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Conjugate Additions and Transposition of the Allylic Alcohols of Enol Ethers of 1, 2-Cyclohexanedione.

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Conjugate Additions and Transposition of the Allylic Alcohols of Enol Ethers of 1, 2-Cyclohexanedione

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by
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Key words: α,β-unsaturated systems, enone, enolate, silane, transposition, nucleophile

ABSTRACT

Conjugate Additions and Transposition of the Allylic Alcohols of Enol Ethers of 1, 2-Cyclohexanedione

by

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A variety of protected enolic forms of 1, 2-cyclohexanedione was prepared as substrates for conjugate addition studies using organocopper reagents. The sequence involved the enol ether preparation via the enolate, alkylation with an organometalic reagent, and oxidative rearrangement with pyridinium chlorochromate followed by the conjugate addition reactions. Protection of 1, 2-cyclohexanedione was achieved by reacting with chloro tert-butyldimethyl silane and subjected to alkylation. Steric problems were encountered and so an alternative protective group the methoxymethyl acetal was prepared and studied. Alkylation of these derivatives was successful; however, the oxidation was problematic and although evidence for rearrangement was observed in one case, it did not provide the desired ketone.

DEDICATION

I dedicate this research and thesis to the memory of my late father Rev. Clarence Asamatey Otoo.

ACKNOWLEDGEMENTS

I am most grateful to the Almighty God through his son Jesus Christ for strength, grace, and love that has sustained me through my life and throughout the research period.

I am also highly indebted to my research advisor Dr. David Young for allowing me to work in his lab and for constantly guiding and advising me throughout the period. A big and sincere thank you also goes to Dr. Waderska, Dr. Eagle, Dr. Ho, Dr. Jiang, Dr. Sun, Ms Susan Campbell, Mrs. Rasnick, Tom, and all faculty and staff of the chemistry department of ETSU for being there and guiding me when need arises. I am also very grateful to ETSU and the government and people of USA for affording me the opportunity to study at ETSU.

I could not also have come this far without a supportive family. I acknowledge the commitment to my cause and constant prayers of my mum and siblings. God bless you. I also highly appreciate the prayers, support, and love given me by Dr. and Mrs. Nyarambi of the College of Education.

Finally, I wish to recognize and appreciate the contributions and efforts of colleague graduate students, past and present, and the Ghanaian community in Johnson City towards my successful stay and study at ETSU. God bless you all.

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LIST OF SCHEMES

Scheme Page

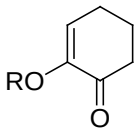
LIST OF ABBREVIATIONS

Ac	Acyl
Bu_3P	Tributylphosphine
Et_2O	Diethyl Ether
Et_3N	Triethylamine
ETA_C	Ethylacetate
g	Grams
MeCN	Cyanomethane
MeLi	Methyl Lithium
MeMgBr	Methyl Magnesium Bromide
mL	Milliliters
mmol	Millimoles
MOM	Methoxymethyl
NMR	Nuclear Magnetic Resonance
P – TSA	Para–Toluene Sulfonic Acid
PCC	Pyridiniumchlorochromate
PhH	Benzene
$PhNEt_2$	N, N –Diethylaniline
PhSH	Thiophenol
PPM	Parts Per Million
Pyr	Pyridine
TBDMS	t-Butyldimethyl Silyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1 Oxyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethyl Silane
TMSCl	Chloro Trimethyl Silyl
δH	Proton Chemical Shift

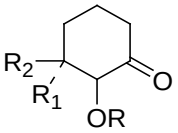
CHAPTER 1

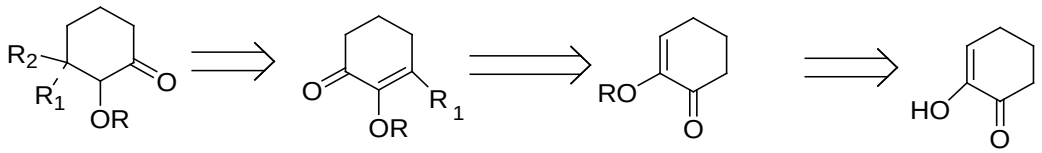
INTRODUCTION

As part of a project aimed at the preparation of a [3. 3. 1] bicyclononanone core, preparation of enol ether of the following structure was required.



The projected pathway was to involve alkyl addition. The retrosynthetic analysis in scheme 1 shows how this might be done starting from cuprate additions to 1, 2-cyclohexanedione to arrive at

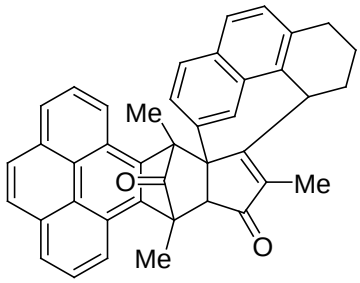




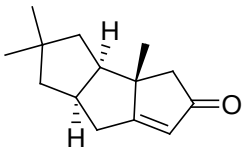
Scheme 1: Retrosynthetic Analysis of Intermediate to [3. 3. 1] Bicyclononanone Core

α,β-Unsaturated Systems

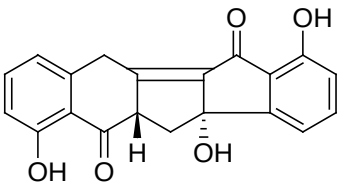
The chemistry of 1, 2-enones and enals (α, β-unsaturated systems) have been widely exploited in various fields either as final products or as intermediates in the synthesis of very useful chemicals. Enones are the conjugated ketones, enals are the conjugated aldehydes, and enamines conjugated amines. The following are examples of chemicals with the α, β-unsaturated systems:



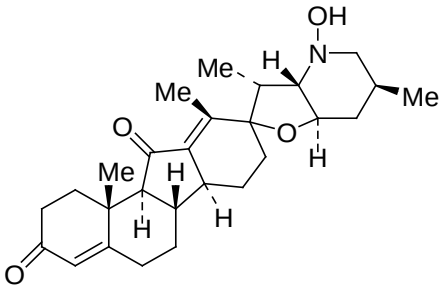
A pyrene based florescent probe for detection of micelle concentrations [1]



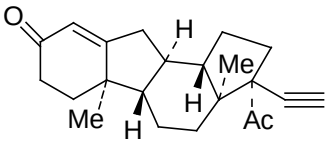
An intermediate in the synthesis of (+)-1-desoxyhypnophilin [2]



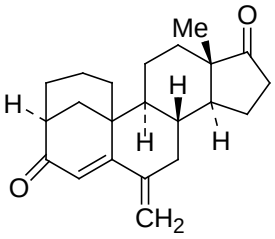
Pterocaryquinone - showed apoptosis activity toward mouse cancer [3]



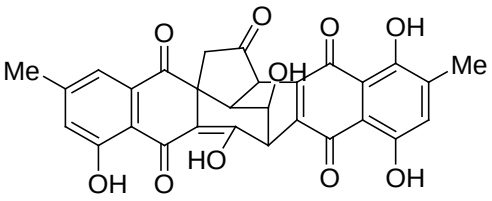
A jrevine steroidical alkaloid derivative. Can be used as antineoplastic agent for treating pancreas and lung cancer. [4]



Known to have anabolic and antiandrogenic properties [5]



Steroid: aromatase inhibitor [6]



deoxypurpurogenone: a minor pigment of Penicillium purpurogenum [7]

Scheme 2: Examples of some Significant Chemicals with α, β-Unsaturated Systems

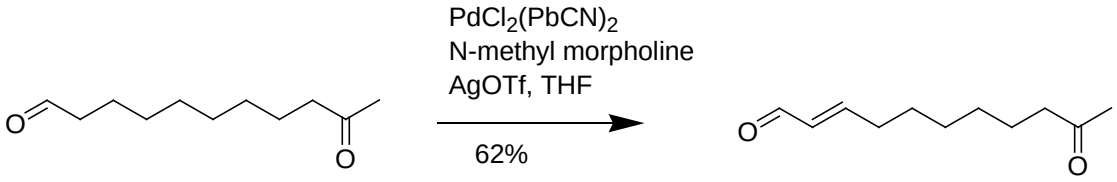
The uniqueness of these systems emanate from the fact that the conjugative effect of the functional groups involved generates a whole new but interesting chemistry.

Preparation of α, β-Unsaturated Systems [8]

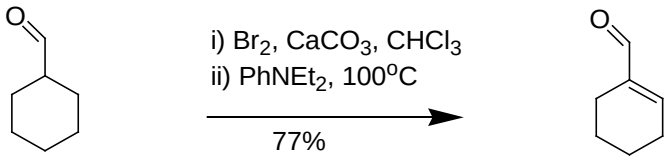
Often α, β-unsaturated systems occur as intermediates in reactions where they are not the major product and as such do not attract much focus. A good number of procedures have been used however to prepare α,β-unsaturated systems. In order to effectively discuss these routes, it is important to categorize the final products. These categories include: α, β-unsaturated systems without further unsaturation, α, β-unsaturated systems with further unsaturation, halogenated α, β-unsaturated systems, Oxygen substituted α, β-unsaturated systems, selenium substituted α, β-unsaturated systems, Nitrogen substituted α, β-unsaturated systems, and α, β-unsaturated systems substituted with other elements.

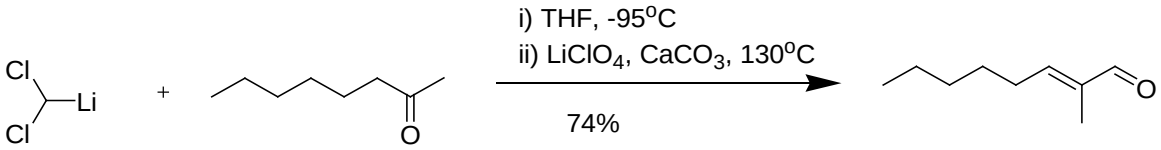
α, β-Unsaturated Systems Without Further Unsaturation.[8]

By Oxidative Elimination of Hydrogen

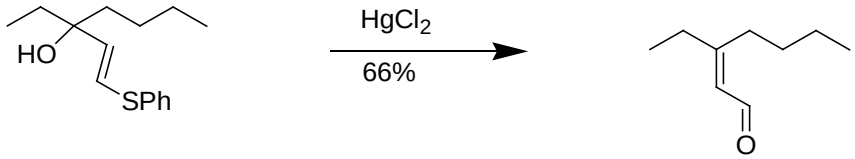


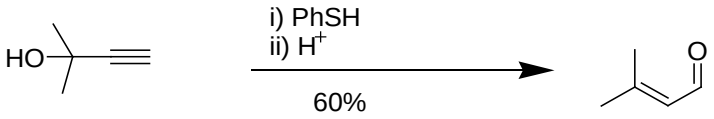
By Elimination of Halide from α-Halo Aldehydes



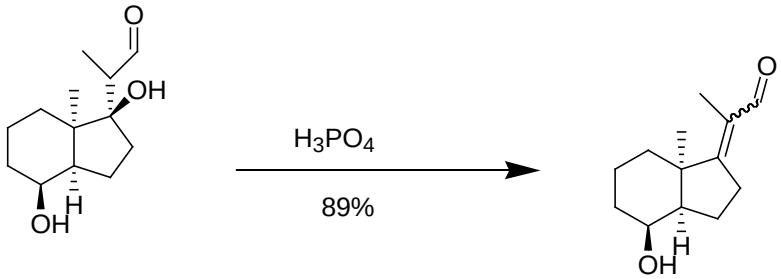


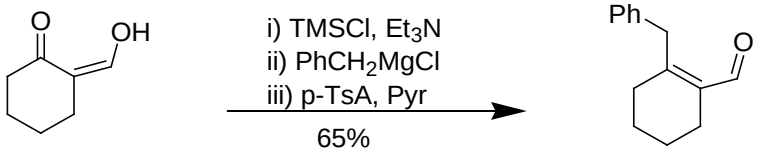
By Elimination from Alkoxy Enol Ethers and Thioenol Ethers





By Elimination from β-Hydroxy and Alkoxy Aldehydes

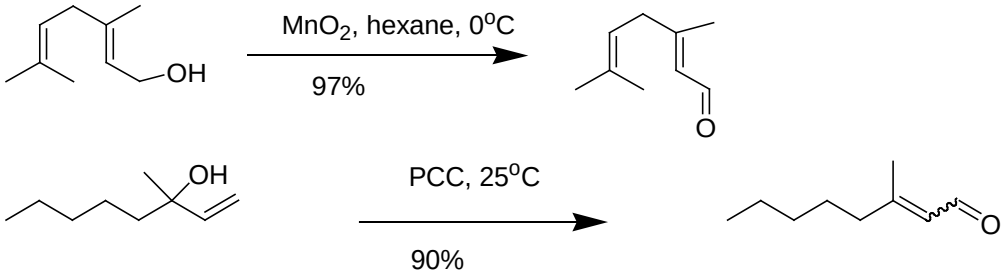




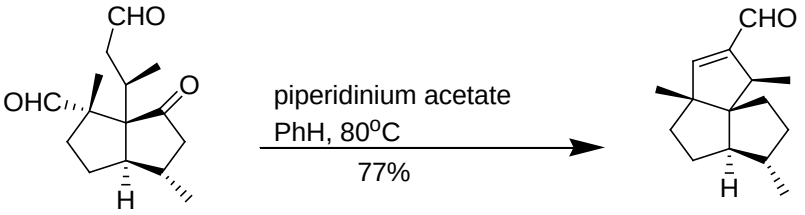
By Elimination of Selenoxides

By Elimination of Sulfones

Oxidations of Alcohols and Their Equivalents [8]

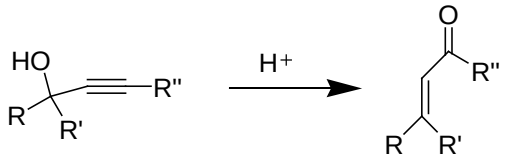


Aldol Condensations

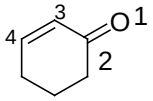


Other Procedures include: formylation of alkenes, rearrangements of α-acetylenic alcohols, displacement of β-leaving groups, wittig reactions, diels alder reactions, isomerizations, reductions of conjugated acyl chlorides, from epoxides, and other miscellaneous reactions

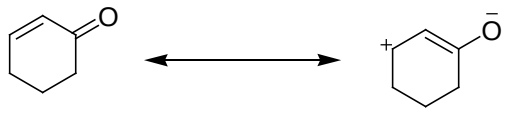
Enone synthesis is also done by the Knoevenagel [29] condensation, the Meyer-Shuster rearrangement, and other miscellaneous reactions. The Meyer-Shuster [28] rearrangement is described as acid – catalyzed rearrangement of secondary and tertiary propargyl alcohols



Chemistry of α, β-Unsaturated Systems



For the purposes of these systems, the atoms are numbered such that the oxygen is one and the last carbon of the alkene is 4. The conjugation between the alkene and the ketone effectively produces two nucleophilic sites; carbon 2 and carbon 4.



