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FACILITATING PHEROMONE SYNTHESIS

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FACILITATING PHEROMONE SYNTHESIS

by

Christine G.I. Beshay Boles

A thesis
submitted in partial fulfillment
of the requirements for the
Master of Science Degree
State University of New York
College of Environmental Science and Forestry
Syracuse, New York
August 2019

Approved: Department of Chemistry

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Abstract

C.G. Beshay-Boles. Facilitating Pheromone Synthesis. 97 pages, 23 Schemes, 3 Tables. American Chemical Society style guide used.

Integrated pest management (IPM) is an area of agriculture research secondary to the negative impacts of conventional pesticides. Pheromones have been shown to be effective approaches in pest control with minimal risk to humans and the environment. We describe projects that contribute to pheromone research.

Firstly, we describe a method for synthesis of the pheromone *exo*-brevicommin (7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane) using tosylation of alcohol followed by alkylation and cyclization. This stereoselective method is unique compared to others.

Secondly, we describe a method for the oxidation of primary alcohols to aldehyde using trichloroisocyanuric acid and 2,2,6,6-tetramethyl-1-piperidinyloxy in the presence of sodium bicarbonate or *p*-toluenesulfonic acid. Also described is the direct conversion of a primary alcohol to alpha-chloroaldehyde. This has future potential in pheromone research.

Finally, we explored conditions for a cost-effective and efficient direct mixed Claisen condensation using LDA as base to yield ketoesters that can then be converted to ketones. The Claisen condensation can be used to further synthesize the pheromone 7-Methyl-1,6-dioxaspiro[4.5]decane.. This method is more efficient and potentially more cost-effective than other previously described methods.

Key Words: pheromone synthesis, Claisen condensation, oxidation reaction, spiroketal, *exo*-brevicommin, butyrophenone

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Chapter 1: Introduction

Integrated pest management (IPM) strategies have come to the forefront of agriculture concern throughout the world secondary to the negative impacts of conventional pesticides on health, environment, and organisms. The goal of IPM is to allow for safer insect control and pose the least risks while maximizing benefits and reducing costs. Moreover, IPM assists in combatting increasing resistance of insects to pesticides. Included in these strategies, the use of insect pheromones has become a heavy area of research as it offers an effective alternative selection in agricultural and forest pest control. Pheromones have been shown to be one of the most effective approaches in pest control by way of achieving mass trapping and killing of harmful pests selectively with minimal risk to human health and the surrounding environment.¹

Native bark beetles are among the largest nuisance to western North American forests. Bark beetles are insect pests inhabiting the subcortical tissues of trees, and account for much of the loss of timber in coniferous forests throughout the northern hemisphere.² Species, such as the western pine beetle *Dendroctonus brevicomis*, Douglas-fir beetle *Dendroctonus pseudotsugae*, fir engraver *Scolytus ventralis*, western balsam bark beetle *Dryocoetes confusus*, and pine engravers *Curculionidae Scolytinae* have been destroying and killing trees at significant levels. In the early 1990's and 2014, outbreaks occurred that were the largest within the past century, leading to devastating damage to the commercial timber industry with massive economic and ecological impact. Consequently, by not only biologists, but also physical scientists/geographers, social scientists, and policy makers have taken interest in the topic of pest control.³ Moreover, population control of these beetles is quite difficult because of rapid development and broad geographic extent of outbreaks.^{4,5}

The rapid and challenging reproductive nature of the bark beetle population is strongly influenced by environmental factors such as weather and climate, and thus is prone to the effect of global climate change over time. It is thought that shifts in temperature and precipitation patterns associated with climate change are what is driving such large-scale outbreaks. Warming temperatures increase beetle survival and reduce time necessary to complete a generation. The trees themselves also are influenced by climate change to create a more favorable condition for population growth of beetles. In addition, reduced rain weakens the defense of the host-tree.⁵

When approaching population control of the bark beetle, two general techniques have been explored: indirect treatments that increase the resilience to attack and direct measure that target population density. Although indirect methods are more effective and long-lasting, they are also economically demanding and labor intensive. Therefore, direct measures have been more closely studied: these include sanitation harvesting, insecticides, and behavioral chemicals. Insecticides have a disadvantage of posing potential risk of harm to other non-target animals such as fish, birds, pollinators, and other natural enemies of the bark beetle.⁶ Behavioral chemicals have therefore become an attractive area of study for bark beetle control. Moreover, use of these chemicals to consolidate populations for use of insecticides has also been explored. In fact, some of the first insect pheromones isolated in the field of chemical ecology have been from bark beetles.⁵

Silverstein ⁷ categorized the practical applications of pheromones as (a) monitoring and surveying (i.e., used in lures for trapping insects to identify newly infested areas and/or to estimate size of insect populations); (b) luring insects to specific areas for targeted use of

insecticides or pathogens; (c) mass trapping for population suppression; and (d) mating or aggregation disruption (also for population suppression). The general thought was to use pheromones to optimize application of insecticides.

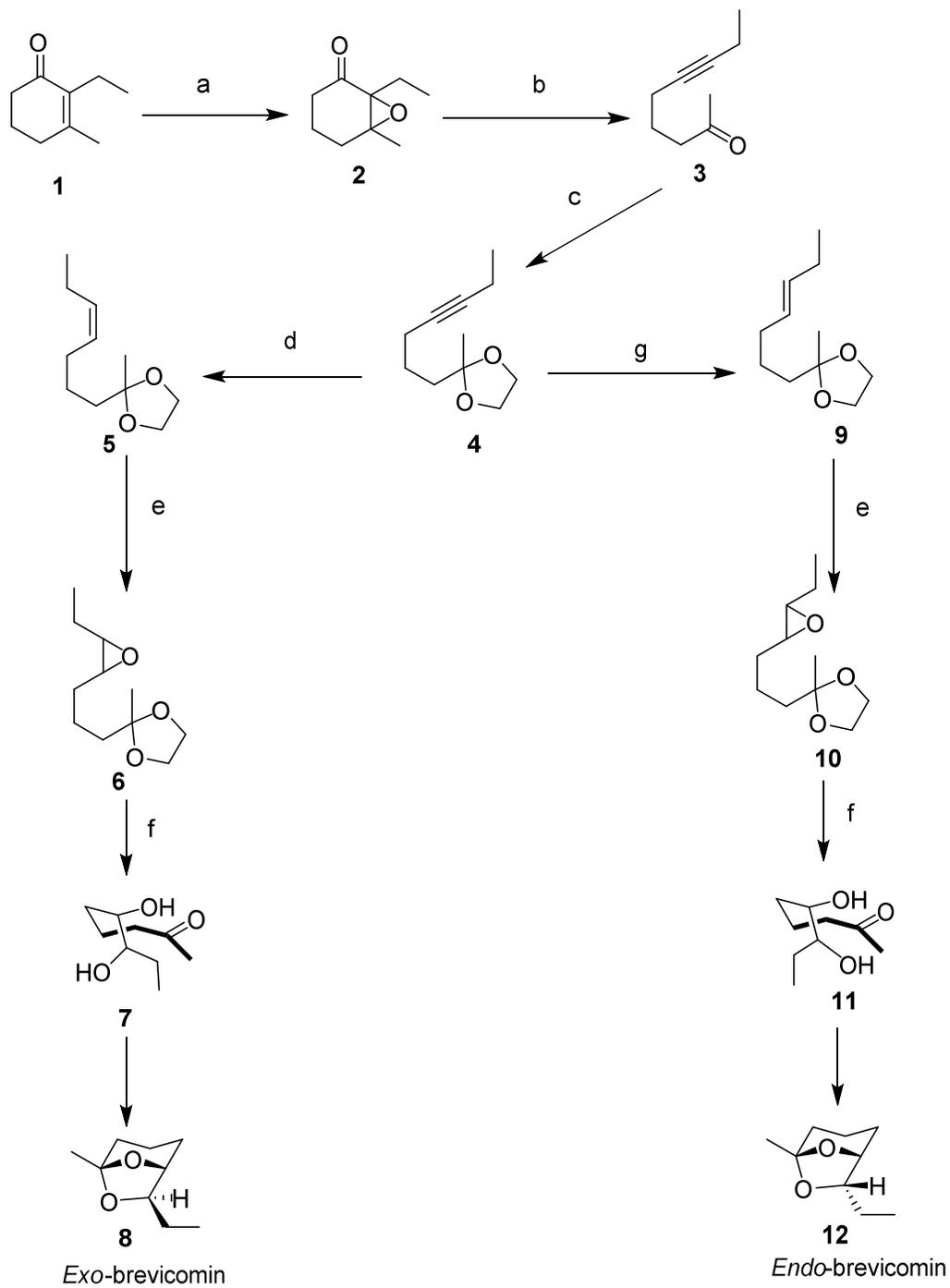
Male and female *D. ponderosae* respond to two α -pinene derivatives, *trans*- and *cis*-verbenol, released by pioneering females.⁸ Both sexes produce *exo*-brevicomin, which is attractive mainly to males at low concentrations but inhibitory at high concentrations.⁹ *Trans*-verbenol increases the attraction of females to *exo*-brevicomin. Attraction is synergized by monoterpenes such as α -pinene, myrcene, and terpinolene. As the number of males increases, concentrations of *trans*- and *cis*-verbenol and host monoterpene co-attractants decline and increasing levels of male-secreted *exo*-brevicomin reduce the attractiveness of the tree to colonizing beetles.⁵

Given that brevicomin is made by both sexes of several species of bark beetles, it has been identified as the principal component of the sex attractant produced and an attractive target for population control. The biologically active enantiomer is (+)-*exo*-brevicomin. Brevicomin is *exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane. A corresponding *endo* isomer has been identified, but is inactive.^{10,11} The *endo* isomer has been reported to be an anti-aggregation pheromone for the southern pine beetle *Dendroctonus frontalis*. Racemic *exo*-brevicomin is naturally produced by these beetles. This ring system is an unusual structure for a natural product and plays an important role in the mating process. The effects of racemic *exo*-brevicomin on *D. ponderosae* include anti-aggregation to attraction, depending on the release rate of the pheromone, as well as on the host and location of the population.

D. ponderosae discriminate between different chiral isomers of *exo*-brevicomin. *Exo*-brevicomin (7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane), was isolated by Silverstein et al.¹² in 1968 as the aggregation pheromone of the western pine beetle, and in 1974 he enabled their biological evaluation. Bioassays revealed that (+)-*exo*-brevicomin, only, is the bioactive against the western pine beetle, and was a possible target for population control¹³.

Many methods for synthesis of brevicomin have been described including achiral^{14,15}, diastereoselective^{16,17} and enantioselective^{17,18} paths. An enantioselective route is the most synthetically demanding but the most advantageous given the beetle's responsiveness to only the (+)-isomer. Navalkishore et al described synthesis of brevicomin yielding diastereomers for brevicomin¹⁹, and Philip et al synthesis both *exo* and *endo* brevicomine but not in a pure form²⁰ (**Scheme 1**). Philip et al. had *exo*-brevicomin **8** prepared in from the acetylenic ketal **4** by a three-step sequence involving reduction of the acetylene with BHS.Me₂S followed by protonolysis to give first the *cis* olefin **5**. Epoxidation of **5** followed by acid-catalyzed cleavage of the resultant *cis* epoxide **6** with concomitant hydrolysis of the ketal function afforded *exo*- brevicomin **8**. No attempt was made to isolate or detect the presumed *threo* keto-diol intermediate **7**. The *exo*-brevicomin thus obtained was contaminated with <1% of the *endo* isomer **12** by VPC analysis. Similarly, *endo*- brevicomin **12** was prepared in three steps from the acetylenic ketal **4** by Na-NH₃ reduction of **4** to the *trans* olefin **9**. Epoxidation of **9** followed by acid hydrolysis gave the intermediate *erythro* keto-diol **11**, which cyclized under the reaction conditions to give *endo*-brevicomin **12**, which was contaminated with <1% of the *exo* isomer **8** by VPC analysis.

Scheme 1. Synthesis of *exo*- and *endo*-brevicomins



a, H_2O , -NaOH/Me ; b, $\text{p-TsNHNH}_2/\text{CH}_2\text{Cl}_2, \text{-HOAc}$;
 c, $\text{HOCH}_2\text{CH}_2\text{OH}$, H^+ ; d, $\text{BH}_3, \text{Me}_2\text{S-ether}$, HOAc ; e,
 $\text{m-ClC}_6\text{H}_4\text{CO}_3\text{H}$; f, 0.1N HClO_4 ; g, Na-NH_3

During our experiments, our goal was to synthesize *exo-brevicom* in a stereoselective and efficient method when compared to what others reported in the past. Here we describe a method for the synthesis of *exo-brevicom* (7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane) using tosylation of a readily available alcohol followed by alkylation and cyclization. This method is unique compared to others reported previously and provides a stereoselective method for *exo-brevicom*. The method proved safe to the extent that it was used during an Organic Chemistry III course with students. It also can be synthesized in a shorter time compared to others that are more time consuming.

Another pheromone that has been of great interest in IPM research is *E-7-methyl-1,6-dioxaspiro[4.5]decane*, a spiroketal known from male ash bark beetles, *Leperisinus varius* (*C. Scolytidae*), and has been found in the frass of the fir bark beetle. Spiroketal is a cyclic ketal (acetal) in which two rings are joined by a single atom, the spiro atom, and the two ketal oxygens flanking the spiro atom each belong to one of the rings.²¹ Spiroketal has gained popularity in research since they are found as subunits of several biologically potent natural products such as polyether antibiotics, the avermectins and milbemycins, potent antiparasitic agents, marine and plant toxins, and a number of insect pheromones.²²

7-Methyl-1,6-dioxaspiro[4.5]decane was first isolated and identified by Francke et al.³⁴ as a pheromone component of the common wasp, *Paravespula vulgaris*. Very recently, it was identified as a component of the volatiles produced by the males of the jack pine tip beetle, *Conophthorus banksianae*, the red pine cone beetle, *C. resinosae*, and the white pine cone beetle, *C. coniperda*. Efficient and cost-effective synthesis of this pheromone has potential benefit in

the IPM industry. In our studies, we examined the use of Claisen condensation reactions to synthesize this pheromone with a goal of achieving a more efficient and timely method that avoids self-condensation with good yield.

In 1881, Rainer Ludwig Claisen discovered that beta-keto esters were produced during the condensation of esters under basic conditions.²⁷ This C-C bond forming reaction has great utility and as such is important in the synthesis of natural products and other fine chemicals. Included in these natural products, potentially are pheromones.

Cross ester condensation has not yet become a promising procedure for the synthesis of ketoesters because of many challenges inherent to the procedure. The selectivity is not as great as in the cross aldol. Furthermore, it seems that there are no general conditions that work in every case, unlike the aldol reaction. Byproducts are frequently formed.

Past literature has shown that using an alkoxide base and under extreme conditions yields primarily self-condensation²⁶ rather than cross coupling. However, changing the molar equivalents of the reagents achieved cross coupling in low yield. Z.Zhang et al.³¹ reported that the addition of LDA (1 eq.) and LiHMDS (1 eq.) yielded cross coupling condensation products with good yield²² or using only LDA (1 eq.)^{32,33}.

This methodology is best employed when only one of the two esters possesses an alpha hydrogen. This is because the enolizable ester will serve as the sole nucleophile, reacting with

the non-enolizable ester electrophile. If both esters possess an alpha hydrogen, then as many as four products can be formed: two products of self-condensation and two of cross condensation.

Another promising future direction in the synthesis of pheromones for use in IPM development is the use of oxidation of primary alcohols. Others have used aldehyde compounds starting from alcohols as intermediates leading to pheromone synthesis. Therefore, efficient oxidation methods for primary alcohols has potential benefit in pheromone synthesis. Pheromone synthesis related to the Pear Barkminer Moth and *Spulerina astaurota* have been described using the transformation of an alcohol to an aldehyde.³⁵

Several methods for the oxidation of primary alcohols have been reported.^{22,23} However, these approaches often use metals or expensive reagents. For example, Jones oxidation technique uses $\text{CrO}_3/\text{H}_2\text{SO}_4$, Corey-Suggs Oxidation utilizes Pyridinium Chlorochromate (PCC), Corey-Schmidt Oxidation uses Pyridinium Dichromate (PDC), and Collins reagent method utilizes $\text{CrO}_3 \cdot 2$ Pyridine. The Swern oxidation^{24,25} has been found to be effective towards the oxidation of alcohols; however, volatile and odorous dimethyl sulfide is formed as a byproduct. Expanding upon previous data, we report a very efficient procedure for the oxidation of primary alcohols to aldehydes or α -chloro aldehydes using inexpensive reactants that are metal free with no over oxidation to the carboxylic acid. Trichloroisocyanuric acid (TCCA) is a commercially available, non-toxic²⁶ reactant used as an oxidizing^{27,28} and chlorinating reagent, and it has many applications in medicinal chemistry.²⁷ Our goal was to establish conditions for the oxidation of primary alcohols that are safe, reliable, and efficient.

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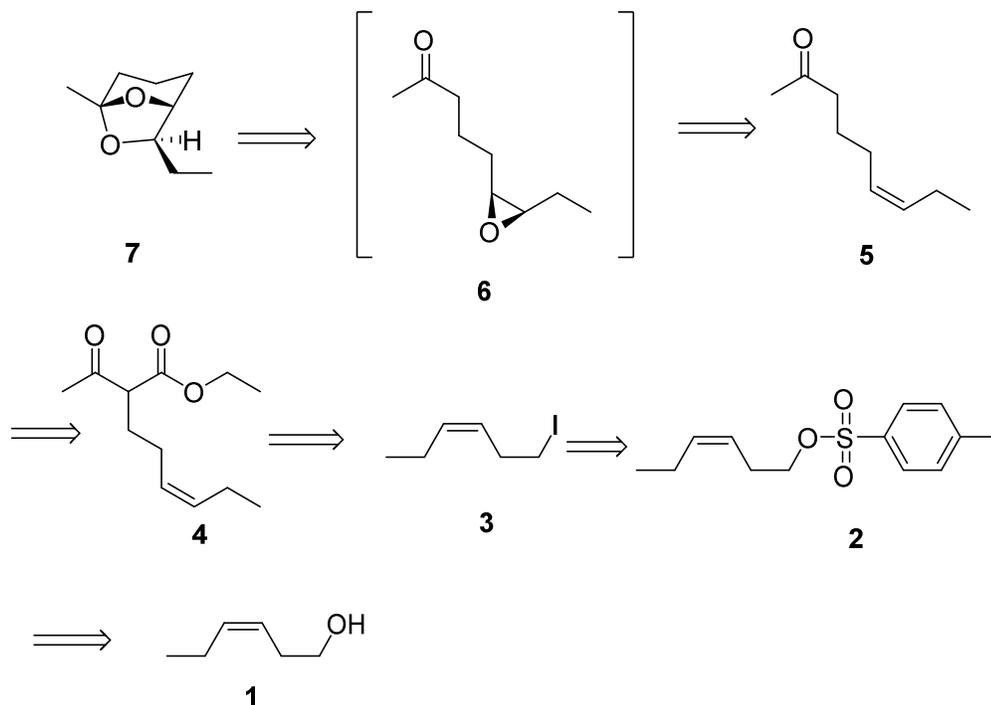
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Chapter 2: Synthesis of *Exo*-7-ethyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane

As shown in the retrosynthetic analysis (**Scheme 2.1**), ketal **7** can be prepared through an acid-catalyzed cyclization of epoxy-ketone **6**. Compound **6** can be formed by the epoxidation of *cis*-alkene **5** using *m*-chloroperoxybenzoic acid (*m*CPBA). There are several reports of alkene epoxidation in the literature, using oxidants such as: molecular oxygen¹, NaClO₃² and peroxy acids³. Ketone **5** can be prepared by saponification and decarboxylation of keto-ester **4**. Intermediate **4** is prepared through the alkylation of ethyl acetoacetate. The alkylation and decarboxylation steps have precedent in the literature^{4,5}. Iodide **3** can be prepared from the corresponding tosylate ester **2** by nucleophilic substitution with the iodide anion (Finkelstein reaction)⁶. Tosylate **2**, in turn, can be prepared by reaction of *cis*-3-hexen-1-ol (leaf alcohol) **1** with *para*-toluenesulfonyl chloride^{7,8}.

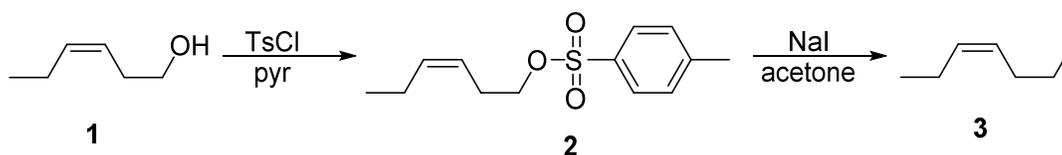
Scheme 2.1. Retrosynthetic analysis for exobrevicomin



Part 1: Tosylation and Nucleophilic Substitution

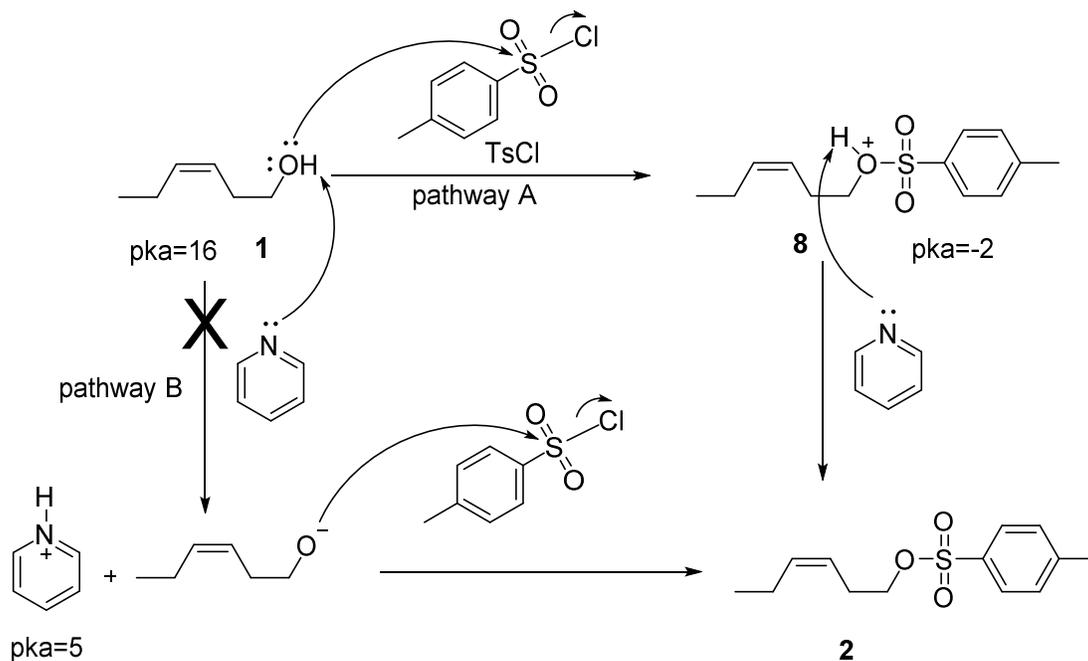
(Z)-Hex-3-en-1-ol **1** was converted to (Z)-hex-3-en-1-yl(4-toluenesulfonate) **2** through reaction with *p*-toluenesulfonyl chloride in a solvent of pyridine. The basic solvent drives the reaction forward through the removal of a product (HCl) from the reaction mixture. Mechanistically, the lone pair of the alcohol oxygen attacks the sulfur of the tosyl chloride, which results in the expulsion of chloride from the sulfur center. Pyridine removes the proton of the original alcohol to complete the transformation to **2** as shown in **Scheme 2.2**.

Scheme 2.2. Preparation of the Iodide of Leaf Alcohol



Pyridine, while basic, is not a strong enough base to deprotonate an alcohol ($\text{pK}_a \sim 16$). This is because the pK_a of the conjugate acid of pyridine, the pyridinium cation, has a pK_a of ~ 5 which is lower than 16. This information allows us to rule out pathway B in **Scheme 2.3**. above, as the operative mechanism. The pK_a of intermediate **8** is ~ -2 , therefore, it can be deprotonated by pyridine, which is consistent with pathway A.

