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Synthetic Studies toward Gold(I)-catalyzed preparation of Trifluoromethyl Compounds

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Abstract

In this project gold(I)-catalyzed reactions on triple bonds has been investigated, with the trifluoromethyl group incorporated. Initially the goal was to develop a new gold(I)-catalyzed trifluoromethylation reaction, as shown below. This goal has not been reached. Several attempts in order to prepare a trifluoromethylated di-hydropyran derivate, both by direct trifluoromethylation and via trifluoromethylated precursors.

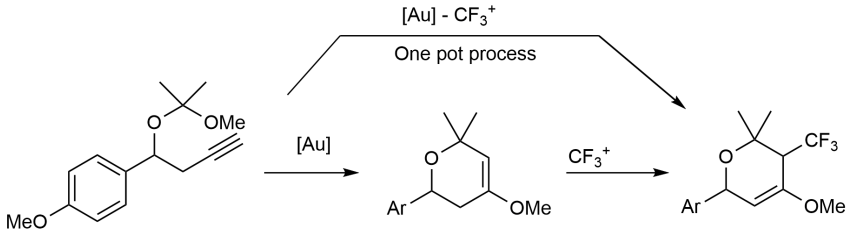
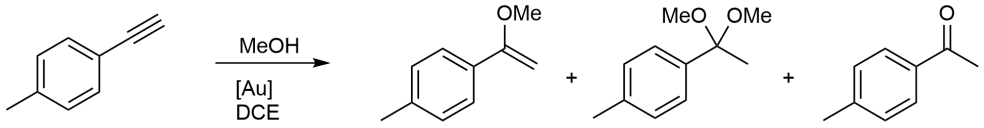
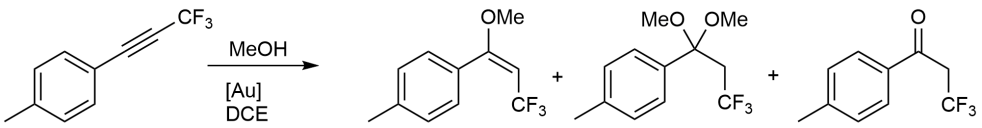


Figure 0.1: The synthesis of the trifluoromethylated product was the first objective of this project.

A study of the reactivity of a trifluoromethylated alkyne in regard to gold(I)-catalysis has been performed in order to obtain a better understanding of reactions on similar substrates. The study has been performed by GLC analysis of a range of small scale reactions, as shown below, performed under different conditions. The study showed that the nucleophilic attack on the gold activated CF_3-alkyne triple bond is highly favored towards generating a vinyl compound. While terminal alkynes react further to form unsaturated products, the trifluoromethyl substrate is fairly stable at the alkene stage, although it will react further given tougher conditions. NMR has been essential for the structure elucidation and monitoring of reactions throughout the project.



(a) Terminal alkyne and reaction products



(b) Trifluoromethylalkyne and reaction products

Figure 0.2: The reactions performed for reactivity comparison.

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Sammendrag

I dette prosjektet har gull(I)-katalyserte reaksjoner på trippelbindinger, med CF_3, blitt studert. Opprinnelig var målet med prosjektet å utvikle en gull(I)-katalysert prosedyre for trifluormetylering, som vist under. Dette målet har ikke blitt nådd. Flere forsøk på fremstilling av et trifluormetylert di-hydropyran derivat er utført, både ved direkte trifluormetylering, og via trifluormetylering av forløpere til di-hydropyran derivatet.

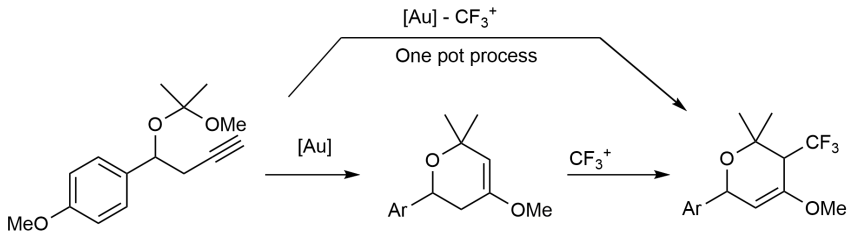
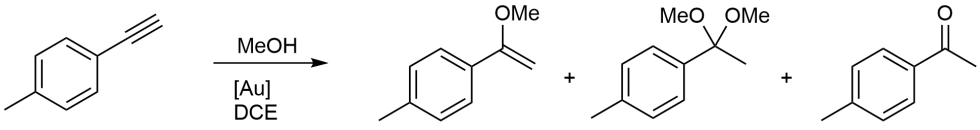
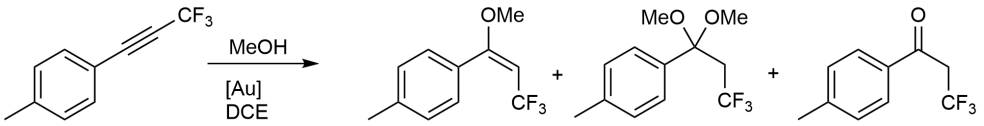


Figure 0.3: The synthesis of the trifluoromethylated product was the first objective of this project.

En studie av reaktiviteten til en trifluormetylalkynforbindelse med hensyn på gull(I)-katalyse har blitt utført for å bedre forstå reaksjoner på lignende substrat, som illustrert under.Studiet har blitt utført ved GLC analyser av en rekke småskala reaksjoner, utført med forskjellige betingelser. Studiet viste at nukleofile angrep på den gull(I)-aktiverte CF_3-trippelbindingen er høyst favorisert mot generering av vinyl forbindelser. Mens terminale alkyner reagerer videre til dannelse av umettede produkter, er trifluormetyl produktet ganske stabilt ved alken stadiet, selv om det reagere videre ved tøffere betingelser. NMR har vært essensielt for strukturoppklaring og overvåking av reaksjoner gjennom hele prosjektet.



(a) Terminalt alkyn og reaksjonsprodukter.



(b) Trifluormetylalkyn og reaksjonsprodukter.

Figure 0.4: Reaksjoner utført for reaktivitets sammenligning.

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Contents

1 Introduction

1.1 Project description

This report describes the project performed as the master thesis, at the end of the 5 year program in chemical engineering at the Norwegian university of science and technology (NTNU). The project deals with organic synthesis, specifically homogenous gold(I)-catalysis and trifluoromethyl groups.

The project was performed for the Fiksdahl group, at the Department of Chemistry, and builds on the previous work performed by Anne Fiksdahl *et. al.* The Fiksdahl group has for a number of years conducted research in the field of gold(I)-catalysed organic reactions, and developed a number of synthetic pathways utilizing gold(I).

For this project we were interested in examining the possibilities for either performing gold-catalysed trifluoromethylation, or gold-catalysed reactions on trifluoromethylated substrates. Ideally this would lead to expansion of already existing pathways to include new trifluoromethylated products.

Initially we wanted to study some of the more recently developed reactions with homopropargyl substrates. The idea was to develop a reaction analog to the fluorination of the dihydropyran[1] substance **(1.4)** with electrophilic trifluoromethylation. The general scope is illustrated in Fig 1.1.

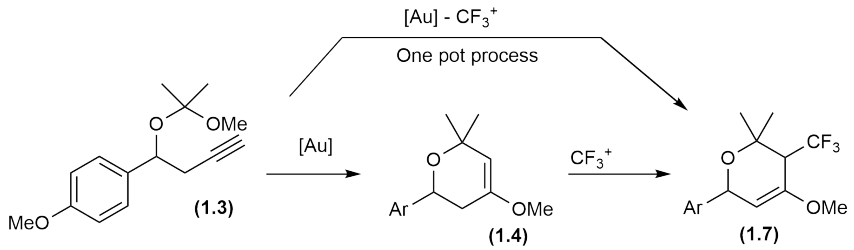
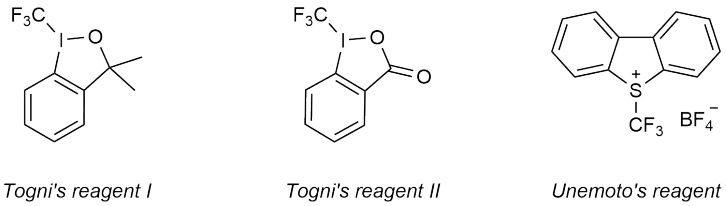


Figure 1.1: The synthesis of compound **(1.7)** was the first objective of this project.

This was to be achieved with recently developed trifluoromethylating agents shown in Fig. 1.2, which have enabled a broad substrate scope.[2–5]



Togni's reagent I *Togni's reagent II* *Unemoto's reagent*

Figure 1.2: The recently developed trifluoromethylating agents we initially wanted to investigate

We wanted to investigate the synthetic application of the trifluoromethylation reagents in Fig. 1.2 compared to Selectfluor, which has been used in previous research.[1]

Also the compatibility of the elecrophilic trifluoromethylation reagents, in Fig. 1.2, with the gold catalyst, in Fig. 1.7, was to be investigated.

This project has changed a lot during it's course. Mainly from beeing rather substrate specific, to a more general study of gold catalysis on trifluoromethylated alkynes.

1.2 Previous work

Previously the preparation of the substrates shown in Fig. 1.3, with the exception of the trifluoromethylated product **(1.7)**. The preparation of Togni's reagent II at a small scale has been studied. And modifications to accommodate this scale has been made. Some preliminary attempts at trifluoromethylation with the use of Togni's reagent II has been made.

1.3 Reactions

The reactions and substances synthesized in this project has been divided into different parts, dependent on the starting substance. In general there are 2 main structures. These are the homopropargyl substances, which are given numbers **(1.X)** and **(2.X)**, and the aromatic alkyne substances numbered: **(3.X)-(6.X)**. A list of all the numbered substances in this text is given in Appendix A, and characterizations of them are given in subsequent appendices. Initially the main interest was the previously developed reactions shown in Fig. 1.3, with the addition of a trifluoromethylated compound **(1.7)**. The starting material for this synthesis is commercially available *p*-methoxy benzaldehyde **(1.1)**.

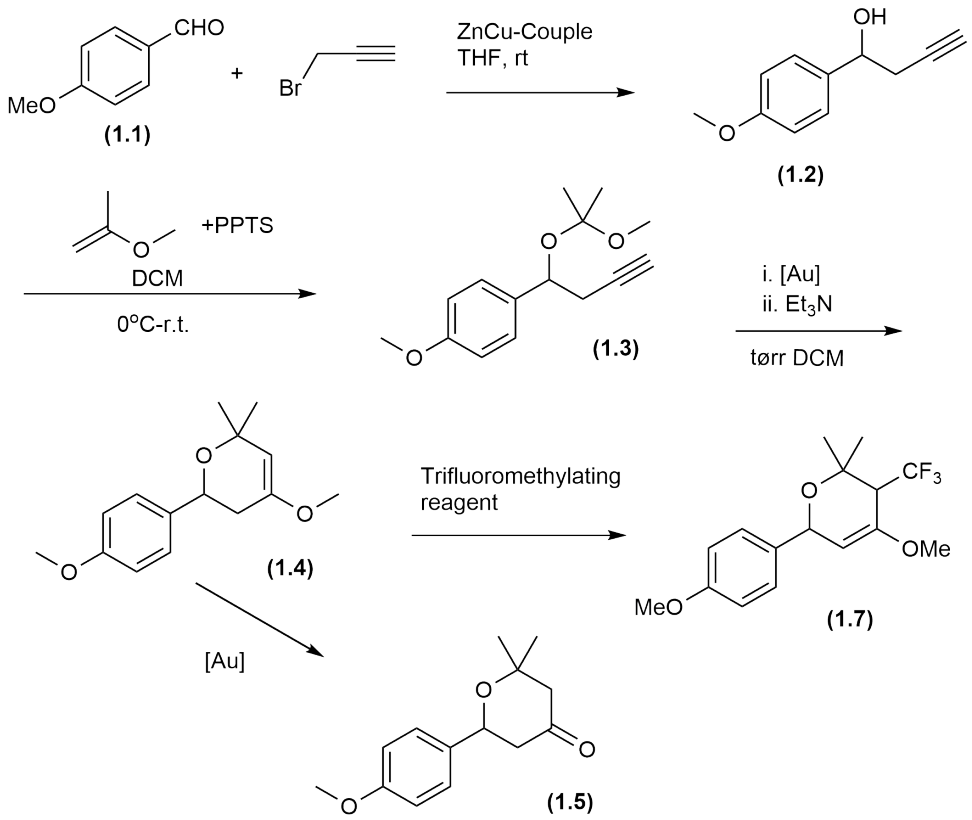


Figure 1.3: Reaction scheme showing the synthesis of the tetrahydropyran-4-one derivative **(1.4)** and the desired product **(1.5)**.

We also wanted to investigate the compatibility of the gold catalyst and the elctrophilic trifluoromethylating reagents, Fig 1.2. Similar research has previously been performed with Selectfluor.[6] Fig. 1.4 shows the scheme for this experiment, as previously performed with Selectfluor and the planned trifluoromethyl equivalent.

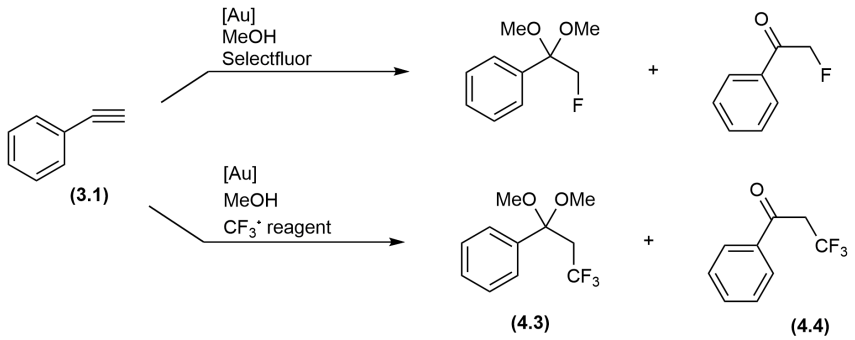


Figure 1.4: Reaction scheme showing the experiments performed to test the compatibility of the gold catalyst and CF_3^+-reagents.

During the course of the project we wanted to examine an alternate route to synthesize

compound **(1.7)**. By performing the trifluoromethylation on a terminal alkyne **(1.3)** and then the gold catalyzed cyclization, as illustrated in Fig. 1.5.

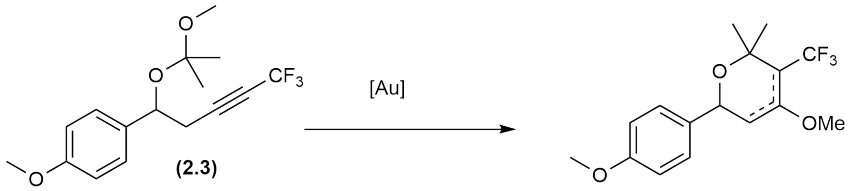
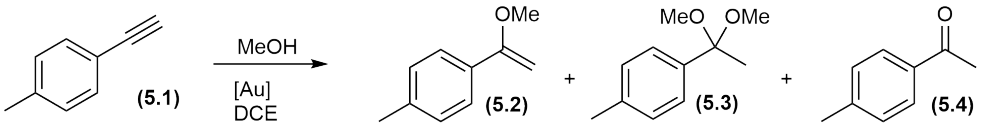
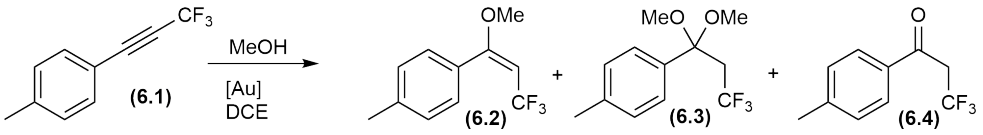


Figure 1.5: Reaction scheme showing the alternate synthesis of compound **(1.7)** that has been explored.

It is also of interest to investigate the gold catalyzed reactivity of a trifluoromethylated triple bond in a more general case. To do this we decided upon comparing the reactions of ethynyltoluene and a terminally trifluoromethylated analog. Fig 1.6 shows these reactions.



(a) Terminal alkyne and reaction products



(b) Trifluoromethylalkyne and reaction products

Figure 1.6: The two reactions performed to investigate the reactivity of the trifluoromethyl alkyne.

The structure of gold catalyst, (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate, which has been used throughout this project is shown in Fig. 1.7, and is in this report be reffered to as the gold catalyst or [Au]. The catalyst is bought form Sigma-Aldrich, and may also be known by the name JohnPhos Au(MeCN)SbF_6.

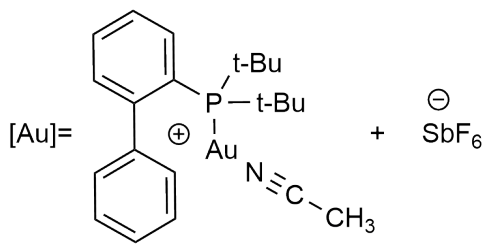


Figure 1.7: The gold catalyst used in this project

2 Theory

2.1 Homogeneous gold(I) catalysis

Organometallic chemistry has been a central part of modern chemistry since the very beginning. The first organometallic compounds was the Ziese's salt, a platinum olefin complex. The noble metal gold, on the other hand, has been thought of as a very unreactive element, an thus not very interesting for modern chemistry. Today however, gold is widely known for it's catalytic properties. This in spite of the first experiments with gold, reported that gold had no special catalytic properties.[7] Gold is today applied both as homogeneous and heterogeneous catalysts, and have recently seen an immense growth in the field of synthetic organic chemistry. As a homogeneous catalyst gold is interesting for several reasons. Gold catalysts are exceptionally alkynophilic, while at the same time less oxophilic than other Lewis acids, and activates for nucleophilic attack as shown in Fig. 2.1. Also the high oxidation potential from Au(I) to Au(III) allows most reactions to be performed without inert conditions. Furthermore gold catalysis is highly selective and provides access to complex products from much simpler starting materials.[8] The Fiksdahl group at NTNU has for several years been researching homogeneous gold catalysis, studying new synthetic pathways and their mechanism.[1,9–17]

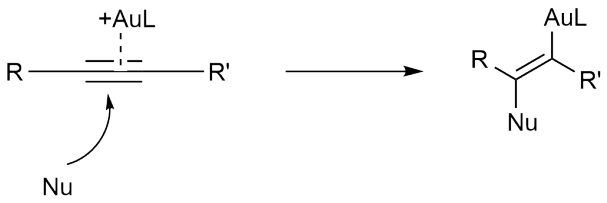


Figure 2.1: The gold catalyst activates for nucleophilic attack.

Propargyl acetals have shown by Fiksdahl *et al.* interesting properties when combined with gold catalysis, and have been used to preform [2+3] cycloadditions,[10] [2+5] cycloadditions[9] and tandem cyclizations,[16] shown i Fig. 2.2.

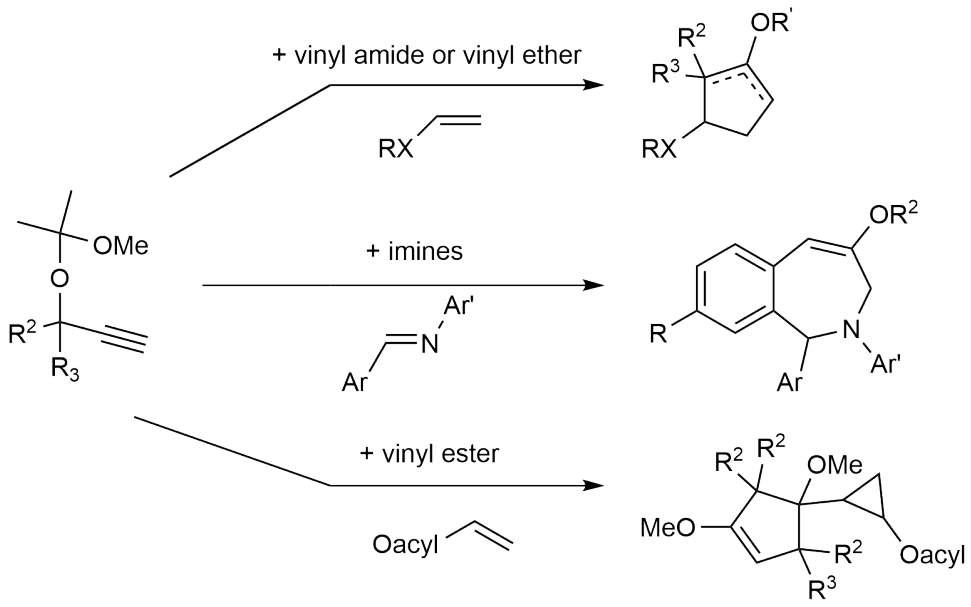


Figure 2.2: The different reactions available from propargyl acetals with gold catalysis.

The versatility of the propargyl substances inspired an investigation of the homopropargyl analogs. Two of the most recent publications by Fiksdahl *et al.* explore the preparation of 3-Halotetrahydropyran-4-one derivatives from homopropargylacetal. [1,17]

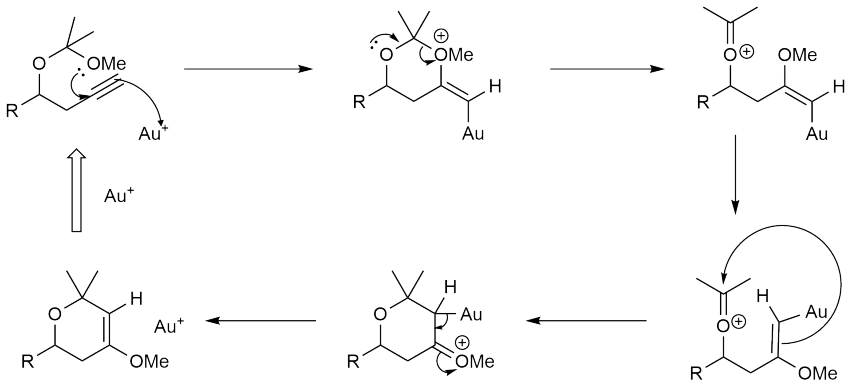


Figure 2.3: Scheme showing the catalytic cycle of gold in the Petasis-Ferrier rearrangement

The developed one-pot methods, for incorporation of halides, utilizes the gold(I) catalyst, (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate, together with NBS, NBI or Selectfluor, as illustrated in Fig. 2.4. The proposed mechanism goes via the Petasis-Ferrier rearrangement as shown in Fig. 2.3

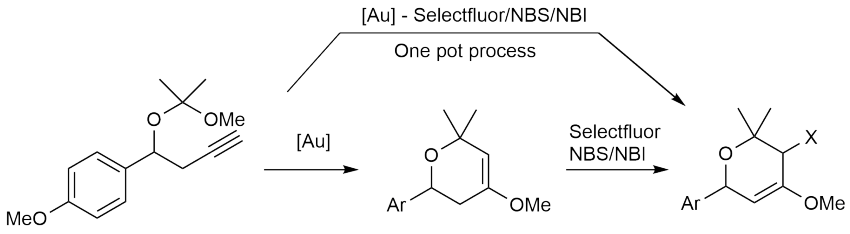


Figure 2.4: Scheme showing the general scope of the recent homopropargyl discoveries

2.2 Fluorination

The introduction of fluorine in a molecule is very interesting in organic chemistry. The fluorine group adds unique properties to a molecule, especially interesting for potential drug candidates. Fluorination enables modulation of pK_a values in proximal groups, and can result in increased membrane penetration. Also fluorinated molecules generally have higher lipophilicity than their non-fluorinated counterparts.[18] Fluorine's high electronegativity ensures a strong bond to carbon, because of the coulombic attraction over the polarized covalent bond. The partial negative charge of fluorine also contributes to attractive interactions between hydrogen-bond donors, and other polar groups. Furthermore, fluorinated compounds often have increased stability against oxidative metabolism.[18] For these reasons as much as 20 % of all medical and 35 % of all argochemical molecules have fluorine incorporated,[3] which is remarkable considering that not even a dozen naturally occurring organic substances contain fluorine.

Although the first reports of synthetic fluorination in organic chemistry happened over 150 years ago,[19] the methods for incorporating fluorine has been limited, and required special equipment. First with the development of specialized chemicals for fluorination, like DAST[20] and Selectfluor,[21] the development of safe and simple fluorination methods began.

Fluorination may be performed as a nucleophilic, radical or electrophilic reaction. Electrophilic fluorination were, and still are, considered more difficult than nucleophilic fluorination, due to the instability of F^+. Trifluoromethylation faces the same problem, and the electrophilic methods have seen a later and less satisfactory development than the nucleophilic. Again this is due to the difficulty in generating the CF_3^+ cation, compared to the CF_3^- anion. Radical fluorination[22] and trifluoromethylation[23] faces many of the same problems, and is limited by the access to safe sources of fluor and trifluormethyl.

A great advantage with fluorinated compounds is the ease of identification in NMR.

Since 19F is a NMR-active isotope the incorporation of fluorine is easily detectable by ^{19}F-NMR. In addition H−F and C−F couplings are also visible in ^{1}H-NMR and ^{13}C-NMR, due to the high nuclear momentum of ^{19}F. Monofluorinated compounds display doublets with large coupling constants, and trifluoromethylated compounds display quartets with large coupling constants.

2.2.1 Monofluorination and Selectfluor

The introduction of a fluorine atom in the fluoropyran **(1-5)**, Fig. X, as previously mentioned, has been reported by the Fiksdahl group.[1] This procedure utilizes Selectfluor to add the fluor atom. The reaction does not require a catalyst, but is compatible with the gold catalyst, so that a one-pot method is possible. Selectfluor is a stable white crystalline solid at room temperatur. And can be stored in a fridge with no special precautions. It is also relatively safe regarding selfaccelerating decomposition and has a low toxicity.[24] Selectfluor has a very high reduction potential and is one of the strongest oxidants in the N-F series of fluoronating agents.[25] All this makes Selectfluor an ideal source for F^+. The compatibility of gold(I) catalysis with electrophilic fluorination was tested by de Haro and Nevado in 2010.[6] Selectfluor was used to perform a hydrofluorination, as shown in Fig. 2.5

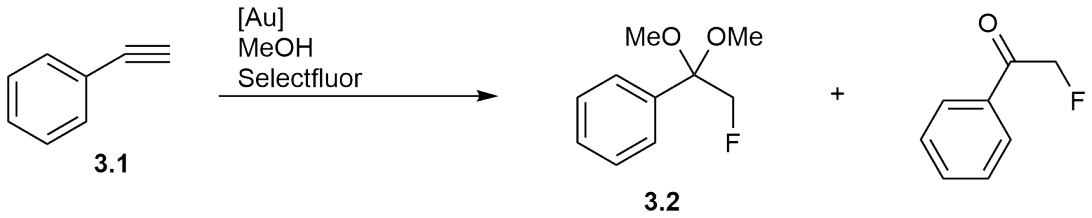


Figure 2.5: Hydrofluorination combined with $Ph_3PAuNTf$ catalyst.

Their hypothesis is that the reaction is at least partially gold catalyzed, which they demonstrated by performing a reaction with 1-methoxy-1,2-diphenylethene and Selectfluor in MeOH, as illustrated in Fig. 2.6.

From this result they arrived at the conclusion that the mechanim at least partially went via reductive elimination at the gold center. The proposed mechanism is shown in Fig. 2.7.

2.2.2 Trifluoromethylation

The reasons for introducing a trifluoromethyl group may often be similar to the reasons for monofluorinating, but the process is considerably different. Whereas monofluorination

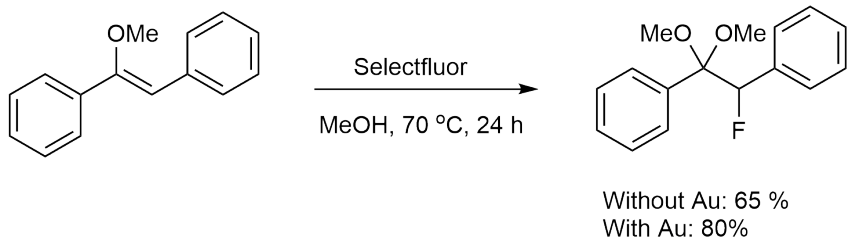


Figure 2.6: The reaction used to determine whether $Ph_3PAuNTf$ did partake in the reaction

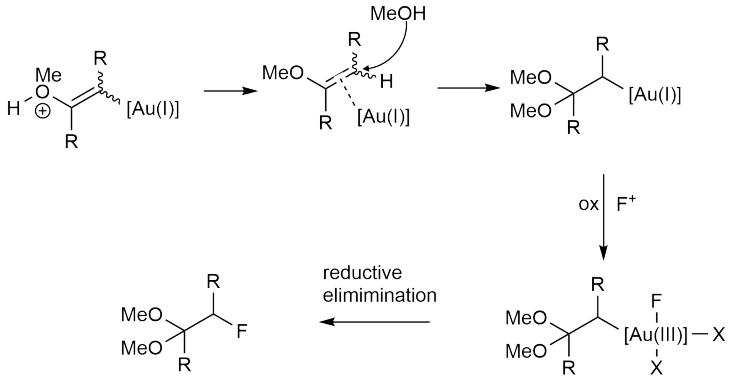


Figure 2.7: The proposed mechanism for gold catalyzed hydrofluorination, with oxidative addition and reductive elimination.

is the formation of a carbon fluorine bond, the introduction of a trifluormethyl group in most cases requires a carbon-carbon bondforming reaction. Therefore is CF_3-R often made from readily available building blocks with the trifluoromethyl group already incorporated. In some cases the trifluoromethyl group can be made from different precursors, but this often involves highly toxic or aggressive chemicals, like anhydrous HF.[26] The limitation of readily available building blocks or undesired reaction conditions explains why development of new methods of trifluoromethylation is so desired.

Fig. 2.8 shows how popular trifluoromethylation has become as a research topic recent years, especially since 2009. Nucleophilic trifluoromethylation saw a much earlier development than the electrophilic counterpart, and is to day a more or less fully developed field of organofluorine chemistry. For which much of the credit belongs to Ruppert-Prakash reagent (Me_3SiCF_3), and the extensive surrounding research.[26]

Only this year we have seen the first attempts of combining gold catalysts with the trifluoromethyl group,[27,28] here the goal has been to produce Ar-Au(III)-CF_3 complexes for reductive elimination of Au(III) $\rightarrow$ Au(I) to form $Ar-CF_3$. These gold complexes are made from nucleophilic sources of CF_3.

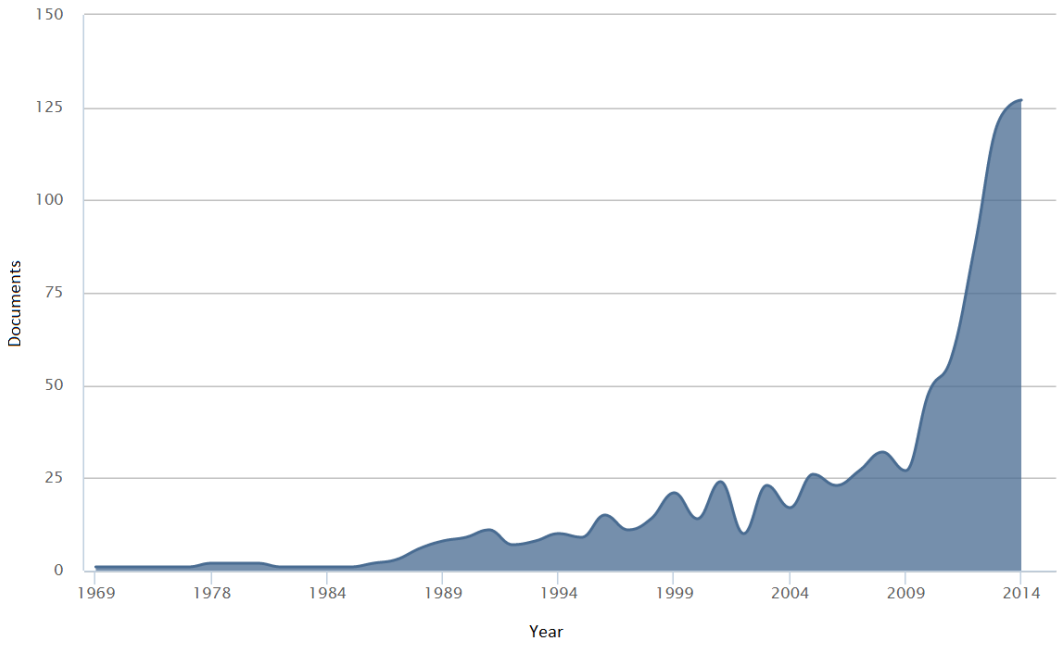


Figure 2.8: Plot showing the number of articles containing "Trifluoromethylation", in the title or as a key word, by publishing year.

Electrophilic trifluoromethylation is more challenging, and techniques for this has been developed more recently than nucleophilic and radical trifluoromethylation. Gold catalysts have yet to be combined with electrophilic trifluoromethylation.

2.2.3 Trifluoromethylation reagents

The Togni Reagents was first reported in 2006, from the research group of Antonio Togni, at ETH-Zürich.[29] Since then they have, together with several other trifluoromethylation reagents, played an important role in the recent spike in trifluoromethylation chemistry.[4]

The reagents are both hypervalent iodine compounds, with three bonding partners to the iodine atom. They are both air stable, but decomposes in a matter of weeks at room temperature, and should be stored in a fridge or a freezer. The pure substances are white crystalline with a reported melting point of 54-56 °C and 122 °C for the Togni's reagent I & II respectively.[29] Both compounds have also been reported to have explosive properties.[30] Togni's reagent II has a higher reduction potential than Togni's reagent I, though they are both mild reagents compared to e.g. Selectfluor.

Togni's research group have recently reported a nitro substituted variant[31] of Togni's reagent II, with similar properties, except for being thermally more stable, and more susceptible for acid catalysis. Three different versions of Togni's reagent are shown in

Fig. 2.9.

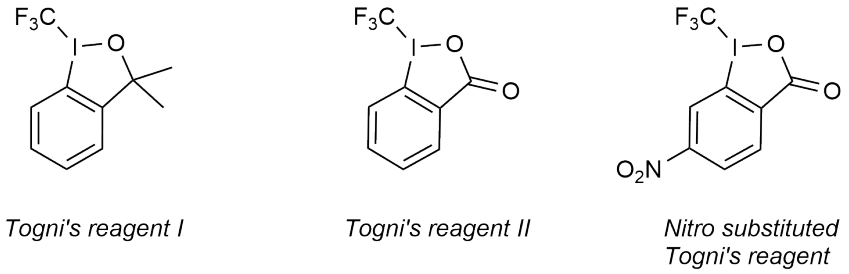


Figure 2.9: Togni's reagent I and II and the recently reported nitro substituted variant of Togni's reagent II.

The older procedures for synthesis where long and technically difficult with a low overall yield.[2,3,32] But recently, Charpentier *et al.* released a review explaining new and improved methods of synthesis. For Togni's reagent II this has been reduced to an one pot procedure.[33] This procedure was much simpler than previous methods,[4] which had at the most 4 steps. The more recently developed methods was based on both cheaper and less dangerous chemicals.

Different ways of activating for trifluoromethylation by Togni's reagents have been investigated,[4] and both Lewis acids, Brønsted acids and metal salts or catalyst have been used. Fang *et al.*[34] recently reported on a copper catalyzed regioselective C−H α-trifluoromethylation of α,β-unsaturated carbonyl compounds(enones), using Togni's reagent II . The scope of this article is illustrated in Fig. 2.10.

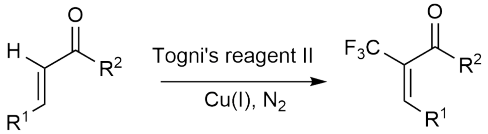


Figure 2.10: The scope of Fang *et al.*'s recent article.

Umemoto's reagents was first introduced in 1993 by Teruo Umemoto.[35] The reagents are a collection of trifluoromethyl dibenzoheterocyclic salts, of which some examples of are included in Fig. 2.11.

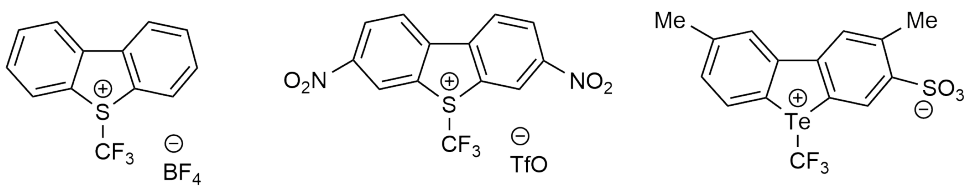


Figure 2.11: Some variants of the Umemoto trifluoromethylation reagents.

The strength of the reagent can be varied by exchanging the sulfur atom with selenium or tellurium,[35] elements in lower periods in the same group of the periodic table. The thermally unstable oxygen version has also been utilized,[36] at extremely low temperatures with in-situ generation. The oxygen variant allowed direct electrophilic trifluoromethylation of O- and N-centered nucleophiles. Some examples of this is shown in Fig. 2.12

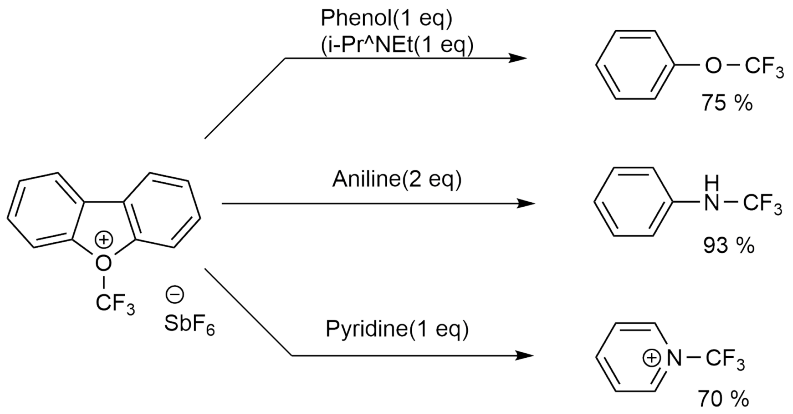


Figure 2.12: Some examples showing the possibilities with the oxygen variant of Umemoto's reagent.

In addition to the exchanging of the CF_3 carrying atom, the substituents can also be changed to tune the reactivity. The most reactive version is the di-nitro substituted, and on the other end of the scale is the alkyl group. Together these modes of varying the reactivity makes for a very versatile group of reagents.

2.3 Trifluoromethylation reactions

Trifluoromethylation reactions have been active research topic for some years now and a fair amount of procedures for incorporate trifluoromethyl exists. Fang *et al.*[34] adds CF_3^- to a double bond α, β to a carbonyl group. This a highly active site both α to a carbonyl group and electron deficient due to the double bond. This site is likely a little more activated than the active site on **(1.4)**. Xiong *et al.*[37] recently reported on the use of Togni's reagent II to add CF_3^+ to propargylic alcohols yielding the same α-CF_3-enone structure element in the product as produced by Fang *et al.*. Scope of this article is shown in Fig. 2.13.

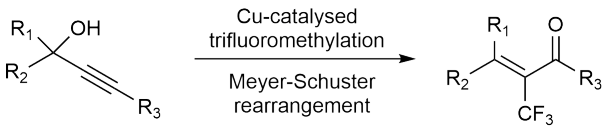
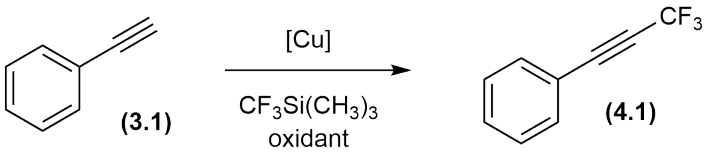


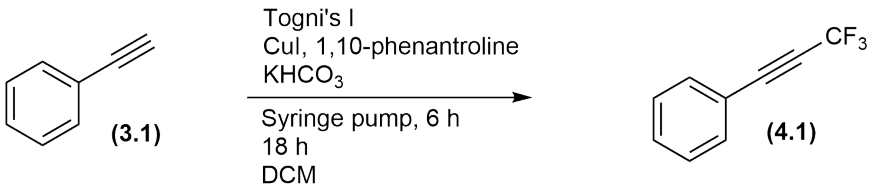
Figure 2.13: The scope of Xiong *et al.*'s recent article.

Propargylic alcohols exhibit many of the same properties as homopropargyl alcohols, and gives reason to expect that some form of reaction is also possible for **(1.2)** or the derivatives thereof.

Jiang *et al.*[38] in 2012 reported a method to trifluoromethylate terminal alkynes to produce trifluoromethyl acetylenes. This method utilized trifluoromethylsilane and quite aggressive conditions, with 100 °C and 5 equivalents of trifluoromethylating agent. Weng *et al.*[39] has since developed a milder method based upon an electrophilic approach. The mild procedure with Togni's reagent I has been used several times during this project, with a high rate of success.



(a) Jiang *et al.*'s[38] procedure.



(b) Weng *et al.*'s[39] procedure.

Figure 2.14: Two different methods for producing the trifluoromethyl phenyl acetylene **(4.1)**.

2.4 Reactions with trifluoromethyl alkynes

Often can be quite difficult to incorporate the CF_3 group at a wanted position. One strategy often used, especially before the recent development of methods for direct trifluoromethylation, is building the molecule from building blocks with CF_3. Trifluoromethyl acetylenes can be used as a CF_3 containing building block. For this to be effective it's

important that there exists versatile methods that can be applied to a broad substrate scope.

In 2008 Zhang *et al.*[40] published an article that demonstrates the versatility of the trifluoromethyl acetylene. The reaction with LiI to form vinyl iodide, opens a wide range of possibilities. One of these possibilities is shown in Fig. 2.15. Vinyl iodides are known for their versatility and a wide arrange of preexisting chemistry can be utilized for further reactions.

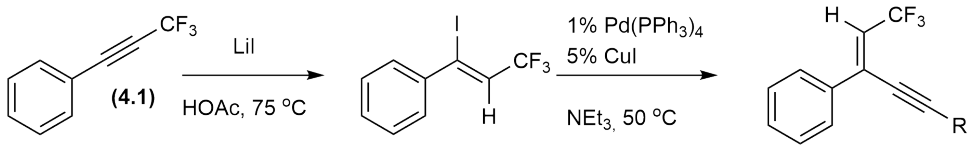


Figure 2.15: The scope of Zhang *et al.*'s[40] recent article.

Another article published by Alkhafaji *et al.*[41] uses the CF_3-acetylene to generate vinyl cations. In a variant of this reaction they managed to add benzene and other aryl structures β to the trifluoromethyl group. This required the use of superacids. Fig. 2.16 shows an example of a reaction done via the vinyl cation.

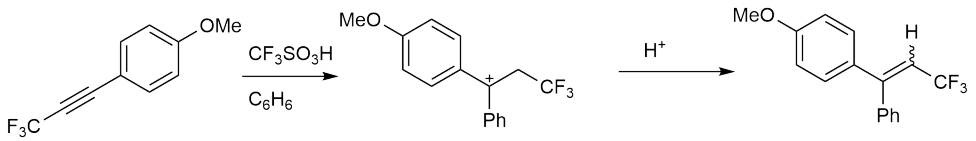


Figure 2.16: The scope of Alkhafaji *et al.*'s[41] recent article.

3 Results and Discussion

3.1 Direct trifluoromethylation

The first attempts at performing trifluoromethylations were performed on the pyran substrate **(1.2)**. The goal was to expand the previously published procedures for halogenated derivates,[1,17] with a CF_3-derivate. Although ultimately unsuccessful some interesting results were observed during the attempts. The first attempts where simply performed by adding Togni's reagent II to a solution of the pyran **(1.2)** in DCM. Under these conditions no reaction was observed with TLC. The reaction mixture was added [Au]-catalyst to aid the reaction. This yielded the same product **(1.5)** as in a reaction without trifluoromethylating reagents. And it was obvious that the [Au]-catalysed reaction from the pyran **(1.4)** to the ketone **(1.5)** went much faster than any competing trifluoromethylation reaction. Based upon an article by Janson *et al.*[42] it was expected better results using CuI as a catalyst for the reaction. At room temperature there was no visible reaction after 2 hours. The solvent was changed to DCE to allow higher temperatures, and after 2 hours at 50 °C the formation of 2 products was observed with TLC. After 4 hours most of the starting material was consumed and 2 products were isolated. A picture of one of these TLC plates with samples taken at 2, 4, 6 and 24 hours, is shown in Fig. 3.1. By NMR analysis one of the lower TLC spot was found to be the ketone **(1.5)**. The higher TLC spot, was after more comprehensive elucidation with 2D NMR found to be a di-metoxy acetal **(1.6)**, probably formed as an intermediate between the pyran **(1.4)** and the ketone **(1.5)**. This formation of an acetal as an intermediate between an enol ether and a ketone is quite common and something we also observed with other substrates.

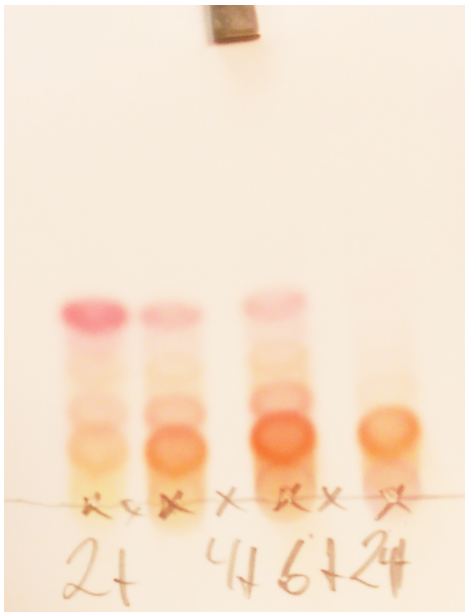


Figure 3.1: Picture of TLC-plate from reaction shown in Fig. 3.2. (Eluent: 10 % EtOAc in n-pentane)

Trifluoromethylation of the pyrane **(1.4)** was attempted again with conditions based upon an article for trifluoromethylation at terminal alkyne sites.[39] This procedure included 1,10-phenantroline as a ligand and potassium bicarbonate as a base. During this experiment Togni's I, II and Umemotos reagent was tested. All three reagents gave the same products **(1.5,1.6)**, as

shown in Fig. 3.2. A control experiment which included the pyran **(1.4)**, [Cu]-catalyst, ligand and base under the same conditions, but without any trifluorometylating reagent, was also performed. Interestingly there was no reaction in the control experiment. As all of the vessels containing a CF_3-reagents had the similar development, in regards to both products and reaction rate, it is obvious that the trifluoromethylation reagents in some way catalyze the reaction.

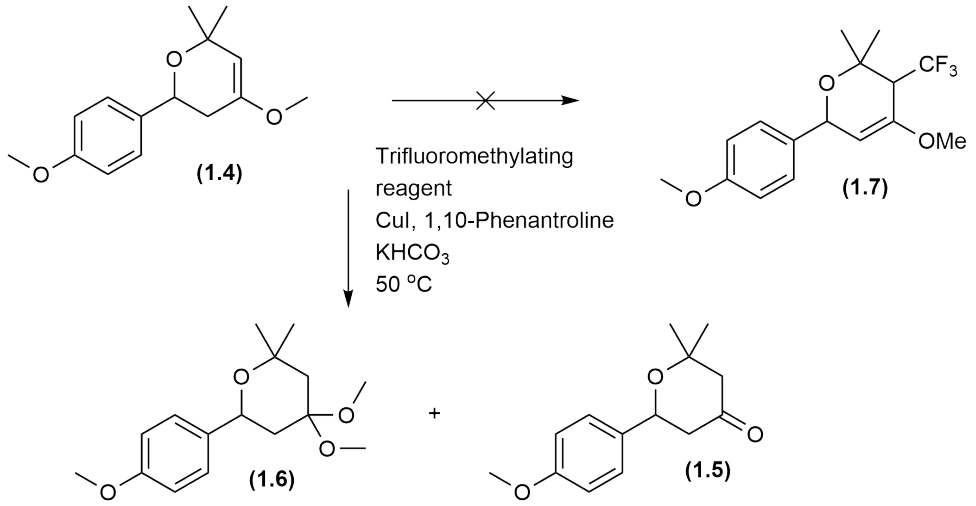


Figure 3.2: The attempted reaction of trifluoromethylation of **(1.4)**. Tongi's I, II and Umemoto was tried in different reactions.

3.2 Alkyne trifluoromethylation

Attempts at trifluoromethylation at a terminal alkyne were also performed. For these experiments a simple substrate without any complicating neighbouring groups was needed. For this purpose phenylacetylene is often used. The problem with phenylacetylene is it's molecular weight, which is pretty low, especially compared to Togni's reagents. This meant that we would need a large amount of an expensive chemical, to yield a relatively low amount of product. 160 mg of reagent would be needed to perform a stoichiometric reaction with 50 mg of substrate. In addition reactions with Togni's reagent are often performed with 1.3 - 1.5 equivalents of the trifluoromethylating agent. To circumvent this problem we decided to utilize Togni's reagent II, and attempt to use the iodobenzoic acid formed in the reaction as a nucleophile. The heavy iodobenzoic acid group would attack the tipple bond α to the terminal position to form an ester product. This would make the product simpler to isolate due to a higher mass. This has previously been performed by Janson *et al.*,[42] with CuI catalysis, in a microwave vials. As microwave-vials in an

appropriate size was not available the reaction was performed in a pressure resistant vessel (100 mL) with several smaller vials (2 mL) inside. The larger vessel was charged with the same solvent as the reactions in the vials (DCE), so the pressure from boiling solvents would be moved from the small vials to the outside vessel. With the exception of markings on the vials beeing washed off due to the boiling solvent this worked unexpectedly good.

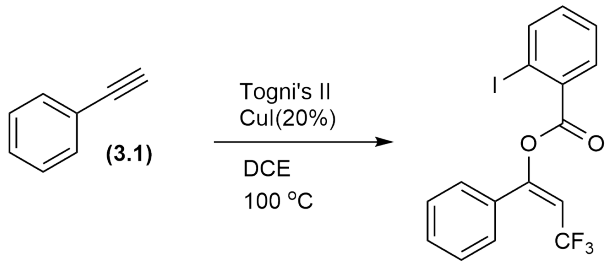


Figure 3.3: CuI catalysed electrophillic addition of CF_3 and nucleohpillic addition of iodobenzoic acid

With CuI as catalyst, the results from Janson *et al.* were replicated. The reaction was then attempted under the same conditions, with the [Au]-catalyst. Four different variations were tested, varying the solvent ()DCE and $MeNO_2$) and trifluoromethylating agent(Togni's I and II). A TLC plate with all the different reactions and the CuI reaction as a reference is shown in Fig. 3.4.

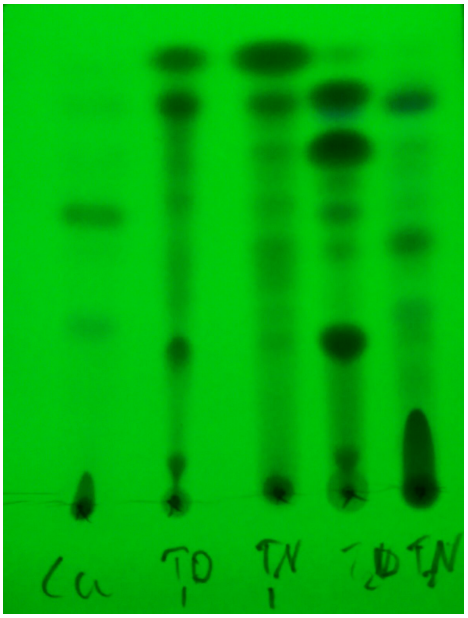
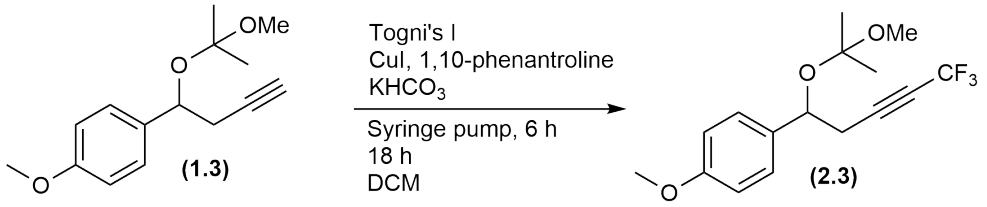


Figure 3.4: Picture of TLC-plate from reactions with [Au] and Togni's I and II. From left to right: Reference CuI reaction, Togni I and DCE, Togni I and $MeNO_2$, Togni II and DCE, Togni II and $MeNO_2$. (Eluent: 10 % EtOAc in n-pentane).

