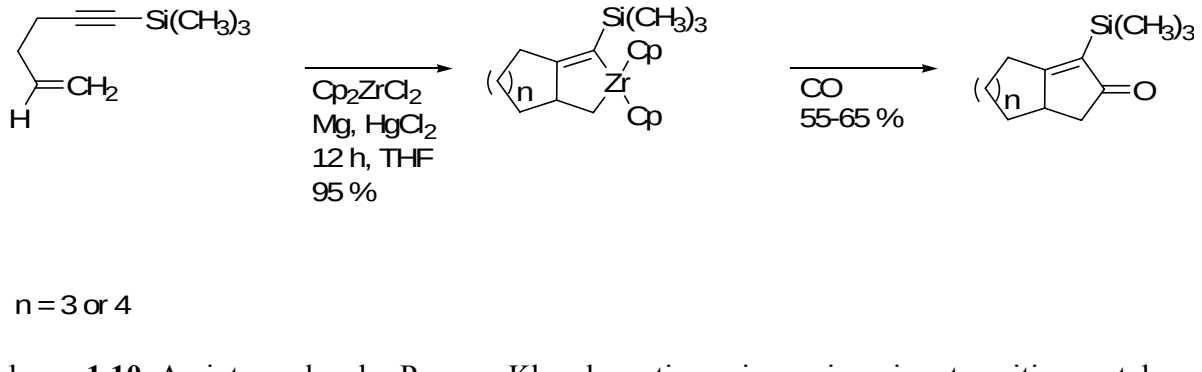
1.7.1. Zirconium Transition Metal Complex

Negishi and coworkers reported synthesizing bicyclic ketones from trialkylsilyl enynes and a Cp_2ZrCl_2 complex using an intramolecular PK reaction (Scheme **1.10**). This reaction was

done stoichiometrically with a 1:1 ratio of the zirconium transition metal complex and the vinyl–silyl–enynes.[14] These α–silyl cyclopentanones were made in moderate to good yields. Bicyclic α–silyl cyclopentanones can be employed to produce more complex molecules.



Scheme **1.9.** The catalytic intramolecular Pauson–Khand reaction.

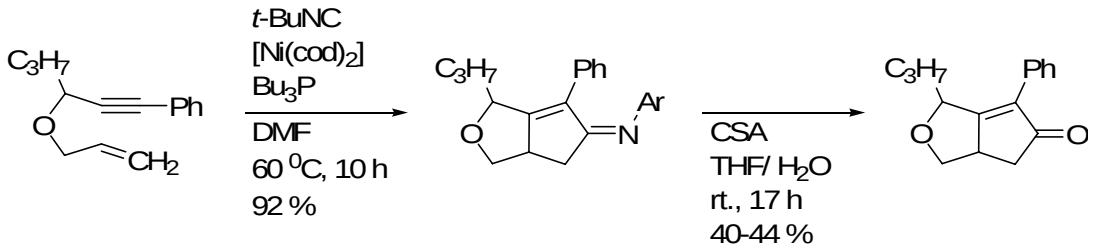


Scheme **1.10.** An intramolecular Pauson–Khand reaction using a zirconium transition metal complex.

1.7.2. Nickel Transition Metal Complex

Tamao and reported utilizing a Ni(0) complex, enynes, and isocyanides to produce 1–imino–2–cyclopentenes in moderate to good yields (Scheme **1.11**). The 1–imino–2–cyclopentenes could later be hydrolyzed into cyclopentenones.[15] These cyclopentanones were

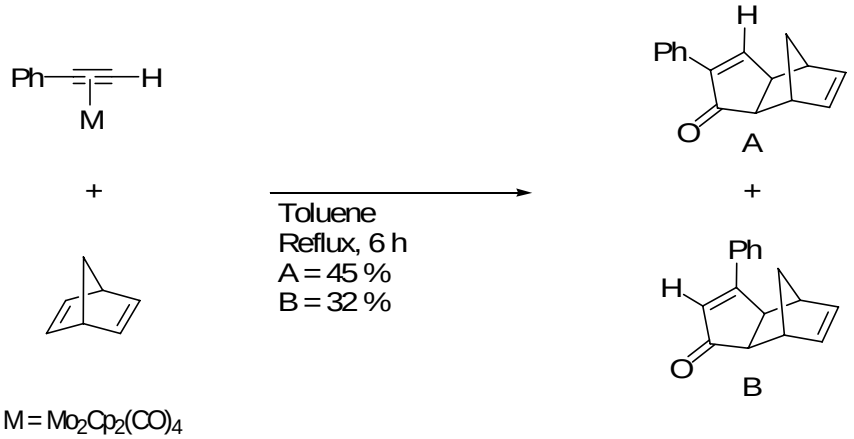
made in good to excellent yields and it showed that nickel complexes can be employed to make carbon–carbon bond forming reactions.



Scheme **1.11.** Synthesis of cyclopentenones using a Nickel transition metal complex.

1.7.3. Molybdenum Transition Metal Complex

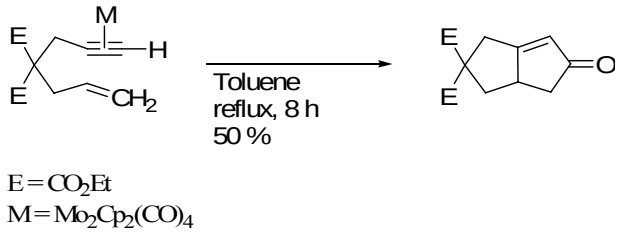
Hanaoka and coworkers used a molybdenum–alkyne complex to synthesize both 3–substituted and 2–substituted cyclopentenones utilizing an intermolecular PK reaction. What makes this procedure interesting is that both 2 and 3–substituted cyclopentenones (A & B) were both isolated in poor to moderate yields for the first time (Scheme **1.12**). One of the problems with this intermolecular PK reaction is that regioselectivity cannot be controlled and the yields of the product need to be improved considerable.



Scheme **1.12.** An intermolecular Pauson–Khand reaction using a molybdenum transition metal complex.

The molybdenum complex was also used for an intramolecular PK reaction to synthesize a bicyclic ketone (Scheme **1.13**).[16] The bicyclic cyclopentenone produced in this reaction was

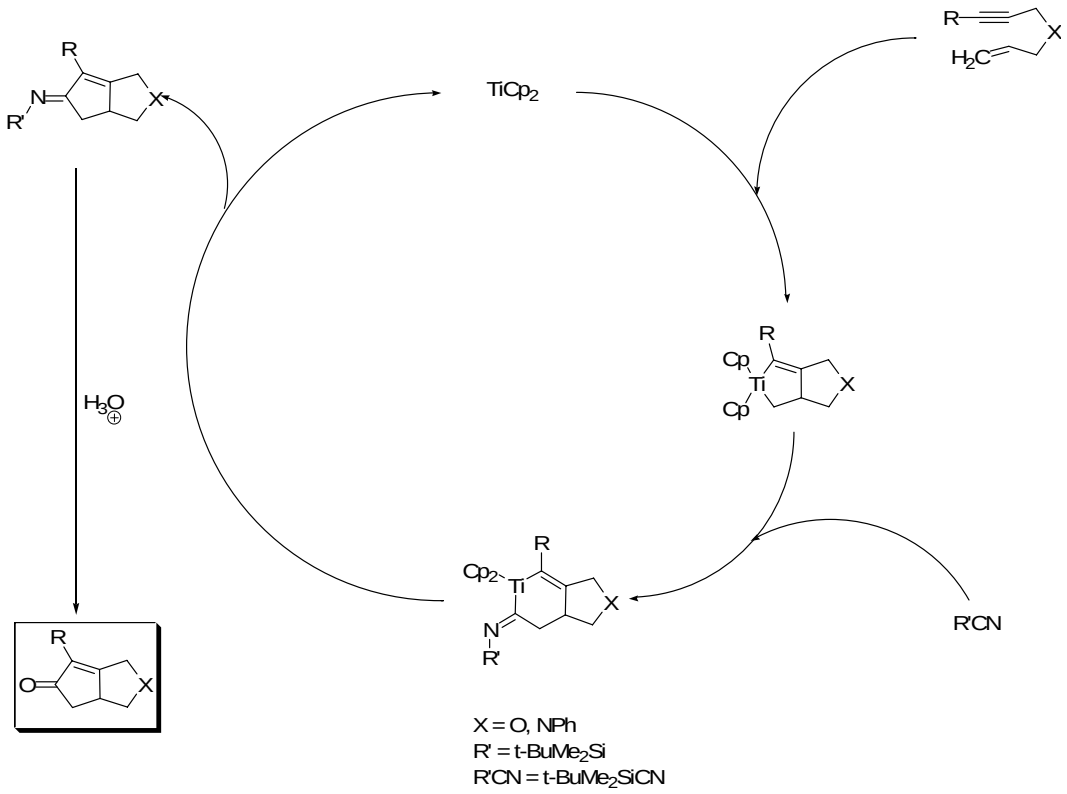
made in moderate yields. The molybdenum–alkyne complex that is used for the PK reactions are not as good as other transition metal complexes employed to execute the PK reaction.



Scheme **1.13.** An intramolecular Pauson–Khand reaction using a molybdenum metal complex.

1.7.4. Titanium Transition Metal Complex

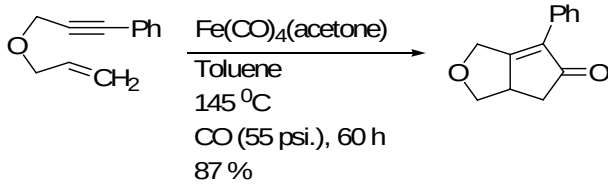
Buchwald and coworkers were the first to use titanium complexes to create bicyclic cyclopentenones hydrolyzed from iminocyclopentenones (Scheme **1.14**).[17] This reaction incorporated the use of $Cp_2Ti(PMe_3)_2$ catalytically with a CO insertion and substituted enynes to produce substituted bicyclic cyclopentenones in moderate to good yields.



Scheme **1.14.** Cyclopentanones synthesis using a titanium metal complex.

1.7.5. Iron Transition Metal Complex

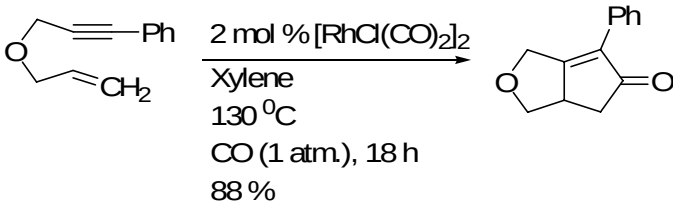
Pearson and coworkers were the first to use an iron carbonyl complex to do an intramolecular Pauson–Khand cycloaddition on enyne and diyne substrates (Scheme **1.15**).[18] Pearson stated that the iron carbonyl complexes were cheaper to purchase than the corresponding dicobalt octacarbonyl complexes.



Scheme **1.15.** An intramolecular Pauson–Khand reaction using an iron transition metal complex.

1.7.6. Rhodium Transition Metal Complex

Naraska and coworkers purchased a commercially available Rhodium di–nuclear complex, $[RhCl(CO)_2]_2$, to prepare an intramolecular Pauson–Khand reaction utilizing 1,6–enynes and carbon monoxide at atmospheric pressure catalytically (Scheme **1.16**).[19] The procedure that was created by Naraska and coworkers can be used on both *N,N*–allyl propargyl sulfonamides and allyl propargyl ethers to make derivatized cyclopentenones. The cyclopentanones made from this procedure were made in moderate to excellent yields.

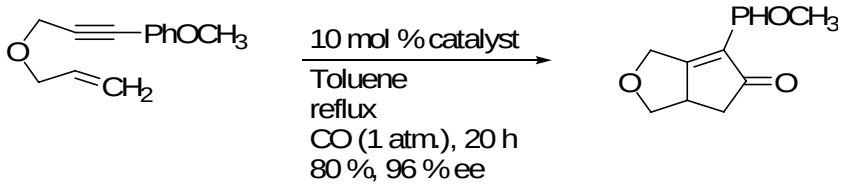


Scheme **1.16.** An intramolecular Pauson–Khand reaction using a dirhodium complex.

1.7.7. Iridium Transition Metal Complex

Shibata and coworkers made a chiral iridium(I) catalyst to produce cyclopentanones with high enantioselectivity from either an inter or intramolecular Pauson–Khand reaction.[20] It used

1,6–enynes and other similar substrates with CO at atmospheric pressure and a chiral iridium–phosphine complex (Scheme **1.17**). The reaction produced cyclopentenones at moderate–good yields with high ee. The chiral catalyst was prepared *in situ* from commercially available $[Ir(COD)Cl]_2$ and tolBINAP. The iridium complex employed in the Pauson–Khand reaction of this paper was originally used for hydrogenation reactions.



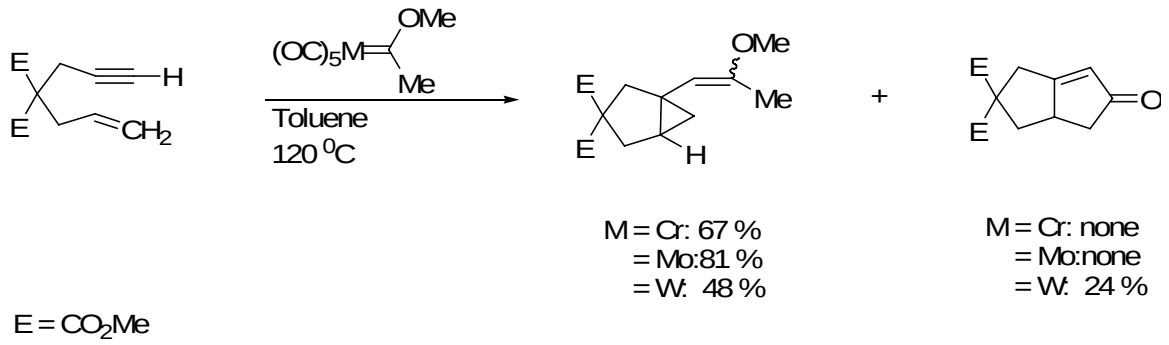
catalyst = $[Ir(COD)Cl]_2$ + 2(*S*)-tolBINAP

Scheme **1.17.** Catalytic intramolecular Pauson–Khand reaction using a chiral iridium catalyst made *in situ*.

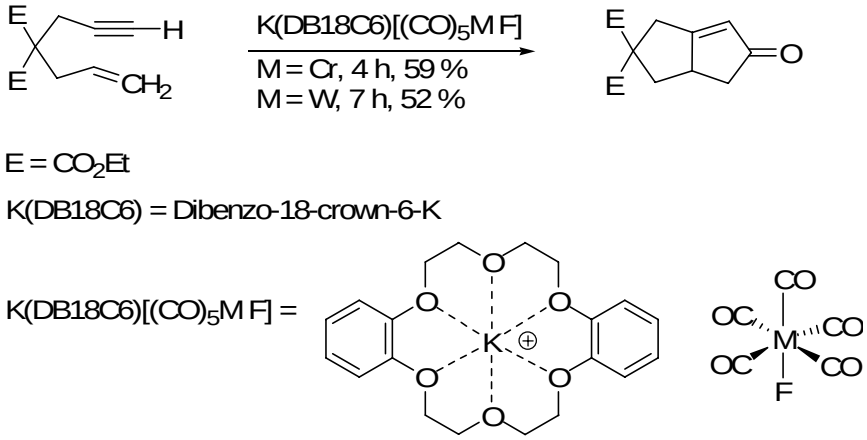
1.7.8. Tungsten and Chromium Transition Metal Complexes

Hoye and coworkers compared utilizing group six transition metal Fisher carbene complexes with a variety of 1,6–enynes.[21] They were able to obtain substituted cyclopropane substrates from any of the group six Fisher carbene complexes. It was discovered that the molybdenum carbenes reacted faster than the chromium carbenes which in turn reacted faster than the tungsten carbenes in the reactions that were done. In addition to producing the substituted cyclopropane substrates; the tungsten carbenes also produced a bicyclic cyclopentenones and it was hypothosized that it was made because the tungsten carbene reacts slower and can make a seven–coordinate intermediate and allow the CO insertion to take place and also allow the subsequent reductive elimination (Scheme **1.18**).

Moreto demonstrated that an intramolecular Pauson–Khand reaction can be done from 1,6–enynes and a protodesilyated group six transition metal carbene complexes.[22-25] The protodesilyated carbene complexes were prepared *in situ* from fluoride ions to activate the complexes (Scheme **1.19**).



Scheme **1.18.** Synthesis of cyclopentanones using Group VI carbenes.

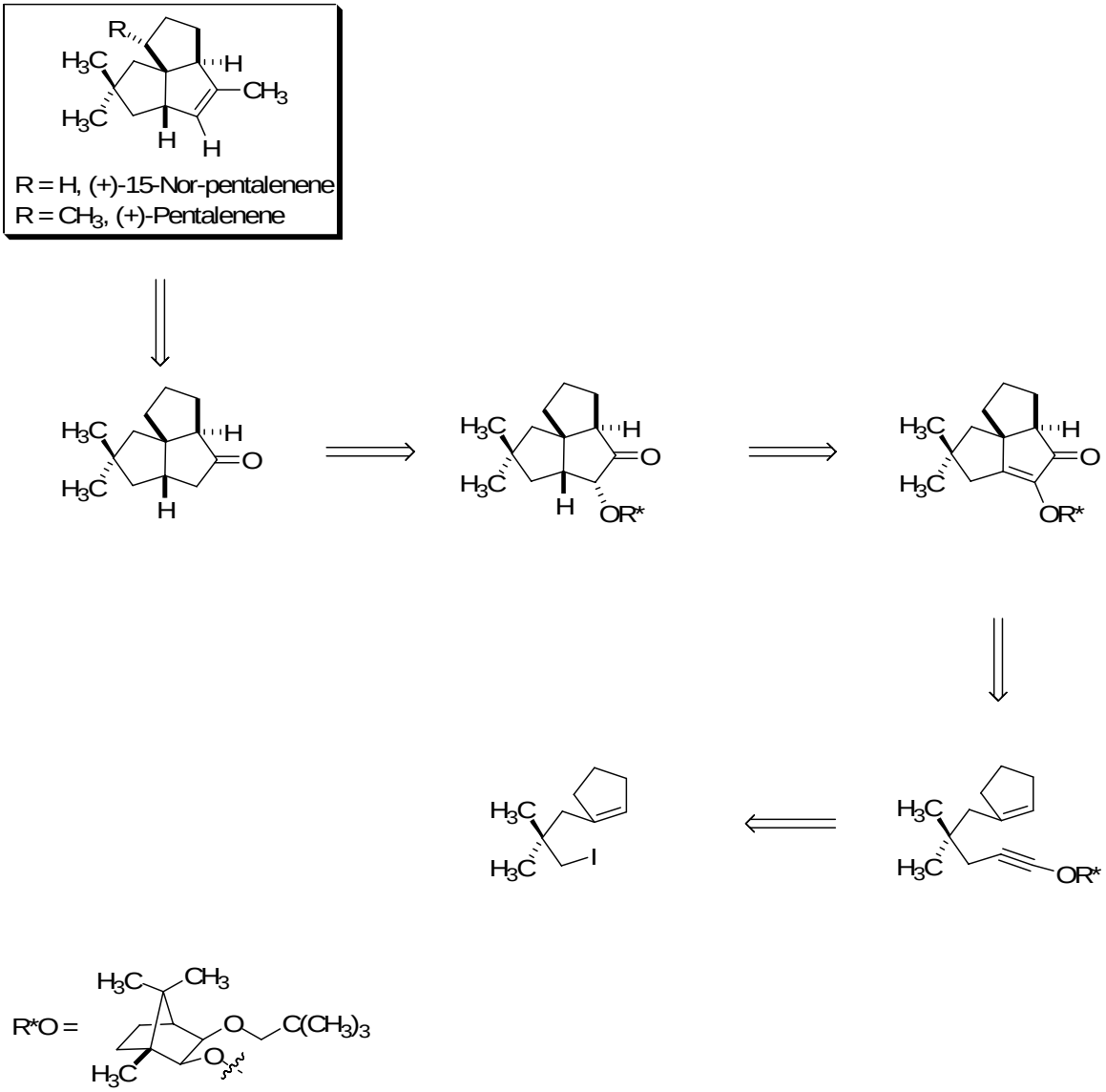


Scheme **1.19.** An intramolecular Puson–Khand reaction using Group VI carbenes generated in situ from fluoride ions.

1.8. Synthetic Utility

The Pauson–Khand reaction can be used to synthesize a variety of complex molecules found in natural products that contain cyclopentenone moieties and exhibit interesting biological and chemical properties. Here are a few examples of synthesized cyclopentenone natural products made from the PK reaction. Both Moyano and Pericas reported synthesizing (±)–15–nor–pentalenene from an intramolecular PK reaction (Scheme **1.20**).[26] The (±)–15–nor–pentalenene is interesting, because is that it shares the same core structure as (+)–pentalenene. (+)–Pentalenene was first synthesized by Paquette and coworkers.[27] Because of problems at the C–9 juncture, it resulted in the racemization of the final product. Hua reported the first

enantioselective synthesis of (+)–pentalenene.[28] It was created from a racemic *cis*–crotyl phenyl sulfoxide and (–)–S–7,7–dimethyl bicycle[3.3.0]–2–octen–3–one and used an intramolecular Pauson–Khand reaction. He never produced (±)–15–nor–pentalenene. An advantage of the Pauson–Khand reaction is that the stereocenters are set after the reaction is completed.

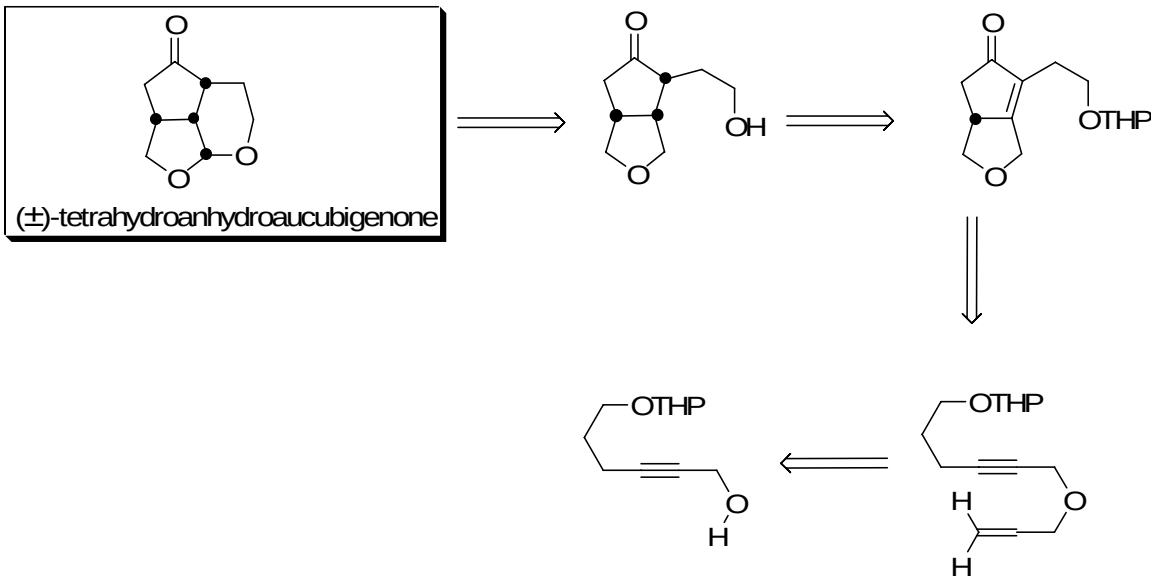


Scheme **1.20.** Retro–synthesis of (±)–15 nor–pentalenene using an intramolecular Pauson–Khand.

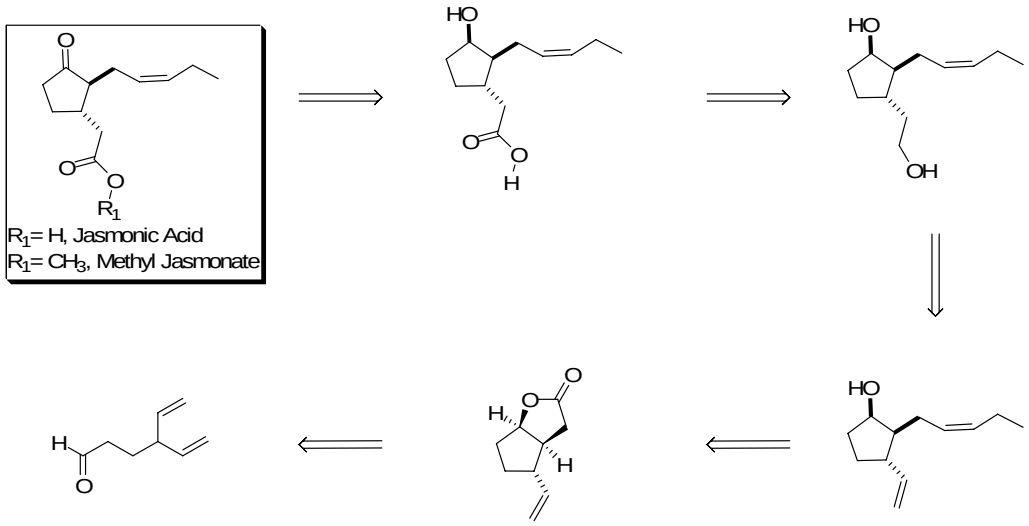
Billington reported the synthesis of (±) tetrahydroanhydroaucubigenone from an intramolecular Pauson–Khand cycloaddition utilizing substituted allyl–propargyl ethers (Scheme

1.21).[29] The synthesis of (±) tetrahydroanhydroaucubigenone was done in few steps from commercially available reagents.

Methyl jasmonate was synthesized using the hetero Pauson–Khand reaction. The synthesis of this substrate will be discussed further in Chapter 3 (Scheme **1.22**).

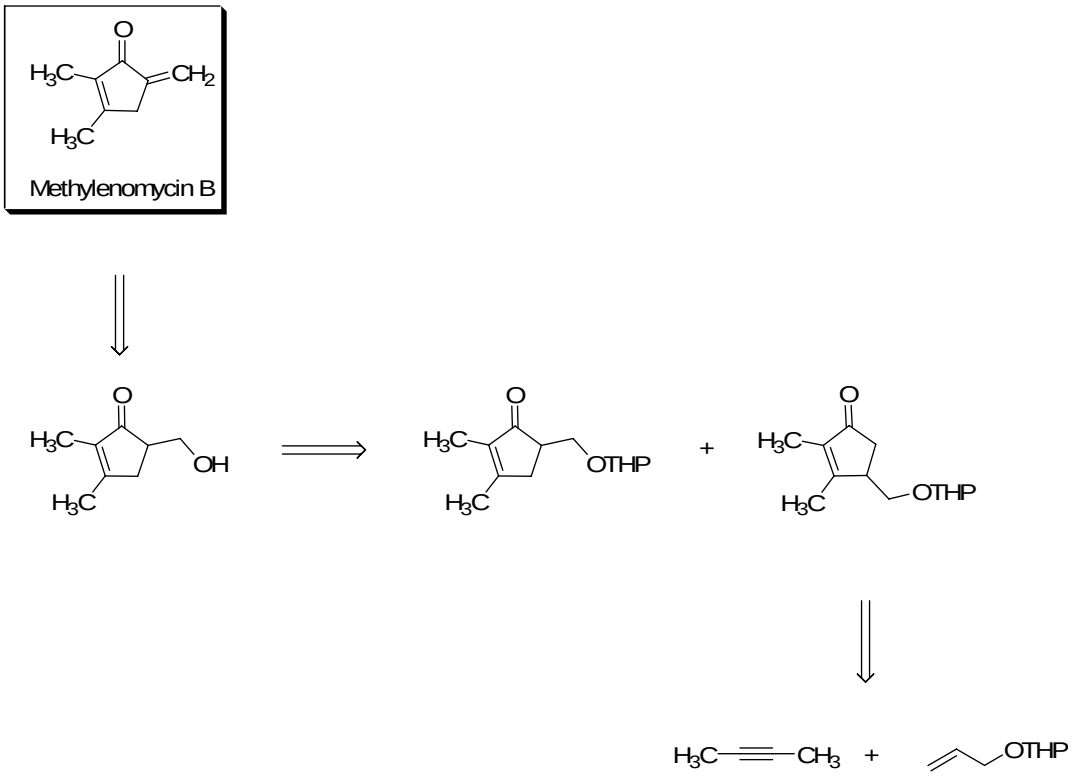


Scheme **1.21.** Total synthesis of (±) tetrahydroanhydroaucubigenone using an intramolecular Pauson–Khand.



Scheme **1.22.** Total synthesis of methyl jasmonate using an intramolecular hetero Pauson–Khand reaction.

The natural product methylenomycin B was made by Billington using an intramolecular Pauson–Khand reaction (Scheme **1.23**).[30] Jernow and coworkers were the first to produced methylenomycin B from 2,3–dimethyl cyclopent–2–en–1–one.[31] A mistake because the structure of methylenomycin A was as incorrectly assigned as methylenomycin B.[32] Methylenomycin A structure contains an oxirane whereas methylenomycin B structure does not contain an epoxide.

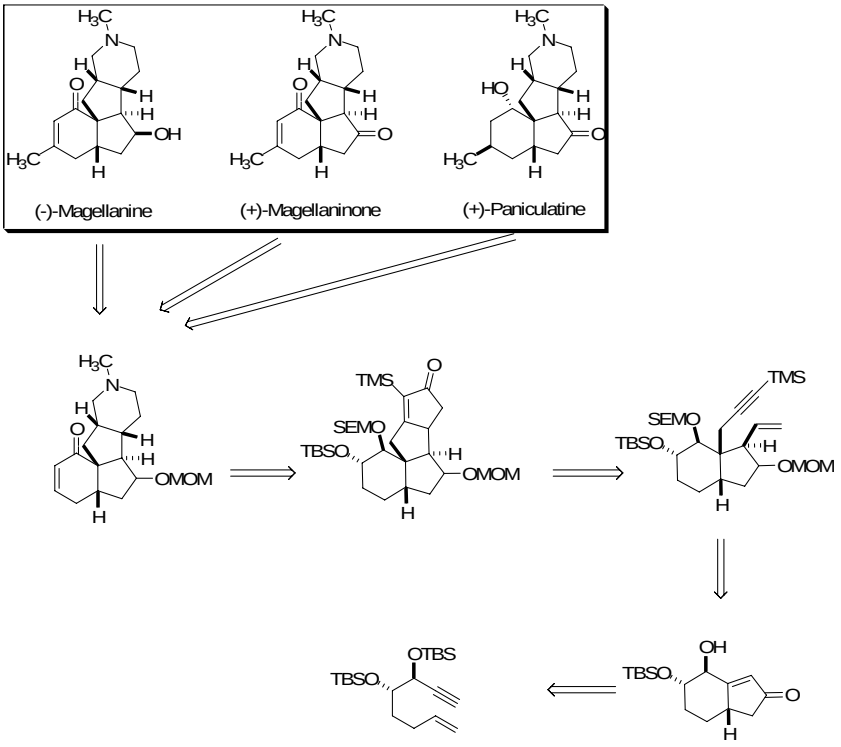


Scheme **1.23.** Total synthesis of methylenomycin B from an intramolecular Pauson–Khand reaction.

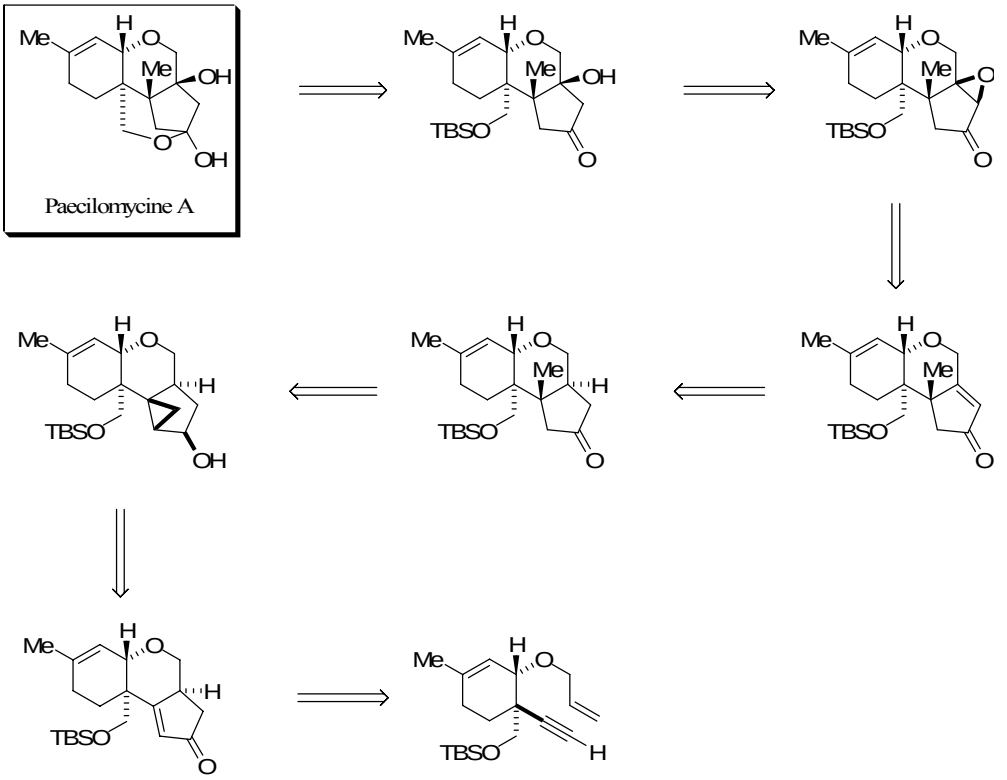
Mukai reported the syntheses of (–)–magellanine, (+)–magellaninone, and (+)–paniculatine from two intramolecular Pauson–Khand reactions which was the main step in producing the 6–5–5–6 macrocycle (Scheme **1.24**). (–)–Magellanine was synthesized in 43 steps and at 1.7% yield, (+)–Magellaninone was made in 43 steps in 1.9% yield and (+)–paniculatine was produced in 45 steps with an overall yield of 2.8%.[33] Overman and coworkers were the first to make (–)–magellanine and (+)–magellaninone from the Prins–pinacol

rearrangement to produce the 6–5–5–6 core structure.[34] Both (–)–magellanine and (+)–magellaninone and were both created in 25–26 steps from the starting reagent (1*R*,5*S*)–bicycle[3.2.0]heptenone. Sha was the first to create (+)–paniculatine using an α–carbonyl radical–initiated tandem cyclization to make a tricyclic ketone core structure.[35] This tricyclic structure was converted to (+)–paniculatine in two steps. An advantage of the Mukai and coworkers synthetic strategy is that (–)–magellanine, (+)–magellaninone, and (+)–paniculatine can all be made from the same starting reagents using two intramolecular Pauson–Khand reactions.

Danishefsky and coworkers were the first group to synthesize Paecilomycine A.[36] Paecilomycine A was made from a Diels–Alder cycloaddition and an intramolecular Pauson–Khand reaction (Scheme **1.25**). The enyne employed in the intramolecular Pauson–Khand reaction proved problematic because only 37 % of the desired product was obtained.



Scheme **1.24.** Total synthesis of (–)–magelanine, (+)–magellaninone, and (+)–paniculatine from two tandem intramolecular Pauson–Khand reactions.



Scheme **1.25.** Synthesis of paecilomycine A using an intramolecular Pauson–Khand reaction.

1.9. References

1. Pauson, P. L.; Khand, I. U.; Knox, G. R.; Watts, W. E. *J. Chem. Soc. Chem. Comm.* **1971**, 36.

2. Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977-981.

3. Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32-42.

4. Brummond, K. M.; Kent, J. L. *Tetrahed.* **2000**, *56*, 3263-3283.

5. Gibson, S. E.; Mainolfi, N. *Angew. Chem. Int. Ed.* **2005**, *44*, 3022-3037.

6. Gibson, S. E.; Stevenazzi, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1800-1810.

7. Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436-5438.

8. Pauson, P. L. *Tetrahed.* **1985**, *41*, 5855-5860.

9. Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289-5292.

10. Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771-773.

11. Rautenstrauch, V.; Megard, P.; Conesa, J.; Kuester, W. *Angew. Chem.* **1990**, *102*, 1441-1443 (See also Angew Chem , Int Ed Engl , 1990, 1429(1412), 1413-1416).

12. Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637-7640.

13. Belanger, D. B.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7641-7644.

14. Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568-2569.

15. Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286-1288.

16. Mukai, C.; Uchiyama, M.; Hanaoka, M. *J. Chem. Soc. Chem. Comm.* **1992**, 1014-1015.

17. Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 4912-4913.

18. Pearson, A. J.; Dubbert, R. A. *J. Chem. Soc. Chem. Comm.* **1991**, 202-203.

19. Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249-250.

20. Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852-9853.

21. Hoye, T. R.; Suriano, J. A. *Organometal.* **1992**, *11*, 2044-2050.

22. Cihonski, J. L.; Levenson, R. A. *Inorg Chem.* **1975**, *14*, 1717-1720.

23. Gokel, G. W.; Cram, D. J.; Liotta, C. L.; Harris, H. P.; Cook, F. L. *J. Org. Chem.* **1974**, *39*, 2445-2446.

24. Jordi, L.; Segundo, A.; Camps, F.; Ricart, S.; Moreto, J. M. *Organometal.* **1993**, *12*, 3795-3797.

25. Pedersen, C. J. *Org. Synth.* **1972**, *52*, 66-74.

26. Tormo, J.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4851-4856.

27. Annis, G. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4504-4506.

28. Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835-3837.

29. Billington, D. C.; Willison, D. *Tetrahedron Lett.* **1984**, *25*, 4041-4044.

30. Billington, D. C.; Pauson, P. L. *Organometal.* **1982**, *1*, 1560-1561.

31. Jernow, J.; Tautz, W.; Rosen, P.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 4212-4213.

32. Jernow, J.; Tautz, W.; Rosen, P.; Blount, J. F. *J. Org. Chem.* **1979**, *44*, 4210-4212.

33. Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147-10154.

34. Hirst, G. C.; Johnson, T. O. J.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992-2993.

35. Sha, C.–K.; Lee, F.–K.; Chang, C.–J. *J. Am. Chem. Soc.* **1999**, *121*, 9875-9876.

36. Min, S.-J.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2199-2202.

CHAPTER 2

α–METHYLENE–γ–BUTYROLACTONE SYNTHESIS AND BACKGROUND VIA THE HETERO PAUSON–KHAND REACTION

2.1. Introduction

An allene is a 1,2–diene system and the smallest allene unit is called propadiene. This is illustrated in Figure **2.1**. The first allenic acid, glutinic acid, was synthesized in 1887 by Burton,[1] but its structure was confirmed by ultraviolet absorption and infrared spectrometry in 1954.[2]

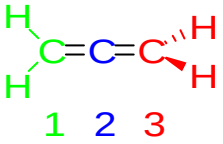


Figure **2.1.** An unsubstituted allene.

Allenes can be found and isolated from a variety of natural products. Mycomycin or 3,5,7,8,–tridecatetracene–10,12–diynoic acid is the second naturally occurring allene $C_{13}H_{10}O_2$. It was isolated from *Norcardia acidophilus* by Johnson and Burdon in *1947* and it is an antibiotic. Dr. Walter D. Celmer and Dr. I. A. Solmons were later able to isolate mycomycin as a colorless crystalline needle(s) when it was crystallized in dichloromethane, CH_2Cl_2, at –40 ^{0}C (Figure **2.2)**.[3-6]

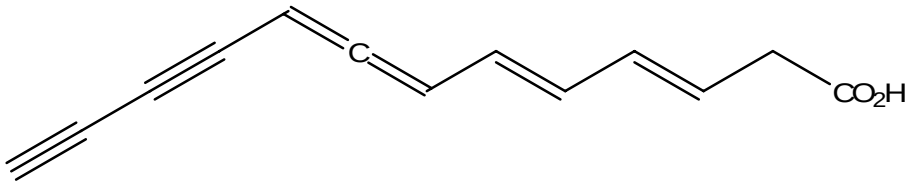


Figure **2.2.** The second naturally occurring allene compound.

Allenes are interesting compared to an olefin because it has two consecutive double bonds that can be used in synthetic reactions. Allenes can be mono, di, tri or tetra–substituted (Figure **2.3)**.

Today, allenes can be synthesized in a variety of ways and these methods have been summarized in review articles.[7-21]

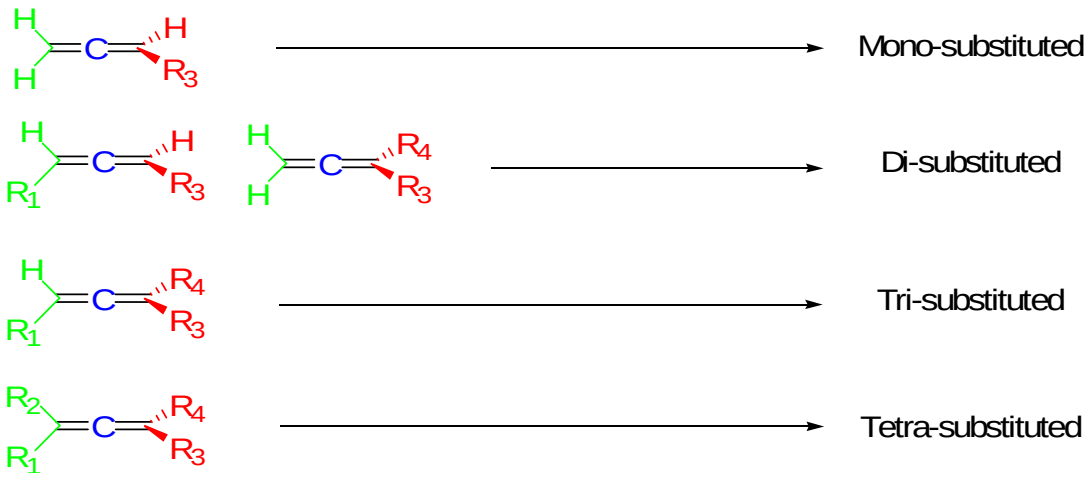
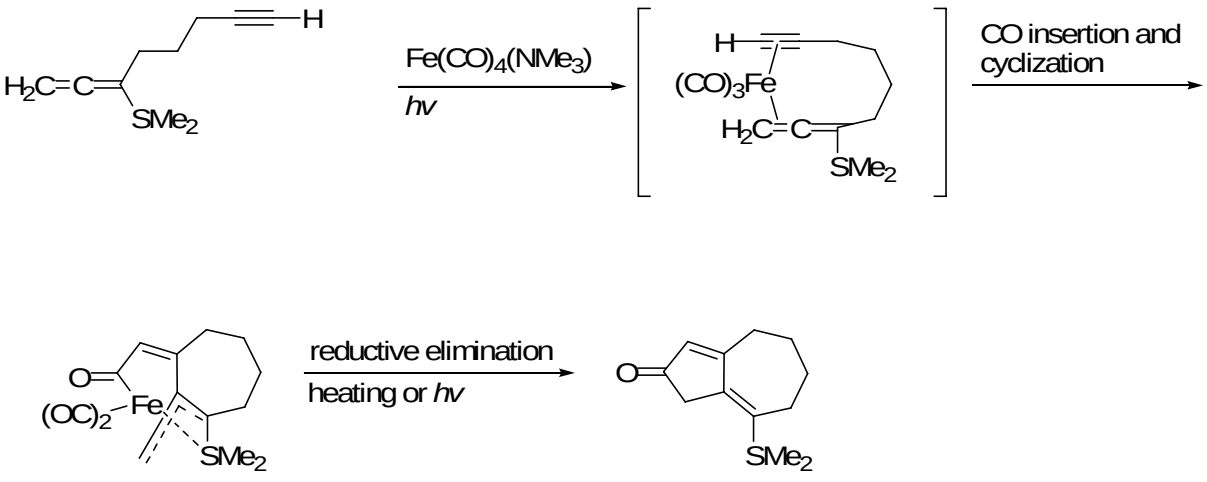


Figure **2.3.** Mono, di, tri and tetra–substituted allenes.

2.2. The First Allenic Pauson–Khand Reaction

The allenic Pauson–Khand was first done by Narasaka and coworkers[22, 23] They discovered that 4–alkylidene cyclopentanones or dienones can be made from photo irradiation, $Fe(CO)_4(NMe_3)$, at ambient temperatures. The dienone was formed from an η^3–allyl mononuclear iron complex intermediate and the structure was isolated and identified using x–ray crystallography (Scheme **2.1**).[24]



Scheme **2.1.** The first allenic intramolecular Pauson–Khand reaction.

2.3. Allenic π–Bond Selectivity

The regular allenic Pauson–Khand reaction demonstrates that an *allenic alkyne* can be reacted via two pathways. The reaction through pathway 1 uses the internal π–bond of the allene to produce an α–methylene cyclopentenone or compound A. The reaction through pathway 2 uses the external π–bond of the allene to create a 4–alkylidene cyclopentenone or compound B.[25, 26] This is illustrated in Figure **2.4**.

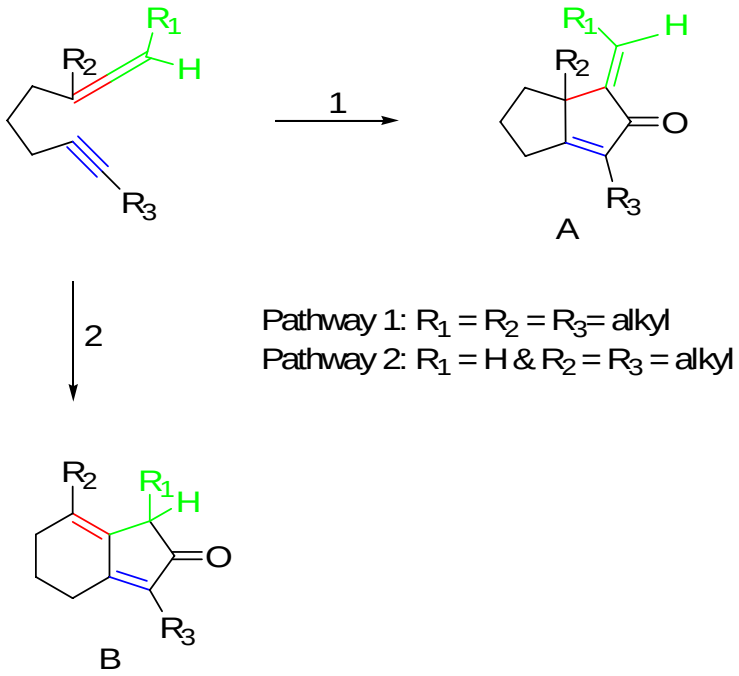
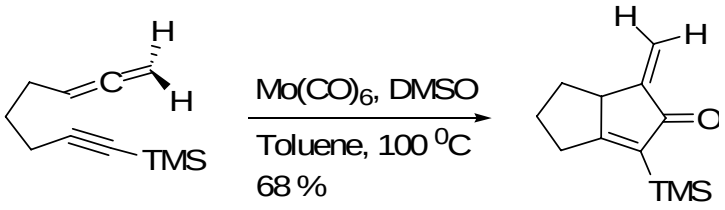


Figure **2.4.** π–Bond selectivity of allenes.

2.3.1. Mono–Substituted Allenes

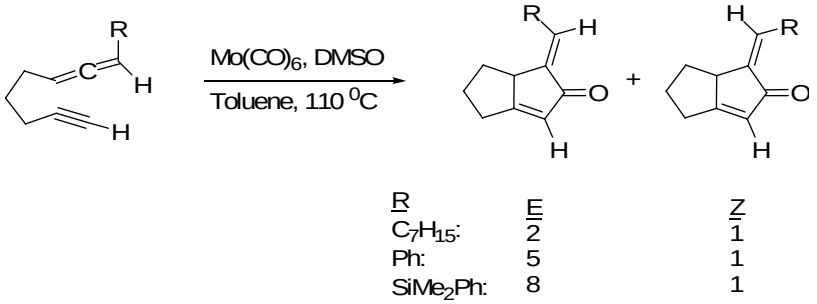
It was discovered that mono–substituted allenes reacted via the internal π–bond and pathway 1 to produce an α-methylene cyclopentenone (Scheme **2.2**).[25-27]



Scheme **2.2.** An intramolecular PK reaction of mono–substituted allene.

2.3.2. 1,3–Disubstituted Allenes

1,3–Disubstituted allenes also produced the same results as the mono–substituted allenes when the Pauson–Khand conditions are applied to the starting substrate. When using transition metal complexes such as $Co_2(CO)_8$ and $Mo(CO)_6$ with 1,3–disubstituted allenes, α–methylene cyclopentenone products are formed as a mixture of E– and Z–isomers. Because carbonyl ligands are not sterically bulky, moderate E–selectivity can be produced when using a limited group of substrates with sterically bulky terminal groups on 1,3–disubstituted allenes (Scheme **2.3**).[23,25,26] It was discovered that by changing the metal complex and ligands used in the reaction, the product ratio and regiochemistry can be controlled.



R	E	Z
C_7H_{15}:	2	1
Ph:	5	1
$SiMe_2Ph$:	8	1

Scheme **2.3.** An intramolecular PK reaction of a 1,3–disubstituted allenes.

When a transition metal complex such as $Cp_2Zr(n\text{-}Bu)_2$ is used, only the E–isomers were obtained. This is because the cyclopentadienyl ligands, Cp, produced unfavorable steric interactions with the R–group on the end of the allene. This is shown in Figure **2.5**. Pathway 1 shows the unfavorable steric interaction between the Cp ligands and R_1. Pathway 2 shows the favorable steric interaction between the Cp ligands and R_1.[25]

2.3.3. 3,3–Disubstituted Allenes

3,3–Disubstituted allenes react via pathway 2 and the external π–bond. The reason for this observation is that the reaction is taking place at the least hindered π–bond (Scheme **2.4**).[23, 26]

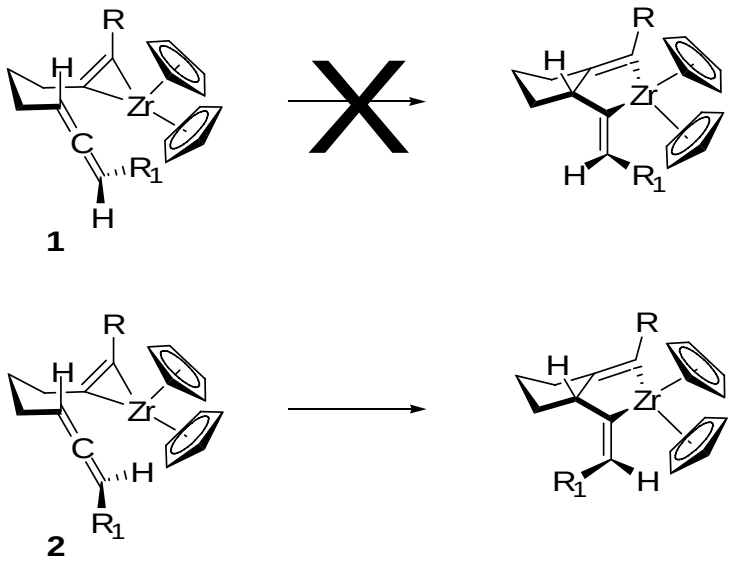
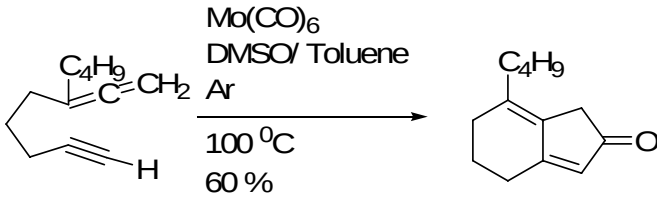


Figure **2.5.** Unfavorable steric interactions between the cyclopentadienyl ligands and R_1.

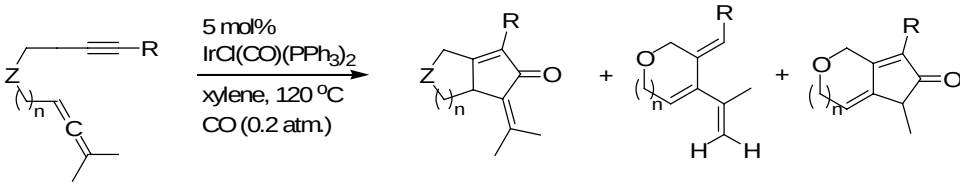


Scheme **2.4.** An intramolecular PK reaction of 3,3–disubstituted allene.

2.3.4. 1,1,3–Trisubstituted Allenes

Trisubstituted allenes also react using the least hindered π–bond.[25,26,28,29] Shibata and coworkers used an iridium complex, CO at 0.2 atm., and an allenyne substrate with two methyl groups at the end of the allene functionality to produce an α–methylene cyclopentenone as the major product and a triene as a by–product.[30] They did not create any diene substrate from this reaction. Next, they replaced the iridium complex with a rhodium transition metal complex and subjected it to the same reaction conditions and starting reactants. This time the first two products were prepared as the major compounds and a diene compound was also produced as the minor product. The percent yield of the α–methylene cyclopentenone decreased significantly while the percent yield of the triene increased significantly. Lastly, they used the same iridium transition metal complex and reaction conditions and changed only alkynyl allene substrate by

having only one methyl group on the terminus of the allene. The diene compound was the major product obtained, and α–methylene cyclopentenones as a mixture of E/ Z isomers. This reaction shows that this methodology is not only based on the reaction conditions, but also on the nature of the allenyne substrate (Scheme **2.5**).



R = Ph, Me, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, and Me_2PhSi
Z = O, TsN, and $(EtO_2C)_2C$

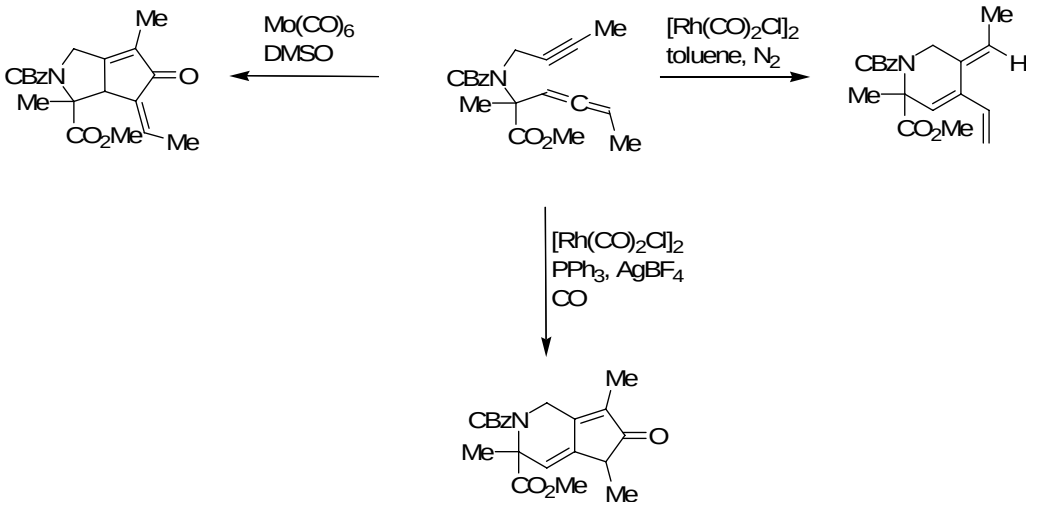
Scheme **2.5.** Syntheses of both α–methylene cyclopentanones and cyclic trienes.

2.3.5. Regio–chemistry and Atmospheric Gas Effects

Brummond reported the syntheses of three different substrates from a single alkynyl allene substrate (Scheme **2.6**). The outcome of the reaction depended on which type of transition metal complex used in the reaction and if the reaction was carried out in the presence or absence of a CO atmosphere. [31]

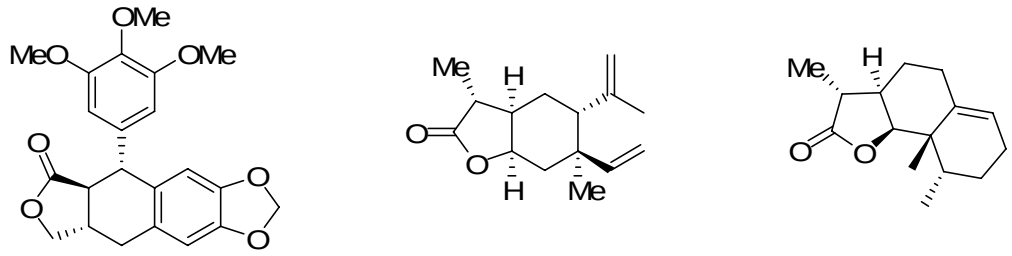
2.4. γ–Butyrolactones

γ–Butyrolactones are precursors to many different α–methylene–γ–butyrolactones found in nature.



Scheme **2.6.** Syntheses of three substrates from one synthesized starting material.

In nature, γ–butyrolactones exist as mono to polycyclic ring systems which can be found in more complex molecules. These compounds exhibit a wide range of biological properties, ranging from antibiotic to anti–inflammatory. These compounds are interesting candidates for new drugs.[32] Natural products can obtained from γ–butyrolactone intermediates and the methods to producing these compounds are summarized in several review articles.[32-36] Figure **2.6** shows a few γ–butyrolactone examples.



Isodeoxypodophyllotoxin Callitrin Dilatanolide A

Figure **2.6.** Several γ–butyrolactone examples

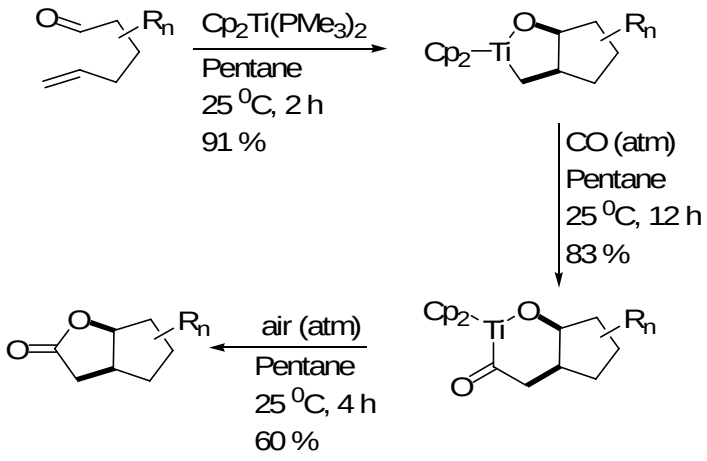
2.4.1. γ–Butyrolactones Syntheses Using Titanium in the Transition Metal Complex

Crowe and coworkers were the first to utilize a titanium complex for a stoichiometric intramolecular hetero Pauson–Khand reaction for the synthesis of bicyclic γ–butyrolactones (Scheme **2.7**). The phrase hetero Pauson–Khand reaction, HPKR, was coined because the carbonyl group replaces one of either alkyne or alkene substrate in the reaction.[37]

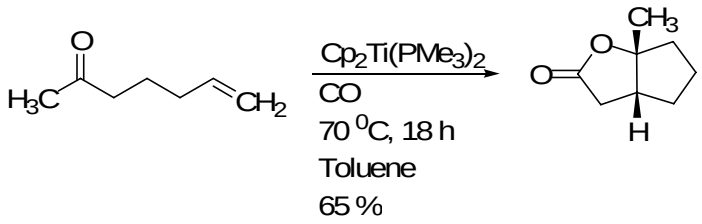
Buchwald and coworkers reported a titanium complex–mediated or titanium complex as a pre–catalyst HPK reaction for the diastereoslective synthesis of bicyclic γ–butyrolactones from enones (Scheme **2.8**).[38] Substituted γ–butyrolactones were also synthesized using catalytic amounts of either $Cp_2Ti(PMe_3)_2$ or $Cp_2Ti(CO)_2$ and aryl ketone substrates from enones. This method was limited to aryl ketone substrates (Scheme **2.9**).[39]

Crowe reported synthesizing γ–butyrolactones from completing an intramolecular HPK reaction using enals and enones and a catalytic amount of an asymmetric titanium catalyst. The

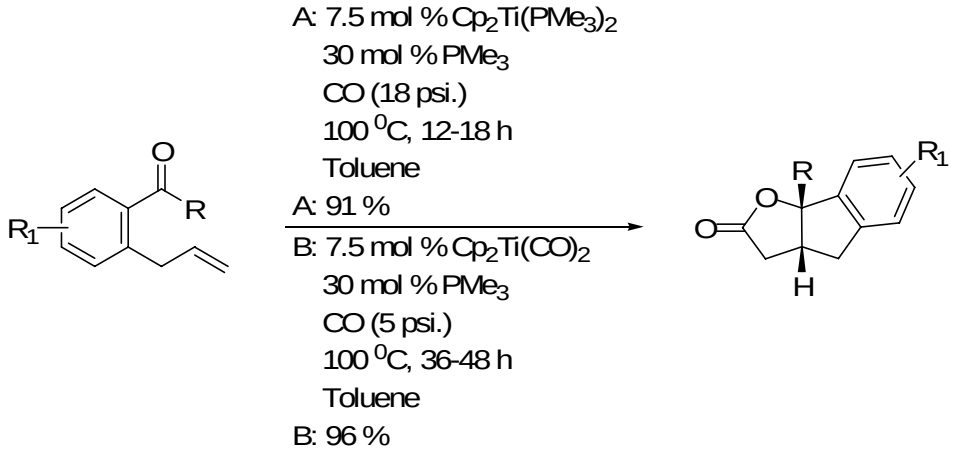
γ–butyrolactones were obtained in good–excellent yields and moderate–high enantioselectivity (Scheme **2.10**).[40]



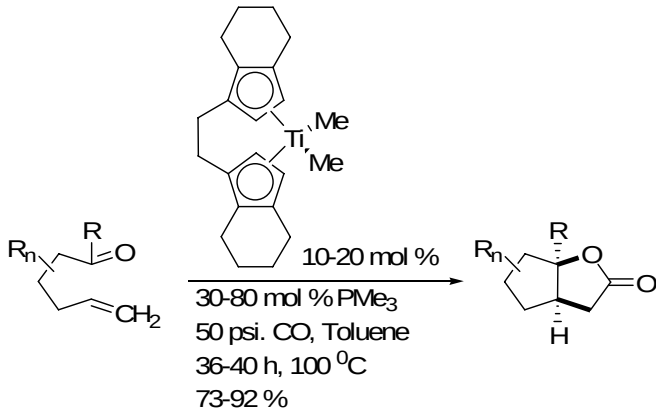
Scheme **2.7.** Syntheses of γ–butyrolactones from a titanium transition metal complex catalyst.



