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Gabriela Lukas

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1 Introduction

1.1 General Information

Nowadays, GABA-receptors are a very popular topic because a lot of different drugs are able to react with these receptors. These substances activate variable binding sites of GABA-receptors and therefore they lead to numerous helpful effects.

This diploma thesis is about design, optimisation as well as synthesis of novel GABA_A-receptor ligands. Our emphasis lied on synthesising new GABA_A-receptor ligands.

1.2 GABA-receptors

Gamma-aminobutyric acid is a major inhibitory neurotransmitter in the human brain. It is built up out of glutamate with help of the glutamate-decarboxylase. Glutamate is synthesised out of glutamine or alpha-ketoglutarate. To reduce the effect of the neurotransmitter, gamma-aminobutyric acid is removed out of the synaptic cleft. The return transport is interfered with help of a transporter called CAT-1. There are two options. On the one hand the regained GABA could be stored again or on the other hand it is transformed to succinate and included into the citric acid cycle. There glutamate is built out of succinate again [1].

Gamma-aminobutyric acid binds to so called GABA-receptors, which triggers important effects in the human body depending on the receptor type. There are two main types of GABA-receptors which are GABA_A-receptors and GABA_B-receptors. GABA_A-receptors are pharmacological important because a lot of drugs are acting via these receptors [2].

Most of GABA_A-receptors are built up out of five subunits. Usually there are two alpha-, two beta-, and one gamma-subunit. These subunits are assembled out of six possible alpha-subunits, three gamma-subunits and three different beta-

subunits. In rare cases there could also be a sigma-subunit instead of a gamma-subunit [3].

GABA_A-receptors are activated through gamma-aminobutyric acid which results into opening chloride channels and a hyperpolarisation [4].

GABA_B-receptors act G-protein-coupled with potassium-channels and so there is a higher potassium outflow as normal, which also leads into a hyperpolarisation [4].

GABA_C-receptors are only located in the retina of the eye. It is also a ligand controlled chloride channel, which is activated through cis-aminocroton acid. In contrast, the GABA_C-receptor consists out of only two subunits instead of five and there are lower concentrations needed to activate the GABA_C-receptor [5].

1.3 Chirality

A molecule is indicated as a chiral one if it cannot be realigned on its mirror image by reorientation (rotation etc.). A chiral molecule acts to its mirror image as the left hand to the right hand. There are two main types of chirality which are central and axial chirality. Normally, central chiral molecules have as an asymmetry central an asymmetric substituted carbon. Instead of the asymmetric carbon there could also be heteroatoms such as nitrogen, phosphor and so on. Axial chirality means that there are not only asymmetric substituted carbons or heteroatoms but there is also a chiral axis instead of an asymmetric centre. So every molecule which does not have a mirror symmetry is a chiral one. Therefore there are a lot of other alternatives for being a chiral molecule as an asymmetric substituted carbon or heteroatom. To name an example for drugs central chirality plays the most important role [6].

Structures which are not mapped to each other are called enantiomers. For comparison a diastereomer does not behave like image and mirror image. On the one hand the chemically and physically effects of two diastereomers are different and on the other hand two enantiomers have the same chemically and physically

effects. There is one exception and this regards linearly polarised light. If this light moves through a solution of one enantiomer, the plane of polarisation turns right or left. The direction depends on which enantiomer is used. That is a good way to identify which of the two enantiomers is present [7].

Chiral substances are very important because a lot of substances which are available at the market are chiral, all biological receptors are chiral and the most important point is that two enantiomers could have different pharmacological activity. Often enantiomer compounds are obtained through isolation from natural sources. This makes us dependent on nature. There are many ways to receive an enantiomer pure substance. On the one hand the compound could be synthesised in racemic form and separated complexly and on the other hand there is a bacterium or plant which can produce it. Another way which is becoming more and more popular are asymmetric syntheses [8].

1.4 Asymmetric synthesis

An asymmetric synthesis is defined as a reaction in which an achiral compound is converted into a stereoisomeric product which is produced in unequal amounts [9].

In other words an achiral substance is converted into a chiral, nonracemic one with help of a chiral reagent [10].

1.5 SAMP-hydrazones

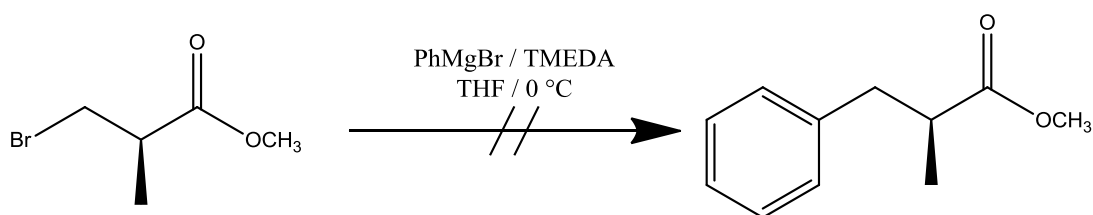
SAMP is standing for (S)-1-amino-2-methoxymethylpyrrolidin which is a chiral adjuvant. It is used for stereoselective alkylation. RAMP is called the enantiomer of SAMP and it is produced out of D-glutamic acid. By selecting the appropriate chiral adjuvant the provided stereochemistry can be realised [11].

1.6 Grignard reaction

A Grignard reaction consists out of two parts:

1. The reaction of magnesium and an organic halide in a solvent.
2. The reaction of this magnesium halide as a nucleophile with an electrophile substrate [12].

In our case, for example, an aryl-magnesium halide reacts with a bromide which is seen in the picture below.



1.7 Dess-Martin-Periodinane

Dess-Martin-periodinane was introduced by two men called Dess and Martin. This substance is used to convert alcohols into aldehydes and ketones. It is a hypervalent iodine which is very stable and dissolves easily in organic solvents. Dess-Martin-Periodinane had to be handled warily because it is a very explosive compound [13].

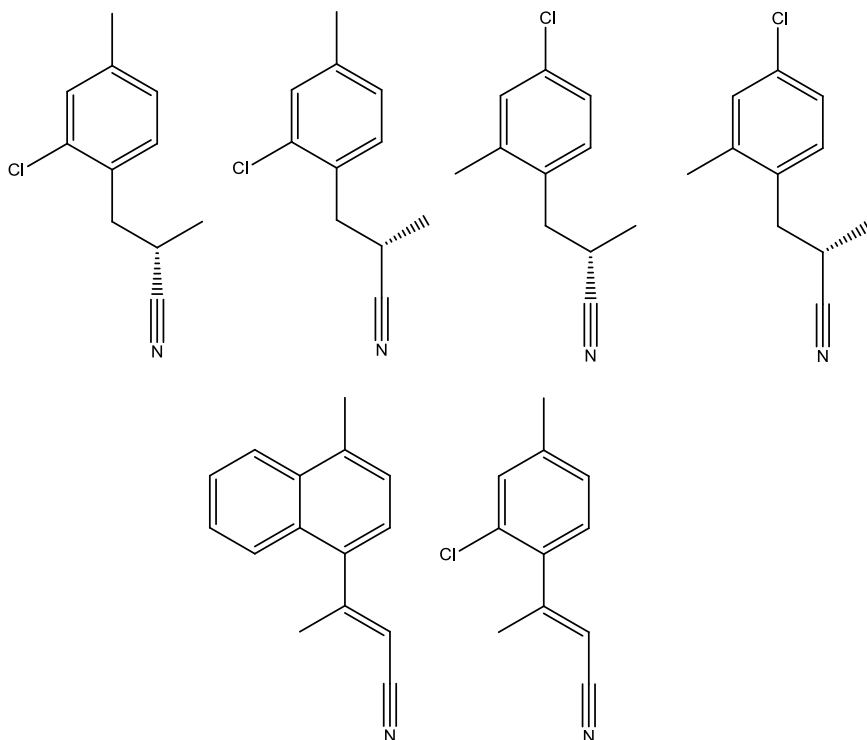
2 Aim of project

Aim of the diploma thesis was to design, optimise and synthesise novel GABA_A-receptor ligands.

The main task was to try different synthetic approaches, to purify the resulting products and evaluate the respective ¹H-, ¹³C- and 2D-NMR spectra.

On the one hand our emphasis laid on the synthesis of chiral GABA_A-receptor ligands with help of organolithiums, sparteine, Grignard reagents and organozinc halides. On the other hand our focus laid on the synthesis of achiral GABA_A-receptor ligands with help of Dess-Martin-Periodinane. We also tried to create enantiomerically pure structures with help of SAMP-hydrazones.

SAMP is standing for (S)-1-amino-2-methoxymethylpyrrolidine and it helps to get high yielded and chemoselective reactions without racemisation [14].



3 Results and discussion

3.1 Synthesis of (S)-2-(3-chloro-4-methylphenyl)-2-methylpropionitrile

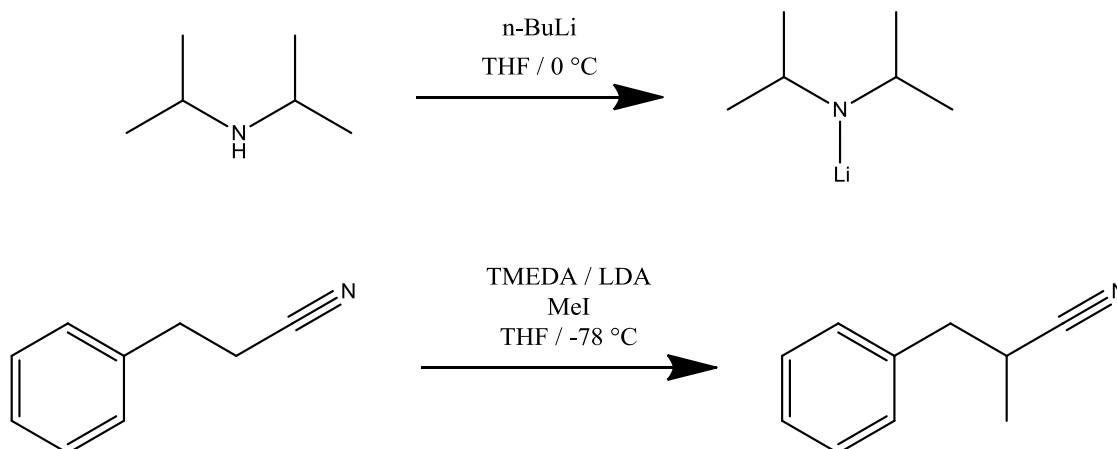
To produce enantioselective GABA_A-receptor ligands we used the following synthesis which are described below.

At the beginning we tried a metallation to see whether we were able to introduce a methyl group through alpha-alkylation or not. At first, we used organolithiums and later even sparteine to get chiral compounds.

Before we used sparteine we tried whether the methylation with TMEDA, LDA (Diisopropylamine and n-BuLi) and methyl iodide worked or not due to the fact that sparteine is very expensive.

3.2 Metallation and methylation of 3-phenylpropanenitrile via organolithiums

First we tried to synthesise 2-methyl-3-phenylpropanenitrile to see whether the methylation worked or not.



So we prepared a solution of LDA (lithium diisopropylamide) which is a strong base and used for deprotonation of CH-acidic compounds. For this we dissolved

diisopropylamine in THF, cooled down the reaction to 0°C and dropped *n*-BuLi into it [15].

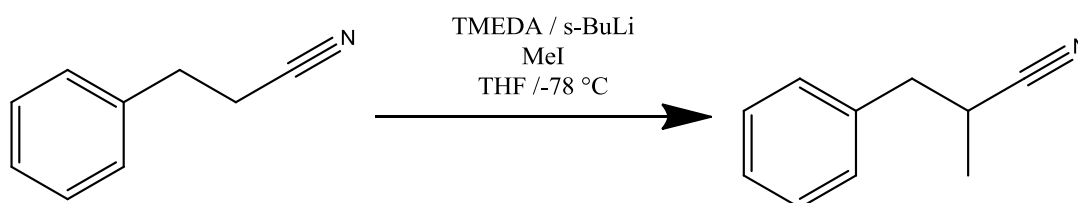
Then we solved 3-phenylpropanenitrile in THF and added TMEDA.

TMEDA is a chelate complex which is trapping lithium ions because the nitrogens of TMEDA occupy two of four coordination sides of lithium and therefore breaks up the hexameric accumulations of BuLi. As a result, BuLi could get a stronger base with TMEDA than without it [16].

After this we cooled the flask with the solution of LDA down to -78°C with dry ice and acetone and added the mixture of 3-phenylpropanenitrile, THF and TMEDA. After stirring for a half hour we dropped methyl iodide into it. Due to the alpha-deprotonation through the base lithium diisopropylamide a methylation could be performed with help of methyl iodide.

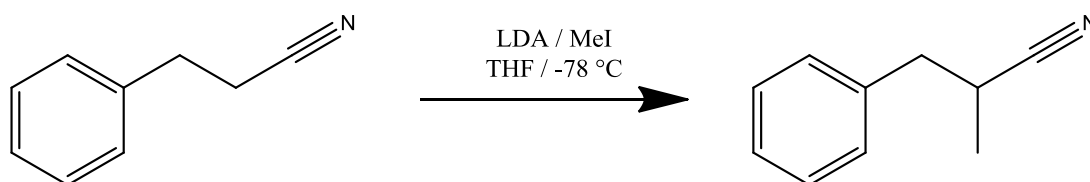
Our reaction with LDA worked very well and so we exchanged LDA with *sec*-BuLi. *Sec*-BuLi is also a very good substance for deprotonation and it is more nucleophile than *n*-BuLi [17].

So we lithiated 3-phenylpropanenitrile with *sec*-BuLi and also introduced the methyl group with methyl iodide.



3.3 Changed reaction conditions

After this we wanted to optimise our reaction conditions and so we repeated the reaction with LDA and methyl iodide but without TMEDA. There was also a product in this reaction but with the use of TMEDA the results were better.



CuCN * 2 LiCl and ZnCl₂ were also used with TMEDA, *sec*-BuLi and methyl iodide to see if the reaction conditions are deteriorated and if it is still produced a product there. Also tBuONa which is a much weaker base was taken for the reaction but there was no product.

We received two side products which are shown in the NMR-spectra added at the end of the thesis.

After we saw that the reaction worked very well we also wanted to discover the optimal time when all the starting material was converted to the maximum of the product. So we repeated the reaction and took a sample after two, four, six and twenty-four hours measured from the time when we started the reaction. We obtained the best yield after four hours.

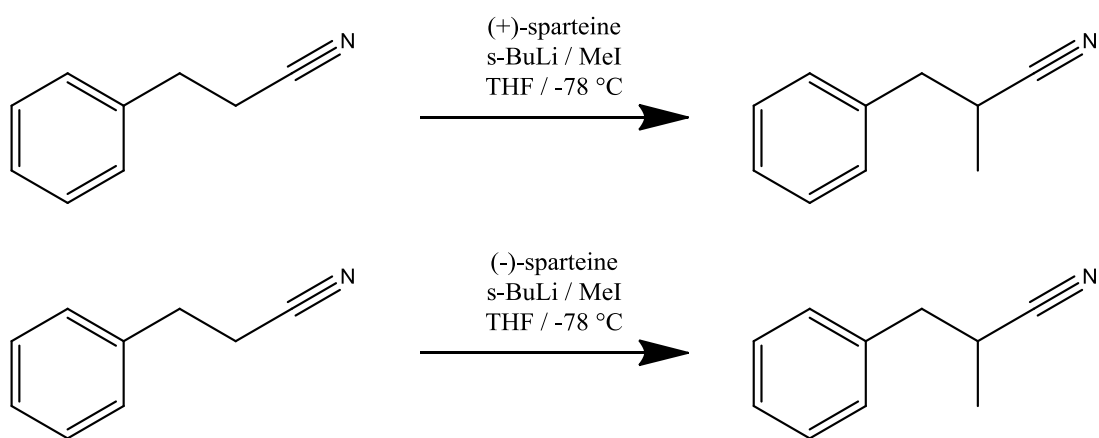
3.4 Metallation and methylation of 3-phenylpropanenitrile with sparteine

After we knew that the alpha-alkylation worked we wanted to produce pure enantiomers. For this we used (-)-sparteine and (+)-sparteine.

(-)-Sparteine could work as a bidentate ligand and it is extracted out of some members of the papilionaceae family for example common broom also called *Cytisus scoparius* [18].

When a lithium-ion which is provided with a chiral ligand for example (-)-sparteine interacts with a carbanion it is forcing the carbanion into a specific configuration. In addition to a stereospecific substitution we found a good way to obtain enantiomer pure compounds [19].

For the reaction we dissolved the starting material (3-Phenylpropanenitrile) in THF which is an organic solvent and added (+) - or (-)-sparteine dropwise. Then we added *s*-BuLi at -78°C which was chelated by (+)-sparteine and after 30 minutes of stirring we added methyl iodide to get an enantiomer pure compound.

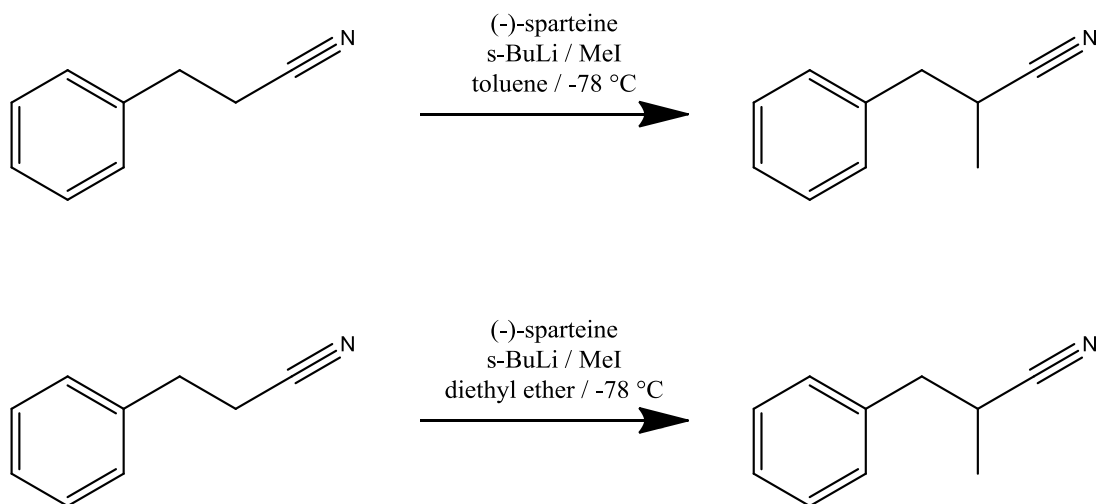


With (+)-sparteine our reaction also worked but the reaction was not that clear as with (-)-sparteine. It was very important to distill (-) – or (+)-sparteine before it was used in a reaction because it is easily oxidised by atmospheric oxygen. Otherwise we received very low yield of product.

3.5 Metallation and methylation of 3-phenylpropanenitrile with sparteine and changed solvents

With THF as our solvent the purity of our product was less. We just achieved about 75% of our desired enantiomer.

It was very interesting to see that whether we used THF (ee = 0), diethyl ether (ee = 50%) or toluene (ee = 56%) the enantioselectivity was less or more.

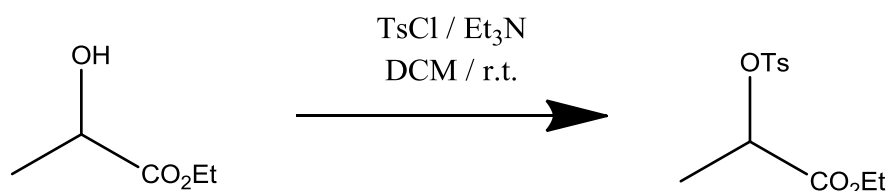


We did the same reaction with (-)-sparteine as before but one time with toluene and the other time with diethyl ether as a solvent and then we compared our results with the reaction where we used THF as solvent. Measurements of enantiomeric purity with a HPLC showed that least enantiomeric purity appeared when we used THF as solvent which was the most polar out of the three. Then there was the reaction with diethyl ether and at least the reaction with toluene.

After this we wanted to optimise our reaction conditions to get more pure enantiomers but (-)-sparteine disappeared from the market and so we had to strike a new path.

3.6 Synthesis of our chiral compound with ethyl 2-(tosyloxy)propanoate and PhCH_2MgCl

Our next attempt was to synthesise our chiral structure with help of a chiral starting material which is called ethyl (-)-L-lactate and a solution of benzylmagnesium chloride. For this we used a Grignard reaction. An arylmagnesium halogenid reacts as a nucleophile with a very electrophile compound.



We dissolved (-)-L-lactate in DCM and then we added p-toluenesulfonyl chloride and trimethylamine. After stirring the reaction for 6 hours our predicted product was there [20].

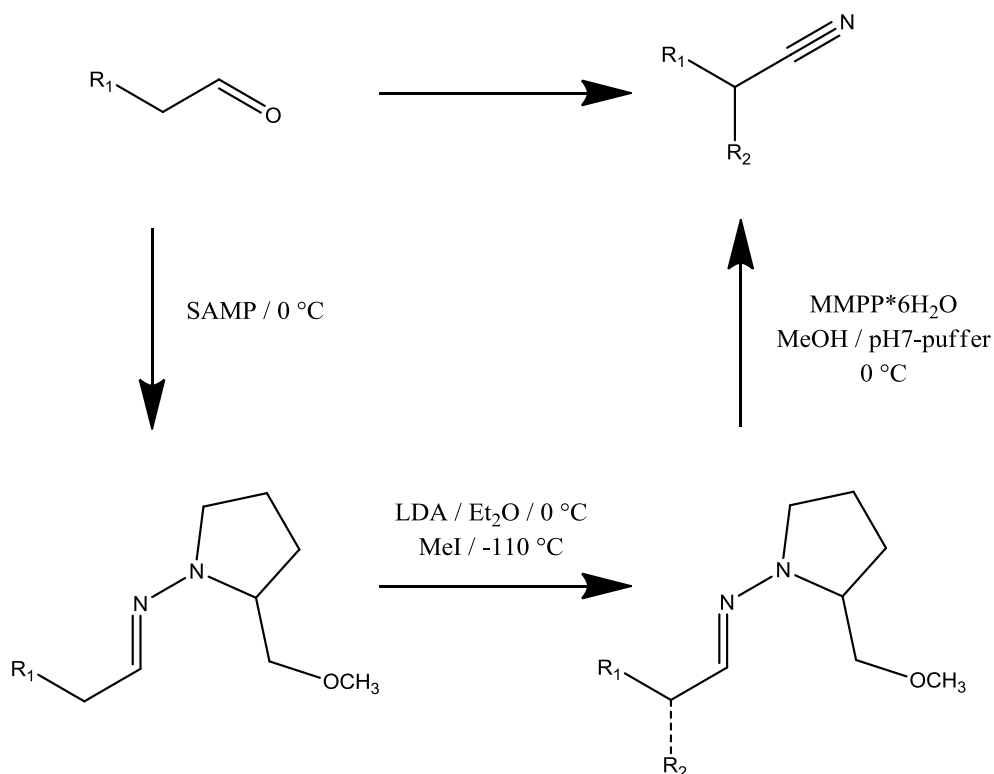
Then we dissolved our product in THF, added TMEDA and made a Grignard reaction with help of PhCH_2MgCl at 0°C . This reaction did not work.

The ^1H -NMR-spectra showed that there was only starting material in this reaction.

3.7 Synthesis of pure enantiomers with help of SAMP-hydrazones

As mentioned before the other way to create structures with high enantioselectivity was to use SAMP-hydrazones. SAMP-hydrazones are known as useful reagents for asymmetric synthesis of carbonyl compounds.

The synthetic way to produce our structures is shown in the following scheme.



At first, we produced an aldehyde out of a substituted aromatic system and allyl alcohol.

The aldehyde of the reaction was changed into a SAMP-hydrazone with the help of (-)-(S)-1-amino-2-(methoxymethyl)pyrrolidine. Secondly, the hydrazone was deprotonated by LDA (lithium diisopropylamide) and an azaenolate was formed [21].

Additionally methyl iodide was used as an electrophile to make an alkylation. We cooled down the reaction to -110 °C with help of liquid nitrogen and pentane.

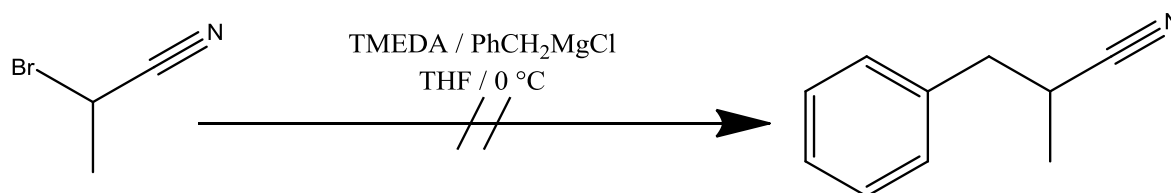
For this reaction we used the description out of the paper “Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy” but stirred the mixture only for 4 hours instead of 8, cooled down the reaction to -110°C instead of -100°C and used methyl iodide for the alkylation [22].

The problem with this strategy was that the reactions worked very well until the methylation. We were not able to introduce our methyl-group into the structure.

3.8 Synthesis of our enantiomer with Grignard reagents and organozinc halides

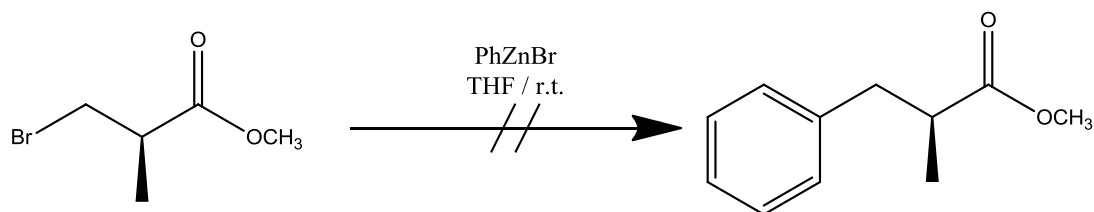
In the next step we tried to synthesise our product with help of Grignard reagents as well as organozinc halides and supported them with different catalysts.

First we wanted to combine benzylmagnesium chloride with 2-bromopropionitrile to form our product called 2-methyl-3-phenylpropionitrile. For this we dissolved our starting material (2-bromopropionitrile) in THF and added TMEDA at room temperature. After this we dropped a solution of benzylmagnesium chloride into the reaction and stirred overnight. But next day we did not receive any product and so we tried the same reaction again but changed the temperature from room temperature to 0 °C. Unfortunately this did not change anything and there was still no product. Therefore we added NiCl₂ as a catalyst.



After we saw that even with a catalyst there was no product, we started to use another starting material which was called methyl (R)-(+)-3-bromo-2-methyl-propionate. This structure was a stronger nucleophile as the structure we used before which was 2-bromopropionitrile and there was already the right position of our methyl group in the compound. So we just wanted to combine our starting material with an aromatic system through a Grignard reaction or with help of organozinc halides. But this also turned out to be very tricky.

At the beginning of these reactions we tried to use organozinc halides (phenylzinc bromide) to interact with methyl (R)-(+)-3-bromo-2-methyl-propionate.



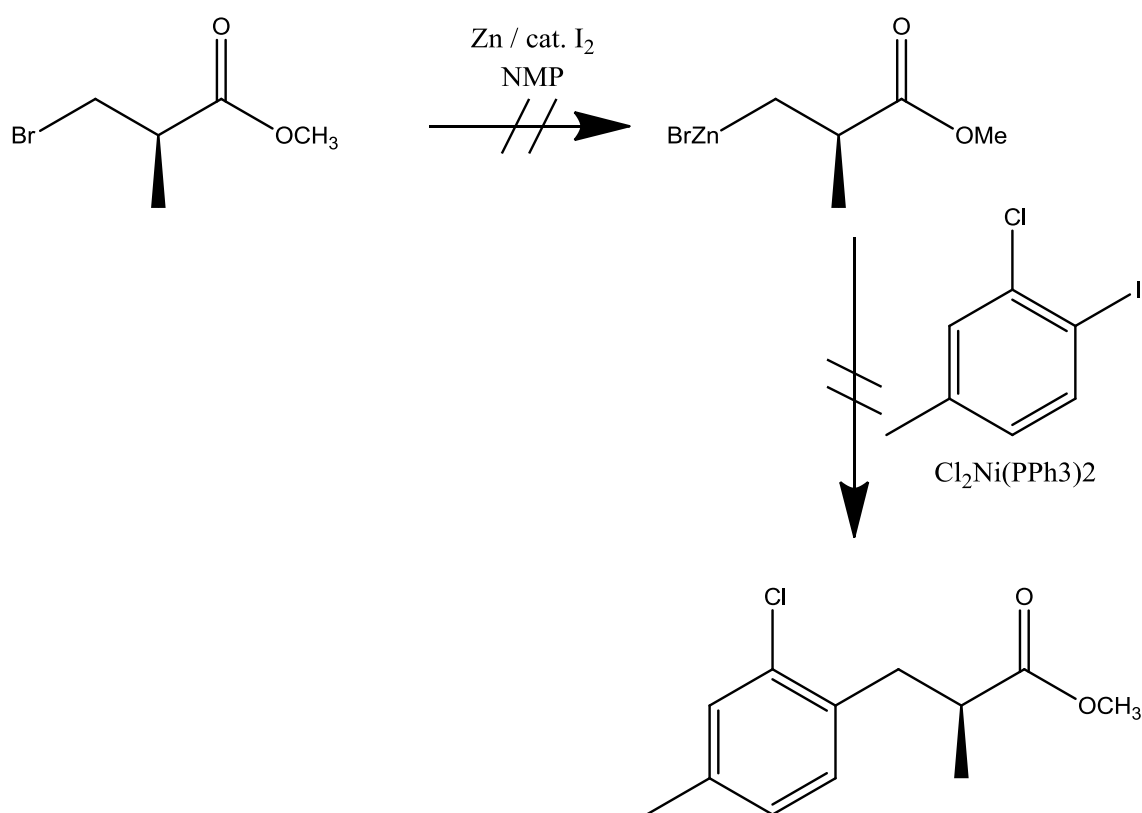
We dissolved phenylzinc bromide in a flask and added THF at room temperature. Afterwards we dropped methyl (R)-(+)-3-bromo-2-methyl-propionate into the reaction and stirred this overnight but we did not receive the product we wanted to have.

In the following step we wanted to improve the reaction by using catalysts. So we tried the reaction again with NiCl_2 , $\text{CuCN} \cdot 2 \text{LiCl}$, FeCl_3 , CuCl and LiCl but we never obtained the predicted substance. There was always just starting material in our reaction.

We also used CuCl and LiCl in combination and tried to change the way the reaction interacts. Before methyl (R)-(+)-3-bromo-2-methyl-propionate always was the electrophile but now we used it as nucleophile.

We prepared an alkylzinc bromide with zinc metal activated with I_2 . Normally this zinc reagent reacts easily with aryl halides with help of a catalyst. For this we put zinc dust and I_2 in a flask under argon and used 1-methyl-2-pyrrolidone as a solvent. It was very important to use a polar solvent to achieve the zinc insertion

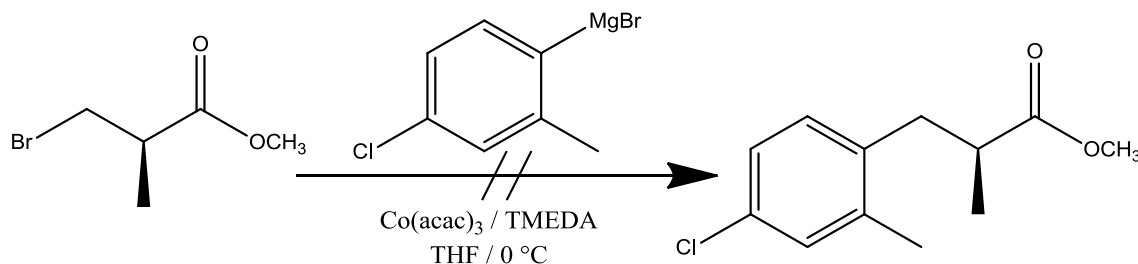
because with a less polar solvent such as THF there was no zinc reagent built. We stirred the mixture at room temperature until all the red colour of iodine moved away. Methyl (R)-(+)-3-bromo-2-methyl-propionate was dropped into the reaction at 80 °C. After the zinc insertion reaction the mixture was cooled down to room temperature and 3-chloro-4-iodo-toluene and $\text{Cl}_2\text{Ni}(\text{PPh}_3)_2$ as a catalyst were added. In our structure there was a cycloalkyl-group and so it could be that the zinc insertion runs very slowly. There was a slower exchange of iodide and bromide because of steric hindrance of the cycloalkyl-group [23]. This facts could be a reason why there was no product in our reaction.



Our next attempt to synthesise our product was to use the complex $\text{Co}(\text{acac})_3/\text{TMEDA}$ (1:1) which was looking promising. We weighed cobalt(III) acetylacetonate which is a catalyst into a flask under argon and dissolved it in THF. After this we added TMEDA and dropped the starting material (methyl (R)-(+)-3-bromo-2-methyl-propionate) which was the electrophile into the reac-

tion at 0 °C. Finally we added the Grignard reagent which was 4-chloro-2-methyl-phenyl-magnesiumbromide [24].

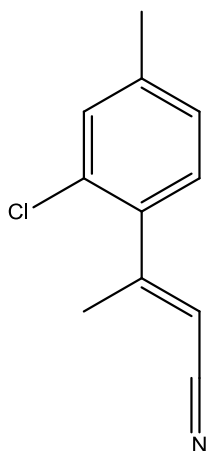
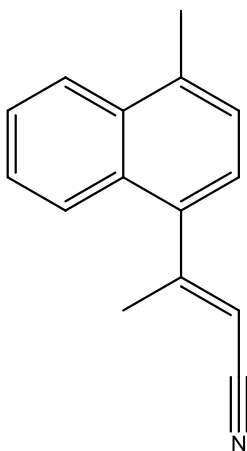
In this reaction we did not receive the predicted product because there was only starting material in the NMR-spectra.



As our last option we tried to use a tosylate which is a very well leaving group as our starting material. In addition we used again a lot of different types of catalysts to improve our reaction. But even with FeCl_3 , Cobalt(III) acetylacetonate, CuCl and NiCl_2 we did not receive the predicted product because there was also only starting material in the NMR-spectra.

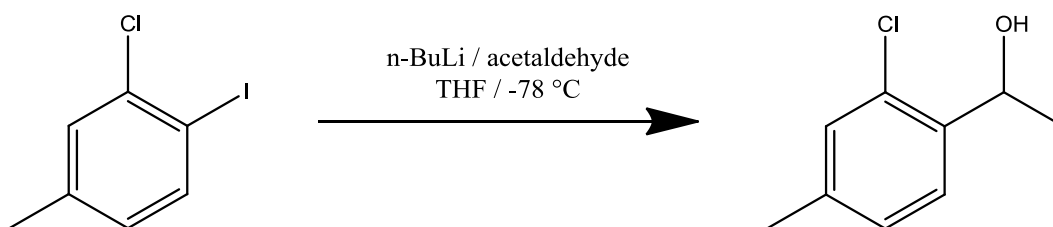
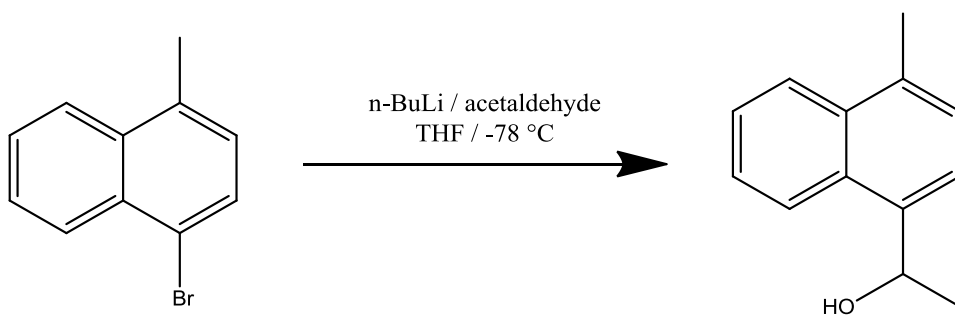
3.9 Synthesis of 3-(2-chloro-4-methylphenyl)but-2-enenitrile and 3-(4-methylnaphthalen-1-yl)but-2-enenitrile

At the end we managed to synthesise two achiral GABA_A -receptor ligands which are shown in the picture below. The activity on the GABA_A -receptor of both structures was tested. The result was that 3-(2-chloro-4-methylphenyl)but-2-enenitrile was the most active one out of the whole series which was tested.



Both structures were synthesised in the same way:

In the first step we introduced two additional carbon atoms with help of *n*-BuLi and acetaldehyde. We added 1-bromo-4-methylnaphthalene and 2-chloro-1-iodo-4-methylbenzene into a flask under argon and dissolved both in THF which was used as solvent. Then we cooled down the reaction to -78°C with dry ice and acetone and dropped *n*-BuLi into the reaction.

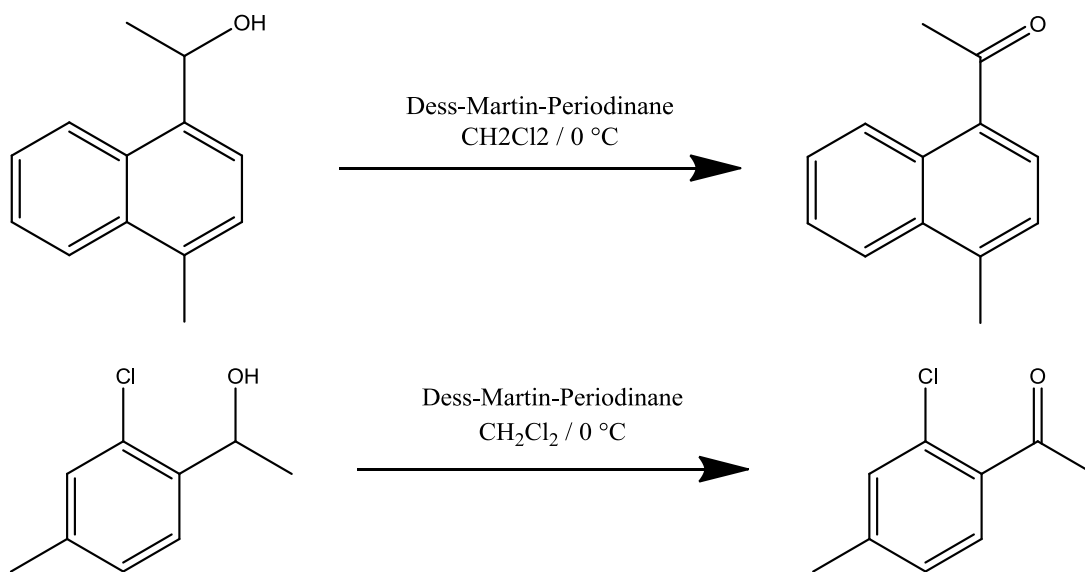


In the second step we wanted to oxidise the alcohol to the ketone. For this we used a reagent which is called Dess-Martin-Periodinane.

The Dess-Martin-Periodinane is a hypervalent iodine material and oxidises secondary alcohols [25].

At the beginning of the reaction the alcohol attacked iodine nucleophilic and then the alcohol was oxidised through a proton elimination. With help of Dess-Martin-Periodinane we managed to form our ketone out of the alcohol.

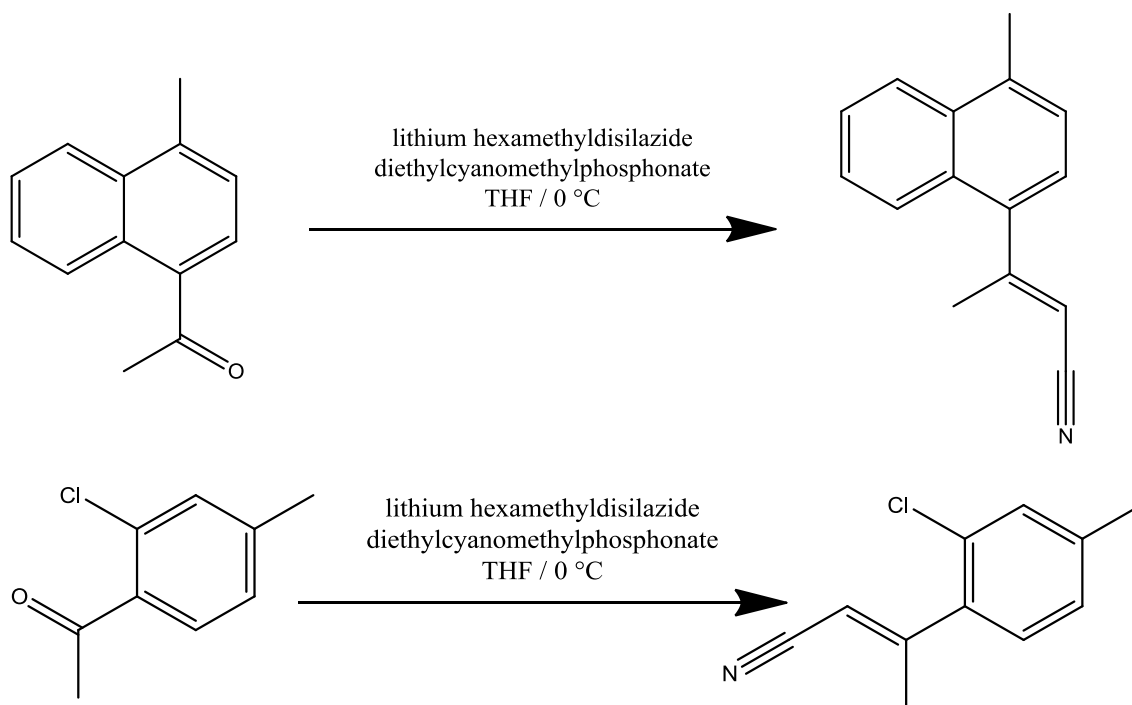
For this we filled the respective alcohol into a flask under argon and dissolved it in dichloromethane. Afterwards Dess-Martin-Periodinane was added at 0 °C which transformed the alcohol into the ketone.



In the last step of our reaction the nitrile was formed by using diethylcyanomethylphosphonate and lithium hexamethyldisilazide which was added as a catalyst.

Both are dissolved in THF in a flask under argon at room temperature and after 30 minutes this solution was added dropwise into a solution of the ketone.

After stirring for some hours we managed to achieve our two predicted substances.



4 Experimental work

4.1 Chemicals

Most of chemicals were purchased from Sigma Aldrich.

4.2 Solvents

Solvents which had to be anhydrous were distilled at a separated place in the laboratory.

Tetrahydrofuran (THF) was dried by adding sodium and then heated until the colour turned blue after adding benzophenone.

Calcium chloride was used to dry dichloromethane (DCM).

4.3 Reaction

Before the reaction was started all the flashes had to be dried in the drying cabinet at 120°C. It was important that the whole reaction was running under argon. For this, the flasks had to be gassed about five minutes before the reaction was started. All liquid substances were added by a syringe which was available in different sizes. At the beginning of the reaction solid substances had to be added before Argon was used or when they were needed during the reaction they had to be dissolved in some solvent in an extra flask and then injected. It was also important to use a magnetic stirrer to get a homogeneously solution. For reactions which had to be heated there was a reflux condenser and an oil bath needed. On the other hand sometimes reactions needed very deep temperatures. To achieve about -78°C, dry ice and acetone were needed in a matching ratio.

4.4 Chromatography

There were two types of chromatography used to identify and purify reactions. On the one hand there was thin layer chromatography (TLC) used to detect whether the reaction worked or not. On the other hand flash-chromatography separated starting material, side products and product from each other.

Both silica and silica gel plates were produced by a very famous company called Merck.

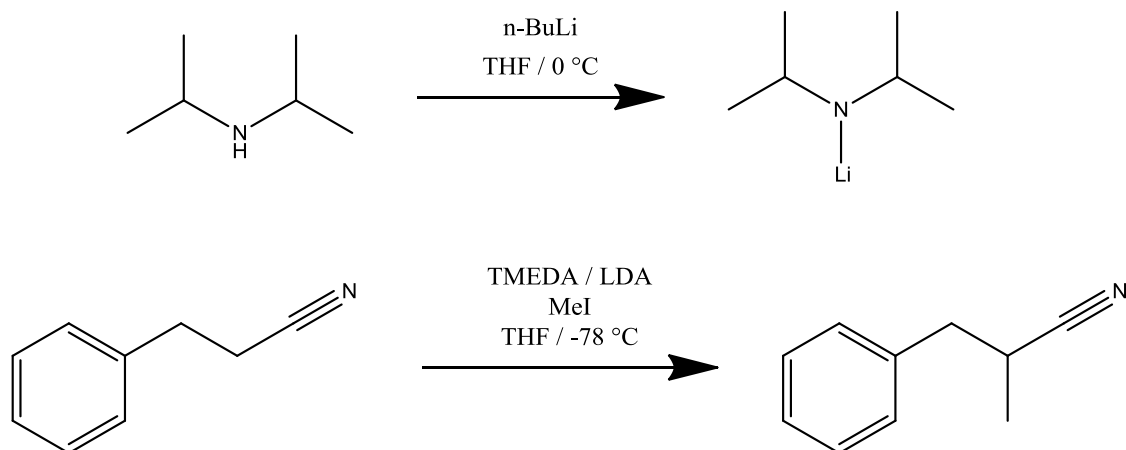
Silica which was needed for flash-chromatography had to be suspended in an appropriate amount of solvent and then filled into the flask. To get the stationer phase air-free it was important to push the mobile phase through the column with pressure. Then the mixture which should be separated was dissolved in an appropriate amount of solvent and was applied. After that the column was carefully filled up with mobile phase, so the separation could be started.

4.5 ^1H - and ^{13}C -NMR-Spectra

For ^1H - and ^{13}C -NMR-measurements there was a Bruker Avance nuclear magnetic resonance spectrometer used which was calibrated by the signal of CHCl_3 at δ 7.26 ppm for ^1H -measurements and at δ 77.00 ppm for ^{13}C -measurements.

4.6 Synthesis

4.6.1 Synthesis of 2-methyl-3-phenylpropanenitrile with LDA



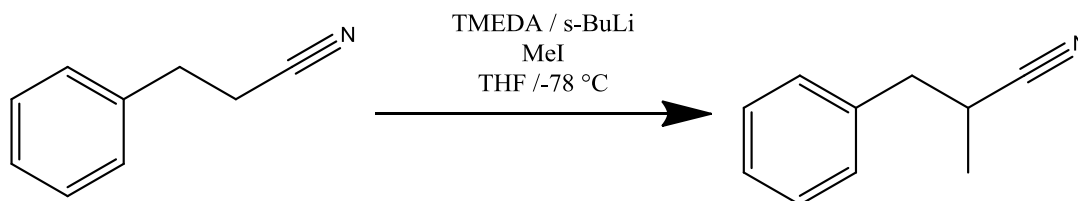
Diisopropylamine (0.219 g, 2.172 mmol) was dissolved in 4 mL THF and then the reaction was cooled down to 0°C . This temperature was reached by application of water and ice. After this, *n*-Buthyllithium (0.915 mL of a 2.5 M solution in hexane) was added dropwise and the reaction was stirred for 30 minutes. The colour of the reaction was light yellow now.

3-Phenylpropanenitrile (0.301 g, 2.287 mmol) was also dissolved in 4 mL THF and TMEDA (0.775 g, 6.861 mmol) was added dropwise. In addition, the flask with LDA was cooled down to -78°C with dry ice and acetone. The previous solution was added dropwise and stirred for 30 minutes. Then methyl iodide (1.623 g, 11.43 mmol) was also dropped into the flask and the reaction stirred overnight.

On the next day the reaction was stopped with ammonium chloride solution (5 mL) and then extracted with ethyl acetate (3x20 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure with the rotary evaporator.

The product was a yellow-brown liquid (0.01 g, 3.01 %).

4.6.2 Synthesis of 2-methyl-3-phenylpropanenitrile with *s*-BuLi



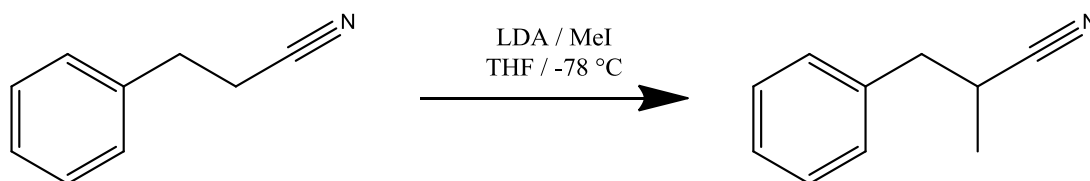
The difference to the previous reaction was that in this experiment *s*-BuLi was used instead of LDA. 3-Phenylpropanenitrile (0.3 g, 2.287 mmol) was solved in THF under Argon and TMEDA (0.797 g, 6.861 mmol) was added dropwise. After the flask was cooled down to -78°C with acetone and dry ice *s*-BuLi (1.76 mL of a 1.3 M solution in cyclohexane/hexane) was added dropwise and the reaction was stirred for 30 minutes. Additionally, methyl iodide (1.623 g, 11.43 mmol) was dropped into the flask and the reaction was stirred overnight.

On the next day the reaction was stopped with an ammonium chloride solution (5 mL) and extracted with ethyl acetate and a separating funnel. The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure.

We received a different product than expected (0.234 g, 70.5 %) which is shown in the chapter “NMR-spectra” at the end of the thesis.

For our synthesis we received the information from “Dieter Hoppe, Folker Hintze, Petra Tebben, Chiral Lithium-1-oyalkanides by Asymmetric Deprotonation; Enantioselective Synthesis of 2-Hydroxyalkanoic Acids and Secondary Alkanols, VCH Verlagsgesellschaft, Weinheim, 1990”

4.6.3 Synthesis of 2-methyl-3-phenylpropanenitrile with LDA and without TMEDA



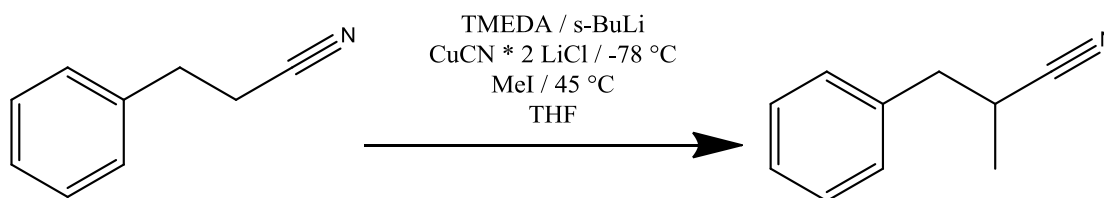
Diisopropylamine (0.219 g, 2.172 mmol) was dissolved in 4 mL THF and then the reaction was cooled down to 0°C. 0°C was reached by application of water and ice. After this, *sec*-BuLi (1.760 mL of a 1.3 M solution in cyclohexane/hexane) was added dropwise and the reaction was stirred for 30 minutes. The colour of the reaction was light yellow now.

3-Phenylpropanenitrile (0.301 g, 2.287 mmol) was also dissolved in 4 mL THF and then the flask with LDA was cooled down to -78°C with dry ice and acetone. The previous solution was added dropwise and stirred for 30 minutes. Then methyl iodide (1.623 g, 11.43 mmol) was also added dropwise and the reaction stirred overnight.

On the next day the reaction was stopped with an ammonium chloride solution (5 mL) and then extracted with ethyl acetate (3x 20 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure with the rotary evaporator.

The product was a yellow-brown liquid but the yield was not as good as with TMEDA.

4.6.4 Synthesis of 2-methyl-3-phenylpropanenitrile with CuCN * 2 LiCl

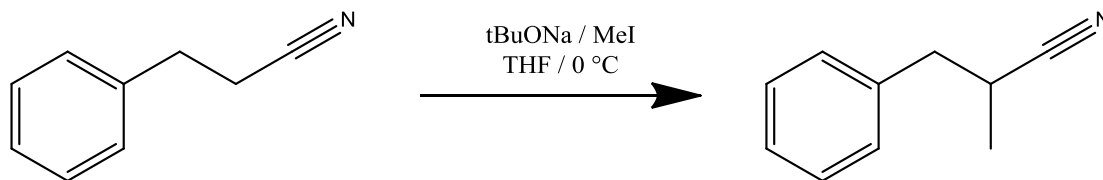


3-Phenylpropanenitrile (0.301 g, 2.287 mmol) was solved in THF under Argon and TMEDA (0.797 g, 6.861 mmol) was added dropwise. After the flask was cooled down to -78°C with acetone and dry ice s-BuLi (1.76 mL of a 1.3 M solution in cyclohexane/hexane) was added dropwise and the reaction was stirred for 30 minutes. CuCN * 2 LiCl was added at -78°C and then the temperature was lowered at -45°C with a little bit dry ice and a lot of acetone. After stirring for one hour, methyl iodide (1.623 g, 11.43 mmol) was dropped into the flask and the reaction was stirred overnight.

On the next day the reaction was stopped with an ammonium chloride solution (5 mL), extracted with ethyl acetate and a separating funnel. The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure.

There was a product as a yellow-brown liquid but the reaction with CuCN * 2 LiCl was not as pure as without it.

4.6.5 Synthesis of 2-methyl-3-phenylpropanenitrile with tBuONa but without TMEDA

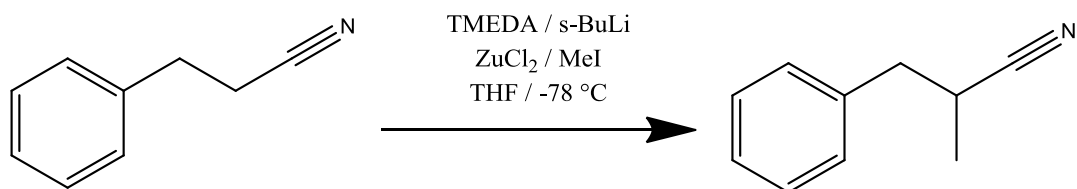


3-Phenylpropanenitrile (0.301 g, 2.287 mmol) was solved in THF under Argon. In a second flask, tBuONa (0.220 g, 2.287 mmol) was solved in THF too. Then the bottle with 3-phenylpropanenitrile and THF was cooled down to 0°C and the solution of tBuONa in THF was added dropwise and stirred for 30 minutes. After this methyl iodide (1.623 g, 11.43 mmol) was dropped into the reaction and it was stirred about four hours.

After four hours the reaction was stopped with an ammonium chloride solution (5 mL) and extracted with ethyl acetate and a separating funnel. The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

4.6.6 Synthesis of 2-methyl-3-phenylpropanenitrile with ZnCl_2

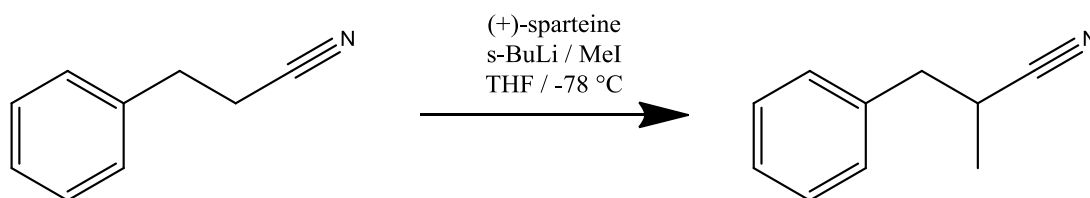


3-Phenylpropanenitrile (0.301 g, 2.287 mmol) was solved in THF under Argon and TMEDA (0.797 g, 6.861 mmol) was added dropwise. After the flask cooled down to -78°C , s-BuLi (1.76 mL of a 1.3 M solution in cyclohexane/hexane) was added dropwise and stirred for 30 minutes. After this, ZnCl_2 (0.312 g, 2.287 mmol) was dropped into the reaction and after 30 minutes stirring methyl iodide (1.623 g, 11.43 mmol) was added.

On the next day the reaction was stopped with an ammonium chloride solution (5 mL) and extracted with ethyl acetate and a separating funnel. The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure.

There was a different product than expected which is shown under chapter “NMR-spectra” at the end of the thesis.

4.6.7 Synthesis of 2-methyl-3-phenylpropanenitrile with (+)-sparteine



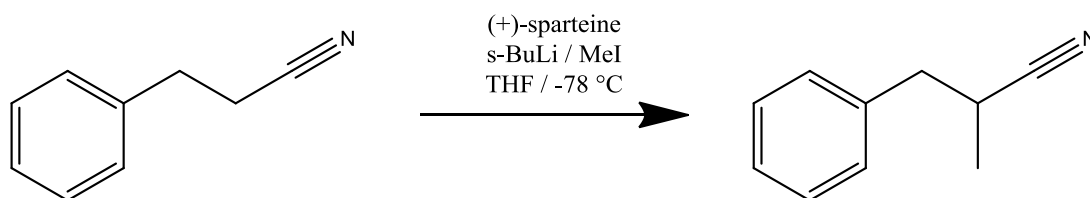
3-Phenylpropanenitrile (0.131 g, 1 mmol) was solved in THF under Argon and then (+)-sparteine (0.352 g, 1.5 mmol) was added. Additionally, the flask was cooled down to -78°C and s-BuLi (0.769 mL of a 1.3 M solution in cyclohexane/hexane) was dropped into the reaction. After 30 minutes of stirring methyl iodide (0.709 g, 5 mmol) was added and reaction was stirred overnight.

On the next day the reaction was stopped with an ammonium chloride solution (5 mL) and then extracted with ethyl acetate (3x 20 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure with the rotary evaporator.

The ^1H -NMR-spectra showed that there was just a little bit of product (0.10 g). The reason could be that (+)-sparteine was oxidised during storage.

For our synthesis we received the information from “Dieter Hoppe, Thomas Hense, Enantioselective Synthese mit Lithium/(-)-Sparteine-Carbanion-Paaren, Wiley-VCH Verlag, Weinheim, 1997”

4.6.8 Synthesis of 2-methyl-3-phenylpropanenitrile with distilled (+)-sparteine



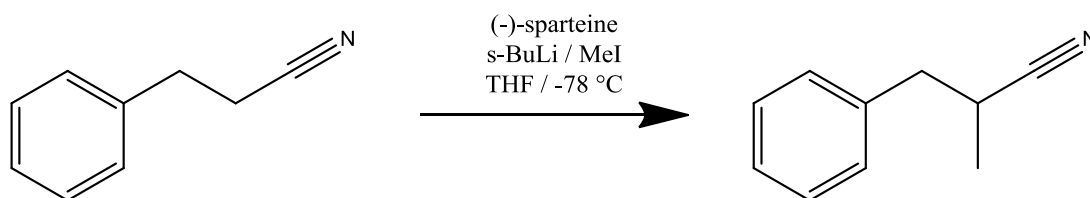
In this reaction we used more (+)-sparteine, which was distilled directly before the reaction.

3-Phenylpropanenitrile (0.131 g, 1 mmol) was solved in THF under Argon and then (+)-sparteine (0.716 g, 4.5 mmol) was added. Additionally, the flask was cooled down to -78°C and s-BuLi (0.769 mL of a 1.3 M solution in cyclohexane/hexane) was dropped into the reaction. After 30 minutes of stirring methyl iodide (0.709 g, 5 mmol) was added and reaction was stirred overnight.

On the next day the reaction was stopped with an ammonium chloride solution (5 mL) and then extracted with ethyl acetate (3x 20 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure with the rotary evaporator.

Now we received more product (0.02 g, 13.8 %).

4.6.9 Synthesis of 2-methyl-3-phenylpropanenitrile with distilled (-)-sparteine

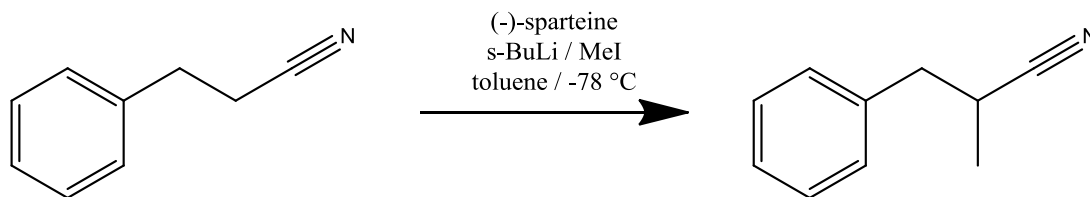


3-Phenylpropanenitrile (0.571 g, 0.4351 mmol) was solved in THF under argon and then (-)-sparteine (0.716 g, 4.5 mmol) was added. Additionally the flask was cooled down to -78°C and s-BuLi (0.335 mL of a 1.3 M solution in cyclohexane/hexane) was dropped into the reaction. After 30 minutes of stirring methyl iodide (0.309 g, 2.18 mmol) was added and reaction was stirred overnight.

On the next day the reaction was stopped with an ammonium chloride solution (5 mL) and then extracted with ethyl acetate (3x 20 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure with the rotary evaporator.

There was a product (0.011 g, 17.4 %).

4.6.10 Synthesis of 2-methyl-3-phenylpropanenitrile with distilled (-)-sparteine solved in toluene

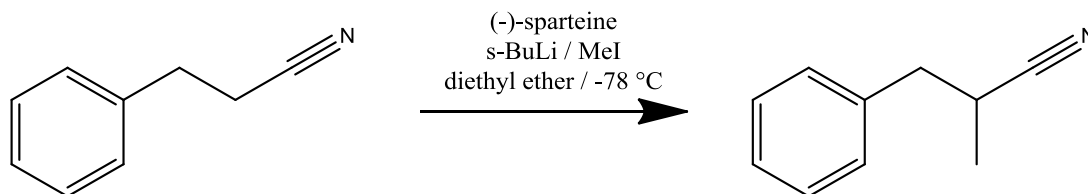


3-Phenylpropanenitrile (0.131 g, 1 mmol) was dissolved in 6 mL toluene under argon. After this (-)-sparteine (0.352 g, 1.5 mmol) was added dropwise and the flask was cooled down to -78°C. Then s-BuLi (0.769 mL of a 1.3 M solution in cyclohexane/hexane) was dropped into the reaction and it was stirred for 30 minutes. After this methyl iodide (0.710 g, 5 mmol) was added and the mixture was stirred for four hours.

Four hours later the reaction was stopped with an ammonium chloride solution (5 mL), extracted with ethyl acetate and a separating funnel. The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure.

There was a yellow-brown product (0.005 g, 3.44 %).

4.6.11 Synthesis of 2-methyl-3-phenylpropanenitrile with distilled (-)-sparteine solved in diethyl ether

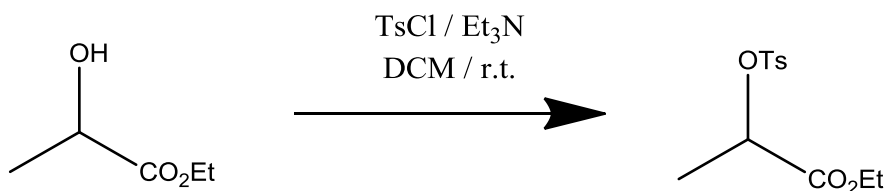


3-Phenylpropanenitrile (0.131 g, 1 mmol) was dissolved in 6 ml toluene under argon. After this (-)-sparteine (0.352 g, 1.5 mmol) was added dropwise and the flask was cooled down to -78°C. Then s-BuLi (0.769 mL of a 1.3 M solution in cyclohexane/hexane) was dropped into the reaction and it was stirred for 30 minutes. After this methyl iodide (0.710 g, 5 mmol) was added and the mixture was stirred for four hours.

Four hours later the reaction was stopped with an ammonium chloride solution (5 mL), extracted with ethyl acetate and a separating funnel. The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure.

The result was a yellow-brown product (0.01 g, 6.89 %).

4.6.12 Synthesis of ethyl-2-(tosyloxy)propanoate with (-)-ethyl L-lactate



In one flask (-)-Ethyl L-lactate (6.00 g, 50.79 mmol) was dissolved in 3 mL anhydrous DCM. In another flask there was resolved p-toluenesulfonyl chloride (19.37 g, 101.6 mmol) in 7 mL DCM. The solution of p-toluenesulfonyl chloride in DCM was added to the first flask with (-)-ethyl L-lactate in DCM and 10 mL trimethylamine was added. The colour of the reaction was changing to yellow. After this, the reaction was stirring for 24 hours at room temperature.

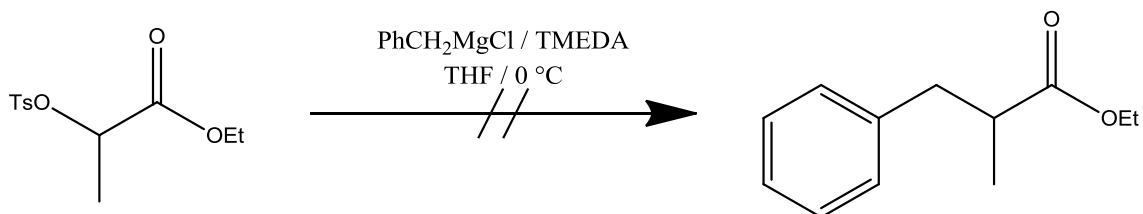
The reaction was stopped next day with ammonium chloride solution (5 mL) and extracted with ethyl acetate (3x 20 mL) with 1 N HCl (3x 10 mL) and at least three times with water. The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure.

After flash-chromatography there was the product as a transparent liquid (5.85 g, 42.29 %).

The results of the measuring of the $[\alpha]_D$ was $[\alpha]_D = -177^\circ\text{C}$ which indicated that there was received a left-handed product.

For our synthesis we received the information from “Maria G. Perrone et al., Stereospecific synthesis and bio-activity of novel beta₃-adrenoceptor agonists and inverse agonists, Elsevier, 2007”

4.6.13 Synthesis of methyl 2-methyl-3-phenylpropanoate with benzylmagnesium chloride



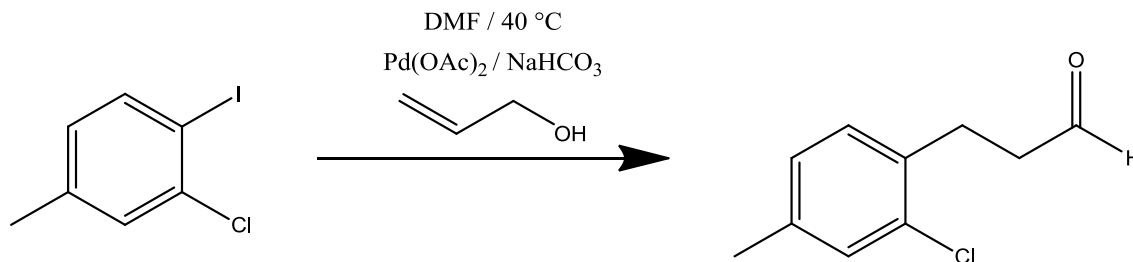
Ethyl-2-(tosyloxy)propanoate (0.500 g, 1.836 mmol) was filled into a flask under argon and was dissolved in THF. After this, TMEDA (0.853 g, 7.344 mmol) was added and the flask was cooled down to 0 °C. Additionally, a benzylmagnesium chloride solution (1.574 mL of a 1.4 M solution in THF) was added and the reaction was stirred overnight at room temperature.

On the next day the reaction was stopped with an ammonium chloride solution and extracted with ethyl acetate. After this, it was dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received the information from “Maria G. Perrone et al., Stereospecific synthesis and bio-activity of novel beta3-adrenoceptor agonists and inverse agonists, Elsevier, 2007”

4.6.14 Synthesis of 3-(2-chloro-4-methylphenyl)propanal with 3-chloro-4-iodotoluene and allyl alcohol



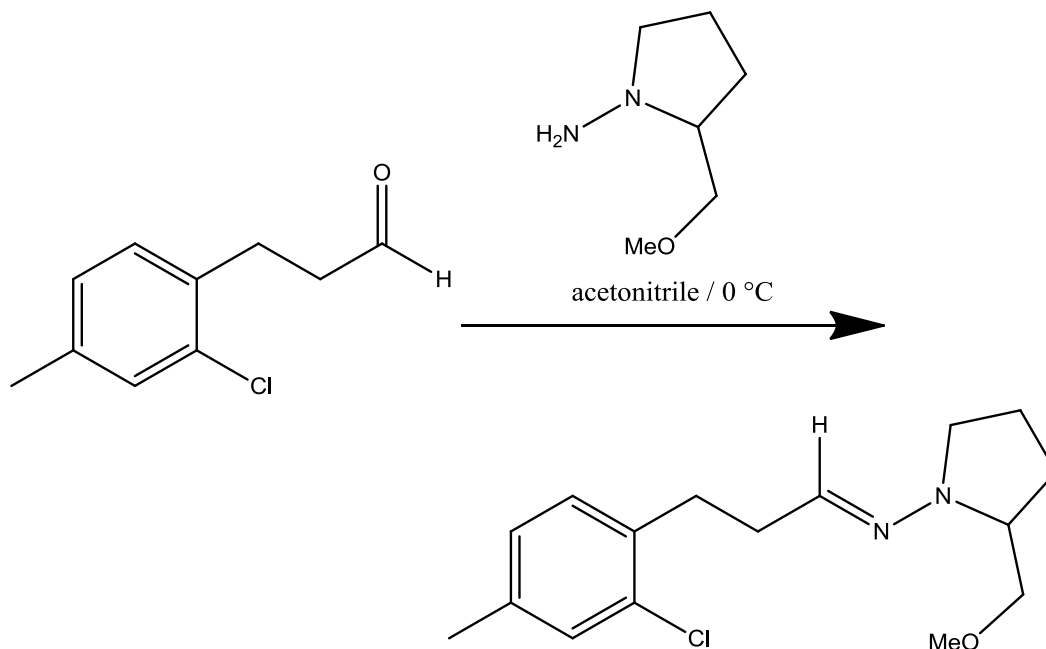
A flask connected with argon was filled with Pd(OAc)₂ (5 %) (0.280 g, 1.25 mmol), tetrabutylammonium bisulfate (6.95 g, 25 mmol) and NaHCO₃ (5.25 g, 62.5 mmol). After this, 50 mL DMF were added and after stirring for 10 minutes 3-chloro-4-iodotoluene (6.312 g, 25 mmol) was dropped into the reaction. Then, the flask was moved into an ice bath and allyl alcohol (2.178 g, 37.5 mmol) was put into the reaction. Afterwards, the reaction was stirred overnight at 40°C by using a reflux condenser and a bath of oil.

The following day the reaction was worked up with ethyl acetate, brine and water. First, there was a suction filter used to remove all interfering substances particularly Pd(OAc)₂. The reaction was dried over Na₂SO₄ and evaporated under reduced pressure with the rotary evaporator.

The resulting product (1.03 g, 22.56 %) was a yellow-brown liquid.

