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„Configurationally stable Lithium Carbenoids for Applications in Synthetic Medicinal Chemistry“

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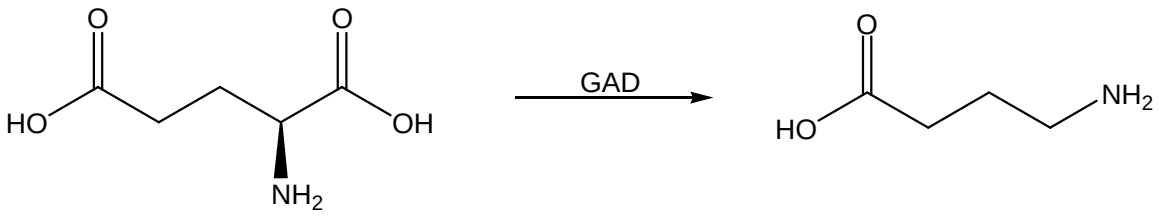
Introduction

The nervous system coordinates all life processes with the help of neurons sending electrochemical signals via their axons. These signals can cause the releasing of various substances, the so called neurotransmitters, at junctions called synapses. By activating or inhibiting multiple receptors and ion channels these transmitters can excite, inhibit or otherwise modulate a cell on the other side of the synapse. Furthermore the neuron can re-uptake the substances for determination of the signal transduction. They can also be taken up by the postsynaptic cell or can be degraded by enzymes for the same purpose. In any way a precise regulation of neuronal activity by various neurotransmitters is important for a healthy brain function. The diversity of chemical neurotransmission made these substances interesting for a lot of therapy approaches. [1]

1. γ-Aminobutyric Acid (GABA)

The amino acids glutamate and the γ-aminobutyric acid are common known neurotransmitters. Whilst glutamate leads to excitatory signalling, GABA prevents the system from overreacting by damping postsynaptic depolarization, which leads to a reduced likelihood of the initiation of action potentials.
γ-aminobutyric acid is the main inhibitory neurotransmitter, it occurs in approximately 30% of the synapses. The effect of GABA results from acting via chloride channels ($GABA_A$ receptors) or via the slower metabotropic receptors ($GABA_B$ receptors). [2]



L-glutamic acid GABA

GABA is synthesized from alpha-decarboxylation of glutamate by glutamic acid decarboxylase (GAD). Its signals are terminated by re-uptake of the neurotransmitter into nerve terminals or into surrounding glial cells by GABA transporters (GAT), where it is metabolized to its succinate by the GABA transaminase (GABA-T) and succinic semialdehyde dehydrogenase (SSADH). [3], [4]

2. GABA Receptors

There are two types of GABA receptors, the $GABA_A$ receptor and the $GABA_B$ receptor, both can be located in the pre- and post-synaptic membrane. [4]

2.1. The $GABA_A$ Receptor

$GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the mammalian brain.
The $GABA_A$ receptor has a structure, where five subunits are arranged around a central pore forming a pentamer, as pictured in **figure 1**. Humans have genes encoding for 19 different subunits of the $GABA_A$ receptor which have been subdivided into the families α1-6, β1-3, γ1-3, δ, ε, θ, π and ρ1-3. [5]

“Each subunit is made out of a 200- to 250-amino acids-long extracellular N-terminal domain, a loose bundle of four membrane-spanning α-helices (TM1–TM4), a large intracellular loop between the TM3 and TM4 domain (between 85 and 255 amino acid residues) and a short C-terminal segment. Residues from the TM2 domain line the ion-conducting pore.” [6]

$GABA_C$, also called $GABA_A$- ρ receptor, is a subclass of $GABA_A$ receptors composed entirely of rho (ρ) subunits. [7]

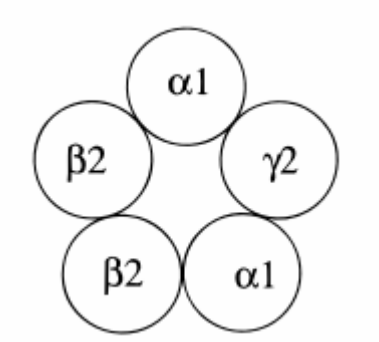


Figure 1 [8]

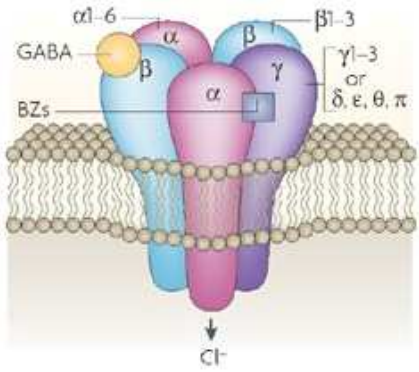
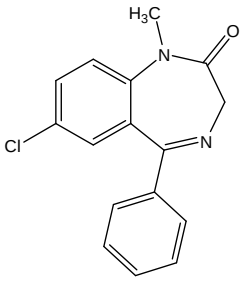
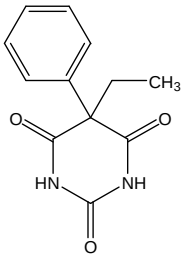


Figure 2 [9]

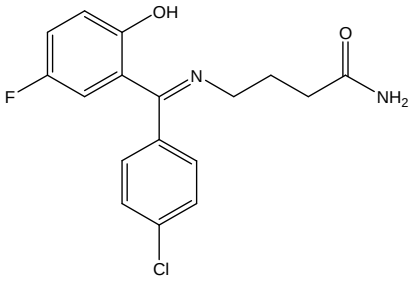
The $GABA_A$ receptor is a ligand-gated ion channel, which is permeable to Cl^- and HCO_3^- as pictured in **figure 2**. This means that when a ligand, in this case GABA, is approaching to its binding site at the extracellular part of the $GABA_A$ receptor, the receptor will open the chloride ion-sensitive pore and chloride would escape from the inter- into the extracellular matrix. The increased chloride conductance inhibits the starting of a new action potential, which results in for instance sedative effects of $GABA_A$ allosteric agonists like the benzodiazepine diazepam or the barbiturate phenobarbital. The anticonvulsive acting progabide and the narcotic propofol are also common known $GABA_A$ receptor agonists, whereas the alkaloid bicuculline is working as antagonist on this receptor. [1]



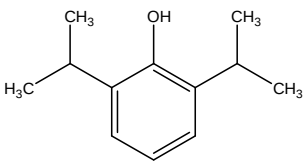
Diazepam



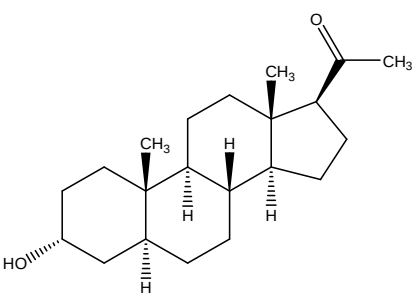
Phenobarbital



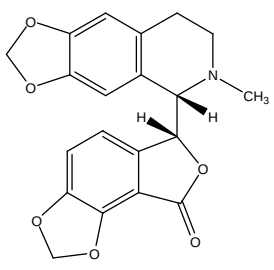
Progabide



Propofol



Allopregnanolone



Bicuculline

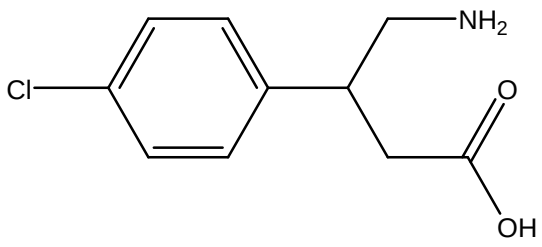
Due to the various sites on the $GABA_A$ receptor complex a large number of $GABA_A$ receptor modulators with different chemical structures can affect the chloride conductance on this channel. [8]

Benzodiazepines (BZD) for example enhance the chloride conductance by binding on their specific BZD site on the receptor and causing allosteric modulation of slower signal transduction. On that basis BZDs are used as tranquilizer for therapy of sleeping disorders.
Similar to this the barbiturates are docking on their own site on the $GABA_A$ receptor and acting as positive allosteric modulator [1]

Other binding sites have also been identified for example the binding site of neurosteroids like allopregnanolone. [10]

2.2. The $GABA_B$ Receptor

The $GABA_B$ receptor is a G-protein coupled receptor build up of seven transmembrane segments. When activated it reduces via G_i-protein the likelihood of opening calcium channels and stimulates the opening of potassium channels as pictured in **figure 3**. The slower influx of excitation causing calcium and the increased potassium efflux leads to hyperpolarization of the cell. Under these conditions the starting of action potentials is reduced and the signal transduction is minimized. There are two isoforms of $GABA_B$ receptors, $GABA_{B1}$ and $GABA_{B2}$. The $GABA_B$ receptor is made up as a heterodimer of these two types. A selective agonist of this receptor is for example the skeletal muscle relaxant baclofen. [1]



Baclofen

3. Inactivation of GABA

For termination of GABAergic actions in the synapse, neurons and glial cells have a special uptake- system, the GABA transporters **figure 3**. [3]
When the neurons take up GABA it can be repackaged in vesicles for further use. In glial cells GABA will be metabolized by GABA-T and SSADH, and the formed intermediates will be reused in the citric acid cycle. The metabolites can also be transformed into glutamine, which can result in re-synthetisation of GABA. The anticonvulsants valproate and vigabatrin slower degradation of GABA leading to increased GABA signalling. [1]

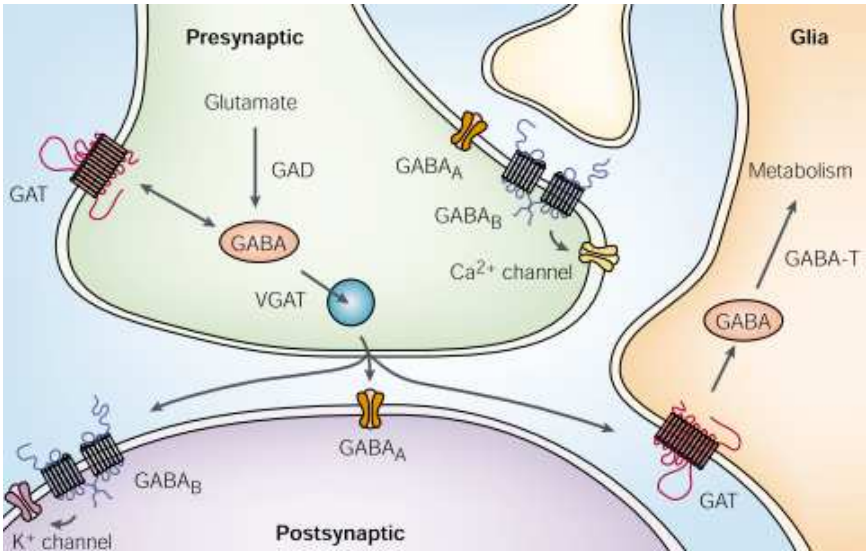


Figure 3 [4]

4. Epilepsy

Epilepsy is one of the most common brain disorders characterized by unpredictable epileptic seizures. These seizures are a result of abnormal and excessive nerve cell activity in the brain and are manifested for example in reduced consciousness and spasms of muscles.
There are two types of seizures on the one hand the primary generalized epilepsy, which affects both brain hemispheres and on the other hand focal seizures also called partial seizures, impairing initially one hemisphere of the brain.

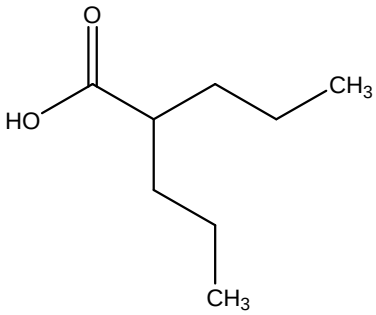
The therapy of epilepsy is based on symptomatic treatment with anticonvulsants. The fact that GABAergic substances slower the transmission of excitation, leads to the common use of GABA increasing pharmaceuticals in anticonvulsive therapy. The BZDs diazepam and clonazepam increase the frequency of $GABA_A$ channel opening, whereas barbiturates like phenobarbital increase the opening period of this chloride channel when activated by GABA.
As mentioned at point three vigabatrin is blocking the GABA-T as a consequence the decomposition of GABA is blocked. Furthermore tiagabin increases the concentration of GABA in the synaptic cleft by blocking GABA re-uptake. Valproate and its GABAergic effect will be considered in the next point.

Among others there are antiepileptic drugs with a different mechanism of action. Phenytoin, carbamazepine and oxacarbazepine are stabilizing the inactivated state of voltage-gated sodium channels. Furthermore zonisamide and topiramate as well inactivate voltage dependent sodium channels. Ethosuximide is also used for therapy of epilepsy due to its ability of blocking T-type Ca^{2+} channels and gabapentin and pregabalin are blocking other Ca^{2+} channels.

The status epilepticus is a life-threatening, more than 30 minutes lasting epileptic seizure or series of seizures without returning of the person to the normal state. The cause is for instance drug withdrawal (especially alcohol), stroke and non-compliance to some anticonvulsants.
More than 10% of status epilepticus have a deadly outcome due to respiratory standstill or acidosis. Therefore therapy must be applied quickly. Even if the condition is stabilized massive brain damage can result. Diazepam or clonazepam are most common in use for emergency medication of status epilepticus. [1]

5. Valproic Acid

Valproic acid or valproate (VPA) is a substance primarily used in the therapy of epilepsy, bipolar disorder and preventive treatment of migraine headache.
More than a century ago valproic acid was synthesized as an analogue of valeric acid, found in *Valeriana officinalis*. Later the usage of valeric acid as solvent for organic compounds was common until the anticonvulsant effect of VPA was coincidentally discovered when screening other compounds for antiseizure activity dissolved in VPA. [11]
The anticonvulsive effect of VPA results from blockade of voltage dependent sodium channels, lowering the flow of calcium at T-type Ca^{2+} channels and increasing GABA levels in synaptic gaps by blocking the GABA-T and SSADH. [1]
Furthermore it was found that VPA is inhibiting the histone deacetylases, which enables the histones to wrap the DNA tightly, leading VPA to become an interesting compound for application in cancer therapy. [12]
Beside its widely usage in epilepsy treatment VPA has some severe side effects for example teratogenicity and liver-toxic effects.



Valproic acid

6. Access of possible Valproic Acid Analogues via Organolithium Alkylation

The wide usage in epilepsy therapy, potential use in cancer therapy and the various mechanisms of action made VPA an interesting drug, despite the side effects. Possible improvement of the positive effects and finding a possibility to eliminate the side effects also made medicinal chemistry interested in synthesizing VPA analogues.

In this diploma thesis the access of possible VPA analogues was attempted by the strategy of organolithium alkylation.

With organolithium alkylation the deprotonation of a compound by organolithium reagents leads to the formation of a lithium-carbenoid, which converts into a nucleophilic species that reacts with electrophiles like alkyl halides. [13]

The most common organolithium reagents are n-butyllithium and the more potent and selective sec-butyllithium and tert-butyllithium. To increase the rate of metalation the complexing and chelating reagent tetramethylethylenediamine (TMEDA) can be used.
There is also another class of strong bases, the lithium dialkylamides ($LiNR_2$), of which lithium diisopropylamide (LDA) is the most widely used in organolithium reactions. [14]

Aim

The aim of this diploma thesis was to synthesize enantiopure VPA- analogues for further pharmacological testing.
The emphasis was on synthesis paths were we used 2-(2,4-dichloro-phenoxy)-acetonitrile as starting material and also the synthesis path for enantiopure 2 -propionic acid ethyl esters of substituted phenols.
Another aim was to increase my knowledge base in reactions with organolithium species.
Furthermore the task of this diploma thesis consisted of characterizing the synthesis products by ^{1}H-NMR and ^{13}C-NMR.

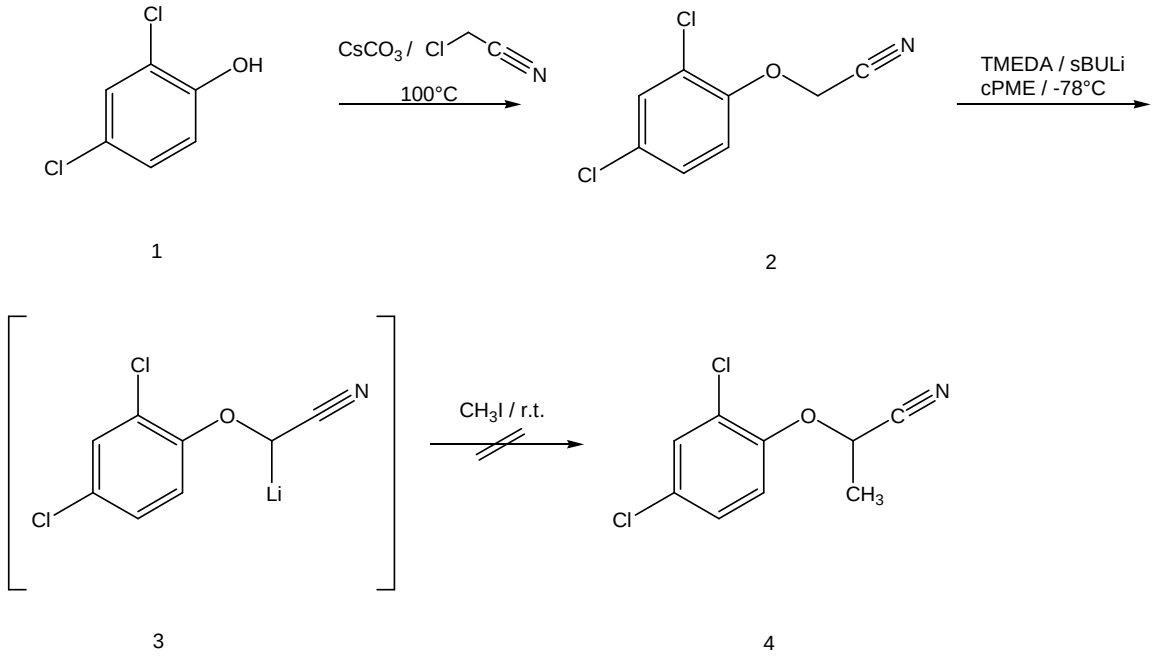
Synthesis, results and discussion

1. Synthesis of 2-(2,4-Dichloro-phenoxy)-propanenitrile **4**

We initially attempted to access the potential VPA analogue 2-(2, 4-dichlorophenoxy)-propanenitrile **4** via methylation of 2-(2,4-dichloro-phenoxy)-acetonitrile **2** by organolithium alkylation as drawn in **scheme 1**.

If this reaction would have been successful, we would use (-)-sparteine together with butyllithium as chiral base, for the methylation of 2-(2,4-dichloro-phenoxy)-acetonitrile **2** to get an enantiopure 2-(2,4-dichlorophenoxy)-propanenitrile **4**. [15]

Scheme 1: *Path for synthesis of 2-(2,4-dichlorophenoxy)-propanenitrile **4***



1.1. Synthesis of 2-(2,4-Dichloro-phenoxy)-acetonitrile **2** via Nucleophilic Substitution

As starting material we used 2,4-dichloro-phenol **1** which reacted in a SN_1-reaction with chloroacetonitrile as nucleophile and caesium carbonate as base for deprotonation. The nucleophilic substitution was very successful as we could see in ^{1}H-NMR with a yield of 97.4 %. (**Table 1**)

Table 1: *Synthesis of 2-(2,4-dichloro-phenoxy)-acetonitrile **2***

Base	Solvent	Conditions	Time	Yield
Cs_2CO_3	acetonitrile	100°C reflux	over night	97.4 %

1.2. Experimental Synthesis of 2-(2,4-Dichlorophenoxy)-propanenitrile **4**

1.2.1. Experimental Alkylation of 2-(2,4-Dichloro-phenoxy)-acetonitrile **2** by External Quenching with Iodomethane

For this organolithium alkylation we used sec-butyllithium as base for deprotonation and added iodomethane as electrophile at the end, which means external quenching, in order to alkylate the 2-(2,4-dichloro-phenoxy)- acetonitrile **2**. The expected product **4** did not form, but with a yield of 41.34% we saw that the starting material **1** reacted with itself by homocoupling.

To prevent this homocoupling we attempted to use another base, namely lithium diisopropylamide. After two hours, by checking with TLC, there was no reaction, therefore we left the reaction over night. The next day in the ^{1}H-NMR we saw, that there was still no reaction performed.

We also assumed that the homocoupling could happen due to the reagents being close to each other, so we decided to lower the concentration of the reagents by adding more solvent. Also we decided to use another solvent, but this time the

reaction was not successful. In ^{1}H-NMR we only saw the starting material, which means the alkylation did not happen.
Furthermore we changed the base by using tert-butyllithium instead, but here again the nucleophilic substitution did not succeed as we only saw the starting material in ^{1}H-NMR. (**Table 2**)

Table 2: *Attempts for synthesis of 2-(2,4-dichlorophenoxy)-propanenitrile **4** via external quenching*

Base	Solvent	Concentration	Conditions	Time	Yield
s-BuLi	cPME (dry)	0.2 M	-78°C	2h	41,34% homocoupling
LDA	THF (dry)	0.14 M	-78°C	o.n.	no reaction
s-BuLi	THF (dry)	0.01 M	-78°C	2h	no reaction
t-BuMgCl	toluene	0.01 M	-78°C	2h	no reaction

1.2.2 Experimental Alkylation of 2-(2,4-Dichloro-phenoxy)-acetonitrile **2** by Internal Quenching

The homocoupling could also happen due to adding the electrophile iodomethane after the base sec-butyllithium and TMEDA, so the base could react with the 2-(2,4-dichloro-phenoxy)-acetonitrile **2** and allow it to perform the homocoupling. In this case the addition of the electrophile iodomethane afterwards, this means external quenching, has no effect, so the alkylation could not happen. Therefore we decided to do the internal quench with iodomethane by adding it before we add the base.
But this trial was also not successful in getting the 2-(2,4-dichlorophenoxy)-propanenitrile **4**, although we used different solvents.
We assumed that the carbenoid might not be stable under this condition, so we also tried to lower temperature with dry ice, but with no success. Also with changing of the base we came to the same result. (**Table 3**)

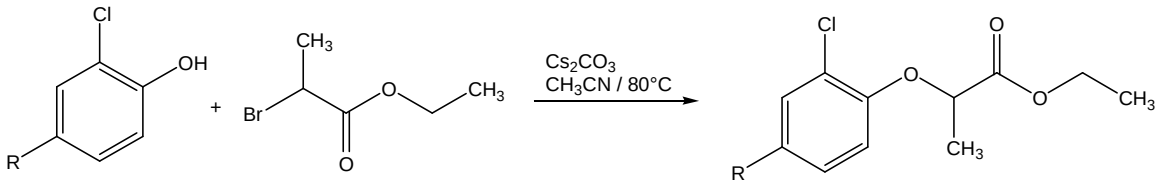
Table 3: *Attempts for synthesis of 2-(2,4-dichlorophenoxy)-propanenitrile **4** via internal quenching*

Electrophile	Base	Solvent	Concentration	Conditions	Time
MeI	s-BuLi	Et_2O	0.01 M	-78°C	2h
MeI	s-BuLi	toluene	0.01 M	-78°C	2h
MeI	s-BuLi	THF	0.01 M	-78°C	2h
MeI	s-BuLi	Me-THF	0.01 M	-78°C	2h
MeI	s-BuLi	cPME	0.01 M	-78°C	2h
MeI	s-BuLi	toluene	0.01 M	-95°C	2h
MeI	s-BuLi	toluene	0.01 M	-95°C	7h
MeI	LDA	THF	0.01 M	-78°C	2h
MeI	t-BuMgCl	toluene	0.01 M	-78°C	2h
Me-OTF	s-BuLi	toluene	0.01 M	-78°C	2h

2. Alkylation of Substituted Phenols **5**

As the synthetic path for synthesis of enantiopure 2-(2,4-dichlorophenoxy)-propanenitrile **4** was not successful we started a new synthesis strategy.
For this attempt we followed the general synthesis of 2-phenoxypropionic acids using ortho- and para- substituted phenols **5**. [16]
This experiment aimed to synthesize the ethyl esters of 2-phenoxypropionic acid **7** out of the phenols **5** with a SN_1- reaction. Therefore we used caesium carbonate as base to form the nucleophile out of the phenol, so the phenol could perform the nucleophilic attack on the electrophile ethyl 2- bromopropionate **6** as seen in **scheme 2**. As solvent we used acetonitrile.

Scheme 2: *Synthesis of 2-phenoxypropionic acid esters*



5 6 7

5a ... R=CH_3
5b ... R=Cl

7a ... R=CH_3
7b ... R=Cl

2.1. Alkylation of 2-Chloro-p-cresol **5a**

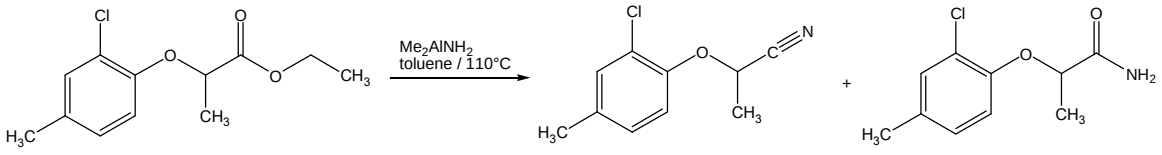
With this reaction we were able to synthesize the 2-(2-chloro-4-methylphenoxy)-propionic acid ethyl ester **7a**, a transparent, viscous liquid with a yield of 100%.

2.1.1. Attempt with Aminodimethylalane

The received ester **7a** was used for another experimental synthesis as drawn in **scheme 3**.

For this attempt we used the method for conversion of esters to amides with aminodimethylalane, described by Anwer Basha et al. 1977. [17]
With this method we were able to transform the 2-(2-chloro-4-methylphenoxy)-propionic acid ethyl ester **7a** into 2-(2-chloranyl-4-methyl-phenoxy) propanenitrile **8** with a yield of 69% and 2-(2-chloranyl-4-methyl-phenoxy) propanamide **9** with a yield of 31%.
Therefore aminodimethylalane was created *in situ* with ammonia in dioxane 0.5M and trimethylaluminum. [18]

Scheme 3: *Transformation of 2-(2-chloro-4-methylphenoxy)propionic acid ethyl ester **7a***



7a 8 9

The transformation of the ester **7a** into its nitrile **8** we could see in ^{1}H-NMR due to the lost of signals at 1.30 ppm and 4.12 ppm, whilst the amide **9** has an additional signal at 6.0 ppm deriving from the amide protons (NH_2).

2.2. Alkylation of 2,4-Dichloro-phenol **5b**

With caesium carbonate as base and the electrophile ethyl 2- bromopropionate we were also successful in obtaining the 2-(2,4-dichlorophenoxy) propionic acid ethyl ester **7b** with a yield of 100%.

3. Enantiopure Alkylation of Substituted Phenols **12**

Another synthetical strategy followed the procedure for synthesis of alkyl 2-phenoxypropanoates using caesium fluoride and (-)-2-[(p-tolyl sulfonyl)- oxy] propionic acid ethyl ester **11** as seen in **scheme 4**. [19]

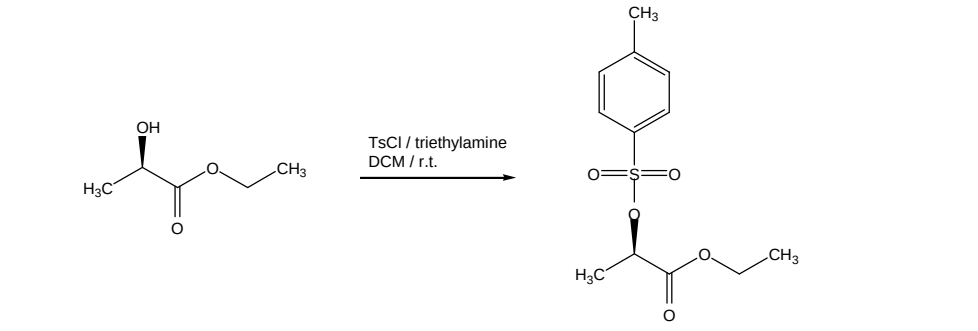
With this strategy we attempted to access the enantiopure 2 - propionic acid ethyl esters **13** of ortho- and para- substituted phenols **12**.

The tosyl group in (-)-ethyl 2-[(p-tolyl sulfonyl)- oxy] propionic acid ethyl ester **11** is a good leaving group, this means that the propionic acid ethyl ester will be added to the phenol **13** in a nucleophilic substitution, whilst the tosyl group would be released from the bond. [20]

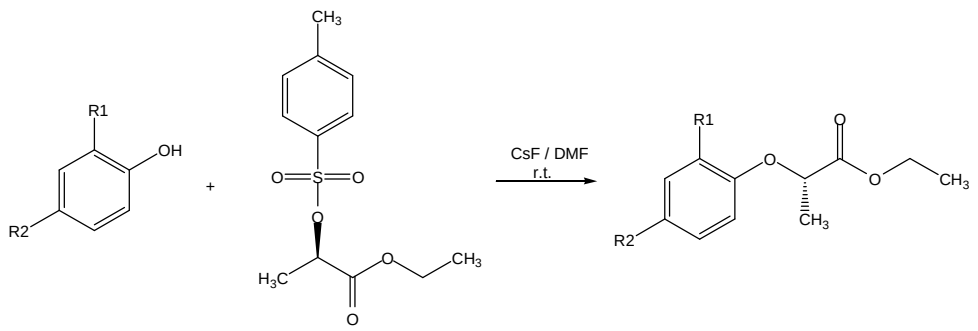
Therefore we needed to synthesize the (-)-2-[(p-tolyl sulfonyl)- oxy] propionic acid ethyl ester **11** first, using (−)-ethyl L-lactate **10** and TsCl with triethylamine in DCM. [21]

The synthesis of (-)-2-[(p-tolyl sulfonyl)- oxy] propionic acid ethyl ester **11** succeeded with a yield of 38%.

Scheme 4: *Synthesis of enantiopure 2- phenoxy- propionic acid ethyl esters* ***(13)***



10 11



12 11 13

12a ... R1= Cl, R2= CH_3
12b ... R1= Cl, R2= Cl
12c ... R1= CH_3, R2= Cl

13a ... R1= Cl, R2= CH_3
13b ... R1= Cl, R2= Cl
13c ... R1= CH_3, R2= Cl

3.1. Enantiopure Alkylation of 2-Chloro-p-cresol **12a**

With this synthetical strategy as shown in **scheme 4** we were able to synthesize the (2S)- 2-(2-chloro-4-methylphenoxy)- propionic acid ethyl ester **13a** with a yield of 16.8%.
In the ^{1}H-NMR spectra we see a triplet at 1.30 ppm and a doublet at 1.61 ppm, furthermore two quartet signals at 4.12 ppm and 4.70 ppm. Whereas the 2-chloro-p-cresol **12a** has no shifts at these ppms.

3.2. Enantiopure Alkylation of 2,4-Dichloro-phenol **12b**

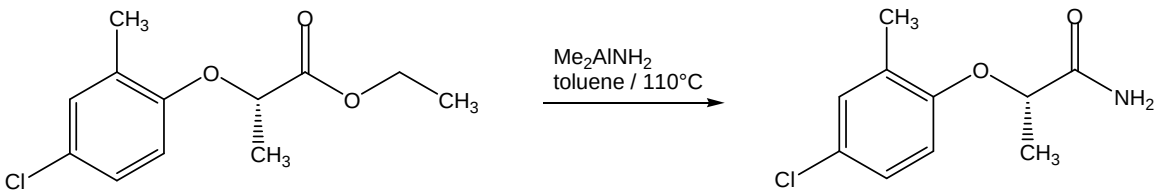
Also the synthesis of (2S)- 2-(2,4-dichlorophenoxy)- propionic acid ethyl ester **13b** worked, with a yield of 7.5%.
This can be seen in ^{1}H-NMR spectra with a triplet signal at 1.30 ppm and 4.12 ppm, which comes from the hydrogens of the ethyl ester, and a doublet signal at 1.61 ppm and 4.70 ppm of the hydrogens from the propionic acid. These shifts could not be seen in the spectra of 2,4-dichloro-phenol **12b**.

3.3. Enantiopure Alkylation of 4-Chloro-o-cresol **12c**

The synthesis of (2*S*)- 2-(4-chloro-2-methylphenoxy)- propionic acid ethyl ester **13c** was successful with a yield of 20.8%.
The ^{1}H-NMR spectra shows a triplet signal at 1.30 ppm and 4.12 ppm from the hydrogens of the ethyl ester, and a doublet signal at 1.61 ppm and 4.70 ppm of the hydrogens from the propionic acid, whereas the 4-chloro-o-cresol **12c** has no shifts at these ppms.

With this ethyl ester **13c** the synthesis of (2S)- 2-(4-chloro-2-methylphenoxy)-propanamide **14** with aminodimethylalane was attempted as shown in **scheme 5**. The reaction worked with a yield of 24.9%.

Scheme 5: *Synthesis of the propanamide **14***



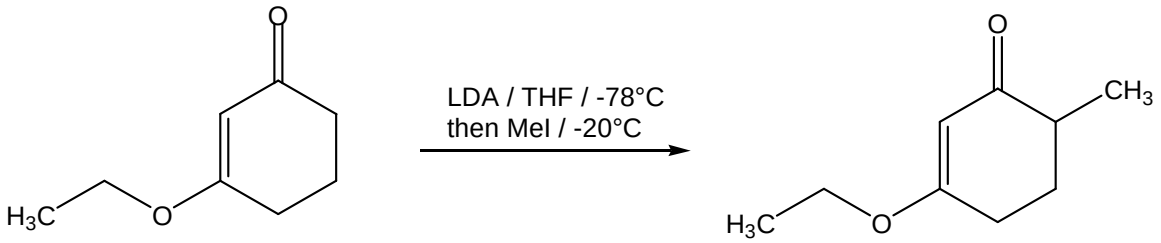
13c 14

The (2S)- 2-(4-chloro-2-methylphenoxy)- propanamide **14** we recognized by ^{1}H-NMR with a proton peak shifted at 6.0 ppm, which is characteristic for the hydrogens of the amide group.

4. Synthesis of 3-Ethoxy-6-methyl-2-cyclohexen-1-one **16**

We performed also other reactions with organolithium reagents like the methylation of 3-ethoxy-2-cyclohexenone **15**. Therefore we used LDA as base. The synthesis pathway can be seen in **scheme 6**. [22]
LDA would be prepared in situ with diisopropylamine and n-butyllithium. [23]
The methylation product **16** was obtained successfully with a yield of 87.2%

Scheme 6: *Synthesis of 3-ethoxy-6-methyl-2-cyclohexen-1-one **16***

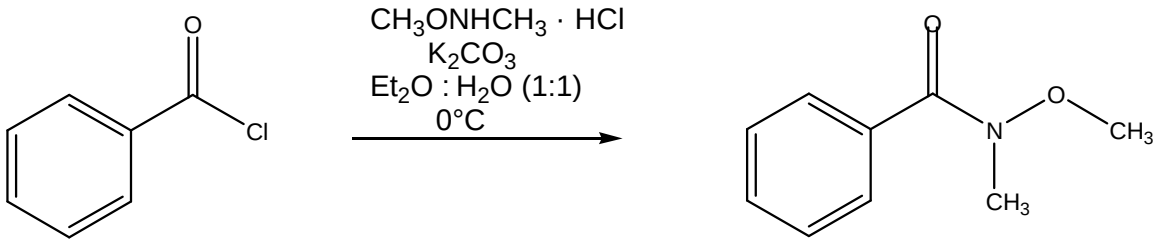


15 16

5. Synthesis of N-Methoxy-N-methyl-benzamide **18**

The synthesis of a weinreb-amide **18** via nucleophilic acyl substitution was also performed **(Scheme 7)**. By adding N, O-dimethyl hydroxylamine hydrochloride to benzoyl chloride **17** we were able to synthesize the N-Methoxy-N-methyl-benzamide **18** with a yield of 70.7%. [24]

Scheme 7: *Synthesis of a weinreb-amide **18***

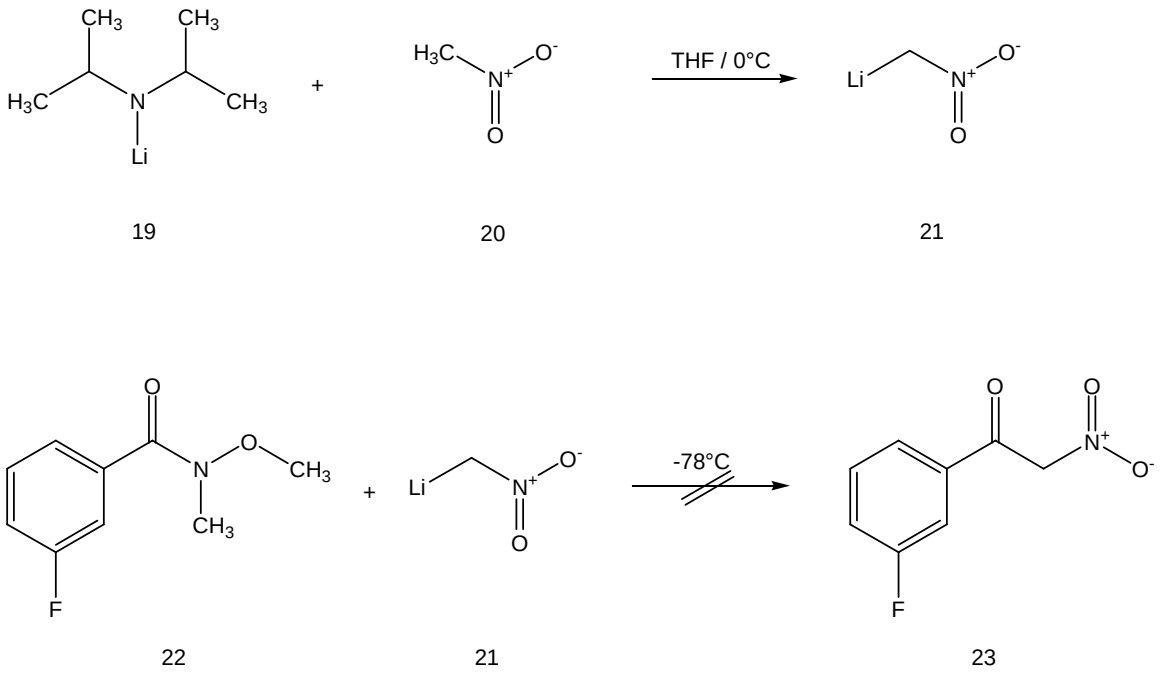


17 18

6. Attempt of Synthesis of 1-(3-Fluoro-phenyl)-2-nitro-ethanone **23** via Weinreb Ketone Synthesis

The Weinreb ketone synthesis enables the synthesis of ketones by acylation of Weinreb-amides with the help of organolithium reagent. [24]
With this attempt we wanted to add a nitromethyl group to a Weinreb-amide **22** by performing the Weinreb ketone synthesis with the lithium salt of nitromethane **21**, as seen in **scheme 8**.
This organolithium reagent **21** was supposed to form in situ with letting LDA **19** and nitromethane **20** react. Later the Weinreb-amide **22** was added, but the attempt to access the 1-(3-fluoro-phenyl)-2-nitro-ethanone **23** was not successful, as the TLC and the ^{1}H-NMR spectra showed only the starting material **22**.

Scheme 8: *Attempt of synthesis of 1-(3-fluoro-phenyl)-2-nitro-ethanone*



7. Attempt with Phenyl isocyanate **24**

Another experiment aimed to add a nitromethyl group to phenyl isocyanate **24** by nucleophilic acylation with lithium salt of nitromethane **21** as seen in **scheme 9**.
The expectation was to access the 2-nitroacetanilide **25**, but the ^{1}H-NMR showed a different product **26**. 1,1-Diisopropyl-3-phenylurea **26** was formed with a yield of 72.8%.
Also after changing the procedure, as we increased the temperature before adding phenyl isocyanate **24**, the unexpected product **26** was formed again with a yield of 91%.
The conclusion is that maybe the lithium salt of nitromethane **21** was not formed out of LDA **19** and nitromethane **20**, it is expected that the LDA is reacting with the starting material **24** getting a different product **26**.
Therefore we tried the reaction with different bases. By using t-BuOK and DABCO on TLC we could see a yellow product, which showed a characteristical shift at 5.35 ppm for the two protons next to the nitro group, proving the successful access of **25**. With imidazole as base **25** was not formed. (**Table 4**)

Scheme 9: *Attempt with phenyl isocyanate **24***

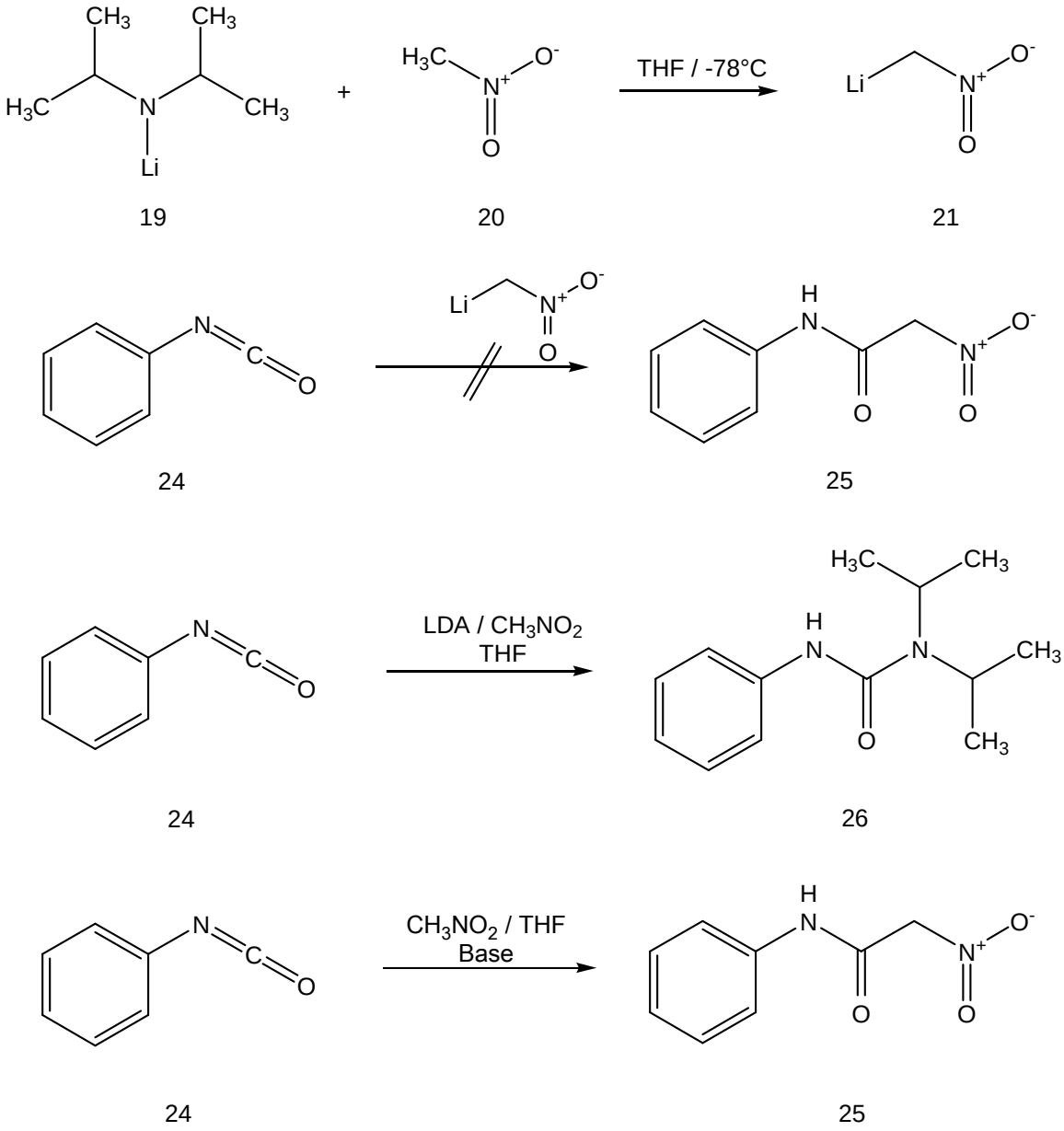


Table 4: Attempt with phenyl isocyanate **24**

Base	Solvent	Conditions	Time	Result
LDA	THF	-78°C	2h	**26**
LDA	THF	0°C	1h	**26**
t-BuOK	THF	0°C	2h	**25**
DABCO	DMSO	r.t.	o.n.	**25**
DABCO	DMSO	50°C	o.n.	**25**
imidazole	DMSO	r.t.	1h	STM

Abstract

The main task of this diploma thesis was to synthesize enantiopure VPA-analogues for further pharmacological testing.

We started with the attempt of synthesizing the 2-(2,4-dichloro-phenoxy)-propanenitrile **4** by producing the starting material **2**. The subsequent methylation of the acetonitrile **2** was not successful. The first attempt of this procedure resulted in homocoupling of the starting material **2**, the other attempts showed no reaction even when the time of adding the iodomethane was changed.

Therefore we started a new strategy, by synthesizing two aryloxy substituted ethyl esters **7**. With one ester **7a** we tried a procedure with aminodimethylalane, were the nitrile **8** and the amide **9** were produced.

Then we synthesized three enantiopure phenolic esters **13a-13c** by alkylating their phenols **12a-12c** with the help of a tosyl ester **11**.

Furthermore a Weinreb-amide **18** was synthesized and we attempted an experiment with another Weinreb-amide **22**, nitromethane and LDA, but with no reaction.

We also attempted the same procedure with phenylisocyanate **24** getting the compound **26**.

Zusammenfassung

Die Hauptaufgabe dieser Diplomarbeit bestand darin enantiomerenreine VPA-Analoga zu synthetisieren.

Dabei begannen wir mit dem Versuch der Synthese von 2-(2,4-dichloro-phenoxy)-propannitril **4**, wobei zunächst das Edukt **2** erfolgreich hergestellt wurde. Die Methylierung des Acetonitrils **2** erwies sich jedoch als problematisch, da die Reaktion bis auf einen Versuch, bei dem eine Homokupplung stattfand, erfolglos blieb. Auch die Änderung des Zeitpunktes der Zugabe des Iodomethans konnte daran nichts ändern.

Deswegen wurde eine andere Synthesestrategie gewählt. Zunächst wurden zwei strukturanaloge aryloxy- substituierte Ethylester **7** synthetisiert. Bei einem Ester **7a** wurde ein Versuch zur Umwandlung in ein Amid **9** mit Hilfe von Aminodimethylalan durchgeführt, wobei das gewünschte Nitril **8** und das Amid **9** entstand.

Danach wurde die Synthese von drei verschiedenen enantiomerenreinen phenolischen Estern **13**, durch Alkylierung der jeweiligen Phenole **12** mit Hilfe eines Tosylesters **11**, erfolgreich durchgeführt.

Weiters synthetisieren wir ein Weinreb-Amid **18** und führten einen erfolglosen Versuch mit einem anderen Weinreb-Amid **22**, Nitromethan und LDA durch. Auch mit Phenylisocyanat **24** wurde ein Versuch mit Nitromethan und LDA durchgeführt, wobei **26** als unerwartetes Produkt entstand.

Experimental Procedures and Spectra Data

The ^{1}H- and ^{13}C-NMR- spectra were recorded on Bruker Avance 200 nuclear resonance spectrometer and Bruker Avance 500 spectrometer (UltraShield) using a 5 mm switchable probe (PA BBO 500SB BBF-H-D-05-Z, 1H, BB = 19F and 31P - 15N) with z axis gradients and automatic tuning and matching accessory (Bruker BioSpin). The resonance frequency for ^{1}H NMR was 500.13 MHz and for ^{13}C NMR 125.75 MHz. All measurements were performed for a solution in fully deuterated chloroform at 298 K. Standard 1D and gradient-enhanced (ge) 2D experiments, like double quantum filtered (DQF) COSY, NOESY, HSQC, and HMBC, were used as supplied by the manufacturer. Chemical shifts are referenced internally to the residual, non-deuterated solvent signal for chloroform ^{1}H (δ 7.26 ppm) and to the carbon signal of the solvent for chloroform ^{13}C (δ 77.00 ppm).

The thin layer chromatography (TLC) was performed on Merck TLC ready-to-use plates. For column chromatography Merck silica gel (Si 60, 40-63 µm) was used. The needed amount of column materials was suspended in approximately four parts of solvent and filled in the column. The mobile phase would be pressed with a pump until the stationary phase was free from air bubbles and the column was impacted until the silica was compact. The mixture to be separated would be dissolved or diluted in two times as much mobile phase and applied plainly onto the silica gel. After adding some sea sand or cellulose the separation was performed.

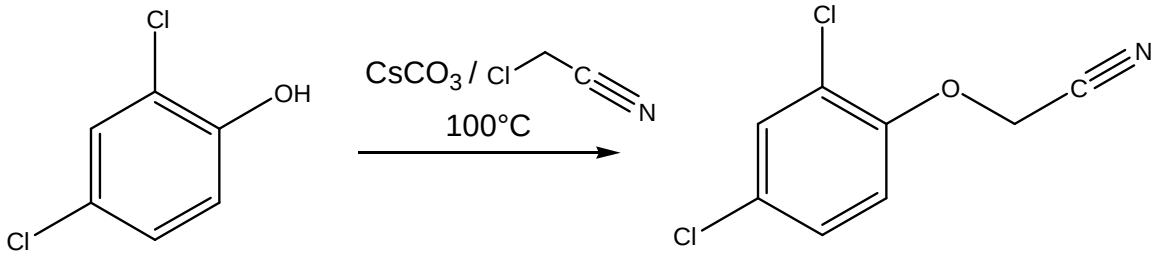
Dry THF was prepared every day via distillation under argon atmosphere, drying it with sodium. Benzophenone was used as indicator for this procedure, its intense blue color showed a good quality of dry THF. Other solvents were dried by addition of molecular sieve (3 Å). Ether refers to diethyl ether. Dioxane refers to 1, 4-dioxane. Brine refers to a saturated solution of sodium chloride in water.

For cooling of the reaction mixture to -78°C, the reaction flask was put into a bath filled with dry ice (solid form of carbon dioxide) and ethanol.

For temperatures of 0°C a bath of normal ice with water and if needed sodium chloride was used.

All secondary products and other residues from the syntheses were disposed as chemical waste.

1. Synthesis of 2-(2,4-Dichloro-phenoxy)-acetonitrile 2



1 2

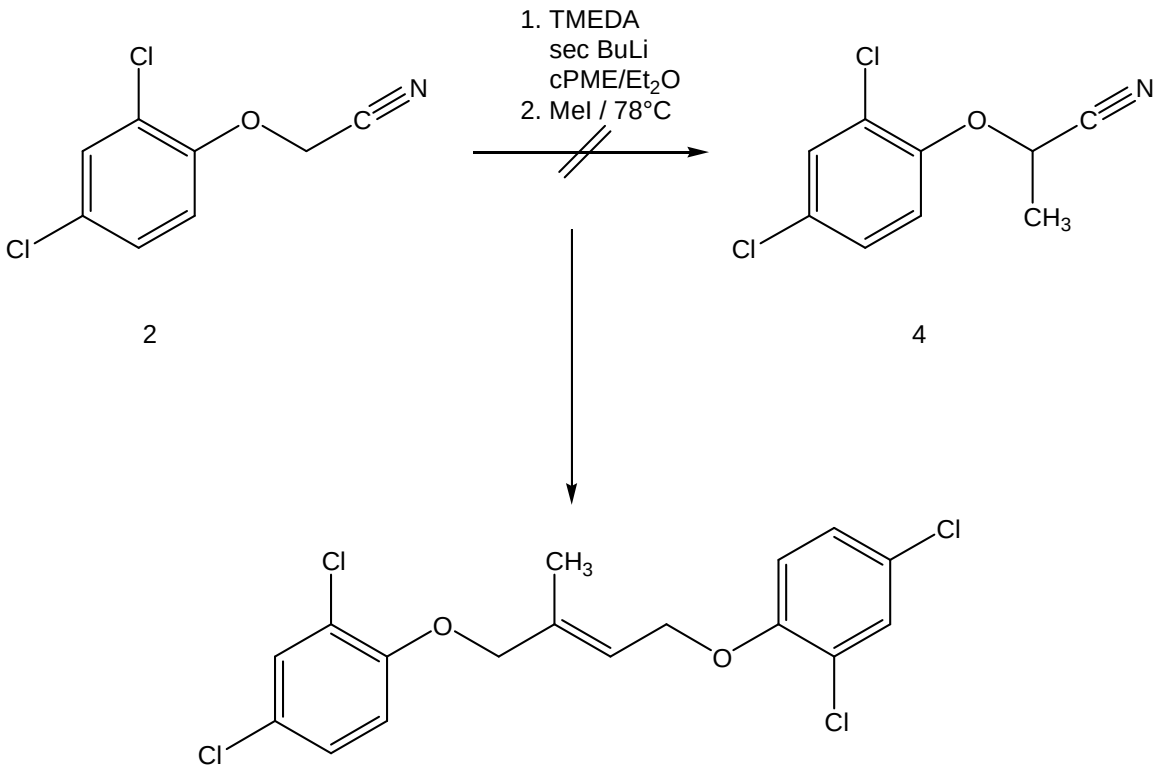
2,4-Dichlorophenol **1** (4g, 24.54 mmol) was put into a two necked round bottom flask equipped with a magnetic stirrer and reflux condenser. Then caesium carbonate (12g, 36.81 mmol) was added and the flask was closed with a septum. The reaction system was set under argon atmosphere and chloroacetonitrile (1.71ml, 26.99 mmol) was added via syringe. In the same way 30 ml acetonitrile was added and the flask was heated under reflux, with 100°C bath temperature over the night.

After cooling down to room temperature the extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The product was white brownish coloured and had an amorphic structure. NMR-Analysis showed the desired product **2**.