1, 4-Nucleophilic Additions

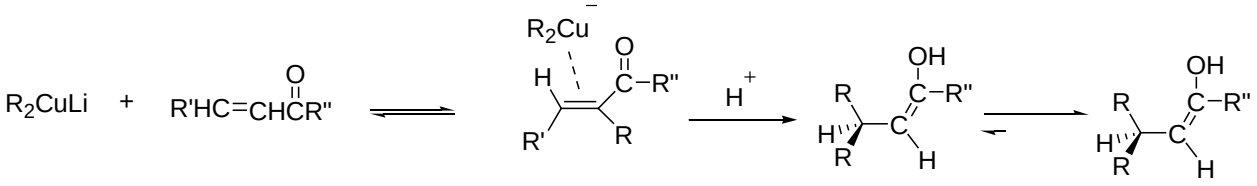
In 1941 Kharash [9] discovered that the reaction of Grignard reagent with cyclohexenone in the presence of copper (I) resulted in a 1, 4-addition instead of 1, 2-addition. This triggered a lot of research in that field. Before then Gilman had prepared methylcopper reagent. Further work led to the preparation by Gilman of dialkylcuprates, otherwise known as Gilman's reagent or simply cuprates that are very useful in 1, 4-addition reactions.

Cuprates [10] are prepared by the reaction of Grignard /alkyllithium [11] reagents and copper (I) iodide in a 2:1 molar ratio. In recent times cuprates with two different copper substituents have been developed for various reactions. One important kind of such mixed cuprates is the higher-order cyanocuprates. [12] These are prepared from a 2:1 molar ratio of alkyllithium and CuCN [10]. Qualitatively cyanocuprates react in a similar fashion as the dialkylcuprates but they are more stable [13].

Because cyanocuprates are used to transfer just one group, it is usual to incorporate a group that cannot be transferred like a thienyl group into the cyanocuprate to enhance its activity and economize useful chemicals.

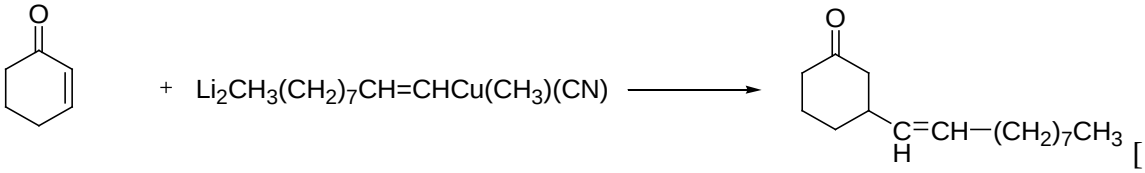
Mechanism of Conjugate Addition

Copper (I) is less electropositive than the group 1 and 2 metals. The result of this is that in the presence of group 1 and 2 metals copper preferably coordinates to the alkene while the group 1 and 2 metals coordinate to the oxygen. Because the β-carbon in the conjugate system is partially electrophilic, copper's coordination to the double bond enables a nucleophilic attack on the β carbon, thus 1, 4-addition.

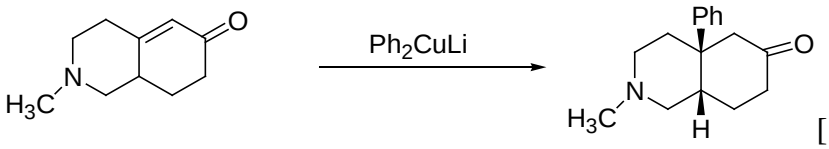


[13]

Examples [13]

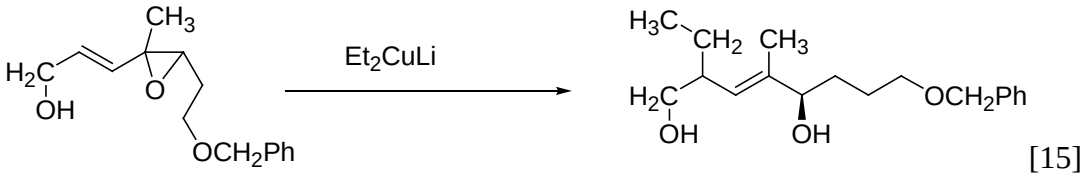


[10]

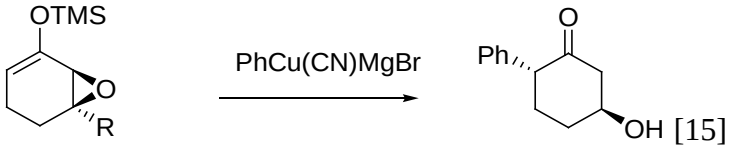


[14]

Cuprate additions also work on conjugated epoxides. It opens the epoxide to form alcohols.



[15]

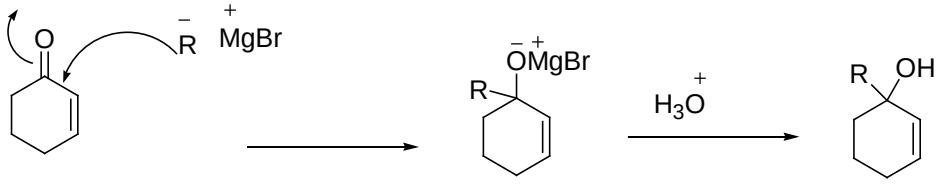


[15]

1, 2-Nucleophilic Additions

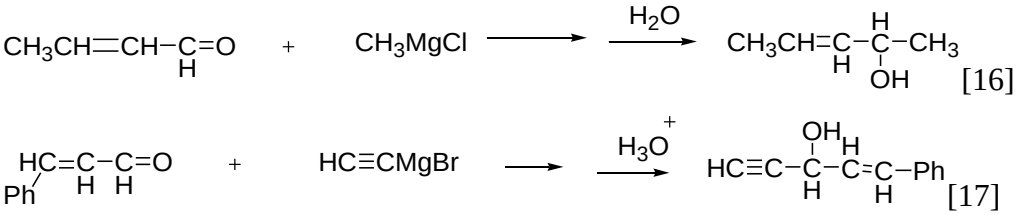
The addition of a Grignard /alkyl lithium reagent to a conjugated ketone or aldehyde is not influenced by the conjugate system. The nucleophile attacks the nucleophilic carbonyl carbon. The oxoanion then picks a proton from a proton donor.

Mechanism



Scheme 3: Mechanism of 1, 2 –Nucleophilic Additions to α,β-Unsaturated Systems

Examples [13]

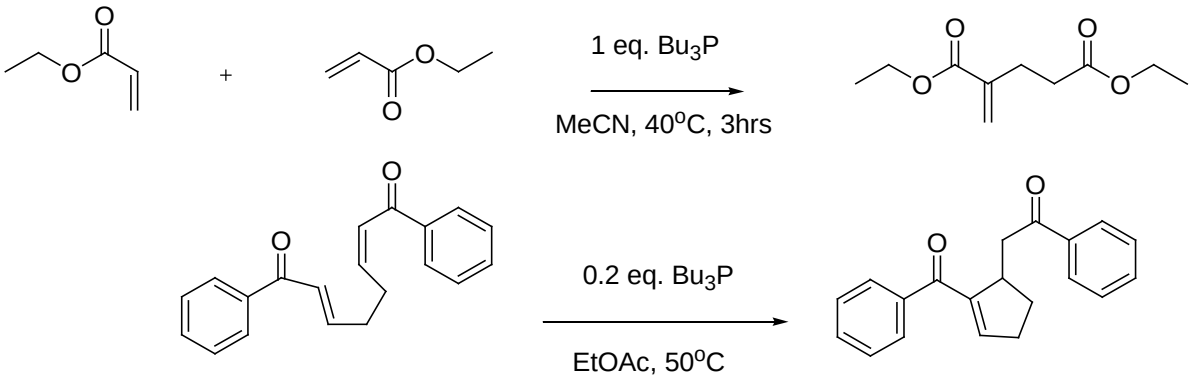


[16]

[17]

Rauhut–Currier Reactions

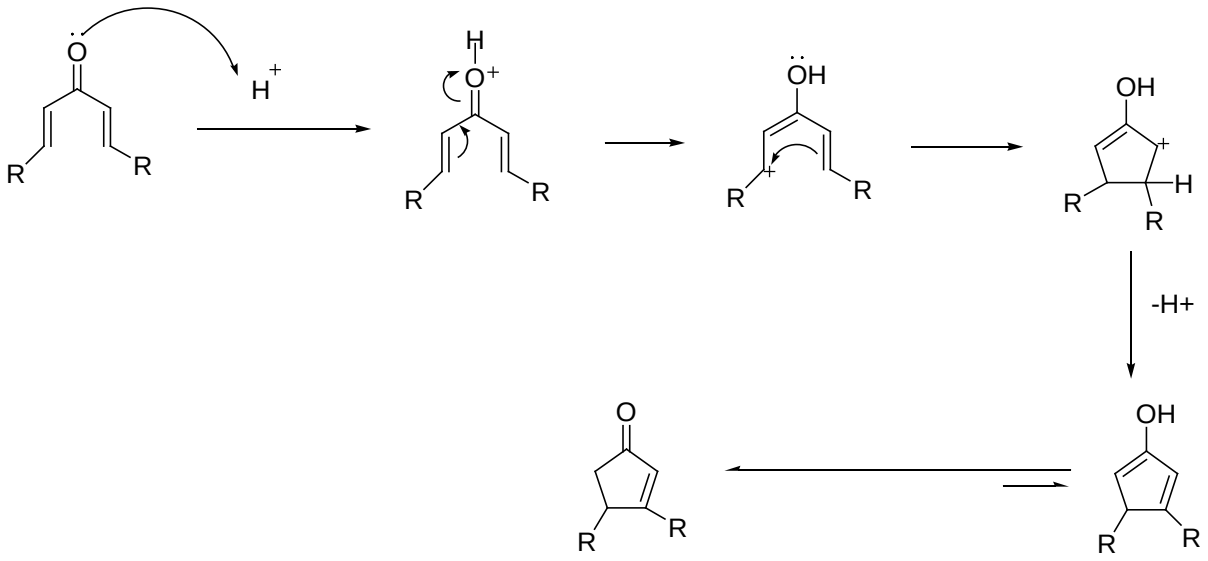
In the presence of organophosphine [18] enones can dimerize. The result of this reaction is usually another enone [19].



Nazarov Cyclization Reaction [20][21]

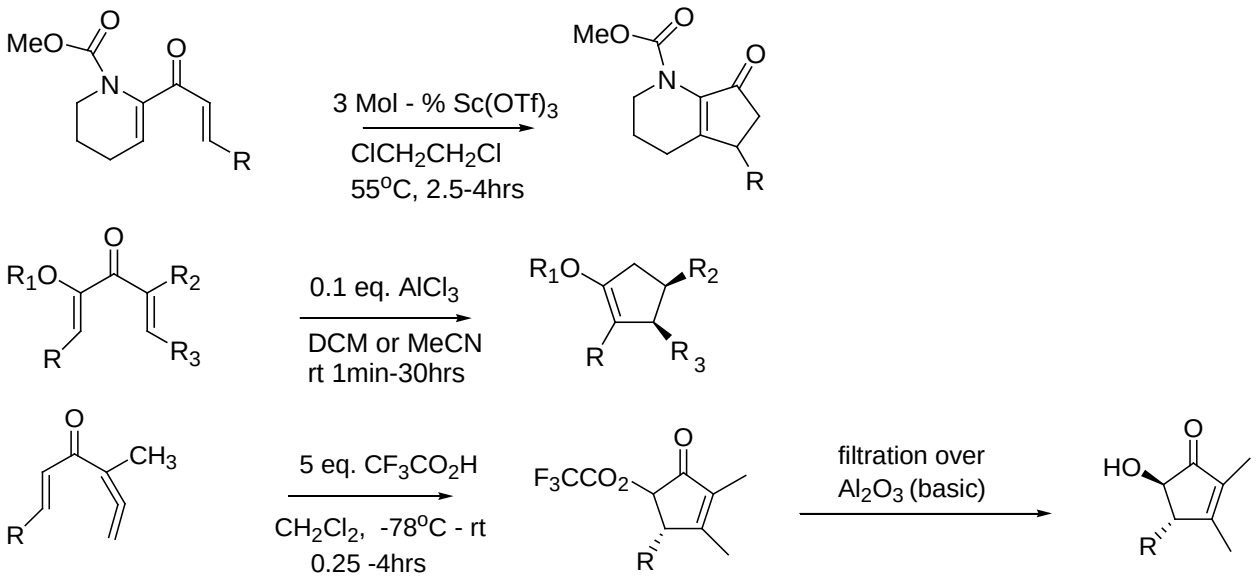
The Nazarov cyclization leads to the synthesis of cyclopentenones. The starting material is usually a divinyl ketone or any chemical that can give a divinyl ketone. The reaction is catalysed by strong Lewis acids or Bronsted acids.