For our synthesis we received the information from “Shin-itsu Kuwabe, Karen E. Torraca, Stephen L. Buchwald, Palladium-Catalyzed Intramolecular C-O Bond Formation, American Chemical Society, 2001”

4.6.15 Synthesis of N-(3-(2-chloro-4-methylphenyl)propylidene)-2-(methoxymethyl)pyrrolidine-1-amine



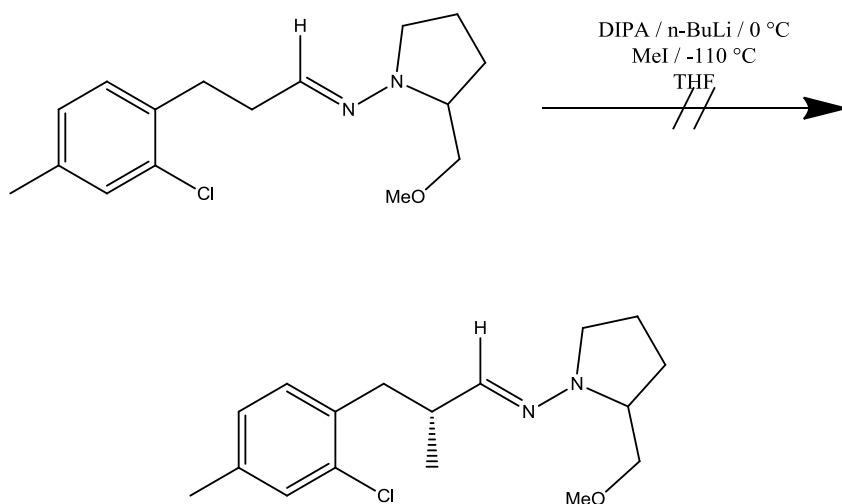
In one flask the product of the reaction before which was 3-(2-chloro-4-methylphenyl)propanal (0.716 g, 3.918 mmol) was dissolved in 1 mL anhydrous acetonitrile under argon. Another flask was filled up with (-)-(S)-1-amino-2-(methoxymethyl)pyrrolidine (0.5 g, 3.841 mmol) and the solution of the first flask was added dropwise at 0 °C. After the addition of the aldehyde the reaction was stirred at room temperature for four hours.

Afterwards, the reaction was extracted with ethyl acetate, dried over Na₂SO₄ and evaporated with the rotary evaporator.

The resulting product (1.01 g, 87.43 %) was a yellow liquid.

For our synthesis we received the information from “D. Enders et al., *Asymmetric Syntheses via Metalated Chiral Hydrazones*, Elsevier, 1984”

4.6.16 Synthesis of (E)-N-(3-(2-chloro-4-methylphenyl)-2-methylpropylidene)-2-(methoxymethyl)pyrrolidine-1-amine



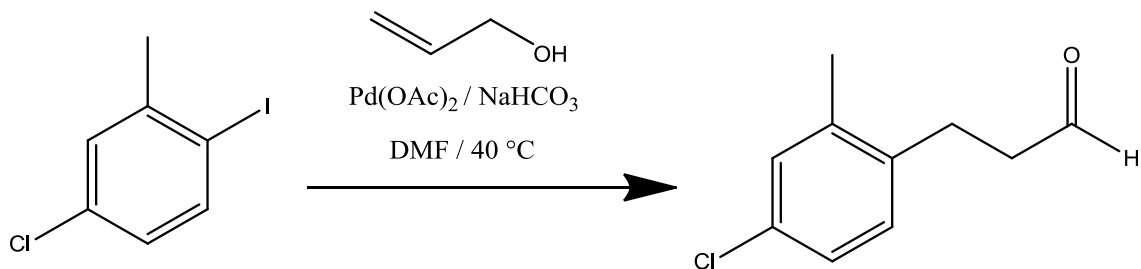
At the beginning a flask was flushed with argon and cooled down to 0°C. Then dry THF and dry DIPA (0.010 g, 0.392 mmol) were added and after this *n*-BuLi (0.245 mL of a 1.6 M solution in hexane) was dropped into the reaction. After stirring for 10 minutes the SAMP-hydrazone (0.110 g, 0.373 mmol) which was also solved in THF was added. Then stirring was continued and the lithiated hydrazone precipitated. After four hours, the mixture was cooled down to -110°C (diethyl ether/liquid nitrogen bath) for 15 minutes. Lastly methyl iodide (0.058 g, 0.410 mmol) was added and the mixture was stirred at room temperature overnight.

The reaction was extracted with diethyl ether and water. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure with the rotary evaporator.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received the information from “K.C. Nicolaou et al., Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy, American Chemical Society, 1997”

4.6.17 Synthesis of 3-(4-chloro-2-methylphenyl)propanal with 5-chloro-2-iodotoluene and allyl alcohol



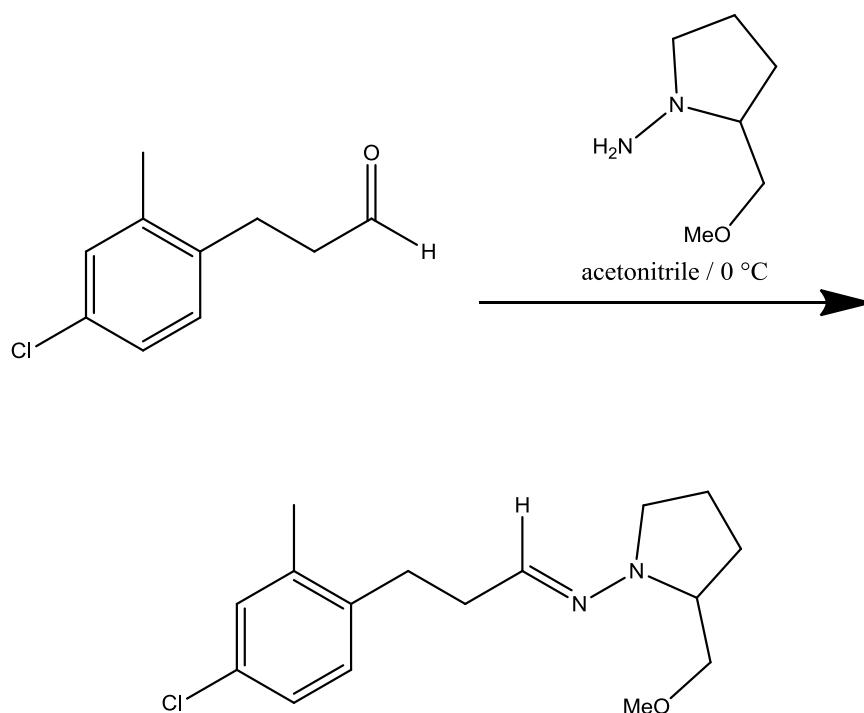
A flask connected with argon was filled with Pd(OAc)₂ (5 %) (0.280 g, 1.25 mmol), tetrabutylammonium bisulfate (6.95 g, 25 mmol) and NaHCO₃ (5.25 g, 62.5 mmol). After this, 50 mL DMF were added and after stirring for 10 minutes 5-chloro-2-iodotoluene (6.312 g, 25 mmol) was dropped into the reaction. Afterwards, the flask was moved into an ice bath and allyl alcohol (2.178 g, 37.5 mmol) was put into the reaction. Then the reaction was stirred overnight at 40 °C by using a reflux condenser and a bath of oil.

The following day the reaction was worked up with ethyl acetate, brine and water. First there was a suction filter used to remove all interfering substances particularly Pd(OAc)₂. The reaction was dried over Na₂SO₄ and evaporated under reduced pressure with the rotary evaporator.

The resulting product (1.03 g, 22.6 %) was a yellow-brown liquid.

For our synthesis we received the information from “Shin-itsu Kuwabe, Karen E. Torraca, Stephen L. Buchwald, Palladium-Catalyzed Intramolecular C-O Bond Formation, American Chemical Society, 2001”

4.6.18 Synthesis of N-(3-(4-chloro-2-methylphenyl)propylidene)-2-(methoxymethyl)pyrrolidine-1-amine



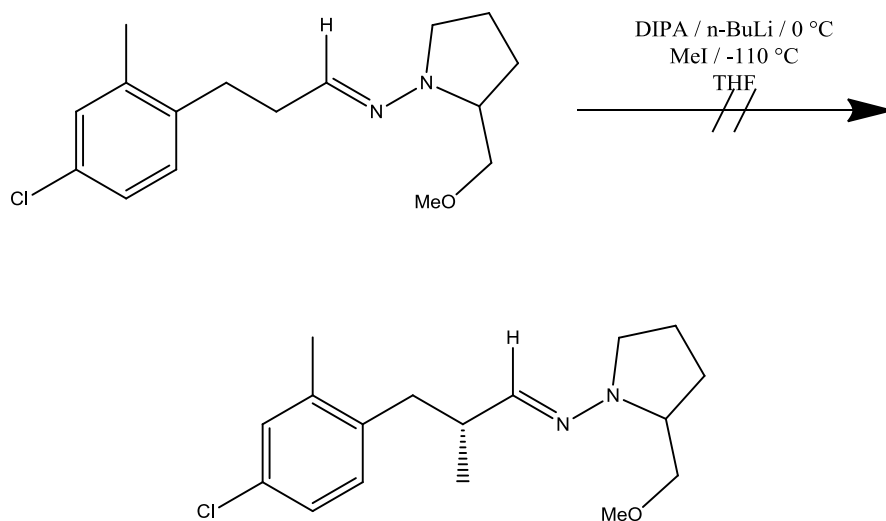
In one flask the product of the synthesis before which was 3(4-chloro-2-methylphenyl)propanal (0.716 g, 3.918 mmol) was dissolved in 1 mL anhydrous acetonitrile under argon. Another flask was filled up with (-)-(S)-1-amino-2-(methoxymethyl)pyrrolidine (0.5 g, 3.841 mmol) and the solution of the first flask was added dropwise at 0°C. After the addition of the aldehyde the reaction was stirred at room temperature for four hours.

After this the reaction was extracted with ethyl acetate, dried over Na₂SO₄ and evaporated with the rotary evaporator.

Our product (0.11 g, 9.52 %) was a yellow liquid.

For our synthesis we received the information from “D. Enders et al., Asymmetric Syntheses via Metalated Chiral Hydrazones, Elsevier, 1984”

4.6.19 Synthesis of (E)-N-(3-(4-chloro-2-methylphenyl)-2-methylpropylidene)-2-(methoxymethyl)pyrrolidine-1-amine

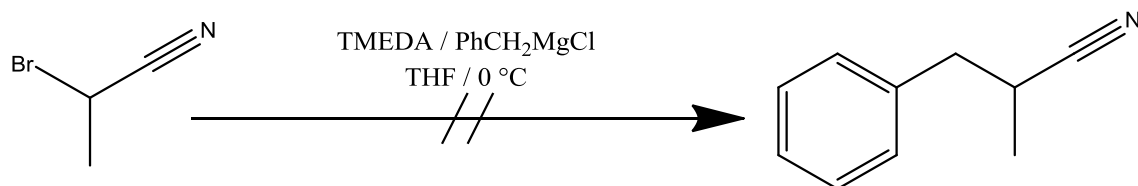


At the beginning a flask was flushed with argon and cooled down to 0°C. Then dry THF and dry DIPA (0.010 g, 0.392 mmol) were added and after this *n*-BuLi (0.245 mL of a 1.6 M solution in hexane) was dropped into the reaction. After stirring for 10 minutes the SAMP-hydrazone (0.110 g, 0.373 mmol) which was also solved in THF was added. Then stirring was continued and the lithiated hydrazone precipitated. When four hours were over the mixture was cooled down to -110°C (diethyl ether/liquid nitrogen bath) for 15 minutes. At last, methyl iodide (0.058 g, 0.410 mmol) was added and the mixture was stirred at room temperature overnight.

The reaction was extracted with diethyl ether and water. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure with the rotary evaporator.

The ¹H-NMR-spectra showed that there was only starting material (0.300 g) in the reaction.

4.6.20 Synthesis of 2-methyl-3-phenylpropanenitrile with benzylmagnesiumchloride solution

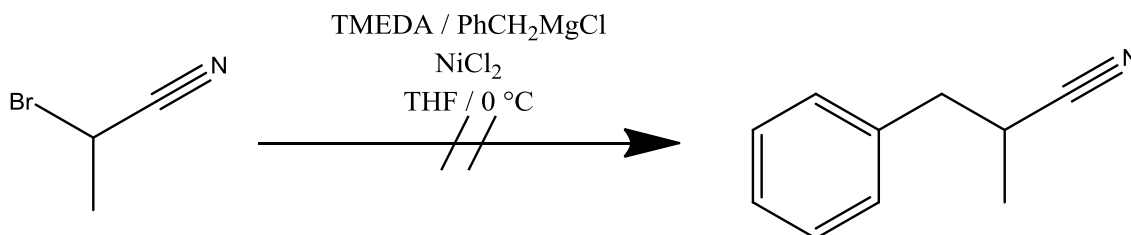


2-Bromopropionitrile (0.500g, 3.732 mmol) was dropped into a flask under argon, dissolved in THF and TMEDA (1.927g, 16.59 mmol) was added at 0 °C. Then a benzylmagnesiumchloride solution (2.9 mL of a 1.4 M solution in THF) was added dropwise. The reaction was stirred overnight and was allowed to reach room temperature.

On the next day the reaction was stopped with an ammonium chloride solution and was extracted with ethyl acetate and dried over Na₂SO₄.

After using the evaporator there was no product just starting material in the NMR.

4.6.21 Synthesis of 2-methyl-3-phenylpropanenitrile with benzylmagnesium chloride solution and nickel(II) chloride

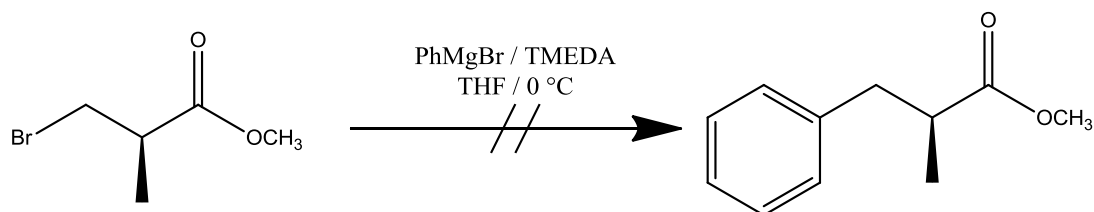


First, NiCl₂ (0.108 g, 0.8294 mmol) was weighed up into a flask and then left for 10 minutes under argon. After this the flask was brought to 0°C and NiCl₂ was dissolved in THF. 2-Bromopropionitrile (0.323 g, 3.732 mmol), TMEDA (2.487 g, 16.59 mmol) and a benzylmagnesium chloride solution (2.900 mL of a 1.4 M solution in THF) were added dropwise.

The reaction was stirred at room temperature overnight and stopped with an ammonium chloride solution. Then it was extracted with ethyl acetate and dried over Na₂SO₄.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

4.6.22 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate

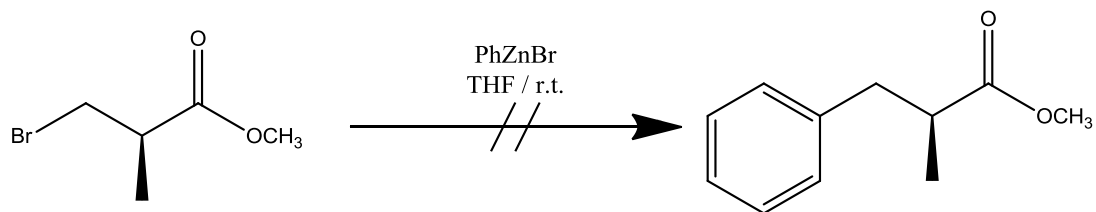


In a flask under argon a phenylmagnesium bromide solution (0.329 mL of a 2.8 M solution in diethyl ether) was added, dissolved in THF and the flask was cooled down to 0°C. After this TMEDA (0.428 g, 3.683 mmol) and methyl (R)-(+)-3-bromo-2-methyl-propionate (0.1500 g, 0.829 mmol) were dropped into the reaction. Finally, the flask was brought to room temperature and the reaction was stirred overnight.

On the next day it was stopped with an ammonium chloride solution and extracted with ethyl acetate. After this it was dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

4.6.23 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with phenylzinc bromide solution

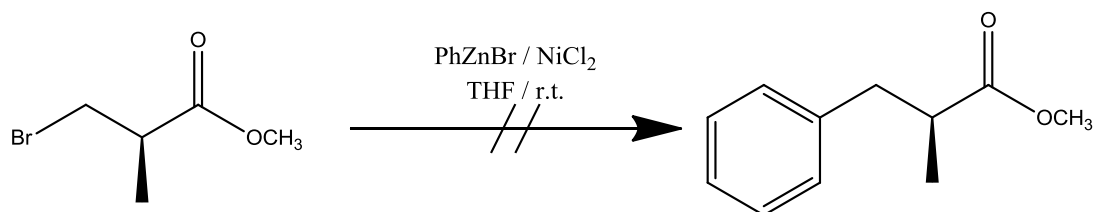


(R)-(+)-3-bromo-2-methyl-propionate (0.070 g, 0.387 mmol) was dissolved in THF under argon and then a phenylzinc bromide solution (0.100 mL of a 0.5 M solution in THF) was added dropwise.

After stirring for one hour the reaction was stopped with an ammonium chloride solution. Finally, it was extracted with ethyl acetate, dried over Na₂SO₄ and evaporated under reduced pressure.

The NMR only showed starting material but no product.

4.6.24 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with nickel(II) chloride

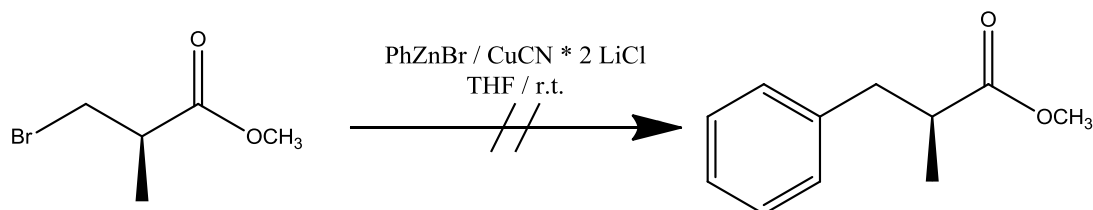


NiCl₂ (0.011 g, 0.086 mmol) was filled into a flask and put under argon for ten minutes. After this it was dissolved in THF and (R)-(+)-3-bromo-2-methylpropionate (0.070g, 0.387 mmol) was dropped into the reaction. Finally, a phenylzinc bromide solution (0.860 mL of a 0.5 M solution in THF) was added.

The reaction was stirred at room temperature overnight and then stopped with ammonium chloride solution and extracted with ethyl acetate.

After evaporation with reduced pressure there was only starting material in the NMR.

4.6.25 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with CuCN * 2 LiCl

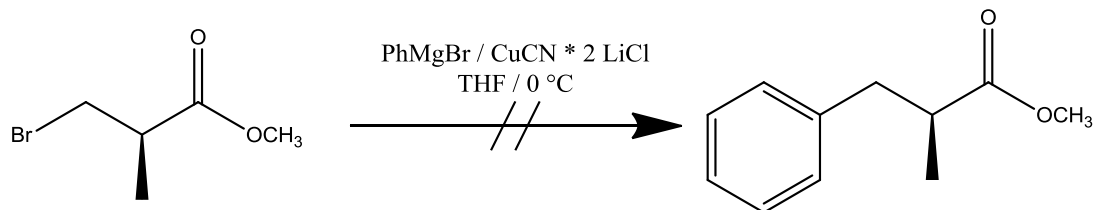


(R)-(+)-3-bromo-2-methyl-propionate (1.422 g, 0.077 mmol) was dropped into a flask under argon and dissolved in THF. After this a phenylzinc bromide solution (0.019 mL of a 0.5 M solution in THF) and CuCN * 2 LiCl (0.003 g, 0.017 mmol) at 0°C were added dropwise and the reaction was stirred for one hour. One hour later the reaction should reach room temperature and was stirred overnight.

On the next day it was stopped with water and after the extraction with ethyl acetate the reaction was dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

4.6.26 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with a phenylmagnesium bromide solution and $\text{CuCN} \cdot 2 \text{LiCl}$

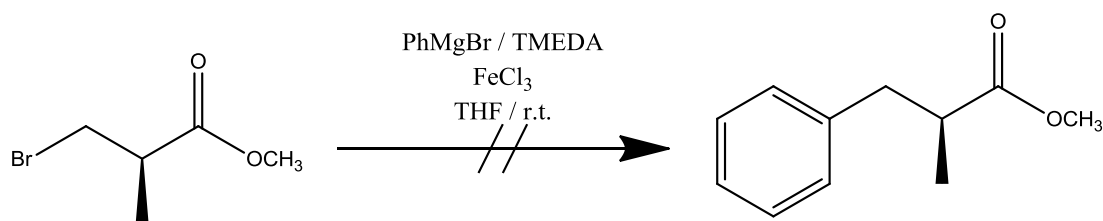


(R)-(+)-3-bromo-2-methyl-propionate (0.014 g, 0.077 mmol) was dissolved in THF and a phenylmagnesium bromide solution (0.031 mL of a 2.8 M solution in diethyl ether) was added dropwise. After this, $\text{CuCN} \cdot 2 \text{LiCl}$ (0.003 g, 0.017 mmol) was added at 0°C and the reaction was stirred overnight.

On the next day it was stopped with water and extracted with ethyl acetate. Then it was dried over Na_2SO_4 and evaporated.

The ^1H -NMR-spectra showed that there was only starting material in the reaction.

4.6.27 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with FeCl₃



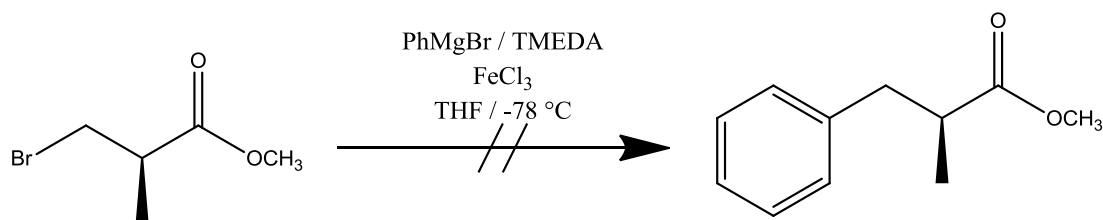
FeCl₃ (0.003 g, 0.017 mmol) was put into a flask under argon and was dissolved in THF. After this, TMEDA (0.030 g, 0.258 mmol) and (R)-(+)-3-bromo-2-methyl-propionate (0.014 g, 0.077 mmol) were added dropwise and finally a solution of phenylmagnesium bromide (0.031 mL of a 2.8 M solution in diethyl ether) was put into the reaction.

The reaction was stopped with an ammonium chloride solution and extracted with ethyl acetate. After this, it was dried over Na₂SO₄ and evaporated with reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received the information from “Masaharz Nakamura, Keiko Matsuo, Shingo Ito, Eiichi Nakamura, Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents, American Chemical Society, 2004”

4.6.28 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with FeCl₃



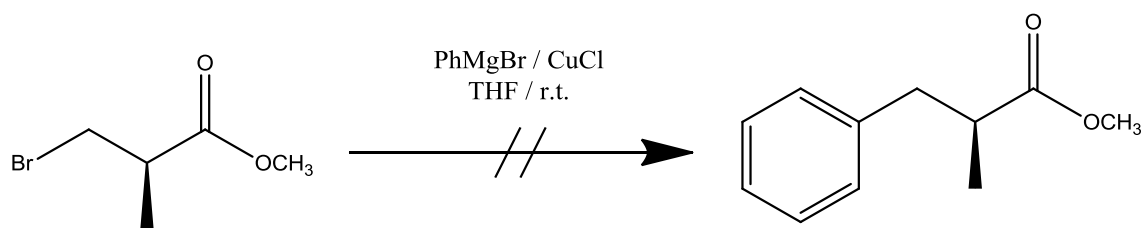
A flask with FeCl₃ (0.003 g, 0.017 mmol) was connected with argon for 10 minutes and then FeCl₃ was dissolved in THF. TMEDA (0.139 g, 1.200 mmol) was added and the whole reaction was cooled down to -78°C. (R)-(+)-3-Bromo-2-methyl-propionate (0.181 g, 1.000 mmol) and a phenylmagnesium bromide solution (1.25 mL of a 2.8 M solution in diethyl ether) were dropped into the reaction over 30 minutes.

On the next day the reaction was stopped with water and extracted with ethyl acetate. After drying over Na₂SO₄ the reaction was evaporated with reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received the information from “Masaharz Nakamura, Keiko Matsuo, Shingo Ito, Eiichi Nakamura, Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents, American Chemical Society, 2004”

4.6.29 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with CuCl

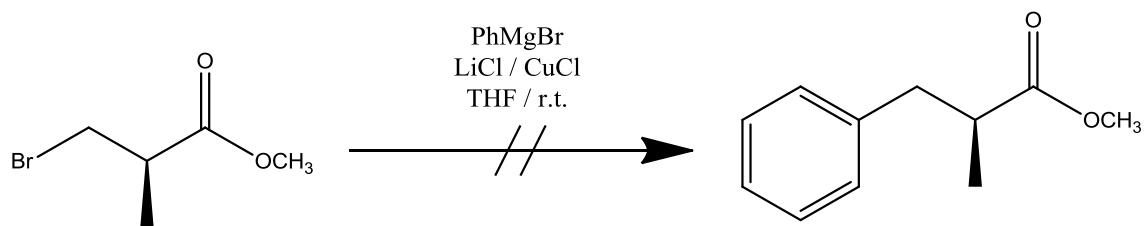


CuCl (0.006 g, 0.044 mmol) was filled into a flask under argon and was dissolved in THF. After this, (R)-(+)-3-bromo-2-methyl-propionate (0.200 g, 1.105 mmol) and also a phenylmagnesium bromide solution (1.105 mL of a 1.0M solution in THF) were added. The reaction was stirred at room temperature overnight.

Then it was stopped with water, extracted with ethyl acetate, dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

4.6.30 Synthesis of (S)-methyl 2-methyl-3-phenylpropionate with CuCl and LiCl

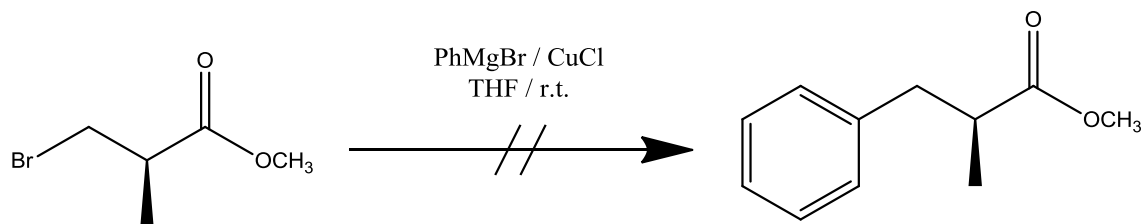


A flask was filled with CuCl (0.006 g, 0.044 mmol) and was put under argon for 10 minutes. After this, THF was added and also (R)-(+)-3-bromo-2-methylpropionate (0.200 g, 1.105 mmol) was dropped into the reaction. Then a separate prepared solution of LiCl (0.08 mL of a 0.5 M solution in anhydrous tetrahydrofuran) in THF was dropped into the other flask. At last a phenylmagnesium bromide solution (1.10 mL of a 1.0 M solution in THF) was added over 10 minutes.

After 1 hour the reaction was stopped with an ammonium chloride solution and extracted with ethyl acetate. The reaction was dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

4.6.31 Synthesis of (S)-methyl 3-(4-chloro-2-methylphenyl)-2-methylpropionate with CuCl

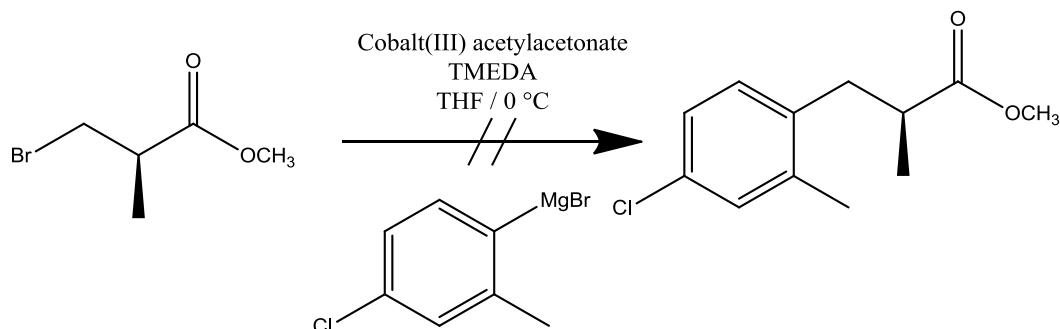


First, CuCl (0.009g, 0.066 mmol) was filled into a flask which was under argon and then it was dissolved in THF. (R)-(+)-3-Bromo-2-methyl-propionate (0.300 g, 1.657 mmol) was dropped into the reaction and finally 4-chloro-2-methyl-phenyl-magnesium bromide (3.31 mL of a 0.5 M solution in THF) was added.

After stirring for one hour the reaction was stopped with ammonium chloride solution.

The ^1H -NMR-spectra showed that there was only starting material in the reaction.

4.6.32 Synthesis of (S)-methyl 3-(4-chloro-2-methylphenyl)-2-methylpropionate with cobalt(III) acetylacetonate



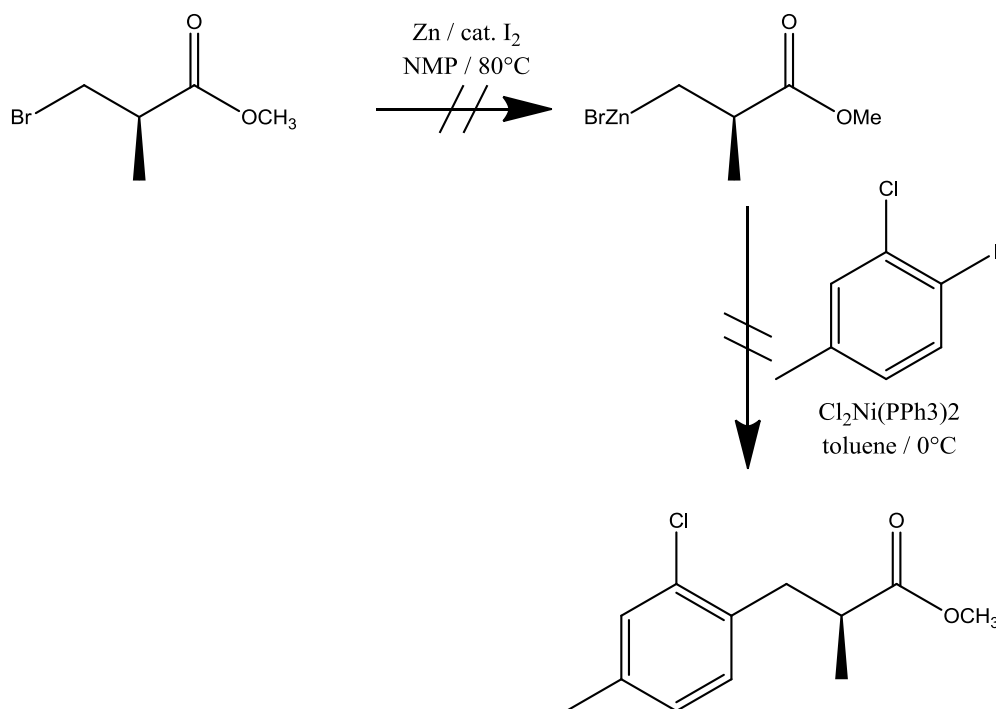
Cobalt (III) acetylacetonate (0.039 g, 0.111 mmol) was filled into a flask under argon. Then, THF and TMEDA (0.013 g, 0.111 mmol) were added and (R)-(+)-3-bromo-2-methyl-propionate (0.200 g, 1.105 mmol) was dropped into the reaction. After this 4-chloro-2-methyl-phenyl-magnesium bromide (2.43 mL of a 0.5 M solution in THF) was added for 30 minutes.

On the next day the reaction was stopped with an ammonium chloride solution and extracted with ethyl acetate. Then it was dried over Na₂SO₄ and evaporated.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received the information from “Gérard Cahiez, Christophe Chaboche, Christophe Duplais, Alban Moyeux, A New Efficient Catalytic System for the Chemoselective Cobalt-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Primary and Secondary Alkyl Bromides, American Chemical Society, 2009”

4.6.33 Synthesis of (S)-methyl 3-(2-chloro-4-methylphenyl)-2-methylpropionate with zinc powder and iodine



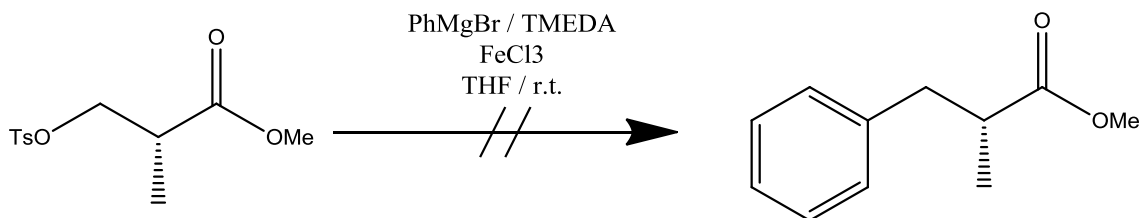
1-Methyl-2-pyrrolidone, iodine and zinc powder was filled into a flask under argon and then it was stirred until the red colour disappeared. Then the reaction was heated up to 80°C and 3-chloro-4-iodo-toluene was added. After stirring for 3 hours, the reaction was cooled down to room temperature and a solution of Cl₂Ni(PPh₃)₂ in toluene was added.

The reaction was stirred over the weekend and then stopped with an ammonium chloride solution, extracted with ethyl acetate, dried over Na₂SO₄ and evaporated with reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received the information from “Shouquan Huo, Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents from Unactivated Alkyl Bromides and Chlorides, American Chemical Society, 2003”

4.6.34 Synthesis of (R)-methyl 2-methyl-3-phenylpropanoate with FeCl_3



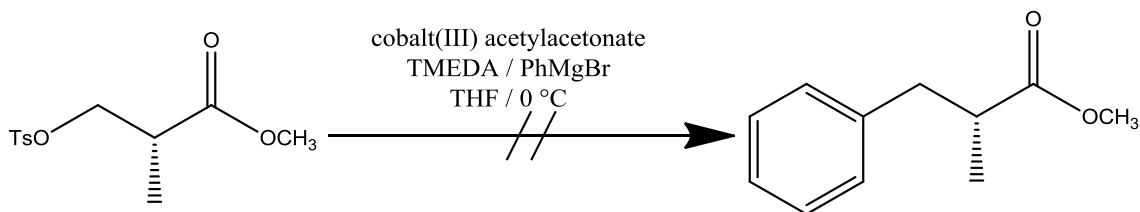
A flask with FeCl_3 (0.003 g, 0.018 mmol) was put under argon and 10 minutes later THF was added. After this, (S)-methyl 2-methyl-3-(tosyloxy)propanoate (0.050 g, 0.184 mmol) and TMEDA (0.032 g, 0.275 mmol) were dropped into the reaction and finally a solution of phenylmagnesium bromide (0.092 mL of a 3.0 M solution in diethyl ether) was added.

The reaction was stirred overnight and then stopped with an ammonium chloride solution. After the extraction with ethyl acetate the reaction was dried over Na_2SO_4 and evaporated.

The ^1H -NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received the information from “Masaharu Nakamura, Keiko Matsuo et al., Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents, American Chemical Society, 2004”.

4.6.35 Synthesis of (R)-methyl 2-methyl-3-phenylpropanoate with cobalt (III) acetylacetonate



Cobalt (III) acetylacetonate (0.007 g, 0.018 mmol) was filled into a flask under argon and was dissolved in THF. After this, TMEDA (0.002 g, 0.018 mmol) and (S)-methyl 2-methyl-3-(tosyloxy)propanoate were dropped into the reaction at 0°C. Finally, a solution of phenylmagnesium bromide (0.067 mL of a 3.0 M solution in diethyl ether) was added and the reaction was stirred overnight.

On the next day it was stopped with an ammonium chloride solution, extracted with ethyl acetate, dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received information from “Gérard Cahiez, Christophe Chaboche et. al., A New Efficient Catalytic System for the Chemoselective Cobalt-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Primary and Secondary Alkyl Bromides, Organic Letters, Vol. 11, No. 2, American Chemical Society, 2009”.

4.6.36 Synthesis of (R)-methyl 2-methyl-3-phenylpropanoate with CuCl

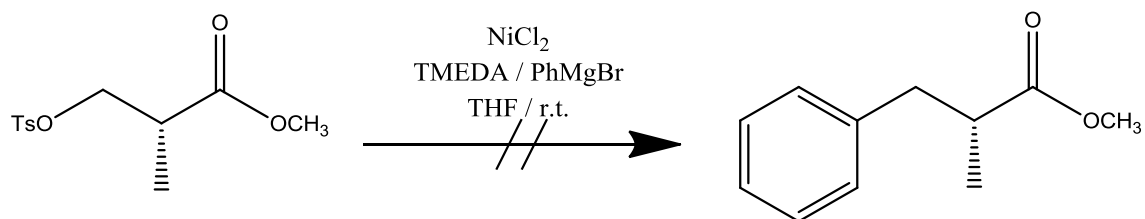


CuCl (0.001 g, 0.007 mmol) was put into a flask under argon and was dissolved in THF. Then (S)-methyl 2-methyl-3-(tosyloxy)propanoate (0.050 g, 0.184 mmol) was added and a solution of phenylmagnesium bromide (0.061 mL of a 3.0 M solution in diethyl ether) was dropped into the reaction. It was stirred at room temperature overnight.

Finally, the reaction was stopped with water and extracted with ethyl acetate. Then it was dried over Na₂SO₄ and evaporated.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

4.6.37 Synthesis of (R)-methyl 2-methyl-3-phenylpropanoate with NiCl₂

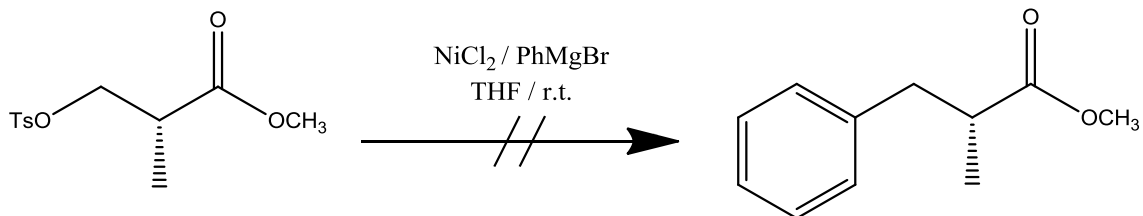


NiCl_2 (0.005 g, 0.041 mmol) was weighed into a flask under argon and was dissolved in THF. After this TMEDA (0.005 g, 0.041 mmol) was added and (S)-methyl 2-methyl-3-(tosyloxy)propanoate (0.050 g, 0.184 mmol) was put into the reaction. Finally, a phenylmagnesium bromide solution (0.070 mL of a 3.0 M solution in diethyl ether) was dropped into the reaction.

After stirring overnight at room temperature the reaction was stopped with an ammonium chloride solution, extracted with ethyl acetate and dried over Na_2SO_4 . Then, it was evaporated under reduced pressure.

The ^1H -NMR-spectra showed that there was only starting material in the reaction.

4.6.38 Synthesis of (R)-methyl 2-methyl-3-phenylpropanoate with NiCl_2 and without TMEDA

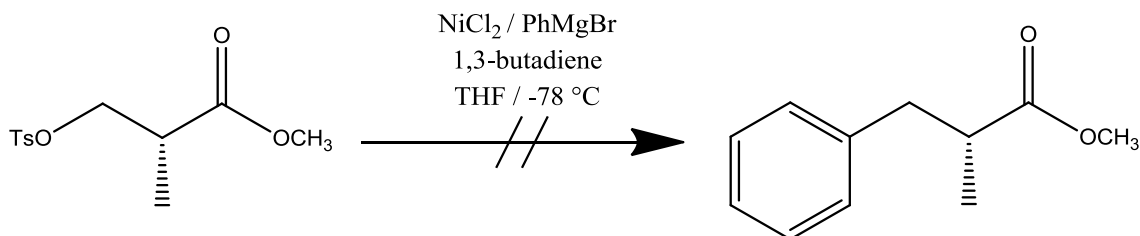


NiCl_2 (0.005 g, 0.041 mmol) was put into a flask under argon and was dissolved in THF. Additionally TMEDA (0.005 g, 0.041 mmol) was dropped into the reaction and (S)-methyl 2-methyl-3-(tosyloxy)propanoate (0.050 g, 0.184 mmol) was added. After this, a phenylmagnesium bromide solution (0.070 mL of a 3.0 M solution in diethyl ether) was dropped into it.

After stirring overnight at room temperature the reaction was stopped with an ammonium chloride solution, extracted with ethyl acetate and dried over Na_2SO_4 . Finally it was evaporated under reduced pressure.

The ^1H -NMR-spectra showed that there was only starting material in the reaction.

4.6.39 Synthesis of (R)-methyl 2-methyl-3-phenylpropanoate with 1, 3-butadiene

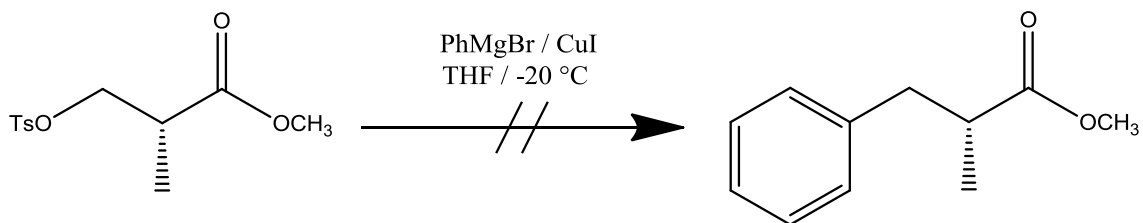


(S)-Methyl 2-methyl-3-(tosyloxy)propanoate (0.050 g, 0.184 mmol) and a phenylmagnesium solution (0.080 mL of a 3.0 M solution in diethyl ether) were added into a flask under argon at -78°C . Then 1, 3-butadiene (0.090 mL of a 2.0 M solution in tetrahydrofuran) and after this NiCl_2 (0.001 g, 0.006 mmol) were put into the reaction. After stirring for 30 minutes the reaction was stopped and worked up.

The ^1H -NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received information from “Jun Terao, Hideyuki Watanabe et al., Nickel-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Alkyl Halides and Tosylates: Remarkable Effect of 1,3-Butadienes, American Chemical Society, 2002”.

4.6.40 Synthesis of (R)-methyl 2-methyl-3-phenylpropanoate with CuI



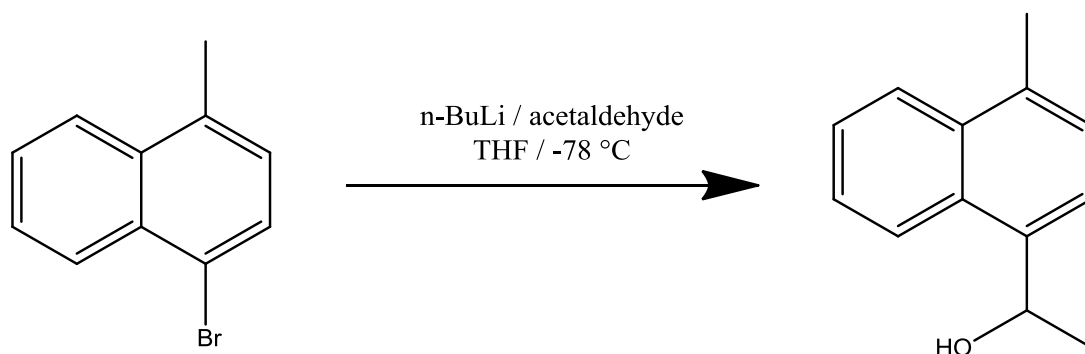
CuI (0.112 g, 0.588 mmol) was filled into a flask under argon and was dissolved in THF. After 10 minutes (S)-methyl 2-methyl-3-(tosyloxy)propanoate (0.050 g, 0.184 mmol) and a solution of phenylmagnesium bromide (0.245 mL of a 3.0 M solution in THF) were dropped into the reaction at -20°C.

After stirring overnight at room temperature the reaction was stopped with an ammonium chloride solution and extracted with diethyl ether. Then it was dried over Na₂SO₄ and evaporated under reduced pressure.

The ¹H-NMR-spectra showed that there was only starting material in the reaction.

For our synthesis we received information from “Shnji Tanimori, Koichi Tanimoto, Mitsunori Kiriata, Easy access to both enantiomers of C7-C12 segment of epothilones, Synthetic communications, Marcel Dekker, 1999”.

4.6.41 Synthesis of 1-(4-methylnaphthalen-1-yl)ethanol with *n*-BuLi and acetaldehyde



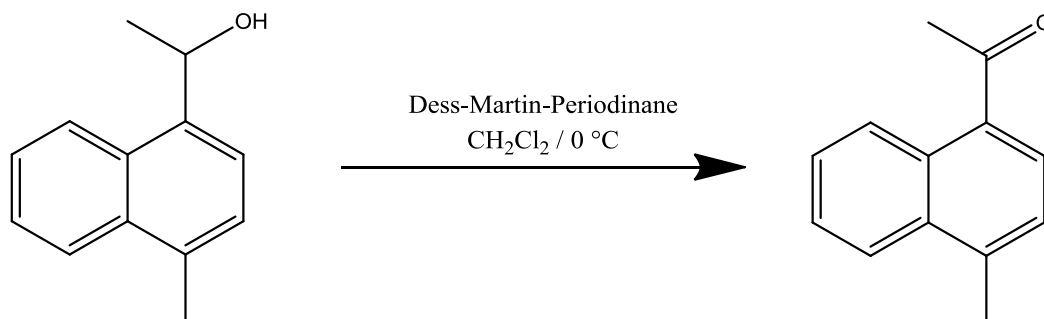
1-Bromo-4-methylnaphthalene (0.150 g, 0.680 mmol) was filled into a flask under argon and was dissolved in THF. Then, the reaction was cooled down to -78°C. Afterwards, *n*-BuLi (0.27 mL in a 2.5 M solution in hexane) was dropped into the reaction and after stirring for 30 minutes acetaldehyde (0.042 g, 0.540 mmol) was added.

After stirring overnight at room temperature the reaction was stopped with an ammonium chloride solution and extracted with ethyl acetate. Then it was dried over Na₂SO₄ and evaporated under reduced pressure.

The NMR showed that there was the expected product (0.120 g, 94.75 %) in our reaction.

For our synthesis we received information from “J. Clayden, Organolithiums: Selectivity for Synthesis, Pergamon, Oxford, 2002”

4.6.42 Synthesis of 1-(4-methylnaphthalen-1-yl)ethanone with Dess-Martin-Periodinane



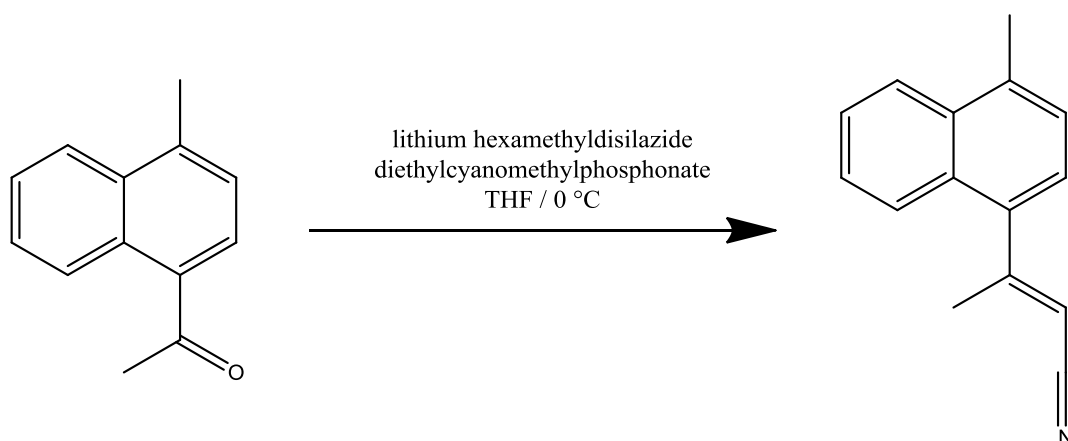
A flask was filled with 1-(4-methylnaphthalen-1-yl)ethanol (0.120 g, 0.644 mmol). Then it was put under argon and the substance in the flask was dissolved with dichloromethane. Dess-Martin-Periodinane (0.546 g, 1.288 mmol) was added at $0\text{ }^\circ\text{C}$ and the reaction was stirred at room temperature for two hours.

After this the reaction was stopped with a solution of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (1:1) and extracted with ethyl acetate. Then it was dried over Na_2SO_4 and evaporated under reduced pressure.

We received the predicted product (0.062 g, 52.25 %).

For our synthesis we received information from “Readily Accessible 12-I-5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones, D.B. Dess, J.C. Martin, J. Org. Chem., 1983”

4.6.43 Synthesis of 3-(4-methylnaphthalen-1-yl)but-2-enenitrile



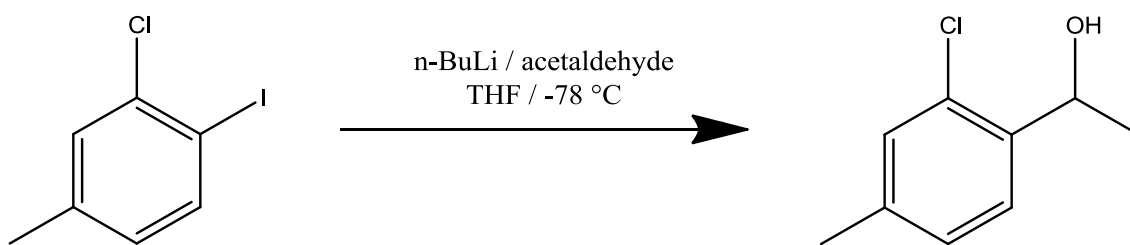
A solution of lithium hexamethyldisilazide (0.370 mL of a 1.0 M solution in THF) was added to a solution of diethylcyanomethylphosphonate (0.060 g, 0.373 mmol) in THF at room temperature. After 30 minutes it was dropped into a solution of the ketone (0.062 g, 0.339 mmol) which was produced the reaction before. The reaction was stirred at 0°C for 10 minutes and then at room temperature for 45 minutes.

Afterwards the reaction was stopped with an ammonium chloride solution, extracted with ethyl acetate, dried over Na₂SO₄ and evaporated under reduced pressure.

We received the predicted product (0.05 g, 71.15 %).

For our synthesis we received information from “Bruce E. Maryanoff, Allen B. Reitz, The Wittig Olefination reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism, and Selected Synthetic Aspects, American Chemical Society, 1989”

4.6.44 Synthesis of 1-(2-chloro-4-methylphenyl)ethanol with *n*-BuLi and acetaldehyde



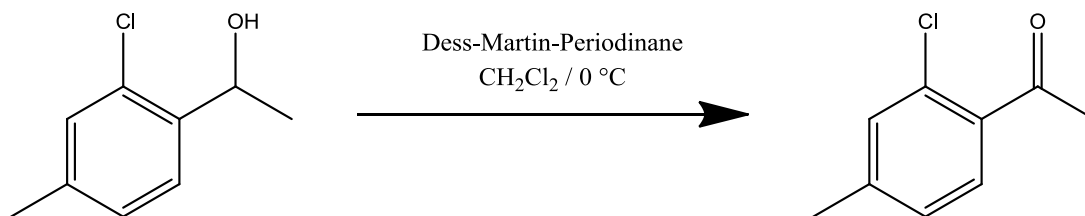
2-Chloro-1-iodo-4-methylbenzene (0.150 g, 0.680 mmol) was in a flask under argon and was dissolved in THF. Then *n*-BuLi (0.27 mL in a 2.5 M solution in hexane) was dropped into the reaction at -78°C. After stirring for 30 minutes acetaldehyde (0.042 g, 0.540 mmol) was added and the reaction was stirred at room temperature overnight.

On the next day the reaction was stopped with an ammonium chloride solution, extracted with ethyl acetate, dried over Na₂SO₄ and evaporated under reduced pressure.

We received the predicted product (0.064 g, 55.16 %).

For our synthesis we received information from “J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, 2002”

4.6.45 Synthesis of 1-(2-chloro-4-methylphenyl)ethanone with Dess-Martin-Periodinane



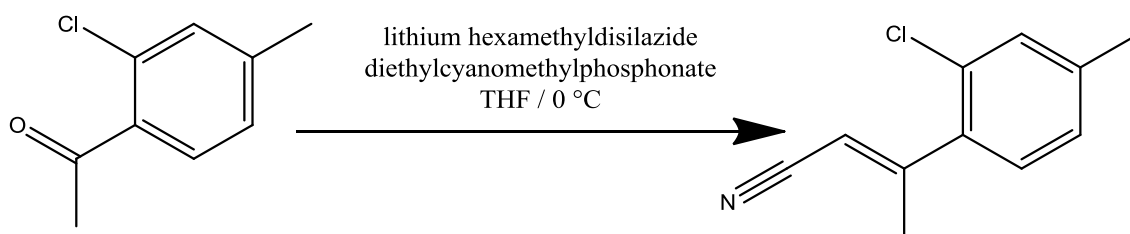
A flask with 1-(2-chloro-4-methylphenyl)ethanol (0.064 g, 0.352 mmol) was put under argon and after 10 minutes the substance was dissolved in dichloromethane. Then the flask was cooled down to $0\text{ }^\circ\text{C}$ and Dess-Martin-Periodinane (0.298 g, 0.703 mmol) was added. After this, the reaction was stirred at room temperature for 2 hours.

Then the reaction was stopped with a solution of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (1:1), extracted with ethyl acetate, dried over Na_2SO_4 and evaporated under reduced pressure.

There was the predicted product (0.059 g, 99.4 %).

For our synthesis we received information from “D.B. Dess, J.C. Martin, Readily Accessible 12-I-5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones, J. Org. Chem., 1983”

4.6.46 Synthesis of 3-(2-chloro-4-methylphenyl)but-2-enenitrile



A solution of lithium hexamethyldisilazide (0.37 mL of a 1.0 M solution in THF) in THF was prepared in a flask and was then added to a solution of diethylcyanomethylphosphonate (0.070 g, 0.373 mmol) in THF at room temperature. Then the reaction was stirred for 30 minutes and afterwards it was dropped into a solution of the ketone (0.059 g, 0.339 mmol) which was produced in the last reaction. It was stirred at 0°C for 10 minutes and after that at room temperature for 45 minutes.

Then the reaction was stopped with an ammonium chloride solution, extracted with ethyl acetate, dried over Na₂SO₄ and evaporated under reduced pressure.

We received our product (0.05 g, 76.96 %).

For our synthesis we received information from “Bruce E. Maryanoff, Allen B. Reitz, The Witting Olefination reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism, and Selected Synthetic Aspects, American Chemical Society, 1989”

5 Zusammenfassung/Abstract

5.1 Zusammenfassung

Zuallererst versuchten wir, mittels asymmetrischen Synthesen, reine Enantiomere herzustellen. Da wir nur sehr wenig Produkt durch diese Reaktionen erhielten, versuchten wir anschließend unsere Reaktionsschemen zu verbessern. Dieser Weg konnte aber nicht weiter beschritten werden, da eine für die Reaktion sehr wichtige Chemikalie, namens (-)-Sparteine, auf einmal nicht mehr am Markt erhältlich war. Sobald (-)-Sparteine wieder am Markt erwerblich ist, wäre es sehr interessant, diese Reaktionen weiterzuverfolgen.

Als nächstes versuchten wir unsere chiralen Strukturen mittels SAMP-Hydrazonen zu synthetisieren. Es gelang uns zwar das SAMP-Hydrazon herzustellen, aber dafür missglückte die anschließende enantioselektive Methylierung unseres Moleküls.

Wir versuchten einige andere Reaktionen um unsere enantiomerenreinen Produkte herzustellen. Dafür verwendeten wir Grignard Reagentien und Alkyl-Tosylate, die wir mit den unterschiedlichsten Katalysatoren zu unterstützen versuchten. Jedoch erhielten wir bei beiden Reaktionsarten nie das gewollte Produkt.

Anschließend aktivierten wir mittel Iod Zink und generierten ein Alkylzinkbromid. Mit Hilfe eines geeigneten Katalysators synthetisierten wir daraus unser Alkylbromid. Leider erhielten wir auch mittels dieser Reaktion nicht das gewollte Produkt.

Am Schluss hatten wir Erfolg und konnten zwei achirale GABA_A-Rezeptor Liganden, mit Hilfe von einem Reagens namens Dess-Martin-Periodinan, synthetisieren. Diese zwei Substanzen wurden am Department für Pharmakologie getes-

tet, ob sie am GABA_A-Rezeptor eine Aktivität aufweisen, oder nicht. Dabei stellte sich heraus, dass eine der beiden Substanzen sehr aktiv ist.

5.2 Abstract

At the beginning, we started to synthesise enantiomerically pure compounds with help of asymmetric synthesis. We were able to produce an enantiomerically pure product but only in a small yield. So we spent a lot of time to optimise our reaction scheme. Although our structures were very promising, we had to stop soon with further research, due to the fact that one of the most important substances which was (-)-sparteine was no longer available on the market. It would be very interesting to follow these reactions further as soon as (-)-sparteine is available on the market again.

After this we tried to create enantiomerically pure structures with help of SAMP-hydrazones. The synthesis of the SAMP-hydrazones worked very well, but the enantioselective methylation of our compound failed.

We also tried a lot of other ways to get enantiomerically pure compounds for example Grignard reagents and alkyl tosylates powered with different catalysts. Both reactions turned out to be not effective.

Subsequently we tried to use I_2 to activate zinc and a suitable catalyst to produce an alkyl bromide out of an alkyl zinc bromide. However, even in this reaction there was only starting material and no product.

At the end we were able to produce two achiral GABA_A-receptor ligands with help of Dess-Martin-Periodinane. These substances were tested at the Department of Pharmacology to determine whether they act with the GABA_A-receptor or not. One of them turned out to be very active.

6 References

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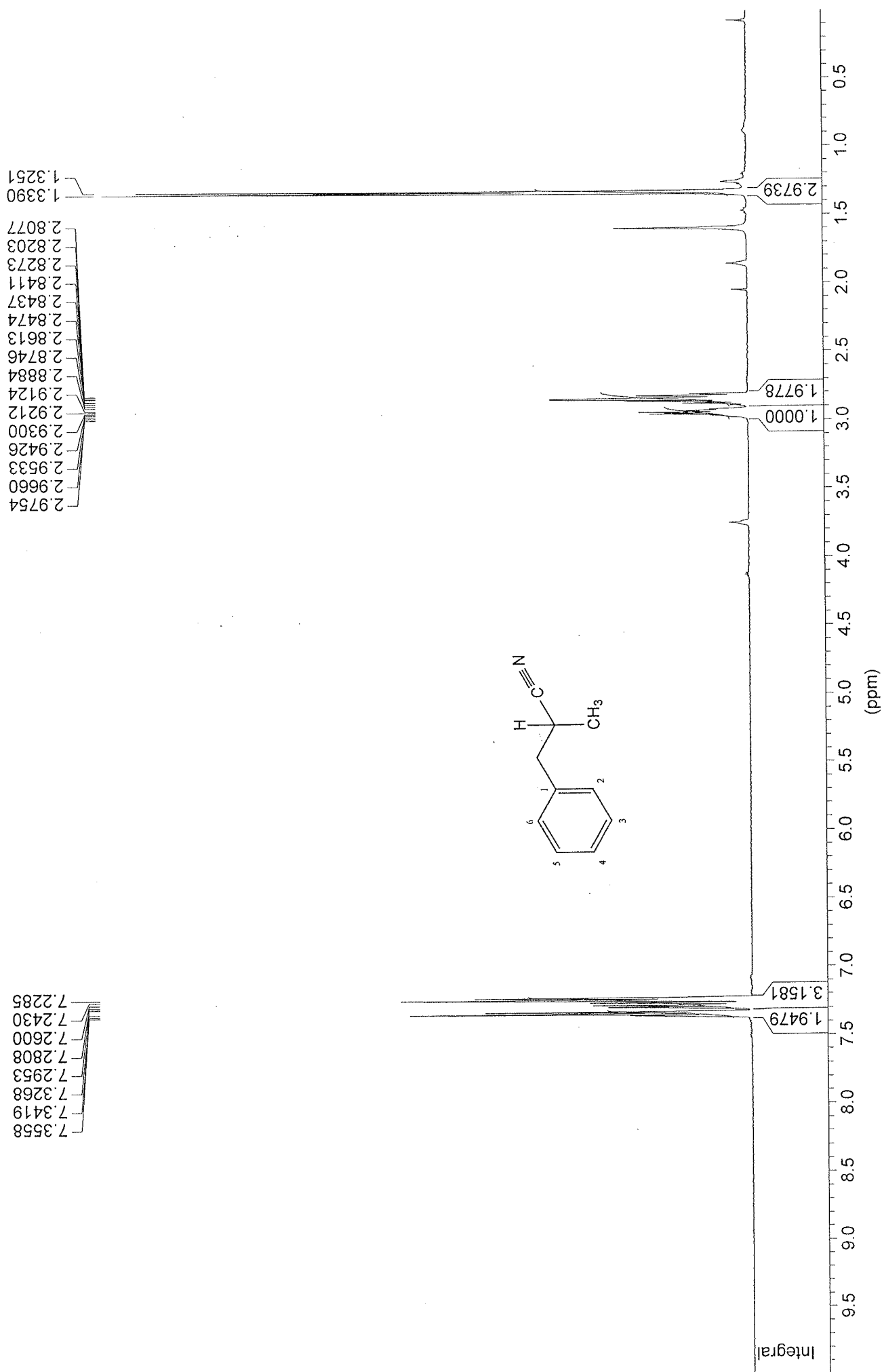
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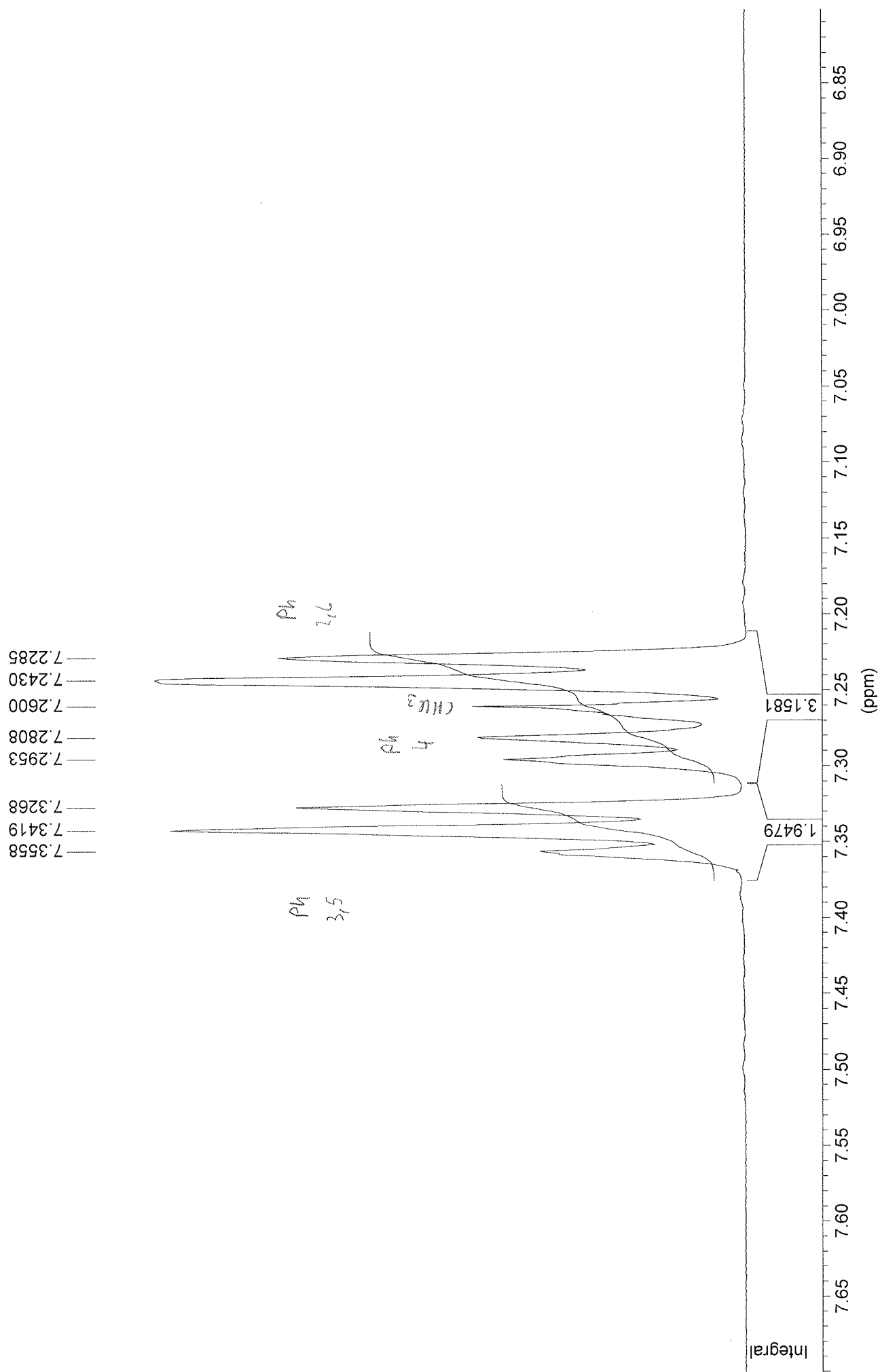
7 List of abbreviations

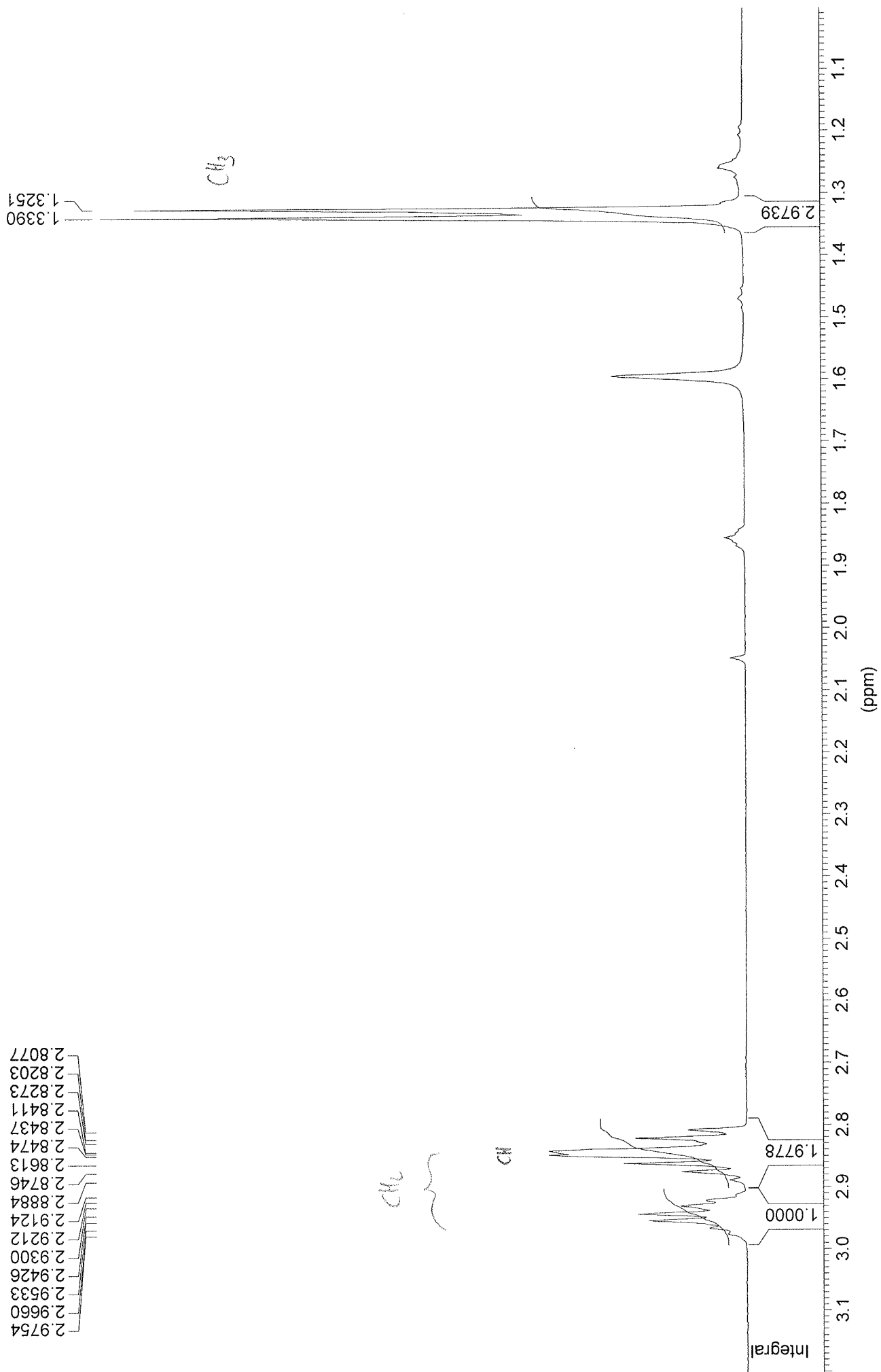
BuLi	buthyllithium
CAT-1	cationic amino acid transporter-1
CH ₂ Cl ₂	dichloromethane
Cl ₂ Ni(PPh ₃) ₂	dichlorobis(triphenylphosphin)nickel(II)
Co (acac) ₃	cobalt(III) acetylacetonate
CuCN * 2 LiCl	copper(I) cyanide di(lithium chloride)
DCM	dichloromethane
DMF	dimethylformamide
Et ₃ N	triethylamine
FeCl ₃	iron(III) chloride
GABA	gamma-aminobutyric acid
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
I ₂	iodine
LDA	lithium diisopropylamide
MeI	methyl iodide
MeOH	methanol
MMPP	magnesium monoperoxyphthalate
NiCl ₂	nickel(II) chloride
NMR	nuclear magnetic resonance
Pd (OAc) ₂	palladium(II) acetate
Ppm	parts per million