Scheme 2.3. Reaction of alcohol with p-toluene sulfonylchloride



Upon completion of the reaction, the product **2** was extracted into hexane and then washed with acid to remove pyridine. The solvent was removed under reduced pressure. Product **2** was obtained in good yield (88%). The product was characterized by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy in CDCl_3 solvent. The spectra were consistent with the intended product structure.

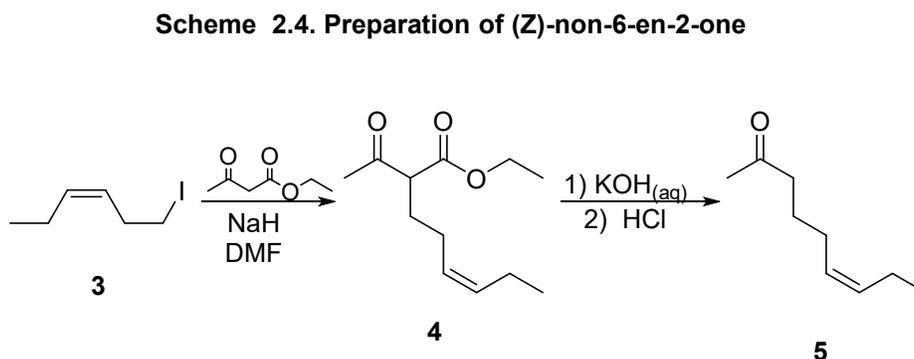
Tosylation reactions are useful because they transform alcohols (which have poor reactivity as leaving groups in $\text{S}_{\text{n}}2$ reactions) to a tosylate ester which is an excellent leaving group in these conditions. The activity of the tosylate ester as a leaving group has led to it being called a “pseudo-halide”. Although the tosylate is a good leaving group, we decided to use the corresponding iodide as the alkylating agent in the synthesis of keto-ester **4** in **Scheme 2.1**. This decision will be explained further in Part 2.

One facile method of obtaining organic iodide compounds is through the Finkelstein reaction. The reaction takes place between an organic halide and an iodide salt in acetone. The solvent plays an important role in driving the reaction forward because the ionic product often has poor solubility in acetone. This causes it to precipitate out of the reaction mixture, driving the equilibrium forward by Le Chatelier's principle.

This substitution reaction was refluxed for half an hour in acetone. Upon completion, vacuum filtration was used to remove the ionic product. The solvent was removed under reduced pressure. As solvent was removed, additional salt precipitated out. This was remedied by adding hexane and water to the mixture. The salt partitioned into the aqueous layer and the organic product partitioned into the hexane. The aqueous layer was discarded with the aid of a separatory funnel. The solvent was removed under reduced pressure, leaving (Z)-1-iodohex-3-ene **3** in good yield (83%). The product was characterized by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy in CDCl_3 solvent. The spectra were consistent with the structure of the intended target.

Part 2: Acetoacetic Ester Synthesis

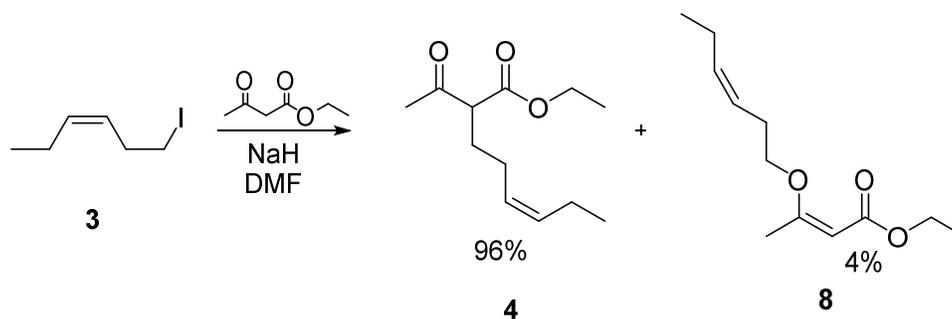
The reaction of (Z)-1-iodohex-3-ene **3** with ethyl acetoacetate in the presence of sodium hydride afforded ethyl (5Z)-2-acetyl-oct-5-enoate **4** (**Scheme 2.4**). Mechanistically, sodium hydride abstracts a proton that is alpha to both the ketone and ester in ethyl acetoacetate. This generates a resonance stabilized carbanion enolate which will serve as the nucleophile in a substitution with the iodide group of **3**. We have found that the regiochemistry of this reaction depends strongly on the nature of the leaving group in the electrophile. When the tosylate ester **2** was used as the alkylating agent in the reaction above, the intended product **4** only comprised 46% of the product mixture. The remaining 54% of the product mixture was enol ether **8** in **Scheme 2.5**. However, when the iodide **3** was used instead, the intended keto-ester **4** was found to comprise 96% of the product mixture, while the proportion of enol ether byproduct was decreased to 4%.



Formation of the intended keto-ester **4** is a result of C-alkylation, while the enol ether is formed from the O-alkylation pathway. The enolate of ethyl acetoacetate is a bidentate nucleophile where the negative charge exists on the alpha carbon and the oxygen of the ketone in the different resonance forms. One explanation for the regiochemical course of this reaction lies in

the Hard-Soft Theory of Acids and Bases. Hard leaving groups such as the tosylate promote O-alkylation and softer leaving groups like the iodide result in C-alkylation.

Scheme 2.5. Reaction of alkyl iodide with ethyl acetoacetate



After alkylation, the product **4** was converted to a carboxylic acid through saponification using potassium hydroxide. The carboxylic acid functionality was removed through an acidic decarboxylation step to give (Z)-non-6-en-2-one **5** the desired product in **Table 2.1**.

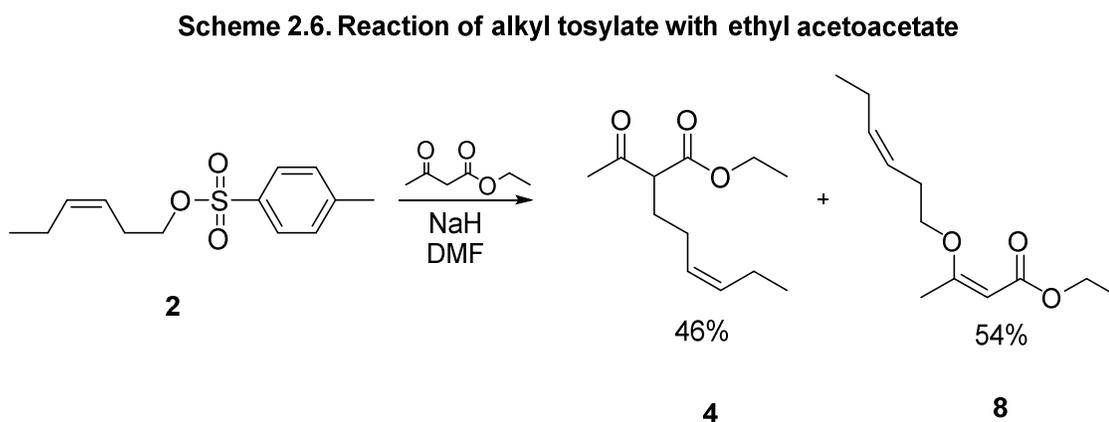
The alkylation reaction was heated at 90 °C for two hours. The product was extracted into hexane and the solvent was removed under reduced pressure. Aqueous potassium hydroxide 6 M was refluxed with the keto-ester **4** for 30 minutes and then 6 M HCl was added. The mixture was heated at reflux until the generation of carbon dioxide had ceased. The product was extracted into hexane and the solvent was removed under reduced pressure. The crude ketone **5** was purified by vacuum distillation. The pure ketone **5** was obtained in a yield of 54 %. We noticed that increasing the time of reflux of tosylate compound **2** with ethyl acetoacetate tended to result in better yields as when we refluxed for 2hr we got very low yield 20%. By increasing

the time of refluxing we got better yield. The yield was 50%, 70%, and 72% after 4, 6, and 8 hours of reflux time, respectively (**Table 2.1**).

Time of Reflux (hours)	Percent Yield of ketone
2	20
4	50
6	70
8	72

Table 2.1. Dependence of yield on the time of refluxing tosylate compound with ethyl acetoacetate

The product was characterized by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy in CDCl_3 solvent. The spectra were consistent with the structure of the intended target.

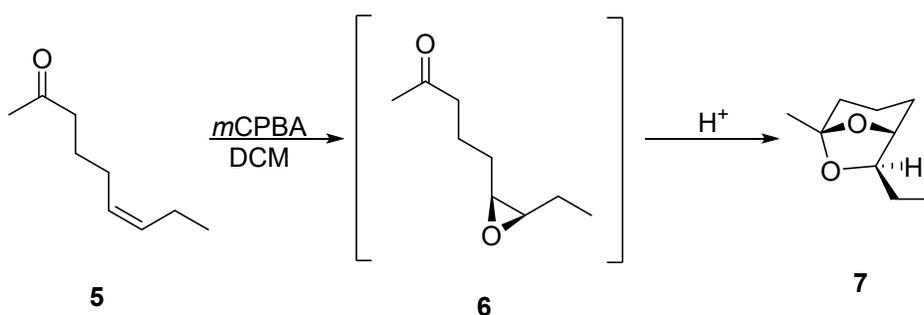


Our results suggested that converting alkyl tosylate to alkyl iodide followed by an alkylation step with ethyl acetoacetate and increasing the time of refluxing is superior than reacting alkyl tosylate with ethylacetoacetate due to the formation of by product.

Part 3: Cyclization

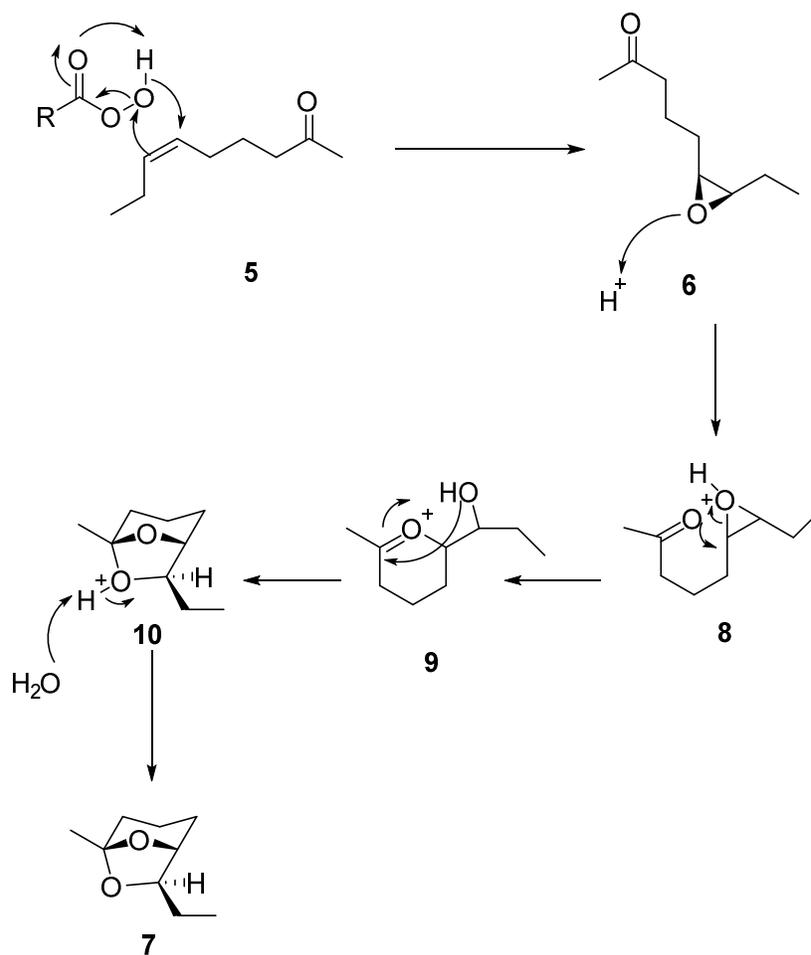
The reaction of (Z)-non-6-en-2-one **5** with *m*-chloroperoxybenzoic acid forms (6*S*,7*R*)-6,7-epoxy-nonan-2-one **6** (not a single enantiomer). One advantage of this reaction is its stereospecificity. A *cis* alkene yields a *cis* epoxide and vice-versa³. The mechanism is depicted in **Scheme 2.8**.

Scheme 2.7. Epoxidation and cyclization to *exo*-brevicomin



Upon addition of *p*-toluenesulfonic acid, the cyclization occurred to form *exo*-brevicomin **7**. The solvent, DCM was removed by fractional distillation at atmospheric pressure rather than simple distillation at reduced pressure in order to limit the loss of the volatile ketal product. The crude product was purified by vacuum distillation, distilling over at 75 °C, 5 mm Hg and obtained in a yield of 41%. The product was characterized by ¹H-NMR and ¹³C-NMR spectroscopy in CDCl₃ solvent. The spectra were consistent with the structure of the intended target.

Scheme 2.8. Mechanism of epoxidation and cyclization for *exo*-brevicomine synthesis



Discussion and Results

The goal of this project was to synthesize *exo*-7-ethyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane **7**.

In the transformation of **1** to **2**, the $^1\text{H-NMR}$ showed an appearance of a singlet peak at δ 2.40 which was due to the methyl group on the tosylate and two doublets at δ 7.35 and δ 7.75 located on the aromatic ring of the tosylate. The $^{13}\text{C-NMR}$ data is also consistent with this analysis.

In the transformation of **2** to **3**, the $^1\text{H-NMR}$ showed a disappearance of the singlet peak at δ 2.40 and a disappearance of the two doublet peaks at δ 7.35 and δ 7.75 of **2**. The $^{13}\text{C-NMR}$ data is also consistent with this analysis.

In the transformation of **3** to **5** the $^1\text{H-NMR}$ showed the appearance of a singlet peak at δ 2.12 which is due to the methyl ketone of **5**. The $^{13}\text{C-NMR}$ data revealed a peak at 209.05 which is consistent with a carbonyl carbon of a ketone.

In the final transformation of **5** to **7** the $^{13}\text{C-NMR}$ data showed a disappearance of the peak at 209.05, which is consistent with the transformation of a ketone into a ketal.

Experimental:

NMR data were obtained on a 600 MHz Bruker Avance spectrometer in CDCl₃.

Hexane was used directly from the bottle.

(Z)-hex-3-en-1-yl(4-toluenesulfonate) (2)

To a 250 mL round-bottom flask, para-toluenesulfonyl chloride (25 g, 129 mmol), pyridine (75 mL, 932 mmol) and a magnetic stir bar was added. The mixture was stirred until the para-toluenesulfonyl chloride was completely dissolved. The mixture was cooled on an ice-water bath until the temperature of the mixture was less than 5° C. *Cis*-3-hexen-1-ol (10 g, 11.79 mL, 100 mmol) was added to the flask slowly. Stirring was resumed upon completion of the addition. The ice bath was removed and an oven-dried drying tube was fit to the apparatus. The mixture was allowed to stir at room temperature for 2 hours. To quench the reaction, 75 mL water was added and allowed to stir for fifteen minutes. The mixture was transferred to a 250 mL separatory funnel. The product was extracted into 40 mL hexane a total of three times. The aqueous layer was discarded. The combined organic extracts were washed with 40 mL of 4 M HCl a total of three times. The combined organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure to give **2** as a pinkish-brown viscous oil in a yield of 88%.

¹H NMR (600MHz, CDCl₃): δ 7.75(d), δ 7.35(d), δ 5.45(q), δ 5.67(q), δ 3.97(t), δ 2.40(s), δ 2.35(q), δ 1.95(qui), δ 0.89(t)

¹³CNMR: δ 144.68, δ 135.35, δ 133.24, δ 129.78, δ 127.81, δ 122.146, δ 69.80, δ 26.94, δ 21.48, δ 20.52, δ 13.98

(Z)-1-iodohex-3-ene (3)

To a 250 mL round-bottom flask, sodium iodide (23 g, 150 mmol), acetone (120 mL), (22g, 88 mmol) of compound **2**, a magnetic stir bar, a few boiling chips were added. The mixture was stirred and refluxed for thirty minutes. Upon completion, the reaction mixture was cooled to below 10 °C and filtered. The solids were washed with an additional 60 mL of acetone until the pink color was washed away, leaving a pearlescent white solid. The solvent was removed under reduced pressure. Additional salt precipitated out. The crude product was combined with hexane and water and added to a separatory funnel. The aqueous layer was extracted with 20 mL hexane a total of three times. The combined organic extracts were dried by shaking with brine, and then further with solid magnesium sulfate. The solvent was removed under reduced pressure to afford **3** as a pink oil in a yield of 83%.

¹H NMR (600MHz, CDCl₃): δ 5.53(q), δ 5.28(q), δ 3.13(t), δ 2.63(q), δ 2.05(q), δ 0.98(t)

¹³CNMR: δ 134.27, δ 127.16, δ 31.42, δ 20.74, δ 14.13, δ 5.51

(Z)-non-6-en-2-one (5)

To a 500 mL three neck round-bottom flask, sodium hydride (4.19 g, 105 mmol), DMF (35 mL) and a magnetic stir bar were added. A mineral oil bubbler was fit to one of the necks of the flask and the mixture was stirred. Ethyl acetoacetate, 3 M in DMF, was added slowly with the aid of an addition funnel. Hydrogen gas was evolved. Compound **3** was added slowly with the aid of an addition funnel as a 2 M solution in DMF. A condenser fit with an oven-dried drying tube was connected to the flask. The flask was heated to 90 °C for two hours with the aid of a sand bath. Upon completion, the reaction mixture was extracted into hexane (25 mL) a total of three

times. The combined organic extracts were washed with 1 M HCl (60 mL) a total of three times. The combined organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure.

To a 500 mL three-neck round-bottom flask equipped with a condenser, compound **4** and 3 M aqueous potassium hydroxide (75 mL) were added. The mixture was refluxed for thirty minutes. The apparatus was fit for simple distillation and the ethanol was distilled off. The flask was placed on ice and 4 M HCl (100 mL) was added slowly. A mineral oil bubbler was fit to the apparatus. The mixture was refluxed until the production of carbon dioxide had ceased. The mixture was transferred to a 250 mL separatory funnel and extracted into hexane (25 mL) a total of three times. The combined organic extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure to afford **5** as a colorless oil in a yield of 54%.

$^1\text{H NMR}$ (600MHz, CDCl_3): δ 5.40(q), δ 5.27(q), δ 2.42(t), δ 2.12(s), δ 2.01(q), δ 1.64(qui), δ 2.04(q), δ 0.95(t)

$^{13}\text{CNMR}$: δ 209.05, δ 132.65, δ 128.02, δ 43.03, δ 29.88, δ 26.37, δ 23.72, δ 20.51, δ 14.30

GC-FID data: only one peak appears at retention time 13.108

Exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (7)

To a 250 mL round-bottom flask, compound **6** (15 g, 100 mmol), 100 mL DCM and a stir bar was added. The mixture was stirred until **6** was completely dissolved and then *m*CPBA (23.5 g, 105 mmol) was added. The flask was fit with an oven-dried drying tube and the mixture was stirred at room temperature for an hour. *Para*-toluenesulfonic acid monohydrate (0.47 g, 2.5 mmol) was added and the mixture was stirred for 45 minutes at room temperature. The mixture

was vacuum filtered and transferred to a 250 mL separatory funnel. The product was washed with saturated sodium sulfite (30 mL) twice, 1 M KOH (40 ml) three times and brine (20 mL) once and then dried with magnesium sulfate. Starch-iodide paper was used to test the product for unreacted *m*CPBA. If any oxidant remained, then the washing steps were repeated. The solvent was fractionally distilled to yield the crude product. The crude product was purified by vacuum distillation, distilling over at 75 °C, 5 mm Hg. The product was obtained as a fragrant colorless oil in a yield of 41%.

¹H NMR (600MHz, CDCl₃) δ 4.10(t), δ 3.91(t), δ 1.90-1.81(m), δ 1.79-1.73(m), δ 1.61-1.54(m), δ 1.51-1.41(m), δ 1.39(s), δ 0.88(t)

¹³CNMR δ 107.65, δ 81.13, δ 78.26, δ 34.93, δ 28.54, δ 27.94, δ 25.01, δ 17.16, δ 9.73

GC-FID data: one peak appear at retention time 12.310 min

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Chapter 3: Efficient Oxidation of Primary Alcohols

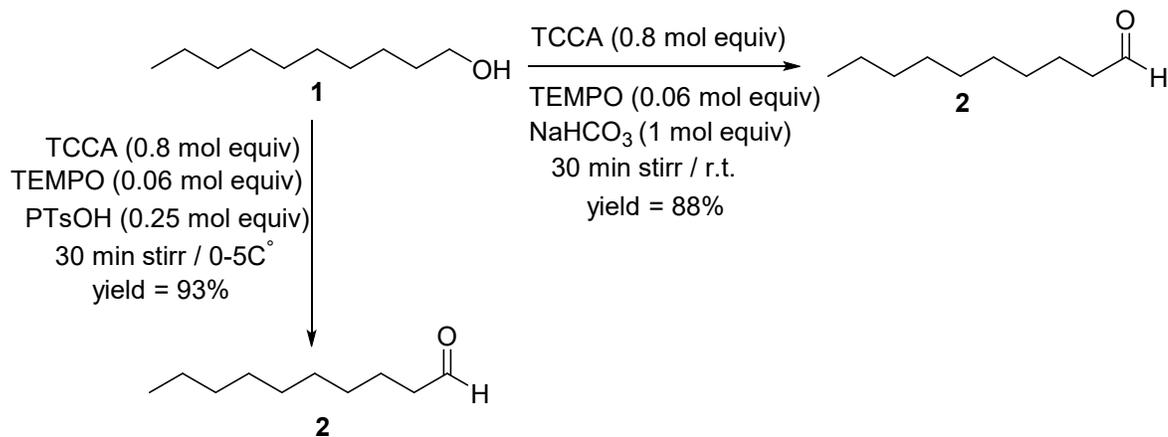
Previously reported oxidation methodologies have used TCCA and TEMPO as primary reagents within the reactions. However, results have been variable and without consistency.³ In fact, in our lab, we attempted to reproduce the results of experiments published in the past without success. Attempts were made using stoichiometric catalytic oxidation conditions from the literature with unreliable outcomes using different alcohols such Citronellol, 6-chlorohexanol, and decanol. These attempts resulted in a mixture between aldehyde and alpha chloroaldehyde. We persisted in our attempts to create conditions that would create efficient oxidation with reliable, reproducible results. Here we report specific conditions under which we can obtain aldehydes and α -chloroaldehydes in good yield using inexpensive, non-toxic¹ materials that are metal free²⁻⁴ without over oxidation to the carboxylic acid. Our oxidation method using TCCA and TEMPO is environmentally less toxic than other oxidation methods previously reported that depend on CrO_3 .

In 1975, Cella et al. demonstrated⁵ that alcohols can be oxidized to carboxylic acids by treatment with m-chloroperbenzoic acid in the presence of a catalytic amount of TEMPO. While in all TEMPO-mediated oxidations of primary alcohols to carboxylic acids oxoammonium salts are the primary oxidants for the transformation of alcohols into aldehydes, the subsequent oxidation of aldehydes to carboxylic acids may sometimes be affected by the oxidant present in excess rather than by the oxoammonium salts. Sometimes the secondary oxidant for the transformation of alcohols into aldehydes is the primary oxidant for the oxidation of aldehydes to carboxylic acids.