The mechanism involves first the protonation of the ketone to form the enolate. The carbocation is the attacked by the pi electron of the nearby alkene followed by deprotonation and keto enol tautomerism into the desired product. The types of substituents on the compound are therefore very important to obtain the desired product.



Scheme 4: Mechanism of the Nazarov Cyclization Reaction

Examples



PCC Mediated Rearrangement of Allylic Alcohols Generated from 1, 2-Nucleophilic Additions on α, β-Unsaturated Systems

The transposition of one functional group to another is a very vital tool in organic syntheses. Various reagents and catalysts have been developed to aid the respective rearrangements. It is known that in the presence of Lewis acids and a suitable catalyst, it is possible to cause the oxidative rearrangement of tertiary allylic alcohols. The scope of work that

has gone on in the development of a good method for these transpositions shows how important it is to the synthetic organic chemists. Jean –Michel Vatele [22] in a recent article described the use of a new catalyst, TEMPO, used in combination with other reagents like PhIO, $Bi(OTf)_3$ and/or $CuCl_2$ to effect such rearrangements. But even before then work done by Babler [23], Trost [24] and other chemists in the 60s and 70s led to the discovery that PCC can effectively transpose tertiary allylic alcohols into enones in a 1,3-oxidative rearrangement process. Since then it has been a useful tool in the synthesis of many biologically significant molecules and intermediates to others. The industrial solvent, isophorone, used in inks, lacquers, paints, adhesives, and pesticides was prepared by the transposition of the alcohol in 1,5,5-trimethylcyclohex-2-en-1-ol. This work was carried out by William and Drake [26] in 1974 using PCC in dichloromethane. A yield of 40% was obtained.

PCC was first prepared by Corey [25] by addition of pyridine to chromic acid and concentrated hydrochloric acid.

$$C_5H_5N + HCl + CrO_3 \rightarrow (C_5H_5NH)(CrO_3Cl)$$

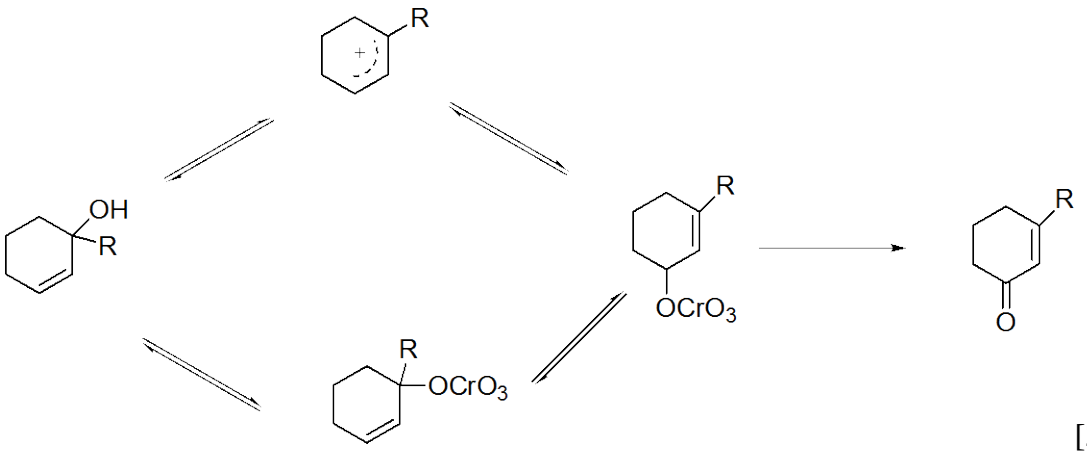
Alternatively, treatment of chromium(VI)Oxide with pyridinium chloride also yields PCC

$$[C_5H_5NH^+]Cl^- + CrO_3 \rightarrow (C_5H_5NH)(CrO_3Cl)$$

It is effective in oxidizing primary and secondary alcohols to aldehydes and ketones. Apart from having milder acid properties, it is also a milder oxidizing agent compared to other members of the chromate family and as such rarely over-oxidizes to carboxylic acids.

Mechanism

The mechanism of PCC transposition of tertiary allylic alcohols is not explicitly understood. William and Drake [26] have, however, postulated a mechanism that involves first of all the acid catalyzed dehydroxylation of the alcohol to form a carbocation that is stabilized by resonance across the first and third carbons. Once this is achieved the chromate then can oxidize one of the resonance carbocations. However, according to Saytzeff's rule the highly substituted alkene is the most stable. As such the alkene is transposed to the carbon-1, carbon-2 bond as the chromate oxidizes carbon-3. The process is expected to involve a six-membered intermediate that includes carbons 1-3, the alcoholic oxygen, the new oxygen on the carbon-3, and the chromate. Alternatively a chromate ester might be formed first followed by the transposition.

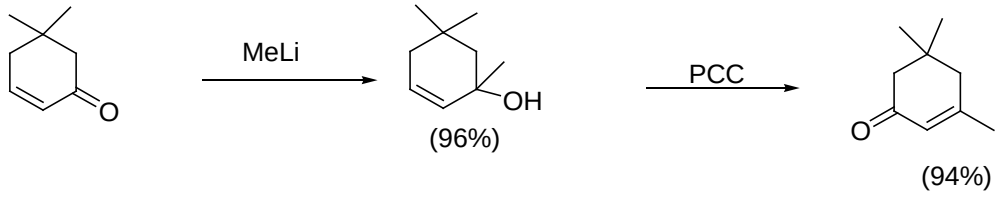


[26]

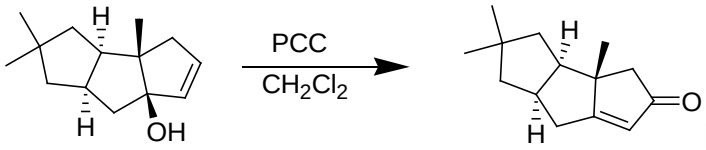
Scheme 5: Proposed Mechanism of the PCC Mediated Tertiary Allylic Alcohol Transposition

Examples

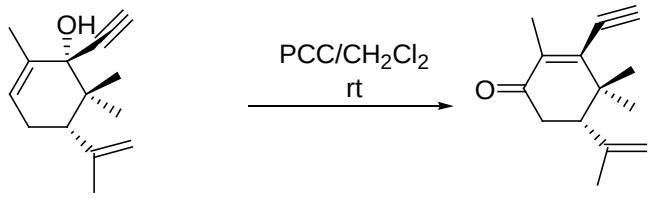
PCC based rearrangements have been used to synthesize a lot of compounds. Below are a few examples.



Isophorone [26]



[30]



[31]

Protective Groups [13]

Chemical transformations on a functional group in a multifunctional group compound sometimes require that one or more other functional groups are first protected so they don't get involved in the reaction. Protection implies the conversion of the functional group into another

functional group by reactions that can easily be reversed. An example is the conversion of aldehydes into acetals before effecting any nucleophilic reaction.

Alcoholic protons can easily interfere in most reactions of alcohols. As a result, various protective groups have been adopted to help protect the oxoanion in the absence of the proton. These same groups are useful in the protection of other kinds of oxoanions like enolates. Once the oxoanion is produced, it is trapped by the protective group as ether, an acetal, or an ester. Table 1 gives examples of the various groups of hydroxyl protecting groups. The R represents the compound of interest and source of the hydroxyl group.

Table 1. Examples of Hydroxyl Protective Groups [13]

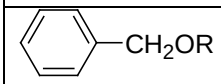
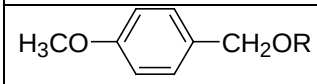
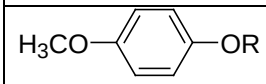
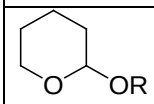
ETHERS		
STRUCTURE	**NAME**	**ABBREVIATION**
	Benzyl	Bn
	*p*-Methoxybenzyl	PMB
	*p*-Methoxyphenyl	PMP
Ph_3COR	Triphenylmethyl (trityl)	Tr
SILYL ETHERS		
STRUCTURE	**NAME**	**ABBREVIATION**
$(CH_3)_3SiOR$	Trimethylsilyl	TMS
$(CH_3)_3CSi(CH_3)_2OR$	*t*-Butyldimethylsilyl	TBDMS
$[(CH_3)_2CH]_3SiOR$	Triisopropylsilyl	TIPS
ACETALS		
STRUCTURE	**NAME**	**ABBREVIATION**
	Tetrahydropyranyl	THP
CH_3OCH_2OR	Methoxymethyl	MOM
$CH_3OCH_2CH_2OCH_2OR$	2-Methoxyethoxymethyl	MEM

Table 1. (continued)

ESTERS			**ESTERS**
STRUCTURE	**NAME**	**ABBREVIATION**	**STRUCTURE**
CH_3CO_2R	Acetate	Ac	CH_3CO_2R
$PhCO_2R$	Benzoate	Bz	$PhCO_2R$

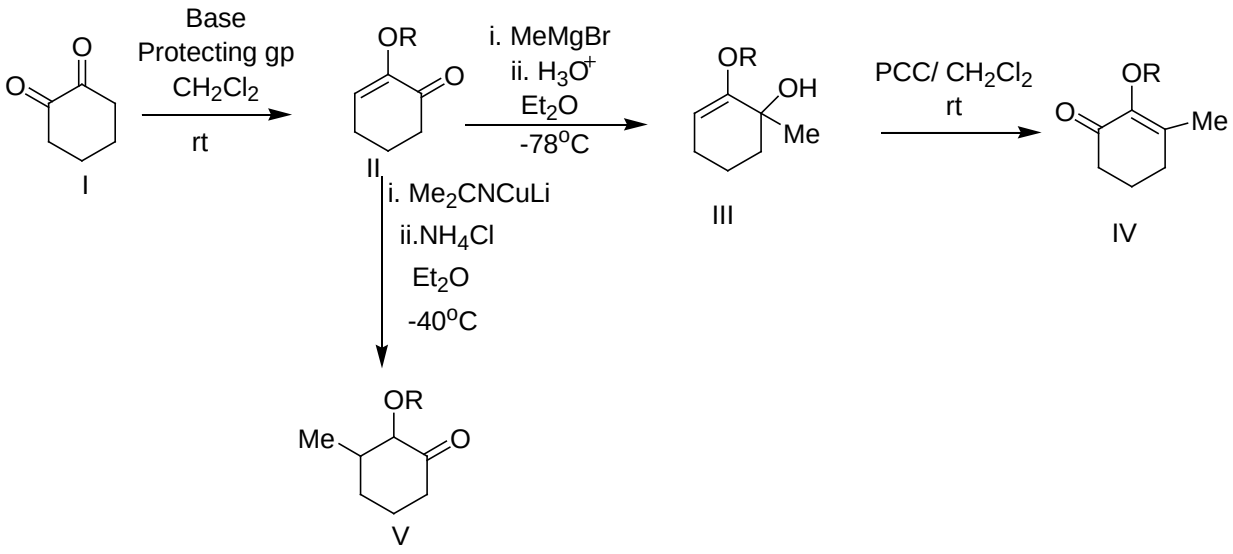
The specific choice of one protecting group over the others is determined by a series of factors including the type of reaction to be run subsequently, effect of steric factors, resonance effects, stability of the group to be protected, availability, and ease of attachment/detachment.

Objective of Research

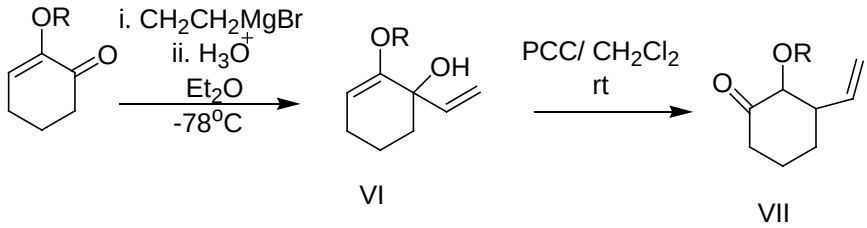
Enones with different substituent at various positions have been used in reactions with varying levels of success. Some of these reactions have found important uses in medicine, agriculture and other areas of applied chemistry.

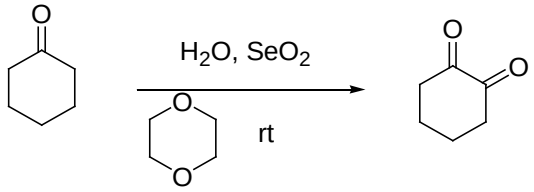
Retrosynthetic analysis of the intermediate in the synthesis of a [3. 3. 1] bicyclononanone core, illustrated above in scheme 1, shows that conjugate addition of an alkyl group to the enol ether would yield a useful intermediate for further alkylation. Alternatively alkylation of the 1, 2-cyclohexanedione enol ether followed by 1, 3-transposition of the resulting alcohol also gives a similar intermediate. The purpose of this research is to investigate the feasibility of using these two routes towards the synthesis of the target molecule.

