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## ABSTRACT

The aim of this work was the chemical synthesis of certain target molecules which could show P-glycoprotein inhibition. Prior to this work, the molecules were designed via molecular modelling Univ.-Prof. Dr. Gerhard Ecker's group, based on findings of Colabufo[1, 2].

P-glycoprotein is important in multidrug resistance (MDR) which influences drug metabolism. MDR is partially responsible for resistance to antibiotics and antimycotics, but also the majority of secondary treatment failure in tumour therapy with cytostatics.

For the past few years, an essential field of drug research has focused on the development of P-glycoprotein modulators in order to improve the unsatisfactory cure rate of tumour diseases.

Subsequent to this work, the biologic activity of the synthesized target molecules should be tested by cell assays.

Organometallic chemistry was chosen as the method for the synthesis as it can save 2 synthesis steps compared to similar, currently known methods.

After the preparation of some reagents, the synthesis strategy contained 2 steps: An initial Kumada cross coupling was followed by another cross coupling of the metalated Kumada cross coupling product and an aldehyde.

This strategy should have produced the desired secondary alcohol product. However, since the second step was not successful, another strategy was developed which would have lead to a desirable ketone via the coupling of a nitrile with a Grignard reagent. Unfortunately, this method also did not work.

The modelled target molecules could not be synthesized in the course of this work, but instead new findings of Kumada cross coupling were investigated: The coupling runs best without a catalyst, with additional TMEDA, in THF solvent, at 0°C and within 1 hour. It was not known until this work that a catalyst is not required for the coupling. Furthermore, it is a surprising and new insight that the lithiation of 1-(2-bromophenethyl)-3-methoxybenzene proceeds smoothly, but the subsequent trapping of the electrophile, 2-(3,4-dimethoxyphenyl)acetaldehyde, does not work.

## ZUSAMMENFASSUNG

Ziel dieser Arbeit war die chemische Synthese bestimmter Zielmoleküle, welche als P-Glycoprotein-Inhibitoren wirken könnten. Diese Moleküle wurden vor Beginn dieser Arbeit von der Arbeitsgruppe um Univ.-Prof. Dr. Gerhard Ecker, basierend auf Erkenntnissen von Colabufo [1, 2] mittels Molecular Modelling ermittelt.

P-Glycoprotein spielt eine zentrale Rolle bei der Multidrugresistance (MDR), welche in den Arzneistoffmetabolismus eingreift. Neben der Resistenz gegenüber Antibiotika und Antimykotika ist die MDR unter anderem auch für einen Großteil der sekundären Therapieversagen bei zytostatischer Tumorthherapie verantwortlich. Daher steht die Entwicklung von Inhibitoren des P-Glycoproteins seit einigen Jahren im Fokus der Arzneistoffforschung, um die oftmals enttäuschend niedrige Heilungsrate von Tumorerkrankungen zu steigern.

Im Anschluss an diese Arbeit sollten die synthetisierten Zielmoleküle in Zellassays auf ihre biologische Aktivität getestet werden.

Die Idee war es, die Synthese mittels metallorganischer Reaktionen durchzuführen, da dadurch zwei Syntheseschritte gegenüber ähnlichen, bisher bekannten Synthesewegen eingespart werden können. Die hier angewandte Synthesestrategie umfasste neben der Herstellung mancher Reagenzien zwei Schritte: Zuerst eine Kumada-Kupplung und anschließend eine weitere Kreuzkupplung zwischen dem metallierten Kumada-Kupplungsprodukt und einem Aldehyd, die zum gewünschten sekundären Alkohol führen sollte. Nachdem der zweite Schritt dieser Strategie nicht erfolgreich war, entwickelten wir einen alternativen Weg, welcher über die Kupplung eines Nitrils mit einem Grignard Reagens ein Keton ergeben sollte. Allerdings hat auch diese Strategie nicht das erwünschte Ergebnis geliefert.

Zwar konnten im Zuge dieser Arbeit die modellierten Zielmoleküle nicht synthetisiert werden, dafür wurden neue Erkenntnisse zur Kumada-Kupplung gewonnen: Die Kupplung läuft am besten unter Abwesenheit eines Katalysators, mit TMEDA als Hilfsreagens, in THF, bei 0°C und innerhalb einer Stunde ab. Dass dabei kein Katalysator nötig ist, war bisher nicht bekannt.

Weiters ist die Tatsache, dass zwar die Lithiierung von 1-(2-bromophenethyl)-3-methoxybenzen problemlos abläuft, eine anschließende Kupplung mit 2-(3,4-dimethoxyphenyl)acetaldehyd aber nicht funktioniert, sehr überraschend und in der Literatur bisher nicht bekannt.

# 1 INTRODUCTION

## 1.1 MDR and P-Glycoprotein

MDR (multi drug resistance) is responsible for 50% of all secondary failures of cancer treatment with chemotherapeutic agents and is caused by cells over expressing some ABC transporters like P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multi drug resistance protein 1-7 (MRP1-7) and lung resistance protein (LRP). This can lead to (1) increased drug efflux, (2) decreased drug uptake into the cell, (3) activation of detoxifying enzymes, and (4) defective apoptotic pathways what results in less intracellular concentration and reduces effectiveness of the drug.

ABC transporters (ATP-binding cassette) build a family of different transmembrane proteins which efflux various molecules from cells. ABC transporters are active transporters as they transfer compounds against the concentration gradient by using ATP hydrolysis energy.

This efflux is a physiological mechanism that should protect the body from xenobiotics and toxins.

MDR leads to cross resistance of tumour cells exposed to one cytotoxic drug. This resistance affects not only the applied drug, but also structurally and functionally unrelated molecules. Other drugs, such as antibiotics, antimycotics and herbicides in plants are also affected by MDR. Mutations in ABC-transporter related genes can induce serious diseases like cystic fibrosis.

P-glycoprotein (P-gp, permeability glycoprotein) was the first characterized ABC-transporter in 1972 and is also known as ABCB1. It is physiologically expressed in various cells: in intestine cells, hepatocytes, the kidney, the blood-brain-barrier, the blood-liquor-barrier, the blood-placenta-barrier, the blood-gonads-barrier, the blood-retina-barrier, the immune system, and capillary endothelial cells of nerves. As a result P-glycoprotein influences absorption, distribution and excretion of drugs. P-glycoprotein expression is highest in tumours of epithelial cells of the colon, kidney, adrenal, pancreas and liver.

Since then, three decades of research has focused on the inhibition of P-gp activity in order to reverse MDR, and increasing the success of often unsatisfactory cancer treatments.



The first generation of P-gp inhibitors, for example: verapamil, cyclosporine A or calmodulin antagonists, show low binding affinity and therefore have to be used in high doses, which causes unacceptable toxicity. Furthermore, they display little selectivity and also act as substrates for other transporters and enzymes, which leads to strong side effects and unpredictable drug interactions. The second generation of P-gp modulators such as dexverapamil, biricodar or dexniguldipine are more potent and less toxic, but still show unacceptable toxicity as they inhibit the metabolism and excretion of cytostatics. The anthranilamide derivatives tariquidar and elacridar represent third generation P-gp inhibitors that should also inhibit BCRP, and are in clinical development.

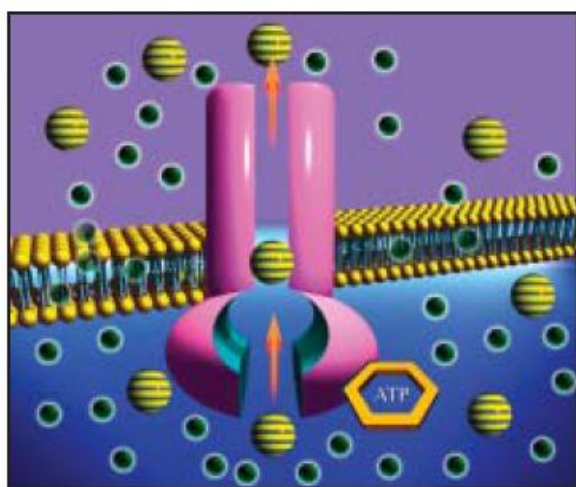


Fig 2. — Competitive inhibition of the P-glycoprotein transporter. First- and second-generation modulators compete as a substrate with the cytotoxic agent for transport by the pump. This limits the efflux of the cytotoxic agent, increasing its intracellular concentration.

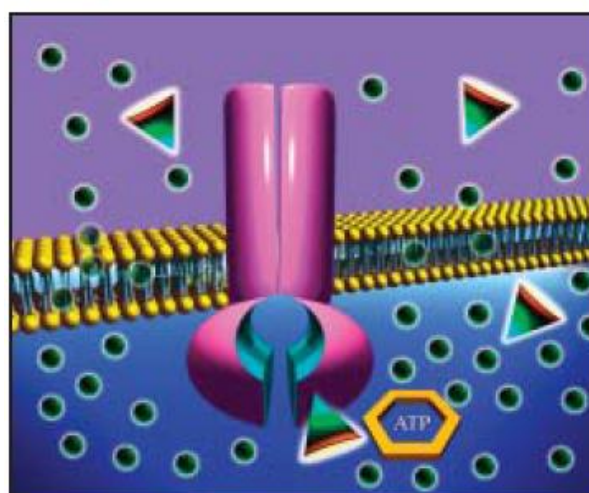


Fig 3. — Noncompetitive inhibition of the P-glycoprotein transporter. Third-generation inhibitors of P-gp, such as tariquidar, bind with high affinity to the pump but are not themselves substrates. This induces a conformational change in the protein, thereby preventing ATP hydrolysis and transport of the cytotoxic agent out of the cell, resulting in an increased intracellular concentration.

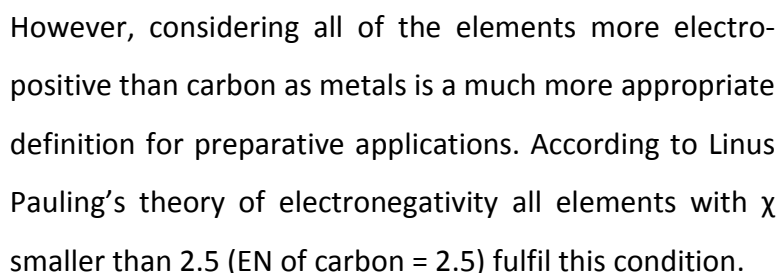
**Fig.1:**Comparison of first and second generation P-gp modulators, from [3]

Undesired P-gp inhibition is caused by some blockbusters like cyclosporine A, ketoconazole, nelfinavir, quinidine, ritonavir, saquinavir, tacrolimus, valspodar, verapamil, elacrida, reserpine, and has to be considered when employing co-medication. [1-15]

## 1.2 Principles of organometallic chemistry

In the beginning of the 20<sup>th</sup> century, V. Grignard discovered organomagnesium compounds as highly reactive reagents for organic synthesis. This was the start of the now indispensable field of organometallic chemistry [16]. Since then, several metals have been examined for their potential as organometallic reagents. Lithium, magnesium, zinc, boron, silicon, tita-

Usually, **metals** are defined by their bonding type. Metallic bonding means the formation of a metallic lattice (made out of metal ions), filled with an electron gas.

[illegible]

**Organometallics** are molecules containing a bond between carbon and a metal atom. The large difference in the electronegativity of the atoms (e.g. carbon 2.55; lithium 0.98) causes a highly polarized C-Li bond. Although it is sometimes described as a lithium cation and a carbon anion, it is actually a covalent bond, not an ionic bond. The ionic character of a C-Li

bond is 40%, compared to 35% in C-Mg bonds, which explains the lower reactivity of organomagnesium compounds. The electron-deficient character of BuLi is responsible for its high reactivity towards Lewis bases.

### 1.2.2 Aim of organometallics

A great advantage of organometallics is their ability to generate carbon nucleophiles. The level of nucleophilic character increases with the EN of the cation:  $\text{Sn} < \text{Al} < \text{Zn} < \text{Mg} < \text{Li}$ . Usually in organic chemistry carbon bonds to more electronegative elements, and is therefore always polarized positively and reacts as an electrophile e.g. alkylhalides, whereas in carbon organometallics, the carbon atom is polarized negatively and reacts as a nucleophile.



The forming of carbon-metal bonds is called metalation, and because of the change of polarity it is also named umpolung. This change to the dipole moment of the carbon atom implements a modification to the reactivity of the nucleophile, which behaves like a carbanion, and is strongly basic.

The electrophilic C-atom on the halide becomes nucleophilic and changes its reactivity. In arylhalides the C-atom is the electrophilic centre, but metalation converts the  $\text{C}^{\delta^+}-\text{X}^{\delta^-}$  group to  $\text{C}^{\delta^-}-\text{M}^{\delta^+}$ , so the dipole moment is changed. After that, the nucleophilic C-atom acts like a carbanion. It is strongly basic because carbon has a very low electronegativity and does not have the ability to distribute negative charges. This basicity also causes the incompatibility of organometallics with moisture, OH-groups, and other acidic functional groups. With water, the organolithium reagent undergoes hydrolysis as shown in figure 4, forming an unreactive metal hydroxide and an alkane as products. Therefore metalorganic reactions have to be done under completely anhydrous conditions.

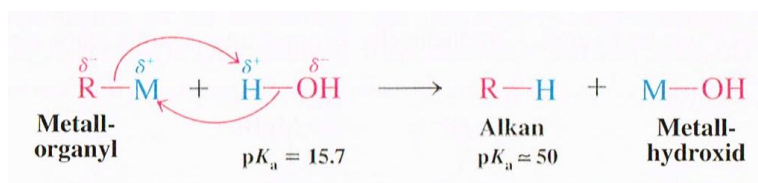
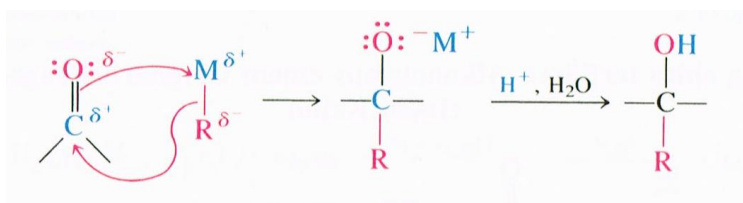


Fig. 4: Mechanism of hydrolisation, from [19], p.349

**Mechanism:**

The negatively polarized alkyl group attacks the nucleophilic carbonyl C-atom with its bonding pair of electrons. The carbonyl oxygen accepts the metal and forms a metal alkoxide. The addition of dilute aqueous acid hydrolyses the oxygen-metal-bond and generates an alcohol and a metal alkoxide. [19]



**Fig. 5:** Mechanism of alcohol synthesis via aldehyde or ketone and metalorganic reagent, from[19], p.351

In these cross couplings the utilization of lithium instead of magnesium can avoid the undesired Grignard-reduction.

By far the most important application of organometallics is the reaction with the opposite polarity: electrophiles. Nearly all types of electrophiles can be utilized to yield the product R-E and a metallic salt  $M^+X^-$ .

As carbon – carbon bond formation is the main interest of synthetic chemistry, carbon electrophiles like alkylhalides, arylhalides, alkenylhalides or carbonyl compounds are employed mostly in metalorganic reactions.



As a rule organometallics are employed in organic synthesis to generate metal free molecules, the metal is just an additive and is not contained in the product, but gives a metal salt. The separation of the metal salt and the organic product is generally not a problem, as the metal salt is water soluble, while the organic compound is not.

### 1.2.3 Mechanism of lithiation

The work performed for this thesis mainly focused on organolithium reagents, so other metalations have been omitted from this report

There are six possible ways to prepare organolithium compounds: (1) direct synthesis, (2) lithiation via lithium salts out of radical anions, (3) halide-metal exchange, (4) metal-metal exchange (transmetalation), (5) deprotonation, and (6) fragmentation.

**(1) Direct synthesis:**



The conversion of two atoms of lithium with the appropriate alkyl- or arylhalide produces alkyl- or aryllithium compounds. The driving force of this reaction is the high bond enthalpy of the yielding lithium salt. LiX has very high bond energy, so is extremely stable and is preferably produced.

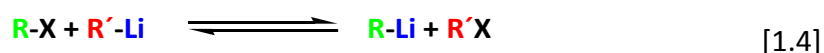
Although this is a strongly exothermic reaction, the rate of reaction is often slow, as the reaction takes place on the surface of the metal. Constitution of the surface (e.g.: the presence of an oxide layer) therefore has big impact of reaction rate.

Lithium is readily ignitable and reacts immediately with atmospheric oxygen, water and carbon dioxide, which leads to inactivation of organolithium molecules. As a result, the application of metallic lithium and organolithium requires a protective gas, preferably argon.

The mechanism of the preparation of organolithium through direct synthesis is a Single Electron Transfer (SET).

Reactivity in direct synthesis of halide compounds R-X increases in the following order: X=F << Cl < Br < I. However, the tendency of undesired and side product (R-R) by Wurtz coupling rises in the same order. Most of the commercial available organolithium reagents (MeLi, nBuLi, sBuLi, tBuLi, Ph-Li, nHexLi) are produced via direct synthesis.

**(3) Halide-metal exchange:**



The acid-base equilibrium shown above is a high rate reaction in solution. The equilibrium lies on the right side, as R stabilizes negative charges better than R'. According to thermodynamics, chemical reactions always strive to move towards the lowest energy level, therefore the  $\Delta G$  of R-Li has to be lower than the  $\Delta G$  of R'-Li, which is why the equilibrium is on the right. A lower  $\Delta G$  corresponds to a more stable molecule. As R-Li is more stable, the R has a

greater ability to distribute the shared electron from the lithium atom. Distribution of charges can be estimated through acidity; R-H has to be stronger acid than R'-H. Mostly alkyl-, alkenyl- or arylhalides are utilized as R-X and nBuLi or tBuLi is utilized as R'-Li. The halide-metal exchange can produce R-R' from Wurtz coupling. This can be avoided by employing two equivalent of R'-Li [20, 21].

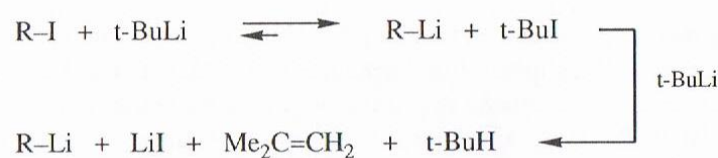


Fig. 6: Avoidance of Wurtz-product, from [18], p.9

Yielding lithium halide, this reacts with the second equivalent of the lithium compound via elimination to inert hydrocarbons and is so no longer available for coupling reaction.

#### (4) Metal-metal exchange (transmetalation):



This is again an acid-base reaction, with almost the same necessary conditions as the halide-metal exchange reaction. The equilibrium is on the right hand side if R-H is stronger acid than R'-H. Another possible way to force the reaction to the product side is precipitation of a product, to remove it from the equilibrium.

Transmetalation in general is very useful to prepare reagents with different selectivity.

### 1.2.4 Advantages of organometallic reactions

100% purity and quantitative yield is the unattainable aim of synthetic chemistry. While this is not possible, the efficiency and selectivity of reactions have to be increased to develop an ecological friendly and economical synthesis. Efficiency can be improved by avoiding protective groups or performing laborious purifications, and by minimizing the accrual of waste. Highly selective reactions enable this and are therefore essential for an ideal synthesis. Protecting groups and purifications are not necessary in highly chemo-, regio- and stereo-selective conversions because side products and isomers are not generated.

For various reasons, organometallics are the preferred reagents for selective synthesis: There are about 70 metals with different reactivity and selectivity which are used as the bricks of organometallics. Ligands and conditions, for example the solvent used, have a big influence on the yield of the products. Some reactions cannot be done via classical organic synthesis.

Rieke et al [22] writes about the significance of the Grignard reaction, the first metalorganic reaction to be discovered: *"...every chemist has carried out the Grignard reaction at least once in his lifetime..."*.

Jana R. et al [23] described it as:

*"The emergence of cross-coupling as a popular method in synthesis arises from both the diversity of organometallic reagents utilized in these reactions and the broad range of functional groups which can be incorporated into these reagents. Since initial submission of this review, the importance of this general class of reactions was recognized by the awarding of the Nobel Prize in chemistry to Richard Heck, Eiichi Negishi and Akira Suzuki 'for palladium-catalyzed cross-couplings in organic synthesis'."*

### 1.2.5 Problems and challenges of organometallics [19]

- Some metals utilized in organometallics are toxic, e.g. cadmium or nickel, and should be avoided as long as appropriate alternatives exist.
- Metals from the first and second main groups in the periodic table are readily ignitable and so have to be handled and stored with great care.
- Organometallics are destroyed when they come into contact with oxygen. As a result, it is essential that air is completely excluded. Metal-carbon bonds are weak compared to metal-oxygen or metal-halide bonds: an aluminium-carbon bond has a bonding energy of 274kJ/mol, while an aluminium-oxygen bond has an energy of about 500kJ/mol. Therefore, reactions which exchange metal-carbon to metal-oxygen or metal-halide bonds are thermodynamically favourable.
- Organometallic compounds are strong bases. They can be seen as the basic equivalent of the corresponding very weak acid hydrocarbons e.g. alkanes, alkenes or aryls. Basicity increases in order:  $n\text{BuLi} < s\text{BuLi} < t\text{BuLi}$ . This basicity causes the incompatibility of organometallics with moisture, OH-groups, and other acidic functional groups. In



the presence of water, an organolithium reagent undergoes hydrolysis, forming unreactive metal hydroxide and an alkane.

As a result, the application of organometallics requires protective gas, preferably argon. This is also why metalorganic reactions have to be done under complete anhydrous conditions.

- Some organometallic reagents are not stable and so have to be prepared in situ.

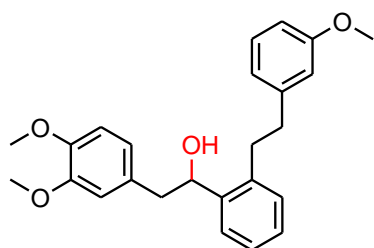


## 2 AIM

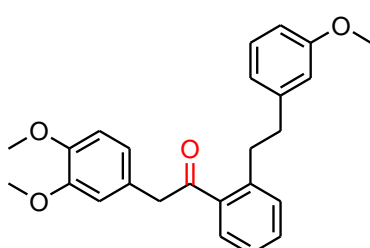
The aim of this research was the organic synthesis of the structures below. These molecules, designed by Univ. Prof. Dr. Gerhard Ecker and his team, should be inhibitors of P-glycoprotein. The design is based on some previous publications from the group led by Nicola Antonio Colabufo [1, 2]. Subsequently, the biological activity of these structures should be tested by cell assays to gain more knowledge about the structure-activity relationship (SAR) of P-glycoprotein modulators.

### 2.1 Target molecules

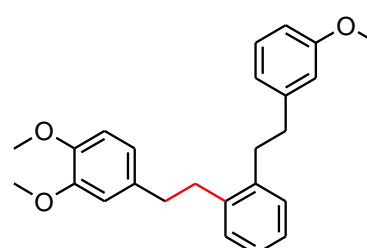
The structures of the desired molecules are shown below:



1-(2-(3-methoxyphenethyl)phenyl)-2-(3,4-dimethoxyphenyl)ethanol



1-(2-(3-methoxyphenethyl)phenyl)-2-(3,4-dimethoxyphenyl)ethanone



1-(2-(3,4-dimethoxyphenethyl)phenethyl)-3-methoxybenzene

## 3 METHODS

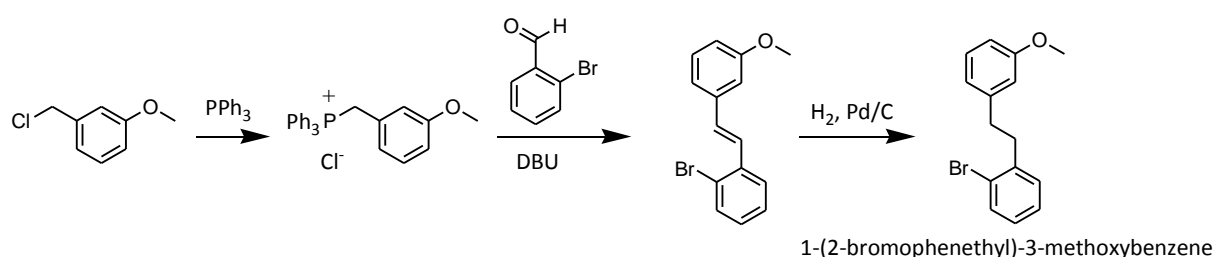
The following sections describe the synthesis strategy and contain a discussion of the problems that were encountered.

### 3.1 Strategy for the synthesis

The desired molecules have never been synthesized before, yet parts are similar to molecules that other groups already made. However, this research employed a completely new synthesis strategy.

#### 3.1.1 Previous strategies for arylmethoxyphenyl derivatives

Colabufo et al [1] used Wittig's reaction and subsequent catalytic hydrogenation for the preparation of arylmethoxyphenyl derivatives. They started with the phosphonium salt, added the appropriate benzaldehyde and DBU to receive a mixture of cis and trans isomers. Catalytic hydrogenation then removed the double bond between the aryls.

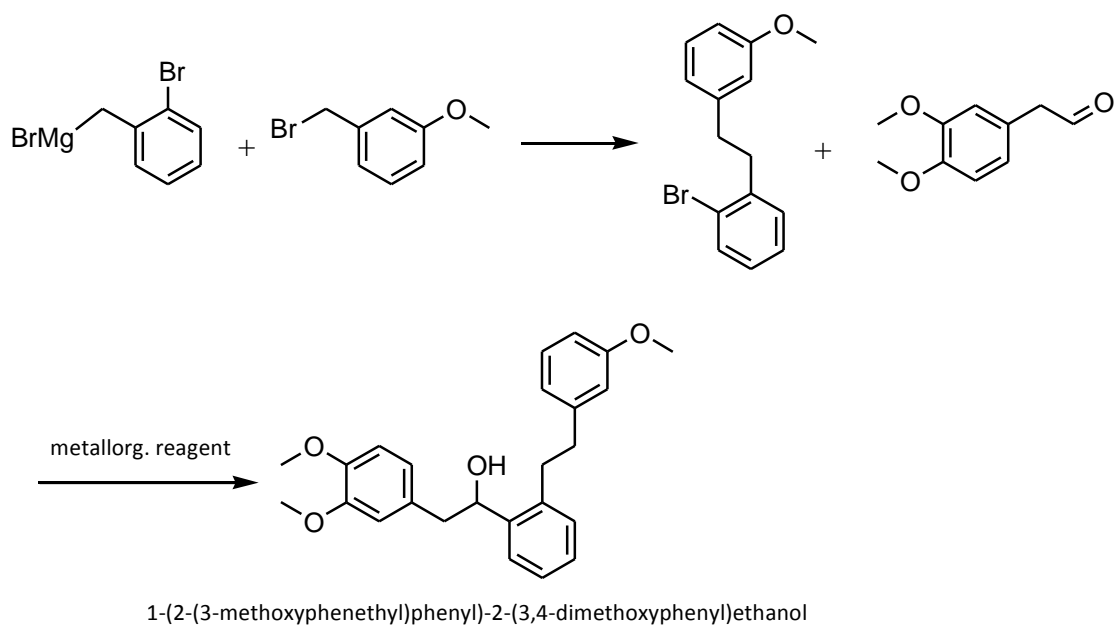


[3.1]

Following this strategy, 3 reaction steps, shown above, have to be performed to generate 1-(2-bromophenethyl)-3-methoxybenzene, which is the first brick of the target molecules.

### 3.2 Strategy 1

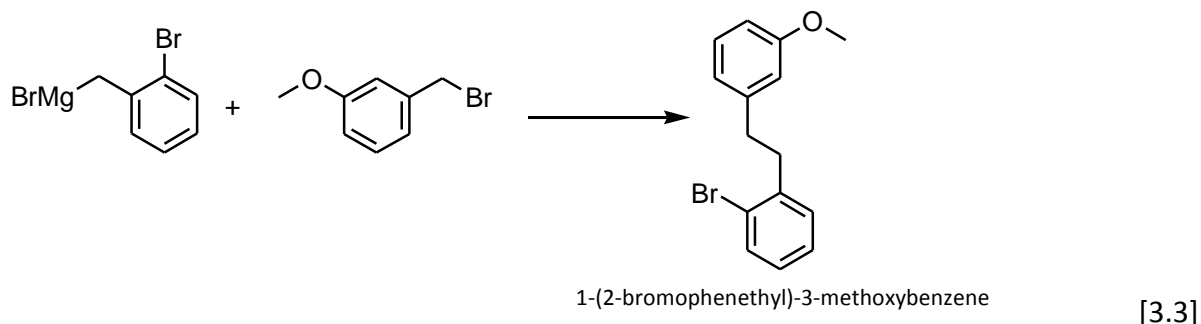
The idea behind this strategy was to generate the target molecules via metalorganic reactions, because this synthesis would be faster and easier than existing options. In this strategy, just 1 synthesis step has to be done to generate the 1-(2-bromophenethyl)-3-methoxybenzene product.



The first step is done via Kumada cross coupling, while the second is another metalorganic cross coupling reaction.

### 3.2.1 Synthesis Step 1: Kumada cross coupling

Preparation of 1-(2-bromophenethyl)-3-methoxybenzene



The Kumada cross coupling reaction is one of the best metal-catalyzed carbon-carbon bond forming reactions between unreactive alkenyl and aryl halides [24]. It is a stereoselective cross coupling reaction between aryl- or alkenyl- halides and Grignard reagents in the presence of a catalytic amount of a nickel-phosphine complex. The use of various palladium complexes as catalysts gives the opportunity to employ highly versatile organolithium reagents, because nickel catalysts only work with Grignard reagents. One enormous advantage of the Kumada cross coupling, compared to other cross coupling reactions such as Negishi

coupling or Stille coupling, is that even alkyl ( $sp^3$ ) Grignard reagents with  $\beta$ -hydrogens react selectively, without undesired  $\beta$ -hydride elimination.

Beyond organomagnesium and organolithium reagents, the Kumada cross coupling also works with organosodium (RNa), organocopper ( $R_2CuLi$ ), organoaluminium, organozinc, organotin, organozirconium and organoboron compounds. Nevertheless Grignard and organolithium reagents are most often used, especially organolithiums, as these are by far the most versatile compounds, since they can be prepared in many different and easy ways, including the direct lithiation of hydrocarbons. The polarity of the organomagnesium and organolithium reagents is incompatible with base-sensitive functional groups.

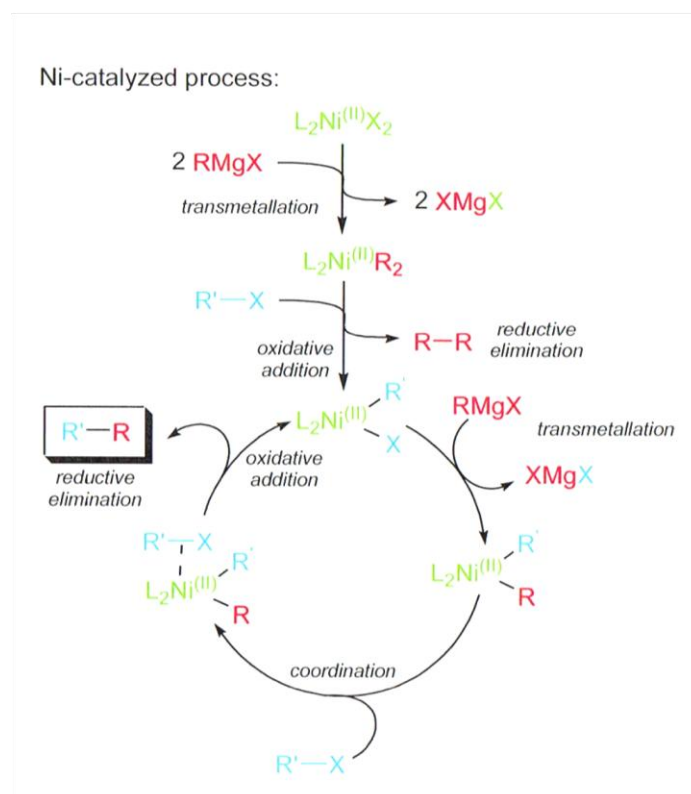
Side reactions rarely occur, but homocoupled and reductive products do occasionally occur. These can be avoided by taking three precautions. Firstly, the slow addition of the organolithium reagent, because otherwise  $\alpha$ -halide alkenyllithiums are built that give lithium acetylides under rearrangement, which reduces the overall yield. Secondly, the (palladium) catalyst has to be clean and highly active, and finally, an excess of any reagent should be avoided. [25]

As usual for a metalorganic reaction, the Kumada cross coupling has to be done under an argon atmosphere and completely anhydrous conditions.

The mechanism of Kumada-cross coupling is very similar to all other cross coupling reactions. A cross coupling reaction means that a carbon-carbon bond is formed between two different molecules, under organometallic catalysis.

#### **Mechanism with nickel catalysis:**

Different activity of the reaction partners is necessary to afford asymmetric coupling and avoiding the undesired homocoupled product. At first, the metal atom inserts in the aryl-/alkenyl halide via oxidative addition, after which a transmetallation of the residue of the Grignard reagent to the nickel-complex proceeds. Finally, the asymmetric coupled product is built via a reductive elimination reaction and the catalyst regenerates via an oxidative addition of another aryl-/alkenyl halide [25].



**Fig. 7:** Mechanism of Ni-catalyzed Kumada cross coupling, from [25], p.258

As described above, nickel or palladium are usually used for catalysis. Other, less toxic, eco-friendly and cheap Kumada cross coupling catalysts were also explored during this work.

Until 1900, C-C bond formation utilizing Grignards was dominated by palladium and nickel catalysts. Since then a new generation of catalysts, which are more compatible with sustainability, are being developed. Iron and manganese are the most promising candidates as reagents in eco-friendly synthesis, as are cobalt, copper and silver. [24, 26]

The toxicity is an especially important consideration for drug synthesis. The complete absence of any traces of toxic reagents has to be guaranteed for this application, and since purification is always difficult, large-scale and expensive, the use of non-toxic substances would be safer, and save time and money.

Scarcity in the earth's crust and the low availability of noble metals causes the high cost of precious metals, although the use of noble metals in organic synthesis is on the rise. Taking into account the fact that Pd exists in lower quantities than Pt in the lithosphere, the dependence and demand of Pd as a catalyst in synthesis of drugs and other essential chemicals has to be decreased. [27]

Therefore, reaction step 1 was run under many different conditions with different catalysts. These results are presented in table 1 below.

catalyst	TMEDA	solvent	temp	duration	yield
FeCl <sub>3</sub>	yes	THF	-40°C	20h	22.12%
NiCl <sub>2</sub>	yes	THF	-40°C	2h	59.69%
NiCl <sub>2</sub>	-	THF	-40°C	2h	-
FeCl <sub>3</sub>	yes	THF	0°C	2h	no column done
FeCl <sub>3</sub>	yes	THF	0°C	1h	~50%
CuCN.2LiCl	yes	THF	0°C	1h	-
CeCl <sub>3</sub>	yes	THF	0°C	1h	-
CoCl <sub>2</sub>	yes	THF	0°C	1h	-
CuCl <sub>2</sub>	yes	THF	0°C	1h	-
MnCl <sub>2</sub>	yes	THF	0°C	1h	-
Fe(acac) <sub>3</sub>	yes	THF	0°C	1h	-
-	DMEDA	THF	0°C	1h	-
-	HMTA	THF	0°C	1h	-
-	yes	THF	0°C	1h	-
FeCl <sub>3</sub>	-	THF	0°C	1h	-
-	-	THF	0°C	75min	-
-	yes	THF	0°C	1h	<b>98.56%</b>

**Table 1**

According to [26], aryl Grignard reagents react very well with secondary alkyl halides in the presence of iron salts and TMEDA.

At first the FeCl<sub>3</sub>catalyzed and NiCl<sub>2</sub>catalyzed reactions were compared: Both lead to the desired product, however, the iron catalyzed reaction had a lower yield, but also less impurity. Since this step runs without the need for toxic nickel, this reaction was then optimized in order to generate a yield as high as the nickel reaction.

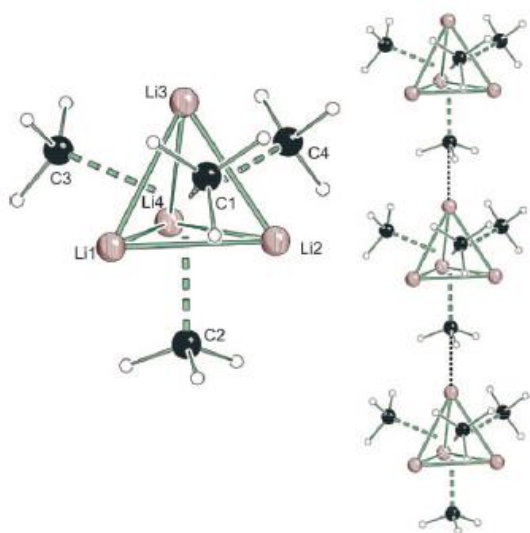
Increasing the temperature from -40°C to 0°C lead to a better result. With copper, cerium, cobalt, manganese and tris(acetylacetonato)iron, it was not possible to prepare the 1-(2-bromophenethyl)-3-methoxybenzene, or only a very low yield could be achieved.

Finally, it was found that the presence of TMEDA is absolutely essential. The reaction runs without any catalyst, but does not run without TMEDA. Other comparable auxiliary agents such as DMEDA and HMTA could not replace TMEDA. Furthermore, it was found that the duration of the reaction also influences reaction product. The highest yield was achieved without any catalyst, additional TMEDA, at 0°C, in 1 hour and using THF as the solvent.

### 3.2.1.1 Effect of TMEDA

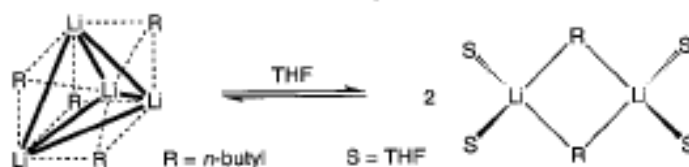
TMEDA is an efficient and inexpensive ligand [26] and is often added in reactions containing organolithium as a deaggregation additive. Organolithium compounds tend to aggregate due to the delocalized covalent bonds between the lithium and the terminal carbon of the butyl chain [28].

One explanation for the effect of TMEDA in this Kumada coupling is the stabilisation of the negative polarity of the Grignard reagent.



**Fig.8:** Left: Tetrameric methyllithium ( $\text{MeLi}$ )<sub>4</sub>; staged conformation in methyllithium tetrahedron. Right: Subset of the three-dimensional network, from [28]

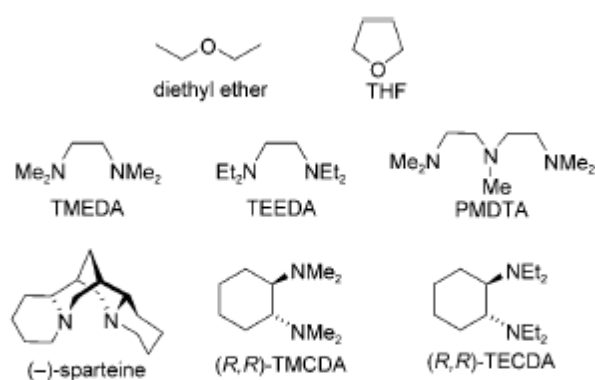
Gaseous organolithium compounds as well as liquid organolithium in hydrocarbons or ethereal solvents exist as oligomers (e.g. dimers, tetramers or higher aggregates). TMEDA prevents aggregation by building complexes with organolithium. [29, 30]



**Fig.9:** Dimer-tetramer equilibrium of  $n\text{BuLi}$  in THF, from [31]

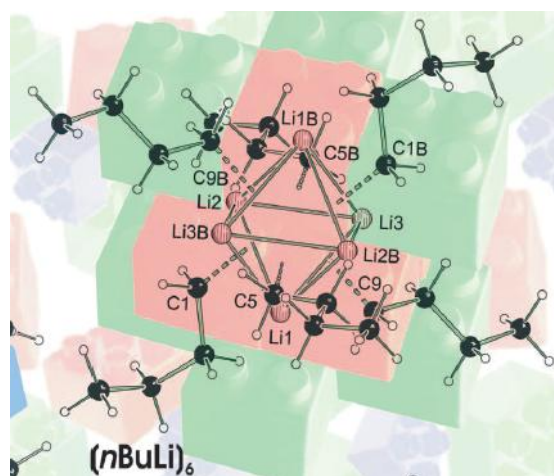
Lewis bases like THF, Et<sub>2</sub>O, TMEDA or HMPA have a big impact on the structure of organolithium compounds [32]. Desaggregation by additive Lewis bases, which results in smaller products like dimers and monomers, causes better solubility and can increase reactivity [33, 34]. Complexation of the Li-cation strongly polarizes the Li-C bond and enables desaggregation [31].

Monomeric organolithium compounds are known to be the most reactive, and so the rate-determining species in reactions. Sterically demanding ligands or substituents at the alkyllithium are essential to stabilize the monomers. Therefore tBuLi is one of a few monomeric alkyllithium bases.[28]



**Fig.10:** Often used Lewis bases for the coordination of organolithium compounds, from [28]

Cluster building can cause a reduction of reactivity, but the degree of aggregation does not always correlate with reactivity of organolithium compounds. In some reaction pathways, dimers or oligomers are the reactive agents. [35]

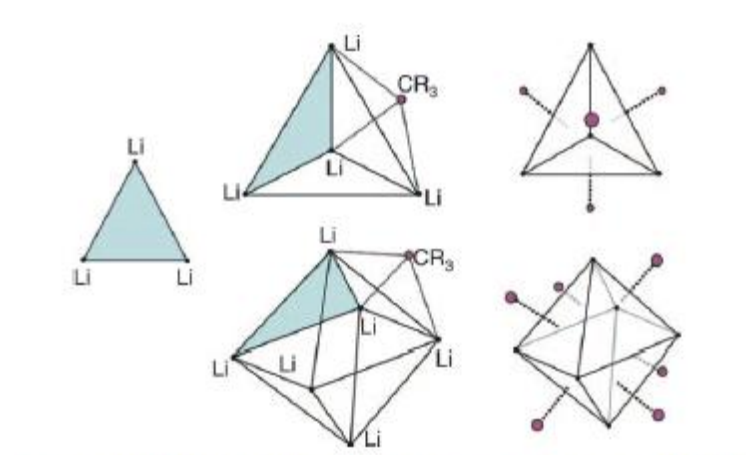


**Fig.11:** Complex of  $(n\text{BuLi})_6$ , from [28]



Three factors affect the molecular structure of lithium organics: (1) electrostatic interactions between opposite charges (localised and delocalised), (2) the coordination sphere of the lithium atom (e.g. solvent, coordinating Lewis bases) and, (3) the steric demand of the either more or less bulky substituents at the lithiated carbon centre and/or the ligand [28].

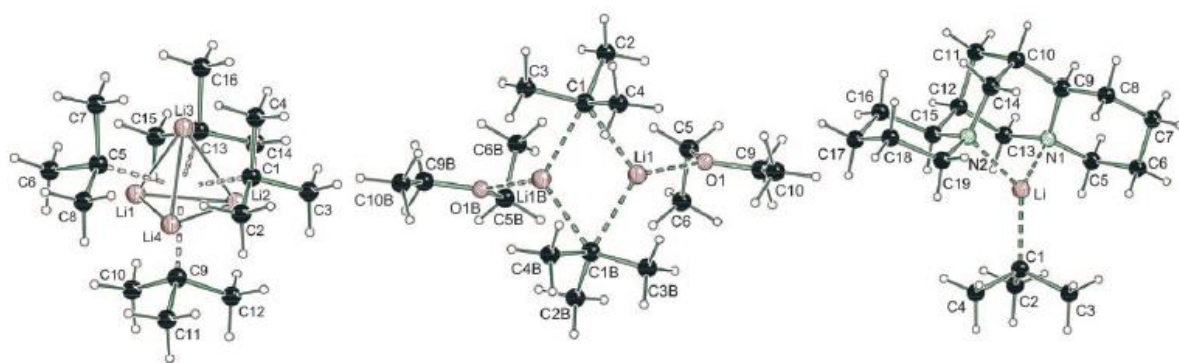
Generally, the lithium atoms arrange to  $\text{Li}_3$  triangles.



**Fig.12:** Formation principles of tetraeric and hexameric organolithium structures, from [28]

As methyllithium is the smallest alkyl lithium base, it is very difficult to stabilise as a monomer or a dimer. Lewis bases are not able to break the methyllithium tetramer [28, 33].

TMEDA leads to both a reduction in the degree of aggregation and increase of nucleophilicity of alkyl lithium reagents [32, 34].



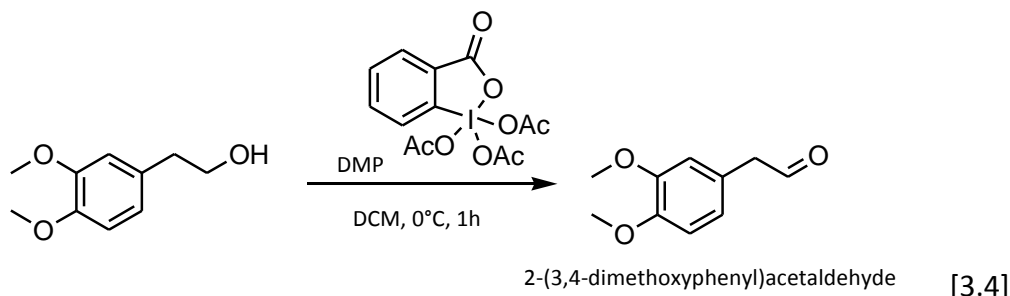
**Fig.13:** Deaggregation of tetrameric  $(\text{tBuLi})_4$  to dimeric  $(\text{tBuLi.Et}_2\text{O})_2$  and monomeric  $\text{tBuLi-(-)-sparteine}$ , from [28]

Bedford et al [36] found out that TMEDA suppresses competing, unselective pathways in reactions by trapping intermediates.

### 3.2.2 Preparation of 2-(3,4-dimethoxyphenyl)acetaldehyde

#### Dess-Martin oxidation

AW040



Before continuing with the second step of this synthesis strategy, the appropriate aldehyde (2-(3,4-dimethoxyphenyl)acetaldehyde) had to be prepared.

Following Stöckmann et al [37] the Dess-Martin oxidation was used to synthesize 2-(3,4-dimethoxyphenyl)acetaldehyde, which yielded 54% product.

The Dess-Martin oxidation is the reaction of choice for the oxidation of alcohols to their corresponding carbonyl compounds. It has some advantages compared to other oxidations such as Swern- or Jones oxidation: Less toxicity, higher yields, shorter reaction time, easier workup, mild conditions (rt, neutral pH), high chemoselectivity, suitability for substrates containing sensitive functional groups, and along shelf-life and thermal stability. [25, 38-40]

#### Mechanism:

In the reaction, one acetyl group of the DMP is replaced via a nucleophilic attack by the alcohol to give diacetoxyalkoxyperiodinanes. In the presence of two equivalents of the alcohol, a double displacement takes place to produce acetoxydialkoxyperiodinanes. Subsequent  $\alpha$ -proton transfer from the alcohol to the acetyl group leads to the carbonyl compound and a molecule of iodine [25].

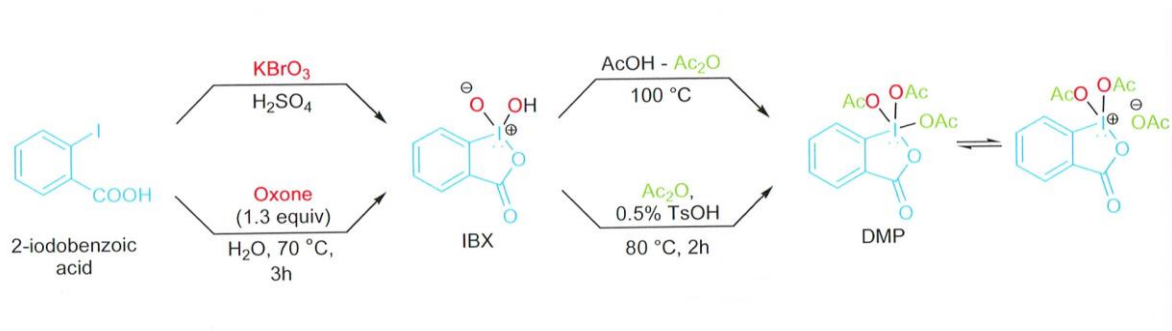
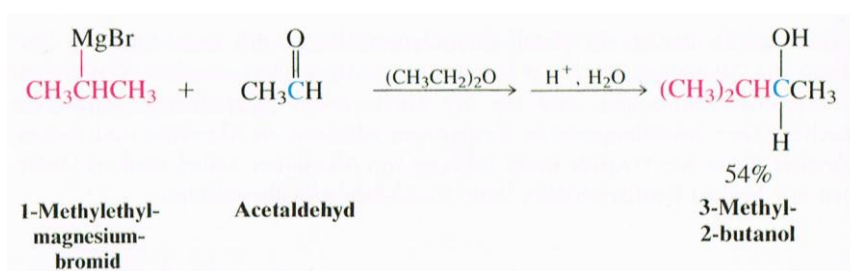


Fig.14: Mechanism of Dess Martin oxidation, from [25], p.136

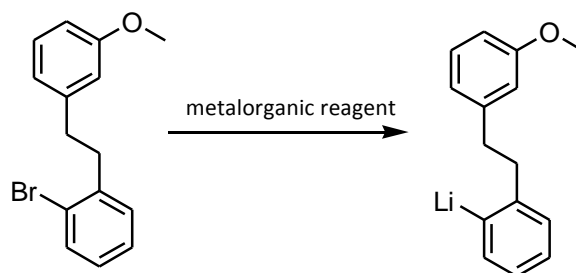
### 3.2.3 Synthesis step 2

The final synthesis step to reach the target molecules should have been the coupling of 1-(2-bromophenethyl)-3-methoxybenzene with 2-(3,4-dimethoxyphenyl)acetaldehyde.

The use of organometallics (organomagnesium or organolithium) and an aldehyde to generate secondary alcohols is a very common strategy in literature. Usually Grignard reagents are used for the conversion of carbonyl compounds, but in the case of substrates with low reactivity organolithium is preferred [19, 41].



**Fig.15:** Mechanism of preparation of secondary alcohol via Grignard reagent and aldehyde, from [19]



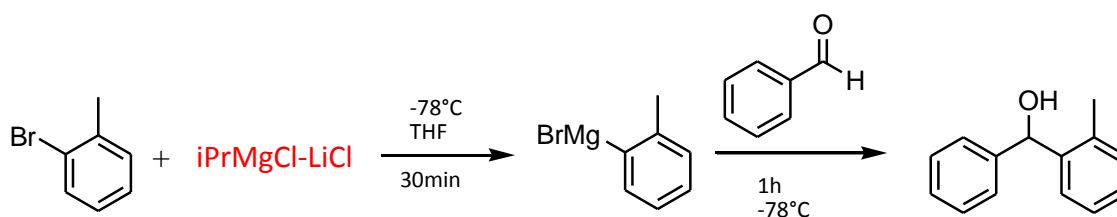
[3.5]

In the first part of this reaction, the substituted arylbromine has to be metalated and subsequent aldehyde and organolithium undergo coupling, which results in secondary alcohol.

#### 3.2.3.1 First trials for synthesis step 2

Before the prepared reagents from 3.2.2 and 3.2.3 were used, trials with different reagents were performed.

AW008

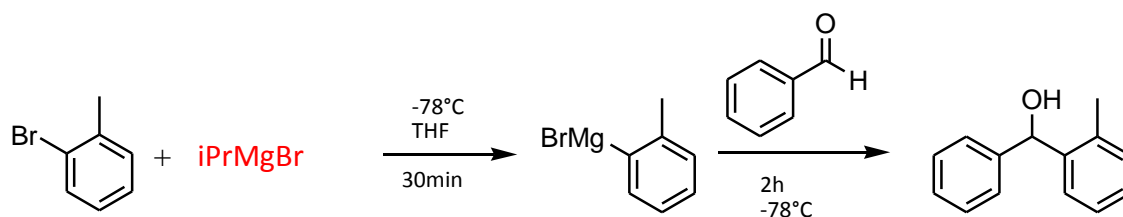


[3.6]

The reaction was not successful, as the expected product was not formed.

The reaction was done following a modified literature procedure [42-44].

#### AW009

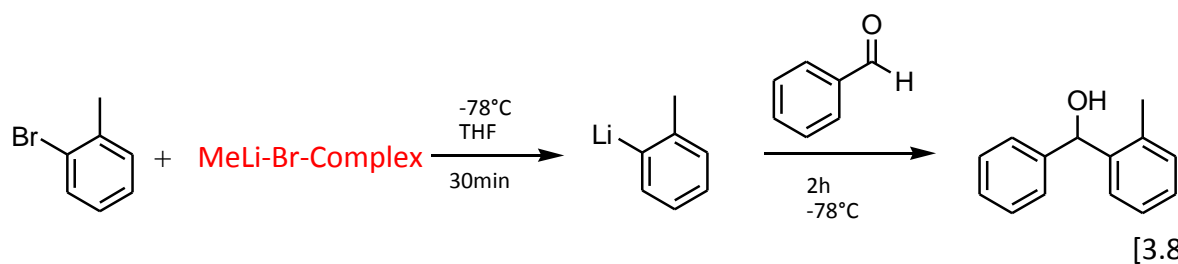


[3.7]

The reaction was not successful, as the expected product was not formed.

The reaction was done following a modified literature procedure [42-44].

