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Synthesis of Chiral Surfactants for Enantioselective Organic Synthesis

A thesis

Presented to

the faculty of the Department of Chemistry

East Tennessee State University

In partial fulfillment

of the requirements for the degree

Master of Science in Chemistry

by

Kalyan Mondal

August 2003

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Keywords: Chiral surfactants, Dimethyl leucinol, Functionalized monomer based on vinylbenzyl chloride, Alkyl halide, Enantiomers, Enantioselective.

ABSTRACT

Synthesis of Chiral Surfactants for Enantioselective Organic Synthesis

by

Kalyan Mondal

The first step of the synthesis of the hydrocarbon-based chiral surfactant (**2**) involved the methylation of (S)-leucinol to give (2S)-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide (2.92 g, 67%). The chiral surfactant was synthesized by reacting (2S)-N,N-dimethyl-2-amino-4-methyl-1-pentanol (**1**) with bromohexadecane (2.06 g, 71%). The functionalized styrene for the polymer supported chiral catalyst (**6**) was synthesized by reacting (**1**) with 4-vinylbenzyl chloride. The polymerization was carried out with 10% of the functionalized monomer (**5**) (1.26g, 70.2%), 5% cross-linking agent divinylbenzene, and 85% of styrene with AIBN as the initiator. The structure of each of the products was confirmed by using FTIR and NMR spectroscopy. The activity of the hydrocarbon surfactant and polymeric catalyst were examined by using them as additives in a standard reduction of 2-pentanone with sodium borohydride to yield (R)- and (S)-2-pentanol (**3**) (4gm, 25%). The resulting alcohol was then esterified with (2S)-methylbutyric acid with iodine as the catalyst and the ester was characterized.

*This dissertation is dedicated to all those people
who have always given me the love, trust, and support
to come to this stage of my life*

-To My Family-

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CHAPTER 1

INTRODUCTION

Chirality

The concept of "chirality" has been known in chemistry since the 1870s, although it would be nearly a hundred years before chemists began using this term. In fact, in the first edition of Eliel's "Stereochemistry of Carbon Compounds" in 1962¹, the word chiral is not mentioned, although it would be prominent in later editions⁵. In extremely simple terms, chirality is "handedness," - that is, the existence of left/right opposition. For example, the left hand and right hand are non-superposable mirror images and therefore are "chiral" in nature. The term Chiral is derived from the Greek name "kheir" meaning "hand" and apparently was coined by Lord Kelvin in 1904, in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light in which he stated:

"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."

In technical terms, a given molecule, or object in general is said to be chiral or dissymmetric if it does not possess improper rotation axis S_n of any order n , where S_1 corresponds to a symmetry plane (σ) and S_2 to an inversion center (i). A consequence of this definition is that chiral objects are not superimposable on their mirror images and are able to rotate plane-polarized light.

Importance of Chirality in Life

It is now widely accepted that nature itself is chiral, where amino acids, terpenes, carbohydrates, and alkaloids all are natural occurring substances that are often enantiopure or at least enantioenriched, i.e. one of the enantiomers predominates over the other. The presence of chirality in Nature implies that usually only one enantiomer of a certain compound produces the correct response on a living organism. As a consequence, normally only one enantiomer of a given drug has the desired activity. Hence, medicinal chemistry has a very strong need for enantioselective process in drug development.

Thalidomide is chiral molecule that was prescribed as a sedative drug for pregnant women, from 1957 into the early 60s. It was present in at least 46 countries under different brand names. However, it restricted the proper growth of the fetus resulting in horrific birth defects in

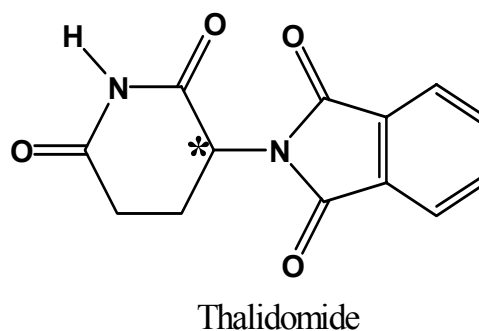


Figure 1. Chiral drug thalidomide.

thousands of children around the world. An estimated 12,000 children were born with certain kind of disability because of this harmful side effect. These resulted from the chiral nature of the molecule. Because of the presence of the chiral carbon, thalidomide has two enantiomeric forms. Laboratory tests after the thalidomide disaster showed that in some animals the 'R' enantiomer was teratogenic but the 'S' isomer was an effective sedative. The drug was marketed as 50/50 mixture. Of the molecules, the left-handed one (S) had the sedative action while the R isomer was found to cause the fetal abnormalities later. However, the tragedy could be avoided if the physiological impact of

the individual molecules had been tested prior to marketing the product. It is now known that even when a stereoselective sample of thalidomide (only one of the optical isomers) is administered in the body, racemization may occur under the body pH condition. This means that both enantiomers are formed in a roughly equal mix within the blood. So even if the one enantiomer, say the (S) one, is used the disaster cannot be averted.

Aspartame and Carvone are the two other examples of chiral molecules. However, all the above given examples are just the tip of the iceberg. DNA, proteins, amino acids, and sugars are all chiral. Mirror image amino acids are called L- and D-amino acids. Human proteins are exclusively built from L-amino acids. The origin of this fundamental dissymmetry is still mysterious. When interacting, these molecules recognize each other just as your right hand distinguishes another right hand from a left when you shake hands. This is why mirror image molecules, like mirror image of thalidomide, so often have radically different fates in our bodies.

Drug synthesis is an enormous worldwide market. As a consequence, issues related to chirality have gradually pervaded chemical research. This background is to be kept in mind when appreciating the importance of chirality, whether in science or in everyday life. However, this is not the only field where processes of this kind are being developed. Tastes and smells may also depend on enantiomers, which raises the importance of chirality in the food flavoring and perfumery industries. Agrochemicals may be easier or harder to degrade depending on which enantiomer of the chemical substance is used. Due to the growing concern about environmental aspects in modern society, this branch of industry has therefore an increasing need for enantioselective processes in the preparation of their products.

Chirality and Synthetic Organic Chemistry

In South Africa, researchers at CSIR Bio / Chemtek have developed a process to produce *l*-menthol from the readily available raw material *m*-cresol¹¹. Alkylation of *m*-cresol generates thymol. Hydrogenation of thymol yields four pairs of diastereomers. These are \pm -menthol, \pm -isomenthol, \pm -neomenthol, and \pm -neoisomenthol. Acylation of this mixture using a stereoselective lipase yields *l*-Menthyl acetate in at least 96% enantiomeric excess (ee). *l*-Menthyl acetate is separated from the unreacted isomers by distillation and is subsequently hydrolyzed to get back the *l*-menthol.

The flow chart shown in Figure 2 suggests that the formation of *l*-menthol becomes possible only in presence of the Lipase Resolution. The first step of the synthesis involves the alkylation of *m*-cresol, one of the easily available starting materials for the synthesis of *l*-menthol. The alkylation gives thymol, which on hydrogenation produces a mixture of 4-pairs of diastereoisomers of products, \pm -menthol, \pm -isomenthol, \pm -neomenthol, and \pm -neoisomenthol. But it is very difficult to separate the *l*-menthol from that mixture. The next step involves the acylation of the mixture in presence of Lipase Resolution, which facilitates the acylation of *l*-menthol only and not even that of *d*-menthol. As a result we get only *l*-menthyl acetate, which is then easily separated from the unreacted alcohols by simple distillation and a subsequent hydrolysis regenerates the *l*-menthol.

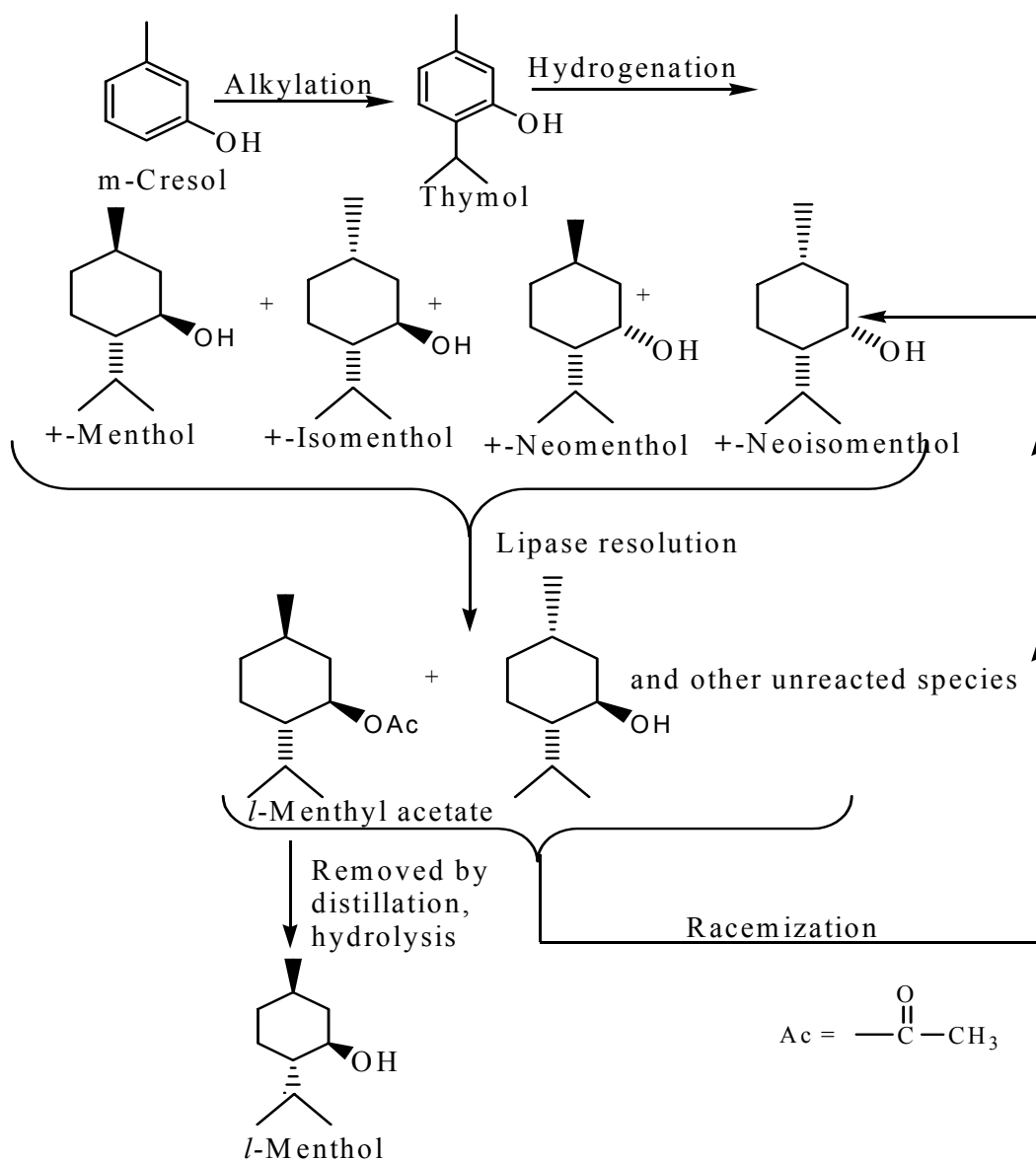


Figure 2. Lipase resolution synthesis of *l*-menthol¹¹.

The enzymatic resolution has been demonstrated in a continuous process at 1 kg per hour. Enzyme activity is retained even after 2,000 hours of operation. Furthermore, isomerization / racemization of the unreacted isomers regenerates the original mixture of diastereomers, which is routed again to enzyme resolution. Over several cycles, thymol is almost fully converted to *l*-menthol.

Enantiomeric Purity and Drug Industry

Worldwide sales of single-enantiomer drugs head past \$ 123 billion¹⁵. According to Erb and Zhou, the drug industry will continue to spur strong growth in Chiral compounds because of its importance for the improvement of drug efficacy and the reduction in the development costs. For the effective use of drugs, chemists are concerned about the role played by target enzymes, hormones, and other compounds in patients' cells and in cells of microorganisms. Additional targets are receptors on cell surfaces. These compounds along with the receptors are made up of chiral amino acids, carbohydrates, and lipids. Therefore, any drug intended to interact with them must be enantiomerically pure. The following table shows the importance of single enantiomeric drug in the overall drug industry.

Table 1. Worldwide Sales of Single-Enantiomer Drugs¹⁵.

	<u>TOTAL MARKET FOR</u>		<u>SINGLE – ENANTIOMER</u>	
	<u>ALL KINDS OF DRUG</u>		<u>DRUGS</u>	
	1999	2000	1999	2000
Cardiovascular	42.7	46.6	24.8	26.9
Antibiotics/ antifungals	29.3	31.7	23.9	23.9
Hormones	20.0	22.0	13.8	14.6
Cancer	13.7	15.6	9.4	10.4
Central nervous system	47.7	53.9	8.6	9.0
Hematology	16.5	15.4	8.6	9.1
Antiviral	17.7	19.1	6.2	6.5
Respiratory	36.5	40.5	5.1	6.1
Gastrointestinal	43.9	47.2	3.0	3.5
Vaccines	6.5	7.3	2.0	3.0
Ophthalmic	7.1	7.4	1.8	2.0
Dermatological	17.9	18.4	1.3	1.2
Analgesic	21.5	23.0	1.0	1.3
Other	39.0	41.9	5.5	5.6
Total	\$360.0	\$390.0	\$115.0	\$123.3

“TOTAL MARKET” represents the sale of both single-enantiomeric drugs as well as the racemic mixture drugs together with drugs having non-chiral chemical structure. However, this shows the tip of the iceberg if we think about how a particular

enantiomeric form of a chemical species acts to prevent diseases while the other one aggravates it.

Critical Factors for the Application of Enantioselective Catalysts

In any catalytic reaction there are two major factors that control the application of an enantioselective catalyst. The first question is whether the cost of the production can compete with any other alternative pathways or not. The second major concern is whether it is possible or not to develop the catalytic step within the given time frame¹. Besides these two major factors, we have to take care of a number of other factors, including whether the catalyst under consideration is able to give maximum enantiomeric excess, i.e. maximum [% desired - % undesired]. For example, an enantioselective catalyst capable of giving >90% ee in Pharmaceutical Industries and >80% in Agricultural Industries is considered to be excellent. Additionally availability and the cost of the particular ligands must be considered. Finally chemo selectivity, i.e. the capability of the reactant or the product to tolerate a particular functional group, its application, and removal from the reaction system are particularly important in the case of multi-steps reaction pathway.

Overall, the Industrial Scale use of enantioselective catalysts depends on several factors such as the field of application, the cost of the active compound, and the scale of the process. Additionally, the technical experience and the product facilities of a company and the maturity of the catalytic process must be considered. Last but not the least, the chemist who plans the synthesis must be aware of the catalytic route. There are

three basic methods to perform the synthesis of enantiomerically pure or enriched compounds.

Resolution

This is the oldest of all the processes for manufacturing enantiomerically pure or enriched compounds, and the method is based on the synthesis of the racemic target molecule or intermediate in its synthetic sequence. The material is then resolved with the help of an enantiomerically pure compound. Although resolution is still considered to be one of the most important and widely accepted processes, it suffers from a major drawback, i.e. the production of unwanted material in a minimum of 50%, which in turn reduces the actual yield. This drawback can usually be overcome by simple recovery/recycling of the unwanted product.

Chiral Pool

In this process, we use commercially available and enantiomerically pure starting material to start the synthesis of the desired product. The success of this process depends on the availability of the appropriate starting material every time. Besides this fact, usually only one of the enantiomers of the starting material is naturally occurring and this restricts the synthesis further. Moreover, the cost factor is also very important, as most of the man-made unnatural enantiomers are very expensive.

Asymmetric Synthesis

This method involves the introduction of chirality by the action of a chiral reagent, auxiliary, or catalyst that is not incorporated in the final product. Of the three processes mentioned, the asymmetric synthesis provides the widest of possibilities. During the last few decades a variety of asymmetric transformations have been developed.

Chiral Ligands

Chiral ligands are the most effective enantioselective catalysts¹. For the last few years a number of ligand types and families have been prepared. These show a wide variety of activities in different chemical reactions and Jacobson¹ described them as of ligands of “privileged” status. This means that these types of ligands have a very broad scope in various applications. They often play the role of a modular; they can easily be tailored for a specific substrate, and are available in large quantities. Many of these catalysts tolerate a wide range of functional groups and are also chemo selective. Now, the question arises of how a chiral molecule can be employed in a chemical reaction. It can be introduced either as a single reacting reagent or being attached to another molecule. An alternate way is to introduce the chiral reagent as a surfactant, which helps to develop a relatively compact chiral environment.

Surfactants

Surfactants find application in almost every chemical industry, including the drug industry, detergents, paints, dyestuffs, cosmetics, pharmaceuticals, fibers, and plastics.

They play a significant role in oil industry too^{2, 4}. The word surfactant comes from the terms Surface Active Agent. A small quantity of the surfactant molecules rests upon the water-air interface and decreases the surface tension value (the force per unit area needed to make available surface). That is why the molecules are called “Surface active agents”.

Every surfactant molecule is comprised of two parts, the hydrophilic and the hydrophobic part as shown in the Figure 3.

Most surfactants have a long hydrocarbon

tail that can be linear or branched.

Being non-polar and hydrophobic, it has very weak interaction with the polar part of the medium (e.g. water).

The hydrophilic part is relatively small

ionic or polar group and interacts

strongly with the polar part via dipole- dipole or ion-dipole interaction.

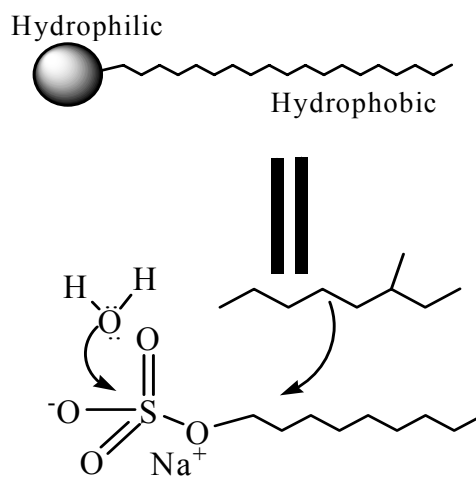


Figure 3. Structure of a surfactant.

When the concentration of the surfactant exceeds the *critical micelle concentration* [CMC], the excess surfactant molecules aggregate together to form small colloidal particles, called micelles. Thus with the concentration of the surfactant exceeding the CMC, a solution state changes to the colloidal state resulting in decrease of the free energy of the system and is accompanied by the decrease in surface tension. A number of physical properties such as electrical conductivity, ion activities, and viscosity undergo a sharp change and such a change is considered as an indication of attaining CMC for a given solution¹². CMC values are in the range of 0.001-0.1 mol/L, with most surfactants having values in lower end of the range. The CMC values are affected by

different factors, e.g. temperature, the length of the hydrocarbon part, the nature of the counter ions, and the existence of salts and organic additives¹³.

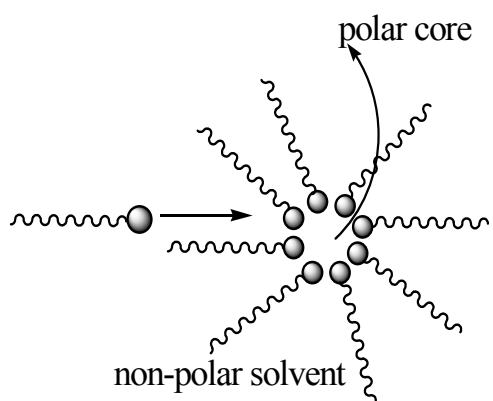
Micellar Structure and Properties

As the concentration of the surfactant in the solution exceeds the CMC value, the surfactants start to coagulate with each other to form micelles. Typical micelles have dimensions in the range of 2-10 nm with each micelle containing 50-100 surfactant molecules¹². Micelles may be spherical or rod-like depending upon the nature of the surfactants as well as the concentration. Usually at a concentration close to CMC micelles are mostly spherical with a few being rod-like. As the concentration of the surfactants increases, they become larger and, after a certain concentration, they get elongated and converted into the rod-like structures. Depending upon the nature of the solvent medium (whether polar or non-polar) micelles are of two types. In a polar solvent like water, the hydrocarbon

Figure 4. Structure of micelle.

part of the surfactant locates inside the core of the micelle, and the polar head groups are projected outwards of the surfactants, into the polar bulk solution and are located at the interface between micelles and the polar solvent. This arrangement shields the hydrocarbon part from the polar molecules. The kind of micelle formed in a polar solvent is called a *normal micelle* and is shown in the Figure 4.

Aggregation of the surfactants is also possible in non-polar solvents like hexane



and cyclohexane. In this case, the polar head groups of the surfactants are located inside the cores of the micelles, while the hydrophobic parts are projected into the bulk of the solvent. Thus, here the hydrophobic part of the surfactants protects the polar part from

Figure 5. Structure of reverse micelle. These types of micelles are called *reverse micelles* or *inverted micelles*¹³. The structure of the reverse micelle is shown in Figure 5.

Solubilization of the Substrate

Solubilization of the substrate being facilitated by the presence of micelle is defined as a particular mode of bringing into solution those substances, which are otherwise insoluble in a given medium. It involves the previous presence of a colloidal solution whose particles take up and incorporate within or upon them the otherwise insoluble substances¹³. The function of the micelles depends upon the nature of the solvent. Let us take the case of the normal micelle. In this case, the hydrocarbon parts are projected inside the core of the micelle with the hydrophilic part being oriented towards polar bulk solvent. Thus, within a polar medium there is a non-polar medium developed by the hydrocarbon part, and any substance insoluble in polar medium or slightly soluble in such a medium will have a relatively very high degree of solubility as it penetrates towards the hydrocarbon core. Here the micellar core acts as an organic (or non-polar)

phase and the favorable hydrophobic interaction between the non-polar core and the non-polar substance plays a significant role in the solubilization of the substance.

The opposite principle is true for the reverse micelle. Here the micelle core is polar in nature. Therefore, any polar substance that is insoluble in a non-polar medium can be solubilized with the addition of the surfactant in non-polar medium. In this case the hydrophilic force between the polar substance and the polar micelle core plays the significant role for the solubilization of the polar substance in a non-polar medium. The solubilization of substances in micellar media leads to a dynamic equilibrium of solute between micelles and the bulk phase. Several factors affect the solubilization, of which the structure of the surfactant and the solute, temperature, and the addition of any electrolytes and non-electrolytes are probably the most important.

Impact of Micelle

Presence of micelle in a reaction medium can have a number of effects as outlined below. Micelles can serve to increase the concentration of the reactants. As the substrate gets incorporated into the micelle, it may come in close proximity with the reagents, which may either be attracted to the micelle, electrostatically or may also be incorporated into the “functional micelles” by chemical interaction. Micelles can offer a “cage effect” that is capable of holding two reactive species together for a relatively longer time than a homogeneous medium can do. Because of this cage effect, the probability of the reactions and hence the reactivities are increased. Micelles are considered to be a novel environment for the photochemical reactions. They can promote photo induced electron

or proton transfer by compartmentalization, prohibit back-charge transfer, and, thereby, permit the control of the charge separation across the interface¹³.

Functional micelles can influence the mechanism of chemical reactions. They can act as effective bases or nucleophiles by virtue of the reactive groups present in the surfactant molecules or in the co-components in the co-micelles and, hence, catalyzes the reaction. Where the reaction is influenced by the pH of the medium, micelles have a strong impact because the reactivities of the nucleophiles increases with the decreases of the cationic micellar media.

The micelles have an impact on the stereoselectivity of the product¹³. It has been found that with the presence of micelles, the formation of one enantiomer is preferred over the other. It is expected that the functional group of such micelles is involved in some kind of interaction with the reactants facilitating the formation of one product over the other. In this work, we are trying to find out how the presence of a chiral surfactant can influence the stereochemical outcome of a reaction.

Optically active amines play a very important role for the manufacturing of synthetic drugs, resolving agents, and natural compounds. However, there are few examples of asymmetric synthesis to yield optically active amines⁴. There are several ways to obtain optically active amines, such as optical resolution of racemic amines with chiral carboxylic acids, and also the derivatization from natural products⁴. In the preparation of enantiomerically pure compounds, chiral catalysts play a significant role in asymmetric synthesis. The catalyst controls the reaction mechanism in such a way that only one enantiomer formation gets preference at the expense of the other. The catalytic

advantage of the chiral molecule can further be enhanced if a polymer-supported chiral catalyst is used instead of a hydrocarbon based chiral species.

There are many advantages of having the polymer-based chiral surfactant over their low molecular counterpart. The fact that the polymers are insoluble offers purification advantage² for the product, because separation and washing of the chiral reaction products from the chiral catalyst requires simple gravity filtration instead of the complex chromatography technique. The polymers can be recycled and reused, which drastically reduces the manufacturing cost. These are immobilized species and are usually non-toxic⁶ Finally, the polymers may provide a unique microenvironment for the reaction, which may result in enhanced stereoselectivities⁴.

The rate of reduction of a ketone to an alcohol was found to be remarkably slower with the polymeric reagents than with the corresponding soluble reagents, and the degree of cross-linking of the polymer supports significantly affected the reaction rate⁷. The rate for the reduction of a series of alkyl phenyl ketones and dialkyl ketones have been found to be very slow with the 8% cross-linked polymeric reagent with only 17% conversion after 170 hours at 30°C⁷. However, recently Montanari and co-workers⁸ found that the rate of the reduction of a ketone to alcohol could be improved markedly by inserting some suitable spacers between the catalytic part, or the hydrophilic part, of the surfactant catalyst and the polymer backbone. Experimental results suggest that the reduction of ketones occurs at a relatively faster rate with the polymeric reagent from the polymer-bound (S)-N-benzylprolinol than that with the polymer-bound (S)-prolinol. The former reduction took about 48 hours for completion, whereas the later requires about 48-72 hours to reach 70-100% conversion⁷.

Enantioselective Reaction and the Role of Chiral Catalyst

In enantioselective synthesis, e.g. reduction of ketone to alcohol, polymer-based chiral catalysts can play a significant role. Here the function of such chiral catalysts matches with the role played by the enzymes in an enantioselective synthesis. In such reactions enzymes lead the chiral influence. Because of this fact, many enzymes find application in synthetic organic chemistry. However, they have one draw back and that is specificity. The act of enzymes can be best described by lock and key technology, which means only a particular enzyme is good for a particular reaction. This in turn increases the overall cost of the production, as these enzymes cannot be used in a broader way.

There are some inorganic catalysts that also play a similar role. For example, enantioselective hydrosilylation for the synthesis of alcohols from alkenes and alkynes gives about 95-99% enantiomeric excess product in the presence of chiral phosphine ligands. However, such inorganic catalysts are also reaction specific and may be toxic. With respect to both the inorganic catalysts and the enzymes' role in the enantioselective synthesis, the chiral micellar media offers a relatively clean viable alternative.

The advantage of chiral micelles is that they can concentrate the reactants within the micelle core. Thus, instead of locating through out the entire reaction medium, the reactants are now confined within a small area, which increases availability of the reactants for the reaction. These micelles also influence the orientation of the substrate and help to stabilize the substrate, the intermediate, or the product, too. Thus, they can alter the reaction rate, mechanism, and the stereochemistry of a synthesis. Unlike enzymes or inorganic catalysts, they can be applied to a range of reactions.

In addition of having all the above mentioned advantages the polymer-based catalysts can be recycled and reused along with the non-toxicity of the immobilized species. This thus offers an economical alternative to the traditional chiral solvents while at the same time reducing chemical waste. The polymer-based catalyst can best be prepared by carrying out polymerization in the presence of the functionalized monomer instead of grafting the functionalized group on the preformed polymer backbone. The major advantage is that the functionalized part of the polymer is then projected outward, toward the surface. As a result, the group can participate in interaction with the intermediate during the enantioselective synthesis and hence can control the reaction mechanism to give the desired product in a relatively higher percentage over the undesired one. The ^{13}C NMR of the ester using polymer-supported catalyst was taken with the relaxation-delay of 5 sec (usual relaxation-delay time of 1 sec) in presence of the chemical shift reagent $\text{Eu}(\text{fod})_3$.

The polymerization of the functionalized monomer may take place in two ways. During the polymerization process the polar functionalized monomer may come close to each other and the polymerization would take place on the outer side resulting in the development of chiral pool inside the polymer core. On the other hand, the functionalized monomers may be projected outward and the polymerization would take place inside. The actual way of the polymerization depends upon the nature of the solvent. Now this functionalized monomer part of the polymer can actually influence the reaction. They can have chemical or physical interaction with the reactant or can develop the chiral atmosphere that will influence the reaction to give the desired enantiomerically enriched or enantiomerically pure product. Any kind of physical or chemical interaction (for

example the formation of the hydrogen bond as predicted in our case) may improve the stability and selectivity. The type of polymer backbone used is polystyrene crosslinked with ~5% of divinylbenzene (DVB). The polymerization also includes the functionalized monomer based on (S)-leucinol in order to make some of the phenyl rings functionalized. This system is compatible with a wide range of solvents: e.g., DMF, NMP, alcohols, THF, acetonitrile, dichloromethane.

CHAPTER 2

EXPERIMENTAL

Instrumentation and Materials

The ^1H NMR and the 2D-cosy (^1H vs. ^1H) NMR spectra were recorded at 400 MHz on a JEOL Eclipse instrument. The ^{13}C NMR and the 2D-chsf (^1H vs. ^{13}C) NMR spectra were recorded at 100.6 MHz on a JEOL Eclipse instrument. TMS free CDCl_3 (Cambridge Isotopes) was used as the solvent for the NMR spectra. The infrared spectra were recorded on Mattson Genesis II FTIRTM Spectrometer. The purification of the samples was determined by gas chromatography on a Varion STAR 3400 $\text{C}\chi$ Gas Chromatograph. The ^1H and 2D-cosy NMR for 2-pentanol in presence of the chemical shift reagent was determined at a temperature of -25°C . The ^{13}C NMR of the ester made from the alcohol (S)-2-pentanol generated with the polymer-supported catalyst was taken in presence of the chemical shift reagent $\text{Eu}(\text{fod})_3$ with a relaxation delay of 5 sec.