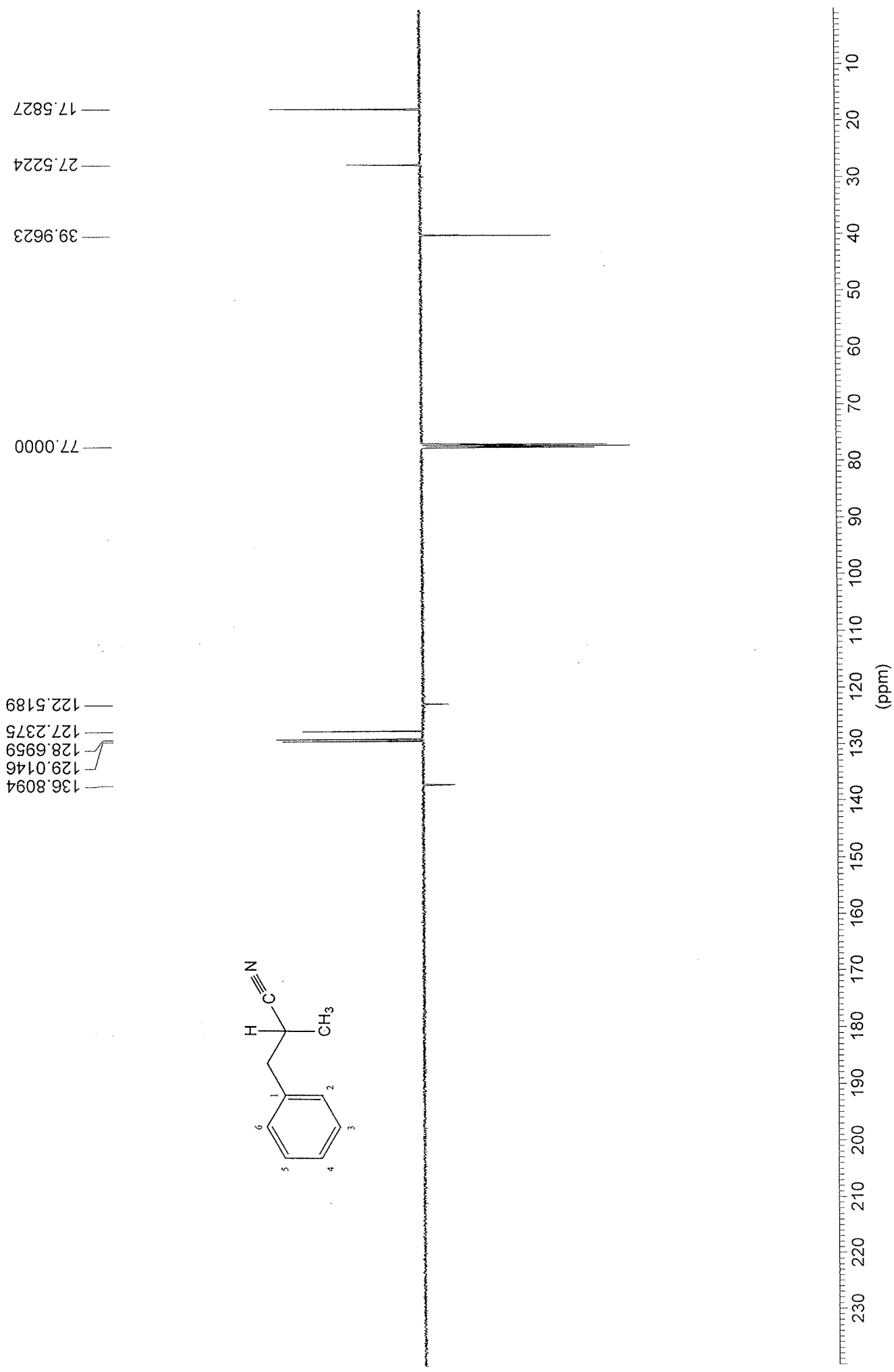
SAMP	(S)-1-amino-2-methoxy-methylpyrrolidine
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TsCl	toluenesulfonyl chloride
ZnCl ₂	zinc(II) chloride

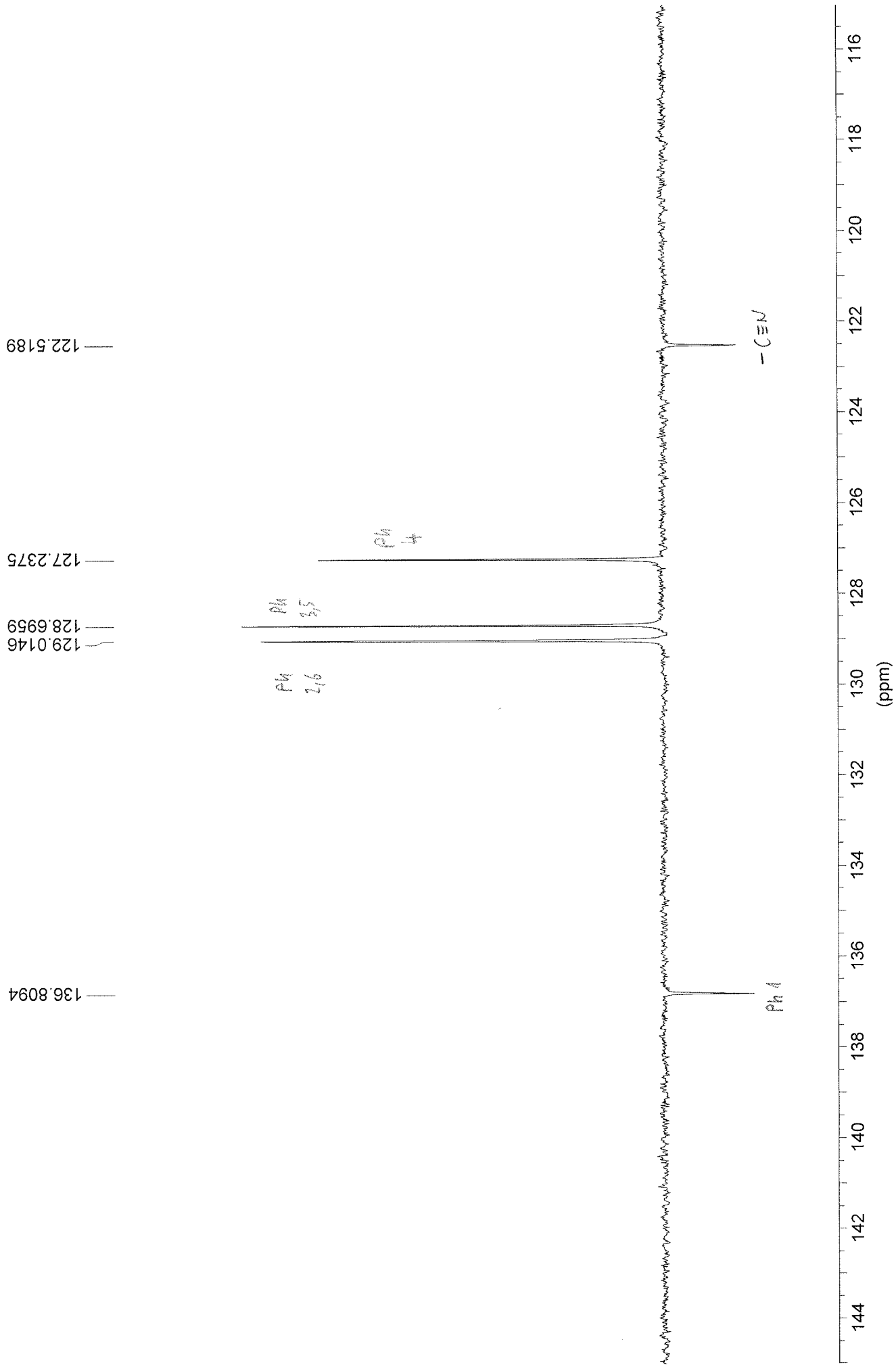
8 Appendix: NMR-spectra

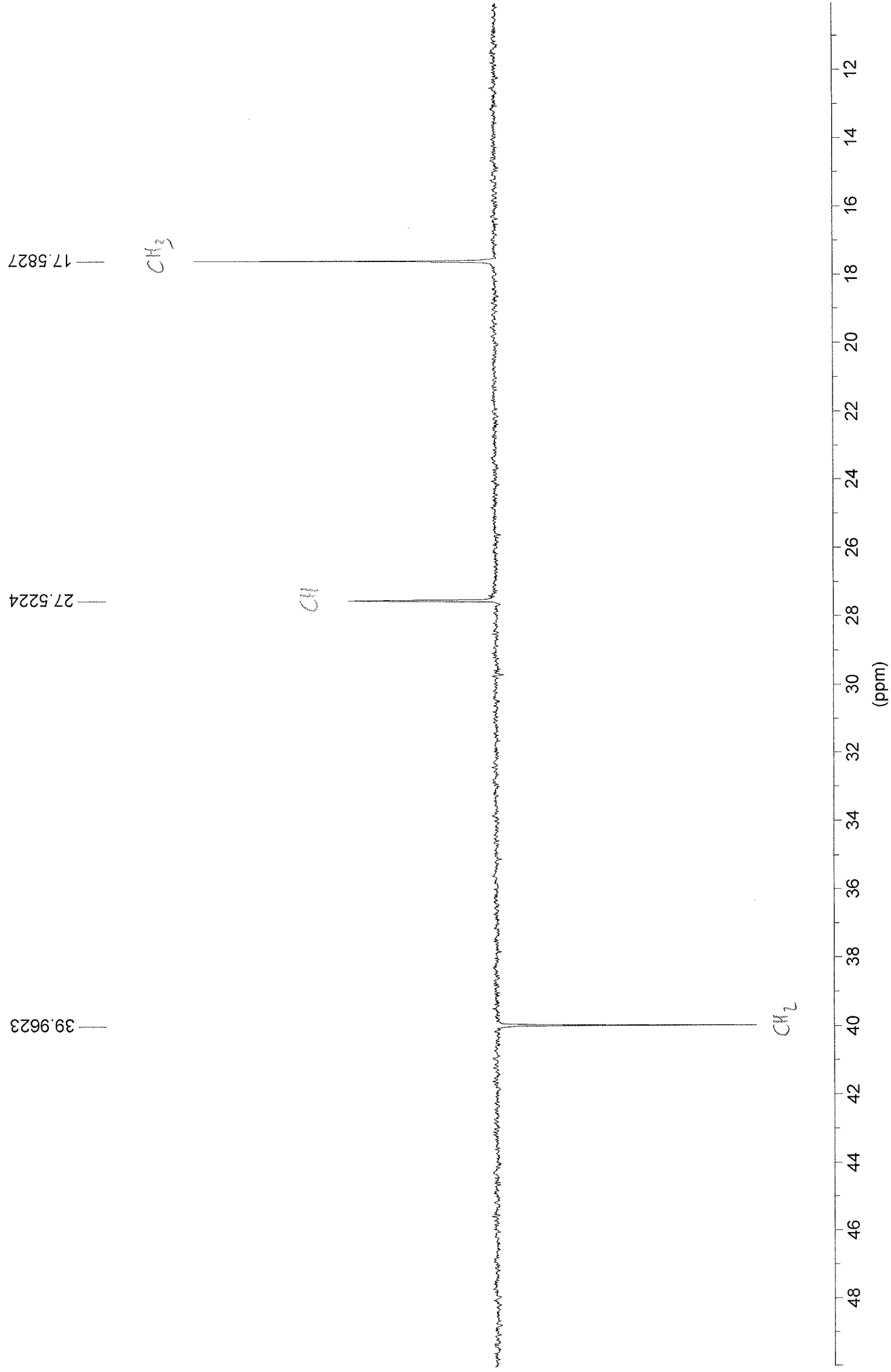


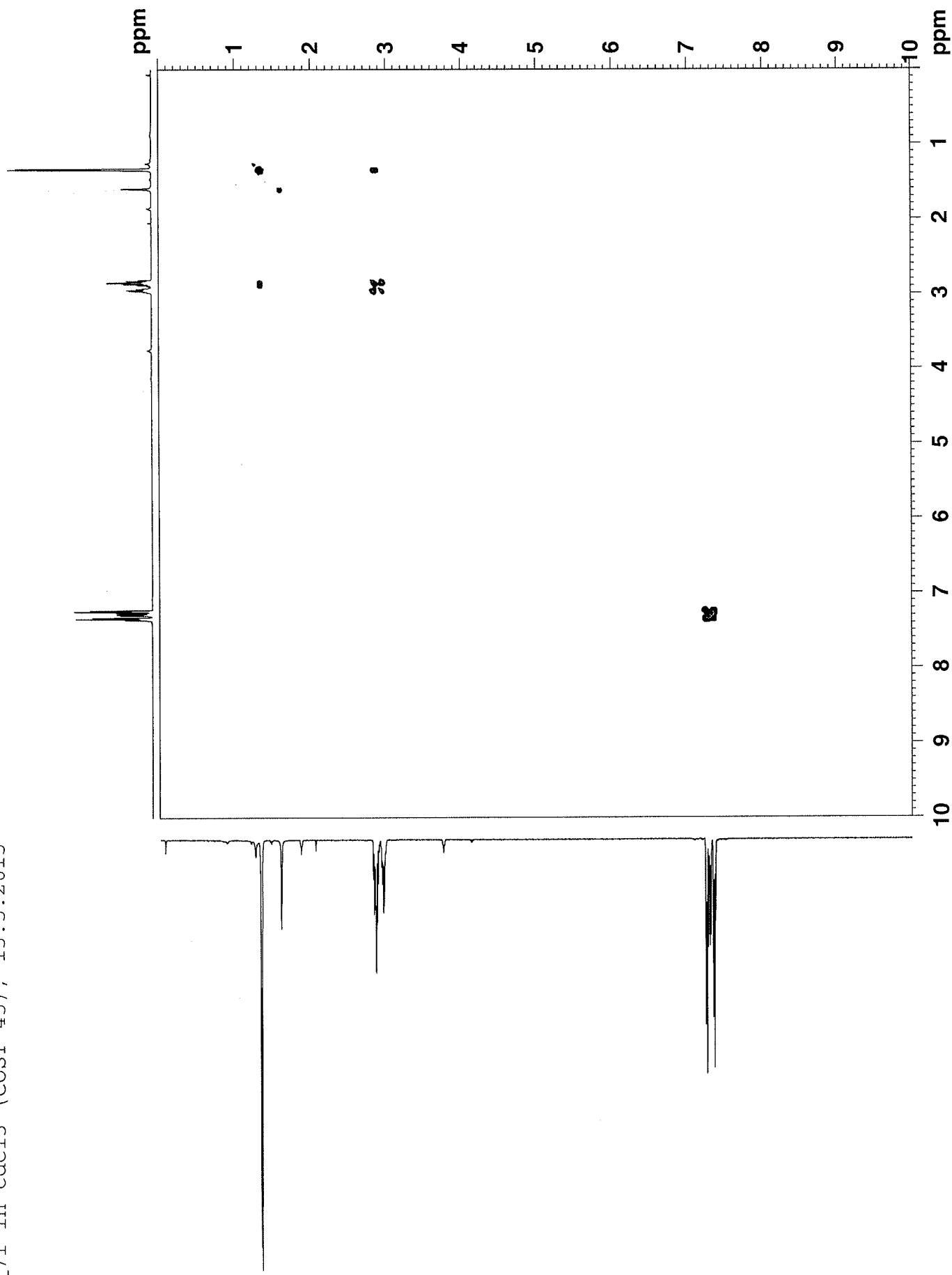


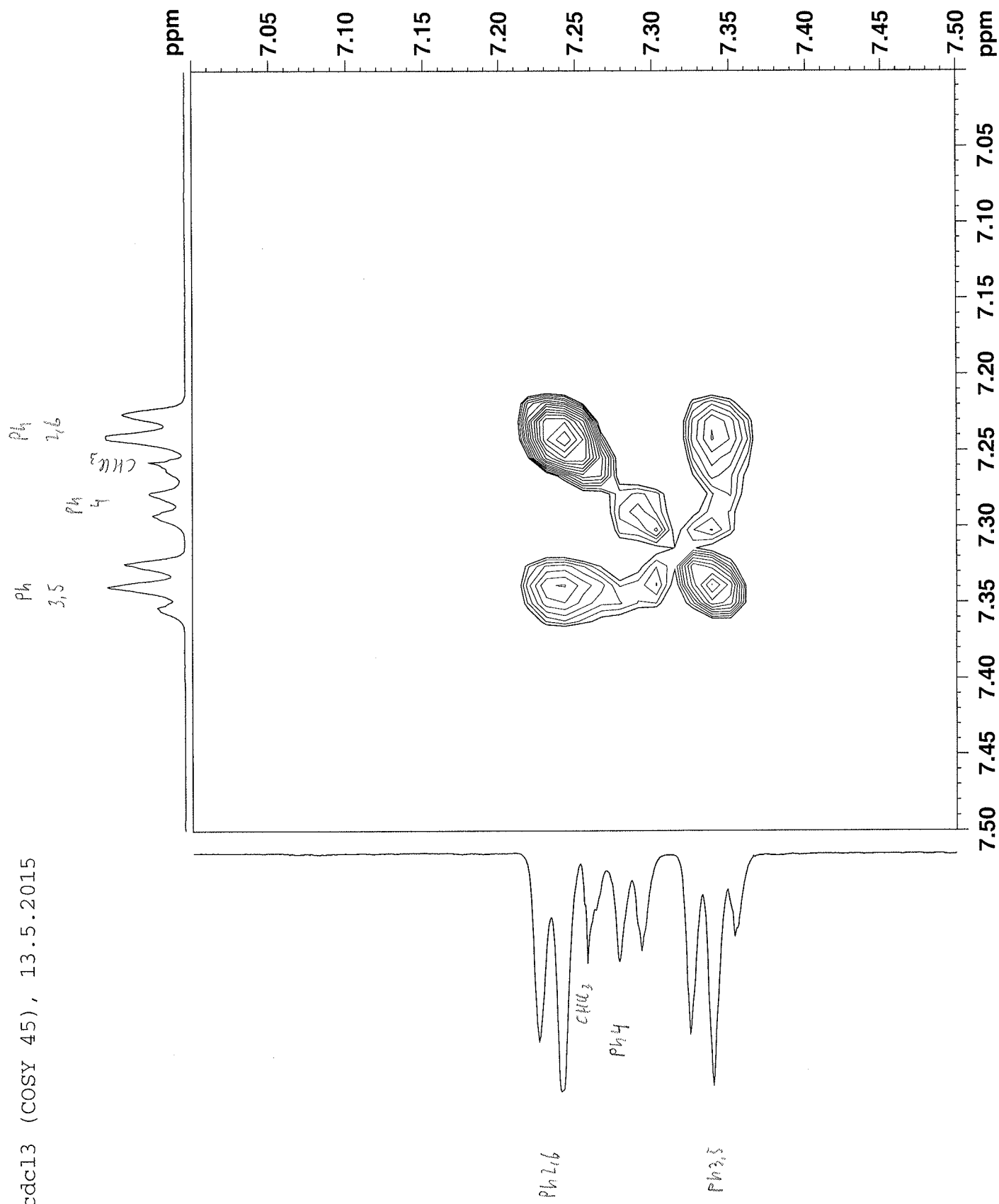


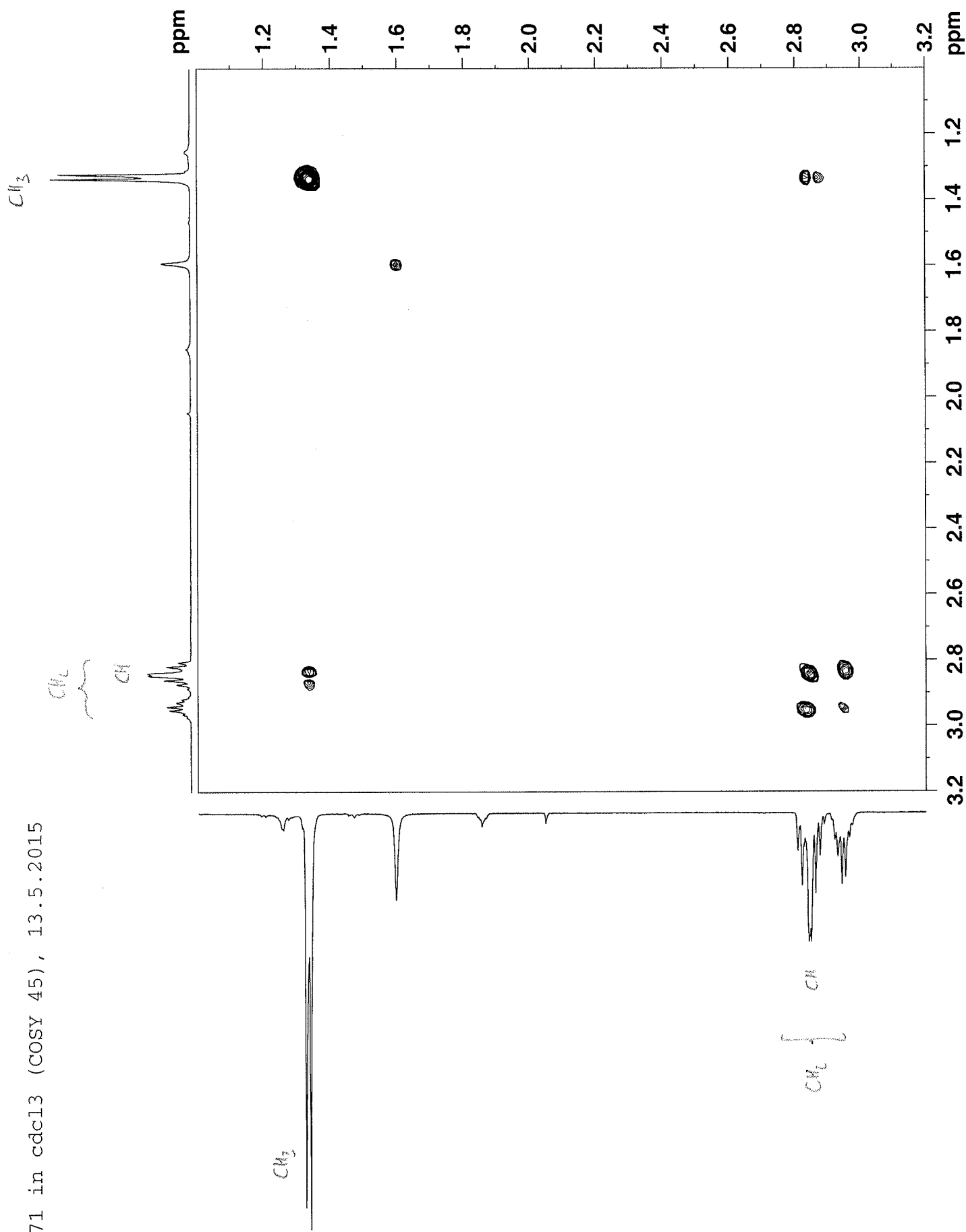




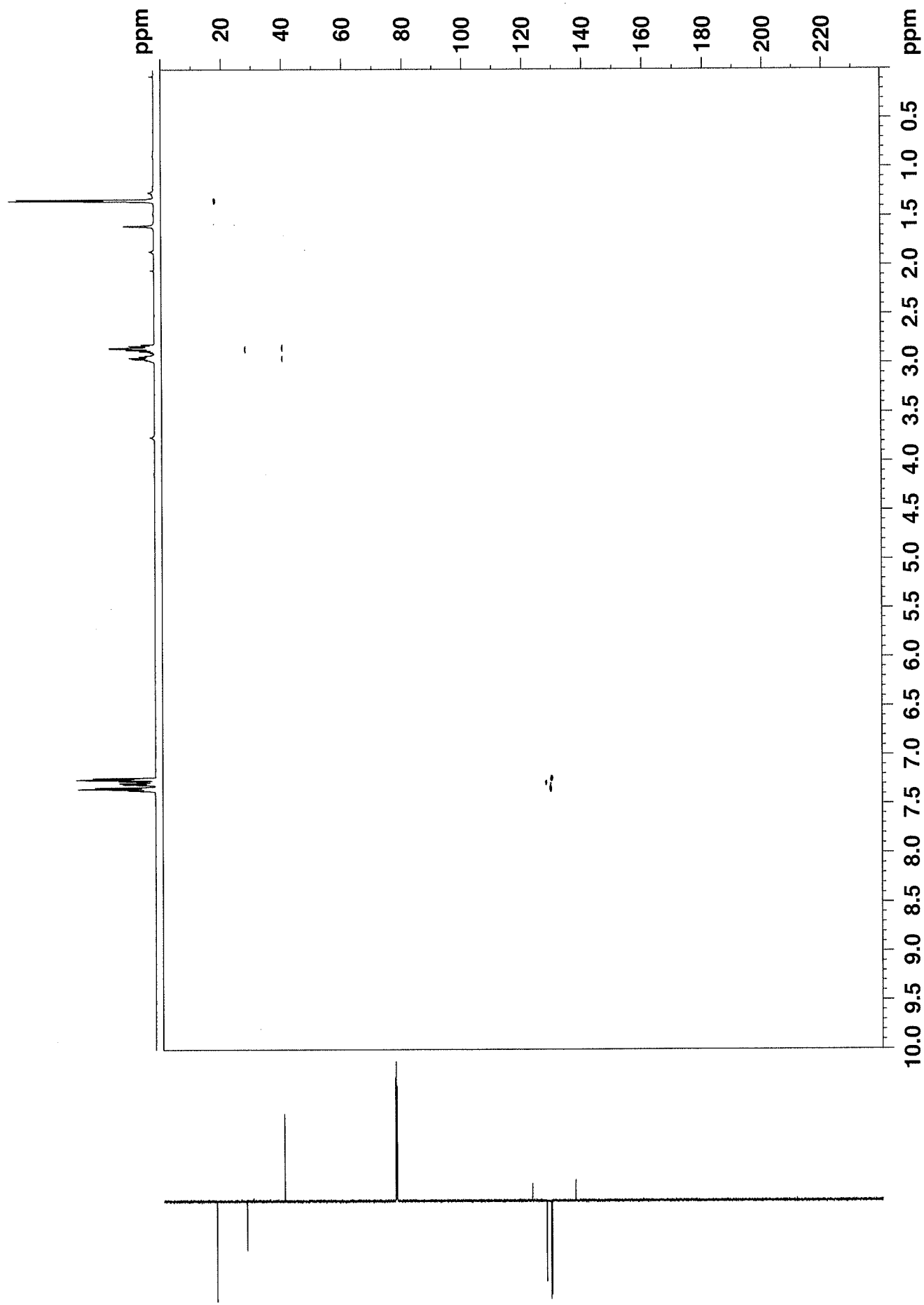




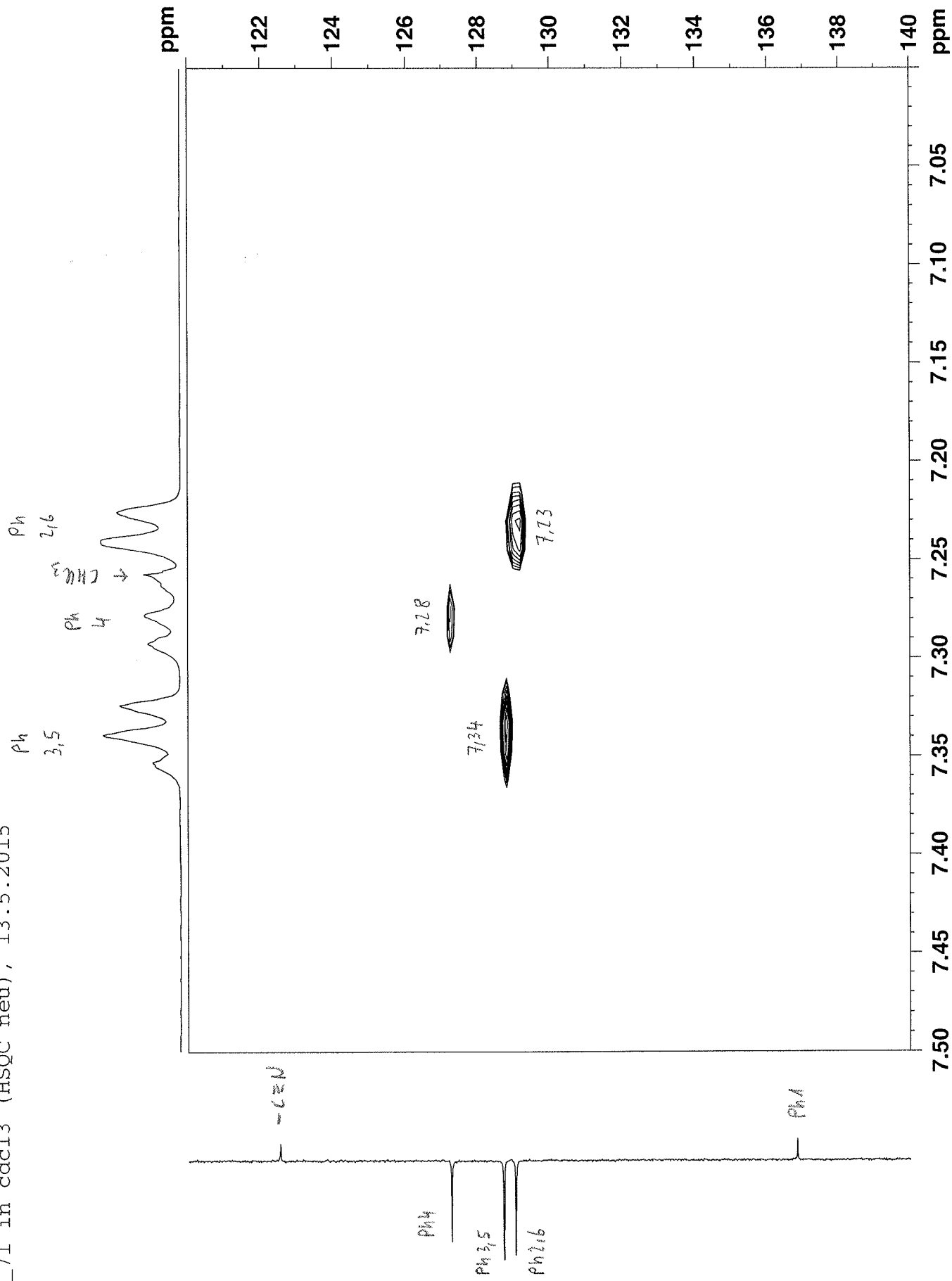


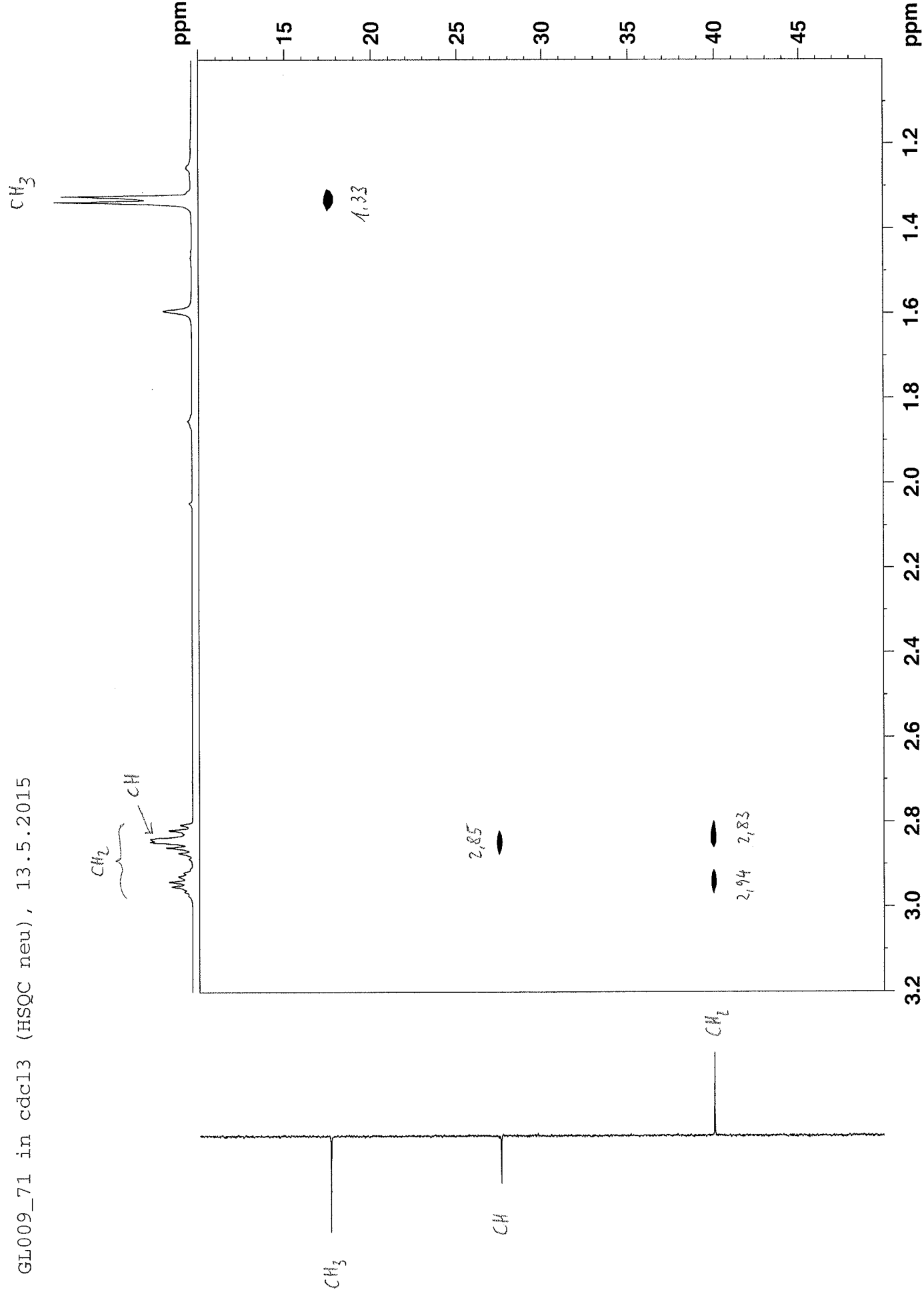


GL009_71 in cdcl3 (HSQC neu), 13.5.2015

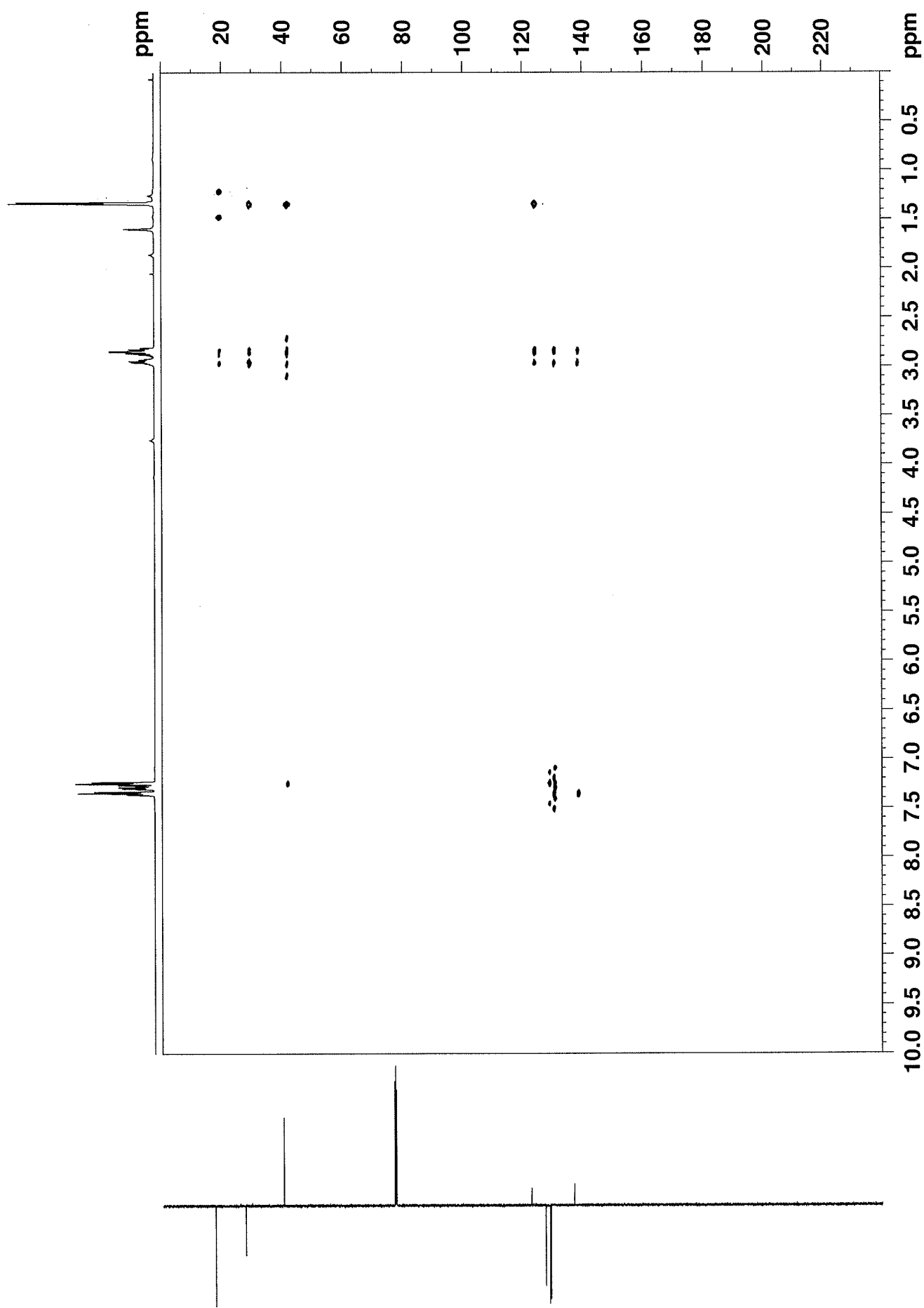


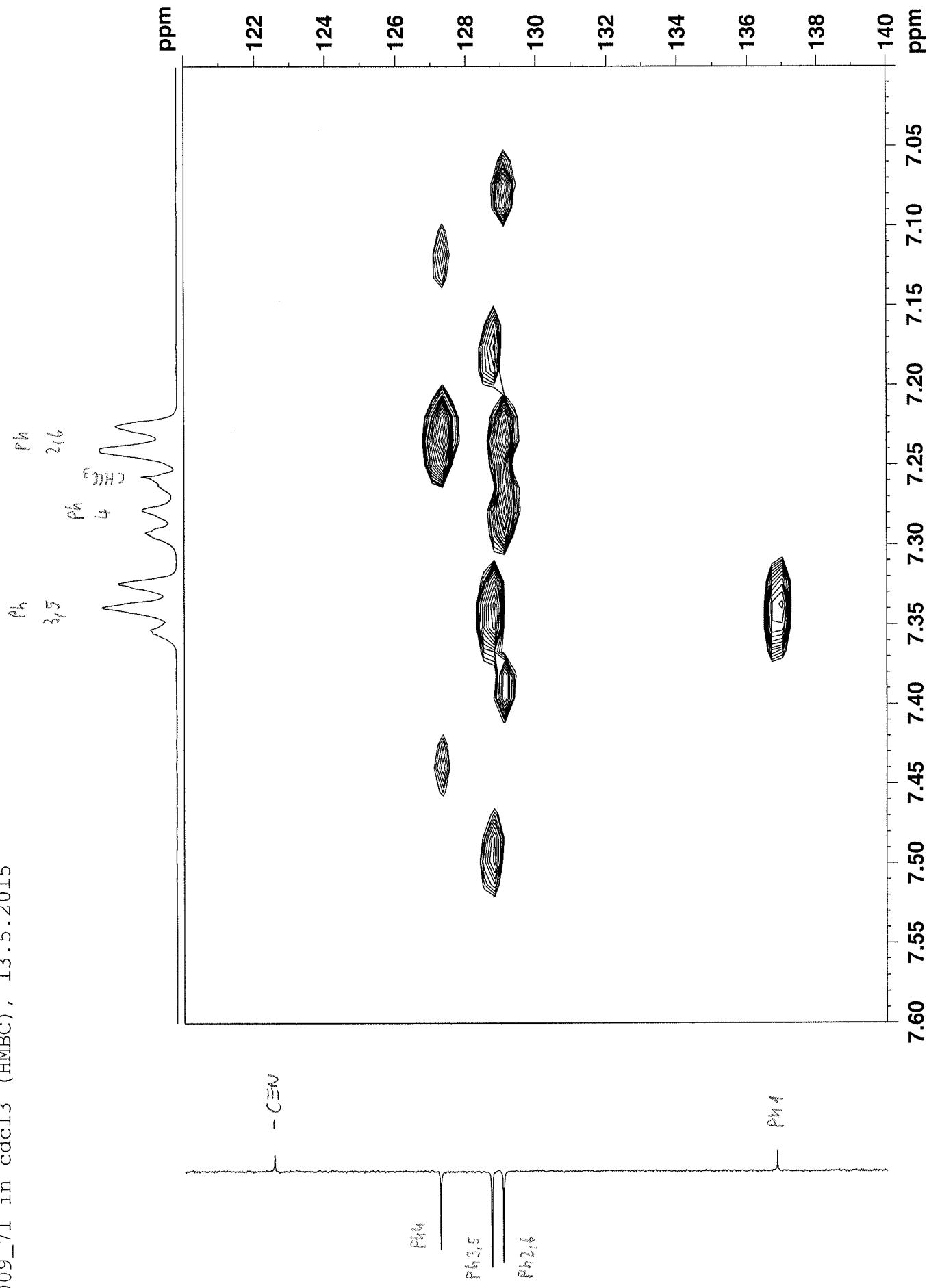
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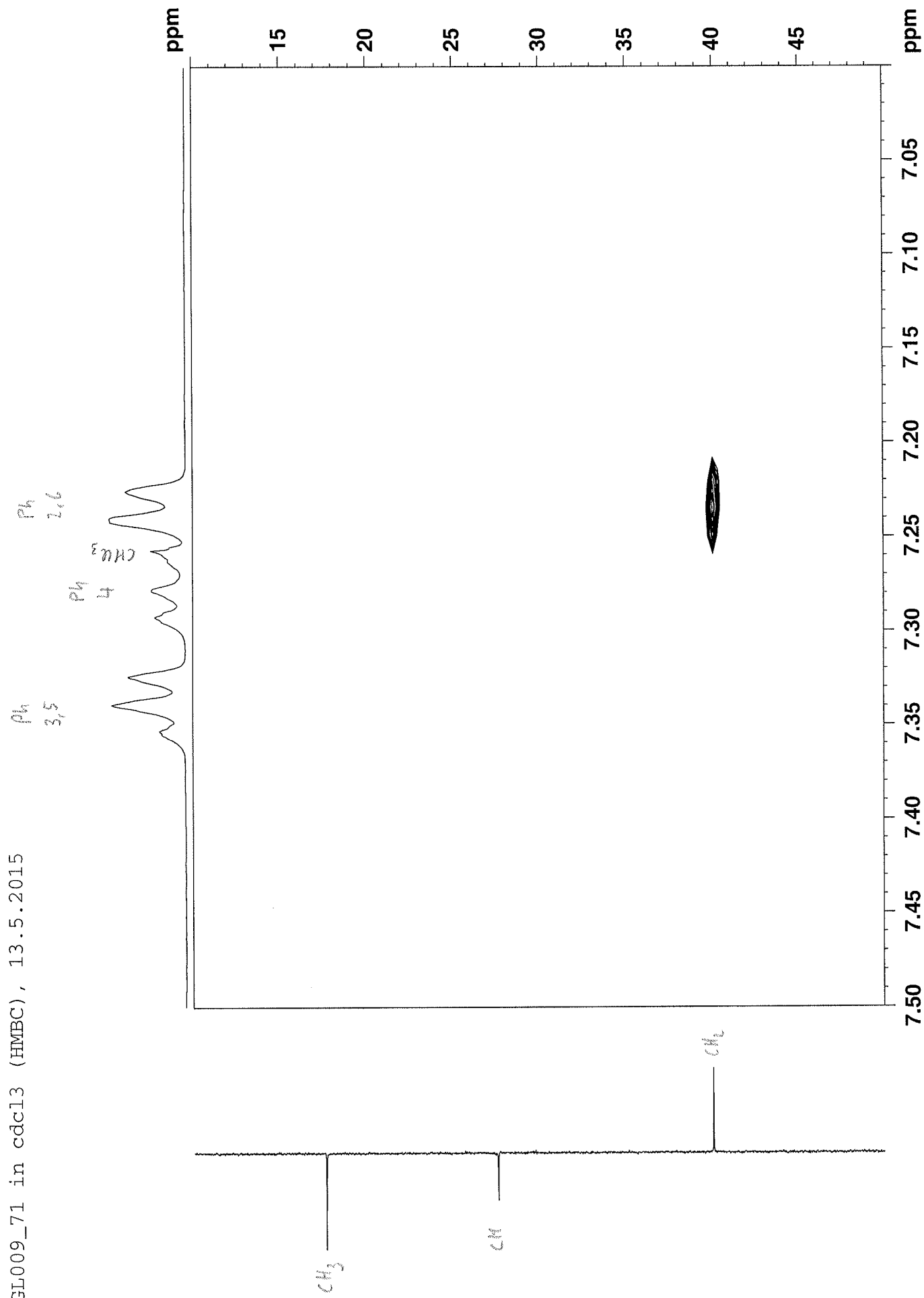


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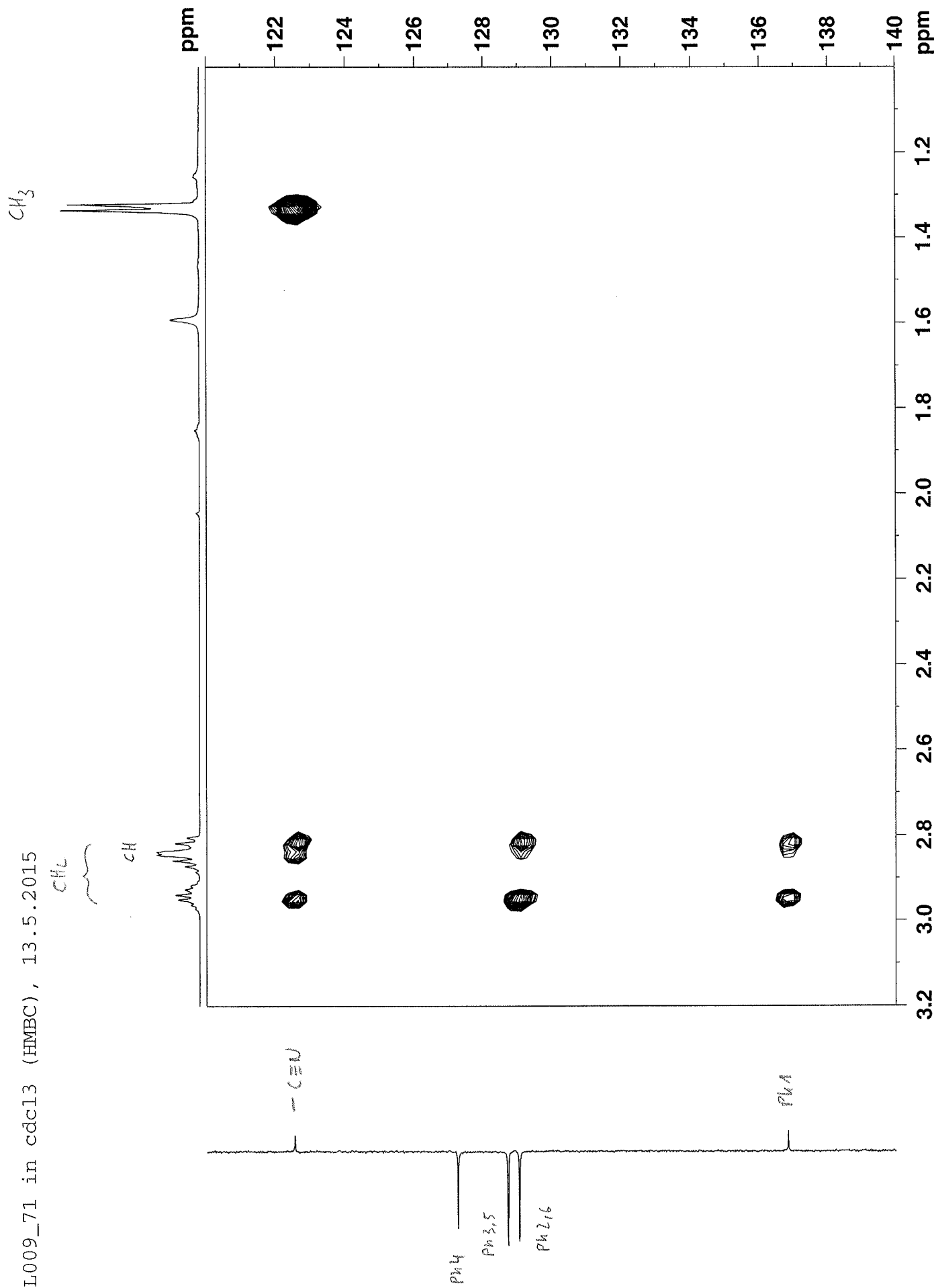




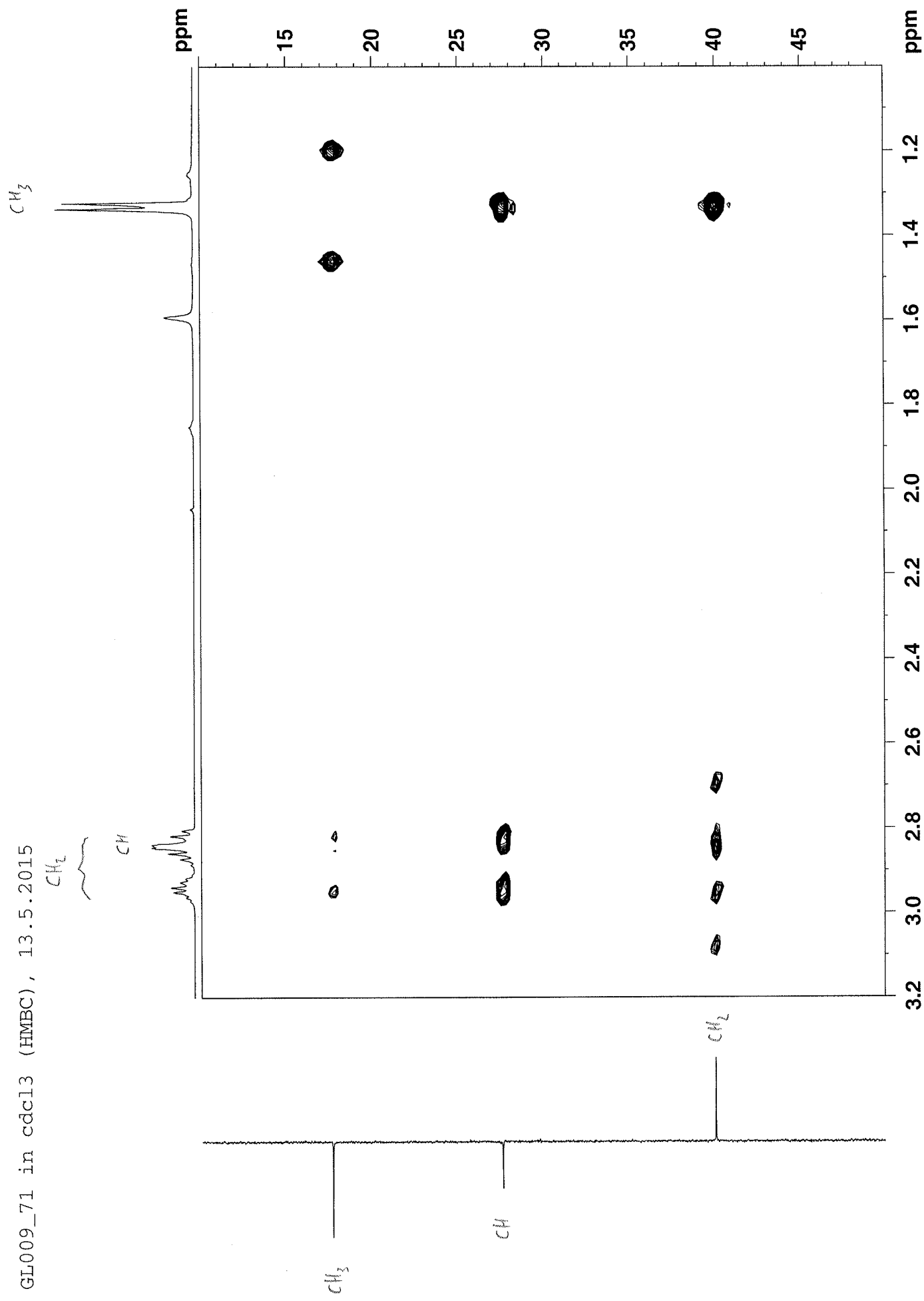
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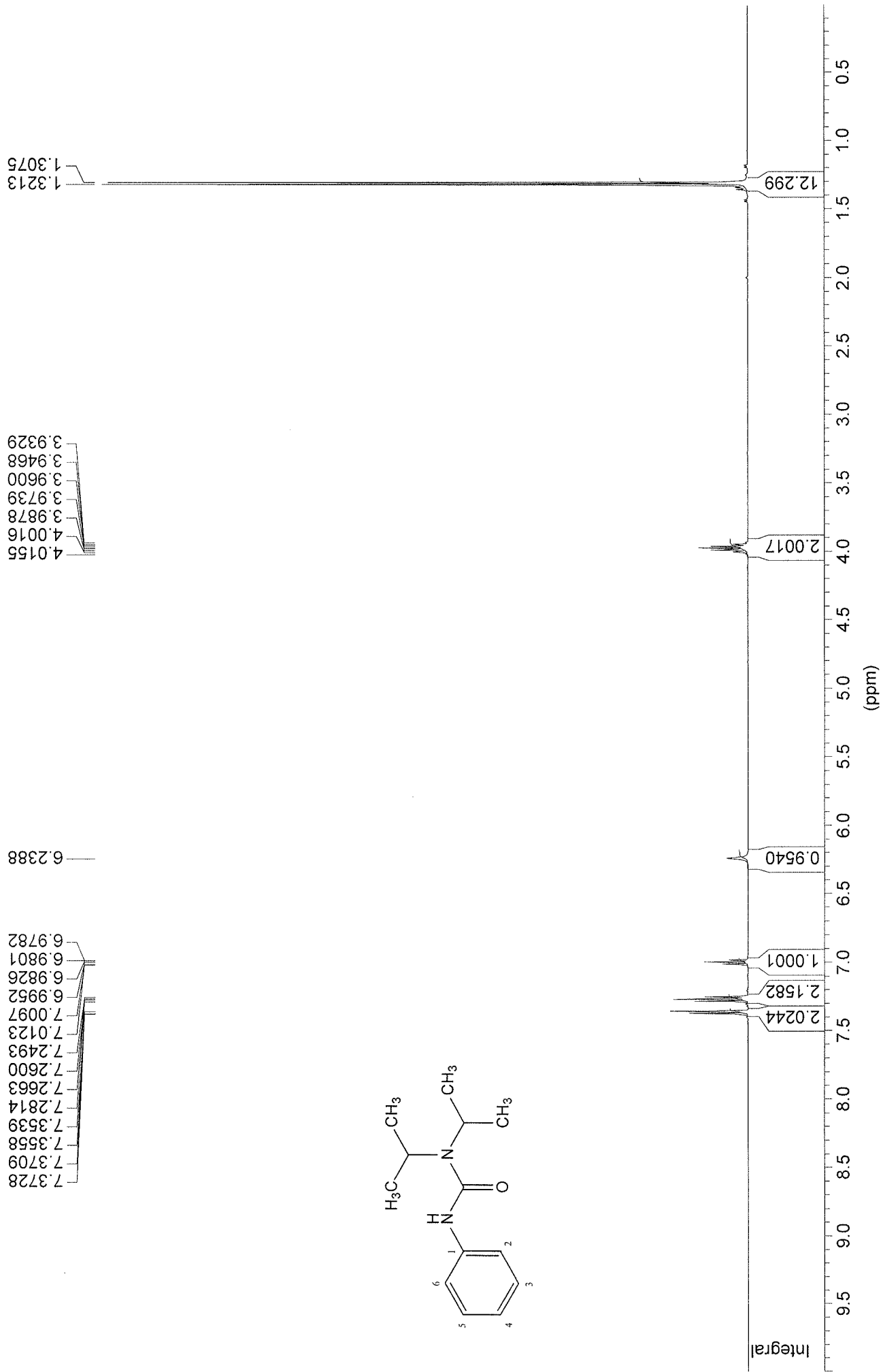


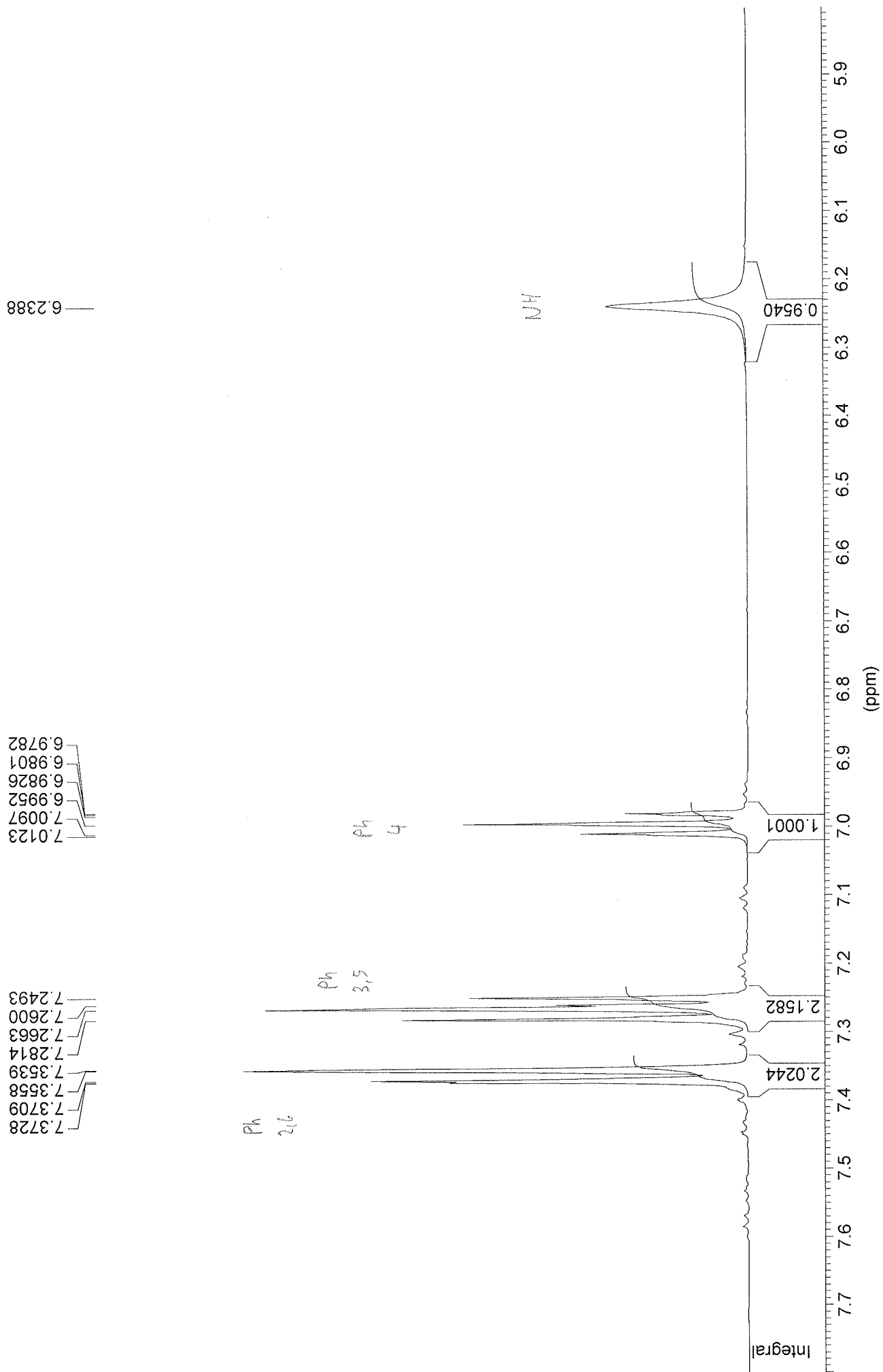
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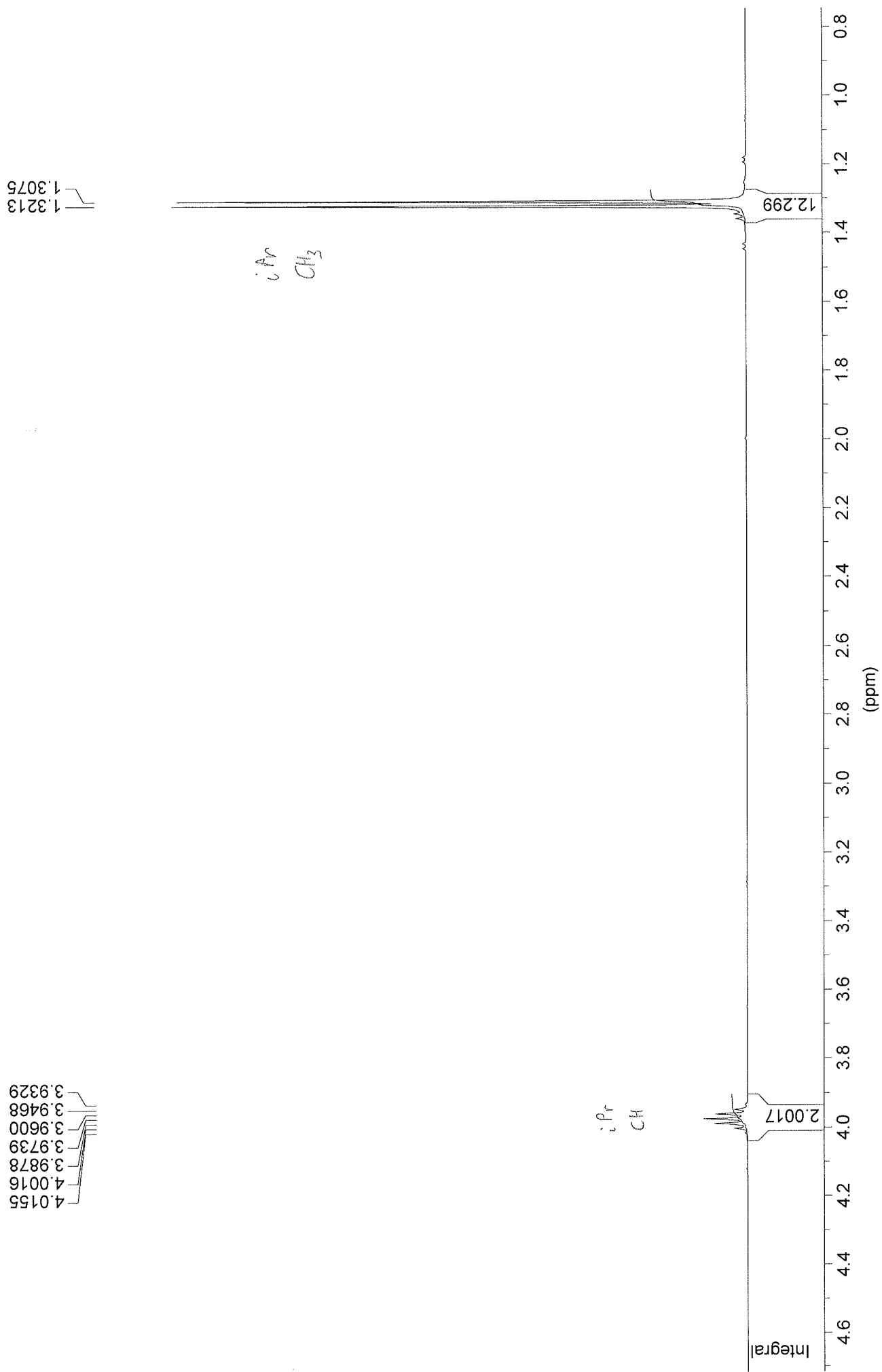


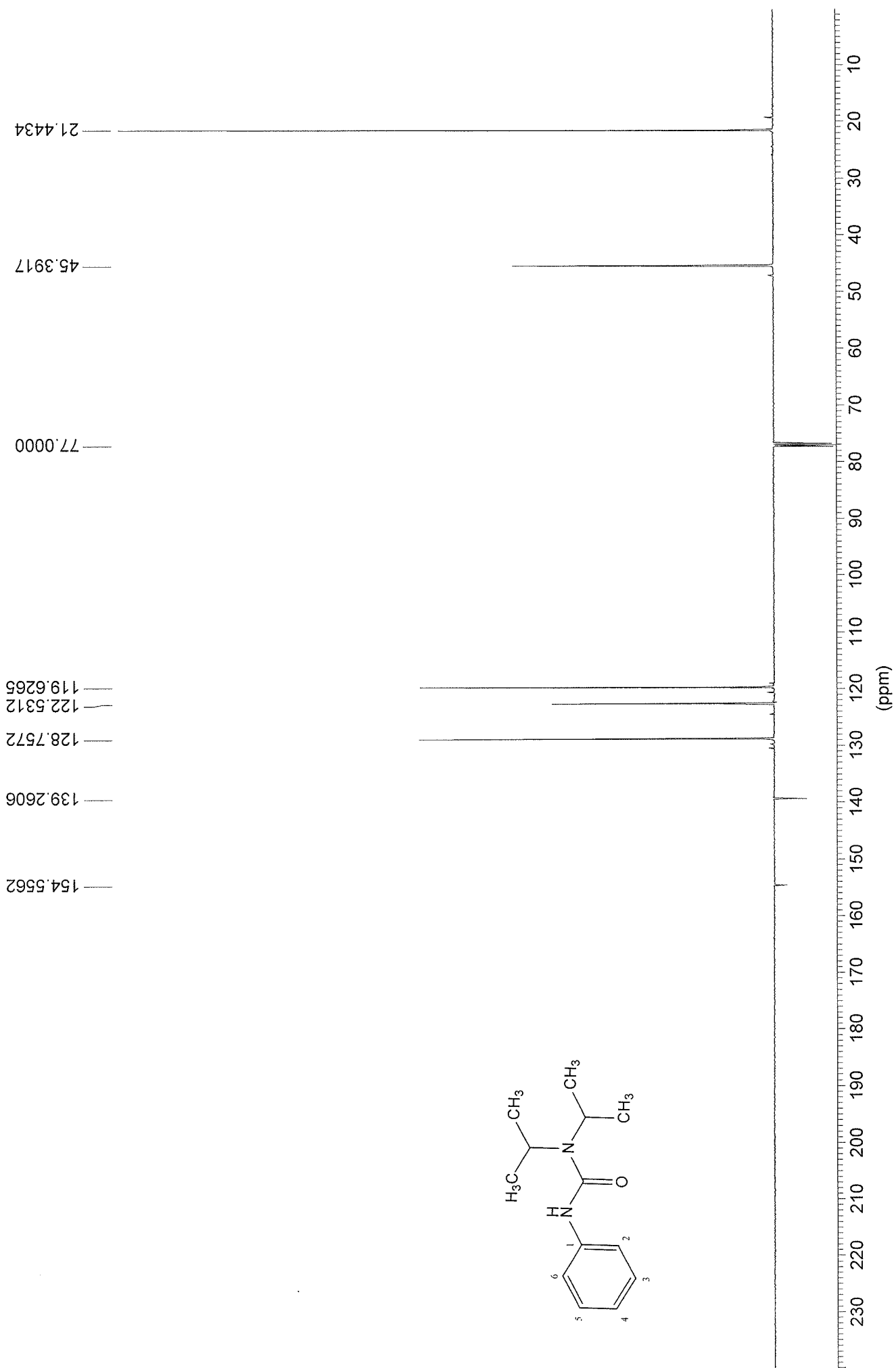
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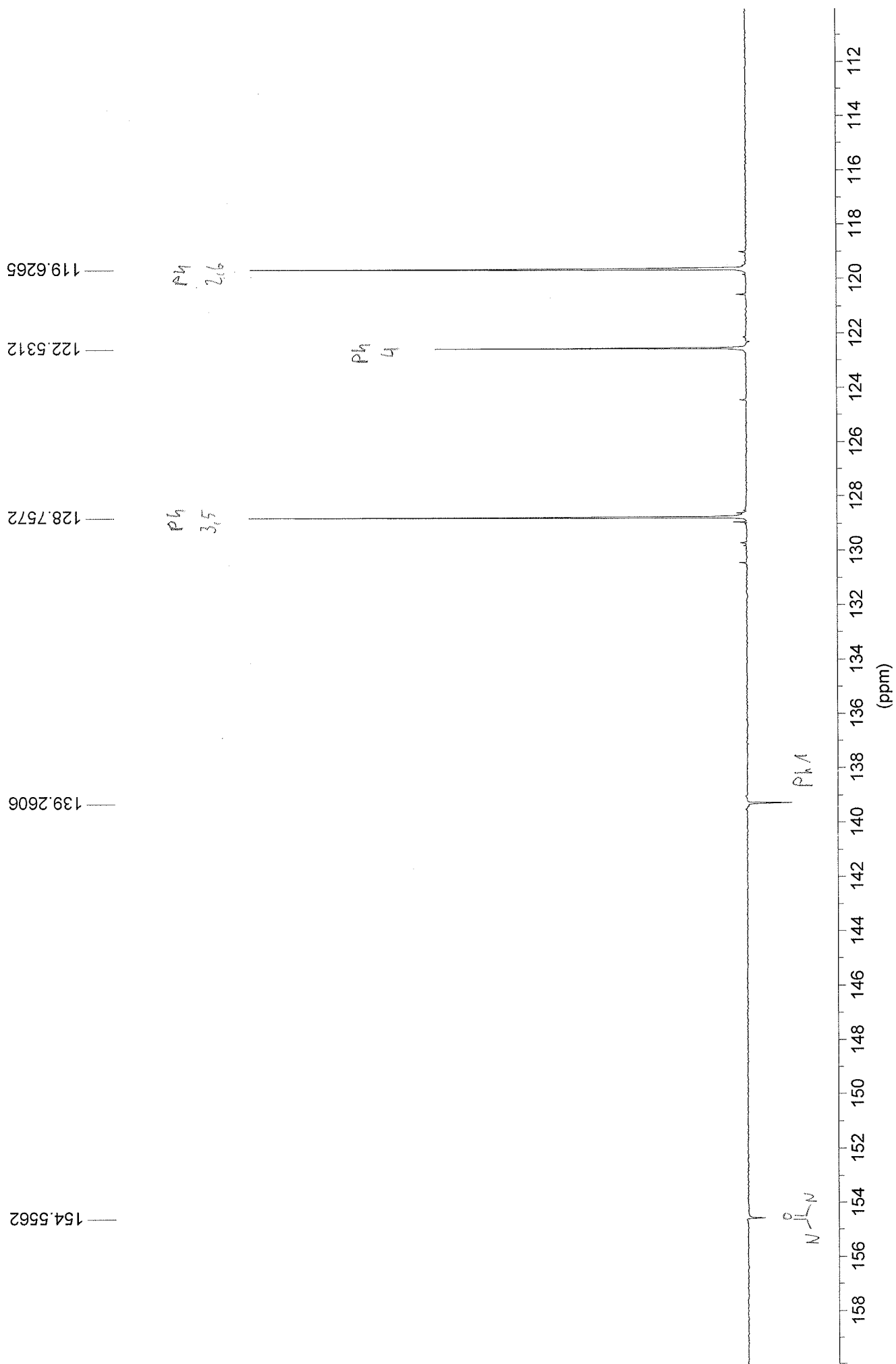