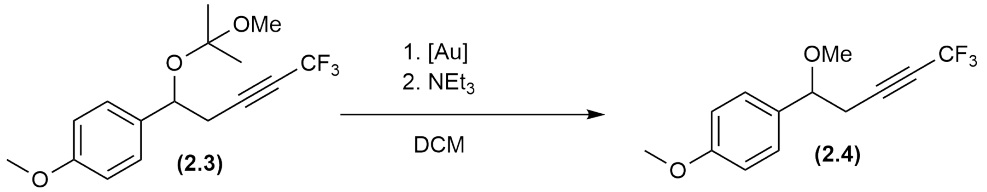
All the reactions failed to produce the wanted ester, and NMR analysis of the reactions showed only decomposition products from the trifluoromethylating reagents.

3.3 Homopropargyl trifluoromethylation

Another plan for producing the goal substance **(1.7)** was to first create the trifluoromethylated homopropargylacetal, and then performing the cyclization with the CF_3 group already in the terminal alkyne position. Both the homopropargyl alcohol and the homopropargyl acetal were prepared using the method developed by Weng *et al.*. Both the products were produced in yields comparable to those achieved by Weng *et al.* at 60-80 %. The Acetal product showed sings of instability, decomposing to the alcohol at a rate of 80 % in 8 days at room temperature. This was discovered as an accident when the NMR had downtime for about a week and the sample was left there awaiting analysis. A later batch was stored in the freezer and did not show any sign of decomposition after several weeks. The instability obeservation may just have been due to uncontrolled unforeseeable circumstances.



(a) Trifluoromethylation of **(1.3)** to form **(2.3)**.



(b) Attempt at cyclization of **(2.3)** yielded **(2.4)**.

Figure 3.5: Attempt to produce compound **(1.7)** via an alternate synthesis route.

To achieve best possible results, a new larger batch of the homopropargylacetal was prepared just prior to attempting the [Au]-catalyzed cyclization. After 15 minutes TLC showed full conversion of the starting material. The product was isolated and analyzed by NMR. Both NMR and MS results indicate that the product from this reaction was a trifluoromethylated methoxy ether **(2.4)**. The triple bond was intact but the acetal had

reacted. ^1H-NMR of the crude mixture showed a strong signal at 2.07 ppm, indicating that acetone may have been formed in the reaction. As seen in fig. 3.6 acetone is an expected leaving group in the 3rd step, if the [Au] coordinated carbon is not nucleophillic enough to react with the carbonyl carbon. Reduced nucleophilicity next to a trifluoromethylgroup is expected as fluorine has a high electronegativity.

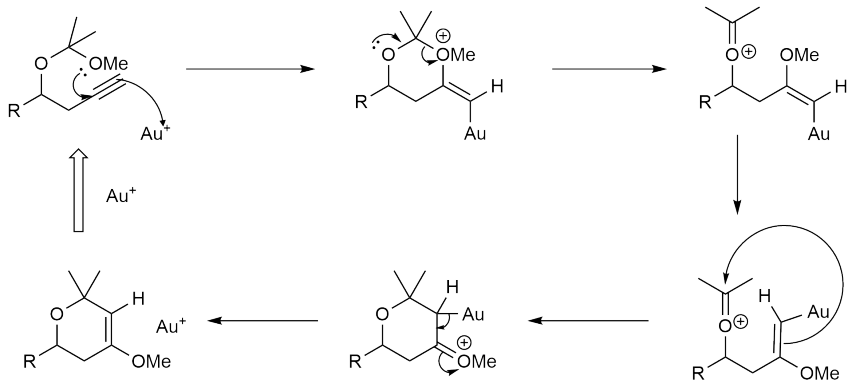
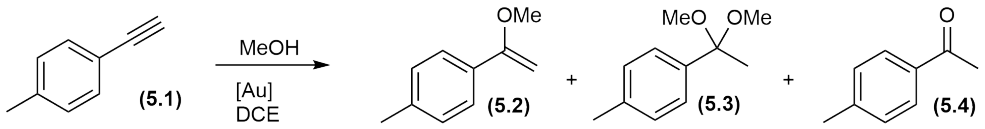


Figure 3.6: Scheme showing the catalytic cycle of gold in the Petasis-Ferrier rearrangement

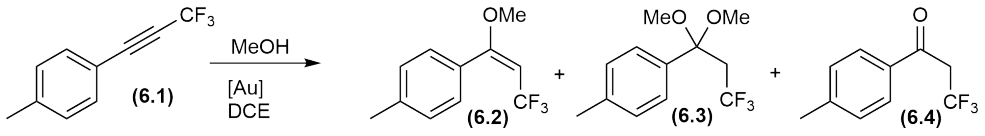
3.4 Nucleophilic addition to alkyne substrates reactivity study

To study the activity of the trifluoromethyl alkyn towards gold catalysis in an isolated system, we decided to investigate the gold catalyzed addition of methoxy to form the enol ether, acetal and eventually the ketone. The substrate was initially the phenylacetylene. The procedure from Weng *et al.* was used to produce (3,3,3-trifluoroprop-1-yn)benzene. The workup of this product proved to be difficult as concentration under vacuum the rotavapor resulted in loss of product. To aid this problem the substrate was changed to the paramethyl analog.

The two reactions studied is illustrated in fig 3.7



(a) Terminal alkyne and reaction products



(b) Trifluoromethylalkyne and reaction products

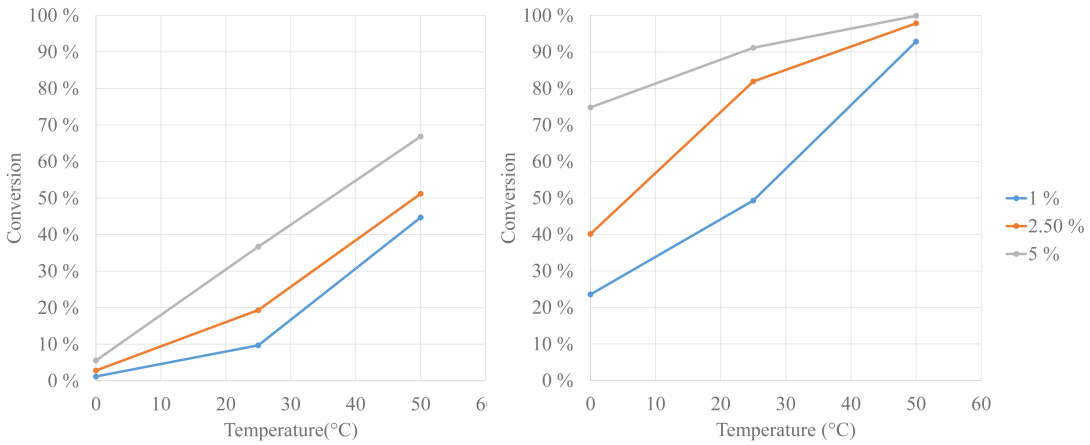
Figure 3.7: Illustration of the reactions performed for reactivity comparison.

To screen a large number of conditions with minimum effort, gas chromatography was utilized. A larger batch of the reaction was run to uncover what products where formed. These products were purified by flash chromatography and analyzed by NMR, and later run as standard solutions to identify the peaks shown in the chromatogram. This way we were able to identify all products formed in the reaction so simple GC analysis could be used to monitor the reaction, with high accuracy.

3.4.1 Temperature and catalyst loading

The first conditions varied were catalyst loading and temperature. All reactions where run for 30 minutes. To stop the reaction a quenching solution of water, NEt_3 and acetone in 1:1:1 ratio were prepared. The idea behind the quenching solution was for the amine to deactivate the catalyst, water to extract inorganic substances. Acetone was needed to mix water and NEt_3, and luckily the water phase separated out when the quenching solution was added to the reaction. Considering the results it is assumed the quenching was effective.

As shown in Fig. 3.8 the conversion is higher for the CF_3 substituted alkyne



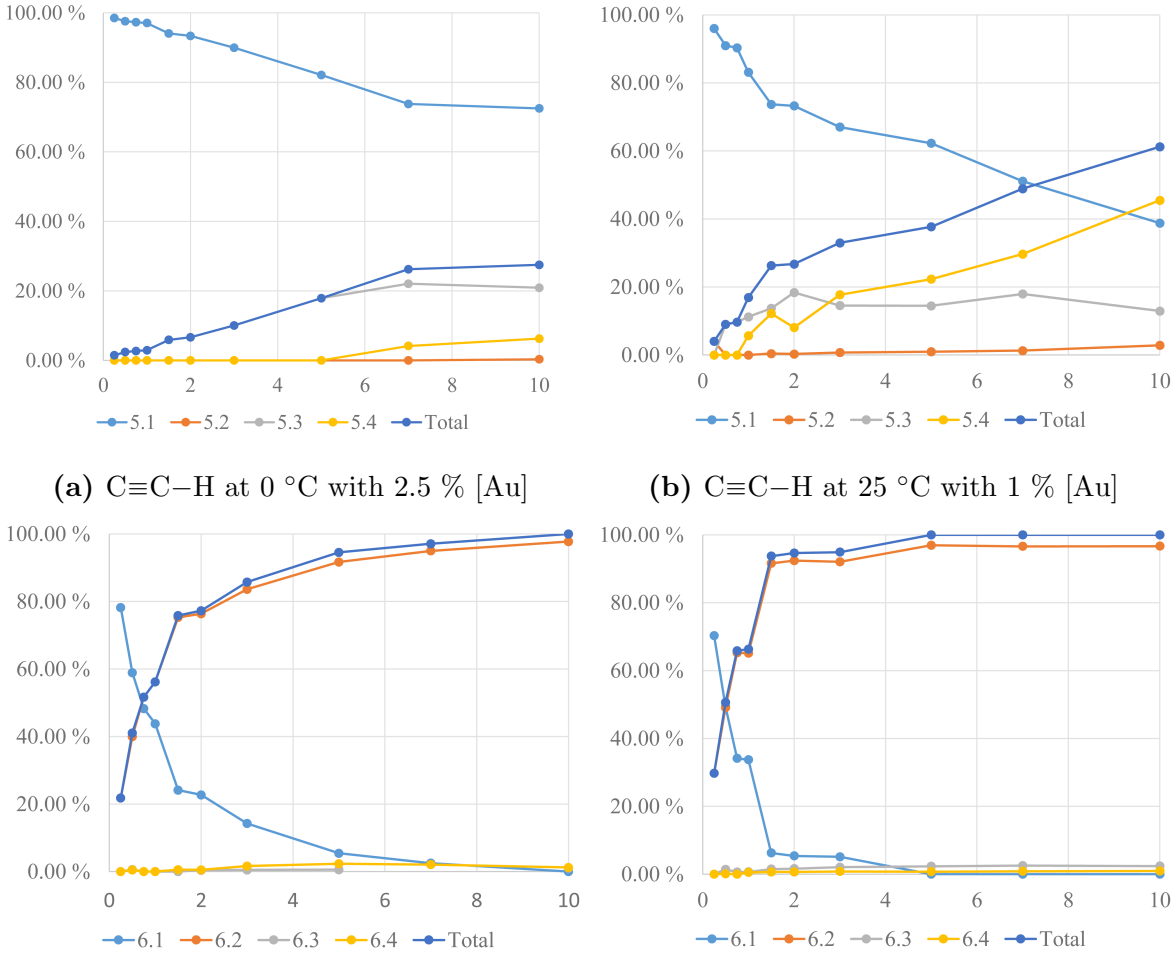
(a) Terminal alkyn **(b)** Trifluoromethylalkyn

Figure 3.8: Plot showing the conversion with different catalyst loadings with variable temperature

3.4.2 Time and selectivity

The first sets of results indicated that the reaction rate was increased for the trifluoromethylated substrate. Showing almost a full conversion at all reactions at 50 °C . To effectively monitor the reaction over time, reactions with a relatively low conversion over 30 minutes were chosen for further investigation(2.5 % [Au] at 0 °C and 1 % [Au] at r.t.). The reactions where run under the same conditions at times ranging from 15 minutes to 10 hours.

As Fig. 3.9 illustrates both the reaction rate and selectivity is higher for the trifluoromethyl substituted alkyn**(6.1)**. The CF_3-substrate forms the enol ether**(6.2)** very quickly and almost without any byproducts. From the larger batch reaction we know that also the acetal **(6.3)** and the ketone **(6.4)** are formed at higher temperatures and with longer reaction times. The terminal alkyne **(5.1)** on the other hand has a much slower reaction, and the formation of the ketone **(5.4)** begins long before the starting material **(5.1)** was fully consumed. Also the enol ether **(5.2)** is barely observed while the acetal **(5.3)** is the main product in the beginning.



(a) C≡C−H at 0 °C with 2.5 % [Au]

(b) C≡C−H at 25 °C with 1 % [Au]

(c) C≡C−CF_3 at 0 °C with 2.5 % [Au]

(d) C≡C−CF_3 at 25 °C with 1 % [Au]

Figure 3.9: Plot showing the conversion with different catalyst loadings with variable temperature from 15 minutes to 10 hours

3.4.3 Other nucleophiles

After performing the necessary reactions for the reactivity study we had some trifluoromethylacetylene left, and thought we would do 2 small scale reactions. The first reaction was an attempt to create a vinyliodide product with the method developed by Zhang *et al.*,[40] substituting heat and acetic acid with [Au]. The reaction was added the catalyst, and left for 24 hours and no reaction was observed. Applying heat and a few drops of acid did not help the reaction. The reaction is illustrated in Fig. 3.10.

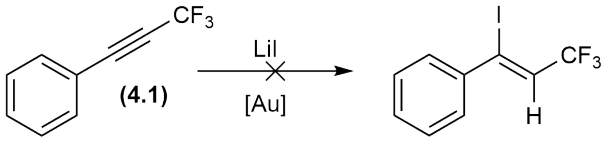


Figure 3.10: The attempted reaction to produce a trifluoromethylated vinyliodide.

The second reaction was an attempt at adding anisole with the same procedure Alkhafaji *et al.* used to add phenyl, substituting the superacid with [Au]. After 24 hours no reaction was observed. The reaction is illustrated in Fig. 3.11.

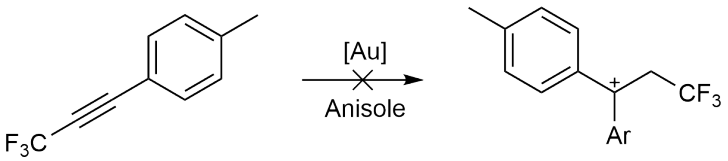
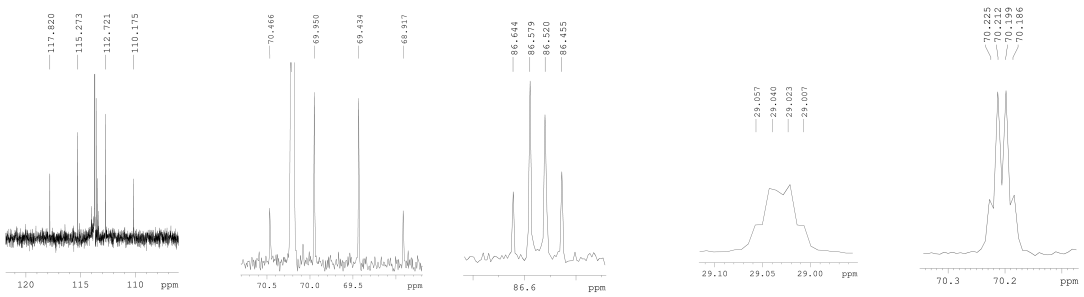


Figure 3.11: The attempted reaction to add anisole to a yield a vinyl cation.

3.5 NMR and MS results

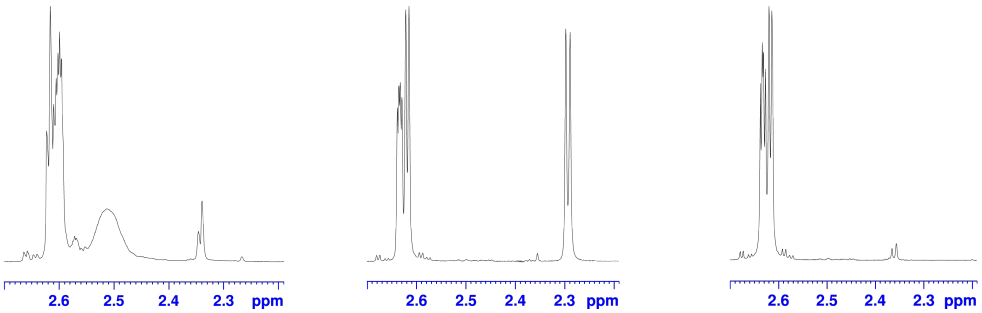
The big advantage with trifluoromethylated compounds is that one gets couplings in ^{1}H- and ^{13}C-NMR. These couplings are easily visible, sometimes as far as ^{5}J between ^{19}F and^{13}C. For the trifluoromethylgroup the carbon has had a coupling at between 250 and 300 Hz. The coupling constant gradually decreases through the bonds. This makes elucidation fairly simple with a ^{13}C-NMR. An example of these couplings in compound **(2.3)** is shown in Fig. 3.12



(a) ^{1}J 256 Hz **(b)** ^{2}J 52 Hz **(c)** ^{3}J 6.3 Hz **(d)** ^{4}J 1.6 Hz **(e)** ^{5}J 1.3 Hz

Figure 3.12: The quartet couplings in a trifluoromethylated substance **(2.3)**

^{1}H-NMR of the homopropargyl alcohol has a multiplet around 2.6 ppm, which often is poorly resolved. We wanted to see if this was caused by the OH-group. Adding a drop of D_2O to the sample would eliminate the OH-peak by swapping the OH-group with a OD-group. Comparing the two NMR spectra would indicate which peak belonged to OH-group. A comparison of the area in three different samples is shown i Fig. 3.13



(a) ^{1}H-NMR of **(1.2)** with problem

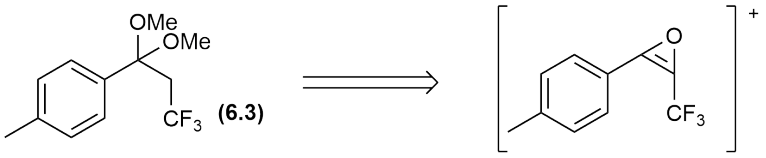
(b) ^{1}H-NMR of **(1.2)** prior to adding D_2O.

(c) ^{1}H-NMR of **(1.2)** after adding D_2O.

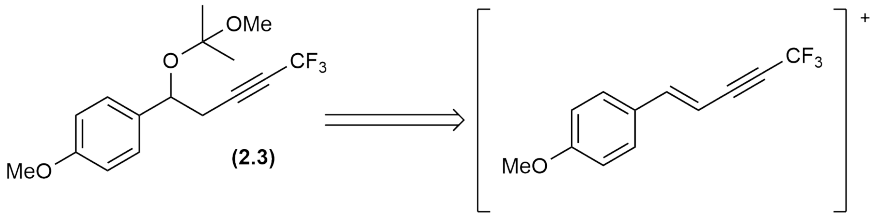
Figure 3.13: Different ^{1}H-NMR of **(1.2)**.

Fig. 3.13a illustrated the problem, with a broad peak just below 2.6 ppm. Fig. 3.13b is the sample prepared for the D_2O experiment just prior to adding D_{20}. Fig. 3.13c shows the sample after adding D_2O. The experiment indicates that the broad peak is caused by an impurity not present in this specific sample since it is not visible in the spectra prior to adding D_2O. The spectra after adding D_2O indicates that the OH-peak has a value of approximately 2.3 ppm.

MS analysis of the acetal compounds has been difficult as the structure is not stable enough to survive ionization, even with mild techniques as electron spray ionization. Upon analysis of compound **(6.3)** there were two strong peaks at m/z 201.0526 and m/z



(a) Suggestion of the structure of **(6.3)** upon ionization.



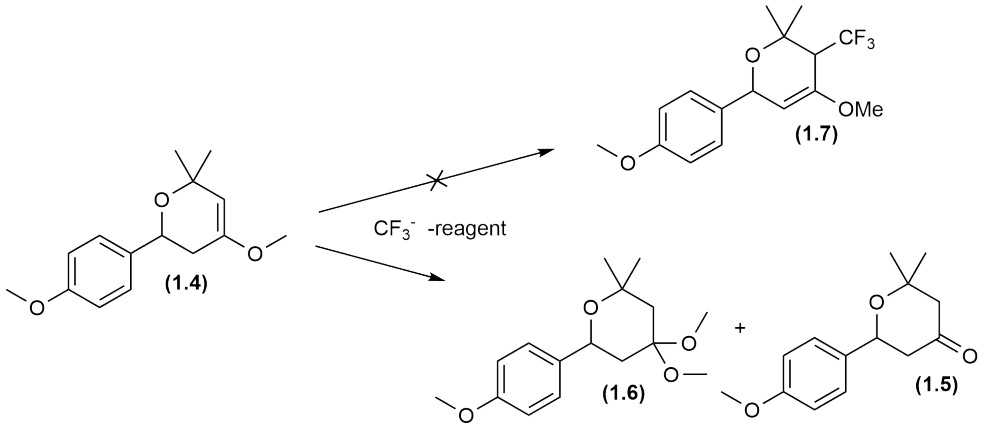
(b) Suggestion of the structure of **(6.3)** upon ionization.

Figure 3.14: Suggestion on the acetal ions structures.

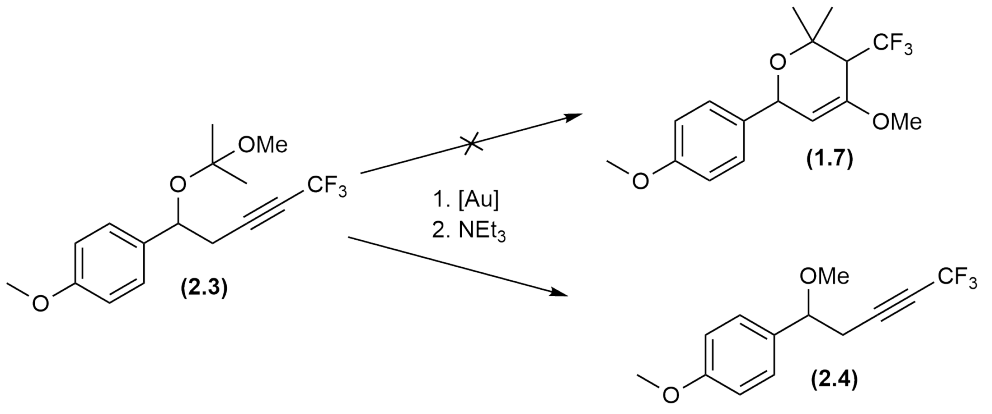
217.0842. The 217 peak is in accordance with $[M^+H]^+$ for **(6.2)**. Also the 217 peak was fragmented further and it was found that the 201 peak is not a fragment of the 217 peak. A mass of 201.0526 is a $[M^+H]^+$ ion corresponding to the molecular formula $C_{10}H_7OF_3$. This comes from a loss of C_2H_8O which equals metanol and methane. Previously there had been problems with analyzing **(2.3)** as well. After the discoveries regarding fragmenting of the acetal**(6.3)** the MS-results of **(2.3)** was investigated further, where a similar result was found. A suggestion to how the structure of these ions is illustrated in Fig. 3.14.

4 Conclusion

This project was originally aiming at studying the preparation of a 3-trifluoromethyl dihydropyran **(1.7)**. However during the course of the project the focus has been shifted to also include the studies of the gold(I)-catalyzed reaction of trifluoromethyl acetylenes. The initial goal of creating a method to prepare compound **(1.7)** has not yet been reached. The synthesis has been attempted a number of times with different conditions and from two different substrates, **(1.4)** and **(2.3)**. An illustration showing the failed step for both approaches is given in Fig. 4.1.



(a) Attempted direct trifluoromethylation of substrate **(1.4)** resulted in products **(1.5)** and **(1.6)**



(b) Attempted cyclization of acetal **(2.3)** resulted in ether **(2.4)**

Figure 4.1: Illustration of the two main different apporaches for synthesizing **(1.7)**.

The direct trifluoromethylation of substrate **(1.4)** has been attempted with both [Au]- and [Cu]-catalysis, combined [Cu/Au] catalysis. The resulting product from the

synthesis was ketone **(1.5)** and acetal **(1.6)**.

The attempt at trifluoromethylating the precursor substances **(1.2)** and **(1.3)** has been successful by employing a method developed by Weng *et al.*.[39] However The approach ultimately failed during the attempt at performing a [Au]-catalyzed cyclization at the trifluoromethylated acetal **(2.3)**. The resulting product from the reaction was a methoxy ether **(2.4)**.

The failed reactions with the homopropargyl**(2.3)** and pyran **(1.4)** substances inspired a more general study. The idea was to attach a trifluoromethyl group to a terminal alkyne by utilizing [Au]-catalysis, as illustrated in Fig. 4.2. There were made several attempts, all unsuccessful.

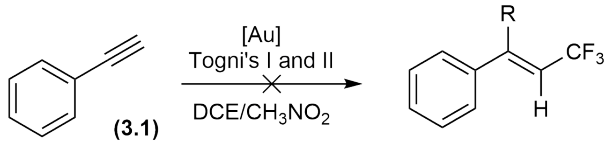
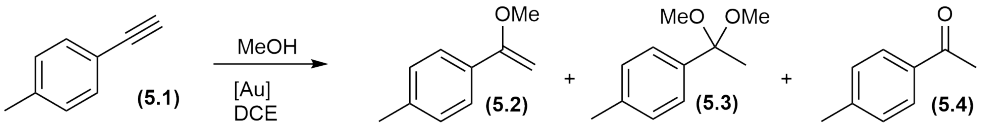
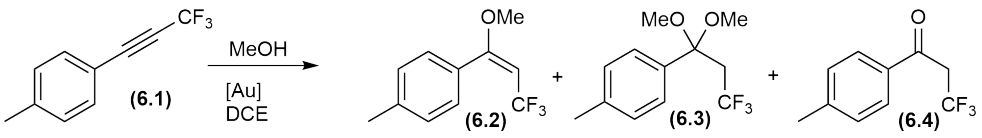


Figure 4.2: Illustration of the failed attempts at [Au]-catalyzed trifluoromethylation of phenylacetylene **(3.1)**

The failed attempt at cyclization of the trifluoromethylated acetal **(2.3)**, indicated that the first step of the mechanism with the transfer of a methoxy group from the acetal to the activated triple bond had been successful. Therefore we wanted to perform a comparative study on the activity of [Au]-activated CF_3-triple bond. The two reactions we decided to compare are shown in Fig. 4.3.



(a) Terminal alkyne and reaction products



(b) Trifluoromethylalkyne and reaction products

Figure 4.3: Illustration of the reactions performed for reactivity comparison.

The reactivity study into the [Au]-catalyzed reaction of trifluoromethyl acetylene compared to a terminal alkyne showed that nucleophilic attack of a methoxy group at the

activated triple bond was highly favored at the trifluoromethylated substance. However the attack of a second methoxy group at the same site was disfavored in the trifluoromethyl substrate compared to the terminal alkyne. Indicating that the enol ether intermediate is a lot less active with CF_3 incorporated.

4.1 Future work

As the initial objective of this project has yet to be fulfilled, further studies has to be done regarding the trifluoromethylation of the pyran derivate **(1.4)**. Co-catalysis with both [Cu] and [Au] has not yet been attempted, and might be worth considering. We know the [Cu]-catalyst interacts with Togni's reagents, and takes on the CF_3^- group. In this case the [Cu]-complex carrying the CF_3^- group to a [Au]-activated site, might be more successful.

Reactions with a trifluoromethylated propargyl substrate might also be interesting. A lot of exiting chemistry has been done with propargylic acetals by the Fiksdahl group.[9–16] Some of these reactions has also included non-terminal alkynes which may be more suited for attempts with trifluoromethylated variants.

To complete the reactivity study of trifluoromethylated acetylenes, the reactivity of a, non-fluoroinated, methylated alkyne should also be taken into account, and compared to the reactivity of trifluoromethylated alkynes.

Futher investigation into the formation of vinyl substrates with gold catalysis should also be performed. During this project only one attempt at iodation of trifluoromethyl alkyne, and one on aromatic addition to trifluoromethyl alkyne, was made. Although this attempt was unsuccessful there might be a great potential in developing new reactions in this area.

5 Experimental

5.1 General

The work has been carried out in the Fiksdahl group research laboratory, at Realfagsbygget, NTNU. All compounds produced during the project has been characterized by ^{1}H-NMR and ^{13}C-NMR, at the NTNU, Gløshaugen, NMR-laboratory, or at the MR-center at St. Olavs Hospital in Trondheim. Substances that are either new or new to the Fiksdahl group have in addition been characterized with 2D-NMR and MS. Accurate mass determination in positive and negative mode was performed on a "Synapt G2-S" Q-TOF instrument from Waters. Samples were ionized by the use of ASAP probe (APCI). Calculated exact mass and spectra processing was done by Waters Software (Masslynxs V4.1 SCN871). All reagents used has been of pro analysi quality. The gold catalyst used is (Acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate, from Sigma-Aldrich, shown in Fig.

5.2 Preparation of Zn/Cu-couple

5.2.1 From Ma *et al.*[43]

Zink powder(6.54 g, dust) and deionized water (45 mL) in a 100 mL roundbottomflask, was dropwise added HCl(1.25 mL, conc.) while vigorously stirred. After 10 minutes $CuSO_4$ (2.71 g, anhydrous) was added, and stirring continued for 15 minnutes. The black powder was filtered and washed with deionized water(3×15 mL), acetone (3×10 mL) and diethyl ether(2×15 mL). The powder was then dried for 3 hours at 100 °C .

5.2.2 From LeGoff[44]

Acetic acid(25 mL, anhydrous) was heated to 65 °C and added $Cu(OAc)_2$ (1.0 g, monohydrate). While stirring vigorously Zink powder (17.5 g, dust) was added. After about 2 minutes more acetic acid (25 mL, anhydrous) was added to prevent it from boiling dry. The reaction was stirred until the boiling discontinued. After the deposition of copper had finished the black silt was washed with diethyl ether(3×100 mL) and dried under vacuum at 100 °C .

5.3 Synthesis of the homopropargyl alcohol (1.2)

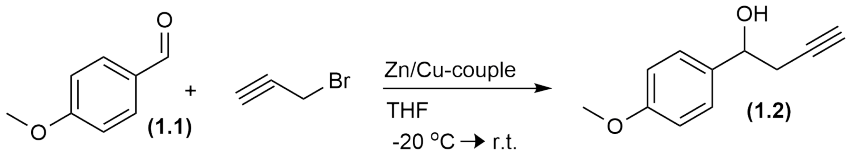


Figure 5.1: Synthesis scheme for **(1.2)**

A mixture of THF(100 mL), Zn/Cu-couple (7.0 g) and *p*-methoxybenzaldehyde **(1.1)** (5.0 mL, 30 mmol) was put on stirring on a brine-ice bath(-20 °C). Propargylbromide (6.5 mL, 80 % in Toluene, 1.2 eq)was carefully added. The reaction was left overnight, while slowly coming to room temperature. The reaction mixture was filtered on Celite, diluted in EtOAc (100 mL) and washed with $NH_4Cl_{sat.}$ (200 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified on a silicagel column(20:80 EtOAc:n-Pentane), to yield pure **(1.2)** (3.5167, 49 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.30 (d, $J = 8.44$ Hz, 2 H, H_{Ar}), 6.87 (d, $J = 8.76$ Hz, 2 H, H_{Ar}), 4.80 (t, $J = 6.14$ Hz, 1 H, CH), 3.79 (s, 3 H, CH_3O), 2.61 (t, $J = 2.6$ Hz, 1 H, CH_2), 2.60 (dd, $J = 2.60, 1.60$ Hz, 1 H, CH_2), 2.54 (s, 1 H, OH), 2.05 (t, $J = 2.64$ Hz, 1 H, C≡CH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 159.31 (s, 1 C, MeO**C**$_{Ar}$), 134.78 (s, 1 C, C_{Ar}), 127.05 (s, 2 C, C_{Ar}), 113.83 (s, 2 C, C_{Ar}), 80.89 (s, 1 C, C≡CH), 71.97 (s, 1 C, CH_2), 70.82 (s, 1 C, C≡C−C), 55.26 (s, 1 C, OCH_3), 29.34 (s, 1 C, CH_2).

5.4 Synthesis of the homopropargyl acetal (1.3)

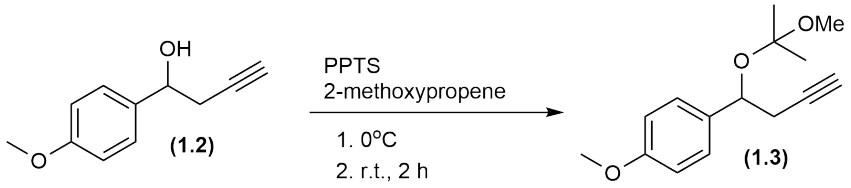


Figure 5.2: Synthesis scheme for **(1.3)**

The alcohol **(1.2)** (1,0858 g, 6,16 mmol) was dissolved in methoxypropene (10 mL) and put on an ice bath. Pyridinium-p-toluensulfonate (50 mg, 3 mol %) was added, under vigorous stirring. After 20 minutes the ice bath was removed, and the reaction continued

for 2 hours and 40 minutes. The mixture was diluted in DCM (200 mL) and washed with deionized water (2×100 mL) and brine(1×100 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified with flash chromatography(silica gel, 2.5 % EtOAc and 0.5 % NEt_3 in n-pentane) to yield 991,0 mg (64 %) pure acetal **(1-3)**.

^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.29 (d, J = 8.64 Hz, 2 H, H_{Ar}), 6.85 (d, J = 8.76 Hz, 2 H, H_{Ar}), 4.79 (d, J = 13.32 Hz, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.11 (s, 3 H, OCH_3), 2.65 (ddd, J = 16.60, 6.11, 2.67 Hz, 1 H, CH_2), 2.50 (ddd, J = 16.59, 7.26, 2.66 Hz, 1 H, CH_2), 1.93 (t, J = 2.64 Hz, 1 H, CH), 1.41 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 158.81 (s, 1 C, MeO**C**$_{Ar}$), 135.76 (s, 1 C, **C**$_{Ar}$), 127.57 (s, 2 C, **C**$_{Ar}$), 113.46 (s, 2 C, C$_{Ar}$), 101.19 (s, 1 C, O**C**O), 81.36 (s, 1 C, CH_2**C**$_{alkyne}$), 71.18 (s, 1 C, HCC$_{Ar}$), 70.11 (s, 1 C, **C**≡CH), 55.15 (s, 1 C, OCH_3), 49.33 (s, 1 C, OCH_3), 29.19 (s, 1 C, CH_2), 25.94 (s, 1 C, CH_3), 25.05 (s, 1 C, CH_3).

5.5 Synthesis of the dihydropyran (1.4)

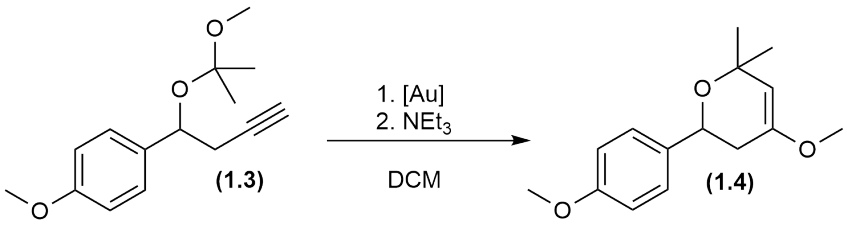


Figure 5.3: Synthesis scheme for **(1.4)**

The acetal **(1.3)** (64.1 mg, 0.258 mmol) was dissolved in DCM (1 mL), in a roundbottom flask, and added the gold catalyst(10.9 mg, 5 mol%) in DCM (1 mL). The red liquid was stirred for 20 minutes, before quenching with 5 drops of NEt_3. The yellow liquid was filtered on a pad of Celite, subsequently flushed with DCM (50 mL). The crude product was obtained by concentrating the filtrate under vacuum. The product was purified with flash chromatography (VersaFlash, 1 % EtOAc in n-pentane), to yield pure pyrane **(1.4)** (33.4 mg, 52 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.32 (d, J = 8.44 Hz, 2 H, H_{Ar}), 6.88 (d, J = 8.76 Hz, 2 H, H_{Ar}), 4.74 (dd, J = 10.84, 3.20 Hz, 1 H, H−2), 4.60 (d, J = 1.96 Hz, 1 H, H−5), 3.79 (s, 3 H, CH_3OC_{Ar}), 3.54 (s, 3 H, CH_3O), 2.37 (ddd, J = 16.10, 10.85, 2.01 Hz, 1 H, H−3), 2.14 (dd, J = 16.11, 3.26 Hz, 1 H, H−3), 1.36 (d, J = 0.68 Hz, 6 H, 2 CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 159.06 (s, 1 C, MeO**C**$_{Ar}$), 152.3 (s, 1 C, C−4), 134.66 (s, 1 C, C$_{Ar}$), 127.51 (s, 1 C, C$_{Ar}$), 113.85 (s, 1 C, C$_{Ar}$), 101.73 (s, 1 C, C−5), 73.44 (s, 1 C, C−6), 70.55 (s, 1 C, C−2), 55.32 (s, 1 C, **C**H$_3$O$_{Ar}$), 54.01 (s, 1 C, CH$_3$O), 35.32 (s, 1 C, C−3), 31.27 (s, 1 C, CCH$_3$), 27.34 (s, 1 C, CCH$_3$),

5.6 Synthesis of the trifluoromethylhomopropargylalcohol(2.2)

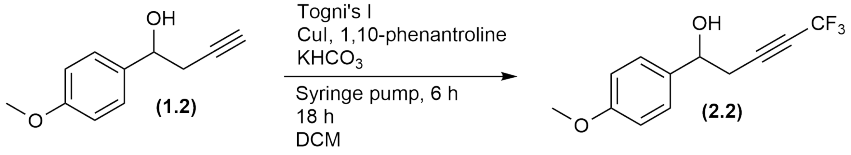


Figure 5.4: Synthesis scheme for **(2.2)**

Togni's reagent I(1.5 eq.), CuI(20 mol%), 1,10-phenantrolin (40 mol%) and $KHCO_3$(2 eq.) was added to a predried Schlenk tube, and the tube was evacuated and flushed with N_2. The reaction was kept under constant N_2-flow. DCM (1.4 mL, dry) was added with a syringe. The homopropargylalcohol **(1.2)** (35 mg, 0.2 mmol) was dissolved in DCM (1.6 mL, dry) and added with a syringe pump over 6 h. The reaction continued for another 18 h, before quenching with NH_4Cl (aq.sat., 3 mL). The mixture was transferred to a separating funnel and added DCM (20 mL) and water (20 mL). The organic phase was further washed with water (2 × 20 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified with flash chromatography (VersaFlash, 1:5 EtOAc in n-pentane). The purified product(34.4 mg, 72 %), a slightly yellow oil, were recovered

^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.30 (d, J = 8.72 Hz, 2 H, H$_{Ar}$), 6.91 (d, J = 8.68 Hz, 2 H, H$_{Ar}$), 4.90 (td, J = 9.06, 3.41 Hz, 1 H, CH), 3.81 (s, 3 H, OCH$_3$), 2.74 (m, J = 3.15 Hz, 2 H, CH$_2$), 2.14 (d, J = 3.36 Hz, 1 H, OH)

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 159.69 (s, MeO**C**$_{Ar}$), 134.04 (s, **C**$_{Ar}$), 126.92 (s, **C**$_{Ar}$), 114.07 (s, COH**C**$_{Ar}$), 113.94 (q, J = 256.62 Hz, **C**F$_3$), 85.71 (q, J = 6.34 Hz, **C**≡CCF$_3$), 71.43 (q, J = 1.46 Hz, **C**H), 70.18 (q, J = 52.21 Hz, **C**CF$_3$), 55.31 (s, O**C**H$_3$), 28.90 (d, J = 1.39 Hz, **C**H$_2$)

5.7 Synthesis of the trifluoromehtylhomopropargylacetal (2.3)

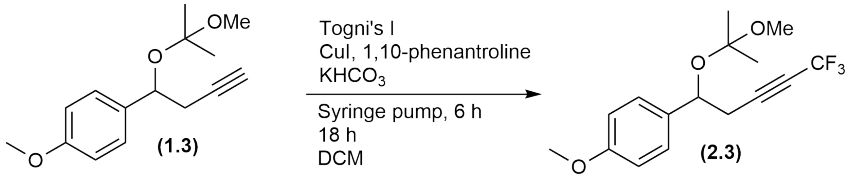


Figure 5.5: Synthesis scheme for **(2.3)**

Togni's reagent I(1.5 eq.), CuI(20 mol%), 1,10-phenantrolin (40 mol%) and $KHCO_3$(2 eq.) was added to a predried Schlenk tube, and the tube was evacuated and flushed with N_2. The reaction was kept under constant N_2-flow. DCM (1.4 mL, dry) was added with a syringe. The homopropargylacetal **(1.3)** (50 mg, 0.2 mmol) was dissolved in DCM (1.6 mL, dry) and added with a syringe pump over 6 h. The reaction continued for another 18 h, before quenching with NH_4Cl (aq.sat., 3 mL). The mixture was transferred to a separating funnel and added DCM (20 mL) and water (20 mL). The organic phase was further washed with water (2 × 20 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified with flash chromatography (VersaFlash, 1:5 EtOAc in n-pentane). The purified product (44.9 mg, 78 %), a colorless oil, were recovered.

^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.26 (d, J = 8.6 Hz, 2 H, H_{Ar}), 6.86 (d, J = 8.64 Hz, 2 H, H_{Ar}), 4.86 (t, J = 6.5 Hz, 1 H, CH), 3.79 (s, 3 H, OMe_{Ar}), 3.11 (s, 3 H, OMe), 2.72 (m, J = 3.46 Hz, 1 H, CH_2), 2.59 (m, J = 3.39 Hz, 1 H, CH_2), 1.41 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3)

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 159.11 (s, $MeOC_{Ar}$), 135.05 (s, C_{Ar}), 127.26 (s, C_{Ar}), 114 (q, J = 256.37 Hz, CF_3), 113.7 (s, C_{Ar}), 101.43 (s, OCO), 86.55 (q, J = 6.35 Hz, C≡CCF_3), 70.21 (q, J = 1.3 Hz, CH), 69.69 (q, J = 51.97 Hz, CCF_3), 55.16 (s, OMe_{Ar}), 49.35 (s, OMe), 29.03 (q, J = 1.65 Hz, CH_2), 25.90 (s, CH_3), 24.90 (s, CH_3)

5.8 Synthesis of the trifluoromethylhomoporpargylether (2.4)

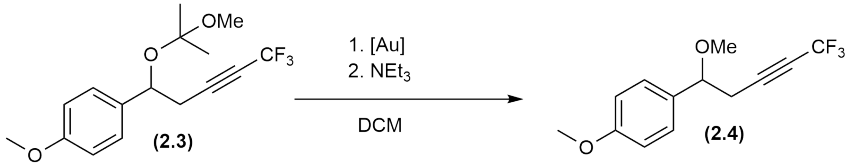


Figure 5.6: Synthesis scheme for **(2.4)**

The trifluoromethylacetal **(2.3)** (20 mg) was dissolved in DCM(0.5 mL) and added a solution of [Au] catalyst (10 mg, 20 mol %) in DCM(0.5 mL) in a pressure resistant tube (Ace-glass, 2.5 mL, 150 psi). The tube was sealed and heated with a heat-gun until the solvent boiled inside the tube. By carefully heating the tube the reaction was kept at boiling temperature inside the pressure vessel for 5 minutes. The tube was rapidly cooled under running water and TLC showed full conversion of the starting material **(2.3)**. The crude material was purified with flash chromatography (VersaFlash, 2.5 % EtOAc in n-pentane) to yield a colorless oil (11.7 mg, 48 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.26 (d, J = 8.6 Hz, 2 H, H_{Ar}), 6.93 (d, J = 8.68 Hz, 2 H, H_{Ar}), 4.33 (t, J = 6.44 Hz, 1 H, CH), 3.84 (s, 3 H, OCH_3), 3.27 (s, 3 H, OCH_3), 2.78 (m, J = 3.46 Hz, 1 H, CH_2), 2.65 (m, J = 3.37 Hz, 1 H, CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 159.69 (s, $MeOC_{Ar}$), 131.58 (s, C_{Ar}), 127.71 (s, C_{Ar}), 113.99 (s, C_{Ar}), 113.98 (q, J = 256.36 Hz, CF_3), 85.89 (q, J = 6.5 Hz, C≡CCF_3), 80.32 (q, J = 1.46 Hz, CH), 69.13 (q, J = 52.19 Hz, CCF_3), 56.81 (s, OMe), 55.28 (s, OMe_{Ar}), 27.83 (q, J = 1.76 Hz, CH_2)

5.9 Gold catalyzed reaction with phenylacetylene (3.1)

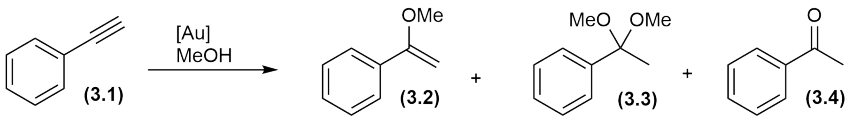


Figure 5.7: Synthesis scheme for [Au] catalyzed reaction with **(3.1)**

Phenylacetylene (100 mg, 0.86 mmol) was dissolved in MeOH (1 mL) and added a solution of [Au]-catalyst (33 mg, 5 mol%) in DCM (1 mL). The reaction continued for 8 hours while monitored by TLC. When TLC showed formation of all three products **(3.2, 3.3, 3.4)** the reaction was quenched with 5 drops of NEt_3 and concentrated under vacuum. The mixture of products were separated with flash chromatography(VersaFlash, 2.5 % EtOAc in n-pentane).

5.9.1 Characterization of 1,1-dimethoxyethylbenzene (3.3)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.49 (d, J = 7.98 Hz, 2 H, H_{Ar}), 7.35 (t, J = 7.83 Hz, 2 H, H_{Ar}), 7.28 (t, J = 7.32 Hz, 1 H, H_{Ar}), 3.19 (s, 6 H, OCH_3), 1.54 (s, 3 H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ(ppm) 142.75 (s, C_{Ar}), 127.94 (s, C_{Ar}), 127.39 (s, C_{Ar}), 126.10 (s, C_{Ar}), 101.53 (s, C_q), 48.83 (s, OCH_3), 25.96 (s, CH_3).

5.9.2 Characterization of acetophenone (3.4)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.97 (d, $J = 8.04$ Hz, 2 H, H_{Ar}), 7.57 (t, $J = 7.41$ Hz, 1 H, H_{Ar}), 7.47 (t, $J = 7.86$ Hz, 2 H, H_{Ar}), 2.61 (s, 3 H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ(ppm) 198.07 (s, C=O), 137.08 (s, C_{Ar}), 133.02 (s, C_{Ar}), 128.50 (s, C_{Ar}), 128.24 (s, C_{Ar}), 26.53 (s, CH_3).

5.10 Synthesis of (3,3,3-trifluoroprop-1-yn-1-yl)benzene (4.1)

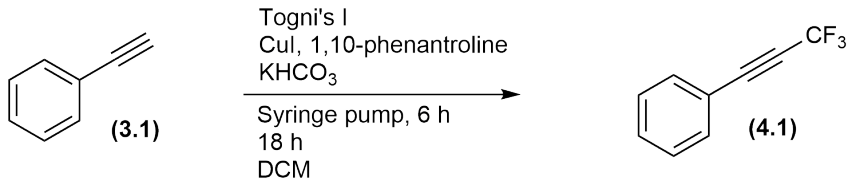


Figure 5.8: Synthesis scheme for **(4.1)**

Togni's reagent I(1.5 eq.), CuI(20 mol%), 1,10-phenantrolin (40 mol%) and $KHCO_3$(2 eq.) was added to a predried Schlenk tube, and the tube was evacuated and flushed with N_2. The reaction was kept under constant N_2-flow. DCM (1.4 mL, dry) was added with a syringe. Phenylacetylene **(3.1)** (20 mg, 0.2 mmol) was dissolved in DCM (1.6 mL, dry) and added with a syringe pump over 6 h. The reaction continued for another 18 h, before quenching with NH_4Cl (aq.sat., 3 mL). The mixture was transferred to a separating funnel and added DCM (20 mL) and water (20 mL). The organic phase was further washed with water (2 $\times$ 20 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified with flash chromatography (VersaFlash, 1:5 EtOAc in n-pentane). The purified product (8 mg, 38 %), a colorless oil, were recovered.

^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.56 (d, $J = 7.12$ Hz, 2 H, H_{Ar}), 7.47 (t, $J = 7.5$ Hz, 1 H, H_{Ar}), 7.39 (t, $J = 7.46$ Hz, 2 H, H_{Ar}).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 132.43 (d, $J = 1.23$ Hz, C_{Ar}), 130.85 (s, C_{Ar}), 128.63 (s, C_{Ar}), 118.53 (q, $J = 1.91$ Hz, C_{Ar}), 114.85 (q, $J = 256.64$ Hz, CF_3), 86.51 (q, $J = 6.37$ Hz, C$\equiv$CCF_3), 75.71 (q, $J = 53.04$ Hz, CCF_3).

5.11 Gold catalyzed reaction with (3,3,3-trifluoroprop-1-yn-1-yl)benzene (4.1)

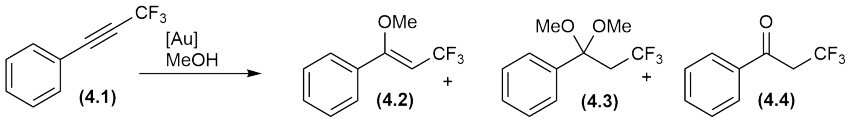


Figure 5.9: Synthesis scheme for [Au] catalyzed reaction with **(4.1)**

Phenylacetylene (100 mg, 0.86 mmol) was dissolved in MeOH (1 mL) and added a solution of [Au]-catalyst (33 mg, 5 mol%) in DCM (1 mL). The reaction continued for 8 hours while monitored by TLC. When TLC showed formation of all three products **(3.2, 3.3, 3.4)** the reaction was quenched with 5 drops of NEt_3 and concentrated under vacuum. The mixture of products were separated with flash chromatography(VersaFlash, 2.5 % EtOAc in n-pentane). **(4.2)** (E/Z) and **(4.3)** eluted together (116 mg) and NMR analysis was performed on a mixture. Proton NMR are reported below, while carbon spectra are given in Appendix K. The ketone (8 mg) was also isolated.

5.11.1 Characterization of (3,3,3-trifluoro-1-methoxyprop-1-en-1-yl)benzene (4.2)

E-isomer:^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.41 (m, J = 7.26 Hz, 5 H, H_{Ar}), 4.96 (q, J = 7.66 Hz, 4 H, CH), 3.75 (s, 2 H, OCH_3). Z-isomer:^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.41 (m, J = 7.26 Hz, 5 H, H_{Ar}), 5.27 (q, J = 7.8 Hz, 1 H, CH), 3.62 (s, 3 H, OCH_3).

5.11.2 Characterization of (3,3,3-trifluoro-1,1-dimethoxypropyl)benzene (4.3)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.41 (m, J = 7.26 Hz, 5 H, H_{Ar}), 3.18 (s, 6 H, OCH_3), 2.81 (q, J = 10.44 Hz, 2 H, CH_2).

