EASY AND WIDE-RANGING VICINAL DIFUNCTIONALIZATION OF ALKENES

An abstract of

A Thesis

Presented to the

Department of Chemistry

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In Partial Fulfillment

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Masters of Science

By

Hima Bindu Gottam

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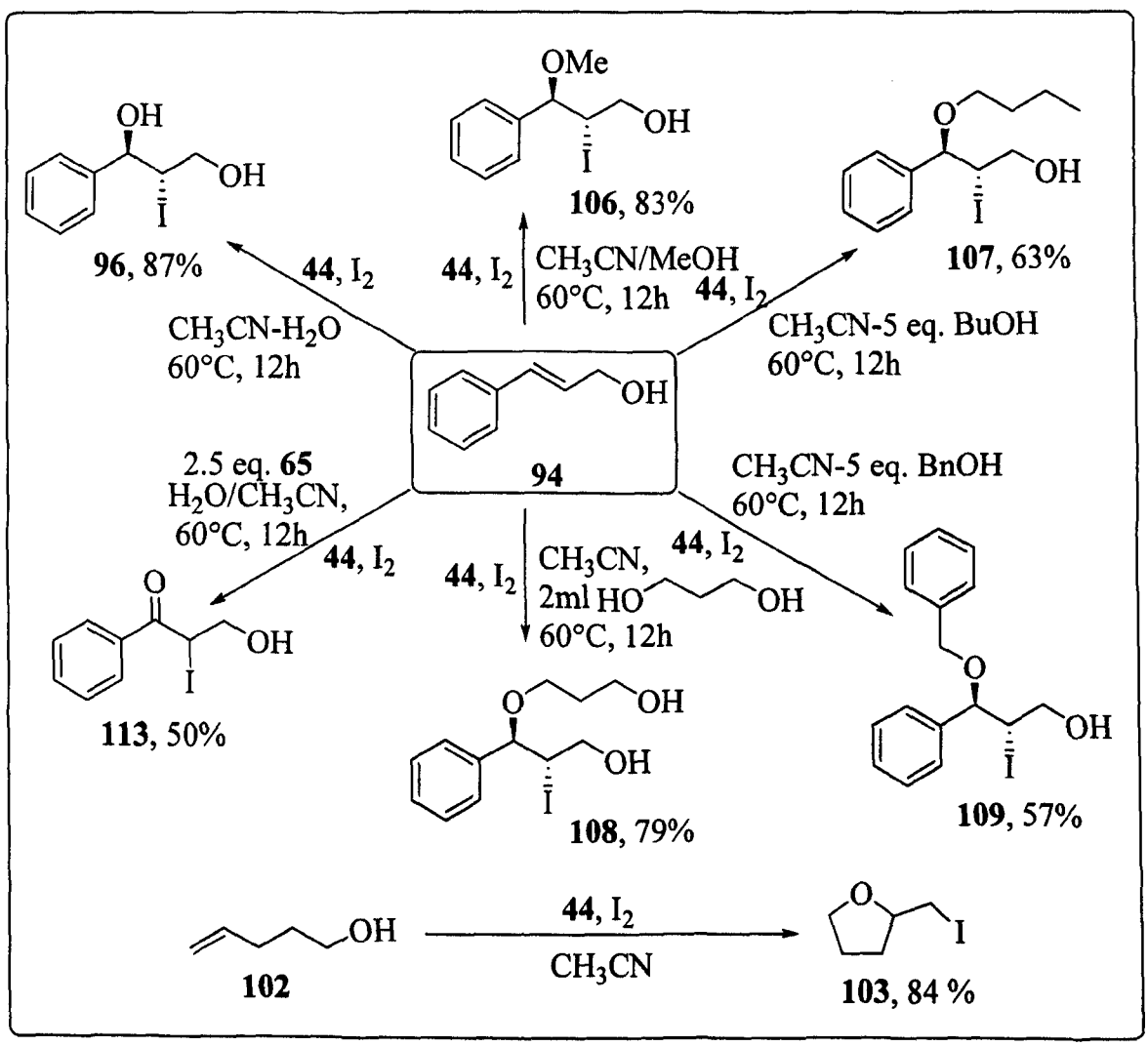
ABSTRACT

Regio- and stereoselective 1,2-addition to alkenes resulting in the incorporation of two different vicinal functional groups is a highly sought synthetic manipulation. Here in we wish to report our results from a systematic exploration of the co-addition of I-Nu across the double bonds using in situ generated acyl-hypoiodite intermediates **78** and **80** (not shown here) obtained from the oxidation of elemental iodine with hypervalent iodine reagents, **44** and **65** respectively, a variety of nucleophiles can be used, often as co-solvents in the reaction or tethered nucleophiles in the substrate as in **102** to obtain the highly functionalized products shown in the box.



APPROVAL PAGE

This thesis by Hima Bindu Gottam is accepted in its present form by the Department of Chemistry of Western Illinois University as satisfying the thesis requirement of the degree Master of Science.

Chairperson, Examining Committee

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Dec 9, 2009

Date

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TABLE OF CONTENTS

List of Figures

List of Tables

List of Abbreviations

IBX	*o*-Iodoxybenzoic acid
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
THF	Tetrahydrofuran
$KBrO_3$	Potassium Bromate
S-IBX	safe IBX
m-IBX	modified IBX
NMR	Nuclear Magnetic Resonance
D_2O	Deuterium Oxide
IR spectra	Infra Red spectra
CH_3CN	Acetonitrile
Equiv.	Equivalents
BDE	Bond Dissociation Energy

1. INTRODUCTION

1.1 Functionalization of Alkenes

Functionalization of alkenes[1] is one of the most important transformations in organic synthesis. Although, there are a multitude of methodologies for convenient functionalization of alkenes, organic chemists continue to search for new functionalization protocols or for new eco- and user-friendly[2] alternatives for already existing procedures. A large variety of synthetically important organic compounds can be synthesized from alkenes by functionalization. The utility of these compounds over the starting materials (alkenes) can be attributed by the introduction of new functional groups on the carbon backbone, the possibility of further manipulation of the newly introduced groups and more importantly the change of hybridization from sp^2 to sp^3 during the reaction make the final molecules stereogenic.[3] Regio[4] and stereocontrol[3, 4] during the functionalization reaction allows for the synthesis of useful chiral molecules.

The ready functionalization of alkenes is a result of the weak π- bond present. Carbon-carbon multiple bonds act as a nucleophilic source as the pi-electrons are delocalized[5] and are readily available to form bonds with an electron deficient source, an electrophile. Carbocations are often involved as intermediates in these reactions and are formed in the slow rate determining step of the reaction. Once the carbocation is formed, the subsequent reaction is fast because of the instability of the charged species. In the second step, usually a nucleophile attacks the carbocation giving the 1,2-electrophilic[5] addition product. Using this simple and common strategy, a wide variety of functional

groups can be attached across the double-bonded carbon atoms to increase the molecular complexity[6] and the functional group richness[6, 7] of the final products.

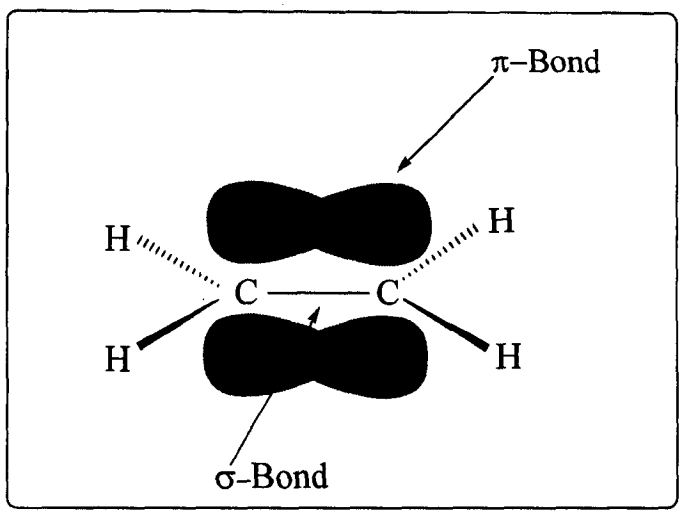


Figure 1. Carbon-carbon double bond showing σ and π bonds.

Though electrophilic addition is one of the most common methods for the functionalization of alkenes, one could also introduce functional groups and/or substituents using non-electrophilic[5] procedures. A classic example is the hydrogenation[5] of alkenes to synthesize the corresponding saturated analogs. Though hydrogenation is addition of simple diatomic hydrogen or simply a hydrogen molecule to the alkene, actually it involves a complex mechanism and this reaction requires either a homogeneous or a heterogeneous catalyst.[5] As the addition takes place on the metal surface the reaction gives a syn-addition[5, 7] product.

1.1a Hydrogenation/Catalytic Hydrogenation

This reaction is also known as "catalytic hydrogenation" as a catalyst is involved in the reaction mechanism. In this reaction, molecular hydrogen binds to the active sites of the metal catalyst breaking the H-H bond and forms metal-H species. Then, the

hydrogen atom from this species will be adsorbed by the alkene present in the reaction medium giving syn-addition product.

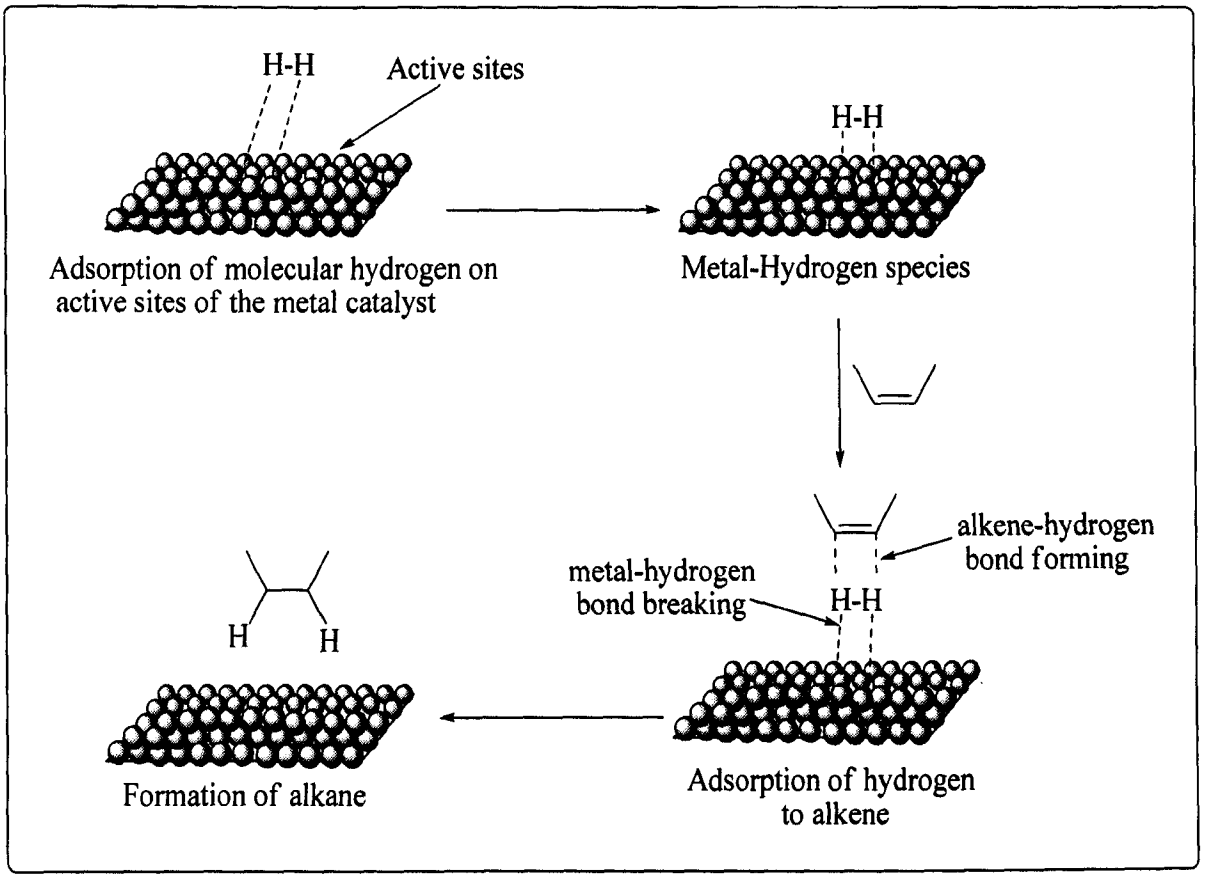
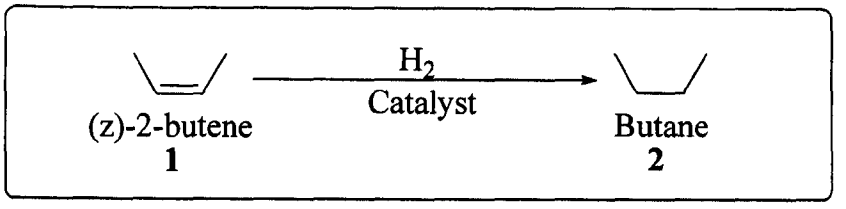


Figure 2. Schematic representation of catalytic hydrogenation

The nature of the catalyst is more important in this reaction. Homogeneous catalysts are more efficient over heterogeneous catalysts because of the solubility of homogeneous catalysts in the reaction medium that can make entire matrix of the catalyst to be exposed to the hydrogen and alkene as well. The number of active sites is then more for a homogeneous catalyst compared to the insoluble heterogeneous metal catalyst. This explains the need of large quantities of heterogeneous metal catalyst for effective hydrogenation compared to the use of small quantities of homogeneous catalyst for the same molar amounts of alkene. Wilkinson's catalyst[5] which is chlorotris(triphenyl-

phosphine)rhodium, $RhCl(PPh_3)_3$ is one of the most widely used homogeneous catalysts whereas Pt is found as effective metal catalyst in heterogeneous category. The other commonly used catalysts are Pd, Ni, Ru, Rh, Ir, PtO_2 and Vaska's catalyst[5], $IrCOCl(PPh_3)_2$ [bis(triphenylphosphine)iridiumcarbonylchloride].



The important feature of this reaction is stereoselectivity and the selectivity depends on the type of catalyst and steric hindrance of the alkene to be reduced. The selection of a suitable catalyst should be based on the type of alkene to be reduced and stereochemistry of the desired product. For example, using a chiral catalyst in hydrogenation, one can achieve asymmetric induction[5] on the final derivative. A catalyst with a chiral ligand is useful in asymmetric catalytic hydrogenation and examples of chiral ligands[5] include: a C_2 chiral diphosphine ligand obtained from tartaric acid, DIOP, **3**; a C_2 symmetric chelating bisphosphine ligand, DIPAMP, **4**; bis(aminophosphine) ligand, PNNP, **5** and (2,2-bis(diphenylphosphino)-1,1-binaphthyl),BINAP, **6**.

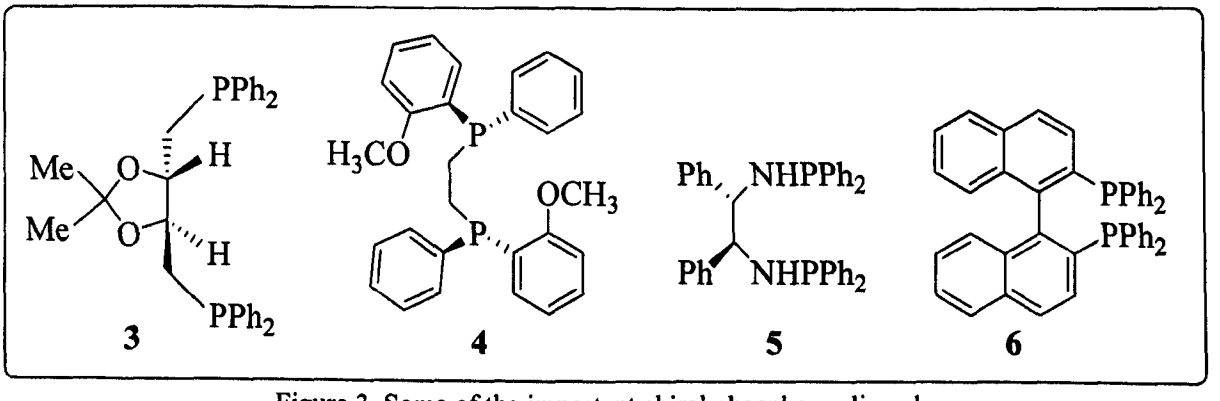
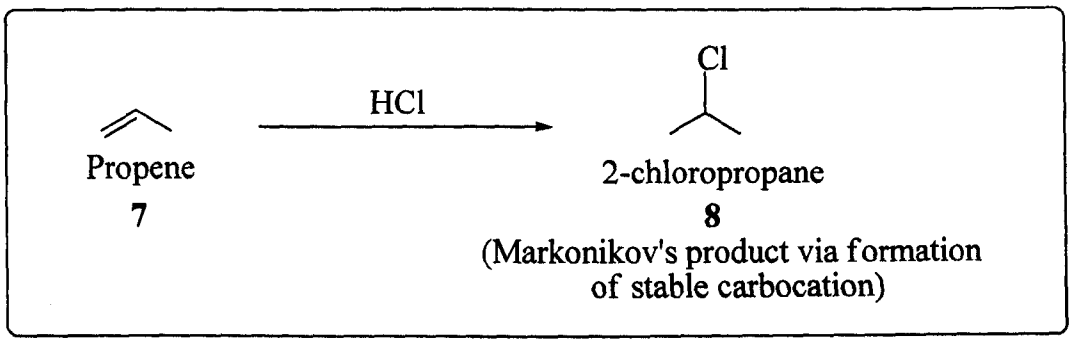


Figure 3. Some of the important chiral phosphorus ligands

As indicated earlier, addition of diatomic hydrogen to the alkene is a non-electrophilic process, in which both hydrogen atoms are added at a time to the double bonded carbons is totally different from the electrophilic addition reactions where the addition takes place in two different steps and one of the easily understandable examples of this type is hydrohalogenation reaction of alkenes.

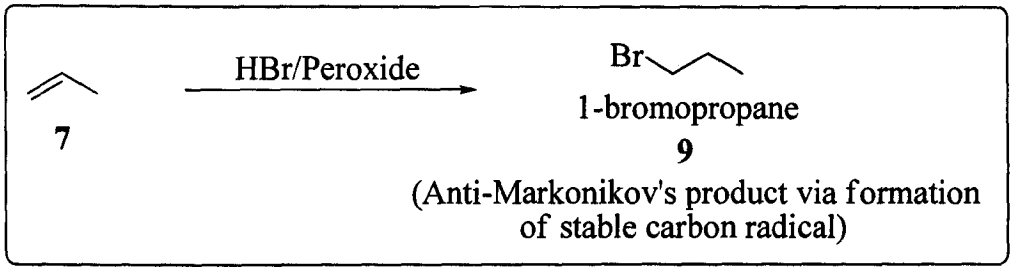
1.1b Hydrohalogenation

Addition of hydrogen and halogen to the double bond of an alkene is known as hydrohalogenation which is carried out[5, 7] by the reaction of alkene with hydrohalic acid. Generally, the addition gives Markonikov's product[5] in which halogen is added preferentially to the carbon having less number of hydrogens. The regiochemistry of addition is explained by the mechanism which involves a carbocation intermediate. Depending upon the stability of the carbocation the reaction proceeds to the forward direction to give a more stable intermediate followed by forming the corresponding product.



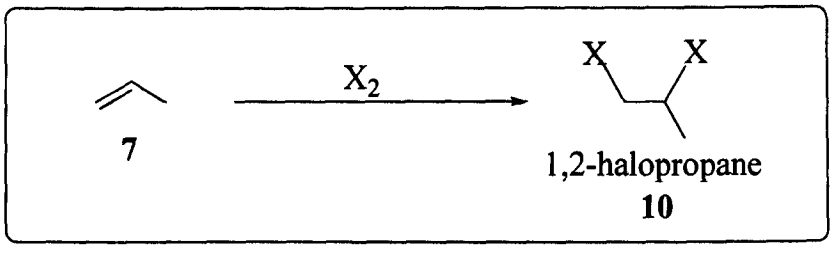
Anti-Markonikov's product[5] can also be obtained when hydrobromic acid is added to alkenes in presence of peroxides in which radicals[7] are formed as intermediates.

Addition of HCl and HI cannot be carried out in an Anti-Markonikov fashion using peroxides.



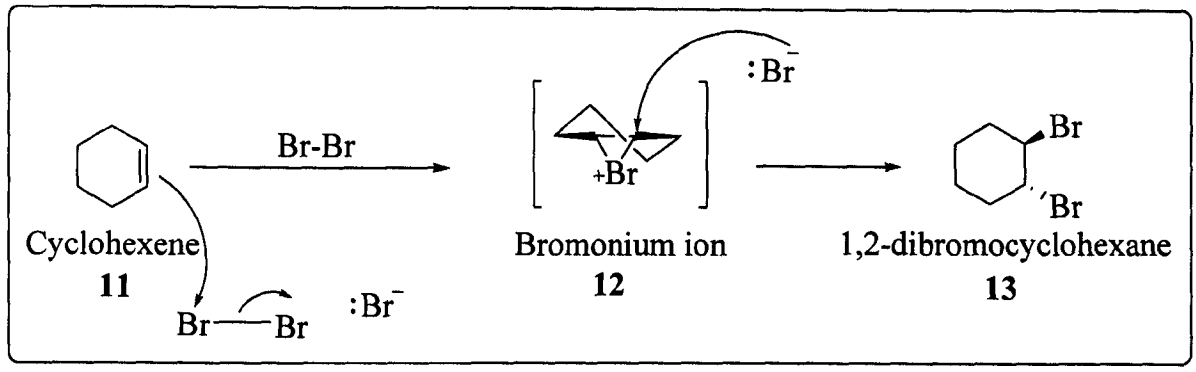
1.1c Halogenation

Halogenation is the addition of halogen to the alkene yielding a dihaloalkane via formation of a halonium ion intermediate.



The mechanism for bromination reaction is explained here. The characteristic feature of this reaction is the formation of cyclic bromonium ion[5, 7] intermediate **12**. Involvement of cyclic intermediate accounts for the stereospecificity.[7] The initially formed cyclic bromonium ion intermediate immediately undergoes further transformation by reacting with the bromide ion which is formed in the first step. Because of the large size of bromide ion, it has to come from the opposite side of the bromonium ion **12** to open up the ring giving a trans product **13**. If the compound is asymmetric and cyclic,

then both stereo and regio-selectivity play role in determining the major product. These reactions have to be strictly carried out in non-nucleophilic[7] medium.



Iodination occurs the same way but is considerably slower because of the reversibility of the reaction. In order to enhance the reaction rate, metallic salts[8] have to be added to the reaction mixture. Iodo compounds are synthetically[9] very important in synthetic organic and medicinal chemistry.[10] In organic synthesis, iodo compounds are important because of the ease of replacement of iodine with other nucleophilic functional groups through substitution. In medicinal chemistry, iodo compounds are used as important diagnostic agents as radioactive isotope of iodine can be readily introduced through this reaction. Diatrizoic acid, **14** is one of the extensively used diagnostic agents whereas triiodothyronine, **15** and thyroxine, **16** are the two forms of thyroid hormone.[10]

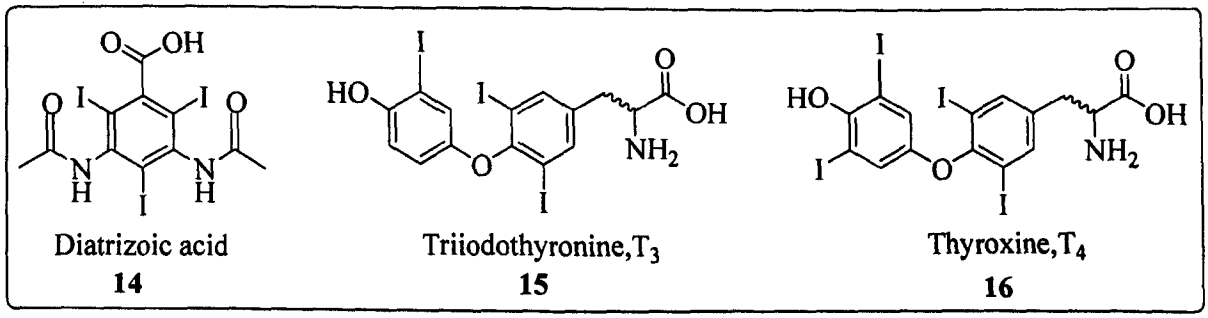
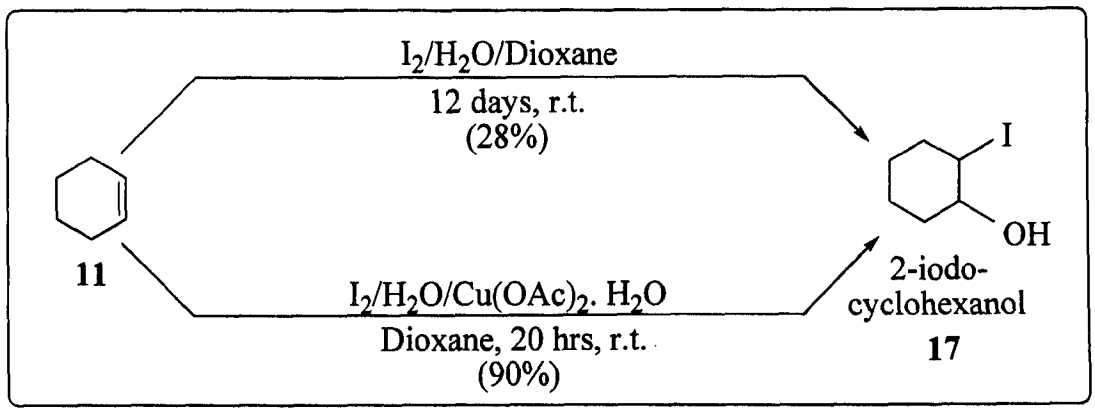


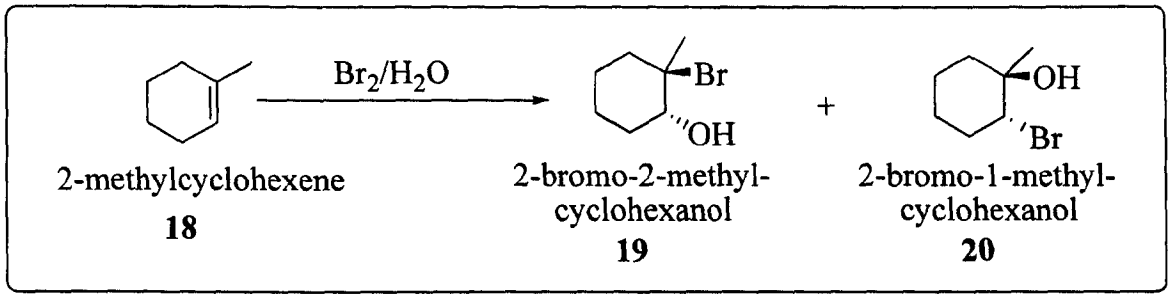
Figure 4. Some of the important iodocompounds

1.1d Halohydrins

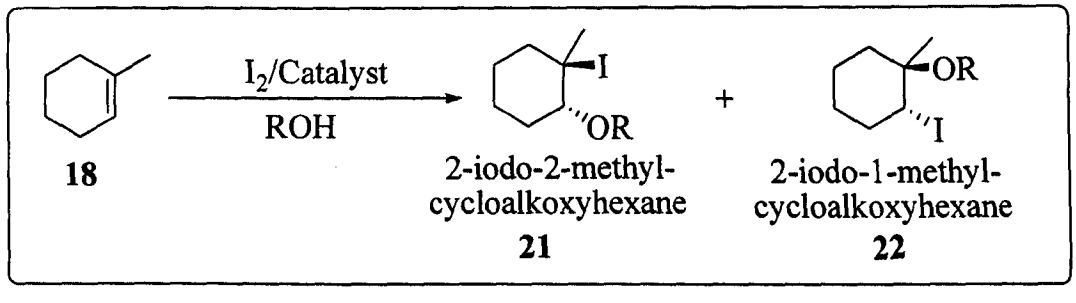
When an alkene is iodinated in presence of water the product is an iodohydrin. It is reported[8] that co-iodination (a process by which an iodine atom and a heteroatom are added in one step across a double bond) which was carried out by adding molecular iodine/water/dioxane to the alkene gave 28% of 2-iodocyclohexanol[8], **17** after 12 days of reaction at ambient temperature and the same reaction was completed in 20 hrs with 90% yield by maintaining the same conditions except $Cu(OAc)_2$ is added. This clearly indicates that addition of metallic salts along with aqueous iodine increases the rate of the reaction.



As indicated above, these halohydrins can be formed by 1,2- electrophilic addition reaction of alkenes in aqueous halogen solutions. As in halogenation, the mechanism of the reaction is through the formation of the cyclic halonium ion intermediate which upon attack by the nucleophilic water molecule gives halohydrin as the final product. The mechanism guarantees anti-addition[5] products formed in a stereospecific manner.



The basic difference in the synthesis of bromohydrins and iodohydrins is that bromohydrins can be prepared directly from the dilute aqueous bromine solutions and alkenes. But the same procedure is not favorable for iodohydrin preparation because of reversibility of the reaction by the presence of hypoiodous acid which is produced as the byproduct of the reaction. This situation thus necessitates finding out alternative procedures[11] for synthesizing iodohydrins. Similarly by using alcohols as solvents one can easily prepare iodoalkoxy[1, 11] compounds in the same manner.



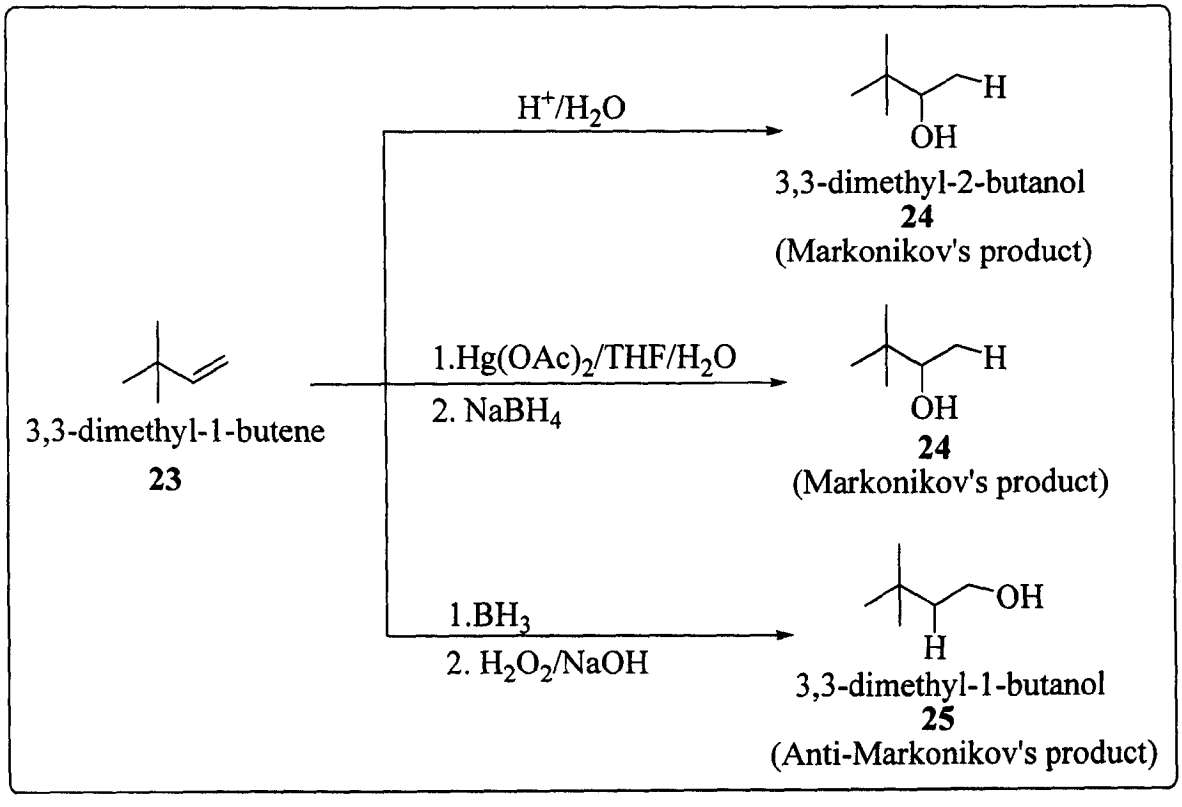
Alternative methods for iodohydrins include the use of triiodide ion[13], dimethyldioxirane in methyl iodide[14], sonochemical iodohydrin synthesis[15], and use of hypervalent iodine reagents.[4]

Though, the target of all these reported methodologies is to prepare iodofunctionalized products, the mechanisms through which the reaction occurs may be quite different.

1.1e Hydration and Hydroxylation of Alkenes

The two well known reactions of alkenes which are widely used in synthesis and in chemical industries are hydration and hydroxylation reactions where the alkene carbon atoms are oxidized. Though hydration of alkenes is easily carried out using aqueous acid, this method is not frequently used in the synthesis of complex molecules due to undesired side reactions that often accompanies the acid catalyzed hydration. Better hydration methods include oxymercuration-demercuration and hydroboration-oxidation methods.[5-7] While the first procedure produces the Markonikov's product, the latter protocol gives rise to anti-Markonikov addition product.

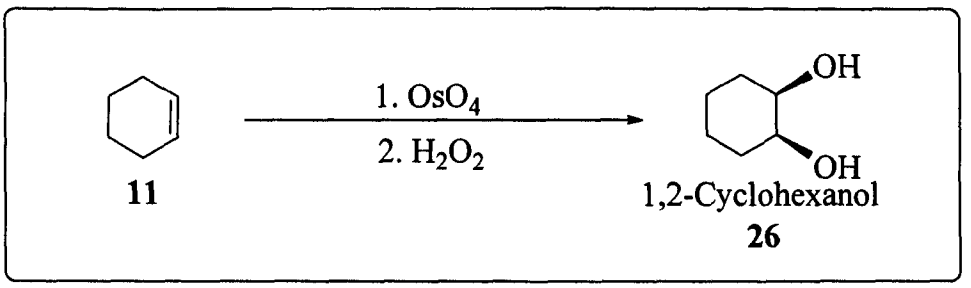
Acid catalyzed hydration of alkene is an example of a simple 1,2- electrophilic addition method, while oxymercuration-demercuration method follows a mechanism similar to the bromination reaction. In the first step of the reaction the electrophile, $^{+}Hg(OAc)$ is added on to the alkene in a Markonikov fashion. Because of the large size of mercury atom and the lone pair of electrons on it, it forms cyclic bridge intermediate which is then opened up in the second step by the nucleophile (water or alcohol) from the opposite side leading to the trans geometry addition product. In the final step, the carbon-mercury bond is reductively cleaved using sodium borohydride, a hydride delivering agent.