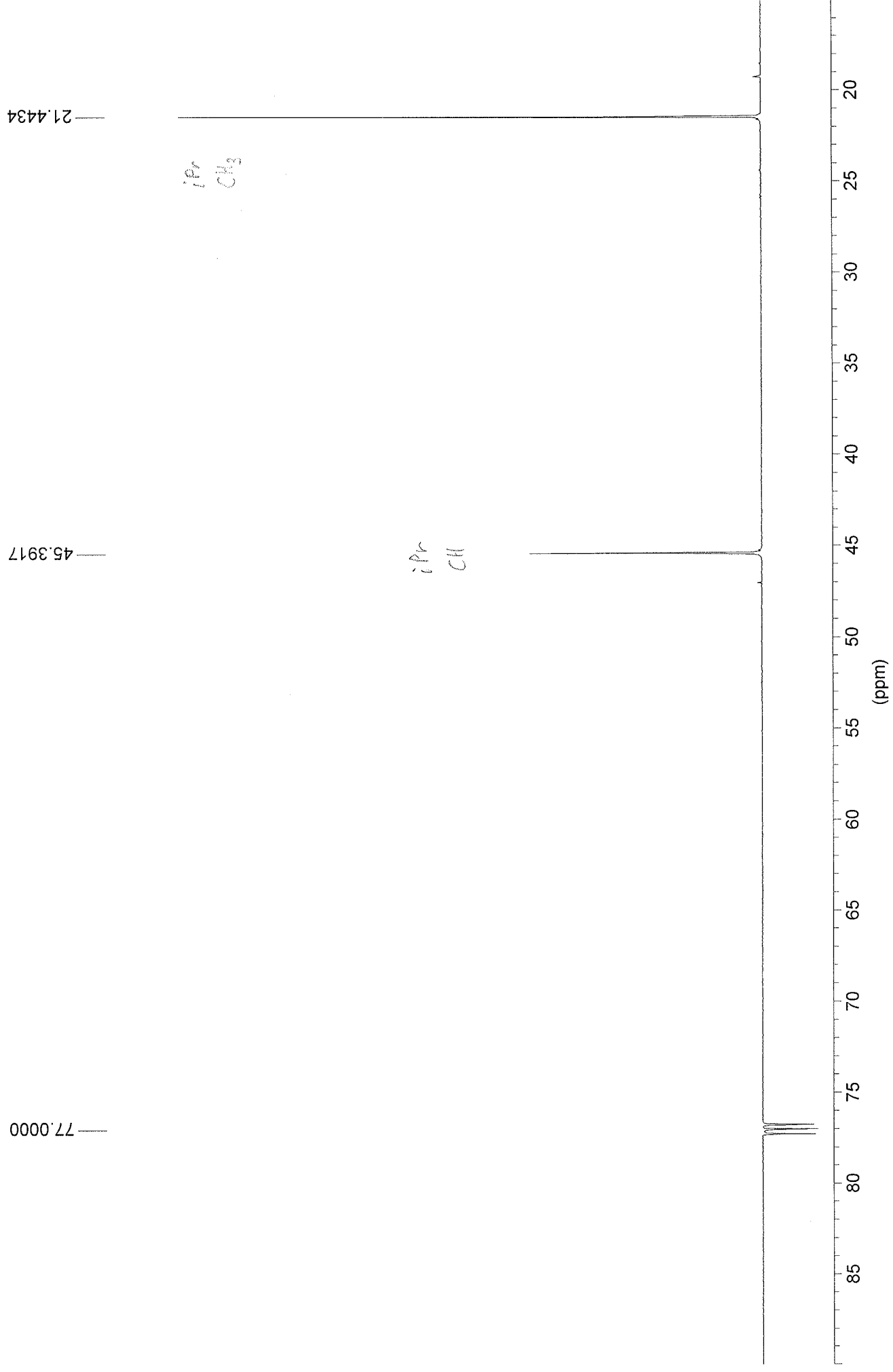




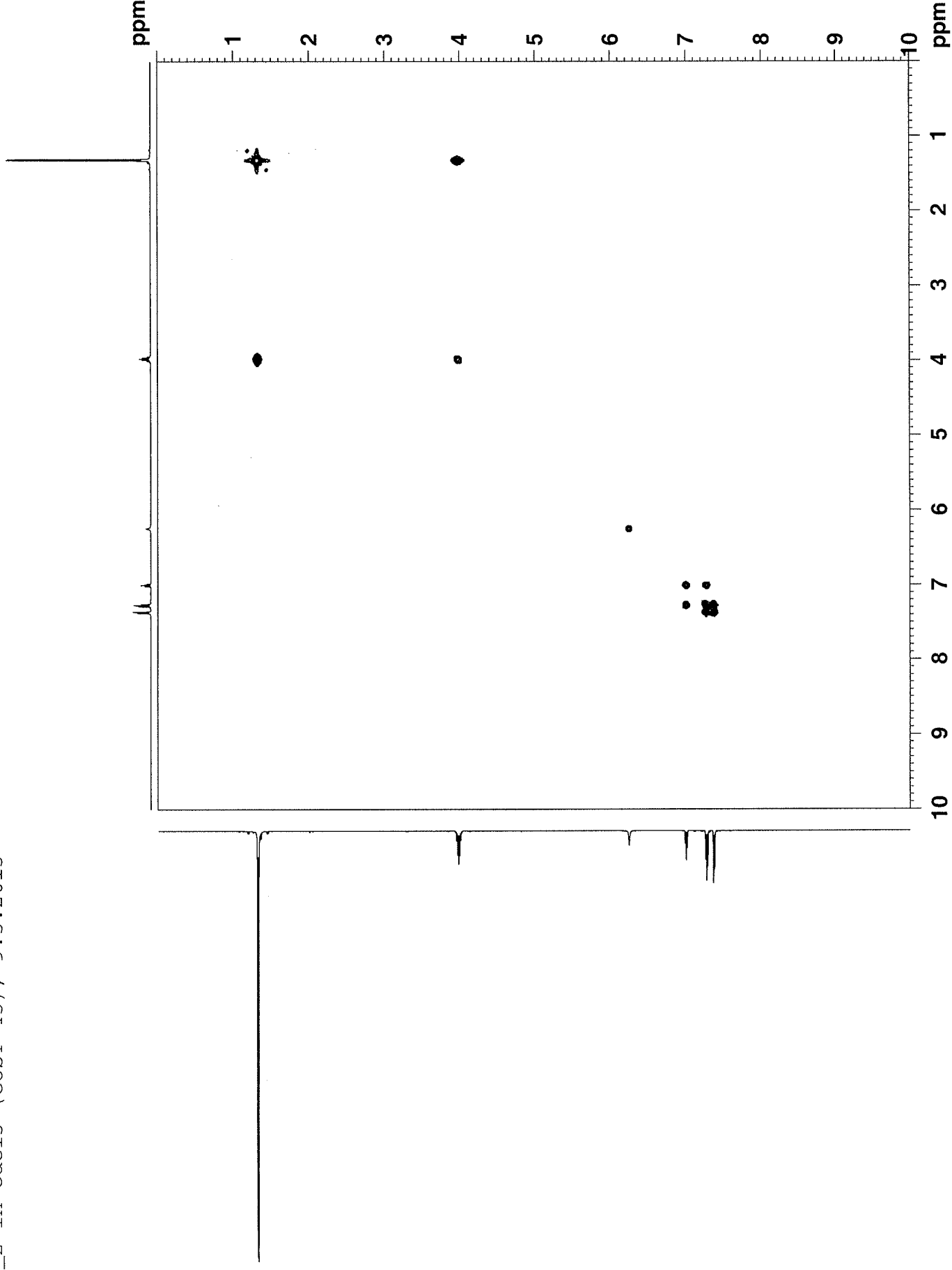


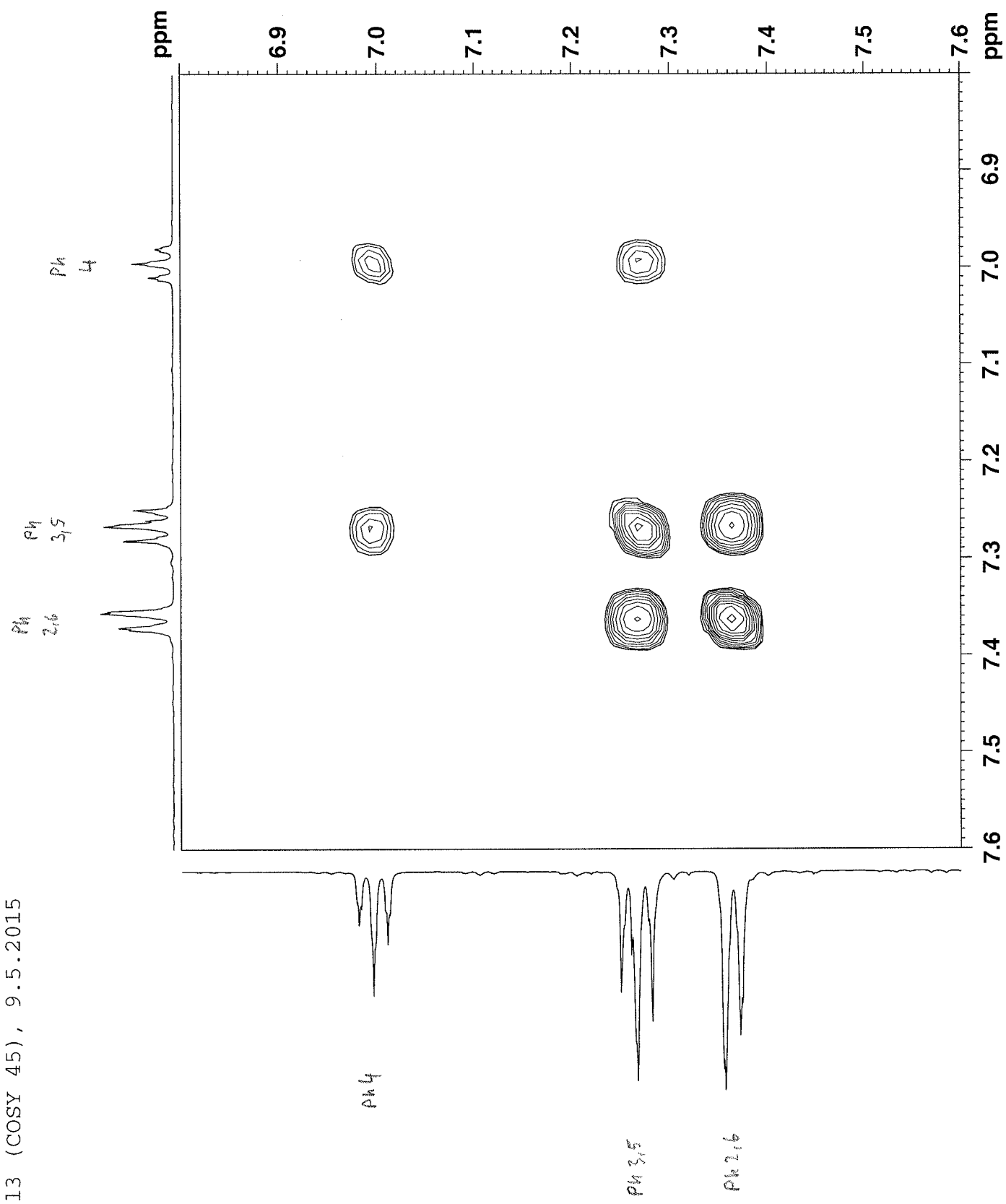


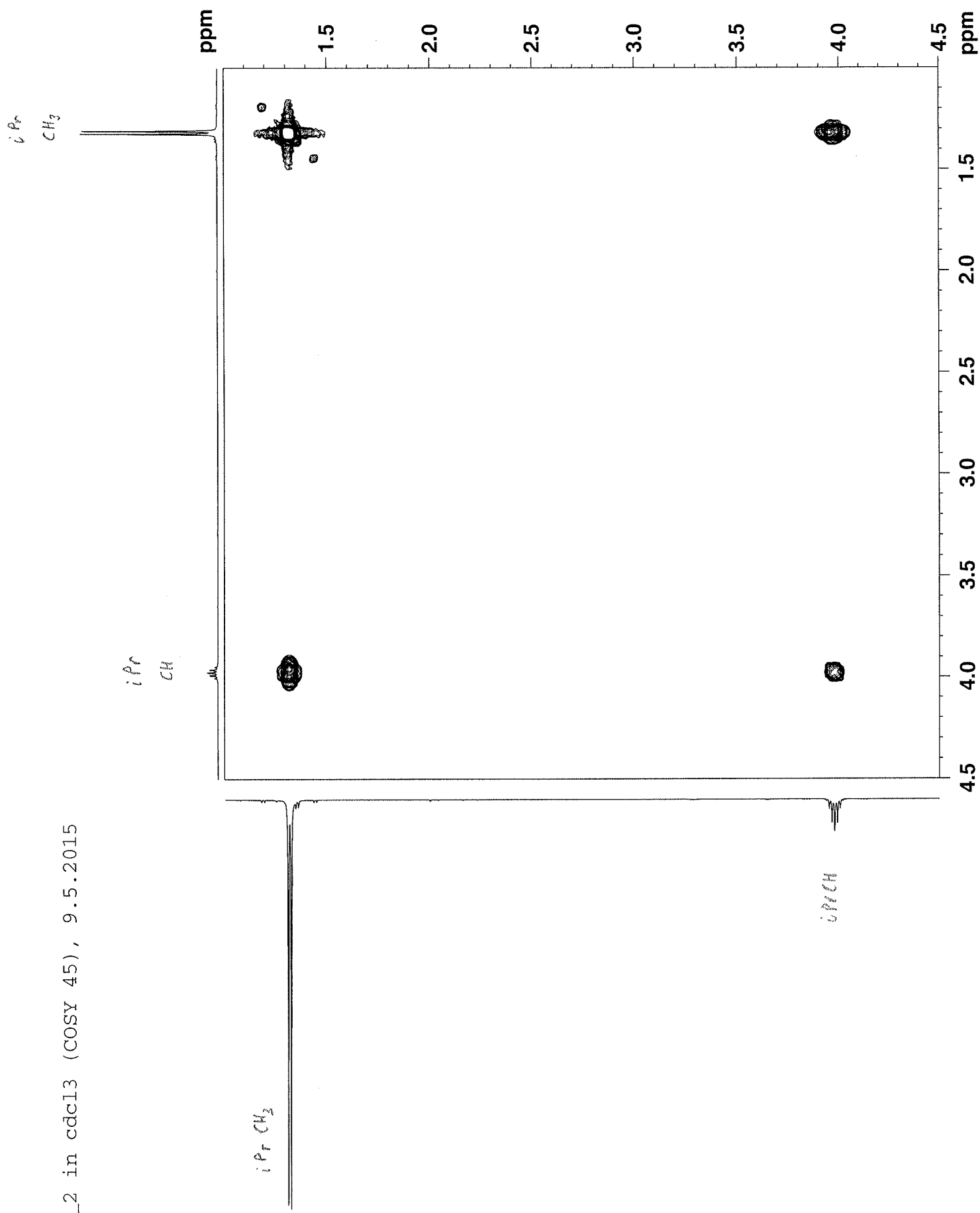




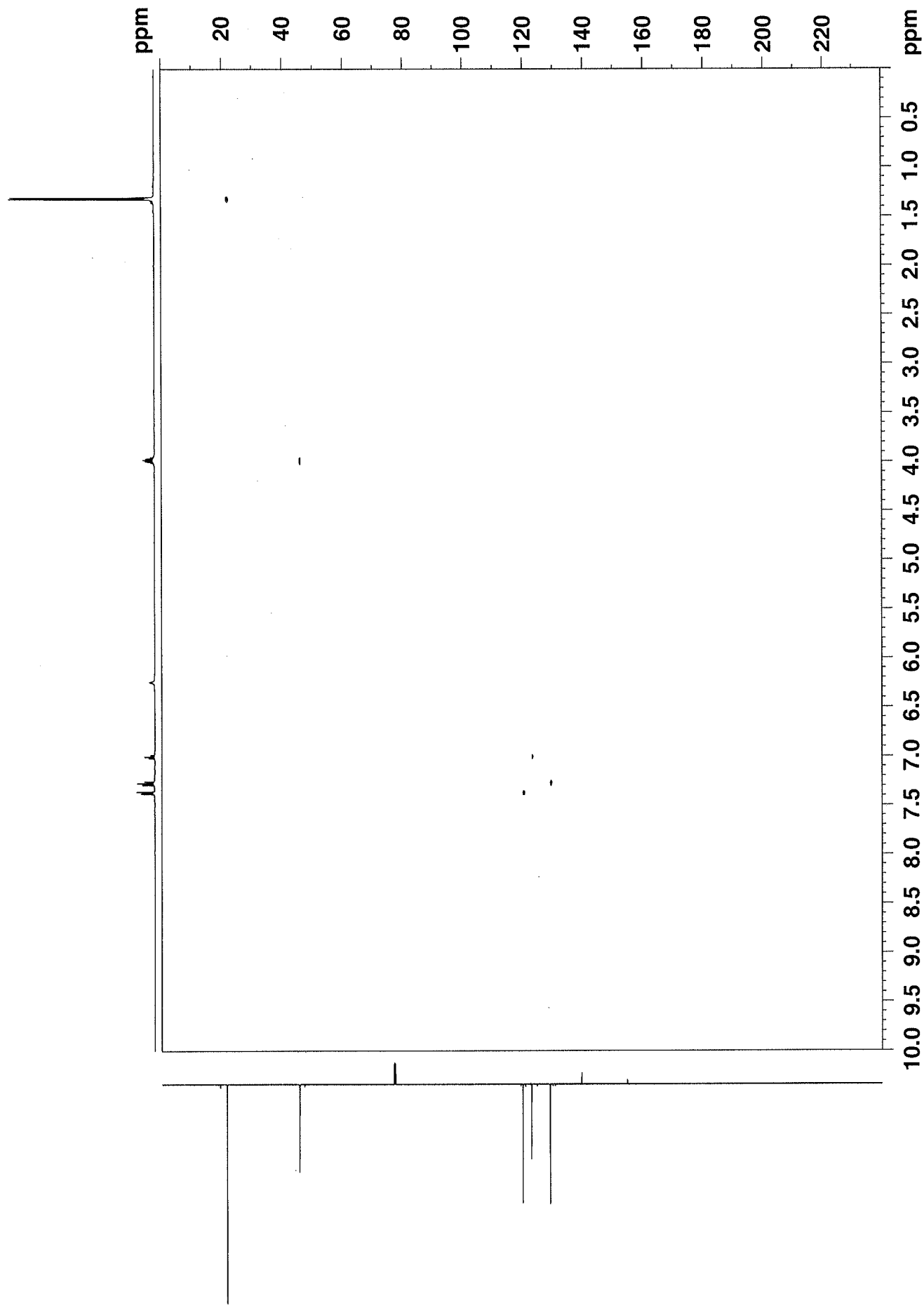
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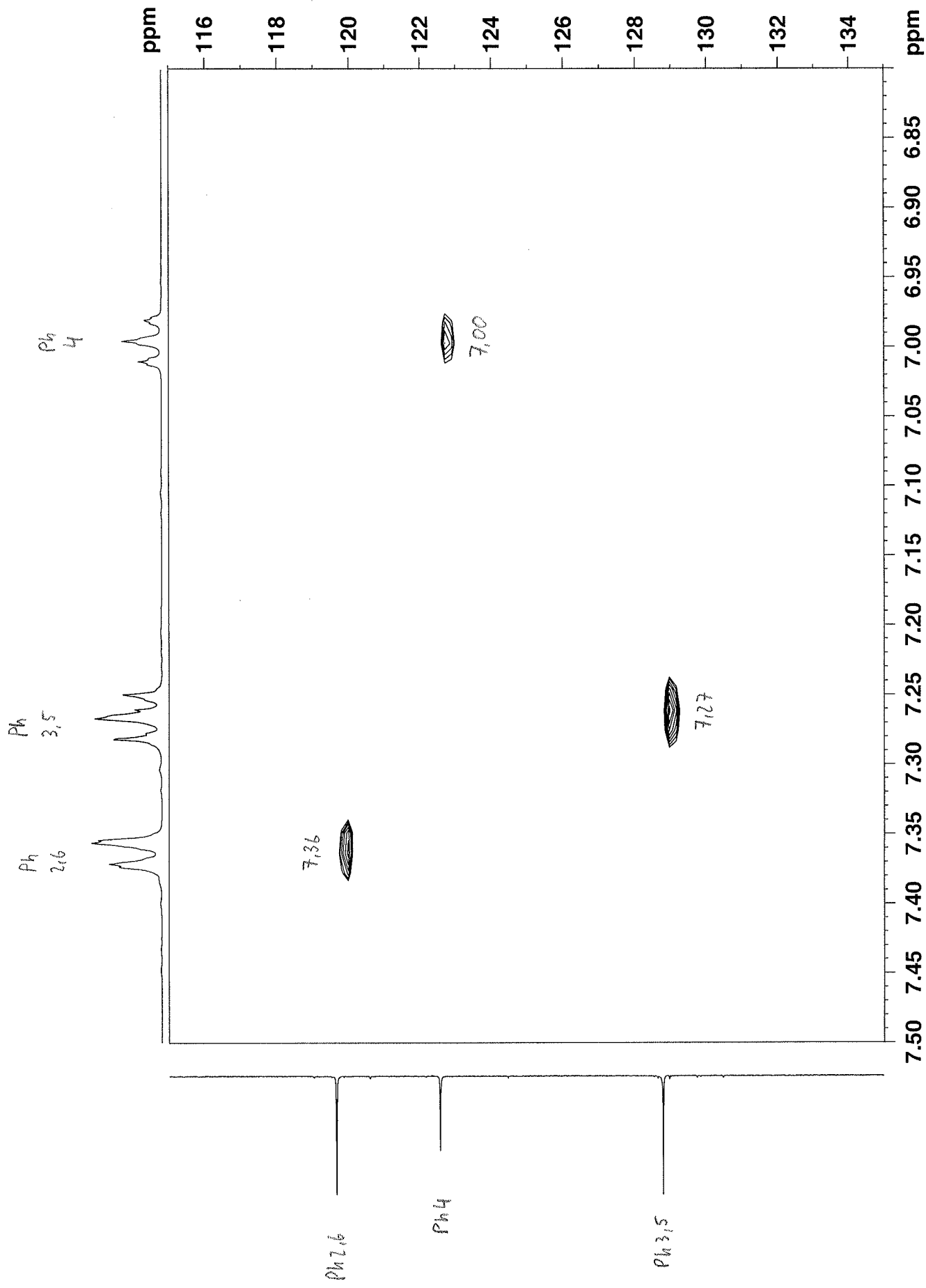






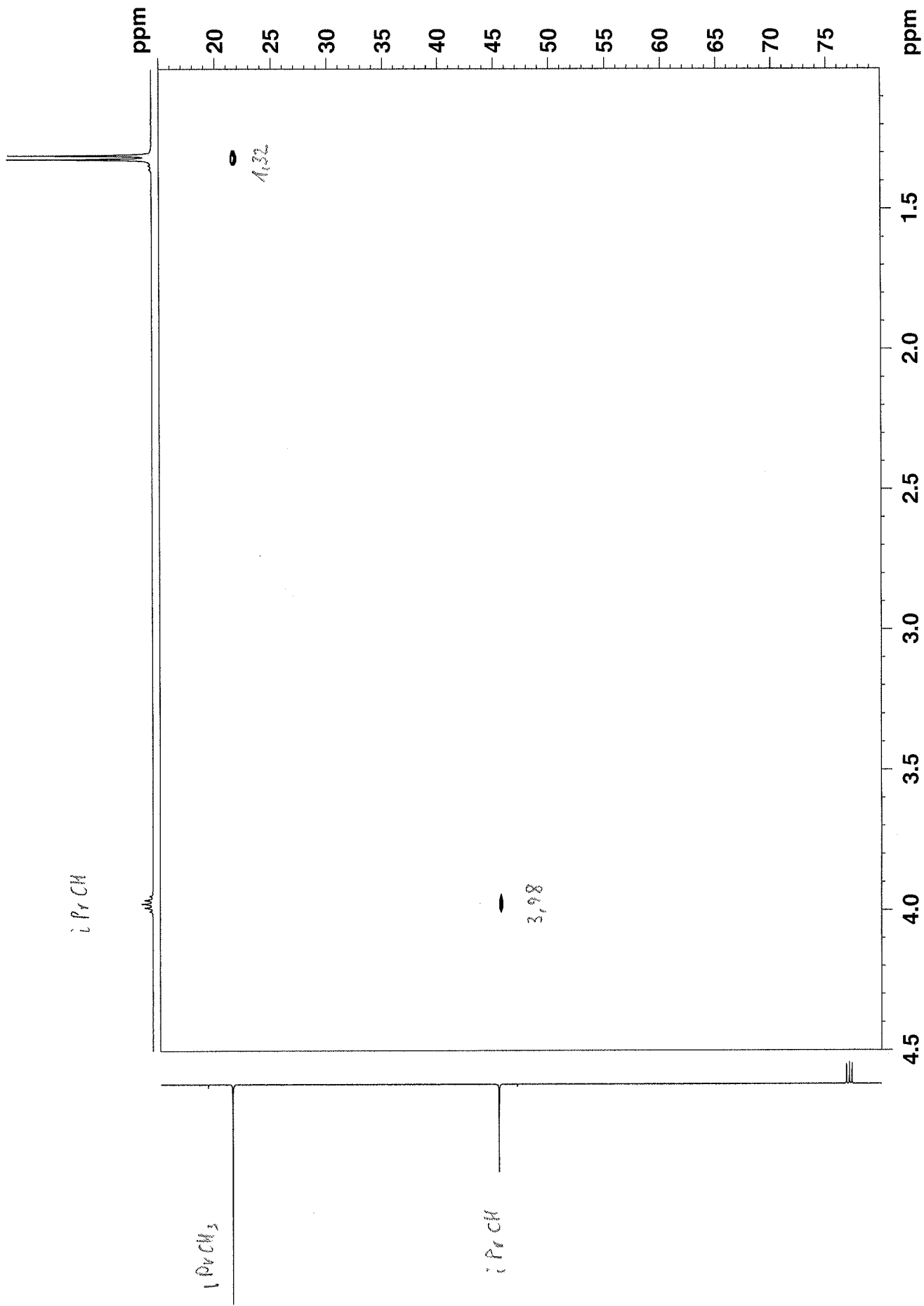
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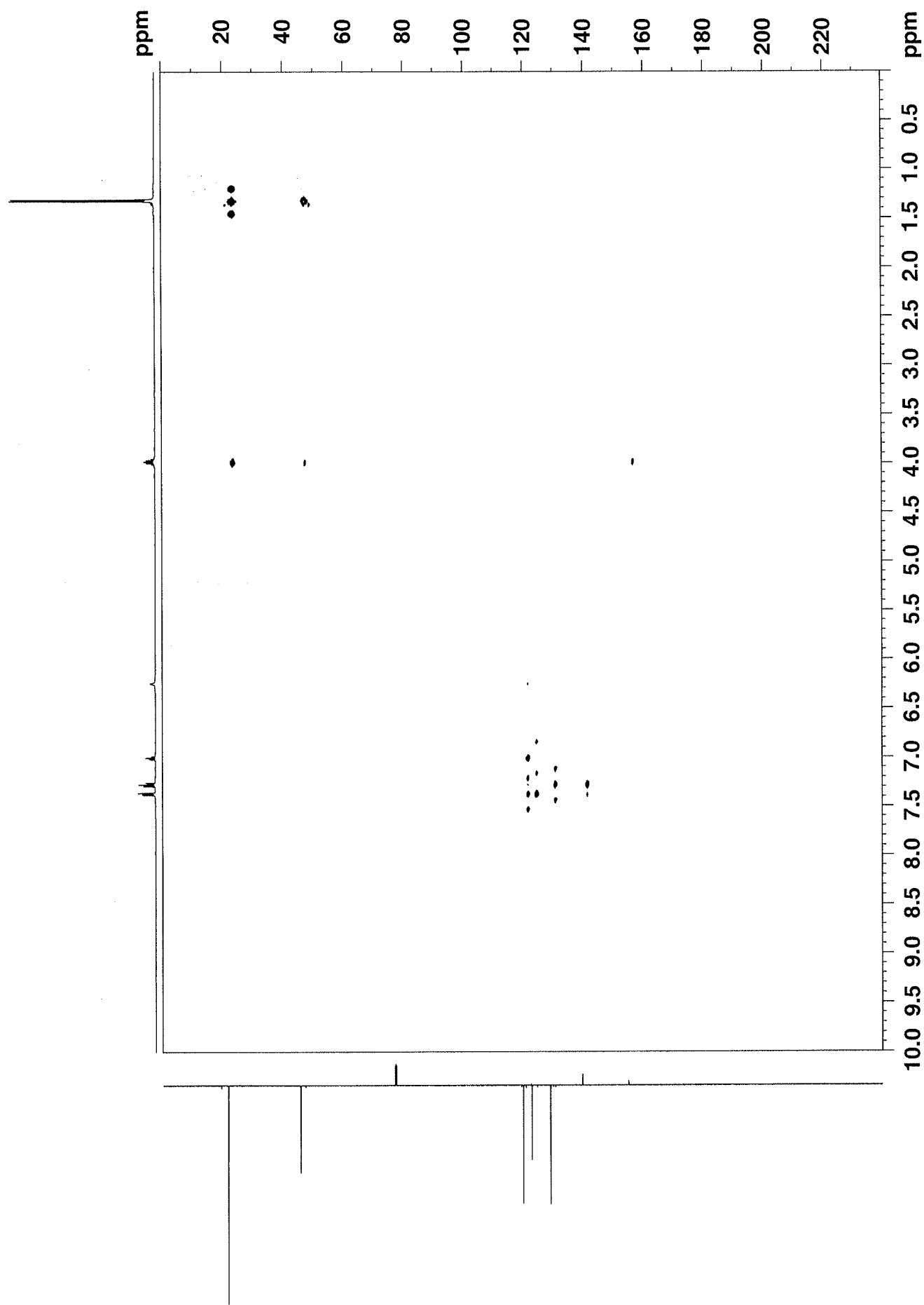


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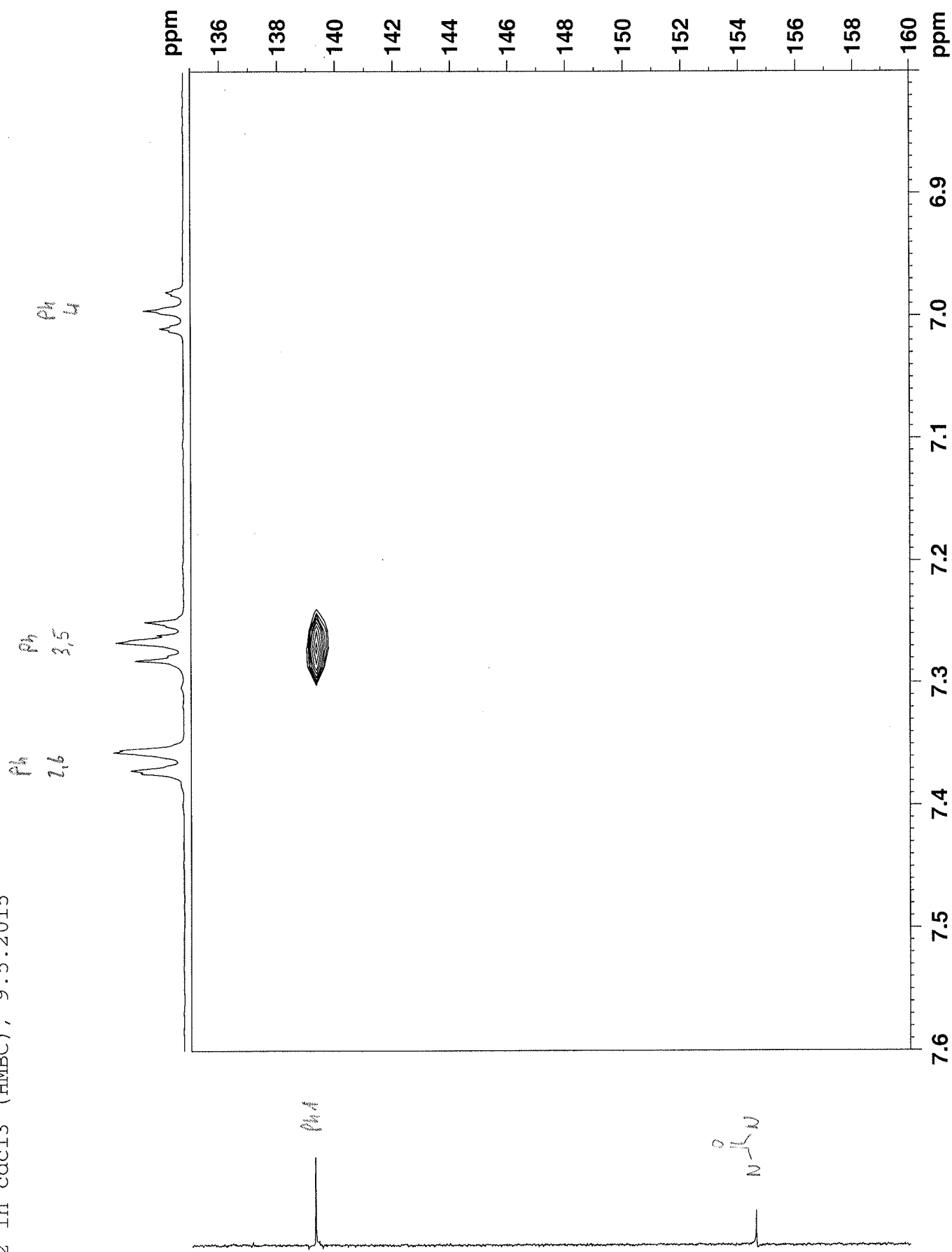
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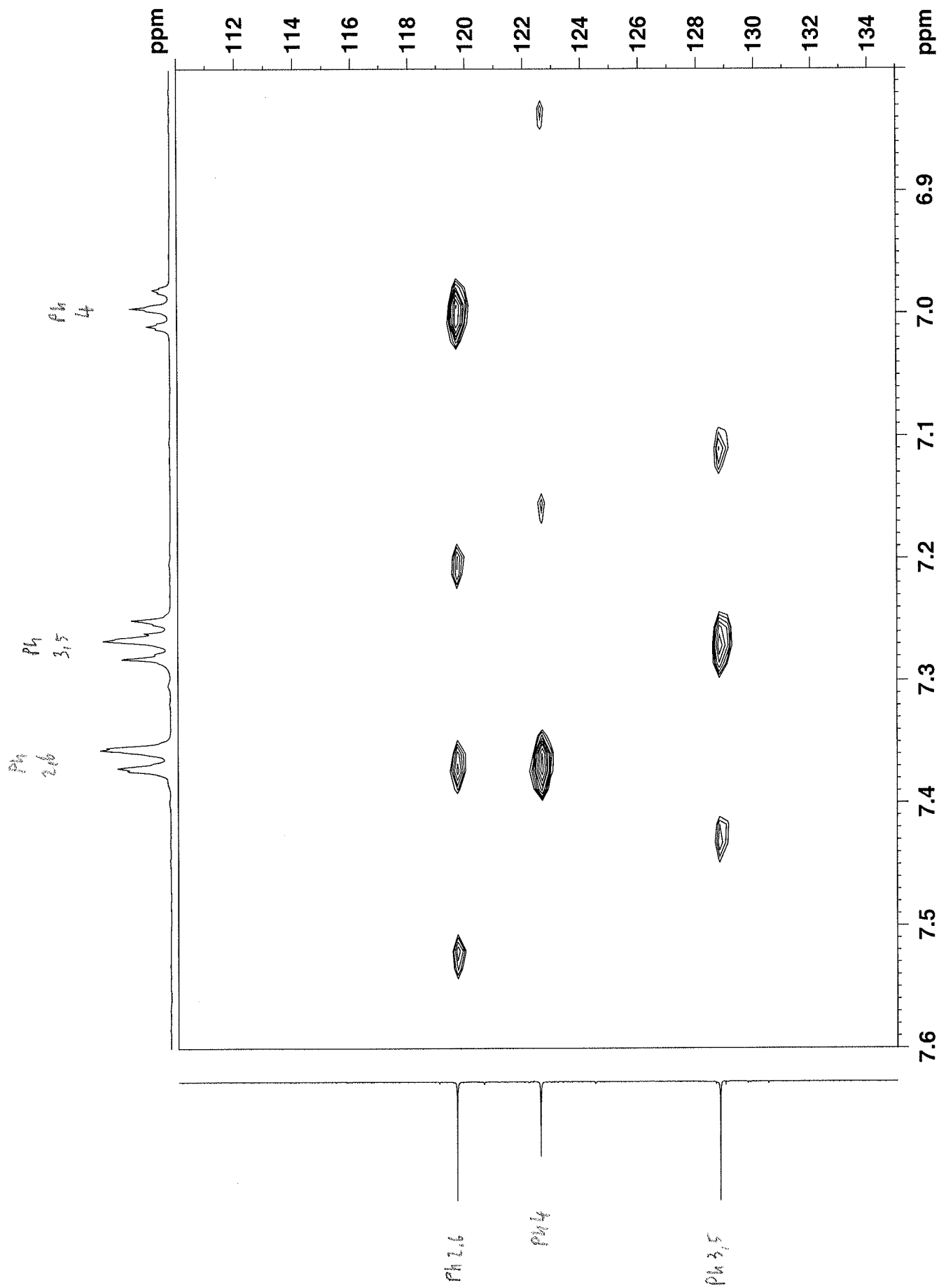


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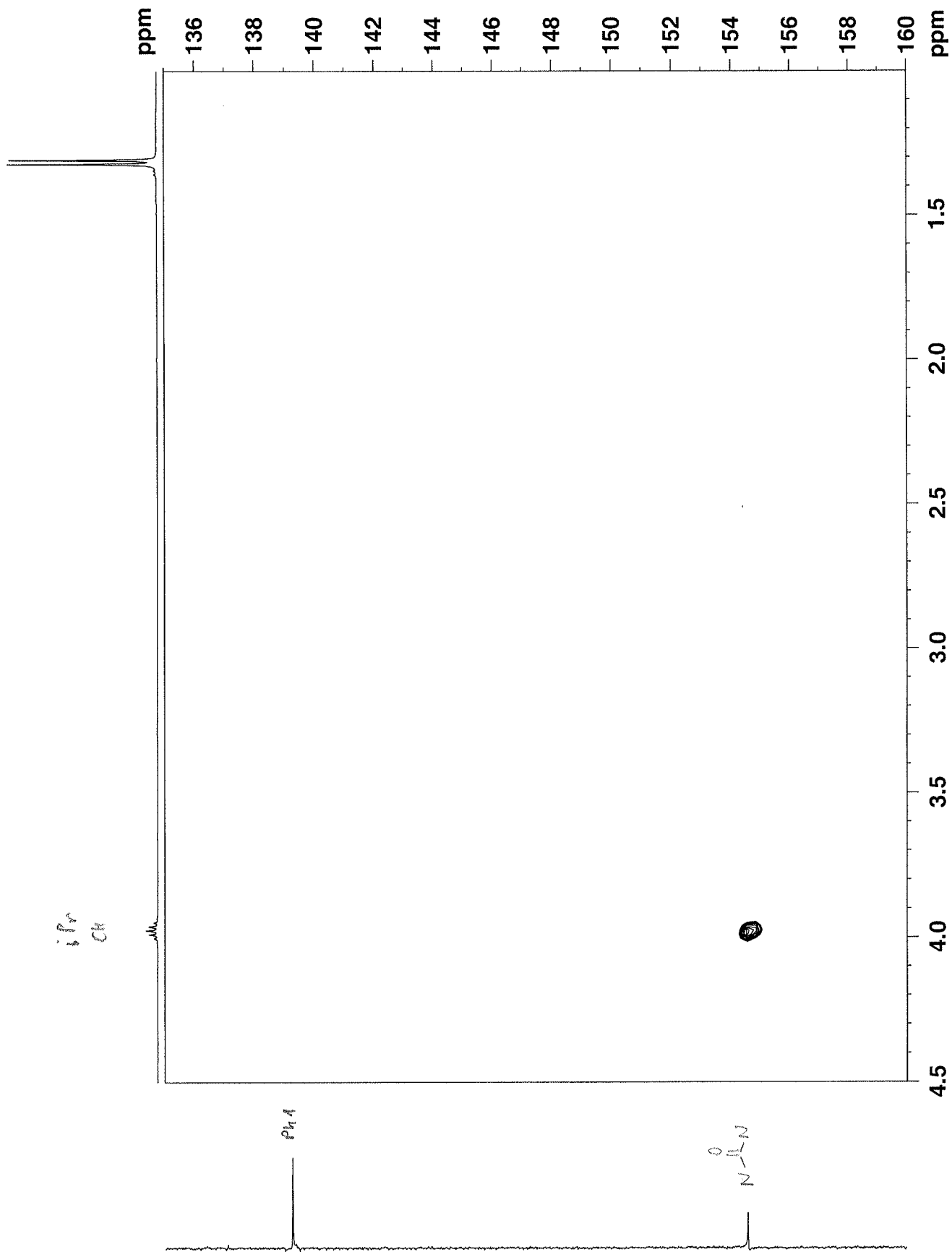
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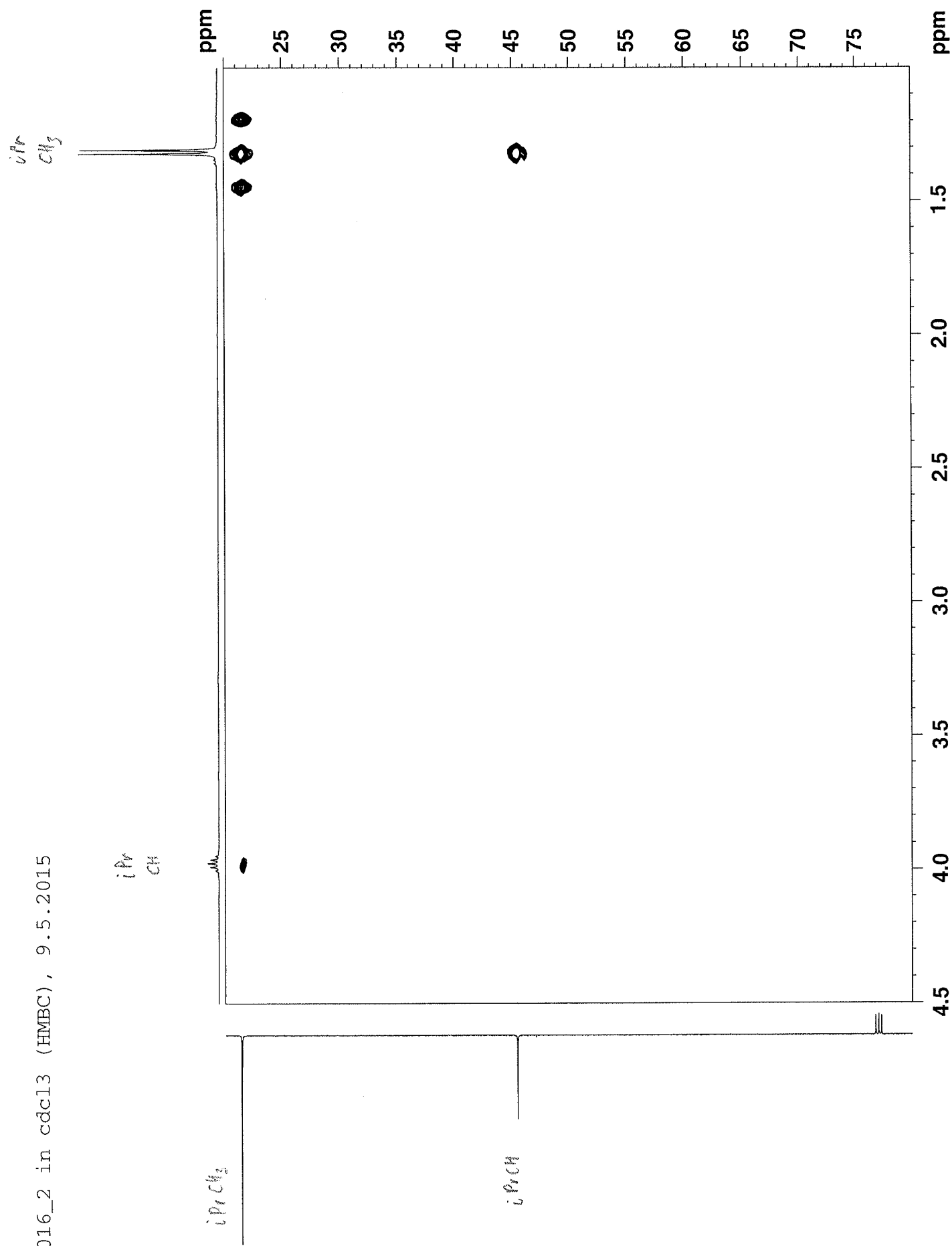




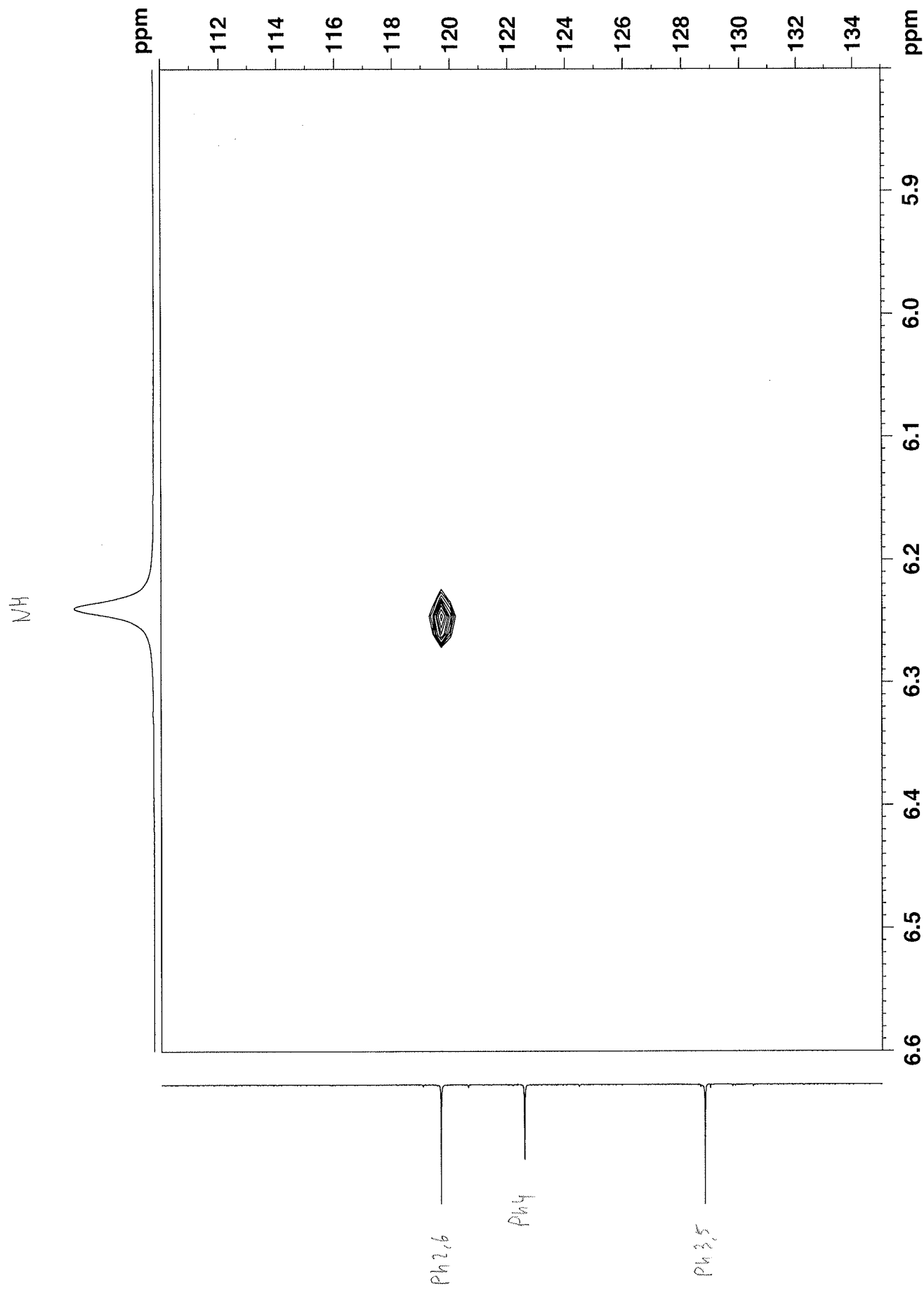
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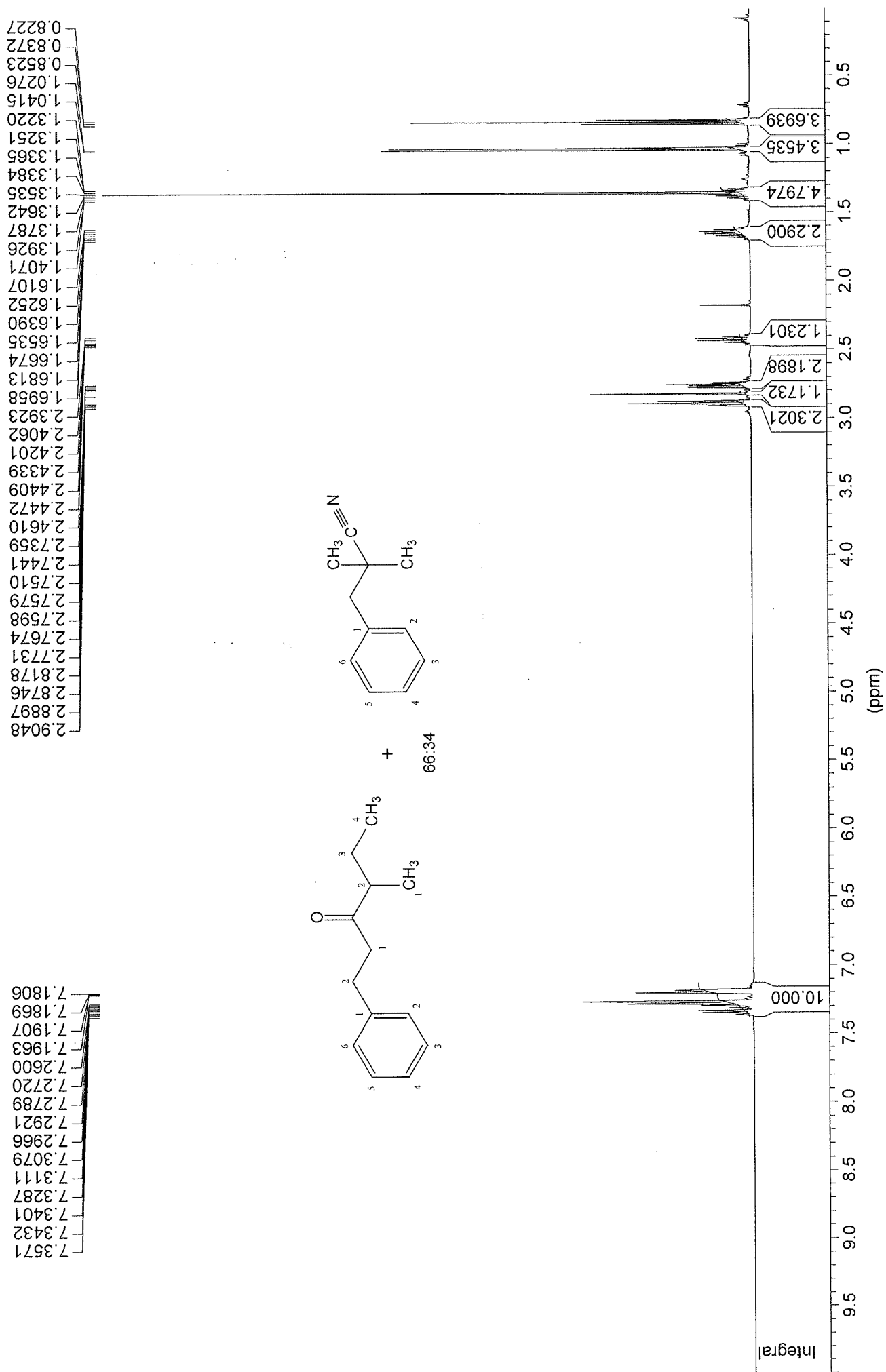
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GL016_2 in cdcl3 (HMBC), 9.5.2015





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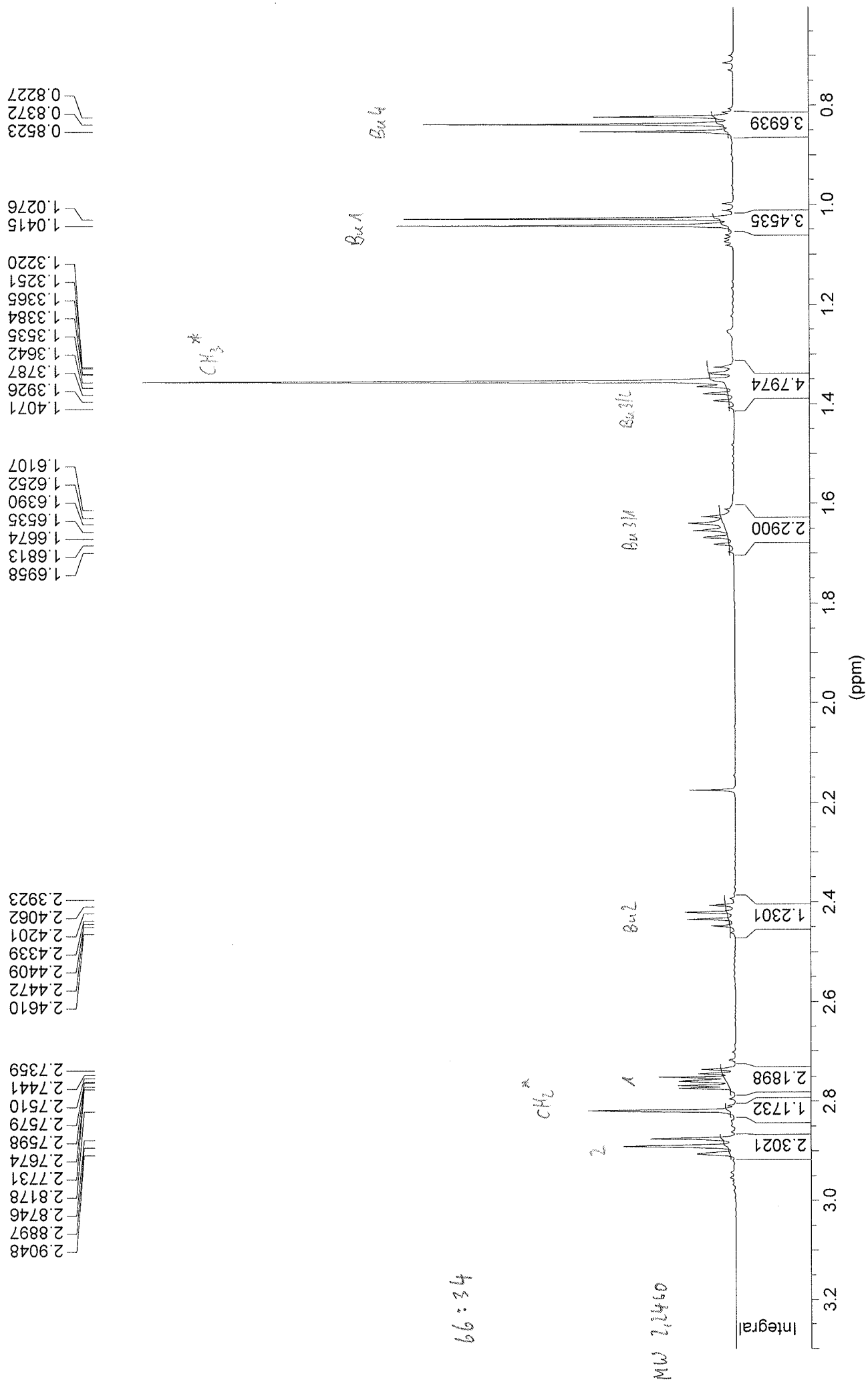
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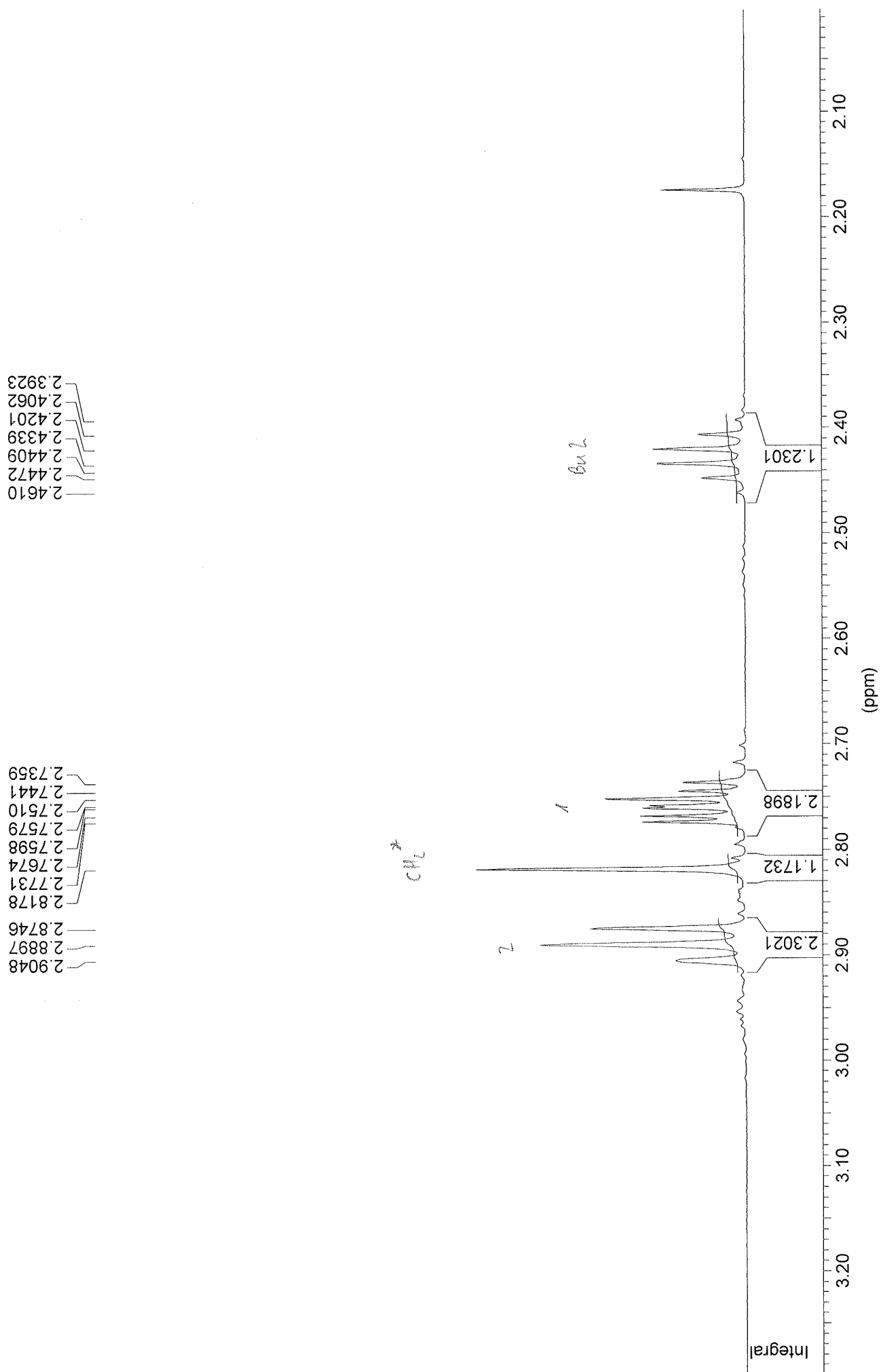
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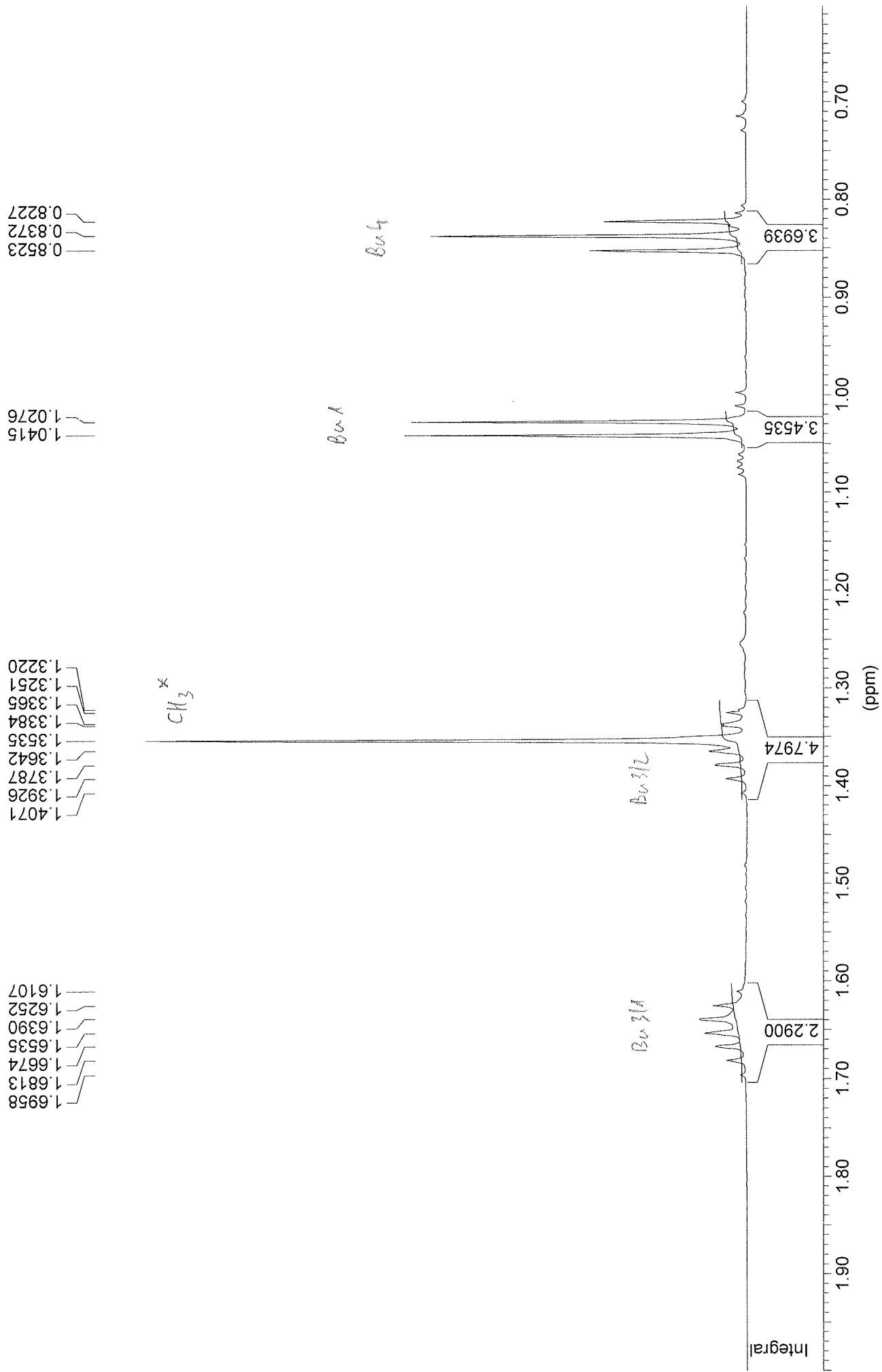
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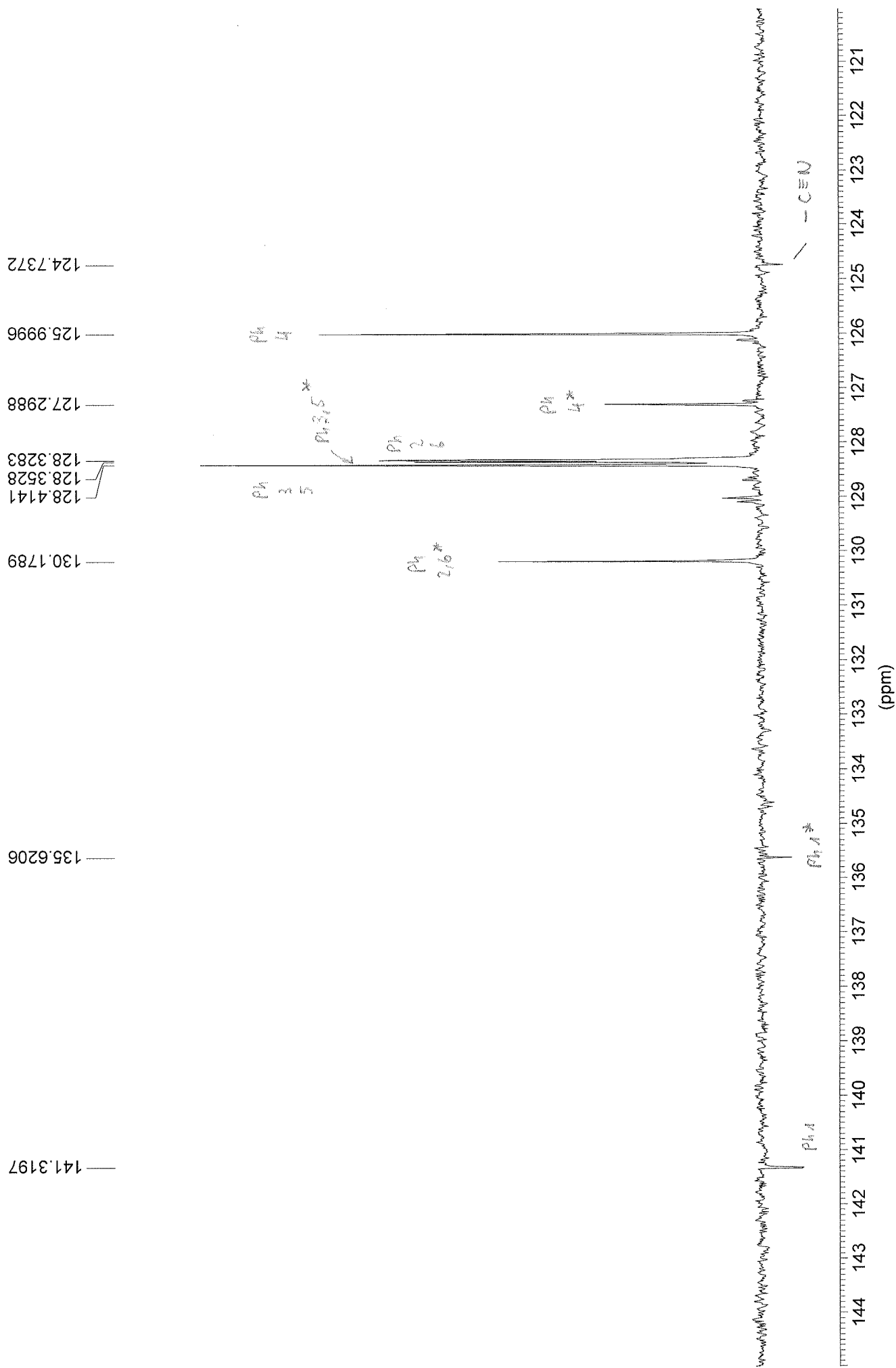