#### AW010

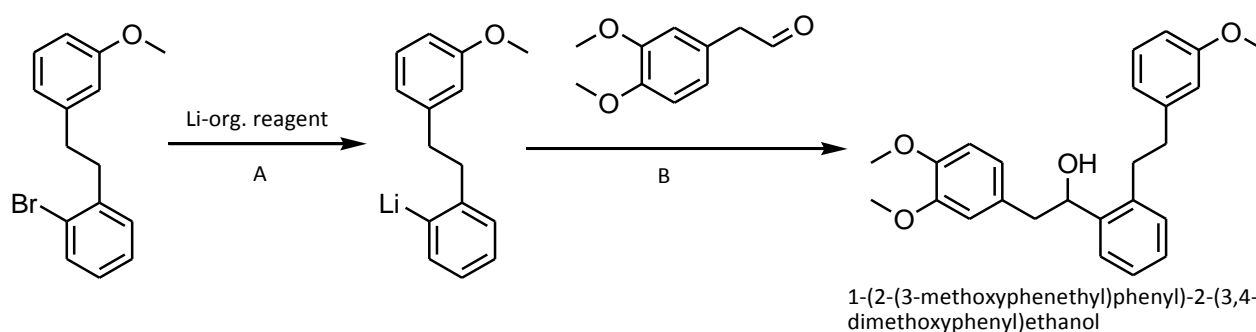


[3.8]

The reaction was not successful, as the expected product was not formed.

The reaction was done following a modified literature procedure [42-44].

### 3.2.3.2 With organolithium reagents



[3.9]

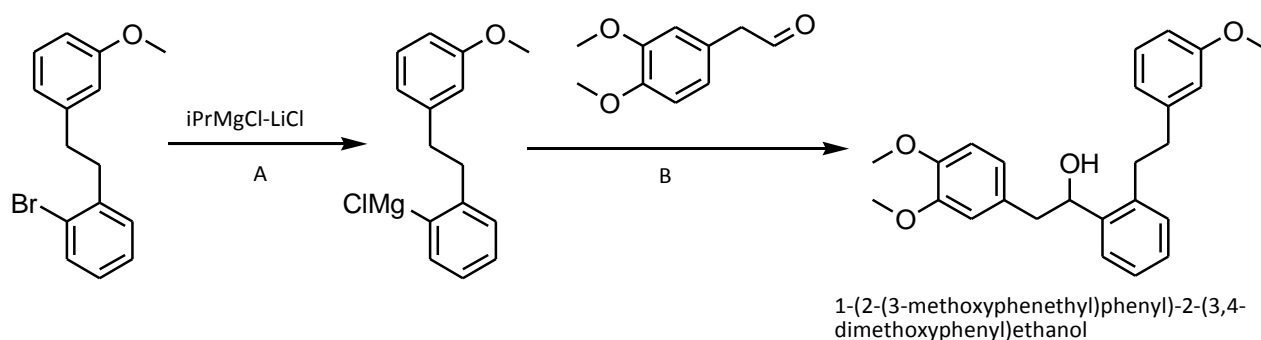
This reaction should prepare the target molecules. The reaction was run under different conditions, summarised in table 2.

	A					B	
reaction	Li-org. reagent	solvent	temp.	duration	additives	temp.	duration
AW045	MeLi-LiBr	THF	-78°C	1h	-	-78°C	19h
AW046	tBuLi	Et <sub>2</sub> O	-78°C	100min	-	-78°C	3h
AW048	nBuLi	THF	-78°C	90min	TMEDA	-78°C	155min
AW050	nBuLi	THF	-20°C	2h	TMEDA	rt	20h
AW051	nBuLi	THF	-20°C	2h	-	rt	20h
AW053	tBuLi	THF	-20°C	2h	-	rt	20h
AW054	tBuLi	THF	-20°C	3h	-	rt	20h
AW067	tBuLi	THF	-78°C	15min	-	-78°C to rt	19h
AW068	nBuLi	THF	-78°C	15min	-	-78°C to rt	19h

Table 2

As none of the reactions above lead to the desired target molecules, other methods of metalation were tried.

### 3.2.3.3 With iPrMgCl-LiCl



[3.10]

	A				B	
reaction	Mg-halide	solvent	temp.	duration	temp.	duration
AW047	iPrMgCl-LiCl	Et <sub>2</sub> O	-30°C	1h	-30°C	3h
AW049	iPrMgCl-LiCl	THF	0°C	160min	rt	20h
AW055	iPrMgCl-LiCl	THF	40°C	3,5h	rt	17.5h

Table 3

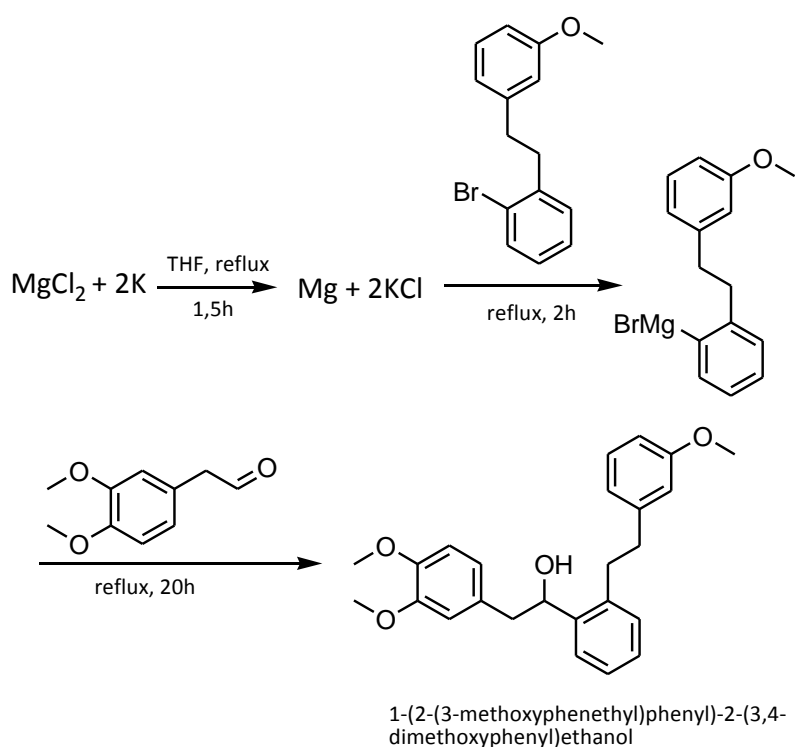
The target molecules were not produced by these reactions.

### 3.2.3.4 With Rieke-Mg

Rieke and Beles [45] developed a method to generate highly reactive magnesium via reduction of magnesium salts with potassium or sodium. This reaction yields activated magnesium in the form of a fine black powder, finely divided and free of metal oxides.

According to their work, many Grignard reagents, which cannot be generated easily or not be generated at all via the usual procedures, can be prepared using this method. A further great advantage is the possibility to prepare Grignard reagents at  $-78^{\circ}\text{C}$ , which permits the use of temperature sensitive reagents. A 10% excess of  $\text{MgCl}_2$  prevents unreacted potassium and an excess of magnesium affords complete conversion of the halide to Grignard [22].

AW056

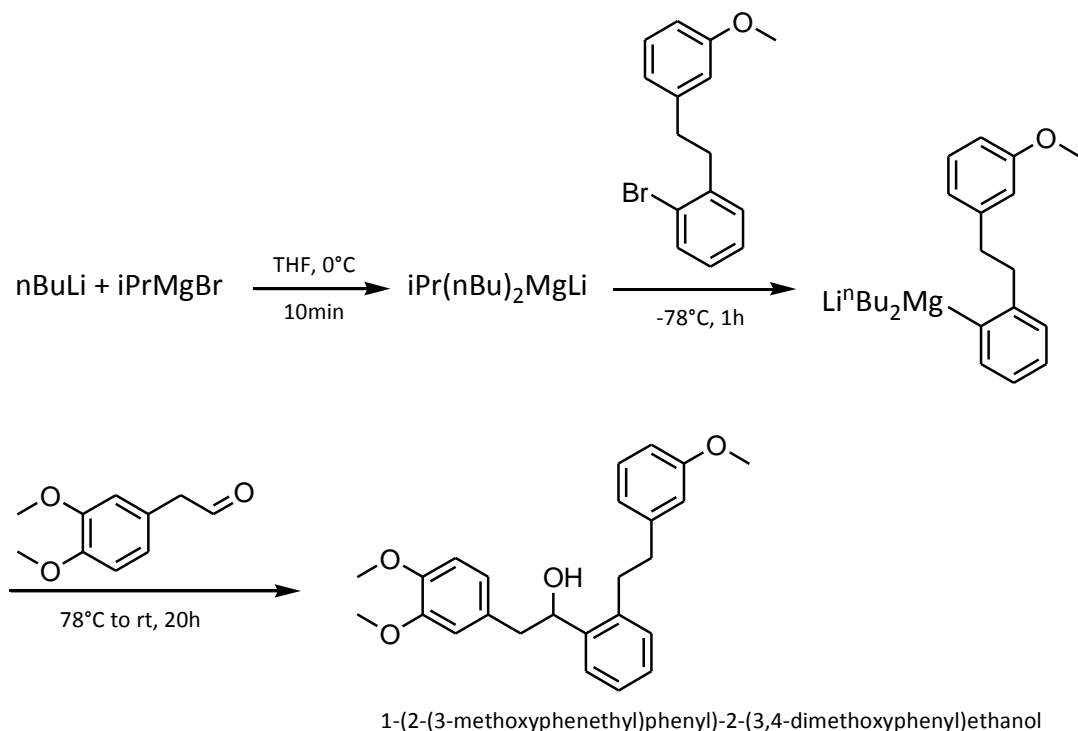


[3.11]

This reaction did not produce the target molecule.

### 3.2.3.5 With $i\text{Pr}(\text{nBu})_2\text{MgLi}$

AW070



[3.12]

Selective halogen-magnesium exchange can be done via organomagnesium complexes at low temperatures, yielding very reactive Grignard reagents.

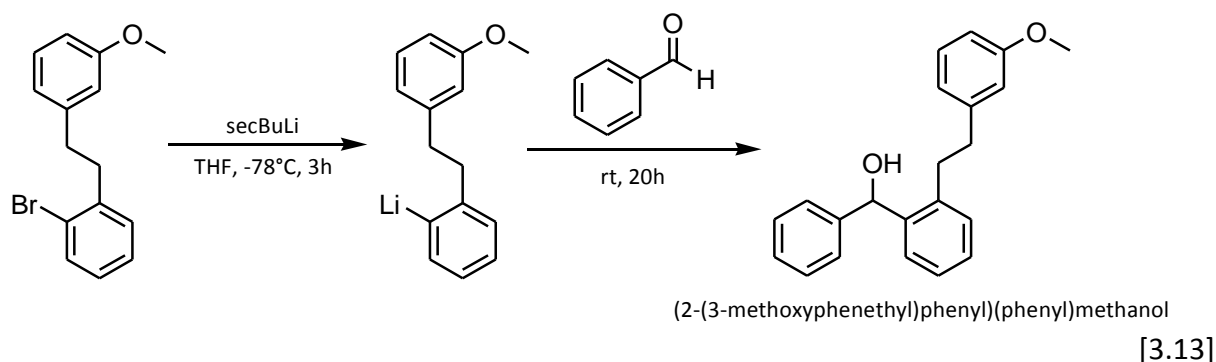
Inoue et al [46] efficiently converted several aryl bromides into the corresponding arylmagnesium compounds which could be trapped by various electrophiles like aldehydes and allyl bromide. They could also metalate sterically hindered halides, including ortho-substituted arylhalides, although the reaction did not yield in the desired molecule.

### 3.2.3.6 Trials with different aldehydes

To verify if the electrophile with its methoxy groups (2-(3,4-dimethoxyphenyl)acetaldehyde) is disturbing the reaction, the reaction was run with different aldehydes:

### 3.2.3.6.1 With benzaldehyde

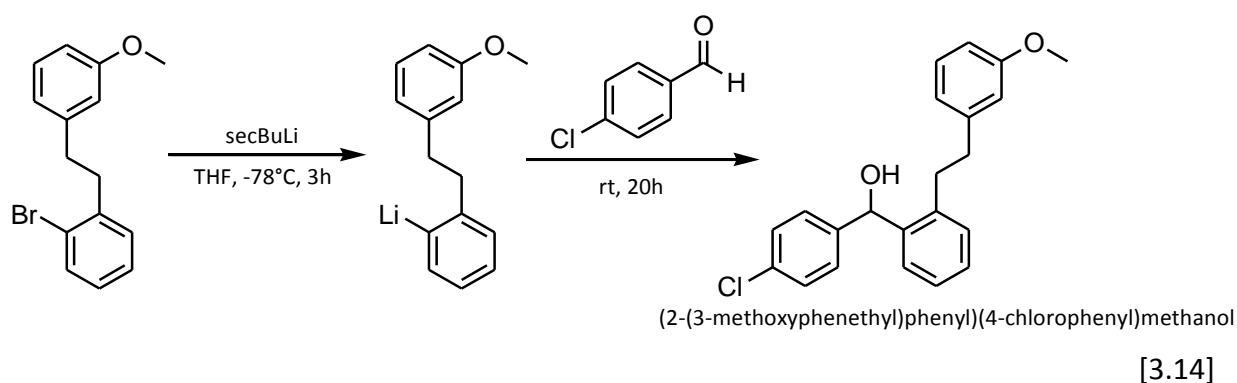
AW061



The cross coupling of 1-(2-bromophenethyl)-3-methoxybenzene and benzaldehyde did not work.

### 3.2.3.6.2 With 4-chlorobenzaldehyde

AW066



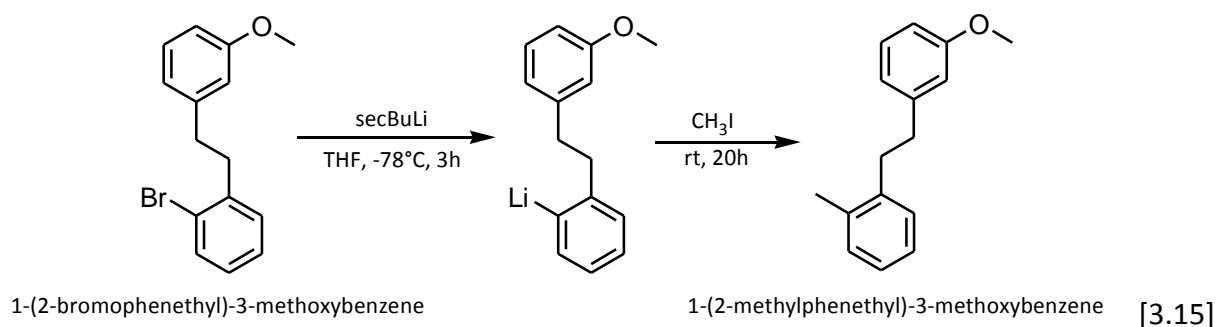
The use of 4-chlorobenzaldehyde instead of 2-(3,4-dimethoxyphenyl)acetaldehyde did not lead to successful cross coupling.



### 3.2.3.7 Trial of methylation

To rule out that 1-(2-bromophenethyl)-3-methoxybenzene is not compatible with aldehydes, methylation of 1-(2-bromophenethyl)-3-methoxybenzene was attempted.

AW065

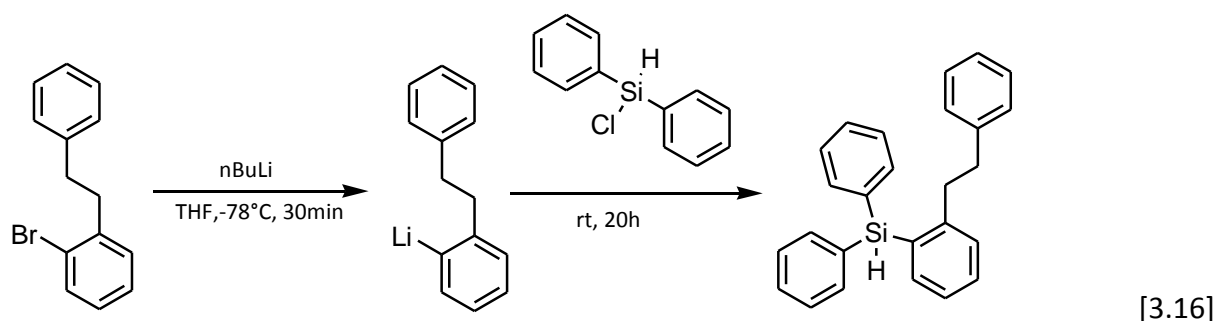


1-(2-methylphenethyl)-3-methoxybenzene could not be generated.

### 3.2.3.8 Trial of silylation

Usually silylation of organometallics works very easily; therefore silylation of 1-bromo-2-phenethylbenzene was attempted, following a modified literature procedure [47].

AW071



The reaction was modified according to [47]. The reaction did not yield the expected product.

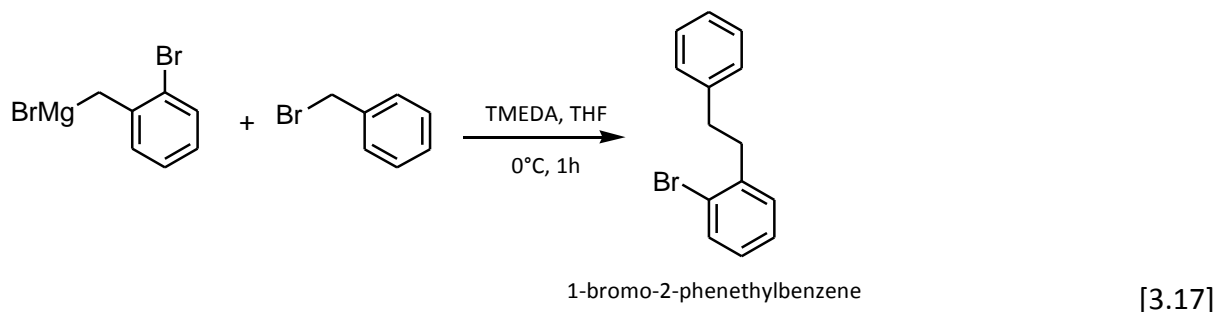
### 3.2.3.9 Trials without methoxy groups and different aldehydes

As all trials thus far did not lead to the target molecules, the same reaction (cross coupling) was run without methoxy groups and with benzaldehyde, to assess whether the methoxy residues were too bulky and disturbing the reaction. These were just experiments to understand the reaction mechanism, as according to Colabufo et al [1, 2], the methoxy groups are essential to SAR. The target molecules without methoxy groups will not show inhibition of p-glycoprotein.

### 3.2.3.9.1 Preparation of starting material (1-bromo-2-phenethylbenzene)

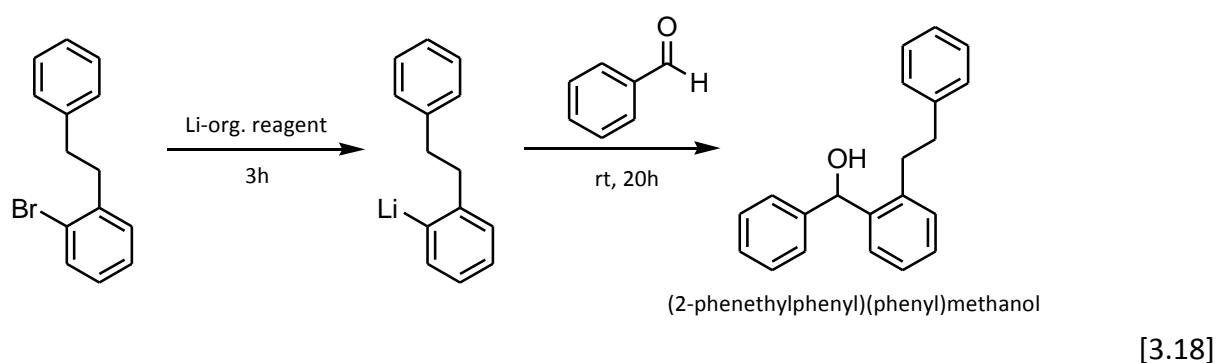
1-bromo-2-phenethylbenzene was prepared via Kumada cross coupling.

AW058



The Kumada cross coupling again worked very well without any catalyst and afforded a yield of 83% product.

### 3.2.3.9.2 Cross coupling with benzaldehyde



Using different lithium organic reagents, the following results were observed:

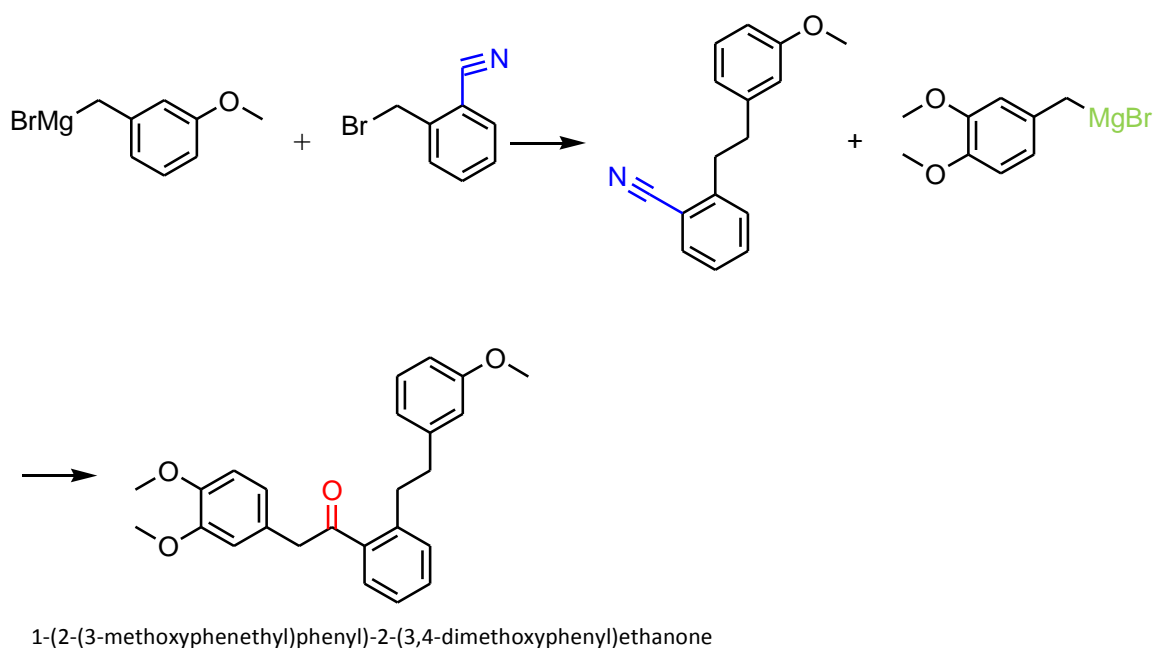
reaction	Li-org. reagent.	temp.
AW059	tBuLi	$-20^\circ\text{C}$
AW060	nBuLi	$-20^\circ\text{C}$
AW062	sBuLi	$-78^\circ\text{C}$

Table 4

These reactions also did not lead to the expected coupling product, but these trials showed that the methoxy groups are not the reason that the target molecules cannot be produced via cross coupling.

## 3.3 Strategy 2

Since the first strategy could not produce the target molecules another synthesis strategy was developed. Three things were changed: (1) substitution of the bromine in the 1-(2-bromophenethyl)-3-methoxybenzene to a nitrile group (2) instead of an aldehyde, the corresponding Grignard reagent was employed, and (3) the reaction was changed to yield the ketone, instead of the alcohol.

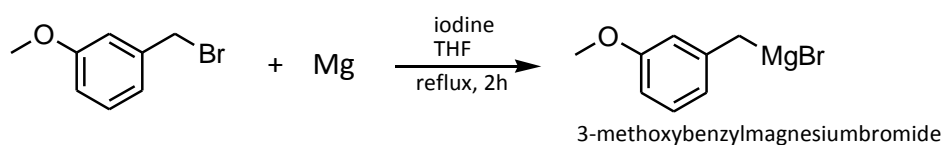


[3.19]

The use of nitriles to generate ketones is common in literature [31].

### 3.3.1 Preparation of 3-methoxybenzylmagnesiumbromide

AW080



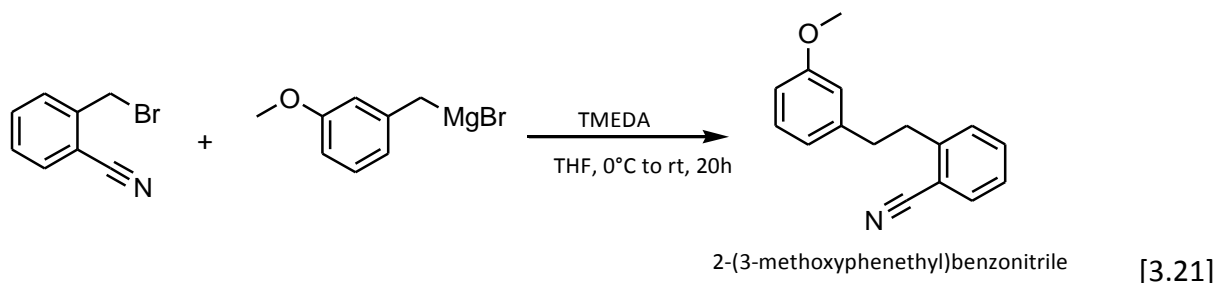
[3.20]

This reaction was done following a literature procedure [48].

### 3.3.2 Synthesis step 1: Kumada coupling

Preparation of 2-(3-methoxyphenethyl)benzonitrile

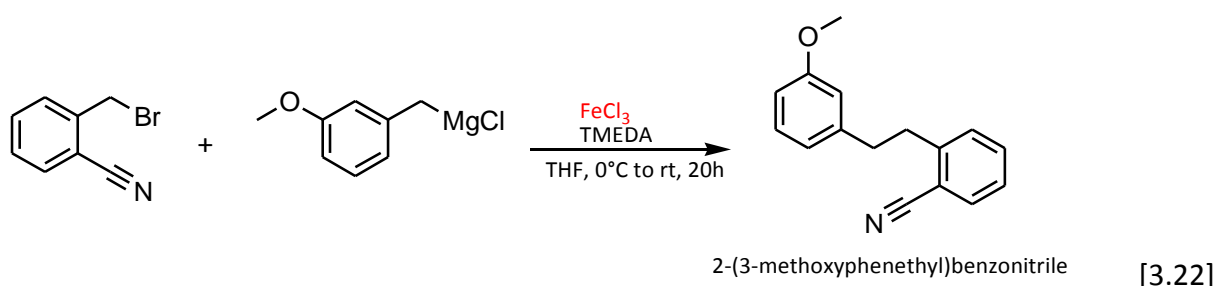
AW081



2-(3-methoxyphenethyl)benzonitrile was prepared via Kumada cross coupling, but this time the compound with the methoxy group was the Grignard reagent. The Coupling was again done in presence of TMEDA, without any catalyst.

To examine the effect of  $\text{FeCl}_3$  as a catalyst, the reaction was also run with catalytic amounts of  $\text{FeCl}_3$ :

AW076



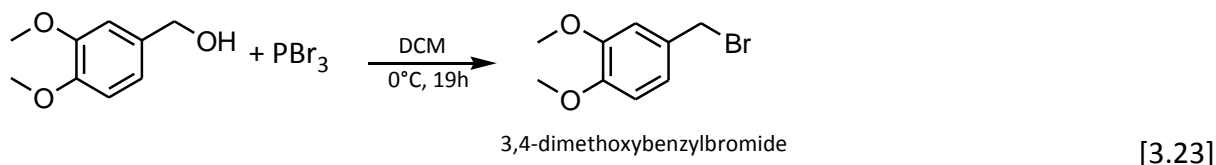
Preparatory work showed that less starting material was present in the product of the reaction without the presence of the iron catalyst.

### 3.3.3 Preparation of 3,4-dimethoxybenzylmagnesiumbromide

3,4-(dimethoxyphenyl)methanol was transformed into the bromine compound, and afterwards converted into the Grignard reagent.

### 3.3.3.1 Preparation of 3,4-dimethoxybenzylbromide

AW079

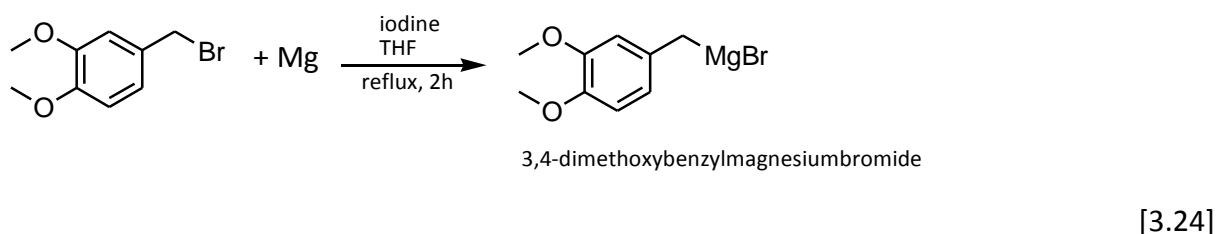


92% yield was achieved.

The synthesis was modified according to [49].

### 3.3.3.2 Preparation of 3,4-dimethoxybenzylmagnesiumbromide

AW083

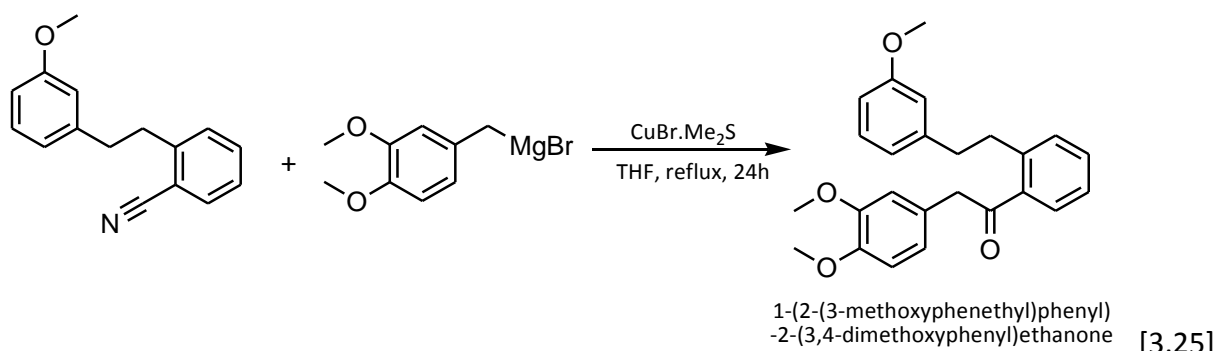


For this conversation into the Grignard reagent, a literature procedure was employed [48].

## 3.3.4 Synthesis step 2

Coupling of the nitrile with the Grignard reagent:

AW085



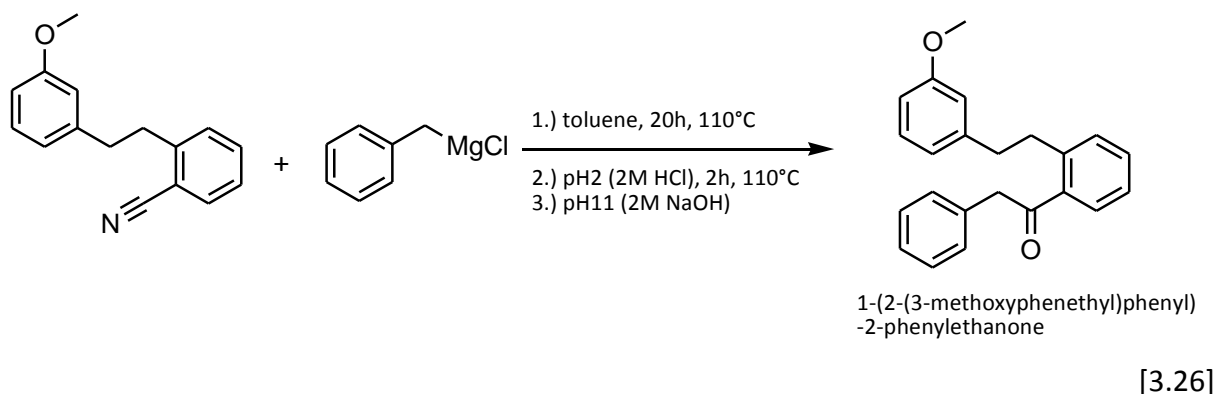
The reaction did not lead to the desired target molecule.

The reaction was done according to [50].

### 3.3.4.1 With different Grignard reagent

The reaction was run with benzylmagnesiumchloride instead of 3,4-dimethoxybenzylmagnesiumbromide.

AW088



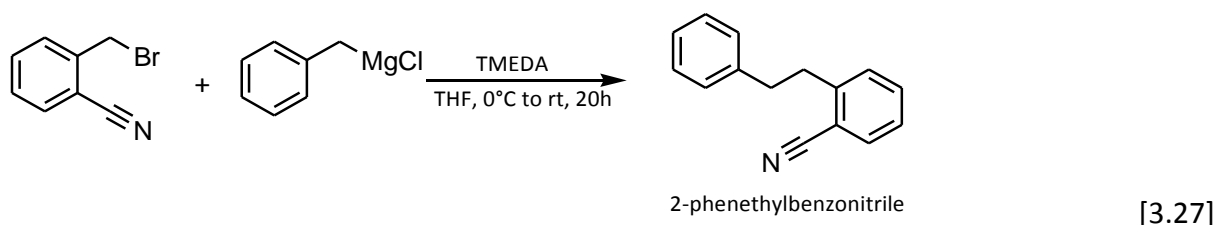
This reaction could not produce the target molecule.

### 3.3.4.2 Trials without methoxy groups

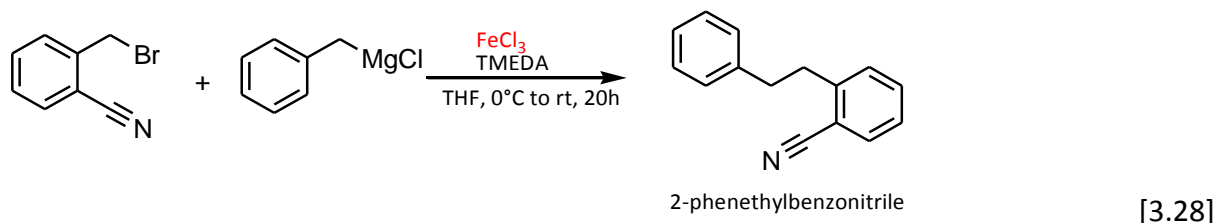
To avoid steric hindrance, the reaction was attempted without any bulky methoxy groups.

#### 3.3.4.2.1 Preparation of 2-phenethylbenzonitrile

AW077

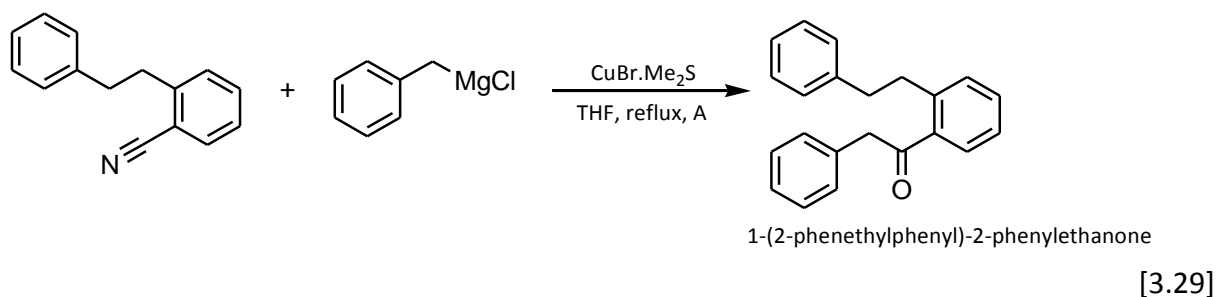


AW078



For the preparation of the starting material for the cross coupling again Kumada cross coupling was employed. Both reactions were run, one at a time, with and without the FeCl<sub>3</sub> catalyst, and again the reaction without iron led to better results, containing less of the starting material in the product.

### 3.3.4.2.2 Coupling of the nitrile with the Grignard reagent



This reaction was run under different conditions, but none could afford the expected and desired product.

The reactions were done according to [50].

reaction	A
AW082	2h
AW084	24h

Table 5

## 4 RESULTS AND DISCUSSION

Before starting the experimental work, it was expected that the first step, the Kumada cross coupling, would be the limiting and critical step and that the second step would not be a problem. However, this turned out not to be the case. The Kumada cross coupling worked as expected from the beginning. The fact that TMEDA is the essential substance in this reaction and that no catalyst was needed was very surprising and took a lot of work to realise.

The second step, the coupling of the Kumada cross coupling product with the aldehyde did not work, although many different conditions and organometallic reagents were tried. According to the literature, this reaction should not be a problem and should work very easily [19, 41].

Normally, in most cases of cross coupling reactions, the metalation is the limiting factor. From this, it was thought that the metalation would not work out. Hegedus [51] p.33: “the transmetallation step is almost always the rate limiting step”.

Therefore it was tried under many different conditions and using many different organometallics, but none resulted in the desired molecules.

Finally, it was found that the trapping of the electrophile was the problem.

Alkali organometallics in general can lead to different reactions: metalation, reduction, alkylation of transition-metal halides and addition on multiple bonds [31]. Usually, the electrophilicity predominates the reducing power by a significant amount. Organolithium compounds especially are known as faint reducing agents. Therefore, the results obtained are more interesting.

Another achievement of this work concerns the Kumada cross coupling: Bedford [36] mentions a yield of 14-35% in iron catalyzed cross couplings of benzyl Grignard reagents. However, this work achieved a yield of 98% in Kumada cross coupling of benzyl Grignard reagent with a benzyl halide (see [3.3]). The following conditions were established to be the best: THF, TMEDA, 0°C, 1h. Kumada cross coupling in absence of any catalyst is new.

The fact that 1-(2-bromophenethyl)-3-methoxybenzene and 2-(3,4-dimethoxyphenyl)acetaldehyde cannot be coupled via diverse organomagnesium or organolithium compounds is very surprising and has not been seen in literature.



This project was continued by a subsequent master student. Eventually, he was able to prepare the target molecules by converting the organolithium compound to an organozirconium via transmetalation. Organozirconium compounds are known to be even less reductive than organolithium. Beside the transmetalation and the use of iodine compound instead of bromine compound, he used the first synthesis strategy described in this thesis. As the cell assays are still running, the SAR was not known at the time of writing.

## 5 EXPERIMENTAL SECTION

### General methods:

All reactions except the Dess-Martin oxidation were done under anhydrous condition, using argon as protective gas. This is therefore not mentioned in each of the procedures below.

Glass equipment was dried in an oven with a temperature of at least 100°C over night. Before adding any reagent or solvent, the reaction apparatus was flushed with argon for several minutes. All reagents were added using syringes.

A mixture of dry ice and ethanol was used to generate the appropriate temperatures.

The solvents THF and DCM were freshly distilled with Na<sup>0</sup>. THF also contained benzophenone as an indicator. Commercially available dry toluene and diethylether were used from Aldrich. All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich) or Acros Organics and were used without further purification.

Reactions were monitored by TLC, performed on aluminium plates coated with silica gel 60 f254 from Macherey-Nagel (Alugram® Xtra SIL G/UV<sub>254</sub> 0,2mm), using hexane:ethylacetate in different concentrations as eluents. Visualization was done using UV light ( $\lambda=254$ ).

Column chromatography was performed with silica gel 60 M 0.04-0.63 mm by Macherey-Nagel.

Organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>.

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> by using Bruker Avance 500, 400 or 200 MHz Nuclear Magnetic Resonance spectrometer instruments. Chemical shifts are expressed in parts per million ( $\delta$  in ppm) downfield from CDCl<sub>3</sub> [ $\delta$ (<sup>1</sup>H)=7,26ppm] and [ $\delta$ (<sup>13</sup>C)=77,00ppm]. High resolution mass spectra were measured by Bruker maXis HD.

## 5.1 Strategy 1

### 5.1.1 Preparation of 1-(2-bromophenethyl)-3-methoxybenzene

THF (1ml) was put into a small three-neck flask and TMEDA (300 $\mu$ l, 2.0mmol) was added. The solution was stirred and cooled to the appropriate temperature shown in table below. 2-bromobenzlmagnesiumbromide solution (2.0mmol, 0.25M in Et<sub>2</sub>O) was then added slowly. While stirring vigorously, slow addition of 3-methoxybenzylbromide (1.0mmol) followed.

Reaction mixture was stirred at a particular temperature, followed by TLC and quenched by H<sub>2</sub>O (5ml) after the time shown in the table below. Extraction of the organic products was done by using CH<sub>2</sub>Cl<sub>2</sub> or EtOAc (3x10ml). It was dried over Na<sub>2</sub>SO<sub>4</sub> and further by using rotary evaporator and a vacuum pump. The product was then identified by NMR spectroscopy.

Purification was done by flash chromatography with silica gel as the stationary phase and hexane:ethylacetate 9:1 as the mobile phase.

If a catalyst was used, the amount added was about 8mg, and it was dissolved in THF before the addition of TMEDA.

DMEDA and HMTA were used instead of TMEDA in the same amounts.

catalyst	TMEDA	solvent	temp	duration	yield
FeCl <sub>3</sub>	yes	THF	-40°C	20h	22.12%
NiCl <sub>2</sub>	yes	THF	-40°C	2h	59.69%
NiCl <sub>2</sub>	-	THF	-40°C	2h	-
FeCl <sub>3</sub>	yes	THF	0°C	2h	no column done
FeCl <sub>3</sub>	yes	THF	0°C	1h	~50%
CuCN.2LiCl	yes	THF	0°C	1h	-
CeCl <sub>3</sub>	yes	THF	0°C	1h	-
CoCl <sub>2</sub>	yes	THF	0°C	1h	-
CuCl <sub>2</sub>	yes	THF	0°C	1h	-
MnCl <sub>2</sub>	yes	THF	0°C	1h	-
Fe(acac) <sub>3</sub>	yes	THF	0°C	1h	-
-	DMEDA	THF	0°C	1h	-
-	HMTA	THF	0°C	1h	-
-	yes	THF	0°C	1h	

FeCl <sub>3</sub>	-	THF	0°C	1h	-
-	-	THF	0°C	75min	-
-	yes	THF	0°C	1h	<b>98.56%</b>

Table 6

Synthesis was modified according to [24, 26, 36].

### 5.1.2 Preparation of 2-(3,4-dimethoxyphenyl)acetaldehyde

**Dess-Martin oxidation:** 2-(3,4-dimethoxyphenyl)ethanol (2.0g) were put into a flask, dissolved in DCM (17ml) and cooled to 0°C. Subsequent Dess-Martin periodinane (9.31g) was added. This reaction was followed by TLC and quenched by H<sub>2</sub>O (9ml) after 1h. Cave: it is frothing!

Extraction of the organic products was done by using EtOAc (3x20ml). It was dried over Na<sub>2</sub>SO<sub>4</sub>, and further by using rotary evaporator and a vacuum pump. The product was then determined by NMR spectroscopy.

Purification was done by flash chromatography with silica gel as the stationary phase and hexane:ethylacetate 1:1 as the mobile phase. The yield was 54.3%.

The synthesis technique was taken from [37, 39].

### 5.1.3 Synthesis step 2

#### 5.1.3.1 First trials for synthesis step 2

2-bromotoluene (1.55g) were put in a three neck flask and dissolved in THF (10ml). The mixture was stirred and cooled to -78°C. Subsequent organometallic reagent (3 equ.) was added in drops and vigorously stirred for 30 minutes. Benzaldehyde (300mg) was then added, with the solution again stirred for 1 or 2 hours (see 3.2.3.1). The reaction was followed by TLC and quenched by saturated NH<sub>4</sub>Cl-solution (10ml).

Extraction of the organic products was then performed using EtOAc (3x20ml). They were then dried over Na<sub>2</sub>SO<sub>4</sub> and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

The reactions were done following a modified literature procedure [42-44].

### 5.1.3.2 With organolithium reagents or $i\text{PrMgCl-LiCl}$

1-(2-bromophenethyl)-3-methoxybenzene (0.17 mmol) was put in a three neck flask and dissolved in THF (1ml). The mixture was stirred and cooled to the temperature shown below. Subsequently, the organometallic reagent (0.17 mmol) was added in drops and the reaction mixture was vigorously stirred for the time shown in the table 7 or 8 below (duration A). 2-(3,4-dimethoxyphenyl)acetaldehyde (0.15 mmol) was dissolved in THF and subsequent added to the reaction mixture in drops at temperature showed below (temp. B). Reaction was followed by TLC, stirred for the time and at temperature shown in the table below (duration B). It was quenched by saturated  $\text{NH}_4\text{Cl}$ -solution (5ml).

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$  and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

If TMEDA was used, it was dissolved in THF before cooling it.

reaction	A					B	
	Li-org. reagent	solvent	temp.	duration	additives	temp.	duration
AW045	MeLi-LiBr	THF	-78°C	1h	-	-78°C	19h
AW046	tBuLi	$\text{Et}_2\text{O}$	-78°C	100min	-	-78°C	3h
AW048	nBuLi	THF	-78°C	90min	TMEDA	-78°C	155min
AW050	nBuLi	THF	-20°C	2h	TMEDA	rt	20h
AW051	nBuLi	THF	-20°C	2h	-	rt	20h
AW053	tBuLi	THF	-20°C	2h	-	rt	20h
AW054	tBuLi	THF	-20°C	3h	-	rt	20h
AW067	tBuLi	THF	-78°C	15min	-	-78°C to rt	19h
AW068	nBuLi	THF	-78°C	15min	-	-78°C to rt	19h

Table 7

reaction	A				B	
	Mg-halide	solvent	temp.	duration	temp.	duration
AW047	$i\text{PrMgCl-LiCl}$	$\text{Et}_2\text{O}$	-30°C	1h	-30°C	3h
AW049	$i\text{PrMgCl-LiCl}$	THF	0°C	160min	rt	20h
AW055	$i\text{PrMgCl-LiCl}$	THF	40°C	3.5h	rt	17.5h

Table 8

### 5.1.3.3 With Rieke-Mg

THF (5ml) was put in a three neck flask, freshly cut potassium (37mg) was added and then washed with THF (3x5ml).  $\text{MgCl}_2$  (49mg) was then added, and the mixture was heated to 60-70°C, and then stirred and refluxed for 1.5 hours. A solution of 1-(2-bromophenethyl)-3-methoxybenzene (68mg) in THF was added and stirred for 2 hours. This reaction was followed by TLC. 2-(3,4-dimethoxyphenyl)acetaldehyde (38mg) was dissolved in THF, added to the reaction mixture and it was vigorously stirred and refluxed for 20 hours. The reaction was then quenched and the excess potassium was destroyed by 2-propanol (3ml). On the following day, another amount of 2-propanol (3ml) and  $\text{H}_2\text{O}$  (5ml) were added. Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$  and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

Purification was done by flash chromatography with silica gel as the stationary phase and hexane:ethylacetate 9:1 (further 8:2) as the mobile phase.

The synthesis was from [45].

### 5.1.3.4 With $\text{iPr}(\text{nBu})_2\text{MgLi}$

THF (0.5ml) was put in a three neck flask and cooled to 0°C.  $\text{iPrMgBr}$  (0.213mmol) and  $\text{nBuLi}$  (0.426mmol) were added and stirred for 10 minutes. Subsequently, the mixture was cooled to -78°C. A solution of 1-(2-bromophenethyl)-3-methoxybenzene (50mg) in THF (0.5ml) was added in drops, and vigorously stirred for 1 hour. 2-(3,4-dimethoxyphenyl)acetaldehyde (154mg) was then dissolved in THF, added in drops and stirred for 20 hours with increasing temperature from -78°C to 0°C. The reaction was quenched by saturated  $\text{NH}_4\text{Cl}$  solution (5ml).

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$  and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

Synthesis was done after [46].

#### 5.1.3.5 Trials with different aldehydes

1-(2-bromophenethyl)-3-methoxybenzene (50mg) was put in a three neck flask, dissolved in THF (1ml), the mixture was stirred and cooled to  $-78^{\circ}\text{C}$ . sBuLi (0.255mmol) was added in drops and stirred for 3 hours. Subsequent benzaldehyde or 4-chlorobenzaldehyde (0.15mmol) was added, the reaction mixture was stirred for 20 hours at increasing temperature to rt, and then quenched by saturated  $\text{NH}_4\text{Cl}$  solution.

Extraction of the organic products was performed using EtOAc (3x10ml). It was then dried over  $\text{Na}_2\text{SO}_4$  and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

#### 5.1.3.6 Trial of methylation

1-(2-bromophenethyl)-3-methoxybenzene (50mg) was put in a three neck flask, dissolved in THF (1ml), the mixture was stirred and cooled to  $-78^{\circ}\text{C}$ . sBuLi (0.255mmol) was added in drops and stirred for 3 hours. Subsequent a solution of  $\text{CH}_3\text{I}$  (0.85mmol) in THF was added, the reaction mixture was stirred for 20 hours at increasing temperature to rt and quenched by saturated  $\text{NH}_4\text{Cl}$  (5ml) solution.

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$  and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

#### 5.1.3.7 Trial of silylation

1-bromo-2-phenethylbenzene (50mg) was put in a three neck flask, dissolved in THF (0.5ml), the mixture was stirred and cooled to  $-78^{\circ}\text{C}$ . sBuLi (0.285mmol) was added in drops and stirred for 30minutes. Subsequent chlordiphenylsilane (0.285mmol) was added, the reaction mixture was stirred for 20 hours at increasing temperature to rt and quenched by saturated  $\text{NH}_4\text{Cl}$  (5ml) solution.

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$  and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

Synthesis was modified after [47].

### 5.1.3.8 Trials without methoxy groups and different aldehydes

#### 5.1.3.8.1 Preparation (1-bromo-2-phenethylbenzene)

THF (3ml) was put into a small three-neck flask and TMEDA (3.75mmol) was added. The solution was stirred and cooled to 0°C. 2-bromobenzlmagnesiumbromide solution (3.75mmol, 0.25M in Et<sub>2</sub>O) was added slowly. While stirring it vigorously, slow addition of benzylbromide (1.875mmol) followed. Reaction mixture was stirred at 0°C, followed by TLC and quenched by H<sub>2</sub>O (10ml) after 80 minutes.

Extraction of the organic products was performed using CH<sub>2</sub>Cl<sub>2</sub> or EtOAc (3x10ml). It was dried over Na<sub>2</sub>SO<sub>4</sub>, and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

Purification was done by flash chromatography with silica gel as the stationary phase and hexane:ethylacetate 9:1 (further 8:2) as the mobile phase.

Synthesis was modified after [24, 26, 36].

#### 5.1.3.8.2 Cross coupling with benzaldehyde

1-bromo-2-phenethylbenzene (50mg) was put in a three neck flask, dissolved in THF (1ml), the mixture was stirred and cooled to the temperature shown below. tBuLi (0.76mmol), nBuLi (0.76mmol) or sBuLi (0.175mmol) was added in drops and stirred for 3 hours. Subsequently, benzaldehyde (0,17mmol) was added, the reaction mixture was stirred for 20 hours at increasing temperature to rt and quenched by saturated NH<sub>4</sub>Cl solution.

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over Na<sub>2</sub>SO<sub>4</sub> and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

reaction	Li-org. reagent.	temp.
AW059	tBuLi	-20°C
AW060	nBuLi	-20°C
AW062	sBuLi	-78°C

Table 9



## 5.2 Strategy 2

### 5.2.1 Preparation of 3-methoxybenzylmagnesiumbromide

Mg shavings (1.5g) were put in a three neck flask, diluted with THF (16.67ml) and 4 balls of iodine were added. Half the amount of a solution of 3-methoxybenzylbromide (15.0mmol) in THF (16.67ml) was added to the reaction mixture in drops. Another 16.67ml THF was added to the dilution and subsequently added to the reaction mixture in drops. The mixture was refluxed for 2 hours.

The synthesis was done following [48].

This procedure was used for every preparation of the Grignard reagents required.

### 5.2.2 Preparation of 2-(3-methoxyphenethyl)benzonitrile

THF (7ml) was put into a small three-neck flask and TMEDA (5.1mmol) was added. The solution was stirred and cooled to 0°C. 3-methoxybenzylmagnesiumbromide (5.1mmol, 0.3M in THF) was added slowly. While stirring it vigorously, slow addition of a solution of 2-(bromomethyl)benzonitrile (2.56mmol) in THF (2ml) followed.

Reaction mixture was stirred at increasing temperature to rt, followed by TLC and then quenched by H<sub>2</sub>O (10ml) after 20 hours. Extraction of the organic products was performed using CH<sub>2</sub>Cl<sub>2</sub> or EtOAc (3x10ml). It was dried over Na<sub>2</sub>SO<sub>4</sub>, and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

Purification was done by flash chromatography with alumina gel as the stationary phase and hexane:ethylacetate 9:1 as the mobile phase (graduated elution until 6:4).

If a catalytic amount of FeCl<sub>3</sub> was used, it was at first put into the flask and dissolved with THF.

### 5.2.3 Preparation of 3,4-dimethoxybenzylmagnesiumbromide

#### 5.2.3.1 Preparation of 3,4-dimethoxybenzylbromide

DCM (7ml) was put into a flask, cooled to 0°C, 3,4-dimethoxybenzylalcohol (1.0g) was added and followed by the addition of PBr<sub>3</sub> (1.92g). The reaction was followed by TLC and then quenched after 20 hours using ice.

Extraction of the organic products was performed using CH<sub>2</sub>Cl<sub>2</sub> or EtOAc (3x10ml). It was dried over Na<sub>2</sub>SO<sub>4</sub>, and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

The synthesis was modified from [49].