Hydroboration-oxidation method is a convenient method for hydrating an alkene in Anti-Markonikov fashion. The first step of this involves electrophilic addition of boron to the alkene followed by a simultaneous transfer of it from boron-hydrogen bond to the other carbon of the alkene. This step namely hydroboration step is an example of syn-addition reaction. In the next step, the boron atom is oxidatively removed from carbon using oxidizing agent resulting in final anti-Markonikov product.

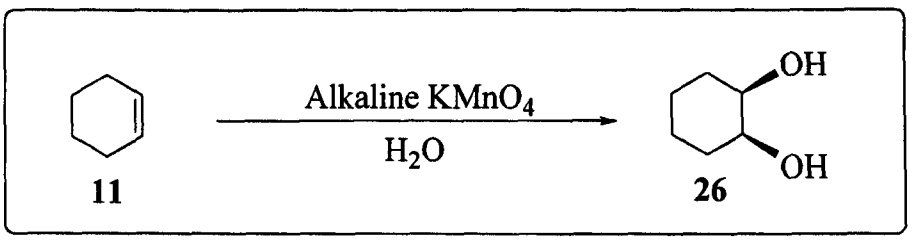
In hydroboration-oxidation method, boron acts as electrophile because of its empty p- orbital and this reaction is via a stable four-member bridge transition state in which all the members get partial charges and upon oxidation using hydrogen peroxide it leads to the final anti-Markonikov's product. As the addition occurs on the same side of alkene the product formed is syn-addition product.

Hydroxylation of alkenes is quite easily accomplished using OsO_4 in conjunction with H_2O_2 or using alkaline $KMnO_4$ at low temperature. Both protocols give rise to syn addition product and are believed to occur through the intermediate of an osmate ester or manganate ester respectively.



11 1,2-Cyclohexanol **26**

Similarly cold, alkaline potassium permanganate solution can oxidize alkenes yielding vicinal diols via a stereospecific syn-addition. This reaction is used for identification of presence of olefinic double bond.



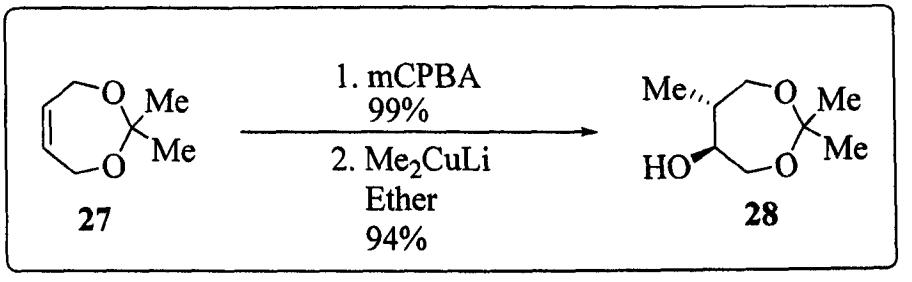
11 **26**

All the above mentioned methods are well known conventional methods for functionalization of alkenes and have been used over the decades. Synthetic chemists continue to be interested in devising protocols for easy functionalization of alkenes in predictable region and stereochemical fashion and are also in search of co-functionalization of alkenes.

1.2 1,2-Co-Functionalization of Alkenes

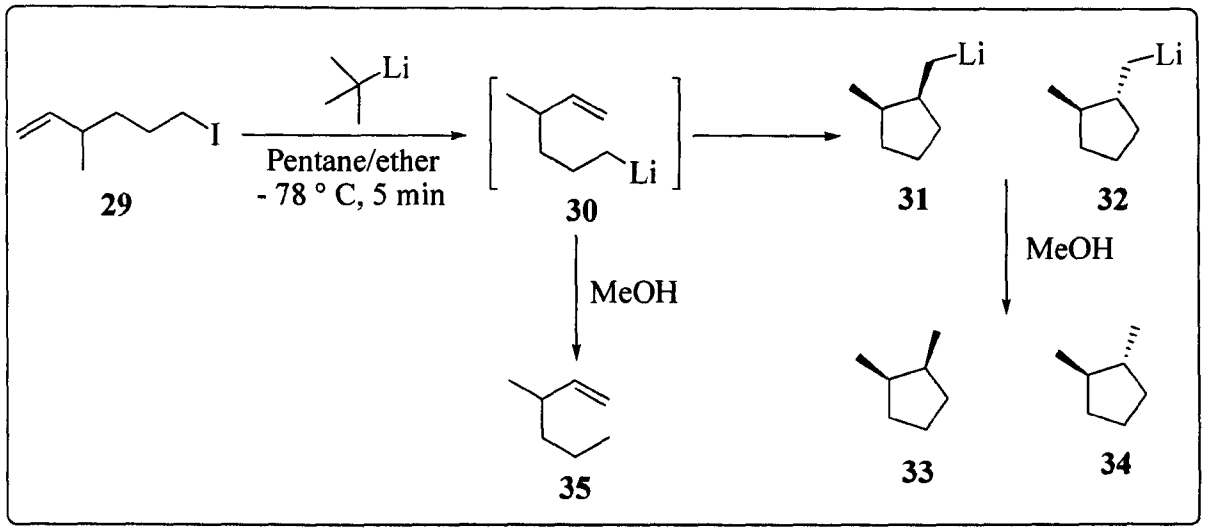
Regio- and stereoselective addition of two different functional groups on vicinal carbons of an olefinic double bond results in 1,2-co-functionalization of alkenes. Cohalogenation[5, 16] is an example of 1,2-co-functionalization reaction where a halogen and a nucleophile are added to a C=C bond. These reactions have been extensively studied over the years to introduce multiple functional groups selectively. The use of iodine in such co-halogenation reactions is suitable and relevant choice because of the importance of iodo derivatives in medicine and pharmaceutical industries.[17]

In Silverstein's synthesis of α-cubebane[5], one of the sequential steps require manipulation of **27** to give **28**. Manipulation of a primary alcohol and a methyl group across the double bond can be carried[5] out using mCPBA and Me_2CuLi in ether. In first step, an epoxide is formed in 99% upon reaction of **27** with mCPBA and this can be easily methylated using Gilman reagent, lithium dimethylcuprate $(CH_3)_2CuLi$ yielding 94% of **28**. This is an example of 1,2-co-functionalization of alkenes where a methyl and a hydroxyl group are added across the double bond.



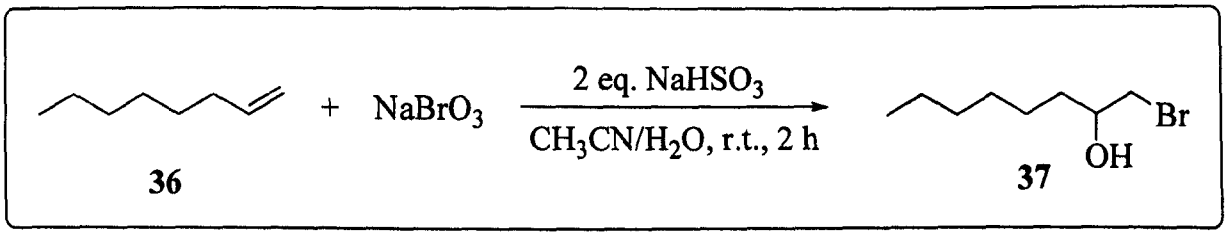
27 **28**

Alkenes also undergo intramolecular addition reactions with organolithium reagents and give cyclization products as shown in **33** and **34**.

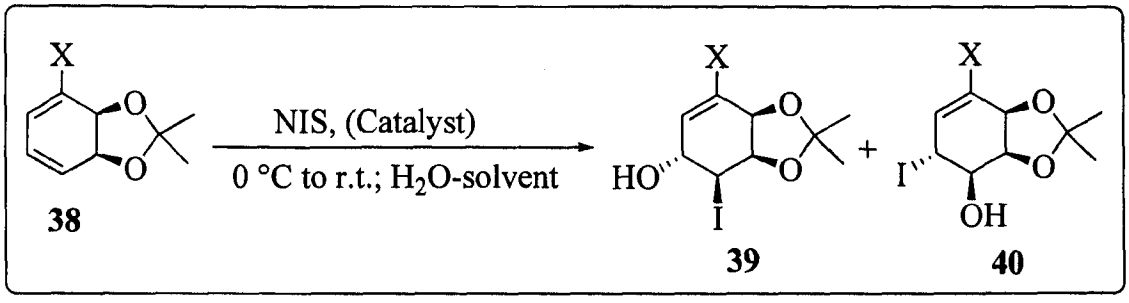


Bailey reported[5] that both the *t*-butyllithium exchange reaction and the cyclization reaction are very rapid even at low temperatures. Reaction of 6-iodo-3-methyl-1-hexene, **29** with *t*-butyllithium in a mixture of pentane and ether at -78 °C for 5 minutes gives rise to a lithium compound, **30**, which cyclized immediately to a mixture of **31** and **32**. These derivatives upon quenching with methanol at low temperatures lead to the formation of **33** and **34** respectively along with a trace amount of uncyclized[5] product **35**.

A simple method[18] was introduced for synthesizing bromohydrins using $NaBrO_3$ and $NaHSO_3$ from alkenes. When octene, **36** is treated with a combination of $NaBrO_3$ and 2 equivalents of $NaHSO_3$ in aqueous-acetonitrlie mixture at room temperature for 2 hours corresponding bromohydrin, **37** is observed as the product.

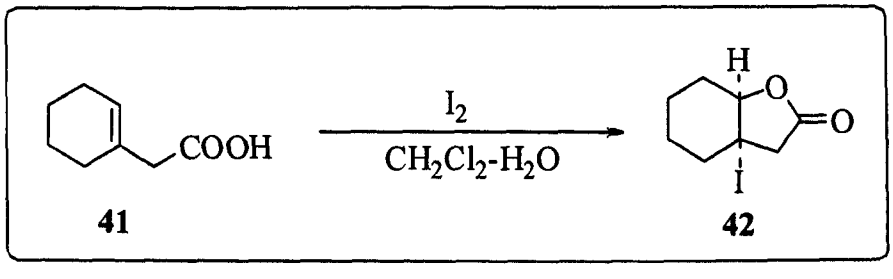


A related methodology[5, 19] for synthesizing iodohydrins (a co-functionalized product) is by using N-iodosuccinimide (NIS) in water. When compound **38** is treated with NIS under 0 °C to room temperature conditions, it gives two regioisomers **39** and **40** as expected.



38 **39** **40**

Similarly, intramolecular iodofunctionalization[9] is observed when compound **41** is treated with molecular iodine using methylene chloride and water as a solvent mixture. The reaction between **41** and the molecular iodine produces the iodonium ion intermediate and the suitably positioned internal nucleophile opens up the iodonium ring, yielding **42** as the product.



41 **42**

The importance of iodofunctionalization methods are already mentioned earlier. In Figure 5 schematically below shows a select few examples of 1,2-cohalogenation of alkenes using iodine electrophile in conjunction with suitable nucleophiles. Iodination of alkenes in presence of water or alcohols readily produces iodohydrins or iodoalkoxy

compounds as noted earlier. Reaction of alkenes with iodine in glacial acetic acid or iodination of alkenes with carboxy appendages easily produces iodoacetoxy[20] and/or iodocarboxy compounds. The introduction of phosphoric acid[16] moiety as a nucleophile in 1,2-cohalogenation though limited, is known, and finds extensive application in sugar chemistry. Similarly azide and amide groups can be introduced as nucleophiles in these reactions to improve and increase the functional group complexity[16] of the final product.

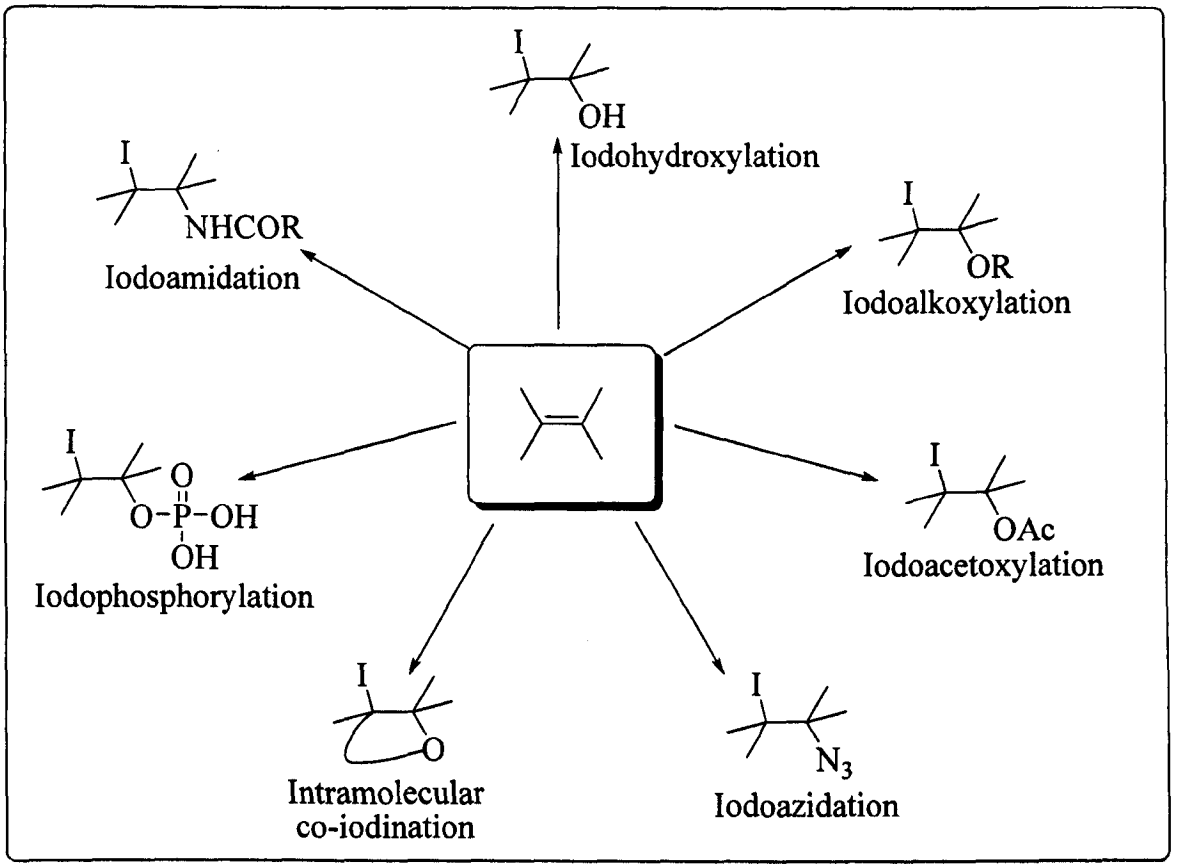


Figure 5. Iodofunctionalization of alkenes

Other nucleophiles such as thiolate anions, cyanide ion etc which are not mentioned here but could also be potentially added to the carbon-carbon double bonds to make synthetically useful co-functionalized derivatives. These reactions occur via the intermediate of an iodonium ion in which the iodonium ring is opened up by the

nucleophile from the opposite side attacking either of the carbon atoms. This mechanistic feature of the reaction explains the regio and stereo chemical outcome of these 1,2-coiodination reactions. The mechanism of these reactions is a simple 1,2- electrophilic addition necessitating[21, 22] the need for an electrophilic iodine reagent to initialize the reaction. The iodine atom in hypervalent iodine reagents are known to be electrophilic in nature and can thus potentially behave as the needed electrophilic source in these reactions.

1.3 Hypervalent Iodine Reagents

The term hypervalency[22] refers to the ability of an atom in a molecule to expand its valency beyond the limits of Lewis octet rule. A hypervalent molecule can be defined as the molecule which contains one or more typical elements generally of group 1, 2, 13-18, and formally bearing more than eight electrons in its valence shell.[22]

Iodine forms relatively stable hypervalent or polycoordinate or multivalent compounds because of its large atomic size and low ionization potential. Hypervalent iodine reagents are well known oxidizing agents[22, 23] and have received more attention over the other hypervalent compounds because of the low toxicity and relatively benign[22] nature of these compounds compared to other heavy metal oxidizing agents such as Hg(II), Tl(III) and Pb(IV) which exhibit similar reactivity. Iodine atom in hypervalent iodine reagents are electrophilic (*vide infra*) and as such these reagents are commonly used as electrophilic reagents for the functionalization of alkenes. A select few examples of hypervalent iodine compounds that have attained the status of reagents in organic synthesis[22] are shown below in Figure 6.

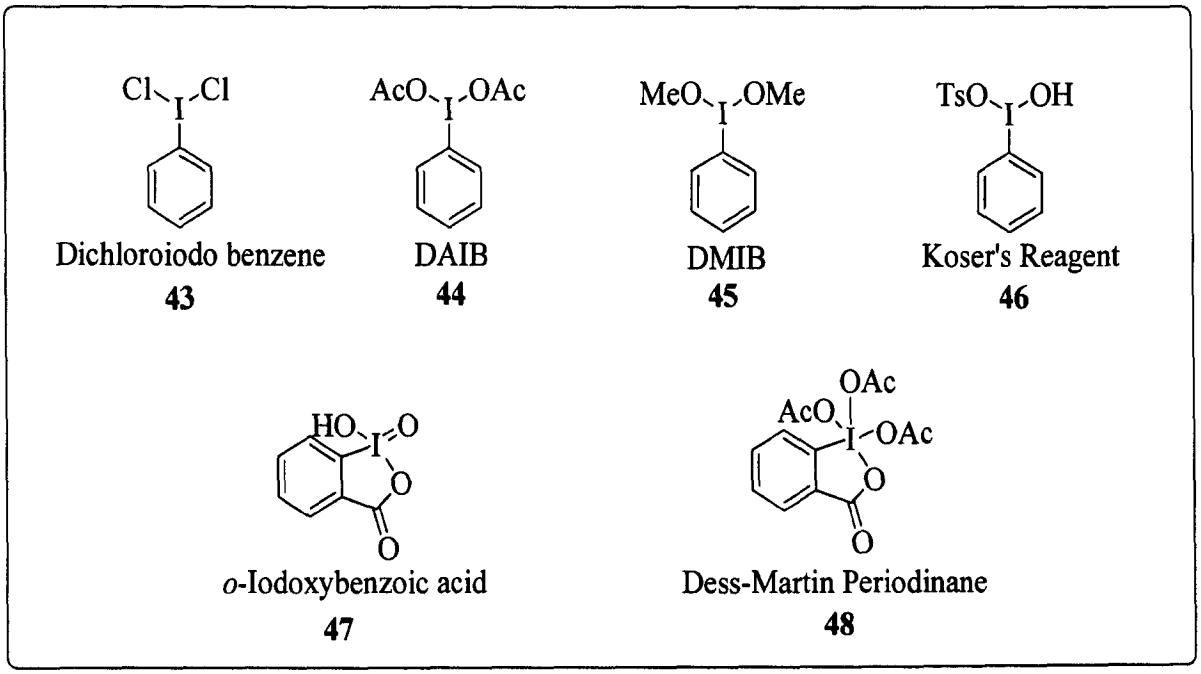


Figure 6. Some examples for hypervalent iodine compounds

1.3a Hypervalent λ^3- Iodine Derivatives

The first polyvalent organoiodine compound reported is dichloroiodo benzene[22, 25], **43**, $PhICl_2$. Since this report, a large variety of hypervalent iodine compounds have been synthesized and many have attained the status of reagents in organic synthesis. Hypervalent iodine compounds are conveniently prepared from iodine (I) compounds using strongly electrophilic (oxidizing) reagents under proper conditions which can lead to the formation of either trivalent or pentavalent iodine compounds. These hypervalent iodine compounds belong to two general structural types.[22] The first one is iodine (III) compounds which are referred to as λ^3-iodanes and the other type is iodine (V) compounds which are referred to as λ^5-iodanes.

The N-X-L notation is often used to represent hypervalent compounds where N indicates the number of valence electrons on the central atom, X represents the chemical symbol of the central atom and L indicates the number of ligands to the central atom. The

λ^3-iodanes are mostly 10-I-3 compounds which exhibit pseudotrigonal bipyrimidal geometry. Elemental iodine being a Group VIIA or Group 17 member, contains seven electrons in its valence shell and thus in a λ^3-iodane has three more electrons donated by the ligands making a decet structure.

1.3b Functionalization of Alkenes with λ^3-Iodanes

Some of examples of hypervalent λ^3-iodanes are: (dichloroiodo)benzene (**43**), (diacetoxyiodo)benzene (DAIB, **44**), (dimethoxyiodo)benzene (**45**), bis(trifluoro-acetoxy)iodo benzene (BTIB), hydroxyl(tosyloxy)iodobenzene (HTIB, **46**) which is also called as Koser's reagent and hydroxyl(bisphenylphosphoryloxy) iodobenzene. The iodine atom in λ^3-iodine reagents are electrophilic in nature and thus found use as electrophilic reagents for alkene functionalization[22]. These compounds also act as mild oxidizing agents. Several comprehensive reviews describing the use of λ^3-hypervalent iodine reagents for alkene functionalization[16, 22, 24] are now available and thus a detailed summary of such reactions are not attempted here. The two examples shown below highlight the use of electrophilic iodine center in λ^3-iodine reagents for the functionalization of alkenes.

Reaction of alkenes with a combination[5] of DAIB, **44** and trimethylsilyl isothiocyanate gives rise to 1,2-dithiocyanates as shown in Figure 7. Similarly, the reaction of protected glycals[5] (**50**) with [bis(acyloxy)iodo]arenes with $BF_3.Et_2O$ at low temperatures results in formation of trans-1,2-bis(acyloxy)glycosides, **51**. Here, the purpose of using $BF_3.Et_2O$ is to activate the catalyst and enables the conversion of protected glycal to compound **51**.

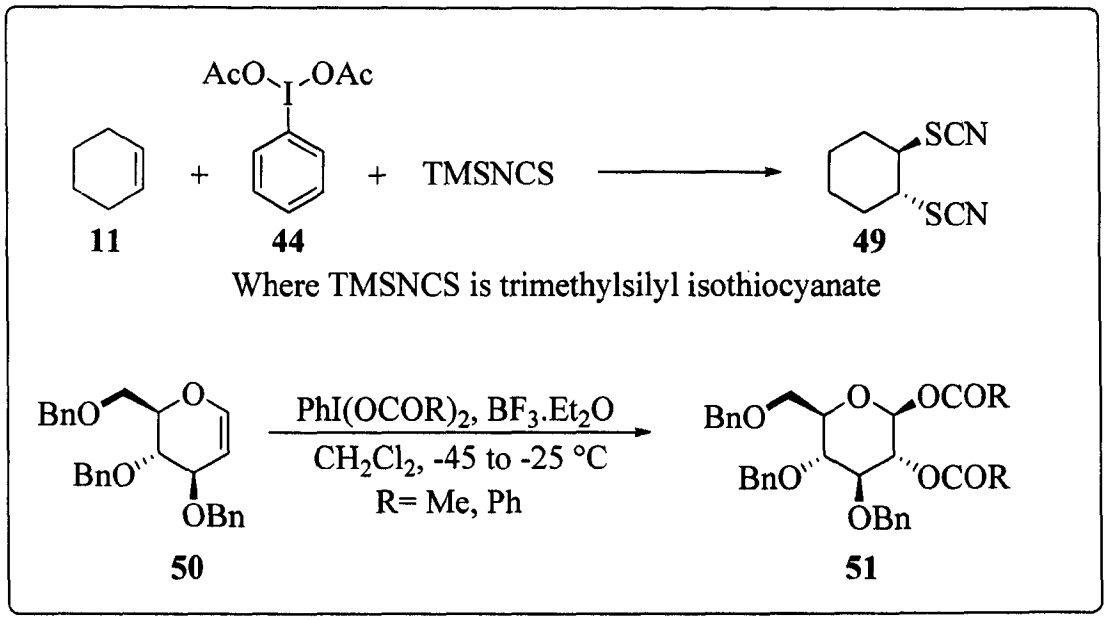


Figure 7. Examples for alkene functionalization reactions using λ^3-iodanes

1.3c Oxidation of Organic Compounds with λ^3-Iodanes

λ^3 hypervalent iodine reagents are also employed as mild and selective oxidizing agents. Primary alcohols, **52** can be oxidized[5, 25] to aldehydes, **53** without over oxidation, by using TEMPO/PhI(OAc)$_2$. The use of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) radical with **44** is necessary for the selective oxidation of primary alcohols to the corresponding aldehydes in good yields. Disulfides, **54** can be easily oxidized[5] to sulfonic esters or thiodulfonic *S*-esters, **55** depending on the reaction conditions. Also diselenides and ditellurides can be oxidized[5] quite easily using λ^3-iodanes.

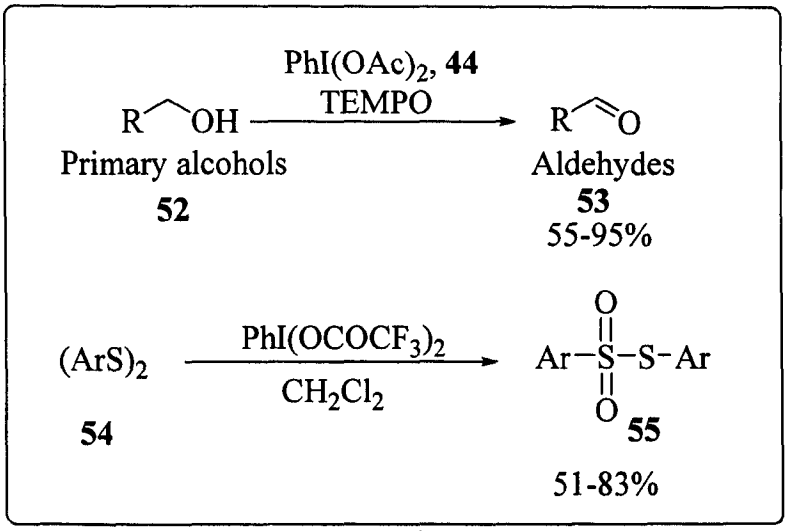


Figure 8. Examples for oxidation behavior of λ^3-iodanes with different organic compounds

1.3d Hypervalent λ^5-Iodine Derivatives

Similar to λ^3-iodane, in a λ^5- iodane five more electrons donated by the ligands to the iodine atom forming a dodecet structure. Two important members of the λ^5- iodine hypervalent iodine reagents are **47** and **48** (shown in Figure 6). *o*-Iodoxybenzoic acid, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, IBX(**47**) was first synthesized in 1893 by the direct oxidation of 2-iodobenzoic acid and the compound was synthesized merely as a structural curiosity.[26] The interest in IBX reemerged in mid 1980's when Dess and Martin used this as a precursor for the synthesis[25, 32] of DMP, **48**. By mid 1980's Santogostino and Fregerio reported the first use of IBX itself as a mild and selective oxidizing agent[22, 27] for alcohols.

1.3e Oxidation of Alcohols using λ^5- iodanes

IBX has become a reagent of choice for the oxidation of alcohols using DMSO as solvent. Some of the typical alcohol oxidations carried out using IBX is shown below. Primary alcohols and secondary alcohols are oxidized[27] to aldehydes and ketones

resepectively using IBX, **47** without danger of over oxidation which is seen in oxidation of compounds **56** and **58**. One of the main advantage of IBX as an oxidizing agent for alcohol is that the reagent is chemo selective and does not oxidize other atoms like 'S' and 'N'. The selectivity exhibited by IBX is clearly evident from the oxidation of compound **60** where sulfur atom is not oxidized.[34]

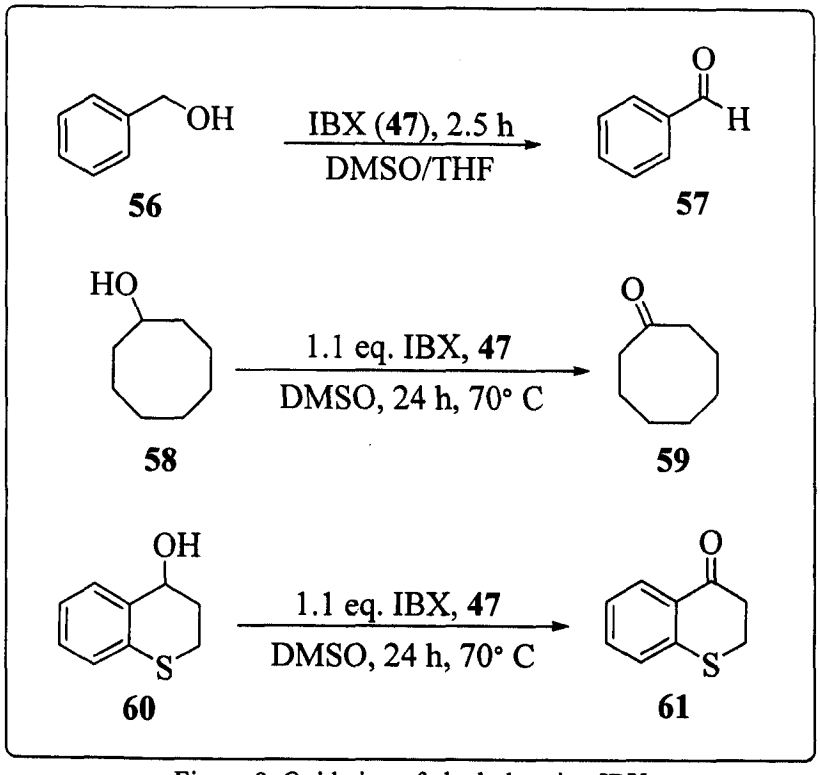


Figure 9. Oxidation of alcohols using IBX

1.4 Plausible Mechanism for the Oxidation Behavior of IBX in DMSO

Figure 10 shows the accepted ligand exchange mechanism[31] for the oxidation behavior of IBX in DMSO. According to the mechanism, the first step is a ligand exchange with the hydroxyl group on the hypervalent iodine being replaced by the alcohol as an alkoxy moiety. This step is in equilibrium with water which is formed as the byproduct and also this is a fast step. In the next step, reductive elimination occurs by

which iodosobenzoic acid is eliminated giving an oxidative transformation of alcohol as the product.

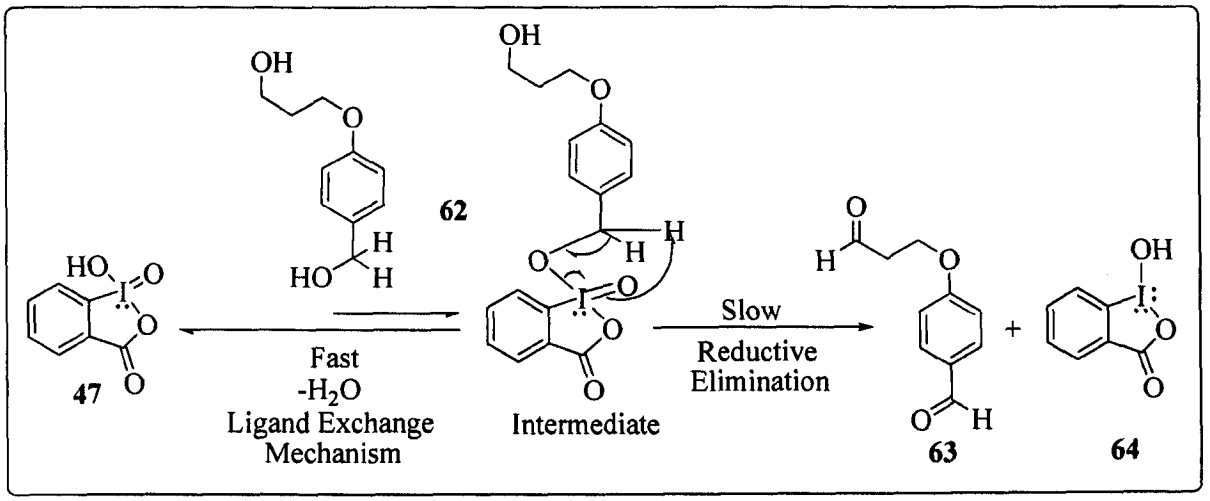


Figure 10. Mechanism of oxidation in DMSO

1.5 Drawbacks of IBX

The mild and selective oxidation behavior of IBX clearly demonstrates the synthetic utility of this reagent. However, this reagent is not free of problems. One of the drawbacks of IBX is limited solubility[22, 31] in organic solvents other than DMSO. A crystal structure determination of IBX revealed that the poor solubility of IBX is due to extended linkage of intermolecular secondary I...O bonding interactions essentially making IBX a polymeric reagent and is potentially explosive and thus, cannot be prepared and stored in large quantities.[30, 35] The high boiling point of DMSO makes up the workup procedure rather cumbersome. Recently, there have been many reports describing the synthesis of structurally modified IBX derivatives which are soluble in solvents other than DMSO. Our group has made significant contributions towards the synthesis and development of IBX derivatives[28, 29] that are soluble in water.

Another reported disadvantage of IBX is its shock sensitive[22, 31] nature. It is presumed that the shock sensitivity is behavior of IBX, stems from the presence of residual $KBrO_3$ left over from the oxidation of 2-iodobenzoic acid to produce a reagent.

1.6 Synthesis of Water-Soluble IBX Derivatives

Due to the limited solubility of IBX in organic solvents other than DMSO and also due to its shock sensitive nature of IBX, chemists are engaged in the synthesis of suitable and user-friendly analogs of IBX. [28, 29, 36-38] Some of those IBX analogues include polymer supported IBX analogues[37], IBX esters and amides[38], F-IBX[38], S-IBX[36] and water-soluble IBX derivatives. [28, 29] Two examples of water-soluble IBX derivatives synthesized in our laboratory are shown below. These derivatives bear a carboxylic acid group on the aromatic ring which increases the water-solubility of the reagents.

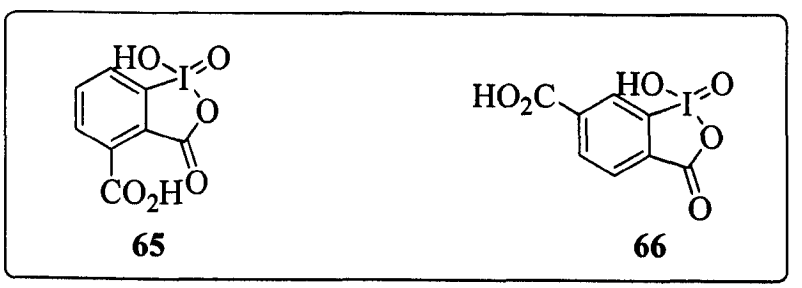


Figure 11. Examples for water-soluble IBX derivatives

Water-soluble IBX derivative **65** is prepared in 5 steps from commercially available 3-nitrophthalic acid.[28] The circuitous synthetic route for this compound prompted us to search for other water-soluble IBX derivatives which can be readily synthesized. Compound **66**, another water-soluble IBX derivative was recently synthesized in 2 steps from readily available terphthalic acid.[29] Though both these

derivatives exhibited identical reactivity pattern to that of IBX in polar aprotic solvents their oxidation behavior in aqueous solvent systems were quite unique. In aqueous solvent mixtures, both these reagents exhibited unique selectivity towards benzylic alcohols over non-benzylic alcohols. The selectivity is pronounced when the solvent was water-THF mixture. The selectivity is diminished in aqueous acetonitrile and the reagent was completely ineffective and did not oxidize alcohols in aqueous acetone. [29, 31] Figure 12 shows the representative oxidation of diol **62** using both **65** and **66** provided the oxidation products here.