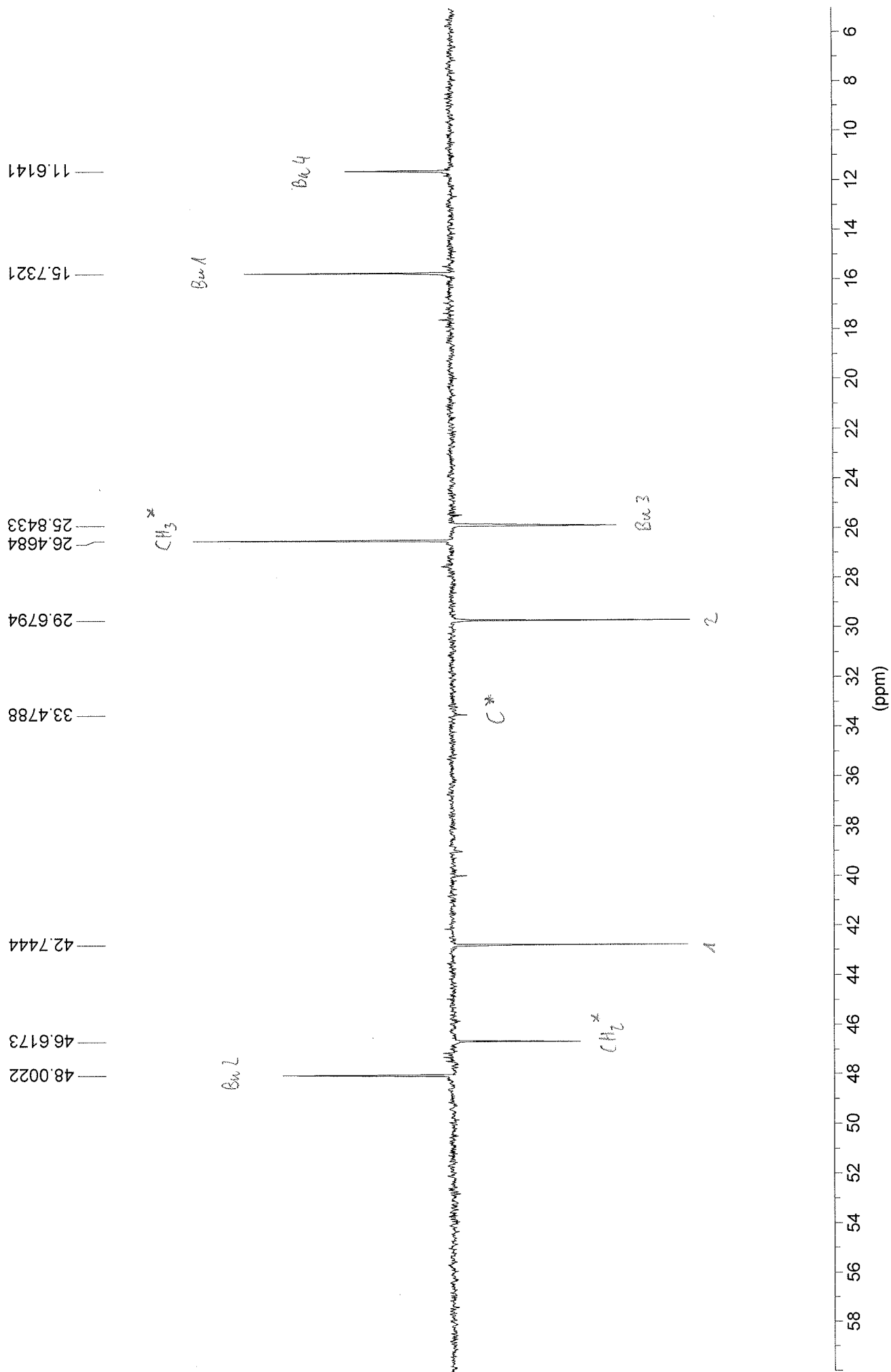
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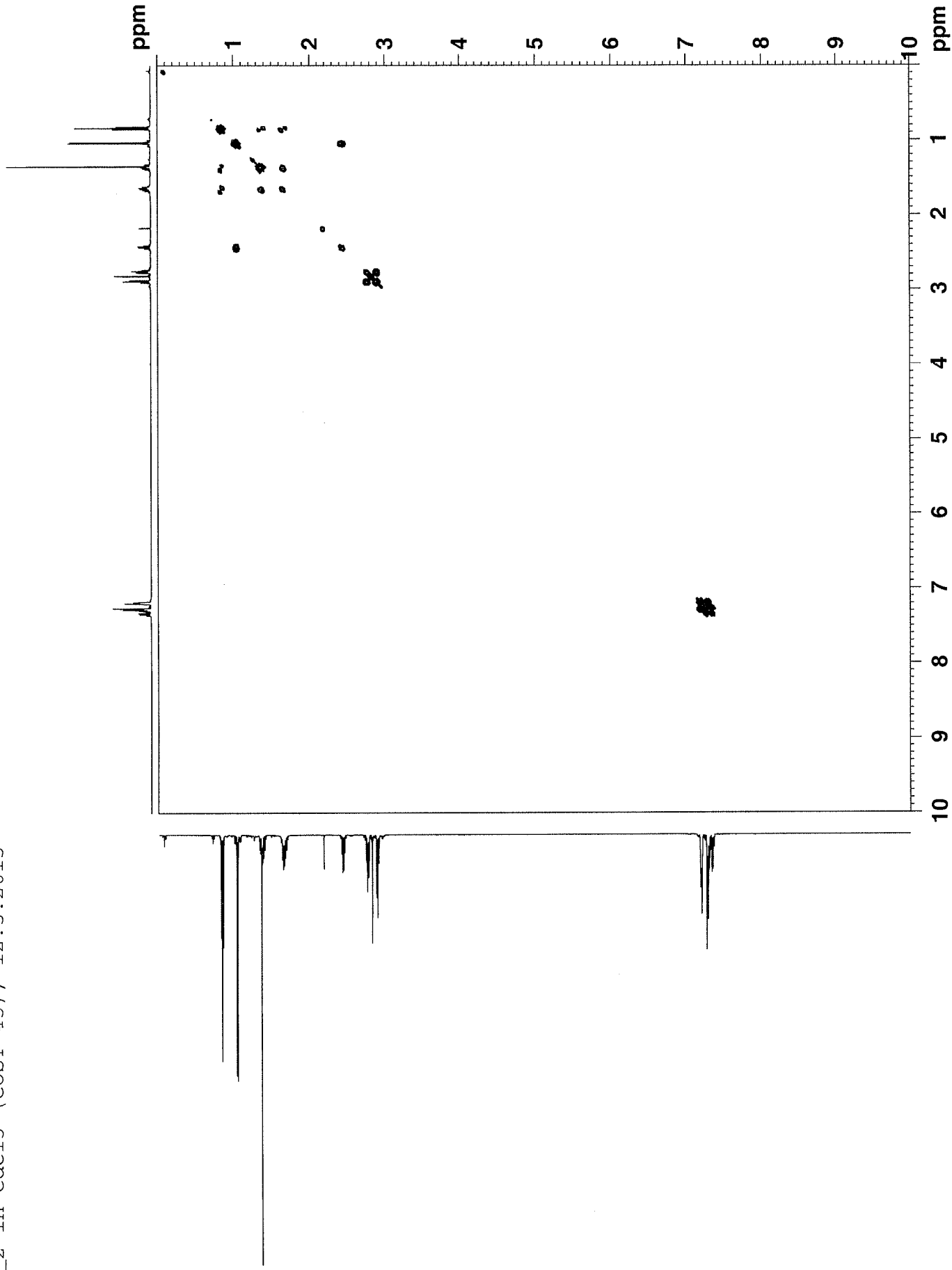
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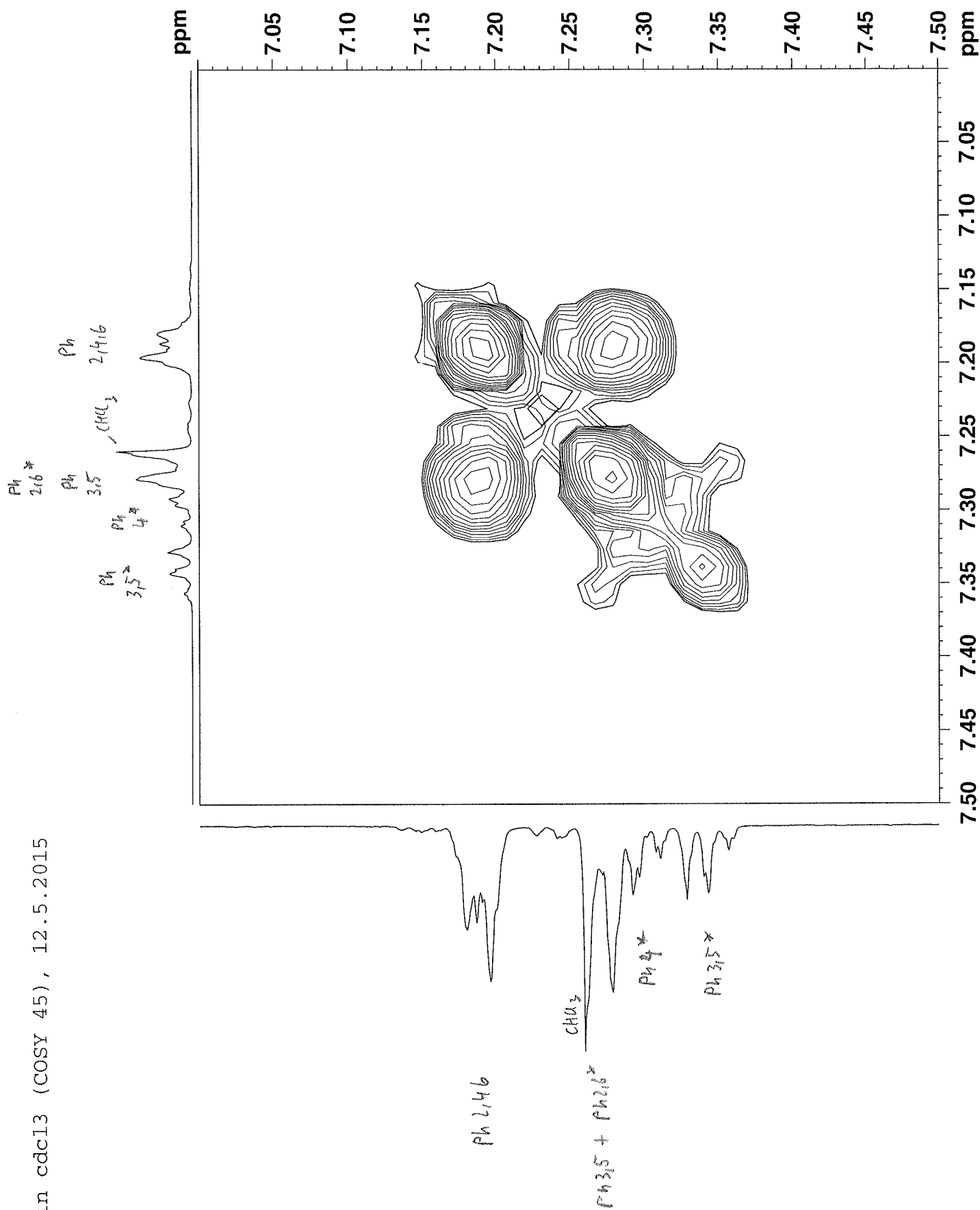
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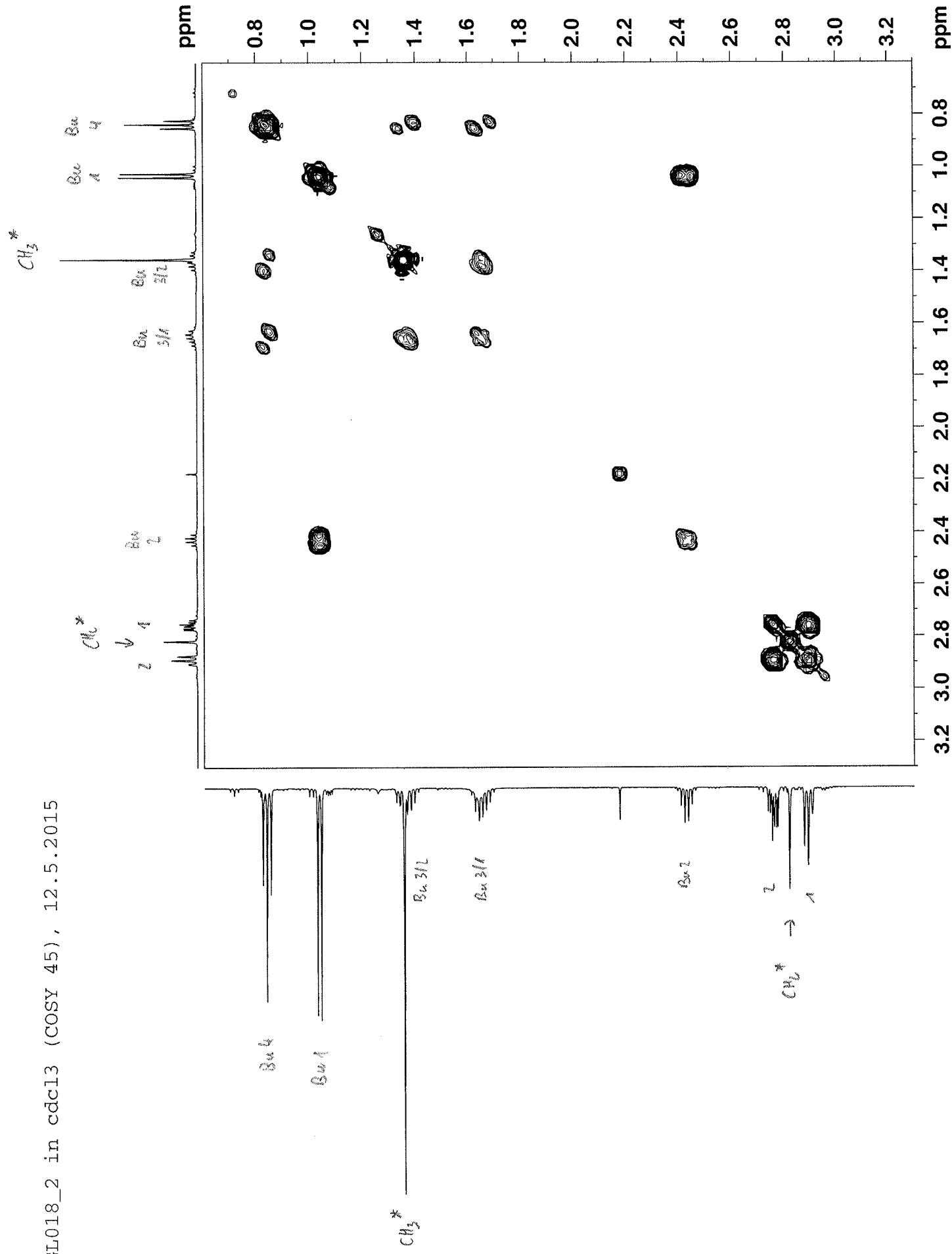




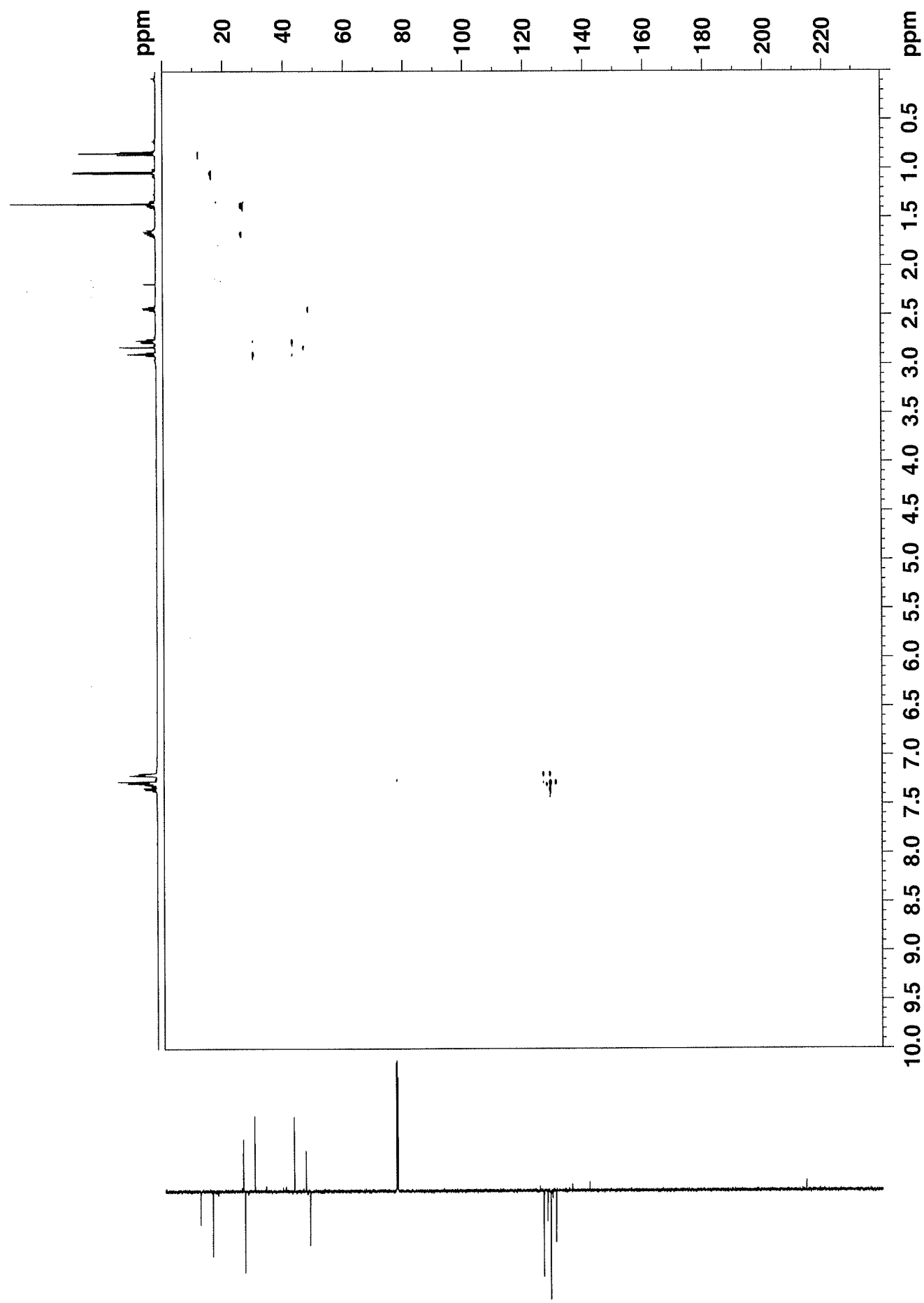
GL018_2 in cdcl3 (COSY 45), 12.5.2015

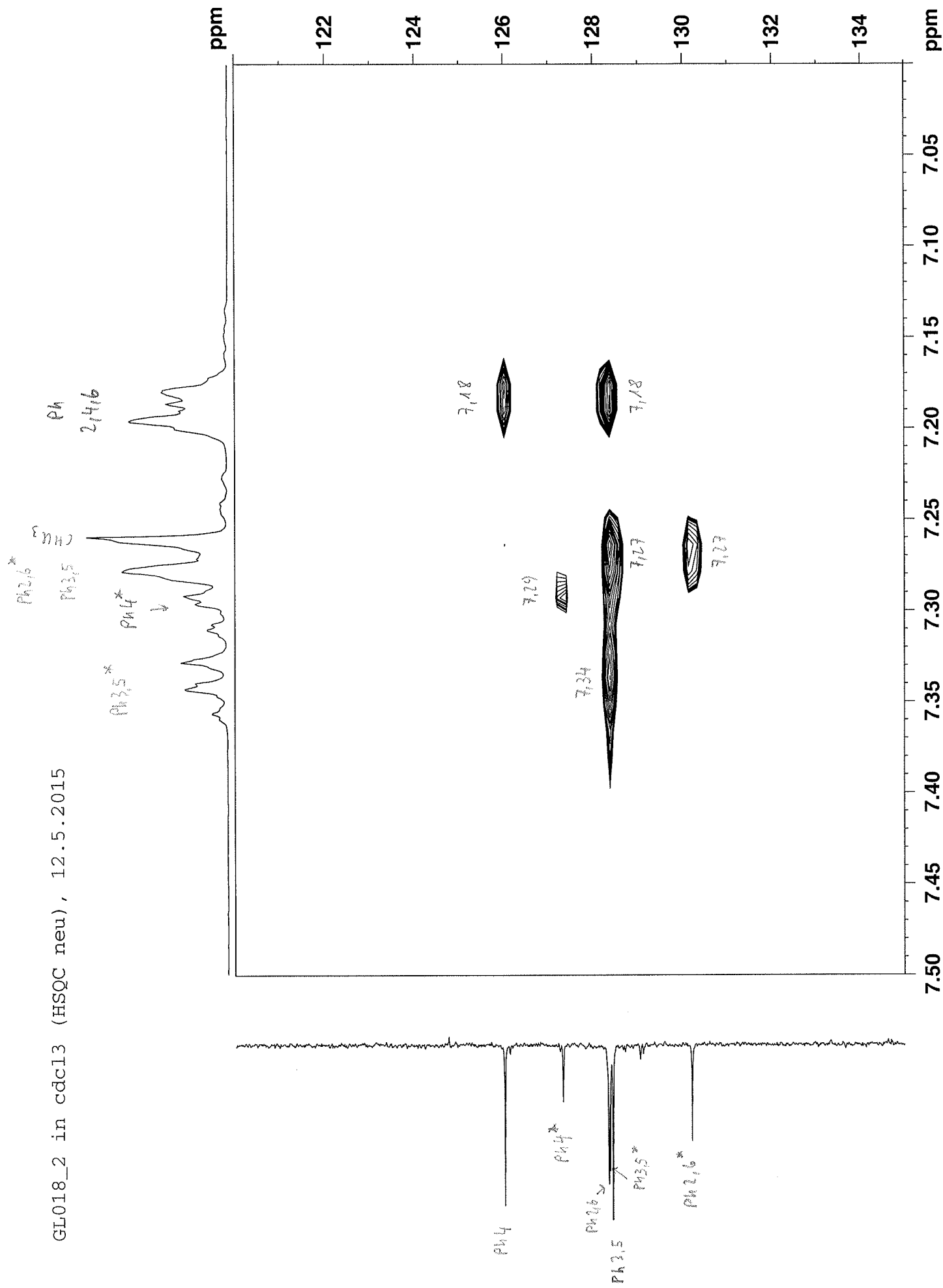


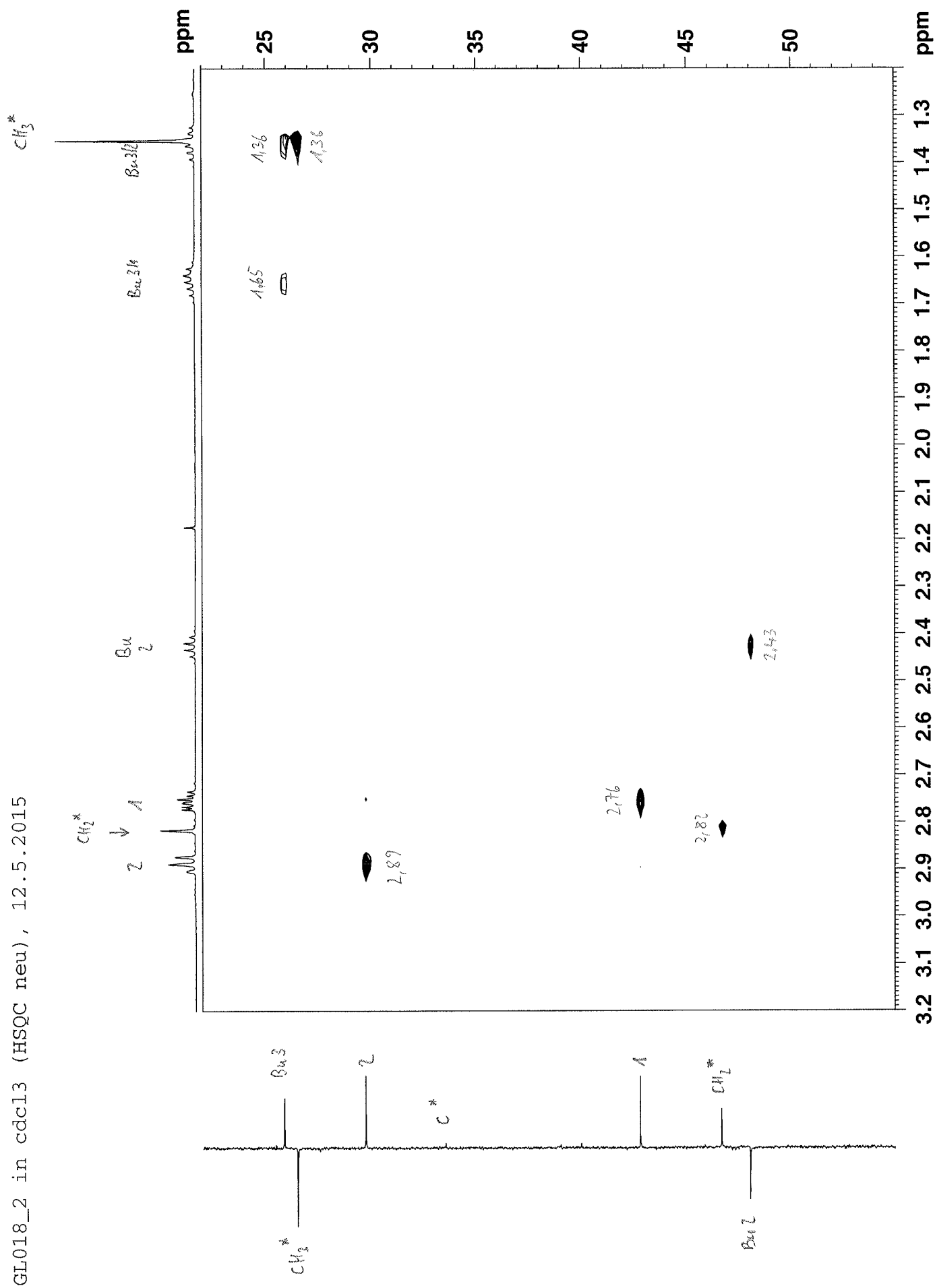




GL018_2 in cdcl3 (HSQC neu), 12.5.2015



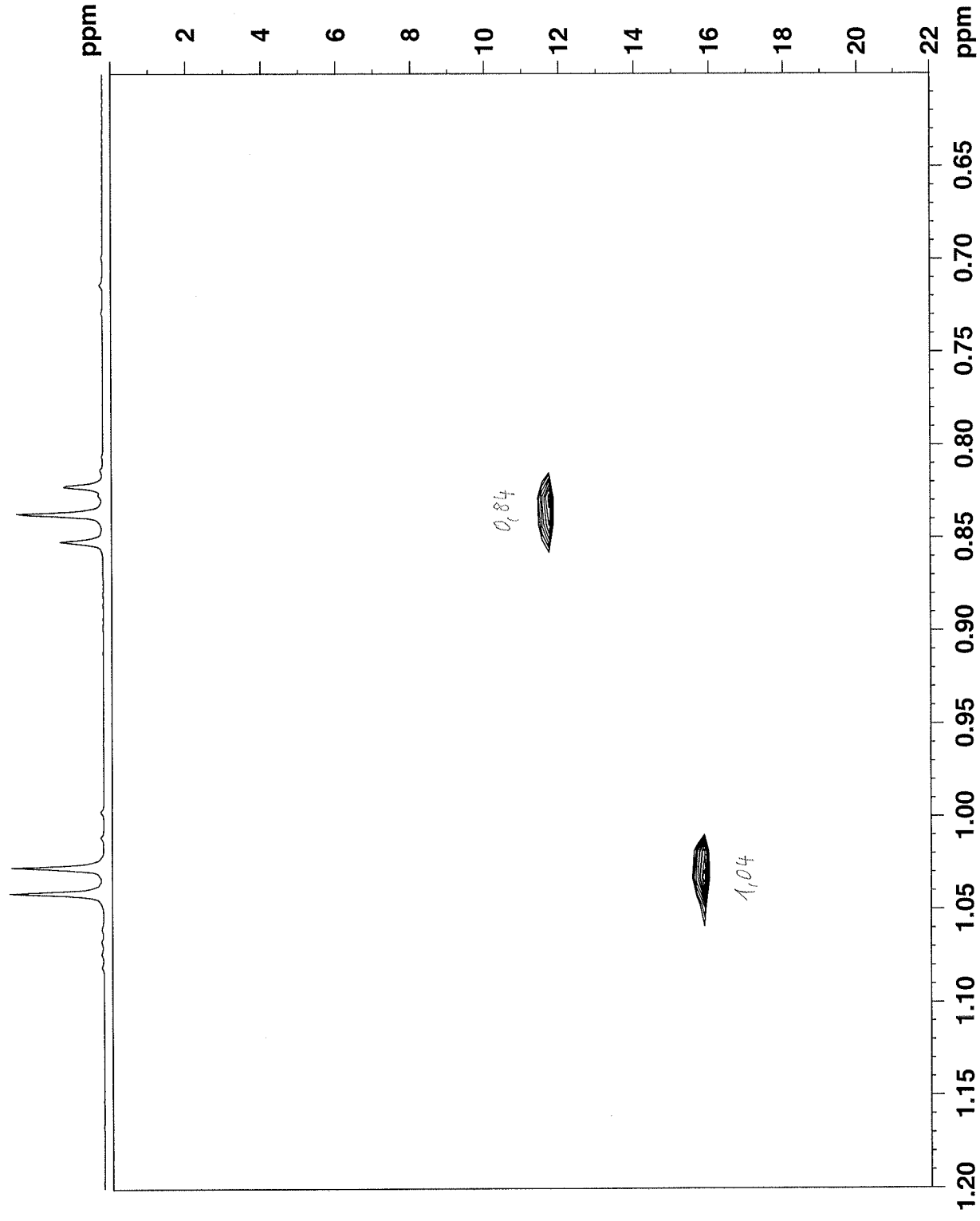




GL018_2 in cdcl3 (HSQC neu), 12.5.2015

Bu4

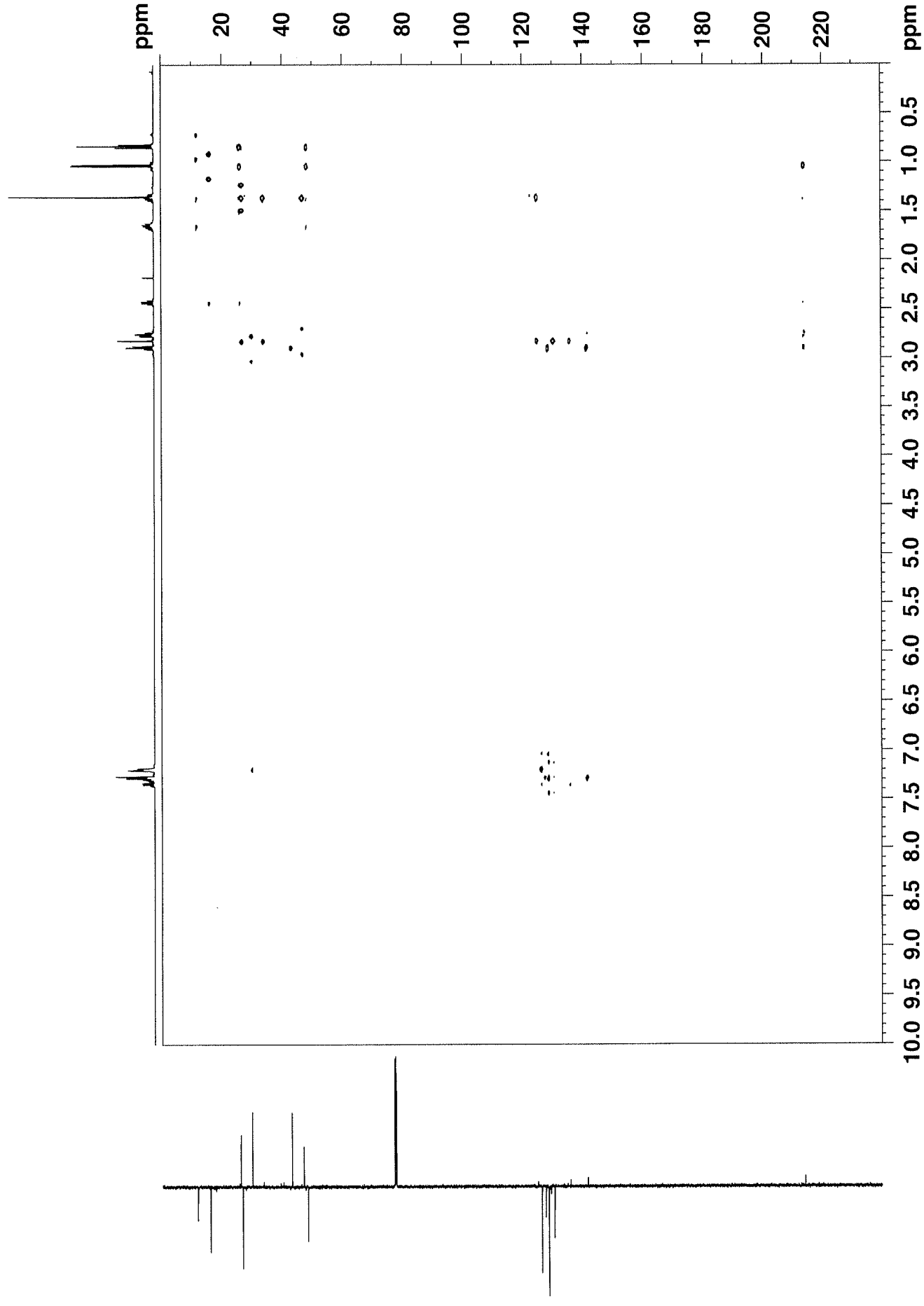
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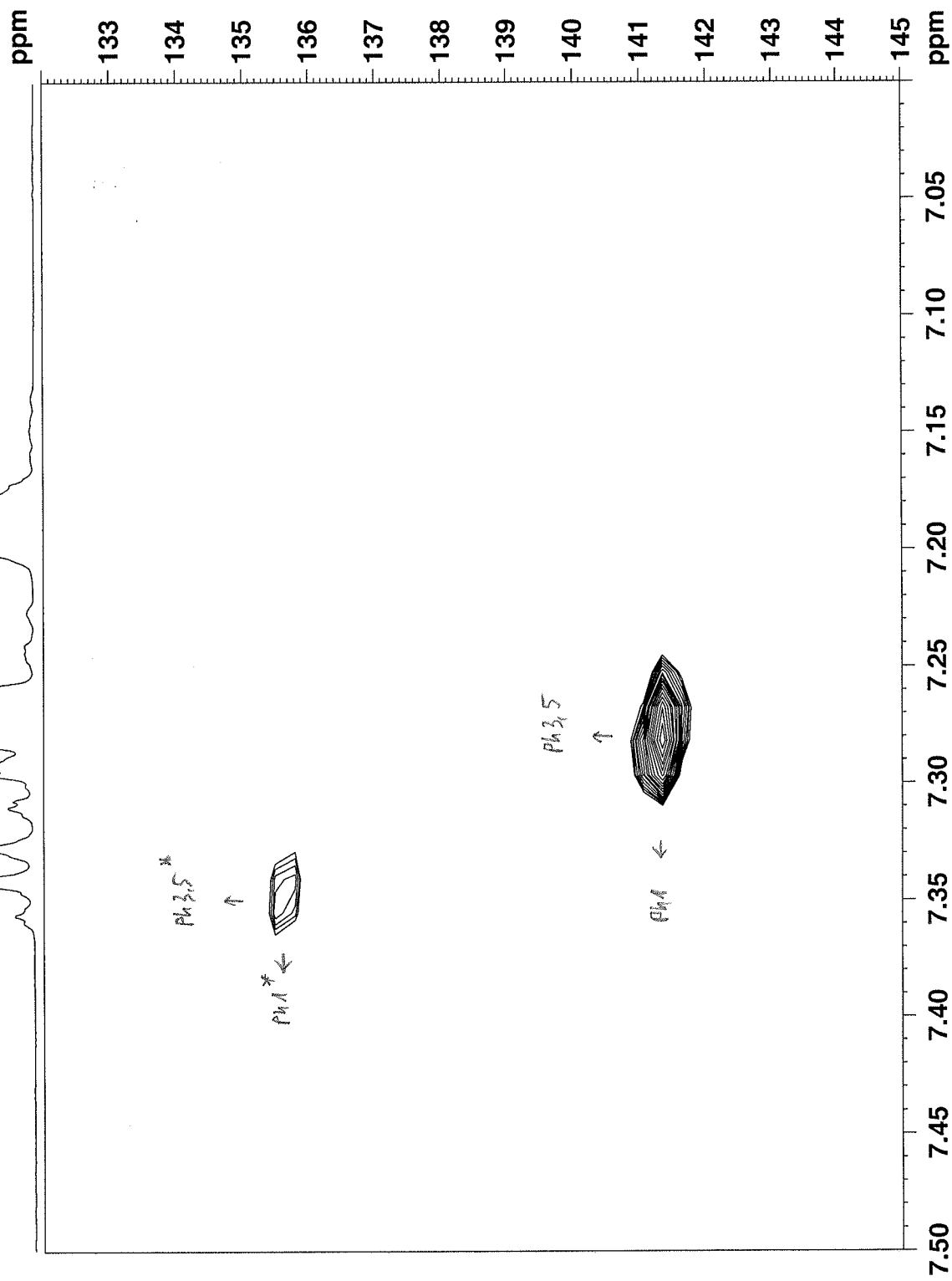


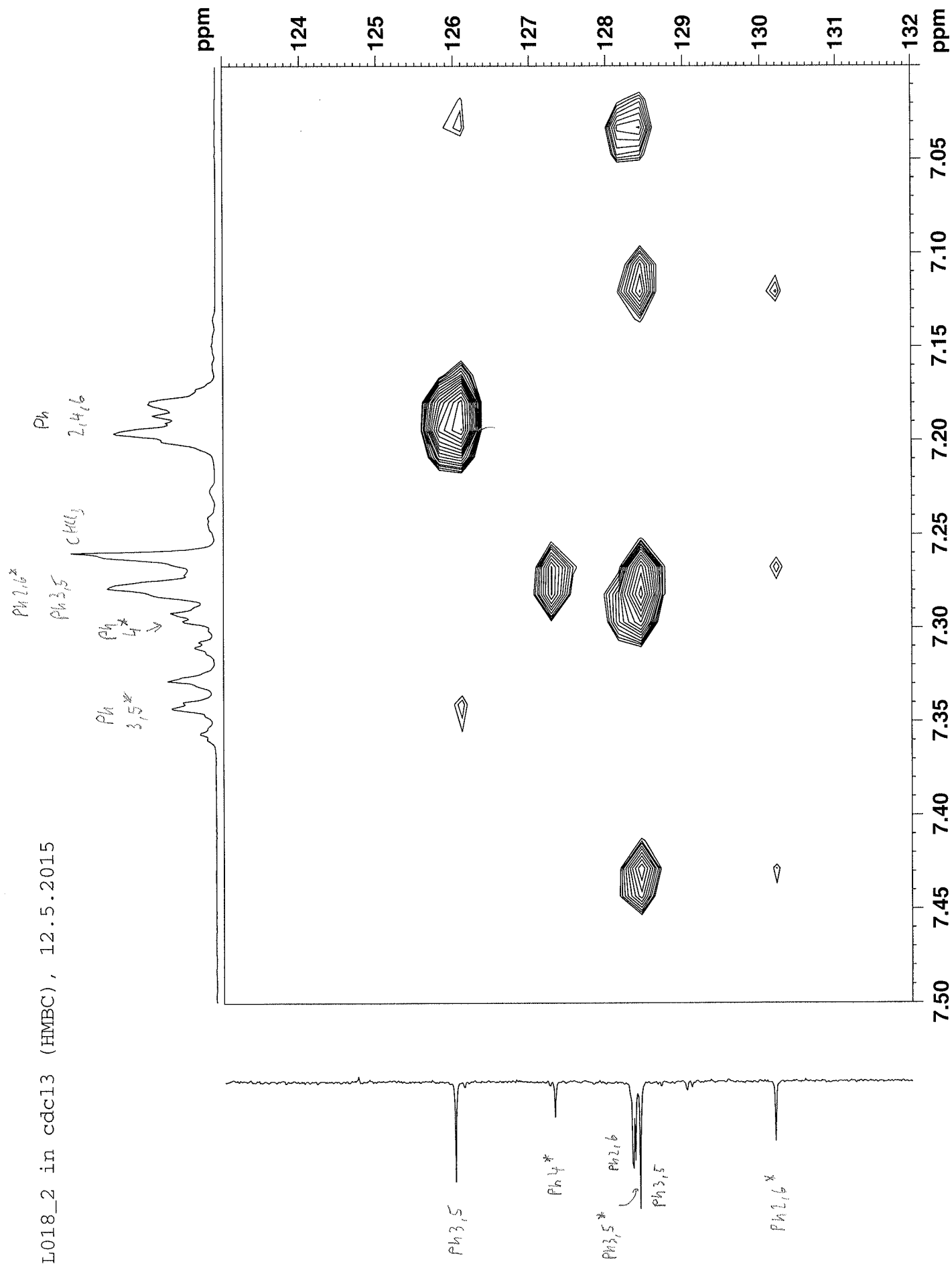
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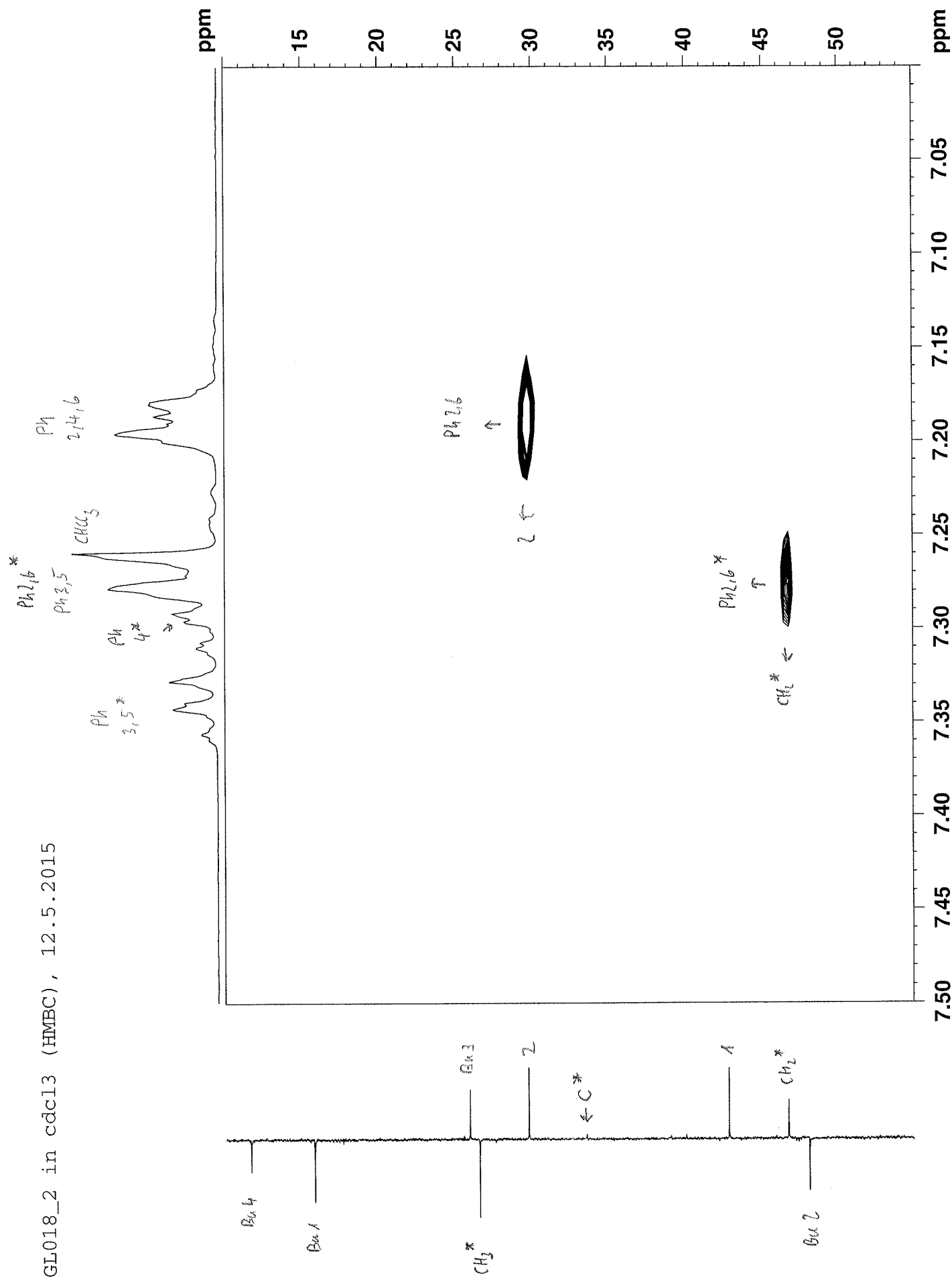
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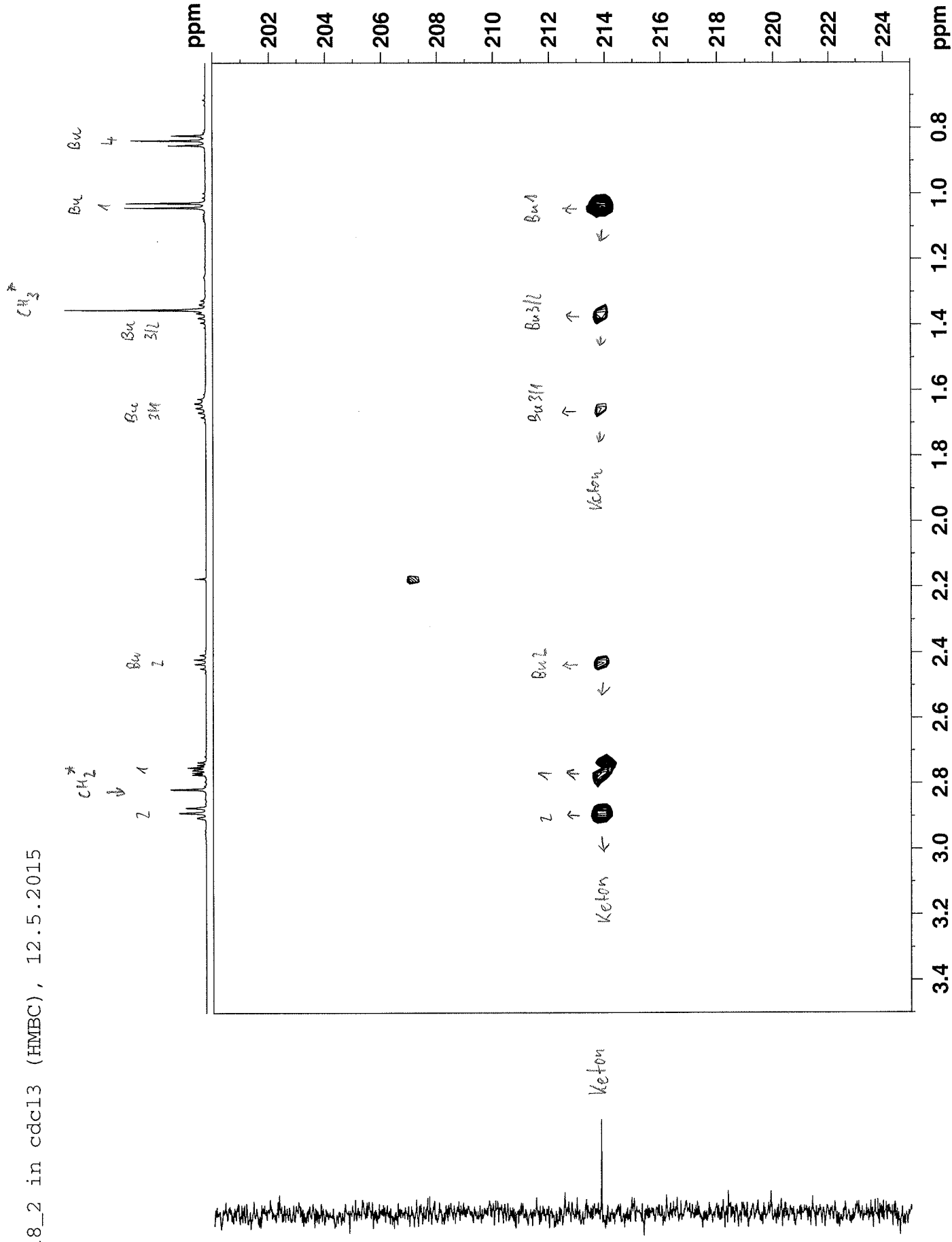
GL018_2 in cdcl3 (HMBC), 12.5.2015

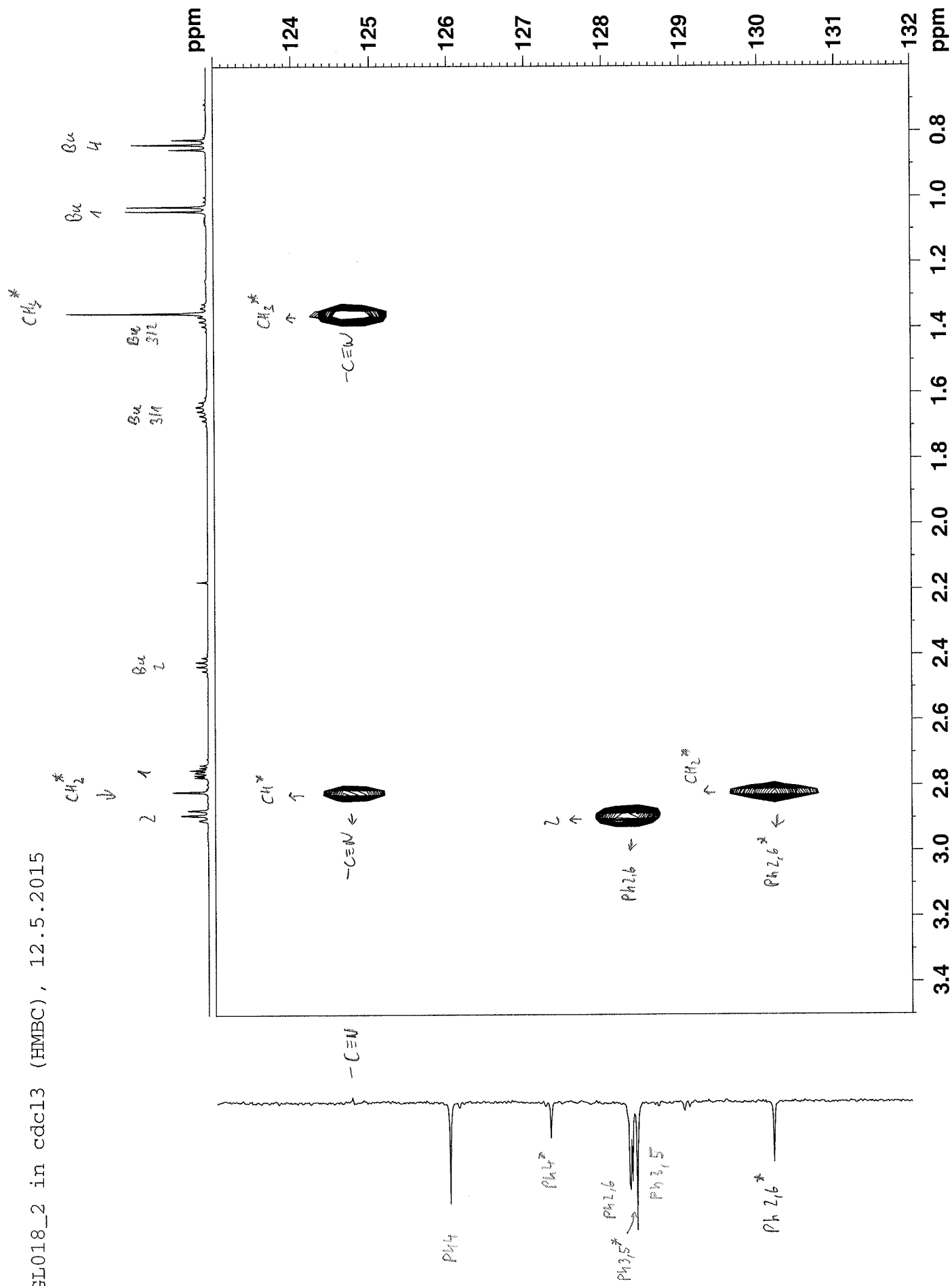


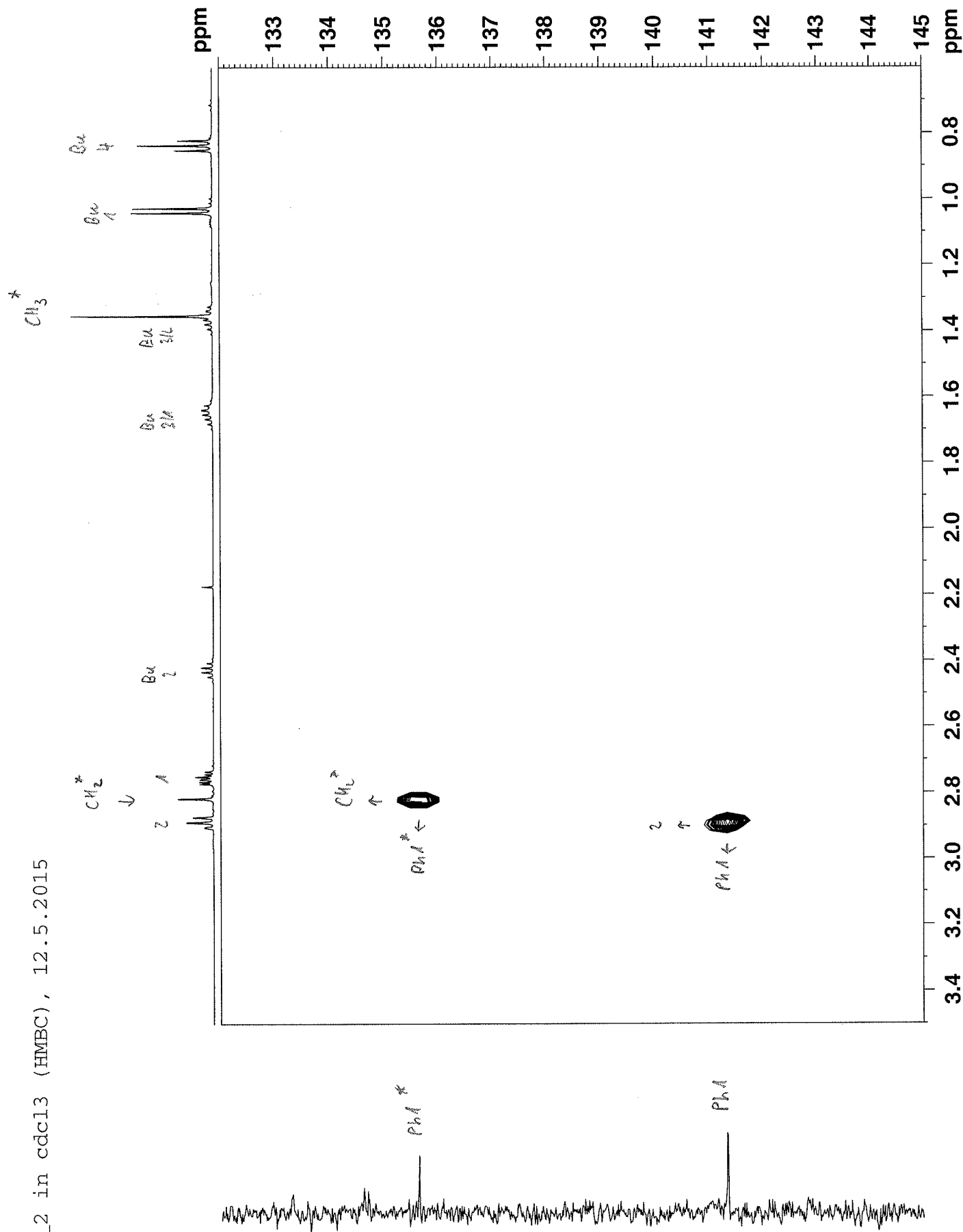


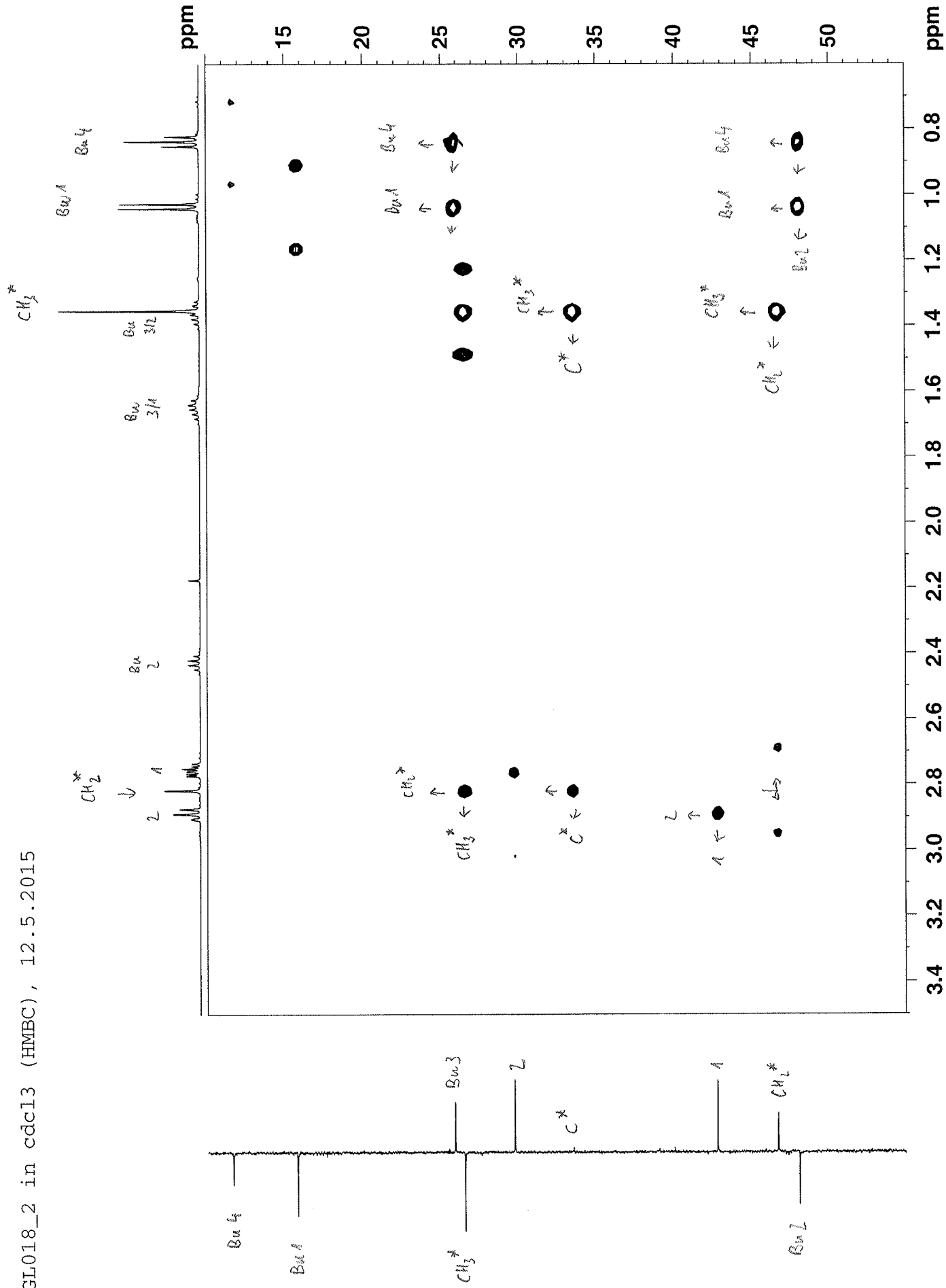


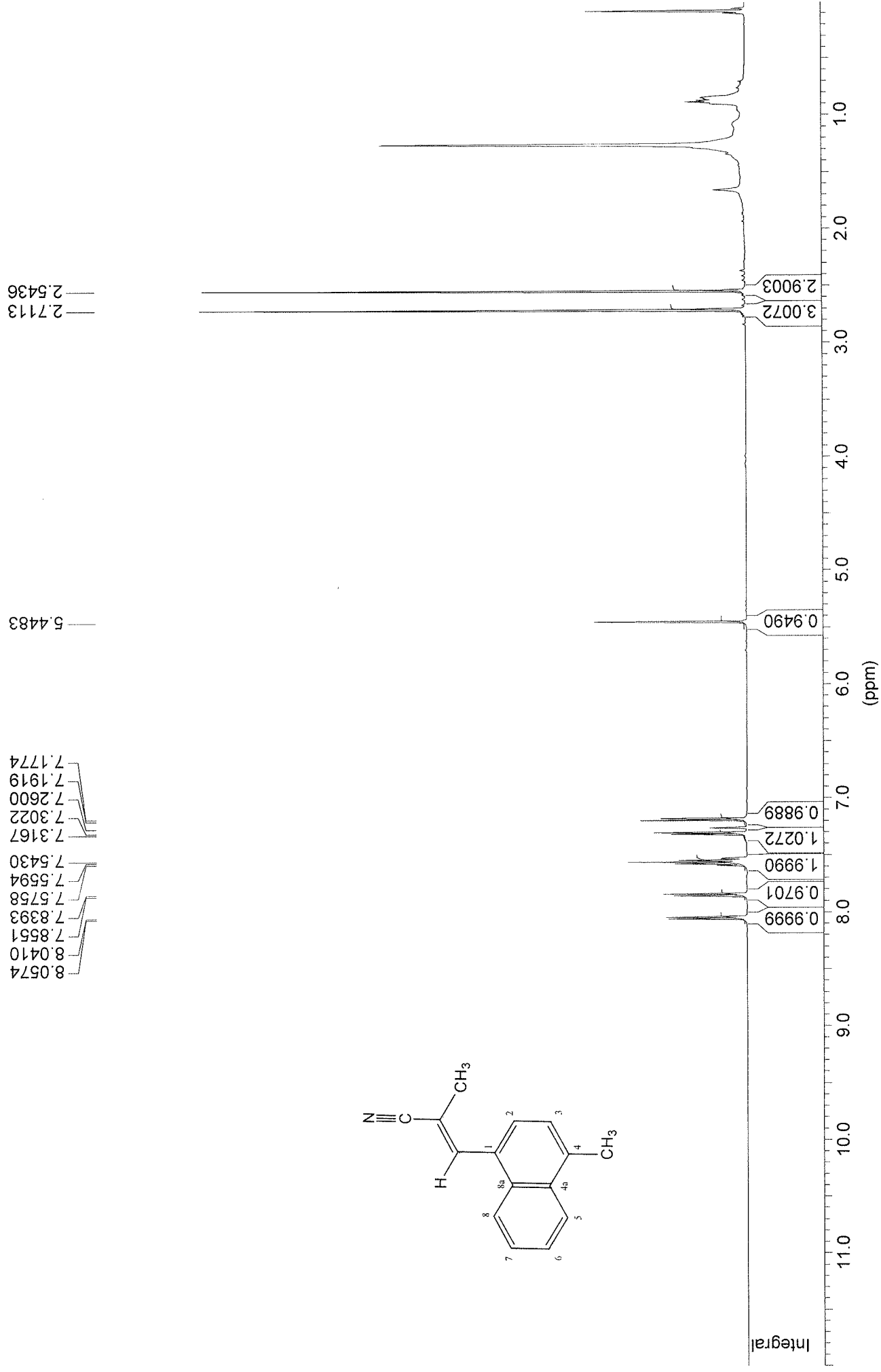
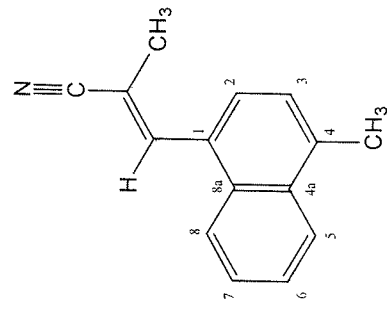


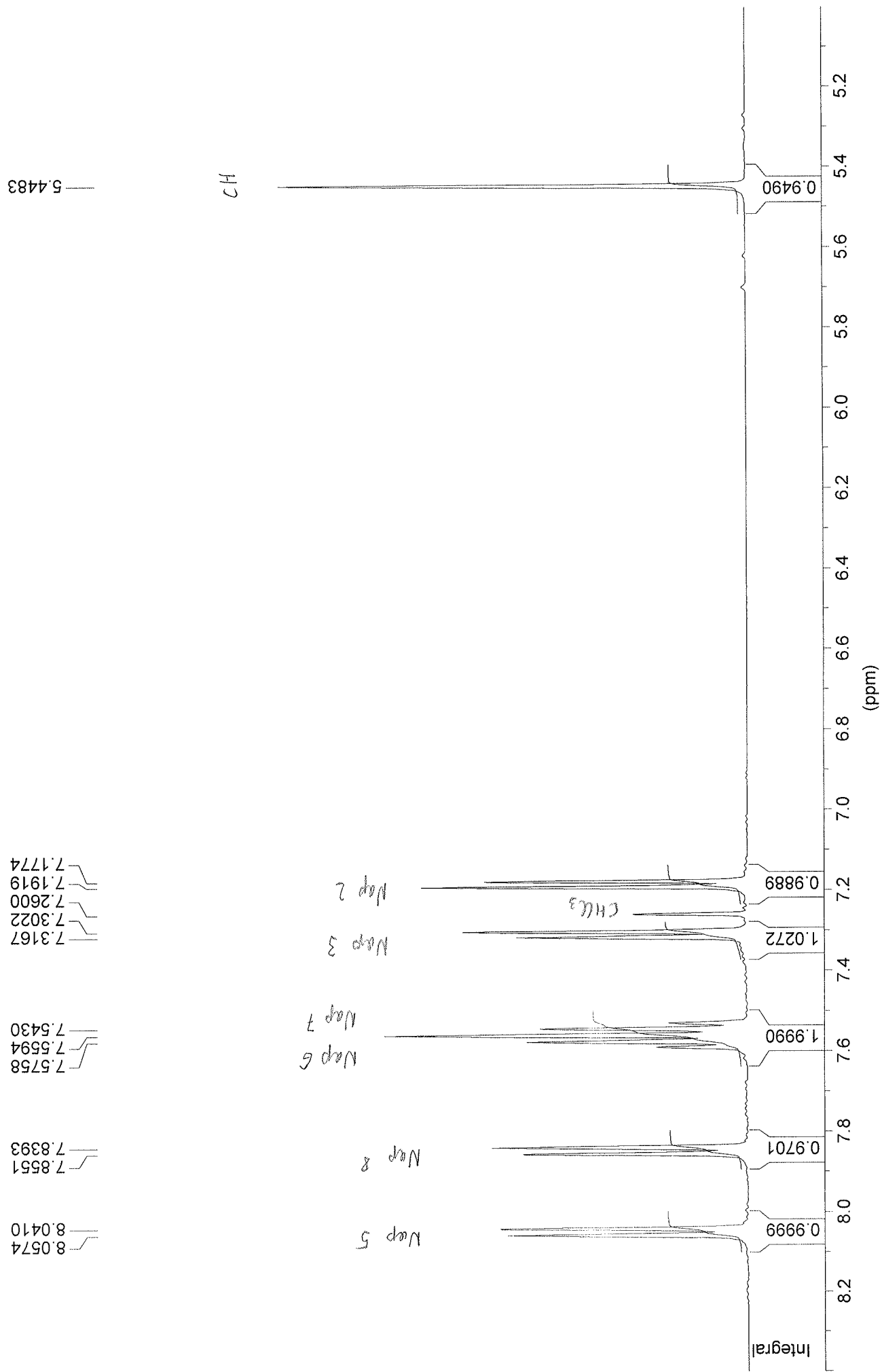


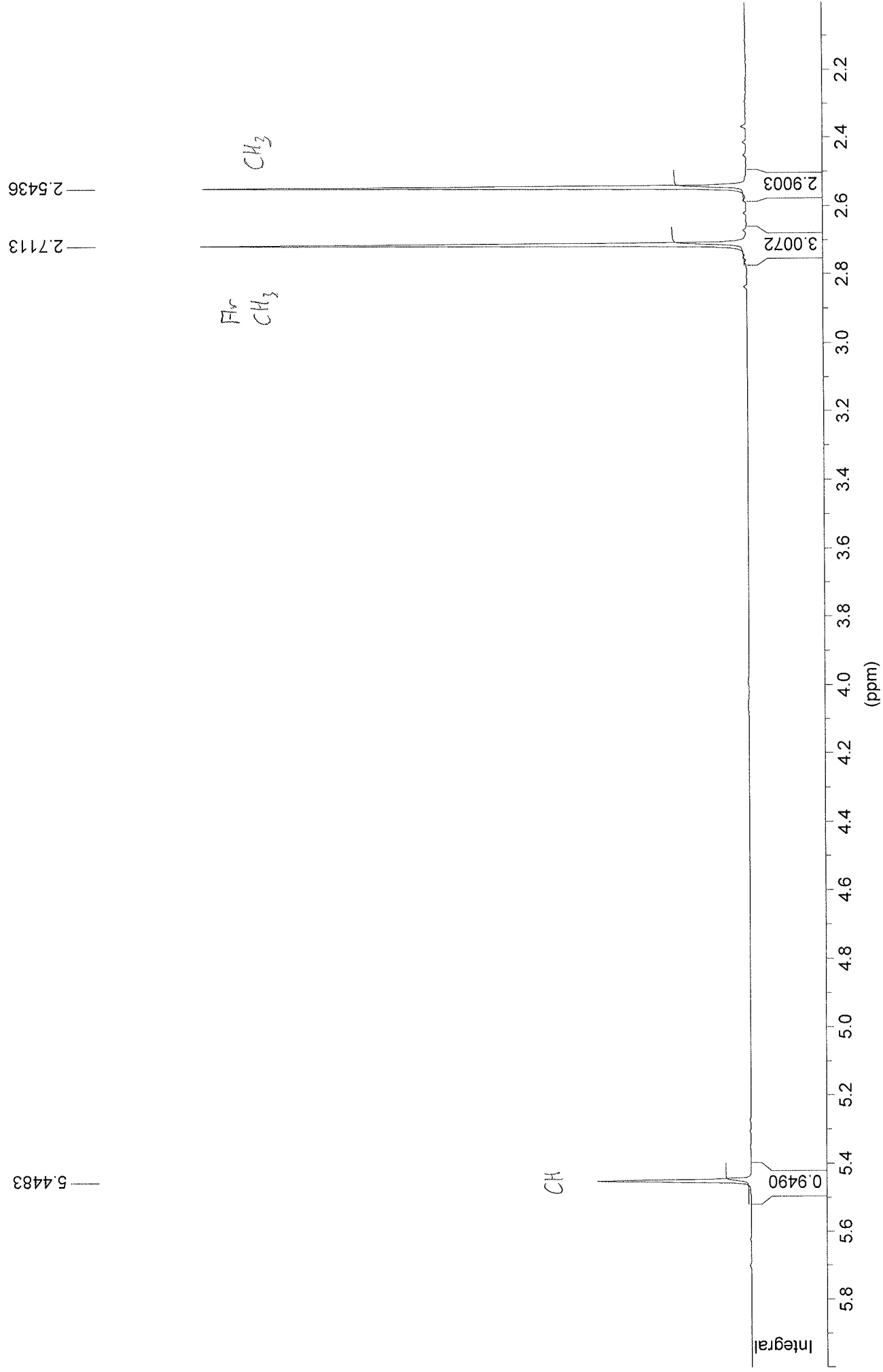


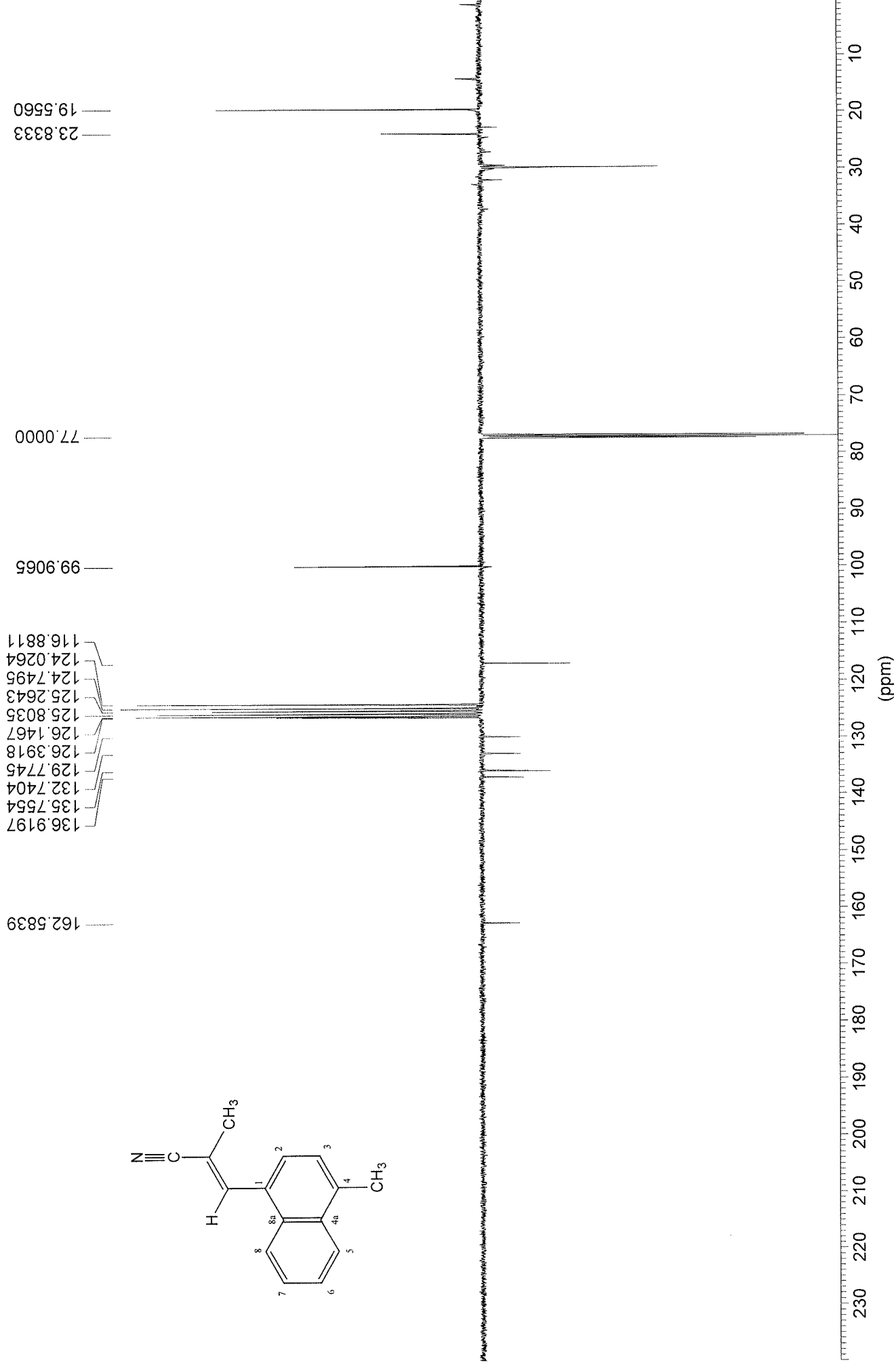
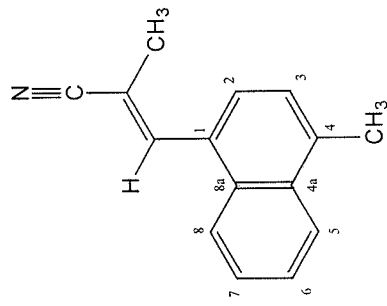