Firstly, we attempted the oxidation reaction of decanol **1** with trichloroisocyanuric acid (TCCA) and 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO) in the presence of sodium bicarbonate or p-toluenesulfonic acid to afford the corresponding aldehyde decanal **2**. (**Scheme 3.1**)

Secondly, the direct conversion of a primary alcohol to the corresponding alpha-chloroaldehyde **3** using TCCA and TEMPO was executed. (**Scheme 3.2**)

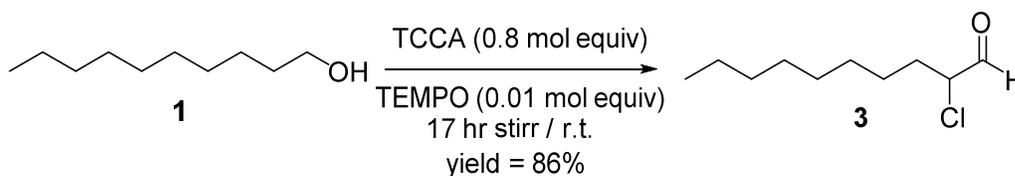
Scheme 3.1. Direct conversion of alcohol to the corresponding aldehyde



These reactions were used in an effort to create conditions for the efficient oxidation of decanol **1** to decanal **2** without overoxidation to the corresponding acid. Constituents in different amounts added at different times were trialed with decanol **1** (Figure I). We found that the reaction of decanol with TCCA 0.8 equiv. at one min followed by the addition of TEMPO 0.06 equiv at room temperature yielded the corresponding aldehyde in 71% yield. The same reaction using 0.01 equiv of TEMPO to decanal **2** yielded in 86% yield, and the yield when using 1 equiv of TCCA added at 20 min at 0-5 °C was 56%.

Certain trials performed under the acidic and basic conditions produced decanal **2** in better yield. The reaction of decanol with TCCA 0.8 equiv added at one min, then TEMPO (0.06 equiv) at 0°C followed by adding sodium bicarbonate yielded the corresponding aldehyde at 88%. A similar reaction but with the addition of TCCA at 20 min and p-TSOH at 0-5 °C yielded decanal at 93% and pure. (Scheme 3.1)

Scheme 3.2. Direct conversion of alcohol to the corresponding α -Chloro aldehyde



Other trials performed, gave a mix of decanal **2** and α -chlorodecanal **3**. When the reaction of decanol with TCCA 0.8 equiv added at 20 min with TEMPO 0.03 equiv at 0-5 °C for 30 min, the mixture of the corresponding aldehyde and α -chloroaldehyde yielded at 17%. Using 0.06 equiv of TEMPO, the mix but was 86% yield, but using 0.01 equiv of TEMPO for 17hr α -chlorodecanal was the main product yielded.

Other trials that were of less value are shown in **Table 3.1**.

TCCA	TEMPO	NaHCO ₃	PTSOH	HCl	Condition	Aldehyde	Yield
0.8 eq. 1 min	0.06 eq.	0	0	washing	r.t/30min	decanal	71%
1mol eq. 20min	0.06 eq.	0	0	washing	0-5 °C/30 min	decanal	56%
0.8 eq. 1 min	0.06 eq.	1 mol eq.	0	washing	r.t/30min	decanal	88%
0.8 eq. 20 min	0.06 eq.	washing	0.25 eq.	0	0-5 °C /30 min	decanal	93%
1mol eq. 25min	0.01 eq.	washing	0	0	0-5 °C /30 min	decanal	86%
0.8 eq. 20 min	0.03 eq.	0	0	washing	0-5 °C /30 min	mix (alpha chloro major)	17%
0.8 eq. 20min	0.01 eq.	washing	0	washing	r.t/17 hr	alpha chloro main product	86%
0.8 eq. 20 min	0.06 eq.	0	0	washing	0-5 °C /30 min	mix (alpha chloro major)	86%
0.8 eq. 1 5min	0.06 eq.	0	0	washing	r.t/30min	mix(decanal and alpha chloro)	26%
0.8 eq. 20min	0.09 eq.	0	0	washing	r.t/30min	mix(decanal and alpha chloro)	32%
1mol eq. 20min	0.01 eq.	0	0	washing	r.t/60min	mix(decanal and alpha chloro)	69%
1mol eq. 20min	0.01 eq.	washing	0	washing	r.t/30min	mix(decanal and alpha chloro)	74%

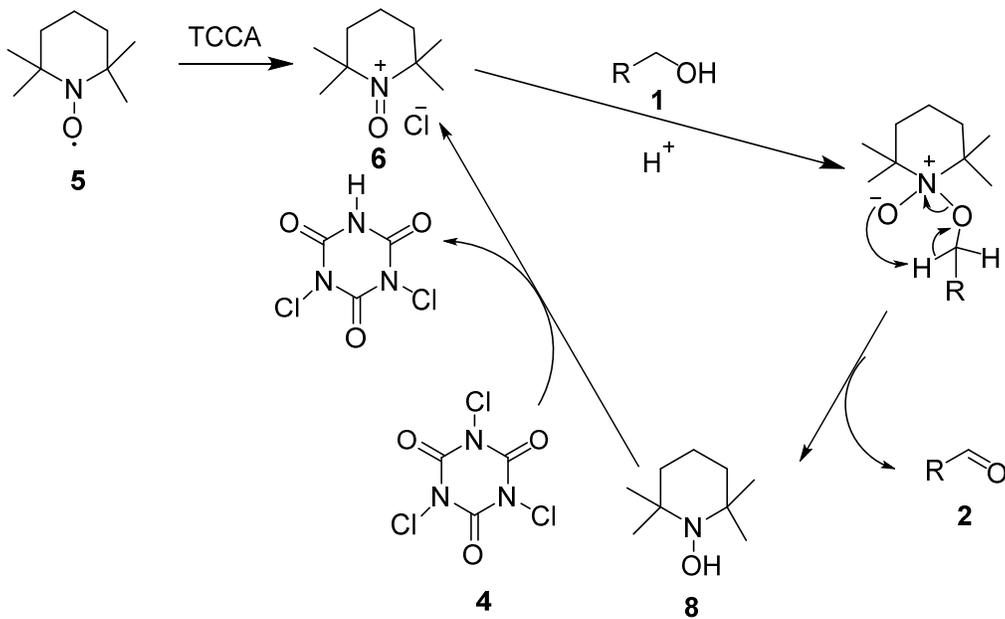
Table 3.1. Trials of oxidation

Discussion

Based on the experiments described above, we found a good yield of aldehyde with TEMPO as the primary oxidant. TEMPO is a stable radical that is further oxidized in the reaction to the oxoammonium salt and operates as the primary oxidant. Moreover, conditions which gave better yield were low temperature and irrespective duration of addition. When TCCA was used as the primary oxidant, alpha-chloroaldehyde was obtained in a good yield under condition of room temperature and long of duration.

The experimental data are consistent with the mechanism shown below (**Scheme 3.3**), in which TCCA **4** as a secondary oxidant transforms TEMPO **5** to an oxoammonium salt **6** that works as the primary oxidant, transforming the alcohol **1** into the corresponding aldehyde **2**. This results in the formation of a hydroxylamine **8** that is oxidized to a TEMPO radical, thus completing the catalytic cycle.⁶

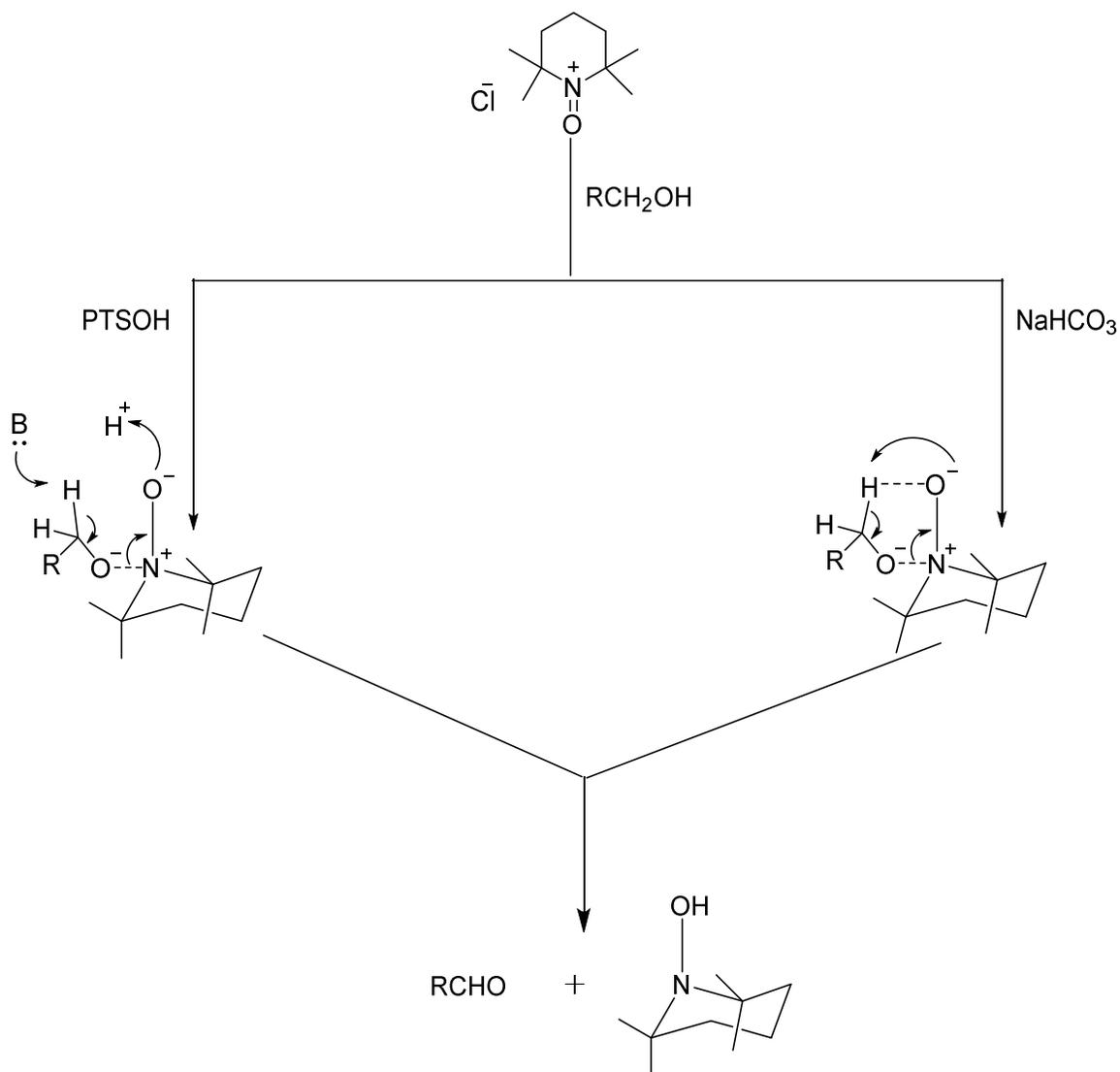
Scheme 3.3. Mechanism of synthesis aldehyde from alcohol



The oxidation of primary alcohols with oxoammonium salts can work either via a compact five-membered transition state under basic conditions or via a linear transition state under acidic conditions, as shown in **Scheme 3.4**. Under basic conditions there is a compact and sterically demanding five membered transition state for the oxidation of alcohols with oxoammonium salts, while under acidic conditions a less sterically demanding linear transition state. This results in faster oxidation of primary alcohols to aldehydes and more purification.

We also found that TCCA must be added slowly (over the period of one minute) when the aldehyde desired is under basic conditions. The reaction mixture is neutralized by the addition of hydrochloric acid under basic conditions and sodium bicarbonate under acidic conditions.

Scheme 3.4. Transition state in the presence of sodium bicarbonate and p-toluenesulfonic acid



Temperature was also found to have a significant impact on yield. The rate of oxidization of primary alcohols to aldehydes decrease by increasing the temperature, due to the decomposition of oxoammonium salts, which are very stable at 0 °C, but decompose very quickly at high temperature. It was essential that the system be between 0 – 5 °C before TCCA was added.

Alpha chloroaldehyde was the main product in the absence of acidic or basic conditions. Under these circumstances, TCCA and oxoammonium salt compete to oxidize the alcohol first. If

TCCA is the primary oxidant, alpha-chloro aldehyde will be the product, whereas if TEMPO is the primary oxidant, the aldehyde will be the product. In this case it is theorized that the primary oxidants, which consist of oxoammonium salts, are very quickly decomposed at room temperature, leading to an actual decrease of oxidation rate with increasing temperature. Therefore, the reaction temperature must be kept close to 0 °C during the mixing of the reagents as soon as oxoammonium salts are generated. This may demand the slow addition of stoichiometric TCCA, which serves as the secondary oxidant. TCCA was present in catalytic quantities and, therefore, was less able to produce undesired chlorination products. The stoichiometric quantity of TEMPO acted as scavenger of chlorine.⁷

A trace quantity of 1 mol% of TEMPO is normally enough for an efficient oxidation, although because of the low price of TEMPO and its easy elimination during the workup, the use of ca. 4–10 mol% is common. Boger et al. found that a quantity as high as 1–1.5 equivalents of TEMPO is sometimes used to eliminate unwanted chlorination products. However, this high concentration was not trialed in our experiments.^{7,8}

In the optimization of this reaction it was found that 0.06 equivalents of TEMPO were necessary to obtain the desired oxidation product. If a catalytic amount (ca. 0.01 equivalents) of TEMPO was employed, alpha chloroaldehyde was isolated as the major product. Presumably the TEMPO scavenges any chlorine which is liberated during the reaction that afforded aldehyde.⁷

With regard to future directions, we think that the oxidation of primary alcohols to aldehydes under these conditions can be selectively achieved for the oxidation of primary alcohols versus secondary ones.⁹ This selectivity is the result of the steric hindrance around the oxoammonium

functionality in the oxoammonium salts derived from TEMPO-like radicals, resulting in a much easier attack by the relatively less hindered primary alcohols.

Decanal **2** under basic and acidic conditions was characterized by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy in a CDCl_3 solvent. The spectra were consistent with the intended product structure. In $^1\text{H-NMR}$ there is a specific peak for the aldehyde group which appeared as triplet at δ 9.75 due to the presence of a methylene group beside it that appeared at δ 2.40. In $^{13}\text{C-NMR}$ there are two specific peaks at δ 202.86, δ 43.89 for aldehyde and CH_2 group respectively.

Alpha chloro decanal **3** was characterized by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy in a CDCl_3 solvent. The spectra were consistent with the intended product structure. In $^1\text{H-NMR}$ there is a specific peak for the aldehyde group at δ 9.46 which appeared as doublet due to the presence of methylene group beside to it that appeared at δ 4.14. In $^{13}\text{C-NMR}$ there are two specific peaks at δ 195.31, δ 63.98 for aldehyde and CH group respectively.

Experimental:

NMR data were obtained on 600 MHz Bruker Avance spectrometer in CDCl₃.

Dichloromethane was used directly from the bottle.

Decanal (2) under (Basic Conditions)

TCCA (0.46 g, 1.97mmol) was added portion wise at one minute to a suspension of decanol (0.41 g, 2.59mmol), dichloromethane (13 mL) and sodium bicarbonate (0.21g, 2.49mmol) at 0 °C. TEMPO (0.027g, 1.17mmol) was added in one shot. The mixture was stirred at room temperature for 30 min. The organic layer was washed with 1N HCl, and brine. The organic layer was dried with MgSO₄, and the solvent was removed under reduced pressure. the yield was 88%.

¹H NMR (600MHz, CDCl₃): δ 9.75 (1H, t), δ 2.40 (2H,t), δ 1.62 (2H, quin), δ 1.30 (12H,m), δ 0.87 (3H,t).

¹³CNMR: δ 202.86, δ 43.89, δ 31.82, δ 29.36, δ 29.33, δ 29.21, δ 29.15, δ 22.62, δ 22.07, δ 14.04.

Decanal (2) (under acidic Conditions)

TCCA (0.46 g, 1.97mmol) was added portion wise over a period 15-25 min to a solution of decanol (0.41 g, 2.59mmol) and dichloromethane (13 ml) at 0 °C. TEMPO (0.027g, 1.17mmol) was added in one shot and then p-toluene sulfonic acid (0.11g, 0.68mmol). The mixture was stirred at 0-5 °C for 30 min. The organic layer was washed with 5% NaHCO₃, and brine. The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure. the yield was 93%.

¹H NMR (600MHz, CDCl₃): δ 9.77(1H, t), δ 2.41(2H,t), δ 1.69 (2H, quin), δ 1.30 (12H,m), δ 0.89 (3H, t).

^{13}C NMR: δ 202.88, δ 43.96, δ 31.88, δ 29.41, δ 29.38, δ 29.26, δ 29.20, δ 22.68, δ 22.13, δ 14.10.

α -Chlorodecanal (3)

TCCA (0.46 g, 1.97mmol) was added portion wise over a period 15-25 min to a solution of decanol (0.41 g, 2.59mmol) and dichloromethane (20 ml) at 0C° . TEMPO (0.0057g, 0.03mmol) was added in one shot. The mixture was stirred at room temperature for 17 hours. The organic layer was washed with 5% NaHCO_3 . 1N HCl and brine. The organic layer was dried with MgSO_4 and the solvent was removed under reduced pressure. the yield was 86%.

^1H NMR (600MHz, CDCl_3): δ 9.46(1H, d), δ 4.14 (1H,t), δ 1.85 (2H, m), δ 1.25 (12H,m), δ 0.86 (3H, t).

^{13}C NMR: δ 195.31, δ 63.98, δ 32.06, δ 31.77, δ 29.24, δ 29.11, δ 28.92, δ 25.53, δ 22.61, δ 14.04.

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Chapter 4: Efficient Claisen Condensation Methodology

Another pheromone of interest in IPM research is 7-Methyl-1,6-dioxaspiro[4.5]decane **11** which was first isolated and identified by Francke et al. as a pheromone component of the common wasp, a pest known to hinder the agriculture industry.¹ Efficient and cost-effective synthesis of this pheromone has potential benefit in the IPM industry. In our studies, we examined the use of Claisen condensation reactions to synthesize this pheromone and found the method to be efficient and potentially more cost-effective than other previously described methods.

Cross ester condensation has not yet become a promising procedure for the synthesis of ketoesters because of many challenges inherent to the procedure. The selectivity is not as great as in the cross aldol. Furthermore, it seems that there are no general conditions that work in every case, unlike the aldol reaction. Byproducts are frequently formed.

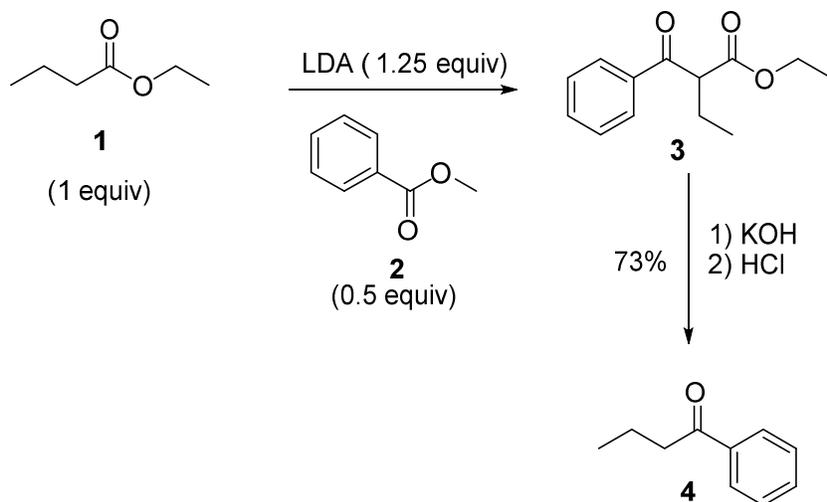
Phase I: Optimizing conditions for Claisen Condensation

Herein we report efficient directed Claisen condensations^{2,3} (methyl phenylacetate or methyl benzoate with ethyl butyrate) with yields of 71% and 73% respectively in addition to others mentioned below. The resulting ketoesters can be converted to butyrophenone derivatives through saponification and decarboxylation of these butyrophenone derivatives and are useful intermediates in the synthesis of haloperidol⁴ and other anti-psychotics⁵. More importantly, we were able to use them to further the field of pheromone synthesis.

Herein we synthesized 1-phenyl-1-butanone **4** and 1-phenyl-2-pentanone **7**. A two-step reaction has produced **4** in 73% yield and **7** in 71% yield.

As shown in **Scheme 4.1**, addition of ethyl butyrate **1** (1 eq.) to a solution of Lithium diisopropylamide (LDA) (1.05 equiv) in THF at $-60\text{ }^{\circ}\text{C}$, followed by the addition of a solution of methyl benzoate **2** (0.5 mol) at $-30\text{ }^{\circ}\text{C}$, and finally, addition of LDA (0.25 equiv) in THF leads to complete conversion within 2 hours at r.t. and afforded the crude product, which was saponified and decarboxylated to give the desired ketone **4** in high yield (73%) (entry 1) shown in **Table 4.1**.

Scheme 4.1. Crossed reaction with non-enolizable phenyl ester



However, the reaction of ethyl butyrate (1 mol) and methyl benzoate (1 mol) in the presence of only 1.05 mole of LDA produced 25% yield (entry 3). Also, when less than a full second equivalent (0.25 eq) of LDA was added to the mixture, the yield was 30% (entry 2), and the addition of 1.05 equivalent of LDA afforded mixed ketones (entry 4).

After condensation, the keto-ester **3** was converted to a carboxylic acid through saponification using potassium hydroxide. The carboxylic acid functionality was removed through an acidic decarboxylation step to give 1-phenyl-1-butanone **4**, the desired product in Scheme I. The condensation reaction was stirred at room temperature for two hours. The product was then extracted into hexane and the solvent was removed under reduced pressure. Aqueous potassium hydroxide 1.98 M was refluxed with keto-ester **3** for one hour and then 4N HCl was added. The mixture was heated at reflux until the generation of carbon dioxide had ceased. The product was extracted into hexane and the solvent was removed under reduced pressure. The crude ketone 1-phenyl-1-butanone **4** was obtained in a yield of 73 %. The product was characterized by ¹H-NMR and ¹³C-NMR spectroscopy in a CDCl₃ solvent. The spectra were consistent with the intended product structure as there is the specific peak in ¹³C- NMR of a ketone that appeared at δ 200.42.

The order of addition in Claisen condensation reaction was found to be important. The enolizable ester must be added to 1.05 equivalent of the base at low temperatures (-60 °C). Then, the non-enolizable ester is added (-30 °C). Finally, an additional equivalent of base is added.

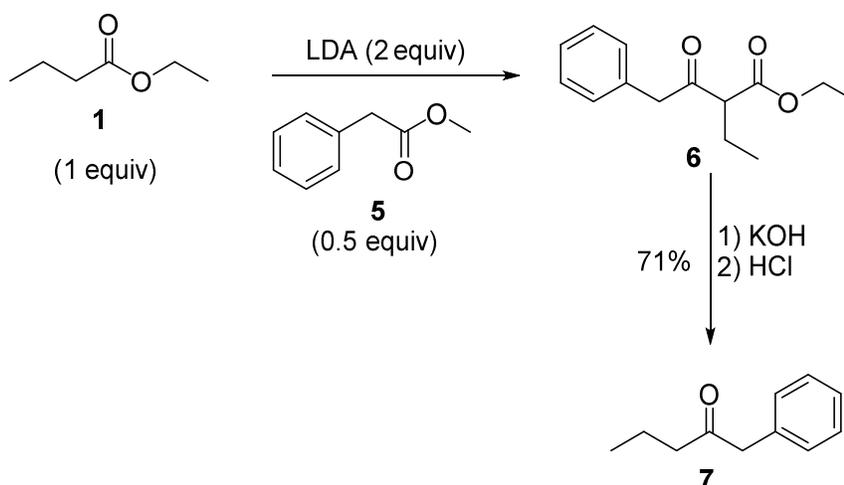
Entry	second ester/mole	second equiv of LDA	product	Yield
1	Me bezoate/0.5	0.25 equiv	ketone 4	73%
2	Me bezoate/1	0.25mole	ketone 4	30%
3	Me bezoate/1	None	ketone 4	25%
4	Me bezoate/1	1.05 equiv	mixed ketone	95%
5	Me Ph acetate/ 0.5	1.05 equiv	Ketone 7	71%
6	Me Ph acetate/ 0.5	None	Ketone 7	20%
7	Me Ph acetate*/ 1	1.05 equiv	mixed ketone	32%

* Me Ph acetate was added at 0°C

Table 4.1. Trials of Cross Condensation

As shown in **Scheme 4.2**, addition of ethyl butyrate **1** (1 mol) to a solution of LDA (1.05 equiv) in THF at $-60\text{ }^{\circ}\text{C}$, followed by the addition of a solution of methyl phenylacetate **5** (0.5 mol) at $-30\text{ }^{\circ}\text{C}$, and finally, addition of LDA (1.05 equiv) in THF, led to complete conversion within 2 hours at r.t. to give the desired ketone **7** in high yield (71%) (entry 5).