Scheme of Work



Compound	R
A	TBDMS
B	MOM
C	Ac





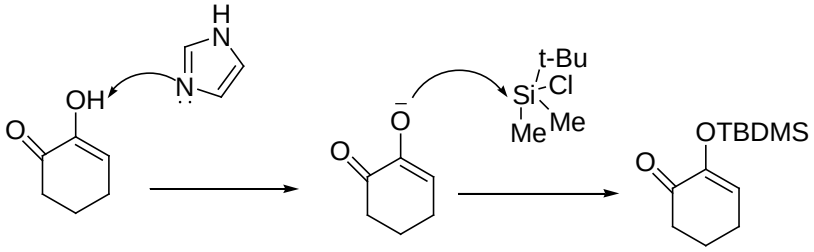
Scheme 6: Scheme of Work for the Research

CHAPTER 2

RESULTS AND DISCUSSION

The Silanes

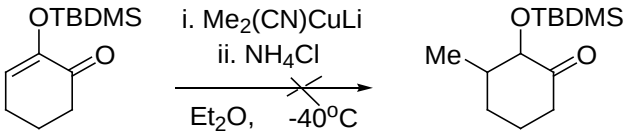
The addition of the silane was relatively easy and yielded between 95 -99% of the expected product. The mechanism involves the abstraction of an α-proton by the base (imidazole). The resulting enolate then displaces the chloride in the chloro t-butyldimethylsilane. The reaction also involves the release of HCl that deposits as white imidazole hydrochloride right upon setting the reaction up.



Scheme 7: Mechanism for the Formation of TBDMS Enolate

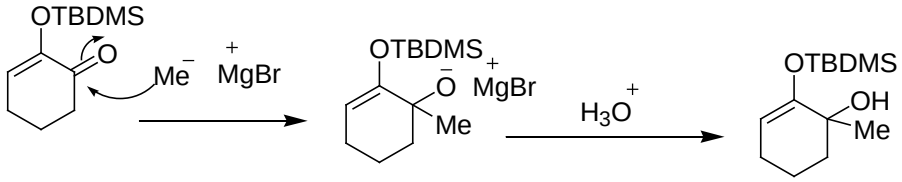
Cuprate Methylation (1, 4 – Addition)

This was attempted using higher order cuprates but was not successful. The reaction resulted in 1, 2 - addition products and not the 1, 4 - addition product.



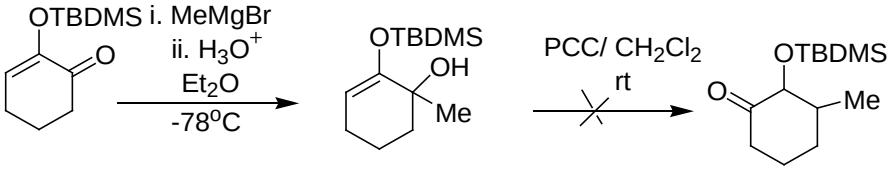
Methylation Followed by PCC Rearrangement Attempt

The methylation was done using methylmagnesium bromide to give 60% yields. Methyllithium was also used but gave yields around 60% with starting material impurities. The mechanism involves a nucleophilic attack on the carbonyl carbon and follows the 1, 2 - alkylation mechanism.



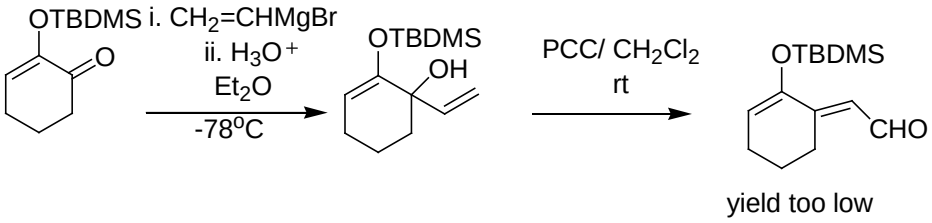
Scheme 8: Mechanism for the Grignard Methylation of the TBDMS Enolate

The next stage of the process was to effect the PCC mediated rearrangement of the vinyl alcohol. This was done several times under different conditions but did not work. The starting material keeps coming back.



At this stage two possible explanations could be given for the failure of the reaction to work. Accessibility of the hydroxyl group: the hydroxyl group is in close proximity to a very bulky group and somehow inaccessible to the PCC. The PCC mechanism involves a six-membered ring intermediate. In this case this intermediate would be difficult to achieve because of the bulky nature of the protecting group.

To prove these postulates two approaches were adopted. The first was to use a vinyl nucleophile instead of the alkyl nucleophile. The ketone was vinylated and was subjected to the PCC reaction under various conditions. Under one of those conditions, where NaOAc was used to buffer the PCC, the nmr showed glimpses of an aldehyde. But the quantity was too small to be isolated and the reaction was not reproducible.



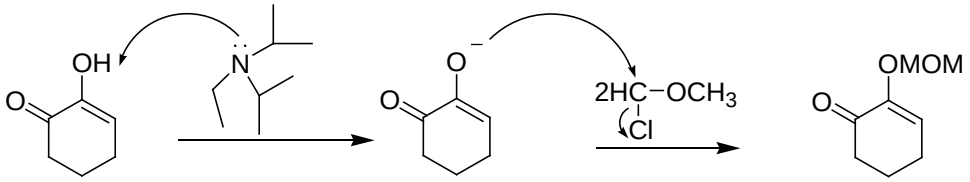
The other alternative was to change the protecting group to a less bulky group.

Methoxymethyl Protecting Group

The methoxymethoxy group became the protecting group of choice to replace the silane. The only case in literature where chloromethoxymethane was successfully used to protect cyclohexanedione gave reported 30% yield and the reaction was run for two days. This would make it difficult to run the subsequent reactions in higher quantities and would take a lot of time, the first attempt at using the methoxy methoxy protecting group was to increase the yield and where possible decrease the reaction time. The carbon – chlorine bond in chloromethoxymethane is more covalent than the silicon – chlorine bond.

A series of bases were used in an attempt to increase the yield but none of them gave any reasonable yield.

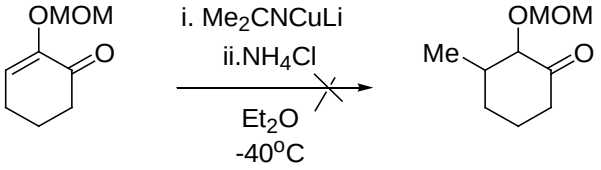
The diisopropylethyl amine route as present in literature was therefore adopted. Enone yields of 22% were obtained.



Scheme 9: Mechanism for the Formation of the MOM Enolate using N, N – Diisopropylethylamine as Base.

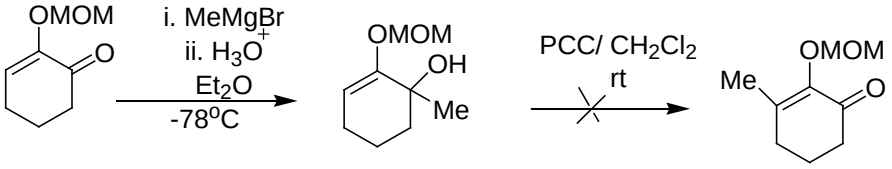
Cuprate Addition

This reaction was run but this time, unlike the silane, the starting material was not recovered. However, the product obtained was also not the expected product. Nmr indicated the absence of the protecting methoxymethoxy group from the product. Probably the presence of so many lone pairs of electrons and a transition metal caused some free radical mechanism that ultimately removed the protecting group.

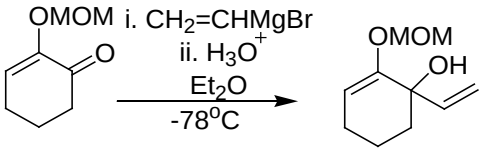


Methylation Followed by PCC Rearrangement

Methylation of the enone was successfully effected using methyl magnesium bromide with yields between 50-65%. Once again attempts to effect the PCC rearrangement reaction proved futile under various conditions



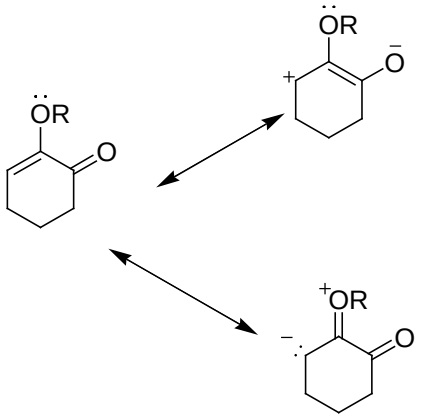
Vinylation of the enone resulted in 50% of the vinylated product, but this was too small for any further reaction.



At this point it became evident that either there was an inherent problem with the α, β - unsaturated systems obtained from cyclohexadione and probably other vicinal diones that inhibits them from undergoing these prominent reactions of α, β - unsaturated systems or the choice of protecting groups was wrong. Most of the reactions were, however, run at 1-5 mmol quantities of starting materials and that would make it difficult to detect and isolate yields less than 10%. It is therefore possible that some of these reactions when run at higher concentrations of their respective starting materials could give some amounts of the expected results.

However, a critical look at the enone show something very important to this research that was until this point not considered. Carbon-2 and carbon-4 are expected to be nucleophilic in the general chemistry of α, β - unsaturated systems. However, carbon 4 is not really nucleophilic in this case.

There is a resonance contribution of nonbonding electrons from the oxygen on carbon-3 which makes carbon-4 electrophilic. This means that the electrophilicity or nucleophilicity of carbon-4 depends on the direction and effectiveness of resonance. In my opinion however, the resonance that leads to its electrophilicity is stronger especially when using methoxymethoxy group as the protecting group.



Scheme 10: Possible Resonance Paths for the 1, 2 – Cyclohexadione Enolates

The result of this is that even the less electropositive copper would rather coordinate with the oxoanion and not the electron rich carbon-3, carbon-4 bond. It even becomes more difficult for any nucleophile to attack carbon-4 due to repulsion. Hence the oxoanion in PCC cannot be placed on carbon-4 as well as the alkyl nucleophiles in the cuprates. Additionally, for an acetyl protecting group like methoxy methoxy PCC is acidic enough to cause its removal.

The next course of action was to look for a protecting group that would also occupy the lone electrons on the oxygen and prevent the kind of resonance that makes carbon-4 electrophilic. Thus, an electron withdrawing group is required. But the electron withdrawing group must also not be susceptible to nucleophilic attack. So far the only way of achieving that is by finding an alternative way of getting to the allylic alcohol with an electron withdrawing protecting group without going through the nucleophilic addition route. Probably a whole new synthetic route not involving cyclohexadione is required. On the other hand, considering that cuprate addition have been successful on 1,2,3 - trioxygen systems as well as epoxides, probably a change in protecting group to an ether can bring about success.

Another reaction run in this research was to convert cyclohexanone to cyclohexadione. The reaction itself is a simple one but the purification (primarily distillation under reduced pressure) caused a bit of a problem. While the nmr proved that the product was forming, it became obvious that, the 5:1 cyclohexanone /selenious acid ratio did not give enough yields to distil out cyclohexadione under our lab conditions. Various means were therefore adopted to improve the relative yield. These included varying the reaction temperature and the reaction time. Ultimately, a 3:1 cyclohexanone/selenious acid ratio and a reaction time spanning 2 days did the trick. A good yield of the cyclohexadione was obtained.

A successful attempt was also made to form the enone by protecting the enolate with acetate. The yield was excellent but this route could not be pursued any further because acetate has a electrophilic site and that will hinder the nucleophilic additions.

Conclusion

Due to steric, resonance, and other factors, the TBDMS and MOM enol ethers of 1, 2 –cyclohexadione did not undergo conjugate additions as well as PCC mediated transposition of their allylic alcohols derived from 1, 2 –methylation. It is expected that a good choice of protecting group could help effect these reactions. However, some intermediates synthesized in the process are new compounds. These are: 2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-vinyl-2-cyclohexen-1-ol (IIIB), 2-(methoxymethoxy)-1-methyl-2-cyclohexen-1-ol (VIA), and 2-(methoxymethoxy)-1-vinyl-2-cyclohexen-1-ol (VIB).

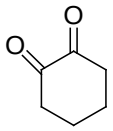
CHAPTER 3

EXPERIMENTAL

General Methods

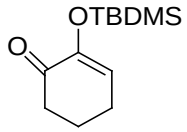
Cyclohexadione and other commercial reagents were used without further purification. Whenever THF was used, it was distilled just before use. All proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on JEOL-NMR Eclipse spectrometer operating at 400 MHz and 100 MHz for proton and carbon nuclei respectively. Spectra were obtained using $CDCl_3$ unless otherwise stated. Chemical shifts were recorded as delta values in parts per million (ppm) relative to TMS. The multiplicity of signals is reported as follows: s, singlet; d, doublet; m, multiplet. Thin layer chromatography (TLC) was performed with silica gel plate using appropriate solvent mixture and visualized under UV fluorescent indicator and cerium sulfate solution. Column chromatography was performed using silica gel and appropriate solvent. All weighings were done using Mettler PB 1502 and Denver Instrument TR 105 scales unless otherwise stated. Unless otherwise stated, all reactions were done in flame dried flasks and under Nitrogen gas.

