ABSTRACT

Synthesis of 4-*cis*-butyl-1-arylcyclohexanamine and Examination of 4-tert-butyl-1-arylcyclohexanamine as a Gelling Agent

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Agents capable of gelling organic liquids comprise a special area of chemistry because our understanding of gel formation is still relatively unknown. Even now, such materials are typically discovered inadvertently. Although there are many well-known aqueous gels, gelled organic phases are much rarer and less understood. These materials are of interest because gels represent something between the liquid and solid phase.[1] Although various organic gelling agents may have different properties (potency, range of liquids gelled, clarity of gels), the gels are all characterized by cross-linking that creates a 3D network. *trans*-4-Tert-butyl-1-arylcyclohexanol is an organic gelling agent discovered at Baylor. The goal of this project is to synthesize the corresponding amine, *trans*-4-tert-butyl-1-arylcyclohexanamine, and to determine whether it also exhibits gelling properties .

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SYNTHESIS OF 4-*CIS*-BUTYL-1-ARYLCYCLOHEXANAMINE AND EXAMINATION OF 4-*TRANS* -BUTYL-1-ARYLCYCLOHEXANAMINE AS A GELLING AGENT

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CHAPTER ONE

Gelling Agents

Gels comprise a special area of chemistry because the entirety of the understanding of gel chemistry is still relatively unknown. Therefore, many researchers today are devoting their efforts to study how gels form and what new types of gels could be used for consumer products and scientific research in the world today. Gels are designed to interact with either aqueous or organic solvent, and the gels remain somewhere between the liquid and solid phase.[1] Due to the liquid or solid properties of gels, gels have been utilized in a variety of different manners because they have varying physical properties that can make a specific gel ideal for a consumer product or a research aid in a laboratory. Although each gel may have different properties, the gels can be classified by the type of cross-linking that creates their 3 D networks and by their use as an aqueous or organic gel. The classifications are based on the gel's status as an artificial or natural gel, the shape and size of the gel configuration, and the types of solvents the gel can absorb.[2] Currently, the functions of gels are seemingly endless, and many aqueous gels are used in hygiene products, drying agents, pharmaceuticals, air fresheners, food, cosmetics, artificial muscles, insulators, fertilizer additives, beds, toys, and much more.[3] However, organic gels are different from aqueous gels because the main purpose is to convert organic liquids into a gel state.[4] Nevertheless, the development of a new organic gelling agent may have many applications in a variety of industries because companies and researchers may be able to utilize a new gel to improve their product or remove impurities from chemical reactions. Therefore, the goal of this project is to

synthesize a new potential organic gelling agent, *trans*-4-tert-butyl-1-arylcyclohexanamine, and to determine its properties to understand if the compound may have a particular use in either a consumer or research market.

To best gain an understanding of the properties of gels and how they function, the classifications of various gels must be understood. The cross-linking of the gel is a major factor that affects the physical properties of gels. Some of the cross-linking can be formed through chemical reactions that form covalent bonds, hydrogen bonds, ionic bonds, and polymers. If the majority of the cross-linking is formed by chemical reactions that form covalent bonds, then the gels cannot be dissolved. As a result, these gels are known as irreversible gels.[5] Conversely, physical gels demonstrate reversible liquid to gel phase transition from a somewhat solid state to a thick liquid at temperatures below 150°C. The main reason for the phase transition is due to the cross-linking involving van der Waals interactions that may be reinforced by hydrogen bonding, ionic bonding, coordination bonding, helix formation, and hydrophobic bonding. Additionally, some physical gels are composed of small molecules, and the low molecular weights of the molecules can cause water or various organic solvents to gel.[6] Many of the reversible gels form polymer chains, which hold the gel together. Since the base units of many reversible cross-linking gels form polymers, the synthesis of the gel can be accomplished by creating cross-linking during the polymerization process or by creating the polymer chains and further polymerizing the polymer with a divinyl compound.

Different gels can also be classified and examined based on the weight of the gel. To help classify the gels by shape and size, the average molecular weight between the cross-links is utilized to report the size. Additionally, the permeability of the gel to solute

determines the spatial size by using the dynamic modulus, which is the ratio of stress to strain during vibration of the gel. Both of these methods are used to determine if the gel is a microgel or a macrogel. Microgels are composed of tightly compact cross-linking and have little capability to swell in the presence of solvent, and macrogels contain larger compounds that create larger cross-linkages and can absorb more solvent. If the solution is dilute, then the distance between the gel molecules is greater. As a result, the cross-linking becomes more difficult and fluctuations in the cross-linking occur, which can create small localized microgels. In fact, the high concentration of cross-linking at one point in the gel solution may cause the microgel to precipitate out of the solution. For macrogels, the cross-links are not uniform, and higher energy flux of light on the surface of the solution can form stronger portions of the gel. However, the cross-linking is usually more dispersed, and the gel can easy contain more solvent.[7]

The remaining methods of gel classification consist of determining the origin of the gel and analyzing what solvents the gel can immobilize through absorption. Many gels are synthesized naturally, but others are produced artificially in research labs. Today, most of the gels are artificially manufactured, and these gels are commonly used in both research and consumer products. For example, the two most popular artificial aqueous gels can be found in women's cosmetic products and soft contact lenses. In addition to the origin of the various gelling agents, the ability for a gel to absorb solvent serves as a major method of characterizing a gel. To determine what solvent the gel will immobilize, numerous tests have to be done in a laboratory setting to determine which solvent works the best with each gelling agent. By performing tests with various solvents, the gel's maximum high elastic shear moduli and high yield stresses can be determined.[8]

For this experiment, the focus of the synthesis of new gelling agents was based around the various gelling derivatives of *trans*-4-tert-butyl-1-arylcyclohexanol because the gel is successful at immobilizing a wide range of organic solvents. Organic gelation agents usually contain long unbranched alkyl chains or they have significant hydrogen binding capabilities. *Trans*-4-tert-butyl-1-arylcyclohexanol is one of the smallest known organic gelling agent as well as one of the most structurally simple.[9] Additionally, *trans*-4-tert-butyl-1-arylcyclohexanol is unique because only the isomer with an axial aryl group serves as a gelling agent, and the alcohol can be identified as a physical gel. Therefore, the reversible gel to liquid phase transitions was observed through experimental laboratory testing. Experimentation also showed that the thermal stability of the gel depended on the organic solvent that was suspended in the gels. *Trans*-4-tert-butyl-1-arylcyclohexanol served as a gelling agent of interest because the more polar *trans* diastereomer was capable of forming gels, but the *cis* diastereomer with the aryl group in the equatorial configuration had none of the properties of gels. Furthermore, the *trans*-4-tert-butyl-1-arylcyclohexanol gel was able to form a gel at low concentrations (0.5-1% wt%) with hydrocarbons and higher concentrations (2-5%) with aromatic hydrocarbons, halocarbons, ethers, and esters. However, *trans*-4-tert-butyl-1-arylcyclohexanamine was unable to gel protic solvents, and the gel precipitated during the attempt to create a gel with organic solvents that contained protic function groups. Also, the melting point of the gel increased as the concentration of the *trans*-4-tert-butyl-1-arylcyclohexanol increased in the mixture.[10]

Since 4-tert-butyl-1-arylcyclohexanol absorbed most organic solvents, this gelling agent shows some hydrophobic and limited hydrophilic properties. The carbon structure

of the molecule composes the hydrophobic region of the gelling agent, but the alcohol group serves as a localized hydrophilic portion of the molecule due to the polarity of the alcohol group and the hydrogen bonding that can occur. Nevertheless, the majority of the gelling agent has hydrophobic properties; therefore, the gelling agent is designed to better absorb relatively nonpolar organic solvents. Other more polar solvents may be absorbed in small quantities due to the presence of the alcohol group, but a significantly less amount of polar solvent could be absorbed, which would not provide the optimal stability for the gel. Therefore, the properties of the gel indicate a large degree of swelling in nonpolar organic solvents and a relatively small amount of swelling in the presence of water and polar organic solvents.[11]

In a paper by Garner and Terech, a study of the mechanism of the 4-tert-butyl-1-arylcyclohexanol gel was provided to study why the gelling process occurs. To examine the mechanism of the process, various derivatives were prepared with different functional groups substituted amongst the aryl group that was in the axial position. However, when the carboxymethyl, methyl, and other hydrocarbons were added to the aryl group, no gelling agents were perceived. The only observed gelling agents from the derivatives were ring-fluorinated compounds. Furthermore, the fibrous 4-tert-butyl-1-arylcyclohexanol gelling agent was found to be strong in nonpolar organic solvents due to the high elastic shear moduli at 70350 Pa and a high yield stress of 620 Pa with 2.2% weight of dodecane. Further compound characterization of the 4-tert-butyl-1-arylcyclohexanol gel showed that the gel to liquid transition demonstrated a hysteresis effect, and many of the low molecular weight gel particles would precipitate out of the solution.[12]

The synthesis of 4-tert-butyl-1-arylcyclohexanol is performed by treating 4-tert-butylcyclohexanone with phenylmagnesium bromide in a dry ice and acetone bath with ether. After warming the reaction outside of the cold bath and filtering the organic phase, water is added to the reaction with ammonium chloride. However, the reaction does not yield only the *trans* diastereomer of 4-tert-butyl-1-arylcyclohexanol; therefore, a mixture of the *cis* and *trans* diastereomers are present. The experiment shows the *trans* to *cis* ratio was approximately 62:38, and the diastereomers were successfully separated using silica column chromatography or radial chromatography in dichloromethane. Upon evaporating the dichloromethane from the *trans* diastereomer, a rubber-like substance was left behind, which was the first indication of the potential gelling properties of the *trans* diastereomer of 4-tert-butyl-1-arylcyclohexanol.[13]

Through IR spectroscopy, data showed the forces that influenced the mechanism for the aggregation of the gelling agent were hydrogen bonding of the equatorial alcohol group, van der Walls forces, and dipole interactions. The forces' interactions were observed through the crystalline-like colloids that formed during the phase transition.[14] From this observation, a theory can be formulated that other organic functional groups could replace the axial alcohol. If the new functional group had the ability to undergo hydrogen bonding, van der Waals forces, and dipole movement, then the new compound may be able to serve as a gelling agent.

Despite the interesting stereochemistry and intermolecular forces of the 4-tert-butyl-1-arylcyclohexanol gelling agent, the gel has had few practical applications to date. The main use of the gel is currently to suspend various organic compounds in organic solvents. By suspending specific organic compounds in the gel, recrystallization is

inhibited because the organic compounds cannot easily change their orientation in the gel to aggregate in a manner that is optimal for crystal formation. Therefore, the gel can aid in the storage of organic molecule if there is a desire to inhibit crystallization. Other than suspending organic compounds, there has only been one attempt to utilize the gel in a consumer product. A chemical company found that the 4-tert-butyl-1-arylcyclohexanol gelling agent could be added in small amounts to a Plexiglas polymer in order to make the Plexiglas clearer. However, the gelling agent was not incorporated into the final product because of the difficulty to produce the gel on an industrial scale, and the expense necessary to synthesize the gel were greater than other competing gel products.[15]

Overall, the study of gels with specific stereochemistry has not been greatly researched. Therefore, it is necessary to continue to explore this category of gelling agents because many of the products may have potential uses for consumers, industrial companies, and researchers. In order to study gels with specific stereochemistry, the best starting point would be to synthesize an organic molecule that may share similarities in structure and function with the 4-tert-butyl-1-arylcyclohexanol gelling agent to better understand how the stereochemistry may affect a gel's properties. One organic functional group that has the ability to undergo hydrogen boding, van der Walls forces, and dipole interactions is an amine. Therefore, it may be possible to synthesis a new gelling agent that uses an amine functional group instead of an alcohol. Yet, many of the major properties of the *trans* form of 4-tert-butyl-1-arylcyclohexanol would be retained in a 4-tert-butyl-1-arylcyclohexanamine compound. However, there could be differences in the amount of organic solvent that the gel may hold, and an amine gelling agent may also support organic solvents of varying polarities in a different manner in comparison to the

alcohol gel because the hydrogen bonding of the amine would be different from its alcohol counterpart. If 4-tert-butyl-1-arylcyclohexanamine is capable of forming a gel through cross-linkages, then the hydrophilic and hydrophobic properties of the potential gel would be best suited for the suspension of large amounts of nonpolar organic solvents and smaller amounts of polar organic solvents and water.

Similarly to the 4-tert-butyl-1-arylcyclohexanol gel, the amine equivalent, 4-tert-butyl-1-arylcyclohexanamine, would not be synthesized with a specific practical purpose in mind because numerous tests would have to be done to determine the optimal solvent, high elastic shear moduli, and high yield stress of the gelling agent. Theoretically, the method to synthesize the amine gelling agent could be done by starting with the alcohol organic gelling agent, performing a dehydrogenation of the compounds, and adding a halogen, such as chlorine, in place of the alcohol group. At this point, a substitution reaction could occur with an azide, which could be reduced by lithium aluminum hydride to form the final amine product. Another mode of potential synthesis would be similar to the synthesis of the 4-tert-butyl-1-arylcyclohexanol proposed by Garner and Terech. The starting component could be 4-tert-butylcyclohexanone, which could undergo a reaction with benzylamine to form an imine. At this step, the compound could be reacted with etherate and a phenyl organometallic to reduce the imine to an amine while adding the aryl group at the 1 position of the cyclohexane ring. Finally, a hydrogenation reaction could be performed with a metal catalyst, such as palladium, to reduce the benzyl amine to a normal amine. For more information on the reaction schemes, please see chapter 2.

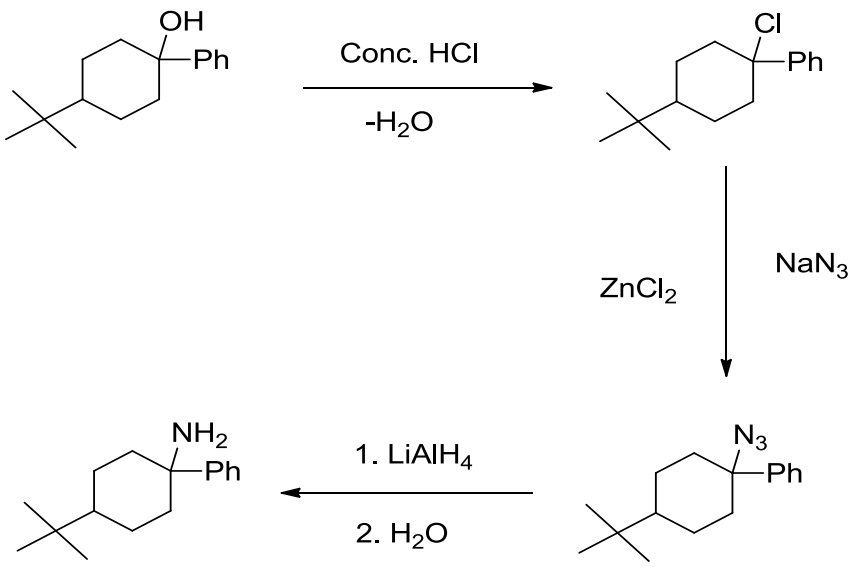
Overall, gels form a unique area of relatively unexplored chemistry. Despite the large use of gels throughout a variety of both consumer and research entities, there are

still numerous questions as to why specific gelling agents aggregate and form cross-linkages. Additionally, even less information is known about gelling agents that are specific to certain stereochemical orientations. Therefore, the research done in the project is designed to gain a better understanding of gels that are dependent on stereochemistry in order to determine if these gels could be used by consumer and research entities. To study the stereochemistry of stereospecific gels, 4-tert-butyl-1-arylcyclohexanamine will be synthesized, which is theorized to have some gelling properties. Then, the chemical and physicals properties of the compound will be examined in an attempt to better understand why a gel was or was not formed. If a gel is present, then numerous tests will be conducted to determine the optimal solvent for absorption, the strength of the gel, and practical uses for the gelling agent.

CHAPTER TWO

Reaction Theory and Methods

The initial step of the project is centered on finding a way to synthesize *trans*-4-tert-butyl-1-arylcyclohexanamine in order to examine the compound for potential organic gelation agent properties. A large amount of a crude 4-tert-butyl-1-arylcyclohexanamine will be obtained from an advanced organic laboratory at Baylor University. The 4-tert-butyl-1-arylcyclohexanamine was made by using the alcohol equivalent amine gelling agent, 4-tert-butyl-1-arylcyclohexanol. With the addition of concentrated hydrochloric acid, 4-tert-butyl-1-arylcyclohexanol can undergo dehydrogenation and the addition of chlorine to the molecule. At this point, sodium azide was added to the reaction mixture, which caused a substitution reaction that should replace the chlorine molecule with the azide group. Then, the azide can be reduced with lithium aluminum hydride to form 4-tert-butyl-1-arylcyclohexanamine. Ideally, this synthesis should provide both the *cis* and the *trans* diastereomers of the desired amine gelation agent.

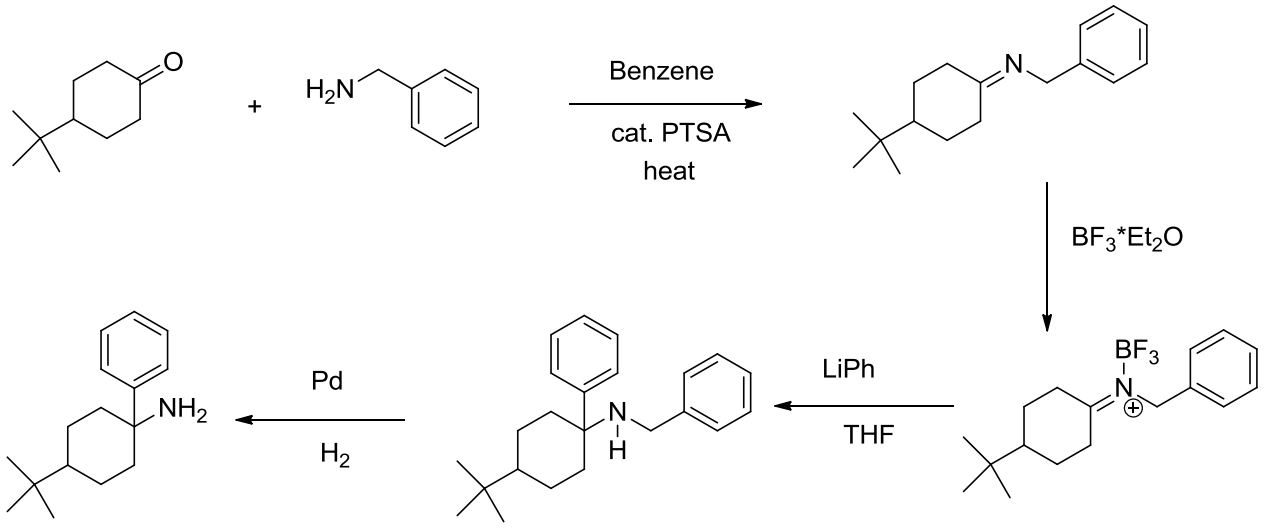


Scheme 1: Azide Reduction Synthesis of 4-tert-butyl-1-arylcyclohexanamine

Due to the potential that impurities may be present in the 4-tert-butyl-1-arylcyclohexanamine that is synthesized through the azide reduction, it is necessary to purify the product by recrystallization to determine if only one or both diastereomers of the amine were formed. The presence or absence of the diastereomers should be apparent through gas chromatography and mass spectroscopy (GCMS).

After GCMS of the amine product was run, it was apparent that only the *cis* diastereomer of the amine gelation agent was formed by using the azide reduction mechanism. Therefore, it was necessary to develop another potential method to synthesize the *trans* diastereomer of 4-tert-butyl-1-arylcyclohexanamine. For this new mechanism, 4-tert-butylcyclohexanone will undergo a reaction with benzylamine in benzene with a catalytic amount of p-toluenesulfonic acid and heat to form an imine. Then, the imine could be reacted with trifluoroboron etherate and phenyl lithium in tetrahydrofuran to reduce the imine to an amine while adding the aryl group at the 1

position of the cyclohexane ring. Finally, a hydrogenation reaction could be performed with a metal catalyst, such as palladium, to reduce the benzyl amine to a normal amine.



Scheme 2: Synthesis of 4-tert-butyl-1-arylcyclohaxanamine from 4-tert-butylcyclohexanone

For the initial part of this reaction scheme, the 4-tert-butylcyclohexanone and the benzylamine must be placed in a Dean-Stark apparatus with benzene and be allowed to reflux overnight. To remove the benzene, the reaction mixture can be placed in a rotary evaporator to remove any remaining solvent. Furthermore, a short distillation apparatus must be utilized because the benzylamine should be in excess in the initial reaction, and it is necessary to remove the benzylamine from the reaction before continuing to the next part of the reaction. GCMS should be performed after this step to confirm that the product is both pure and present after the removal of the benzylamine. Then excess trifluoroboron etherate and phenyl lithium should be added to the compound sequentially while ensuring that the compound is dissolved in tetrahydrofuran to promote a safe reaction with the organometallic. After allowing the reaction to set overnight, a small

amount of distilled water must be added to the possible amine product. To enhance the separation of the aqueous and organic layers, ammonium chloride can be added to the reaction mixture. The aqueous layer can be separated from the organic layer by using a Pasteur pipette, and sodium sulfate needs to be added to the organic layer to absorb any of the water remaining. To ensure that all of the aqueous phase is removed, the organic layer can be run through a Pasteur pipette containing sodium sulfate. Then GCMS can be done to examine the contents of the organic layer following the reaction of the imine with excess etherate and phenyl lithium.

After obtaining the organic phase from the previous step, separation of the various components of the organic phase is necessary to isolate the desired compound. In this experiment, preparative thin layer chromatography (TLC) will be done to isolate the various components of the organic layer. To determine the best solvent for preparative TLC, many smaller TLC plates can be spotted with the organic layer and run in various solvents to observe which solvent has the best separation. The solvent with the best separating power will be utilized for the preparative TLC, and each layer of the TLC plate will be removed by a razor blade. The contents of each layer will be dissolved in dichloromethane, and each layer will be run through a Pasteur pipette containing cotton to remove the silica gel from each layer. At this point, each of the layers will undergo GCMS to determine the purity of the layer and also which layer corresponds with the desired compound for the next step in the reaction.

If the desired compound appears with other compounds or impurities in the GCMS data, then it is necessary to perform further purification. A silica gel column is an excellent way to achieve increased separation of compounds that may be found in the

same layer on a preparative TLC plate. First, a regular TLC plate should be prepared of the desired layer to determine which organic solvent gives the best separation power. After the ideal solvent is determined, a silica gel column can be constructed by making a slurry of the desired organic solvent and the silica gel. After placing the silica gel slurry in the column, sand will be added on top to make the loading of the organic mixture more uniform on the column. After the organic layer is seated in the silica gel, the ideal solvent will be added to the top of the column slowly, and the organic compounds will pass through the silica gel column at different rates based on their intermolecular forces. Usually, the more nonpolar compounds will run off the column first, and the more polar compounds will come off the column later. Shortly after the column begins to run, fractions will be collected. After elution from the column is complete, the fractions will undergo TLC to determine which samples are pure. Then GCMS can be used to identify which compound is desired.

Radial chromatography would be another possible method that would properly separate the organic compounds from the same layer on a preparative TLC plate. For a radial chromatotron, the compound could be first tested on a regular TLC plate with a variety of organic solvents to determine which solvent gives the best separation. Then, a circular silica disk would be selected with a specific thickness that is appropriate for the amount of the compound that needs to be separated. The plate should be conditioned with the ideal organic solvent by dripping the solvent onto the middle of the disk with a dropper that utilizes gravity to move the solvent from a separatory funnel to the dropper. The disk rotates at a rapid rate, which would create a centrifugal force that pushes the solvent from the inside of the disk to the outside of the disk. Once the solvent reaches the

outside of the disk, there is another dropper that releases the solvent that passes through the disk in dropwise increments. Once the disk is saturated with solvent, a concentrated sample of the compound of interest can be loaded on the disk. After the compound is loaded on the disk, the solvent dropper will be added to the appropriate slot that drips solvent onto the center of the disk. At this point, the radial chromatotron will operate similarly to a silica gel column because the compounds in the organic mixture will move to the perimeter of the disk at different rates based on the intermolecular forces that the molecules share with the silica. Additionally, it will be possible to monitor the progress of some compounds through the radial chromatotron disk during the run by shining a UV light next to the disk, which may reveal the location of the compound on the disk as the solvent runs through the disk. In the end, fractions can be collected for TLC to determine which fractions contain the desired compound.