5.11.3 Characterization of 3,3,3-trifluoro-1-phenylpropan-1-one (4.4)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.94 (d, J = 7.98 Hz, 2 H, H_{Ar}), 7.64 (t, J = 7.23 Hz, 1 H, H_{Ar}), 7.52 (t, J = 7.71 Hz, 2 H, H_{Ar}), 3.80 (q, J = 9.88 Hz, 2 H, CH_2).

^{13}C-NMR (150 MHz, $CDCl_3$): δ(ppm) 189.68 (q, J = 2.41 Hz, C=O), 135.84 (q, J = 1.75 Hz, C_{Ar}), 134.20 (s, C_{Ar}), 128.95 (s, C_{Ar}), 128.37 (s, C_{Ar}), 123.99 (q, J = 276.96 Hz, CF_3), 42.13 (q, J = 28.3 Hz, CH_2).

5.12 Gold catalyzed reaction with ethynyltoluene (5.1)

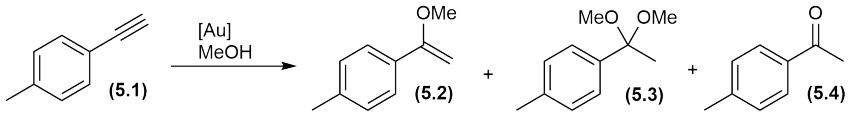


Figure 5.10: Synthesis scheme for [Au] catalyzed reaction with **(5.1)**

Ethynyltoluene (100 mg, 0.86 mmol) was dissolved in MeOH (1 mL) and added a solution of [Au]-catalyst (33 mg, 5 mol%) in DCM (1 mL). The reaction continued for 8 hours while monitored by TLC. When TLC showed formation of all three products **(3.2, 3.3, 3.4)** the reaction was quenched with 5 drops of NEt_3 and concentrated under vacuum. The mixture of products were separated with flash chromatography(VersaFlash, 2.5 % EtOAc in n-pentane).

5.12.1 Characterization of 1-(1,1-dimethoxyethyl)-4-methylbenzene (5.3)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.37 (d, $J = 8.28$ Hz, 2 H, H_{Ar}), 7.15 (d, $J = 7.44$ Hz, 2 H, H_{Ar}), 3.17 (s, 6 H, OCH_3), 2.33 (s, 3 H, CH_3C_{Ar}), 1.52 (s, 3 H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ(ppm) 139.99 (s, C_{Ar}), 137.12 (s, C_{Ar}), 128.78 (s, C_{Ar}), 126.20 (s, C_{Ar}), 101.69 (s, C_q), 48.89 (s, OCH_3), 26.13 (s, CH_3), 21.08 (s, CH_3C_{Ar}).

5.12.2 Characterization of 1-(p-tolyl)ethan-1-one (5.4)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.86 (d, $J = 8.16$ Hz, 2 H, H_{Ar}), 7.26 (d, $J = 7.98$ Hz, 2 H, H_{Ar}), 2.58 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3C_{Ar}).

^{13}C-NMR (150 MHz, $CDCl_3$): δ(ppm) 197.86 (s, C=O), 143.88 (s, C_{Ar}), 134.74 (s, C_{Ar}), 129.25 (s, C_{Ar}), 128.45 (s, C_{Ar}), 26.53 (s, CH_3), 21.64 (s, CH_3C_{Ar}).

5.13 Synthesis of (3,3,3-trifluoroprop-1-yn-1-yl)toluene (6.1)

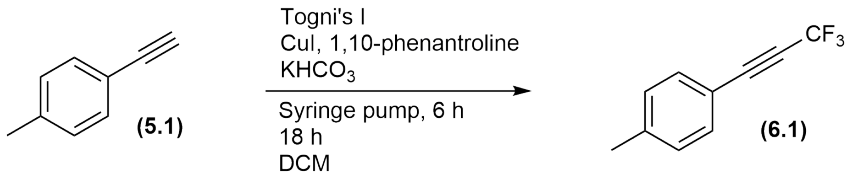


Figure 5.11: Synthesis scheme for **(6.1)**

Togni's reagent I(358 mg, 1.5 eq.), CuI(33 mg, 20 mol%), 1,10-phenantrolin (61.9 mg, 40 mol%) and $KHCO_3$(172 mg, 2 eq.) was added to a predried Schlenk tube, and the tube was evacuated and flushed with N_2. The reaction was kept under constant N_2-flow. DCM (1.4 mL, dry) was added with a syringe. Etynyltoluene **(1.2)** (100 mg) was dissolved in DCM (1.6 mL, dry) and added with a syringe pump over 6 h. The reaction continued for another 18 h, before quenching with NH_4Cl (aq.sat., 3 mL). The mixture was transferred to a separating funnel and added DCM (20 mL) and water (20 mL). The organic phase was further washed with water (2 × 20 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified with flash chromatography (VersaFlash, 1:5 EtOAc in n-pentane). The purified product (116 mg, 73 %), a colorless oil were recovered.

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.44 (d, J = 8.1 Hz, 2 H, H_{Ar}), 7.19 (d, J = 8.34 Hz, 2 H, H_{Ar}), 2.39 (s, 3 H, CH_3C_{Ar}).

^{13}C-NMR (150 MHz, $CDCl_3$): δ(ppm) 141.47 (s, C_{Ar}), 132.35 (s, C_{Ar}), 129.41 (s, C_{Ar}), 115.43 (q, J = 1.88 Hz, C_{Ar}), 114.95 (q, J = 256.57 Hz, CF_3), 86.94 (q, J = 6.42 Hz, C≡CCF_3), 75.24 (q, J = 52.38 Hz, CCF_3), 21.69 (s, CH_3).

5.14 Gold catalyzed reaction with (3,3,3-trifluoroprop-1-yn-1-yl)toluene (6.1)

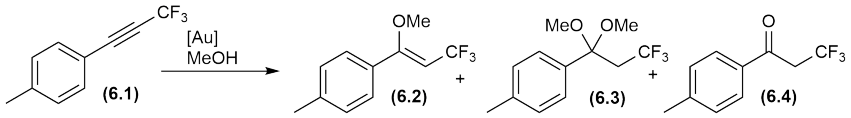


Figure 5.12: Synthesis scheme for [Au] catalyzed reaction with **(6.1)**

(3,3,3-trifluoroprop-1-yn-1-yl)toluene (87 mg, 0.47 mmol) was dissolved in MeOH (1 mL) and added a solution of [Au]-catalyst (18 mg, 5 mol%) in DCM (1 mL). The reaction continued for 10 hours while monitored by TLC. When TLC showed formation of the ketone **(3.4)** the reaction was quenched with 5 drops of NEt_3 and concentrated under vacuum. The mixture of products were separated with flash chromatography(VersaFlash, 2.5 % EtOAc in n-pentane). Yielding two fractions with enol ether **(6.2)** / acetal **(6.3)** mixture (125 mg) proton NMR are reported below, while carbon spectra are given in Appendix S. The ketone **(6.4)** (9 mg) was also isolated.

5.14.1 Characterization of (3,3,3-trifluoro-1-methoxyprop-1-en-1-yl)toluene (6.2)

E-isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.27 (s, 4 H, H_{Ar}), 4.92 (q, J = 7.7 Hz, 1 H, CH), 3.73 (s, 3 H, OCH_3), 2.37 (s, 3 H, CH_3C_{Ar}).

Z-isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.27 (s, 4 H, H_{Ar}), 5.24 (q, J = 7.82 Hz, 1 H, CH), 3.61 (s, 3 H, OCH_3), 2.39 (s, 3 H, CH_3C_{Ar}).

5.14.2 Characterization of (3,3,3-trifluoro-1,1-dimethoxypropyl)toluene (6.3)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.27 (s, 4 H, H_{Ar}), 3.16 (s, 6 H, OCH_3), 2.79 (q, J = 10.48 Hz, 2 H, CH_2), 2.35 (s, 3 H, CH_3C_{Ar})

5.14.3 Characterization of 3,3,3-trifluoro-1-(p-tolyl)propan-1-one (6.4)

^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.83 (d, J = 8.28 Hz, 2 H, H_{Ar}), 7.30 (d, J = 8.46 Hz, 2 H, H_{Ar}), 3.76 (q, J = 10.04 Hz, 2 H, CH_2), 2.44 (s, 3 H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ(ppm) 189.28 (q, J = 2.03 Hz, CH_3C_{Ar}), 145.3 (s, C_{Ar}), 133.44 (s, C_{Ar}), 129.62 (s, C_{Ar}), 128.53 (s, C_{Ar}), 124.06 (q, J = 276.58 Hz, CF_3), 42.03 (q, J = 28.09 Hz, CH_2), 21.74 (s, CH_3).

5.15 General procedure for small scale reactivity testing

Four stock solutions in DCE were prepared, as shown in table 5.1. A vial with the alkyne and MeOH solution was prepared. For the 0 °C reactions the vials were precooled in an ice bath. Then the solution of [Au]-catalyst was added and a screw top lid applied. The vial was kept at the appropriate temperature for the duration of the experiment. The reactions were quenched by adding 100 μL of the quenching solution. The water phase separated out and 0.5 mL of the reaction mixture was diluted to 1 mL with DCM. The diluted solution was analyzed by GC, at a low temperature program. The results from the screening are given in detail in Appendix B.

5.16 Purification of nitromethane

A roundbottomflask with nitromethane (200 mL) was added CaH_2 (40 g) under a nitrogen stream. The flask was attached a distillation apparatus with a vigreux column (20 cm) and a oil bath (135 °C). After the first 1-2 mL had been distilled the collection flask was attached, containing predried molecular sieves (4 Å). The distillation continued until most

Table 5.1: Showing stock solutions an volumes

	Volume per reaction	
Substrate	**(5.1)**	**(6.1)**
Alkyne/IS (5 mg/mL + 1.4 mg/mL)	1 mL	1 mL
MeOH (1:4)	22 μL	35 μL
[Au] (10 mg/mL)	21 μL/%[cat]	33 μL/%[cat]
Quenching solution (1:1:1 NEt_3:aceton:Water)	100 μL	100 μL

of the nitromethane had been distilled. The flask containing the purified nitromethane, was closed with a septum and covered in aluminum foil.

5.17 Purification of dichloroethane

200 mL of 1,2-dichloroethane was sequentially washed with H_2SO_4 (50 mL, conc.) , water (50 mL, deionized), aqueous $NaHCO_3$ (50 mL, sat.) and water (50 mL, deionized). The dichloroethane phase was then refluxed with CaH_2 for 30 minutes, before distillation. The purified solvent was stored over predried molecular sieves (4Å).

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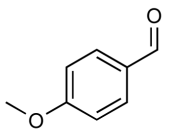
Appendix

A List of numbered compounds

For the readers convenience this list with numbers and structures of the most important molecules is presented.



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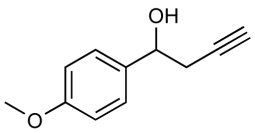

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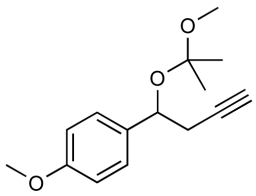

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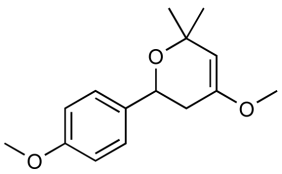

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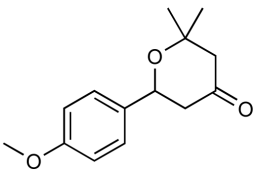

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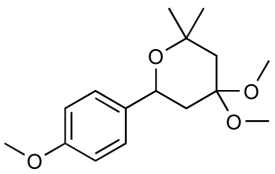

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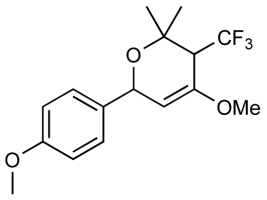

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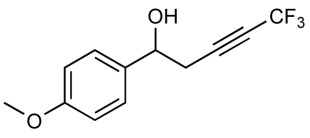

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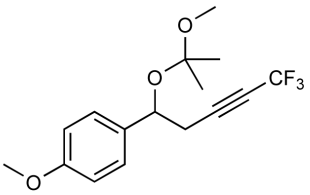

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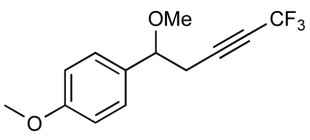

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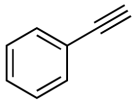

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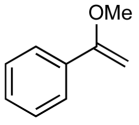

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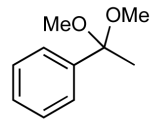

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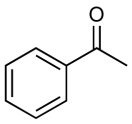

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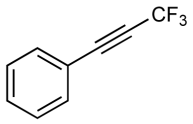

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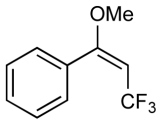

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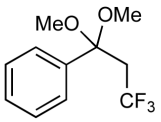

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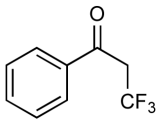

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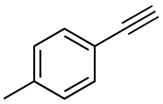
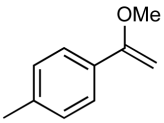


(5.1)



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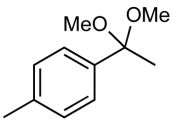

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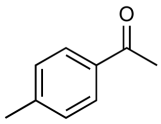

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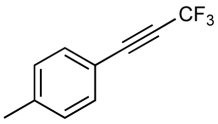
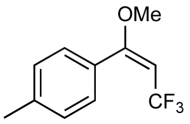


(6.1)



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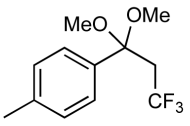

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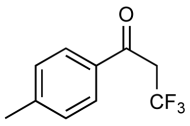


(6.4)

B GC-results from reactivity testing

B.1 Catalyst and temperatur testing for 5.1

Reaction conditions: Terminal alkyne, 30 minutes reaction time, variable temperature and catalyst loading

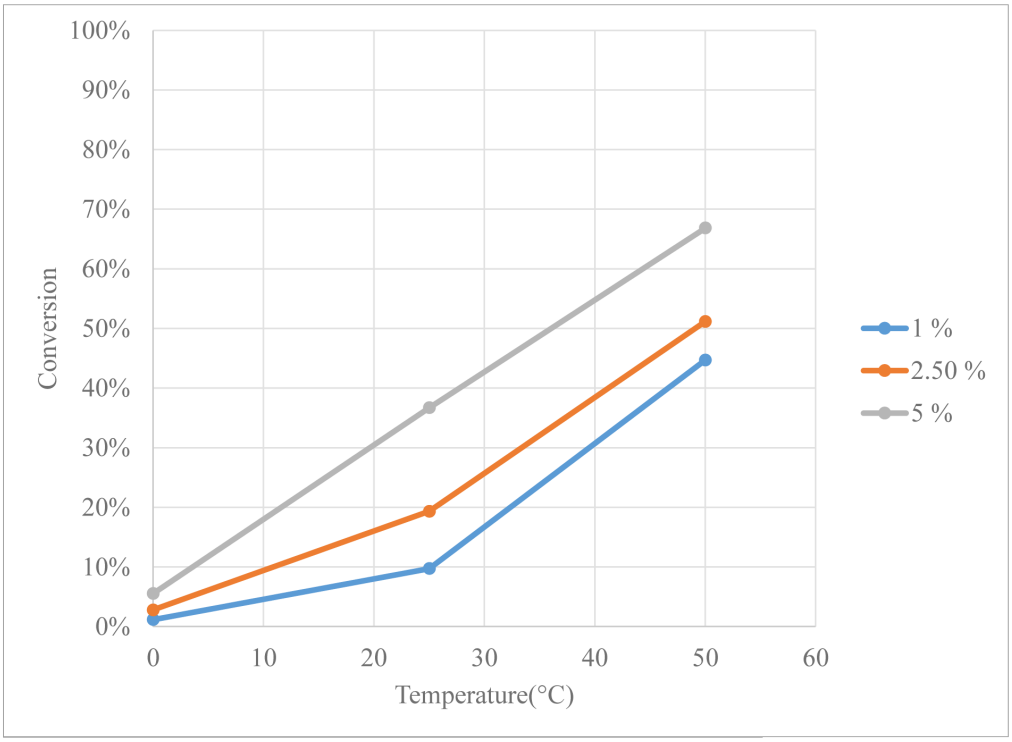


Figure B.1: Showing the total yield as a function of temperature

Table B.1: Showing the calculated concentrations from GC results.

[Au]	Temp	Remaining 5.1	5.2	5.3	5.4	Total yield
1.0 %	0	98.82 %	0.00 %	1.18 %	0.00 %	1.18 %
1.0 %	25	90.28 %	0.00 %	9.72 %	0.00 %	9.72 %
1.0 %	50	55.30 %	0.00 %	44.70 %	0.00 %	44.70 %
2.5 %	0	97.20 %	0.00 %	2.80 %	0.00 %	2.80 %
2.5 %	25	80.66 %	0.20 %	12.47 %	6.67 %	19.34 %
2.5 %	50	48.82 %	1.55 %	15.26 %	30.36 %	47.16 %
5.0 %	0	94.45 %	0.00 %	5.55 %	0.00 %	5.55 %
5.0 %	25	63.29 %	0.67 %	17.35 %	18.69 %	36.71 %
5.0 %	50	33.16 %	1.99 %	20.40 %	33.81 %	56.21 %

B.2 Catalyst and temperatur testing for 6.1

Reaction conditions: CF_3-alkyne, 30 minutes reaction time, variable temperature and catalyst loading

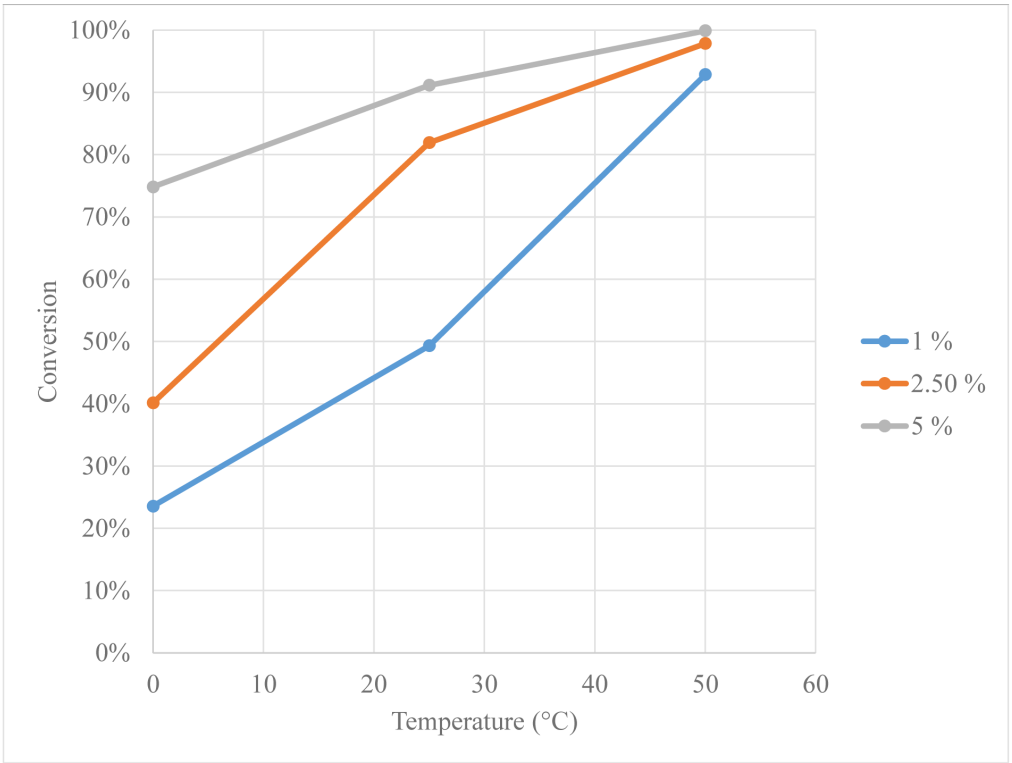


Figure B.2: Showing the total yield as a function of temperature

Table B.2: Showing the calculated concentrations from GC results.

[Au]	Temp	Remaining 6.1	6.2	6.3	6.4	Total yield
1.0 %	0	76.44 %	22.98 %	0.53 %	0.04 %	23.56 %
1.0 %	25	50.69 %	47.83 %	1.36 %	0.12 %	49.31 %
1.0 %	50	7.14 %	68.54 %	17.98 %	6.34 %	92.86 %
2.5 %	0	59.87 %	39.10 %	0.57 %	0.46 %	40.13 %
2.5 %	25	18.08 %	80.32 %	1.32 %	0.28 %	81.92 %
2.5 %	50	2.15 %	92.74 %	4.44 %	0.67 %	97.85 %
5.0 %	0	25.18 %	73.25 %	1.34 %	0.23 %	74.82 %
5.0 %	25	8.84 %	88.93 %	1.78 %	0.45 %	91.16 %
5.0 %	50	0.10 %	60.52 %	21.24 %	18.15 %	99.90 %

B.3 Reaction rate and selectivity monitoring 5.1

Reaction conditions: Terminal alkyne, 2.5 % catalyst, 0 °C, variable time

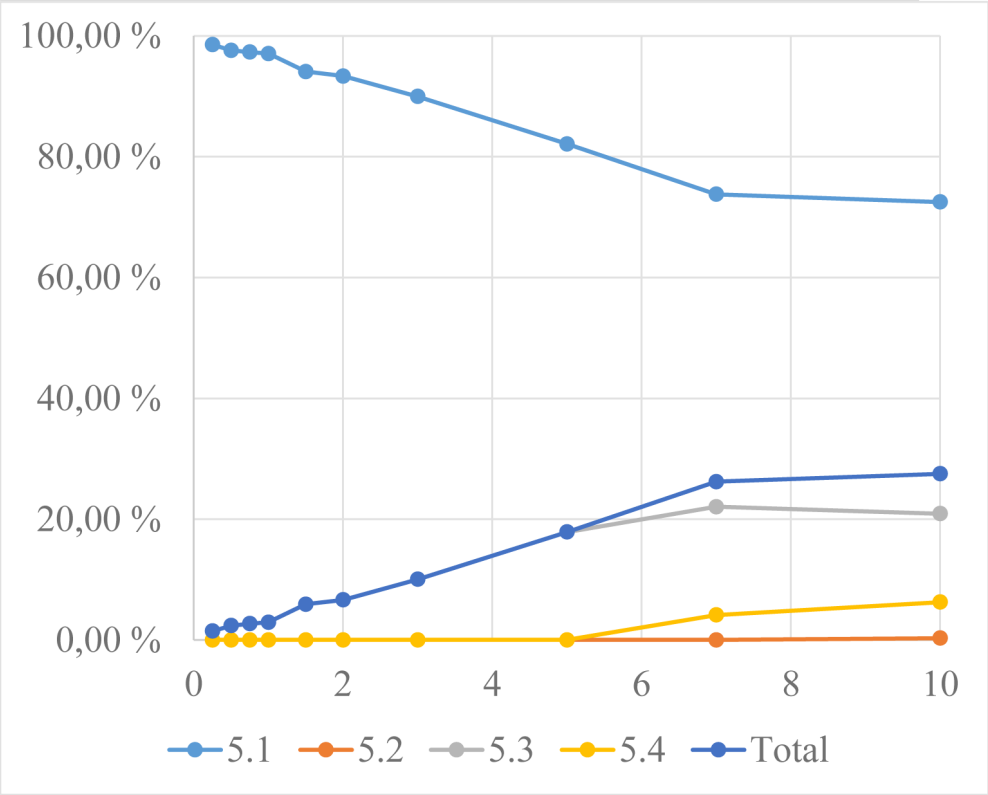


Figure B.3: Showing the relative concentrations of compounds at the given hours.

Table B.3: Showing the calculated concentrations from GC results.

Hours	Remaning 5.1	5.2	5.3	5.4	Total yield
0.25	98.53 %	0.00 %	1.47 %	0.00 %	1.47 %
0.5	97.60 %	0.00 %	2.40 %	0.00 %	2.40 %
0.75	97.30 %	0.00 %	2.70 %	0.00 %	2.70 %
1	97.07 %	0.00 %	2.93 %	0.00 %	2.93 %
1.5	94.09 %	0.00 %	5.91 %	0.00 %	5.91 %
2	93.36 %	0.00 %	6.64 %	0.00 %	6.64 %
3	89.96 %	0.00 %	10.04 %	0.00 %	10.04 %
5	82.11 %	0.00 %	17.89 %	0.00 %	17.89 %
7	73.78 %	0.00 %	22.06 %	4.15 %	26.22 %
10	72.50 %	0.31 %	20.92 %	6.27 %	27.50 %

B.4 Reaction rate and selectivity monitoring 6.1

Reaction conditions: CF_3-alkyne, 2.5 % catalyst, 0 °C

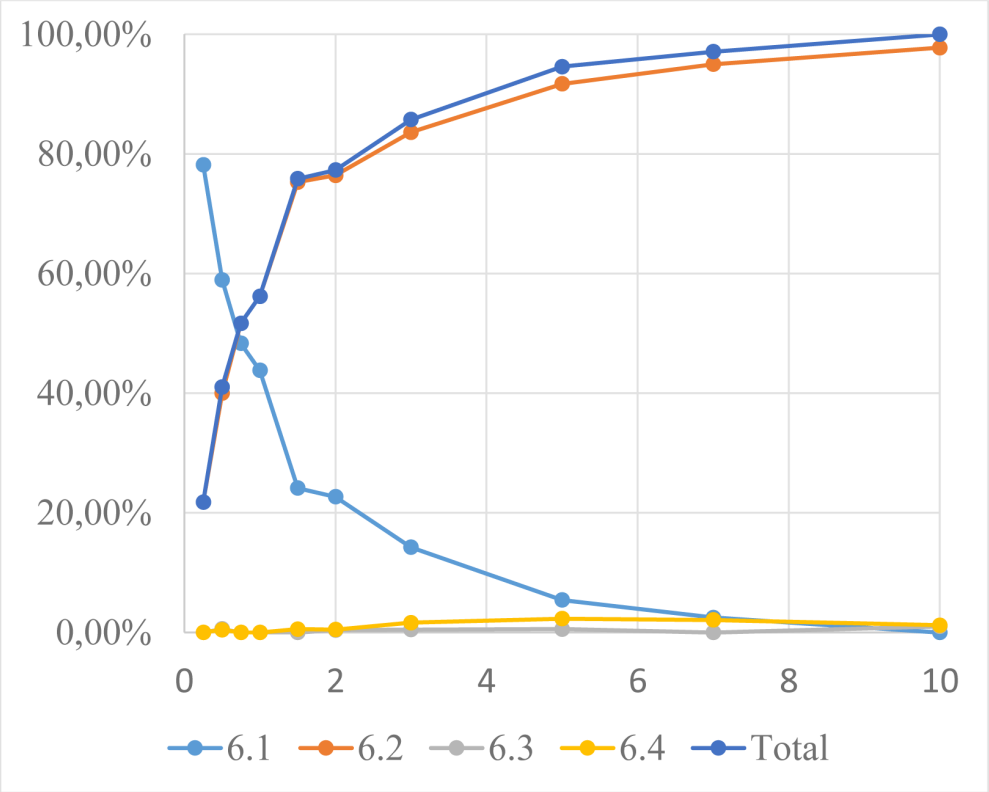


Figure B.4: Showing the relative concentrations of compounds at the given hours.

Table B.4: Showing the calculated concentrations from GC results.

Hours	Remaining 6.1	6.2	6.3	6.4	Total yield
0.25	78.20 %	21.80 %	0.00 %	0.00 %	21.80 %
0.5	58.95 %	39.99 %	0.59 %	0.47 %	41.05 %
0.75	48.32 %	51.68 %	0.00 %	0.00 %	51.68 %
1	43.81 %	56.19 %	0.00 %	0.00 %	56.19 %
1.5	24.14 %	75.28 %	0.00 %	0.58 %	75.86 %
2	22.70 %	76.41 %	0.40 %	0.49 %	77.30 %
3	14.24 %	83.61 %	0.50 %	1.65 %	85.76 %
5	5.42 %	91.71 %	0.56 %	2.32 %	94.58 %
7	2.50 %	95.00 %	0.00 %	2.09 %	97.09 %
10	0.00 %	97.77 %	1.01 %	1.22 %	100.00 %

B.5 Reaction rate and selectivity monitoring 5.1

Reaction conditions: Terminal alkyne, 1 % catalyst, 25 °C

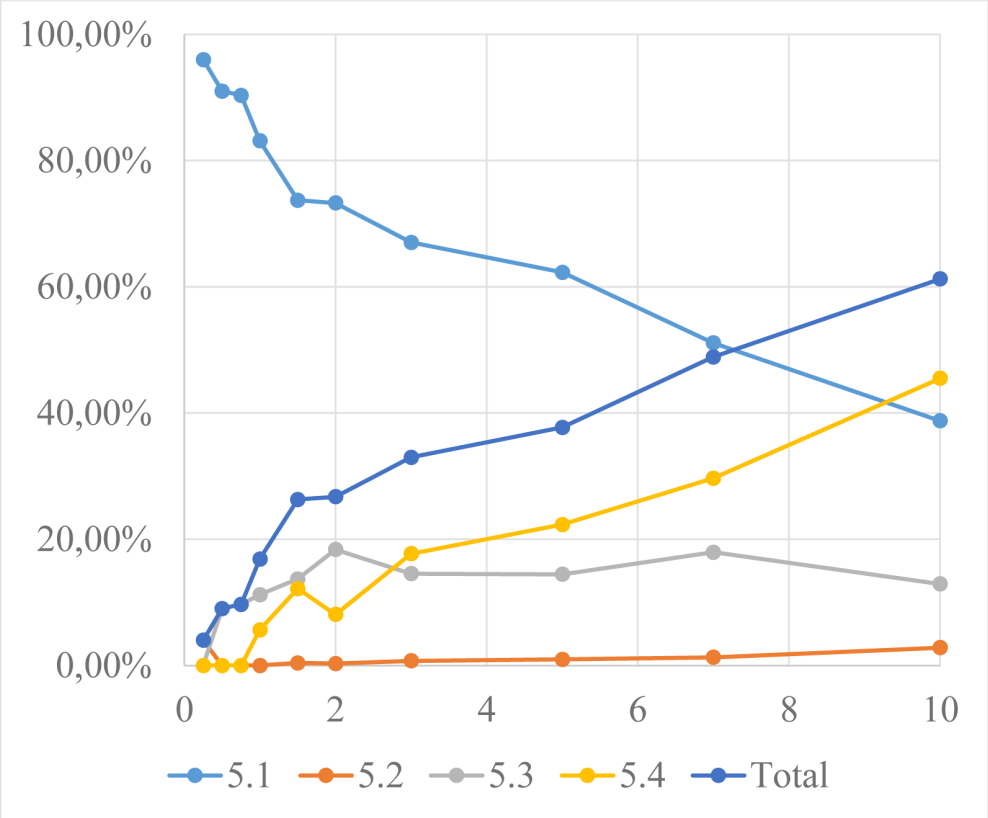


Figure B.5: Showing the relative concentrations of compounds at the given hours.

Table B.5: Showing the calculated concentrations from GC results.

Hours	Remaining 5.1	5.2	5.3	5.4	Total yield
0.25	96.00 %	4.00 %	0.00 %	0.00 %	4.00 %
0.5	90.98 %	0.00 %	9.02 %	0.00 %	9.02 %
0.75	90.32 %	0.00 %	9.68 %	0.00 %	9.68 %
1	83.13 %	0.00 %	11.22 %	5.66 %	16.87 %
1.5	73.70 %	0.41 %	13.70 %	12.19 %	26.30 %
2	73.27 %	0.29 %	18.36 %	8.08 %	26.73 %
3	67.03 %	0.72 %	14.53 %	17.71 %	32.97 %
5	62.28 %	0.95 %	14.45 %	22.31 %	37.72 %
7	51.11 %	1.28 %	17.95 %	29.67 %	48.89 %
10	38.77 %	2.82 %	12.92 %	45.49 %	61.23 %

B.6 Reaction rate and selectivity monitoring 6.1

Reaction conditions: CF_3-alkyne, 1 % catalyst, 25 °C

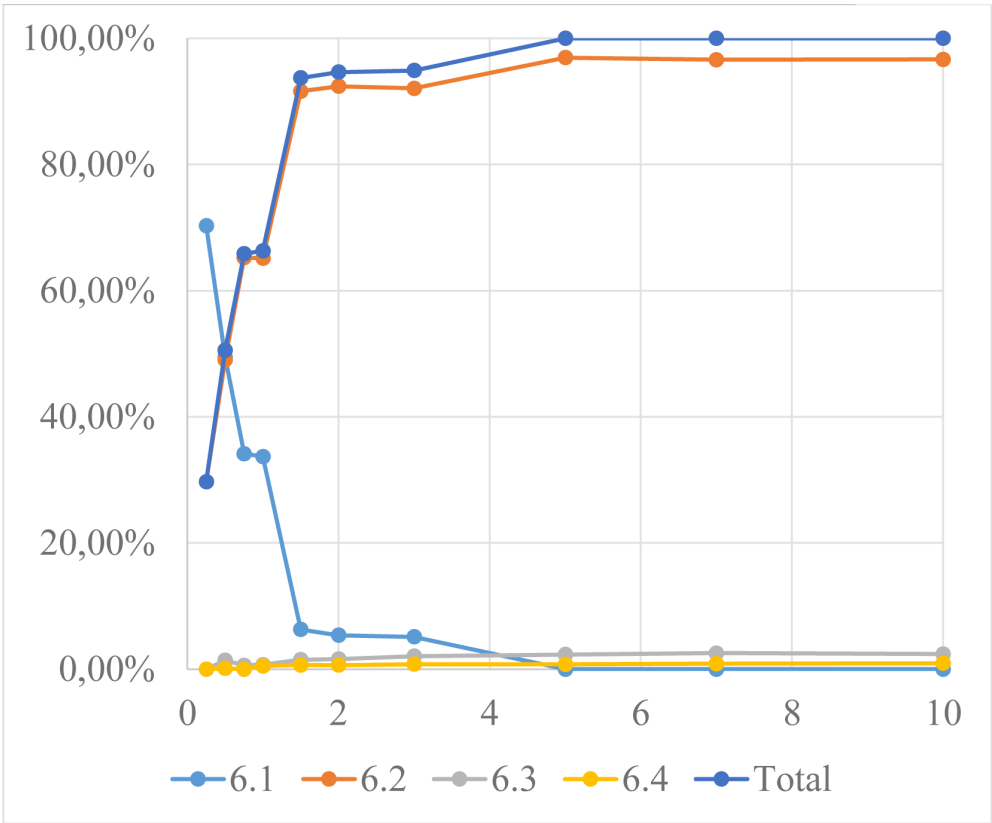


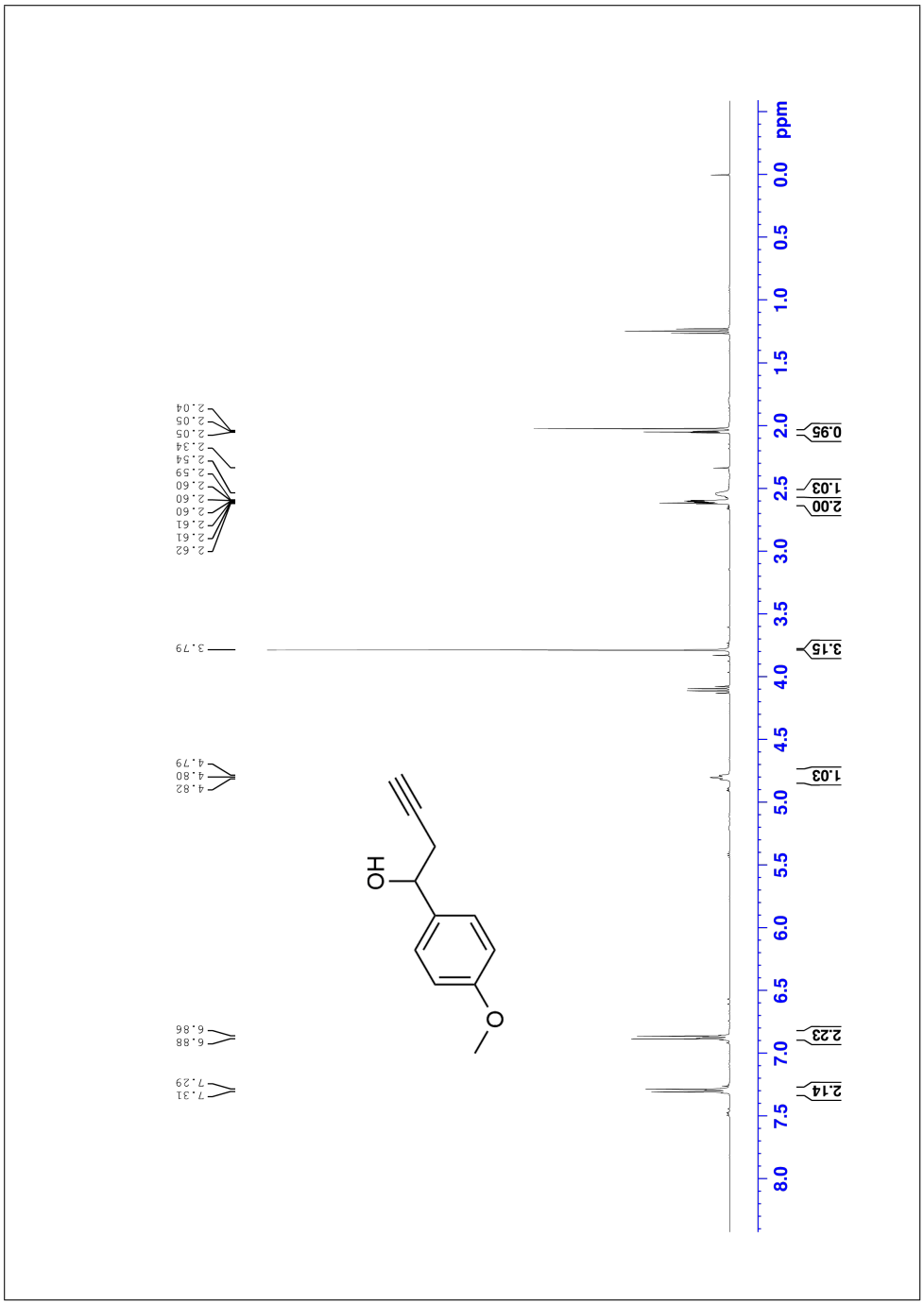
Figure B.6: Showing the relative concentrations of compounds at the given hours.

Table B.6: Showing the calculated concentrations from GC results.

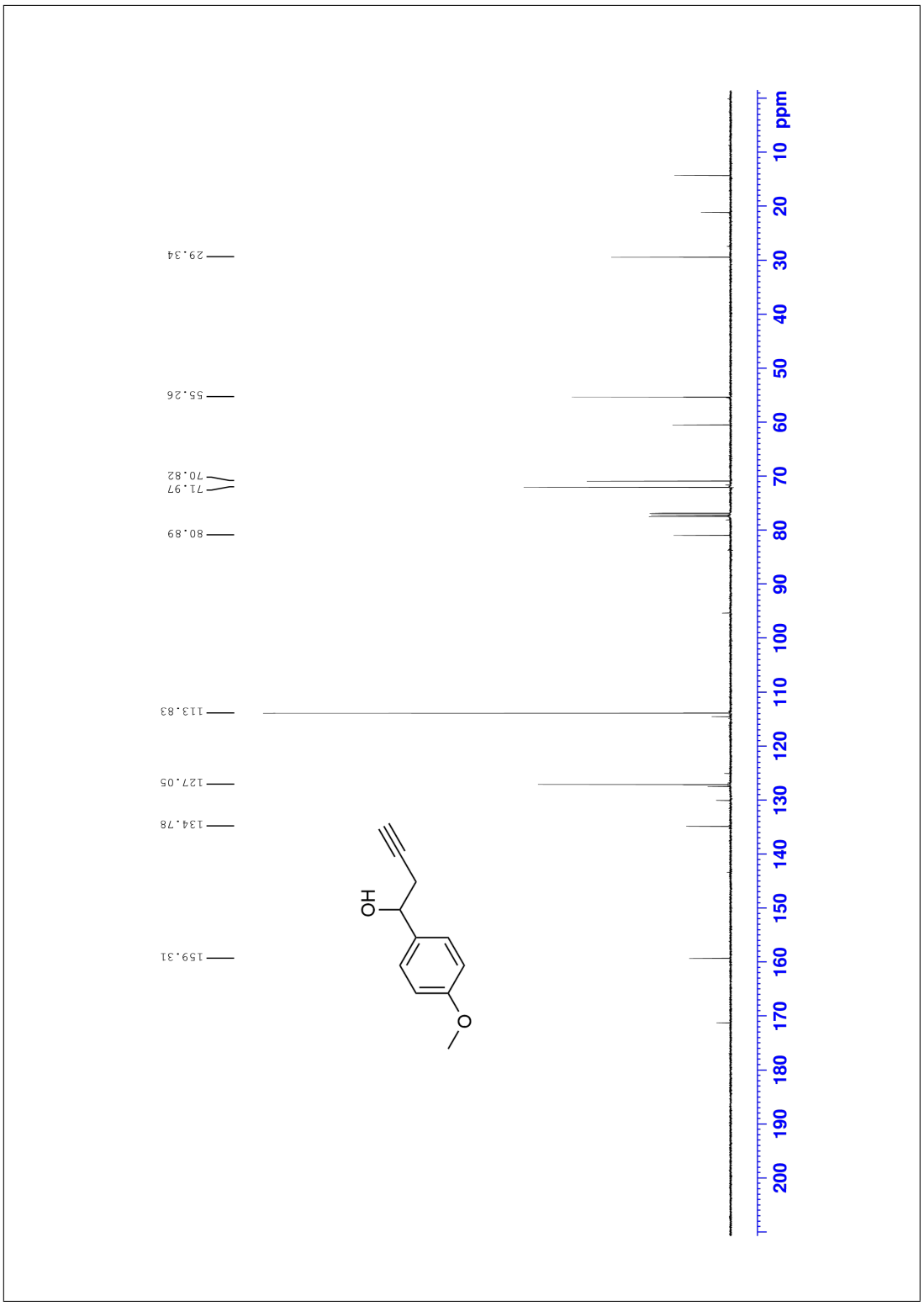
Hours	Remaining 6.1	6.2	6.3	6.4	Total yield
0.25	70.29 %	29.71 %	0.00 %	0.00 %	29.71 %
0.5	49.43 %	49.05 %	1.40 %	0.12 %	50.57 %
0.75	34.15 %	65.25 %	0.60 %	0.00 %	65.85 %
1	33.69 %	65.12 %	0.69 %	0.49 %	66.31 %
1.5	6.28 %	91.60 %	1.48 %	0.64 %	93.72 %
2	5.37 %	92.39 %	1.60 %	0.64 %	94.63 %
3	5.11 %	92.06 %	2.05 %	0.79 %	94.89 %
5	0.00 %	96.94 %	2.31 %	0.75 %	100.00 %
7	0.00 %	96.60 %	2.53 %	0.87 %	100.00 %
10	0.00 %	96.67 %	2.39 %	0.94 %	100.00 %

C Characterisation of compound (1.2)

C.1 Compound 1.2 ^{1}H-NMR

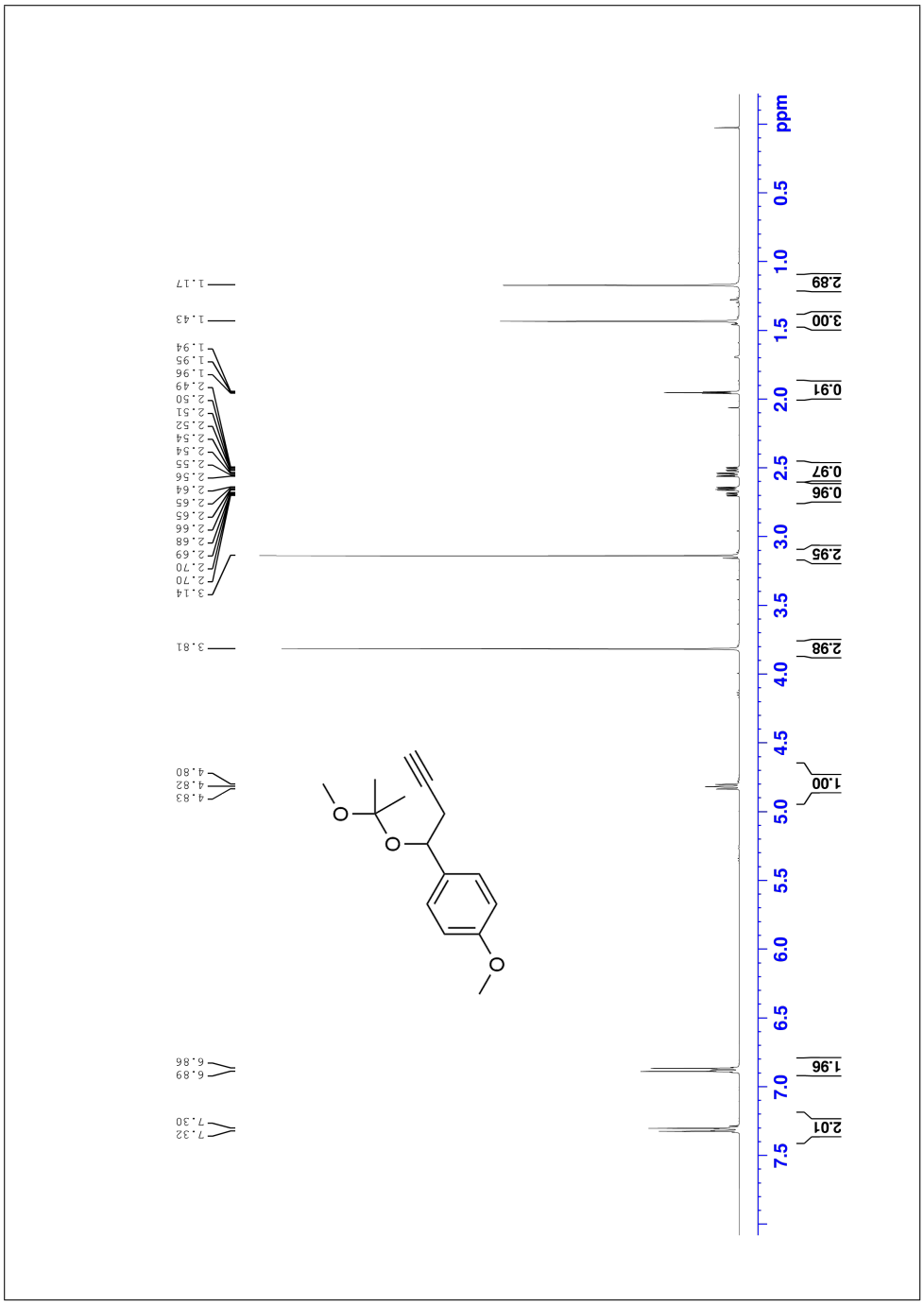


C.2 Compound 1.2 ^{13}C-NMR

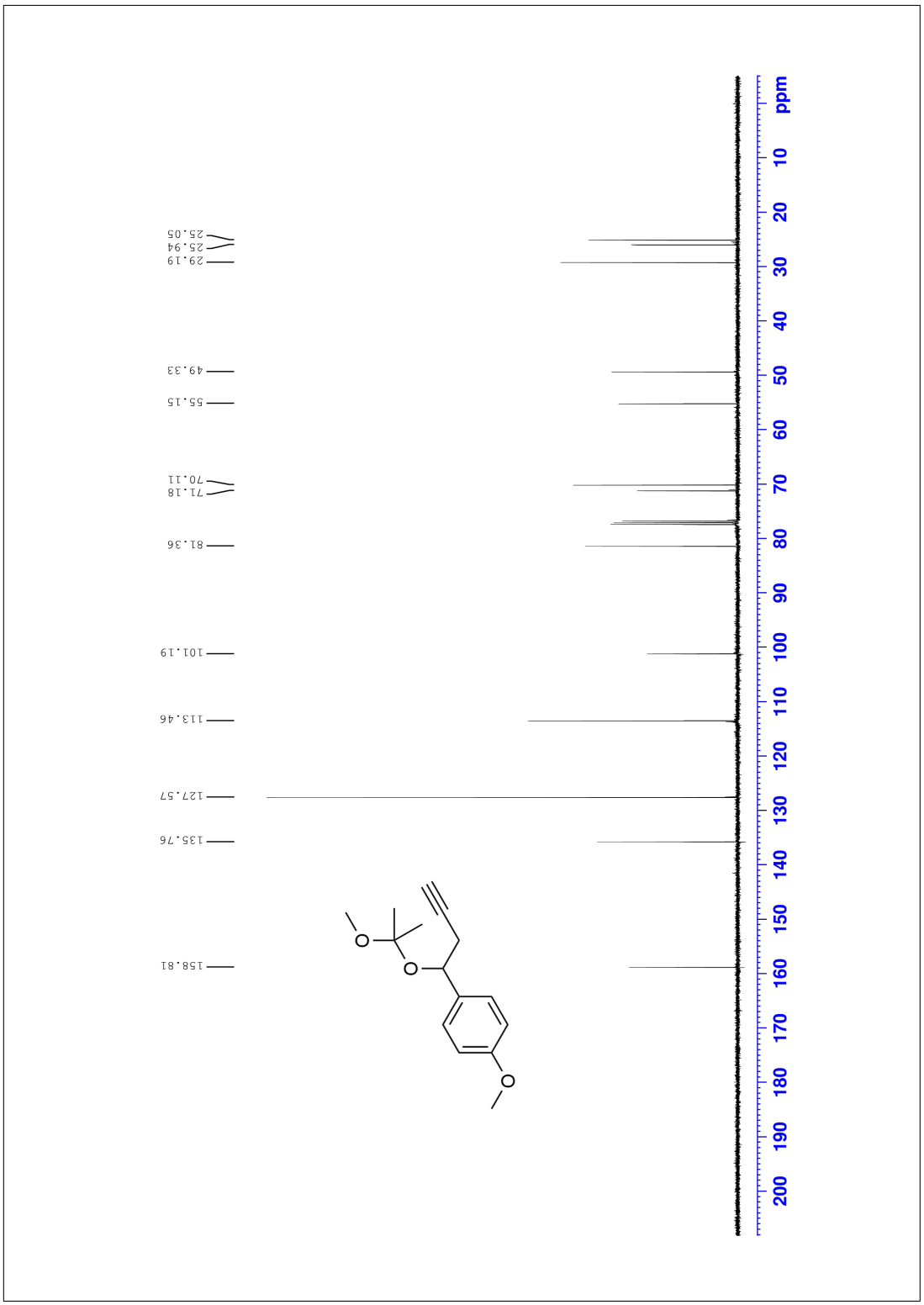


D Characterisation of compound (1.3)