(S)-(+)-Leucinol (96%), 1-bromohexadecane (97%), AIBN (2,2'-Azobisisobutyronitrile 98%), 4-vinylbenzyl chloride, (S)-2-methylbutyric acid, and sodium borohydride (99%) were obtained from Aldrich. Anhydrous sodium sulfate (Na_2SO_4) was obtained from EM SCIENCE, an affiliate of MERCK KGaA. Anhydrous magnesium sulfate (MgSO_4), divinylbenzene, styrene, Sodium hydride (57-63% oil dispersion), and N,N-dimethylformamide (DMF) were obtained from Alfa Aesar. Toluene, Tetrahydrofuran (THF), and 2-pentanone were obtained from Fischer Scientific. N,N-dimethylformamide and tetrahydrofuran (THF) were freshly redistilled onto molecular sieves. Divinylbenzene (DVB) and styrene were treated with aqueous sodium

thiosulfate solution. Remaining chemicals were used without further purification. Chemical shift reagent Eu(fod)₃ [Europium(III)tris(1,1,1,2,2,3,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)] was obtained from NORELL CHEMICAL CO. INC.

Preparation of the Hydrocarbon-based Surfactant

Preparation of (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol (**1**)^{17, 18, 19}

In a 100-mL three-neck round bottom flask equipped with a magnetic stirrer and a reflux condenser, (S)-2-amino-4-methyl-1-pentanol (leucinol) [3.90 mL, 30.00 mmol], 88% formic acid [5.25 mL, 121.80 mmol], and 9 mL water were added. The reaction mixture was then stirred for about 10-15 minutes and then 37% of formaldehyde [9.60 mL, 120.00 mmol] was added drop wise. The reaction mixture was heated to 100°C and the reflux was continued for 8 hrs. The solution was then cooled to room temperature and 30 mL 5M aqueous NaOH was added. The solution was extracted with diethyl ether (3*30 mL). The organic phase was washed with 20 mL of 5M NaOH and then with 30 mL brine and 30 mL distilled water. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed by rotovap to yield a pale yellow oil of (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol (2.92 g, 67%) **1**.

IR: $\nu_{\text{max}}/\text{cm}^{-1}$ 3412.51(-NH₂ and -OH), 2968, 1466.70, 1366.91, 1060.92;
¹H NMR (400MHz, CDCl₃); δ = 0.8652 ppm (6H, m, -CH(CH₃)₂), δ = 1.1455 ppm (2H, t, 3-HH), δ = 1.6556 ppm (1H, m, 4-H), δ = 2.2912 ppm (6H, s, -N(CH₃)₂), δ = 2.8692 ppm (1H, m, 2-H), δ = 3.2053 ppm and δ = 3.5121 ppm (1H, dd, 1-HH).
¹³C NMR (100 MHz, CDCl₃); δ = 22.2022 ppm (C₆), δ = 23.4027 ppm (C₅), δ = 24.7102 ppm (C₄), δ = 43.5738 ppm (C₃), δ = 50.6390 ppm (C₂), δ = 66.9869 ppm (C₁);

2D-chsf (^1H vs. ^{13}C) NMR; signal correlates $\delta = 0.8652$ ppm and $\delta = 22.2022$ ppm and $\delta = 23.4027$ ppm ($-\text{C}-(\text{C}_{5,6}\text{H}_3)_2$), signal correlates $\delta = 1.1455$ ppm (^1H) and $\delta = 43.5738$ ppm ($-\text{C}_3\text{H}_2$), signals correlates $\delta = 1.6556$ ppm and $\delta = 24.7102$ ppm ($-\text{C}_4\text{H}$), signal correlates $\delta = 2.8692$ ppm and $\delta = 50.6390$ ppm ($-\text{C}_2\text{H}$), signal correlates $\delta = 3.2053$ ppm and $\delta = 3.5121$ ppm and $\delta = 66.9869$ ppm ($-\text{C}_1\text{H}_2$).

Preparation of (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide (2)^{20, 21}

In a 100 mL three-neck round bottom flask equipped with a magnetic stirrer and a reflux condenser, compound **1** (2.9 g, 20 mmol), 1-bromohexadecane (6.30 g, 20 mmol), and absolute ethanol (10 mL) were stirred under the argon atmosphere. The mixture was refluxed for about 15 hours at a temperature of 80°C under the argon atmosphere. It was then cooled down to room temperature. The product was precipitated out with the addition of 75 mL of diethyl ether under ice-cold condition. The precipitate was then gravity filtered and the pale white color solid, (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide **2**, was recovered and recrystallized from ethyl acetate (2.06 g, 71%).

IR: $\text{Vmax}/\text{cm}^{-1}$ 3429.32 ($-\text{OH}$), 2958, 1485.74, 1367.78, 1052.92; ^1H NMR (400MHz, CDCl_3); $\delta = 0.8469$ ppm (6H, m, $\text{CH}(\text{CH}_3)_2$), $\delta = 1.2563$ ppm (3H, m, 3-HH), $\delta = 1.4523$ ppm (1H, m, 4-H), $\delta = 2.2335$ ppm ($-\text{N}(\text{CH}_3)_2$), $\delta = 2.6118$ ppm (1H, m, 2-H), $\delta = 3.1742$ ppm and $\delta = 3.4389$ ppm (1H, dd, 1-HH). ^{13}C NMR (100 MHz, CDCl_3); $\delta = 22.0646$ ppm (C_6), $\delta = 23.8462$ ppm (C_5), $\delta = 25.3908$ ppm (C_4), $\delta = 32.8307$ ppm (C_3), $\delta = 39.8500$ ppm (C_7 and C_8), $\delta = 61.2445$ ppm (C_1), $\delta = 62.3226$ ppm (C_2); 2D-

chsf (^1H vs. ^{13}C) NMR; signal correlates $\delta = 0.8469$ ppm and $\delta = 22.0646$ ppm and $\delta = 23.8462$ ppm ($\text{C}-(\text{C}_{5,6}\text{H}_3)_2$), signal correlates $\delta = 1.2563$ ppm (^1H) and $\delta = 32.8307$ ppm ($-\text{C}_3\text{H}_2$), signals correlates $\delta = 1.4523$ ppm and $\delta = 25.3908$ ppm ($-\text{C}_4\text{H}$), signal correlates $\delta = 2.2335$ ppm and $\delta = 39.8500$ ppm ($-\text{N}(\text{C}_{7,8}\text{H}_3)_2$), signal correlates $\delta = 2.6118$ ppm and $\delta = 62.3226$ ppm ($-\text{C}_2\text{H}$), signal correlates $\delta = 3.1742$ ppm and $\delta = 3.4389$ ppm and $\delta = 61.2445$ ppm ($-\text{C}_1\text{H}_2$).

Activity of the Surfactant

Reduction of 2-Pentanone to 2-Pentanol (3) ¹⁶

In a 250 mL round bottom flask equipped with a magnetic stirrer, 2-pentanone (20 g), ethanol (50 mL, 95%), and compound **2**, the hydrocarbon based surfactant were mixed. The solution was cooled in an ice-water bath contained in a large beaker for 15 minutes. While the flask was in ice-water bath, sodium borohydride (2.0 g) was added carefully. After the vigorous reaction had ceased, the flask was removed from the ice-water bath, and allowed to stand at room temperature for 45 minutes. After 45 minutes, 5 mL of 5 M sodium hydroxide solution was added to decompose the borate ester. Water (40 mL) was added to separate the solution into two layers. The solution was extracted with diethyl ether (3*30 mL) and dried with anhydrous sodium sulfate. Diethyl ether was finally removed by rotovap. It was subjected for fractional distillation to remove ethanol from the 2-pentanol (4 g, 25%) **3**.

^1H NMR (400MHz, CDCl_3); $\delta = 0.9220$ ppm (3H, t, 5-HH), $\delta = 1.1775$ ppm (3H, d, 1-HH), $\delta = 1.4047$ ppm (4H, m, 3-HH, 4-HH), $\delta = 3.7878$ ppm (1H, m, 2-H).

^{13}C NMR (100 MHz, CDCl_3); $\delta = 14.1506$ ppm (C_5), $\delta = 19.0214$ ppm (C_4),

$\delta = 23.5480$ ppm (C_1), $\delta = 41.5934$ ppm (C_3), $\delta = 67.9733$ ppm (C_2); 2D-cosy (^1H - ^1H) NMR; the signal correlating triplet at $\delta = 0.9220$ ppm and multiplet at $\delta = 1.4047$ ppm represents the influence of the hydrogens attached to C_4 and C_3 carbon atoms on the hydrogens of C_5 . The signal correlating the multiplet at $\delta = 3.7878$ ppm and the doublet at $\delta = 1.1775$ ppm represents the influence of hydrogen attached to C_2 on the hydrogens of C_1 carbon atom. The signals correlating the multiplet at $\delta = 3.7878$ ppm, the doublet at $\delta = 1.1755$ ppm, and the triplet at $\delta = 0.9220$ ppm along with the multiplet at $\delta = 1.4047$ ppm represents the influence of hydrogens attached to C_2 , C_1 , and C_5 on the hydrogens attached to C_3 , C_4 .

Esterification of the 2-Pentanol (4)³

(S)-(+)-2-methylbutyric acid (1.0 g, 9.80 mmol) and 4.31 g (49.00 mmol) of 2-pentanol **3** and iodine (50 mg) were taken in a 100 mL of round bottom flask equipped with a magnetic stirrer. It was then refluxed for about 12 hours and was monitored periodically by TLC. After the reaction was completed, the excess alcohol was removed under reduced pressure and the residue was extracted with diethyl ether. The ether extract was then washed with a solution of sodium thiosulfate and subsequently with distilled water. It was then dried over anhydrous sodium sulfate and was concentrated in vacuum to yield the crude product. It was finally purified by column chromatography (hexane: ether, 8:3) to obtain the desired carboxylic ester **4**.

^1H NMR (400MHz, CDCl_3); $\delta = 4.8951$ ppm (1H, m, 4-H), $\delta = 2.3022$ ppm (1H, m, 6-H), $\delta = 1.6127$ ppm and $\delta = 1.4074$ (2-H, m, H_a , H_b), $\delta = 1.2883$ ppm (2-H, m, H_p , H_q). ^{13}C NMR (100 MHz, CDCl_3); $\delta = 13.9518$ ppm (C_1), $\delta = 20.0996$ ppm

(C₂), $\delta = 41.4710$ ppm (C₃), $\delta = 70.2978$ ppm (C₄), $\delta = 176.4749$ ppm (C₅),
 $\delta = 38.1775$ ppm (C₆), $\delta = 36.8589$ ppm (C₇), $\delta = 11.6579$ ppm (C₈), $\delta = 18.9678$ ppm
(C₉), $\delta = 16.7810$ ppm (C₁₀).

Preparation of the Polymer-supported Catalyst

Formation of the Functionalized Monomer (5)⁴

In a 200 mL three-neck round bottom flask equipped with a magnetic stirrer and a reflux condenser, **1** (1.0 g, 6.85 mmol) and 50 mL dry DMF were placed under the argon atmosphere. NaH (60% in mineral oil, 0.29 g, 7.25 mmol) was added slowly with constant stirring. After the complete evolution of hydrogen 4-vinylbenzyl chloride (1.18 g, 7.74 mmol, dried over molecular sieves) in dry DMF (20 mL) was added. The resulting mixture was then stirred at room temperature for 5 hours under the argon atmosphere. Water (40 mL) was added and the reaction mixture was extracted with ethyl ether (3*30 mL). The ether extract was dried over anhydrous magnesium sulfate and was evaporated to give a pale yellow color liquid product **5** (1.26g, 70.2%).

IR: V_{\max}/cm^{-1} Absence of any peak around 3200 cm^{-1} and 3500 cm^{-1} represents the fact that the product did not have any hydroxyl group. The other important peaks include 2953.51, 2926.51, 1742.89, and 1630.44. ¹H NMR (400MHz, CDCl₃); $\delta = 0.8753$ ppm (6H, m, CH(CH₃)₂), $\delta = 1.2471$ ppm (2H, m, 3-HH), $\delta = 1.6080$ ppm (1H, m, 4-H), $\delta = 2.2262$ ppm (-N(CH₃)₂), $\delta = 2.7373$ ppm (1H, m, 2-H), $\delta = 3.3628$ ppm and $\delta = 3.4975$ ppm (1H, m, m, 1-HH). $\delta = 4.4958$ ppm (2H, s, 9-HH), $\delta = 5.2120$ ppm and $\delta = 5.7149$ ppm (two single H. d, 17-H_a and 17-H_b), $\delta = 6.7123$ ppm (1H, m, 16-H), $\delta = 7.3479$ ppm and $\delta = 7.3928$ ppm (4H, m, d-HH and e-HH). ¹³C NMR (100 MHz,

CDCl₃); $\delta = 22.7298$ ppm (C₆), $\delta = 23.0892$ ppm (C₅), $\delta = 25.3984$ ppm (C₄),
 $\delta = 36.8526$ ppm (C₃), $\delta = 41.1499$ ppm (C₇ and C₈), $\delta = 61.2904$ ppm (C₉),
 $\delta = 69.9996$ ppm (C₁), $\delta = 72.9587$ ppm (C₂), $\delta = 113.7673$ ppm (C₁₅), $\delta = 126.2461$ ppm
(C₁₁), $\delta = 127.8365$ ppm (C₁₂), $\delta = 136.6375$ ppm (C₁₄), $\delta = 136.9127$ ppm (C₁₀),
 $\delta = 138.2585$ ppm (C₁₃);

From the 2D-cosy (¹H vs. ¹H) NMR of the **5**, the correlation between the two signals at $\delta = 0.8753$ ppm and $\delta = 1.6080$ ppm shows the influence of H_z on the hydrogen atoms attached to the carbon atoms C₅ and C₆. However, the two signals on the 2D diagram showed the influence of each one on the other. The signal for the hydrogen H_p at $\delta = 2.7373$ ppm correlates with the signals for the hydrogen atoms H_m and H_n at $\delta = 3.3628$ ppm and at $\delta = 3.4975$ ppm suggesting the influence of the hydrogen attached to C₃ carbon atom on the hydrogens attached to C₁ carbon atom. Similarly the 2D-cosy NMR also shows the influence of H_a and H_b on each other as well as the influence of H_c on H_a and H_b. the two hydrogens attached to C₁₂ and C₁₁ carbon atoms do not have any hydrogen atom other than themselves and the 2D shows the impact of H_d on H_f and vice-a-versa.

Polymerization of the Functionalized Monomer (6)⁴

In a 200 mL three-neck round bottom flask equipped with a magnetic stirrer, a solution of 0.38 g of **5**, 0.38 g of divinylbenzene (DVB) and 6 g of styrene in 40mL of THF and 40 mL of toluene was taken. Water (50 mL) was added to develop two different phases. 0.50 g of AIBN was added as an initiator for the reaction. The temperature was raised to 80⁰C and the reaction mixture was stirred vigorously for 18 hours. The resulting

beads were filtered and washed with water. Further washing was done with 50 mL each of water-methanol, methanol, THF, and methanol followed by drying under reduced pressure at 40⁰C. This resulted in the formation of the desired polymer **6**.

A comparative analysis was performed for the ¹H NMR and ¹³C NMR of the polymer-based catalyst with that of the functionalized monomer and the crosslinked-polystyrene with out the functional group. Because the polymer-based catalyst produced is virtually insoluble even in the solvent CDCl₃ for the NMR, only few peaks were observed. However, this was sufficient enough to identify the structure of the product. For example, the peaks at $\delta = 7.2526$ ppm and $\delta = 7.1940$ ppm represent the hydrogen atoms as a part of the benzene ring of the polystyrene based catalyst. Similarly the peaks at $\delta = 6.7123$ ppm (1H, m), $\delta = 5.2120$ ppm and $\delta = 5.7149$ ppm (two single H. d, 17-H_a and 17-H_b) are as expected from previous work with **5**. At $\delta = 2.5205$ ppm, we see the signal for the polymer backbone. ¹³C NMR (100 MHz, CDCl₃) analysis shows peaks at $\delta = 21.5829$ ppm (C₆), $\delta = 23.5556$ ppm (C₅), and $\delta = 25.7119$ ppm (C₄) representing the carbon atoms in the functionalized monomer. The peak at $\delta = 128.3259$ ppm represents the presence of the aromatic ring, $\delta = 40.6605$ ppm (C₇ and C₈, the carbon atoms attached to the nitrogen atom of the functionalized part of the polymer catalyst), $\delta = 61.2904$ ppm (the carbon attached to benzene group), and $\delta = 137.9756$ ppm represents the aromatic part coming from the functionalized monomer.

CHAPTER 3

RESULTS AND DISCUSSION

Synthesis of the Hydrocarbon-based Surfactant

Preparation of the Methylated Derivative of Leucinol

The preparation of the chiral surfactant began with the methylation of a commercially available amino acid derivative, (S)-leucinol. The leucinol was dimethylated in the presence of formaldehyde and formic acid as shown in the Figure 6. This reaction formed (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol, compound **1** in good yield. The overall reaction has been shown below.

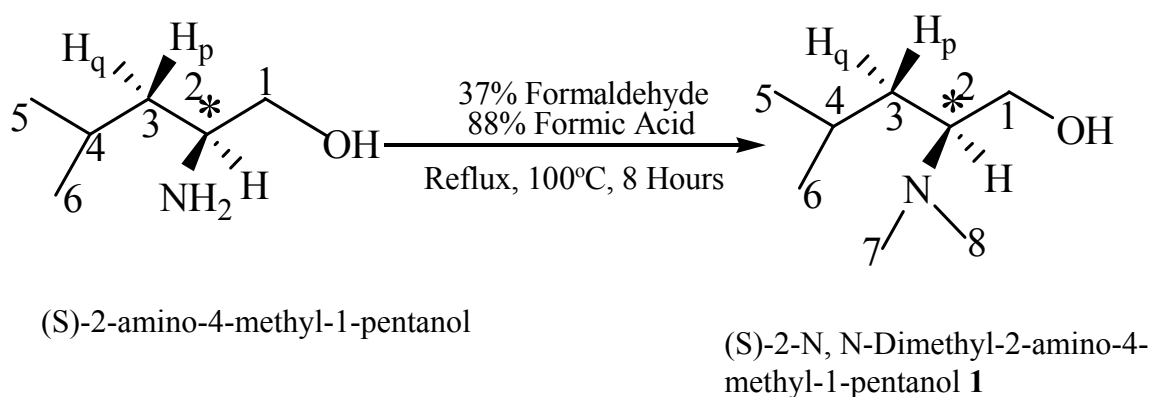
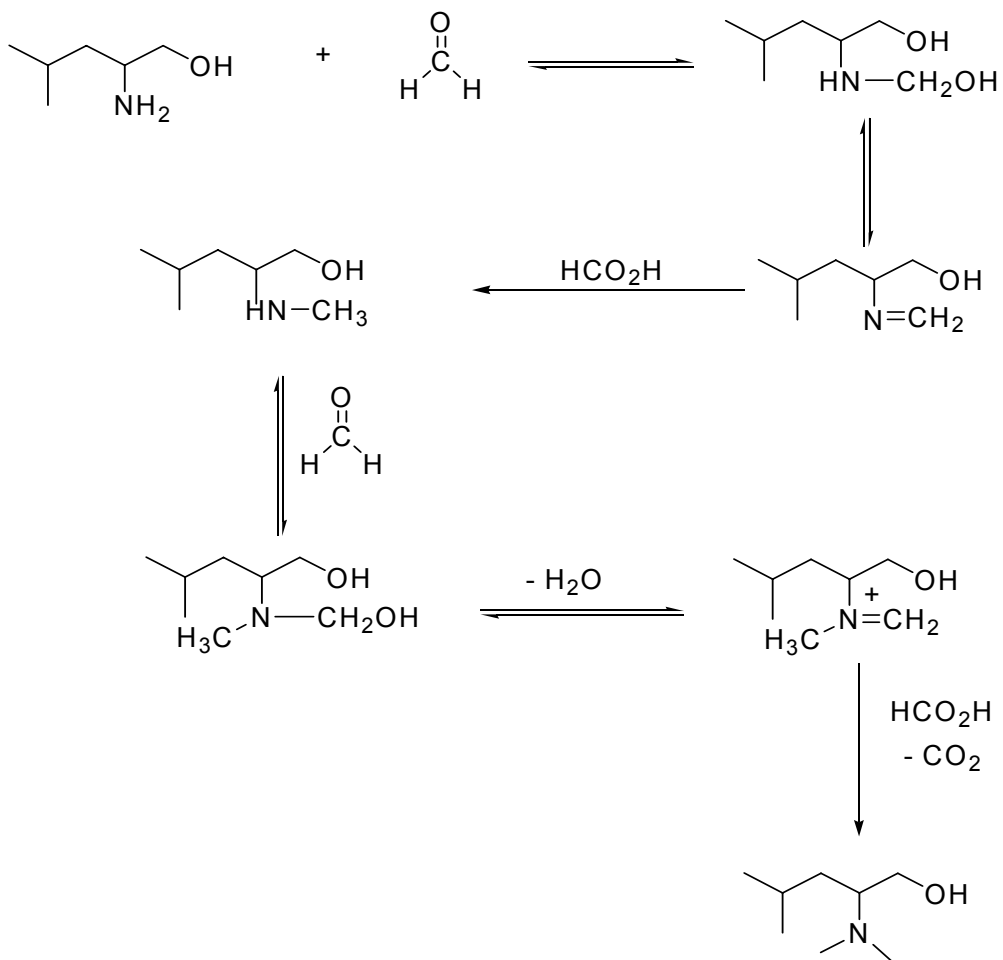


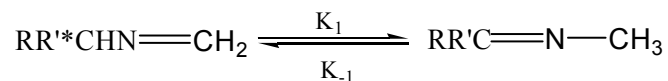
Figure 6. Formation of leucinol derivative.

The reaction proceeds through the formation of a Schiff base by reduction with the formic acid and subsequent loss of carbon dioxide. Addition of a second mole of formaldehyde readily leads to the formation of tertiary amine species as shown in the Scheme 1⁹.



Scheme 1. Mechanism for methylation of leucinol.

It has been demonstrated that the methylation of an optically active amine in which the nitrogen atom is connected to an asymmetric carbon atom does not lead to loss of optical activity in the resulting tertiary amine⁹.



The comparison of the FTIR diagram for (S)-leucinol and that of N,N-dimethyl leucinol, **1** (Figures 7 and 11) gave some information about the incorporation of the two-

methyl groups at the nitrogen part of the leucinol. The FTIR diagram for (S)-leucinol showed a broad peak at 3412.51 cm^{-1} . The other important FTIR signals include 2968 cm^{-1} , 1466.70 cm^{-1} , 1366.91 cm^{-1} , and 1060.92 cm^{-1} . For **1** the FTIR diagram showed a relatively narrow peak around 3429.32 cm^{-1} . This is because the peak at 3412.51 cm^{-1} for (S)-leucinol arises due to the functional groups $-\text{OH}$ and $-\text{NH}_2$ whereas in case of the methylated derivative of leucinol there is no $-\text{NH}_2$ making the peak around 3400 cm^{-1} relatively a narrower one. The other important FTIR signals are 2950 cm^{-1} , 1485.74 cm^{-1} , 1367.78 cm^{-1} , and 1052.92 cm^{-1} .

Comparison of the ^1H , ^{13}C NMR, and 2D-chsf (^1H vs. ^{13}C) NMR of both (S)-leucinol and N,N-dimethyl leucinol confirmed the structure of the product. For the (S)-leucinol (Figure 8) in the ^1H NMR spectrum the multiplet at $\delta = 0.8652\text{ ppm}$ represents the hydrogens attached to the two terminal $-\text{CH}_3$ groups, $(-\text{C}(\text{CH}_3)_2)$. The multiplet at $\delta = 1.1455\text{ ppm}$ represents the two hydrogens attached to the C_3 carbon atom. The multiplet at $\delta = 1.6556\text{ ppm}$ represents the multiplet for the hydrogen attached to the C_4 carbon atom. The singlet at $\delta = 2.2912\text{ ppm}$ represents the presence of $-\text{NH}_2$ group. The multiplet at $\delta = 2.8692\text{ ppm}$ represents a single hydrogen attached to the C_2 carbon atom. The two multiplets at $\delta = 3.2053\text{ ppm}$ and at $\delta = 3.5121\text{ ppm}$ represent the hydrogens attached to the C_1 carbon atom. These hydrogens (i.e. the two hydrogens attached to C_1) are pro-chiral in nature and there by shows two multiplets instead of a single one.

From the ^{13}C NMR (Figure 9), the NMR signals at $\delta = 22.2022\text{ ppm}$ and at $\delta = 23.4027\text{ ppm}$ represent the non-equivalent C_5 and C_6 carbon atoms, signal at $\delta = 24.7102\text{ ppm}$ represents C_4 , signal at $\delta = 43.5738\text{ ppm}$ represents C_3 , signal at

$\delta = 50.6390$ ppm represents C_2 carbon atom while the signal at $\delta = 66.9869$ ppm represents the C_1 carbon atom.

In ^1H NMR of the (S)-2-N,N-dimethyl leucinol **1** (Figure 12) the multiplet at $\delta = 0.8469$ ppm represents the hydrogens of the two terminal $-\text{CH}_3$ groups ($-\text{C}(\text{CH}_3)_2$). The multiplet at $\delta = 1.2563$ ppm represents the two hydrogens attached to the C_3 carbon atom ($-\text{CH}_2$). The multiplet at $\delta = 1.4523$ ppm represents the multiplet for the hydrogen attached to the C_4 carbon atom ($-\text{CH}$). The large singlet at $\delta = 2.2335$ ppm represents the hydrogens of the two methyl groups attached with the nitrogen of the amine part of the leucinol derivative ($-\text{N}(\text{CH}_3)_2$). This is the basic difference between leucinol and its methyl derivative. The multiplet at $\delta = 2.6118$ ppm represents a single hydrogen attached to the C_2 carbon atom. The two multiplets at $\delta = 3.1742$ ppm and at $\delta = 3.4389$ ppm represent the hydrogens attached to the C_1 carbon atom. These two hydrogens (i.e. the hydrogens attached to C_1) are pro-chiral in nature and therefore show two multiplets instead of a single one.

From the ^{13}C NMR (Figure 13) for **1**, the NMR signals at $\delta = 22.0646$ ppm and at $\delta = 23.8462$ ppm represent non-equivalent C_5 and C_6 carbon atoms, signal at $\delta = 25.3908$ ppm represents C_4 , signal at $\delta = 32.8307$ ppm represents C_3 , signal at $\delta = 39.8500$ ppm represents the carbon atoms C_7 and C_8 , signal at $\delta = 61.2445$ ppm represents the C_1 carbon atom while the signal at $\delta = 62.3226$ ppm represents the C_2 carbon atom.

The 2D-chsf NMR spectrum of the leucinol (Figure 10) and its derivative dimethylated leucinol (Figure 14) helps to identify the structural difference of the two compounds. In comparison to the leucinol, the methylated derivative has two methyl groups attached to the nitrogen atom of the amine part. The signal correlating the large

singlet of the ^1H NMR at $\delta = 2.2335$ ppm and the ^{13}C peak at $\delta = 39.8500$ ppm represents those two methyl groups attached to the nitrogen atom of compound **2**. In case of leucinol there is no such signal in its 2D-chsf NMR. The detailed discussion about the 2D-chsf spectrums of both leucinol and its methyl derivative is given in the appendix.

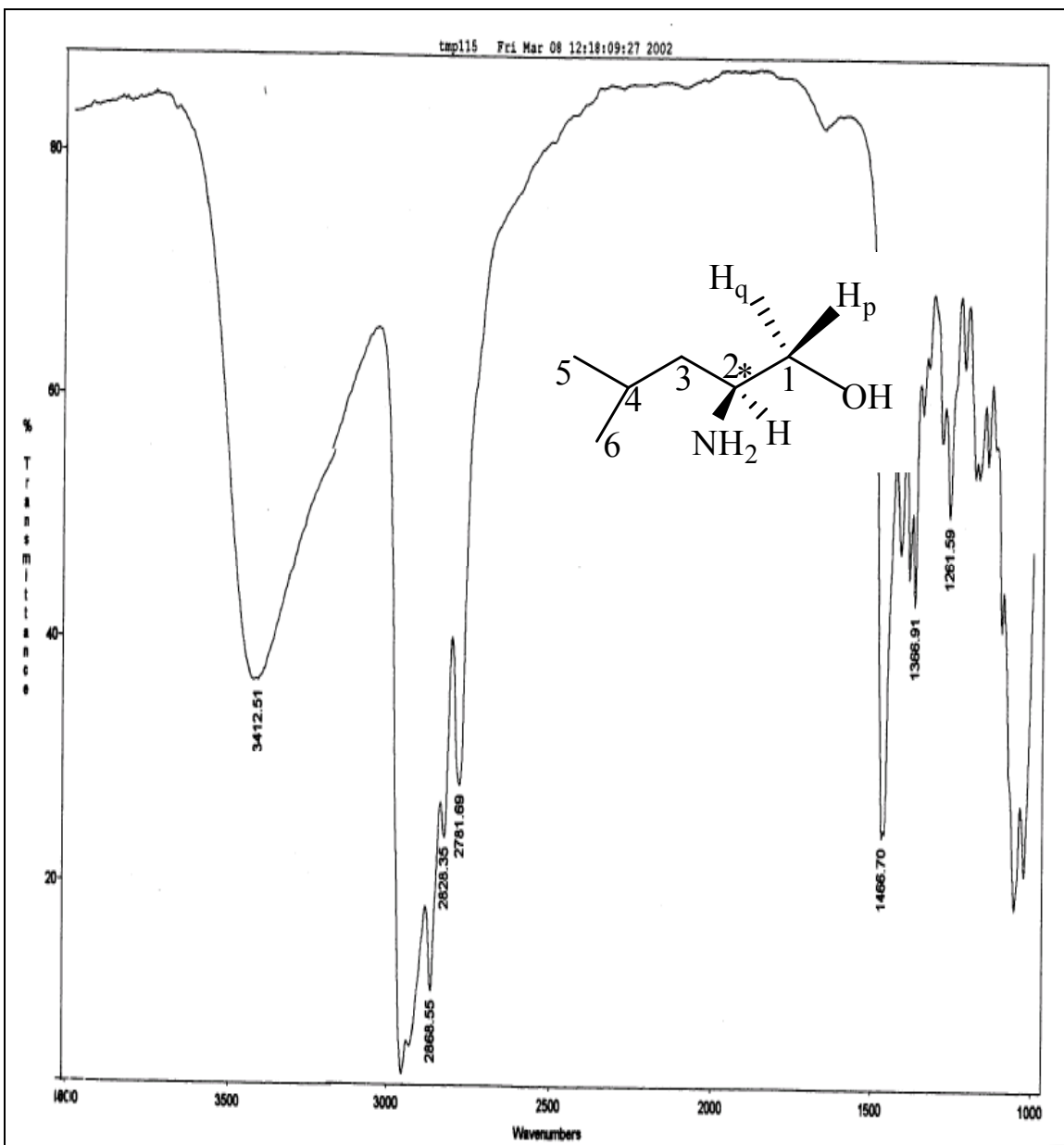


Figure 7. FTIR of (S)-2-amino-4-methyl-1-pentanol.