After the purification of the organic layer from the reaction of the imine with the etherate and phenyl lithium, it is possible to proceed with attempts to elucidate the reaction mechanism. As a result, a catalytic amount of palladium on 10% carbon can be added to the reaction vessel containing the desired organic compound. Then, the reaction must be placed under vacuum to remove all air from the reaction chamber. At this point an inert gas, such as argon, can fill the chamber because the reaction will not be disrupted by the presence of an inert gas. After placing the reaction vessel under vacuum and filling the flask with argon several times, all air should be removed from the reaction. Following this step, a balloon filled with hydrogen gas will be attached to the reaction vessel so that hydrogen could fill the flask. Then, the flask should be left to set overnight.

After this reaction, as much of the organic layer should be retrieved from the reaction flask as possible without picking up any palladium, which may cause impurities or other problems when attempting to isolate the diastereomer(s). GCMS and NMR will be done to confirm that the sample contains the correct compound with minimal to no traces of palladium.

However, if the GCMS and NMR data are inconclusive regarding compound characterization, then other methods of identifying the structure of the compound should be attempted. If a high resolution mass spectrometer is unavailable at the current time, then a different method employing concentrated hydrochloric acid vapor can be used to characterize the compound after the palladium reaction. For the method involving hydrochloric acid vapor, some of the amine can be placed in a vial with hexanes, and the vial should be placed in a larger vial containing a shallow amount of HCl at the bottom. The vial containing the amine should be left open and the vial containing the HCl should be closed. As the vials sit, the acid vapor will react with the amine, which will cause the amine to form a solid. Since a solid product will be formed, the solid crystals can be examined by x-ray crystallography to determine the structure of the compound(s) that are present in the product of the reaction.

CHAPTER THREE

Experimental Information

The first attempt to examine the potential gelation properties of 4-tert-butyl-1-arylcyclohexanamine came from examining approximately 2.5 g of 4-tert-butyl-1-arylcyclohexanamine that had been synthesized by an advanced organic laboratory at Baylor University. The synthesis of the compound relied on a previously known gelation agent 4-tert-butyl-1-arylcyclohexanol that underwent reaction with HCl, NaN_3, and $LiAlH_4$ to potentially form a mixture of the diastereomers of an amine version of the previously known alcohol based gelling agent. To examine the 4-tert-butyl-1-arylcyclohexanamine made by the advanced organic lab, the amine product was added to hexanes, but the amine was only slightly soluble. As a result, ethanol was added to the amine and hexanes mixture to make the amine more soluble. Then, we attempted to grow crystals of the amine by placing the mixture in a freezer. However, no crystals were formed from placing the mixture in the freezer, and the mixture was placed under a rotary evaporator to eliminate the ethanol. Periodically, more hexanes were added to the solution between cycles on the rotary evaporator. Eventually, a foamy solid formed indicating the super solubility of the amine in ethanol. A GCMS sample was run of the potential amine after the hexanes were added, where the starting oven temperature was 100 $^{\circ}$C, which increased at a rate of 5 $^{\circ}$C per minute until the oven reached a temperature of 180 $^{\circ}$C (see appendix 1). The solid was dissolved in hexanes, and the solution was left to set in the freezer in an attempt to grow crystals.

After the amine had several days to set, the flask contained some white solid on the walls of the flask. A GCMS sample was made using DCM as the solvent where the oven temperature increased from 100-230 °C at a rate of 10 °C a minute. Through GCMS, the solid showed similar results to the GCMS trial run previously (see appendix 2). However, the GCMS data up to this point showed only the *cis* diastereomer of 4-tert-butyl-1-arylcyclohexanamine. As a result, we had to explore a different synthesis in an attempt to make some of the *trans* diastereomer of 4-tert-butyl-1-arylcyclohexanamine. The new synthesis utilized 4-tert-butylcyclohexanone and benzylamine to make an imine, which could be reacted with trifluoroboron etherate, an organometallic, and palladium in series to create 4-tert-butyl-1-arylcyclohexanamine.

During the first attempt at this mechanism, 4.04 g of 4-tert-butylcyclohexanone and 2.14 mL of benzylamine was placed with benzene and a catalytic amount of p-toluenesulfonic acid (PTSA) in a Dean-Stark apparatus with 4 Å molecular sieves and allowed to reflux overnight in the presence of nitrogen gas. An excess molecular equivalent of benzylamine was used in the reaction, which made 4-tert-butylcyclohexanone the limiting reagent of the reaction. After the reaction had been allowed to reflux, the mixture was placed on a rotary evaporator to remove benzene from the sample. Then the sample was distilled using a short distillation apparatus to remove the excess benzylamine from the sample. Finally, a GCMS sample was taken of the product after distillation to confirm that it was the desired product. For this GCMS, the initial oven temperature was 100 °C, and the temperature of the oven increased at a rate of 10 °C per minute until the oven reached a temperature of 250 °C (see appendix 3).

For the next step of the reaction, we decided to use 2 molar equivalents of trifluoroboron etherate and 1.1 molar equivalents of phenyl grignard in comparison to the imine. Therefore, approximately 1 mL of the 8 M etherate and 1.5 mL of the 3 M phenyl grignard was used for the reaction. A septum was placed over the flask, and the air was removed and replaced with argon gas. The trifluoroboron etherate was added first. Then, tetrahydrofuran was added to the reaction prior to the addition of the phenyl grignard. Then the reaction vessel was left to set in a dry ice and acetone bath overnight. Following the reaction with the organometallic, 5 mL of distilled water were added to the organic mixture. In addition, a small amount of NH_4Cl was added to the mixture to achieve better separation between the organic and aqueous layers. At this point, the aqueous layer was discarded and a small amount (~0.474 g) of sodium sulfate was added to the organic layer to remove any traces of water still present in the sample. The organic layer was run through a Pasteur pipette containing sodium sulfate to further dry the organic layer and remove the sodium sulfate from the organic layer. After isolating the organic layer, an NMR sample was run on the organic sample to determine if the desired imine was present. (see appendix 4).

However, the NMR data did not show any conclusive data that the desired imine was synthesized. Therefore, we chose to repeat the reaction and use phenyl lithium instead of the phenyl grignard as the organometallic. Since the previous reaction attempt yielded a small amount of the imine, we decided to use more initial starting material so that we may be able to synthesize more of the final product. As a result, 8.006 g of the 4-tert-butylcyclohexanone was placed in a 14/20 joint 250 mL round bottom flask, and 7.1 mL of benzyl amine was added to the reaction with a small amount of PTSA. The

reaction mixture was suspended in a Dean Stark apparatus containing 4 Å molecular sieves with benzene as the solvent. The reaction was left to reflux overnight under nitrogen gas. The benzene was removed through rotary evaporation, and the benzyl amine was removed via distillation. However, the short distillation apparatus yielded a peculiar result during this trial. Two different layers distilled due to the potential of some of the solvent still being present in the sample at the time of distillation. Furthermore, the high heat that the compound distilled at was characteristic of polymer formation, and at the expected boiling point of the imine, no compound was distilled. Therefore, the compound isolated from the short distillation was determined to not be the imine of interest, and the experiment must be redone in order to correctly isolate the imine.

The third trial of the synthesis started with 7.9558 g. of 4-tert-butyl-cyclohexanone, 7.1 mL of benzyl amine, and a small amount of PTSA. A 45 mL volume of benzene was added to the mixture, and the reaction was carried out overnight in a Dean-Stark apparatus under nitrogen in the presence of 4 Å molecular sieves. Once again, the mixture was placed in a rotary evaporator to eliminate benzene, and the sample was left in the rotary evaporator for an extended period of time to ensure that a polymer did not form during the simple distillation process. During the simple distillation process, the distillation occurred under vacuum. The benzyl amine distilled at 31 $^{\circ}$C, and the imine product distilled between 135-220 $^{\circ}$C. The total weight of the imine after the distillation was measured to be 4.705 g, and GCMS was done to confirm the presence of the appropriate imine structure. The GCMS parameters consisted of the initial oven temperature being set at 100 $^{\circ}$C, and the temperature increased at a rate of 10 $^{\circ}$C per minute until the oven reached a temperature of 300 $^{\circ}$C (see appendix 5). The imine was

transferred by cannula into a 100 mL recovery flask, and the previous flask containing the imine was washed with 15 mL of THF, which was transferred by cannula to the reaction flask. Then, the organometallic reaction was cooled in a dry ice and acetone bath overnight.

After the reaction vessel was allowed to stand overnight, 1 mL of distilled water was added, and the reaction vessel was again allowed to stand overnight. Upon returning to the reaction, a dark amber layer and a white layer were present. A GCMS sample was performed on the amber layer with a starting oven temperature of 100 °C, and the temperature of the oven increased at a rate of 10 °C per minute until the oven reached a temperature of 300 °C (see appendix 6). A water work-up was performed on the organic layer by extracting the organic layer twice using a separatory funnel. Following the extraction of the organic layer, sodium sulfate was added to the organic mixture. Additionally, the organic mixture was filtered in a Pasteur pipette containing sodium sulfate, and the organic residue was washed with dichloromethane (DCM). All of the organic mixture was placed in a rotary evaporator to remove all of the solvent from the organic layer. A brown layer and a small clear layer remained in the flask after the solvent was removed. Then, an additional GCMS sample of the possible amine product was run. To obtain the GCMS data, the beginning oven temperature was 180 °C and the temperature increased at a rate of 10 °C per minute until the oven reached a temperature of 300 °C (see appendix 7).

After observing a small clear layer in the rotary evaporator, additional magnesium sulfate and sodium sulfate was added to the organic layer to remove any potential water from the mixture. However, the organic mixture was too viscous to pass through the

Pasteur pipette containing magnesium sulfate and sodium sulfate. As a result, DCM was added to help the organic mixture pass through the pipette. The DCM was evaporated in a rotary evaporator to isolate the organic mixture remaining from the organometallic reaction. The organic mixture was placed under a vacuum pump overnight to bring the flask to a constant weight and to insure all water had been removed from the mixture.

Once the organic mixture was isolated, it was necessary to isolate the various components of the organic layer in order to determine which component contained the desired amine. As a result, several TLC plates were spotted with the organic mixture and run in pure hexanes, 10% ethyl acetate in hexanes, 15% ethyl acetate in hexanes, and 50% ethyl acetate in hexanes to determine which solvent gave the best separating power. Additionally, 1% triethyl amine was added to the solvent to prevent potential tailing of the amine on the TLC plate. From the TLC plates, hexanes was determined to be the solvent with the best separating power, and the components were only visible under ultraviolet light. After the initial TLC trials, a preparative TLC plate was prepared with all of the organic mixture. Each layer from the preparative TLC plate was scraped off with a razor blade, and each compound was dissolved in DCM. Each of the separate layers was passed through a Pasteur pipette that contained cotton to filter all of the silica gel that was scraped off the TLC plate out of the various samples. Next, each of the layers of the preparative TLC were examined with GCMS and compared to previous GCMS samples to determine which layer corresponded with the correct amine. The boundaries for the GCMS of the various TLC layers were an initial oven temperature of 180 $^{\circ}$C, which increased at a rate of 10 $^{\circ}$C per minute until the oven reached a temperature of 250 $^{\circ}$C (see appendix 8).

Of the various layers from the preparative TLC plate, the bottom plate seemed to most accurately reflect the desired amine. However, gas chromatography revealed that the bottom layer was not completely pure. As a result, more TLC was done on the bottom layer on the preparative TLC plate, and 20% ethyl acetate in hexanes gave the best separation with an R_f of 0.36. Once the solvent for ideal separation was determined, a silica gel column was prepared in a 24/40 column, and the silica was added to the column in a 20% ethyl acetate in hexanes slurry. Sand was placed on top of the silica powder to allow for the organic compound to be evenly placed on the column before additional 20% ethyl acetate in hexanes was added to the column. Initially, 100 mL of 20% ethyl acetate in hexanes was added to the column, and the concentration of the ethyl acetate in the ethyl acetate and hexanes mixture increased by 10% every 100 mL until TLC confirmed that all of the various components of the organic layer had come off the column and been collected in fractions, which used approximately 800 mL of solvent. Then, every other fraction underwent TLC to determine which fractions contained a pure sample of the various components of the organic mixture. Overall, 5 different GCMS trials were performed to find the compound that most resembled the desired amine. Fractions 22-28 of the 58 fractions were found to most likely contain the amine out of all the fractions collected due to the match between the GCMS spectrum and previous GCMS data (see appendix 9). For the GCMS sample of fractions 22-28, the starting oven temperature was set to 180 $^{\circ}$C, and the temperature increased at a rate of 10 $^{\circ}$C per minute until the oven reached a temperature of 300 $^{\circ}$C All of the fractions were placed in a 14/20 100 mL pear flask and placed on a rotary evaporator, which resulted in a yield of 0.524 g of the supposed amine. After removing the solvent, a NMR sample was prepared for a proton

spectrum (see appendix 10). However, the NMR showed patterns that were not representative of the desired amine, which caused us to examine other possible fractions of the column to find the amine.

After reviewing the GCMS data from the column in more detail, the first compound that eluted off of the column seemed to be the next most likely location to find the amine. As a result, appropriate fractions were collected and the solvent was removed by rotary evaporation, which yielded a mass of 2.026 g. The remaining compound had a viscous brown appearance, and a small amount of the compound was used to create a GCMS sample as well as a proton and carbon NMR sample. The GCMS sample was run with the parameters of the starting oven temperature at 180 $^{\circ}$C, and the temperature increased at a rate of 10 $^{\circ}$C per minute until the oven reached a temperature of 300 $^{\circ}$C (see appendix 11). The GCMS and NMR data revealed that the fractions contained more than one compound. As a result, further purification was necessary before proceeding to the next reaction in the mechanism. A TLC was run of the organic mixture to determine the solvent that gave an ideal separation. 10% ethyl acetate in hexanes provided the best separation power, and the compound was visible on the TLC plate by both ultraviolet light and phosphomolybdic acid stain (PMA). Then, a 4 cm thick silica gel disc was prepared for radial chromatography by being saturated with 10% ethyl acetate in hexanes. Approximately 0.992 g of the organic mixture was added to the radial chromatotron, and the process of the movement of the compound on the silica gel disc was monitored by ultraviolet light. Before the compound reached the edge of the disc, fractions were collected, and additional solvent was added to the system until all of the components of the organic mixture came off the silica gel disc. Every other fraction was spotted on a

TLC plate to determine and examine both the purity and the separation of the various compounds after being run through the radial chromatotron. Of all the fractions, fraction 6 showed a high concentration in one spot, which was developed by both UV and PMA, on a TLC in 10% ethyl acetate in hexanes. Therefore, a sample was taken from fraction 6 for GCMS analysis to determine if the compound is the desired amine. The GCMS of fraction 6 was run with an initial oven temperature at 180 $^{\circ}$C, where the temperature increased at a rate of 10 $^{\circ}$C per minute until the oven reached a temperature of 300 $^{\circ}$C (see appendix 12).

The GCMS data from fraction 6 showed a GCMS pattern that resembled the amine of interest. Therefore, fractions 4-7 from the radial chromatotron were collected in a 14/20 100 mL pear flask and placed under rotary evaporation to remove any organic solvent. The weight of the potential amine remaining was 0.504 g. Of the compound collected, approximately 41.0 mg were utilized to create a proton and carbon NMR sample (see appendix 13). The GCMS and NMR data showed positive results that the isolated compound was the amine of interest. Following the NMR, the NMR sample was placed back in the 100 mL pear flask containing the rest of the compound, and the sample was placed under rotary evaporation again to remove any of the solvent that was used for the NMR. As a result, 56 mg of palladium on 10% carbon as well as a flea stir bar were added to the 100 mL pear flask containing 0.504 g of the amine. Then, a septum was placed over the pear flask, and all of the air was removed from the reaction vessel by a vacuum pump. After removing the air, argon gas was pumped into the pear flask, and this process was repeated 3 times. After removing the argon for the third time, a balloon containing hydrogen was connected to the reaction vessel to allow the hydrogen to enter

the reaction and carry out the hydrogenation reaction with palladium catalyst for three months to turn the secondary amine in the primary amine, 4-tert-butyl-1-arylcyclohexanamine.

Upon returning to the reaction, the palladium on 10% carbon had settled on the bottom of the reaction vessel. As a result, a small amount of the organic layer on top was used to create a GCMS sample. The GCMS was set to begin with an oven temperature at 180 °C, and the temperature increased at a rate of 10 °C per minute until the oven reached a temperature of 300 °C (see appendix 14).The GCMS results showed one major peak indicating that only 1 compound was present. Since only one peak was present on the gas chromatography data it is unlikely that both the *cis* and *trans* diastereomers of 4-tert-butyl-1-arylcyclohexanamine formed from the purposed mechanism. However, the M peak from the mass spectrometry data was unclear, and it was difficult to determine if 4-tert-butyl-1-arylcyclohexanamine was the product of the reaction.

At this time, as much of the potential 4-tert-butyl-1-arylcyclohexanamine compound was isolated without contaminating the compound with palladium. The amine was placed in a 14/20 50 mL pear flask and placed under rotary evaporation to remove any solvent. The amine was then placed under house vacuum and brought to a constant weight, and the weight of the remaining amine was measured to be 0.171 g. In an attempt to confirm the structure of 4-tert-butyl-1-arylcyclohexanamine, a proton NMR sample was created (see appendix 15). Nevertheless, no conclusive data was gained regarding information about the structure or the stereochemistry of the compound that was created. To further aid in compound characterization, a high resolution mass spectrometry

(HRMS) sample was prepared, but the HRMS was not in operation. As a result, alternative methods that may aid in characterizing the compound needed to be explored.

One possible way to identify the compound is to perform an additional reaction that may provide a clear mass through mass spectrometry or a better proton NMR sample. Therefore, an attempt was made to convert the amine group on the potential 4-tert-butyl-1-arylcyclohexanamine compound to an amide group. To do this conversion, 25.6 mg of the compound was placed in a vial with 1 mL of DCM, a small amount of 4-dimethylaminopyridine (DMAP), 0.2 mL of triethyl amine, and 0.2 mL of acetic anhydride. A small stir bar was placed in the reaction vessel, and the reaction was left to stir overnight.

Upon returning to the reaction, the organic mixture was placed in a separatory funnel with distilled water to do a water work-up. The aqueous layer was discarded, and the organic phase was collected in a separate flask. Sodium sulfate was added to the organic layer. Furthermore, the organic layer was passed through a Pasteur pipette containing a cotton plug and sodium sulfate to remove all traces of water from the organic mixture. Following the water work-up, a GCMS sample was done of the organic layer to determine if the amide was formed. The GCMS run began with an oven temperature at 180 $^{\circ}$C, and the oven temperature increased at a rate of 10 $^{\circ}$C per minute until the oven reached a temperature of 300 $^{\circ}$C (see appendix 16). The results seemed to indicate that the 4-tert-butyl-1-arylcyclohexanamide had formed. A NMR sample was also prepared, but the NMR data revealed that some water was still present in the sample. As a result the compound was placed under rotary evaporation to remove any solvent from the organic compound. Subsequently, the 4-tert-butyl-1-arylcyclohexanamide was

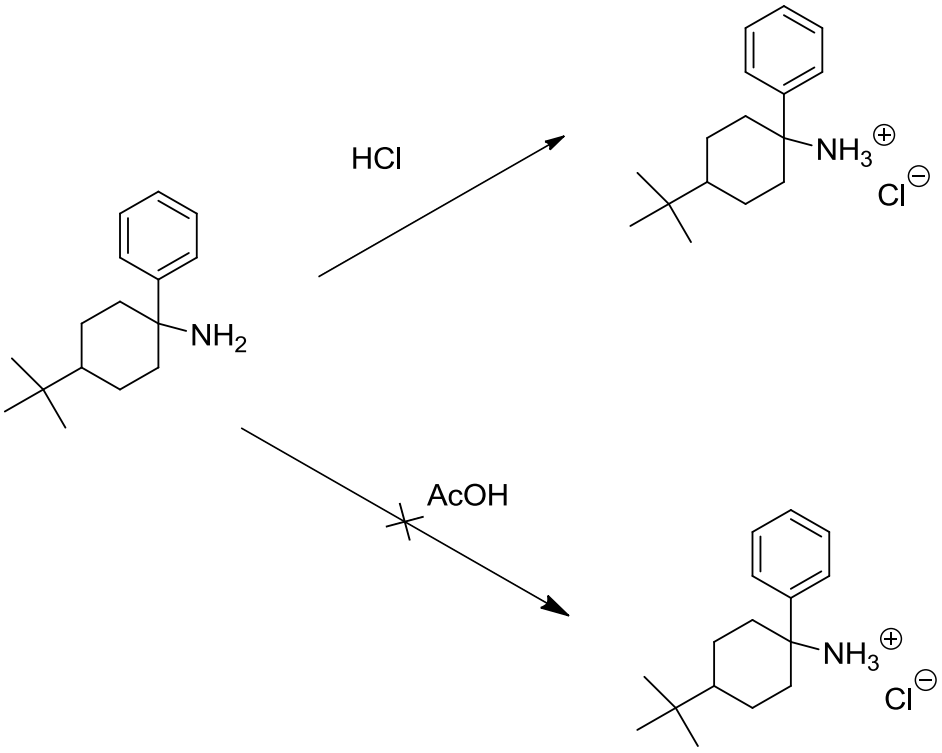
left under house vacuum in an attempt to remove any water and preserve the sample for future TLC and NMR.

Despite the promising results from the gas chromatography data for the amide, several peaks were also present with the amide peak. As a result, further purification of the amide needed to be performed before an accurate NMR sample could be made. As a result, TLC was done on the amide to determine which solvent had the best separating power for the organic mixture. The TLC of the organic mixture showed that optimal movement of the organic compound was achieved in 30% ethyl acetate in hexanes. Therefore, a 4 cm silica gel disc was conditioned with pure hexanes prior to the compound being spotted on the silica gel disc. After the compound was spotted, the concentration of ethyl acetates in the hexanes increased by 5% every 100 mL of solvent to aid in the separation of the organic layer. The movement of the organic layer on the silica gel disc was monitored by ultraviolet light to insure that no compounds were missed when collecting fractions. After the entire organic compound had been collected into fractions, TLC was done on every other fraction to determine which fractions contained specific compounds in their pure form. PMA staining on the TLC plates revealed a compound present in fractions 6-10, and these fractions were collected in a 14/20 100 mL pear shaped flask and placed under rotary evaporation to remove any organic solvent from the compound. Then, a sample of the amide was prepared for GCMS. The amide GCMS sample was prepared with a starting oven temperature of 180 $^{\circ}$C, and the temperature of the oven increased at a rate of 10 $^{\circ}$C per minute until the oven reached a temperature of 300 $^{\circ}$C (see appendix 17). Finally, the remainder of the amide sample was placed under house vacuum until further use.

Next, an NMR sample of the 4-tert-butyl-1-arylcyclohexanamine was needed to confirm that all of the functional groups were present. However, the amide was not soluble in deuterated chloroform ($CDCl_3$), and clathrates formed when $CDCl_3$ and the amine came into contact. Since the compound would not dissolve, the NMR spectrum could not be obtained. Due to the unusual clathrate formation, it was thought that water contaminated the amide sample. To test this theory, blue dye #2 was added to the NMR because the dye would turn any water molecules present in the solution blue and the remaining organic solution should remain clear. However, the addition of the blue dye #2 caused the solution inside the NMR tube to turn green, and the clathrates persisted inside the NMR tube. At this point, pH paper was used to measure the pH of the solution of the compound in $CDCl_3$. The pH paper turned bright red indicating a pH of approximately 2 inside the NMR tube. The unusual phenomenon of the clathrates formation made it difficult to determine how to proceed, and the amide sample was placed in the freezer. As a result, the problems with the NMR made the NMR spectrum for the supposed 4-tert-butyl-1-arylcyclohexanamide compound a non-viable solution to aid in the compound characterization of the potential amine.