Scheme **2.8.** An intramolecular HPK reaction using titanium.



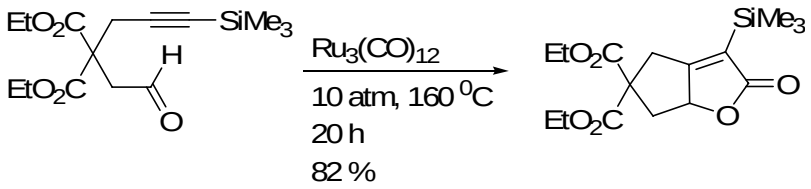
Scheme **2.9.** An intramolecular HPK reaction using a catalytic amount of a titanium complex.



Scheme **2.10.** HPK reaction using an asymmetric titanium catalyst.

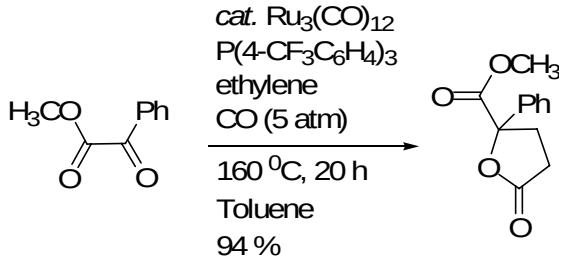
2.4.2. Ruthenium Catalyzed Synthesis of γ–Butyrolactones

Murai and coworkers reported that late transition metals such as ruthenium can facilitate the intramolecular HPK reaction (Scheme **2.11**).[41] They utilized yne–aldehydes substrates, CO, and a catalytic amount of $Ru_3(CO)_{12}$ for the reaction.



Scheme **2.11.** HPK reaction using a catalytic amount of a ruthenium complex.

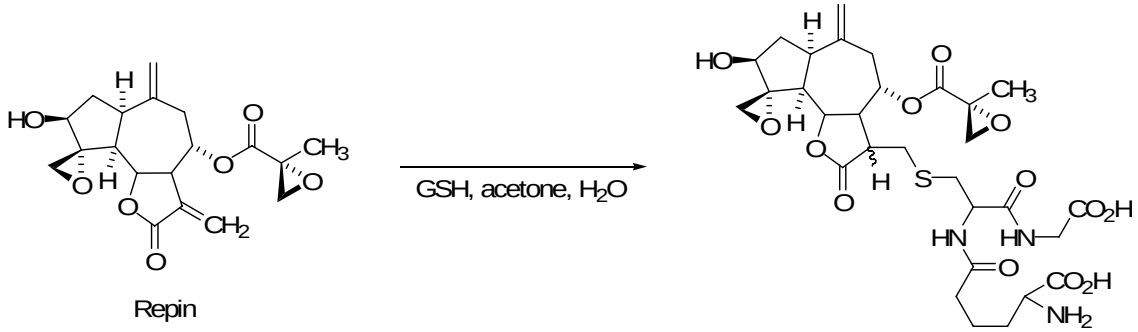
They also employed the same metal for an intermolecular HPK reaction to produce γ–butyrolactones (Scheme **2.12**). For this reaction, catalytic amounts of $Ru_3(CO)_{12}$, P(4-$CF_3C_6H_4)_3$, ethylene, CO and an aldehyde or ketone substrate were used to obtain the γ–butyrolactones. Unfortunately, they were not able to explain the effects of the phosphine on the proposed mechanism for the "role of a C=X (O or N) moiety adjacent to the ketones."[42]



Scheme **2.12.** An intramolecular HPK reaction using a ruthenium complex.

2.5. α–Methylene–γ–Butyrolactones

Compounds containing an α–methylene–γ–butyrolactone functionality make-up about 10 % of the known natural products.[43] α–Methylene–γ–butyrolactones exibit a wide range of biological activities. The activities discovered are anti-tumor, cytotoxic, allergic contact dermatitis, phytotoxic, antibiotics, insect anti-feedant, vertebrate poisoning, and chemoprophylaxis.[43-45] α–Methylene–γ–Butyrolactones are synthesized from a variety of methods that are summarized in several review articles.[33,36,43,44,46] Gadepalli and Rimoldi reported that repin bonds covalently with glutathione and other biological molecules with cysteine sulfhydryl groups at α–methylene functionality (Scheme **2.13**).[47]



GSH = Glutathione

Scheme **2.13.** Nucleophilic addition of GSH to Repin.

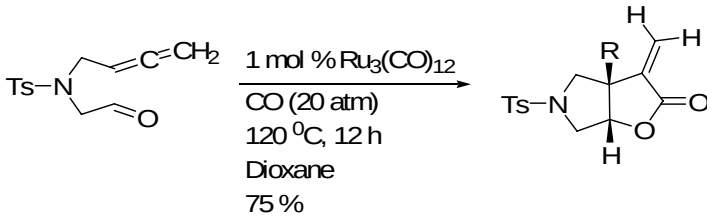
2.5.1. α–Methylene–γ–Butyrolactones Synthesis from Ruthenium Catalyzed Hetero–Pauson–Khand Reaction

Kang and coworkers reported a catalytic intramolecular HPK reaction on various substituted allenyl aldehyde and ketone substrates to produce α–methylene–γ–butyrolactones (Scheme **2.14**). They also synthesized α–methylene–γ–butyrolactam from a δ–allenyl imine in a 53 % yield.[48]

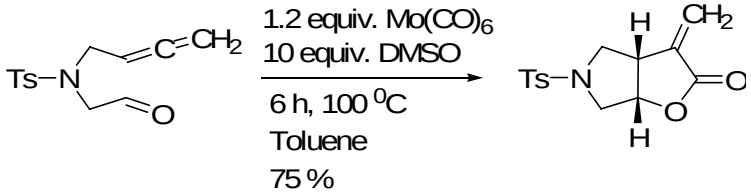
2.5.2. Molybdenum Mediated Cyclocarbonylation of α–methylene–γ–butyrolactones

Yu and coworkers demonstrated that they could accomplish intramolecular HPK reactions with substituted allenyl aldehydes and ketones substrates to produce α–methylene–γ–butyrolactones in moderate to good yields (Scheme **2.15**). They were not able to determine

what the role of DMSO was in the reaction or the reaction's exact mechanistic pathway. They just speculated on the probable reaction route.[27]



Scheme **2.14.** An allenic HPK reaction using a ruthenium catalyst.



Scheme **2.15.** An allenic HPK reaction using a molybdenum catalyst.

2.6. Project Overview

What is known is that from the literature is that substituted α–methylene–γ–butyrolactones are synthesized by incorporating ruthenium and molybdenum transition metal catalyst into HPK reactions.[27,48] Can α–methylene–γ–butyrolactones also be created by employing titanocene derived transition metal complexes? The focus of this project was to create mono, di, tri and tetra–substituted tethered allene aldehydes and allene ketones that will be converted to α–methylene–γ–butyrolactones using titanium mediated intramolecular hetero Pauson–Khand reaction. The general reaction scheme is presented in Figure **2.7**.

2.7. Discussion

The decision was made to use a tethered mono-substituted allene aldehyde substrate, since the goal of the project was to produce an α–methylene–γ–butyrolactone from a titanium promoted cyclocarbonylation (Scheme **2.16**). To accomplish this goal, it was decided to first

create the tether that will be used in the HPK reaction from a relatively cheap reagent, tetrahydrofuran.[49]

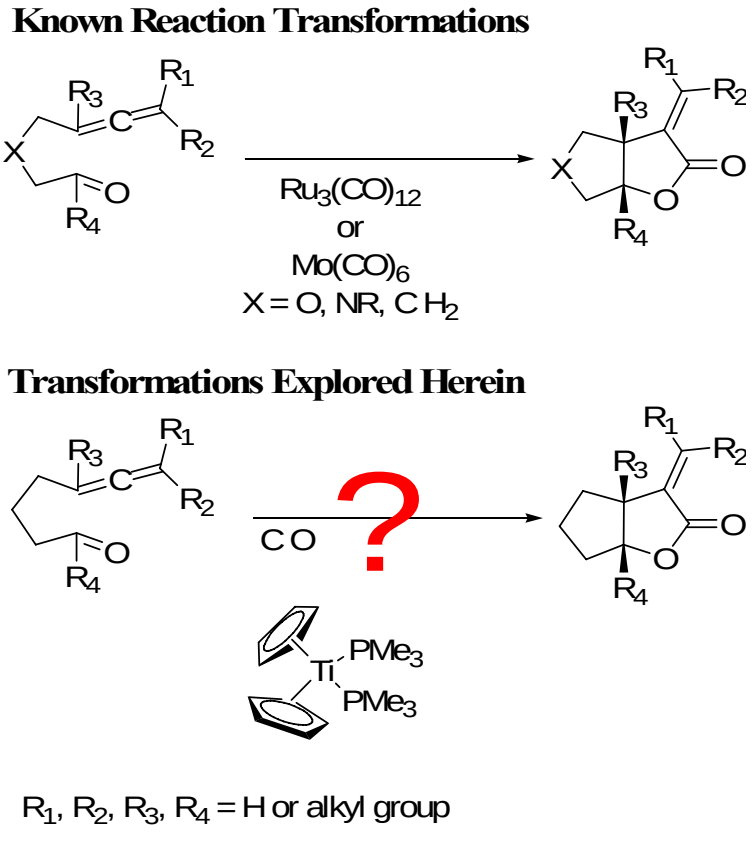


Figure **2.7.** A general allenic HPK reaction.

Scheme **2.16.** Production of the iodide starting material.

To further facilitate the goal of the project, it was decided to add the starting material to the propargyl chloride substrate and obtain compound **2.3**. Figure **2.8** shows the proposed mechanism to produce compound **2.3**.[50] After purification by column chromatography, a mixture of both products **2.2** and **2.3,** were obtained and determined by ^{1}H NMR. The overall yield was 50 percent (Scheme **2.17**). Based on the calculations about 30% of the final product was the unreacted iodide starting reagent. To obtain the mono–substituted allene substrate **2.3**;

we decided to try and trap the iodide starting material, **2.2**, by converting it into an ammonium salt and trapping it in silica gel during purification (Scheme **2.18**).[51]

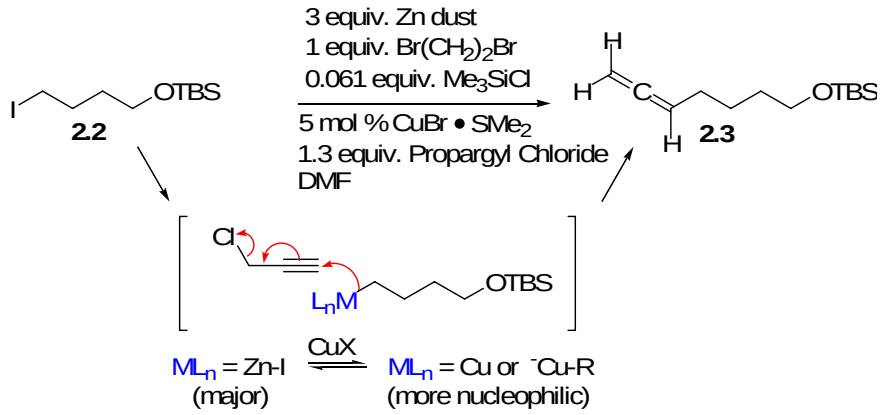
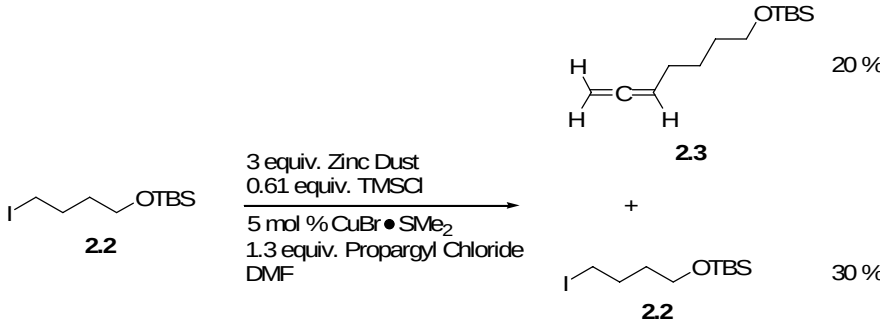
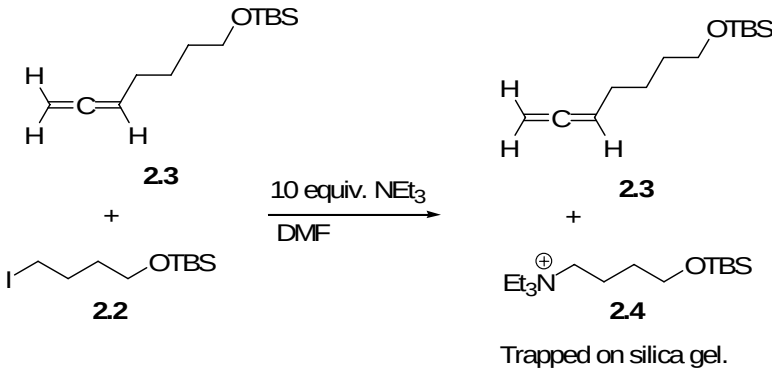


Figure **2.8.** Nucleophilic addition to the electrophile to make substrate **2.3**.



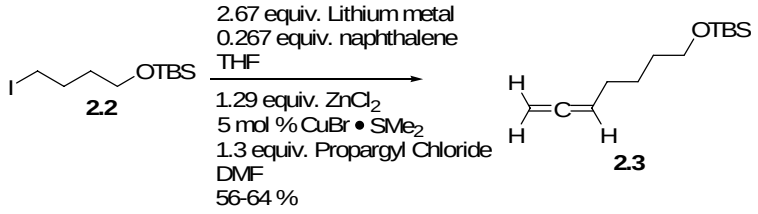
Scheme **2.17.** Syntheses of both products **2.2** & **2.3**.

The procedure generally worked, but the yields generated were not as good because of separating a mixture of products with a moderate to poor percent yield. We found a better method of activating the zinc was found. This method was called the Rieke zinc.



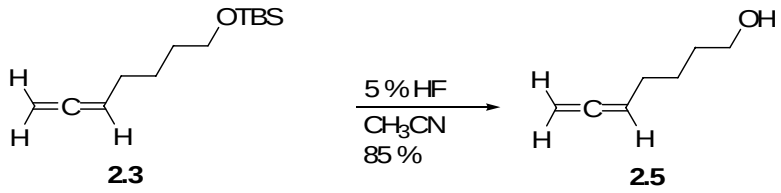
Scheme **2.18.** Trapping of the substrate **2.2** to produce only substrate **2.3**.

This particular method initially required the use of a catalytic amount of naphthalene, $C_{10}H_8$. The procedure was changed that to a stoichiometric amount because of low yields obtained from the reaction. The procedure gave only the protected allene **2.3** (Scheme **2.19**).[52, 53]



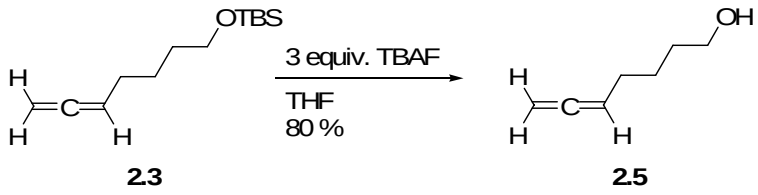
Scheme **2.19.** Synthesis of substrate **2.3** from the Reike Zinc method.

Next, 5 % hydrofluoric acid in acetonitrile was used to cleave the silyl ether protecting group from the protected allene. These reactions were done using glass containers and gave low yields. Since it was known that the fluoride anion somehow reacted with the boro–silicate glassware, the reactions were ran in polypropylene flasks (Scheme **2.20**).[54]



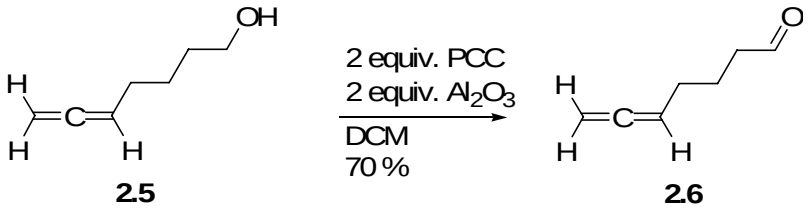
Scheme **2.20.** De–protection of the silyl ether group with HF to produce substrate **2.5** from **2.3**.

Milder conditions for the desilylation of the silyl ether group on substrate **2.3** were employed because of the hazards involved in using hydrofluoric acid (Scheme **2.21**).[55]



Scheme **2.21.** De–protection of the silyl ether group with TBAF to produce substrate **2.5** from **2.3**.

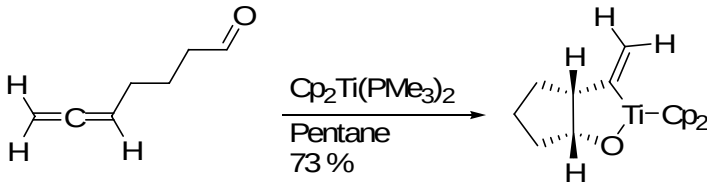
Oxidizing the primary allenic alcohol to the corresponding aldehyde worked well and produced the desired results (Scheme **2.22**).



2.5 **2.6**

Scheme **2.22.** Oxidation of the primary alcohol.

Substrate **2.7** was produced from the titanium metal–complex, $Cp_2Ti(PMe_3)_2$, insertion into substrate **2.5** (Scheme **2.23**).[56] A crystal structure was also obtained (Figure **2.9**). Unfortunately, none of the other allenic aldehyde or ketone substrates produced crystals that could be isolated.



2.6 **2.7**

Scheme **2.23.** Metallacycle prepared from a tethered mono–substituted allene.

A tethered mono–substituted allenic ketone substrate was synthesized to use in a HPK reaction (Scheme **2.24**). It was decided to prepare the silyl protected iodo tether first from 2–methyltetrahydrofuran. The procedure was similar to the previous allenic aldehyde substrate.[57] It was discovered that 2–methyltetrahydrofuran (**2.8**) would make two different substrates when compound **2.11** was oxidized. That is because 2–methyltetrahydrofuran was unsymmetrical and would produce *tert*–butyl–(4–iodo–1–methyl–butoxy)–dimethyl–silane and a *tert*–butyl–(4–iodo–pentloxy)–dimethyl–silane. The allenic enal substrate eluted first from the chromatography column and was followed by the allenic ketone substrate. The allenic ketone substrate was the major product and the allenic enal compound was the minor product.

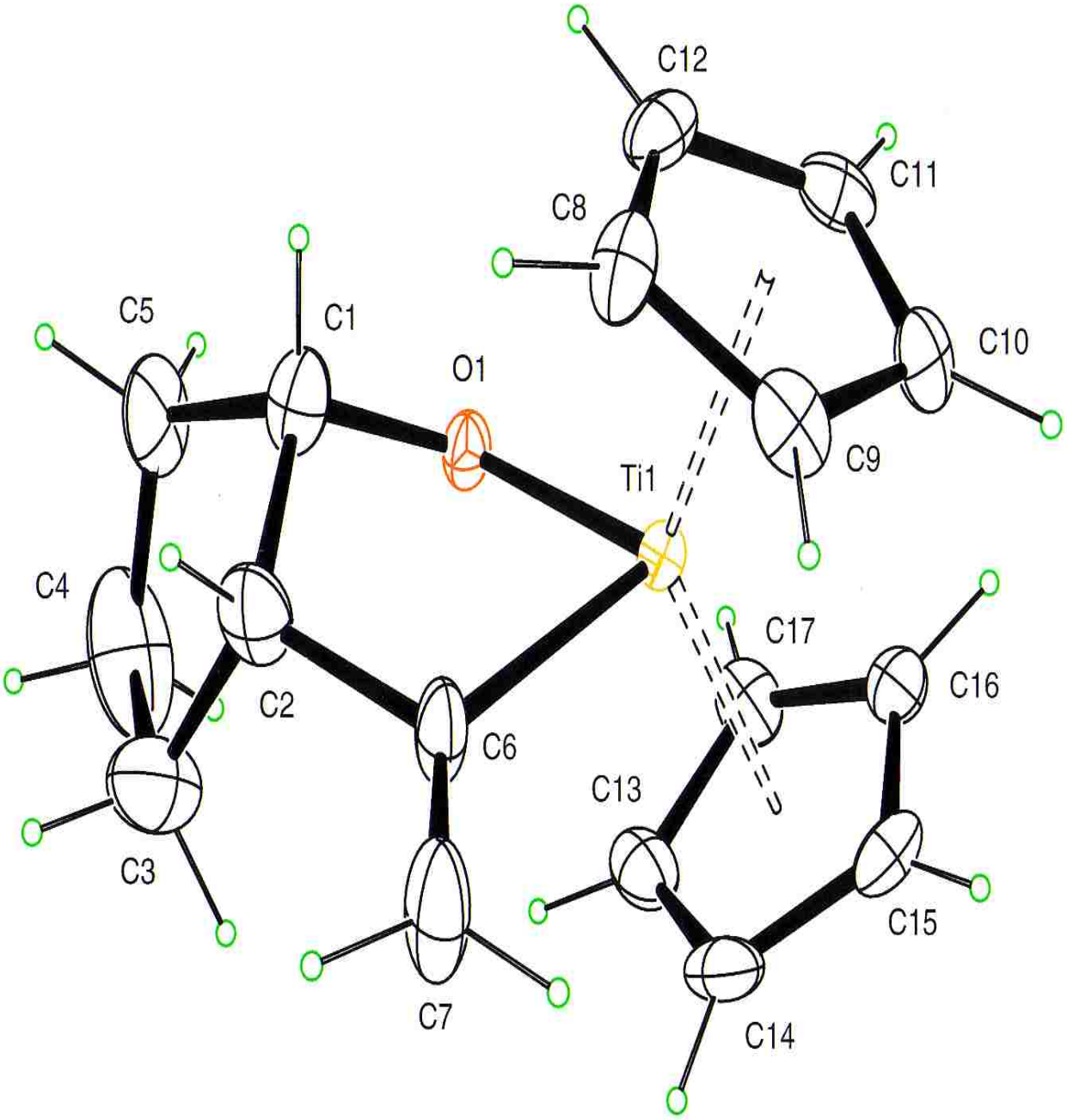
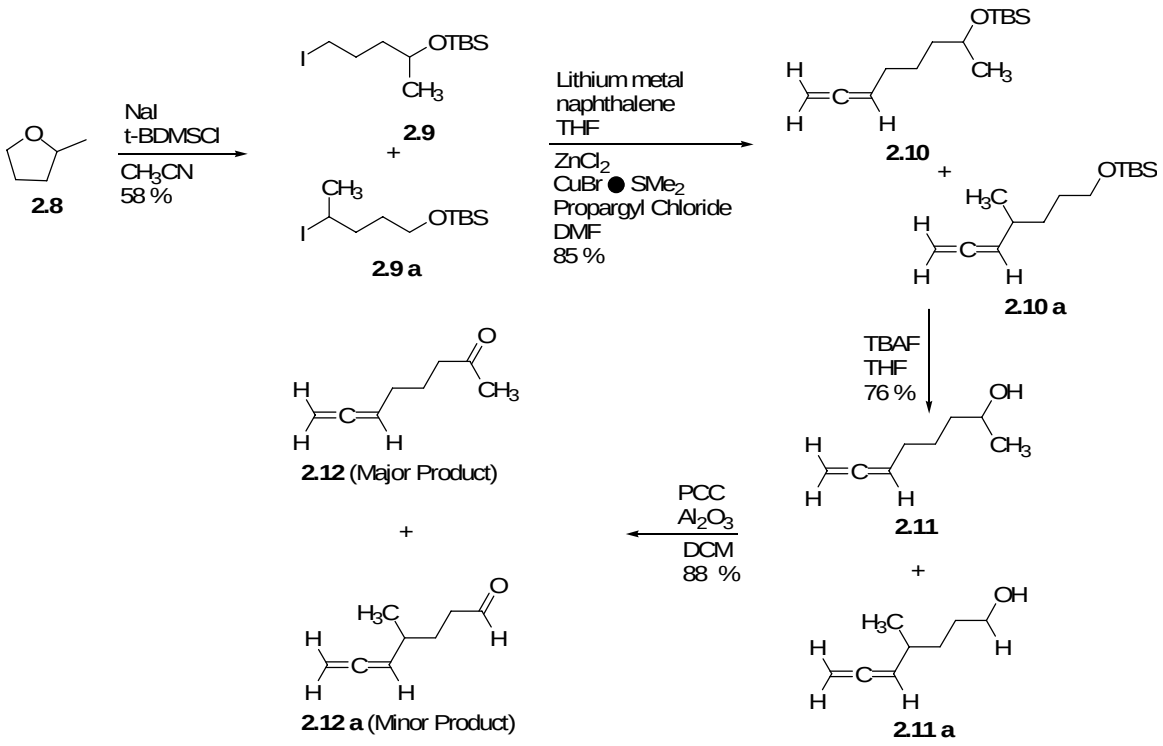
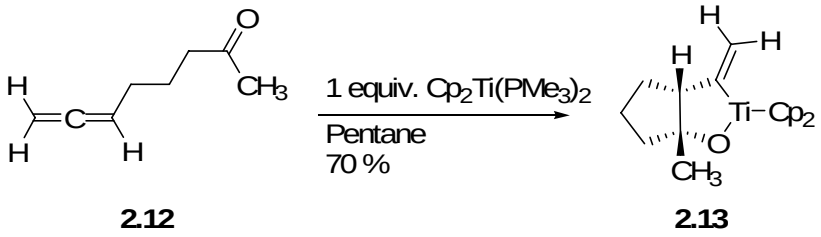


Figure **2.9.** ORTEP plot of substrate **2.7**.



Scheme **2.24.** Production of substrates **2.12** & **2.12a** from substrate **2.8**.

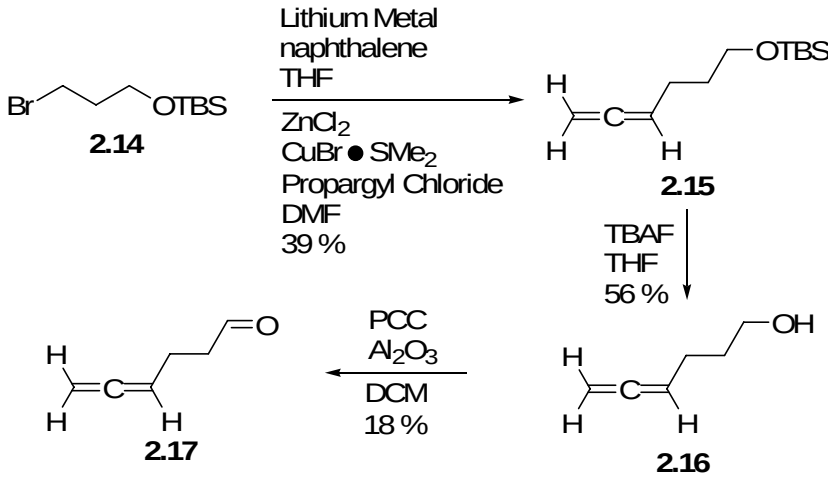
Metallacycle **2.13** was made in a 70 % yield from substrate **2.12** (Scheme **2.25**).



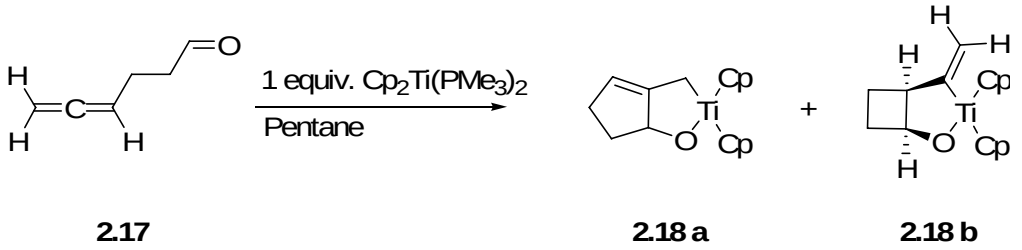
Scheme **2.25.** Metallacycle **2.13** produced from HPK reaction of substrate **2.3**.

What kind of allenic substrates would be made from a mono–substituted allene with a tether that was shortened by one methylene unit (Scheme **2.26**). If the internal π–bond of hex–4,5–dienal would react with the titanium complex in the metal insertion; we obtain substrate (**2.18 b**). It was hypothesized that the major product would the bicyclic substrate, **2.18 a**, created from the metal insertion with the titanium complex and the external π–bond (Scheme **2.27**). That is because a five–membered ring in more stable than a four–membered ring. The

same procedures used to make the first mono–substituted allene were used on this particular allene.

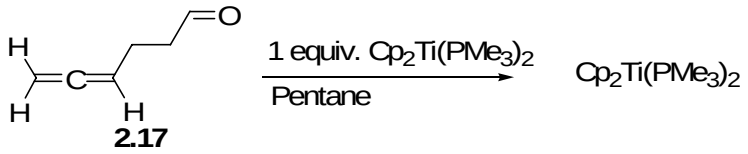


Scheme **2.26.** Creation of substrate **2.17** from substrate **2.14**.



Scheme **2.27.** The probable metallacycles **2.18a** & **b** that could be prepared from substrate **2.17**.

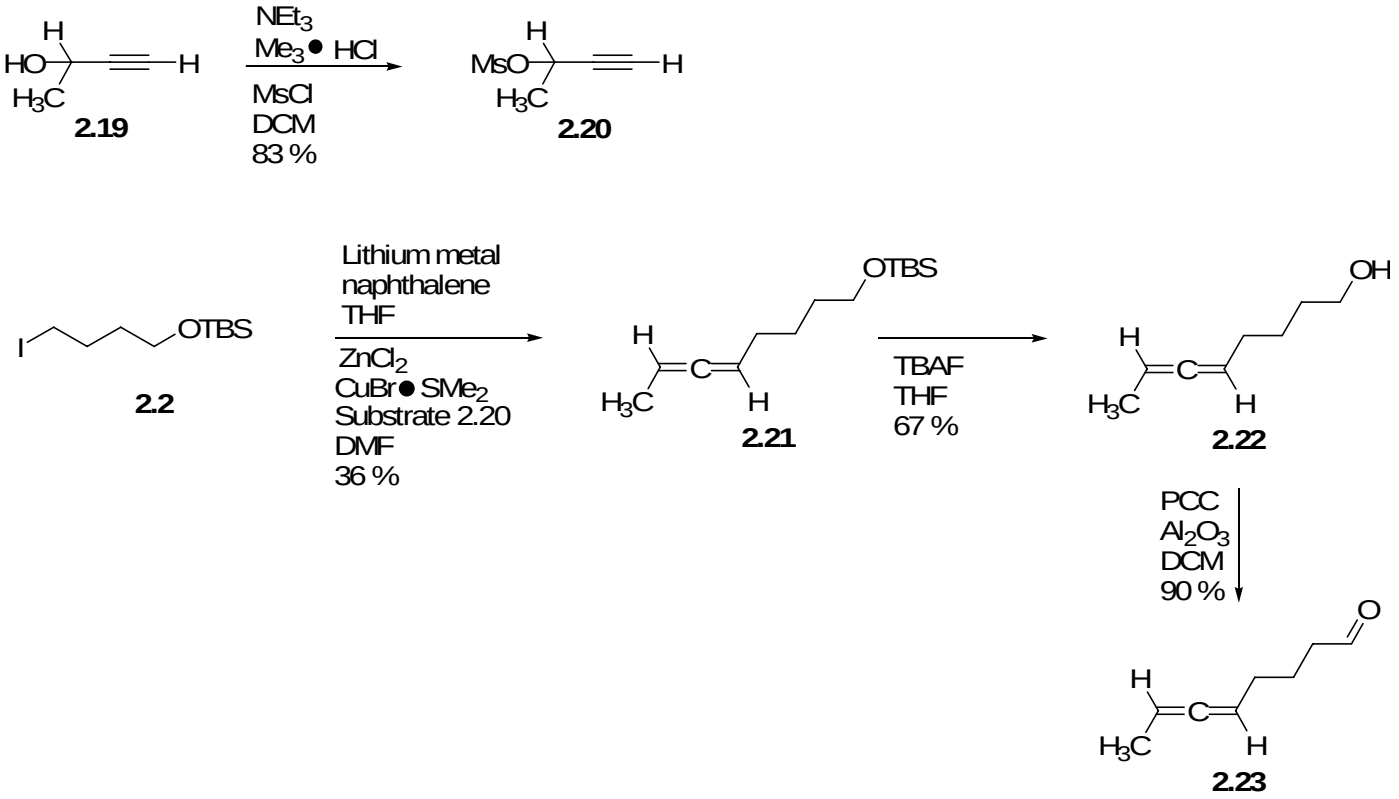
When hex–4,5–dienal reacted with the titanium complex for the metal insertion; only the titanium complex was recovered (Scheme **2.28**).



Scheme **2.28.** The recovered titanium catalyst from the attempted allenic HPK reaction from intermediate **2.17**.

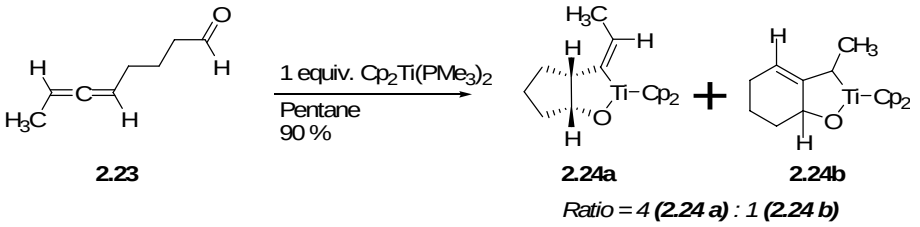
Next, disubstituted allenes were synthesized and subjected to cyclocarbonylation. We first focused on making the 1,3–disubstituted allene and it would be followed by the 3,3–disubstituted allene. A mixture of products for the 1,3–disubstituted allene was anticipated for

the π–bond selectivity of alkynyl allenes. Propargyl chloride was replaced with methanesulfonic acid 1–methyl–prop–2–ynyl–ester. Methanesulfonic acid 1–methyl–prop–2–ynyl–ester, **2.20**, was created from but–3–yn–2–ol, **2.19**, in an 83 % yield.[58] Substrate **2.21** was made using the "Rieke procedure", methanesulfonic acid 1–methyl–prop–2–ynyl–ester, **2.20**, as the electrophile and the iodide starting material **2.2**. The silyl ether protecting group was cleaved to produce substrate **2.22** in a 67 % yield and it in turn was oxidized to create substrate **2.23** in a 90 % yield (Scheme **2.29**).



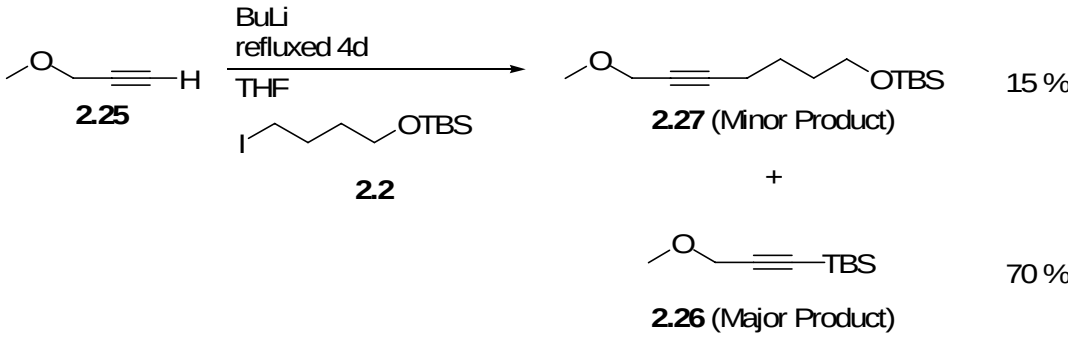
Scheme **2.29.** Synthesis of substrate **2.23** from **2.19**.

Both compounds **2.24a** and **2.24b** were obtained as a mixture (4:1 ratio) from starting material **2.22** in a 90 % yield (Scheme **2.30**).



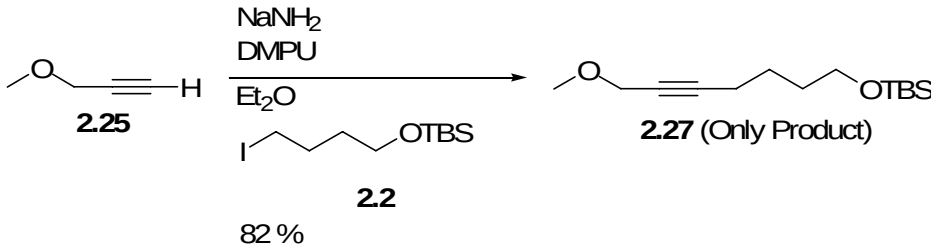
Scheme **2.30.** Metallacycles **2.24a** & **b** produced from substrate **2.23**.

Next, the 3,3–disubstituted allene, **2.28**, was synthesized from a Grinard addition to an internal alkyne substrate **2.27** (Scheme **2.31**). Butyllithium was employed to abstract a proton from methyl propargyl ether, **2.25**, to make it undergo a S_N2 reaction with the iodide substrate **2.2** to create substrate **2.27** which could be used to produce a 3,3–disubstituted allene, **2.28**. Based on proton NMR, it was found that substrate **2.26** was made as the major product and **2.27** as the minor product.[59]

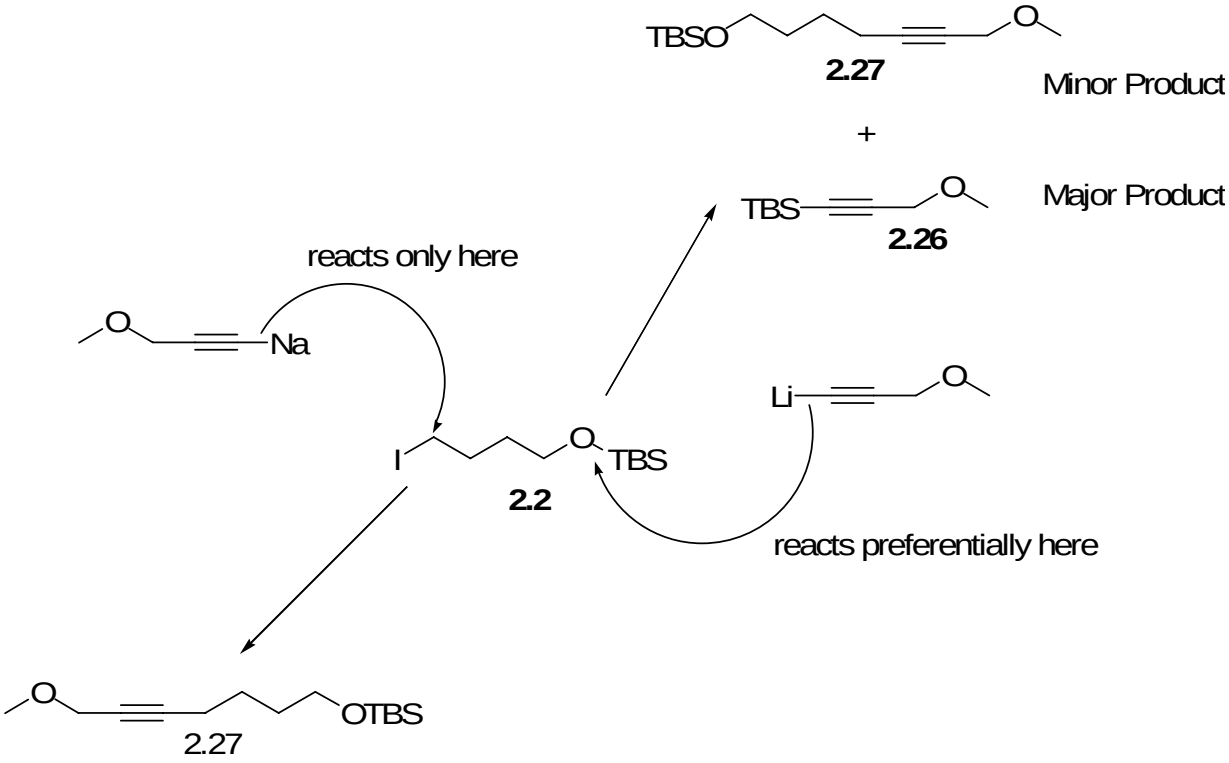


Scheme **2.31.** Production of the undesired major product **2.26**.

Product **2.27** was obtained as the only product when we changed to a new procedure.[60] This procedure used sodium amide, $NaNH_2$ and DMPU instead of butyllithium to de–protonate substrate **2.25.** It reacted with **2.2** to produce the desired compound in an 82 % yield (Scheme **2.32**). It appears that the sodium acetylide reacts mainly at the methylene / iodide bond in **2.2**, whereas the lithium acetylide reacts preferentially at the oxygen / silicon bond to produce mainly compound **2.26** as the main produce instead of **2.27**. (Scheme **2.33**)



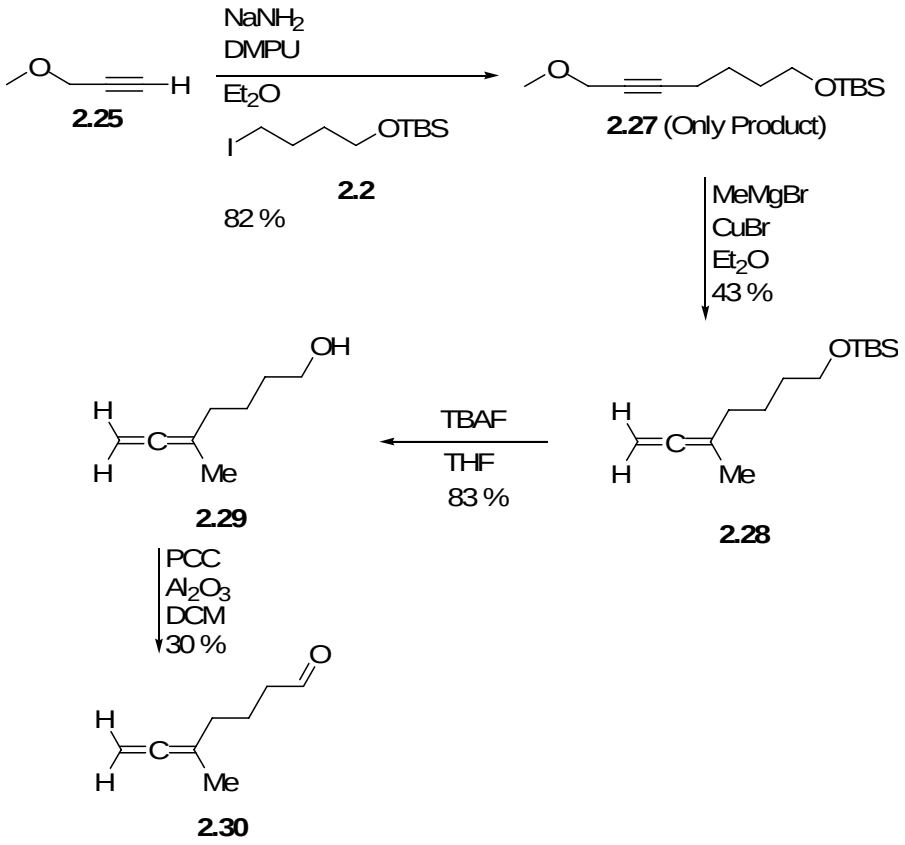
Scheme **2.32.** Production of the desired substrate **2.27**.



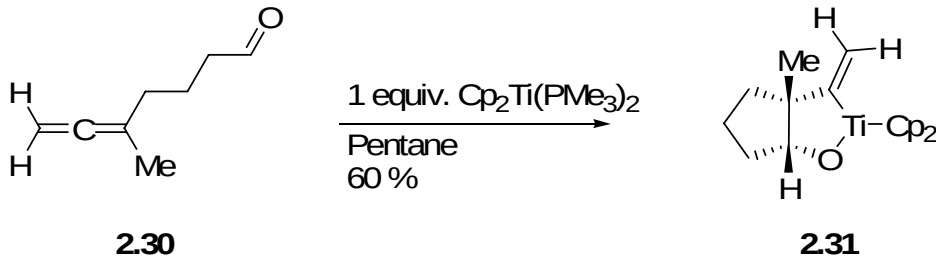
Scheme **2.33.** Lithium and Sodium acetylide's reaction with starting reagent **2.2**.

A 3,3–disubstituted allene **2.28** was created from **2.27** using a copper–catalyzed addition of methyl magnesium bromide.[61] The silyl ether group on **2.28** was cleaved using the deprotection procedure that we optimized to produce substrate **2.29** in an 83 % yield. Substrate **2.29** was then oxidized to **2.30** and we predicted that the a 3,3–disubstituted allene would react via the internal or more hindered π–bond to produce an *α*–methylene–*γ*–lactone (Scheme **2.34** & **2.35**). Metallacycle **2.31** was obtained as the only product. Substrate **2.32** was created following the same procedure used to obtain compound **2.28** from starting material **2.27** (Scheme

2.36). The *tert*–butyl–dimethyl silane functional group on **2.32** was removed using TBAF to produce compound **2.33** in 72 % yield. It was then oxidized to obtain **2.34** in a 35 % yield.



Scheme **2.34.** Production of substrate **2.30** in several steps from substrate **2.25**.

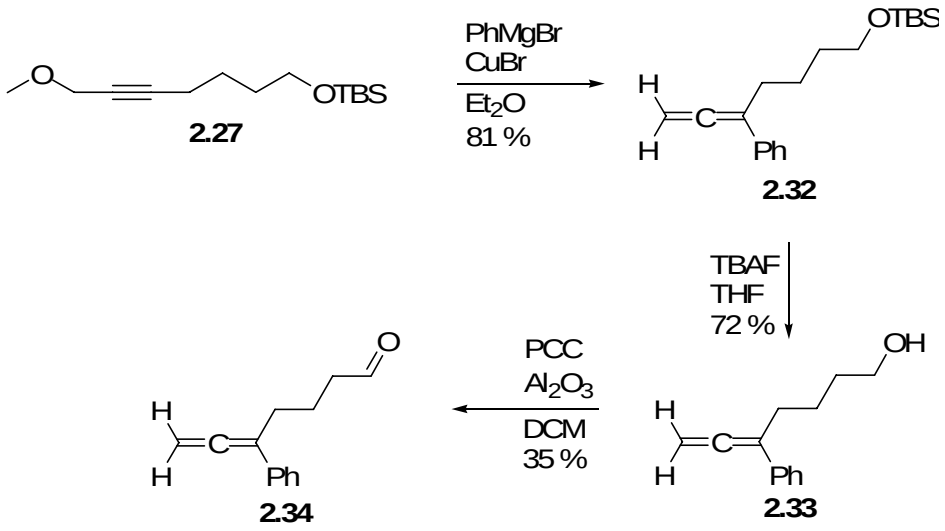


Scheme **2.35.** Titanacene macrocycle **2.31** prepared from substrate **2.30**.

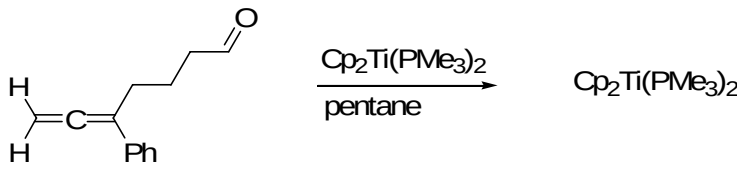
2.7.1. Substrate Synthesis and Metallacycle Formation

Metallacycle **2.35** was never made when it was reacted with the titanium catalyst. Instead, only the catalyst was recovered (Scheme **2.37**). In the end, the desired α–methylene–

γ–butyrolactones were not produced but the metallocycle synthesis was improved. It was shown that THF is the best solvent for this reaction (Scheme **2.38**).



Scheme **2.36.** Conversion from compound **2.27** to allenal **2.34**.



Scheme **2.37.** The failed allenic HPK reaction.

2.7.2. Carbonylation Studies

The HPK reaction was attempted using 1 equiv. of compound **2.6**, 1equiv. of $Cp_2Ti(PMe_3)_2$, and CO in pentane. The reaction color changed from red-maroon to yellow in color with some precipitate formation (Scheme **2.39**). Judging from the yellow color, the desired lactone was not produced. The experiment was repeated with only the solvent being varied. This time diethyl ether was utilized instead of pentane. Initially, the reaction color was red–maroon for the first two hours; but once again the color changed and the precipitate started forming in the reaction flask. It assumed that there were some sort of unfavorable interactions between substrate **2.6**, the titanium catalyst, CO and the solvent. We were able to form titanocycle substrates from allenyl aldehyde and ketone substrates in good to excellent

yields, with the titanium catalyst and THF as a solvent. Substrate **2.6** was subjected to the cyclocarbonylation at 25 psi. CO and it failed to produce the desired result. The reaction was repeated and only the pressure of CO was varied from 25 to 60 psi. CO. The desired was not obtained lactone.

The HPK reaction was executed with substrate **2.12** in deuterated benzene at 225 psi. CO. No product was obtained after one day of reaction time; but a decrease in CO pressure from 225 to 202.5 psi. was observed. (Scheme **2.40**) The reaction was heated between 60–75 ^{0}C to see if it would aid in creating the lactone and ran it for about 2 days using substrate **2.30**. Again, the desired product was not obtained. Compound **2.30** was used in this reaction because it is made in higher yields and a shorter synthetic route.

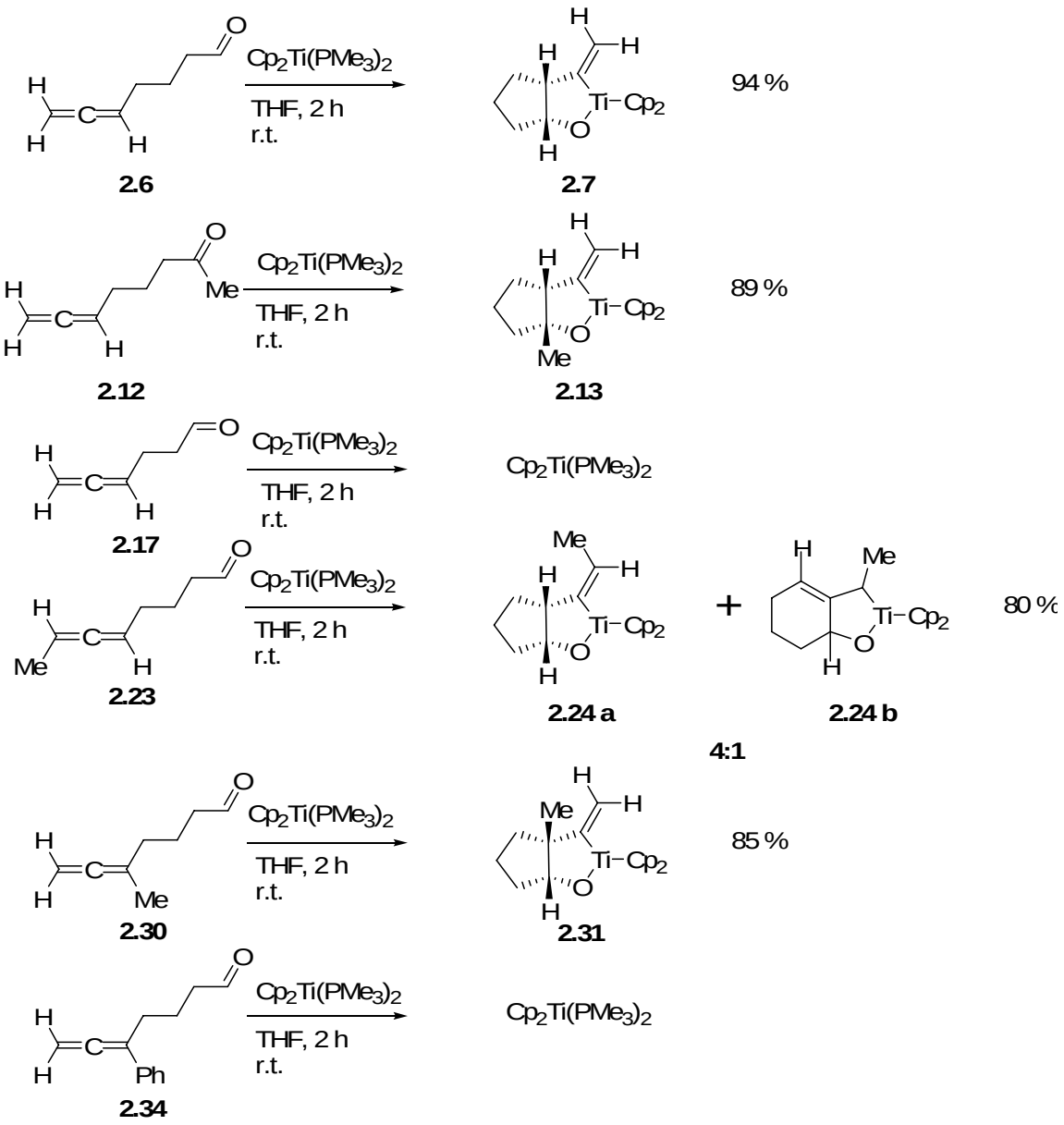
Compound **2.30** was used in a cyclocarbonylation that was gradually increased from 100 to ~ 380 psi. CO and ran the reaction for ~ 55 hours. The product was red–orange dark oil with crystals in the round-bottom. The crystals were taken to the crystallographer, but it apparently decomposed because its color faded from red–orange to a dirty brown. (Scheme **2.41**)

2.8. Conclusion

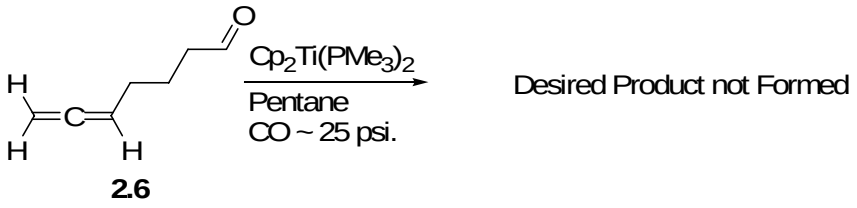
Several metallocycles were the only compounds produced in the attempt to excecute the HPK reaction and the substituted α–methylene–γ–butyrolactones were never synthesized.

2.9. Future Work

The syntheses of α–methylene–γ–butyrolactones could be completed by using a high pressure apparatus that can maintain CO pressure as a high as 1500 psi. A different titanocene catalyst can be employed in the HPK reaction to determine if the lactones can be created from the corresponding allenyl aldehyde and ketone compounds. Once the methodology for the production of α–methylene–γ–butyrolactones are successful, it could be used to produce lactones from 1,1,3–trisubstituted allenyl aldehyde and ketone substrates.

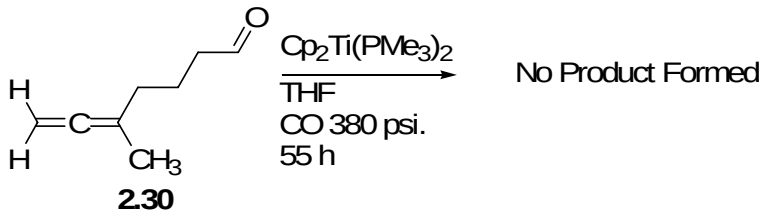


Scheme **2.38.** Improvements to the titanium metallocycle product.



Scheme **2.39.** The first HPK reaction attempted.

Scheme **2.40.** Attempted carbonylation of compound **2.30** at high CO pressure.



Scheme **2.41.** Attempted HPK reaction ran over time using THF and higher CO pressure.

2.10. Experimental Section

All the solvents used in reaction were distilled to dryness according to the following procedures. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were both distilled from sodium / benzophenone ketyl under nitrogen. Pentane was distilled from sodium / benzophenone ketyl / tetraglyme. Acetonitrile, CH_3CN, and methylene chloride, CH_2Cl_2, were both distilled using calcium hydride, CaH_2, under nitrogen. The titanocene complex was made as according to the literature procedure.[56,62]

Analytical thin–layer chromatography, TLC, was performed on Sorbent Technologies silica gel plates with plastic backing. Components were visualized by illumination with long wave ultraviolet light, exposure to iodine vapor, or by standing with one of the following reagents (followed by heating): *p*-anisaldehyde (or vanillin) in ethanol/sulfuric acid; 7% phosphomolybdic acid in ethanol; 0.04 M ammonium molybdate in 10% sulfuric acid. Solvents for extraction and chromatography were reagent grade and used as received. Flask column chromatography was performed using Sorbent Technologies 60 Å Silica Gel standard grade.

2.11. Preparative Procedures

***tert*–Butyl–(–4–iodo–butoxy–)–dimethyl–silane (2.2)**. *tert*-Butyldimethylsilyl chloride (10.1g, 66.3 mmol, 1 equivalent) was first added to a 500 mL three–necked round–bottom flask equipped with a stirbar. Sodium Iodide (19.89g, 132 mmol, 2 equivalents) was dissolved in acetonitrile (112 mL) which was introduced by syringed into the three–necked round–bottom flask from the left neck. THF (17.46g, 242 mmol, 3.65 equivalents), 19.64 mL, **2.1**, was also introduced into the three–necked round–bottom flask. A temperature probe was attached to the right neck of the flask to maintain a temperature of 55 ^{0}C. The resulting mixture was stirred overnight at 55 ^{0}C under nitrogen. The flask was covered in aluminum foil to protect the iodide from exposure to light. The reaction mixture was quenched with approximately 200 mL of water and the combined organic phases from previous extractions were concentrated into an orange oily liquid to yield 18.95g (60.3 mmol, 91 % yield). This protected iodo alcohol became substrate **2.2**. The iodide starting material, **2.2**, should be stored in a refrigerator and wrapped in aluminum foil to avoid light decomposition. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.67 (t, *J*=6.2 Hz, 2H), 3.23 (t, *J*=7.0 Hz, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 62.3, 33.9, 30.6, 26.3, 18.7, 7.6, – 4.9.

***tert*–Butyl–hepta–5,6–dienyloxy–dimethyl–silane (2.3).** Activated Zinc dust (325 mesh, 10.8g, 47.7 mmol, 3 equivalents) was added to a 50 mL RBF with a side arm. The flask was dried by heating under vacuum and it was flushed with nitrogen. Dry DMF (20 mL) and TMSCl (0.146g, 0.975 mmol) were added to the zinc dust and stirred at room temperature for approximately 30 minutes. In separate flask, substrate **2.2** (5g, 15.9 mmol) was added to the dry DMF (20 mL) under nitrogen. Substrate **2.2** was cannulated into the zinc suspension and stirred at 0 ^{0}C. Substrate **2.2** was consumed within 5–15 minutes as confirmed by TLC (petroleum ether/ EtOAc [2:1]). The excess zinc dust was allowed to settle for 5 minutes at 0

^{0}C and the organozinc supernatant was cannulated into a 100 mL RBF containing a mixture of CuBr●S(CH_3)$_2$ (0.16g, 5 mol%) and propargyl chloride (1.54g, 20.7 mmol, 1.30 equivalents) in DMF (25 mL) at –10 ^{0}C. The resultant mixture was allowed to warm to room temperature and stirred for approximately 14 hours. EtOAc (60 mL) was added to the reaction mixture and it was washed with water (3 x 40 mL) and brine (40 mL), then dried over $MgSO_4$ and concentrated to produce the crude product mixture of both substrates **2.2** and **2.3** as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.08 (quin, *J*=6.7 Hz, 1H), 4.62 (m, 2H), 3.59 (t, *J*=6.3 Hz, 2H), 1.94 (m, 2H), 1.49 (m, 2H), 1.34 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 208.9, 90.4, 75.1, 63.5, 32.7, 28.5, 26.4, 25.8, 18.8, – 4.8.

***tert*–Butyl–hepta–5,6–dienyloxy–dimethyl–silane (2.3).** Zinc chloride (1.19 g, 8.72 mmol, 1.29 equivalents) and naphthalene (220 mg, 1.72 mmol, 0.267 equivalents) were weighed in the glove box and placed into separate 30 mL vials. Lithium metal (0.12g, 16.9 mmol, 2.67 equivalents) was weighed and cut into pieces and placed into a 50 mL two–necked round–bottom flask which was then evacuated and purged with N_2. Dried THF, 7.60 mL, was then syringed into the 30 mL vial with the naphthalene and then it was cannulated into the flask containing lithium metal and stirred approximately 15 minutes. $ZnCl_2$, 1.19 g, was dissolved into about 8.72 mL of THF. This solution was then cannulated into a 10 mL addition funnel that was attached to 50 mL two–necked round–bottom flask. The $ZnCl_2$ solution was then added drop–wise, two drops at a time, with long pauses in between to maintain a green color. The addition was intermittently stopped until the green color returned. When the addition of $ZnCl_2$ was complete; the reaction was stirred for 30 minutes and the green color was gone. After 30 minutes of stirring, the stirrer was turned off and the granular grains were allowed to settle. The dark grey supernatant was cannulated into a 30 mL vial sealed with a rubber septa and the Rieke zinc was pumped on to remove the remaining THF. The dark grey supernatant was

quenched slowly with water and taken to the facilities for disposing of chemicals DMF (20 mL) was added to the zinc suspension that was made from the initial reaction. The reaction flask was under ice and at 0 ^{0}C, when substrate **2.2** (2 g, 6.36 mmol, 1 equivalent) was added in 7 mL DMF via cannulation. The ice was removed and then the mixture was stirred for 1.0 hour at room temperature. In another flask, CuBr●S$(CH_3)_2$ (65 mg, 0.318 mmol, 5 mol %) was added to DMF (5 mL) and stirred for 30 minutes. Propargyl chloride (616 mg, 8.27 mmol, 1.3 equivalents) was syringed into the reaction flask that contained the CuBr●S$(CH_3)_2$. The organozinc reaction flask was cooled to –10 ^{0}C for 10 minutes and the zinc suspension was allowed to settle once again. The organozinc supernatant was then cannulated into the flask that contained the propargyl choloride / CuBr●S$(CH_3)_2$. The reaction flask was allowed to warm up from –10 ^{0}C to room temperature and stirred for 14 hours. The reaction mixture was quenched in ethyl acetate and the organic layer was concentrated and purified using silica flash chromatography (hexanes/ ethyl acetates [90:10]) to produce 914 mg (4.04 mmol, 63 % yield) of substrate **2.3** as yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.08 (quin, *J*=6.7 Hz, 1H), 4.62 (m, 2H), 3.59 (t, *J*=6.3 Hz, 2H), 1.94 (m, 2H), 1.49 (m, 2H), 1.34 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 208.9, 90.4, 75.1, 63.5, 32.7, 28.5, 26.4, 25.8, 18.8, – 4.8.