#### 5.2.3.2 Preparation of 3,4-dimethoxybenzylmagnesiumbromide

See 5.2.1

### 5.2.4 Synthesis step 2

2-(3-methoxyphenethyl)benzonitrile (88.0mg) was put into a three-neck flask and dissolved in THF (5ml). The solution was stirred and 3,4-dimethoxybenzylmagnesiumbromide (0.557mmol) and subsequent CuBr.Me<sub>2</sub>S (0.19mmol) were added slowly. Immediately it was refluxed for 24 hours. Afterwards it was cooled to rt and quenched by H<sub>2</sub>O (2.5ml) and H<sub>2</sub>SO<sub>4</sub> (15ml, 15%). This mixture was stirred over night.

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over Na<sub>2</sub>SO<sub>4</sub>, and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

The reaction was done according to [50].

#### 5.2.4.1 With different Grignard reagent

2-(3-methoxyphenethyl)benzonitrile (88.0mg) was put into a three-neck flask and dissolved in toluene (8ml). The solution was stirred and benzylmagnesiumchloride (0.680mmol) was added slowly. Immediately it was refluxed for 24 hours. Afterwards it was cooled to 0°C, adjusted to pH2 with 2M HCl (aqueous) and again refluxed for 2 hours. The reaction mixture was basified with 2M NaOH to pH11.

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$ , and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

#### **5.2.4.2 Trials without methoxy groups**

##### **5.2.4.2.1 Preparation of 2-phenethylbenzonitrile**

THF (15ml) was put into a small three-neck flask and TMEDA (2.56mmol) was added. The solution was stirred and cooled to  $0^\circ\text{C}$ . Benzlmagnesiumbromide solution (2.56mmol, 1.4M in  $\text{Et}_2\text{O}$ ) was added slowly. While stirring vigorously, 2-(bromomethyl)benzonitrile (1.28mmol) was then slowly added. The reaction mixture was stirred at increasing temperature to rt, for 20 hours and was quenched by  $\text{H}_2\text{O}$  (10ml).

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$ , and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

Purification was done by flash chromatography with silica gel as the stationary phase and hexane:ethylacetate 9:1 as the mobile phase.

If a catalytic amount of  $\text{FeCl}_3$  was used, it was at first put into the flask and dissolved with THF.

##### **5.2.4.2.2 Coupling of the nitrile with the Grignard reagent**

2-phenethylbenzonitrile (0.322mmol) was put into a three-neck flask and dissolved in THF (3.5ml). The solution was stirred and benzylmagnesiumbromide (0.290mmol) and subsequent  $\text{CuBr}\cdot\text{Me}_2\text{S}$  (in a catalytic amount) were added slowly. Immediately after this, it was refluxed for 24 hours. Afterwards it was cooled to rt and quenched by  $\text{H}_2\text{O}$  (2.5ml) and  $\text{H}_2\text{SO}_4$  (15ml, 15%). This mixture was stirred over night.

Extraction of the organic products was performed using EtOAc (3x10ml). It was dried over  $\text{Na}_2\text{SO}_4$ , and further by using rotary evaporator and a vacuum pump. The products were then determined by NMR spectroscopy.

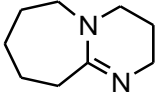
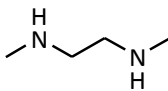
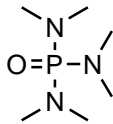

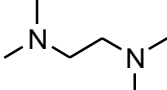
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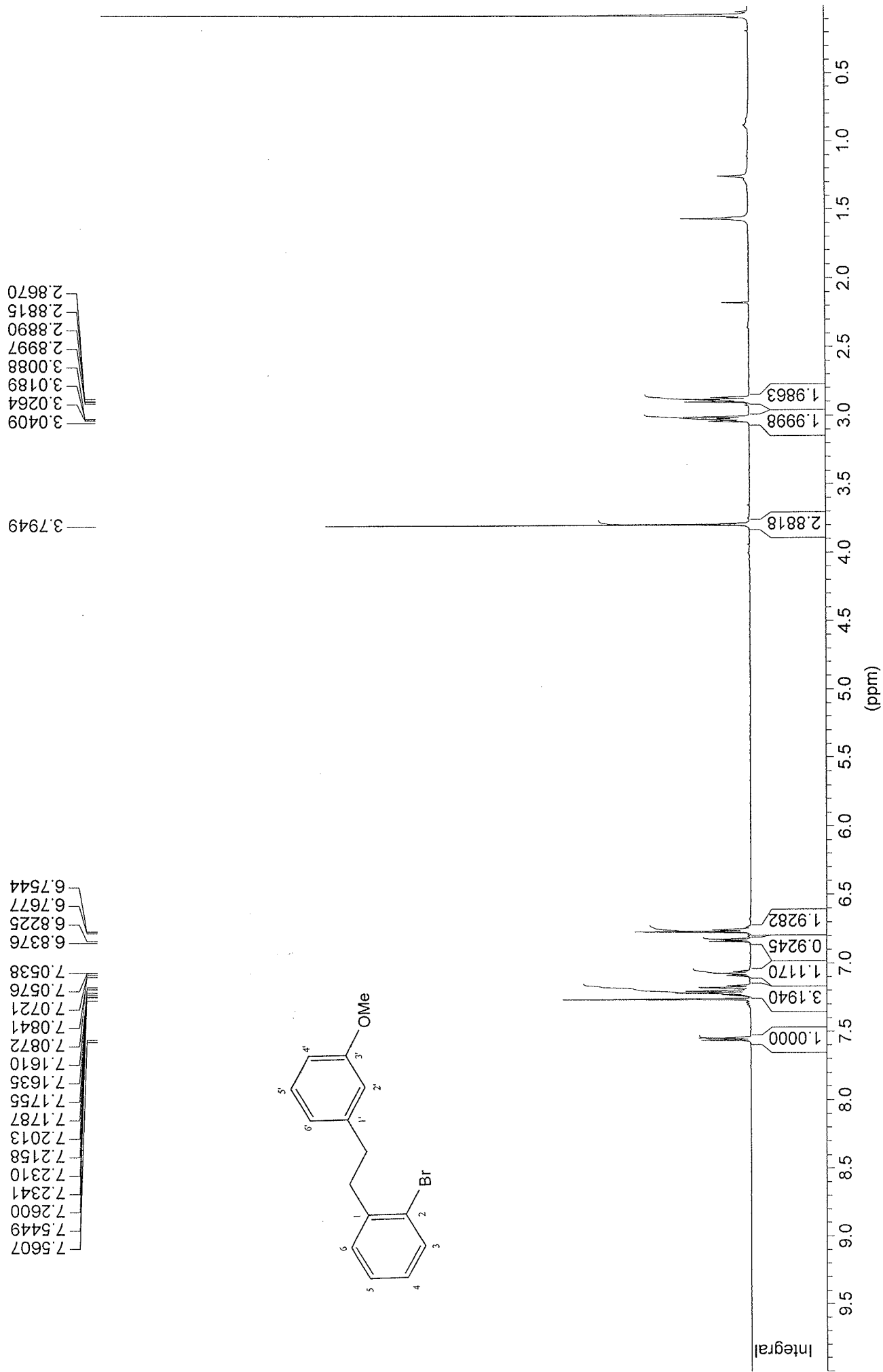
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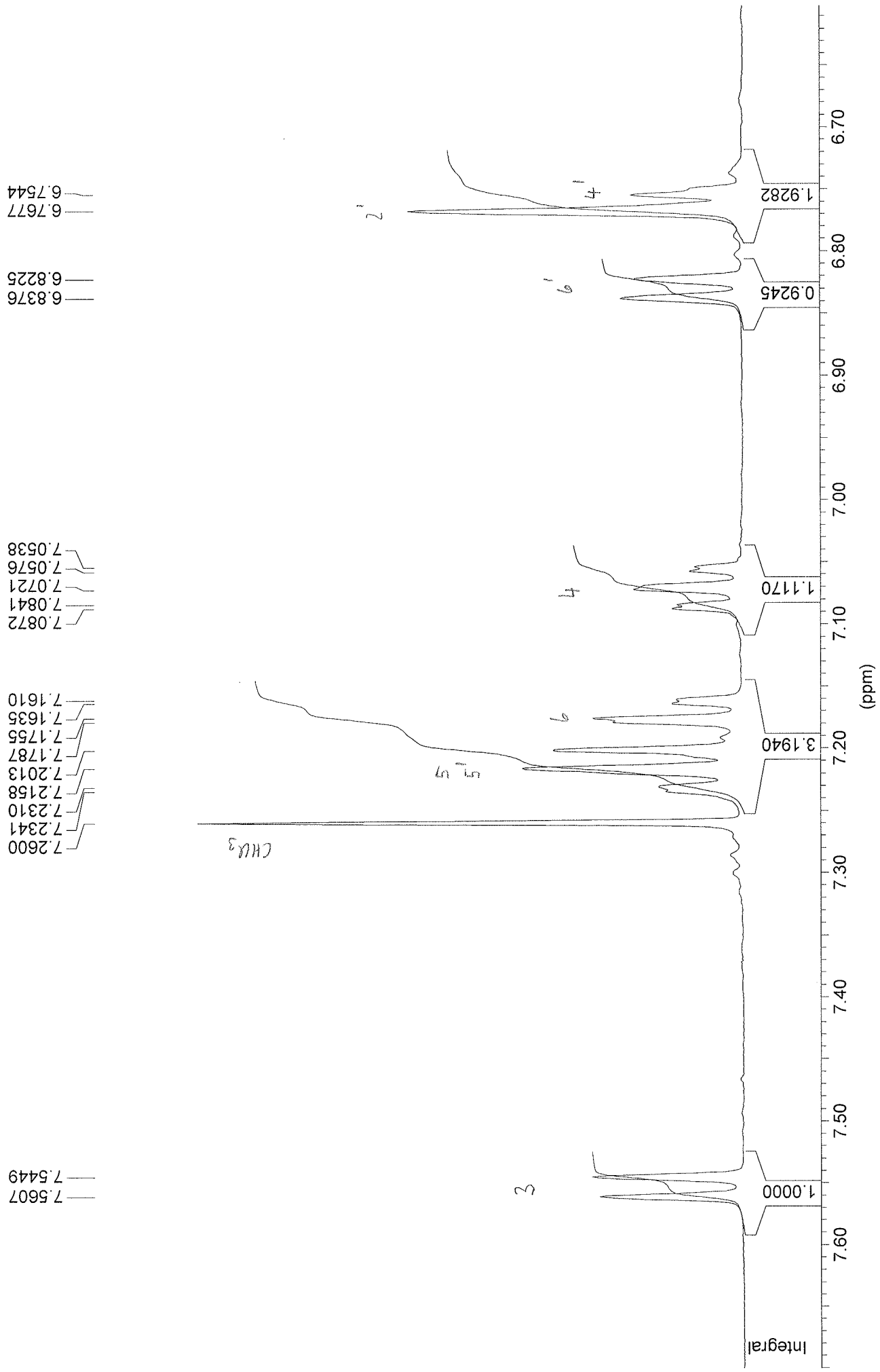
DBU	diazabicycloundecen (a non-nucleophilic base)		DBU
DCM	dichloromethane		
DMEDA	N,N'-dimethylethylenediamine		DMEDA
DMP	Dess-Martin periodinane		
E	electrophile		
equ.	equivalent		
Et <sub>2</sub> O	diethylether		
HMPA	hexamethylphosphoramide		HMPA
HMTA	hexamethylenetetramine		HMTA
M	metal		
MeLi	methyllithium		
nBuLi	normal butyllithium		
nHexLi	normal hexyllithium		
PhLi	phenyllithium		
R	residue		
rt	room temperature		
SAR	structure-activity relationship		
sBuLi	secondary butyllithium		
tBuLi	tertiary butyllithium		
temp.	temperature		
THF	tetrahydrofuran		
TMEDA	N, N, N', N'-tetramethylethylenediamine		TMEDA
X	halide		

## **8 SUPPLEMENT**

### **8.1 NMR-spectra**



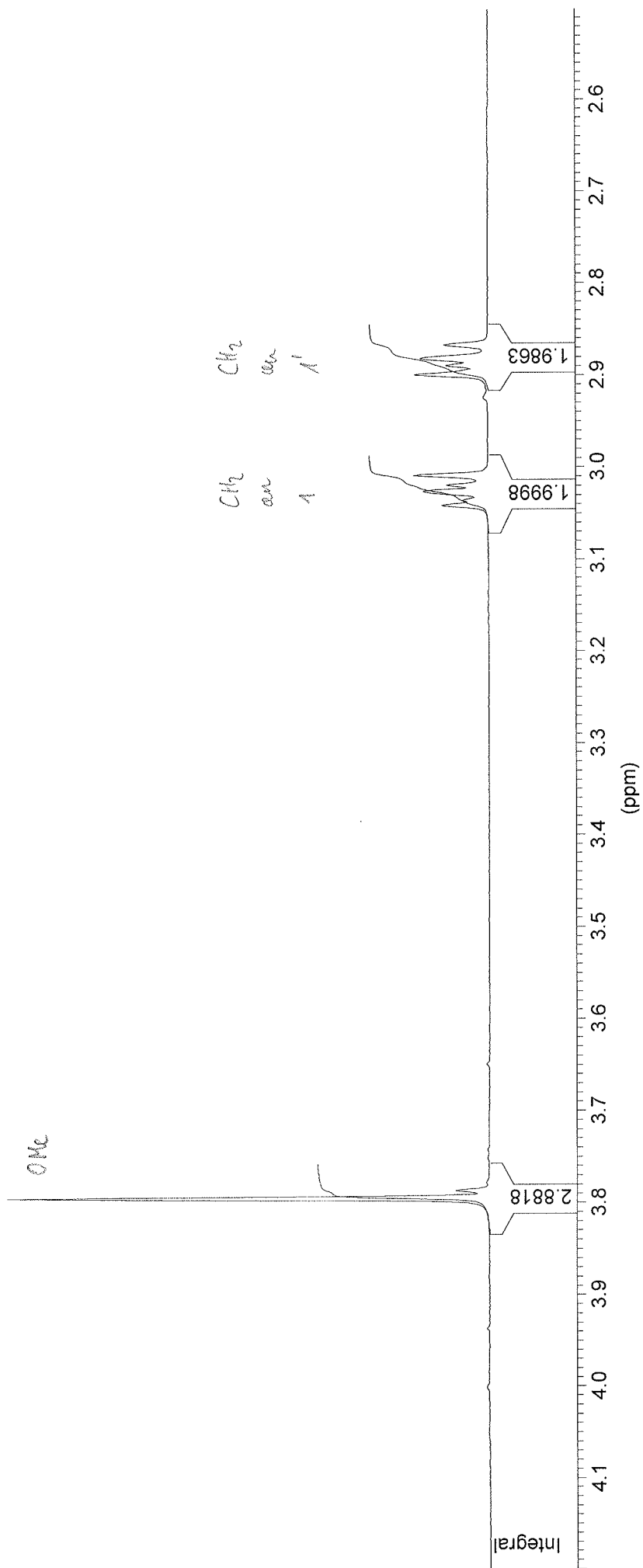


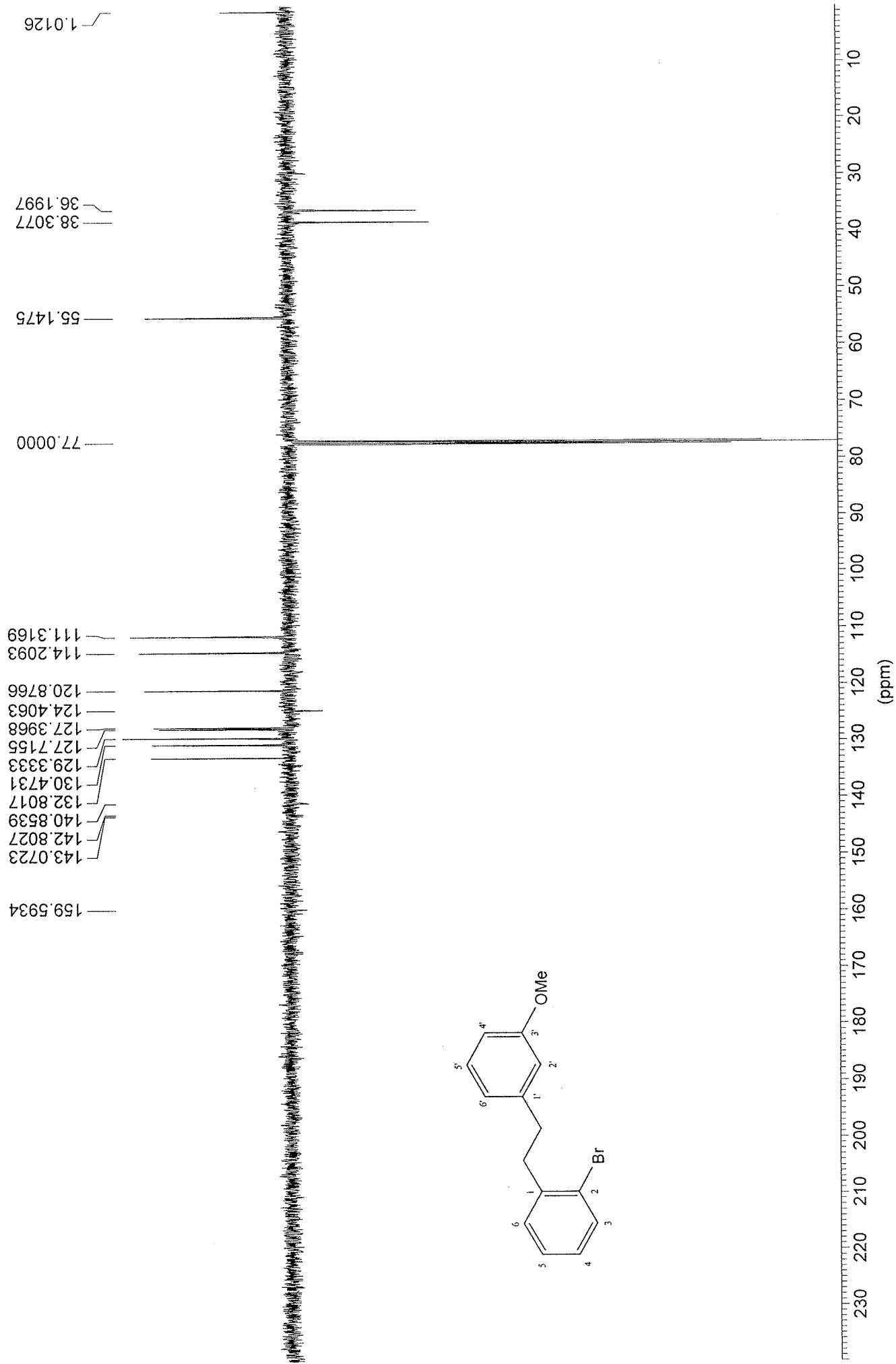


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2.8670

3.0409  
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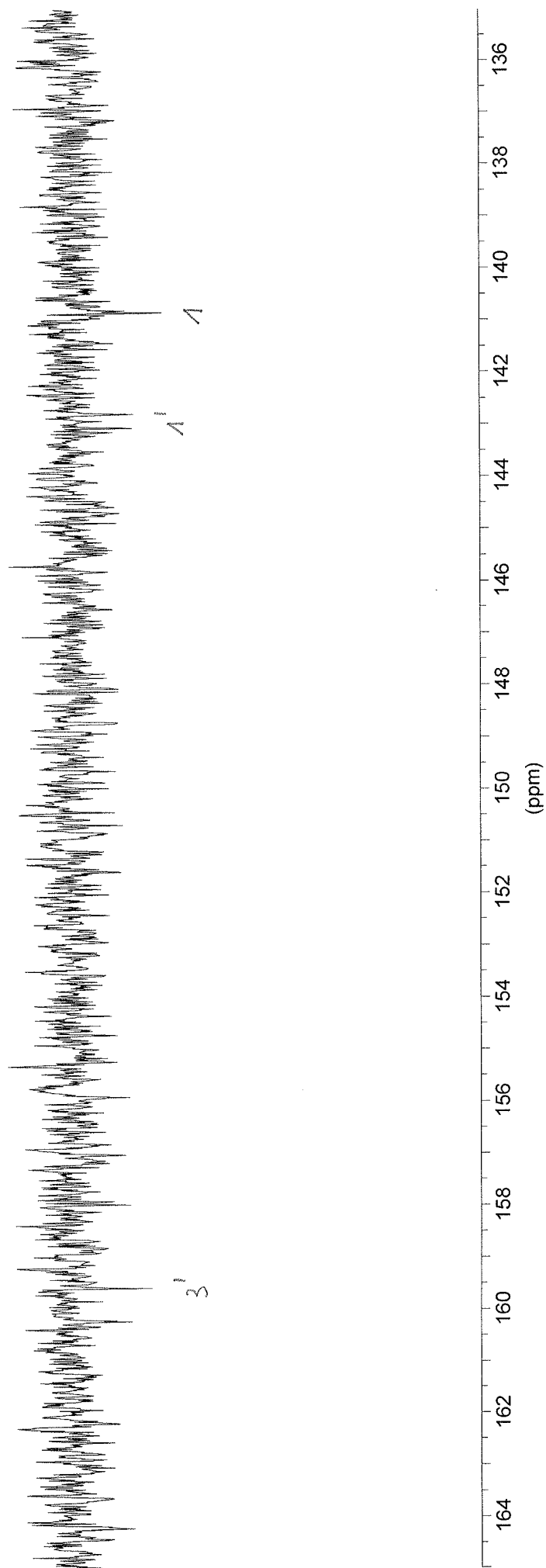
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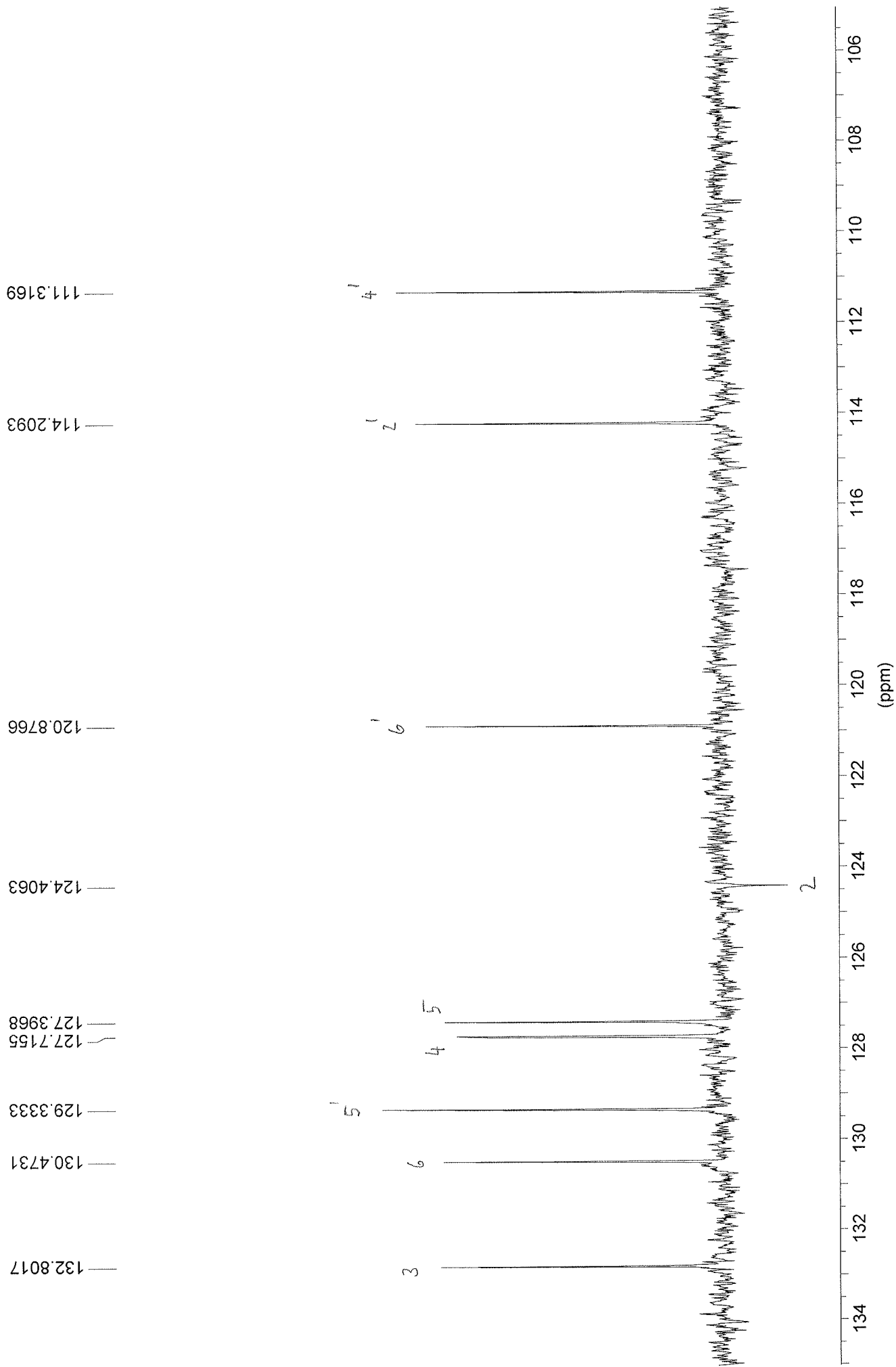


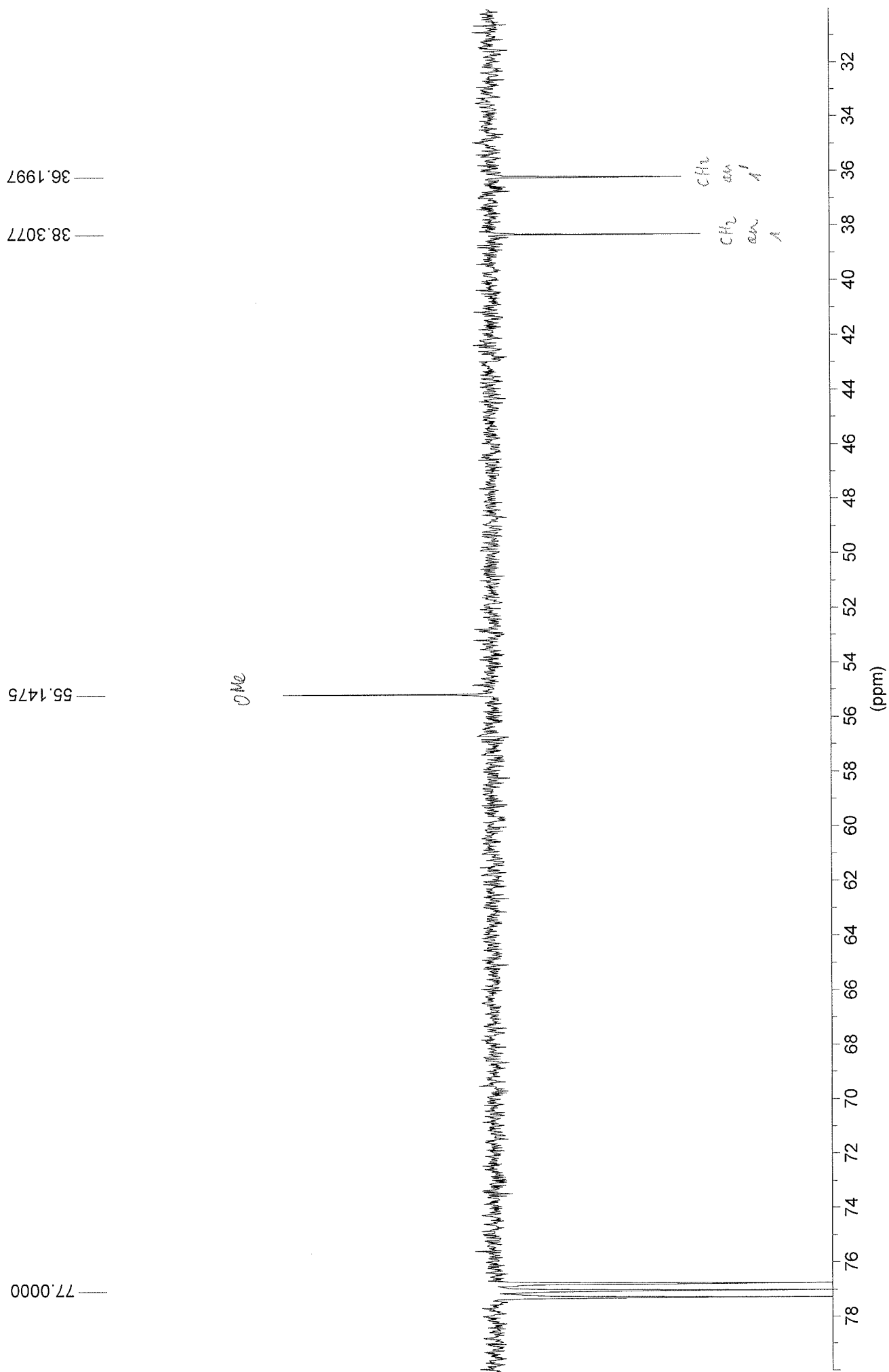


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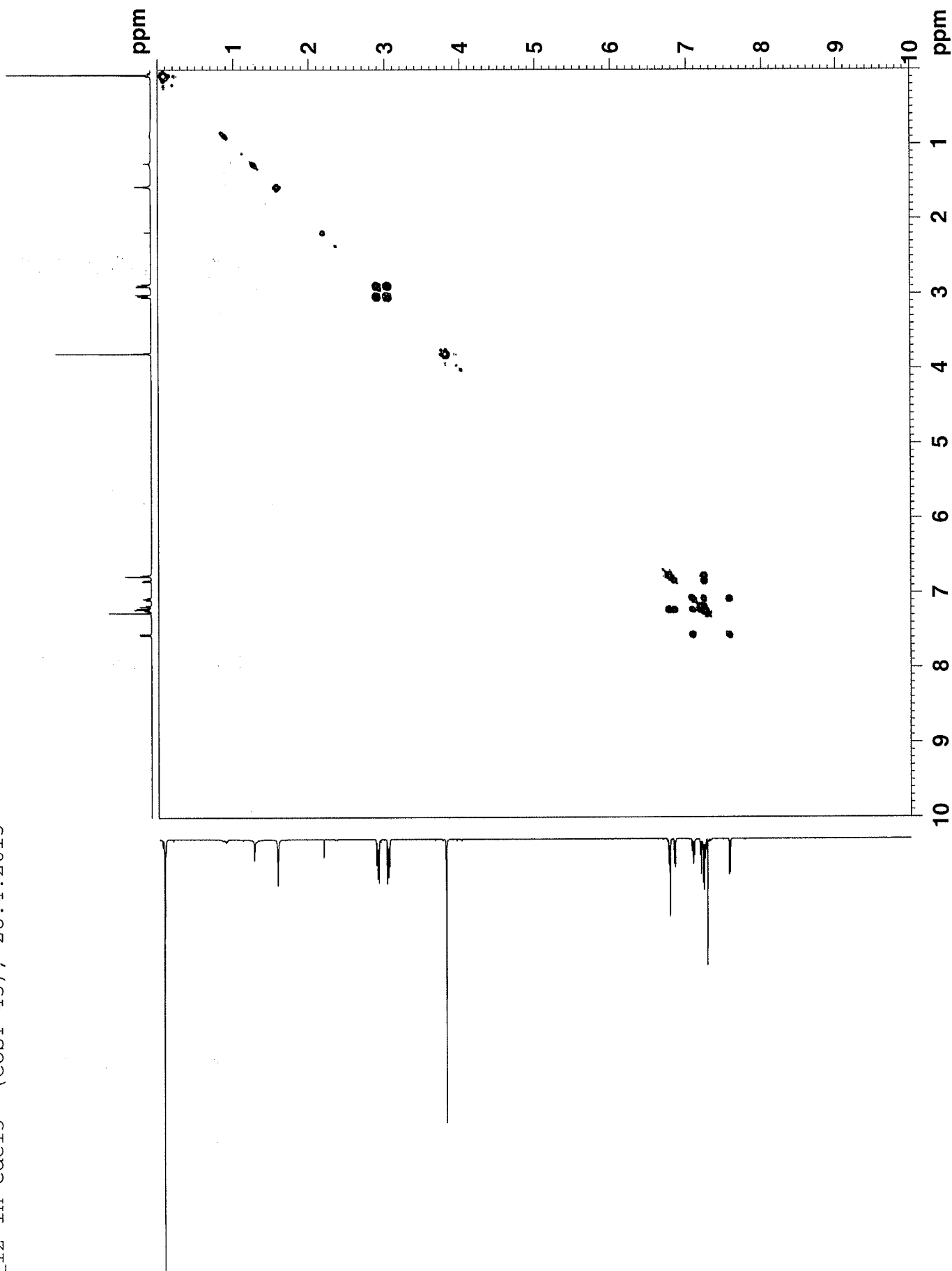
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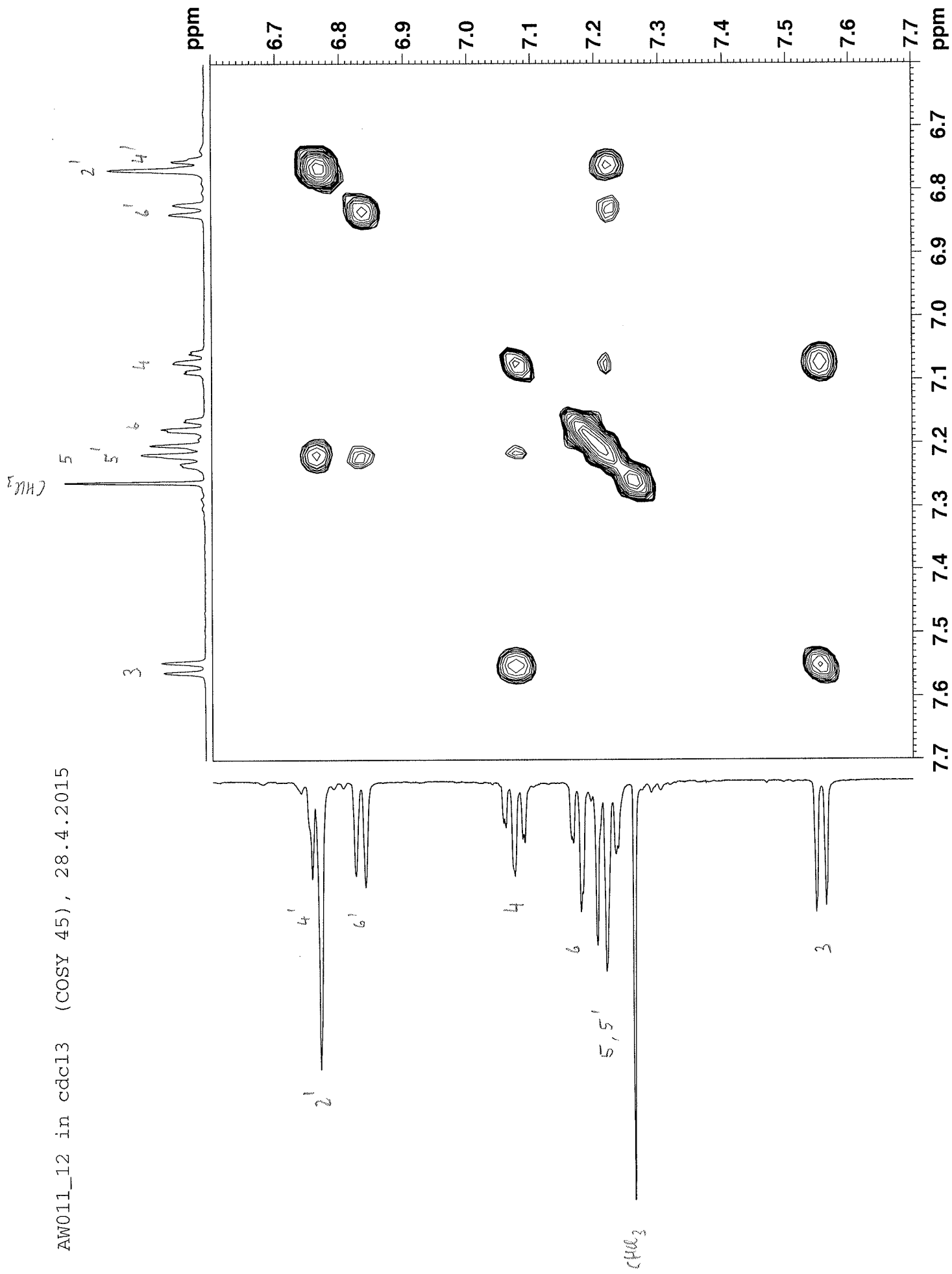


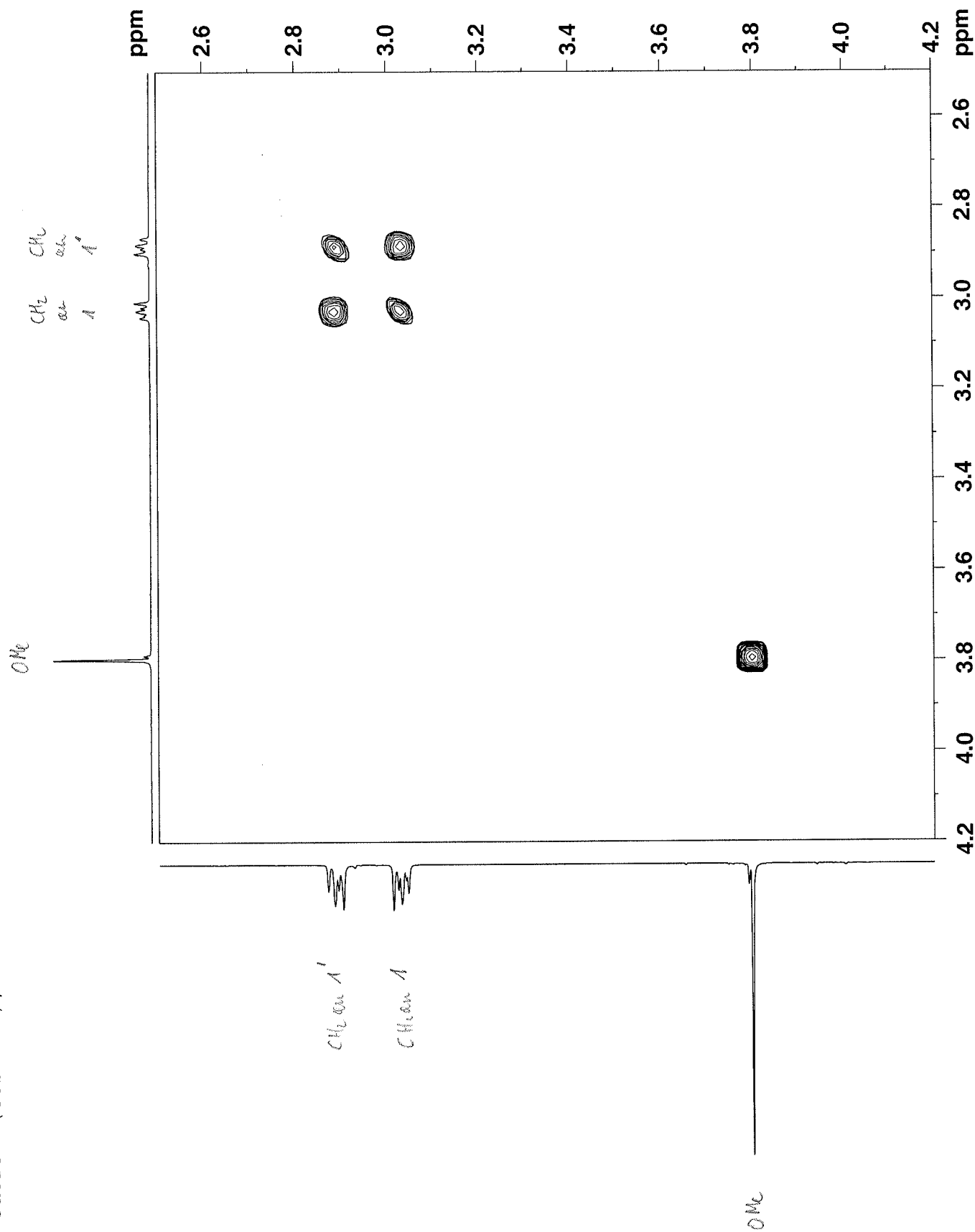


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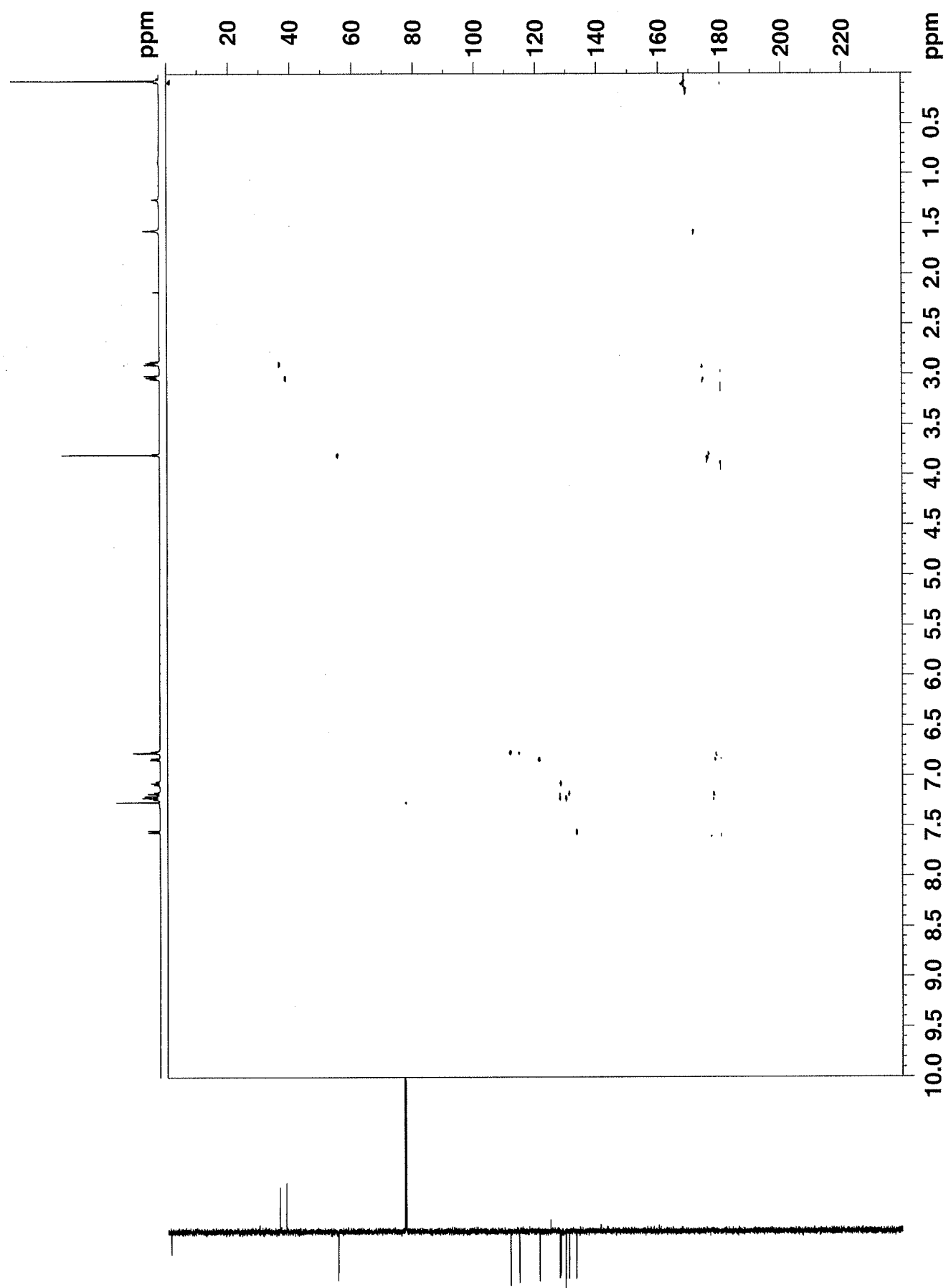


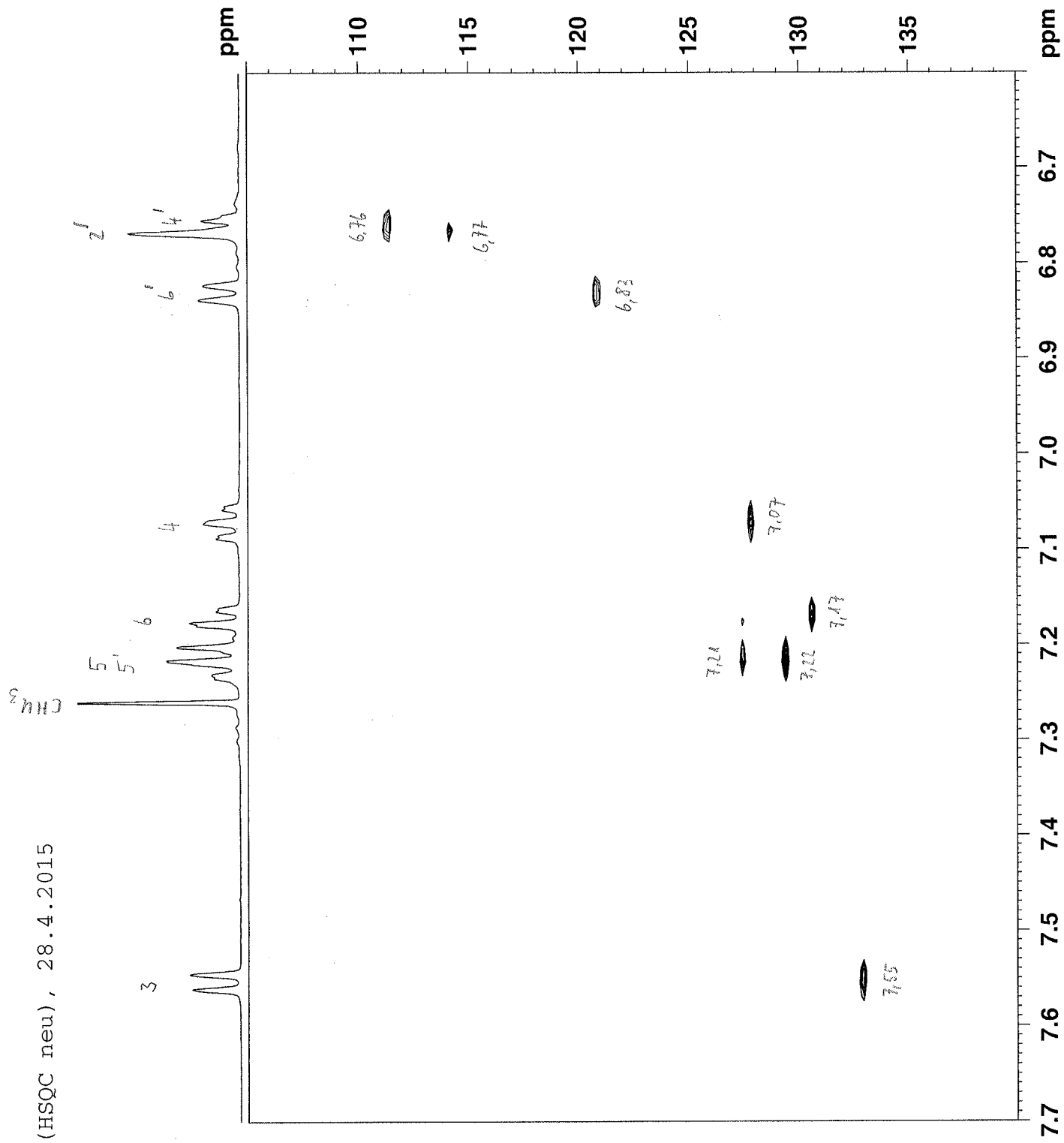




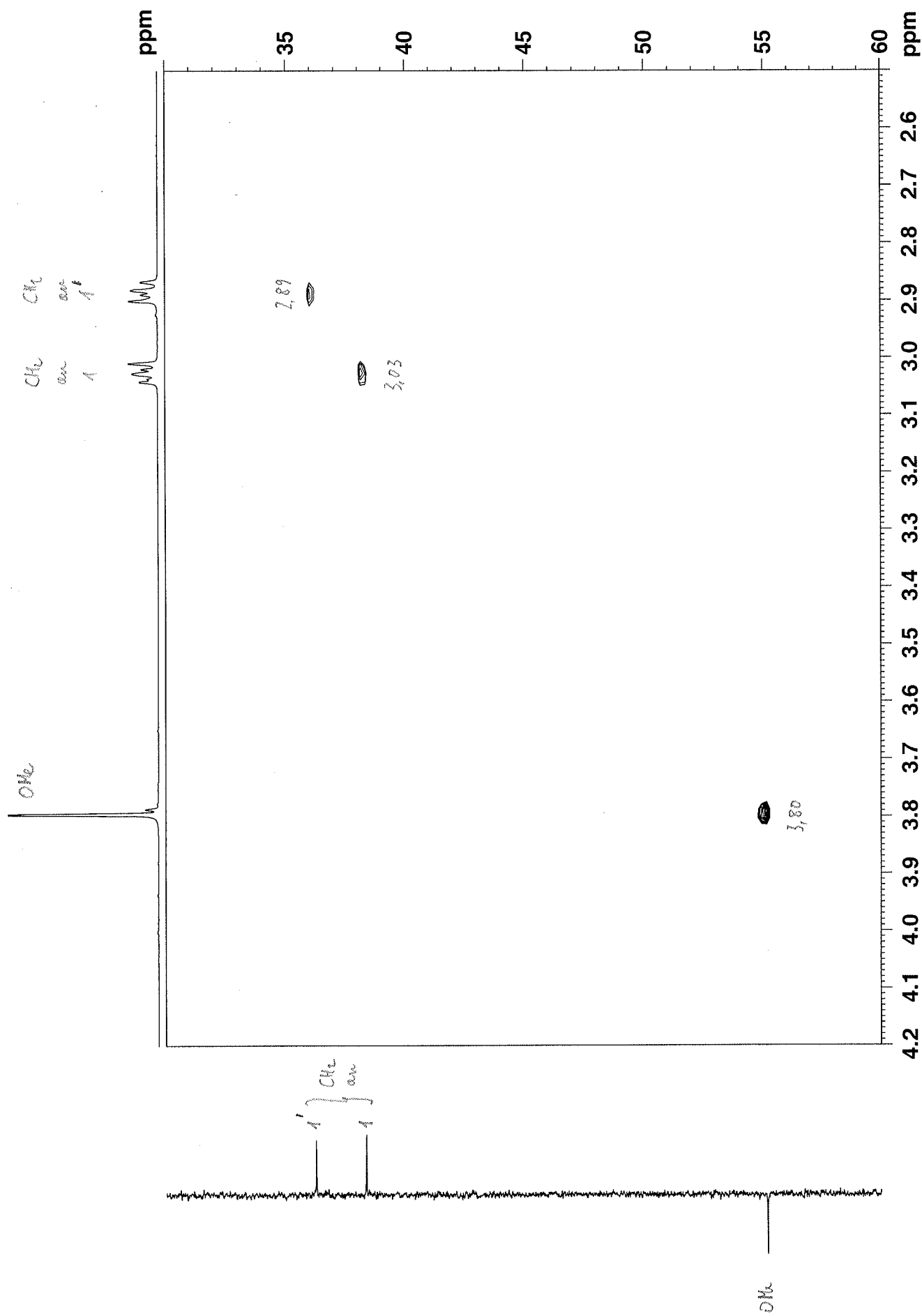


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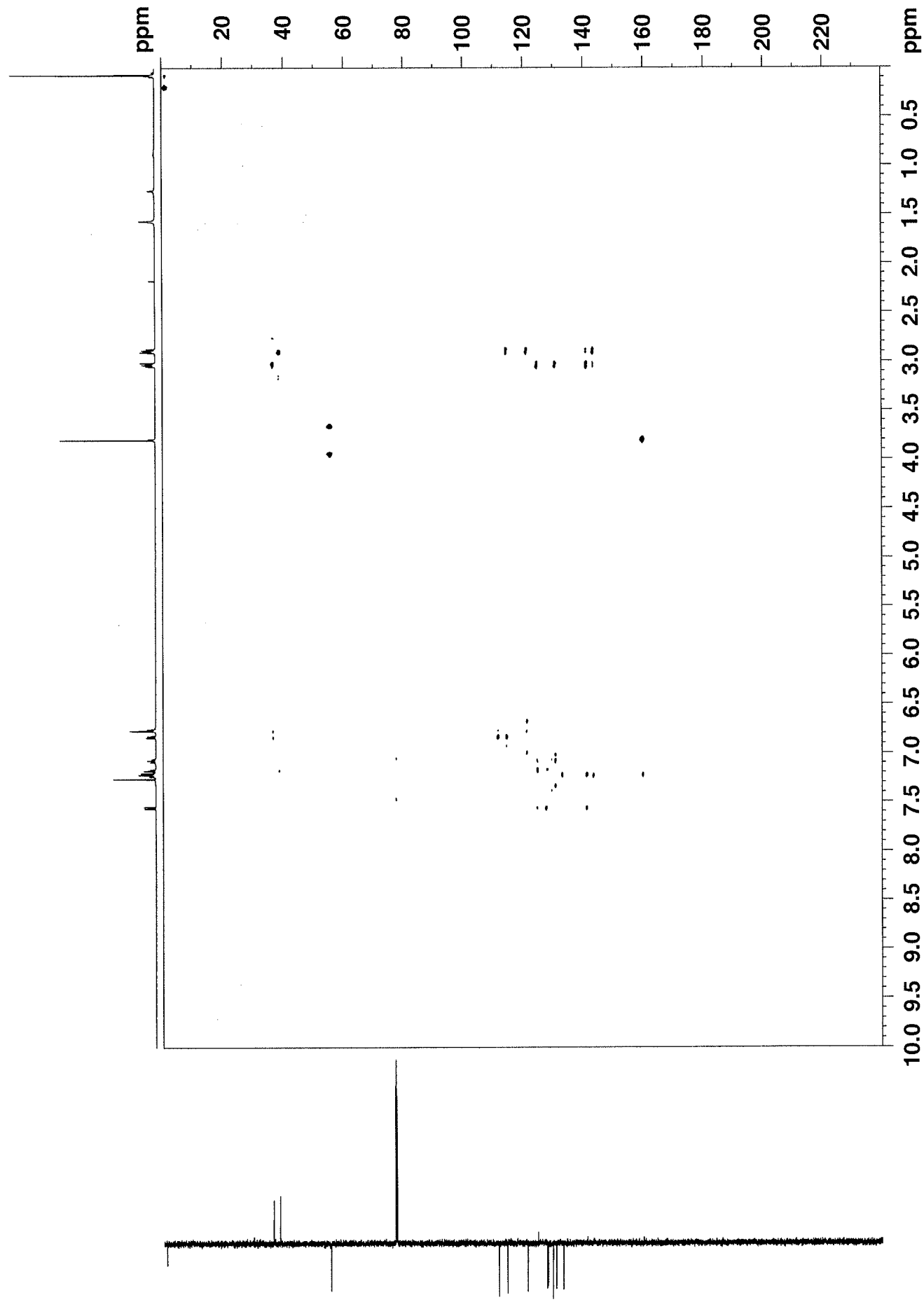