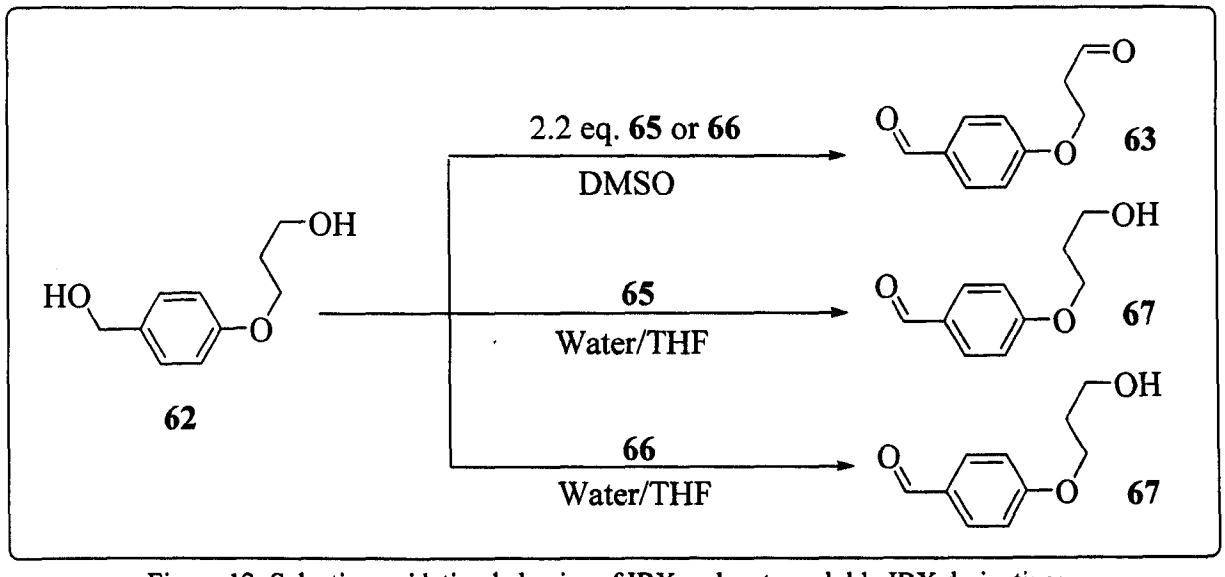


Figure 12. Selective oxidation behavior of IBX and water soluble IBX derivatives

After extensive mechanistic investigations we realized that the selectivity arises out of the differences in the bond dissociation energies (BDE) of the C-H bond from which the H-atom is abstracted in the first step of the newly found mechanism.[29, 31]

Figure 13 below shows the BDE of benzylic bond and the non-benzylic bonds that are involved in the oxidation of two alcohols respectively. It is quite evident that the

reagent would selectively abstract the H-atom from benzylic alcohol to give the resonance stabilized structure and route to the final oxidation of the benzylic alcohol.

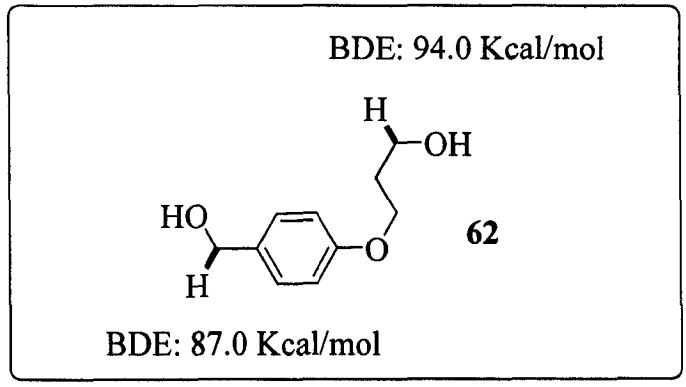


Figure 13. Structure of compound **62** showing two different C-H bonds

1.7 An Accidental Entry into Easy and Wide Ranging Functionalization of Alkenes using Hypervalent Iodine Reagents

After establishing the alternate H-atom abstraction mechanism for the oxidation of alcohols using water-soluble IBX reagents we reckoned that an easily generated benzylic radical could also be potentially utilized in radical cyclizations provided a suitable radical acceptor is built in the same molecule for this purpose. To test this hypothesis, we synthesized ester **68** and hoped that the selective abstraction of H-atom from the C-H bond would produce the resonance stabilized radical **69** which could cyclized into the suitable positioned alkene and eventually abstract an iodine atom from elemental iodine present in the reaction mixture to produce **70** (where X= I).

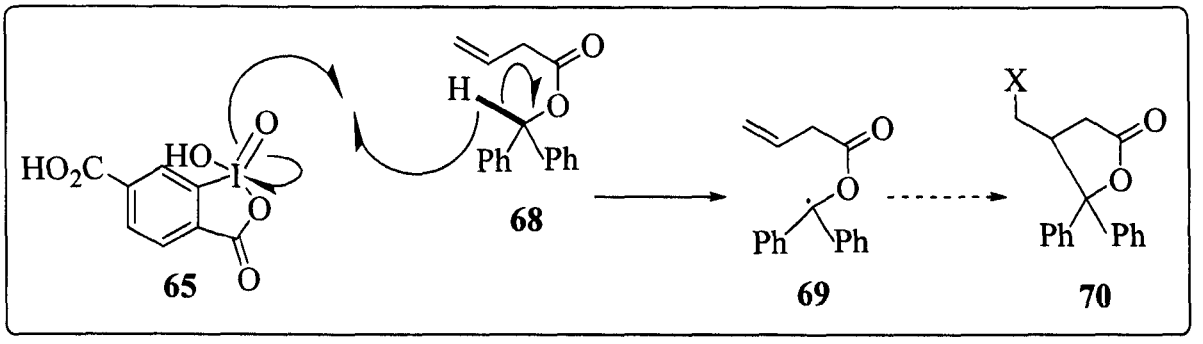
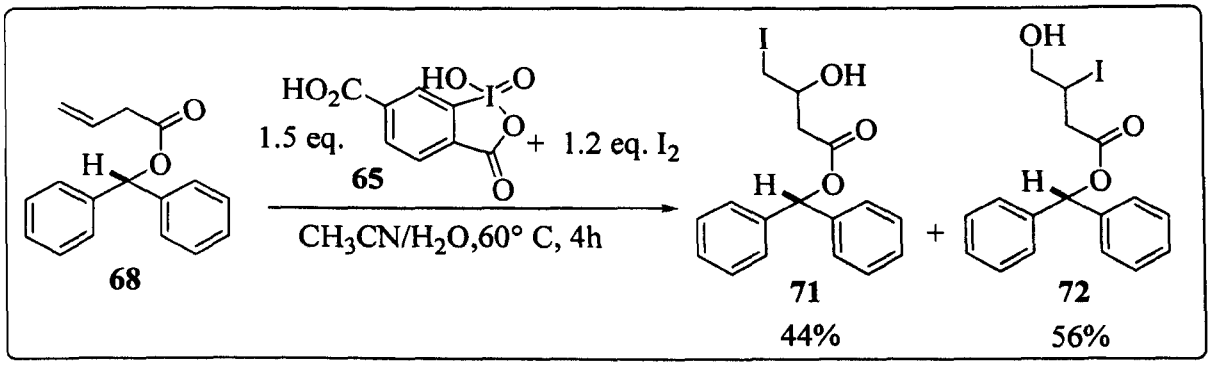


Figure 14. Expected mechanism for the oxidation of given ester using water-soluble IBX and I_2

However, when this reaction was attempted in aqueous acetonitrile using 1.5 equivalents water-soluble IBX along with 1.2 equivalents iodine we isolated a mixture of two products both still carrying the benzylic C-H as evident from its unique resonance in the ^1H NMR spectrum at δ 6.95. The products **71** and **72** were readily identified as iodohydrins by ^1H NMR and IR spectroscopy (*vide infra*). This result clearly indicated to us that the reaction conditions we selected are optimum for the synthesis of iodohydrins from alkenes, a result that was not planned or hoped for. But having realized this we embarked on a systematic investigation to identify suitable reaction parameters for convenient functionalization of alkenes using this protocol.

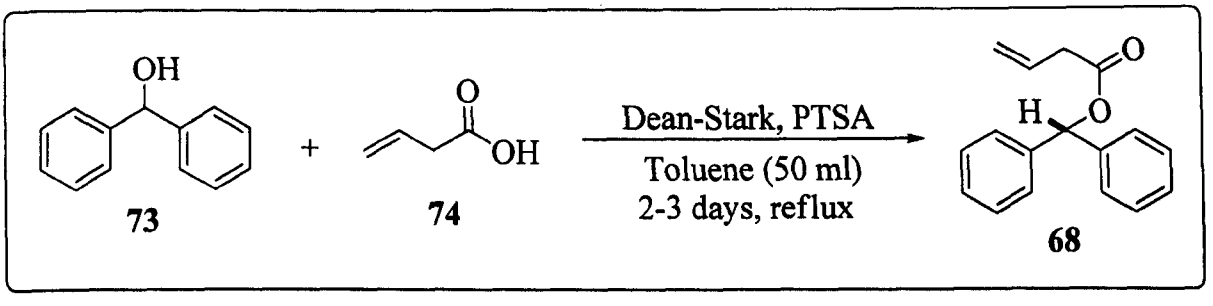


At this juncture, we also realized that we have the liberty to change the solvent mixture to introduce other nucleophiles in this 1,2-co-functionalization reaction. This thesis describes our initial investigation in this area.

2. RESULTS AND DISCUSSION

2.1 Synthesis of Ester 68

Our investigation into the development of an easy and convenient 1,2-co-functionalization protocol for alkenes began with the synthesis of ester substrate, **68**. Treatment of benzhydrol, **73** with vinyl acetic acid, **74** in toluene under Dean-Stark conditions in presence of *p*-toluenesulfonic acid as a catalyst provided **68** in 90% yield after a column purification using a mixture of dichloromethane and petroleum ether. The ester was readily characterized by IR spectrum in which the carbonyl stretching occurred at 1743 cm^{-1} (results not shown). In the ^{1}H NMR spectrum of **68** (Figure 18), the aromatic protons appeared between δ 7.31 and 7.34. The benzylic proton appeared at δ 6.89 and the remaining protons signals appeared as expected in δ 3.21, 5.20 and 5.95 respectively. In the ^{13}C NMR spectrum (Figure 19), the two sp^3 carbons appeared at δ 39.43 and 53.33 whereas aromatic sp^2 carbons appeared as four distinct peaks at δ 127.17, 128.01, 128.59 and 140.21 respectively. The two olefin carbons appeared at δ 118.92 and 130.10 and the carbonyl carbon appeared at δ 170.56 as expected.



73 + 74 → 68

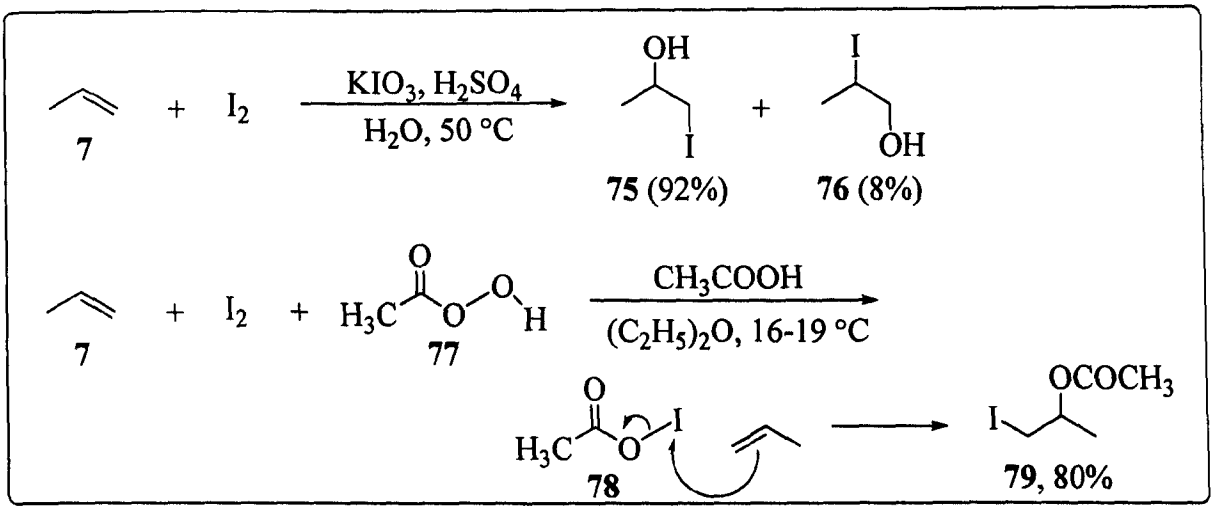
2.2 Initial 1, 2-Co-functionalization Reaction

After the structural characterization of **68**, it was then subjected to the 1, 2-co-functonalization reaction using 1.5 equivalents of **65** along with 1.2 equivalents of iodine in aqueous acetonitrile at 60 °C for 12 h. At the conclusion of this reaction period, the mixture was extracted with dichloromethane (DCM) and the crude product was purified using column chromatography using gradient elution with petroleum ether and DCM. The co-functionalized products **71** and **72** were isolated in 44% and 56% yields respectively with **71** as thick colorless oil and **72** as a solid with melting point range of 52-55 °C. In the IR spectrum of **71** and **72** (not shown), the carbonyl stretching frequencies occurred at 1770 and 1730 cm^{-1} respectively. The regiochemistry of functionalization was readily ascertained from the ^1H NMR spectra of these two compounds. In the ^1H NMR spectrum of **71** (Figure 20), aromatic protons appeared as a multiplet between δ 7.25 and 7.34. The benzylic proton appeared at δ 6.90. The C<u>H</u>-OH proton of **71** appeared as a multiplet at δ 3.99 and the C<u>H</u>$_2$-I appeared as a doublet of doublet centered at δ 2.77. The C<u>H</u>$_2$ protons nearer to the carbonyl carbon appeared as a multiplet at δ 3.28. Fortunately, in the ^1H NMR of this compound the hydroxyl proton appeared as a doublet at δ 3.05 clearly indicating the regiochemistry as noted in the structure with the OH group on the non-terminal carbon as indicated in structure **71**. The ^{13}C NMR spectrum of compound **71** (Figure 21) reveals the presence of four sp^3 carbons at δ 12.11, 41.07, 67.51 and 77.76 respectively. The latter two signals are due to the sp^3 carbons that bear OH groups. The aromatic sp^2 carbons appeared at δ 127.07, 127.20, 128.74 and 139.69 and the carbonyl carbon at δ 170.98 as expected.

The regioisomer **72** was also similarly characterized. In the ^{1}H NMR spectrum of **72** (Figure 22), aromatic protons appeared as a multiplet at δ 7.25-7.40 and the benzylic proton appeared at δ 6.90 whereas the C<u>H</u>$_2$-OH appeared as a triplet at δ 3.78 and the C<u>H</u>$_2$ protons nearer to the carbonyl carbon is appeared as multiplet centered at δ 3.13-3.23 region. The C<u>H</u>-I proton of **72** appeared as a complex multiplet at δ 4.55 the OH proton appeared as a triplet at δ 2.18 which indicates the regiochemistry in the structure as noted with the OH group on the terminal carbon. In the ^{13}C NMR spectrum (Figure 23), the aromatic sp^2 carbons appeared at δ 127.25, 127.29, 128.64 and 139.73 respectively and the carbonyl carbon at δ 169.89. The two new sp^3 carbons appeared at δ 28.13 and 69.10 whereas the benzylic carbon is appeared at δ 42.19.

2.3 Generation of Electrophilic Iodine in the Reaction Medium

It is well known that alkenes form iodohydrins with iodine in presence of oxidizing agents such as iodic acid or peracetic acid.[39] Acetyl hypoiodite, **78** is believed to be intermediate responsible for the iodination shown in the second reaction below. We



speculate that the accidental discovery of the new and convenient method for the iodohydrin formation described in this thesis stems from the oxidation of elemental iodine by the hypervalent iodine reagents (*vide infra*). The following reaction shows a plausible mechanism by which the electrophilic iodine is generated in the reaction medium using the water soluble IBX derivative **65**. IBX derivative **65** oxidizes elemental iodine in aqueous acetonitrile medium generating the acyl hypoiodite **80**.

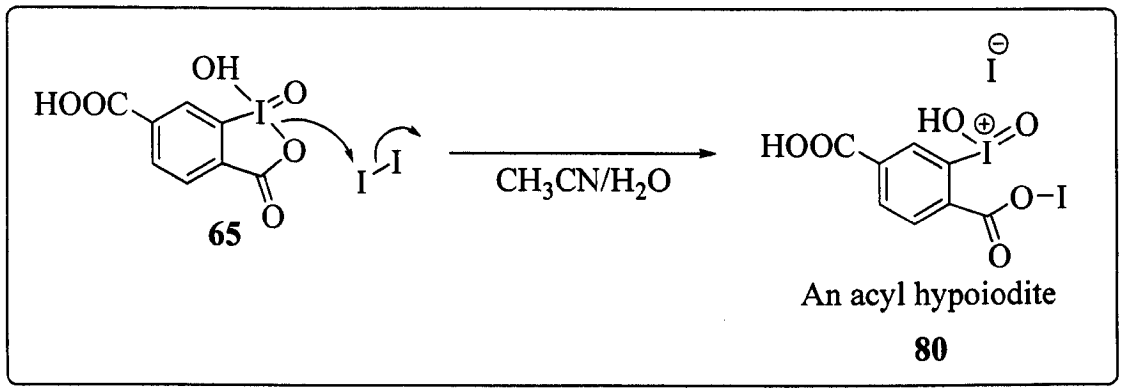


Figure 15. Mechanism showing the generation of an acyl hypoiodite

Considering the difficulty in synthesizing **65** and its stoichiometry use in the reactions described herein, we wondered whether a similar oxidation of elemental iodine could be carried out using diacetoxyiodobenzene, (DAIB, **44**), a conveniently and readily synthesized hypervalent iodine reagent. We were pleasantly surprised when iodohydrins **71** and **72** were obtained from the reaction of **68** with elemental iodine in presence of DAIB in aqueous acetonitrile medium. We believe that the reaction given below shows the formation of acetyl hypoiodite from DAIB, **44** and its potential use in the synthesis of iodohydrins.

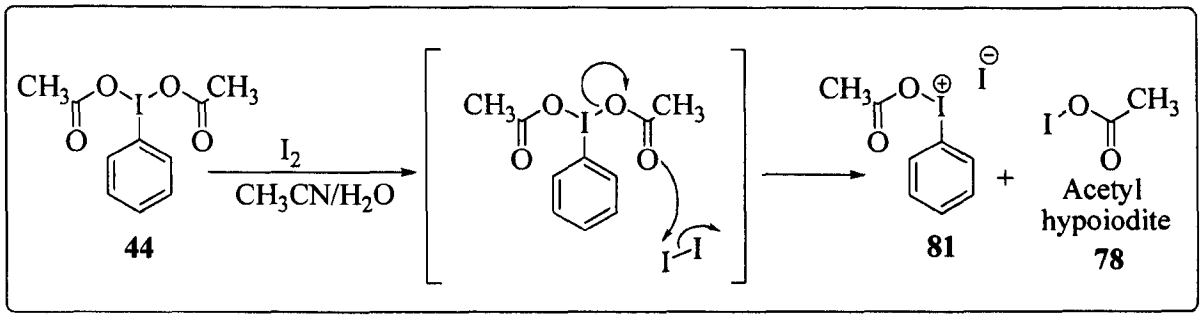
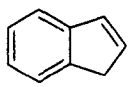


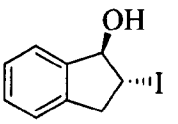
Figure 16. Generation of an acetyl hypoiodite, **78** from DAIB

With the realization that readily prepared DAIB could be used to generate acetyl hypoiodite, **78**, we embarked on a systematic investigation to synthesize a variety of iodohydrins from readily and commercially available alkenes. Table 1 below lists a variety of alkenes subjected to iodohydrin formation using the current methodology. The table also lists the structures of the products isolated. The alkenes selected for this study range from simple and unfunctionalized alkenes (Indene **82**, 4-phenyl-1-butene **85** and 4-allyl anisole **91**) to alkenes that bear functional groups such as an alcoholic group in **94** and an ester functionality along with a nitro group in **97** on the benzene ring or on the side chain. The reaction conditions are non-oxidizing as evident from the non-oxidation of the alcoholic group in alkenes. Reactants **100**, **102** and **104** bear internal nucleophiles to trap the iodonium ion intermediate to form cyclic products.

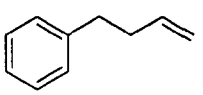
Alkenes → (1.5 eq. DAIB, **44** + 1.2 eq. I_2; CH_3CN/H_2O (1:1); 60 °C; 12h) → Products



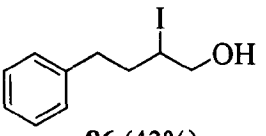
82



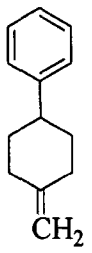
83 (87%) + **84** (1%)



85



86 (43%) + **87** (42%)



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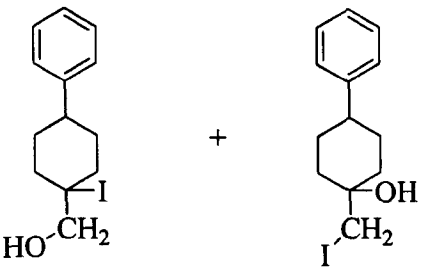
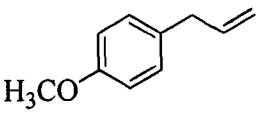


89 (16%) + **90** (79%)



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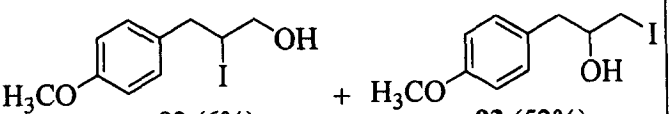
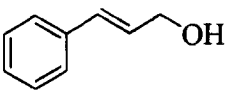


92 (6%) + **93** (52%)



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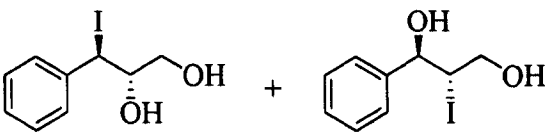
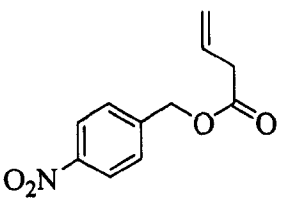
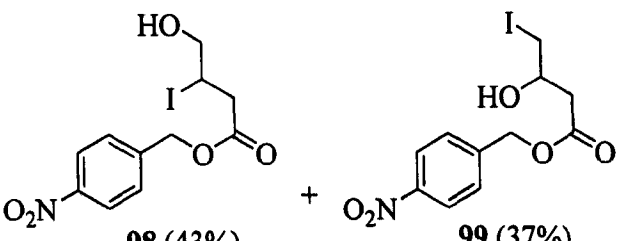


95 (0 %) + **96** (87%)



97



98 (43%) + **99** (37%)

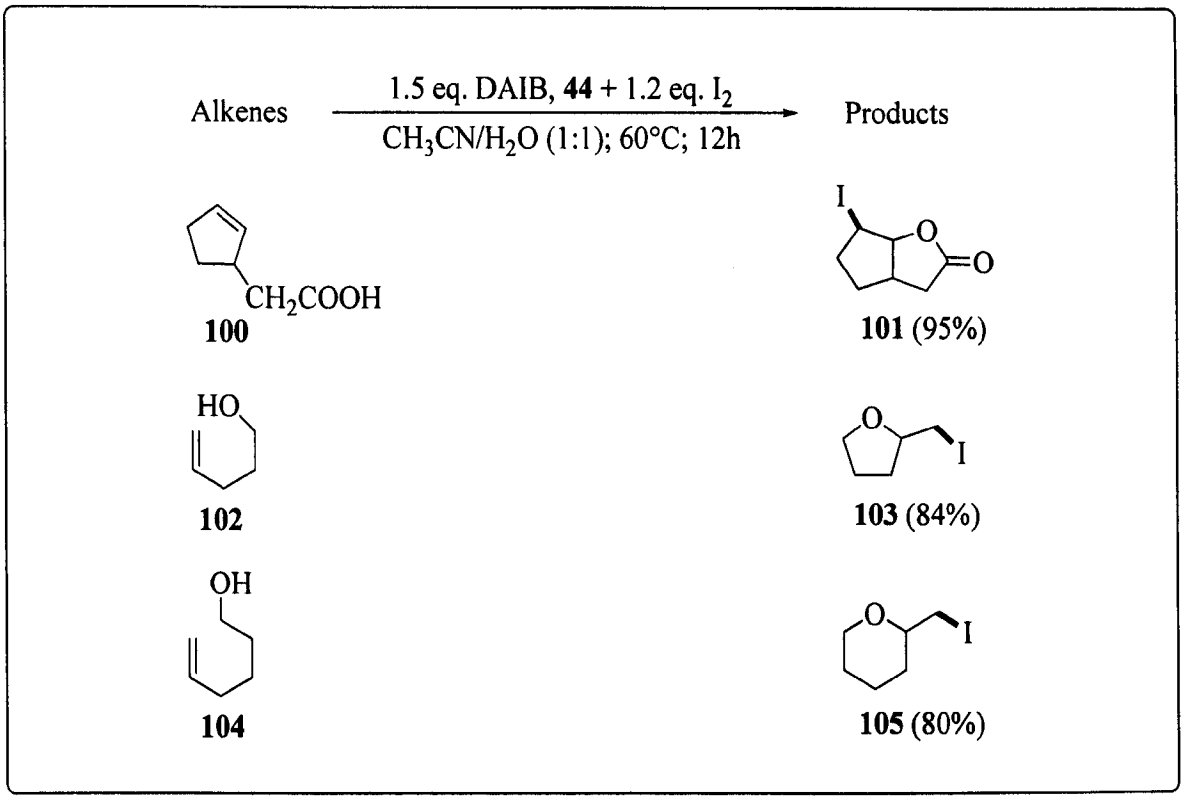


Table 1. Co-iodination/iodohydroxylation of alkenes and corresponding products

2.4 Systematic Investigation of Iodohydrin Formation using DAIB/I_2

Reaction of indene **82** with a combination of DAIB and elemental iodine in 1:1 ratio of aqueous acetonitrile medium provided the expected product **83** along with the trace quantities of oxidized derivative **84** in 87% and 1% yields respectively. The reaction was very clean and the two isomers were easily separated using a gradient elution with petroleum ether and DCM. In the ^{1}H NMR spectrum of **83** (Figure 24), the aromatic protons appeared as a multiplet between δ 7.23-7.29 region. The benzylic CH proton on the carbon bearing the OH group appeared as a triplet (J =6.3 Hz) at δ 5.39. This signal was expected to appear as doublet of doublet. However, the accidental overlap of the two internal lines makes it appear as a triplet. The CH proton on the carbon bearing the iodine appeared as a complex multiplet centered at δ 4.19 and the remaining two CH_2 protons

appeared as doublet of an AB quartet between δ 3.23 and 3.60. The OH proton appeared as a doublet at δ 2.32 (J =6.33 Hz). In the ^{13}C NMR spectrum (Figure 25), the three sp^3 carbons appeared at δ 30.2, 42.4 and 85.1 respectively and all six aromatic sp^2 are different and thus appeared as different peaks between δ 123.92-142.20 respectively. The appearance of the signal for the benzylic carbon bearing the OH group at δ 85.1 substantiates the assigned regiochemistry because of the considerable deshielding. In the ^1H NMR spectrum of **84** (Figure 26), the aromatic protons appeared as a doublet at δ 7.86 (J =7.7 Hz), a triplet at δ 7.66 (J =7.41 Hz) and a multiplet centered at δ 7.42. The C<u>H</u>-I appeared as doublet of doublet at δ 4.94 (J =4.68 Hz) and the remaining two CH_2 protons appeared as a doublet of AB quartet centered at δ 3.50 and 3.87 respectively. In the ^{13}C NMR spectrum (Figure 27), the two sp^3 carbons appeared at δ 19.31 and 39.6 respectively and the six aromatic carbons appeared as six different peaks between δ 125.1- 151.3 range.

Reaction of 4-allyl anisole with 1.5 equivalents DAIB and 1.2 equivalents iodine in 1:1 ratio of aqueous acetonitrile provided the regioisomeric products **92** and **93** in 6% and 52% respectively. Purification of these products free of each other was not readily achieved. The OH protons of **92** (see Figure 28) and **93** (see Figure 30) appeared as a triplet and a doublet respectively at δ 1.91 and 2.01. The benzylic protons in both derivatives appeared as doublets at δ 2.81 and the signals for the remaining protons on the side chain appeared as complex multiplets between δ 3.18 and 3.79. Similarly, the reaction of **85** and **88** also provided regioisomeric products which were identified as a mixture.

We had better luck in isolation and characterization of iodohydrin products from **97** with DAIB in presence of iodine which gave **98** and **99** in 43% and 37% respectively showing essentially no preference for either of the regioisomer. In ^{1}H NMR spectrum of **99** (figure not shown), the CH protons on the carbon bearing the OH group appeared as a multiplet centered at δ 4.46 and the CH_2 protons on the carbon bearing the iodine appeared as a multiplet at δ 3.80. The diastereotopic CH_2 protons adjacent to the carbonyl group appeared as a doublet of AB quartet centered at δ 3.07 and 3.22 respectively. The benzylic CH_2 protons in this derivative appeared as a singlet at δ 5.29. Aromatic protons as expected appeared as two sets of doublets at δ 7.53 and 8.24.

Cinnamyl alcohol, **94** is a unique substrate as it has presence of an allylic hydroxyl group and co-functionalization of the alkene will thus generate three contiguous carbons bearing functional groups. Reaction of **94** with the 1.5 equivalents of DAIB and 1.2 equivalents of iodine provided only a single regioisomeric product namely **96** with the regiochemistry shown in the structure. The formation of **96** is readily explained because of the incipient carbocation would be selectively placed on the benzylic carbon resulting in the introduction of the OH group on the benzylic carbon in the product. In the IR spectrum of this compound (results not shown), the presence of the OH group was indicated by broad band at 3,404 cm^{-1}. The regiochemistry of the addition was clearly evident from the ^{1}H NMR spectrum of the compound **96** (Figure 32) where the two OH protons appeared as a doublet at δ2.89 (J =4.11 Hz) and a triplet at δ 2.52 (J =6.2 Hz) respectively. The doublet at δ 2.90 is assigned to the OH proton on the benzylic carbon and the irradiation of that proton in HOMO decoupling experiment resulted in the simplification of one proton signal due to the CH appeared as doublet of doublet coupled

to both the OH proton as well as the CH proton on the carbon bearing iodine atom, which appeared as a complex multiplet at δ 4.45. The CH_2 protons in the product also appeared as a complex multiplet between δ 3.83 and 3.87. The aromatic protons appeared as a multiplet at δ 7.38. In the ^{13}C NMR spectrum of **96** (Figure 33), the three sp^3 carbons appeared at δ 41.56, 66.01 and 78.63 respectively. The four aromatic carbons appeared at δ 126.58, 128.62, 128.73 and 140.89 respectively.

2.5 Synthesis of Iodocyclicethers and Iodolactones

We were interested in extending this protocol with substrates that bear nucleophilic functional groups capable of intercepting the iodonium intermediate to produce cyclic derivatives. At first, we decided to use 2-cyclopentene-1-aceticacid, **100** as a possible substrate to produce iodolactone **101**. Treatment of **100** with 1.5 equivalents of DAIB and 1.2 equivalents of iodine in aqueous acetonitrile at 60 °C for 12 h clearly provided **101** as a clear liquid after column chromatographic purification. In the IR spectrum of **101** (results not shown), the carbonyl stretch appeared at 1778 cm^{-1}. In the ^1H NMR spectrum (Figure 34), the most deshielded signal appeared as a doublet at δ 5.20. The remaining protons appeared as complex multiplets in the spectrum. In the ^{13}C NMR spectrum (Figure 35), 6 peaks appeared in sp^3 region and the carbonyl carbon appeared at δ176.34.

Iodocyclic ethers **103** and **105** were readily obtained when 4-penten-1-ol, **102** and 5-hexen-1-ol, **104** were subjected to the reaction conditions. In the ^1H NMR spectrum of **103** (Figure 36), the protons α to the ether functionality appeared as a complex multiplet between δ 3.96 and 3.98. The CH_2 proton on the CH_2-I tether again appeared as complex

multiplet at δ 3.22. In the ^{13}C NMR spectrum of this compound (Figure 37), there were 5 signals as expected in sp^3 region with the carbon adjacent to oxygen appeared at δ 69.02 and 78.57 respectively. Similarly, **105** was also readily characterized by its ^{1}H NMR spectrum (Figure 38).

2.6 Easy and Wide Ranging 1, 2-Co-functionalization of Cinnamyl Alcohol using DAIB/I2 Protocol in Presence of Different Nucleophiles

Our success in developing a convenient iodohydrin synthesis for alkenes using in-situ generated acetyl hypoiodite prompted us to extend this study using alternate nucleophilic sources in the reaction medium to generate multiply functionalized products for the synthetic manipulations. We choose cinnamyl alcohol as a suitable substrate to test this hypothesis because of the fact that the substrate itself has a primary alcohol functional group in it and the introduction of additional functional group through this protocol is expected to produce synthetically useful intermediates. The versatility of the method is clearly evident from the results shown in Figure 17. The Table that follows shows the reaction conditions and various nucleophiles used and the products obtained.