Hepta–5,6–dien–1–ol (2.5). Acetonitrile (73 mL) was added to a 500 mL round–bottom flask that had the substrate **2.3** (1.92g, 8.48 mmol, 1 equivalent) and the resulting solution stirred at room temperature. Approximately 19.30 mL of hydrofluoric acid (48–51 % by weight) was syringed into 400 mL beaker that contained 100 mL of CH_3CN. The resulting mixture was then added to substrate **2.3** and stirred for about 30 minutes before the first TLC were taken to determine if the silyl ether group on **2.3** was cleaved to produce **2.5** as a clear oil. The mixture ran for an additional thirty minutes to make certain the reaction ran to completion. Substrate **2.5** was purified utilizing silica flash chromatography (hexanes/ EtOAc [8:2], 85 %

yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.11 (quin, *J*=6.7 Hz, 1H), 4.66 (m, 2H), 3.67 (t, *J*=6.3 Hz, 2H), 2.04 (m, 2H), 1.65–1.46 (m, 4H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 208.9, 90.2, 75.2, 63.2, 32.6, 28.4, 25.6.

Hepta–5,6–dien–1–ol (2.5). Compound **2.3** (2.5g, 11.04 mmol, 1 equivalent) was added to a 100 mL round bottom flask equipped with stir bar and 25 mL of THF. Approximately 34 mL of TBAF (1.0 M solution in THF) was added to the mixture and it was stirred at room temperature for about 1 hour. At the end of the reaction, the THF was removed by roto–evaporation and Et_2O was added to the RBF. The resultant mixture was washed with water and dried over $MgSO_4$. Compound **2.5** was purified using silica–gel flash chromatography (hexanes/ EtOAc [8:2]) to produce a clear oil of 0.99 g (8.83 mmol, 80 % yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.11 (quin, *J*=6.7 Hz, 1H), 4.66 (m, 2H), 3.67 (t, *J*=6.3 Hz, 2H), 2.04 (m, 2H), 1.65–1.46 (m, 4H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 208.9, 90.2, 75.2, 63.2, 32.6, 28.4, 25.6.

Hepta–5,6–dienal (2.6). Pyridinium chlorochromate (5.05g, 23.4 mmol, 2 equivalents) was added to 100 mL round–bottom flask and purged. under vacuum. To this flask, DCM, (20 mL) added via a syringe. Neutral alumina (5.05g, 23.4 mmol, 2 equivalents) was also added to the flask containing the PCC and it was purged under vacuum a second time and stirred for 30 minutes at room temperature. To round–bottom flask containing substrate **2.5** (1.31g, 11.7 mmol, 1 equivalent) DCM (10 mL) was added. Substrate **2.5** was cannulated into the round–bottom flask containingt both the PCC / neutral alumina mixture. That mixture ran for two–three hours at room temperature and was checked by TLC to determine if the alcohol was consumed completely. The reaction was quenched with diethyl ether, Et_2O, and ran thru a silica gel plug. The mixture was then purified by silica flash chromatography (pentane/ diethyl ether [95:05]) and concentrated to make **2.6** in a 70% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ

9.75 (t, *J*=1.7 Hz, 1H), 5.05 (quin, *J*=6.7 Hz, 1H), 4.66 (m, 2H), 2.46 (m, 2H), 2.03 (m, 2H), 1.74 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 209.1, 202.8, 89.4, 75.7, 43.6, 27.9, 21.7.

Substrate (2.7). This reaction was done in the dry box under argon. Anhydrous THF was added to a 30 mL vial containing substrate **2.6** (125 mg, 1.13 mmol, 1 equivalent). To this vial, $Cp_2Ti(PMe_3)_2$ (375 mg, 1.13 mmol, 1 equivalent) was added and the reaction mixture was stirred for 2 hours. The reaction mixture was filtered thru a frit–funnel, with a pad of celite, and into a small round–bottom flask and pumped on to remove the THF. The compound was then rinsed with pentane to produce a reddish solution and then it was re–crystallized to produce substrate **2.7**, 307 mg in 94 % yield. The solvent in the reaction vessel was removed under pressure to produce a reddish-brown or maroon colored solid ^{1}H NMR (300 MHz, C_6D_6): δ 6.00 (s, 5H), 5.91 (s, 5H), 5.71 (t, 1H), 5.05–5.01 (m, 1H), 4.16 (s, 1H), 3.79–3.71 (m, 1H), 2.22–2.18 (m, 1H), 1.94–1.84 (m, 2H), 1.53–1.35 (m, 2H); ^{13}C NMR (62.8 MHz, C_6D_6): δ 204.2, 116.0, 115.1, 114.8, 85.5, 79.1, 37.5, 36.2, 24.9.

***tert*–Butyl–(–4–iodo–1–methyl–butoxy)–dimethyl–silane (2.9).** Substrate **2.9** was prepared using a similar procedure described for substrate **2.2**. The product was purified by silica flash chromatography (hexane/ EtOAc [98:02]) and concentrated into an orange oily liquid to yield 12.67g (58 %). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.84 (m, 1H), 3.20 (t, *J*=7.0 Hz, 2H), 1.89 (m, 2H), 1.52 (m, 2H), 1.13 (d, *J*=6.0 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 68.0, 43.6, 30.3, 26.3, 24.2, 18.5, 7.7, – 4.9.

***tert*–Butyl–dimethyl–(1–methyl–hepta–5,6–dienyloxy)–silane (2.10).** Substrate **2.10** was prepared from procedures for substrate **2.3**. The product was purified using silica gel flash chromatography (hexane/ EtOAc [9:1]) to yield 3.13 g (85 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (quin, *J*=6.7 Hz, 1H), 4.86 (m, 2H), 3.81 (q, *J*=5.5 Hz, 1H), 2.00 (m, 2H),

1.48 (m, 2H), 1.43 (m, 2H), 1.13 (d, *J*=6.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 208.9, 90.4, 75.1, 68.9, 39.5, 28.7, 26.3, 25.8, 24.3, 18.7, – 4.3.

Octa–6,7–dien–1–ol (2.11). Substrate **2.11** was prepared from substrate **2.10** (2.77 g, 11.52 mmol, 1 equivalent) using the procedure described for substrate **2.5**. The product was purified by silica flash chromatography (hexane/ EtOAc [8:2]) to yield 76 % as a transparent oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.16 (quin, *J*=6.7 Hz, 1H), 4.74 (m, 2H), 3.84 (q, *J*=5.6 Hz, 1H), 2.09 (m, 2H), 1.51 (m, 2H), 1.49 (m, 1H), 1.40 (s, 1H), 1.24 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 208.9, 96.2, 75.2, 68.3, 39.1, 28.5, 25.6, 23.9.

Octa–6,7–dien–2–one (2.12). Substrate **2.12** was prepared from substrate **2.11** (1.10 g, 8.79 mmol, 1 equivalent) using the procedure described for substrate **2.6**. The product was purified by silica flash chromatography (pentane/ diethyl ether [95:05]) to yield 962mg (88.26 %) as a clear oil. Compound **2.12** eluted first from the column. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (quin, *J*=6.7 Hz, 1H), 4.68 (m, 2H), 2.48 (m, 2H), 2.15 (s, 3H), 2.00 (m, 2H), 1.74 (m, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 209.1, 206.3, 89.9, 75.2, 42.6, 29.5, 28.0, 23.5. **4–Methyl–hepta–5,6–dienal (2.12a).** Substrate **2.12a** was the minor product isolated in a trace amount from the oxidation of compound **2.11a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (t, *J*=5.8 Hz, 1H), 5.03 (quin, *J*=6.7 Hz, 1H), 4.74 (m, 2H), 2.52 (m, 3H), 2.21 (m, 2H), 1.07 (d, *J*=6.8 Hz, 3H).

Metallacycle **2.13** was prepared from substrate **2.12** (200 mg, 1.61 mmol, 1 equivalent) using the improved procedure described for substrate **2.7**. The product was collected as a reddish oil to yield 435 mg (89 %). ^{1}H NMR (300 MHz, C_6D_6): δ 5.98 (s, 5H), 5.95 (s, 5H), 5.74 (s, 1H), 4.22 (s, 1H), 3.93 (m, 1H), 2.18 (m, 2H), 1.77 (m, 2H), 1.33 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (62.8 MHz, C_6D_6): δ 203.9, 115.5, 115.2, 114.9, 94.2, 82.0, 42.8, 35.3, 30.4, 24.7.

***tert*–Butyl–hexa–4,5–dienyloxy–dimethyl–silane (2.15).** Substrate **2.15** was prepared using the procedure for substrate **2.3**. The product was purified using silica flash chromatography (hexane/ EtOAc [98:02]) to yield 1.64 g (39 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15 (quin, *J*=6.7 Hz, 1H), 4.69 (m, 2H), 3.64 (t, *J*=4.0 Hz, 2H), 2.09 (m, 2H), 1.69 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 208.9, 90.1, 75.3, 62.8, 32.4, 26.4, 24.8, 18.7.

Hexa–4,5–dien–1–ol (2.16). Substrate **2.16** was prepared from substrate **2.15** (1.64 g, 7.72 mmol, 1 equivalent) using the procedure described for substrate **2.5** a. The product was purified by silica flash chromatography (hexane/ EtOAc [8:2]) to yield 428mg (56 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (quin, *J*=6.7 Hz, 1H), 4.65 (m, 2H), 3.65 (t, *J*=6.0 Hz, 2H), 2.03 (m, 2H), 1.99 (m, 1H), 1.67 (m, 2H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 208.9, 89.8, 75.5, 62.7, 32.3, 24.8.

Hexa–4,5–dienal (2.17). Substrate **2.17** was prepared from substrate **2.16** (428 mg, 4.36 mmol, 1 equivalent) using the procedure described for substrate **2.6**. The product was purified by silica flash chromatography (pentane/ diethyl ether [95:05]) to yield 74.4 mg (18 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 5.20 (m, 1H), 4.76 (m, 2H), 2.59 (m, 2H), 2.33 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 210.0, 203.5, 90.2, 78.0, 43.9, 22.1.

Methanesulfonic acid 1–methyl–prop–2–ynyl–ester (2.20). To a 500 mL round–bottom flask equipped with a stir bar; NEt_3, (18.04 g, 178.3 mmol, 2.5 equivalents) [24.85 mL] was syringed into a solution of but–3–yn–2–ol, 2.19, (5 g, 71.33 mmol, 1 equivalent) in DCM (120 mL). Me_3N●HCl (6.82 g, 71.33 mmol, 1 equivalent) was also added to the reaction mixture. The round–bottom flask was cooled to 0 ^{0}C before the syringing in the mesyl choloride (12.26 g, 107 mmol, 1.5 equivalents) in DCM (20 mL). The mixture was then stirred for about 1 hour and quenched with water. It was then extracted with ethyl acetate and the

organic phase was washed with brine and water. The combined organic phase was dried with Na_2SO_4, and concentrated and purified by silica flash chromatography (hexane/ EtOAc [95:05]) to produce 8.76 g (83 %) of substrate **2.20** as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.28 (qd, *J*=6.7 Hz, *J*=2.1 Hz, 1H), 3.12 (s, 3H), 2.70 (d, *J*=2.0 Hz, 1H), 1.65 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 80.6, 76.6, 67.9, 39.5, 21.4.

***tert*–Butyl–dimethyl–octa–5,6–dienloxy–silane (2.21).** Substrate **2.21** was prepared using the procedure for substrate **2.3**. The product was purified using silica flash chromatography (hexane/ EtOAc [98:02]) to yield 1.39 g (36 %) as clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (m, 2H), 3.65 (t, *J*=6.3 Hz, 2H), 2.20 (m, 2H), 1.68 (m, 3H), 1.62–1.44 (m, 4H), 0.97 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 206.3, 91.8, 87.1, 64.7, 33.8, 30.2, 27.5, 27, 19.9, 16.1, – 3.7.

Octa–5,6–dien–1–ol (2.22). Substrate **2.22** was prepared from substrate **2.21** (1. 2 g, 4.49 mmol, 1 equivalent) using the procedure described for substrate **2.5a**. The product was purified by silica flash chromatography (hexane/ EtOAc [8:2]) to yield 421 mg (67 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.03 (m, 2H), 3.63 (m, 2H), 1.99 (m, 2H), 1.62 (m, 3H), 1.60–1.48 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 206.3, 91.6, 87.2, 64.3, 33.7, 30.1, 26.8, 16.1.

Octa–5,6–dienal (2.23). Substrate **2.23** was prepared from substrate **2.22** (421 mg, 3.34 mmol, 2 equivalents) using the procedure described for substrate **2.6**. The product was purified by silica flash chromatography (pentane/ diethyl ether [95:05]) to yield 373mg (90 %) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (s, 1H), 5.02 (m, 2H), 2.45 (m, 2H), 2.02 (m, 2H), 1.73 (m, 2H), 1.65 (dd, *J*=3.3 Hz, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 206.2, 205.3, 90.1, 86.1, 43.5, 28.4, 22.4, 14.8.

Metallacycles **2.24a** and **b** were both prepared as mixture (ratio 4:1) from substrate **2.23** (200 mg, 1.61 mmol, 1 equivalent) using the procedure described for substrate **2.7**. The product

was collected as a reddish oil to yield 391 mg (80 %). Substrate **2.24a**: ^{1}H NMR (300 MHz, C_6D_6): δ 6.11 (s, 5H), 6.02 (s, 5H), 5.22 (m, 1H), 4.29 (m, 1H), 3.90 (m, 1H), 2.18–1.35 (m, 6H), 1.74 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, C_6D_6): δ 191.5, 124.9, 116.2, 115.4, 86.3, 76.1, 38.5, 34.9, 26.2, 17.8. Substrate **2.24b**: ^{1}H NMR (300 MHz, C_6D_6): δ 6.18 (s, 5H), 6.08 (s, 5H), 5.96 (m, 1H), 5.15 (m, 1H), 3.70 (m, 1H), 1.66–1.35 (m, 6H), 1.22 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, C_6D_6): δ 192.4, 124.0, 115.5, 114.5, 85.7, 80.9, 38.7, 37.7, 25.8, 20.7.

***tert*–Butyl–(7–methoxy–hepta–5–ynyloxy)–dimethyl–silane (2.27)**. Butyllithium (33.7 mL of 2.0 M solution in hexanes, 69.4 mmol) was added to substrate **2.25** (5 g, 71.3 mmol) over a 40 minutes in 500 mL of dried THF at 0 ^{0}C. Substrate **2.2** (11.2 g, 35.6 mmol) was added via a syringe. The reaction was refluxed for four days and cooled to room temperature and quenched with approximately 100 mL of water. The THF was removed via reduced pressure and the residue was extracted using diethyl ether (5x50 mL). The combined organic phase was dried over $MgSO_4$ and purified using flash column chromatography (hexanes/ EtOAc [9:1]) to yield 15 % (1.34 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (t, *J*=2.1 Hz, 2H), 3.62 (t, *J*=5.9 Hz, 2H), 3.36 (s, 3H), 2.26 (m, 2H), 1.60 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 87.4, 76.3, 63.0, 60.6, 57.8, 32.3, 26.3, 25.5, 19.0, 18.7, – 4.9.

***tert*–Butyl–(7–methoxy–hepta–5–ynyloxy)–dimethyl–silane (2.27)**. To 250 mL round–bottom flask equipped with a stir bar and in the dry box; sodium amide (1.65 g, 42.3 mmol, 1.29 equivalents) was added and then 45 mL of dry THF was syringed into the flask. The flask was cooled to –78 ^{0}C and methyl propargyl ether, **2.25**, (2.3 g, 32.8 mmol, 1 equivalent), 2.77 ml in 5 mL of THF, was syringed into the flask. The reaction mixture was then cooled to –78 ^{0}C for 1 hour and then warmed to room temperature for 1 hour to make certain that the acetylide had formed. The mixture was once again cooled to – 78 ^{0}C and DMPU, (7.99 g, 62.3 mmol, 1.9 equivalents), 7.54 mL, was syringed into the flask. Substrate

2.2 (12.27 g, 39 mmol, 1.19 equivalents) in 5 mL of THF was syringed into the flask containing the DMPU, **2.25** and $NaNH_2$. The reaction mixture was ran for 16 hours and quenched with 15 mL of saturated ammonium chloride. The quenched solution was poured into a separatory funnel with about 100 mL of both water and ether in it. The organic phases were washed two more times with water and then dried with $MgSO_4$. It was concentrated and purified by silica flash chromatography (hexane/ EtOAc [9:1]) to produce substrate, **2.27**, in 82 % yield (6.91 g) as a clear oil. Substrate **2.27** was separated into three aliquots. Substrate **2.28** was made from 3 g of **2.27**, **2.32** was made from 3.62 g of **2.27** and the remainder was used for a NMR and IR samples. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (t, *J*=2.1 Hz, 2H), 3.62 (t, *J*=5.9 Hz, 2H), 3.36 (s, 3H), 2.26 (m, 2H), 1.60 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 87.4, 76.3, 63.0, 60.6, 57.8, 32.3, 26.3, 25.5, 19.0, 18.7, – 4.9.

***tert*–Butyl–dimethyl–(5–methyl–hepta–5,6–dienyloxy)–silane (2.28).** Copper (I) bromide (503.4 mg, 3.51 mmol, 0.30 equivalents) was added to a 250 mL round–bottom flask equipped with a stir bar. To this flask, substrate, **2.27**, (3 g, 11.7 mmol, 1 equivalent) was added in 100 mL of Et_2O. Methylmagnesium bromide (2.79 g, 23.39 mmol, 2 equivalents), [7.80 mL] was syringed drop–wise into the mixture of substrate **2.27** and CuBr. The reaction mixture was stirred at room temperature and then refluxed for 60 hours. After running for 60 hours; the mixture was quenched carefully and drop–wise under ice because it was an exothermic reaction. The organic layers were extracted using ether and washed in brine and dried with Na_2SO_4 and concentrated and purified using silica flash chromatography (hexane/ EtOAc [9:1]) to produce substrate 2.28, 1.15 g (43 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.60 (m, 2H), 3.66 (m, 2H), 1.95 (m, 2H), 1.68 (m, 3H), 1.54 (m, 2H), 1.49 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 206.6, 98.7, 74.3, 63.5, 33.6, 32.8, 26.4, 24.1, 19.0, 18.8, – 4.9.

5–Methyl–hepta–5,6–dien–1–ol (2.29). Substrate **2.29** was prepared from substrate **2.28** (1. 15 g, 4.78 mmol, 1 equivalent) using the procedure described for substrate **2.5**. The product was purified by silica flash chromatography (hexanes/ EtOAc [8:2]) to yield 500 mg (83 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.59 (m, 2H), 3.65 (t, *J*=6.2 Hz, 2H), 1.97 (m, 2H), 1.67 (m, 3H), 1.61–1.50 (m, 4H), 0.05 (s. 6H). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 206.5, 98.6, 74.5, 63.3, 33.5, 32.7, 23.9, 19.1.

5–Methyl–hepta–5,6–dienal (2.30). Substrate **2.30** was prepared from substrate **2.29** (500 mg, 3.96 mmol, 1 equivalent) using the procedure described for substrate **2.6**. The product was purified by silica flash chromatography (pentane/ EtOAc [95:05]) to yield 148 mg (30 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (t, 1H), 4.65–4.45 (m, 2H), 2.42 (m, 2H), 1.97 (m, 2H), 1.79 (m, 2H), 1.67 (m, 3H). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 206.5, 202.9, 97.9, 75.0, 43.7, 32.0, 20.2, 19.1.

Metallacycle **2.31** was prepared as mixture from substrate **2.30** (148 mg, 1.192 mmol, 1 equivalent) using the procedure described for substrate **2.7**. The product was collected as a reddish oil to yield 307 mg (85 %). ^{1}H NMR (250 MHz, C_6D_6): δ 6.09 (s, 5H), 5.98 (s, 5H), 5.84 (s, 1H), 4.82 (m, 1H), 4.09 (s, 1H), 1.71–1.47 (m, 6H), 1.26 (s, 3H); ^{13}C NMR (62.8 MHz, C_6D_6): δ 207.8, 114.9, 114.1, 113.7, 92.0, 82.5, 42.3, 35.0, 26.6, 23.7.

***tert*–Butyl–dimethyl–(5–phenyl–hepta–5,6–dienyloxy)–silane (2.32)**. Substrate **2.32** was prepared from substrate **2.27** (3.62 g, 14.1 mmol, 1 equivalent) using the procedure for substrate **2.28**. The product was purified by silica flash chromatography (hexane/ EtOAc [9:1]) to yield 3.44 g (81 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.23 (m, 5H), 5.11 (m, 2H), 3.66 (m, 2H), 2.49 (m, 2H), 1.67–1.60 (m, 4H), 0.96 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 210.2, 138.0, 129.9, 128.1, 127.6, 106.5, 79.8, 64.6, 34.1, 30.8, 27.6, 25.8, 20.0, – 3.7.

5–Phenyl–hepta–5,6–dien–1–ol (2.33). Substrate **2.33** was prepared from substrate **2.32** (3.44 g, 11.37 mmol, 1 equivalent) using the procedure described for substrate **2.5a**. The product was purified by silica flash chromatography (hexane/ EtOAc [8:2]) to yield 1.54 g (72 %) as a clear oil. ^{1}H NMR (300 MHz, CDCl3): δ 7.42–7.22 (m, 5H), 5.12 (m, 2H), 3.72 (m, 2H), 2.15 (m, 2H), 1.74–1.65 (m, 4H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 209.0, 130.4, 128.6, 127.8, 126.8, 105.2, 78.8, 63.1, 32.8, 29.6, 25.3.

5–Phenyl–hepta–5,6–dienal (2.34). Substrate **2.34** was prepared from substrate **2.33** (1.54 g, 8.18 mmol, 1 equivalent) using the procedure described for substrate **2.6**. The product was purified by silica flash chromatography (pentane/ EtOAc [95:05]) to yield 529 mg (35 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.42–7.34 (m, 5H), 5.12 (m, 2H), 2.56–2.49 (m, 4H), 1.94 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 210.1, 204.0, 137.5, 130.0, 128.4, 127.5, 105.7, 80.3, 45.0, 30.3, 21.8.

2.12. References

1. Burton, B. S.; v. Pechmann, H. *Berr. Dt. Chem. Ges.* **1887**, *20*, 145-149.

2. Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3208-3212.

3. Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 1870-1871.

4. Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 2245-2248.

5. Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 3838-3842.

6. Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 1372-1376.

7. Brandsma, L.; Verkruijsse, H. D. *Studies in Organic Chemistry, Vol. 8: Synthesis of Acetylenes, Allenes and Cumulenes: A laboratory Manual*, 1981.

8. Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795-818.

9. Bruneau, C.; Dixneuf, P. H. *Comprehensive Organic Functional Group Transformations* **1995**, *1*, 953-995.

10. Bruneau, C.; Renaud, J. L. *Comprehensive Organic Functional Group Transformations II* **2005**, *1*, 1019-1081.

11. Cadiot, P.; Chodkiewicz, W.; Pauss-Godineau, J. *Bull. Soc. Chim. Fr.* **1961**, 2176-2193.

12. Huche, M. *Tetrahed.* **1980**, *36*, 331-342.

13. Landor, S. R.; Editor *The Chemistry of the Allenes, Vol. 1: Synthesis*, 1982.

14. Landor, S. R.; Editor *The Chemistry of the Allenes, Vol. 2: Reactions*, 1982.

15. Landor, S. R.; Editor *The Chemistry of the Allenes, Vol. 3: Stereochemical, Spectroscopic and Special Aspects*, 1982.

16. Pasto, D. J. *Tetrahed.* **1984**, *40*, 2805-2827.

17. Petrov, A. A.; Fedorova, A. V. *Usp. Khim.* **1964**, *33*, 3-27.

18. Rutledge, T. F. *Acetylenes and Allenes; Addition, Cyclization, and Polymerization Reactions*, 1969.

19. Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*, 1984.

20. Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317-359.

21. Wei, L.-l.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773-782.

22. Shibata, T.; Koga, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 911-919.

23. Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2004**, 3377-3383.

24. Narasaka, K.; Shibata, T. *Chem. Lett.* **1994**, 315-318.

25. Brummond, K. M.; Kerekes, A. D.; Wan, H. *J. Org. Chem.* **2002**, *67*, 5156-5163.

26. Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535-6545.

27. Yu, C.-M.; Hong, Y.-T.; Lee, J.-H. *J. Org. Chem.* **2004**, *69*, 8506-8509.

28. Brummond, K. M. *Adv. Cycloaddit.* **1999**, *6*, 211-237.

29. Brummond, K. M.; Wan, H. *Tetrahedron Lett.* **1998**, *39*, 931-934.

30. Shibata, T.; Kadowaki, S.; Hirase, M.; Takagi, K. *Synlett* **2003**, 573-575.

31. Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245-2248.

32. Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285-292.

33. Harmon, A. D.; Hutchinson, C. R. *Tetrahedron Lett.* **1973**, 1293-1296.

34. Hutchinson, C. R. *J. Org. Chem.* **1974**, *39*, 1854-1858.

35. Murray, A. W.; Reid, R. G. *J. Chem. Soc. Chem. Comm.* **1984**, 132-133.

36. Yamada, K.; Kato, M.; Hirata, Y. *Tetrahedron Lett.* **1973**, 2745-2746.

37. Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557-1558.

38. Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818-5819.

39. Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424-4431.

40. Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457-6458.

41. Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335-5336.

42. Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160-7161.

43. Hoffmann, H. M. R.; Rabe, J. *Angew. Chem.* **1985**, *97*, 96-112.

44. Sarma, J. C.; Sharma, R. P. *Heterocycles* **1986**, *24*, 441-457.

45. Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochem.* **1976**, *15*, 1573-1580.

46. Grieco, P. A. *Synthesis* **1975**, 67-82.

47. Tukov, F. F.; Anand, S.; Gadepalli, R. S. V. S.; Gunatilaka, A. A. L.; Matthews, J. C.; Rimoldi, J. M. *Chem. Res. Toxicol.* **2004**, *17*, 1170-1176.

48. Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1584-1586.

49. Nystroem, J. E.; McCanna, T. D.; Helquist, P.; Amouroux, R. *Synthesis* **1988**, 56-58.

50. Hunter, C.; Jackson, R. F. W.; Rami, H. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1349-1352.

51. Feng, X.; Senge, M. O. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1030-1038.

52. Sell, M. S.; Hanson, M. V.; Rieke, R. D. *Synth. Commun.* **1994**, *24*, 2379-2386.

53. Chen, T.-A.; Wu, X.; Rieke, R. D. *J. Am. Chem. Soc.* **1995**, *117*, 233-244.

54. Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981-3982.

55. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.

56. Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem.* **1985**, *97*, 425-426.

57. Amouroux, R.; Jatczak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1987**, 505-510.

58. Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahed.* **1999**, *55*, 2183-2192.

59. Johnston, M. I.; Kwass, J. A.; Beal, R. B.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 5419-5424.

60. Ginn, J. D. **1996**.

61. Audin, P.; Doutheau, A.; Gore, J. *Bull. Soc. Chim. Fr.* **1984**, 297-306.

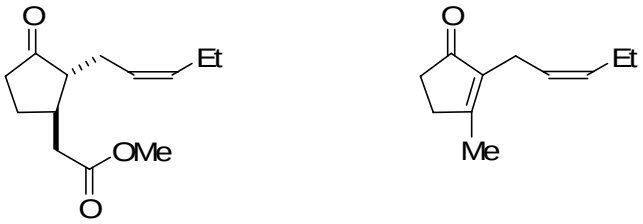
62. Binger, P.; Mueller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Krueger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035-1042.

CHAPTER 3

METHYL JASMONATE SYNTHESIS

3.1. Introduction

Methyl Jasmonate and Jasmone were both isolated from *Jasminium Grandiflorum L.* by Demole and coworkers in 1962.[1] Figure **3.1** shows an illustration of both methyl jasmonate and jasmone.



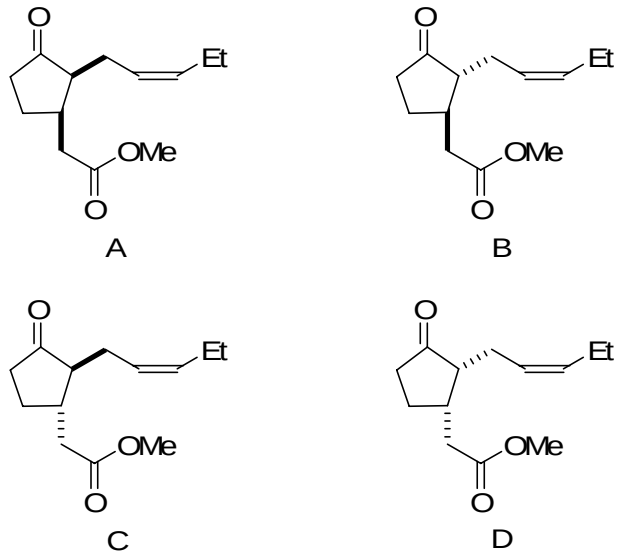
Methyl Jasmonate Jasmone

Figure **3.1.** Images of both Methyl jasmonate & Jasmone.

Four stereoisomers of methyl jasmonate exist. Arcee has shown that 1R, 2S (+)-Z-Methyl Epijasmonate has been known to posses the strongest odor.[2] 1R, 2R (–)–Z–Methyl Jasmonate has a weak odor. They also discovered that both the remaining isomers are odorless. The images of the four stereoisomers are shown in figure **3.2**.

3.2. The Utility of Methyl Jasmonate

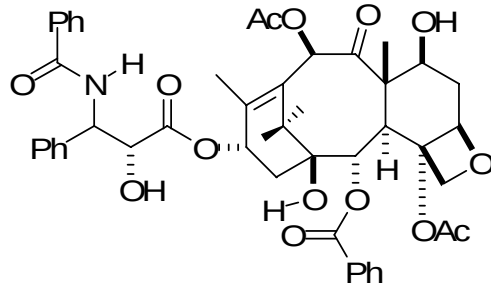
Bonfill and coworkers utilized methyl jasmonate to produce both Paciltaxel and Baccatin III in cell culture.[3] The *Taxus baccata L.* cell suspensions were kept in 175–cm^3 flasks that were capped with magenta B–caps. This suspension was kept at room temperature, stirred at 100 rpm in a shaker–incubator and in the dark. Gamborg's B5 medium used to grow both Paciltaxel and Baccatin III. One advantage of Bonfill's group method is that Paciltaxel can be made with fewer starting materials than when it was extracted.



A = 1R,2S (+)-Z-Methyl Epijasmonate
B = 1R,2R (-)-Z-Methyl Jasmonate
C = 1S,2S (+)-Z-Methyl Jasmonate
D = 1S,2R (-)-Z-Methyl Epijasmonate

Figure **3.2.** Four isomers of Methyl Jasmonate.

The extraction method utilized a large amount of the bark to produce a few grams of the product. What they discovered was that the overall concentration of methyl jasmonate for the Paciltaxel synthesis didn't really matter as long as the production of Paciltaxel was increased. What makes Paciltaxel interesting is that it is an anti–cancer drug that was first isolated from the pacific yew bark, *Taxus Brevifolia* in 1962.[4] Figure **3.3** shows an image of Paciltaxel.



Paciltaxel

Figure **3.3.** An image of Paciltaxel.

Jasmonates are involved in wound response of plants because of external damage caused by grazing animals, insects and microbes.[5]

3.3. The Biosynthesis of Jasmonic Acid & Methyl Jasmonate

Methyl Jasmonate & Jasmonic Acid can be synthesized in plants. The biosynthesis of Jasmonic Acid starts with α–linolenic acid which is converted to 10,11–dihydro–12–oxophytodienoic acid through several steps. Jasmonic Acid is produced from three β–oxidations from 10,11–dihydro–12–oxophytodienoic acid. Jasmonic Acid is converted to Methyl Jasmonate by ester formation and epimerization of the C–7 bond.[5,6] Figure 3.4 shows the biosynthesis of Jasmonic Acid and Methyl Jasmonate from α–linolenic acid.

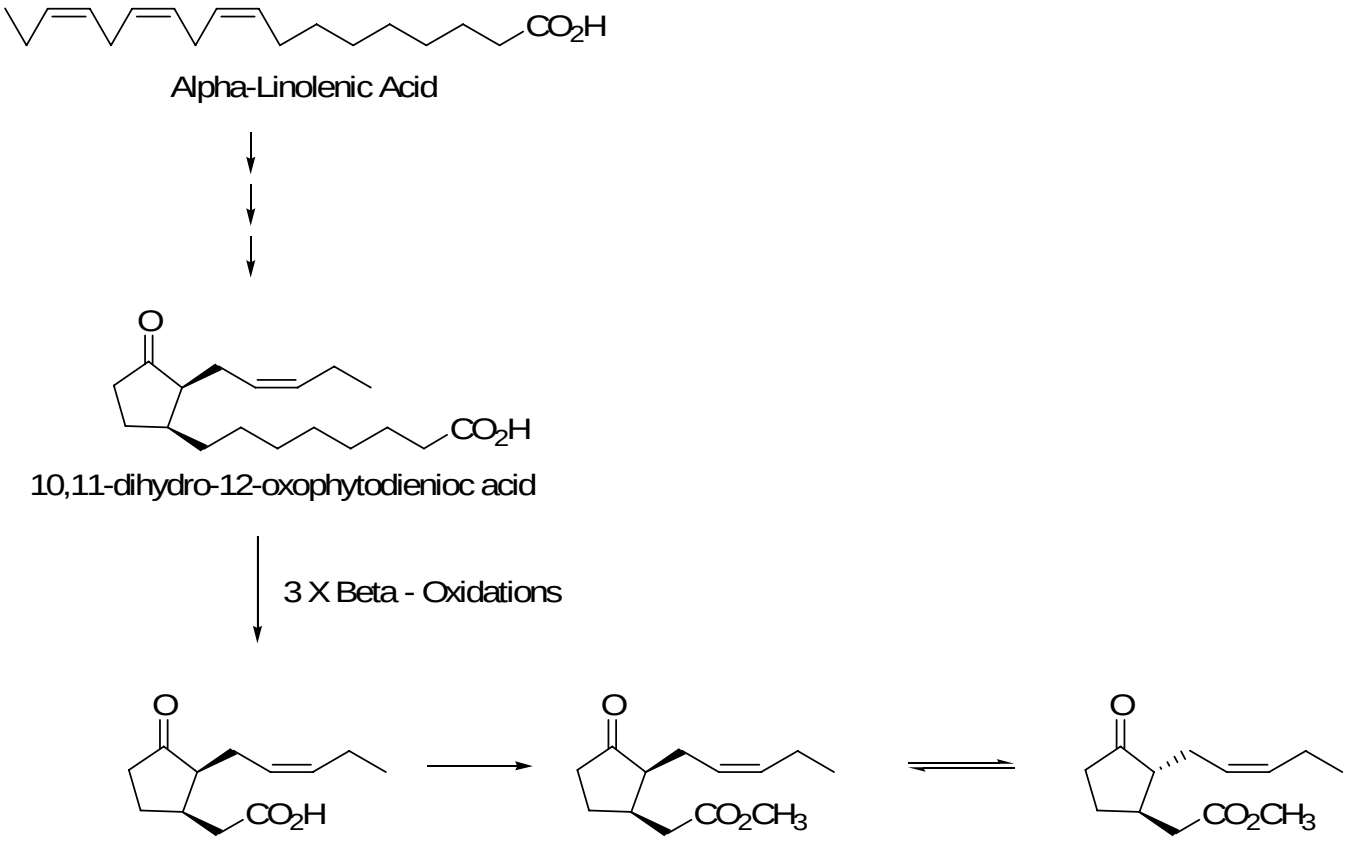


Figure **3.4.** Biosynthesis of Jasmonic Acid & Methyl Jasmonate.

3.4. The Chemical Syntheses of Methyl Jasmonate

Methyl Jasmonate is mainly utilized in the perfume industry because it has a jasmine fragrance. It was later discovered that Methyl Epijasmonate possessed the key jasmine component or fragrance.[7] Because of its importance to perfume industry, many synthetic groups have tried and been successful at producing methyl jasmonate in the lab. Masahisa Nakada's paper presents several dozen references for the synthesis of methyl jasmonate.[8]

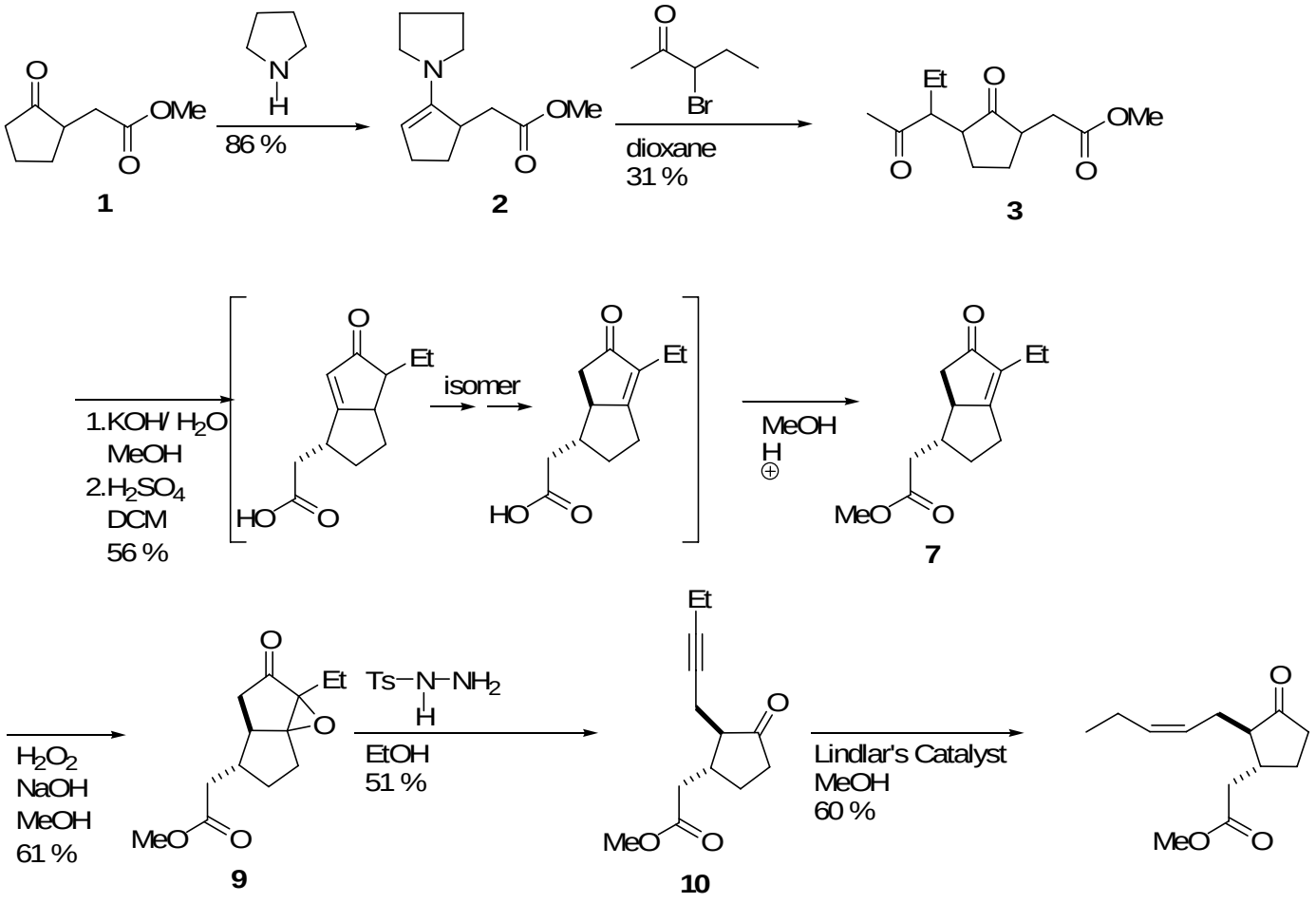
3.4.1. Sisido's Group

Methyl Jasmonate was synthesized from the pyrrolidine enamine of methyl 2–oxocyclopentane–1–acetate in an overall 31 % yield.[9] Substrate **7** was synthesized utilizing an intramolecular aldol condensation of compound **3** and a double bond migration to the more substituted olefin. It was made in a 56 % yield. The olefin in compound **7** was exposed to H_2O_2 in a basic solution to produce substrate **9** which contained an oxirane functionality. Compound **9** was made in a 61 % yield. Compound **9** was converted to substrate **10** in a 51 % yield using an Eschenmoser fragmentation. Methyl Jasmonate was made from compound **10** using a Lindlar Catalyst in 60 % yield. Scheme **3.1** shows the Sisido groups' reaction scheme.

3.4.2. G. Buchi's Group

Methyl Jasmonate was synthesized from 1,3–cyclohexadione by Buchi.[10] 1,3–Cyclohexandione was transformed into compound **3** in an 83 % yield using 1-bromo-2-pentyne in aqueous KOH. Substrate **4** was produced in a 76 % yield when compound **3** was chlorinated with *tert*–butyl hypochlorite. Substrate **5** was not isolated because when cyclopropanones are exposed to high temperatures from refluxing in xylene; they go thru a decarbonylation to produce an olefin such as compound **6** and carbon monoxide. Compound **6** was made in 74 %

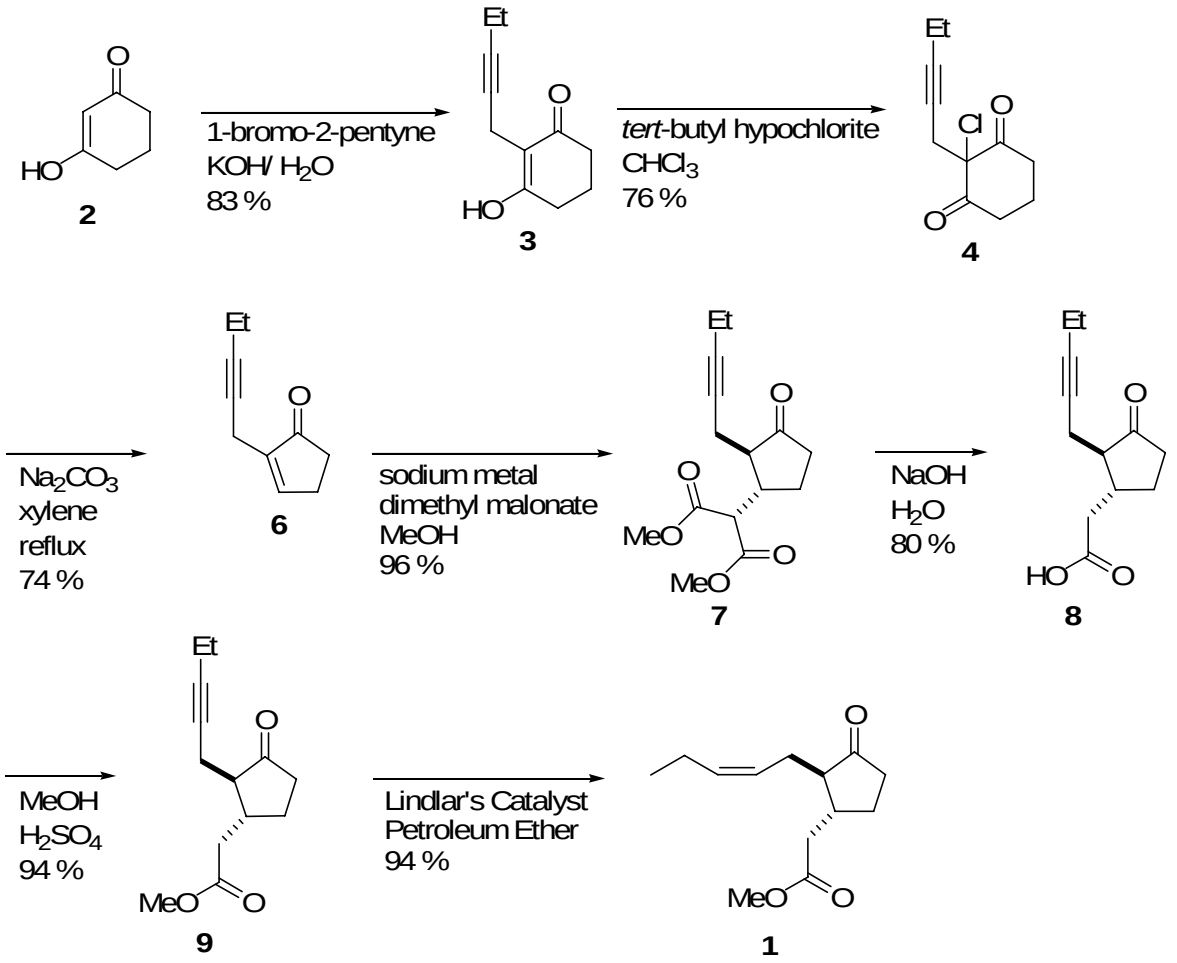
yield when substrate **4** was added to sodium carbonate. They utilized sodium carbonate in this transformation because they needed a base not susceptible to accepting the positive chlorine atom from compound **4**. When the reaction is carried out in the absence of sodium carbonate; compound **3** was the main product obtained instead of the substrate **6.** Compound **7** was made in a 96 % yield. The hydrolysis of compound **7** and its subsequent decarboxylation lead to the production of compound **8** in an 80 % yield. Substrate **8** was esterifies to compound **9** in a 94 % yield and the acetylene functionality of substrate **9** was reduced utilizing Lindlar's catalyst to produce methyl jasmonate, **1**, in a 94 % yield. Buchi group's synthetic scheme can be seen in scheme **3.2**.



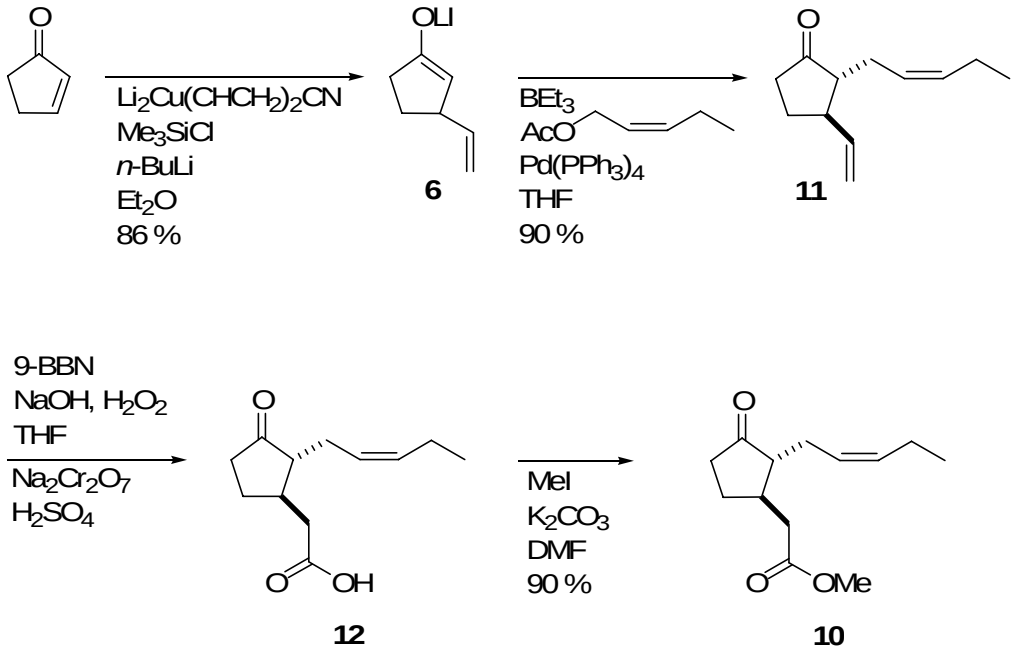
Scheme **3.1.** Sisido's synthesis of racemic Methyl Jasmonate.

3.4.3. Negishi's Group

Negishi synthesized Methyl Jasmonate from a cyclopentenone precursor.[11] A 1,4–cuprate addition to the cyclopentenone starting material produced substrate **6** in an 86 % yield. Substrate **11** was made from compound **6** using a palladium catalyzed cross coupling reaction. Compound **12** was made as a crude product when the external vinyl group on **11** was subjected to hydroboration–oxidation conditions to produce a primary alcohol. This primary alcohol was oxidized in the presence of $Na_2Cr_2O_7$ and H_2SO_4 to make the **12** with the carboxylate functionality. Methyl Jasmonate, **10**, was made in an overall 70 % yield from the cyclopentenone. Scheme **3.3** shows the route designed by Negishi and coworkers.



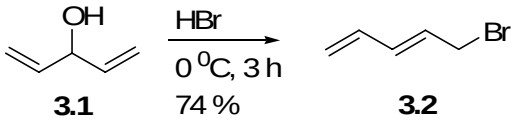
Scheme **3.2.** The Buchi group synthetic route to Methyl Jasmonate.



Scheme **3.3.** Negishi's synthesis of Methyl Jasmonate.

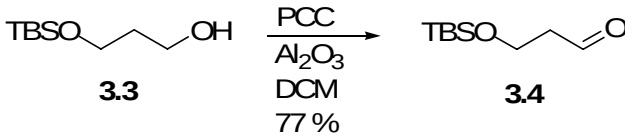
3.5. Discussion

5–Bromo–penta–1,3–diene was prepared from the protonation of the alcohol substituent on penta–1,4–dien–3–ol with HBr and its subsequent rearrangement to form a diene allylic carbocation that added a bromide anion. It was made in 74 % yield as a dark yellow oil. Scheme **3.4** shows the conversion of substrate **3.1** to substrate **3.2**.



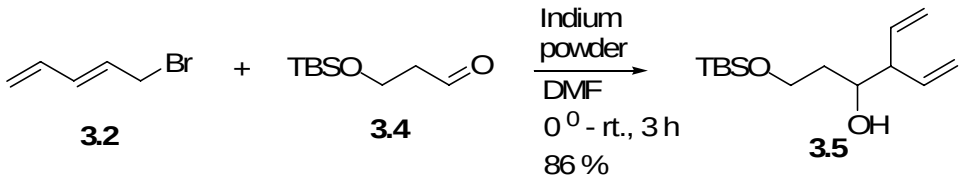
Scheme **3.4.** Production of the divinyl compound **3.2**.

3–(*tert*–Butyl–dimethyl–silanyloxy)–propionaldehyde was prepared from the oxidation of 3–(*tert*–Butyl–dimethyl–silanyloxy)–propan–1–ol using PCC and Al_2O_3. It was produced as a yellow pale oil in ~ 74 % yield. Scheme **3.5** shows the oxidation of the starting material to an aldehyde **3.4**.



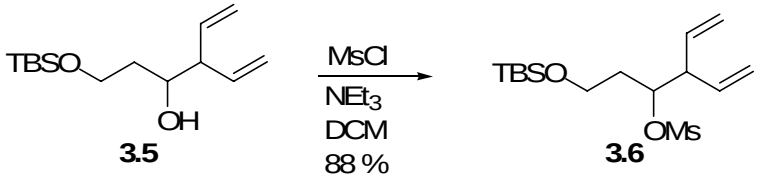
Scheme **3.5.** The oxidation of the primary alcohol to aldehyde **3.4**.

1–(*tert*–Butyl–dimethyl–silanyloxy)–4–vinyl–hex–5–en–3–ol, **3.5**, was prepared by pentadienylation.[12] This reaction used 5–Bromo–penta–1,3–diene**, 3.2,** 3–(*tert*–Butyl–dimethyl–silanyloxy)–propionaldehyde**, 3.4,** and indium to create a clear yellow oil in ~ 86 % yield. Scheme **3.6** illustrates the pentadienylation of compounds **3.2** & **3.4** to produce substrate **3.5**.



Scheme **3.6.** The production of substrate **3.5** from substrates **3.2** & **3.4**.

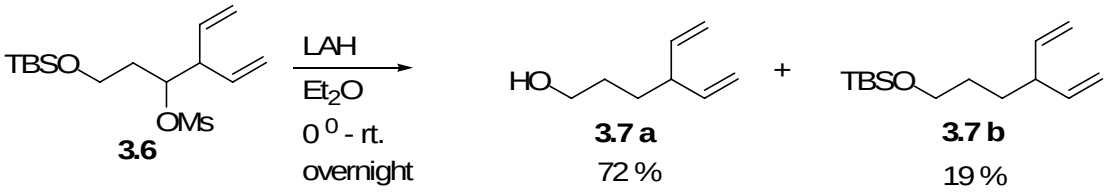
The hydroxyl group which is a poor leaving group on 1–(*tert*–Butyl–dimethyl–silanyloxy)–4–vinyl–hex–5–en–3–ol, **3.5**, was converted into a mesylate group.[13] Mesylate groups are good leaving groups and intermediate 3.5 was converted into methanesulfonic acid 1–[2–(*tert*–Butyl–dimethyl–silanyloxy)–ethyl]–2–vinyl–but–3–enyl ester, **3.6**, as a red-orange oil in 88 %. Scheme **3.7** shows how compound **3.6** was made from **3.5**.



Scheme **3.7.** The production of the mesylated compound **3.6**.

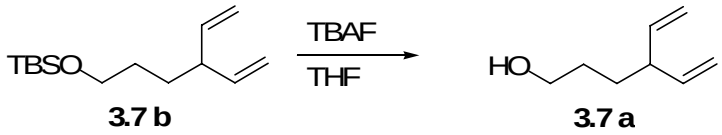
The mesylate functionality on methanesulfonic acid 1–[2–(*tert*–Butyl–dimethyl–silanyloxy)–ethyl]–2–vinyl–but–3–enyl ester, **3.6**, was displaced using an S_N2 mechanism and a hydride from LAH to produce 4–vinyl–hex–5–en–1–ol, **3.7a**. Compound **3.7a** was the desired

and also un–intended product. That is because this compound eliminated the need for an extra reaction. *tert*–Butyl–dimethyl–(4–vinyl–hex–5–enyloxy)–silane, **3.7b**, was also produced and purified from the same reaction. Both compounds made clear yellow oils in 72 % for the alcohol and 19 % for the silyl ether substrate which can be seen in scheme **3.8**.



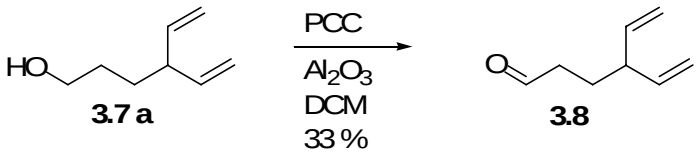
Scheme **3.8.** Products **3.7a** & **b** produced from compound **3.6**.

The silyl ether protecting of *tert*–butyl–dimethyl–(4–vinyl–hex–5–enyloxy)–silane, **3.7b**, was cleaved to produce substrate **3.7a** and it is shown in scheme **3.9**.[14]



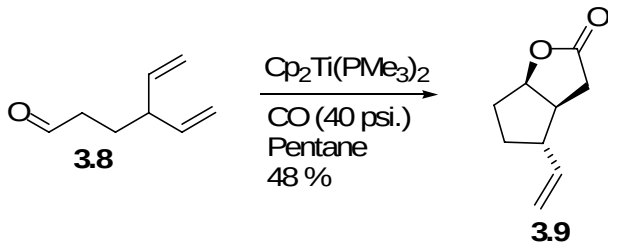
Scheme **3.9.** Conversion from substrate **3.7b** to **3.7a**.

4–vinyl–hex–5–en–1–ol, **3.7 a**, was oxidized to 4–vinyl–hex–5–enal, **3.8**, using PCC and Al_2O_3 to create a yellow clear oil at 33 % yield and it can be seen in scheme **3.10**.



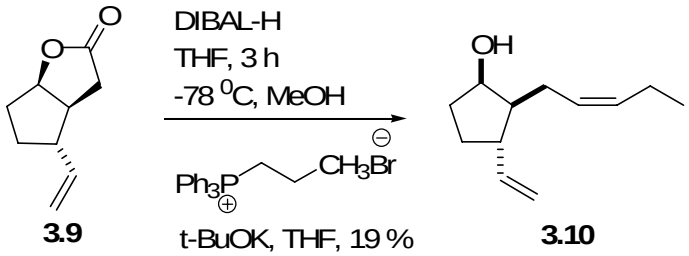
Scheme **3.10.** Oxidation of the primary alcohol to the aldehyde **3.8**.

4–vinyl–hexahydro–cyclopenta[*b*]furan–2–one, **3.9**, was made from utilizing 1 equivalent of 4–vinyl–hex–5–enal, 1 equivalent of $Cp_2Ti(PMe_3)_2$ and ~ 40 psi CO in the hetero Pauson-Khand reaction to make a dark yellow-orange oil in ~ 48 % yield. Scheme **3.11** shows the hetero Pauson–Khand reaction to produce substrate **3.9** from **3.8**.



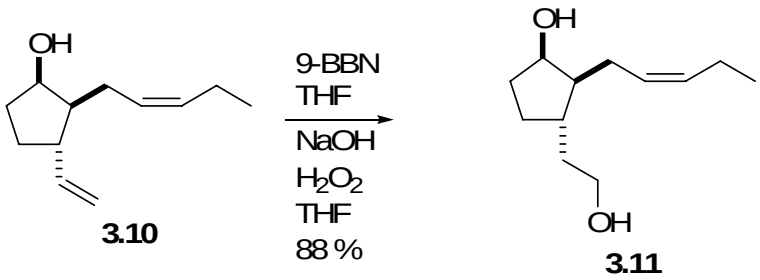
Scheme **3.11.** Conversion of substrate **3.8** to **3.9**.

2–Pent–2–enyl–3–vinyl–cyclopentanol, **3.10**, was made from compound **3.9**.[15] This reaction involved reducing the intermediate **3.9** by DIBAL-H reduction to the lactol which was followed by the subsequent Wittig reaction with $Ph_3P{=}CHCH_2CH_3$. Substrate **3.10** was created in a 19 % yield and the reaction can be seen in scheme **3.12**.



Scheme **3.12.** The production of compound **3.10** from the lactone intermediate **3.9**.

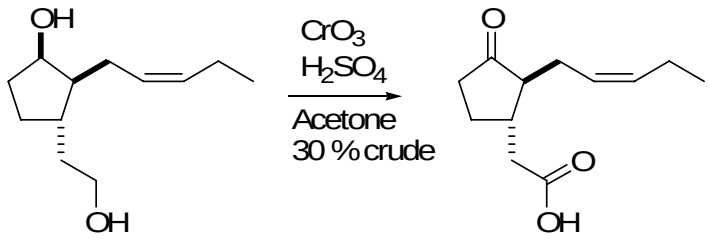
3–(2–Hydroxy–ethyl)–2–pent–2–enyl–cyclopentanol was made by doing a hydroboration–oxidation with 9-BBN on the unsubstituted vinyl group on substrate **3.11**.[16] This reaction produced a yellow clear oil in a 88 % yield and scheme **3.13** illustrates the reaction.



Scheme **3.13.** Hydroboration–oxidation of compound **3.10** to diol **3.11**.

(3–Oxo–2–pent–2–enyl–cyclopentyl)–acetic acid or jasmonic acid, **3.12**, was made from the Jones Oxidation of 3–(2–Hydroxy–ethyl)–2–pent–2–enyl–cyclopentanol, **3.11**.[17] A pale

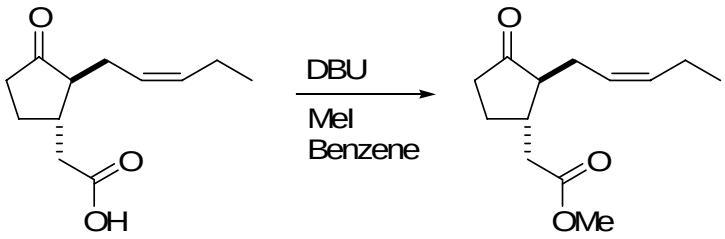
yellow oil was obtain at ~ 10 mg. Scheme **3.14** shows the Jones oxidation of both the primary and secondary alcohols in compound **3.11** to **3.12**.



3.11 **3.12**

Scheme **3.14.** Jones Oxidation of both the primary & secondary alcohols on diol intermediate **3.11** to **3.12**.

Methyl Jasmonate, **3.13** was made from using the crude form of substrate **3.12**.[18] Substrate **3.13** was produced in 60 % yield and the reaction is illustrated in scheme **3.15**.



3.12 **3.13**

Scheme **3.15.** Production of the target molecule Methyl jasmonate **3.13**.

3.6. Conclusion

Methyl jasmonate was synthesized as a pale yellow oil at 14 mg from jasmonic acid.

