

Synthesis of Functionalized Tolanes for Release of Rose Scent

by

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TABLE OF CONTENTS

I. ABSTRACT	4
II. ACKNOWLEDGEMENTS	5
III. INTRODUCTION	6
FRAGRANCES: A SHORT HISTORY	6
PRO FRAGRANCES	8
HEXAPHENYLBENZENES	9
FOCUS OF THE PROJECT	10
SONOGASHIRA COUPLING REACTION	12
PREVIOUS WORK	15
SYNTHETIC ROUTE	16
IV. SYNTHESIS	19
CARBOXYLIC ACID SYNTHESIS	19
ESTER SYNTHESIS	21
TERMINAL ALKYNE SYNTHESIS	25
DIESTER TOLANE SYNTHESIS	30
V. HEADSPACE ANALYSIS	33
GAS CHROMATOGRAPH/HEADSPACE ANALYSIS	33
SURROGATE MOLECULE	34
PRELIMINARY METHOD DEVELOPMENT	35
RESULTS	36
DISCUSSION	44
VI. FUTURE WORK	45
FUTURE SYNTHESIS	45
ALTERNATE SYNTHESIS ROUTES	47
VII. CONCLUSIONS	50
VIII. REFERENCES	51
IX. VITAE	53
X. EXPERIMENTAL PROCEDURES	54
INSTRUMENTATION	54
IODOCARBOXYLIC ACID SYNTHESIS	54
DIESTER TOLANE PRECURSOR SYNTHESIS	55
XI. APPENDIX	58
GC/MS DATA	58
HEADSPACE GC/MS DATA	61
NMR DATA	66

List of Tables and Figures

FIGURE 3.1	9
EQUATION 3.1	10
FIGURE 3.2	11
FIGURE 3.3	11
SCHEME 3.1	13
SCHEME 3.2	14
EQUATION 3.2	14
FIGURE 3.4	15
FIGURE 3.5	16
SCHEME 3.3	17
EQUATION 4.1	19
FIGURE 4.1	20
EQUATION 4.2	22
FIGURE 4.2	23
FIGURE 4.3	24
EQUATION 4.3	26
FIGURE 4.4	28
FIGURE 4.5	29
EQUATION 4.4	31
FIGURE 4.6	32
FIGURE 5.1	33
EQUATION 5.1	34
TABLE 5.1	35
FIGURE 5.2	36
FIGURE 5.3	37
FIGURE 5.4	38
FIGURE 5.5	39
FIGURE 5.6	39
FIGURE 5.7	40
FIGURE 5.8	41
FIGURE 5.9	42

FIGURE 5.10	43
FIGURE 6.1	46
FIGURE 6.2	47
FIGURE 6.3	48
SCHEME 6.1	48

I. ABSTRACT

The long-term objective of this research is to synthesize and develop a set of functionalized hexaphenylbenzenes capable of the controlled release of volatile fragrant molecules, otherwise known as “pro-fragrances”. The focus of current work is on the synthesis of original appropriately substituted 4,4'-diphenylacetylenes (tolanes). These tolanes may be capable of scent release and can be cyclized with catalytic amounts of cobalt octacarbonyl to form hexaphenylbenzene molecules. Efforts have focused on optimizing the conditions and yields for the production of two tolane molecules substituted in the 4,4' positions with phenethyl ester groups. Upon hydrolysis, these ester groups will release the rose-scented 2-phenylethanol molecule. Synthesis of one tolane was accomplished through multiple steps culminating in the sequential modification of the Sonogashira coupling reaction. The required conditions (temperature, pH, time.) for the controlled hydrolysis of the tolane molecules were investigated via preliminary GC/headspace analysis and are strongly dependent on the stability of the tolane molecule.

II. ACKNOWLEDGEMENTS

I would like to acknowledge the A.R. Smith Department of Chemistry at Appalachian State University and its department chair Dr. Claudia Cartaya-Marin for providing me the education and resources to be able to complete this body of work. I would also like to thank Dr. Michael Ramey for his continued support and mentoring of this project for the last three years of my undergraduate career. I would also like to thank Mr. Jason Selong for his influence on me as a scientific writer, and for his support on this project. I would also like to thank Mr. Farrar and Dr. Taubman for providing me with the information I needed to gain a working knowledge of the headspace apparatus. Finally, I would like to thank my family for being so incredibly supportive of me during my undergraduate career, as well as my best friend and boyfriend Brian Clee, for without his encouragement and loving support, this document would not exist today.

III. INTRODUCTION

In a world overcome with stimuli, one of the most influential stimuli seems to fly under the radar – right under one’s nose, as they say. The smell of fresh laundry or perfume is all due to the technology of organic synthesis. Since the 19th century, when it was found that organic synthesis could be utilized to develop synthetic scent that mimicked those of natural essential oils, the fragrance industry has relied on the technology of the organic chemistry field to drive the industry.¹

Fragrances: A short history

Fragrant molecules, by definition, are organic molecules that are sufficiently volatile enough to be transported to the upper part of the nose and detected by olfactory receptors via chemotaxis.² Chemical compounds that are this volatile typically have a small molecular weight, usually less than 300 amu, and are exemplified by ester, alcohol, aldehyde, ketone, or amine functional groups, though this list is in no way exhaustive.²

There are two sources of fragrant molecules, natural sources and synthetic sources. Natural sources of fragrant molecules are derived from plants in the form of essential oils. There are three main ways in which these essential oils can be extracted. The first way is through expression, when essential oils are “pressed” by inducing physical pressure on the oil’s source.¹ Citrus oils are an example of oils produced by pressing.¹ Another common form of oil isolation is through dry and steam distillation.¹ Dry distillation involves high temperatures and direct flame to extract high boiling point oils from their sources. Pine oils, for example, are derived this way. Finally, the most common form of extraction is steam distillation and hydrodiffusion, where steam or

water is added to the raw materials so that the water is codistilled with the oil. Once the oil and water mixture has been distilled, the water is then removed. Many floral oils, such as rose oil are isolated in this manner.¹

Due to the volatile nature of fragrance, large quantities of the plant from which the scent derived from had to be grown and intensively processed. Rose oil, for example, requires approximately 60,000 roses for the extraction of one ounce.¹ Thus, until the 19th century, fragrances were reserved only for the wealthy, as they were the only ones who were able to afford such a costly product.^{1, 2} If the perfume industry still relied solely on essential oils in this manner, it would not be able to function based on the cost alone. The discovery of synthetic fragrant molecules in the 19th century, along with Coco Chanel's idea of bringing high fashion to the "every woman", helped to kick start the transition from natural fragrances to synthetic fragrances. Unlike many natural fragrances, synthetic molecules could be blended with other synthetic fragrances molecules to create new fragrances, which Coco Chanel premiered with her fragrance "Chanel No.5". The popularity of this new fragrance revitalized the industry.¹

As organic synthetic knowledge advanced, synthetic fragrance derivatives that imitated their naturally derived counterparts and were easier and less expensive to make. For example, the extensive process to recover rose oil could now be replaced with a styrene monomer/propylene oxide (SMPO) process, whose efficient and low cost process produces massive amounts of 2-phenylethanol, a rose oil analog.^{1, 3} Thus, fragrance previously reserved only for the elite could now be used as an essential blending molecule for a plethora of other fragrances.¹ Fragrances were also synthesized in such a way to maintain their integrity in more acidic and basic environments, opening the door

for a much wider range of scent applications. Previously unscented products, such, as soaps, bleaches and detergents, were now fragrant and thus more marketable. Ironically, the success of these products has led to a dye and perfume free product movement more recently.

Pro fragrances

The economic production of organic molecules was no longer a problem, but the length of scent release within fragranced products continued to be a tricky. Scent release was short and uncontrolled, due to the organic compound's volatility. Scientists searched for a way to either lengthen the release of scent, or trigger the scent release at the desired time. The idea of pro fragrances began in 1956 when Ashburn and Teague patented a way to create stable aromatics and flavorings in tobacco products.⁴ They found by adding small esters, compounds would remain stable and non-fragrant until burning, when the ester bond would break and aromatic carboxylic acids would be released.^{4a} For the next 50 years, research on the controlled release of bioactive molecules was conducted.⁵

Currently, there are two identified allowing scent release to be controlled and triggered at an appropriate time.³ The first mechanism is through physical microencapsulation of the fragrance of interest. These capsules are made of various polymers, either to exist in more hydrophobic or hydrophilic environments, and allow for the congregation of volatile molecules in the center of the capsule without covalent bonding to the capsule itself.³ However, this type of pro fragrance will not be discussed further in this body of work.

The other category of pro fragrances is similar to an approach used in drug

delivery systems in concept.³ This approach utilizes much larger precursors molecules covalently bonded to volatile molecules, and is the focus of this investigation.³

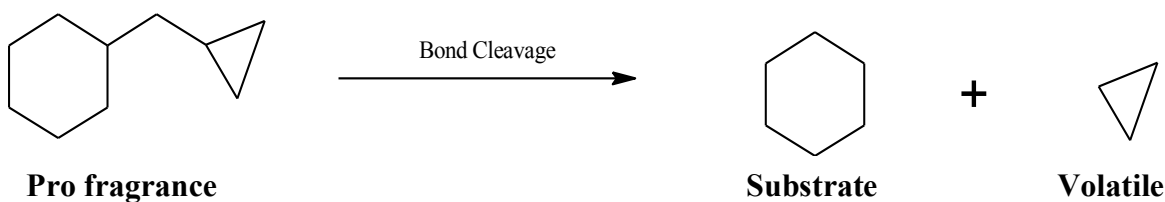
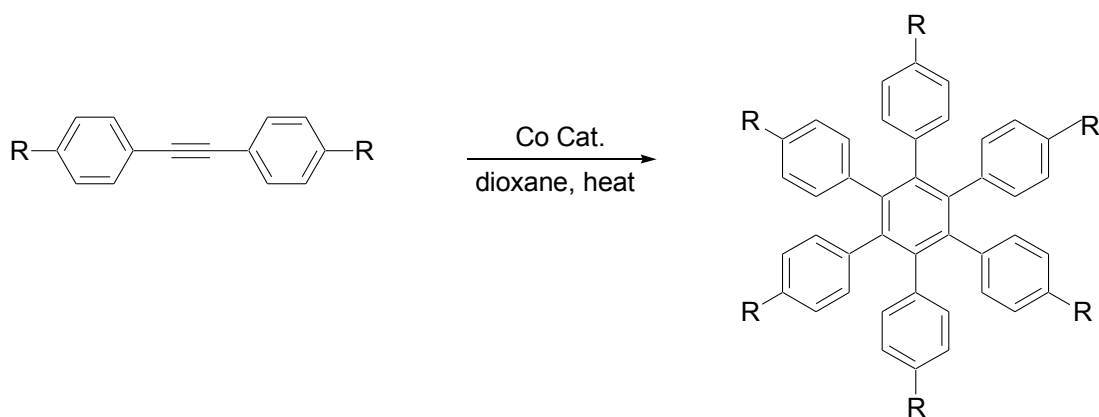


Figure 3.1. General mechanism of pro fragrance

Here a volatile organic molecule is covalently bonded to the much larger substrate molecule, until some sort of stimulus encourages bond cleavage, which splits the fragrance molecule from its substrate (Figure 3.1). Ideally, these large precursors must be relatively stable, but also able to decompose and release the volatile organics under mild conditions.³ It is also desirable for a pro fragrant molecule to be able to release more than one volatile per precursor, as to enhance the economic value of the pro fragrance itself.³ Ester bonds are easily cleavable and release alcohols and carboxylic acids.³ Cleavage of these bonds can happen under various conditions including temperature change, pH change, and light exposure.³ The most common form of bond cleavage found in many products is hydrolysis in pH adjusted aqueous conditions to promote bond cleavage.³ This decomposition system is found in many products containing fragrance, including fabric softeners, laundry detergents, soaps and shampoos.³

Hexaphenylbenzenes

For the last few years, the Ramey research group has been working on the synthesis of various functionalized hexaphenylbenzenes⁶ (HPB), as seen in Equation 3.1.



Equation 3.1. The Co catalyzed synthesis of functionalized hexaphenylbenzenes⁶

By starting with a di-functionalized tolane, the hexaphenylbenzene compound can be synthesized through a cobalt catalyzed cyclization reaction capable of having 6 different substituent groups to be attached to it, and these groups can drastically affect the physical properties of the HPB and its subsequent reactions.⁶ Due to this molecule's unique ability to support six different substituent groups, the question can be asked – can hexaphenylbenzenes act as a highly efficient delivery system for scent release?

Focus of the Project

The focus of this project is to synthesize a precursor-esterified tolane with a methylene spacer that can be cyclized in the future to produce an ester functionalized hexaphenylbenzene pro fragrant molecule. Because many fragrance molecules are alcohols, it is believed that if the six functional arms of the hexaphenylbenzene are substituted with ester groups, these six alcohol molecules can be released upon hydrolysis, leaving the hexaphenylbenzene with carboxylic acid substituted arms, as seen in Figure 3.2.

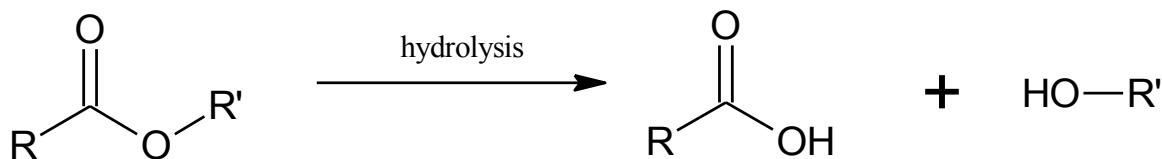


Figure 3.2. General ester hydrolysis reaction

The conjugation of the hexaphenyl group itself, and large size of the molecule will provide ample stability for the molecule until put under hydrolysis conditions. The hexasubstituted esters would give the pro-fragrance more “bang for its buck” with the ability to hydrolyze six ester groups per molecule as opposed to just one. Additionally, the resulting carboxylic acid product can act as an antimicrobial, as carboxylic acids are commonly used for this purpose.³

The rate of hydrolysis for these esters is dependent upon three major factors: the stability of the ester bond in the precursor structure, temperature, and the pH of hydrolysis conditions.³ Primary alcohols, as part of the ester structure, proliferate the rate of hydrolysis better than secondary or tertiary alcohols. Neighboring nucleophilic groups can intramolecularly attack the ester carbonyl thus releasing the alcohol and increasing the rate of hydrolysis.³ Knowing this, the alcohol of interest to be attached to each arm of the hexaphenylbenzene will be the primary alcohol 2-phenylethanol (Figure 3.3).

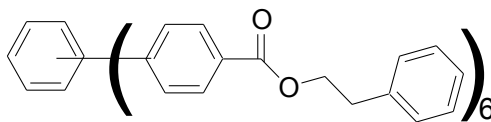
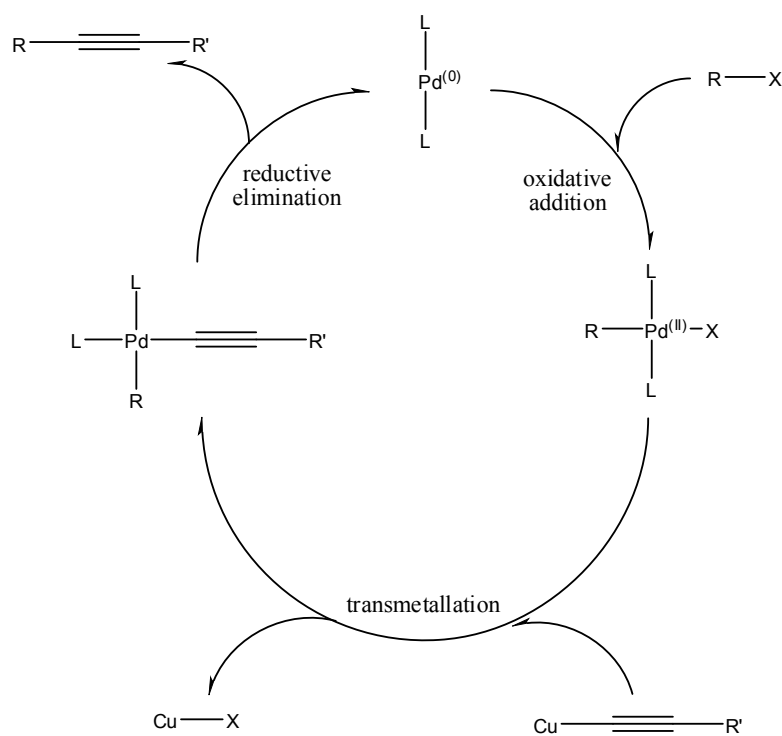


Figure 3.3. 2-phenylethanol functionalized Hexaphenylbenzene

With the phenyl rings out of plane, along with the 2-phenylethanol being a primary alcohol, the ester bond should be able to cleave under relatively mild hydrolysis conditions. The exact conditions of hydrolysis will begin to be determined via GC headspace analysis.

Sonogashira Coupling Reaction

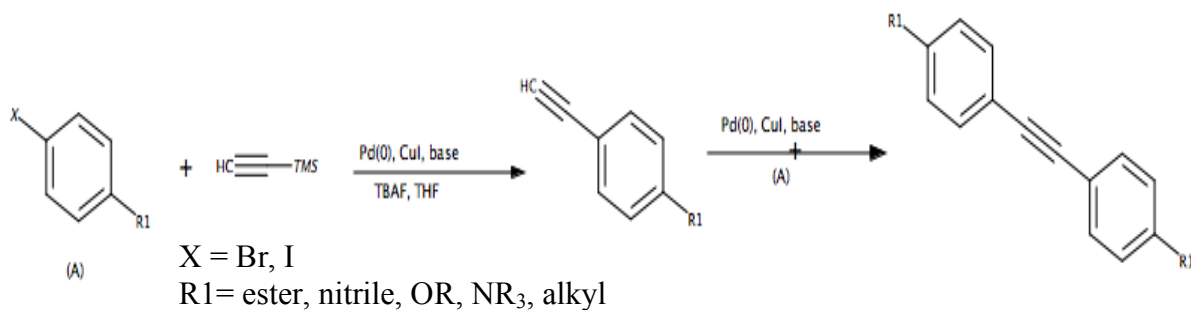
Prior to cyclization to the hexaphenylbenzene, a synthetic route to the tolane precursor must be found. A pro fragrance molecule in its own right, this difunctionalized diphenyl acetylene would have similar properties to the hexaphenylbenzene. Synthesis of the tolane precursor will be completed via the Sonogashira coupling reaction. This palladium-catalyzed reaction is useful in synthesizing carbon-carbon bonds. The mechanism of the Sonogashira coupling reaction, along with other coupling reactions, like the Suzuki and Stille coupling reactions, involves the use of a three step catalytic cycle⁷ (Scheme 3.1).



Scheme 3.1. General Pd(0) catalytic cycle⁸

Once the palladium(II) catalyst is activated to Pd(0) through reduction with copper and terminal alkyne, the Pd(0) reacts with an aryl halide in an oxidative addition to yield a Pd(II) intermediate. This intermediate then undergoes a transmetallation step with a copper acetylide. A terminal alkyne is reacted with a catalytic amount of CuI in a separate cycle. The transmetallation couples the acetylide to the palladium catalyst and expels a copper halide. Finally, in a reductive elimination reaction, the tolane is produced, and the palladium catalyst is regenerated.⁸

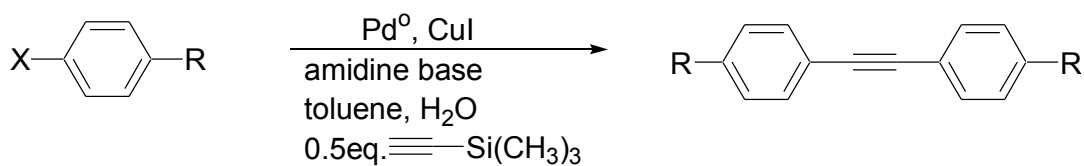
Generally, Scheme 3.2 depicts an aryl iodide that is connected to a terminal acetylene,⁹ which is then used in a second sonogashira reaction with the acetylene again to make a tolane.