The next method examined to aid in the characterization of 4-tert-butyl-1-arylcyclohexanamine was x-ray crystallography. However, the amine compound was in a liquid phase. From the previous azide mechanism synthesis, we knew that 4-tert-butyl-1-arylcyclohexanamine does not readily crystallize. Nevertheless, it is possible to form an amine salt with acid to create a potential crystal that could be analyzed by x-ray crystallography. To do this reaction, 4-tert-butyl-1-arylcyclohexanamine will be diluted in hexanes and approximately half of the amine will be placed in 2 vials. A larger vial

will be filled with approximately 1 mL of HCL and another vial will be filled with 1 mL of acetic acid. Then, each of the small vials will be placed inside of a larger vial containing the acid, and the lids to the small vials will be left off while the lids of the larger vials will be tightly secured and wrapped in Parafilm. The amine in the vials will react with the vapor from the acids, and the vials will be allowed to set for several days.



Scheme 3: Synthesis of Amine Salt

As seen from the scheme above, the acetic acid was unsuccessful at precipitating the solid amine salt, but the concentrated HCl was able to create small solid crystals that precipitated in the vial without being exposed to the concentrated HCl. As a result, the solid was filtered away from the organic solvent and placed in a vial. Several crystals were selected for x-ray crystallography, and the results indicated that only *cis*-4-tert-

butyl-1-arylcyclohexanamine was present in the sample. Therefore, no *trans*-4-tert-butyl-1-arylcyclohexanamine was formed from the second proposed sythesis, and the potential for the *trans* diastereomer to serve as a gelation agent is still unknown because no other synthesis was attempted that would allow the *trans* diastereomer of 4-tert-butyl-1-arylcyclohexanamine to be isolated.

CHAPTER FOUR

Results and Discussion

The initial goal of this research experiment was to determine if *trans*-4-tert-butyl-1-arylcyclohexanamine shared similar gelation agent properties with the known alcohol equivalent, *trans*-4-tert-butyl-1-arylcyclohexanol, which is known to gel organic solvents. The *cis* diastereomer of 4-tert-butyl-1-arylcyclohexanol did not have any gelation agent properties, but the *trans* diastereomer displayed the ability to suspend organic compounds in a variety of solvents. Due to the structural similarities between 4-tert-butyl-1-arylcyclohexanamine and 4-tert-butyl-1-arylcyclohexanol, the experiment's initial hypothesis was that *cis*-4-tert-butyl-1-arylcyclohexanamine would not display organic gel properties, but *trans*-4-tert-butyl-1-arylcyclohexanamine would display gelling agent properties.

In the first attempt to synthesize *trans*-4-tert-butyl-1-arylcyclohexanamine, 4-tert-butyl-1-arylcyclohexanol underwent dehydrogenation with concentrated HCl, which replaced the alcohol group with a chlorine atom. At this point, a substitution reaction (SN1) was thought to occur with the addition of sodium azide. Then, the azide was reduced by lithium aluminum hydride to form 4-tert-butyl-1-arylcyclohexanamine. However, the data showed that only *cis*-4-tert-butyl-1-arylcyclohexanamine was present, which was an unexpected result due to the mechanism of SN1 reactions. SN1 reactions proceed by forming a carbocation on the tertiary carbon, which allows for the reaction to proceed in a stereo-random manner. Therefore, the reaction was expected to produce both the *cis* and *trans* diastereomers of 4-tert-butyl-1-arylcyclohexanamine, which would have

been able to be separated by careful column chromatography. The GCMS data showed that only the *cis*-4-tert-butyl-1-arylcyclohexanamine was present. Therefore, the mechanism did not proceed as anticipated, and identification of the problem within this reaction was difficult. As a result, a decision was made to attempt to synthesize the *trans*-4-tert-butyl-1-arylcyclohexanamine through another synthetic approach. Error may have been present within this first synthesis attempt due to problems with the sodium azide or zinc chloride that were used to place the azide group on the molecule. Additionally, other experimental issues may have resulted from human error or improper usage of the concentrated HCl or $LiAlH_4$.

In the second attempt to synthesize *trans*-4-tert-butyl-1-arylcyclohexanamine, the mechanism was based on some of the previous reaction schemes to create the alcohol gelling agent, 4-tert-butyl-1-arylcyclohexanol. 4-tert-butylcyclohexanone and benzylamine were used as the starting material. However, the initial few steps of the reaction were plagued with various problems. During the first attempt to use the newly proposed sythesis, the reaction with the MgBrPh had a low yield and the compound synthesized was determined to be the incorrect compound. To attempt to solve these problems, the amount of starting 4-tert-butylcyclohexanone was doubled and the organometallic reagent was changed to PhLi. However, the second attempt of the reaction had problems after distillation because the desired product appeared to polymerize. The distillation problems prompted a third synthesis attempt that was successfully able to produce a product that resembled 4-tert-butyl-1-arylcyclohexanamine.

Despite the successful synthesis of 4-tert-butyl-1-arylcyclohexanamine, there were many difficulties in the process of isolating a pure product. At various different

phases of the reaction, water work-ups, preparative TLC, column chromatography, and radial chromatography were all used to try to acquire a pure sample of 4-tert-butyl-1-arylcyclohexanamine. Due to the various purification schemes used, there was a small percent yield. The initial quantity of 4-tert-butylcyclohexane, which served as the limiting reagent, was 7.956 g or 0.0516 M, and the final amount of 4-tert-butyl-1-arylcyclohexanamine synthesized was 0.504 g or .00219 M. By examining the molarity, the percent yield of the mechanism was 4.27%.

Additionally, characterization of the final compound was challenging due to issues with the GCMS and proton NMR data. Since high resolution mass spectrometry was not available during the experiment, other attempts to examine the structure and stereochemistry of the compound were attempted. The first attempt of changing the 4-tert-butyl-1-arylcyclohexanamine into 4-tert-butyl-1-arylcyclohexanamide ended in failure because of the odd clathrate formation that occurred when preparing an NMR sample. However, transforming 4-tert-butyl-1-arylcyclohexanamine into an amine salt in the presence of concentrated HCl vapor proved to be a successful method of forming crystals, which were previously not practical due to recrystallization problems with the liquid 4-tert-butyl-1-arylcyclohexanamine. By forming the crystals of 4-tert-butyl-1-arylcyclohexanamine, x-ray crystallography was used to examine both the structure and stereochemistry of the sample. The x-ray crystallography report showed the presence of only *cis*-4-tert-butyl-1-arylcyclohexanamine, which was not an organic gelling agent. As a result, the proposed synthesis was not successful at synthesizing the potential *trans* gelation agent.

Throughout the many hardships encountered with the synthesis of *cis*-4-tert-butyl-1-arylcyclohexanamine, error was likely to occur. Some of the errors may have been caused by contamination of the product with water or various other compounds that increased the difficulty of obtaining ideal purity, proper GCMS samples, and high quality NMR samples. Furthermore, it may have been difficult to properly isolate the imine step of the reaction with simple distillation. Additionally, a non-ideal reagent may have been used during the mechanism that may have hampered the formation of *trans*-4-tert-butyl-1-arylcyclohexanamine. For example, the phenyl grignard reagent did not yield the amine, but the phenyl lithium was successful at completing the reaction. Other error may have occurred due to problems with the organic solvents used in this experiment. The THF or benzenes may not have been the best solvent to use for the mechanism, and the various solvents used in preparative TLC, column chromatography, and radial chromatography may not have been the best solvents to gain the separation necessary to not only isolate the desired product quickly but also provide the best yield of 4-tert-butyl-1-arylcyclohexanamine. Another category of error worth noting is instrumental error due to problems with the GCMS and NMR instruments.

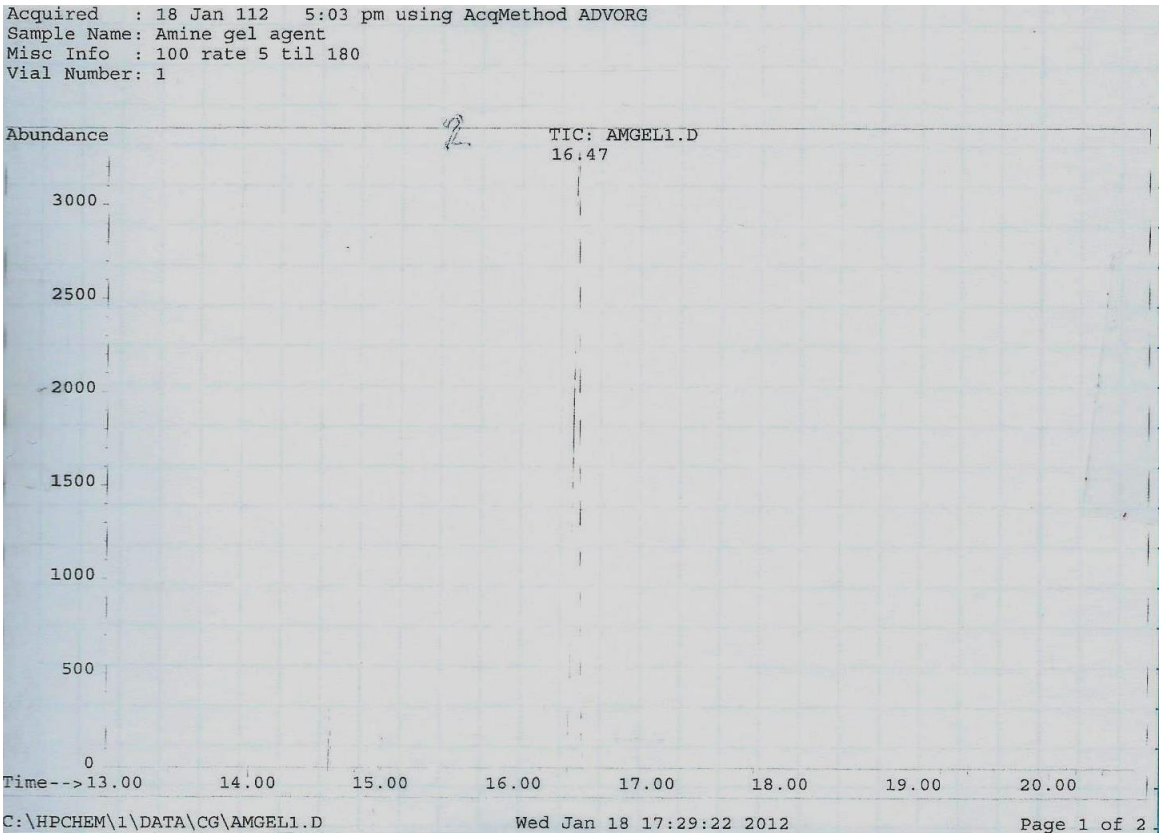
Due to an unsuccessful synthesis of *trans*-4-tert-butyl-1-arylcyclohexanamine, the experiment was unable to examine the potential gelation properties of the compound. Therefore, further research can be done to attempt to synthesize and isolate *trans*-4-tert-butyl-1-arylcyclohexanamine to determine if the compound serves as an organic gelling agent. However, the experiment was successful at verifying two different mechanisms and purification schemes to isolate *cis*-4-tert-butyl-1-arylcyclohexanamine, which did not form an organic gelling agent. The project also provided insight regarding various

mechanistic and purification problems that may challenge those researching the field of organic gels in the future. Also, the 4-tert-butyl-1-arylcyclohexanamide product produced additional questions regarding why clathrates formed in the NMR sample after the addition of $CDCl_3$.

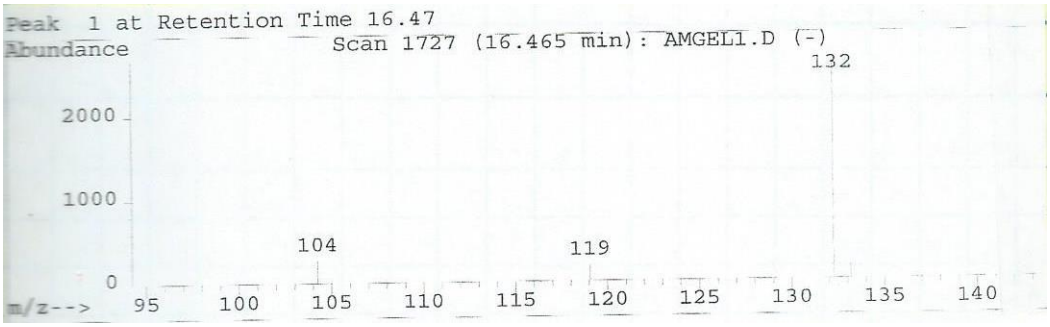
Overall, it may be possible for future researchers to build on the mechanisms and techniques proposed in this experiment to find the best possible manner to produce *trans*-4-tert-butyl-1-arylcyclohexanamine. Then, the gelation agent potential of the compound could be examined to determine the classification and strength of the gel, which would help determine if the gel could be used in various consumer products, research settings, and industrial projects.

APPENDICES

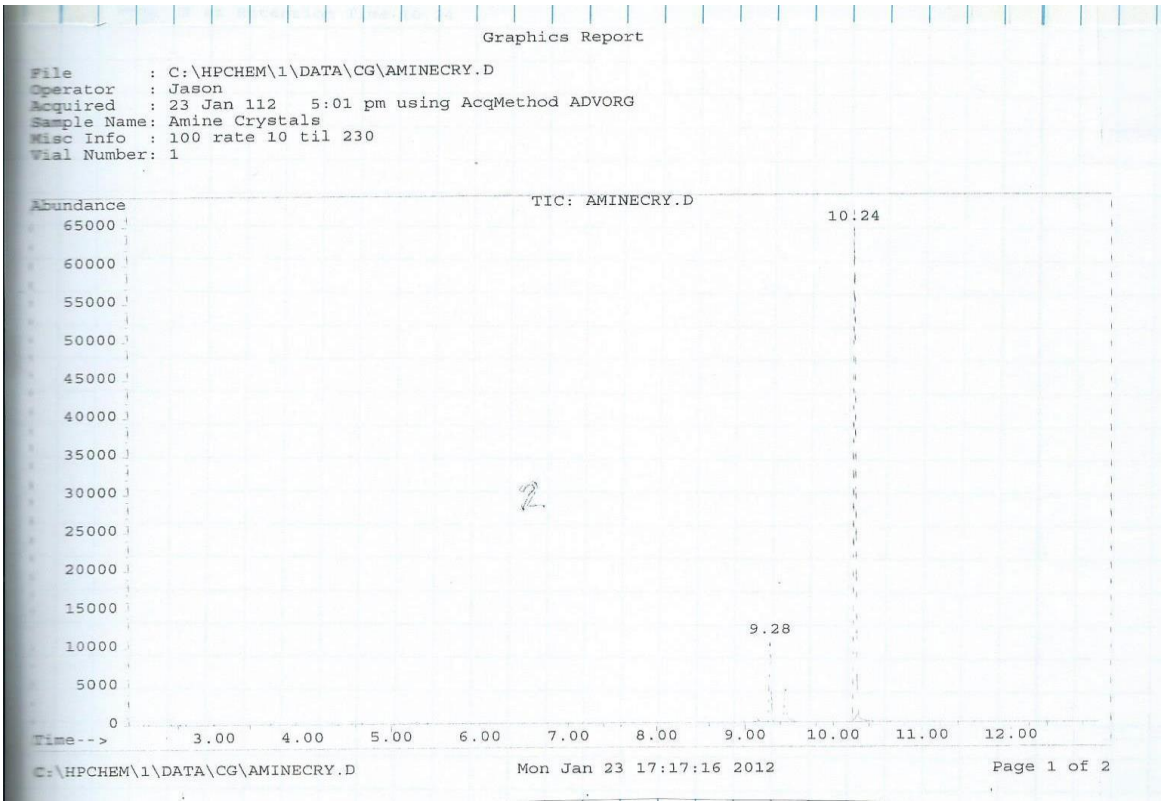
Appendix 1a: GC Data from the initial trial of making the gelling agent



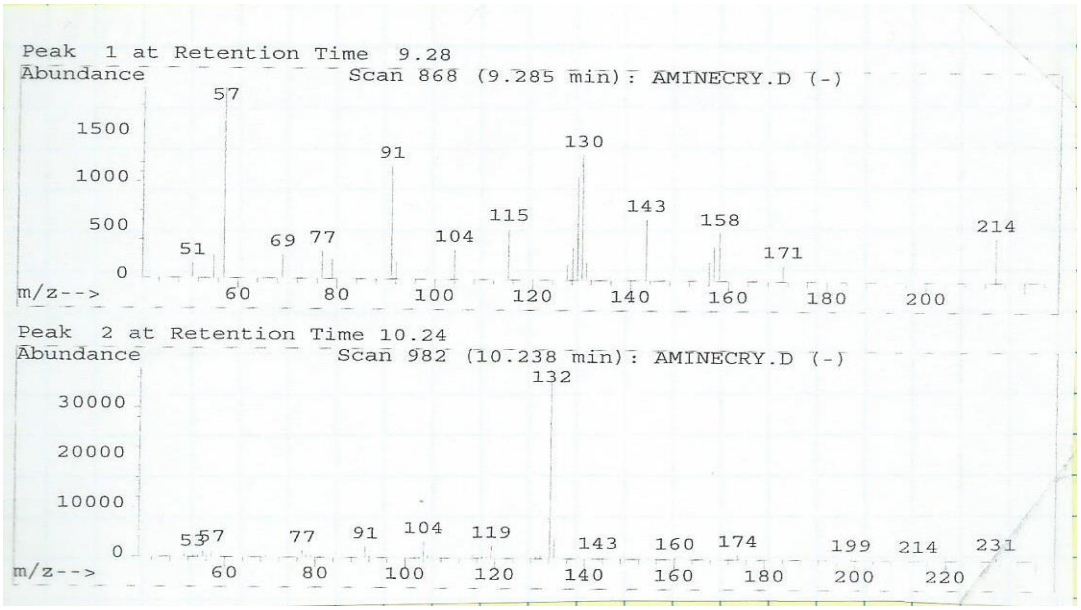
Appendix 1b: MS data from the initial gelling agent, which did not express the MW of the desired compound



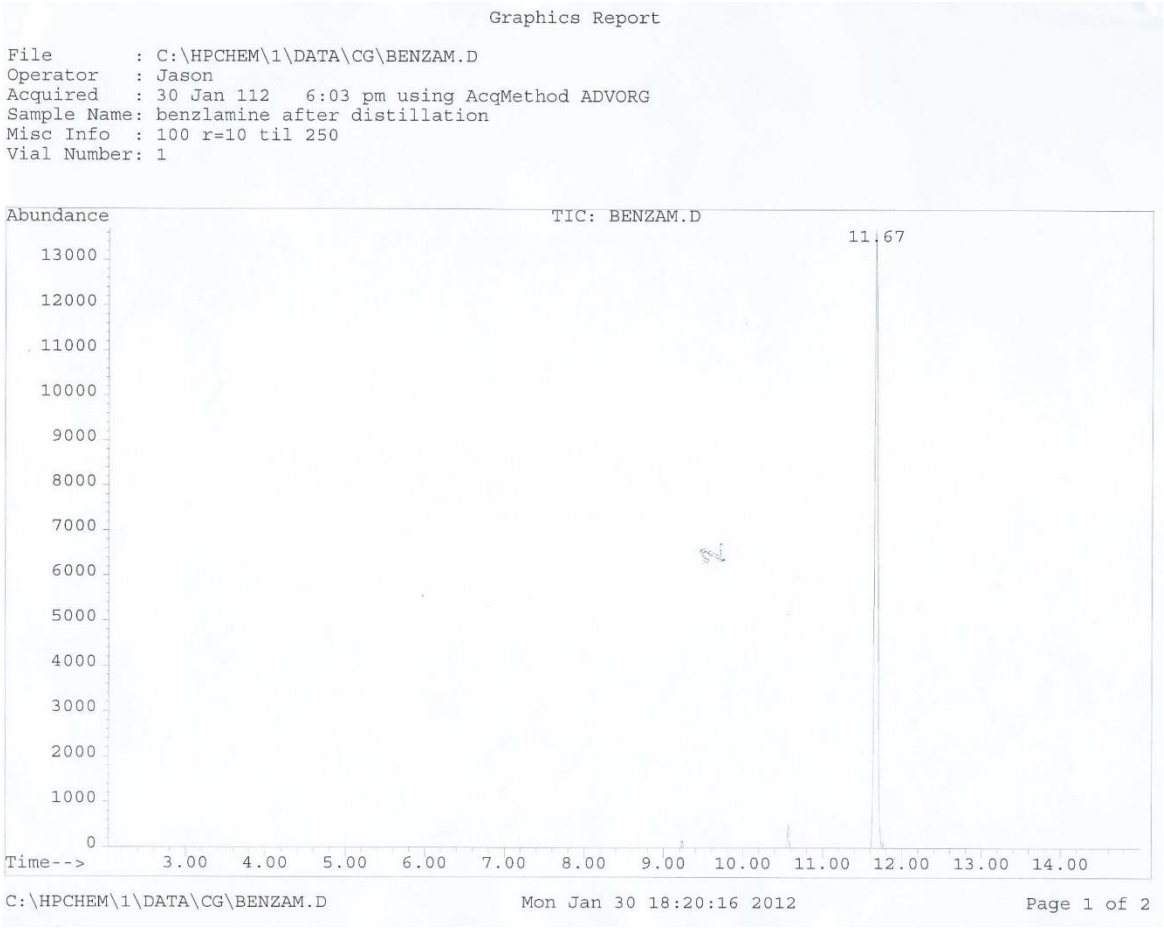
Appendix 2a: Initial potential amine after refrigeration (solid dissolved in DCM)



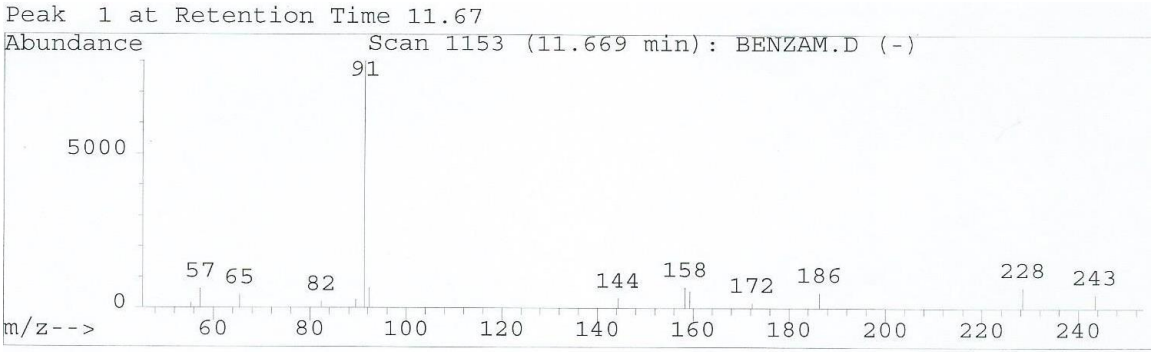
Appendix 2b: MS data from the two compounds present in the GC spectrum