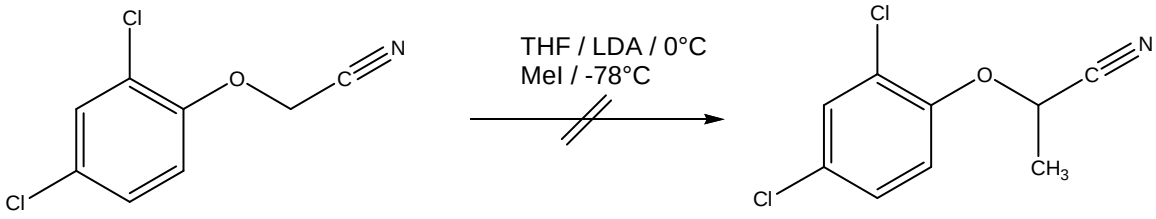
^{1}H-NMR ($CDCl_3$, 500 MHz): 4.82 (s, 2H, OCH_2), 7.02 (m, 1H, aromatic proton), 7.26 (m, 1H, aromatic proton), 7.44 (m, 1H, aromatic proton)

^{13}C-NMR ($CDCl_3$, 500 MHz) 55.09, 114.37, 116.55, 127.99, 129.24, 130.74, 125.17, 150.93

2. Attempt for Synthesis of 2-(2,4-Dichlorophenoxy)-propanenitrile

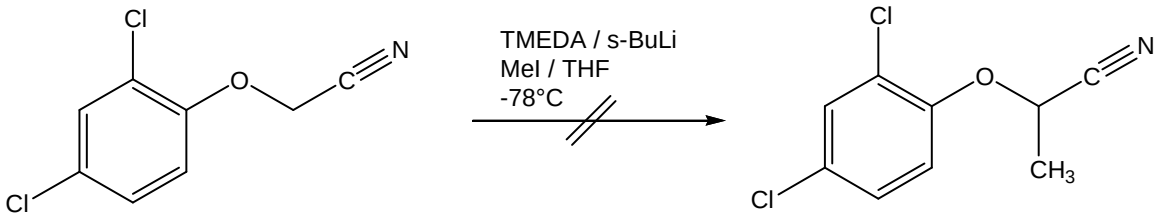


2-(2,4-dichloro-phenoxy)-acetonitrile **2** (201 mg, 1 mmol) was put into a round bottom flask, left under argon atmosphere and 5 ml of the dry solvent cPME was added. Afterwards the system was cooled down to -78°C and TMEDA (348.6 mg, 3 mmol) and a 1.3 M solution of s-BuLi in hexanes (1 ml, 1.3 mmol) were added via syringe, letting it to react for two hours. When the time was over MeI (0.31 ml, 5 mmol) was added dropwise with the syringe leaving it for another two hours. The reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After purification by column chromatography with hexane/ethylacetate 8:2, the first fraction showed a small amount of a white crystal-like powder after evaporation of the solvent, which was not the desired product **4**, but a homocoupling product as in the picture shown above.



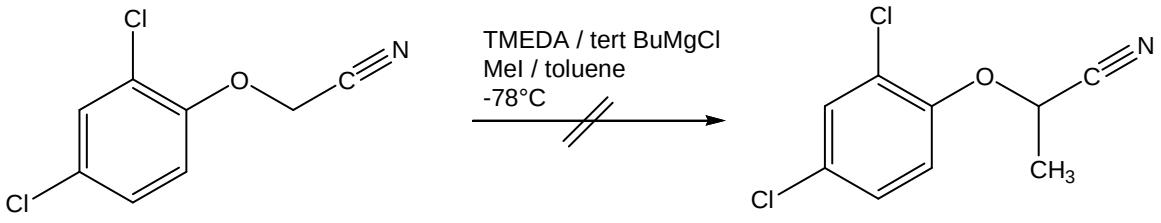
2 4

A three necked 500ml reaction flask, equipped with a magnetic stirrer and septum, was put under argon for 5 minutes and cooled down to 0°C in a bath with normal ice. The reagents were added via syringe, first 25 ml dry THF was added, than LDA was prepared in situ by adding diisopropylamine (0.155 ml, 1.1 mmol) and dropwise a 2.5 M n-BuLi solution in hexanes (0.44 ml, 1 mmol) and letting it to react for one hour. When the time was up the bath would be changed to another one with dry ice to achieve a temperature of -78°C. A solution of 2-(2,4-dichloro-phenoxy)-acetonitrile **2** (201 mg, 1 mmol) in 2 ml THF dry would be added and left for two hours to react, afterwards MeI (0.31 ml, 5 mmol) was added dropwise and the reaction ran over night. The reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material.



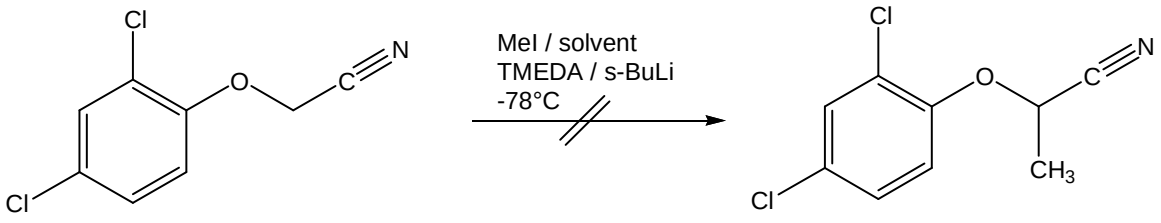
2 4

2-(2,4-dichloro-phenoxy)-acetonitrile **2** (201 mg, 1 mmol) was put into a three necked reaction flask, equipped with a magnetic stirrer and septum, setting it under argon for 5 minutes. After cooling down to -78°C by a bath with dry ice and ethanol, 25 ml of dry THF was added via syringe. TMEDA (348.6 mg, 3 mmol) and a 1.3 M solution of s-BuLi in hexanes (1 ml, 1.3 mmol) were added dropwise via syringe and after 15 minutes MeI (0.31 ml, 5 mmol) was injected dropwise running the reaction for two hours. The reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material.



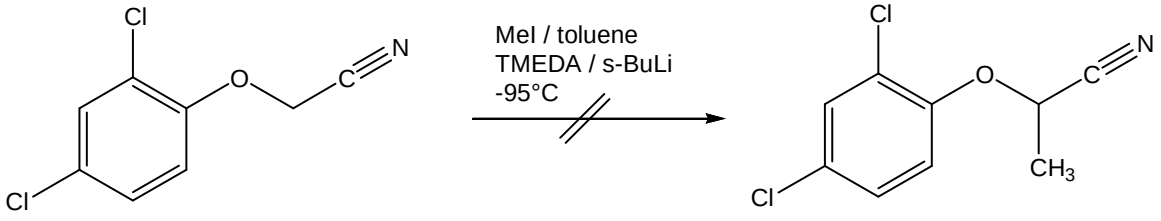
2 4

2-(2,4-dichloro-phenoxy)-acetonitrile **2** (50 mg, 1 mmol) was put into a three necked reaction flask, equipped with a magnetic stirrer and septum, setting it under argon for 5 minutes. After cooling down to -78°C, 25 ml of dry toluene was added via syringe. TMEDA (0.113ml, 3 mmol) and a 1.7 M solution of t-BuMgCl in THF (0.19 ml, 1.3 mmol) were added dropwise via syringe and after two hours MeI (0.08 ml, 5 mmol) was injected dropwise running the reaction for another two hours. The reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material.



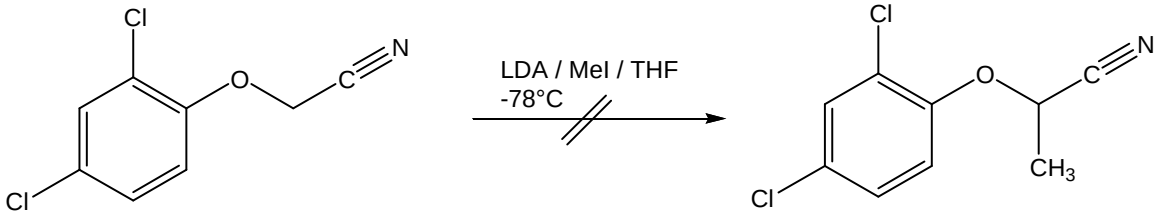
2 4

2-(2,4-dichloro-phenoxy)-acetonitrile **2** (50 mg, 1 mmol) was put into a three necked reaction flask, equipped with a magnetic stirrer and septum, setting it under argon for 5 minutes. After cooling down to -78°C by a bath with dry ice and ethanol, 25 ml dry solvent (diethylether, toluene, THF, Me-THF or cPME) was added via syringe. MeI (0.08 ml, 5 mmol) was injected dropwise. Afterwards TMEDA (0.113ml, 3 mmol) and a 1.3 M solution of s-BuLi in hexanes (0.25 ml, 1.3 mmol) were added dropwise via syringe. The reaction was running for two hours and quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material.



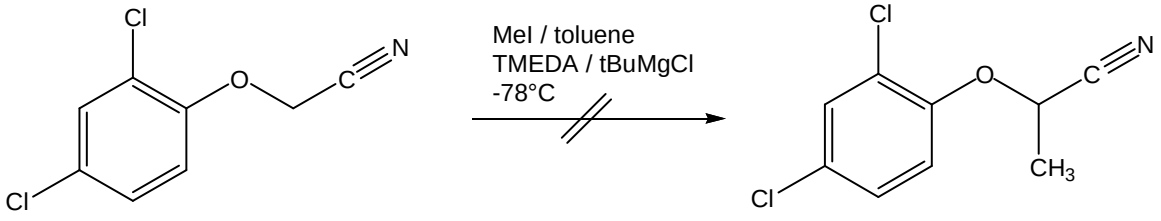
2 4

2-(2,4-dichloro-phenoxy)-acetonitrile **2** (100 mg, 1 mmol) was put into a three necked reaction flask, equipped with a magnetic stirrer and septum, setting it under argon for 5 minutes. After cooling down to -95°C by a bath with liquid nitrogen (which must be added constantly) and diethylether, 25 ml dry toluene was added via syringe. MeI (0.16 ml, 5 mmol) was injected dropwise. Afterwards TMEDA (0.22 ml, 3 mmol) and a 1.3 M solution of s-BuLi in hexanes (0.5 ml, 1.3 mmol) were added dropwise via syringe. The reaction was running for two hours (and seven hours) and quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material.



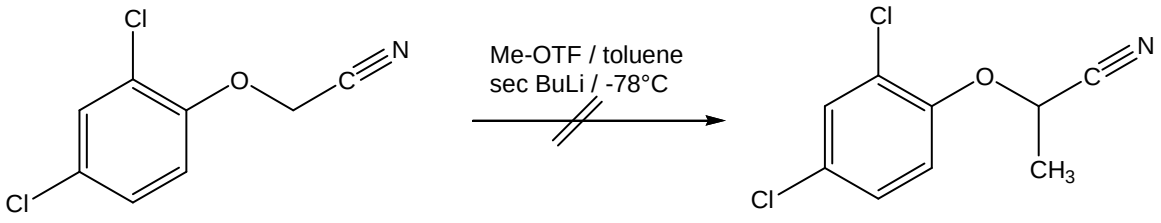
2 4

2-(2,4-dichloro-phenoxy)-acetonitrile **2** (50 mg, 1 mmol) was put into a three necked reaction flask, equipped with a magnetic stirrer and septum, setting it under argon for 5 minutes and cooled down to 0°C in a bath with ice. The reagents were added via syringe, first 5 ml THF-dry was added, than LDA was prepared in situ by adding diisopropylamine (0.08 ml, 1.1 mmol) and dropwise a 2.5 M n-BuLi solution in hexanes (0.2 ml, 1 mmol) and letting it to react for one hour. When the time was over the bath would be changed to another one with dry ice to achieve a temperature of -78°C. A solution of 2-(2,4-dichloro-phenoxy)-acetonitrile **2** (100 mg, 1 mmol) in 45 ml THF dry and MeI (0.16 ml, 5 mmol) would be added to the flask. The reaction was quenched with 5 ml saturated aqueous ammonium chloride solution after two hours. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material.



2 4

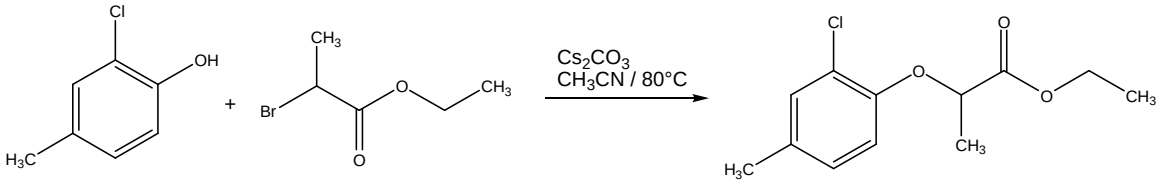
2-(2,4-dichloro-phenoxy)-acetonitrile **2** (50 mg, 1 mmol) was put into a three necked reaction flask, equipped with a magnetic stirrer and septum, setting it under argon for 5 minutes. After cooling down to -78°C by dry ice and ethanol, 25 ml dry toluene was added via syringe. MeI (0.08 ml, 5 mmol) was injected dropwise. Afterwards TMEDA (0.113 ml, 3 mmol) and a 1.7 M solution of t-BuMgCl in THF (0.19 ml, 1.3 mmol) were added dropwise via syringe. The reaction was running for two hours and quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material.



2 4

2-(2,4-dichloro-phenoxy)-acetonitrile **2** (50 mg, 1 mmol) was put into a 100 ml three necked reaction flask, equipped with a magnetic stirrer and septum, setting it under argon for 5 minutes. After cooling down to -78°C by a bath with dry ice and ethanol, 25 ml dry toluene was added via syringe. Me-OTF (0.14 ml, 5 mmol) was injected dropwise and afterwards a 1.3 M solution of s-BuLi in hexanes (0.25 ml, 1.3 mmol) was also added dropwise via syringe. After two hours the reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. TLC and ^{1}H-NMR gave the conclusion, that the reaction was not successful as there was only starting material

3. Synthesis of 2-(2-Chloro-4-methylphenoxy)propionic acid ethyl ester 7a



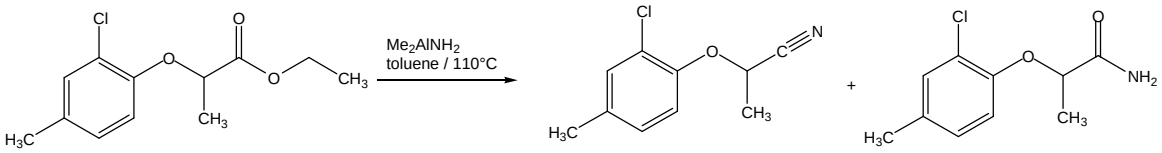
5a 6 7a

Caesium carbonate (4 g, 12.44 mmol) was put into a round bottom flask equipped with a magnetic stirrer, 2-chloro-p-cresol **5a** (0.98 ml, 8.29 mmol) and 19 ml of the solvent acetonitrile were added. The flask was closed with a reflux condenser and after 15 minutes ethyl 2- bromopropionate **6** (1.07 ml, 8.29 mmol) was added, leaving the reaction for three hours at 80°C under reflux. The reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After column chromatography with hexane/ ethylacetate 9:1 the NMR analysis of the first fraction showed the desired product **7a**.

^{1}H-NMR ($CDCl_3$, 500 MHz): 1.25 (t, 3H, Et CH_3), 1.65 (d, 3H, CH_3), 2.26 (s, 3H, Ar-CH_3), 4.21 (q, 2H, EtCH_2), 4.69 (q, 1H, CH), 6.77 (m, 1H, aromatic proton), 6.94 (m, 1H, aromatic proton), 7.18 (m, 1H, aromatic proton),

^{13}C-NMR ($CDCl_3$, 500 MHz): 14.08, 18.47, 20.30, 61.26, 74.46, 115.75, 123.57, 127.96, 130.93, 132.52, 151.21, 171.81

4. Transformation of 2-(2-Chloro-4-methylphenoxy)propionic acid ethyl ester 7a



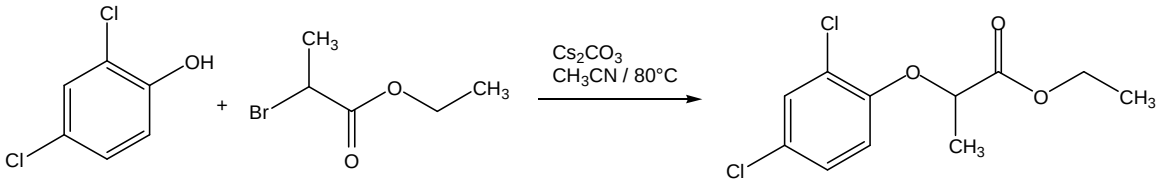
7a 8 9

A three necked reaction flask equipped with a magnetic stirrer, reflux condenser and septum was set under argon atmosphere and cooled down to 0°C in an ice bath. For formation of Me_2AlNH_2, 10 ml toluene, 0.5 M ammonia in dioxane (52.72 ml, 26.37 mmol) and dropwise a trimethylaluminum solution 2.0 M in toluene (12.36 ml, 24.72 mmol) were added and left for one hour to react. Then 2-(2-chloro-4-methylphenoxy)propionic acid ethyl ester **7a** (0.7 ml, 3.296 mmol) was added dropwise and the temperature was put up to 110°C. As one hour of stirring under reflux passed the transparent liquid turned orange and after checking by TLC the reaction was stopped with distilled water. The extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After column chromatography with hexane/ethylacetate 9:1 as mobile phase two fractions were collected. In the first fraction after evaporation of the solvent a transparent reddish coloured liquid was collected, which proved by ^{1}H-NMR analysis to be the desired nitrile **8**. As the solvent was removed from the second fraction the ^{1}H-NMR analysis of this white powder showed the amide **9**.

8: ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.8-2.0 (d, 3H, CH_3), 2.3-2.5 (s, 3H, Ar-CH_3), 4.8-5.1 (q, 1H, CH), 7.05-7.2 (s, 2H, Ph-H), 7.3-7.4 (s, 1H, Ph-H)

9: ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.6-1.8 (d, 3H, CH_3), 2.3-2.6 (s, 3H, Ar-CH_3), 4.6-4.9 (q, 1H, CH), 6.0-6.4 (s, 2H, NH_2), 6.75-7.25 (m, 3H, Ph-H)

5. Synthesis of 2-(2,4-dichlorophenoxy)propionic acid ethyl ester 7b

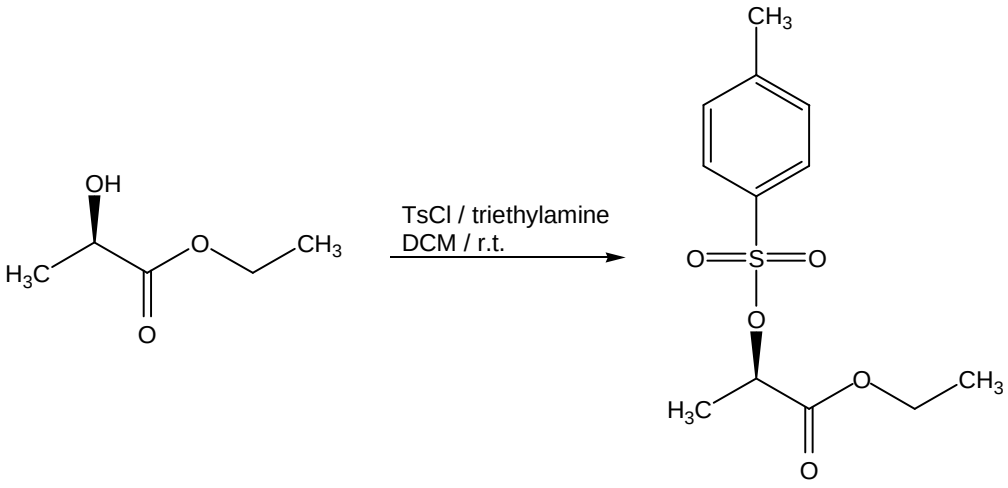


5b 6 7b

Caesium carbonate (4 g, 12.44 mmol) was put into a round bottom flask equipped with a magnetic stirrer, reflux condenser and septum setting it under argon atmosphere. 2,4-dichloro-phenol **5b** (1.35 g, 8.29 mmol) and 10 ml acetonitrile were added. After 15 minutes ethyl 2- bromopropionate **6** (1.07 ml, 8.29 mmol) was added and the flask was closed with a reflux condenser, leaving the reaction for three hours at 80°C under reflux. The reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. NMR analysis showed the desired product **7b**.

^{1}H-NMR ($CDCl_3$, 500 MHz): 1.24 (t, 3H, Et CH_3), 1.66 (d, 3H, CH_3), 4.20 (q, 2H, EtCH_2), 4.70 (q, 1H, CH), 6.77 (m, 1H, aromatic proton), 7.12 (m, 1H, aromatic proton), 7.36 (m, 1H, aromatic proton),

6. Synthesis of (-)-2-[(p-Tolyl sulfonyl)- oxy] propionic acid ethyl ester 11

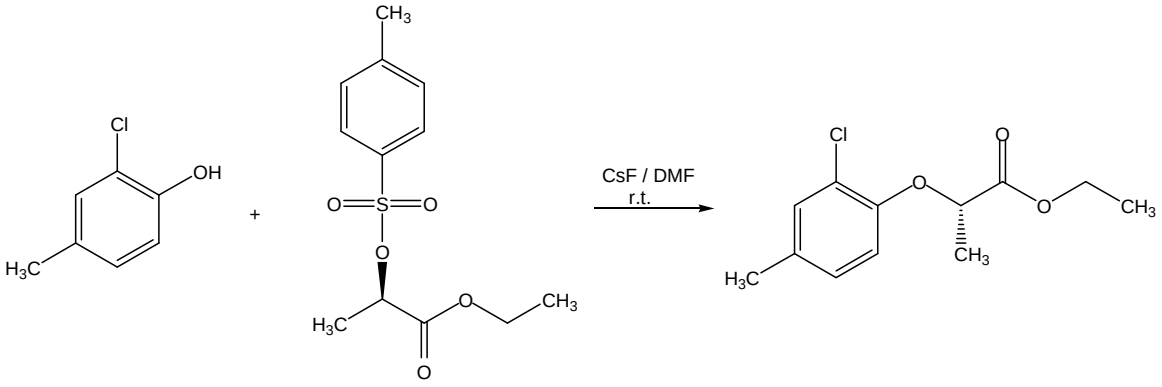


10 11

In a round bottom flask equipped with magnetic stirrer L-(-)-lactate **10** (5 g, 42.44 mmol) was dissolved with 10 ml DCM. After dissolution of p-toluenesulfonyl chloride (16.4 g, 84.66 mmol) in 7 ml DCM the two solutions were combined. Triethylamine (8.47 ml, 42.33 mmol) was added dropwise and the now orange coloured mixture was closed with a septum and left at room temperature for stirring for 18 hours (over night). Extraction was performed three times with ethylacetate and 1N hydrochloric acid and washed three times with distilled water. The organic phase was dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After purification by column chromatography with hexane/ethylacetate 9:1 as mobile phase, the ^{1}H-NMR of the second fraction showed the desired (-) tosyl ester **11**.

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.20-1.35 (t, 3H, $EtCH_3$), 1.5-1.7 (d, 3H, CH_3), 2.4-2.55 (s, 3H, Ar-CH_3), 4.1-4.25 (q, 2H, OCH_2), 4.8-5.05 (q, 1H, OCH_2), 7.3-7.5 (d, 2H, aromatic proton), 7.75-8.0 (d, 2H, aromatic proton)

7. Synthesis of (2S)- 2-(2-Chloro-4-methylphenoxy)-propionic acid ethyl ester 13a

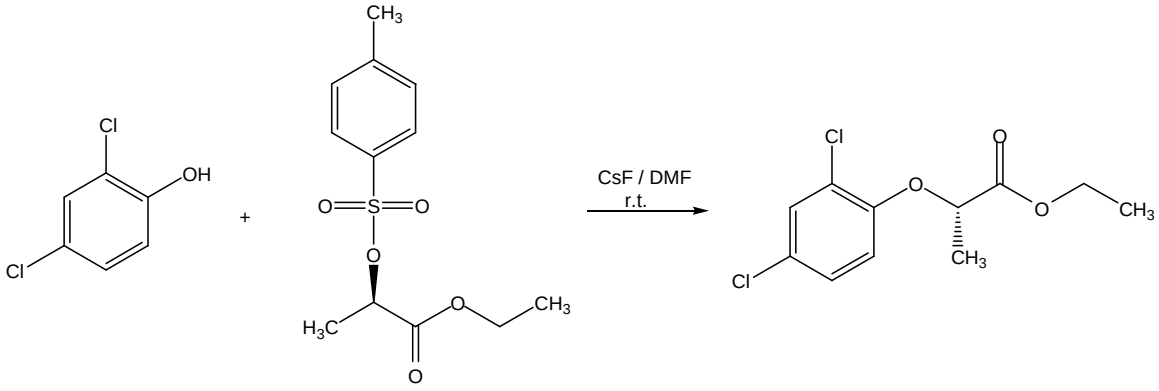


12a 11 13a

Into a three necked reaction flask equipped with a magnetic stirrer caesium fluoride (835.4 mg, 5.5 mmol) was added, the flask was closed with a septum and put under argon atmosphere at room temperature. After addition of 17ml DMF, 2-chloro-p-cresol **12a** (784.2 mg, 5.5 mmol) was added and the mixture was stirred for 20 minutes. Then the (-) tosyl ester **11** (294.1 mg, 1.83 mmol) in 4.25 ml DMF was added dropwise. As 32 hours passed the mixture was diluted with ethylacetate and washed three times with saturated solution of sodium bicarbonate and three times with brine. The organic phase was dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After column chromatography with hexane/ethylacetate 9:1 as mobile phase, the first fraction showed the desired ester **13a** at ^{1}H-NMR analysis.

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.25-1.5 (t, 3H, $EtCH_3$), 1.7-1.85 (d, 3H, CH_3), 2.3-2.5 (s, 3H, Ar- CH_3), 4.2-4.4 (q, 2H, OCH_2), 4.7-4.8 (q, 1H, OCH), 6.75-7.25 (m, 3H, aromatic proton)

8. Synthesis of (2S)- 2-(2,4-Dichlorophenoxy)-propionic acid ethyl ester 13b



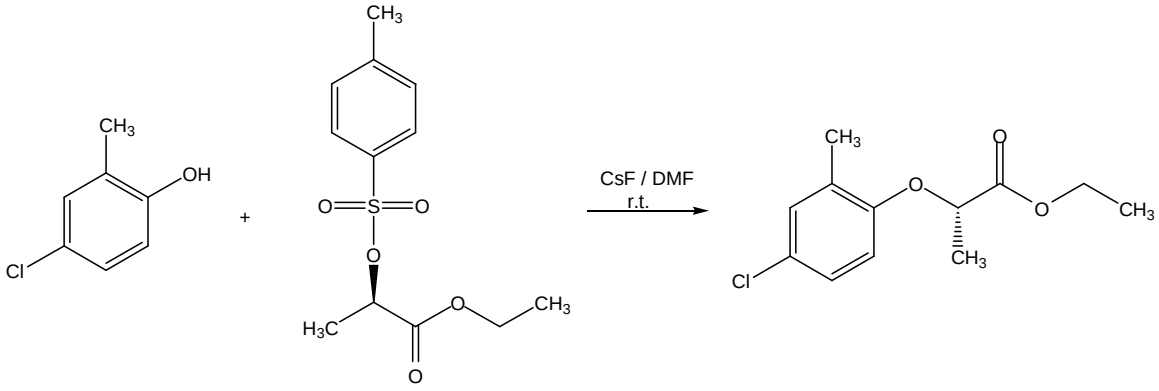
12b 11 13b

A three necked reaction flask equipped with a magnetic stirrer was filled with caesium fluoride (835.4 mg, 5.5 mmol). The flask was closed with a septum and put under argon atmosphere at room temperature. After addition of 17ml DMF, 2,4-dichloro-phenol **12b** (896.5 mg, 5.5 mmol) was added and the mixture was stirred for 20 minutes. Then the (-) tosyl ester **11** (294.1 mg, 1.83 mmol) in 4.25 ml DMF was added dropwise. As 18 hours passed the mixture was diluted with ethylacetate and washed three times with saturated solution of sodium bicarbonate and three times with brine. The organic phase was dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After column chromatography with hexane/ethylacetate 9:1 as mobile phase, the first fraction showed the desired ester **13b** at ^{1}H-NMR and NMR analysis.

^{1}H-NMR ($CDCl_3$, 500 MHz): 1.25 (t, 3H, $EtCH_3$), 1.67 (d, 3H, CH_3), 4.21 (q, 2H, $EtCH_2$), 4.71 (q, 1H, CH), 6.78 (d, 1H, aromatic proton), 7.13 (m, 1H, aromatic proton), 7.38 (d, 1H, aromatic proton)

^{13}C-NMR ($CDCl_3$, 500 MHz) 14.09, 18.39, 61.48, 74.39, 116.06, 124.74, 126.99, 127.46, 130.25, 152.26, 171.29

9. Synthesis of (2*S*)- 2-(4-Chloro-2-methylphenoxy)- propionic acid ethyl ester 13c

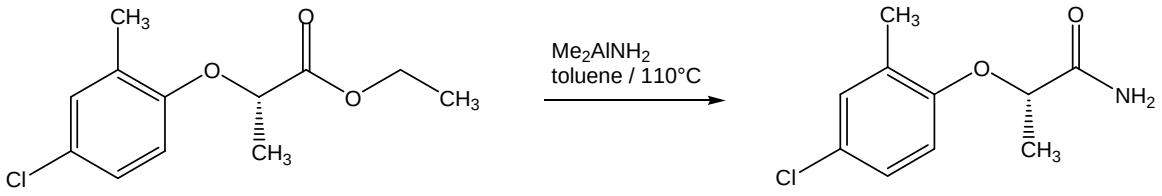


12c 11 13c

A three necked reaction flask equipped with a magnetic stirrer was filled with caesium fluoride (835.4 mg, 5.5 mmol). The flask was closed with a septum and put under argon atmosphere at room temperature. After addition of 8.5 ml DMF, 4-chloro-o-cresol **12c** (784.2 mg, 5.5 mmol) was added and the mixture was stirred for 20 minutes. Then the (-) tosyl ester **11** (294.1 mg, 1.83 mmol) in 3 ml DMF was added dropwise. As 32 hours passed the mixture was diluted with ethylacetate and washed three times with saturated solution of sodium bicarbonate and three times with brine. The organic phase was dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After column chromatography with hexane/ethylacetate 9:1 as mobile phase, the first fraction showed the desired ester **13c** at ^{1}H-NMR analysis.

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.2-1.9 (t, 3H, $EtCH_3$), 1.5-1.75 (d, 3H, CH_3), 2.25-2.4 (s, 3H, Ar- CH_3), 4.2-4.3 (q, 2H, $EtCH_2$), 4.6-4.8 (q, 1H, CH), 6.5-6.7 (d, 1H, aromatic proton), 7.0-7.25 (m, 2H, aromatic proton)

10. Synthesis of (2S)- 2-(4-Chloro-2-methylphenoxy)- propanamide 14



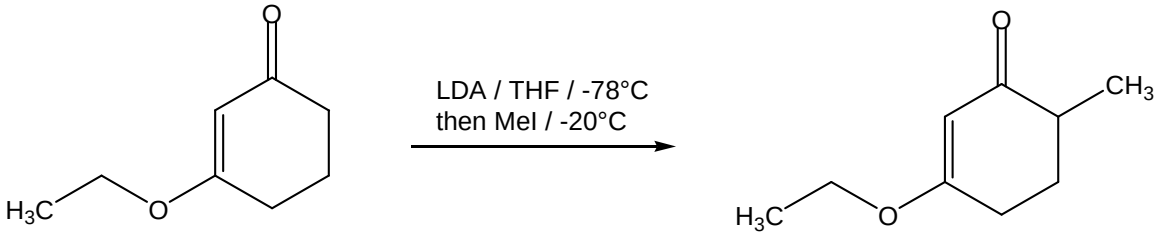
13c 14

A three necked reaction flask equipped with a magnetic stirrer, reflux condenser and septum was set up under argon atmosphere and cooled down to 0°C. For formation of Me_2AlNH_2, 10 ml toluene, 0.5 M ammonia in dioxane (26.22 ml, 13.11 mmol) and dropwise trimethylaluminum solution 2.0 M in toluene (6.14 ml, 12.293 mmol) were added and left for one hour to react. (2*S*)- 2-(4-chloro-2-methylphenoxy)- propionic acid ethyl ester **13c** (396.8 mg, 1.64 mmol) was added dropwise and the temperature was put up to 110°C. As one hour of stirring under reflux passed the TLC showed no reaction so the mixture was left for stirring over night for 18 hours altogether. The transparent liquid turned orange and after checking by TLC the reaction was stopped with distilled water. The extraction was performed three times with ethylacetate and brine. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. After silica gel chromatography with hexane/ethylacetate 9:1 as mobile phase the last fraction showed the amide at ^{1}H-NMR and NMR analysis.

^{1}H-NMR ($CDCl_3$, 500 MHz): 1.59 (d, 3H, CH_3), 2.25 (s, 3H, Ar-CH_3), 4.61 (q, 1H, CH), 5.78 (m, 1H, NH), 6.37 (m, 1H, NH), 6.71 (d, 1H, aromatic proton), 7.10 (m, 1H, aromatic proton), 7.15 (m, 1H, aromatic proton)

^{13}C-NMR ($CDCl_3$, 500 MHz): 16.32, 18.56, 75.32, 113.68, 126.56, 126.71, 129.03, 130.91, 153.59, 174.73

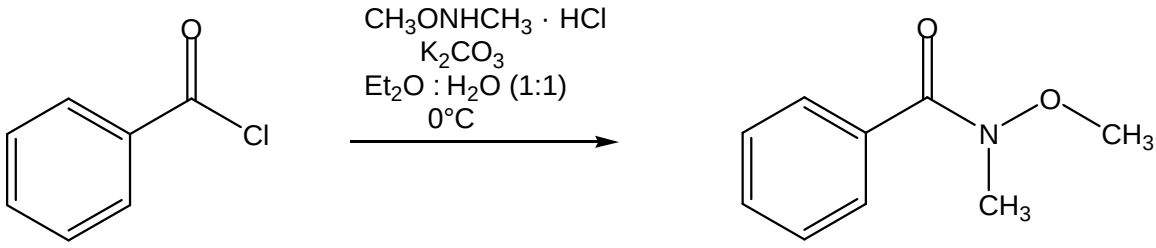
11. Synthesis of 3-Ethoxy-6-methyl-2-cyclohexen-1-one 16



15 16

A three necked reaction flask equipped with a magnetic stirrer and septum was set up under argon atmosphere and cooled down to 0°C. For keeping the argon atmosphere all the reagents were added via syringe. For formation of LDA in situ a 2.5 M n-BuLi solution in hexanes (8.5 ml, 21.4 mmol) was added dropwise to a solution of diisopropylamine (3.31 ml, 23.54 mmol) in 16.81 ml THF dry, letting it to react for one hour. When the time was over the bath would be changed to another one with dry ice to achieve a temperature of -78°C. Then a mixture of 3-Ethoxy-2-cyclohexenone **15** (1.8 ml, 13.48 mmol) and 10.03 ml THF dry was added dropwise. After 30 minutes MeI (4.21 ml, 67.4 mmol) was added dropwise and the reaction was left over night. It was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed two times with ethylacetate and brine and the organic phase was washed with distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The column chromatography was started with hexane/ethylacetate 8:2 as mobile phase and after increasing the polarity the fractions 15-49 showed the desired product **16** at ^{1}H-NMR.

12. Synthesis of N-Methoxy-N-methyl-benzamide 18

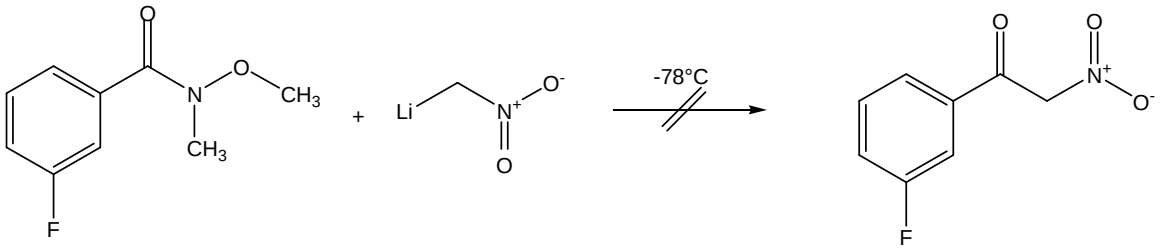


17 18

A three necked reaction flask equipped with a magnetic stirrer was filled with N,O-dimethylhydroxylamine hydrochloride (956 mg, 15.65 mmol) and potassium carbonate (5.899 g, 42.69 mmol). The flask was closed with a septum, set under argon atmosphere and cooled down to 0°C in a bath with ice. 30 ml of a mixture of diethylether and distilled water 1:1 and benzoylchloride **17** (1.65 ml, 14.23 mmol) were added. After one hour of stirring at 0°C the extraction was performed three times with diethylether and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. As the TLC showed a lot of starting material **17** beside the desired product **18** the reaction was repeated, by adding diethylether, N,O-dimethylhydroxylamine hydrochloride and potassium carbonate under argon to the dried mixture. After another 1.5 hours of stirring at 0°C the extraction was performed three times with diethylether and distilled water. The organic phase was collected and again dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The ^{1}H-NMR analysis showed the desired product.

^{1}H-NMR ($CDCl_3$, 200 MHz): 3.4 (s, 3H, CH_3), 3.6 (s, 3H, CH_3), 7.4-7.6 (m, 3H, aromatic proton), 7.7-7.8 (m, 2H, aromatic proton)

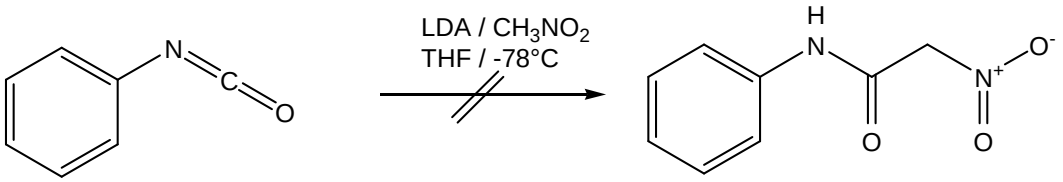
13. Attempt of Synthesis of 1-(3-Fluoro-phenyl)-2-nitro-ethanone 23



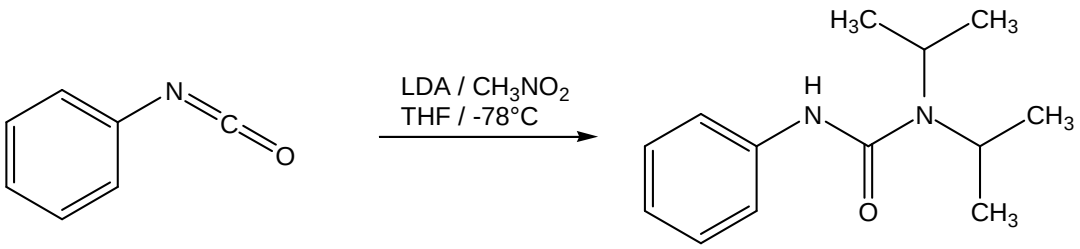
22 21 23

A three necked reaction flask equipped with a magnetic stirrer and septum was set up under argon atmosphere and cooled down to 0°C in a bath with ice. For keeping the argon atmosphere all the reagents were added via syringe. For formation of LDA in situ a 2.5 M n-BuLi solution in hexanes (1 ml, 2.5 mmol) was added dropwise to a solution of diisopropylamine (0.39 ml, 2.8 mmol) in 5 ml THF dry, letting it to react for a half hour. When the time was over the bath would be changed to another one with dry ice to achieve a temperature of -78°C. To form the organolithium reagent **21,** nitromethane (0.16 ml, 3 mmol) was added to the mixture, and left for stirring another half hour, than the weinreb amide **22** was added. After one hour the reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with diethylether and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The TLC and the ^{1}H-NMR showed only the starting material.

14. Attempt for Synthesis of 2-Nitroacetanilide 25



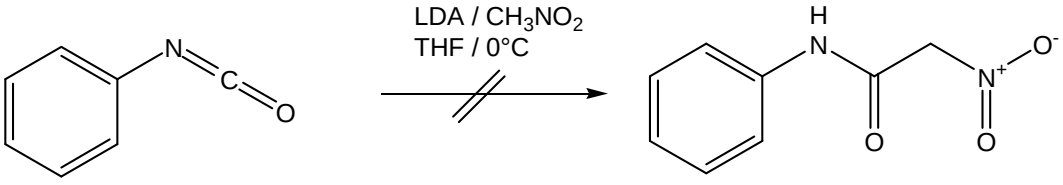
24 25



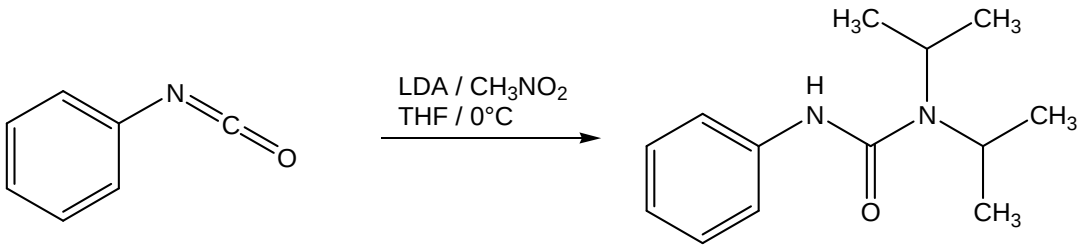
24 26

A three necked reaction flask equipped with a magnetic stirrer and septum was set up under argon atmosphere and cooled down to 0°C in a bath with ice. For keeping the argon atmosphere all the reagents were added via syringe. For formation of LDA in situ a 2.5 M n-BuLi solution in hexanes (1 ml, 2.5 mmol) was added dropwise to a solution of diisopropylamine (0.39 ml, 2.8 mmol) in 5 ml THF dry, letting it to react for a half hour. When the time was over the bath would be changed to another one with dry ice to achieve a temperature of -78°C. To form the organolithium reagent **21,** the LDA mixture was added to another argon atmosphere flask with nitromethane (0.16 ml, 3 mmol) in 2 ml THF dry and left for stirring another half hour at -78°C. Than the phenyl isocyanate **24** (0.11 ml, 1 mmol) was added. After 1.5 hours the reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The ^{1}H-NMR showed not the expected product **25**, but the 1,1-diisopropyl-3-phenylurea **26** was formed.

^{1}H-NMR ($CDCl_3$, 200 MHz): 1.25-1.5 (d, 12H, CH_3), 3.8-4.1 (septet, 2H, CH), 6.2-6.3 (s, 1H, NH), 7.0 (m, 1H, aromatic proton), 7.25-7.5 (m, 4H, aromatic proton)



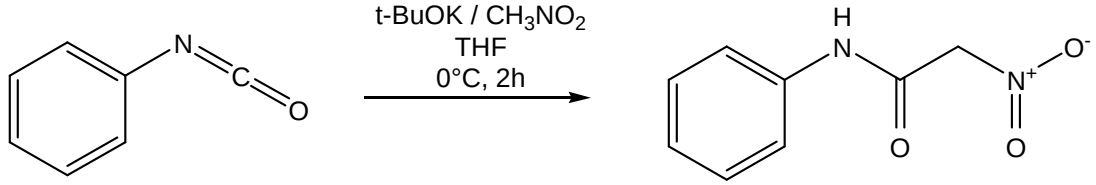
24 25



24 26

A three necked reaction flask equipped with a magnetic stirrer and septum was set up under argon atmosphere and cooled down to 0°C. For keeping the argon atmosphere all the reagents were added via syringe. For formation of LDA in situ a 2.5 M n-BuLi solution in hexanes (1 ml, 2.5 mmol) was added dropwise to a solution of diisopropylamine (0.39 ml, 2.8 mmol) in 5 ml THF dry, letting it to react for a half hour. When the time was over the bath would be changed to another one with dry ice to achieve a temperature of -78°C. To form the organolithium reagent **21,** the LDA mixture was added to another argon atmosphere flask with nitromethane (0.16 ml, 3 mmol) in 2 ml THF dry and left for stirring another half hour at -78°C. Than the temperature was risen to 0°C, changing the dry ice bath to a normal ice- bath, and phenyl isocyanate **24** (0.11 ml, 1 mmol) was added. After one hour the reaction was quenched with 5 ml saturated aqueous ammonium chloride solution. Extraction was performed three times with ethylacetate and distilled water. The organic phase was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The ^{1}H-NMR showed not the expected product **25**, as the 1,1-Diisopropyl-3-phenylurea **26** was formed.

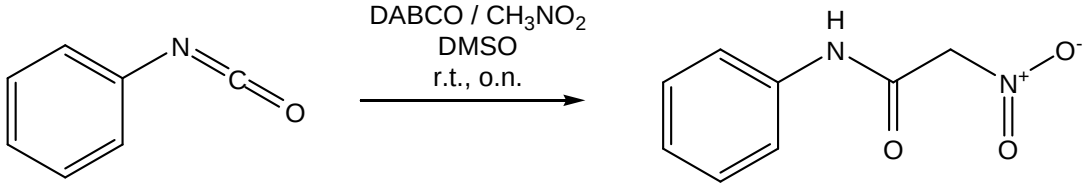
^{1}H-NMR ($CDCl_3$, 200 MHz): 1.25-1.5 (d, 12H, CH_3), 3.8-4.15 (septet, 2H, CH), 6.25 (s, 1H, NH), 7.0 (m, 1H, aromatic proton), 7.25-7.5 (m, 4H, aromatic proton)



24 25

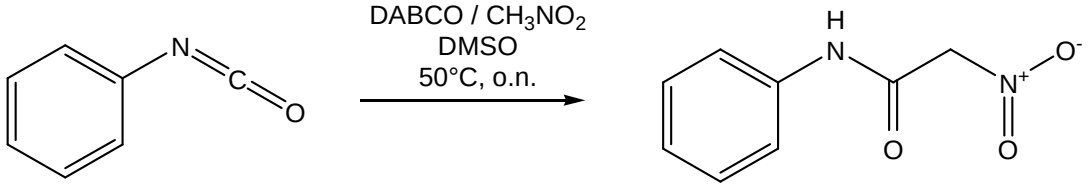
A three necked reaction flask equipped with a magnetic stirrer and septum was set up under argon atmosphere and cooled down to 0°C. For keeping the argon atmosphere all the reagents were added via syringe. Nitromethane (0.05 ml, 1 mmol) in 2 ml THF dry and 1M t-BuOK solution in THF (1 ml, 1 mmol) were added and left for stirring for 30 minutes, whilst the mixture turned yellow.

After addition of phenyl isocyanate **24** (0.10 ml, 0.9 mmol) the yellow colour was more intense. As two hours of stirring passed the reaction was quenched with 5 ml distilled water. Extraction was performed with ethylacetate and the organic phase was washed five times with brine. It was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The ^{1}H-NMR showed that the reaction worked to access the expected product **25**. No column chromatography was performed, because the aim was just to see if this reaction is possible.



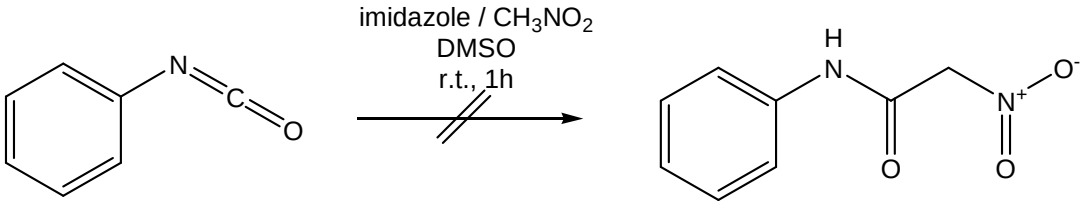
24 25

A three necked reaction flask equipped with a magnetic stirrer and septum was set up under argon atmosphere. For keeping the argon atmosphere all the reagents were added via syringe. Nitromethane (0.05 ml, 1 mmol) in 0.8 ml DMSO and DABCO (0.22 ml, 2 mmol) were added and left for stirring for 30 minutes, whilst the mixture turned yellow. After addition of phenyl isocyanate **24** (0.10 ml, 0.9 mmol) the colour turned red. As two hours of stirring passed the reaction was quenched with 5 ml distilled water. Extraction was performed with ethylacetate and the organic phase was washed five times with brine. It was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The ^{1}H-NMR showed that the reaction worked to access the expected product **25**. No column chromatography was performed, because the aim was just to see if this reaction is possible.



24 25

A three necked reaction flask equipped with a magnetic stirrer, reflux condenser and septum was set up under argon atmosphere. For keeping the argon atmosphere all the reagents were added via syringe. Nitromethane (0.05 ml, 1 mmol) in 0.8 ml DMSO and DABCO (0.22 ml, 2 mmol) were added and left for stirring for 30 minutes at 50°C, whilst the mixture turned yellow. After addition of phenyl isocyanate **24** (0.10 ml, 0.9 mmol) the colour turned red and stirring was continued over night. The reaction was quenched with 5 ml distilled water. Extraction was performed with ethylacetate and the organic phase was washed five times with brine. It was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The ^{1}H-NMR showed that the reaction worked to access the expected product **25**. No column chromatography was performed, because the aim was just to see if this reaction is possible.



24 25

Imidazole (136.3 mg, 2 mmol) was added to a three necked reaction flask equipped with a magnetic stirrer and septum and was set up under argon atmosphere. For keeping the argon atmosphere all the reagents were added via syringe. Nitromethane (0.05 ml, 1 mmol) in 0.9 ml DMSO was added and left for stirring for 30 minutes, whilst the mixture turned yellow. After addition of phenyl isocyanate **24** (0.10 ml, 0.9 mmol) the colour did not change and stirring was continued for one hour. The reaction was quenched with 5 ml distilled water. Extraction was performed with ethylacetate and the organic phase was washed five times with brine. It was collected, dried over sodium sulfate, filtrated and the solvent was evaporated under vacuum. The ^{1}H-NMR showed that the reaction did not work to access the expected product **25**.