Scheme 3.2. Sequential Sonogashira Coupling reaction⁹

Completion of two coupling reactions as shown above, with deprotected acetylene as an intermediate, is called a sequential Sonogashira coupling reaction. Positive aspects of completing a Sonogashira coupling reaction in this manner includes insuring that the proper acetylene intermediate is being synthesized, thus assuring that the final tolane will be produced upon the second coupling. However, this sequential method can be time consuming, and isolation of the terminal acetylene after the first coupling can cause some product loss, which would lower the yield of the final tolane.

Besides the sequential method, the reaction may also occur all at once, called the “one-pot” method, as seen in equation 3.2.¹⁰



Equation 3.2. “One-pot” Sonogashira Coupling reaction

The above method monoprotects and deprotects the acetylene in situ through the use of

amidine base and a small stoichiometric amount of water. This method is much faster than the sequential method. Though, if the stoichiometric amounts are incorrect, there is a chance that the reaction will fail, meaning more precious synthetic material is ruined. However, both methods can be investigated to synthesize any disubstituted tolane of interest.

Previous Work

A diester tolane whereby the ester functional group was directly attached to the benzene ring was successfully synthesized using a one-pot Sonogashira coupling reaction (Figure 3.4). However, it was found via preliminary headspace analysis that the tolane required 1mL of water, acetone and concentrated HCl to release the volatile 2-phenylethanol¹¹ (Figure 3.5).

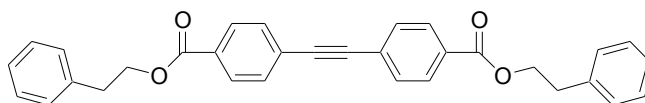


Figure 3.4 - Previous tolane precursor without a CH₂ spacer.

It is believed that the conjugation of the ester caused the tolane to be too stable for the desired mild hydrolytic conditions. It was determined that an ester precursor with a methylene (-CH₂-) spacer between the benzene ring and carbonyl group should lessen the stability and allow for hydrolysis under more mild conditions.

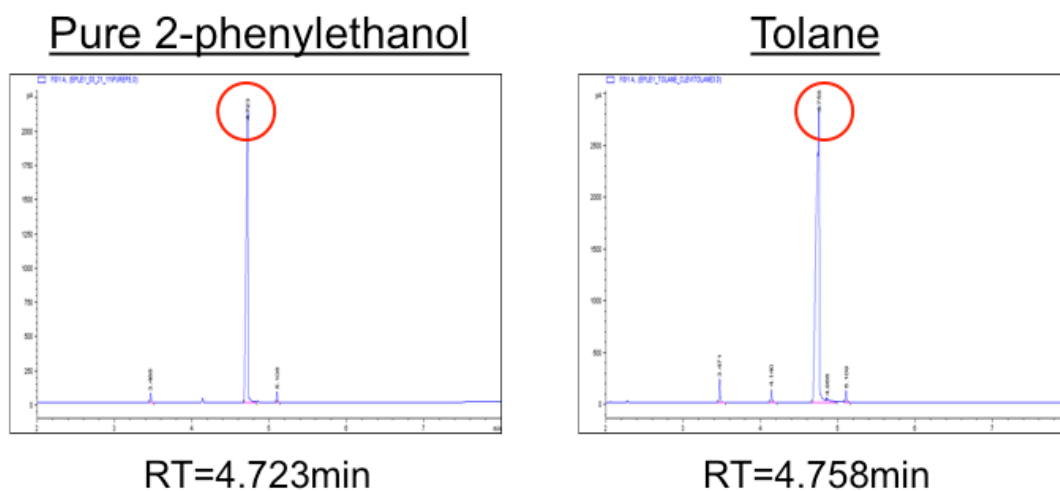
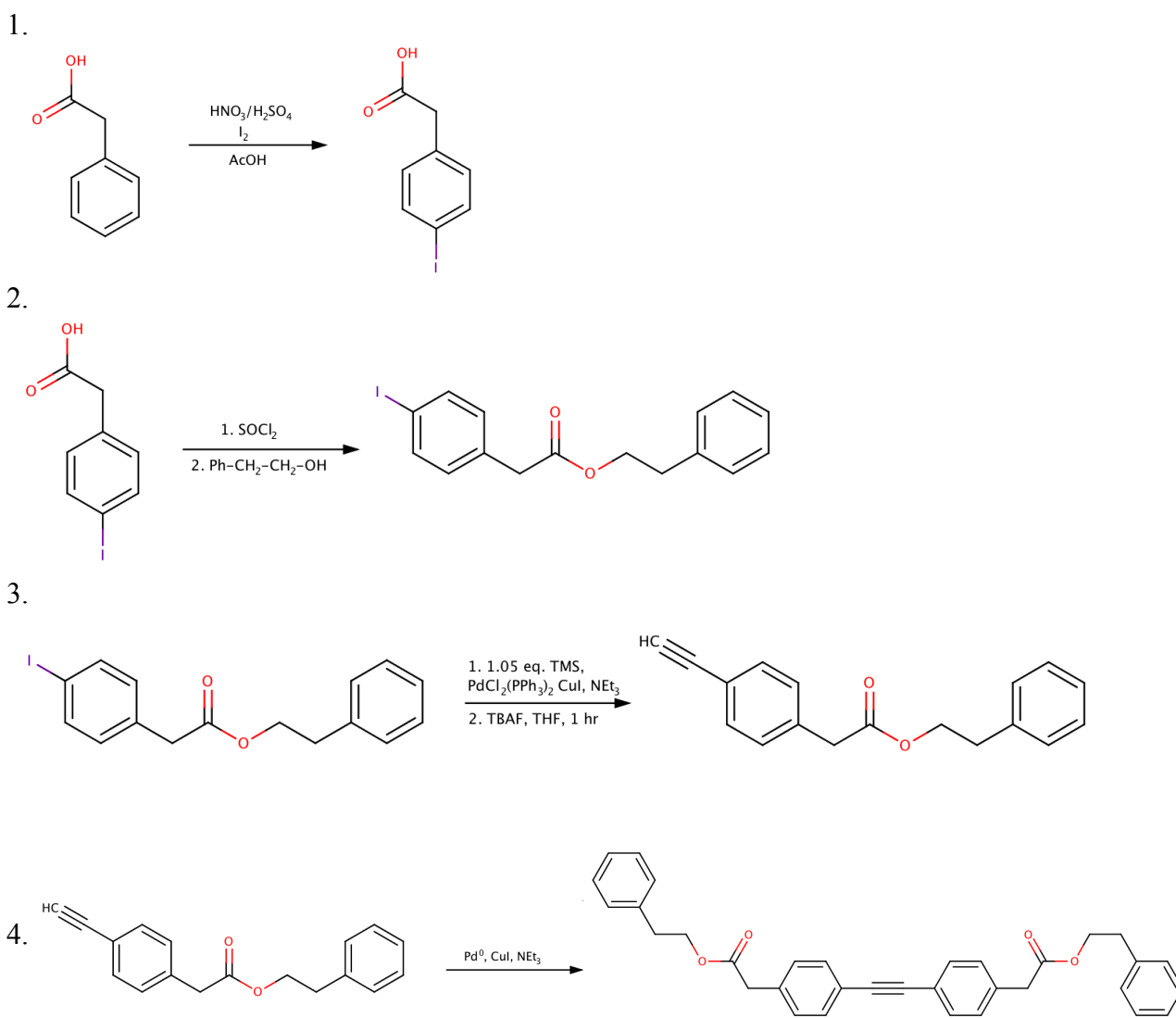


Figure 3.5 - Previous GC headspace analysis results.¹²

Synthetic Route

The proposed route for synthesizing the spacer tolane will involve the sequential Sonogashira coupling reaction to ensure completion of the reaction and for proof of concept, as seen in Scheme 3.3.



Scheme 3.3 – Synthetic route to methylene spacer (-CH₂-) disubstituted ester
functionalized tolane

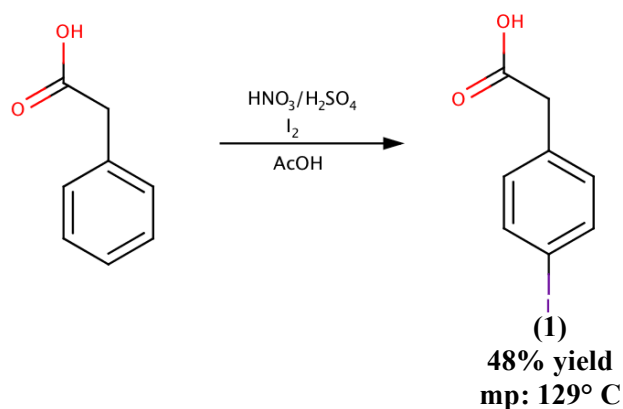
The starting iodinated carboxylic acid can be esterified via nucleophilic acyl substitution of an acid chloride in-situ with the subsequent addition of 2-phenylethanol to yield the aryl ester halide. The synthesized aryl ester halide will then be a part of the successive Sonogashira coupling reactions.

Overall, the project will focus on the stepwise synthesis of a methylene spacer tolane, which will then be tested for its ability to release 2-phenylethanol via mild hydrolysis conditions via a preliminary headspace analysis method.

IV. SYNTHESIS

Carboxylic Acid Synthesis

In order to synthesize a di-substituted diester toluene precursor, a halogenated ester must first be produced. It was found that one of the most efficient ways to produce this ester was to esterify an iodinated carboxylic acid. In order to create a pro-fragrant molecule that could easily degrade under neutral conditions, an ester derived from phenyl-acetic acid was the target molecule. This molecule possesses a CH₂ spacer between the aromatic ring and carbonyl group, making the ester less stable; theoretically making the ester more able to hydrolyze. Iodine was chosen as the halogen due to its excellent behavior in palladium catalyzed reactions. The iodination occurs in one step, involving the basic addition of acid and iodine. Equation 4.1 outlines the iodination procedure used to synthesize (4-iodo-phenyl)-acetic acid (**1**) from phenyl acetic acid, a commercially available reagent.



Equation 4.1. Iodination to synthesize (**1**)¹³

Based on an article by Waybright¹³ and synthesized by Alex Cella, phenyl acetic acid and

iodine were added together with glacial acetic acid, followed by a slow drop wise addition of a 1:4 mixture of concentrated nitric and sulfuric acids. Then, the solution was heated to 60° C for approximately 1.5 hours. The solution was then removed from heat and allowed to stir at room temperature overnight. The mixture was then poured over ice and vacuum filtered. At this point, a pink solid was recovered and recrystallized from hexanes to produce (4-iodo-phenyl) – acetic acid (**1**) in 45% yield. Gas chromatography and mass spectrometry (Figure 4.2) were used to help identify (**1**) with a retention time of 18.25 minutes and a molecular ion peak at 262 m/z.

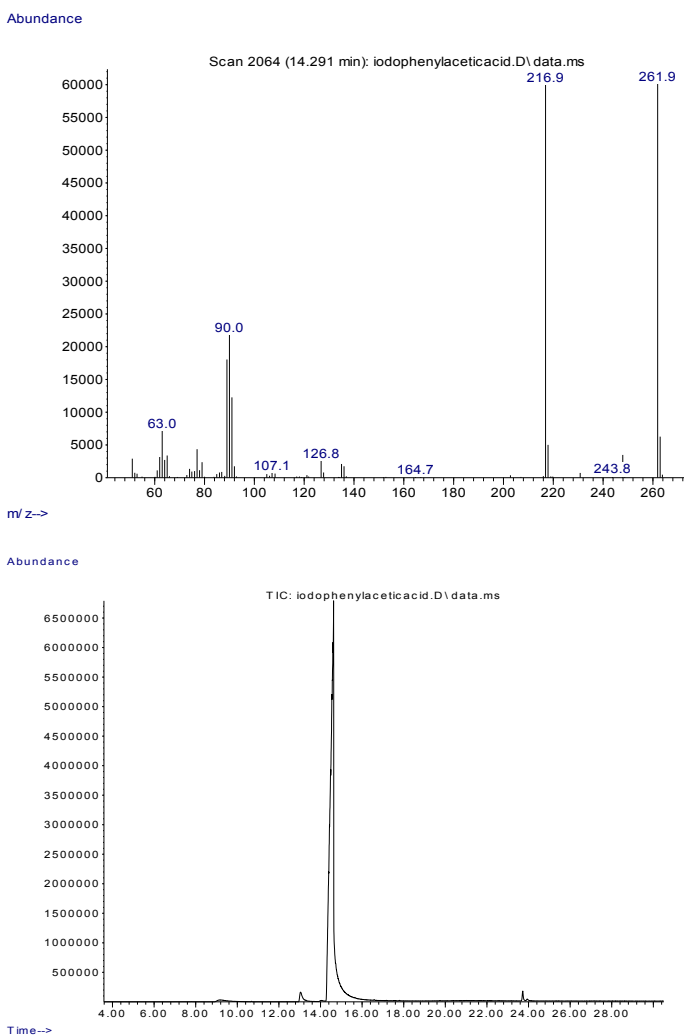
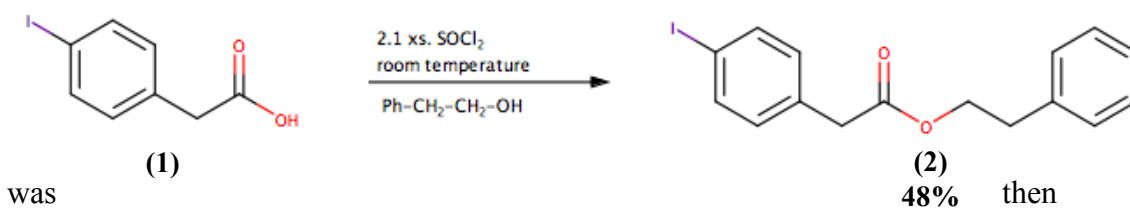


Figure 4.1. Gas chromatogram and mass spectrum of isolated (4-iodo-phenyl)-acetic acid

In addition to GC/MS analysis, ^1H NMR and ^{13}C NMR analysis was conducted, and peaks coincided with literature values.¹³

Ester Synthesis

(4-iodo-phenyl) – acetic acid (**1**) was then dissolved in a 2:1 molar excess of thionyl chloride under a dry nitrogen atmosphere in order to convert the carboxylic acid into a more reactive acid chloride. Once the mixture stirred at room temperature for two hours, excess thionyl chloride was removed from the solution via reduced pressure and temperature by iced vacuum pump. This was done to ensure no excess thionyl chloride remained to interfere with the next step of the reaction. No further purification or characterization was performed on the thionyl chloride intermediate. A 1:1 molar ratio of chilled 2-phenyl-ethanol was then added drop wise to the reaction, as shown by Equation 4.2. The 2-phenyl-ethanol was cooled, and added to the reaction. The reaction was allowed to stir at room temperature under atmospheric conditions overnight. The solution



was

extracted with methylene chloride, washed twice

concentrated sodium

hydroxide, and dried over MgSO₄.

Equation 4.2. Esterification of compound (**1**) to synthesize compound (**2**)¹⁴

This approach to synthesizing (**2**) was much more successful, despite its modest yield (48%), than our previous attempts at a Fischer esterification which did not seem to

produce any product at all. The acidic conditions required for a Fischer Esterification may have degraded the aromatic iodinated compound. Initial GC/MS results showed unreacted 2-phenylethanol in the product. Removal of the alcohol was accomplished by flash chromatography with methylene chloride. The product's R_f value was much higher than the alcohol. Gas chromatograph/mass spectrometry was used to characterize compound (2), with a retention time of 21.2 minutes and a molecular ion peak of 366 m/z. Post column chromatography yielded a relatively pure yellow viscous liquid, whose identity was indicated via gas chromatography and mass spectrometry (Figure 4.2).

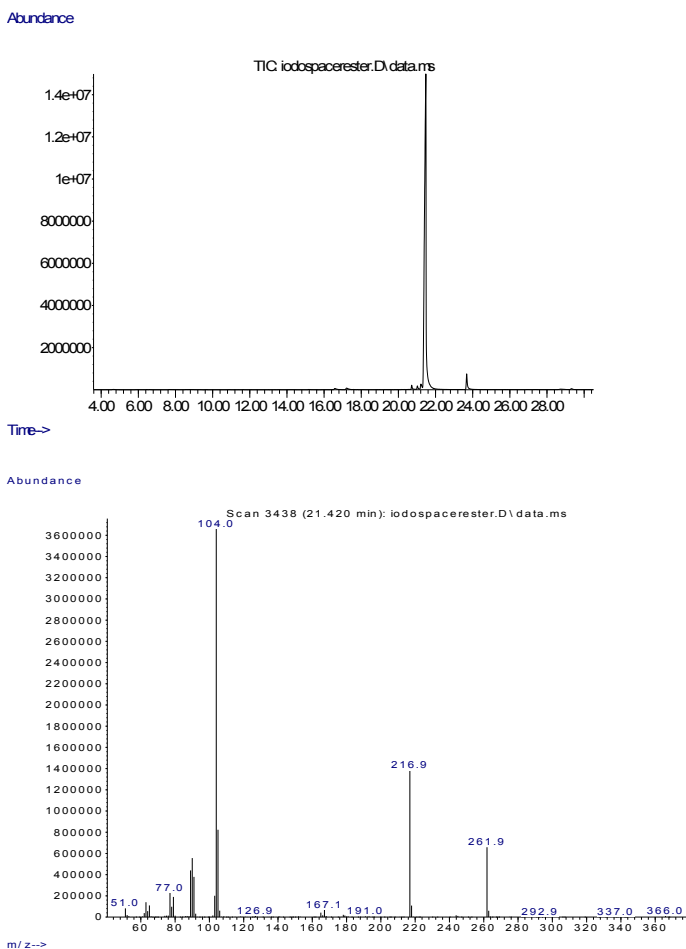


Figure 4.2. Gas chromatogram and mass spectroscopy at 21.42 minutes of isolated (4-iodophenyl) – acetic acid phenethyl ester