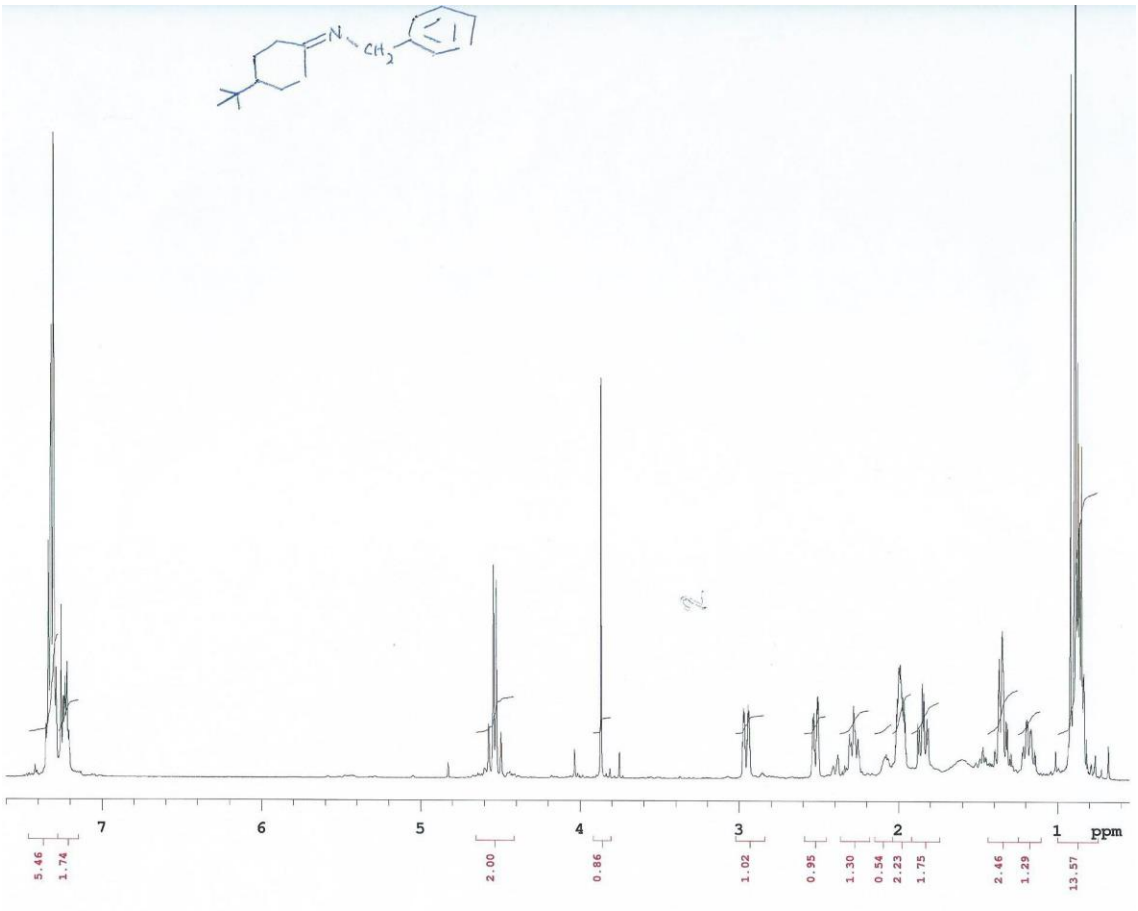
Appendix 3a: GC data following short distillation of the benzylamine synthesis pathway



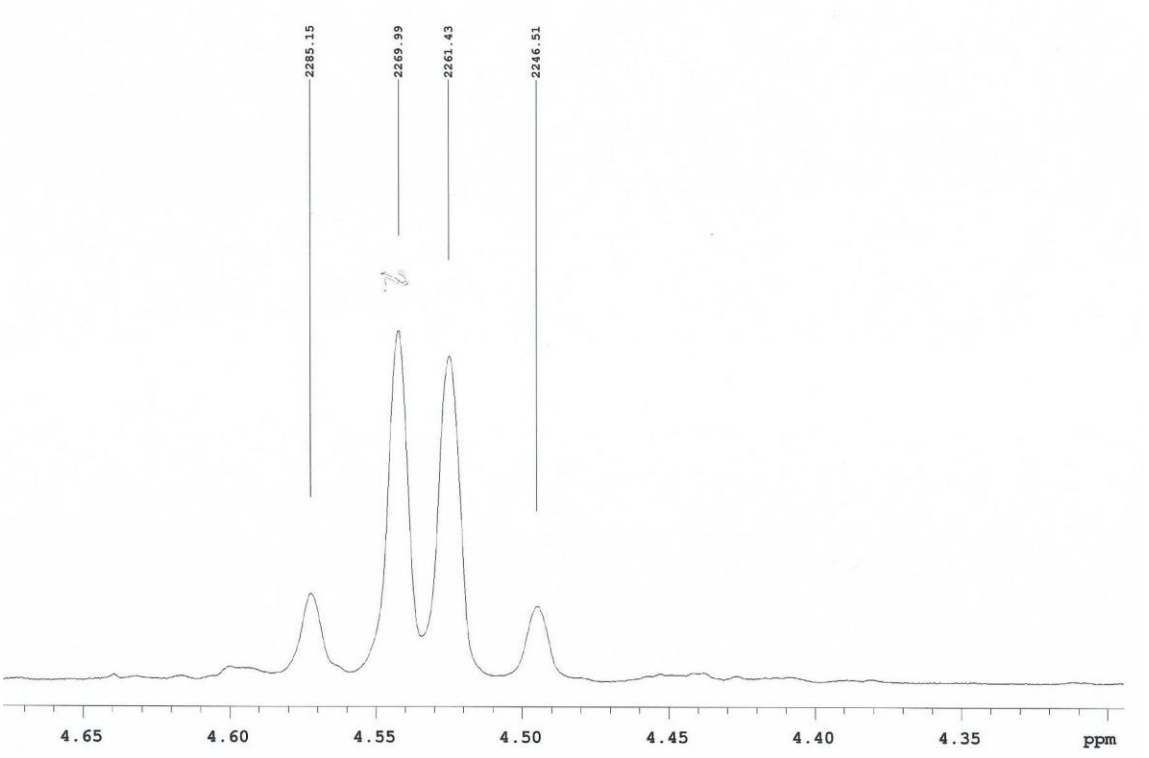
Appendix 3b: MS data from the product after the first attempt at short distillation



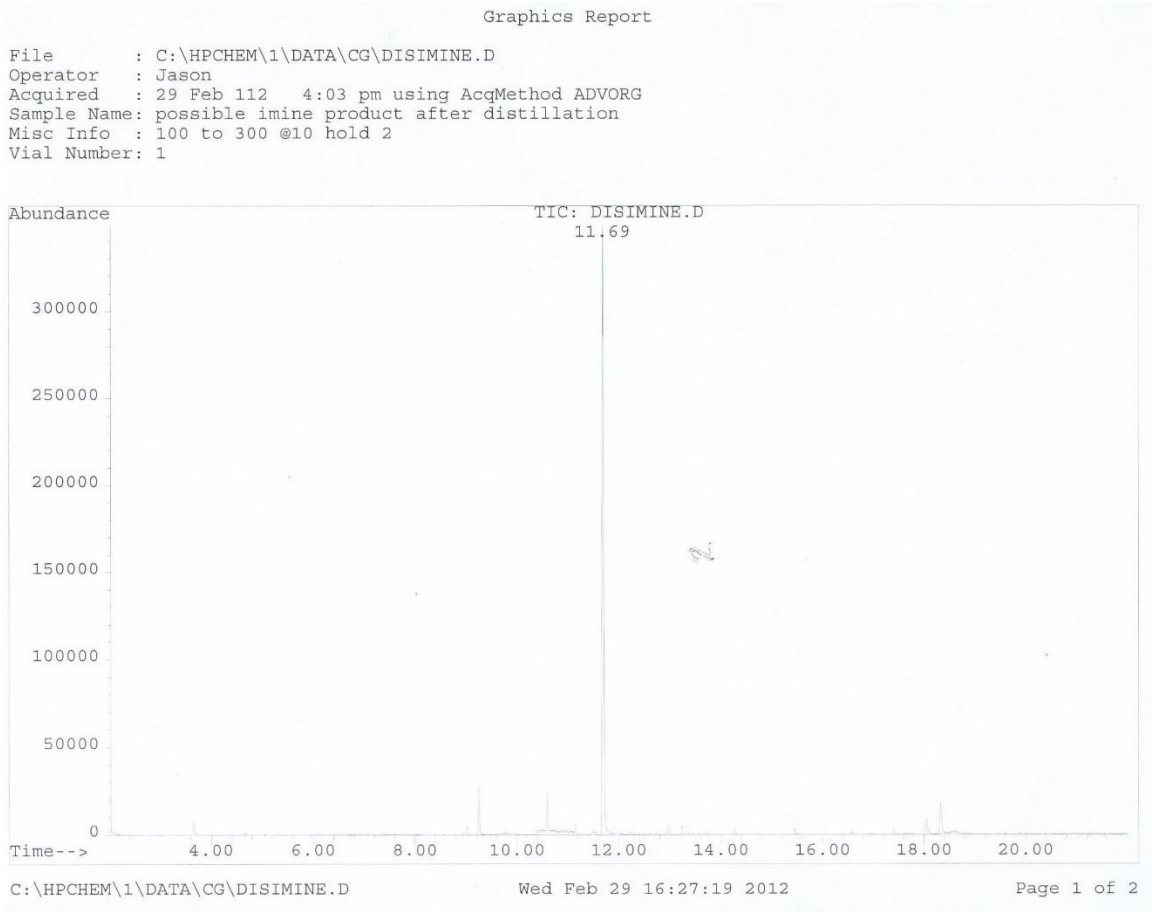
Appendix 4a: Proton NMR data after the addition of etherate and phenyl grignard



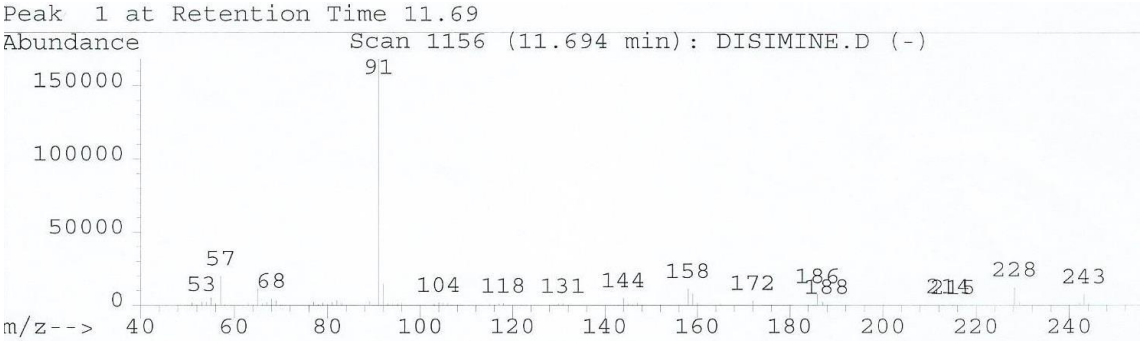
*Appendix 4*b: Quartet from NMR spectrum



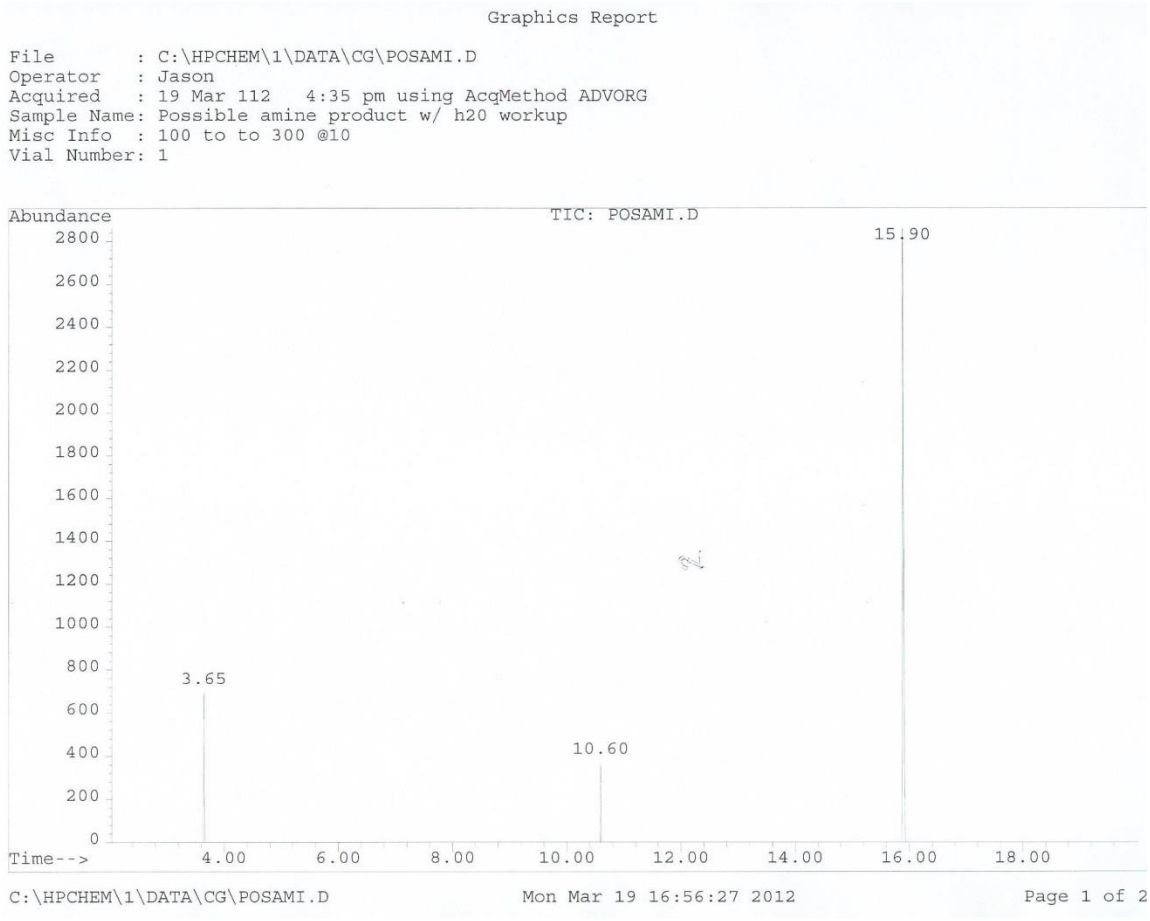
Appendix 5a: GC data from the third synthesis after short distillation



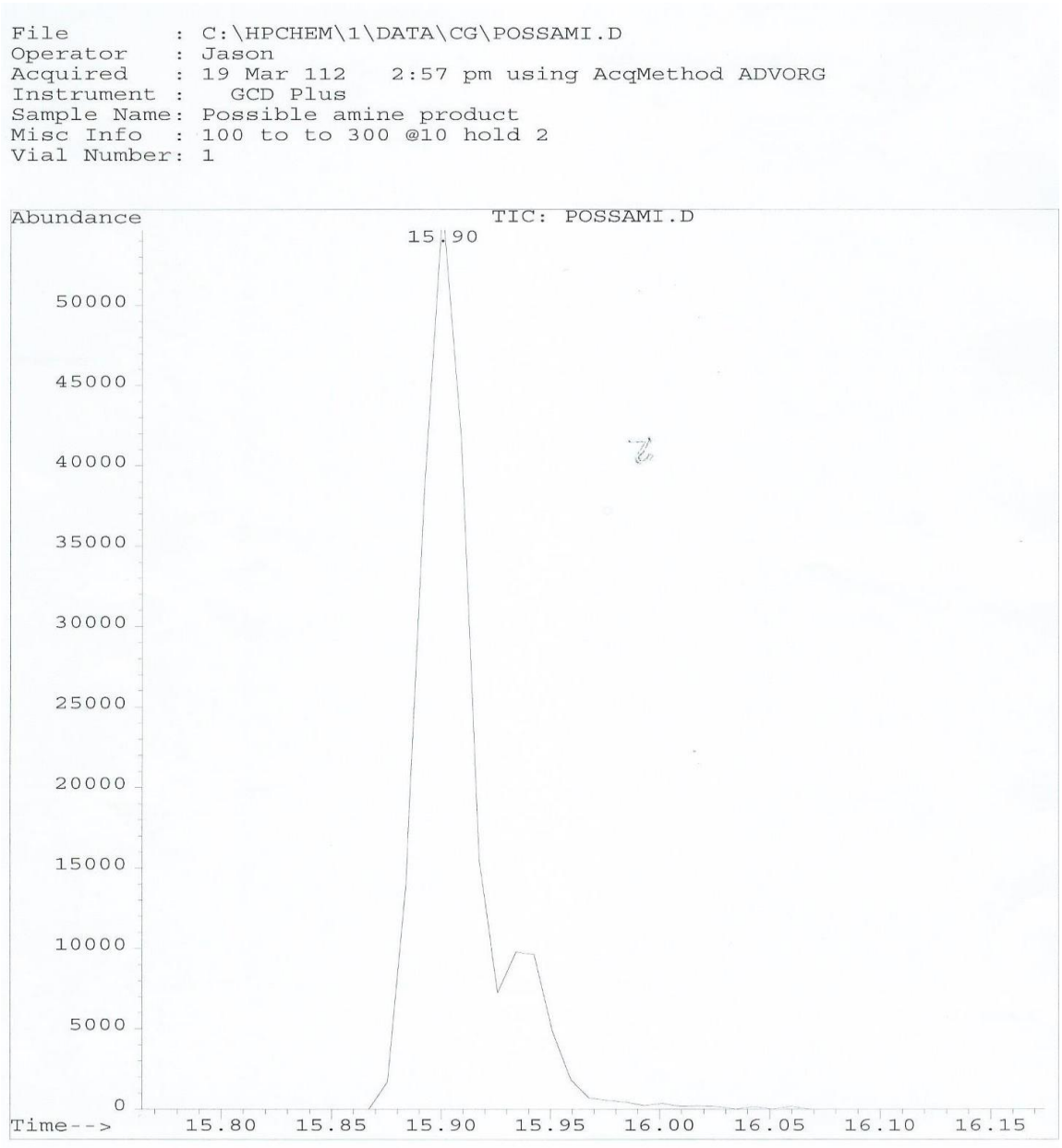
Appendix 5b: MS data after the short distillation of the third trial



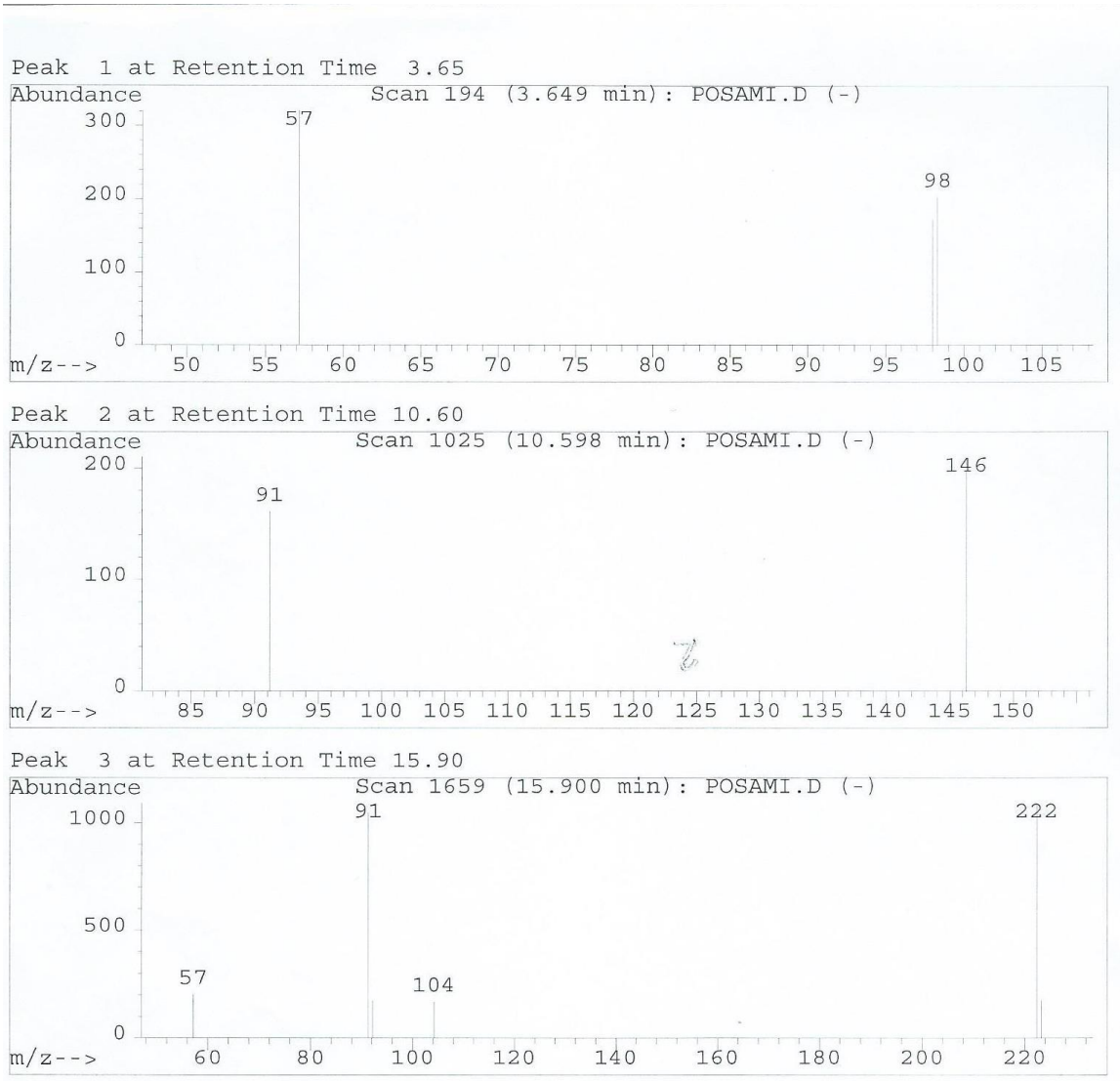
Appendix 6a: GC data after an overnight water work-up following short distillation



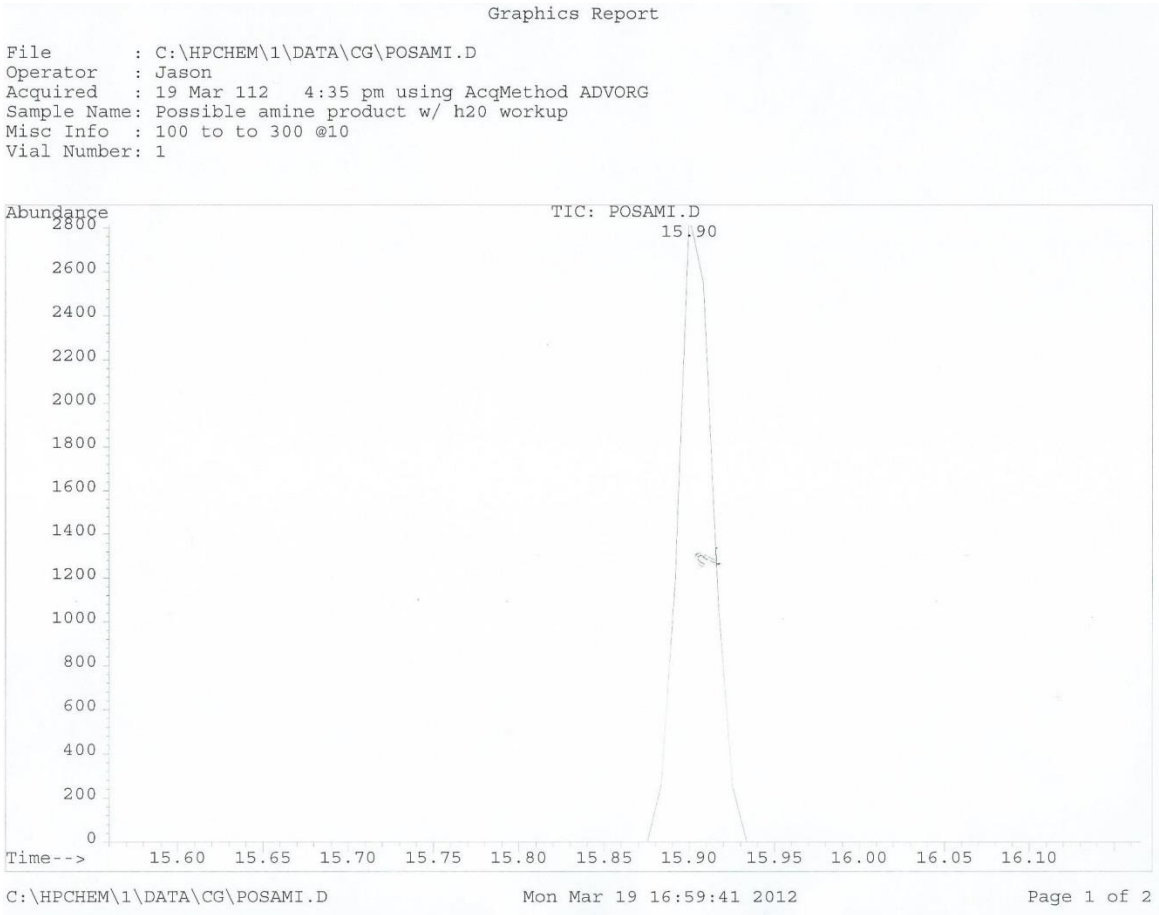
Appendix 6b: Closer view of major peak of the GC showing the potential presence of two diastereomers



Appendix 6c: The MS data that corresponded with the GC data after the water work-up.