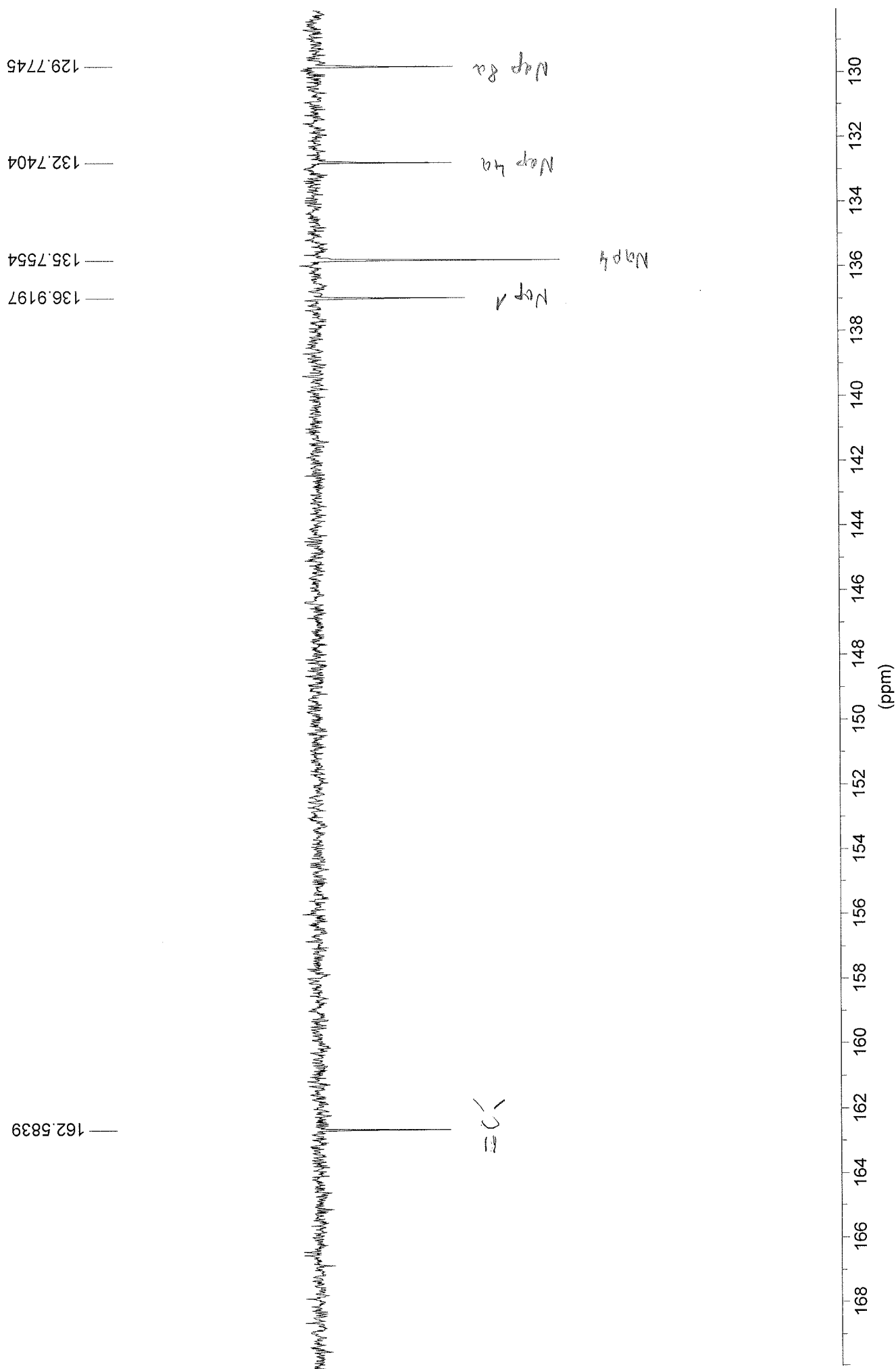


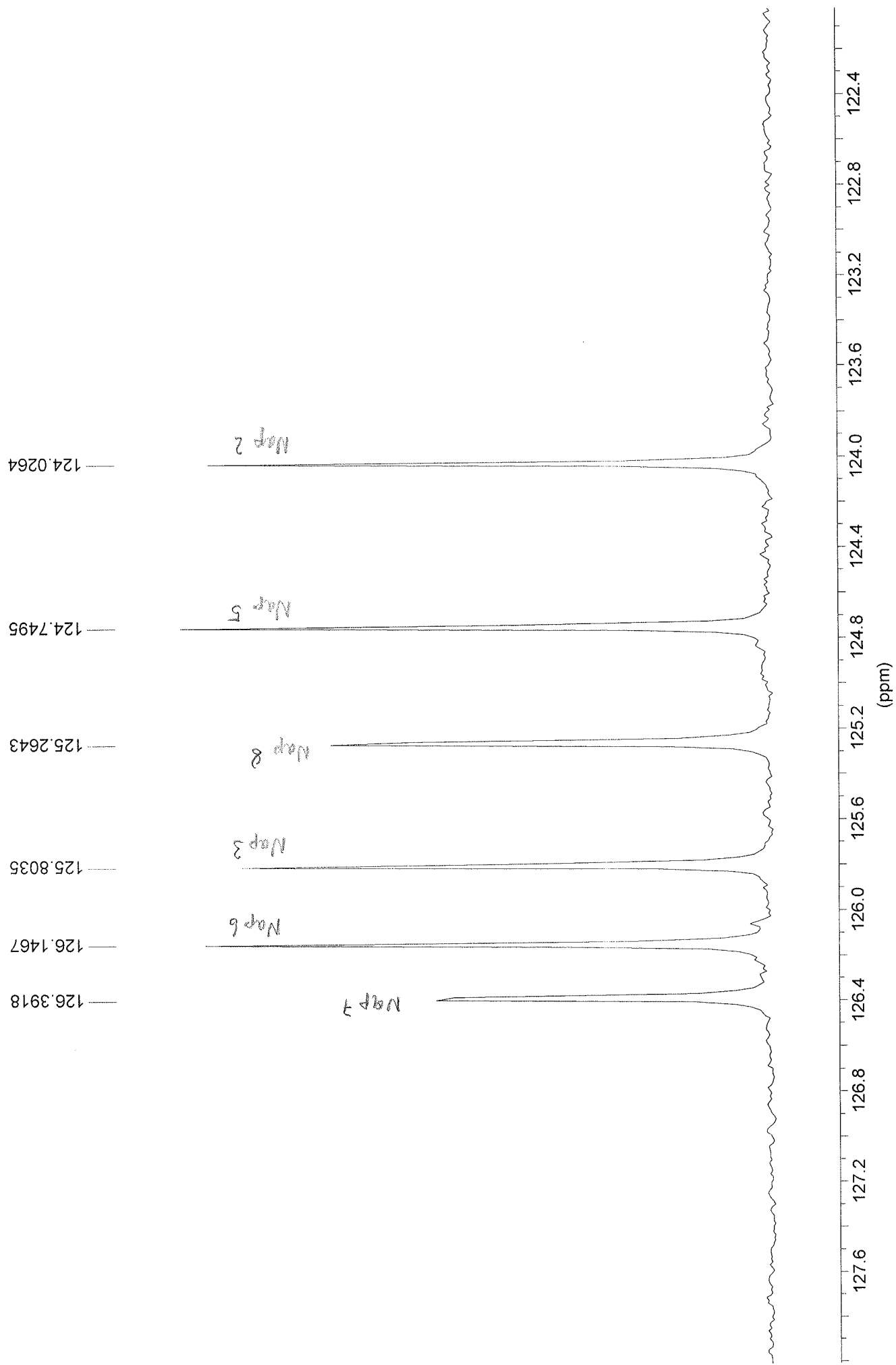


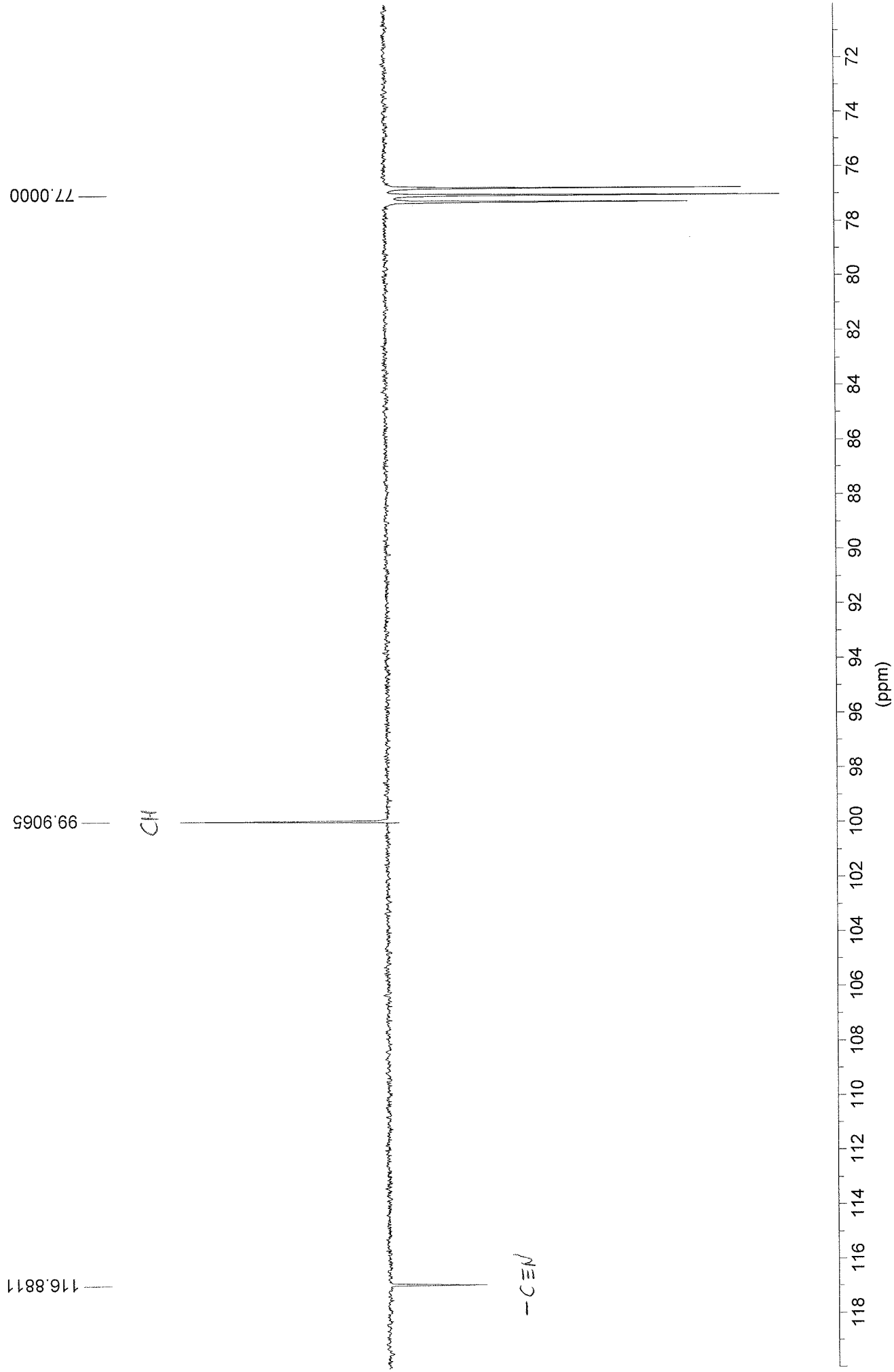


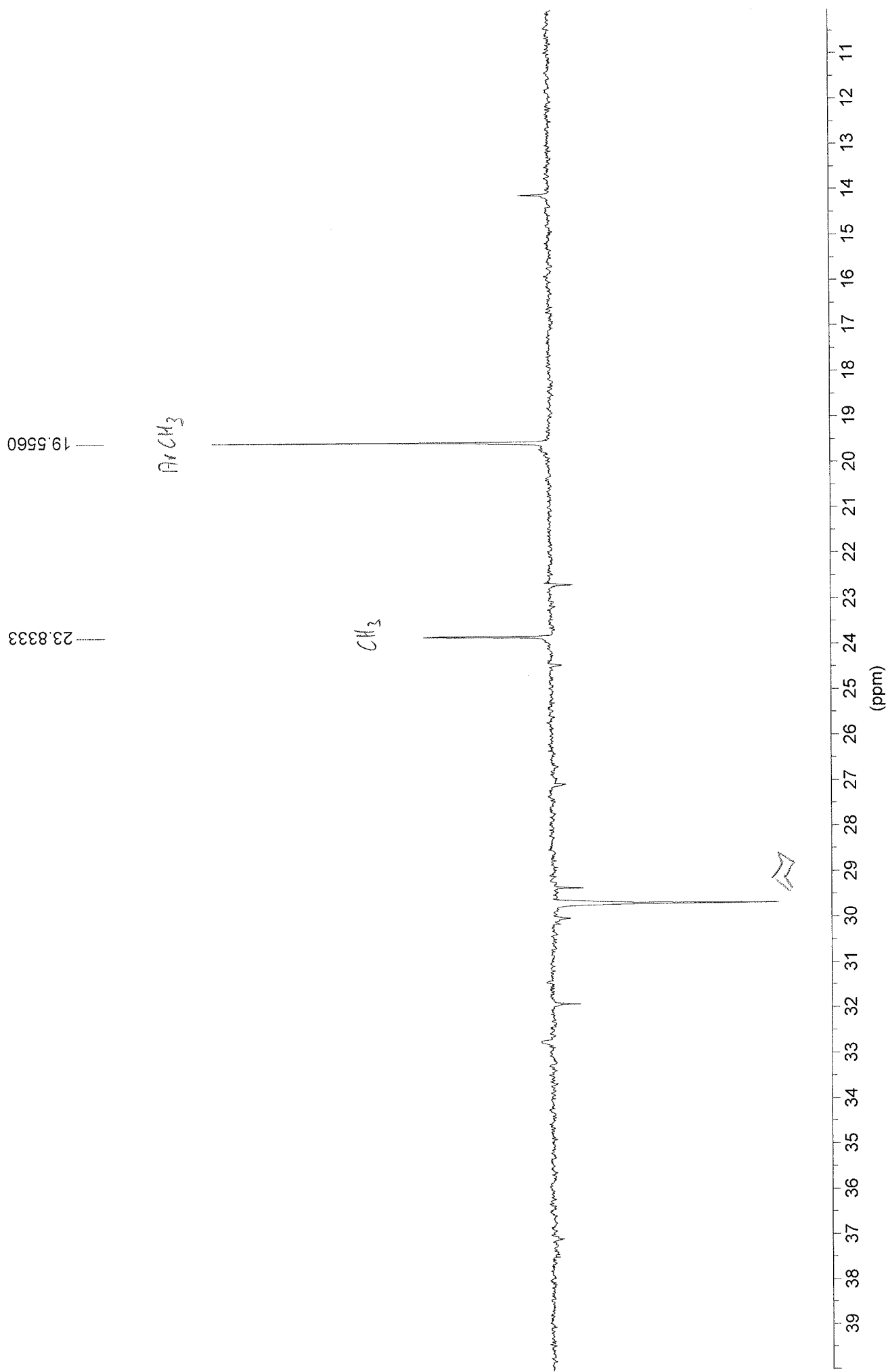




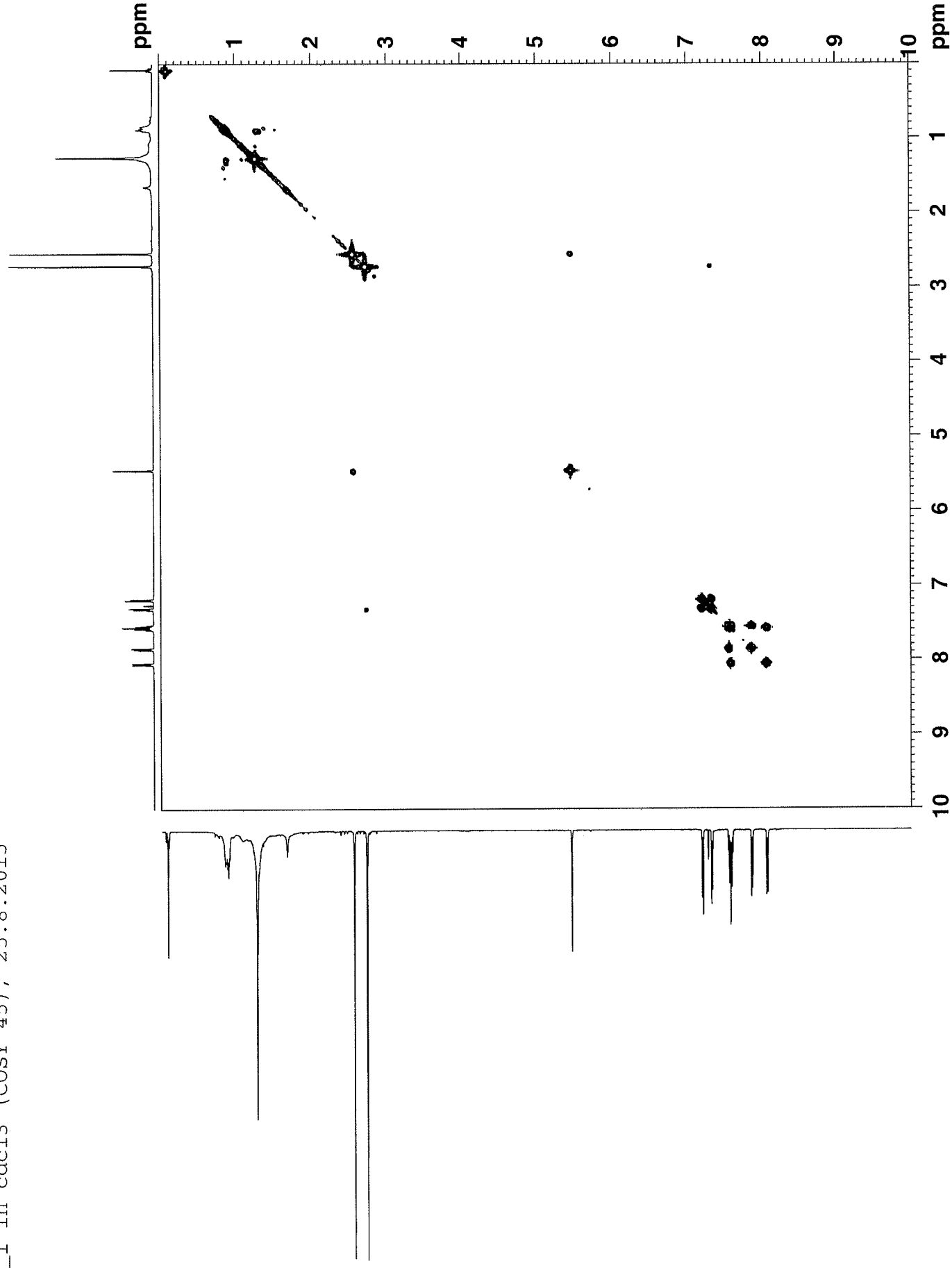


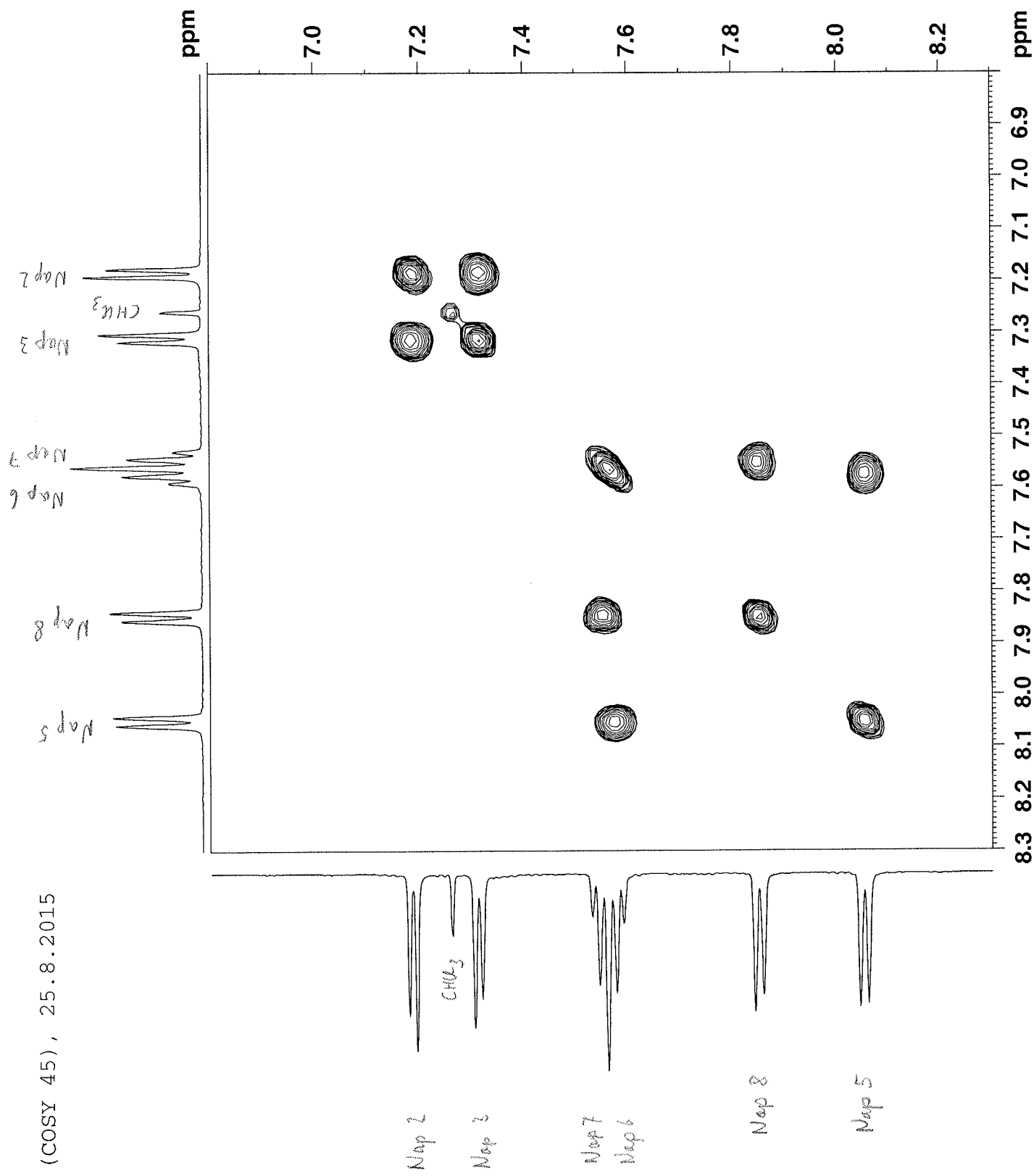


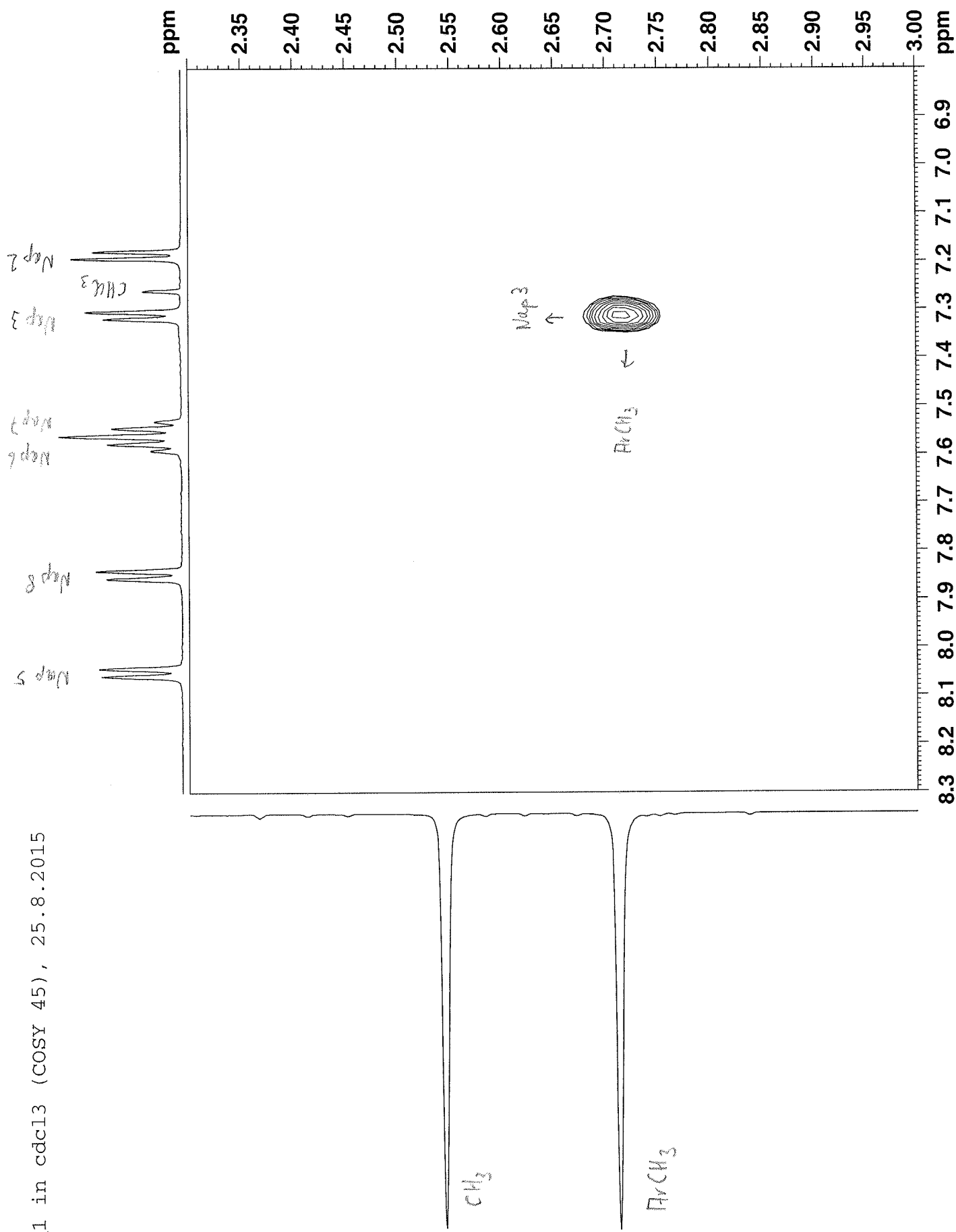




GL052_1 in cdcl3 (COSY 45), 25.8.2015

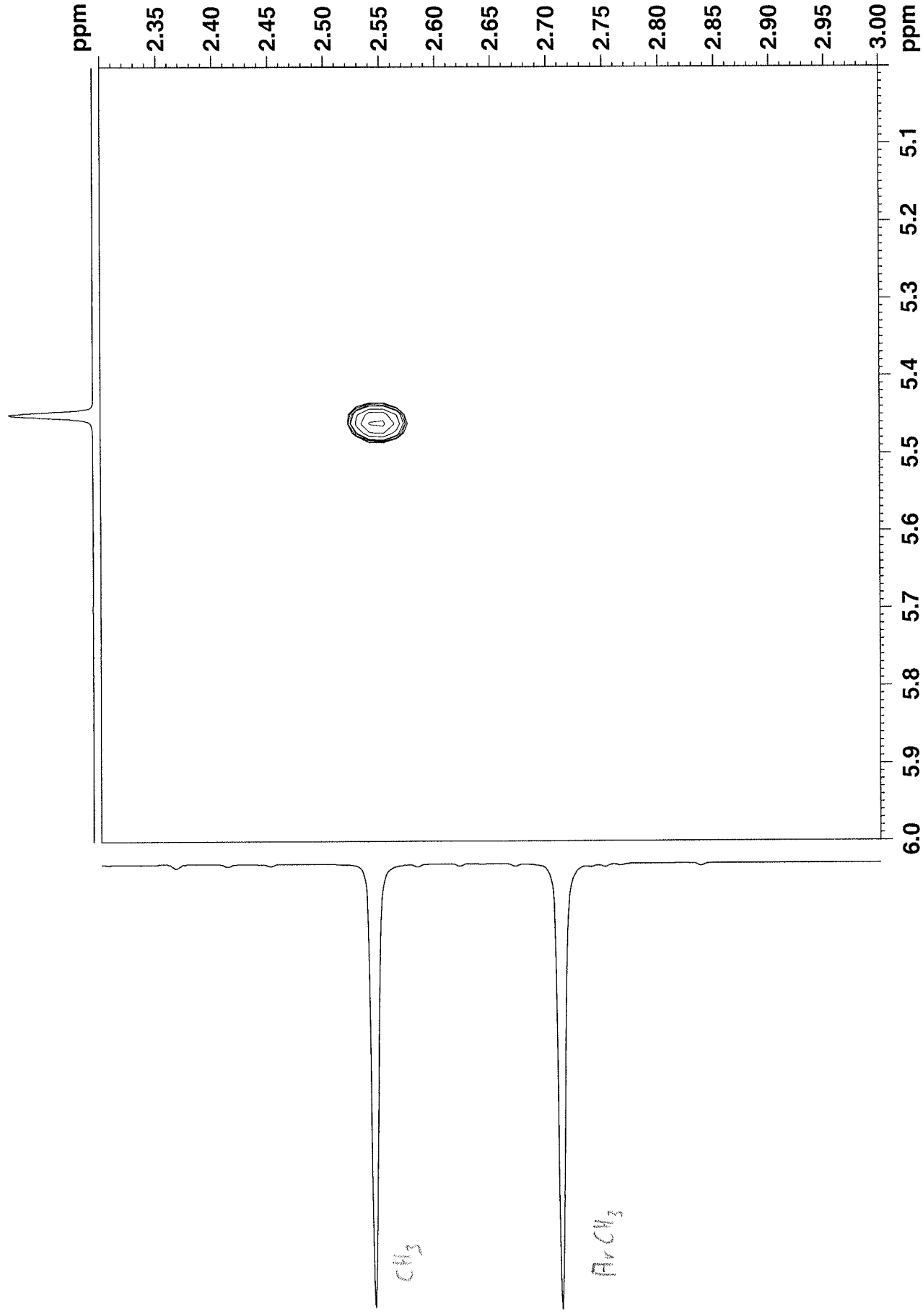




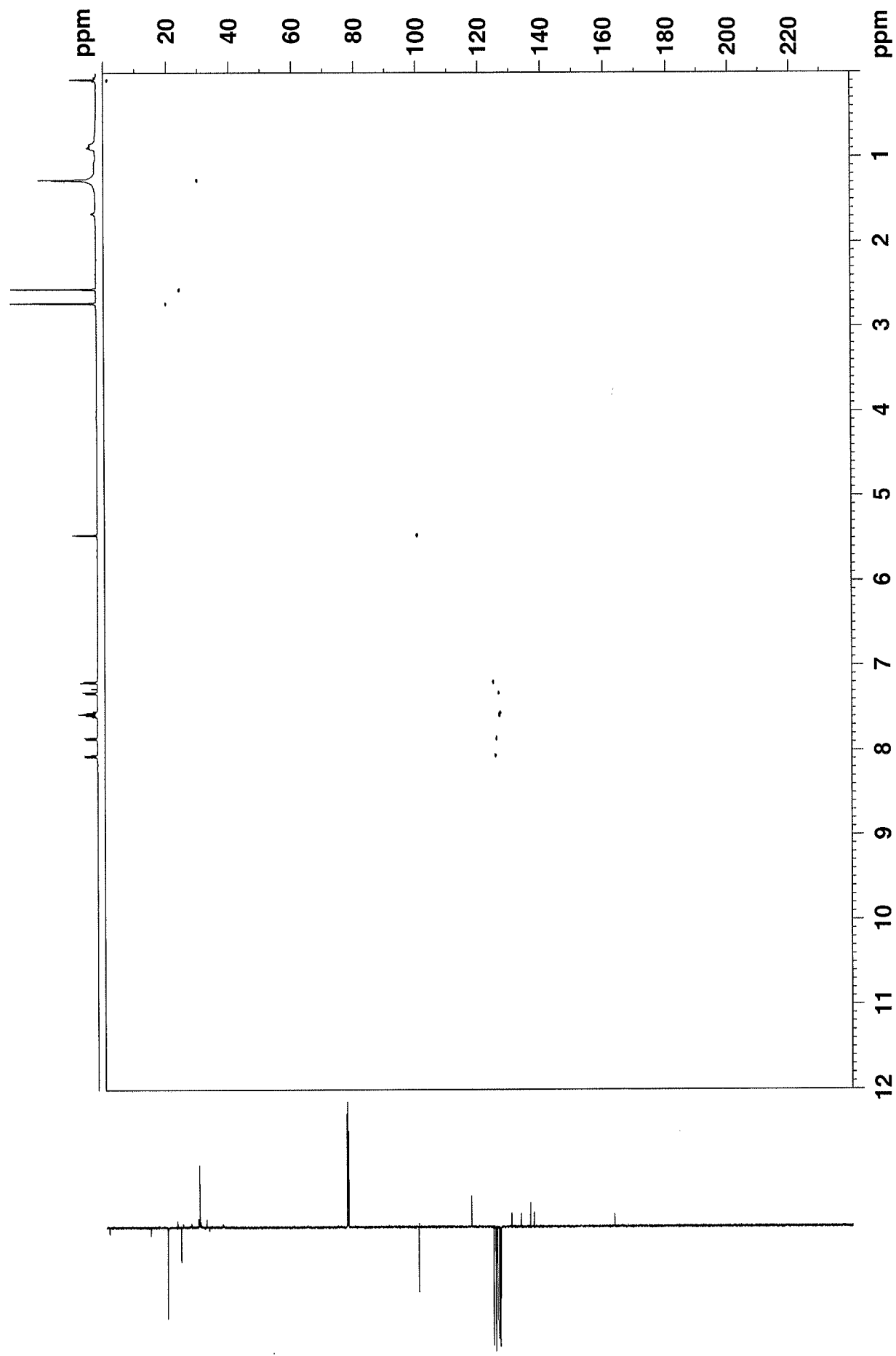


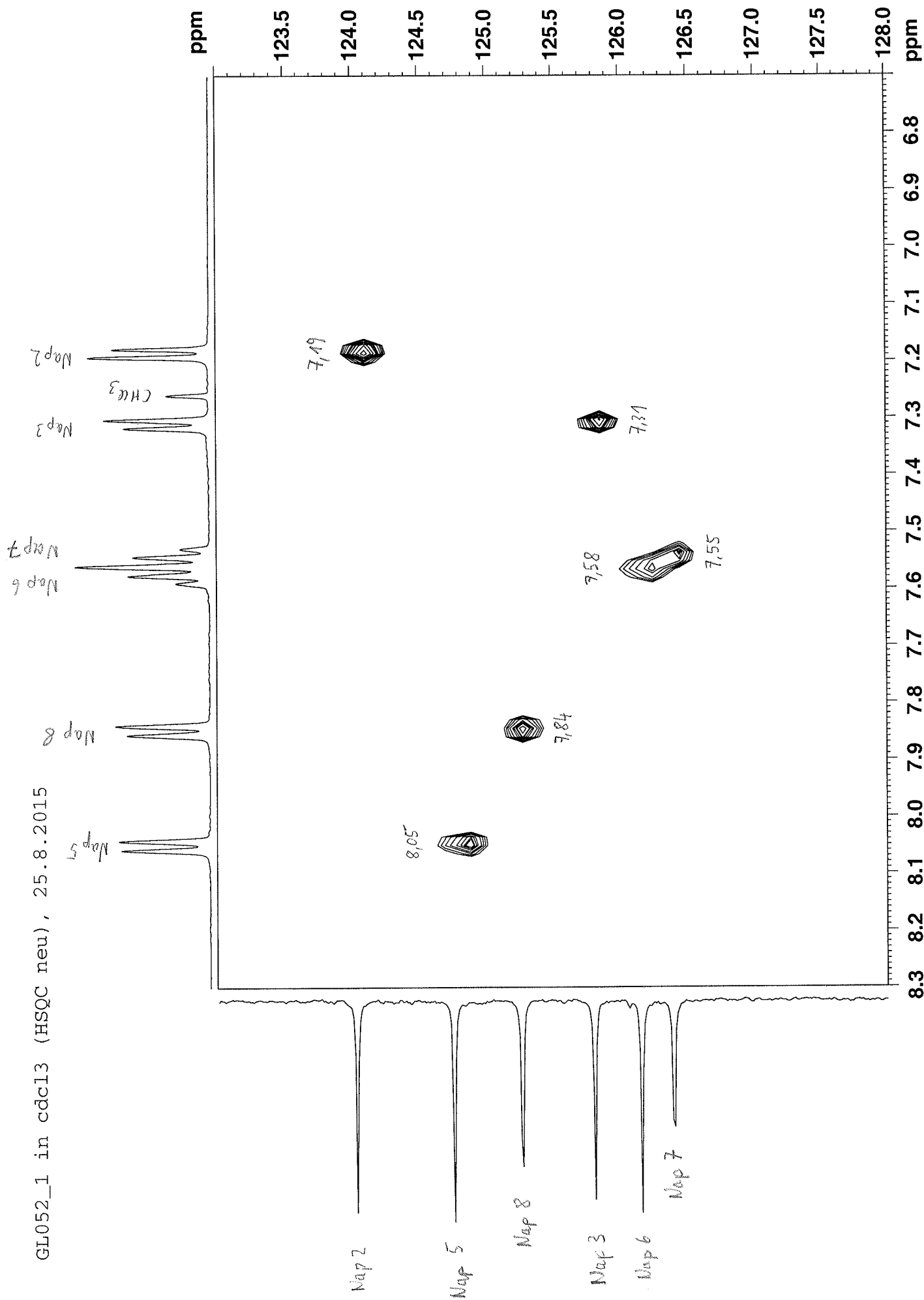
GL052_1 in cdcl3 (COSY 45), 25.8.2015

CH



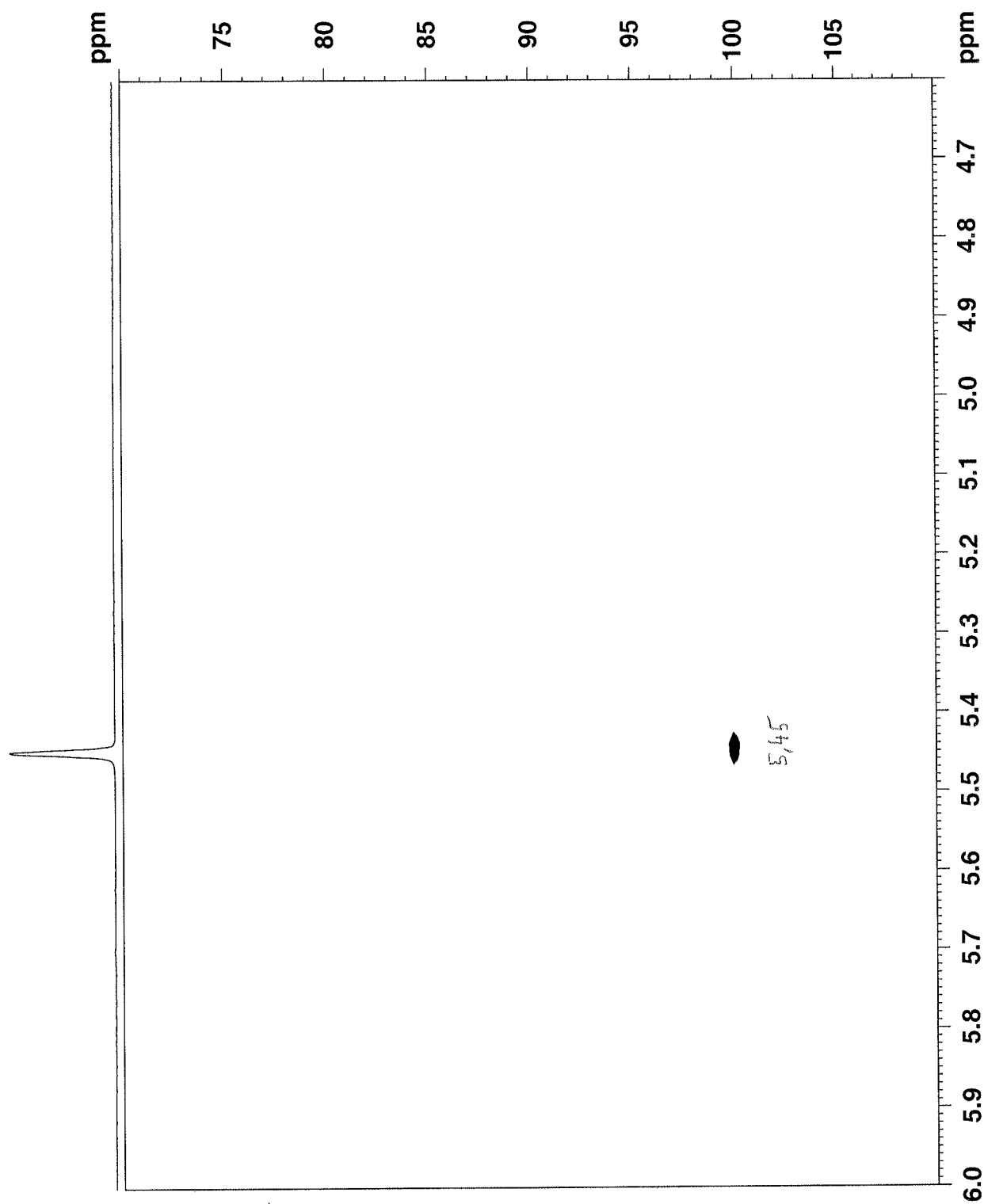
GL052_1 in cdcl3 (HSQC neu), 25.8.2015





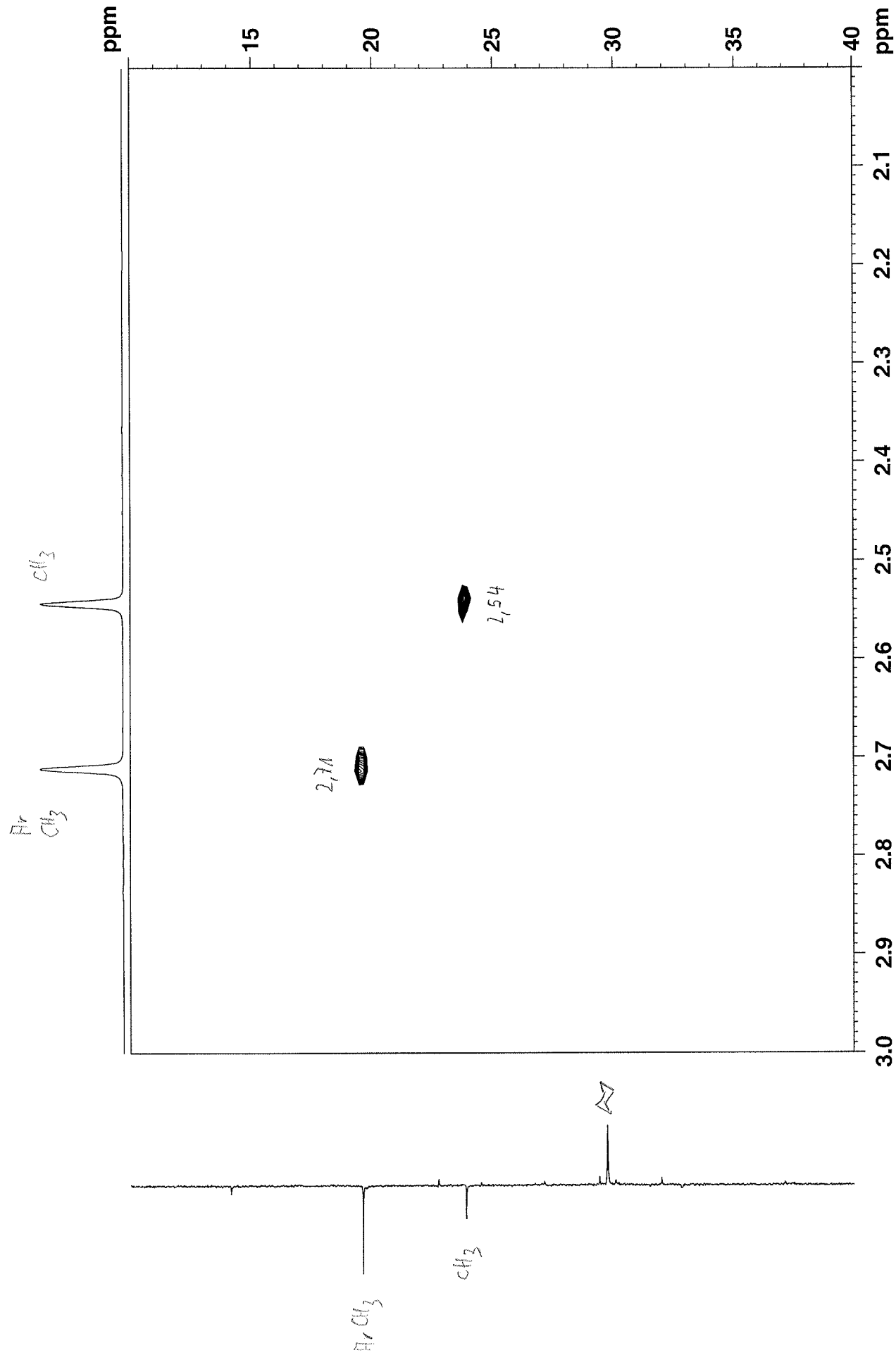
GL052_1 in cdcl3 (HSQC neu), 25.8.2015

CH

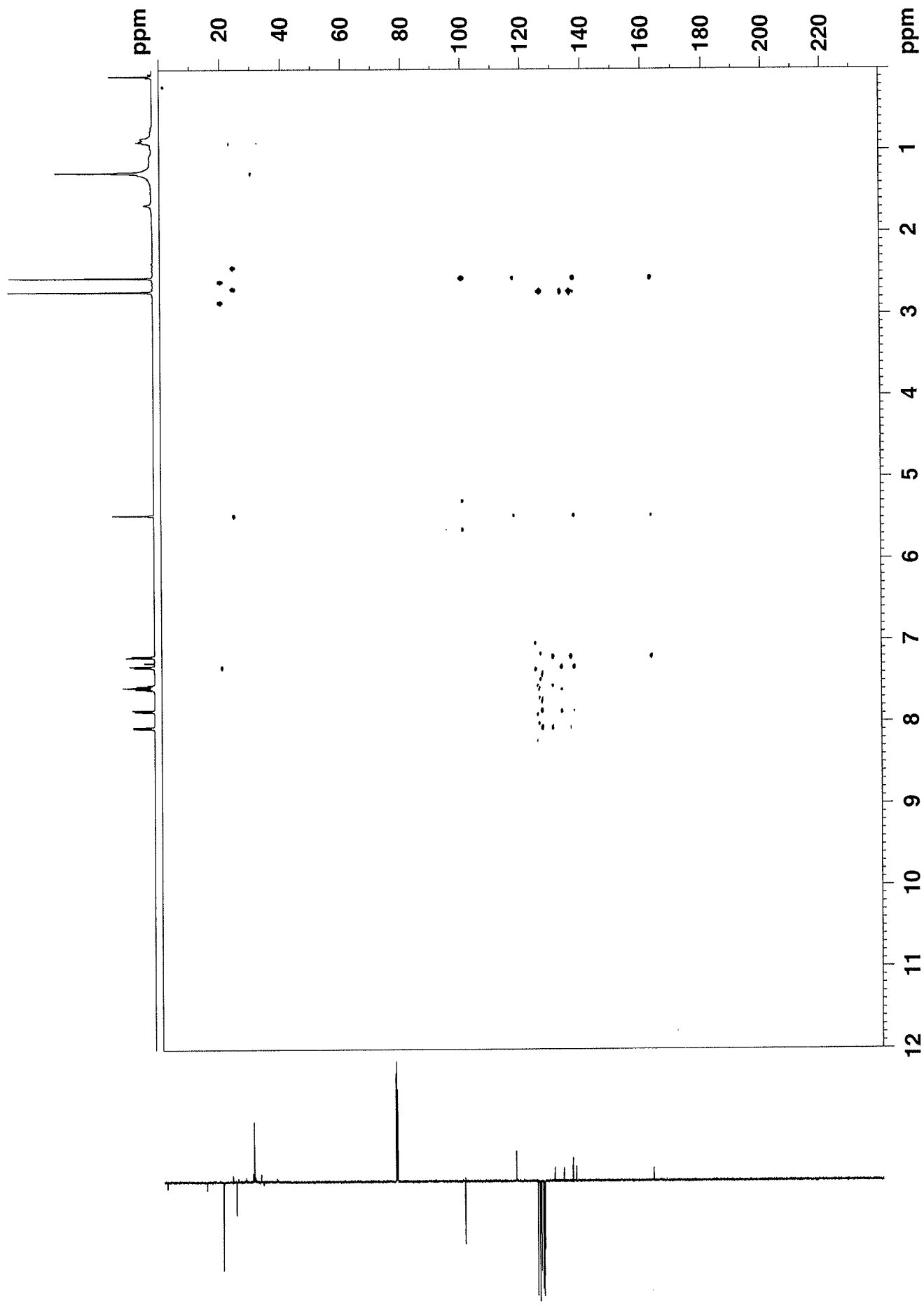


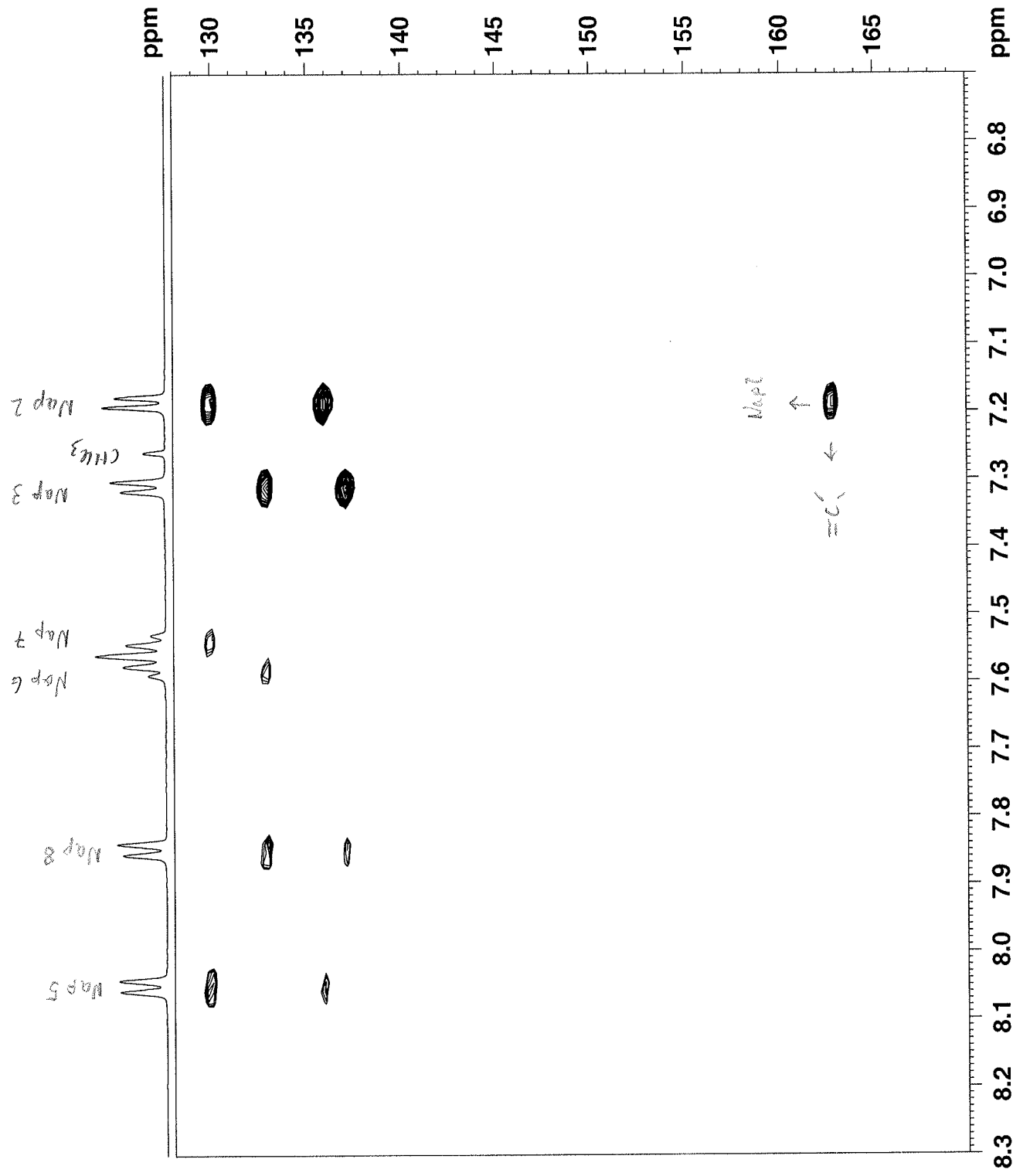
CH

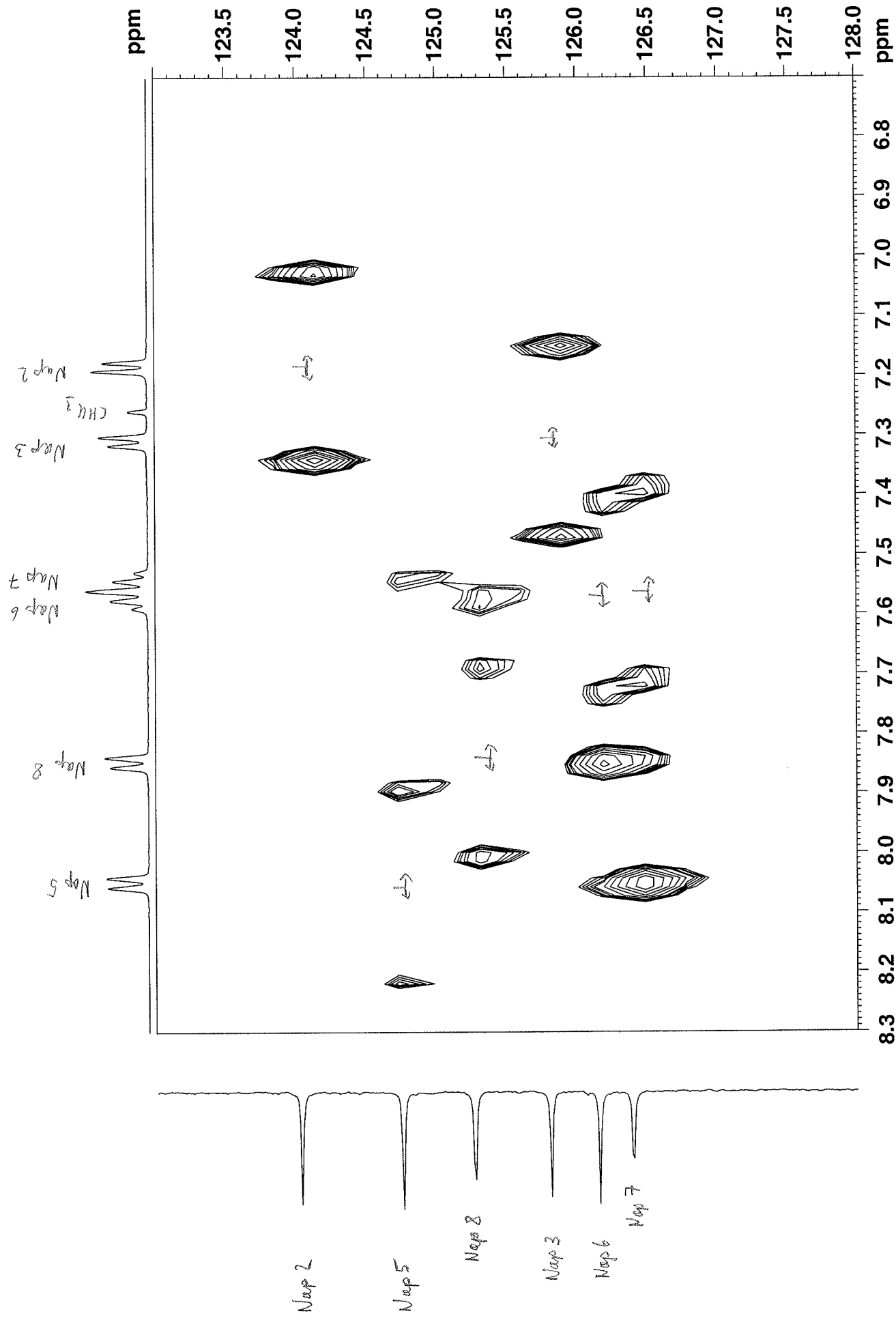
GL052_1 in cdcl3 (HSQC neu), 25.8.2015



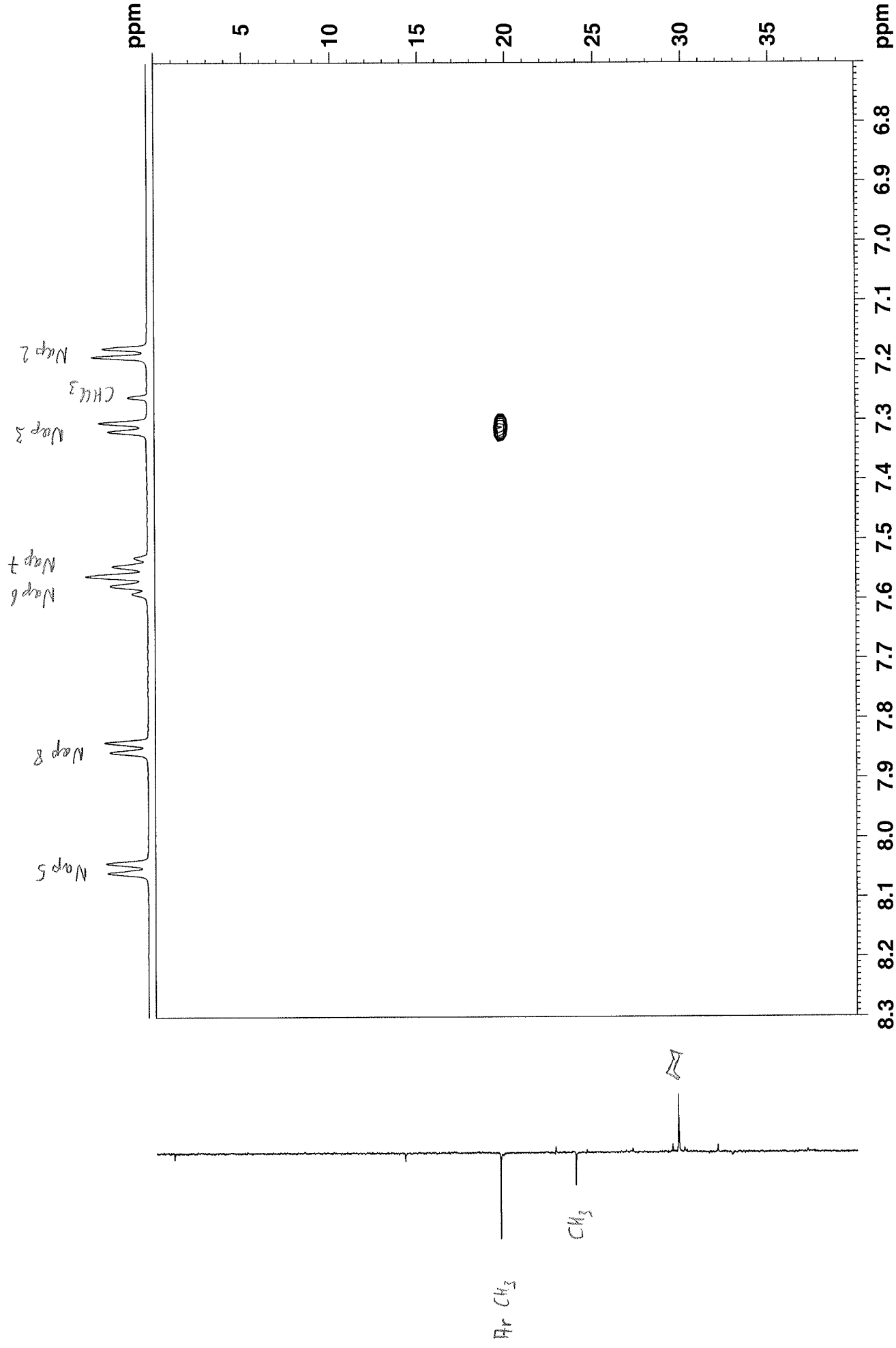
GL052_1 in cdcl3 (HMBC), 25.8.2015

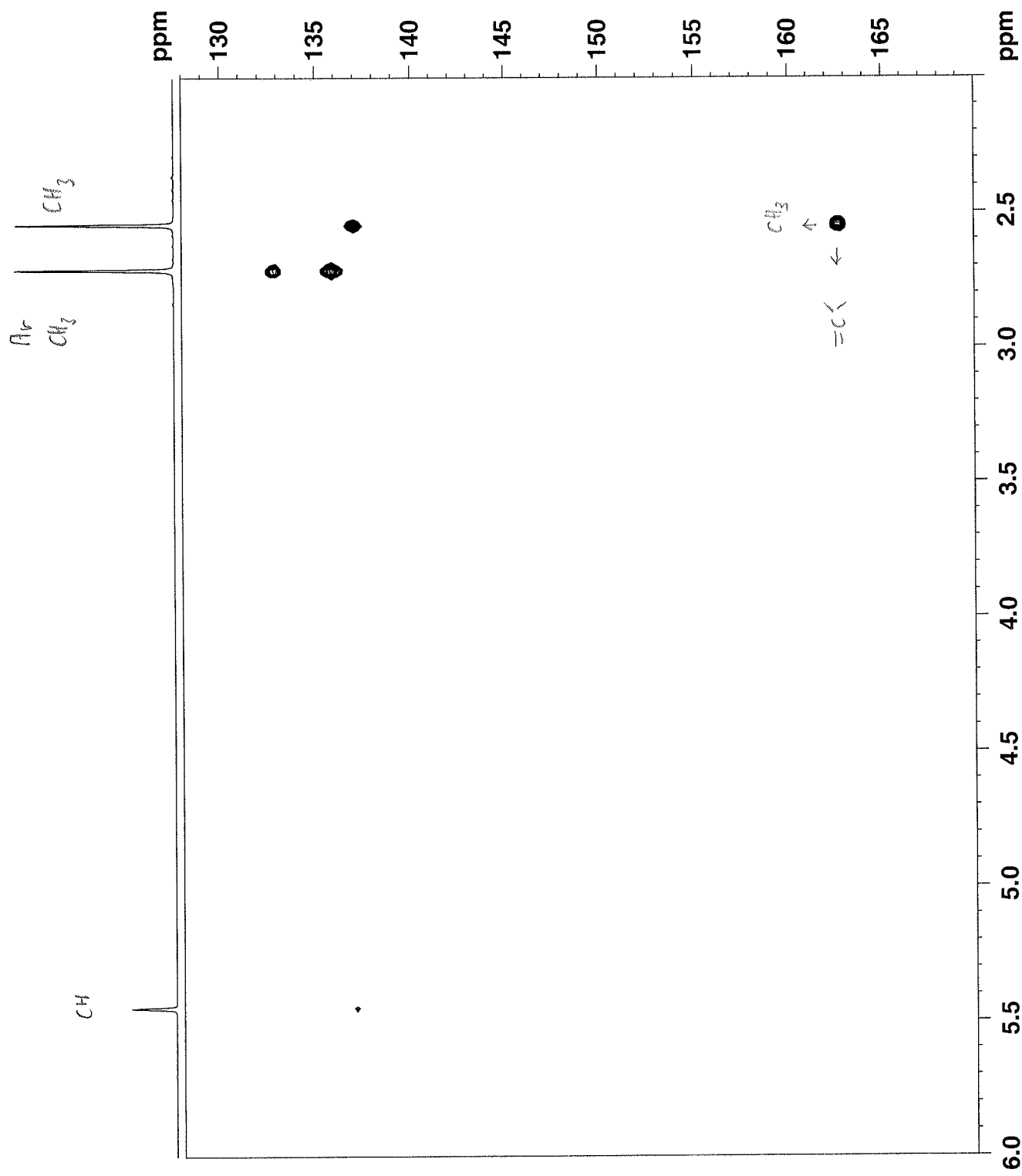


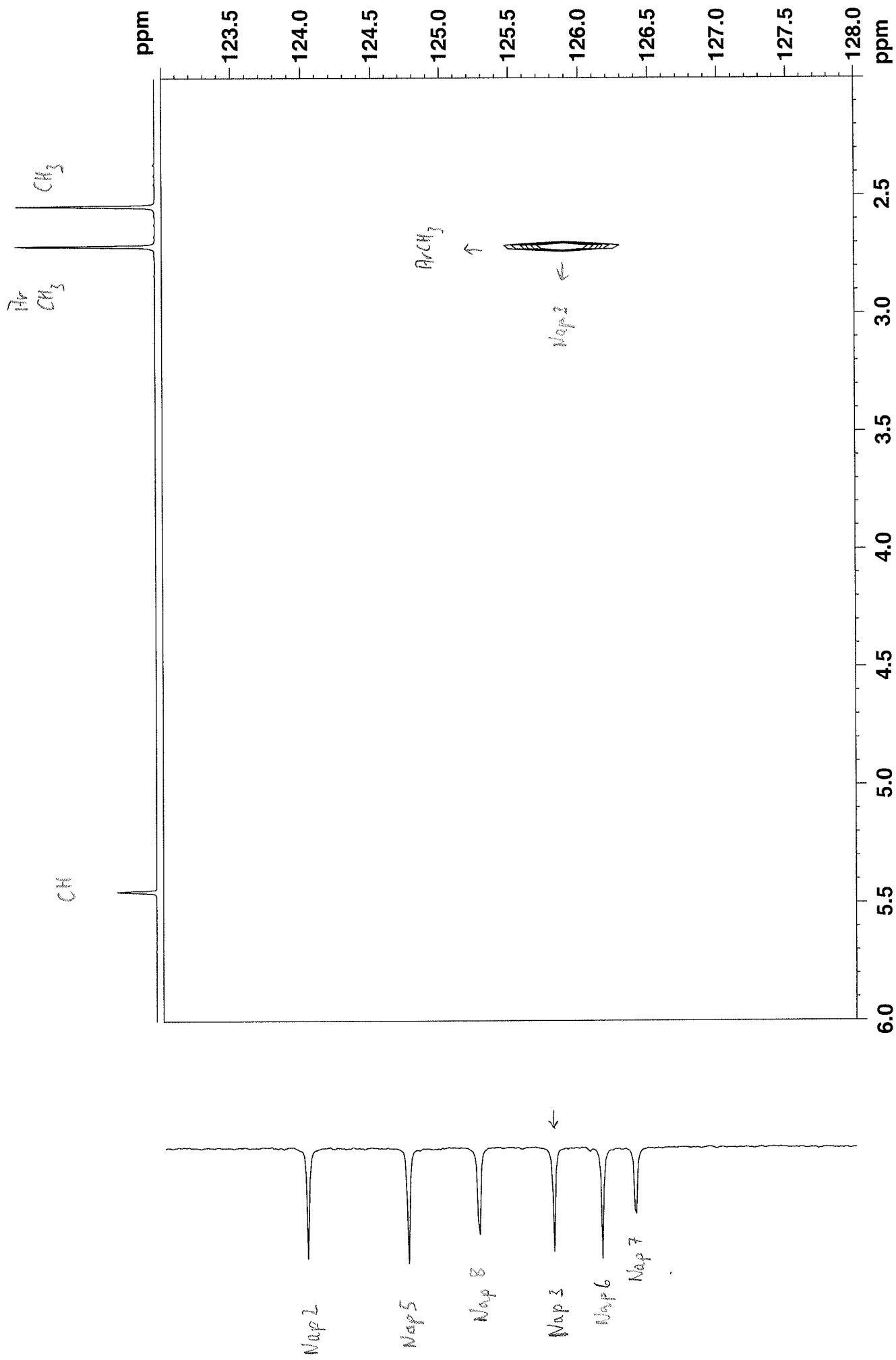




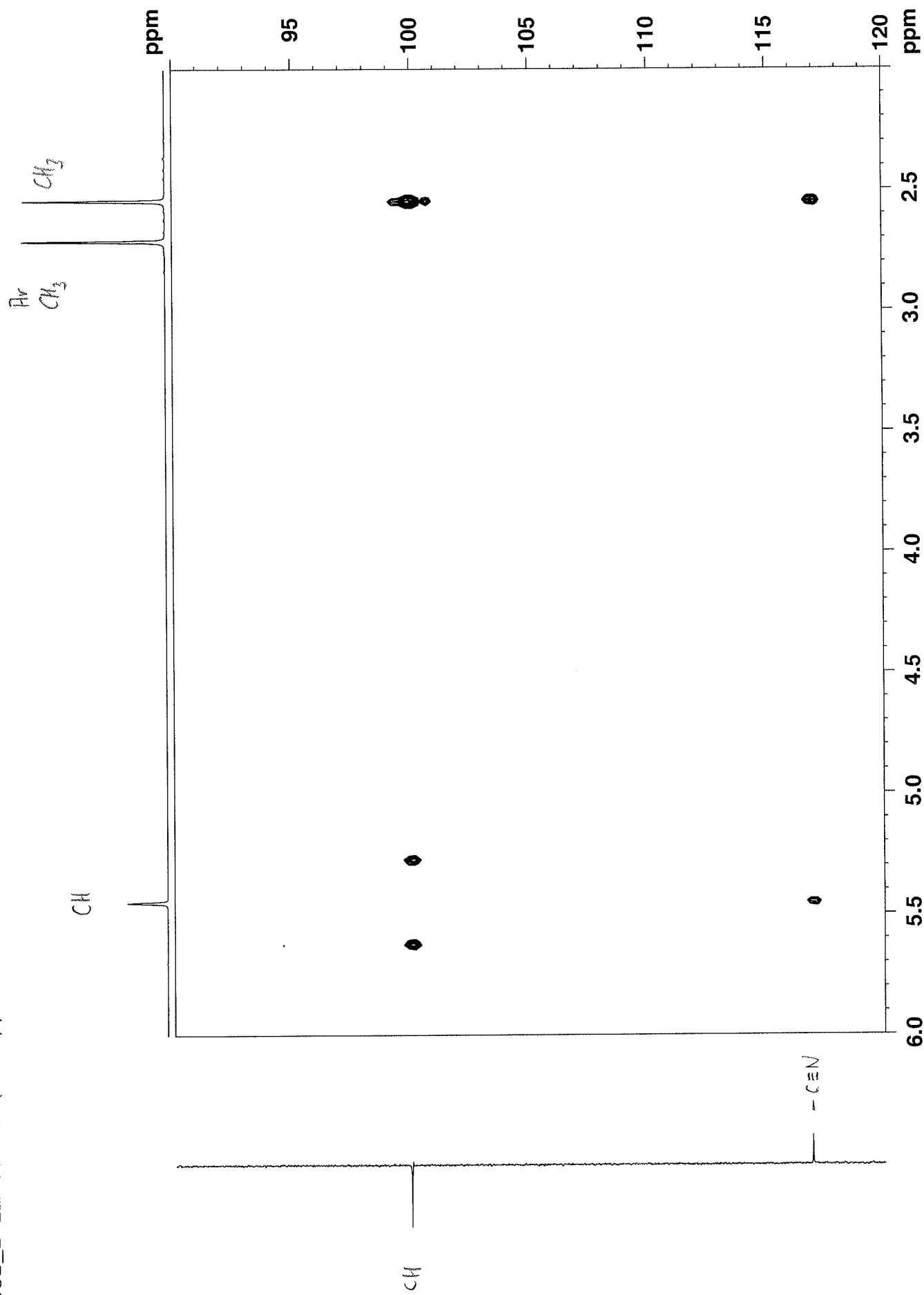
GL052_1 in cdcl3 (HMBC), 25.8.2015