D.1 Compound 1.3 ^{1}H-NMR

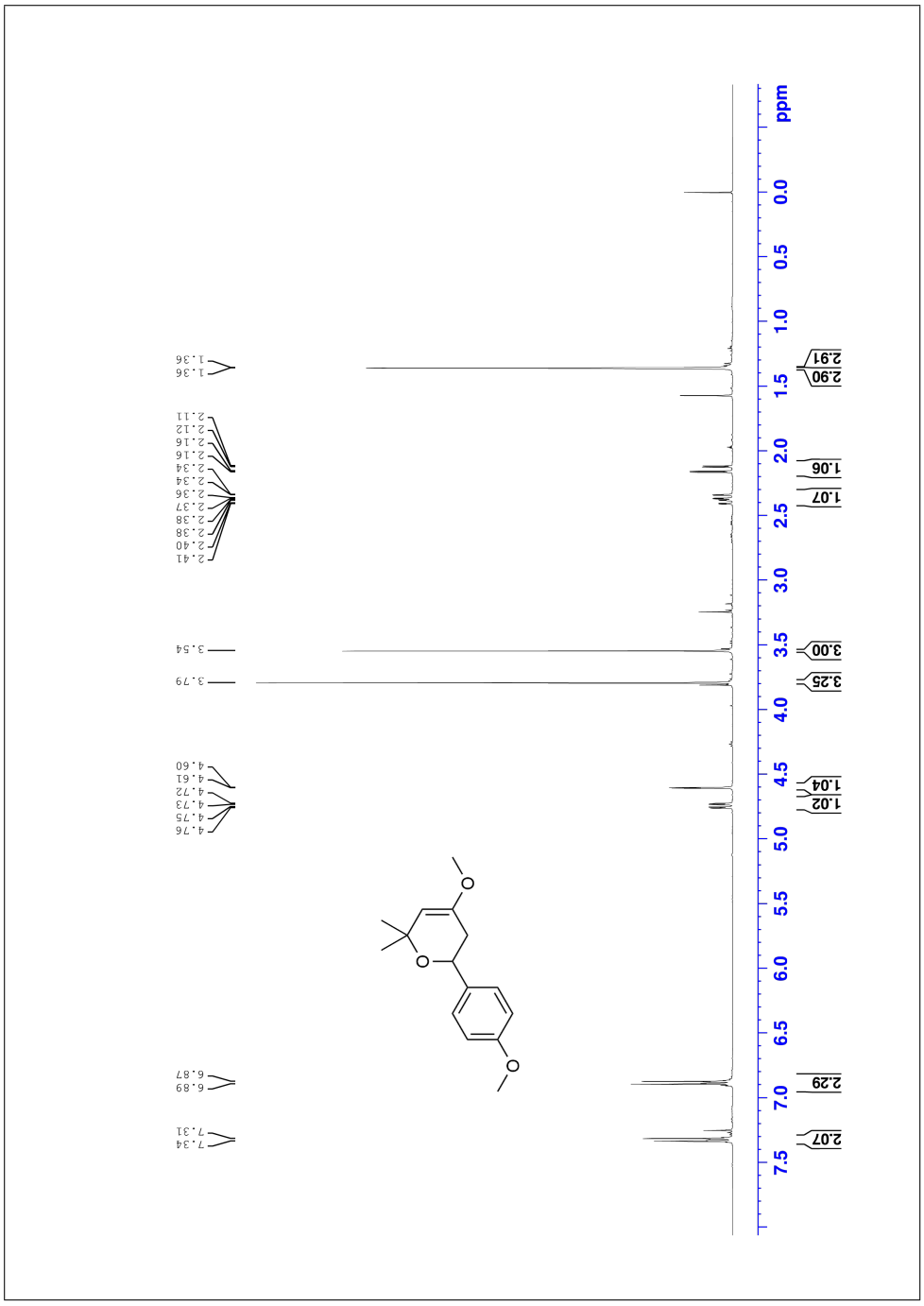


D.2 Compound 1.3 ^{13}C-NMR

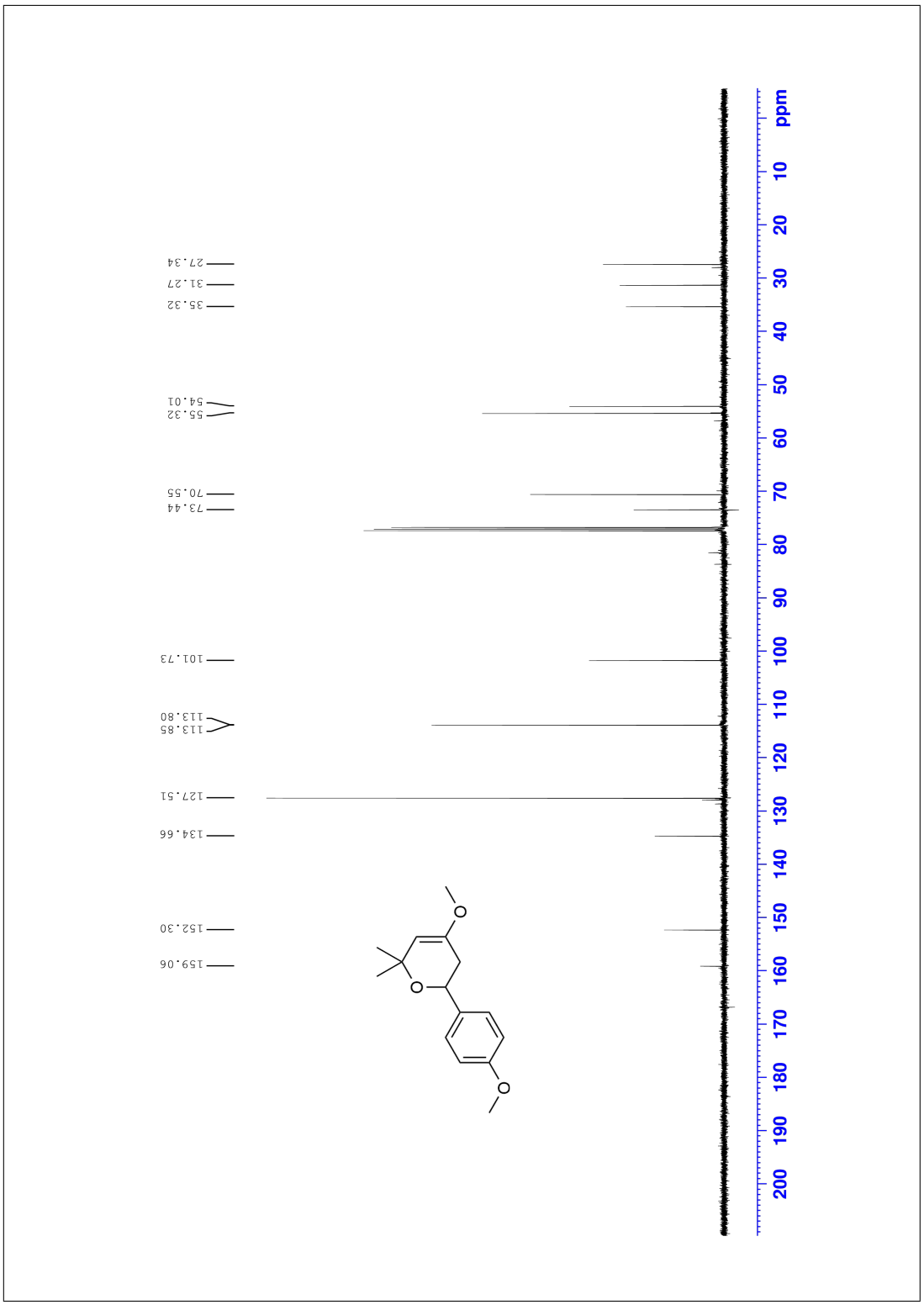


E Characterisation of compound (1.4)

E.1 Compound 1.3 ^{1}H-NMR

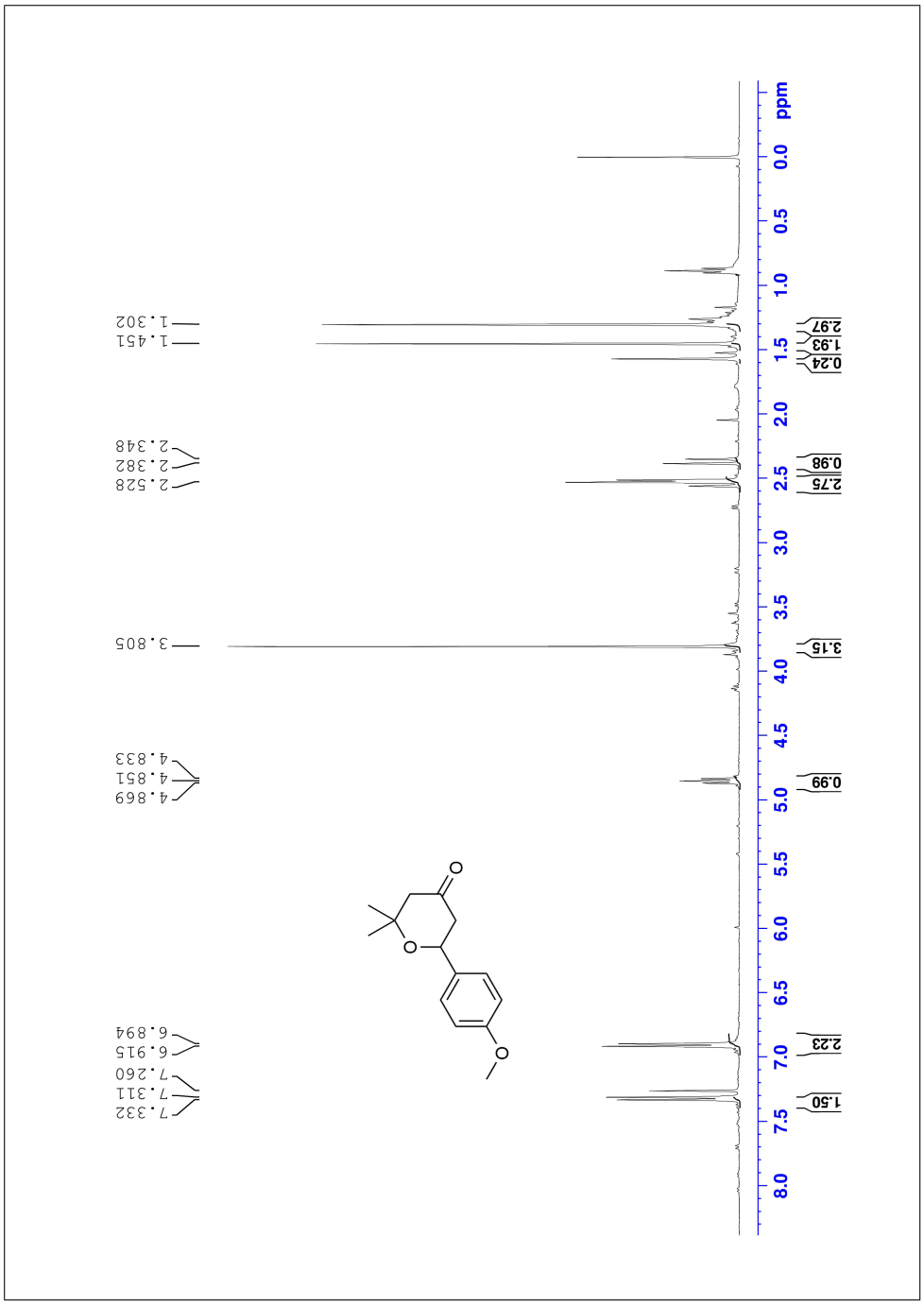


E.2 Compound 1.4 ^{13}C-NMR

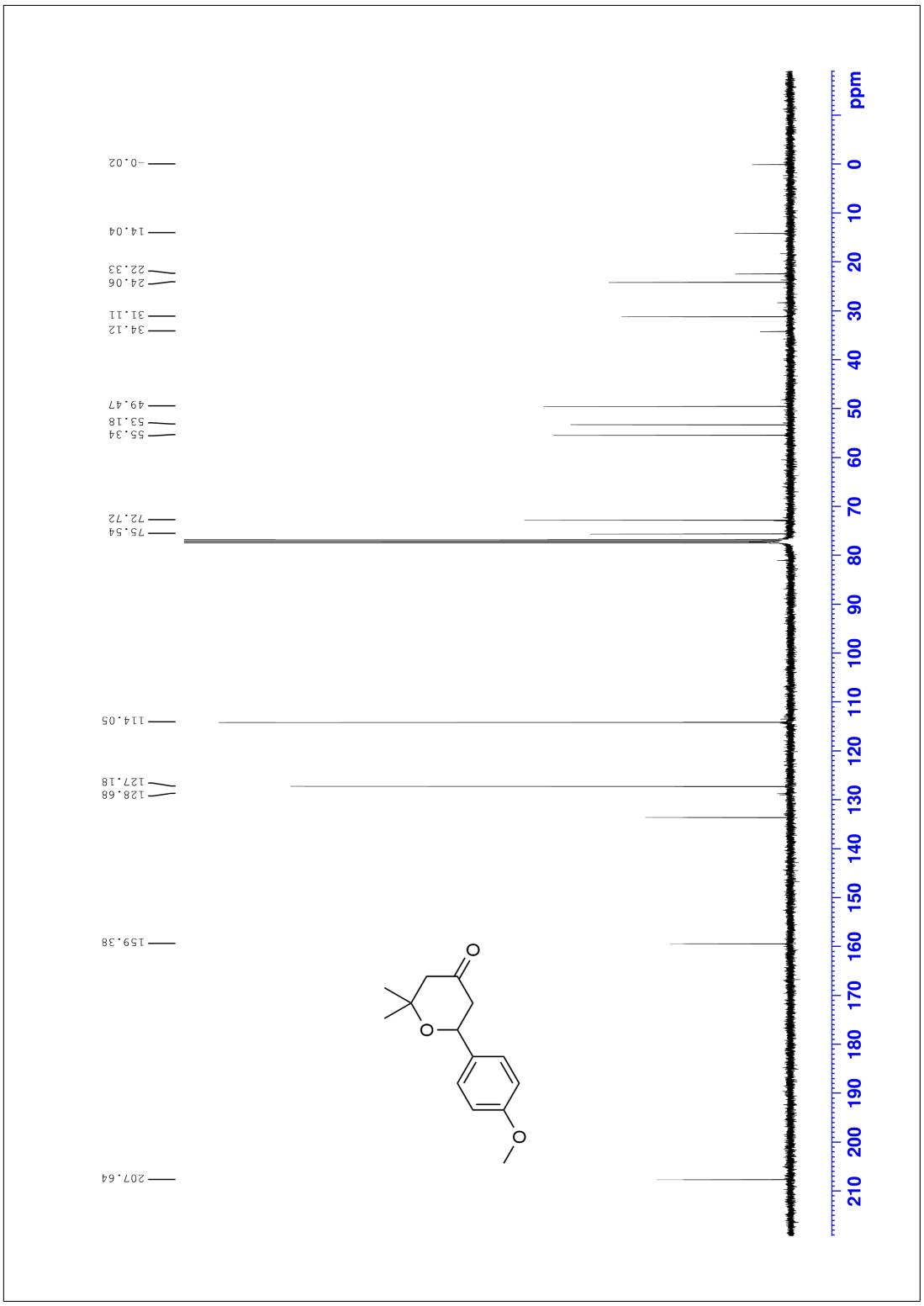


F Characterisation of compound (1.5)

F.1 Compound 1.5 ^{1}H-NMR

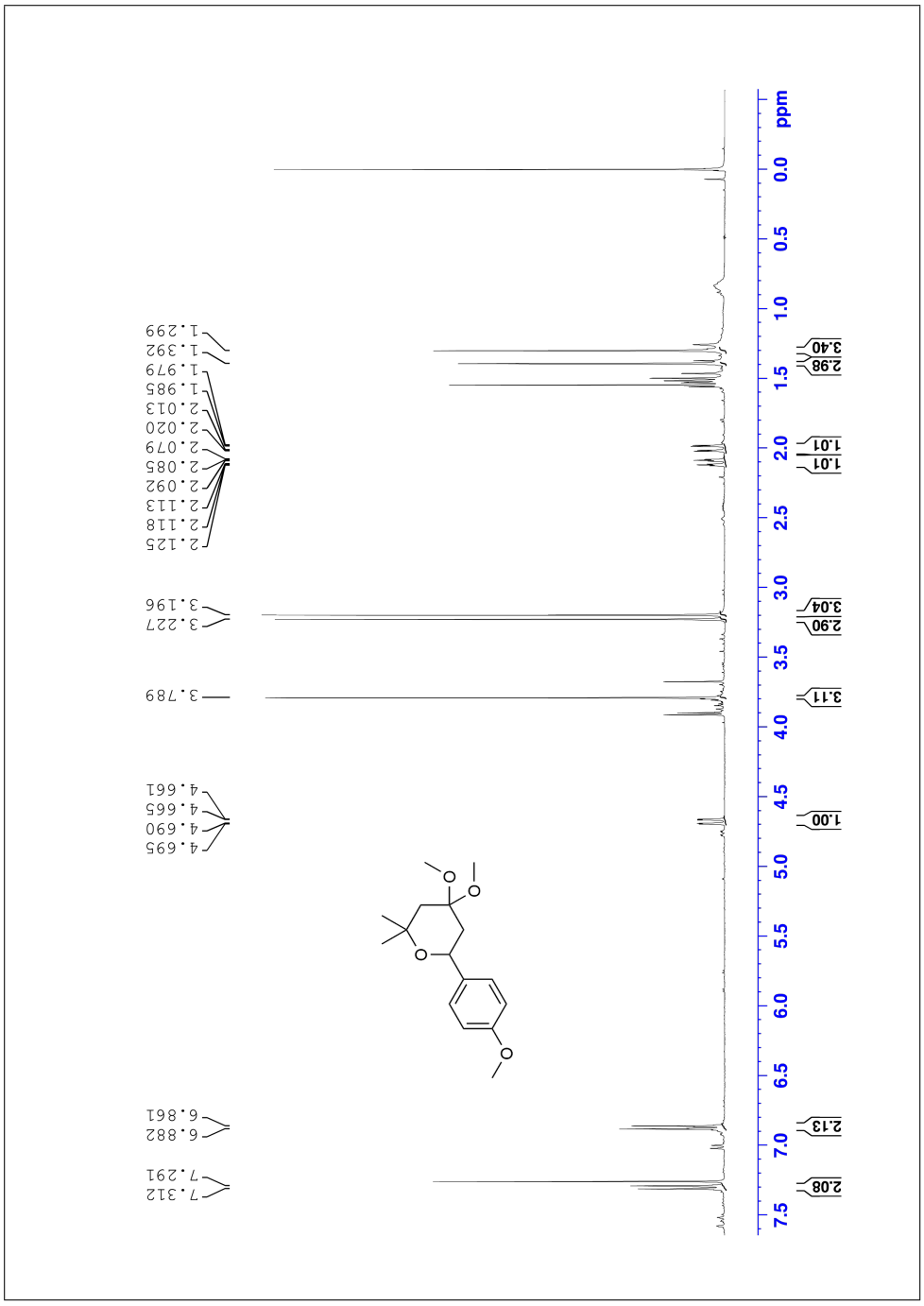


F.2 Compound 1.5 ^{13}C-NMR

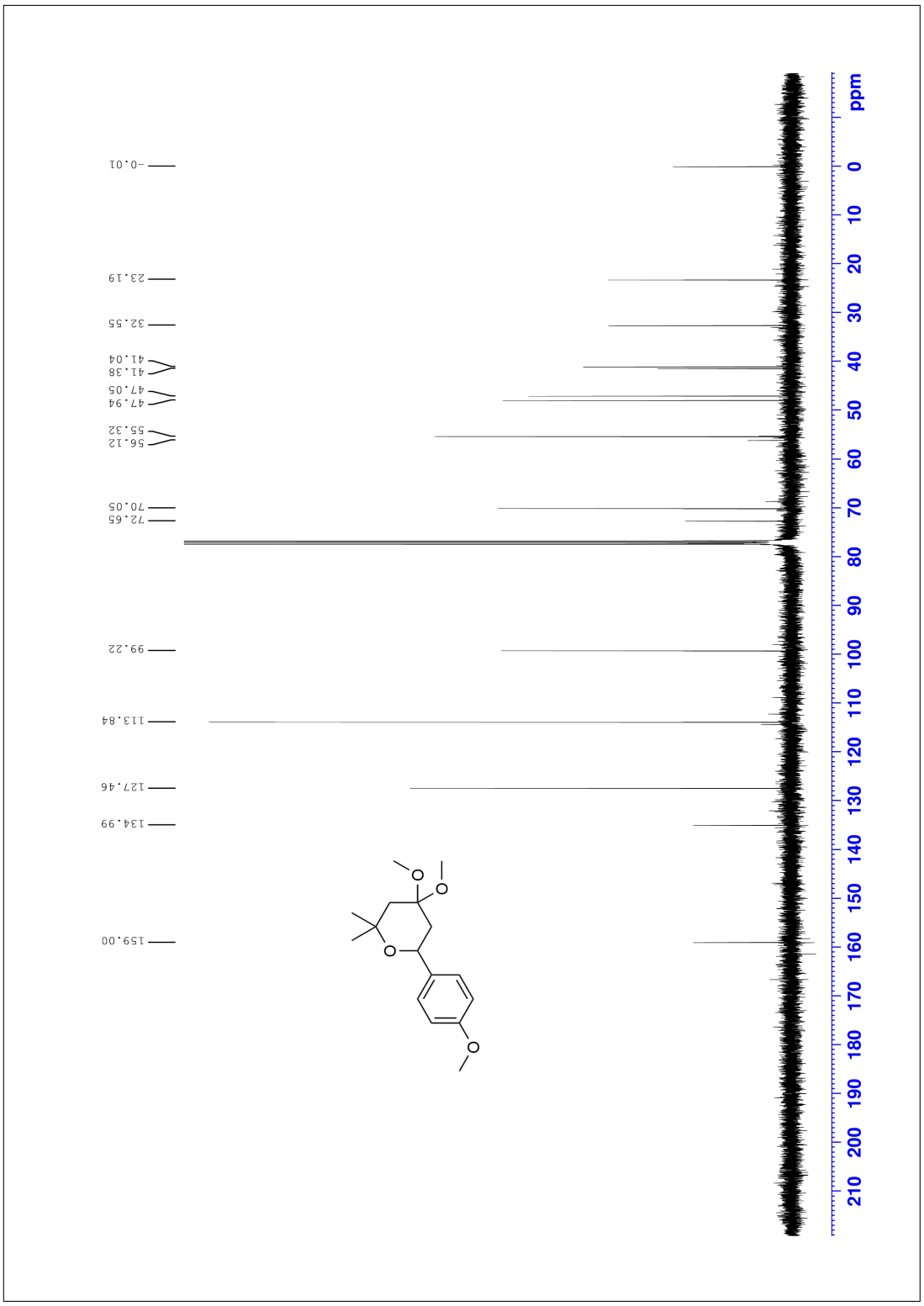


G Characterisation of compound (1.6)

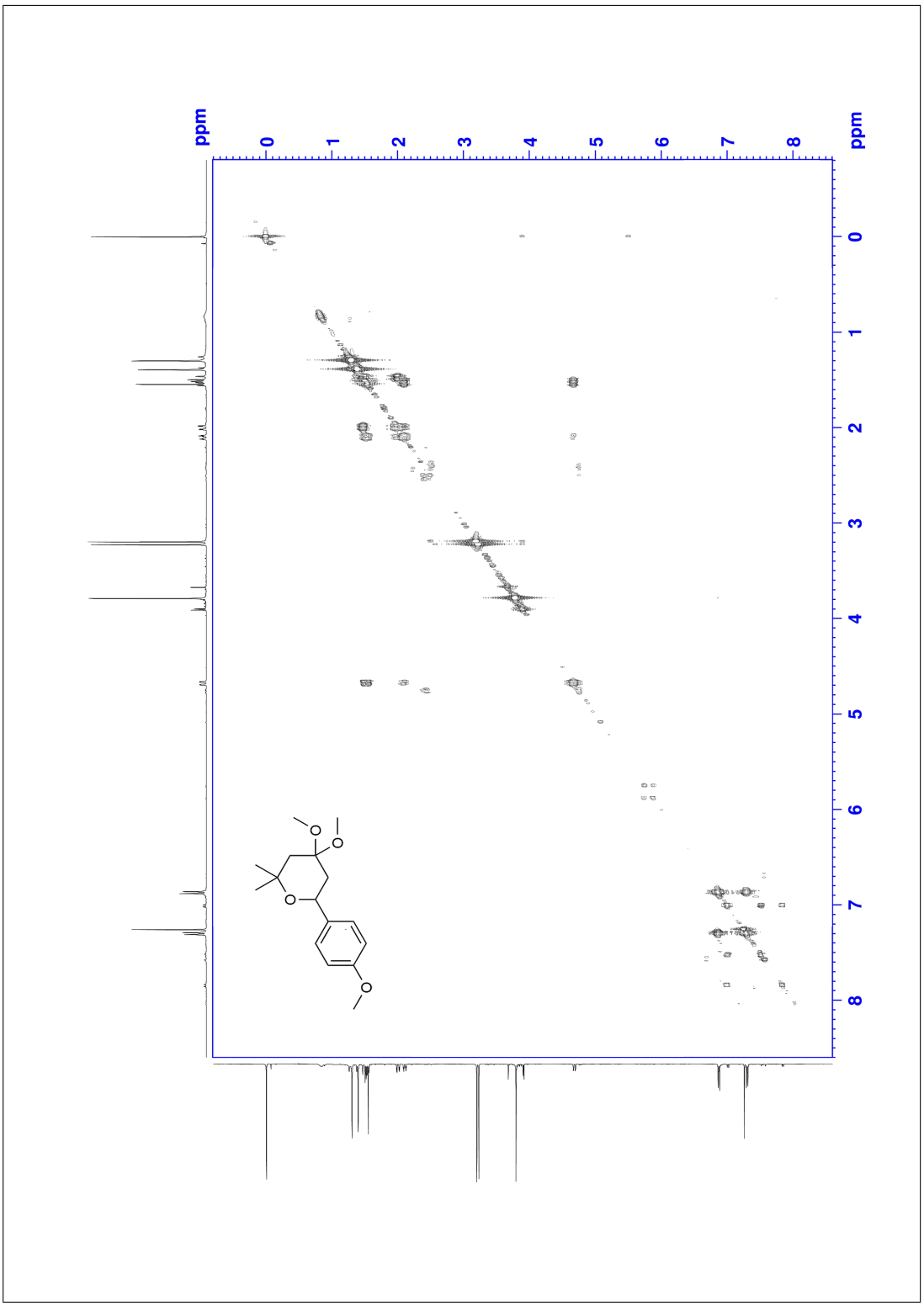
G.1 Compound 1.6 ^{1}H-NMR



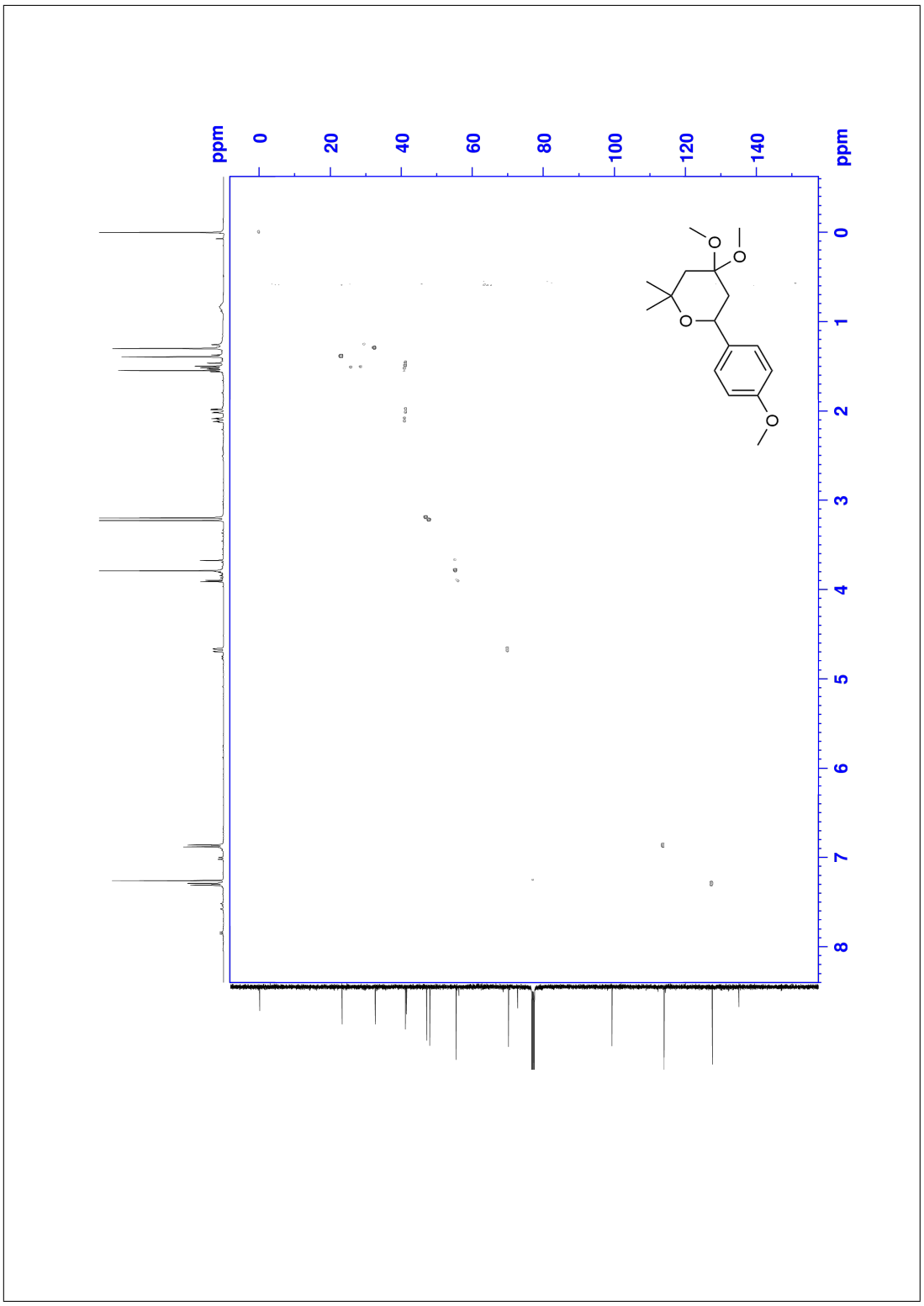
G.2 Compound 1.6 ^{13}C-NMR



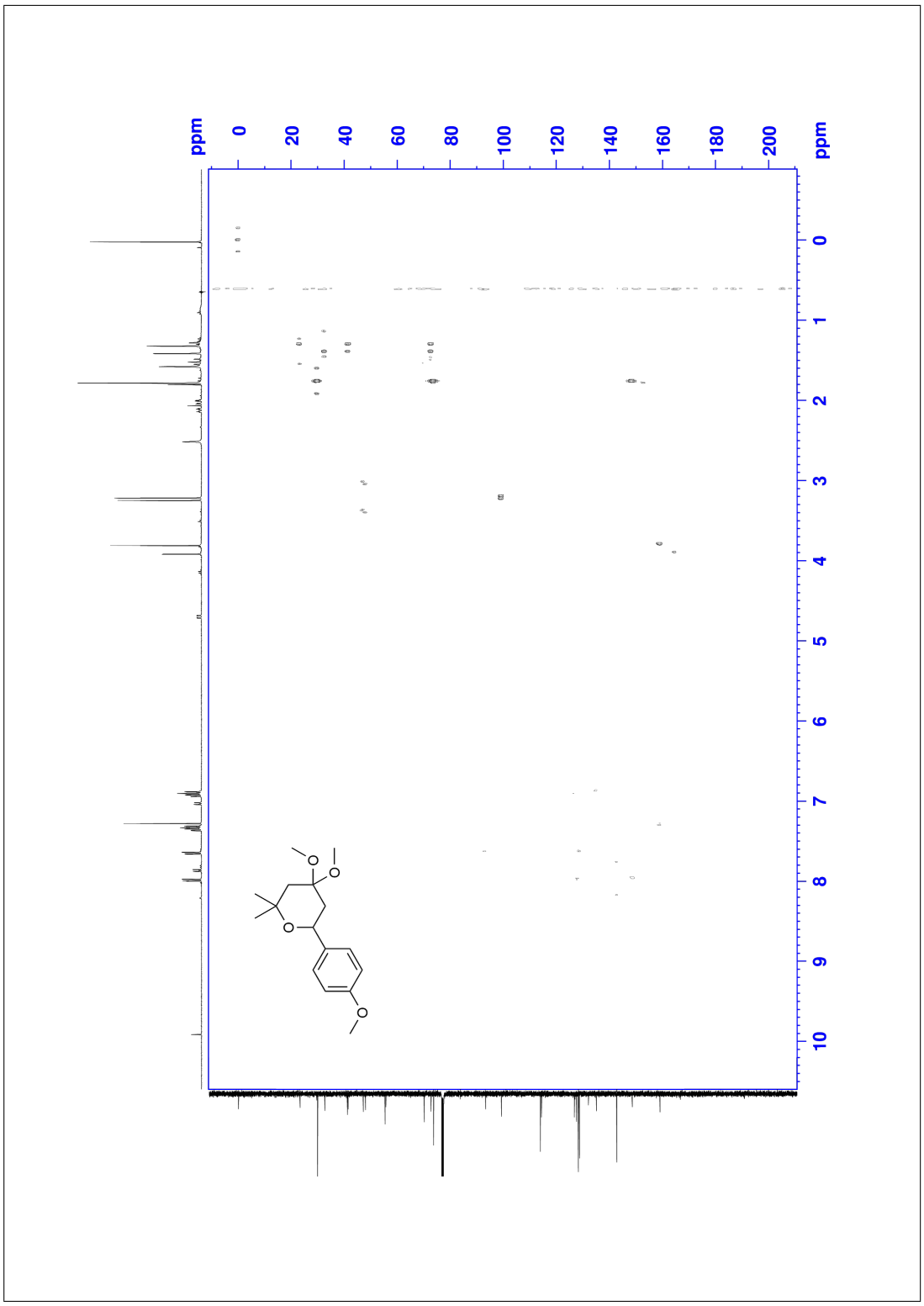
G.3 Compound 1.6 H,H-COSY 2D-NMR



G.4 Compound 1.6 H,C-HSQC 2D-NMR

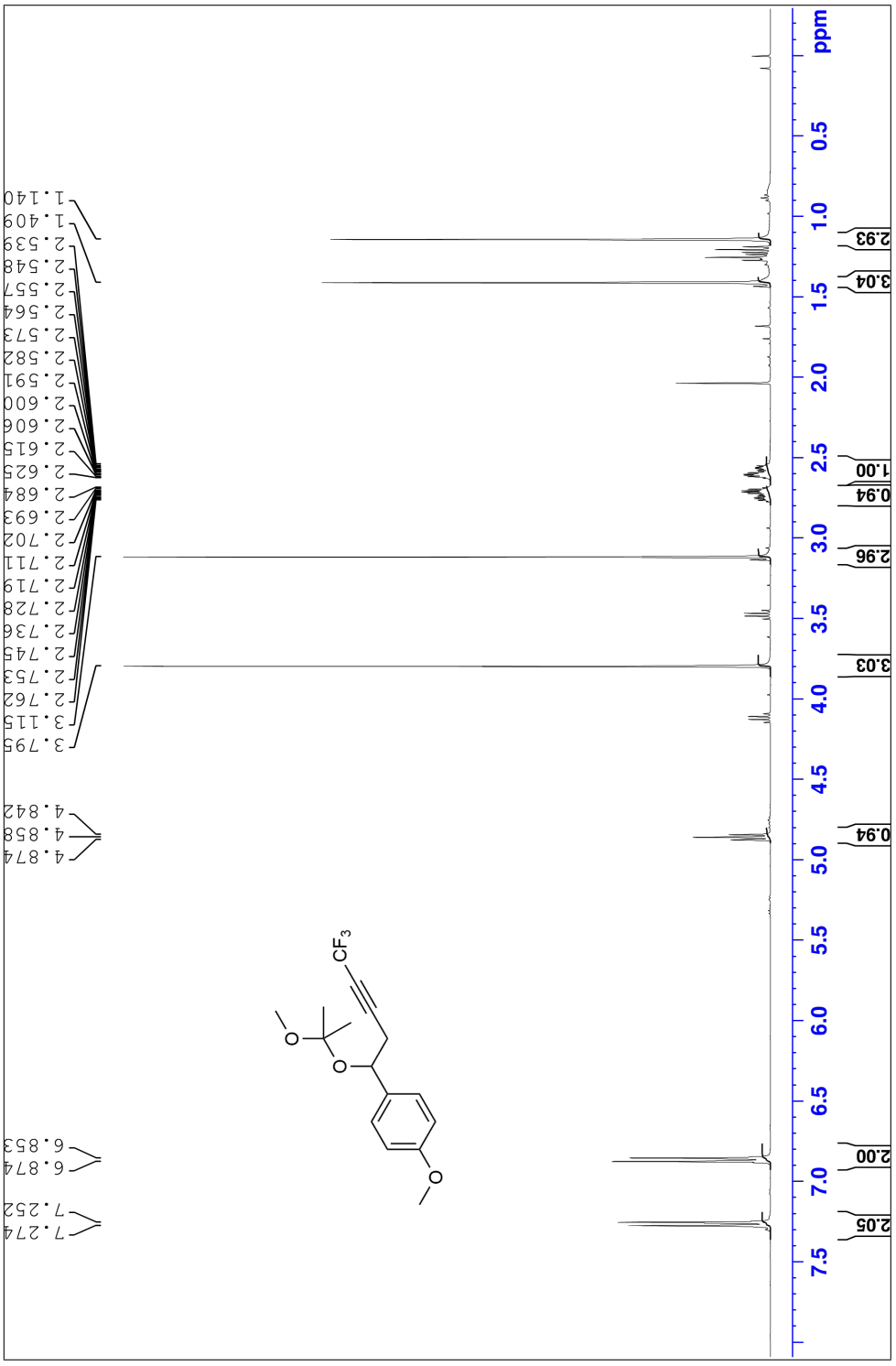


G.5 Compound 1.6 H,C-HMBC 2D-NMR

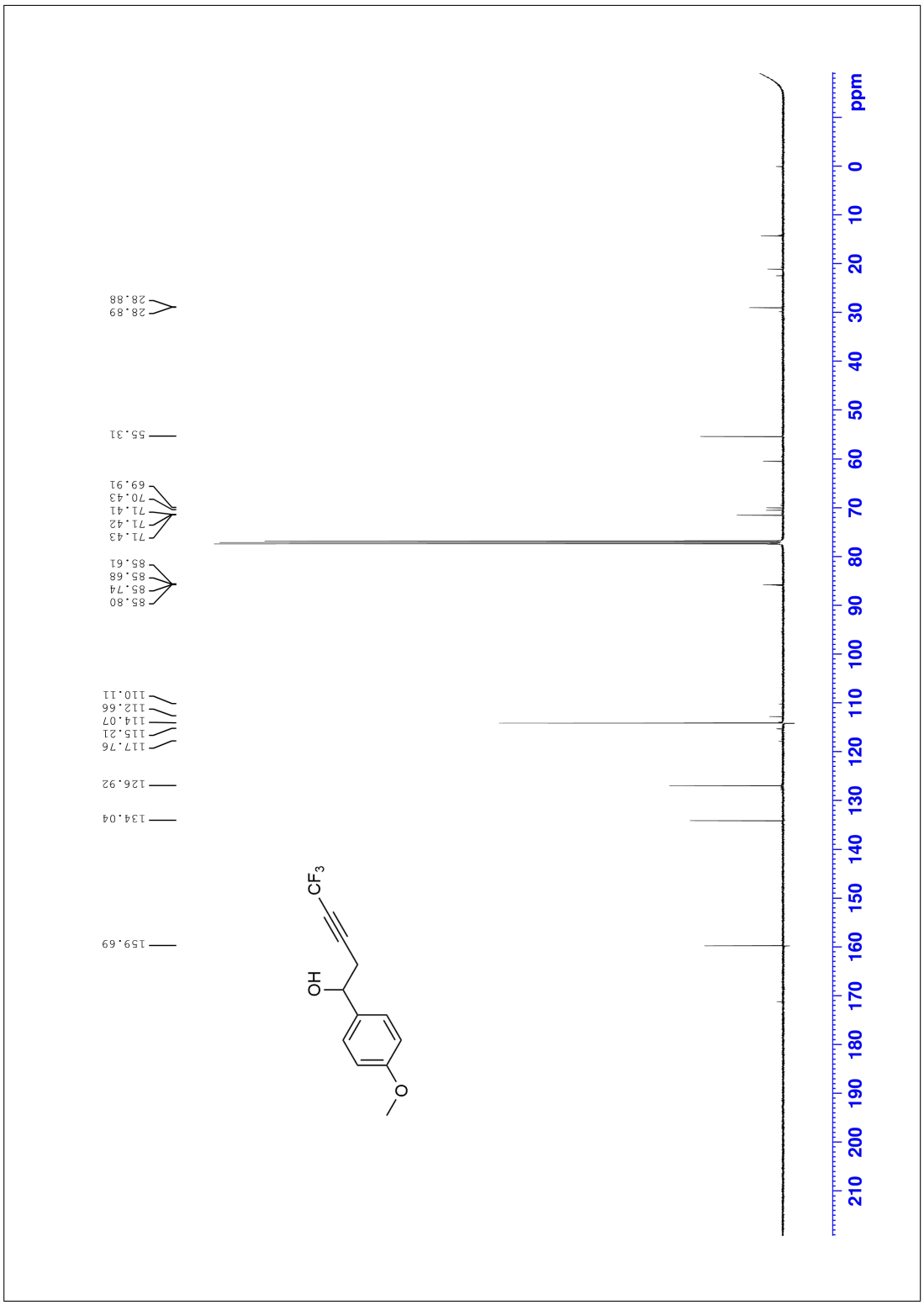


H Characterisation of compound (2.3)

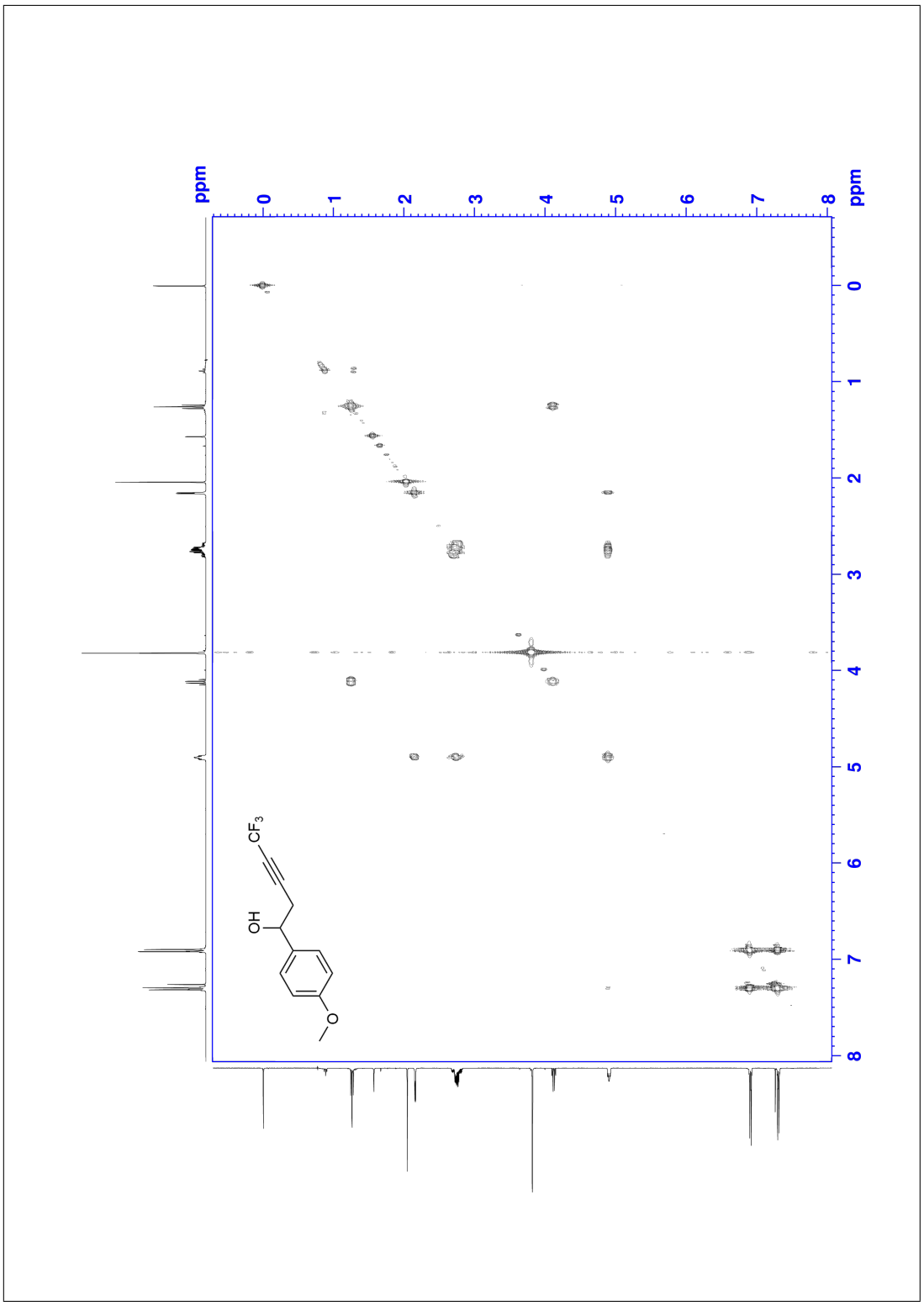
H.1 Compound 2.3 ^{1}H-NMR



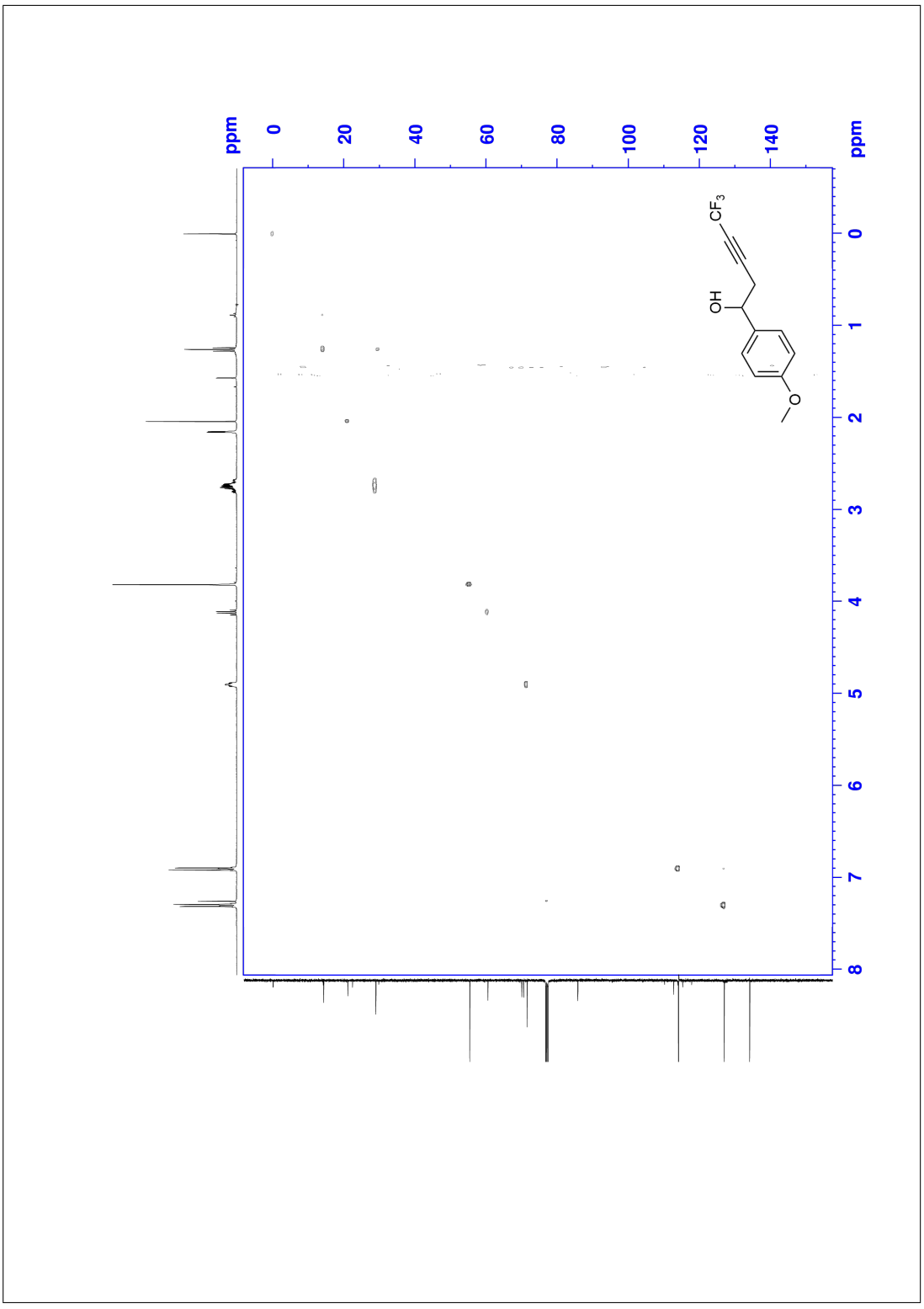
H.2 Compound 2.2 ^{13}C-NMR



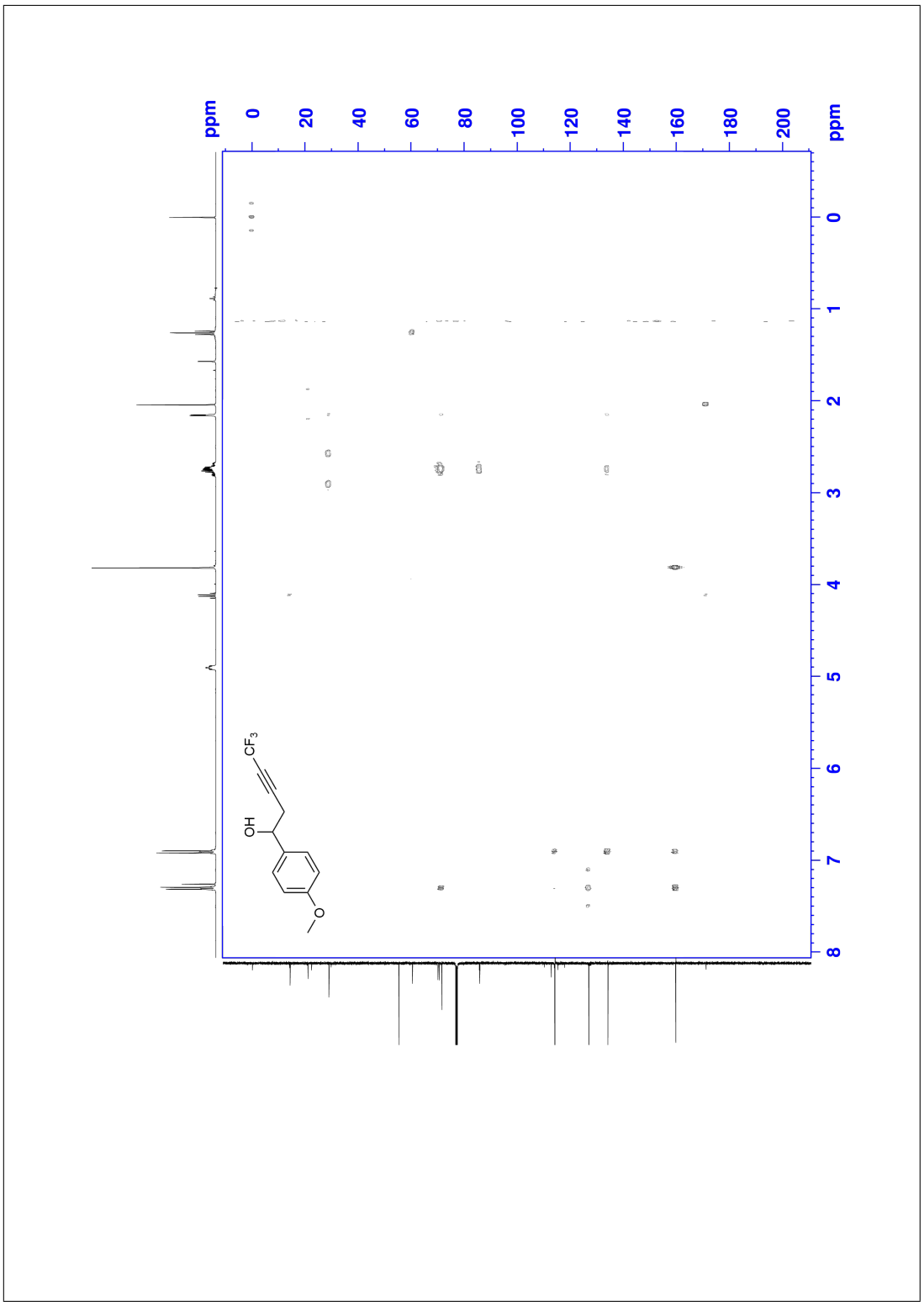
H.3 Compound 2.2 H,H-COSY 2D-NMR



H.4 Compound 2.2 H,C-HSQC 2D-NMR



H.5 Compound 2.2 H,C-HMBC 2D-NMR

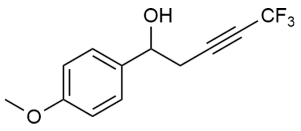


H.6 Compound 2.2 HR-MS

Elemental Composition Report **Page 1**

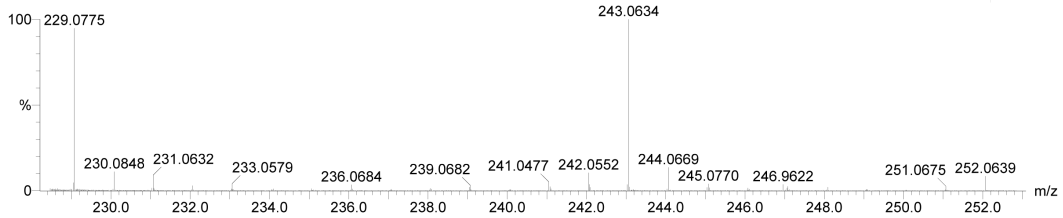
Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1141 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-200 F: 0-5