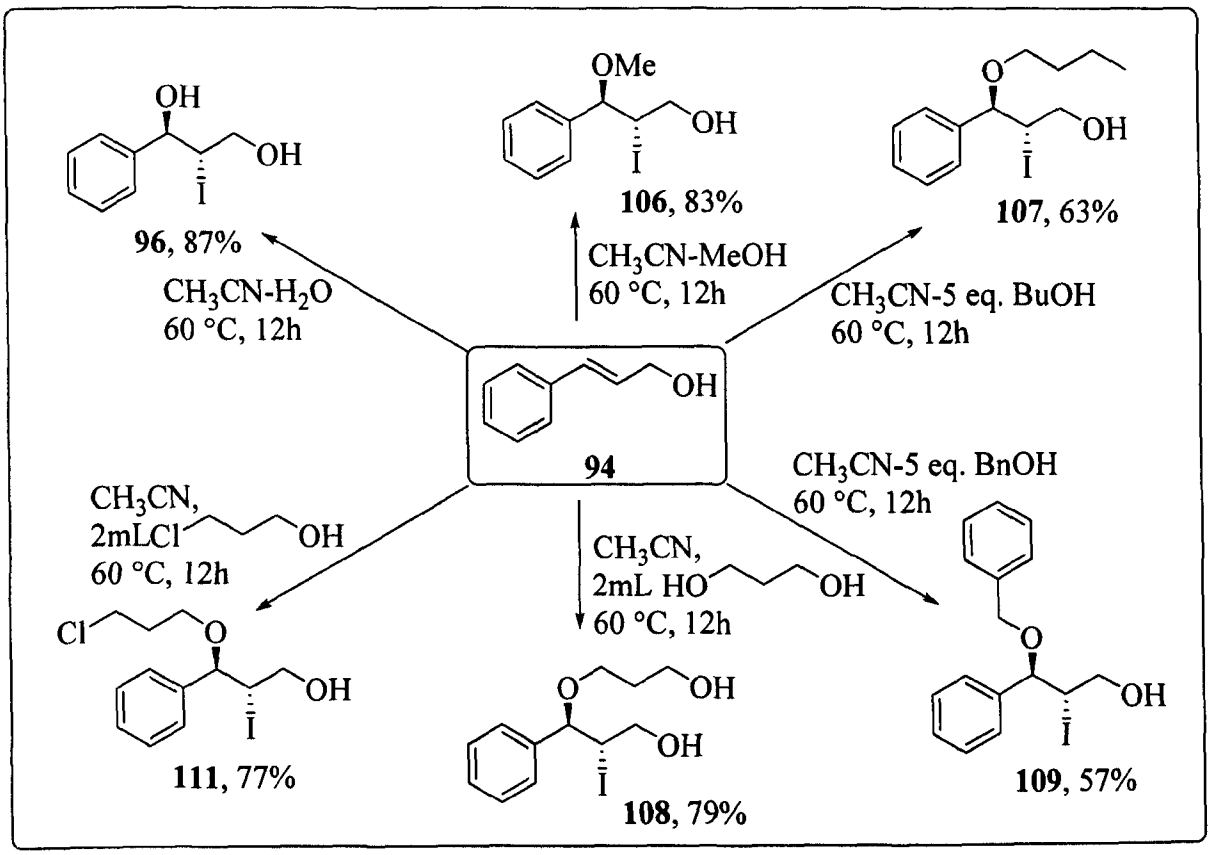
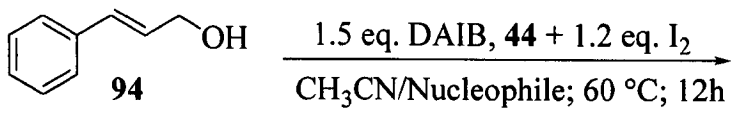


Figure 17. Schematic representation of synthesis of co-iodinated derivatives

When substrate **94** was treated with a combination of DAIB and elemental iodine using methanol as the co-solvent, the product obtained was **106** where the methoxy group was selectively placed on the benzylic carbon and the iodine atom on the adjacent carbon. The characterization of **106** was readily done by its ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum of compound **106** (Figure 39), the OH group appeared as a triplet at δ 2.86 (J =5.76 Hz) and the methoxy group appeared as a singlet at δ 3.27. The CH proton on the benzylic carbon appeared as a doublet at δ 4.50 and the two diastereotopic hydrogens of $C\underline{H}_2$ appeared as complex multiplets centered at δ 3.82 and 3.95. The $C\underline{H}$-I appeared as a multiplet at δ 4.34. The aromatic protons appeared at δ 7.35. In the ^{13}C NMR spectrum (Figure 40), the four sp^3 carbons appeared at δ 39.01, 57.79, 66.45 and 88.06 respectively. The four distinct aromatic sp^2 carbons appeared at δ 127.58, 128.59,

128.73 and 138.69 as expected. In the IR spectrum, the OH stretch appeared as a broad band at 3423 cm^{-1} and the C-O stretch appeared at 1085 cm^{-1} as expected (results not shown).

At this point we decided to see whether 1-butanol can be added as a nucleophile to demonstrate the generality of the procedure for the introduction of alkoxy groups. When we used 1-butanol as the nucleophile under the same reaction conditions, the product obtained was compound **107** as shown in entry 3 (see Table 2). In the ^1H NMR spectrum of **107** (Figure 41), the aromatic protons appeared at δ 7.33 as a multiplet and the OH proton appeared as triplet at δ 3.09 (J =6.18 Hz) and the CH_2 protons nearer to the oxygen atom of the butanol species appeared as a triplet at δ 3.32 (J =6.45 Hz) as expected. The CH_2 protons on the carbon bearing the OH group appeared as a doublet of an AB quartet centered at δ 3.83 and 3.93 respectively. The CH proton on the carbon bearing the oxygen atom appeared as a doublet at δ 4.61 (J =7.14 Hz). The C<u>H</u>-I proton appeared as a multiplet at δ 4.31. The two C<u>H</u>$_2$s of the butyl moiety appeared as two multiplets centered at δ 1.51 and 1.54 whereas the C<u>H</u>$_3$ protons appeared as a triplet at δ 0.85. In the ^{13}C NMR spectrum (Figure 42), there are 7 signals in the sp^3 region as expected with the carbons adjacent to oxygen appeared at δ 66.66, 70.05 and 87.06 respectively. The four aromatic carbons appeared in the range from δ 127.47 to 139.43 as expected. In the IR spectrum, it is observed that the OH stretch appeared as a broad band at 3439 cm^{-1}, the CH aliphatic stretch appeared in the range between 2870 cm^{-1} to 2956 cm^{-1}, the CH bending appeared at 1464 cm^{-1}, the C-O stretch appeared at 1085 cm^{-1} as expected (results not shown).



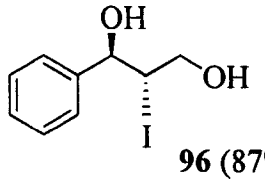
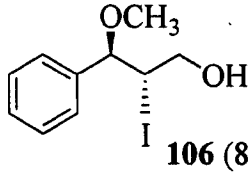
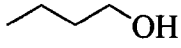
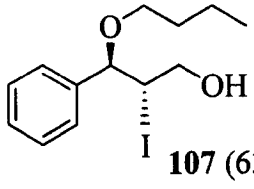
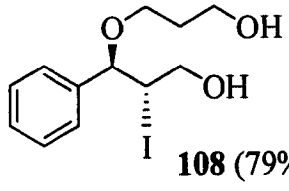
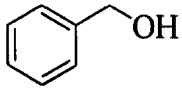
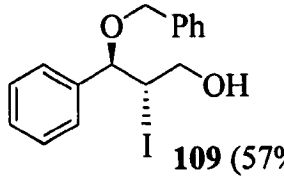
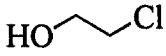
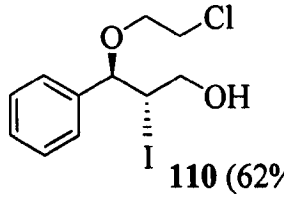
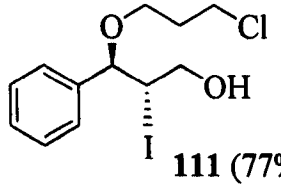
Entry	Nucleophilic Source	Product
1	H_2O	 **96** (87%)
2	CH_3OH	 **106** (83%)
3		 **107** (63%)
4		 **108** (79%)
5		 **109** (57%)
6		 **110** (62%)
7		 **111** (77%)

Table 2. Co-iodination of cinnamyl alcohol using different nucleophiles

We then carried out additional functionalization of cinnamyl alcohol using 1,3-propanediol as the nucleophilic source to produce derivatives with additional functional groups on the added nucleophilic moiety. The reaction of **94** with DAIB and I_2 in acetonitrile gave 79% yield of the product **108** as shown in entry 4 (see Table 2). In this reaction an excess amount of diol was used in order to minimize the formation of dimeric products with the participation of both OH groups of 1,3-diol. The characterization of **108** was readily done using ^{1}H NMR spectrum (Figure 43) of the compound. The presence of two OH signals as broad peaks at δ 2.31 and 2.25 respectively. The CH proton on the carbon bearing oxygen atom is deshielded and appeared as a doublet at δ 4.60 (J =6.87 Hz). The CH_2 protons on the carbon bearing oxygen which is at the benzylic site appeared as a triplet at δ 3.50 (J =6.06 Hz) and the middle CH_2 of the diol appeared as a multiplet at δ 1.80. The CH_2 protons on the side chain of the cinnamyl alcohol appeared as a doublet of doublet centered at δ 3.98 and the remaining protons appeared as complex multiplets as expected. The aromatic protons appeared as multiplet at δ 7.34. In the ^{13}C NMR spectrum (Figure 44), there are 6 signals in sp^3 region where 3 of them are deshielded due to direct attachment to the oxygen atom and appeared at δ 65.76, 68.21 and 85.74 respectively. The 4 aromatic protons appeared in the expected region between δ 127.51-138.91.

Our next attempt was to use benzyl alcohol as a nucleohile in order to obtain a derivative in which the newly introduced secondary alcohol functional group will appear protected as a benzyl ether. A benzyl ether, **109** was obtained as the product when benzyl alcohol was used as the nucleophilic source and the compound **109** was easily characterized from the ^{1}H NMR, ^{13}C NMR and IR spectral data of the compound. In the

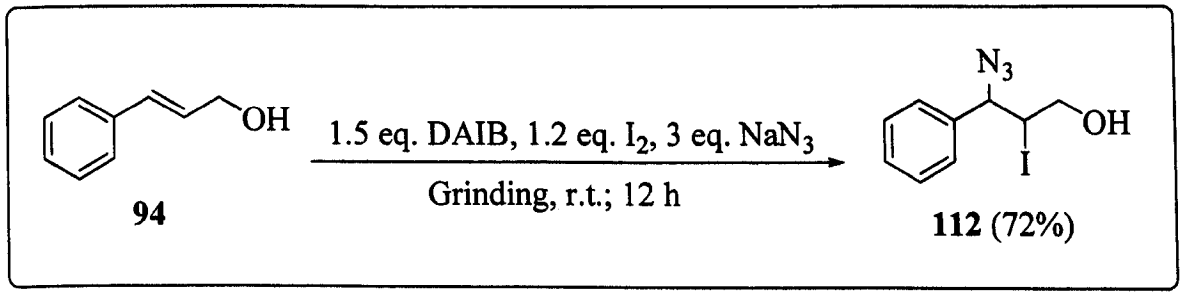
IR spectrum, the hydroxyl group appeared as a broad peak at 3419 cm^{-1} (results not shown). In the ^1H NMR spectrum of **109** (Figure 45), the aromatic protons of both benzene rings appeared as a complex multiplet at δ 7.31-7.39 region. The OH proton of the **109** appeared as a triplet at δ 2.82 (J =5.79 Hz); the CH_2 protons of the benzyl alcohol appeared as AB quartet centered at δ 4.29 and 4.47 respectively. The CH_2-OH protons appeared as a doublet of AB quartet centered at δ 3.82 and 3.98. The CH proton on the carbon bearing the iodine atom appeared as a complex multiplet at δ 4.31 and the CH proton on the carbon bearing the oxygen atom appeared as a doublet in the downfield at δ 4.69 (J =7.41 Hz). In the ^{13}C NMR spectrum of 109 (Figure 46), the four sp^3 carbons appeared at δ 39.37, 66.46, 71.68 and 85.28 while all the aromatic carbons appeared as 6 signals in the range between δ 127-138 as expected.

In addition to the use of the different nucleophilic sources described so far we have also employed 2-chloroethanol and 3-chloropronanol as nucleophilic sources in our reactions to produce derivatives with displaceable halogens on the newly introduced tethers. Compound **110** was isolated when **94** was treated with 1.5 equivalents of DAIB and 1.2 equivalents of iodine in acetonitrile medium using 2-chloroethanol as the co-solvent. In the ^1H NMR spectrum of **110** (Figure 47), the aromatic protons appeared as multiplet at δ 7.25-7.38 region. The OH proton appeared as a triplet at δ 2.83 (J =2.76 Hz). The CH_2 protons on the side chain of the cinnamyl alcohol appeared as a doublet of AB quartet centered at δ 3.90 and 3.99 respectively. The CH proton on the benzylic carbon appeared as a doublet at δ 4.66 and the C<u>H</u>-I appeared as complex multiplet at δ 4.34. The two CH_2s of the 2-chloroethanol appeared as multiplet at δ 3.59. In the ^{13}C NMR spectrum (Figure 48), as expected five signals in the sp^3 region were present at δ

38.88-86.59 range where the carbons bearing the oxygen atom are deshielded and appeared at δ 66.55, 69.66 and 86.59 respectively. The 4 aromatic carbons appeared as four different peaks at δ 127.63, 128.66, 128.95 and 138.71 as expected. In the IR spectrum of **110**, the hydroxyl group appeared as a broad peak at 3450 $cm^{-1}$and C-O stretch appeared at 1101 cm^{-1} as expected (results not shown). Similarly, compound **111** was easily obtained from cinnamyl alcohol, **94** when it was reacted with a combination of DAIB and iodine in acetonitrile medium using 1-choro-3-propanol as the nucleophilic source and the compound **111** was readily characterized using ^{1}H NMR and ^{13}C NMR spectral data (results not shown).

2.7 Solid State Reaction using Sodium Azide

One of the nucleophiles that we really wanted to use was azide anion. The poor solubility of sodium azide in acetonitrile makes this reaction very difficult until we realized that these 1,2-co-functionalization reactions can also be done in solid state. Cinnamyl alcohol was allowed to react with 1.5 equivalents DAIB, 1.2 equivalents iodine and 3 equivalents of sodium azide which gave rise to compound **112**. The mixture was purified by column chromatography using gradient elution with petroleum ether and DCM. Characterization of compound **112** was done using ^{1}H NMR, ^{13}C NMR and IR spectral information.

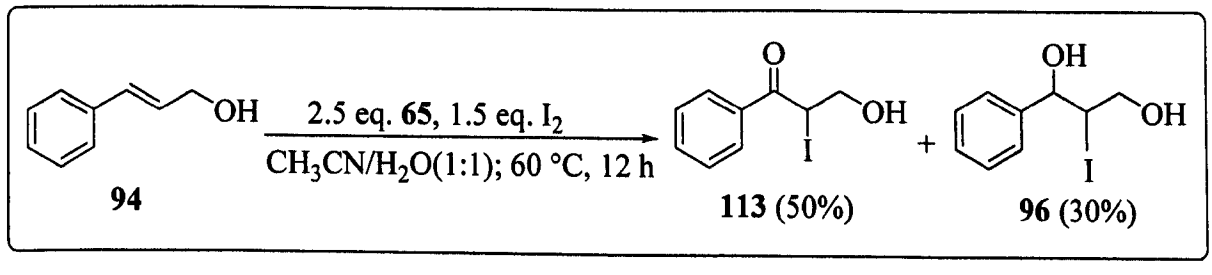


94 **112** (72%)

In the ^1H NMR spectrum (Figure 49), the OH signal appeared at δ 2.79 as a triplet, the CH_2 protons appeared as complex multiplets centered at δ 3.75- 3.85. The CH-I signal appeared as a multiplet at δ 4.50 and the CH-N_3 signal appeared as a doublet in the downfield region at δ 5.99 (J=7.41 Hz). The aromatic protons appeared as a multiplet at δ 7.25-7.37 region as expected. In the IR, the hydroxyl group appeared as a broad peak at 3458 cm^{-1}, the CH aliphatic stretch appeared in the range between 2850 cm^{-1} to 2960 cm^{-1}, the CH bending appeared at 1452 cm^{-1}, C-O stretch appeared at 1066 cm^{-1} and C-N stretch appeared as a multiplet at 1028 cm^{-1} and 1234 cm^{-1} (results not shown). This information confirms the formation of compound **112** as the product.

2.8 Use of IBX Derivative to Investigate Selective Oxidation of the Benzylic Alcohol

As shown earlier, the use of reaction of cinnamyl alcohol with DAIB and iodine in aq. acetonitile provided excellent yields of the iodohydrin. We wanted to see whether use of an excess of the water-soluble IBX reagent, **65** would result in the formation of the iodohydrin and a selective oxidation of the benzylic alohol based on the differences in the C-H bond dissociation energies. Reaction of cinnamyl alcohol with 2.5 equivalents of the water soluble IBX reagent and 1.5 equivalents of iodine gave 30% of the iodohydrin, **96** along with 50% of ketone, **113** where the newly introduced benzyl alcohol is selectively oxidized.



94 **113** (50%) **96** (30%)

Compound **113** was easily characterized using ^{1}H NMR (Figure 50) in which the aromatic protons appeared as four different multiplets located between δ 7.25 and 8.02, the C$\underline{H}_2$ signals appeared as complex multiplets centered at δ 3.97 and δ 4.26 region and the C$\underline{H}$-I signal appeared as a doublet of doublet at δ 5.29. The hydroxyl proton was observed as a broad peak at δ 2.50. In the ^{13}C NMR (Figure 51), signals at δ 23.87 and 64.55 indicates sp^3 carbons and the aromatic carbons appeared as four distinct signals in the range between δ 128 and 134 whereas the carbonyl carbon signal appeared at δ 195.0 as expected. In the IR spectrum, presence of carbonyl stretch at 1678 cm^{-1} confirms formation of the ketone product, **113**. Other signals for CH aliphatic stretch, CH bending and C-I stretch appeared at 2920 cm^{-1}, 1456 cm^{-1} and 460 cm^{-1} respectively (results not shown).

3. CONCLUSIONS

A convenient and versatile 1,2-co-functionalization protocols of alkenes using in situ generated acyl hypoiodite intermediates are described. Oxidation of elemental iodine with hypervalent iodine regents, (diacetoxyiodo)benzene (DAIB), **44** and a water-soluble IBX derivative, **65** conveniently generated the acyl hypoidoite reagents, **78** and **80** respectively. A standardized procedure for iodohydrin synthesis using this methodology involves reacting the alkene with 1.5 eq. of DAIB and 1.2 eq. of elemental iodine in aqueous acetonitrile. This procedure is easily modified to introduce varied nucleophilic entities on the alkene during the 1,2-co-functionalization reaction by simply varying the co-solvent in the reaction. A variety of co-solvents raging from simple alcohols to functionalized alcohols have been used as co-solvents to produce highly functionalized products in one step. Cinnamyl alcohol, **94** which already possess a primary alcohol functionality was used as a prototypical substrate for 1,2-iodofunctionalization reactions in the presence of varied nucleophiles. The products from these reactions gave phenylpropane derivatives bearing functional groups on all three sp^3 carbon atoms. The use of benzyl alcohol as a co-solvent produced **109** where the secondary alcohol moiety is present in the benzyl ether protected form. Selection of substrates bearing nucleophilic appendages gave cyclic products as **101**, **103** and **105**. The use of water-soluble IBX derivate in conjunction with elemental iodine in the iodohydrin synthesis of **94** gave the expected ketone, **113** as the product. This selectivity is easily explained by the solvent dependant chemoselective oxidation property of **65** explained based on the differences in the bond dissociation energies of the relevant C-H bonds.

4. EXPERIMENTAL SECTION

4.1 Materials and Instrumentation

The reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Oxidation reactions were carried out on a 0.2-0.4 mmol scale in aqueous solvent mixtures or as shown in Tables 1 and 2. The ratios of substrate to reagent used in the various oxidation reactions are noted in the appropriate Figures and Schemes. Also noted in the various Figures are the durations of the reactions. Reactions were monitored by thin layer chromatography (TLC) on commercially available Merck silica gel 60 F_{254} plates. Pure products from the oxidation reactions were isolated either by preparative TLC (PTLC) or flash chromatography and the yields reported were for isolated products. PTLC separations were carried out on commercially available silica gel 150° A plates (1000 M) with fluorescent indicator separation of the products. Flash chromatography, for the purification of oxidzed products, was carried out using silica gel 60-200 purchased from Fisher Scientific.

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on JEOL 300 Eclipse Spectrometer. Instrument is calibrated using undeuterated solvent as an internal reference. IR spectra were recorded on Shimadzu-FTIR 8400 instrument. Melting points were determined on a MELT-TEMP II melting point apparatus. The following abbreviations were used to explain the multiplicities; s=singlet, d=doublet, dd=doublet of doublet, dt= doublet of triplet, t=triplet, td= triplet of doublet, q=quartet and m=multiplet.

4.2 Synthesis of Esters, 68 and 97

Ester, 68: A mixture of diphenylmethanol or benzhydrol, **73** (2.14 g, 11.6 mmol) and vinylacetic acid (1.0 g, 11.6 mmol) in 50 mL toluene was taken in a round bottomed flask. *p*-Toluenesulfonic acid (0.03 g, 0.16 mmol) was added to the above mixture and this was maintained at reflux for 2-3 days during which time the solution became yellowish-brown in color. Toluene was subsequently evaporated under reduced pressure and to the residue obtained was added CH_2Cl_2 (10-15 mL) and water (10-15 mL) and the layers separated. The aqueous layer was again extracted with CH_2Cl_2 and the combined organic extract was dried with anhydrous $MgSO_4$ and vacuum filtered and the solvent was evaporated to get the crude product. This was purified by flash chromatography using gradient elution with petroleum ether and CH_2Cl_2 to yield 2.07 g (70.8%) of **68** as yellow colored oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.33 (m, 10 H, Ar-*H*), 6.89 (s, 1H, Ph_2-C*H*-O), 5.95 (m, 1H, CH_2=C*H*-C), 5.20 (m, 2H, C*H*$_2$=CH-C), 3.21 (d, *J* =1.38 Hz, 2H, CH_2=CH-C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.56 (*C*=O), 140.21, 128.59, 128.01, 127.17 (Ar-*Cs*), 118.92 (*C*H$_2$=CH), 130.10 (CH_2=*C*H), 39.43 (*C*H$_2$-CO), 53.33 (Ph_2-*C*H-O).

Ester, 97: A mixture of *p*-Nitrobenzyl alcohol (1.0 g, 6.5 mmol) and vinylacetic acid (0.56 g, 6.5 mmol) in 50 mL of toluene was taken in a round bottomed flask. *p*-Toluenesulfonic acid (0.03 g, 0.16 mmol) was added to the above mixture and this was maintained at reflux for 2-3 days during which time the solution became yellowish-brown colored. Toluene was subsequently evaporated under reduced pressure and to the residue obtained was added CH_2Cl_2 (10-15 mL) and water (10-15 mL) and the layers separated.

The aqueous layer was again extracted with CH_2Cl_2 and the combined organic extract was dried with anhydrous magnesium sulfate and vacuum filtered and the solvent was evaporated to get the crude product. This was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 1.12 g (77.7%) of **97** as yellow colored oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.51 (d, *J* =2.19 Hz, Ar-*H*s), 8.22 (d, *J* =1.92 Hz, Ar-*H*s), 5.21 (s, 2H, Ph-C*H*$_2$), 5.91 (m, 3H, C*H*=C*H*$_2$), 3.18 (td, 2H, C*H*$_2$-CH=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 171.13 (*C*=O), 123.90, 128.44, 129.70, 143.18 (Ar-*C*s), 119.26, 148.23 (*C*=*C*), 39.02 (*C*H$_2$-CH=CH$_2$), 64.99 (Ph-*C*H$_2$-O-CO).

4.3 General Procedure for Iodohydrins Synthesis using DAIB/I_2

DAIB, **44** (1.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of alkene substrate (0.5-1.0 mmol) dissolved in 1:1 water/acetonitrile (30 mL) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction period, the reaction was extracted with the DCM and the layers separated. The organic extract was dried ($MgSO_4$) and evaporated to yield the crude product either as a thick oil or colorless solid which was then purified by flash chromatography and/or PTLC.

4.4 Spectral Characteristics of Compounds

71: ^{1}H NMR (300 MHz, $CDCl_3$): 7.30 (m, 10 H, *Ar-H*), 6.90 (s, 1H, Ph$_2$-C*H*-O), 3.99 (m, 1H, C*H*-OH), 2.77 (dd, 2H, C*H*$_2$-I), 3.28 (m, 2H, C*H*$_2$-C=O), 3.05 (d, *J* =4.92 Hz, 1H, CH$_2$-O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.98 (*C*=O), 127.07, 127.20,

128.74, 139.69 (Ar-*Cs*), 12.11 (*C*H_2I), 41.07 (*C*H_2-C=O), 67.51 (*C*HOH), 77.76 (Ph_2-*C*H-O).

72: ^{1}H NMR (300 MHz, $CDCl_3$): 7.32 (m, 10 H, *Ar-H*), 6.90 (s, 1H, Ph_2-C*H*-O), 4.55 (m, 1H, C*H*-I), 3.78 (t, 2H, CH_2-OH), 3.18 (m, 2H, CH_2-C=O), 2.18 (t, 1H, CH_2-O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 169.89 (*C*=O), 127.25, 127.29, 128.64, 139.73 (Ar-*Cs*), 28.13 (*C*HI), 42.19 (*C*H_2-C=O), 69.10 (*C*H_2OH), 77.55 (Ph_2-*C*H-O).

83: M.P. range: 138-145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.26 (m, *Ar-Hs*), 5.39 (t, *J* =6.3 Hz, 1H, Ph-C*H*-OH), 4.19 (m, 1H, C*H*-I), 3.23, 3.60 (d, AA'BB', 2H, CH_2), 2.32 (d, *J* =6.33 Hz, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 123.92, 124.42, 127.62, 128.90 (*Ar-Cs*), 30.17 (CH_2), 42.37 (*C*H-I), 85.14 (*C*H-OH).

86: ^{1}H NMR (300 MHz, $CDCl_3$): 7.23 (m, 5H, *Ar-Hs*), 2.72 (m, 2H, CH_2-I) 3.33, 3.25 (d, AA'BB', 2H, CH_2-CHOH), 3.55 (m, 1H, C*H*-OH), 1.95 (d, 1H, O*H*), 1.87 (m, 2H, Ph-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 126.17, 128.52, 128.60, 141.37 (*Ar-Cs*), 16.64, 32.01, 38.25, 70.25 (*C*H-OH).

87: M.P. 32 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.22 (m, 5H, *Ar-Hs*), 4.07 (m, 2H, CH_2-OH), 3.90 (t, 1H, O*H*), 1.75 (m, 2H, Ph-CH_2), 2.88 (m, 1H, C*H*-I); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 126.17, 128.52, 128.60, 141.37 (*Ar-Cs*), 13.69, 32.11, 36.55, 70.78 (*C*H_2-OH).

89: ^{1}H NMR (300 MHz, $CDCl_3$): 8.24 (d, *J* =1.92 Hz, 2H, Ar-*H*), 7.53 (d, *J* =8.79 Hz, 2H, Ar-*H*), 7.25 (s, 1H, Ar-*H*), 5.25 (s, 2H, Ar-CH_2), 4.46 (m, 1H, C*H*-OH), 3.80 (m,

2H, C*H*$_2$-I), 3.11 (d of AB, 2H, CO-C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.67, 41.77, 65.42, 68.09 (*C*H-OH), 123.94, 128.68, 142.68 (Ar-*C*s), 170.03 (*C*=O).

93: ^{1}H NMR (300 MHz, $CDCl_3$): 7.11 (m, *Ar-Hs*), 1.91 (t, 1H, O*H*), 2.81 (d, Ph-C*H*$_2$), 3.18 (m, 2H, C*H*-I) 3.79 (m, 1H, C*H*$_2$-OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 67.27, 114.12, 129.75, 131.32 (*Ar-C*s), 29.70 (*C*H$_2$), 40.64 (*C*H-I), 42.83 (*C*H$_2$-OH), 55.34 (O*C*H$_3$).

96: ^{1}H NMR (300 MHz, $CDCl_3$): 7.38 (m, 5H, Ar-*H*s), 2.52 (t, *J* =6.2 Hz, 1H, CH$_2$-O*H*), 2.89 (d, *J* =4.11 Hz, 1H, CH-O*H*), 3.83, 3.87 (m, 2H, C*H*$_2$-OH), 4.54 (m, 1H, C*H*-I), 5.05 (m, 1H, C*H*-OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 126.58, 128.62, 128.73, 140.89 (Ar-*C*s), 41.56 (*C*H-I), 66.06 (*C*H$_2$-OH), 78.63 (*C*H-OH).

98: ^{1}H NMR (300 MHz, $CDCl_3$): 8.23 (d, 2H, Ar-*H*s), 7.51 (d, 2H, Ar-*H*s), 5.27 (s, 2H, Ph-C*H*$_2$) 4.02 (m, 1H, C*H*-I), 2.87 (m, 2H, C*H*$_2$-OH), 3.31, 3.34 (d, AA'BB', 2H, C*H*$_2$-C=O).

99: ^{1}H NMR (300 MHz, $CDCl_3$): 8.24 (d, 2H, Ar-*H*s), 7.53 (d, 2H, Ar-*H*s), 5.29 (s, 2H, Ph-C*H*$_2$) 4.46 (m, 1H, C*H*-OH), 3.80 (m, 2H, C*H*$_2$-I), 3.07, 3.22 (d, AA'BB', 2H, C*H*$_2$-C=O); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 123.94, 128.68, 142.71 (Ar-*C*s), 170.46 (*C*=O), 27.62, 41.77, 65.43, 68.08 (*C*H-OH).

101: ^{1}H NMR (300 MHz, $CDCl_3$): 5.20 (d, *J* =6.03 Hz, 1H, C*H*-OC=O), 1.57, 2.12, 2.40, 2.88, 4.47; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.56, 32.24, 34.67, 36.20, 92.48, 176.34 (*C*=O).

103: ^{1}H NMR (300 MHz, $CDCl_3$): 3.22 (m, 2H, C*H*$_2$-I), 3.96 (m, 1H, C*H*-O), 3.98 (m, 2H, C*H*$_2$O), 2.19, 1.93, 1.65 (m, 2H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 10.51, 26.17, 31.98, 69.02, 78.57 (*C*H$_2$-O).

105: ^{1}H NMR (300 MHz, $CDCl_3$): 4.03 (m, 1H, C*H*-CH$_2$-I), 3.45 (m, 2H, C*H*$_2$O), 3.15 (m, 2H, C*H*$_2$-I), 1.79 (m, 2H, C*H*$_2$-CH$_2$O), 1.50 (m, 4H, 2 C*H*$_2$s).

4.5 Iodination of Cinnamyl Alcohol, 94, in Presence of Methanol as Co-Solvent

Reagent **44** (1.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of cinnamyl alcohol, **94** (0.5-1.0 mmol) dissolved in 1:1 methanol/acetonitrile (30 mL) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction period, the reaction mixture was extracted with DCM and the DCM extract dried ($MgSO_4$) and evaporated to yield **106** as a thick and colorless oil which was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 1.9 g (83%) of **106**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.35 (m, 5H, Ar-*H*s), 2.86 (t, *J* =5.76 Hz, 1H, O*H*), 3.27 (t, 3H, OC*H*$_3$), 4.50 (d, 1H, Ph-C*H*), 3.82, 3.95 (m, 2H, C*H*$_2$), 4.34 (m, 1H, C*H*-I); ^{13}C NMR (75 MHz, $CDCl_3$): 39.01, 57.79, 66.45, 88.06 (*C*H-OCH$_3$), 127.58, 128.59, 128.73, 138.69 (Ar-*C*s).

4.6 Iodination of Cinnamyl Alcohol, 94, in Presence of 1-Butanol as Co-Solvent

A mixture of reagent **44** (1.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of cinnamyl alcohol, **94** (0.5-1.0 mmol) dissolved in acetonitrile (20 mL) along with 1-butanol (3 equiv. or 0.33 mL) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction

period, the reaction was extracted with the DCM, washed with water for several times to get rid of 1-butanol. DCM was readily removed using evaporation under reduced pressure to yield **107** as a thick oil which was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 1.64 g (63%) of **107**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.33 (m, 5H, Ar-*H*s), 3.09 (t, *J* =6.18 Hz, 1H, O*H*), 3.32 (t, *J* =6.45 Hz, 2H, C*H*$_2$-O-C), 3.83, 3.93 (d, AA'BB', 2H, C*H*$_2$-OH), 4.61 (d, *J* =7.14 Hz, 1H, Ph-C*H*-O-), 1.51, 1.54 (m, 2H, C*H*$_2$s), 0.85 (t, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.88, 19.41, 31.85, 38.87, 66.66, 70.05 (*C*H$_2$-O), 87.06 (*C*H-O), 127.47, 128.55, 139.43 (Ar-*C*s).

4.7 Iodination of Cinnamyl Alcohol, 94, in Presence of 1, 3-Propanediol as Co-Solvent

A mixture of reagent **44** (1.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of cinnamyl alcohol, **94** (0.5-1.0 mmol) dissolved in acetonitrile (20 mL) along with 1,3-propanediol (3 mL) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction period, the reaction was extracted with DCM and the solvents were readily removed using evaporation under reduced pressure to yield **108** as a thick liquid which was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 1.99 g (79%) of **108**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.34 (m, 5H, Ar-*H*s), 2.25, 2.31 (broad peaks, O*H*s), 4.60 (d, *J* =6.87 Hz, 1H, C*H*-O), 3.50 (t, *J* =6.06 Hz, 2H, C*H*$_2$), 3.98 (dd, 2H, C*H*$_2$), 1.80 (m, 2H, C*H*$_2$-middle); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 32.23, 39.90, 60.99, 65.85, 68.28, 85.95 (*C*H-O), 115.25, 127.47, 128.65, 128.71, 138.88 (Ar-*C*s).

4.8 Iodination of Cinnamyl Alcohol, 94, in Presence of Benzyl Alcohol as Co-Solvent

Reagent **44** (1.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of cinnamyl alcohol, **94** (0.5-1.0 mmol) dissolved in acetonitrile (20 mL) along with benzyl alcohol (2 equiv. or 0.28 mL) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction period, the reaction was extracted with DCM and the DCM was evaporated under reduced pressure to yield **109** as thick oil which was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 1.56 g (57%) of **109**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.35 (m, 5H, Ar-*H*s), 2.82 (t, J =5.79 Hz, 1H, O*H*), 4.29, 4.47 (AB, 2H, Ph-CH_2), 3.82, 3.98 (d, AA'BB', 2H, CH_2-OH), 4.31 (m, 1H, C*H*-I), 4.69 (d, J =7.41 Hz, 1H, C*H*-OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 39.37, 66.46, 71.68, 85.28 (*C*H-O), 127.78, 128.11, 128.67, 137.30, 138.90 (Ar-*C*s).