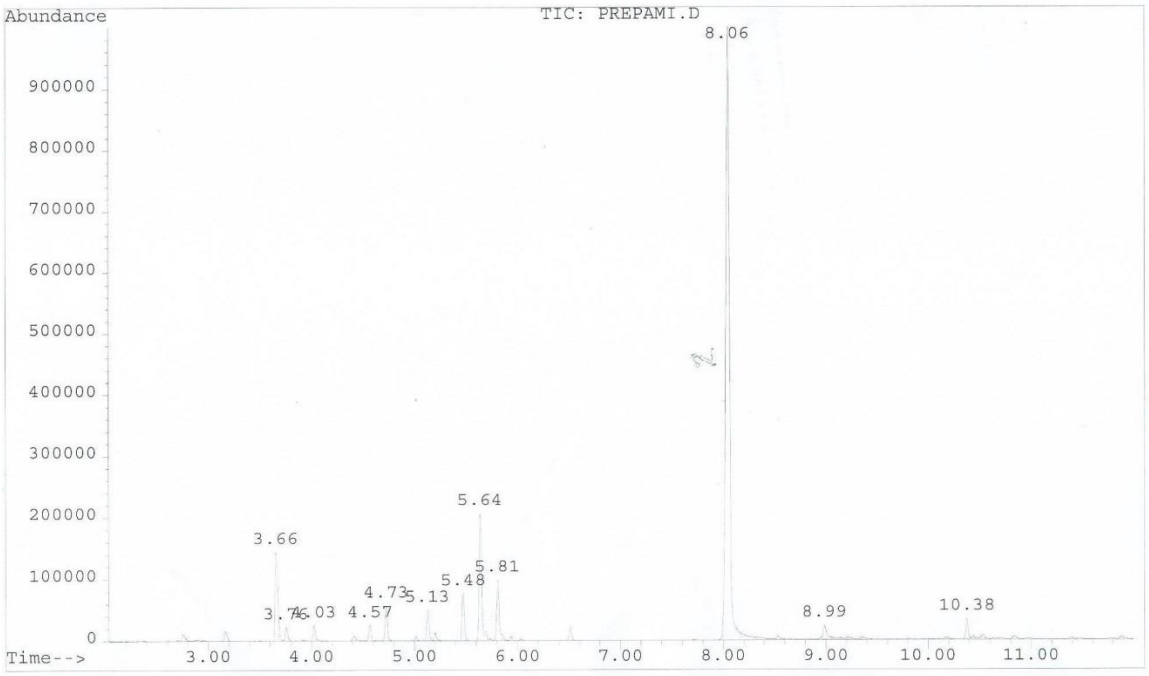
Appendix 7: GC sample of the organic layer after the organic layer had been purified and placed under a rotary evaporator.



Appendix 8a: GC data of the possible amine prior to TLC preparation

Graphics Report

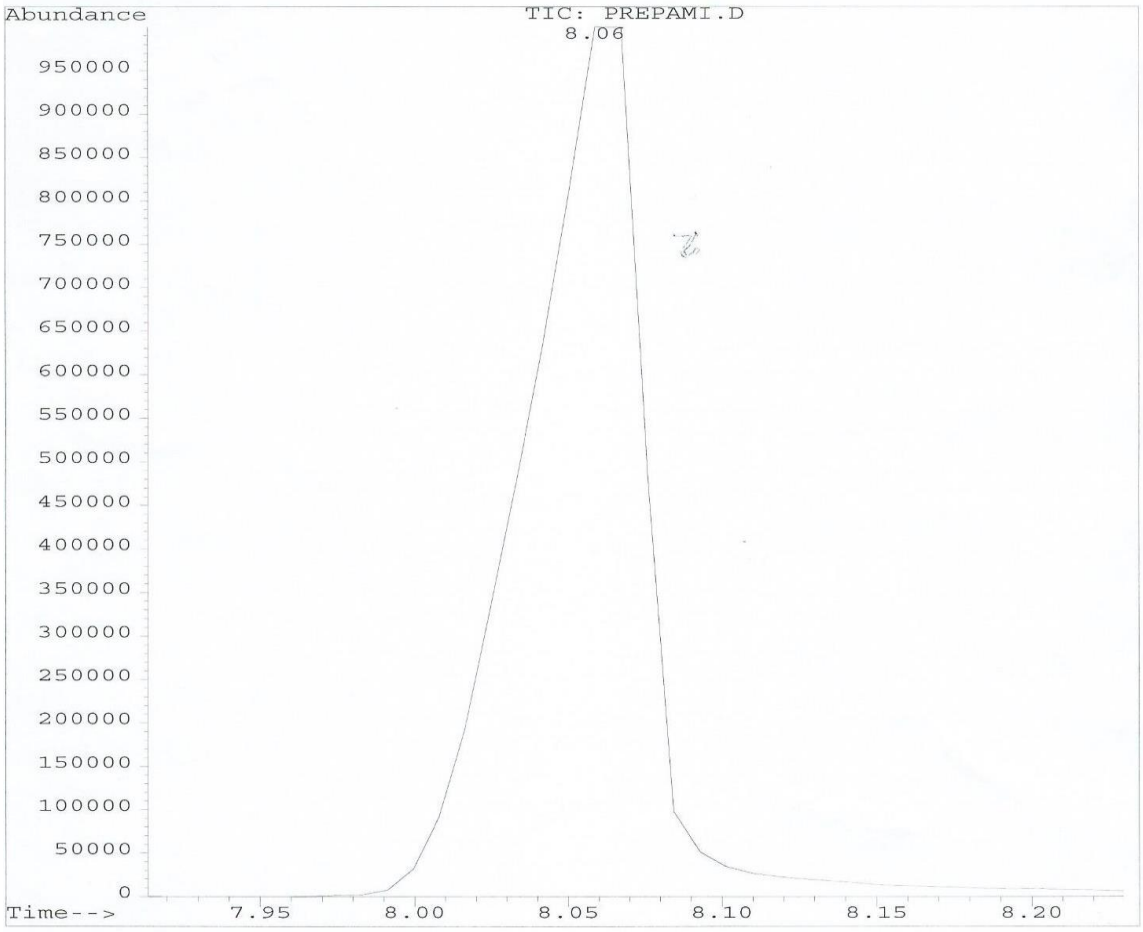
File : C:\HPCHEM\1\DATA\CG\PREPAMI.D
Operator : Jason
Acquired : 26 Mar 112 4:24 pm using AcqMethod ADVORG
Sample Name: possible ami before prep TLC
Misc Info : 180 to 300 @ 10
Vial Number: 1



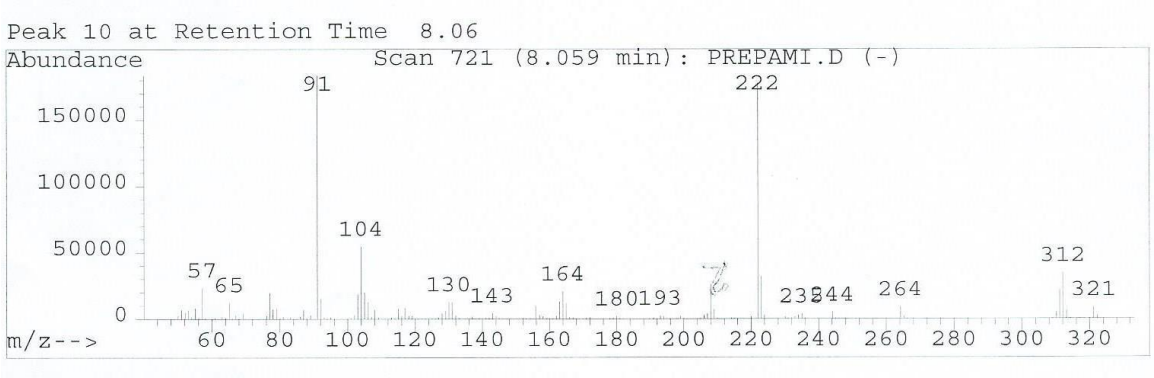
C:\HPCHEM\1\DATA\CG\PREPAMI.D Mon Mar 26 16:40:16 2012 Page 1 of 4

Appendix 8b: Closer look at the main GC peak of the amine sample prior to TLC

```
File         : C:\HPCHEM\1\DATA\CG\PREPAMI.D
Operator     : Jason
Acquired     : 26 Mar 112    4:24 pm using AcqMethod ADVORG
Instrument   :   GCD Plus
Sample Name: possible ami before prep TLC
Misc Info    : 180 to 300 @ 10
Vial Number: 1
```



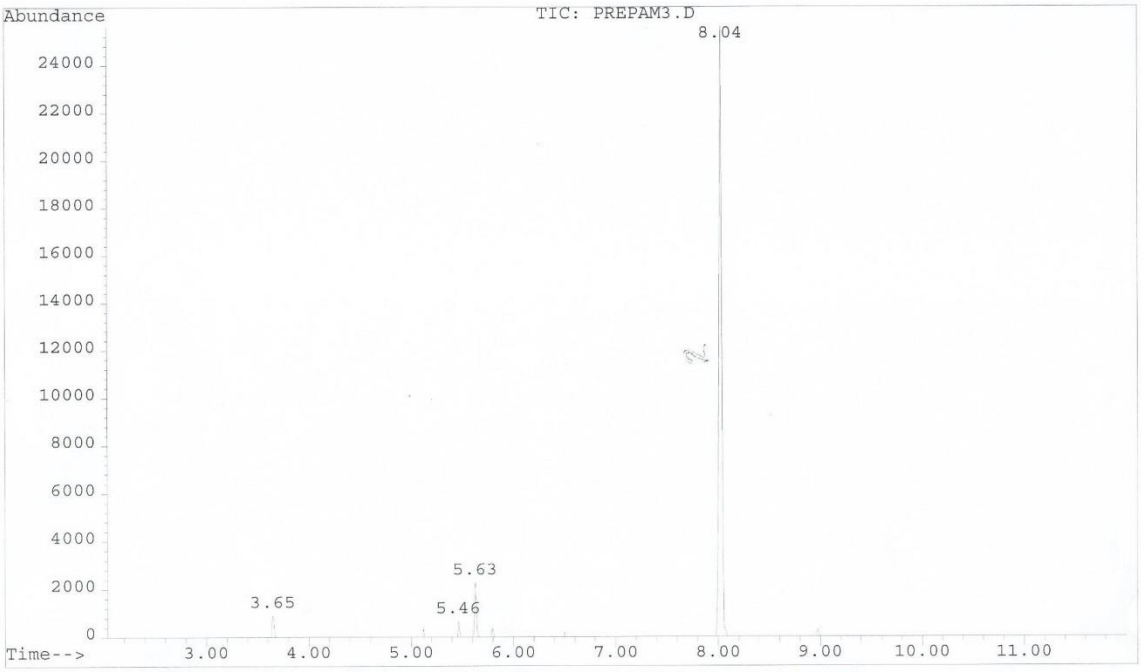
Appendix 8c: MS data from the potential amine prior to TLC



Appendix 8d: The GC data from the 3rd band down starting at the top layer in the preparative TLC

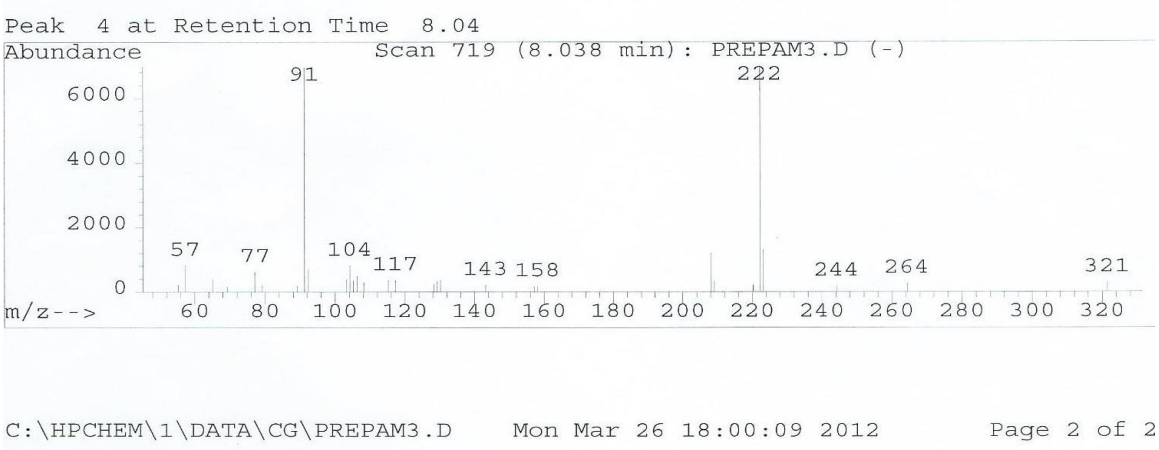
Graphics Report

File : C:\HPCHEM\1\DATA\CG\PREPAM3.D
Operator : Jason
Acquired : 26 Mar 112 5:47 pm using AcqMethod ADVORG
Sample Name: 3rd band in prep TLC in hexanes
Misc Info : 180 to 300 @ 10
Vial Number: 1



C:\HPCHEM\1\DATA\CG\PREPAM3.D Mon Mar 26 17:59:57 2012 Page 1 of 2

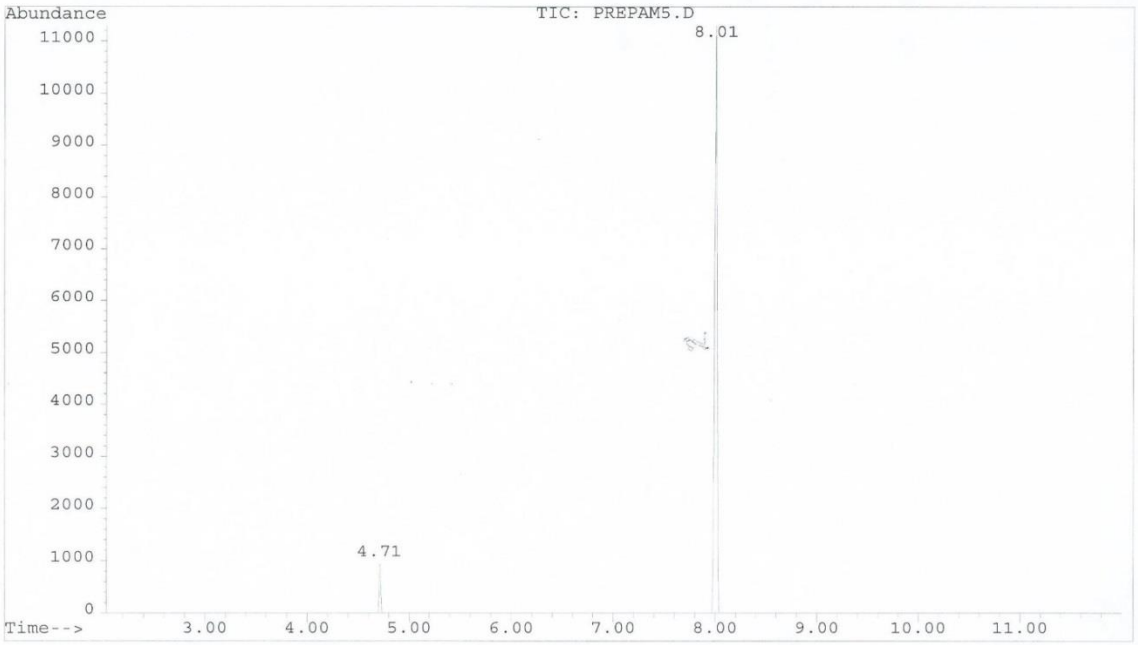
Appendix 8e: MS data from the 3rd band of the preparative TLC plate



Appendix 8f: GC data from the 5th band down starting at the top layer in the preparative TLC

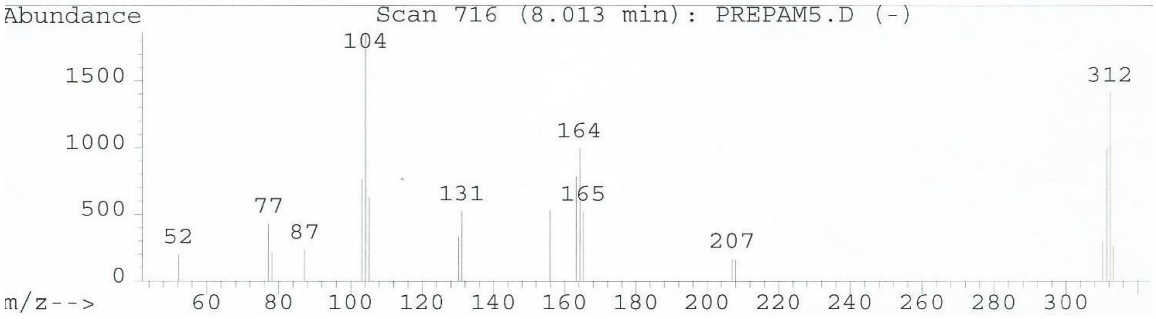
Graphics Report

File : C:\HPCHEM\1\DATA\CG\PREPAM5.D
Operator : Jason
Acquired : 26 Mar 112 6:16 pm using AcqMethod ADVORG
Sample Name: 5th band in prep TLC in hexanes
Misc Info : 180 to 300 @ 10
Vial Number: 1

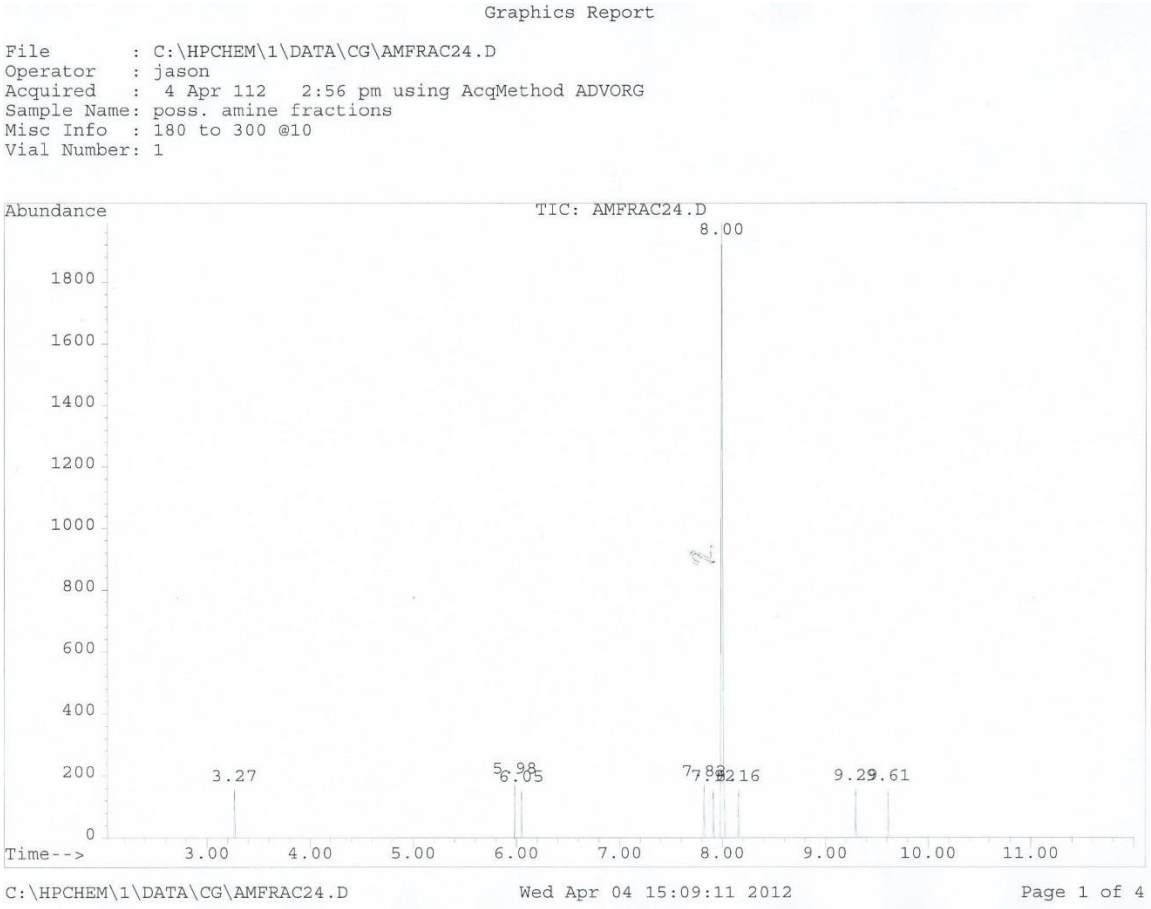


C:\HPCHEM\1\DATA\CG\PREPAM5.D Mon Mar 26 18:30:27 2012 Page 1 of 2

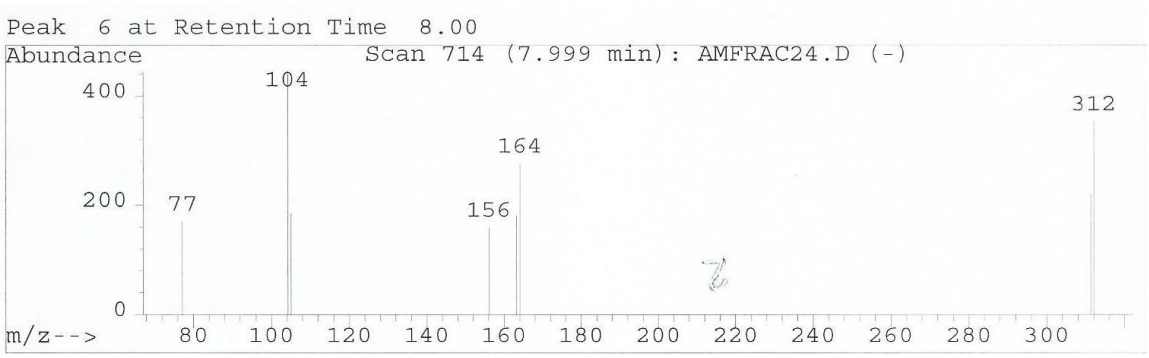
Appendix 8g: MS data from the 5th band of the preparative TLC plate



Appendix 9a: GC data from some of the most likely fractions to contain the amine of interest from the 5th band of the preparative TLC plate.