NT-MSLAB-Operator-SVG
2015-104 83 (1.638) AM2 (Ar,35000.0,0.00,0.00); Cm (13:91)

1: TOF MS ASAP+
2.70e+006

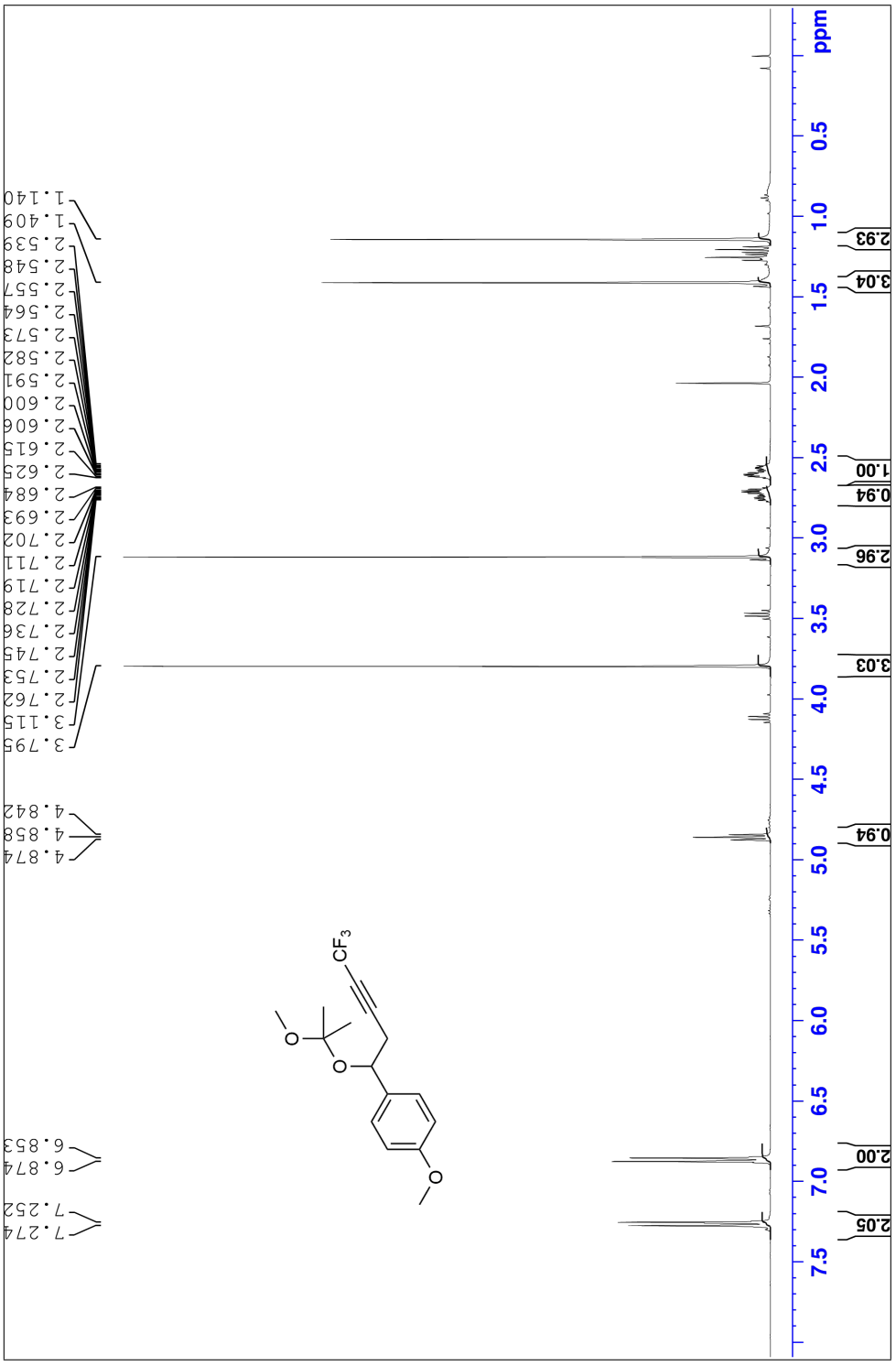


Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
243.0634	243.0633	0.1	0.4	6.5	1830.0	0.437	64.56	C12 H10 O2 F3
	243.0630	0.4	1.6	10.5	1830.6	1.037	35.44	C10 H7 N6 O2

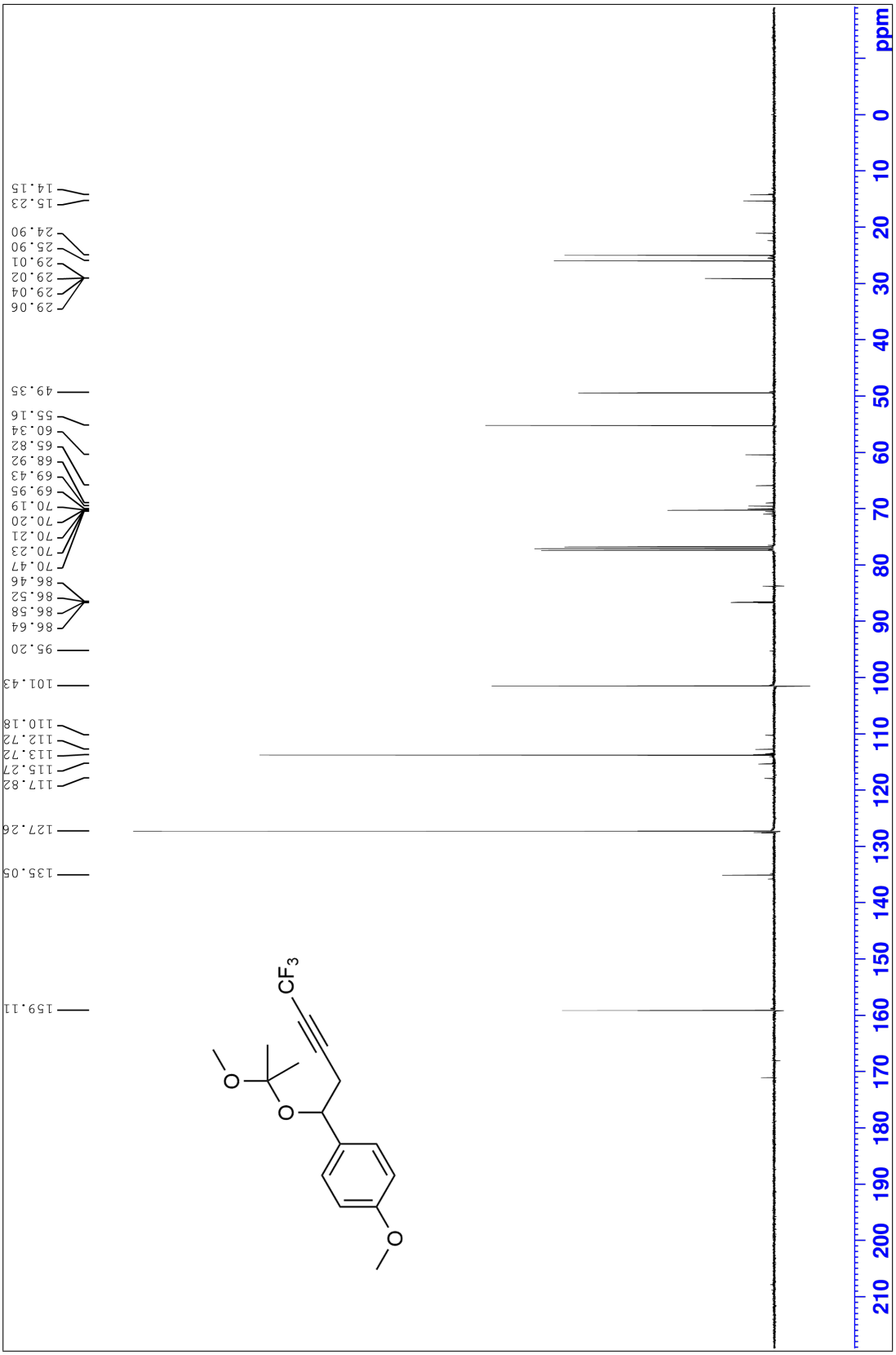
Ion observed [M+H]+

I Characterisation of compound (2.3)

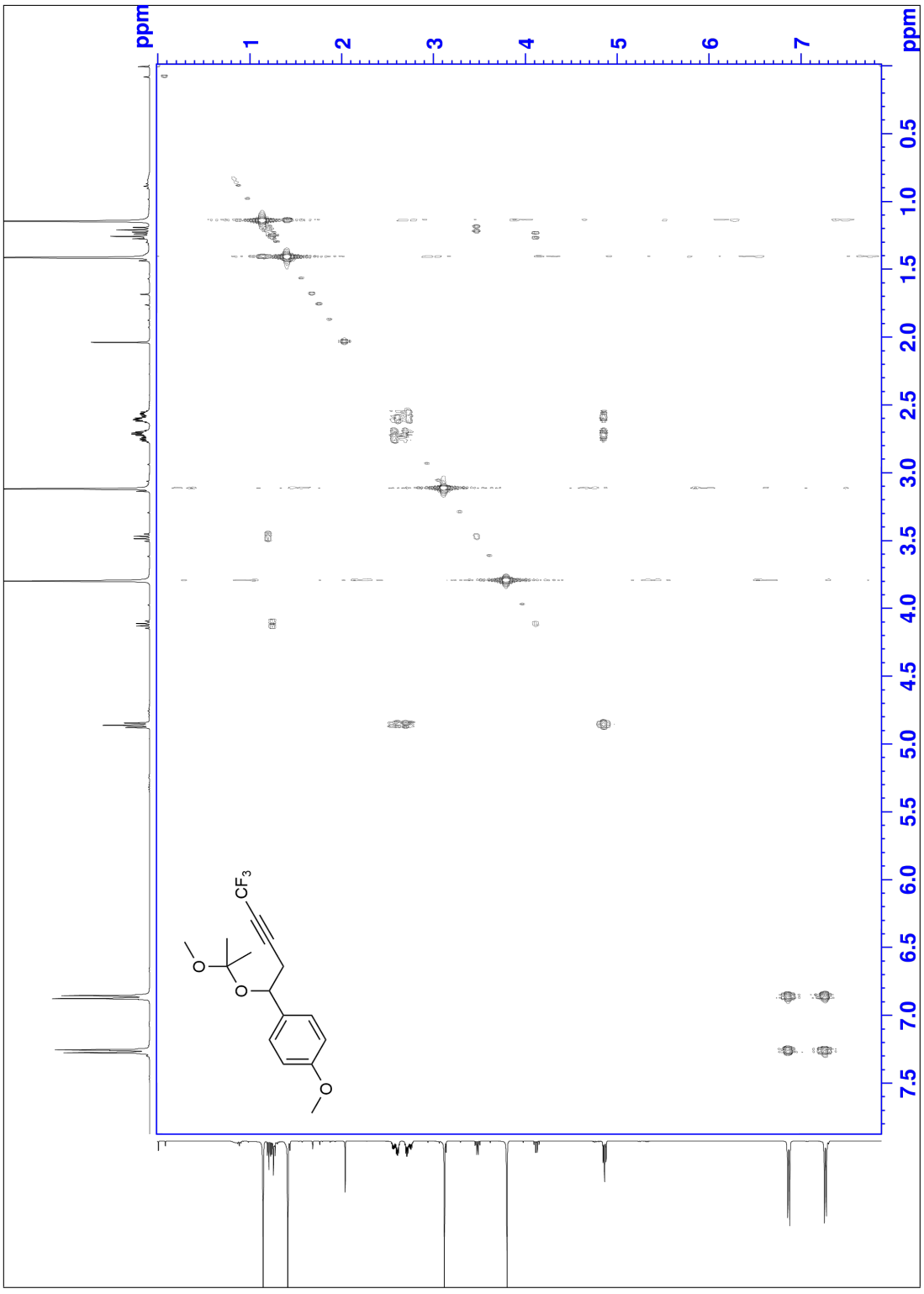
I.1 Compound 2.3 ^{1}H-NMR



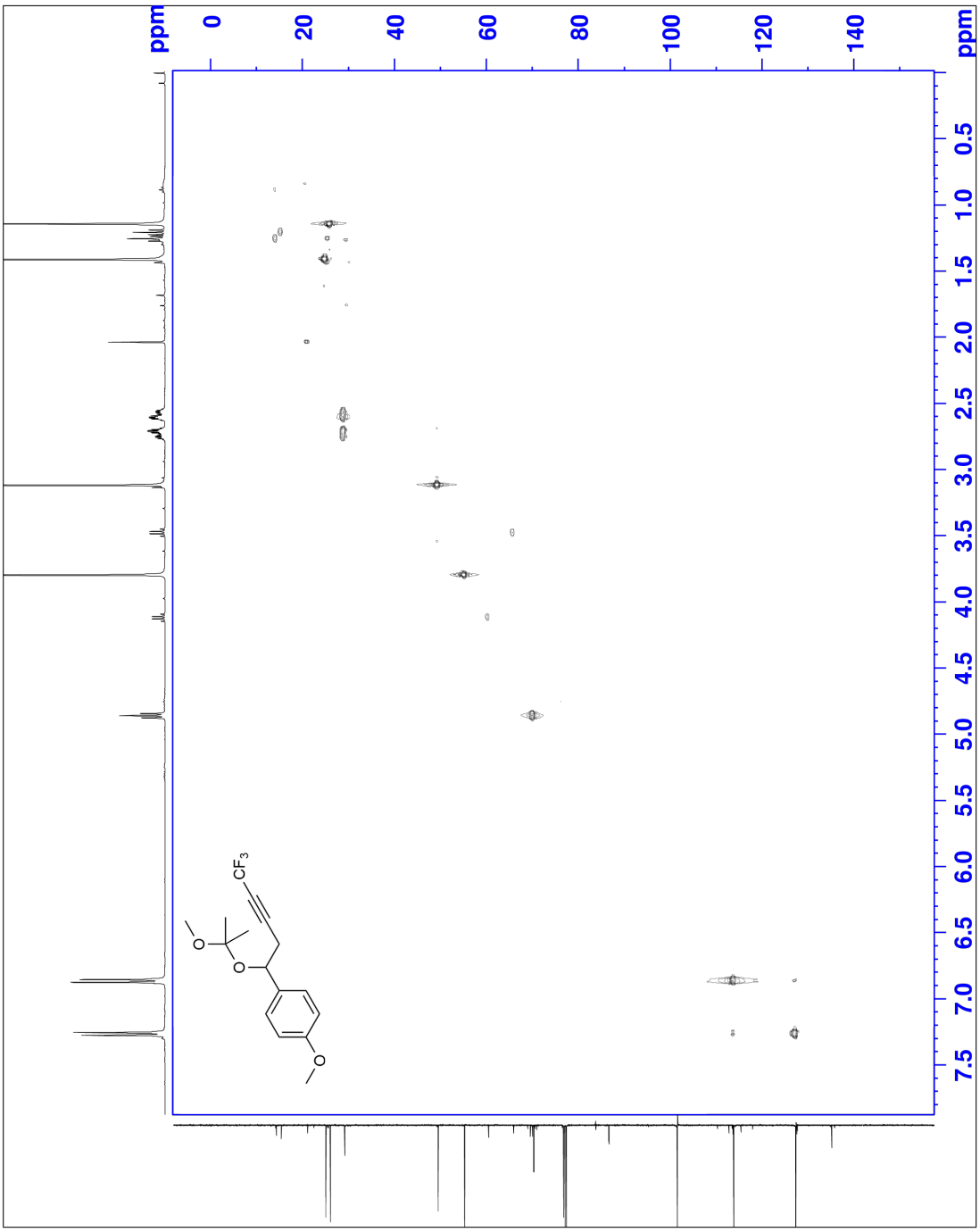
I.2 Compound 2.3 ^{13}C-NMR



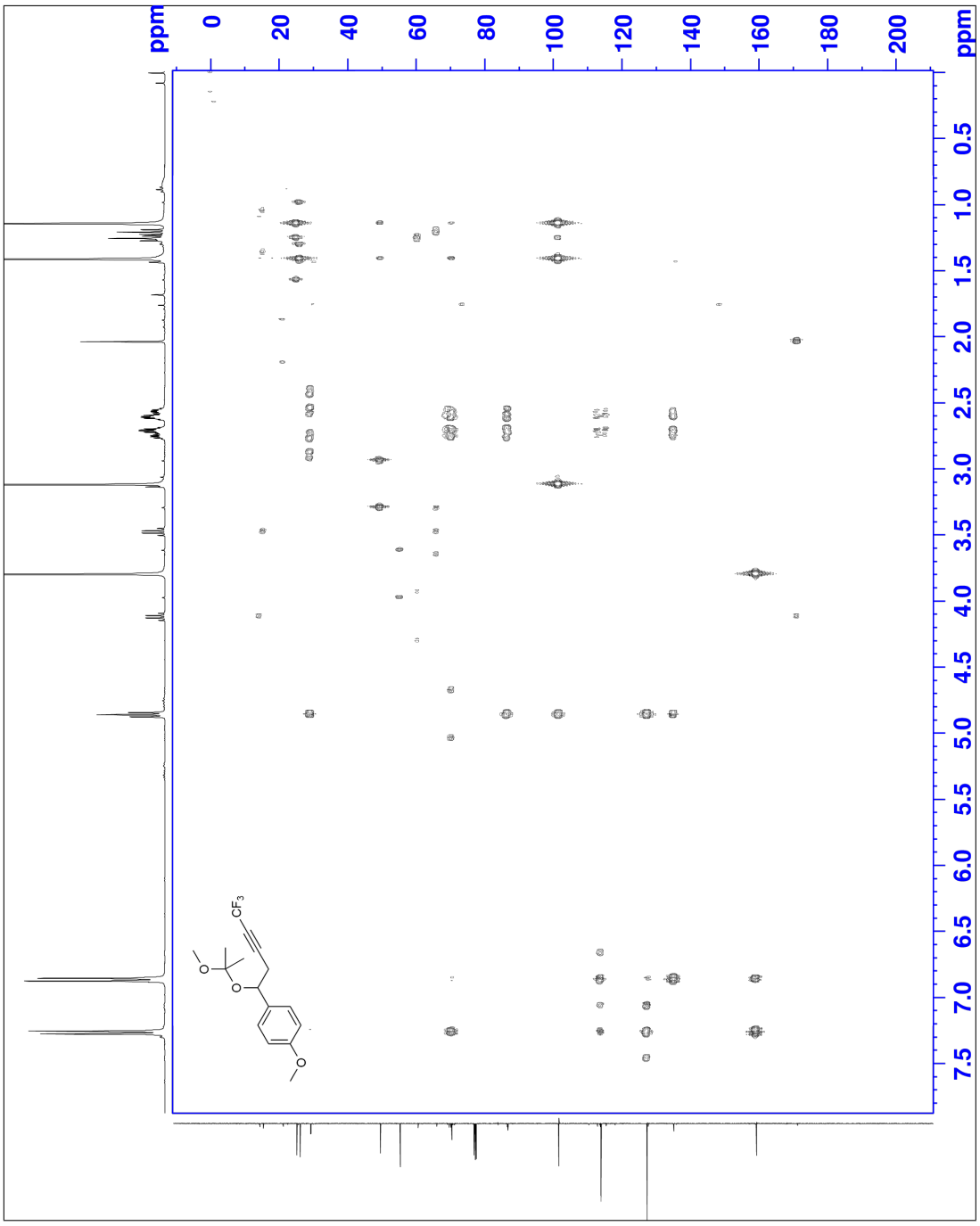
I.3 Compound 2.3 H,H-COSY 2D-NMR



I.4 Compound 2.3 H,C-HSQC 2D-NMR



I.5 Compound 2.3 H,C-HMBC 2D-NMR

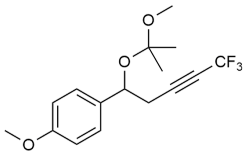


I.6 Compound 2.3 HR-MS

Elemental Composition Report **Page 1**

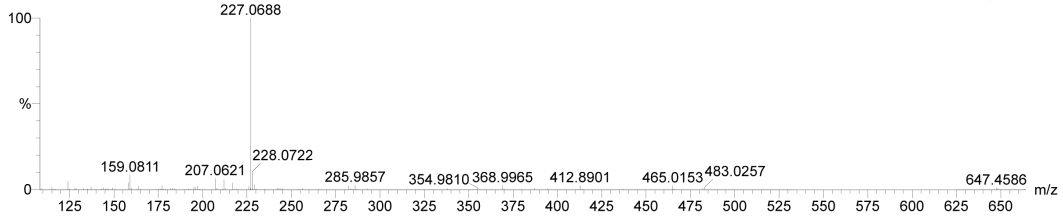
Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1026 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-100 F: 0-5



NT-MSLAB-Operator-SVG
2015-102 125 (2.447) AM2 (Ar,35000.0,0.00,0.00); Cm (125:150)

1: TOF MS ASAP+
5.87e+006



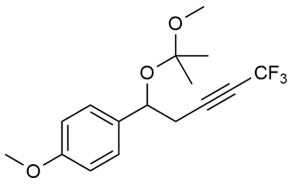
Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
227.0688	227.0684	0.4	1.8	6.5	180.8	0.857	42.43	C12 H10 O F3
	227.0693	-0.5	-2.2	6.5	181.0	1.002	36.73	C7 H8 N6 O2 F
	227.0681	0.7	3.1	10.5	181.5	1.568	20.85	C10 H7 N6 O

Ion observed [M+H]+

I.7 Compound 2.3 HR-MS

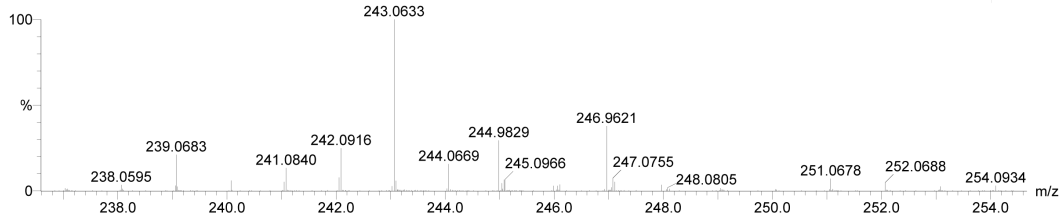
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Monoisotopic Mass, Even Electron Ions
1248 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-100 F: 0-5
NT-MSLAB-Operator-SVG
2015-102 49 (0.984) AM2 (Ar,35000.0,0.00,0.00); Cm (13:56)

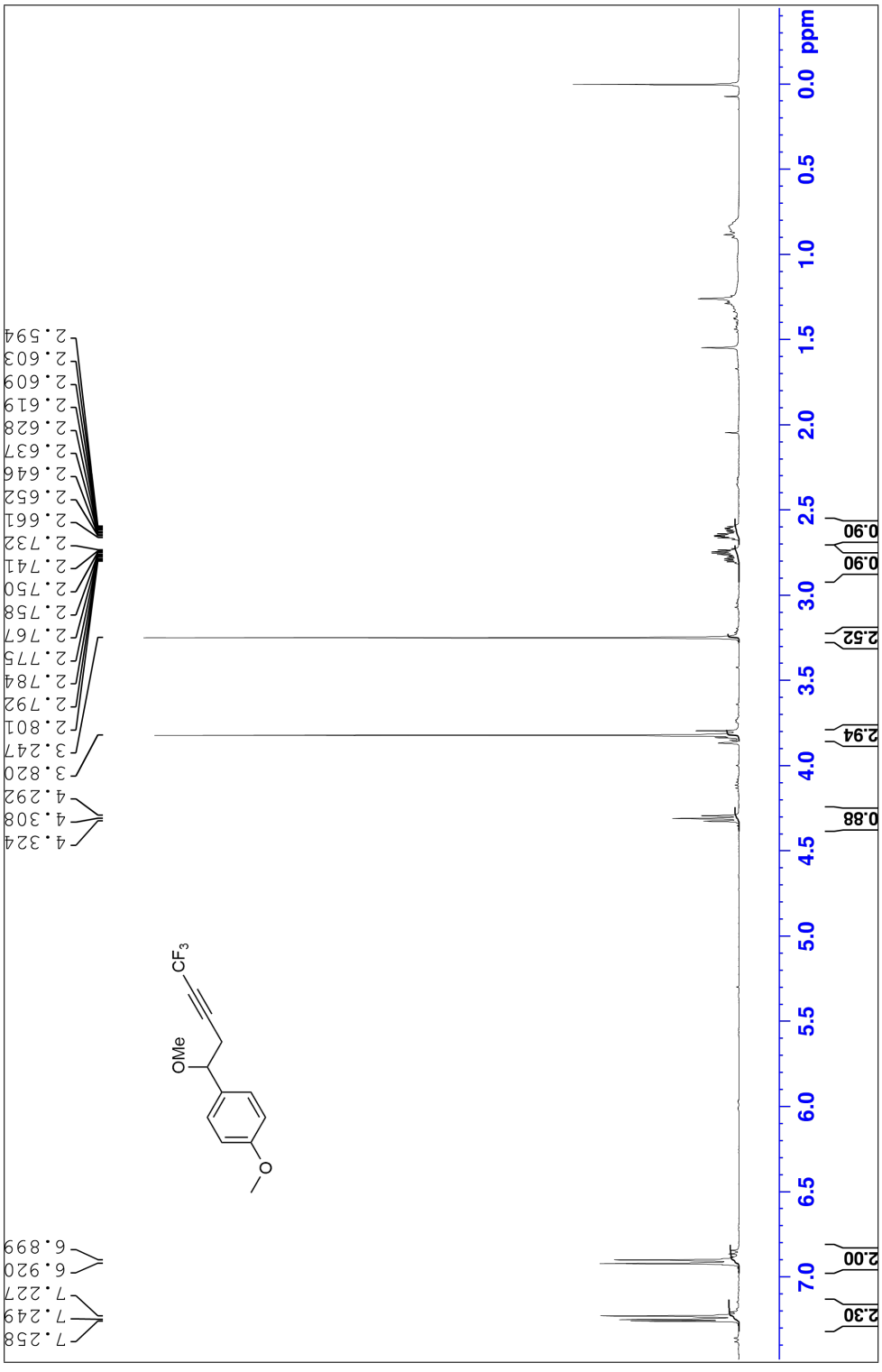
1: TOF MS ASAP+
4.39e+005



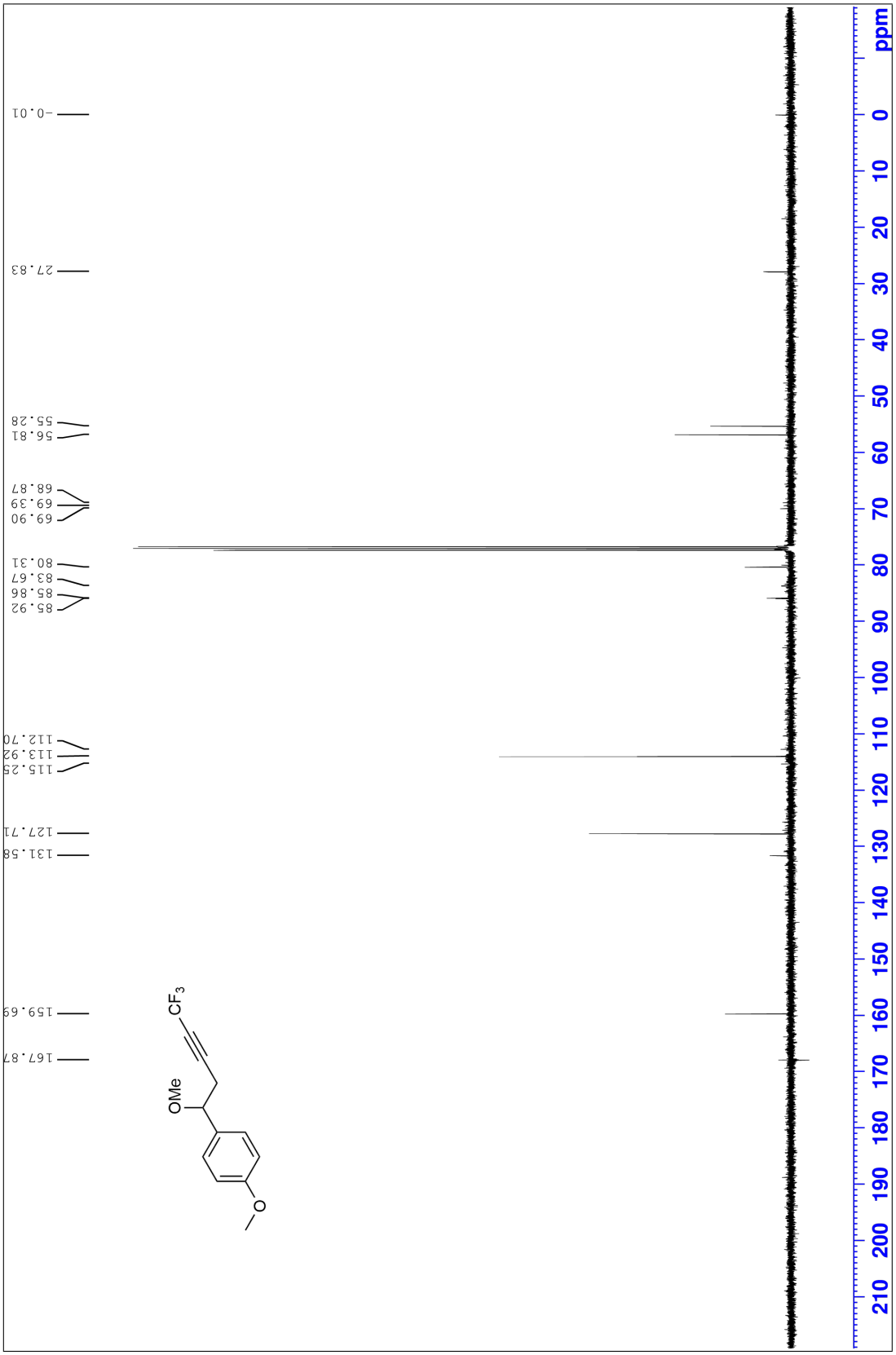
Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
243.0633	243.0633	0.0	0.0	6.5	877.3	0.935	39.24	C12 H10 O2 F3 Ion observed [M+H]+
	243.0630	0.3	1.2	10.5	876.9	0.529	58.91	C10 H7 N6 O2
	243.0629	0.4	1.6	1.5	880.7	4.330	1.32	C6 H12 N2 O7 F
	243.0629	0.4	1.6	-0.5	882.1	5.724	0.33	C2 H8 N6 O2 F5
	243.0626	0.7	2.9	3.5	882.6	6.215	0.20	H5 N12 O2 F2

J Characterisation of compound (2.4)

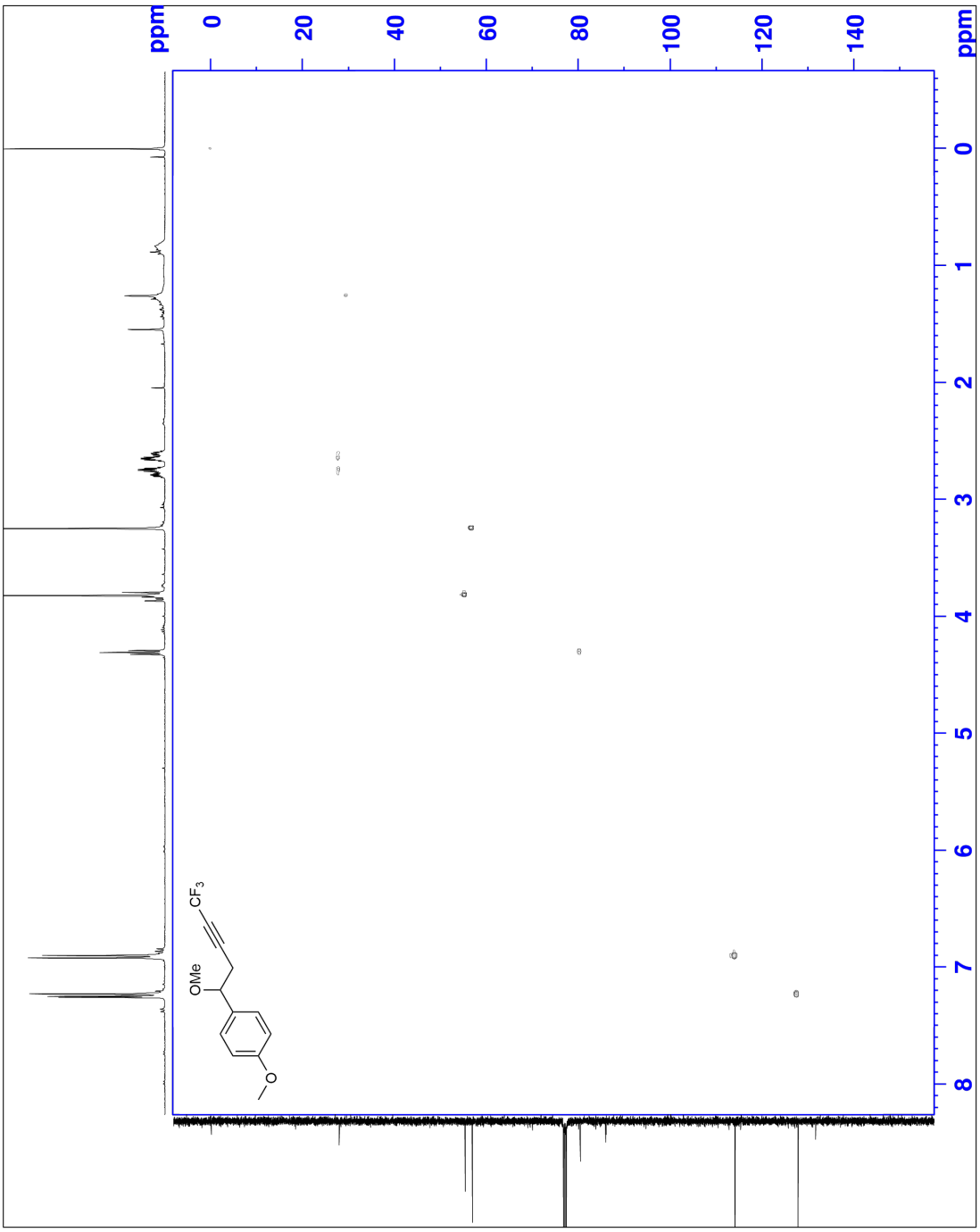
J.1 Compound 2.4 ^{1}H-NMR



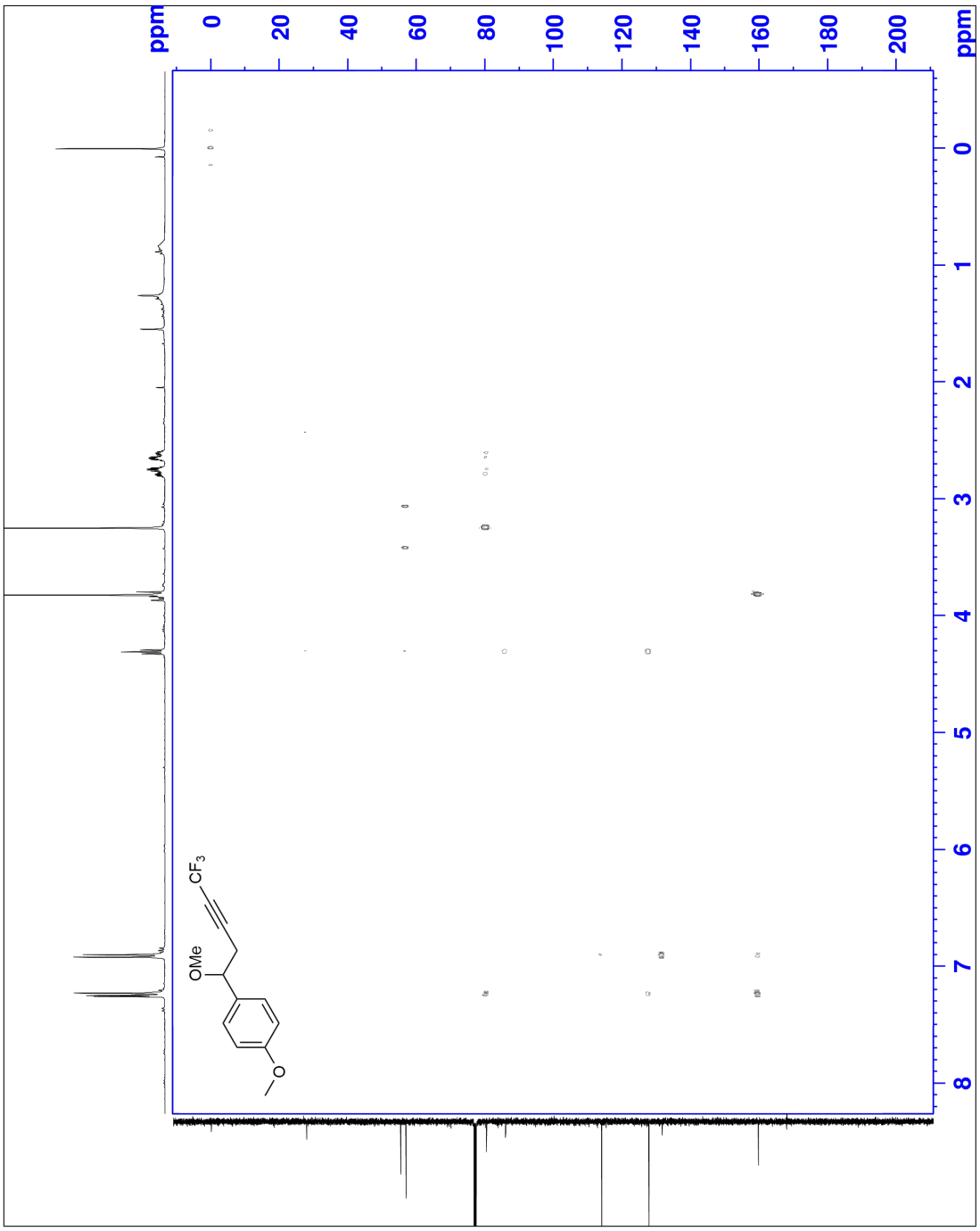
J.2 Compound 2.4 ^{13}C-NMR



J.3 Compound 2.4 H,C-HSQC 2D-NMR



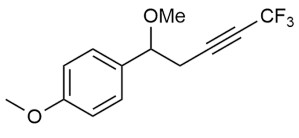
J.4 Compound 2.4 H,C-HMBC 2D-NMR



J.5 Compound 2.4 HR-MS

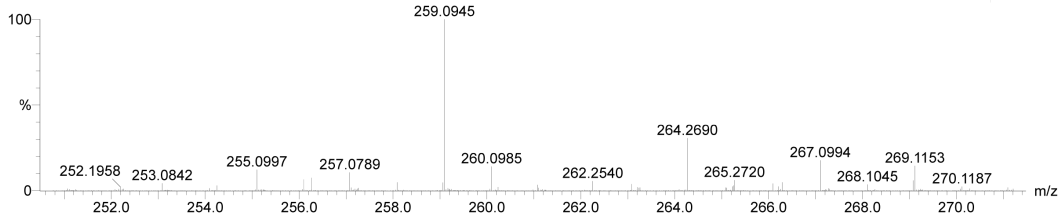
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Monoisotopic Mass, Even Electron Ions
1326 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-200 F: 0-5
NT-MSLAB-Operator-SVG
2015-105 1 (0.054) AM2 (Ar,35000.0,0.00,0.00); Cm (1:7)

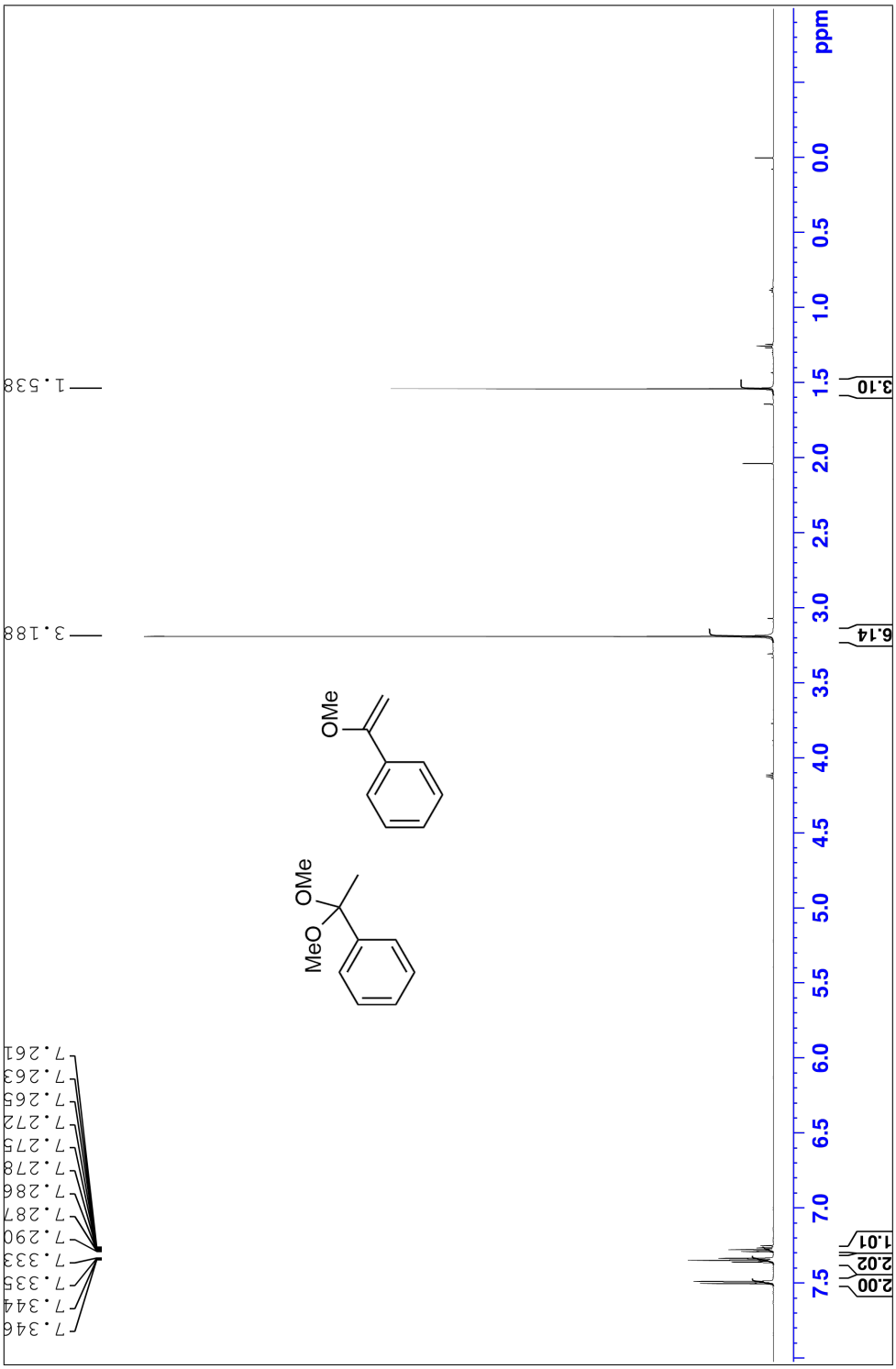
1: TOF MS ASAP+
1.39e+005



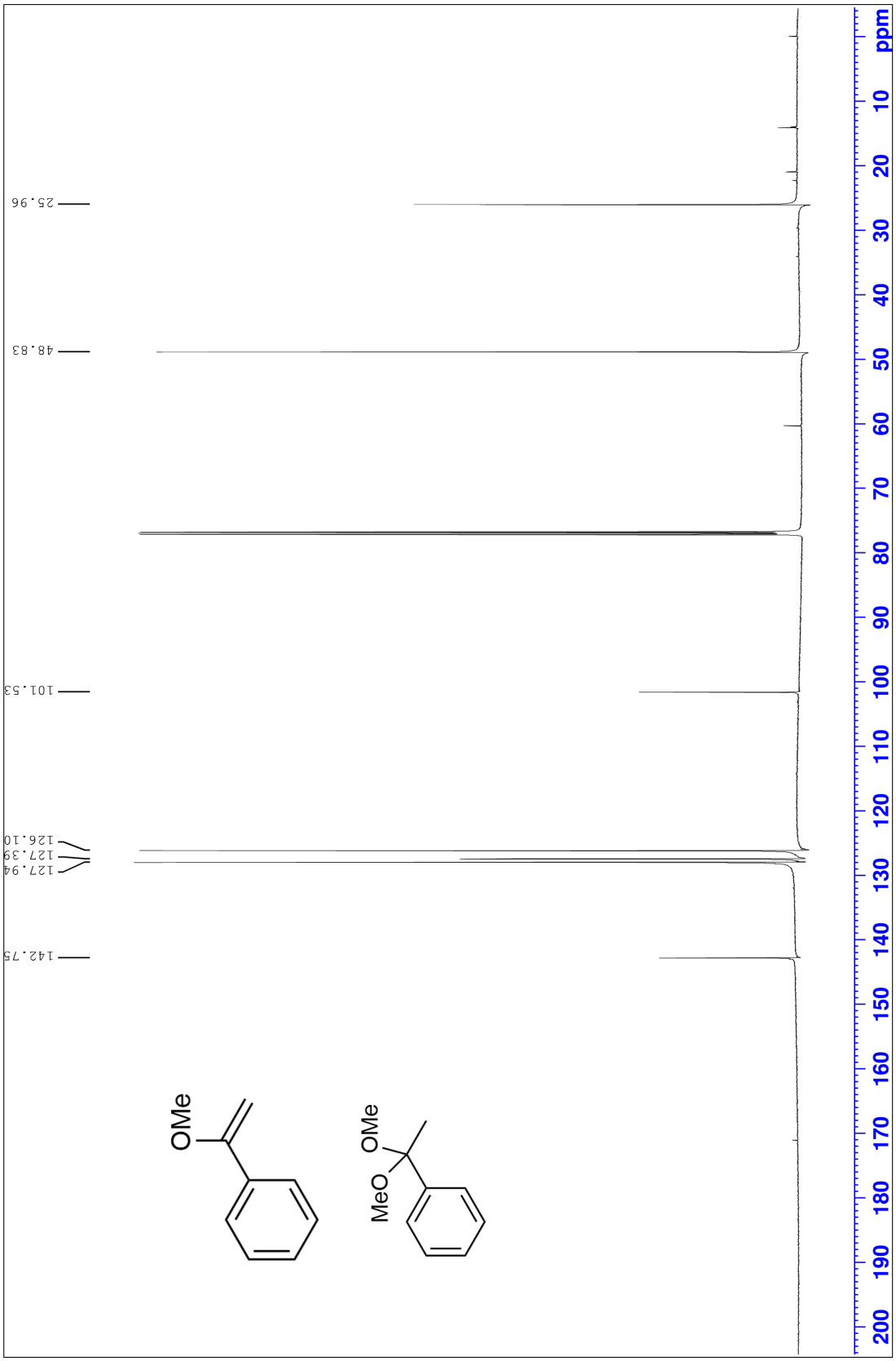
Minimum:				-1.5				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
259.0945	259.0946	-0.1	-0.4	5.5	1041.6	0.008	99.16	C13 H14 O2 F3 Ion observed [M+H]+
	259.0943	0.2	0.8	9.5	1046.4	4.780	0.84	C11 H11 N6 O2
	259.0942	0.3	1.2	0.5	1053.4	11.783	0.00	C7 H16 N2 O7 F
	259.0942	0.3	1.2	-1.5	1057.7	16.087	0.00	C3 H12 N6 O2 F5

K Characterisation of compound (3.2/3.3)