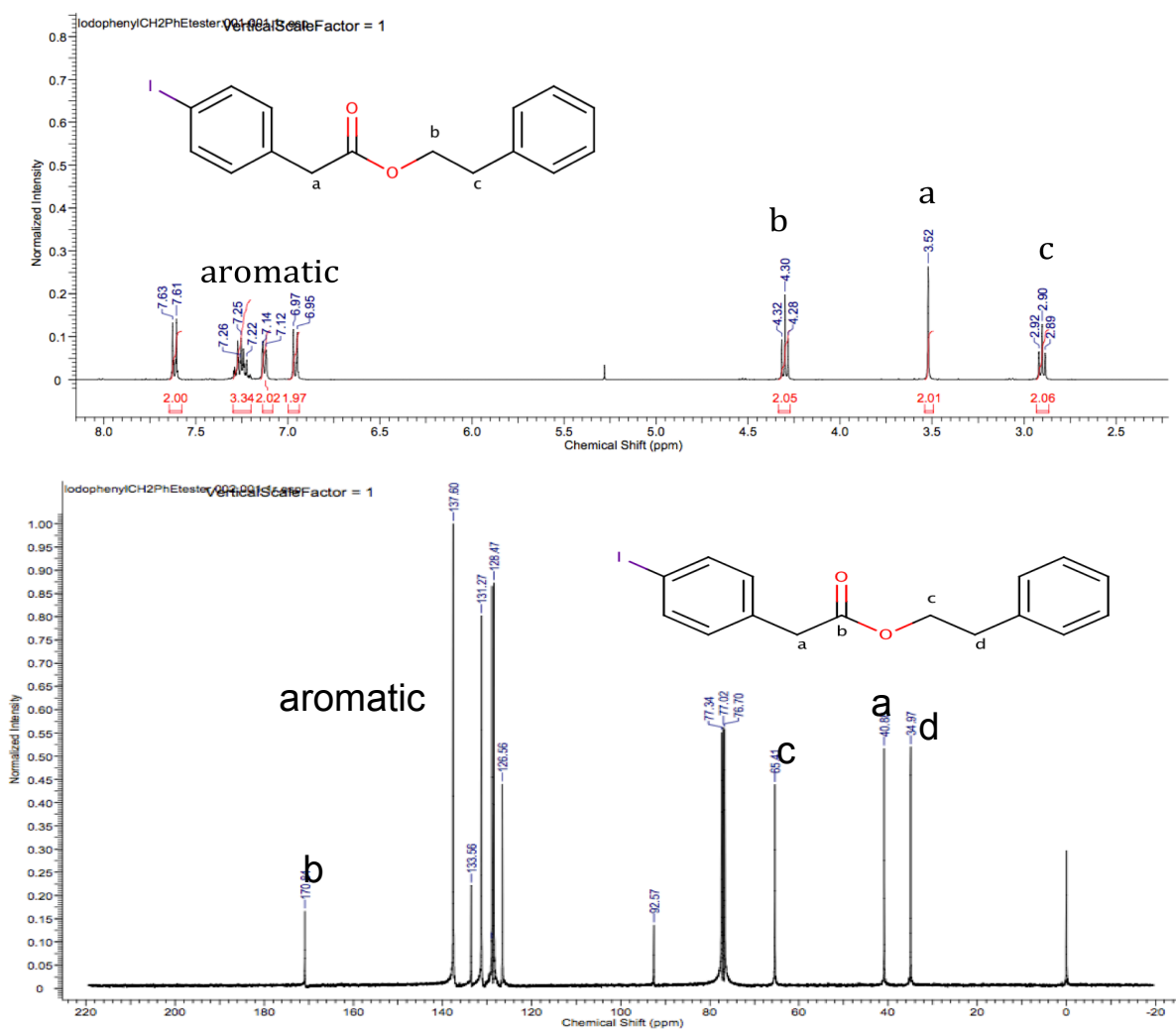


Figure 4.3. ^1H NMR and ^{13}C NMR spectra of compound (2) with atom assignments

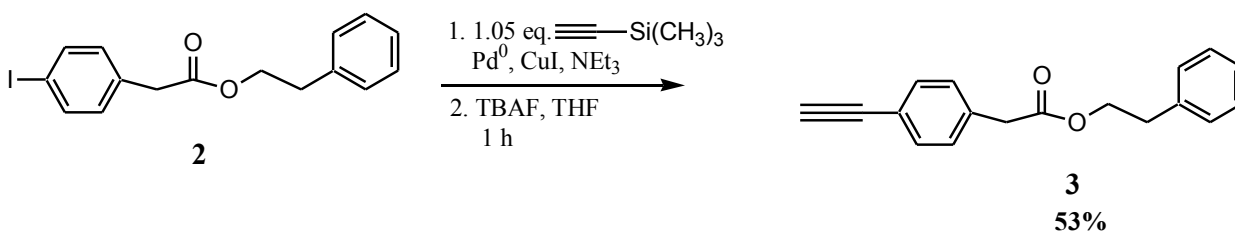
^1H NMR analysis and ^{13}C NMR analysis confirmed the identity of (2), as evidenced in Figure 4.3. The number of peaks from proton NMR matches the number of unique hydrogens predicted on compound (2). The chemical shift (4.3 ppm) and integration (2) of peak b indicates two hydrogens that have high shielding, indicating their location next to a heteroatom such as an ether oxygen. Peak a also has a higher ppm (3.5, singlet) with shielding, indicating its location next to an electron withdrawing group, such as a

carbonyl group or benzene ring. Peak c suggests a higher chemical shift (2.8ppm), but not as dramatic as the other two peaks, which corresponds with the desired compound (2). Additionally, signals in the aromatic region correspond with both the presence of mono-substituted phenyl rings and a disubstituted phenyl ring.

Carbon spectral analysis was also indicative of a confirmed identity of compound (2). Literature values of compound (1)¹³ show that there are only two other carbon peaks besides those associated with the aromatic region; a peak in the carbonyl NMR region, and a peak just below the aromatic region. Figure 2.5 illustrates that the additional peak c (65 ppm) in the ether region and peak d (38 ppm), in addition to the peaks previously listed in the literature about compound (1), confirm the addition of 2-phenylethanol to compound (1) in an ester linkage. Overall, instrumental analysis confirmed the identity of compound (2).

Terminal Alkyne Synthesis

As earlier discussed, it was determined for educational purposes to complete the tolane synthesis via a sequential Sonogashira coupling reaction.^{7,9} Figure 2.6 displays the Sonogashira coupling reaction used to synthesize the first intermediate (4-ethynyl-phenyl)-acetic acid phenethyl ester (**3**).



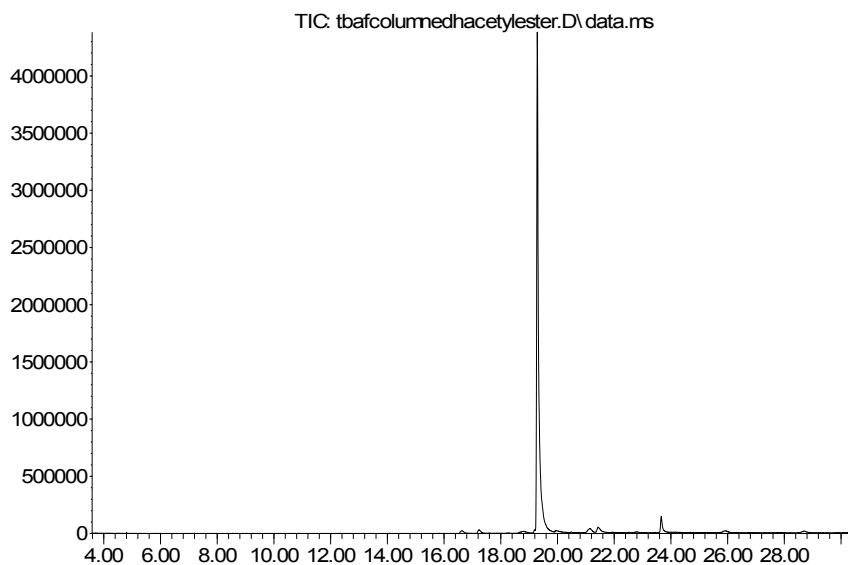
Equation 4.3. Sonogashira coupling reaction to synthesize (4-ethynyl-phenyl)-acetic acid phenethyl ester (**3**)

Under a nitrogen atmosphere, the previously synthesized compound (2) was added to N₂ sparged triethylamine. After the ester dissolved, The Pd and Cu catalysts were added at 3 mole percent to the reaction flask. After addition of the catalysts, trimethylsilylacetylene (TMS acetylene) was added drop wise in slight molar excess in order to account for the small amount consumed during the reduction stage of the Pd (II) catalyst. As the TMS acetylene was added, small white crystals precipitated, thought to be triethylamine salts, indicating that the reaction was working. After addition of the TMS acetylene, the reaction was stirred under a low heat for three hours. After three hours the heat was removed and the solution allowed to stir for 72 hours. After this time, the solution was filtered via vacuum filtration and the solvent removed via rotary evaporation. After removal of the solvent, the crude product was dissolved in methylene chloride and washed with 6M HCl, water and a saturated brine solution, then dried over MgSO₄. After drying, the catalysts were removed via flash chromatography using methylene chloride and the solvent removed via rotary evaporation. TLC analysis was utilized to examine the crude product in comparison with its reagents. TLC found that the TMS-intermediate had an R_f value lower than that of the original ester, indicating that a larger group had been attached during the reaction.

To reduce the TMS protecting group to a terminal hydrogen, The TMS-acetylene intermediate was dissolved in tetrahydrofuran (THF) and reacted with 3 percent molar excess of tetrabutylammonium fluoride (TBAF). This reaction was allowed to stir at room temperature for 1 hour, after which the THF was removed via rotary evaporation. After the solvent was removed, the crude product was extracted with methylene chloride, and washed with 6M HCl, water and brine solutions. Flash chromatography with

methylene chloride was attempted to further purify the product, but isolation of the product was not achieved, and TLC analysis indicated that the product had severe contamination. Because of this contamination, column chromatography using methylene chloride resulted in less than 10% yield. It is uncertain whether future reactions of this nature will need such a high level of purification, so proper utilization of flash chromatography may only be needed. Gas chromatography and mass spectrometry data displayed the product after column chromatography with an R_t of 19.49 minutes and a molecular ion peak of 264 m/z (Figure 4.4).

Abundance



Time-->

Abundance

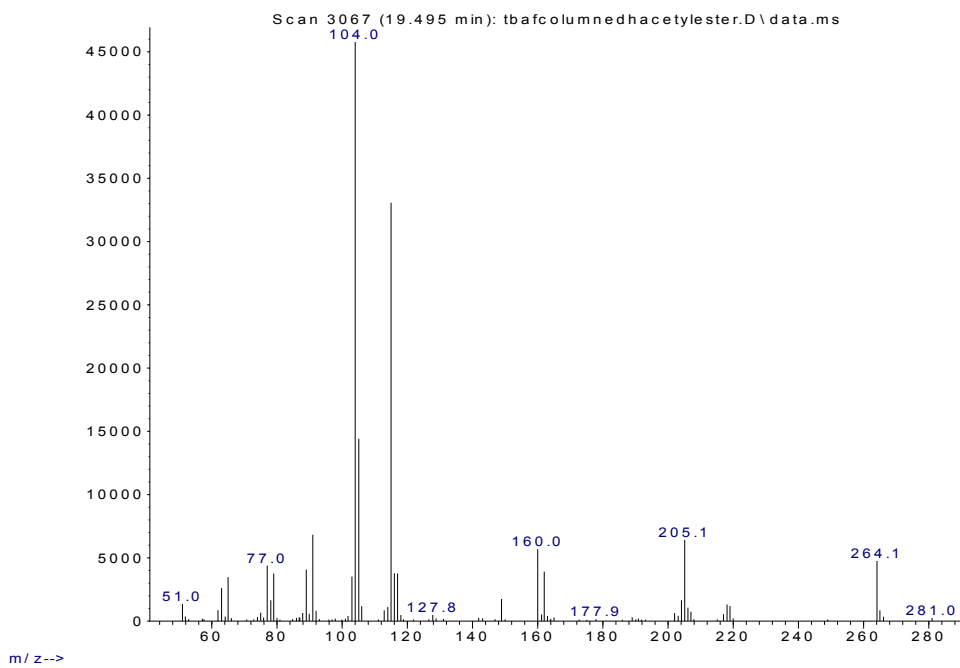


Figure 4.4. Gas chromatography and mass spectrometry of compound (3) at 19.49 minutes.

^1H NMR and ^{13}C NMR analysis indicated that (3) was in fact synthesized in relatively pure form, as indicated in Figure 4.5.

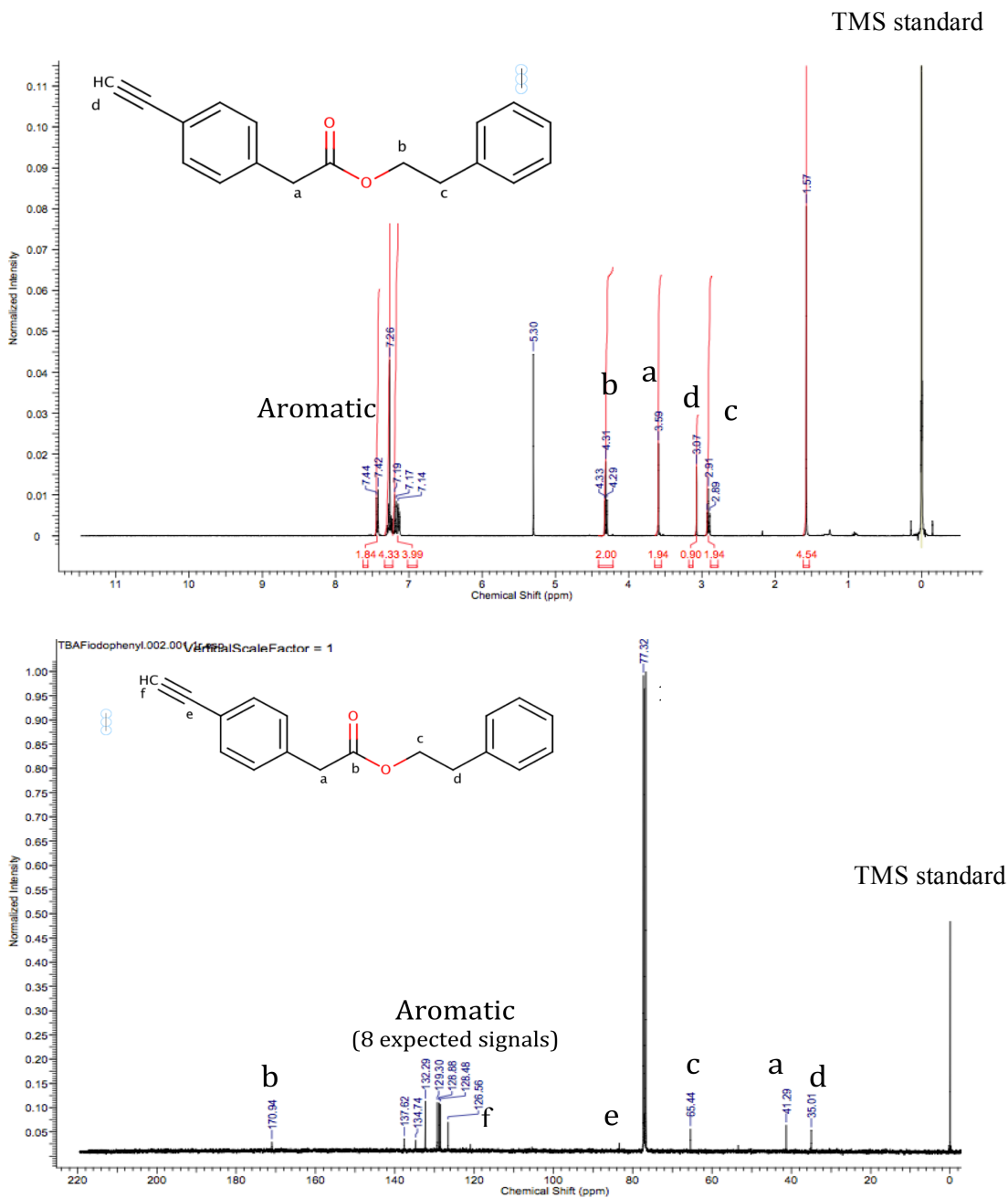
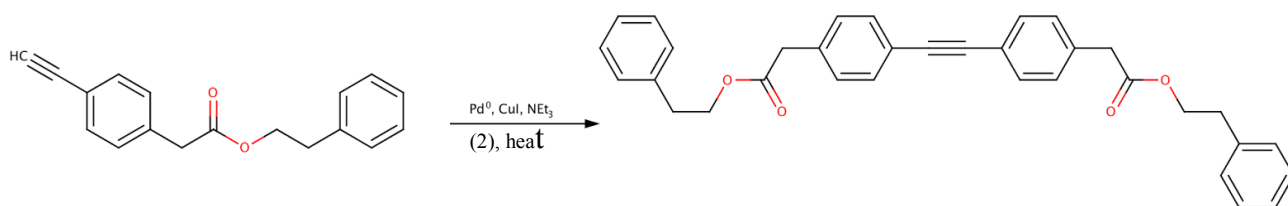


Figure 4.5. ^1H NMR and ^{13}C NMR spectra of compound (3) with atom assignments

Proton NMR, even at a glance indicates that a new compound was synthesized. Unlike proton NMR from Figure 6, there is a new proton singlet (3.1 ppm) that appeared just above peak c (2.8 ppm) and below peak a (3.5 ppm) in the alkyne hydrogen region of the NMR. Further, peaks e (85 ppm) and f (121 ppm) on the ^{13}C NMR shifted downfield denotes an alkyne substituted in the iodine's place from compound (2).

Diester Tolane Synthesis

To synthesize the diester tolane, as depicted in Figure 4.4, compound (3) was reacted with compound (2) in a final Sonogashira coupling reaction. This last coupling reaction differs from the first coupling reaction in that the two reactants are reacted in a 1:1 ratio, not in a 1.05 molar excess. The reaction proceeded by dissolving compound (3) in sparged triethylamine and adding it via syringe to a side arm flask full of N_2 sparged triethylamine put under a nitrogen atmosphere. After, 3 mole percent of CuI and $\text{PdCl}_2\text{P}(\text{Ph}_3)_2$ was added to the side arm flask, compound (2) was added drop wise via syringe into the reaction mixture to yield small white crystals that, as mentioned earlier, indicate progress of the reaction. The mixture was heated and stirred for three hours, the heat was then turned off and the mixture was allowed to stir for 72 hours. After this time, the solvent was removed via rotary evaporation, extracted with methylene chloride, and washed with 6M HCl , water, and brine solutions. To remove catalyst residue, flash chromatography was attempted and the crude mixture was then analyzed via TLC.



Equation 4.4. Sonogashira coupling to produce the desired diester tolane compound (4)

TLC analysis indicated that there was an entirely new spot that had about half of the R_f value of the original ester. This looked promising, so the crude product was analyzed via gas chromatography and mass spectrometry. However, it is uncertain if product was made, since the large size of compound (4) may make gas chromatography an inappropriate method for analysis, and liquid chromatography (LC) was not readily available. A carbon NMR was also run on the crude product (Figure 4.6). It is believed the peaks are present in the spectrum to confirm the synthesis of compound (4). Additional purification would be necessary along with improvements in the synthesis to maximize yields.

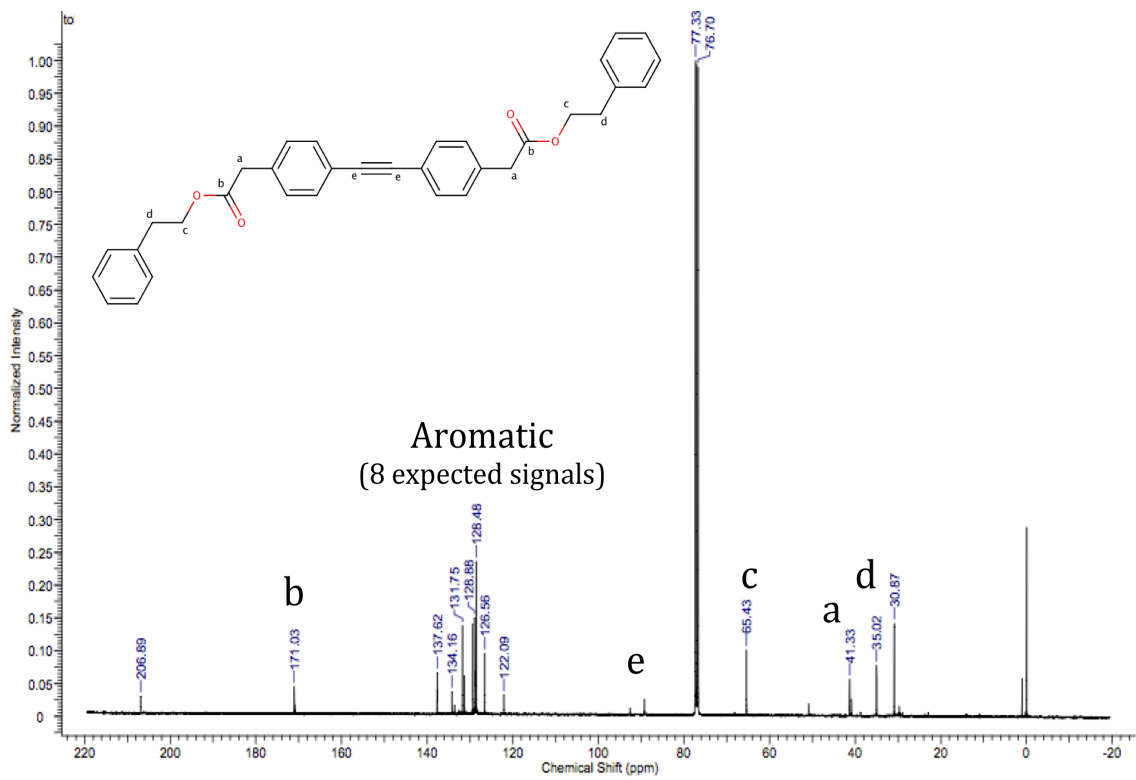


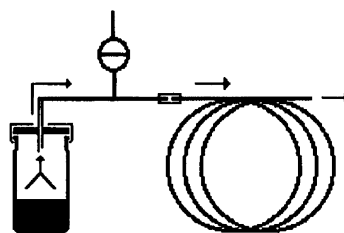
Figure 4.6. ^{13}C NMR of final tolane crude mixture

V. HEADSPACE ANALYSIS

In order to determine whether the spacer tolane molecule is capable of volatile release, the knowledge of headspace analysis needed to be acquired. The conditions under which the tolane hydrolyzes should be mild, and within pH and temperature ranges that can be found in every day applications. Physiological temperature and pH make pro fragrances useful for topical application and more rigorous conditions such as the temperature of a clothes dryer make them more useful for “industrial” applications. Direct injection gas chromatography is useful for molecules that are volatile and easily converted into the gas state. Our pro fragrant molecules would be high molecular weight species that are undergoing a reaction to release volatile components. GC/ headspace analysis is ideal for this application as it acquires the vapor from above the “original sample” regardless of the volatility of the original material.