Synthesis of 1, 2-Cyclohexanedione [32]



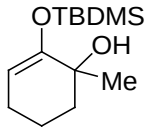
This was done according to the method of Clifford, Charles, and Harvey. To a 112.5 mL (0.9 mol) of cyclohexanone in a round bottom flask in a water bath was added with stirring a mixture of 10 mL of water, 31.5 mL of dioxane, and 33.28g (0.3 mol) of SeO_2 over 3 hours at room temperature. The reaction immediately turned yellow upon addition of the mixture followed by the gradual appearance of the red selenium solid particles. The reaction was allowed to run for 3 hours in the cold water bath after which it was allowed to warm to room temperature and stirred for 2 days. At the end of the reaction the red bulky selenium was removed by filtration under pressure and extracted with 50 mL of 95% boiling ethanol. The extract was added to filtrate above and the mixture was distilled under reduced pressure. The fraction from 65-90^{o}C was cooled to afford 20g of 1, 2-cyclohexanedione crystals.

Synthesis of 2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-cyclohexen-1-one



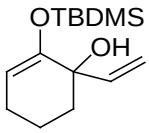
To a solution of 1.12g (10 mmol) of 1,2-cyclohexanedione in 8 mL dichloromethane was added in one portion 0.82g (12 mmol) followed by 1.81g (12 mmol) of t-butyldimethylsilyl chloride also in one portion. A white precipitate was produced immediately on addition of the t-butyldimethylsilyl chloride. The reaction mixture was stirred for 3 hrs at room temperature after which the reaction was quenched with 5 mL of distilled water. The organic phase was washed with 5 mL of brine and the aqueous phase was washed with 10 mL of dichloromethane. The solvent was removed at reduced pressure to afford 85-99% yield. δ_H 6.2(t, =CH), 2.6-1.9(m, 6H), 0.9(s, t-BuSi), 0.1(MeSi). ^{13}C NMR (100 MHZ, $CDCl_3$) δ 195.9, 147.80, 128.02, 38.80, 27.80, 25.40, 23.80, 18.20, -4.40

Synthesis of 2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-methyl-2-cyclohexen-1-ol [32][26]



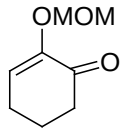
To a solution of 0.46g (2 mmol) of the ketone (IIA) in 5 mL of diethyl ether at -78^{o}C was added dropwise, 0.8 mL of 3M methylmagnesium bromide in Diethyl ether. The reaction was run at -78^{o}C for 30 min and warmed to room temperature for 2 hrs. Five mL of water was added to quench the reaction and the organic phase was extracted and washed with 5 ml of saturated $NaHCO_3$ and dried. The solvent was then extracted under reduced pressure to afford an oil which was further purified with column chromatography using a 5:1 hexanes/ethyl acetate solvent system to afford a colorless oil in 60% yield. δ_H 4.75(t, $=CH_2$), 2.2(s, OH), 2.1-1.4(m, 6H), 1.3(s, CH_3), 0.9(s, t-BuSi), 0.1(s, MeSi). ^{13}C NMR (100 MHZ, $CDCl_3$) δ 152.20, 102.40, 70.50, 37.90, 27.88, 25.80, 24.40, 20.08, 17.80, -4.40

Synthesis of 2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-vinyl-2-cyclohexen-1-ol



To a solution of 0.46g (2 mmol) of the ketone (IIA) in 5mL of THF at -78^{o}C was added dropwise, 2.4 mL of 1M vinylmagnesiumbromide in THF. The reaction was run at -78^{o}C for 30 min and warmed to room temperature for 2 hrs. Five mL of water was added to quench the reaction and the organic phase was extracted and washed with 5 mL of saturated $NaHCO_3$ and dried. The solvent was then extracted under reduced pressure to afford oil that was further purified with column chromatography using a 5:1 hexanes/ethyl acetate solvent system to afford 0.33g (69%) of a light yellow oil. δ_H5.9(q, =CH-), 5.15(doublet of doublet, CH_2=), 4.85(t, =CH), 2.6(s, OH), 2.2-1.5(m, 6H), 0.9(s, t-BuSi), 0.15(s, CH_3-Si). ^{13}C NMR (100 MHZ, $CDCl_3$) δ 142.80, 114.10, 104.05, 73.90, 38.20, 24.90, 22.00, 19.20, 17.80, -4.40,

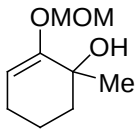
Synthesis of 2-(Methoxymethoxy)-2-cyclohexen-1-one [33]



This was prepared according to the method of Begley, Ladlow, and Pattenden. To a magnetically stirred solution of diisopropylethylamine (4.5 mL, 26 mmol) and Chloromethoxymethane (1.52 mL, 18 mmol) in dry dichloromethane at room temperature was added 1.12g (10 mmol) of cyclohexadione in 4 mL Dichloromethane under Nitrogen. The mixture was stirred for 48 hrs after which it was dried in vacuo. The residue was extracted with diethylether that was washed three times with 10 mL of water. The organic phase was dried and concentrated under vacuo to afford orange oil. The oil was subjected to column chromatography using silica gel as stationary phase and diethylether as eluent to afford 0.34g (2.2 mmol) of a yellow oil.

δ_H6.4 (t, =CH), 5.05(s, OCH_2O), 3.45(s, OMe), 2.7-2.5(m, CH_2-CH_2), 2.0-1.9(m, CH_2)
^{13}C NMR (100 MHZ, $CDCl_3$) δ 194.67, 149.46, 123.87, 94.50, 56.25, 38.81, 24.72, 22.83

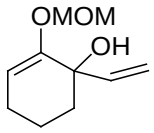
Synthesis of 2-(Methoxymethoxy)-1-methyl-2-cyclohexen-1-ol



To a solution of 0.63g (4 mmol) of the ketone (IIB) in 5mL of diethyl ether at -78^{o}C was added dropwise, 1.35 mL of 3M methylmagnesium bromide in diethyl ether. The mixture turned

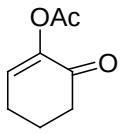
pinkish immediately. The reaction was run at -78^{o}C for 30 min and warmed to room temperature for 2 hrs. Five mL of water was added to quench the reaction and the organic phase was extracted and washed with 5 mL of saturated $NaHCO_3$ and dried. The solvent was then extracted under reduced pressure to afford an oil that was further purified with column chromatography on silica gel using a diethyl ether solvent system to afford 0.41g (60% yield) of a light yellow oil. δ_H 5.0-4.9(doublet of doublet, OCH_2O), 4.95(t, $=CH_2$), 3.4(s, OMe), 2.3(s, OH), 2.1-1.5(m, 4H), 1.45(s, CH_3) ^{13}C NMR (100 MHZ, $CDCl_3$) δ 155.18, 99.97, 94.12, 69.84, 56.06, 38.29, 27.19, 24.34, 19.72

Synthesis of 2-(Methoxymethoxy)-1-vinyl-2-cyclohexen-1-ol



To a solution of 0.63g (4 mmol) of the ketone (IIB) in 5mL of THF at -78^{o}C was added dropwise, 4.2 mL of 3M vinylmagnesium bromide in THF. The mixture turned pinkish immediately. The reaction was run at -78^{o}C for 30 min and warmed to room temperature for 2 hrs. Five ml of water was added to quench the reaction and the organic phase was extracted and washed with 5 mL of saturated $NaHCO_3$ and dried. The solvent was then extracted under reduced pressure to afford an oil that was further purified with column chromatography on silica gel using a diethyl ether solvent system to afford 0.43g (75% yield) of a yellow oil. δ_H 5.93(q, =CH-), 4.98-4.87 (m, $=CH_2$, OCH_2O,=CH) , 3.43(s, OMe), 2.683(s, OH), 2.09-1.56(m, 6H), ^{13}C NMR (100 MHZ, $CDCl_3$) δ 142.90, 132.80, 113.85, 102.00, 94.18, 73.11, 56.24, 36.57, 24.12, 19.06

Synthesis of 2-Acetyloxy-1-methyl-2-cyclohexen-1-one



To a magnetically stirred solution of 0.33g (3 mmol) of cyclohexadione in 4 mL of dichloromethane was added 2.18g of imidazole (3.2 mmol) followed by 3.2 mL (3.2 mmol) of acetic anhydride. The reaction was run overnight after which it was quenched with 10 mL of water. The organic phase was washed with brine, dried, and concentrated in a vacuo to afford

0.37g (80%) of a light orange oil. δ_H 6.6(t, $=CH_2$) 3.6-1.9(9H) ^{13}C NMR (100 MHZ, $CDCl_3$) δ 192.22, 169.00, 144.18, 137, 48.10, 25.30, 23.00, 20.50

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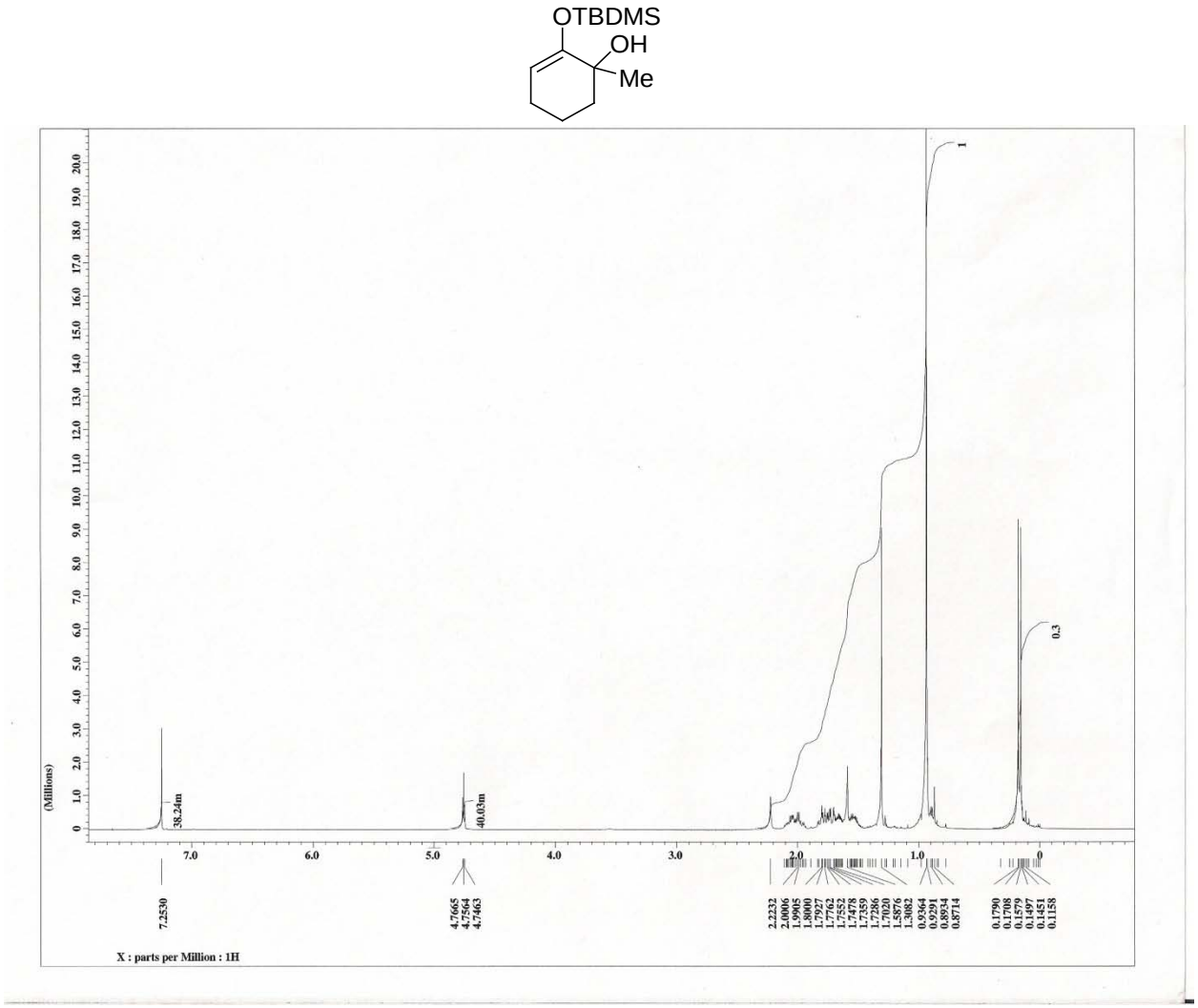
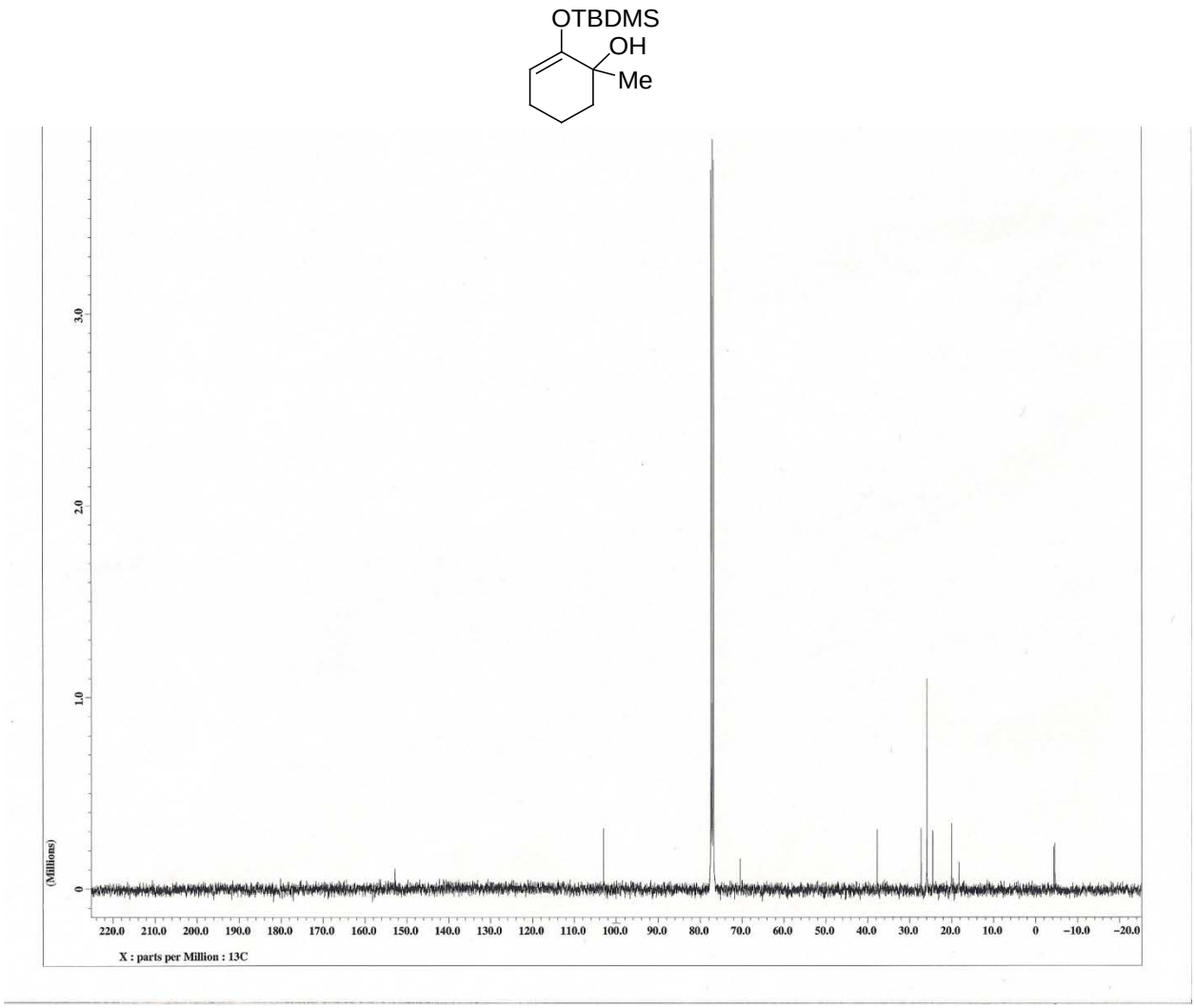
APPENDICES