K.1 Compound 3.2/3.3 ^{1}H-NMR

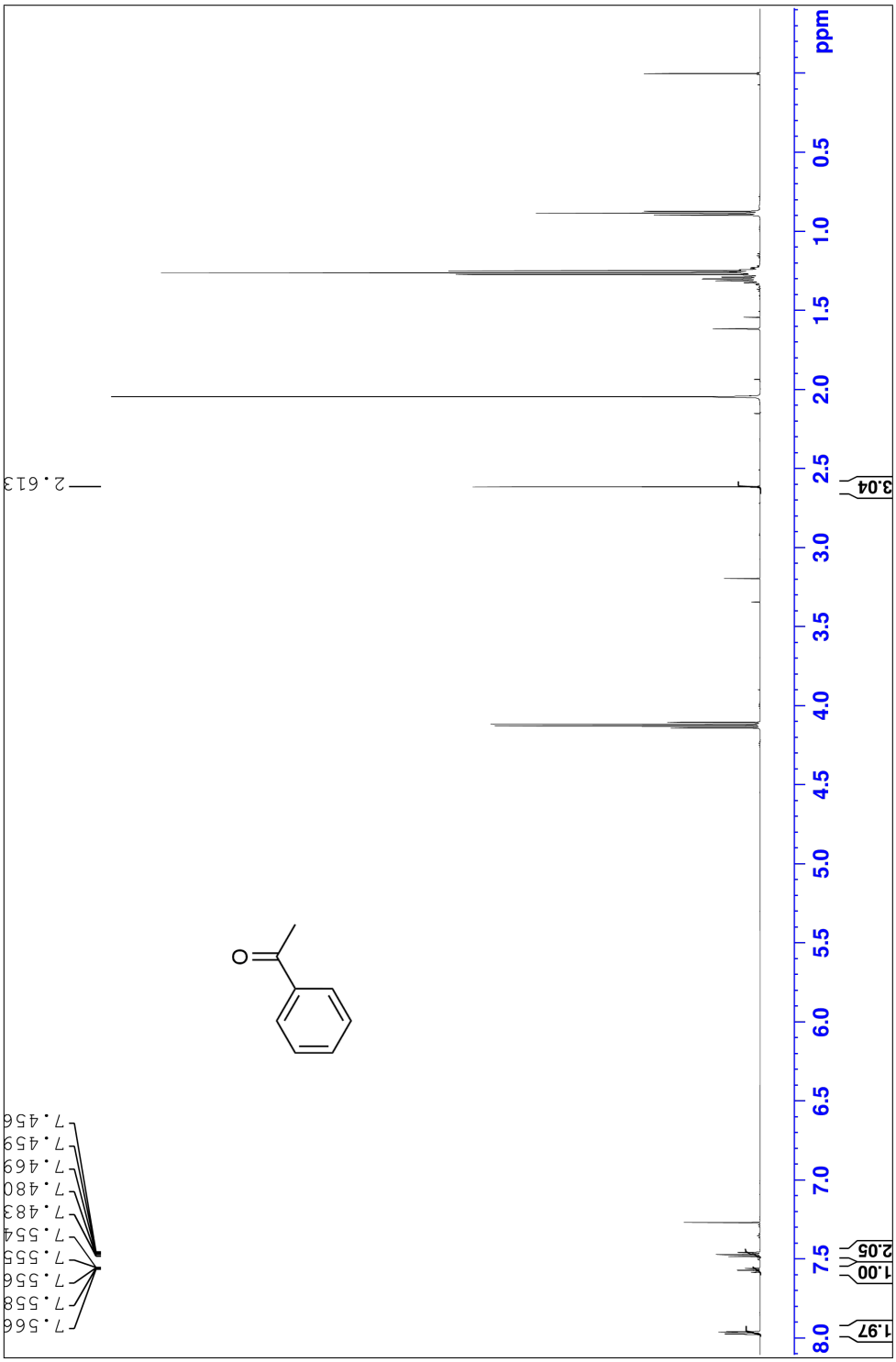


K.2 Compound 3.2/3.3 ^{13}C-NMR

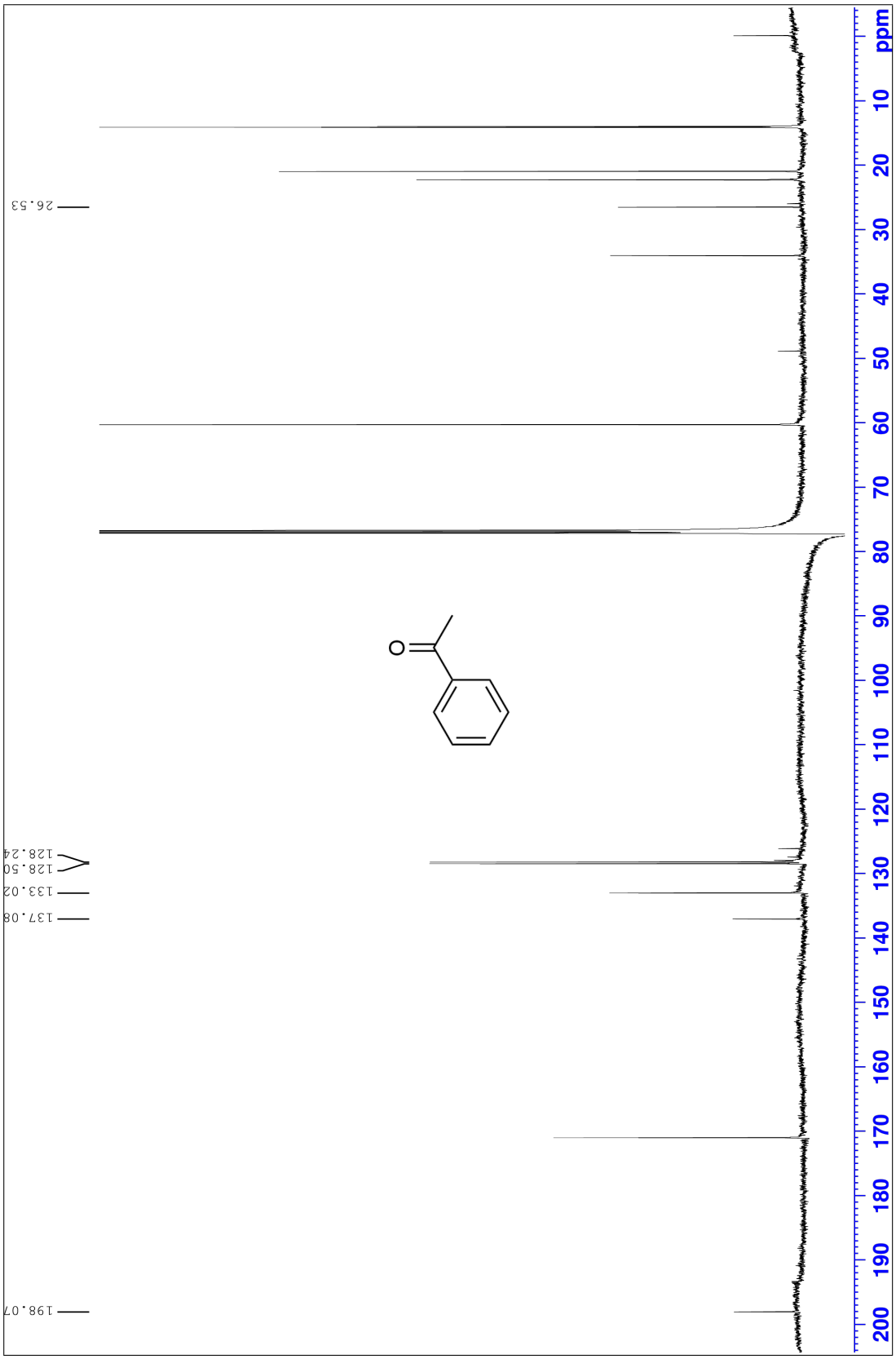


L Characterisation of compound (3.4)

L.1 Compound 3.4 ^{1}H-NMR

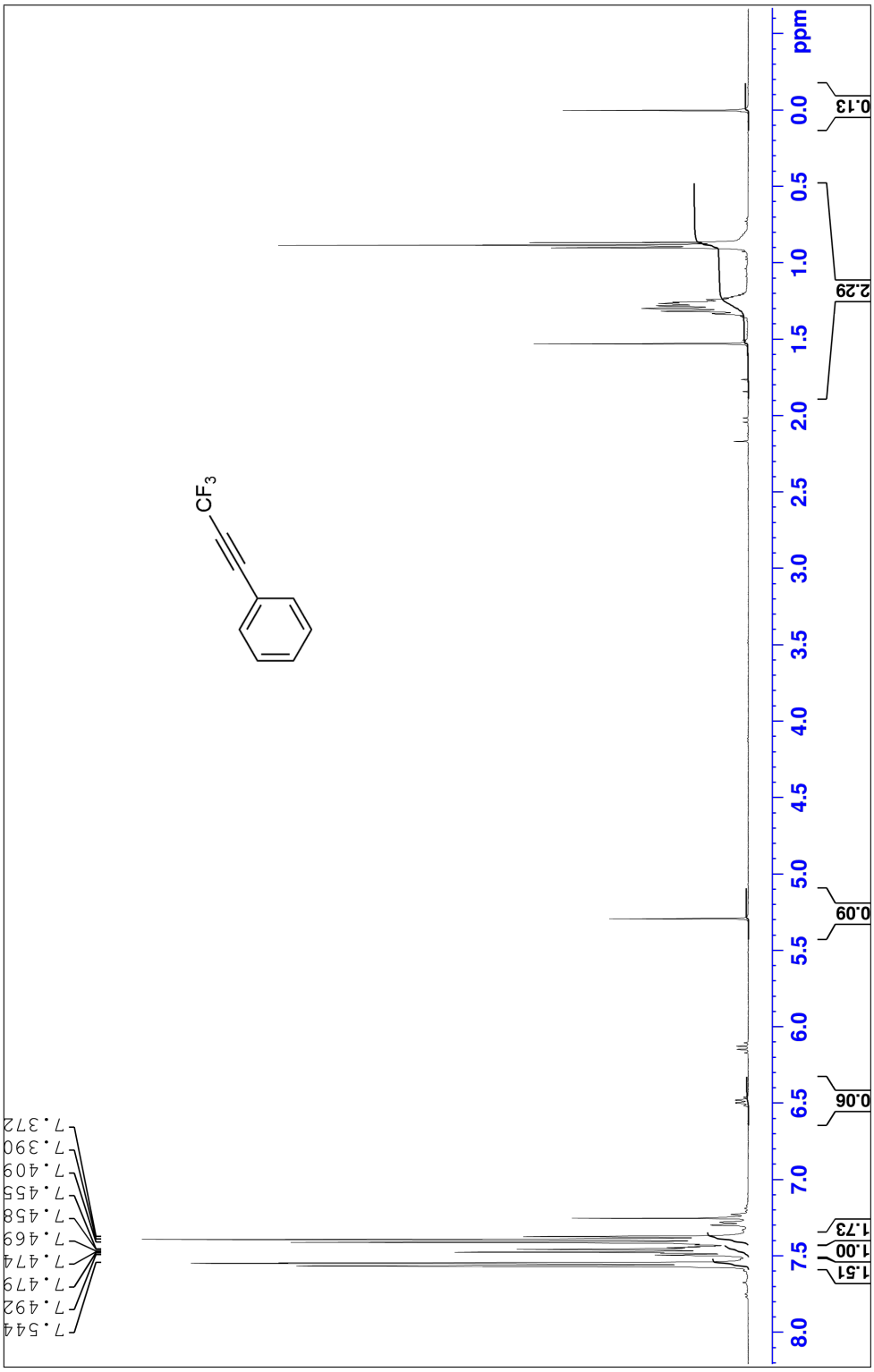


L.2 Compound 3.4 ^{13}C-NMR

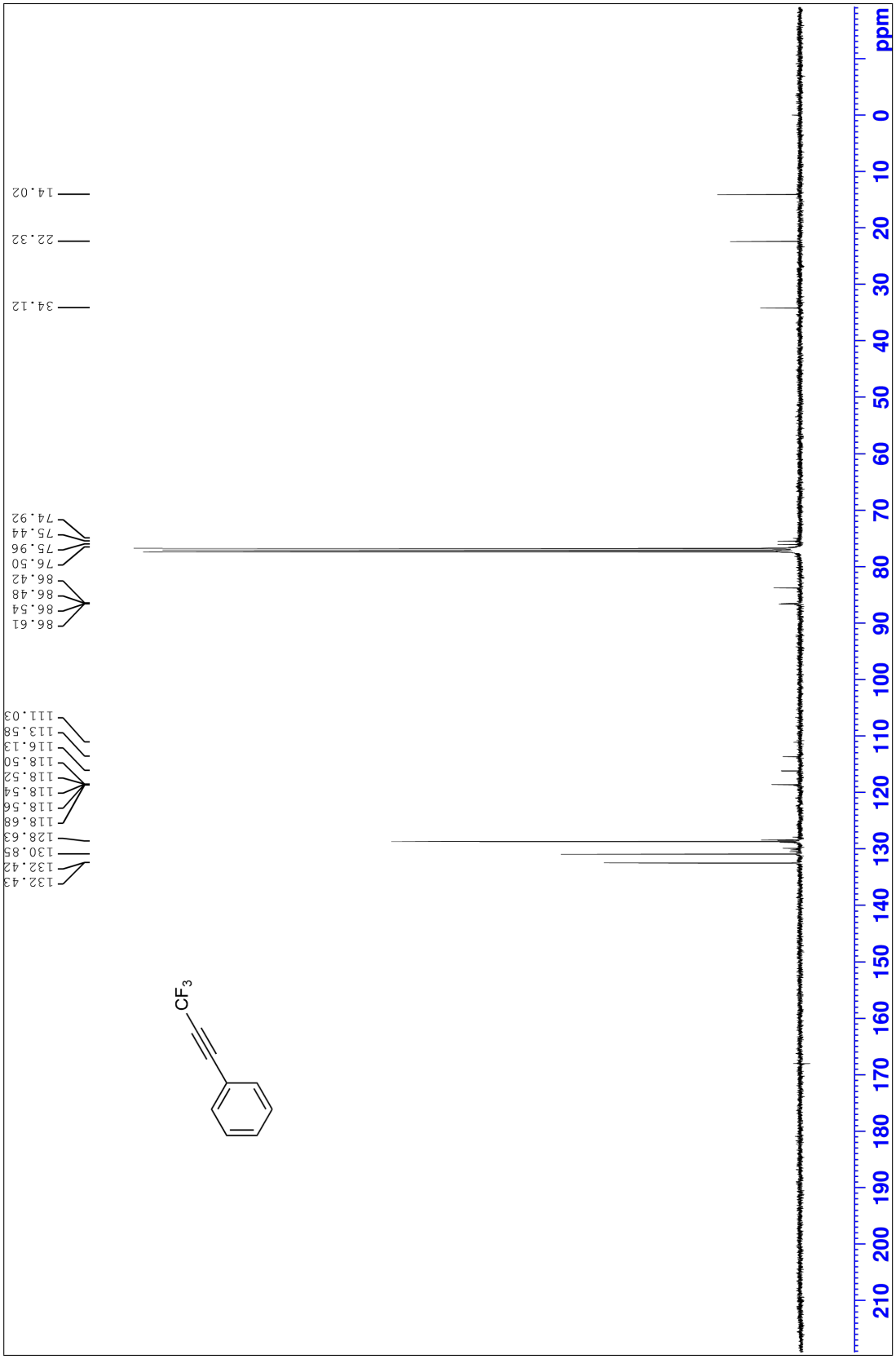


M Characterisation of compound (4.1)

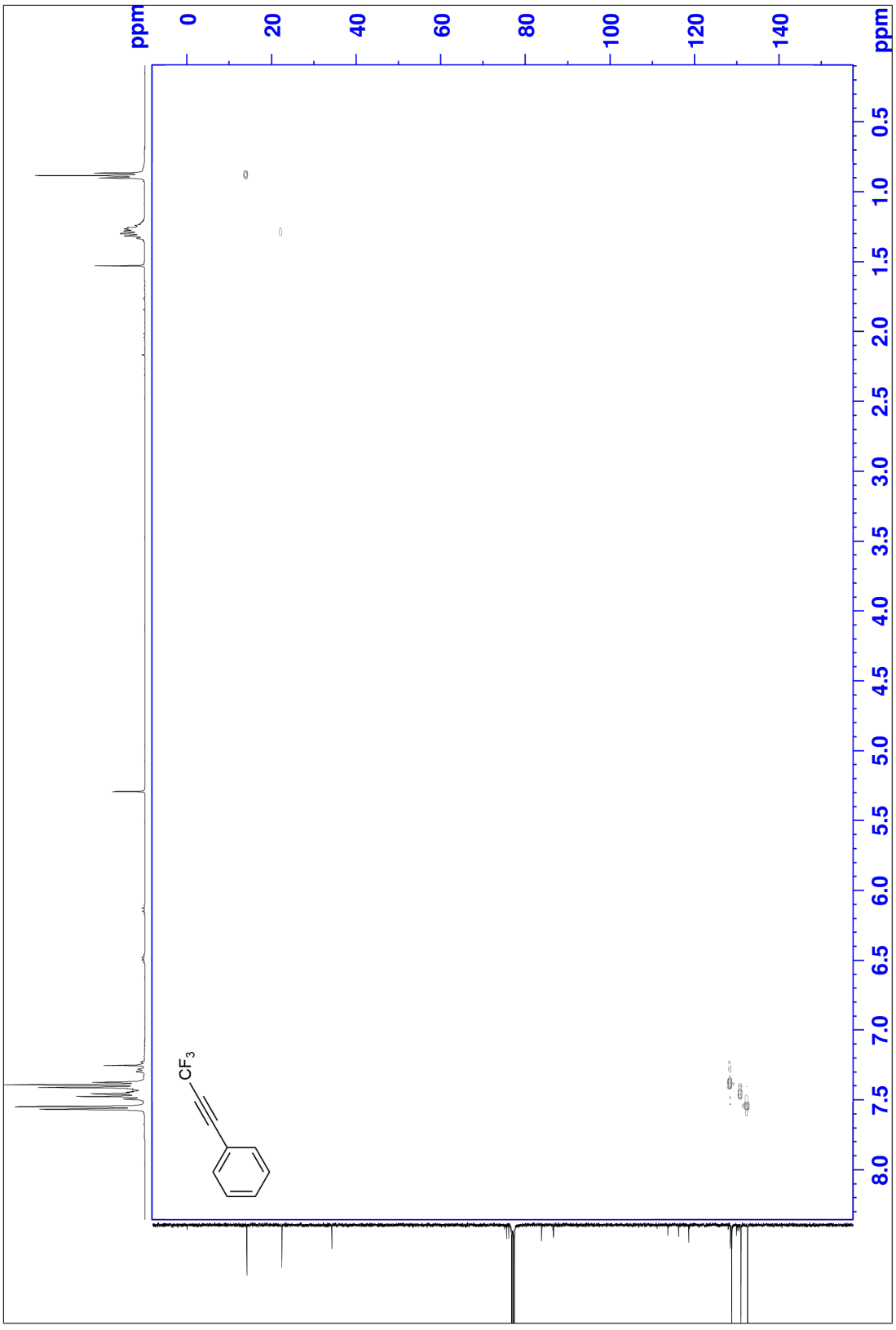
M.1 Compound 4.1 ^{1}H-NMR



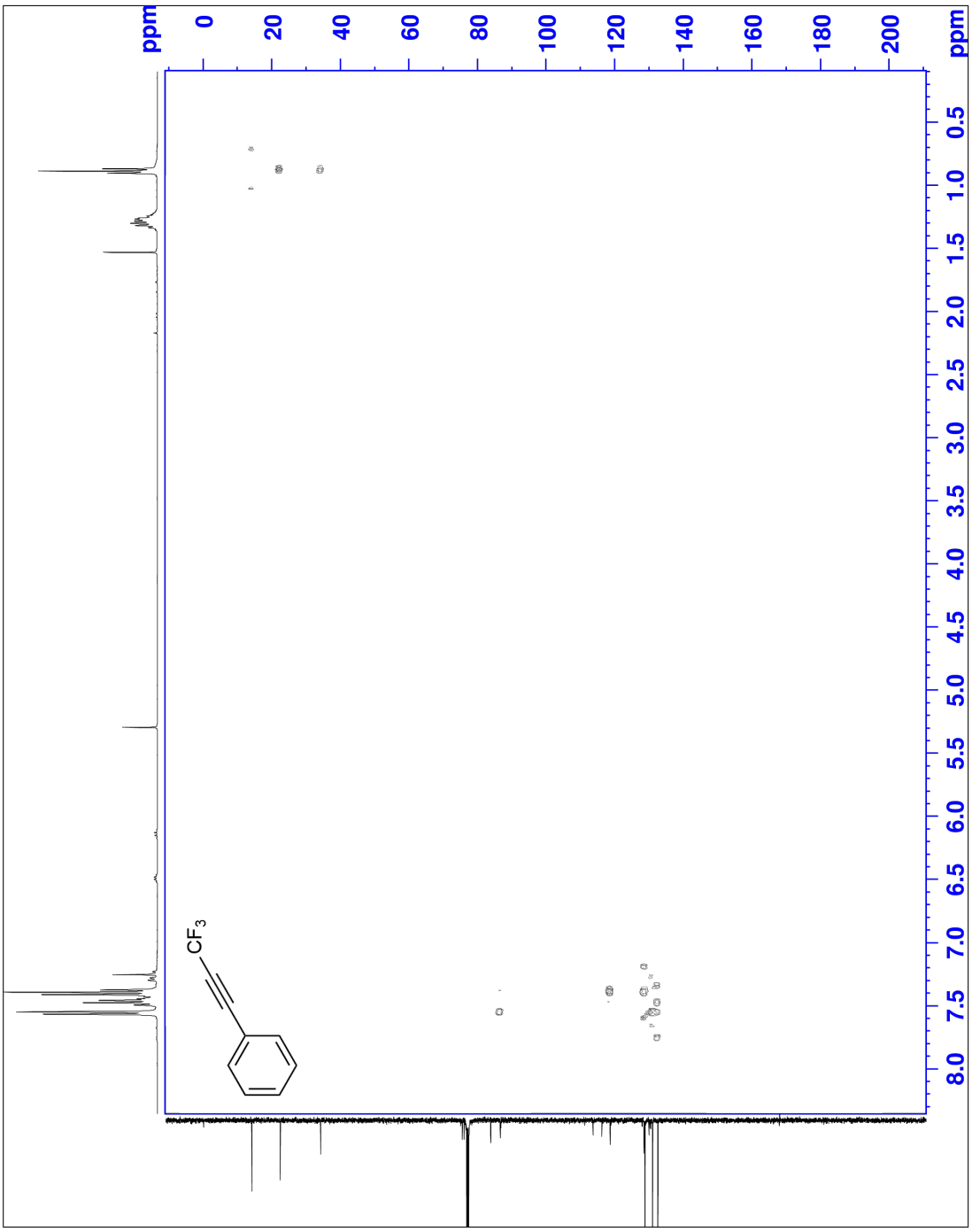
M.2 Compound 4.1 ^{13}C-NMR



M.3 Compound 4.1 H,C-HSQC 2D-NMR

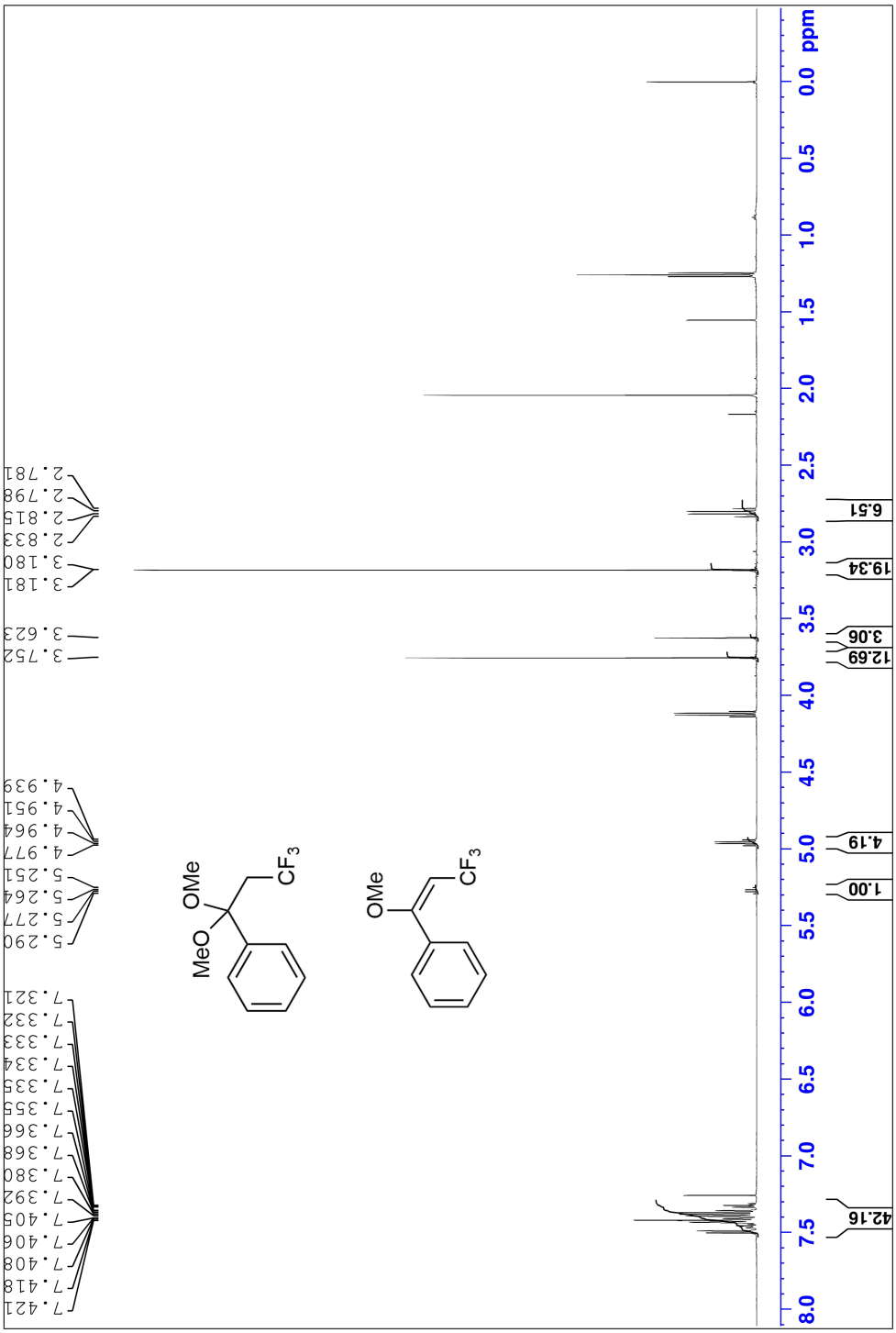


M.4 Compound 4.1 H,C-HMBC 2D-NMR

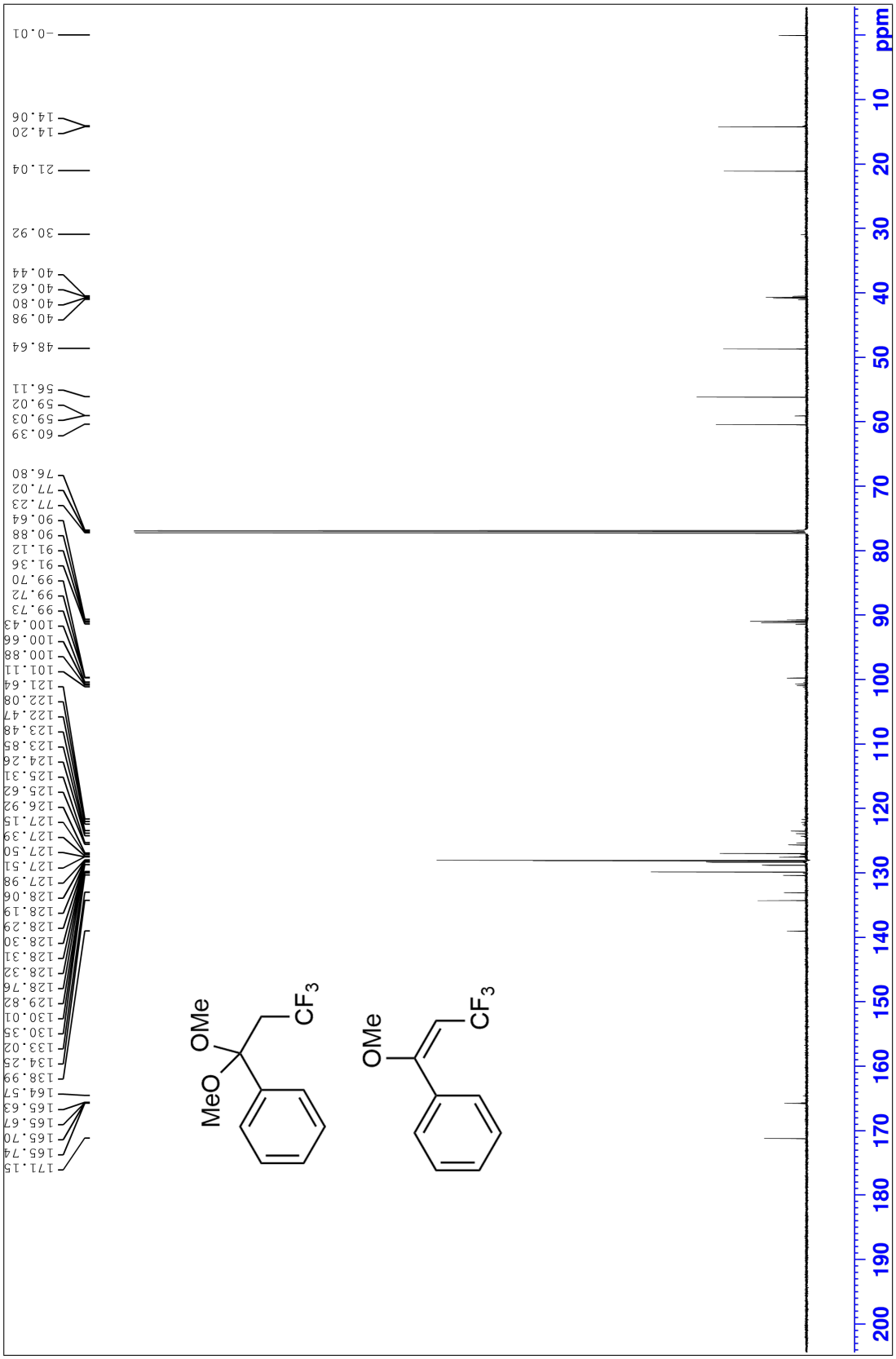


N Characterisation of compound (4.2/4.3)

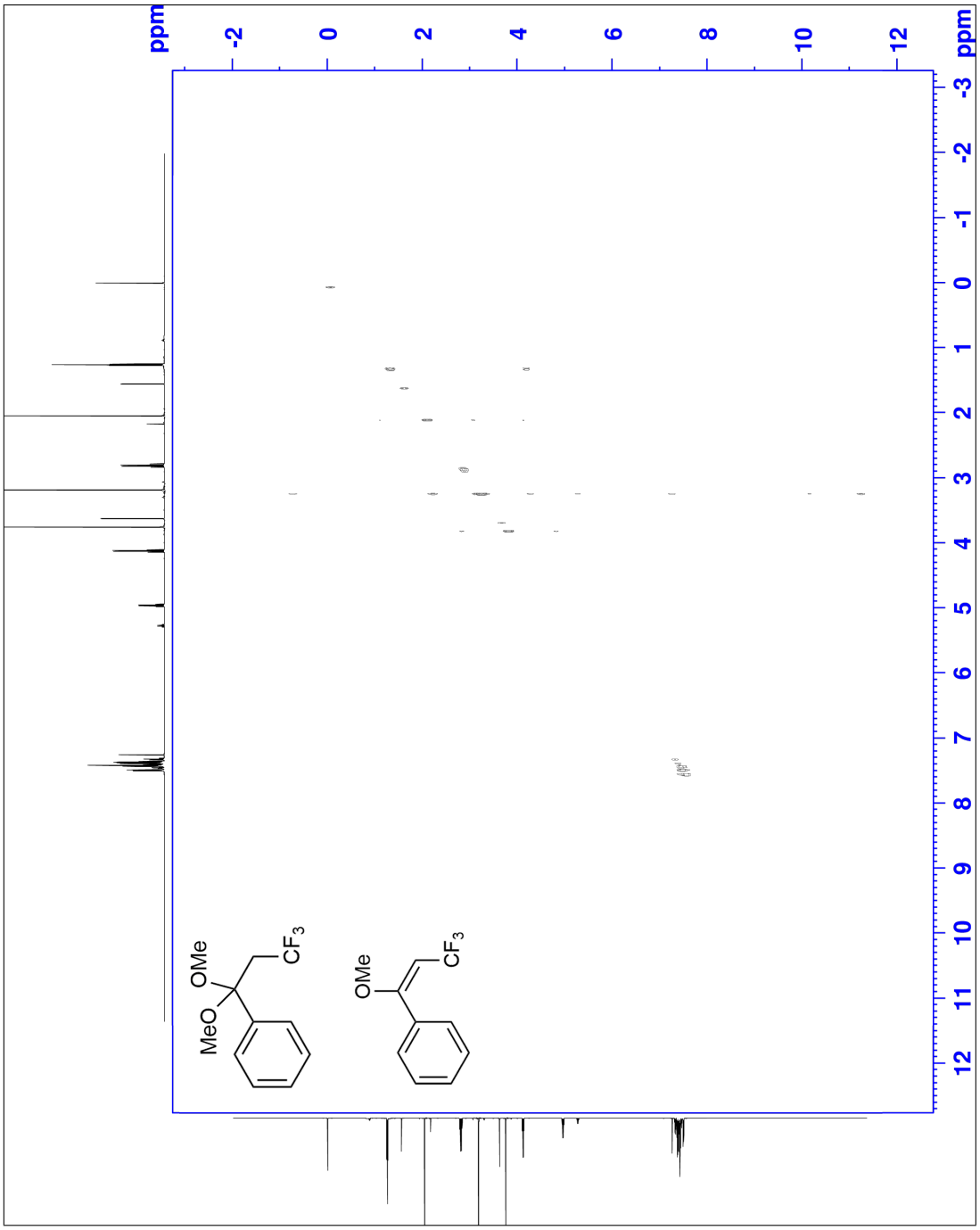
N.1 Compound 4.2/4.3 ^{1}H-NMR



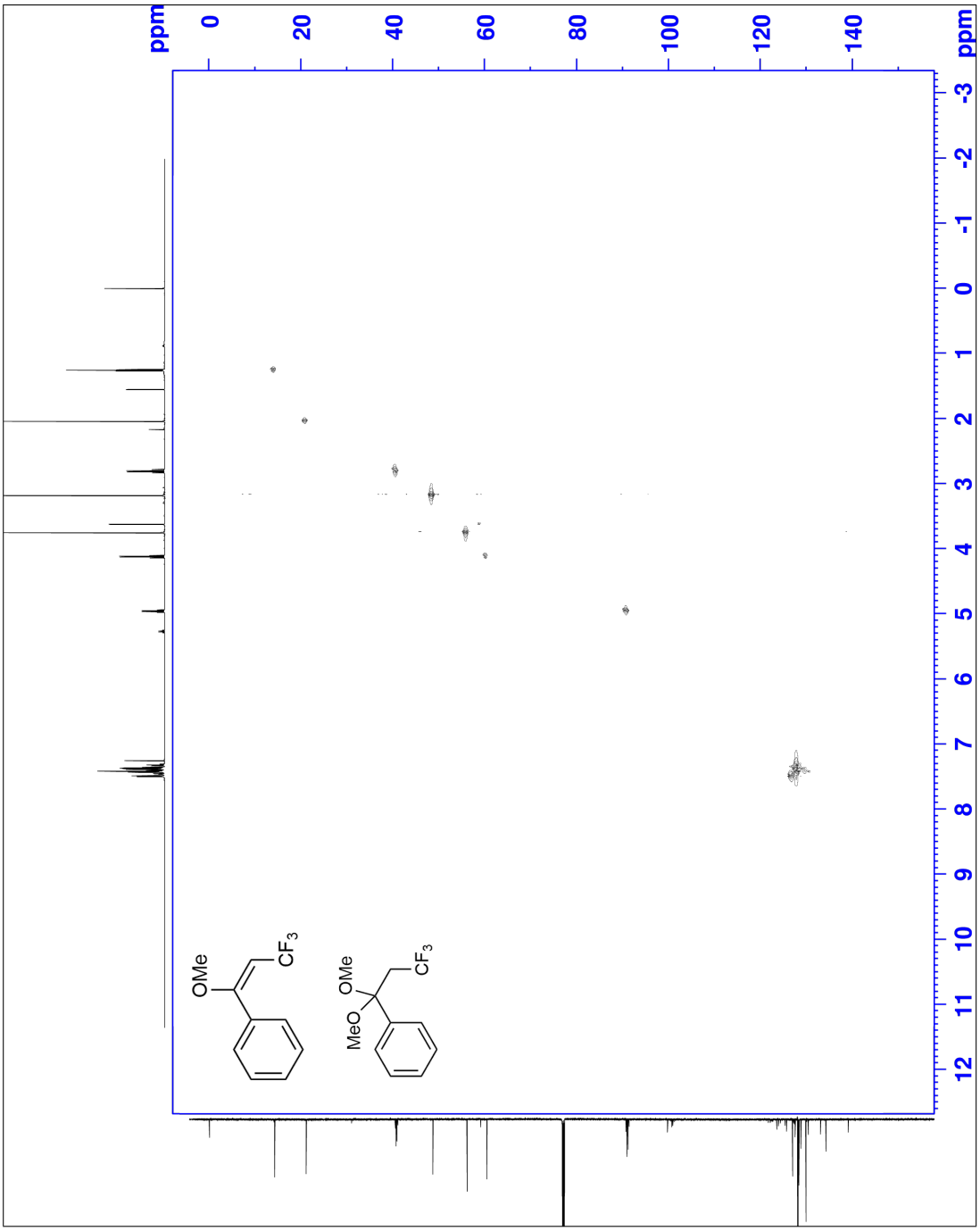
N.2 Compound 4.2/4.3 ^{13}C-NMR



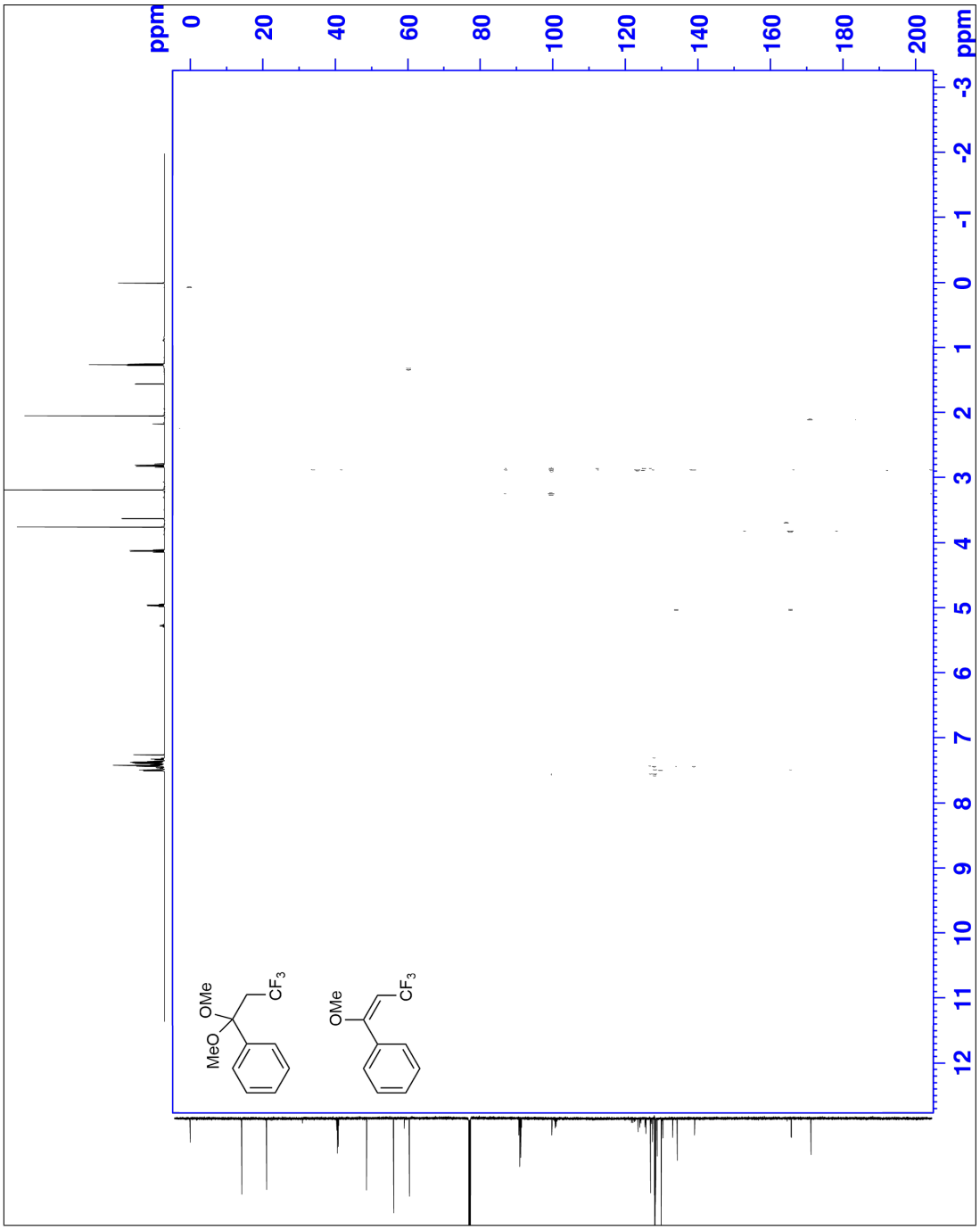
N.3 Compound 4.2/4.3 H,H-COSY 2D-NMR



N.4 Compound 4.2/4.3 H,C-HSQC 2D-NMR

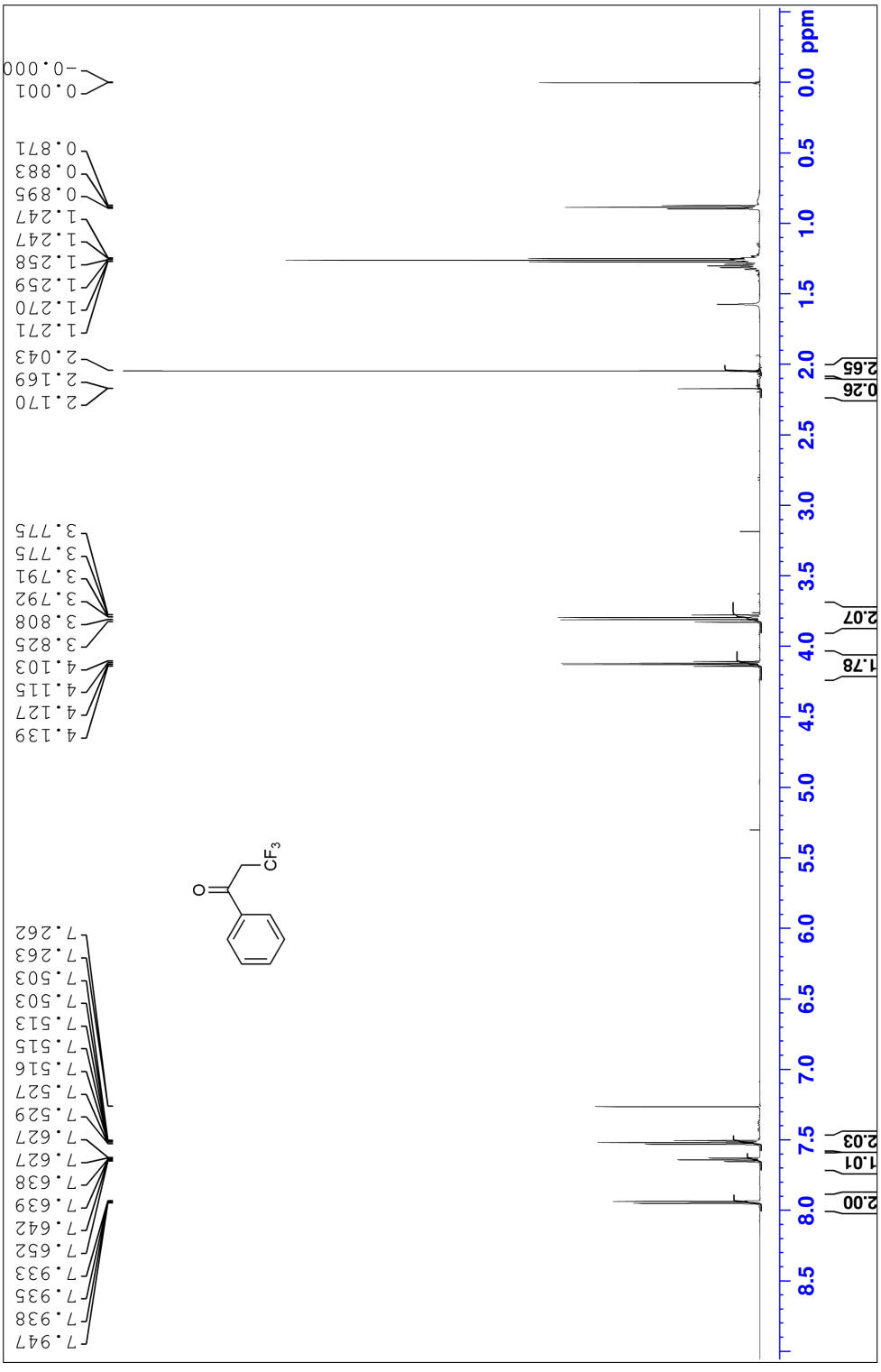


N.5 Compound 4.2/4.3 H,C-HMBC 2D-NMR

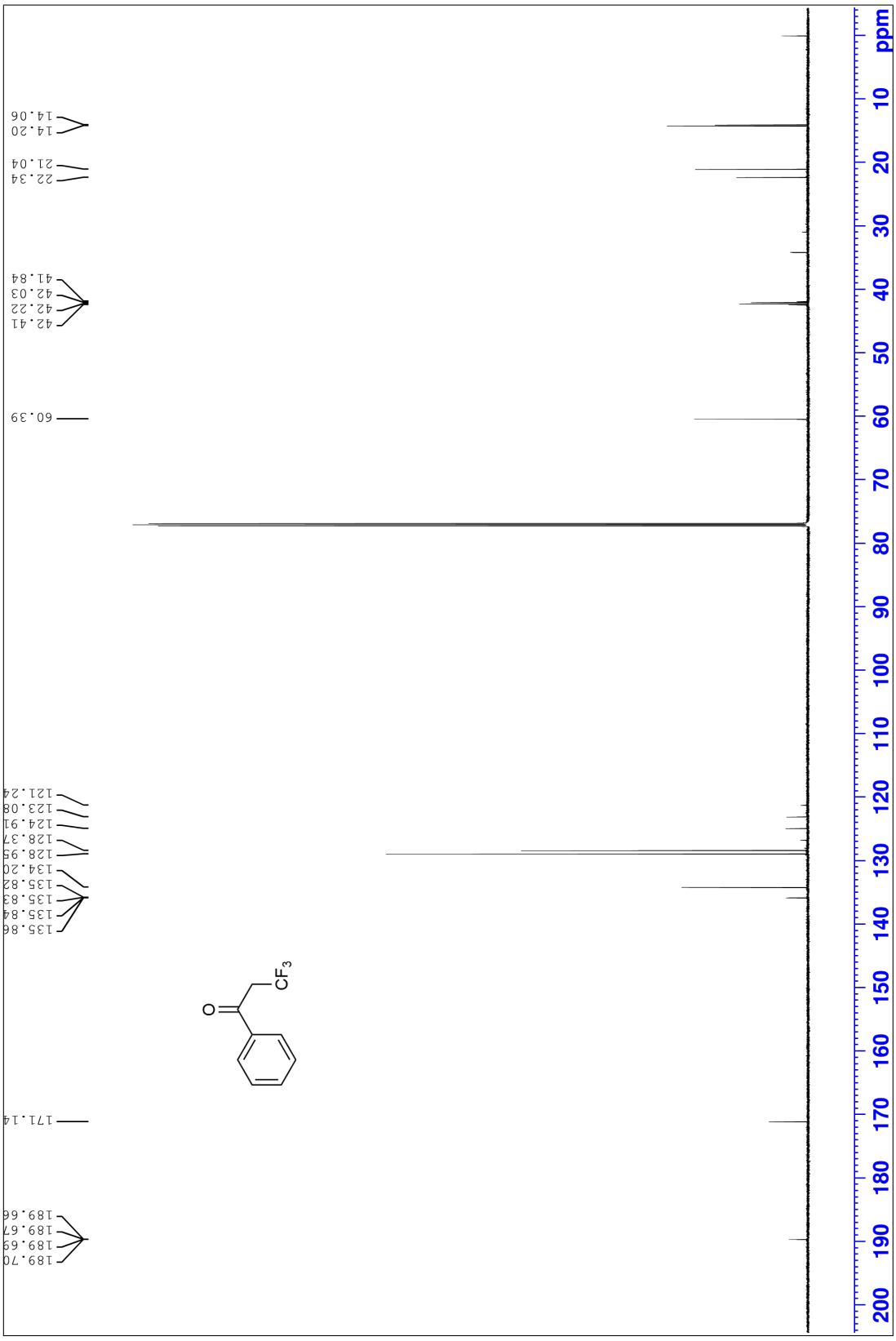


O Characterisation of compound (4.4)