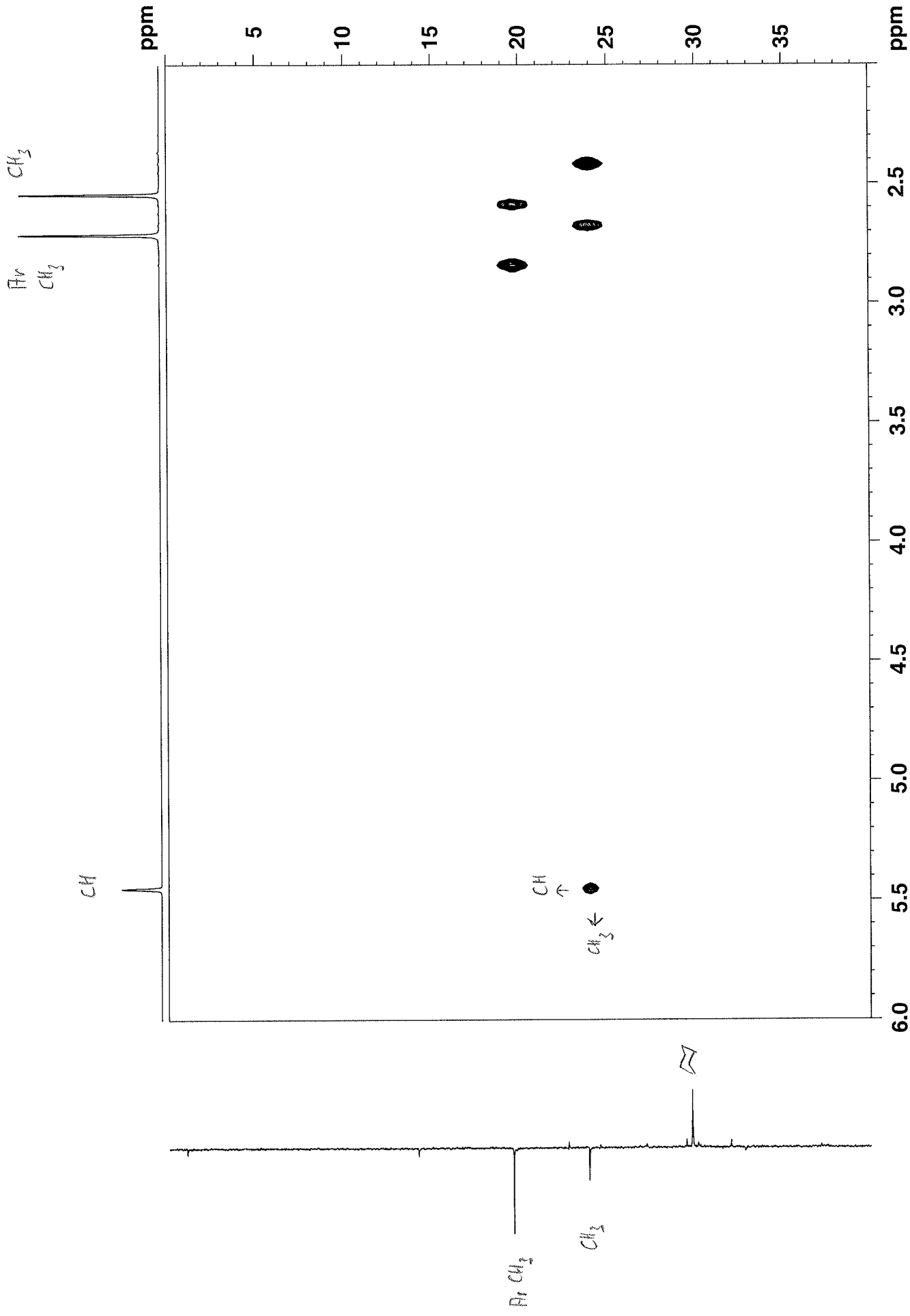




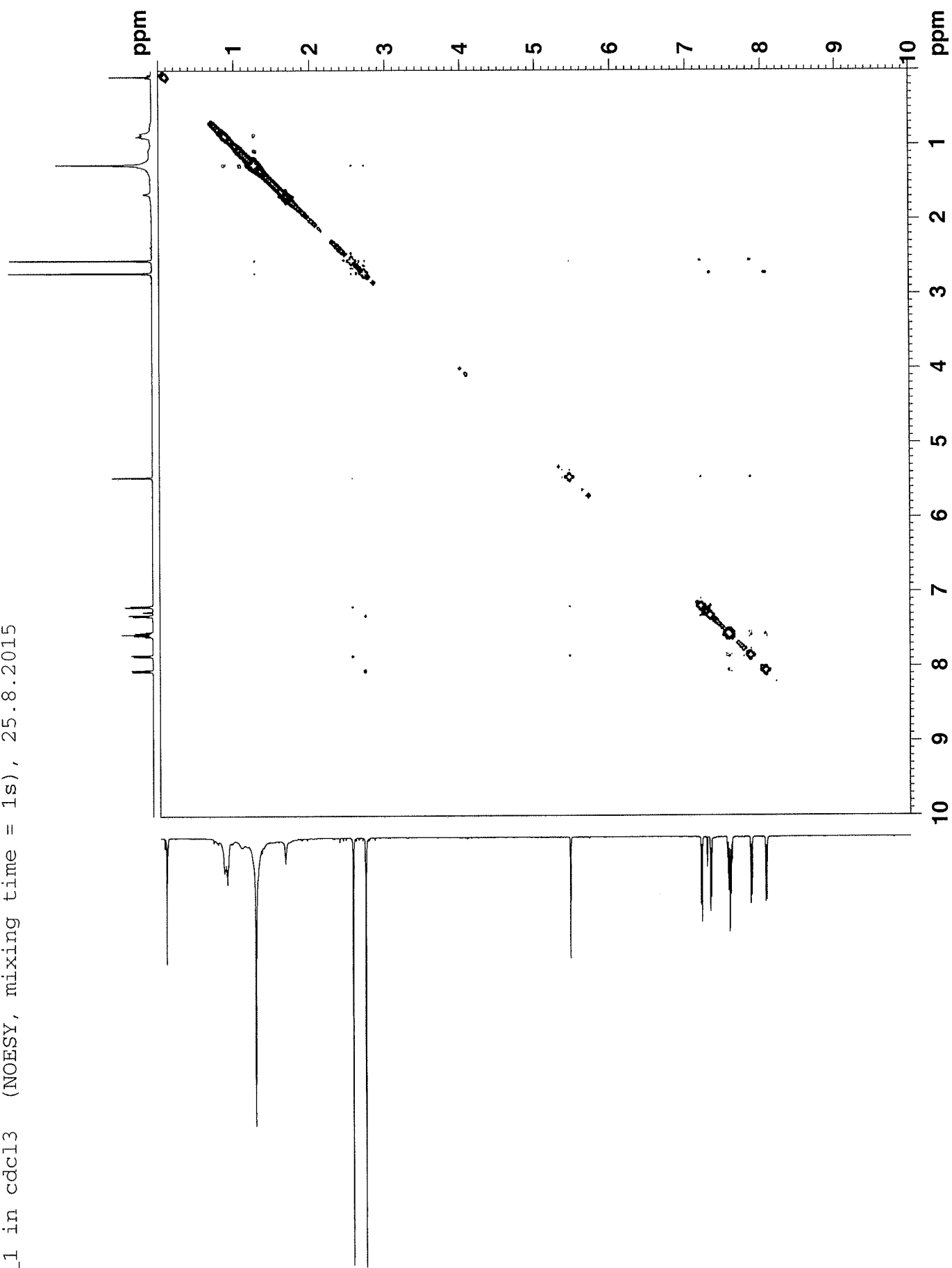
GL052_1 in cdcl3 (HMBC), 25.8.2015



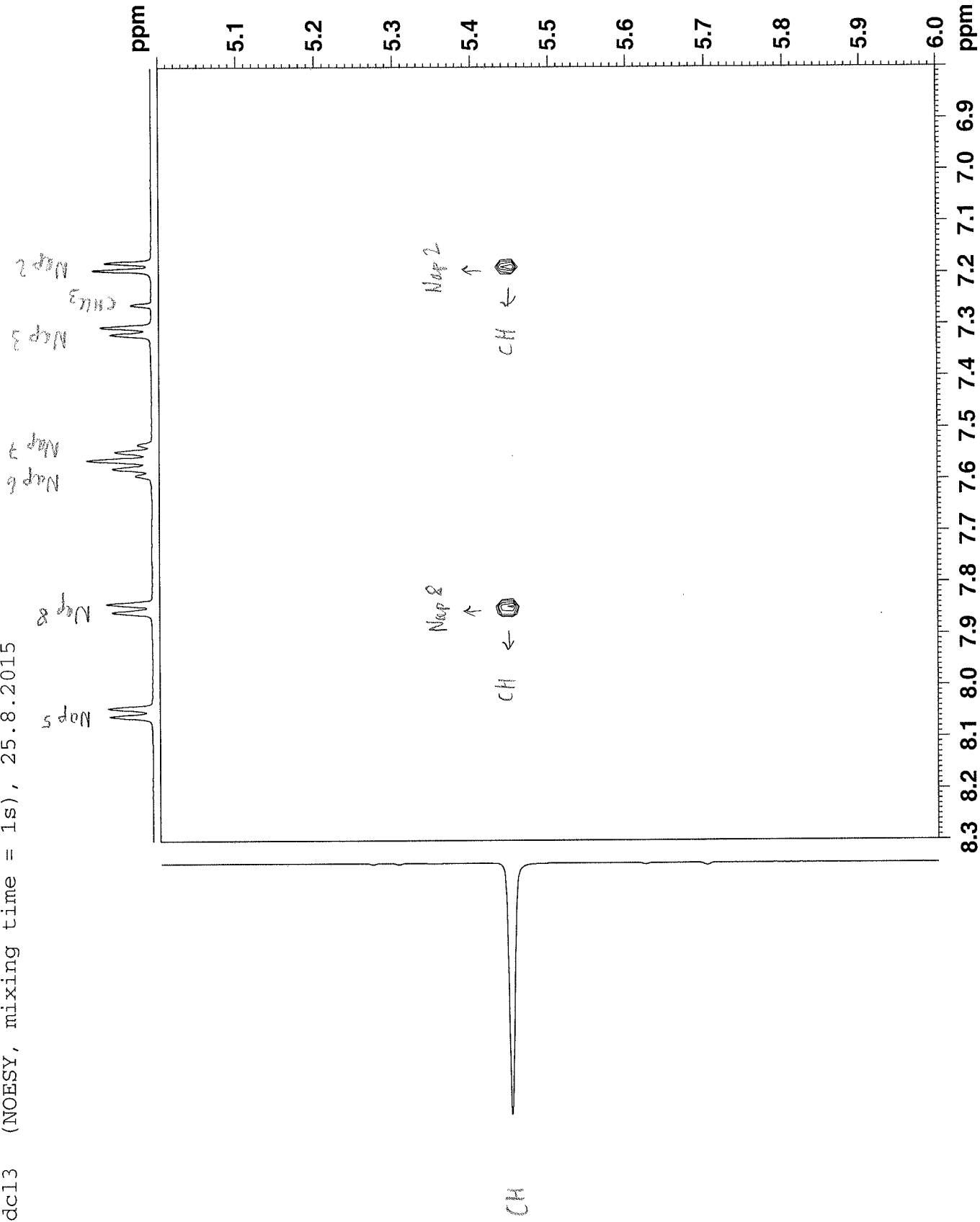
GL052_1 in cdcl3 (HMBC), 25.8.2015



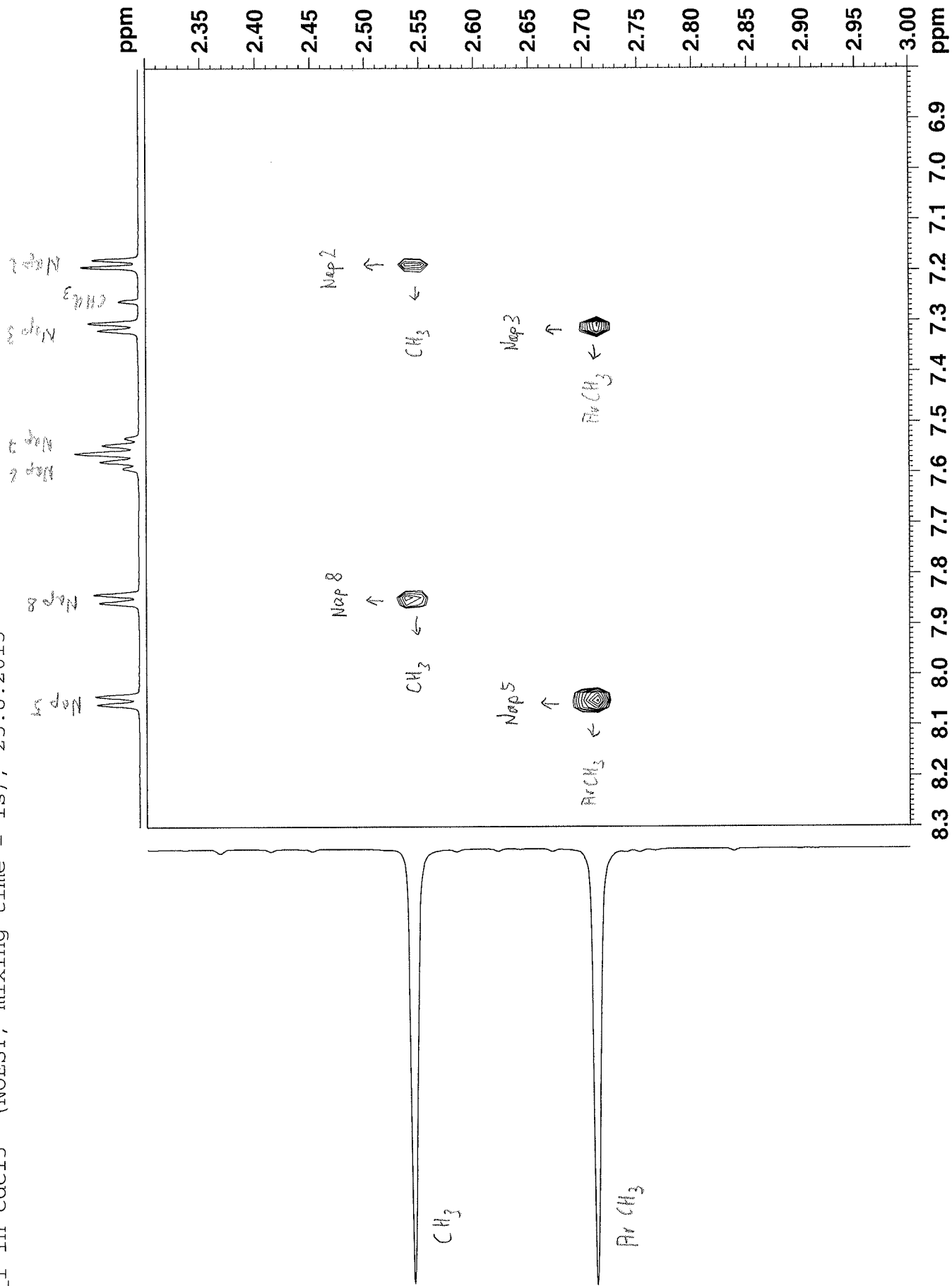
GL052_1 in cdcl3 (NOESY, mixing time = 1s), 25.8.2015

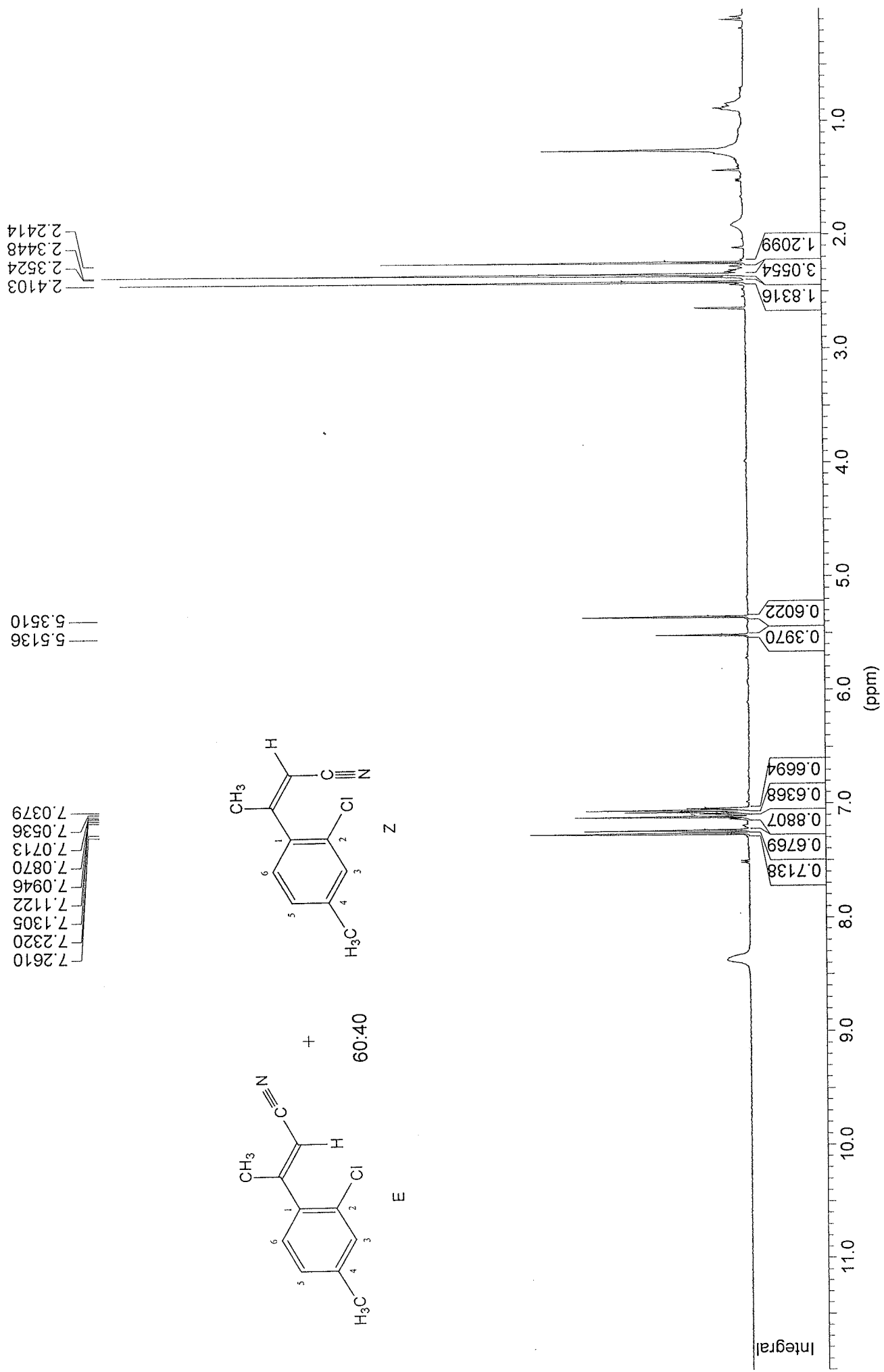


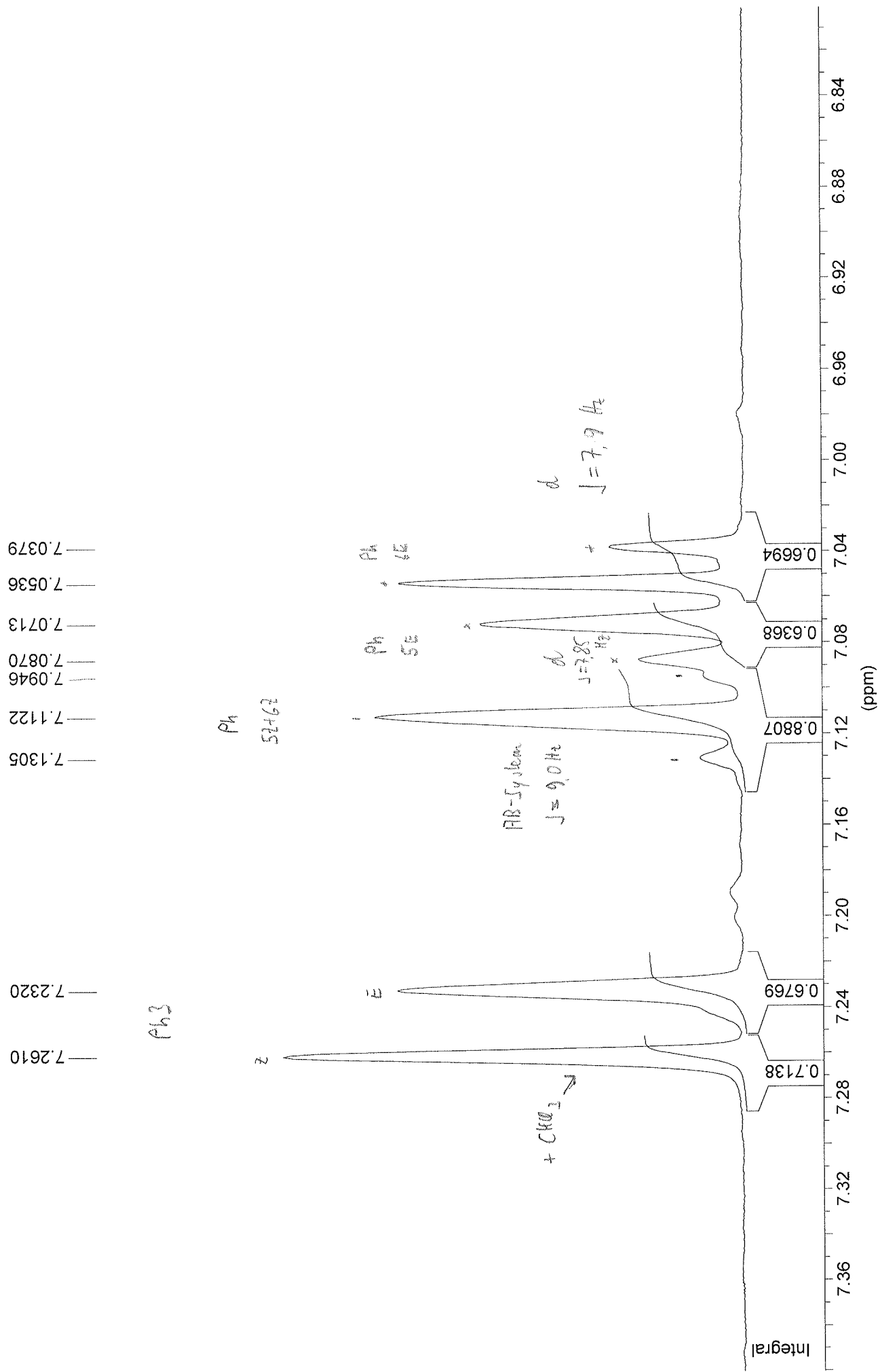
GL052_1 in cdcl3 (NOESY, mixing time = 1s), 25.8.2015

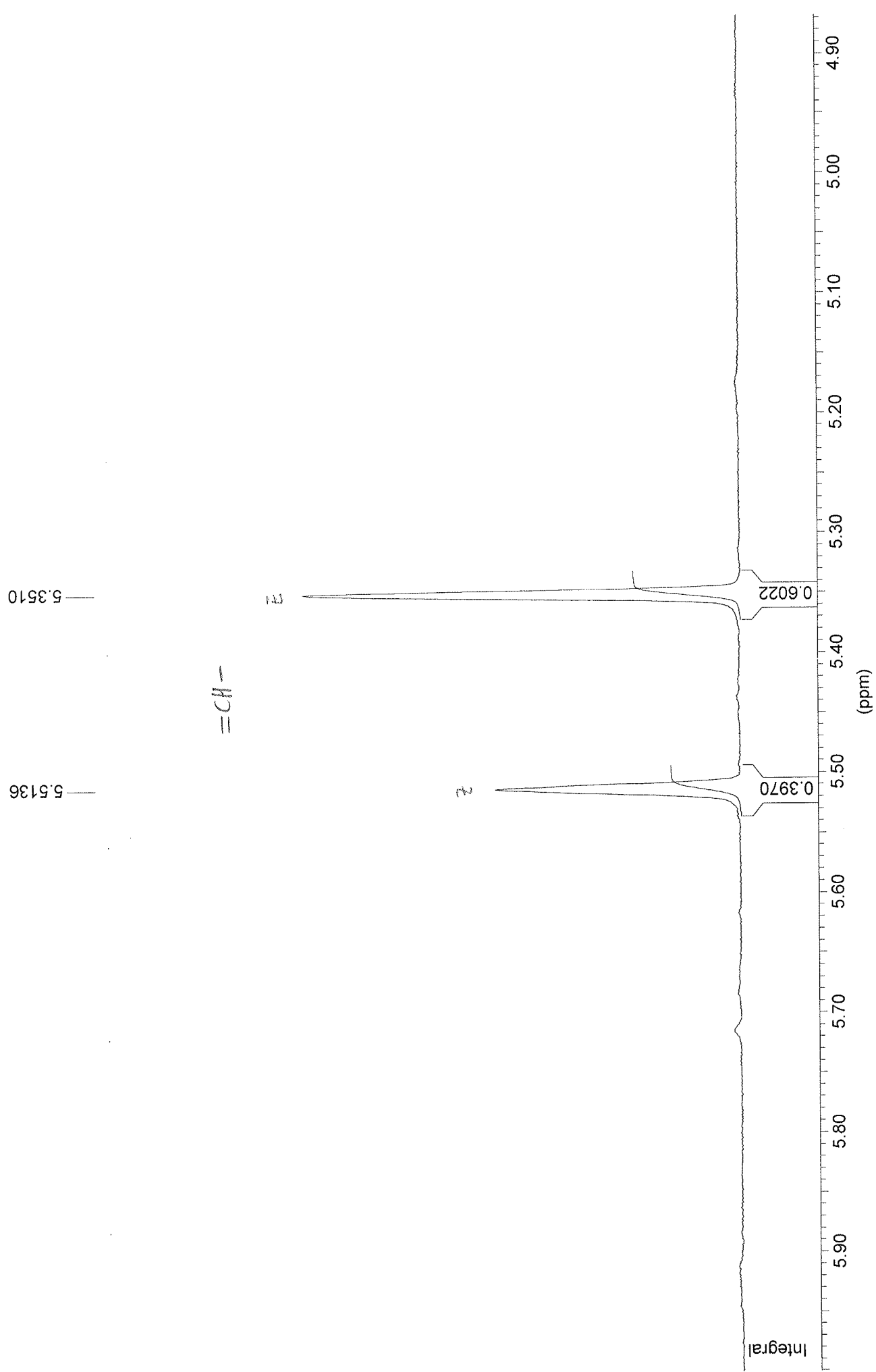


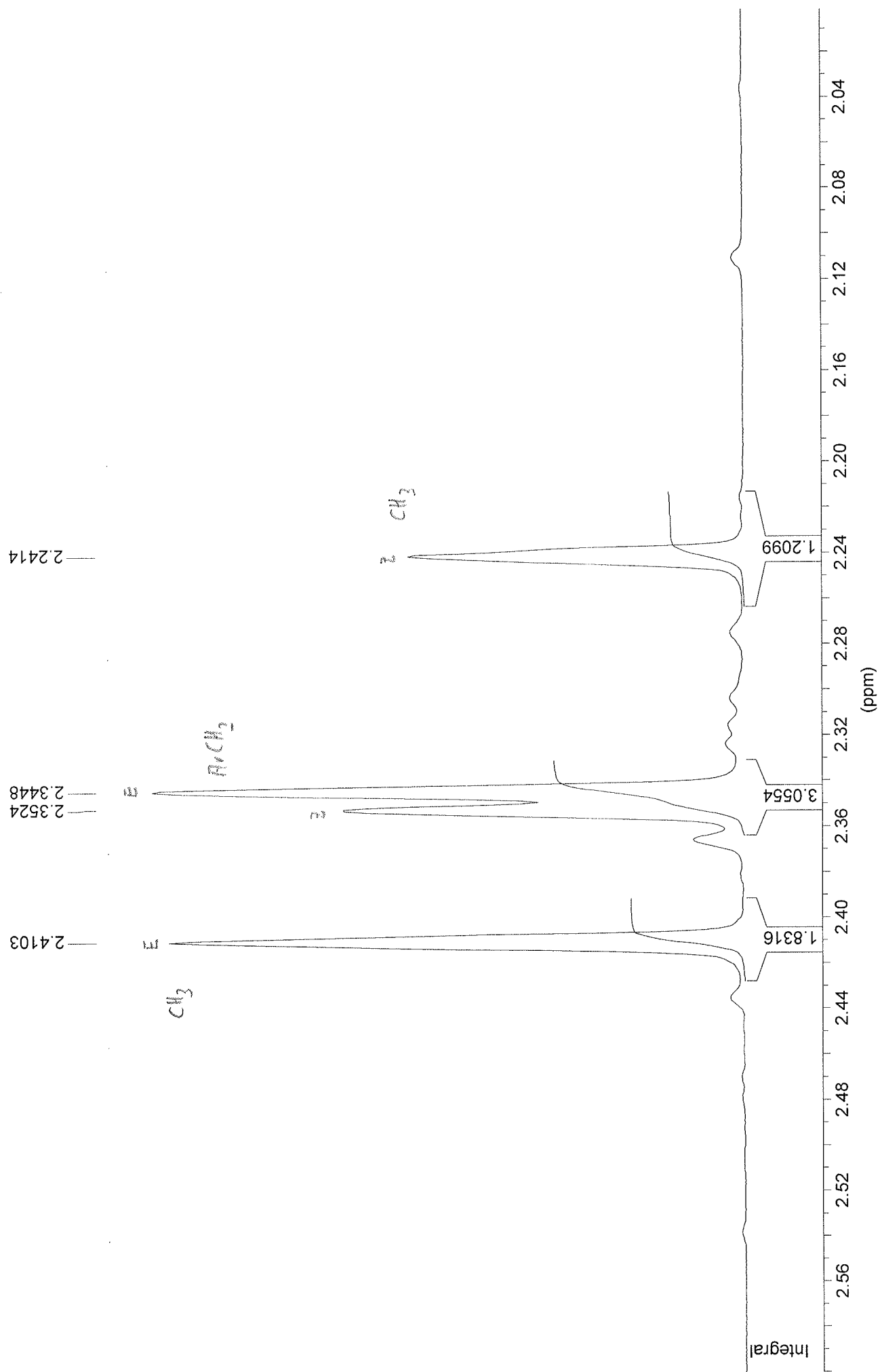
GL052_1 in cdcl3 (NOESY, mixing time = 1s), 25.8.2015

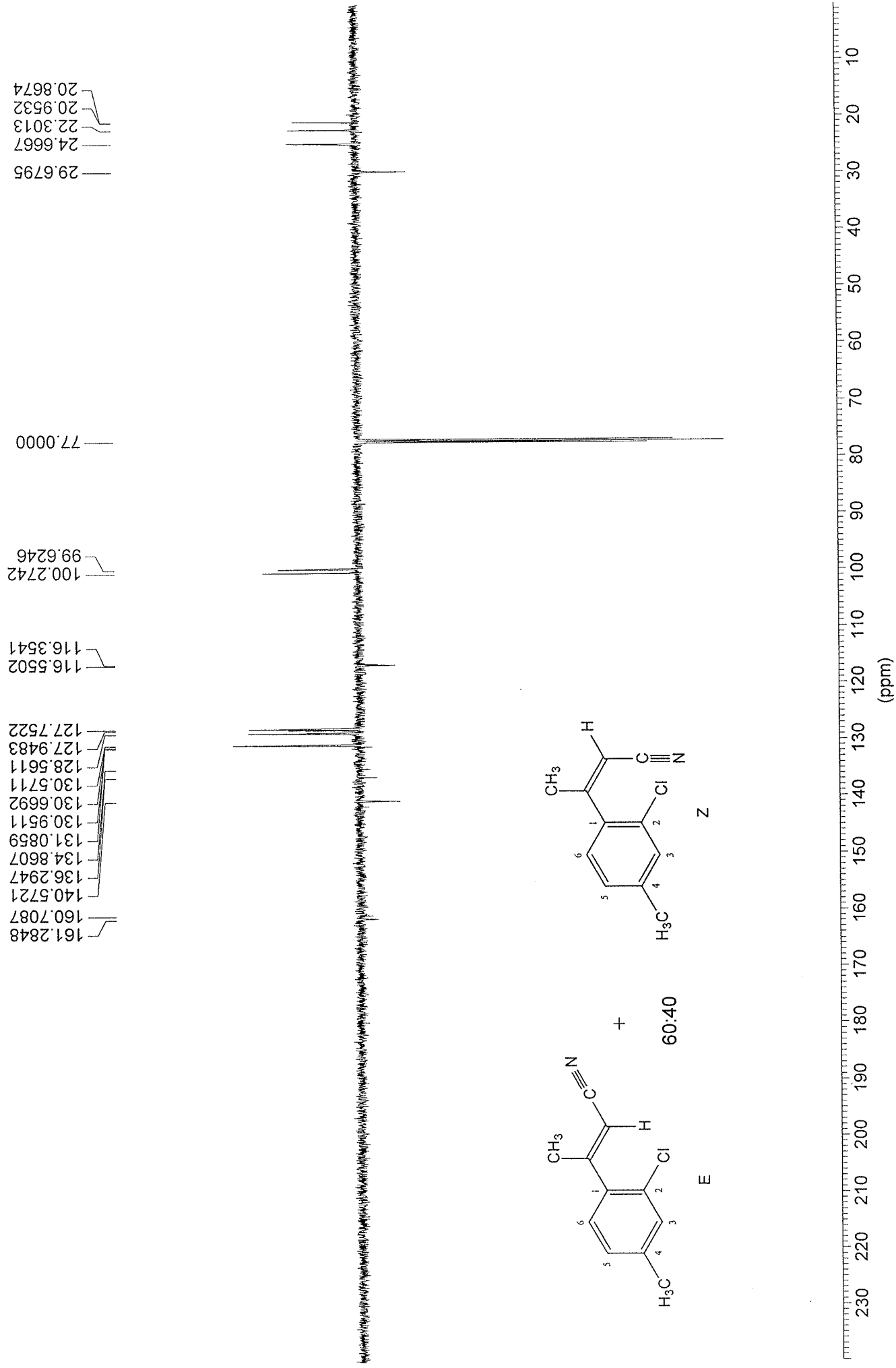




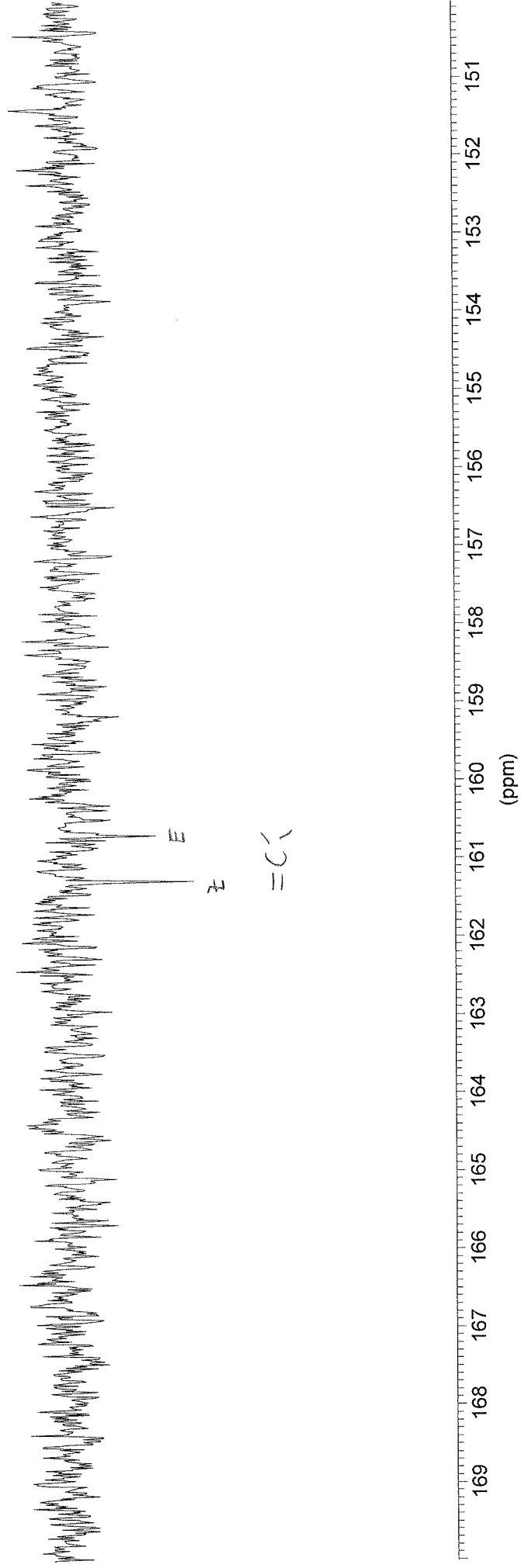


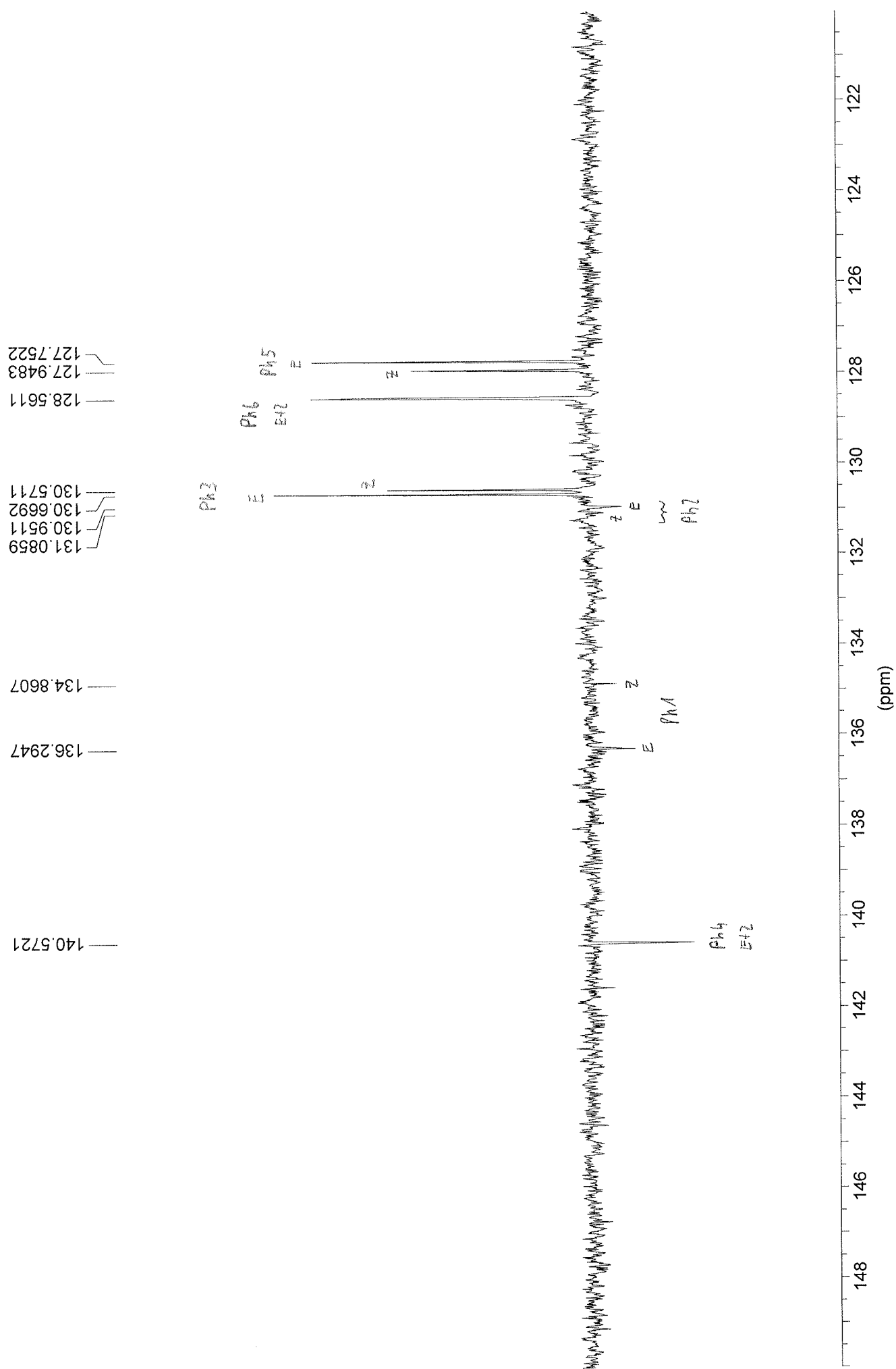






— 161.2848
— 160.7087





116.5502
116.3541

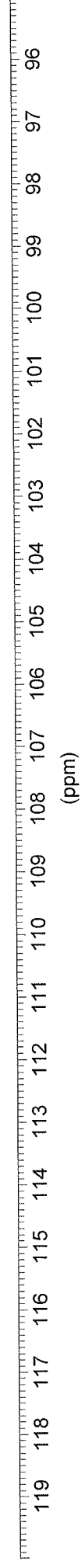
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99.6246

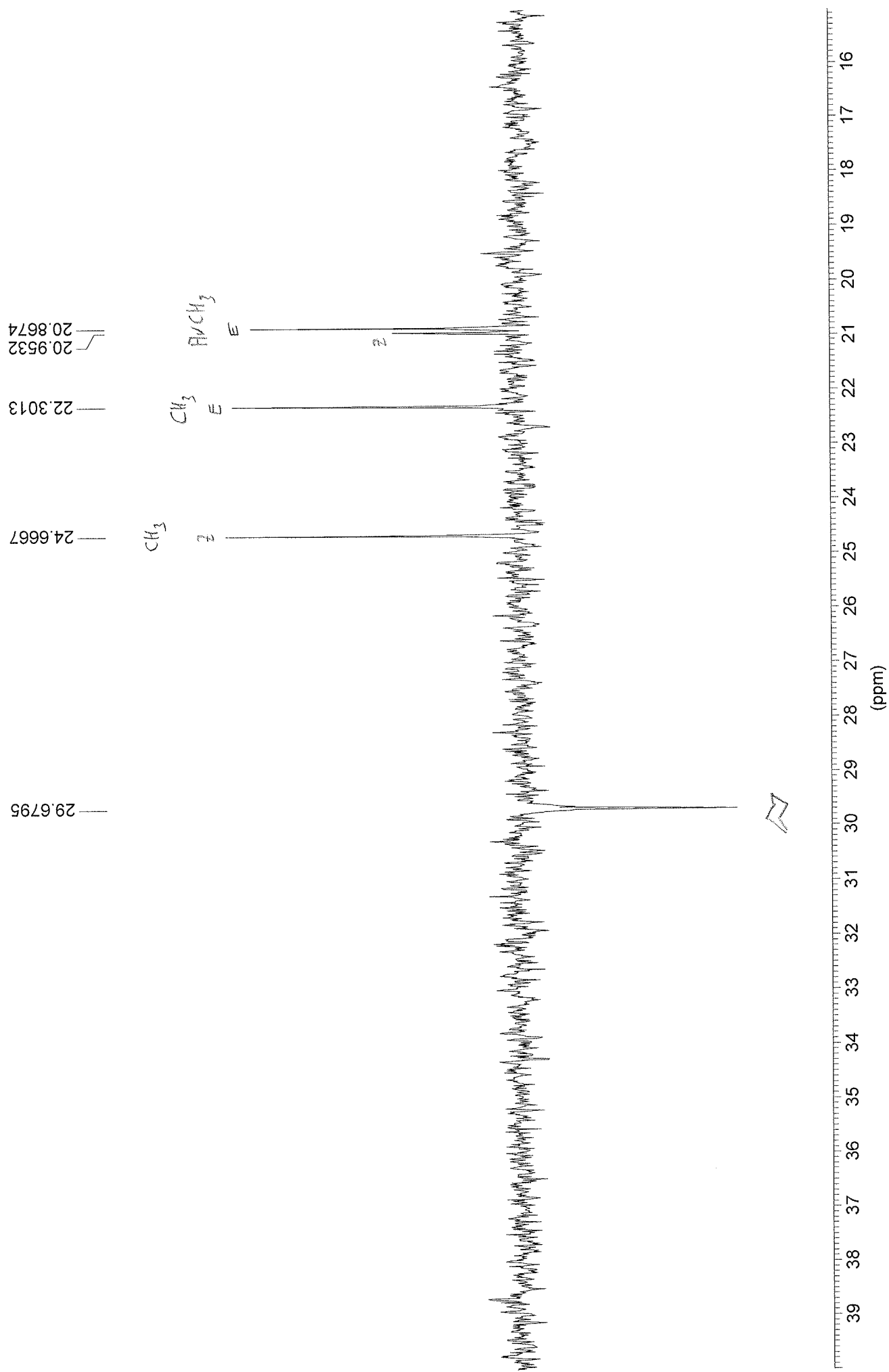
$\equiv CH$

$\equiv$

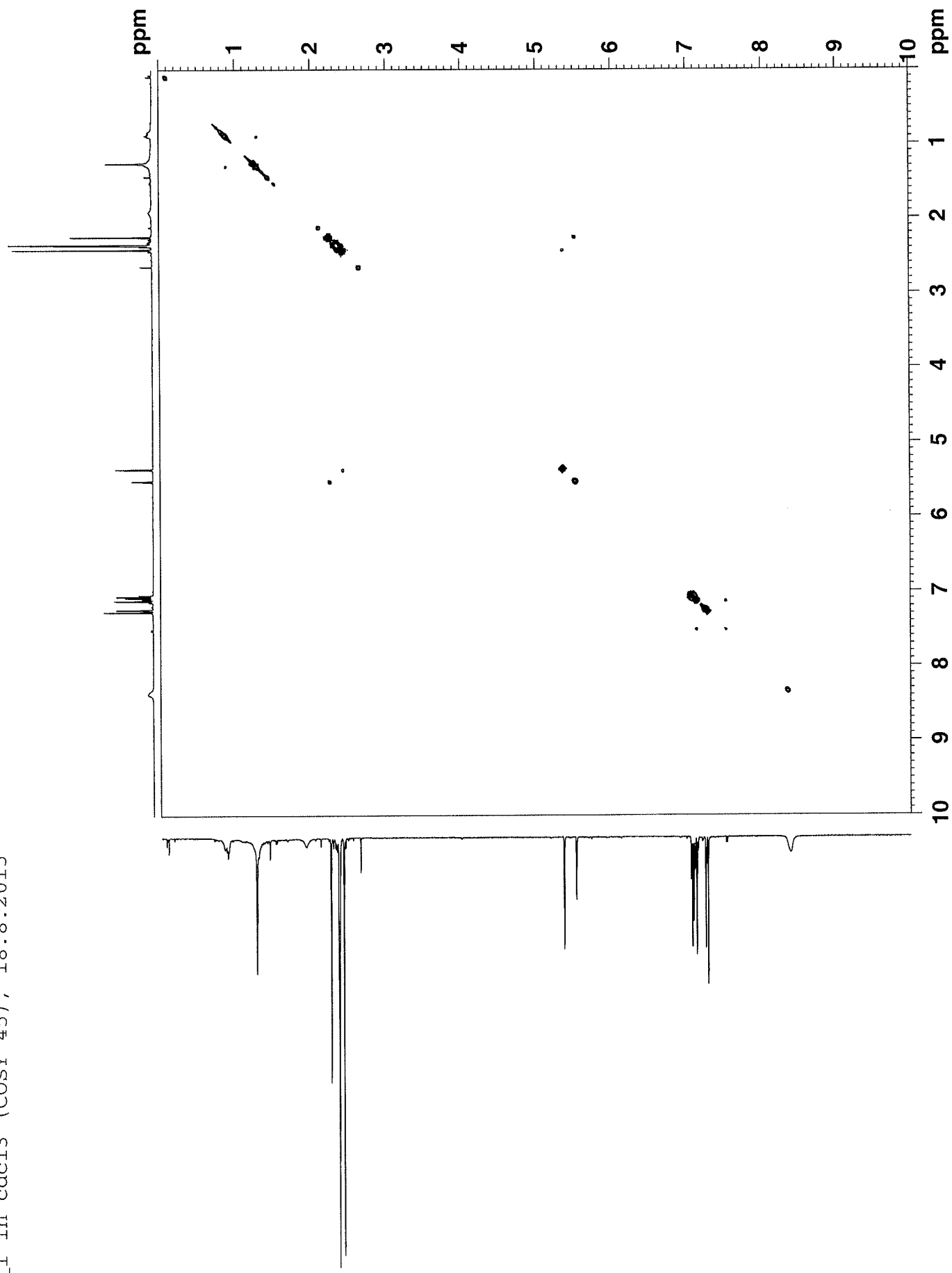
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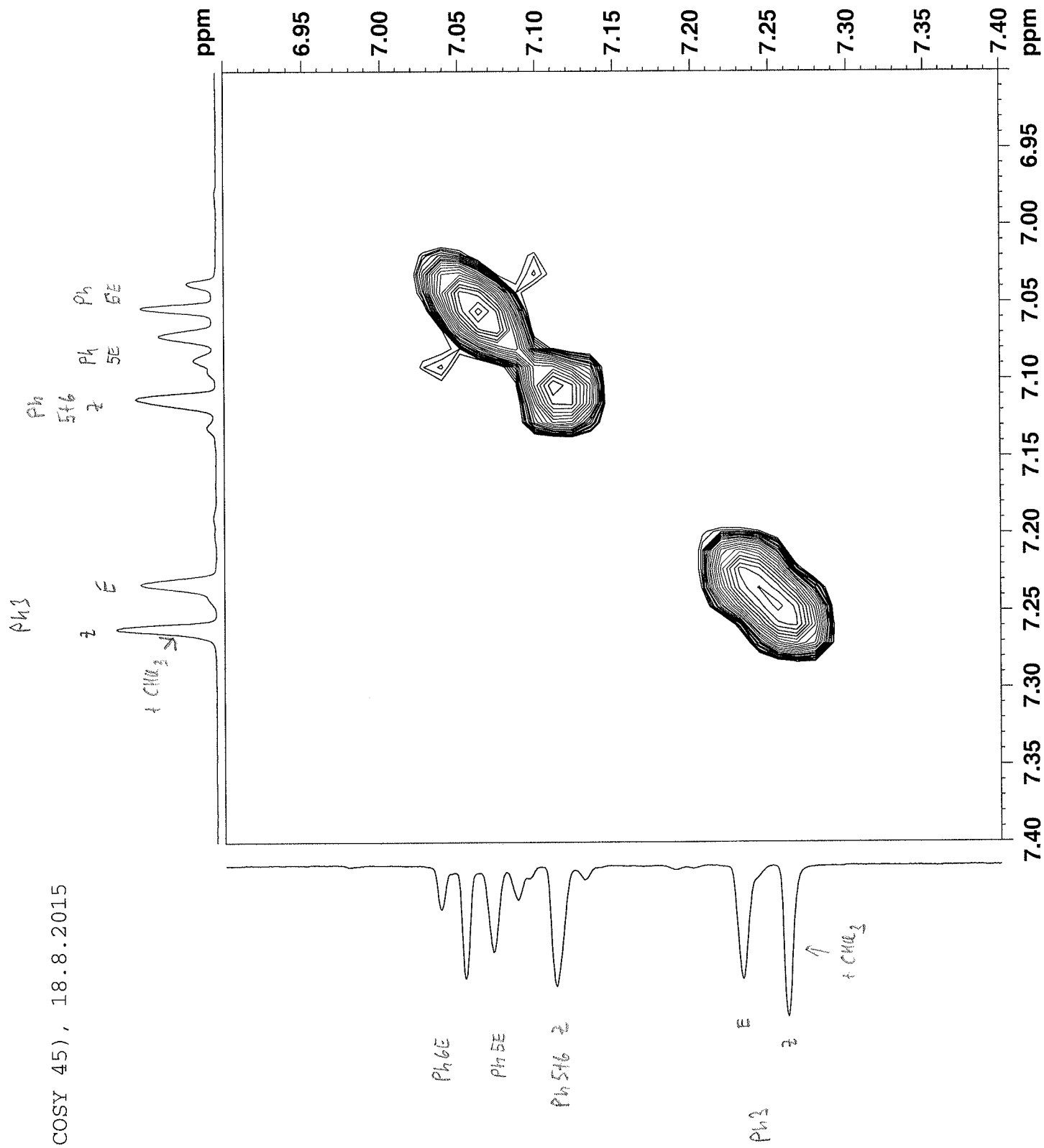
$\equiv C-N$

