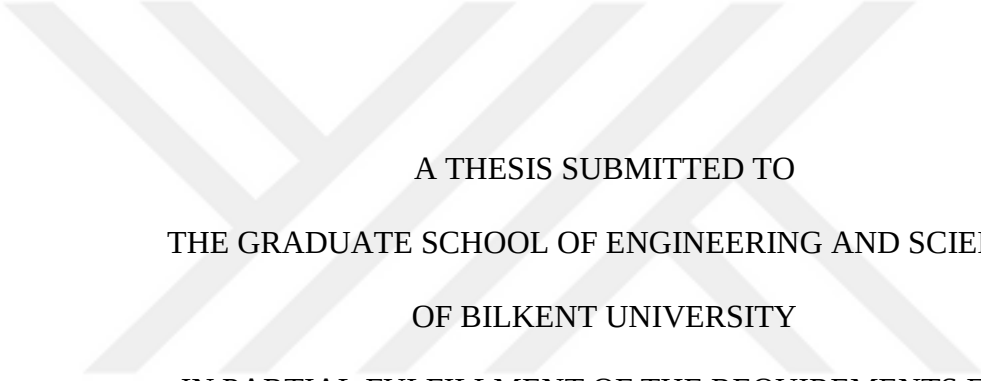


TRANSITION METAL CATALYSIS
FOR AEROBIC C-H OXIDATION REACTIONS AND
FOR THE SYNTHESIS OF FLUORANTHENE DERIVATIVES



A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF ENGINEERING AND SCIENCE
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IN
CHEMISTRY

By
Yeşim ŞAHİN

January 2021

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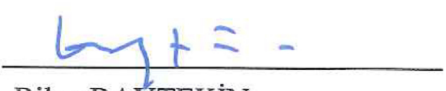
We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.



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ABSTRACT

TRANSITION METAL CATALYSIS FOR AEROBIC C-H OXIDATION REACTIONS AND FOR THE SYNTHESIS OF FLUORANTHENE DERIVATIVES

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M.Sc. in Chemistry

Advisor: Yunus Emre Türkmen

January 2021

Within the past two decades, a powerful class of new reactions that introduces oxidized functionality to (sp³) C-H bonds has emerged and gained tremendous attention since it can revolutionize the chemical industry by placing reactive functional groups directly in a molecule. Usually, precious metals (e.g., Pd, Pt, Ru etc.) are used for the activation of C-H bonds, and finding alternative ways that use less expensive and less toxic first row transition metals to replace precious metal catalysts is necessary. In this work, we have developed a reductive pretreatment system to increase the activity of precious metal-free LaMnO₃ perovskites for C-H oxidation reactions of alkylarenes to ketones or oxidative dimerization of naphthols under mild conditions. Furthermore, a bimetallic nickel-manganese based hydroxide catalyst was synthesized as well and it was proven to oxidize a variety of alkylarenes and alcohols. Using molecular oxygen as the

sole oxidant in C-H oxidation reactions is another advantage of our method since it is green, inexpensive and readily available in nature.

In the second part, two novel methods have been developed for the synthesis of fluoranthenes which are important polycyclic skeletons. They can be found in many natural products, organic electronics, dyes and various materials. These methods employ Pd-catalyzed cross-coupling reactions such as Suzuki-Miyaura and Sonogashira reactions in the first steps using 1,8-dihalonaphthalenes and then use intramolecular Diels-Alder reactions for the formation of tetracyclic ring in the fluoranthene core. Our methods also provide a modular pathway for the synthesis of multi-substituted fluoranthene derivatives from simple molecules because it is designed as a three-component system and each component can be readily prepared or functionalized allowing easy modification.

Keywords: Aerobic C-H oxidation, heterogenous catalysis, perovskite, metal hydroxide, fluoranthene

ÖZET

AEROBİK C-H OKSİDASYON REAKSİYONLARI VE FLORANTEN TÜREVLERİNİN SENTEZİ İÇİN GEÇİŞ METAL KATALİZİ

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Son yirmi yıl içerisinde, çok reaktif olmayan sp^3 -hibritleşmiş C-H bağlarının direkt oksitlenerek fonksiyonellik kazanmasına yönelik yeni bir reaksiyonlar sınıfı ortaya çıkmıştır. Bu alan doğrudan fonksiyonelleşme sağladığından kimya endüstrisinde büyük ilgi görmüştür. C-H bağlarının aktivasyon reaksiyonlarında genellikle platin, paladyum gibi değerli geçiş metalleri kullanılmaktadır. Bu metallerin aşırı pahalı olması nedeniyle daha ucuz ve daha az toksik olan ilk sıra geçiş metallerini kullanan alternatif yollar bulmak gereklidir. Bu çalışmada alternatif olarak kullanılabilecek değerli metal içemeyen perovskit tipi $LaMnO_3$ katalizörünün aktivitesini artırmak için indirgeyici bir ön işlem sistemi geliştirilmiştir. Geliştirilen katalizörün alkilarenlerin ketonlara oksidasyon reaksiyonları veya ılımlı koşullar altında naftollerin oksidatif dimerizasyonu için yüksek verim alarak kullanılabileceği gösterilmiştir. Ayrıca, yeni bir bimetalik nikel-mangan bazlı katalizör sentezlenmiş ve bu katalizörün çeşitli alkilaren ve alkollerini çok yüksek

verimle oksitlediđi gösterilmiřtir. Bu oksidasyon reaksiyonlarında zararsız, ucuz ve doğada fazlasıyla bulunan moleküler oksijen kullanılması ise geliştirilen metoda ayrı bir avantaj sağlamaktadır.

Tezin ikinci bölümünde ise önemli polisiklik iskeletler olan florantenlerin sentezine yönelik iki ayrı metot geliştirilmiştir. Florantenler pek çok doğal ürünün yapısında, boyalarda, organik elektronik alanında veya çeşitli malzemelerde bulunmaktadır. O nedenle bu yapıların sentezi hayli önem kazanmıştır. Bu çalışmada geliştirilen yöntemler ilk aşamalarda 1,8-dihalo-naftalen türevlerini paladyum katalizörleri içeren Suzuki-Miyara ve Sonogashira gibi çapraz bağlanma tepkimelerinde kullanmakta, sonrasında ise Diels-Alder reaksiyonları kullanarak floranten iskeletini oluşturmaktadır. Ayrıca, iki yöntemde de ya satın alınabilen ya da basitçe sentezlenebilen moleküller kullanılmıştır. Yöntemlerin üç-bileşenli olması ise çoklu sübstitüyente edilmiş floranten türevlerinin sentezine olanak sağlamaktadır.

Anahtar kelimeler: aerobik C-H oksidasyonu, heterojen kataliz, perovskit, metal hidroksit, floranten

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LIST OF ABBREVIATIONS

LMO	Lanthanum Manganite
DCM	Dichloromethane
EtOAc	Ethyl acetate
MeOH	Methanol
THF	Tetrahydrofuran
FTIR	Fourier-Transform Infrared
HRMS	High Resolution Mass Spectrometry
TLC	Thin-Layer Chromatography
NMR	Nuclear Magnetic Resonance
TMS	Trimethylsilyl
UV	Ultraviolet
XRD	X-Ray Diffraction
XPS	X-Ray Photoelectron Spectroscopy
Bpin	Pinacolato boronic ester
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
m-CPBA	<i>m</i> -Chloroperoxybenzoic acid
APCI	Atmospheric-pressure chemical ionization

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CHAPTER 1: TRANSITION METAL-BASED HETEROGENEOUS CATALYSTS FOR AEROBIC C-H OXIDATION REACTIONS

1.1. INTRODUCTION

1.1.1. C-H Activation and Oxidation by Catalysis

Molecular synthesis is heavily based on the conversions of pre-existing functional groups to one another, and obtaining such functional groups usually requires a significant number of steps. Within the past two-three decades, a powerful class of new reactions that introduces oxidized functionality directly to (sp³) C-H bonds has emerged¹ and has gained an enormous attention^{2,3} since it can revolutionize the chemical industry by placing reactive groups such as alcohols⁴ or carbonyl containing groups directly in a molecule⁵ or make strong carbon-carbon bonds by cross-coupling reactions.⁶ This approach is also step-economical since it avoids prior functionalization.