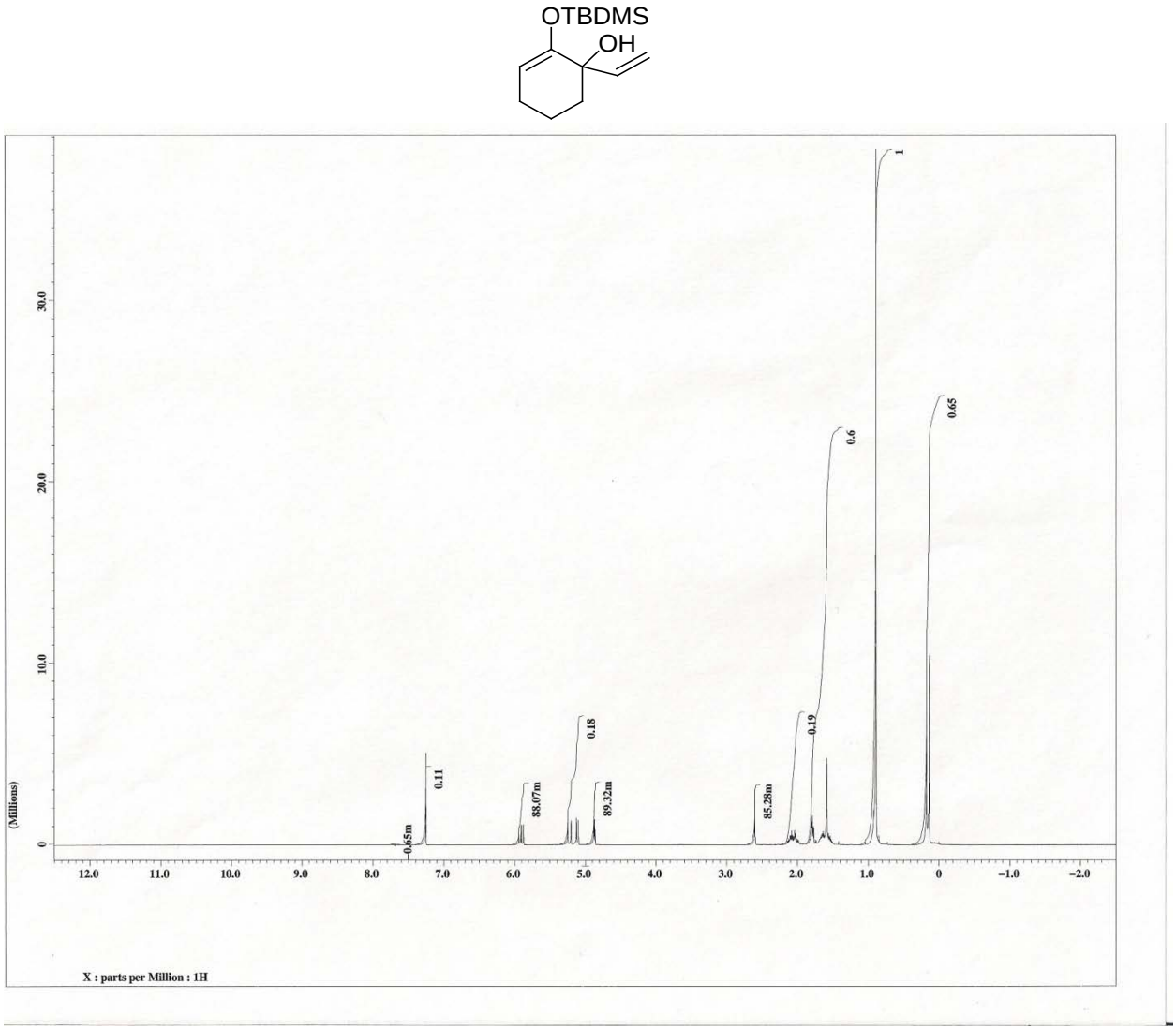
Appendix A: ^{1}HNMR of Compound IIIA in $CDCl_3$



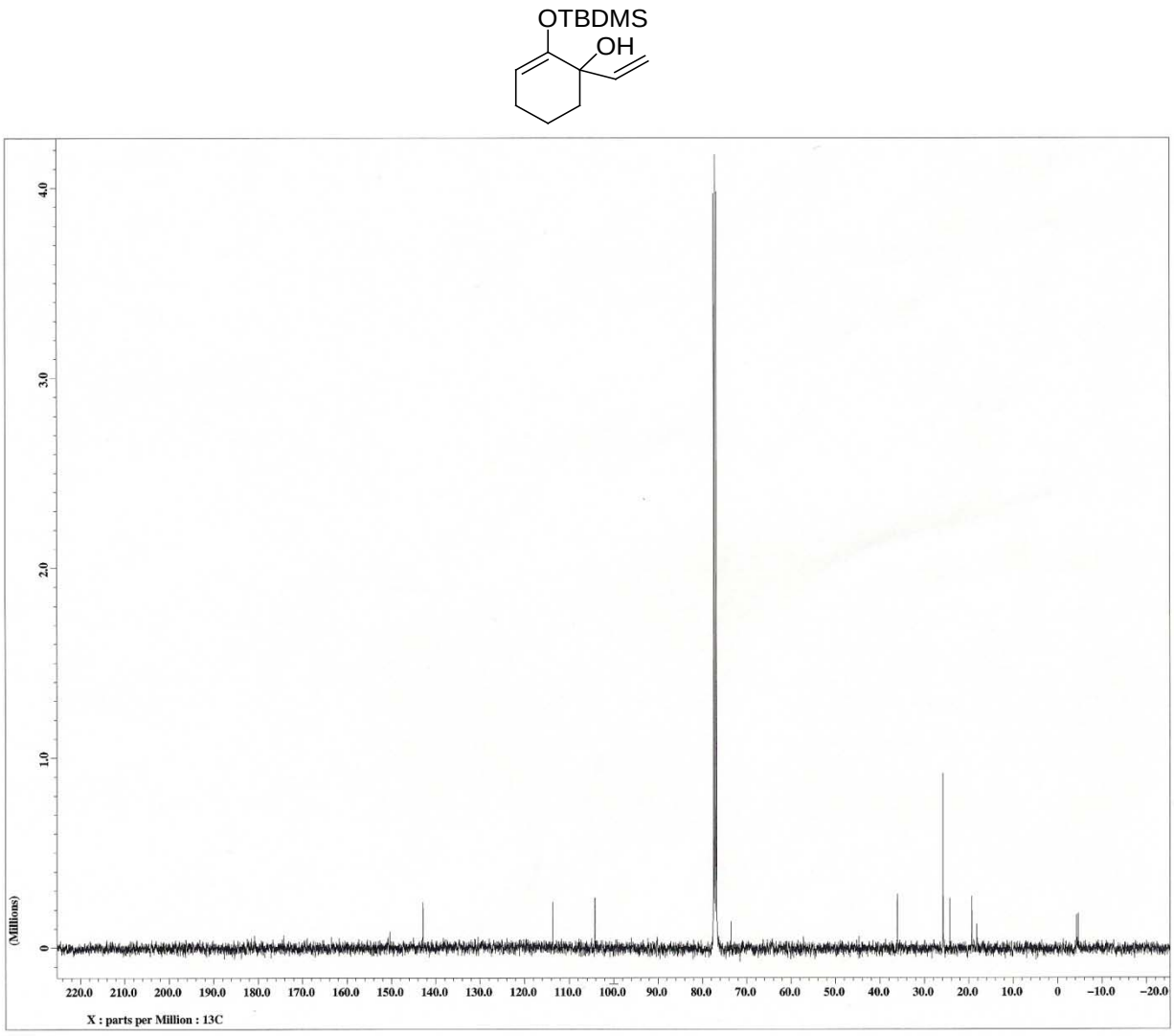
Appendix B: ^{13}C NMR of Compound IIIA in$CDCl_3$



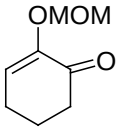
Appendix C: ^{1}HNMR of Compound VIA in $CDCl_3$