3.7. Experimental Section

All the solvents used in reaction were distilled to dryness according to the following procedures. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were both distilled from sodium / benzophenone ketyl under nitrogen. Pentane was distilled from sodium / benzophenone ketyl / tetraglyme. Acetonitrile, CH_3CN, and methylene chloride, CH_2Cl_2, were both distilled using

calcium hydride, CaH_2, under nitrogen. The titanocene complex was made as according to the literature procedure.[19,20]

Analytical thin–layer chromatography (TLC) was performed on Sorbent Technologies silica gel plates with plastic backing. Components were visualized by illumination with long wave ultraviolet light, exposure to iodine vapor, or by standing with one of the following reagents (followed by heating): *p*–anisaldehyde (or vanillin) in ethanol/sulfuric acid; 7% phosphomolybdic acid in ethanol; 0.04 M ammonium molybdate in 10% sulfuric acid. Solvents for extraction and chromatography were reagent grade and used as received. Flask column chromatography was performed using Sorbent Technologies 60 Å Silica Gel standard grade.

3.8. Preparative Procedures

5–Bromo–penta–1,3–diene (3.2). To a 250 mL round bottom flask containing penta–1,4–dien–3–ol, **3.1**, (14.82g, 176.18 mmol, 1 equiv.) that was purged by vacuum and flushed with nitrogen. HBr (21.38g, 264.27 mmol, 1.5 equiv.) was added dropwise at 0 ^{0}C. The reaction mixture was stirred at 0 ^{0}C for 3 hours. The resultant mixture was warmed to room temperature and quenched with cold diethyl ether and extracted two times. The combined organic phase was then washed with NaHCO, dried and concentrated to afford the crude product. This crude product was distilled to produce 5–bromo–penta–1,3–diene as a bright yellow oil at 74 % yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.43–6.21 (m, 2H), 5.9–5.8 (m, 1H), 5.4–5.09 (m, 2H), 4.04–4.01 m (d, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 135.27, 129.09, 119.43, 32.82.

3–(*tert*–Butyl–dimethyl–silanyloxy)–propionaldehyde (3.4). PCC (19.49g, 90.46 mmol, 1.5 equiv.) and Al_2O_3 (19.49g) were both added to a flask equipped with a stir-bar that was purged by vacuum and flushed with nitrogen. To this mixture, DCM was syringed into the flask and stirred at room temperature for a few minutes. 3–(*tert*–Butyl–dimethyl–silanyloxy)–

propan–1–ol, **3.3**, (11.48g, 60.31 mmol, 1 equiv.) in DCM was cannulated into the flask containing the PCC and Al_2O_3 and stirred at room temperature for approximately 2–3 hours. Diethyl ether was added to the reaction mixture and it was concentrated to remove the DCM/ ether. The product was purified using all of the oxidized brown compound and flash chromatography (silica gel: pentane/ diethyl ether (9:1)) to produce a clear yellow oil in a 77 % yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.79 (s, 1H), 3.98 (t, *J*=6.05 Hz, 2H), 2.59 (t, *J*=2.1 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 58.77, 57.39, 46.54, 37.39, 25.79, – 5.45.

1–(*tert*–Butyl–dimethyl–silanyloxy)–4–vinyl–hex–5–en–3–ol (3.5). Indium powder (5.36g, 46.72 mmol, 1 equiv.) was added to a round bottom flask equipped with a stir-bar, purged by vacuum and filled with nitrogen. To this flask, 3–(*tert*–Butyl–dimethyl–silanyloxy)–propionaldehyde, **3.4**, (8.8g, 46.72 mmol, 1 equiv.) in DMF was added and stirred for a few minutes. 5–Bromo–penta–1,3–diene, **3.2**, (13.74g, 93.45 mmol, 2 equiv.) in DMF was added to the reaction mixture and it was stirred at 0 ^{0}C for three hours. The mixture was quenched with 1N HCl and extracted using diethyl ether. It was washed using brine and dried using sodium sulfate. It was column chromatographed (silica gel: pentane/ diethyl ether (95:05)) and concentrated to produce a light clear yellow oil at 86 % yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.9–5.78 (m, 1H), 5.16–5.08 (m, 2H), 3.82–3.77 (m, 2H), 1.7–1.61 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.81, 137.36, 116.73, 116.5, 73.64, 62.58, 54.74, 35.89, 25.86, 18.14, – 5.55.

Methanesulfonic acid 1–[2–(*tert*–Butyl–dimethyl–silanyloxy)–ethyl]–2–vinyl–but–3–enyl ester (3.6). 1–(*tert*–Butyl–dimethyl–silanyloxy)–4–vinyl–hex–5–en–3–ol, **3.5**, (16.15g, 63.47 mmol, 1 eqiuv.) was cannulated into a round bottom flask equipped with a stir-bar and dichloromethane. NEt_3 (16.06g, 158.68 mmol, 2.5 equiv.) was syringed into the RBF

containing the starting material and it was stirred for a few minutes at room temperature. The temperature was lowered to 0 ^{0}C; before MsCl (10.91g 95.21 mmol, 1.5 equiv., 7.4 mL) was syringed into the mixture and it was warmed to room temperature and stirred for 2 hours. Et_2O (800 mL) was added to the reaction and the organic layer was extracted three times. The organic phase was then washed with NaHCO and brine and dried using anhydrous $MgSO_4$. The product was purified by flash chromatography (silica gel: hexane/ ethyl acetate (9:1)) and concentrated to make a dark yellow oil in 96 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84–5.73 (m, 1H), 5.23–5.15 (m, 2H), 3.73–3.69 (m, 2H), 3.02 (s, 3H), 1.89–1.81 (m, 2H), 0.89 (s, 9H), –0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.57, 135.11, 118.48, 118.14, 82.17, 58.65, 51.83, 38.44, 34.54, 25.86, 18.19, – 5.39.

4–vinyl–hex–5–en–1–ol (3.7 a). LAH (16.24g, 427.96 mmol, 7 equiv.) was added to a flask that was purged by vacuum and filled with nitrogen and equipped with a stir-bar. The temperature was lowered to 0 ^{0}C before the methanesulfonic acid 1–[2–(*tert*–Butyl–dimethyl–silanyloxy)–ethyl]–2–vinyl–but–3–enyl ester, **3.6**, (20.33g, 61.14 mmol, 1 equiv.) in Et_2O was cannulated into the mixture. The reaction was allowed to warm up to room temperature and stirred overnight. The reaction mixture was quenched slowly by adding water (225 mL) drop–wise. Cold diethyl ether (100 mL) was also added and the mixture was filtered through celite. The products were purified using flash chromatography (silica gel: pentane/ diethyl ether (8:2)) to produce two compounds. The first compound was a dark clear yellow oil in a 19 % yield and identified to be *tert*–butyl–dimethyl–(4–vinyl–hex–5–enyloxy)–silane, **3.7 b**, and the second compound was the a clear yellow oil in a 72 % yield and the desired compound. Compound **3.7 a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76–5.67 (m, 1H), 5.04–5 (m, 2H), 3.72–3.71 (m, 2H), 1.6–1.5 (m, 2H), 1.49–1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.00, 114.42, 62.90, 47.61, 30.42, 30.36. Compound **3.7 b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76–5.67 (m, 1H), 5.03–4.98

(m, 2H), 3.61–3.58 (t, *J*=12.56 Hz, 2H), 1.54–1.5 (m, 2H), 1.47–1.43 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.21, 114.2, 63.08, 47.58, 30.52, 30.37, 25.96, 18.34, – 5.28.

4–vinyl–hex–5–enal (3.8) PCC (9.76g, 45.3 mmol, 1.5 equiv.) and Al_2O_3 (9.76) were both added to a flask equipped with a stir-bar that was purged and flushed with nitrogen. To this mixture, DCM was syringed into the flask and stirred at room temperature for a few minutes. 4–vinyl–hex–5–en–1–ol, **3.7 a**, (3.81g, 30.2 mmol, 1 equiv.) in DCM was cannulated into the flask containing the PCC and Al_2O_3 and stirred at room temperature for approximately 2–3 hours. Diethyl ether was added to the reaction mixture and it was concentrated to remove the DCM/ ether. The product was purified using all of the oxidized brown compound and flash chromatography (silica gel: pentane/ diethyl ether (9:1)) to produce a clear yellow oil in a 33 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (t, *J*=1.52 Hz, 1H), 5.73–5.65 (m, 1H), 5.06–5.02 (m, 2H), 2.48–2.44 (m, 2H), 1.78–1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.18, 140.10, 115.22, 47.16, 41.60, 26.32.

4–vinyl–hexahydro–cyclopenta[*b*]furan–2–one (3.9). 4-vinyl-hex-5-enal, **3.8**, (2.55g, 20.37 mmol, 1 equiv.) was added to a pressure apparatus equipped with a stir-bar and pentane (40 mL). $Cp_2Ti(PMe_3)_2$ (6.73g, 20.37 mmol, 1 equiv.) was also added to the reaction mixture and stirred for a few minutes. The apparatus was sealed in the glove box and removed shortly afterwards. Carbon monoxide gas (40 psi.) was introduced into the apparatus and it was stirred at room temperature for 24 hours. The reaction mixture was poured into a beaker with Et_2O (100 mL) and stirred for several hours exposed to the air. There was a color change from dark purple to mustard yellow and it was filtered through a silica gel plug to produce a 2.18g of a red–orange oil that was the crude product. The product was obtained by flash chromatography (silica gel: pentane/ diethyl ether (8:2)) as a dark yellow-orange clear oil in 48 % yield. ^{1}HMR

(400 MHz, $CDCl_3$): δ 5.72–5.66 (m, 1H), 5.07–5.03 (m, 2H), 5.00–4.95 (m, 1H), 2.76–2.7 (m, 1H), 2.5–2.48 (d, *J*=7.04 Hz, 1H), 2.39–2.29 (m, 2H), 2.19–2.17 (m, 1H), 1.98–1.9 (m, 2–3H), 1.53–1.48 (m, 1H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 176.89, 139.32, 115.11, 85.78, 50.01, 44.96, 34.14, 31.86, 31.32.

2–Pent–2–enyl–3–vinyl–cyclopentanol (3.10). A 1.5 M solution of DIBAL–H in toluene (9 mL, 13.01 mmol, 1.65 equiv.) was added to 4–vinyl–hexahydro–cyclopenta[*b*]furan–2–one, **3.9**, (1.2 g, 7.88 mmol, 1 equiv.) in THF (8.25 mL) at –78 ^{0}C. After stirring for 3 h; methanol (7.2 mL) was added to the mixture and it was warmed to room temperature. Saturated NH_4Cl (22 mL), Et_2O (108 mL) and saturated sodium potassium tartrate (108 mL) were added to the suspension and it was stirred for 15 minutes to break up the emulsion. The aqueous phase was collected and it was extracted with Et_2O (2 x 23 mL) and the organic phase was dried with $MgSO_4$, filtered, and concentrated to produce the lactol as a crude clear oil at 2.09 g.
To a mixture of $Ph_3^+(CH_2)_2CH_3Br^-$ (6.11 g, 15.85 mmol, 2.01 equiv.) in THF (25 mL) at 0 ^{0}C was added to a solution of potassium *tert*–butoxide in THF (4.14 mL, 33.25 mmol, 4.22 equiv.). After 15 minutes a solution of the lactol (1.2 g, 7.88 mmol, 1 equiv.) in THF (25 mL) was added to the mixture. Saturated KH_2PO_4 was added to the mixture after stirring for 2.5 h and it was warmed to room temperature. The mixture was extracted using EtOAc (4 x 50 mL), dried over Na_2SO_4, filtered, and concentrated to produce 1.94 g of a pale yellow oil. The crude oil was purified using flash column chromatography (silica gel: pentane/ diethyl ether (8:2)) to produce 2–Pent–2–enyl–3–vinyl–cyclopentanol, **3.10**, as a clear yellow oil in 19 % yield. ^1H NMR (250 MHz, $CDCl_3$): δ 5.63–5.59 (m, 1H), 5.44–5.38 (m, 2H), 5.05–4.93 (m, 2H), 4.23 (s, 1H), 4.15–4.07 (dd, *J*=7.15 Hz, 1H), 2.4–2.29 (m,), 2.17–2.04 (m, 2H), 0.99–0.93 (t, *J*=15.05 Hz, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 142.65, 132.95, 128.05, 114.7, 74.46, 47.59, 33.84, 30.29, 25.36, 21.45, 20.99, 14.68.

3–(2–Hydroxyethyl)–2–pent–2–enyl–cyclopentanol (3.11). 2–Pent–2–enyl–3–vinyl–cyclopentanol, **3.10**, (.121g, .671 mmol, 1 equiv.) was added to a flask containing THF and a stir-bar. 9-BBN (2.89 mL) was syringed into the mixture at 0 ^{0}C and it was warmed to room temperature and stirred for 2.5 hours and an additional 9-BBN (.671 mL) was added to the mixture. The reaction was checked by TLC for completion and it was stirred an additional 1 hour. The mixture was exposed to air and 3M NaOH (1.9 mL) was added and the temperature was then lowered to 0 ^{0}C and 30 % H_2O_2 (1.52 mL) was added dropwise. The mixture was allowed to warm-up to room temperature and stirred an additional 1 hour. Et_2O (38 mL) was added to the reaction mixture and it was washed with both $NaHCO_3$ (38 mL) and brine (38 mL) and dried over $MgSO_4$. The product was obtained by flash column chromatography (silica gel: pentane/ diethyl ether (9:1)) to produce a yellow clear oil at 88 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73–5.61 (m, 1H), 5.41 (s, 2H), 5.04–4.95 (m, 2H), 4.24 (s, 1H), 2.39–2.36 (m,), 2.15–1.96 (m,), 1.65–1.58 (m,), 1.43–1.34 (m,), 1.25–1.24 (m,), 0.99–0.94 (t, *J*=7.47 Hz, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 133.06, 128.17, 62.38, 52.01, 39.11, 36.74, 33.78, 27.85, 25.93, 21.04, 14.66.

(3–Oxo–2–pent–2–enyl–cyclopentyl)–acetic acid (3.12). A solution containing CrO_3 (60.5 mg, 0.605 mmol, 3.77 equiv.) in 1.5M H_2SO_4 (0.967 mL, 0.145 mmol, 9.03 equiv.) was kept between 5–10 ^{0}C. 3–(2–Hydroxy–ethyl)–2–pent–2–enyl–cyclopentanol, **3.11**, (31.8 mg, 0.16 mmol, 1 equiv.) in acetone (1.93 mL) was added to the mixture and stirred for 6 hours at between 5–10 ^{0}C. It was stirred an additional 2 hours at room temperature. Et_2O (1.45 mL) was added and the mixture was extracted in brine (3 x 1.45 mL). The organic phase was concentrated and Et_2O (0.96 mL) was added. The mixture was extracted using 1M NaOH (2 x 0.72 mL). The basic extracts were acidified with 6M H_2SO_4 and back extracted in Et_2O (3 x

0.72 mL). The combined Et_2O extracts were washed with water & brine and dried with $MgSO_4$ and concentrated to produce a pale yellow oil in 30 % yield as the crude product.

(3–Oxo–2–pent–2–enyl–cyclopentyl)–acetic acid methyl ester (3.13). To a solution of (3–Oxo–2–pent–2–enyl–cyclopentyl)–acetic acid, **3.12**, (0.0219g, 1.04 mmol, 1 equivalent) and DBU (0.0186g, 0.122 mmol, 1.17 equivalents) in benzene (5.2 mL) was added iodomethane (0.0222g, 0.156 mmol, 1.5 equivalents) in benzene (1.73 mL) at an ice–bath temperature. The reaction was stirred for 2 h at room temperature, poured into cold water (6 mL) and extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated to produce the crude product. The product was obtained by flash column chromatography (silica gel: hexane/ diethyl ether (5:1)) to produce a yellow clear oil at 60 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45–5.42 (m, 1H), 5.26–5.23 (m, 1H), 3.68 (s, 3H), 2.71–2.68 (m, 1H), 2.36–2.31 (m, 2H), 2.28–2.19 (m, 2H), 2.14–2.12 (m, 1H), 2.04–2.02 (m, 3H) 1.89–1.87 (m, 1H), 1.51–1.45 (m, 1H), 0.96–0.93 (t, *J*=15.04 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.79, 172.47, 134.04, 124.92, 53.97, 51.53, 38.78, 37.99, 37.67, 27.18, 25.47, 20.55, 14.03.

3.9. References

1. Demole, E.; Lederer, E.; Mercier, D. *Helv. Chim. Acta* **1962**, *45*, 675-685.

2. Acree, T. E.; Nishida, R.; Fukami, H. *J. Agric. Food. Chem.* **1985**, *33*, 425-427.

3. Bonfill, M.; Bentebibel, S.; Moyano, E.; Palazon, J.; Cusido, R. M.; Eibl, R.; Pinol, M. T. *Biol. Plant.* **2007**, *51*, 647-652.

4. Walsh, V.; Goodman, J. *Med Anthropol* **2002**, *21*, 307-336.

5. Beale, M. H.; Ward, J. L. *Nat. Prod. Rep.* **1998**, *15*, 533-548.

6. Mueller, M. J. *Physiol. Plant.* **1997**, *100*, 653-663.

7. Kiyota, H.; Koike, T.; Higashi, E.; Oritani, T. *Flavour Fragrance J.* **2002**, *17*, 267-271.

8. Takeda, H.; Watanabe, H.; Nakada, M. *Tetrahed.* **2006**, *62*, 8054-8063.

9. Sisido, K.; Kurozumi, S.; Utimoto, K. *J. Org. Chem.* **1969**, *34*, 2661-2664.

10. Buchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021-2023.

11. Luo, F. T.; Negishi, E. *Tetrahedron Lett.* **1985**, *26*, 2177-2180.

12. Hirashita, T.; Inoue, S. i.; Yamamura, H.; Kawai, M.; Araki, S. *J. Organomet. Chem.* **1997**, *549*, 305-309.

13. Tagat, J. R.; McCombie, S. W.; Nazareno, D.; Labroli, M. A.; Xiao, Y.; Steensma, R. W.; Strizki, J. M.; Baroudy, B. M.; Cox, K.; Lachowicz, J.; Varty, G.; Watkins, R. *J. Med. Chem.* **2004**, *47*, 2405-2408.

14. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.

15. Klimko, P.; Hellberg, M.; McLaughlin, M.; Sharif, N.; Severns, B.; Williams, G.; Haggard, K.; Liao, J. *Bioorg Med Chem* **2004**, *12*, 3451-3469.

16. Schrader, T. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998-11000.

17. Millar, J. G.; Oehlschlager, A. C.; Wong, J. W. *J. Org. Chem.* **1983**, *48*, 4404-4407.

18. Lee, W. Y.; Jang, S. Y.; Kim, M.; Park, O. S. *Synth. Commun.* **1992**, *22*, 1283-1291.

19. Binger, P.; Mueller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Krueger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035-1042.

20. Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem.* **1985**, *97*, 425-426.

CHAPTER 4

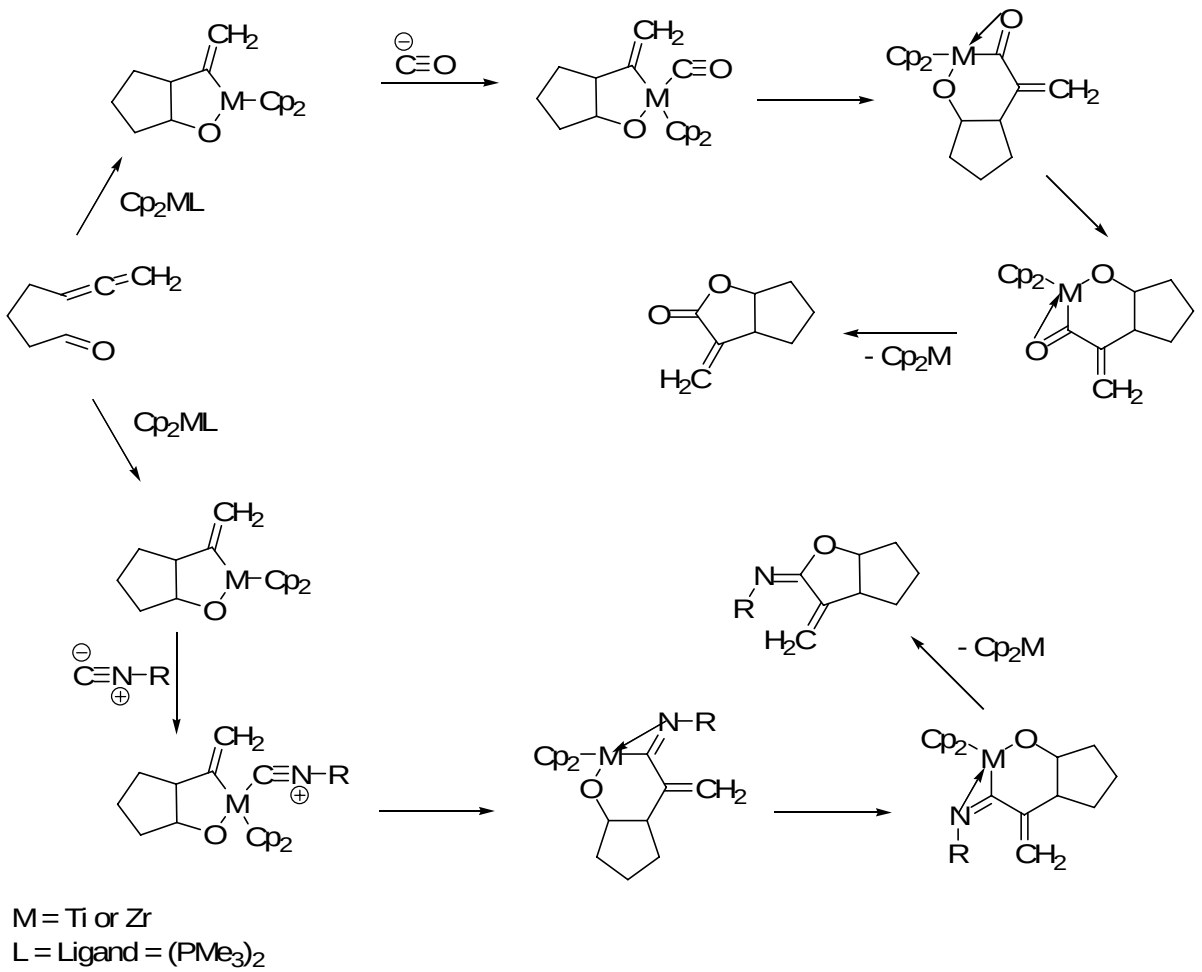
ISONITRILE INSERTIONS

4.1. Ligands other than Carbon Monoxide: Isonitriles NCR

Gautier [1] and Hoffmann [2] both simultaneously discovered isocyanides in 1867. These compounds had an offensive odor, but isocyanides were difficult to synthesize and it was not until the work of Ugi [3-7] that an easy way produce isocyanides became available. Isocyanides are stronger σ donors that CO.[8] Isocyanides are slightly weaker π–acceptors than CO. Like CO, isocyanides and isonitriles both are able to do insertions into metal–carbon bonds (Scheme **4.1**). RNC are better σ–donors because they can stabilize higher oxidation states. The ability of RNC to stabilize higher oxidative states decreases as the number of CO ligands increase on the metal center. When RNC ligands are coordinated to high–valent metal centers; there is an increase in the C–N stretching frequency on the coordination to the metal. Conversely, when RNCs are attached to low oxidative metal centers; they cause the N–C stretching frequency to decrease on the coordination to the metal center.[9]

4.1.1. Carbon Monosulfide, CS

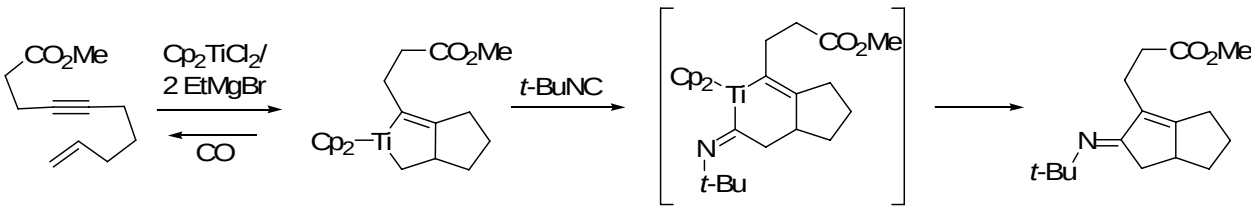
Carbon monosulfide is a compound that is isoelectronic to both carbon monoxide and isocyanides.[10] It is made from photolysis, thermolysis, and or cold electrical discharge. It is a highly reactive gaseous compound that is "short–lived". The amount of time that CS exists depends on several variable factors. These factors include pressure, temperature, and the surface to volume ratio. At high temperatures above – 160 ^{0}C and exposure to sunlight, CS polymerizes readily with itself.



Scheme **4.1.** The CO & CNR insertion into M–C σ bond of allenals.

4.2. Synthetic Reactions using NCR: Buchwald & Grossman

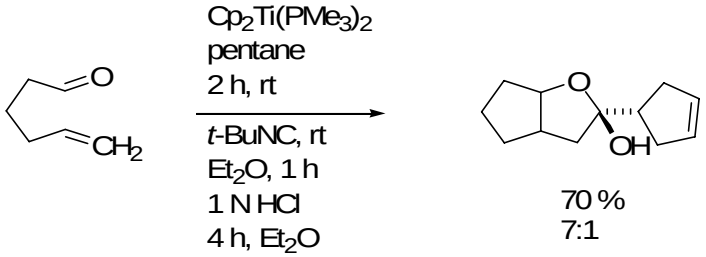
Buchwald and Grossman produced iminocyclopentenes and cyclopentenenones from different substituted enynes utilizing a titanocene carbonylation with either CO or isocyanides.[11,12] One enyne substrate was not able to produce the desired cyclopentenenone. Instead, the only compound that was obtained was the starting material. When the same enyne was converted to the titanocycle; the compound was subjected to isonitrile insertion and produced an iminocyclopentene.



Scheme **4.2.** The synthesis of iminocyclopentenes from 1,6–enynes.

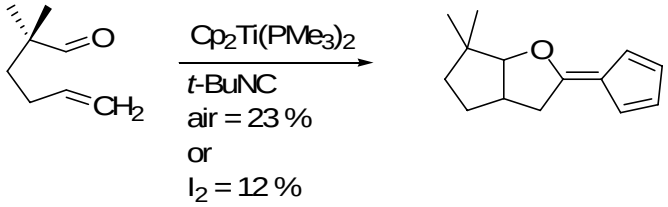
4.2.1. Vu's Reaction

Vu synthesized an azadiene complex from an enal substrate using a titanium catalyst and an isonitrile insertion.[13] When acid was added to the azadiene complex; bicyclic lactol analogs were produced in the reaction. Scheme **4.3** shows the synthesis of the bicyclic lactol.



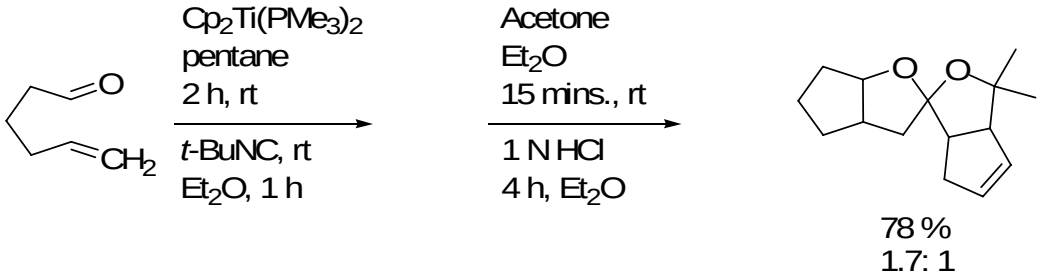
Scheme **4.3.** Synthesis of a bicyclic lactol.

When the reaction is done in the absence of an acid and in the presence of air or I_2; bicyclic fulvenes were produced in 23 % and 12 % yields. Scheme **4.4** shows the bicyclic fulvene synthesis.



Scheme **4.4.** The oxidation of the azadiene complex with air or Iodine.

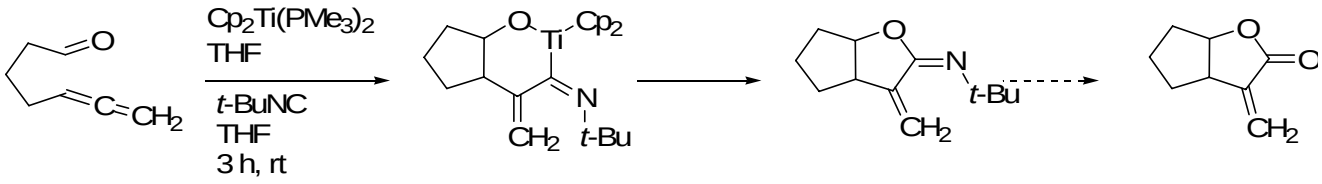
Vu also produced analogs of tetracyclic spiroketal compounds from azadiene complexes when acetone was added before the acid in the reaction. (Scheme **4.5**)



Scheme **4.5.** Production of tetracyclic spiroketal compound

4.2.2. Steve's Reaction

In chapter 2, it was reported that α–methylene–γ–butyrolactones cannot be produced from a titanacene mediated hetero Pauson–Khand reaction. Based on Buchwald's, Grossman's[12] and Vu's[13] research using isonitrile insertions, it was determined that the titanacene allenal macrocycles should be subjected to isonitrile insertions to create derivatives of *tert*–butyl–(3–methylene–hexahydro–cyclopenta[*b*]furan–2–ylidene)–amines. This would later be followed by hydrolysis to produce the desired α–methylene–γ–butyrolactones. The synthesis of α–methylene–γ–butyrolactones via isonitrile insertion is seen in Scheme **4.6**.

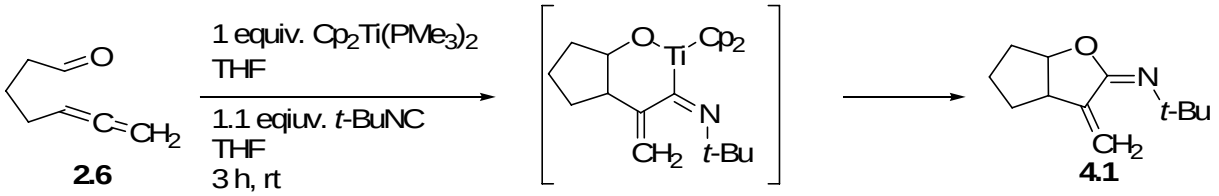


Scheme **4.6.** A proposed synthesis of α–methylene–γ–butyrolactones via isonitrile insertions.

4.3. Discussion and Conclusion

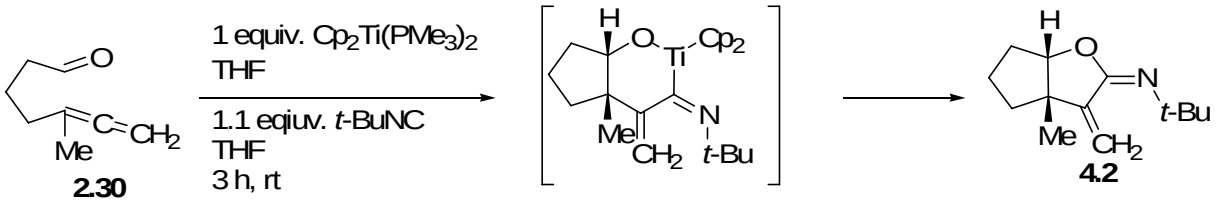
Since the titanium promoted cyclocarbonylation of allene aldehyde substrates failed to produce the desired α–methylene–γ–butyrolactones; it was decided to try and synthesize *tert*–butyl–(3–methylene–hexahydro–cyclopenta[*b*]furan–2–ylidene)–amine analogs instead. These analogs could later be hydrolyzed to the corresponding α–methylene–γ–butyrolactones. To

accomplish this goal, it was first decided to create compound **4.1** from the isonitrile insertion into substrate **2.6**. The synthesis of substrate **4.1** is presented in Scheme **4.7.**



Scheme **4.7.** Proposed synthesis of substrate **4.1** from compound **2.6**.

The synthesis of compound **4.2** was attempted from the starting reagent **2.30**. In the end, both substrates **4.1** and **4.2** were not produced. Scheme **4.8** shows the reaction scheme to create compound **4.2** from the starting material **2.30**.



Scheme **4.8.** Production of compound **4.2** from starting material **2.30**.

4.4. References

1. Gautier, A. *Ju. Lieb. Ann. Chem.* **1867**, *142*, 289-294.

2. Hofmann, A. W. *Ju. Lieb. Ann. Chem.* **1867**, *144*, 114-120.

3. Hahn, F. E. *Angew. Chem.* **1993**, *105*, 681-696 (See also Angew Chem, Int Ed Engl , 1993, 1932(1995), 1650-1665.).

4. Hahn, F. E. *Angew. Chem., Int. Ed.* **1993**, *32*, 650.

5. Ugi, I.; Fetzner, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem.* **1965**, *77*, 492-504.

6. Ugi, I.; Fetzner, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem. Int. Ed.* **1965**, *4*, 472-484.

7. Ugi, I.; Meryr, R. *Chem Ber.* **1960**, *93*, 239-248.

8. Werner, H. *Angew. Chem. Int. Ed.* **1990**, *29*, 1077-1089.

9. Yamamoto, Y. *Coord. Chem. Rev.* **1980**, *32*, 193-233.

10. Moltzen, E. K.; Klabunde, K. J.; Senning, A. *Chem. Rev.* **1988**, *88*, 391-406.

11. Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 4912-4913.

12. Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803-5805.