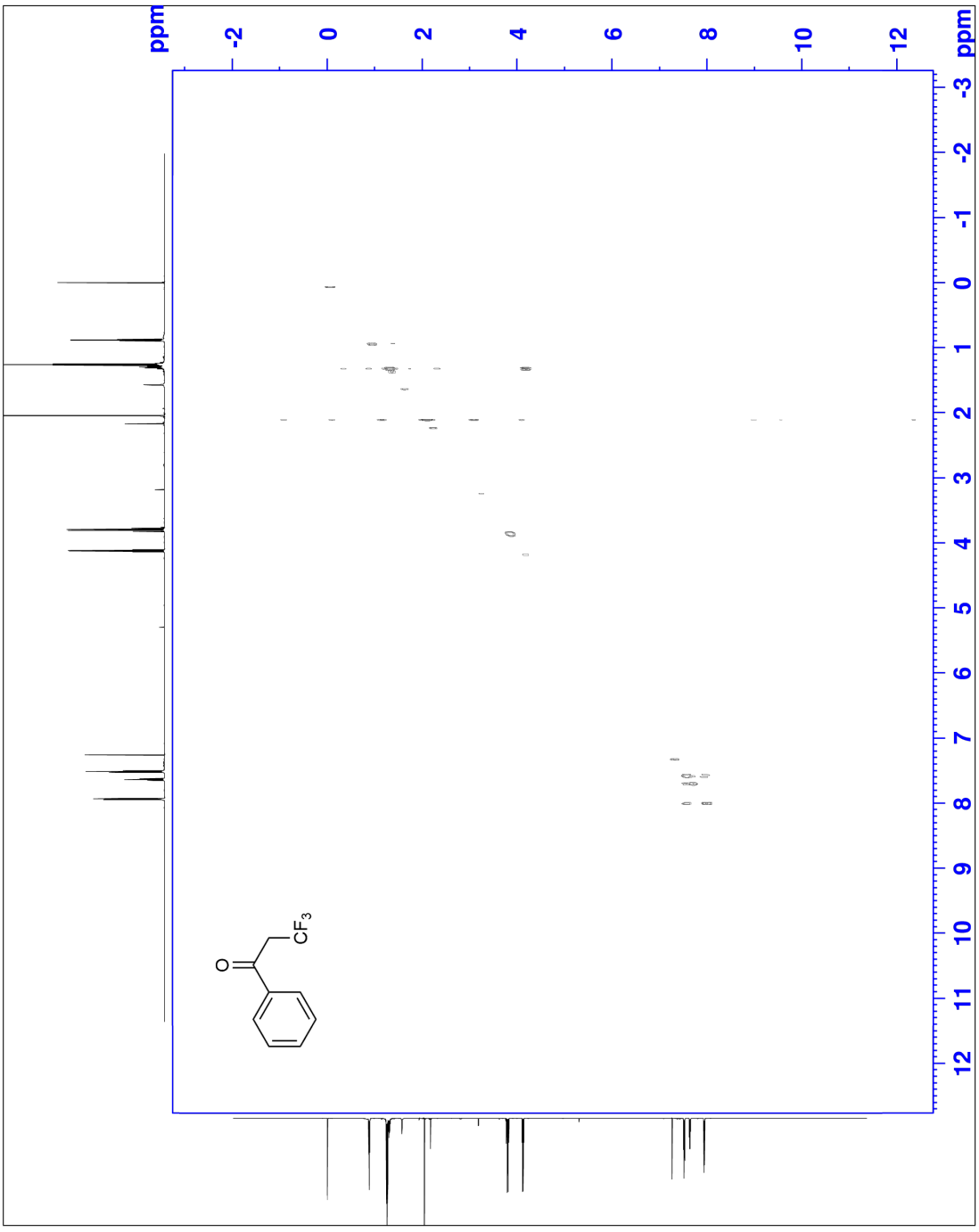
O.1 Compound 4.4 ^{1}H-NMR



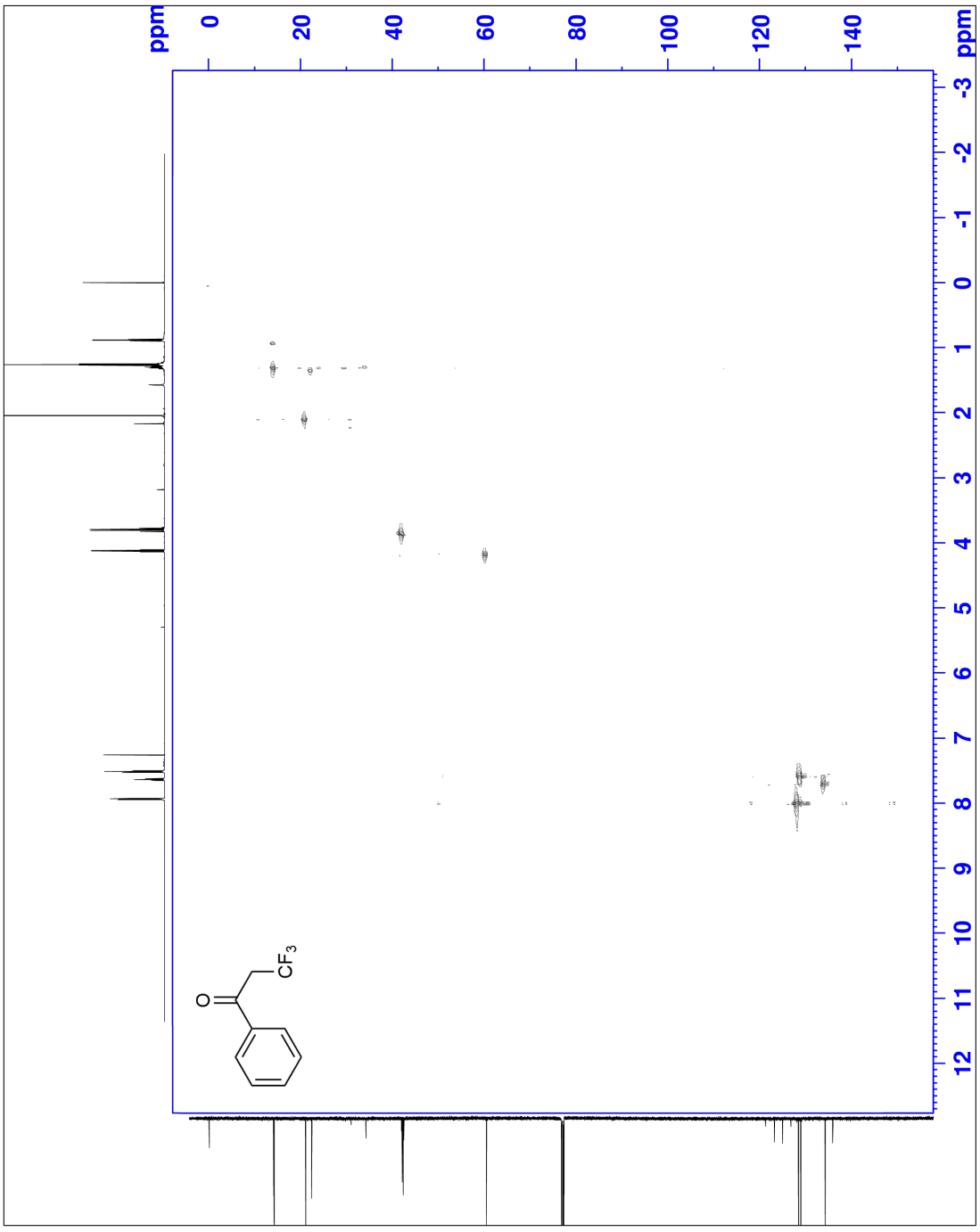
O.2 Compound 4.4 ^{13}C-NMR



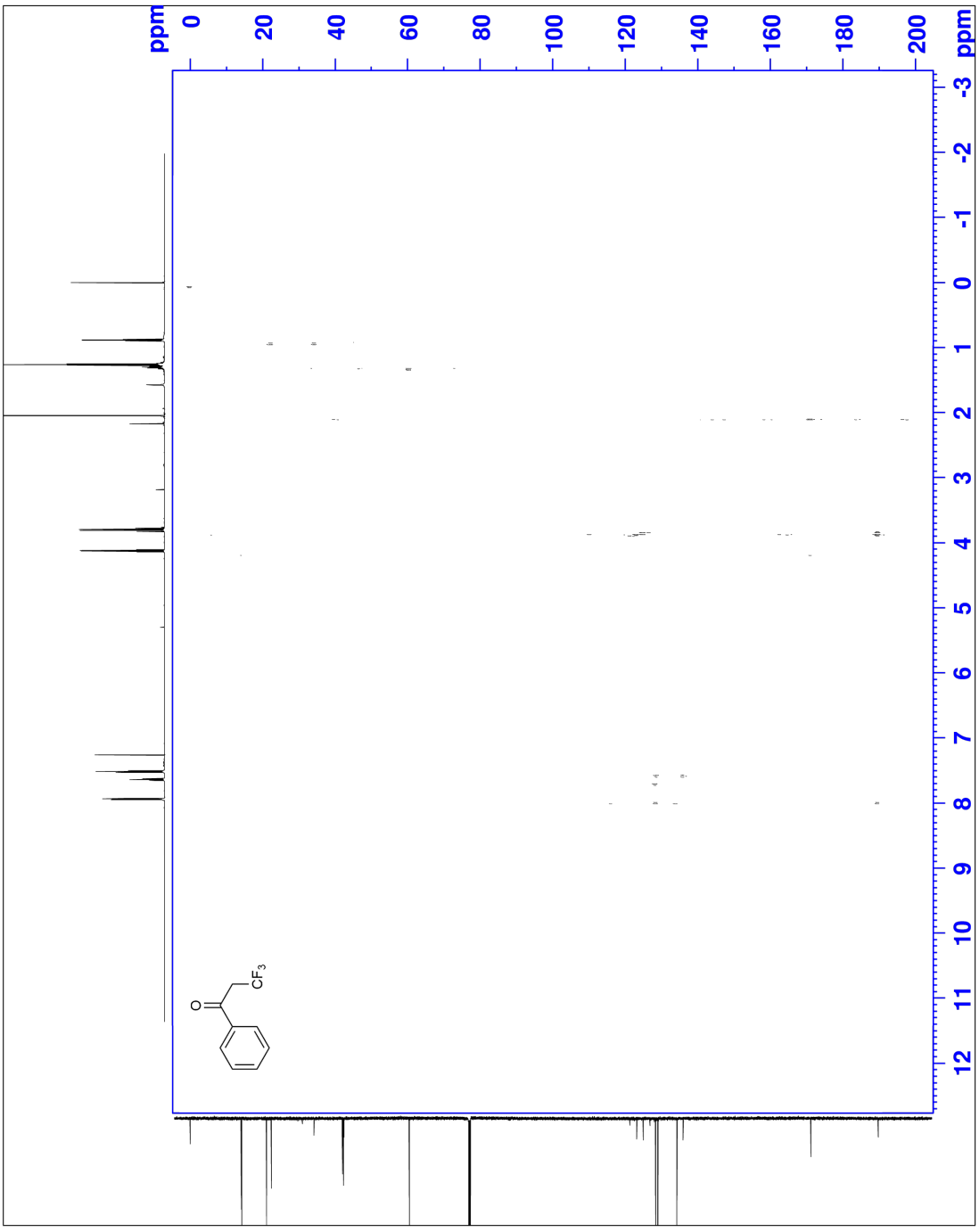
O.3 Compound 4.4 H,H-COSY 2D-NMR



O.4 Compound 4.4 H,C-HSQC 2D-NMR

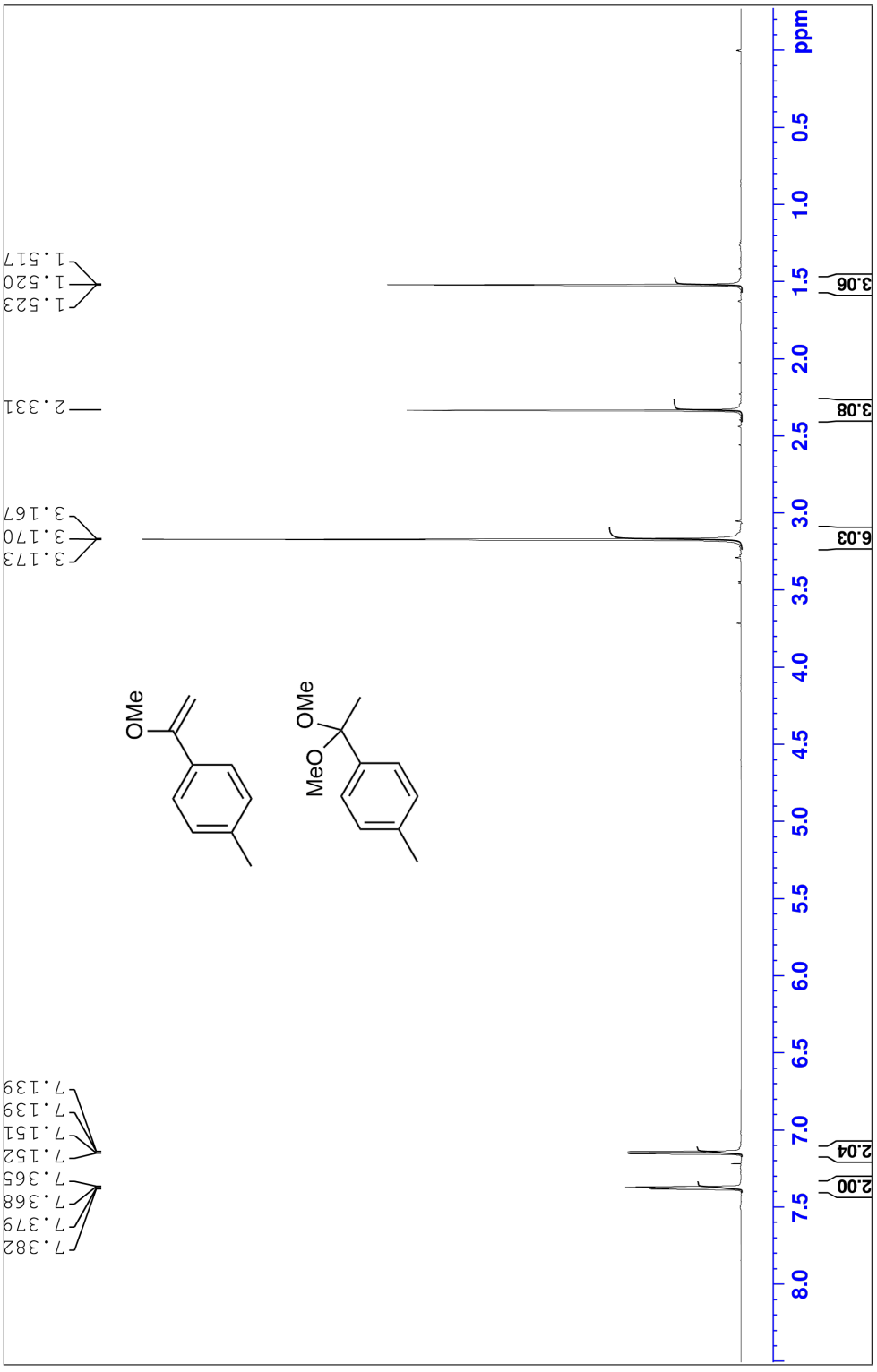


O.5 Compound 4.4 H,C-HMBC 2D-NMR

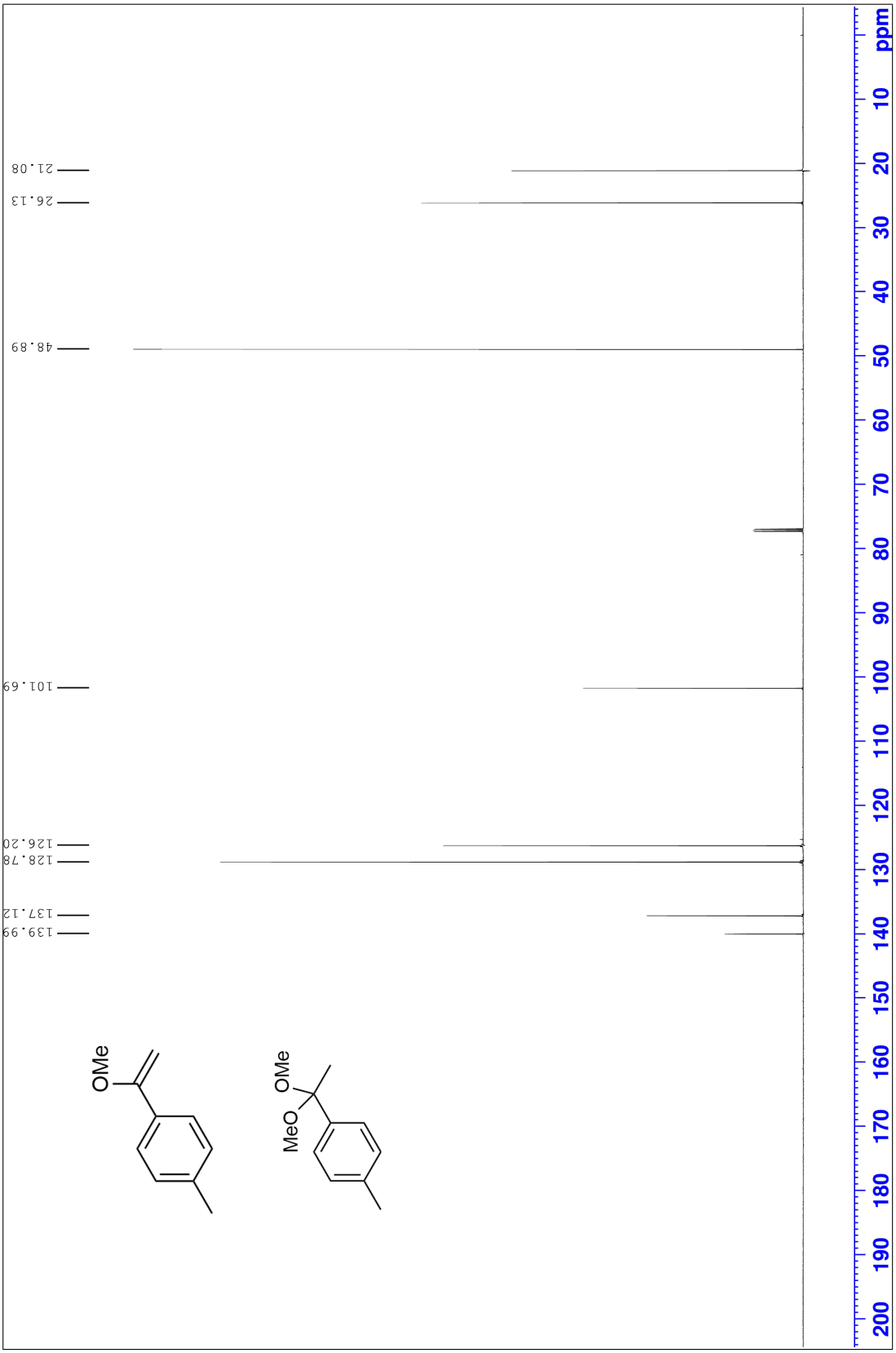


P Characterisation of compound (5.2/5.3)

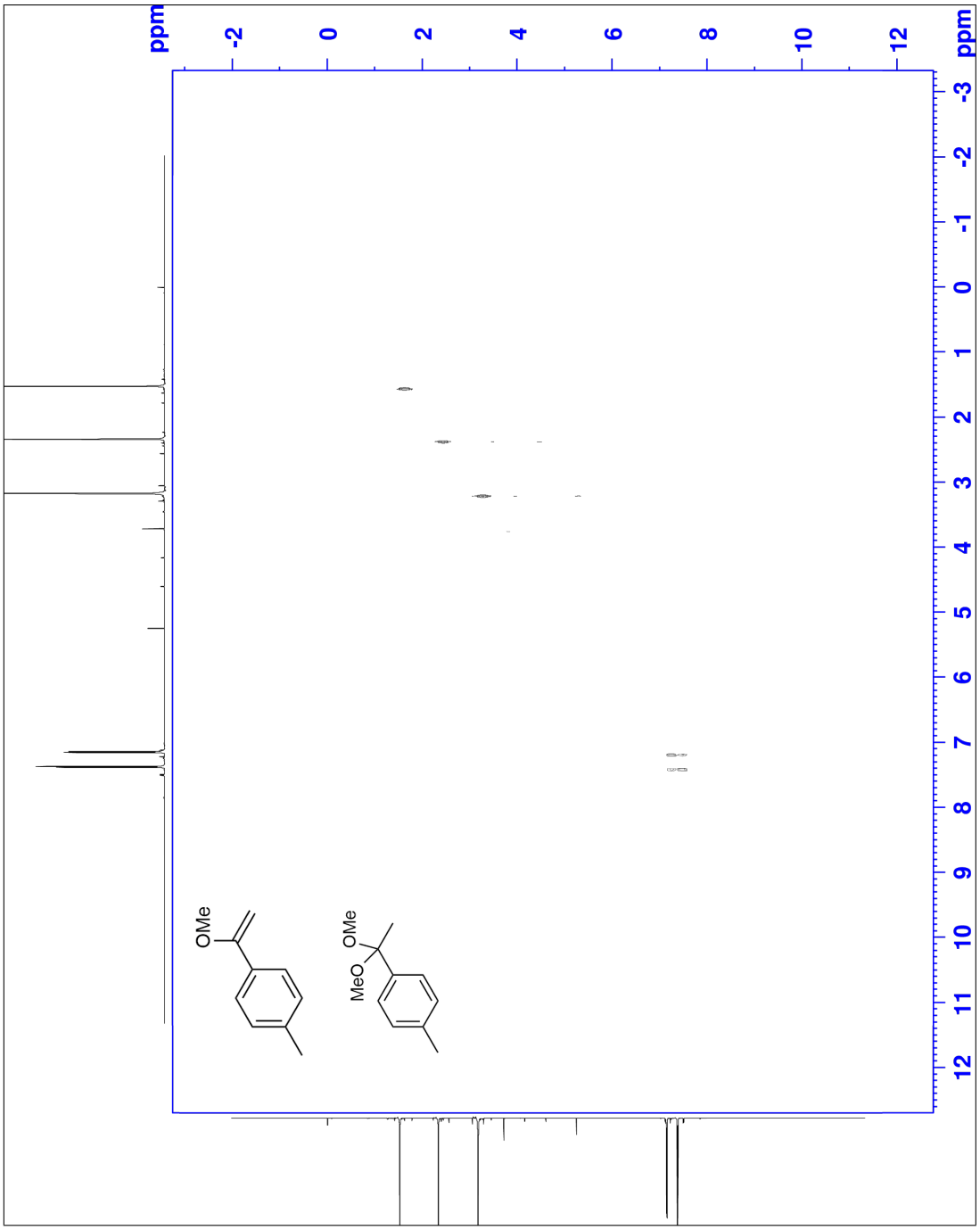
P.1 Compound 5.2/5.3 ^{1}H-NMR



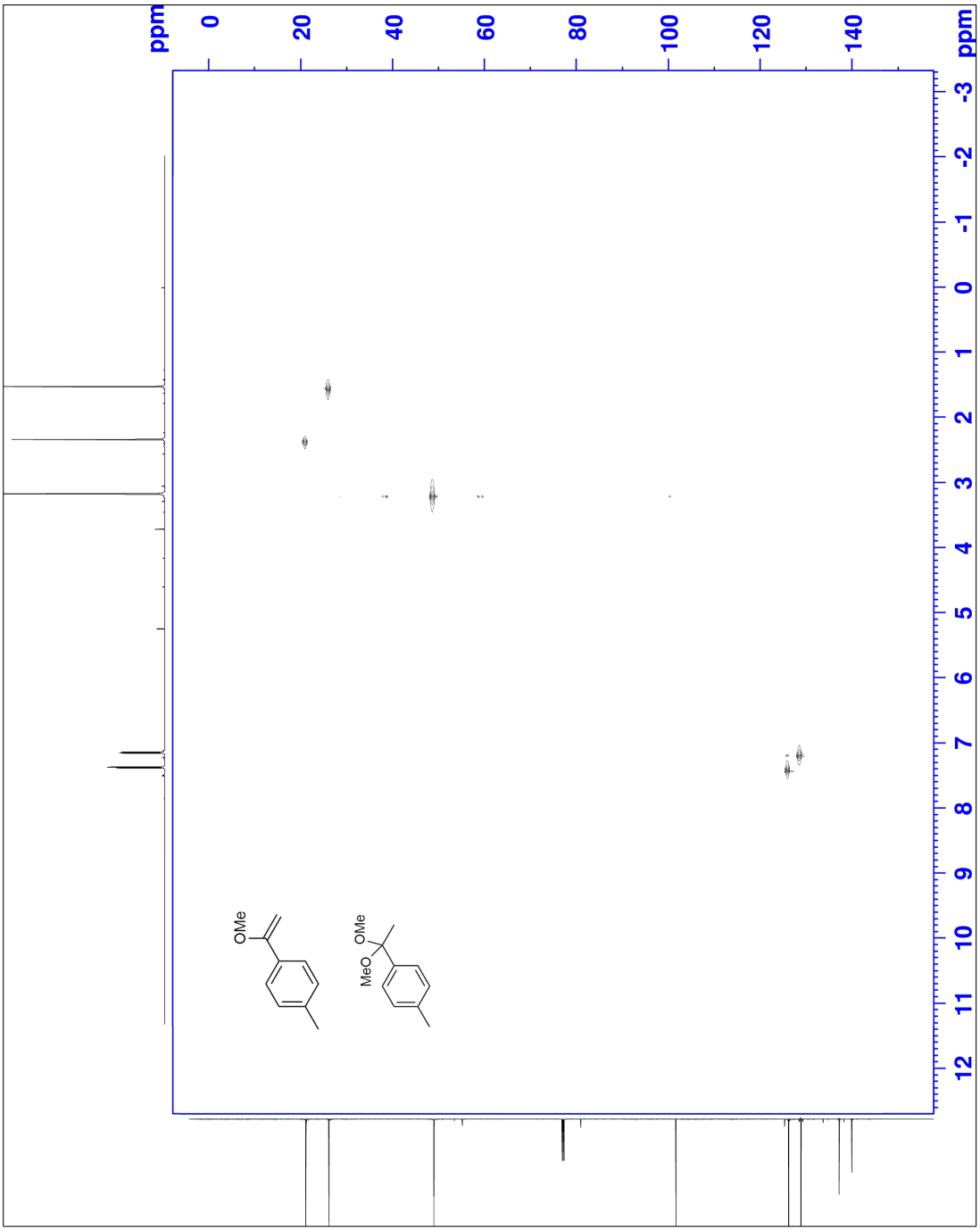
P.2 Compound 5.2/5.3 ^{13}C-NMR



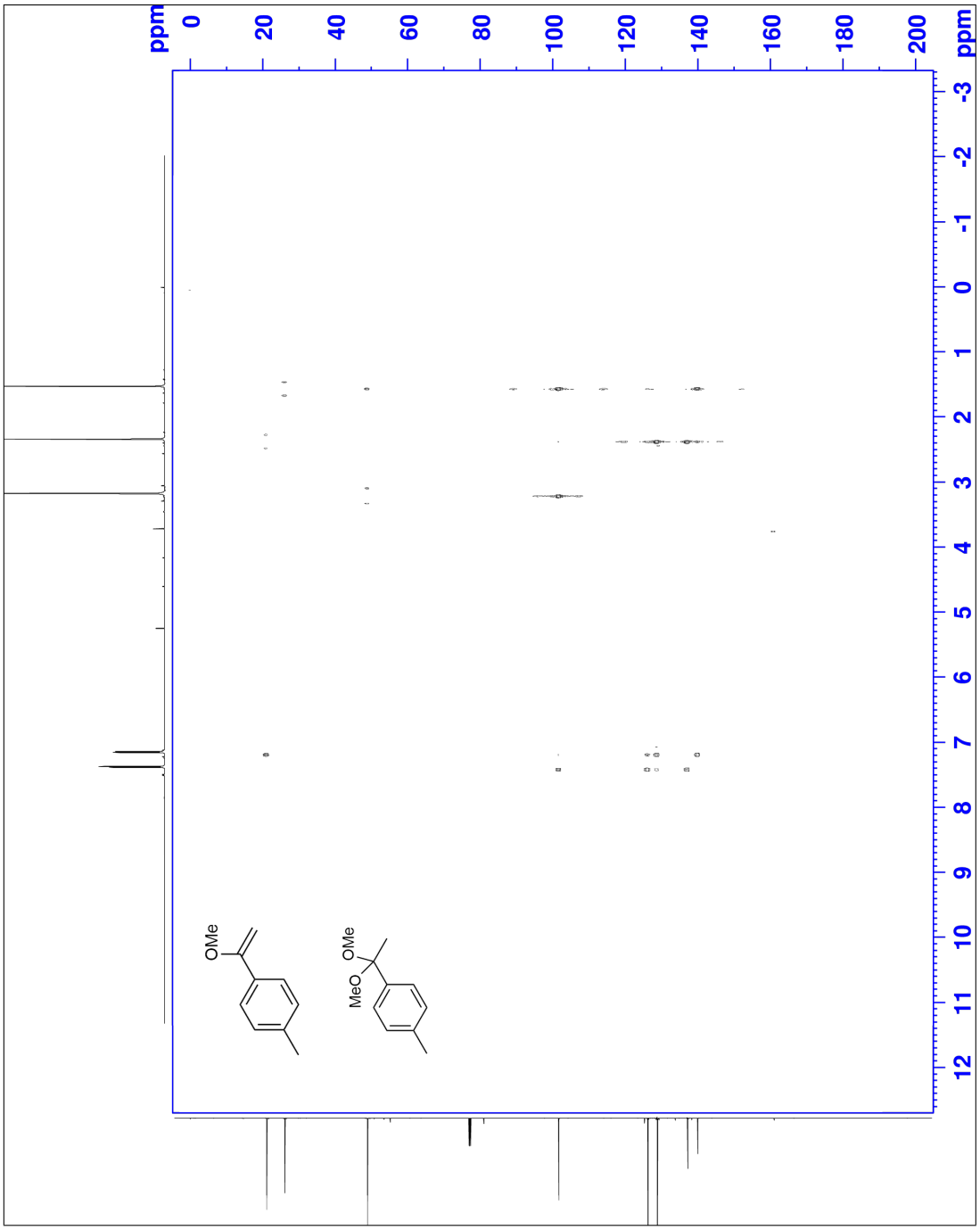
P.3 Compound 5.2/5.3 H,H-COSY 2D-NMR



P.4 Compound 5.2/5.3 H,C-HSQC 2D-NMR

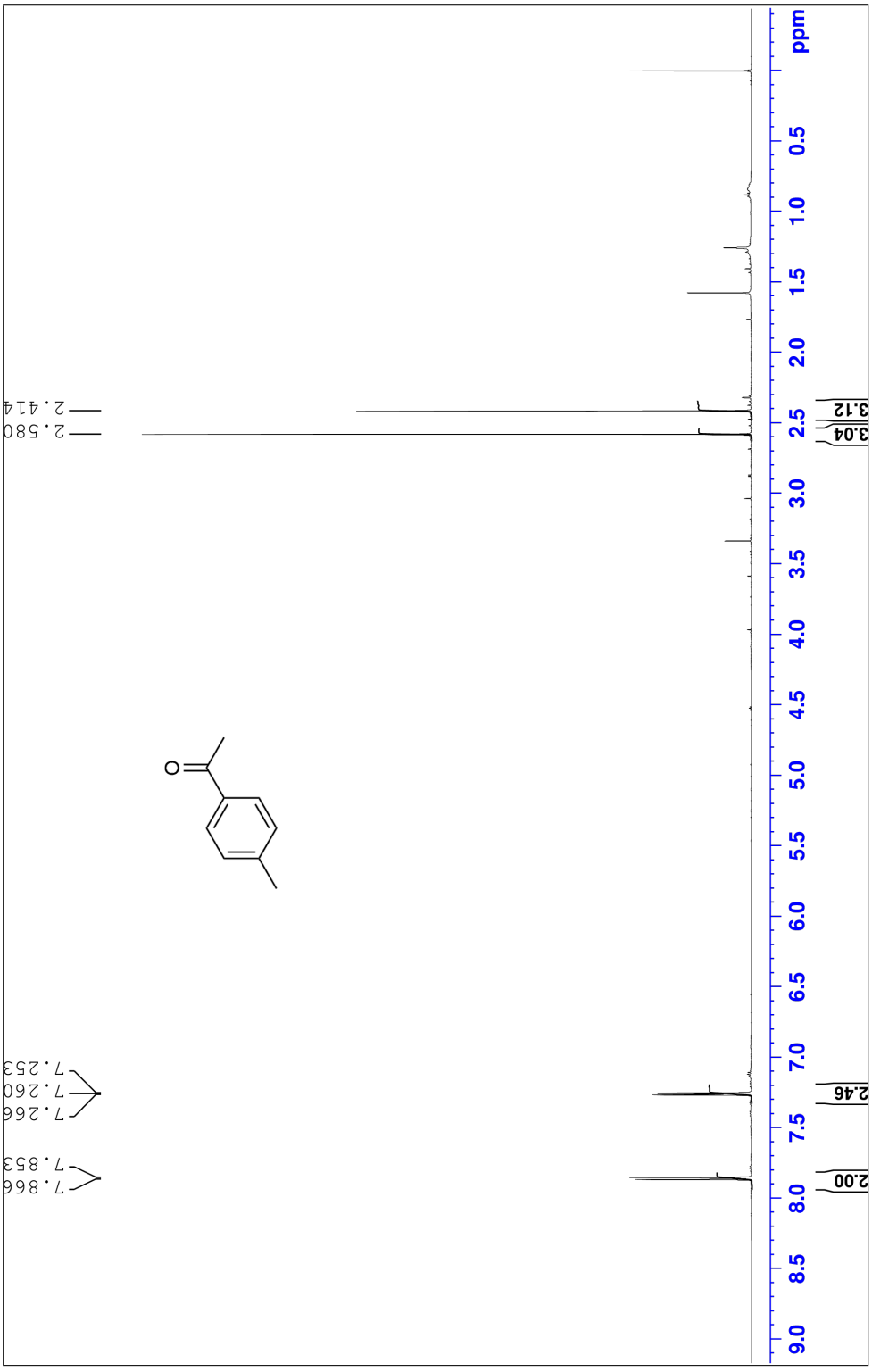


P.5 Compound 5.2/5.3 H,C-HMBC 2D-NMR



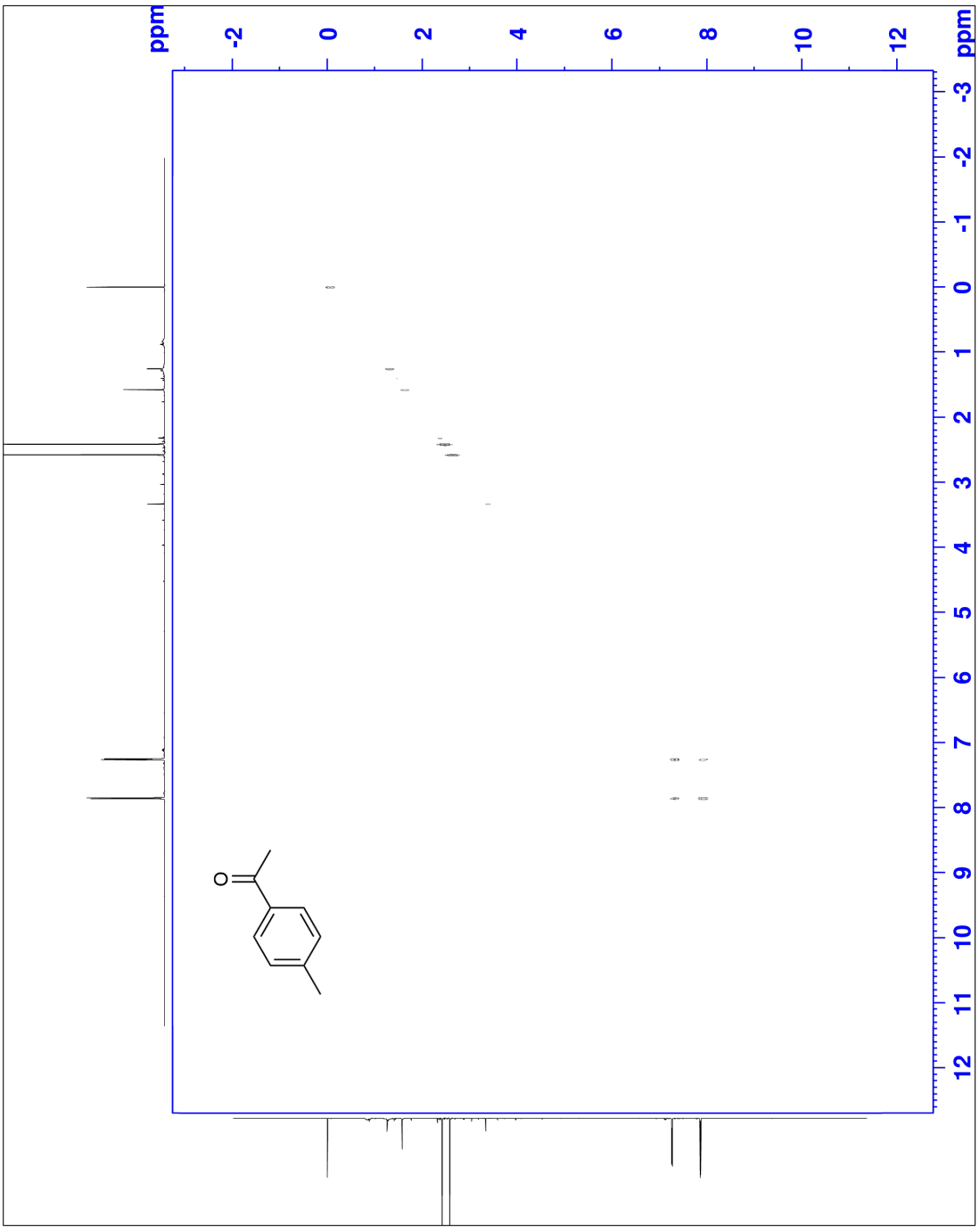
Q Characterisation of compound (5.4)

Q.1 Compound 5.4 ^{1}H-NMR

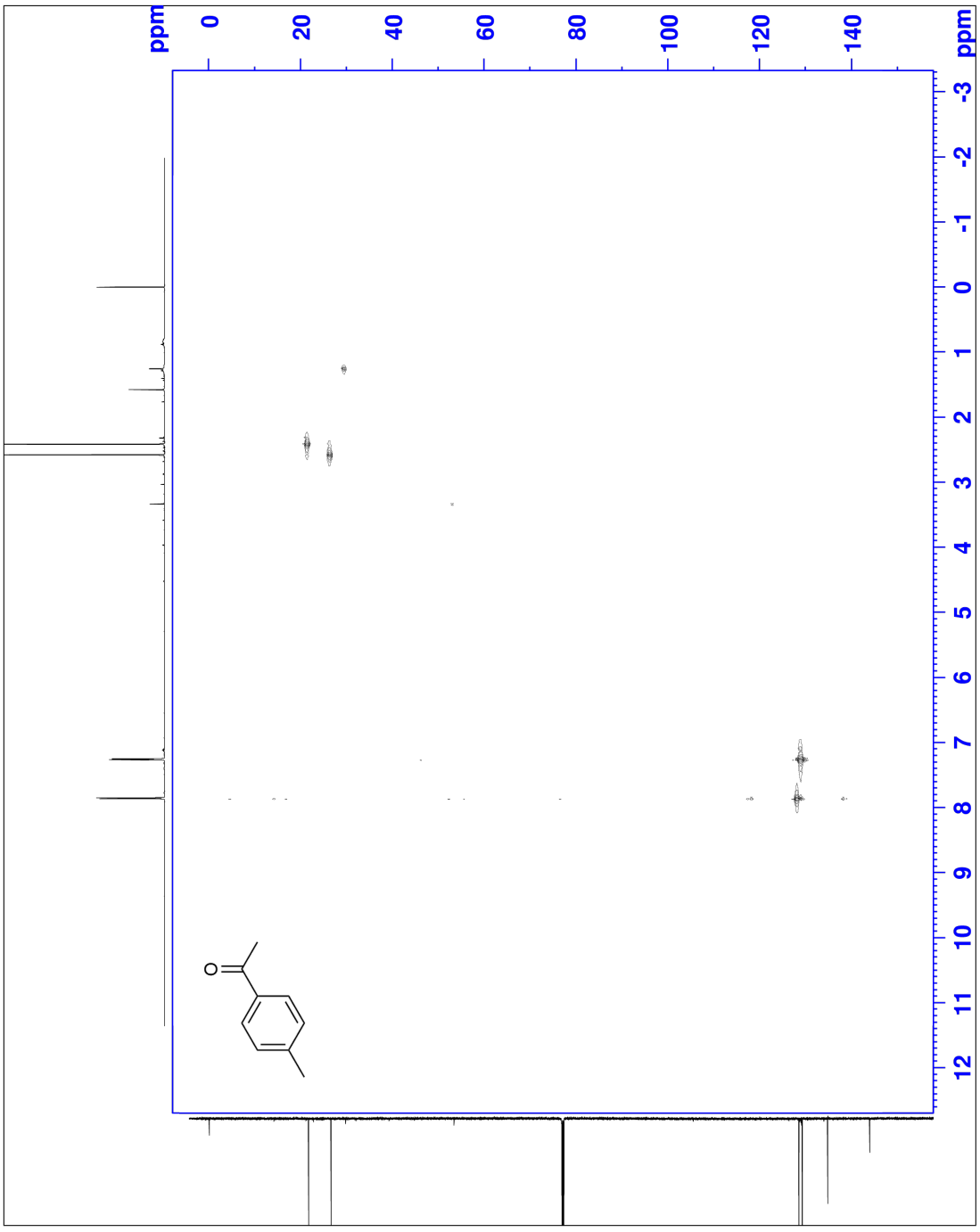


Q.2 Compound 5.4 ^{13}C-NMR

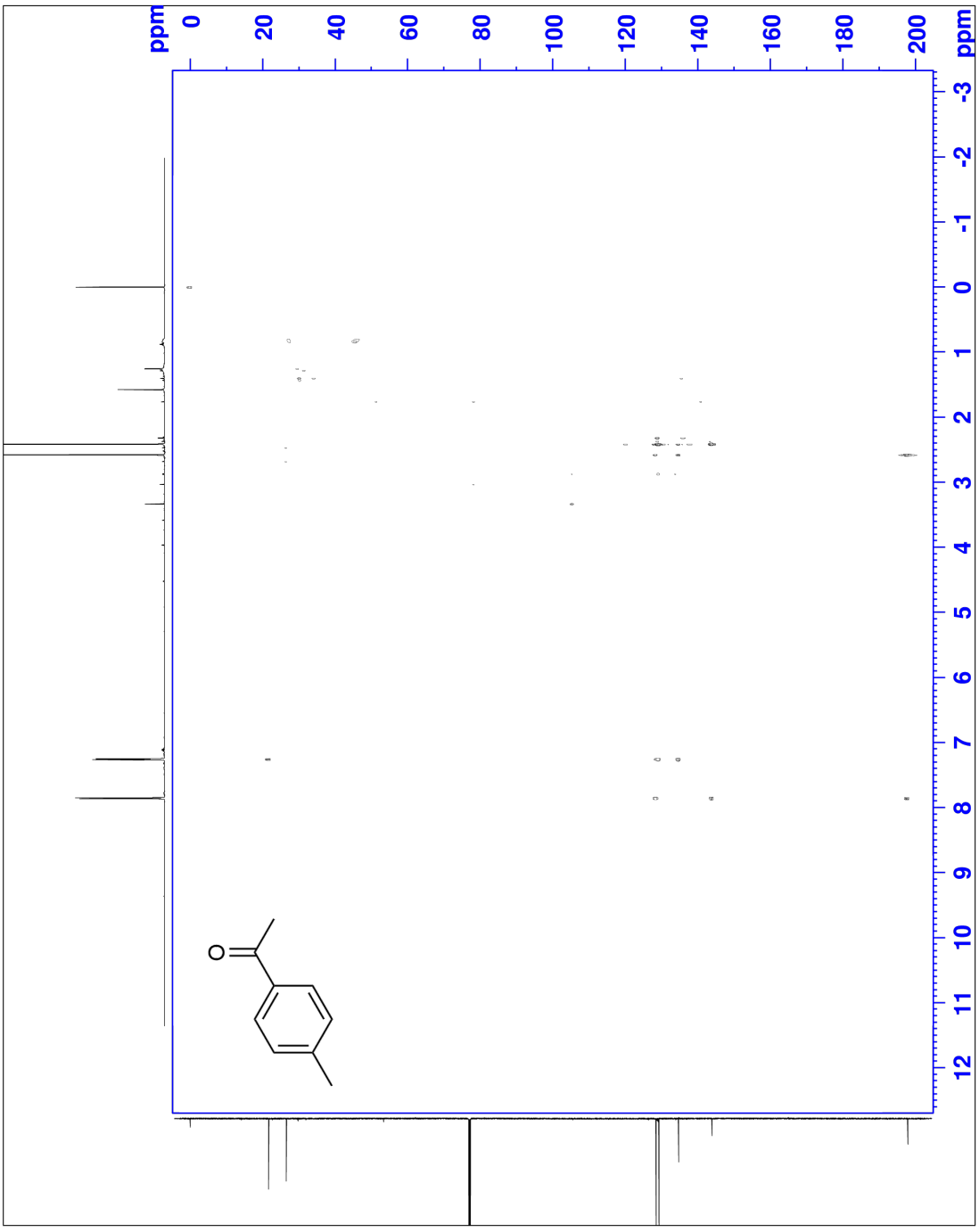
Q.3 Compound 5.4 H,H-COSY 2D-NMR



Q.4 Compound 5.4 H,C-HSQC 2D-NMR

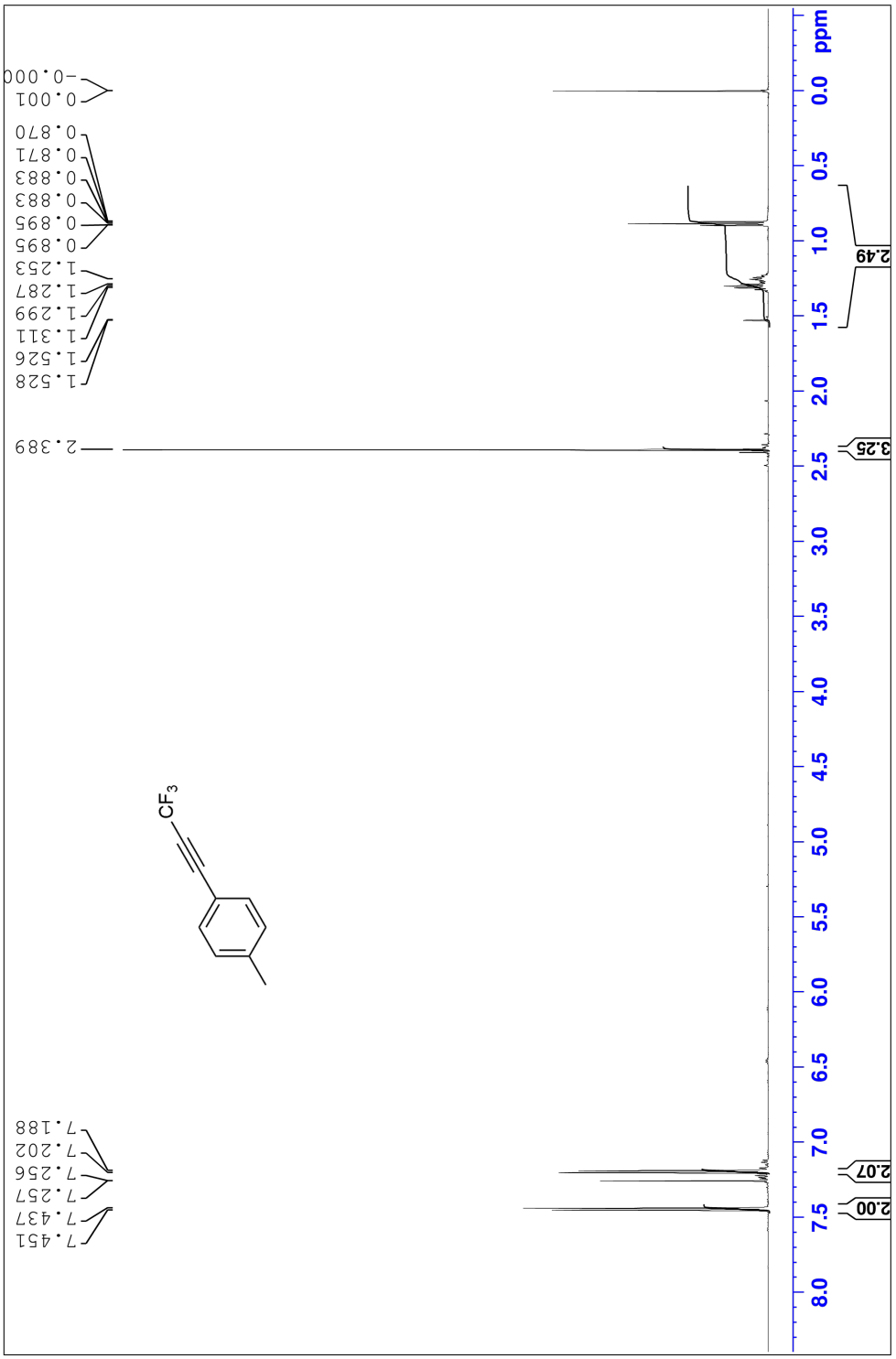


Q.5 Compound 5.4 H,C-HMBC 2D-NMR

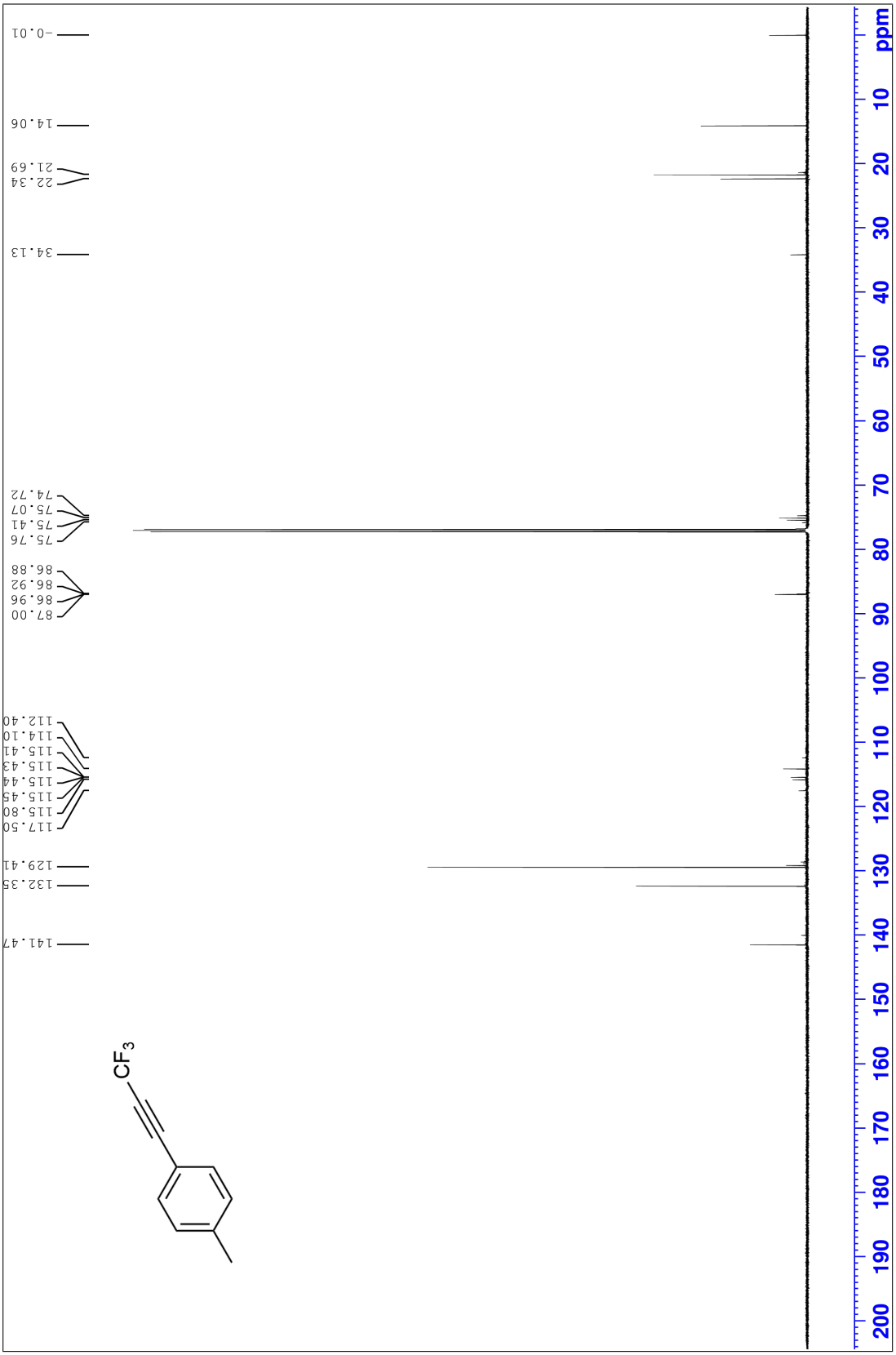


R Characterisation of compound (6.1)