Gas Chromatograph/Headspace Apparatus

Unlike gas chromatography, where the liquid form of the sample of interest is directly injected then volatilized within the column, headspace analysis works a slightly different way.



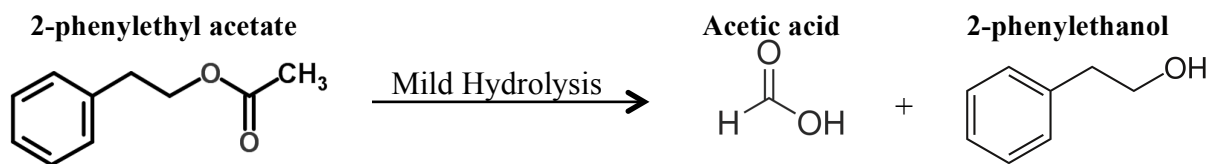
sample introduction

Figure 5.1. Headspace analysis and gas chromatography general mechanism¹⁵

As seen in Figure 5.1, the injector draws from the gaseous volatiles that are located above the liquid sample after it has been exposed to heat or hydrolysis conditions. Once the gas has been extracted from the sample vial, the sample is transferred to the gas chromatograph where it is run through a column to determine retention time.¹⁵ Additionally, mass spectroscopy (MS) may be attached as an additional detector at the end of the instrument. MS detection aides in identifying components in the GC without having to run standards of know materials that could possibly be in the sample.

Surrogate Molecule

In order to conserve previous synthetic tolane materials, it was decided that method development would utilize a surrogate molecule that hydrolyzed into the same types of constituents. Ideally, this surrogate molecule upon hydrolysis would release the alcohol of interest, 2-phenylethanol. It was also desired that this surrogate molecule be commercially available, so that extra synthesis was not needed, and that large quantities could be acquired for method development. An initial SciFinder scholar structure search produced 2-phenylethyl acetate as a suitable surrogate, as shown in Equation 5.2.



Equation 5.1. 2-Phenylethyl acetate hydrolysis

This molecule is commercially available and hydrolyzes into the alcohol of interest and

an acetic acid. Preliminary method development was conducted on this proxy, with the anticipation that hydrolysis conditions for the final tolane would be similarly mild.

Preliminary Method Development

With no prior experience with headspace analysis, development of a workable method included a steep learning curve. As such, a rough method was devised based on another student's previous work that involved analyzing hop essential oils, along with a working knowledge of the conditions under which a pro fragrant sample would ideally volatilize.¹⁵ The column through which the headspace would run through was 15 meters long (more details on the column can be found in the Experimental section). Injection type would be splitless since the sample analyzed would most likely be very dilute. The static headspace sampling technique was to be used.¹⁵

Because the ideal conditions which the alcohol was desired to volatilize under, it was undesirable to have the temperature program go above 100⁰C, as to avoid boiling and over pressurization of the sample vial. Practical applications of this molecule may include its use in a dryer sheet fragrance and typical dryer temperatures approach temperatures around 55-75 ⁰C.¹⁶ As such, the following temperature program was devised (Table 3.1).

Table 5.1. Temperature Program

Stage	Rate (°C/min)	Temp (°C)
Initial injection	----	55
Inlet	----	65
Gas chromatograph	----	75

Heating of the headspace vial was held constant at 55 degrees, but the inlet and gas

chromatograph temperatures were heated ten degrees higher in order to promote volatile movement and separation from injection to inlet to gas chromatograph since pressure for the gas chromatograph was held at 15 psi, and the other end of the loop was not under vacuum to help push the volatiles through the loop. Once volatiles entered the gas chromatograph, they were subject to the Ramey research method. (See Experimental Section for details of this GC program)

Results

To know the retention time of the 2-phenylethanol that would hopefully release from the surrogate molecule, a 1-mL sample of 98% commercially available 2-phenylethanol was run through the preliminary headspace method.

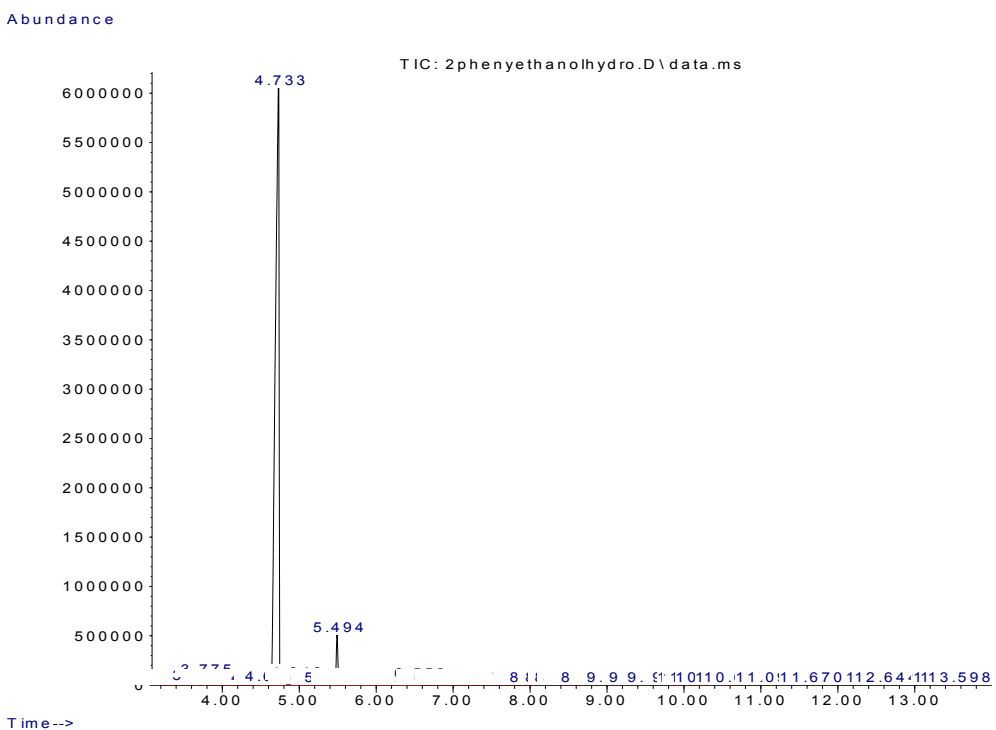


Figure 5.2. Gas chromatograph of 98% pure, commercially obtained, 2-phenylethanol (RT: 4.753 minutes)

As seen by Figure 5.2, because this sample was not completely pure, there was some contamination that showed up in the gas chromatograph, but the largest peak at 4.753 minutes appeared to be 2-phenylethanol. The mass spectrum for the 4.753 peak was analyzed to confirm identity of sample.

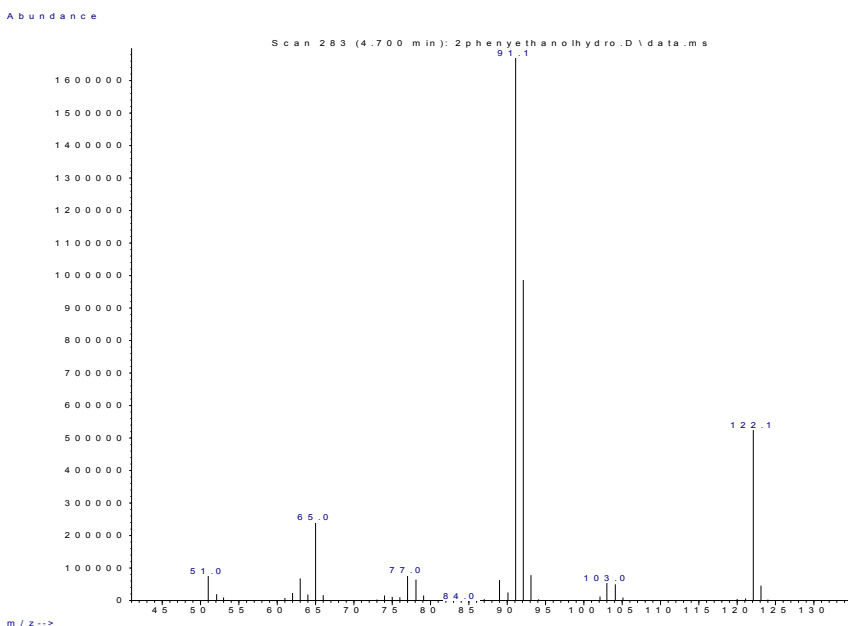


Figure 5.3. Mass spectrum of GC peak at 4.753 minutes

As seen in Figure 5.3, mass spectrometry showed that there was an M^+ peak of 122 and base peak of 91.1, which runs in line with the expected mass spectrum of 2-phenylethanol. This confirmed that 2-phenylethanol has a retention time of about 4.753 minutes in the developed headspace method. Any 2-phenylethanol in a headspace sample should have this approximate retention time and exact MS spectrum.

Once the identity and retention time of 2-phenylethanol was confirmed, 1 mL of 2-phenylethyl acetate sourced from the chemistry department stockroom w

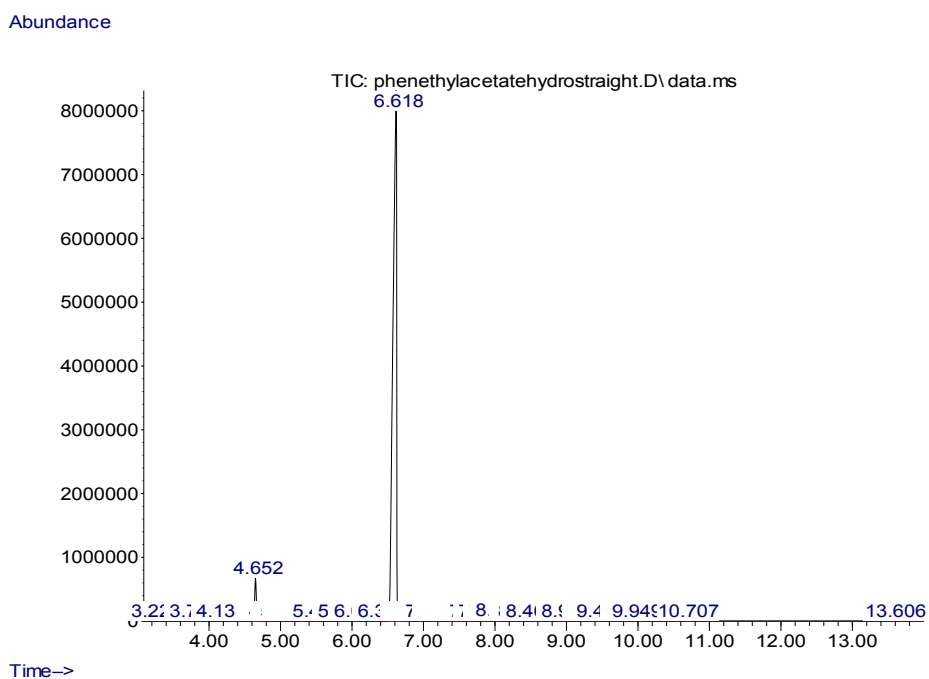
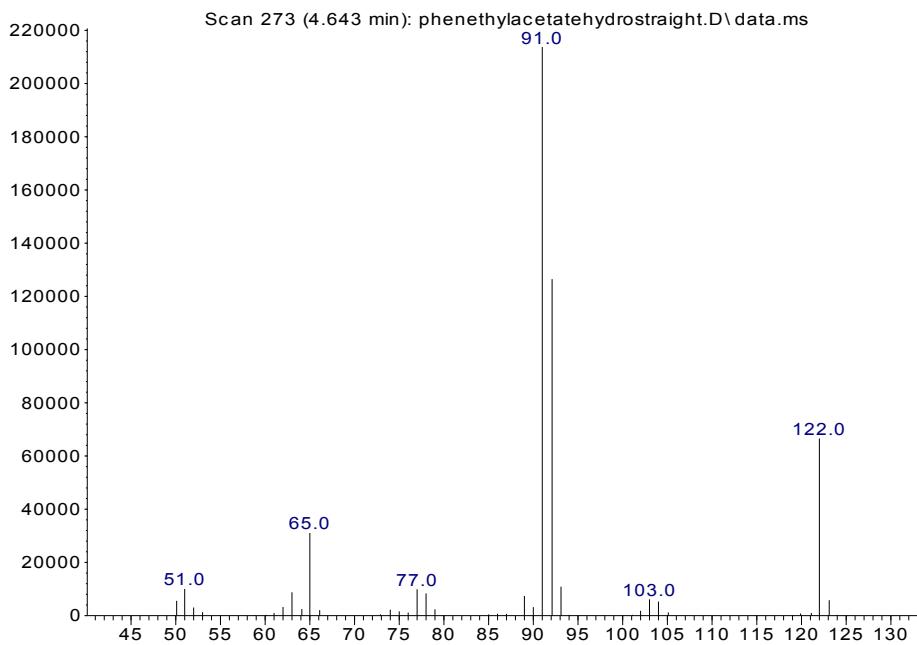


Figure 5.4. Gas Chromatograph of stockroom 2-phenylethyl acetate. No additional reagents added.

As seen from Figure 5.4, there were two major peaks that showed up via GC analysis. Mass spectral analysis of the retention time at 4.652 revealed that this was 2-phenylethanol, as indicated in Figure 5.5.

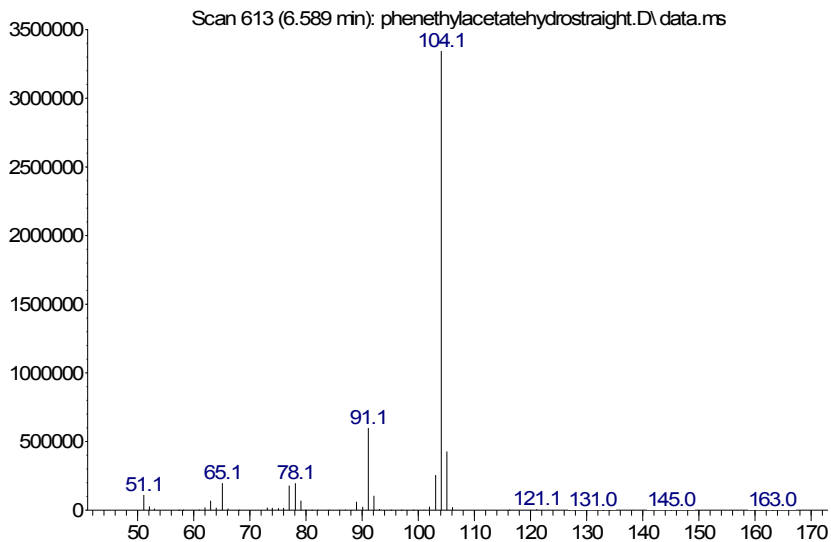
Abundance



m/z-->

Figure 5.5. Mass spectrum of peak at RT 4.652 minutes in stockroom 2-phenethyl acetate sample

Abundance



m/z-->

Figure 5.6. Mass spectrum of peak at RT 6.618 minutes in stockroom 2-phenethyl acetate sample.

Mass spectra analysis was also conducted on the peak at retention time 6.618 minutes. Mass spectral analysis indicated that for the peak at 6.618 minutes, there was an M⁺ of 163, with a base peak of 104.1 (Figure 5.6). These values match ions for the surrogate molecule 2-phenylethyl acetate, which is a volatile ester, unlike our proposed tolane esters, which would not be volatile. From this analysis, it was thus determined that both 2-phenylethanol (RT=4.652) and the surrogate ester (RT=6.618) were present in the headspace sample. Hydrolysis of the stockroom ester sample had occurred during storage or was occurring quite rapidly at the vial temperature of 55 °C.

To try to promote hydrolysis, another sample was prepared and analyzed with 1 mL of DI water and 1 mL of ester.

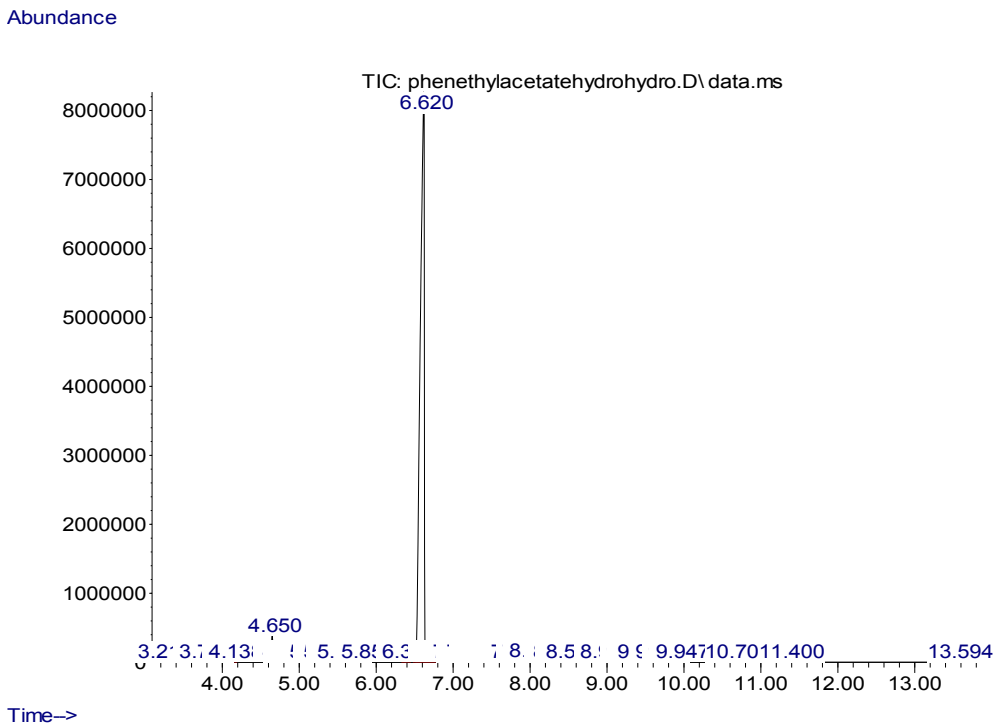


Figure 5.7. GC results of mixture of 1 ml stockroom 2-phenethyl acetate and 1 ml DI water

Gas chromatograph indicated from Figure 5.7 that both the alcohol and ester were present in the headspace sample. In hopes to promote hydrolysis further, various concentrations of hydrochloric acid (HCl) were added to different samples with a 50/50 mixture of 2-phenylethyl acetate and water.