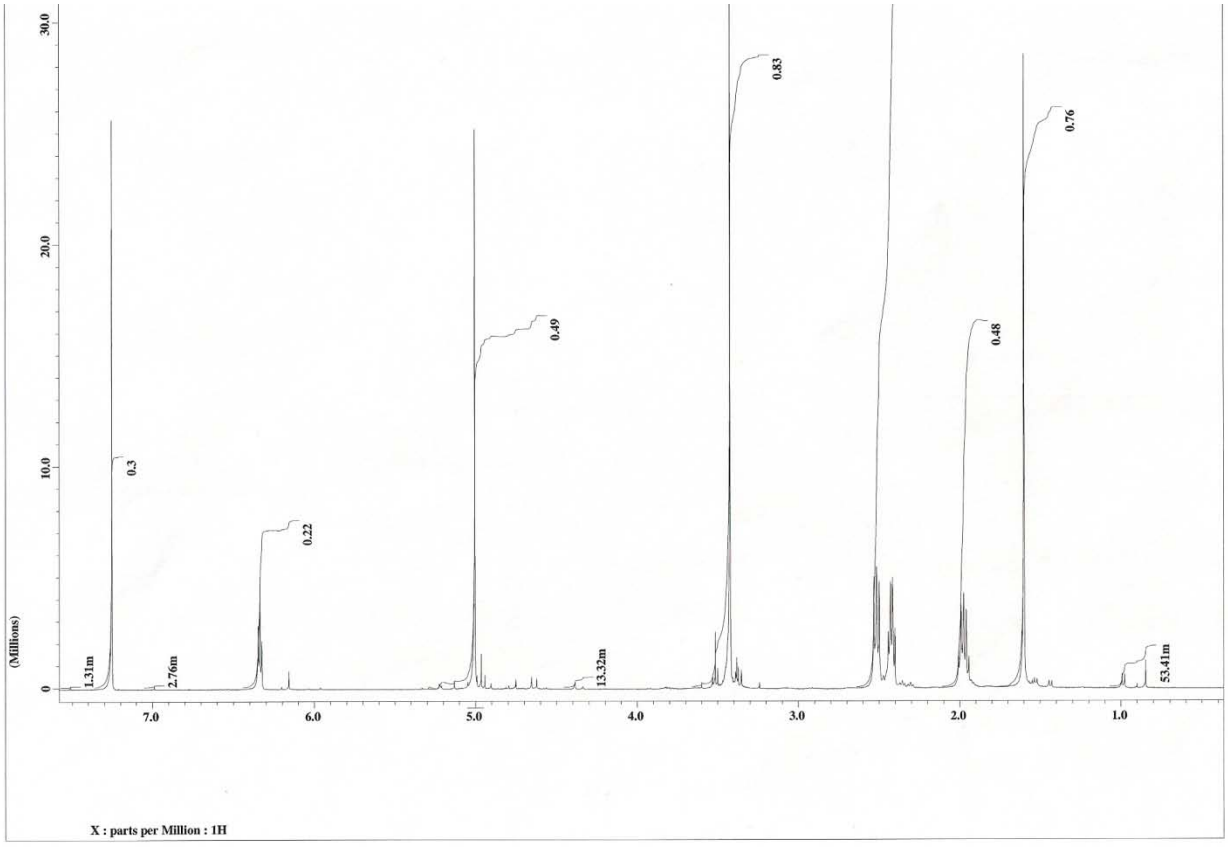


Appendix D: ^{13}C NMR of Compound VIA in$CDCl_3$

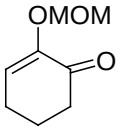


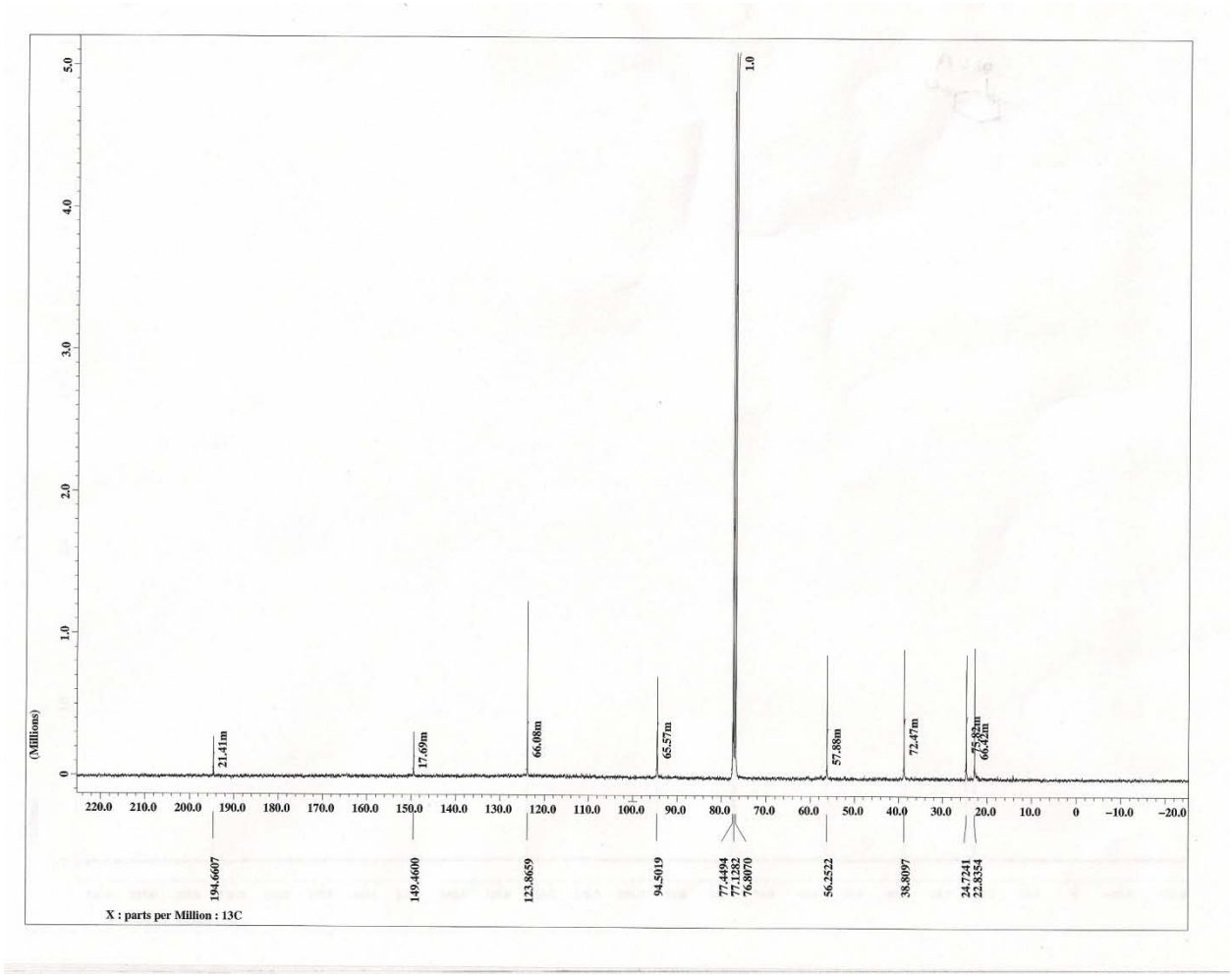
Appendix E: ^{1}HNMR of Compound IIB in $CDCl_3$



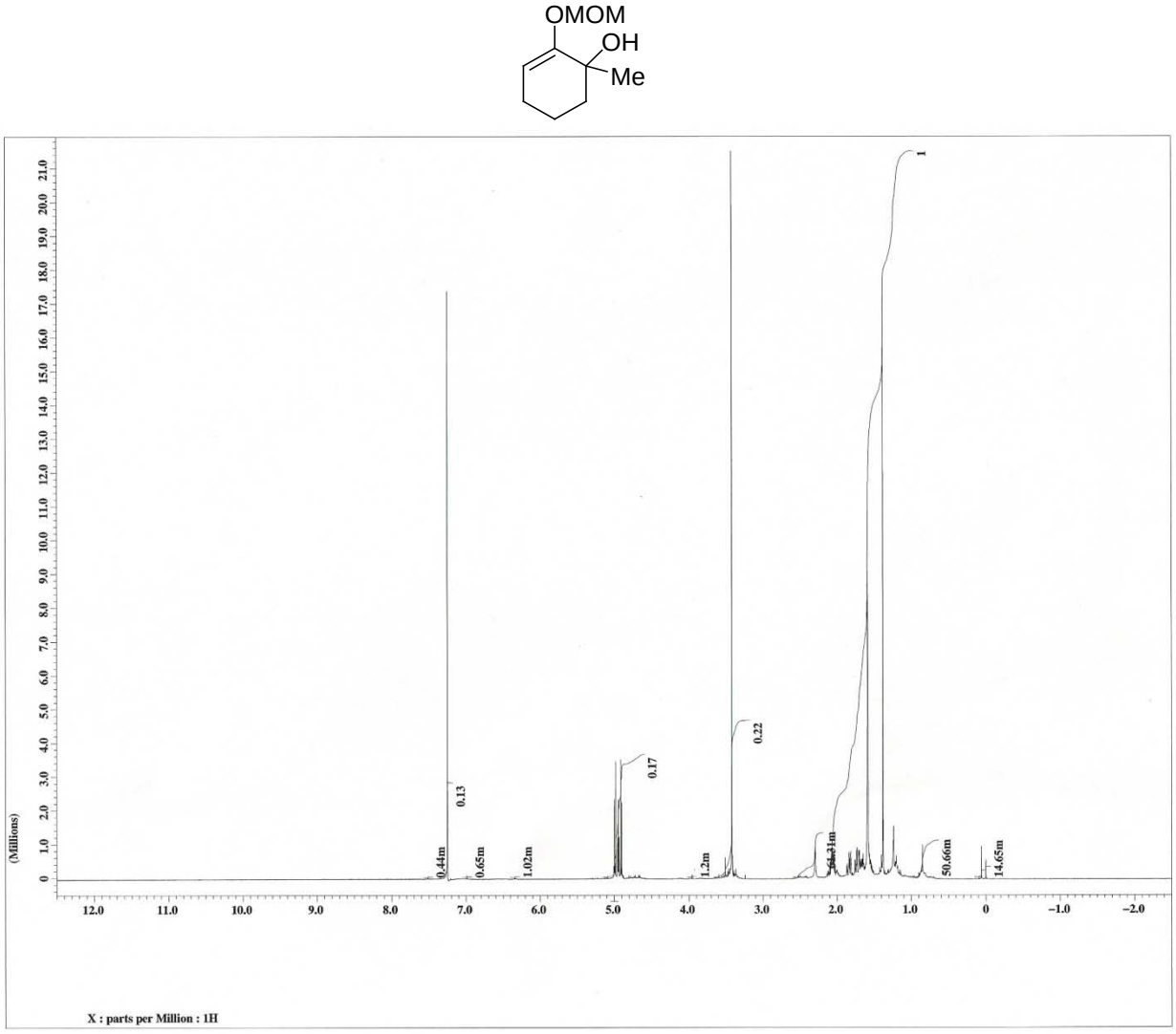


Appendix F: ^{13}C NMR of Compound IIB in $CDCl_3$

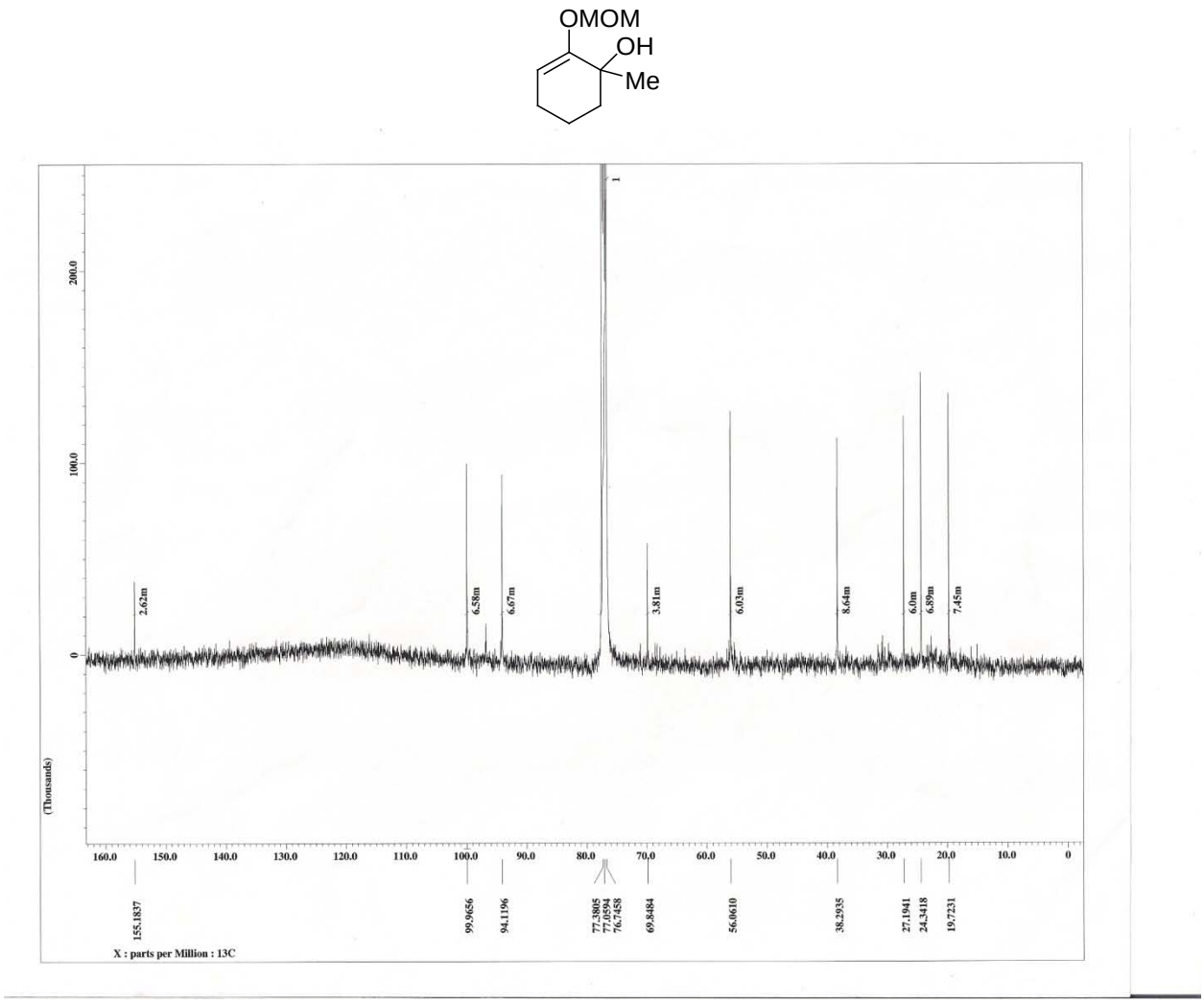




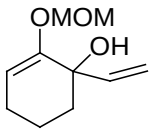
Appendix G: ^{1}HNMR of Compound IIIB in $CDCl_3$