Scheme 4.2. Directed Claisen reaction with enolizable methyl ester



However, the reaction of ethyl butyrate (1 mol) and methyl phenylacetate (0.5 mol) in the presence of 1.05 equiv of LDA and in the absence of second addition of LDA yielded the expected ketone in low yield (20%) (entry 6).

The use of an extra equivalent of base had shown to be beneficial in improving the yield of certain ketones.⁶ High reactivity of rapid Claisen condensation occurs at $-60\text{ }^{\circ}\text{C}$ but at warmer temperatures $0\text{ }^{\circ}\text{C}$ self-condensation of ethyl butyrate was observed as well as the desired cross-coupling product. Also, when the molar ratio between two esters was 1:1, self-condensation of

ethyl butyrate and methyl benzoate were observed as well as the desired cross-coupling product (entry 7).

After condensation, the keto-ester **6** converted to a carboxylic acid through saponification using potassium hydroxide. The carboxylic acid functionality was removed through an acidic decarboxylation step to give 1-phenyl-2-pentanone **7** the desired product in Scheme II. The condensation reaction was stirred at room temperature for two hours. The product was extracted into hexane and the solvent was removed under reduced pressure. Aqueous potassium hydroxide 1.98 M was refluxed with keto-ester **6** for one hour and then 4N HCl was added. The mixture was heated at reflux until the generation of carbon dioxide had ceased. The product was extracted into hexane and the solvent was removed under reduced pressure. The crude ketone 1-phenyl-2-pentanone **7** was obtained in a yield of 71 %. The product **7** was characterized by ¹H-NMR and ¹³C-NMR spectroscopy in a CDCl₃ solvent. The spectra were consistent with the intended product structure. In ¹H-NMR there is a specific singlet peak for methylene group between carbonyl and phenyl groups that appeared at δ 3.67. In ¹³C-NMR there is specific peak for ketone that appeared at δ 208.41.

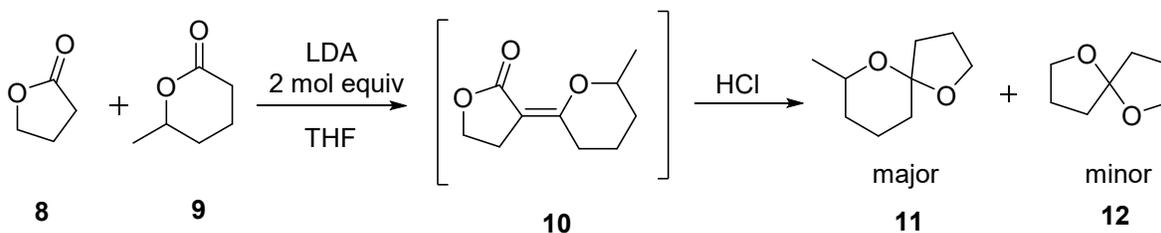
Phase II: Using Claisen Condensation to facilitate Spiroketal synthesis

At a second phase during our experimentation, we further expanded upon Claisen condensation in an effort to synthesize spiroketals, known pheromones.

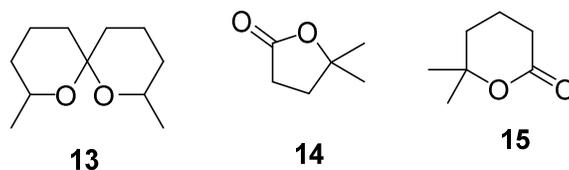
As shown in **Scheme 4.3**, addition of gamma butyrolactone **8** (1 equiv) to a solution of LDA (1 equiv) in THF at -60 °C, followed by the addition of 6-methyltetrahydro-2H-pyran-2-one **9** (1

equiv) at $-30\text{ }^{\circ}\text{C}$, and finally, addition of LDA (1 equiv) in THF led to complete conversion within 2 hours at r.t. and afforded the crude product. This mixture then underwent a thermodynamically controlled acid-catalyzed cyclization to give spiroketals **11** as a major product and **12** as a minor product. The stereochemistry of the resulting spirocenters was governed by the anomeric effect⁷, affording the conformation in which the ring oxygens were axial to the adjacent ring^{7,8}. The mixture of spiroketals was obtained in 60% overall yield.

Scheme 4.3. Synthesis of spiroketal 11



Several trials were needed with substrates after Claisen condensation to finally achieve a spiroketal. When we tried to make the same reaction except for adding 0.5 of LDA as a second addition we got mixture of **11**, **12** and **13** as compound **13** yielded from self- condensation of **9**. And when we tried the same condition but used 0.5 mol of **9** and 1 mole of LDA as a second addition, we didn't get any spiroketals as a product. Claisen condensation reaction between gamma butyrolactone **8** and **14** and the same reaction between **8** and **15** also failed to produce spiroketals as a product.^{7,8}



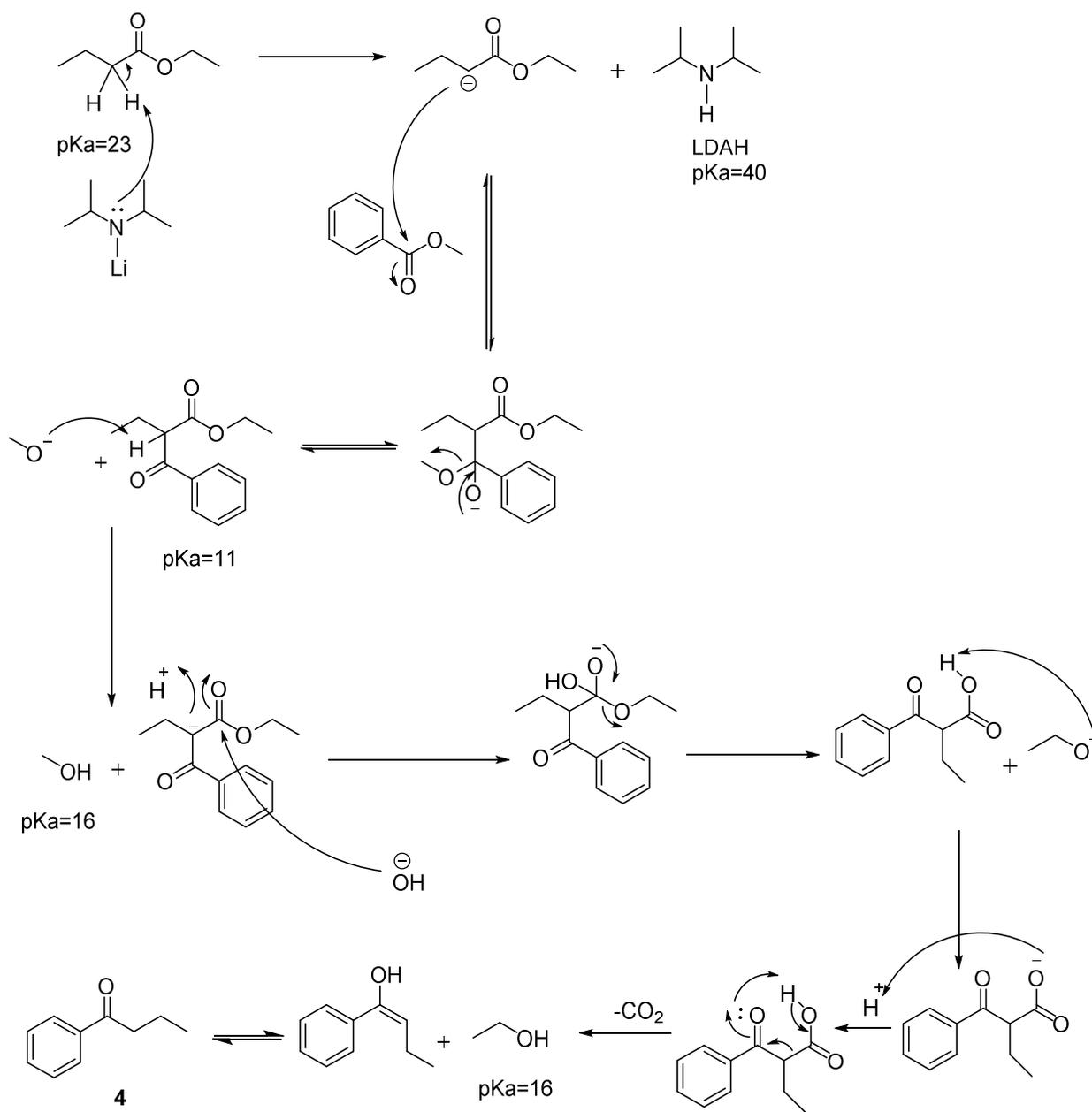
After condensation, addition of hydrochloric acid led to the cyclization that occurred to form 7-methyl-1,6-dioxaspiro[4.5]decane **11**. The solvent, hexane, was removed by fractional distillation at atmospheric pressure rather than simple distillation at reduced pressure in order to limit the loss of the volatile ketal product. The crude product was purified by vacuum distillation, distilling at 65-74 °C, 5 mm Hg and obtained in a yield of 60%. The product **11** was characterized by ¹H-NMR and ¹³C-NMR spectroscopy in a CDCl₃ solvent. The spectra were consistent with the intended product structure. In ¹H-NMR there is a specific doublet peak for methyl group that appeared at δ 1.24. In ¹³C-NMR there is specific peak at 105.99.

Discussion

Our study revealed that the use of an extra equivalent of LDA was key to achieving a high yield and was believed to deprotonate the β-keto ester product as it is formed. The first addition of LDA yielded the enolate, but this step was reversible. To avoid this, the second equivalent of LDA was added, and made the reaction irreversible.

The pKa values must be considered. In the deprotonation step, the pKa of H-LDA is 40, much larger than the starting ester at 23, so the equilibrium strongly prefers formation of enolate, but still there is possibility for a reversible reaction. Therefore, we had to ensure that there is enough starting ester to react. As a result, there was an excess of starting ester around the enolate to react with. Thus, adding excess of LDA prevented this kind of reversibility. The pKa of the internal protons in a β-keto ester is low (~11) compared with the pKa of an alcohol (pKa ~ 16). Upon saponification and decarboxylation of β-ketoester, the reaction mechanism moved through the formation of butyrolactone **4**. (Scheme 4.4)

Scheme 4.4. Mechanism of formation butyrolactone 4

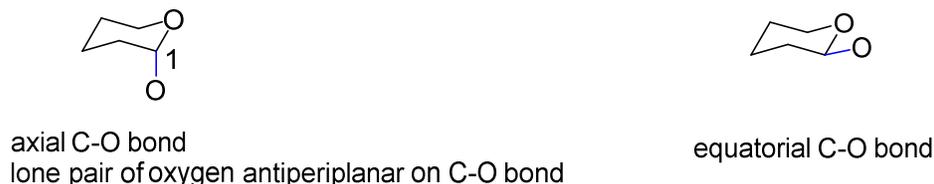


Past literature has shown that using an alkoxide base and under extreme conditions yields primarily self-condensation⁹ rather than cross coupling. However, changing the molar equivalents of the reagents achieved cross coupling in low yield. Z.Zhang et al.² reported that the addition of LDA (1 eq.) and LiHMDS (1 eq.) yielded cross coupling condensation products with good yield¹⁰ or using only LDA (1 eq.)^{3,11}.

We found that our methodology is best employed when only one of the two esters possesses an alpha hydrogen. This is because the enolizable ester will serve as the sole nucleophile, reacting with the non-enolizable ester electrophile. If both esters possess an alpha hydrogen, then as many as four products can be formed: two products of self-condensation and two of cross condensation.

In the case of spiroketal synthesis, anomeric specificity is critical to the spiroketals' overall thermodynamic stability. Anomeric effect is defined as the tendency of an electronegative substituent at the anomeric center (C1) of a pyranose ring to take an axial rather than equatorial orientation despite unfavorable steric interactions (**Scheme 4.5**). This effect is thought to result from a stabilizing interaction between one of the lone pairs on oxygen and the antibonding σ^* orbital of the C-O bond. The overlap is efficient only when one of the lone pairs on the oxygen is antiperiplanar to the C-O bond.¹²

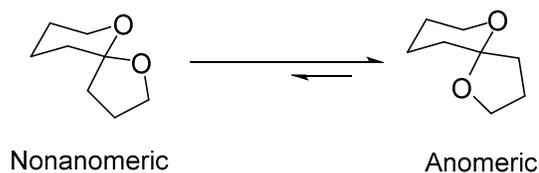
Scheme 4.5. Anomeric Effect Stabilizes the Axial Oxygen Substituent Relative to the Equatorial Substituent



In addition to the anomeric effect, steric interactions, and other chelation effects influence spiroketal conformation.¹³ The most stable conformation is the one where the number of anomeric interactions is maximized and unfavorable steric interactions between the substituents are minimized.

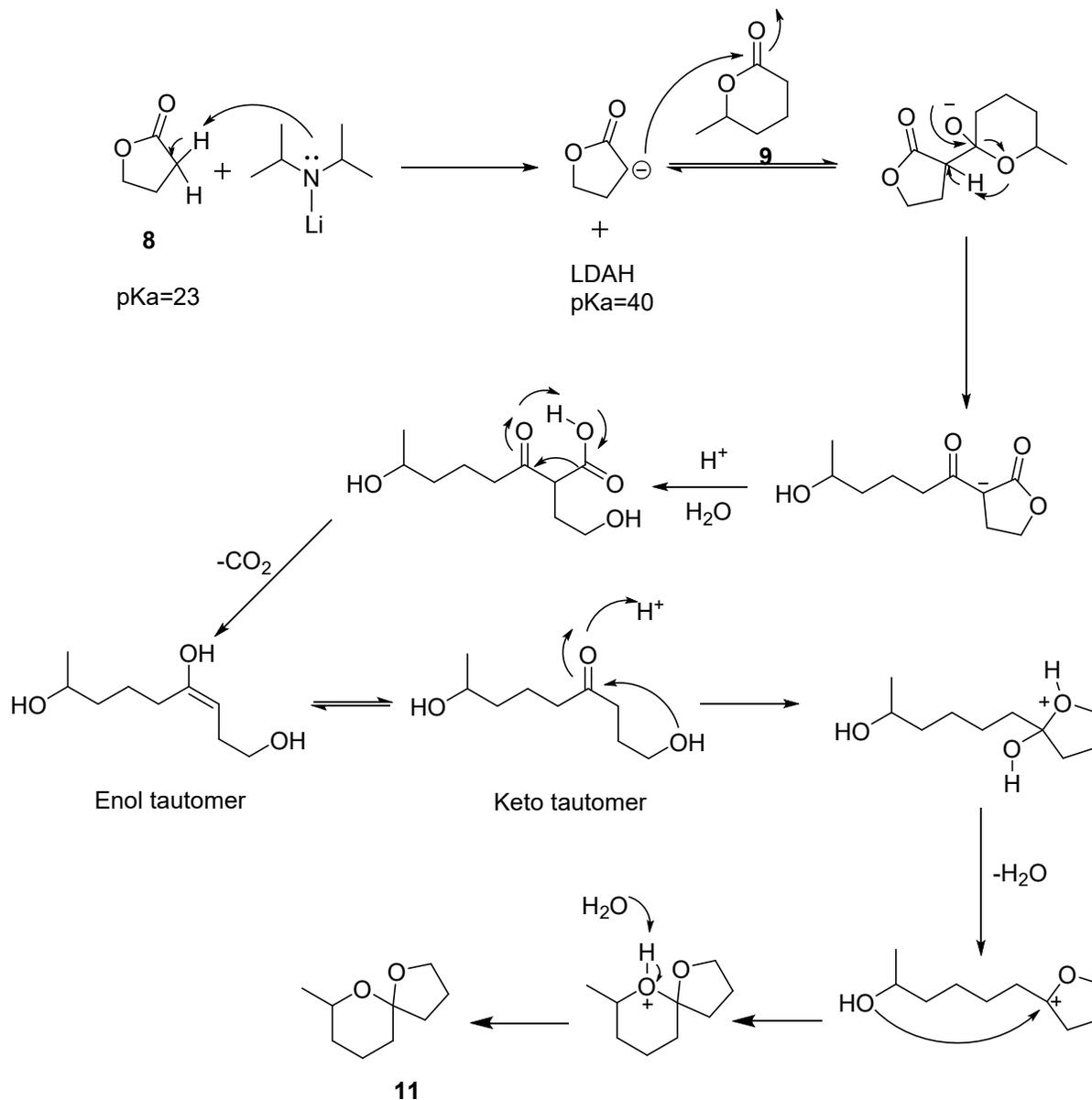
In [5,4]-spiroketal systems, both an anomeric and non-anomeric configuration can be identified. The anomeric configuration bears the axial oxygen substituent and the nonanomeric bears the equatorial oxygen. The nonanomeric configuration is locked by ring fusion or suitably placed equatorial substituents on the six-membered ring. Ring flipping will quickly transform the nonanomeric structure into the more stable anomeric structure. This formation of the anomeric structure is under thermodynamic control because when acids were used in the spiroketalization the nonanomeric form was detected in the initial stages of the reaction, but further equilibration afforded the anomeric form (**Scheme 4.6**).¹⁴

Scheme 4.6. Anomeric and Nonanomeric in [6,5]-Spiroketal Systems



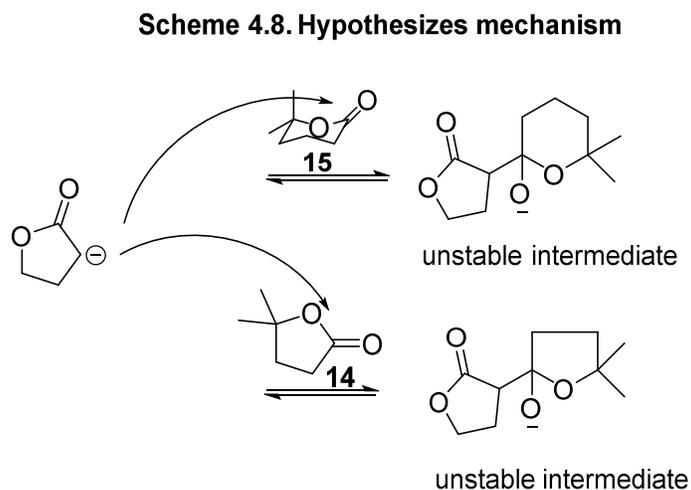
As we mentioned before the pKa values of the reaction must be considered (Scheme 4.7).

Scheme 4.7. Mechanism for the formation of spiroketal 11



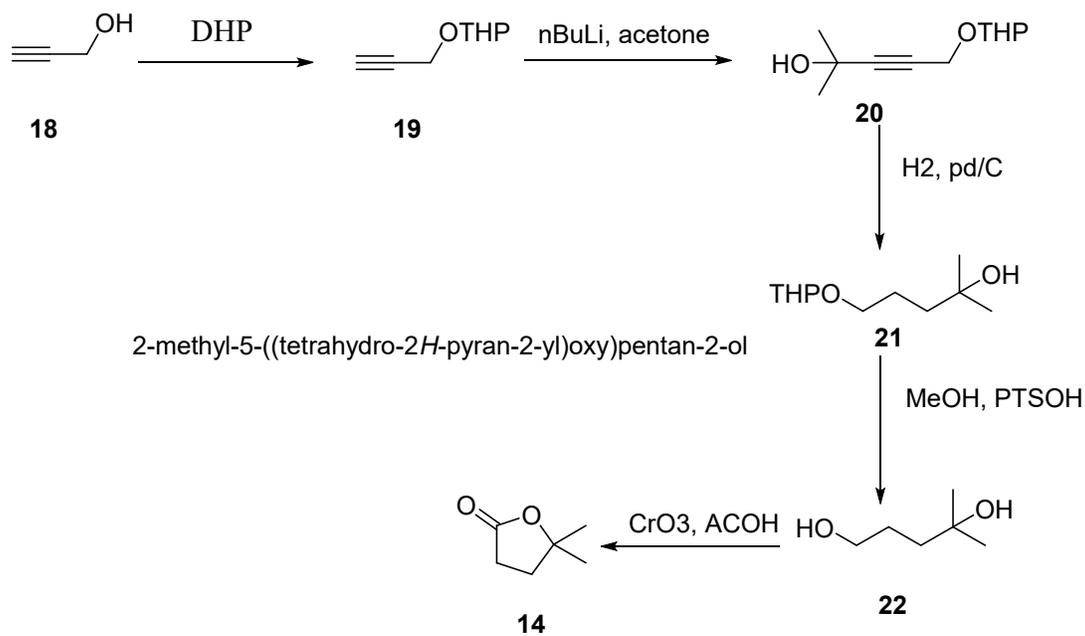
In our efforts, there was a perhaps prolonged period of trial and error with various substrates as discussed previously. Claisen condensation reactions between gamma butyrolactone **8** and **14** and the same reaction between **8** and **15** did not yield spiroketals as a product. The Claisen

condensation reaction performed optimally when we reacted lactone **8** with lactone **9** as it has only one substituent in the 6 position. However, when we tried another lactone that has two substituents instead of one, as in lactone **14** and **15**, the trial failed. We hypothesize it is because the enolate of lactone **8** attacked lactone **14** and **15** resulting in a steric hinderance due to the presence of the two substituents. Another hypothesis is that the reaction proceeded to the formation of an intermediate, and this intermediate was unstable and has high energy rendering this reaction reversible and without product desired (**Scheme 4.8**).



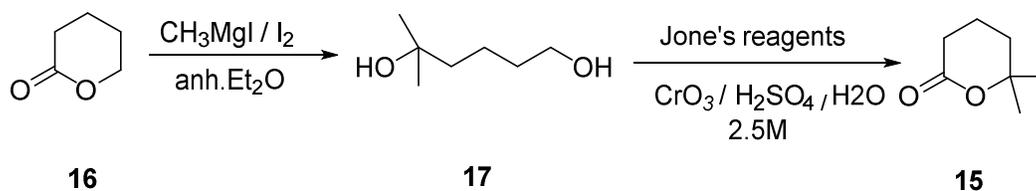
Compounds **14** and **15** are not commercially available and had to be prepared in the lab. Lactone **14** was prepared by the addition of anions of tetrahydropyranyl derivatives of propargylic alcohol **19** to acetone to yield compound **20**. This compound was hydrogenated at low temperature to give compound **21**, which after deprotection led to the diol **22**. Diol **22** was then oxidized to give lactone **14** (**Scheme 4.9**)¹⁵

Scheme 4.9. Synthesis of lactone 14



Lactone **15** was prepared from Valerolactone **16** through Grignard reagent ¹⁶ with methyl iodide followed by the oxidation reaction using Jones reagents. ¹⁷

Scheme 4.10. Synthesis of lactone 15



Experimental:

NMR data were obtained on a 600 MHz Bruker Avance spectrometer in CDCl₃.

Tetrahydrofuran was distilled from any impurities before used.