13. Vu, A. T. **1997**.

APPENDIX A. SUPPLEMENTAL ^{1}H AND ^{13}C–NMR DATA FOR CHAPTER 2

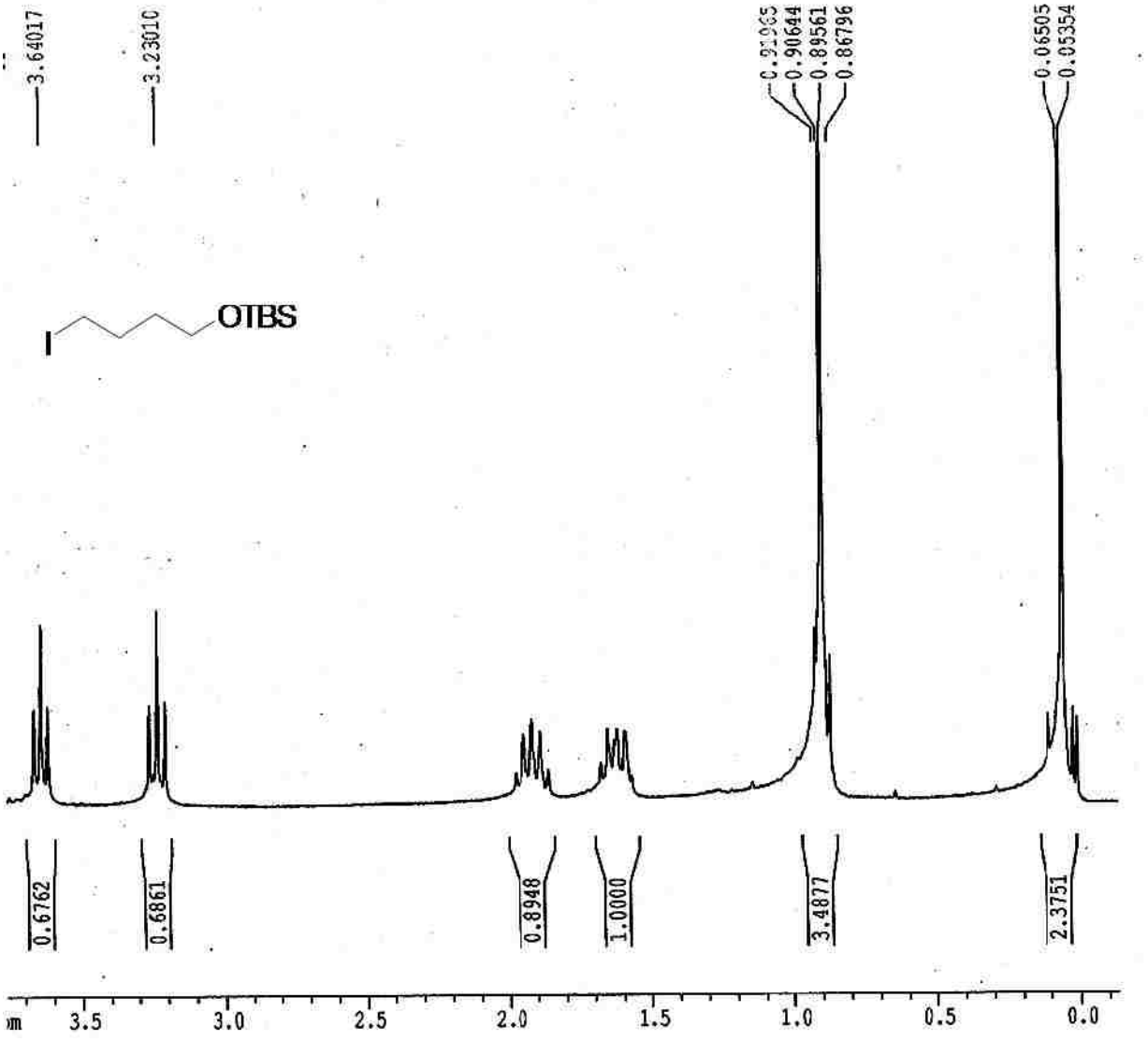


Figure **A.1.** ^{1}H NMR (250 MHz, $CDCl_3$) of compound **2.2**

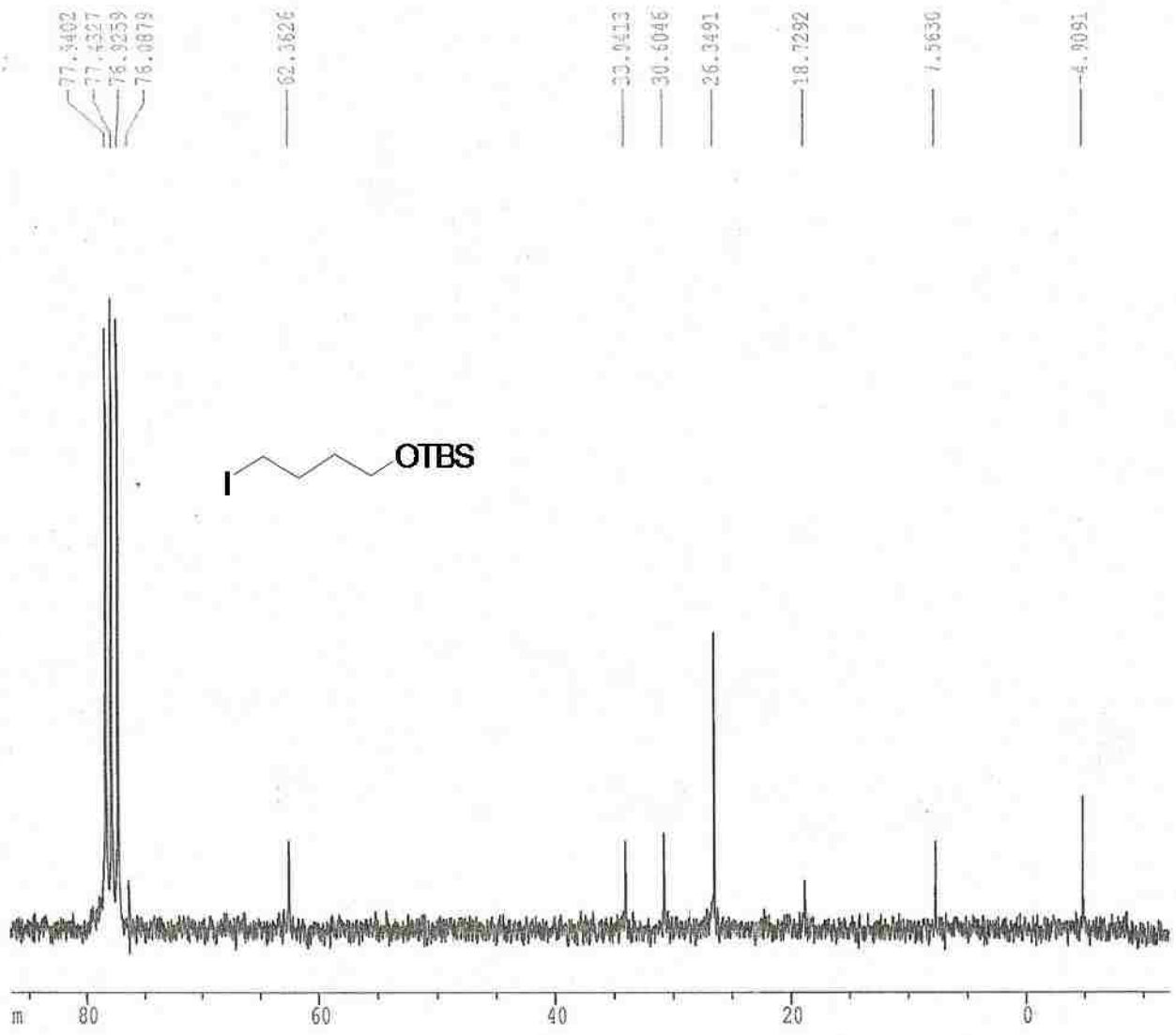


Figure **A.2.** ^{13}C NMR (62.5 MHz, $CDCl_3$) of compound **2.2**

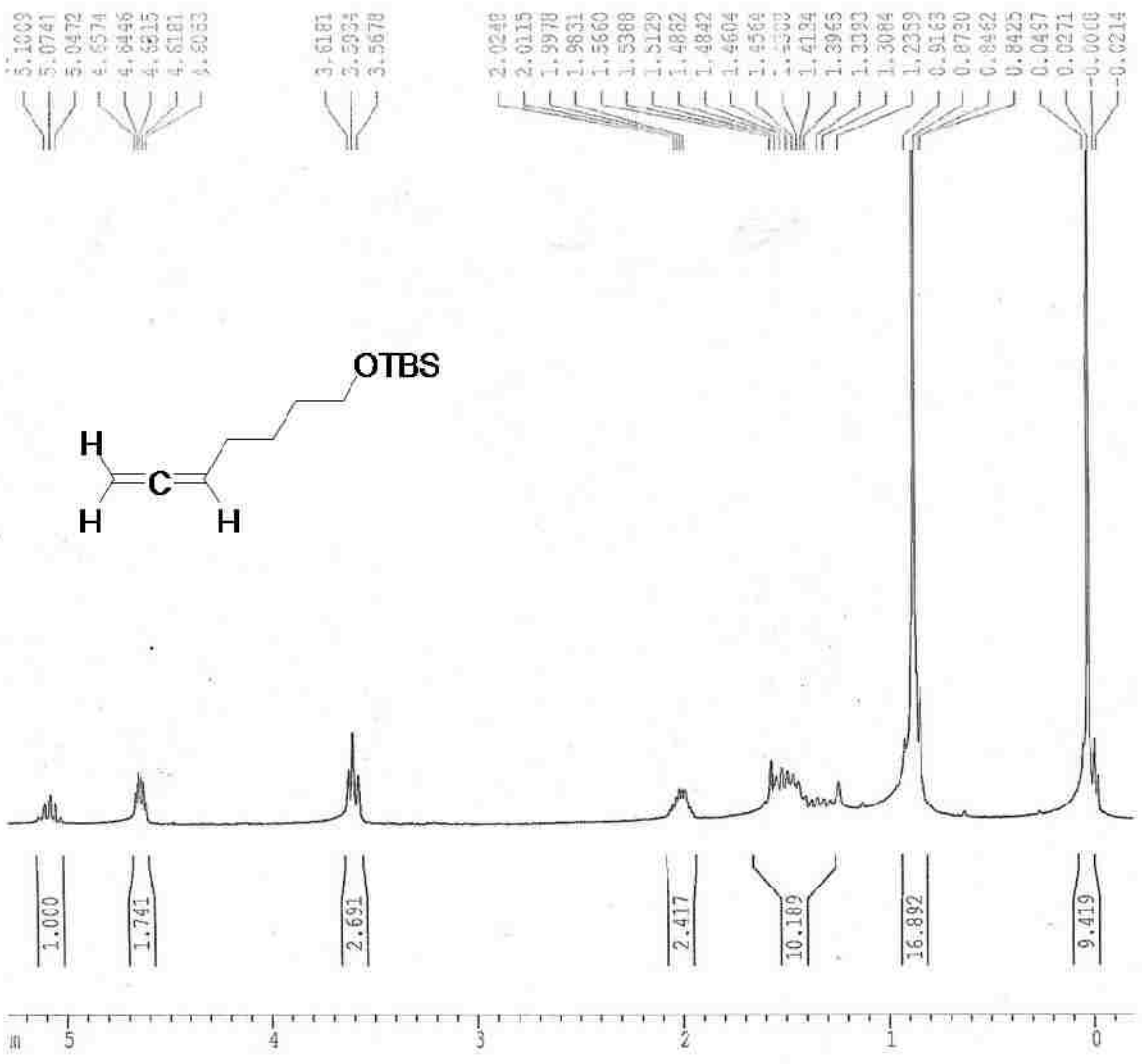


Figure **A.3.** ^{1}H NMR (250 MHz, $CDCl_3$) of compound **2.3**

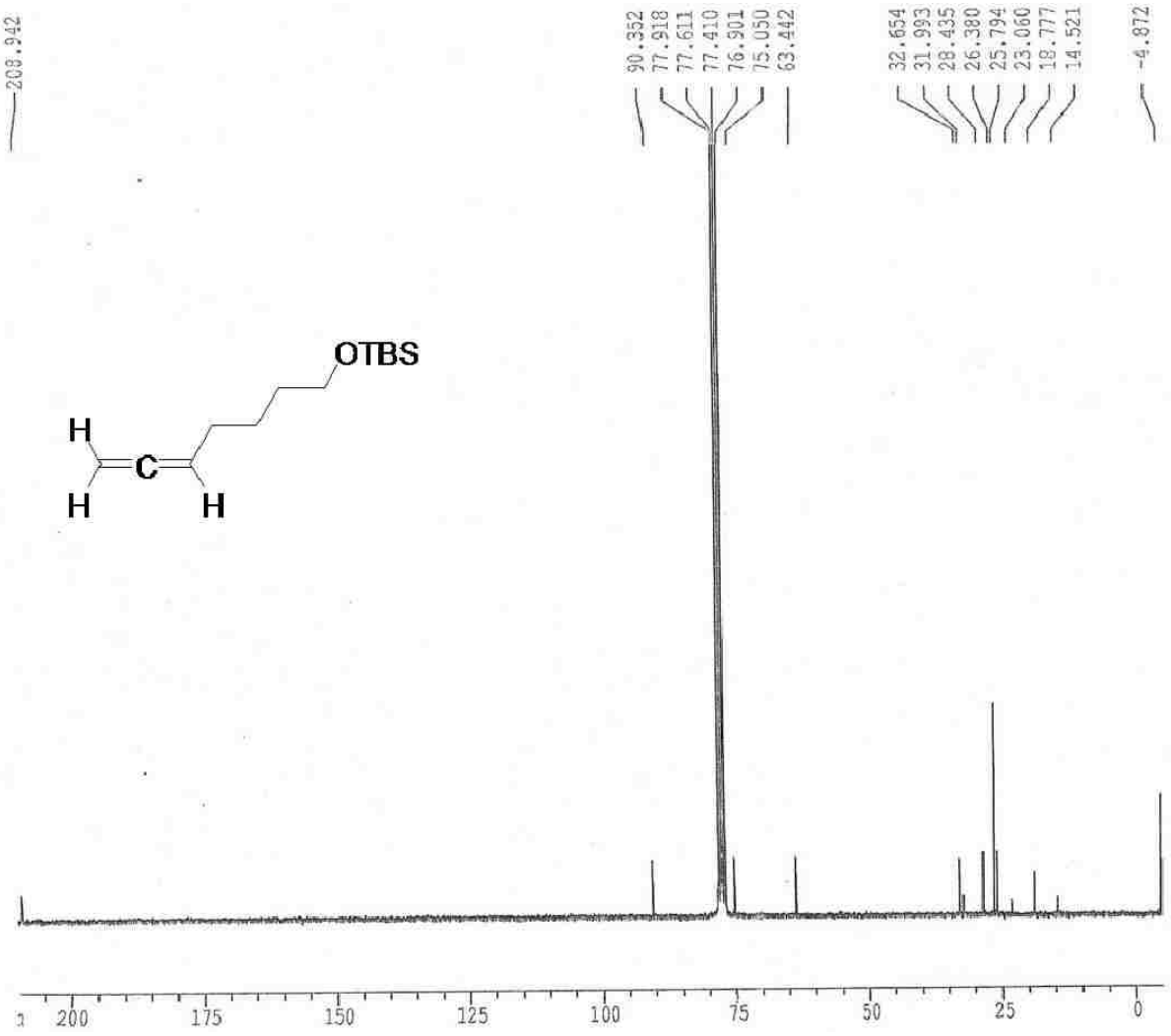


Figure **A.4.** ^{13}C NMR (62.5 MHz, $CDCl_3$) of compound **2.3**

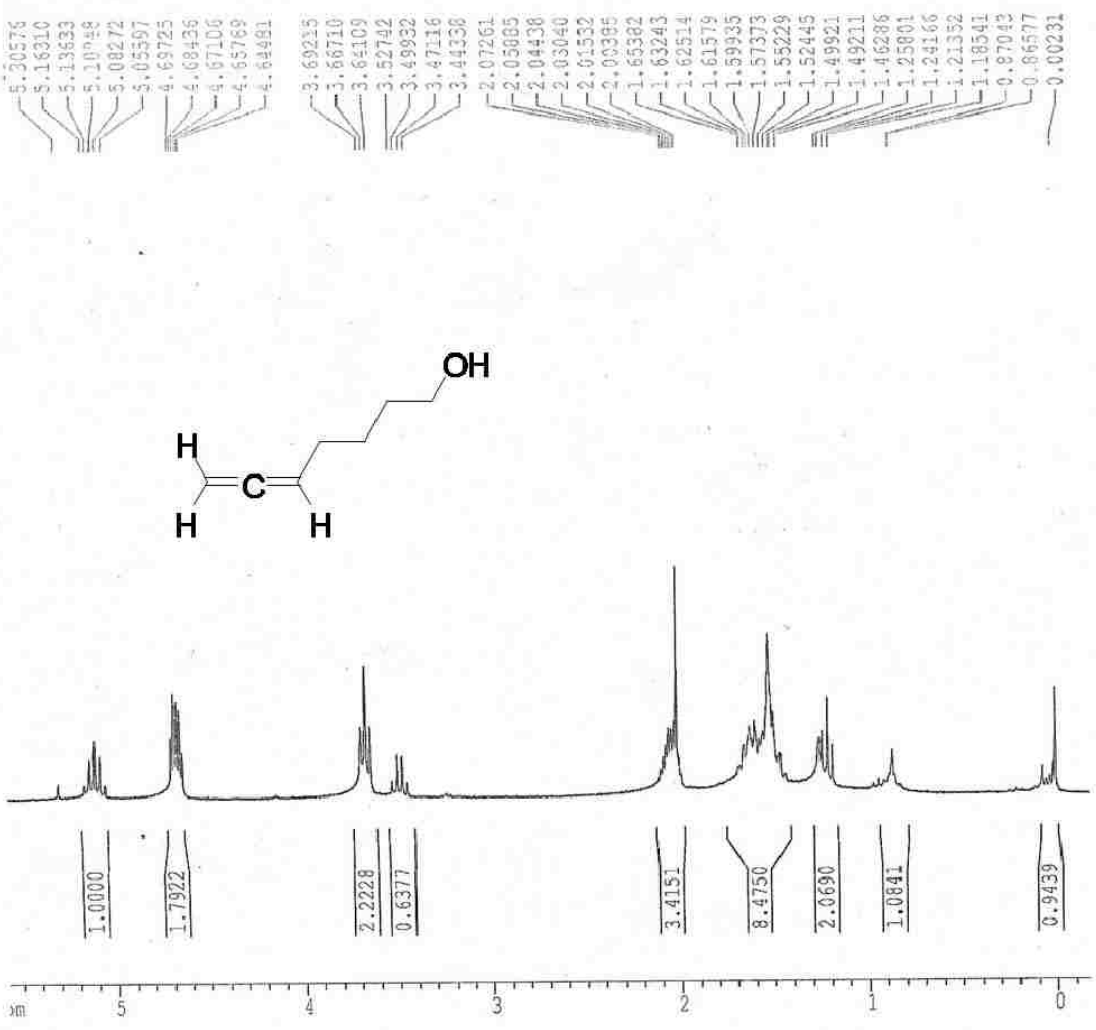


Figure **A.5.** ^{1}H NMR (250 MHz, $CDCl_3$) of compounds **2.5**

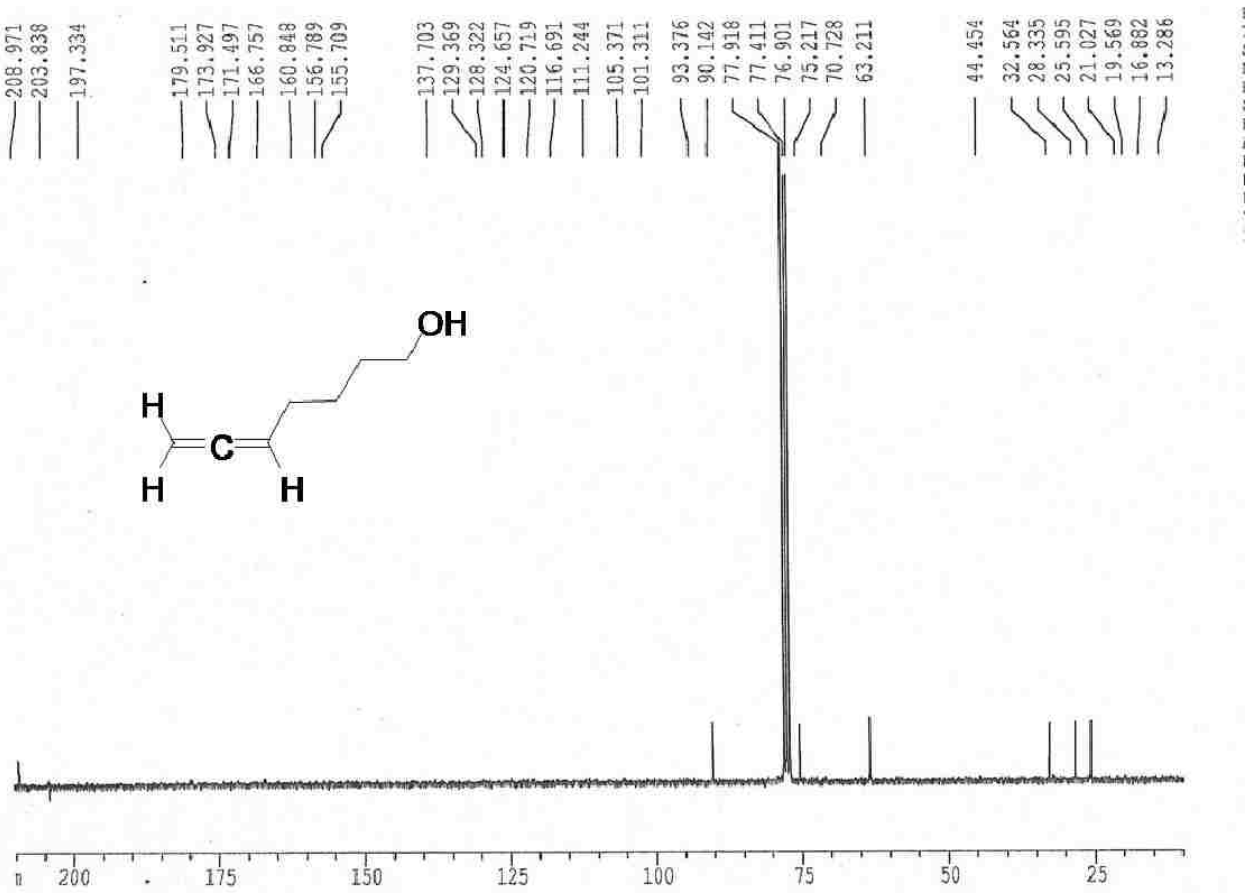


Figure **A.6.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.5**

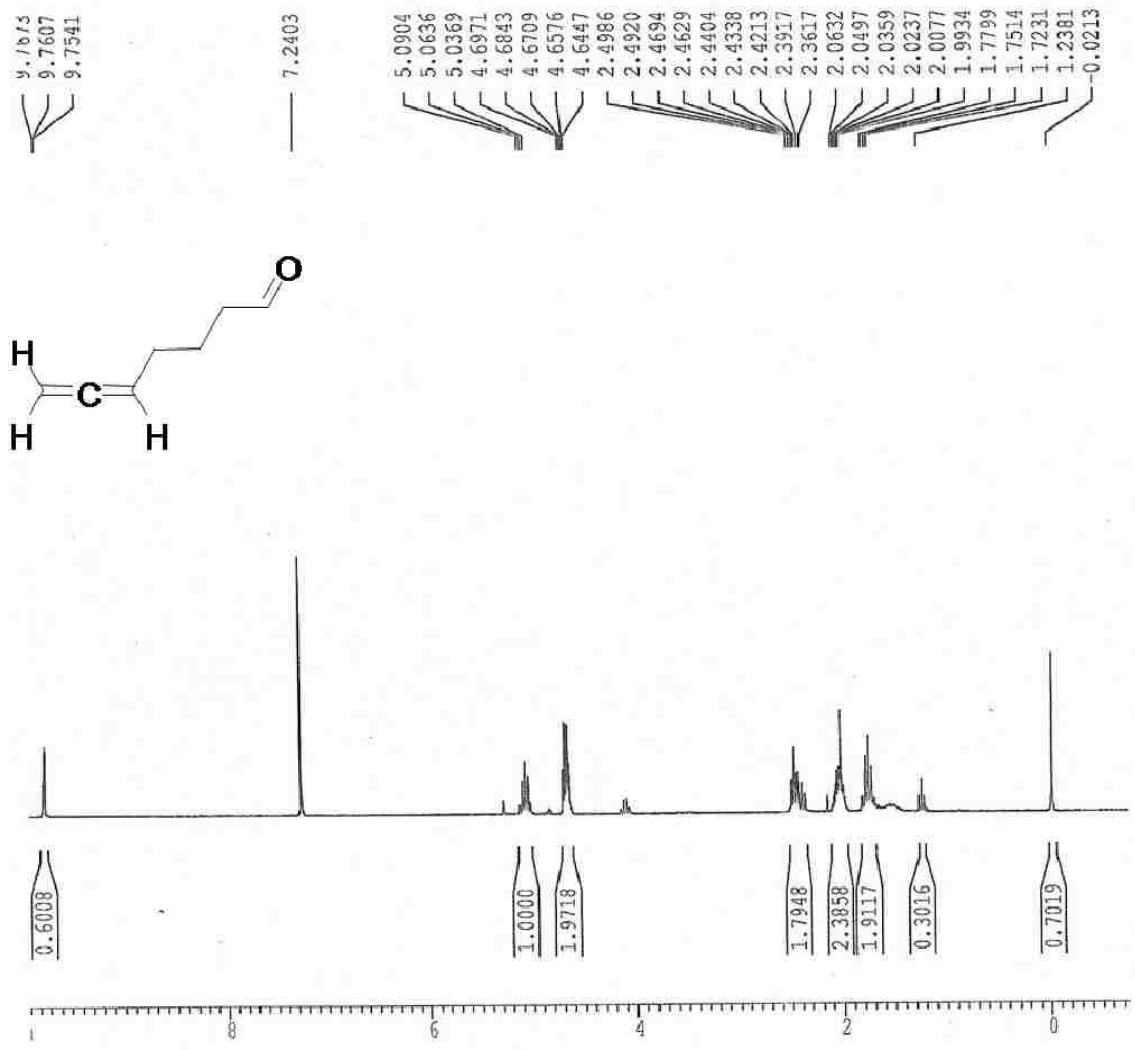


Figure **A.7.** ^{1}H NMR (250 MHz, $CDCl_3$) of compound **2.6**

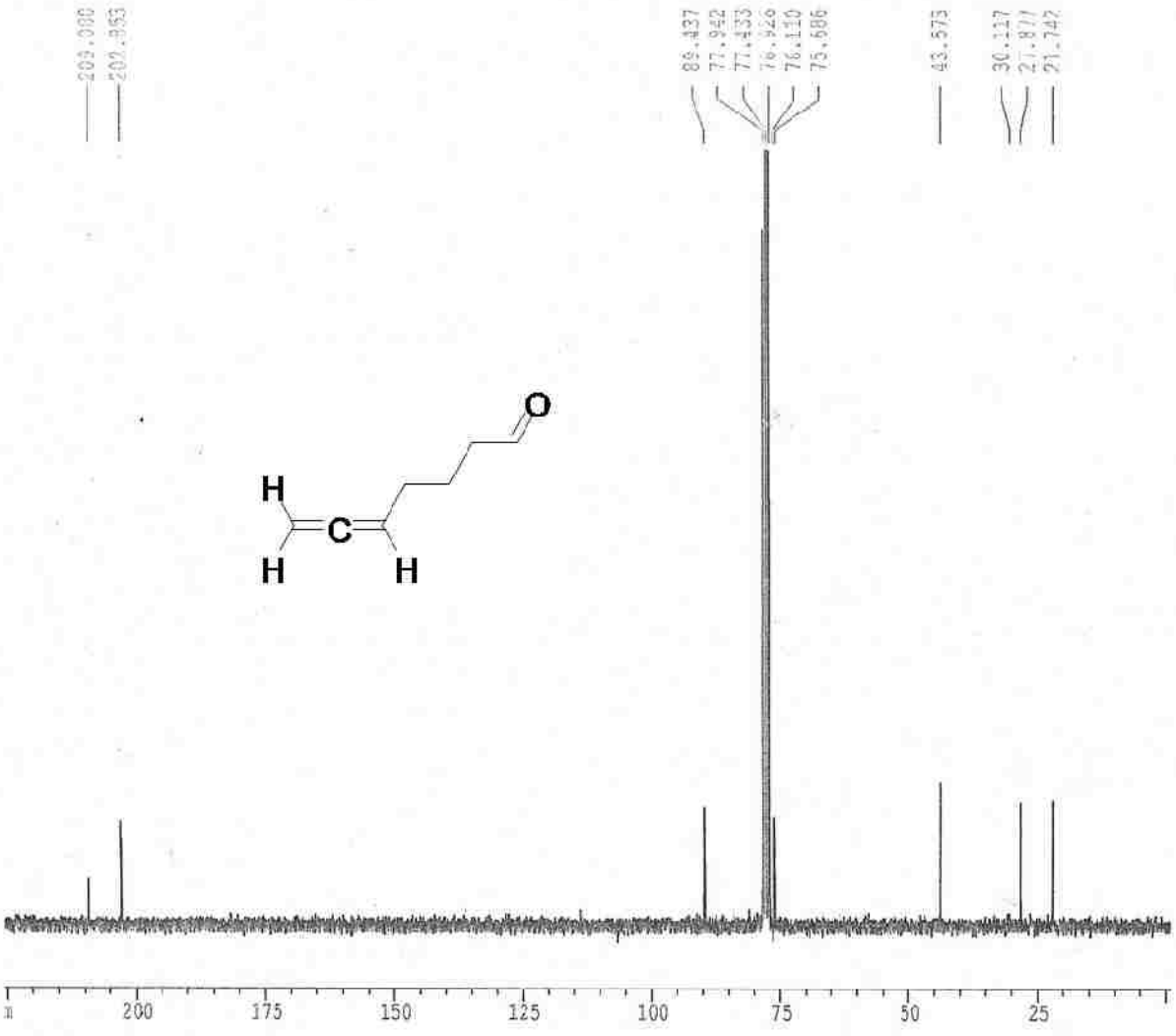


Figure **A.8.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.6**

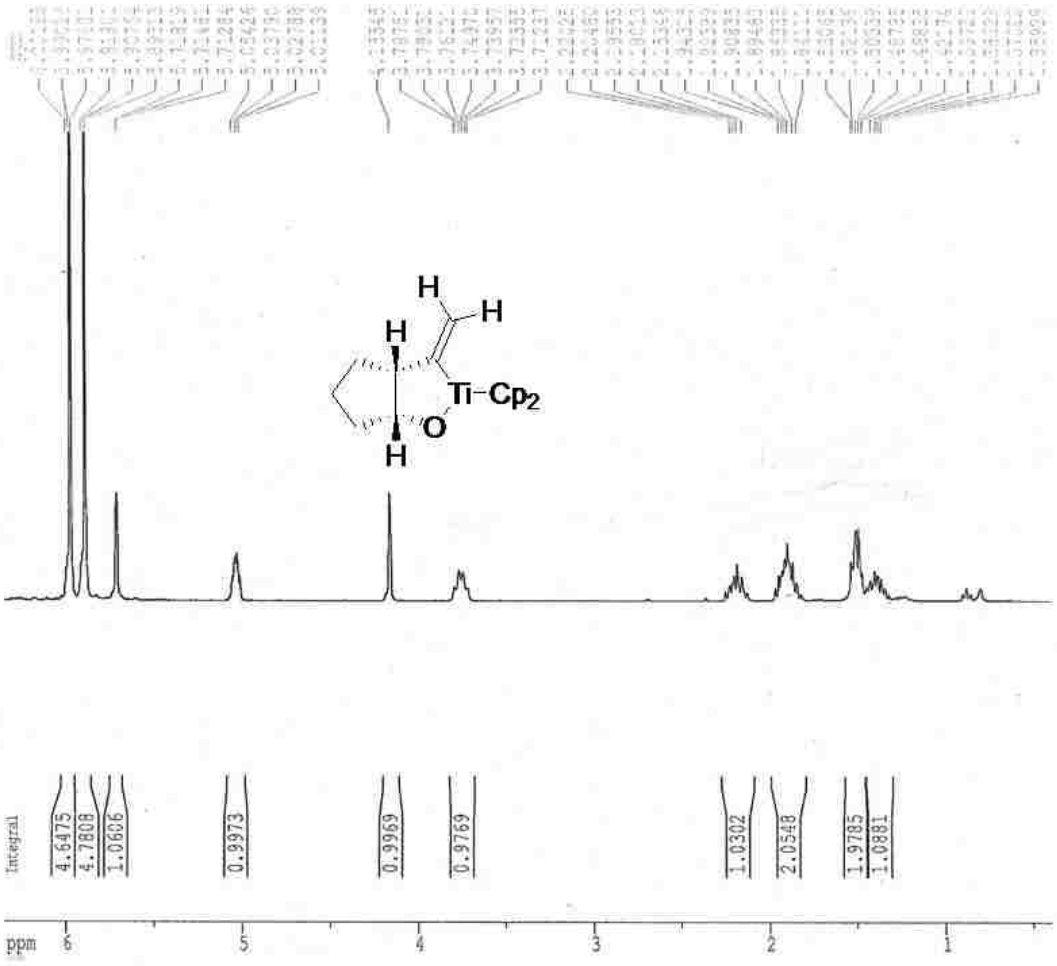


Figure **A.9.** ^{1}H NMR (300 MHz, CD_6CD_6) of compound **2.7**

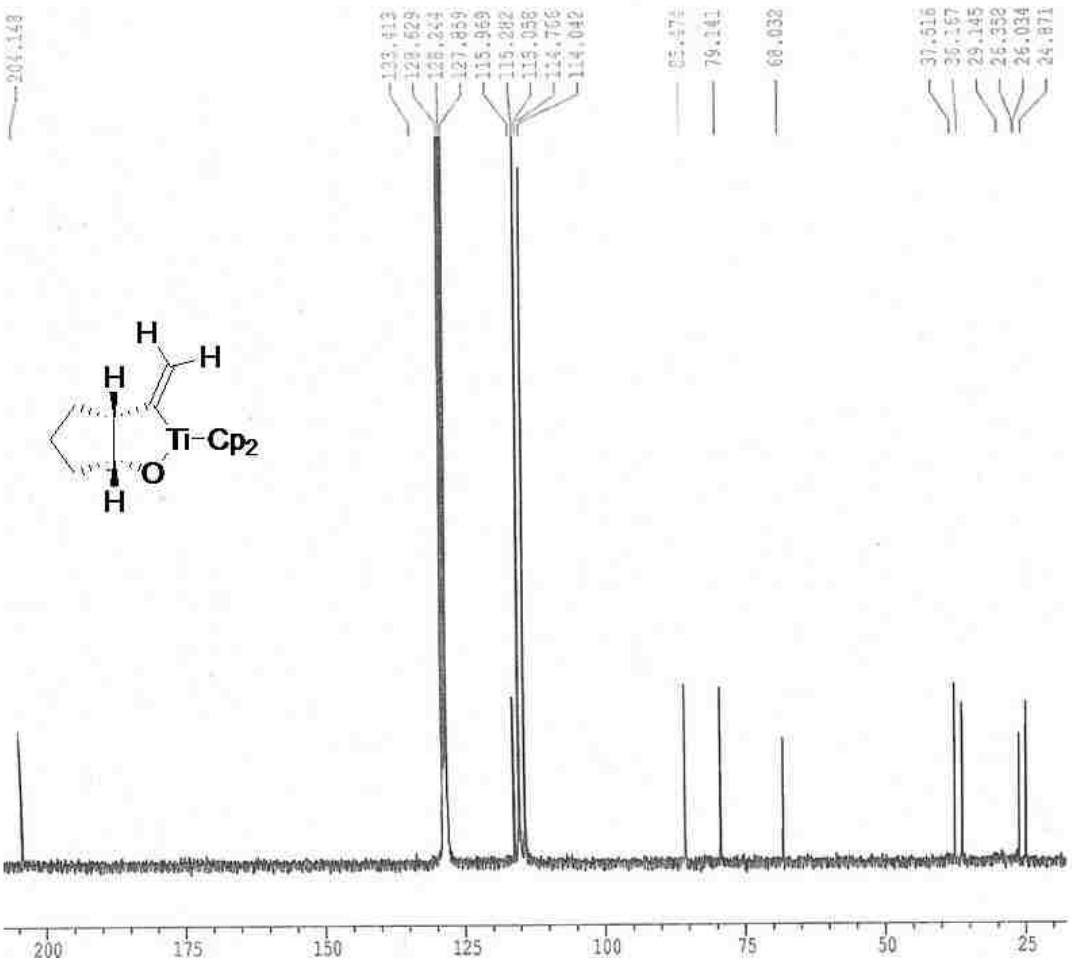


Figure **A.10.** ^{13}C NMR (62.8 MHz, C_6D_6) of compound **2.7**

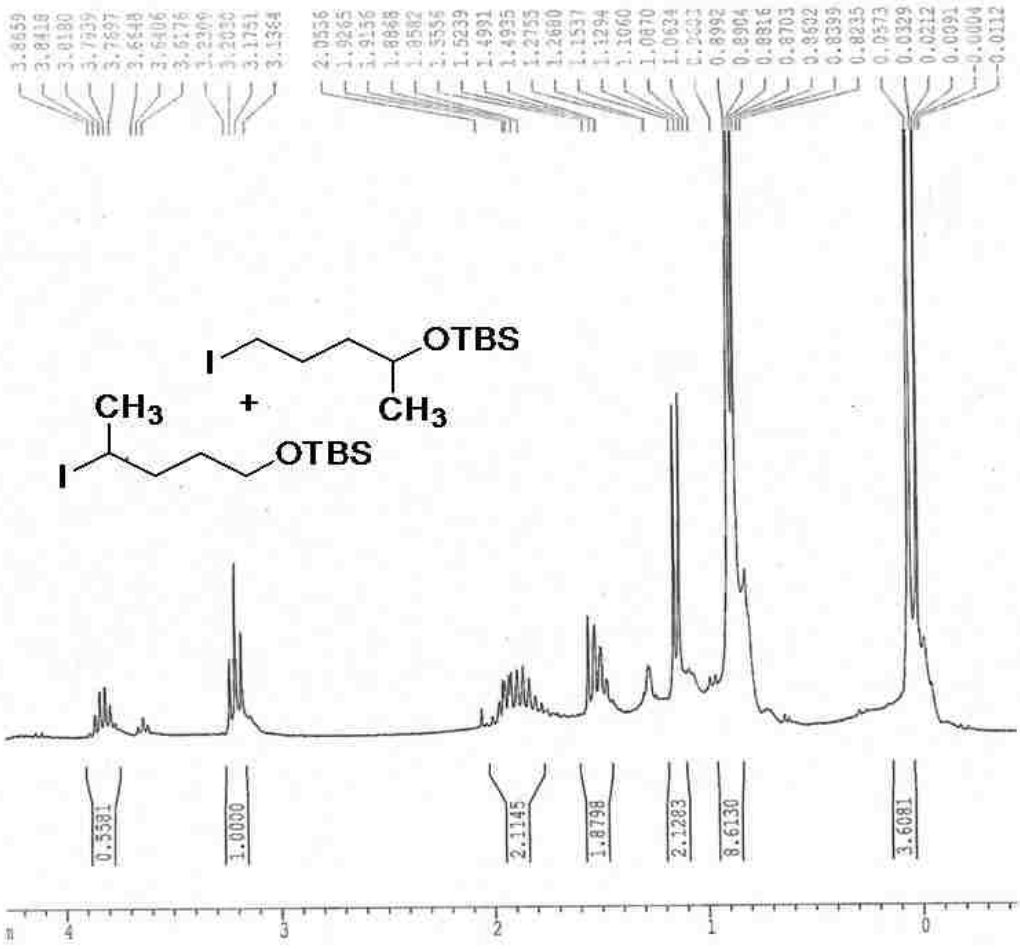


Figure **A.11.** ^{1}H NMR (250 MHz, $CDCl_3$) of compounds **2.9** & **2.9a**

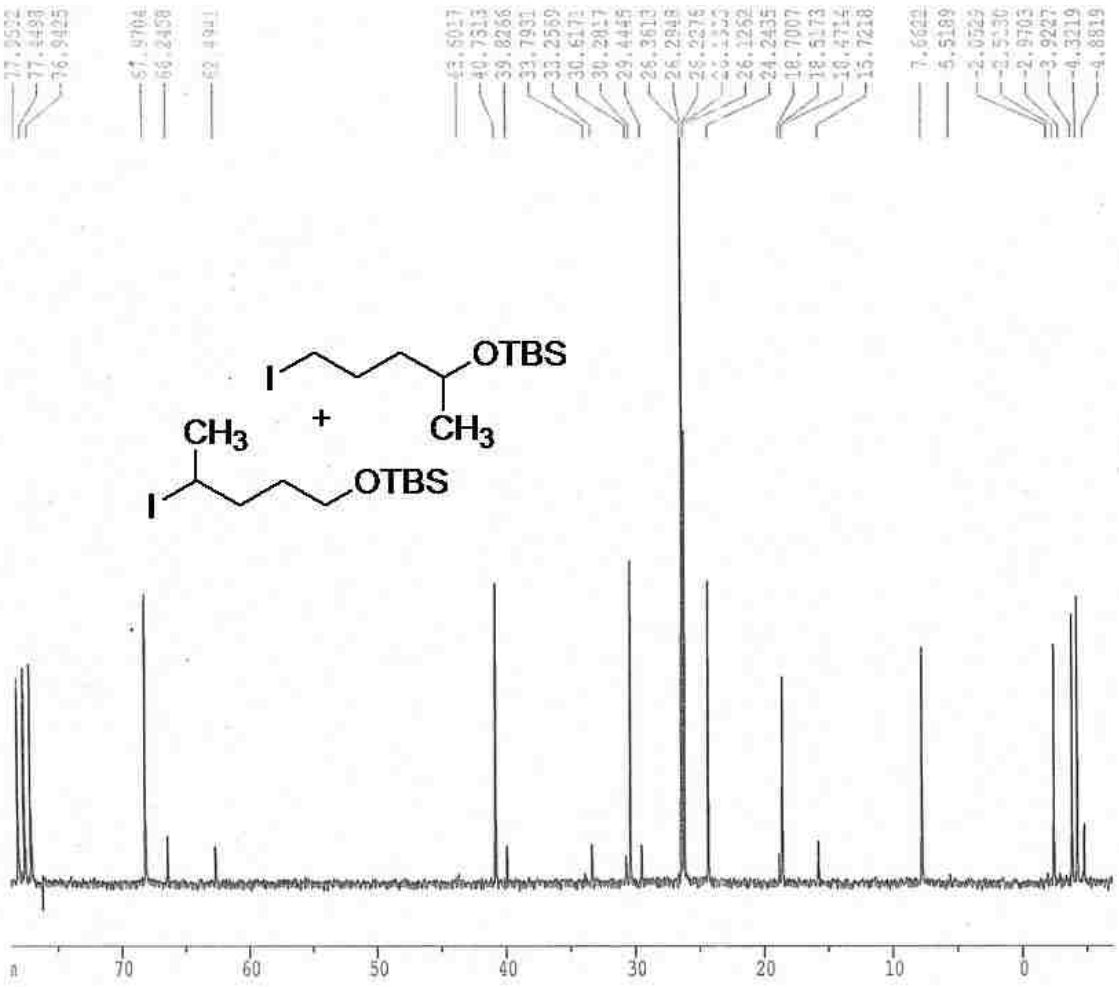


Figure **A.12.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compounds **2.9** & **2.9a**

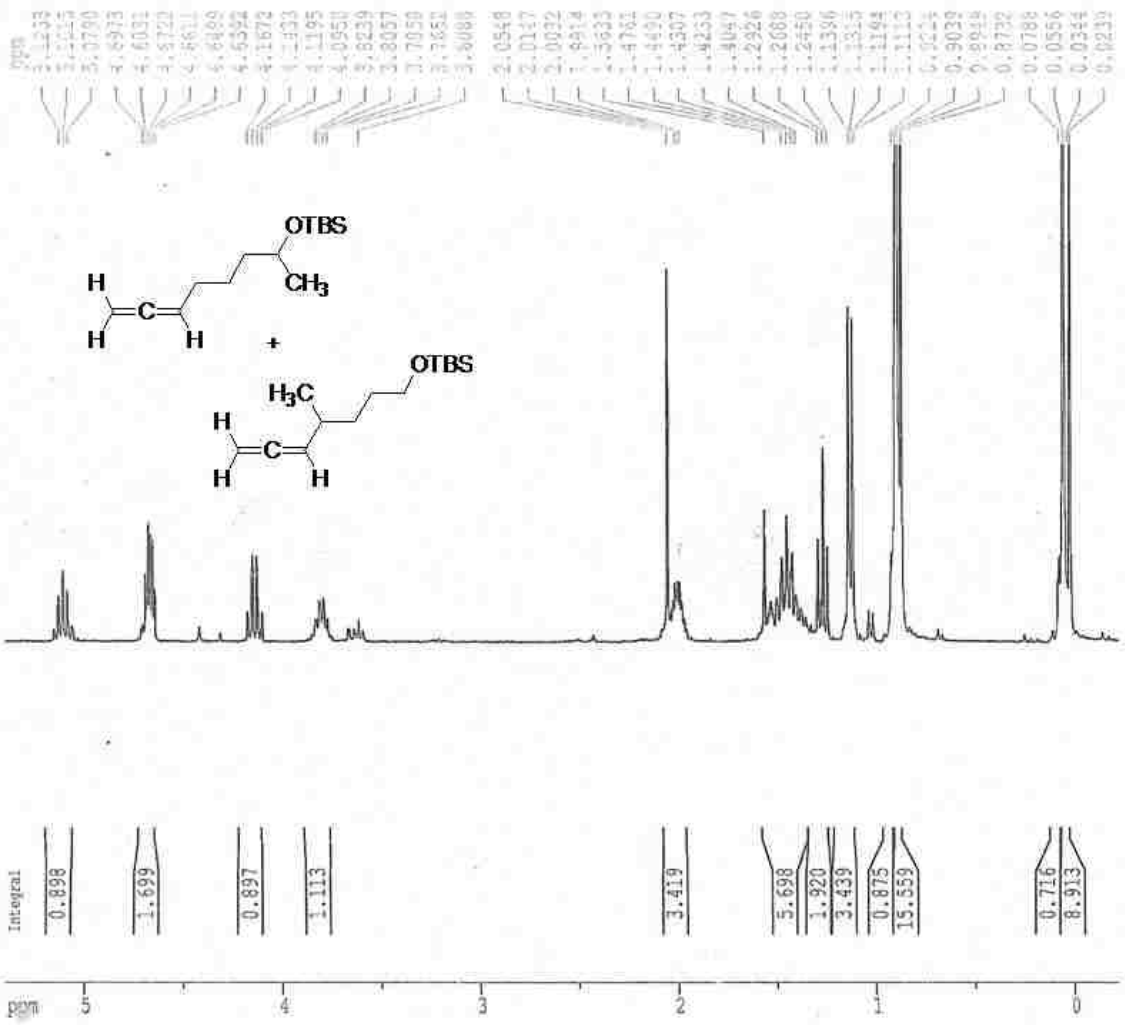


Figure **A.13.** ^{1}H NMR (300 MHz, $CDCl_3$) of compounds **2.10** & **2.10a**

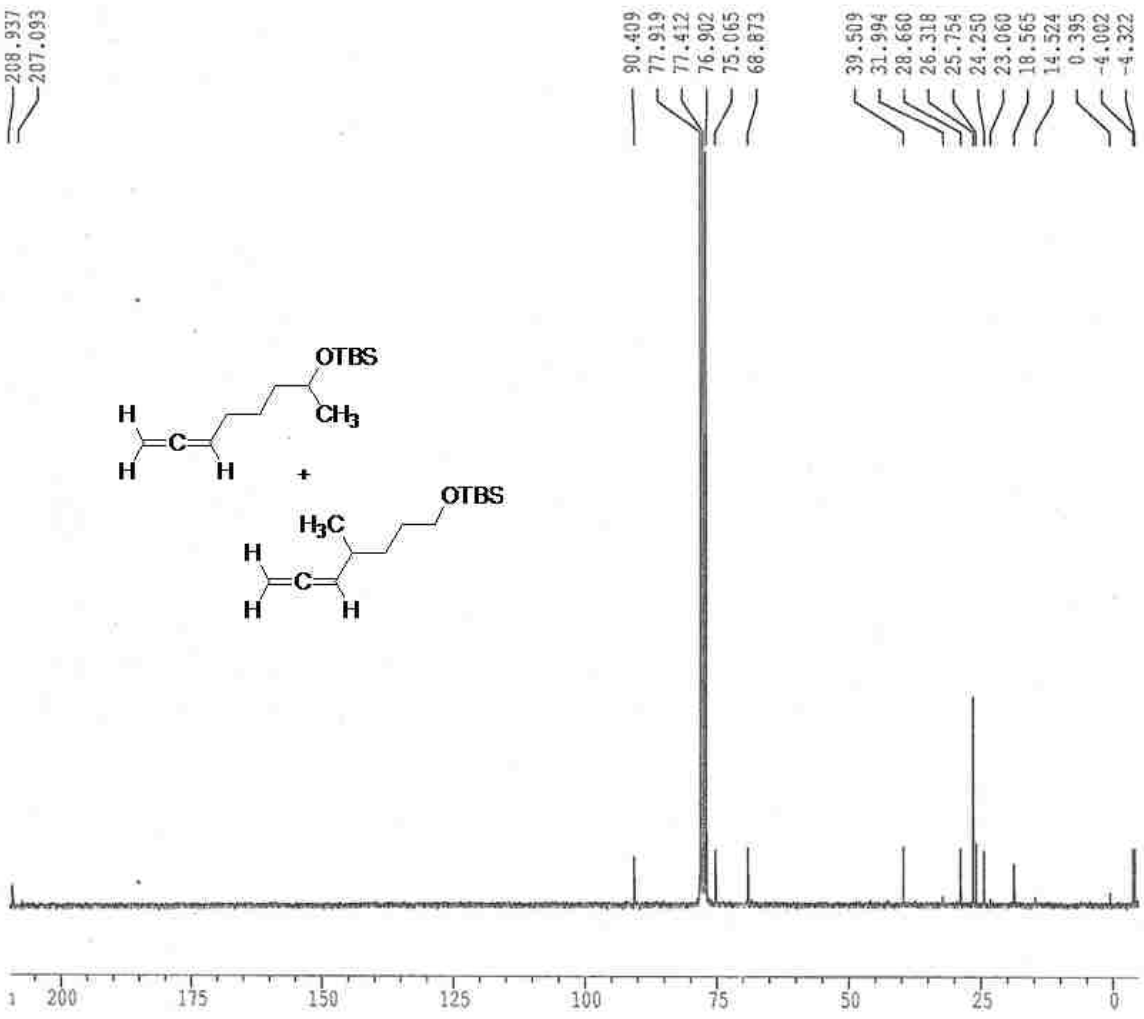


Figure **A.14.** ^{13}C NMR (75.5 MHz, $CDCl_3$) of compounds **2.10** & **2.10a**

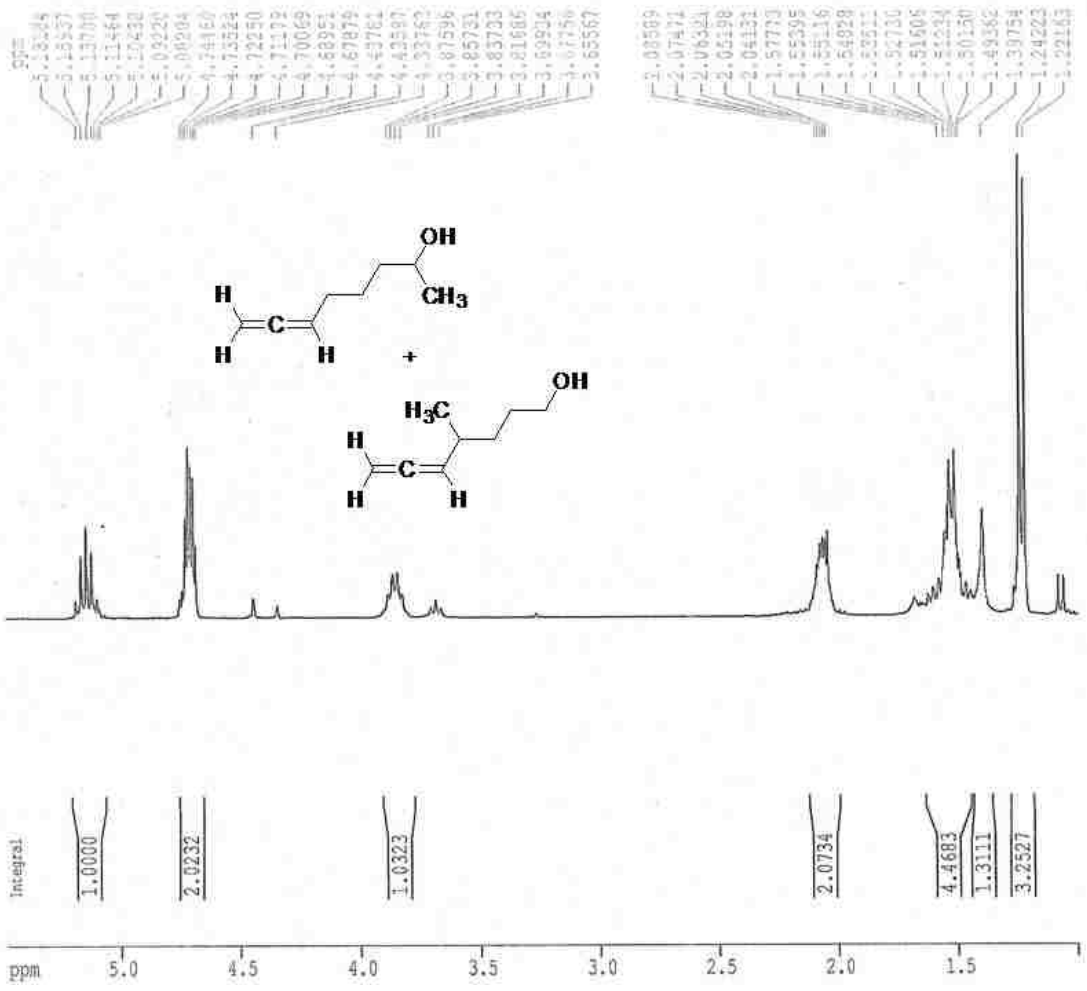


Figure **A.15.** ^{1}H NMR (300 MHz, $CDCl_3$) of compounds **2.11** & **2.11a**

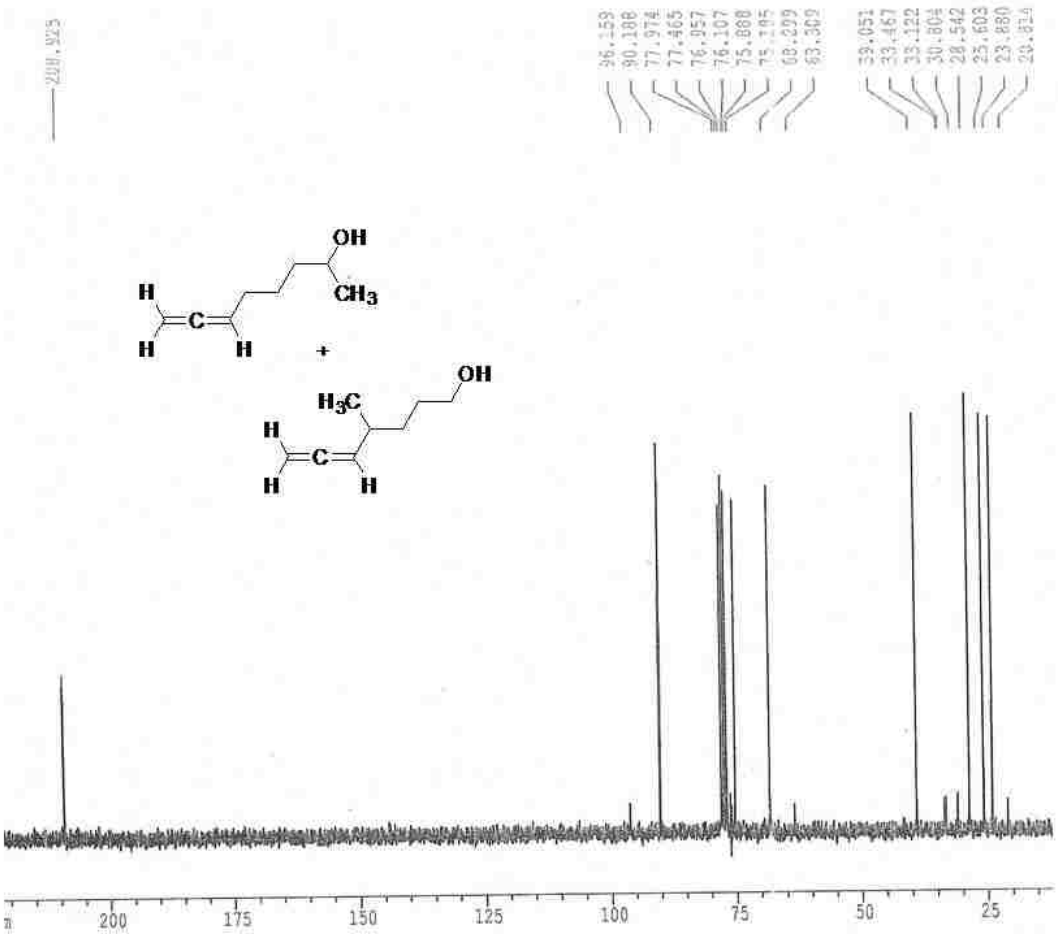


Figure **A.16.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compounds **2.11** & **2.11a**