The first example of modern C-H activation reactions can be taken as Shilov's platinum based partial oxidation of alkanes to alcohols.^{7,8} Since then, both heterogeneous and homogeneous type reactions have been widely studied over the years,^{9,10} and in general, precious transition metals dominate both research areas. While homogeneous catalysis requires a directing group most of the time¹¹ or the use of complex ligand systems,¹² heterogeneous catalysis faces other challenges like deactivation due to chemisorption of some elements (e.g., S, P, Cl), possibility of metals being toxic (e.g., As, Pb) or accumulation of carbon containing species (e.g., CO, unsaturated hydrocarbons) after the reaction runs.¹³ Homogeneous systems are used mostly in organometallics, in biomimetic methodologies for natural product synthesis or late stage functionalization of

peptides¹⁴ while heterogeneous catalysis is used in large scale production of stock materials and preferred by industry due to easy separation and recycling resulting in reduced cost.¹⁵

C-H oxidation is a sub-class of C-H activation reactions, and there are some important parameters that affect the success of such oxidations. C-H bonds are ubiquitous in organic molecules but they are relatively inert towards oxidation due to the large kinetic barrier associated with the C-H bond cleavage and the relatively nonpolar nature of this bond.¹⁶ Inductive effects, electronic environment, steric factors and conjugation/hyperconjugation around the C-H bonds are the main criteria for an oxidation reaction to result in the desired product formation.¹⁷

1.1.2. Aerobic Oxidation

Traditionally, oxidations of saturated hydrocarbons have been catalyzed by dissolved salts of redox-active metals¹⁸ or peroxides, but environmental concerns provide a strong incentive to search for more environmentally friendly catalytic reactions. Hence, developing a new method that employs molecular oxygen as the sole oxidant will have the potential to be beneficial in environmental and economical contexts.¹⁹ As an oxidant, molecular oxygen is suitable with respect to the principles of green chemistry since it is inexpensive, clean and readily available in nature.²⁰ However, there are some challenges of selective functionalization when molecular oxygen is used. These are mainly, the activation of C-H bond, activation of O₂ molecule and control of chemo-, regio- and stereoselectivities in specific molecules.²¹

The O₂ molecule has a nominal bond length of 1.208 Å and 497 kJ/mol of bond dissociation energy. This bond may be extended or broken by coordination to a catalytic center and/or by placing charge on the free molecule.²¹ However, it is in the triplet ground state and cannot easily form reactive oxygen species such as peroxides, hydroxy radicals or singlet oxygen, and thus relatively unreactive toward the strong C–H bonds unless it is activated by highly efficient catalysts.

One example that uses molecular oxygen was reported by Hayashi et. al in 2004, where the benzylic oxygenation of alkylarenes was achieved in the presence of activated carbon at ambient temperature.²² In another study reported in 2004, Mizuno et. al. used Ru(OH)x/Al₂O₃ with a low catalyst loading for the same type of transformation.²³

Kappe and co-workers developed a method²⁴ that employs flow chemistry for Pd-catalyzed oxidative cleavage of olefins with O₂ in 2017. Moreover, Favre-Réguillon et. al studied alcohol oxidation by a Cu(I)/TEMPO mixture.²⁵ In 2014, Rossin et al. reported a chiral metal organic framework containing cobalt for the heterogeneous catalytic oxidation of alkenes under aerobic conditions.²⁶ Moreover, Ir/TiO₂ catalyst was used by Naito et. al. for alcohol and alkylarene oxidations with high yields and selectivity.²⁷

1.1.3. Information on Perovskites

The first perovskite was discovered by the German mineralogist Gustav Rose in 1839 and was the mineral called calcium titanium oxide (CaTiO₃).²⁸ After the discovery, many structures with the formula of ABX₃ was named as a perovskite. The atoms A and B are two cations where B is usually smaller than A whereas X is mostly oxygen.²⁹ They adopt a cubic structure (**Figure 1a**) as the ideal form although it is hard to find perovskites

with cubic structure in nature. On the other hand, there are many examples having orthorhombic (**Figure 1b**) or tetragonal unit cells (**Figure 1c**) depending on the temperature or electronic properties.³⁰

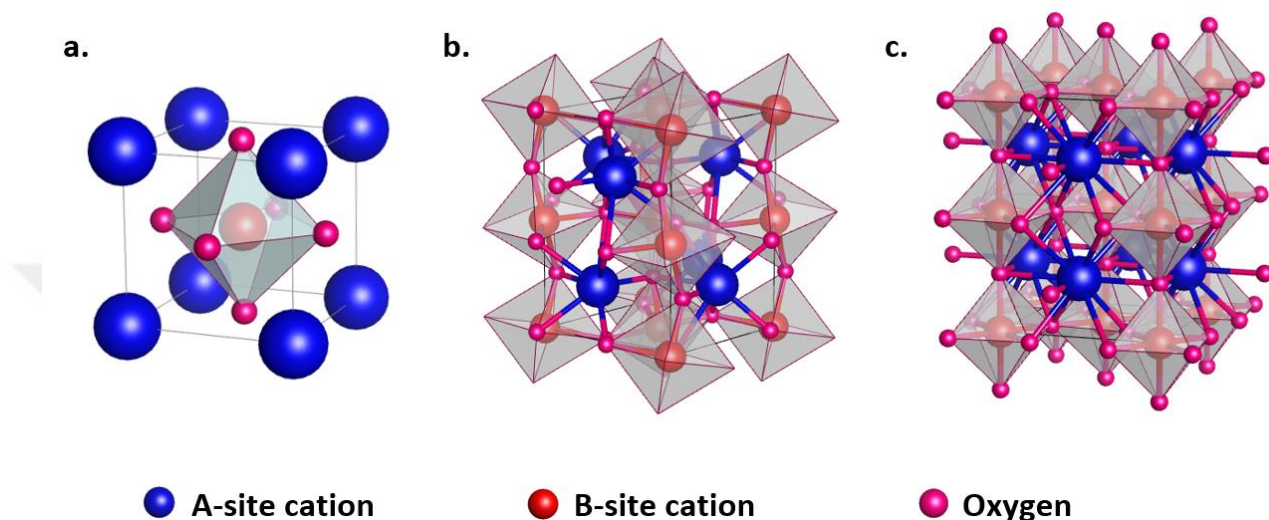


Figure 1: Common perovskite crystal structures: a) cubic crystal b) orthorhombic crystal c) tetragonal crystal.

Perovskites have gained a tremendous attention in chemistry and physics in recent years since they have found applications in photovoltaics, lasers, light-emitting diodes or electrolysis.^{31, 32} There is also a rising trend on the use of less expensive perovskites in catalysis as a substitute for precious metals.³³ They demonstrate unique electronic, magnetic and catalytic properties because of their tunability which originate from the change in A or B site cations as well as the easy formation of defects in the structure.³⁴

1.1.4. Perovskites as Catalysts for C-H Oxidation Reactions

Catalysis area has been under dominance of noble metals for many years and there emerged a need for potential replacements in recent years. In commitment to find an

alternative to expensive transition metal-based catalysts (e.g., Pt, Pd, Rh or Ir), mostly for cost effective reasons, perovskites have proven to be a suitable choice. It is known that they can be used in reduction, oxidation, water depollution, NO_x decomposition reactions³⁵ or coupling reactions.^{36, 37} Benefits of perovskite catalysts can be summarized as: (1) variety in composition and presence of earth abundant elements as the basic components; (2) tunability of physical/electronic properties as well as versatility; (3) ability to form defects such as oxygen vacancy that may act as an active site in the targeted reaction; and (4) cumulative information on the area that helps to improve the performance.³⁸

Changing B-site cations with transition metals that are reducible like Mn, Co or Cr may provide an access to redox active catalytic sites which can facilitate the oxidation reactions.³⁹ Also, oxygen vacancies on the surface or in bulk affect the performance of perovskite catalysts, and the activity can be controlled by the degree of these vacancies for partial oxidation.⁴⁰

Hara and Kamata groups have demonstrated that perovskites are efficient heterogeneous catalysts for different types of oxidation reactions and can facilitate C-C and C-O bond formations.⁴¹ Especially, liquid phase aerobic oxidation reactions have been investigated in detail with using both perovskites and manganese oxides.⁴²

In 2018, Hara and co-workers reported successful oxidation of alkanes like adamantane, cyclooctane and cis-decalin using a hexagonal iron-based perovskite BaFeO_{3-x} where 200 mg of catalyst was used per 1 mmol of substrate in the presence of 1 bar O₂ at 90 °C.⁴³ While there was no need for any additives for activation, the reaction times were quite long ranging between 30 h to 96 h. Other examples from the same group

are the oxidations in the presence of SrMnO_3 of various compounds.⁴⁴ They reported oxidations of alkylarenes to ketones using 200 mg of catalyst per reactant mmol at 80 °C or 110 °C depending on the substrate and obtained moderate to good yields determined by GC analysis. With the use of the same catalyst, thioanisoles were selectively oxidized to the corresponding sulfoxides by using 100 mg of catalyst per mmol at 27 °C in short reaction times. Later, they also developed a method that employs amino-acids in the synthesis of perovskites and showed how the activity of these oxides can be altered by simple changes in preparation.⁴⁵ Another example uses BaRuO_3 perovskite for the oxidation of sulfides with molecular oxygen. Oxidation of aryl sulfides as well as alkyl sulfides were achieved in the presence of 50 mg catalyst per 0.5 mmol of substrate at 40 °C and the oxidation was selective towards sulfoxide formation instead of sulfones.⁴⁶

There also exists a study on transformation of 5-hydroxymethylfurfural (HMF) to 2,5- diformylfuran (DFF) with the use of a lead-halide perovskite under visible light.⁴⁷ This transformation is particularly important since it is one step prior to the formation of 2,5-furandicarboxylic acid (FDCA) which is a valuable starting material for polyester synthesis like PET and can replace terephthalic acid as the monomer.