1-phenyl-1-butanone (4)

To a solution of diisopropylamine (0.45 g, 1.05 mole) in dry THF (4.2 ml), a 2.5M solution of nBuli was added at -25 °C, under nitrogen atmosphere. The temperature was allowed to increase until 0 °C, then the flask was cooled to -60°C and a solution of ethylbutyrate **1** (0.5 g, 1 mole) in THF (4.5 ml) was added dropwise over 15 min. The temperature was allowed to increase until -30 °C, then the solution of methyl benzoate **2** (0.29g, 0.5 mol) in THF (2.1 ml) was added over 10 min then LDA (0.25 equiv) was added immediately. The reaction mixture was allowed to warm and was stirred at room temperature for 2 hr. Then the reaction was quenched with saturated solution of ammonium chloride, extracted two times with ethylacetate. The organic layer was washed with 1 N HCL, brine, dried over magnesium sulphate, and then the solvent was removed in vacuo affording β-keto ester **3**. β-keto ester was added to a solution of 1.98M KOH (15.6 ml, 6.25 equiv) and was refluxed for 1 hr, the reaction was cooled on ice bath, 4 N HCL was added to the mixture until the medium become acidic, the mixture was refluxed using bubbler to decarboxylate. After decarboxylation hexane was used for extraction, the organic layer was washed with brine, dried over magnesium sulphate, and then the solvent was removed in vacuo affording 1-phenyl-1-butanone **4** (0.23g, 73%).

¹H NMR (600MHz, CDCl₃): δ 7.94(2H, d), δ 7.56(1H, t), δ 7.46(2H, t), δ 2.95(2H, t), δ 1.77(2H, td), δ 1.02(3H, t)

^{13}C NMR: δ 200.42, δ 137.16, δ 132.84, δ 128.40, δ 40.53, δ 17.76, δ 13.88.

1-Phenyl-2-pentanone (7)

To a solution of diisopropylamine (0.45 g, 1.05 mole) in dry THF (4.5 ml), a 2.5M solution of nBuli was added at $-25\text{ }^{\circ}\text{C}$, under nitrogen atmosphere. The temperature was allowed to increase until $0\text{ }^{\circ}\text{C}$, then the flask was cooled to $-60\text{ }^{\circ}\text{C}$ and a solution of ethylbutyrate **1** (0.5 g, 1 mole) in THF (4.5 ml) was added dropwise over 15 min. The temperature was allowed to increase until $-30\text{ }^{\circ}\text{C}$, then the solution of methyl phenylacetate **5** (0.323 g, 0.5 mol) in THF (3 ml) was added over 10 min then LDA (1.05 equiv) was added immediately. The reaction mixture was allowed to warm and was stirred at room temperature for 2 hr. Then the reaction was quenched with saturated solution of ammonium chloride, extracted two times with ethylacetate. The organic layer was washed with 1 N HCL, brine, dried over magnesium sulphate, and then the solvent was removed in vacuo affording β -keto ester **6**. β -keto ester was added to a solution of 1.98M KOH (15.6 ml, 6.25 equiv) and was refluxed for 1 hr, the reaction was cooled on ice bath, 4 N HCL was added to the mixture until the medium become acidic, the mixture was refluxed using bubbler to decarboxylate. After decarboxylation hexane was used for extraction, the organic layer was washed with brine, dried over magnesium sulphate, and then the solvent was removed in vacuo affording of 1-Phenyl-2-pentanone **7** (0.242 g, 71%).

^1H NMR (600MHz, CDCl_3): δ 7.33(2H, t), δ 7.26(1H, t), δ 7.21(2H, d), δ 3.67(2H, S), δ 2.43(2H, t), δ 1.58 (2H, td), δ 0.87(3H, t)

^{13}C NMR: δ 208.41, δ 134.40, δ 129.40, δ 128.69, δ 128.69, δ 126.94, δ 50.18, δ 43.90, δ 17.18, δ 13.63.

7-methyl-1,6-dioxaspiro[4.5]decane (11)

To a solution of diisopropylamine (0.58 g, 1 mole) in dry THF (5 ml), a 2.5M solution of nBuli was added at -25 °C, under nitrogen atmosphere. The temperature was allowed to increase until 0 °C, then the flask was cooled to -60°C and a solution of gamma butyrolactone **8** (0.5 g, 1 mole) in THF (4.5 ml) was added dropwise over 15 min. The temperature was allowed to increase until -30 °C, then the solution of 6-Methyltetrahydro-2H-pyran-2-one **9** (0.66g, 1 mol) in THF (6 ml) was added over 10 min then LDA (1 equiv) was added immediately. The reaction mixture was allowed to warm and was stirred at room temperature for 2 hr. 2 N HCL was added to the mixture until the medium become acidic, the mixture was refluxed using bubbler to decarboxylate. After decarboxylation hexane was used for extraction, the organic layer was washed with 1N NaOH, brine, dried over magnesium sulphate. The solvent was fractionally distilled to yield the crude product. The crude product was purified by vacuum distillation, distilling at 65-74 °C, 5 mm Hg. The product was obtained as a fragrant yellow oil in a yield of 60 %.

¹H NMR (600MHz, CDCl₃): δ 3.80-3.75 (m, 2H), δ 3.75 (m, 1H), δ 2.04-1.90 (m, 2H), δ 1.90-1.80 (m, 2H), δ 1.79-1.70 (m, 2H), δ 1.69-1.54 (m, 2H), δ 1.54-1.29 (m, 2H), δ 1.24 (d, 2H)

¹³CNMR: δ 105.9, 66.7,66.4, 37.9, 32.8,32.6, 23.7, 22.0, 20.4

2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (19)

To a solution of propargyl alcohol **18** (10 g, 170 mmol) in DCM (170 mL) at 0 °C, *Para*-toluenesulfonic acid monohydrate (2.9 g, 17 mmol) was added proton-wise. Dihydropyran (22.5 g, 260 mmol) was then added to the mixture. The reaction mixture was allowed to warm and was stirred at room temperature overnight. Potassium carbonate was added to get rid of any *para*-

toluenesulfonic acid monohydrate remaining in the mixture. The solvent was fractionally distilled to yield the crude product. The crude product was purified by vacuum distillation, distilling over at 65-75 °C, 5 mm Hg. The product was obtained as a colorless oil in a yield of 51%.

$^1\text{H NMR}$ (600MHz, CDCl_3): δ 4.58 (t, 1H), δ 4.25 (dd, 2H), δ 3.85 (t, 1H), δ 3.55 (t, 1H), δ 2.4 (t, 1H), δ 1.5-1.9 (m, 6H)

$^{13}\text{CNMR}$: δ 96.88, 79.80, 73.95, 62.02, 54.00, 30.22, 25.34, 19.01

2-Methyl-5-(tetrahydropyran-2-yloxy)pent-3-yn-2-ol (20)

To a stirred solution of tetrahydro-2-(2-propinyloxy)-2H-pyran **19** (0.5 g, 3.56 mmol) in THF (3.5 mL) under nitrogen at -20 °C, a 2.5 M solution of n- BuLi was added dropwise over 5 min. After 10 min, the temperature was kept at -20 °C and acetone was added (0.31gm, 5.34 mmol). The stirring was continued for 1h at -20 °C, followed by the reaction being quenched by the addition of a saturated solution of ammonium chloride while being vigorously stirred and letting the temperature rise slowly to r.t. The resulting solution was diluted with water (12 mL), extracted four times with diethylether, and the combined organic layers were washed with brine and dried over magnesium sulphate. Then the solvent was removed in vacuo affording compound **20** (97%) as a colorless oil.

$^1\text{H NMR}$ (600MHz, CDCl_3): δ 4.58 (t, 1H), δ 4.25 (dd, 2H), δ 3.85 (t, 1H), δ 3.55 (t, 1H), δ 1.5-1.9 (m, 6H), δ 1.5 (s, 6H)

$^{13}\text{CNMR}$: δ 96.67, 90.81, 67.91, 64.96, 61.96, 54.27, 31.31, 30.20, 25.33, 18.94

2-methyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pentan-2-ol (21)

The catalyst 10% Pd/C (0.00162 mg) was added to a solution of **20** (0.239 g, 1.7 mmol) in EtOAc (100 mL), and the suspension was vigorously stirred at r.t. under H₂. After 3 h, the reaction was completed. The mixture was filtered, and the solvent evaporated to give an oil **21** (83%).

¹H NMR (600MHz, CDCl₃): δ 4.58 (t, 1H), δ 3.85 (t, 1H), δ 3.80 (t, 1H), δ 3.35 (t, 2H), δ 1.4-1.6 (m, 4H), δ 1.7-1.9 (m, 6H), δ 1.2 (s, 6H)

¹³CNMR: δ 98.83, 70.42, 68.05, 62.32, 40.75, 30.64, 29.37, 25.42, 24.74, 19.57

4-Methylpentane-1,4-diol (22)

To a solution of **21** in MeOH (5.37 mL) a catalytic amount of p-toluenesulfonic acid (0.80 mg, 0.0047 mmol) was added. After stirring for 1 h, NaHCO₃ (2.284 mg) was added. The mixture was filtered and concentrated to afford the diol **22** (91%) as a viscous colorless oil.

¹H NMR (600MHz, CDCl₃): δ 3.64 (t, 2H), δ 1.65 (quin, 2H), δ 1.55 (t, 2H), δ 1.25 (s, 6H)

¹³CNMR: δ 70.63, 63.13, 40.49, 29.35, 27.37

5,5-Dimethyldihydrofuran-2-one (14)

A mixture of chromium trioxide (0.717 g, 7.1 mmol), water (1 ml) and acetic acid (3 ml) was added to an acetic acid (3ml) solution of **22** (0.53 g, 4.4 mol) at r.t. with stirring. After 3 h, the mixture was extracted with diethyl ether and washed with a 10% sodium carbonate solution, water, and dried over anhydrous sodium sulphate. The solvent was removed, and residue was distilled to give lactone **14** as a pale-yellow oil (60%)

^1H NMR (600MHz, CDCl_3): δ 2.60 (t, 2H), δ 2.05 (t, 2H), δ 1.42 (s, 6H)

^{13}C NMR: δ 176.62, 84.55, 34.70, 27.74, 22.86

GC-FID data: only one peak appears at retention time 10.037

5-methylhexane-1,5-diol (17)

A solution of methyl magnesium iodide in anhydrous diethyl ether was prepared from magnesium (0.72 gm, 29.9 mmol) and methyl iodide (4.25 gm, 29.9 mmol) in standard fashion. It was then added to a mixture of valerolactone **16** (1 g, 9.9 mmol) and diethyl ether at r.t. The reaction mixture was heated for 2 h and quenched with iced ammonium chloride solution. The organic layers were extracted four times with diethylether, and the combined organic layers were washed and dried over magnesium sulphate. The solvent was then removed in vacuo affording compound **17** (62%).

^1H NMR (600MHz, CDCl_3): δ 3.53 (t, 2H), δ 1.3-1.4 (m, 4H), δ 1.42-1.7 (t, 2H), δ 1.25 (s, 6H)

^{13}C NMR: δ 70.99, 62.45, 43.30, 32.99, 29.24, 20.42

GC-FID data: only one peak appears at retention time 13.081

6,6-dimethyltetrahydro-2H-pyran-2-one (15)

To a stirred solution of diol **17** (0.66 g, 4.9 mmol) in acetone (5 mL), a 2.65 M solution of chromic acid was added dropwise over 5 min. The reaction mixture was stirred at room temperature overnight. Isopropyl alcohol (1ml) was added to the acetone solution until the excess of chromic acid was destroyed. The solution was neutralized with saturated aqueous sodium bicarbonate, and the suspension was filtered. After evaporation of acetone, saturated brine

solution was added. The organic layers were extracted four times with ether. The solvent was removed in vacuo affording lactone **15** (76%).

^1H NMR (600MHz, CDCl_3): δ 2.45 (t, 2H), δ 1.75 (t, 2H), δ 1.85 (quin, 2H), 1.39 (s, 6H)

^{13}C NMR: δ 171.20, 82.12, 33.90, 29.08, 28.70, 16.82

GC-FID data: only one peak appears at retention time 13.187

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Chapter 5: Conclusion

Integrated pest management (IPM) strategies have come to the top of agriculture concern world-wide due to the negative impacts of pesticides on health, environment, and organisms. The goal of IPM is to allow for safer insect control and pose the least risks while maximizing benefits and reducing costs. Moreover, IPM assists in combatting increasing resistance of insects to pesticides. One of the predominant areas of research within IPM is the use of insect pheromones. Insect pheromones have been utilized for pest management through methods of mass trapping and killing of harmful pests selectively with minimal risk to human health and the surrounding environment.

One such pheromone is *exo*-brevicomin as the aggregation pheromone of the western pine beetle. Many methods for synthesis of brevicomin have been described including achiral, diastereoselective and enantioselective paths. An enantioselective route is the most synthetically demanding but the most advantageous given the beetle's responsiveness to only the (+)-isomer. In our studies, we were able to synthesize *exo*-brevicomin in a stereoselective and efficient method compared to others proposed in the past. We described a proposed method for synthesis of *exo*-brevicomin (7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane) using tosylation of a readily available alcohol followed by alkylation and cyclization. This method is unique compared to others proposed before and provides a stereoselective method for *exo*-brevicomin. An enantioselective is preferable to diastereoselective syntheses cited because it avoids air/water sensitive organometallic reagents, gaseous reagents, sub-zero temperatures, toxic reagents, photochemistry, rare metal catalysis, chromatography, high pressure reactions and other specific reagents that require special precautions e.g. perchloric acid, dimethyl sulfide and sodium metal,

and long reaction times. The method proved safe to the extent that it was used during an Organic Chemistry III course with students. It also can be synthesized in a shorter time compared to others that are more time consuming.

Another pheromone that has been of great interest in IPM research is *E*-7-methyl-1,6-dioxaspiro[4.5]decane, a spiroketal known from male ash bark beetles, and we successfully synthesized it using Claisen condensation reactions achieving a more efficient and timely methods that avoid self-condensation with good yield. Although cross ester condensation has not yet become a promising procedure for the synthesis of ketoesters because of many challenges inherent to the procedure, we were able to reach favorable conditions when only one of the two esters possess an alpha hydrogen and when both esters possess an alpha hydrogen.

Another promising future direction in the synthesis of pheromones for use in IPM development is the use of oxidation of primary alcohols. Several methods for the oxidation of primary alcohols have been reported; however, these approaches often use metals or expensive reagents.

We reported a very efficient procedure for the oxidation of primary alcohols to aldehydes or α -chloro aldehydes using inexpensive reactants that are metal free with no over oxidation to the carboxylic acid. Trichloroisocyanuric acid (TCCA) is a commercially available, non-toxic reactant used as an oxidizing and chlorinating reagent and has a lot of applications in medicinal chemistry.

Thus, the research presented here, synthesis of *exo*-brovicomin, efficient oxidation of primary alcohols, and spiroketal synthesis, all offer a unique and significant contribution to pheromone

research. Moreover, the findings have potential for use in industry when incorporated into IPM strategies.

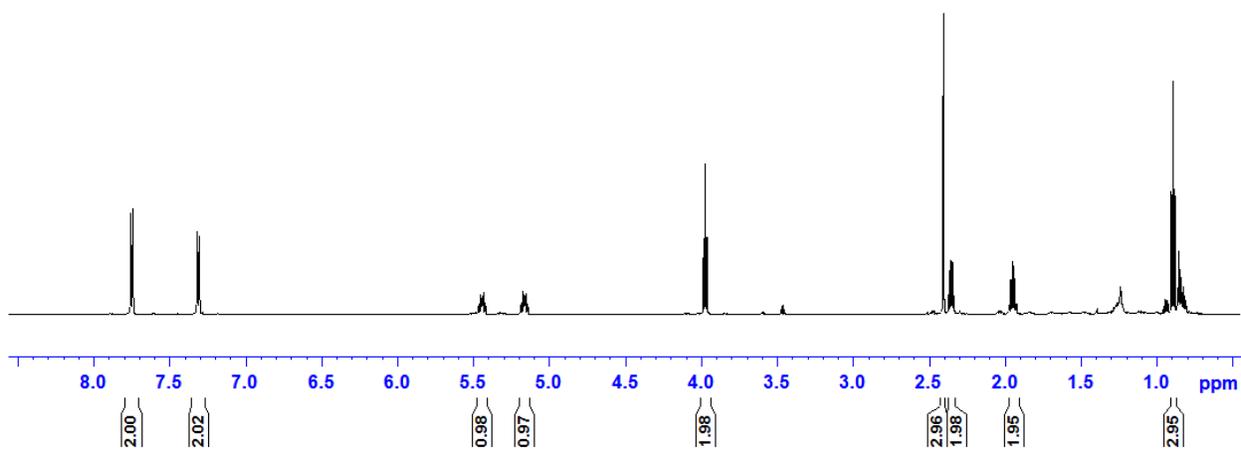
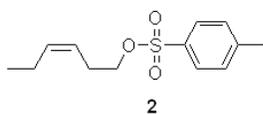
Appendix

NMR spectra for compounds described in chapter 2, 3 and 4

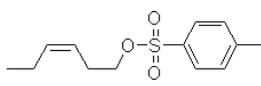
All spectra were obtained in CDCl₃ on a 600 MHz Bruker Avance spectrometer.

Chapter 2

600MHz-HNMR



600MHZ-C13NMR

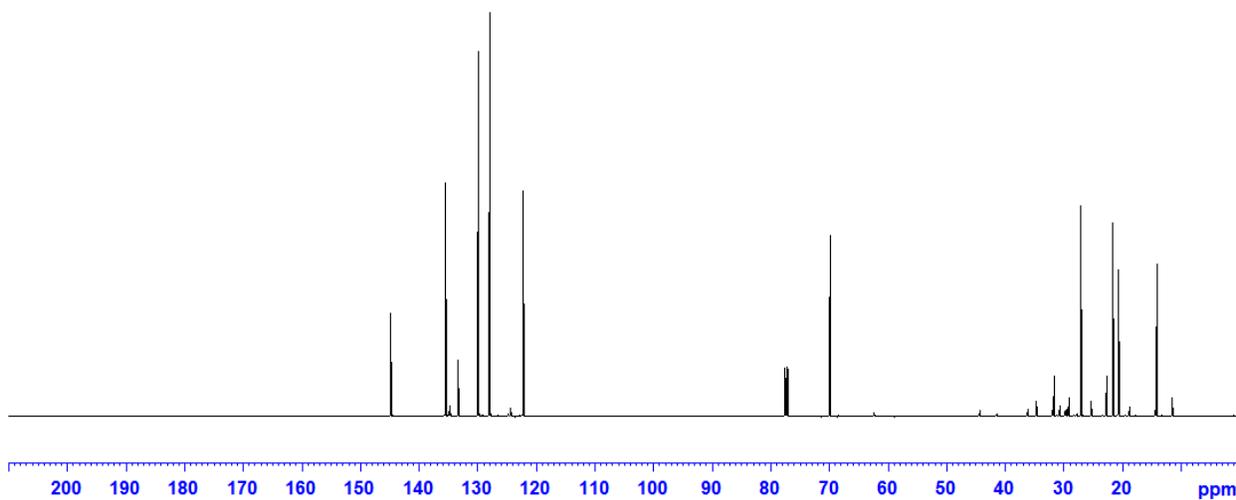


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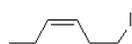
144.69
135.35
133.24
129.79
127.81
122.15

69.80

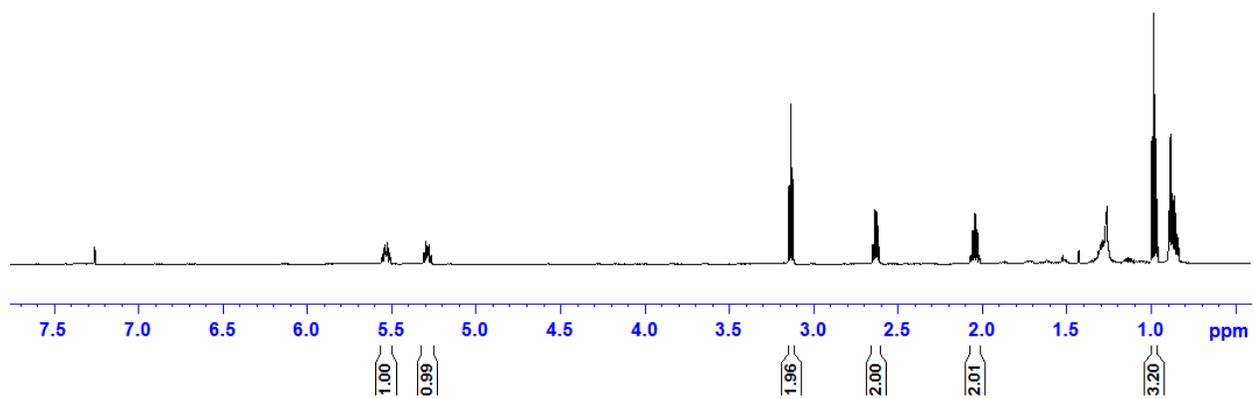
26.94
21.40
20.53
13.90



600MHZ-HNMR



3



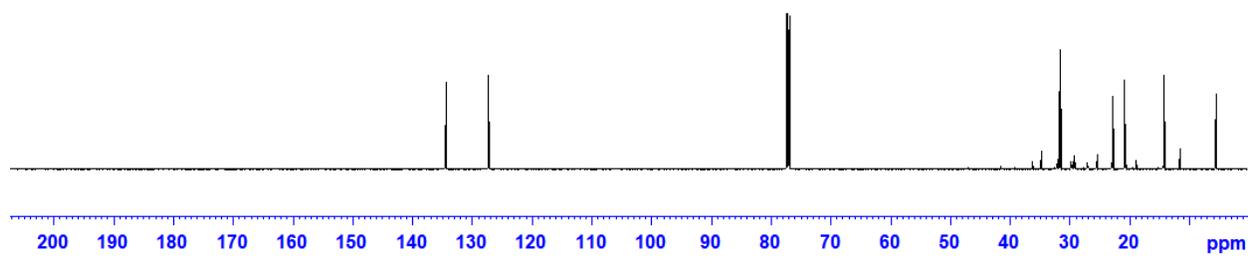
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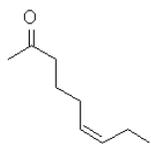
3