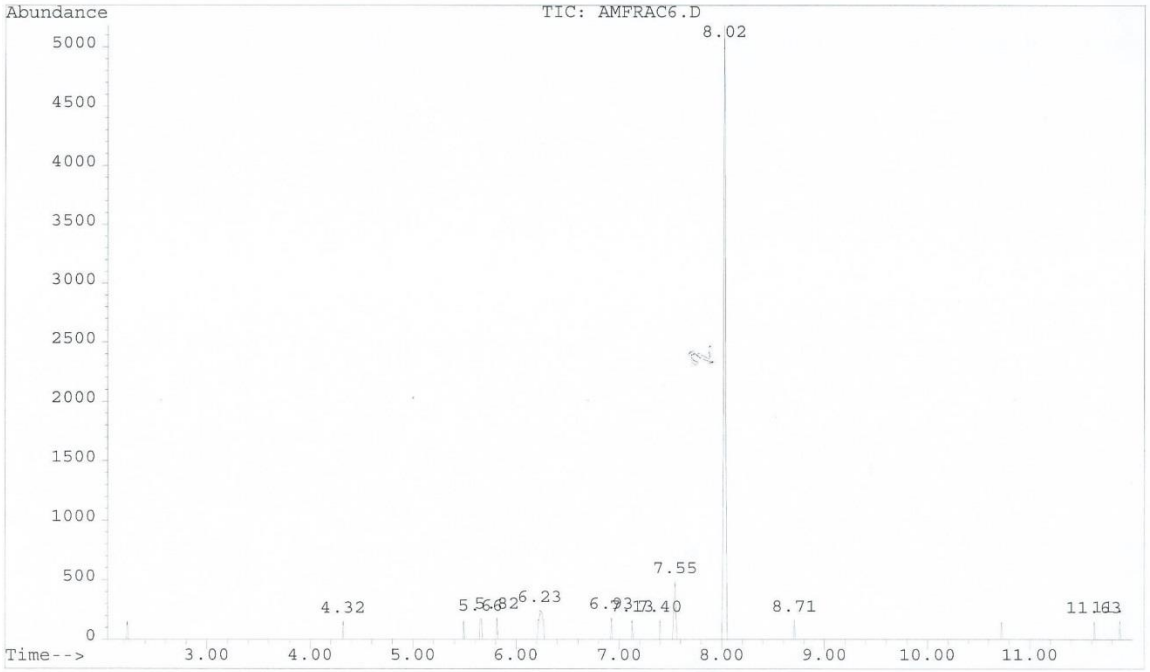
Appendix 9b: The MS data from the group of fractions thought to contain the amine in the 5^{th} layer of the preparative TLC band.



Appendix 9c: Additional GC data from the fractions collected after a purification of the 5th layer of the preparative TLC plate.

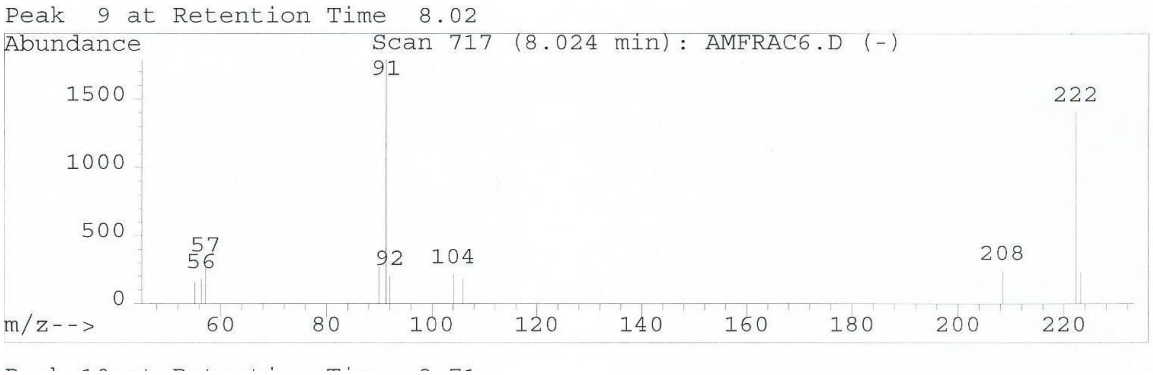
Graphics Report

File : C:\HPCHEM\1\DATA\CG\AMFRAC6.D
Operator : jason
Acquired : 4 Apr 112 2:27 pm using AcqMethod ADVORG
Sample Name: poss. amine fractions
Misc Info : 180 to 300 @10
Vial Number: 1

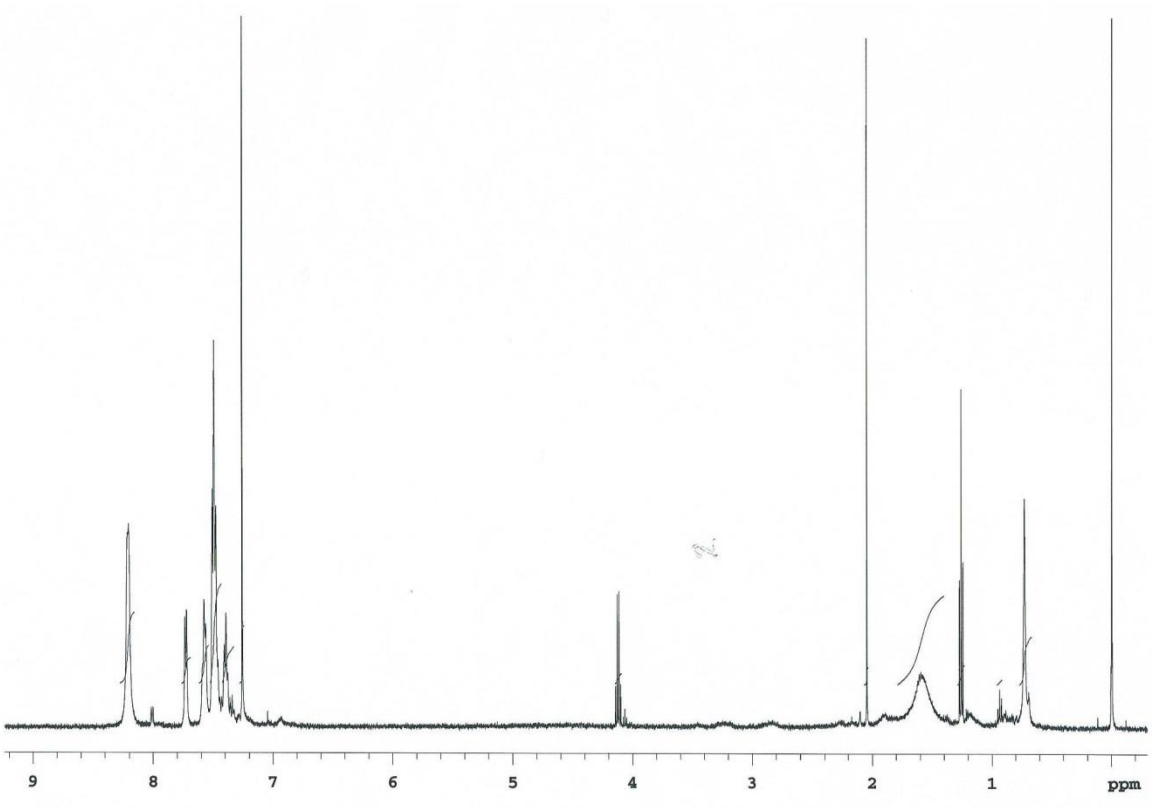


C:\HPCHEM\1\DATA\CG\AMFRAC6.D Wed Apr 04 14:40:00 2012 Page 1 of 4

Appendix 9d: The MS data from the select fractions that showed to not contain the ideal compound that was seen in the MS data from the preparative TLC of band 5.



Appendix 10a: Proton NMR data from fractions 22-28 of the 5th band of the preparative TLC plate after purification under rotary evaporation



Appendix 10b: GC data from fractions 22-28 of the 5th band from the preparative TLC

Graphics Report

File : C:\HPCHEM\1\DATA\CG\F22-27.D
Operator : jason
Acquired : 11 Apr 112 3:41 pm using AcqMethod ADVORG
Sample Name: Fractions 22-27 from column of amine
Misc Info : 100 to 300 @ 10
Vial Number: 1

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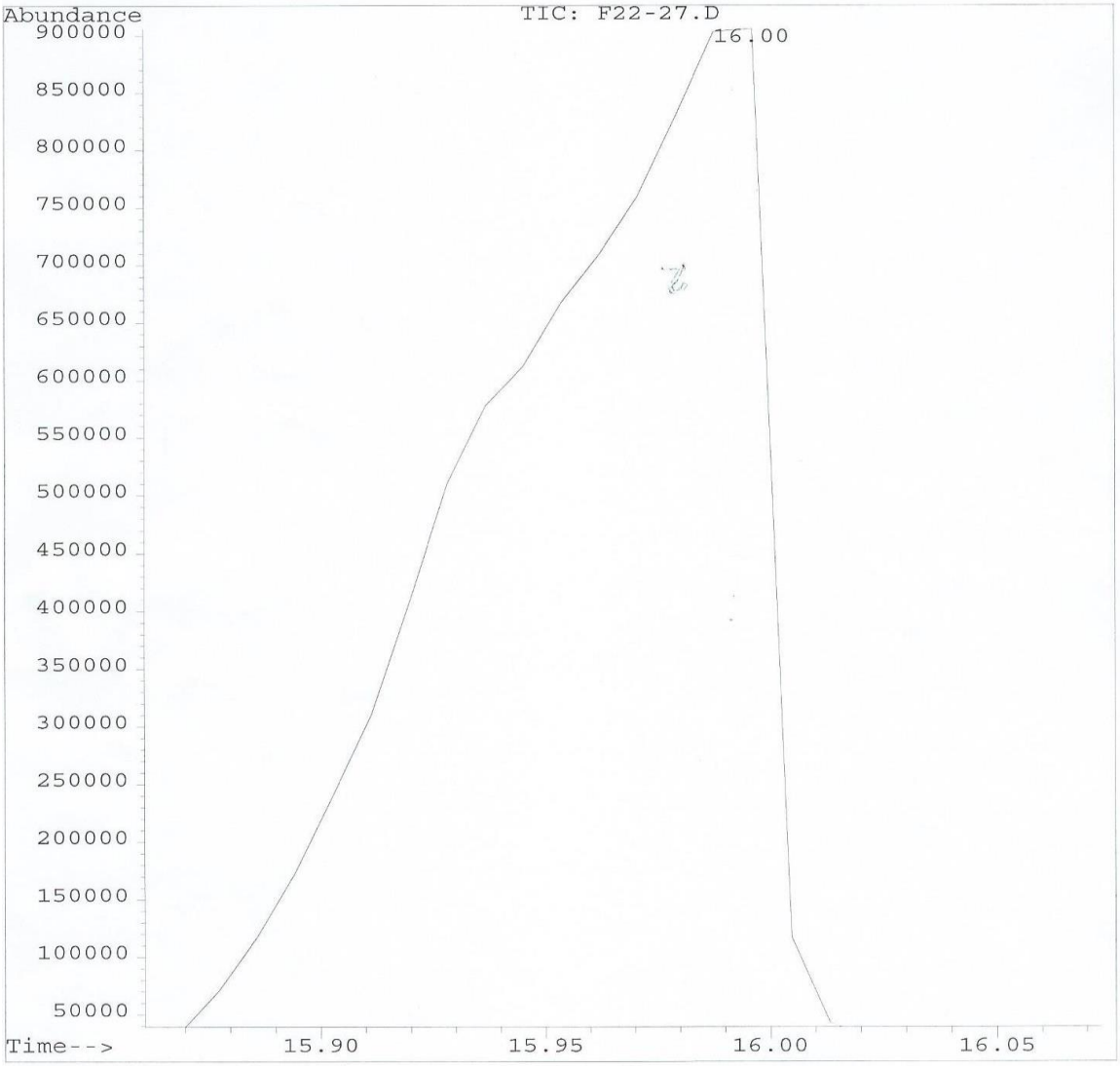
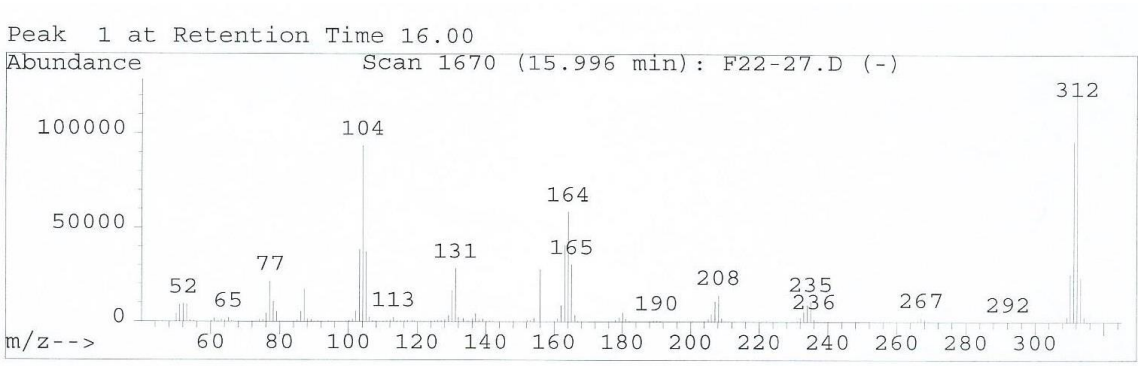
Appendix 10c: A closer look at the main GC peak from fractions 22-28 of the 5th band from the preparative TLC layer.

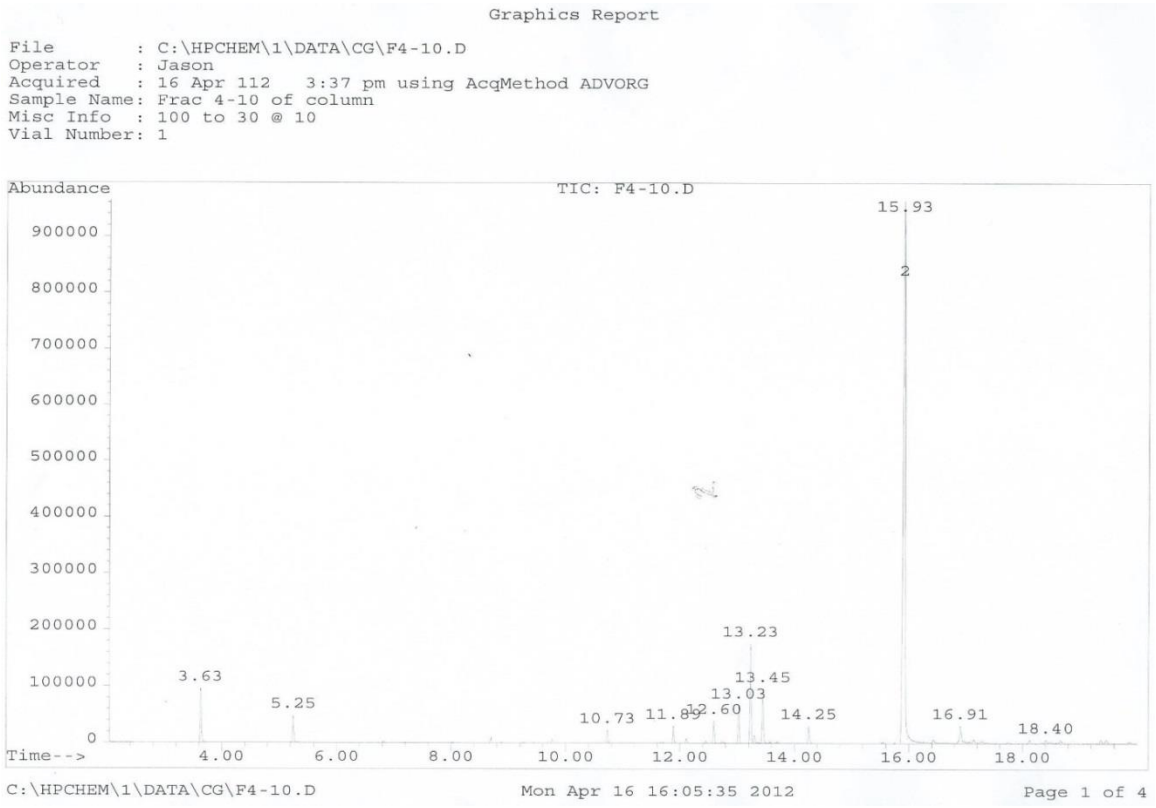
```
File        : C:\HPCHEM\1\DATA\CG\F22-27.D
Operator    : jason
Acquired    : 11 Apr 112    3:41 pm using AcqMethod ADVORG
Instrument :    GCD Plus
Sample Name: Fractions 22-27 from column of amine
Misc Info   : 100 to 300 @ 10
Vial Number: 1
```



Appendix 10d: The MS data from fractions 22-28 of the 5th layer of the preparative TLC layer after purification

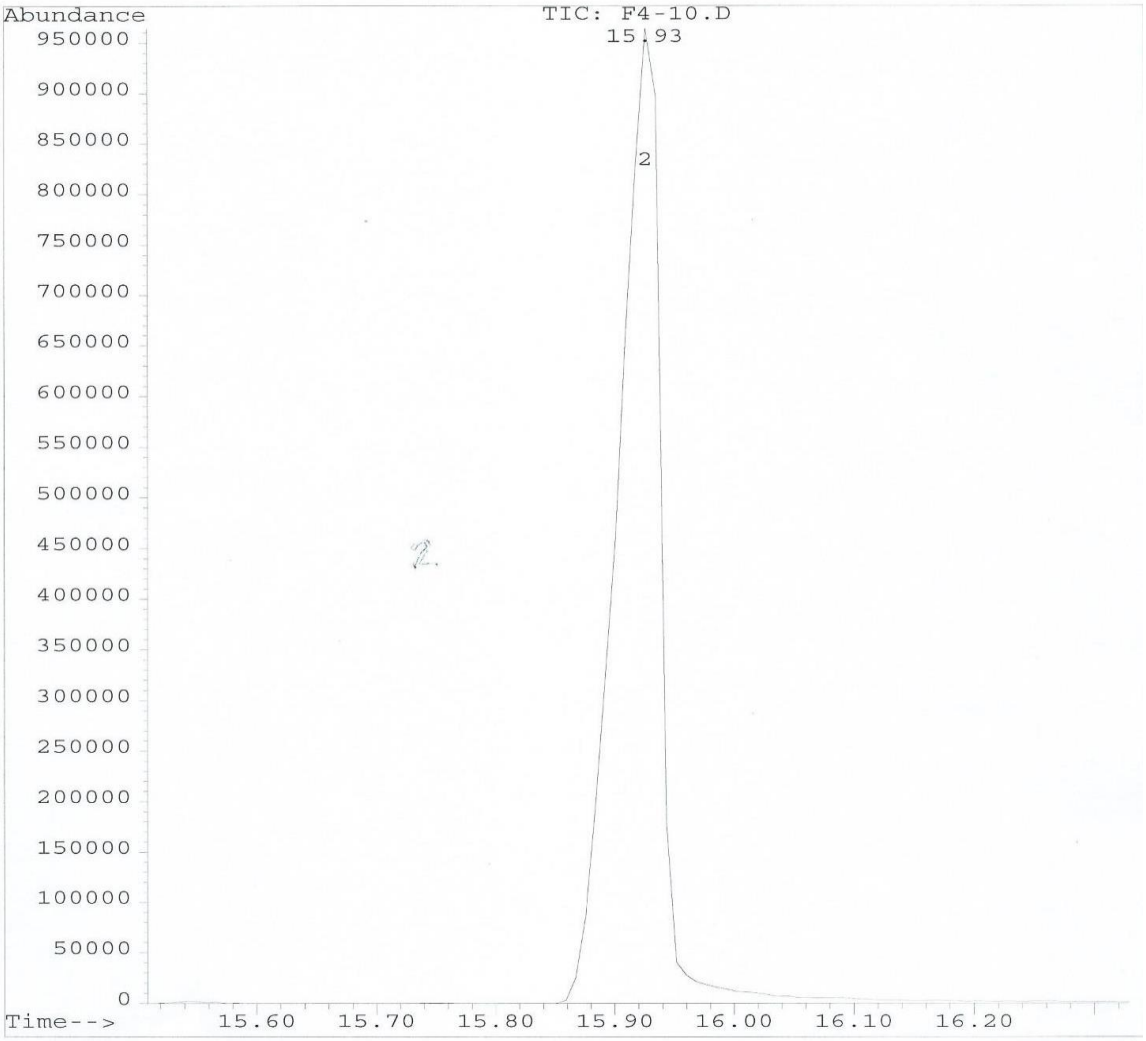


Appendix 11a: The GC data from fractions 4-10 of the column, which was thought to contain the compound of interest

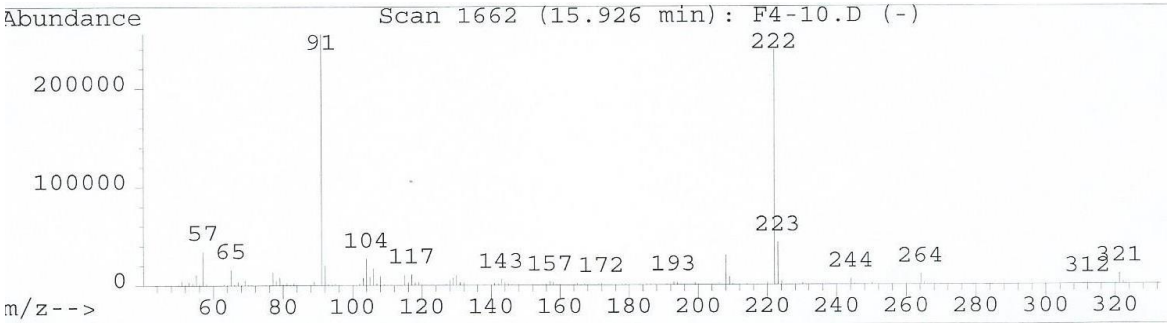


Appendix 11b: A closer look at the main peak of the GC data from fractions 4-10 of the 5th band of the preparative TLC plate

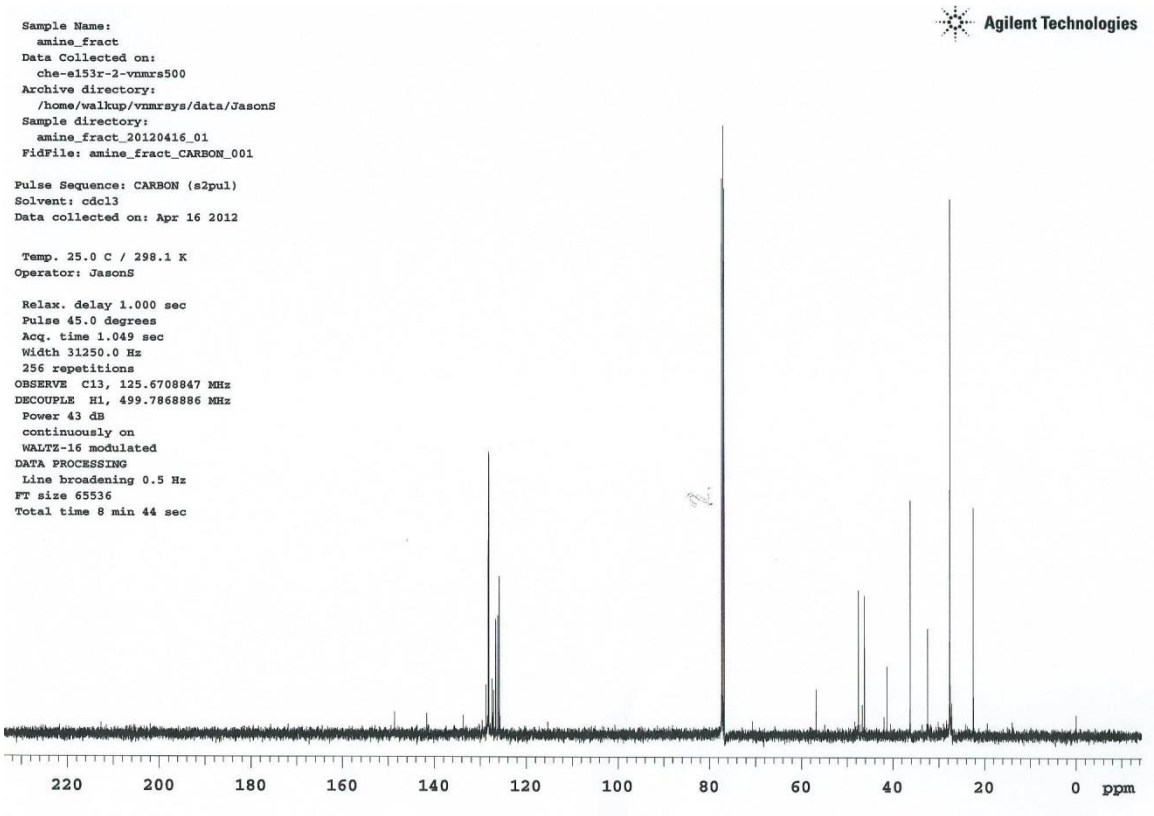
```
File        : C:\HPCHEM\1\DATA\CG\F4-10.D
Operator    : Jason
Acquired    : 16 Apr 112    3:37 pm using AcqMethod ADVORG
Instrument :    GCD Plus
Sample Name: Frac 4-10 of column
Misc Info   : 100 to 30 @ 10
Vial Number: 1
```