1.1.5. Aim of This Work

The main goal of this project was to develop a new methodology to improve the activity of transition metal containing heterogeneous catalysts for aerobic C-H oxidation reactions. The advantage of the presented method in this work comes from the use of oxygen as the sole oxidizing agent instead of expensive or environmentally hazardous oxidants such as potassium permanganate or hexavalent chromium compounds, and from

using earth abundant transition metals like lanthanum and manganese. Also, heterogeneous nature of the catalysts provides easy separation and reusability.

The central focus was on a perovskite-type catalyst (LaMnO_3) and the newly developed reductive pretreatment system for the alkylarene oxidation, whereas the second part focuses on the use of a metal hydroxide-based catalyst ($\text{Ni}_x\text{Mn}_{(1-x)}(\text{OH})_2$) for C-H and alcohol oxidation reactions. This project is a collaboration with Ozensoy Research Group and the synthesis and structural characterization of both catalysts was done by them.

General scheme of the catalytic cycle can be seen in **Figure 2** where the active catalyst is stirred with the dissolved reactant in an appropriate solvent in the presence of molecular oxygen for 24 h at a specific temperature.

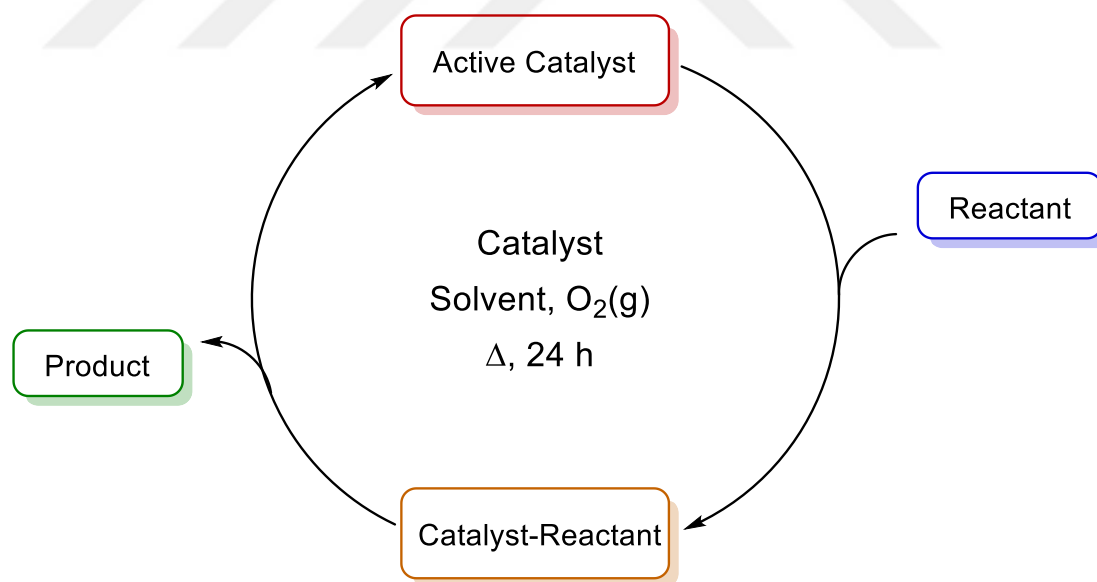


Figure 2: General scheme for aerobic oxidation reactions.

1.2 RESULTS & DISCUSSION

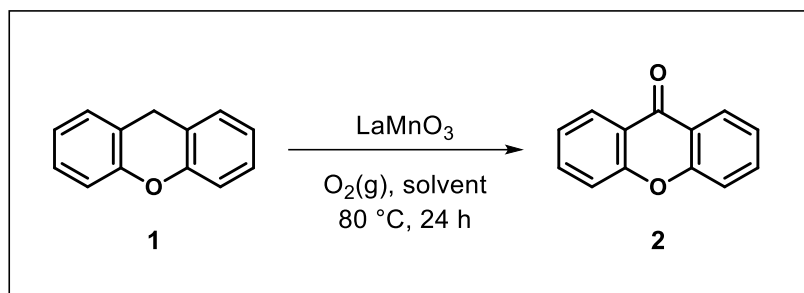
The conditions for the catalytic performance studies were carefully optimized by screening different solvents, temperatures and amounts of the reactants. Optimal conditions were used for the isolated yields using flash silica column chromatography. 9*H*-Xanthene (**1**) was used as a model substrate for LaMnO₃ (LMO) catalysts while 9*H*-fluoranthene (**2**) was the one for Ni_xMn_(1-x)(OH)₂ catalysts.

Our work on LMO catalyzed reactions was accepted for publication in **ACS Applied Materials & Interfaces**. The paper is entitled “Precious Metal-Free LaMnO₃ Perovskite Catalyst with an Optimized Nanostructure for Aerobic C-H Bond Activation Reactions: Alkylarene Oxidation and Naphthol Dimerization”.⁶⁴

1.2.1. Optimization of Solvent

In all optimization studies for aerobic C-H oxidation reactions catalyzed by LaMnO₃, 9*H*-xanthene (**1**) was used as a model substrate. First, the experiments were conducted at 80 °C (400 rpm-24 h) using freshly prepared LMO. Among the different polar and non-polar solvents investigated, it was found that the reaction affords higher yields when a non-polar solvent, mainly heptane, is used (**Table 1**). Although the solubility of the substrate is higher in trifluorotoluene (benzotrifluoride), the high reactivity in non-polar solvents might be related to the heterogeneous nature of the reaction environment. So, heptane was decided to be used in the next set of optimization experiments.

Table 1: Investigation of solvent for the aerobic oxidation of xanthene (**1**) to xanthone (**2**).*



Entry	Solvent	Conversion (%)
1	toluene	54
2	trifluorotoluene	46
3	heptane	96

* 50 mg of LMO, 0.5 mmol of xanthene and 2 mL of solvent was used. The mixtures were heated at 80 °C for 24 h.

1.2.2. Catalytic Performance and Pretreatment Studies

Catalytic activity studies were conducted by examining the catalytic oxidation reaction of xanthene (**1**) to xanthone (**2**). At least two different batches of LMO were prepared at a given time, and each trial was run as duplicates (running four reactions in total: two tubes for each batch) in order to have more reliable and reproducible results, and the conversion values were reported as average. Conversion values were determined by ¹H-NMR spectroscopy.

Initially, 100 mg of LMO catalysts were used per 0.5 mmol of substrate (**X**) in 2 mL of heptane and the mixtures were heated at 80 °C for 24 h. When fresh LMO was used, conversion to xanthone (**1**) was observed to be 77%. At this point, a reductive

pretreatment protocol was adopted and the catalysts were reduced with 4% H₂ in argon for 3 h at specific temperatures in a flow furnace prior to use. Abbreviations shown as LMO-temperature corresponds to this reduction temperatures. For instance, LMO-400 refers to the LaMnO₃ perovskite to which the reductive pretreatment protocol at 400 °C was applied. From now on “LMO-number” acronym will be used denoting the catalysts’ pretreatment temperatures for simplicity. When these reduced catalysts were used for the same transformation, LMO-400, LMO-500, LMO-600 and LMO-700 showed almost full conversion (99%) displaying a serious improvement in catalyst activity (**Figure 3**). LMO-800 activity was significantly lower compared to the pretreatments at other temperatures, and the reason was investigated via a variety of spectroscopic techniques by the Ozensoy research group. It was observed from the XRD results that the fresh catalyst (LMO) has a cubic structure and the reduction treatment causes a morphological change in the structure causing the catalyst to adopt an orthorhombic lattice shape in LMO-500, LMO-600. Further reduction at 700 °C and 800 °C, on the other hand, starts to cause a collapse, and the catalyst is no longer a perovskite but a mixture of lanthanum oxide (La₂O₃) and manganese oxide (MnO) with a trace amount of perovskite. So, the activity decrease can be explained by this structural change in the perovskite.