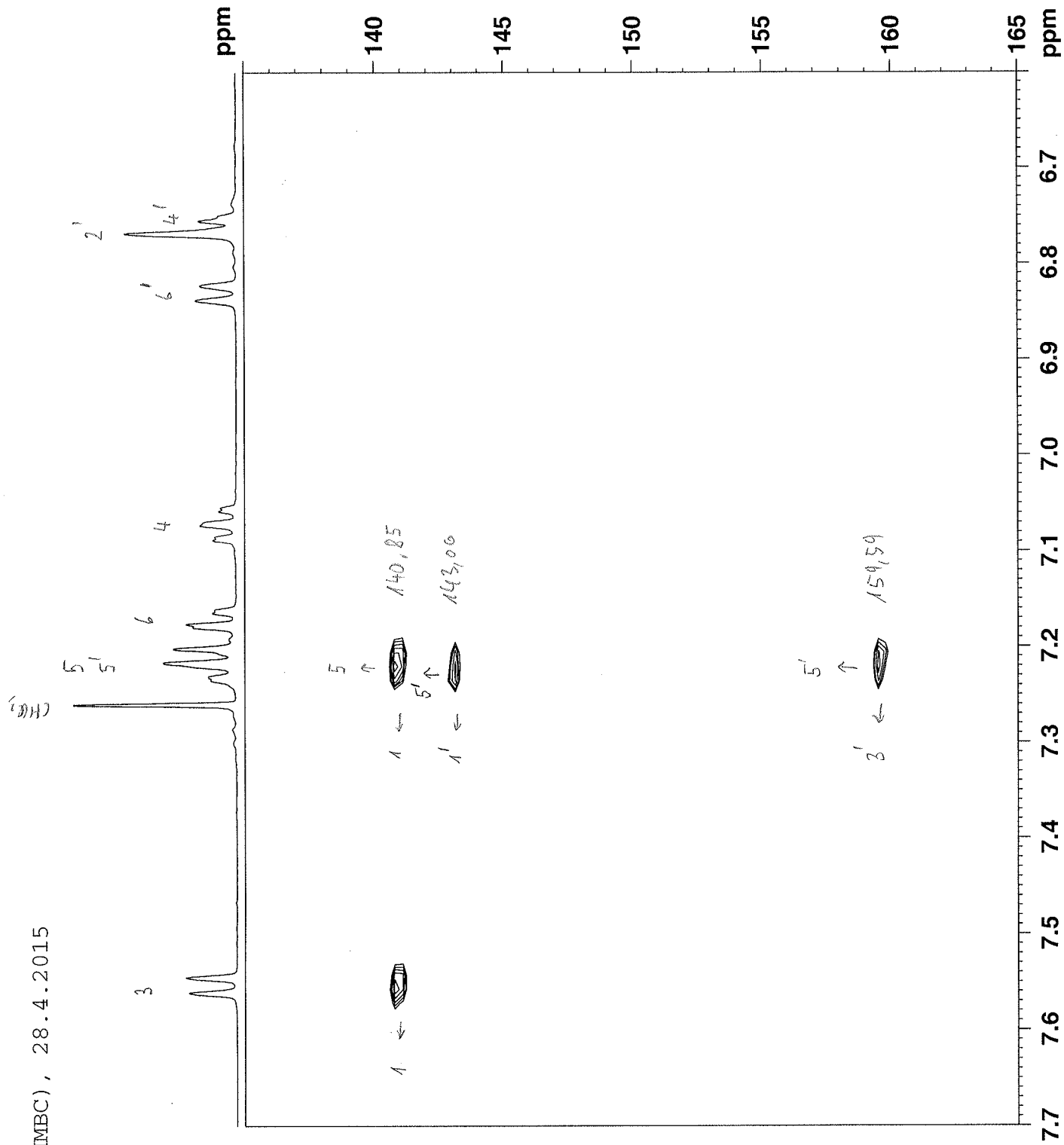


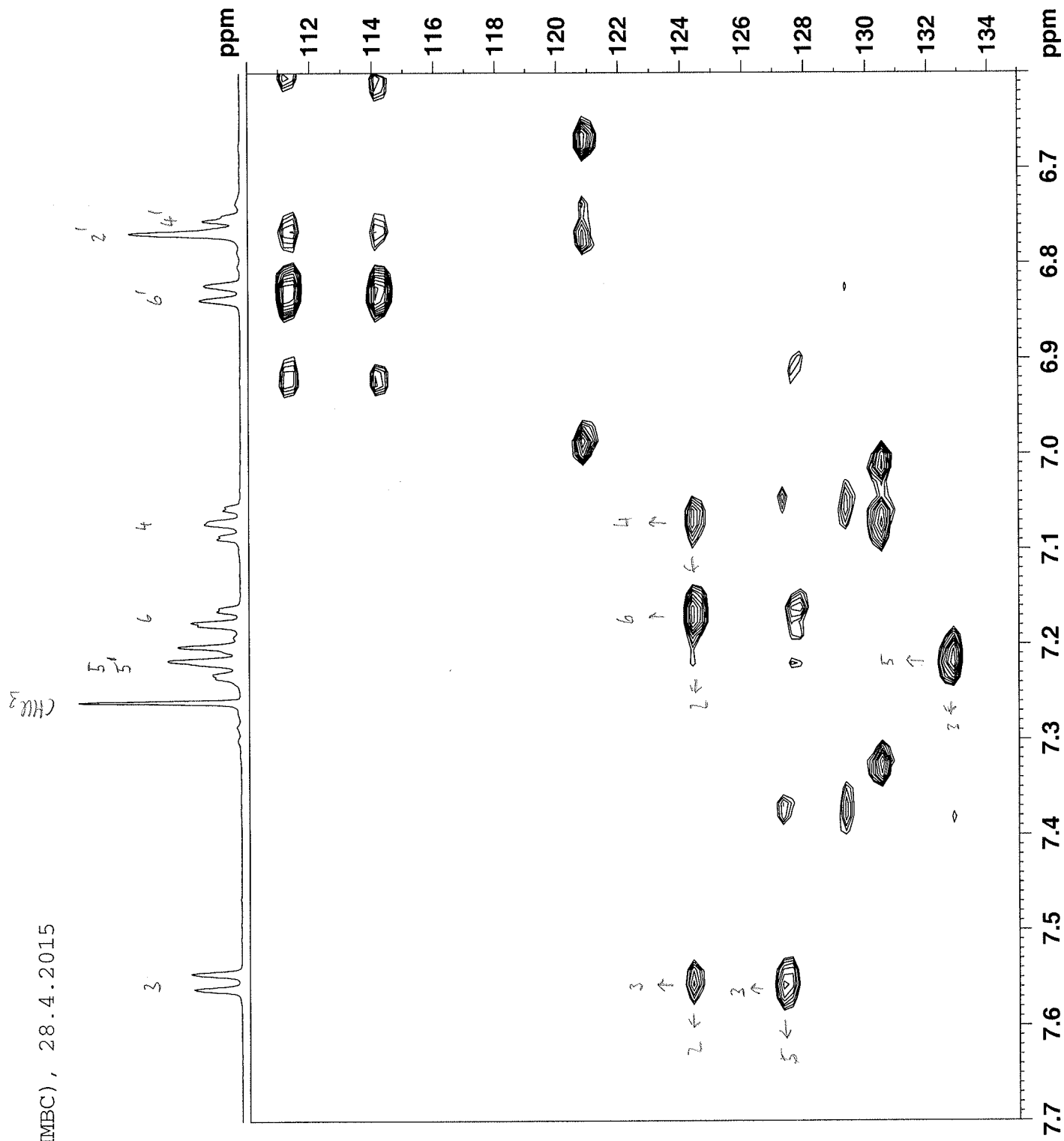
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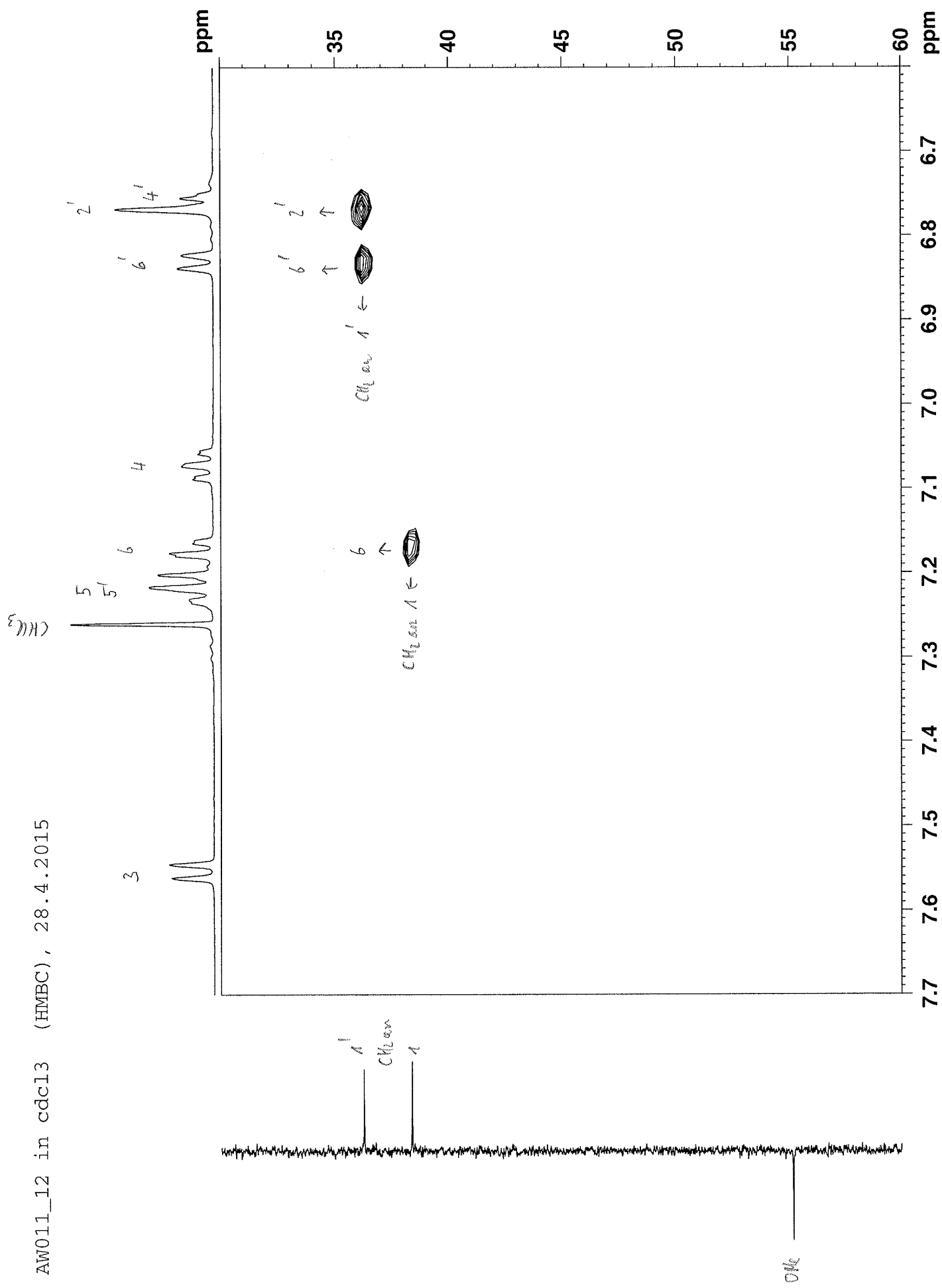
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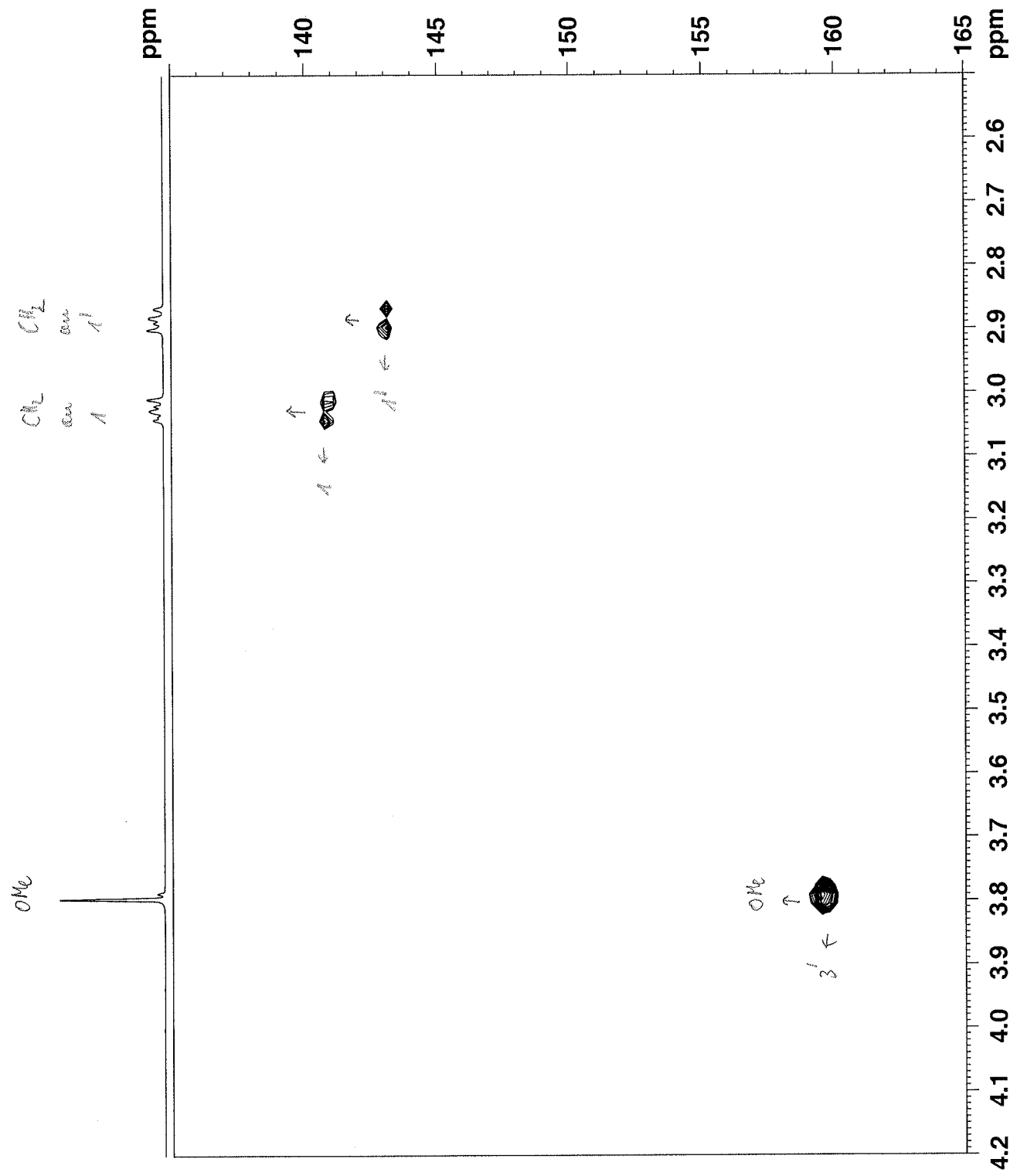


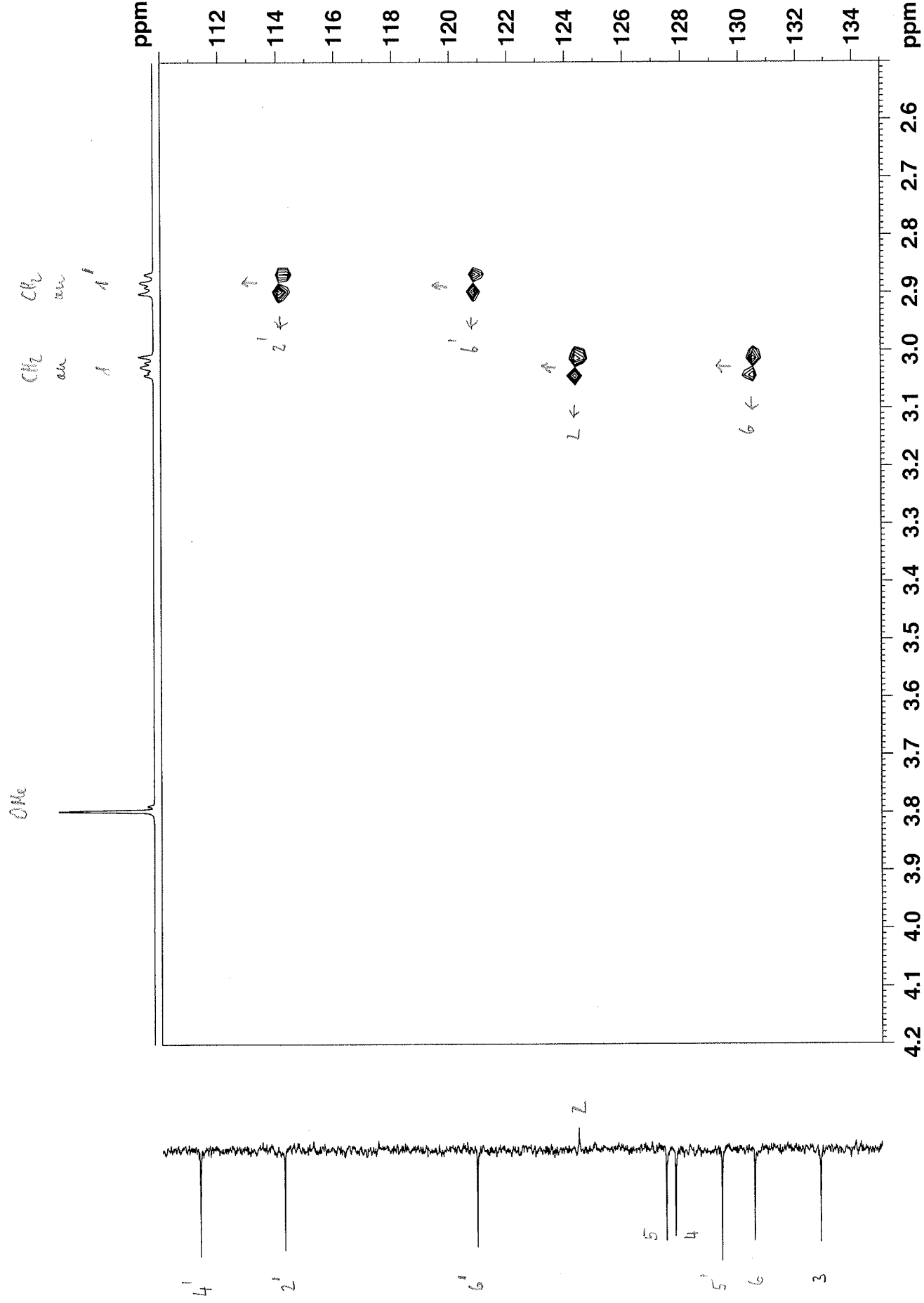


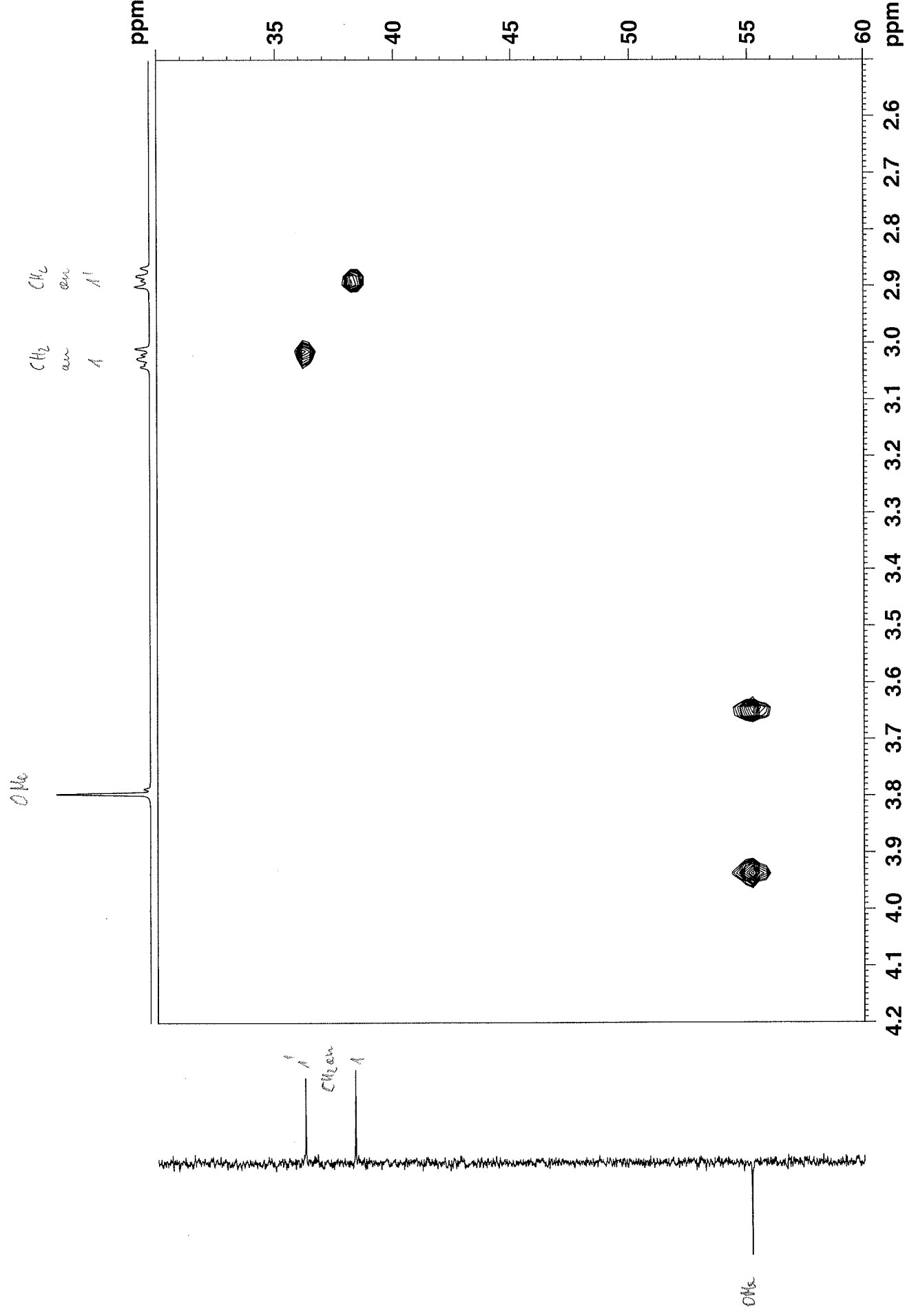


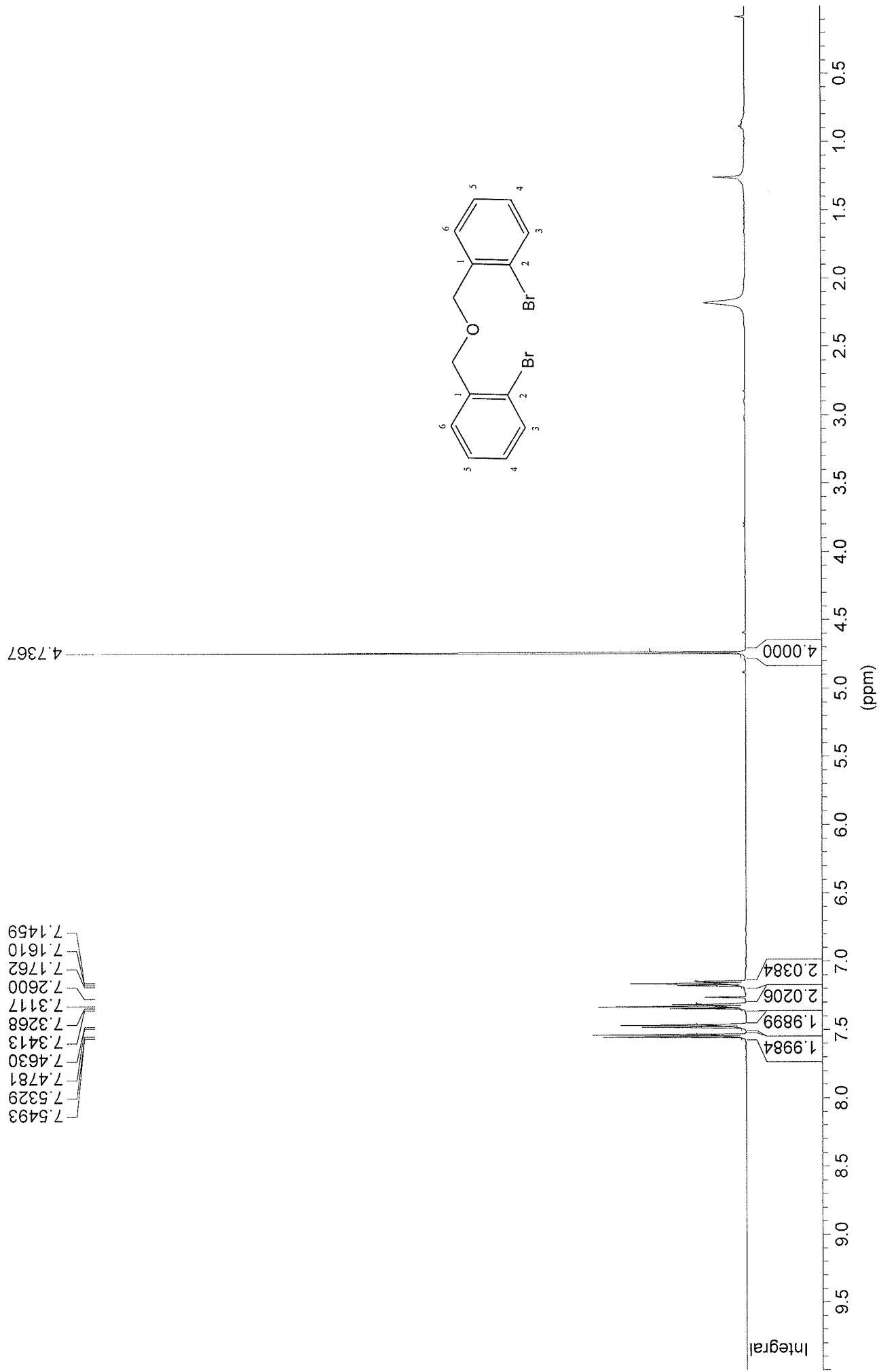


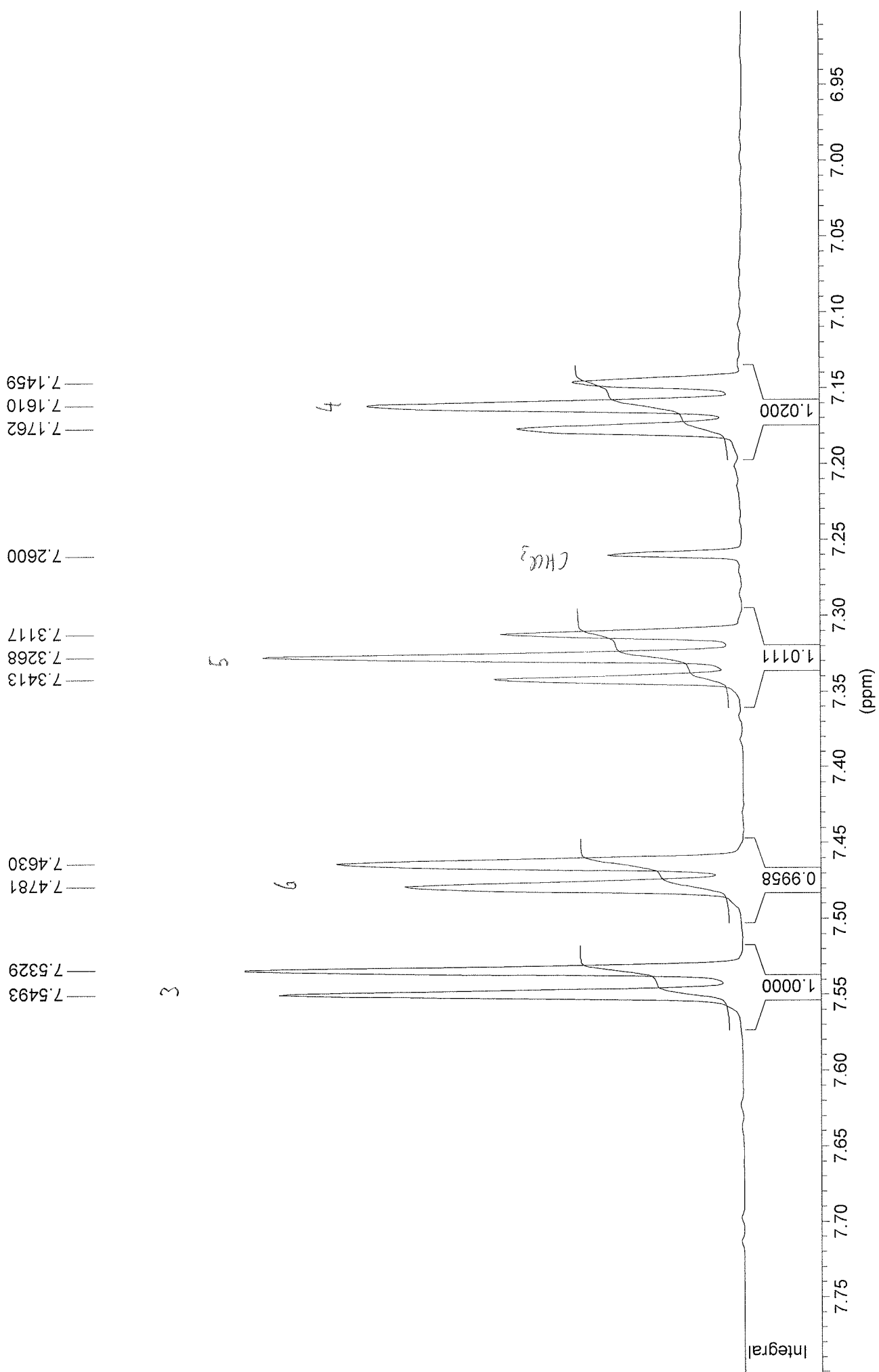


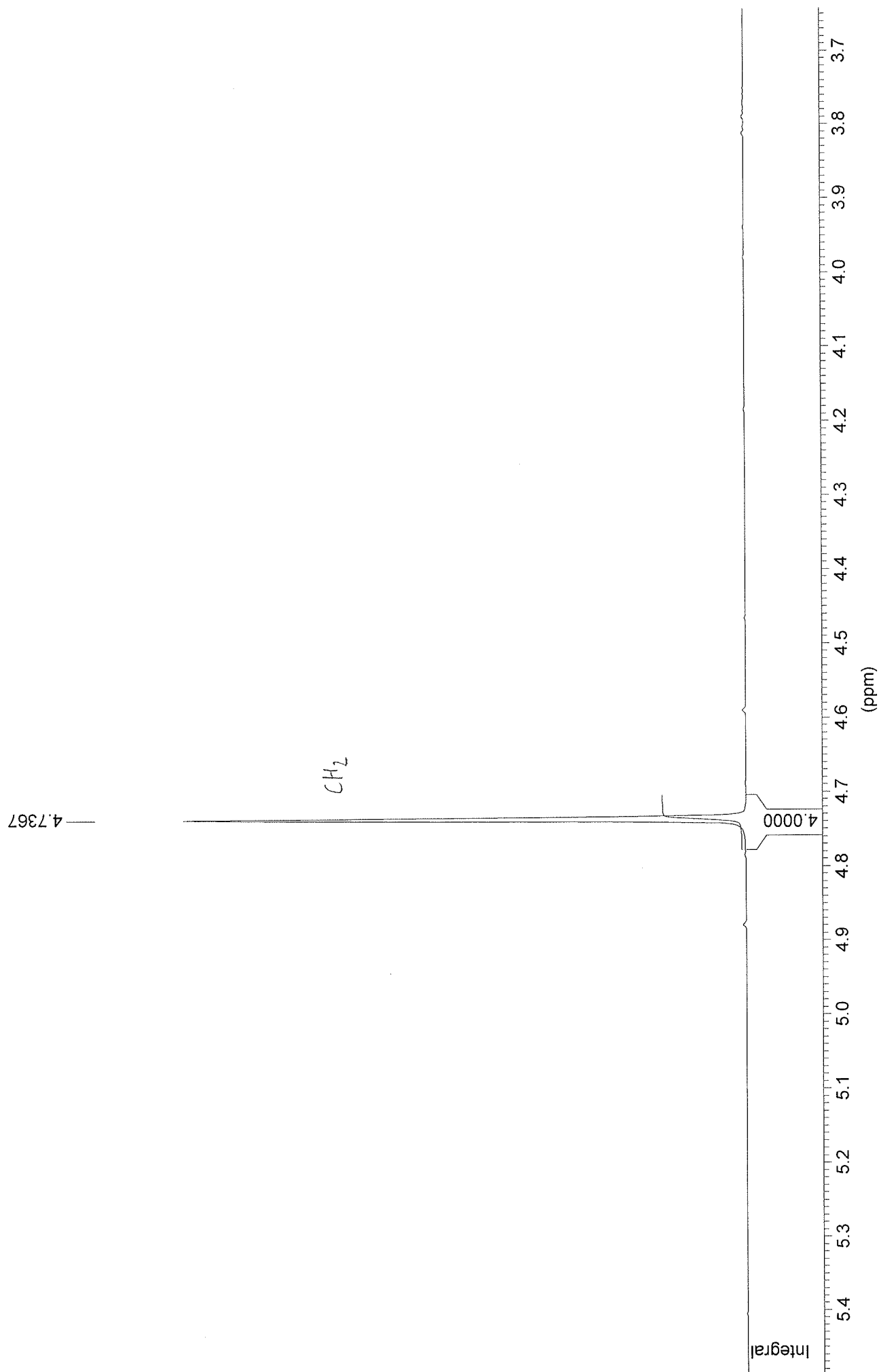


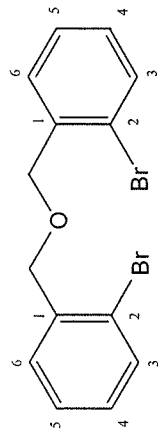








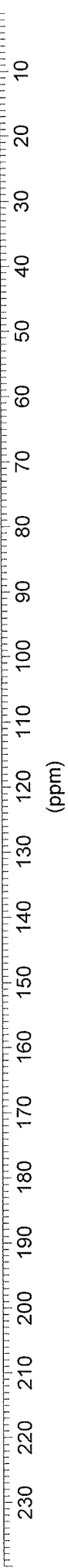




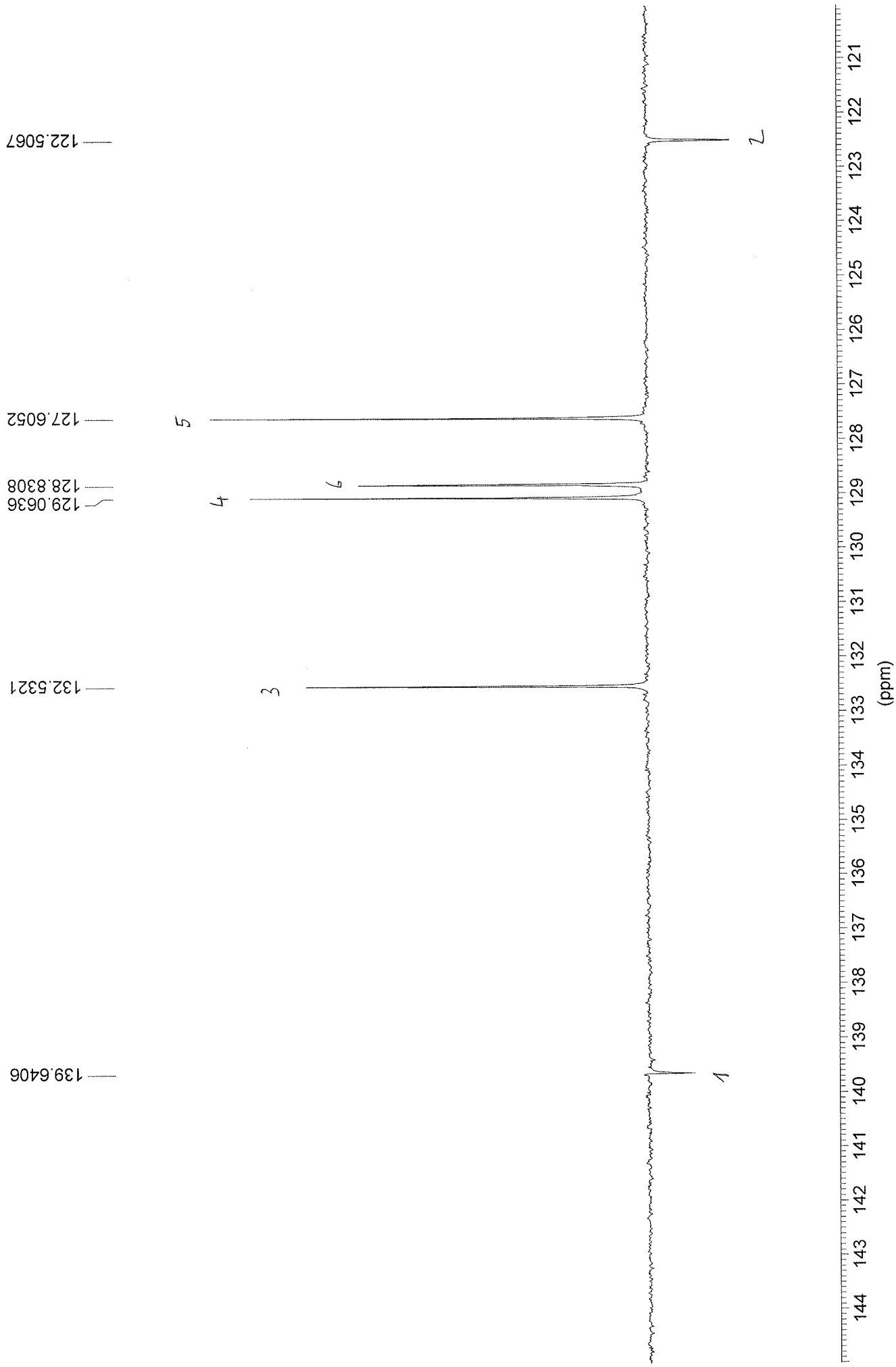
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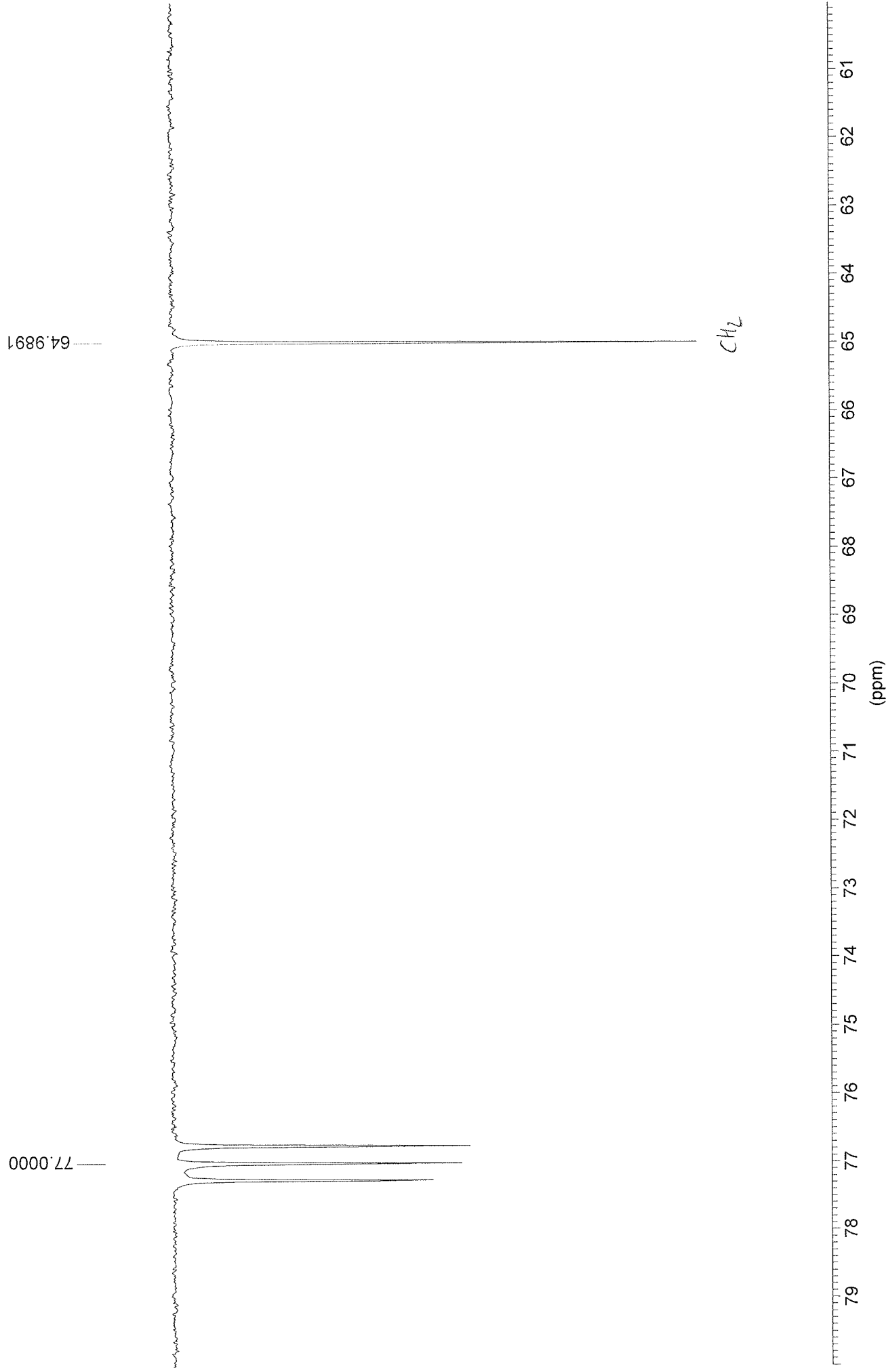
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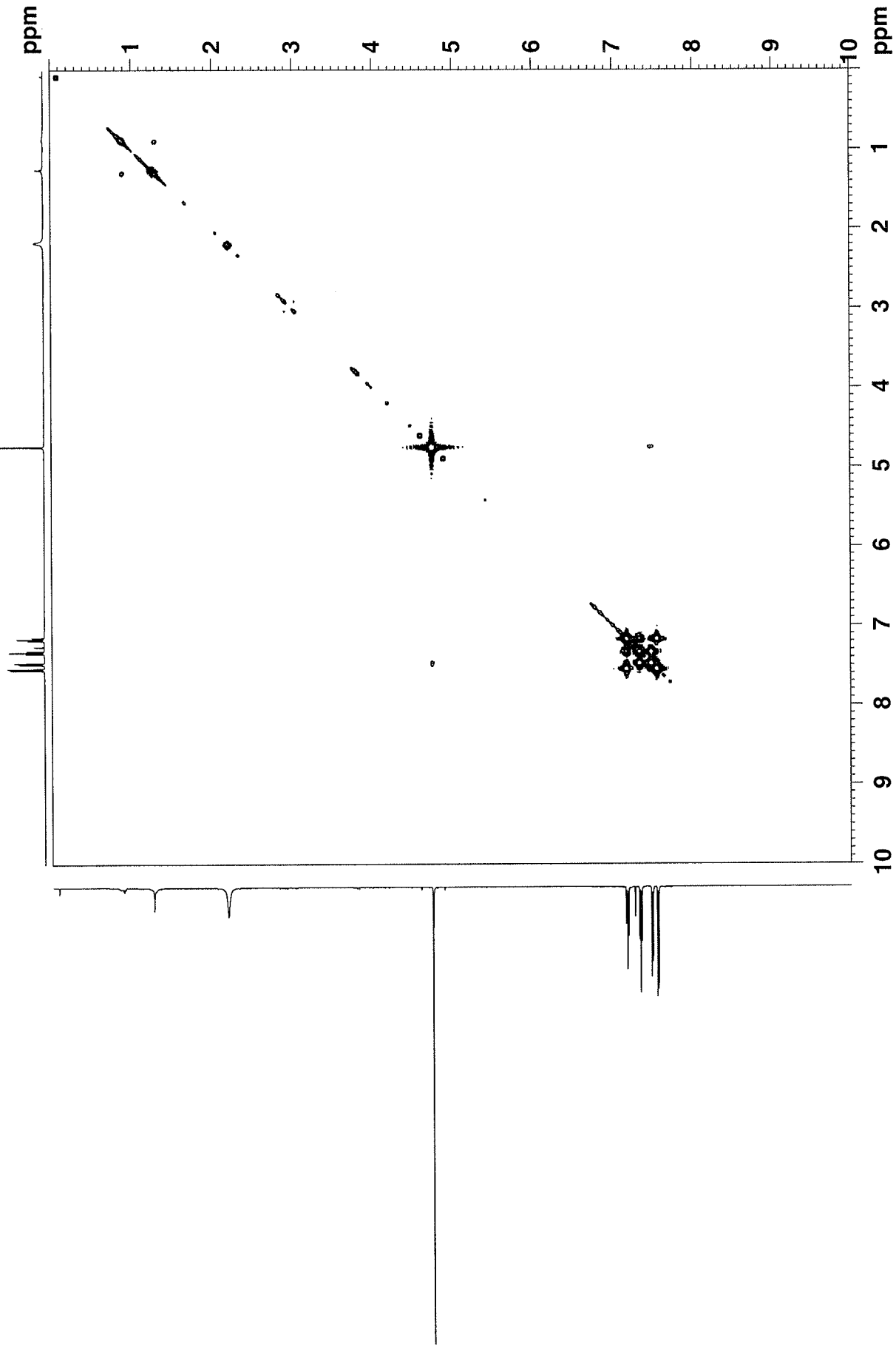