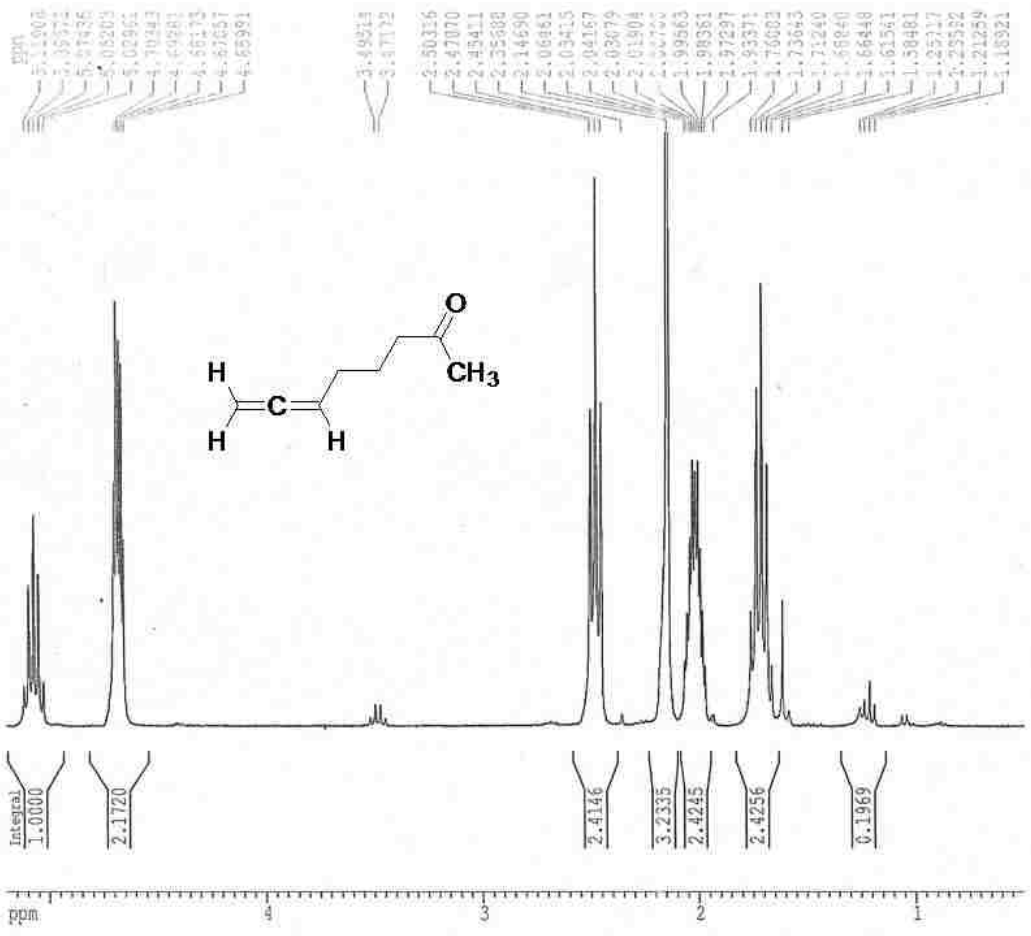


Figure **A.17.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.12**

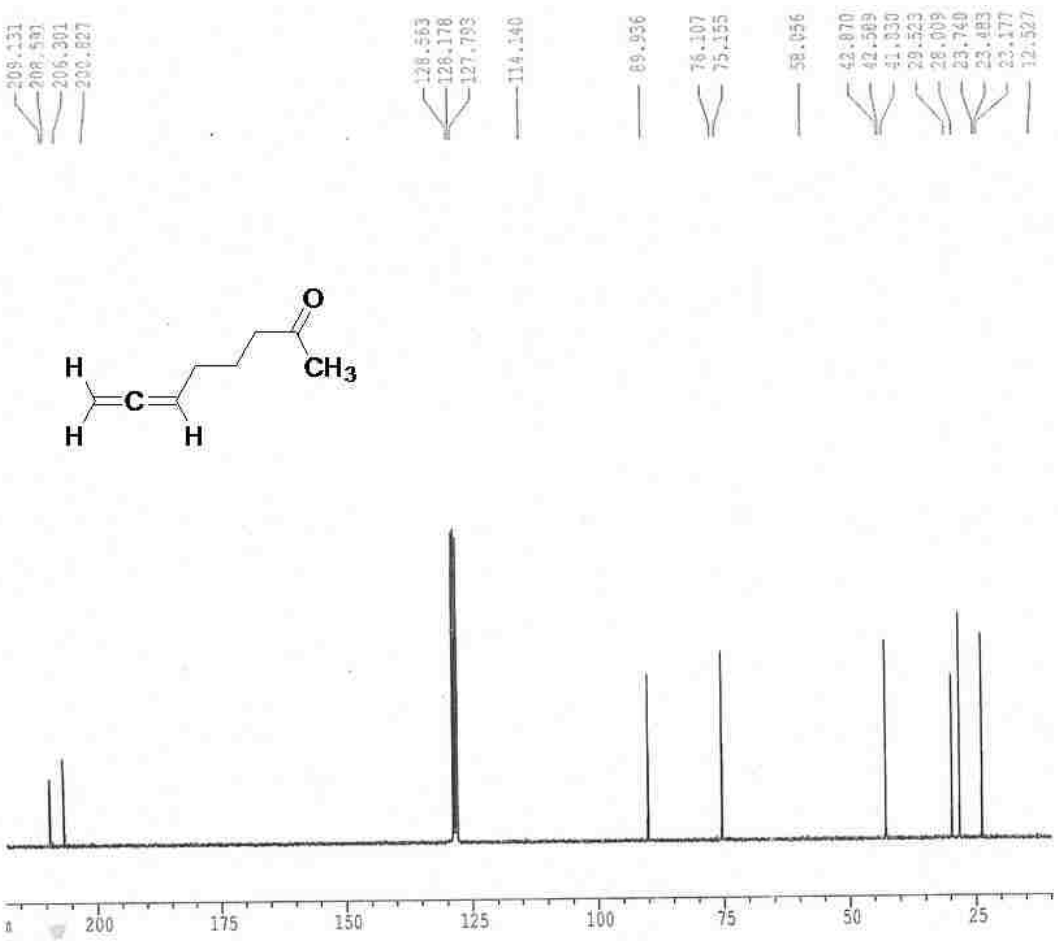


Figure **A.18.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.12**

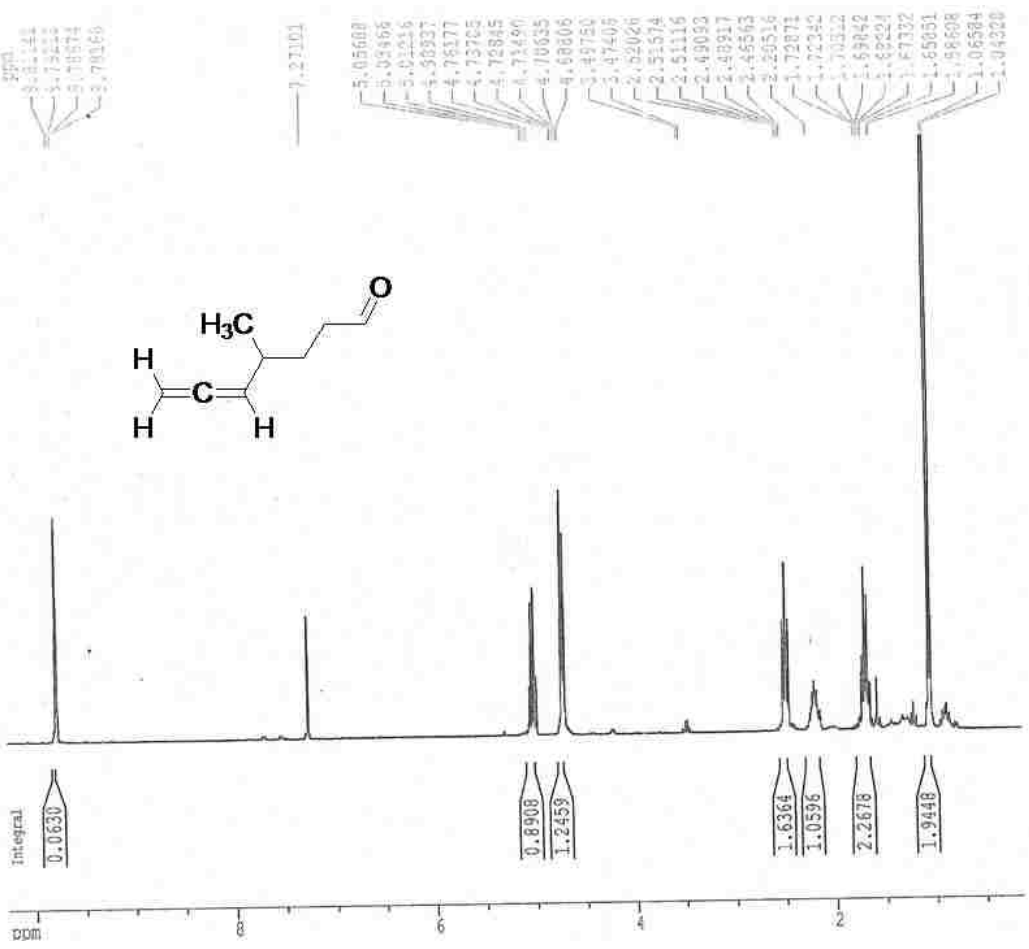


Figure **A.19.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.12 a**

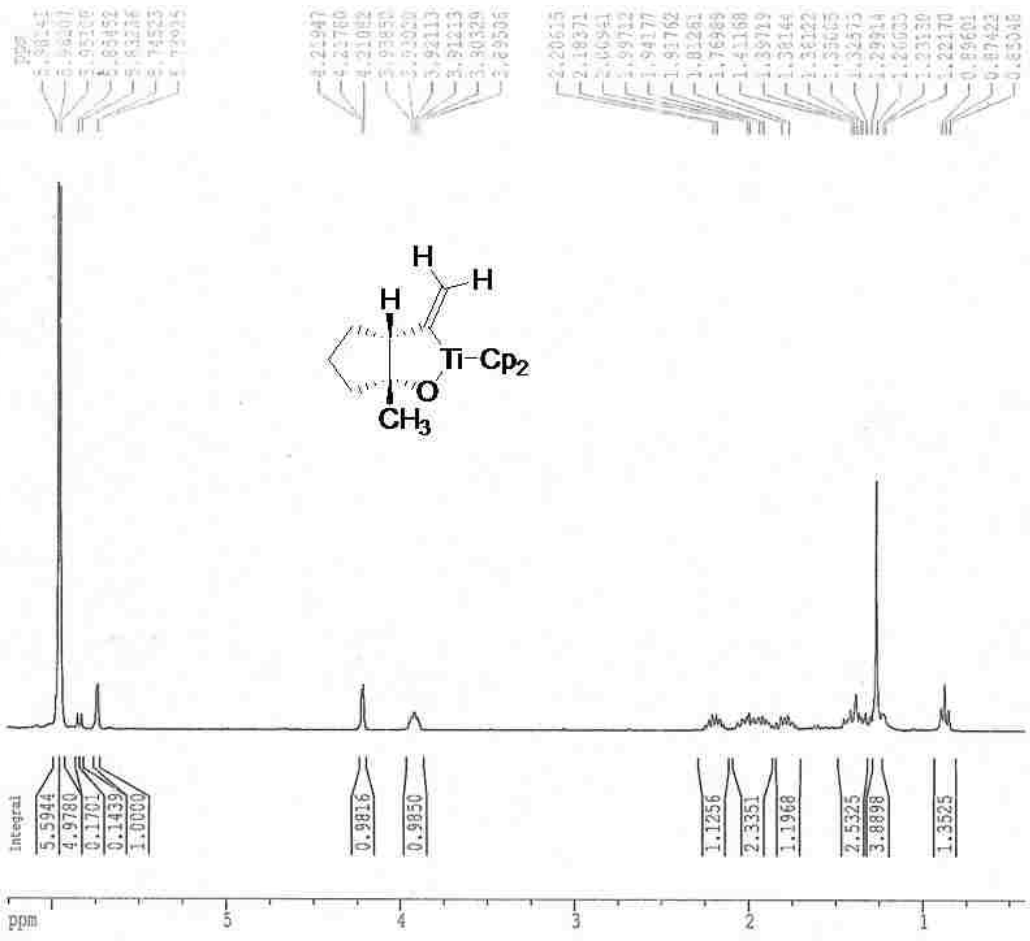


Figure **A.20.** ^{1}H NMR (300 MHz, CD_6CD_6) of compound **2.13**

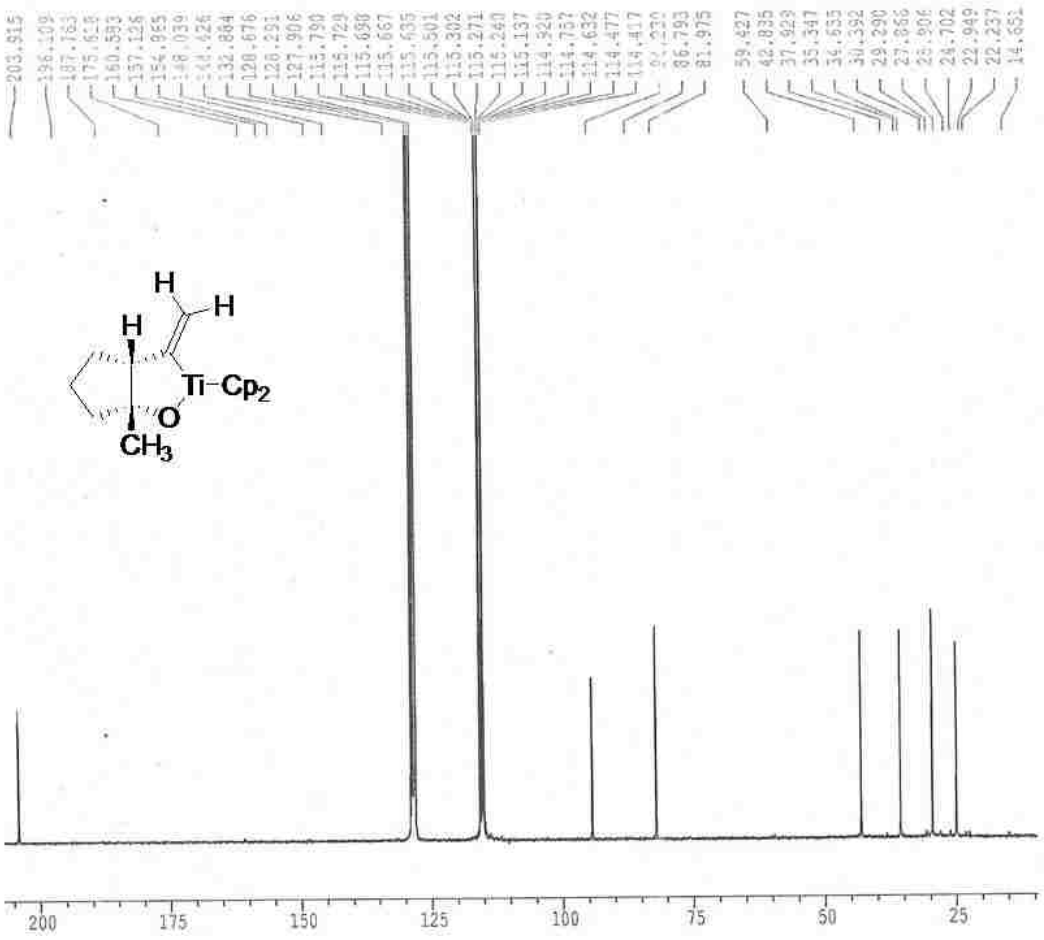


Figure **A.21.** ^{13}C NMR (62.8 MHz, CD_6CD_6) of compound **2.13**

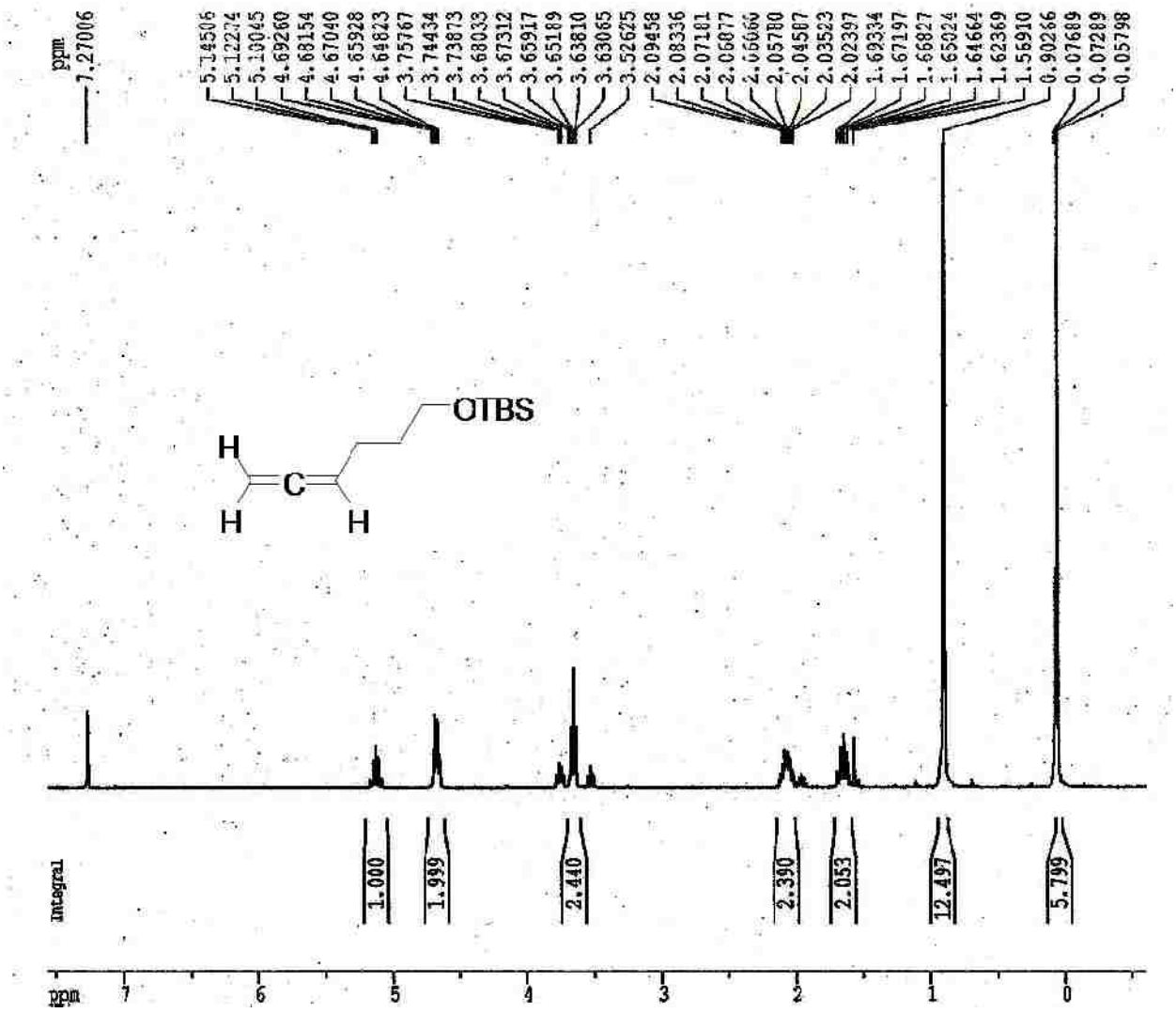


Figure **A.22.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.15**

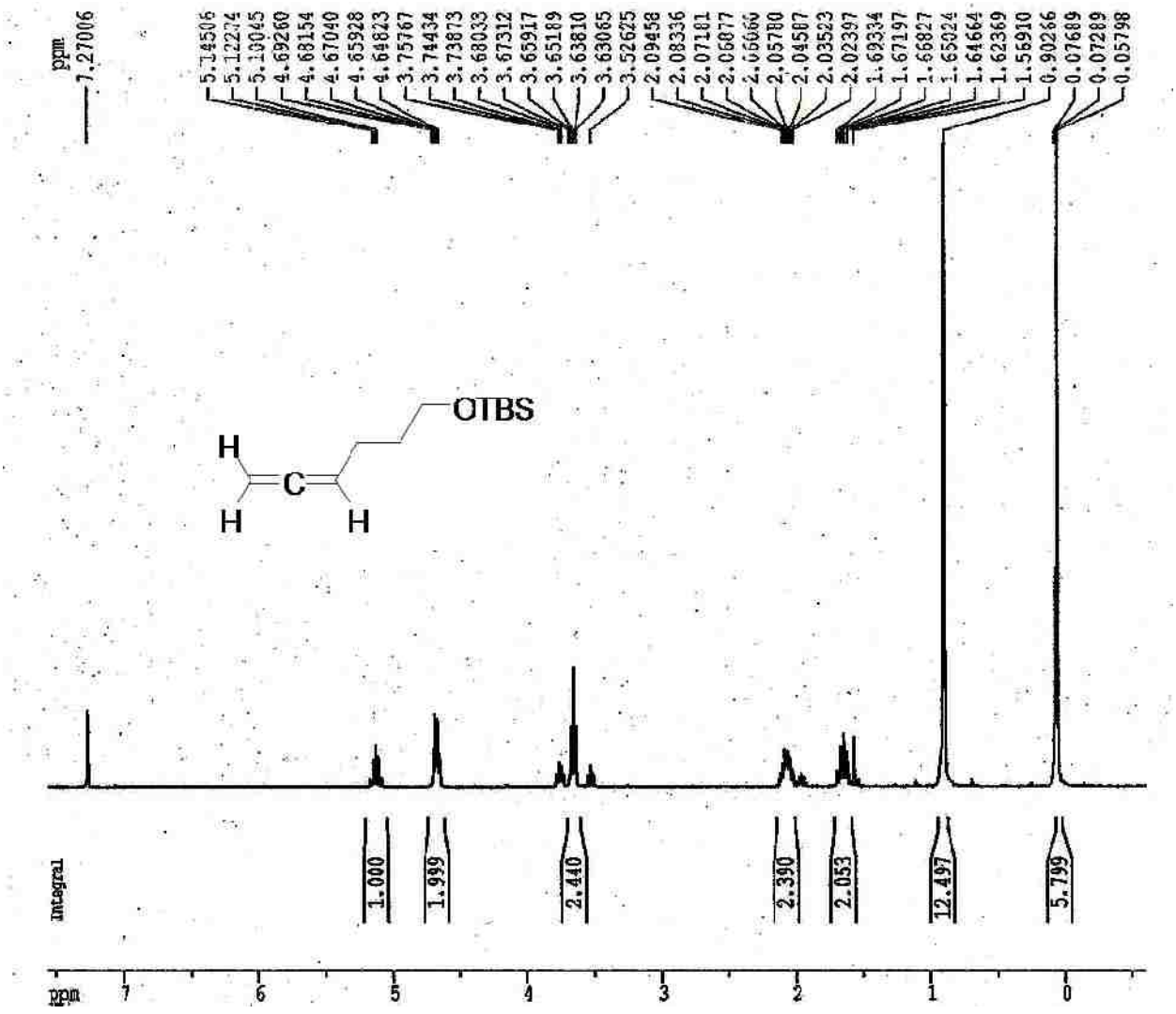


Figure **A.23.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.15**

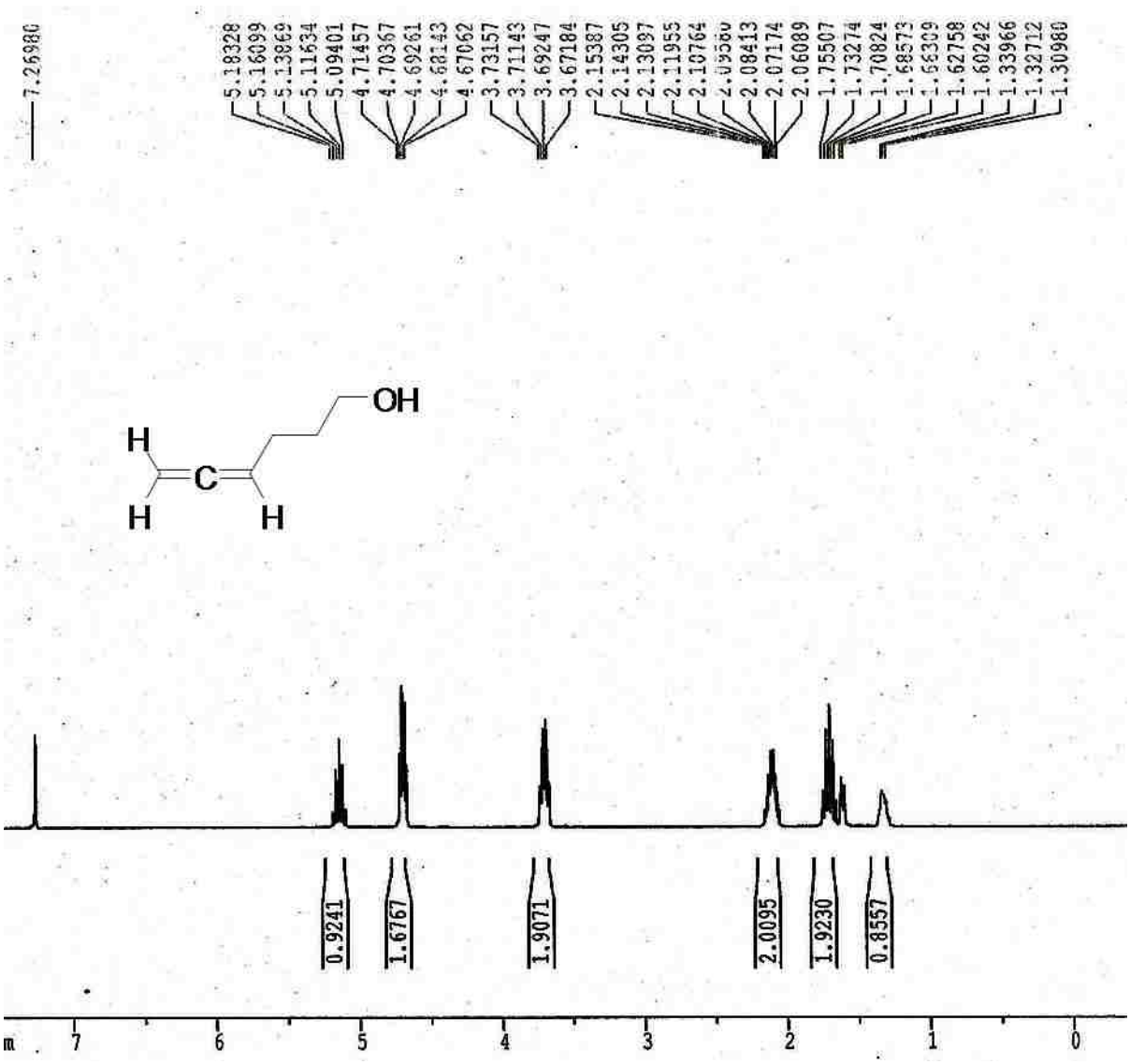


Figure **A.24.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.16**

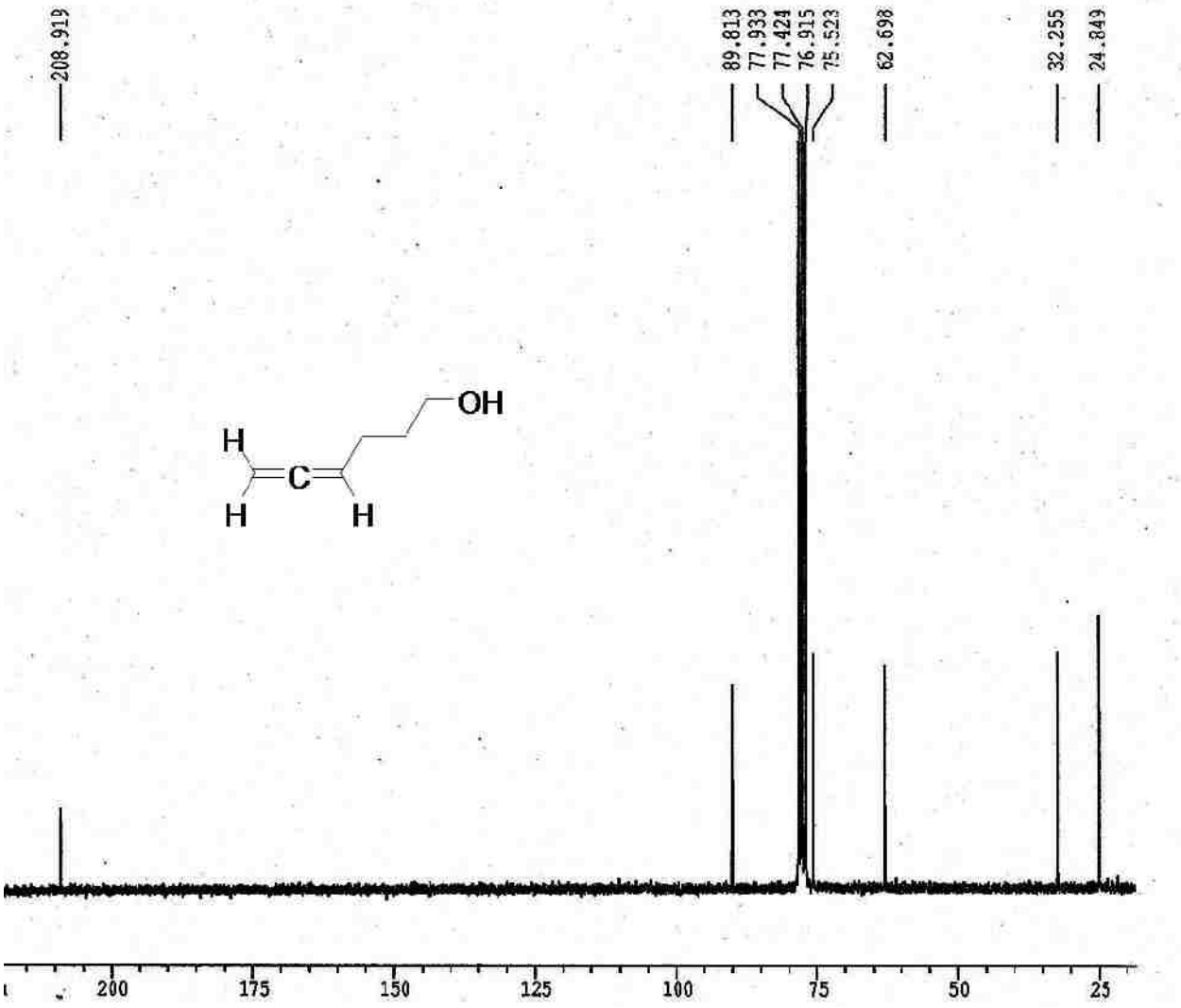


Figure **A.25.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.16**

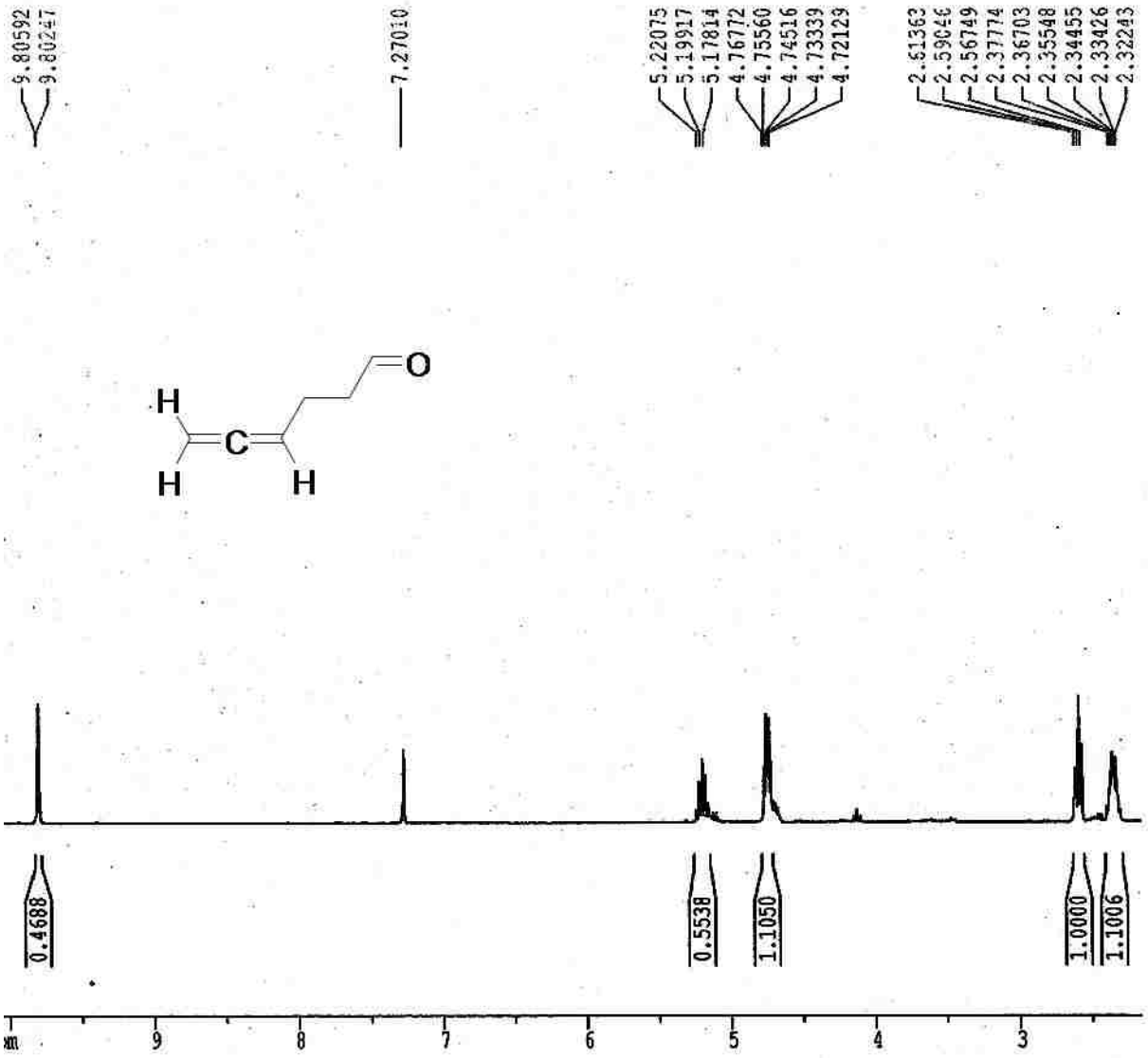


Figure **A.26.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.17**

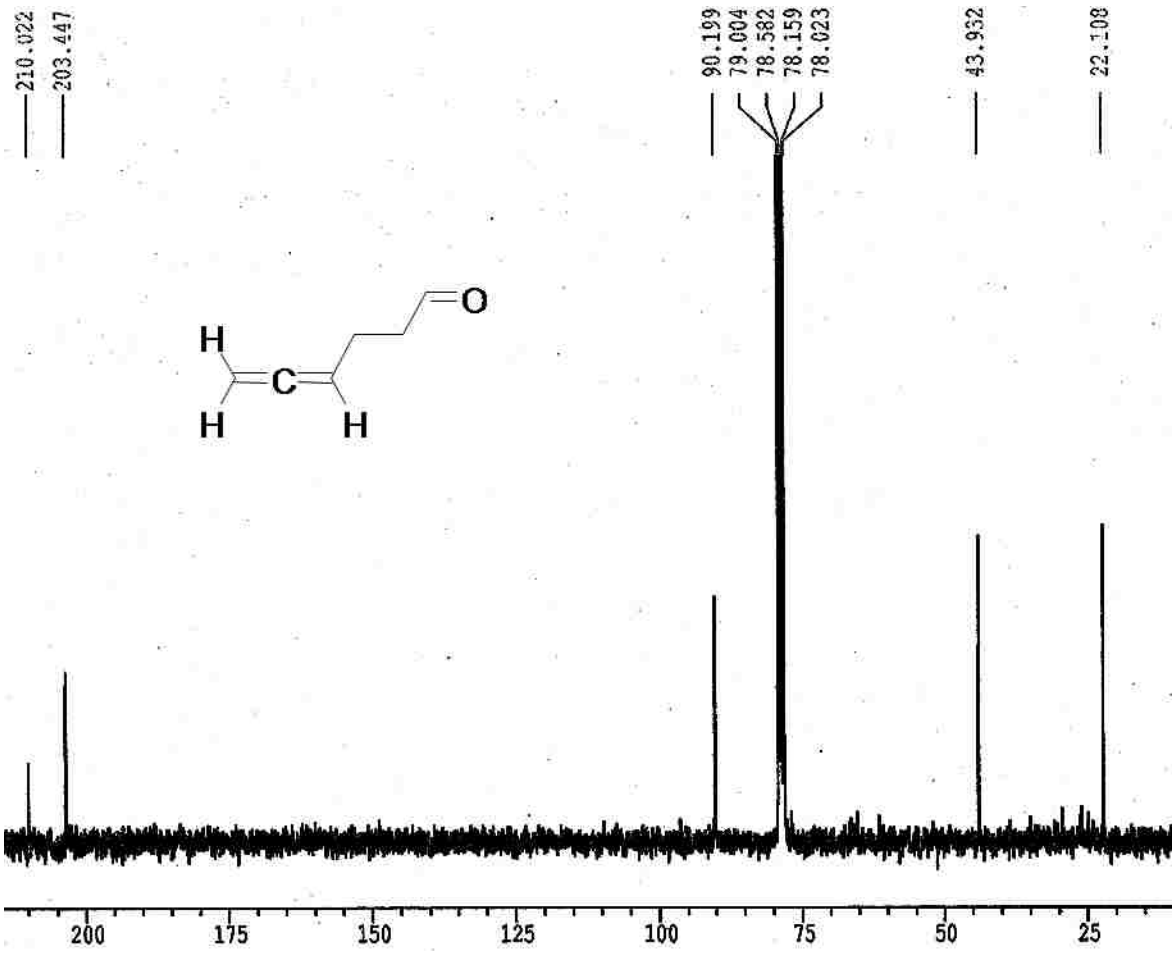


Figure **A.27.** ^{13}C NMR (75.5 MHz, $CDCl_3$) of compound **2.17**

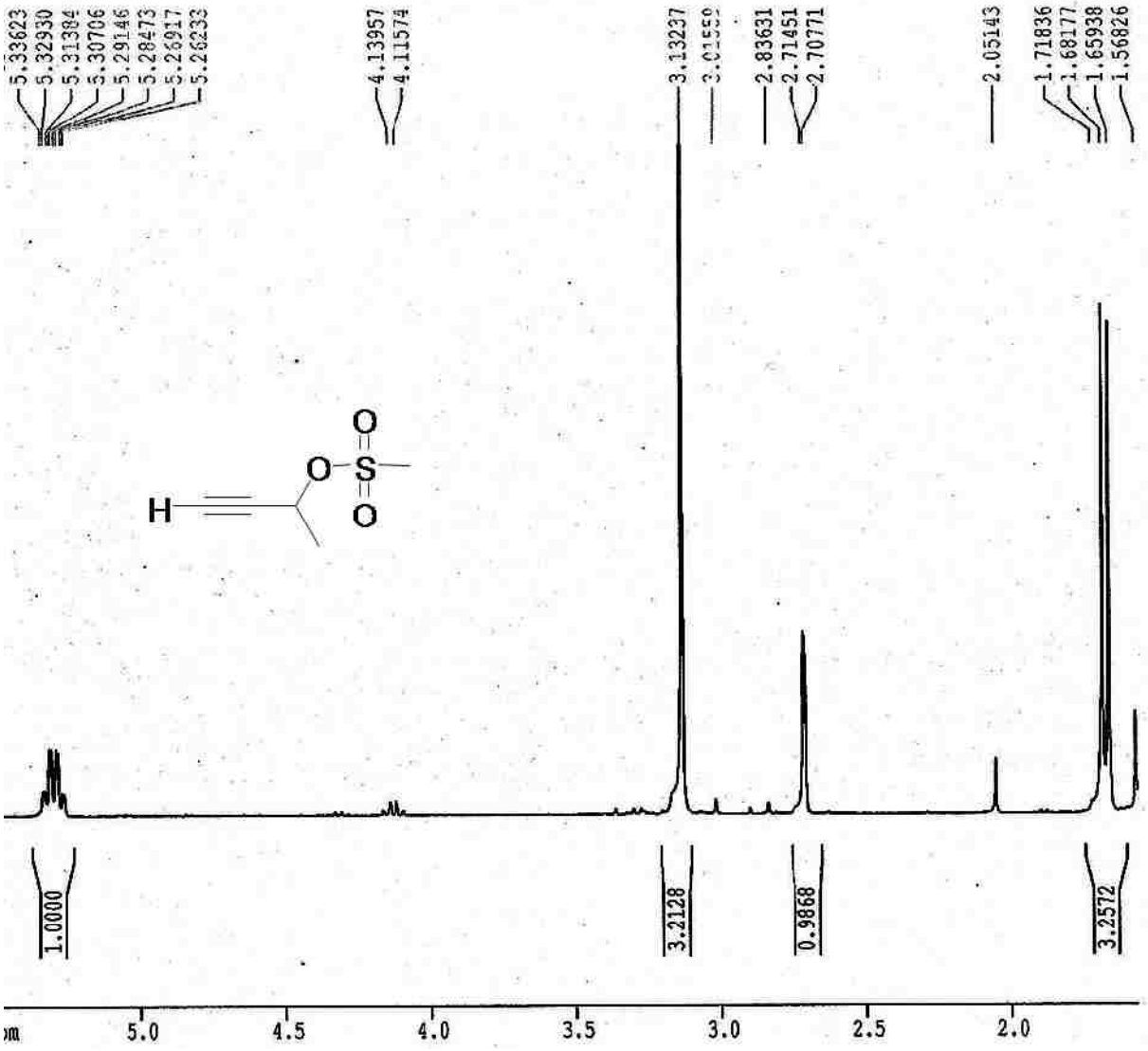


Figure **A.28.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.20**

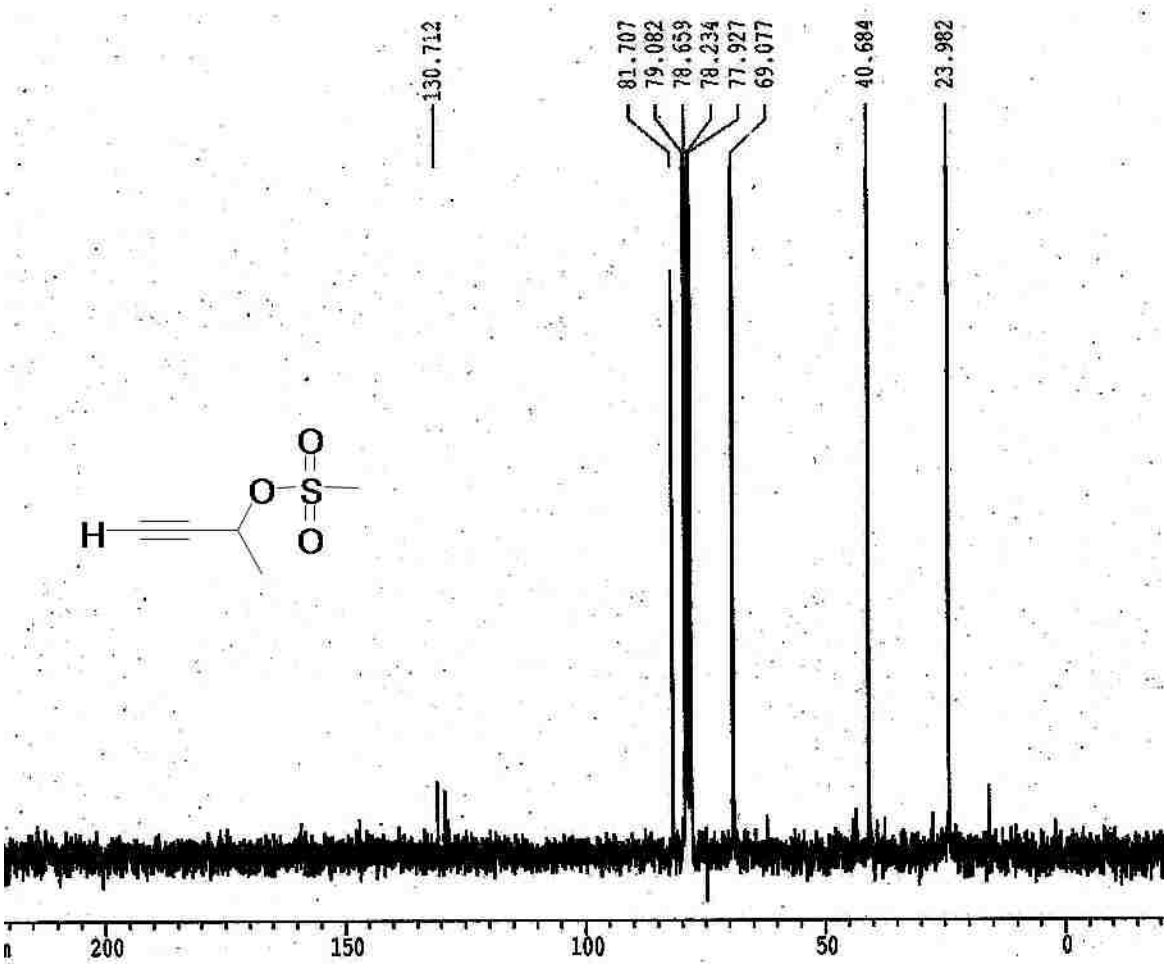


Figure **A.29.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.20**

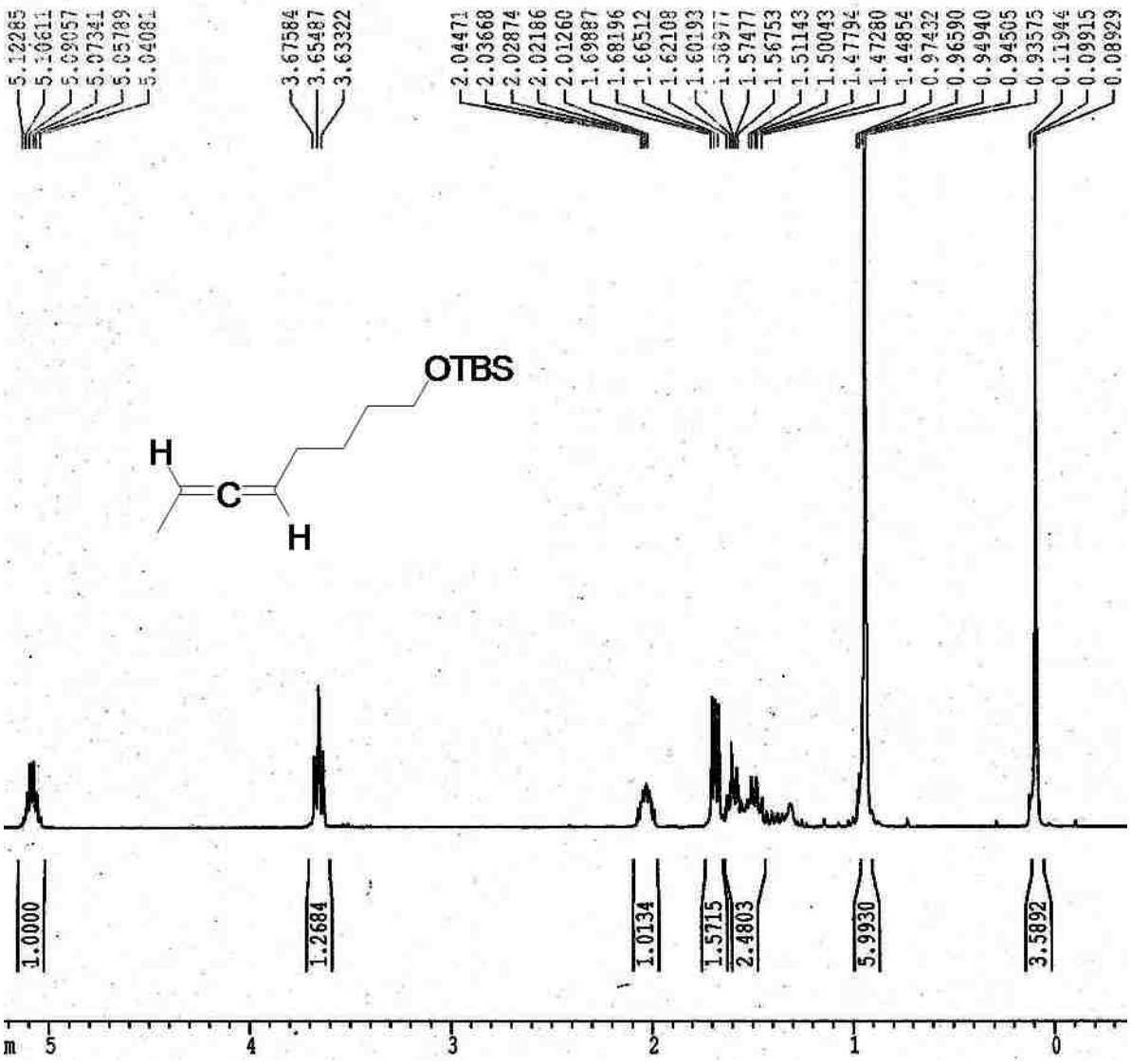


Figure **A.30.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.21**

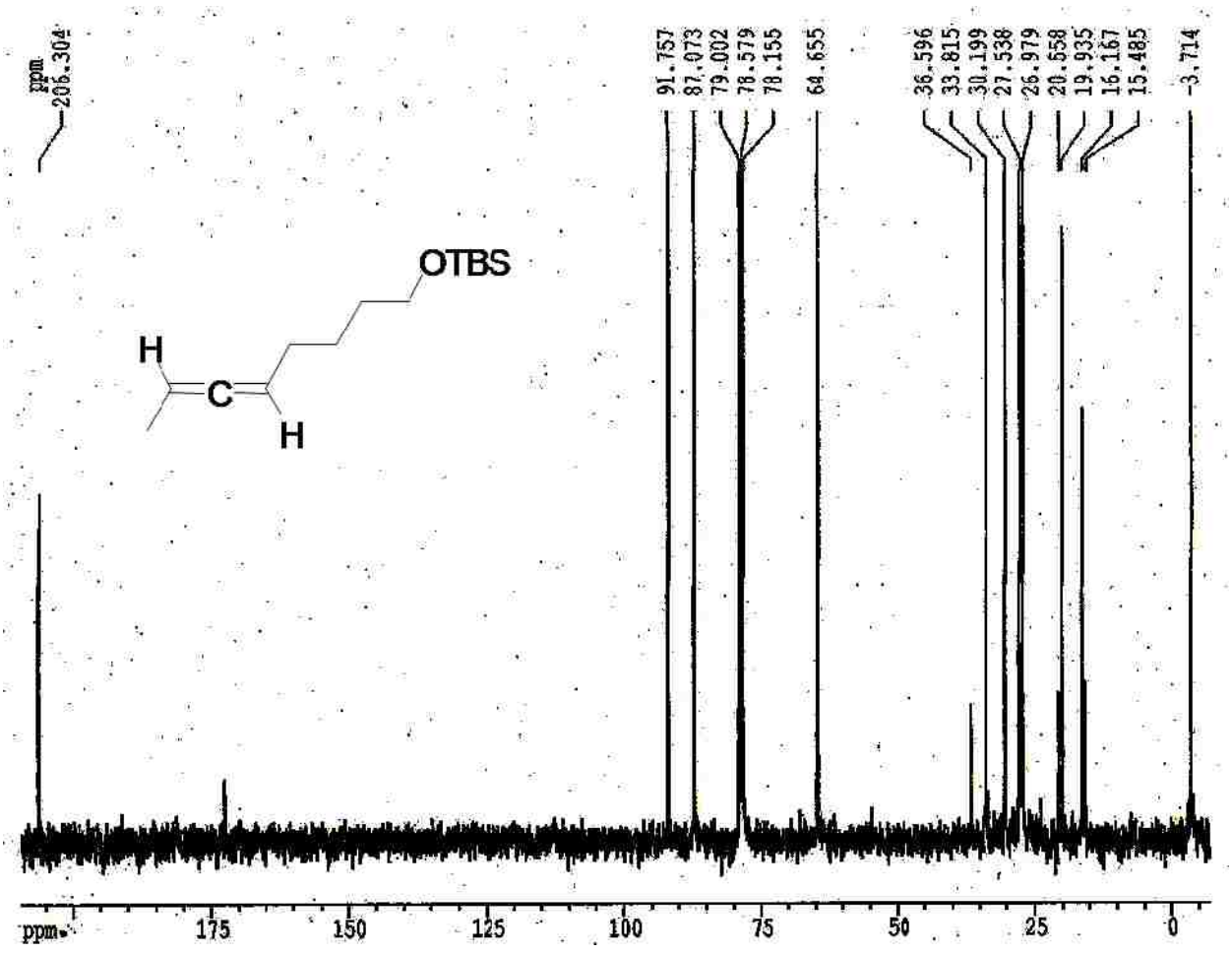


Figure **A.31.** ^{13}C NMR (75.5 MHz, $CDCl_3$) of compound **2.21**

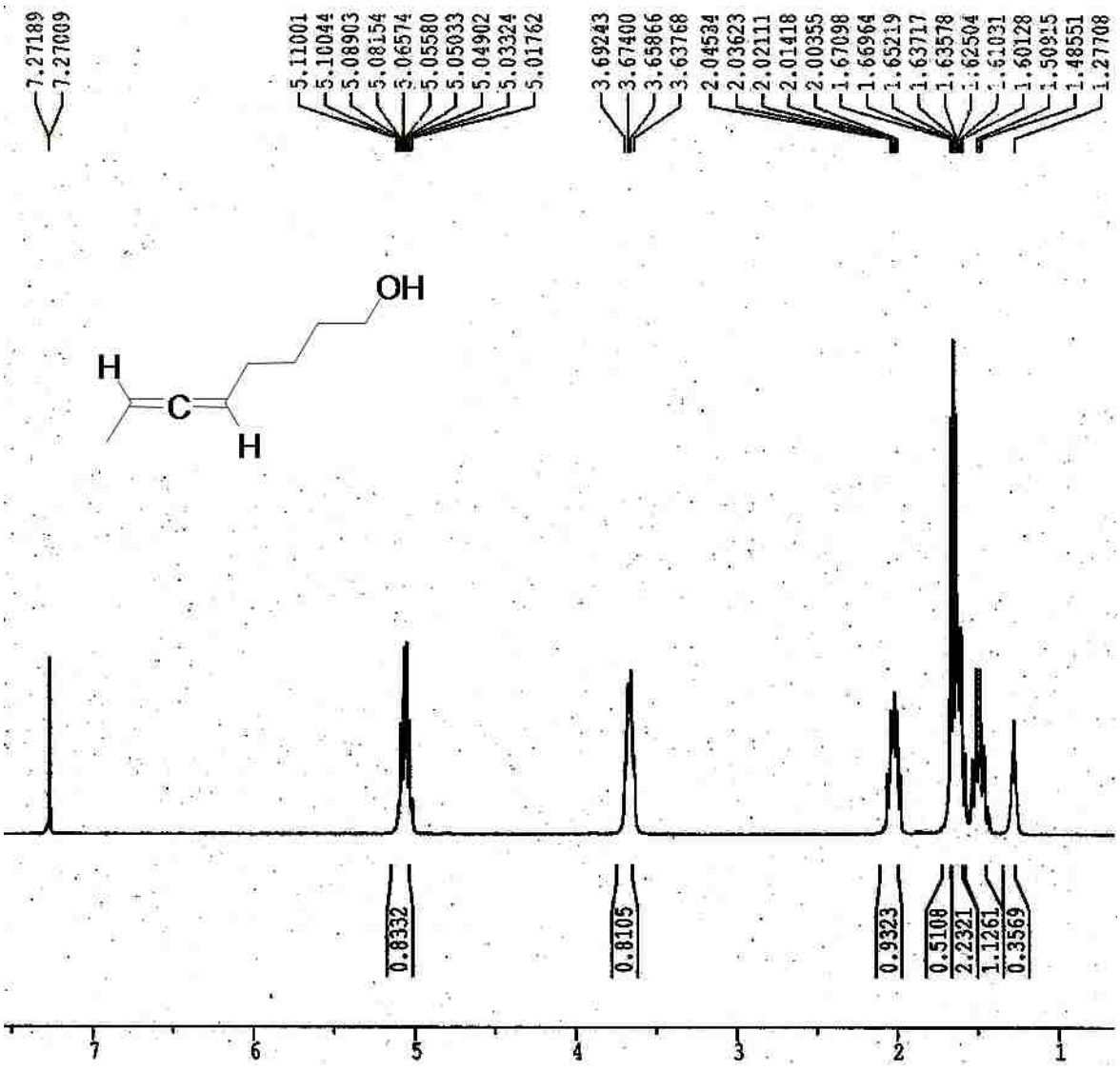


Figure **A.32.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.22**

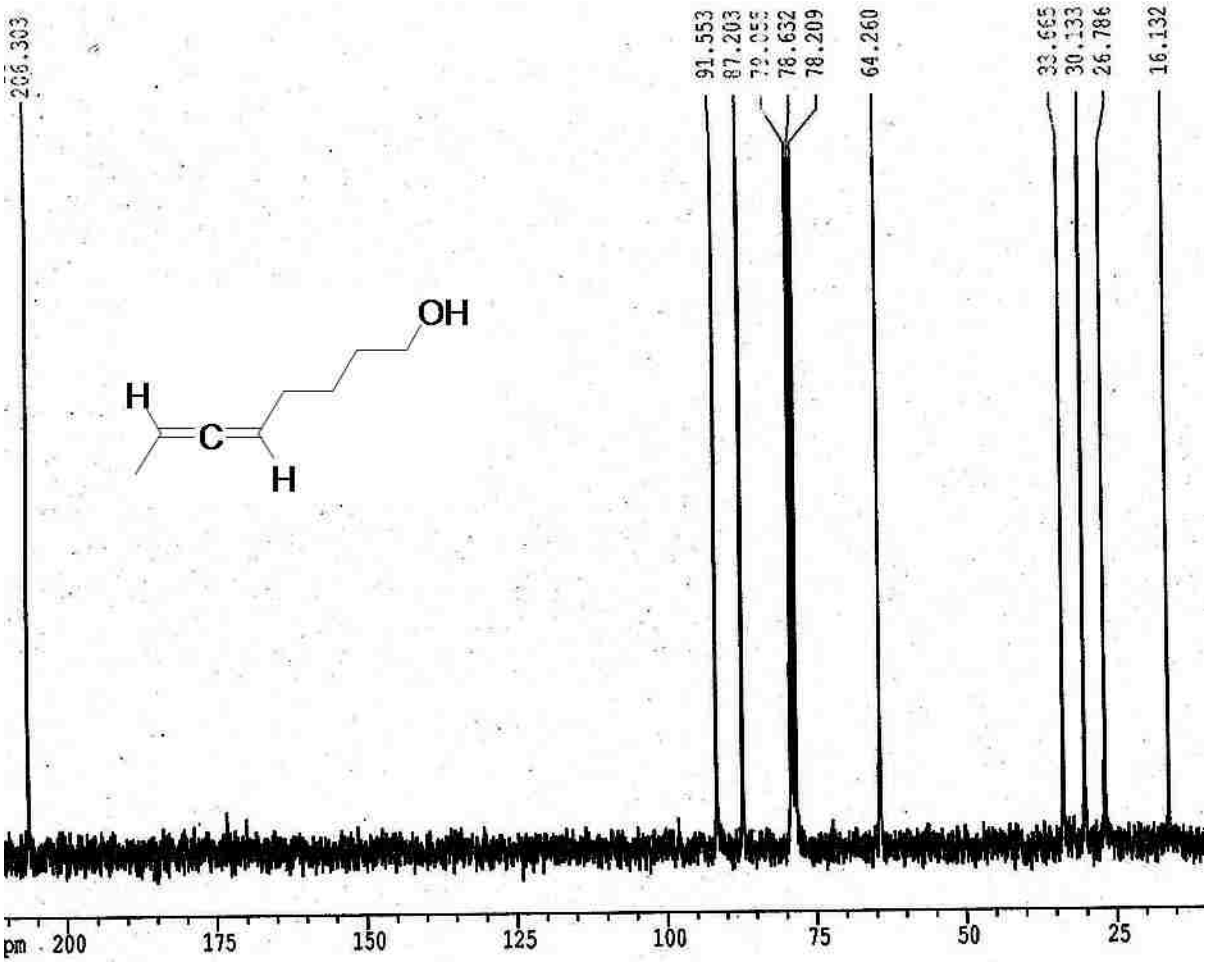


Figure **A.33.** ^{13}C NMR (75.5 MHz, $CDCl_3$) of compound **2.22**

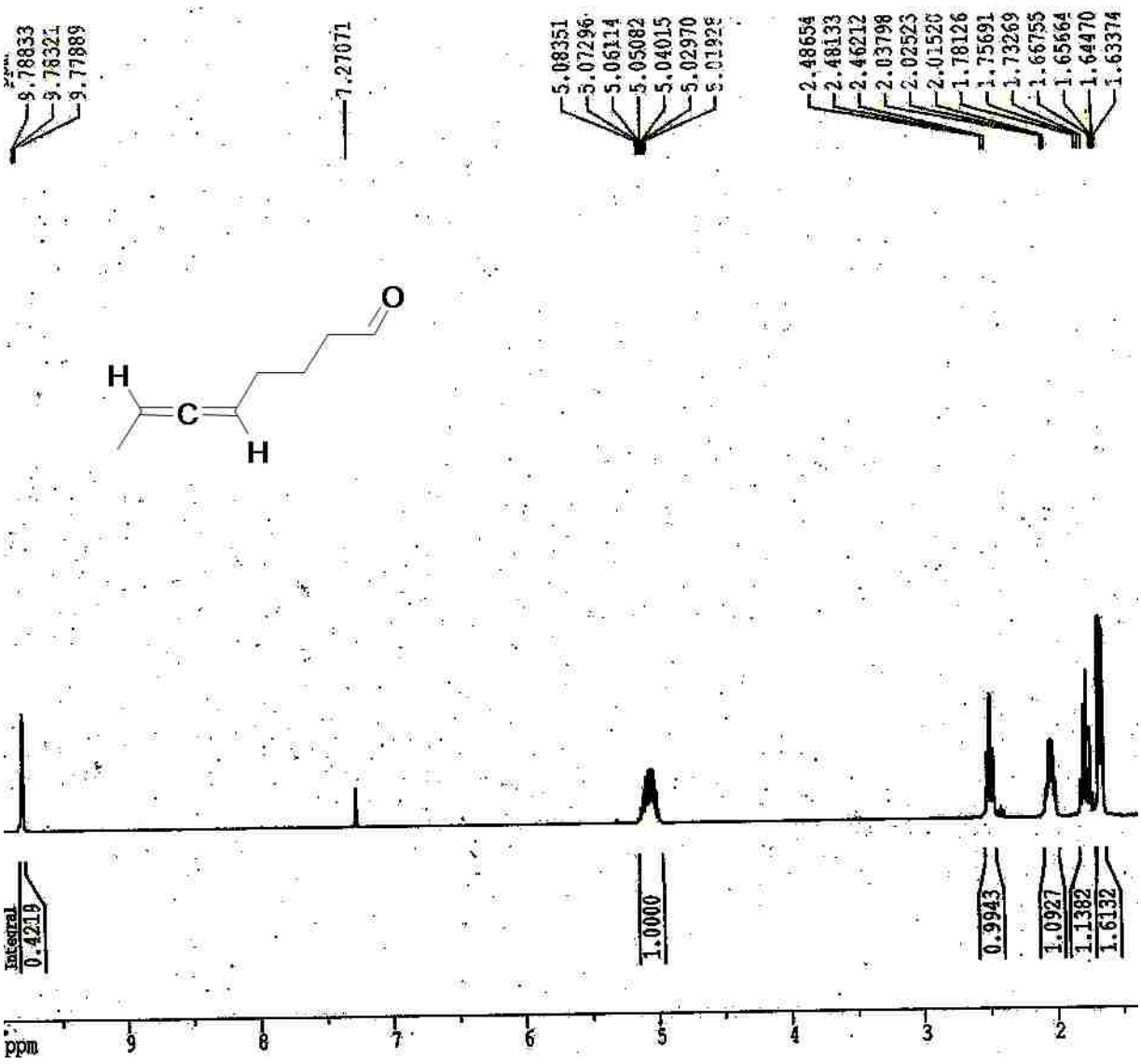