Then, the optimization for the catalyst loading was investigated. Same reaction conditions were applied with a catalyst loading of 50 mg per 0.5 mmol of xanthene (**1**) this time. Delightfully, LMO-600 maintained its catalytic activity at this catalyst loading, and provided 91% conversion to the product. Product (**2**) was isolated by flash column chromatography and obtained in pure form with 97% yield when 100 mg of LMO was

used. Based on these results, it was selected as the optimized catalyst to be used in the next set of studies. The data are summarized in **Figure 3**.

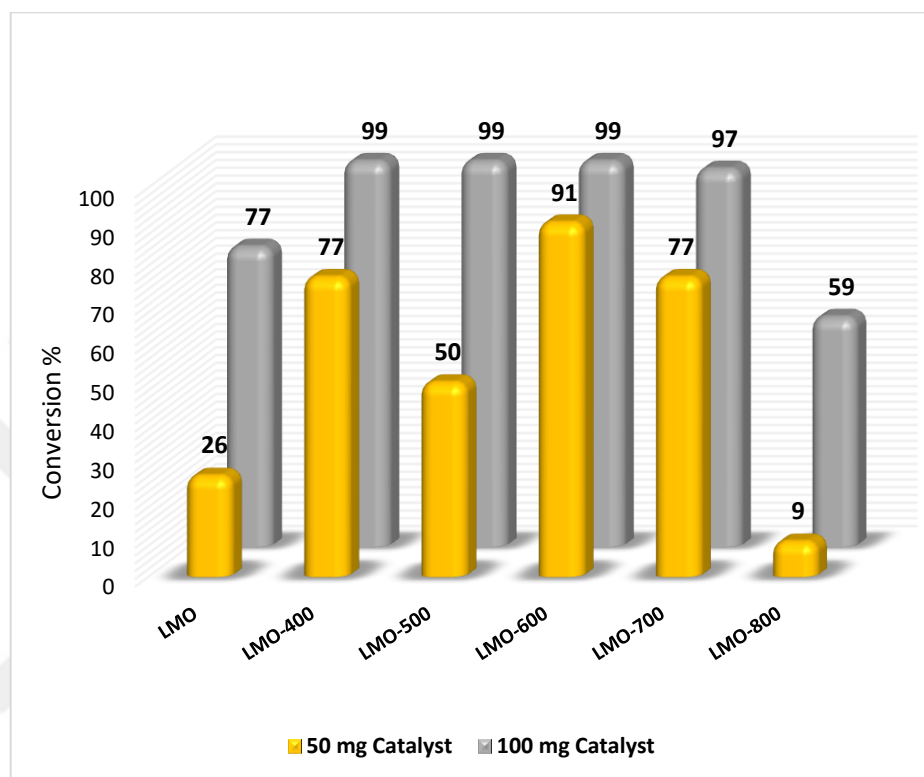
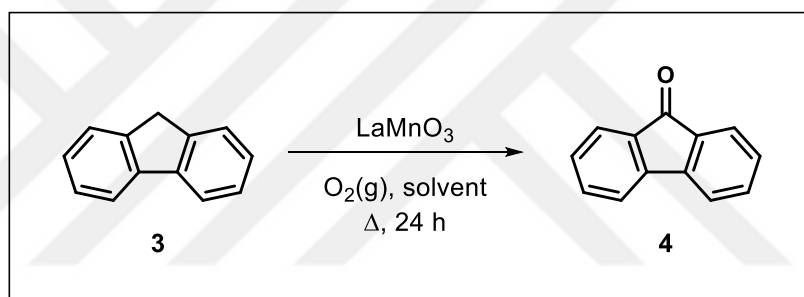


Figure 3: Catalytic activity of unreduced LMO catalyst and its reduced forms at different temperatures. Reaction conditions: $P(O_2) = 1$ bar, 0.50 mmol of xanthene at 80 °C in heptane).

As the successful optimization of catalyst pretreatment has been achieved, the oxidation of other substrates were studied. Essentially, we attempted to oxidize 9*H*-fluorene (**3**) to 9*H*-fluoren-9-one (**4**). Fluorenones form the core structure of various biologically active molecules or organic electroconductive materials⁴⁸ and they are usually synthesized through oxidations with peroxides⁴⁹ or hypervalent iodine derivatives.⁵⁰ It was apparent that the rise in the temperature does not cause a proportional boost in the conversion because there was not a significant difference between results when the

reaction was conducted at 80 °C and 100 °C, giving 52% and 56% conversions respectively. So, increasing the catalyst amount was found to be necessary for full conversion since when fluorene (0.5 mmol) was heated with 150 mg of LMO-600 in heptane at 80 °C for 24 hours, 99% conversion was achieved as compared to the 52% conversion with 100 mg of catalyst loading. Purification by column chromatography afforded pure product **4** in 96% yield. The details of the optimization studies are summarized in **Table 2**.

Table 2: Optimization of fluorene (**3**) oxidation to fluorenone (**4**)

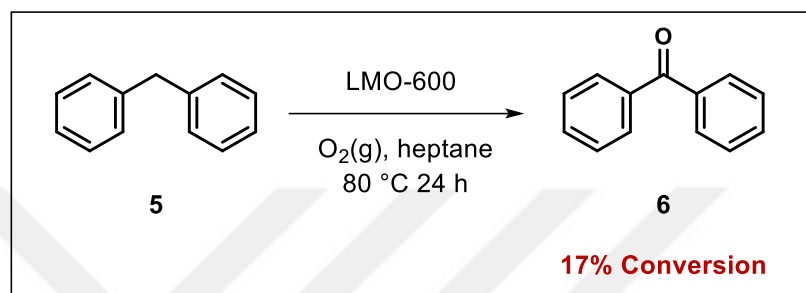


Entry	Pre-treatment T (°C)	Amount of LMO (mg)	Temperature (°C)	Solvent	Conversion %
1	-	50	80	toluene	21
2	600	100	80	heptane	52
3	600	100	100	octane	56
4	600	150	80	heptane	99 (96)*

* Isolated product yield is given in parentheses.

However, the conversion to the ketone was very low when diphenylmethane, a related alkylarene, was used as substrate under the optimum conditions (**Scheme 1**). It was not very surprising though since the stabilization on the formed radical after activation

is not as high as the one in xanthene or fluorene. These two compounds contain a bridge that connects to phenyl rings and the interaction of aromatic rings with the radical is strong, while xanthene has also one oxygen atom causing stabilization. However, the phenyl groups stay almost perpendicular to each other in diphenylmethane (5).

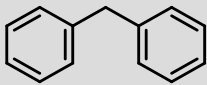


Scheme 1: Oxidation of diphenylmethane (5) to benzophenone (6)

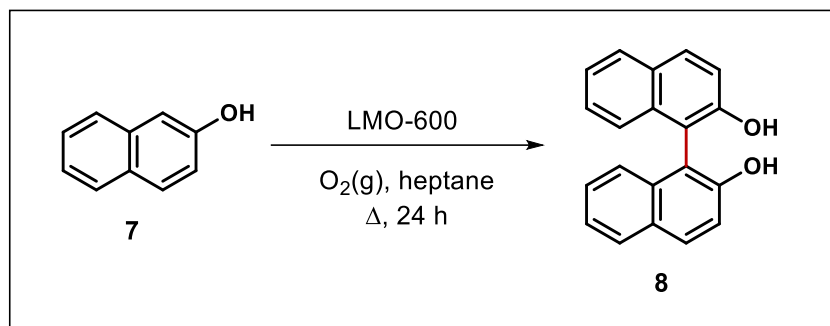
In order to provide a rationale for this difference in reactivity, we examined the homolytic bond dissociation energies of C-H bonds.⁵¹ Expectedly, the difference in these energies was relatively high due to the stabilization environment of the formed radical and thus the activities were in good correlation with the BDEs in reverse order (**Table 3**).

Table 3: Comparison of homolytic bond dissociation energies of various alkylarenes.