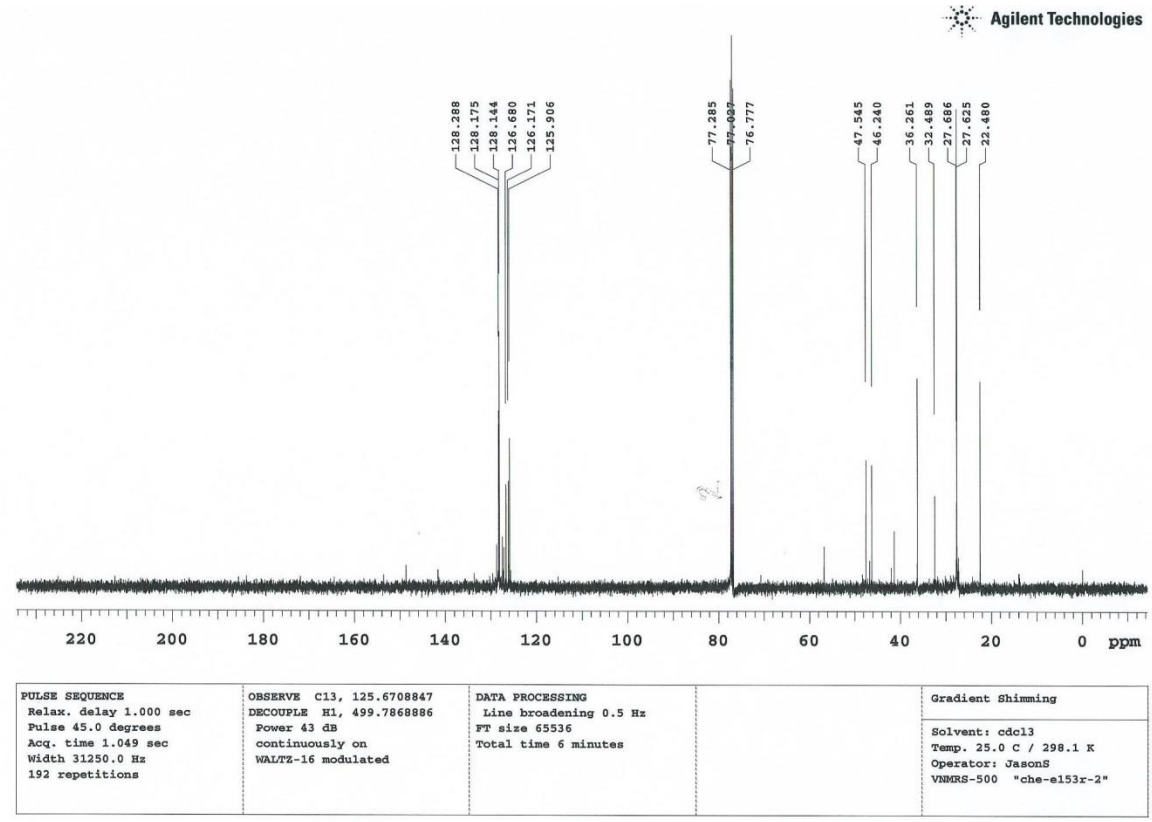
Appendix 11c: The MS data for fractions 4-10, which show the ideal MW of 321.



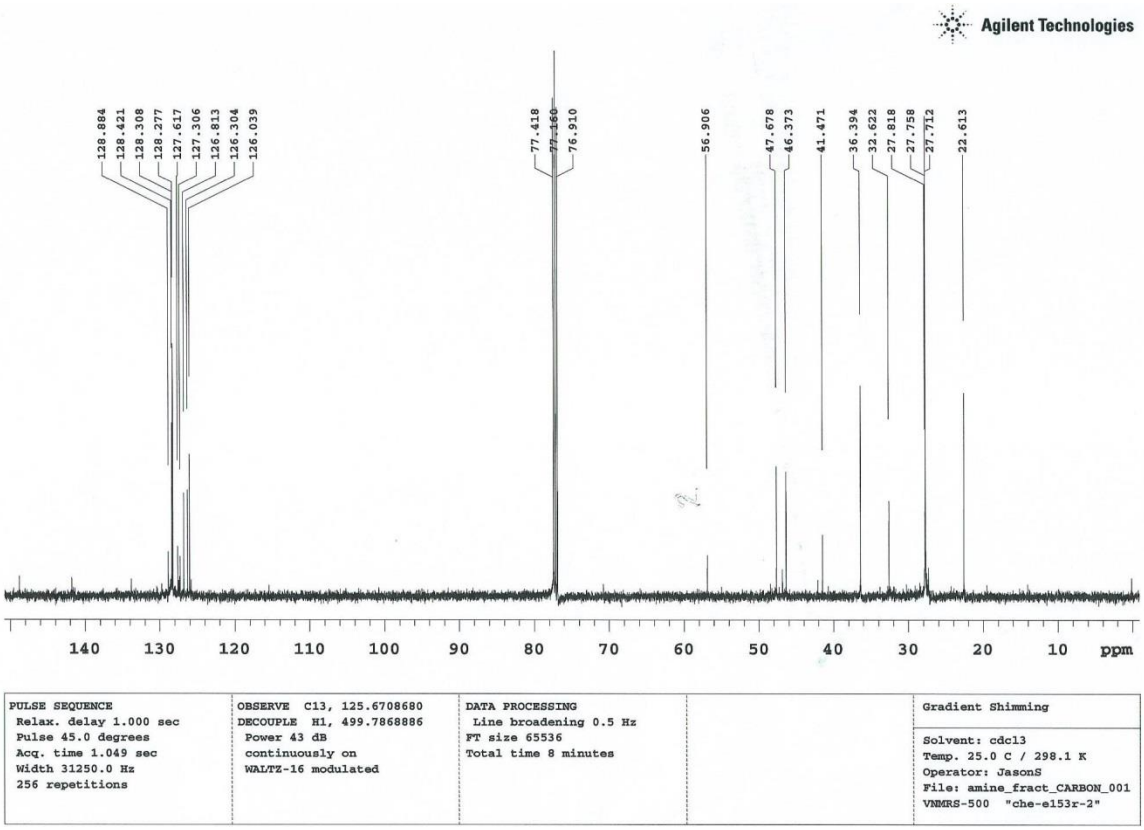
Appendix 11d: A carbon NMR of the data from the fractions 4-10 of the 5th band from the preparative TLC plate



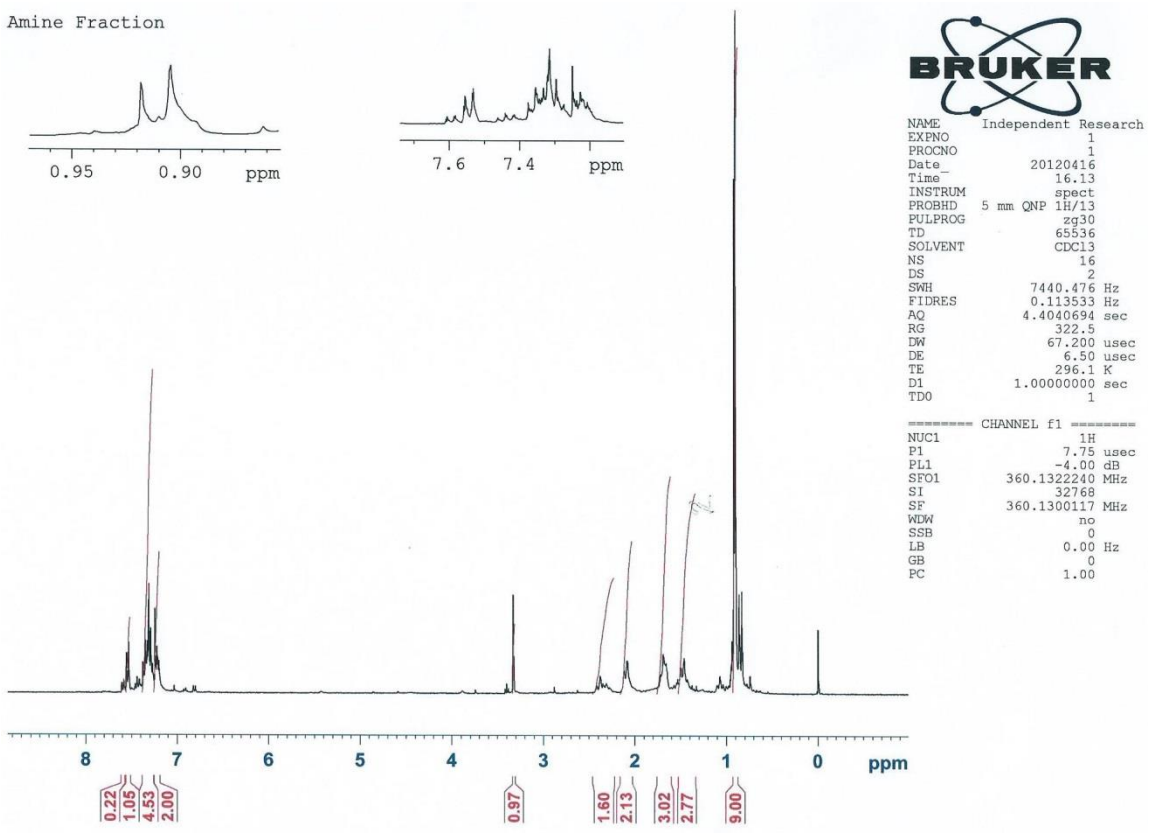
Appendix 11e: A closer look at the carbon NMR from fractions 4-10 from the 5th layer of the preparative TLC plate



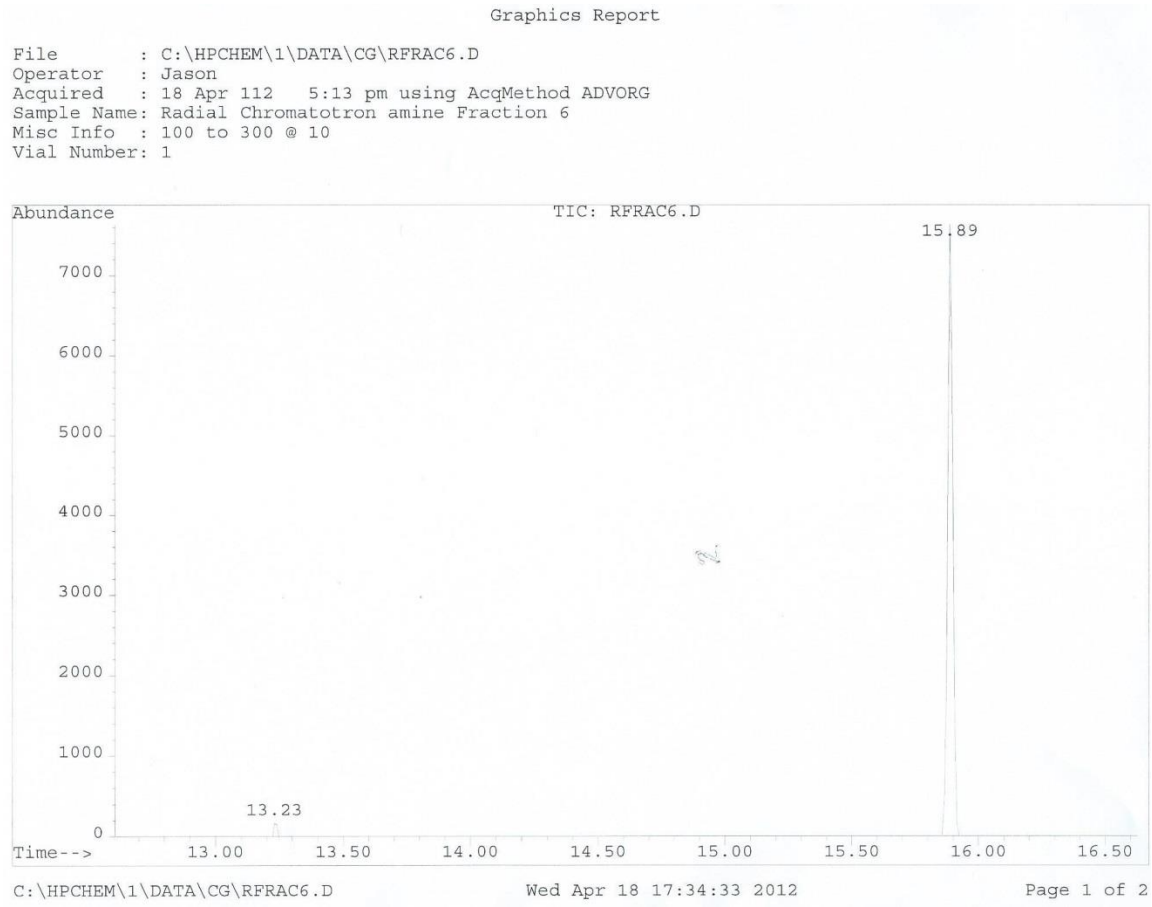
Appendix 11f: Another look at the carbon NMR from fractions 4-10 of the 5th band from the preparative TLC plate



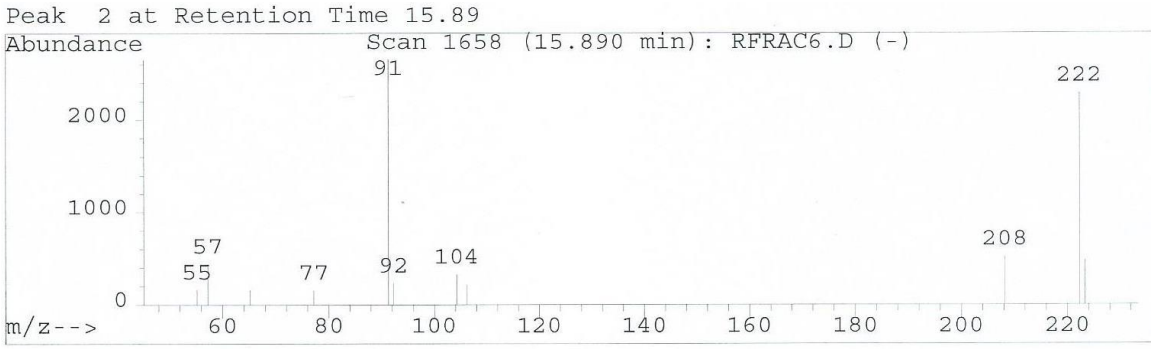
Appendix 11g: A proton NMR of the possible amine with a close look at the peaks of the tert-butyl group and the aromatic region for the compound in fractions 4-10 of the 5th band of the preparative TLC plate



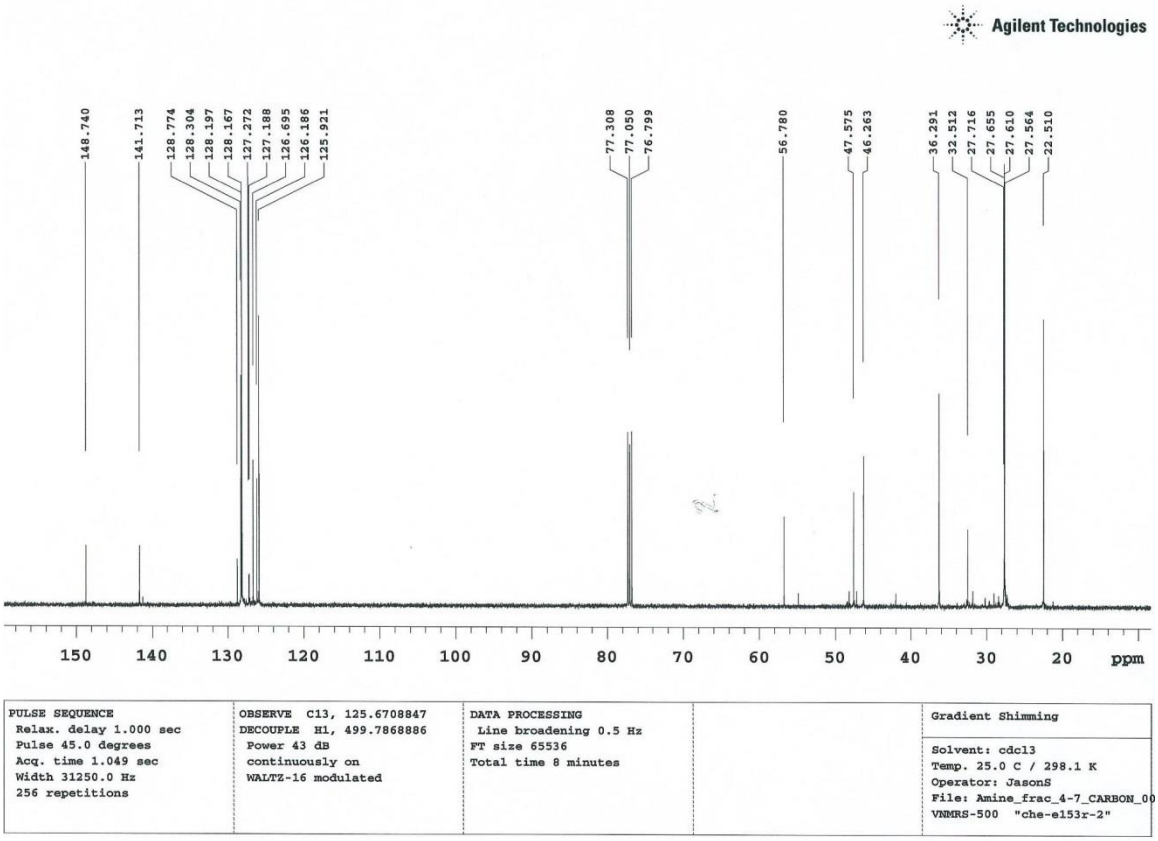
Appendix 12a: Due to impurities in the previous sample from fractions 4-10, the fractions were placed in a radial chromatotron and fractions were collected to collect the most pure sample of the desired amine. Fraction 6 was identified to be the most likely candidate to contain the amine, and the GC data is shown above.



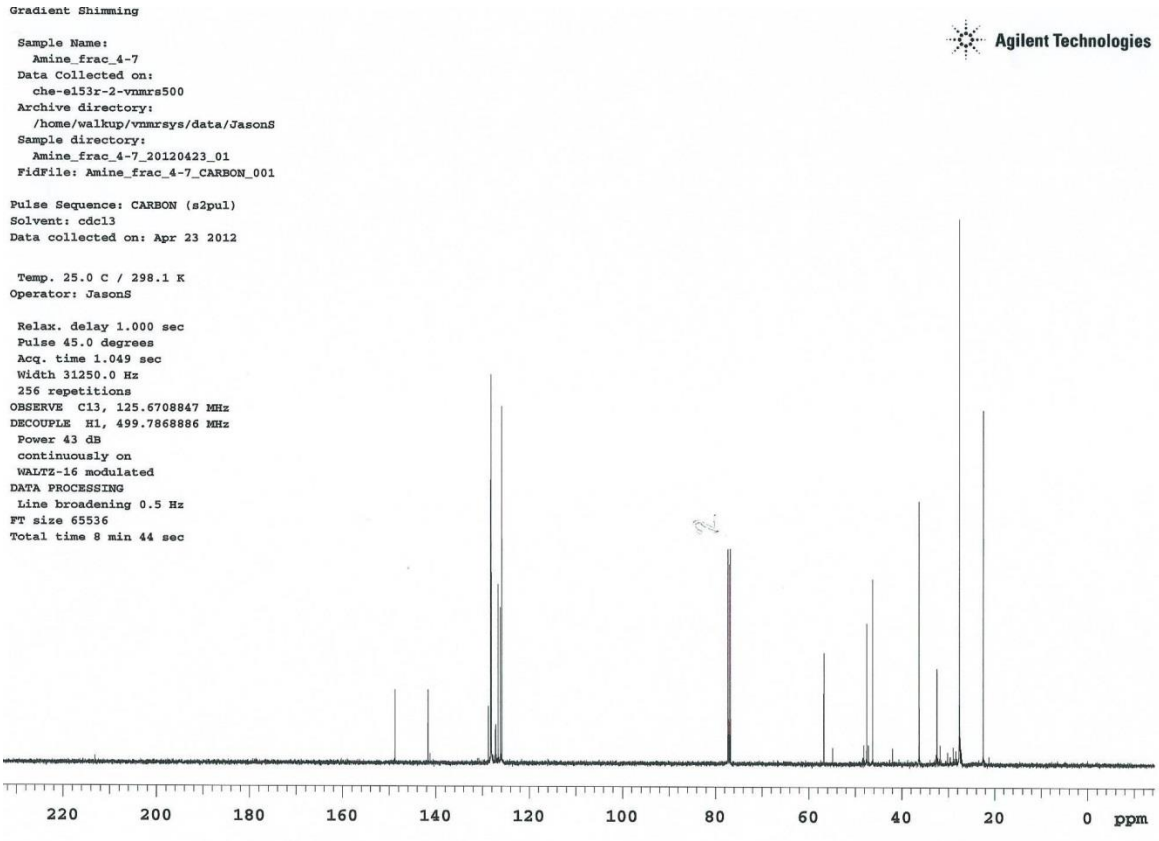
Appendix 12b: The MS data from the sample of fraction 6 from the radial chromatotron.