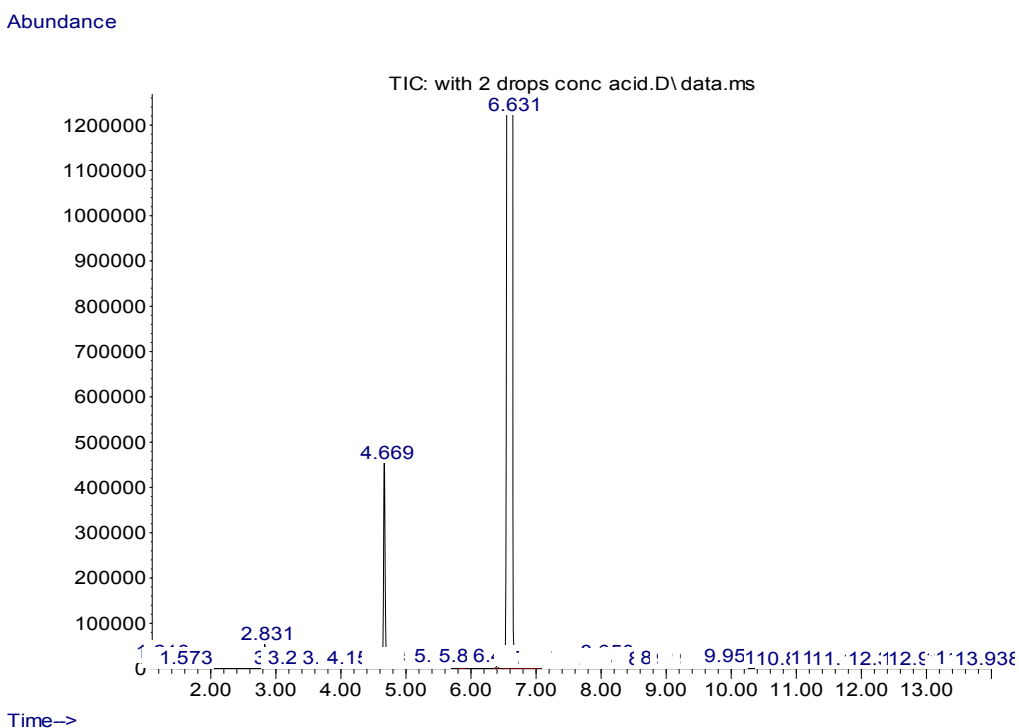


Figure 5.8. GC results of mixture of 1 ml ester, 1 ml DI water, and 2 drops of conc. HCl

Results from adding two drops of HCl seemed to improve results slightly, as seen in Figure 5.8, however the concentration of 2-phenylethanol was still significantly below 1000000 in abundance. So to another sample, 1 mL of 1M HCl was added to a 50/50 mixture of 2-phenylethyl acetate and DI water.

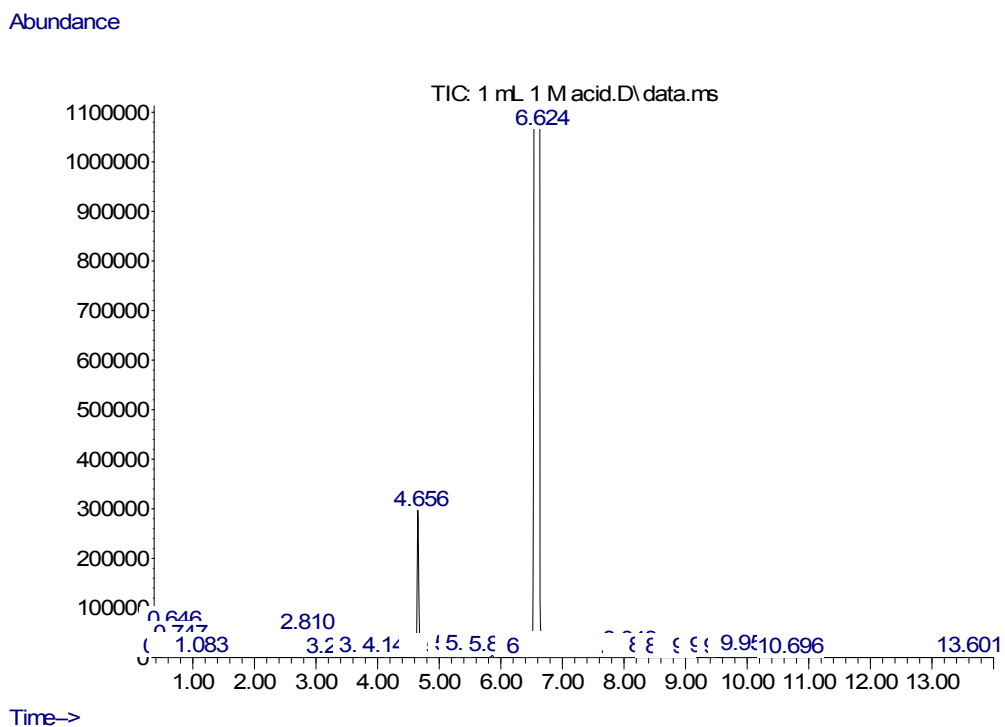


Figure 5.9. GC results of mixture of 1 ml ester, 1 ml DI water, and 1 ml of 1M HCl

Surprisingly, adding 1M HCl did not improve yield of 2-phenylethanol, and actually lowered its concentration, as shown in Figure 5.9. To see if a higher concentration of acid would improve results, 1 mL of 6M HCl was added to a final mixture of 50/50 ester and water.

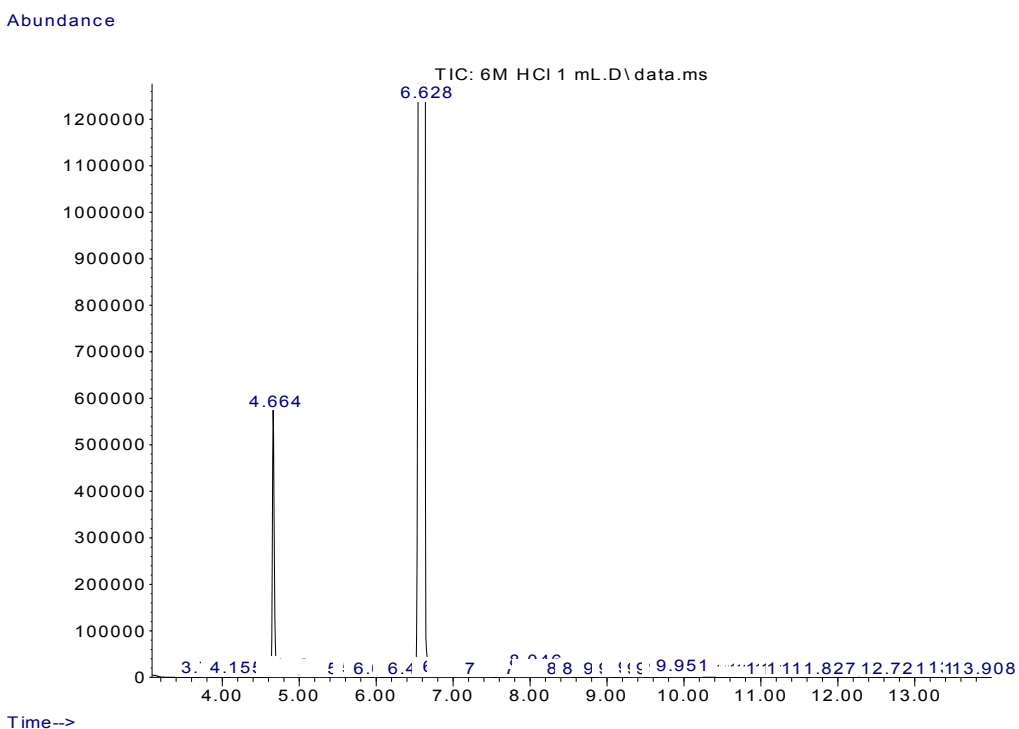


Figure 5.10. GC results of mixture of 1 mL ester, 1 mL DI water, and 1 mL of 6M HCl

As Figure 5.10 indicates, a slightly higher concentration of 2-phenylethanol was found than all other mixture conditions. However, all conditions analyzed did not produce optimal release of 2-phenylethanol. Comparison of the peak integration area of ester to that of the integration area of the alcohol did not seem to indicate improved hydrolysis over the neat stockroom 2-phenethyl acetate sample nor were the results very consistent.

Discussion

Overall, the objectives of this preliminary headspace analysis were to obtain a working understanding of how headspace analysis works, and to establish a rough, preliminary headspace analysis method to analyze the rate of 2-phenylethanol release from a molecule similar to the spacer tolane. Both of these objectives were attained,

however the results of this preliminary analysis were somewhat unanticipated. Though it was not surprising that the surrogate molecule would volatilize along with the 2-phenylethanol due to its low molecular weight, the low concentration of 2-phenylethanol while including acid was surprising at first. One would imagine that acidifying the water would promote hydrolysis of the ester, and to a certain extent this did happen. The progression of release as concentration and volume of HCl was added did increase the concentration of alcohol. However, the concentration of 2-phenylethanol was rather low. However, further literature research did reveal that addition of a buffer system would have been both more realistic for practical applications, and to assist in hydrolysis of the ester bond. Also, all reaction mixtures analyzed were not entirely pure or distilled, and due to the age of the 2-phenylethyl acetate, some decomposition of the molecule may have occurred, and as such the 2-phenylethanol that was observed on the GC was mostly previously decomposed with time. As such, future analysis should include pure 2-phenylethanol and pure, fresh 2-phenylethyl acetate.

Further, because the heating of the mixture was in a closed system, it is also possible that the closed system is preventing the evaporation of 2-phenylethanol, and an open system may need to be used in the future. Finally, it is possible that the lack of 2-phenylethanol release was not due to any of these conditions, but that the headspace analysis was not giving the mixture enough time to hydrolyze the ester bond. Thus, future headspace analysis may include heating the sample for a longer time, or preparing the sample a few hours beforehand to allow the mixture to hydrolyze longer.

In summary, a working understanding of the headspace apparatus was gained, and directions for future work have been determined from this preliminary analysis

VI. FUTURE WORK

In the future there are various experiments that can be performed to expand on this body of work.

Future Synthesis

Due to the inconclusive NMR results for compound (4), another larger scale sequential Sonogashira coupling reaction should be conducted in order to obtain a yield large enough for isolation. Various techniques of purification will be used to isolate the tolane in order to isolate it to a desired purity level. Characterization of a pure sample will allow comparison of the material recovered from other synthetic routes to a known product. If the desired tolane is able to be isolated and characterized, the shorter one-pot method of the Sonogashira reaction will be used to attempt to synthesize compound (4).¹⁰ If the one pot method is able to synthesize compound (4), then this would greatly reduce the time required for overall synthesis. This also assumes that purification steps will not be excessively more difficult than in the sequential method.

If the tolane can be completely isolated, a large enough quantity will be synthesized in order to try to produce the ester-substituted hexaphenylbenzene, as seen by Figure 6.1.

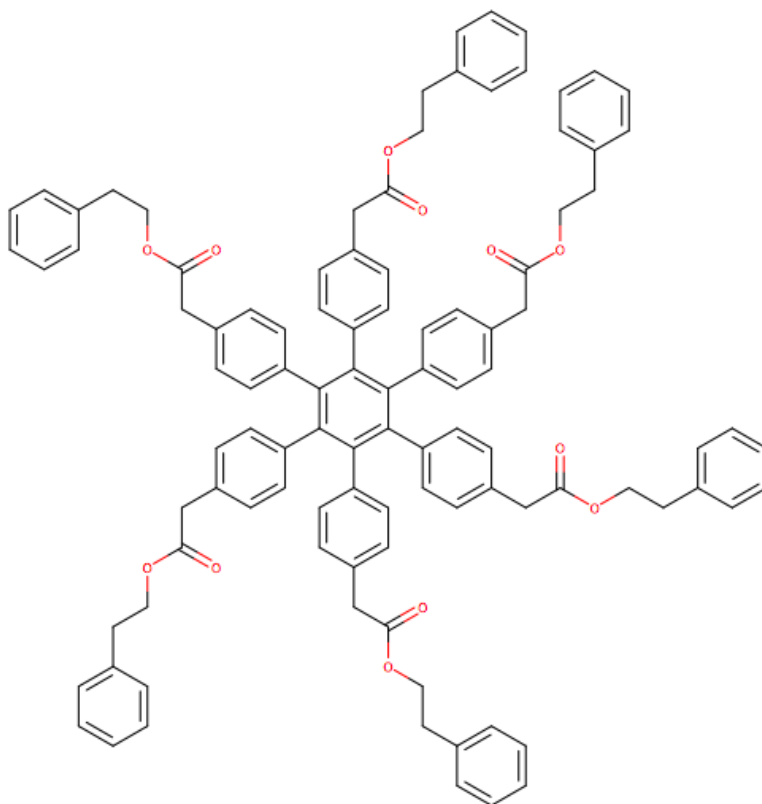


Figure 6.1. Ester substituted hexaphenylbenzene

Previous research students have synthesized a hexaphenylbenzene, for another project, via a cobalt catalyzed cyclization reaction,⁶ which provide some insight on the laboratory methods necessary to execute this scheme. Proposed work up to isolate the hexaphenylbenzene would include flash chromatography, and column chromatography in a 1:1 hexane/ethyl acetate system, as this solvent system has worked to isolate similar product.¹¹ Characterization will include TLC analysis, ¹H NMR and ¹³C NMR, and possibly liquid chromatography, as the molecular weight of the product will be too high to be characterized via GC/MS. Headspace analysis via the method developed will be

used to determine if mild conditions are appropriate for slow release of volatiles.

If the hexaphenylbenzene can be synthesized and headspace analysis suggests that the hexaphenylbenzene structure acts as an appropriate fragrance precursor, then attempts will be made to attach other primary alcohols to compound (2), in particular citronellol, another regularly used primary alcohol in industrial fragrance synthesis, as seen in Figure 6.2.¹

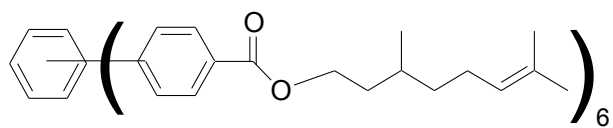


Figure 6.2. Substituted hexaphenylbenzene with citronellol ester bonding

Alternative Synthesis Routes

Another possible route that can be taken to create a less stable ester toluene precursor is through the addition of an electron-withdrawing group, such as a nitro group, on the ortho position of the phenyl ring relative to the carbonyl group. As shown in Figure 6.3, the addition of a small electron-withdrawing group in this position may destabilize the conjugation found in the molecule to the same degree as the methylene spacer. Previous work by Murray et al. successfully synthesized a toluene similar in structure to what is believed to be our alternate desired product.¹⁷

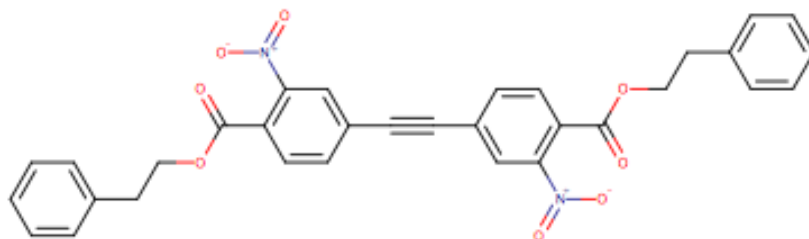
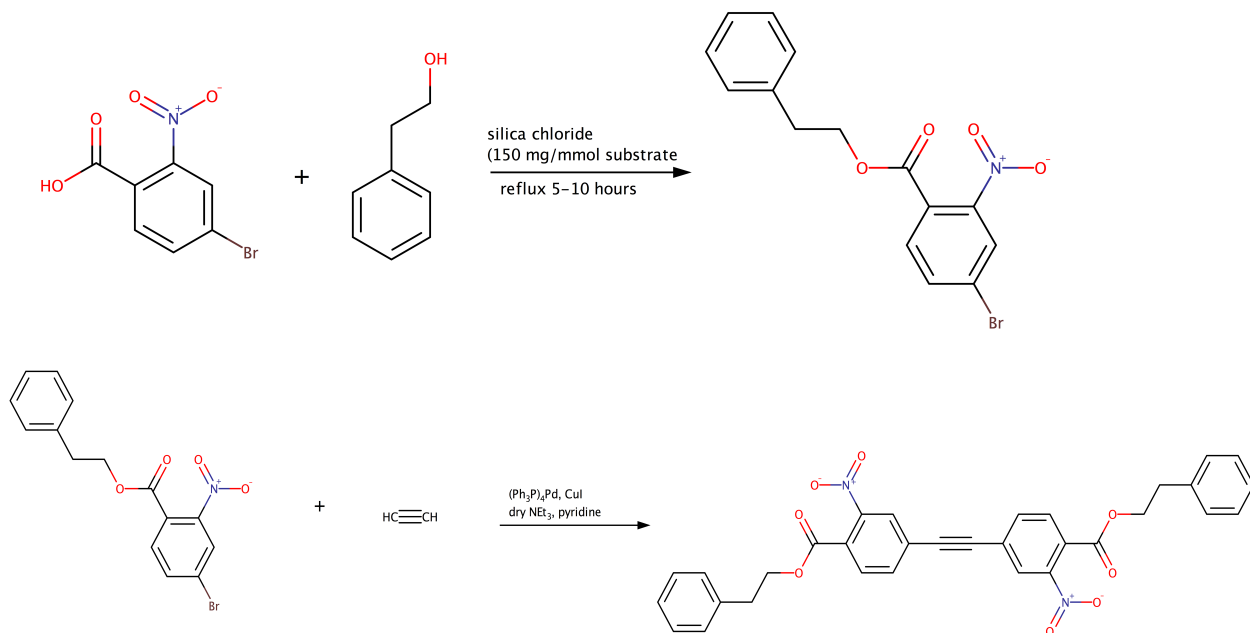


Figure 6.3. Proposed product with electron withdrawing groups in the ortho position relative to the ester carbonyl group

A possible synthetic route, outlined in Scheme 6.1, may be possible based on knowledge of basic organic chemistry and the synthetic method by Murray et al.



Scheme 6.1. Alternate synthetic route

As seen in Scheme 6.1, a commercially available reagent 4-Bromo-2-nitrobenzoic acid (CAS # 99277-71-1) can ideally undergo a Fischer esterification utilizing silica chloride

catalyst¹⁸ with a primary alcohol, like 2-phenylethanol. Utilizing silica chloride catalyst would limit the amount of water in the reaction, which will hopefully make the isolation stage more straightforward. In the case of a Fischer esterification failing, a reaction with thionyl chloride to produce an acid chloride intermediate would also esterify the carbonyl group. Once the benzene has been esterified, it can then undergo the reaction conditions described in Murray et al. with acetylene to create the desired tolane. Upon characterization, the product will then be volatilized via headspace analysis to determine how well it hydrolyzes the ester bond. If this analysis is deemed successful, cyclization to the hexaphenylbenzene product will be attempted, but due to the location of electron withdrawing groups this may interfere with the Co catalyst. Other electron withdrawing groups such as ammonium, cyano groups, or trihalides could be used in place of the NO₂ group.

VII. CONCLUSIONS

In summary, the industry of fragrances is constantly growing along with the organic synthesis behind it. Through the utilization of organic synthesis, the application of pro fragrances was yielded. Through our previous research on the synthesis of hexaphenylbenzenes, we believed that these molecules could serve as an excellent framework for pro fragrances. The purpose of this project was to synthesize a tolane precursor capable of cyclization to a hexaphenylbenzene at a later date.

Though the synthesis of a spacer tolane was not conclusively confirmed, the nuances and process by which this tolane can be produced was studied. This knowledge will be extremely helpful in the future not only for this project, but for any other student interested in synthesizing ester functionalized tolanes in the Ramey Research group. Further, an original ester precursor molecule was created, teaching the concept of trial and error in undergraduate research. A working knowledge of headspace analysis was developed, and will be used in the future to analyze the tolane's ability to release volatile fragrant molecules.

Throughout this process, priceless knowledge of various synthetic techniques and reactions were acquired, along with the ability to classically characterize synthetic molecules. This experience has been invaluable to my learning and undergraduate experience, and I highly recommend undergraduate research to anyone looking to gain experience in converting intellectual knowledge of chemistry into its real world applications.