Entry	Compound	Conversion (%)	Homolytic BDE (kcal/mol)
1	1	99	80.7
2	3	99	82.0

3	5		17	85.0
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As the formation of C-O bonds in different substrates was successfully completed, we next opted to investigate a C-C bond formation reaction by aerobic C-H oxidation. Two mechanistically different reactions were initially studied. Firstly, oxidative homocoupling of 2-naphthol was investigated in several reaction conditions (**Table 4**). Gratifyingly, when 2-naphthol (**7**) was heated with LMO-600 in heptane at 60 °C, the oxidation product BINOL (1,1'-binaphthyl-2,2'-diol) (**8**) was obtained in good yield. The ¹H-NMR yield of the product was calculated by using 1,3,5-trimethoxybenzene as an internal standard (72%), and it was in correlation with the isolated product yield (66%). This reaction is valuable because BINOLs are well-known in enantioselective catalysis⁵² due to their axially chiral structure, and their derivatives are found in many biologically active natural products⁵³ or some materials like sensors.⁵⁴ They can also be used as a precursor in the synthesis of other compounds such as BINAP,⁵⁵ phosphoric acid-type Brønsted acids, or reducing agent BINAL-H.⁵⁶ Also, to the best of our knowledge, this was the first time a perovskite-type catalyst is used for BINOL synthesis.

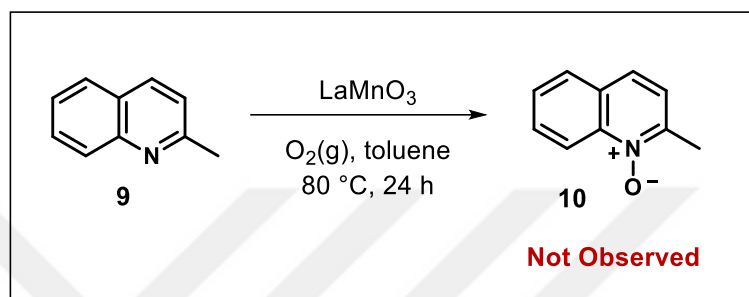
Table 4: Optimization for the synthesis of BINOL (**8**)

Entry ^a	Solvent	Temperature (°C)	Conversion %
1	heptane	80	Decomposition
2	toluene	80	Decomposition
3	heptane	40	26
4	toluene	40	26
5	toluene	60	42
6	heptane	60	72 (66)^b

^a 0.50 mmol of 2-naphthol and 100 mg of LMO-600 were used. ^b Isolated product yield is given in parentheses.

Moreover, the formation of *N*-oxides from azines was studied. *N*-oxides can be found in various heterocyclic compounds as well as some alkaloids,⁵⁷ and their synthesis has been widely studied.⁵⁸ They can be converted to alkenes⁵⁹ and amines⁶⁰ or be used as an oxidant. Thus, our aim was to synthesize 2-methylquinoline *N*-oxide (quinaldine *N*-oxide) (**10**) from 2-methylquinoline (quinaldine) (**9**). For this purpose, quinaldine (**9**) (0.25 mmol) was heated with 50 mg of LMO in toluene at 80 °C for 24 h (**Scheme 2**).

Unfortunately, the reaction did not deliver the desired *N*-oxide under these conditions. This was understandable since the transformation includes a direct oxygen transfer instead of a C-H activation step, and therefore, is mechanistically different compared to the previously investigated C-H oxidation reactions.



Scheme 2: Studies on the oxidation of 2-methylquinoline (**9**) to 2-methylquinoline *N*-oxide (**10**).

Our next objective was to test if LMO could be used as a catalyst for intramolecular cyclization reactions. The first plan was to conduct an experiment with compound **11** using previously optimized conditions and obtain either the aldehyde product **12** or carboxylic acid product **13** at the end of the reaction (**Figure 4**). This transformation was expected to proceed *via* the formation of a radical formed by homolytic cleavage of C-H bond at the benzylic positions of phenyl groups and then the attack of that radical to the alkene carbon constructing a five-membered ring. Later, the resulting radical may react with molecular oxygen to form the final oxidation products.

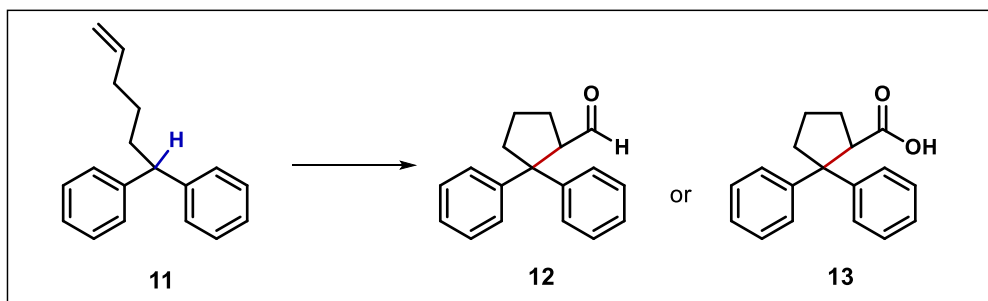
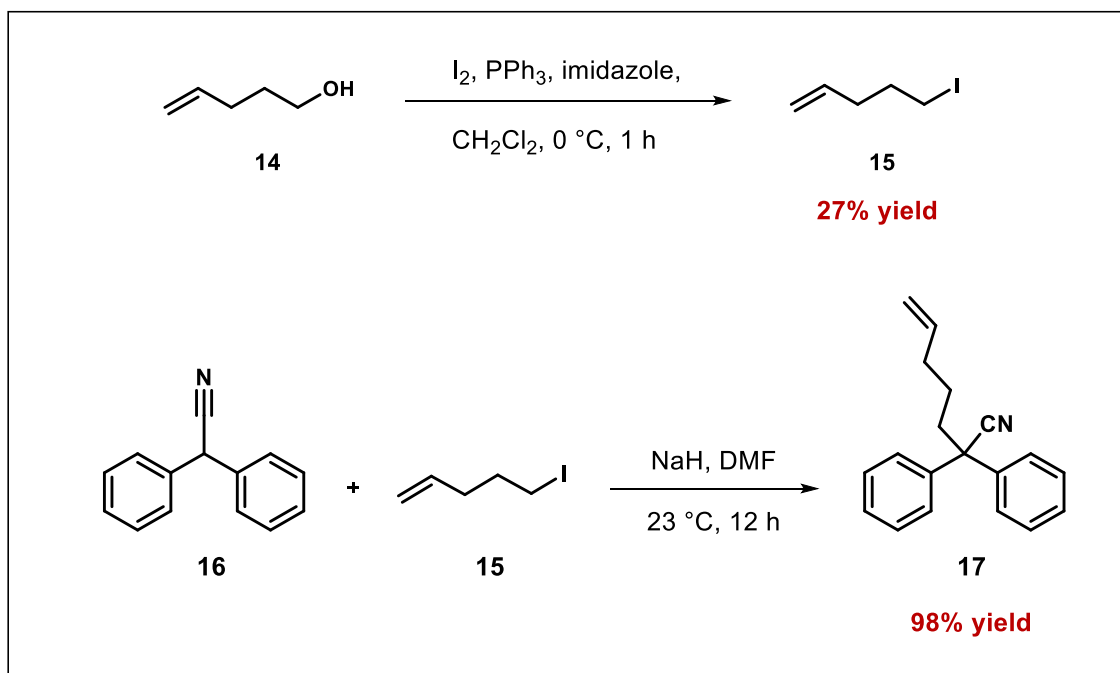


Figure 4: Synthesis plan for the intramolecular cyclization reaction.

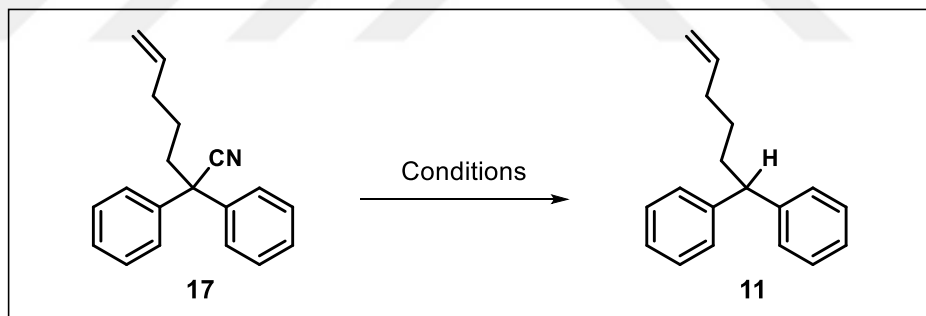
Compound **11** was not commercially available, so it was synthesized in three steps from simple building blocks. First, the Appel reaction of 4-penten-1-ol (**14**) with iodine, triphenylphosphine and imidazole in CH_2Cl_2 at $0\text{ }^\circ\text{C}$ delivered 5-iodo-1-pentene (**15**) in 27% yield. Although the conversion to the product was complete as analyzed by TLC, volatility of the product was a serious problem causing the loss of product during purification. Then, the alkylation of diphenylacetonitrile (**16**) with compound **15** in the presence of NaH in DMF afforded the nitrile product (**17**) in 98% yield (**Scheme 3**).