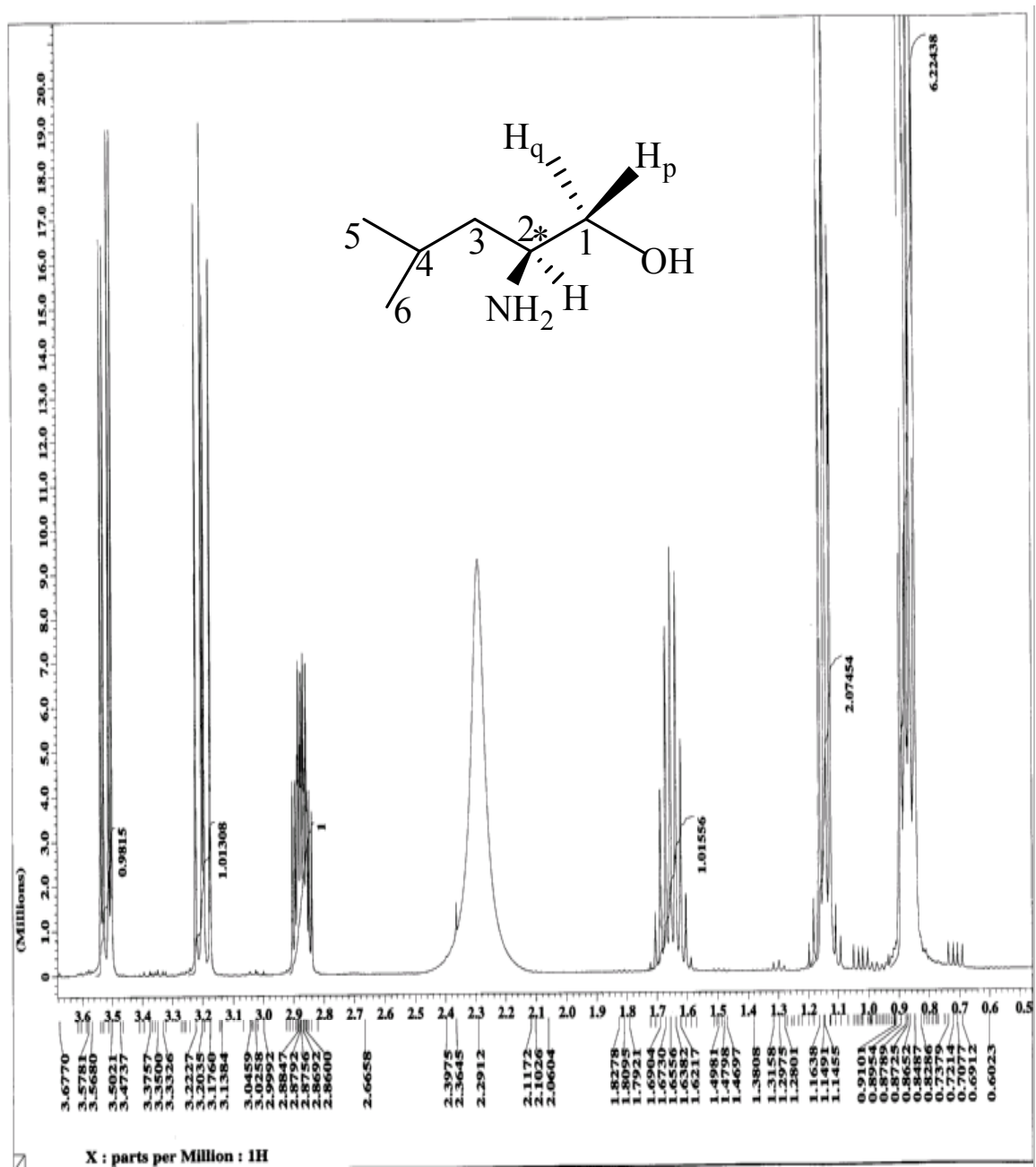


Figure 8. ¹H NMR of (S)-2-amino-4-methyl-1-pentanol.

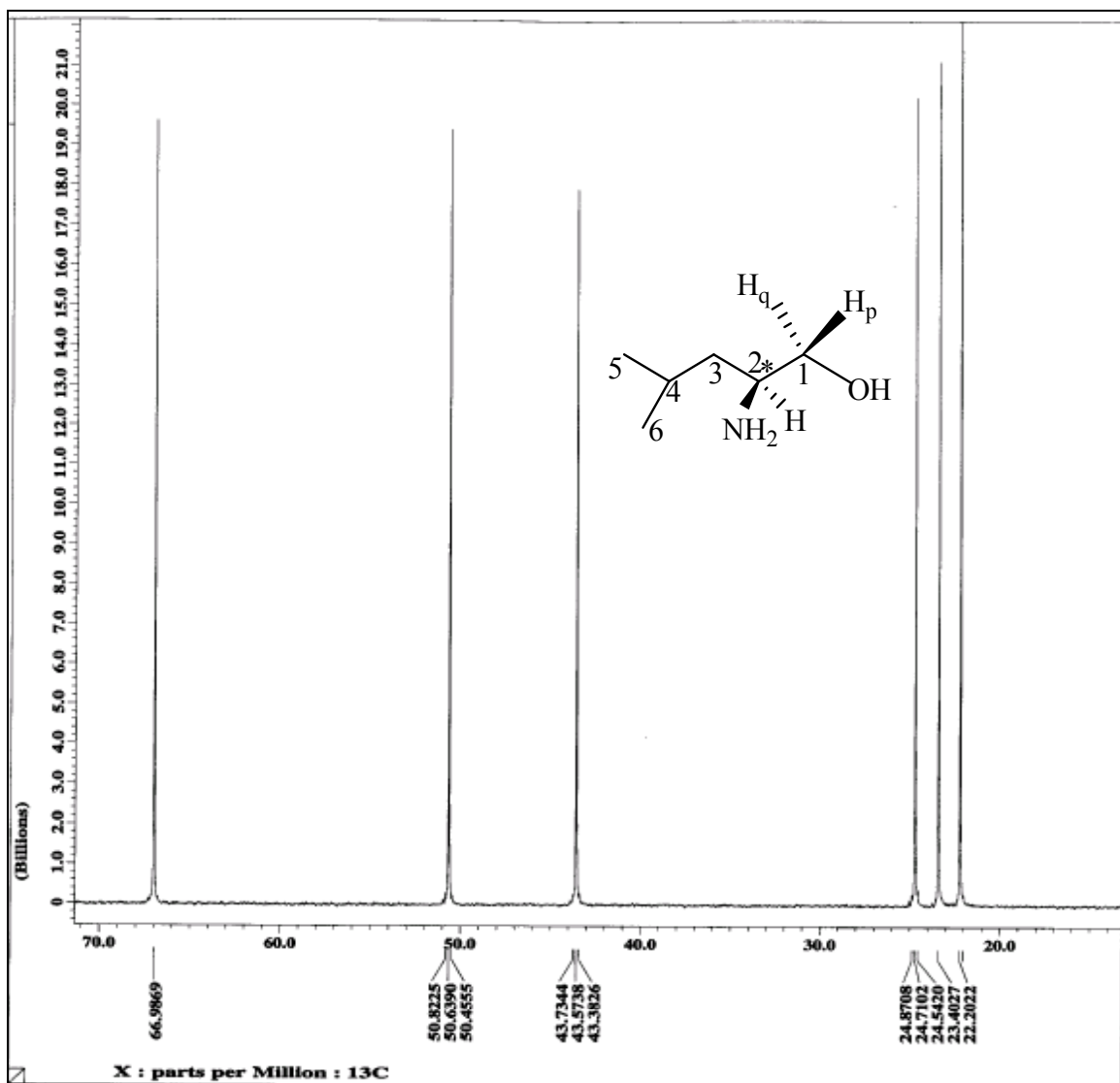


Figure 9. ¹³C NMR of (S)-2-amino-4-methyl-1-pentanol.

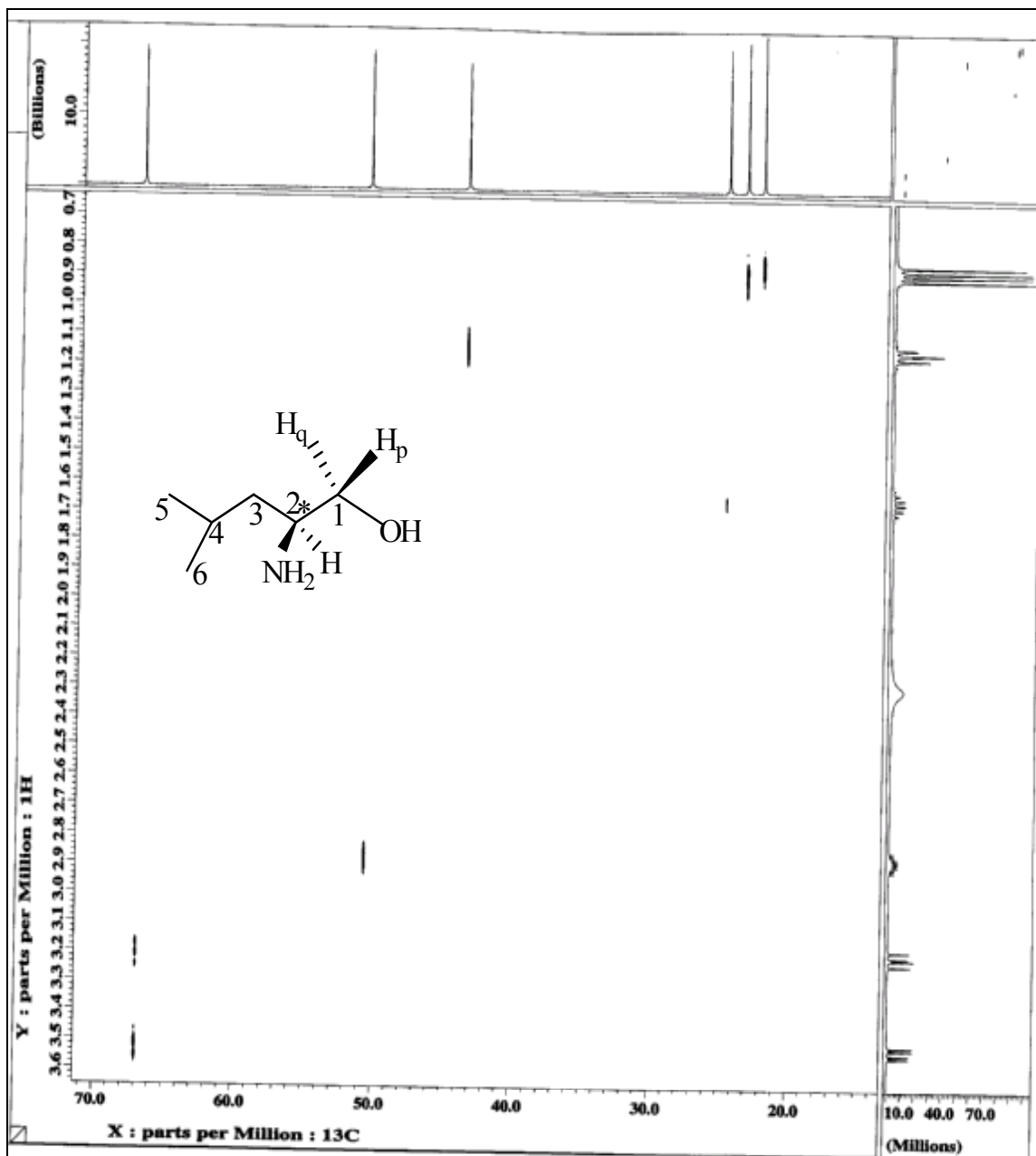


Figure 10. 2D-chsf NMR of (S)-2-amino-4-methyl-1-pentanol.

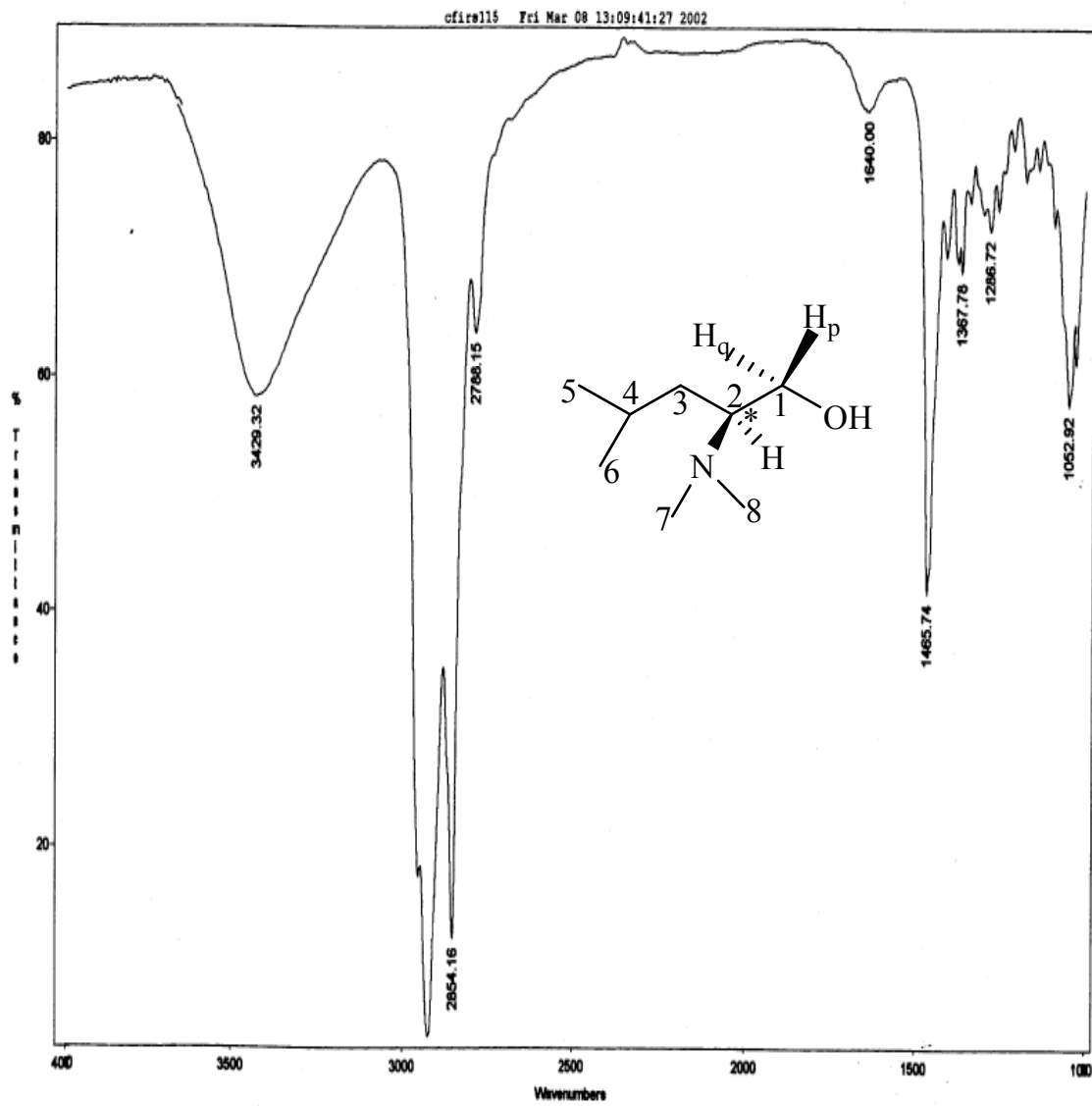


Figure 11. FTIR of (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol.

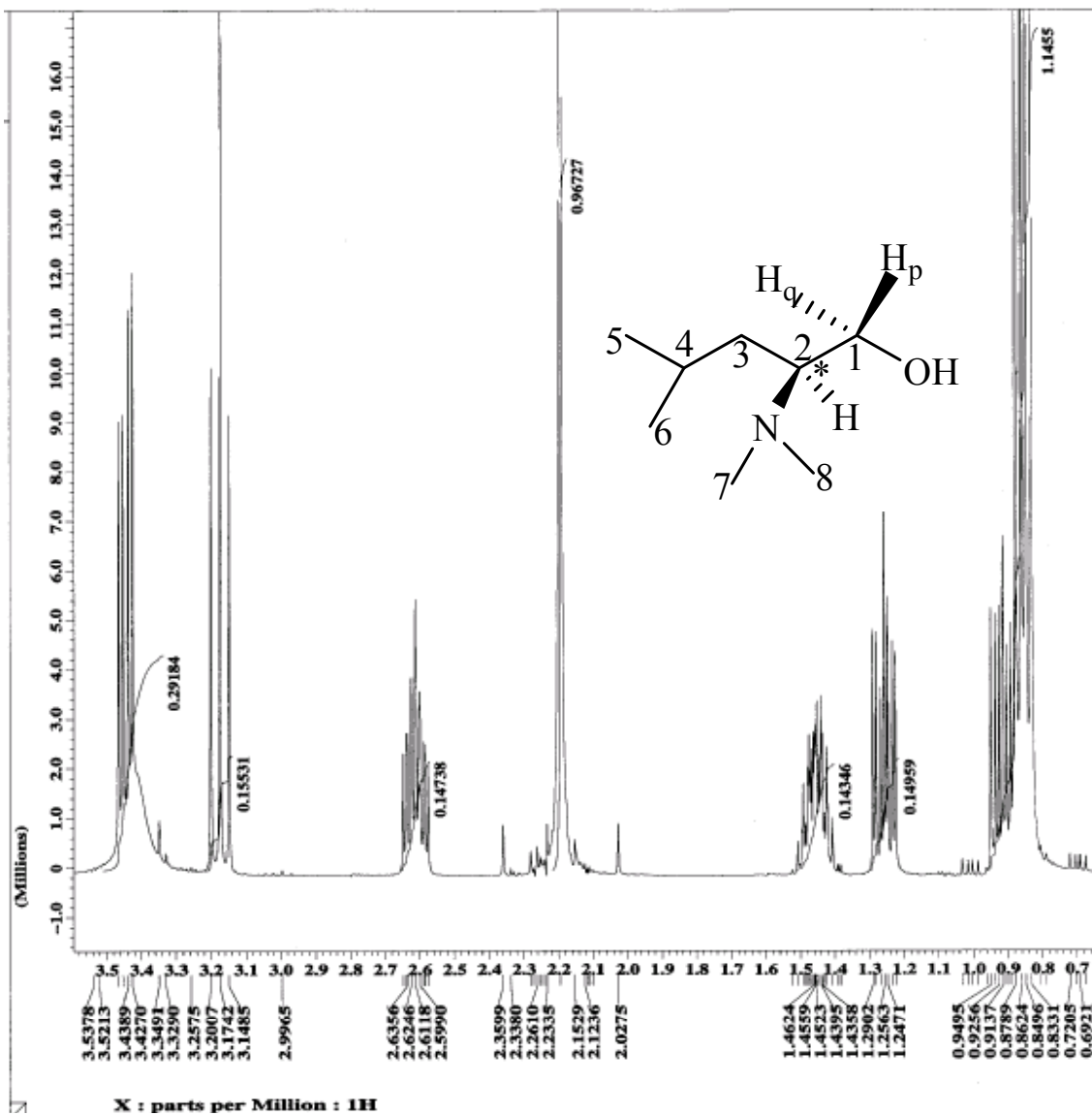


Figure 12. ^1H NMR of (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol.

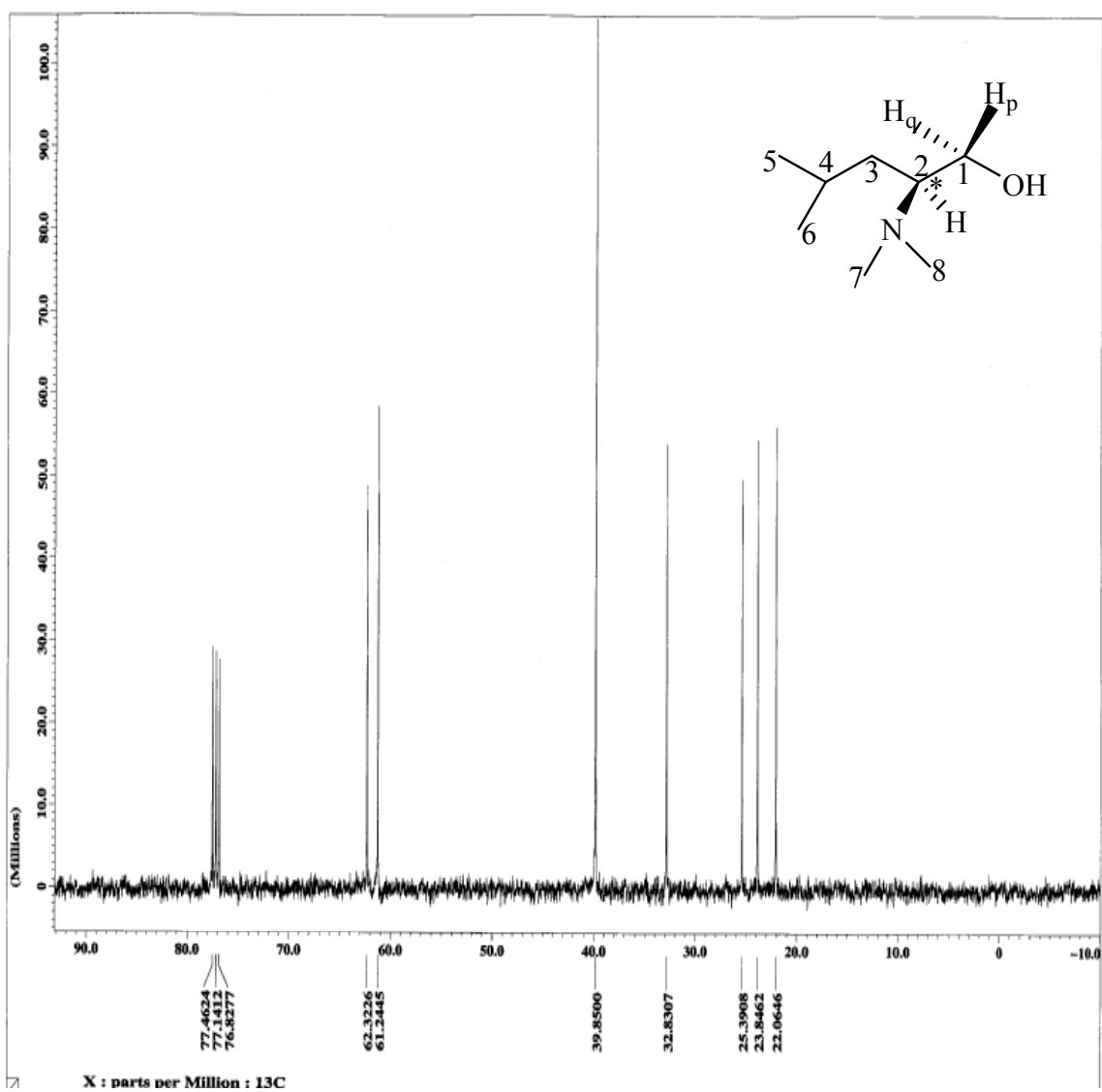


Figure 13. ^{13}C NMR of (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol.

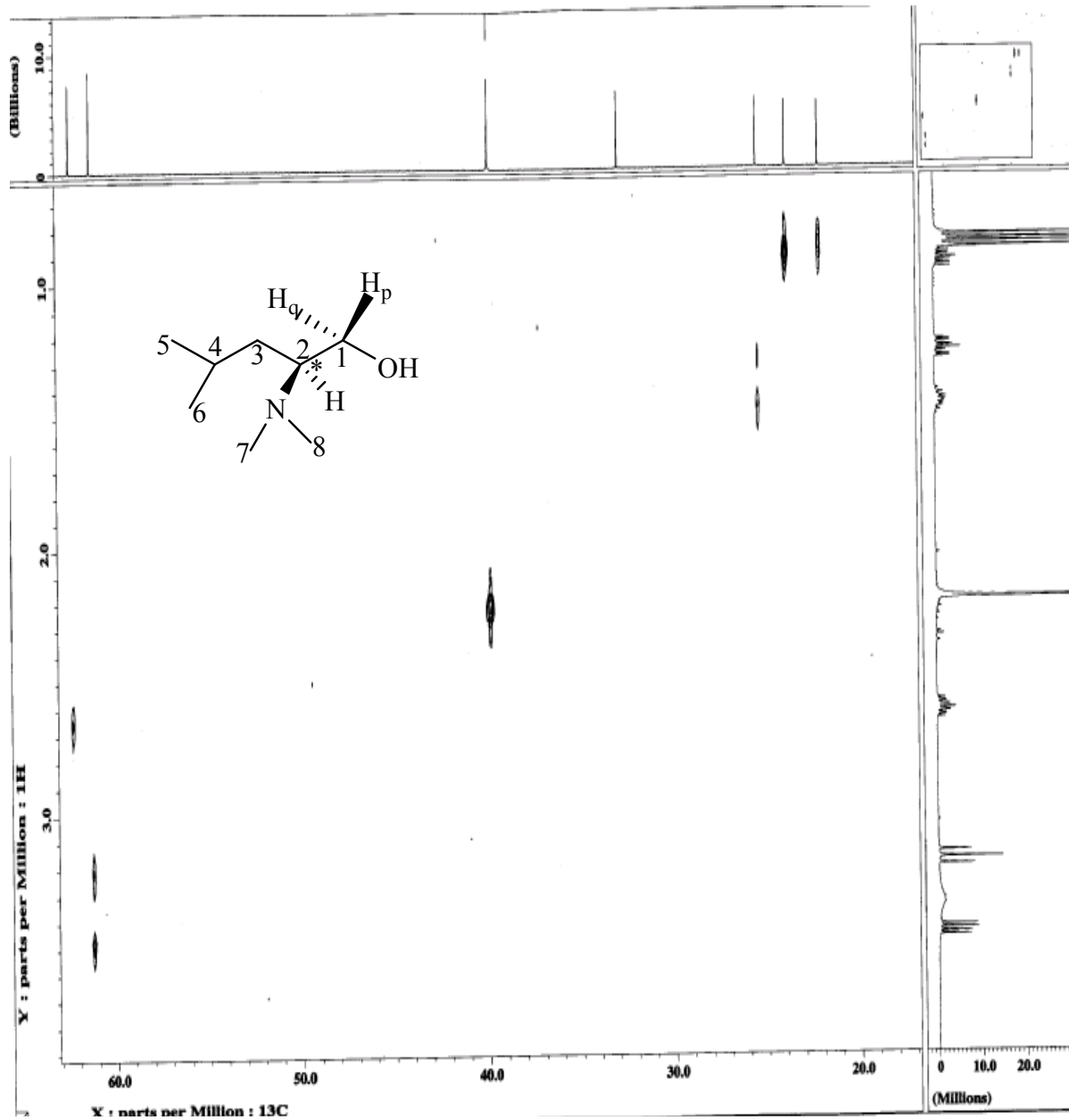
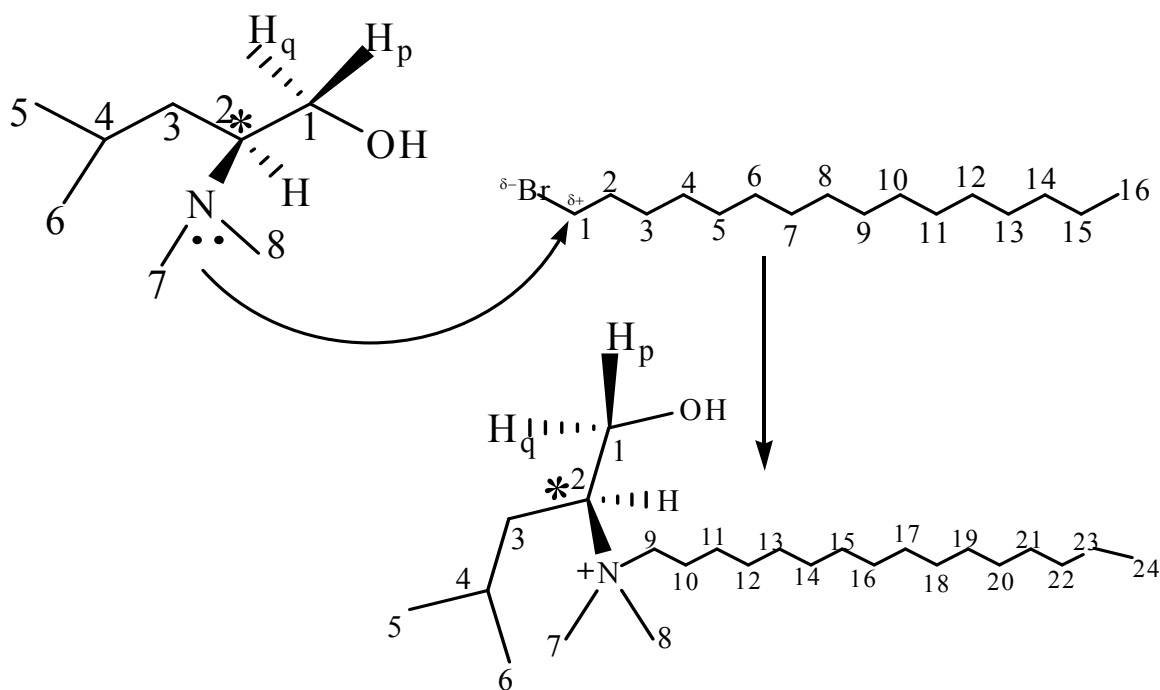


Figure 14. 2D-CHSF NMR of (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol.