Figure **A.34.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.23**

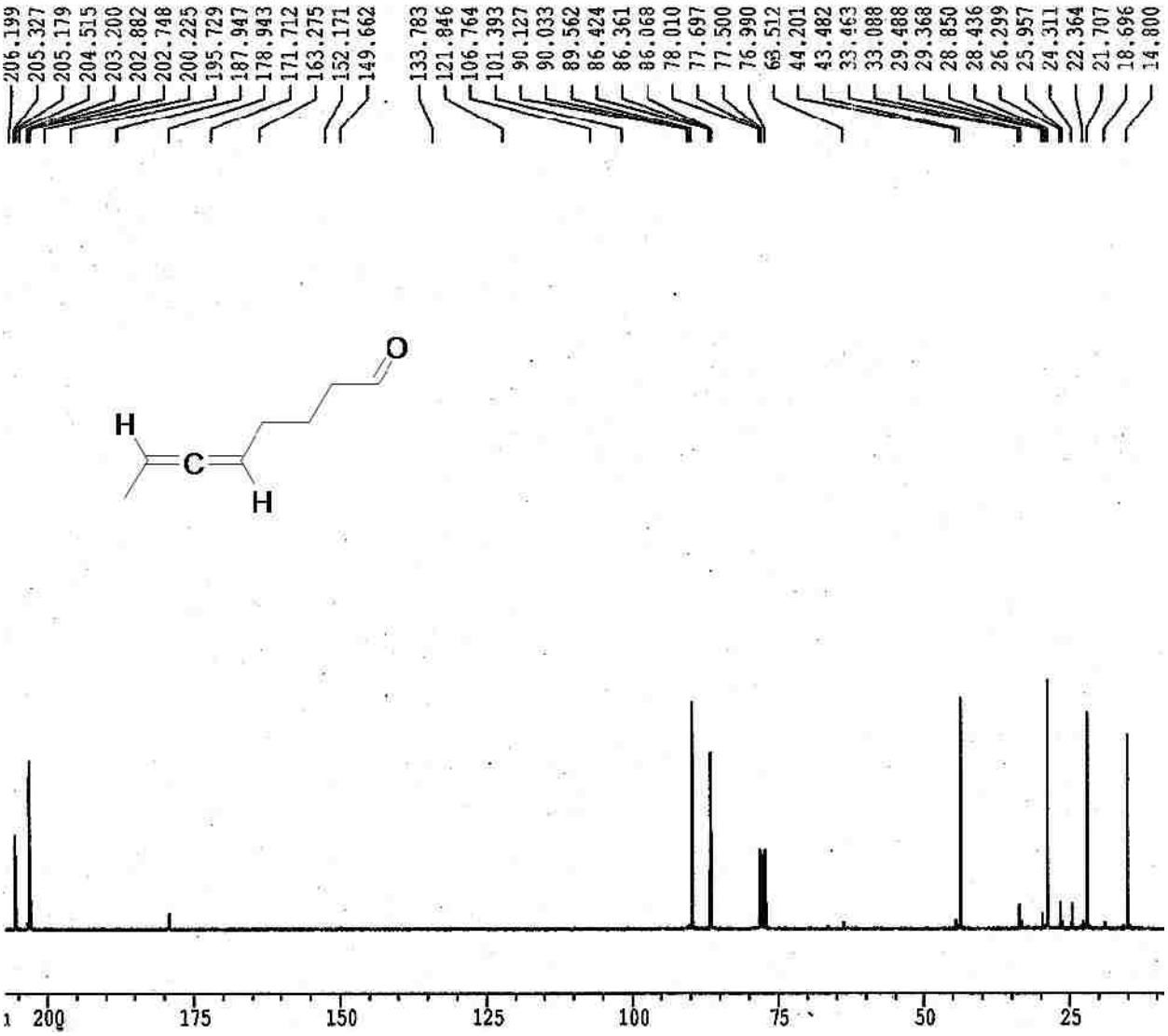


Figure **A.35.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.23**

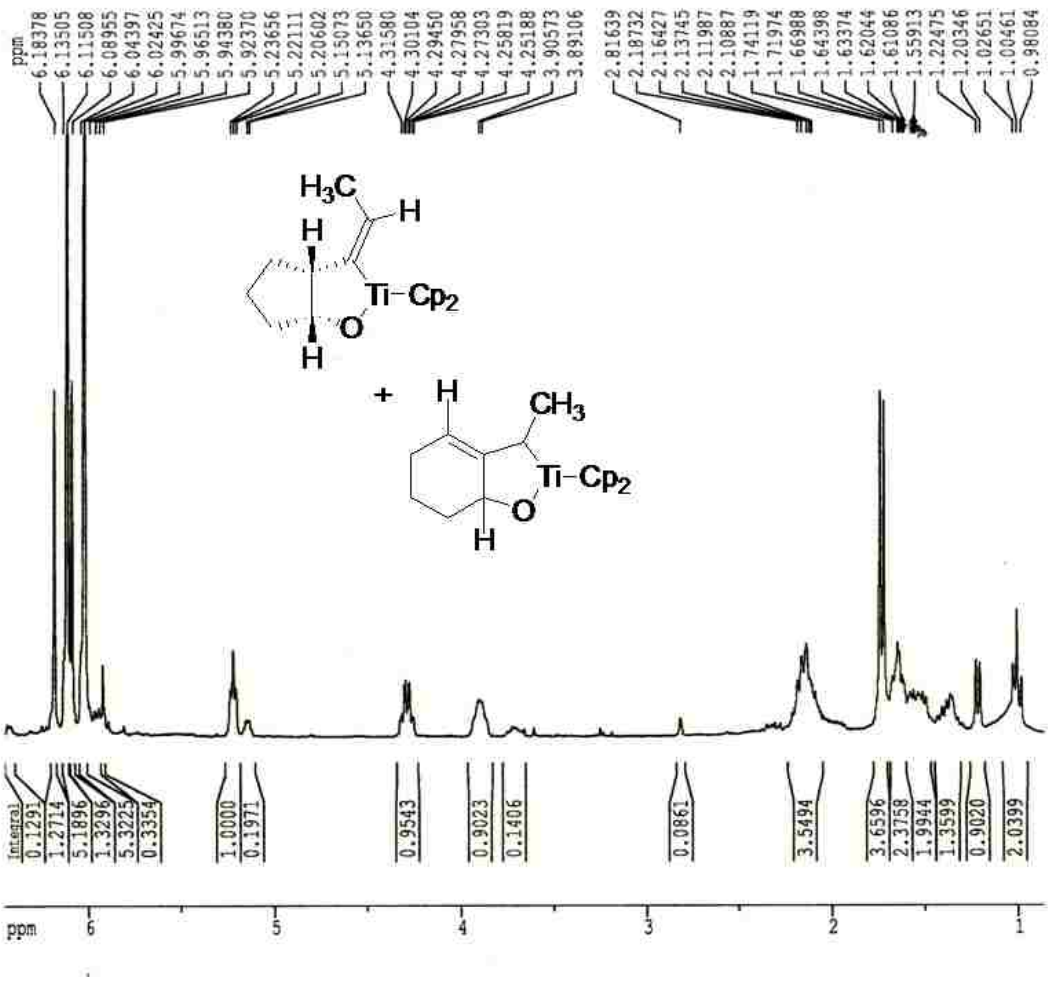


Figure **A.36.** ^{1}H NMR (300 MHz, C_6D_6) of compounds **2.24 a** & **b**

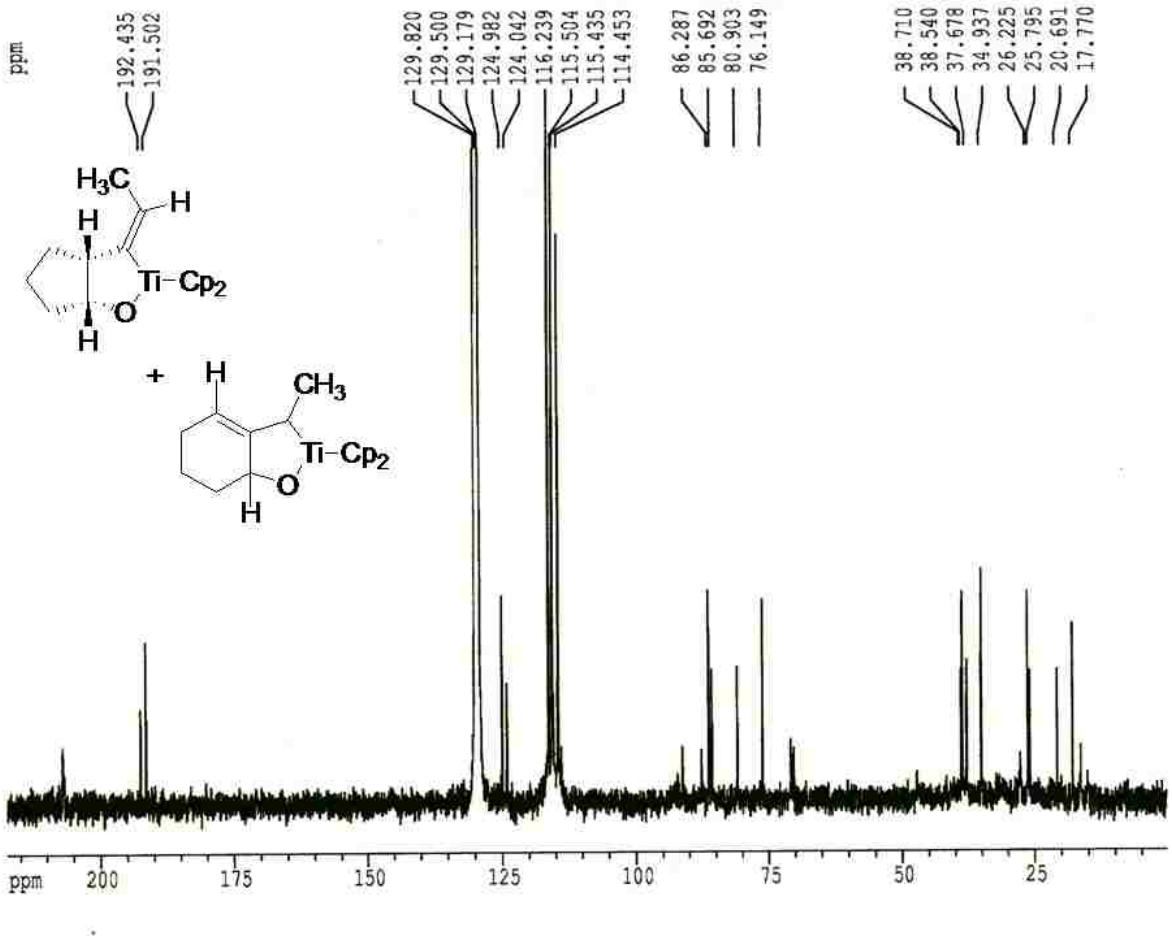


Figure **A.37.** ^{13}C NMR (75.5 MHz, C_6D_6) of compounds **2.24** a & **b**

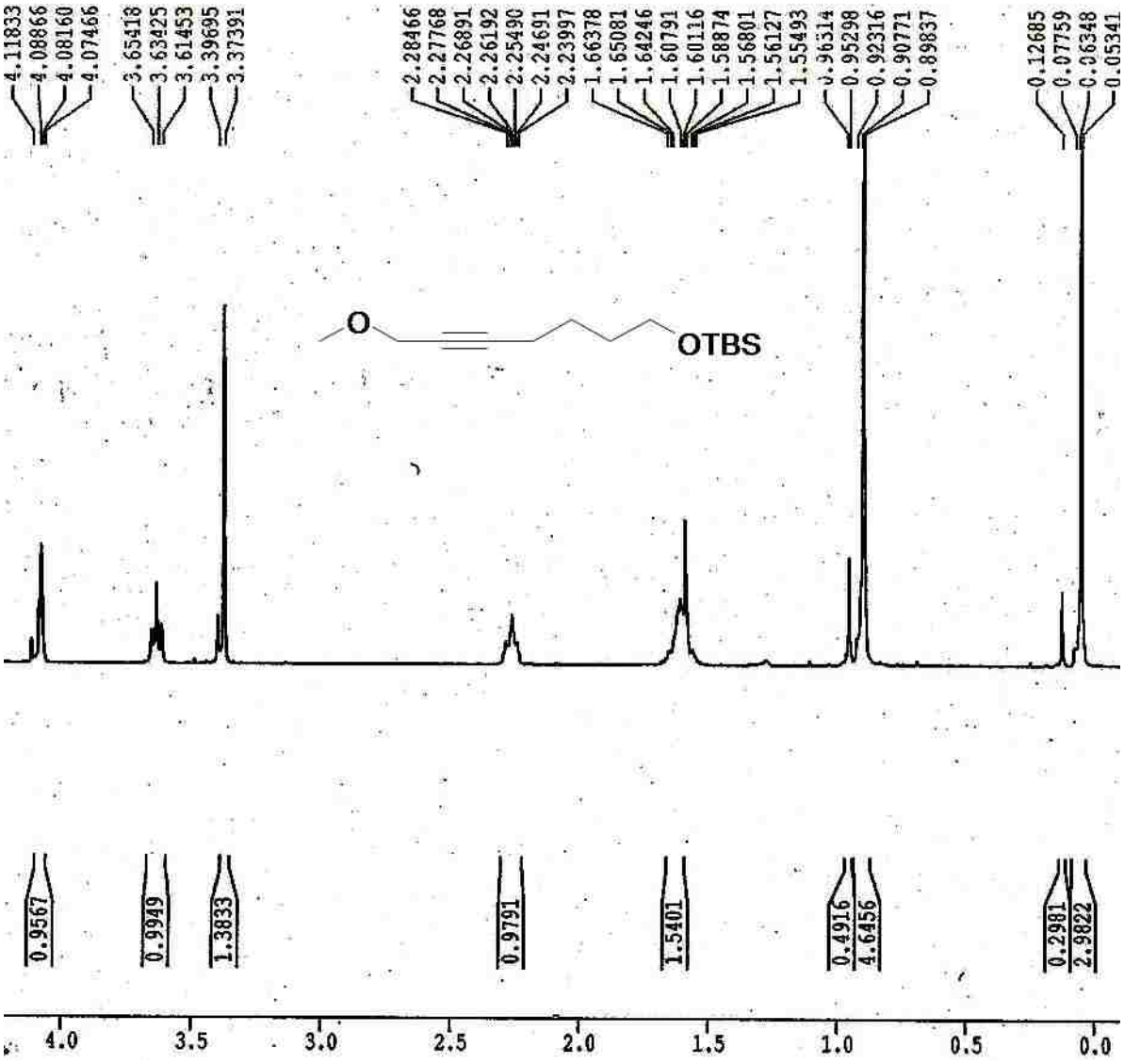


Figure **A.38.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.27**

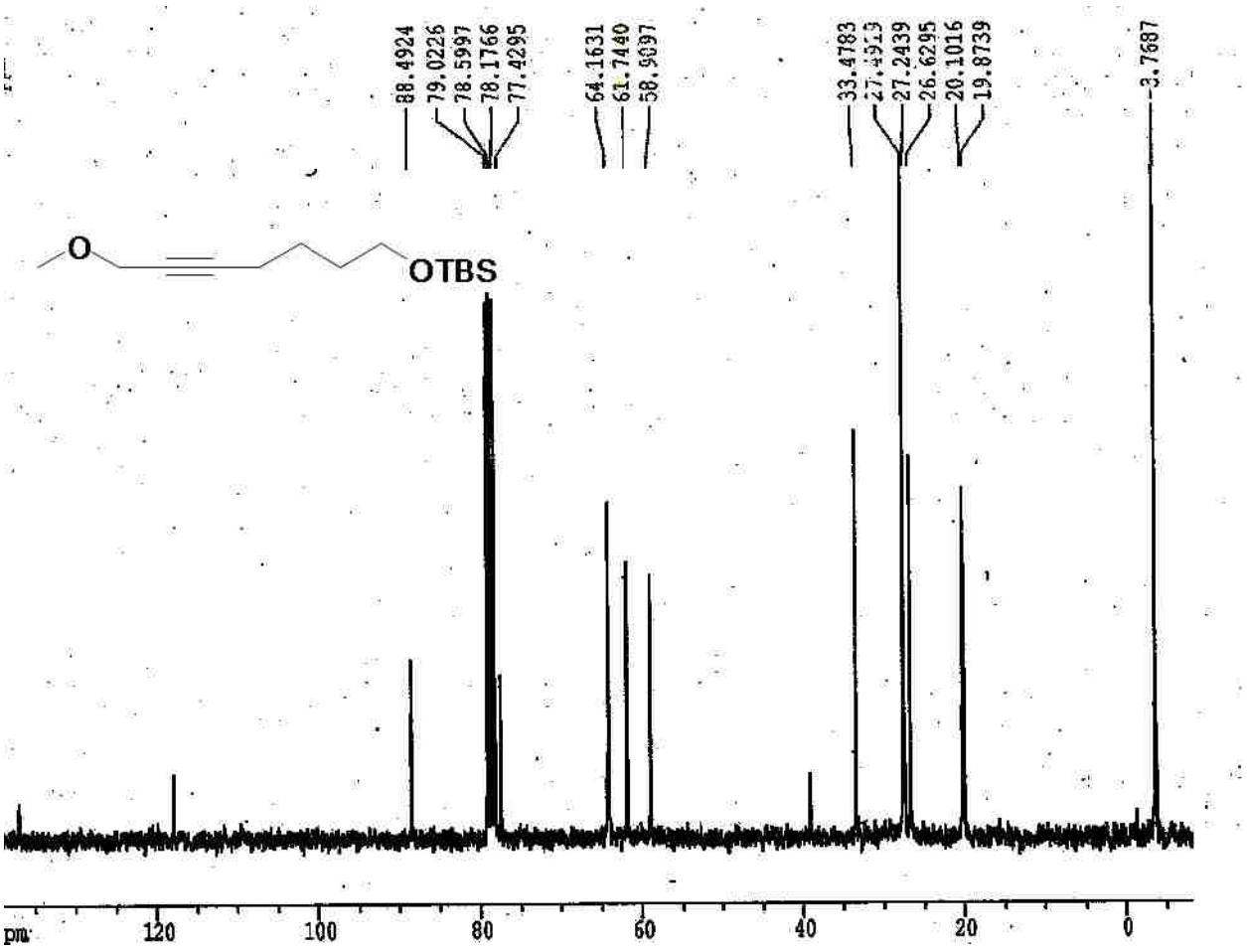


Figure **A.39.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.27**

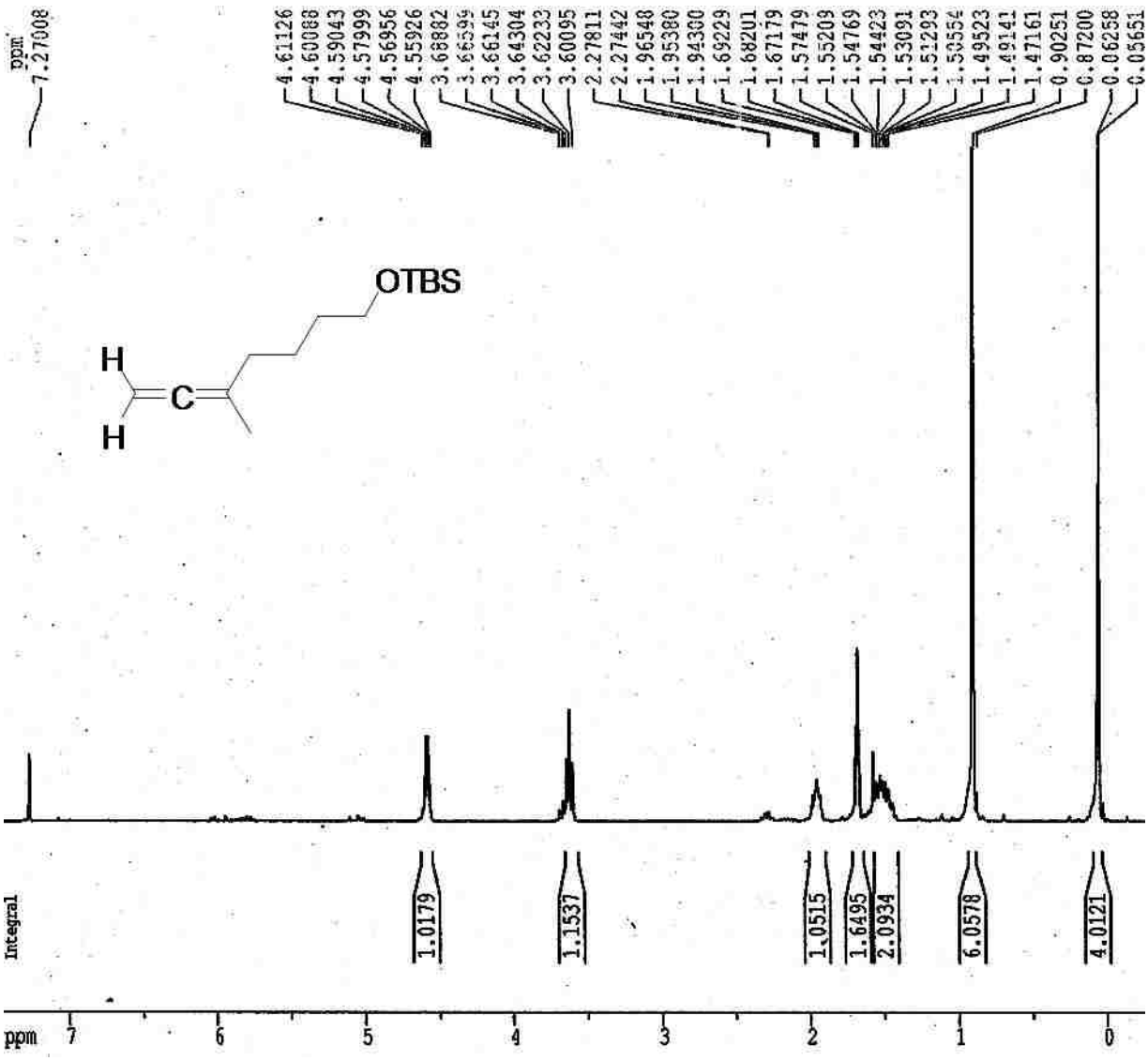


Figure **A.40.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.28**

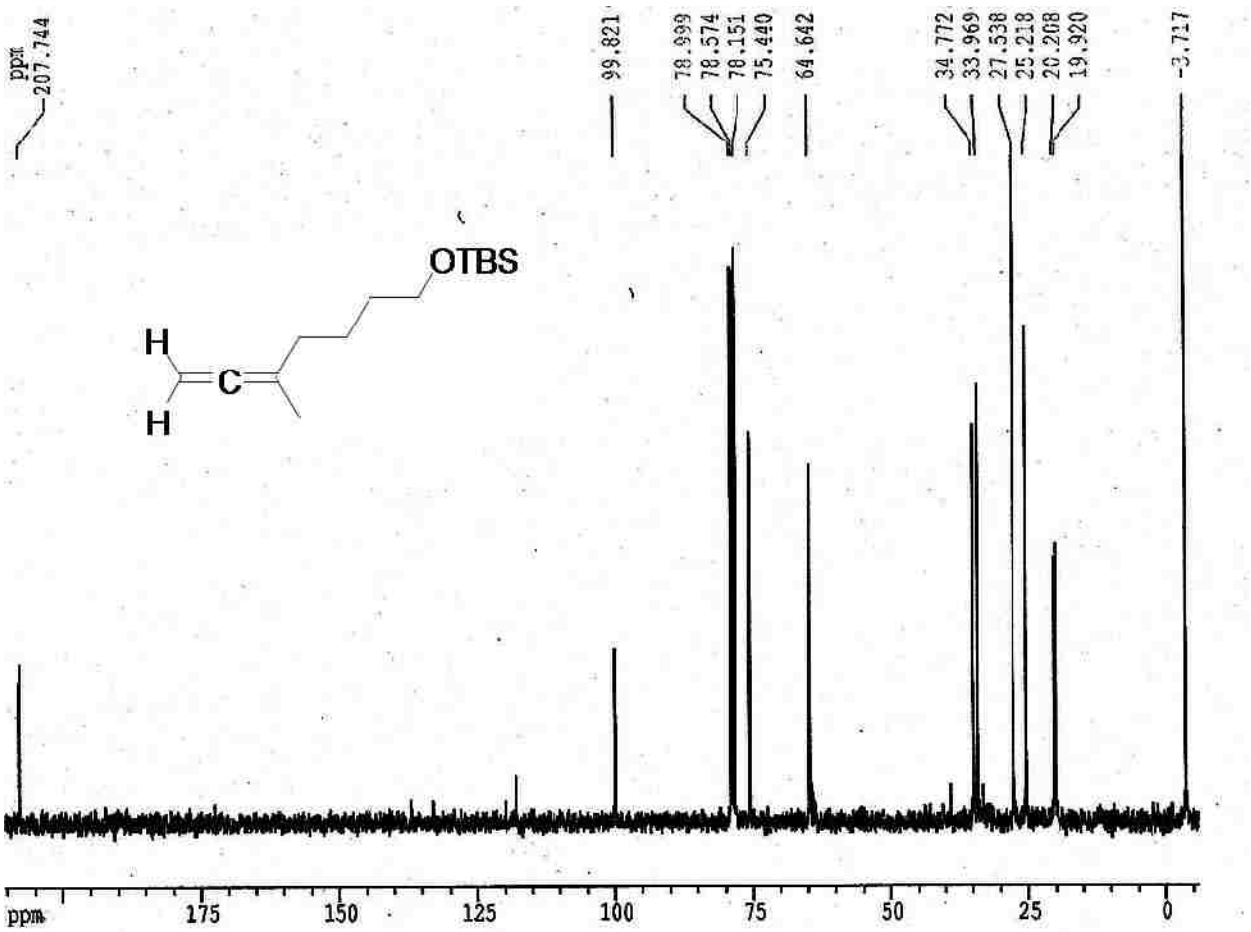


Figure **A.41.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.28**

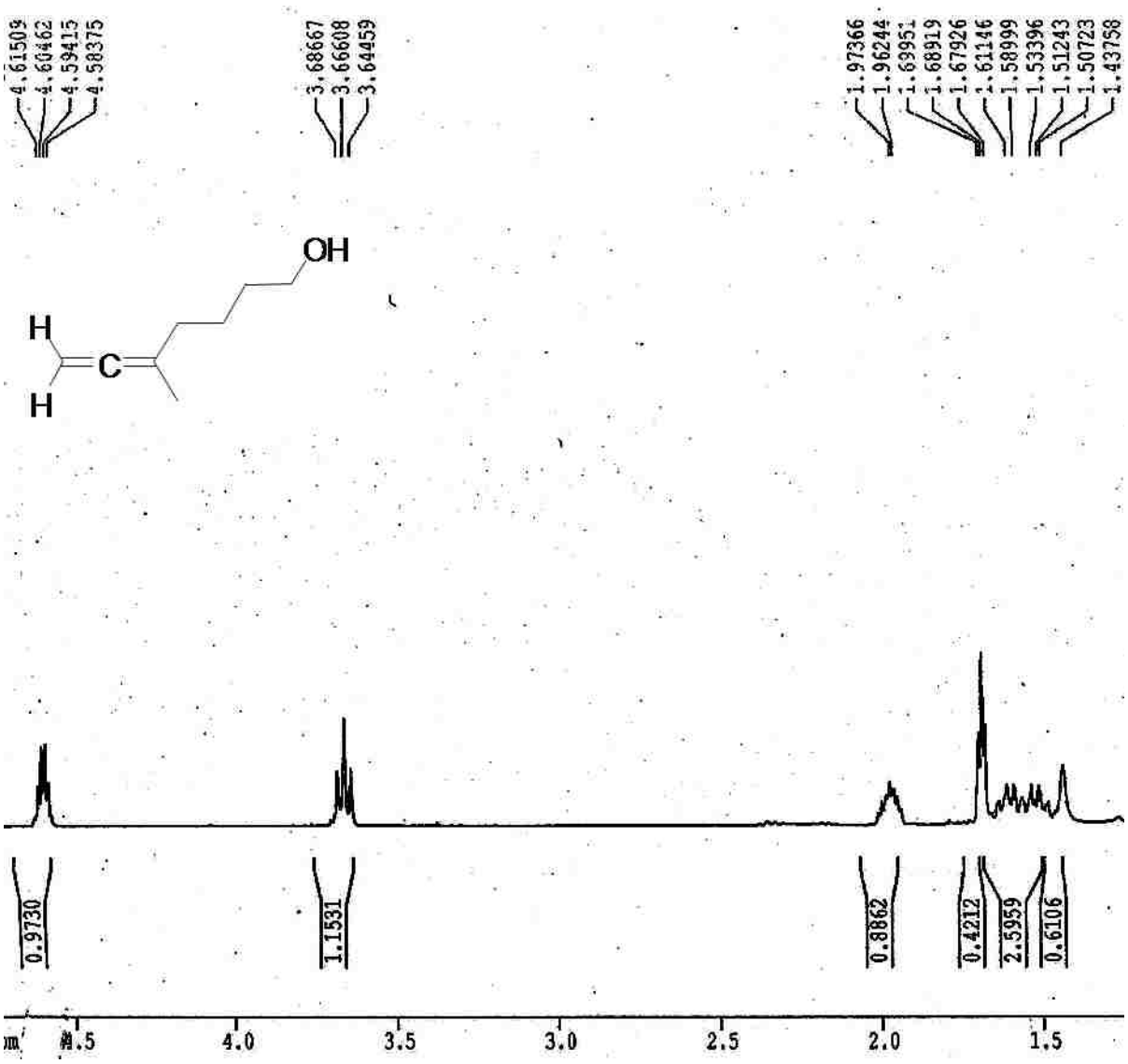


Figure **A.42.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.29**

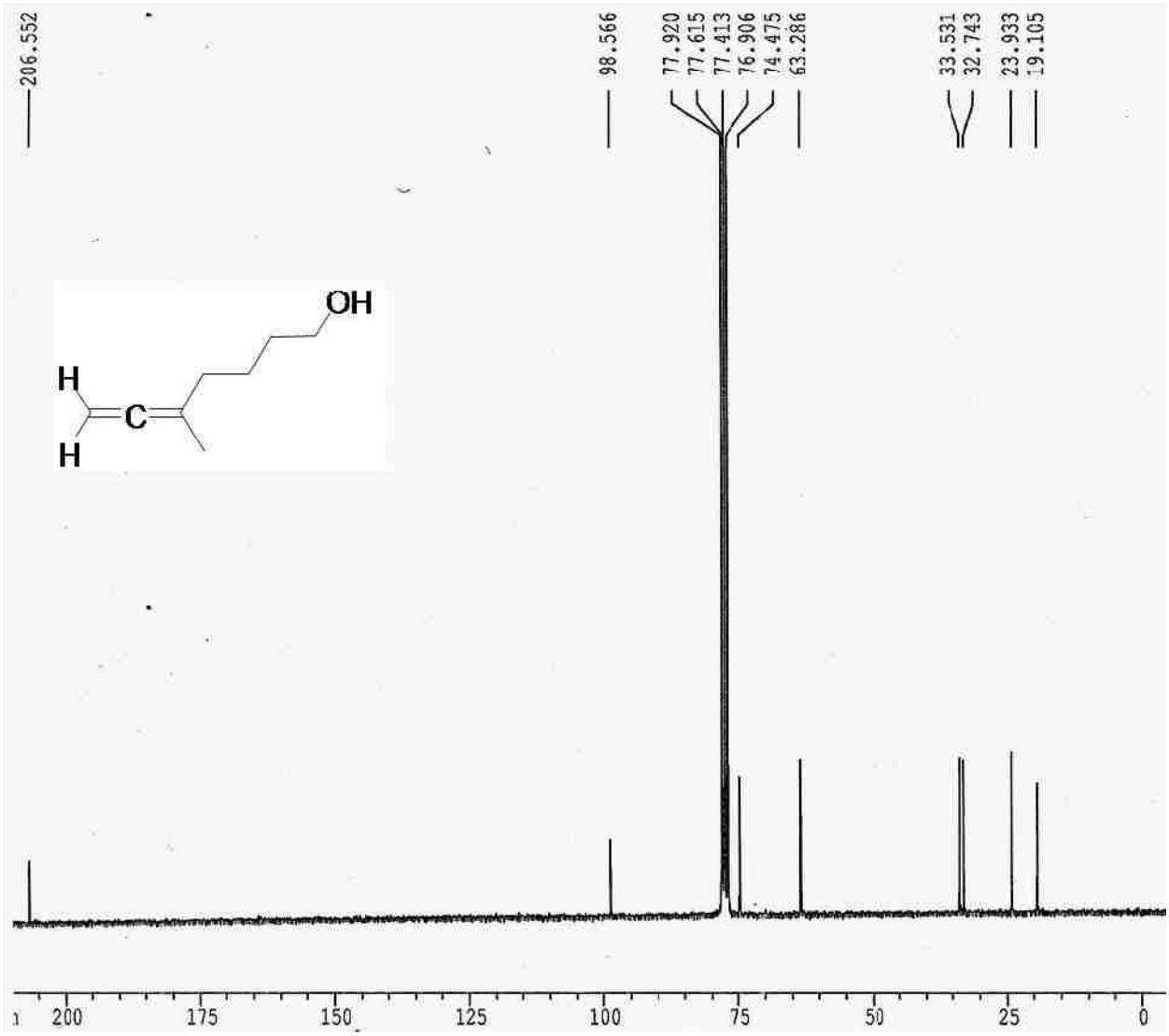


Figure **A.43.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.29**

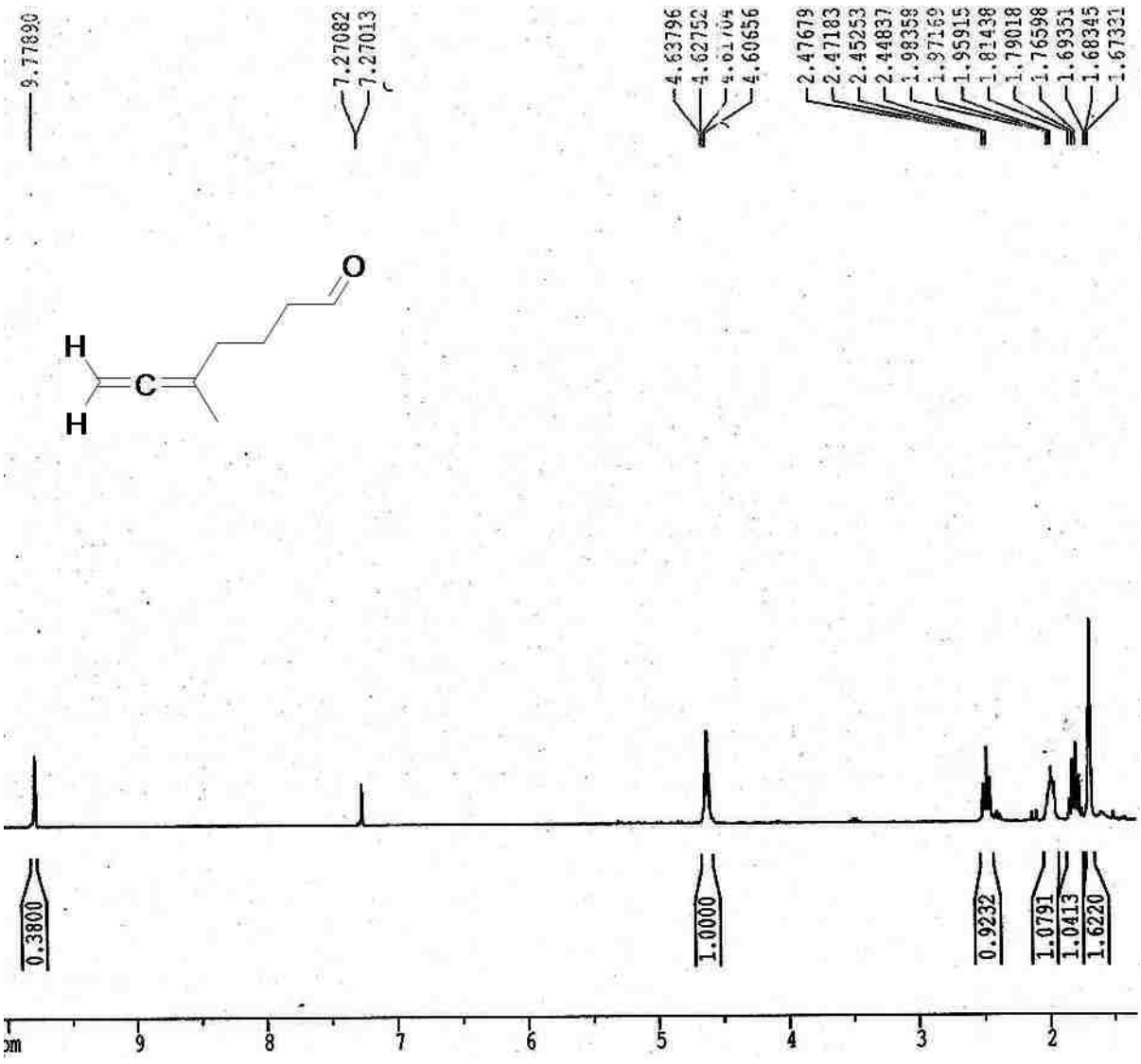


Figure **A.44.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.30**

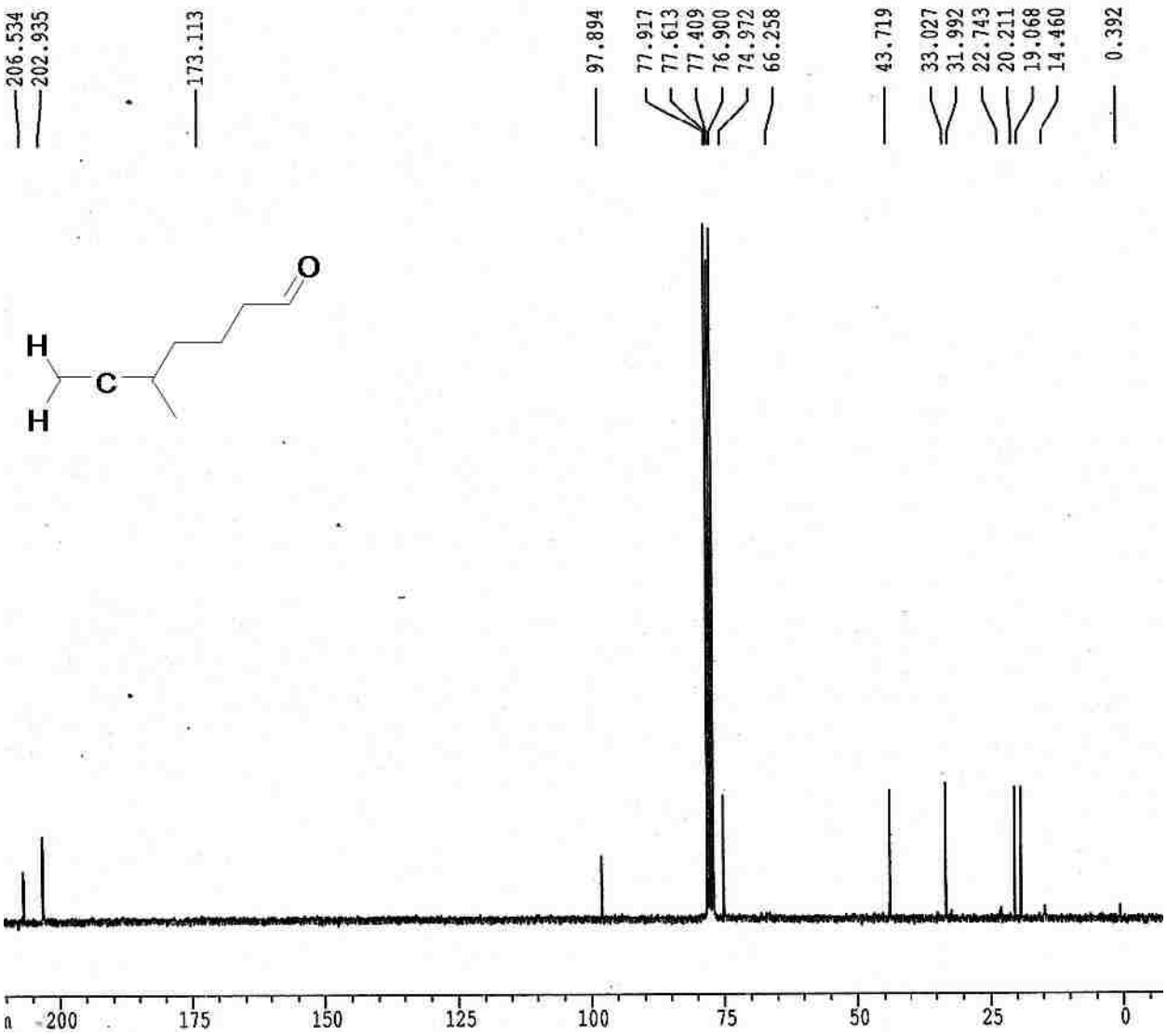


Figure **A.45.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.30**

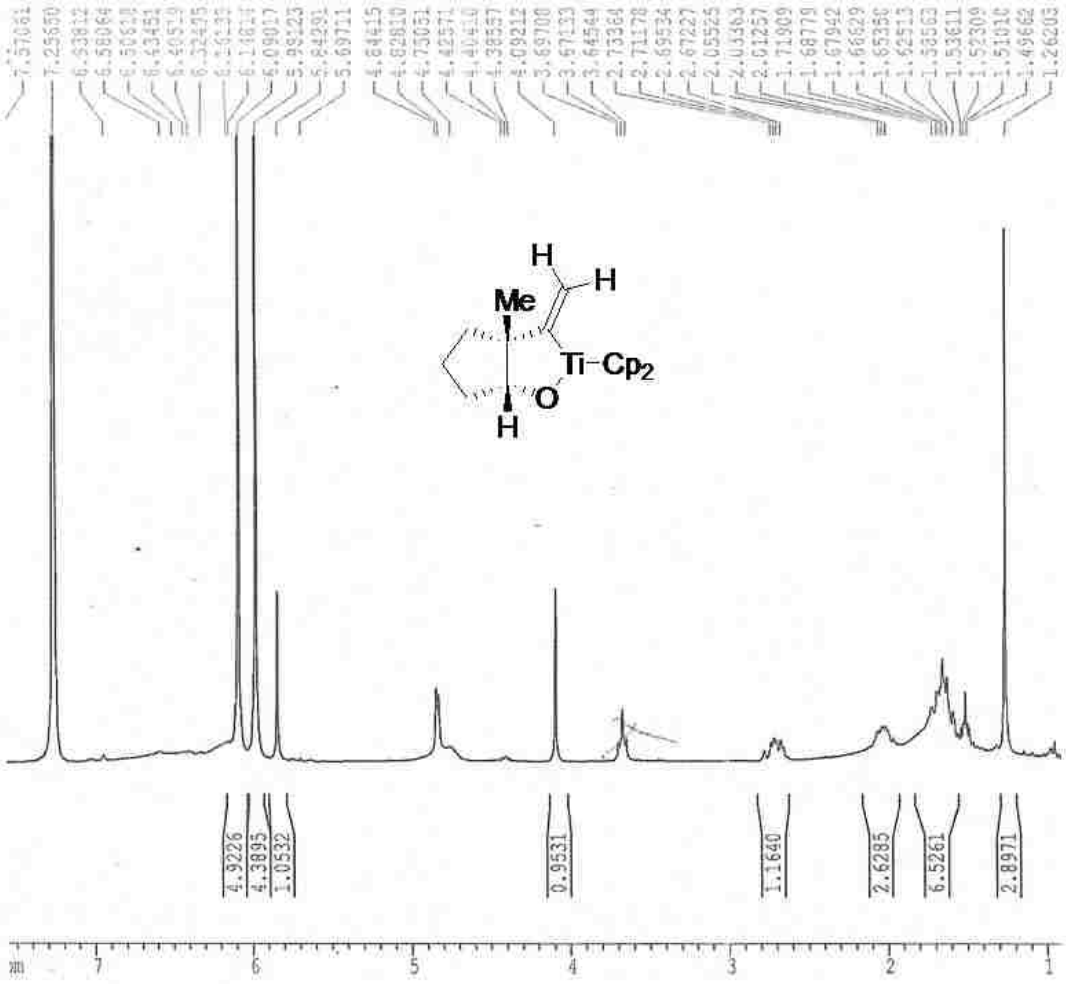


Figure **A.46.** ^{1}H NMR (250 MHz, $CDCl_3$) of compound **2.31**

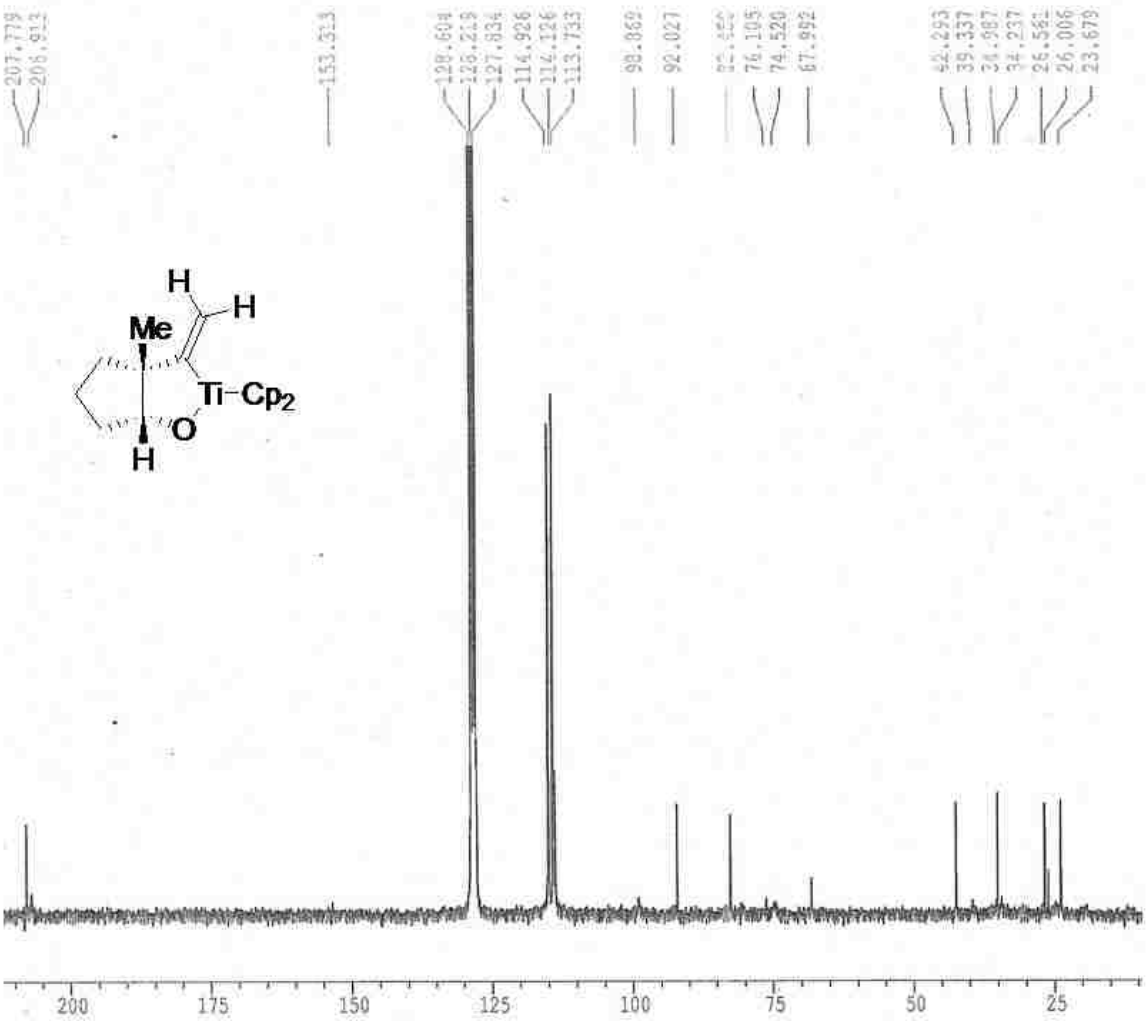


Figure **A.47.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.31**

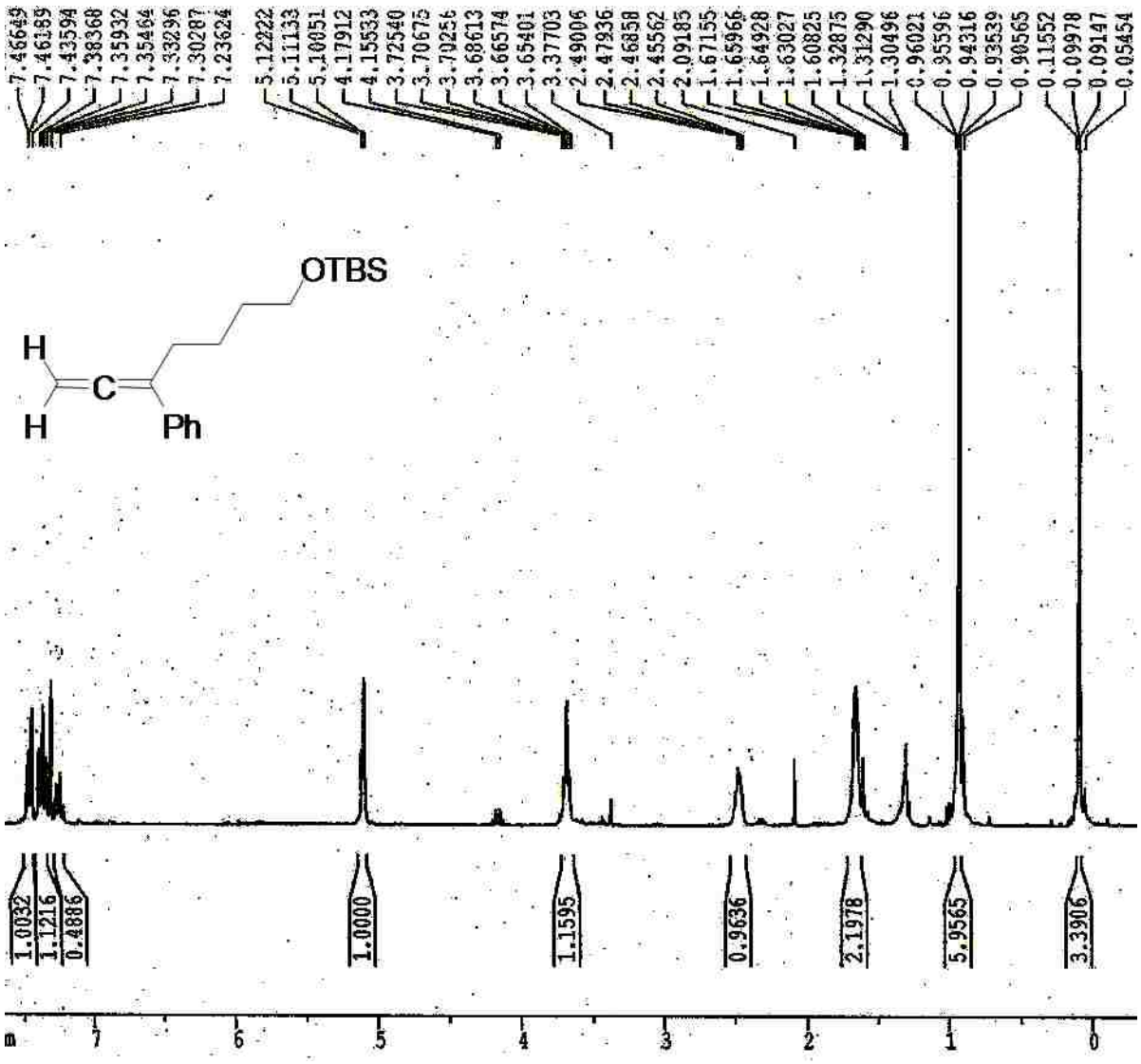


Figure **A.48.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.32**

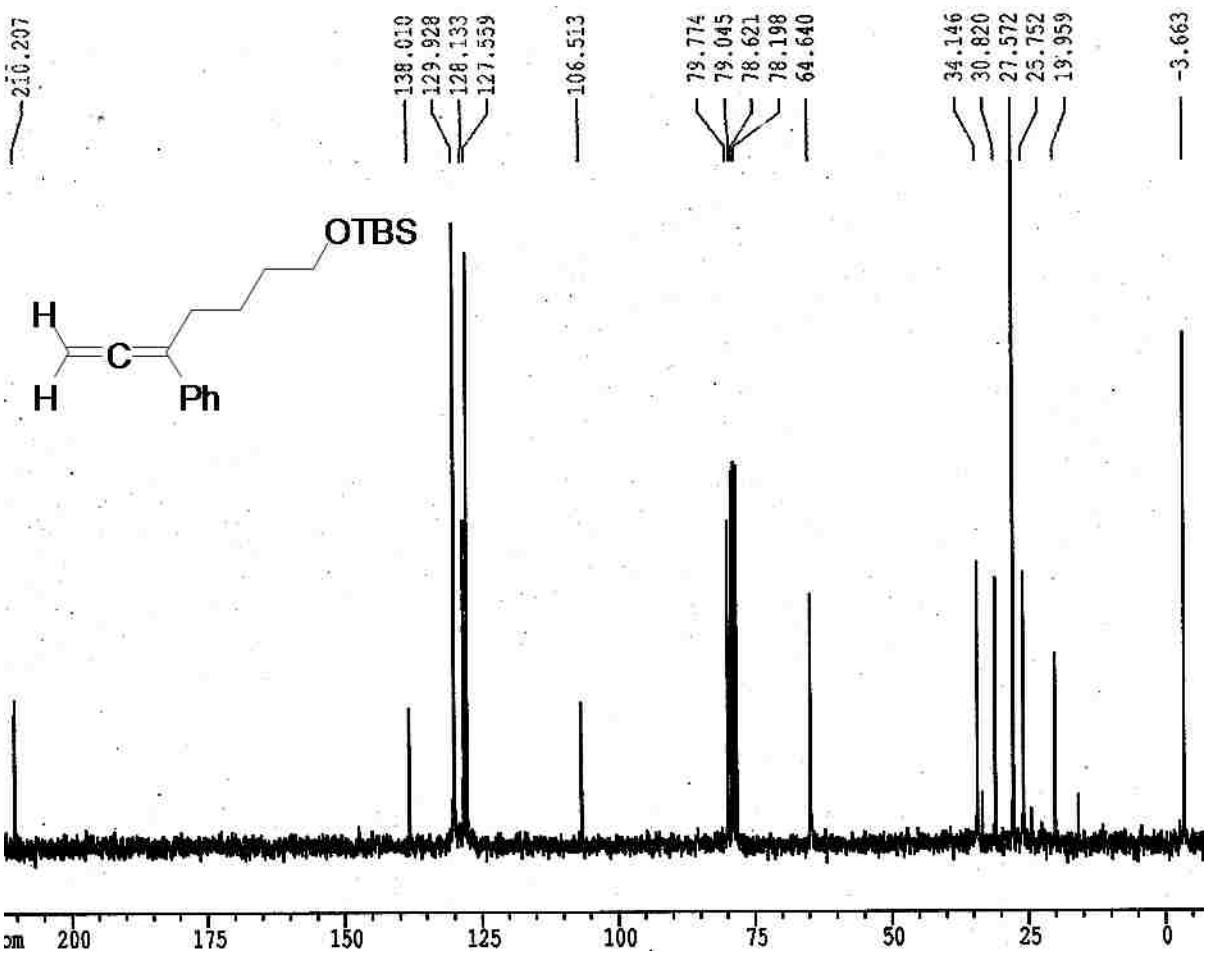


Figure **A.49.** ^{13}C NMR (75.5 MHz, $CDCl_3$) of compound **2.32**

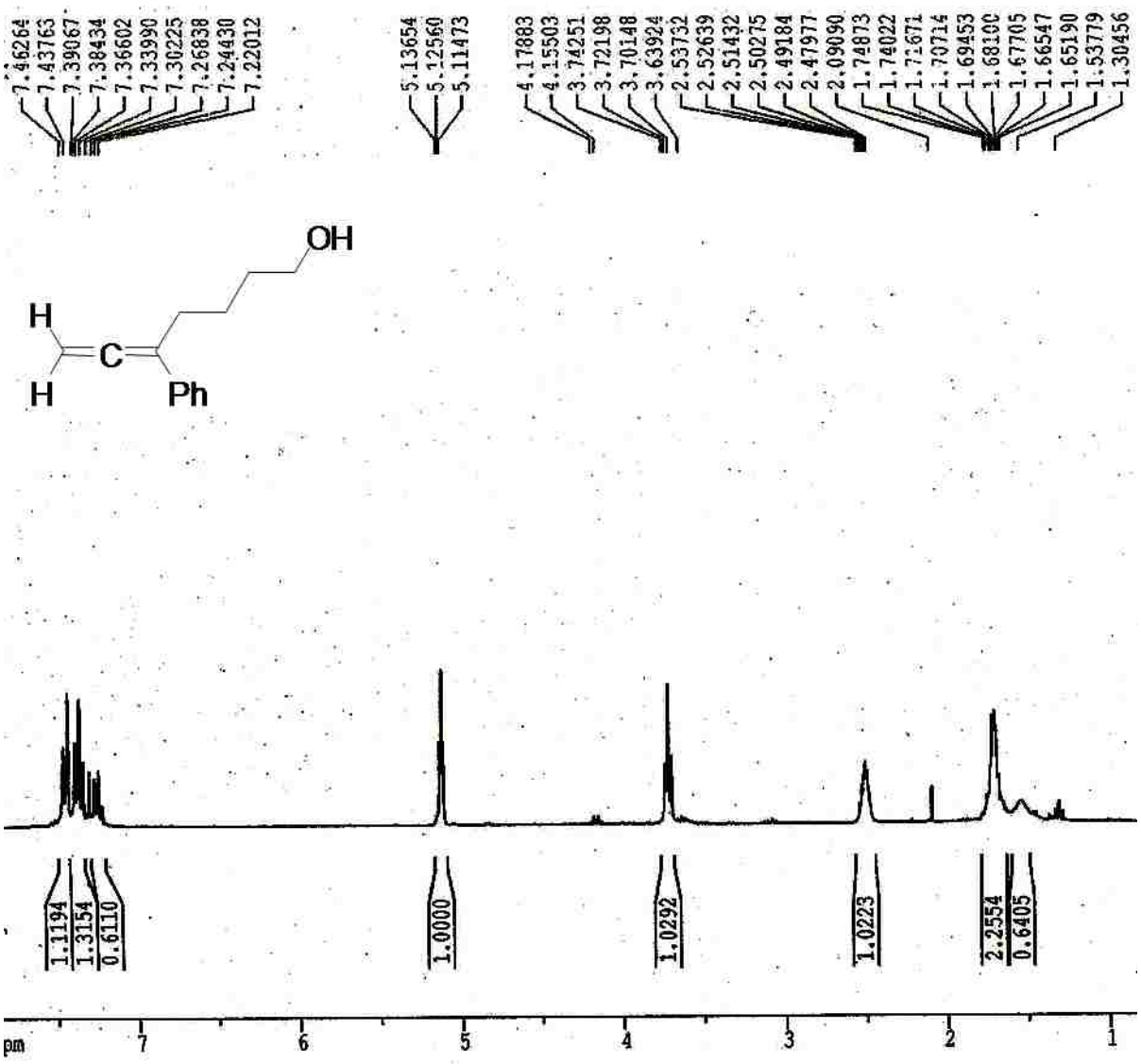


Figure **A.50.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.33**

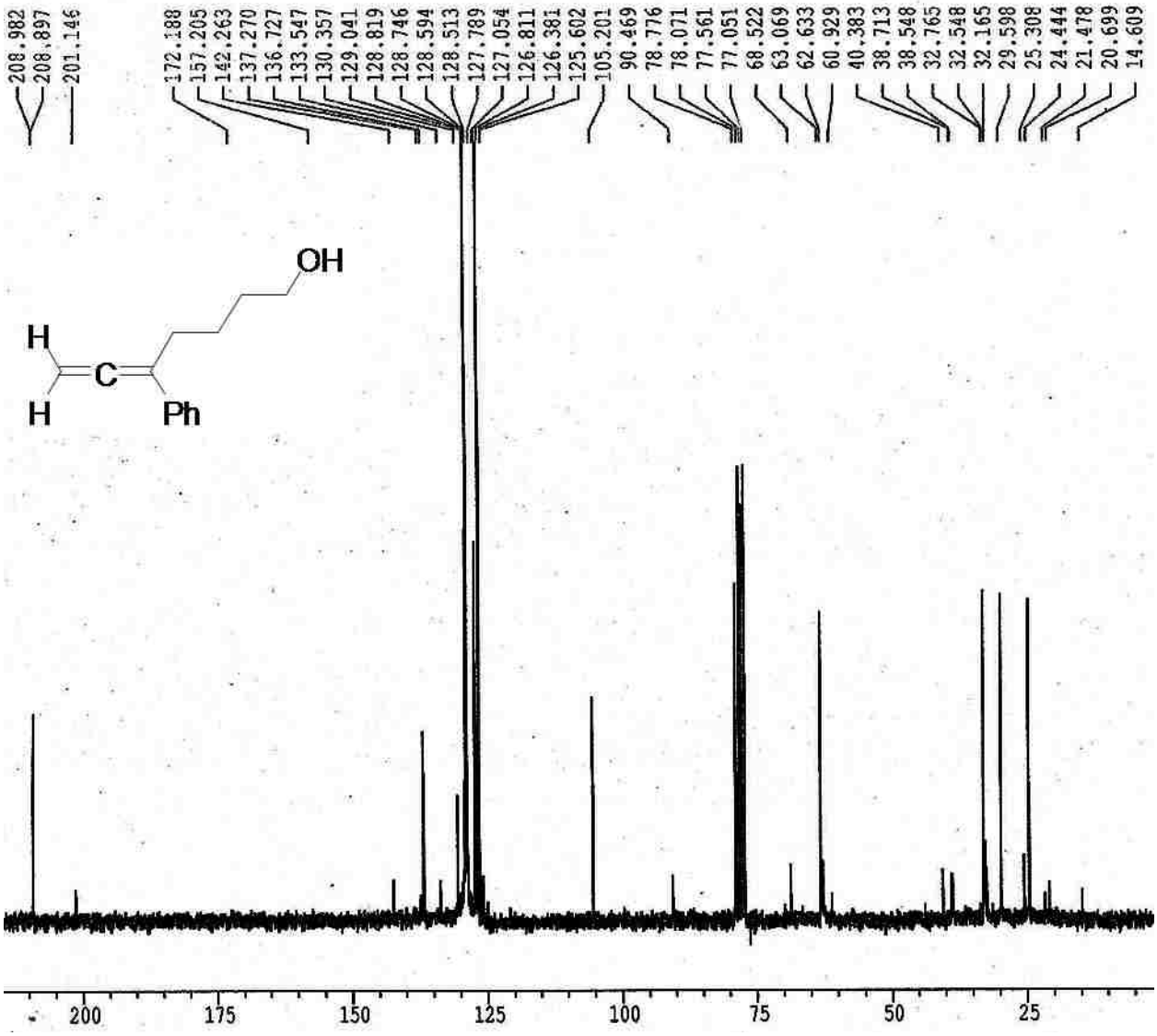


Figure **A.51.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of compound **2.33**