4.9 Iodination of Cinnamyl Alcohol, 94, in Presence of 2-Chloroethanol as Co-Solvent

Reagent **44** (1.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of cinnamyl alcohol, **94** (0.5-1.0 mmol) dissolved in acetonitrile (20 mL) along with 2-chloroethanol (2 equiv) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction period, the reaction was extracted with DCM, dried and evaporated under reduced pressure to yield **110** as thick oil which was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 1.60 g (62%) of **110**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.31 (m, 5H, Ar-*H*s), 2.83 (t, J =2.76 Hz, 1H, O*H*), 3.90, 3.99 (d, AA'BB', 2H, CH_2), 4.66 (d, 1H, Ph-

C*H*), 4.34 (m, 1H, C*H*-I), 3.59 (m, 4H, CH_2S); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 38.88, 43.06, 66.55, 69.66, 86.59 (*C*H-O), 127.63, 128.66, 128.94, 138.71 (Ar-*C*s).

4.10 Iodination of Cinnamyl Alcohol, 94, in Presence of 1-Chloro-3-propanol as Co-Solvent

Reagent **44** (1.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of cinnamyl alcohol, **94** (0.5-1.0 mmol) dissolved in acetonitrile (20 mL) along with 1-chloro-3-propanol (2 equiv) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction period, the reaction was extracted with DCM, dried and evaporated under reduced pressure to yield **111** as a thick oil which was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 2.10 g (79%) of **111**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.34 (m, 5H, Ar-*H*s), 4.62 (d, *J* =6.87 Hz, 1H), 4.34 (m, 1H), 2.62 (t, *J* =6.45 Hz, 1H, O*H*), 2.01 (m, 2H).

4.11 Iodination of Cinnamyl Alcohol, 94, using Water-Soluble IBX Derivative, 65/I_2

Reagent **65** (2.5 equiv) and elemental iodine (1.2 equiv) were added to a solution of cinnamyl alcohol, **94** (0.5-1.0 mmol) dissolved in 1:1 water/acetonitrile (30 mL) and refluxed at 60 °C in an oil bath. The resulting mixture was stirred at this temperature for 12 h. At the end of the reaction period, the reaction was extracted with DCM, dried and the solvent was readily removed using evaporation under reduced pressure to yield **113** as a thick and colorless oil which was purified by flash chromatography using gradient elution with petroleum ether and DCM to yield 1.02 g (50%) of **113**. ^{1}H NMR (300 MHz,

$CDCl_3$): 7.25 (m, Ar-*H*s), 8.02 (m, Ar-*H*s), 3.97, 4.26 (m, 2H, C*H*$_2$s), 5.29 (dd, 1H, C*H*-I), 2.50 (broad peak, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 23.87 (*C*H-I), 64.55 (*C*H$_2$-OH), 128.91, 129.13, 134.07, 134.13 (Ar-*C*s), 195.24 (C=O).

4.12 Solid state Iodination of Cinnamyl Alcohol using Sodium Azide as Nucleophilic Source

A mixture of cinnamyl alcohol, **94**, DAIB, **44** (1.5 equiv), elemental iodine (1.2 equiv) were taken in a mortar and ground with pestle under hood to get a homogenous mixture that appears as a suspension. The reaction mixture was then allowed to stand for 12 h to get rid of iodobenzene which was formed during grinding and the crude product was isolated from the reaction mixture using water and DCM. The organic layer was then dried, evaporated under reduced pressure to yield **112** as a thick liquid. The crude product was then purified using column chromatography using gradient elution with petroleum ether and DCM to yield 2.11 g (72%) of **112**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.35 (m, 5H, Ar-*H*s), 6.00 (d, J =7.41 Hz, 1H, C*H*-N_3), 2.79 (t, 1H, O*H*), 3.80 (m, 2H, C*H*$_2$), 4.50 (m, 1H, C*H*-I).