Preparation of the Hydrocarbon-based Surfactant

The tertiary amine was attached to the long hydrocarbon chain by refluxing the amine derivative **1** with 1-bromohexadecane as shown in Scheme 2. The reaction involves a standard nucleophilic substitution reaction. The nitrogen of the leucinol derivative uses its lone pair to attack the carbon of the C-Br bond of the bromohexadecane. Bromine is more electronegative than carbon making the carbon of the C-Br partially positively charged (δ^+) and makes it susceptible to the nucleophilic substitution reaction, which develops the desired C-N linkage with the elimination of the bromide ion. The Scheme 2 shows the mechanism of this reaction. This 16-member long hydrocarbon chain actually forms the hydrophobic part of the proposed surfactant where as the methylated derivative forms the hydrophilic part.



Scheme 2. Formation of hydrocarbon-based surfactant.

The FTIR diagram for (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide **2** (Figure 16), the hydrocarbon-based surfactant, gave information about the N-C linkage. In the FTIR diagram of 1-bromohexadecane (Figure 15) there is a sharp signal around 1400 cm^{-1} representing the C-Br linkage. During the reaction between methylated leucinol and 1-bromo hexadecane, the nitrogen was expected to use its lone pair to attack at the carbon attaching to the bromine. This was expected to develop an N—C linkage along with the elimination of bromide ion. Therefore, in the FTIR diagram of the surfactant would expect to show the absence of any sharp peak around 1400 cm^{-1} . This is indeed what was observed confirming the formation of N-C linkage.

Comparison of the ^1H NMR (Figure 17), ^{13}C NMR (Figure 18), and 2D-chsf (^1H vs. ^{13}C) NMR (Figure 19) of (S)- 2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide confirmed the structure of the product. In the ^1H NMR of the hydrocarbon surfactant the triplet at $\delta = 0.8469$ ppm represents three hydrogens attached with the terminal carbon of the long hydrocarbon chain (C_{24}). The large multiplet at $\delta = 1.2206$ ppm represents the hydrogens of the long hydrocarbon chain. The two singlets at $\delta = 3.2410$ ppm and $\delta = 3.3546$ ppm represent three hydrogens each attached to the carbon atoms C_7 and C_8 (i.e. hydrogens of $-\text{N}(\text{CH}_3)_2$). The multiplet at $\delta = 3.4782$ ppm represents the hydrogen attached to the carbon atom C_2 . Being closer to the more electronegative nitrogen, it shows the down field shift. The two doublets at $\delta = 3.9289$ ppm and at $\delta = 4.2604$ ppm represent the two prochiral hydrogens attached to the carbon atom C_1 . The multiplet at $\delta = 3.6916$ ppm represents the two hydrogens of the methylene group attached to the nitrogen of the amine part ($-\text{N}-\text{C}_9\text{H}_2-$).

The ^{13}C NMR signal (Figure 18) at $\delta = 14.2118$ ppm represents the last carbon of the long hydrocarbon chain of the surfactant (i.e. C_{24}). The signal at $\delta = 22.8828$ ppm represents the carbon atom adjacent to the terminal carbon atom (i.e. C_{23}). The broad signal at $\delta = 29.4816$ ppm represents 12 carbon atoms (i.e. $\text{C}_{11}\text{-C}_{22}$), the part of the long hydrocarbon tail of the surfactant. The signal at $\delta = 31.9972$ ppm represents the carbon atom C_{10} of the hydrocarbon. Because it is relatively close to nitrogen of the amine part of the surfactant, C_{10} appears at a relatively down field shift compared to the other carbon atoms of the hydrocarbon part. Similarly the carbon atom C_{23} is far away from the amine part and thereby shows relatively upfield shift. The signal at $\delta = 57.5666$ ppm represents the carbon atom attached to the nitrogen of the quaternary amine part (i.e. C_2). The signal at $\delta = 64.1501$ ppm represents the first carbon of the long hydrocarbon tail of the surfactant attached to the nitrogen part (i.e. C_9), and finally the signal at $\delta = 71.6665$ ppm represents the carbon attached to the hydroxyl group (i.e. C_1).

The 2D-chsf (i.e. ^1H vs. ^{13}C) (Figure 19) of the hydrocarbon surfactant gives a lot of information for the identification of the structure of the surfactant. Only the important peaks are mentioned here, while the detailed discussion is in the appendix. A signal correlating the multiplet at $\delta = 0.8469$ ppm of the ^1H NMR and the singlet at $\delta = 14.2118$ ppm of the ^{13}C NMR represents the fact that that particular carbon is C_{24} , i.e. the last carbon atom of the long hydrocarbon tail of the surfactant. The carbon atom of the long hydrocarbon tail adjacent to the nitrogen atom is expected to show a down field shift. The signal correlating the multiplet at $\delta = 3.6916$ ppm of the ^1H NMR with the singlet at $\delta = 64.1501$ ppm of the ^{13}C NMR justifies this. Finally, the two hydrogens attached to the carbon atom C_1 adjacent to the hydroxyl group are pro-chiral in nature and this can be proved with the 2D spectrum of

the surfactant. . The two doublets at $\delta = 4.2421$ ppm and at $\delta = 3.9069$ ppm correlate with the one singlet at $\delta = 71.6665$ ppm of the ^{13}C NMR, which means that particular carbon atom has two different hydrogens showing two different signals on the ^1H NMR spectrum.

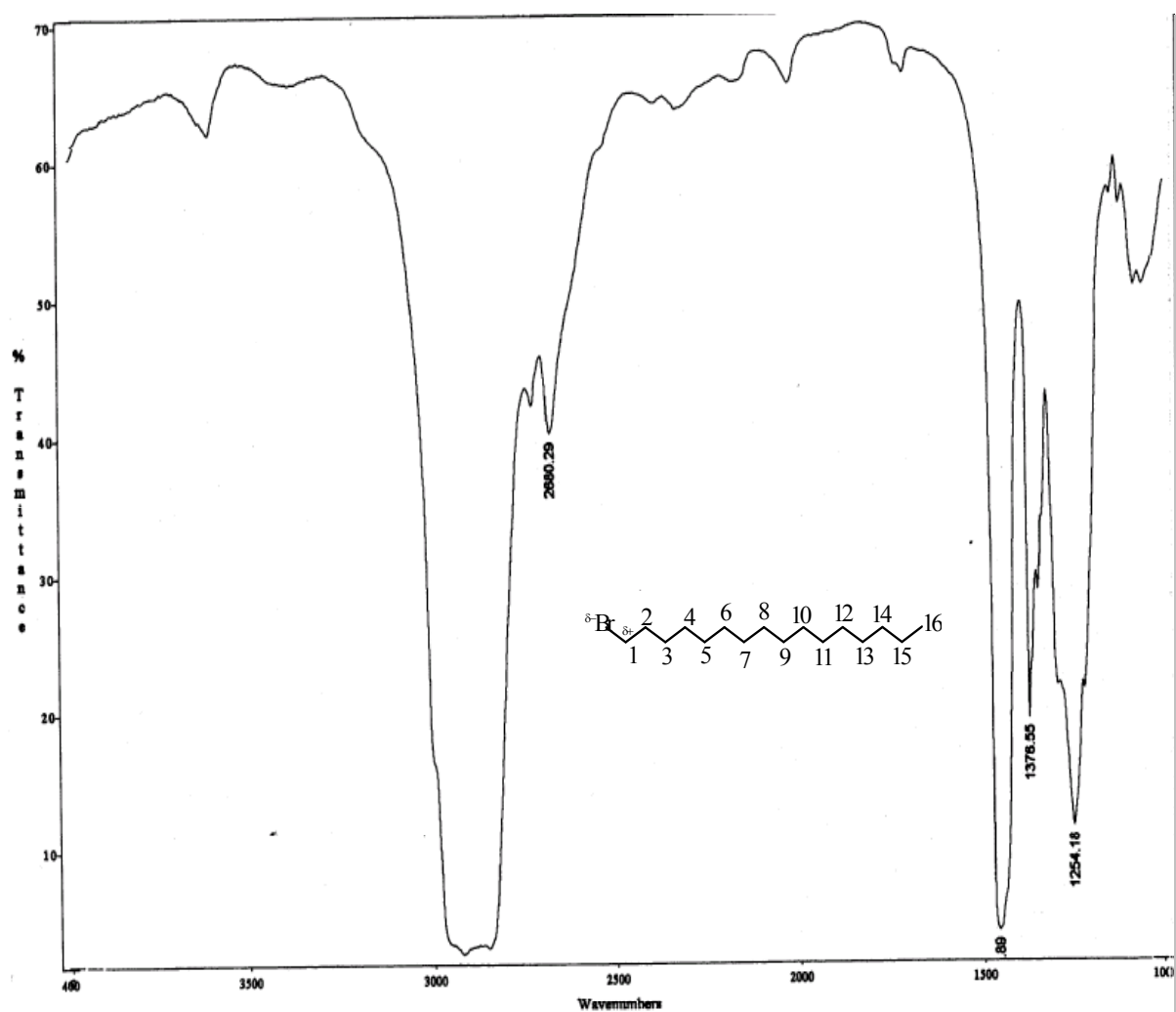


Figure 15. FTIR of 1-bromohexadecane.

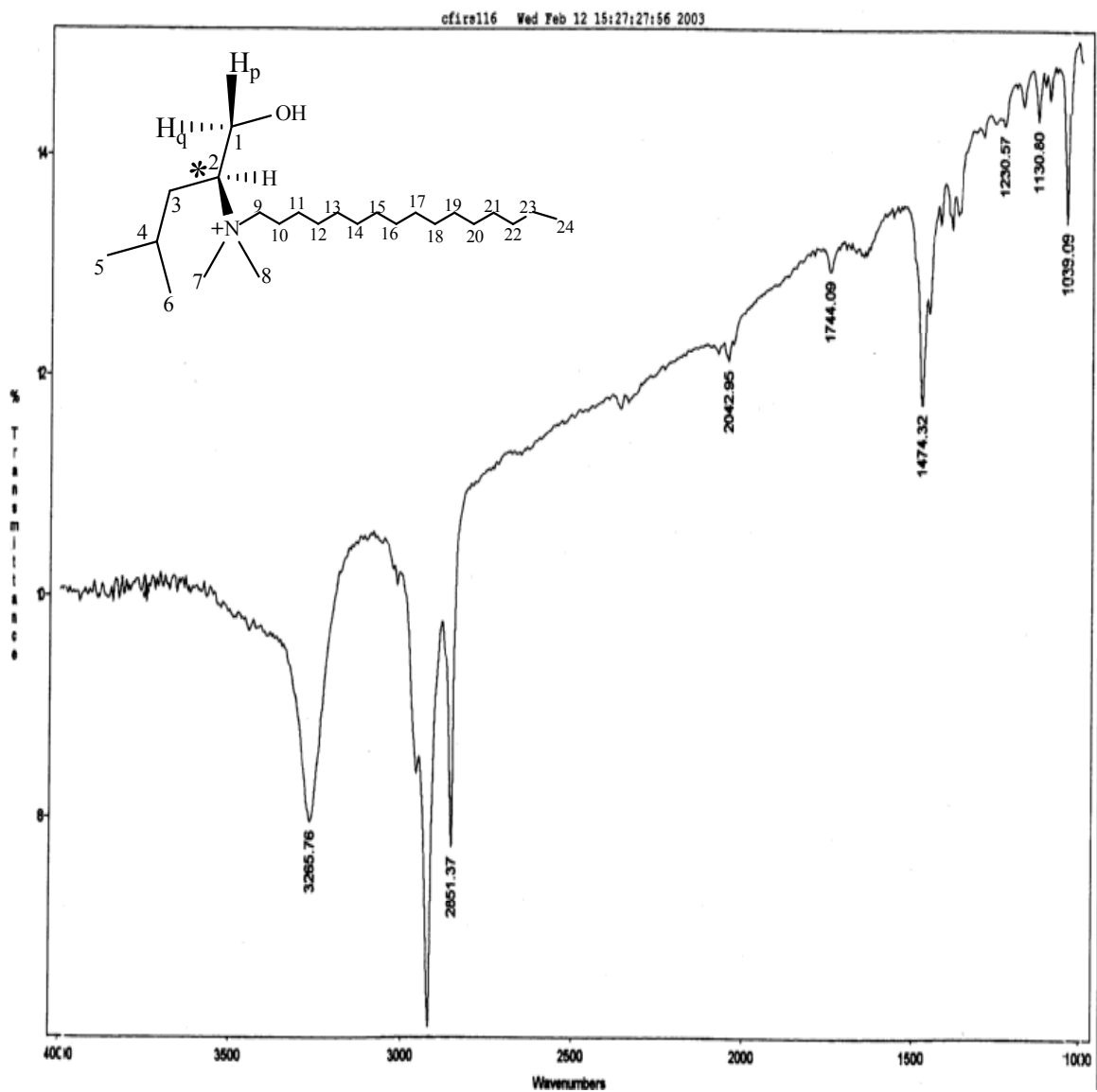


Figure 16. FTIR of (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide.

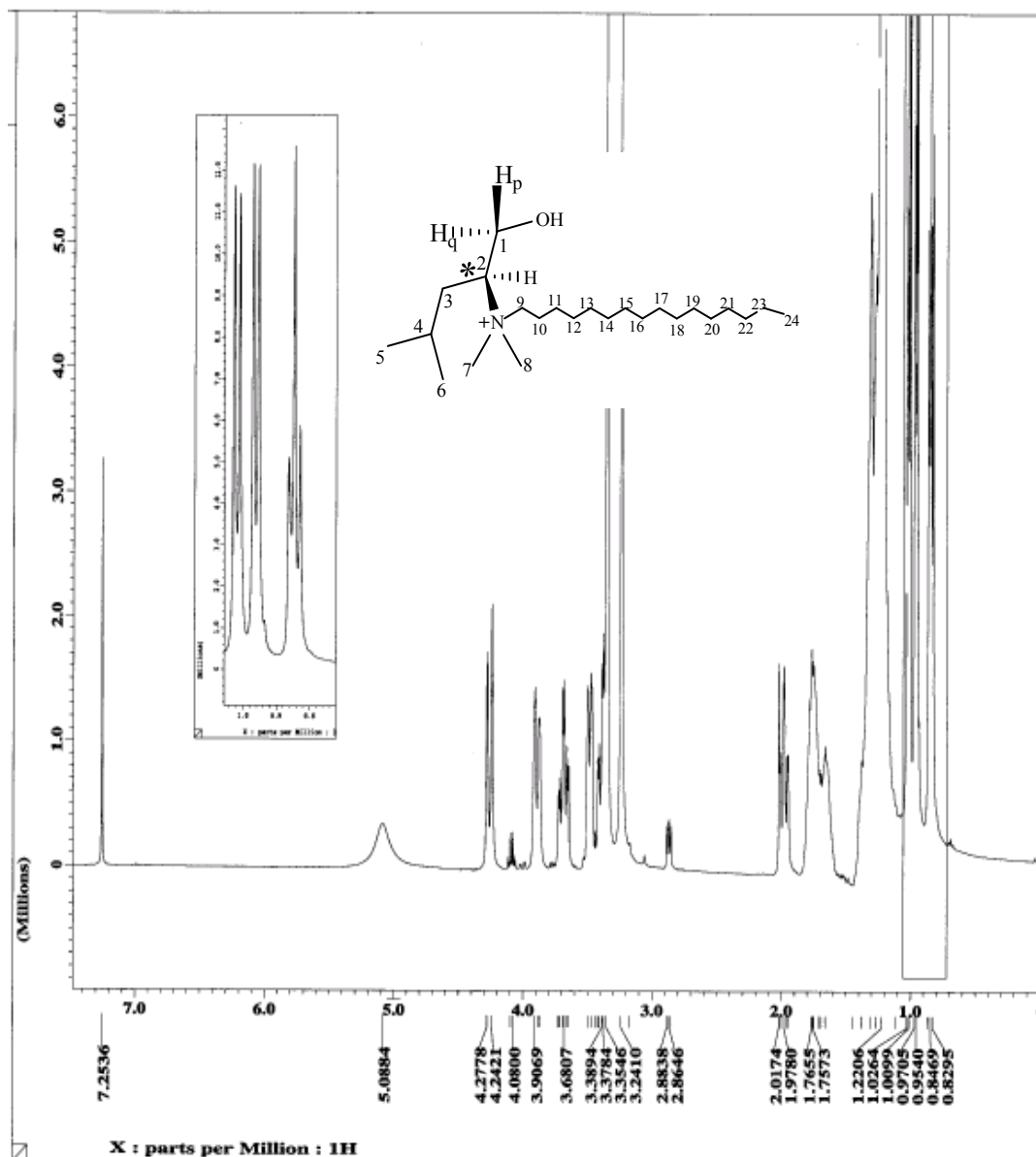


Figure 17. ^1H NMR of (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide.

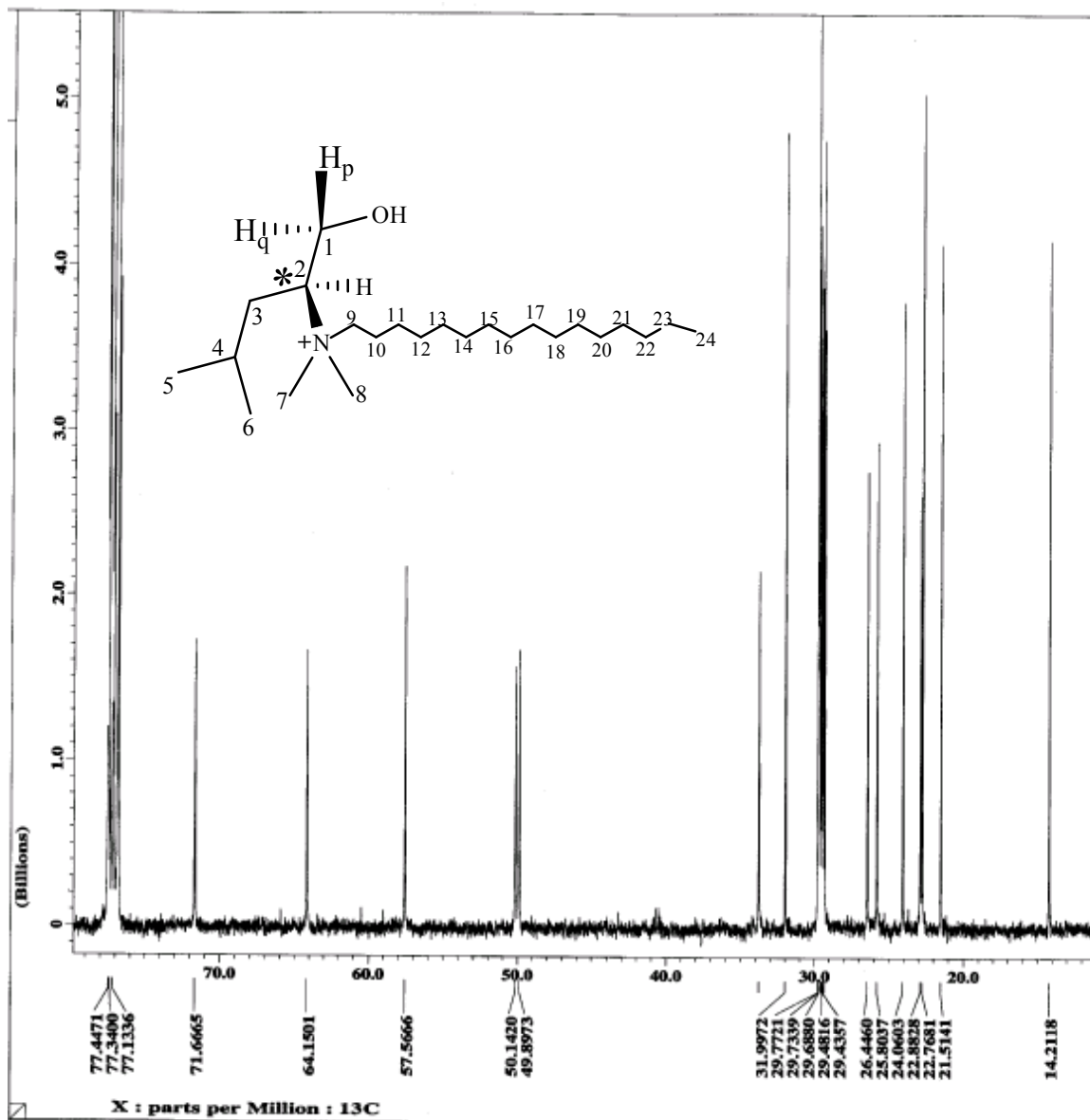


Figure 18. ^{13}C NMR of (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide.

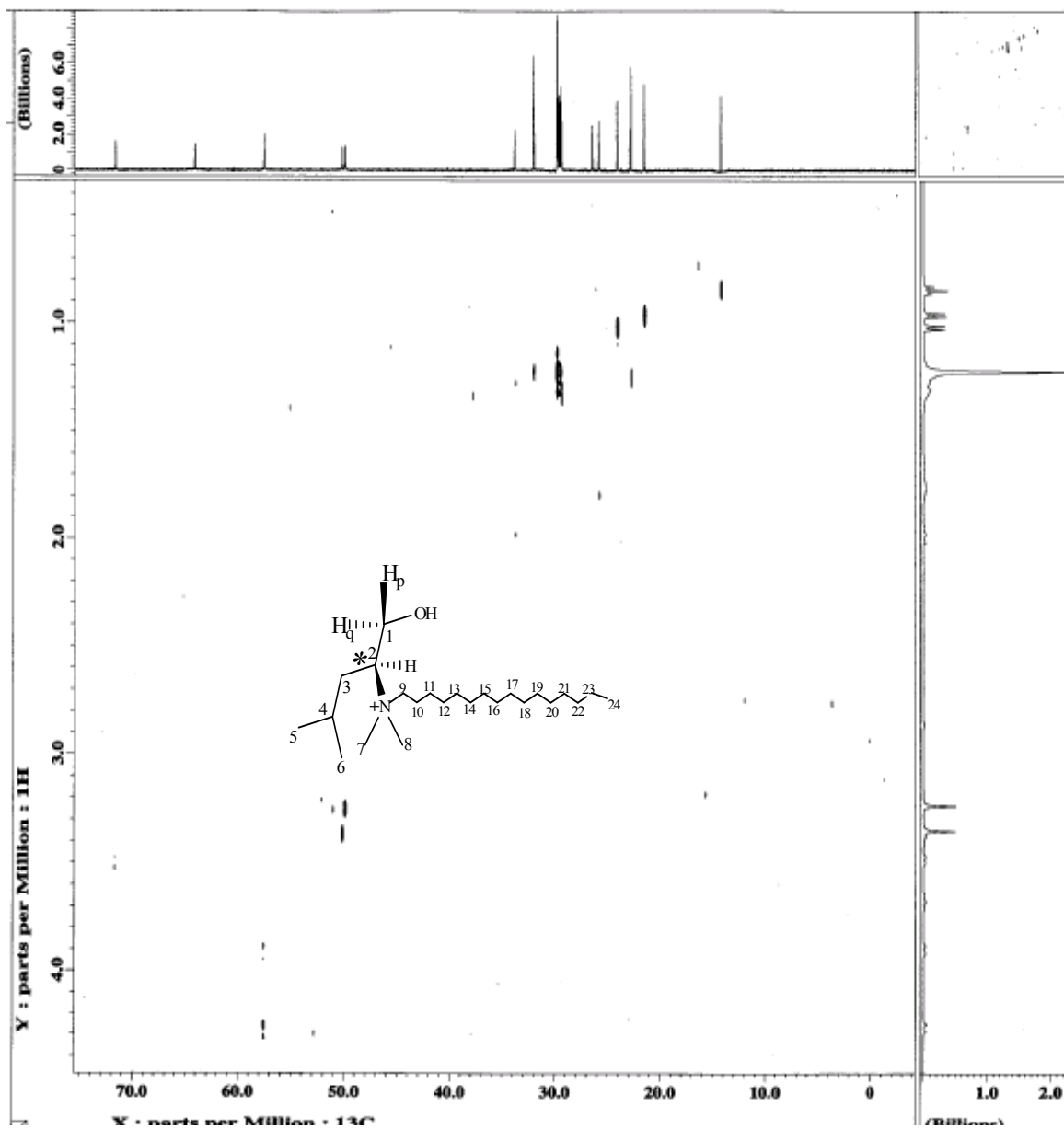
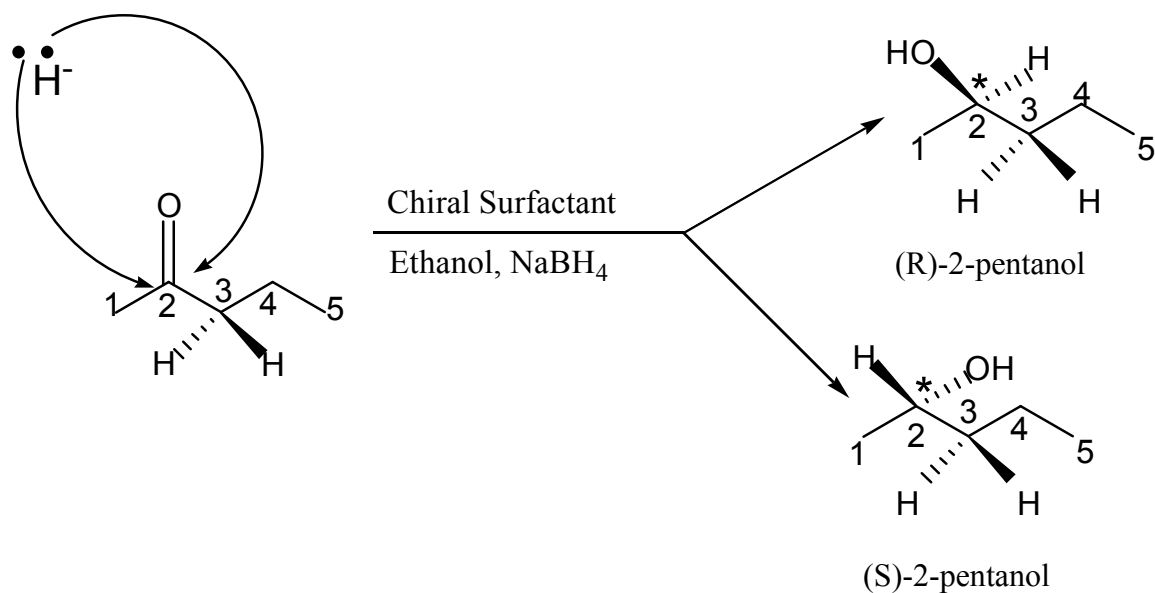


Figure 19. 2D-chsf NMR of (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide.

Activity of the Surfactant

Reduction of 2-Pentanone to 2-Pentanol

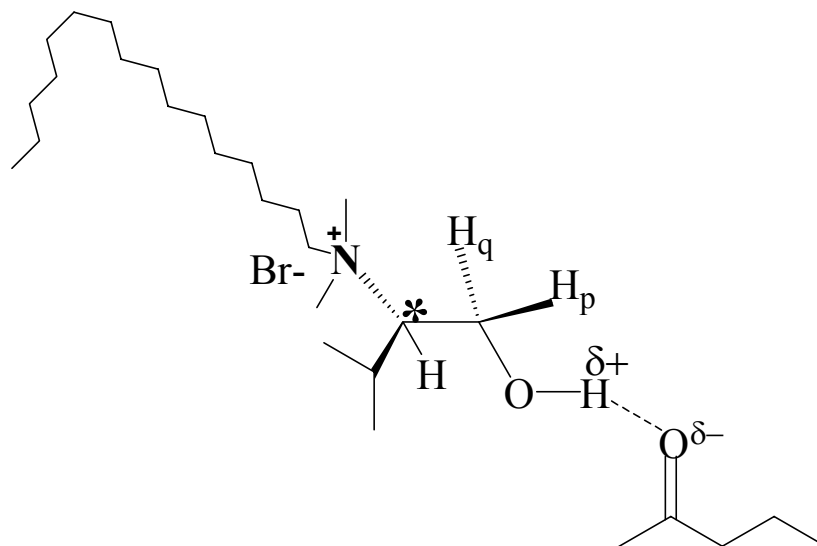
2-Pentanone was reduced to 2-pentanol by treating it with NaBH_4 in presence of the hydrocarbon surfactant. The reaction was carried out in ethanol (95%) acting as a solvent for the system. The scheme for the synthesis of the alcohol from the ketone is shown below. In the presence of the surfactant, one of the enantiomers was expected to be produced in excess over the other.



Scheme 3. Reduction of 2-pentanone to 2-pentanol.

In absence of the added surfactant, the reaction can be expected to give a racemic mixture containing equal amount (50%) of both the (R)- and the (S)- isomers. This is because the reducing agent can attack to the either face of the π -bond (i.e. $\text{C}=\text{O}$ bond) with equal probability. However in presence of the surfactant, it is expected to have one enantiomer in

excess over the other. A mechanism for the formation of excess (S)-2-pentanol over the (R)-2-pentanol is postulated in Scheme 4.



Scheme 4. Proposed mechanism for the synthesis of excess (S)-2-pentanol.

In the proposed mechanism, the surfactant forms a hydrogen bond with the oxygen of the carbonyl carbon and thereby generates steric hindrance on the face that would lead to the formation of (R)-2-pentanol. On the other hand, the approach of the hydride ion to the face that facilitates the formation of the (S)-isomer does not experience as much steric hindrance. Because of this difference in steric factor, the approach of the hydride ion to the face of the carbonyl carbon generating the (S)-isomer is preferred over the other one, resulting in the formation of enantiomerically excess (S)-isomer over the (R)-isomer.

Comparison of the ^1H , ^{13}C , 2D-cosy (^1H vs. ^1H) NMR of 2-pentanol confirmed the structure of the product. In the ^1H NMR spectrum (Figure 20) the triplet at $\delta = 0.9220$ ppm represents the three hydrogens attached to the C_5 carbon atom (i.e. $\text{CH}_3\text{-(CH}_2\text{)-}$). The doublet at $\delta = 1.1775$ ppm represents the hydrogens attached to C_1 carbon atom (i.e. $\text{CH}_3\text{-CH(OH)-}$).