VIII. REFERENCES

1. Sell, C. S., *Chemistry of Fragrances: From Perfumer to Consumer*; Ed. by Charles S. Sell. Royal Society Of Chemistry: Cambridge, United Kingdom, 2006.
2. Fahlbusch, K. G.; Hammerschmidt, F. J.; Panten, J.; Pickenhagen, W.; Schatkowski, D.; Bauer, K.; Garbe, D.; Surburg, H., Flavors and fragrances. *Ullmann's Encyclopedia of Industrial Chemistry* **2003**.
3. Herrmann, A., Controlled release of volatiles under mild reaction conditions: From nature to everyday products. *Angew. Chem.-Int. Edit.* **2007**, *46* (31), 5836-5863.
4. (a) Ashburn, J. G. Tobacco flavorants. 1963; (b) Teague, C. E. J. Tobacco. 1956.
5. Langer, R.; Peppas, N., Chemical and physical structure of polymers as carriers for controlled release of bioactive agents: a review. *Journal of Macromolecular Science-Reviews in Macromolecular Chemistry and Physics* **1983**, *23* (1), 61-126.
6. Kobayashi, K.; Shirasaka, T.; Horn, E.; Furukawa, N., Two-dimensional hexagonal hydrogen-bonded network with triangle-like large cavities: hexakis (4-carboxyphenyl) benzene. *Tetrahedron Letters* **2000**, *41* (1), 89-93.
7. Sonogashira, K.; Tohda, Y.; Hagihara, N., A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Letters* **1975**, *16* (50), 4467-4470.
8. Ramey, M. Synthesis of Variable Bandgap Conjugated Polyelectrolytes via Metal Catalyzed Cross-coupling reactions. University of Florida, 2001.
9. Nagy, A.; Novak, Z.; Kotschy, A., Sequential and domino Sonogashira coupling: Efficient tools for the synthesis of diarylalkynes. *J. Organomet. Chem.* **2005**, *690* (20), 4453-4461.
10. Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A., One-pot synthesis of symmetrical and unsymmetrical bisarylethyne by a modification of the Sonogashira coupling reaction. *Org. Lett.* **2002**, *4* (19), 3199-3202.
11. Jackson, K. *Synthesis of Functionalized Tolanes In-Route to Hexaphenylbenzenes*; Appalachian State University: Boone, NC, 2008.
12. Epley, C. *Synthesis of Functionalized tolans*; Appalachian State University:

2009.

13. Waybright, S. M.; Singleton, C. P.; Wachter, K.; Murphy, C. J.; Bunz, U. H., Oligonucleotide-directed assembly of materials: defined oligomers. *Journal of the American Chemical Society* **2001**, *123* (9), 1828-1833.
14. S. Inouye, S. S. Calcium-binding photoprotein, coelenterazine and imidazole compound which removes NH-proton of pyrazine ring of imidazopyrazine. 2012.
15. Snow, N. H.; Slack, G. C., Head-space analysis in modern gas chromatography. *TrAC Trends in Analytical Chemistry* **2002**, *21* (9), 608-617.
16. Explanation of Dryer temperatures.
<http://www.geappliances.com/search/fast/infobase/10000971.htm>.
17. Murray, M. M.; Kaszynski, P.; Kaisaki, D. A.; Chang, W.; Dougherty, D. A., Prototypes for the polaronic ferromagnet. Synthesis and characterization of high-spin organic polymers. *Journal of the American Chemical Society* **1994**, *116* (18), 8152-8161.
18. Srinivas, K.; Mahender, I.; Das, B., Silica chloride: A versatile heterogeneous catalyst for esterification and transesterification. *Synthesis* **2003**, (16), 2479-2482.

IX. VITAE

Danielle Russell is a Pre-professional/Paramedical Chemistry major at Appalachian State University. She currently resides in Charlotte North Carolina, though her family hails from the Northern Colorado and Southern Wyoming area. Danielle and her best friend Ishna like to eat brownies while making finger puppets for the puppetless masses. Danielle loves living in the Boone area where she runs, hikes and engages in general college shenanigans. Her ultimate goal is to go to medical school next year, though life takes people on interesting journeys. Danielle would like to thank the Office of Student Research for their partial funding and support of this project and her travels to present on this body of work.

X. EXPERIMENTAL PROCEDURES

Instrumentation.

¹H NMR spectra were obtained with a Varian Gemini 300MHz FT-NMR and Bruker 400 MHz FT-NMR. ¹³C NMR spectra were obtained with the same instruments, but at 75 MHz and 100 MHz respectively. Gas chromatography/mass spectrometry and headspace (GC/MS) measurements were obtained with an Agilent 6890N GC network system paired together with an Agilent 5973 inert mass selective detector that utilized a 30-meter long Agilent DB-5MS column. The column used for headspace analysis was the same type used for GC analysis, but was only 15 meters in length. One method was utilized for GC analysis all precursors to the tolane molecule; The method utilizes an inlet temperature of 200°C and an oven temperature of 50°C, holding for 5 minutes, then increasing at 10°C per minute to 250°C, holding at this temperature for 5 minutes, for a total run time of 25.5 minutes.

Iodocarboxylic Acid Synthesis

(4-iodo-phenyl)-acetic acid (1) Based on an article by Waybright et al. and synthesized by student Alex Cella. In a 500-mL round-bottomed flask, phenyl acetic acid (15.21 g, 87.0 mmol) and iodine (14.25 g, 16.65 mmol) were dissolved in in 200 mL of glacial acetic acid and stirred. To the stirred solution, a mixture of 5 mL conc. HNO₃ and 20 mL of conc. H₂SO₄ was added drop wise over a 30 min. period. The mixture was then stirred at 60° C for 1.5 hours, then removed from heat and left to stir overnight, where a white precipitate formed. The mixture was then poured over 500 g of ice and vacuum filtered. The pink solid was recovered and then recrystallized from hexanes to form colorless needles (8.2 g, 45%). mp: 129°C. ¹H NMR (300 MHz, CDCl₃) 7.63 (d, 2H),

7.25 (d, 1H), 7.03 (s, 1H), 3.6 (s, 2H) ppm. ^{13}C NMR (75 MHz, CDCl_3) 177.25, 137.76, 132.77, 131.37, 93.00, 40.47 ppm. GC-MS R_t 18.23 min, single peak, M^+ 262, 218, 90, 63

Diester Tolane Precursor synthesis

(4-iodo-phenyl)-acetic acid phenethyl ester (2). Procedure mimics a similar synthesis, given in a patent by Inouye et al., a 50-mL side-armed pear-shaped flask equipped with magnetic stir bar was flame dried and placed under vacuum and nitrogen. After drying of the glassware, (4-iodo-phenyl)-acetic acid (1.0 g, 3.8 mmol) was added to the flask. Then, thionyl chloride (3 mL, 41.4 mmol) was slowly added drop wise through a syringe into the reaction mixture to yield a pale yellow solution. The reaction was stirred for 2 hours at room temperature. The mixture was then cooled and concentrated by reducing the pressure of the reaction mixture to remove excess thionyl chloride. To the brown oily crude product, chilled 2-phenylethanol (0.5 mL, 4.2 mmol) was added drop wise to the solution and allowed to stir under atmospheric conditions overnight. The solution was then extracted with 15 mL of dichloromethane and 5 mL of 1 M sodium hydroxide. After extraction, the solution was purified via flash chromatography (methylene chloride). The product was a yellow viscous liquid (0.67 g, 48.2%). ^1H NMR (400 MHz, CDCl_3) 7.68 (d, 2H), 7.29 (m, 5H), 7.01 (d, 2H), 4.34 (t, 2H), 3.56 (s, 2H), 2.94 (t, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3) 170.84, 137.64, 133.62, 131.34, 128.96, 128.45, 126.48, 92.59, 77.40, 76.98, 65.41, 40.92, 35.14 ppm. GC R_t 22.23 min, single peak, MS: M^+ 366, 261, 216, 104

(4-Ethynyl-phenyl)-acetic acid phenethyl ester. To a 50-mL side-armed round bottom flask equipped with magnetic stir bar was added (4-iodo-phenyl)-acetic acid phenethyl ester (1.07 g, 2.8 mmol) was then added. Then, 15 mL of triethylamine, previously sparged with N₂ was added via syringe to the reaction flask and allowed to stir. The reaction flask was then heated to 60° C in an oil bath. CuI (0.03 g, 0.09 mmol) and PdCl₂ (0.05 g, 0.09 mmol) were then added to the solution. After addition of the catalysts, trimethylsilylacetylene (0.31 g, 2.8 mmol) was slowly added drop wise and allowed to stir in heat for 3 hours. After 3 hours the reaction was cooled to room temperature, and was allowed to stir for 72 hours. The mixture was filtered and the solvent was removed via rotary evaporation. The crude product was then extracted in 30 mL of dichloromethane, and washed in 15 mL of 6M HCl, water and brine solutions. The organic layer was then dried over MgSO₄. After drying, the crude product was purified via flash chromatography on silica gel using dichloromethane as the solvent. The filtered product was then evaporated down using rotary evaporation and dissolved in 5 mL of tetrahydrofuran THF. To the dissolved solution, tetrabutylammonium fluoride (TBAF) (2.84 mL, 3.7 mmol) was added drop wise and allowed to stir for one hour. THF was then removed by rotary evaporation. Dichloromethane was then added and the solution washed with 6M HCl, and water. The solvent was removed and product was recovered (0.31 g, 53%). ¹H NMR (300 MHz, CDCl₃) 7.44 (d, 2H), 7.14 (m, 5H), 4.30 (t, 2H), 3.59 (s, 2H), 3.2(s, 1H), 2.9 (t, 2H) ppm. ¹³C NMR (300 MHz, CDCl₃) 170.9, 137.6, 134.74, 132.28, 129.29, 128.87, 128.48, 126.56, 120.93, 83.39, 65.53, 53.39, 41.29, 35.00 ppm. GC R_t 22.23 min, single peak, MS: M+ 264, 205, 160, 104

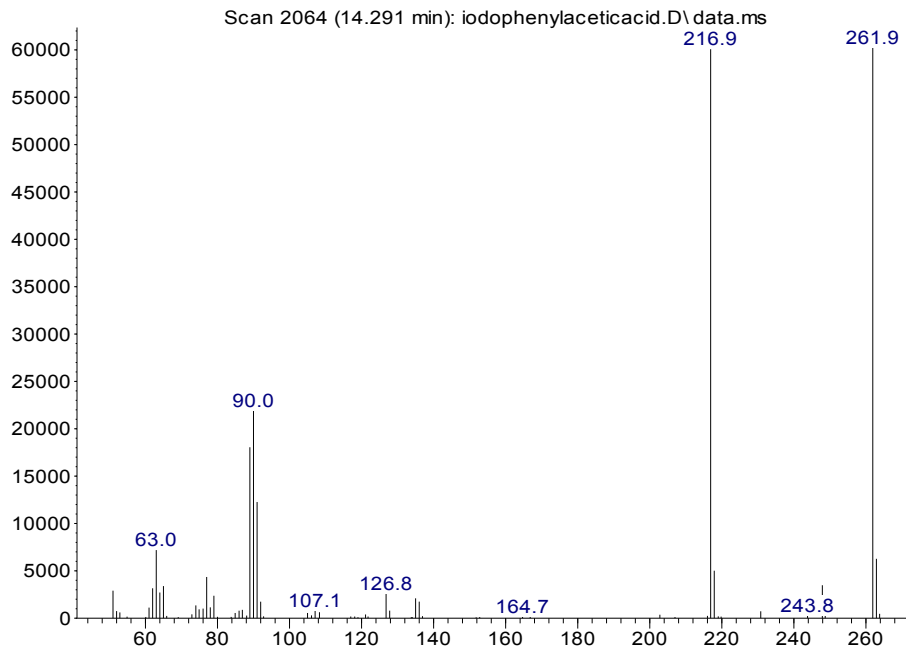
4-[4-(2-Phenylacetoxy-ethyl)-phenylethynyl]-phenyl-acetic acid phenethyl ester To a 50-mL side-arm round bottom flask equipped with magnetic stir bar (4-Ethynyl-phenyl)-acetic acid phenethyl ester (0.11 g, 0.41 mmol) was added. Then, 10 mL of triethylamine, previously sparged with N₂ was added via syringe to the reaction flask and allowed to stir. The reaction flask was then heated to 60° C in an oil bath. CuI (0.002 g, 0.003 mmol) and PdCl₂ (0.01 g, 0.003 mmol) were then added to the solution. After addition of the catalysts, (4-iodo-phenyl)-acetic acid phenethyl ester (0.15 g, 0.41 mmol) was slowly added drop wise and allowed to stir in heat for 3 hours. After 3 hours the heat was removed and the mixture was allowed to stir at room temperature for 72 hours. The mixture was filtered and the solvent was removed via rotary evaporation. The crude product was then extracted with 15 mL of dichloromethane, and washed with 5 mL of 6M HCl, water, and brine solutions. The organic layer was then dried over MgSO₄. After drying, the crude product was purified via flash chromatography on silica gel in dichloromethane and then dried over MgSO₄. Product was not pure at this stage preliminarily. ¹H NMR results and assignments are presented in Appendix I.

Appendix

GC/MS DATA

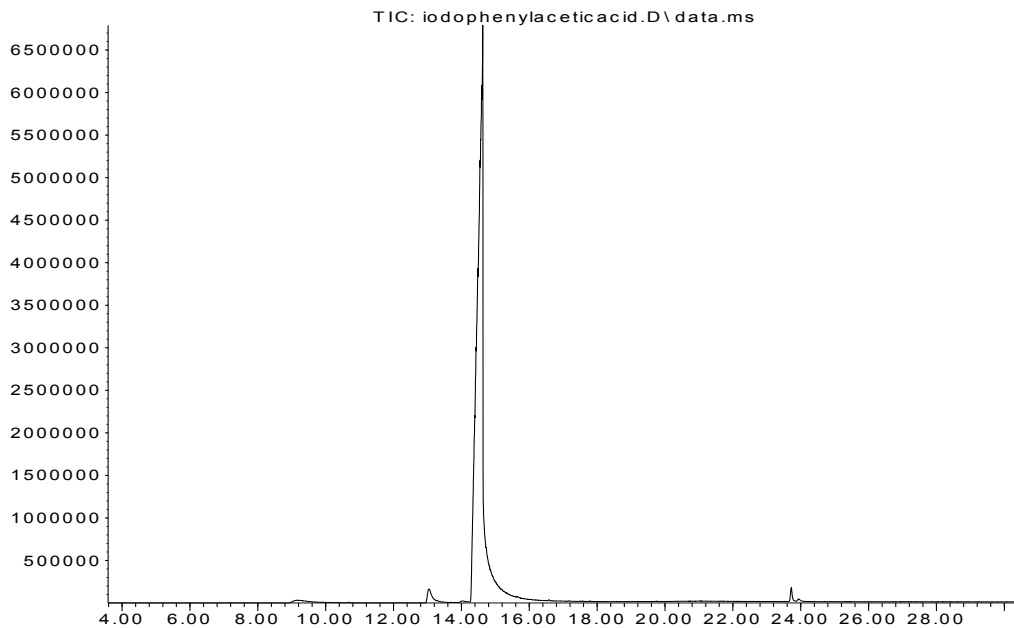
Mass Spectroscopy of (4-iodo-phenyl)-acetic acid

Abundance



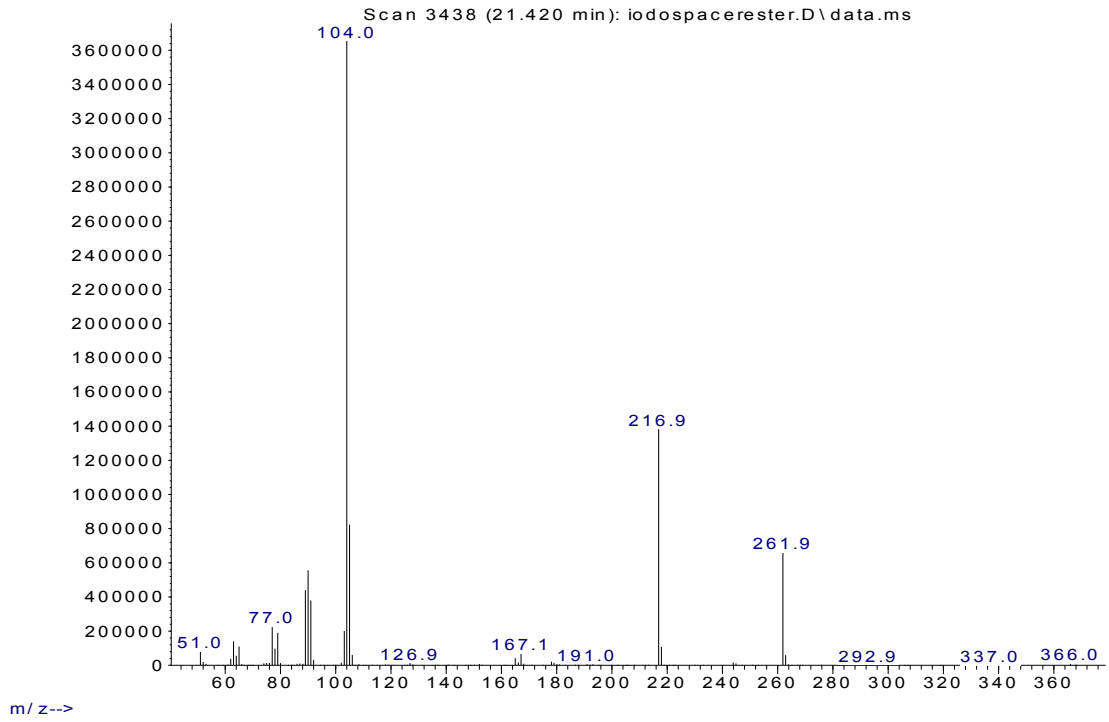
Gas Chromatograph of (4-iodo-phenyl)-acetic acid

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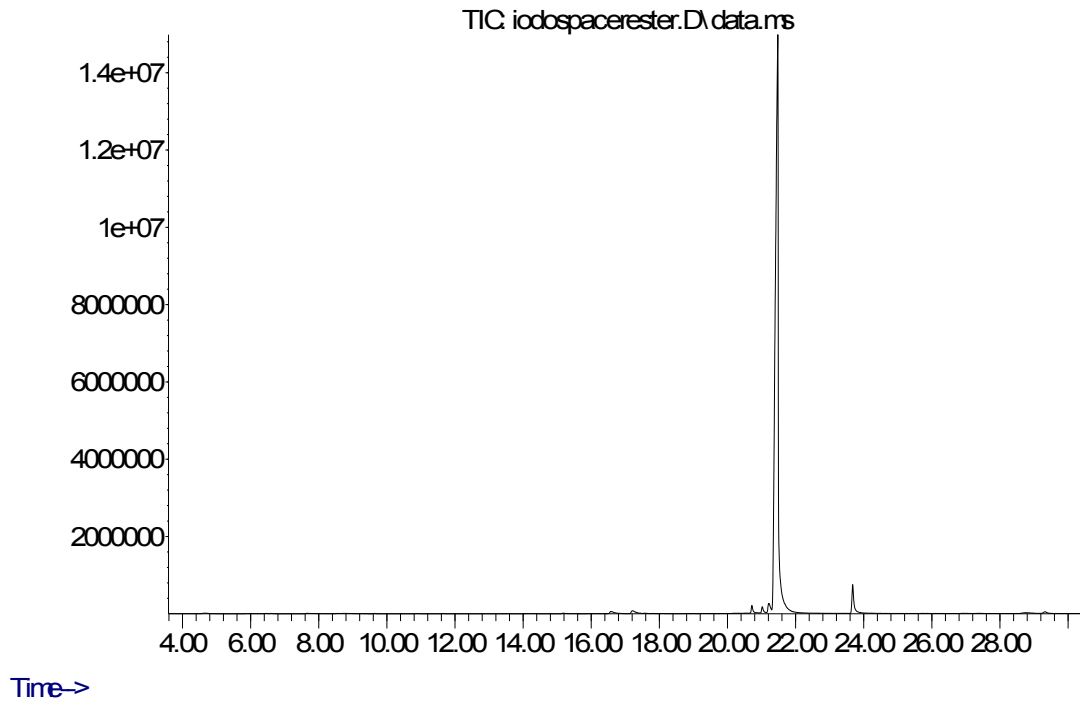
Mass Spectroscopy of (4-iodo-phenyl)-acetic acid phenethyl ester