List of abbreviations

^{13}C-NMR	carbon-13 nuclear magnetic resonance
^{1}H-NMR	proton nuclear magnetic resonance
BZD	benzodiazepines
$CDCl_3$	deuterated chloroform
CH_3CN	acetonitrile
$CH_3ONHCH_3 \cdot HCl$	N,O-dimethylhydroxylamine hydrochloride
Cl^-	chloride
cPME	cyclopentyl methyl ether
$CsCO_3$	caesium carbonate
CsF	caesium fluoride
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DEE, Et_2O	dietheylether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
GABA	γ-aminobutyric acid
GABA-T	GABA-transaminase
GAD	glutamic acid decarboxylase
GAT	GABA transporters
HCO_3^-	bicarbonate
K_2CO_3	potassium carbonate
LDA	lithium diisopropylamide
Me_2AlNH_2	aminodimethylalane
MeI	iodomethane
Me-OTF	methyl trifluoromethanesulfonate
Me-THF	2-methyltetrahydrofuran
n-BuLi	normal-butyllithium
o.n.	over night
r.t.	room temperature
s-BuLi	sec-butyllithium
SSADH	succinic semialdehyde dehydrogenase

STM	starting material
t-BuLi	tert-butyllithium
t-BuMgCl	tert-butylmagnesium chloride
t-BuOK	potassium tert-butoxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	membrane-spanning α-helices
TMEDA	tetramethylethylenediamine
TsCl	p-toluenesulfonyl chloride, tosyl chloride
VPA	valproic acid

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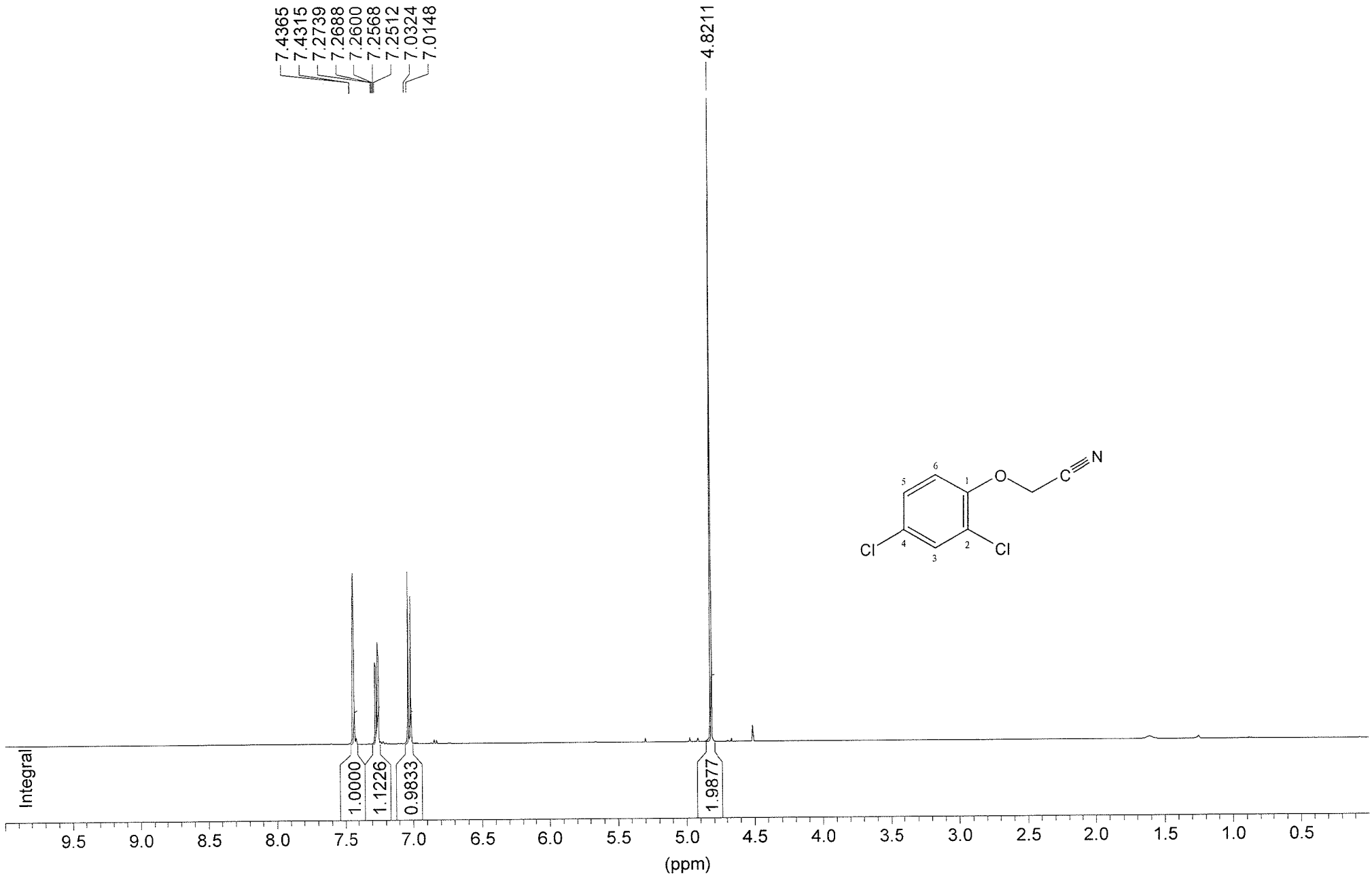
VL001 in cdcl3 (Proton), 13.3.2015



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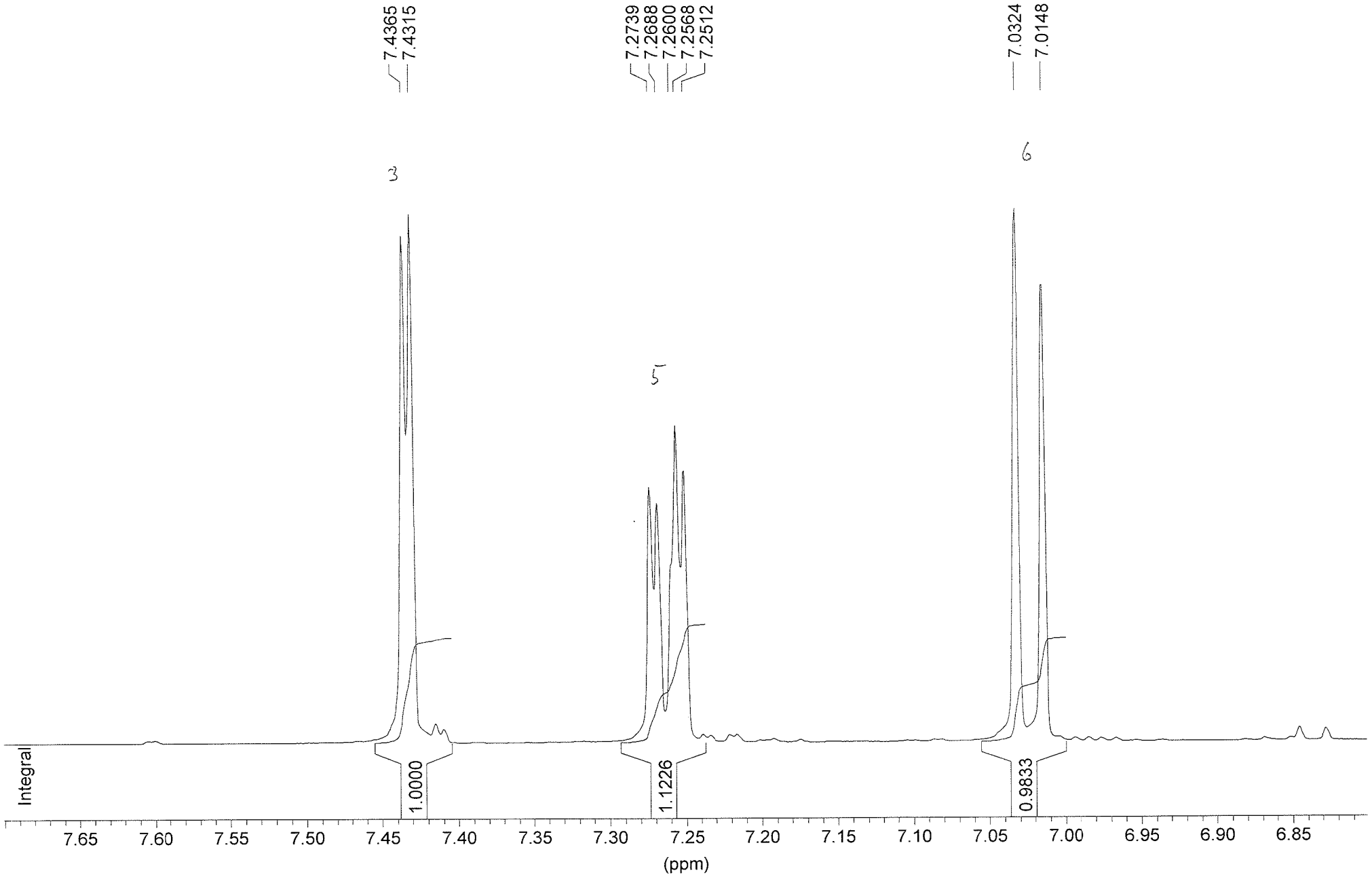

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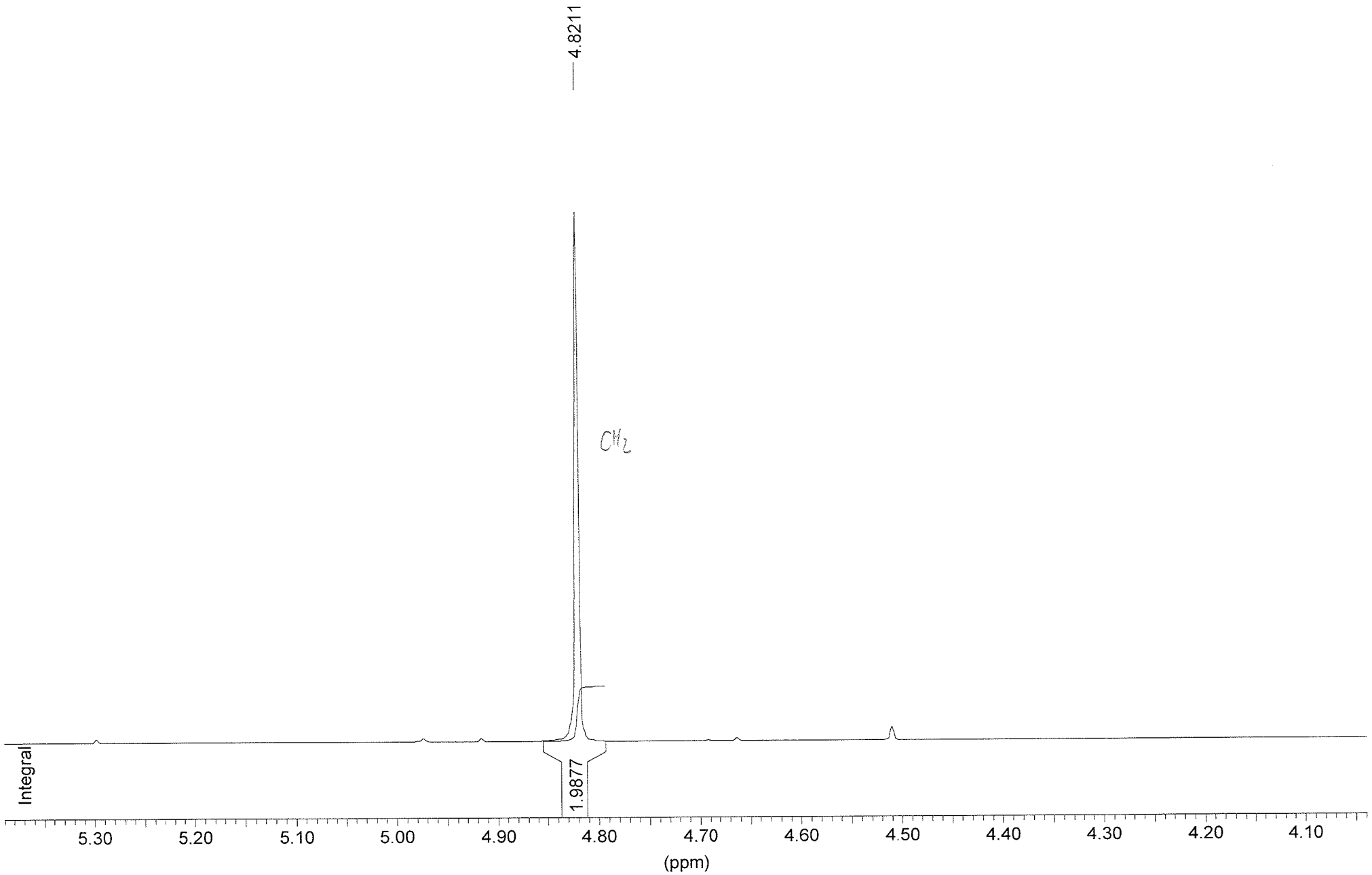

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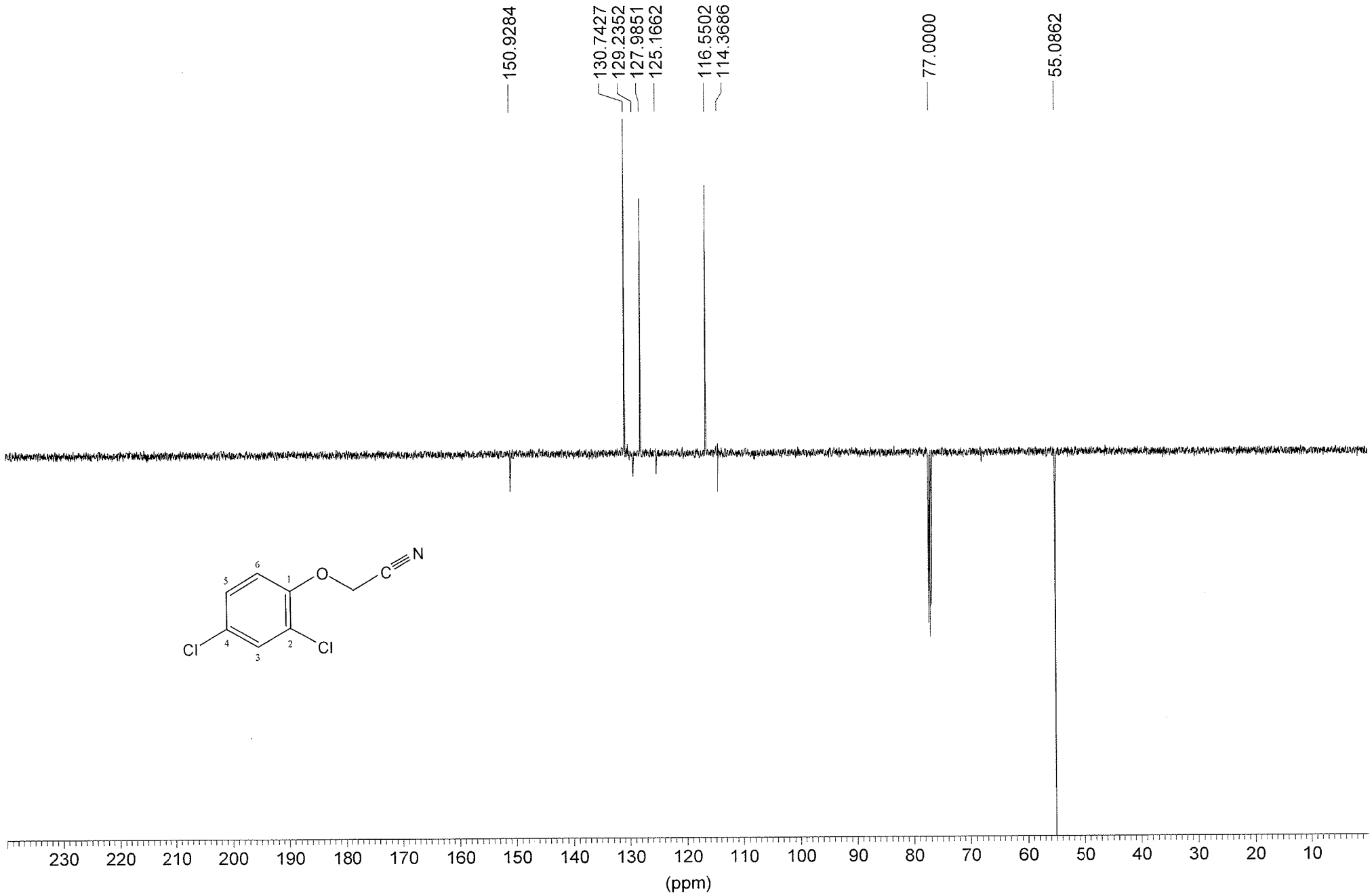

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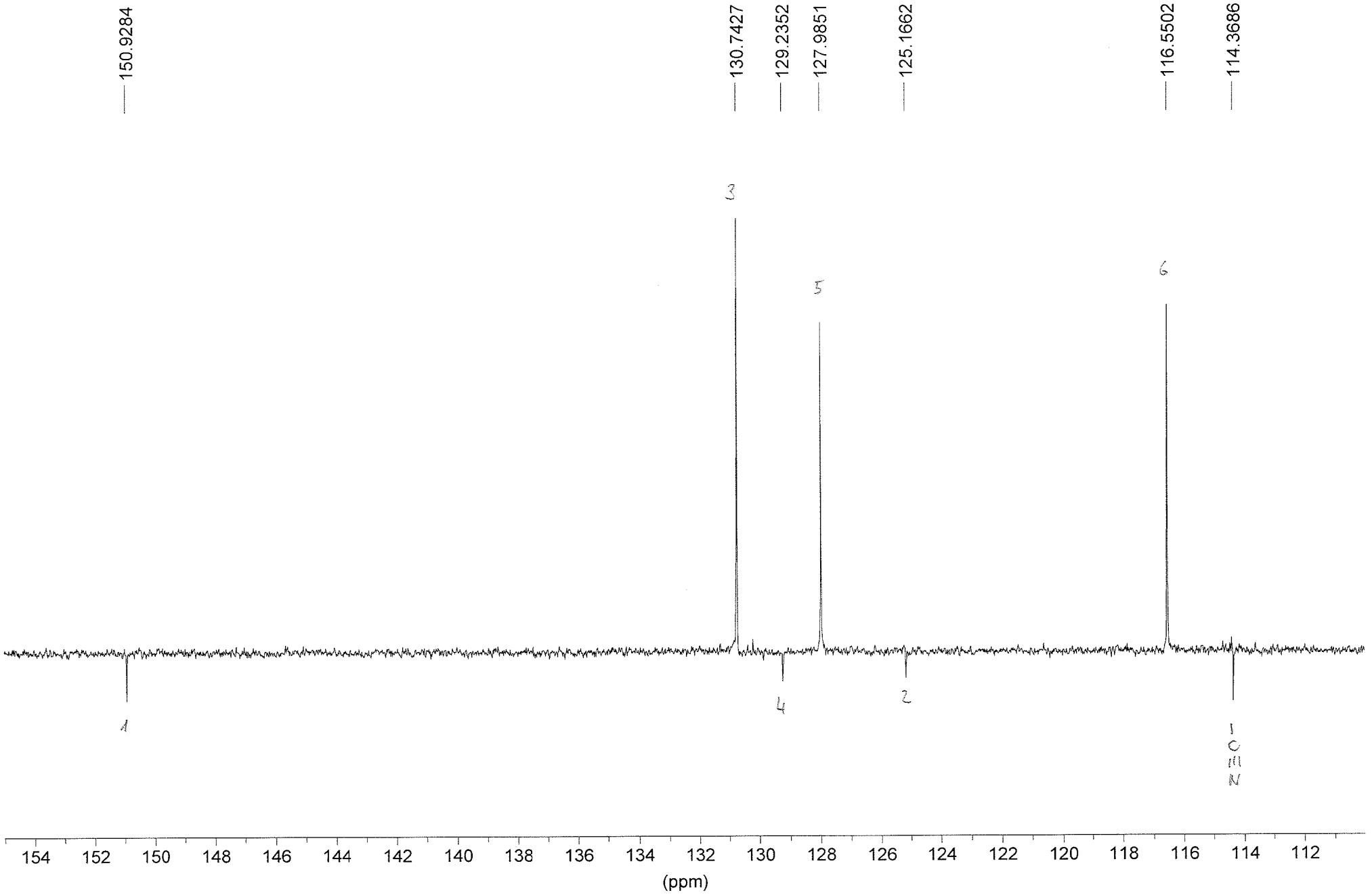

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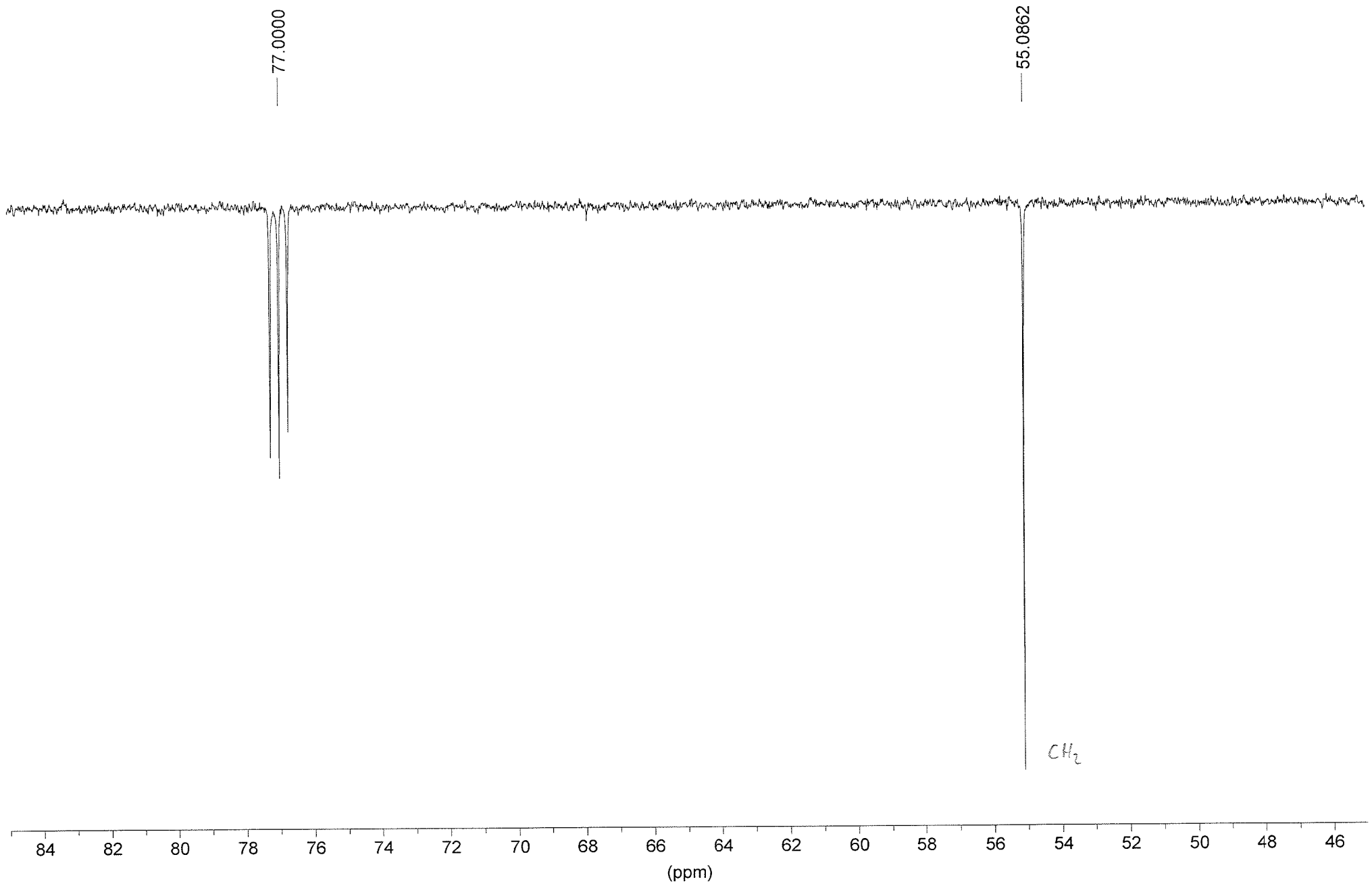

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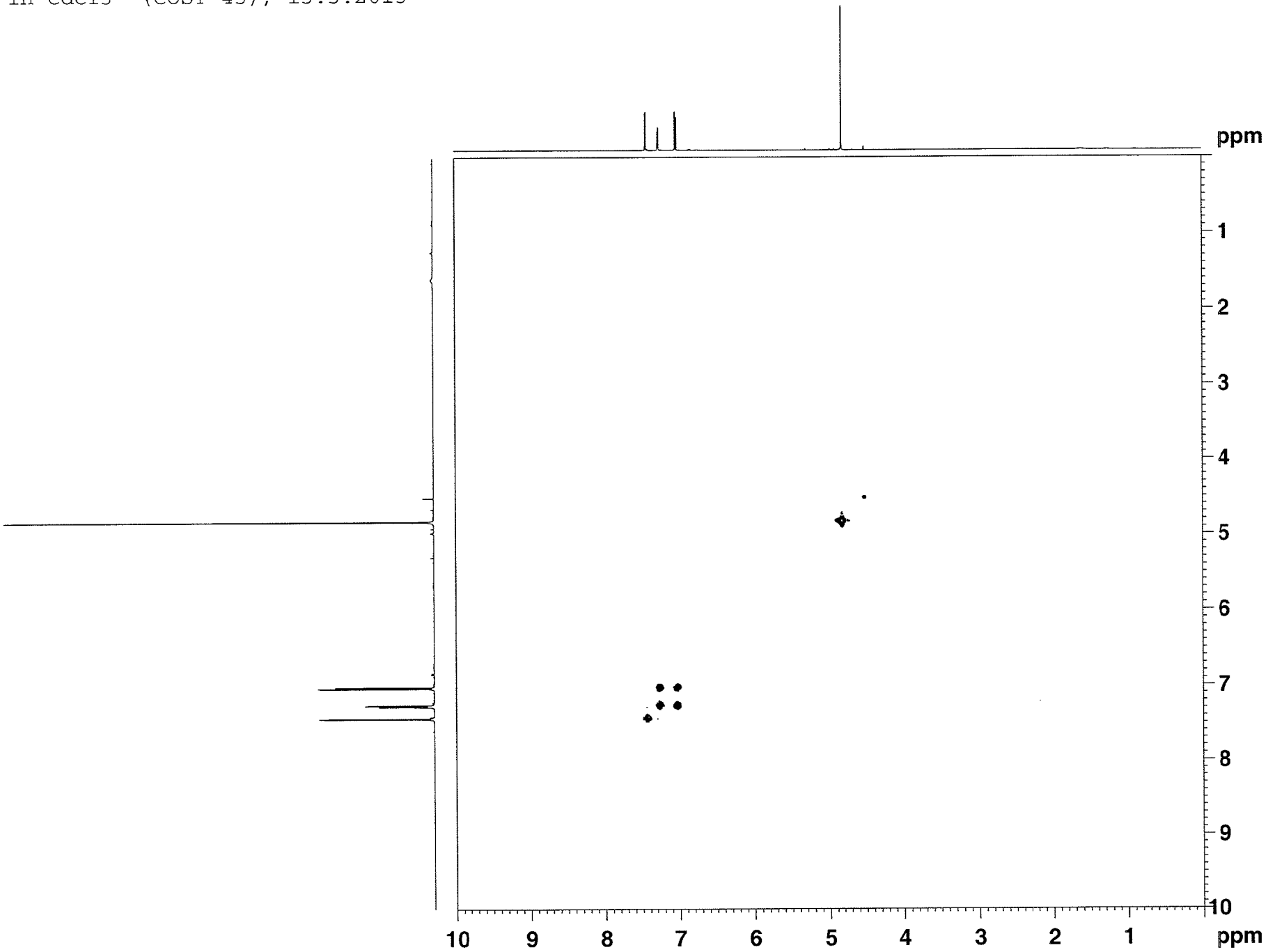

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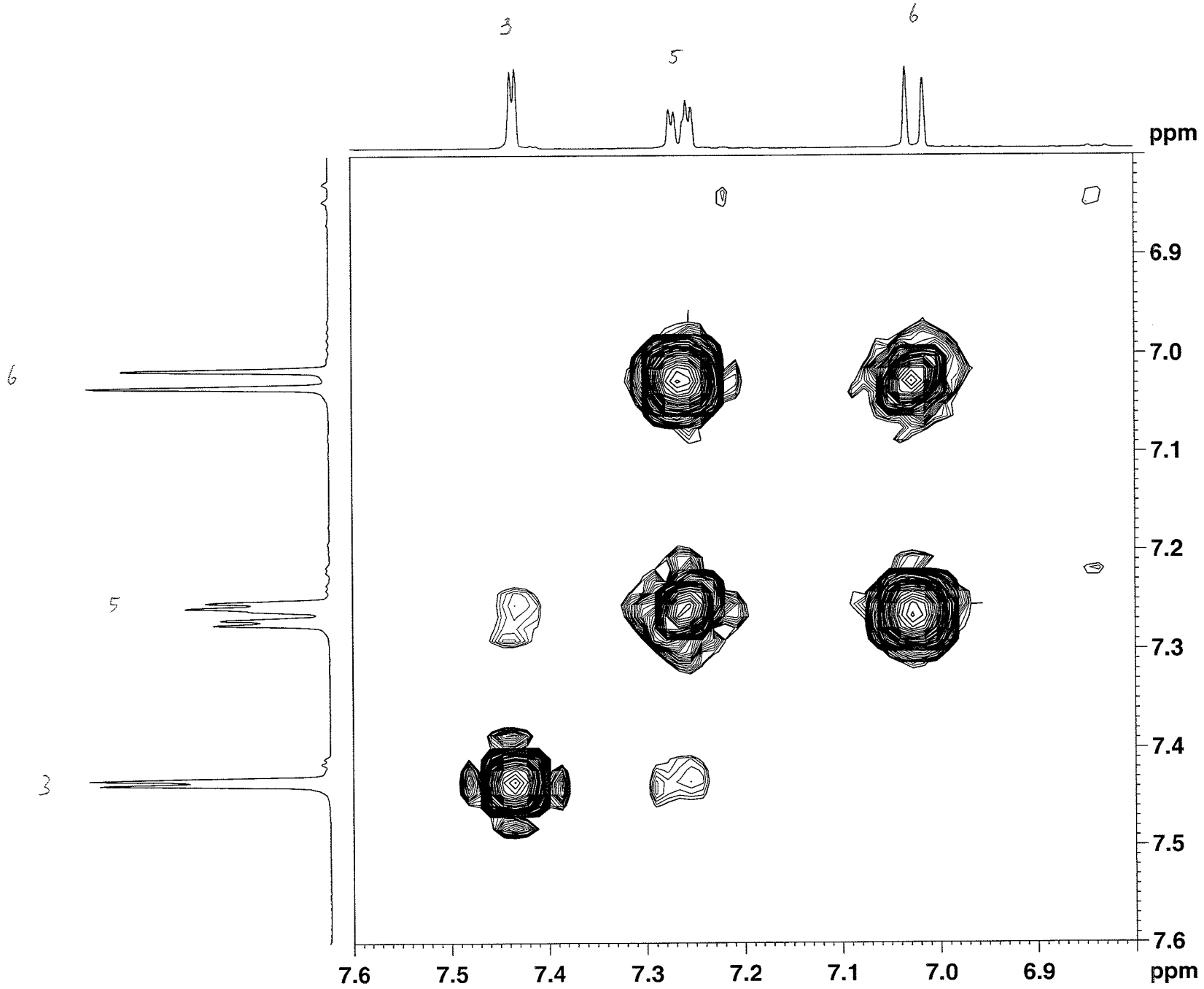

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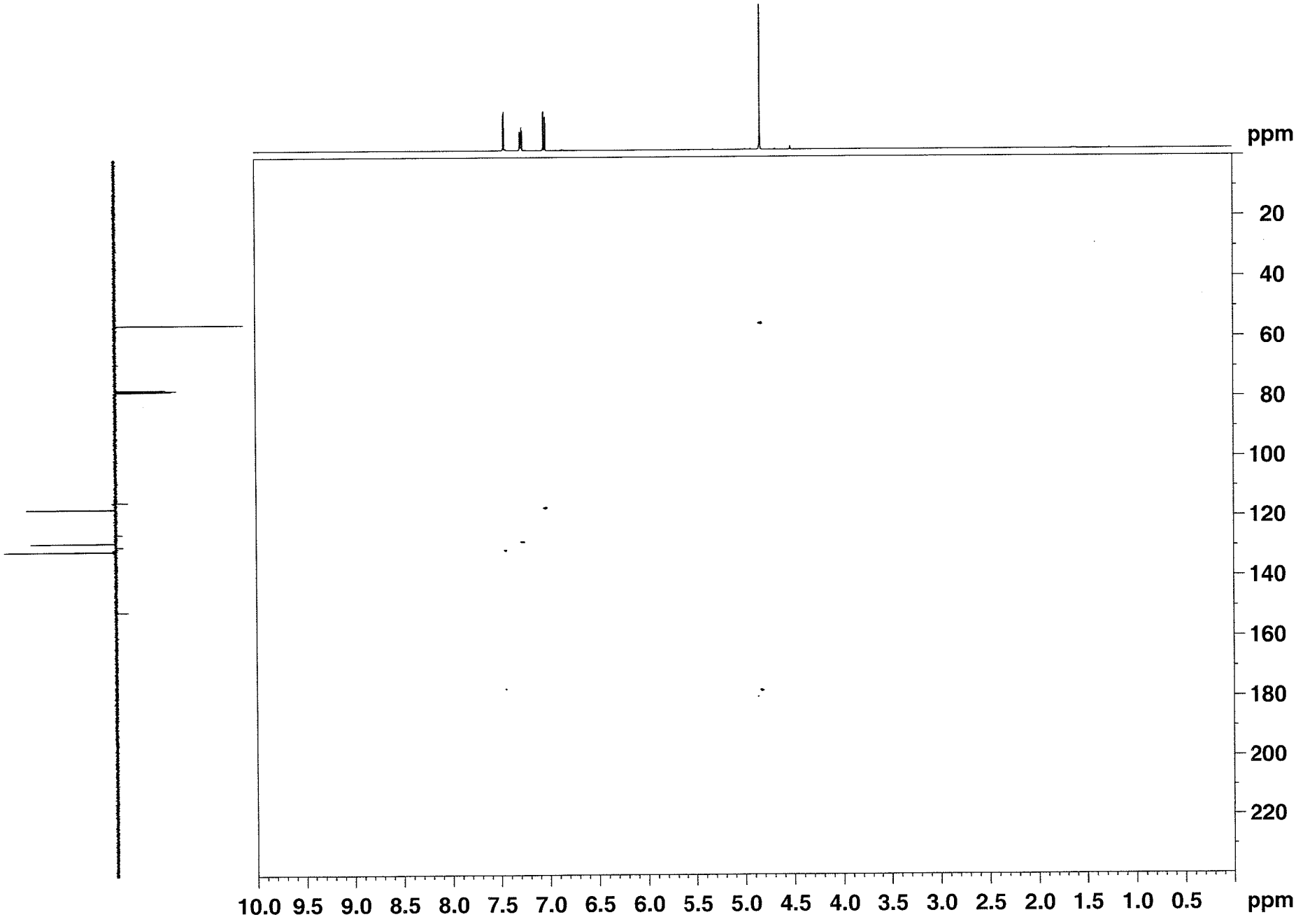

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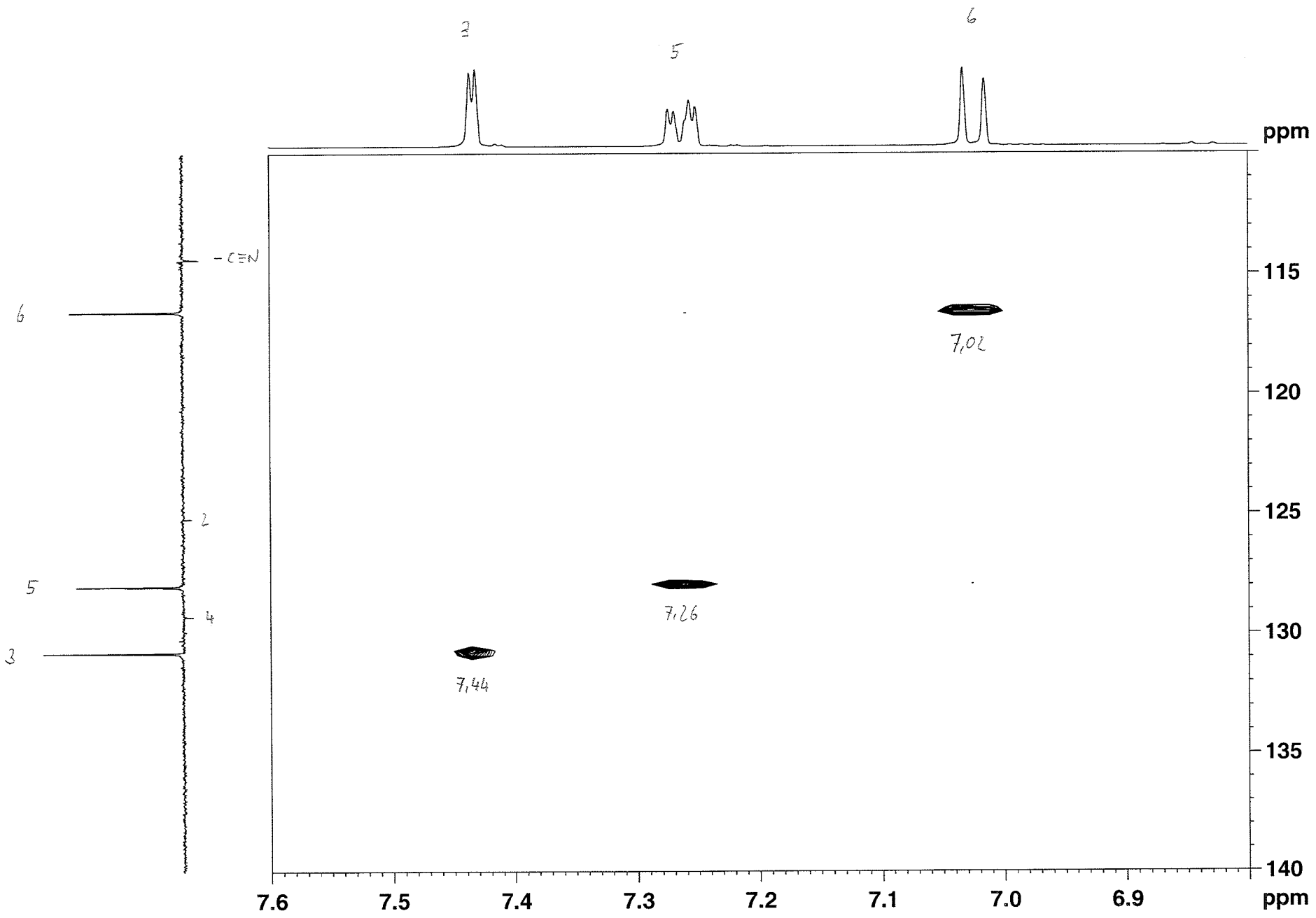

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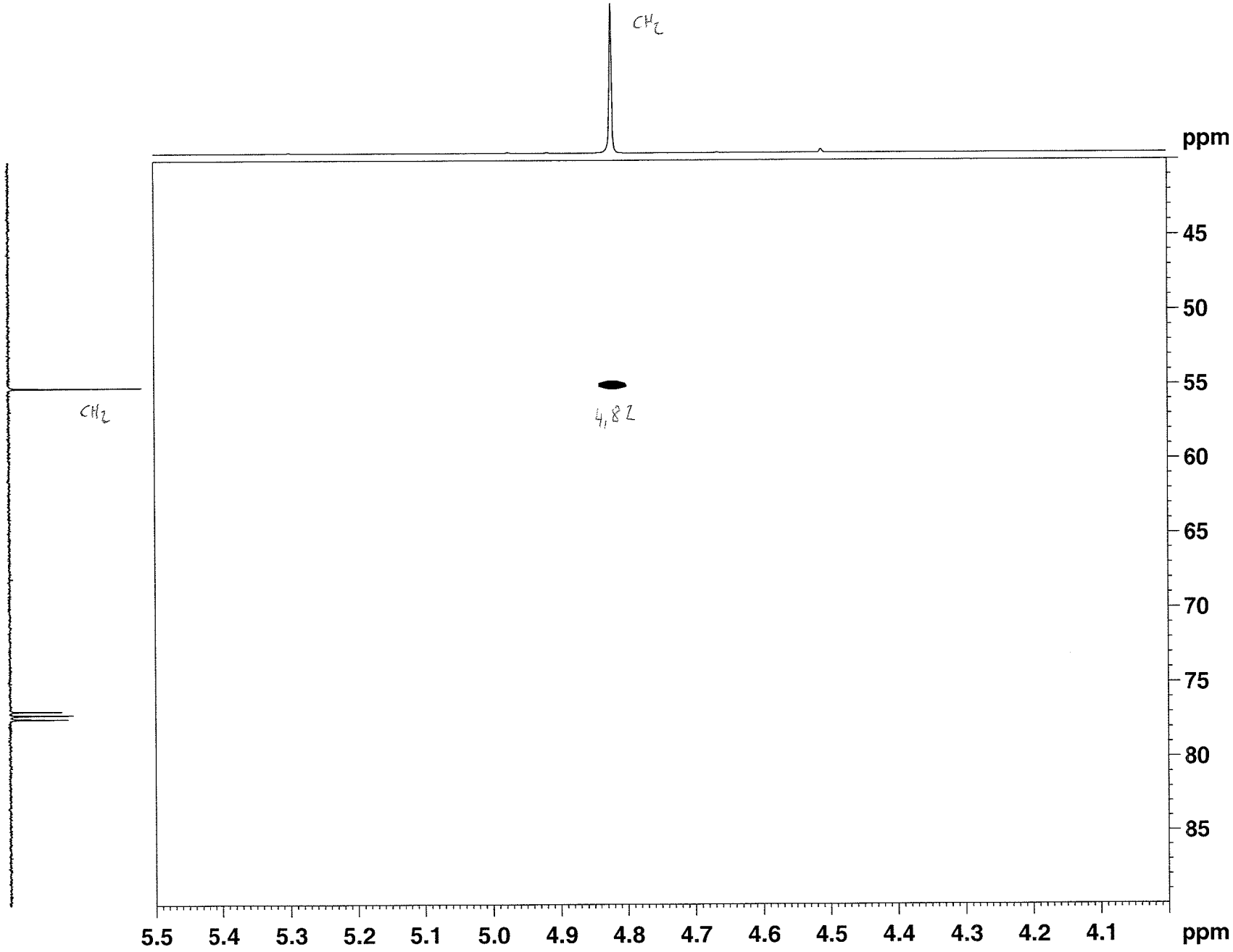

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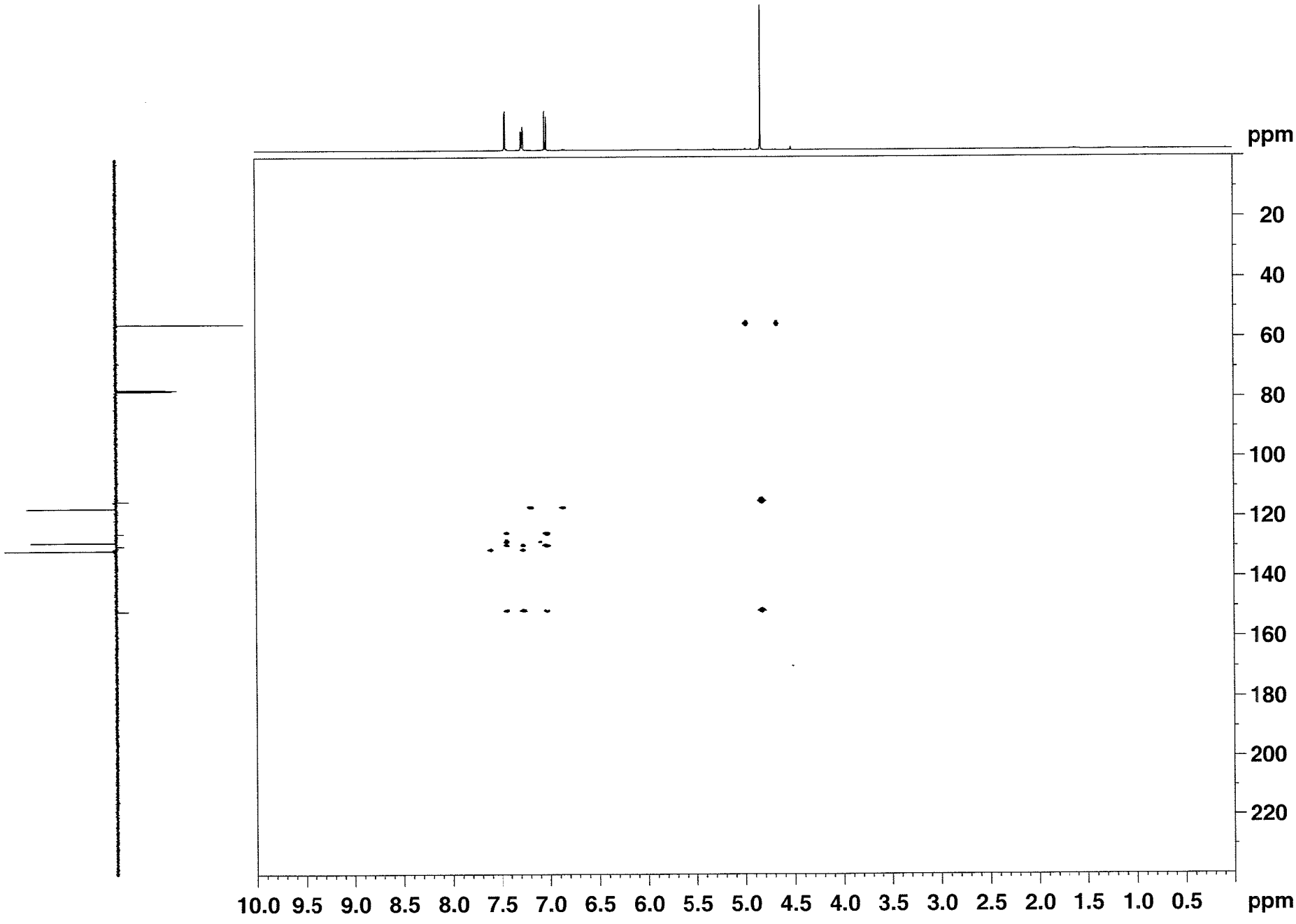

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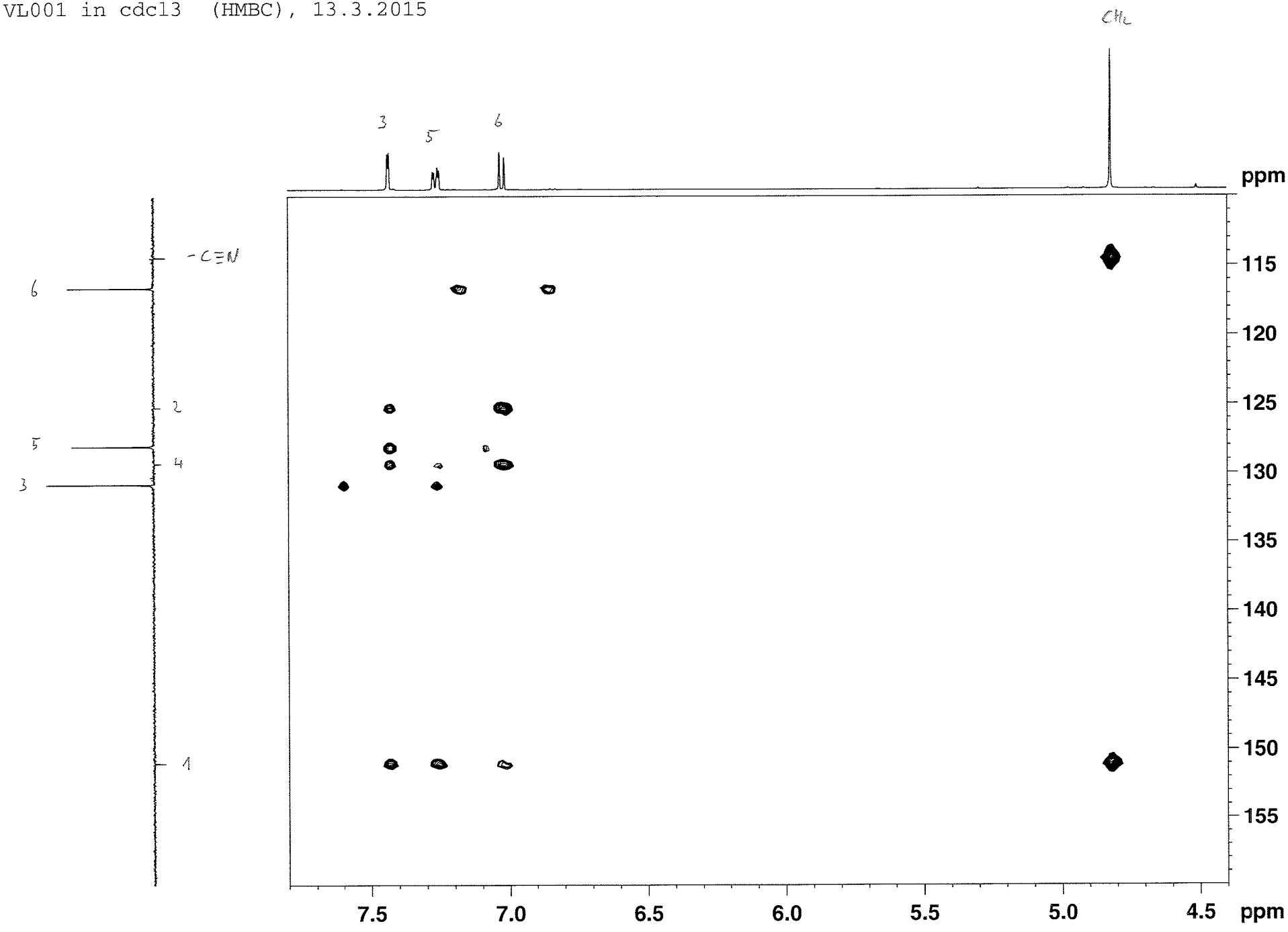

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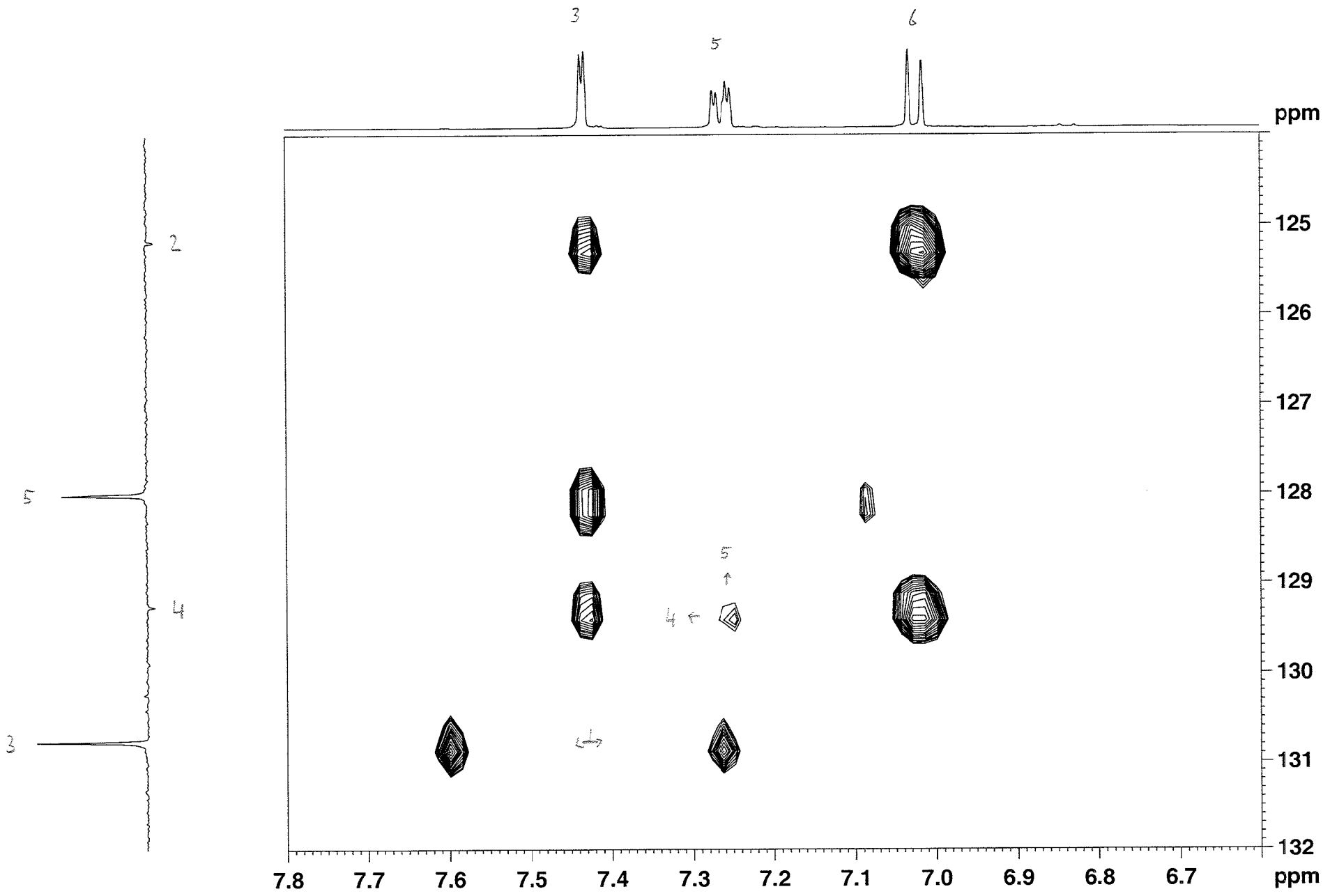

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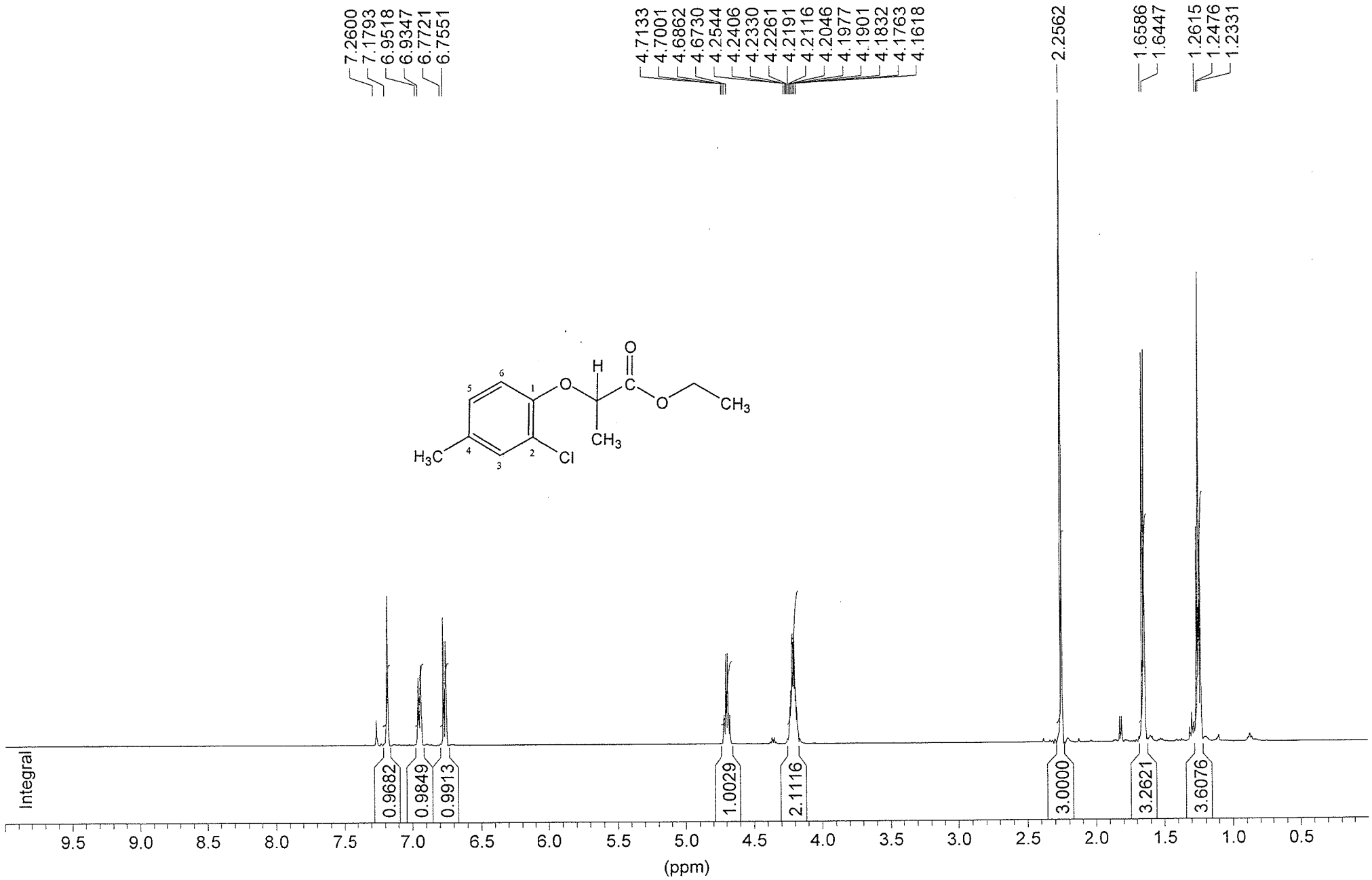