Scheme 3: Synthesis of compounds **15** and **17**.

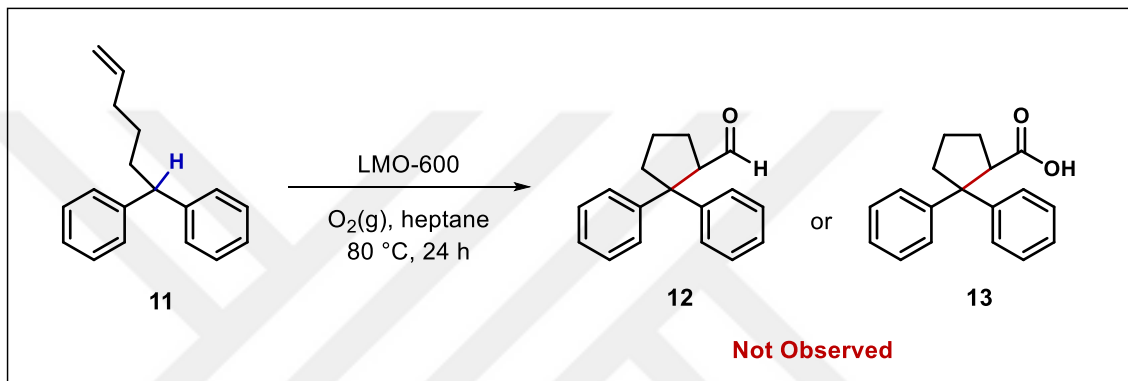
The next step was the reduction of nitrile (**17**) and several conditions were investigated since usual reduction processes of nitriles affords the respected amines. Common conditions for nitrile reduction include procedures that use reagents such as LiAlH_4 ,⁶¹ $\text{BH}_3\text{-THF}$ ⁶² or H_2 + Raney Nickel.⁶³ The use of sodium hydride (NaH) with heating was the first option, however no product formation was observed when different solvents were used (**Table 5**, entries 1-3). Then, we decided to use a strong reducing agent and a decrease in yield with increasing temperature was observed. Satisfyingly, increasing the equivalent of the reagent at room temperature afforded the desired product **11** in 44% yield (entry 5). Even though the yield was not very high, it was acceptable so that we could proceed to catalytic trials.

Table 5: Optimization studies for the reduction of compound **17** to product **11**



Entry	Reagent 1 (equiv.)	Reagent 2 (equiv.)	Solvent	Temperature (°C)	Isolated Yield %
1	NaH (3)	NaI (2)	THF	85	NR
2	NaH (3)	LiI (2)	DME	85	NR
3	NaH (3)	LiI (2)	1,4-dioxane	85	NR
4	LiAlH_4 (2)	-	THF	23	28
5	LiAlH_4 (2)	-	THF	50	18
6	LiAlH_4 (3.5)	-	THF	23	44

Unfortunately, the formation of the targeted cyclization products (**12** or **13**) was not observed under the developed catalytic conditions even when 200 mg of LMO-600 was used for 0.5 mmol of compound **11** at 80 °C (**Scheme 4**). The starting material remained unreacted. The reason might be the large bond strength of that specific C-H bond, and the catalyst activity was not sufficient to cause homolytic cleavage.

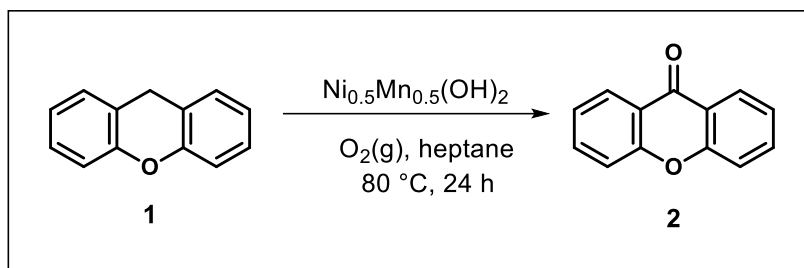


Scheme 4: Catalytic trial for the intramolecular cyclization of compound **11**.

1.2.3. Catalytic Performance of Nickel-Manganese Hydroxides

Later, the focus was switched from LMO as a perovskite-based catalyst, to a metal hydroxide catalyst, $\text{Ni}_x\text{Mn}_{(1-x)}(\text{OH})_2$, which has a bimetallic nature. These catalysts were synthesized and structurally characterized by Ozensoy Research Group. Again, the optimization studies were carried out on xanthene (**1**) oxidation due to our previous experience on this reaction. The first step was the optimization of synthesis method in catalyst preparation, and 1:1 ratio of nickel:manganese was used giving the catalyst $\text{Ni}_{0.5}\text{Mn}_{0.5}(\text{OH})_2$. It was observed that the catalysts synthesized at room temperature exhibited a superior activity compared to the ones that were calcined at high temperatures. The activities were 16%, 58% and 99% for catalysts $\text{Ni}_{0.5}\text{Mn}_{0.5}(\text{OH})_2$ -130°C,

$\text{Ni}_{0.5}\text{Mn}_{0.5}(\text{OH})_2$ -70°C and $\text{Ni}_{0.5}\text{Mn}_{0.5}(\text{OH})_2$, respectively when 10 mg of catalyst and 2 mL of solvent was used for 0.5 mmol of xanthene (**1**) (**Scheme 5**).



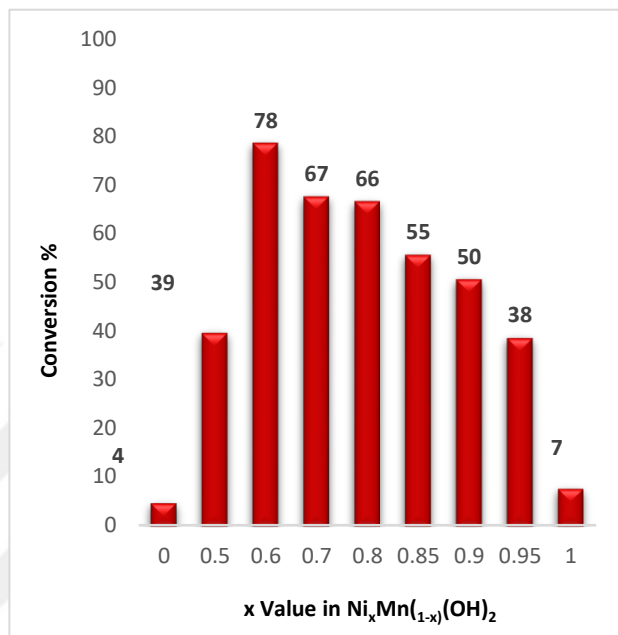
Scheme 5: Aerobic oxidation of xanthene (**1**) to xanthone (**2**) by $\text{Ni}_{0.5}\text{Mn}_{0.5}(\text{OH})_2$

Then, the elemental ratio of Ni:Mn ($x:1-x$) was studied starting from $x=0$ ($\text{Mn}(\text{OH})_2$) to $x=1$ ($\text{Ni}(\text{OH})_2$). Surprisingly, the ratio of 0.6:0.4 gave the highest result with 78% conversion (**Table 6**, entry 3). Thus, $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ was selected for the next set of experiments. Also, a volcano-type plot was seen, meaning that the activity decreases in order when the ratio is different.

Further, the amount of NaOH used during preparation steps was optimized as well since these catalysts are hydroxides and the surface concentration of -OH is related to this addition. So, the chosen catalyst $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ was synthesized with various NaOH stoichiometry and the activation experiments were run on the oxidation of xanthene (**1**) to xanthone (**2**). Mainly, the molarity of the NaOH was changed and S was taken as 2.1 M NaOH concentration and increased gradually to the point of saturation (15 S). It was seen that the catalyst shows superior performance when 6 S NaOH (12.6 M) was used as the OH source as compared to 1 S, 3 S, 9 S, 12 S catalysts and a conversion value of 86% was observed by using only 5 mg of $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ for 0.5 mmol of (**1**).