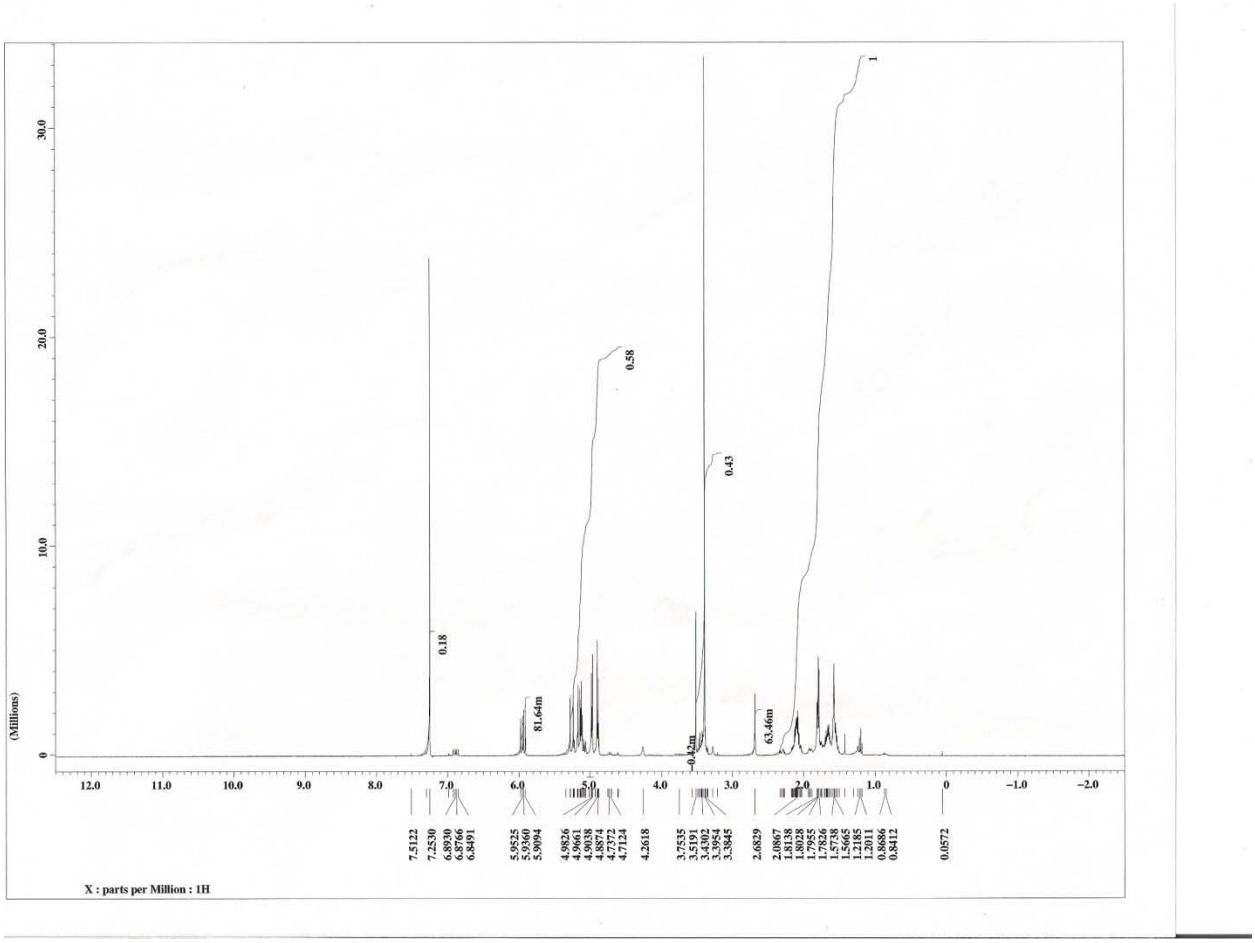


Appendix H: ^{13}C NMR of Compound IIIB in $CDCl_3$

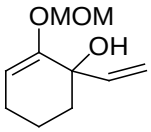


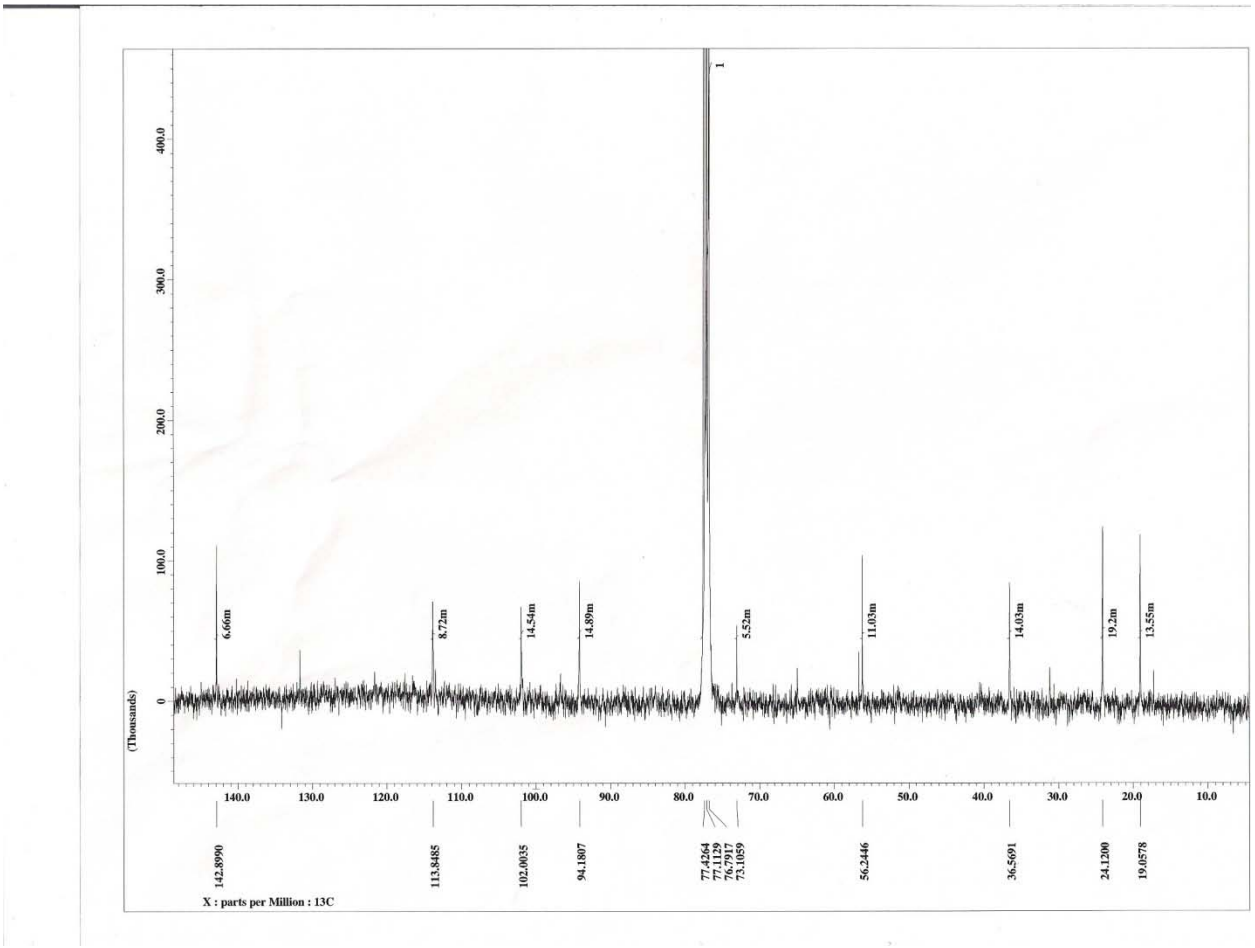
Appendix I: ^{1}HNMR of Compound VIB in $CDCl_3$



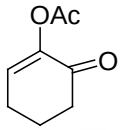


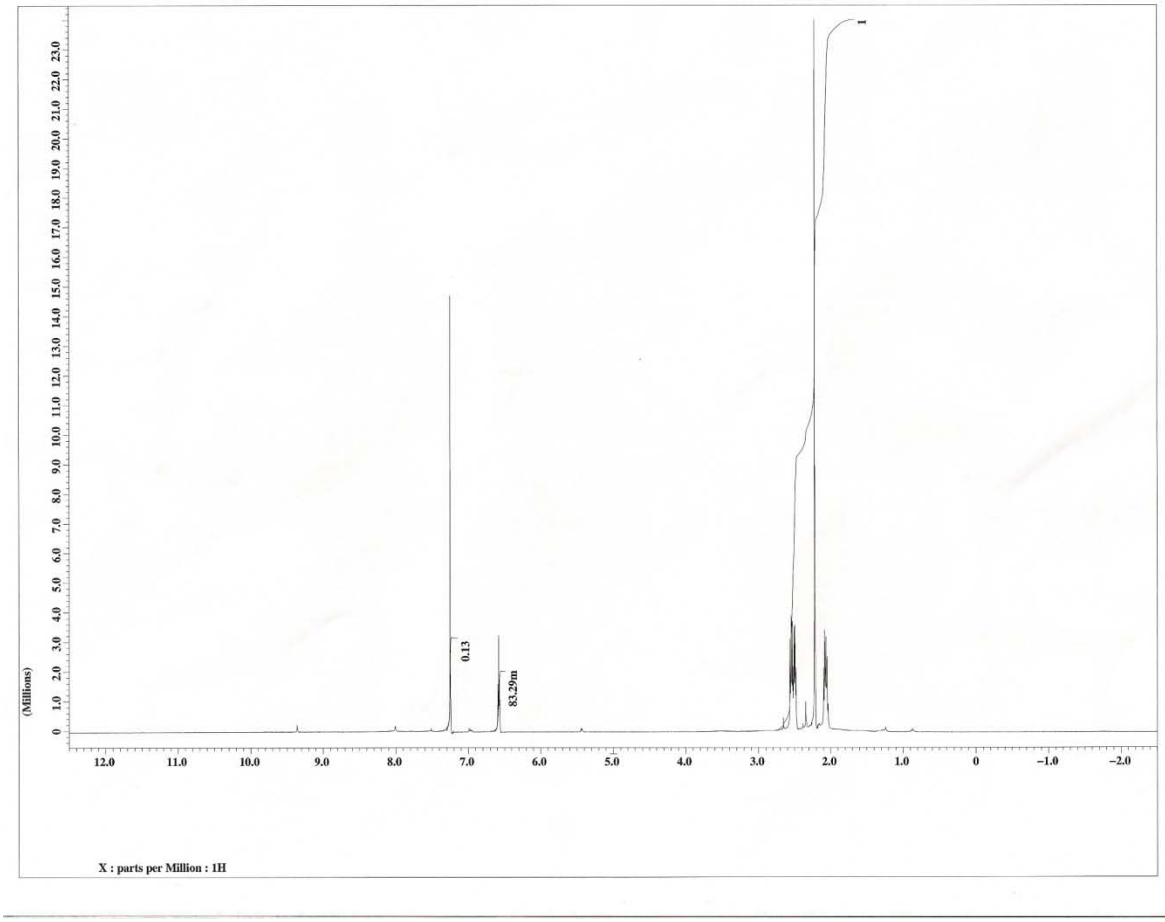
Appendix J: ^{13}C NMR of Compound VIB in$CDCl_3$



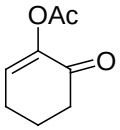


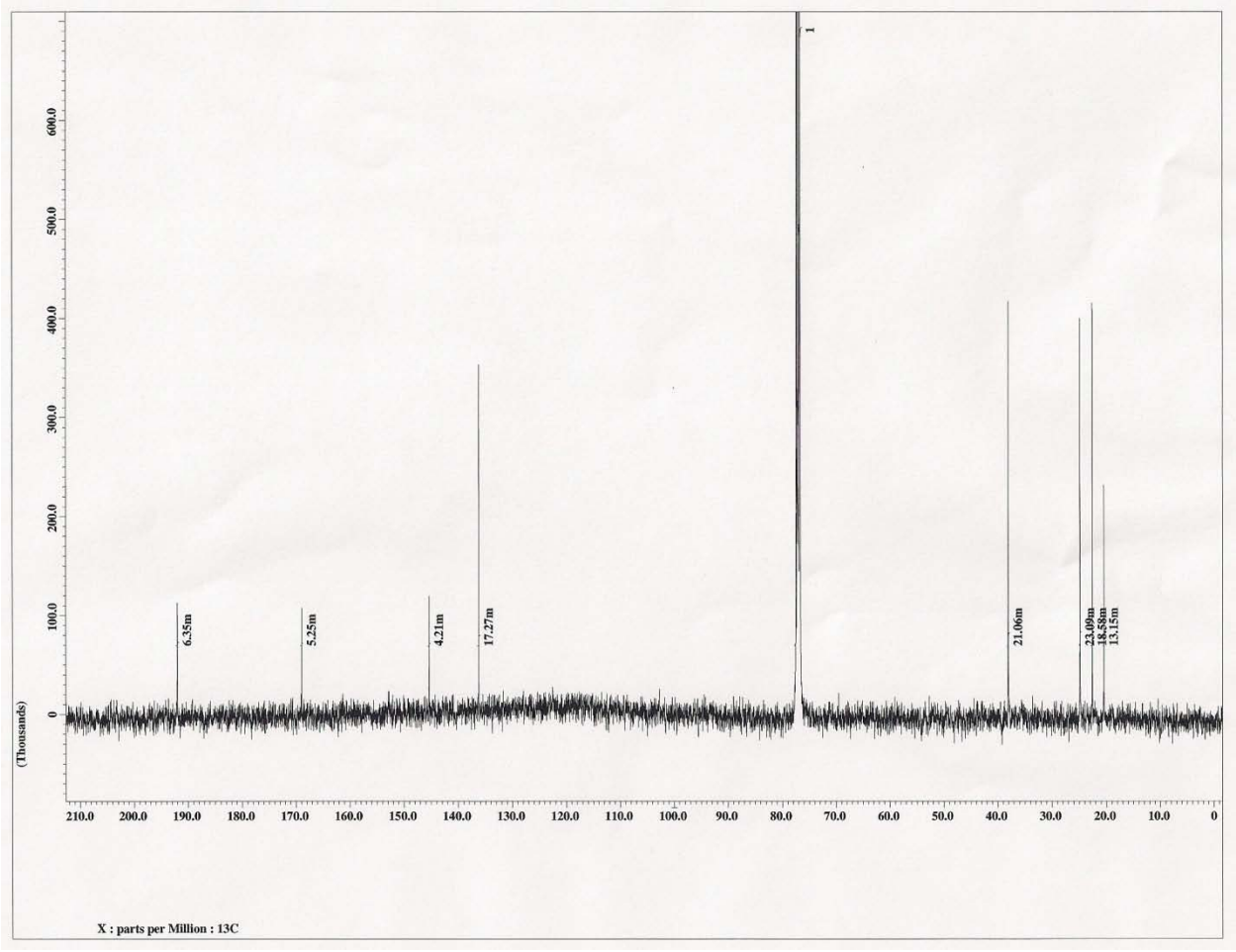
Appendix K: ^{1}HNMR of Compound IIIA in $CDCl_3$





Appendix L: ^{13}C NMR of Compound VIA in$CDCl_3$





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