The multiplet at $\delta = 1.4047$ ppm represents the four hydrogens attached to C₃ and C₄ carbon atoms (i.e. -CH₂-CH₂-). The multiplet at $\delta = 3.7878$ ppm represents the hydrogen attached to the C₂ carbon atom (i.e. -CH(OH)-). From the ¹³C NMR (Figure 21), the NMR signal at $\delta = 14.1506$ ppm represents C₅ carbon atom, signal at $\delta = 19.0214$ ppm represents C₄, signal at $\delta = 23.5480$ ppm represents C₁, signal at $\delta = 41.5934$ ppm represents C₃ carbon atom while the signal at $\delta = 67.9733$ ppm represents the C₂ carbon atom.

The 2D-cosy (¹H vs. ¹H) NMR (Figure 22) represents which hydrogen is close proximity to which hydrogen. The hydrogen attached to the carbon atom C₂ (chiral center) is close proximity with the hydrogens attached to C₁ carbon atom and the hydrogen atoms attached to C₂ / C₃ carbon atom. Now with respect to this hydrogen, the hydrogens attached to the 3rd and 4th carbon are close. Similarly, a signal correlating the multiplet at $\delta = 3.7878$ ppm and the doublet at $\delta = 1.4047$ ppm represents the influence of hydrogens attached at C₃, C₄ carbon atoms on the chiral hydrogen atom. Similarly, a second signal correlating the multiplet at $\delta = 3.7878$ ppm and the doublet at $\delta = 1.1775$ ppm suggests that the proton signal for the chiral hydrogen is influenced by the presence of hydrogens attached to the carbon atom C₁. The details of the 2D-chsf NMR analyses for the 2-pentanol is given in the appendix.

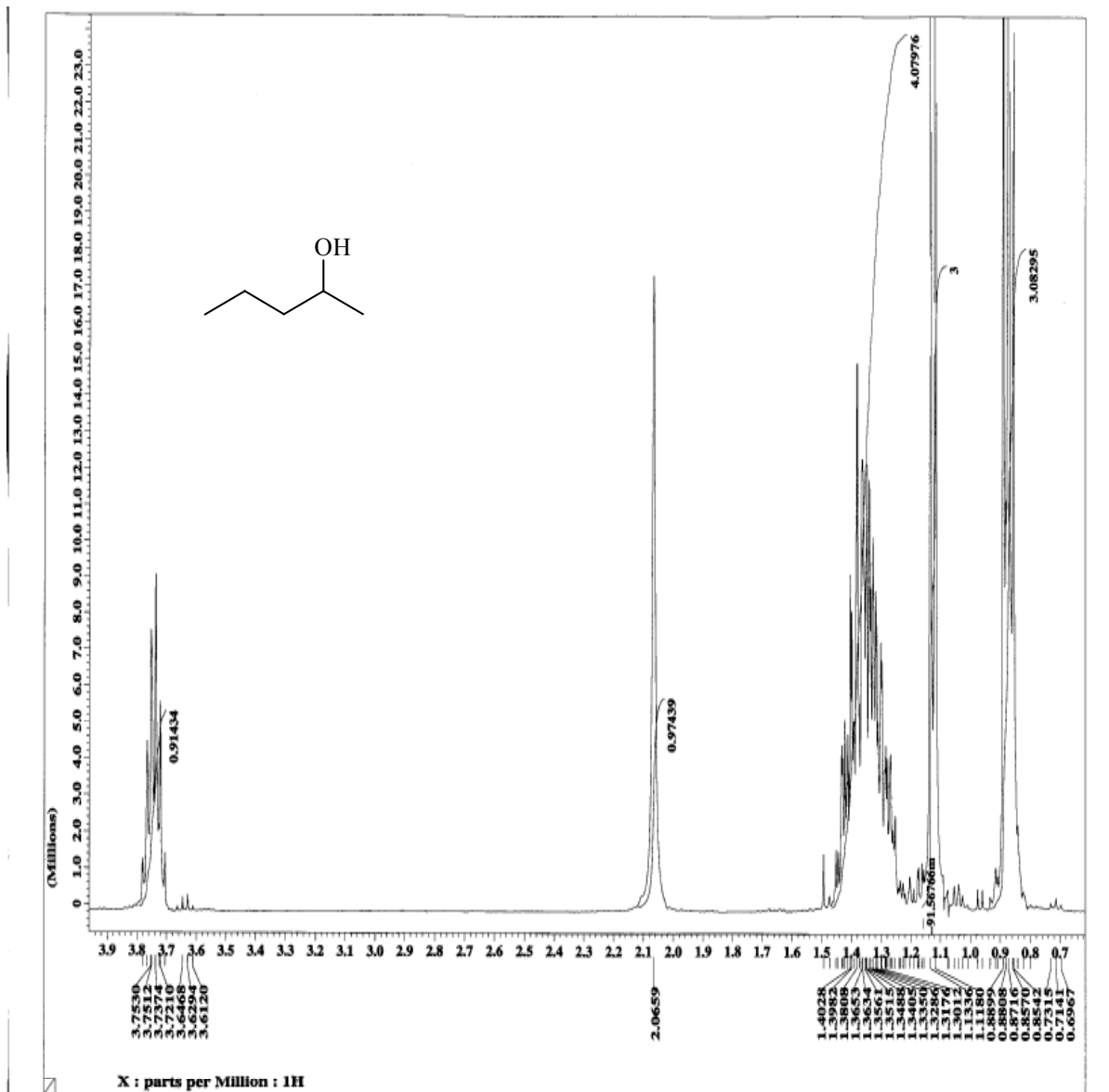


Figure 20. ^1H NMR of 2-pentanol.

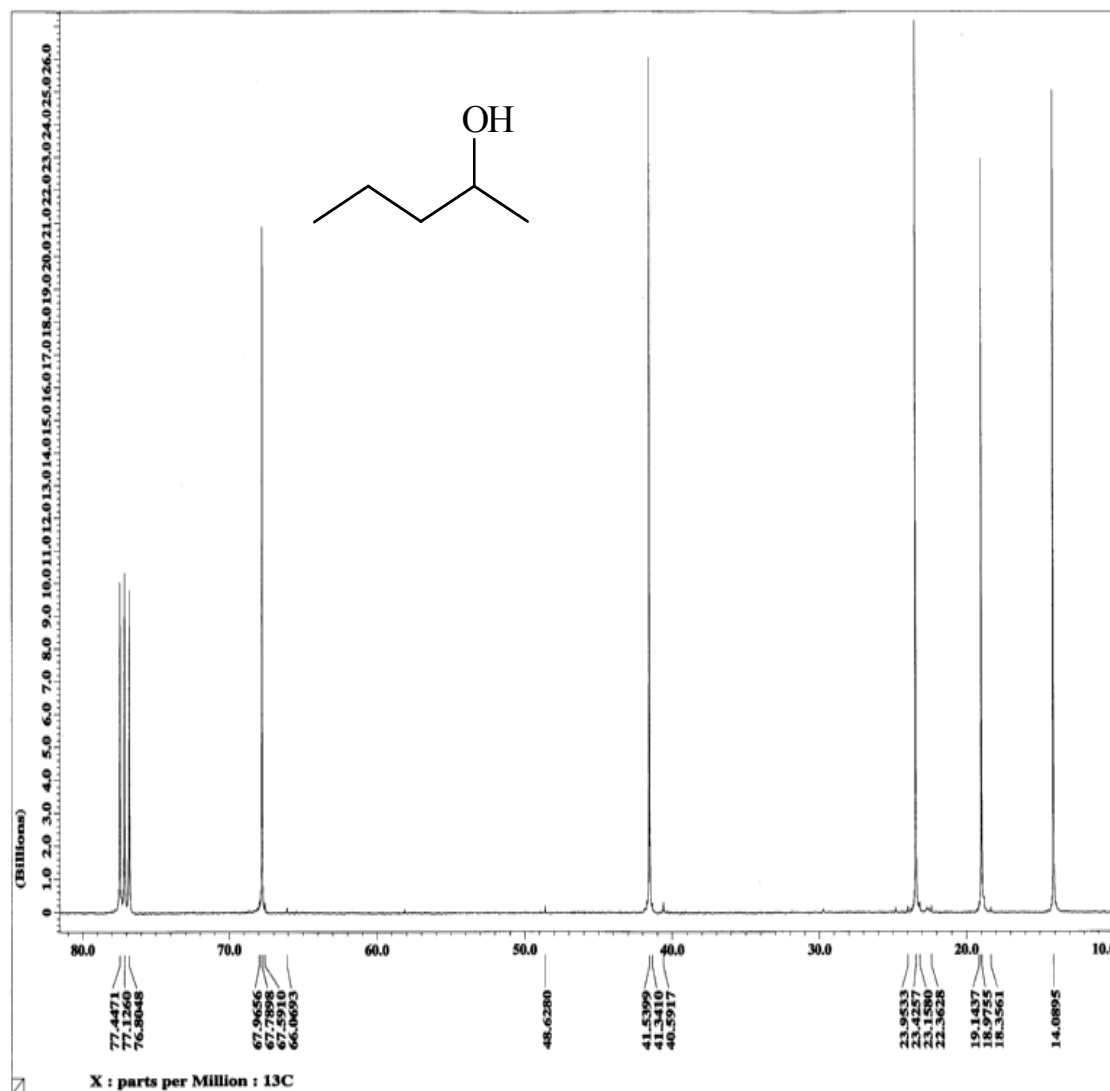


Figure 21. ^{13}C NMR of 2-pentanol.

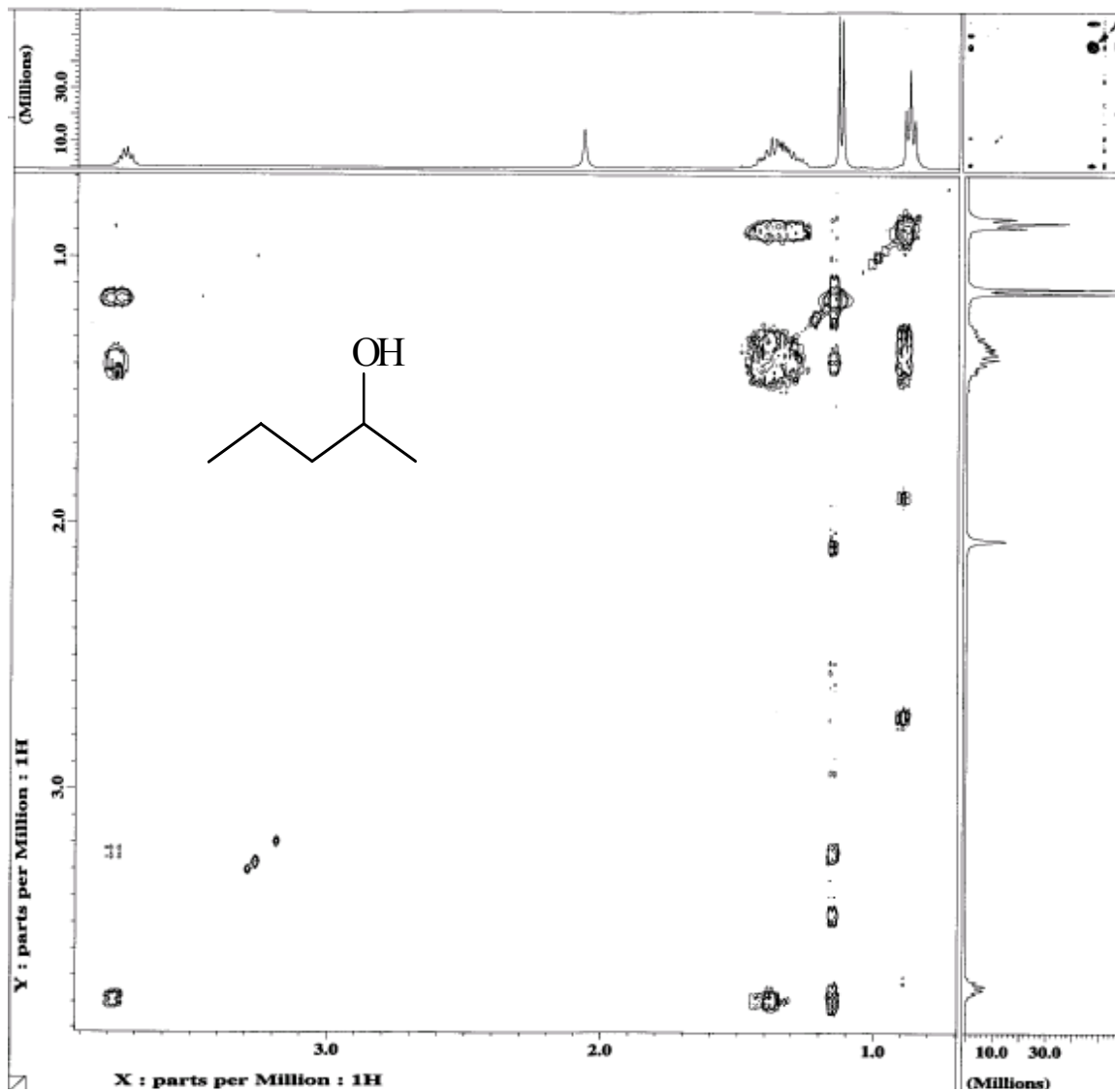
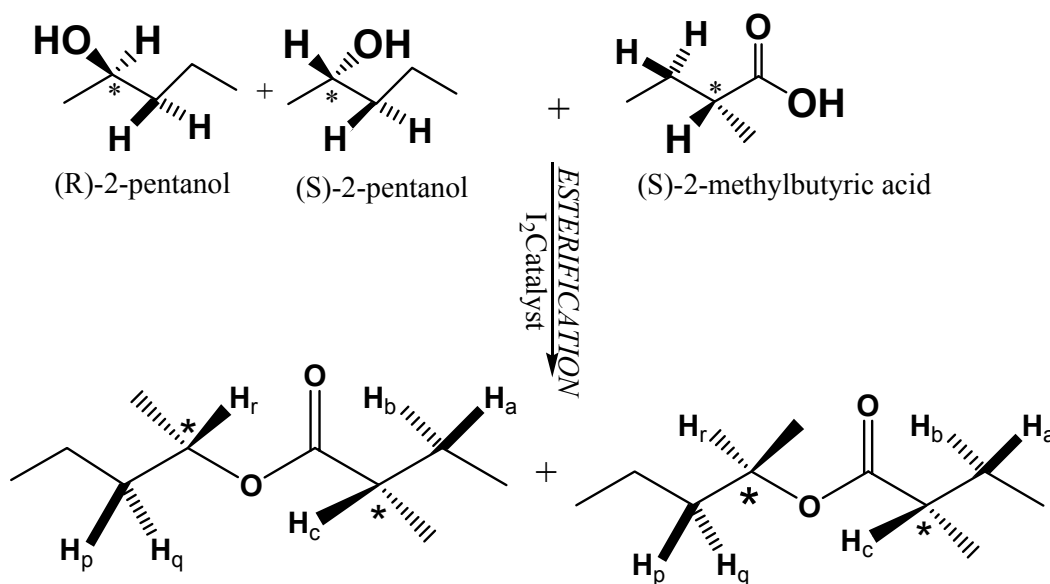


Figure 22. 2D-cosy NMR of 2-pentanol.

Esterification of 2-Pentanol

The percentage of enantiomeric excess in the 2-pentanol can also be determined by using the NMR technique. The alcohol 2-pentanol exists as enantiomers, and the (R)- and the (S)-isomeric forms are not expected to show any significant difference in the NMR. Because diastereoisomers differ in their physical properties, they are also expected to show significant shifts in their NMR. We hoped to use this difference to calculate the percentage of the enantiomers. In order to conduct this study, the alcohol 2-pentanol was treated with (S)-(+)-2-methylbutyric acid to yield the diastereoisomeric esters, as shown in scheme 5. The product was purified by column chromatography using hexane-ether (8:3) as the eluent for the chromatography prior to characterization.



Scheme 5. The (S, S)- and (R, S)- diastereoisomeric esters of 2-pentanol.

The structure characterization of the ester of 2-pentanol was done by NMR. From the proton NMR, the multiplet at $\delta = 4.8951$ ppm represents the hydrogen attached to the C₄ carbon atom. The multiplet at $\delta = 2.3022$ ppm represents the other chiral hydrogen attached to the C₆ carbon atom. The two multiplets at $\delta = 1.6127$ ppm and at $\delta = 1.4074$ ppm represent

the two pro-chiral hydrogens H_a and H_b attached to the C_7 carbon atom. The multiplet at $\delta = 1.2883$ ppm represents the other two pro-chiral hydrogen atoms H_p and H_q attached to the C_3 carbon atom.

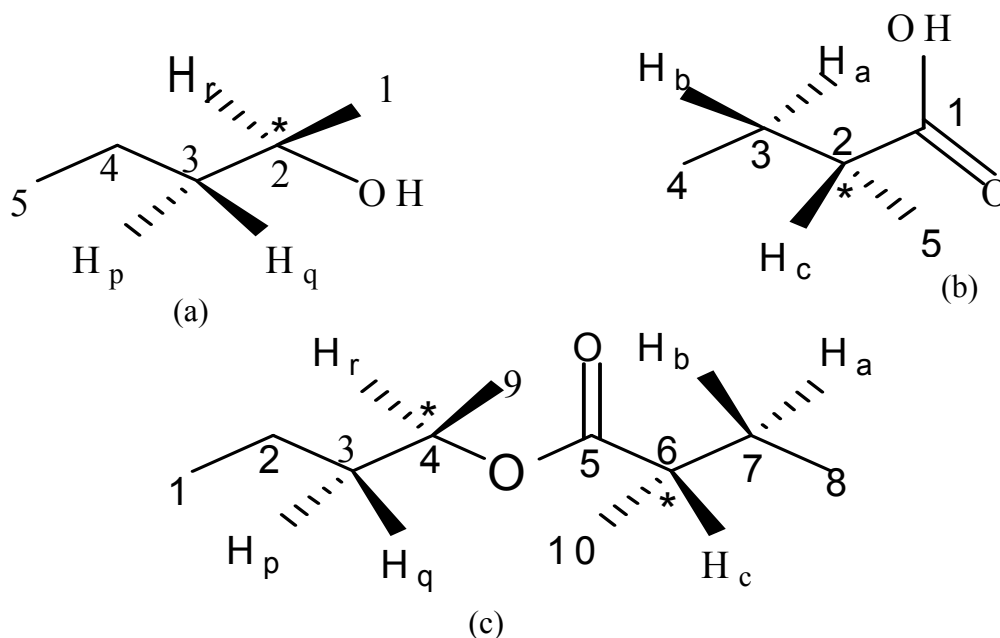


Figure 23. Structure of (a) 2-pentanol, (b) (S)-2-methylbutyric acid and (c) the diastereoisomeric ester.

The ^{13}C NMR values for the acid, alcohol, and the ester has been shown below in the tabular form. The information regarding the assignments of the carbon atoms of the ester was based on the characteristics of the carbons of the acid and the alcohol used in the ester synthesis. The following tables represents the ^{13}C NMR values of 2-pentanol, (S)-2-methylbutyric acid and the ester produced. The values mentioned as the “*Expected δ* ”

value (in ppm)” represent the carbons as expected from the starting reagents, the alcohol and the acid as shown in the tables (Table 2, 3, 4) below.

Table 2. ^{13}C NMR values of (S)-2-methylbutyric acid.

No. of Obs.	Carbon No.	δ value (in ppm)
1	C ₁	183.6702
2	C ₂	40.9740
3	C ₃	26.5836
4	C ₅	16.4140
5	C ₄	11.6044

Table 3. ^{13}C NMR values of 2-pentanol.

No. of Obs.	Carbon No.	δ value (in ppm)
1	C ₃	41.5934
2	C ₂	67.9733
3	C ₁	23.5480
4	C ₄	19.0214
5	C ₅	14.1506

Table 4. Correlation values of ^{13}C NMR for ester.

No. of Obs.	Carbon in Ester	Carbon in Pentanol	Carbon in Acid	Observed δ value (in ppm)	Expected δ value (in ppm)
1	C ₁	C ₅		13.9518	14.1506
2	C ₂	C ₄		20.0996	19.0214
3	C ₃	C ₃		38.1755	41.5934
4	C ₄	C ₂		70.2978	67.9733
5	C ₅		C ₁	176.4979 and 176.4596	183.6702
6	C ₆		C ₂	41.4710	40.9740
7	C ₇		C ₃	26.8589	26.5836
8	C ₈		C ₄	11.6579	11.6044
9	C ₉	C ₁		18.9678	23.5480
10	C ₁₀		C ₅	16.7810	16.4140

It was our aim to use the ^1H NMR signals from the chiral carbon in the alcohol portion of the ester (C₄) to determine the enantiomeric excess in our 2-pentanol. If the alcohol was a racemic mixture then we should obtain different signals for the chiral hydrogens but the integration should be in a 1:1 ratio. On the other hand, if we have an enantiomeric excess then again there should be different ^1H NMR signals but the integration should show different values and from the integration it would be easy to determine the

percentage of enantiomeric excess. However, we could not conclude whether we have a racemic mixture or enantiomeric excess because the spectrum did not show distinct signals for the proton of C₄ carbon atom. There is some interesting information obtained from the ¹³C NMR. In the ¹³C NMR of the ester, there are two distinct ¹³C NMR signals at $\delta = 176.4979$ ppm and $\delta = 176.4596$ ppm representing the C₅ carbon atom (i.e. the carbonyl carbon atom) and their integration gives a ratio of 1:1.10955, which might be an indication of ~ 5% enantiomeric excess of the alcohol, 2-pentanol.

To better see the enantiomeric excess of the 2-pentanol, an NMR shift reagent was used. The purpose of the treatment of the alcohol, 2-pentanol, with the chemical shift reagent, Eu(fod)₃ [Europium(III)tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)], was to find out the R- / S- percentage of the alcohol. It was expected that the chiral carbon, i.e. C₂ carbon atom, would show two distinct peaks corresponding to the (R)-and (S)-2-pentanol. Figure 30 shows the ¹H NMR of the alcohol in the presence of the chemical shift reagent Eu(fod)₃. Figure 20 shows the ¹H NMR spectroscopy for 2-pentanol with out any shift reagent. According to that spectrum the multiplet at $\delta = 1.4047$ ppm represent the four hydrogens attached to the carbon atoms C₃ and C₄. Of these four hydrogens the two attached to the C₃ carbon atom are prochiral in nature. A comparative study of the proton NMR for 2-pentanol in the presence and absence of the chemical shift reagent showed the shift of a number of peaks including the peak for the hydrogen atom attached to C₂ carbon NMR. For the original 2-pentanol NMR spectrum the hydroxyl group is at $\delta = 2.0659$ ppm while in the presence of the shift reagent the hydroxyl peak appeared at $\delta = 6.1261$ ppm. Similarly, the proton peak corresponding to the hydrogen atom attached to the chiral carbon atom C₂ is shifted from $\delta = 3.7878$ ppm to $\delta = 4.8860$ ppm. However, the most significant shift occurred

around $\delta = 1.7518$ ppm and $\delta = 2.1218$ ppm. The proton NMR signal at $\delta = 2.1218$ ppm represents the prochiral hydrogens attached to C_3 carbon atom (Figure 30), while the multiplet at $\delta = 1.7518$ ppm represents the hydrogens attached to the carbon atom C_4 . The distinction of the prochiral hydrogens from the adjacent hydrogens (i.e. distinction of C_3 hydrogens from the C_4 hydrogens) can well be justified with the 2D-cosy of the 2-pentanol in presence of the shift reagent. The cosy NMR (Figure 31) showed a distinct signal correlating the hydrogen peaks at $\delta = 2.1218$ ppm. On the other hand, the signal correlating the proton NMR peaks at $\delta = 1.7518$ ppm simply represents a multiplet for the C_4 hydrogen atoms. The signal correlating the multiplet for C_4 hydrogens with the triplet representing the C_5 hydrogens also justifies this, as hydrogens at C_5 carbon atom can only be influenced by the hydrogens at the C_4 carbon atom. Absence of any such signal corresponding to the C_3 carbon atom definitely proved that the signal at $\delta = 2.1218$ ppm represents the prochiral hydrogen atoms attached to the C_3 carbon atom which could not be identified with the spectra of the alcohol with out the shift reagent.

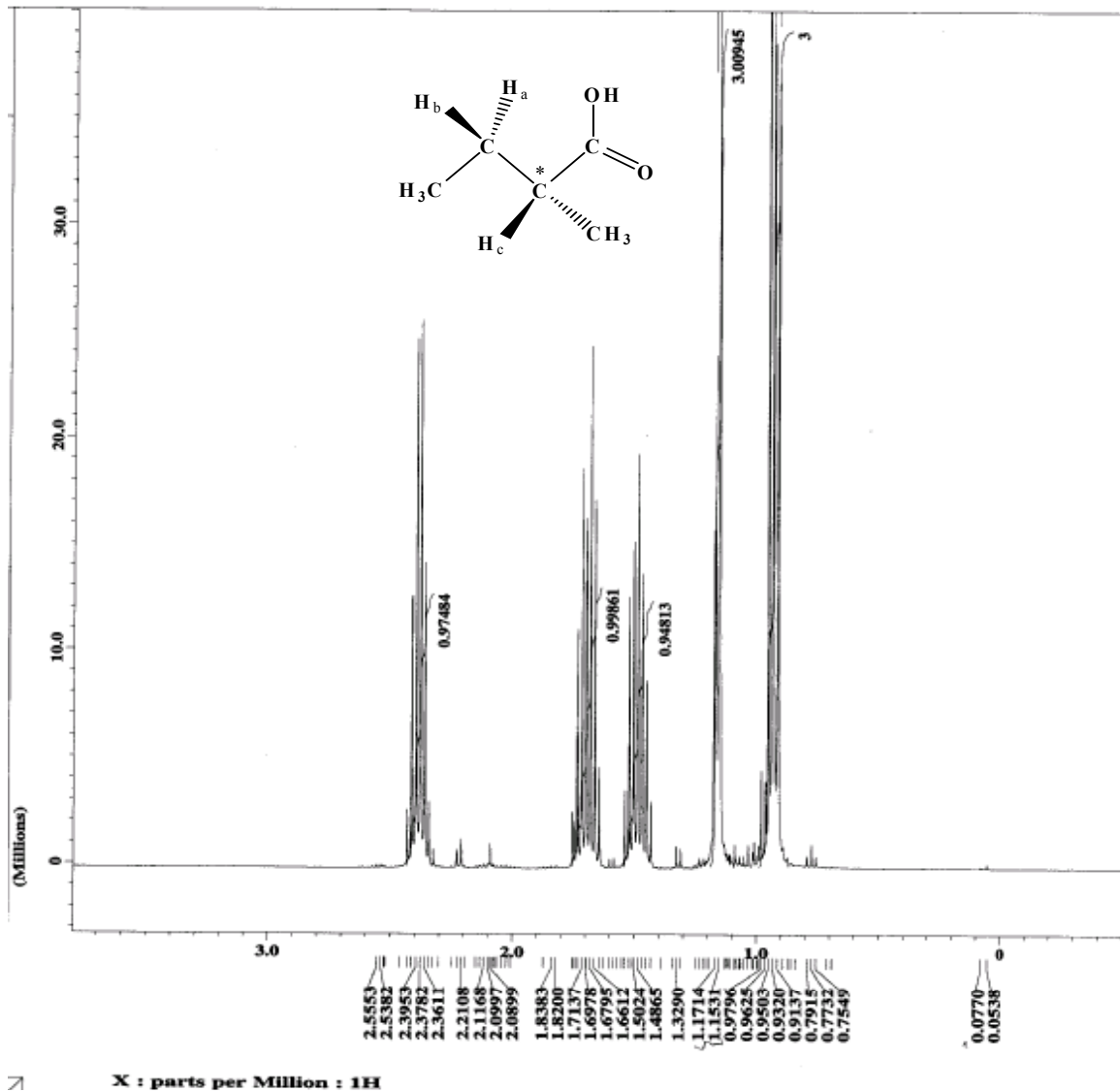


Figure 24. ¹H NMR of (S)-2-methylbutyric acid.