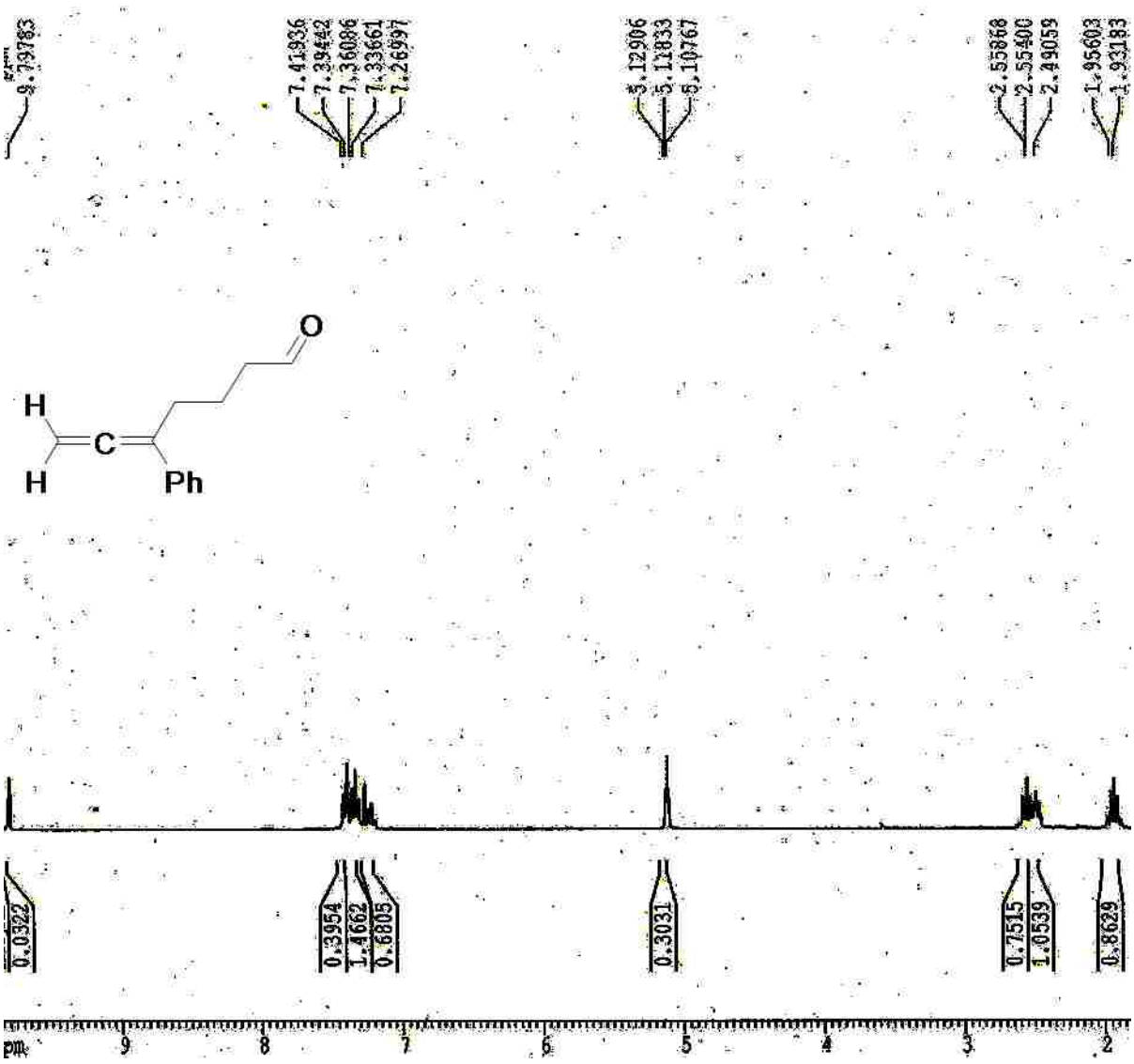


Figure **A.52.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.34**

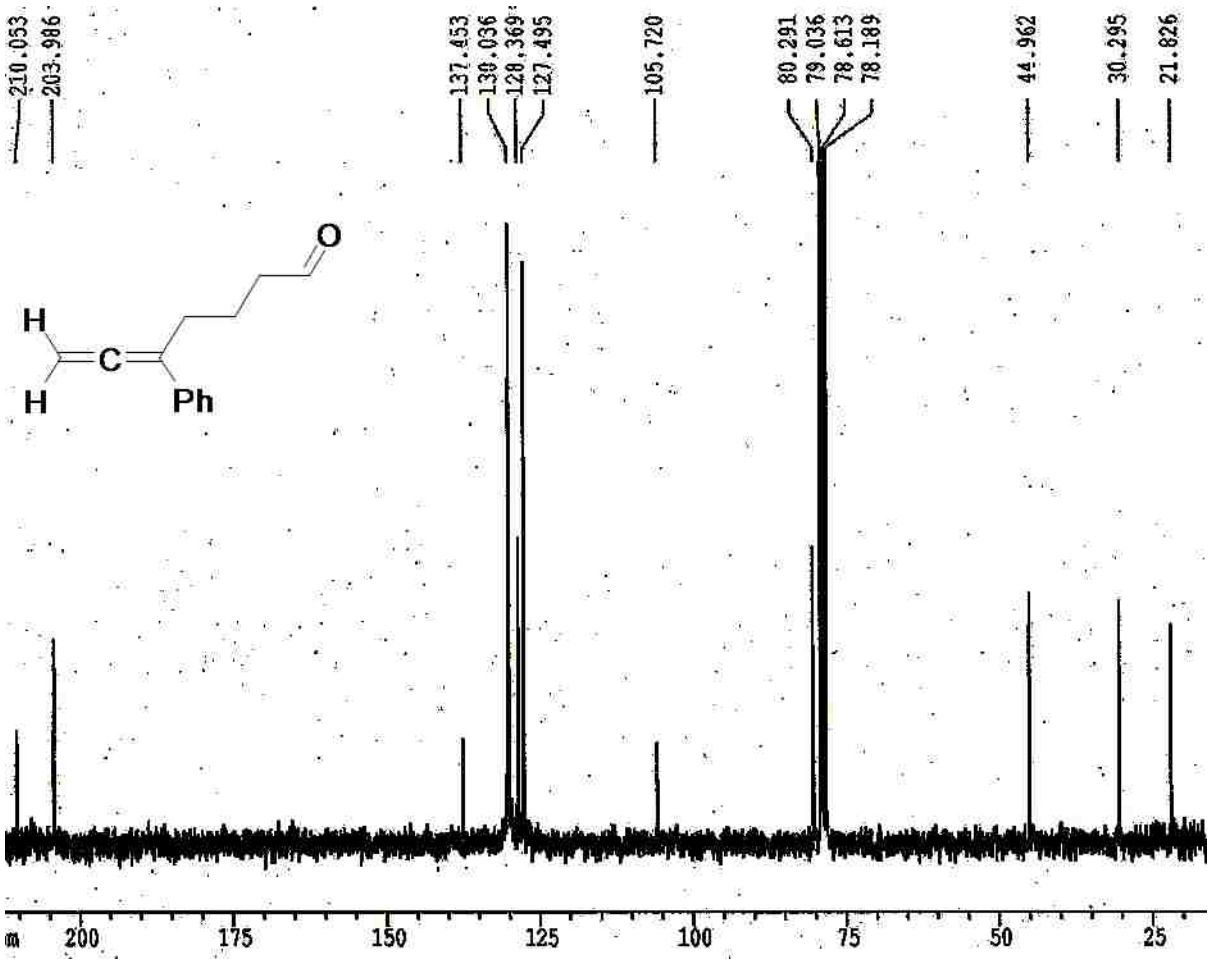


Figure **A.53.** ^{1}H NMR (300 MHz, $CDCl_3$) of compound **2.34**

APPENDIX B. SUPPLEMENTAL ^{1}H AND ^{13}C–NMR DATA FOR CHAPTER 3

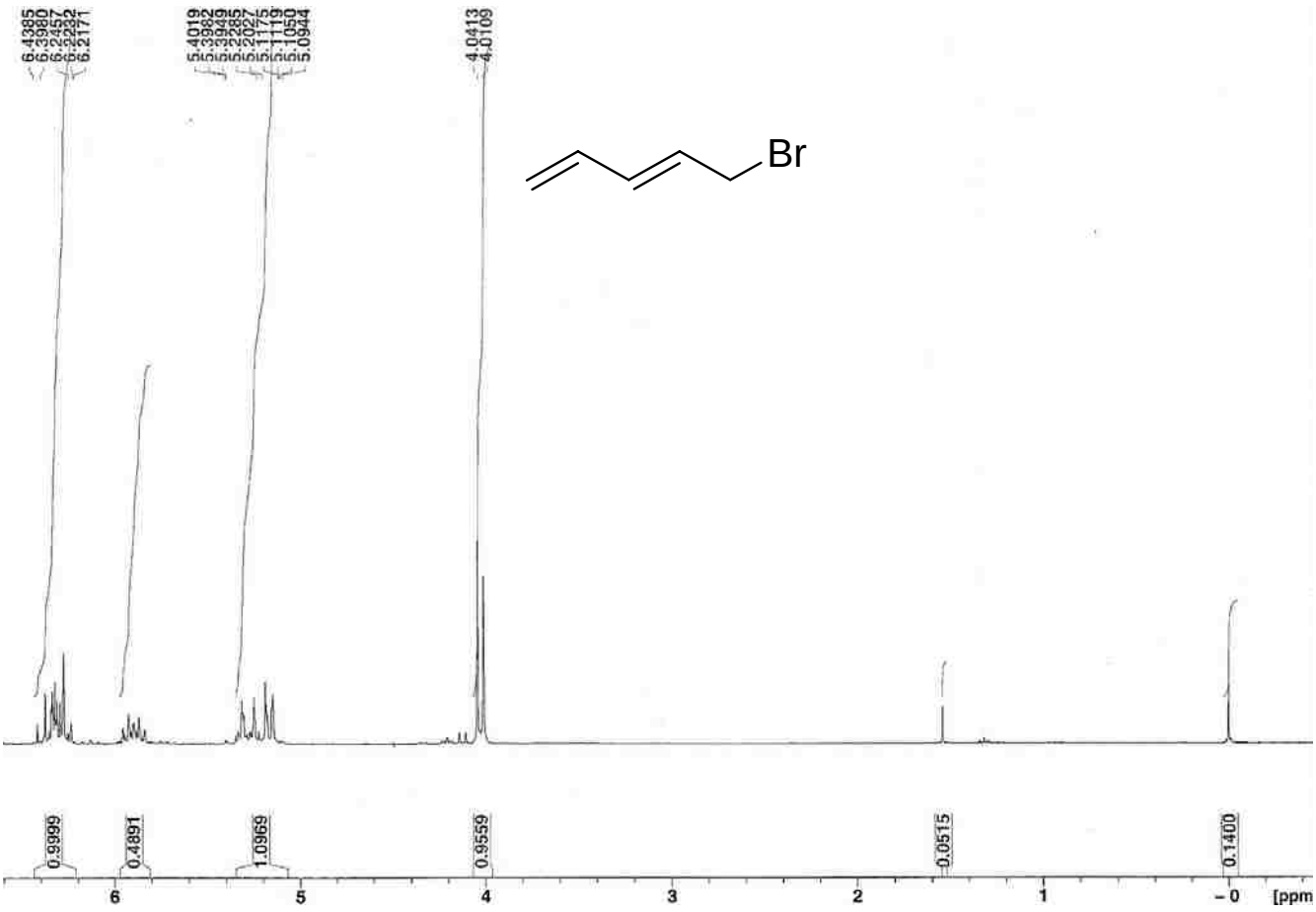


Figure **B.1.** ^{1}H NMR (250 MHz, $CDCl_3$) of Compound **3.2**

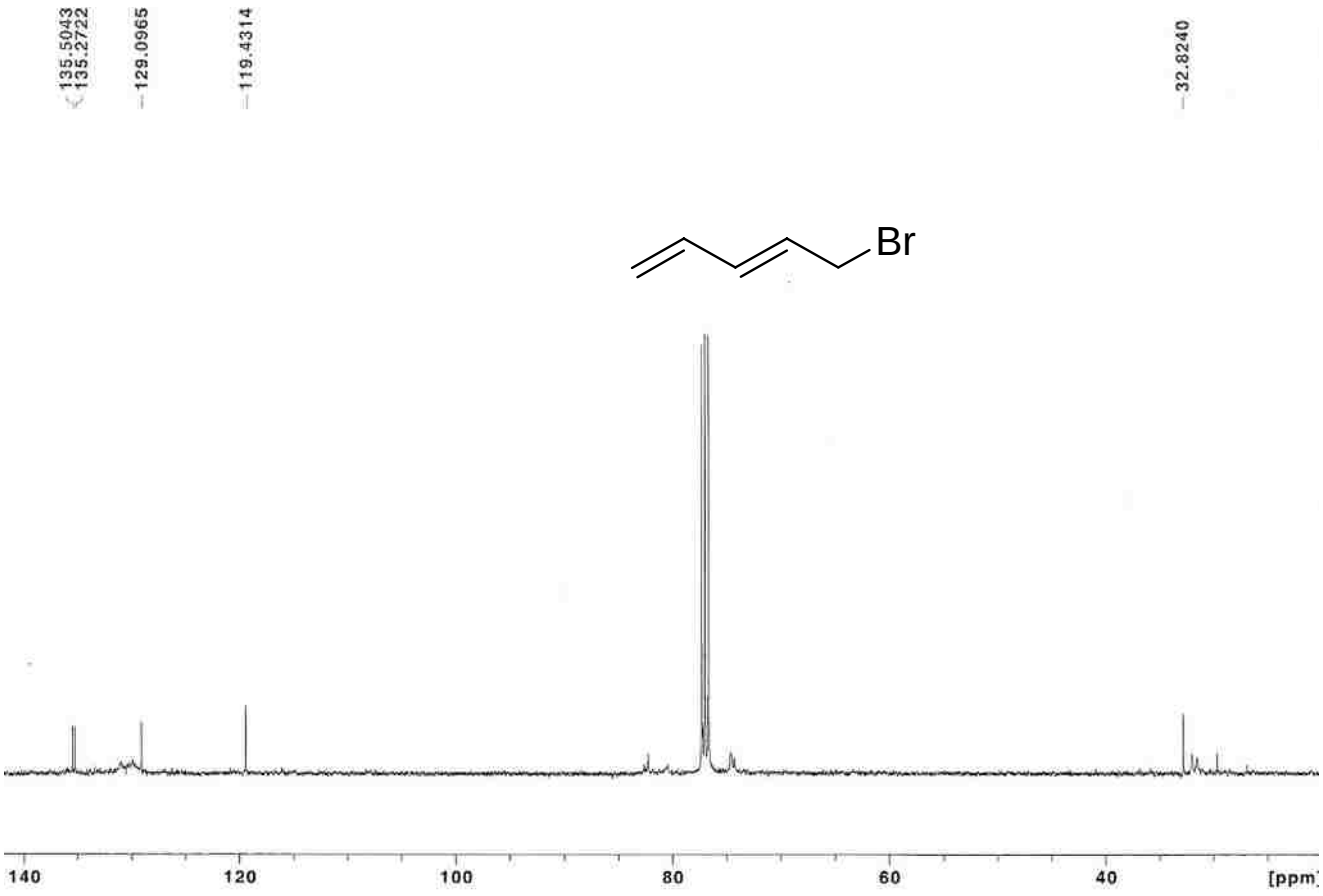


Figure **B.2.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.2**

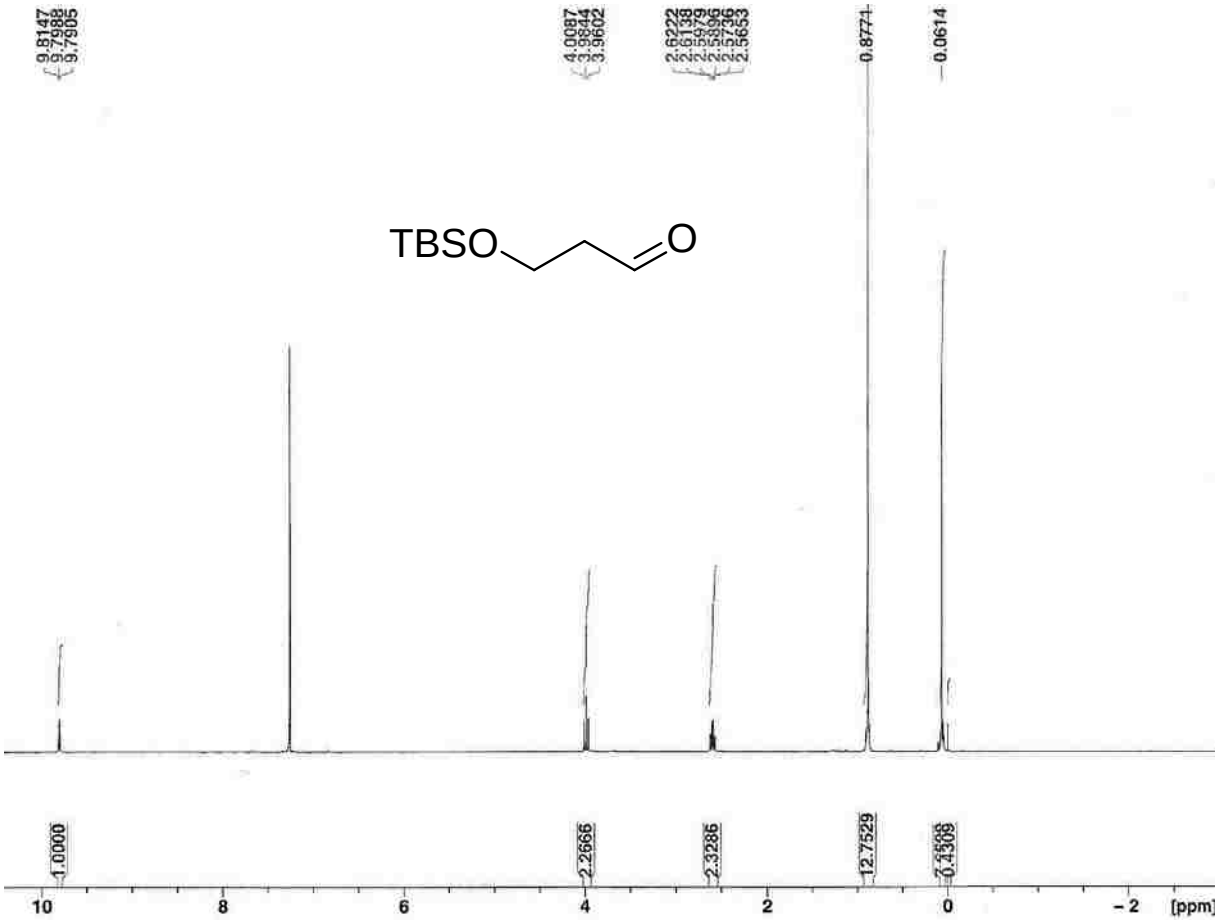


Figure **B.3.** ^{1}H NMR (250 MHz, $CDCl_3$) of Compound **3.4**

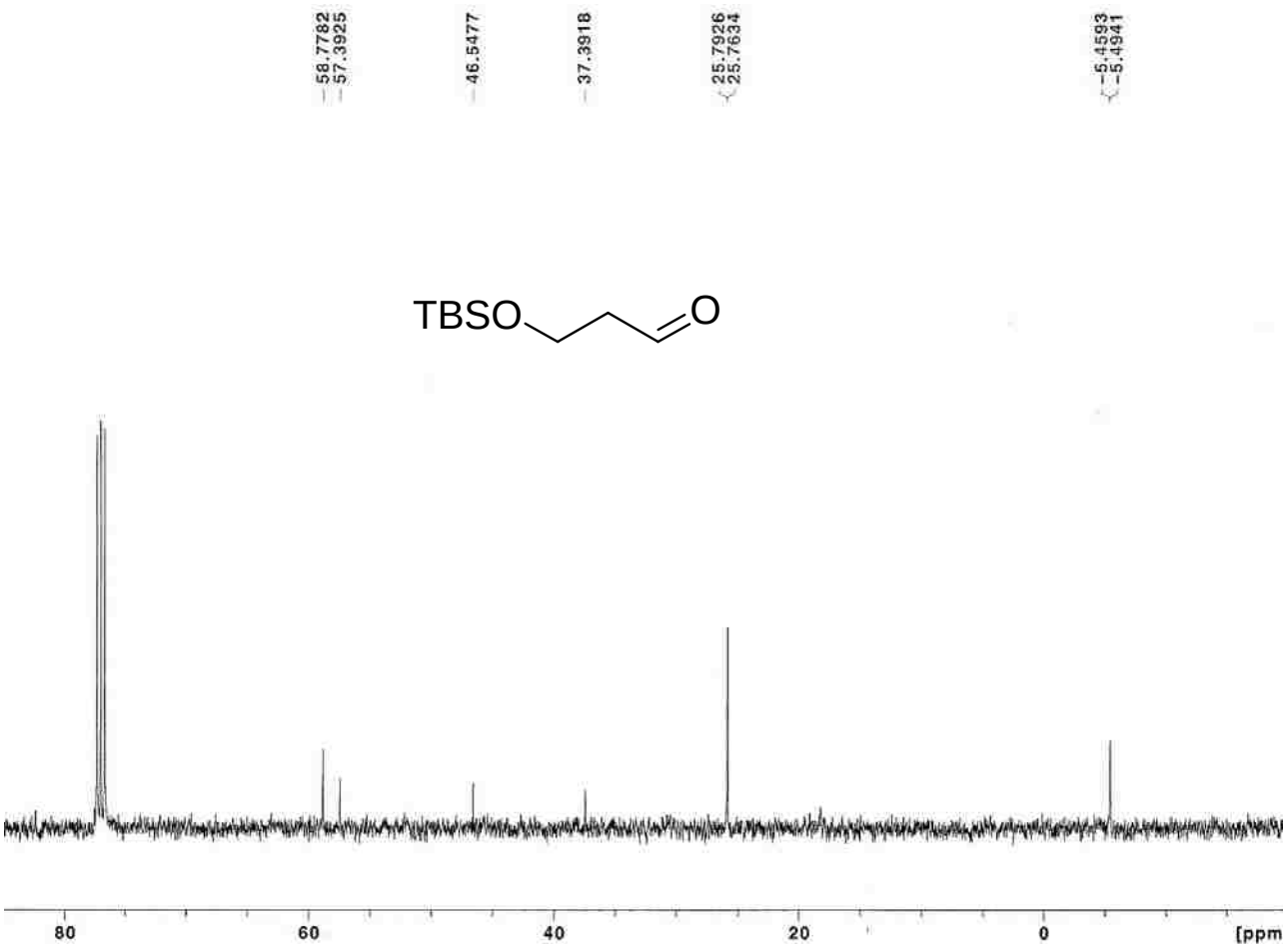


Figure **B.4.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.4**

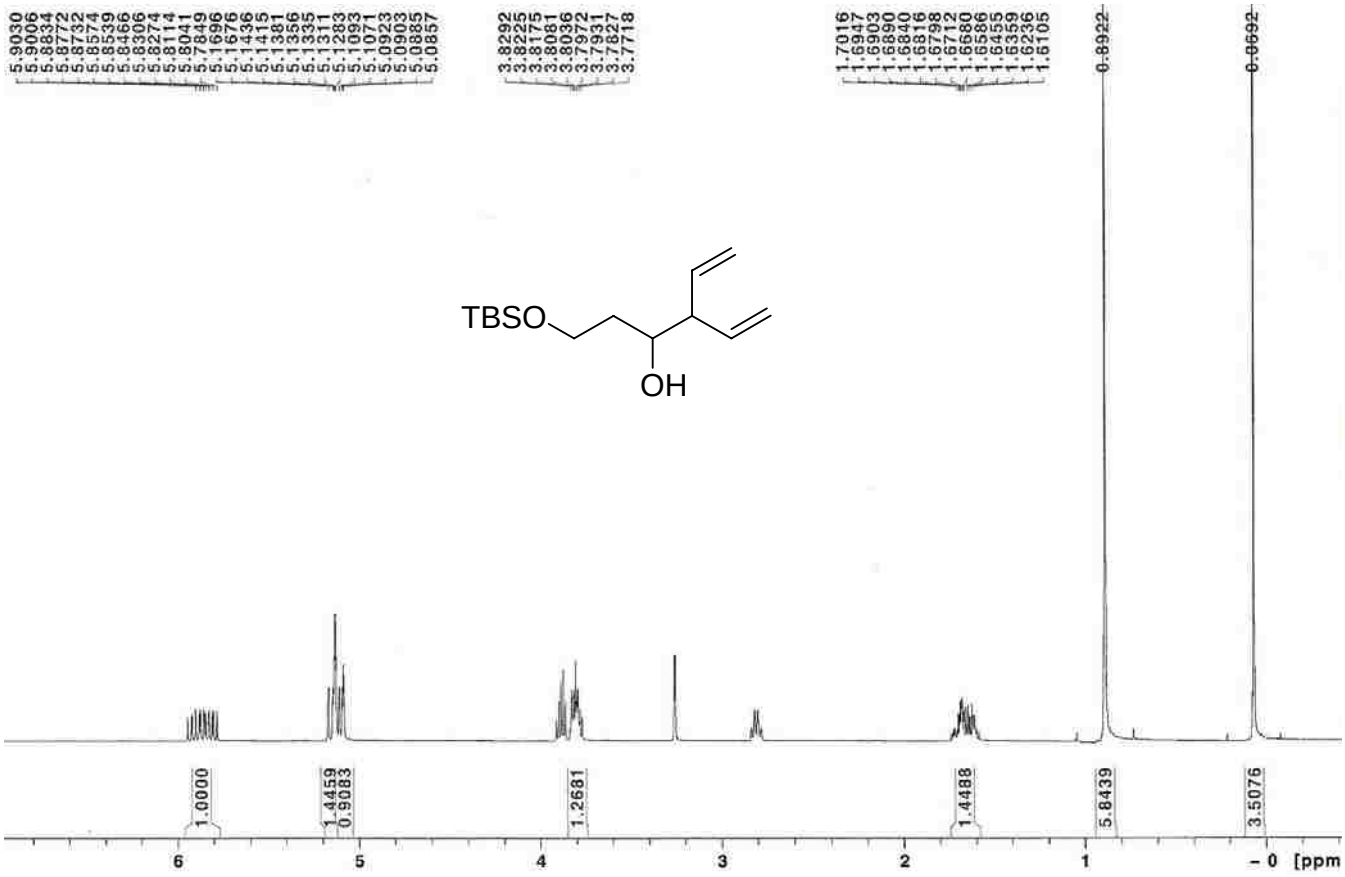


Figure **B.5.** ^{1}H NMR (250 MHz, $CDCl_3$) of Compound **3.5**

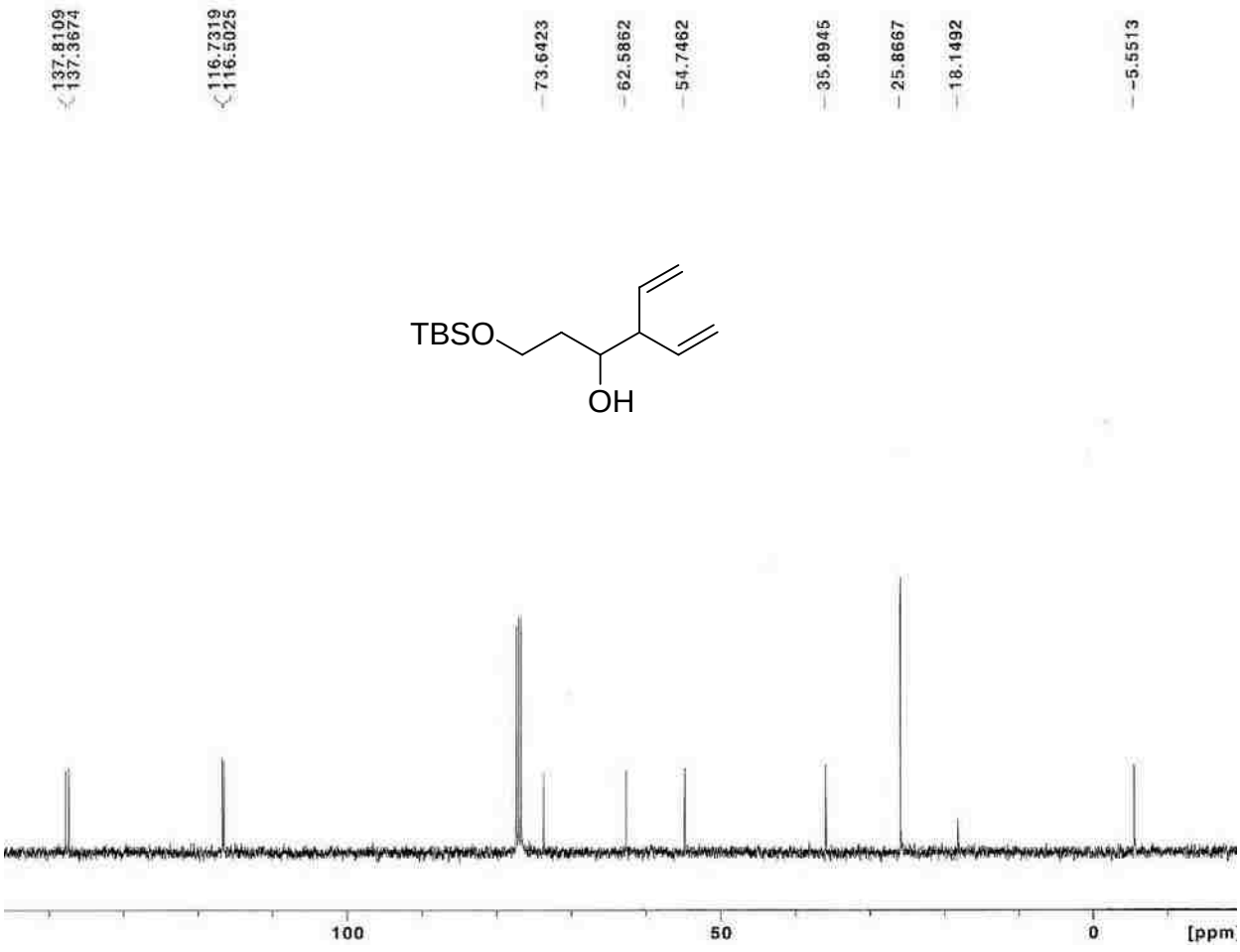


Figure **B.6.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.5**

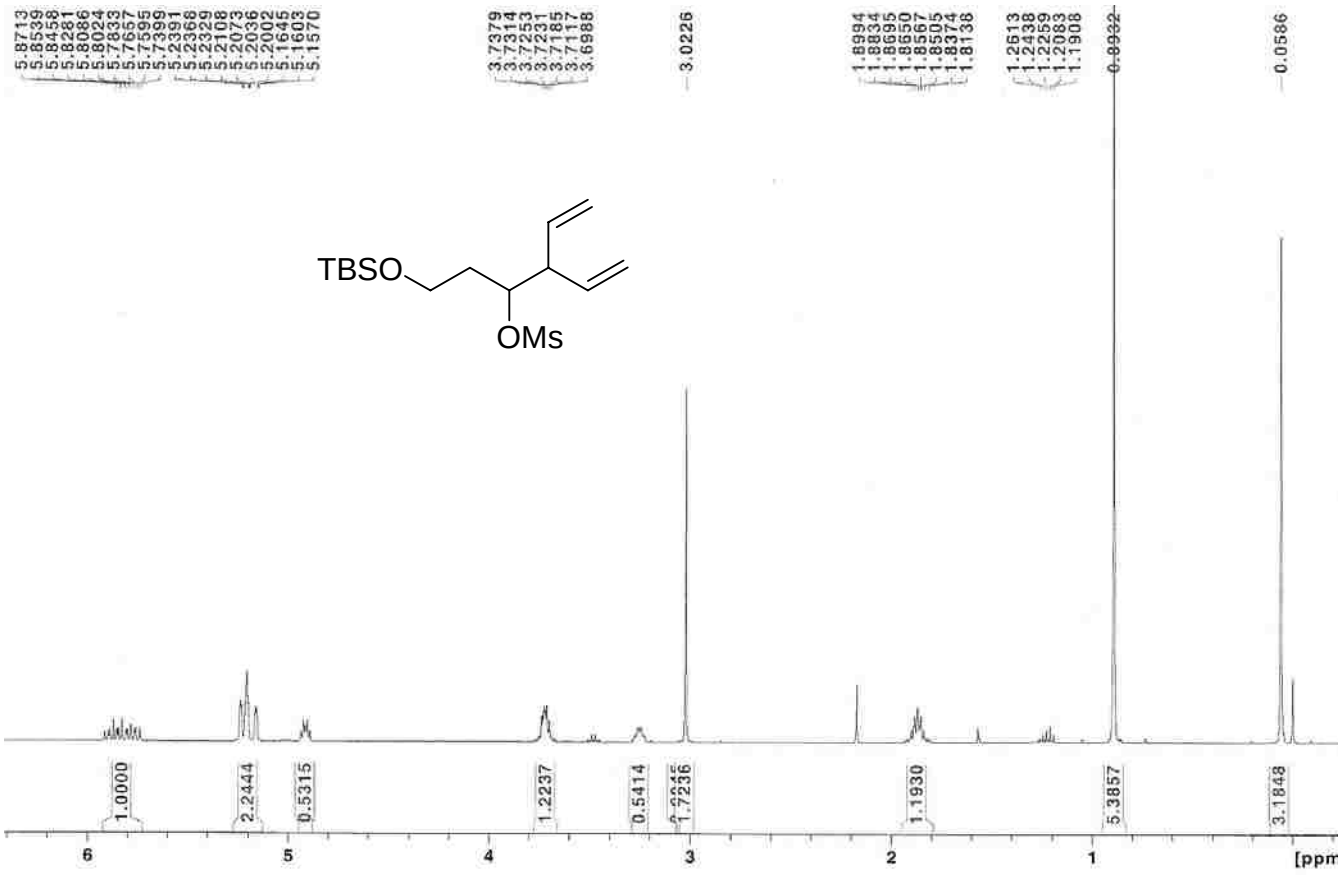


Figure **B.7.** ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **3.6**

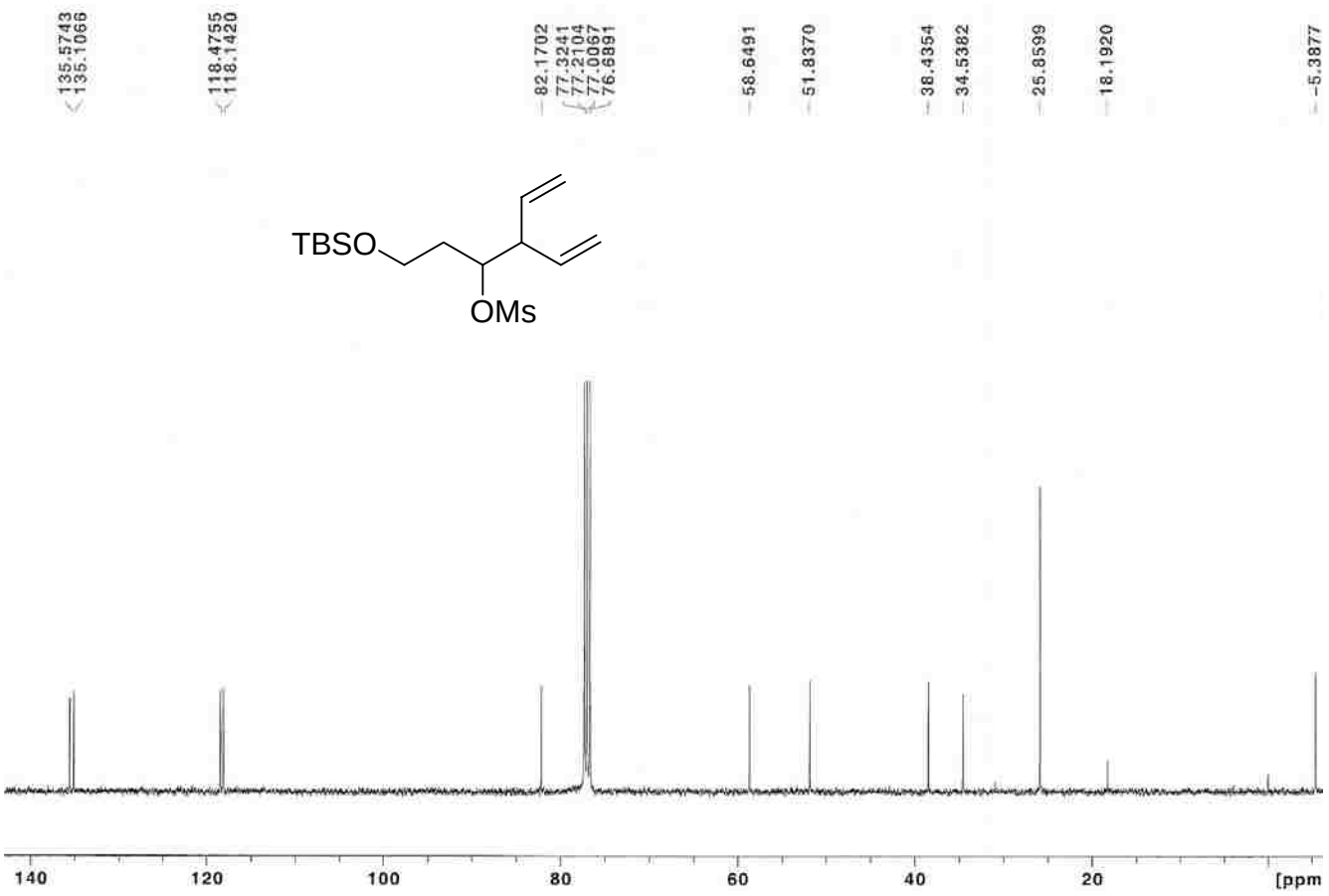


Figure **B.8.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.6**

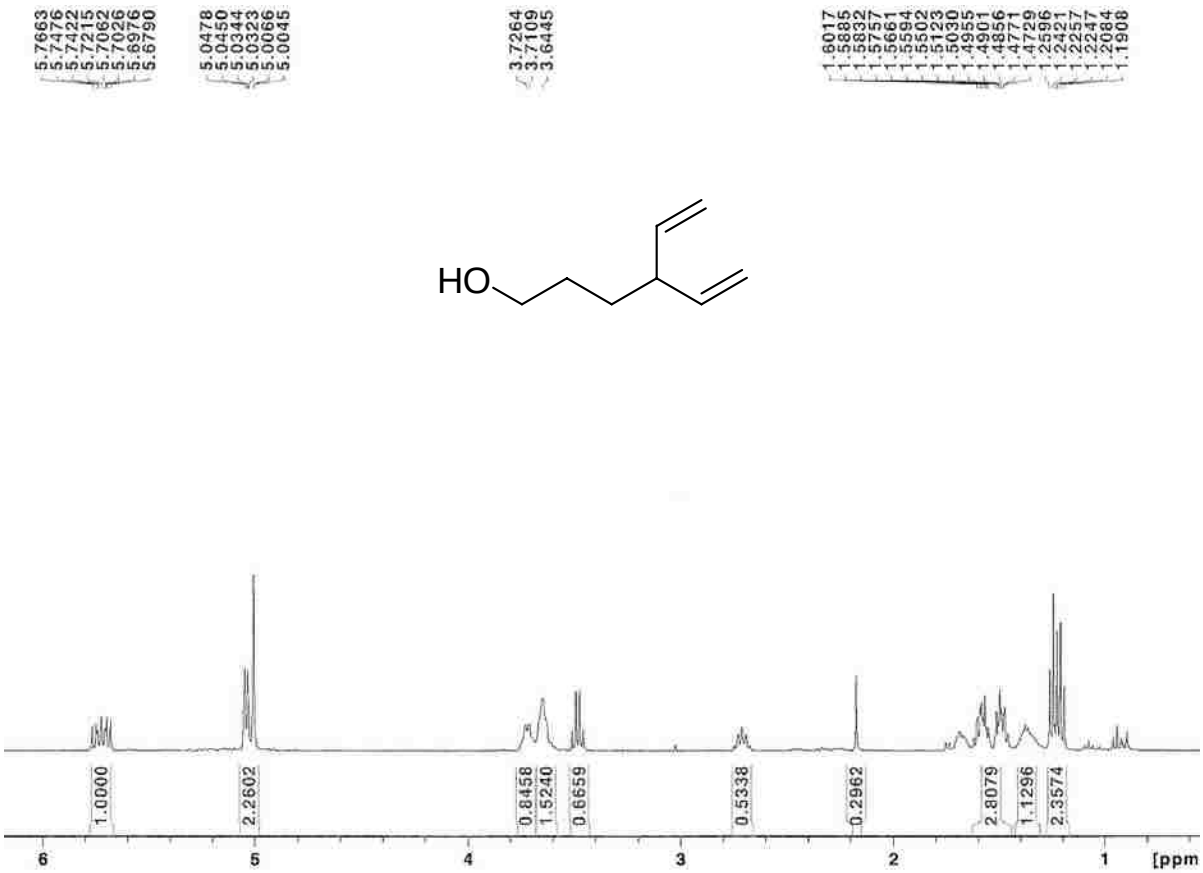


Figure **B.9.** ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **3.7 a**

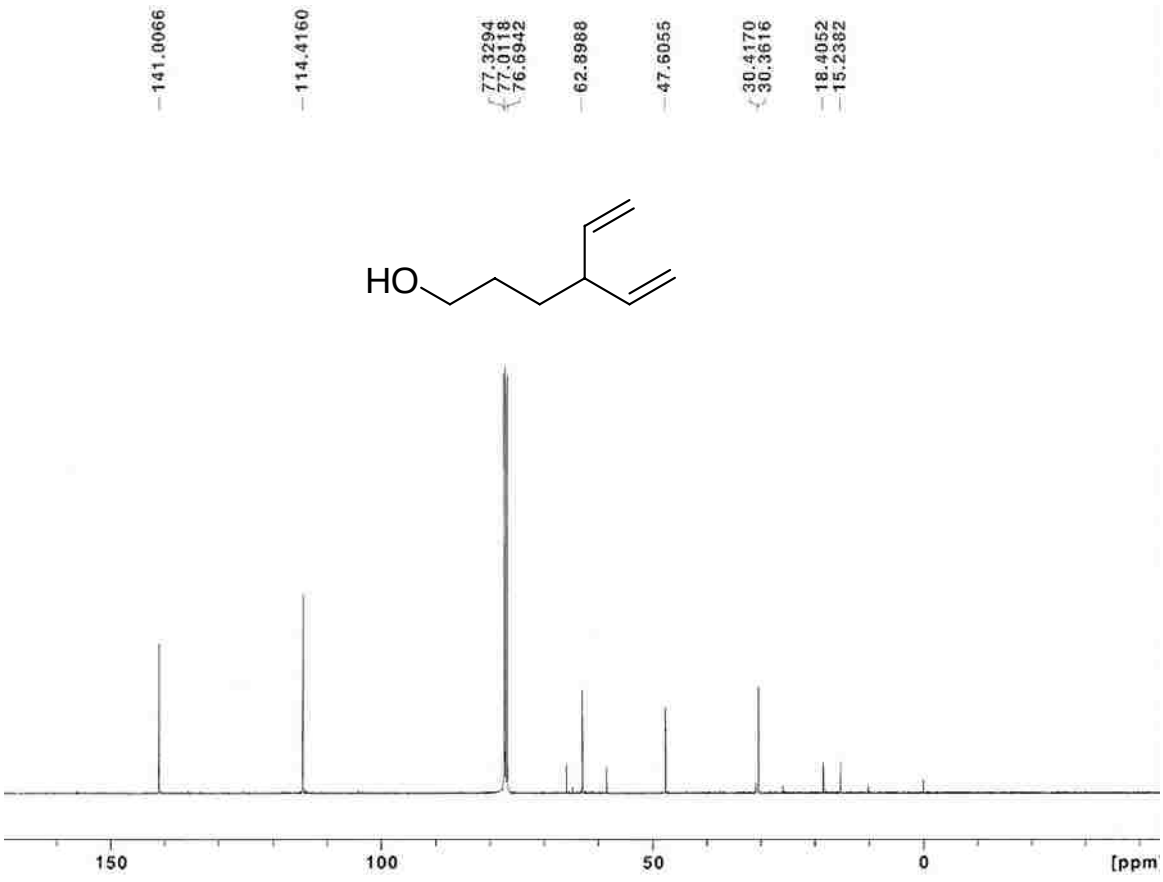


Figure **B.10.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.7 a**

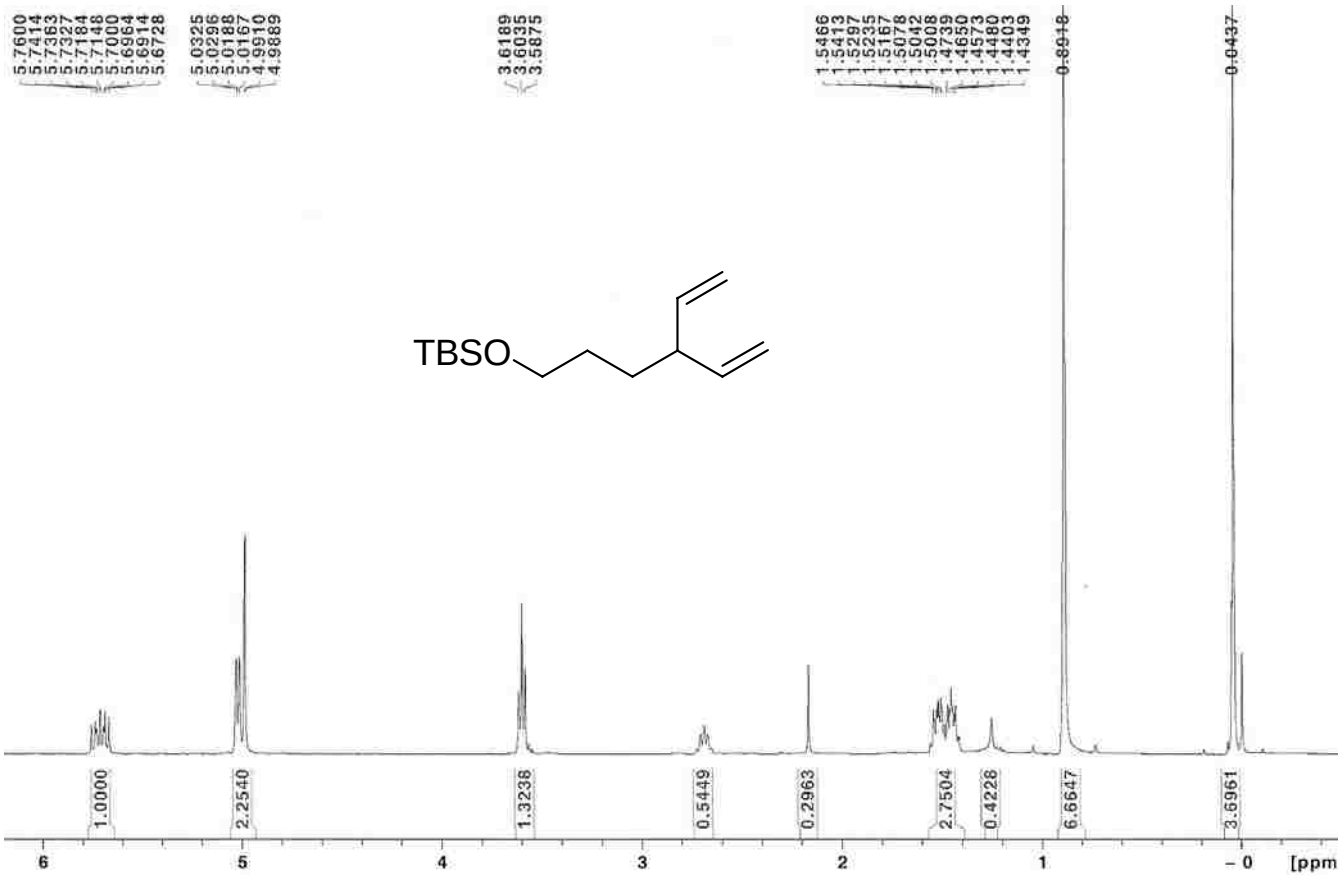


Figure **B.11.** ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **3.7 b**

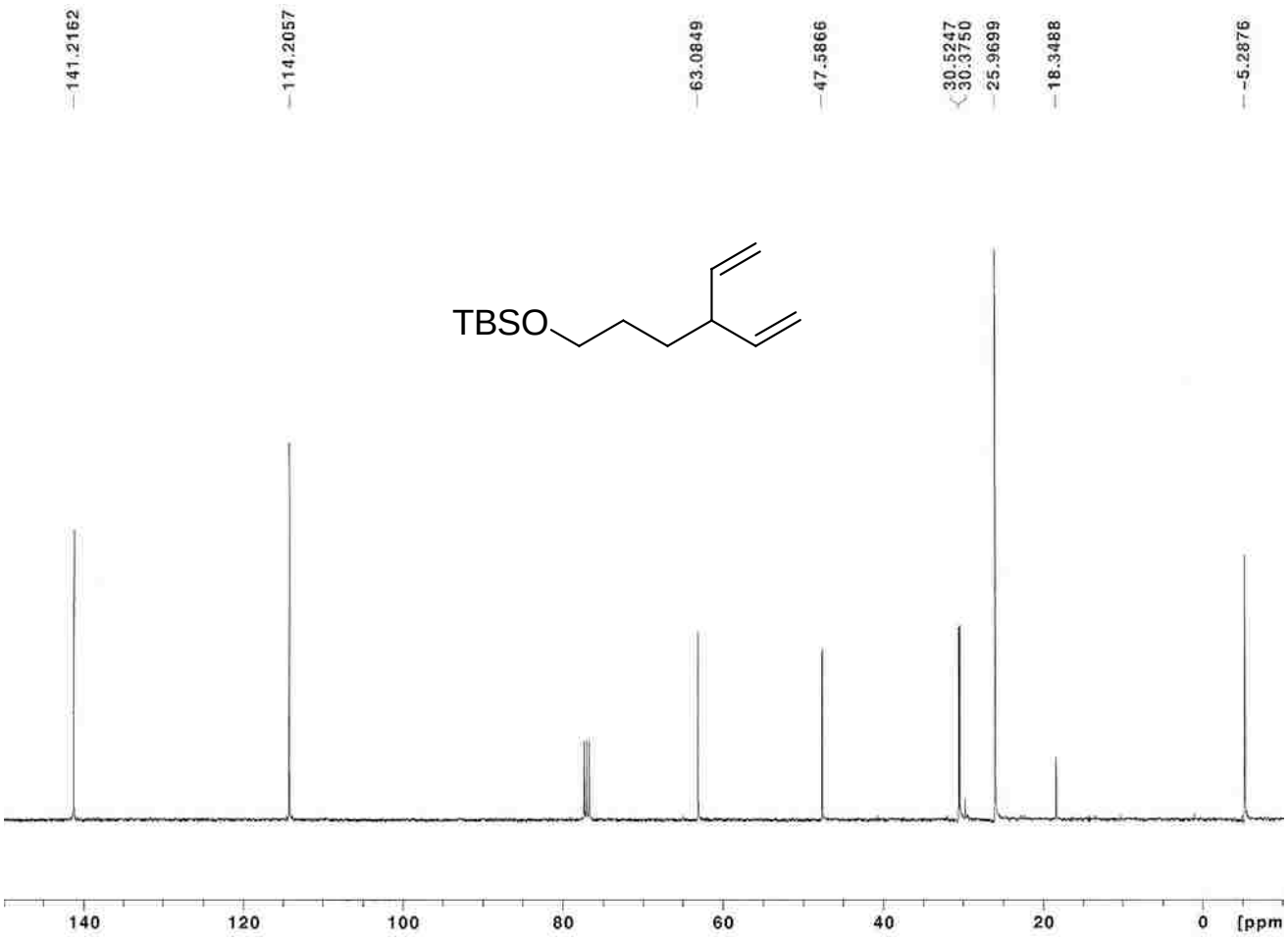


Figure **B.12.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.7 b**

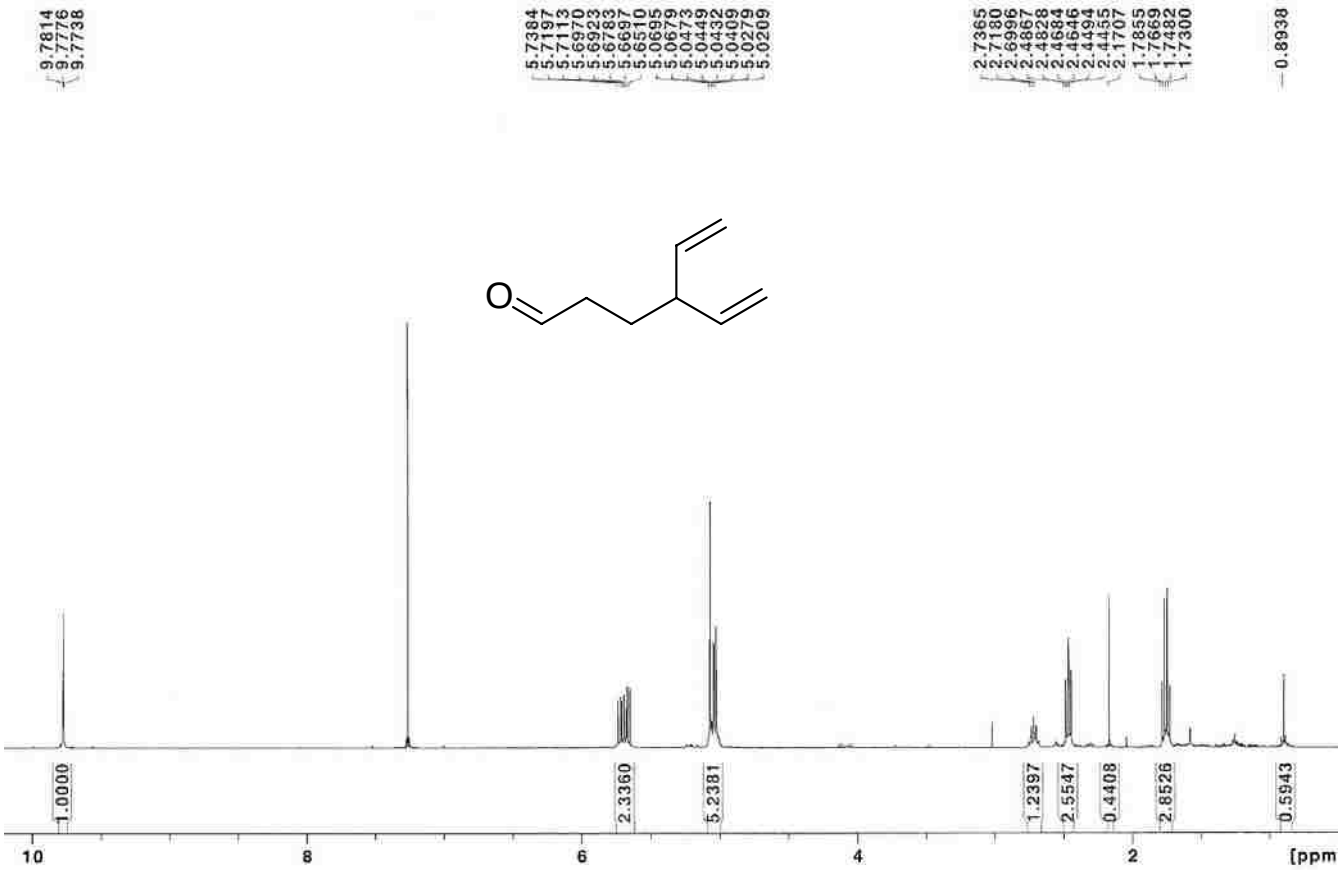


Figure **B.13.** ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **3.8**

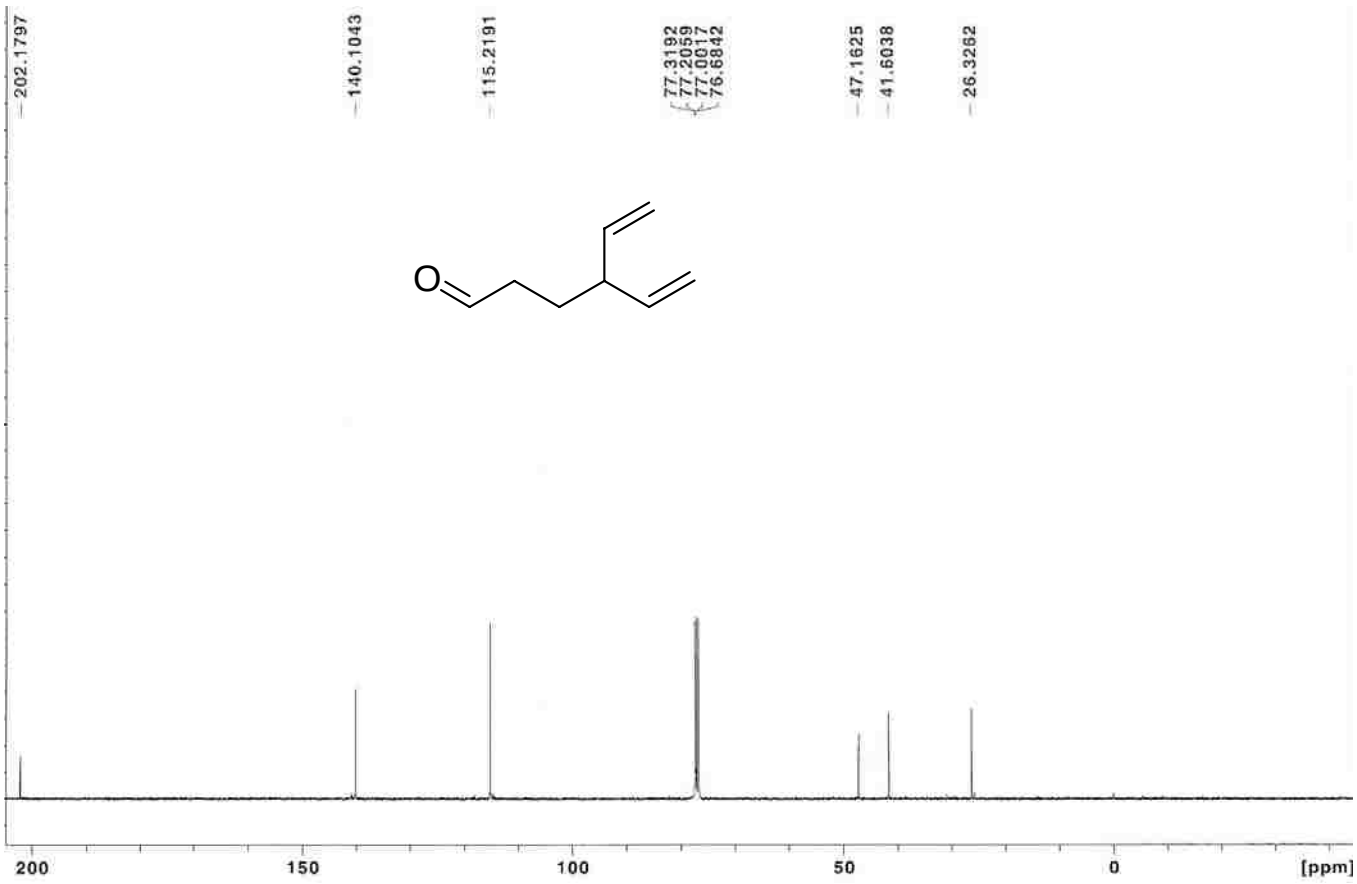


Figure **B.14.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.8**

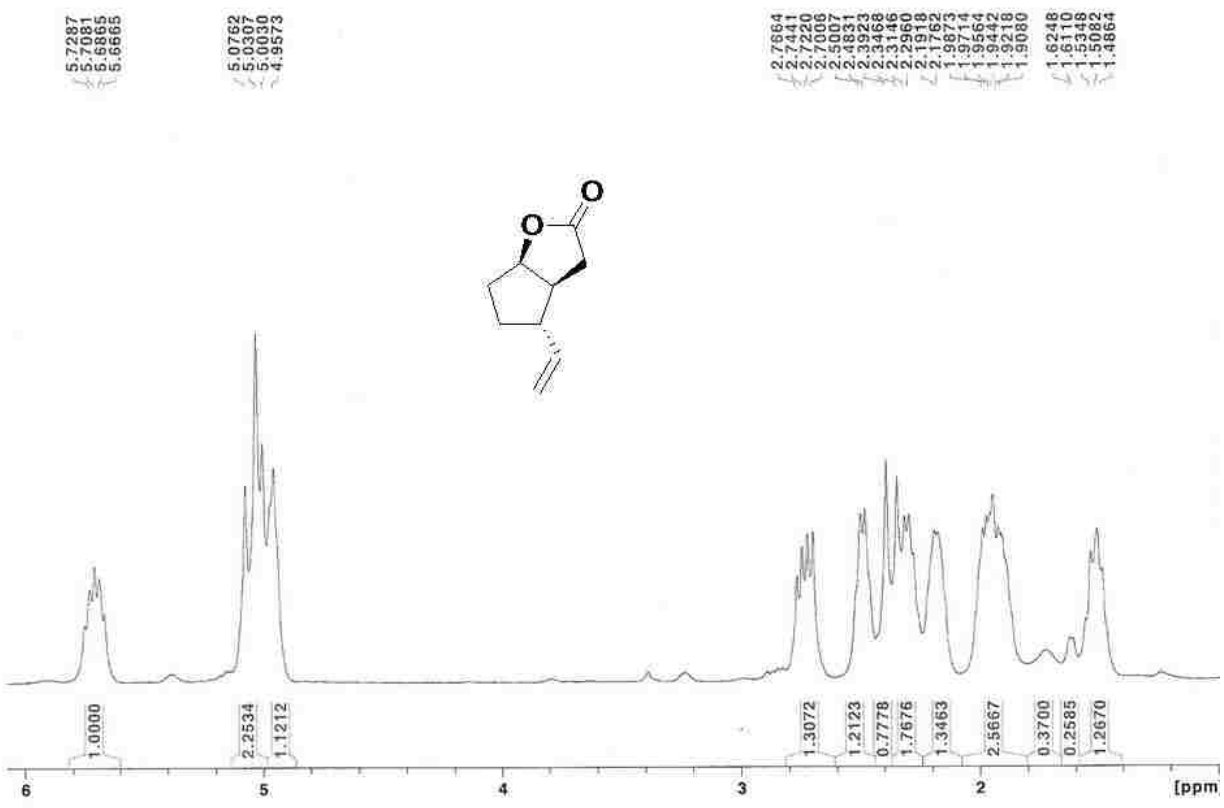


Figure **B.15.** ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **3.9**

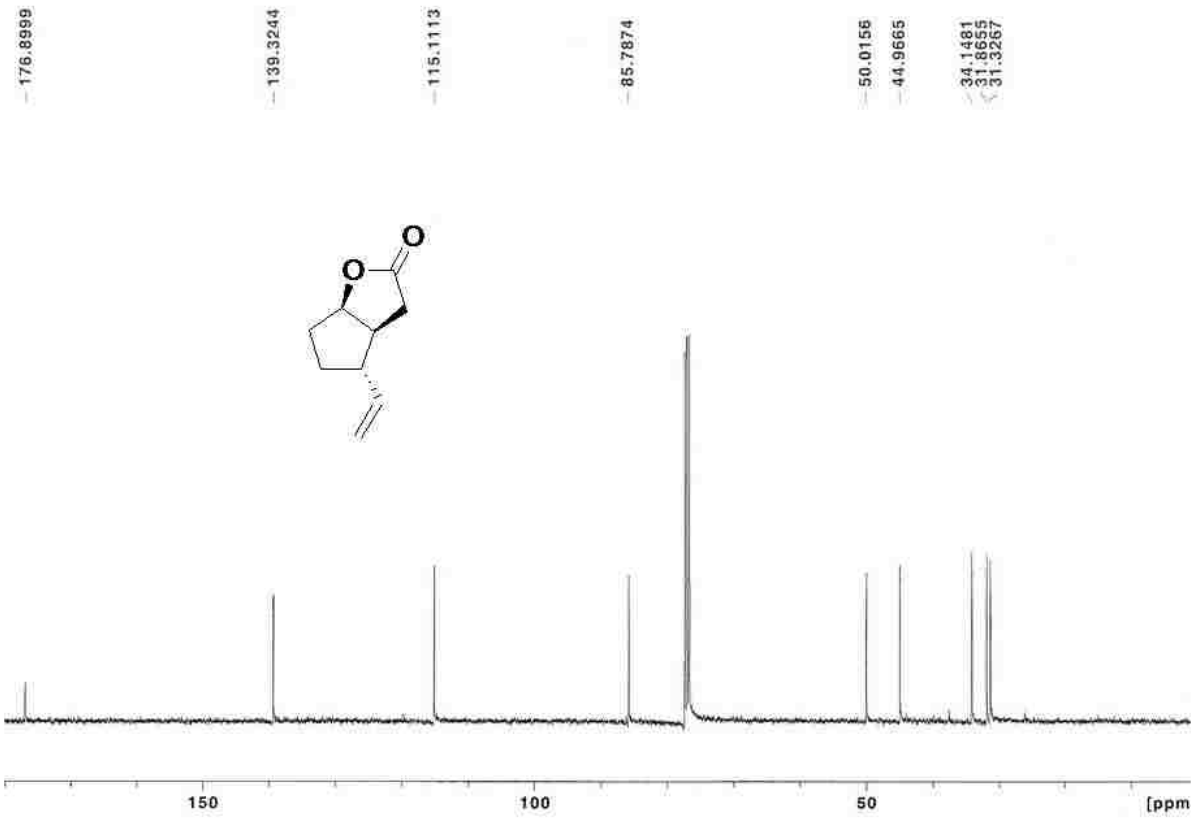


Figure **B.16.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of Compound **3.9**

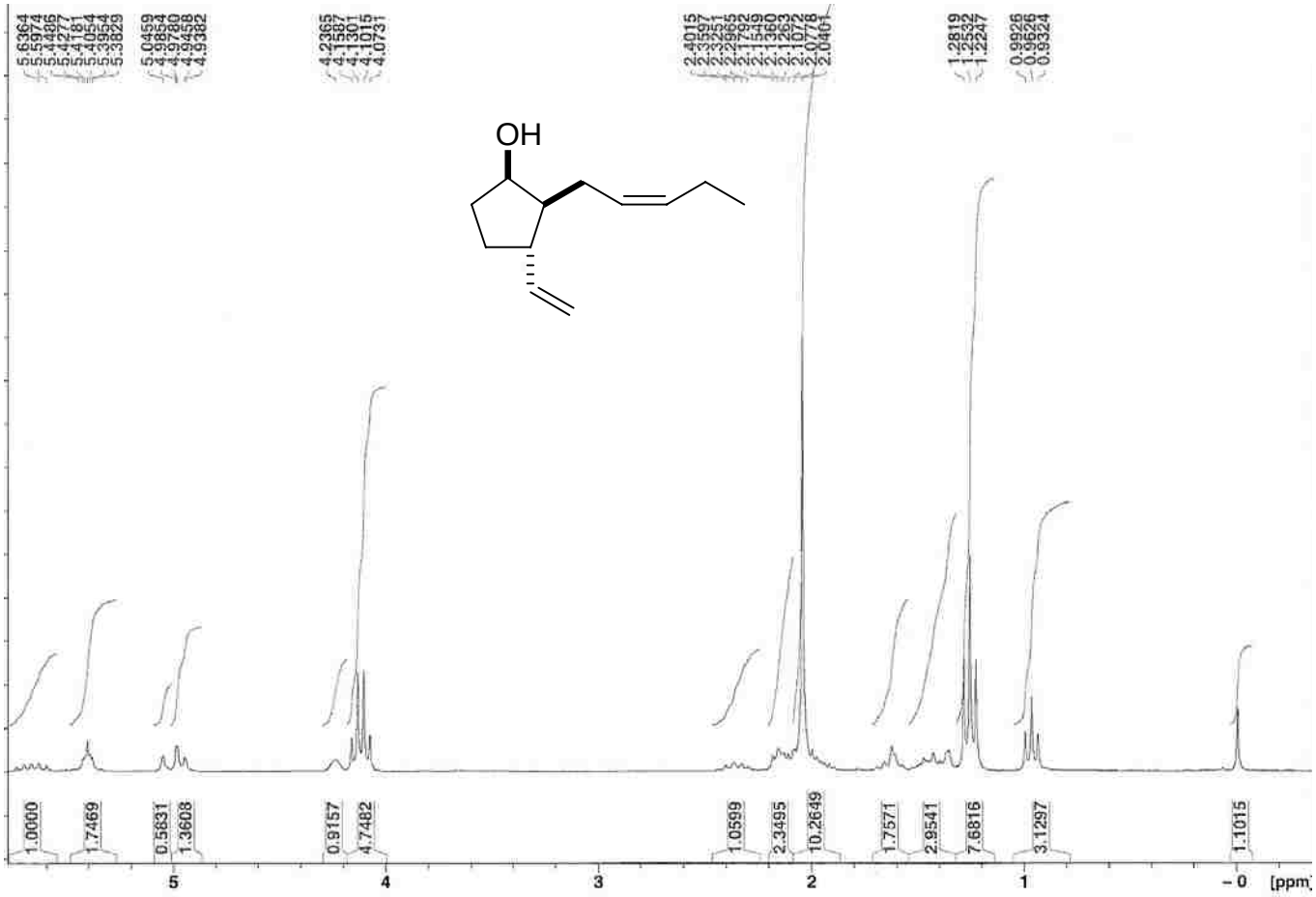


Figure **B.17.** ^{1}H NMR (250 MHz, $CDCl_3$) of Compound **3.10**

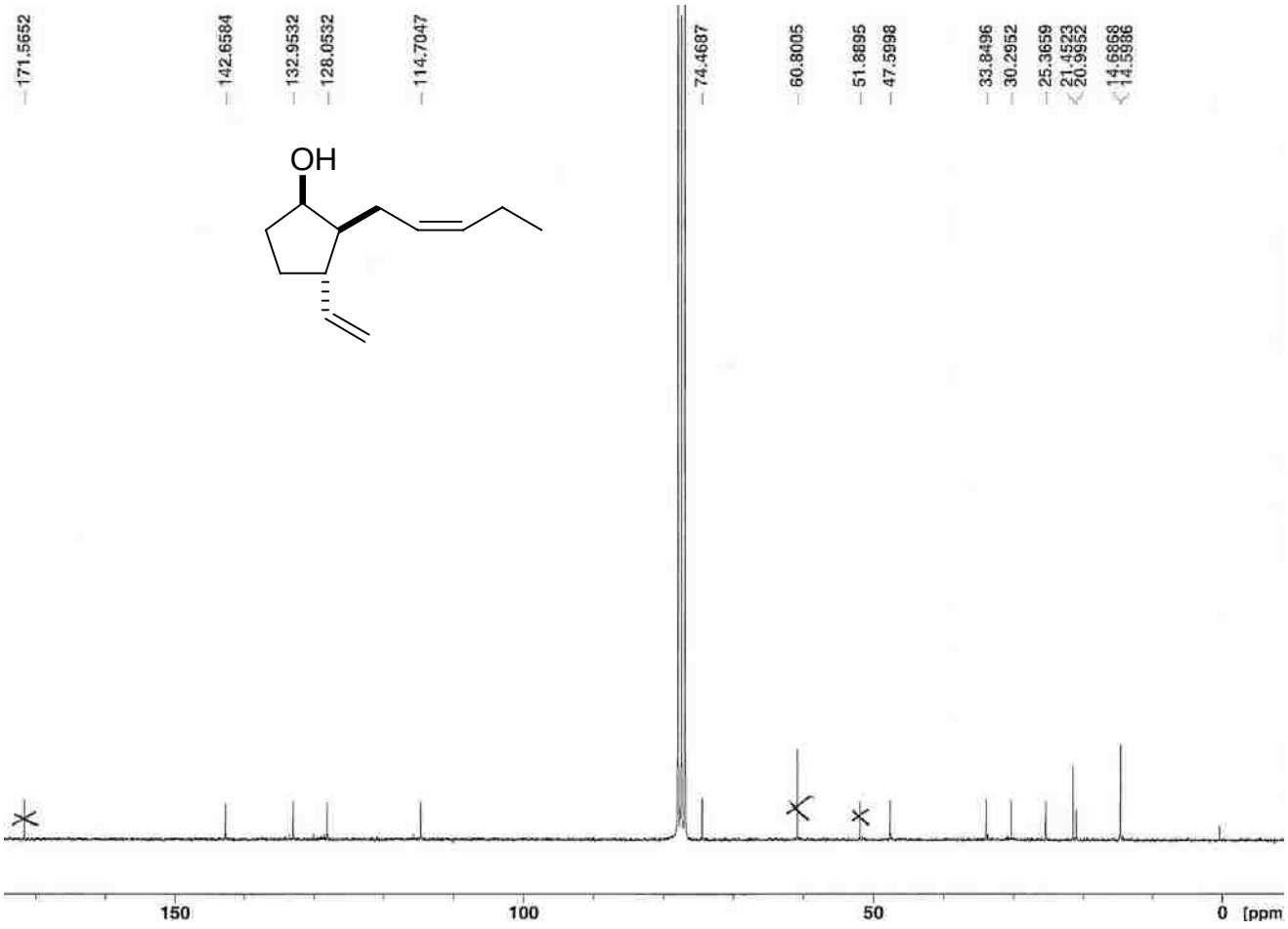


Figure **B.18.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of Compound **3.10**

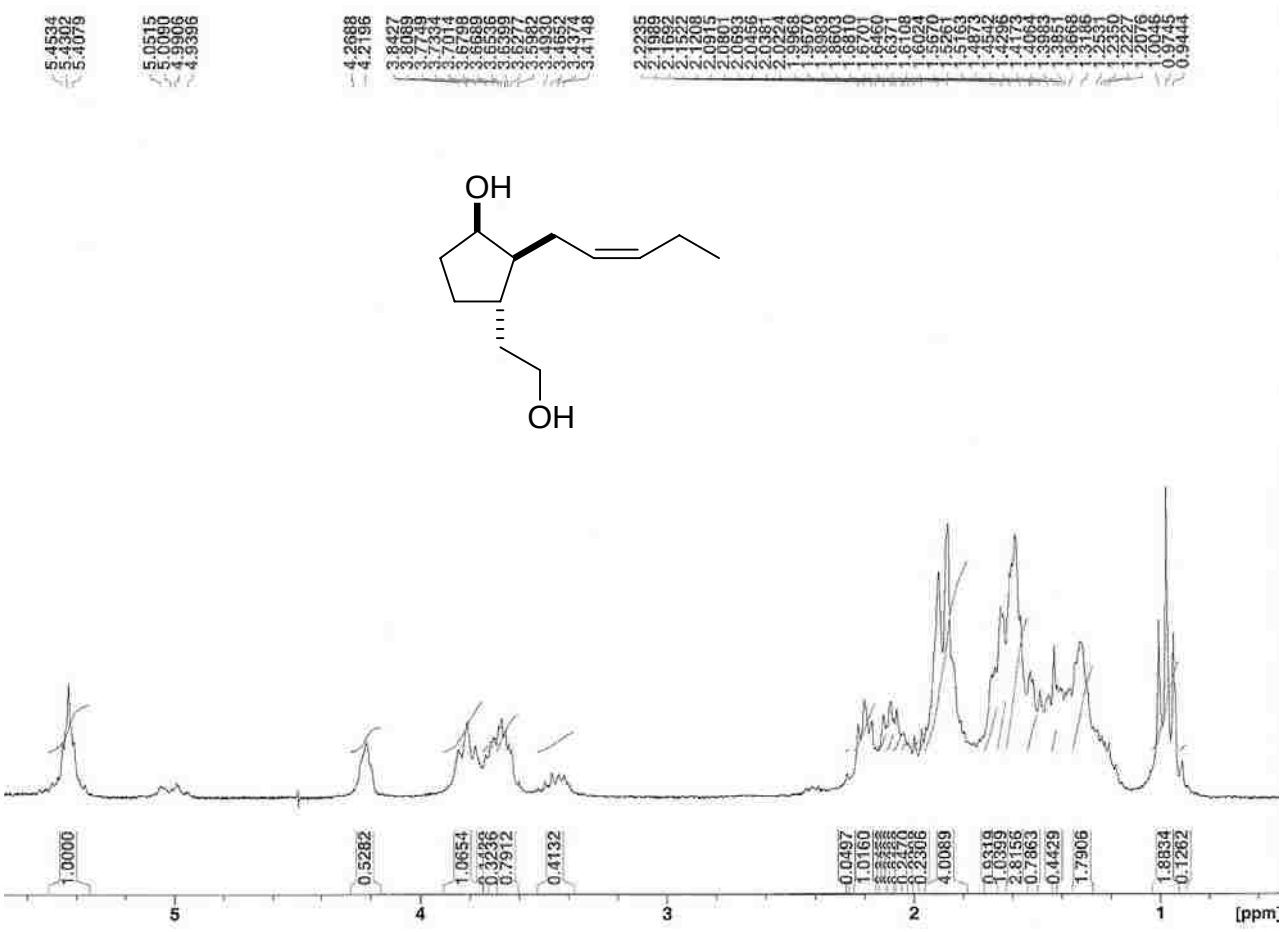


Figure **B.19.** ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **3.11**

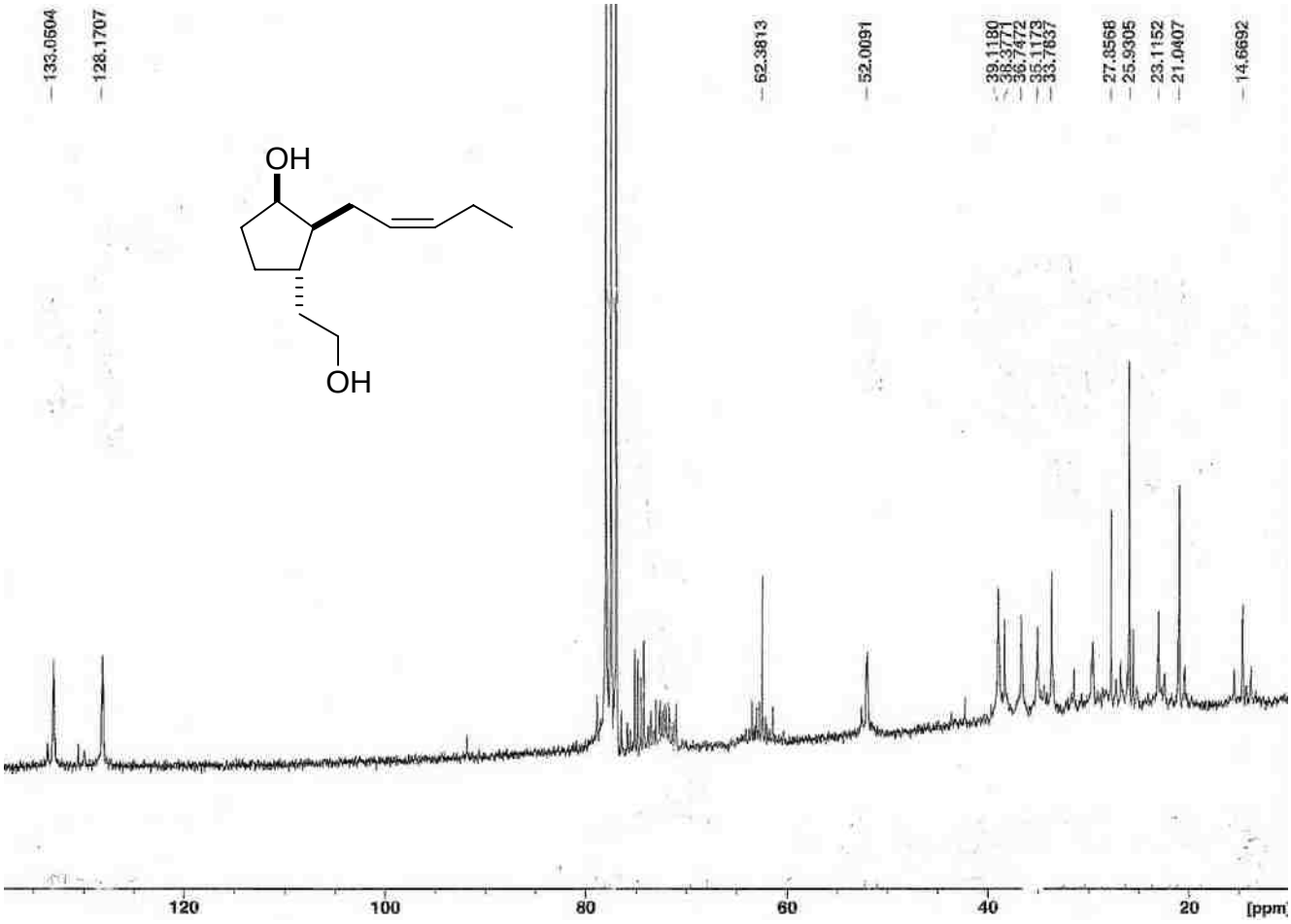


Figure **B.20.** ^{13}C NMR (62.8 MHz, $CDCl_3$) of Compound **3.11**

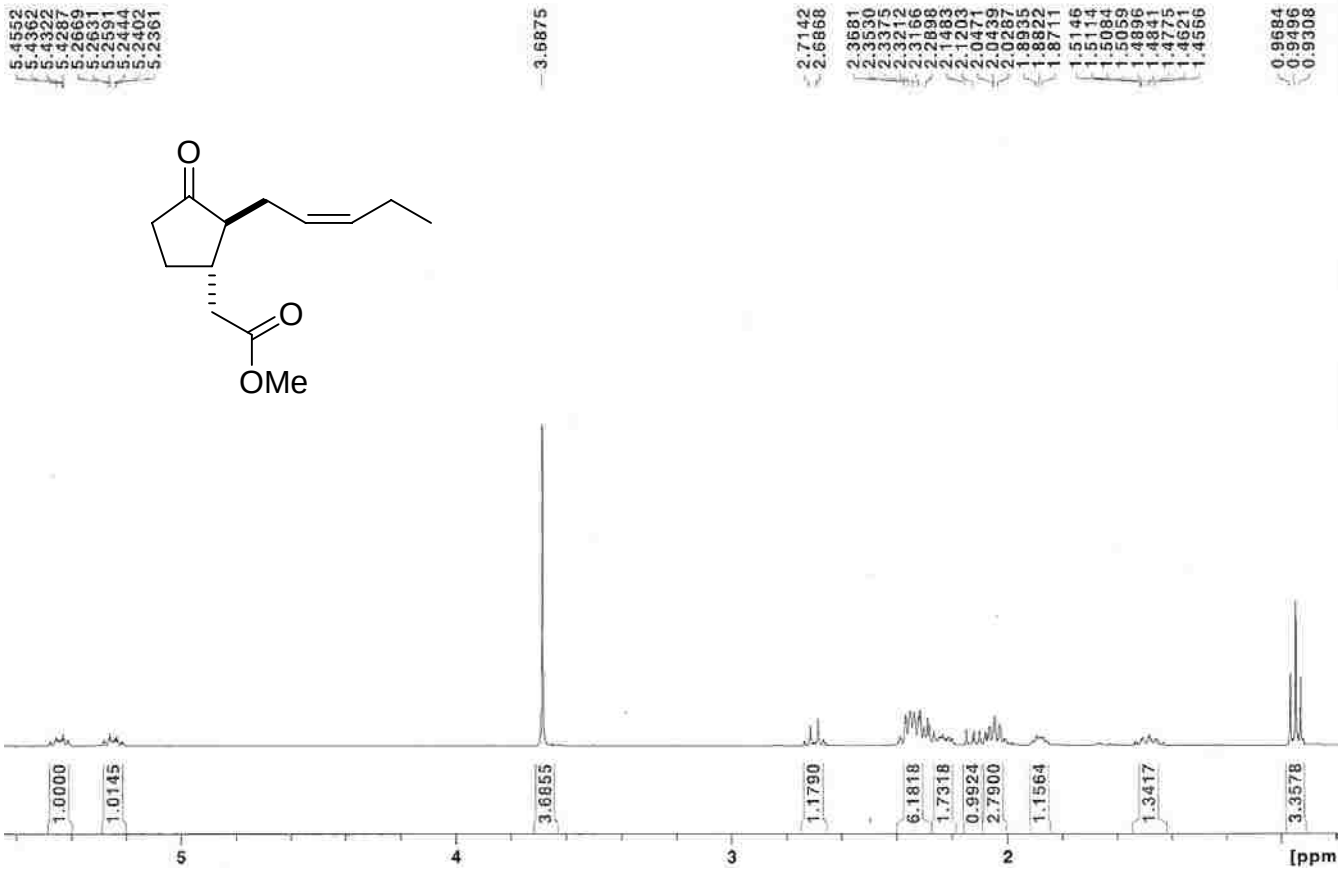


Figure **B.21.** ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **3.13**

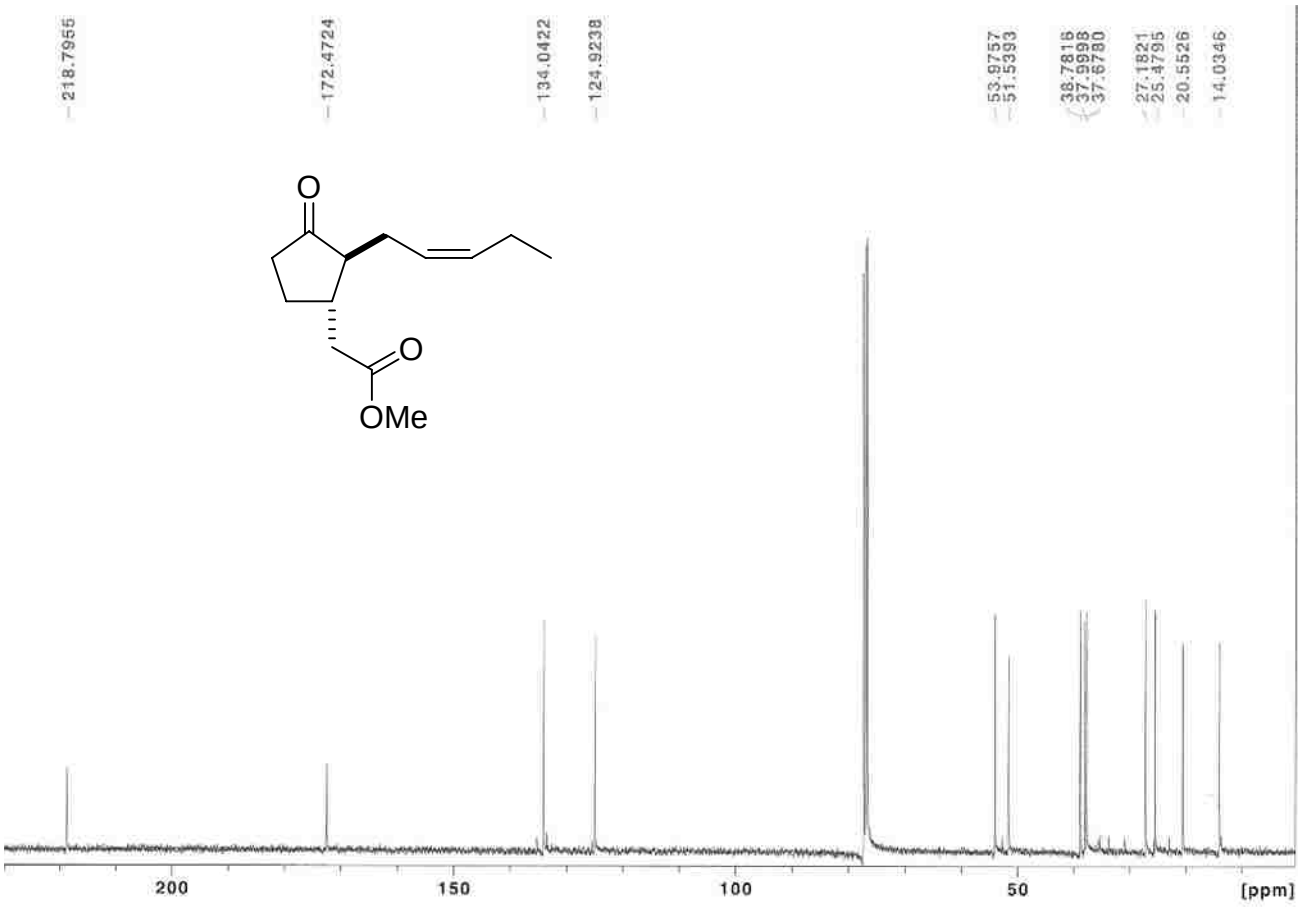


Figure **B.22.** ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **3.13**

VITA

Steve Oliver Lawrence was born in November 1973, in Christiansted, St. Croix, U.S. Virgin Islands. Steve spent his formative years on St. Croix attending public elementary, junior, and senior high schools. On the completion of high school he briefly attended school in Florida where his original goals including pursuing a career as an air traffic controller. However, there was a change in his career interests and he chose to study a more refined science–chemistry. Upon his return home he enrolled in the University of the Virgin Islands and earned a Bachelor of Science degree in chemistry in May 2002. While at the university Steve was able to participate in a number of research projects including his work with *Passiflora* species and the summer he spent as an intern at Purdue University. In the fall of 2002 Steve decided to continue his studies in chemistry and entered the graduate program at Louisiana State University. Steve then joined Dr. William E. Crowe's research group where he was able to learn a variety of techniques and further his research skills. His new research focused on utilizing the hetero–Pauson–Khand reaction to synthesize both *Methyl Jasmonate* and analogs of α–Methylene–γ–Butyrolactones. As an undergraduate and graduate student Steve has been a member of Golden Key National Honor Society, American Chemical Society, and National Organization of Black Chemists and Chemical Engineers (NOBCChE). A Doctor of Philosophy will be conferred on Steve at the May 15, 2009 Spring Commencement ceremony.