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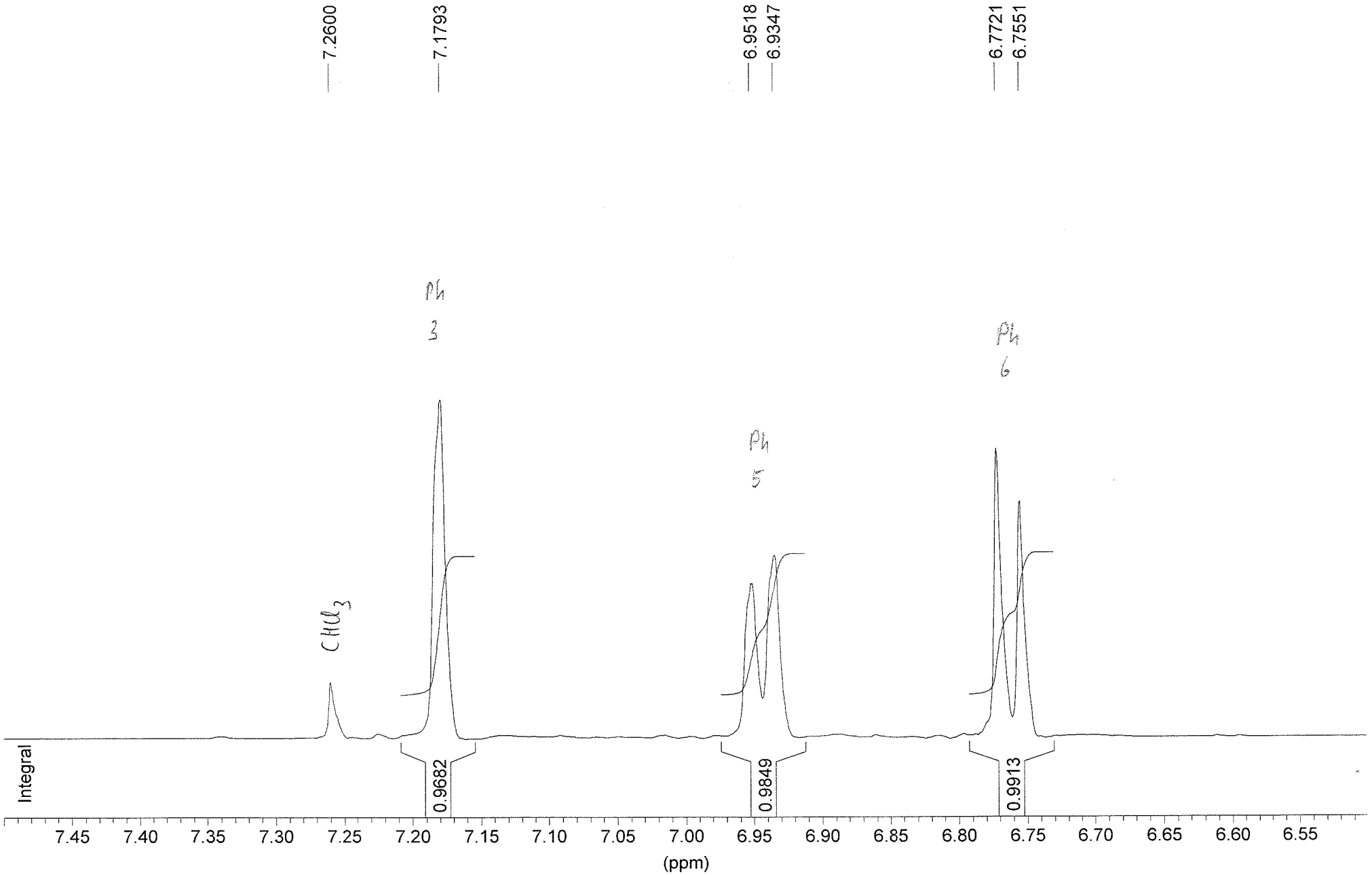

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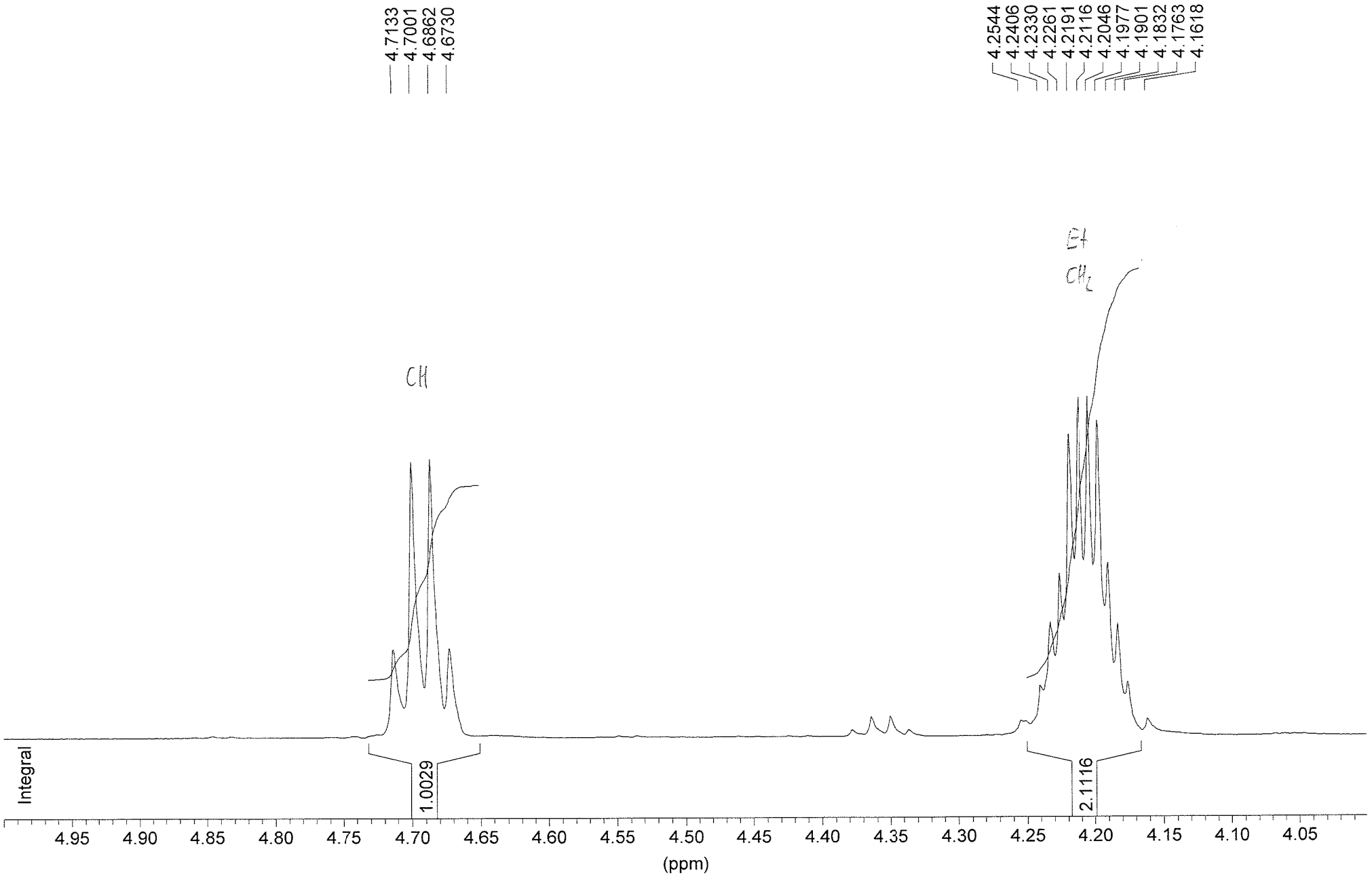

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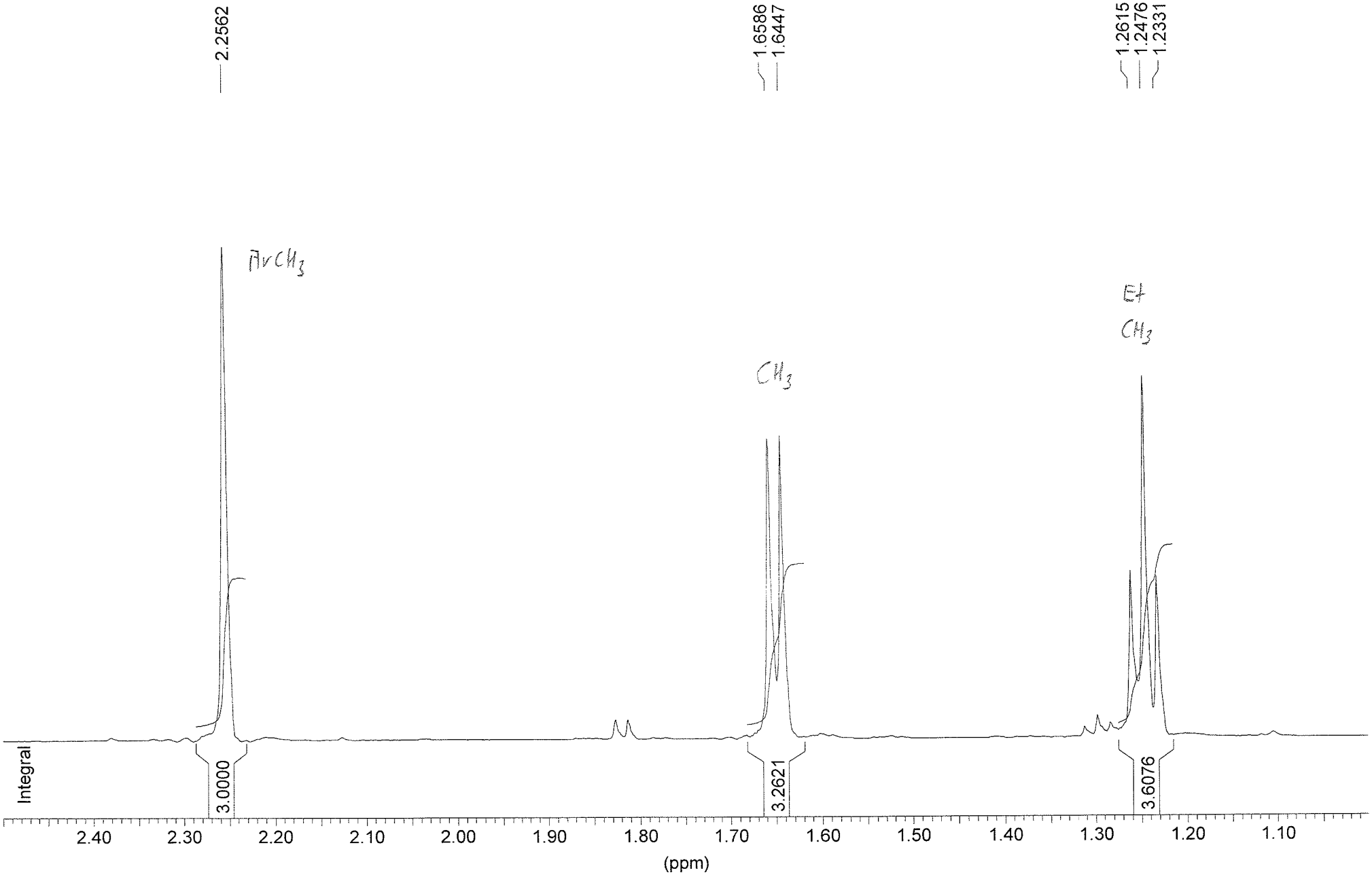

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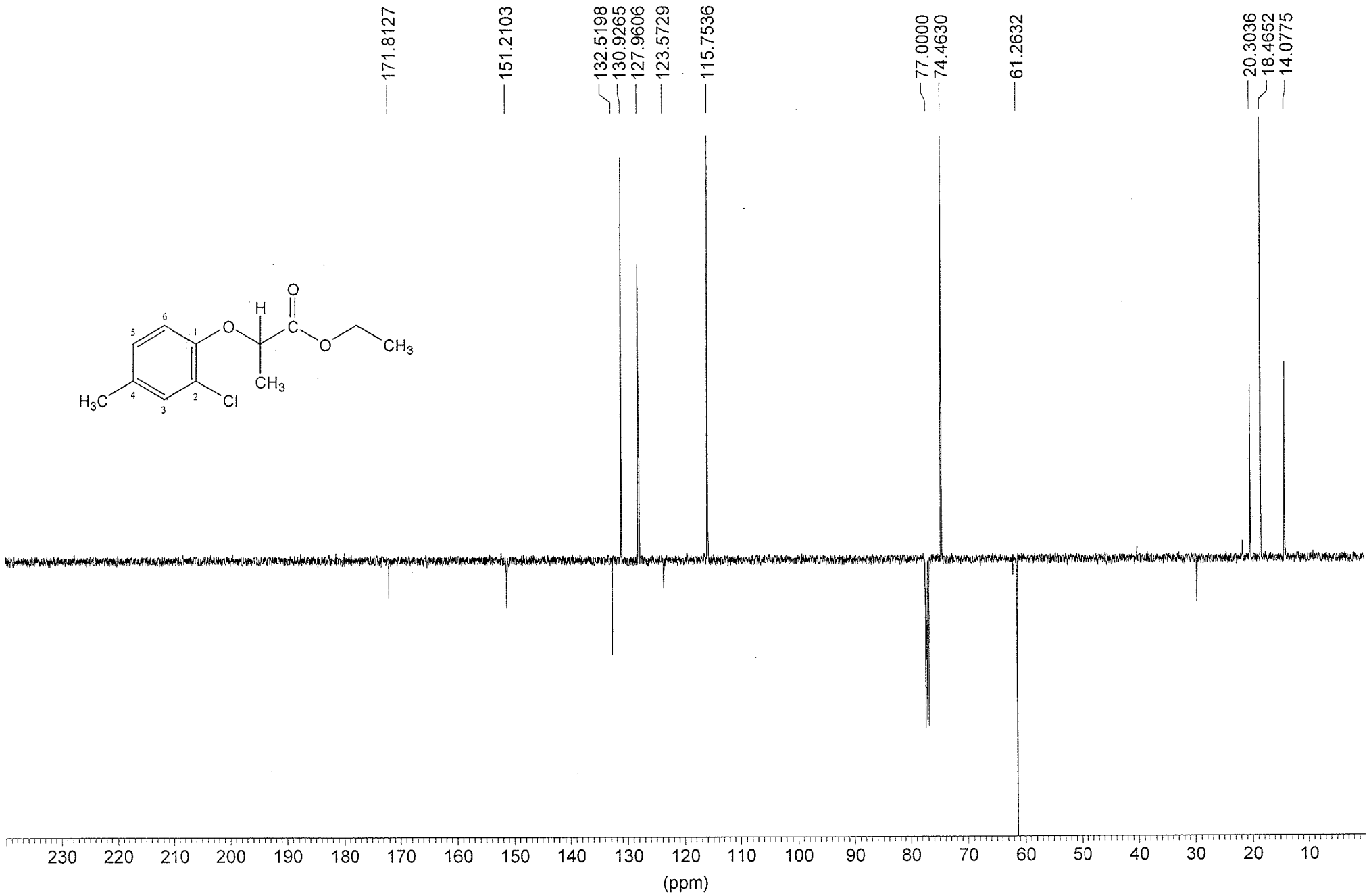

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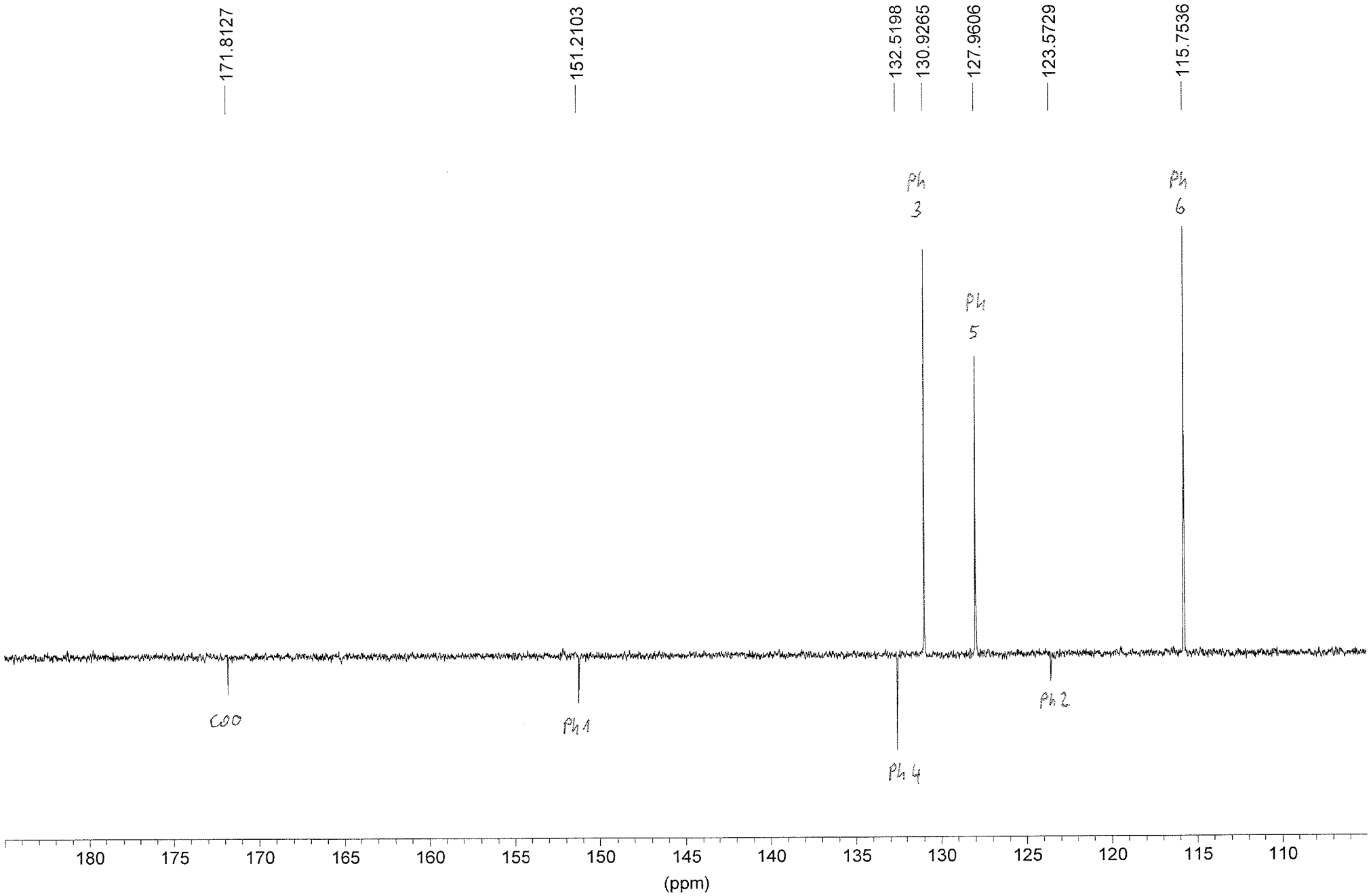

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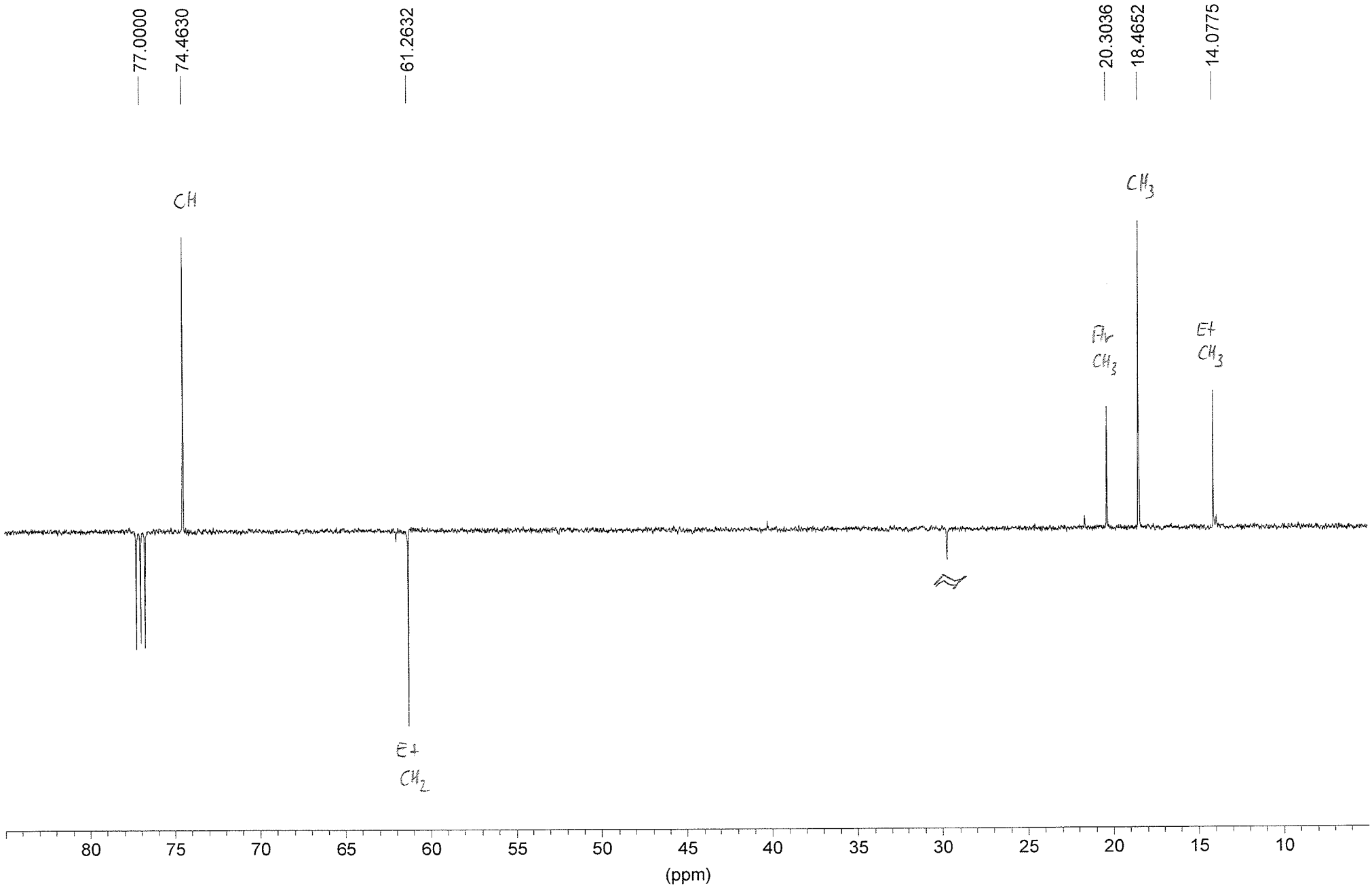

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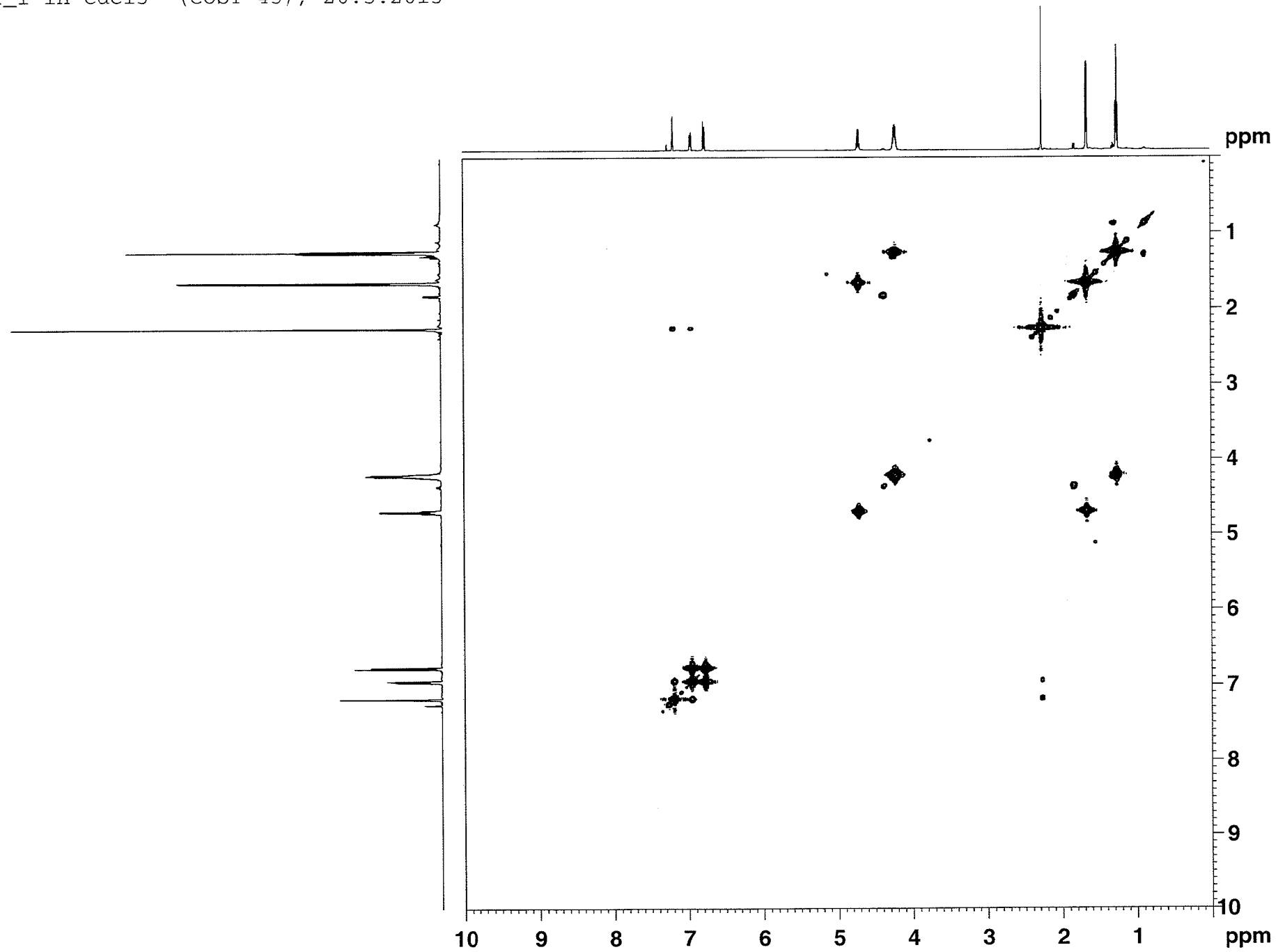

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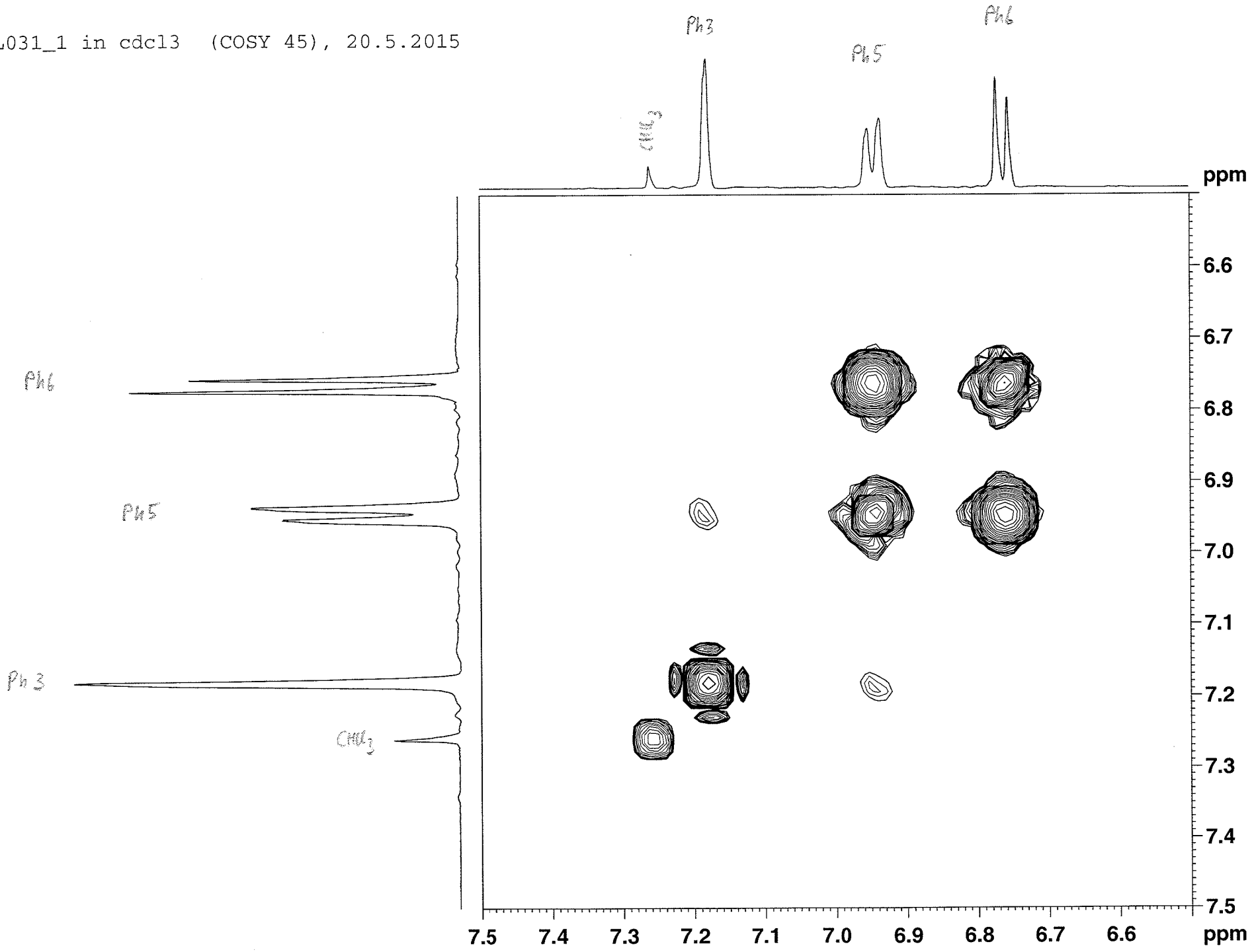

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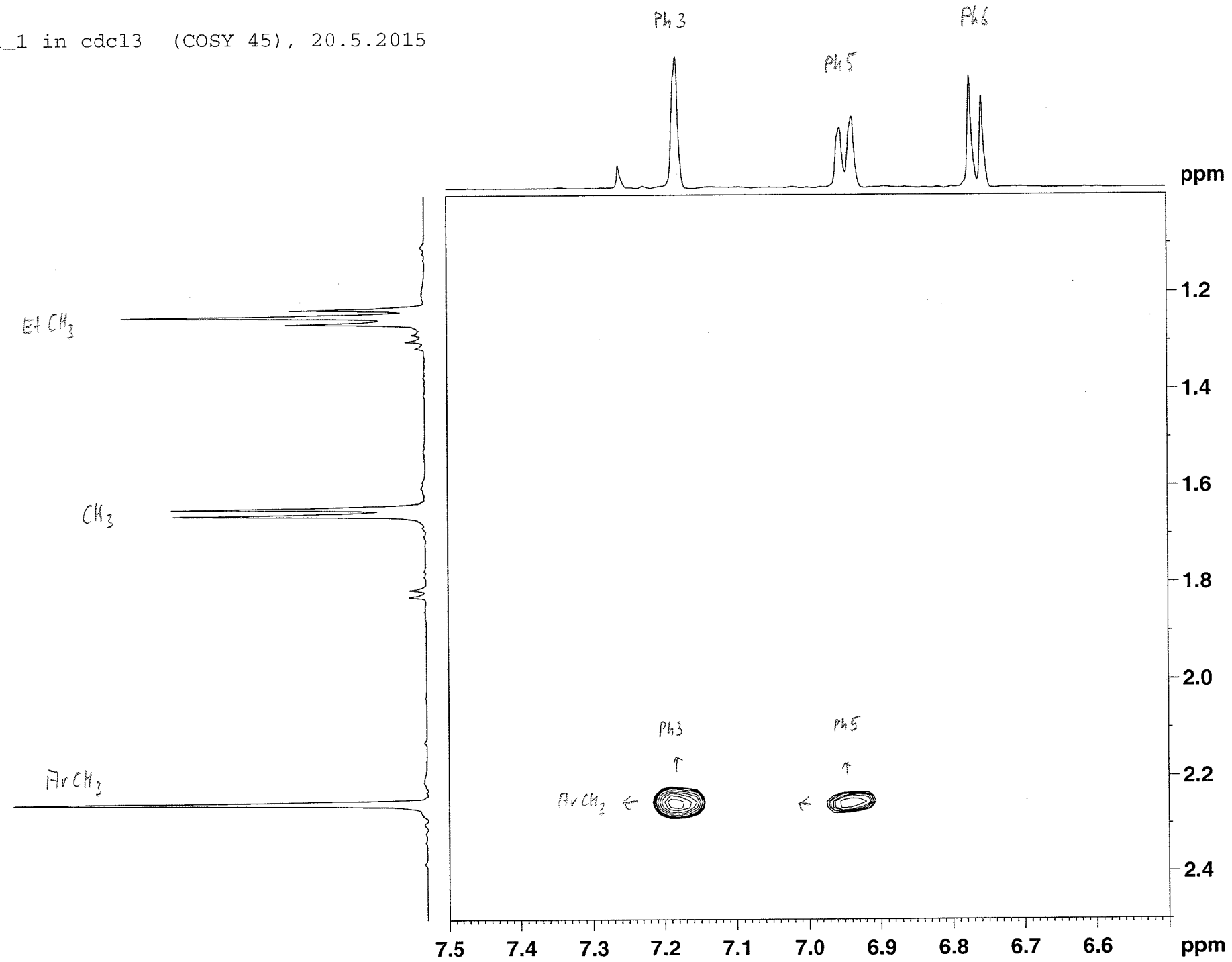

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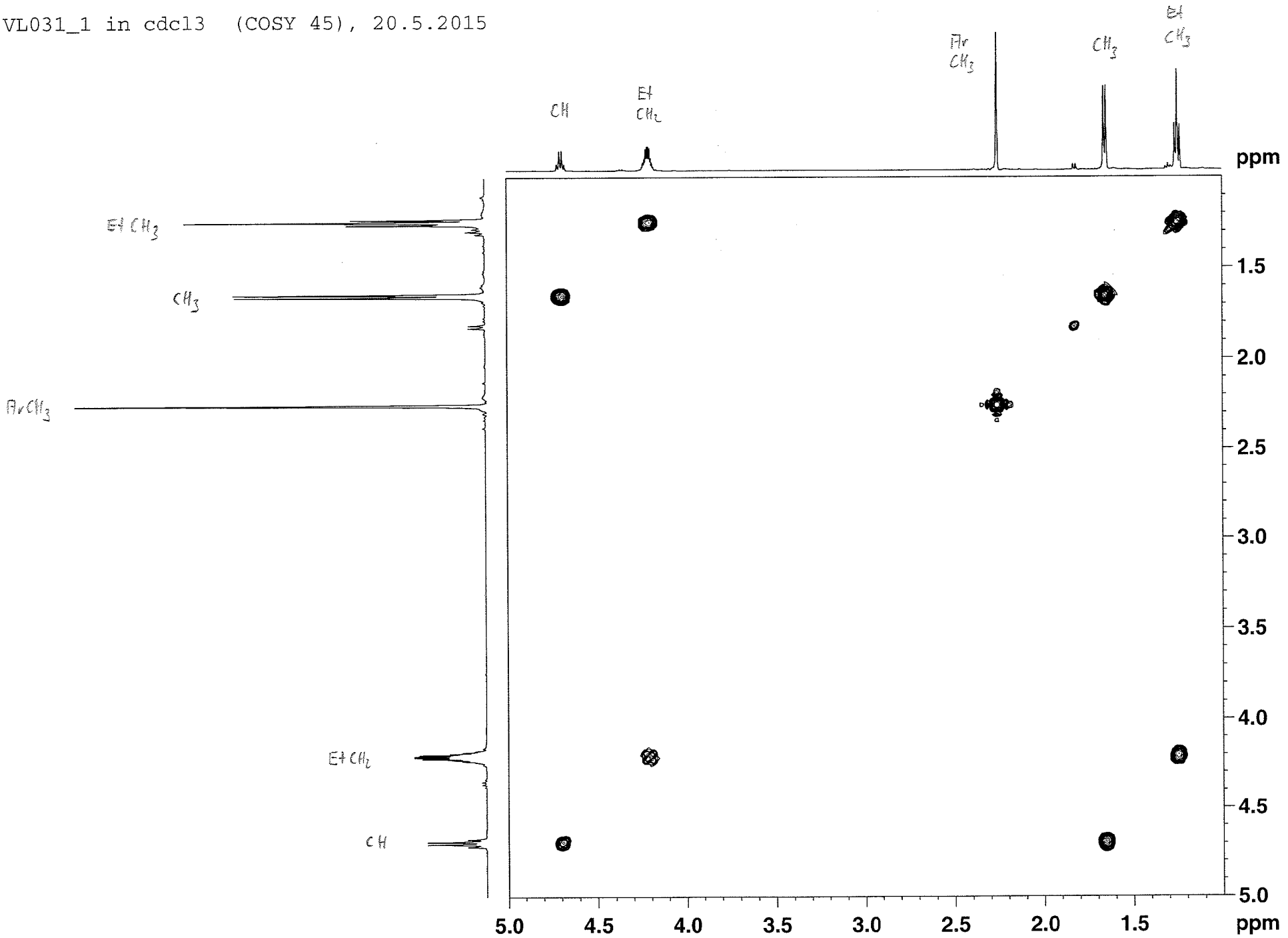

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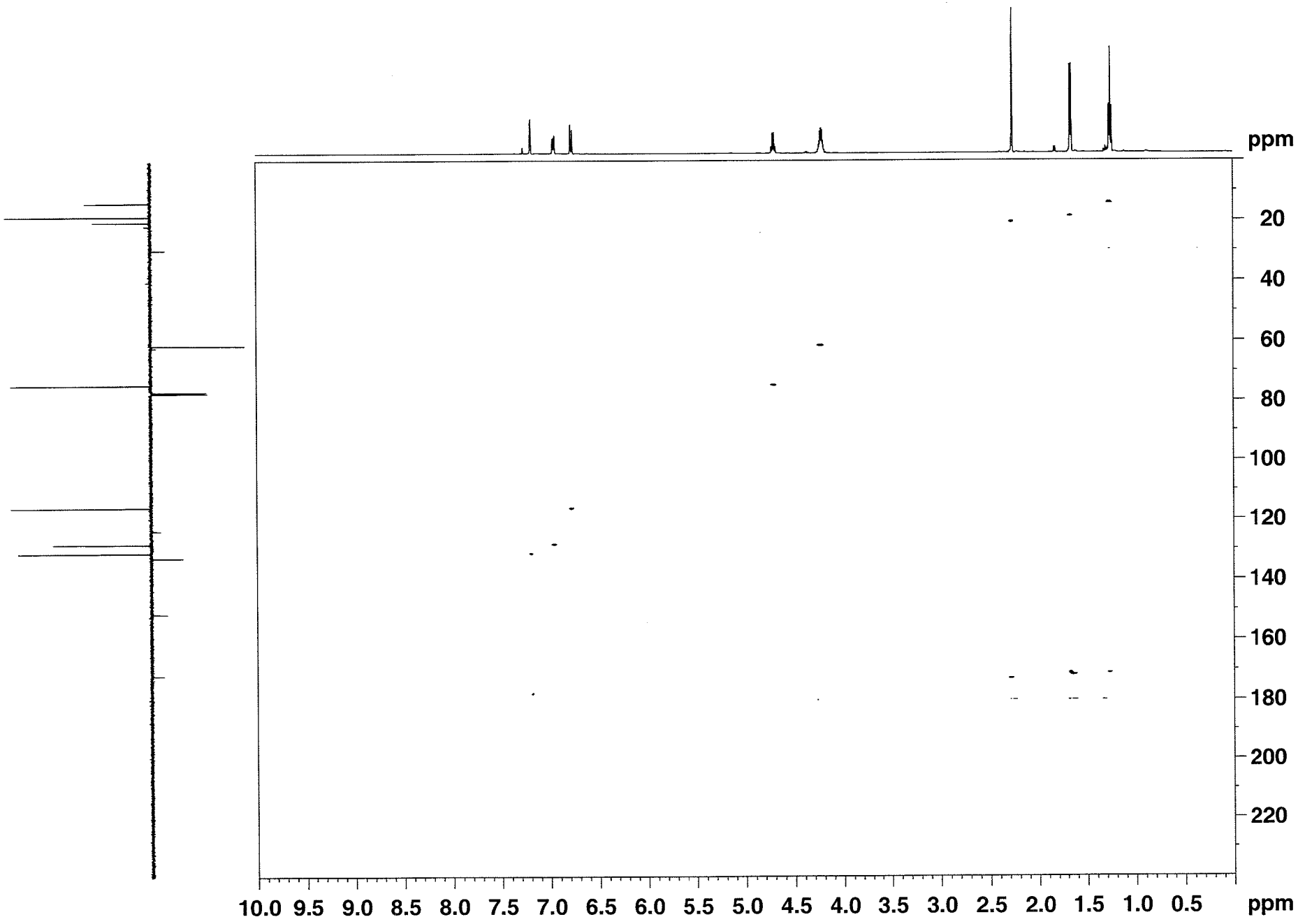
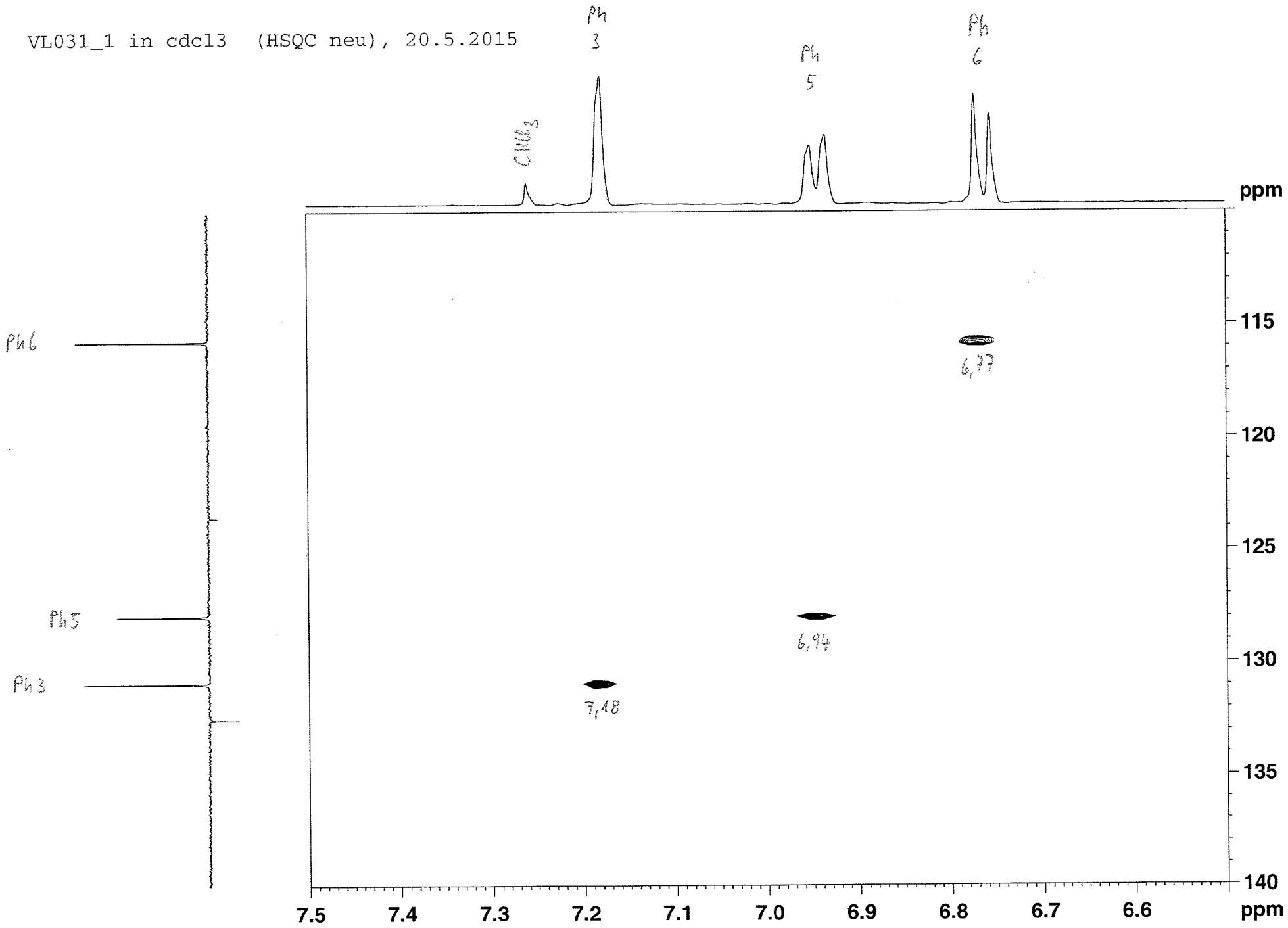
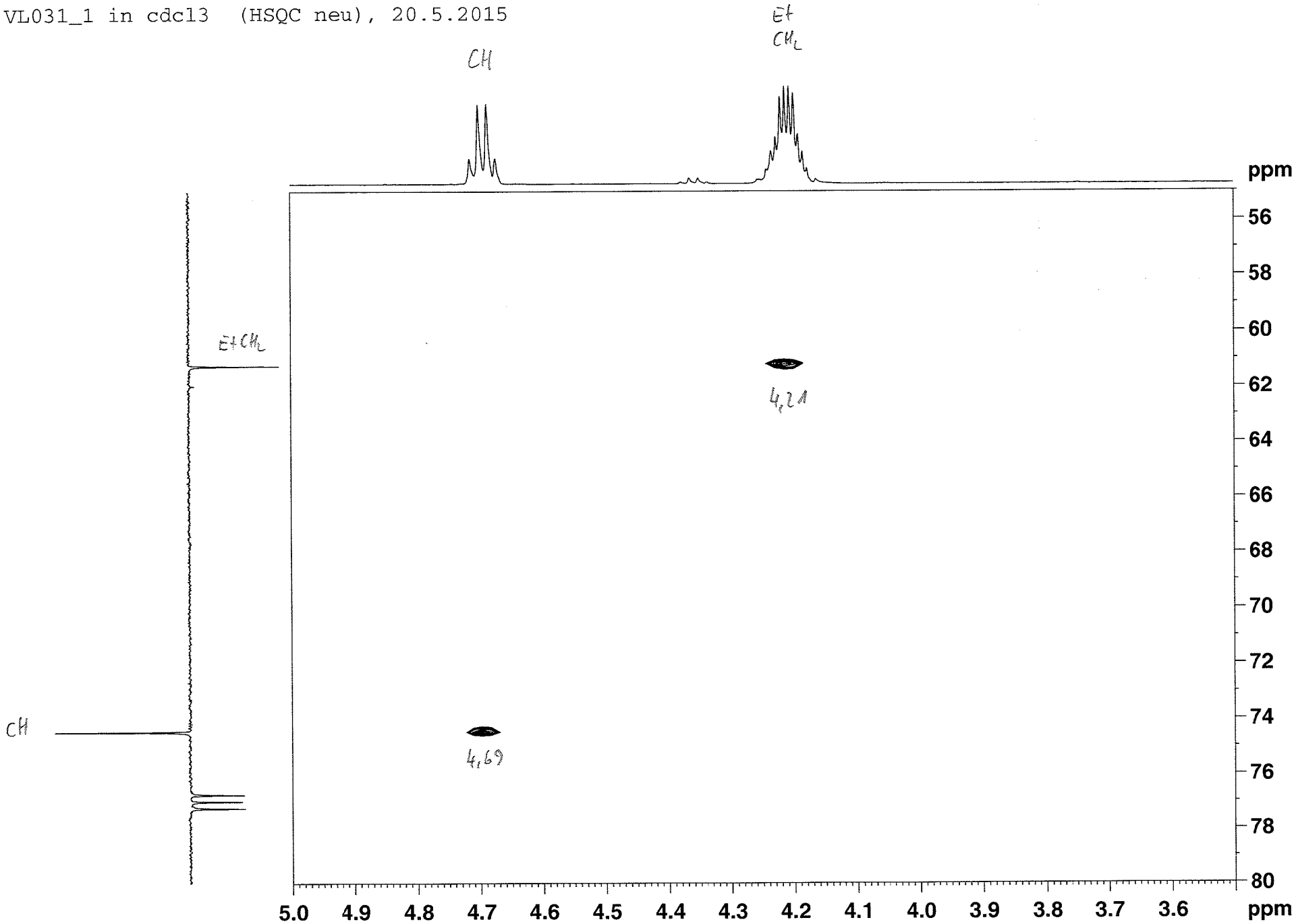



VL031_1 in cdcl3 (HSQC neu), 20.5.2015
Ph 3
Ph 5
Ph 6
CHCl3
ppm
Ph6
Ph5
Ph3
6,77
6,94
7,18
115
120
125
130
135
140
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm

VL031_1 in cdcl3 (HSQC neu), 20.5.2015



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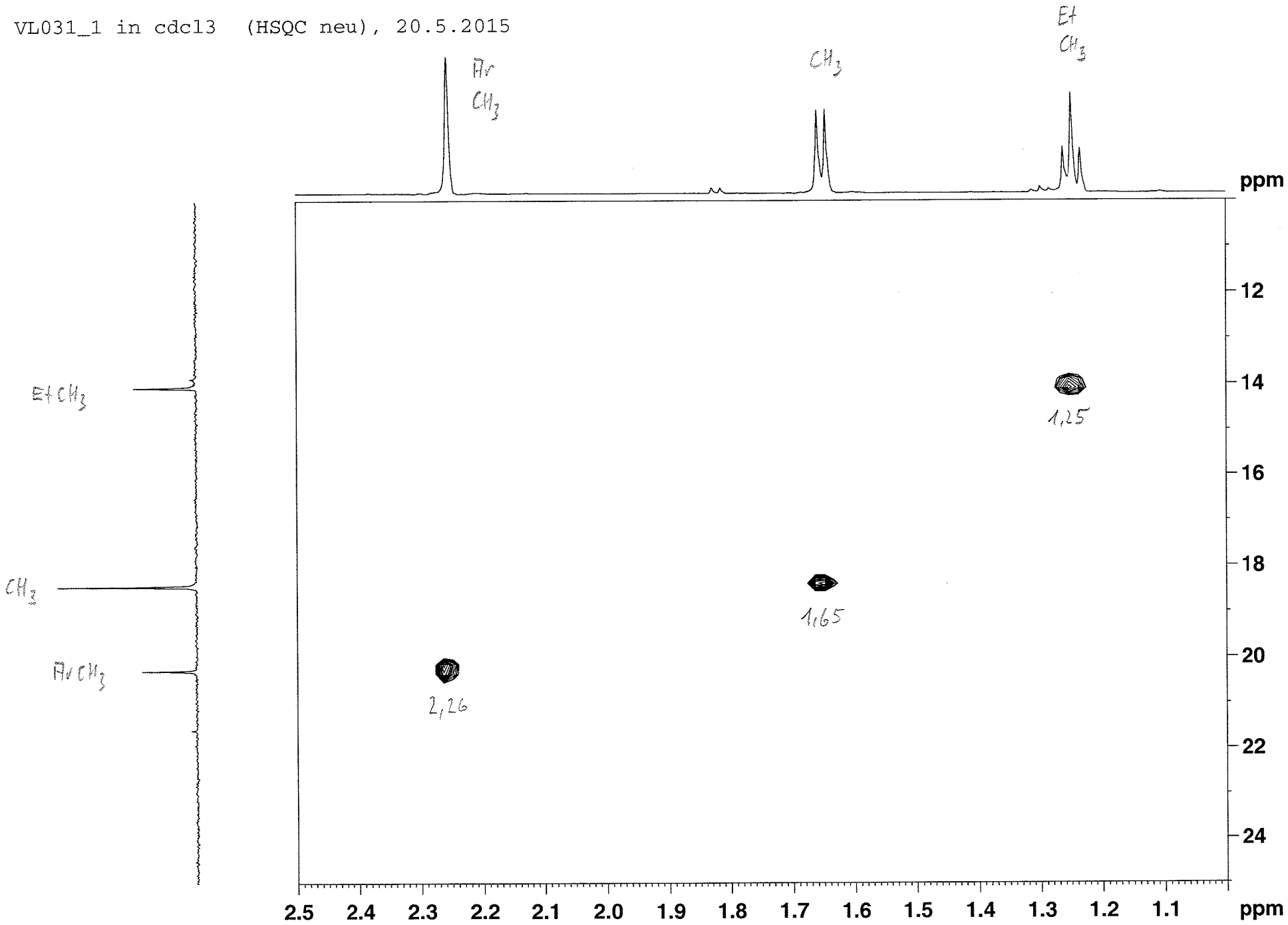

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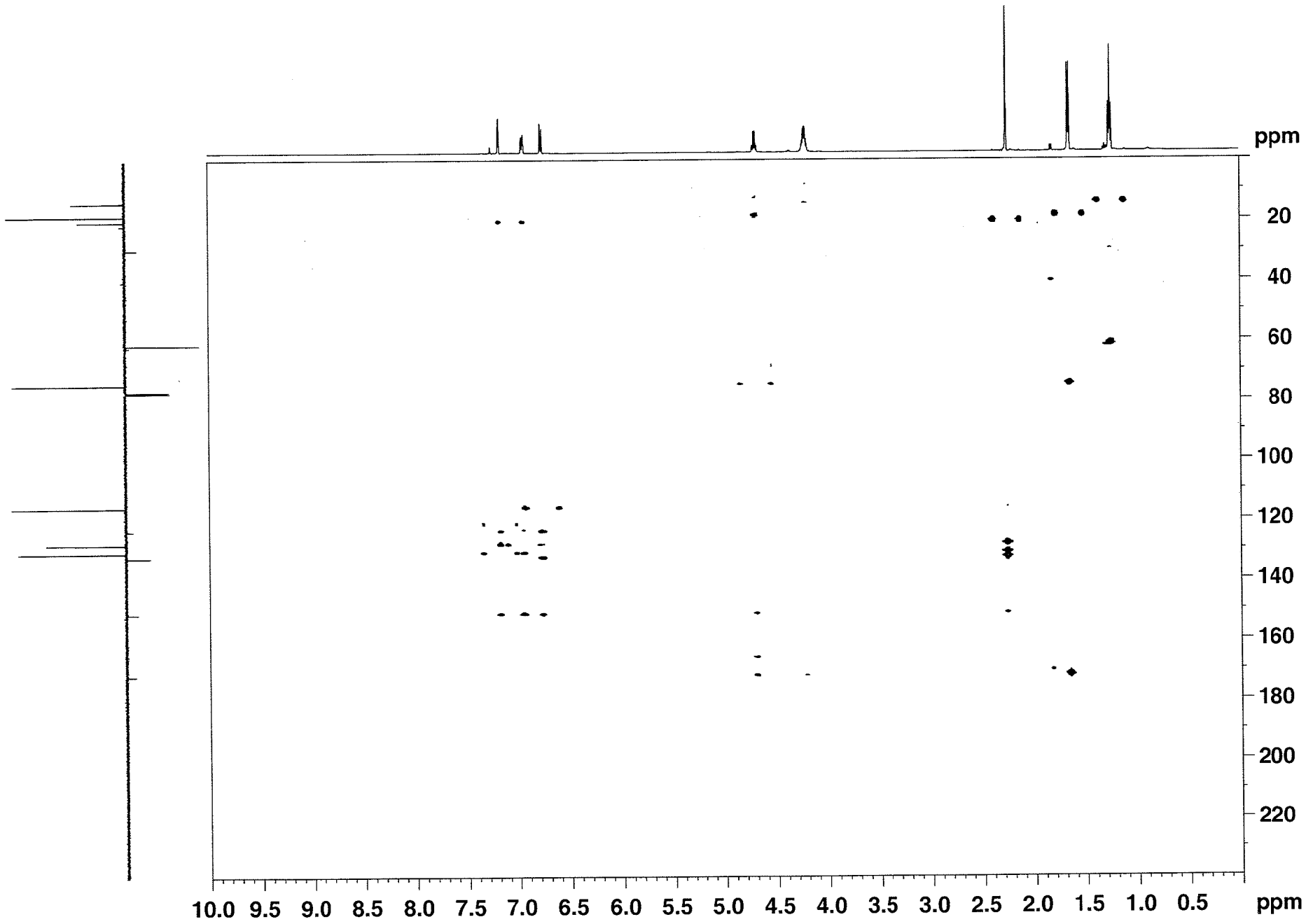