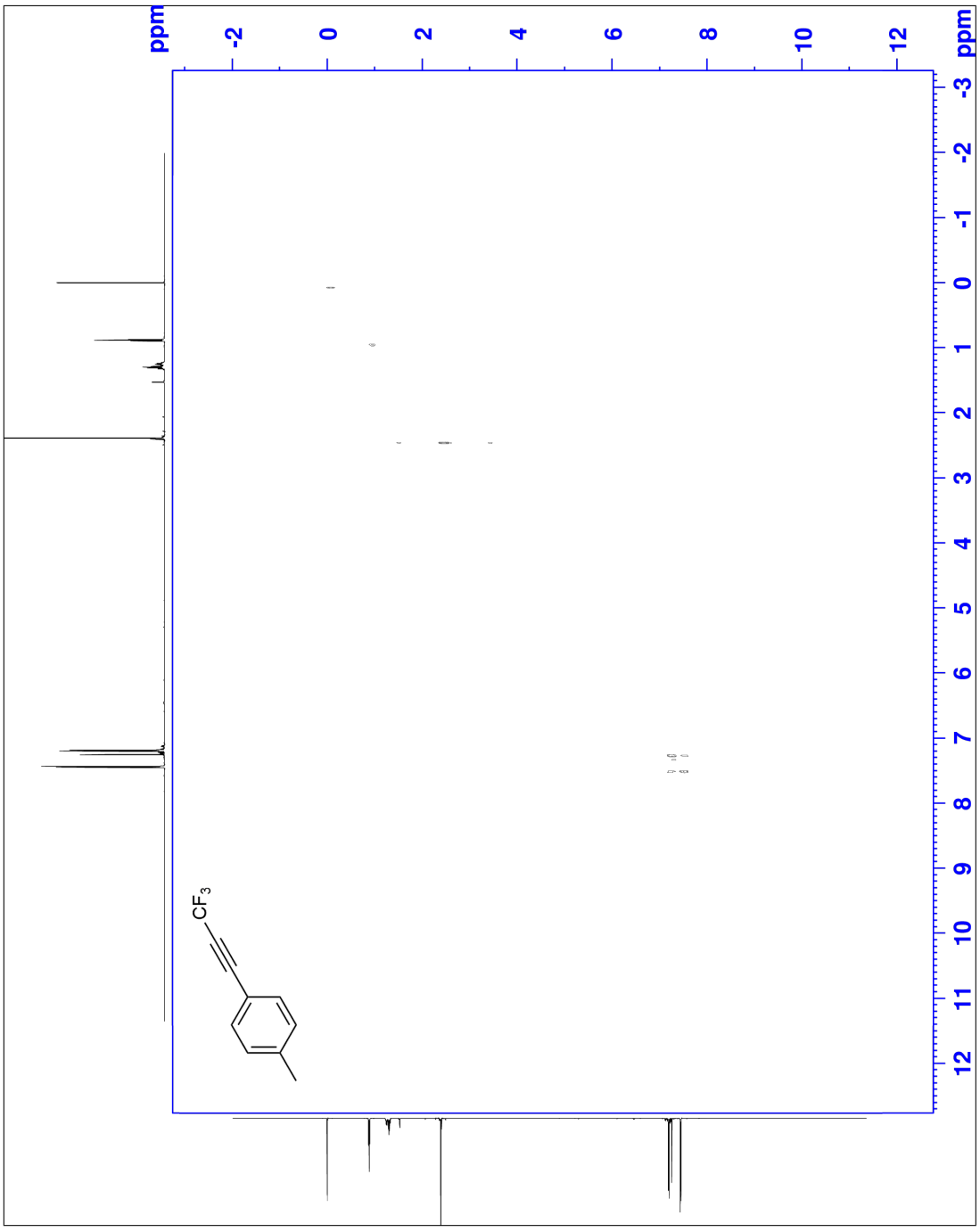
R.1 Compound 6.1 ^{1}H-NMR



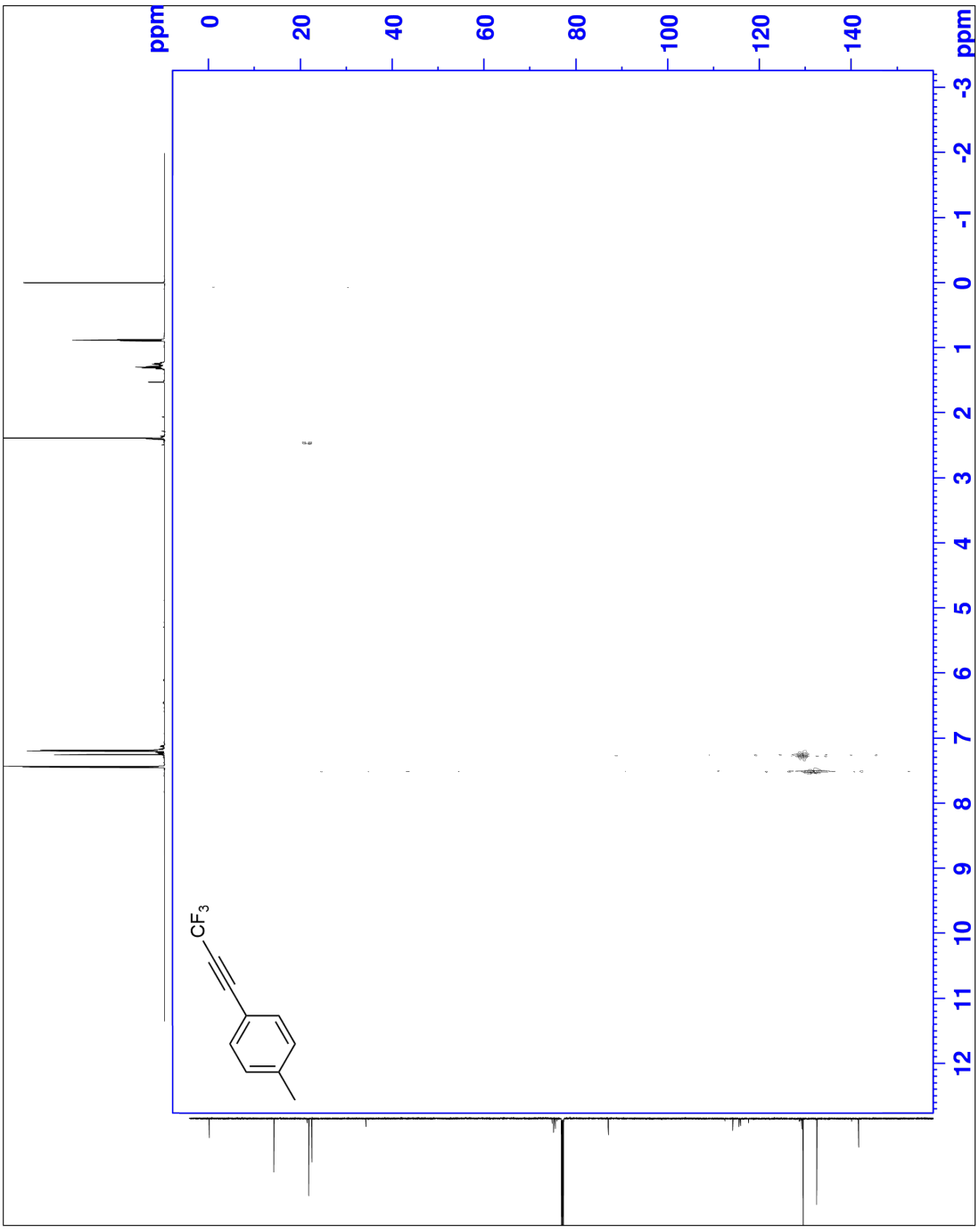
R.2 Compound 6.1 ^{13}C-NMR



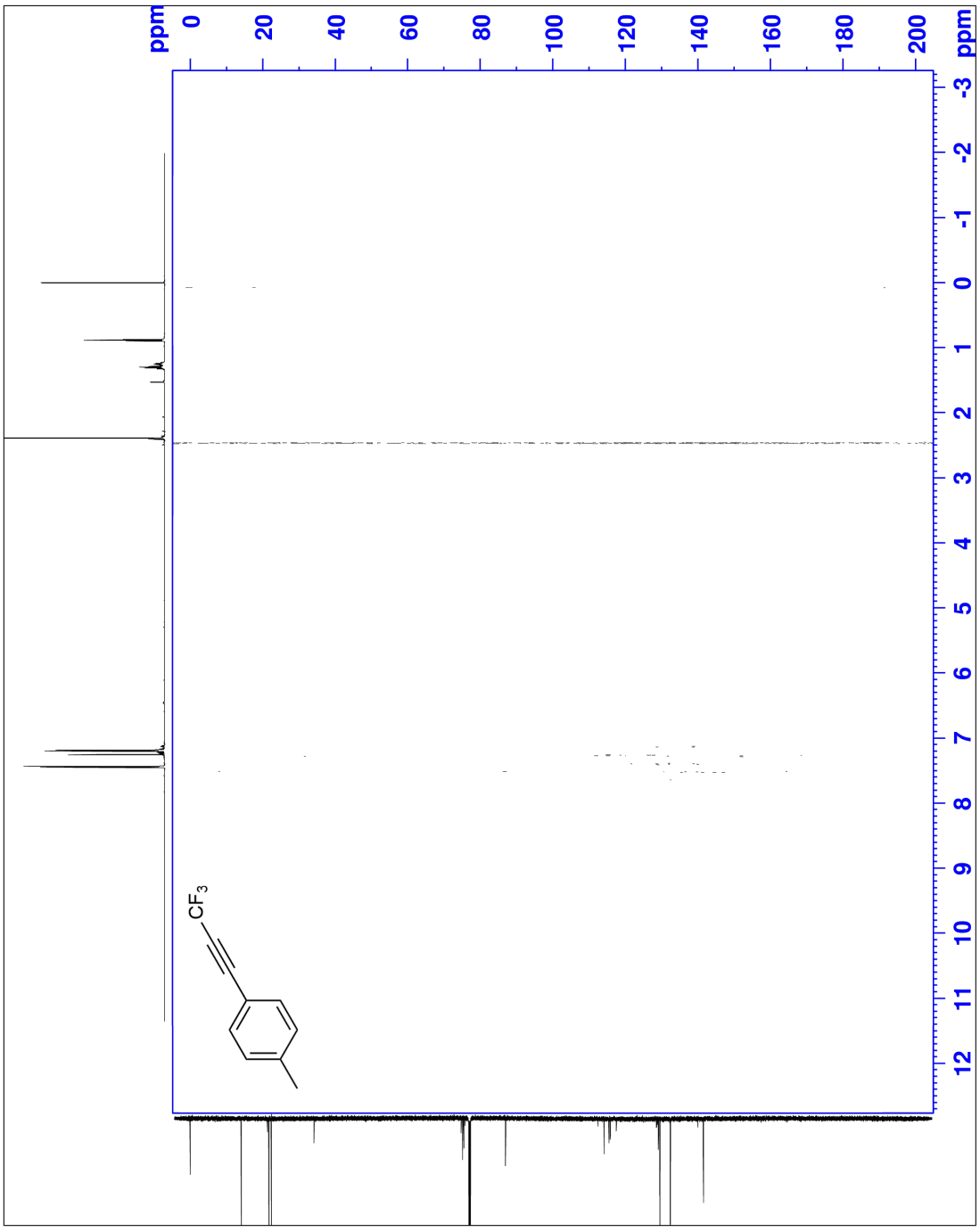
R.3 Compound 6.1 H,H-COSY 2D-NMR



R.4 Compound 6.1 H,C-HSQC 2D-NMR



R.5 Compound 6.1 H,C-HMBC 2D-NMR

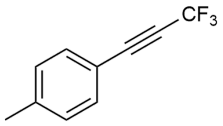


R.6 Compound 6.1 HR-MS

Elemental Composition Report **Page 1**

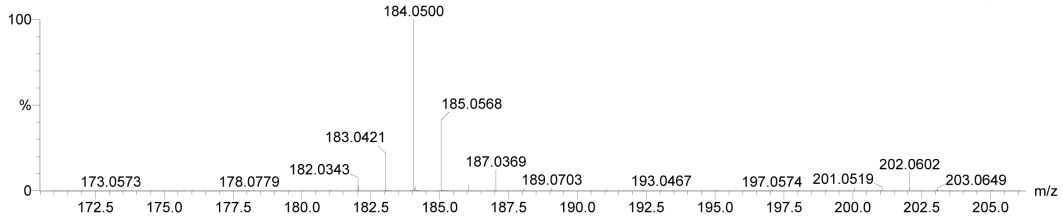
Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
565 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-100 F: 0-5



NT-MSLAB-Operator-SVG
2015-181 11 (0.243) AM2 (Ar,35000.0,0.00,0.00); Cm (11:20)

1: TOF MS ASAP+
1.33e+007

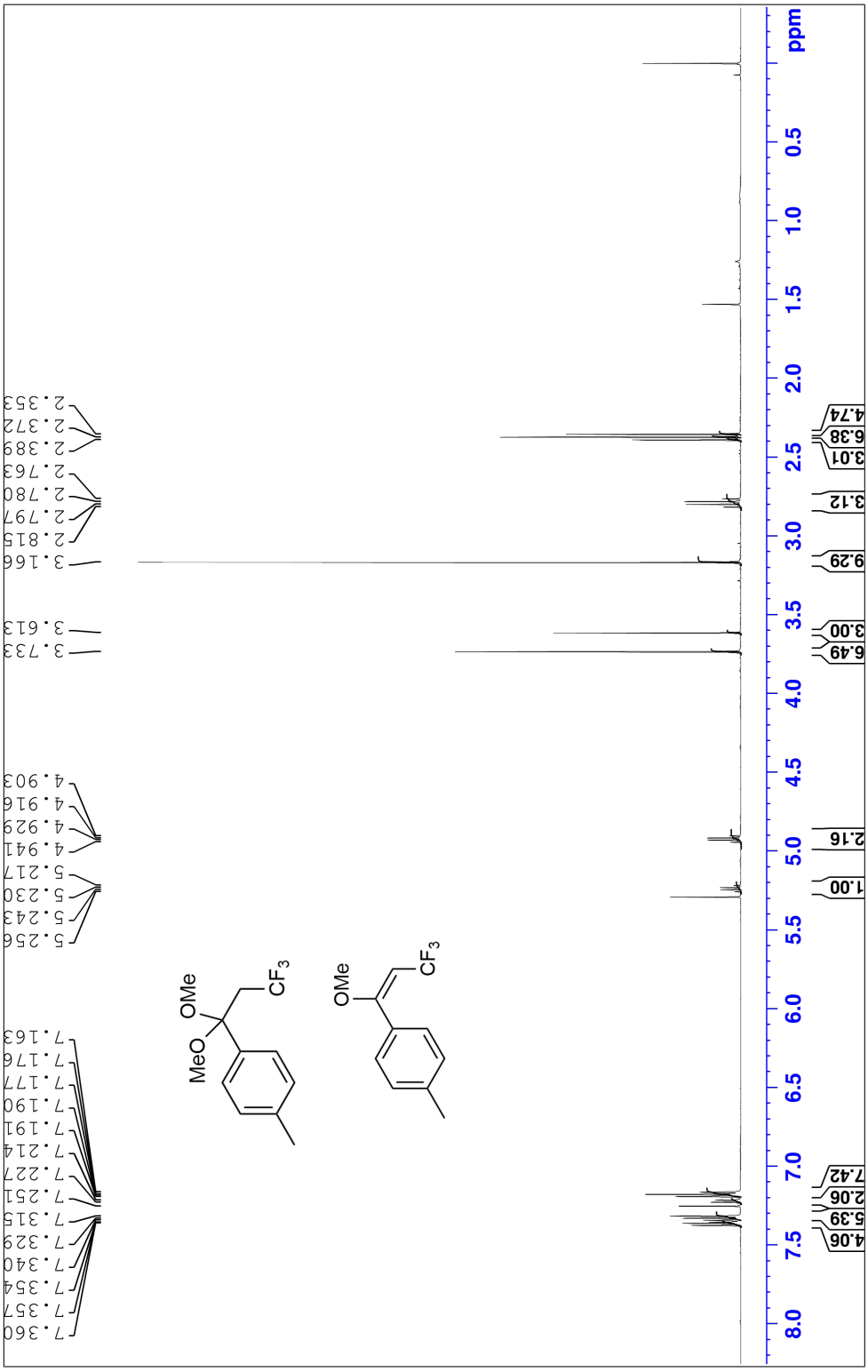


Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
184.0500	184.0500	0.0	0.0	6.0	2500.0	0.216	80.59	C10 H7 F3
	184.0497	0.3	1.6	10.0	2501.9	2.136	11.82	C8 H4 N6
	184.0496	0.4	2.2	-1.0	2506.4	6.616	0.13	H5 N6 F5
	184.0495	0.5	2.7	1.0	2502.4	2.596	7.46	C4 H9 N2 O5 F

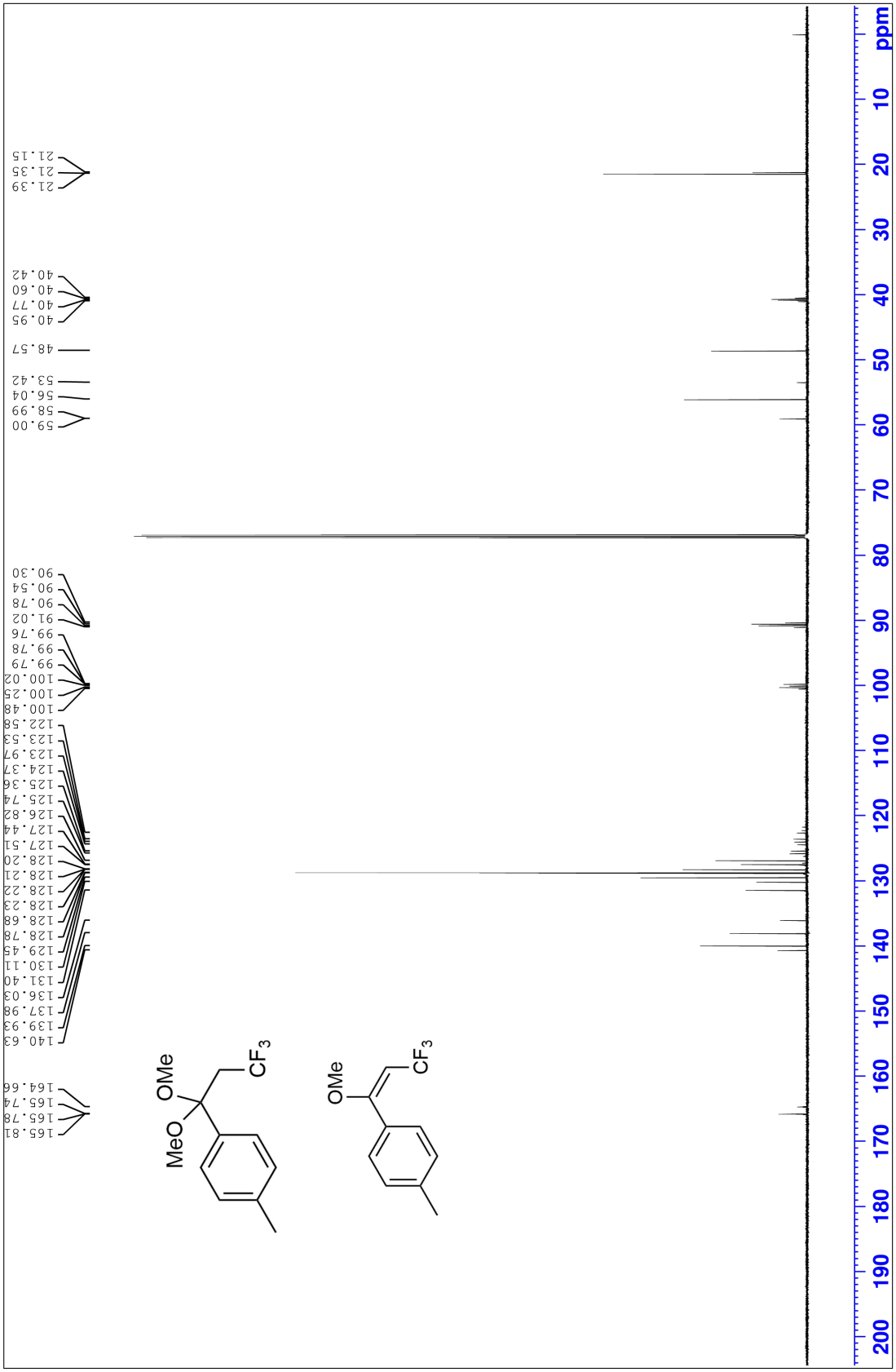
Ion observed [M]*+

S Characterisation of compound (6.2/6.3)

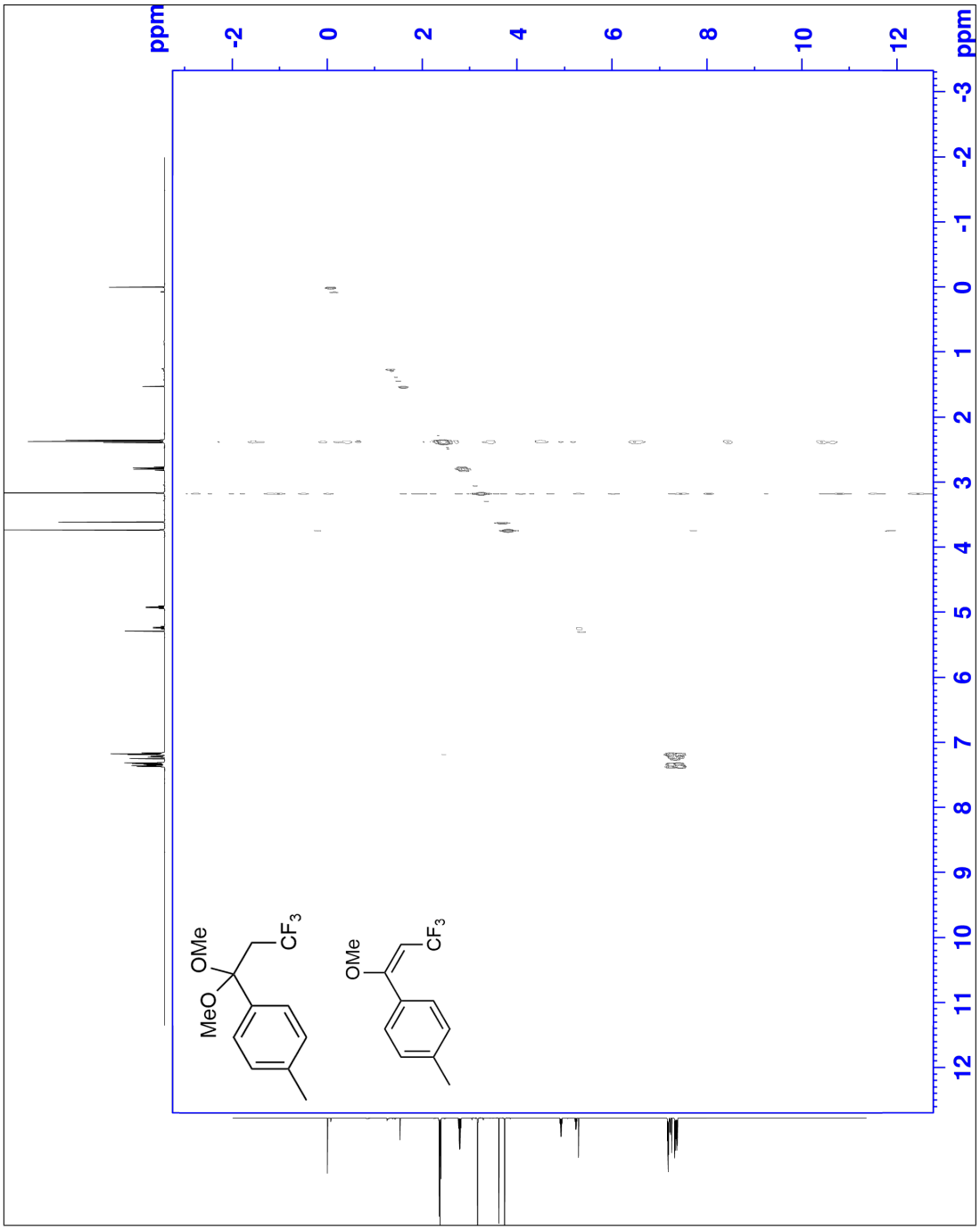
S.1 Compound 6.2/6.3 ^{1}H-NMR



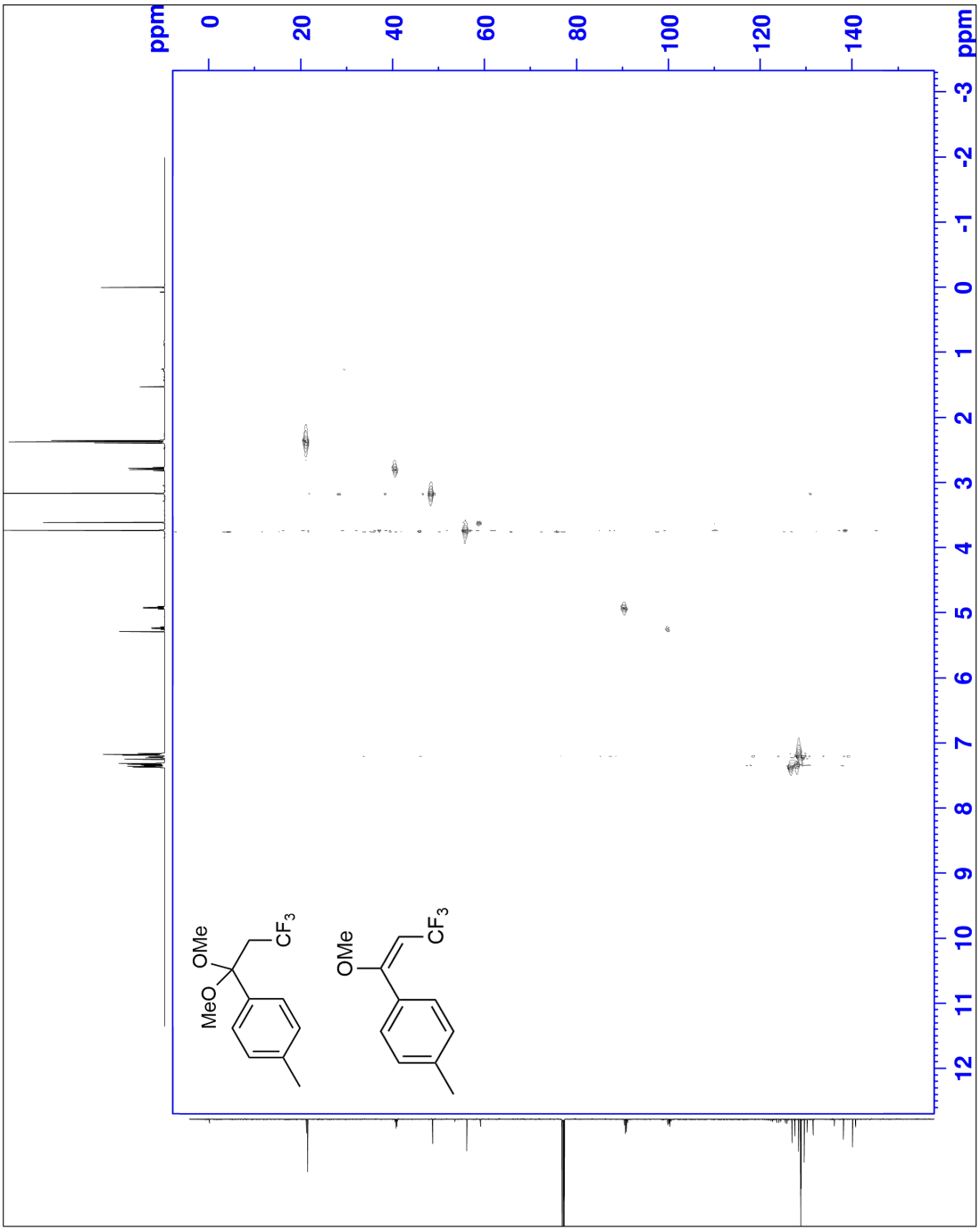
S.2 Compound 6.2/6.3 ^{13}C-NMR



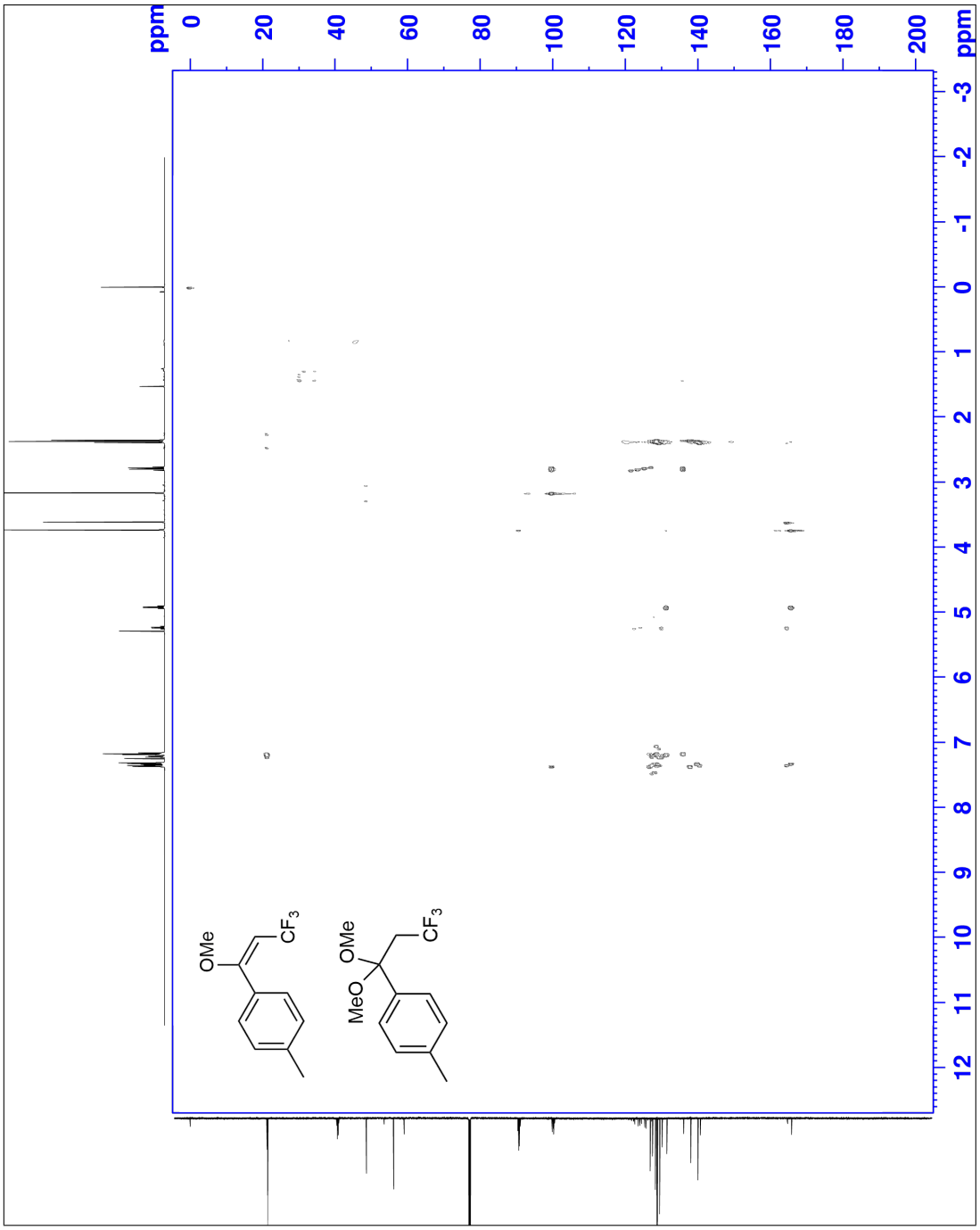
S.3 Compound 6.2/6.3 H,H-COSY 2D-NMR



S.4 Compound 6.2/6.3 H,C-HSQC 2D-NMR



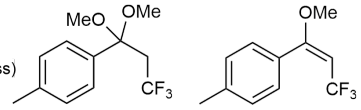
S.5 Compound 6.2/6.3 H,C-HMBC 2D-NMR



S.6 Compound 6.2/6.3 HR-MS

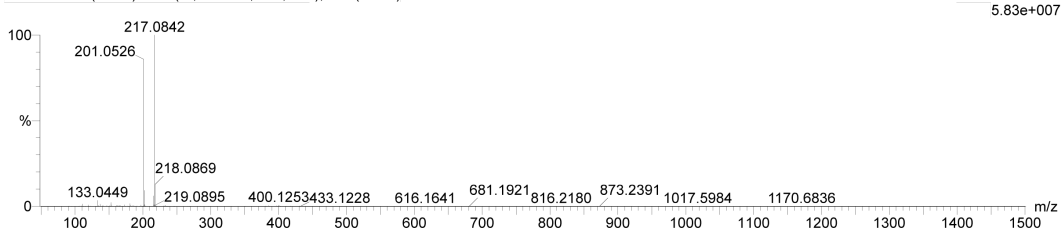
Elemental Composition Report **Page 1**

Multiple Mass Analysis: 2 mass(es) processed
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Monoisotopic Mass, Even Electron Ions
1621 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-100 F: 0-5
NT-MSLAB-Operator-SVG
2015-182 18 (0.381) AM2 (Ar,35000.0,0.00,0.00); Cm (18:24)

1: TOF MS ASAP+
5.83e+007

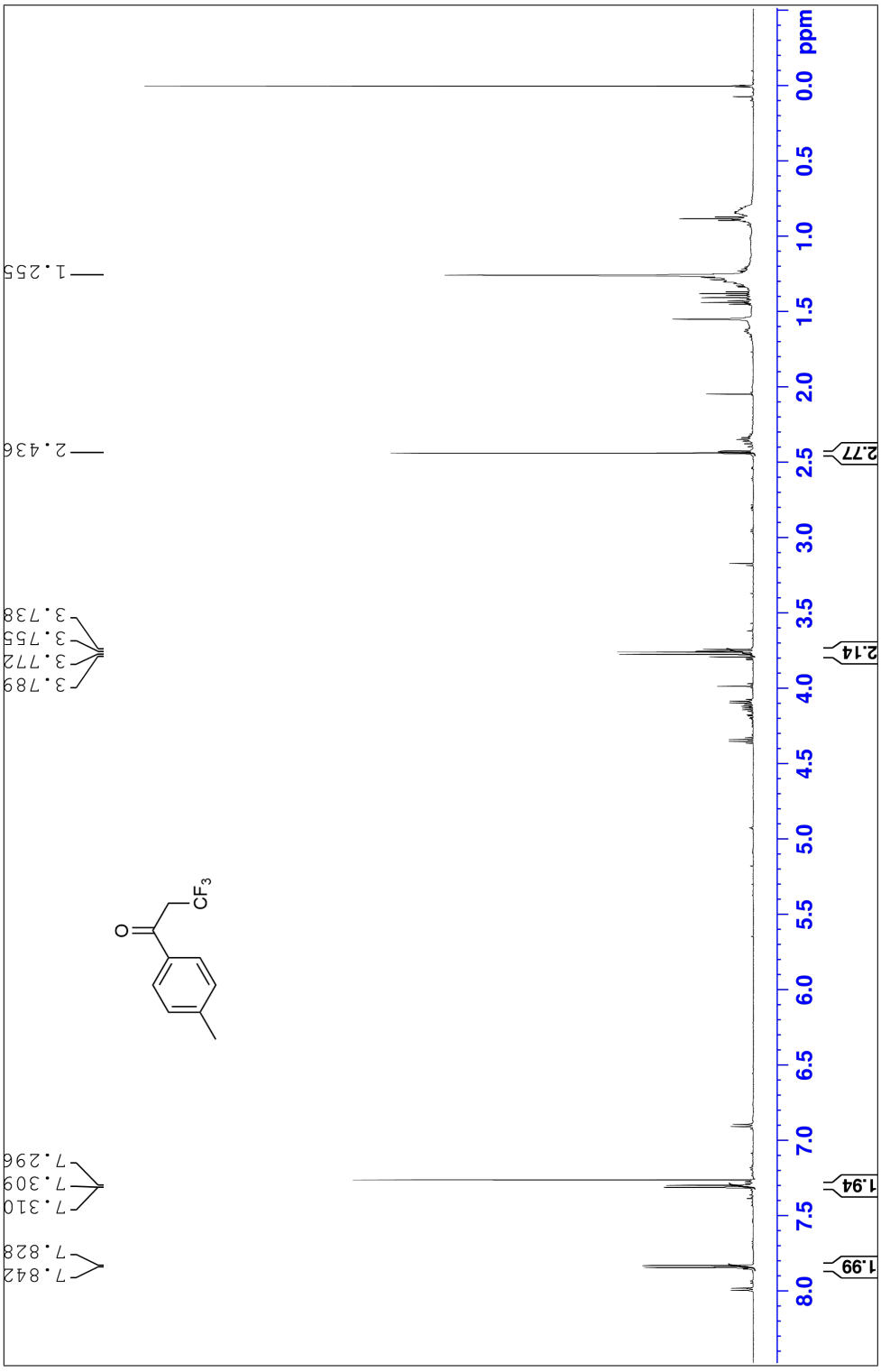


Minimum:	80.00				-1.5				
Maximum:	100.00		5.0	3.0	50.0				
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
201.0526	85.73	201.0527	-0.1	-0.5	5.5	2455.3	0.270	76.33	C10 H8 O F3
		201.0525	0.1	0.5	9.5	2456.5	1.445	23.57	C8 H5 N6 O
		201.0523	0.3	1.5	0.5	2462.1	7.056	0.09	C4 H10 N2 O6 F
		201.0523	0.3	1.5	-1.5	2465.0	9.948	0.00	H6 N6 O F5
217.0842	100.00	217.0840	0.2	0.9	4.5	2273.8	0.235	79.07	C11 H12 O F3
		217.0838	0.4	1.8	8.5	2275.1	1.564	20.93	C9 H9 N6 O
		217.0836	0.6	2.8	-0.5	2283.7	10.092	0.00	C5 H14 N2 O6 F

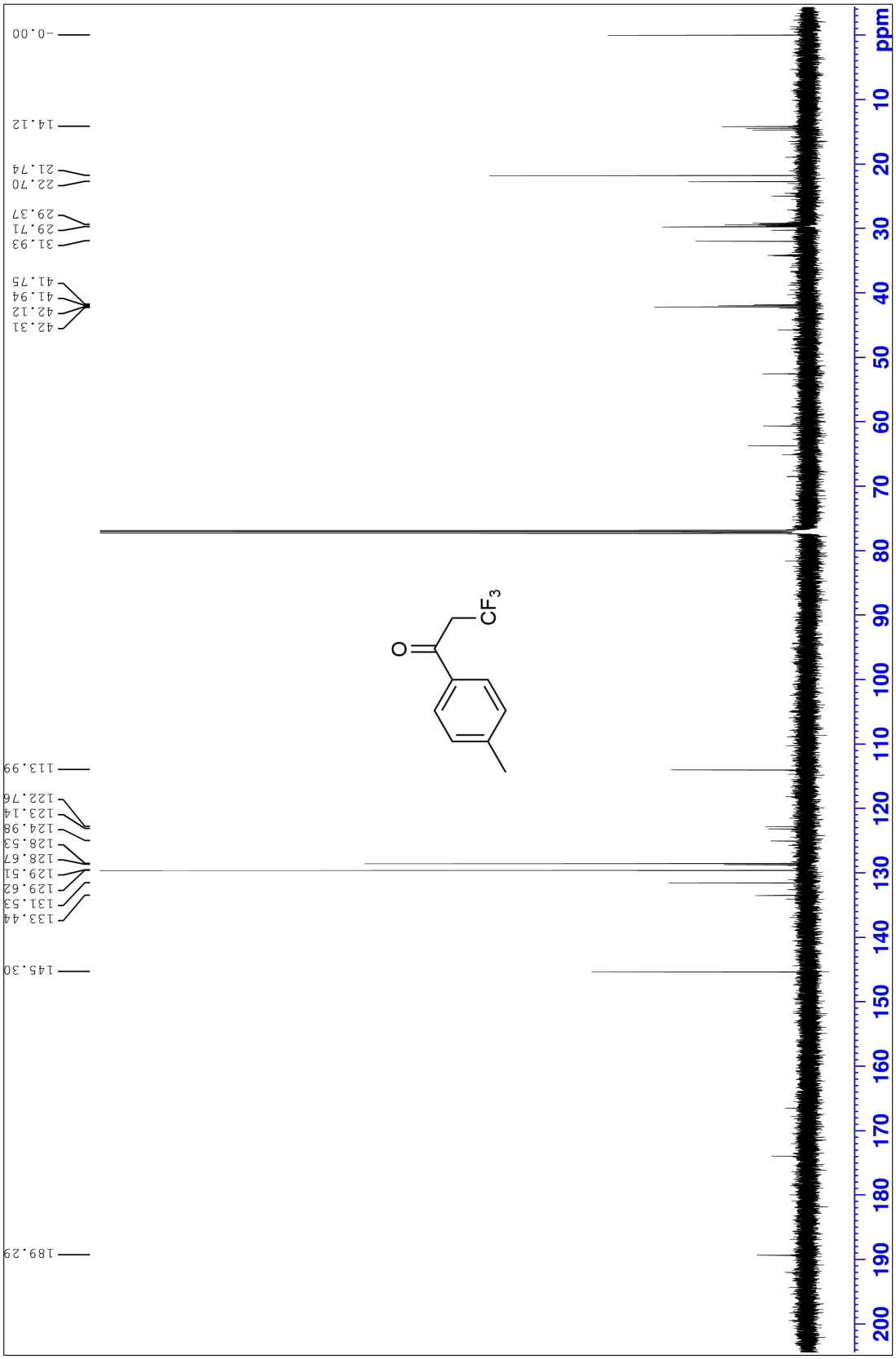
Ion observed [M +H]+

T Characterisation of compound (6.4)

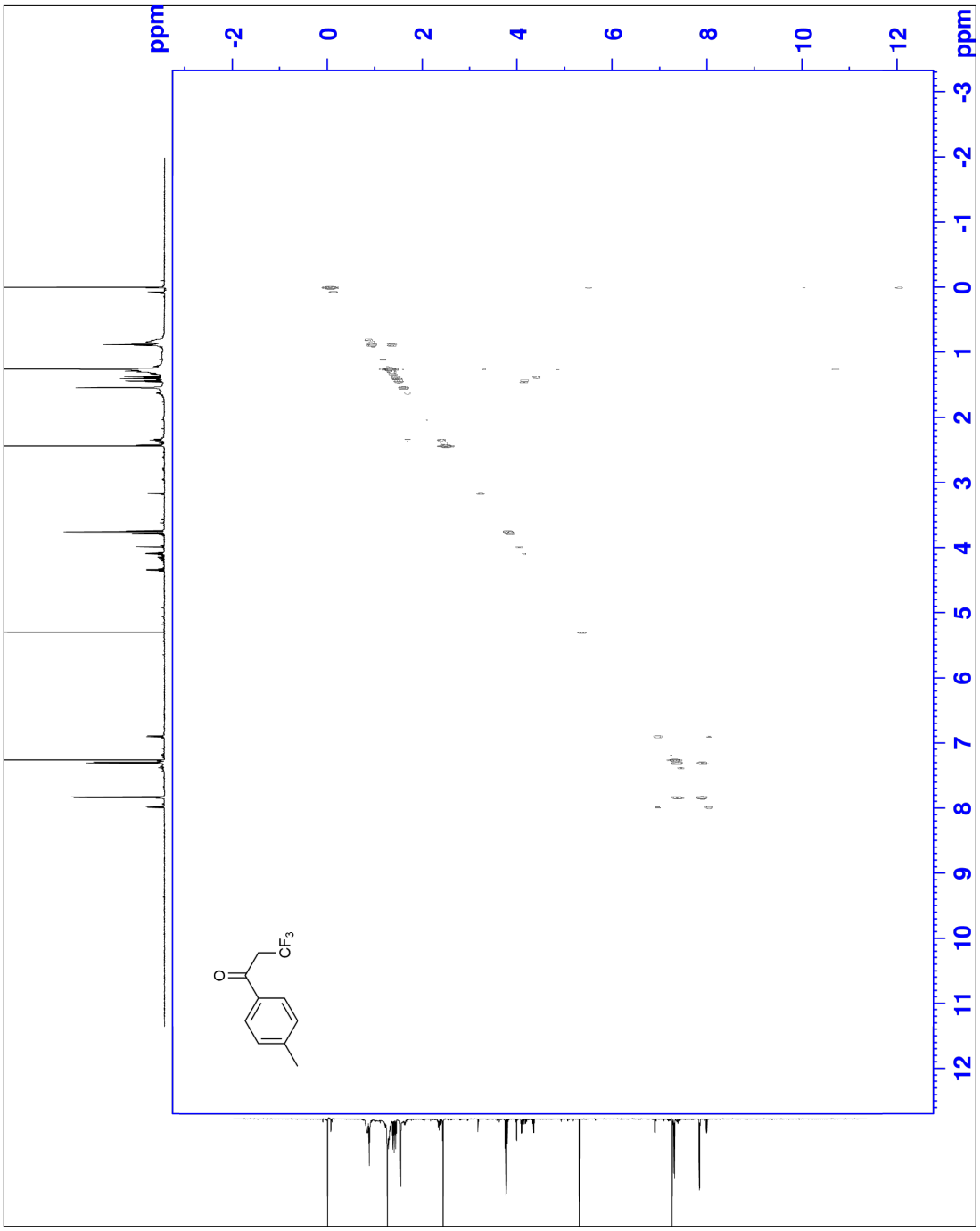
T.1 Compound 6.4 ^{1}H-NMR



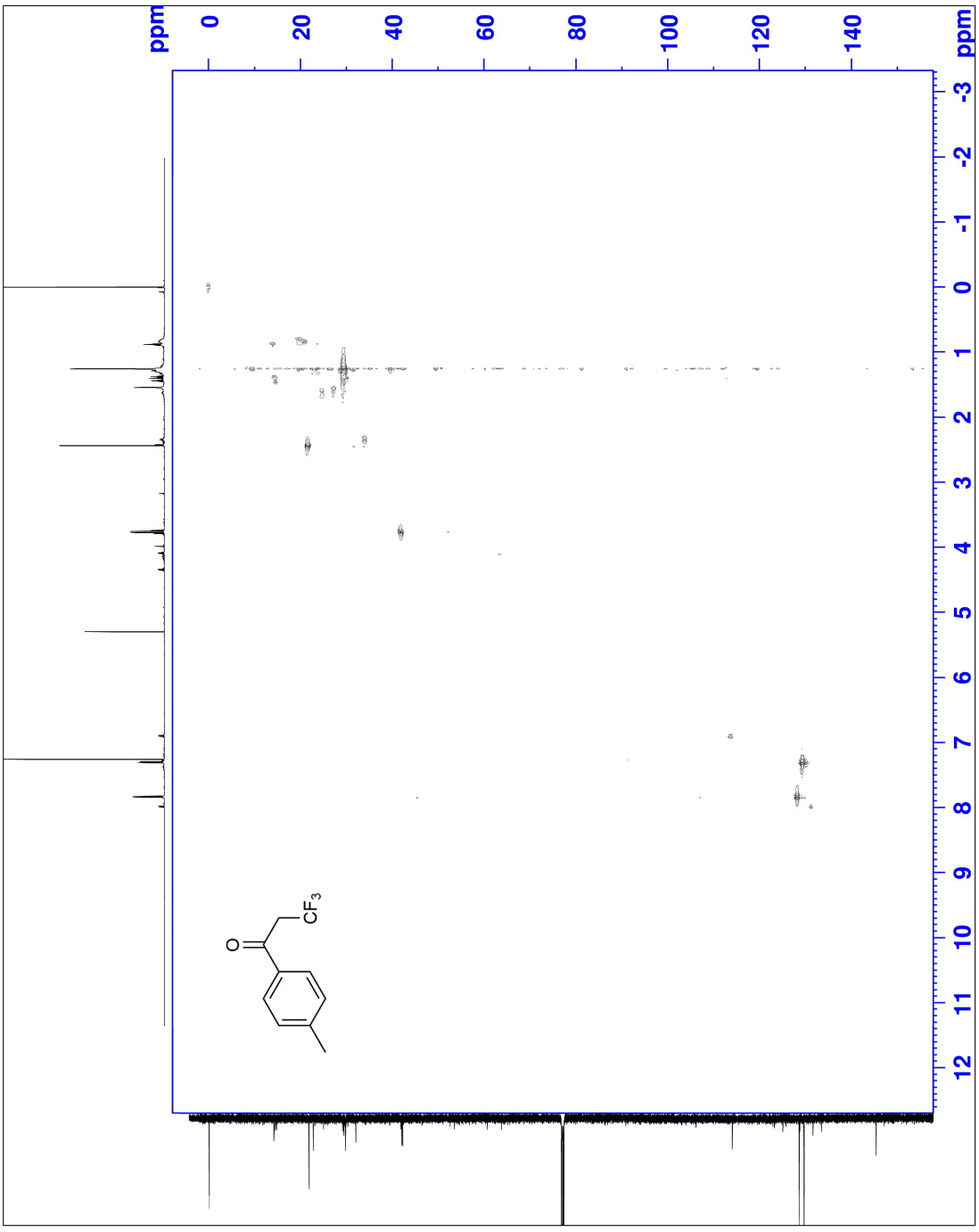
T.2 Compound 6.4 ^{13}C-NMR



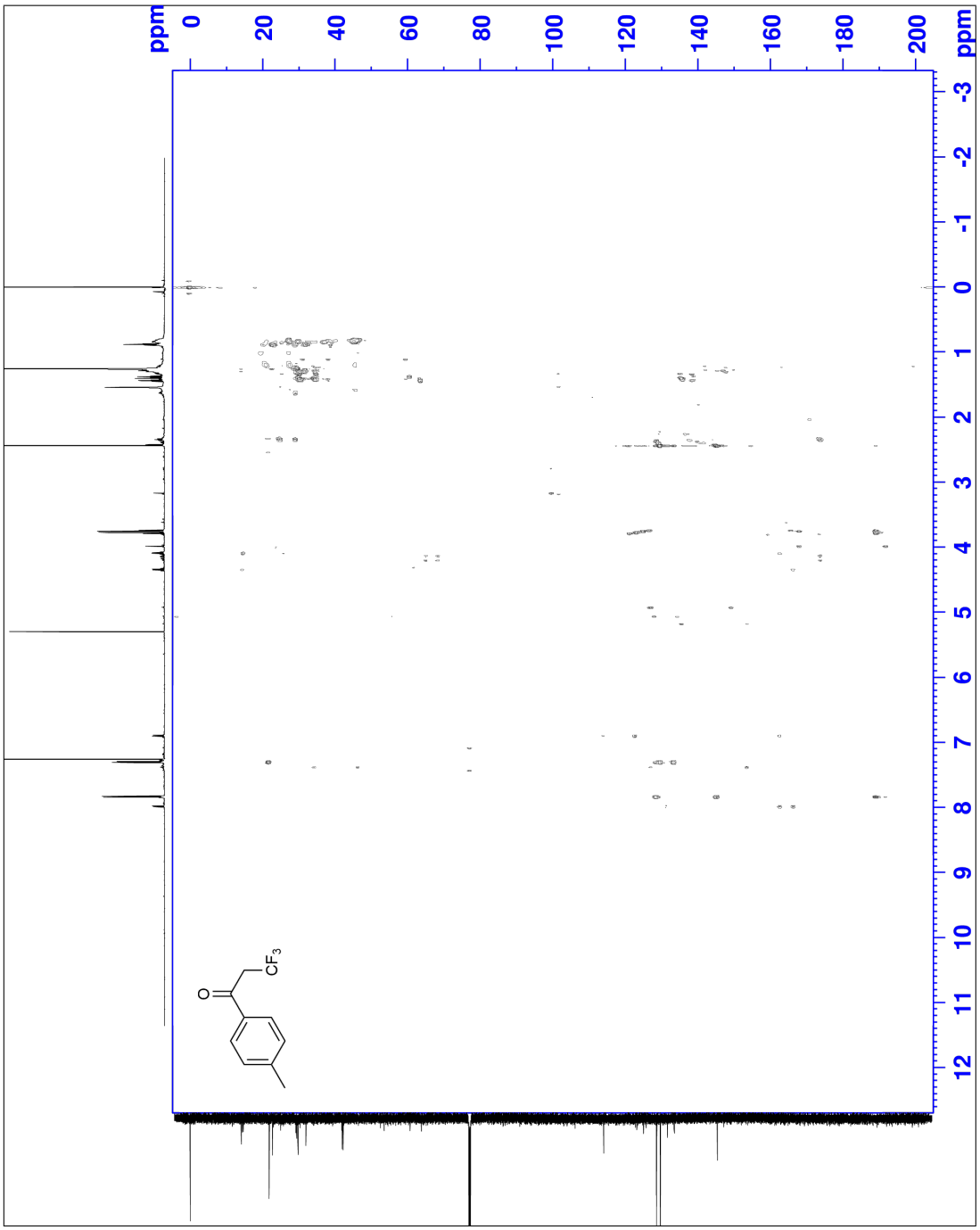
T.3 Compound 6.4 H,H-COSY 2D-NMR



T.4 Compound 6.4 H,C-HSQC 2D-NMR



T.5 Compound 6.4 H,C-HMBC 2D-NMR

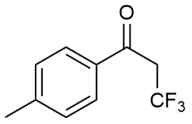


T.6 Compound 6.4 HR-MS

Elemental Composition Report **Page 1**

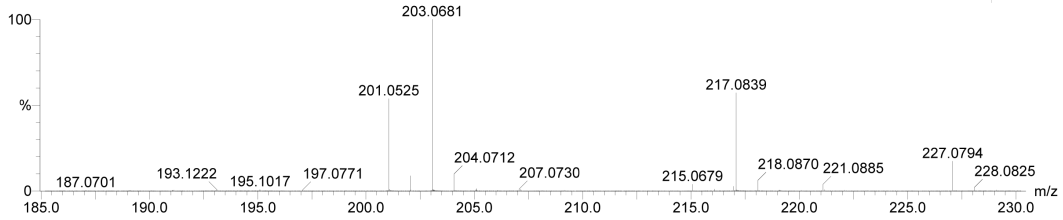
Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
742 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-50 O: 0-100 F: 0-5



NT-MSLAB-Operator-SVG
2015-183 5 (0.121) AM2 (Ar,35000.0,0.00,0.00); Cm (4:5)

1: TOF MS ASAP+
1.62e+006



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
203.0681	203.0684	-0.3	-1.5	4.5	1651.3	0.038	96.24	C10 H10 O F3
	203.0681	0.0	0.0	8.5	1654.6	3.283	3.75	C8 H7 N6 O
	203.0679	0.2	1.0	-0.5	1660.3	9.007	0.01	C4 H12 N2 O6 F