Table 6: Investigation of elemental ratio of Nickel:Manganese in the active catalyst for oxidation of xanthene (**1**) to xanthone (**2**)

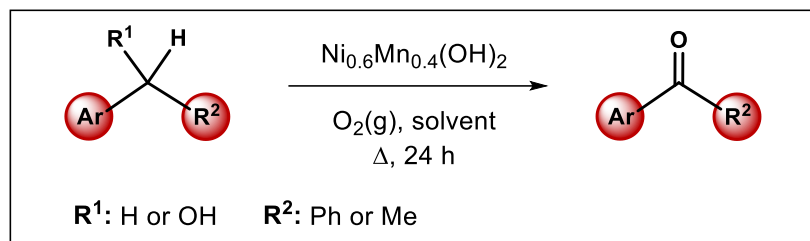
Entry	Catalyst	Conversion %
1	Mn(OH) ₂	4
2	Ni _{0.5} Mn _{0.5} (OH) ₂	39
3	Ni _{0.6} Mn _{0.4} (OH) ₂	78
4	Ni _{0.7} Mn _{0.3} (OH) ₂	67
5	Ni _{0.8} Mn _{0.2} (OH) ₂	66
6	Ni _{0.85} Mn _{0.15} (OH) ₂	55
7	Ni _{0.9} Mn _{0.1} (OH) ₂	50
8	Ni _{0.95} Mn _{0.05} (OH) ₂	38
9	Ni(OH) ₂	7

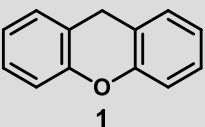
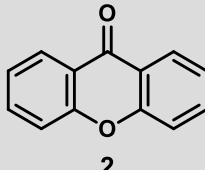
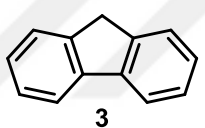
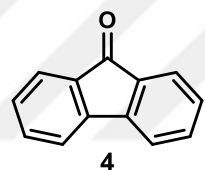
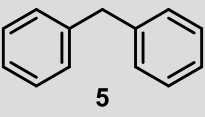
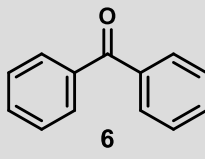
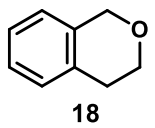
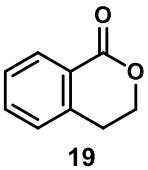
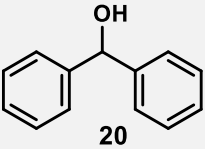
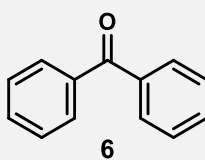
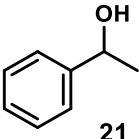
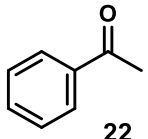


* 0.5 mmol of xanthene, 5 mg of catalyst and 2 mL of heptane was used in these reactions.

The new Ni_{0.6}Mn_{0.4}(OH)₂ catalyst showed a much better performance in terms of oxidation of C-H bonds in comparison to the perovskite LMO-600 and was successful to convert both alkylarenes and secondary alcohols to corresponding ketones. Xanthene (**1**) oxidation can be achieved by using only 7 mg of catalyst (**Table 7**, entry 1) while it was 50 mg of catalyst in the case of LMO-600, and it takes 20 mg of catalyst for fluorene oxidation under the same conditions (entry 2). Furthermore, when 20 mg of Ni_{0.6}Mn_{0.4}(OH)₂ was used at 110 °C, the formation of benzophenone (**6**) was observed with high conversion (92%) and yield (94%) (entry 3). Additionally, isochromanone (**19**) was obtained in high yield (96%) with the use of 20 mg of catalyst (entry 4). This was important since it shows that the catalyst can be used not only in doubly benzylic compounds but in heterocyclic compounds as well. The details of substrate scope can be seen in **Table 7**.

Table 7: Aerobic oxidation of various substrates catalysed by $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$



Entry	Compound	Product	Catalyst Amount (mg)	Reaction Temp. (°C)	Conversion % (Isolated Yield %)	Homolytic BDE (kcal/mole) ⁵¹
1 ^a			7	80	>99 (96)	80.7
2 ^a			20	80	>99 (99)	82.0
3 ^b			20	110	92 (94)	84.5
4 ^b			20	110	96 (96)	-
5 ^a			10	80	>99 (99)	75.4
6 ^a			30	80	>99 (93)	88.3

^aHeptane was used as solvent. ^bOctane was used as solvent.

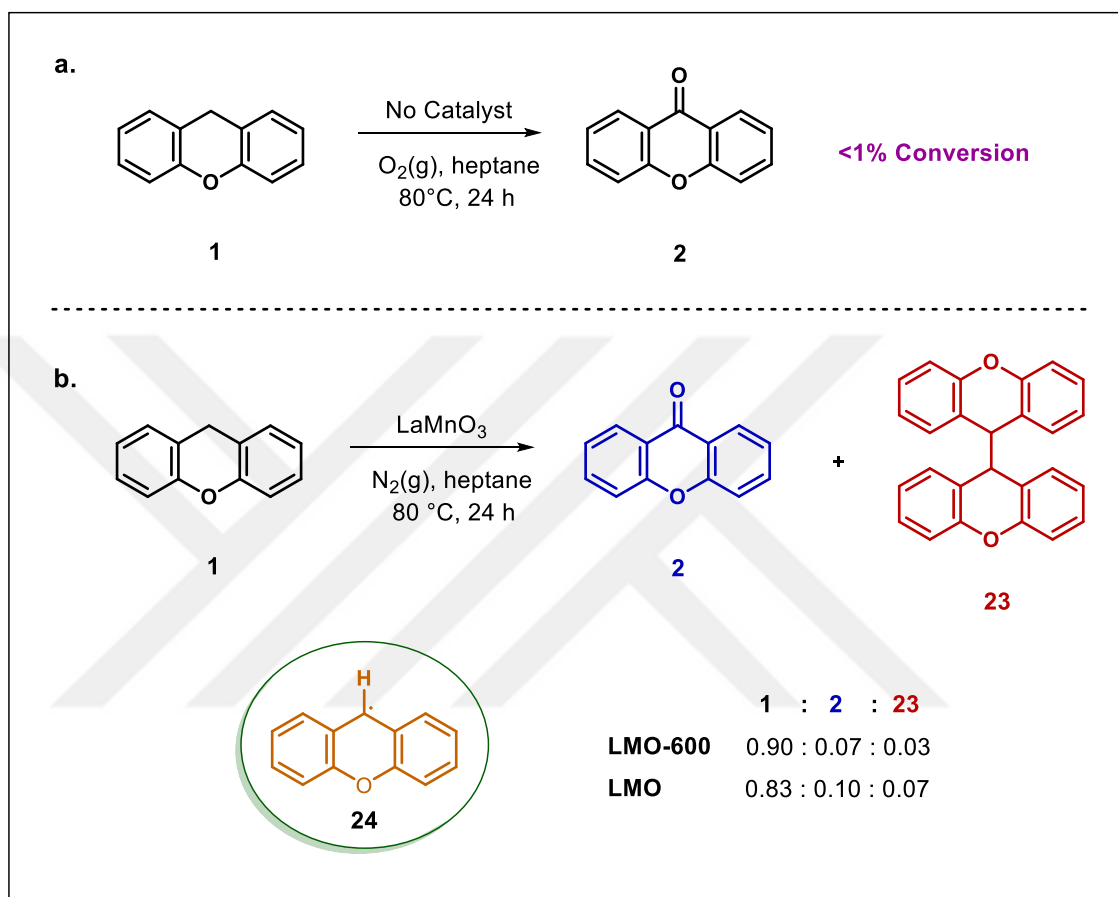
The oxidation of secondary alcohols was also achieved at mild conditions. Heating of diphenylmethanol with 10 mg of catalyst at 80 °C resulted in >99% conversion and product (**6**) was obtained in excellent yield (99%) (entry 5). This is in correlation with the diphenylmethane (**5**) oxidation result since it was expected for alcohols to be oxidized more easily as compare to alkanes. Also, DL-sec-phenylethyl alcohol (**21**) was oxidized to acetophenone (**22**) in the presence of 30 mg of $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ at 80 °C and afforded >99% conversion with 93% yield (entry 6).

1.2.4. Mechanistic Studies

In order to shine light on the details of the mechanism of LMO-catalyzed C-H oxidation reactions, several control experiments have been done. Essentially, the reaction was conducted without the catalyst in the presence of 1 bar $\text{O}_2(\text{g})$ to show that the activation of molecular oxygen and the reactant comes from the catalyst itself and not from heating. In agreement with the expectations, the conversion to xanthone (**2**) was less than <1% demonstrating the importance of the catalyst (**Scheme 6a**).

In addition, the effect of oxygen was investigated as well using the previously optimized conditions. Basically, the mixtures containing the reactant **1**, catalyst and heptane were deoxygenated by freeze-pump-thaw technique (3 cycles each) and then heated under inert atmosphere for 24 h. It was seen that when the pretreated catalyst LMO-600 was used, the reaction gave 7% conversion to xanthone (**2**) while 90% of the reactant **1** remained unreacted. Also, 3% conversion to the dimerization product **23** was observed (**Scheme 6b**). When the fresh catalyst LMO was used, the formation of xanthone (**2**) was 10% while the dimer (**23**) was formed with 7% conversion along with the remaining 83%

xanthene (**1**) unreacted. These results underline the importance of molecular oxygen as the main stoichiometric oxidizing agent in the reaction medium.