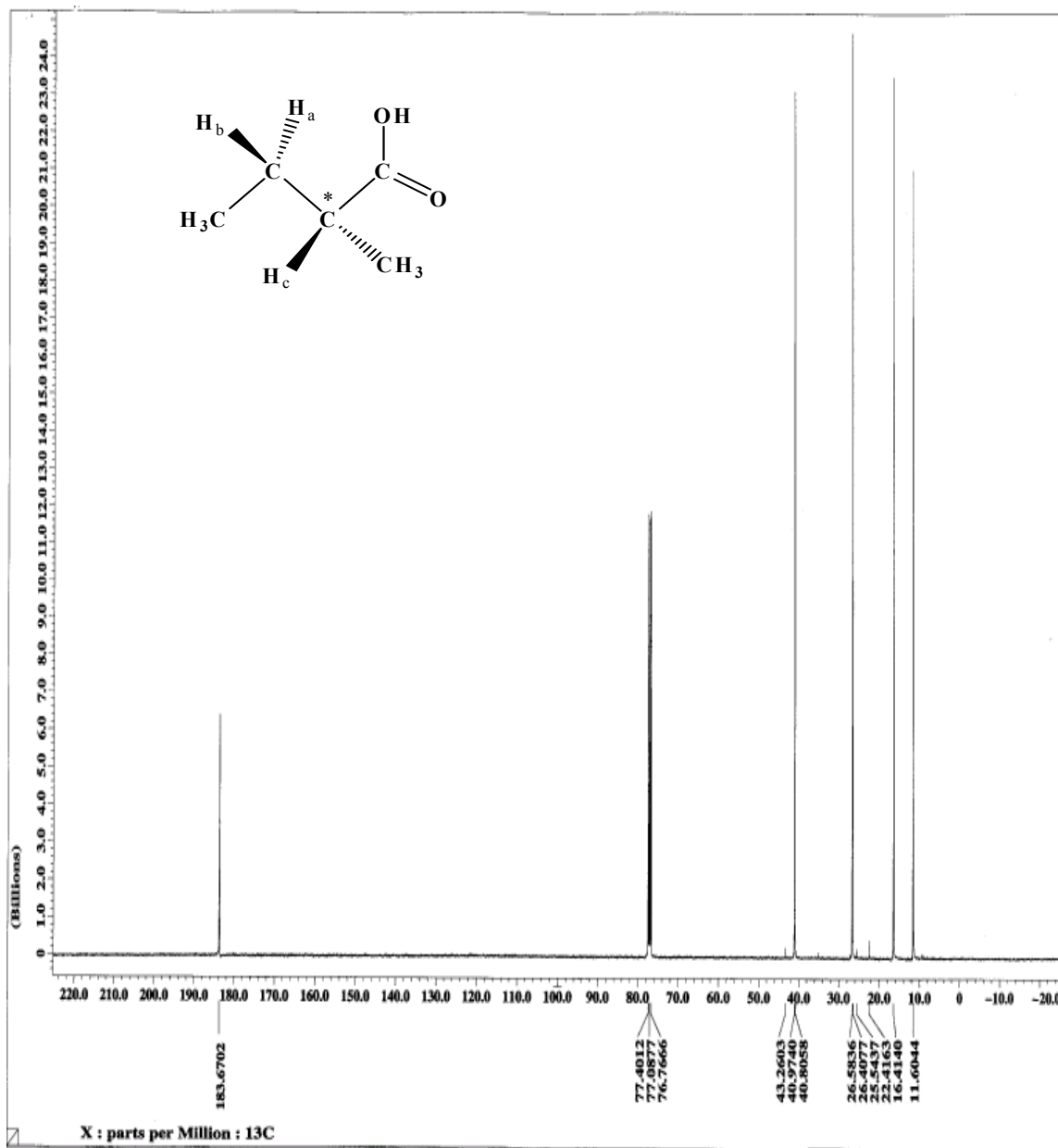


Figure 25. ^{13}C NMR of (S)-2-methylbutyric acid.

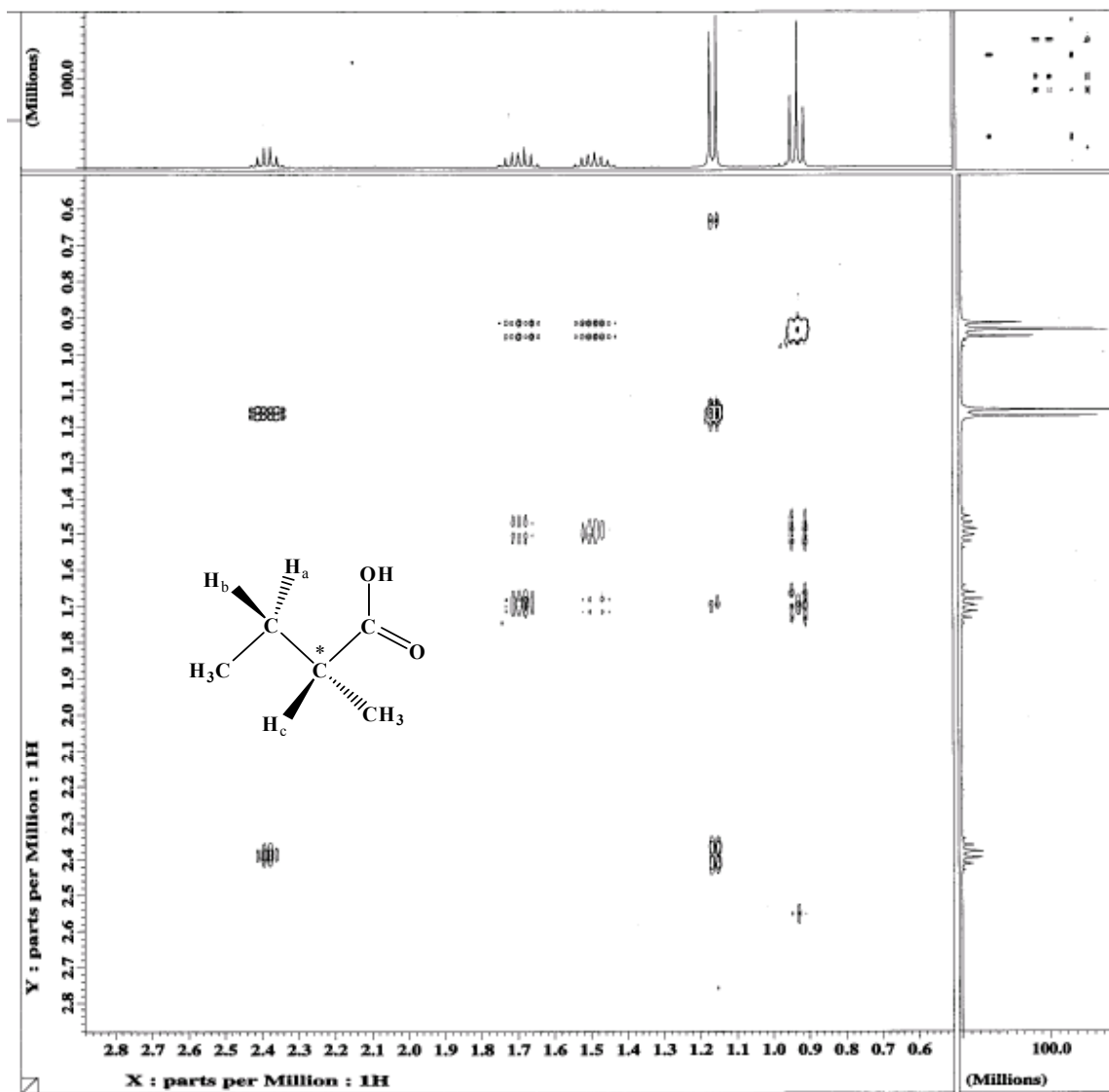


Figure 26. 2D-cosy NMR of (S)-2-methylbutyric acid.

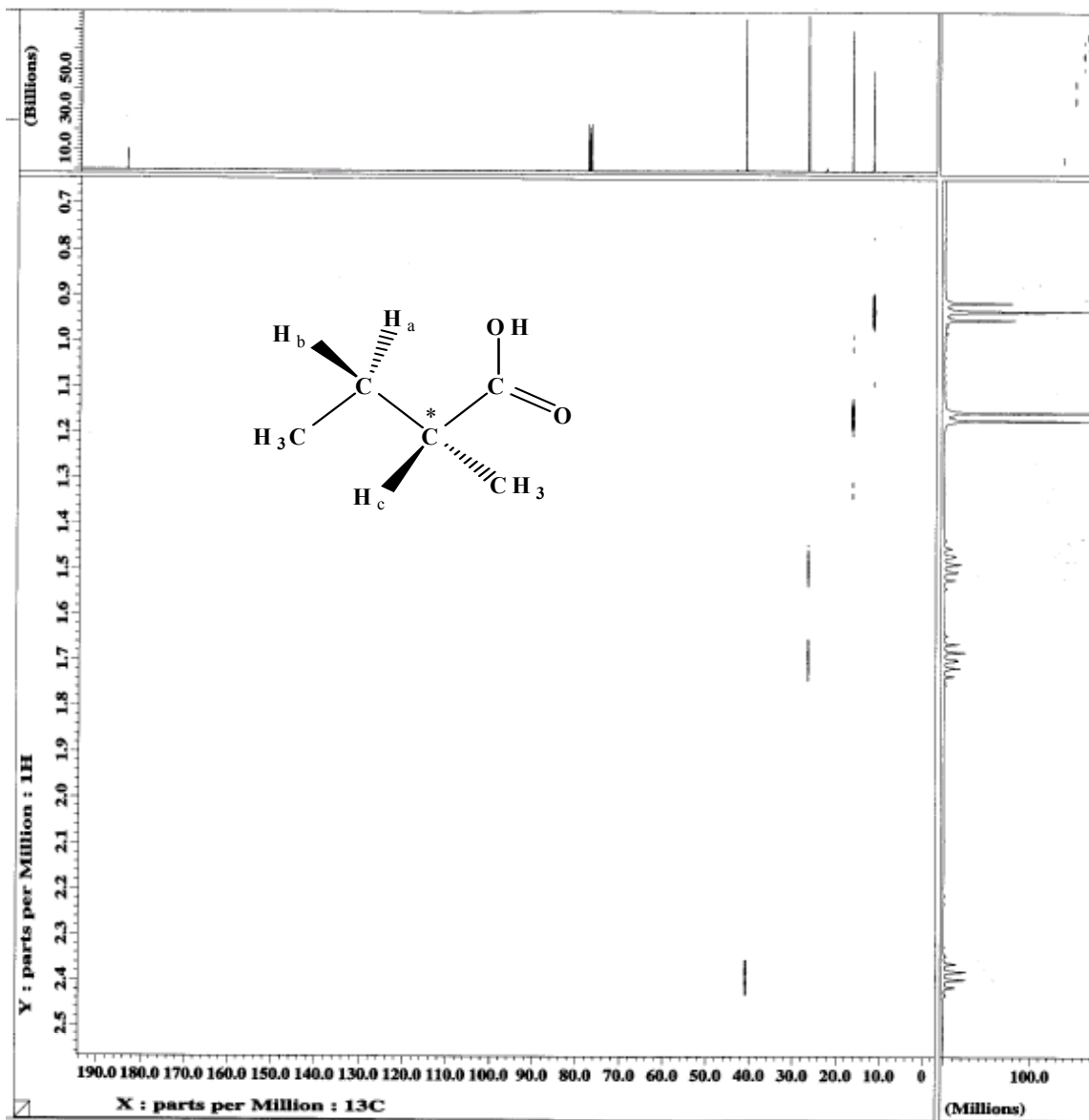


Figure 27. 2D-chsf NMR of (S)-2-methylbutyric acid.

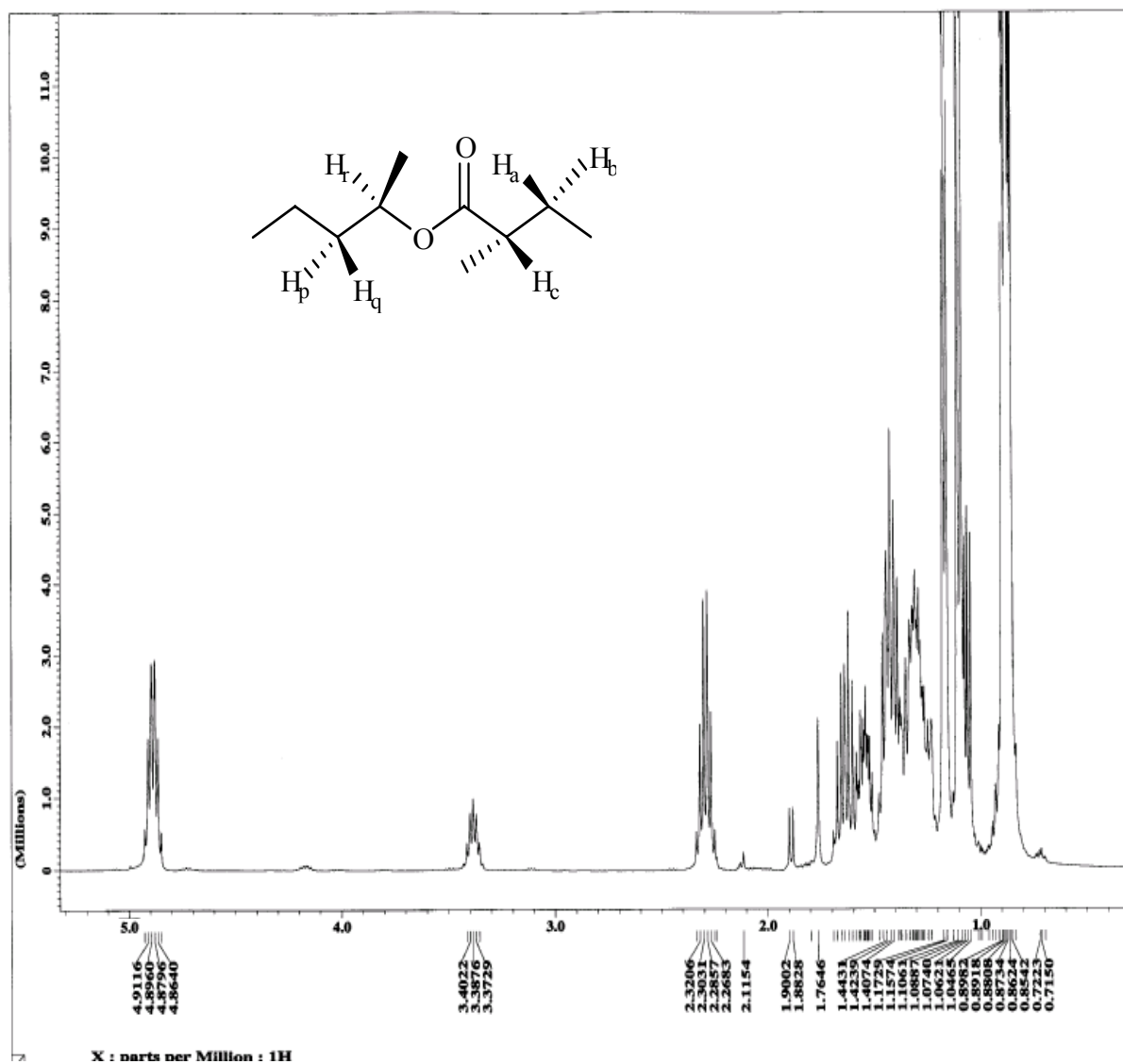


Figure 28. ^1H NMR of the diastereoisomeric ester.

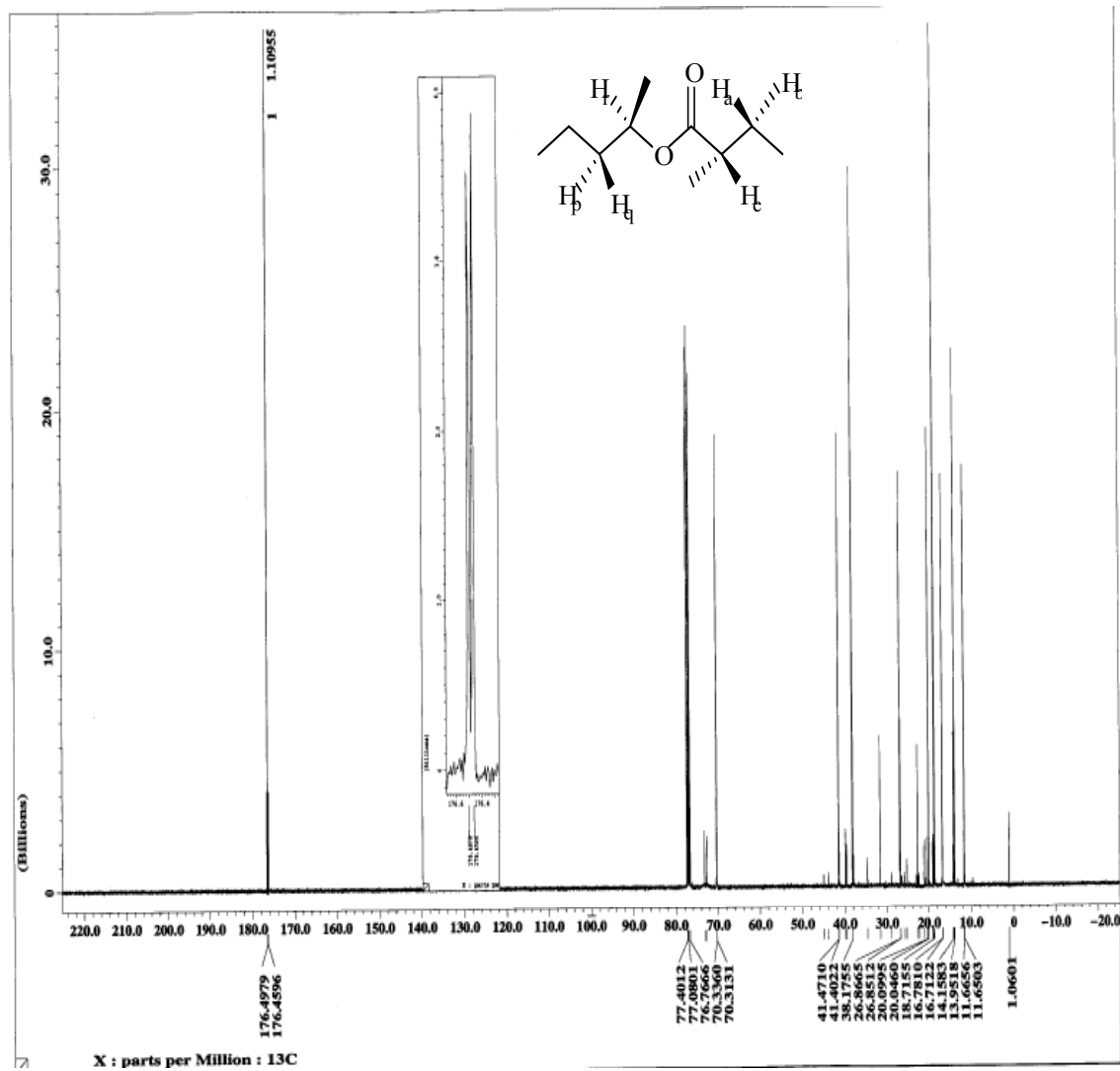


Figure 29. ^{13}C NMR of the diastereomeric ester.

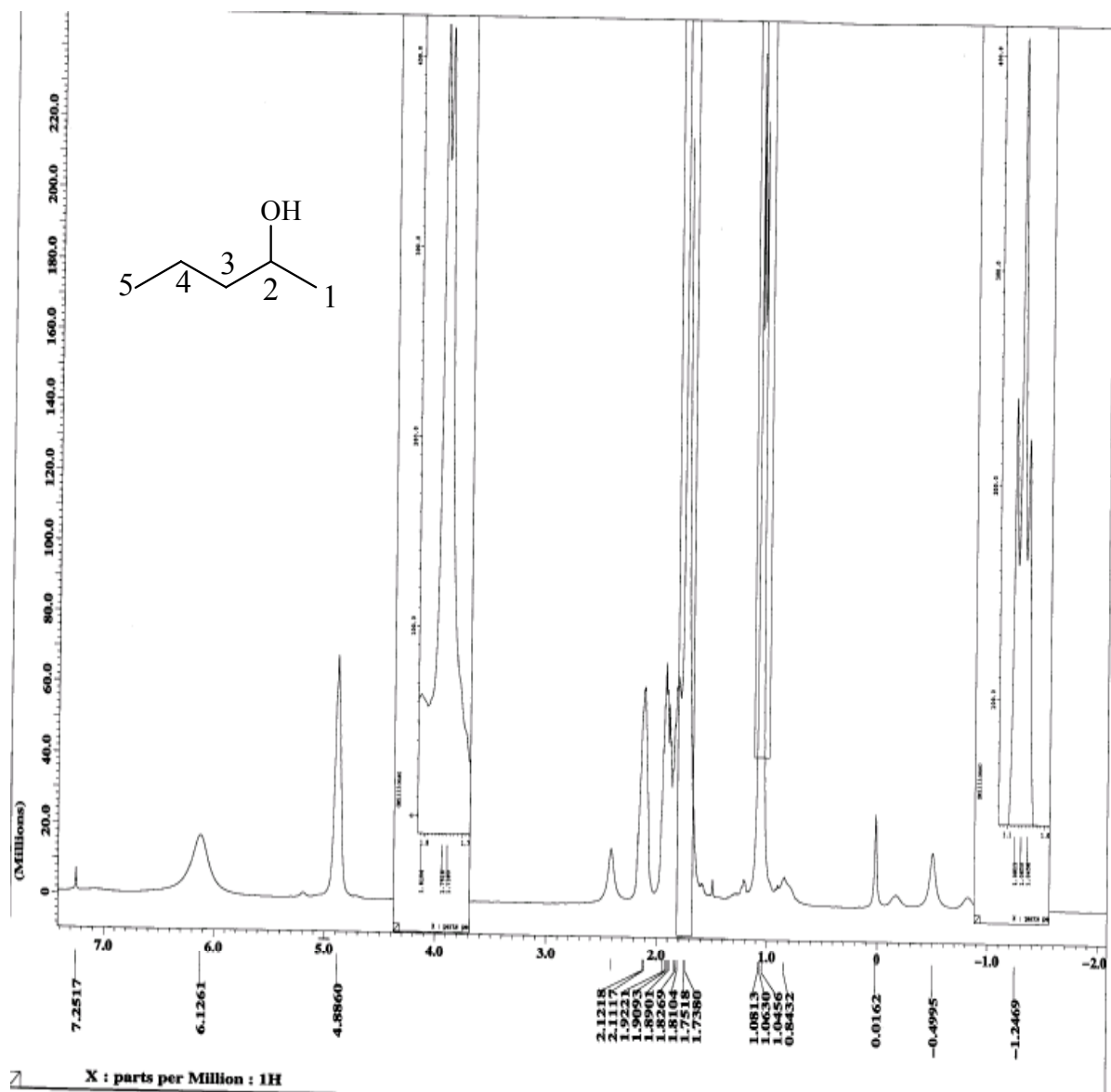


Figure 30. ^1H NMR of 2-pentanol in presence of the $\text{Eu}(\text{fod})_3$.

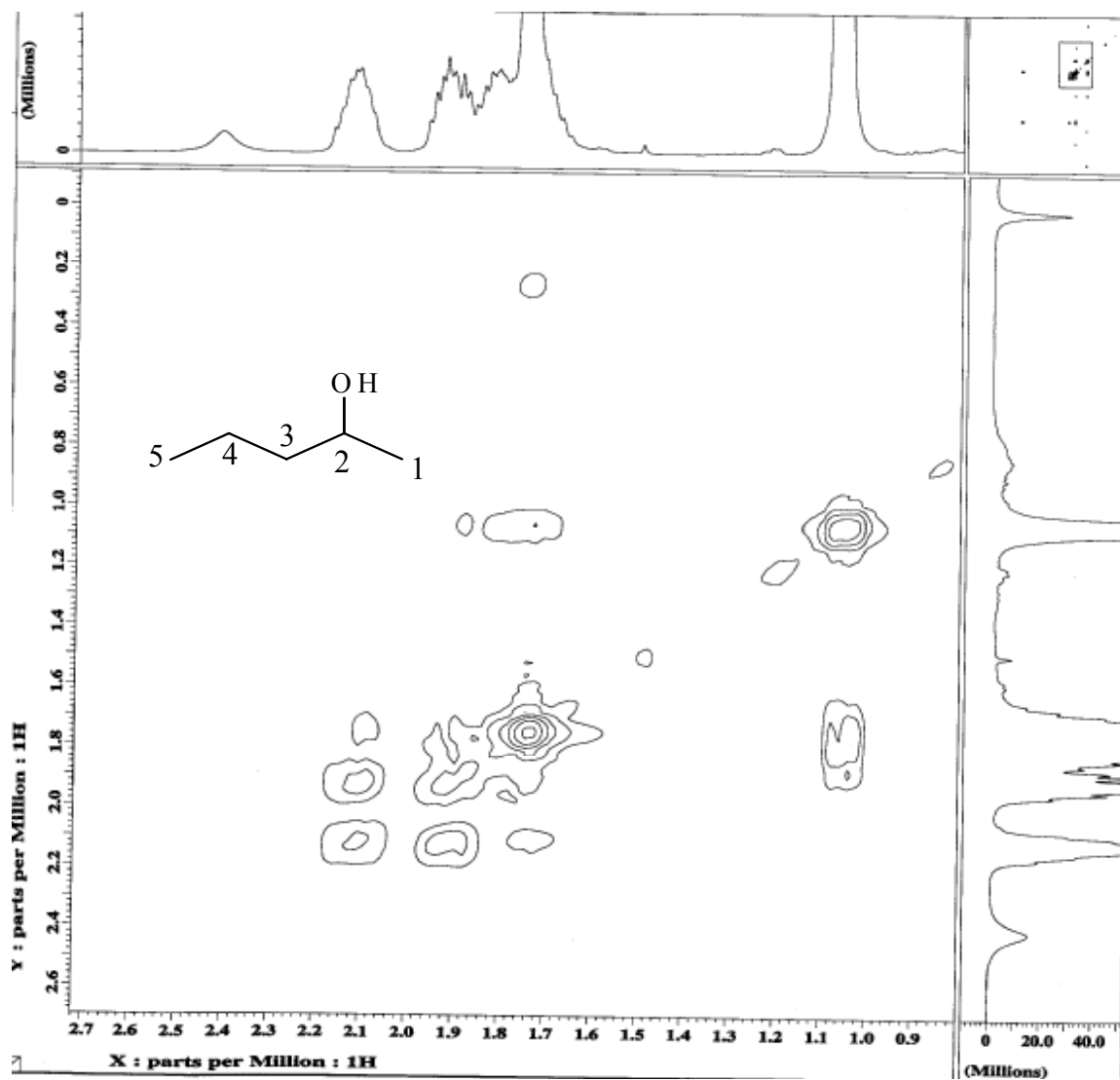


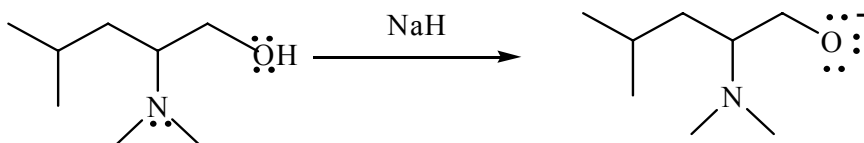
Figure 31. 2D-cosy NMR of 2-pentanol in presence of the Eu(fod)₃.

Synthesis of the Polymer-supported Catalyst

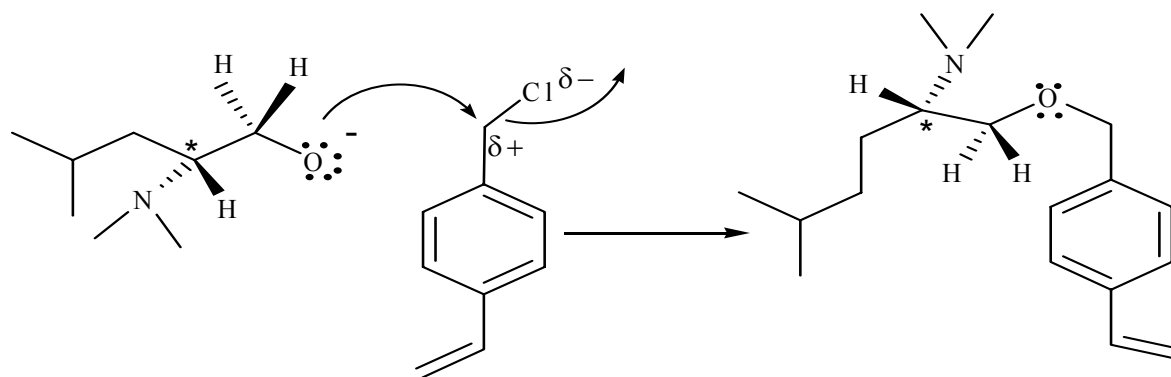
Formation of the Functionalized Monomer

The remainder of the project involved the synthesis of a polymer supported chiral catalyst. The first task was to generate a functionalized styrene monomer. The dimethylated derivative of leucinol **1** was treated with 4-vinylbenzyl chloride in presence of sodium hydride under argon atmosphere. This is an example of a base catalyzed nucleophilic substitution reaction (S_N2). The proposed mechanism for this reaction has been shown below in Scheme 6.

Step:1



Step:2



Scheme 6. Proposed mechanism for the synthesis of the functionalized monomer.

The structure of the product was confirmed by FTIR and ^1H , ^{13}C and 2D-cosy (^1H vs. ^1H) NMR. The FTIR spectrum of the product is a good guide for the determination of

the structure. In the structure of the N,N-dimethyl leucinol **1** there is a hydroxyl group and the corresponding FTIR spectrum (Figure 11) shows a peak at 3429.32 cm^{-1} . However, there is no such peak for the product and this is in accordance with the expectation that an O-C linkage is developed. Similarly, for the other reactant 4-vinylbenzylchloride (Figure 33), there is a 1405.87 cm^{-1} , representing the presence of C-Cl linkage. Again in FTIR spectrum of the product (Figure 34), there is no sharp peak around 1406 cm^{-1} , suggesting the absence of any C-Cl linkage in the product.

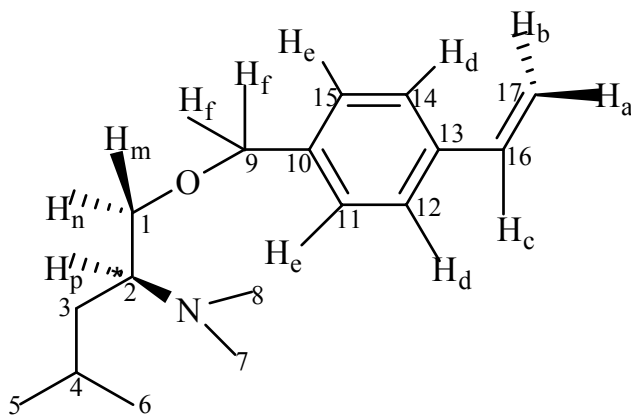


Figure 32. Structure of the functionalized monomer.