134.27
127.16

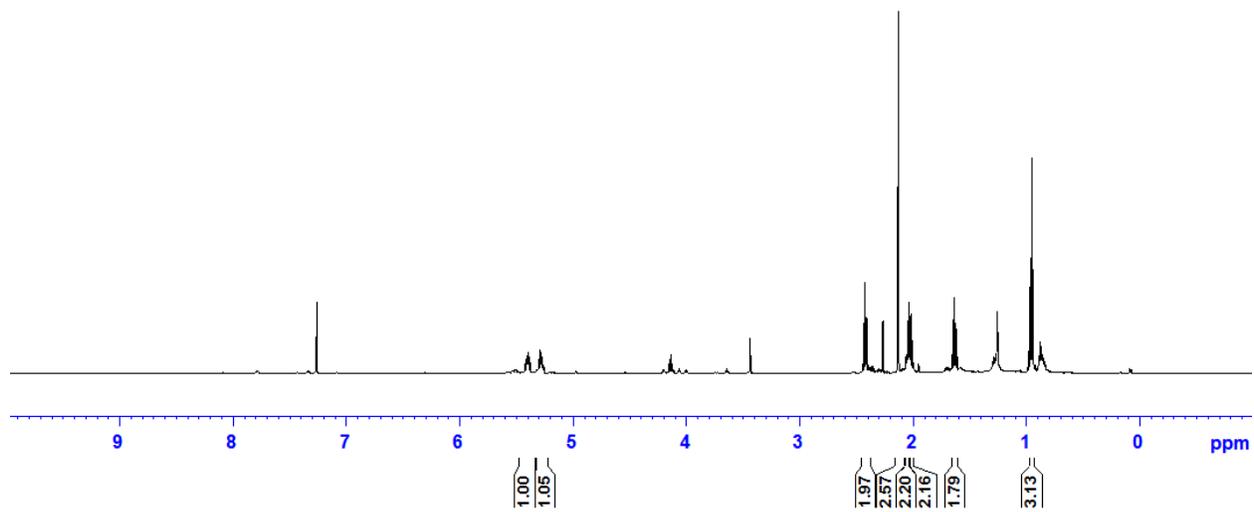
31.45
20.75
14.14
5.45

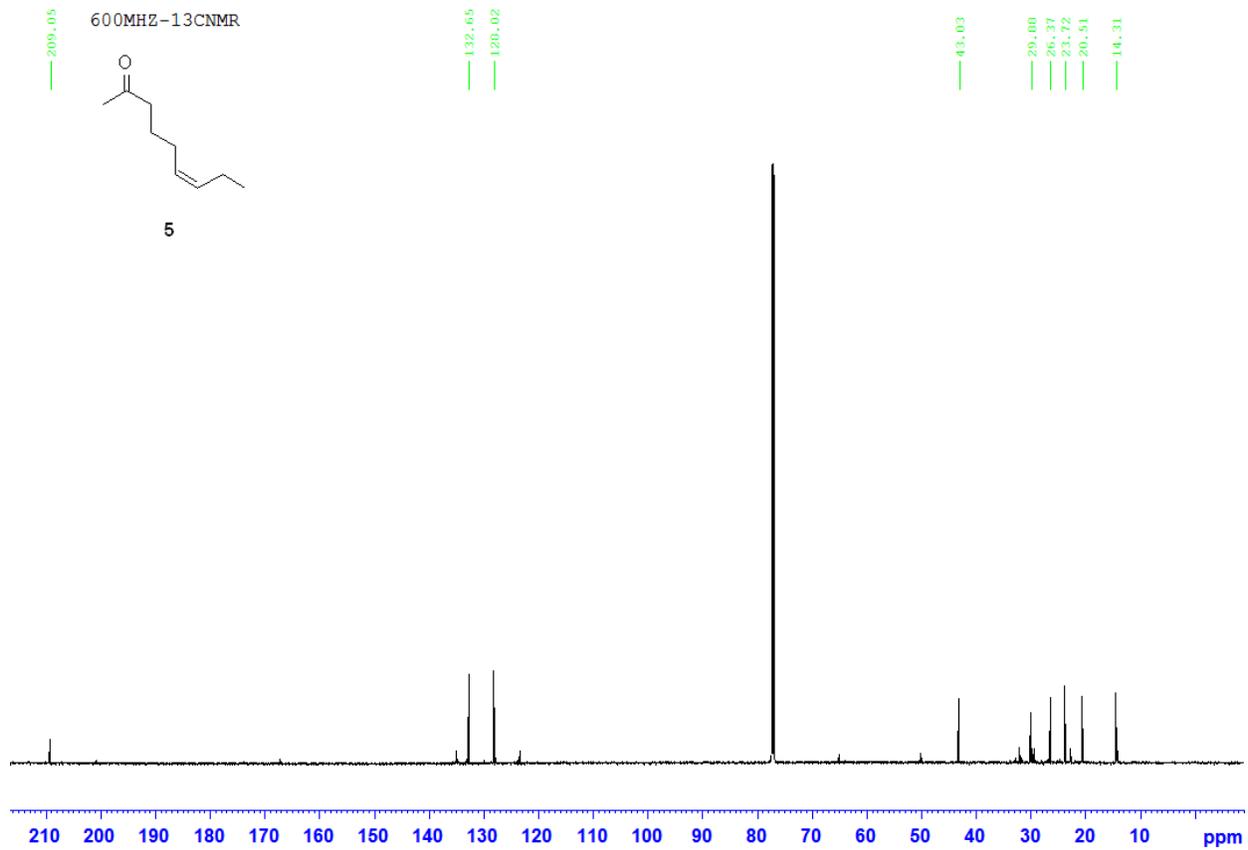


600MHZ-HNMR



5

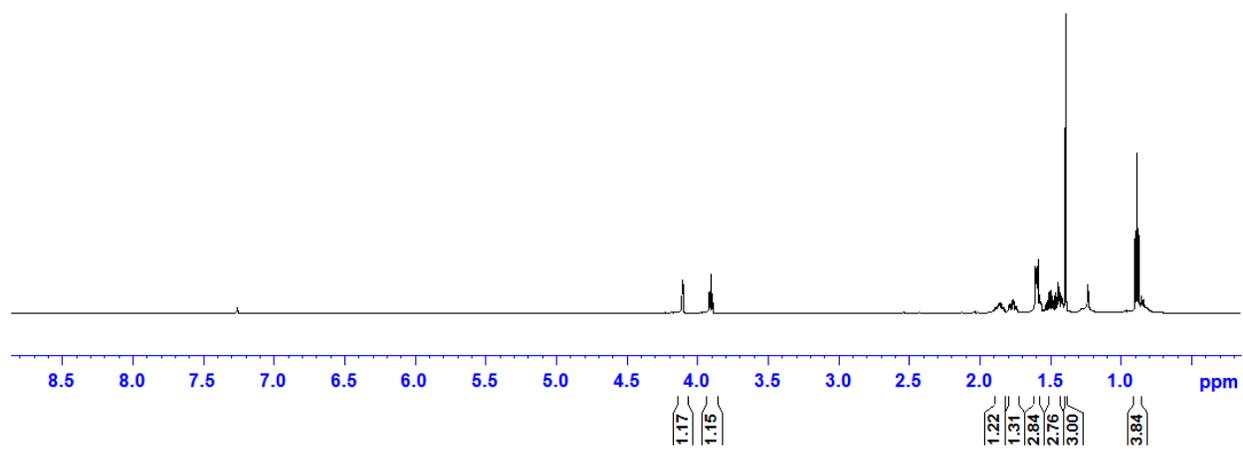




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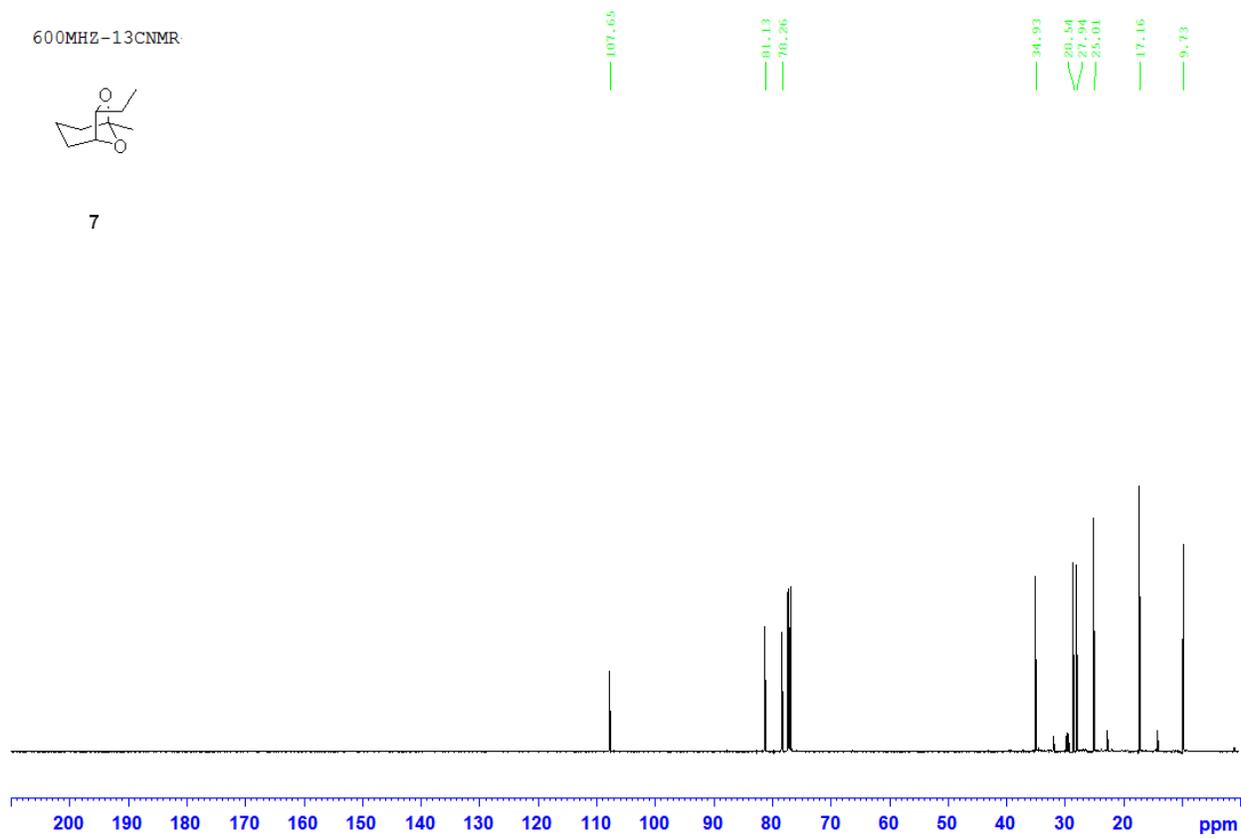
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600MHZ-13CNMR

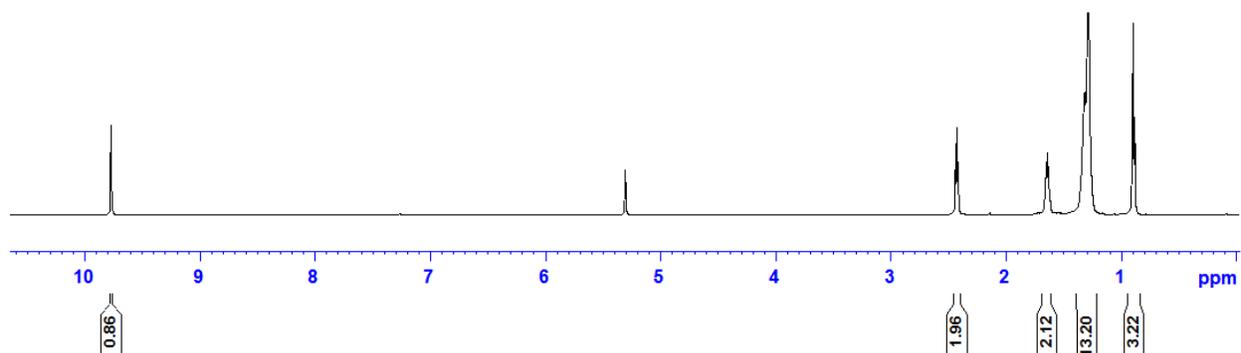
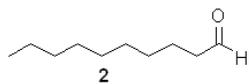


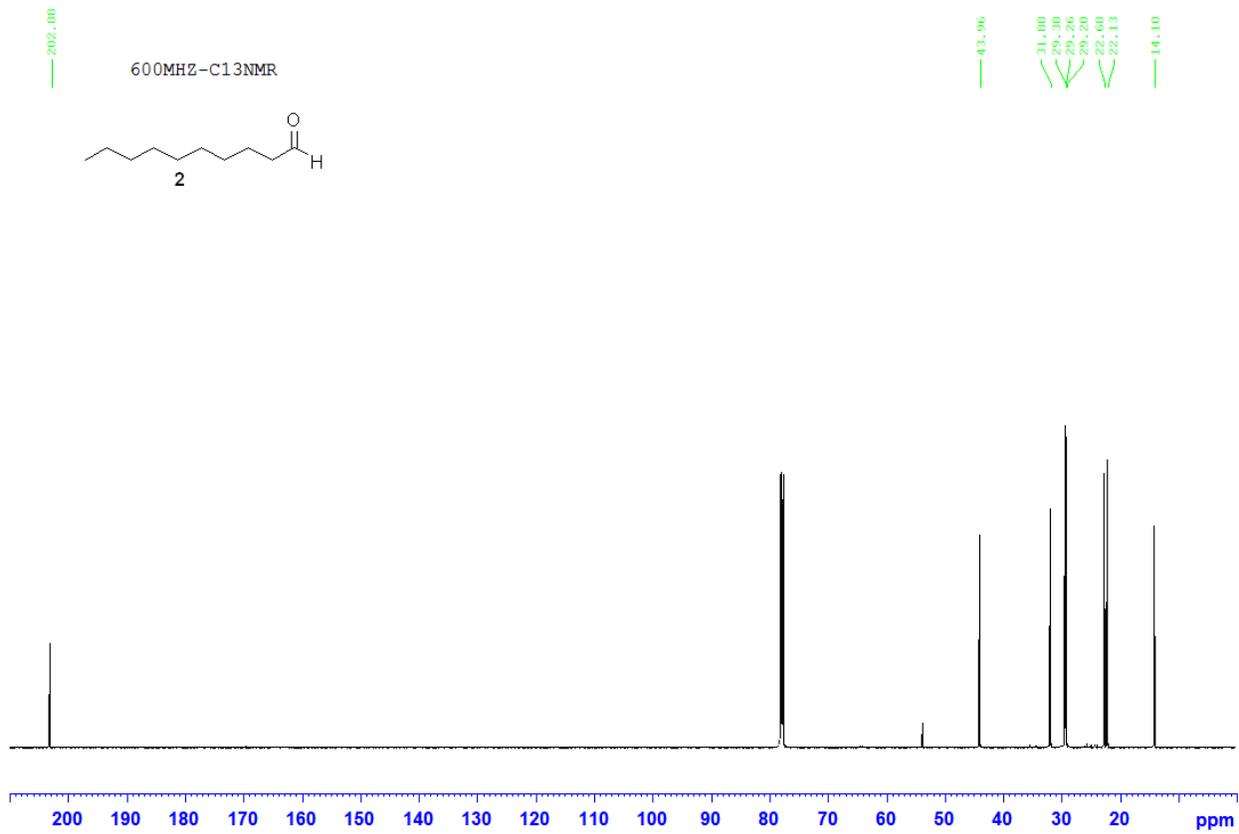
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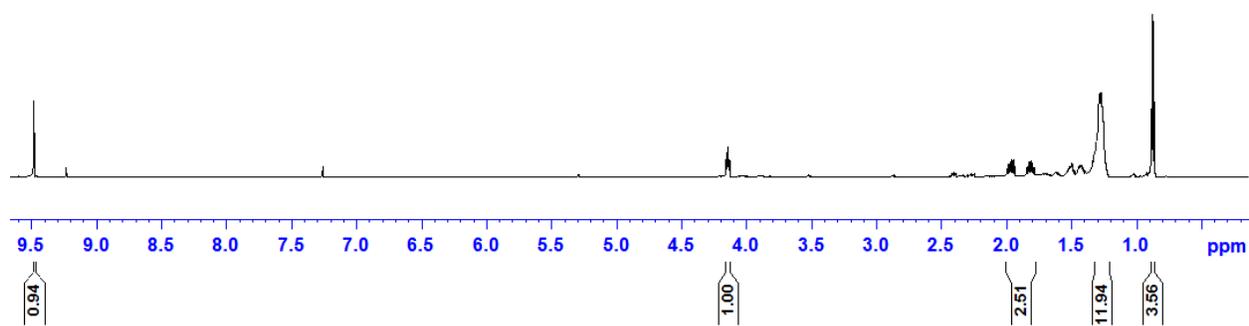
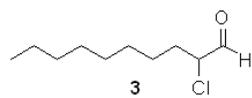
Chapter 3

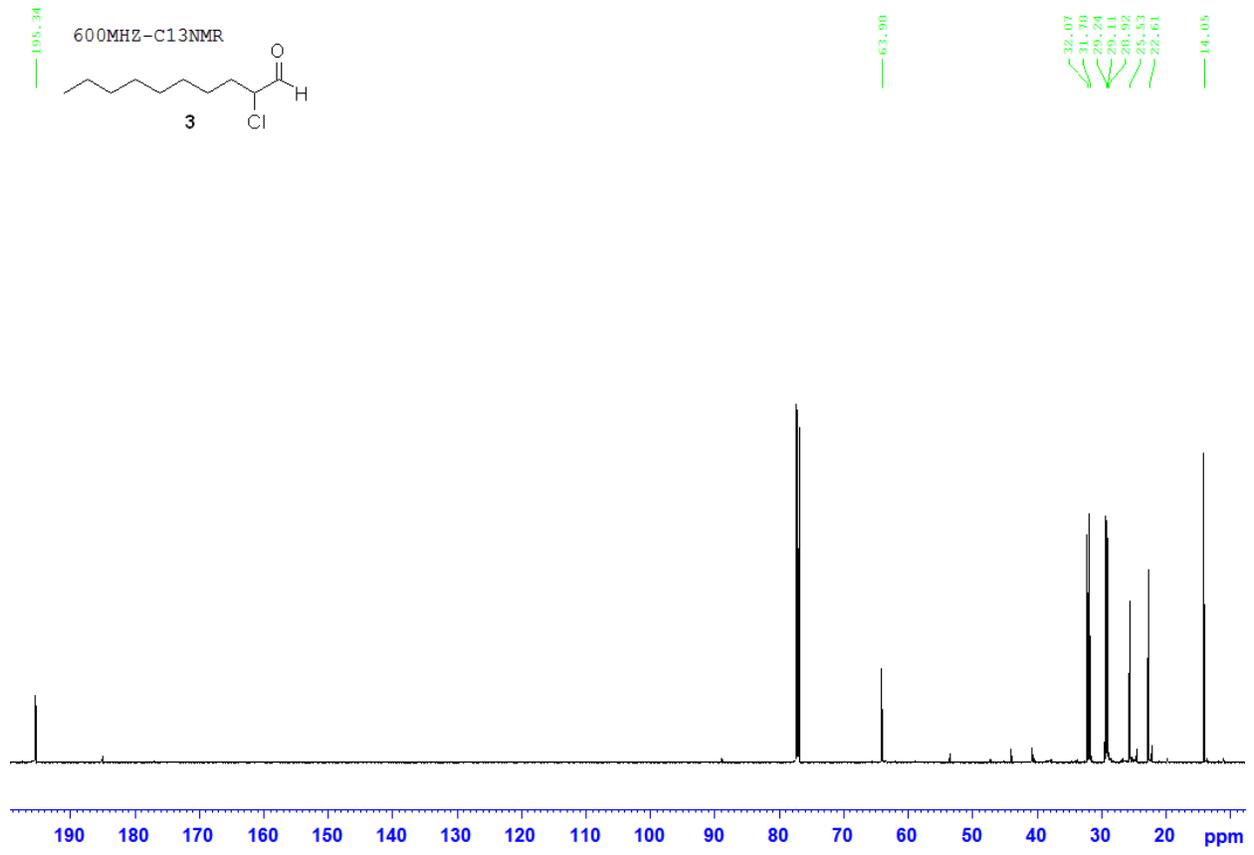
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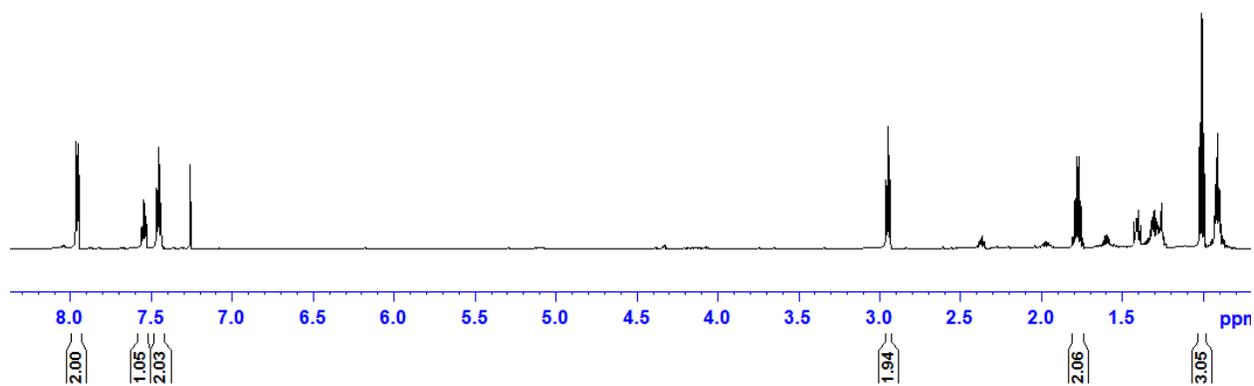
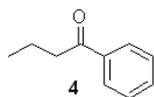
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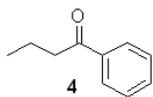


Chapter 4

600MHZ-HNMR



600MHZ-C13NMR



200.42

137.16

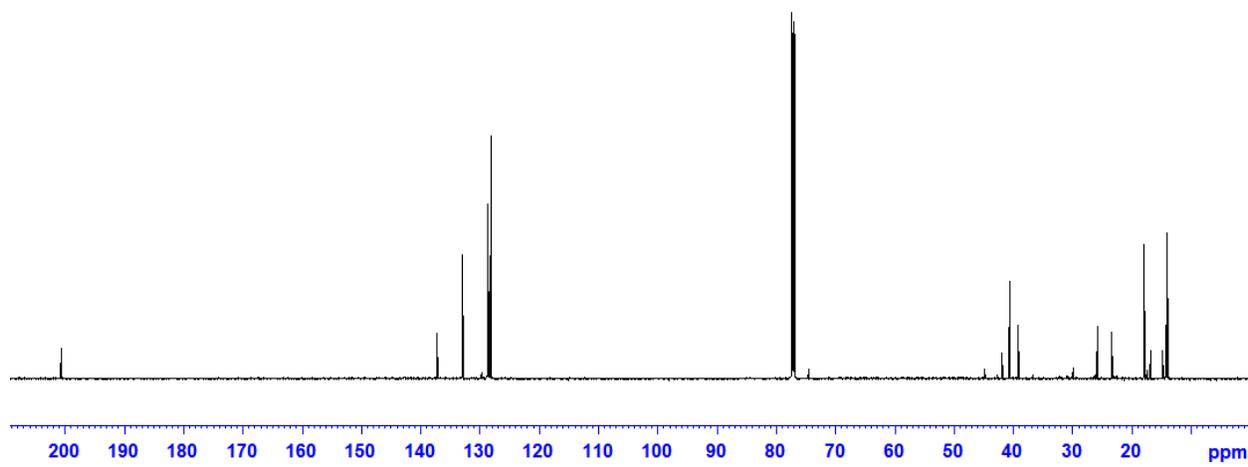
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128.04

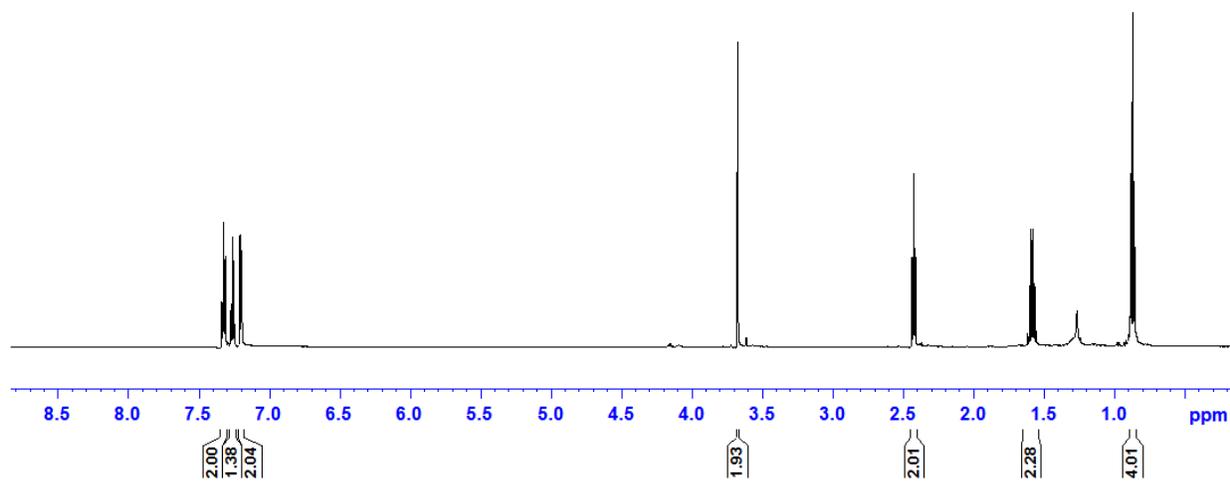
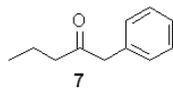
40.53