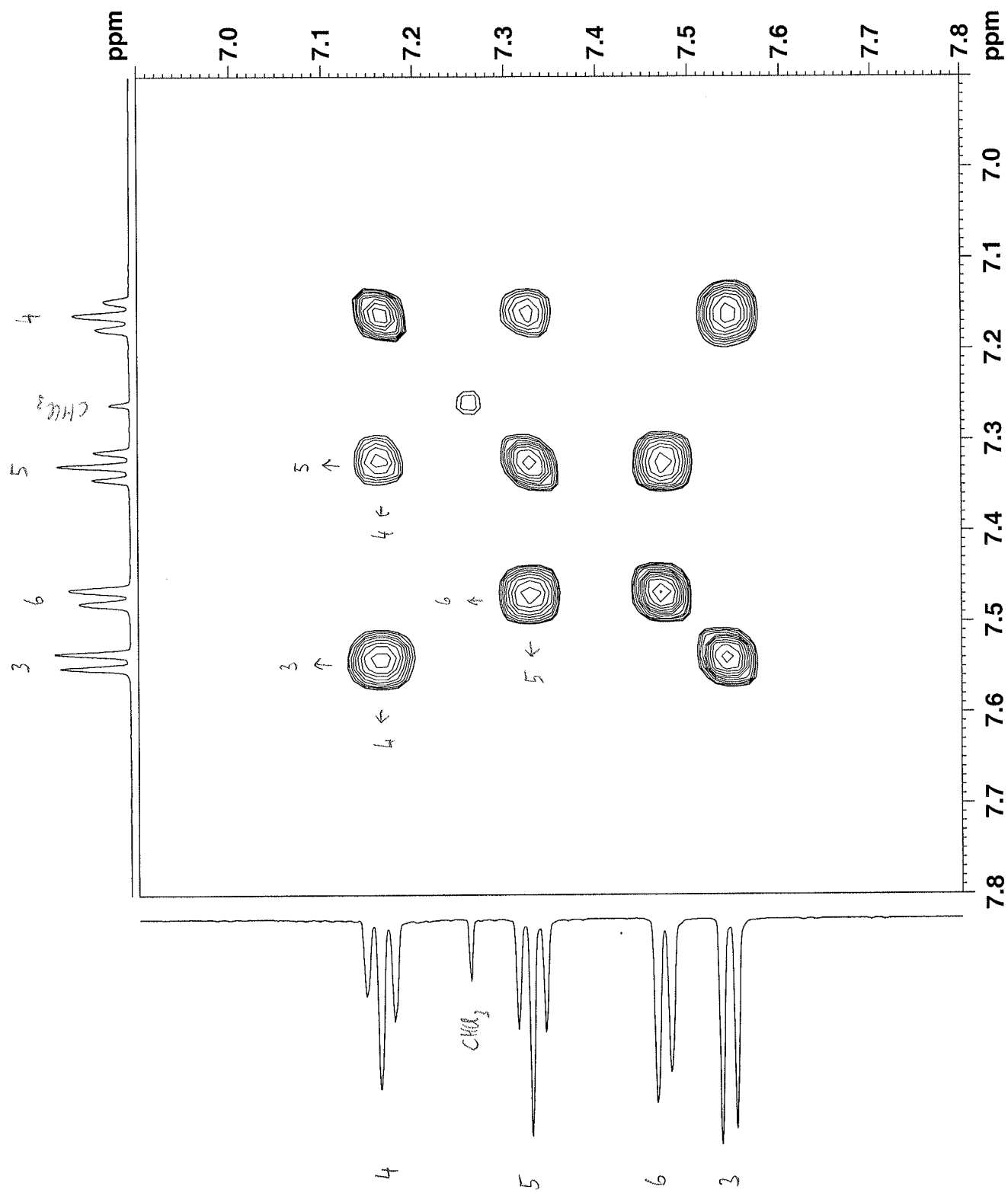


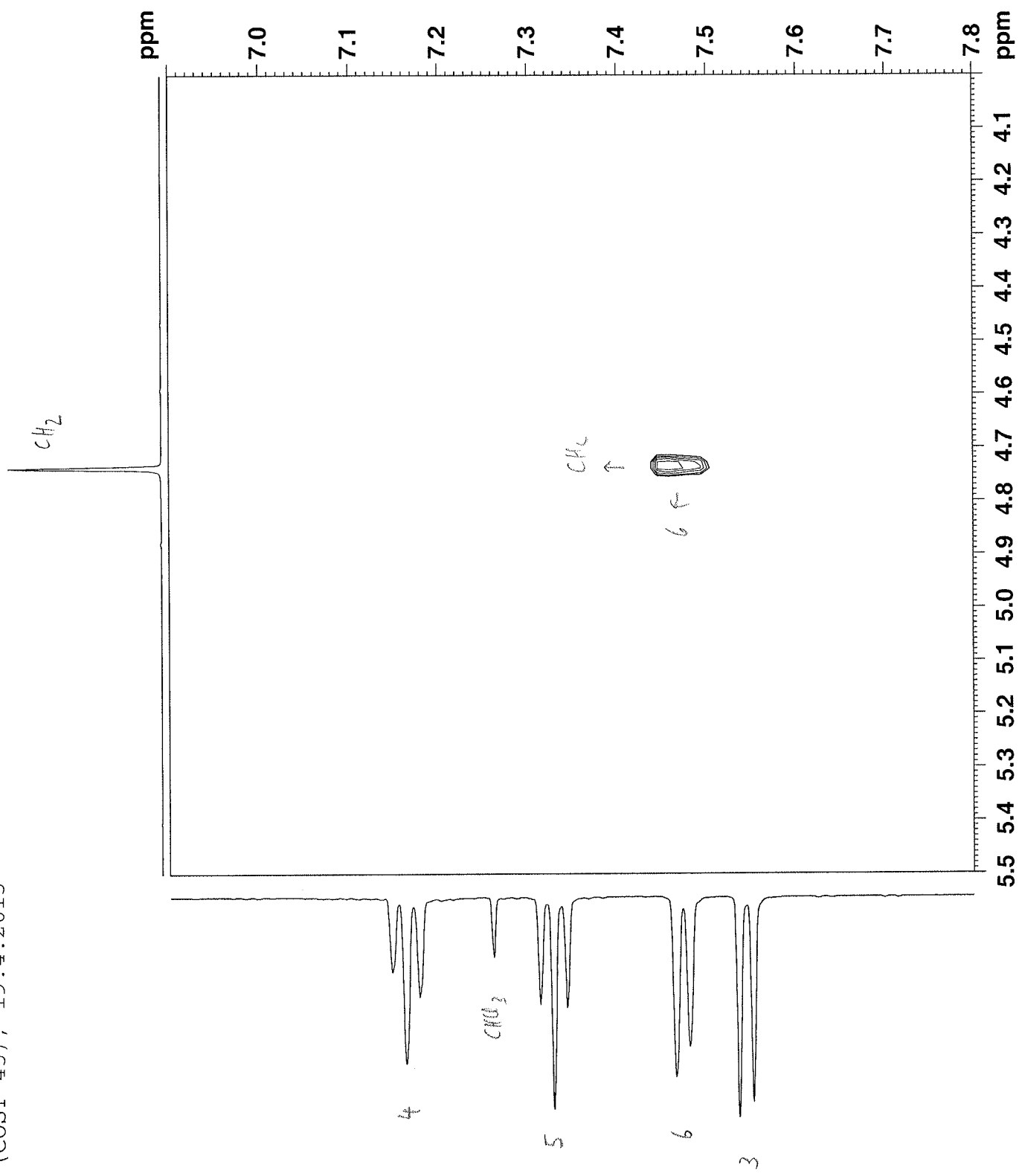




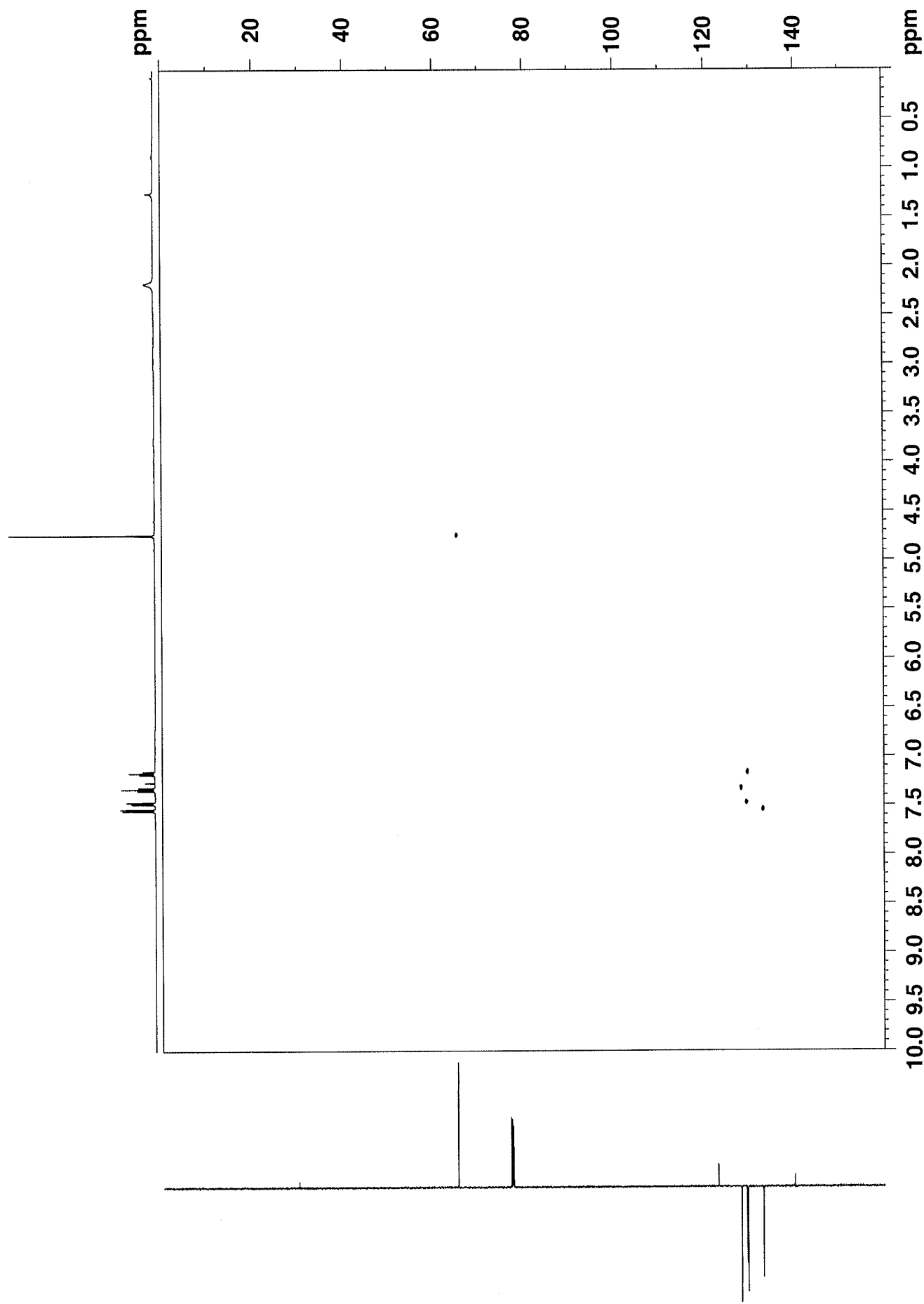
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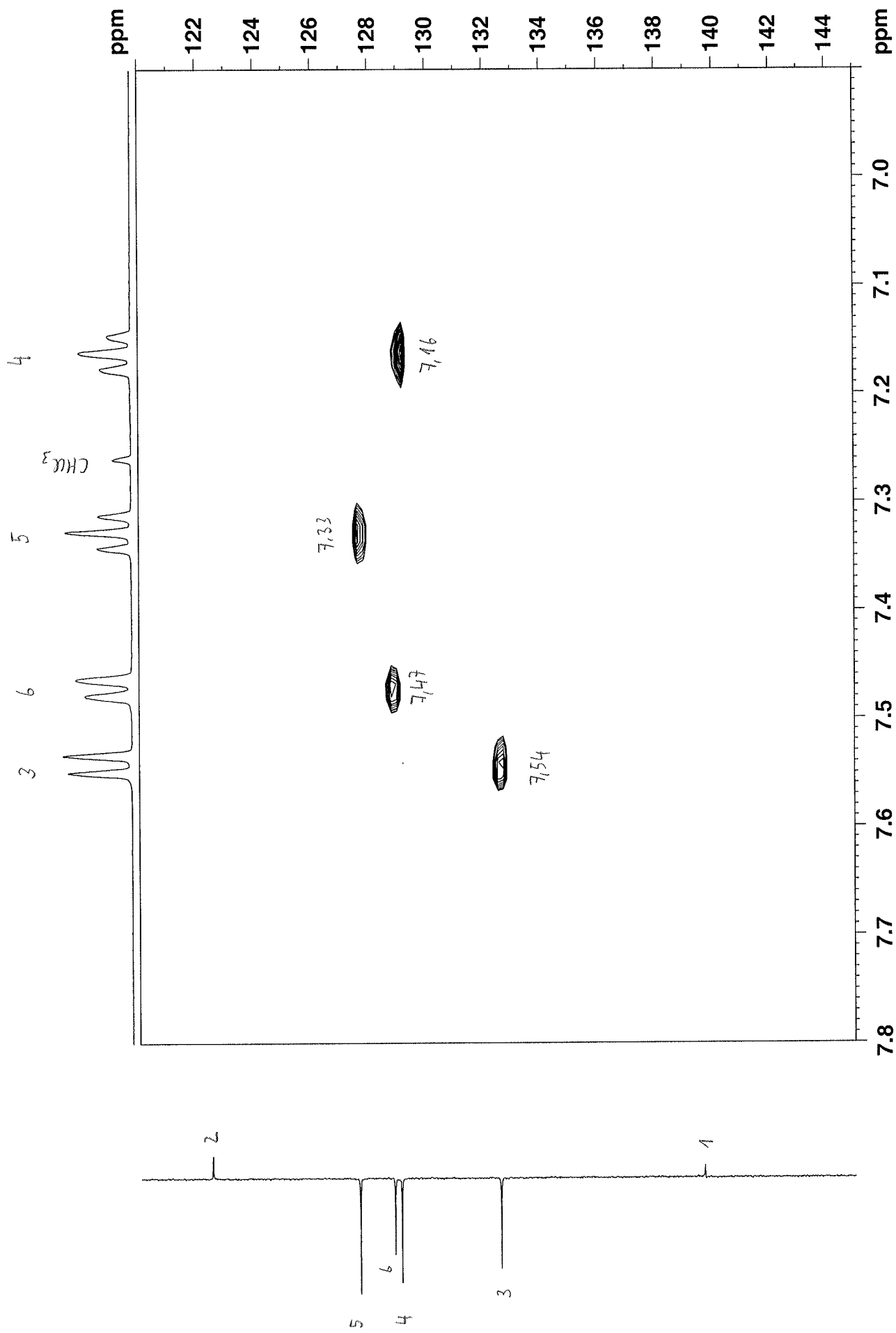




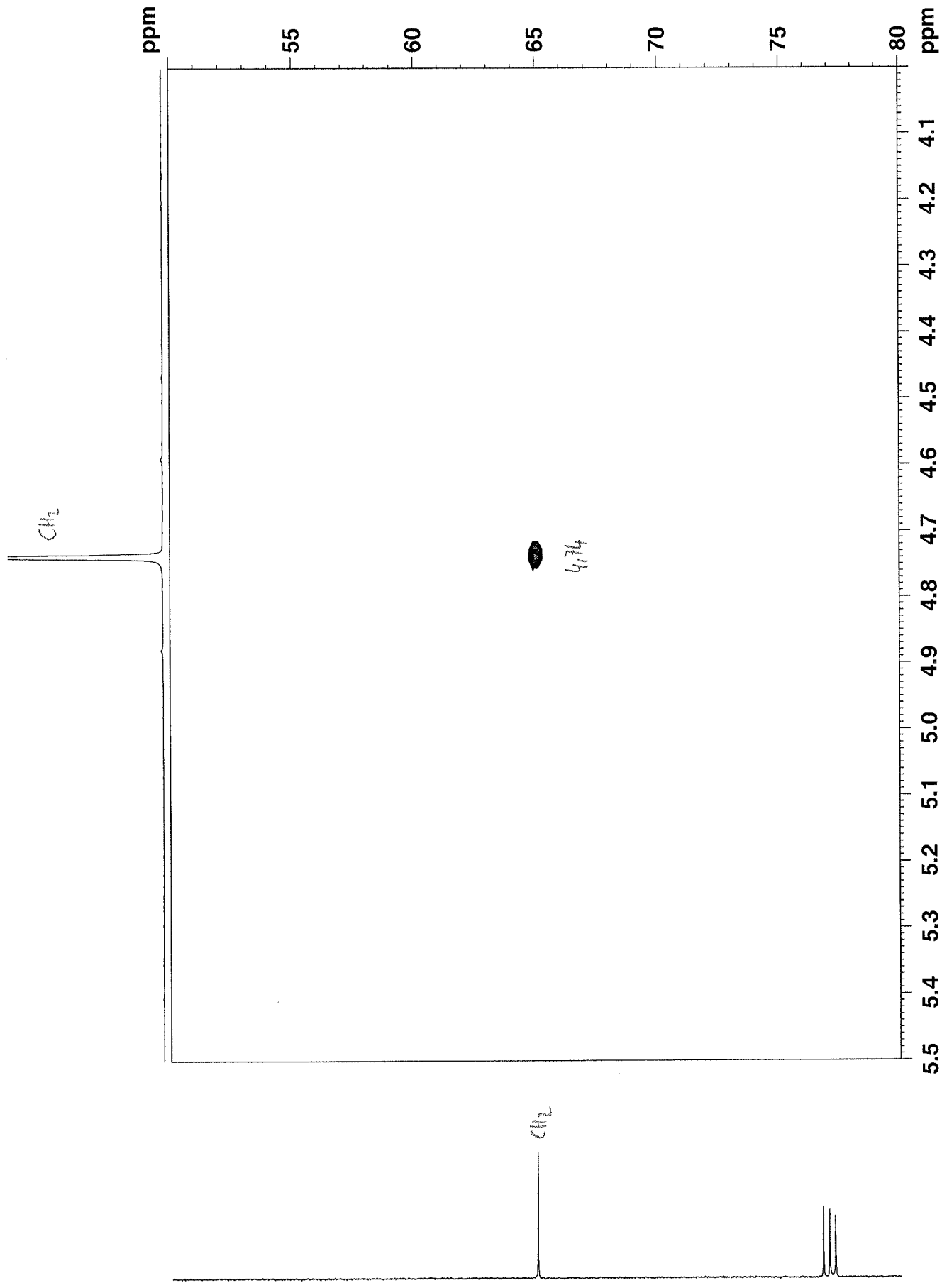


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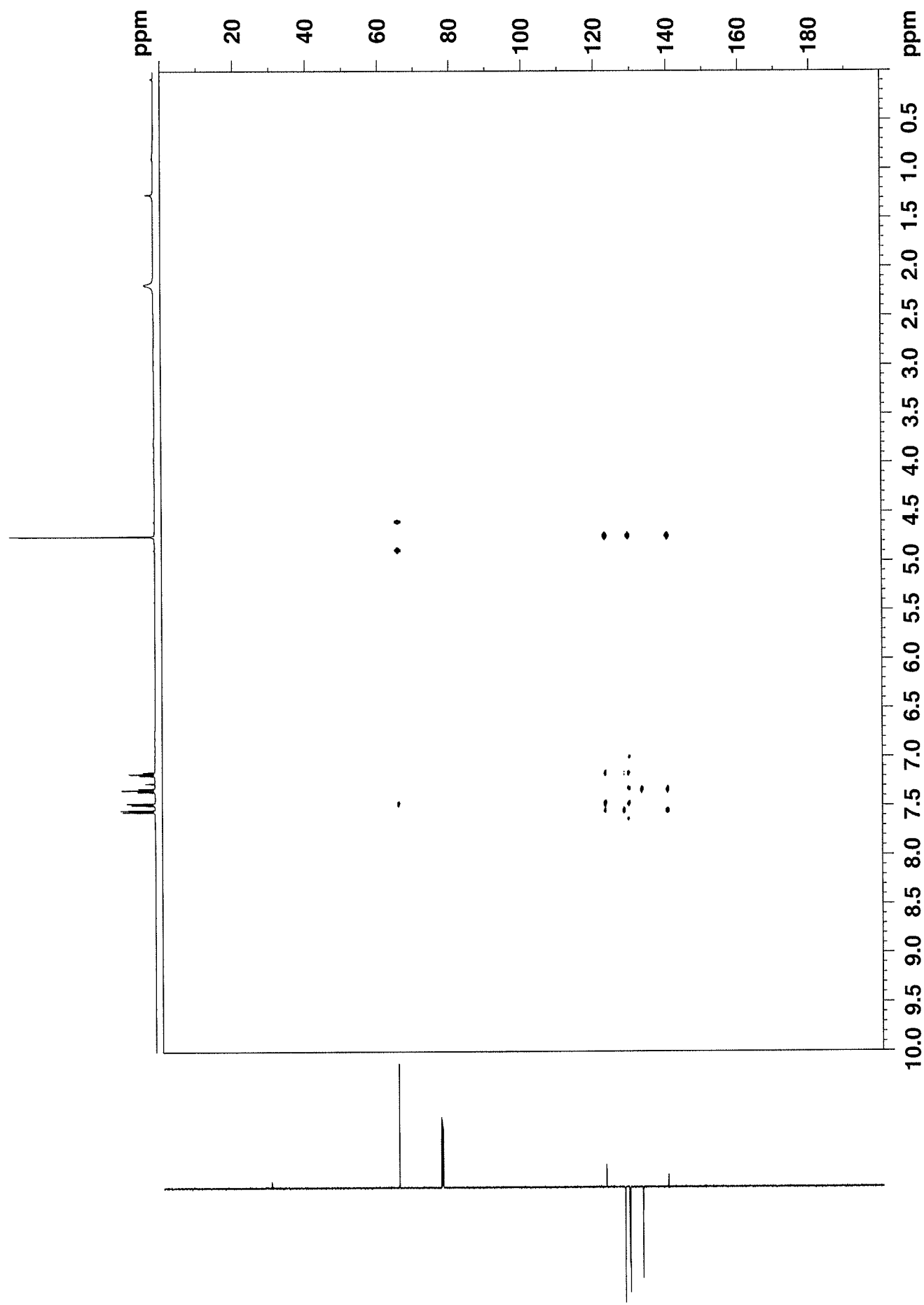


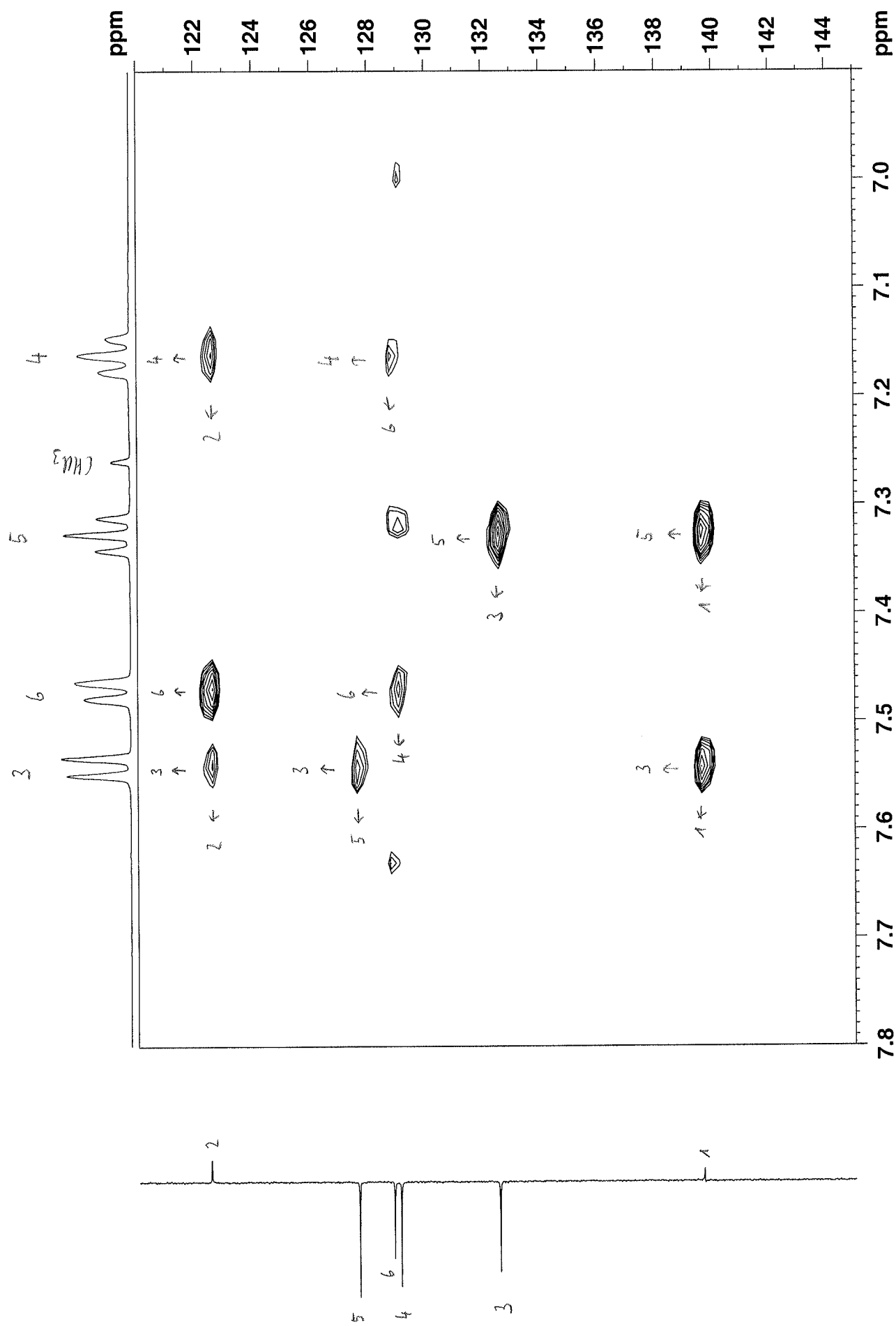
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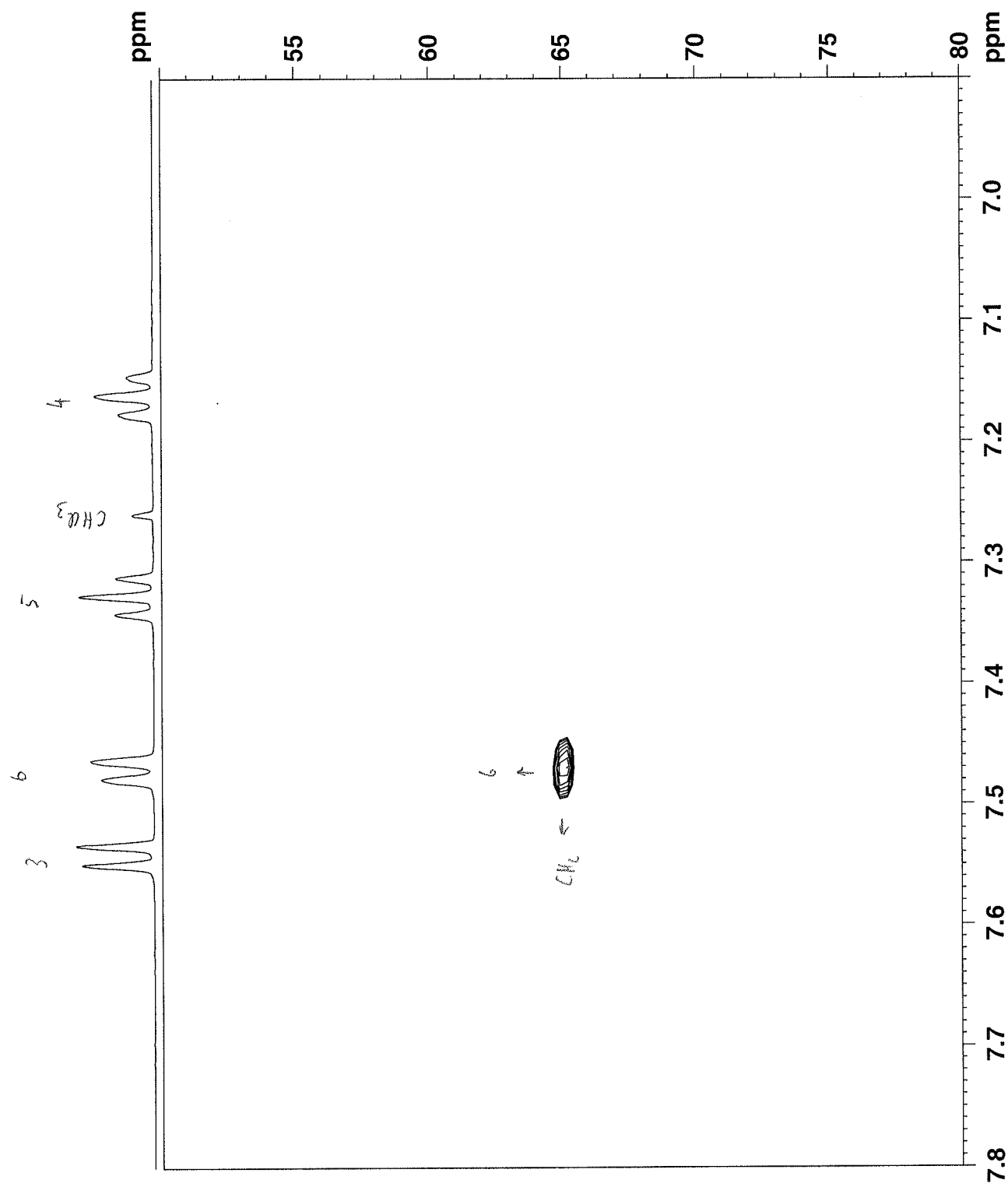


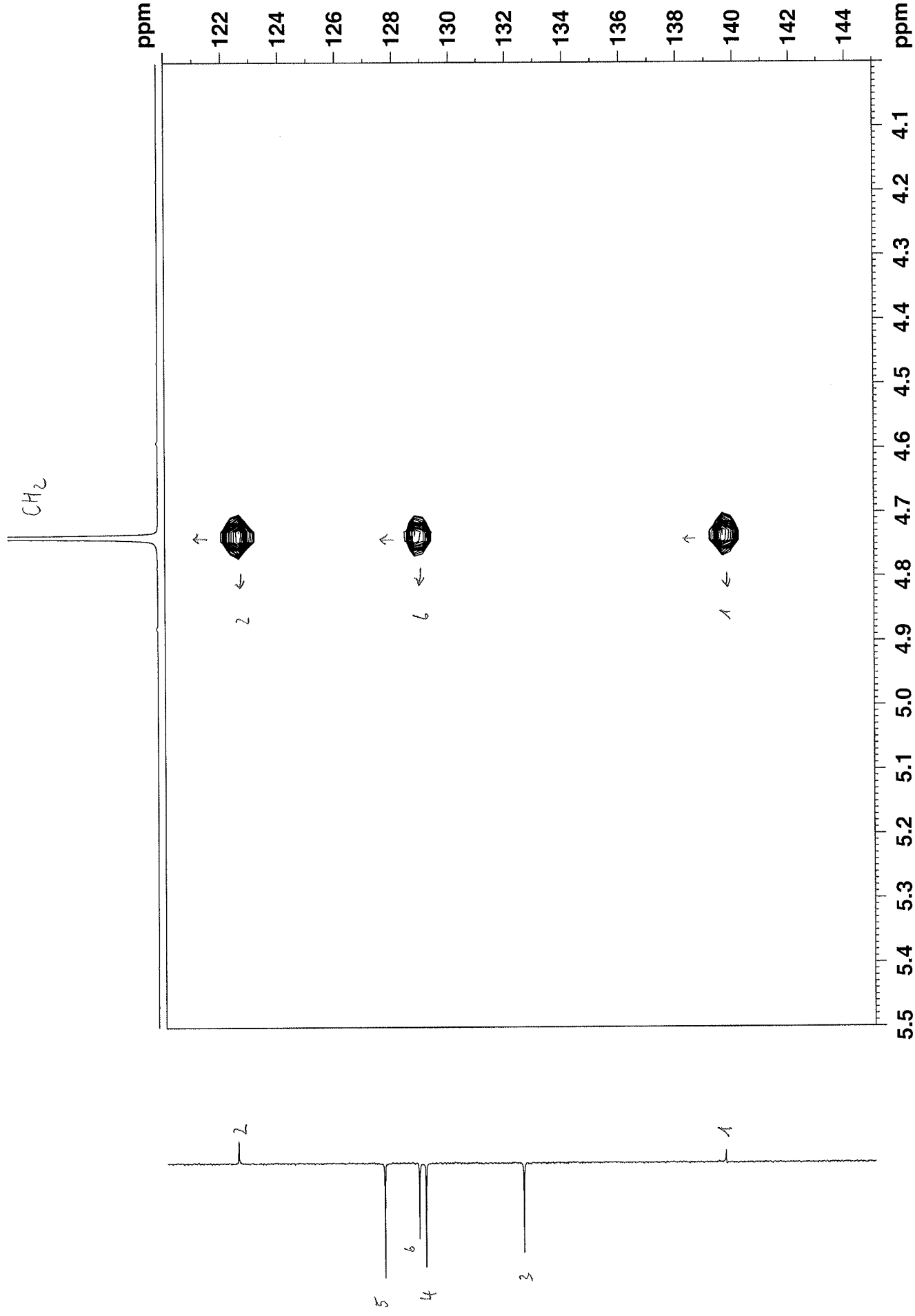


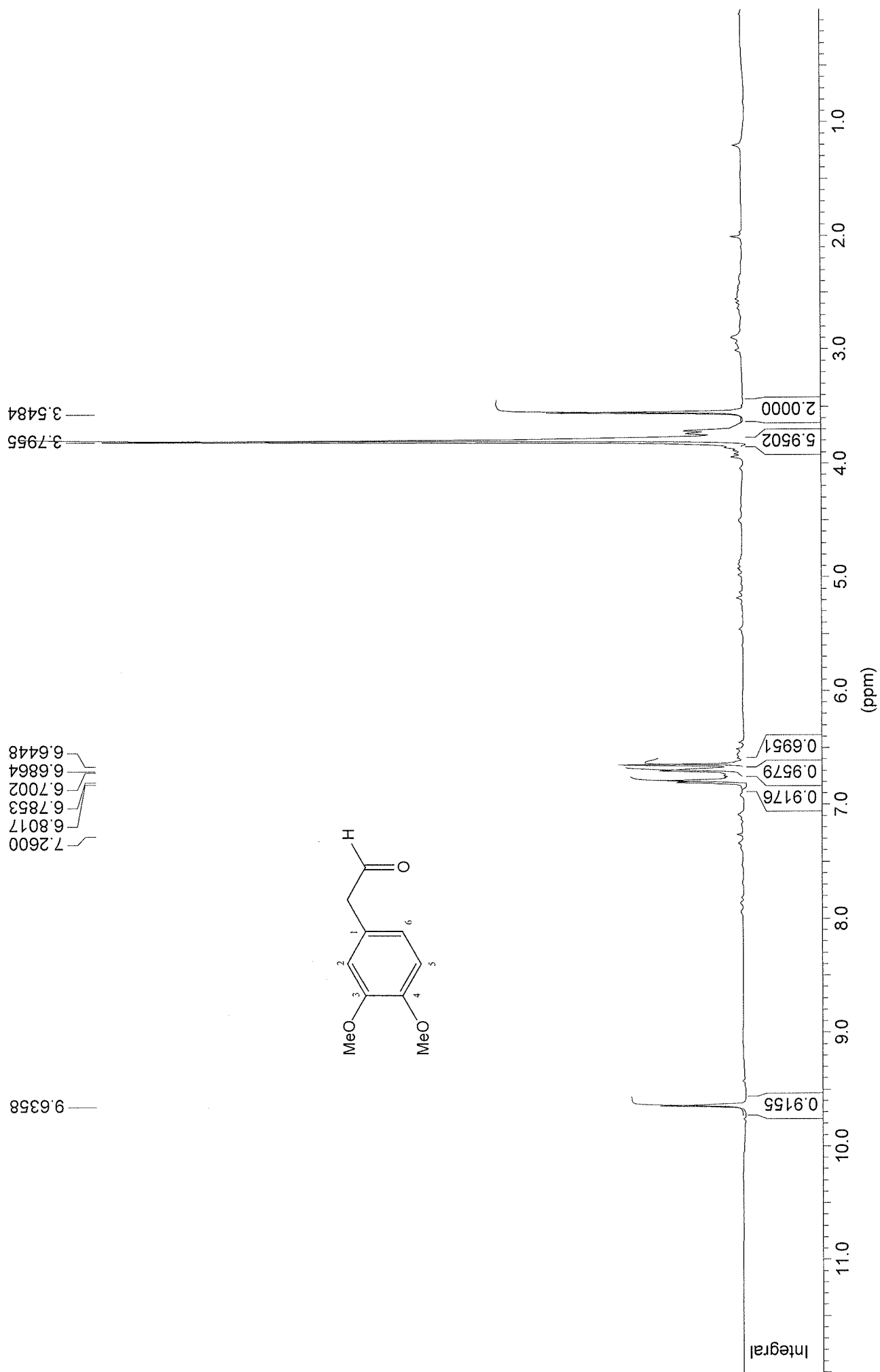
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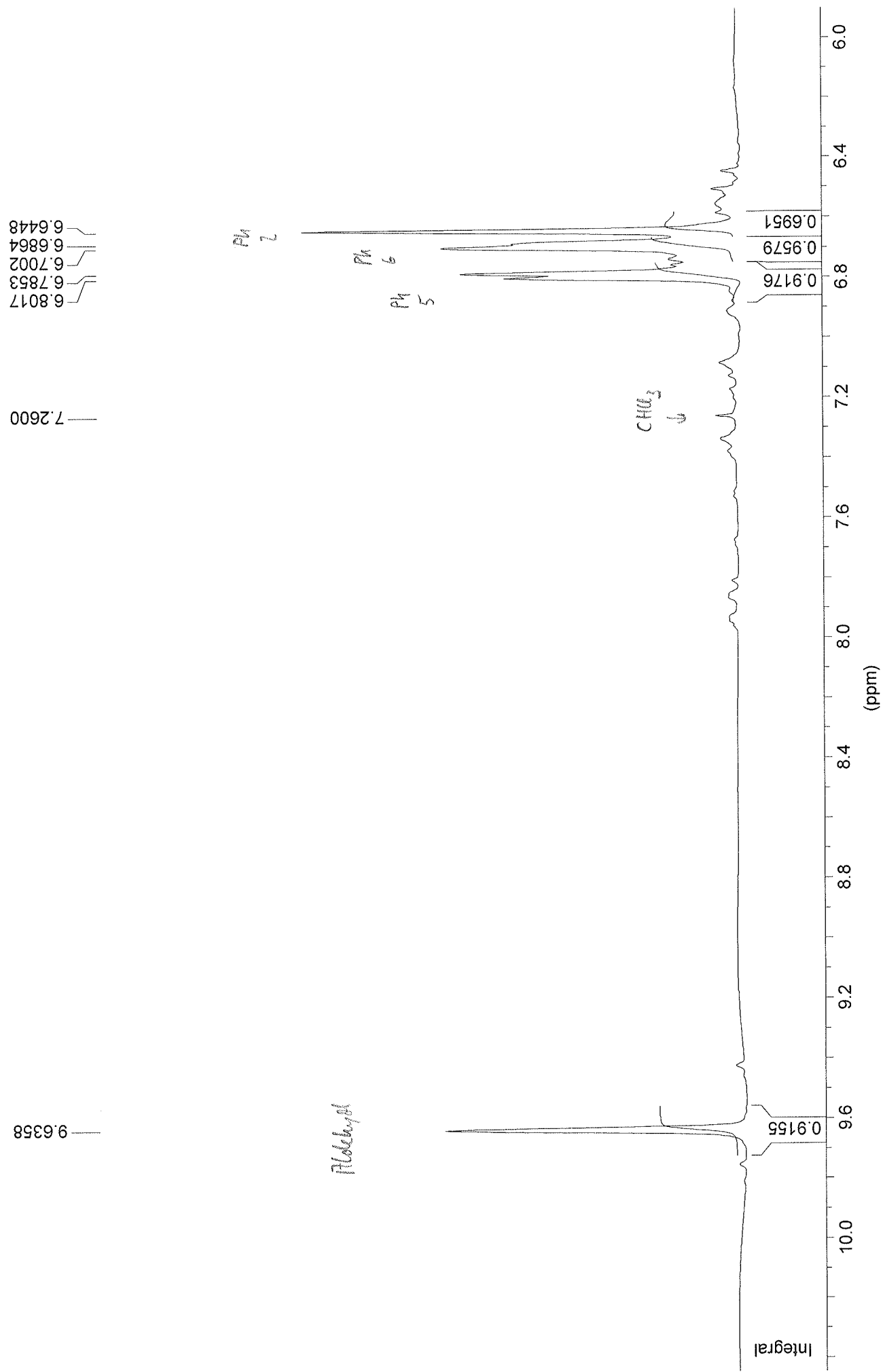


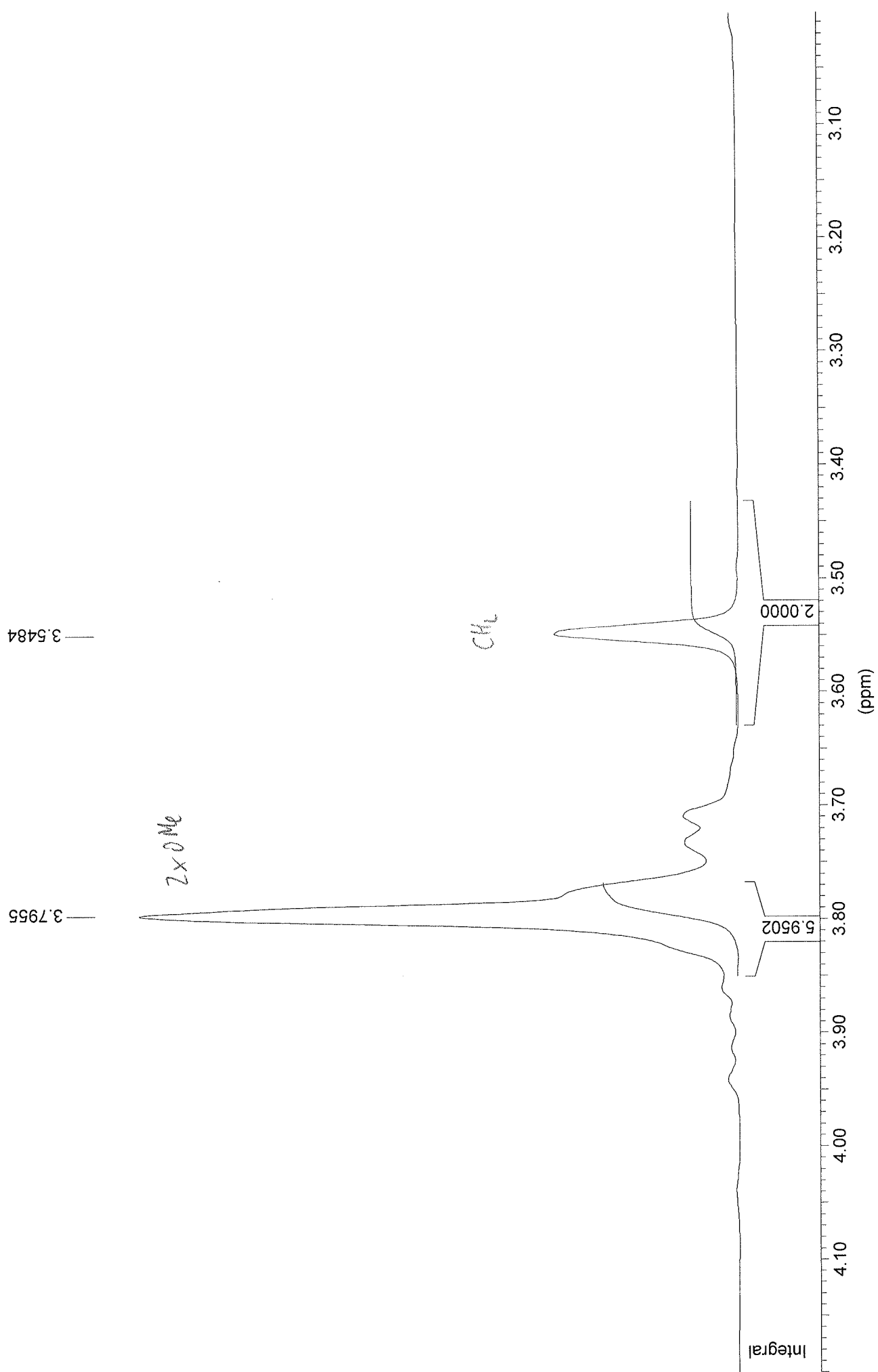






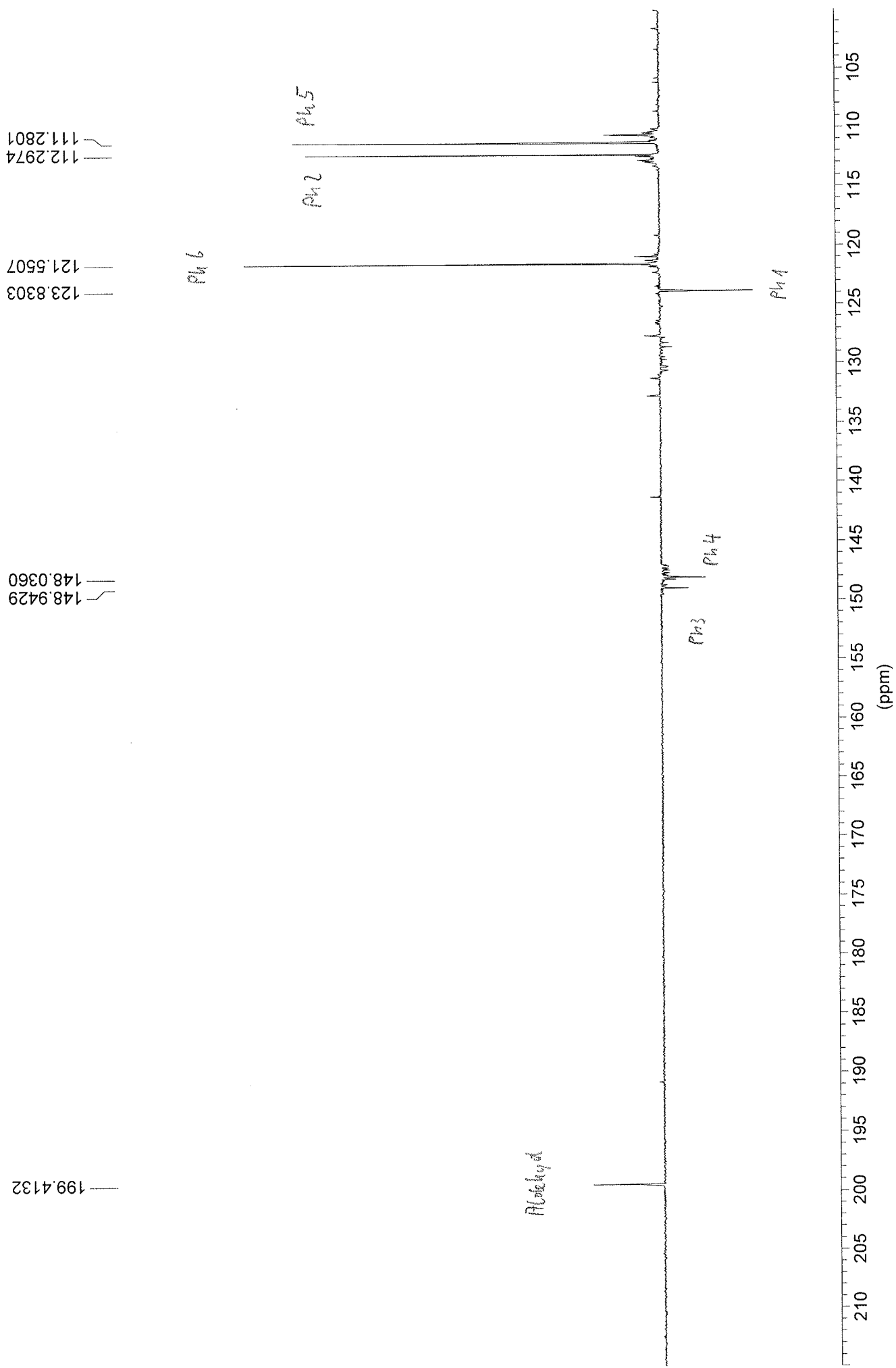


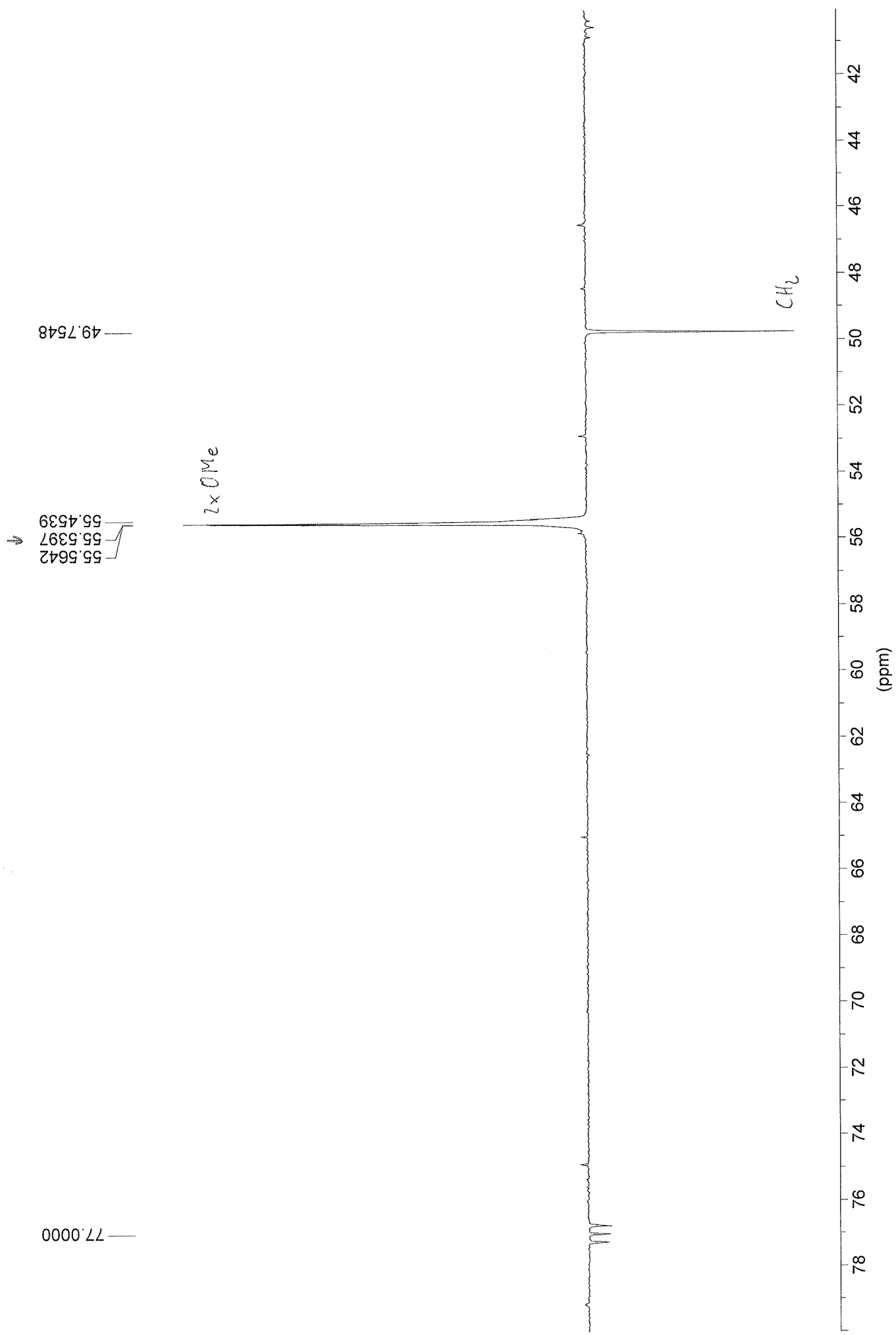




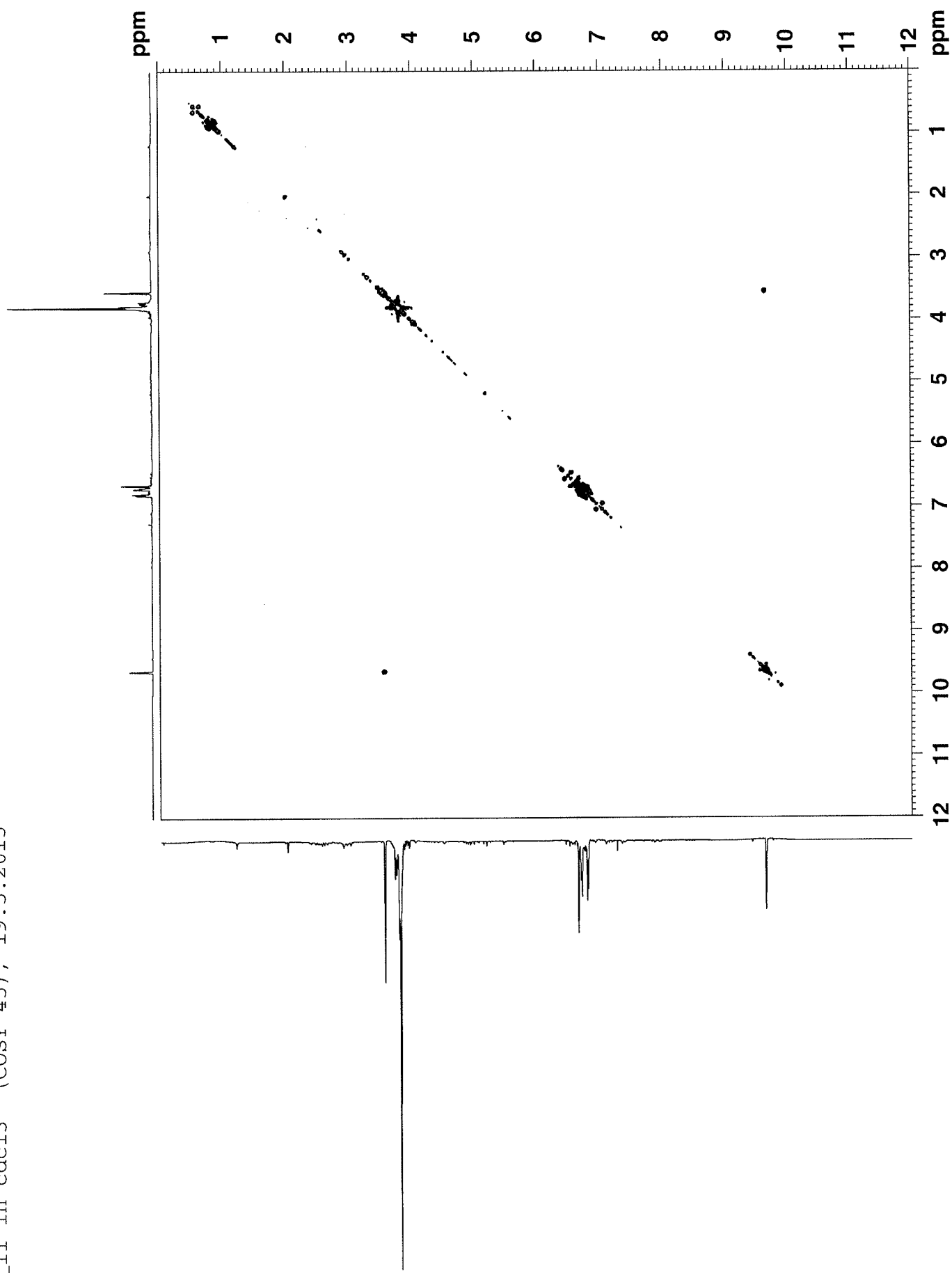


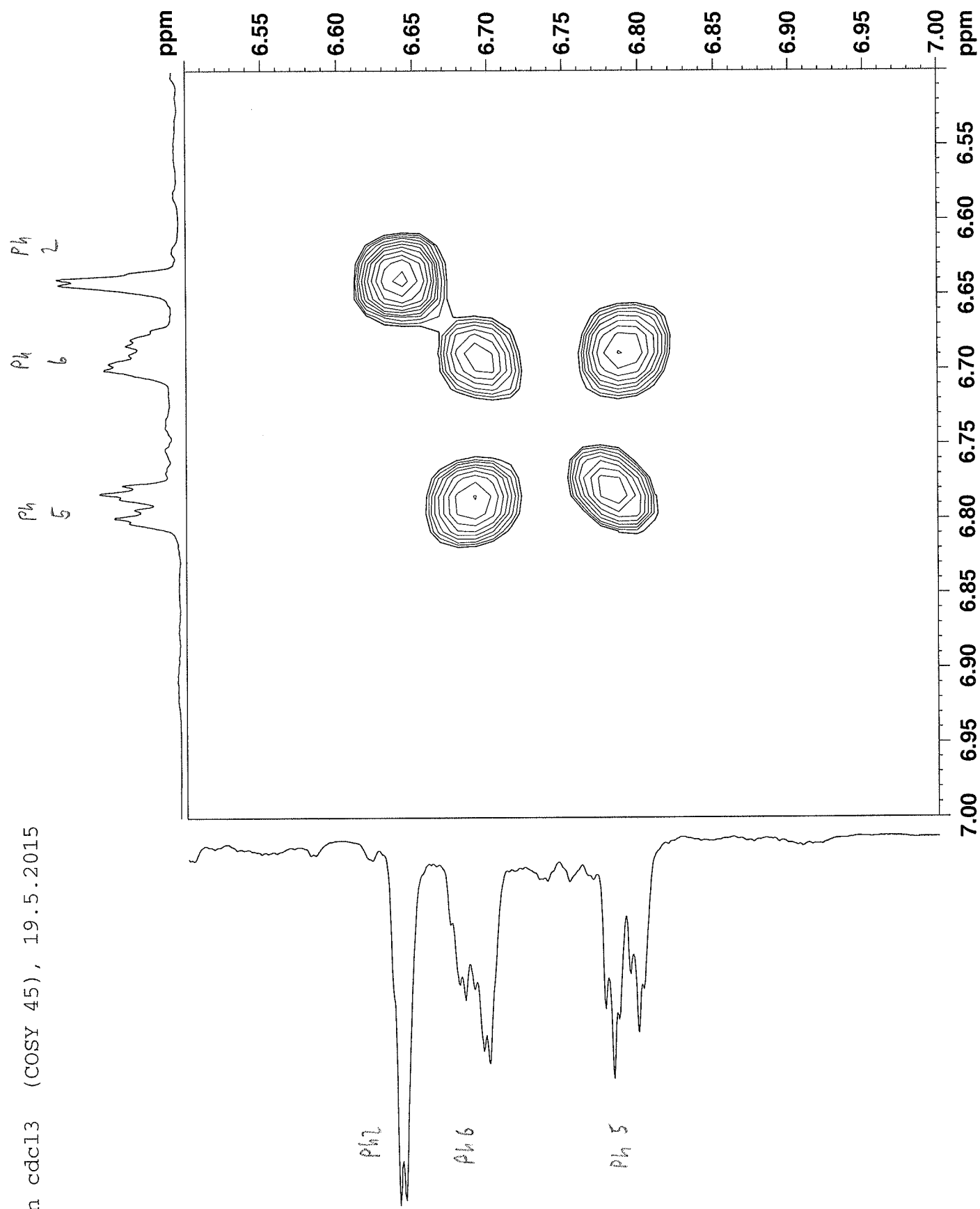






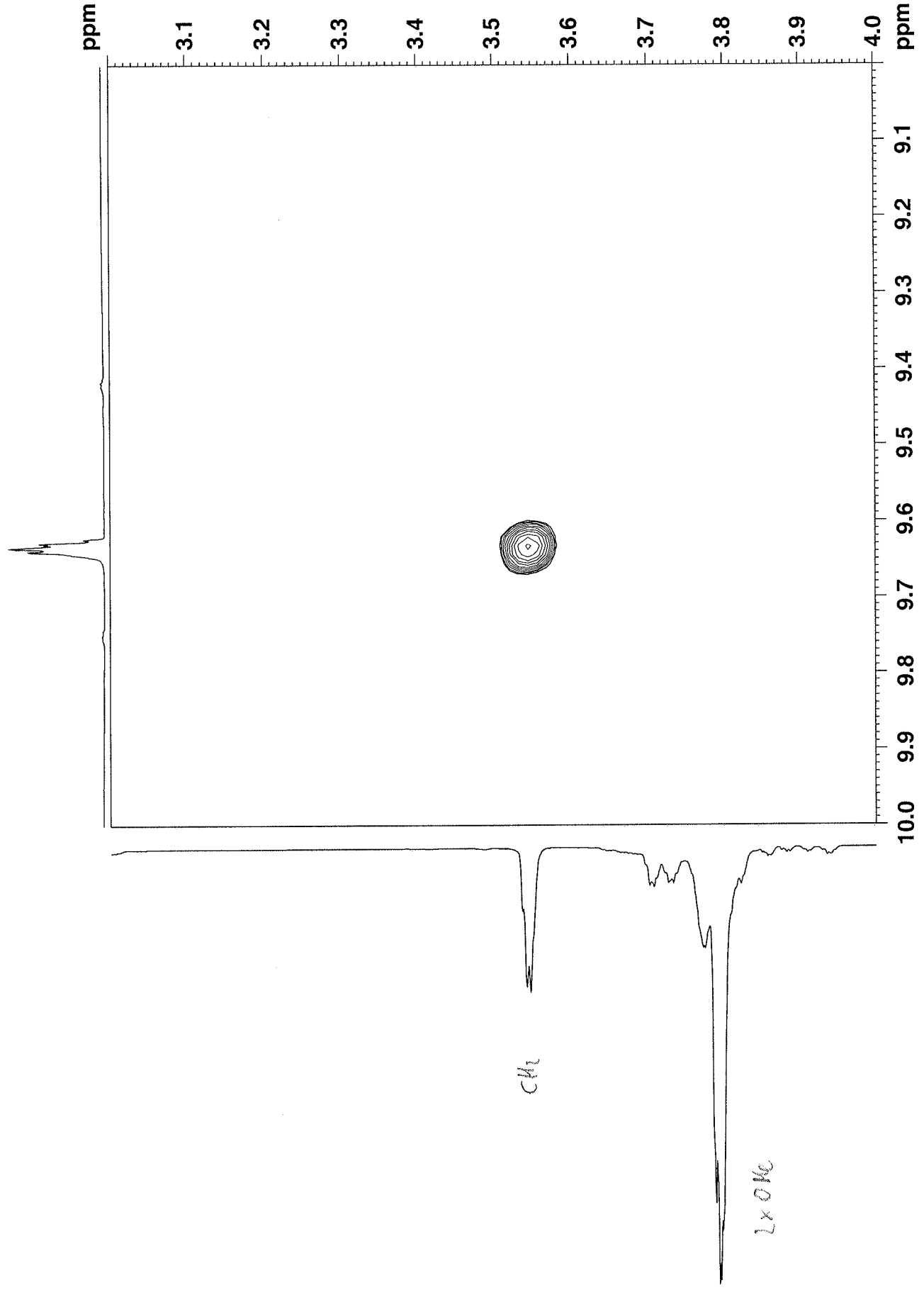
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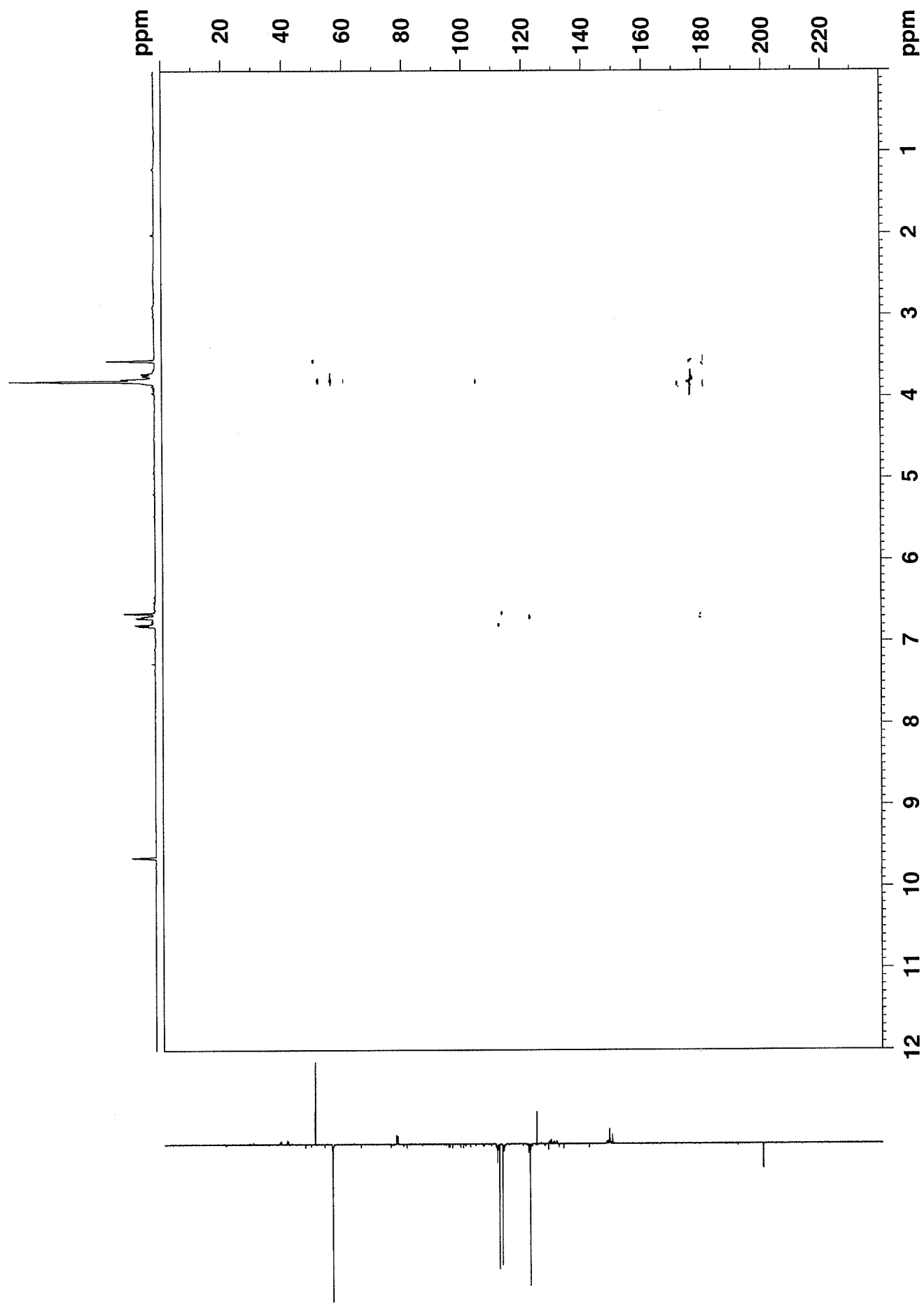