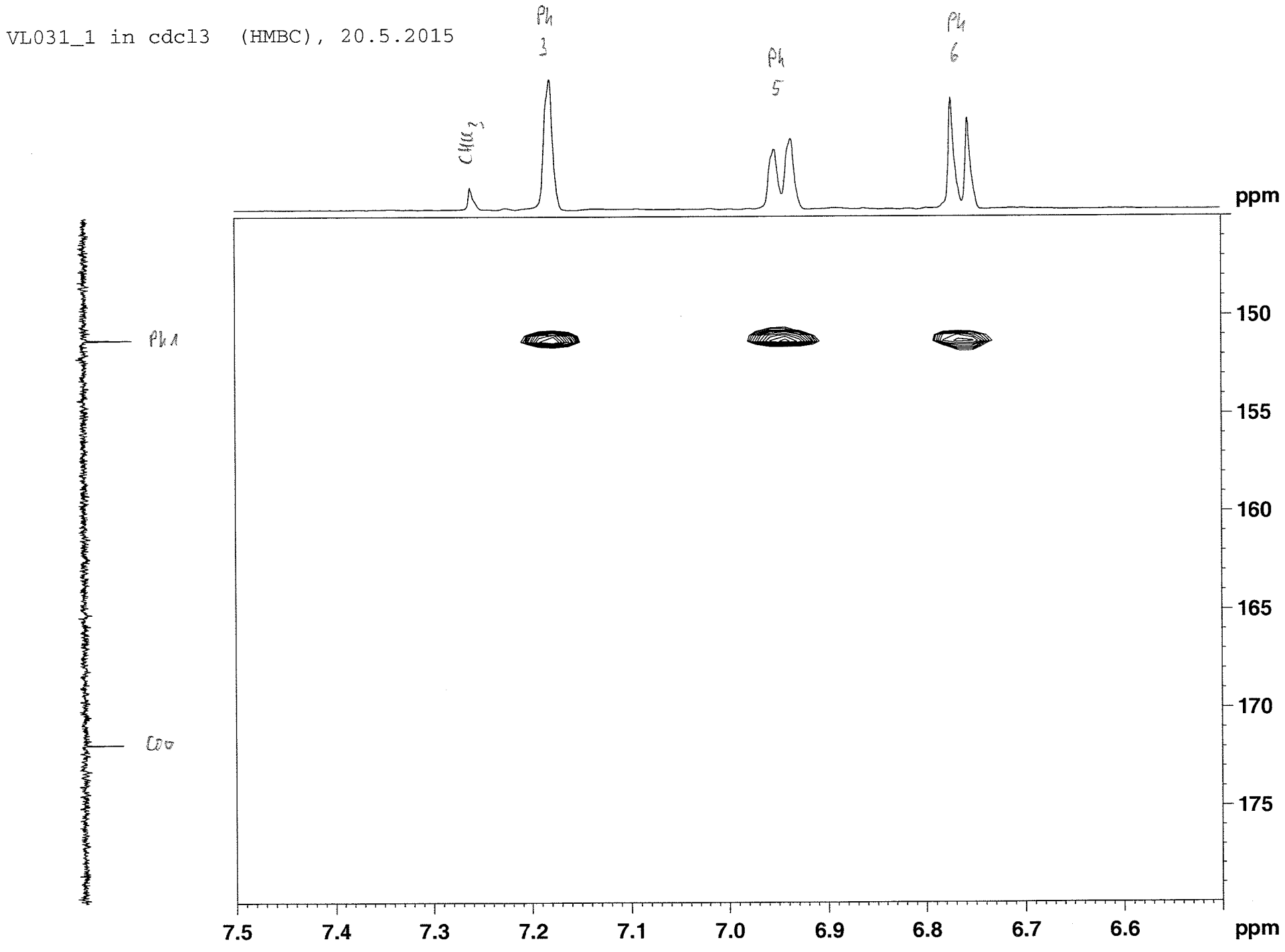
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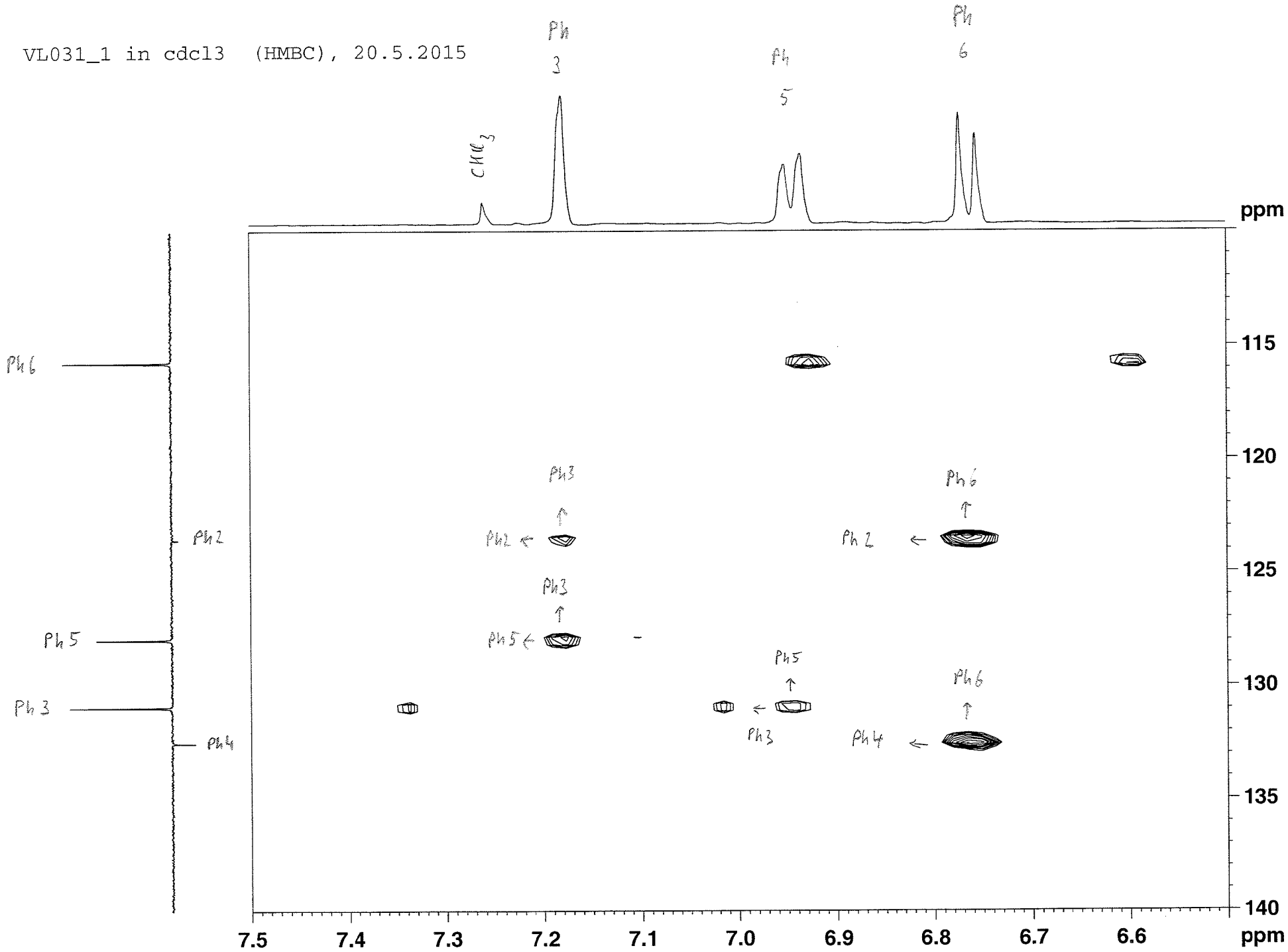
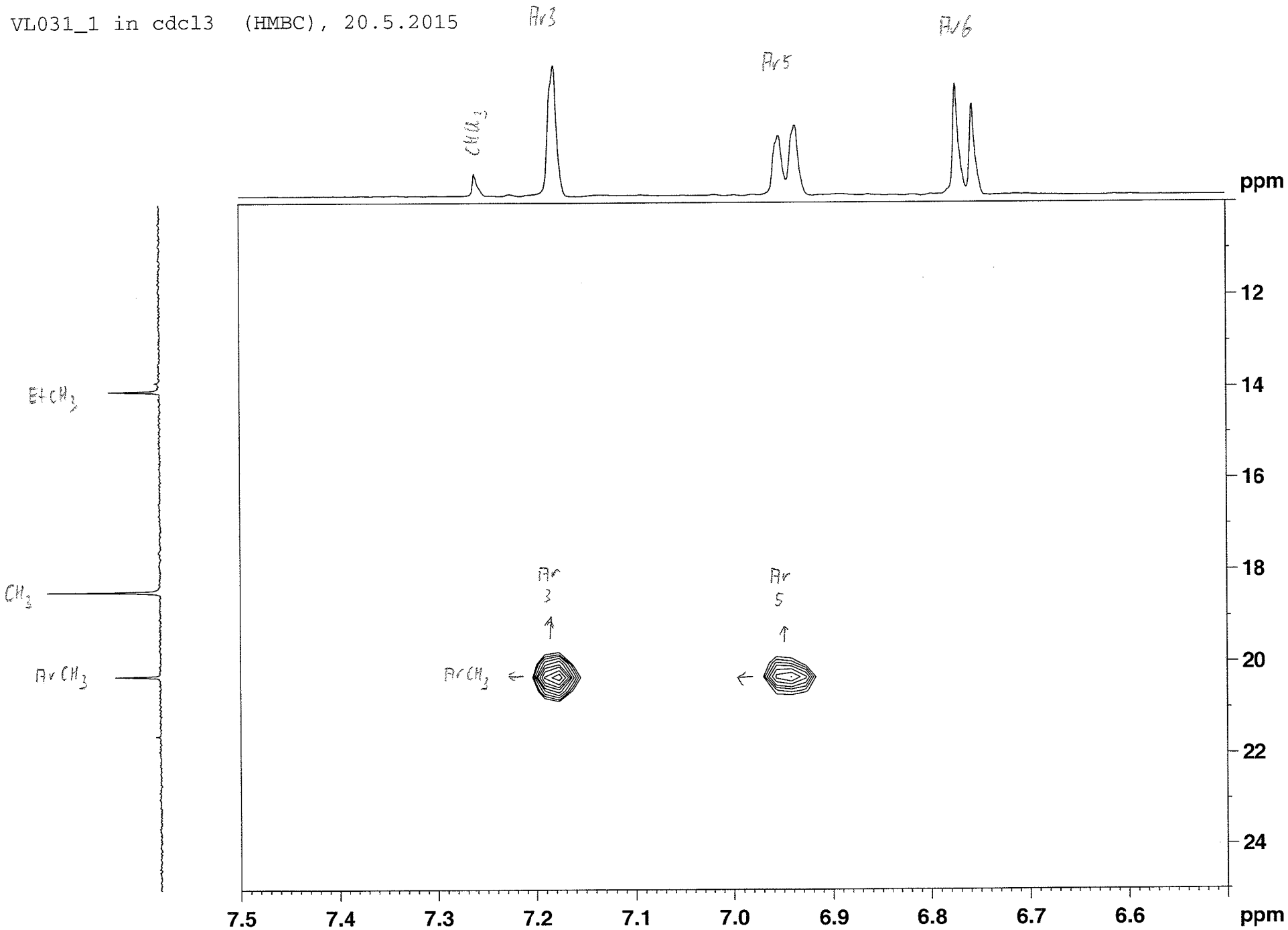
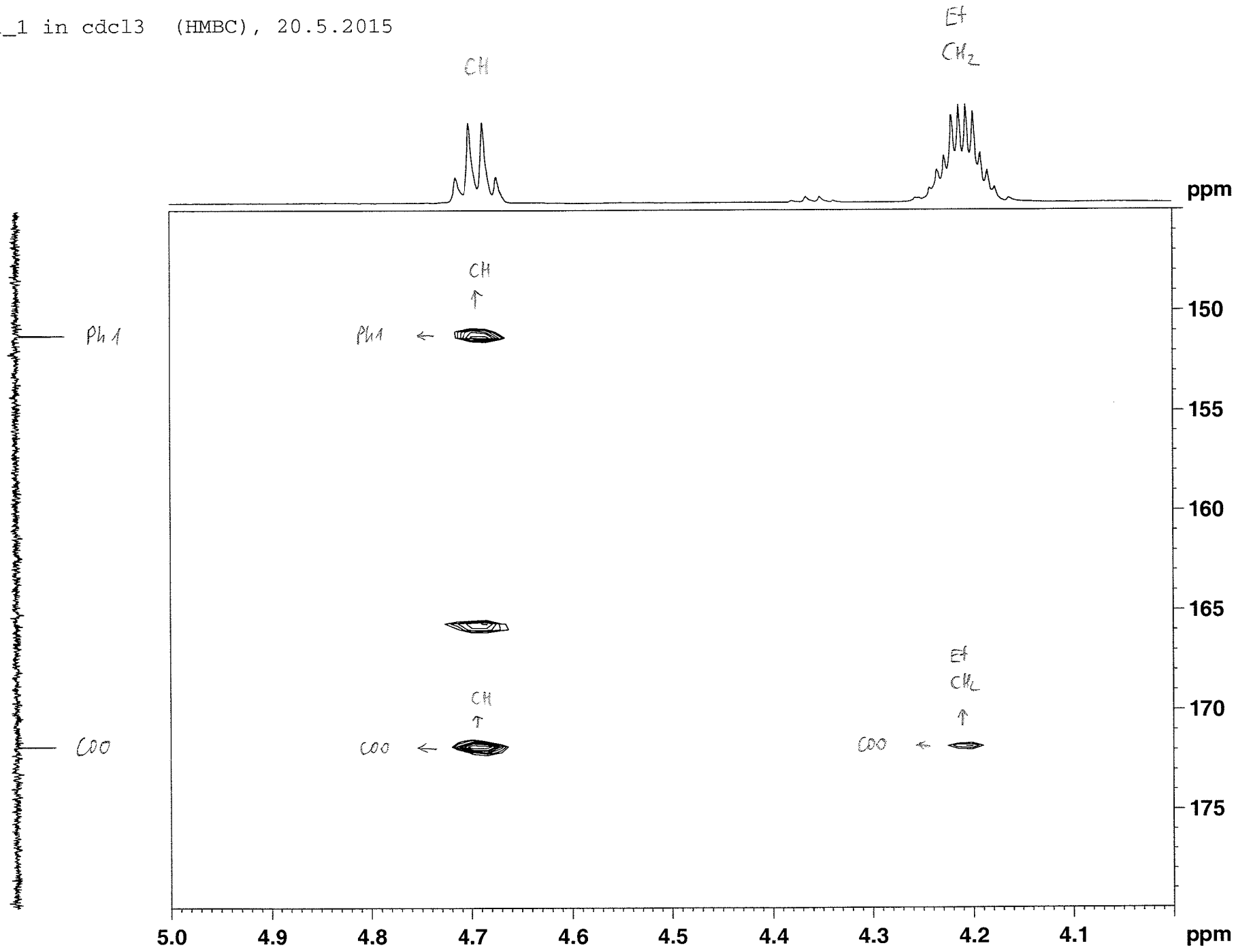
Ph 3
Ph 5
Ph 6
CH2Cl2
ppm
150
155
160
165
170
175
Ph1
C=O
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm


VL031_1 in cdcl3 (HMBC), 20.5.2015
Ph 3
Ph 5
Ph 6
CHCl3
ppm
115
120
125
130
135
140
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm
Ph6
Ph2
Ph5
Ph3
Ph4
Ph3
Ph2
Ph3
Ph5
Ph6
Ph2
Ph5
Ph3
Ph6
Ph4


VL031_1 in cdcl3 (HMBC), 20.5.2015
Ar3
Ar5
Ar6
ppm
12
14
16
18
20
22
24
Ar 3
Ar 5
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm

VL031_1 in cdcl3 (HMBC), 20.5.2015



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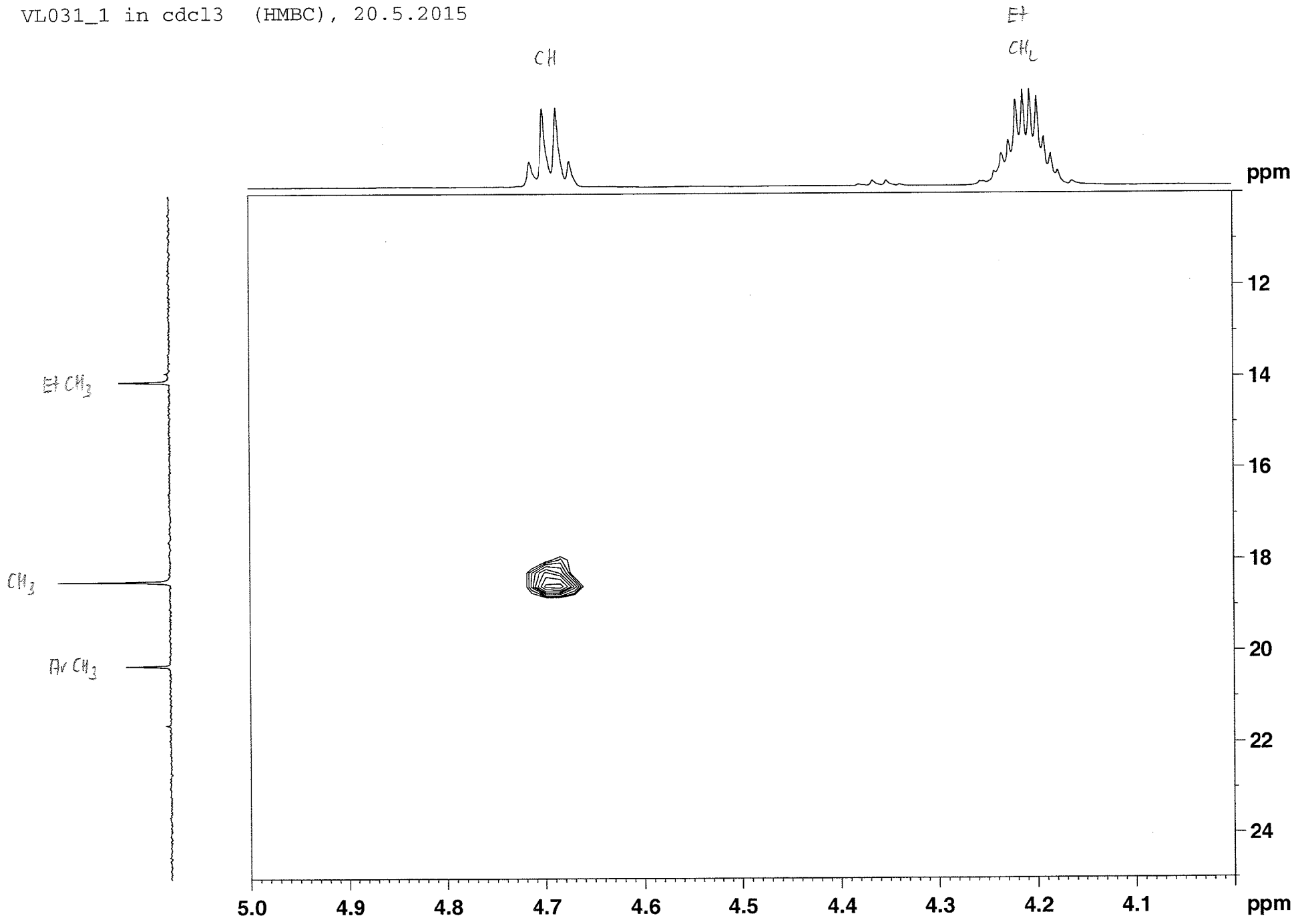

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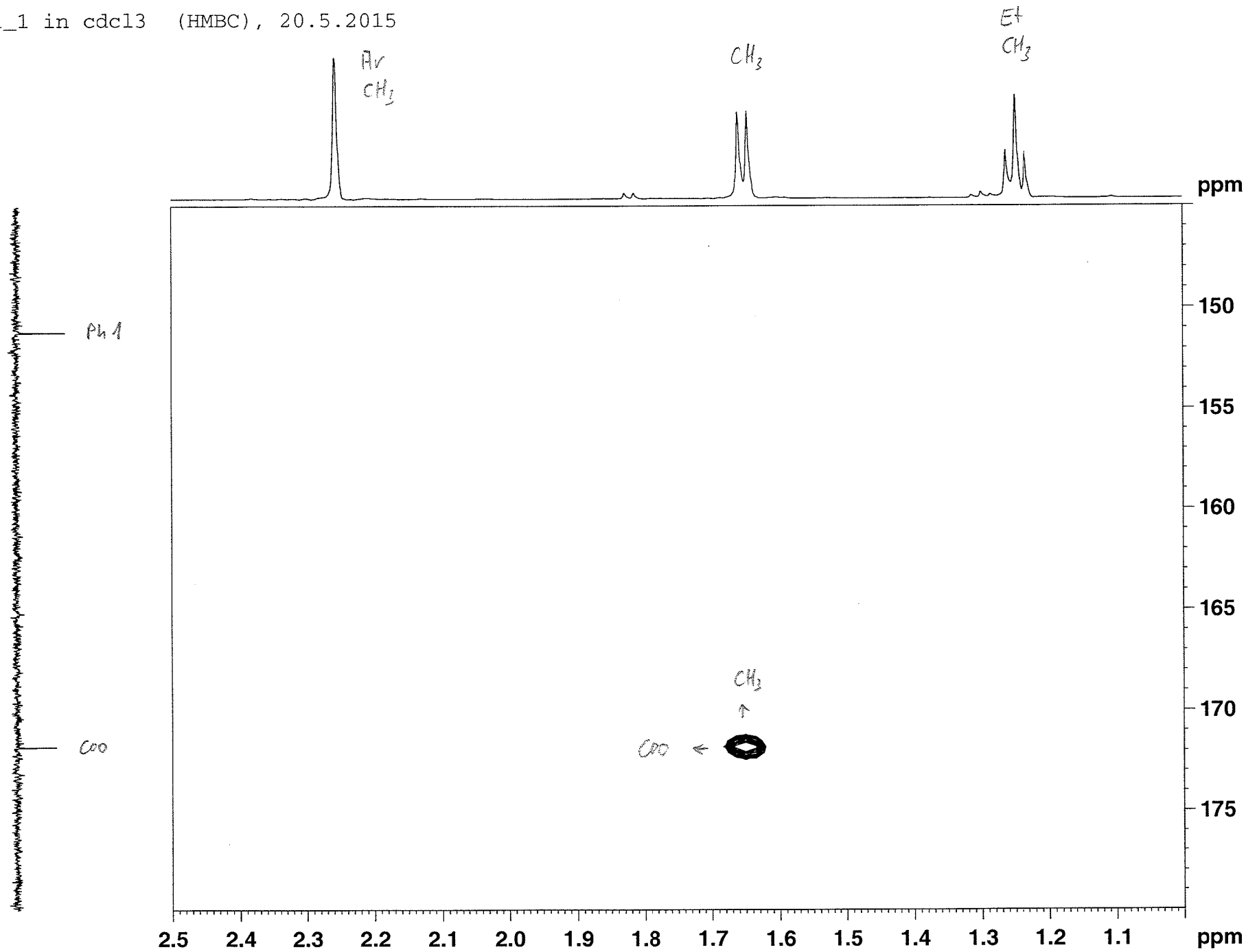
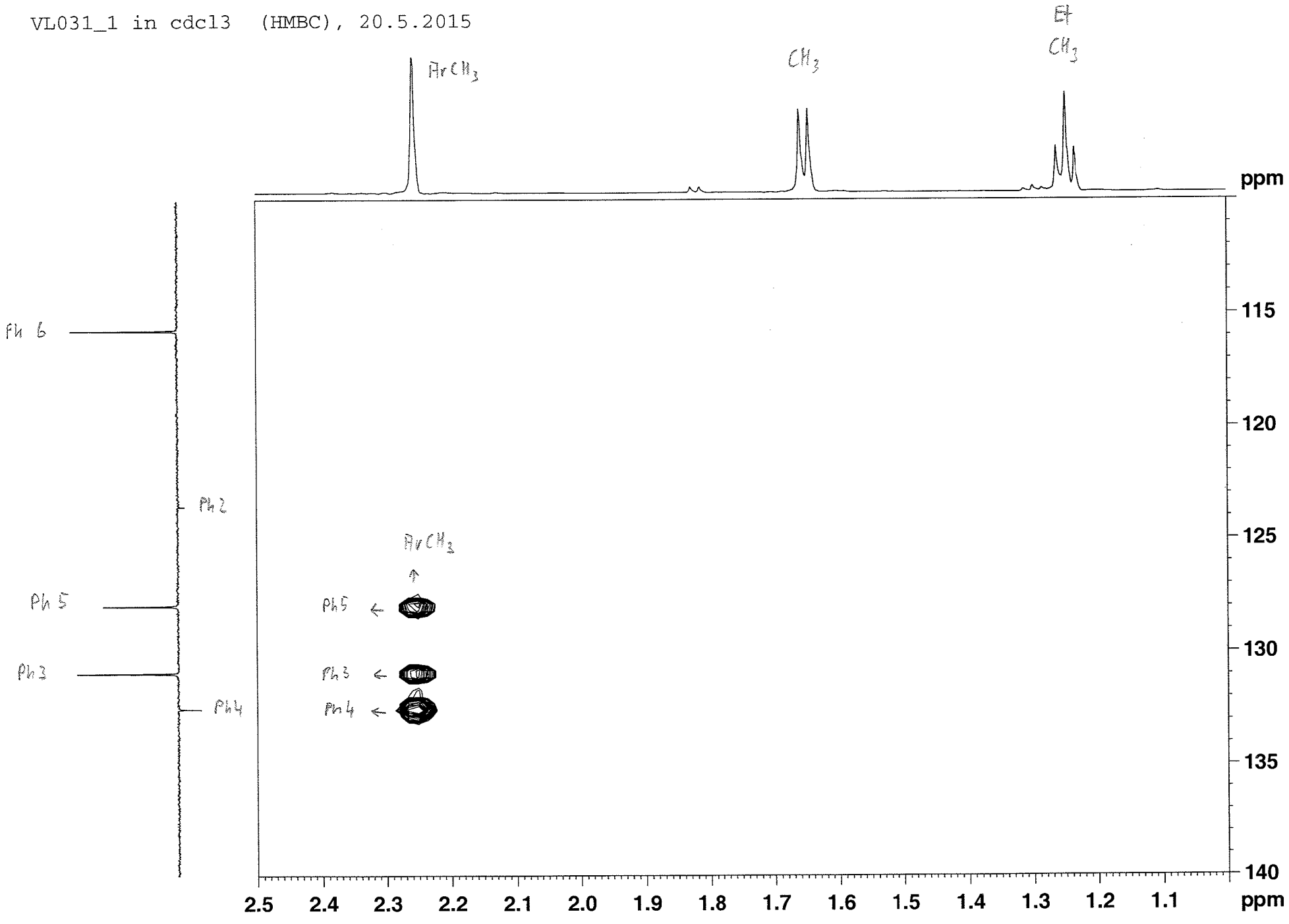
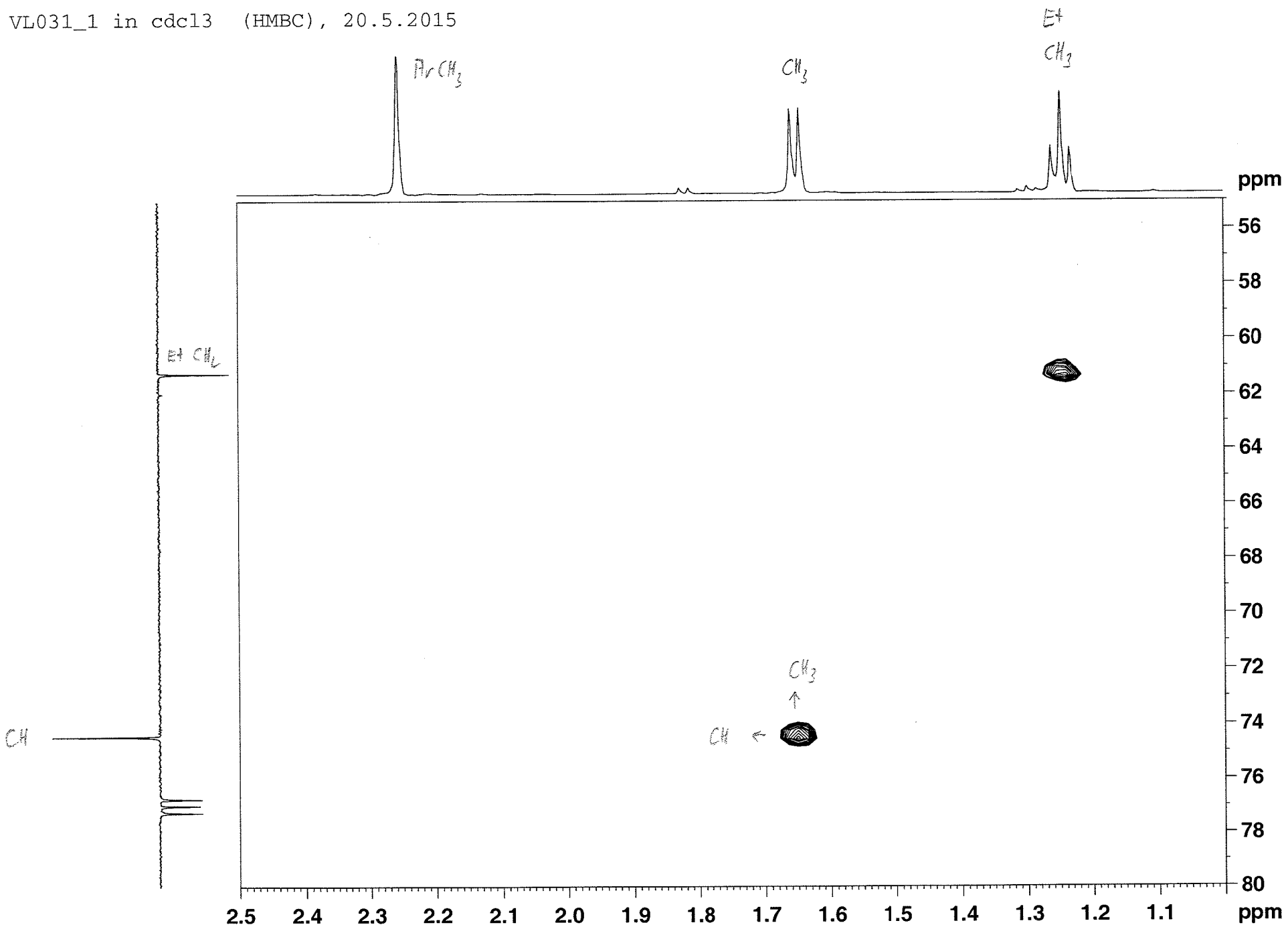
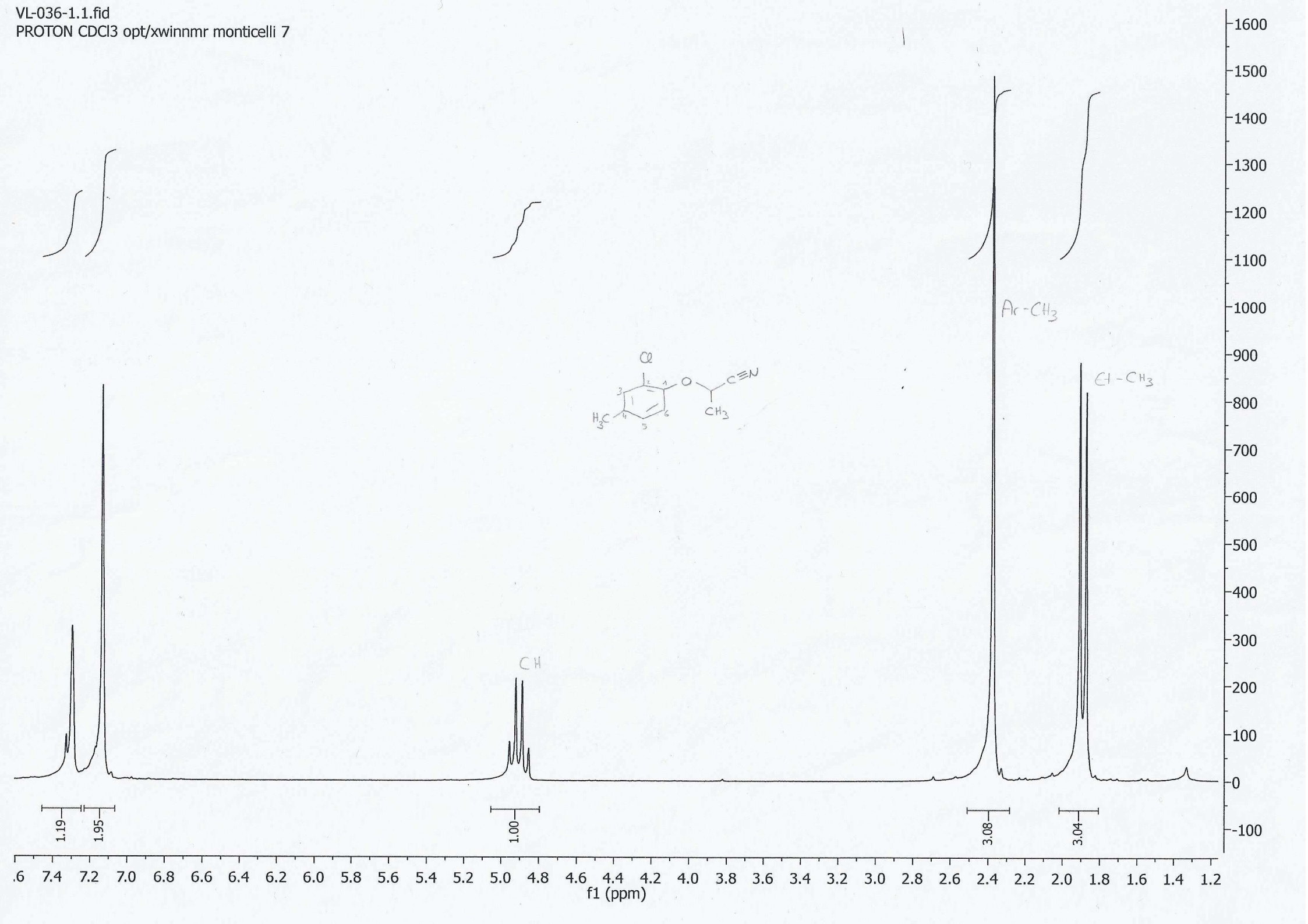



VL031_1 in cdcl3 (HMBC), 20.5.2015
ArCH3
CH3
Et
CH3
ppm
Ph 6
Ph 2
Ph 5
Ph 3
Ph 4
ArCH3
Ph5
Ph3
Ph4
115
120
125
130
135
140
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
ppm

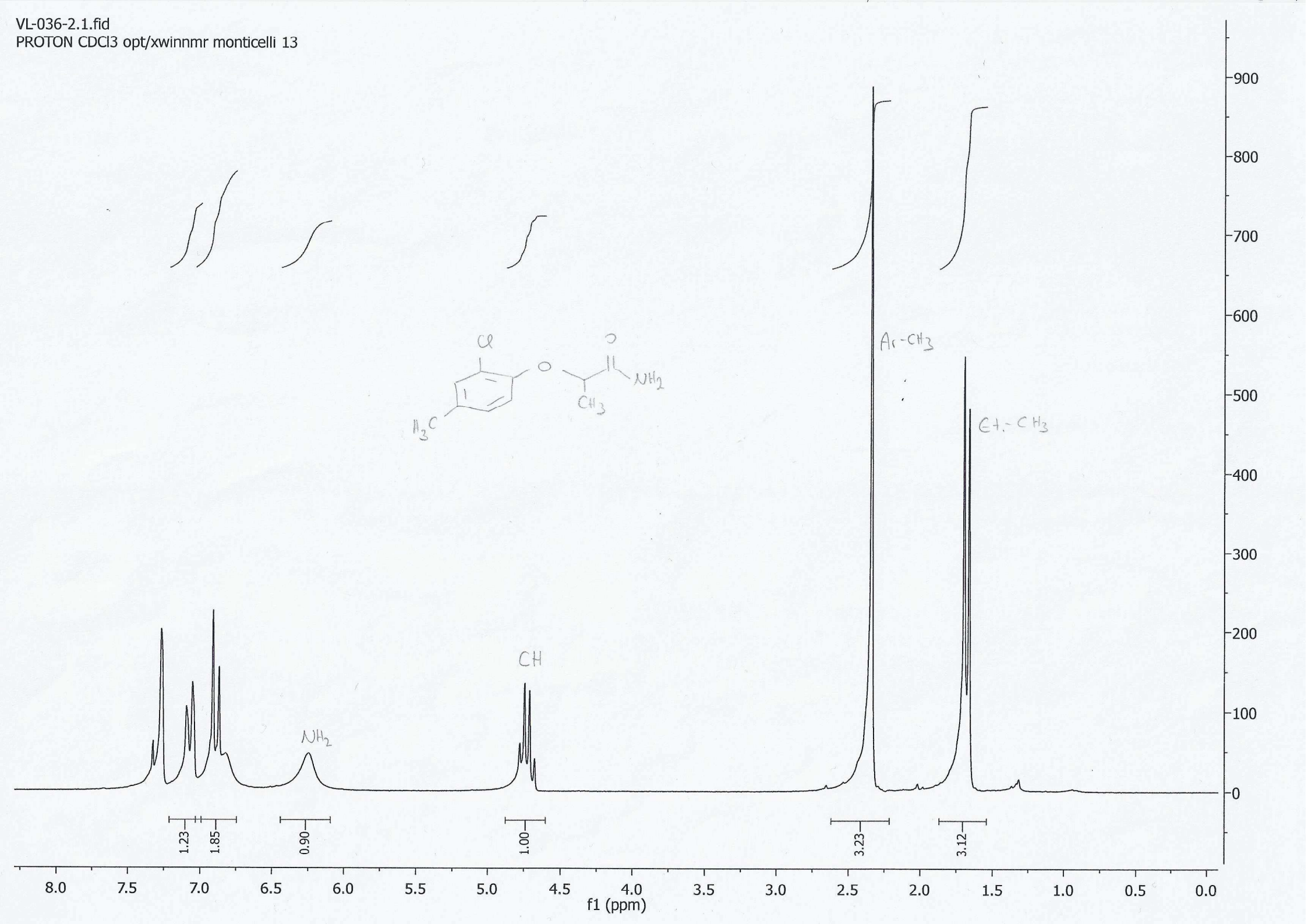
VL031_1 in cdcl3 (HMBC), 20.5.2015



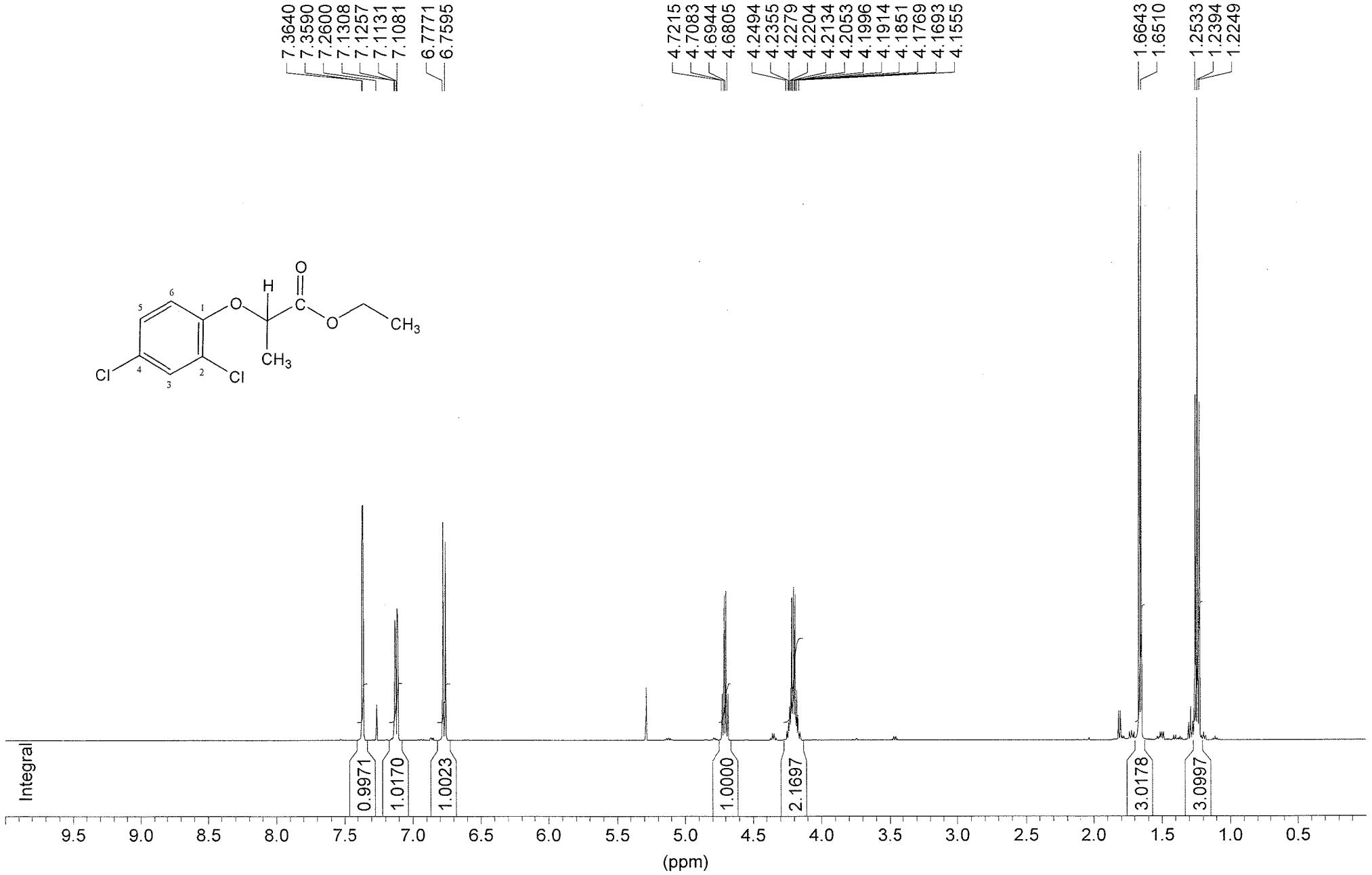
VL-036-1.1.fid
PROTON CDCl3 opt/xwinnmr monticelli 7



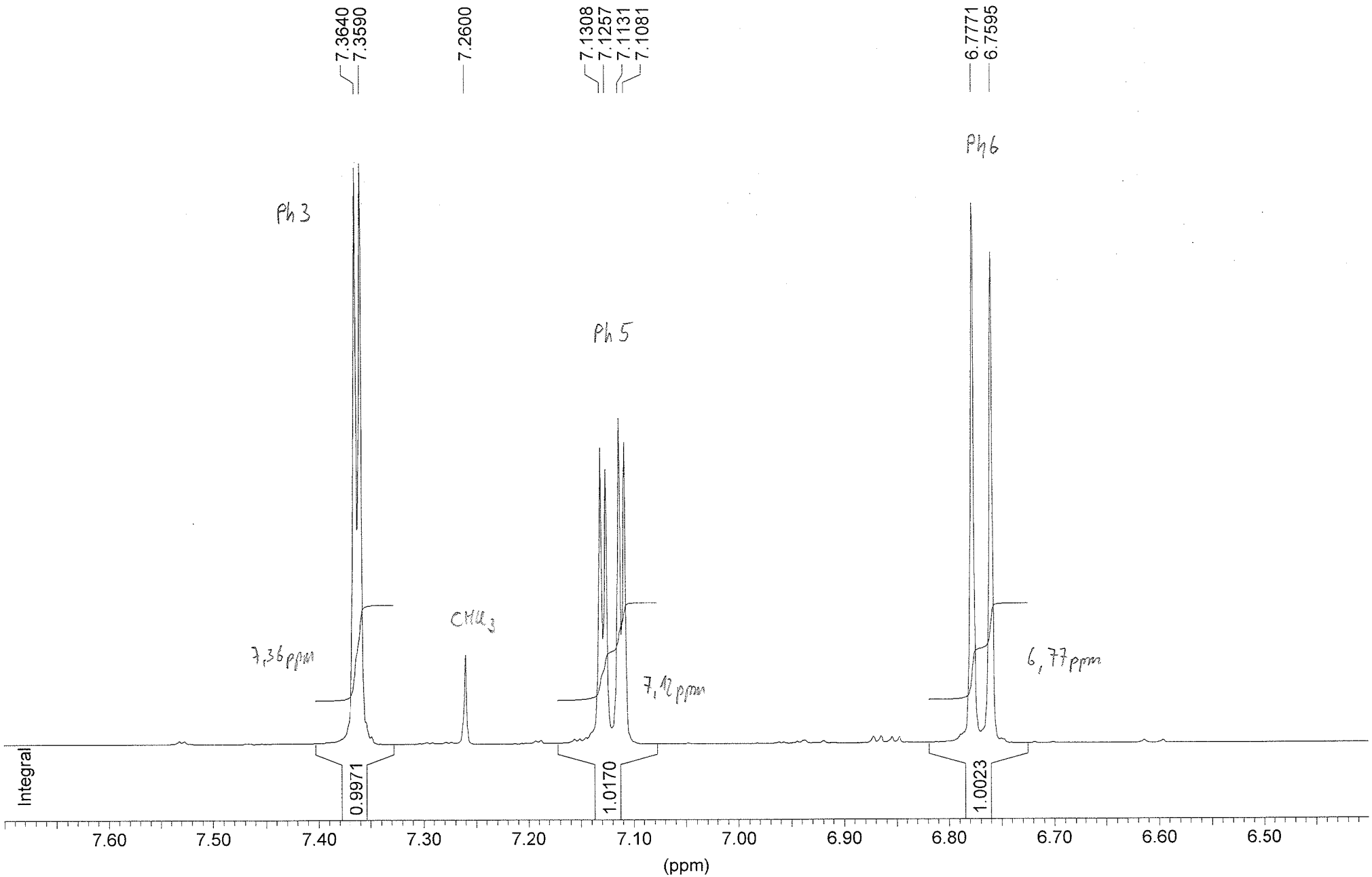
VL-036-2.1.fid
PROTON CDCl3 opt/xwinnmr monticelli 13