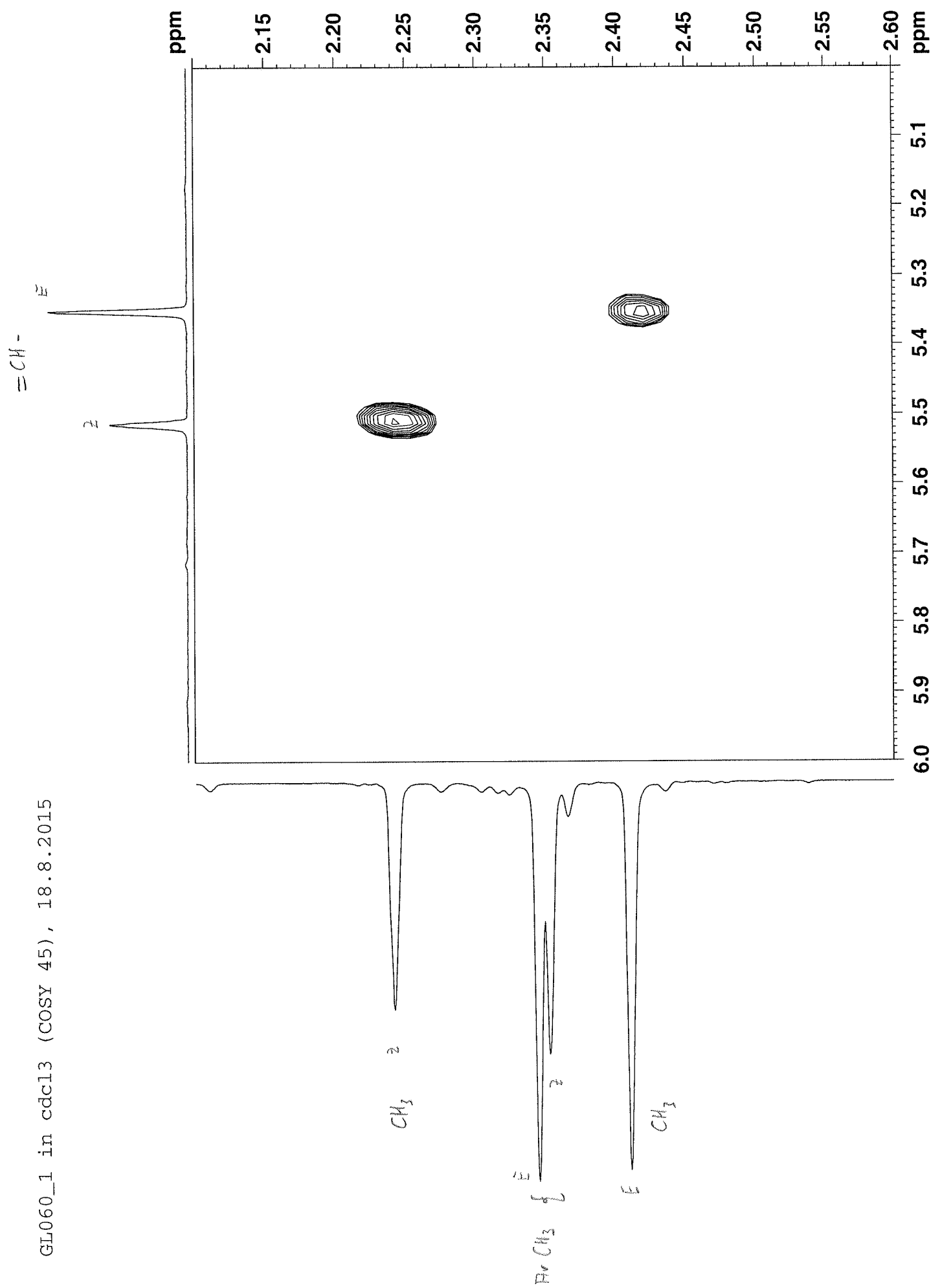




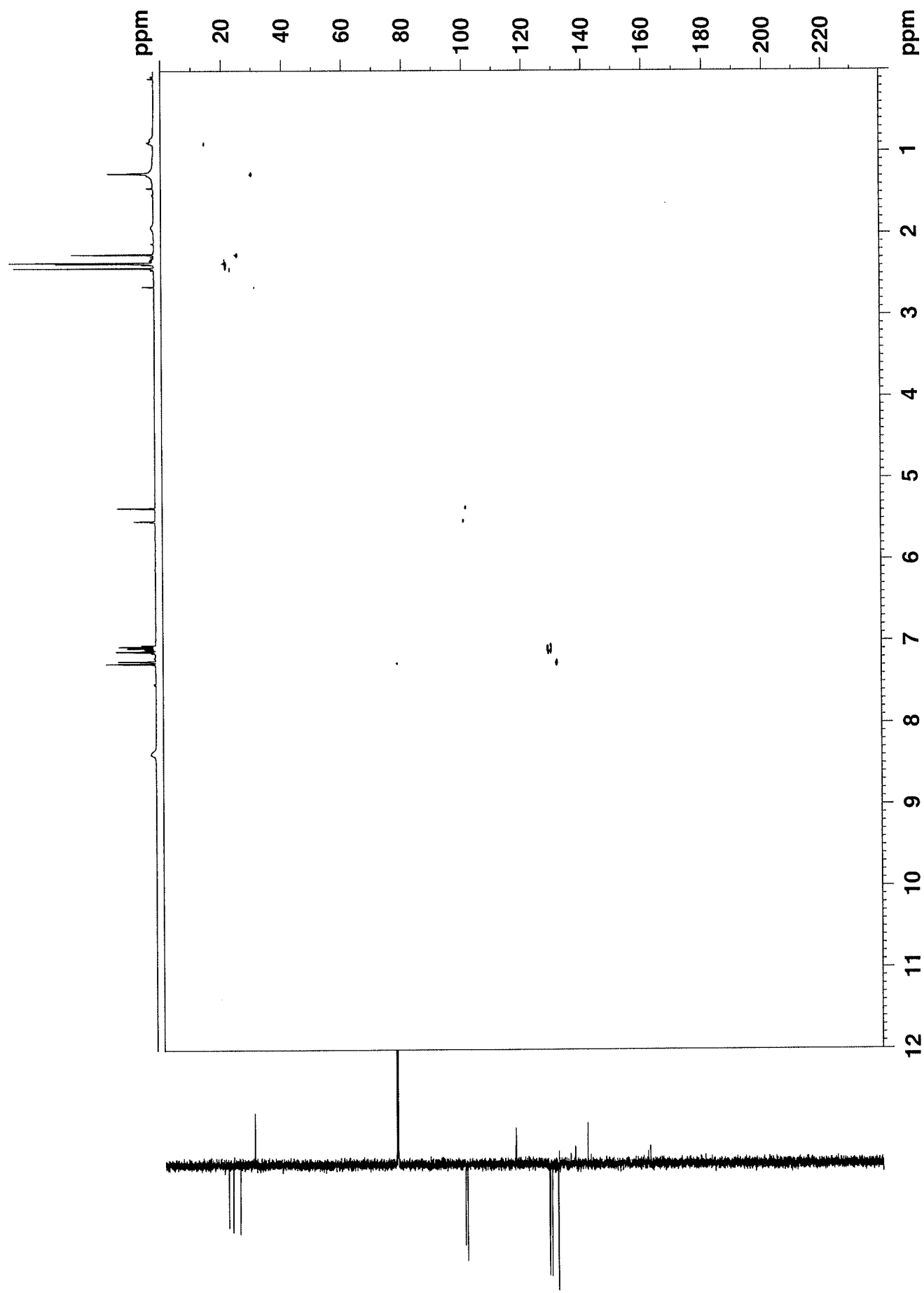
GL060_1 in cdcl3 (COSY 45), 18.8.2015







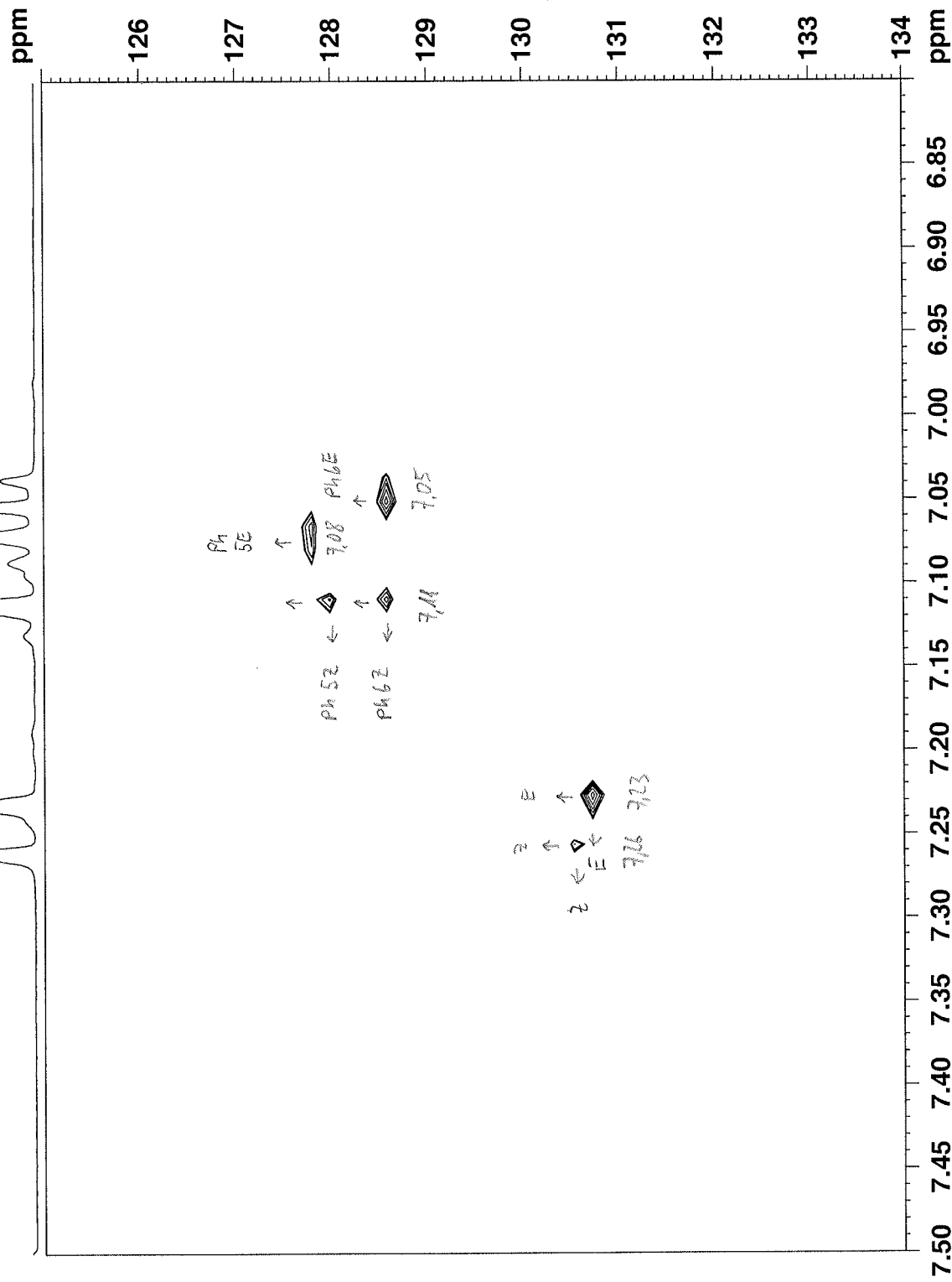
GL060_1 in cdcl3 (HSQC neu), 18.8.2015



Ph
5+6
Ph 5
Ph 6
E
E

z E

CHCl₃

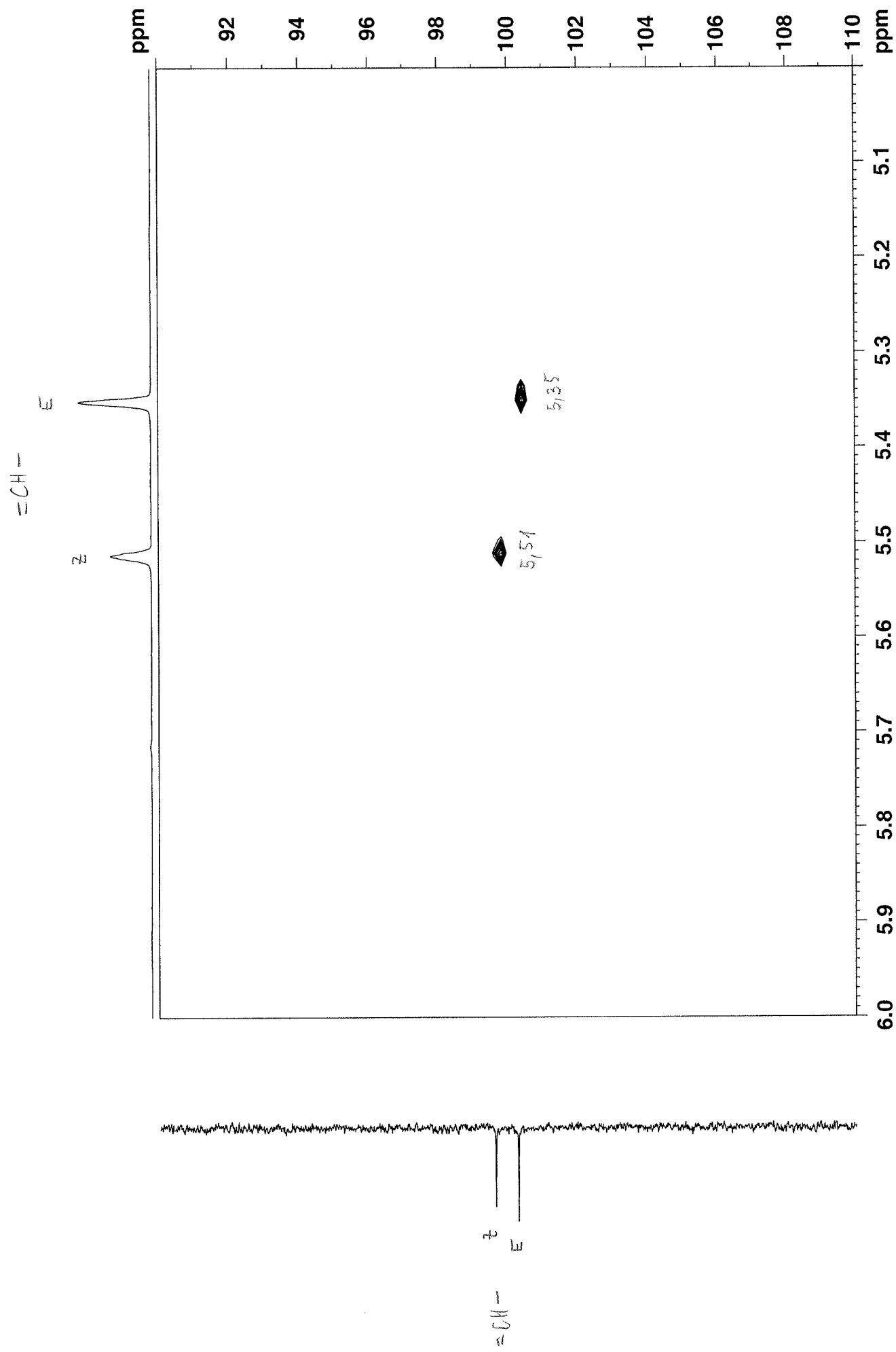


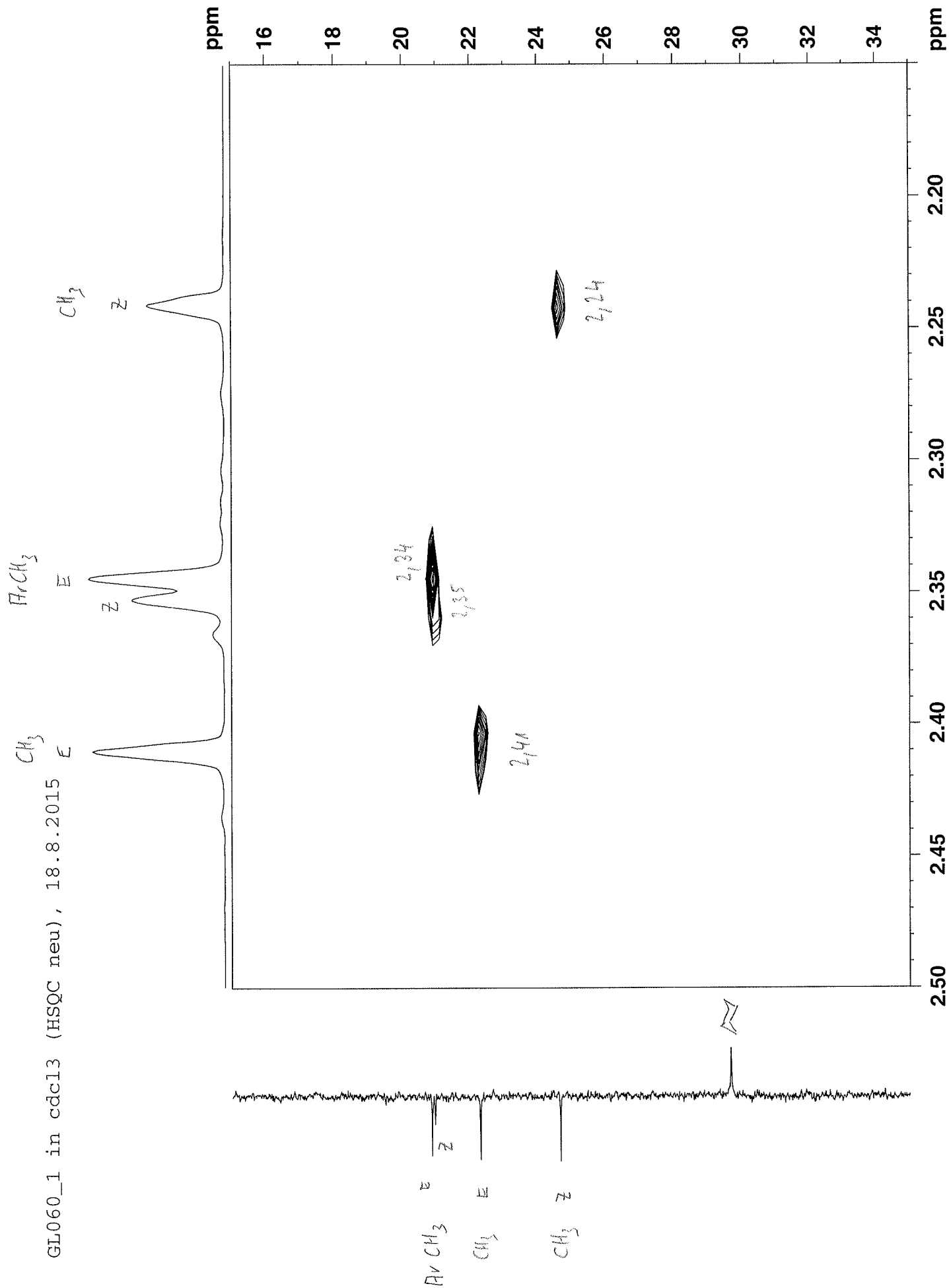
Ph5

Ph6

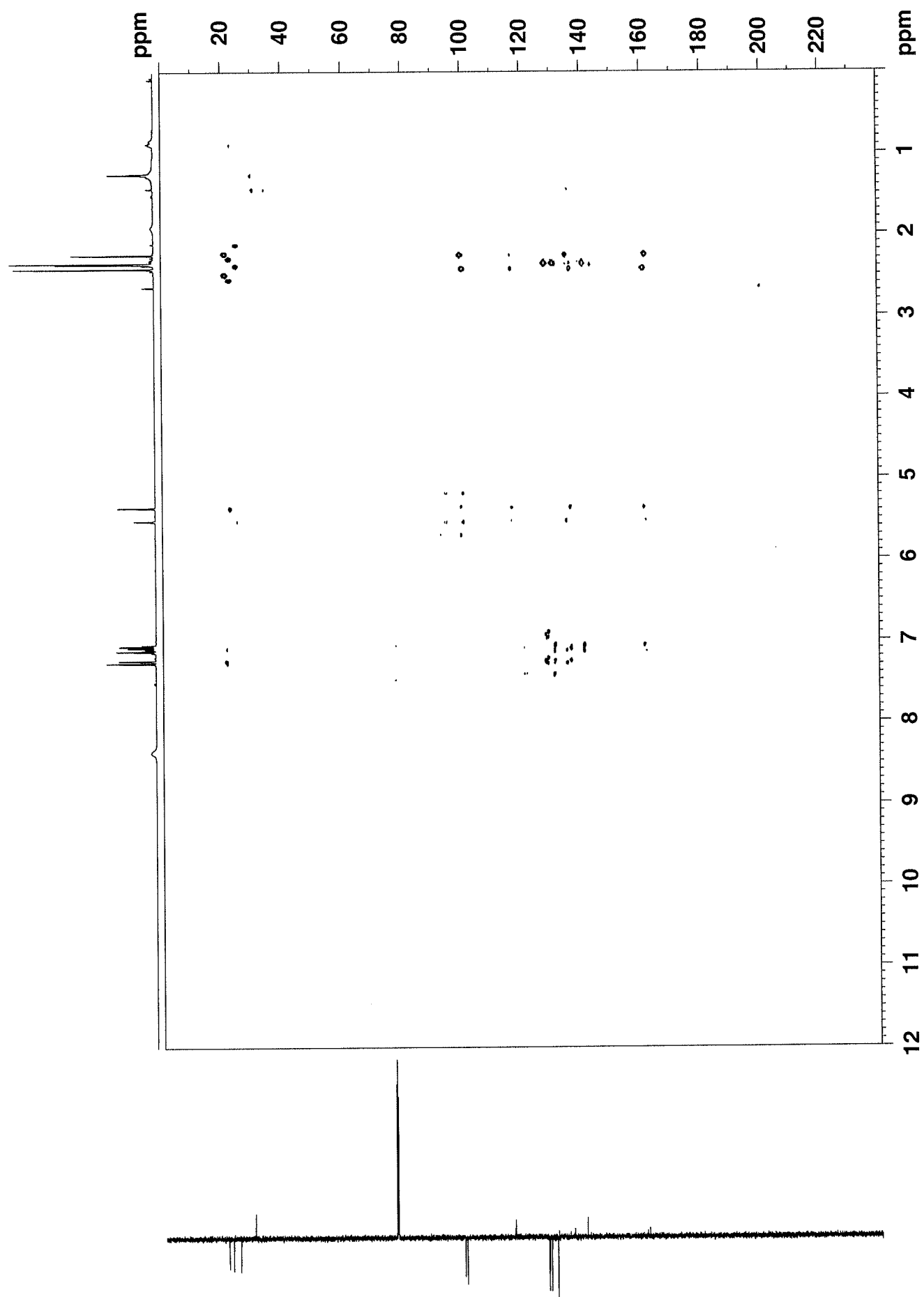
Ph3

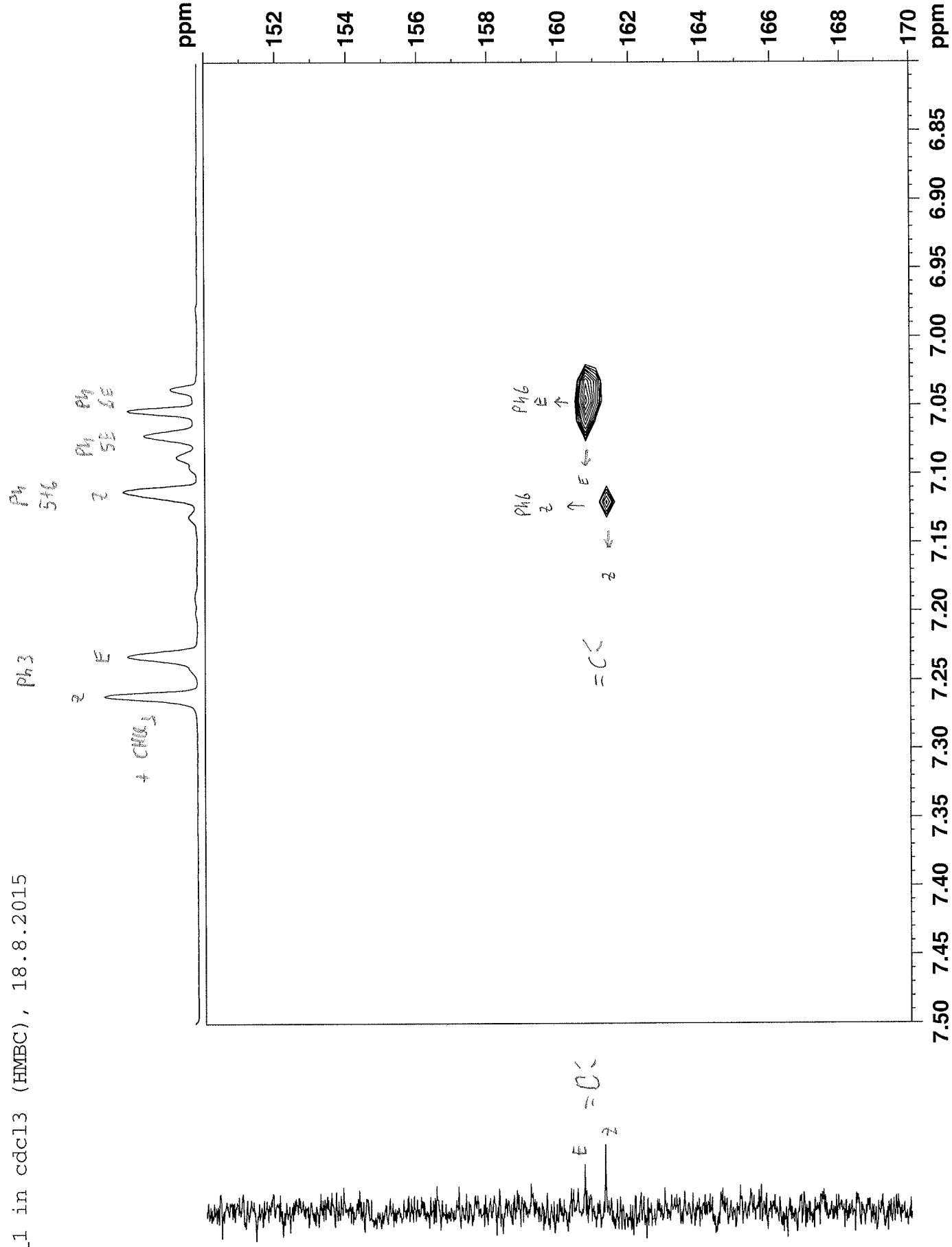
GL060_1 in cdcl3 (HSQC neu), 18.8.2015



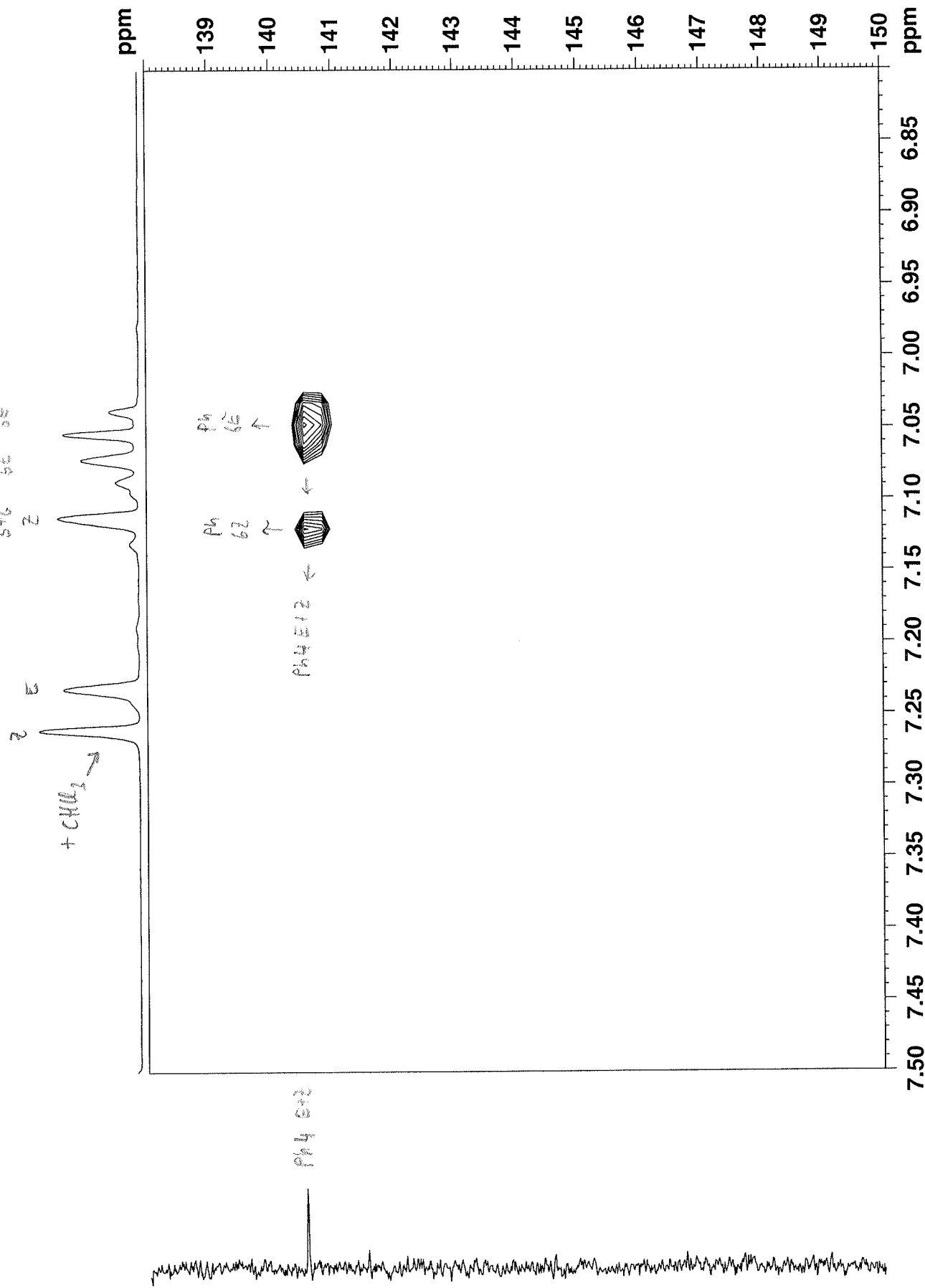


GL060_1 in cdcl3 (HMBC), 18.8.2015

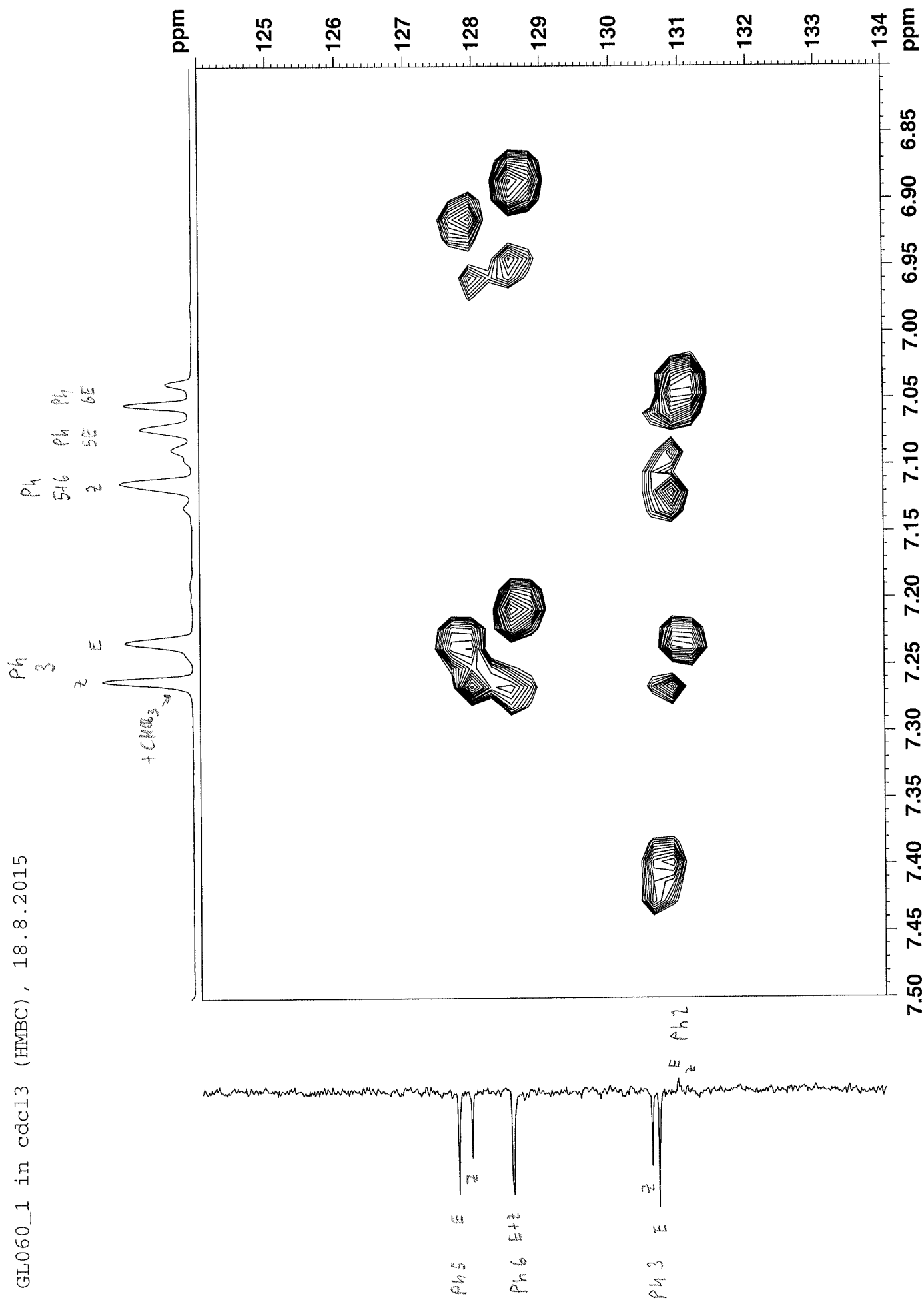


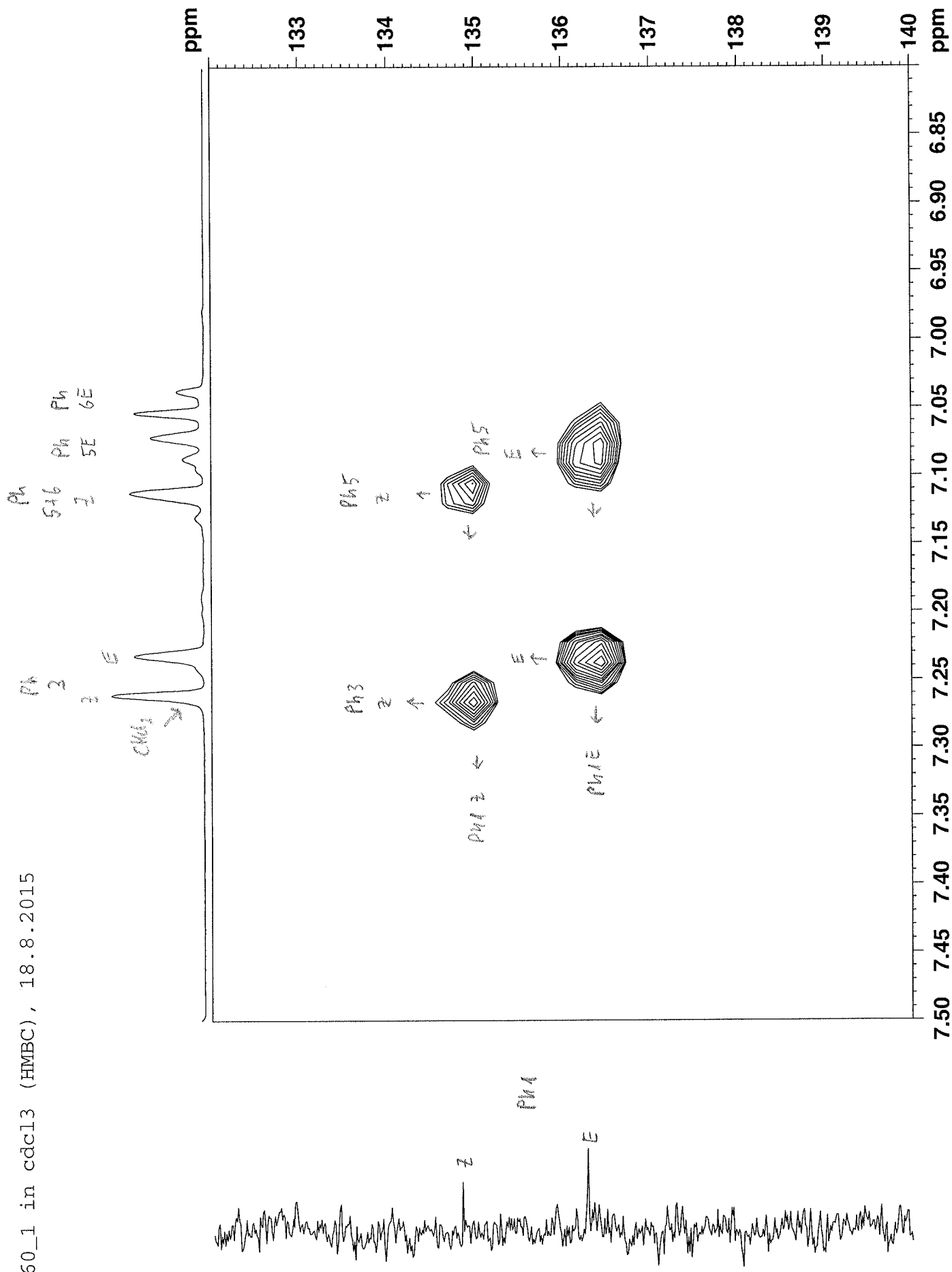


AS 3

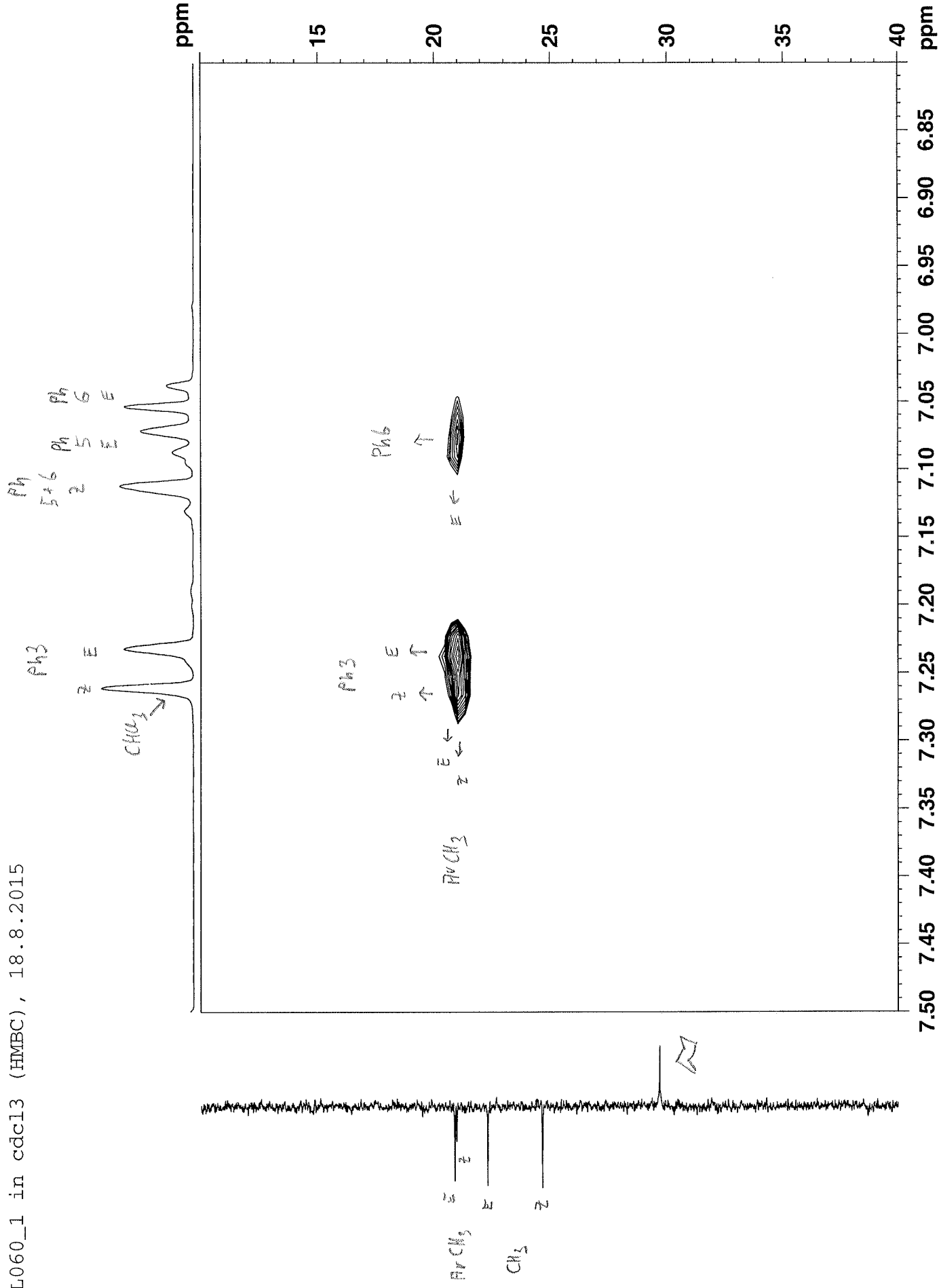


GL060_1 in cdc13 (HMBC), 18.8.2015





GL060_1 in cdcl3 (HMBC), 18.8.2015



GL060_1 in cdcl3 (HMBC), 18.8.2015

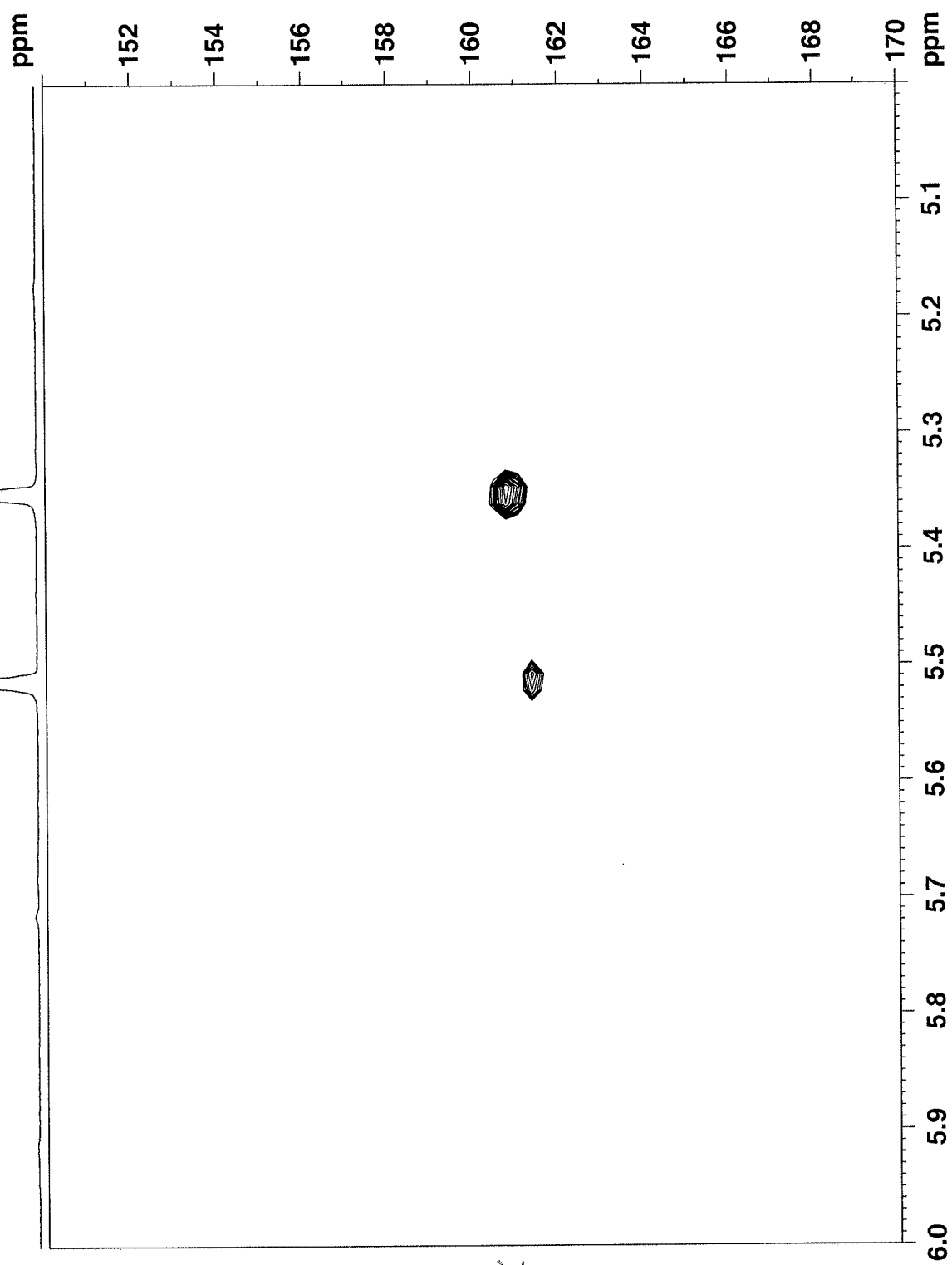
=CH-

z

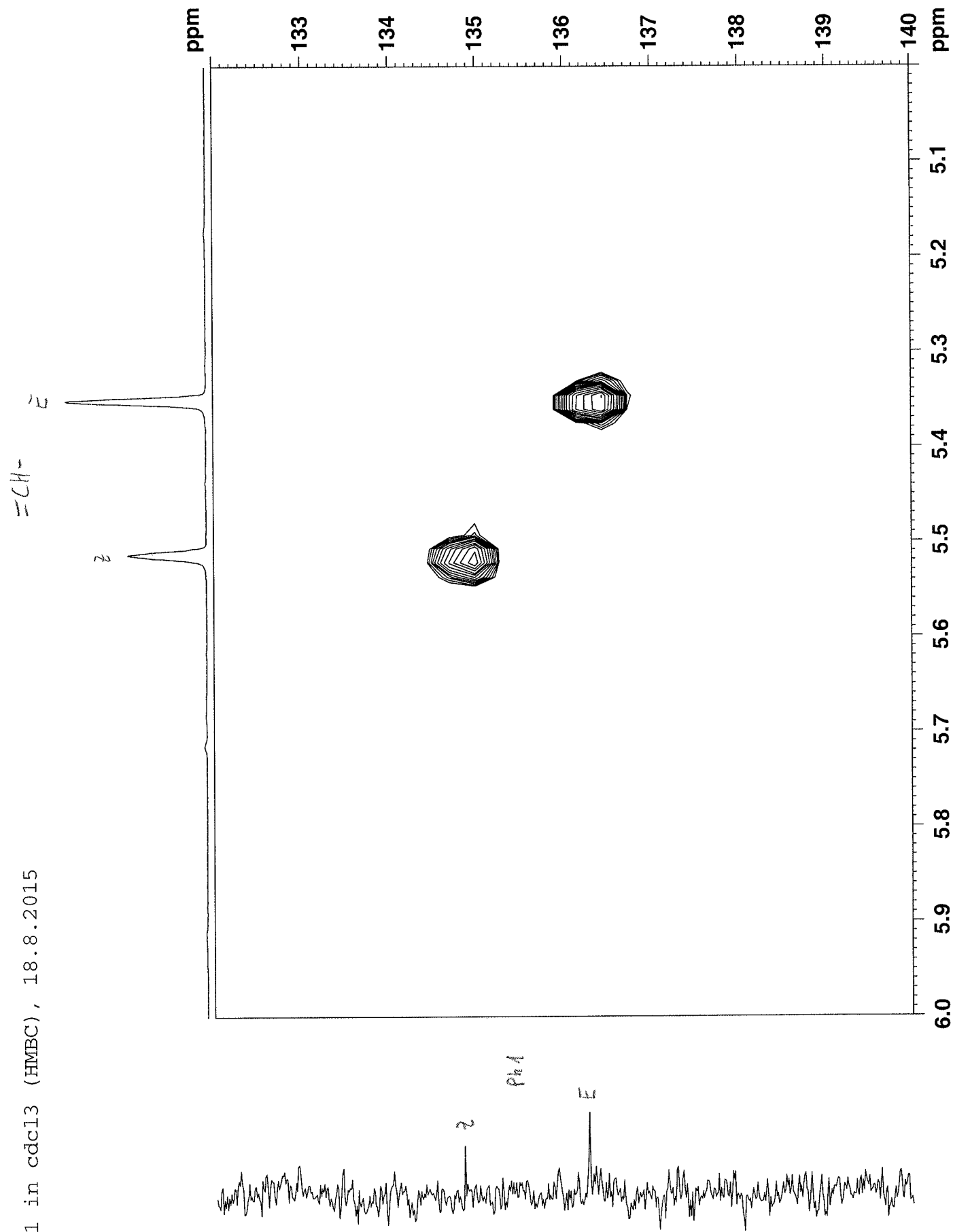
E

=C-

z



GL060_1 in cdcl3 (HMBC), 18.8.2015

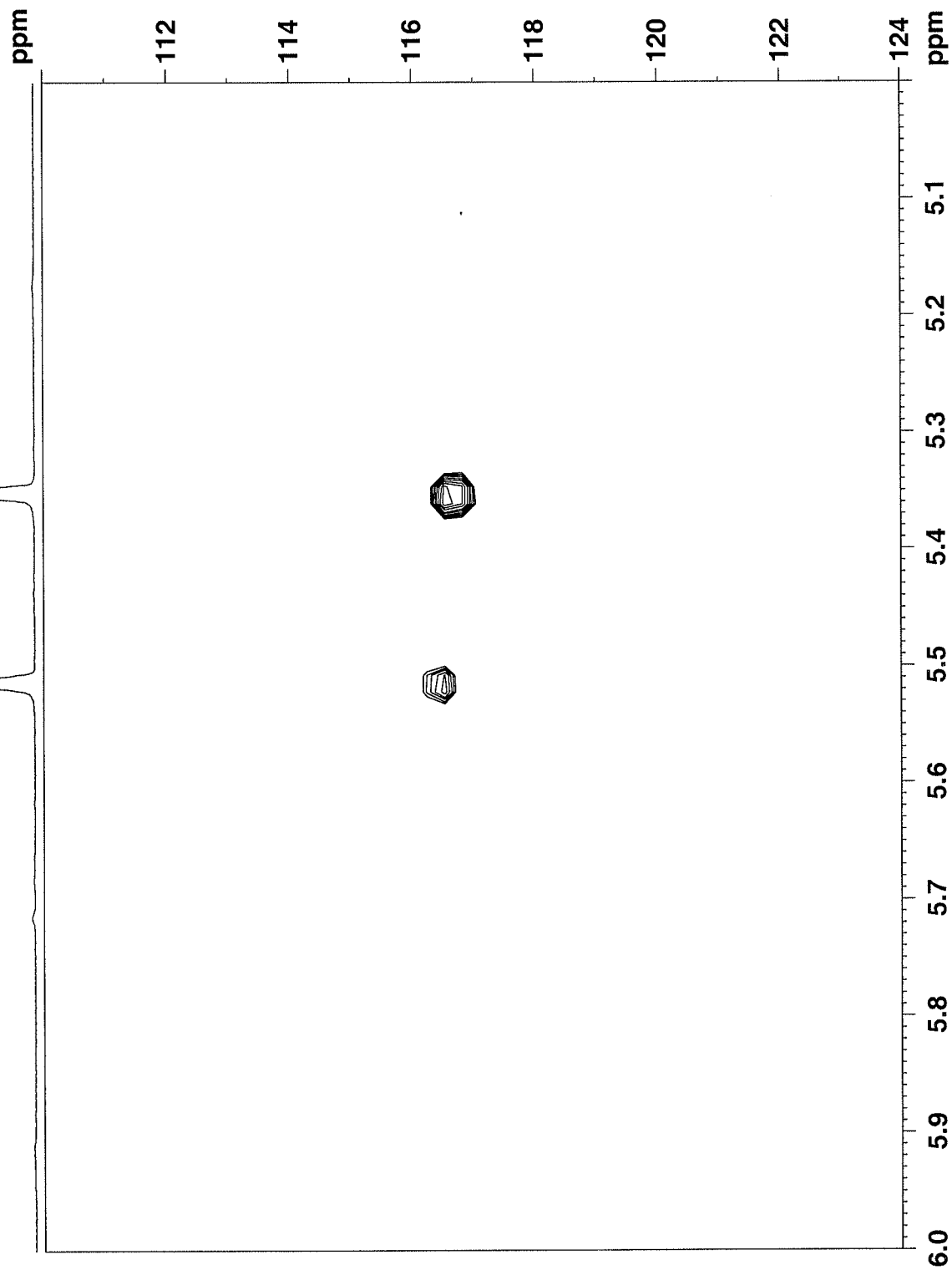


GL060_1 in cdcl3 (HMBC), 18.8.2015

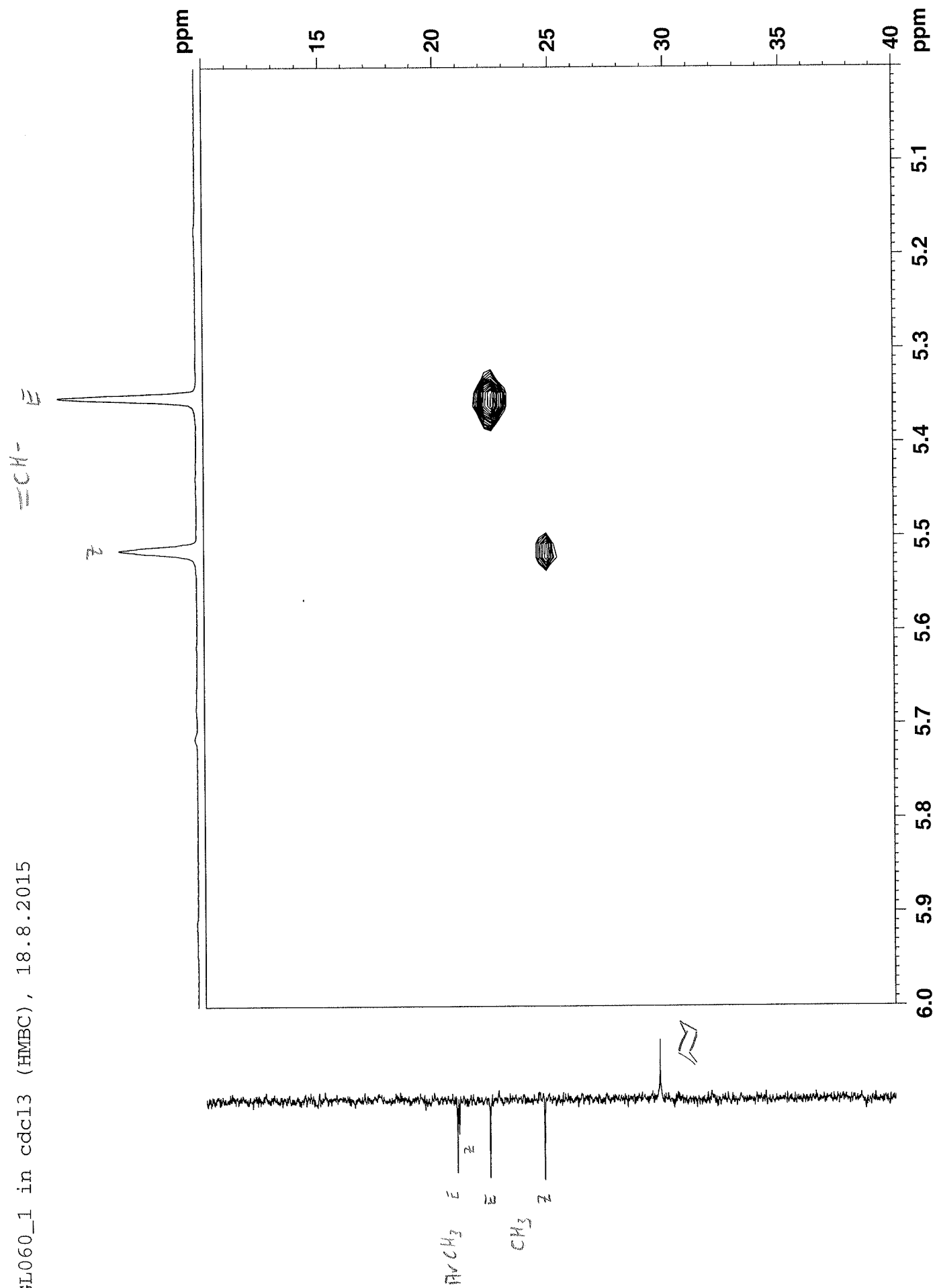
=CH-

E

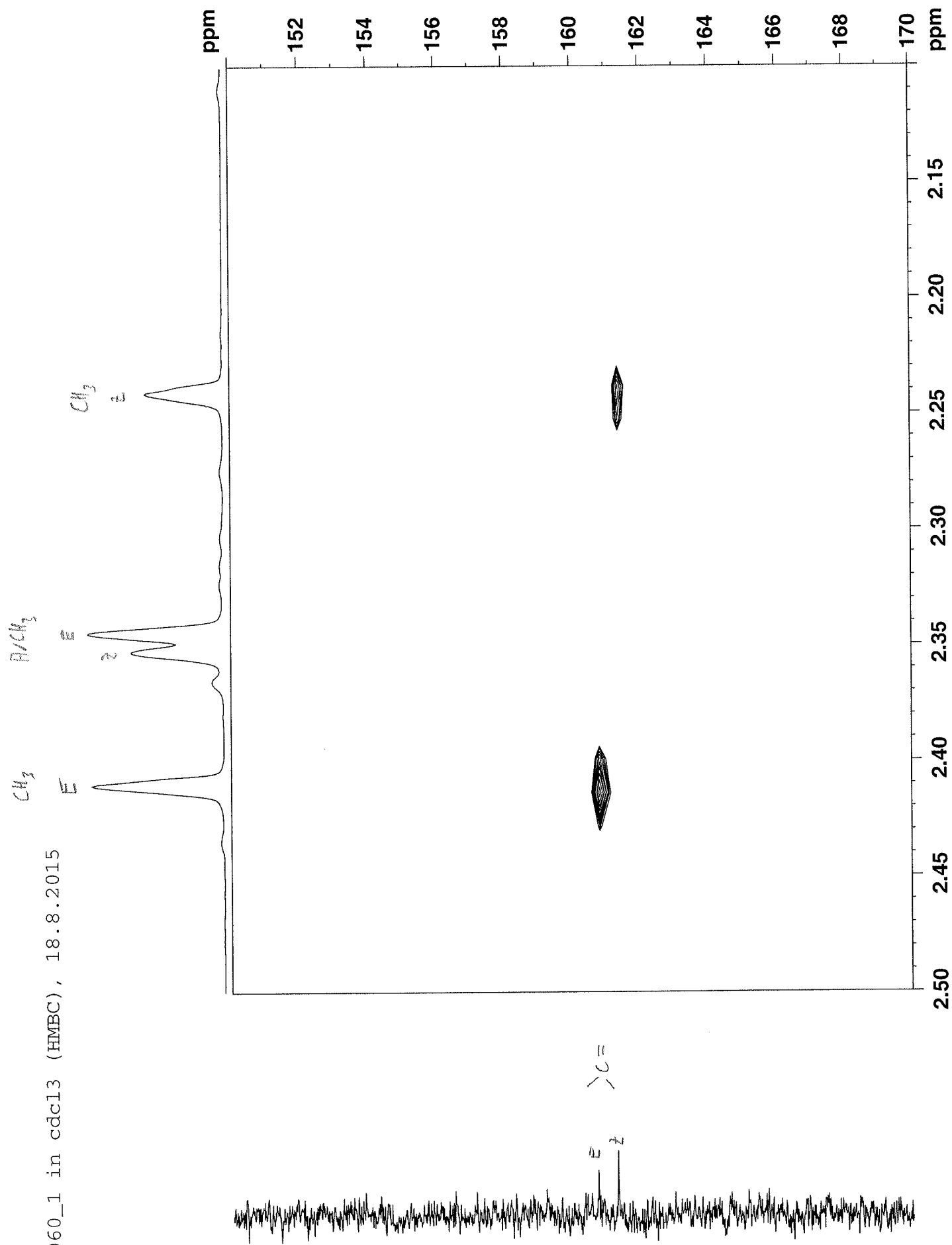
Z



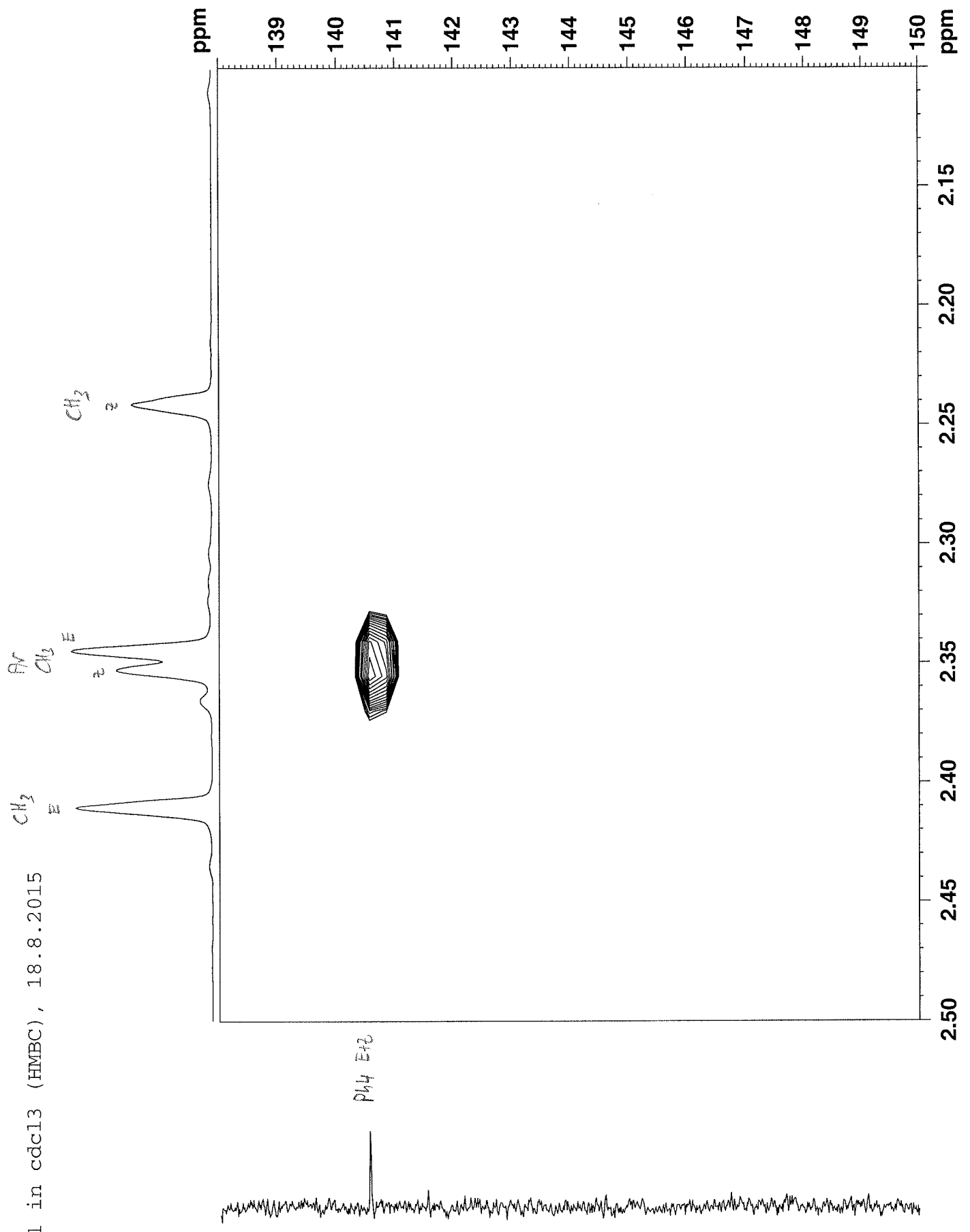
GL060_1 in cdcl3 (HMBC), 18.8.2015



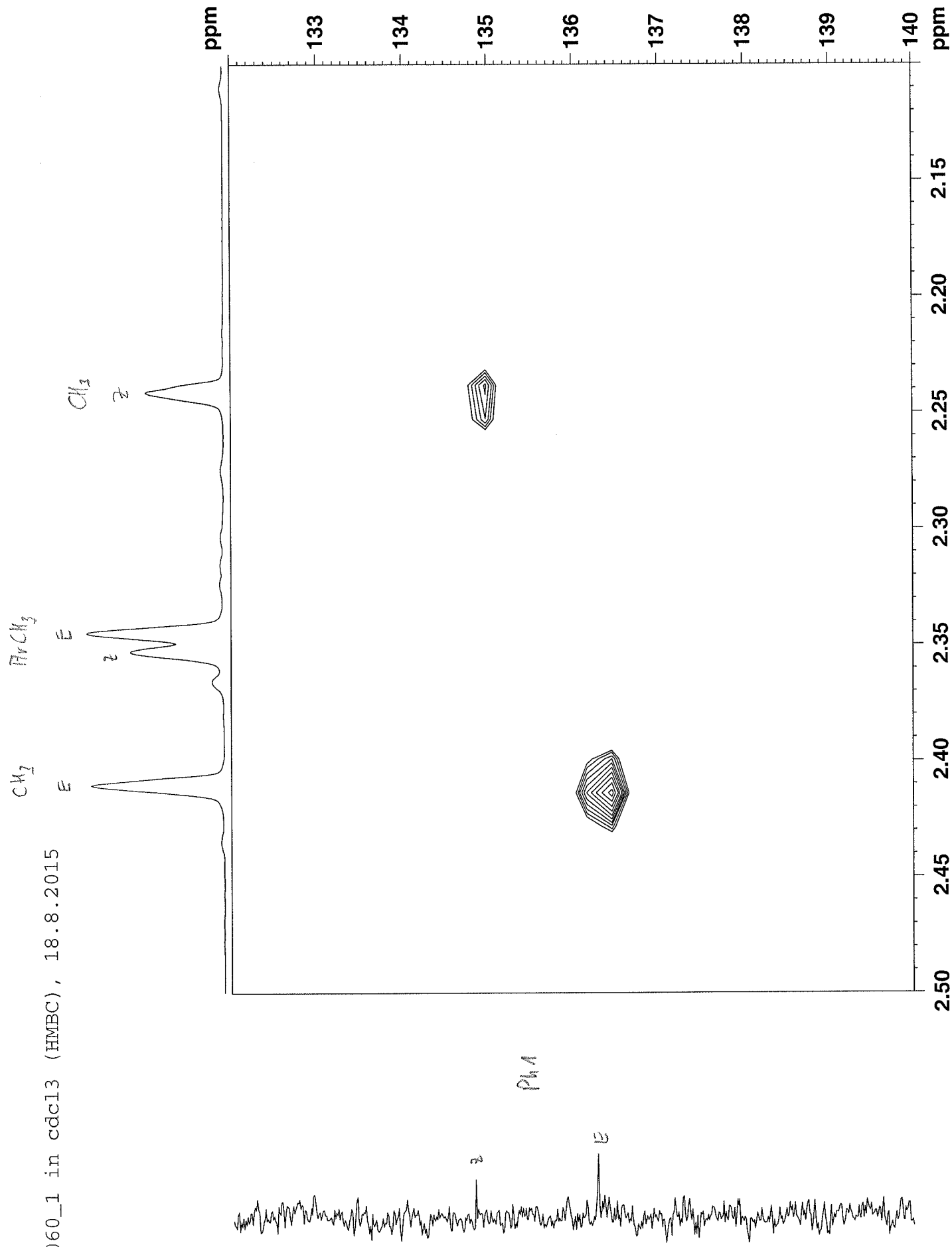
GL060_1 in cdcl3 (HMBC), 18.8.2015



GL060_1 in cdcl3 (HMBC), 18.8.2015



GL060_1 in cdcl3 (HMBC), 18.8.2015



GL060_1 in cdcl3 (HMBC), 18.8.2015

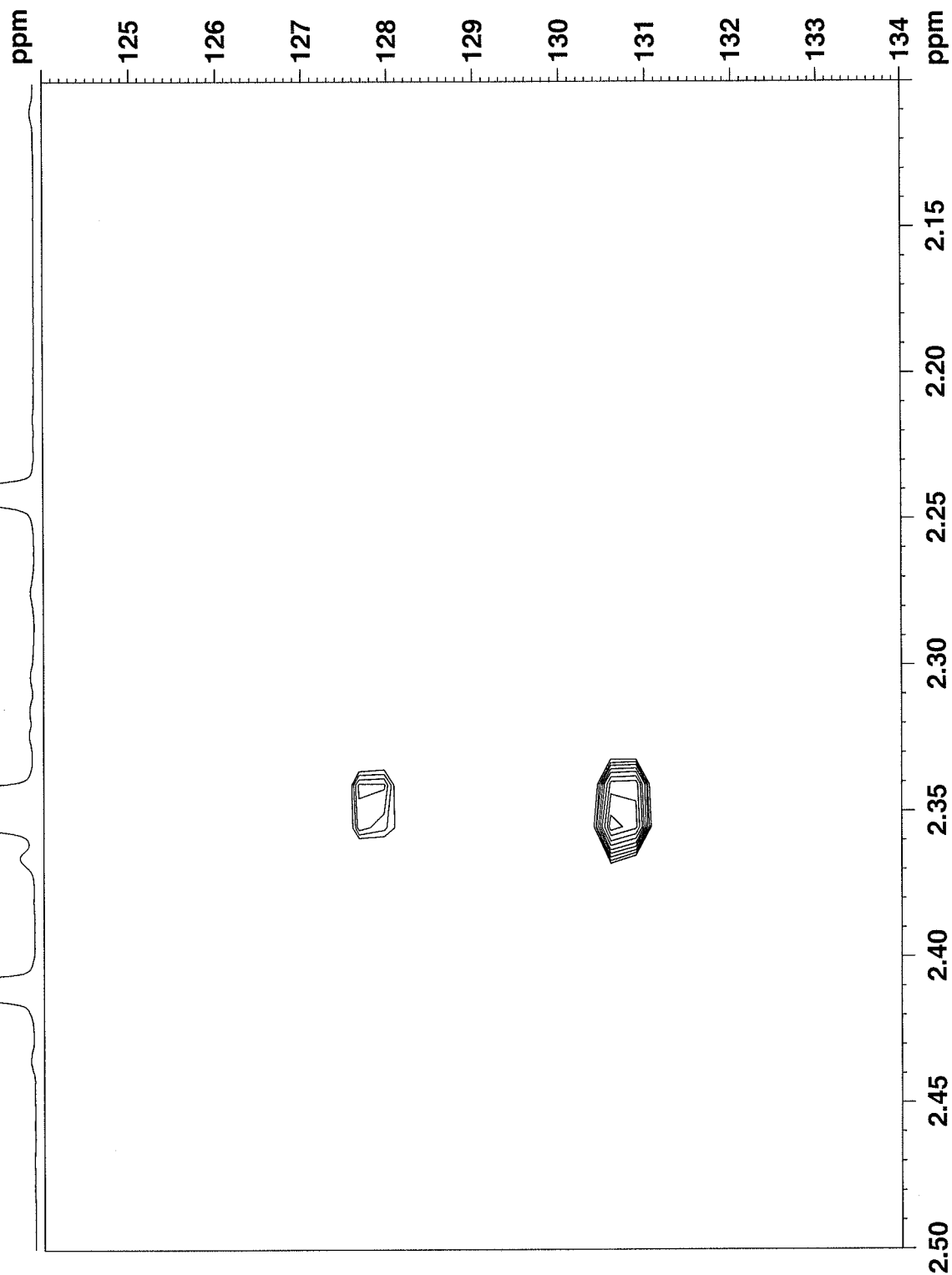
CH₃ ArCH₃

E

CH₂
Z

E

Z



GL060_1 in cdcl3 (HMBC), 18.8.2015

PivCH_3

CH_3

E

E

CH_3

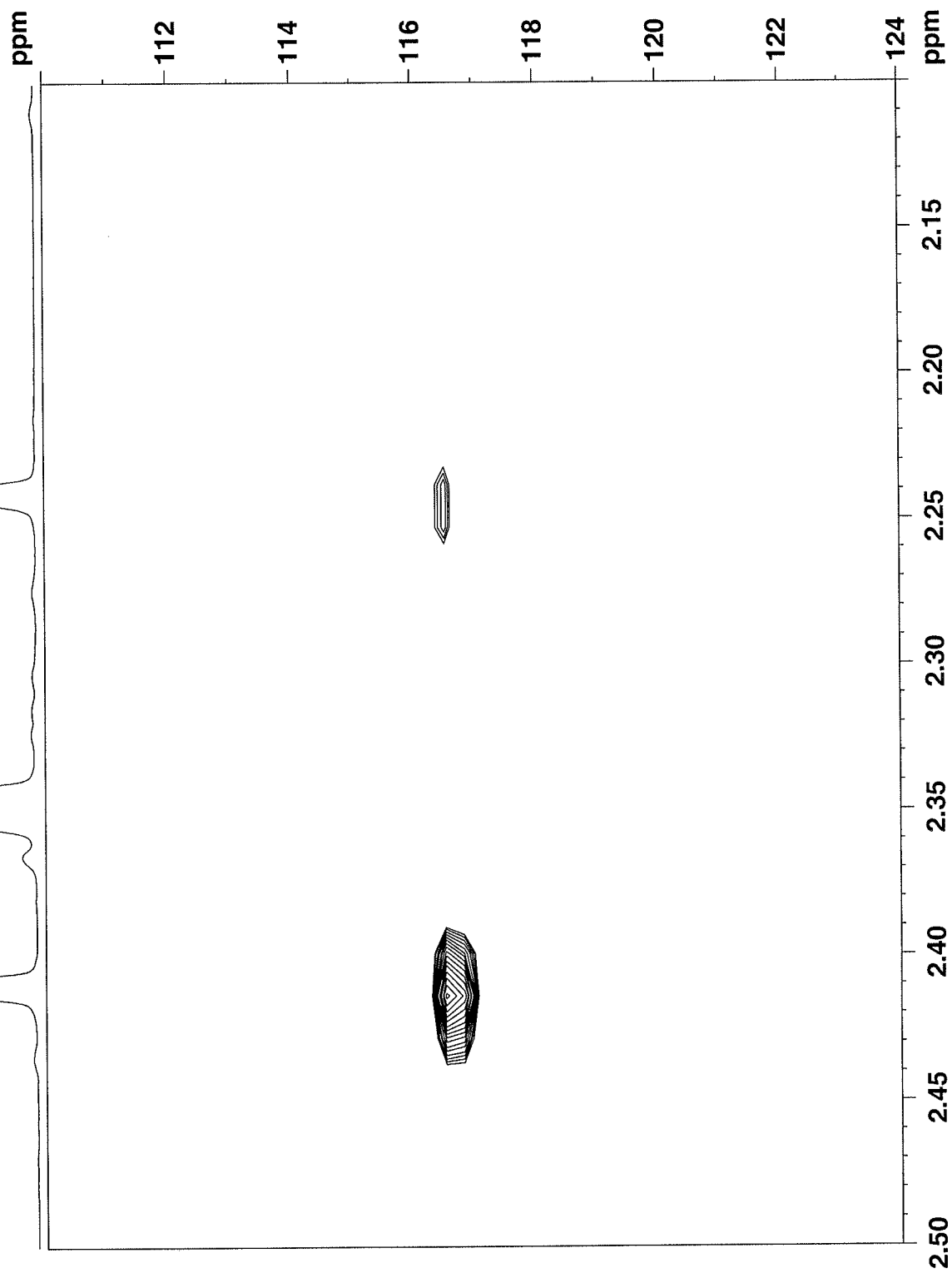
Z

Z

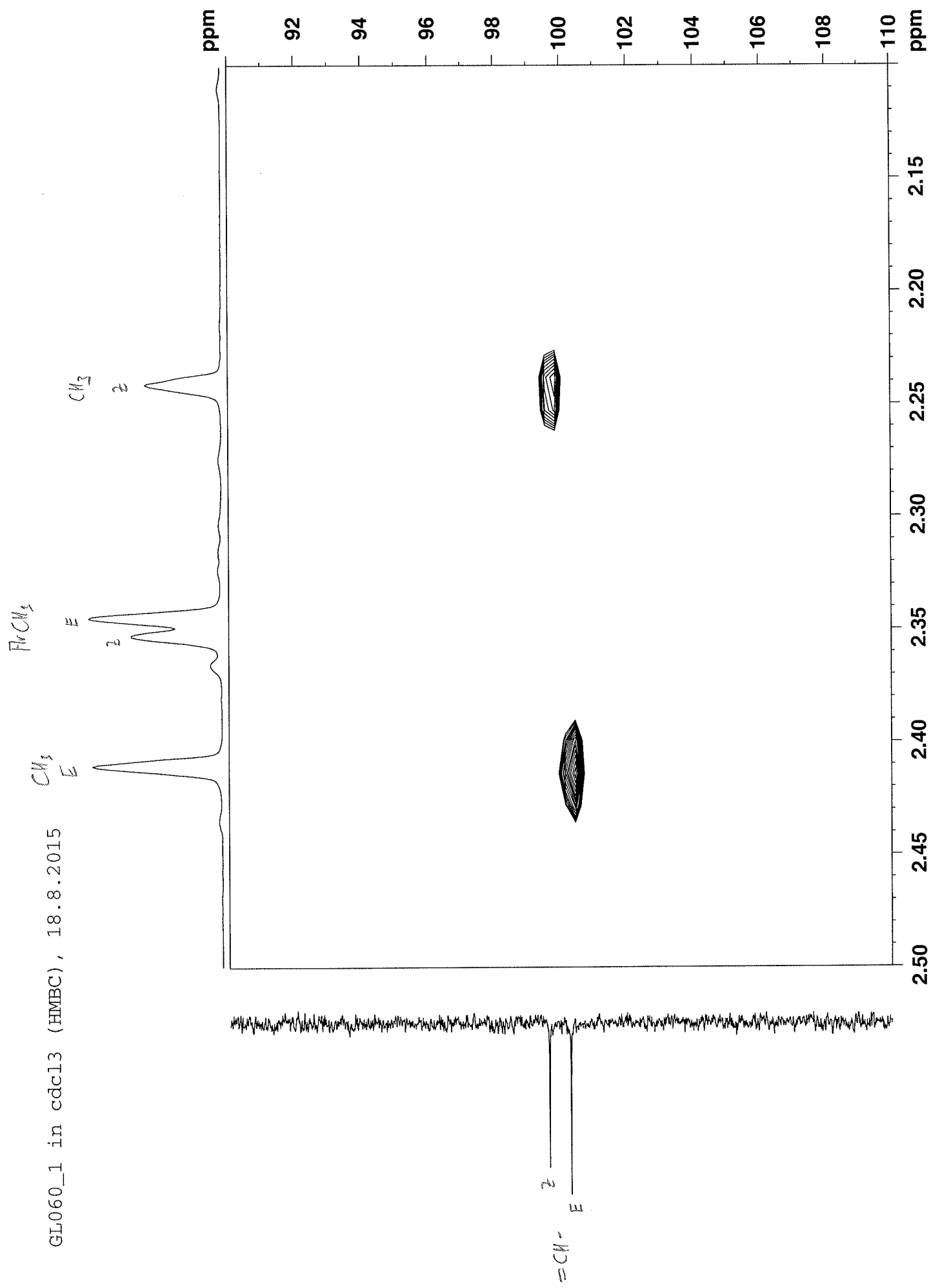
Z

E

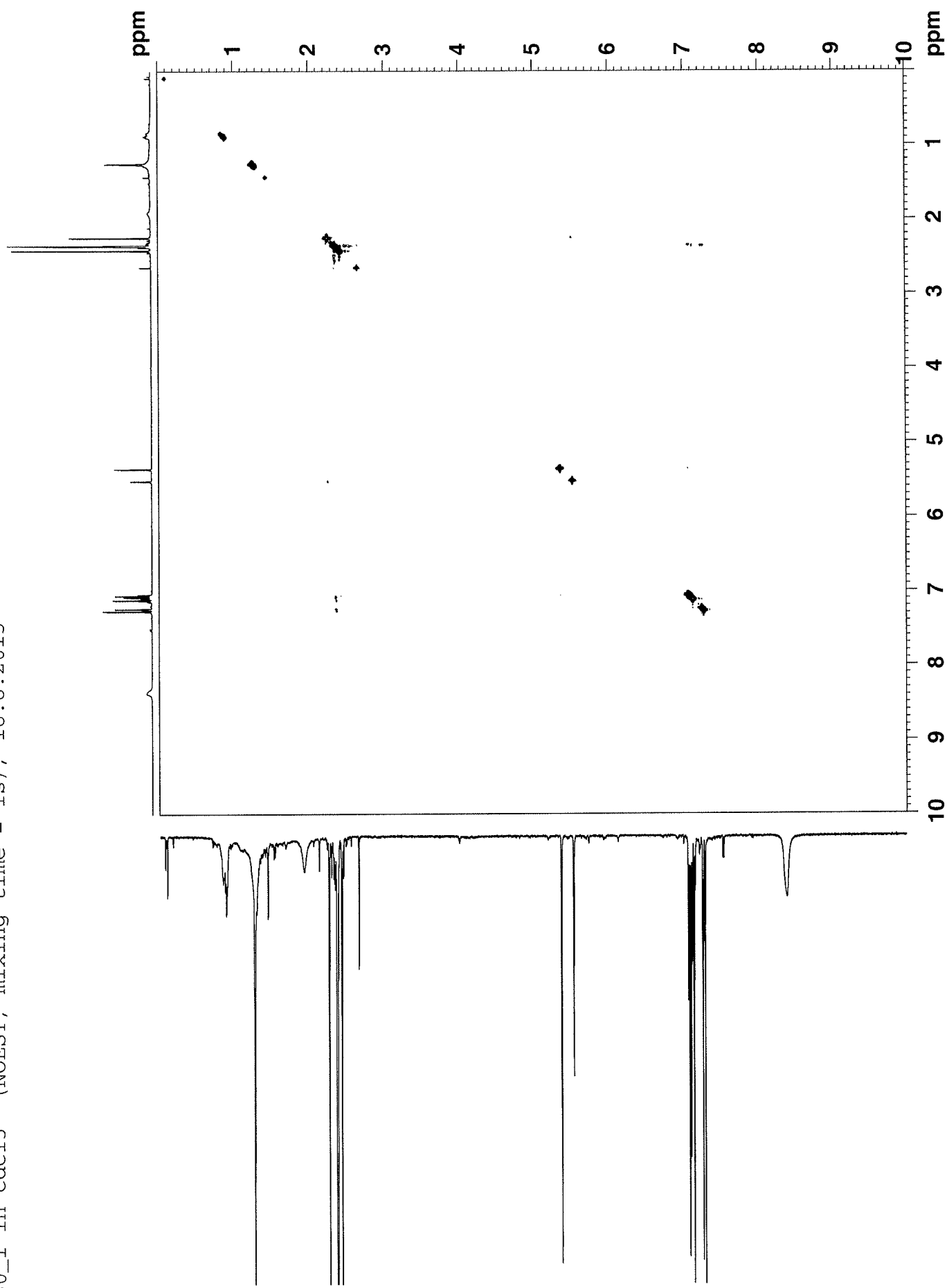
$-\text{C}\equiv\text{N}$



GL060_1 in cdcl3 (HMBC), 18.8.2015



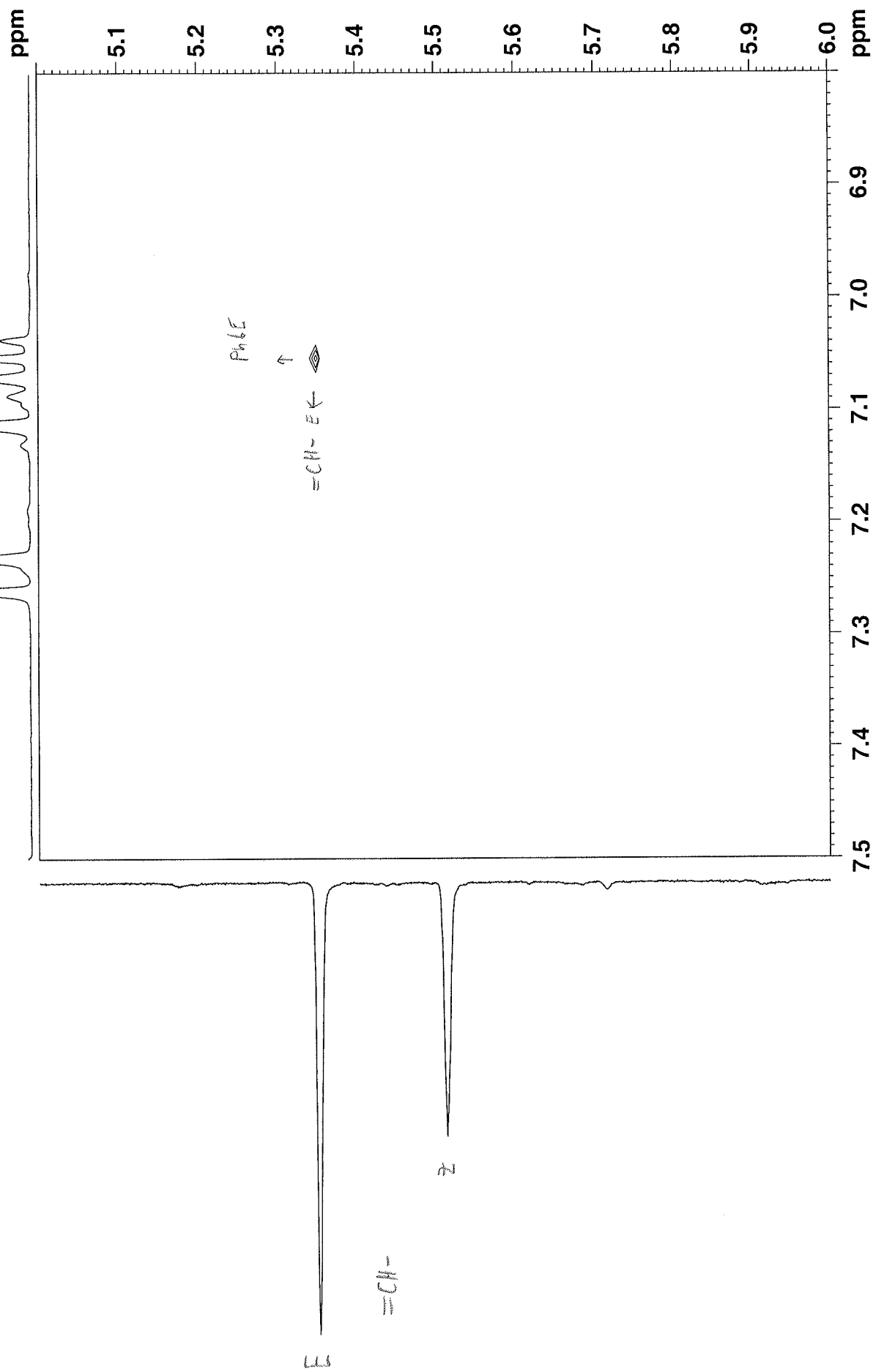
GL060_1 in cdcl3 (NOESY, mixing time = 1s), 18.8.2015



GL060_1 in cdcl3 (NOESY, mixing time = 1s), 18.8.2015

Ph 32 Ph 3E
5+6 Ph 5E
Ph 6E

+ CHCl₃ →



CH_3 