Aldehyde  
H

AW040\_11 in cdcl3 (COSY 45), 19.5.2015



AW040\_11 in cdcl3 (HSQC neu), 19.5.2015



Ph

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Ph

Ph

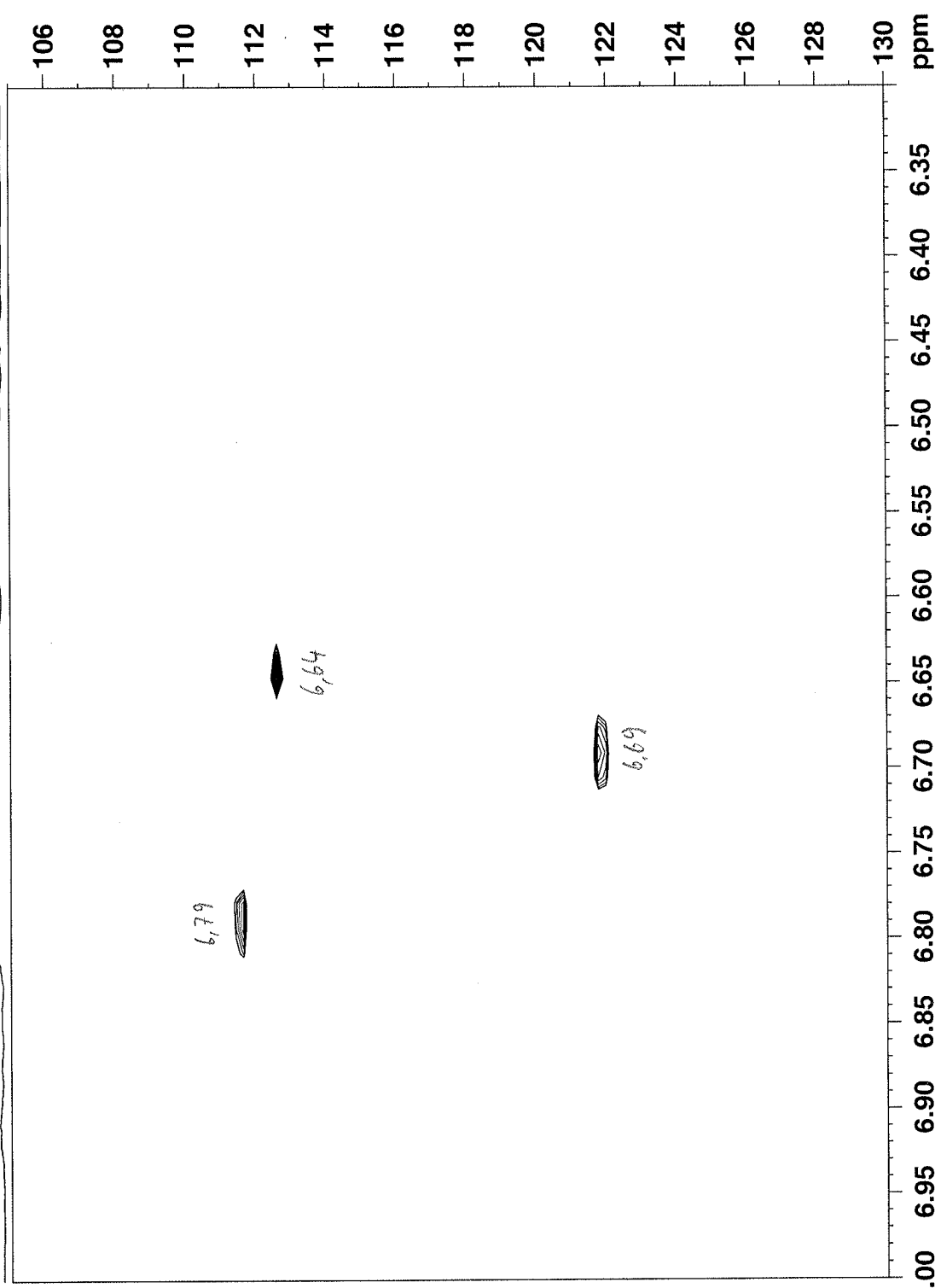
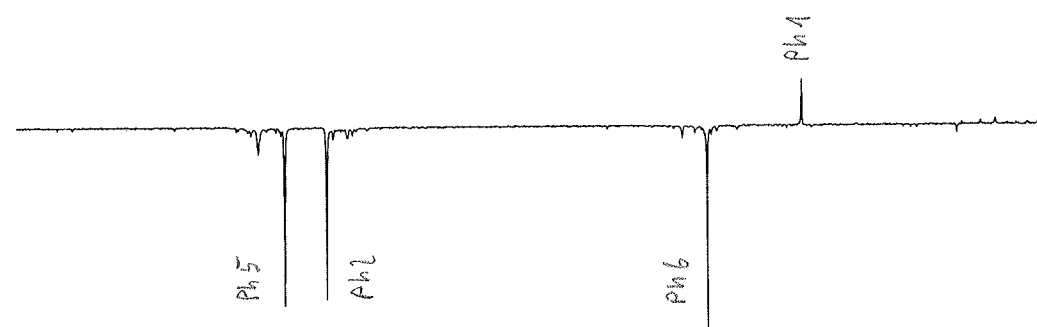
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5

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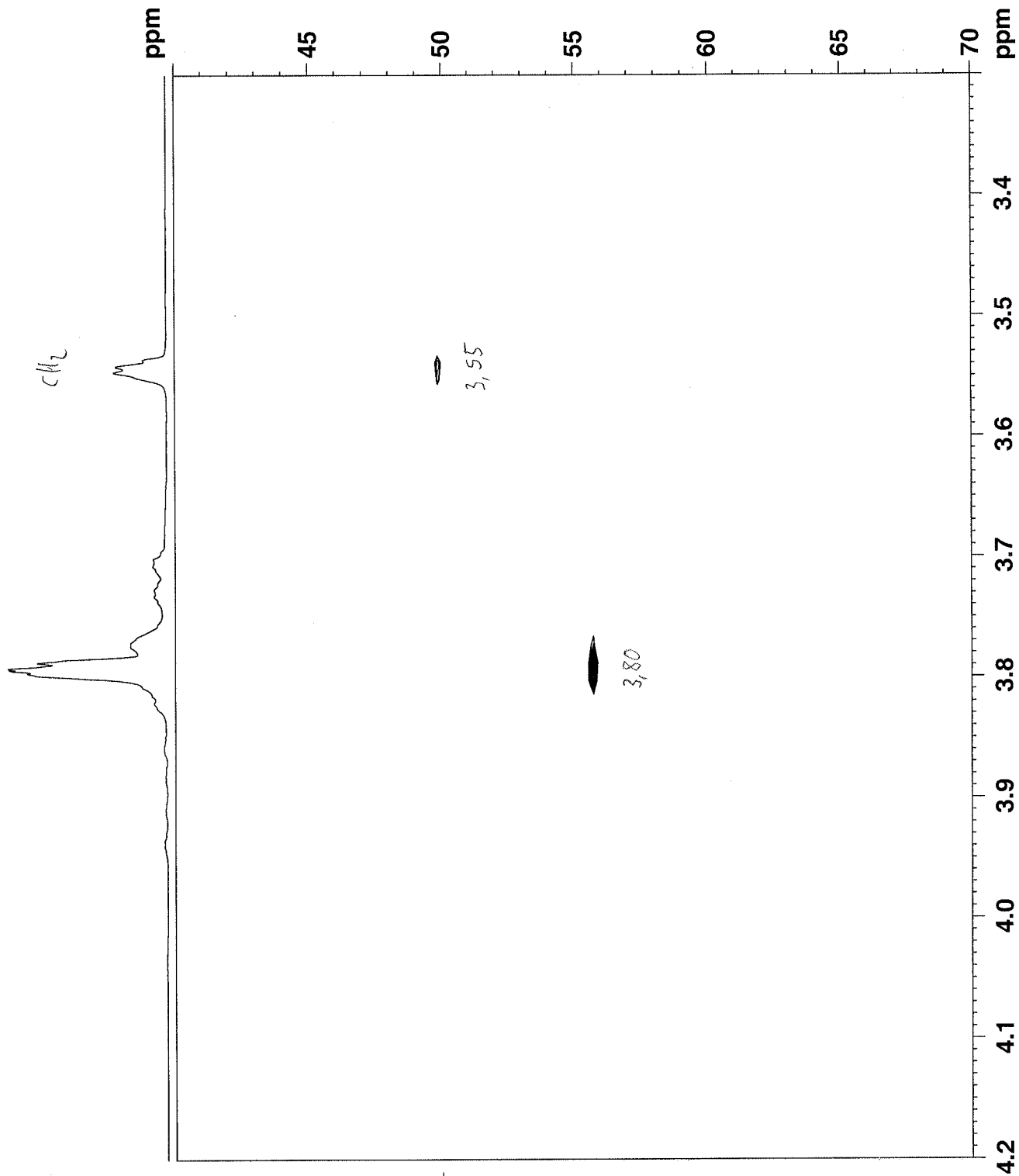
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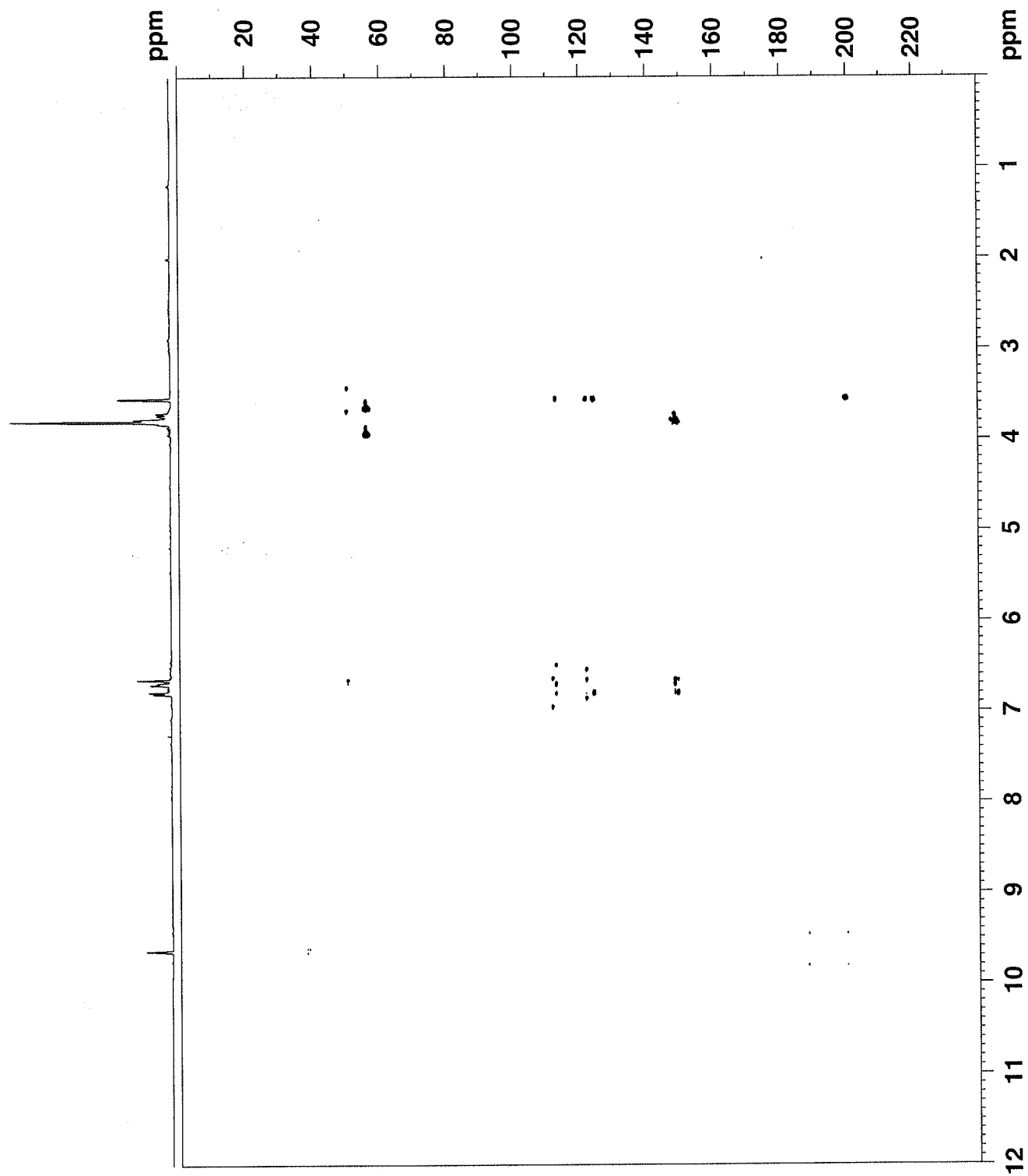
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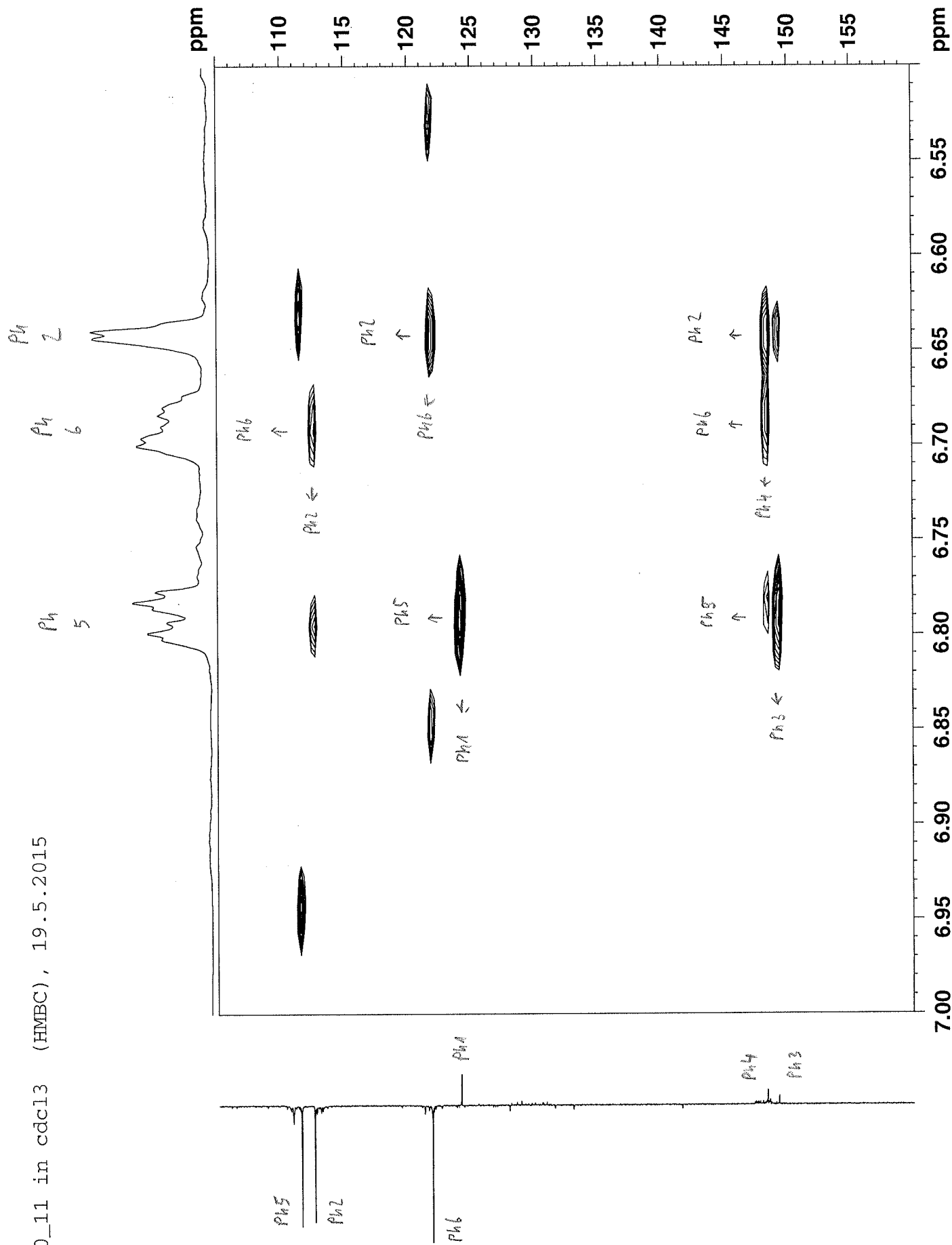


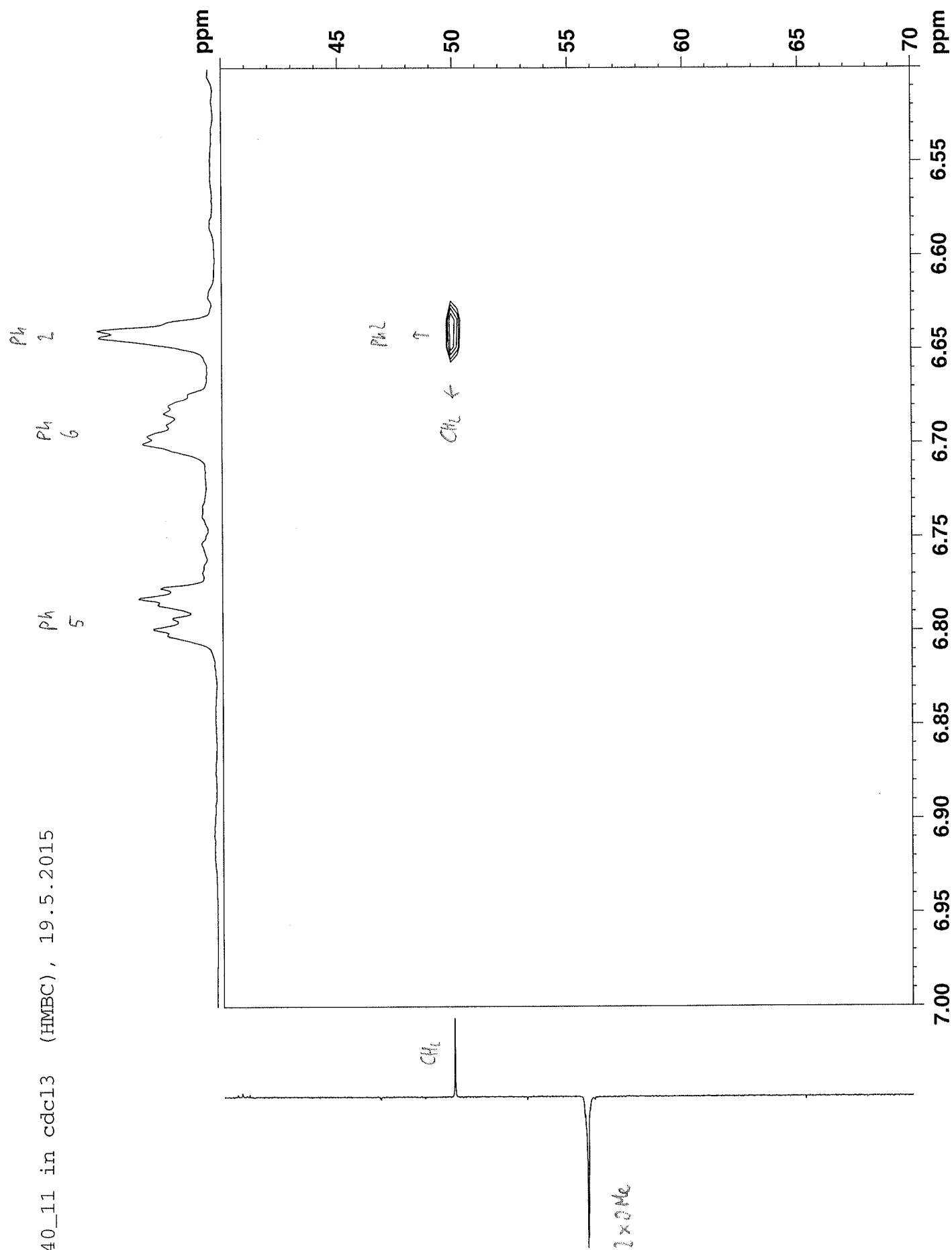
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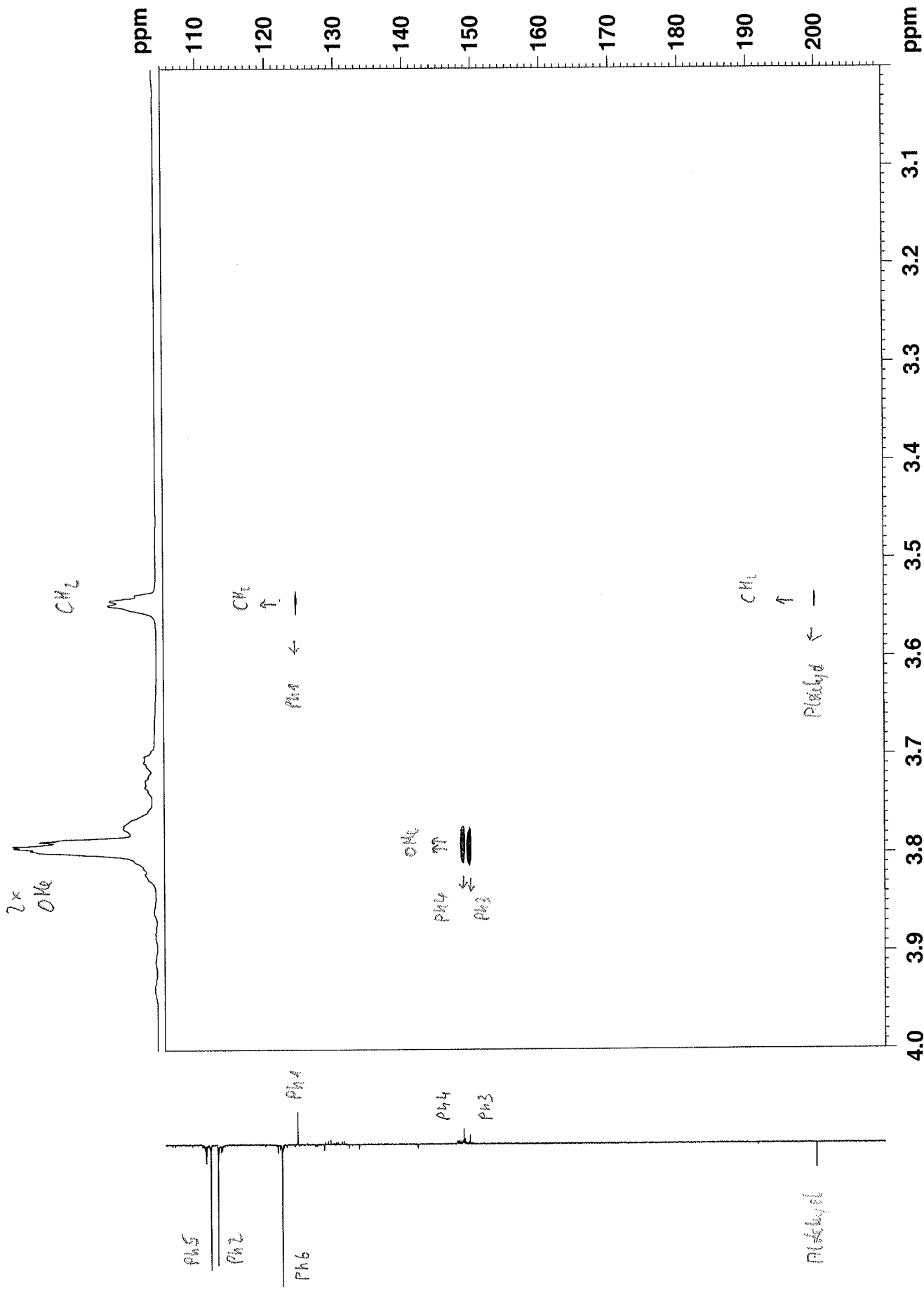


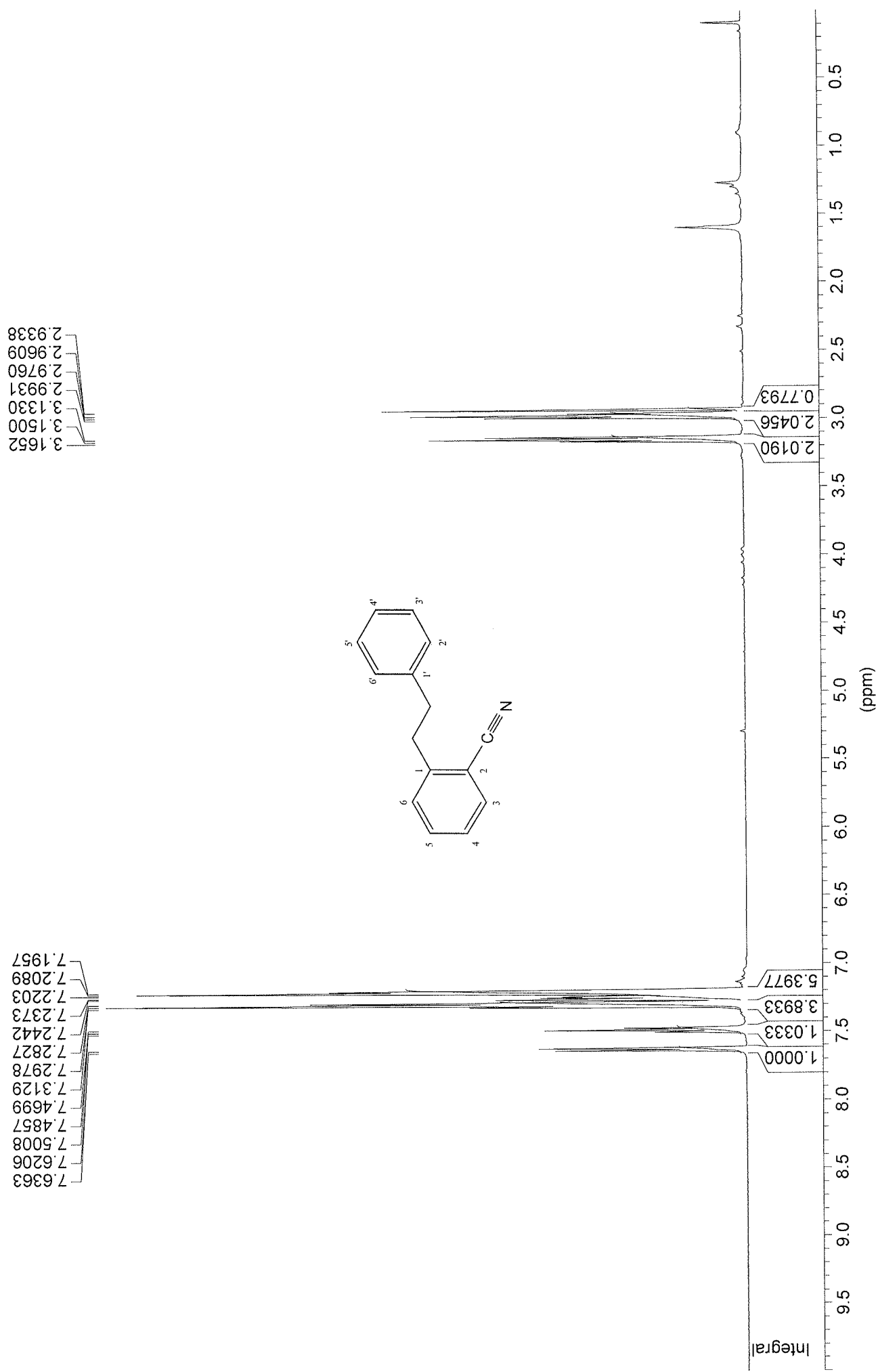
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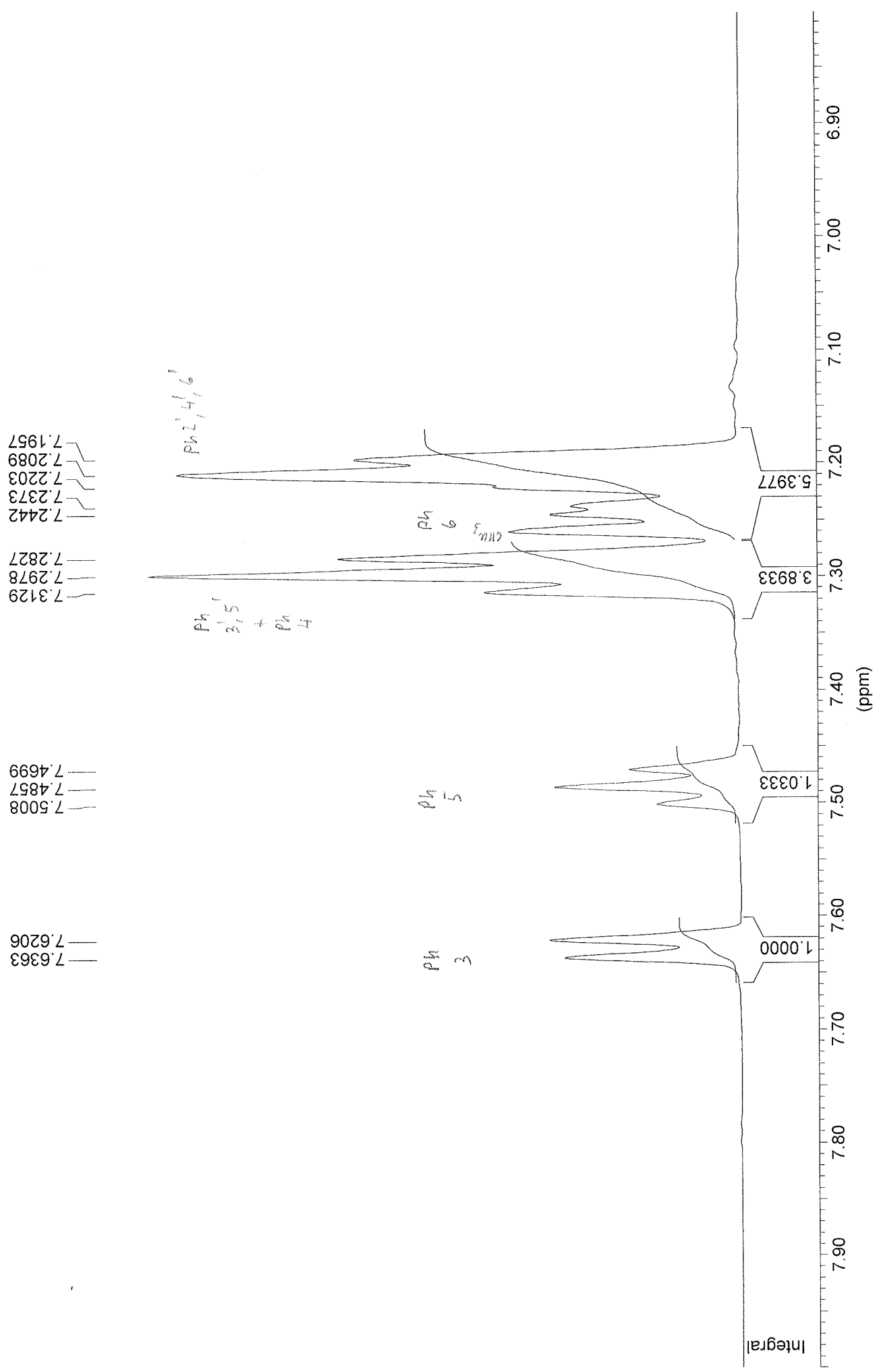










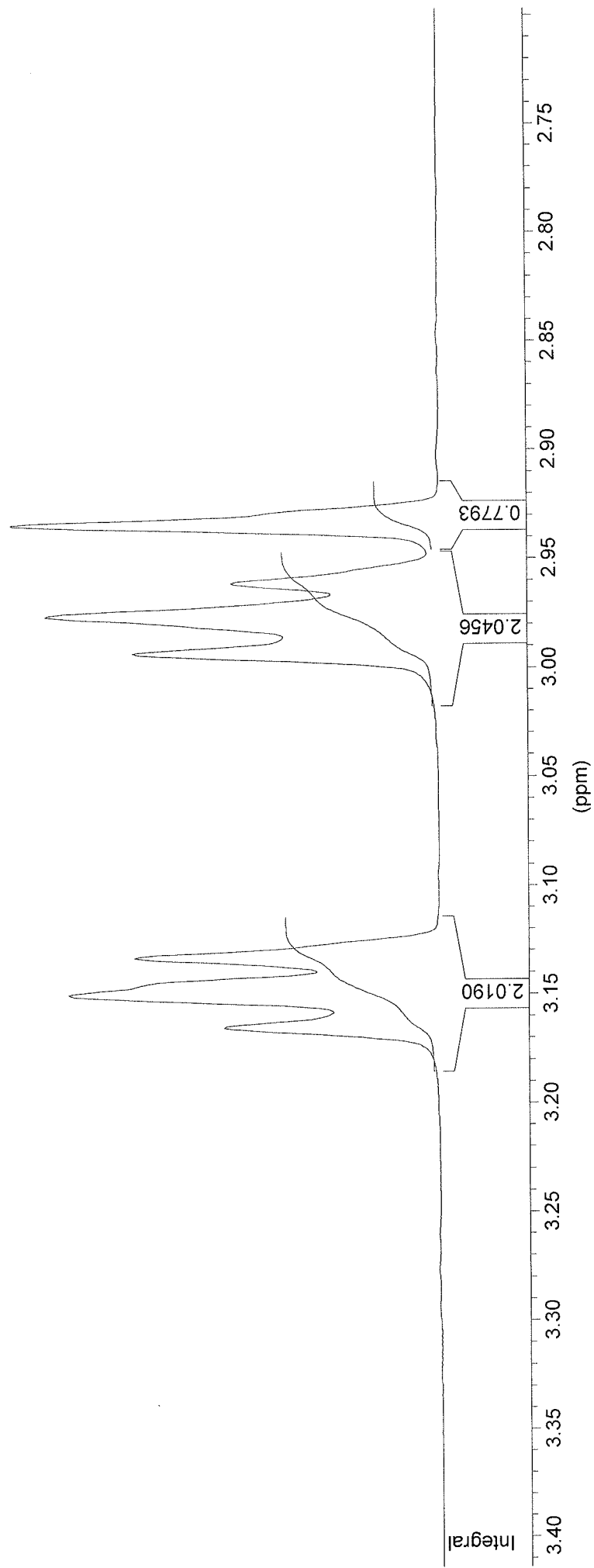


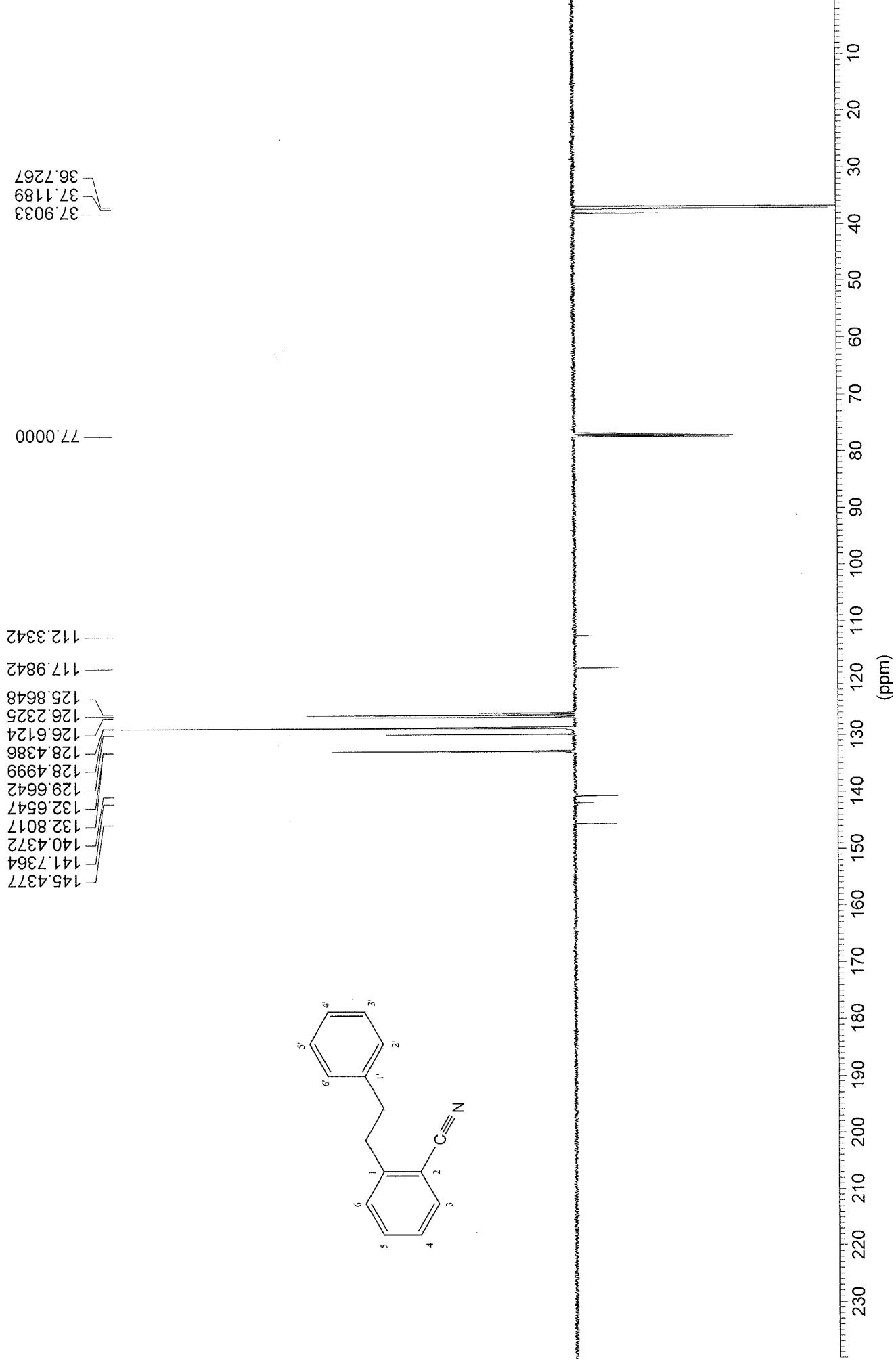
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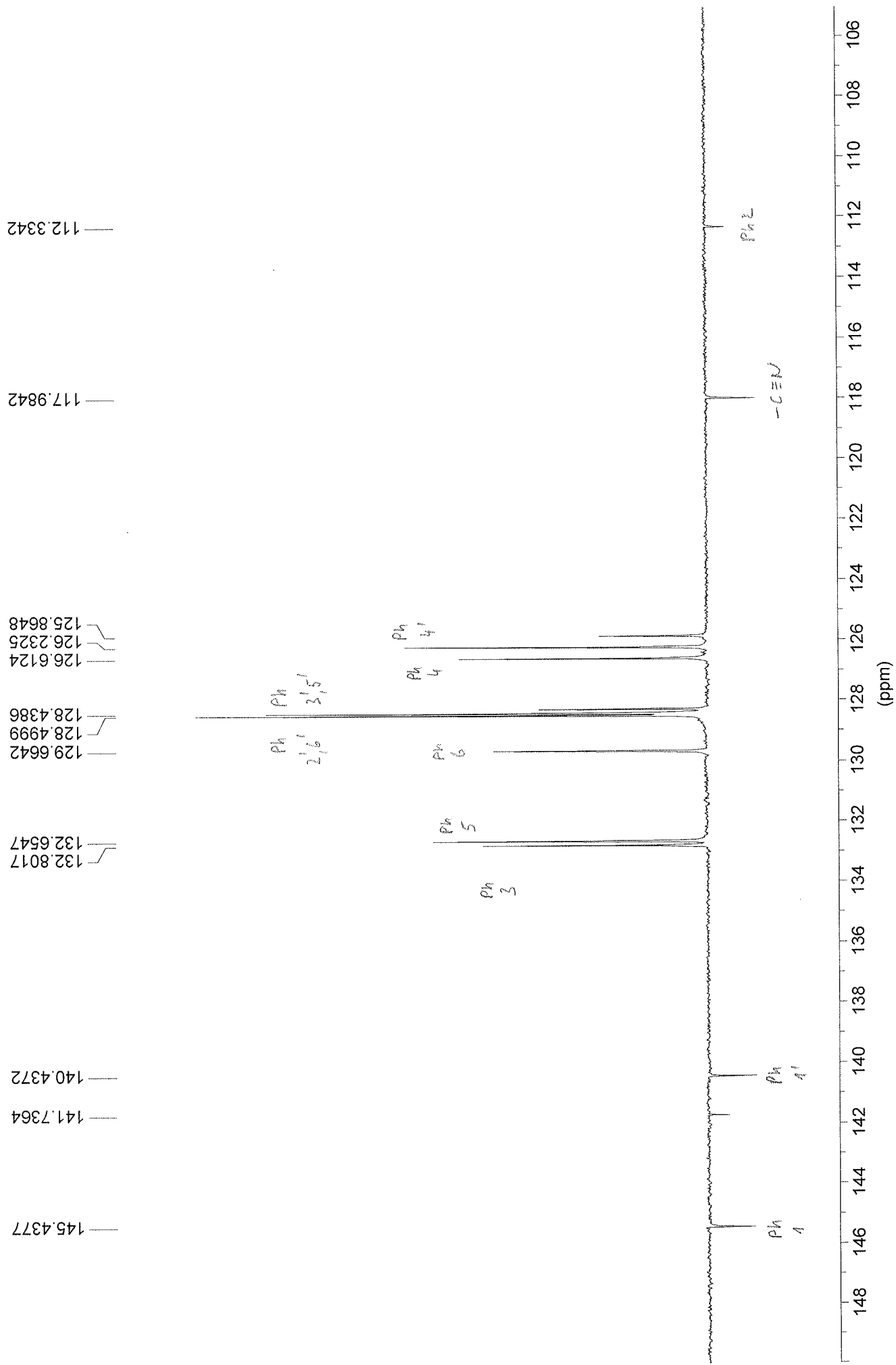
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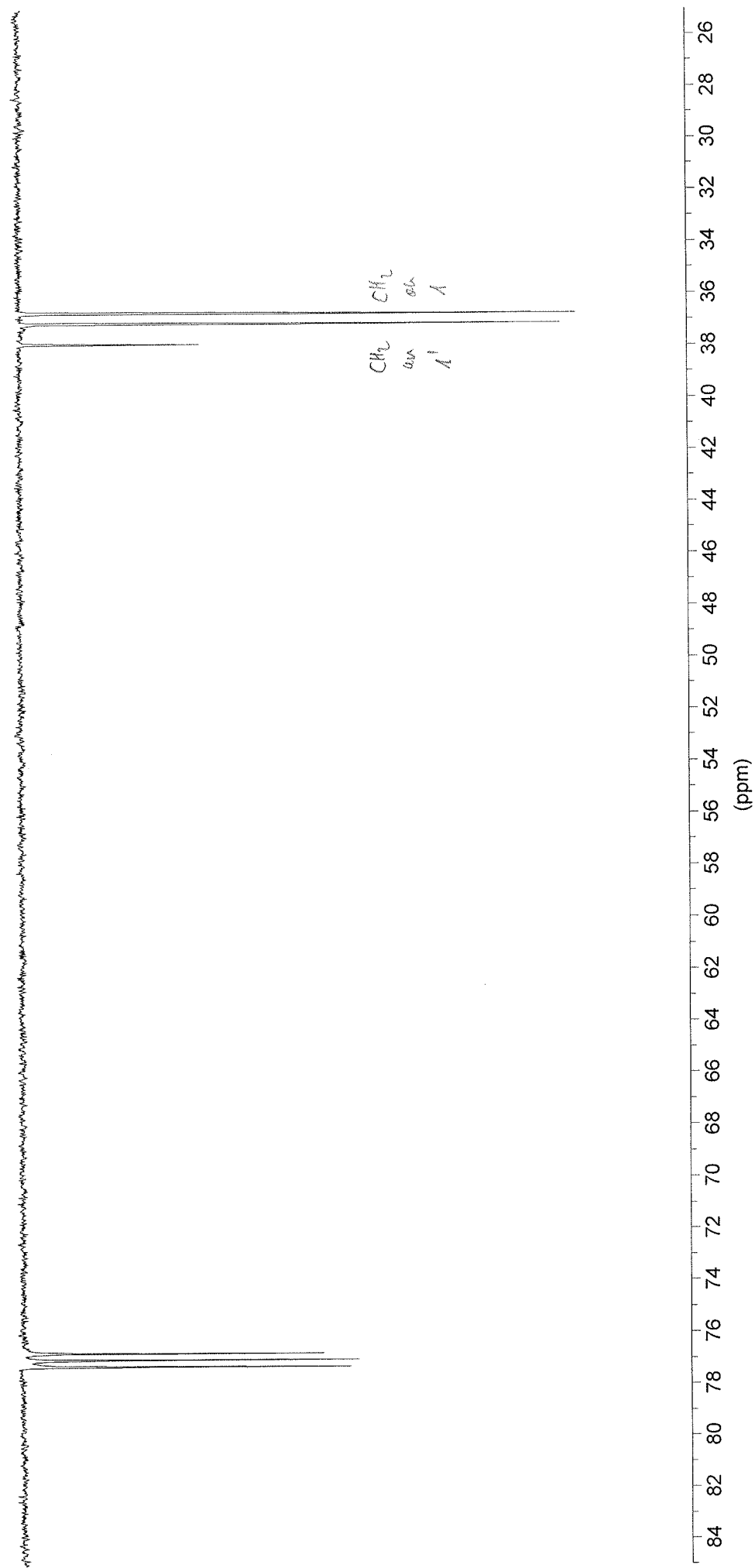