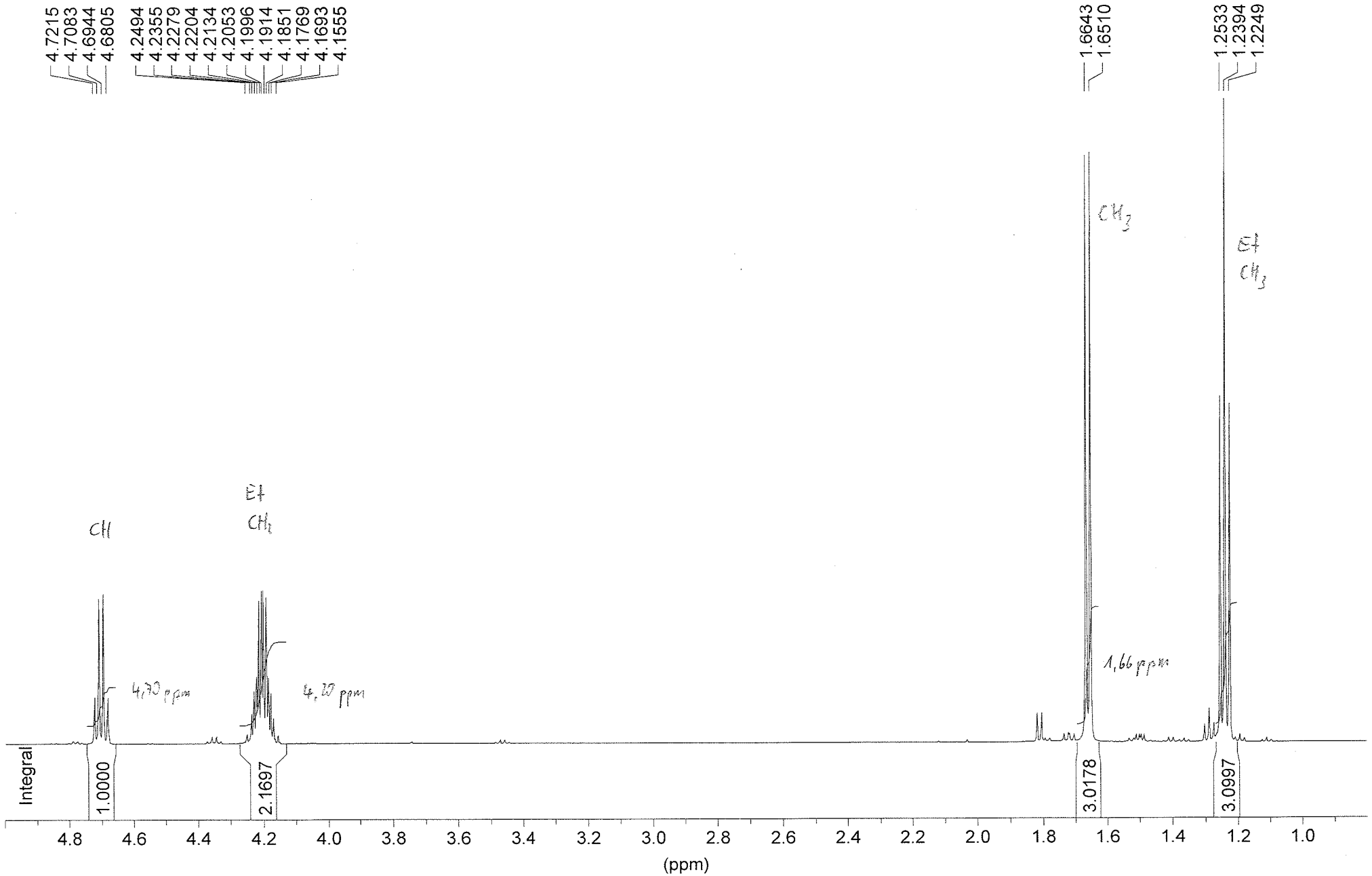
VL038_0 in cdcl3 (Proton), 27.5.2015



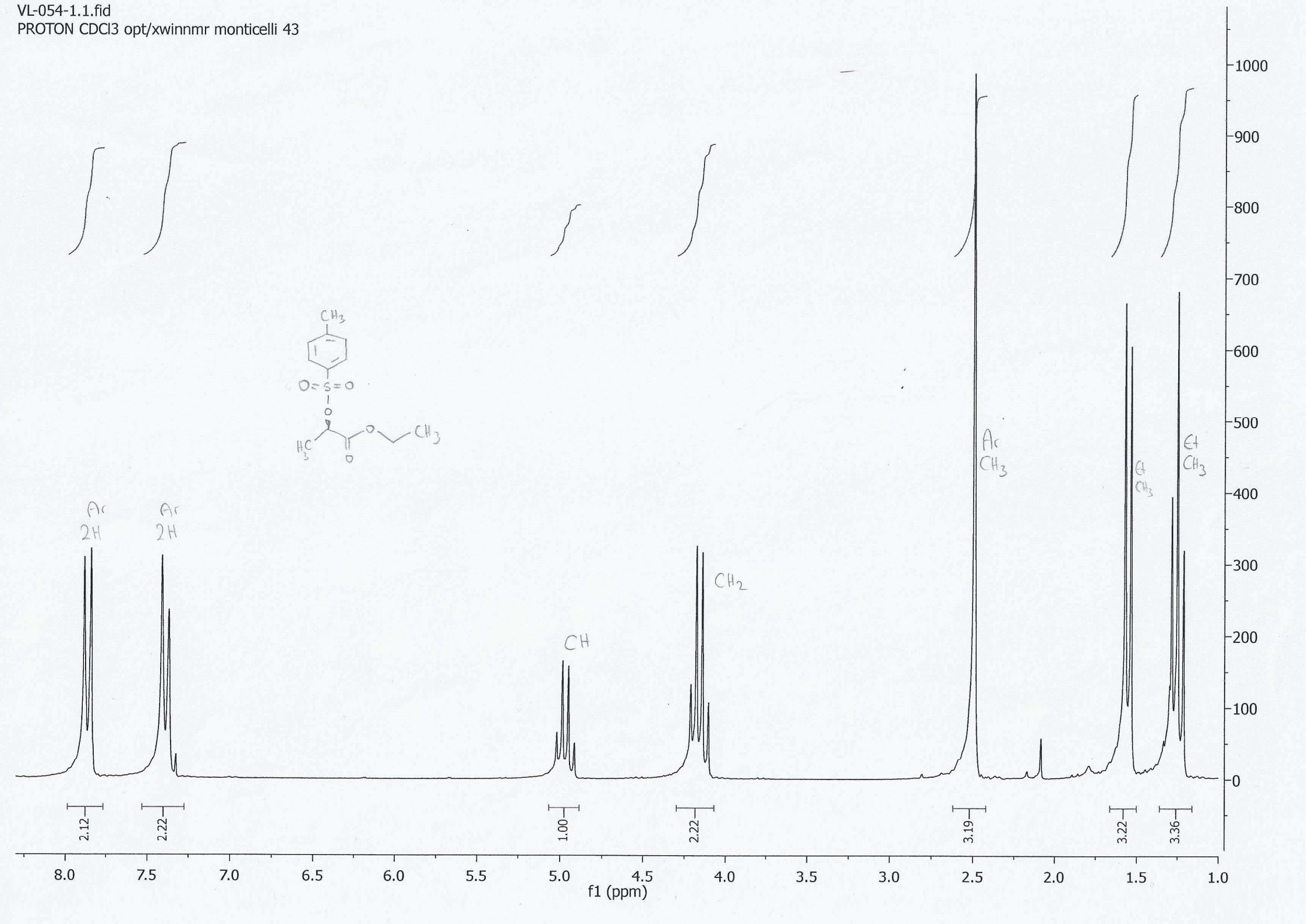
VL038_0 in cdcl3 (Proton), 27.5.2015



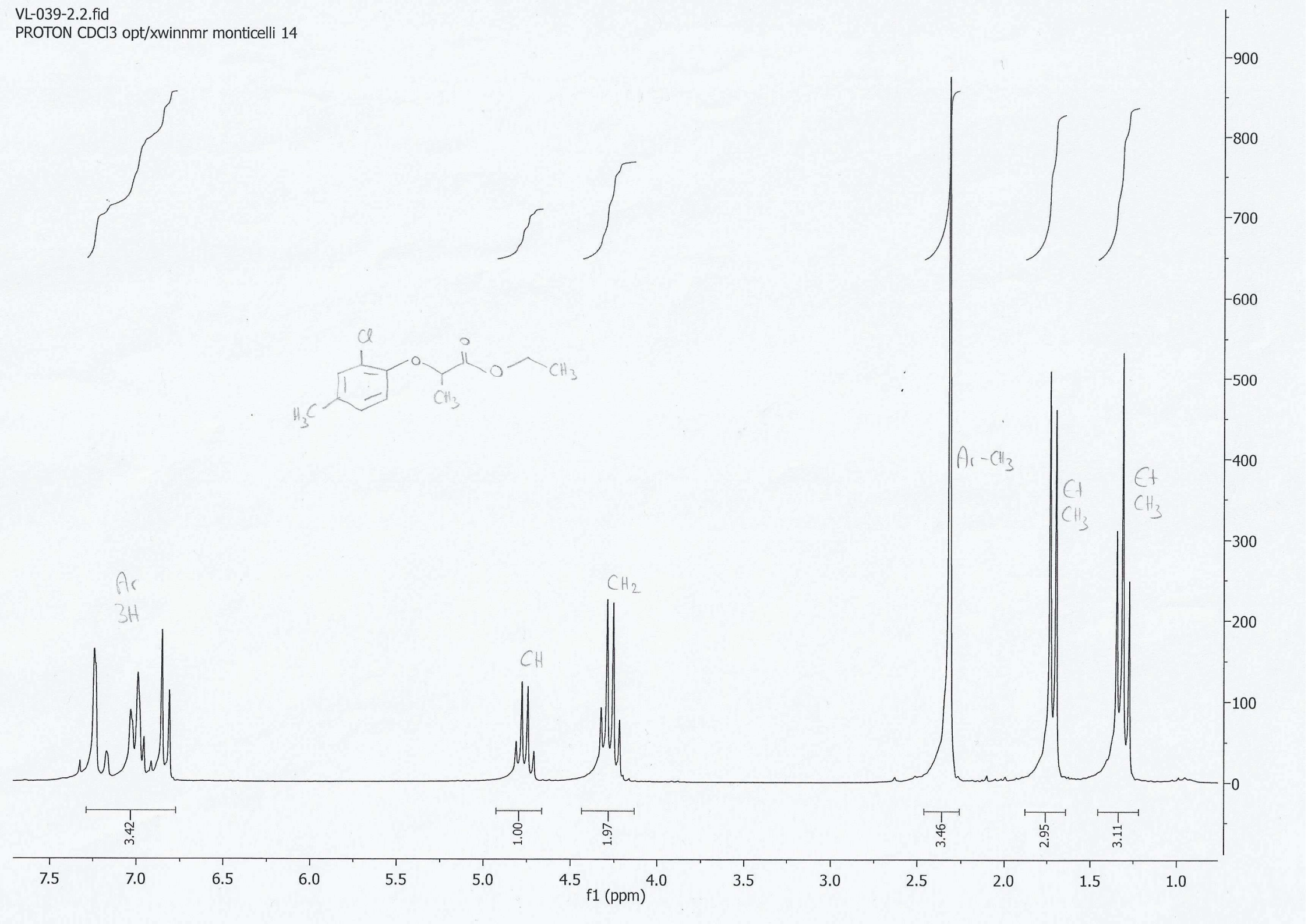
VL038_0 in cdcl3 (Proton), 27.5.2015



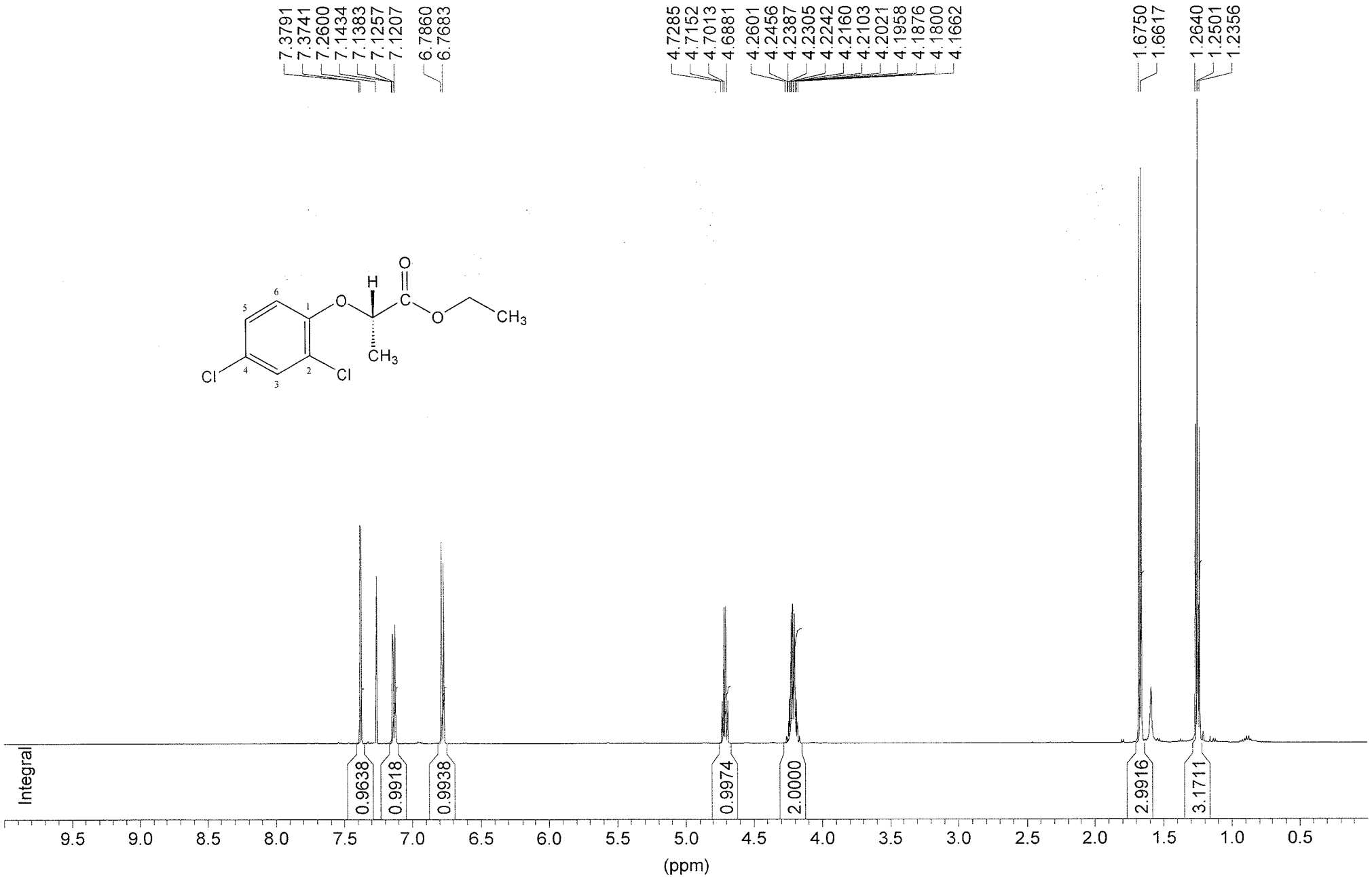
VL-054-1.1.fid
PROTON CDCl3 opt/xwinnmr monticelli 43



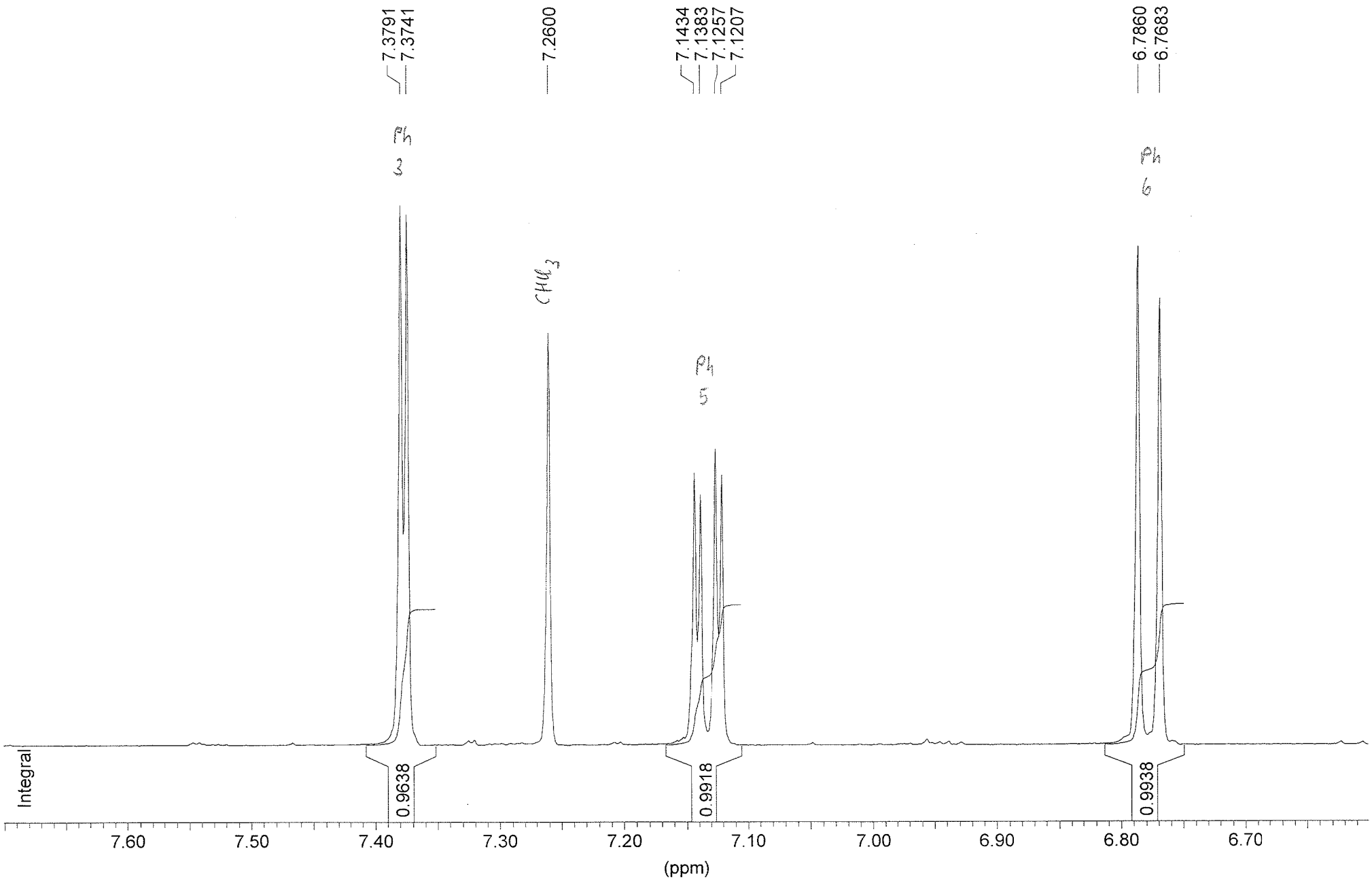
VL-039-2.2.fid
PROTON CDCl3 opt/xwinnmr monticelli 14