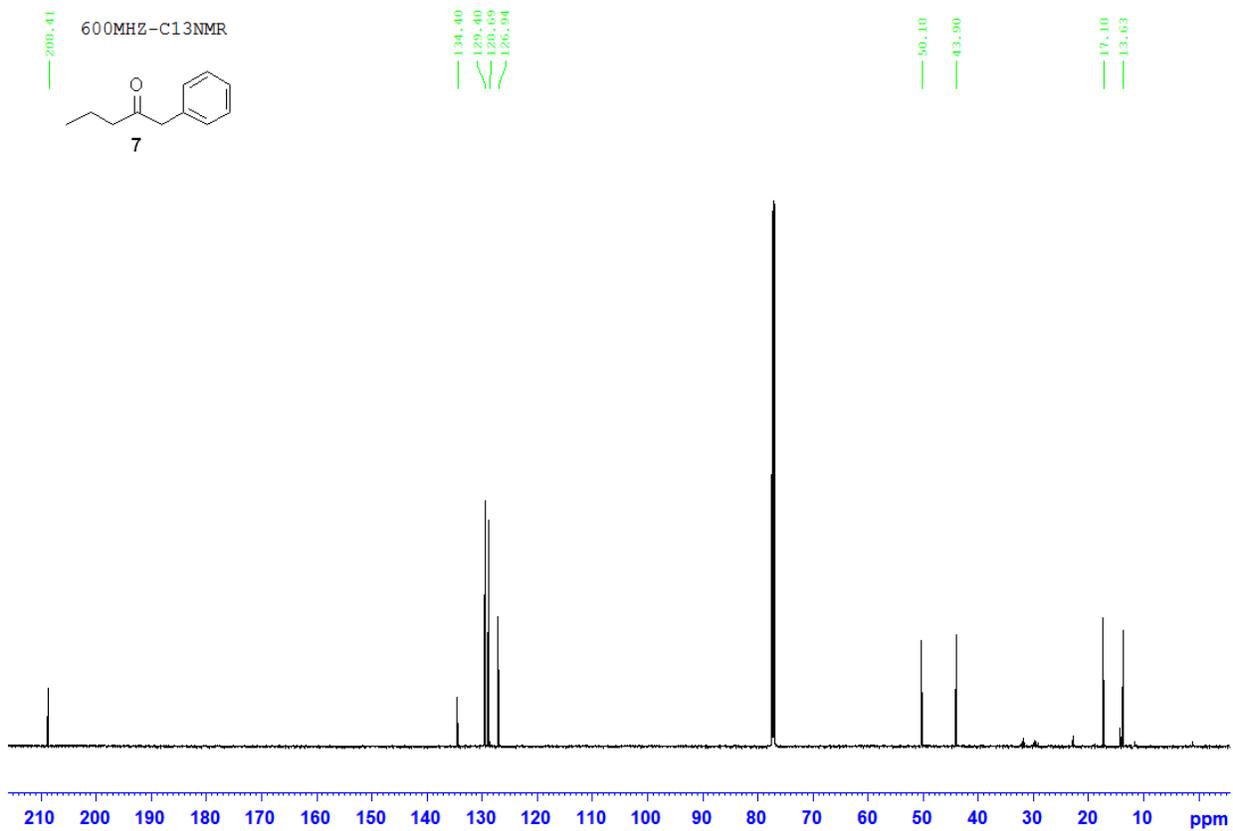
17.79

13.08

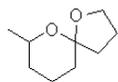


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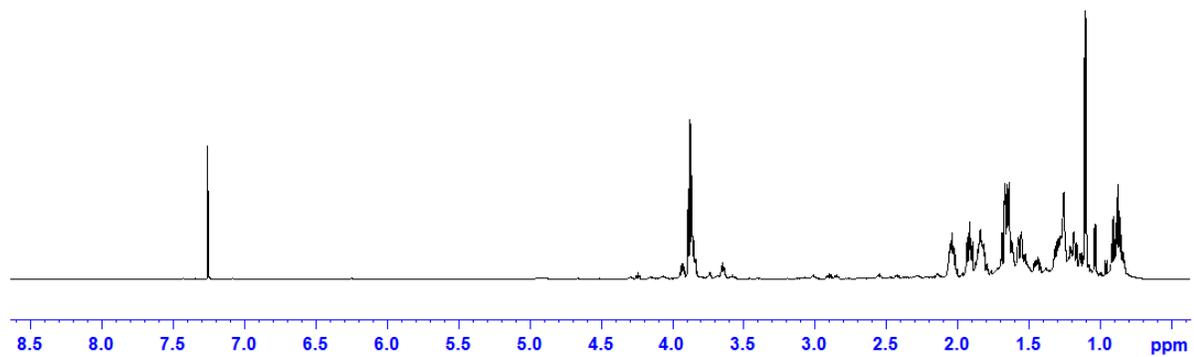




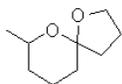
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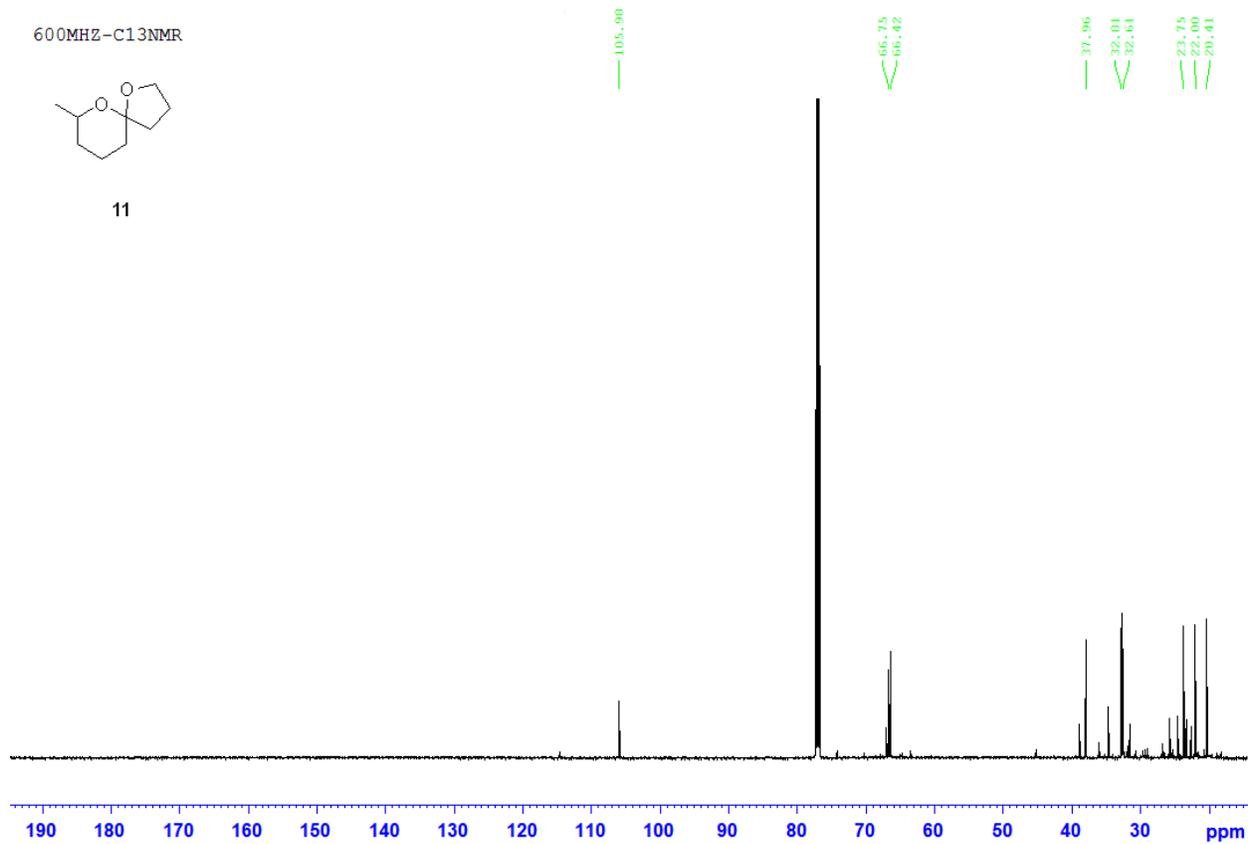
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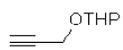
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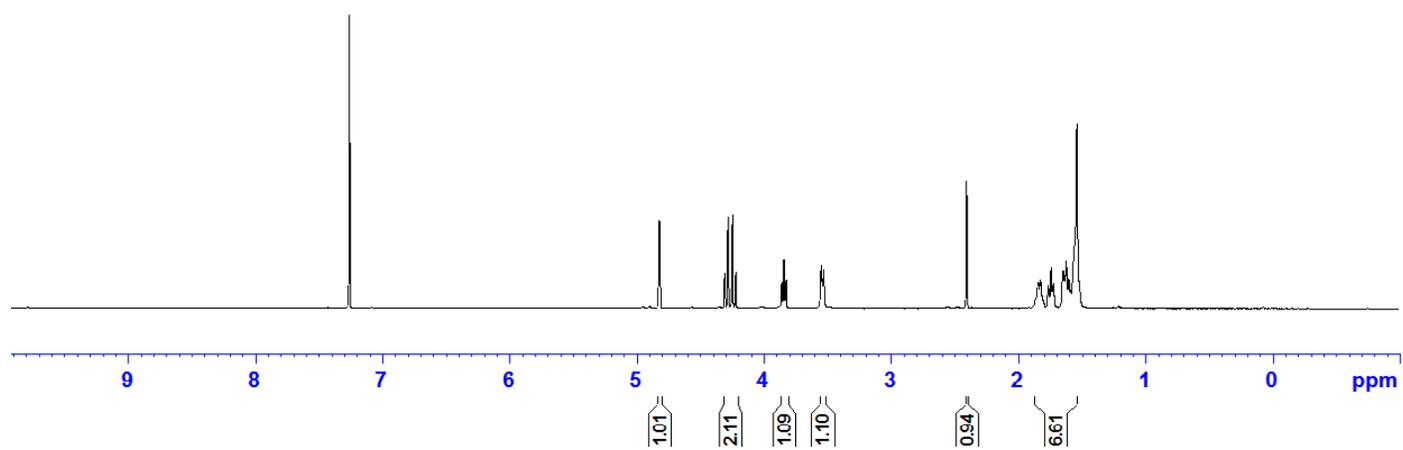
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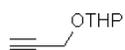
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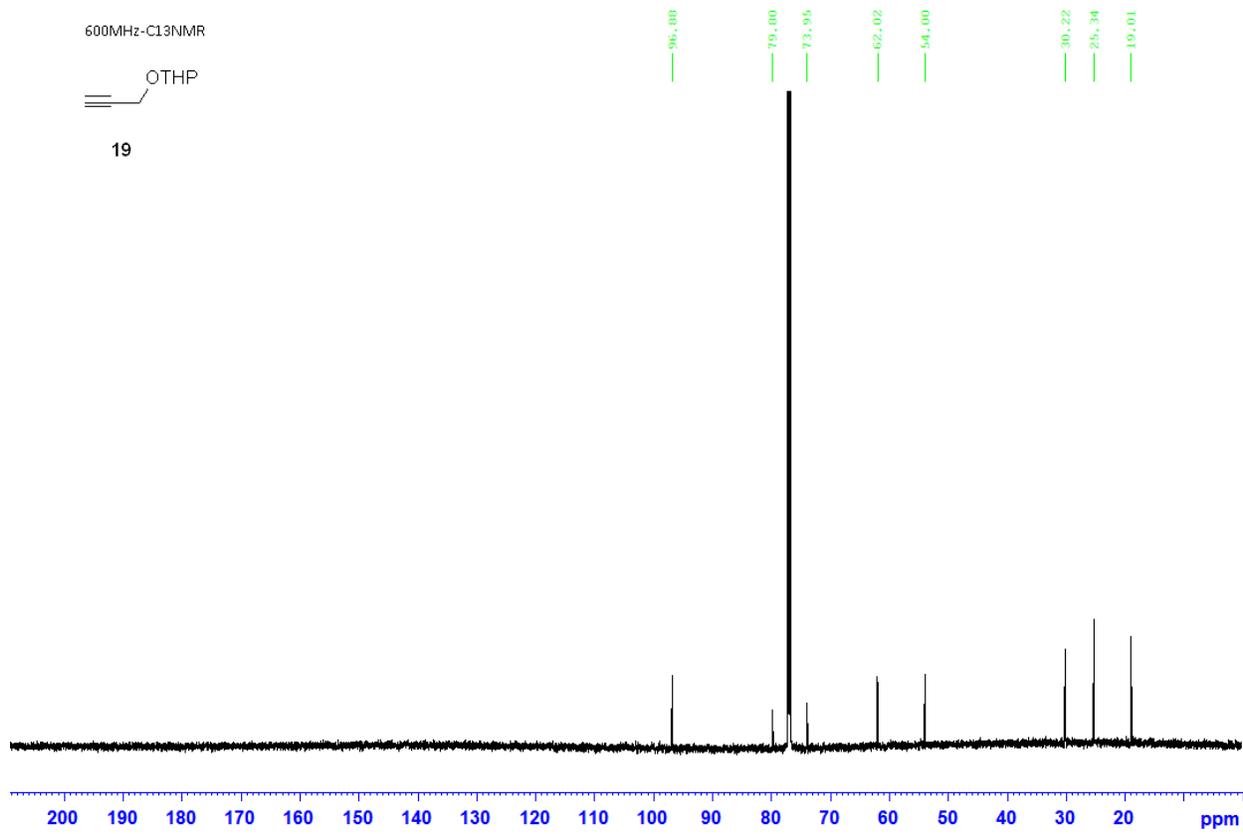
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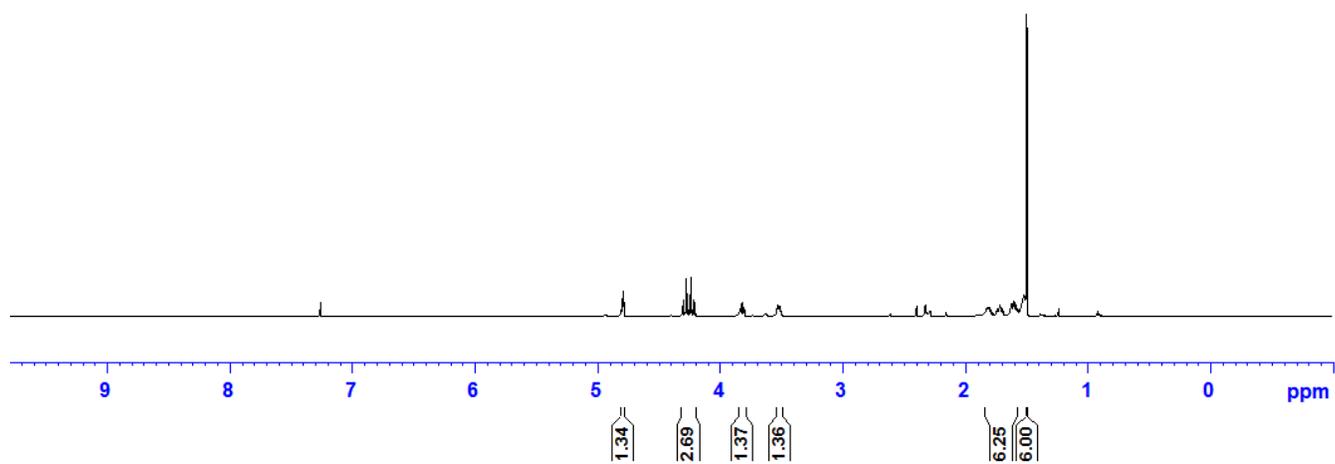
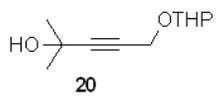
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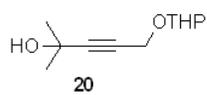
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600MHz-HNMR



600MHz-C13NMR



96.69

90.72

65.05

61.90

54.25

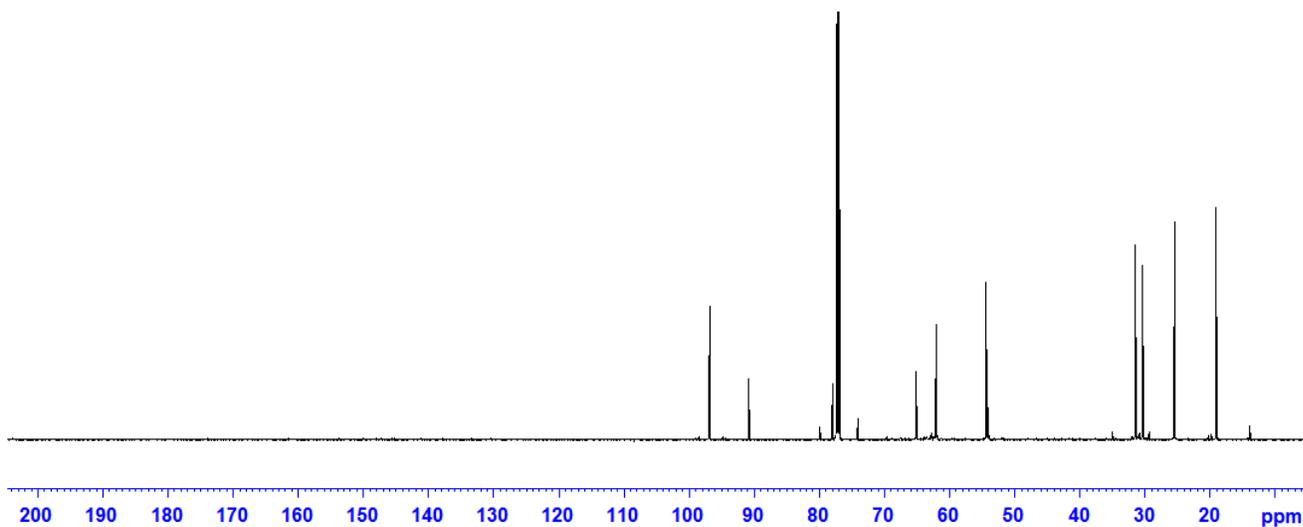
31.35

31.33

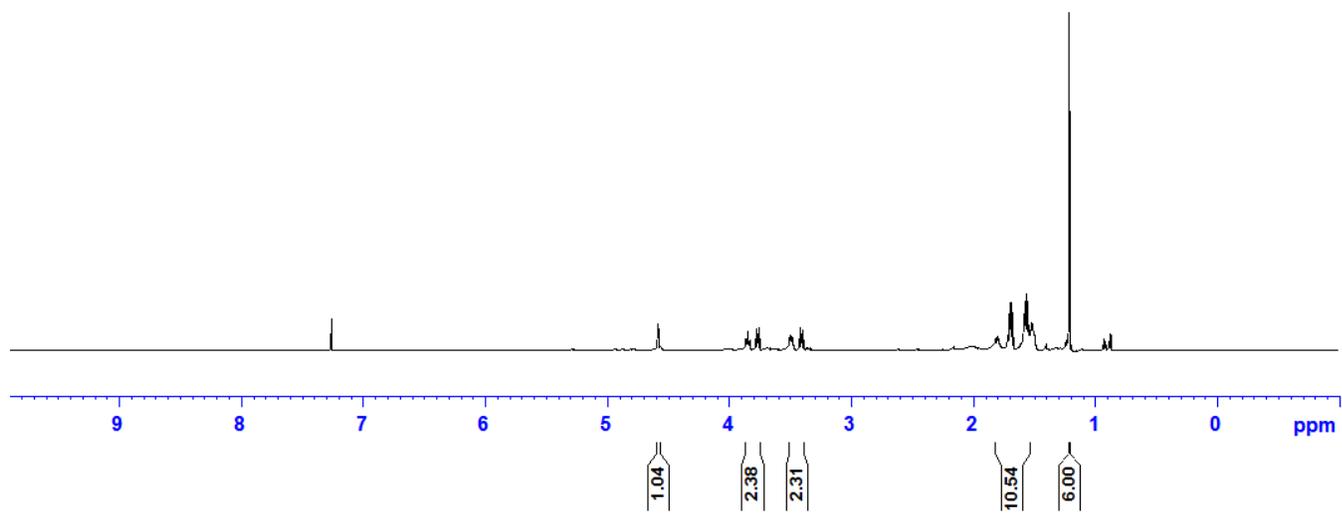
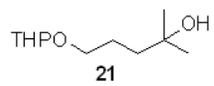
30.22

25.34

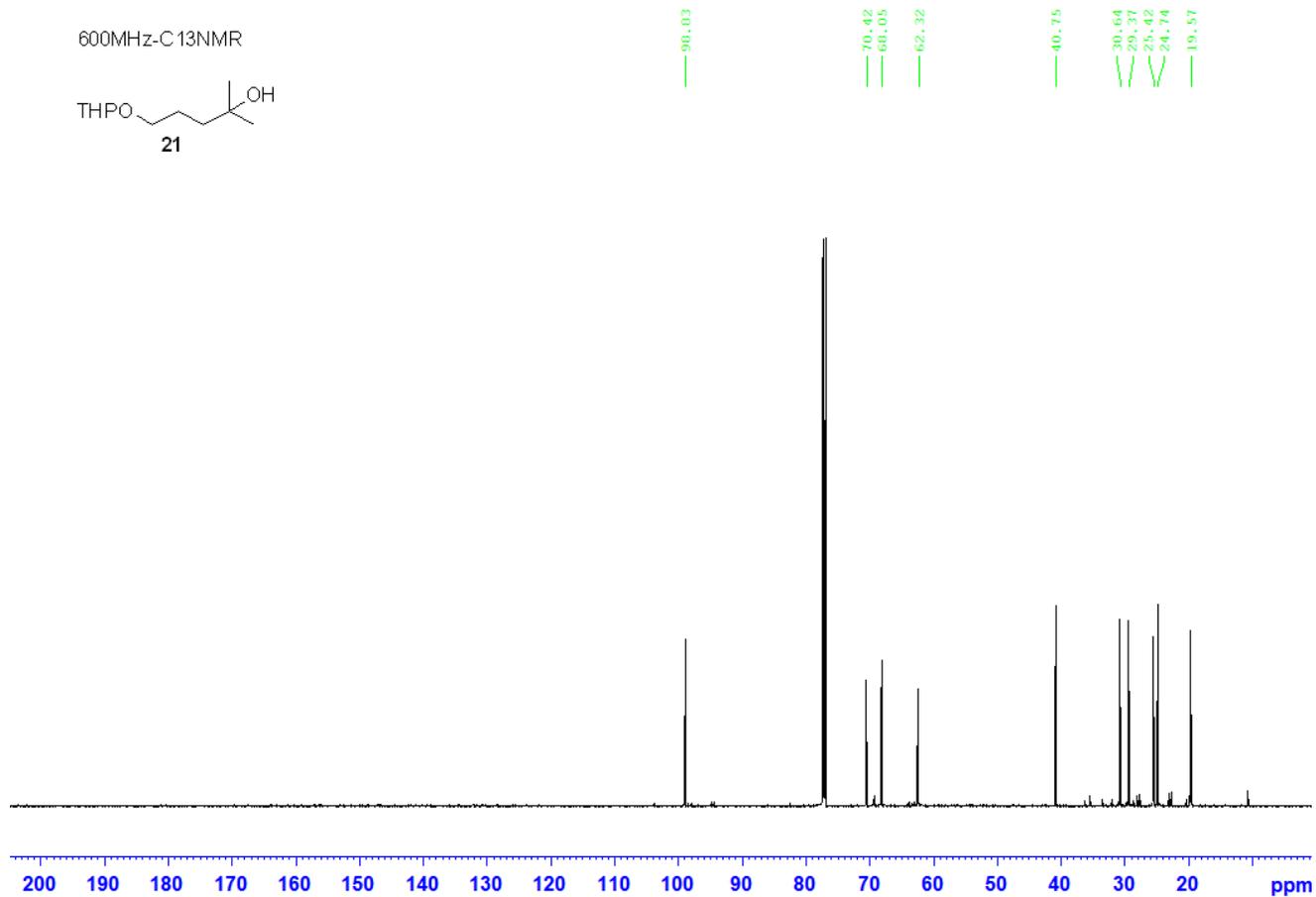
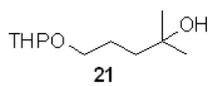
18.97