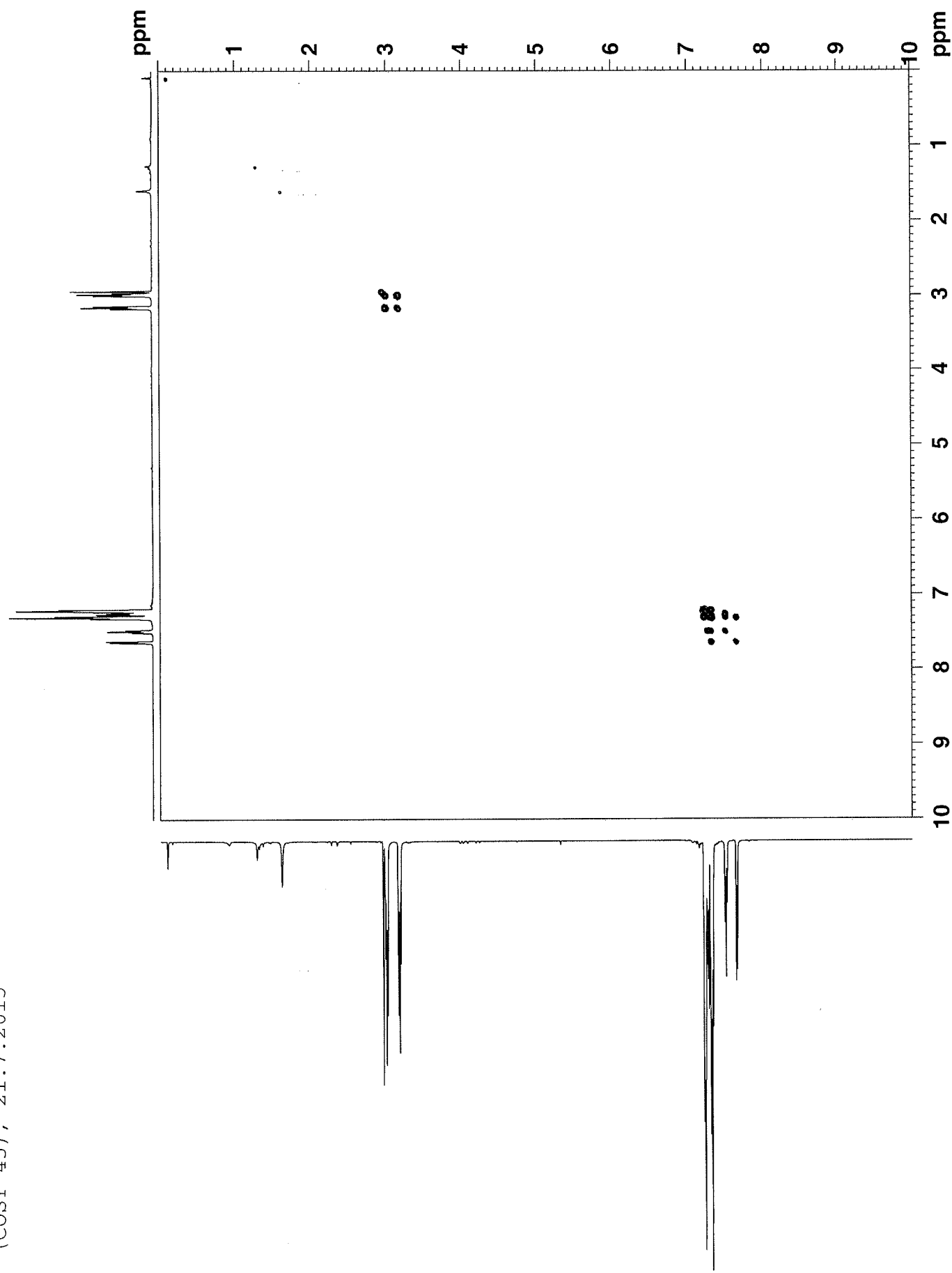


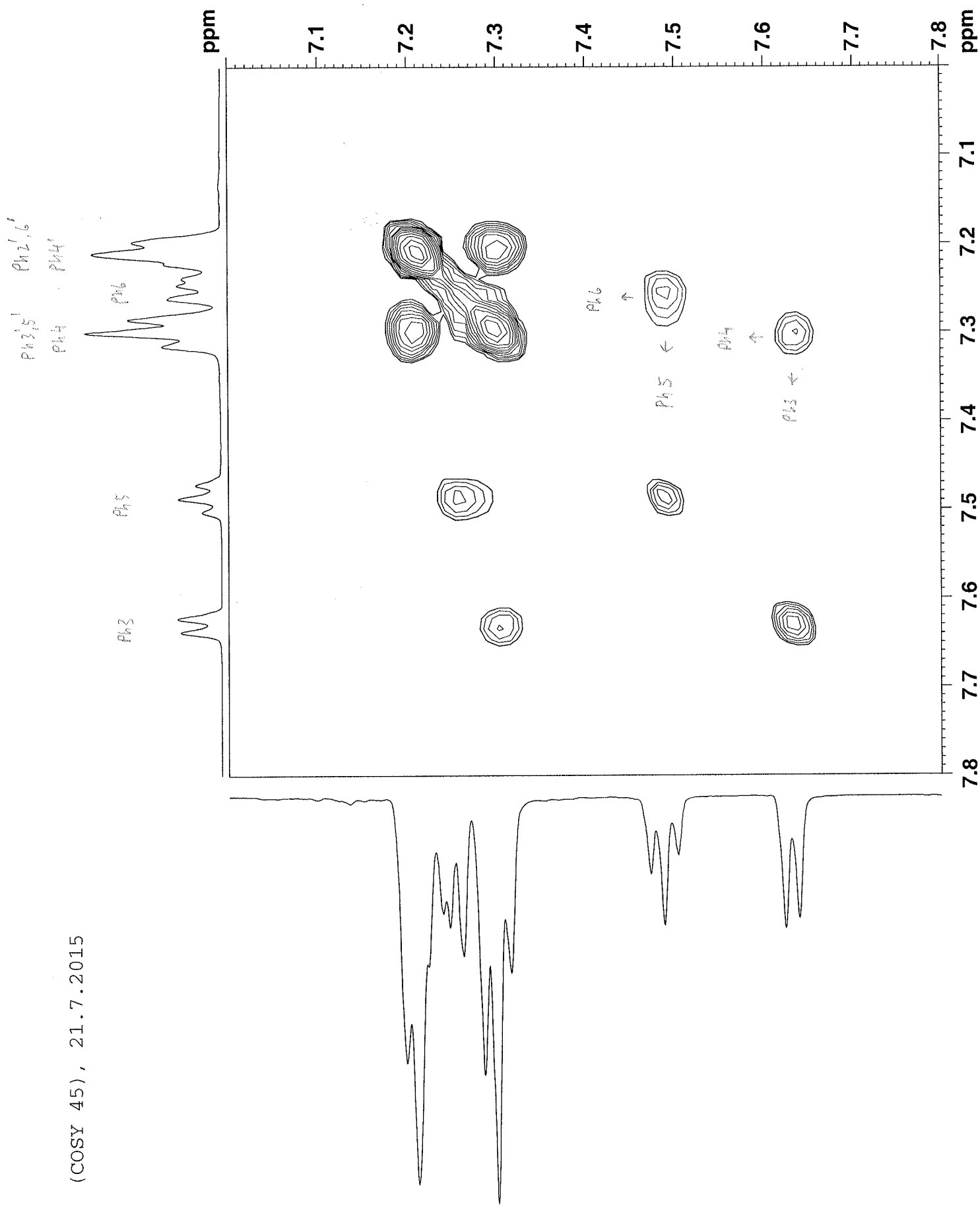
77.0000

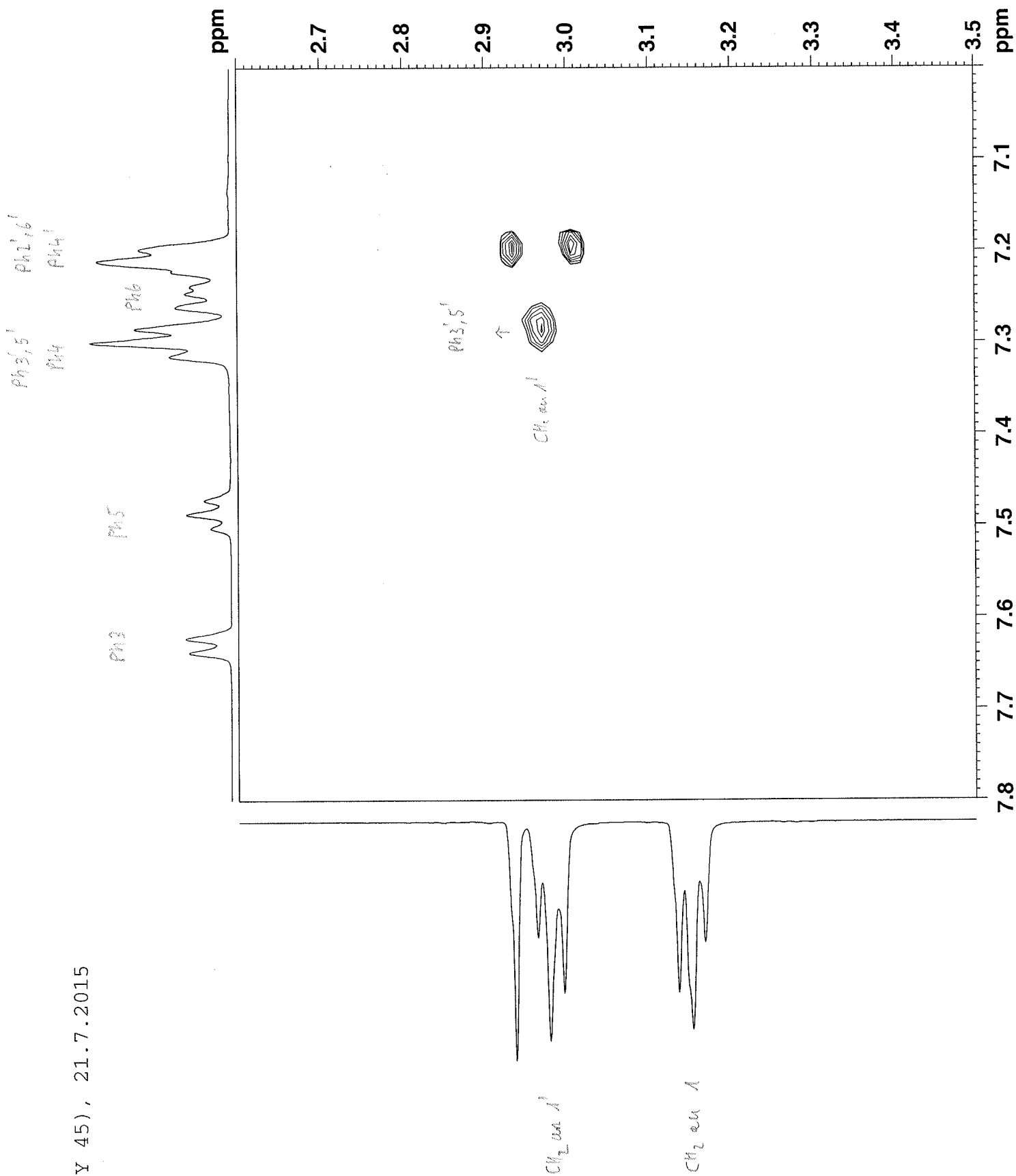
37.9033  
37.1189  
36.7267

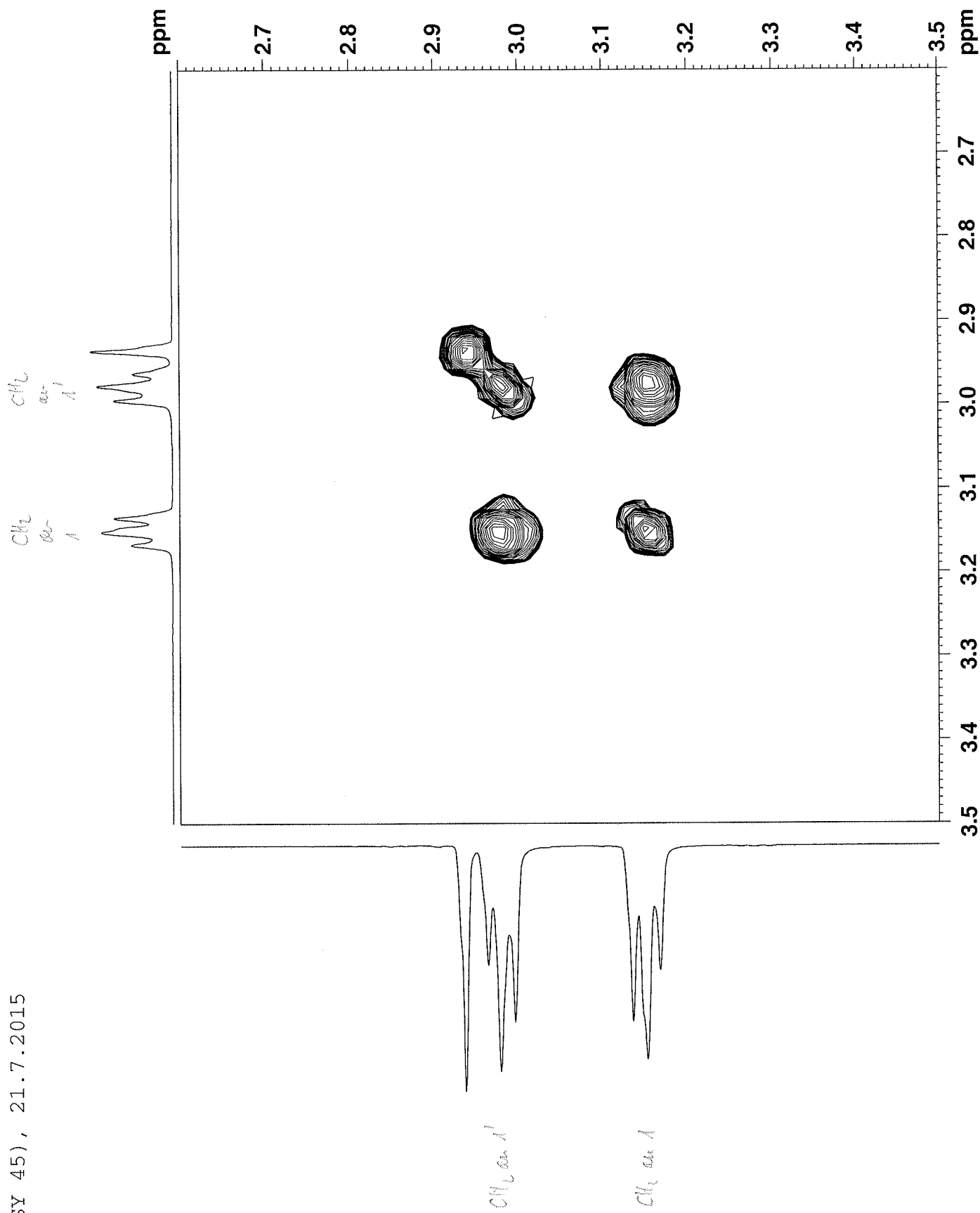


AW077 (COSY 45), 21.7.2015

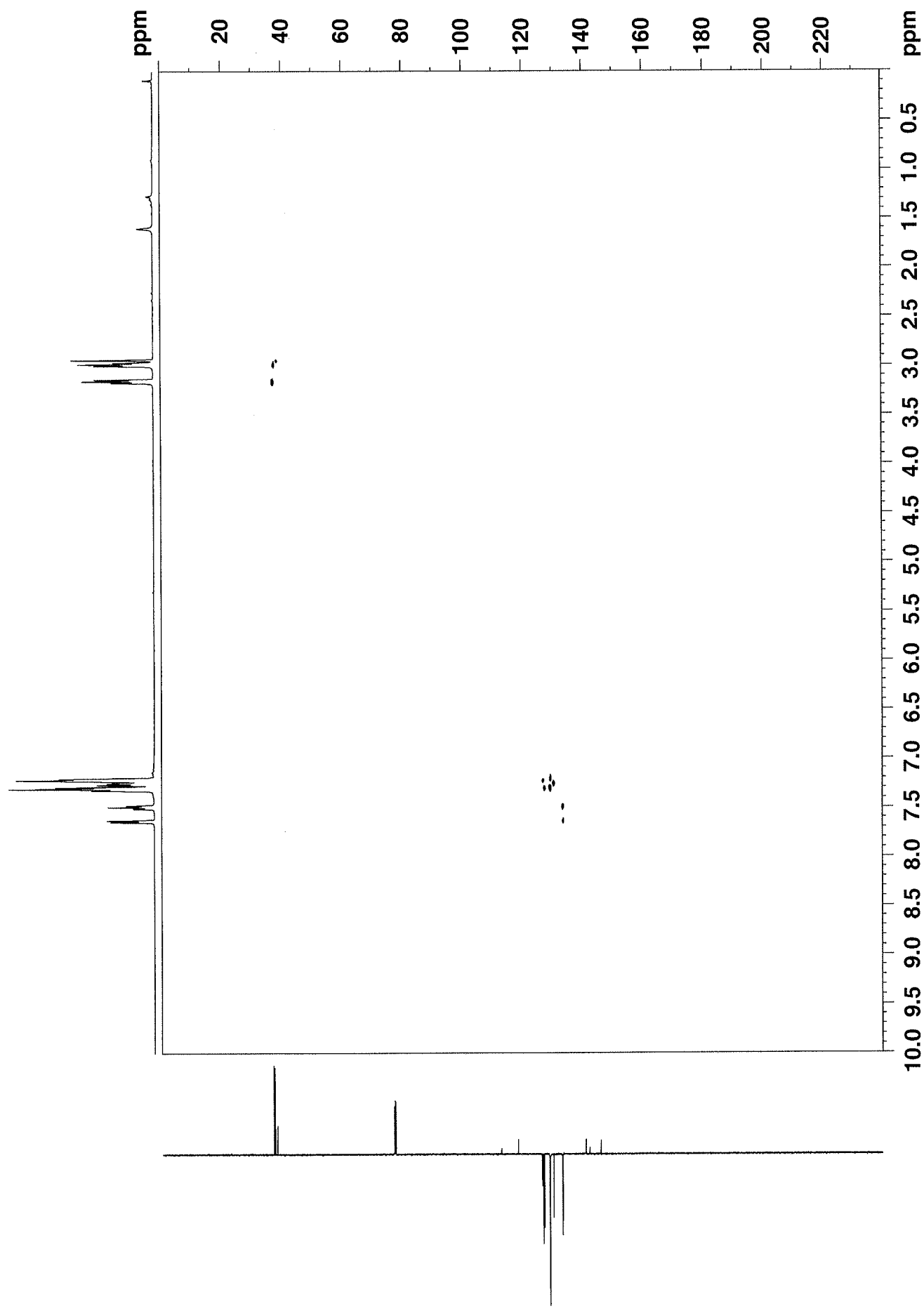




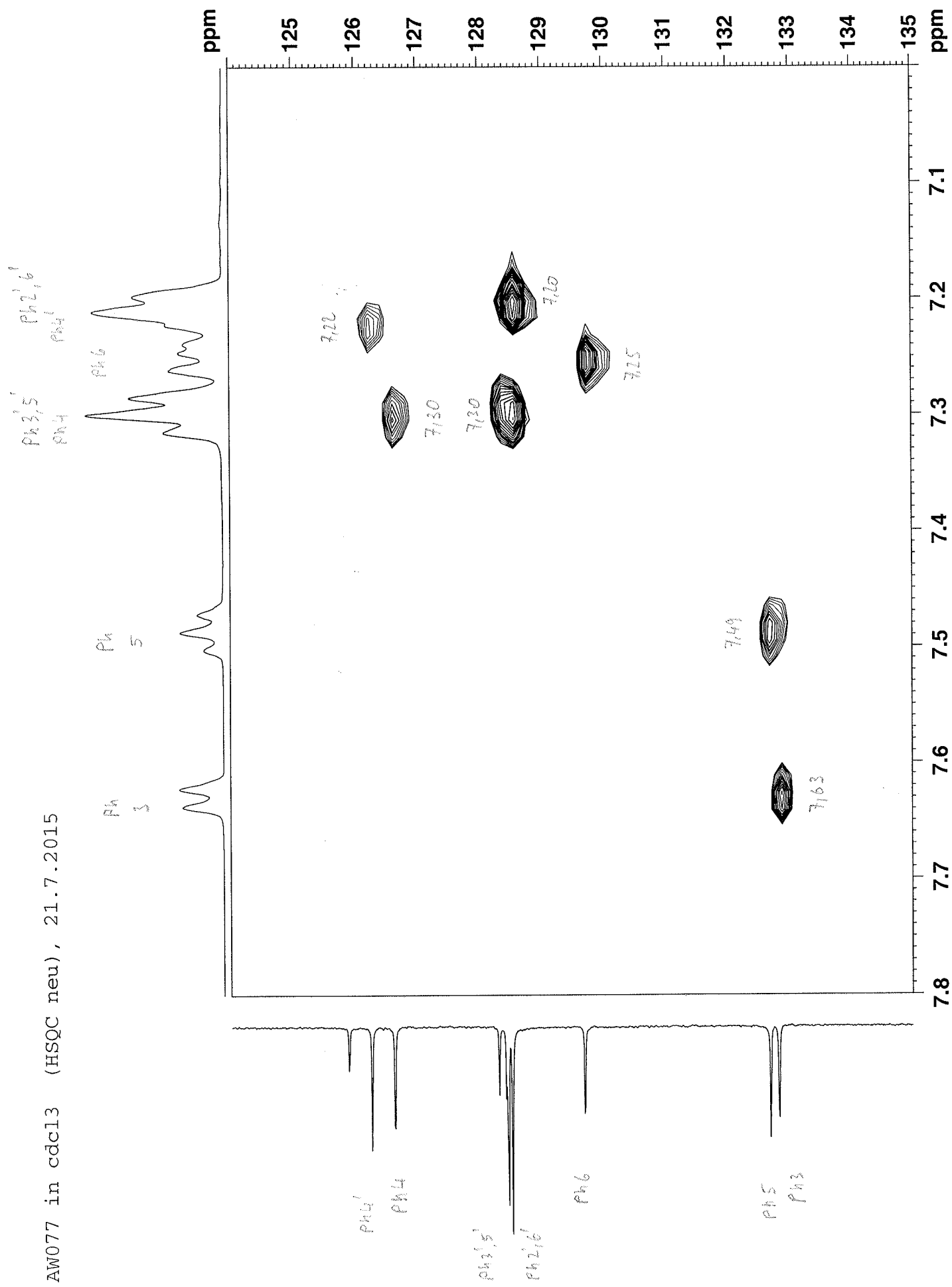




AW077 in cdcl3 (HSQC neu), 21.7.2015

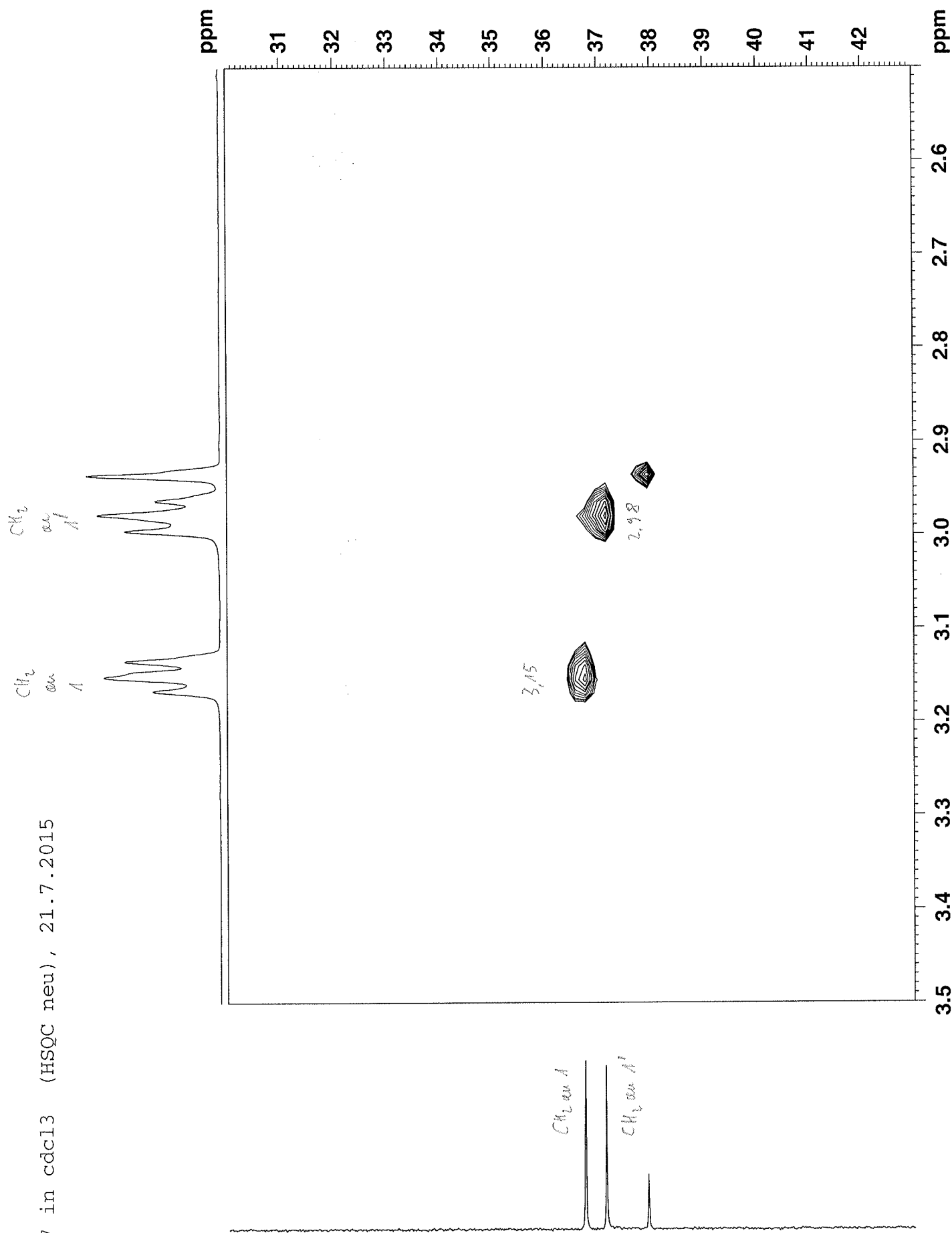


AW077 in cdcl3 (HSQC neu), 21.7.2015

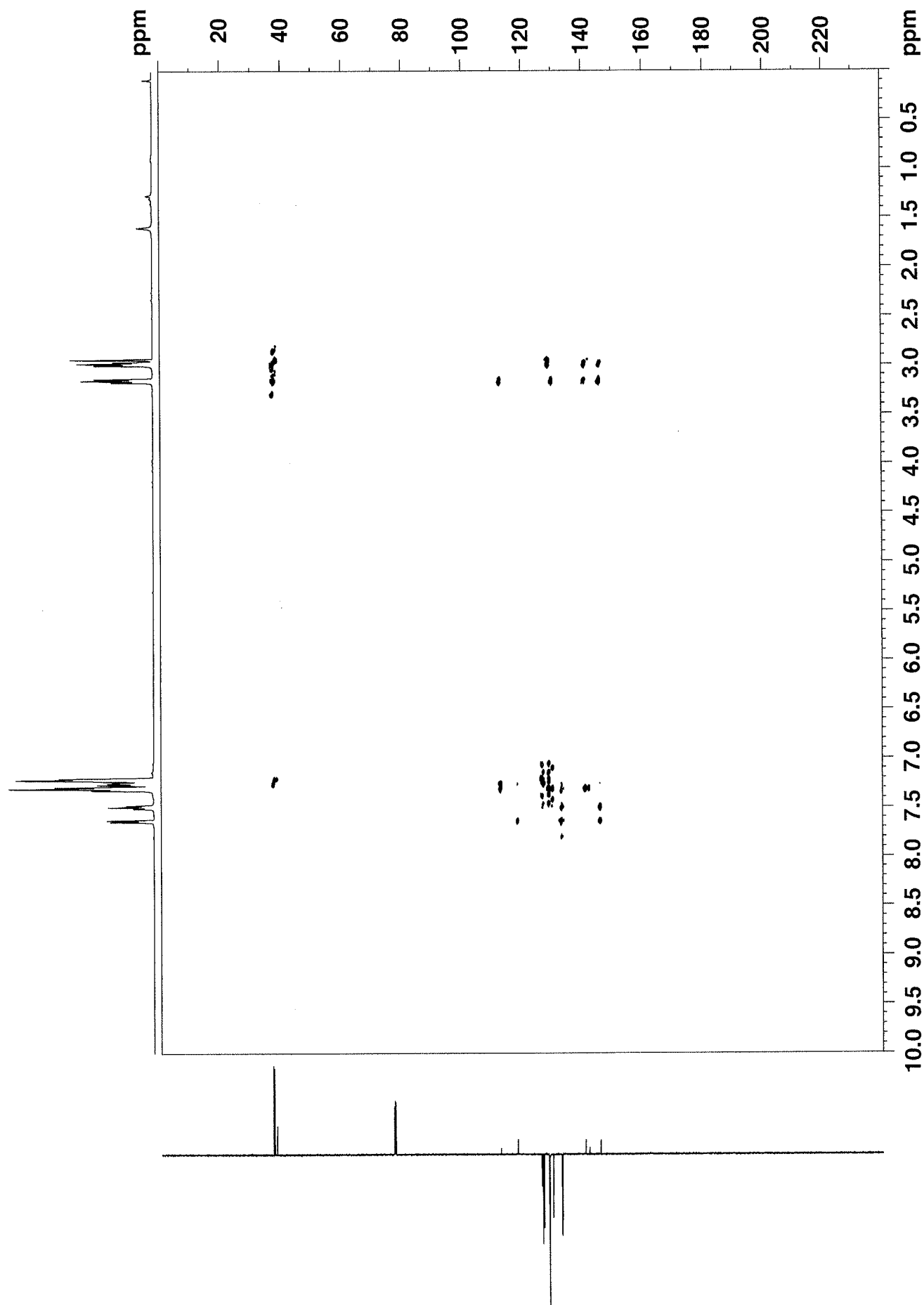


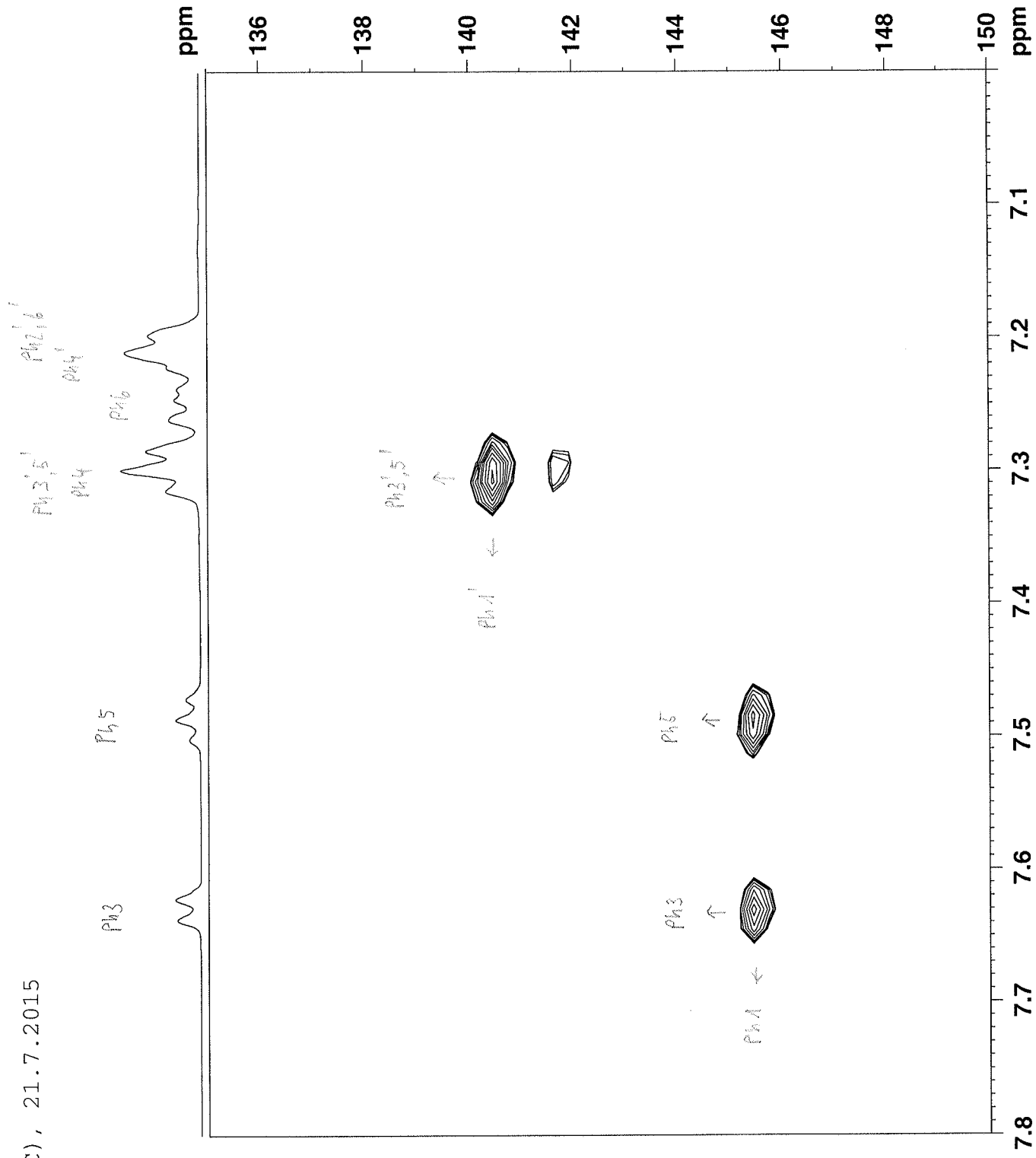


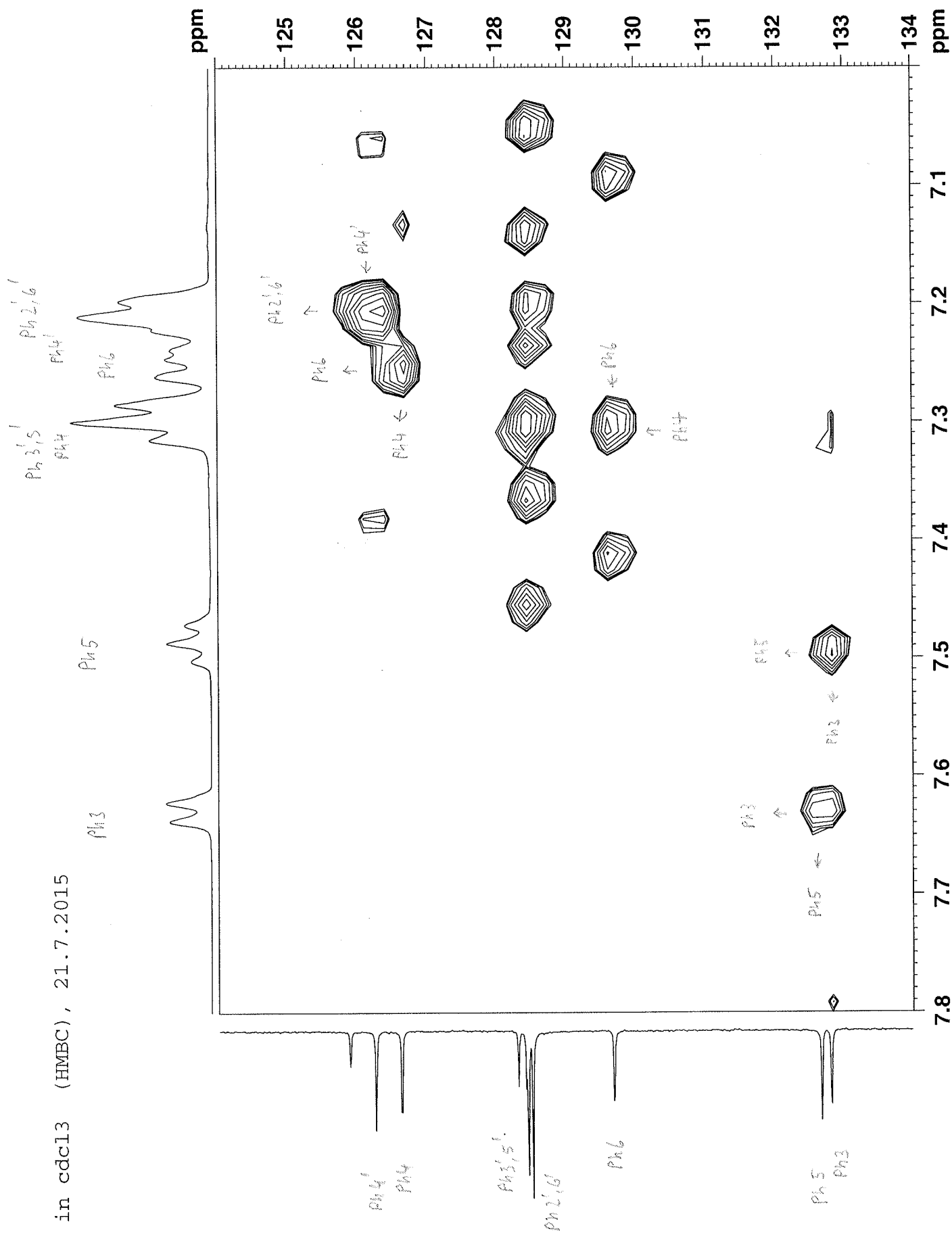
AW077 in cdcl3 (HSQC neu), 21.7.2015



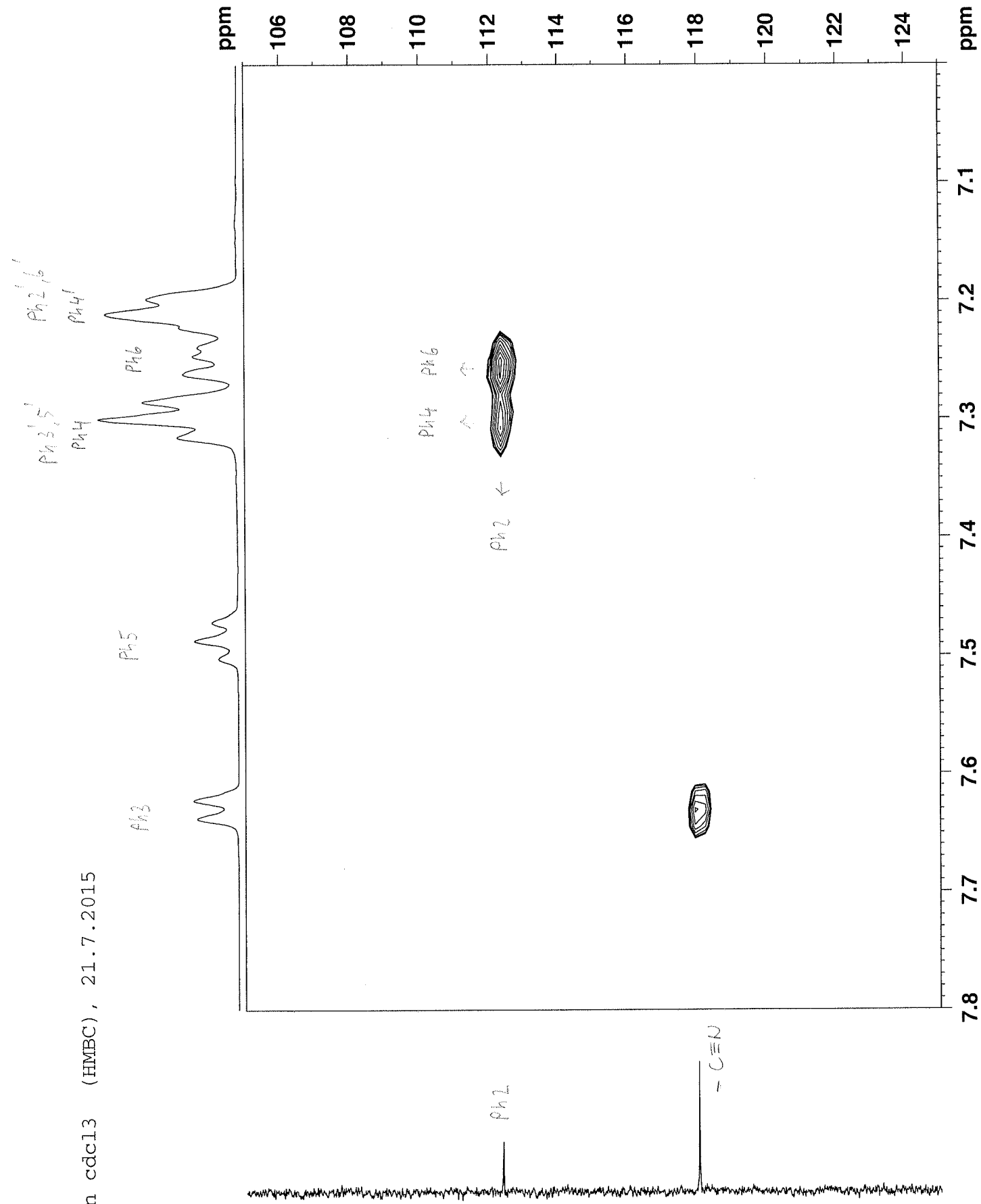
AW077 in cdcl3 (HMBC), 21.7.2015

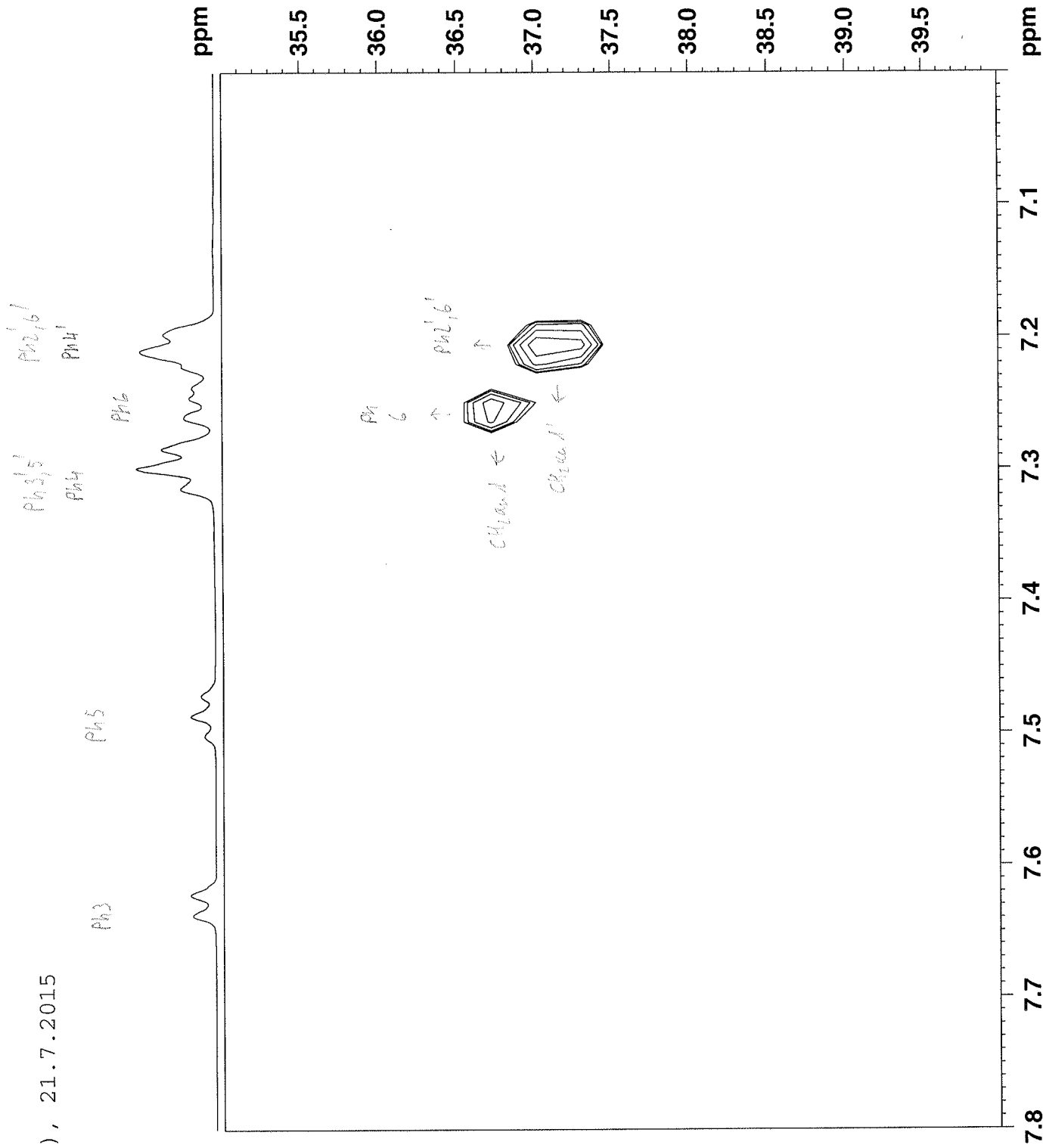




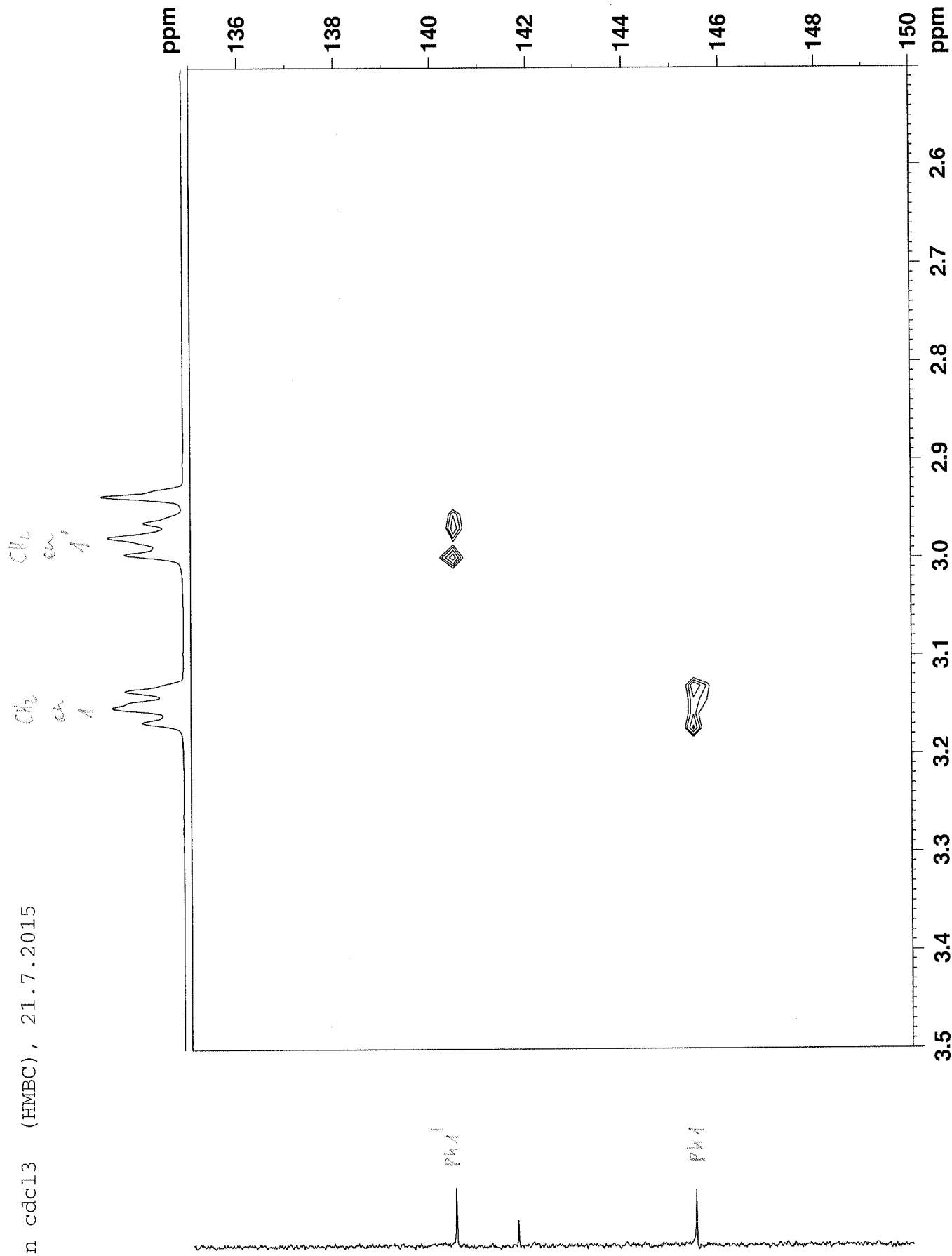


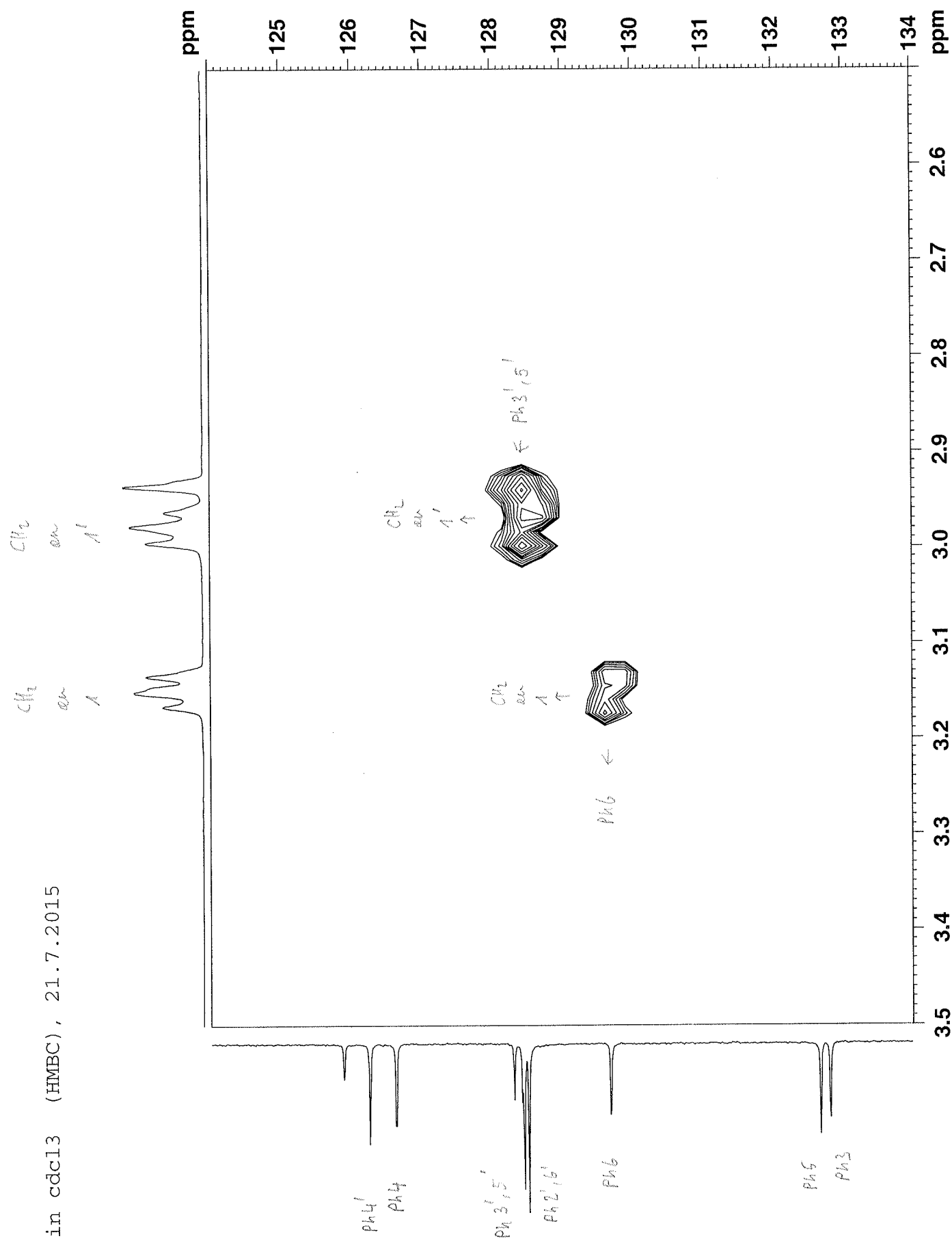
AW077 in cdcl3 (HMBC), 21.7.2015





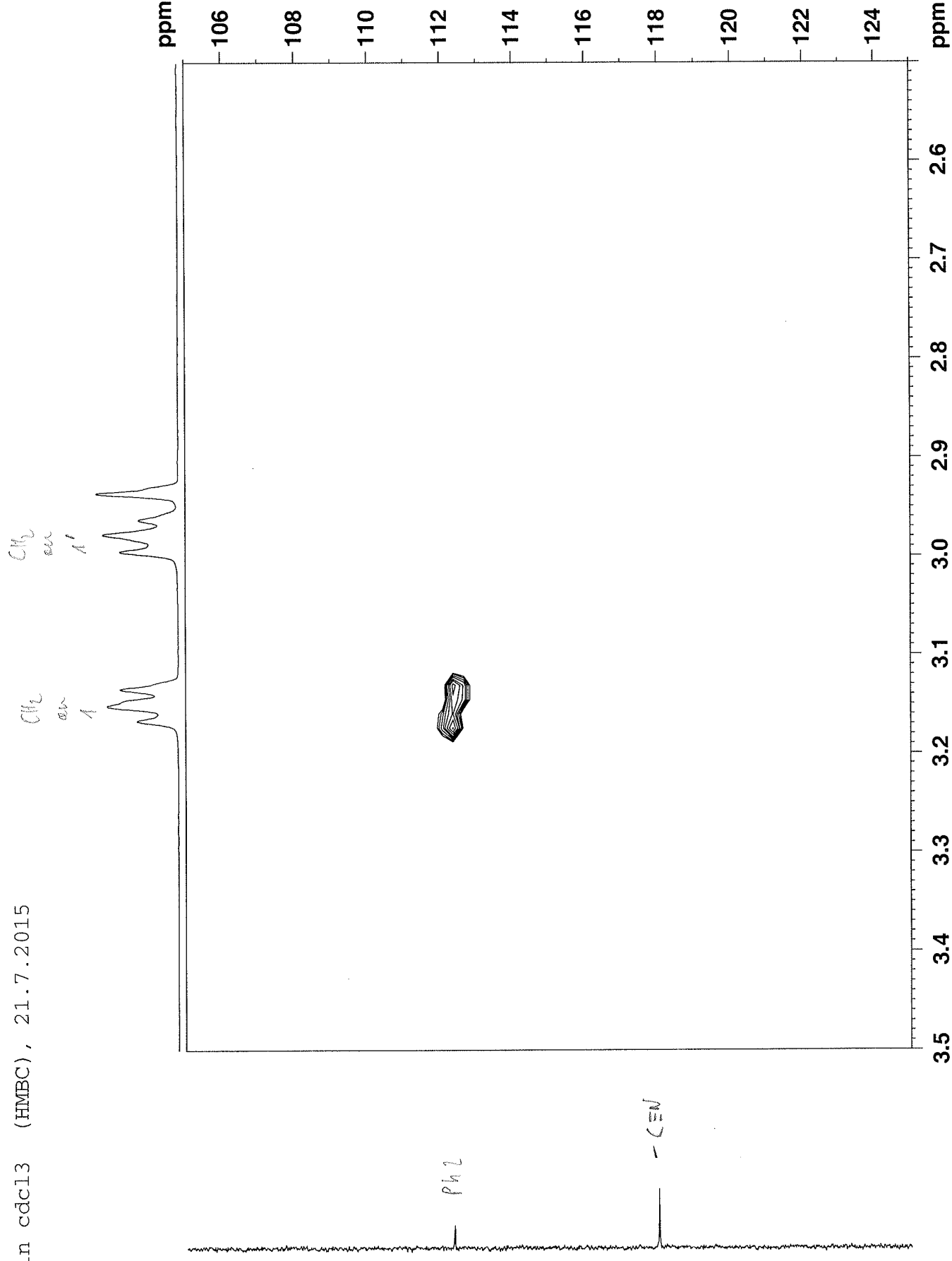