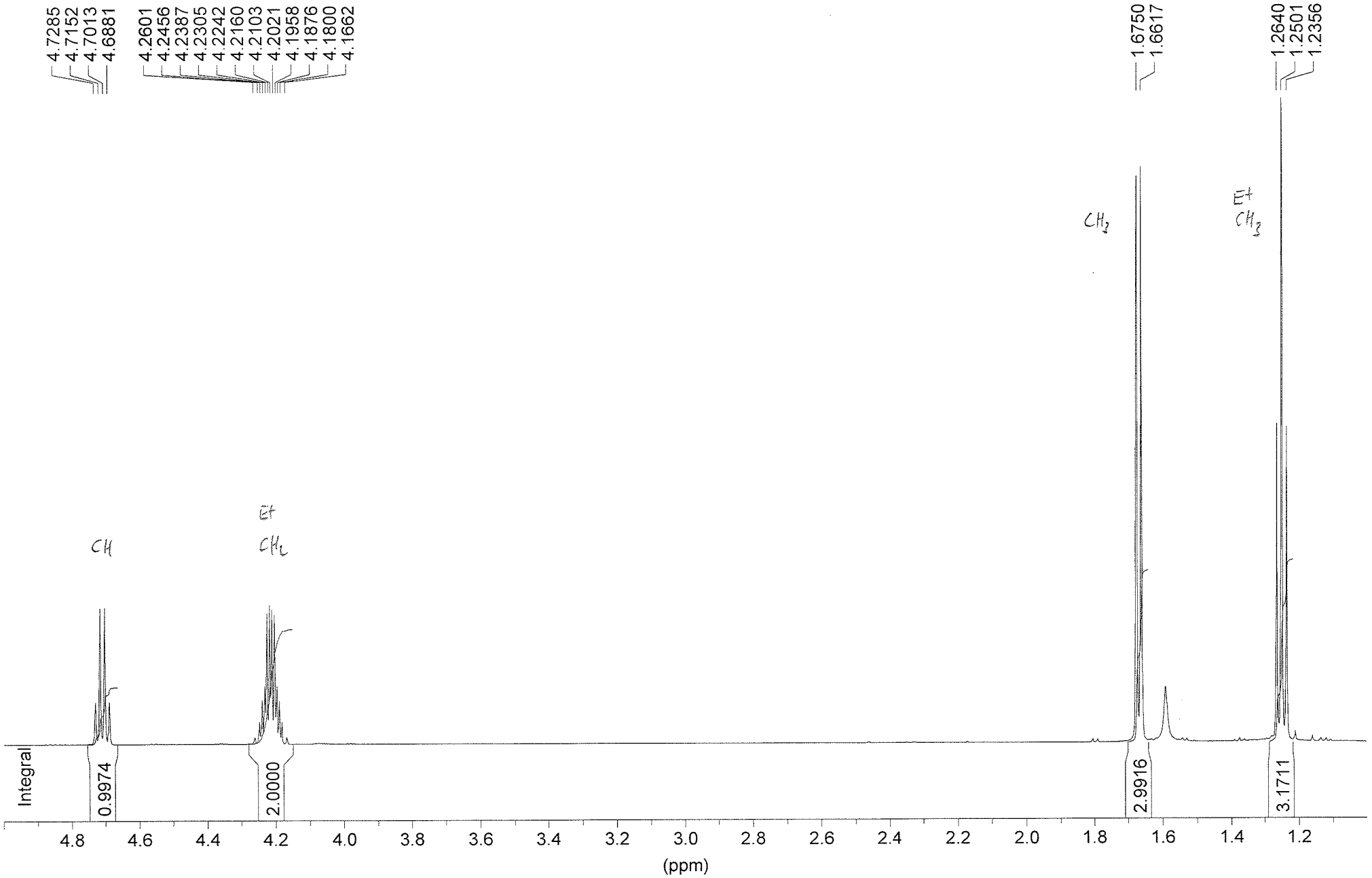
VL037_1 in cdcl3 (Proton), 27.5.2015



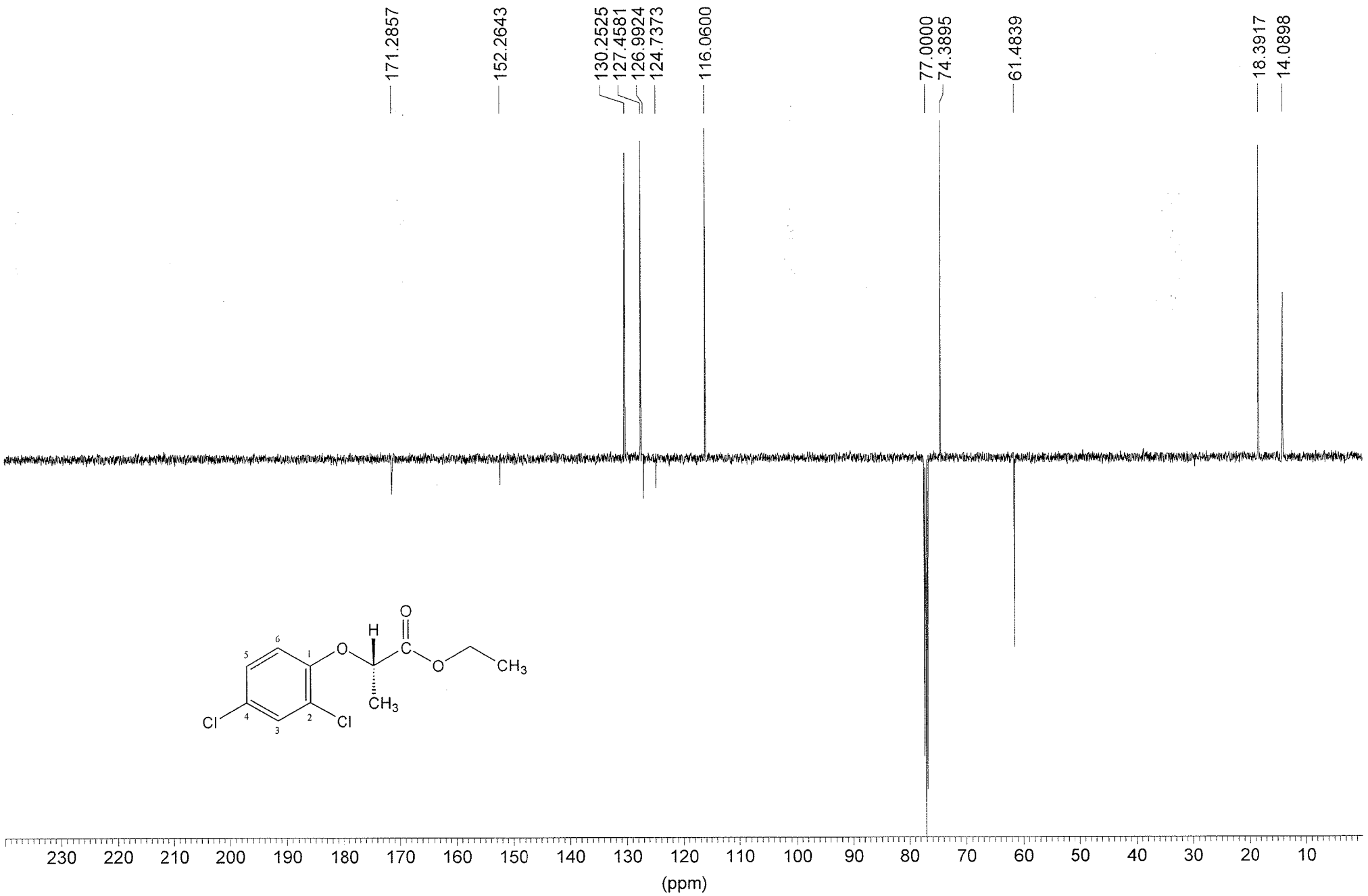
VL037_1 in cdcl3 (Proton), 27.5.2015



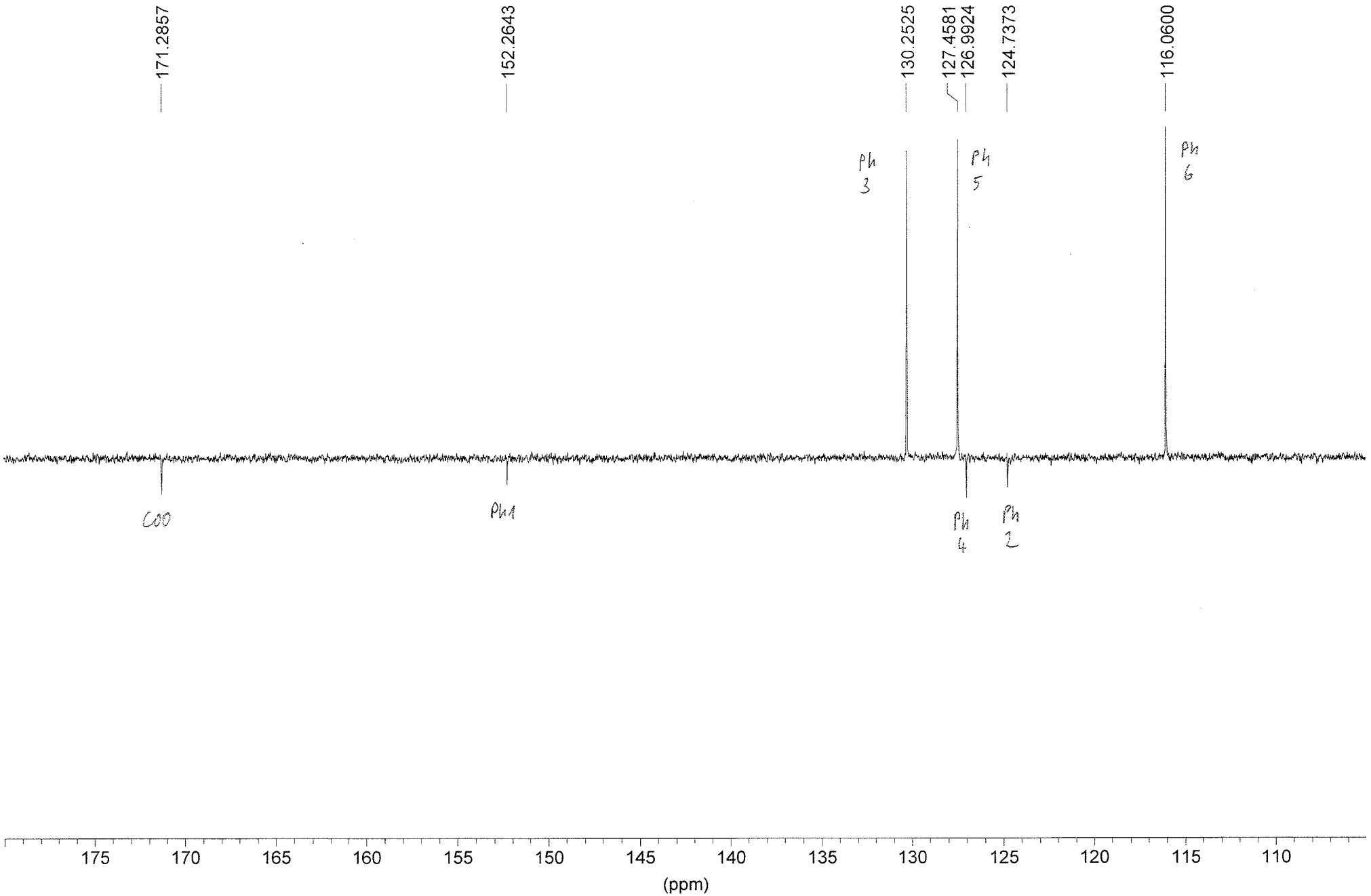
VL037_1 in cdcl3 (Proton), 27.5.2015



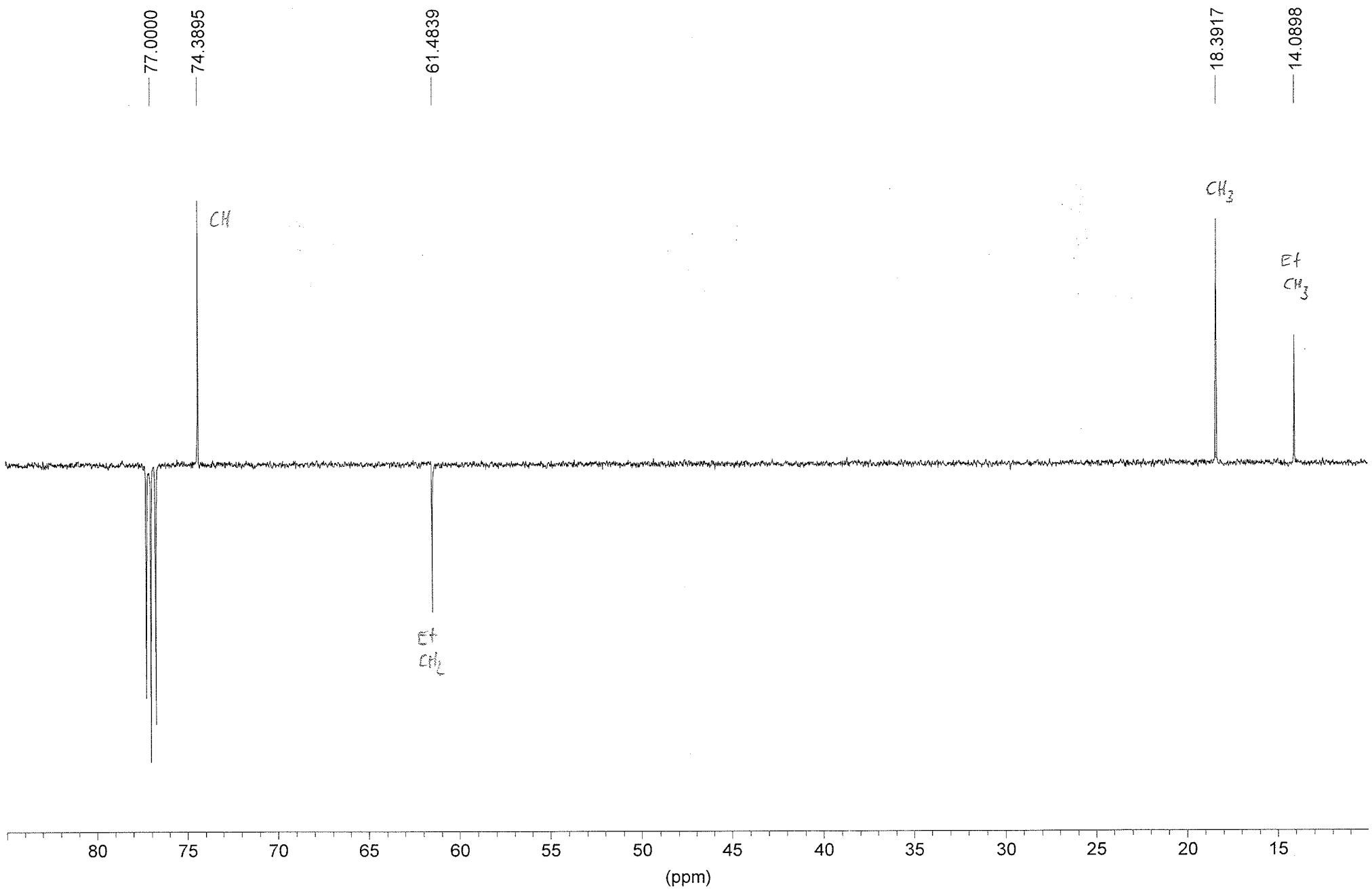
VL037_1 in cdcl3 (APT), 27.5.2015



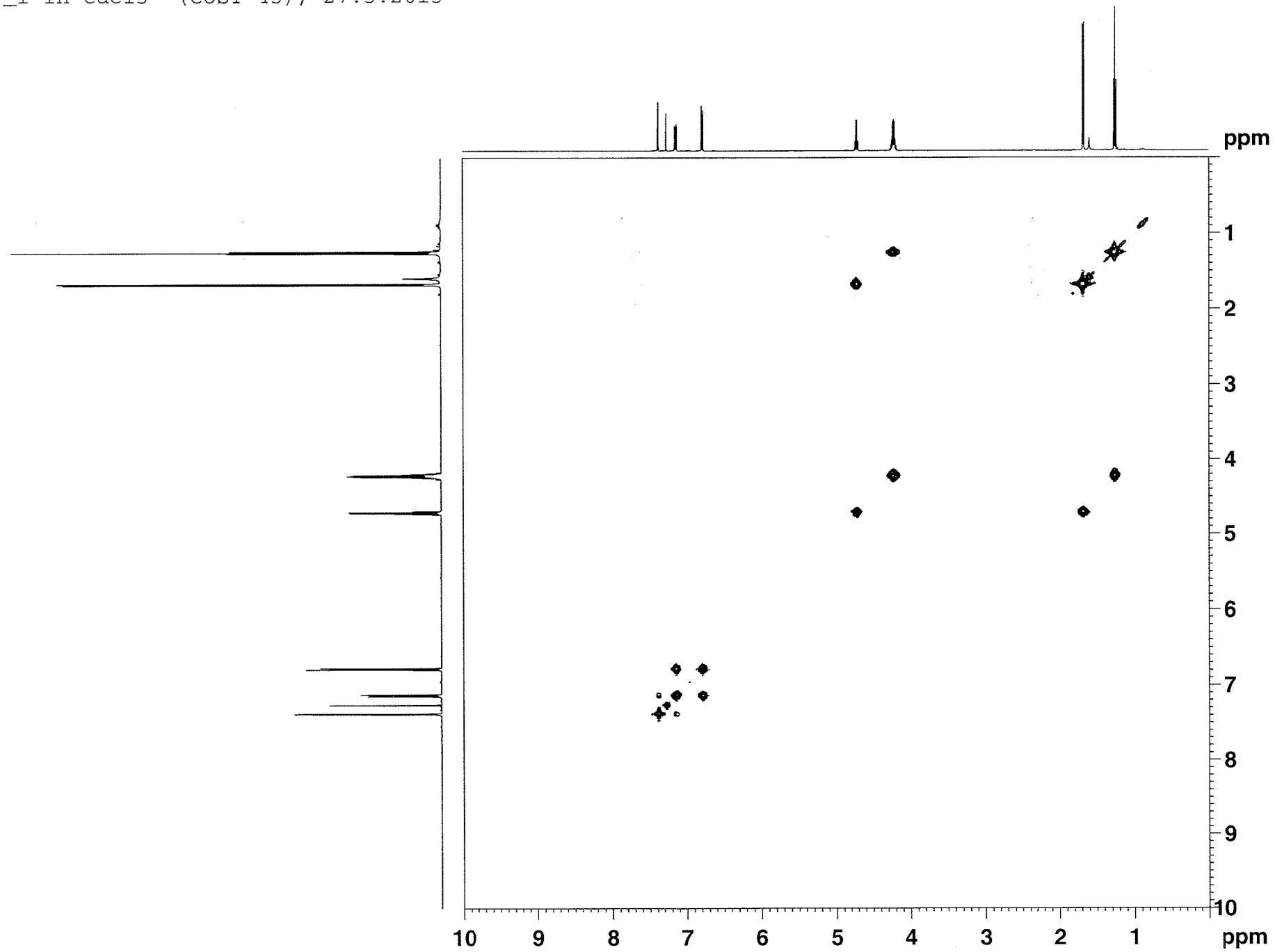
VL037_1 in cdcl3 (APT), 27.5.2015



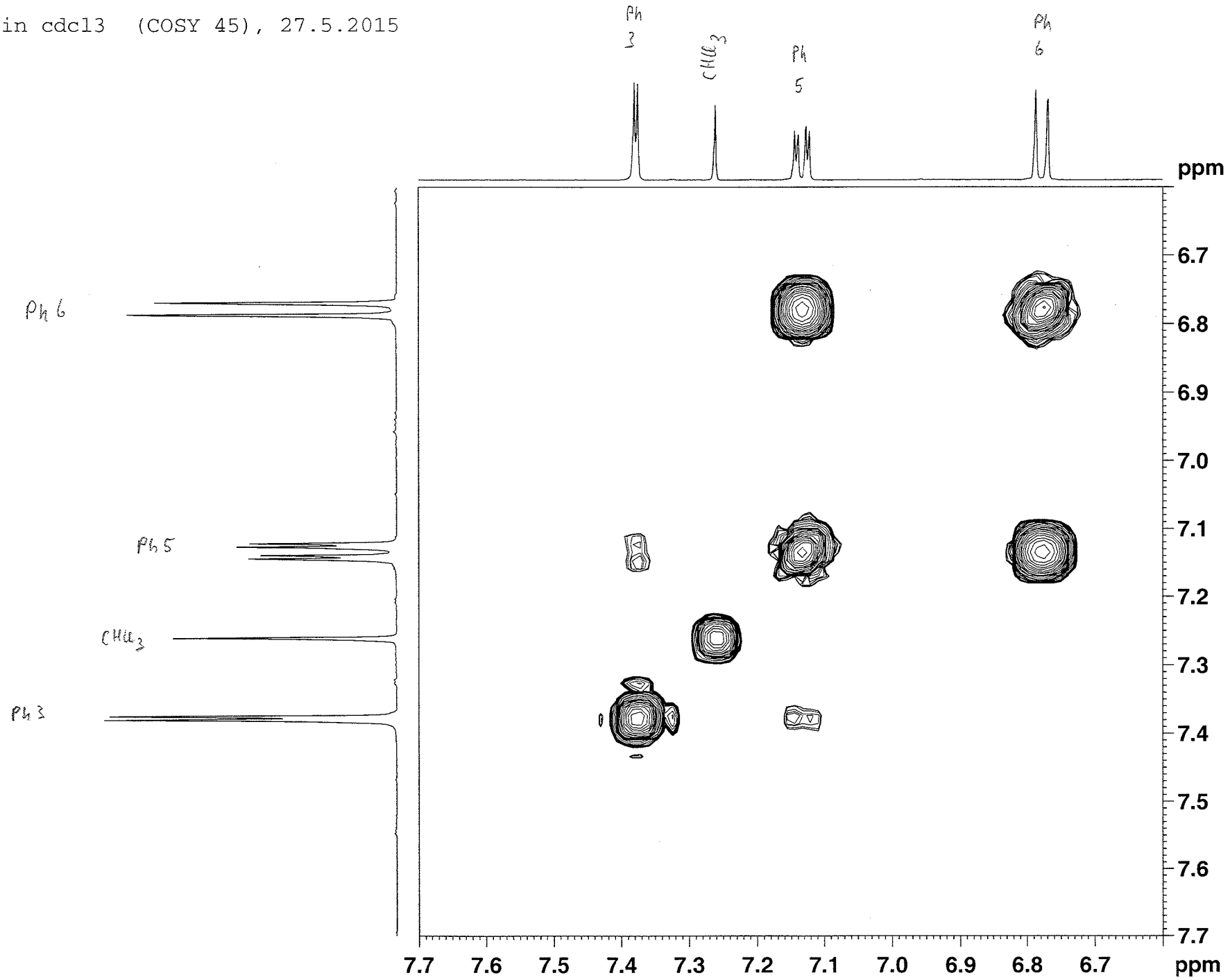
VL037_1 in cdcl3 (APT), 27.5.2015



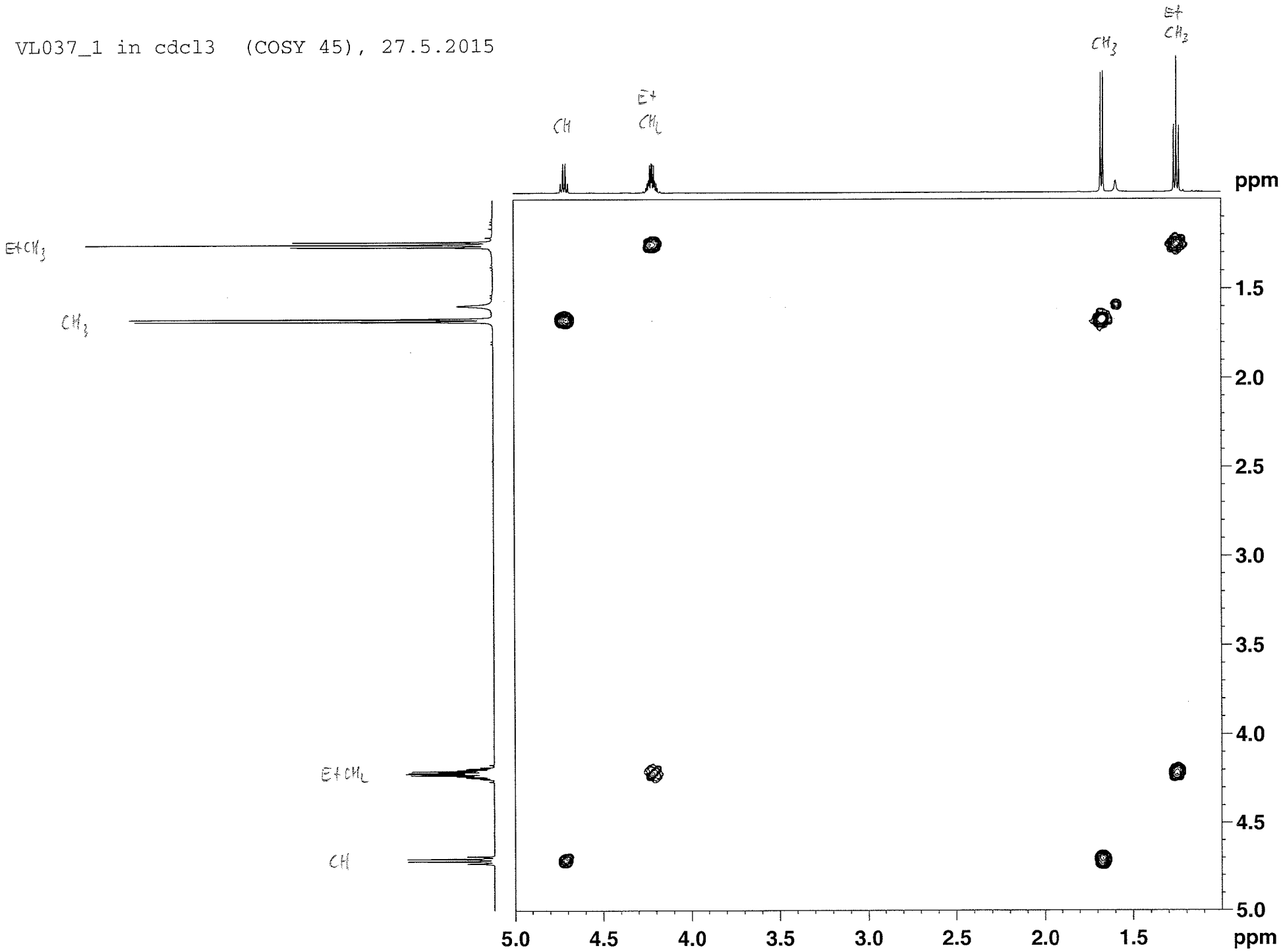
VL037_1 in cdcl3 (COSY 45), 27.5.2015



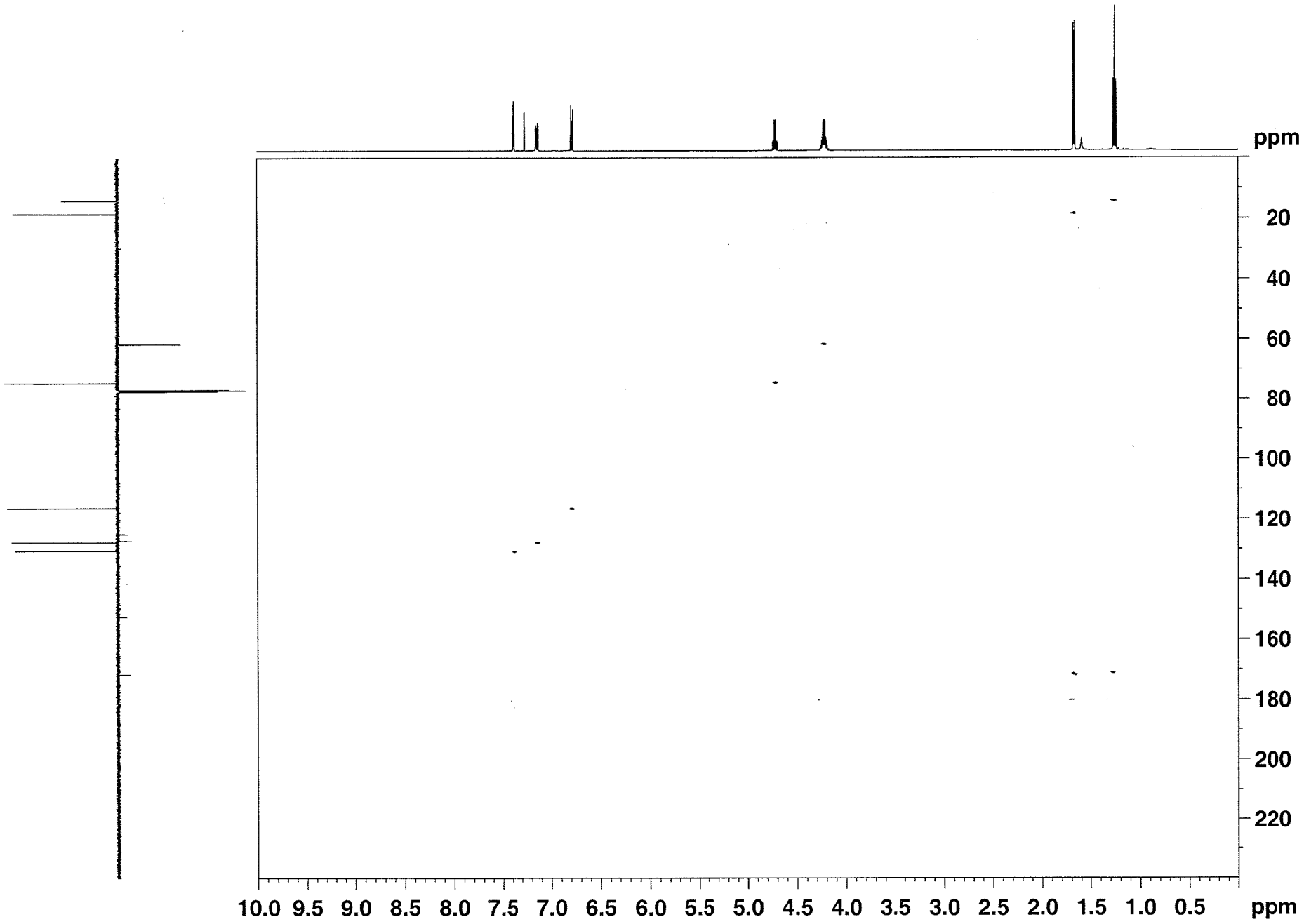
VL037_1 in cdcl3 (COSY 45), 27.5.2015



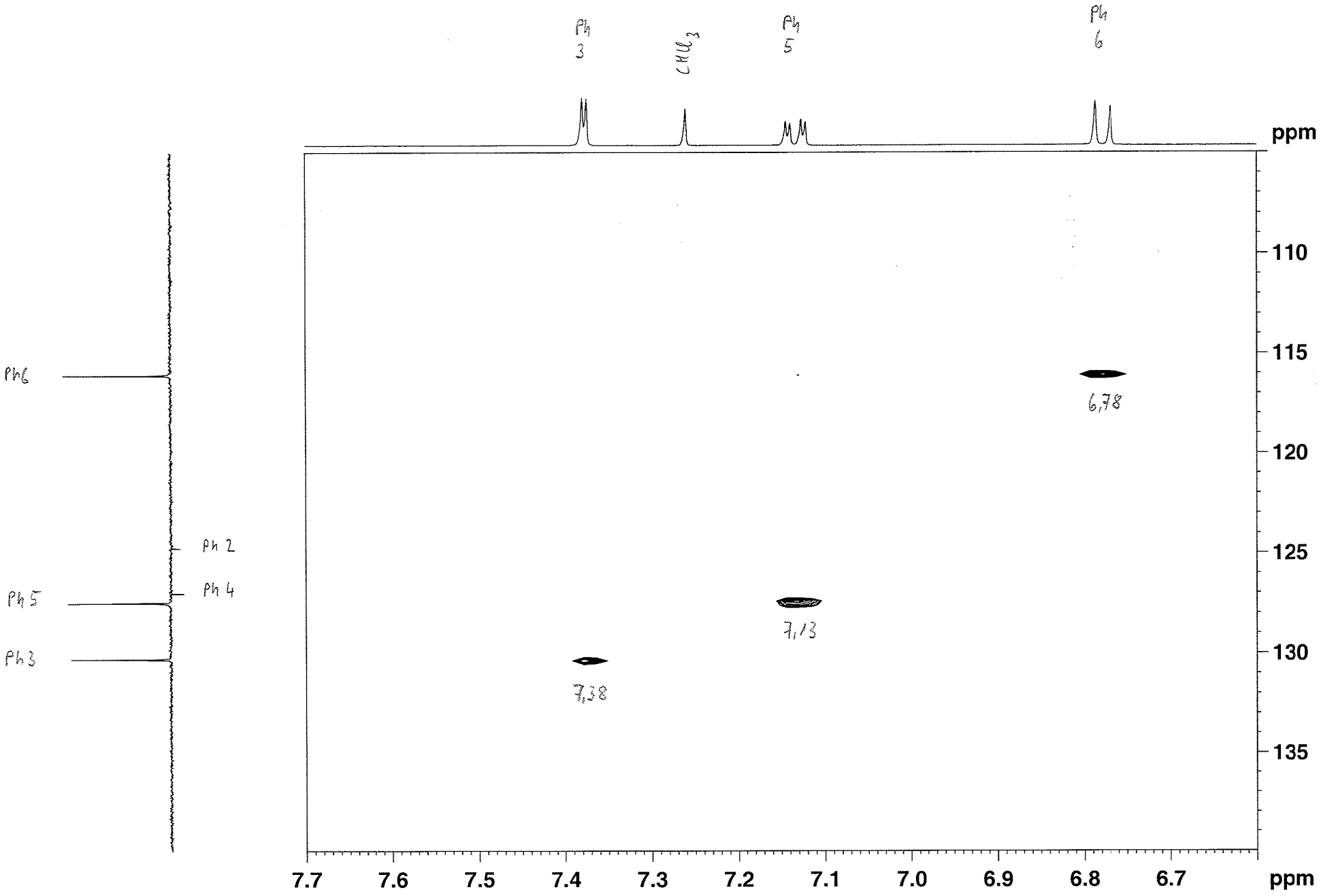
VL037_1 in cdcl3 (COSY 45), 27.5.2015



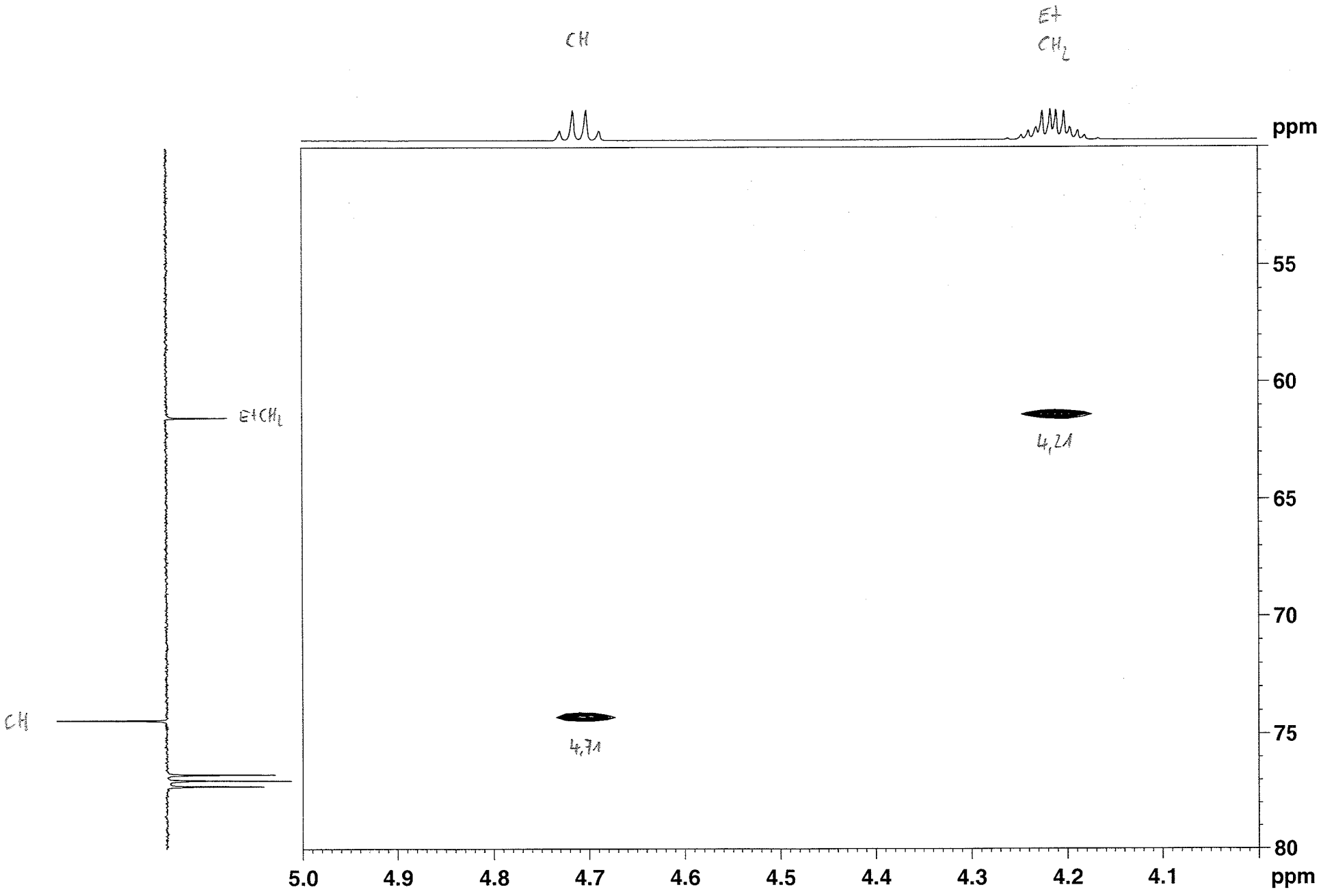
VL037_1 in cdcl3 (HSQC neu), 27.5.2015

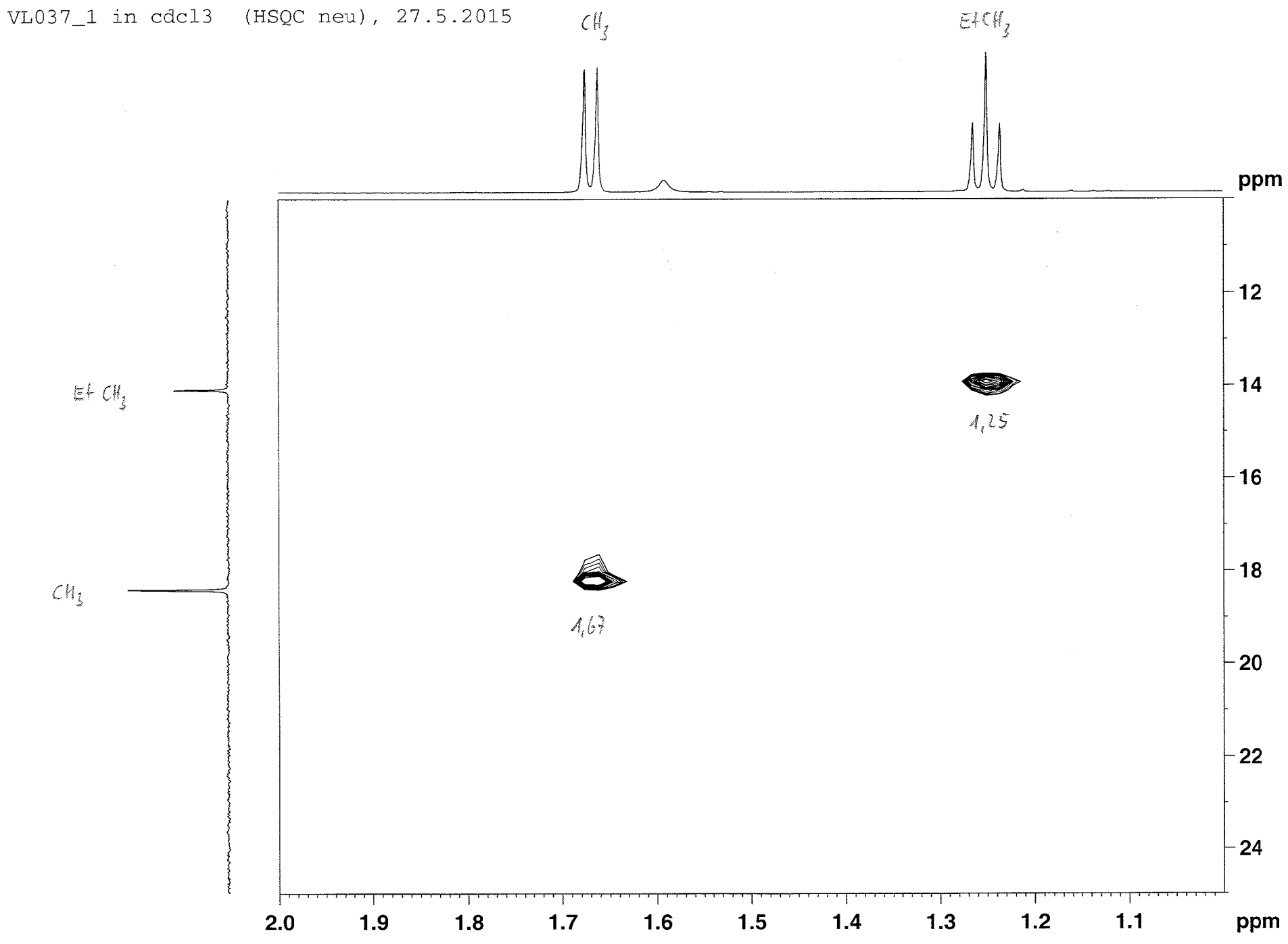


VL037_1 in cdcl3 (HSQC neu), 27.5.2015

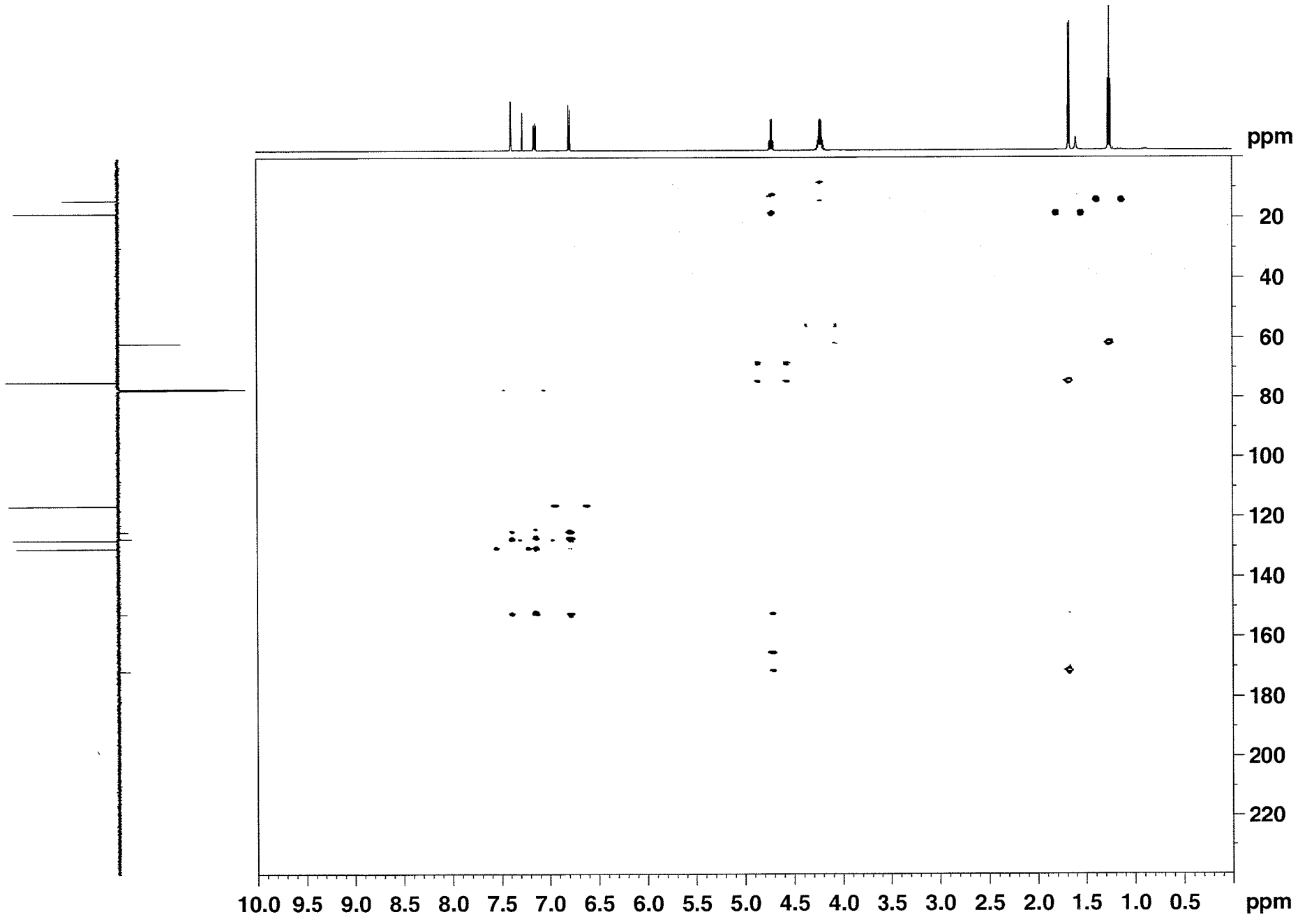


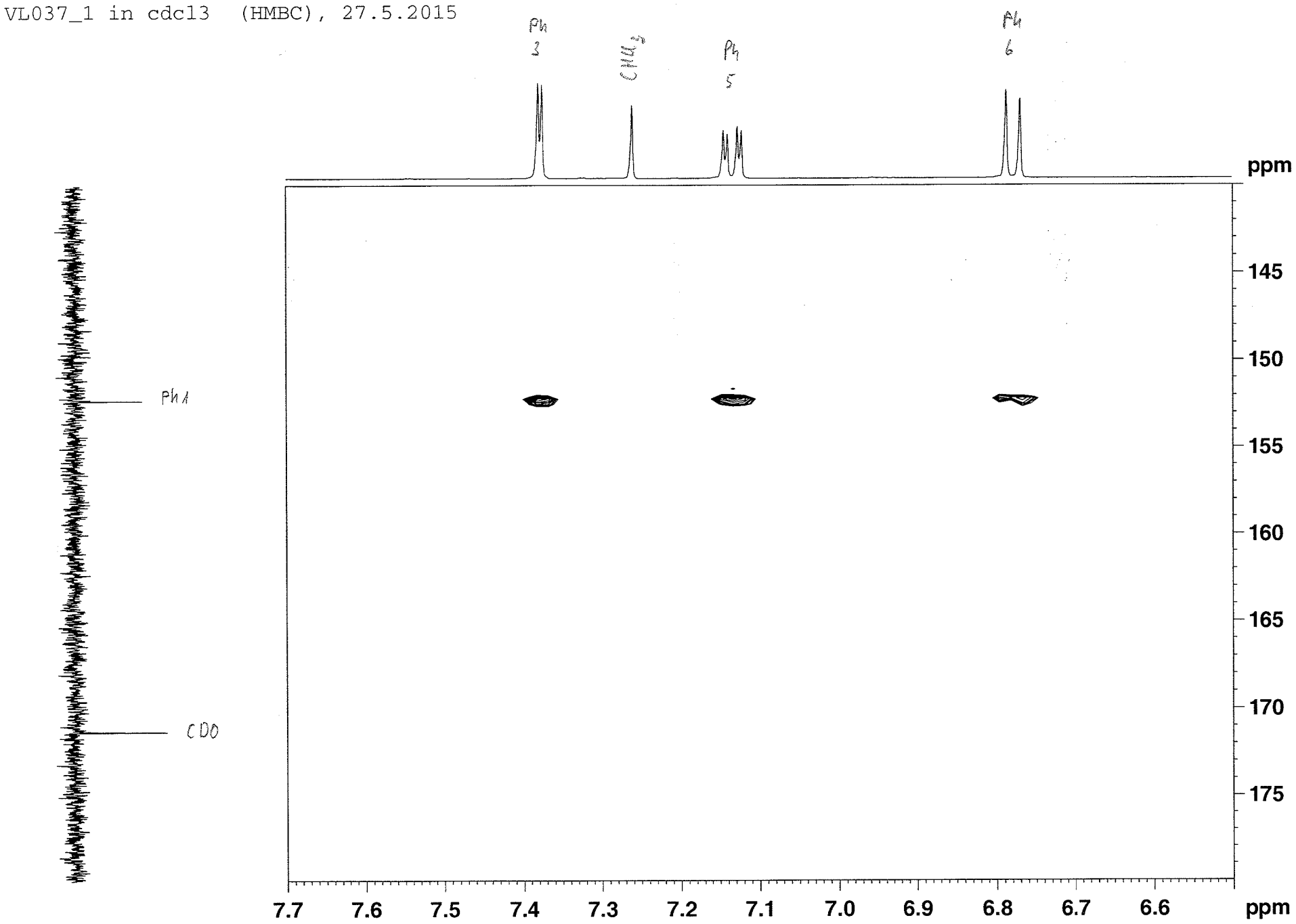
VL037_1 in cdcl3 (HSQC neu), 27.5.2015



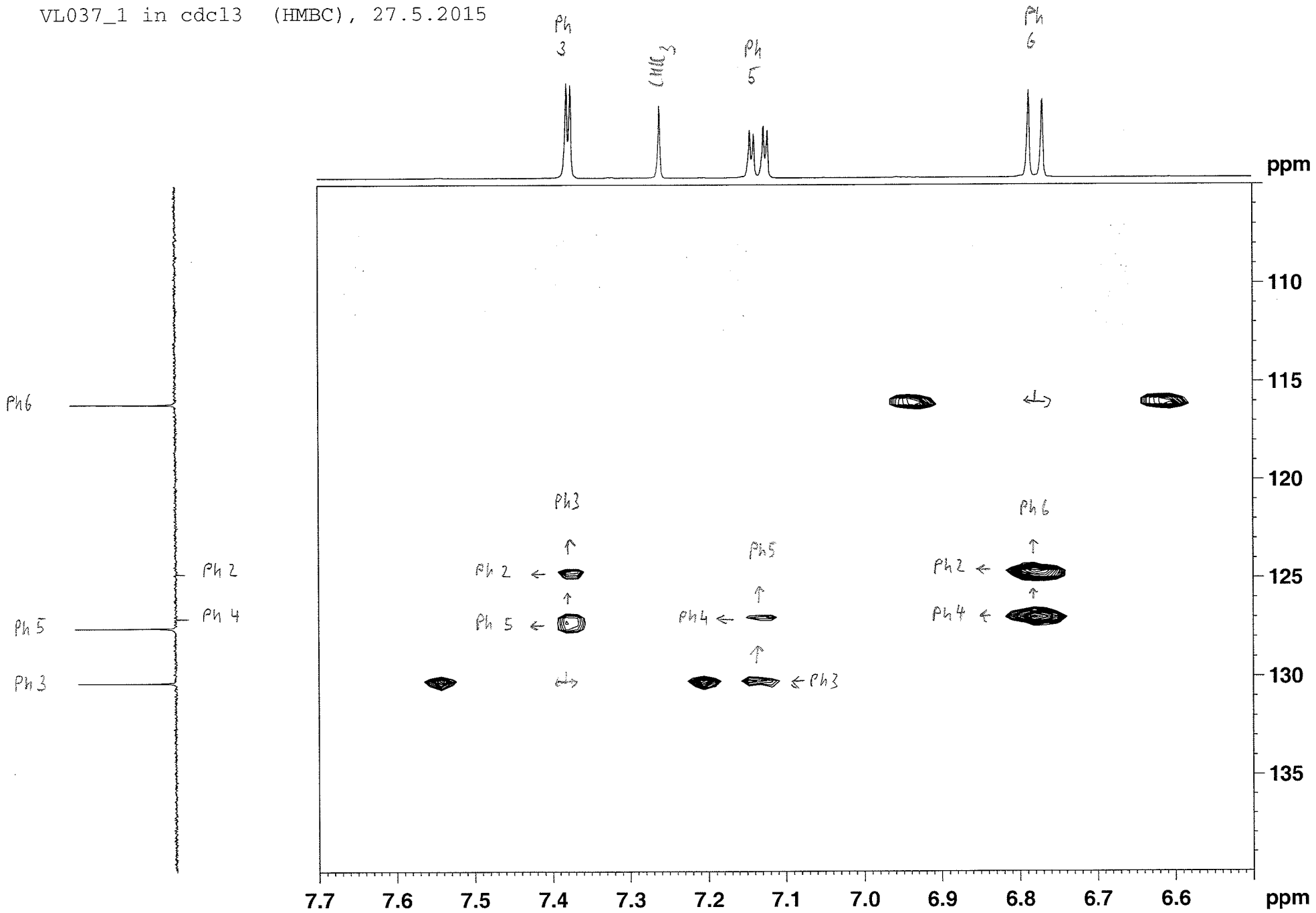

VL037_1 in cdcl3 (HSQC neu), 27.5.2015
CH3
Et CH3
ppm
Et CH3
CH3
1,25
1,67
12
14
16
18
20
22
24
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
ppm

VL037_1 in cdcl3 (HMBC), 27.5.2015

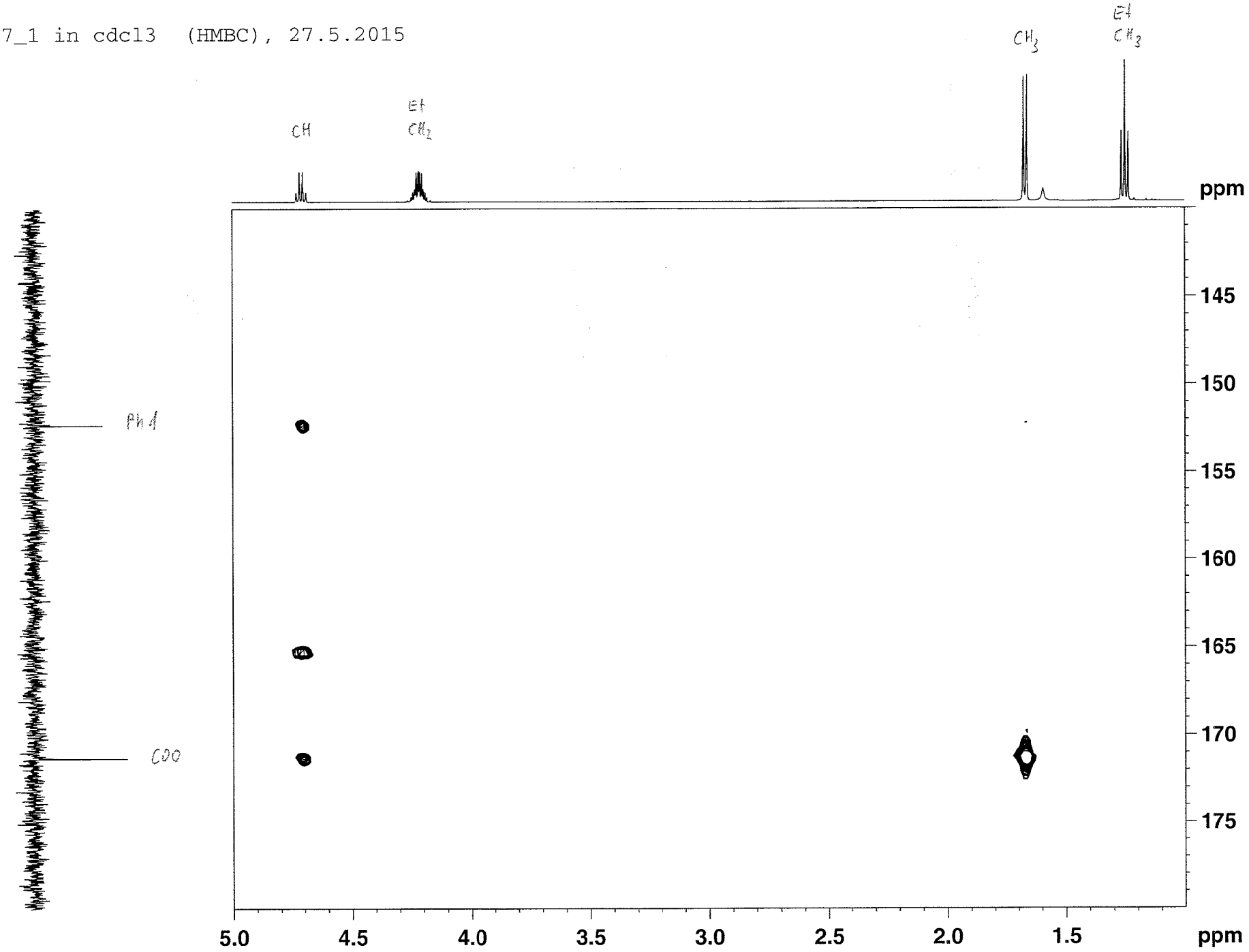



VL037_1 in cdcl3 (HMBC), 27.5.2015
Ph 3
CH3
Ph 5
Ph 6
ppm
145
150
155
160
165
170
175
PhA
CDO
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
ppm

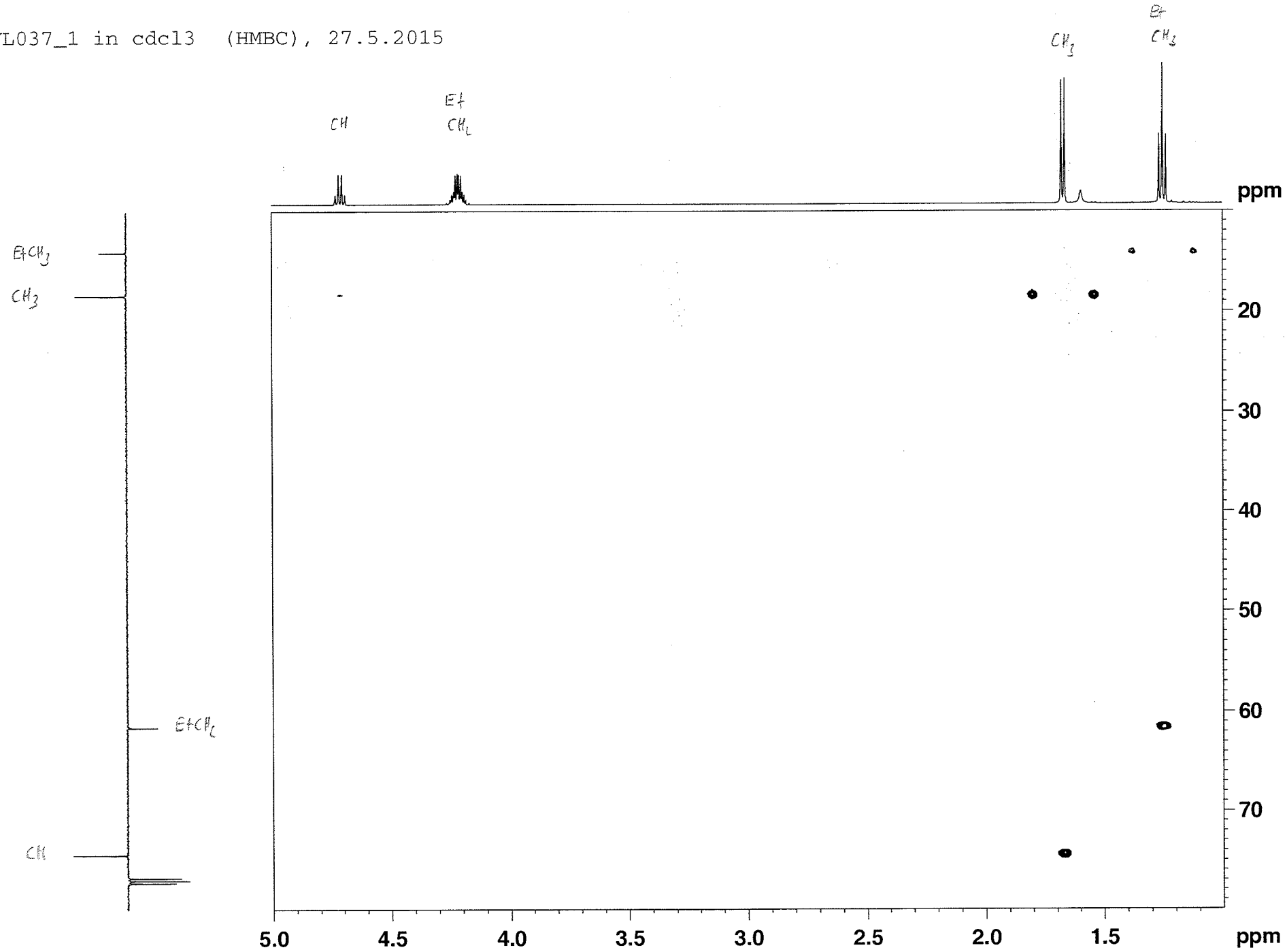
VL037_1 in cdcl3 (HMBC), 27.5.2015



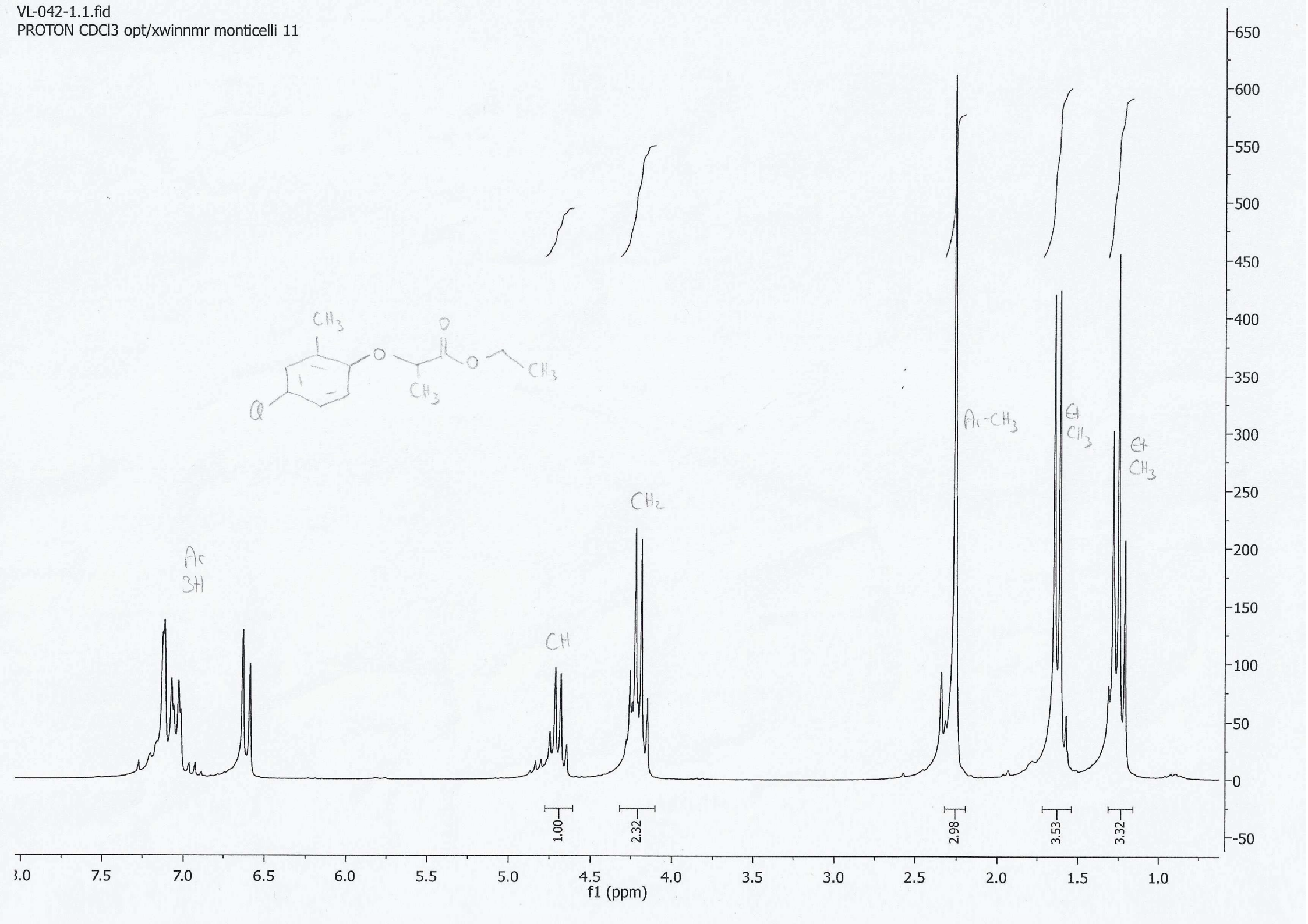
VL037_1 in cdcl3 (HMBC), 27.5.2015



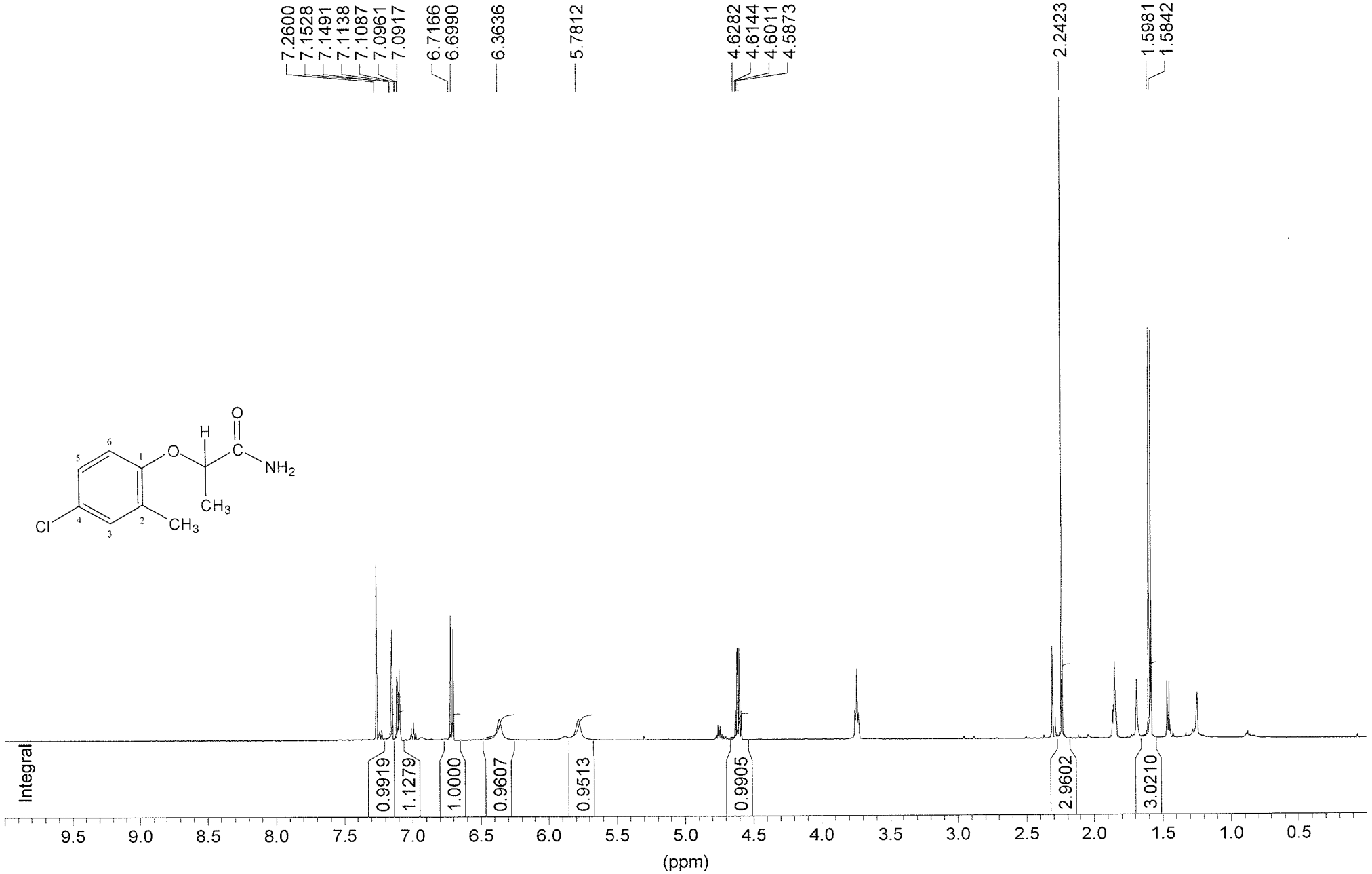
VL037_1 in cdcl3 (HMBC), 27.5.2015



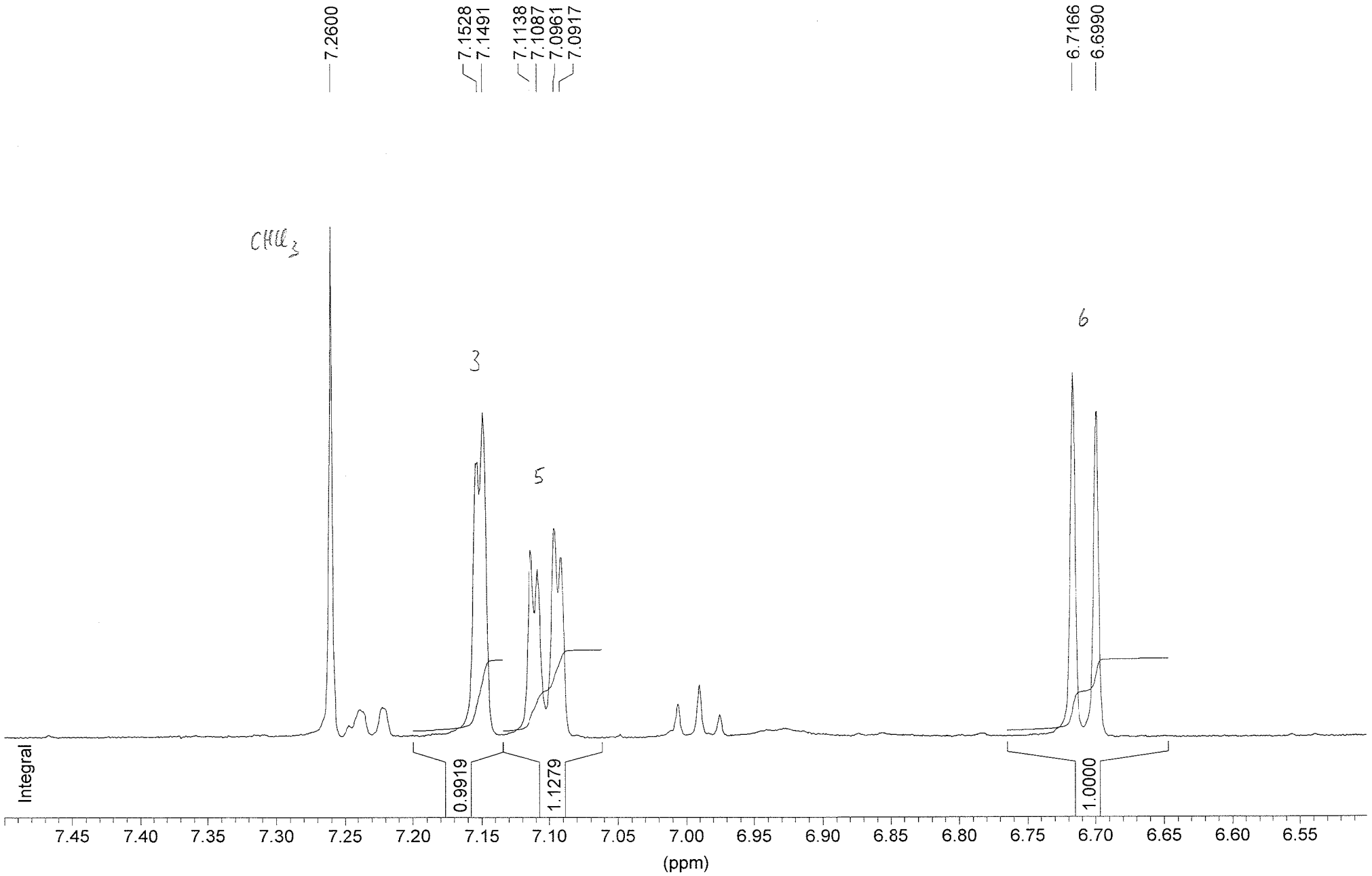
VL-042-1.1.fid
PROTON CDCl3 opt/xwinnmr monticelli 11