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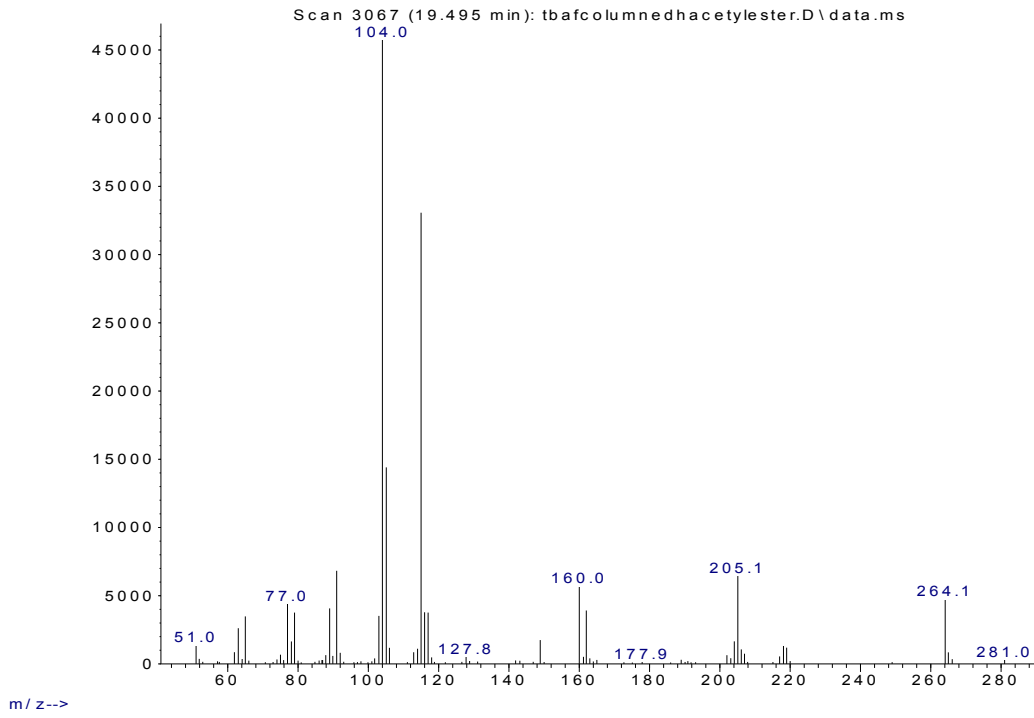
Gas Chromatograph of (4-iodo-phenyl)-acetic acid phenethyl ester

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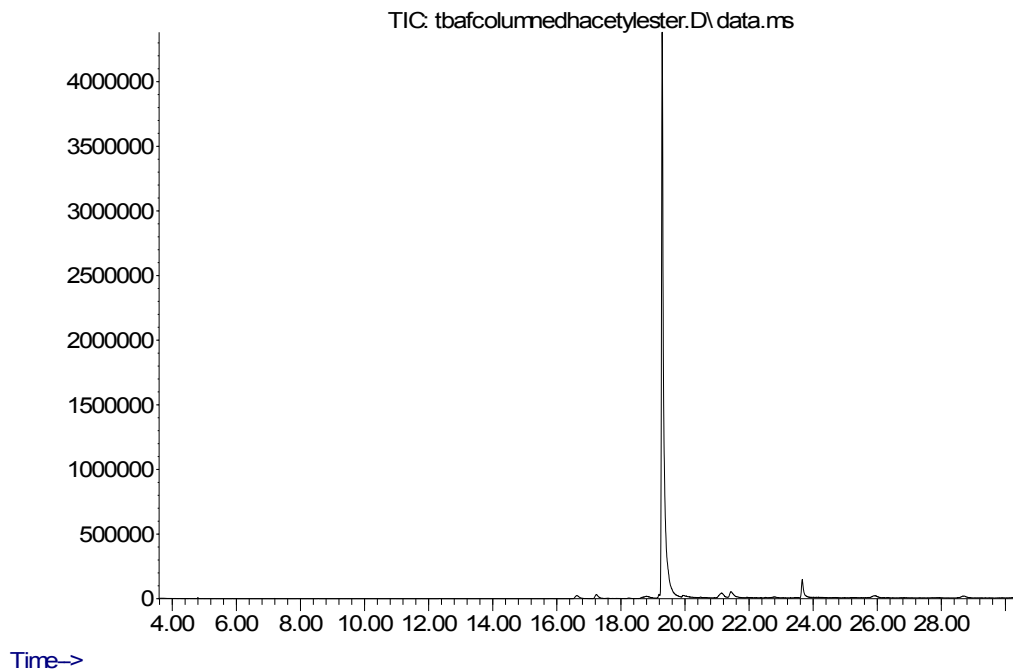
Mass Spectroscopy of (4-Ethynyl-phenyl)-acetic acid phenethyl ester

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Gas Chromatograph of (4-Ethynyl-phenyl)-acetic acid phenethyl ester

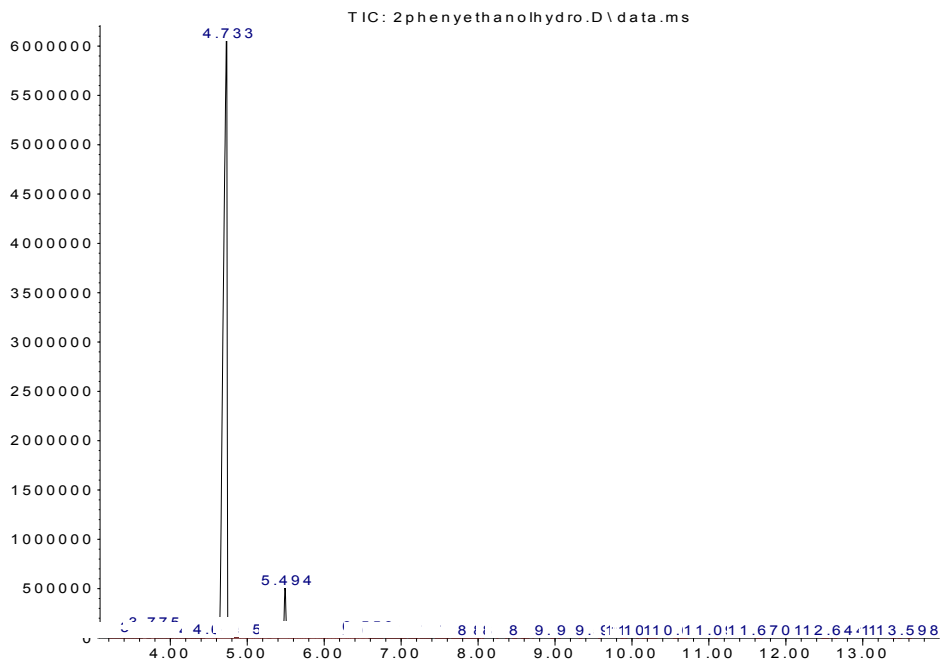
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HEADSPACE ANALYSIS

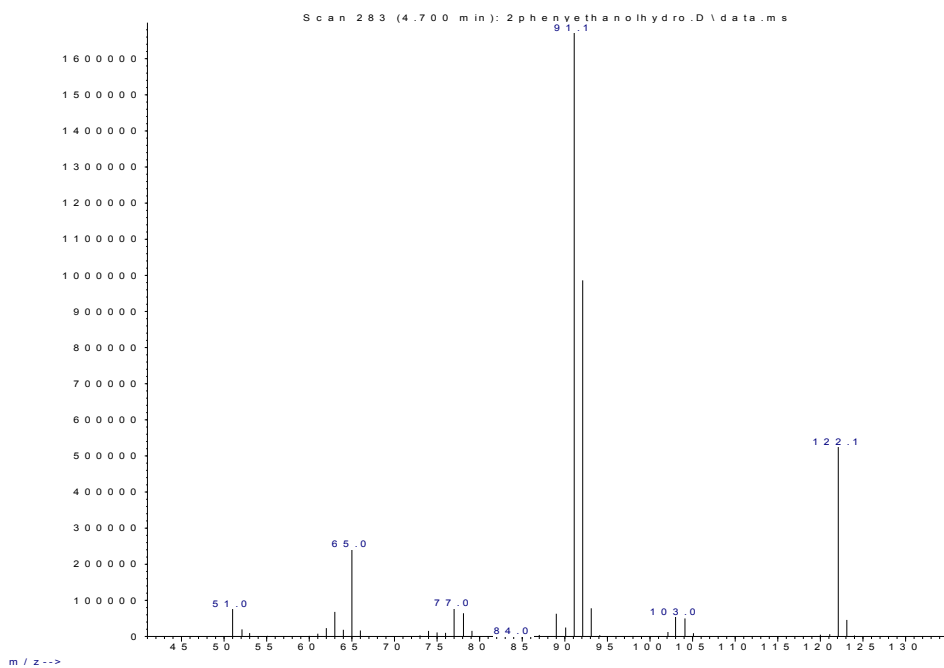
Gas chromatograph of stock 2-phenylethanol

Abundance



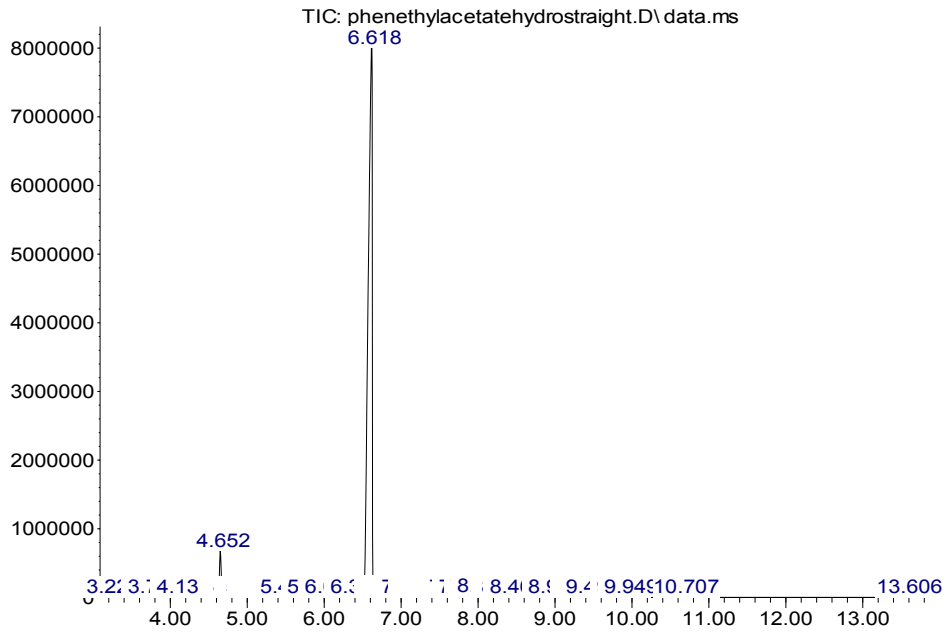
Mass spectrum of stock 2-phenylethanol

Abundance



Gas chromatograph of stockroom 2-phenylethylacetate

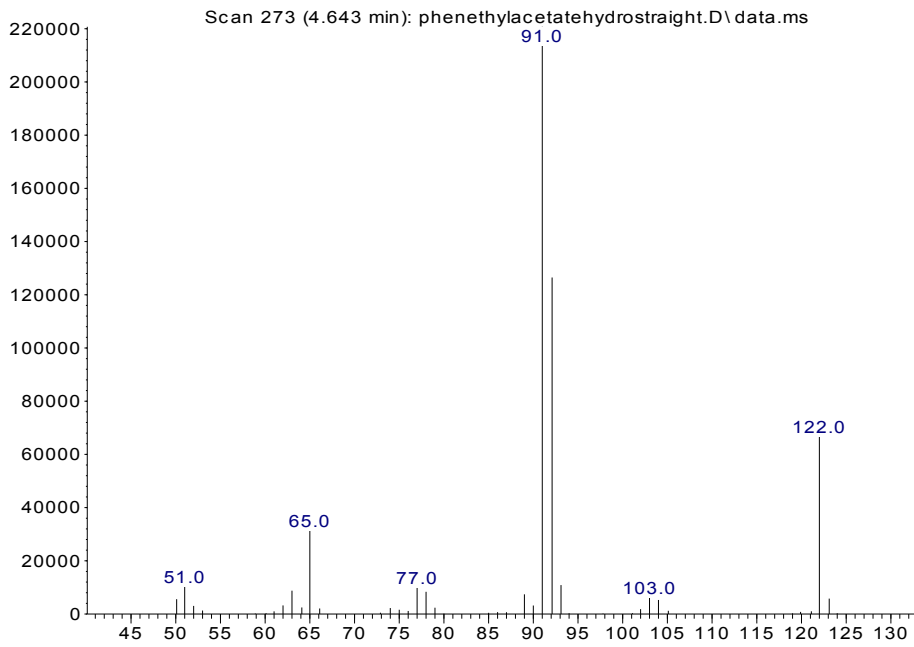
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Time-->

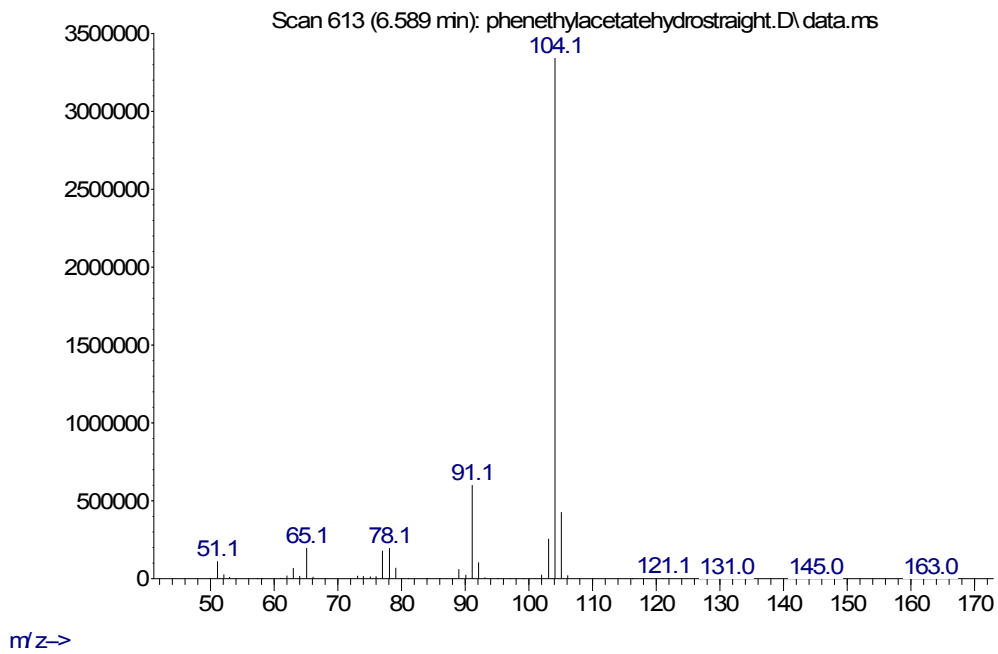
Mass spectrum of peak at RT 4.652 minutes stockroom sample

Abundance

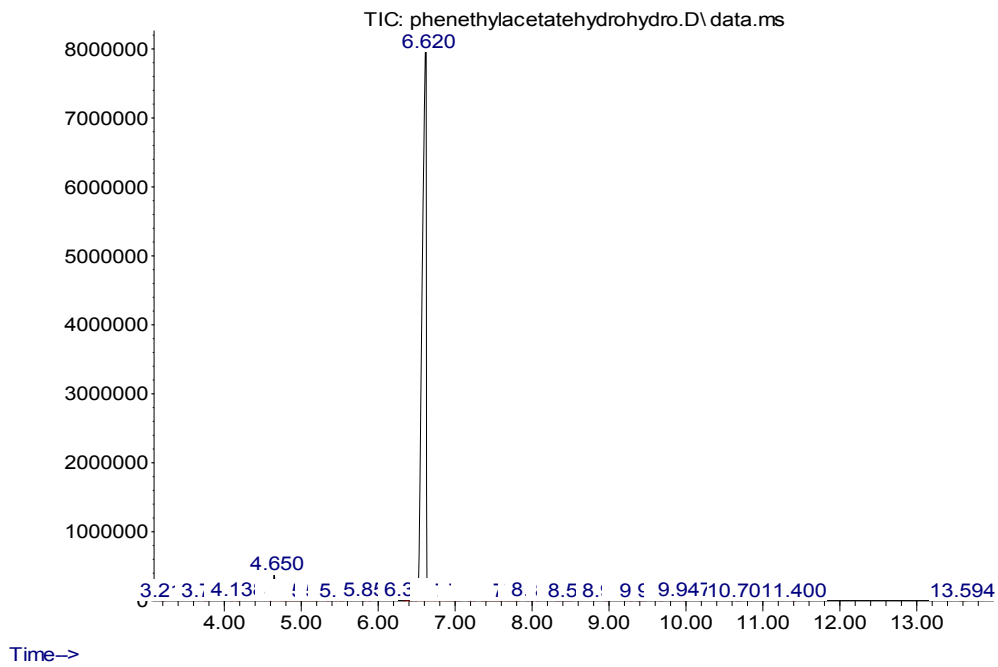


m/z-->

Mass spectrum of peak at RT 6.618 minutes in stockroom 2-phenylethyl acetate sample

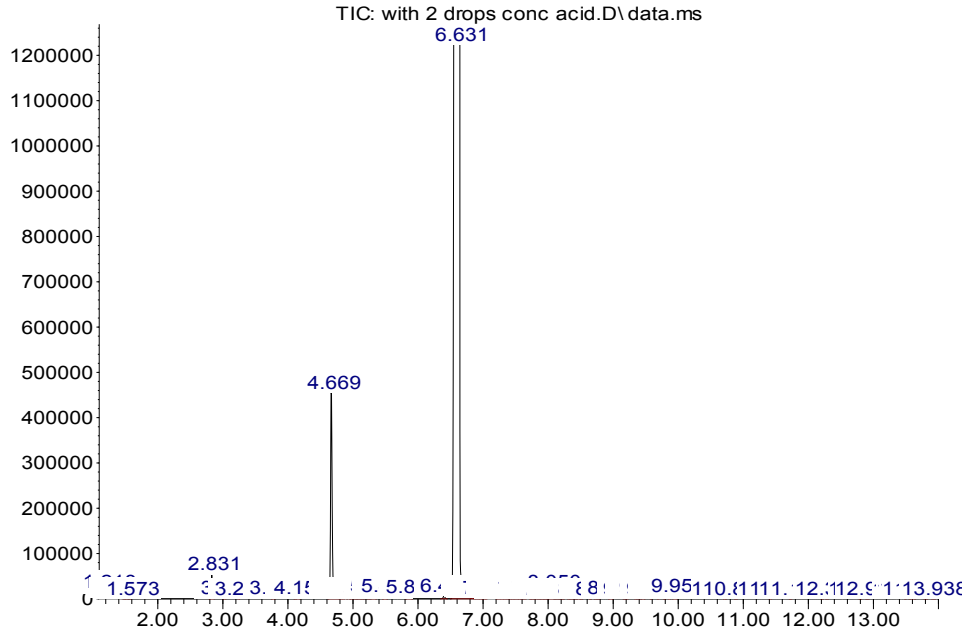


Gas chromatograph of mixture of 1 mL stock 2-phenethyl acetate, 1 ml DI water



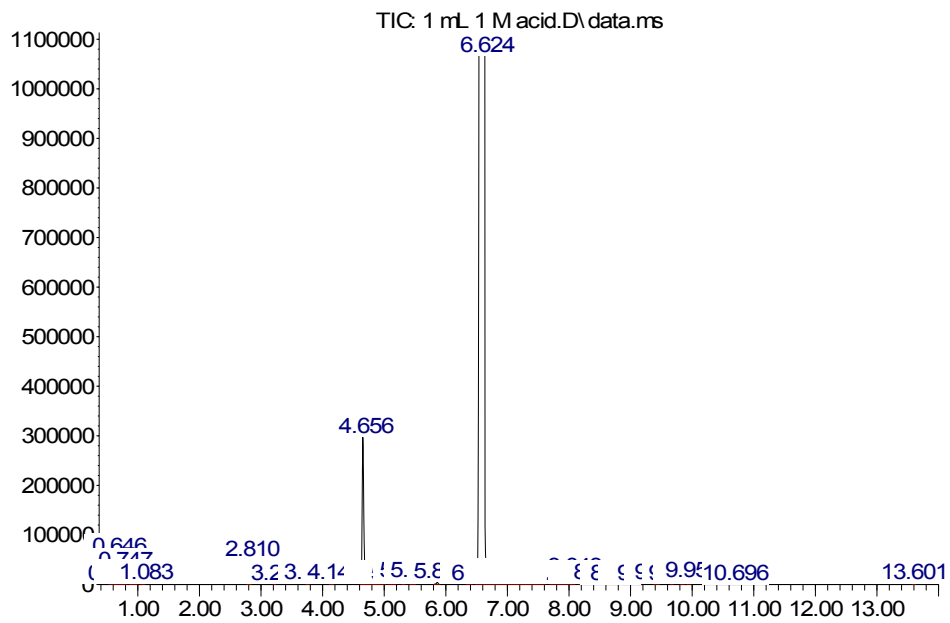
Gas chromatograph of 1 mL of 2-phenethyl acetate, 1 mL DI water, 2 drops conc HCl