AW077 in cdcl3 (HMBC), 21.7.2015

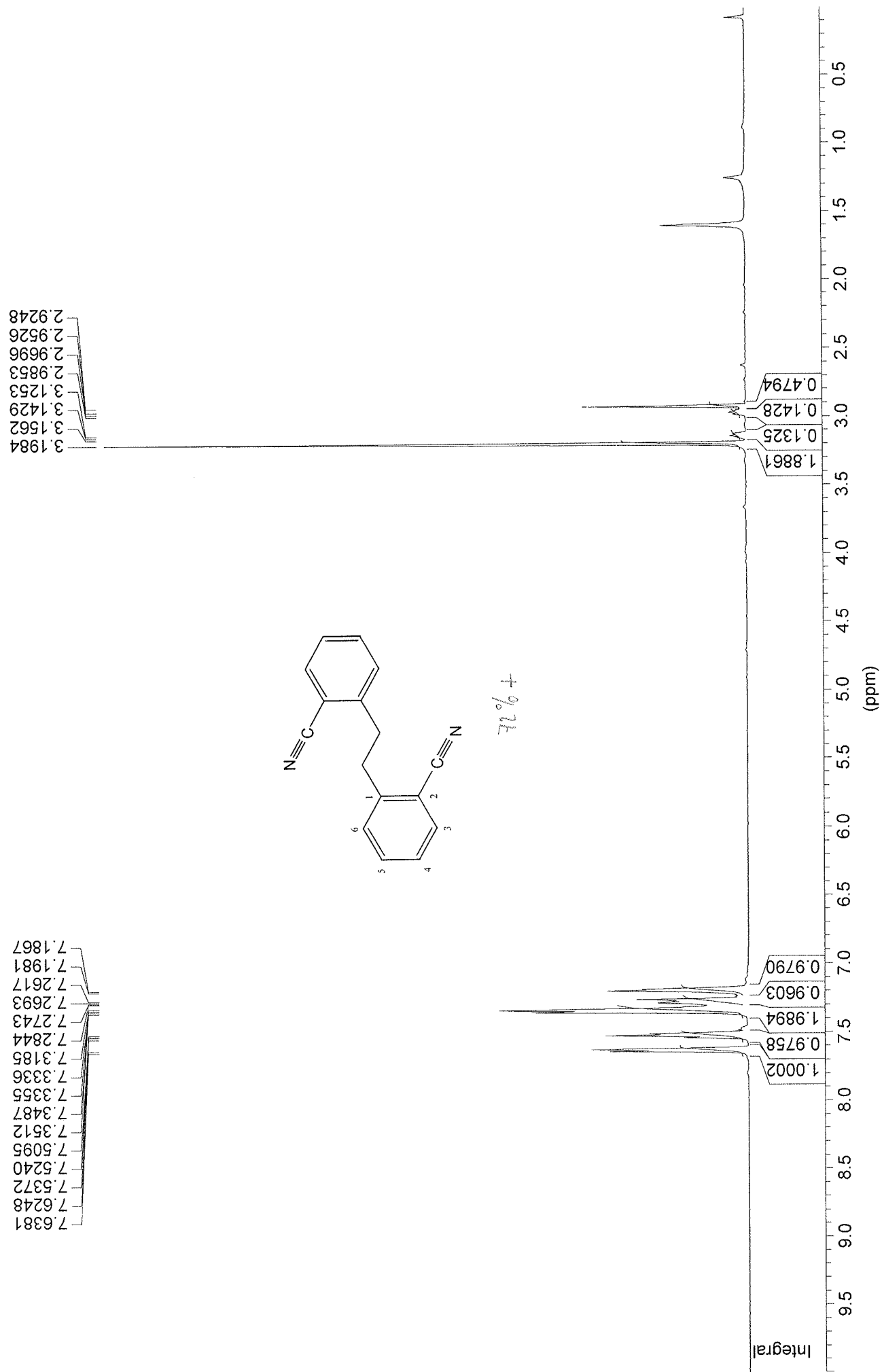


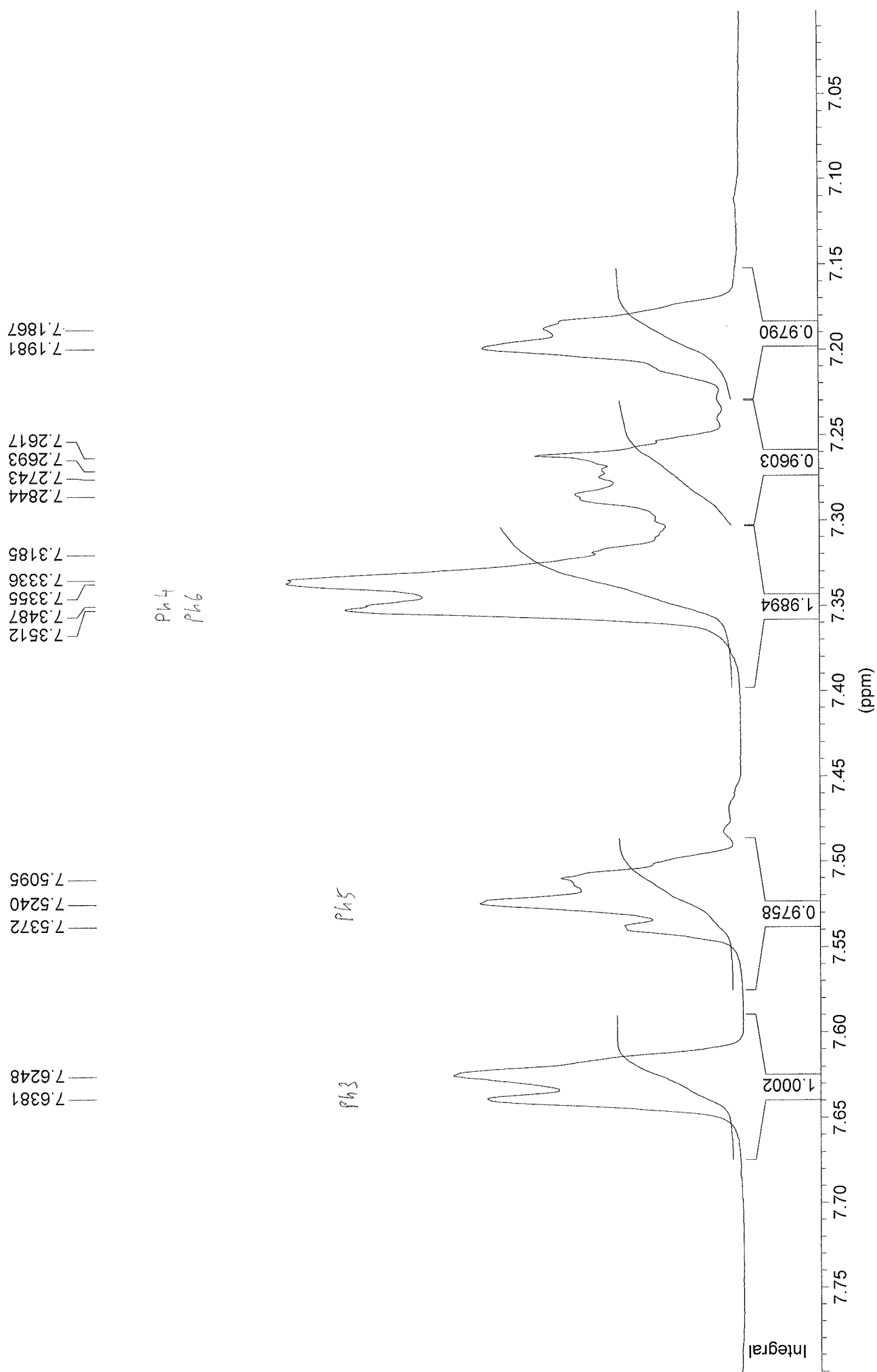


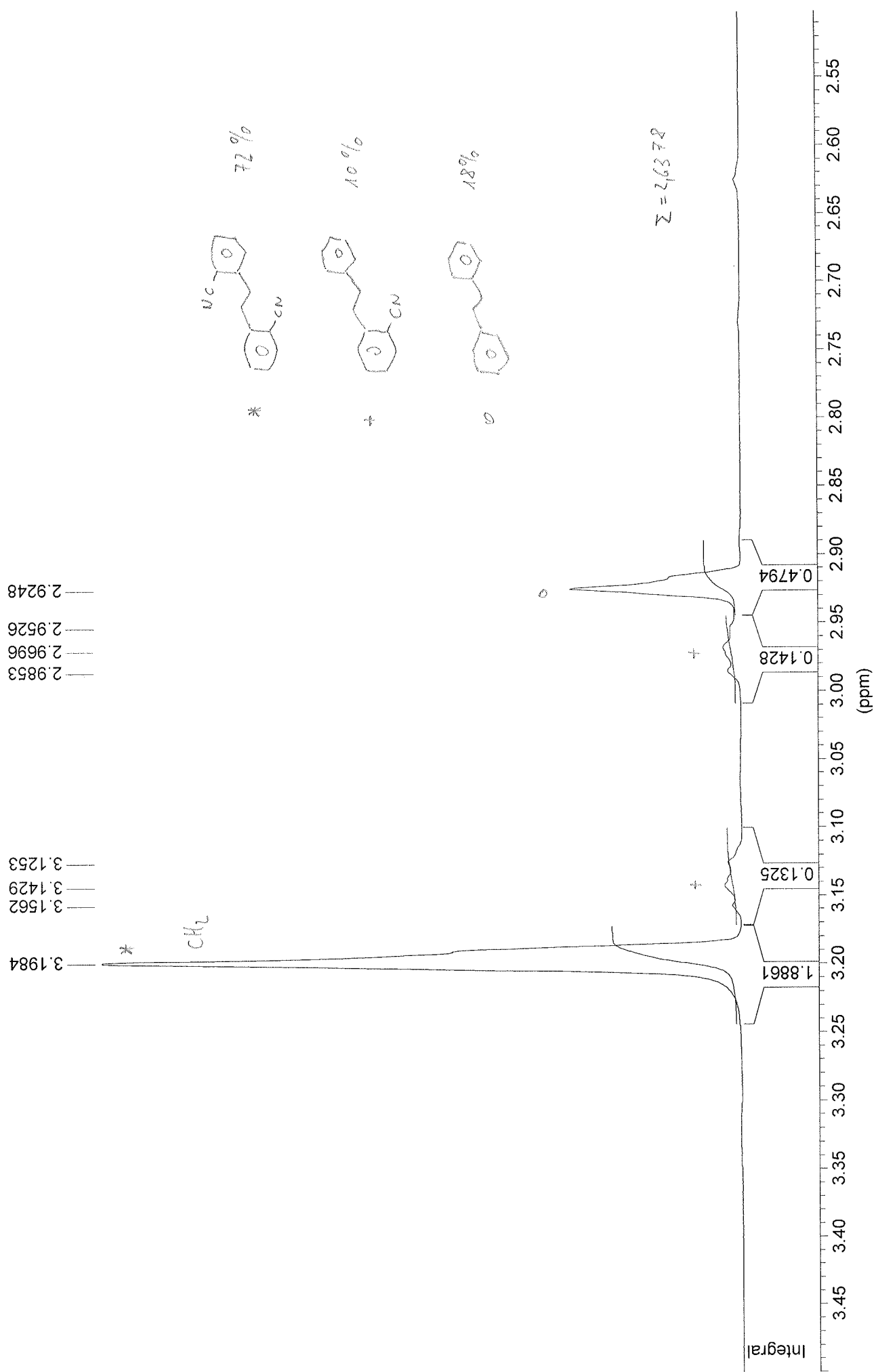


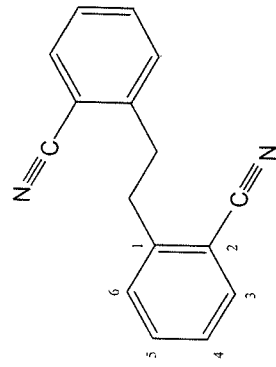
AW077 in cdcl3 (HMBC), 21.7.2015



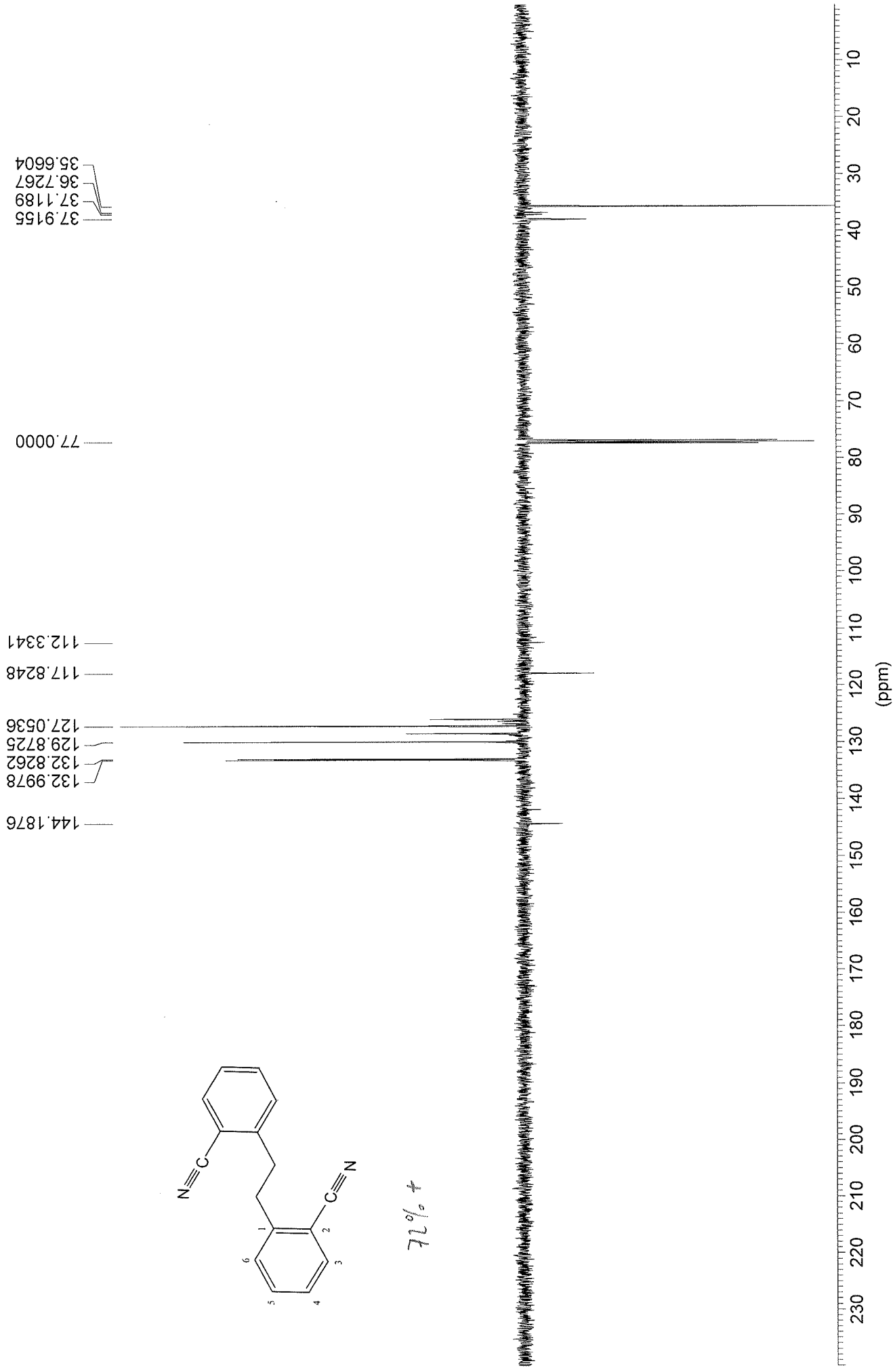


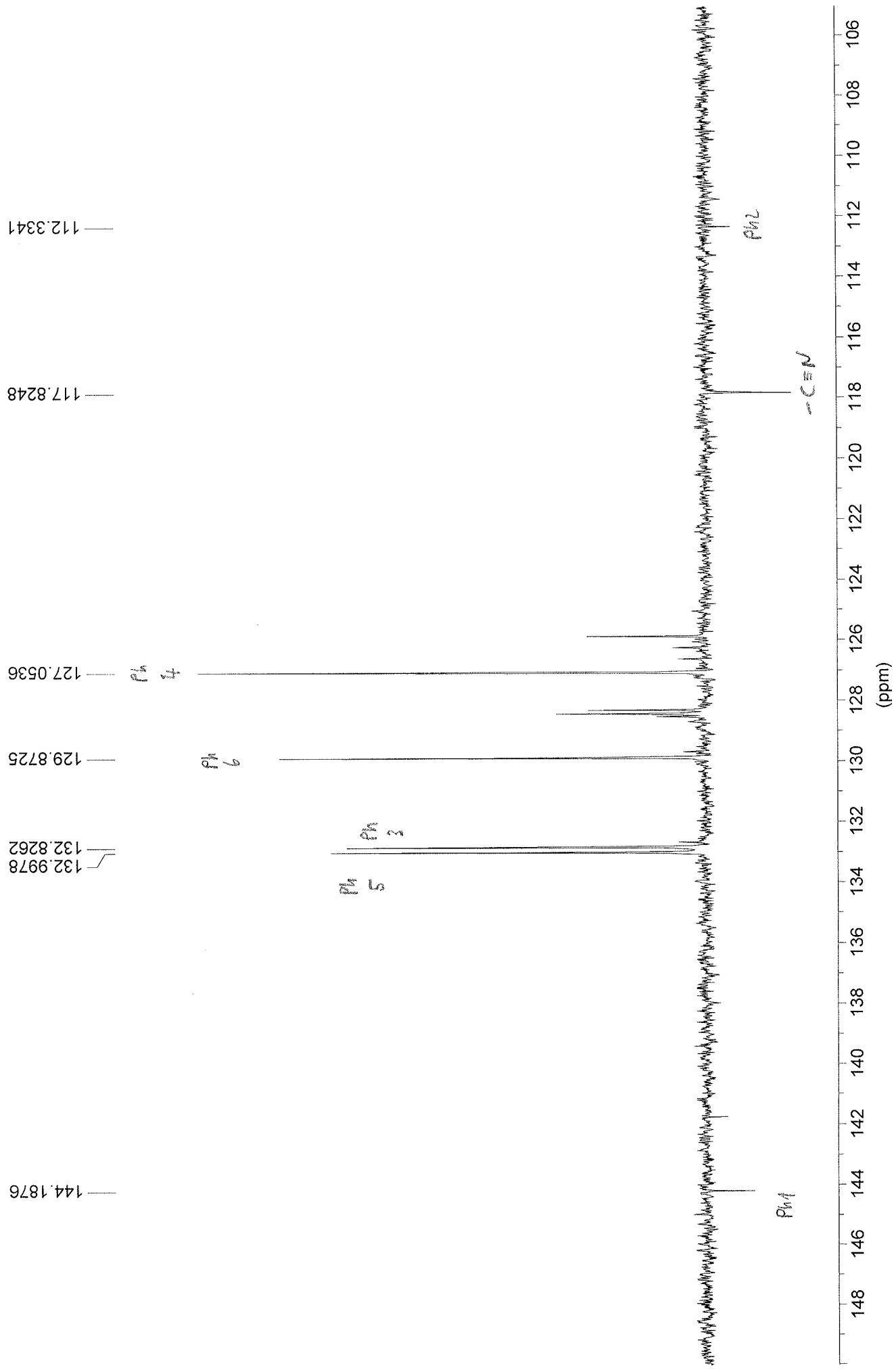


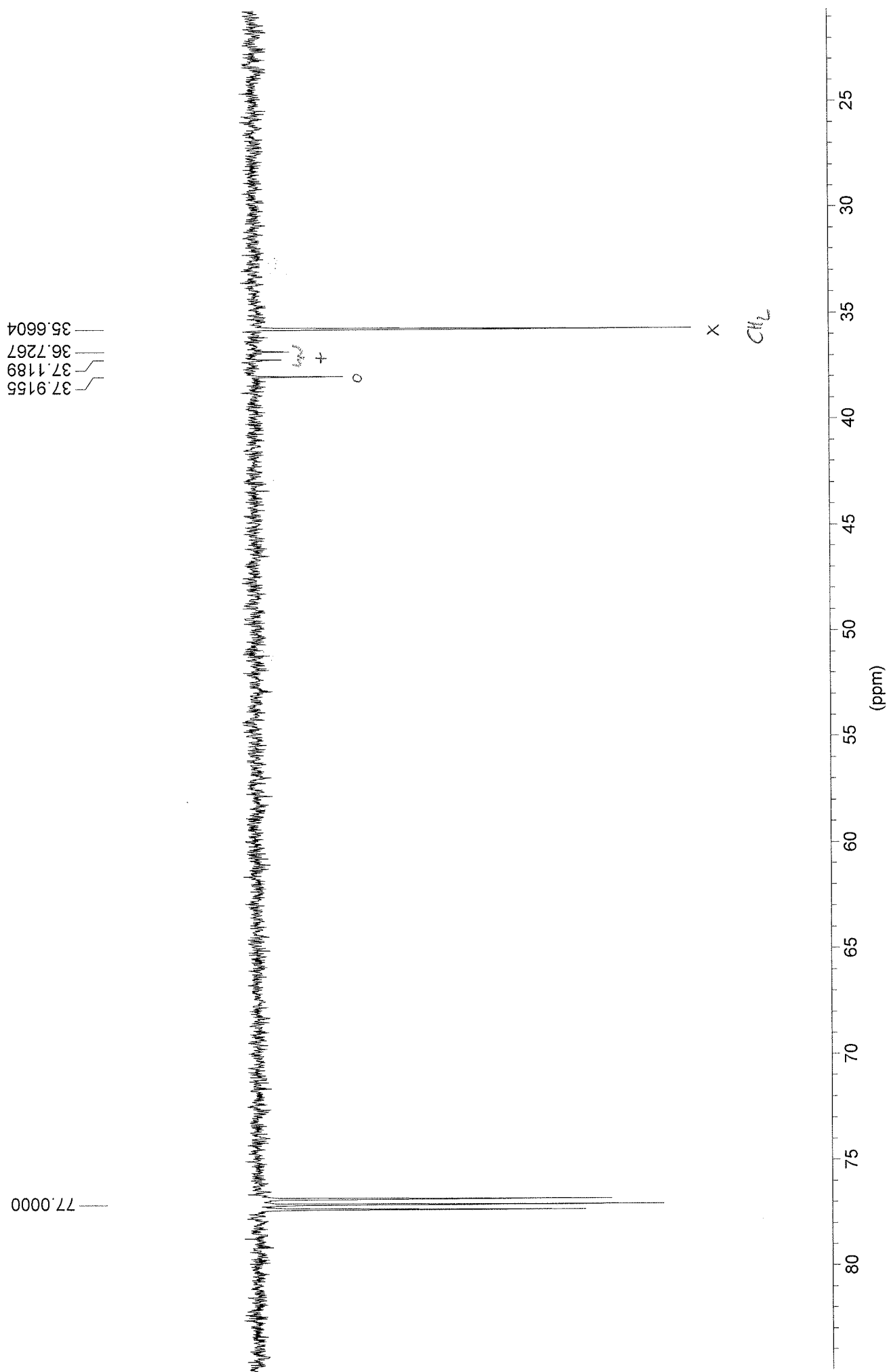




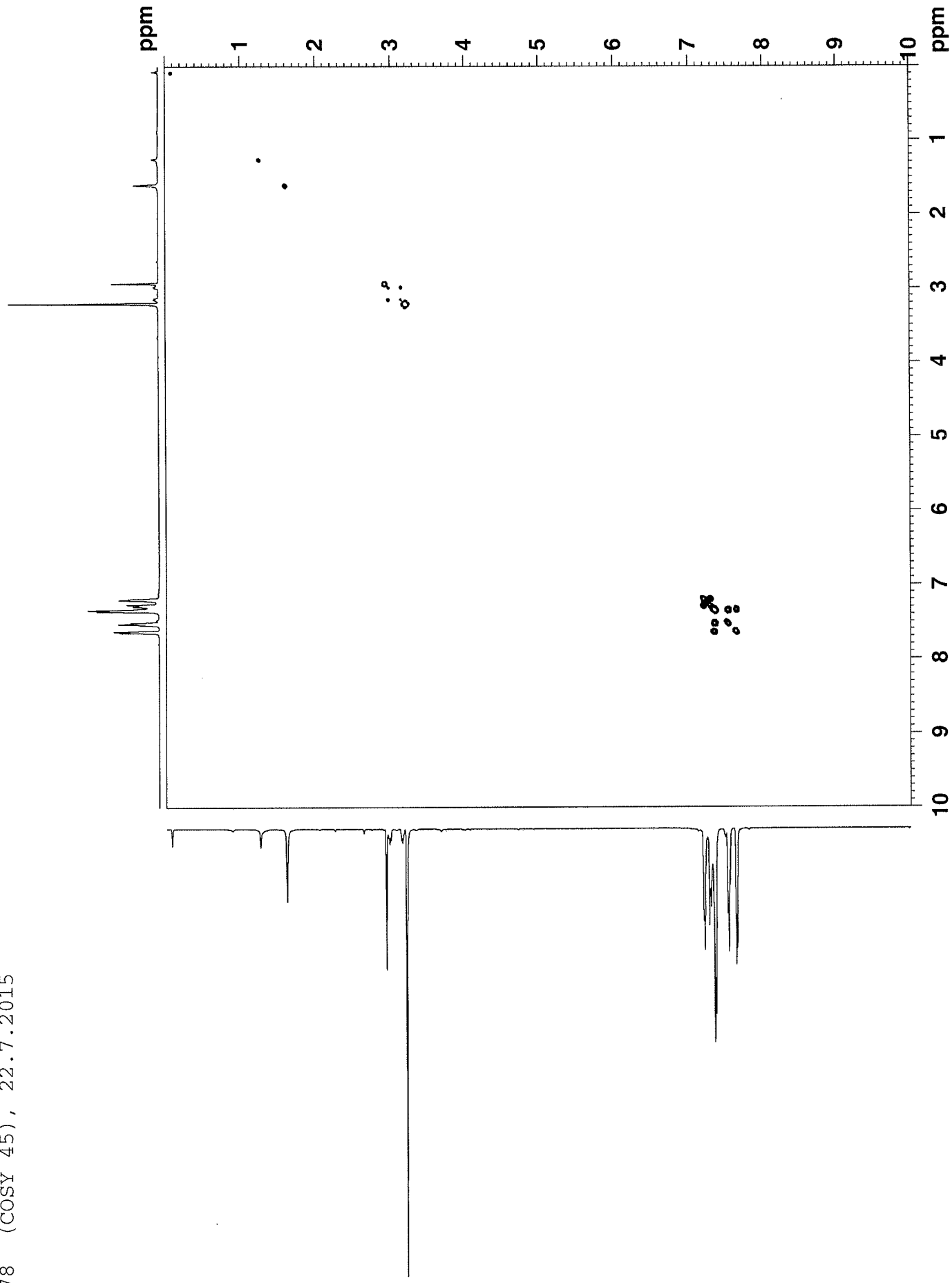
72%



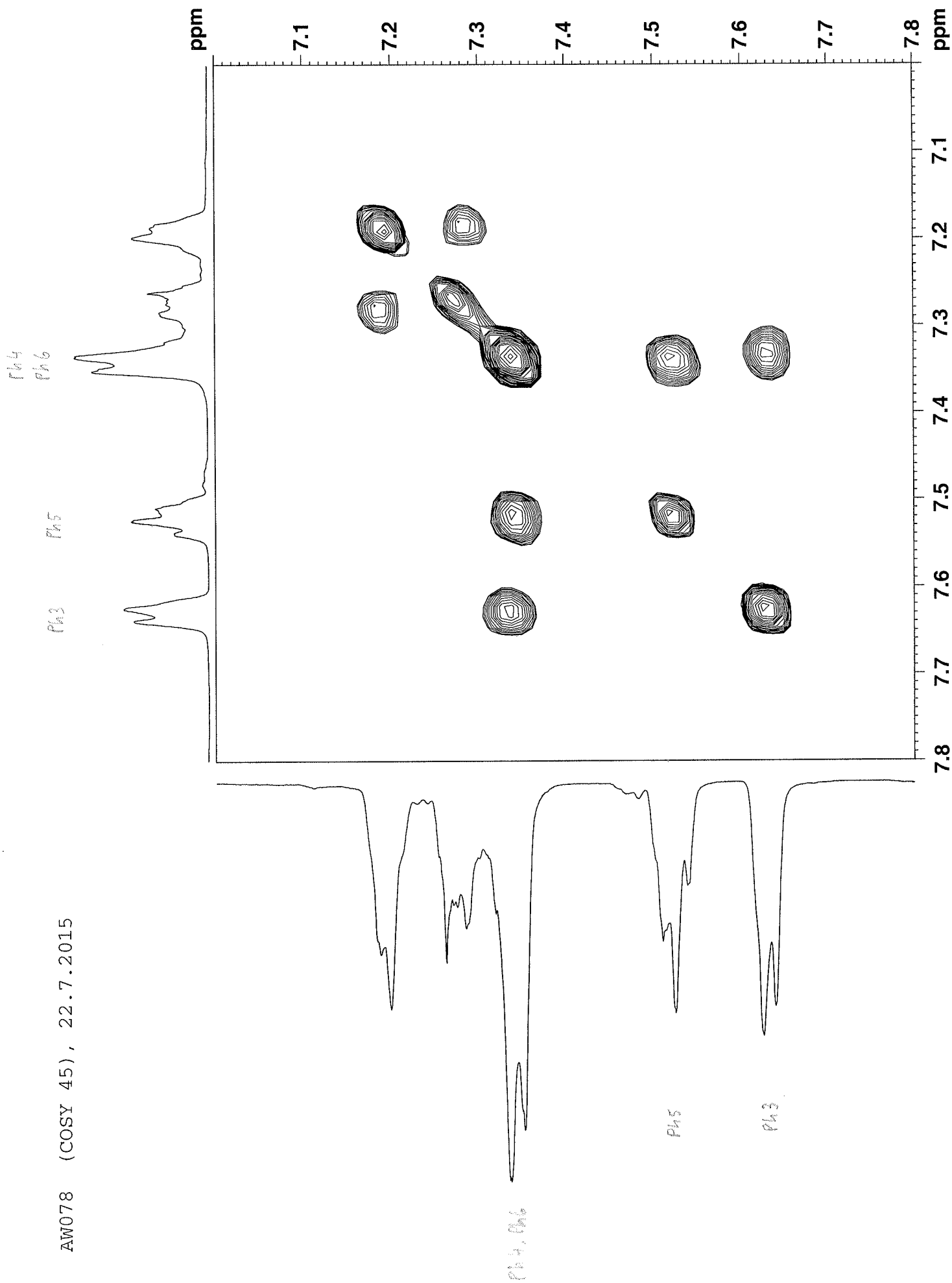




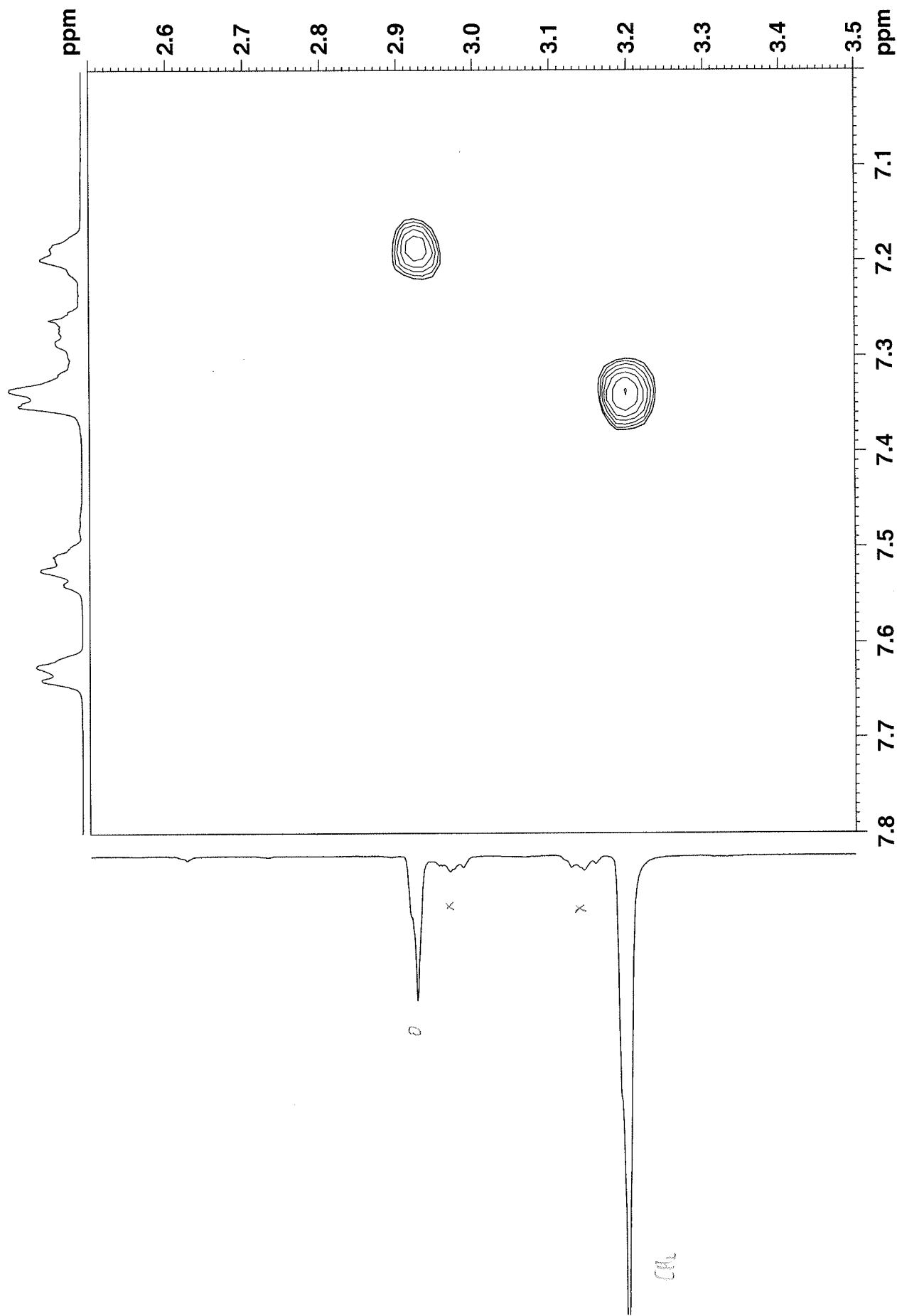
AW078 (COSY 45), 22.7.2015

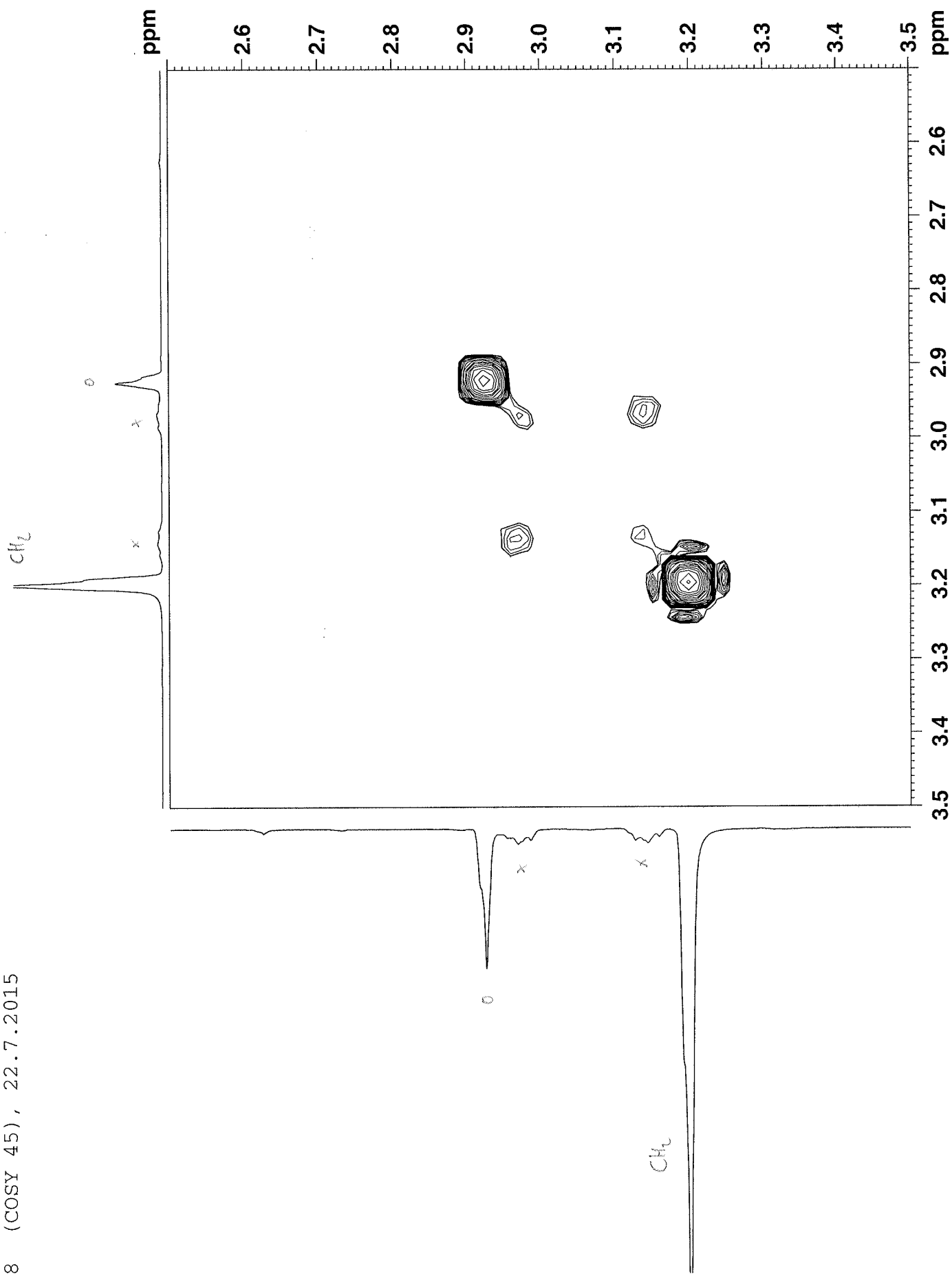




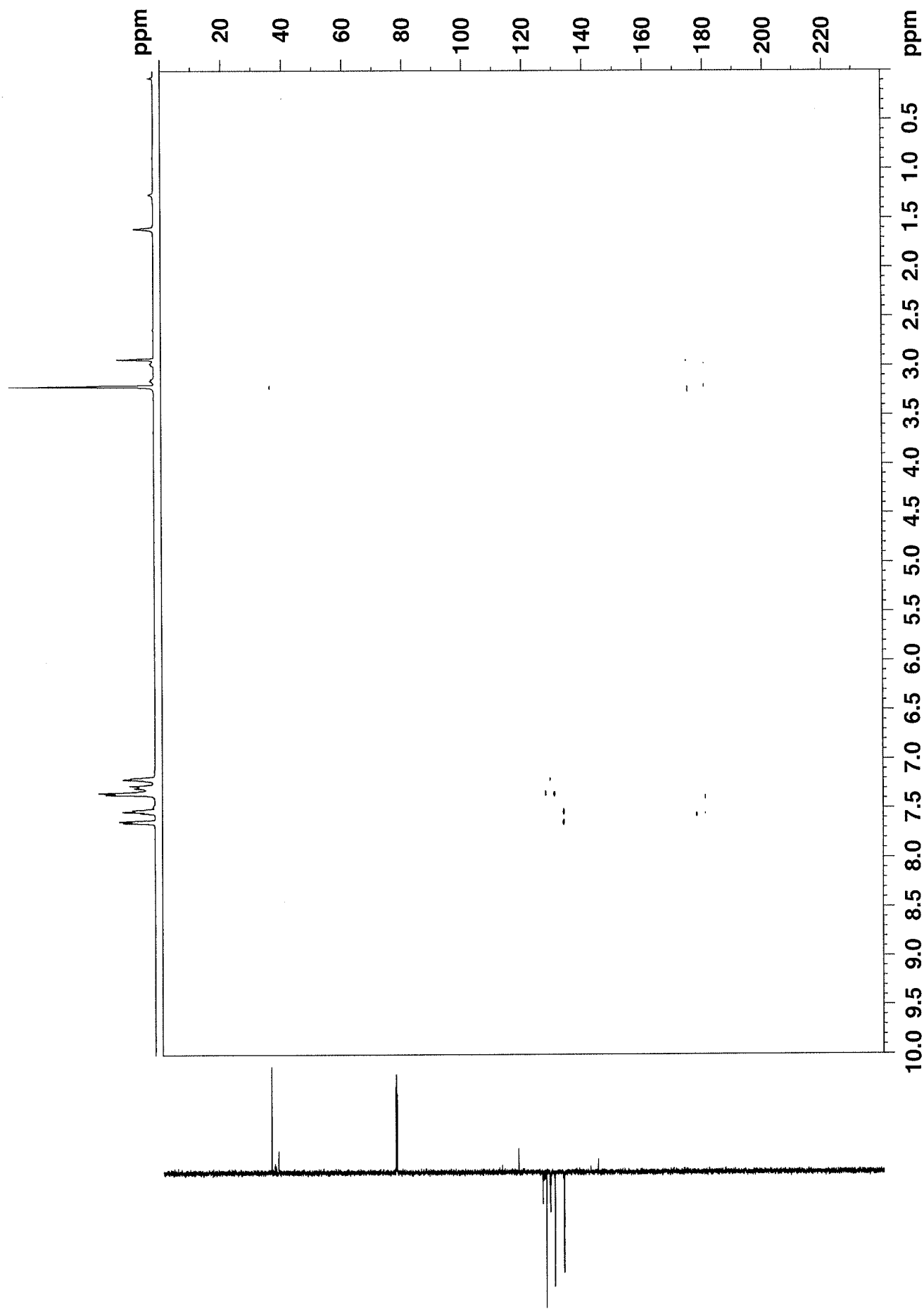


Ph3 Ph5  
Ph4 Ph6

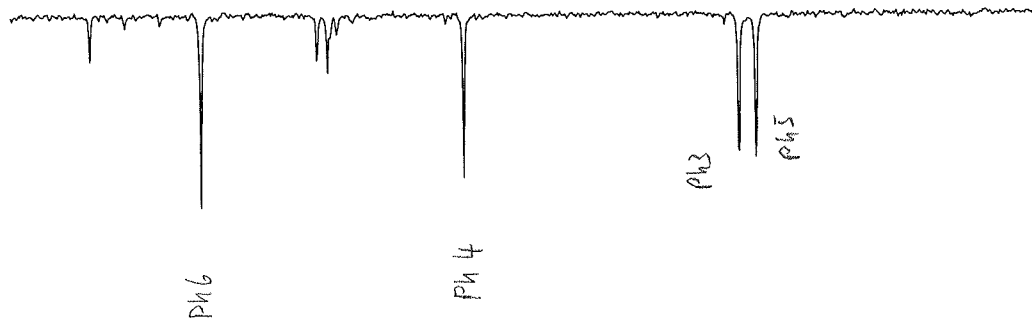
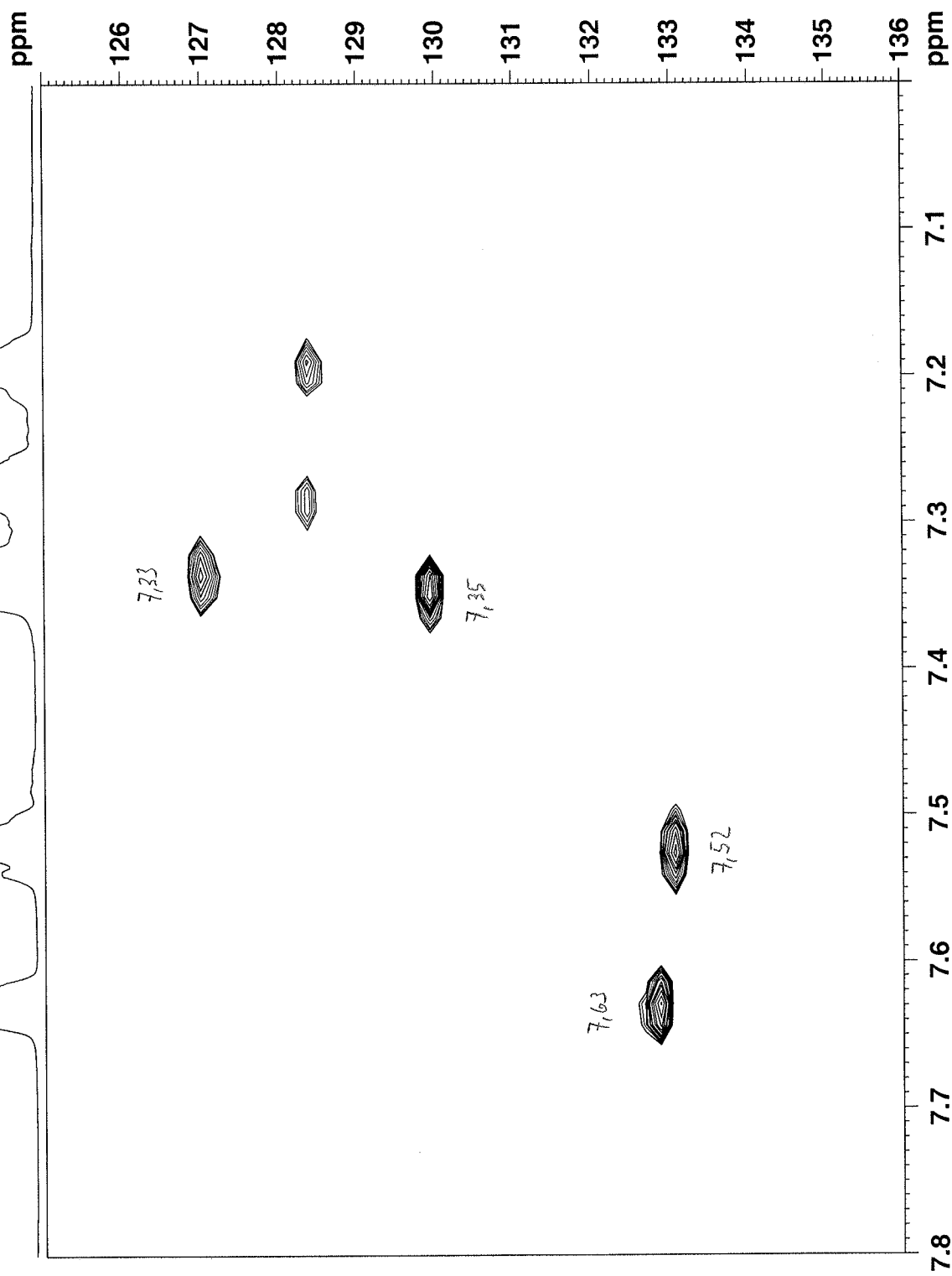




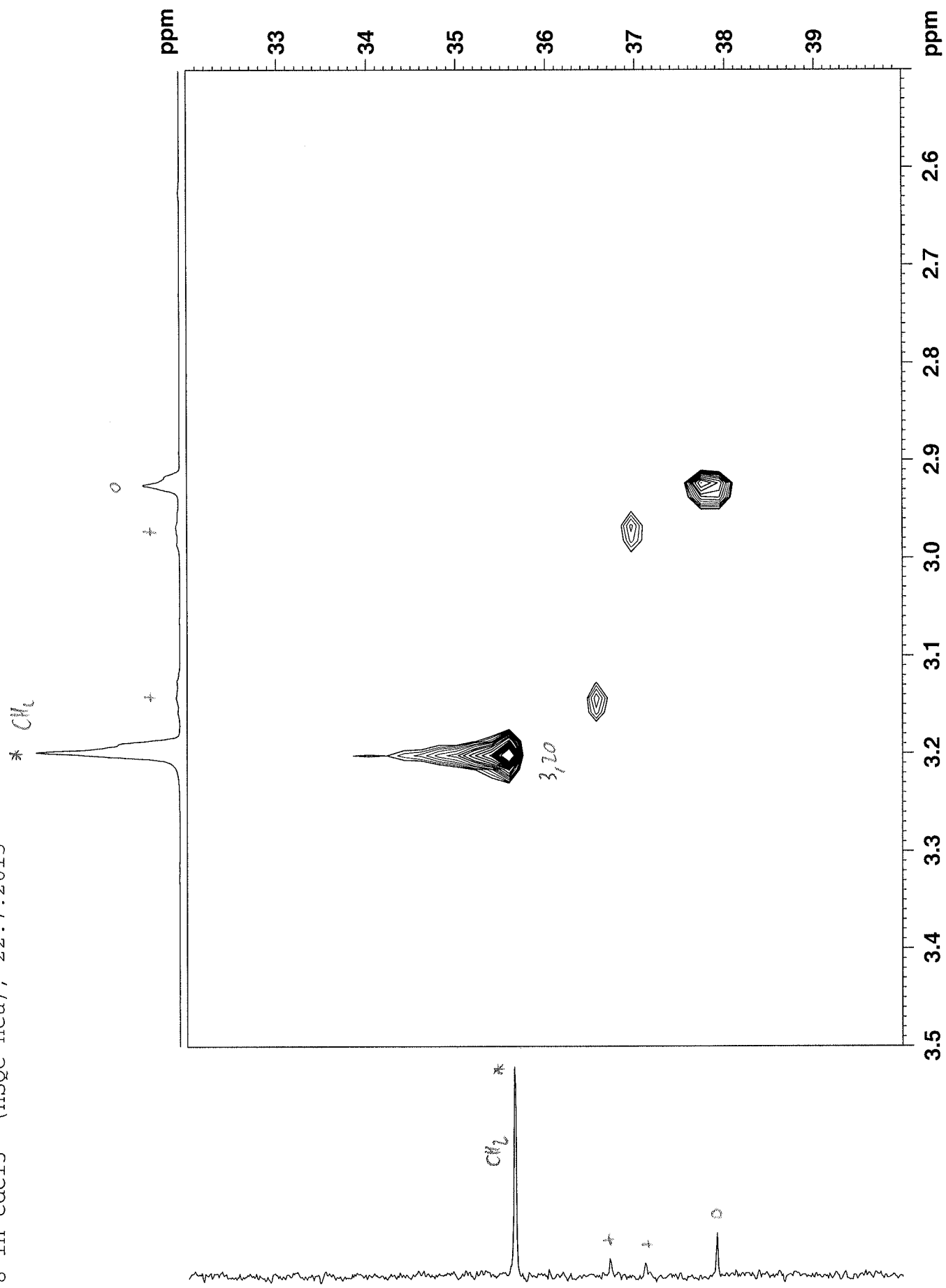
AW078 in cdcl3 (HSQC neu), 22.7.2015



Ph4  
Ph6  
Ph3  
Ph5



AW078 in cdcl3 (HSQC neu), 22.7.2015



AW078 in cdcl3 (HMBC), 22.7.2015