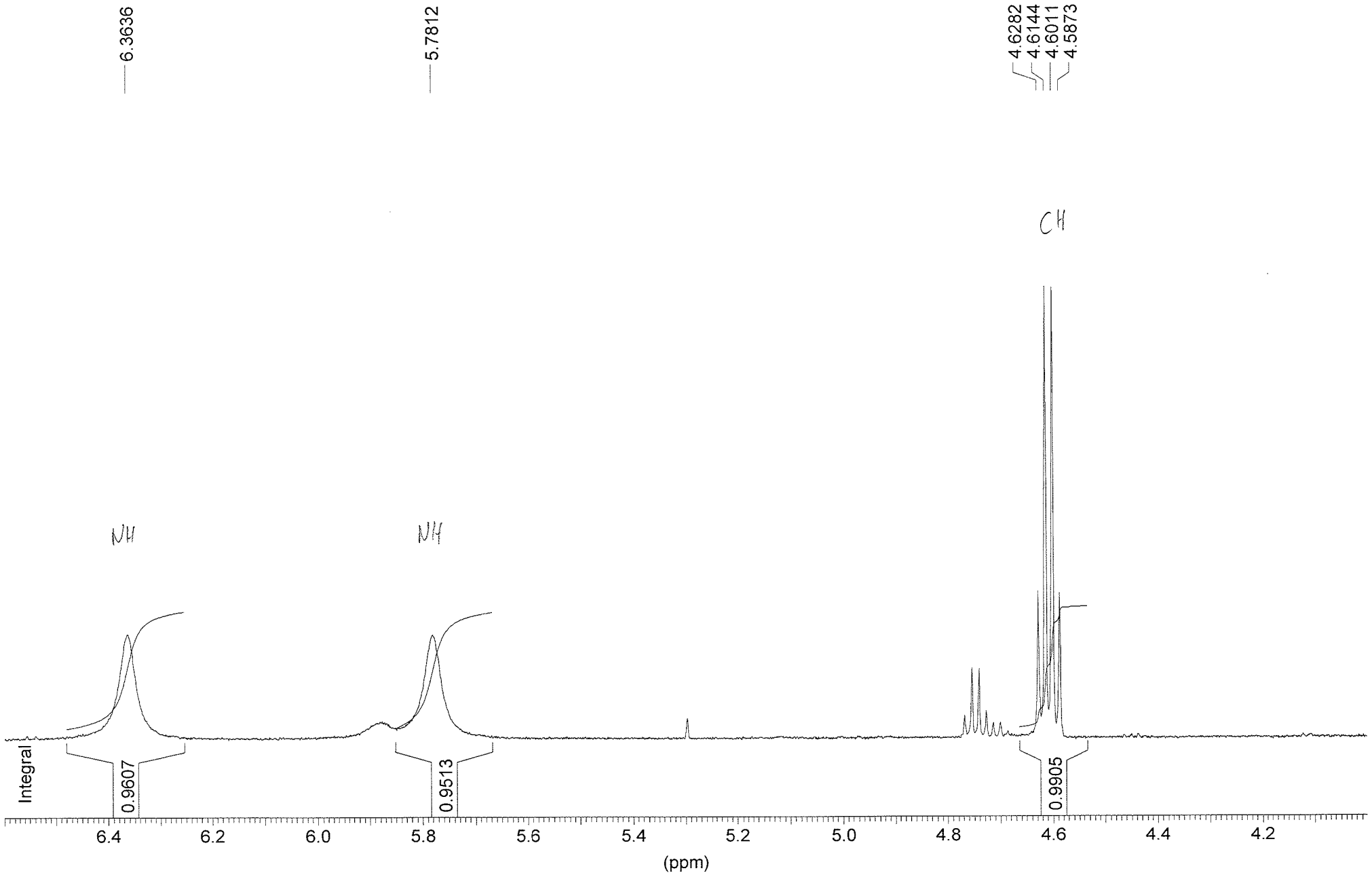
VL057_1 in cdcl3 (Proton), 2.7.2015



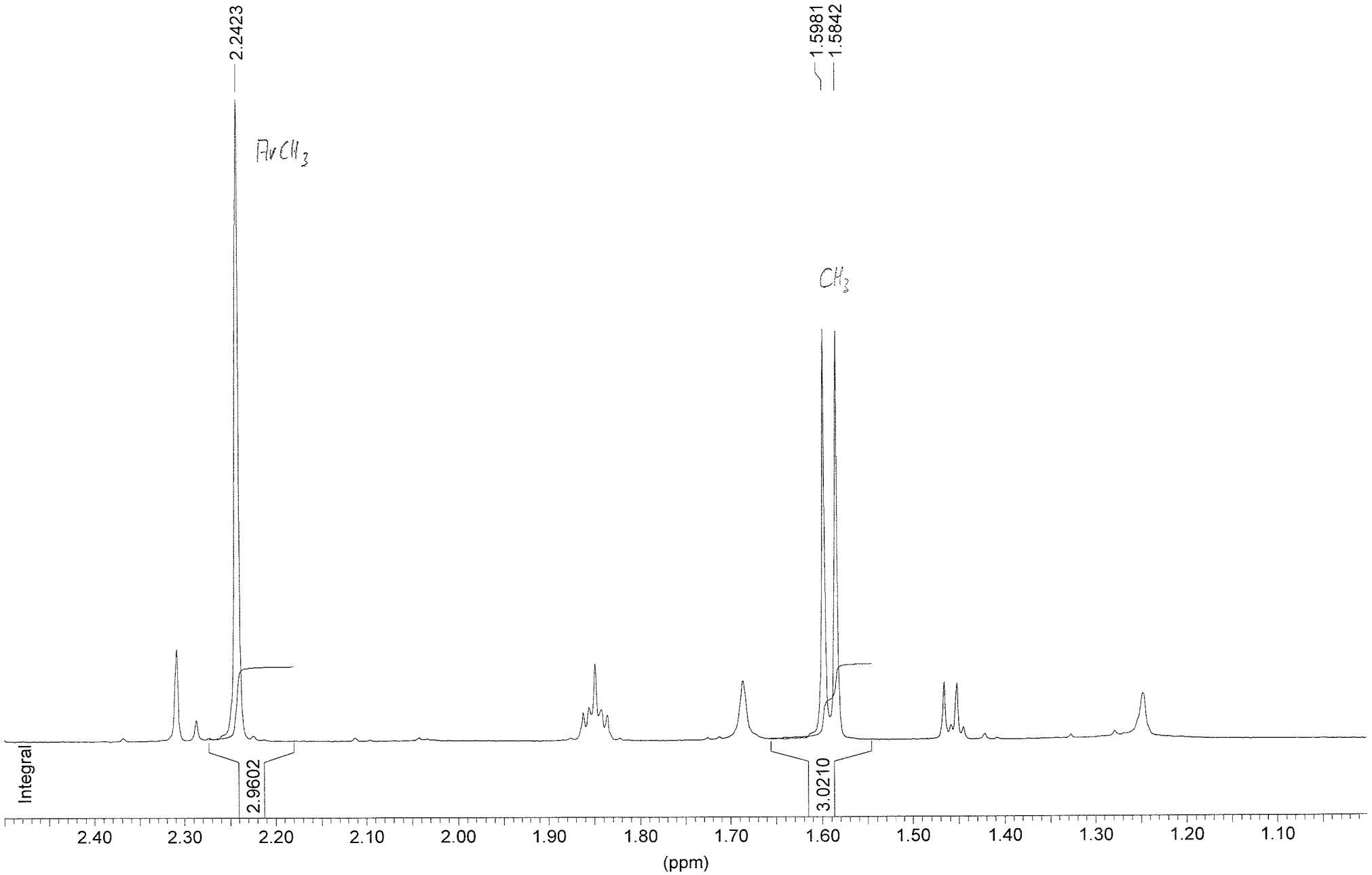
VL057_1 in cdcl3 (Proton), 2.7.2015



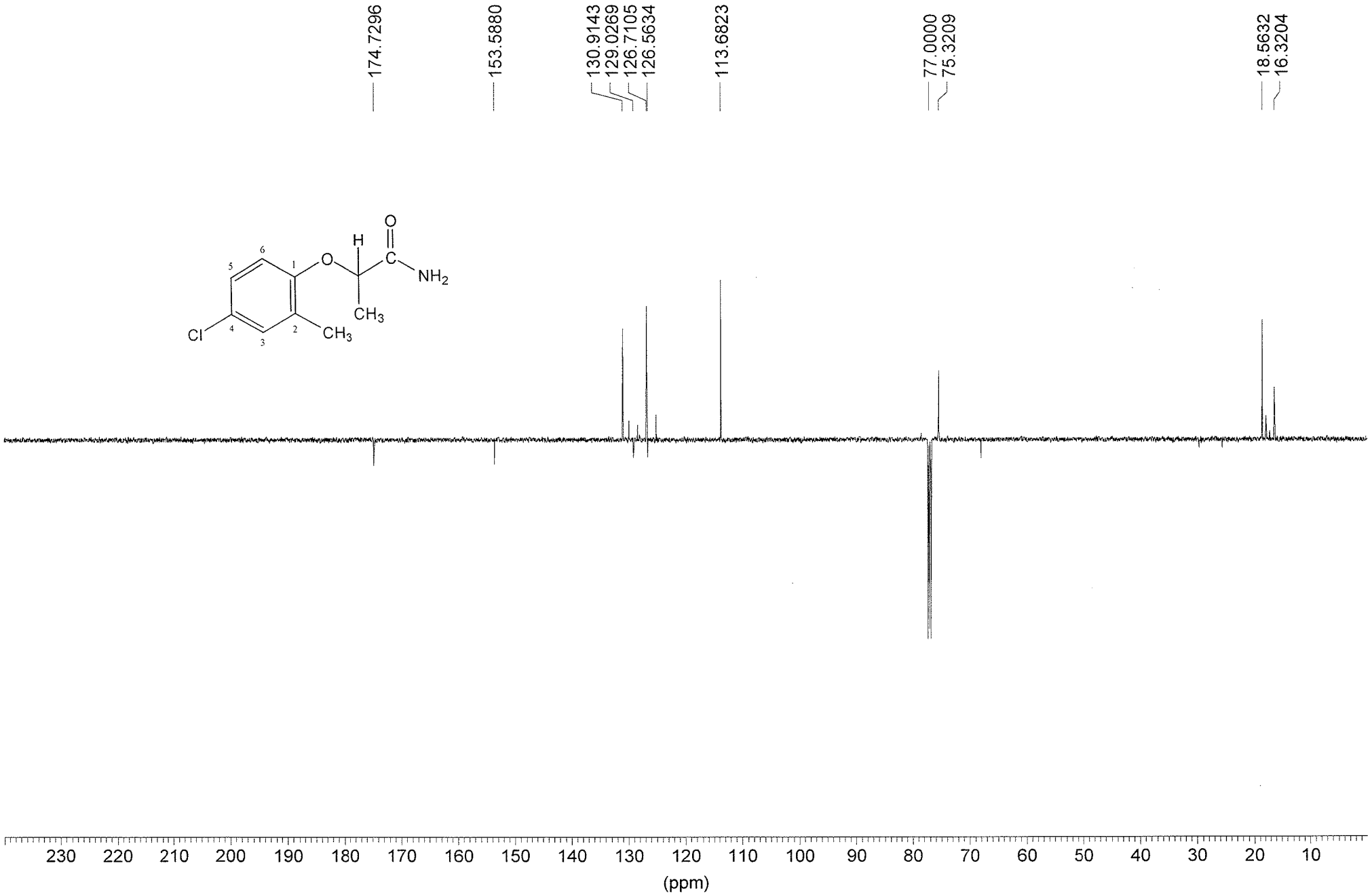
VL057_1 in cdcl3 (Proton), 2.7.2015



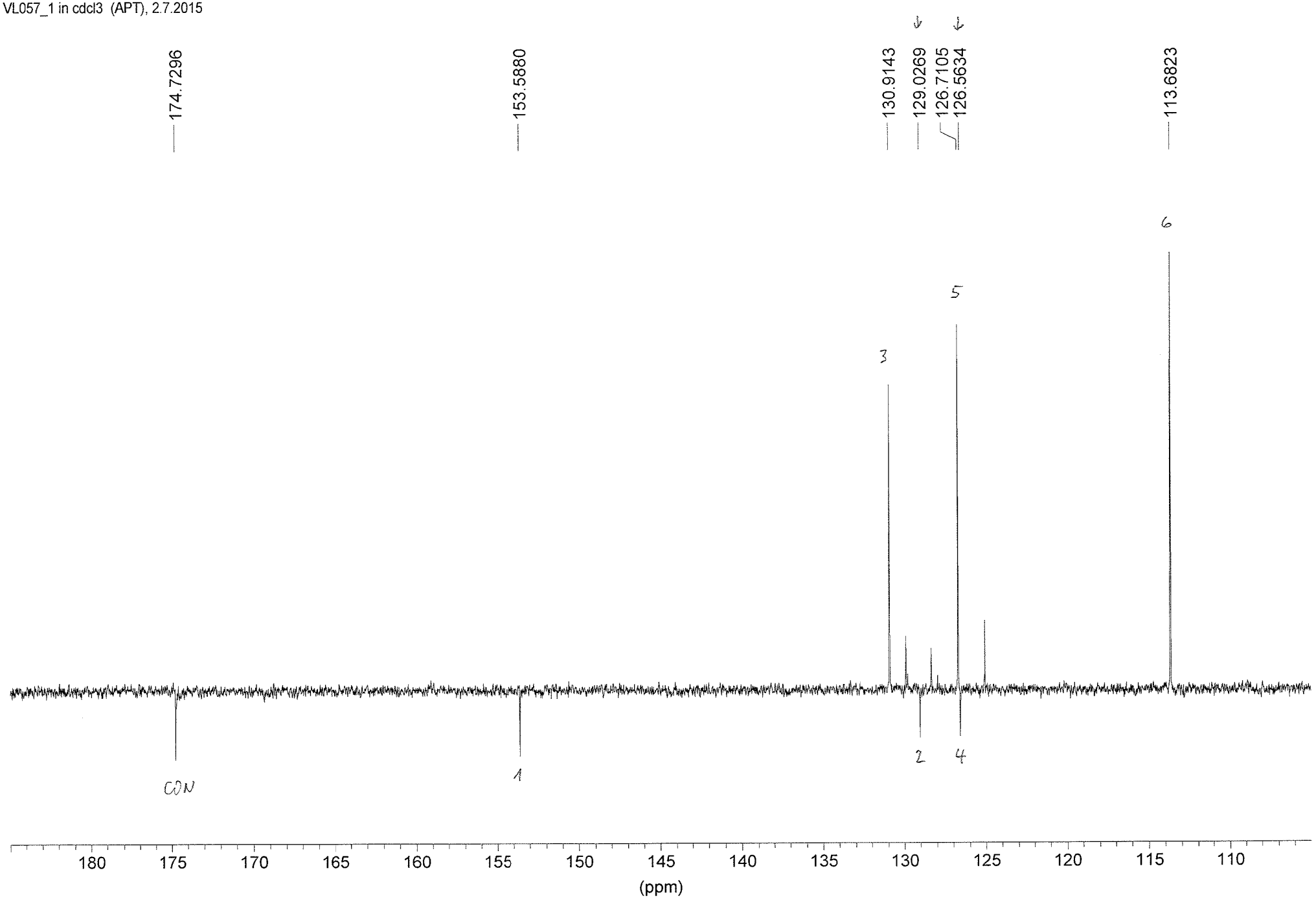
VL057_1 in cdcl3 (Proton), 2.7.2015



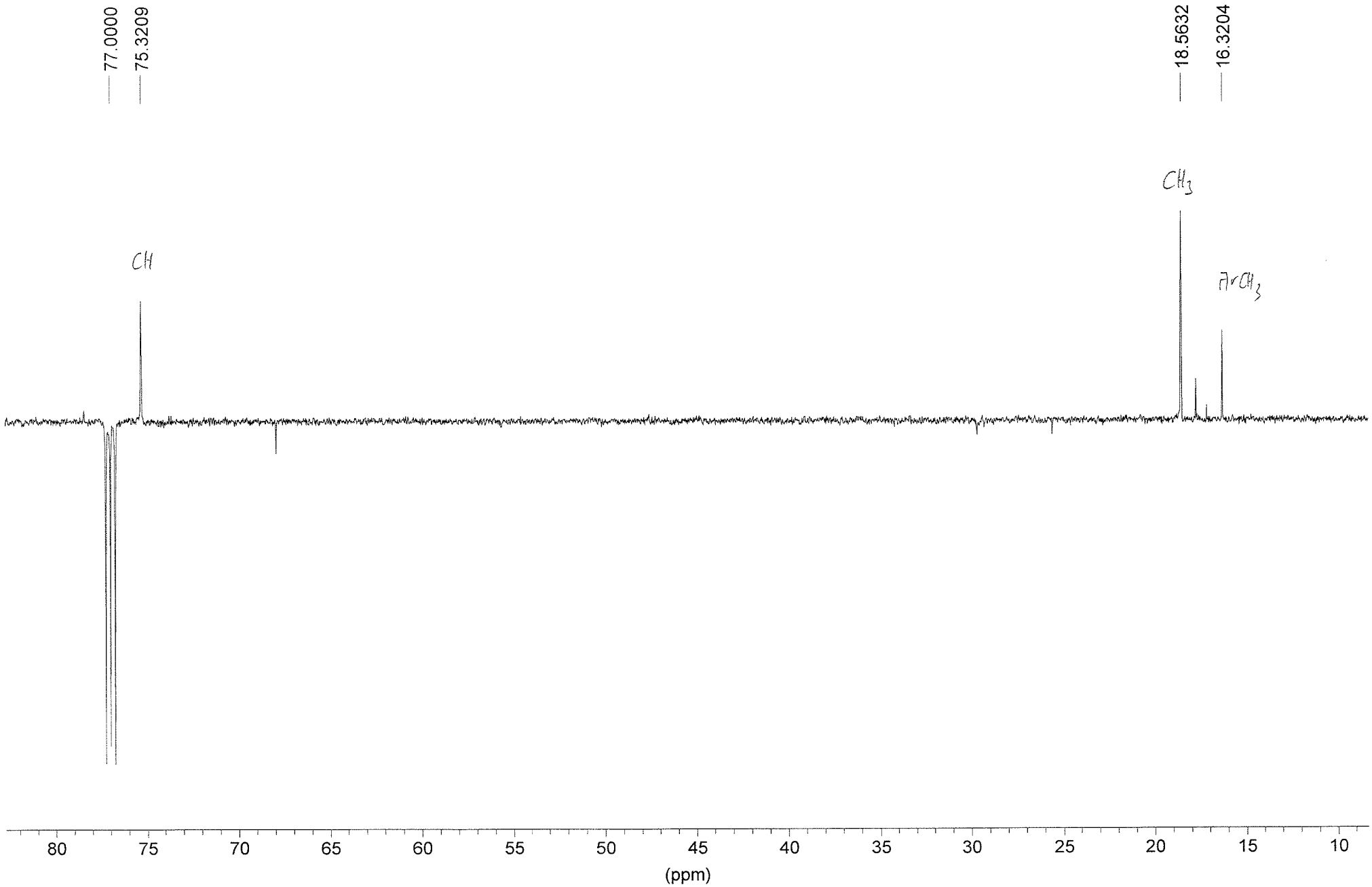
VL057_1 in cdcl3 (APT), 2.7.2015



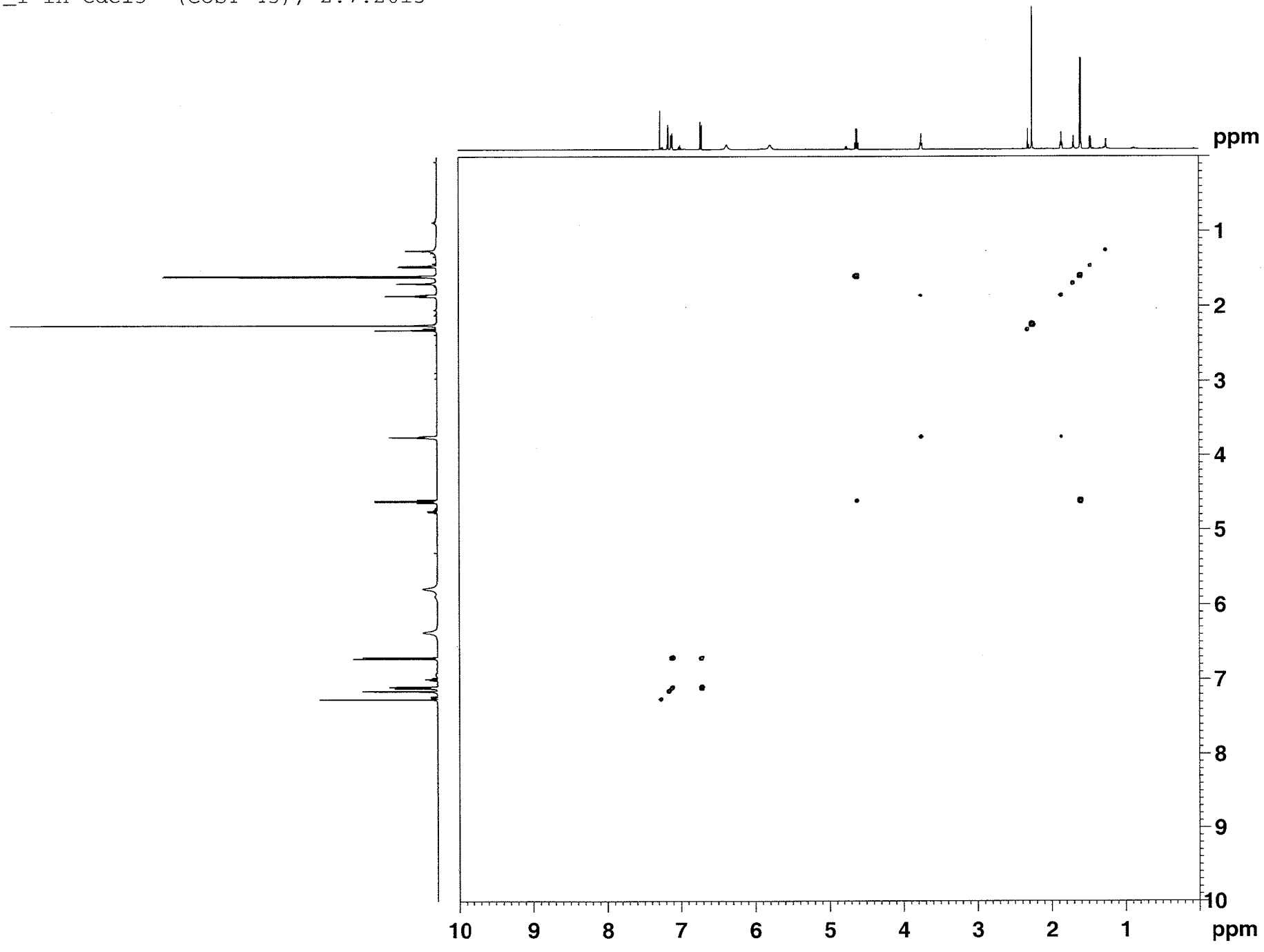
VL057_1 in cdcl3 (APT), 2.7.2015



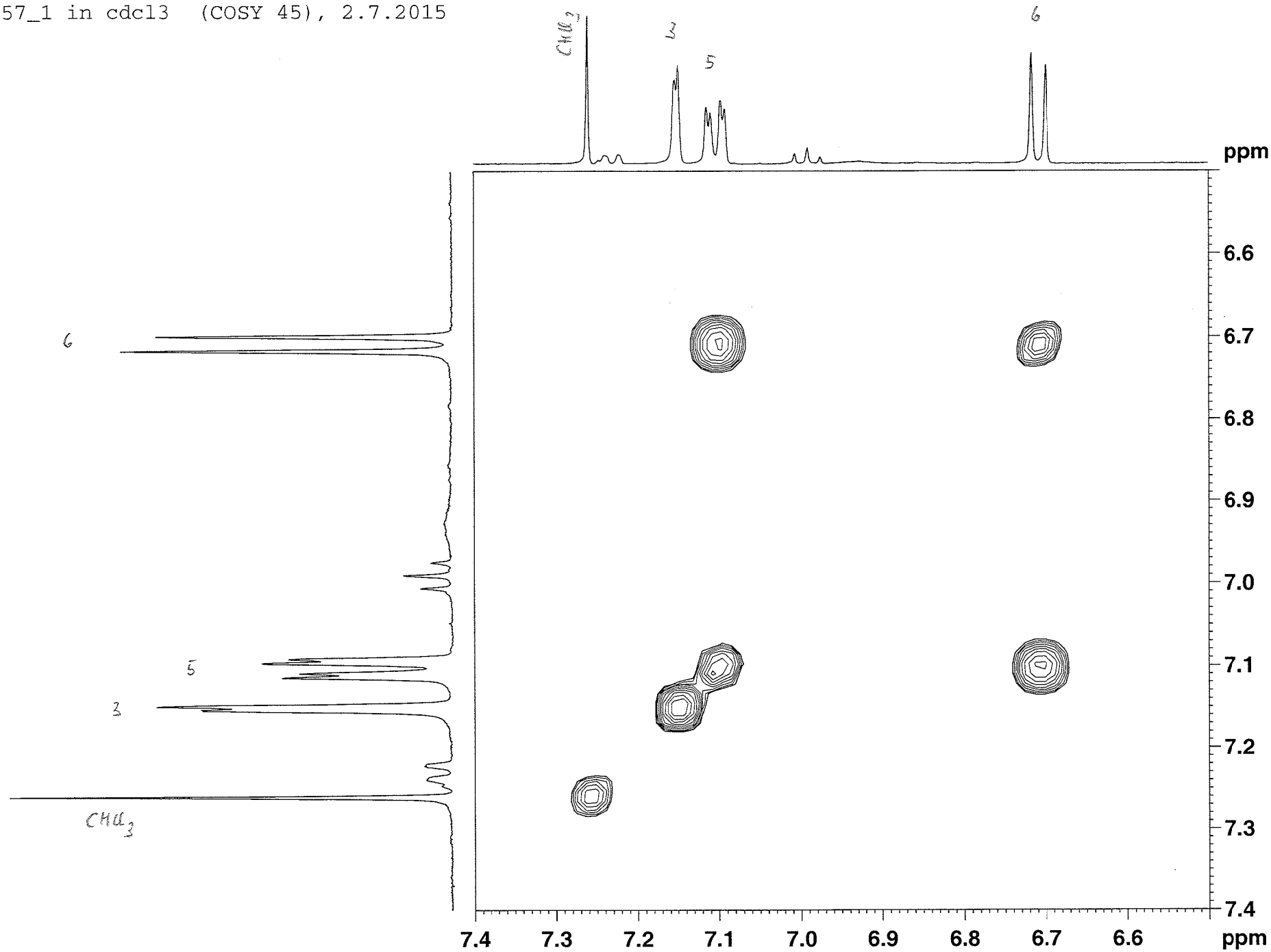
VL057_1 in cdcl3 (APT), 2.7.2015



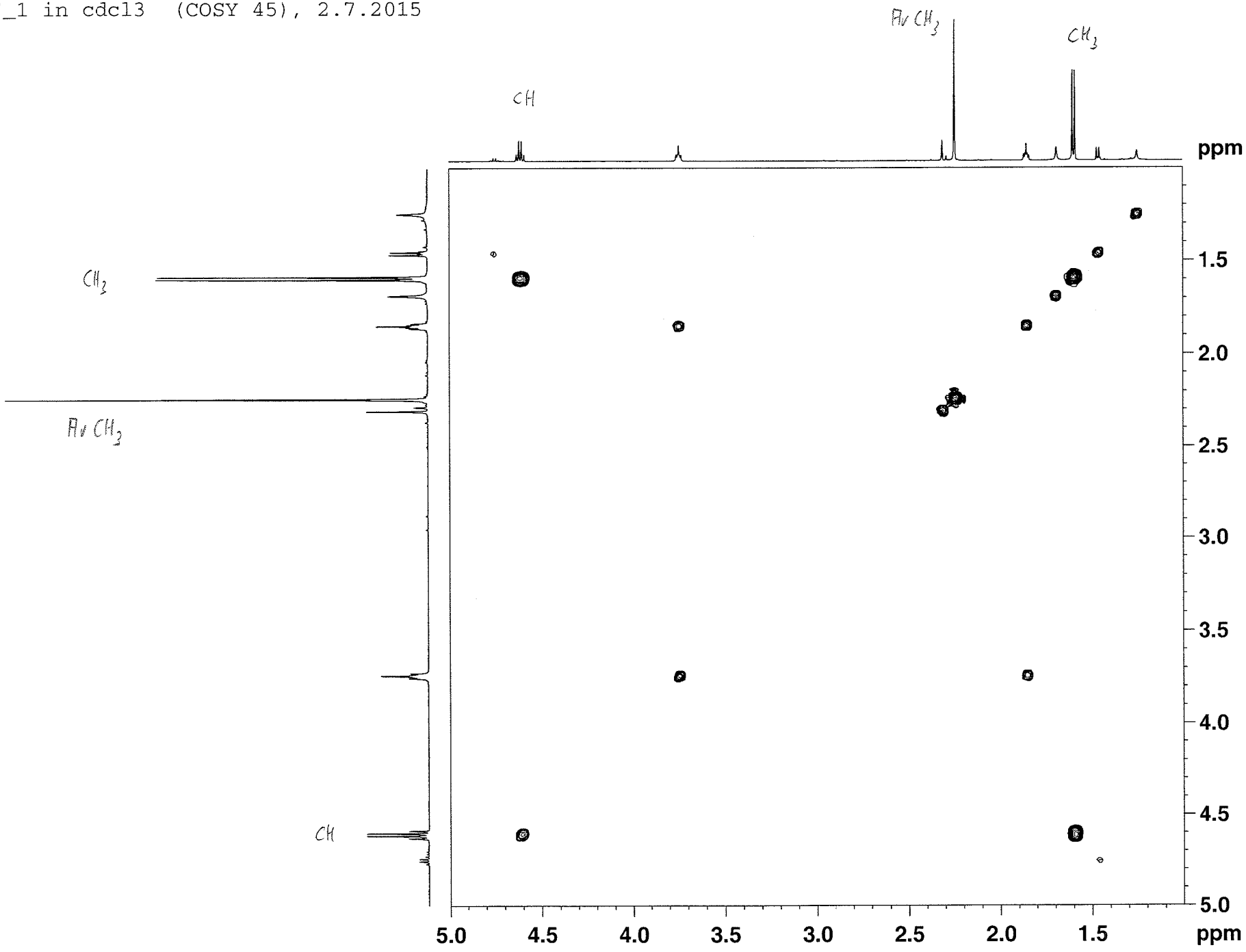
VL057_1 in cdcl3 (COSY 45), 2.7.2015



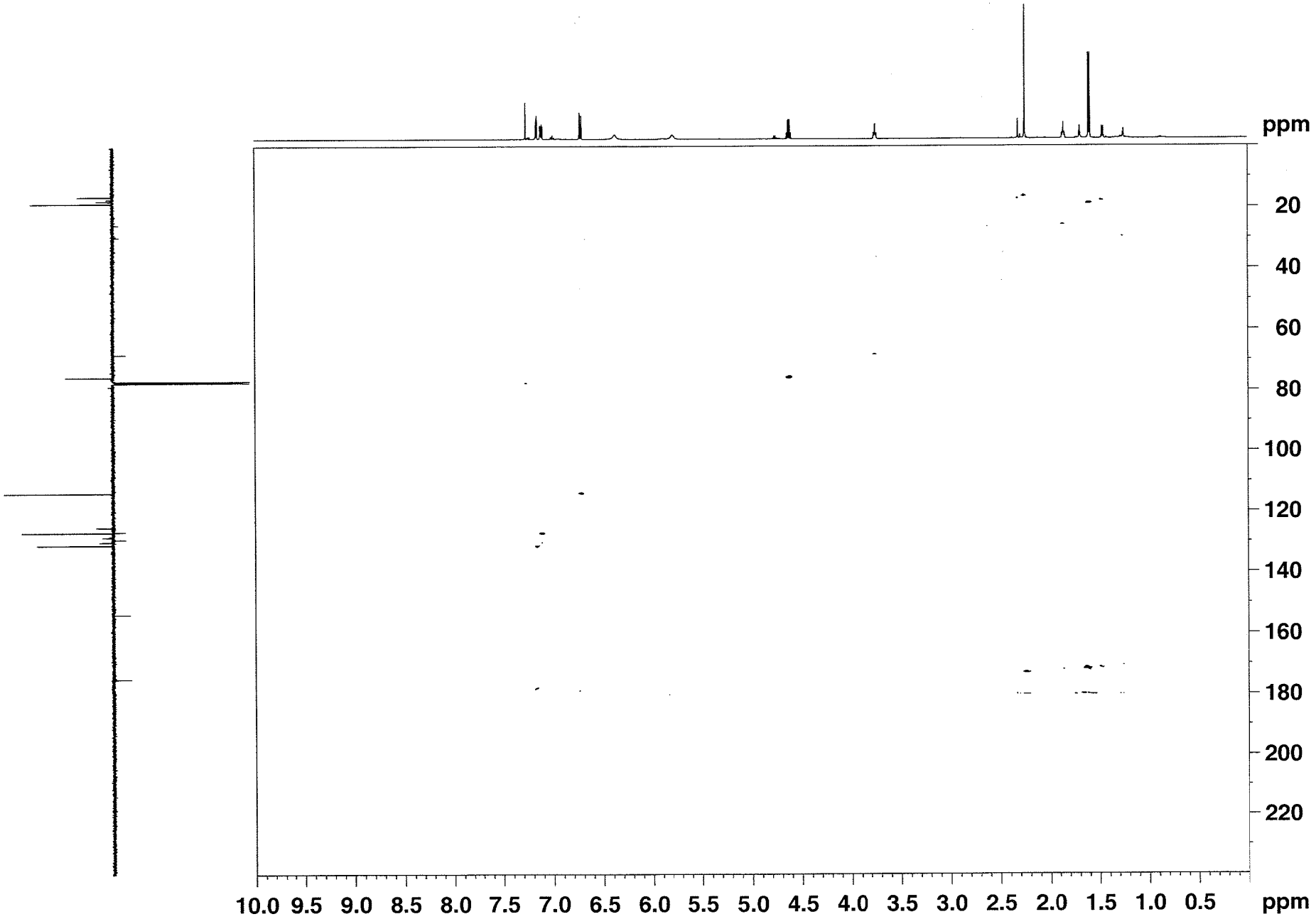
VL057_1 in cdcl3 (COSY 45), 2.7.2015



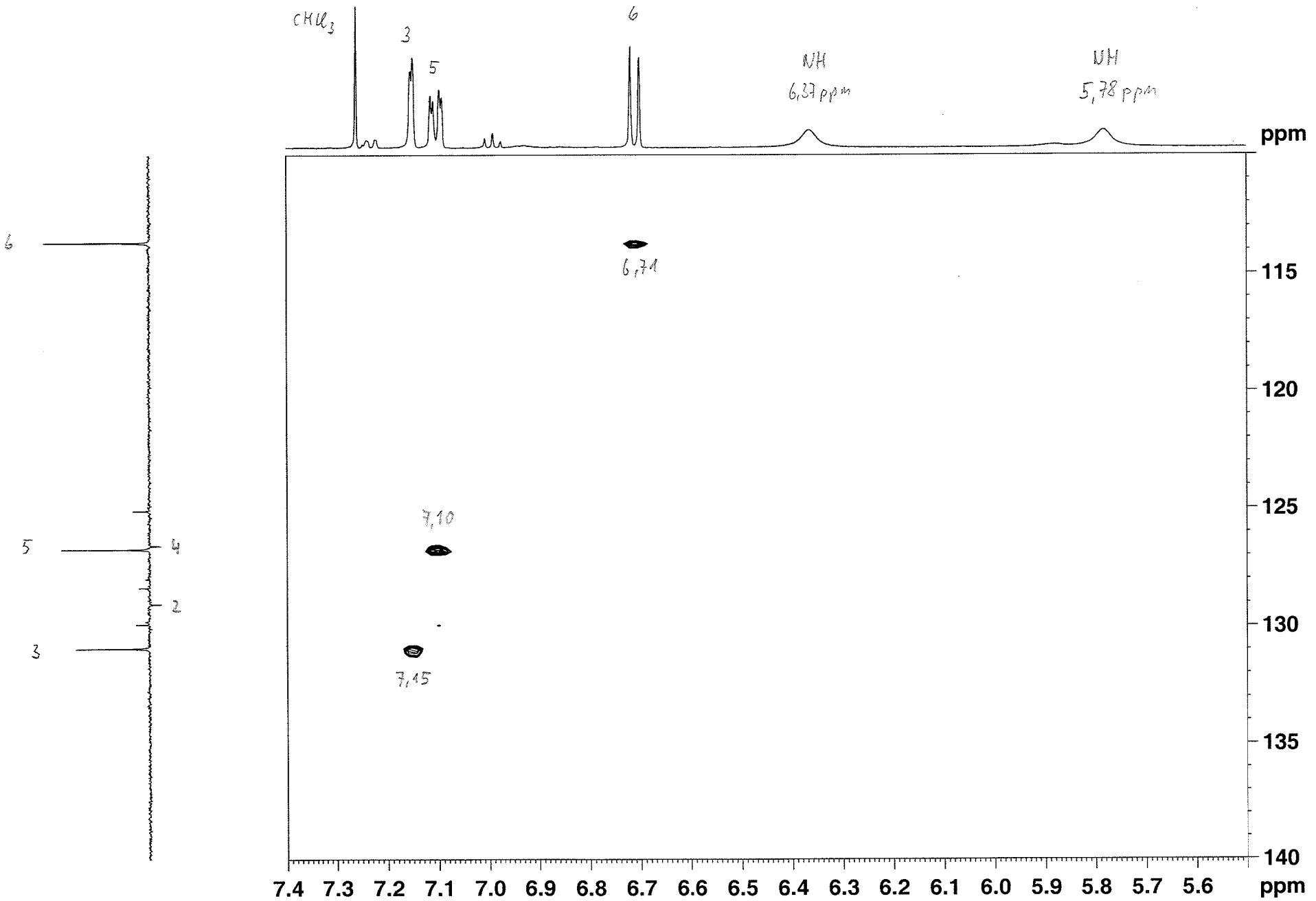
VL057_1 in cdcl3 (COSY 45), 2.7.2015



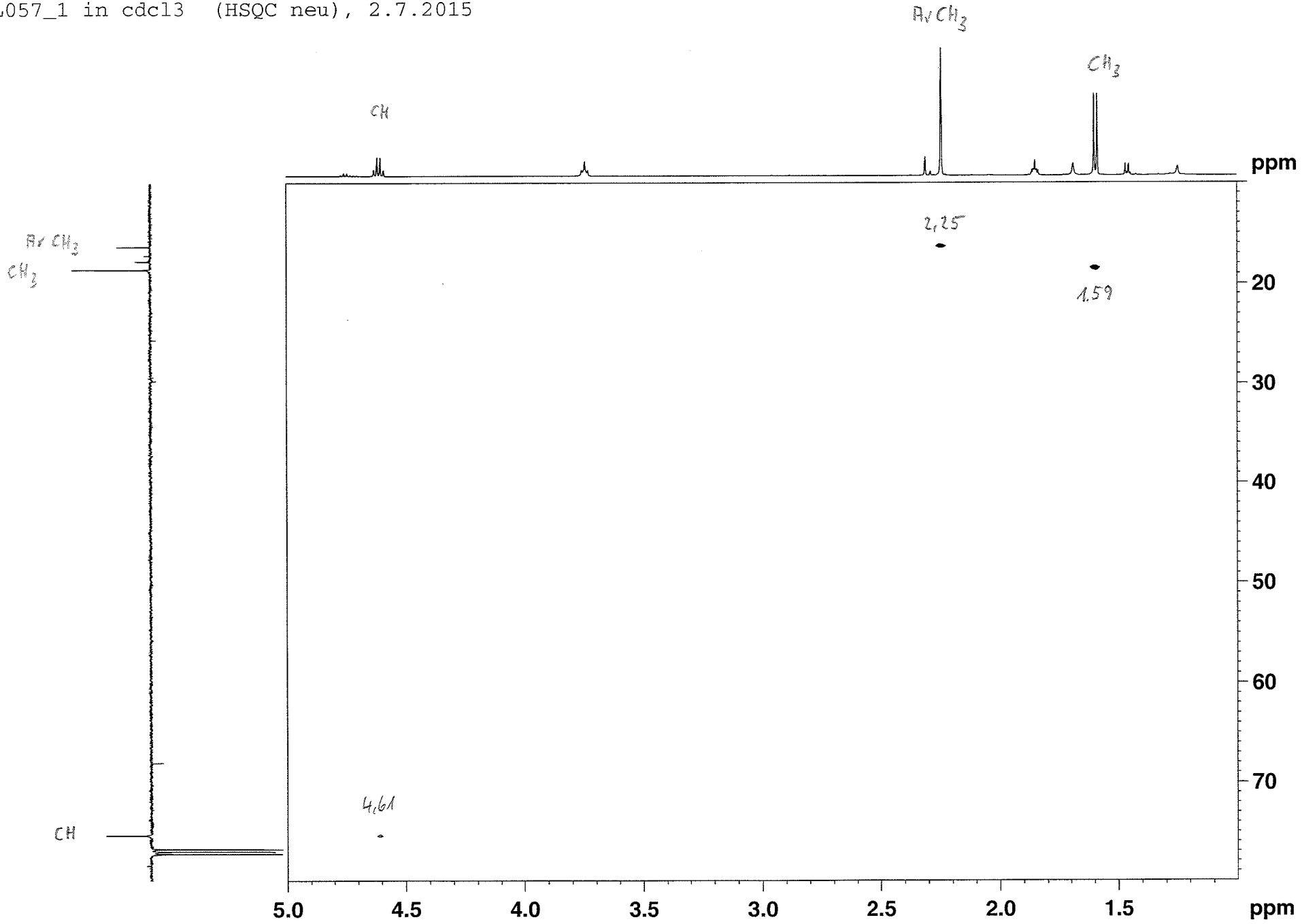
VL057_1 in cdcl3 (HSQC neu), 2.7.2015



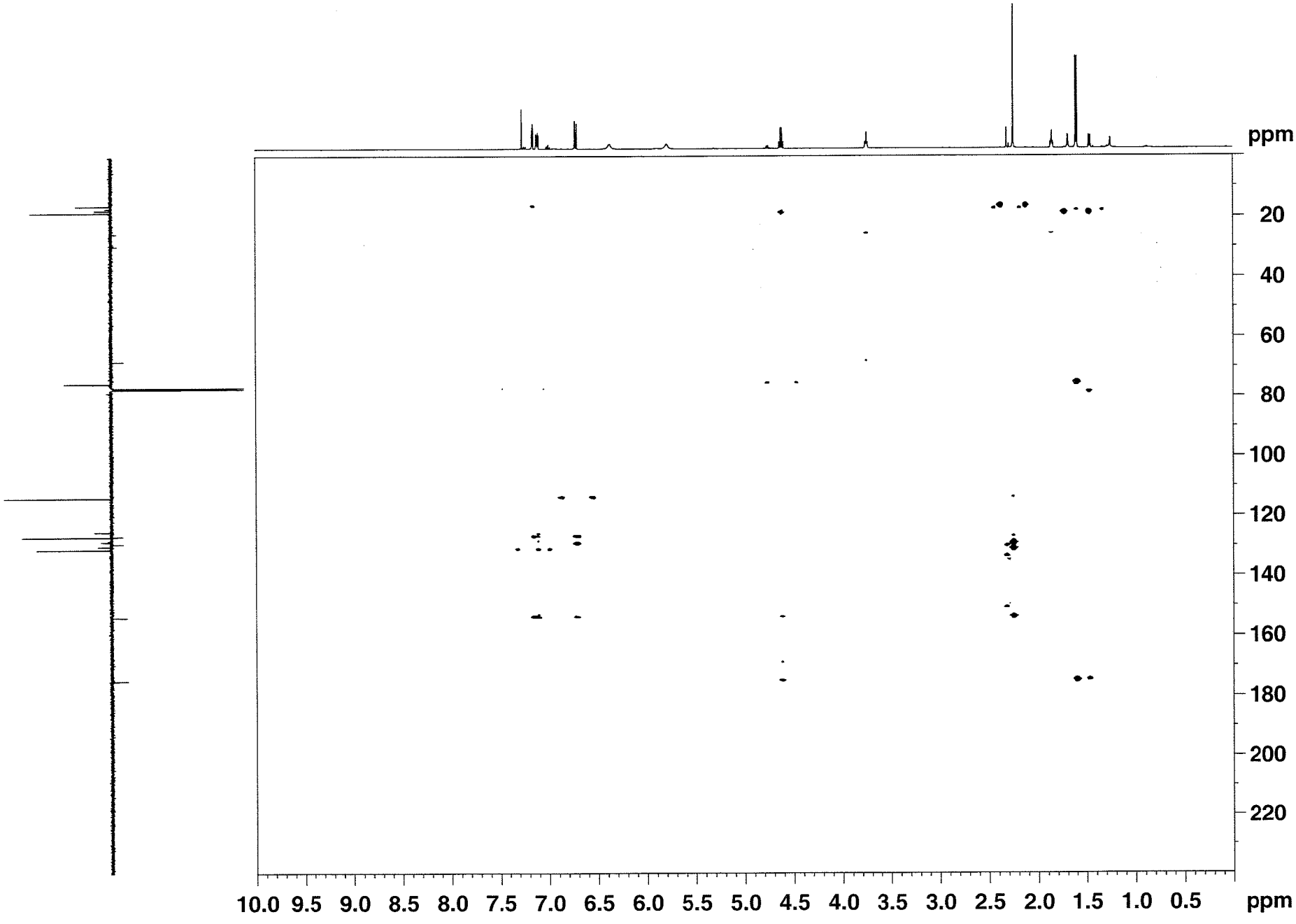
VL057_1 in cdcl3 (HSQC neu), 2.7.2015



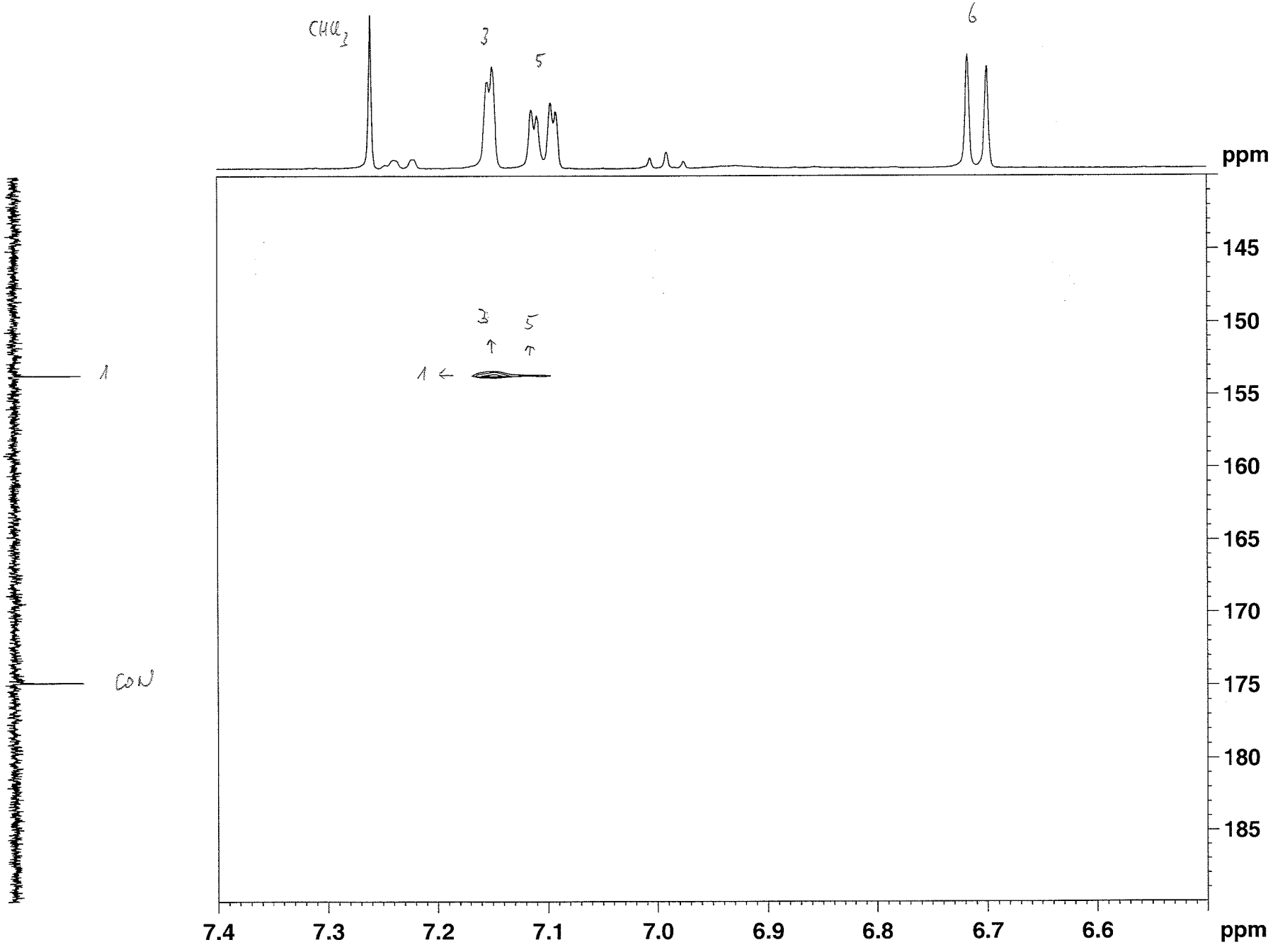
VL057_1 in cdcl3 (HSQC neu), 2.7.2015



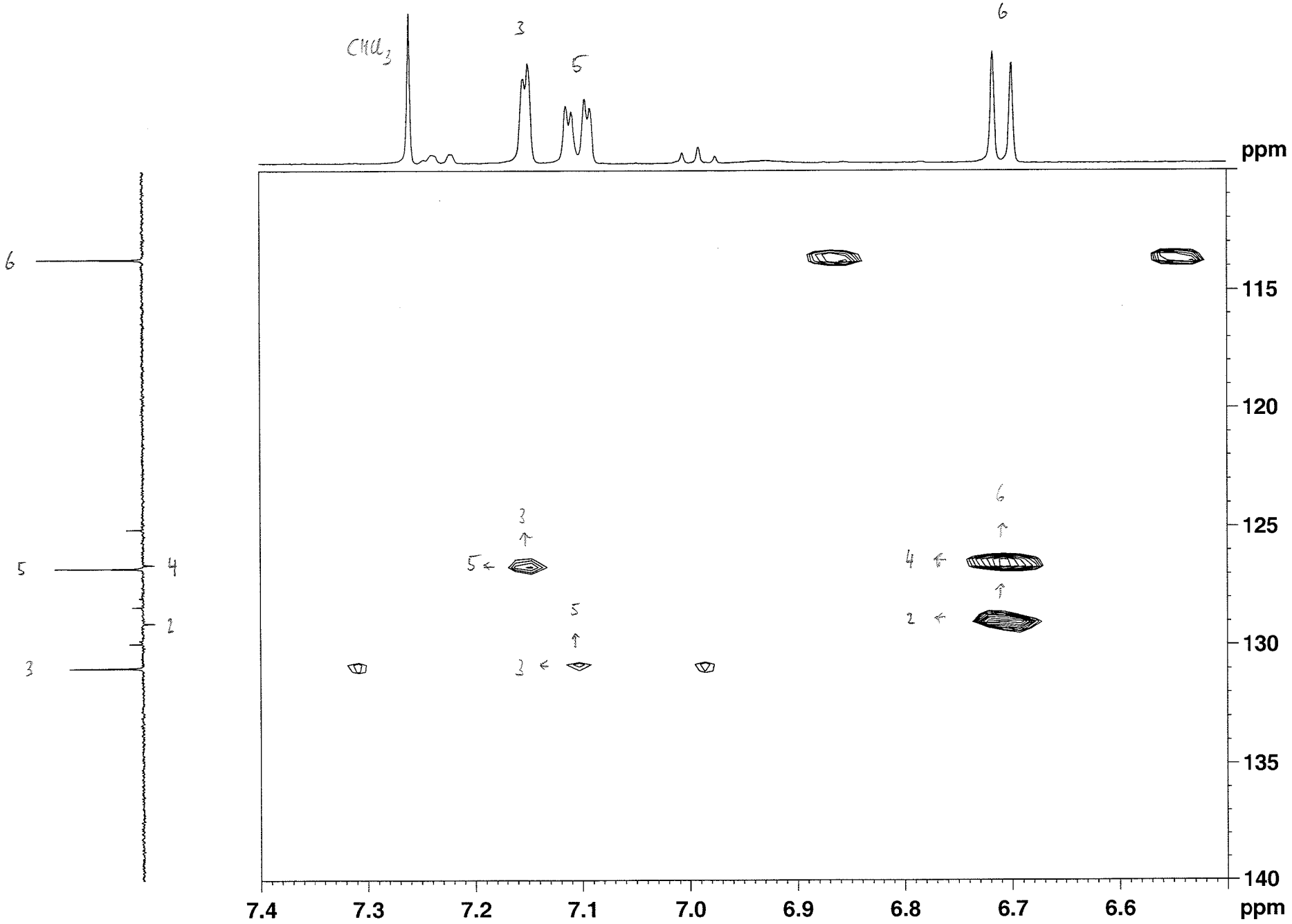
VL057_1 in cdcl3 (HMBC), 2.7.2015



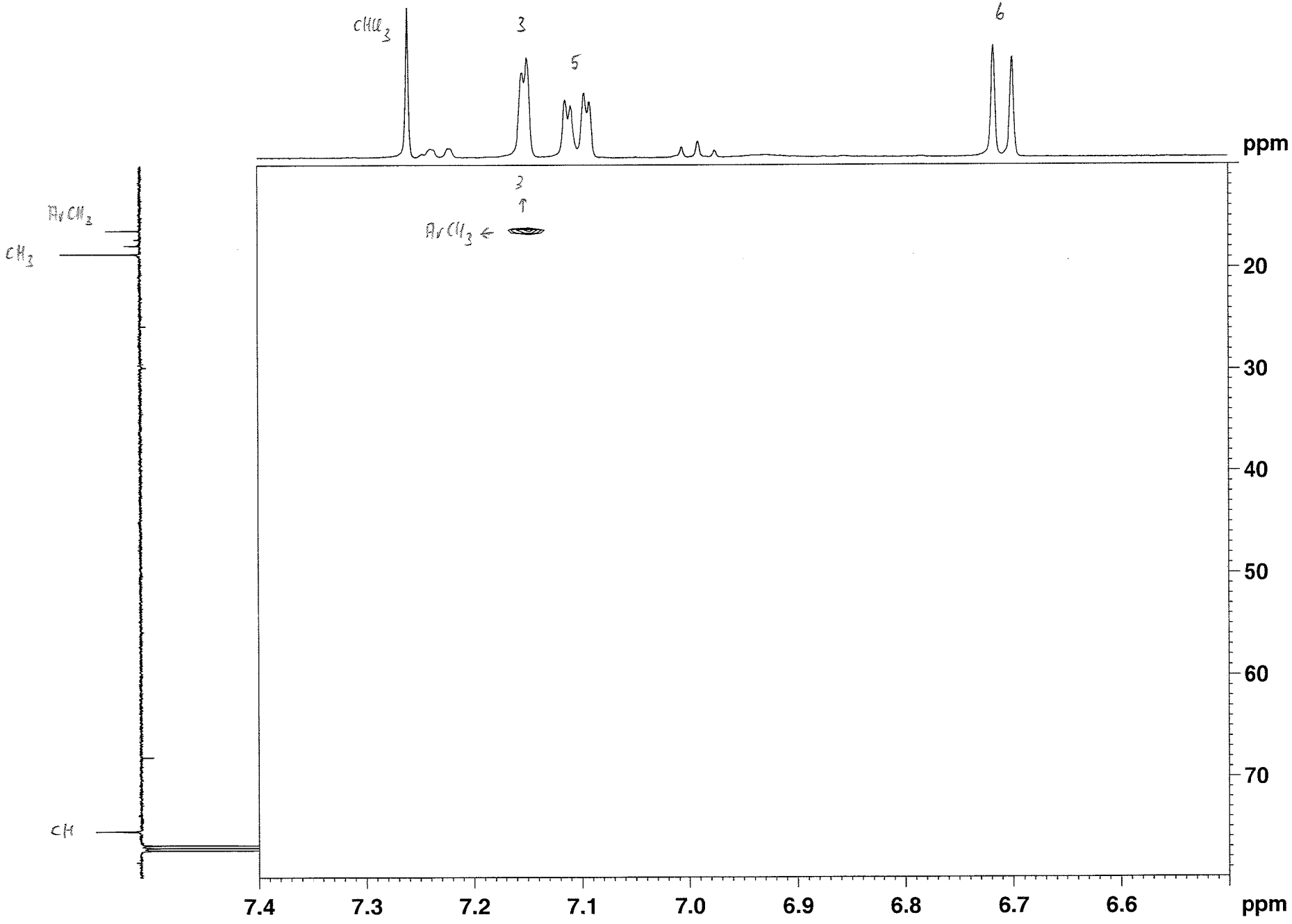
VL057_1 in cdcl3 (HMBC), 2.7.2015



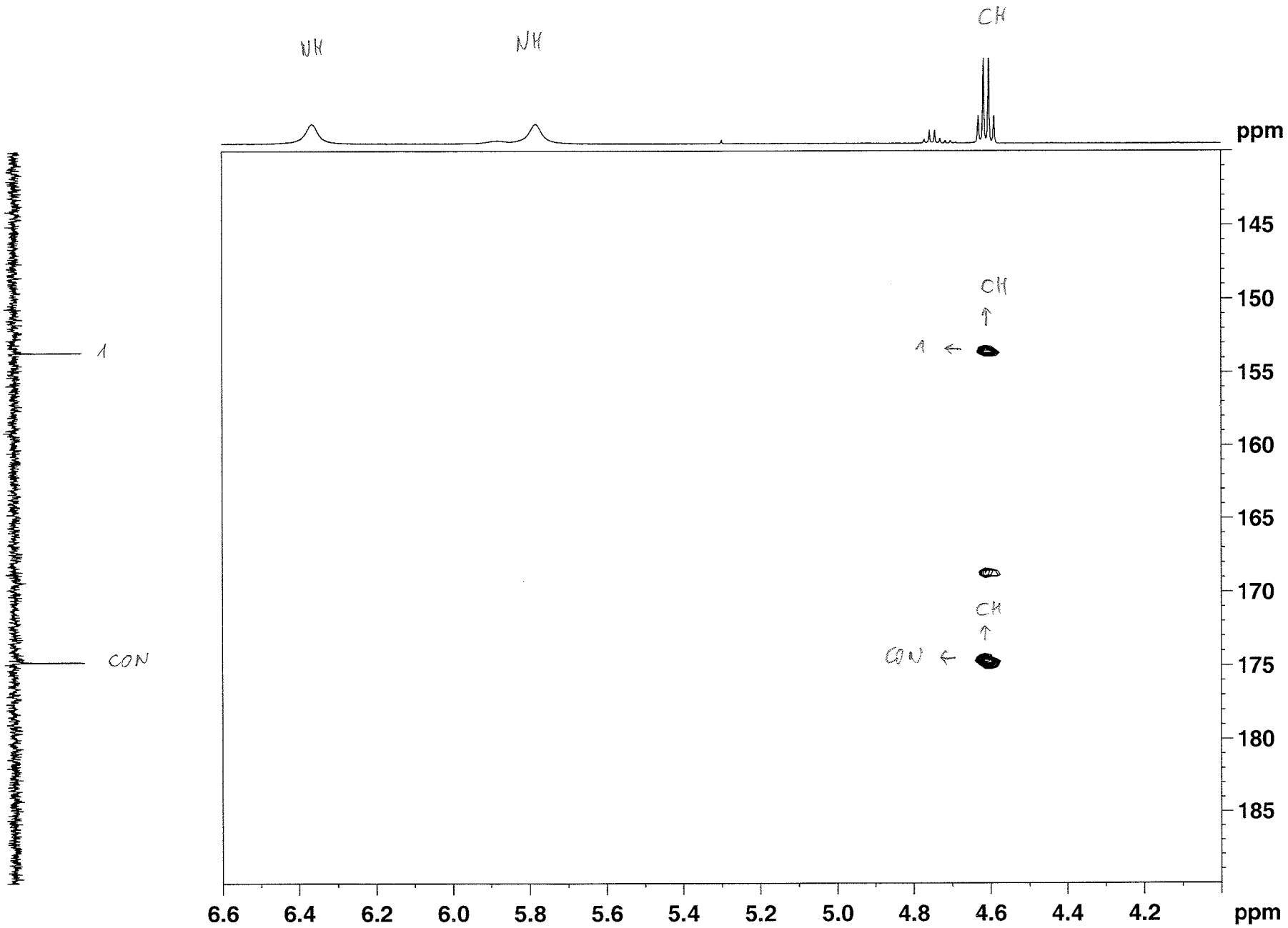
VL057_1 in cdcl3 (HMBC), 2.7.2015



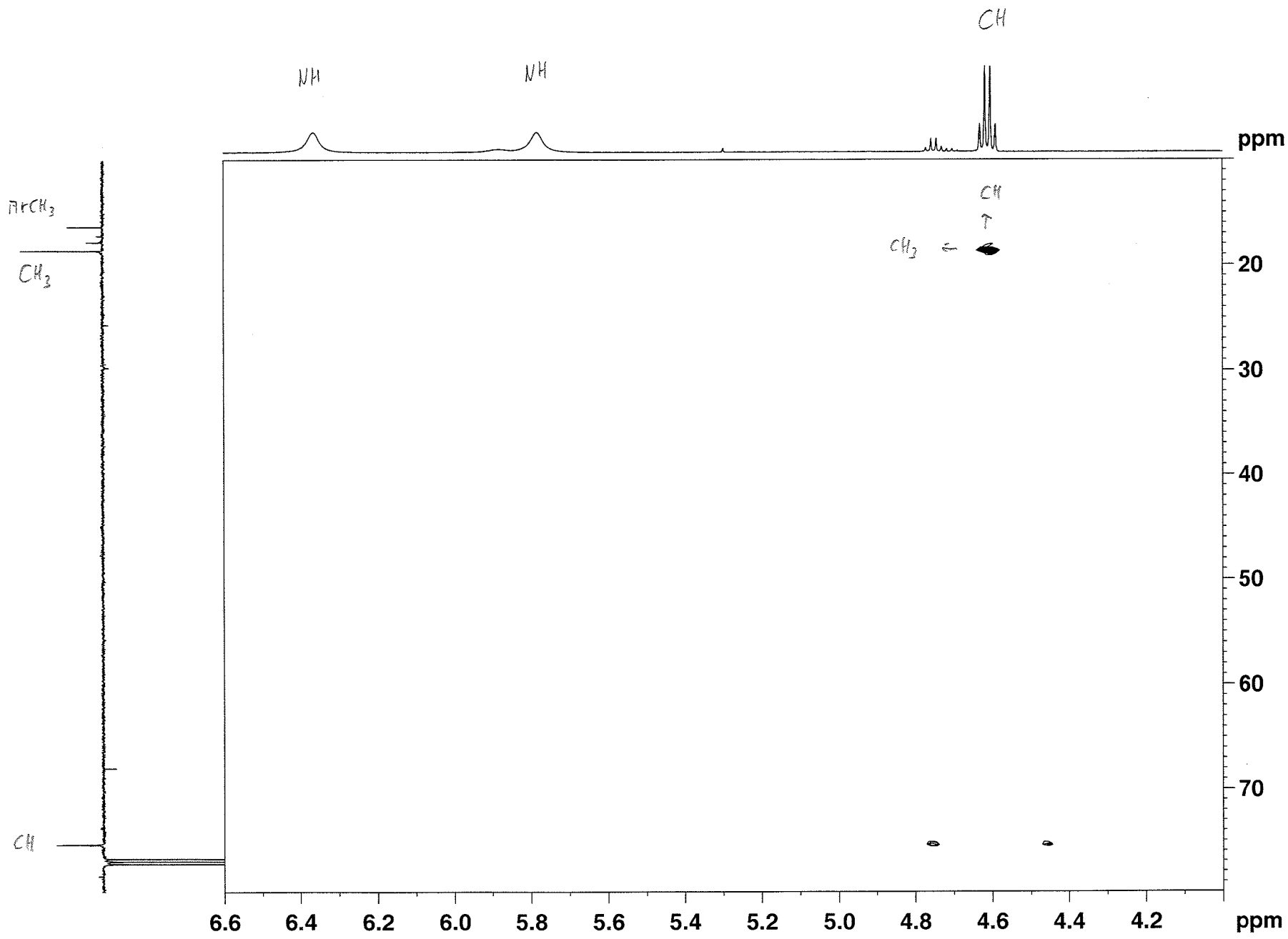
VL057_1 in cdcl3 (HMBC), 2.7.2015



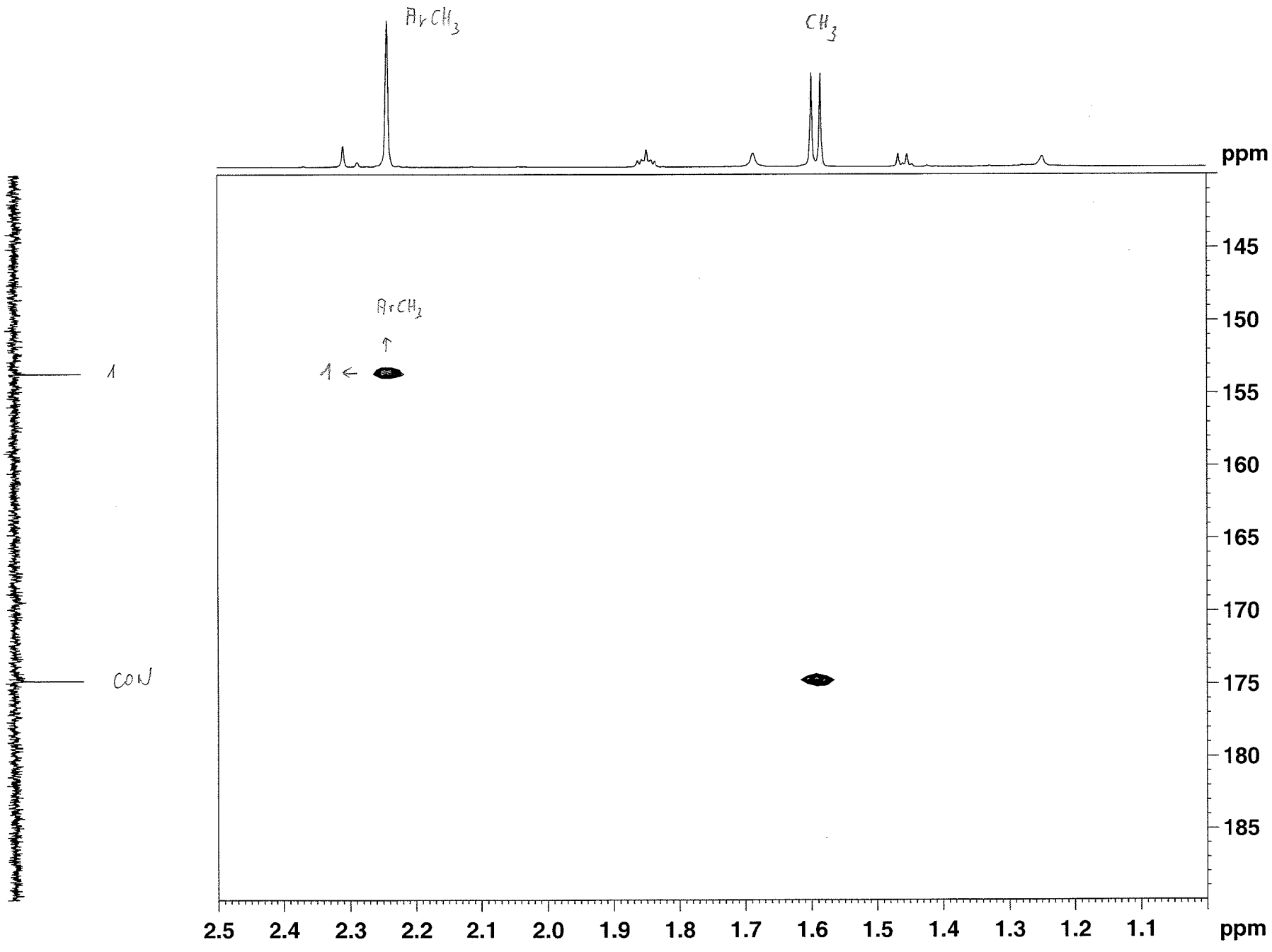
VL057_1 in cdcl3 (HMBC), 2.7.2015



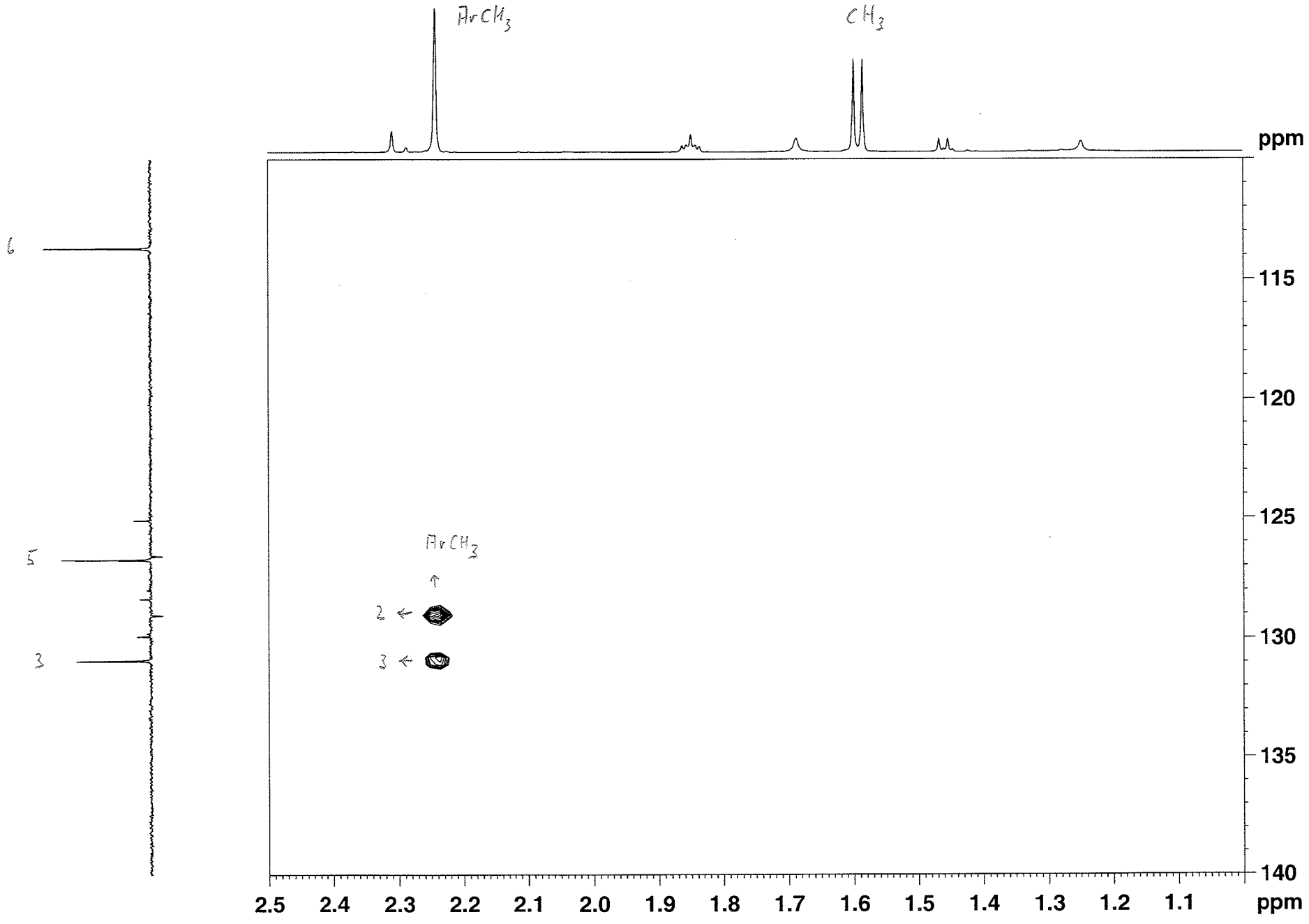
VL057_1 in cdcl3 (HMBC), 2.7.2015



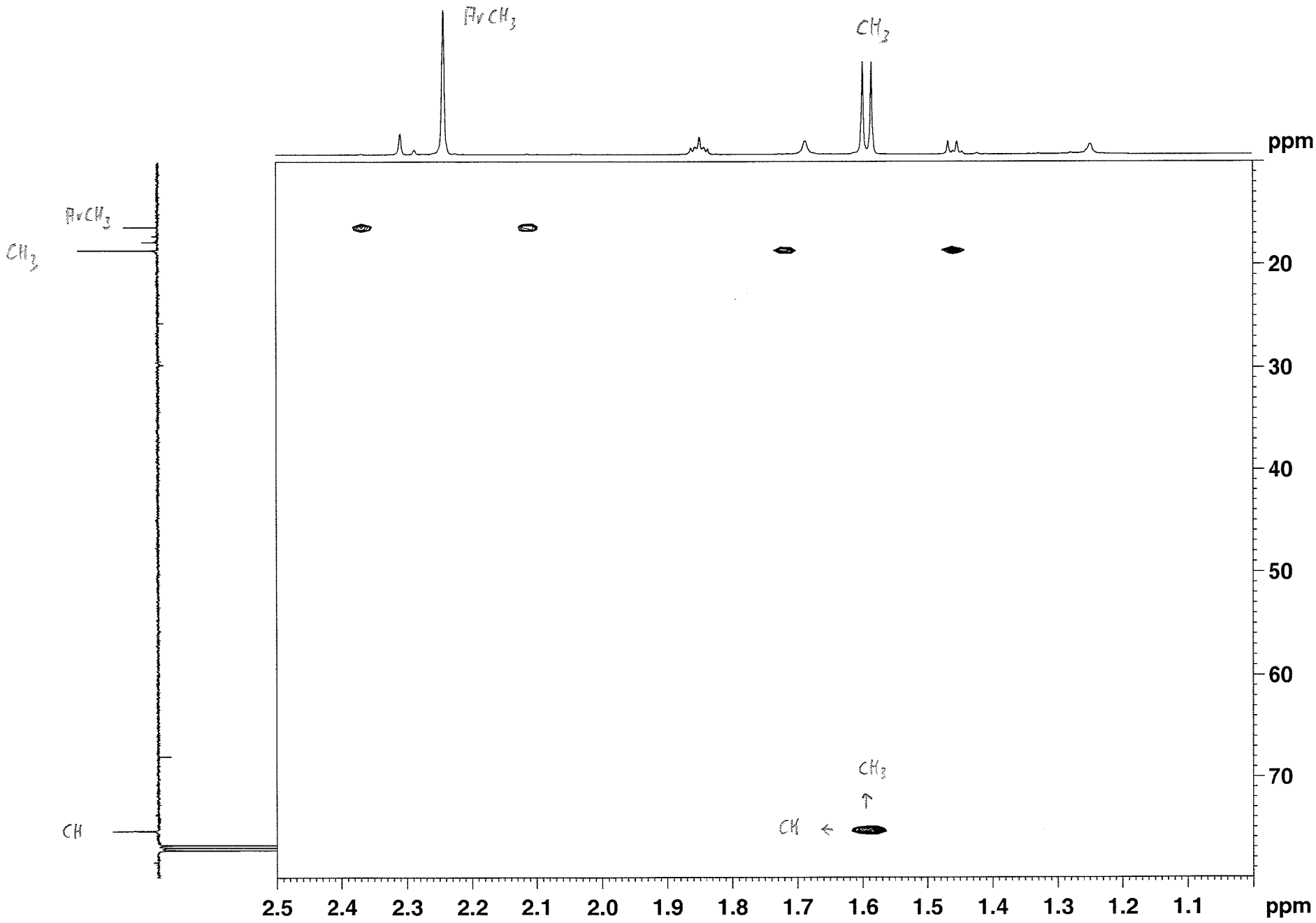
VL057_1 in cdcl3 (HMBC), 2.7.2015



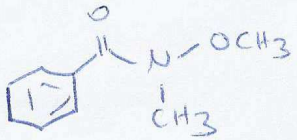
VL057_1 in cdcl3 (HMBC), 2.7.2015



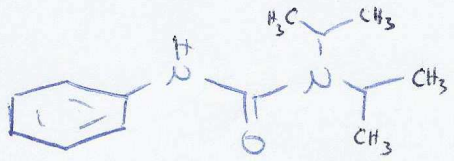
VL057_1 in cdcl3 (HMBC), 2.7.2015



LV-006.1.fid
PROTON CDCl3 opt/xwinnmr parisi 59



VL-026-0.1.fid
PROTON CDCl3 opt/xwinnmr monticelli 60



Ar
5H

NH

2x
CH

4x
Et-
CH_3

f1 (ppm)

VL-027-0.1.fid
PROTON CDCl3 opt/xwinnmr monticelli 38