Comparison of the ^1H , ^{13}C NMR, and 2D-cosy (^1H vs. ^1H) NMR of the functionalized monomer confirmed the structure of the product. Because the reaction involves the incorporation of the styrene derivative to the leucinol derivative so some parts both of the ^1H and ^{13}C NMR spectra are almost identical to that of leucinol derivative with some change in chemical shift due to incorporation of a new group. For example in the ^1H NMR for the functionalized monomer (Figure 35), the multiplet at $\delta = 0.8753\text{ ppm}$ represents the six hydrogens of the two methyl groups attached to the C_4 carbon atom while that in the leucinol derivative (Figure 12) is at $\delta = 0.8469\text{ ppm}$ and so on. The multiplet at $\delta = 2.7373\text{ ppm}$

represents the hydrogen attached to the chiral carbon atom C₂ (i.e. H_p), while the two multiplets at $\delta = 3.3628$ ppm and $\delta = 3.4975$ ppm represent the pro-chiral hydrogen atoms H_m and H_n. The singlet at $\delta = 4.4958$ ppm represents the two hydrogen atoms attached to the carbon atom C₉ (i.e. 2-H_f). The two doublets at $\delta = 5.2120$ ppm and at $\delta = 5.7149$ ppm represents the hydrogen atoms attached to the carbon atom C₁₅ i.e. the hydrogens H_a and H_b. The multiplet at $\delta = 6.7123$ ppm represents the hydrogen atom (i.e. H_c) attached to the carbon atom C₁₄. Now the benzene ring of the product has two different types of hydrogens depending upon the environment. The hydrogen atoms attached to the carbon atoms C₁₁ and C₁₅ (i.e. H_e) are identical in nature for having the identical environment (being close to the ether part). Similarly, the hydrogens attached to the carbon atoms C₁₂ and C₁₄ (i.e. H_d) are identical in nature (being close to the unsaturated part of the product). Now the hydrogen atom H_e is adjacent to H_d and vice-a-versa. Thus each of the two different hydrogens (H_e and H_d) is expected to show doublet. However, the difference in the chemical shifts of the two signals at $\delta = 7.3479$ ppm and at $\delta = 7.3928$ ppm is not significantly larger than the coupling constant, as a result of which the inside peak of the doublet is larger than the outside peak. Another significant signal is the peak of the hydrogens attached to the nitrogen atom of the amine part. The integration of the peak at $\delta = 2.2262$ ppm shows that the peak represents the six hydrogens of the two methyl groups attached to the nitrogen atom. In case of leucinol derivative **1** there was one singlet representing those six hydrogen atoms. This difference can be explained in terms of steric hindrance developed due to the presence of bulky styrene molecule. In **2** the two methyl groups although pro-chiral in nature undergoes free rotation and at any time both the conformation have almost equal contribution to the geometry of **2**. However, in case of **5** the presence of bulkiness due to styrene keeps inversion at nitrogen

from happening resulting in development of two distinct conformations and hence the ^1H NMR spectra showed two singlets rather than only one.

The ^{13}C NMR (100 MHz, CDCl_3) spectrum (Figure 36) showed a distinct peak at $\delta = 61.2904$ ppm corresponding to the carbon atom C_9 . Similarly the signal at $\delta = 113.7673$ ppm represents the carbon atom C_{17} . Depending upon the nature of the adjacent group, i.e. the nature of the environment, the two carbon atoms C_{11} and C_{15} are identical. Similarly, the carbon atoms C_{12} and C_{14} are identical. Therefore, the other two important peaks at $\delta = 126.2461$ ppm and at $\delta = 127.8365$ ppm represent the carbon atoms C_{11} and C_{15} (both identical) and C_{12} and C_{14} (both identical) respectively. The spectrum at $\delta = 136.6375$ ppm represents the carbon atom C_{16} . The spectrum at $\delta = 136.9127$ ppm represents the carbon atom C_{10} and finally the spectrum at $\delta = 138.2585$ ppm represents the carbon atom C_{13} .

Similarly, the structure can also be confirmed by the 2D-cosy (^1H vs. ^1H) NMR (Figure 37). Few important signals are mentioned as follows, while the detailed discussion about the spectrum is in the appendix. There are two signals at $\delta = 3.3628$ ppm and at $\delta = 3.4975$ ppm which correlate with the ^1H peaks along the X-axis as well as Y-axis and proved that the signals on the ^1H spectrum at $\delta = 3.3268$ ppm and at $\delta = 3.4975$ ppm represent the two prochiral hydrogens attached to the C_1 carbon atom. The appearance of two signals on the 2D spectrum confirms that these two hydrogens although attached to the same carbon atom (C_1 carbon atom) are not identical but different—i.e. they are pro-chiral in nature. Because the reaction involves the formation of O-C linkage, so the prochiral nature of the two hydrogens are not expected to be disturbed and this is exactly observed on the spectrum. It also shows the influence of one hydrogen over the other. Similarly, the signal

corresponding to the $\delta = 2.2262$ ppm which correlates with the signal along X as well as Y axis suggests that it represents the hydrogens of the methyl group attached to the nitrogen of the amine part. However, in case of the methylated leucinol a singlet represents the two-methyl groups. From this it can be suggested that the presence of styrene derivative might have some impact. The signal at $\delta = 4.4958$ ppm represents the two hydrogens attached to the carbon atom C_9 . Moreover, it does not have any hydrogen attached to the adjacent atoms and hence no second signal corresponding to these two hydrogens has been observed. The two hydrogens H_a and H_b attached to the carbon atom C_{17} are different in character and are influenced by each other as well as by the adjacent hydrogen atom H_c attached to C_{16} carbon atom in the 2D-cosy diagram.

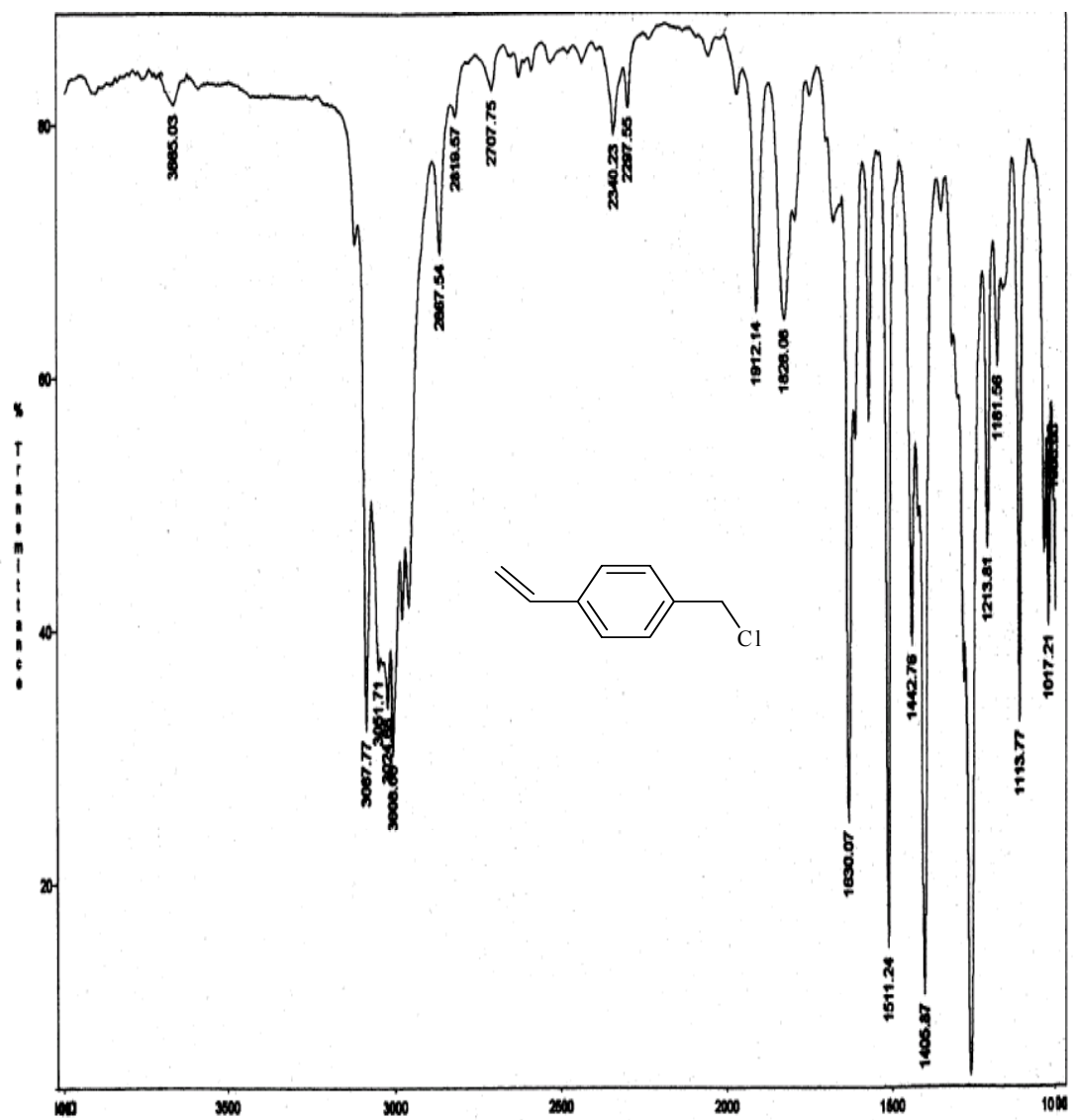


Figure 33. FTIR of 4-vinylbenzyl chloride.

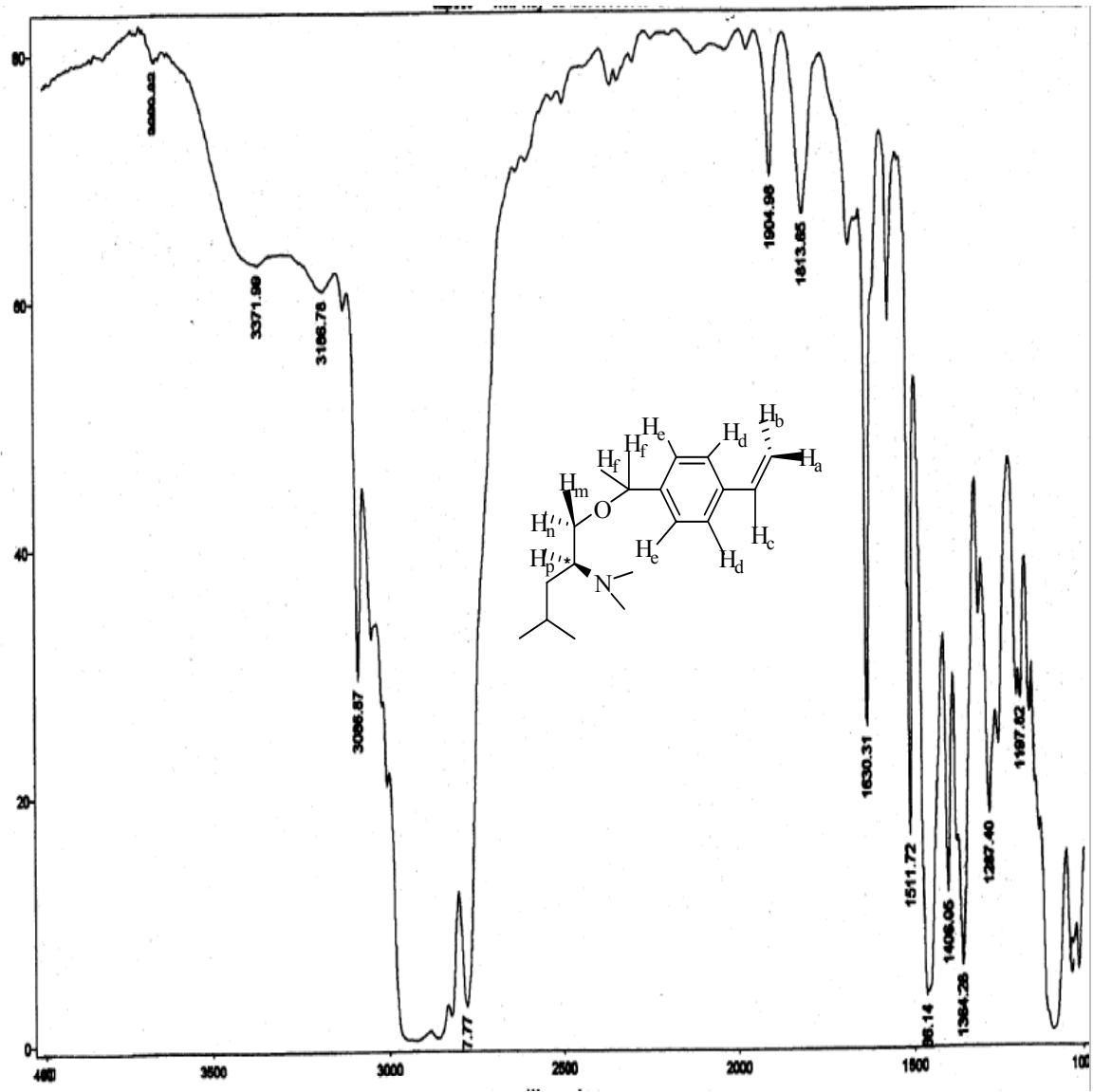


Figure 34. FTIR of the functionalized monomer.

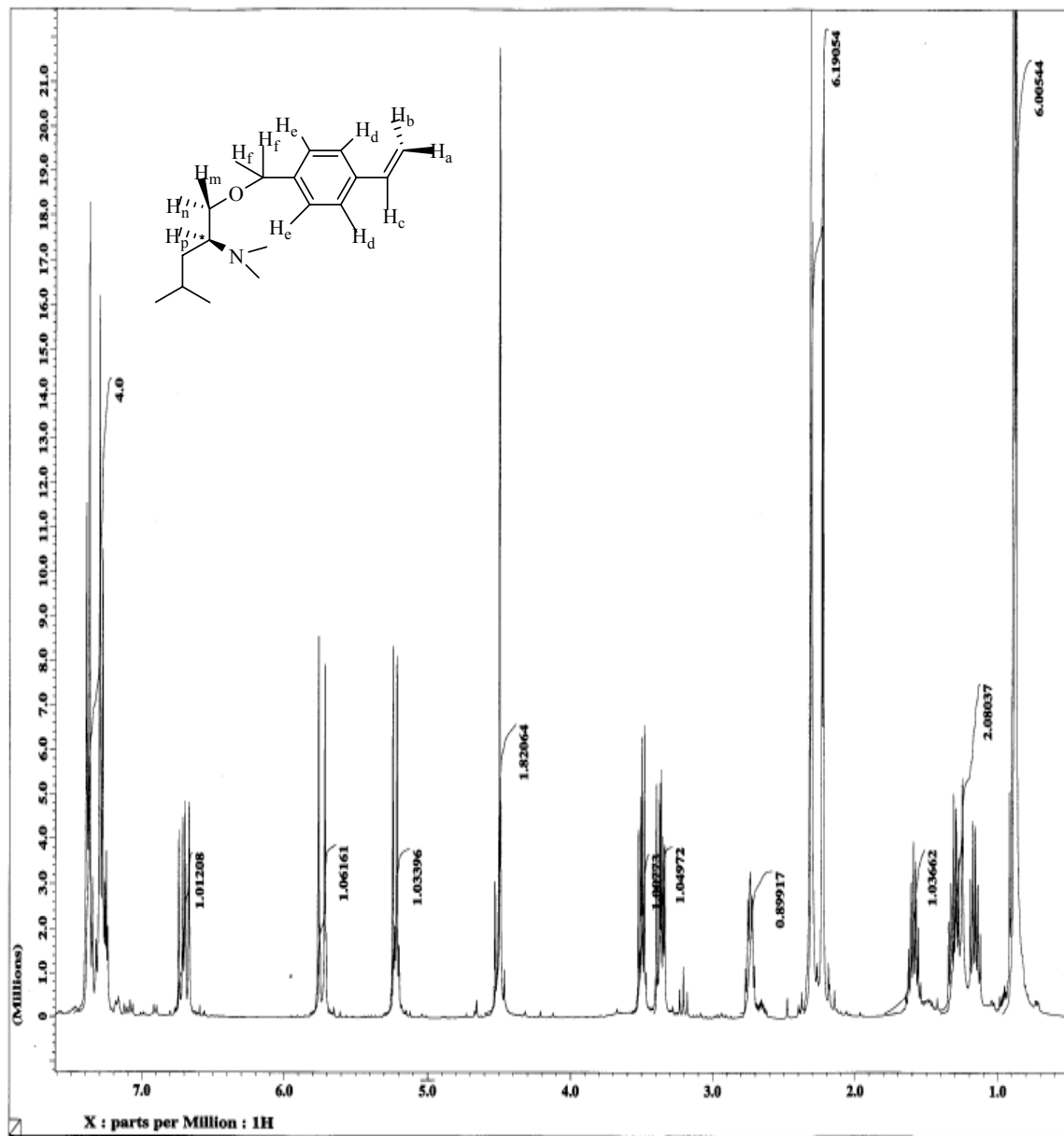


Figure 35. ^1H NMR of the functionalized monomer.

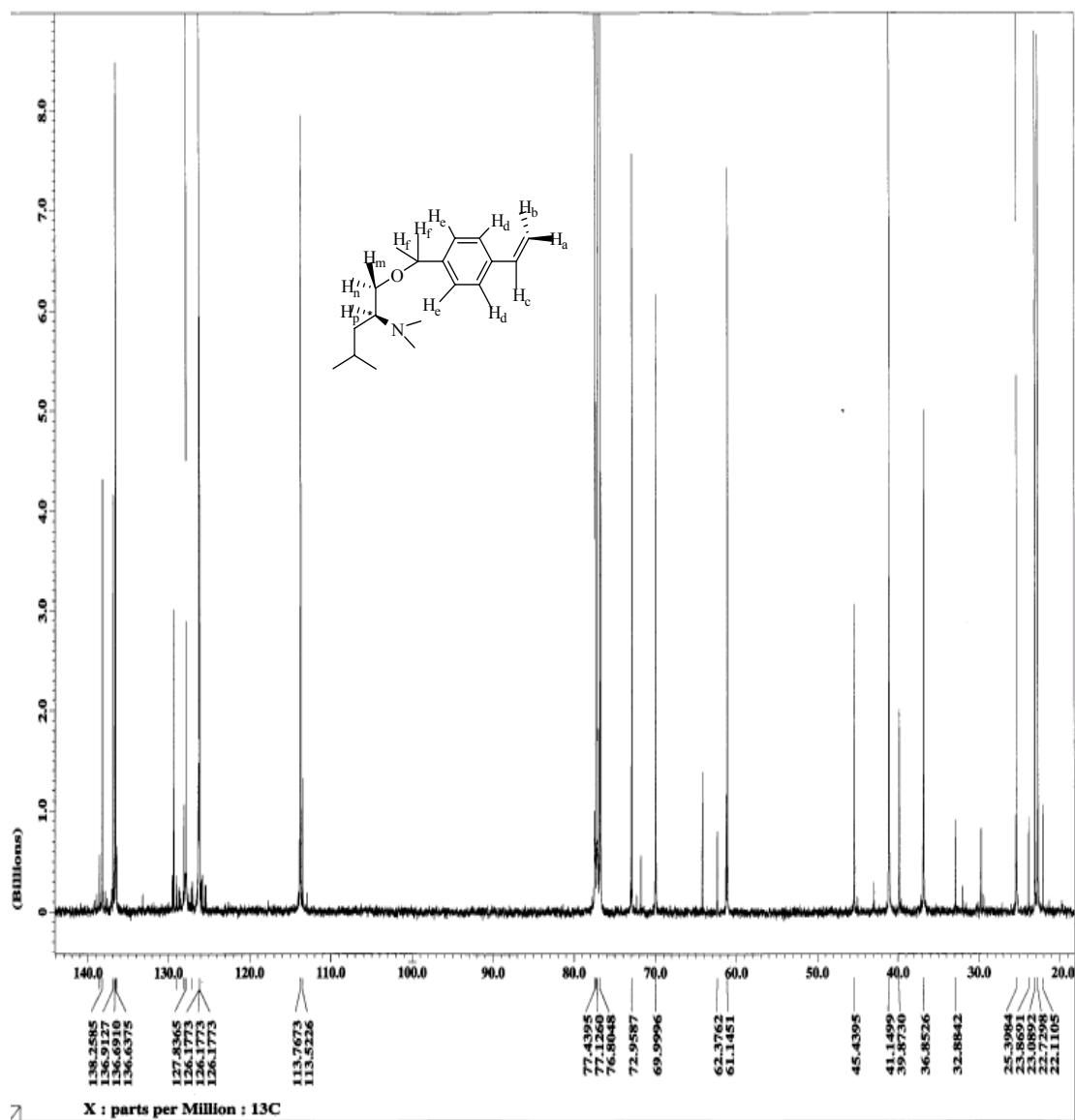


Figure 36. ^{13}C NMR of the functionalized monomer.

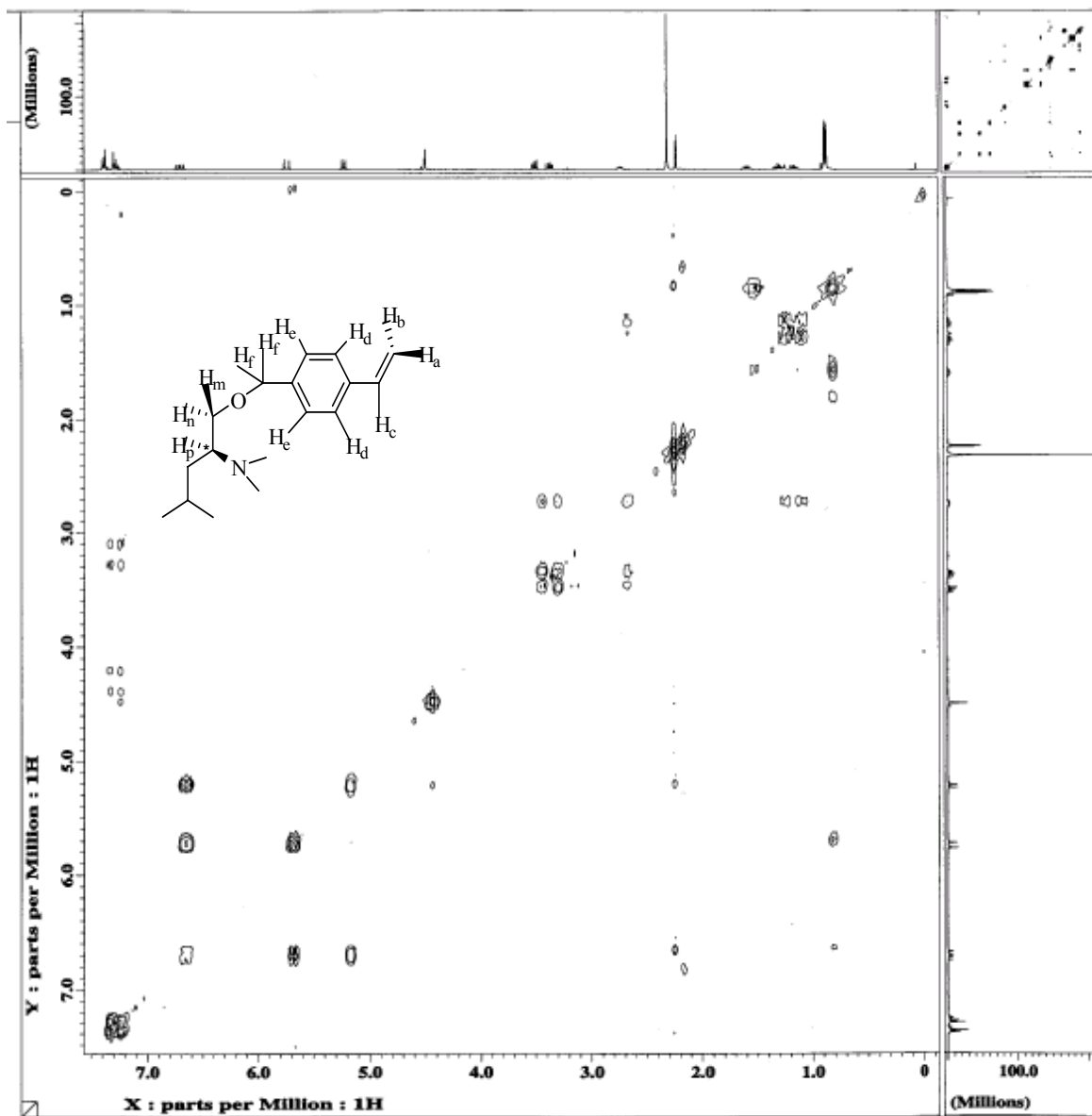


Figure 37. 2D-cosy NMR of the functionalized monomer.

Polymerization of the Functionalized Monomer

The functionalized monomer thus obtained was co-polymerized with styrene using divinylbenzene (DVB) as the cross-linking agent and 2,2'-azobisisobutyronitrile (AIBN) as the initiator. Polymerization was carried out in water as the aqueous phase and toluene/THF as an organic phase. The Figure 38 depicts the polymerization and the Scheme 7 shows the overall chemical equation for the polymerization.

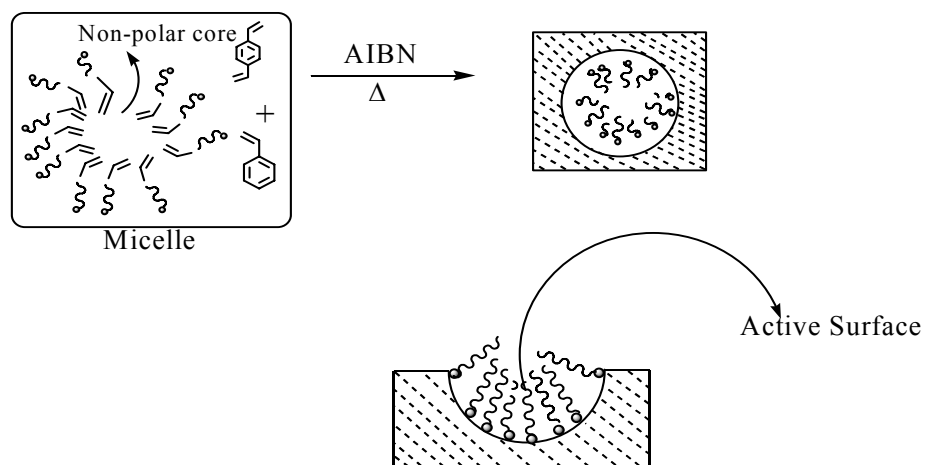
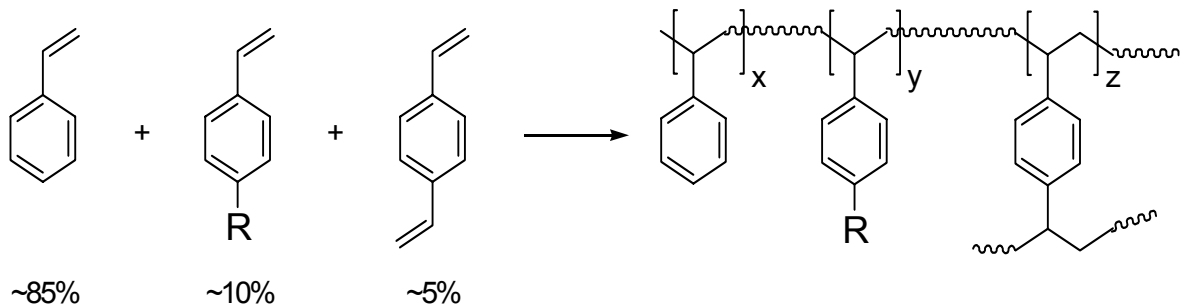


Figure 38. Formation of the polymer-supported catalyst.



Scheme 7. Chemical equation for the polymerization.

The incorporation of the functionalized monomer into the polymer can be done in two ways. In the first case the monomer can be attached to a preformed polymer backbone,

whereas in the second way the functionalized monomer can be polymerized together with the other reagents. In the formation of the polymer based chiral catalyst, the second method has been adopted, where the monomer is mixed with styrene and divinylbenzene (cross-linking agent) in a suspension polymerization. The polymerization is carried out with AIBN used as a thermal initiator. The polar groups of the chiral catalyst remain oriented towards the water bulk, resulting in the formation of normal micelle and thereby orient away from the organic styrene based hydrocarbon part towards the outside of the pool. If we consider the structure of the functionalized monomer as $XArCH_2=CH_2$, where X is the chiral hydrophilic part, the dimethylated leucinol part, then being polar it would like to orient at the water- (toluene and THF) interface with mostly immersed in or near the pools as shown in the figure above. If these pools ultimately transform into the surface irregularities during the polymerization then the polar groups will become fixed to the polymer exterior¹⁴. This functionality should have a considerable influence on the activity of the polymer-supported catalyst.

Comparison of the 1H (Figure 39), and the ^{13}C NMR of the polymer-based catalyst (along with the 1H and ^{13}C NMR of the functionalized monomer, of the crosslinked-polystyrene without the presence of the functionalized monomer) confirmed the formation of the desired product. However, because the crosslinked polymer-based catalyst is virtually insoluble in the solvent $CDCl_3$ used for the NMR analysis, the signals observed are mostly representing the non-crosslinked part of the product. The presence of the multiplet at $\delta = 7.2536$ ppm and $\delta = 7.1864$ ppm represents the hydrogen atoms being part of the benzene ring which may come from styrene, divinyl benzene or the functionalized part of the polymer-based surfactant. Similarly the big peak at $\delta = 2.4039$ ppm represents the hydrocarbon backbone based on polystyrene. Thus the comparative study of the 1H NMR of

the all confirmed the formation of the polymer-supported catalyst. The peak at $\delta = 6.7123$ ppm represents the prochiral hydrogens of the surfactant. Two peaks $\delta = 5.2120$ ppm and $\delta = 5.7149$ ppm represent the benzylic hydrogen atoms. At $\delta = 2.5205$ ppm the hydrocarbon backbone of the styrene based polymer.

From the ^{13}C NMR (100 MHz, CDCl_3) (Figure 40), the peak at $\delta = 21.5829$ ppm and at $\delta = 23.5556$ ppm represent the two carbons (designated as C_6 and C_5 of the functionalized monomer) being part of the functionalized monomer fraction of the catalyst. The peak at $\delta = 128.3259$ ppm represents the presence of the aromatic ring which may be part of the styrene or divinyl benzene or even coming from the functionalized monomer. $\delta = 40.6605$ ppm (C_7 and C_8 , the carbon atoms attached to the nitrogen atom of the functionalized part of the polymer catalyst), $\delta = 61.2904$ ppm (the carbon attached to benzene group), and $\delta = 137.9756$ ppm represents the aromatic part coming from the functionalized monomer.