Abundance



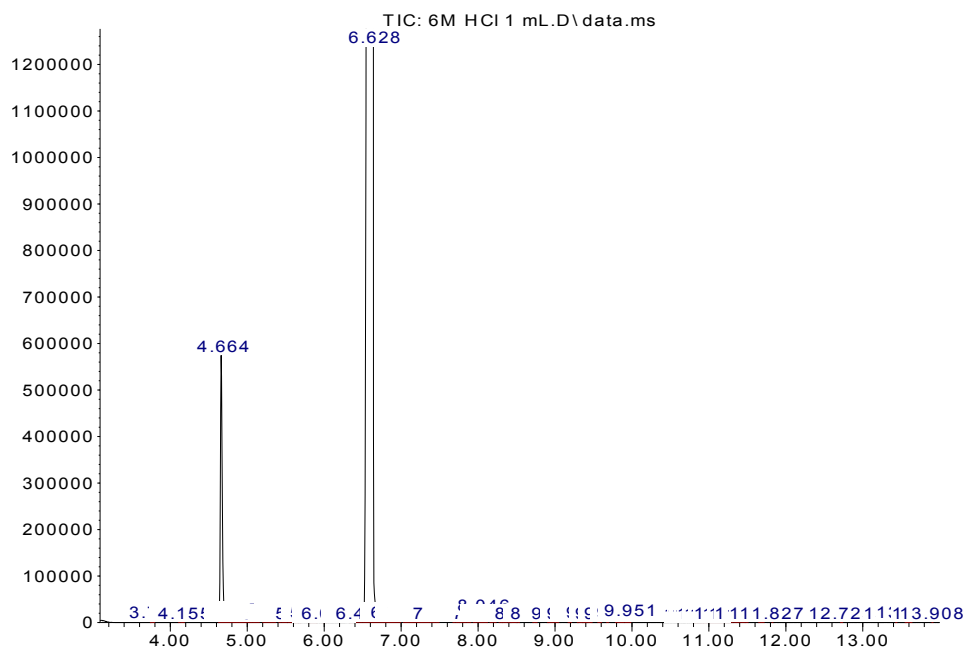
Gas chromatograph of 1 mL 2-phenethyl acetate, 1 mL DI water, 1 mL 1M HCl

Abundance



Gas chromatograph of 1 mL 2-phenethyl acetate, 1 mL DI water, 1 mL of 6M HCl

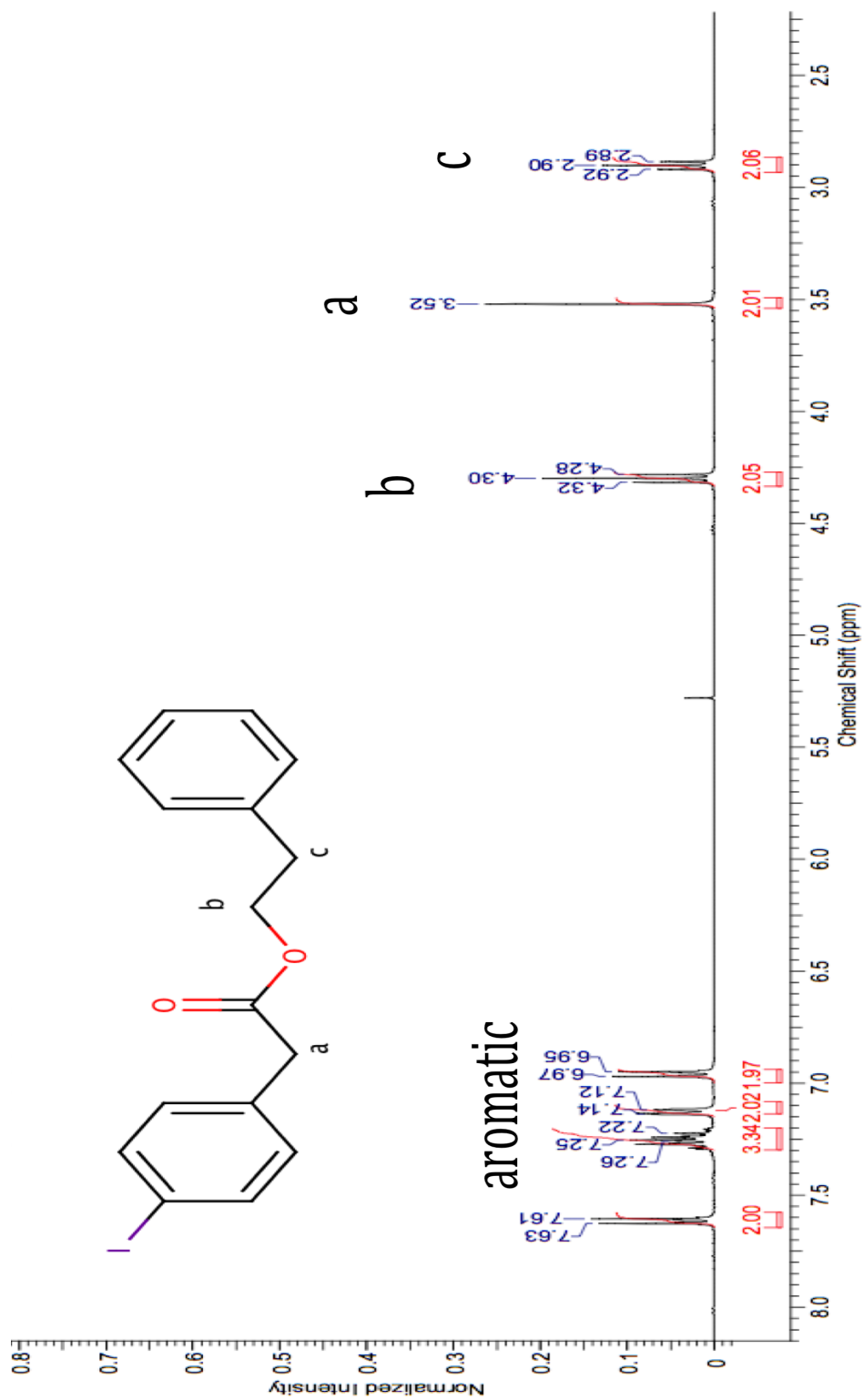
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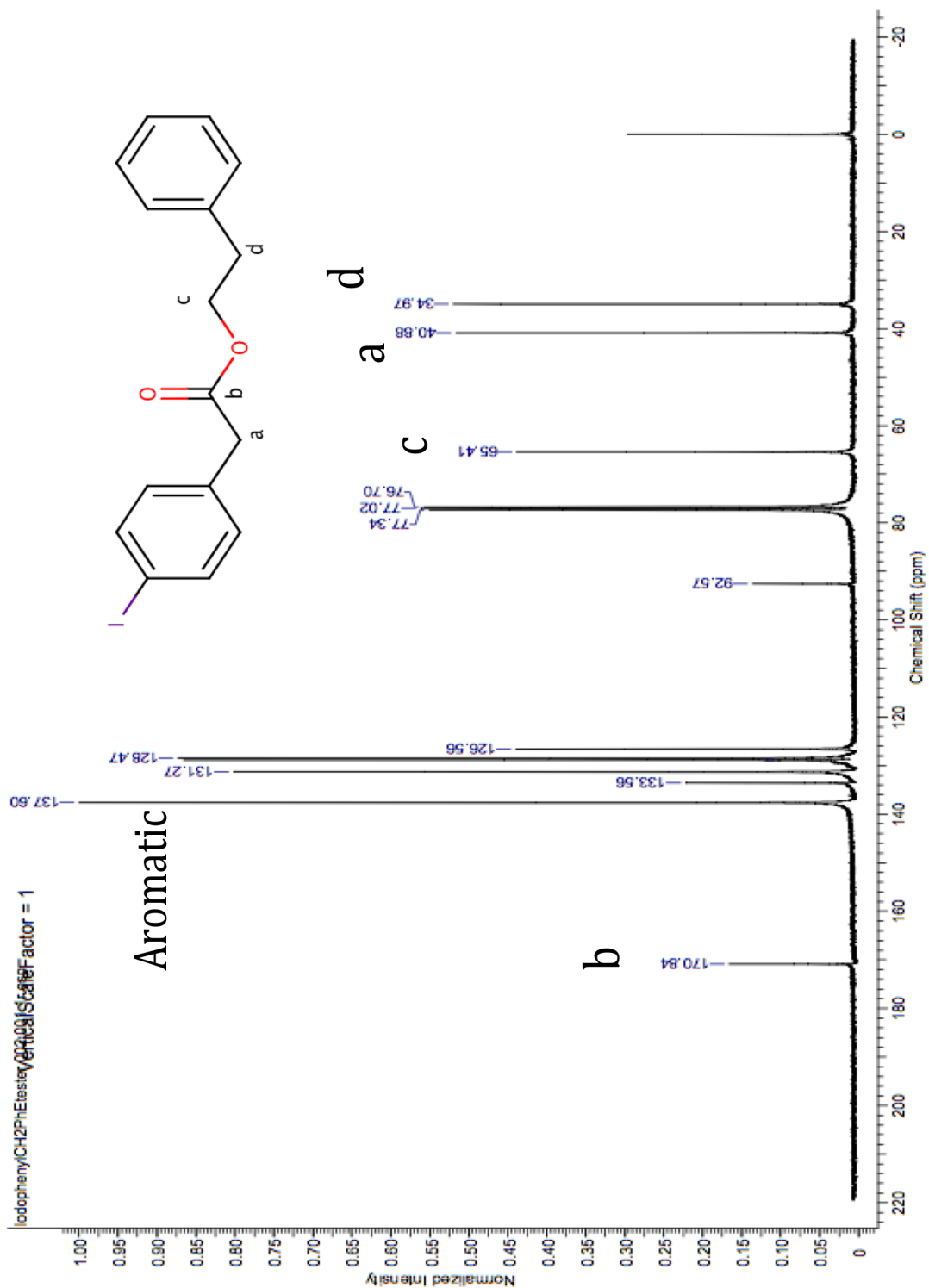
Time-->

NMR DATA

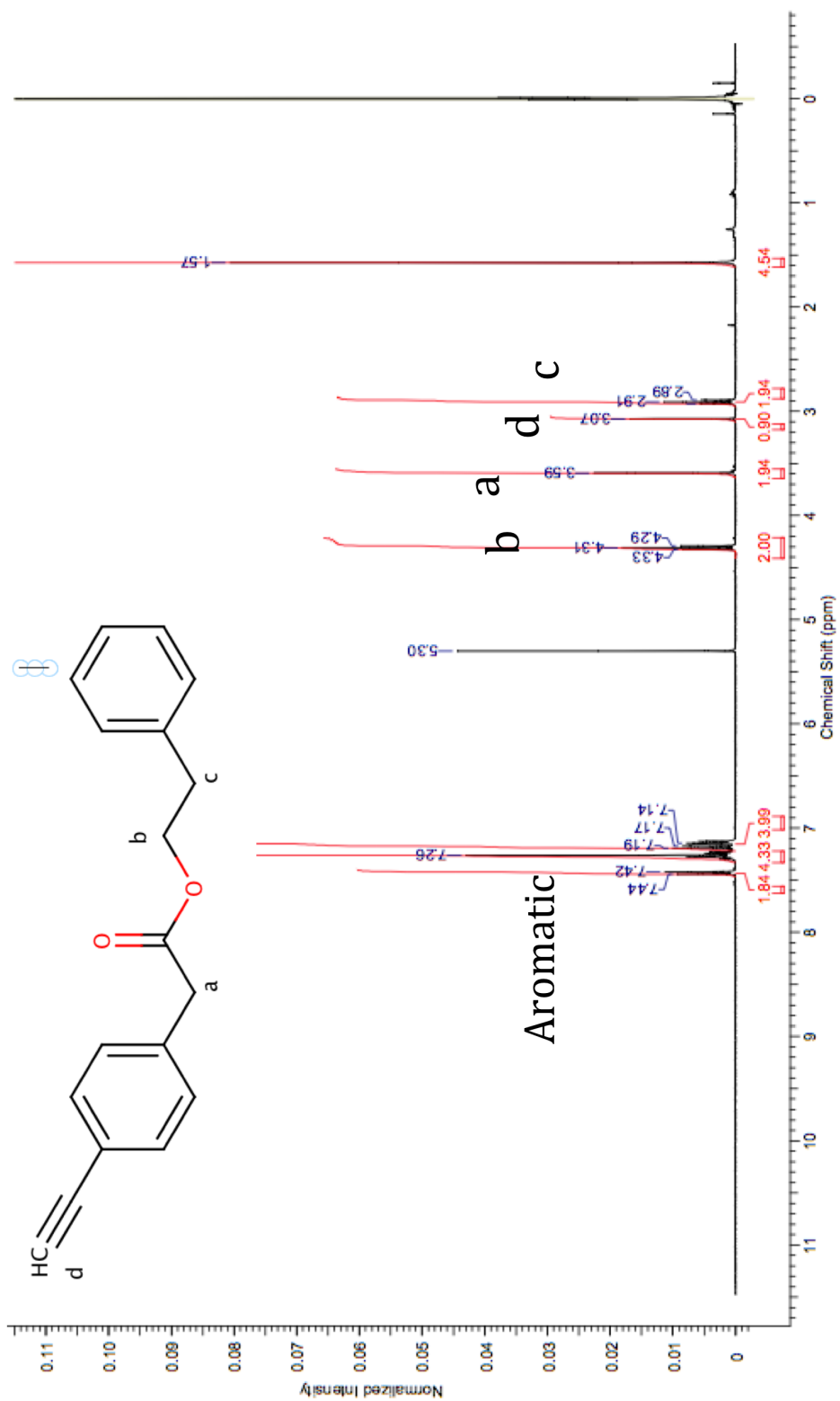
^1H NMR of (4-iodo-phenyl)-acetic acid phenethyl ester (CDCl_3)



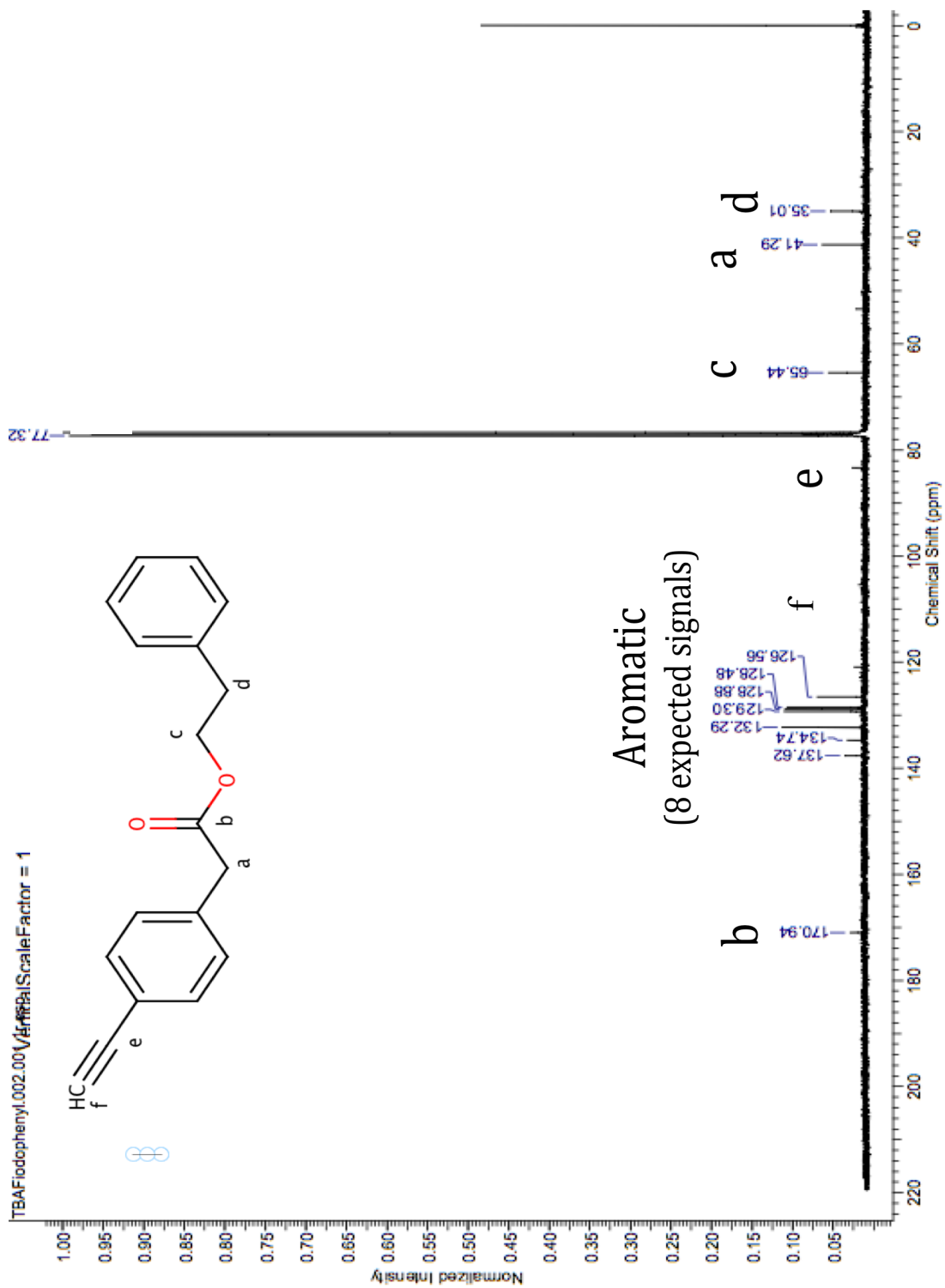
^{13}C NMR of (4-iodo-phenyl)-acetic acid phenethyl ester (CDCl_3)



^1H NMR of (4-Ethynyl-phenyl)-acetic acid phenethyl ester (CDCl_3)



^{13}C NMR of (4-Ethynyl-phenyl)-acetic acid phenethyl ester (CDCl_3)



^{13}C NMR of 4-[4-(2-Phenylacetoxy-ethyl)-phenylethynyl]-phenyl-acetic acid phenethyl ester (CDCl_3)