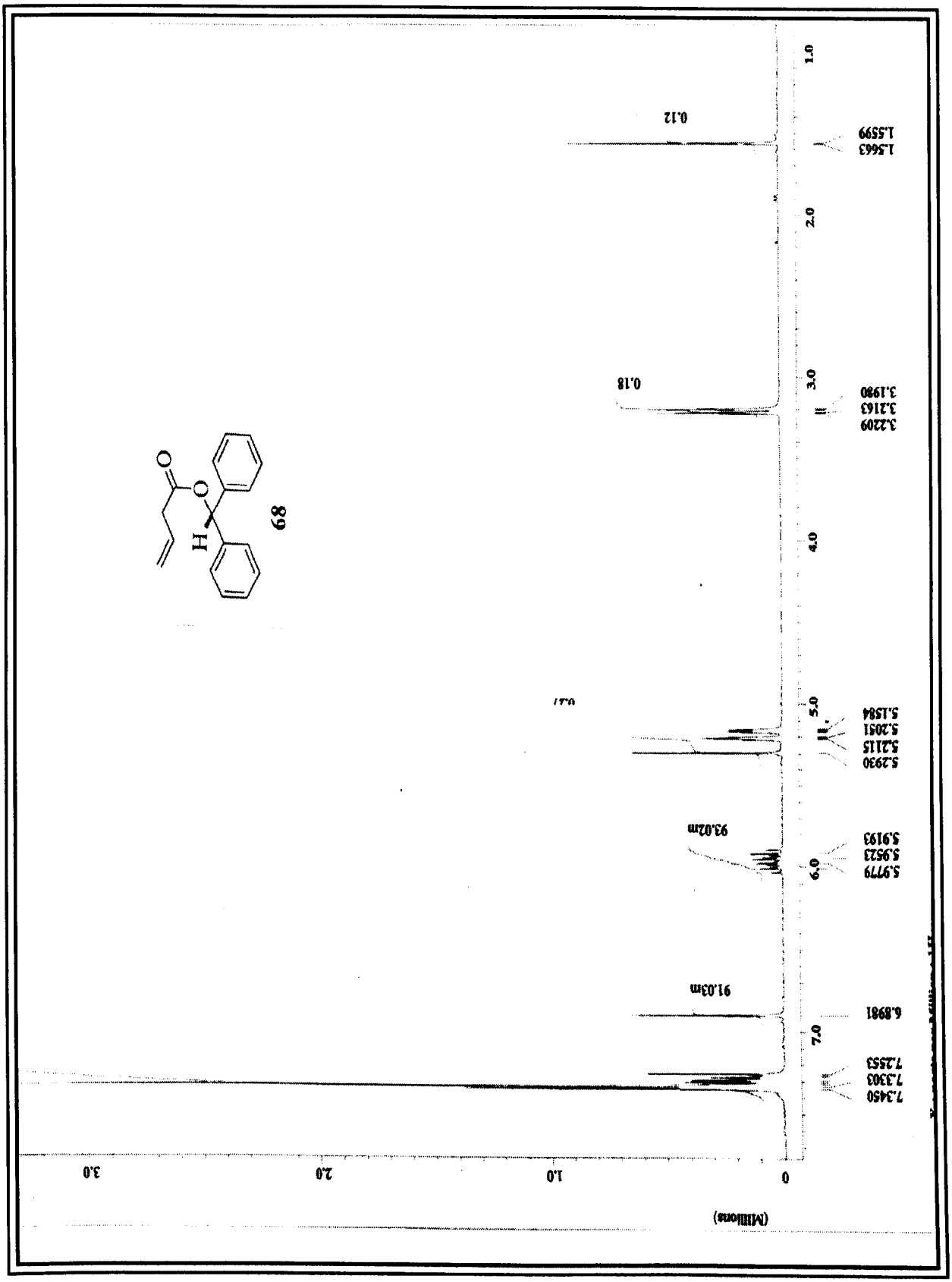


Figure 18: ^{1}H NMR spectrum of compound 68

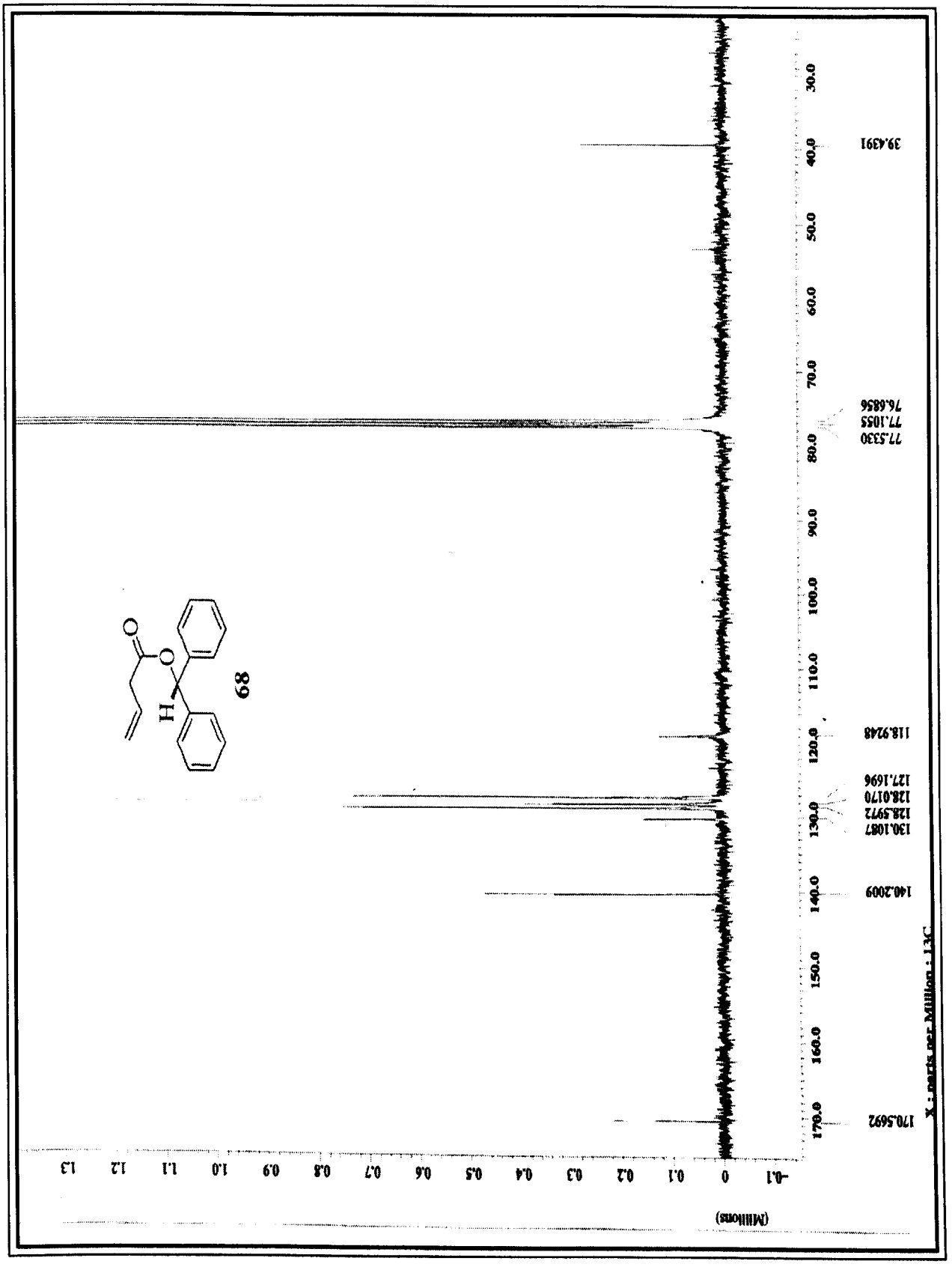


Figure 19: ^{13}C NMR spectrum of compound 68

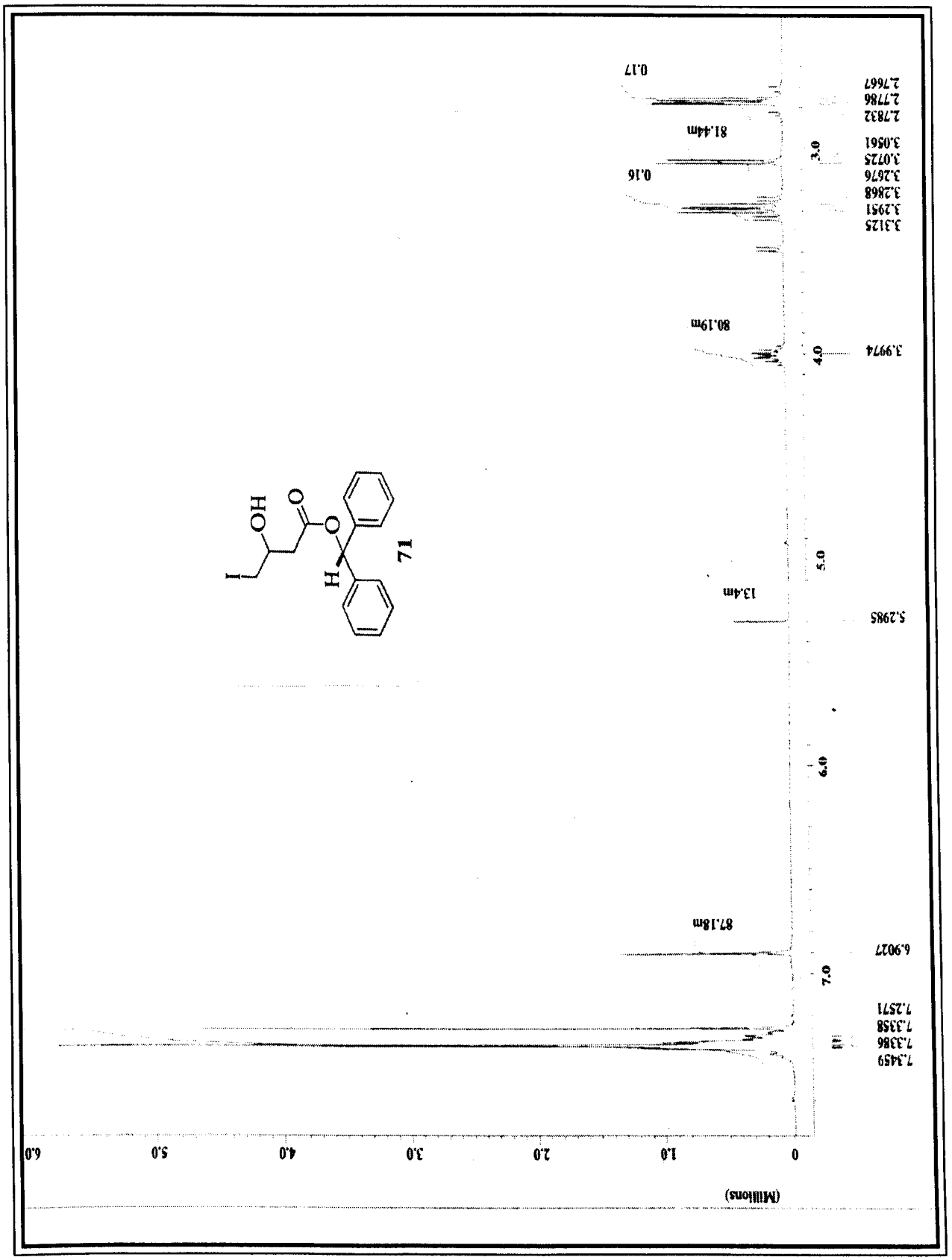


Figure 20: ^{1}H NMR spectrum of compound 71

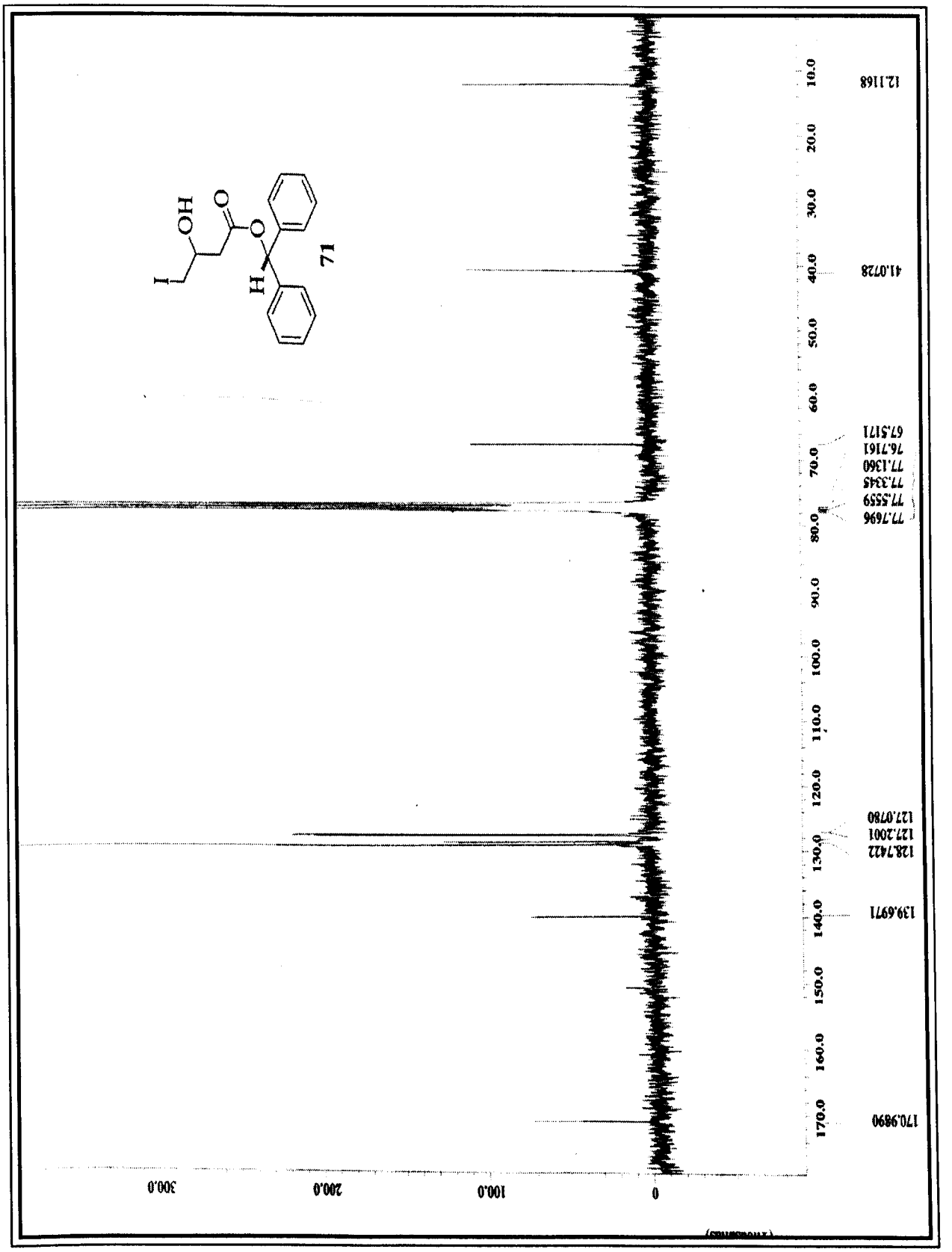


Figure 21: ^{13}C NMR spectrum of compound 71

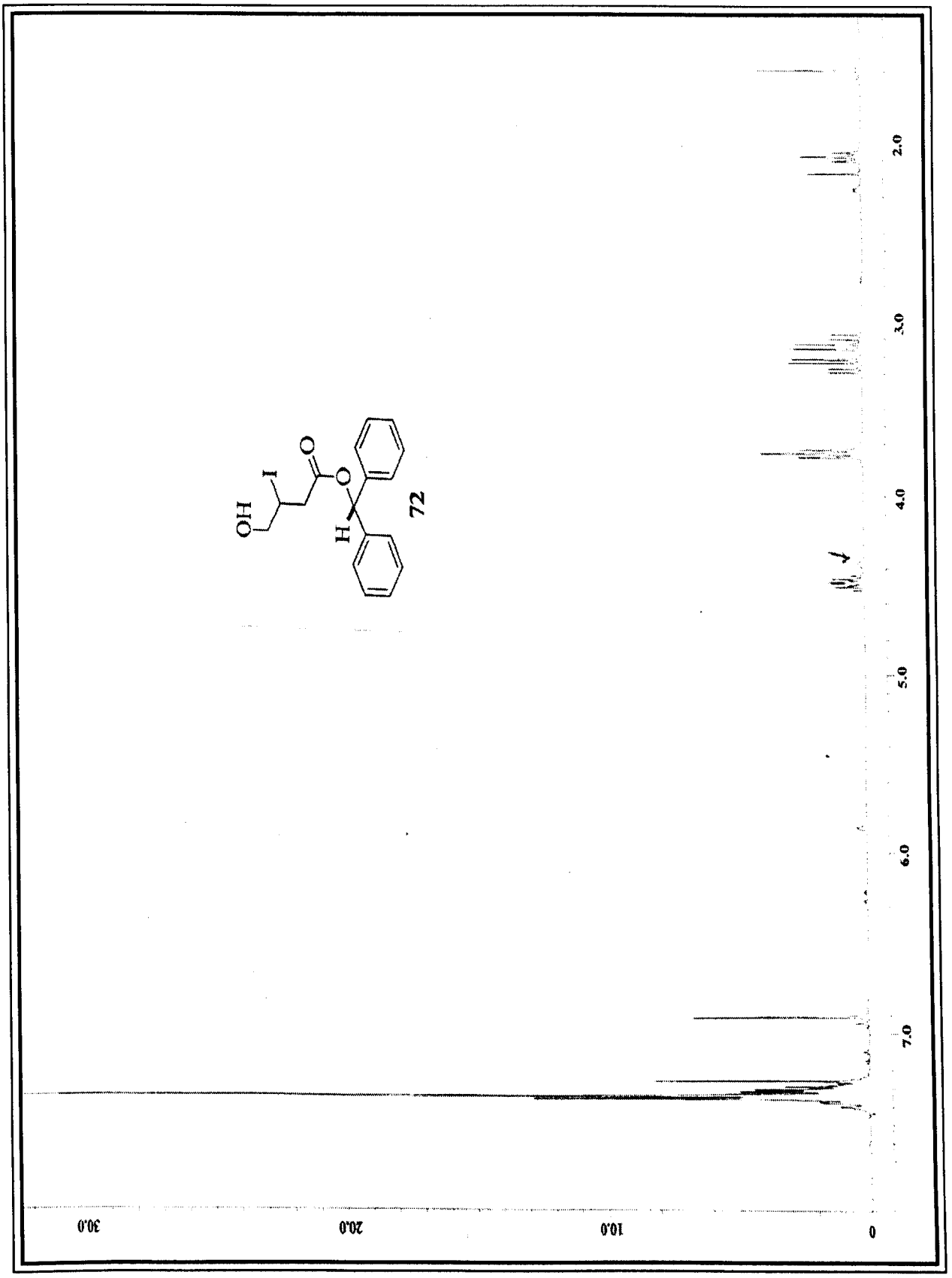


Figure 22: ^{1}H NMR spectrum of compound 72

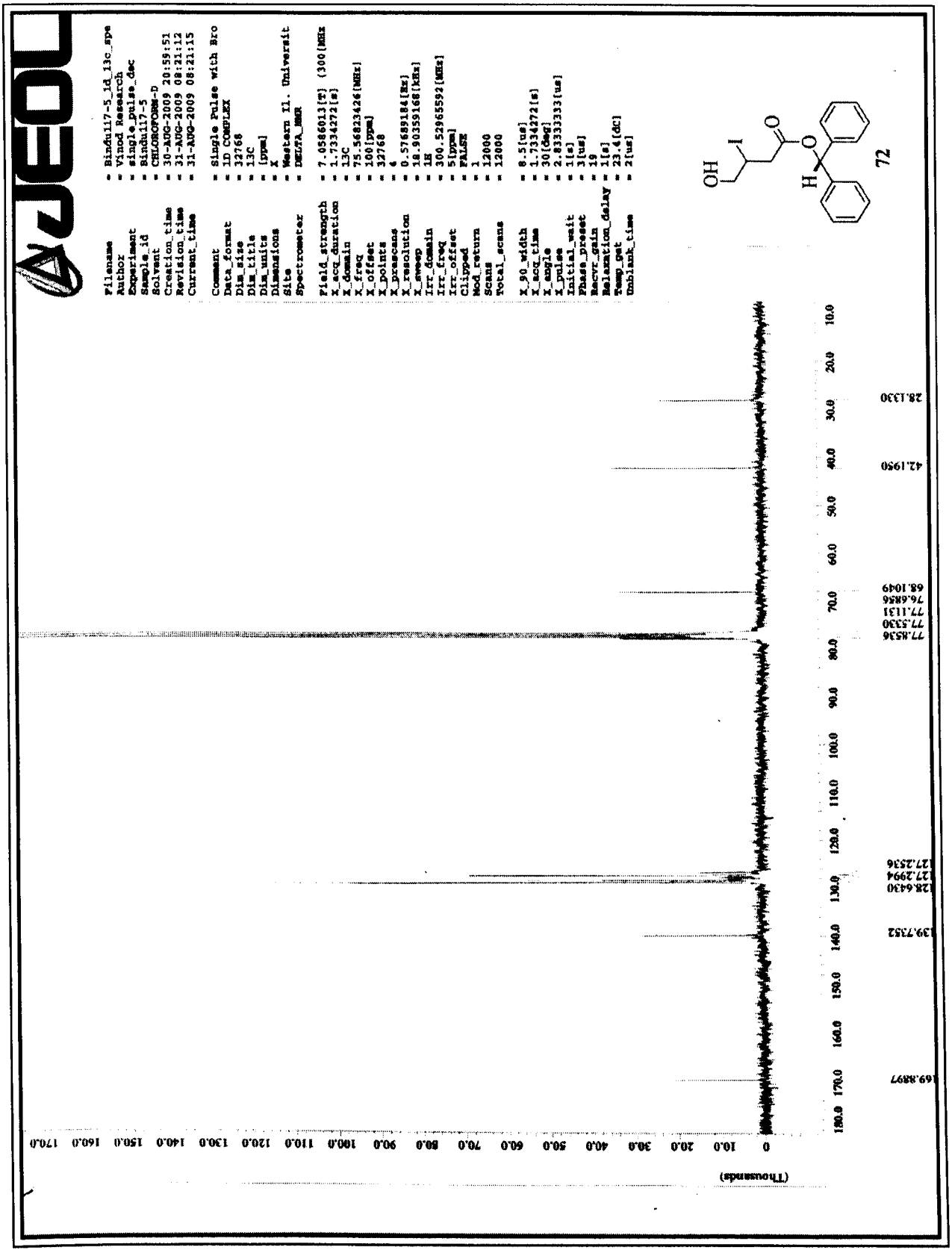


Figure 23: ^{13}C NMR spectrum of compound 72

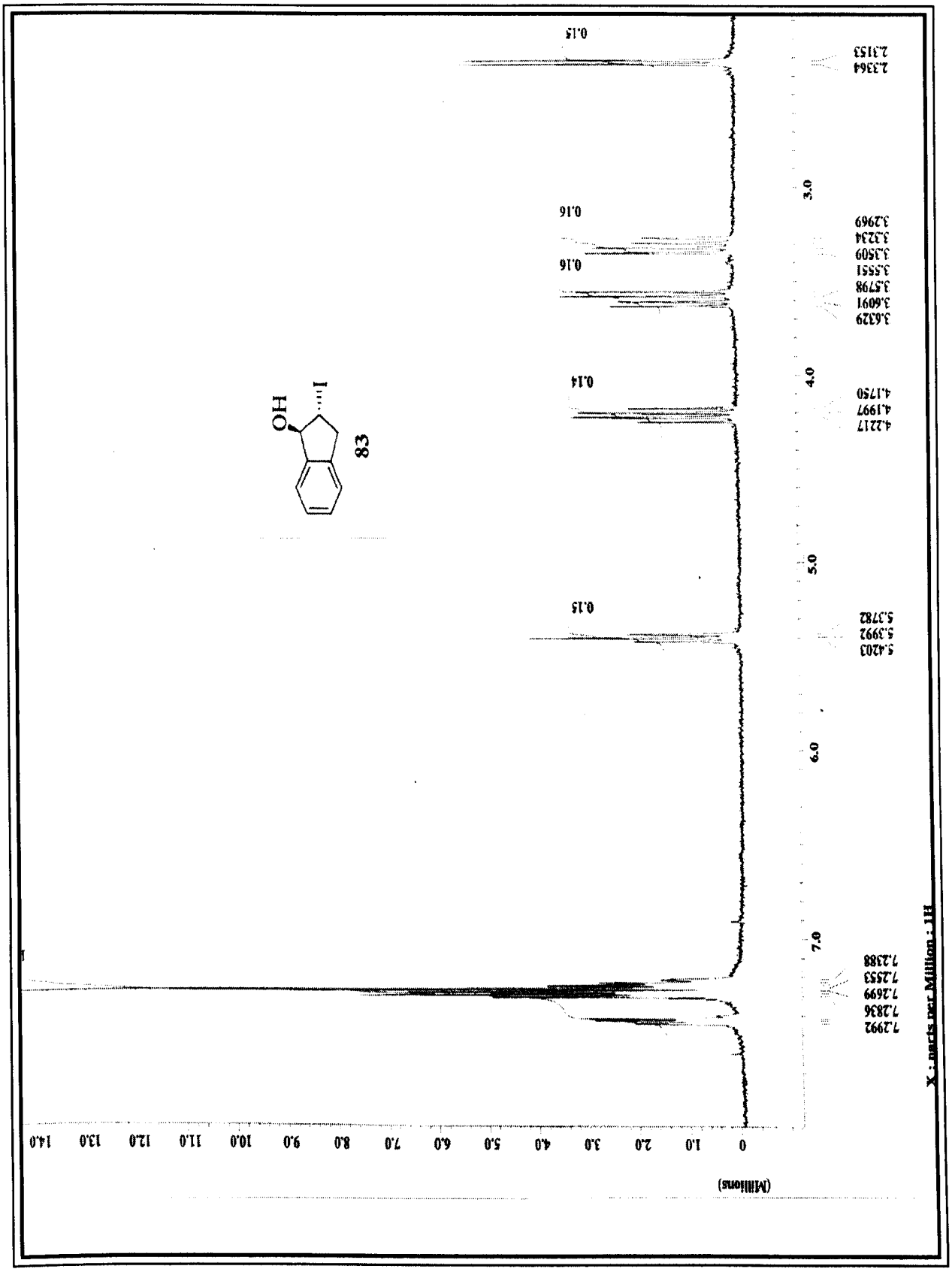


Figure 24: ^{1}H NMR spectrum of compound 83

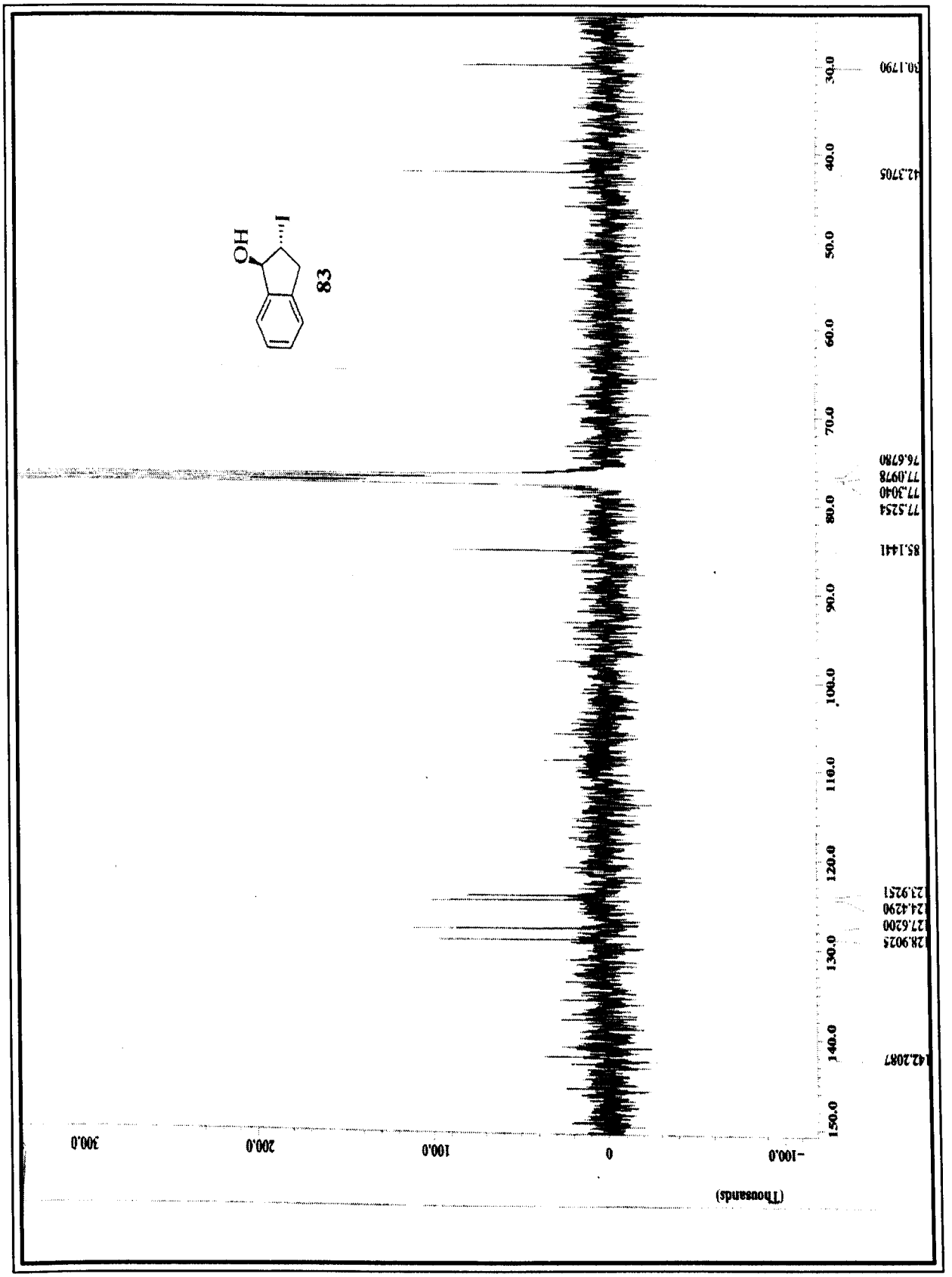


Figure 25: ^{13}C NMR spectrum of compound 83

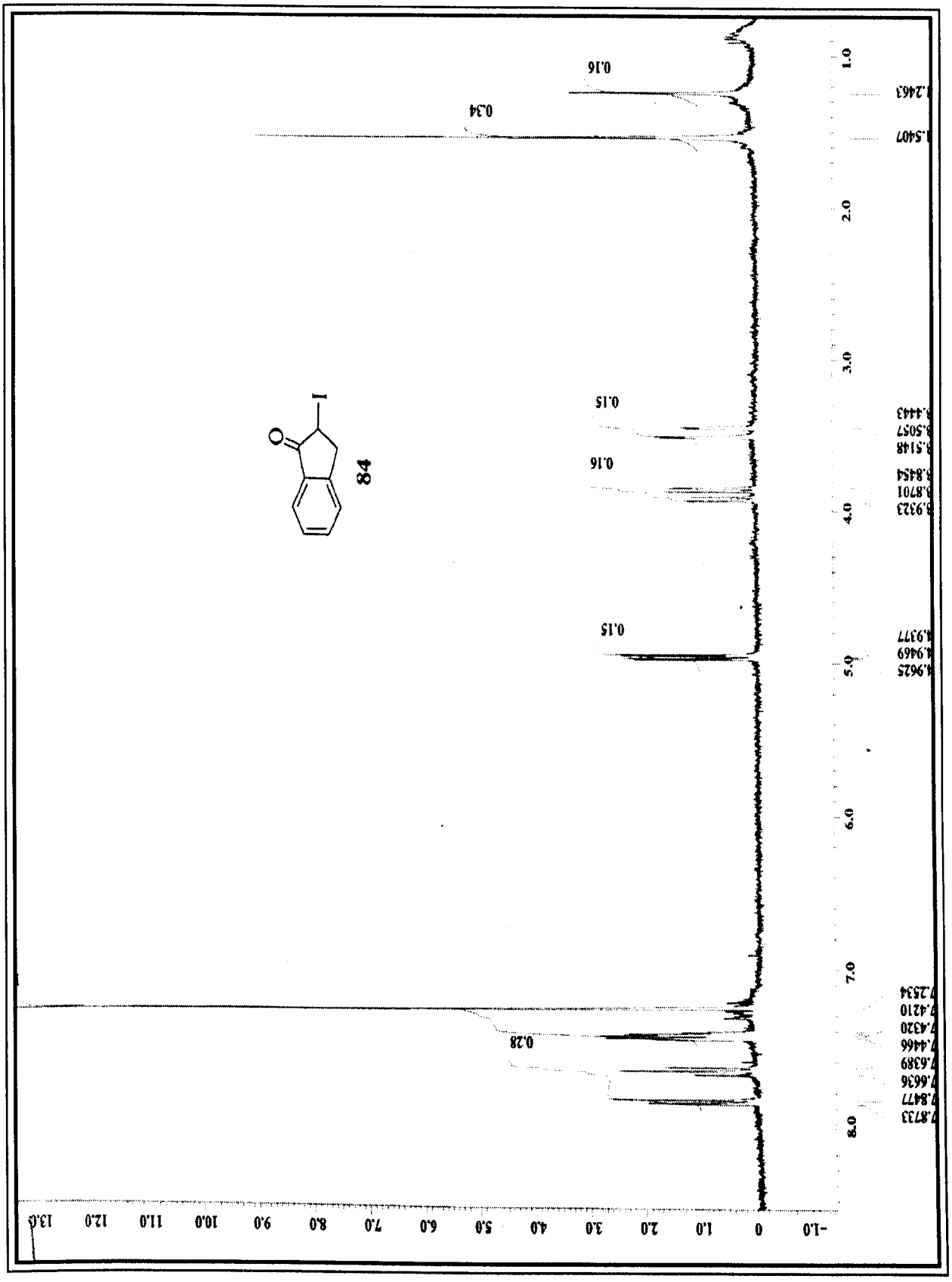


Figure 26: ^{1}H NMR spectrum of compound 84

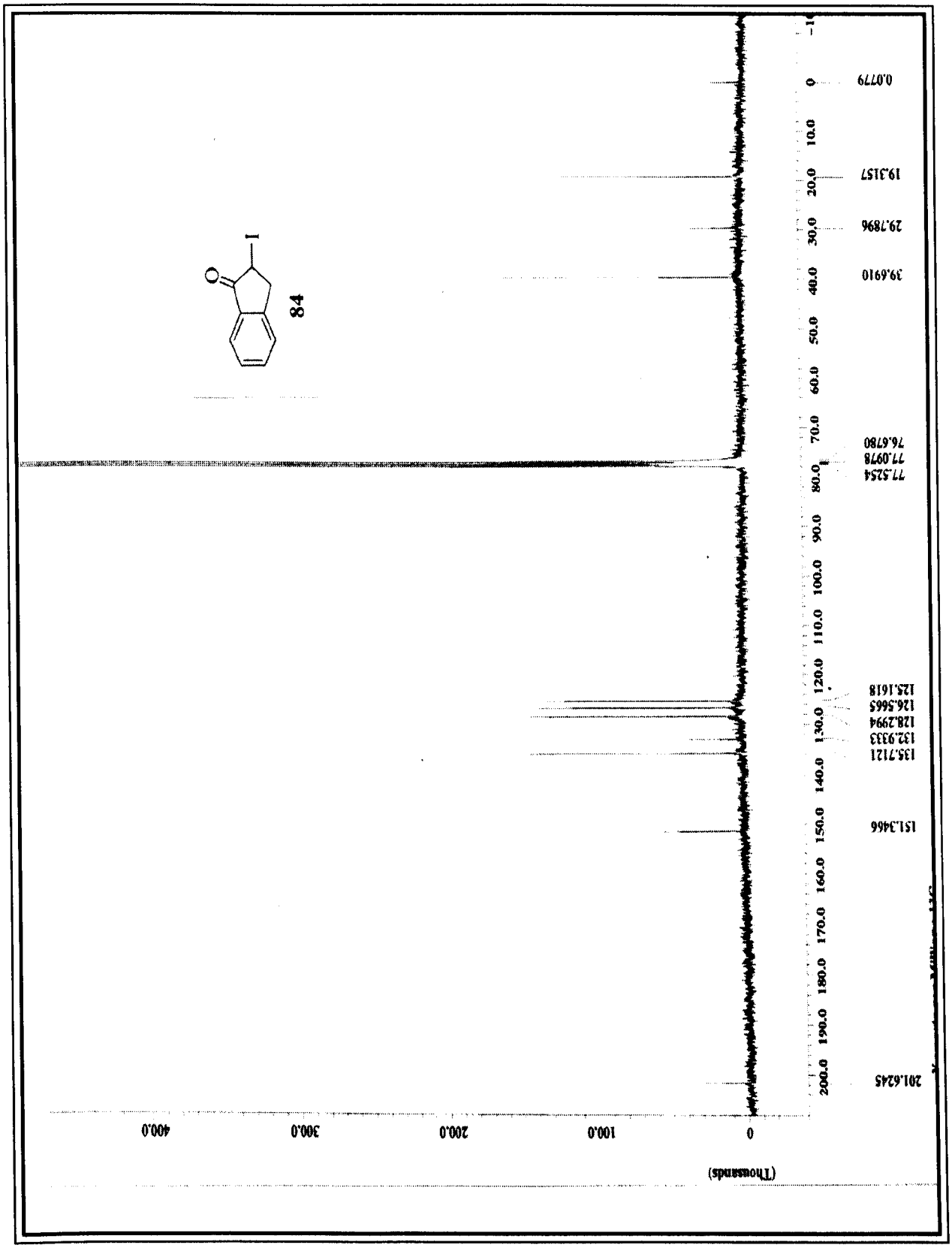


Figure 27: ^{13}C NMR spectrum of compound 84

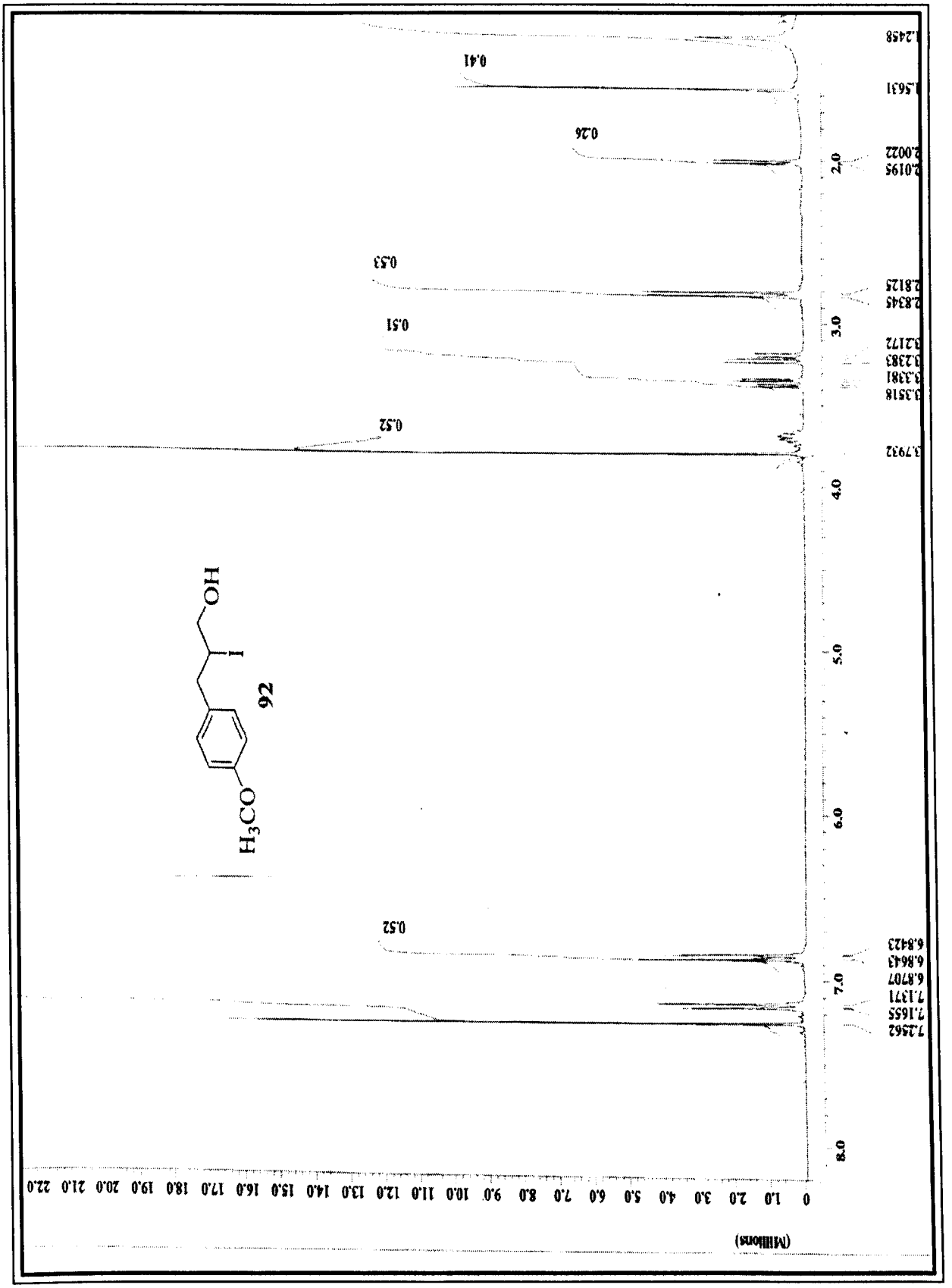


Figure 28: ^{1}H NMR spectrum of compound 92

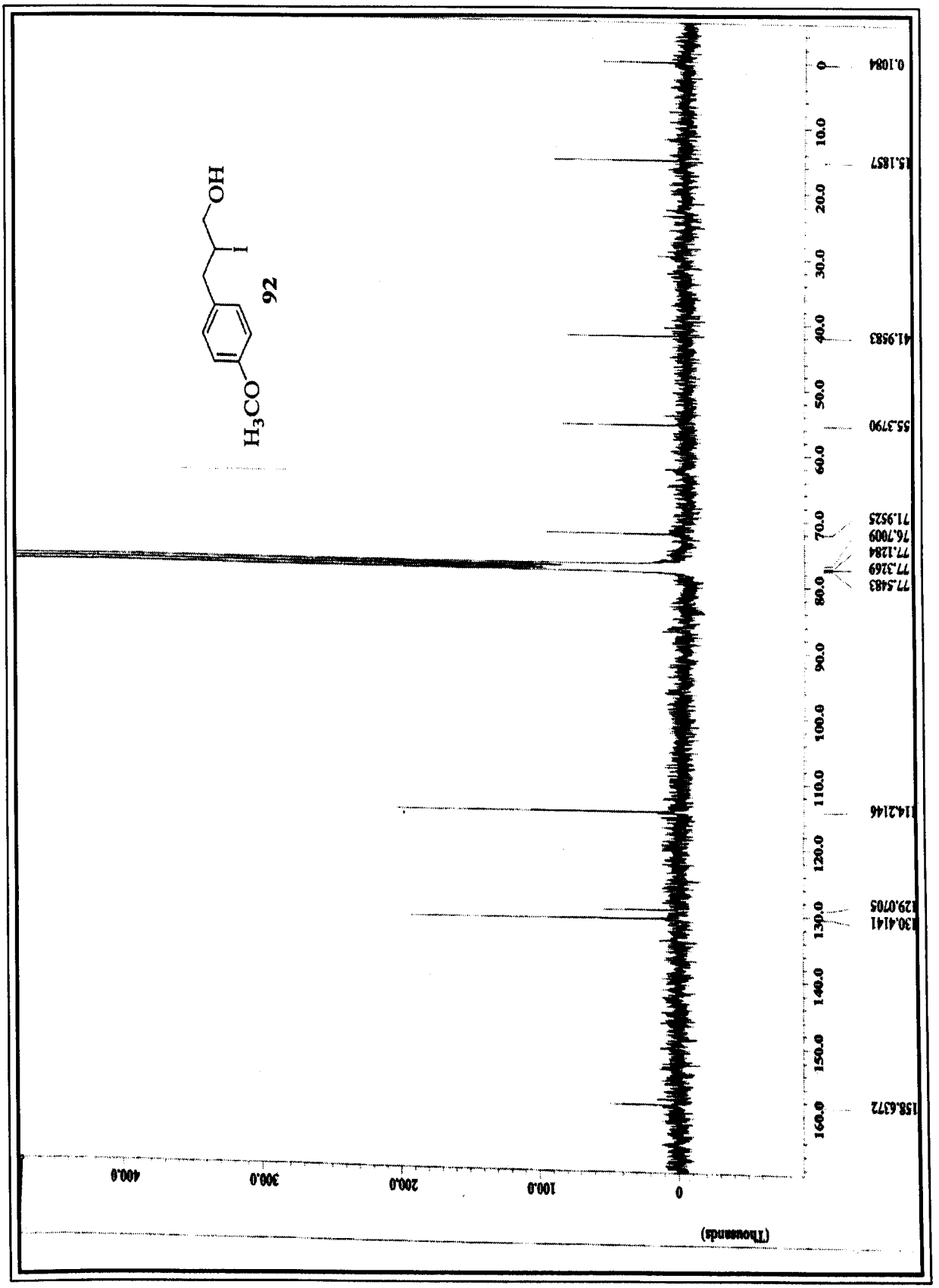


Figure 29: ^{13}C NMR spectrum of compound 92

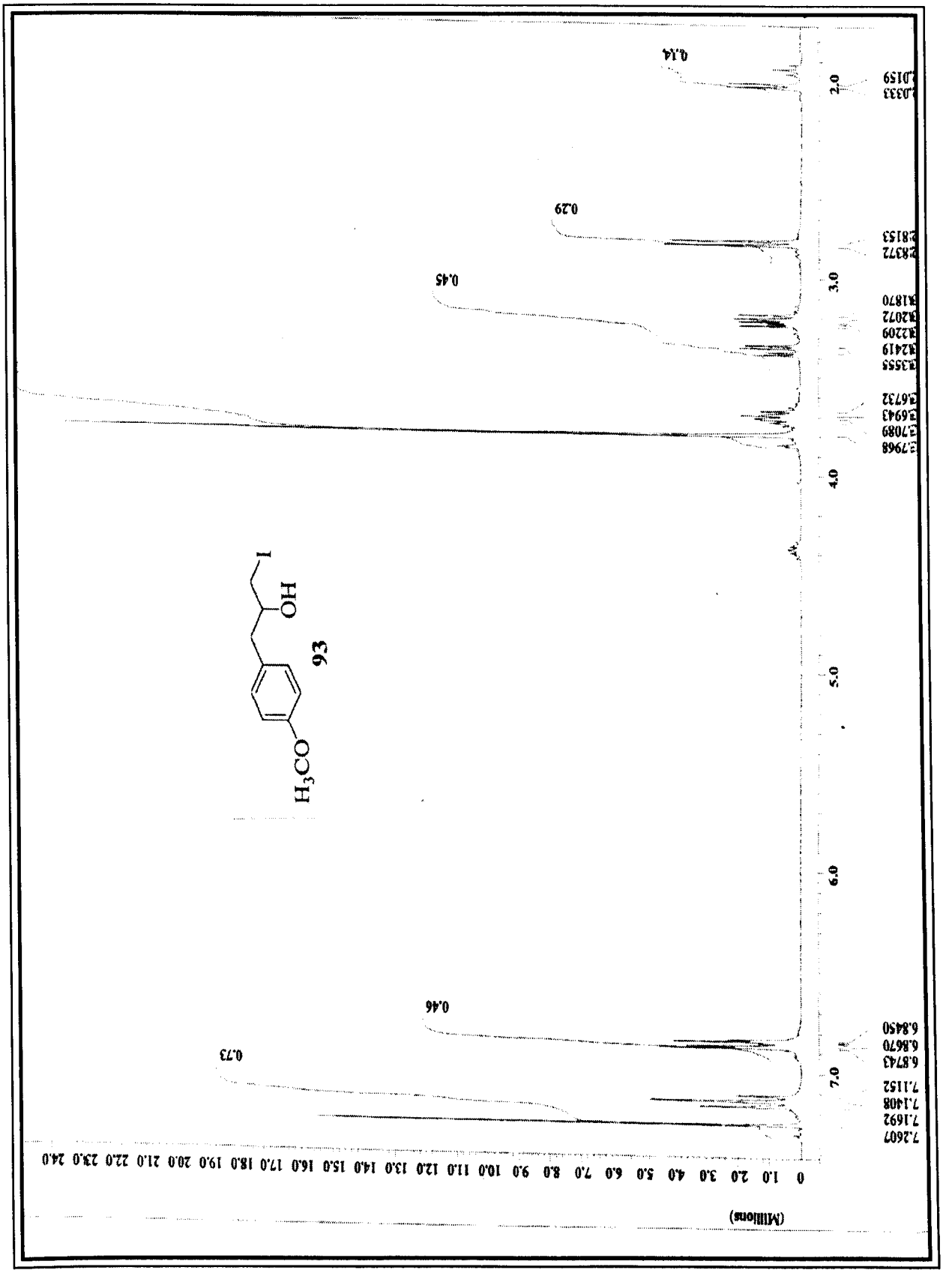


Figure 30: ^{1}H NMR spectrum of compound 93

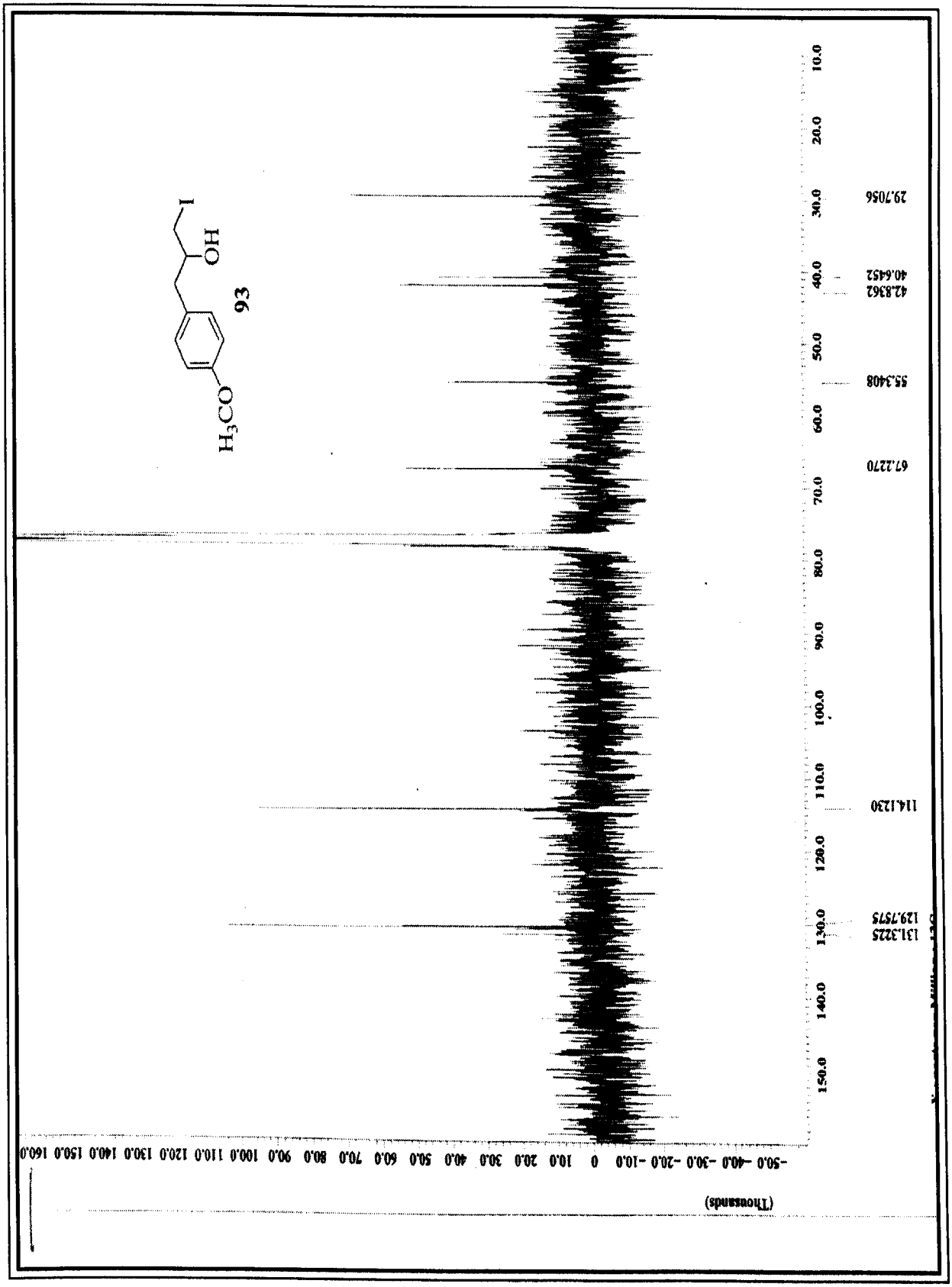


Figure 31: ^{13}C NMR spectrum of compound 93

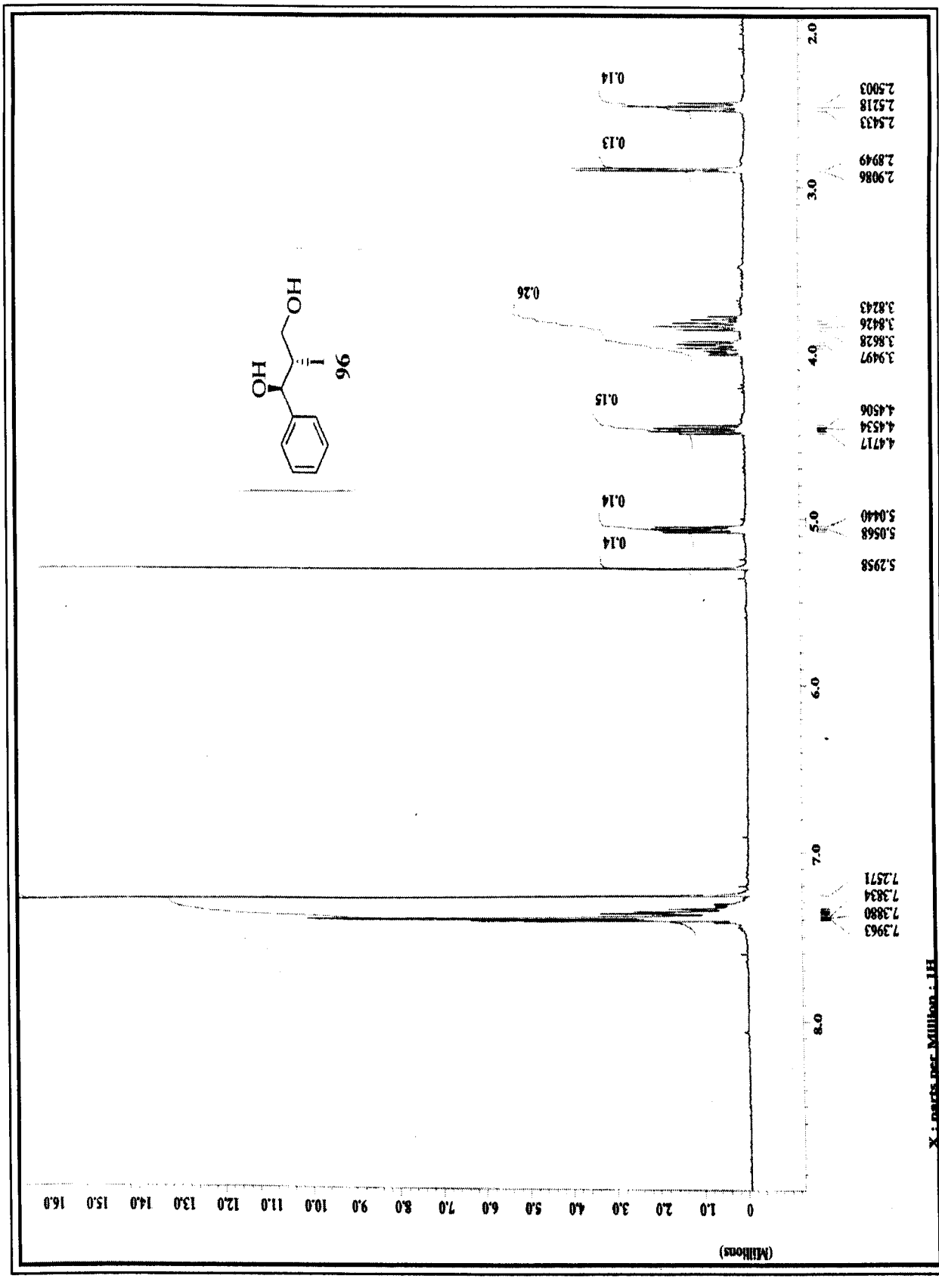


Figure 32: ^{1}H NMR spectrum of compound 96

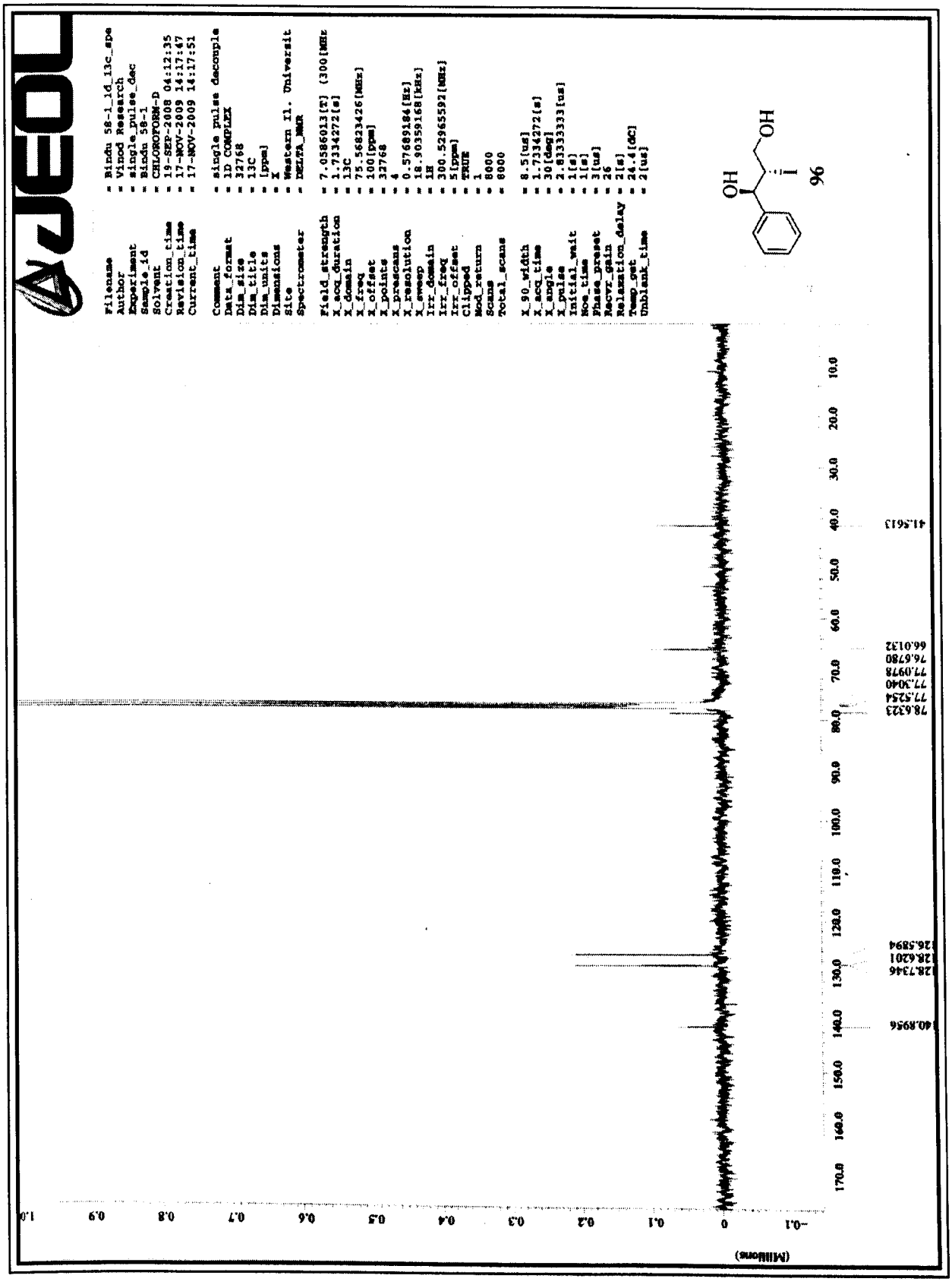


Figure 33: ^{13}C NMR spectrum of compound 96

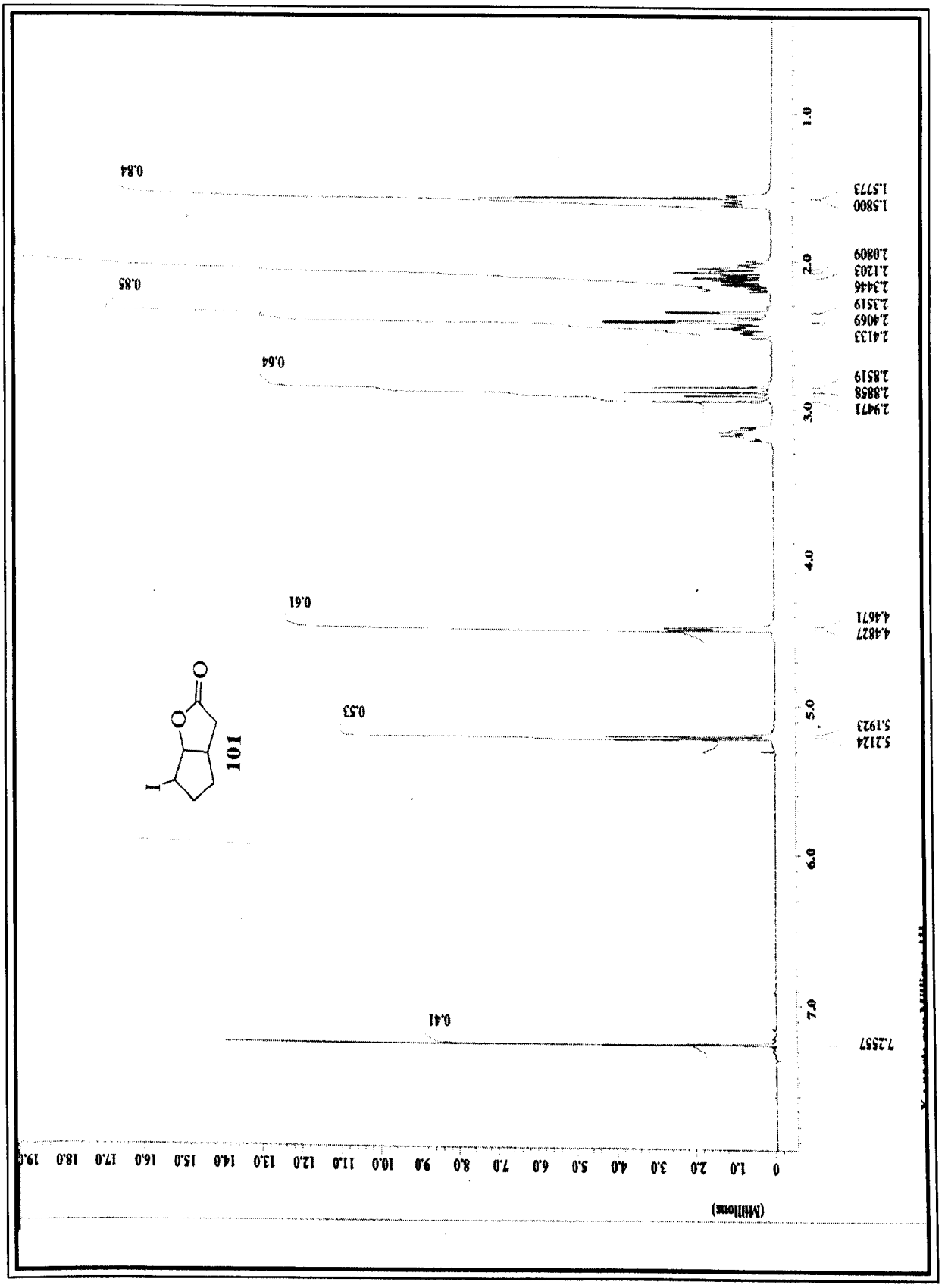


Figure 34: ^{1}H NMR spectrum of compound 101

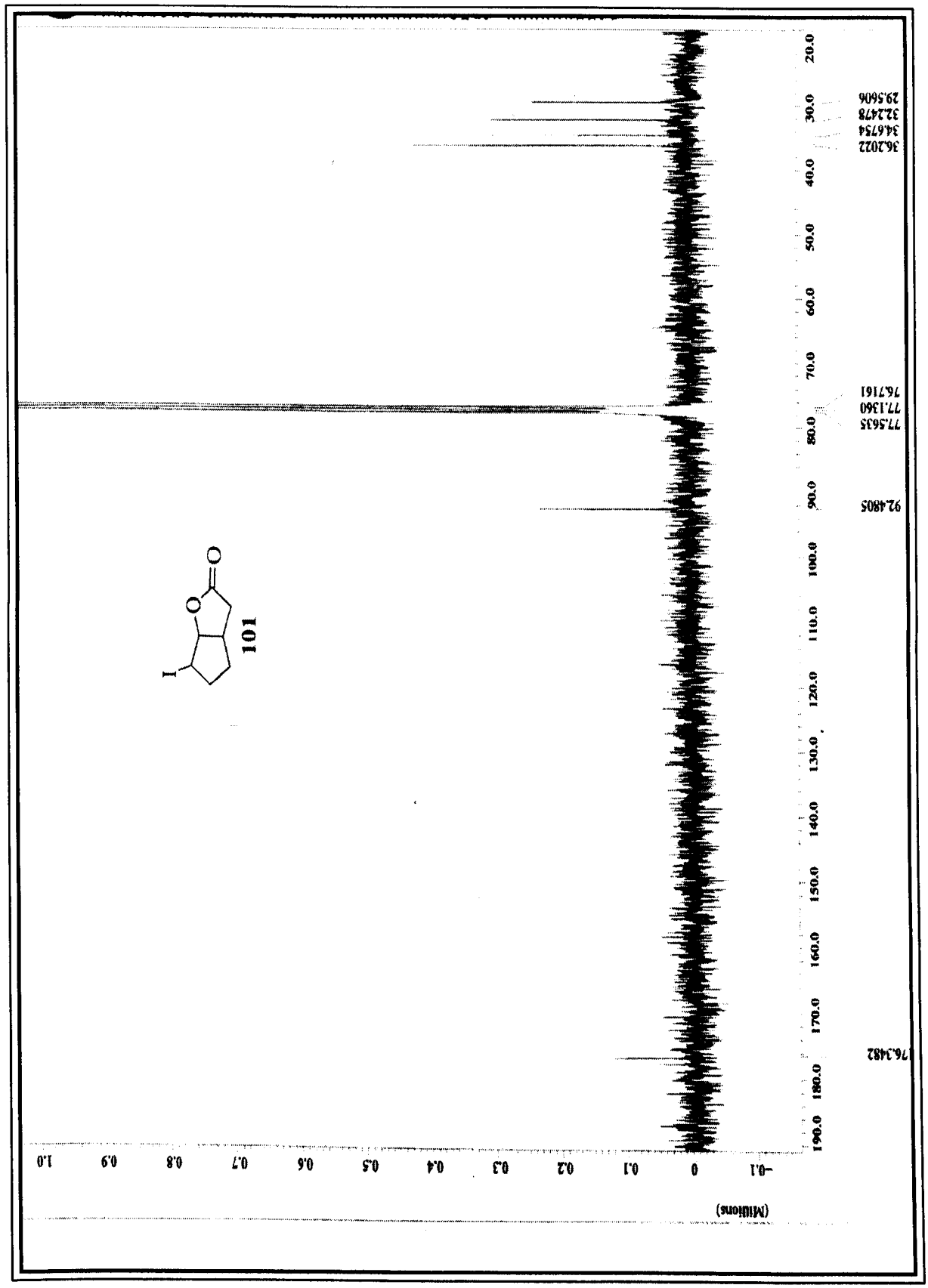


Figure 35: ^{13}C NMR spectrum of compound 101

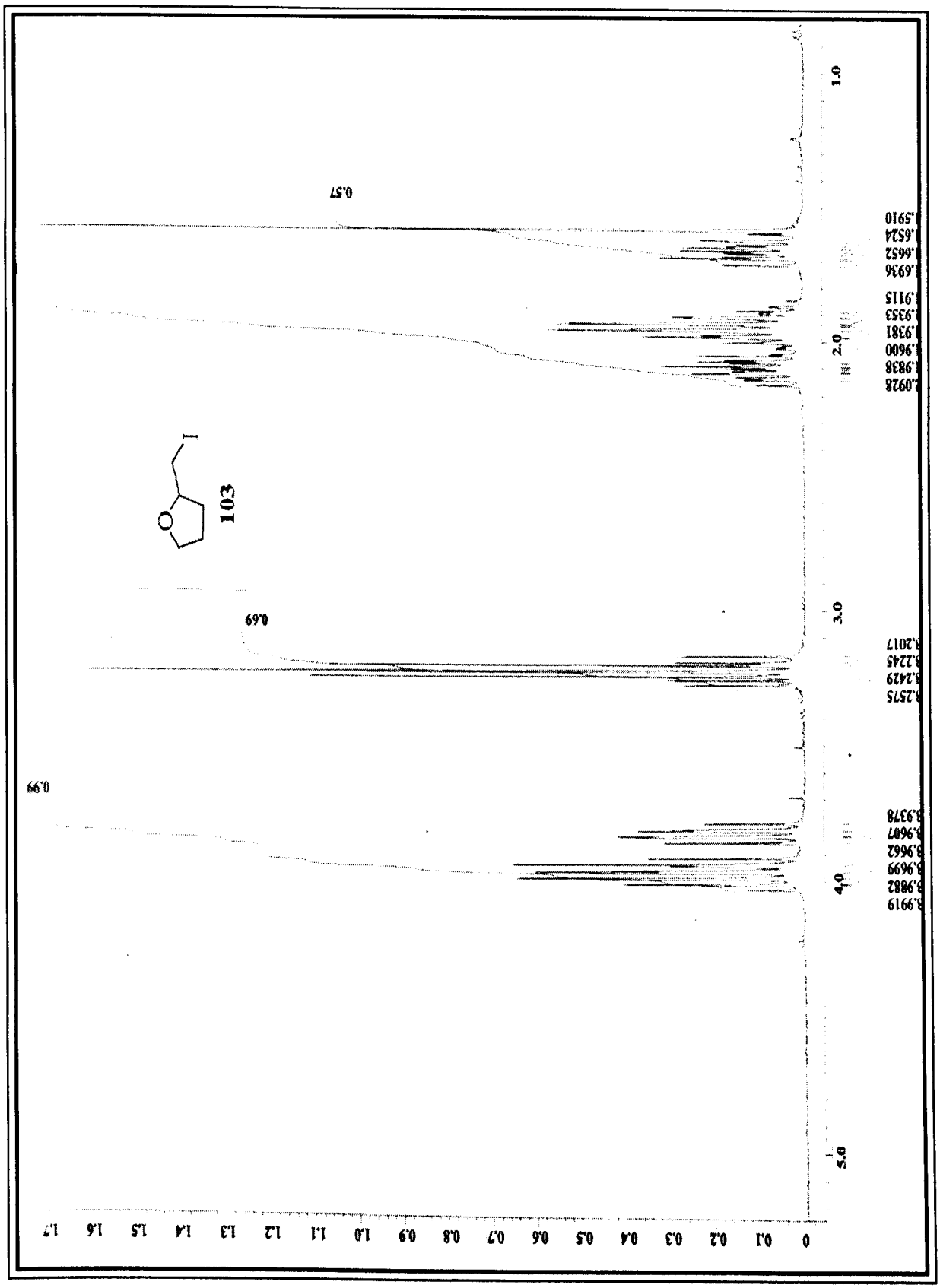


Figure 36: ^{1}H NMR spectrum of compound 103

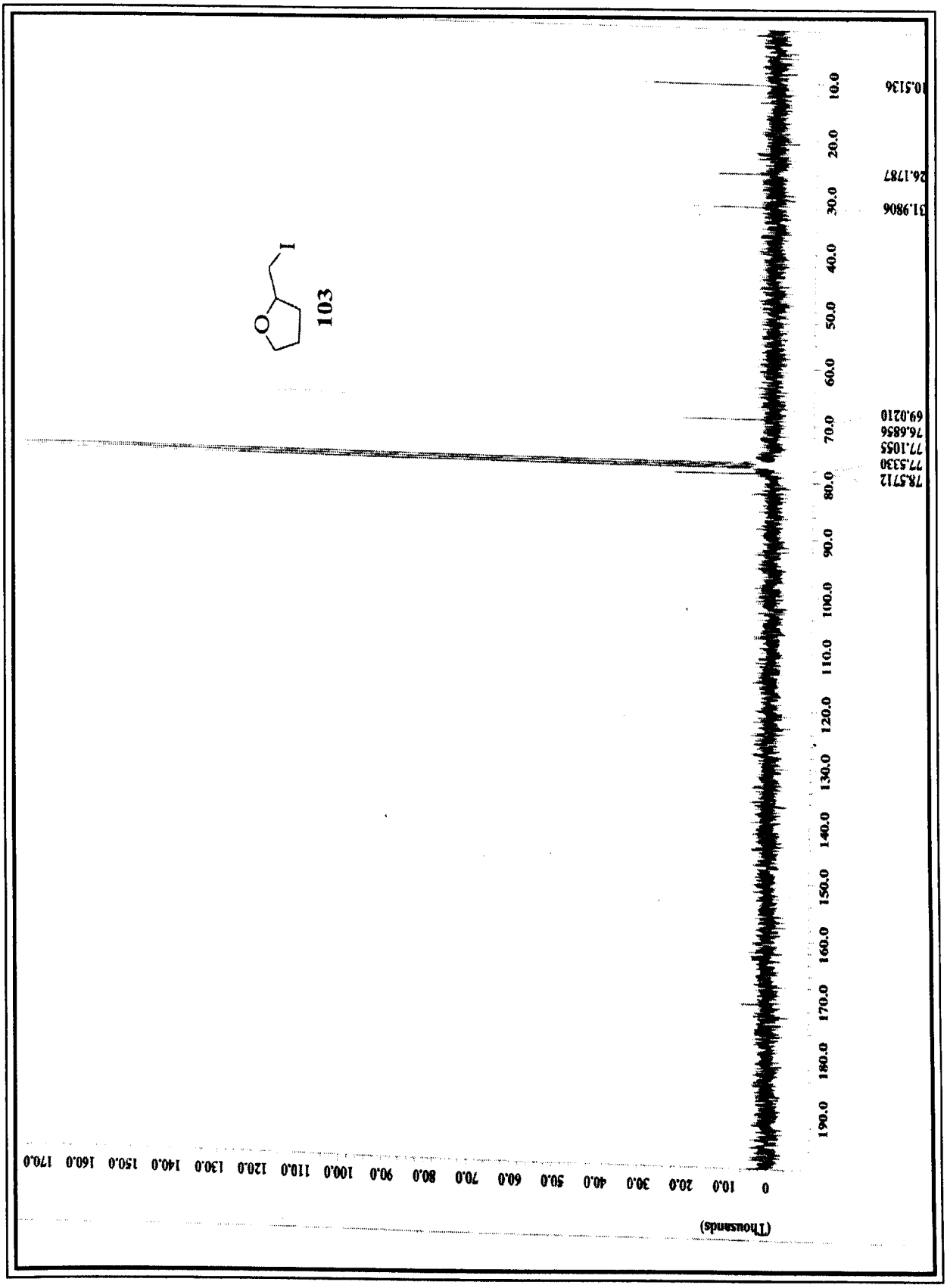


Figure 37: ^{13}C NMR spectrum of compound 103

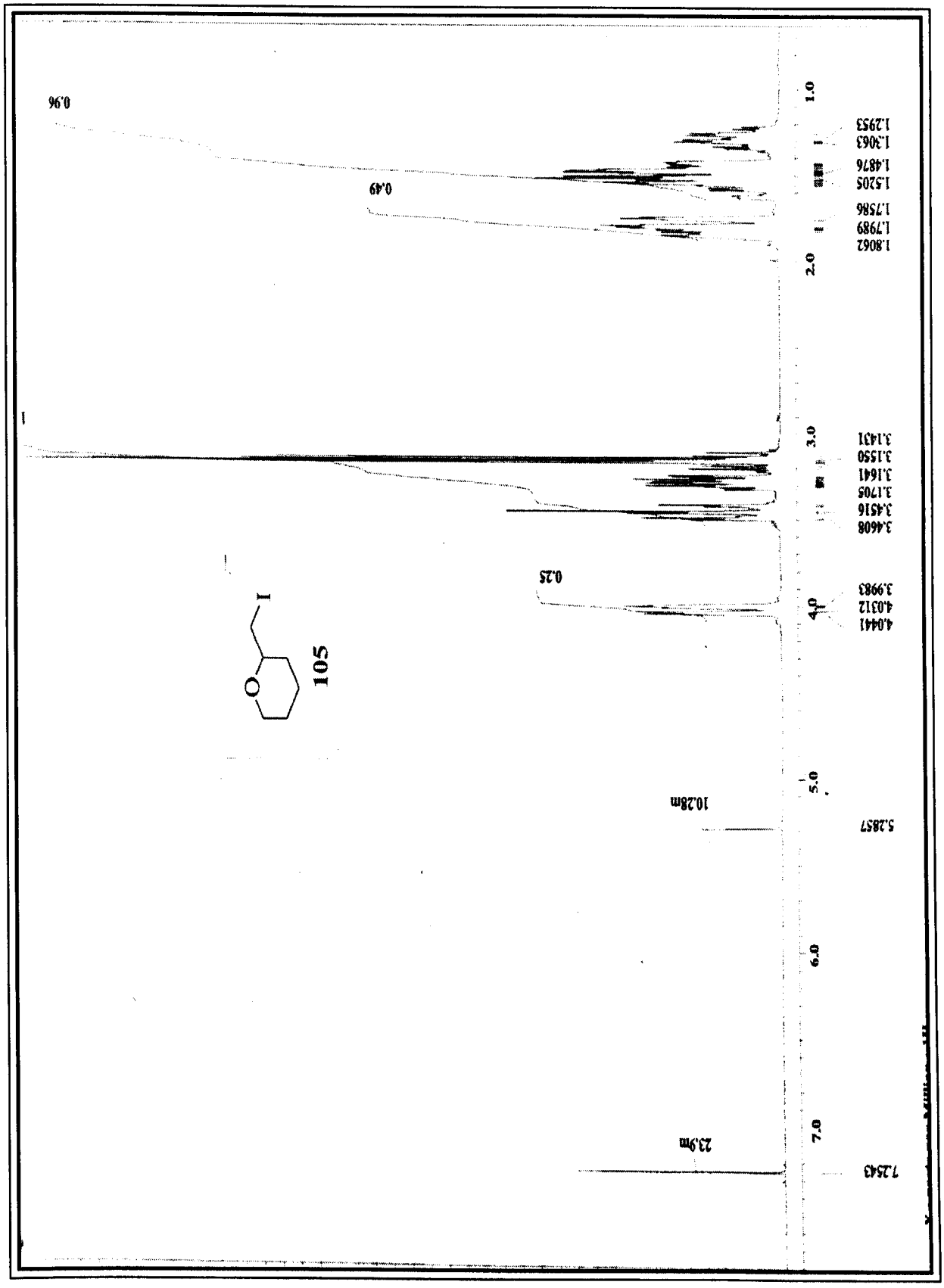


Figure 38: ^{1}H NMR spectrum of compound 105

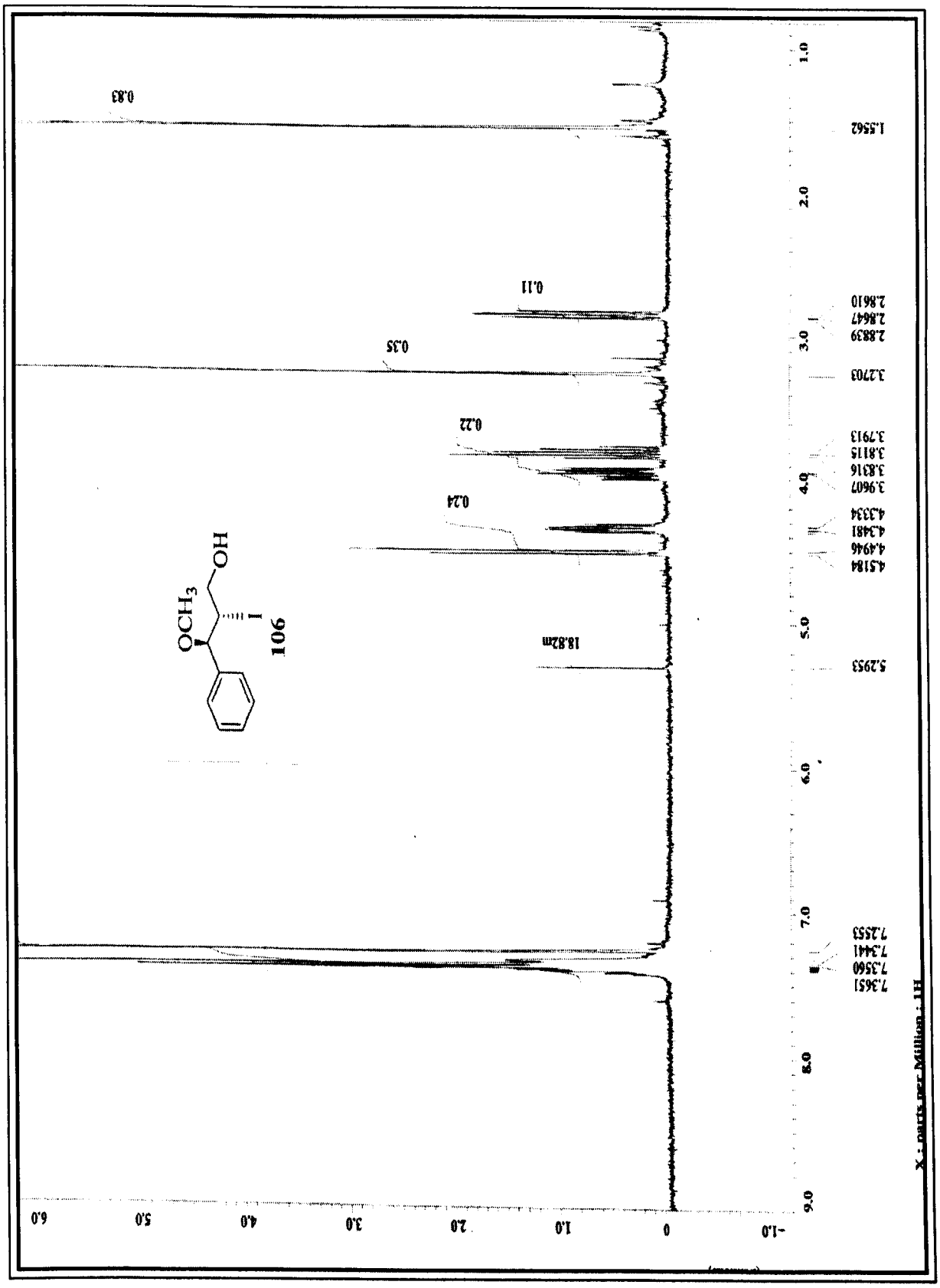


Figure 39: ^{1}H NMR spectrum of compound 106

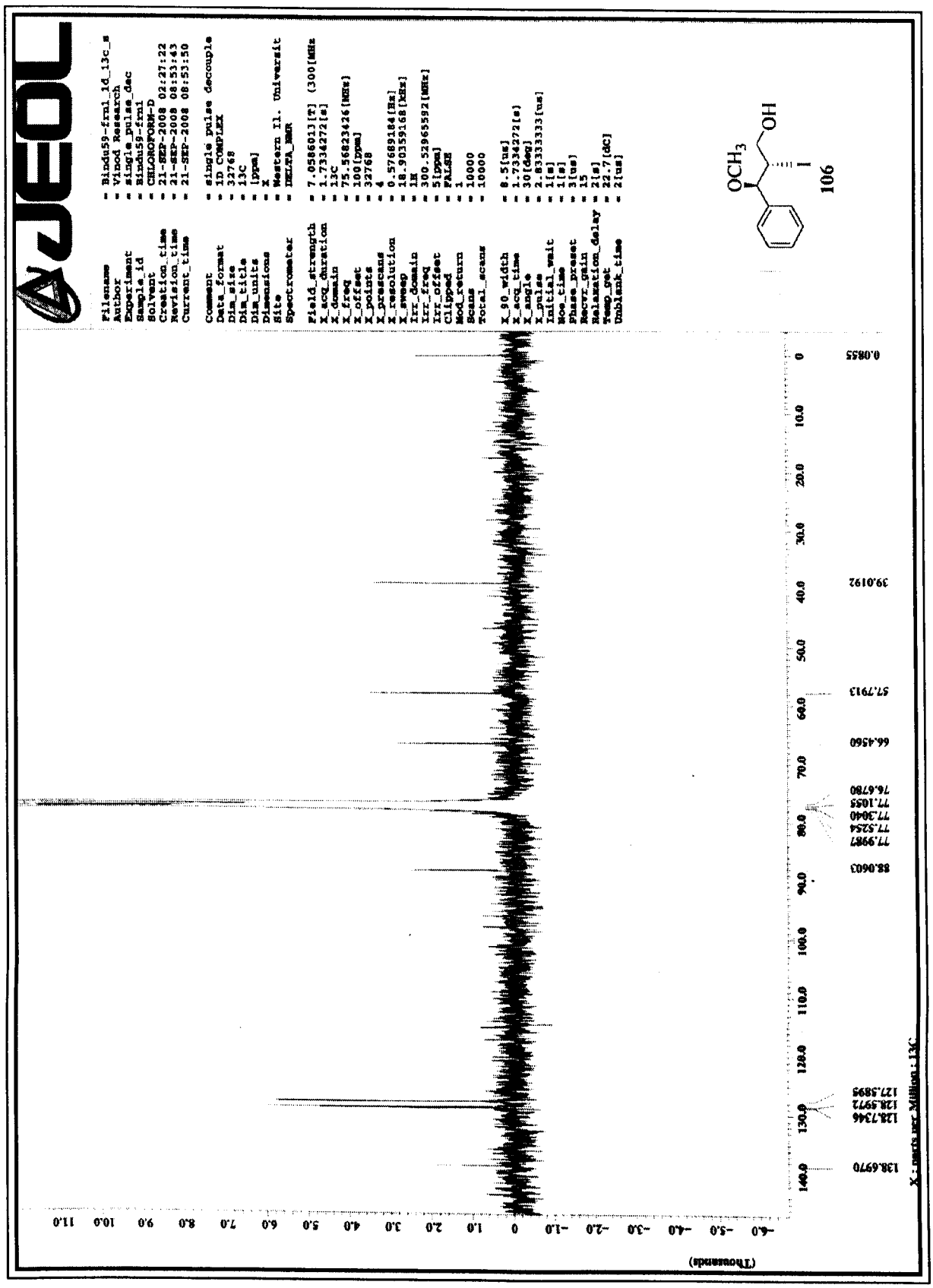


Figure 40: ^{13}C NMR spectrum of compound 106

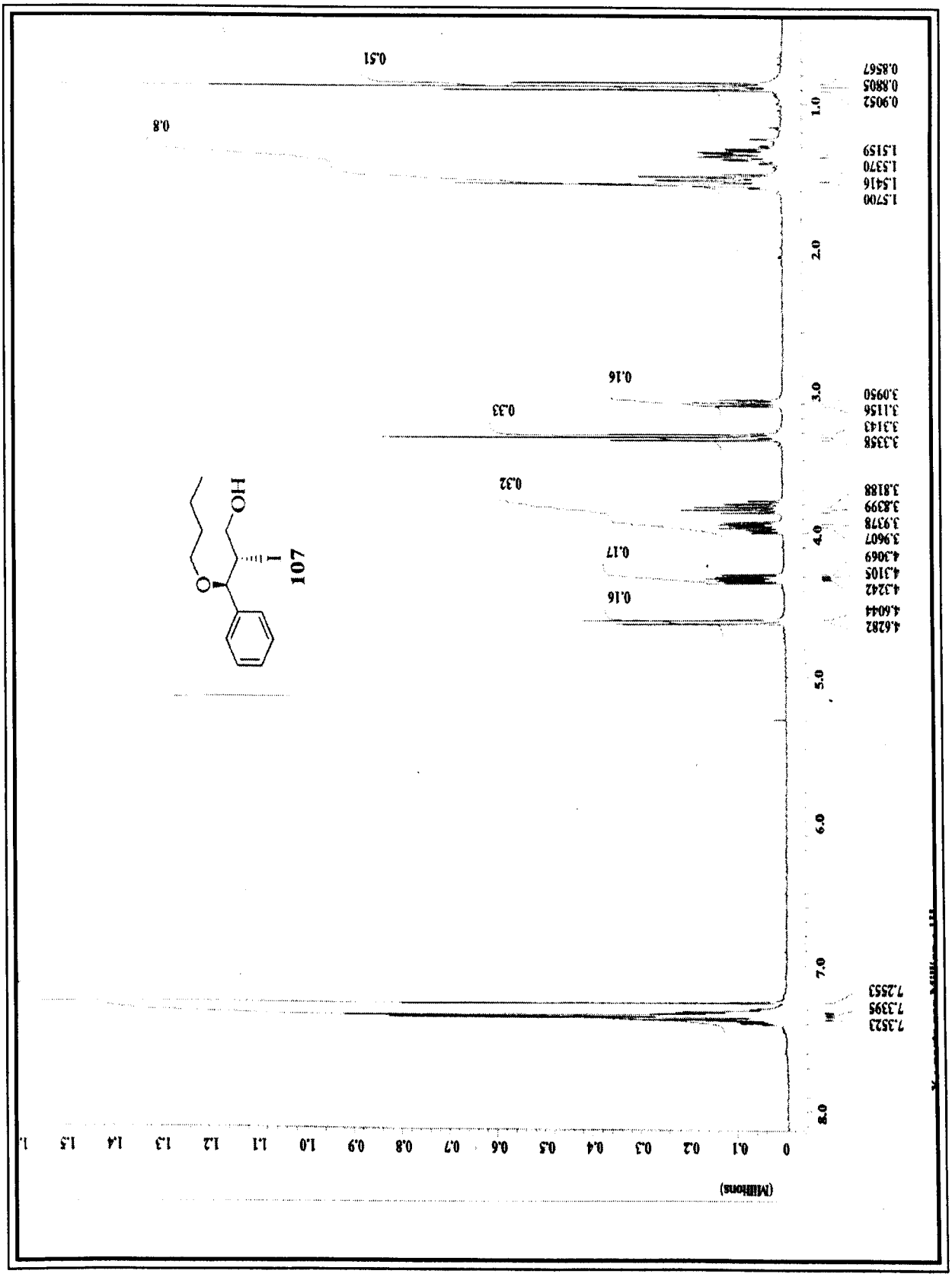


Figure 41: ^{1}H NMR spectrum of compound 107

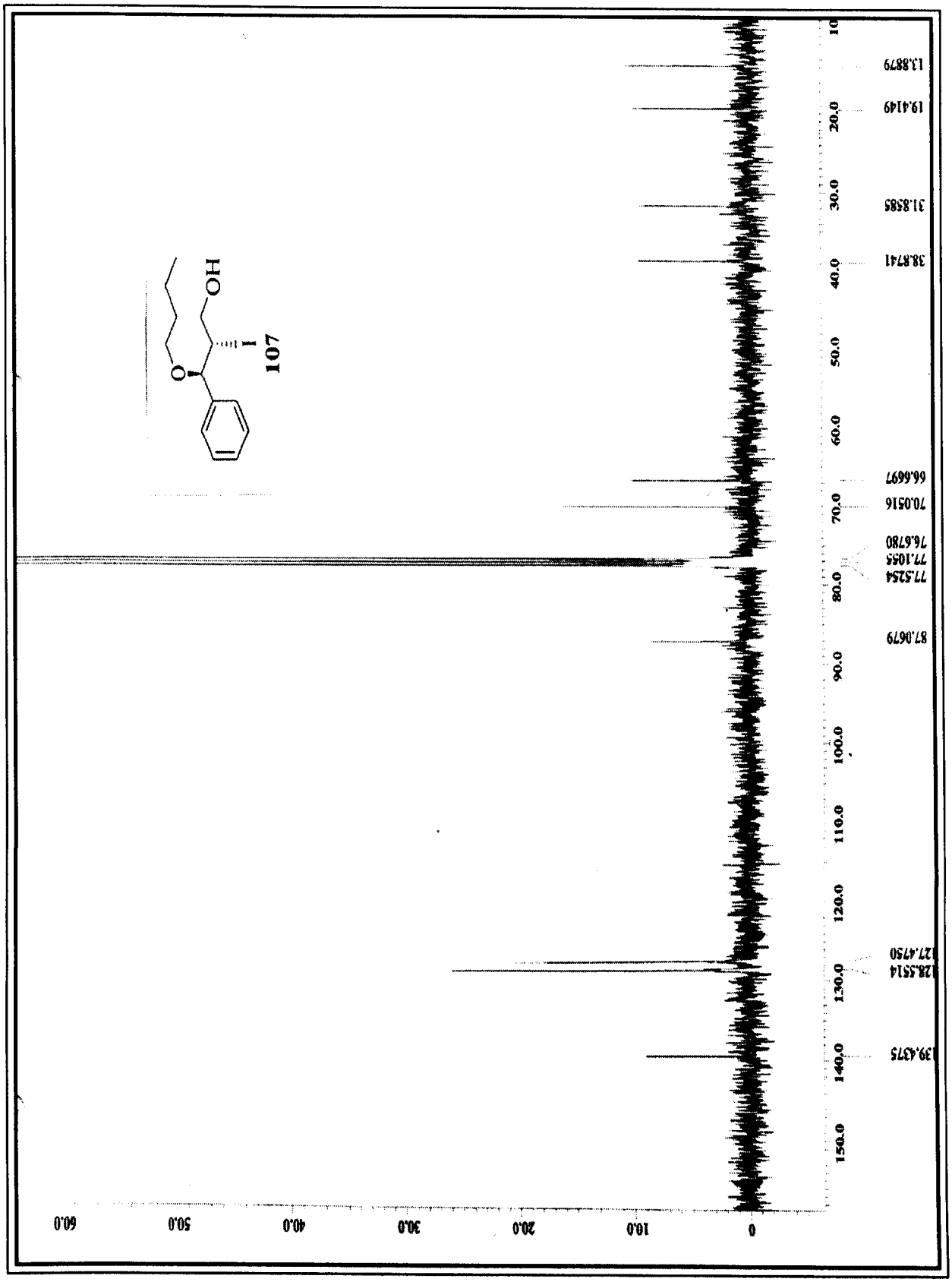


Figure 42: ^{13}C NMR spectrum of compound 107

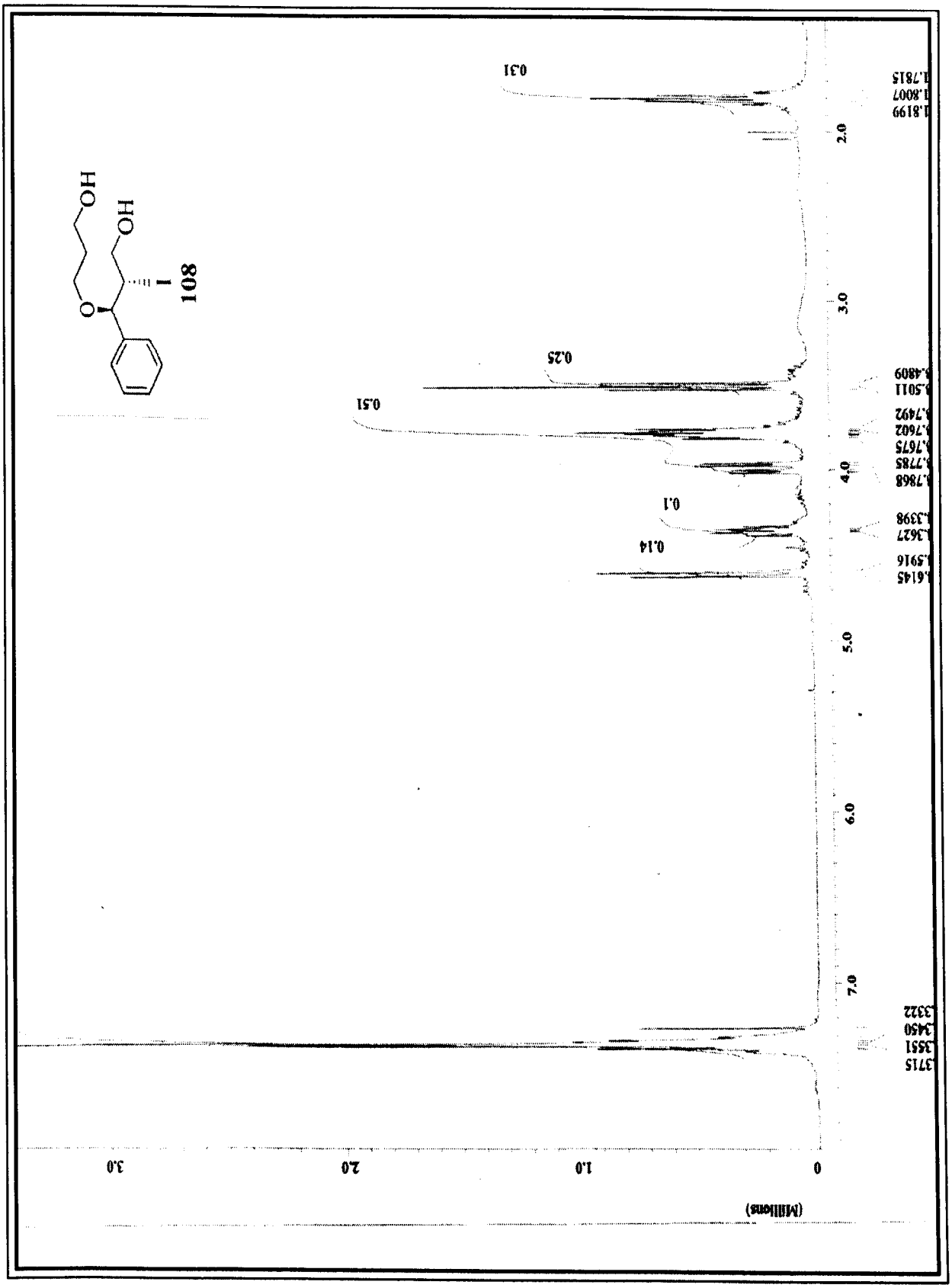


Figure 43: ^{1}H NMR spectrum of compound 108

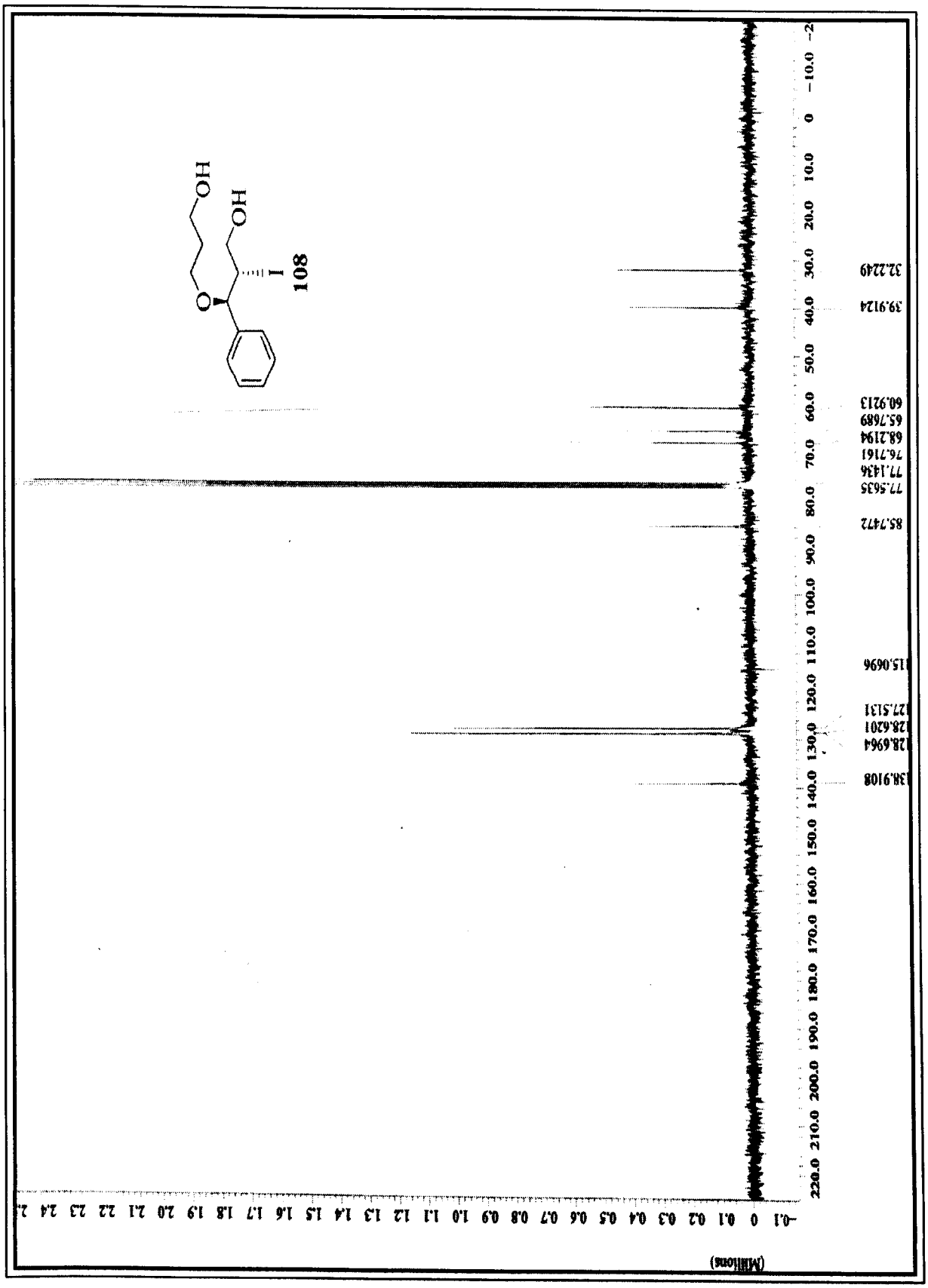


Figure 44: ^{13}C NMR spectrum of compound 108

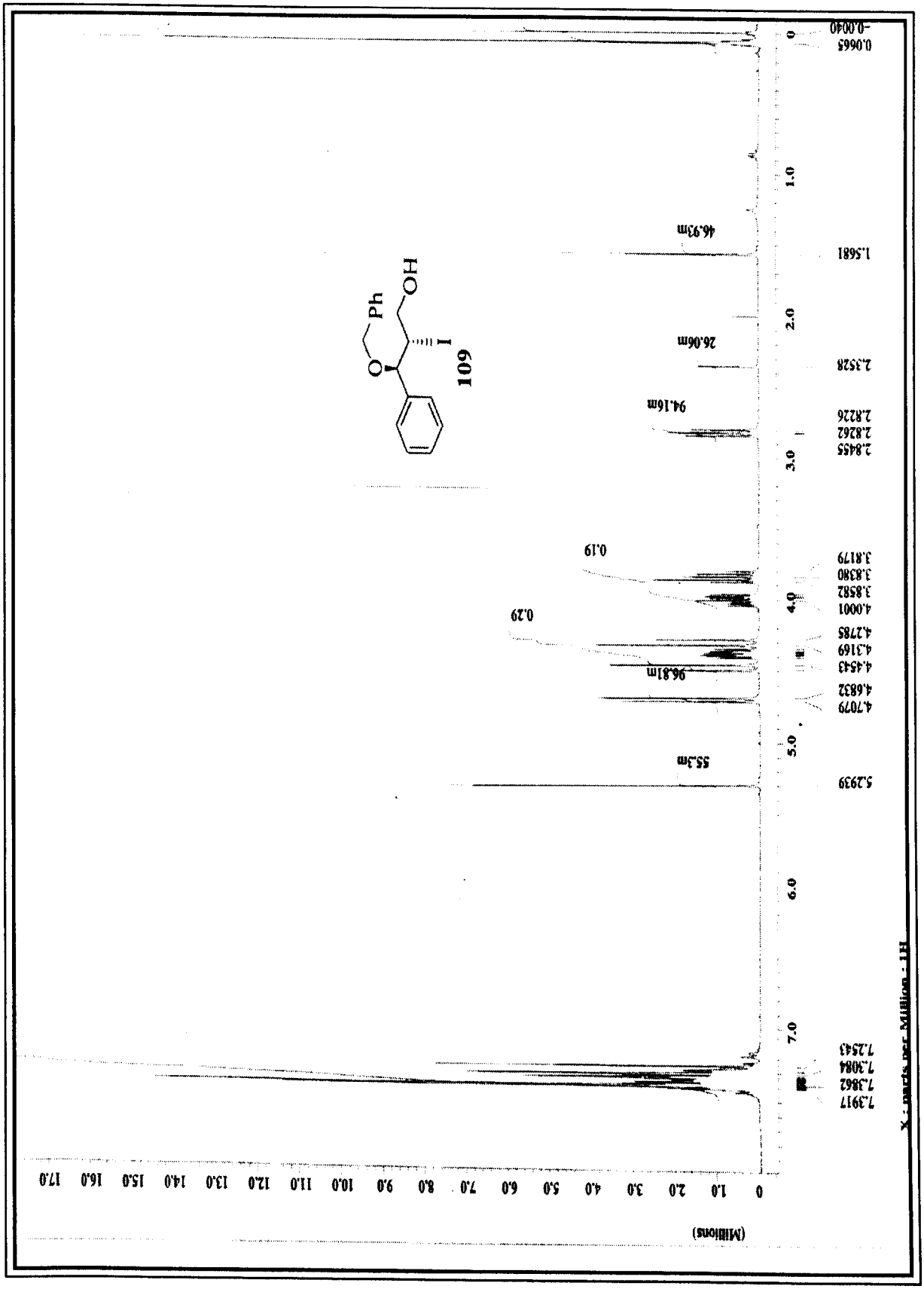


Figure 45: ^{1}H NMR spectrum of compound 109

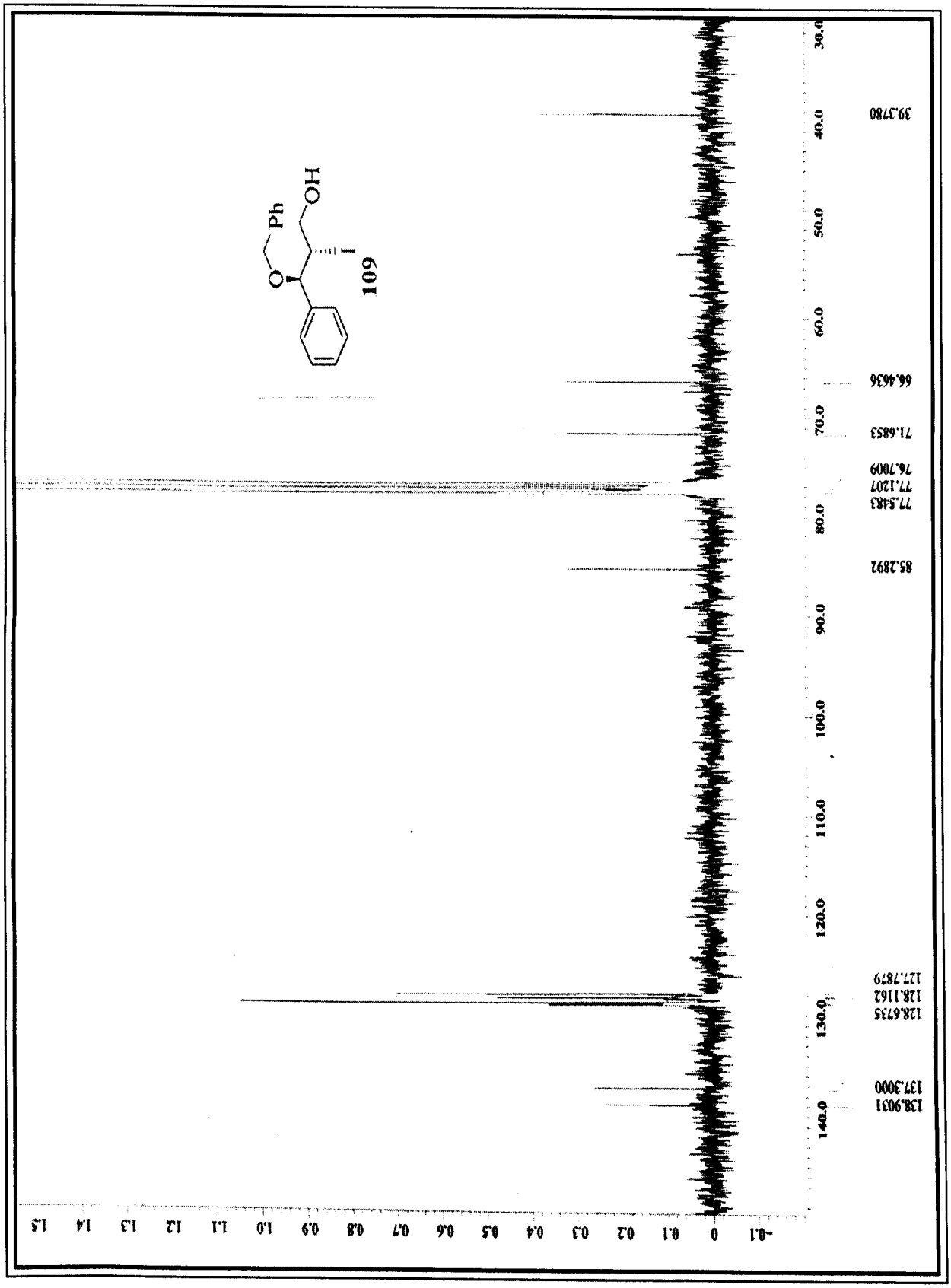