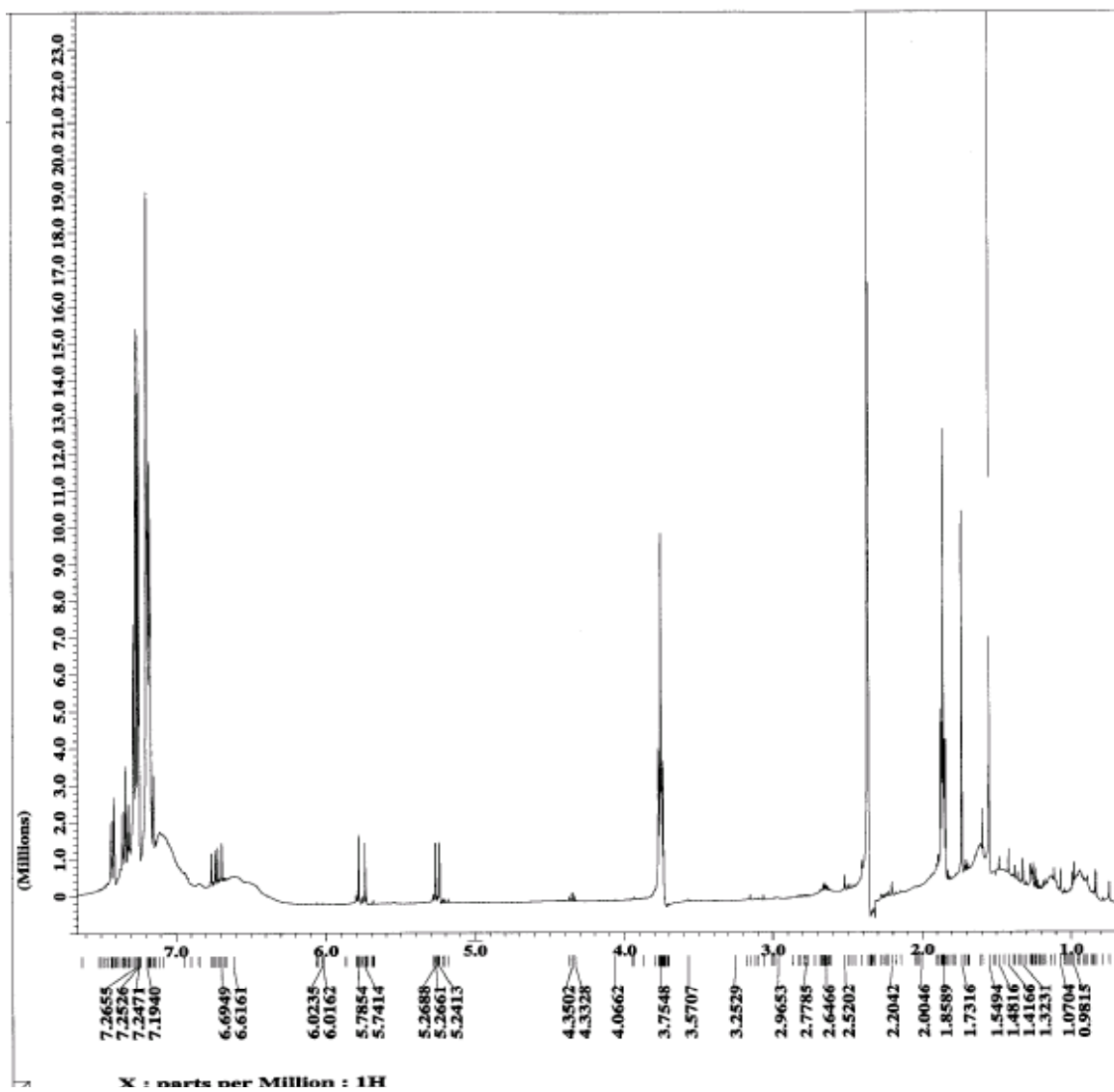


Figure 39. ^1H NMR of the polymer-supported catalyst.

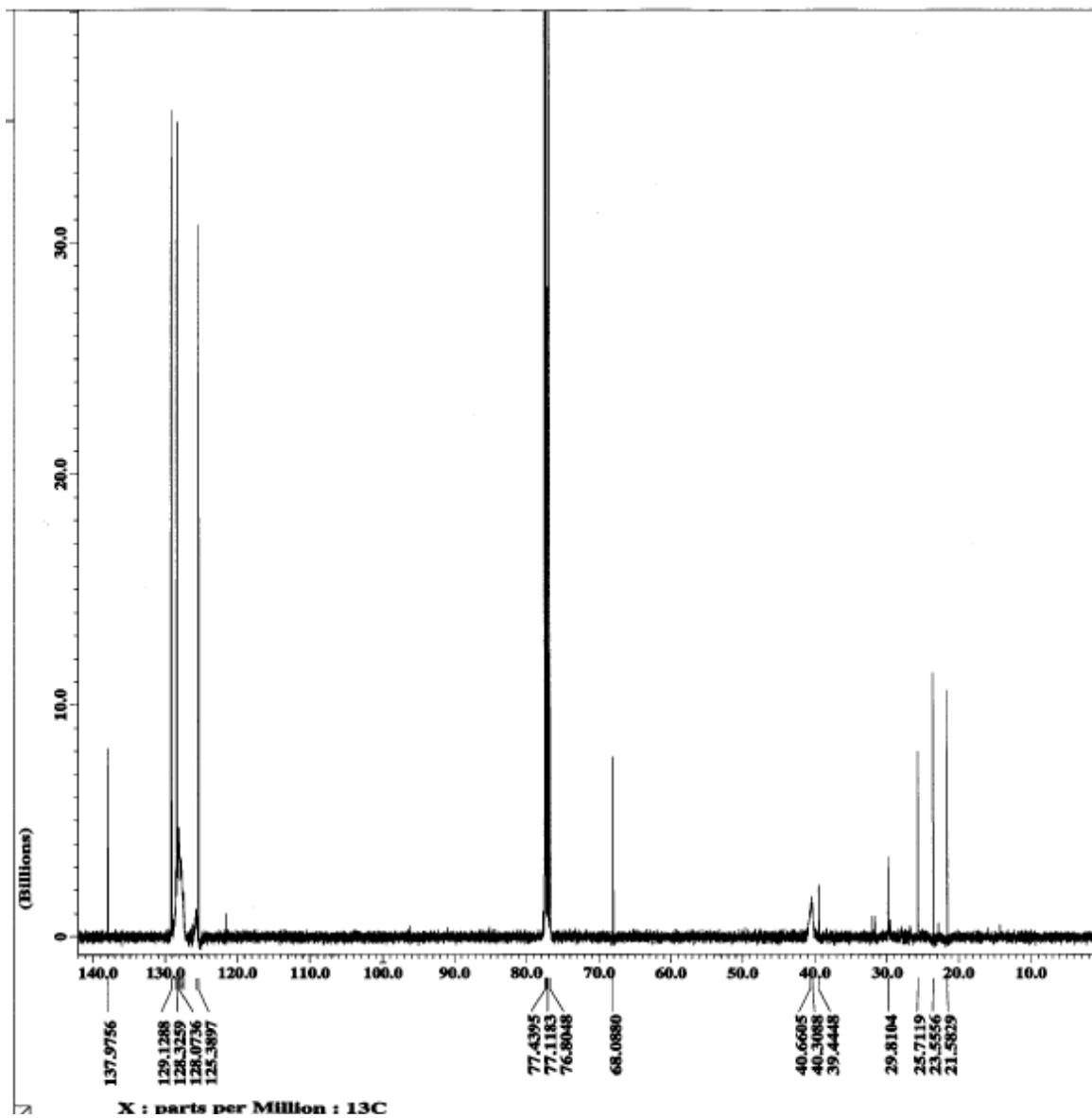


Figure 40. ^{13}C NMR of the polymer-supported catalyst.

Analysis of the ^{13}C NMR of the Ester of 2-Pentanol Using Polymer-supported Catalyst

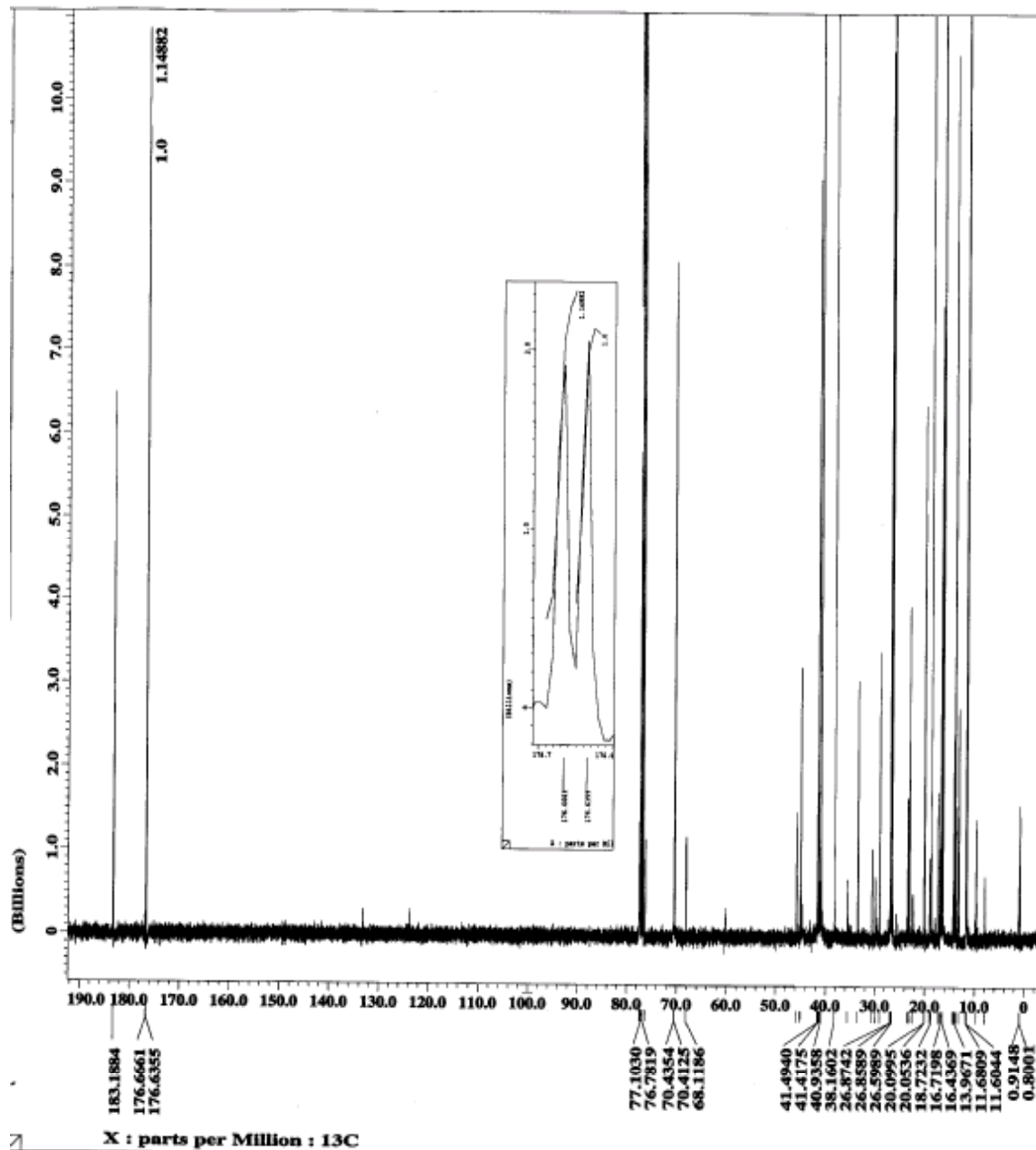


Figure 41. ^{13}C NMR of the ester from 2-pentanol using polymer-supported catalyst.

The Figure 41 represents the ^{13}C NMR of the ester obtained from the alcohol 2-pentanol using polymer-supported catalyst. Similar to the hydrocarbon-based chiral surfactant, the alcohol obtained by the reduction of 2-pentanone in presence of the polymer-supported catalyst is expected to show enantiomeric excess yield. The appearance of two carbon signals at $\delta = 176.6661$ ppm and $\delta = 176.6355$ ppm represent two different carbonyl carbons of the ester and this is possible only if we have two different enantiomeric alcohols. This intern justifies our conclusion that in presence of the polymer-based chiral catalyst the reduction of the alcohol 2-pentanol gave enantiomeric excess. The integration of the two-carbonyl carbon peaks showed a result of approximately 7 % enantiomeric excess of the 2-pentanol.

The ^{13}C NMR (Figure 42) of the ester made from the alcohol (S)-2-pentanol generated with the polymer-supported catalyst was taken in presence of chemical shift reagent $\text{Eu}(\text{fod})_3$. A relaxation delay time of 5 sec was used (usual delay time is 1 sec) to allow quantitative integration. The carbon atoms C_6 and C_4 of the ester are chiral in nature giving rise to the formation of two diastereoisomers. The appearance of two different signals for both the C_4 ($\delta = 70.4583$ ppm and $\delta = 70.4430$ ppm) and C_6 ($\delta = 41.5857$ ppm and $\delta = 41.6622$ ppm) carbon atoms together with the C_5 (carbonyl carbon of the ester having the chemical shift values $\delta = 176.2073$ ppm and $\delta = 176.1691$ ppm) carbon atom and the difference in integration values suggest that they are representing two different esters.

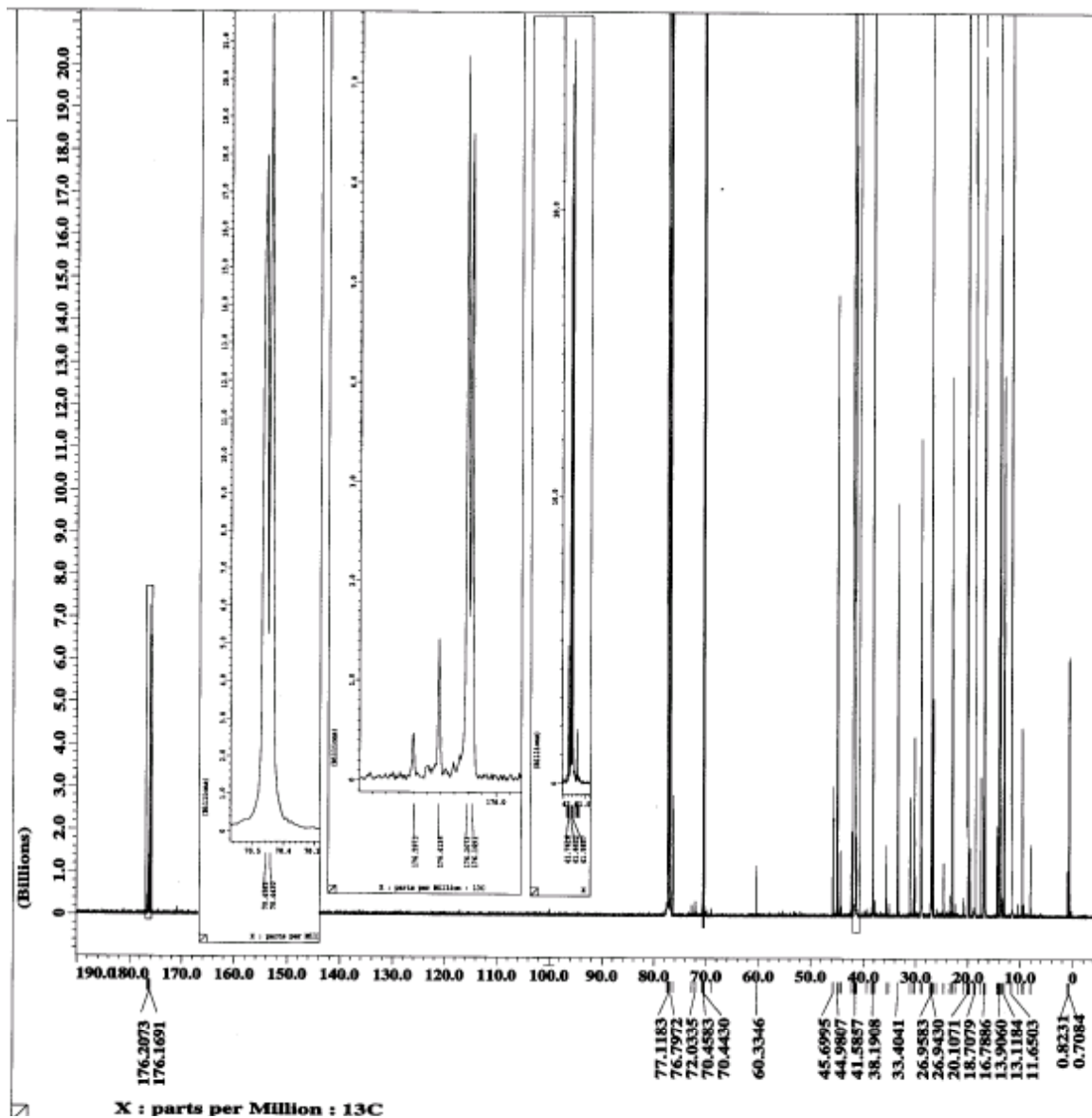


Figure 42. ^{13}C NMR of the ester using polymer-supported catalyst with the shift reagent and relaxation time of 5 sec.

CHAPTER 4

CONCLUSION

We have been successfully able to methylate (S)-leucinol, and we have successfully synthesized the hydrocarbon-based surfactant. We prepared the functionalized monomer based on the methylated leucinol and polymerized it subsequently to produce the polymer-based catalyst. The structures of all these synthetic organic products have been verified with FTIR and NMR (including ^1H , ^{13}C , 2D-cosy and 2D-chsf NMR) spectroscopy. We have attempted to verify the activity of the surfactant by reducing 2-pentanone to 2-pentanol. We successfully prepared a possible enantiomeric mixture of (2R)- and (2S)-pentanol enantiomers. Previous work showed a 6% excess of the (S)-enantiomers. Our products were further tested by esterification with (S)-2-methylbutyric acid. The diastereoisomeric esters have been identified using spectroscopic techniques. The purpose of the synthesis of the ester is to measure the enantiomeric excess of the alcohol using the NMR technique as the diastereoisomers are expected to show different peaks. However, the experimental results from NMR are not well resolved and it was difficult to determine enantiomeric excess from the spectra. If the alcohol was a racemic mixture then we should obtain different signals for the chiral hydrogens but the integration should be in a 1:1 ratio. On the other hand, if we have an enantiomeric excess then again there should be different ^1H NMR signals but the integration should show different values and from the integration it would be easy to determine the percentage of enantiomeric excess. However, we could not conclude whether we have a racemic mixture or enantiomeric excess because the spectrum did not show distinct signals

for the proton of C₄ carbon atom. The ¹³C NMR of the ester gives significant information related to the enantiomeric excess quantity of the two alcohols. Two distinct signals of the carbonyl carbon (one at $\delta = 176.4979$ ppm and the other at $\delta = 176.4596$ ppm) with a integration ratio of 1:1.0955 give some specific information about the formation of an enantiomeric excess (~ 5% ee of 2-pentanol) in 2-pentanol. The activity of the polymer-supported catalyst based on the leucinol derivative was determined by reducing the 2-pentanone into 2-pentanol and subsequently taking the NMR spectrum of the product. Two distinct signals of the carbonyl carbon (one at $\delta = 176.6661$ ppm and the other at $\delta = 176.6335$ ppm) with a integration ratio of 1:1.14882 give some specific information about the formation of an enantiomeric excess (~ 7% ee of 2-pentanol) in 2-pentanol. Both the ¹H NMR as well as the 2D-cosy NMR spectra of 2-pentanol were taken in presence of a chemical shift reagent europium(III)tris(1,1,1,2,2,3,3,-heptafluoro-7,7dimethyl-4,6-octanedione). In absence of the chemical shift reagent 2-pentanol showed a multiplet representing all the four hydrogens attached to the C₃ and C₄ carbon atoms. However, it is expected to observe distinct peaks for the presence of chiral carbon center C₂ close to the C₃ carbon atom of the 2-pentanol. The presence of the chemical shift reagent caused further splitting of the multiplet representing the four hydrogens attached to the C₃ and C₄ carbon atoms and did not show any significant change at C₂ carbon atom. The hydrogens attached to the C₃ carbon atom are prochiral in nature and are expected to show different peaks. Unfortunately, we were unable to come to any definite conclusions using the NMR shift reagent. The percentage of the enantiomeric excess of 2-pentanol and hence the activity of the hydrocarbon-based surfactant as well as the polymer-supported catalyst, can be determined by using a polarimeter. However, we are unable to obtain conclusive results at

this time due to problems with the polarimeter. We hope to obtain information about optical activity in the near future.

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APPENDIX

Analysis of the 2D-chsf NMR spectrums for (S)-2-amino-4-methyl-1-pentanol and (S)-2-N,N-dimethyl-2-amino-4-methyl-1-pentanol (1)

The 2D-chsf NMR spectrums (Figures 10 and 14) give details information regarding the identification of the carbon atoms and their respected hydrogens. This is also very important to justify the change in the structure of the product compared to that of the reactant. In the 2D-chsf NMR spectrum (Figure 10) for (2S)-leucinol there are two signals corresponding to two carbon atoms, which correlate with the signal representing the multiplet at $\delta = 0.8652$ ppm, and this proves that they are C₅ and C₆ carbon atoms. Similarly the signal correlating triplet of the ¹H NMR at $\delta = 1.1455$ ppm and the ¹³C peak at $\delta = 43.5738$ ppm represents the fact that the corresponding carbon atom is C₃. The signal correlating a multiplet of ¹H NMR at $\delta = 1.6556$ ppm and the carbon peak at $\delta = 24.7102$ ppm represents the C₄ carbon atom. The multiplet at $\delta = 2.8692$ ppm and the ¹³C peak at $\delta = 50.6390$ ppm represents the C₂ carbon atom. Finally for the ¹³C peak at $\delta = 66.9869$ ppm there is two signals correlating to the ¹H peaks at $\delta = 3.2053$ ppm and at $\delta = 3.5121$ ppm which proves that the hydrogen atoms attached to the C₁ are pro-chiral in nature. Form the 2D-chsf (¹H vs. ¹³C) NMR (Figure 14) for (S)-2-N,N-dimethyl-leucinol **1** there were two signals corresponding to two carbon atoms $\delta = 22.0646$ ppm and $\delta = 23.8462$ ppm, which correlate with the signal representing the multiplet at $\delta = 0.8469$ ppm of the ¹H NMR, and this proves that they are C₅ and C₆ carbon atoms. Similarly the signal correlating multiplet of the ¹H peak at $\delta = 1.2563$ ppm and the ¹³C peak at $\delta = 32.8037$ ppm represents the fact that the corresponding carbon atom is C₃. The signal correlating a multiplet of ¹H NMR at

$\delta = 1.4523$ ppm and the carbon peak at $\delta = 25.3908$ ppm represents the C₄ carbon atom. The signal correlating the large singlet of the ¹H NMR at $\delta = 2.2335$ ppm and the ¹³C peak at $\delta = 39.8500$ ppm represents the two methyl groups attached to the nitrogen part of the leucinol derivative. For the ¹³C peak at $\delta = 61.2445$ ppm there are two signals correlating to the ¹H peaks at $\delta = 3.1742$ ppm and at $\delta = 3.4389$ ppm which proves that the hydrogen atoms attached to the C₁ carbon atom are pro-chiral in nature. Finally, the signal correlating the multiplet at $\delta = 2.6118$ ppm and the ¹³C peak at $\delta = 62.3226$ ppm represents the C₂ carbon atom.

Analysis of the 2D-chsf NMR spectrum for (S)-2-N-hexadecyl-N,N-dimethyl-(1-hydroxy-4-methyl-1-pentyl)-2-ammonium bromide (2)

The 2D-chsf (i.e. ¹H vs. ¹³C NMR comparison) NMR (Figure 19) of the hydrocarbon surfactant **2** gives a lot of information for the identification of the structure of the surfactant. A signal correlating the multiplet at $\delta = 0.8469$ ppm of the ¹H NMR and the singlet at $\delta = 14.2118$ ppm of the ¹³C NMR represents the fact that that particular carbon is C₂₄, i.e. the last carbon atom of the long hydrocarbon tail of the surfactant. Similarly three signals correlating three peaks of the ¹³C NMR at $\delta = 22.8828$ ppm (i.e. C₂₃), at $\delta = 29.4816$ ppm (i.e. C₁₁-C₂₂), and at $\delta = 31.9972$ ppm (i.e. C₁₀) with the multiplet at $\delta = 1.2206$ ppm suggest that carbon atoms corresponding to these three peaks of the ¹³C NMR spectrum represent the hydrocarbon tail of the surfactant. Similarly, there are two methyl groups attached to the nitrogen of the quaternary amine part of the surfactant. This has been verified from the 2D spectrum. The two signals correlating singlet at $\delta = 3.2410$ ppm of the ¹H NMR with peak at $\delta = 49.8973$ ppm (¹³C NMR) and singlet at $\delta = 3.3546$ ppm (¹H NMR) with the peak

at $\delta = 50.1420$ ppm (^{13}C NMR) justified that expectation. Again the carbon atom of the long hydrocarbon tail adjacent to the nitrogen atom is expected to show a down field shift. The signal correlating the multiplet at $\delta = 3.6916$ ppm of the ^1H NMR with the singlet at $\delta = 64.1501$ ppm of the ^{13}C NMR justifies this. The doublet at $\delta = 3.4782$ ppm of the ^1H NMR represents the hydrogens attached to the carbon atom C_2 as there is a signal correlating the doublet at $\delta = 3.4782$ ppm with the singlet at $\delta = 57.5666$ ppm of the ^{13}C NMR. Similarly the signals correlating the two doublet at $\delta = 0.9705$ ppm and at $\delta = 1.0099$ ppm of the ^1H NMR with the two singlets at $\delta = 21.5141$ ppm and at $\delta = 24.0603$ ppm represent the two terminal methyl groups of the leucinol part of the surfactant (i.e. C_5 and C_6). The signal correlating the multiplet at 1.7573 ppm of the ^1H NMR with the singlet at $\delta = 25.8037$ ppm represents the carbon atom C_4 and the signal correlating the multiplet at $\delta = 2.0064$ ppm with the singlet at $\delta = 33.9927$ ppm represents the carbon atom C_3 . Finally, the two hydrogens attached to the carbon atom C_1 adjacent to the hydroxyl group are pro-chiral in nature and this can be proved with the 2D spectrum of the surfactant. The two doublets at $\delta = 4.2421$ ppm and at $\delta = 3.9069$ ppm correlate with the one singlet at $\delta = 71.6665$ ppm of the ^{13}C NMR, which means that particular carbon atom has two different hydrogens showing two different signals on the ^1H NMR spectrum.

Analysis of the 2D-cosy NMR spectrum for (S)-2-pentanol (3)

In case of 2-pentanol **3** the 2D-cosy (^1H vs. ^1H) NMR (Figure 22) represents which hydrogen is close proximity to which hydrogen. If the signal at $\delta = 0.9220$ ppm represents the hydrogen attached to the 5th carbon of the product, then the signal for this hydrogen must be influenced by the adjacent hydrogens. With respect to this hydrogen, the hydrogens

attached to the 4th and 3rd carbon must show some influence. The appearance of a second signal correlating the triplet at $\delta = 0.9220$ ppm and the multiplet at $\delta = 1.4047$ ppm proves that the hydrogen represented by the triplet is the hydrogen attached to the 5th carbon. Similarly, a second signal correlating the multiplet at $\delta = 3.7878$ ppm and the doublet at $\delta = 1.1775$ ppm suggests that the proton signal for the later is influenced by the presence of the hydrogen attached to the C₂. In the same way, the proton spectrum for the hydrogens attached to the C₃ and C₄ carbon atoms must be influenced by the hydrogens attached to the C₅ and C₂ carbon atoms. The signal correlating multiplet at $\delta = 1.4047$ ppm and the triplet at $\delta = 0.9220$ ppm proves the influence of the hydrogens attached to C₅. Similarly, a signal correlating the multiplet at $\delta = 3.7878$ ppm and the doublet at $\delta = 1.1775$ ppm represents the influence of hydrogens attached at C₃, C₄ and at C₁ carbon atoms on the hydrogen attached to C₂ carbon atom.

Analysis of the 2D-cosy NMR spectrum for the functionalized monomer (5)

From the 2D-cosy (¹H vs. ¹H) NMR (Figure 37); if the signal at $\delta = 0.8753$ ppm represents the hydrogens of terminal methyl groups attached to C₄ carbon atom then the 2D-cosy for the product should show a signal correlating the peak at $\delta = 0.8753$ ppm and peak at $\delta = 1.6080$ ppm. We observe that peak, which definitely proves that the peak at $\delta = 0.8753$ ppm represents the terminal methyl hydrogens and the signal at $\delta = 1.6080$ ppm represents the hydrogen attached to C₄ carbon atom. Similarly, there are two signals at $\delta = 3.3628$ ppm and at $\delta = 3.4975$ ppm which correlate with the ¹H peaks along the X-axis as well as Y- axis and proved that the signals on the ¹H spectrum at $\delta = 3.3268$ ppm and at $\delta = 3.4975$ ppm represent the two prochiral hydrogens attached to the C₁ carbon atom. The

appearance of two signals on the 2D spectrum confirms that these two hydrogens although attached to the same carbon atom (C_1 carbon atom) are not identical but different—i.e. they are pro-chiral in nature. Similarly, signals at $\delta = 1.2471$ ppm shows that the multiplet simply represents the two hydrogens attached to the C_3 carbon atom. It also shows the influence of one hydrogen over the other. Similarly the signal corresponding to the $\delta = 2.2262$ ppm which correlates with the signal along X as well as Y axis suggests that it represents the hydrogens of the methyl group attached to the nitrogen of the amine part. However, in case of the methylated leucinol a singlet represents the two methyl groups. From this it can be suggested that the presence of styrene derivative might have some impact. However, unlike the hexadecane methylated leucinol, there are not sharp two singlets but a multiplet. The signal at $\delta = 4.4958$ ppm represents the two hydrogens attached to the carbon atom C_9 . Moreover, it does not have any hydrogen attached to the adjacent atoms and hence no second signal corresponding to these two hydrogens has been observed. Similarly the hydrogens H_d and H_f are different because of their different environment and the 2D NMR shows signals showing the effect of H_f on H_d and vice-a-versa. The two hydrogens H_a and H_b attached to the carbon atom C_{17} are different in character and are influenced by each other as well as by the adjacent hydrogen atom H_c attached to C_{16} carbon atom in the 2D-cosy diagram.

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