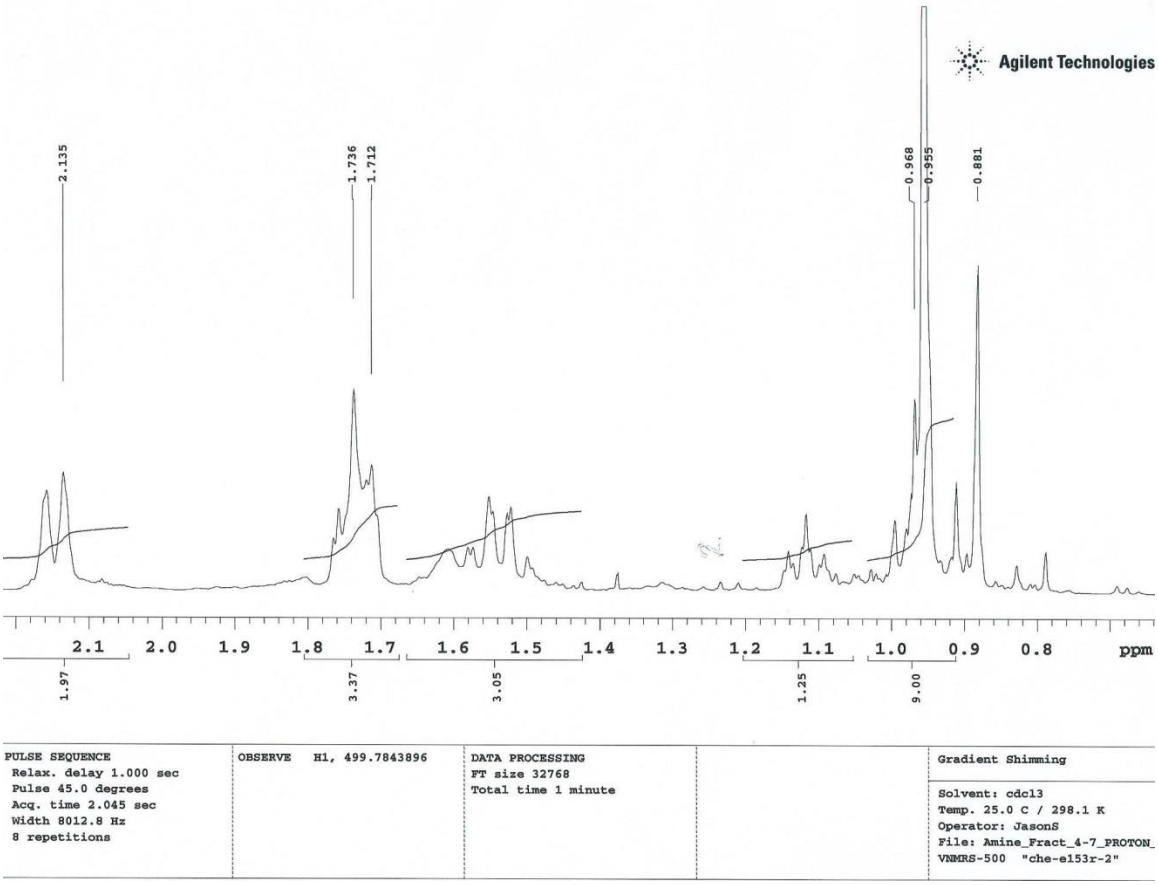
Appendix 13a: The carbon NMR from fractions 4-7 of the radial chromatotron



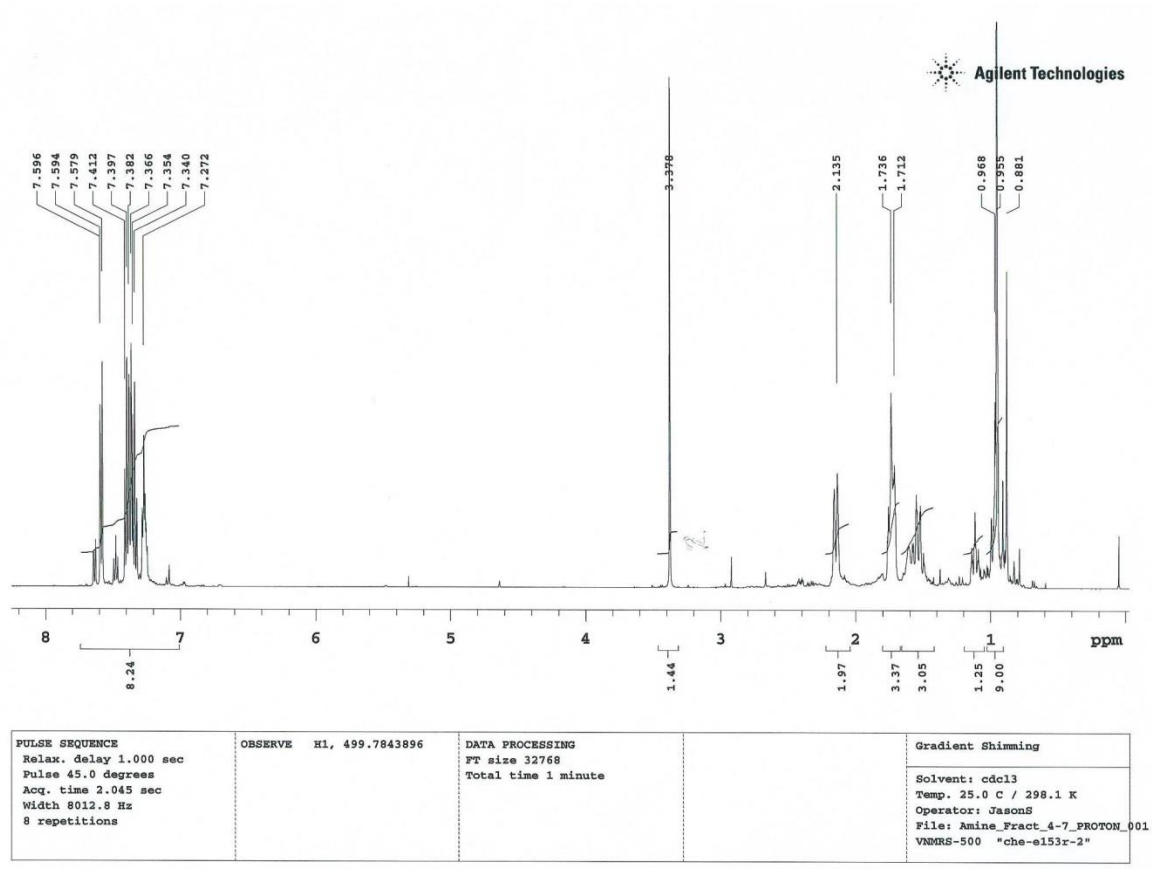
Appendix 13b: An additional look at the carbon NMR data from fractions 4-7 of the radial chromatotron



Appendix 13c: The proton NMR data from fractions 4-7 of the radial chromatotron



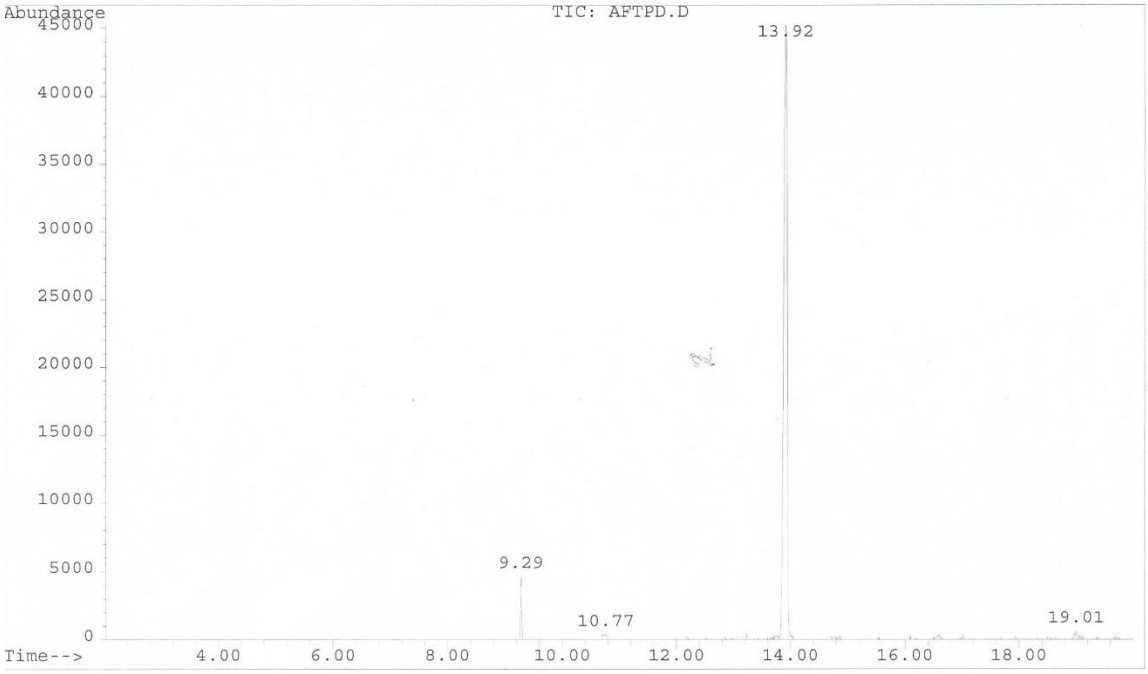
Appendix 13d: An additional look at the proton NMR data from fractions 4-7 of the radial chromatotron



Appendix 14a: The GC data of the organic layer following the reaction with the palladium

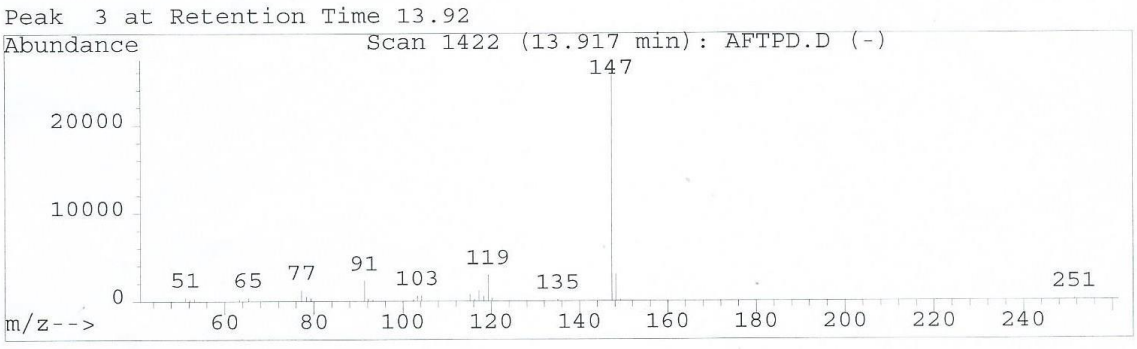
Graphics Report

File : C:\HPCHEM\1\DATA\CG\AFTPD.D
Operator : Jason
Acquired : 29 Aug 112 2:46 pm using AcqMethod ADVORG
Sample Name: amine after palladium
Misc Info : 100 to 300 at 10
Vial Number: 1

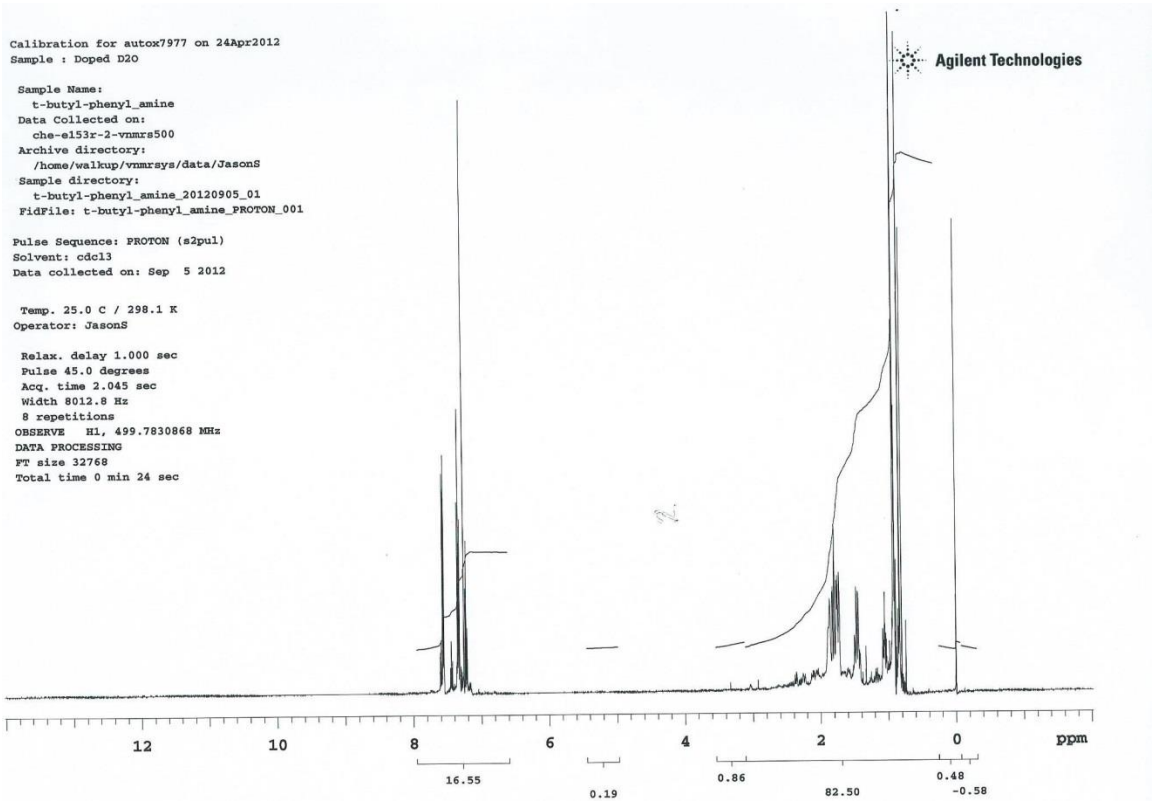


C:\HPCHEM\1\DATA\CG\AFTPD.D Wed Aug 29 15:07:12 2012 Page 1 of 2

Appendix 14b: The MS data of the organic later following the reaction with the palladium



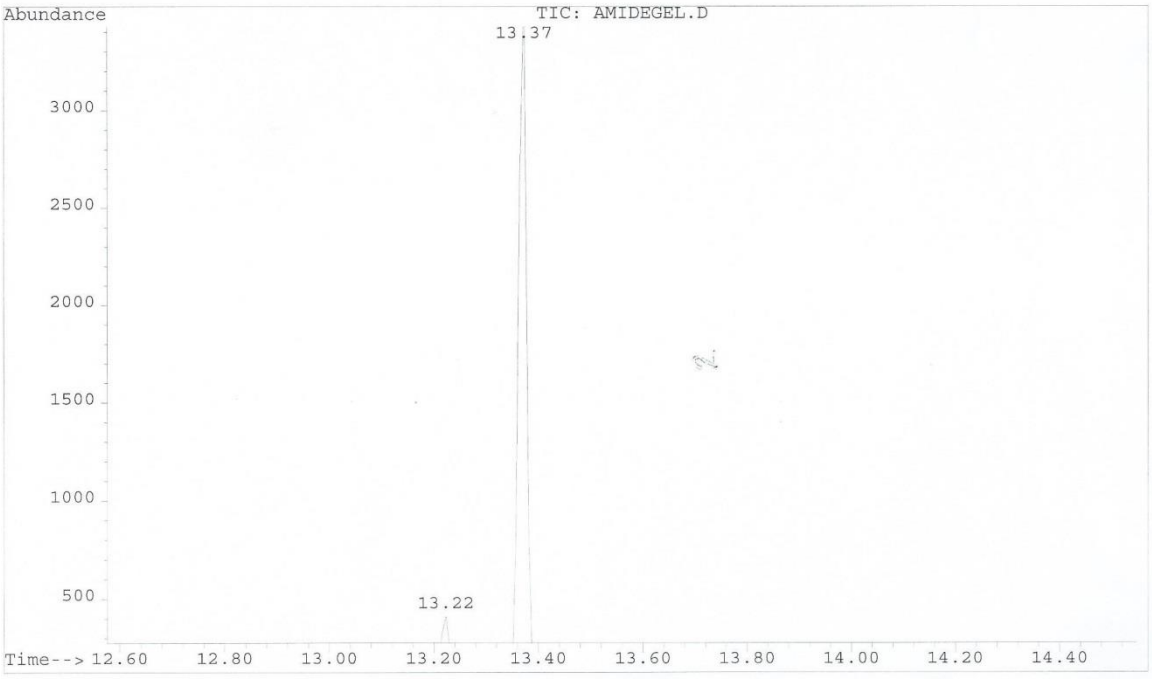
Appendix 15: A proton NMR sample of the organic compound following purification after the reaction with palladium



Appendix 16a: The GC data of the possible amide compound that was synthesized with the intention of identifying the structure of the potential amine product.

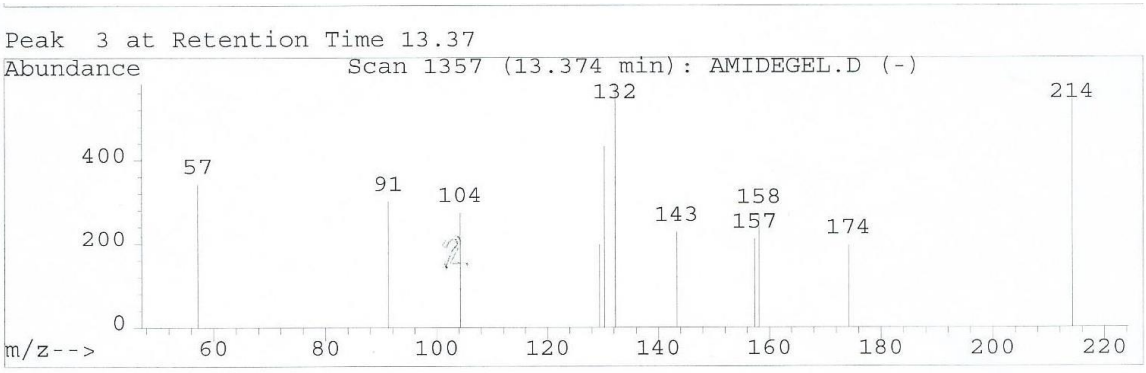
Graphics Report

File : C:\HPCHEM\1\DATA\CG\AMIDEGEL.D
Operator : Jason
Acquired : 12 Sep 112 3:06 pm using AcqMethod ADVORG
Sample Name: possible amide
Misc Info : 100 to 300 at 10
Vial Number: 1



C:\HPCHEM\1\DATA\CG\AMIDEGEL.D Wed Sep 12 15:27:41 2012 Page 1 of 2

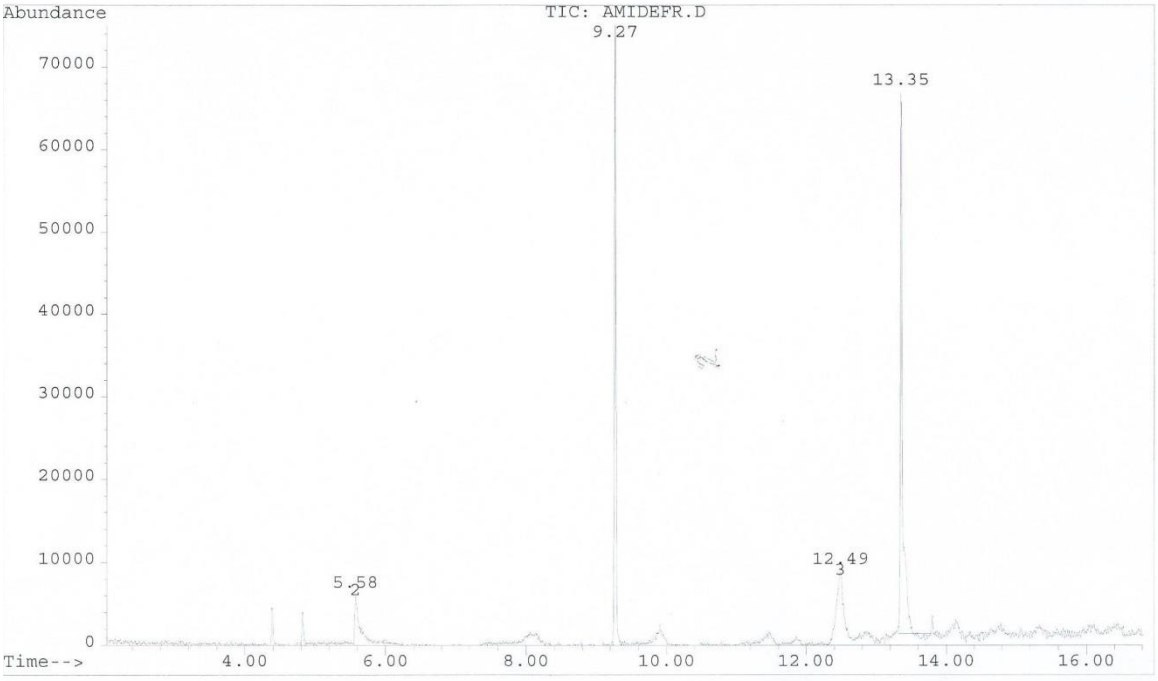
Appendix 16b: The MS data of the possible amine that was synthesized for compound characterization purposes



Appendix 17a: GC data from fractions 6-10 of the amine product following radial chromatography and TLC of the various fractions

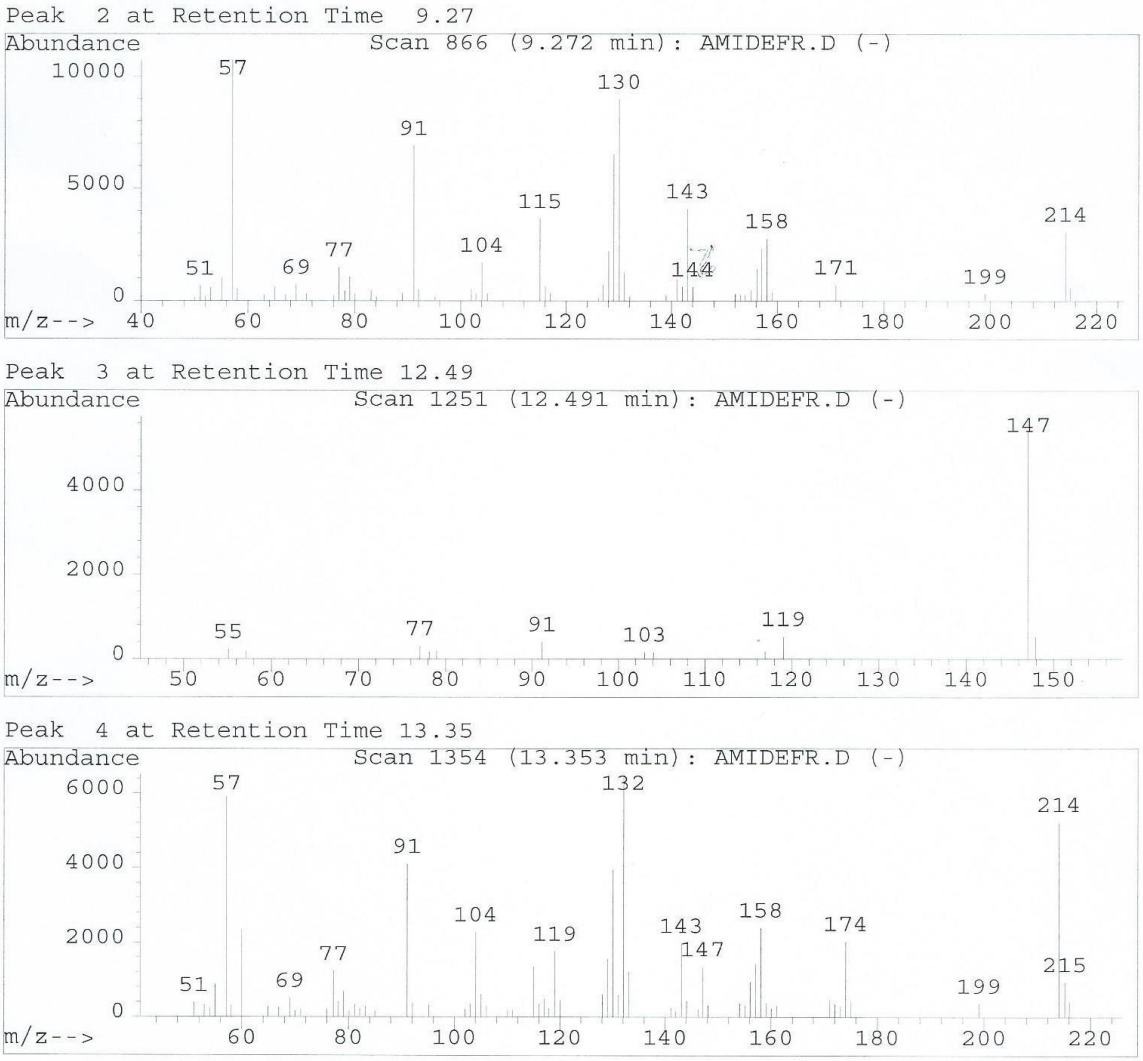
Graphics Report

File : C:\HPCHEM\1\DATA\CG\AMIDEFR.D
Operator : jason
Acquired : 19 Sep 112 5:26 pm using AcqMethod ADVORG
Sample Name: amide fractions
Misc Info : 100 to 300 at 10
Vial Number: 1



C:\HPCHEM\1\DATA\CG\AMIDEFR.D Wed Sep 19 17:44:07 2012 Page 1 of 2

Appendix 17b: The MS data from fractions 6-10 of the amine sample following radial chromatography and TLC of the various fractions



C:\HPCHEM\1\DATA\CG\AMIDEFR.D Wed Sep 19 17:44:18 2012 Page 2 of 2

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