Figure 46: ^{13}C NMR spectrum of compound 109

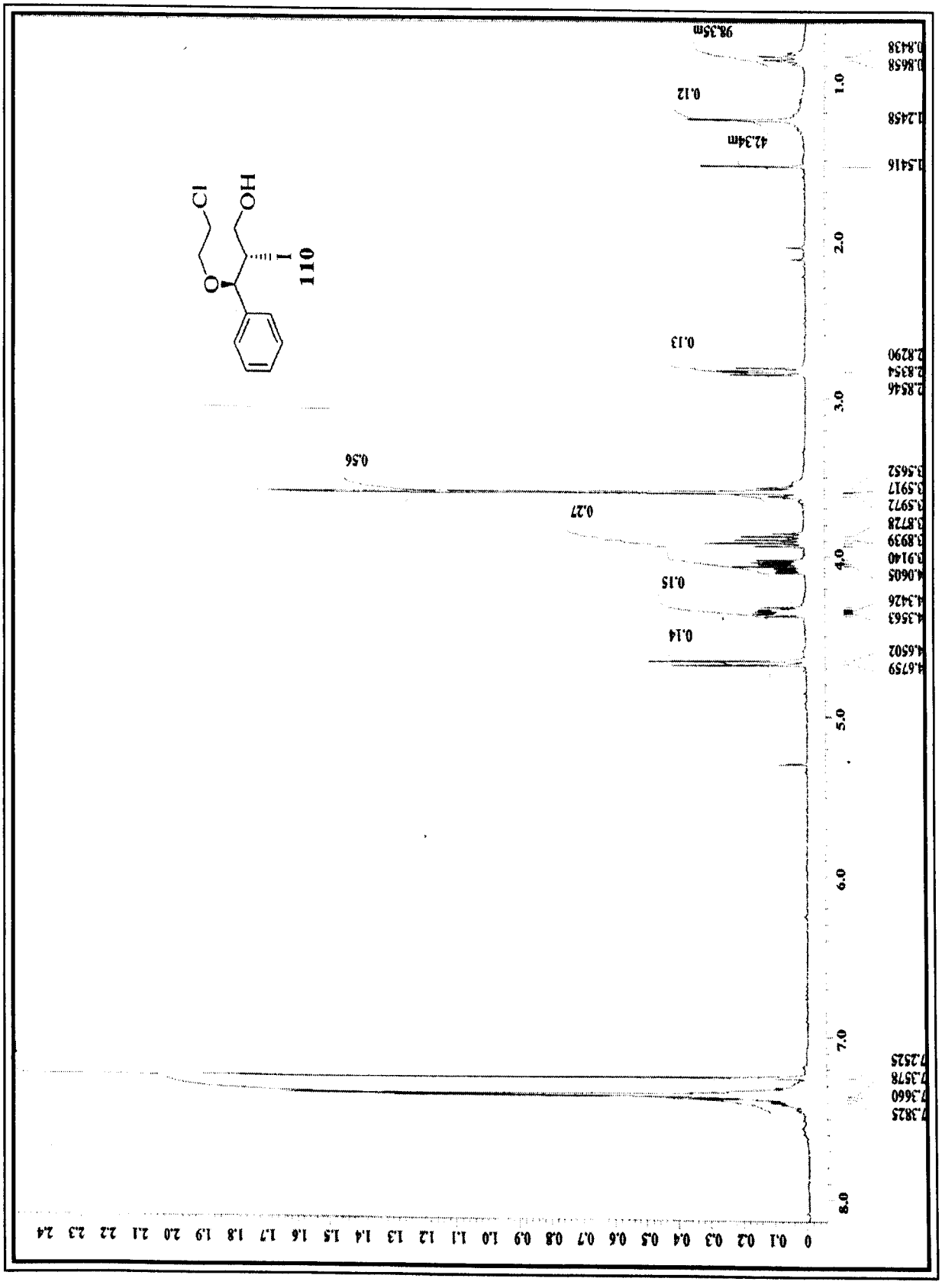


Figure 47: ^{1}H NMR spectrum of compound 110

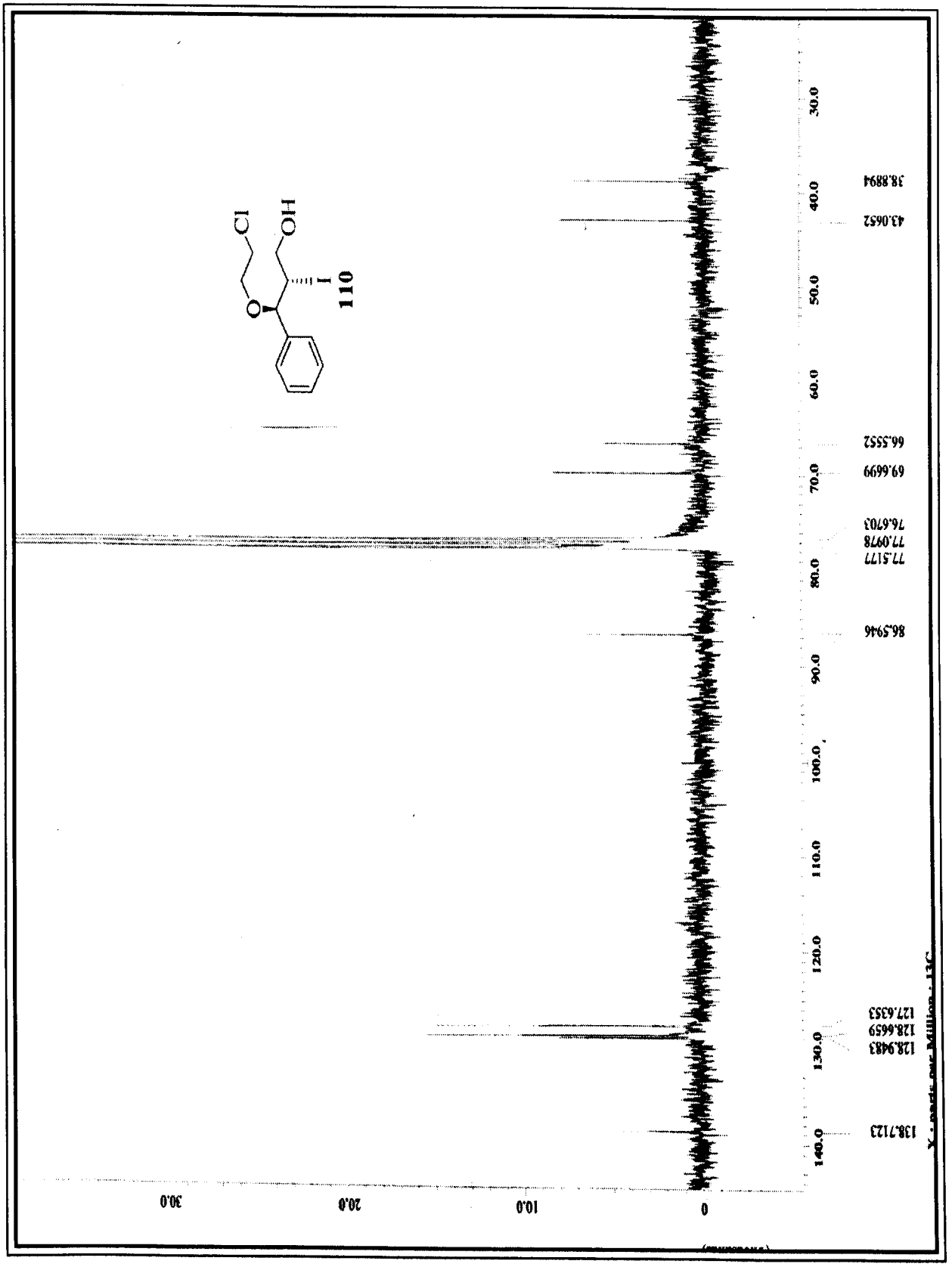


Figure 48: ^{13}C NMR spectrum of compound 110

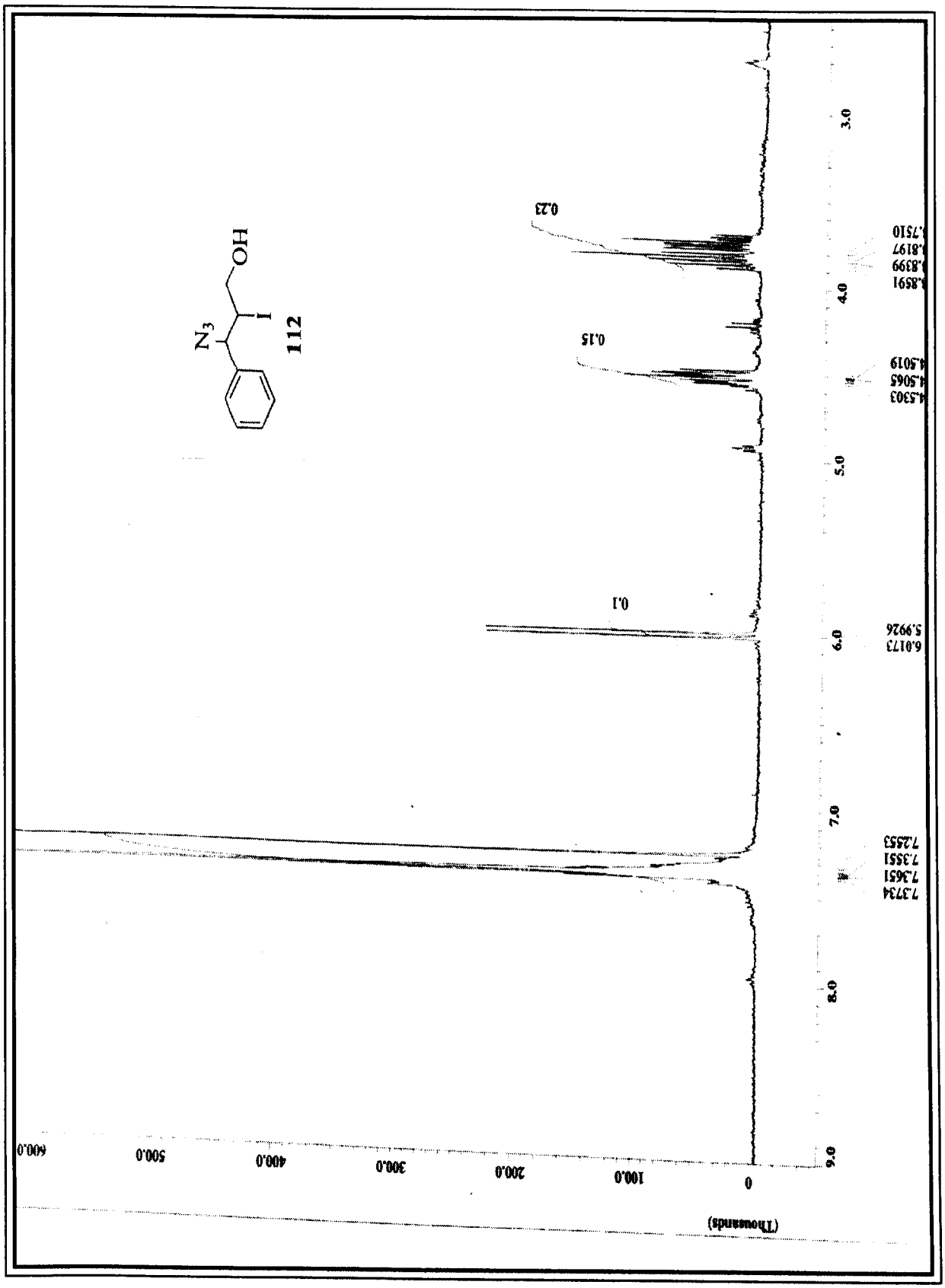


Figure 49: ^{1}H NMR spectrum of compound 112

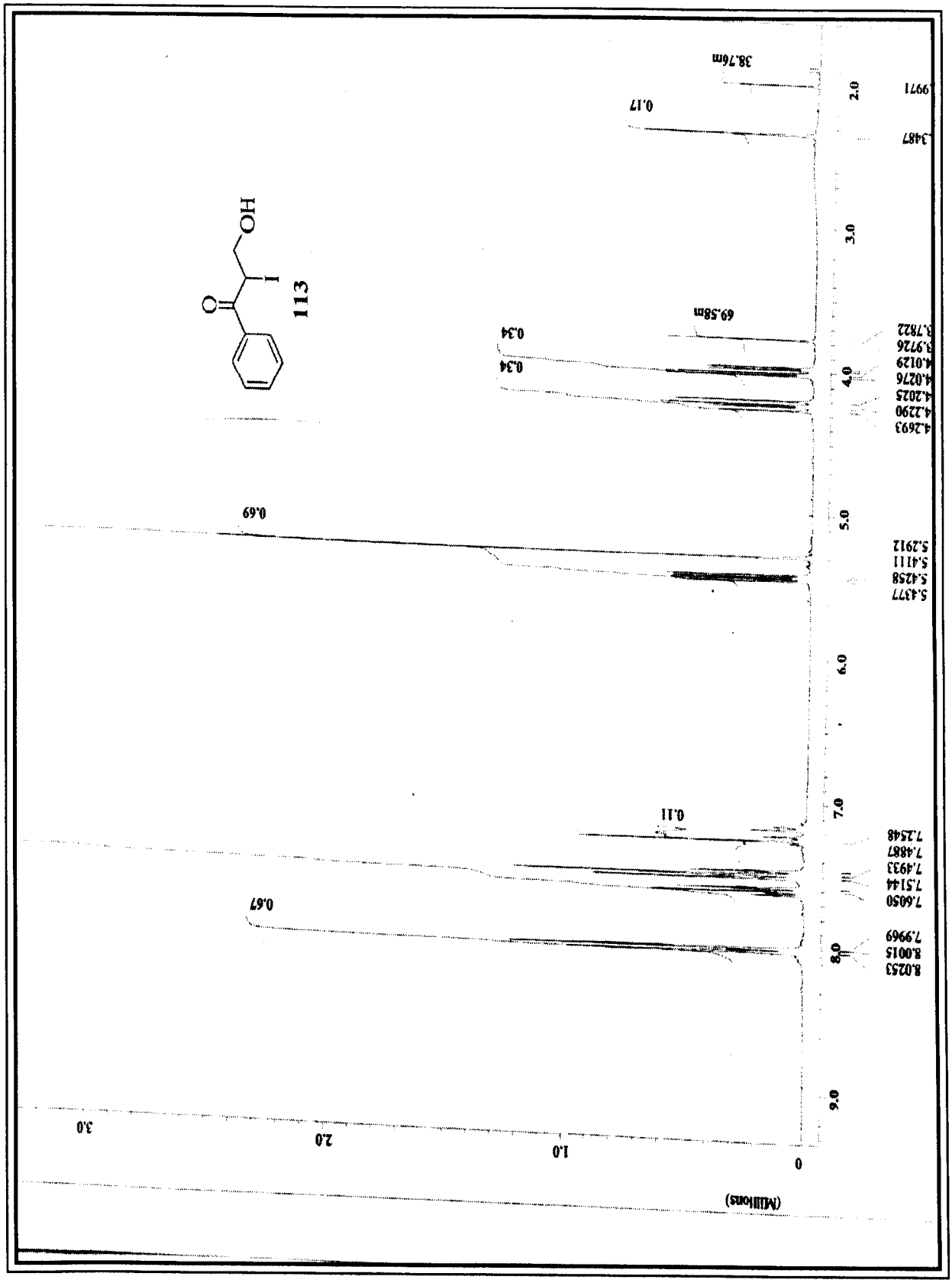


Figure 50: ^{1}H NMR spectrum of compound 113

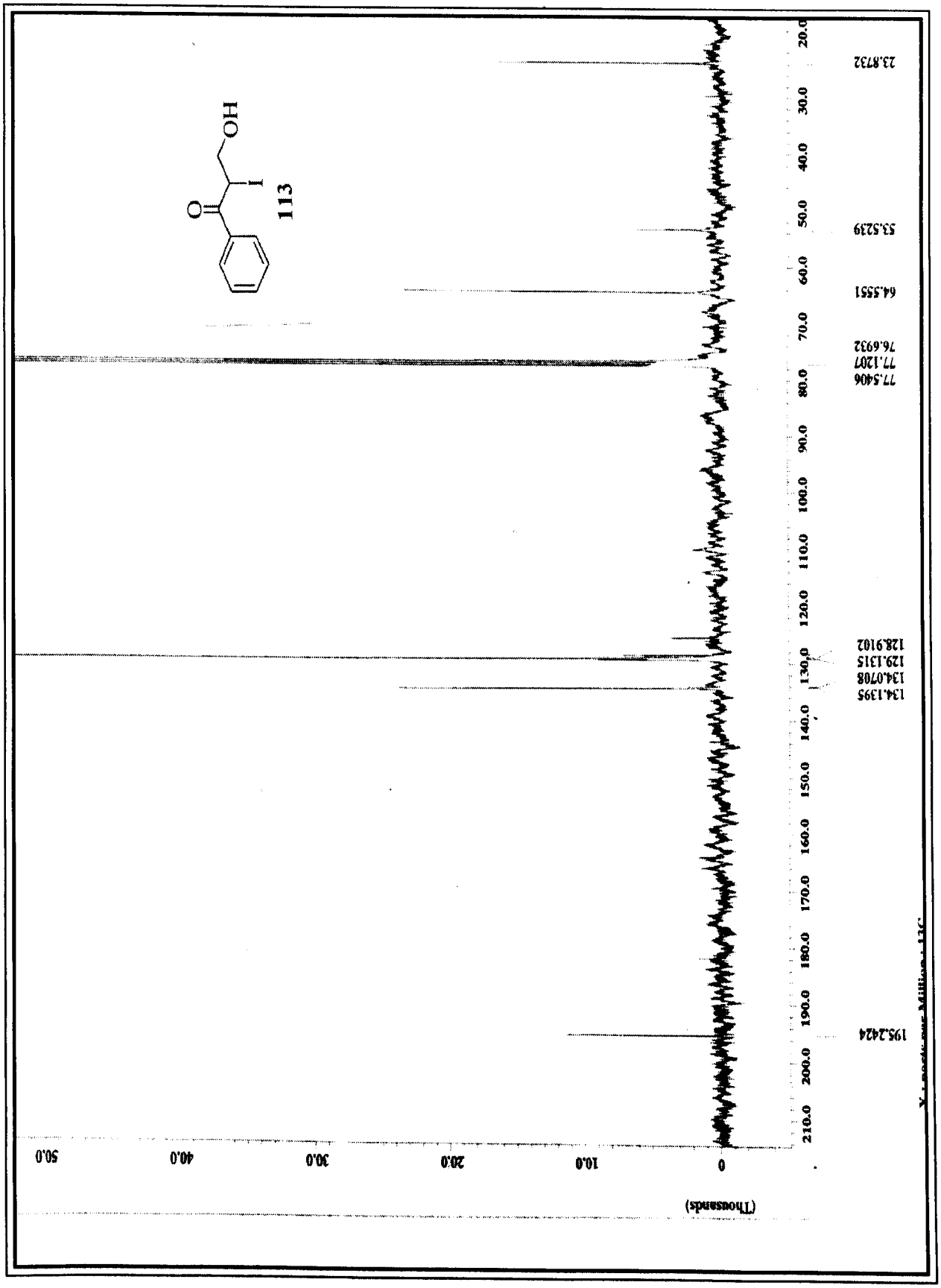


Figure 51: ^{13}C NMR spectrum of compound 113

5. References

1. Barluenga, J.; Gonzalez, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem. Int. Ed.* **1985**, *24*, 4, 319-320.

2. Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893-2903.

3. Gladysz, J. A.; Boone, B. J. *Angew. Chem. Int. Ed.* **1997**, *36*, 550-583.

4. French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354-362.

5. Smith, M. B. *Organic Synthesis*, R. R. Donnelley & Sons Company: United States of America, 1994, 635-645.

6. Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed., Wiley-VCH: New York, 1999.

7. Brown W. H.; Foote C.S. *Organic Chemistry*, 3rd ed., Emily Barrosse: United States of America, 2002.

8. Sanseverino, A. M.; da Silva, F. M.; Jones Jr, J.; de Mattos, M. C. S. *Quim. Nova* **2001**, *24*, 5-13.

9. Dowle, M. D.; Davies, D. I. "Synthesis and Synthetic Utility of Halolactones" *Chem. Soc. Rev.* **1979**, *8*, 2, 171-197.

10. Foye, W. O., Lemke, T. L., Williams, D. A.; Roche, V. F., Zito, S.W. *Foye's Principles of Medicinal Chemistry*, 6th ed., Lippincott Williams & Wilkins: United States of America, 2008.

11. De Mattos, M. C. S.; Sanseverino, A. M. *J. Chem. Res.* **1994**, 440.

12. Ribeiro, R. da S.; Esteves, P. M.; de Mattos, M. C. S. *Tetrahedron Lett.* **2007**, *48*, 8747-8751.

13. Sanseverino, A. M.; de Mattos, M. C. S. *Synthesis* **1998,** 1584.

14. Sanseverino, A. M.; da Silva, F. M.; Jones Jr, J.; de Mattos, M. C. S. *Quim. Nova* **2001,** *24*, 637-639.

15. Fernandes, V. S.; Barboza, J. C. S., Serra, A. A. *Syn. Comm.*, **2007**, *37*, 1433-1436.

16. Muraki, T.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 4679-4684.

17. a) Engel, R. *Chem. Rev.* **1977**, *77*, 349-354. b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*: Pergamon Press: Oxford, 1995.

18. Ohta, H.; Sakata, Y.; Takeuchi, T.; Ishii, Y. *Chem. Lett.* **1990**, 733-736.

19. Carrera, I.; Brovetto, M. C.; Seoane, G. A. *Tetrahedron Lett.* **2006**, *47*, 7849-7852.

20. Kirschning, A.; Plumeier, C.; Rose, L. *Chem. Commun.* **1998**, 33-34.

21. Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Tetrahedron Lett.* **2008**, *49*, 5880-5882.

22. Wirth, T. *Topics in Current Chemistry: Hypervalent Iodine Chemistry Modern Developments in Organic Synthesis*, *224*, 12-27; Springer: Germany, 2003.

23. De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272-9279.

24. Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 2462-2472.

25. a) Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123-1178. b) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers, Inc: New York, 1992. c) Frigerio, M.; Santagostino, M., Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60* (22), 7272–7276.

26. Hartmann, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727-1732.

27. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019-8022.

28. Thottumkara, A.P.; Bowsher, M. S.; Vinod, T. K. *Org. Lett.* **2005**, *7*, 2933-2936.

29. Kommreddy, A.; Bowsher, M.S.; Gunna, M. R.; Botha, K.; Vinod, T. K. *Tetrahedron Lett.* **2008**, *49*, 4378-4382.

30. Dess, D. B.; Martin, J. C. *J. Org. Chem.*, **1983**, *48*, 4155-4156.

31. *Solvent Dependent Chemoselective Oxidation Behavior of Water-soluble IBX derivatives*: M.S. Thesis by Kommareddy, A. submitted to the Department of Chemistry, Western Illinois University, Macomb, Illinois, USA, **2009**, 22-25.

32. Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086-2099.

33. Kuhakarn, C.; Kittigowittana, K.; Pohmakotr, M.; Reutrakul, V. *Tetrahedron*, **2005**, *61*, 8995-9000.

34. Yadav, Y. S.; Reddy, B. V. S.; Basak, A. k.; Narasaiah, A. V. *Tetrahedron Lett.* **2004**, *60*, 2131-2135.

35. Boeckman, R. K.; Shao, P.; Mullins, J.; *J. Org. Synth.* **2000**, *77*, 141-152.

36. a) Zhdankin, V. V.; Koposov, A. Y.; Litvinov, D. N.; Ferguson, M. J.; McDonald, R.; Luu, Tykswinski, R. R. *J. Org. Chem.* **2005**, *70*, 6484-6491. b) Ozanne, A.; Pouysegu, L.; Depernet, D.; Francois, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903-2906.

37. a) Muelbaier, M.; Giannis, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4393. b) Lei, Z. Q.; Ma, H.C.; Zhang, Z.; Yang, Y. X. *React. Funct. Polym.* **2006**, *66*, 840-841.

38. Richardson, R. D.; Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T. *Angew. Chem. Int Ed.* **2007**, *46*, 6529.

39. a) House, O. H. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Inc.: California, 1972, 243-257. b) Cornforth, J. W.; Green, D. T. *J. Chem. Soc.* **1970**, 846. c) Ogata, Y.; Aoki, K. *J. Org. Chem.* **1966**, *31*, 4181.

40. Tang, W.; Zhang, X. *Chemical Reviews* **2003**, *103*, (8), 3029-3069.