600MHz-HNMR



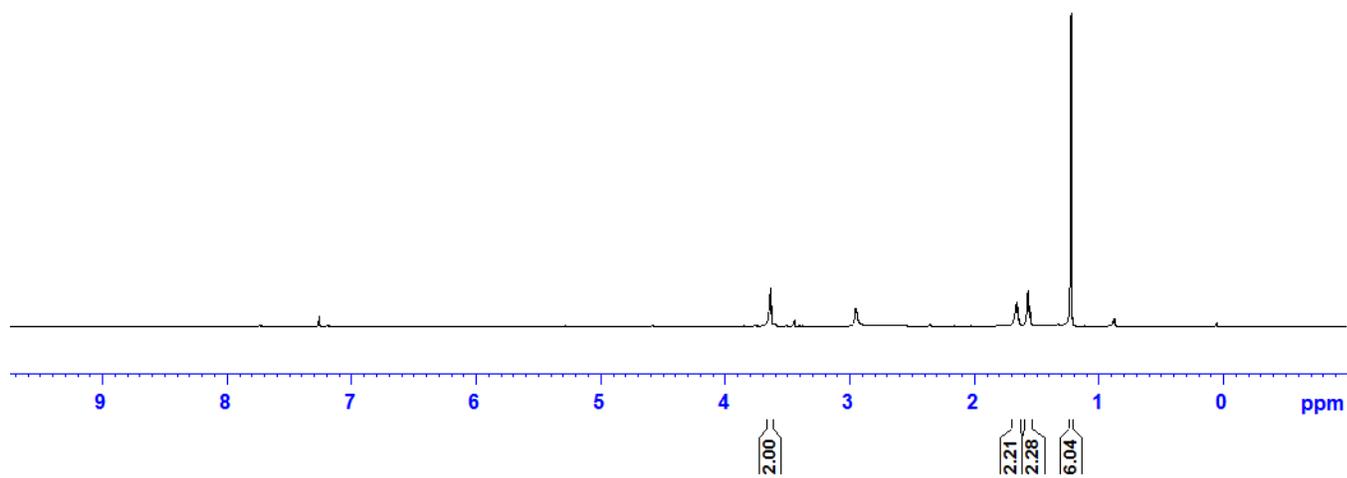
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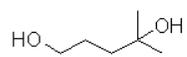
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22

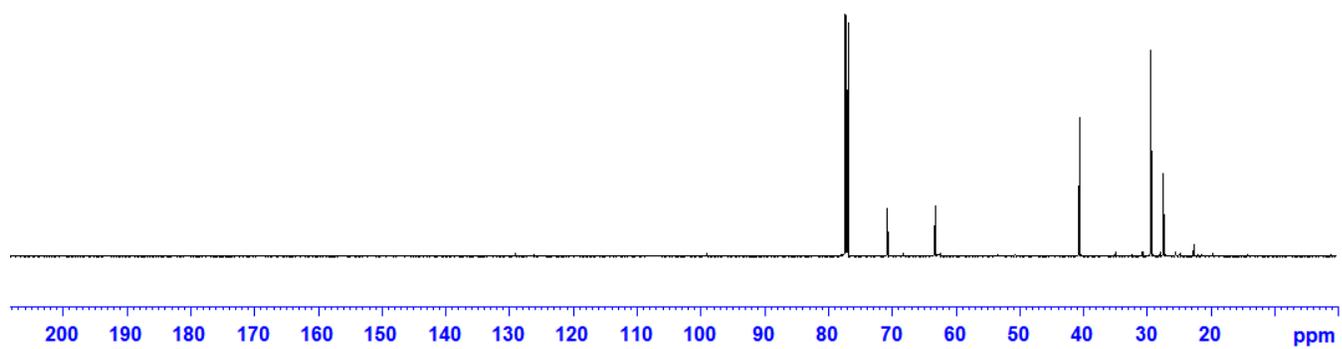


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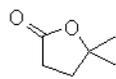


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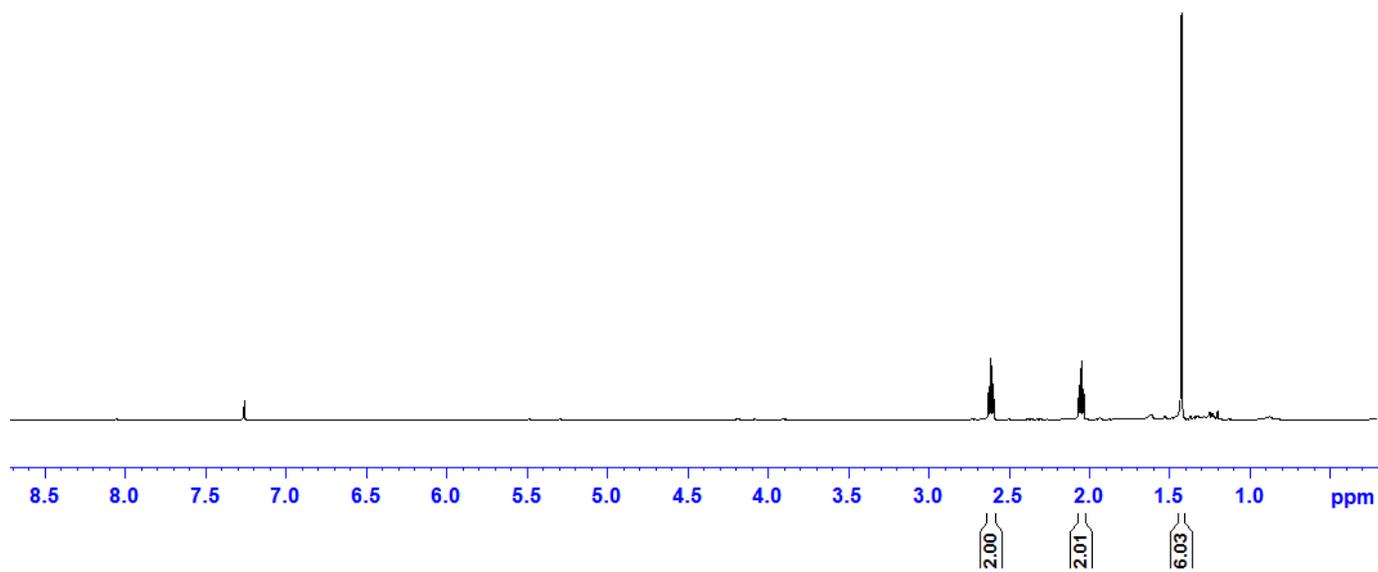
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63.13
40.49
29.35
27.37

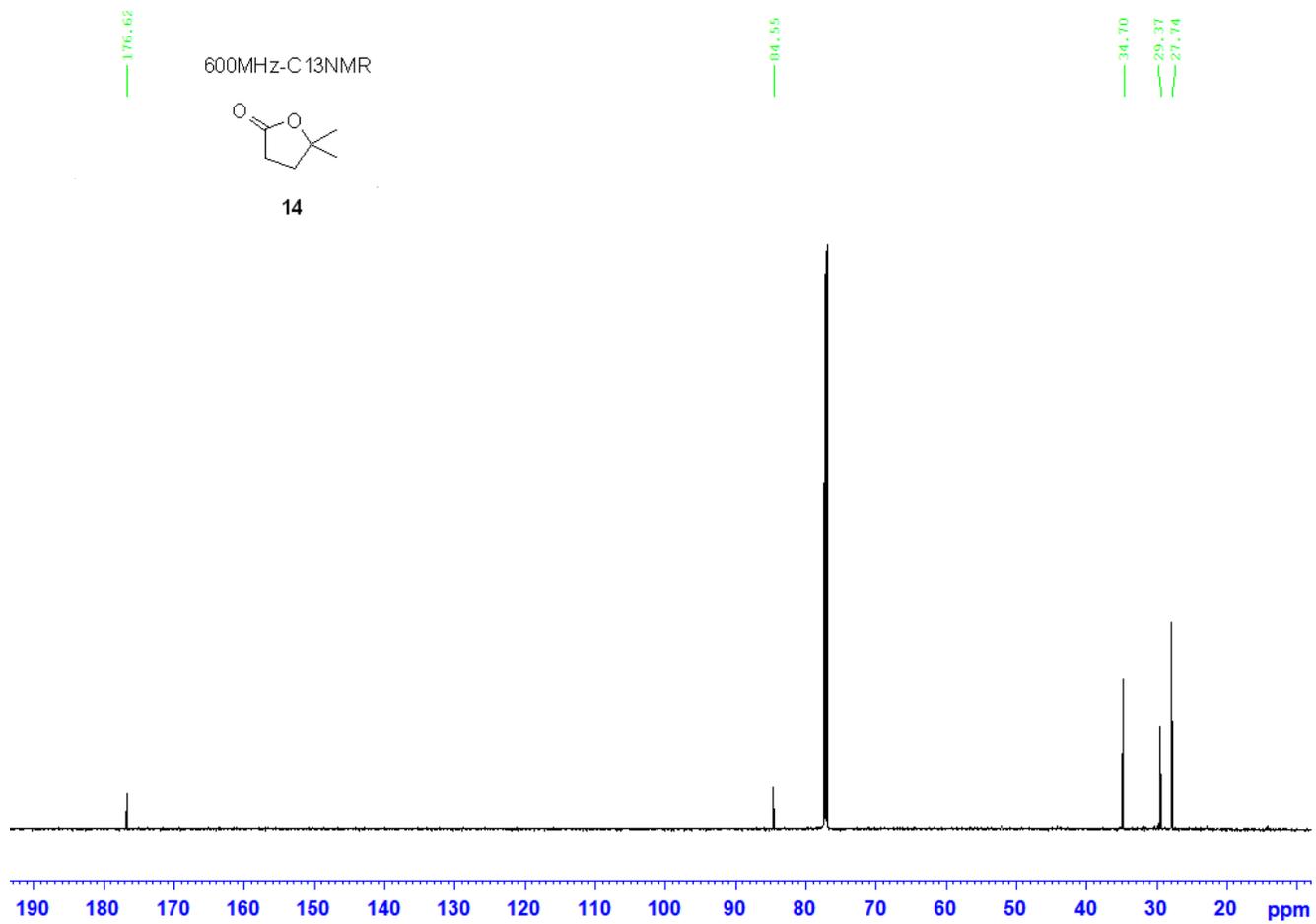


600MHz-¹H NMR

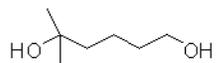


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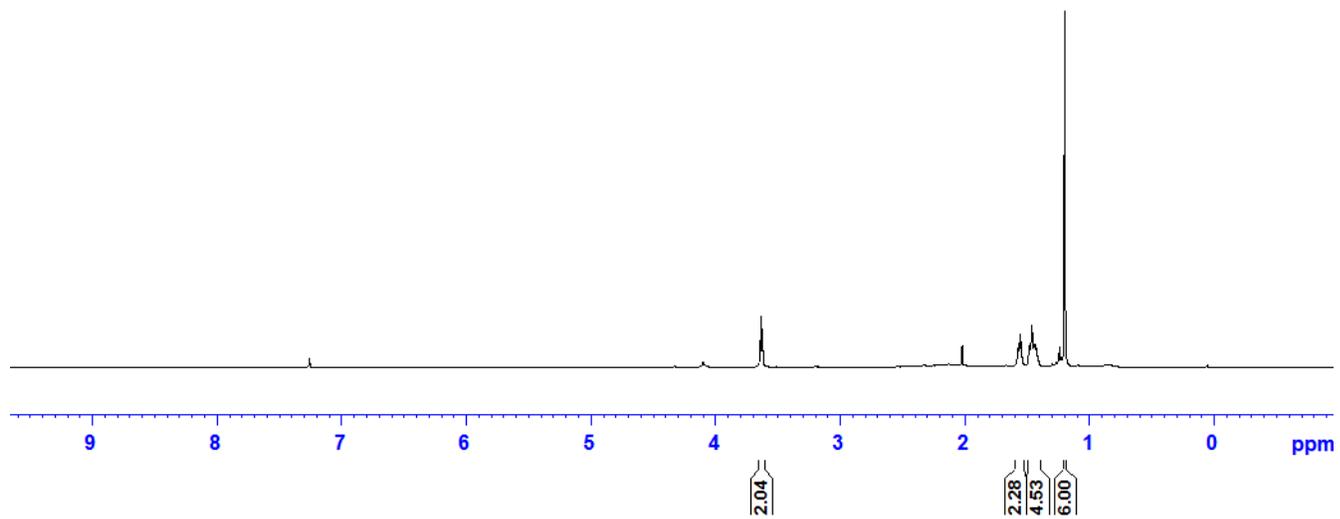




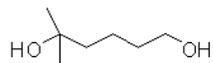
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17

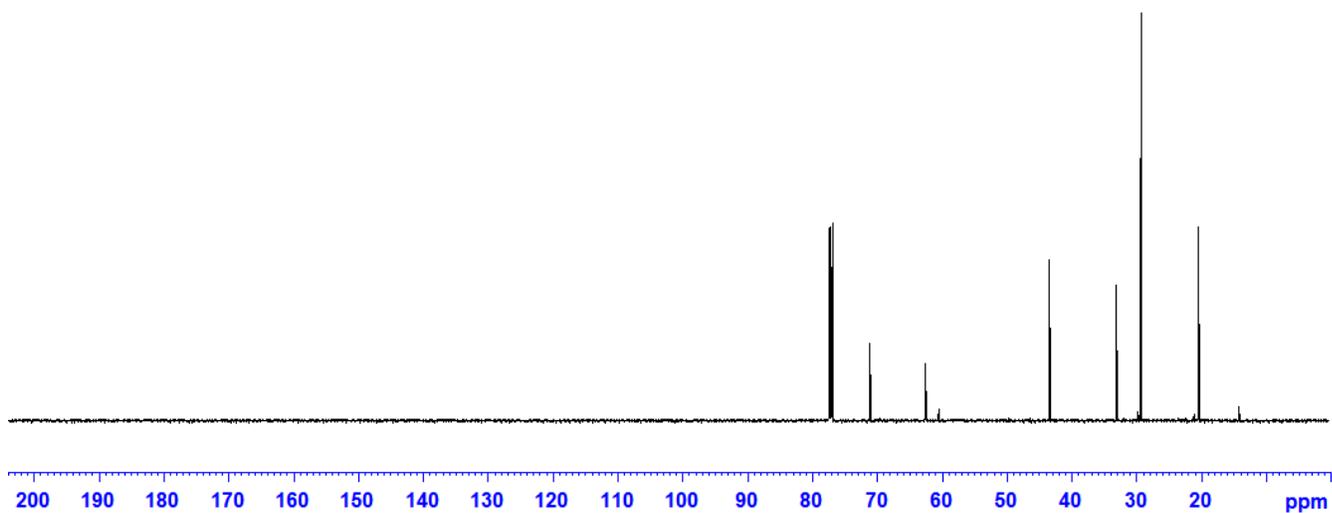


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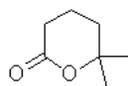


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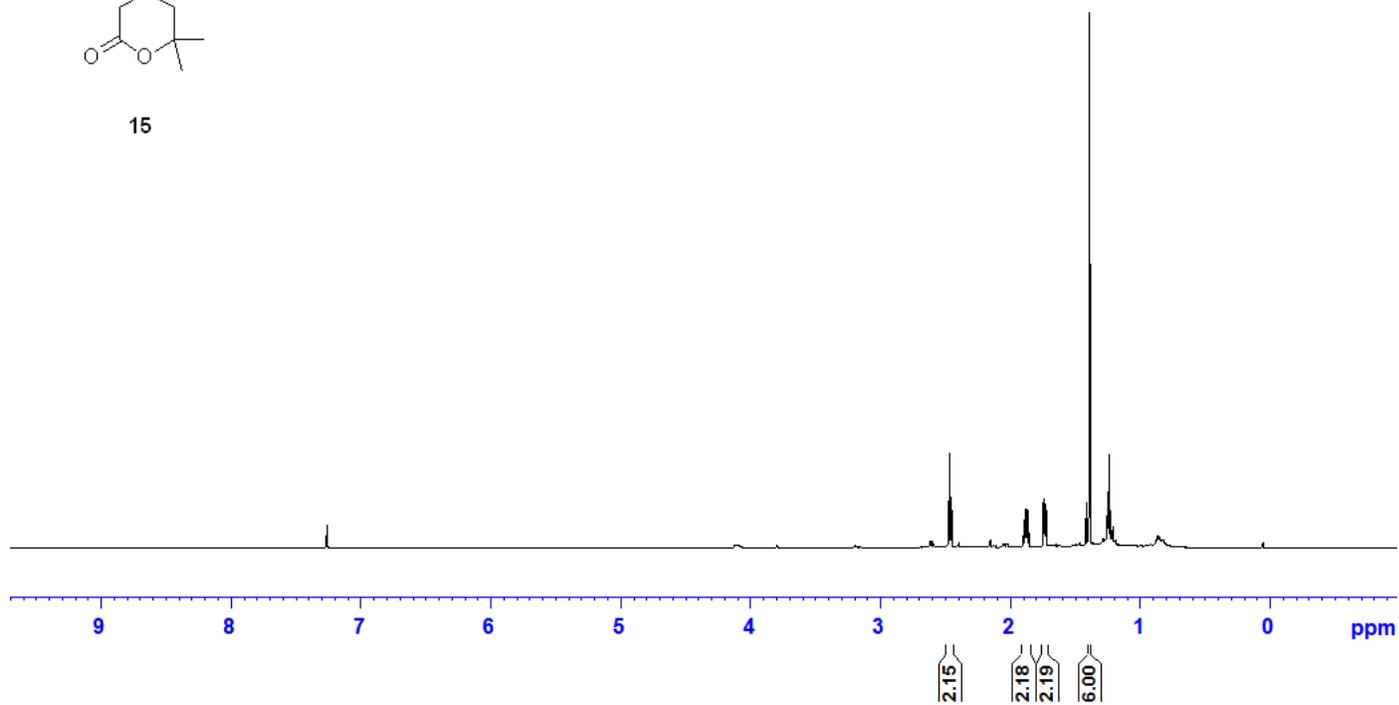
70.99
62.45
43.30
32.99
29.24
20.42



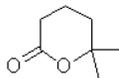
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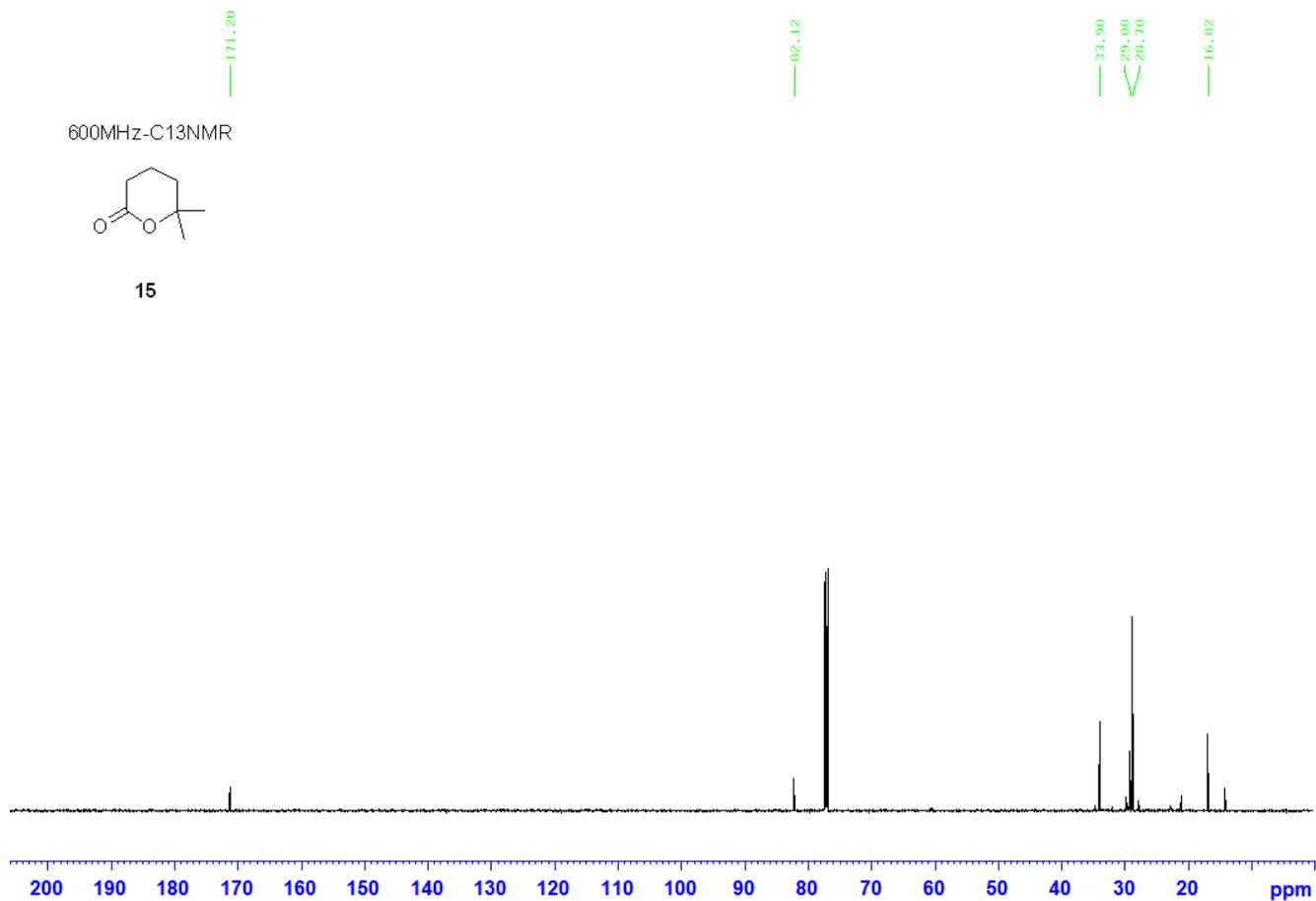
15



600MHz-C13NMR



15



Resume

Christine Beshay

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315-450-0325

Education

SUNY-ESF College / Syracuse/ NY

2019 M.S. in Organic Chemistry of Natural Products.

Ain Shams University / Egypt

2012 M.S. in organic chemistry

2009 Special diploma in organic chemistry and teaching preparation.

2008 General diploma in Science and teaching preparation.

2007 B.S. of Science and Education.

Skills

Instruments and Techniques

- Infrared Absorbance Spectroscopy
- Gas Chromatography-Mass Spectrometry
- Nuclear Magnetic Resonance Spectroscopy (H-NMR/¹³C-NMR)
- Thin Layer Chromatography
- Air/moisture free technique in synthesis (cannula and syringe)
- Use of equipment for reactions, distilling and re-crystallizations

Computer skills

Knowledge of Microsoft Office products Chemdraw, Scifinder and Analytical Systems Software.

Teaching Experience

- Teaching assistant in organic and inorganic chemistry/Ain Shams University (2008-2012)- guide and help the students during the lab and grade them.
- Teaching assistant in general and organic chemistry / SUNY ESF (2015-2019)

Publications

H.M. El-Shaaer, W. R. Abd-Elmonem, S.S. Ibrahim, **C.G.I. Beshay**; An efficient cyclocondensation reactions, antimicrobial activity and molecular orbital calculations of α -benzopyrone derivatives; *European Journal of Chemistry* 3 (2) (2012) 172-178.

H.M. El-Shaaer, W. R. Abd-Elmonem, S.S. Ibrahim, **C.G.I. Beshay**; Study of the Reactivity of 6,8-Dimethyl-4-oxo-4H-1-benzopyran-3-carboxaldehyde Towards Amino-6-oxopyridine-3-carboxylate Derivatives; *J. Heterocyclic Chem.*, 51, E167 (2014).

Graduate Scholarships

Ain Shams University (2008-2012).

Certification

Responsible conduct of research (physical sciences and conflicts of interest)
citiprogram.org

Professional summary

Accomplished and energetic researcher in chemistry with a solid history of achievement in teaching and research.

Reference

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