Scheme 6: Effects of catalyst and oxygen on the reaction results of LMO-catalyzed oxidations.

Also, the formation of the dimerization product (**23**) was quite important in terms of understanding the mechanistic pathways since it can only be formed from the homo-coupling of radical intermediate **24** that would form via a hydrogen atom abstraction from starting xanthene (**1**). This shows that the activation of C-H bond is achieved by the use of pretreated catalyst and the formed radical has to react with itself to construct the dimer in the absence of molecular oxygen. Small amount of oxygen might have remained in the solvent as well.

Based on these information as well as literature precedents, a mechanism was proposed for the C-H oxidation by active LMO perovskite (**Figure 5**).

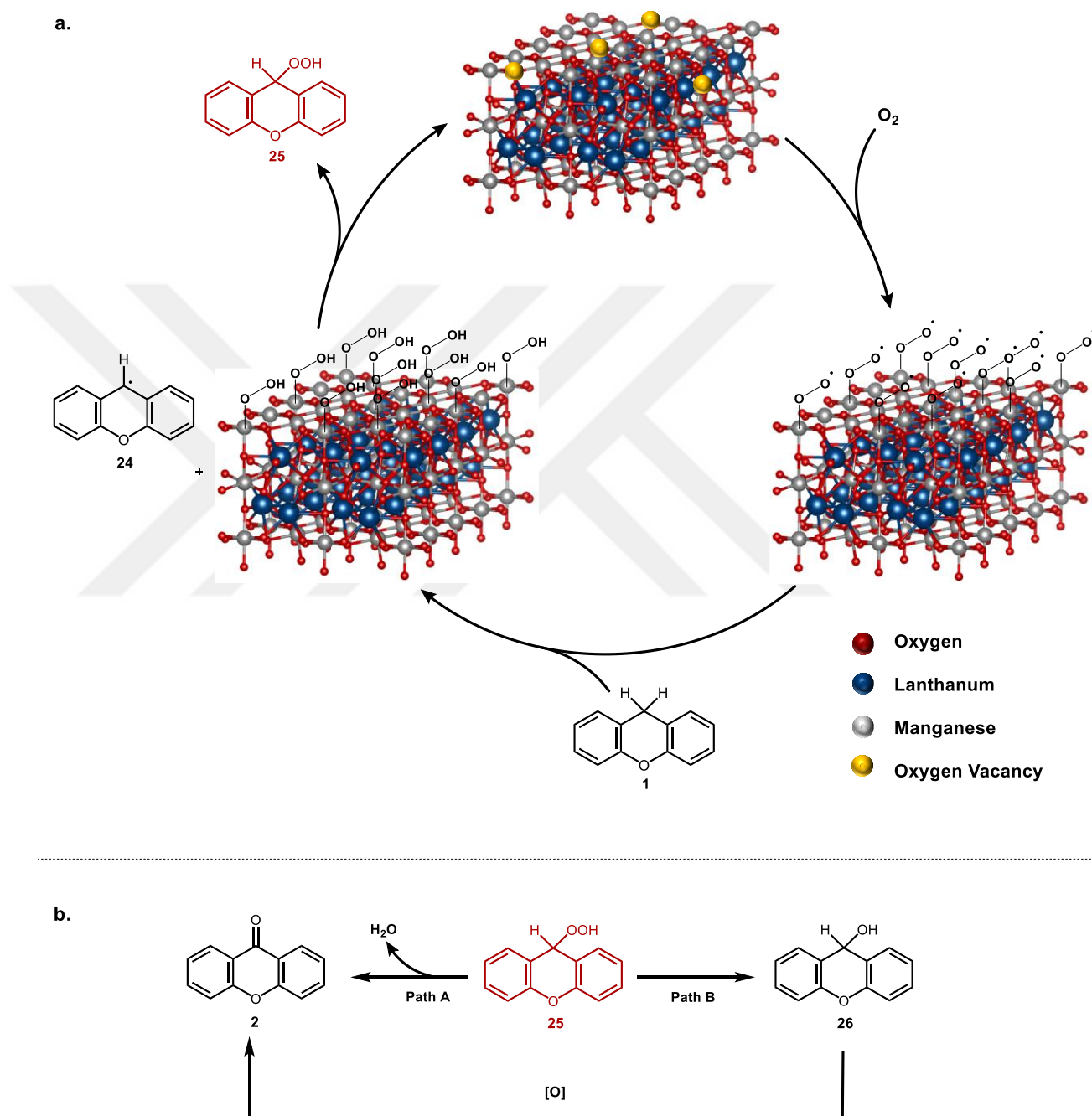
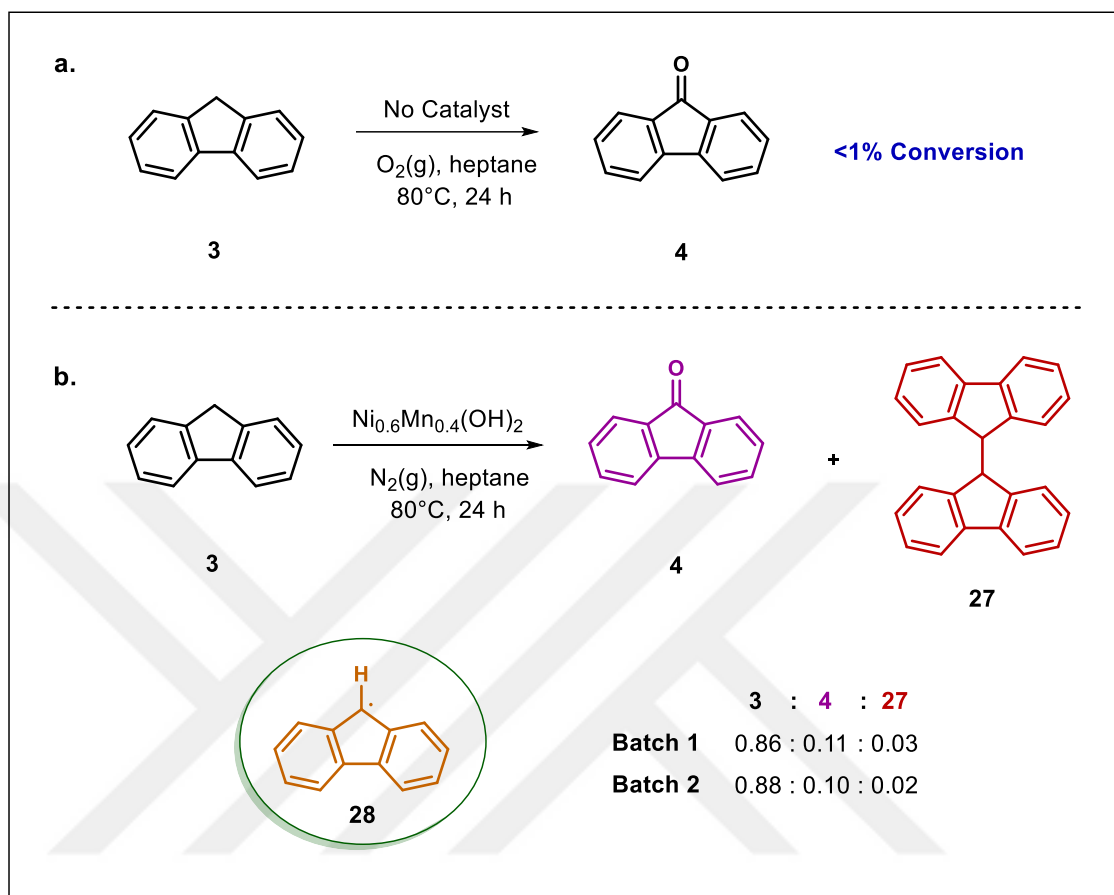


Figure 5: a) Proposed mechanism for the aerobic oxidation of xanthene (1) to xanthone (2) catalyzed by LMO-600. b) Possible reaction pathways for the conversion of intermediate 25 to xanthone (2).

Based on *in-situ* FTIR studies executed by the Ozensoy group, oxygen vacancies were found to be formed with the reductive pretreatment protocol (reduction with 4% H₂/Ar).⁶⁴ As a result, molecular oxygen is proposed to be activated by these vacancies on the surface of the LMO catalyst. This activation results in the formation of highly reactive surface-bound superoxide anions. The hydrogen atom abstraction from xanthene (**1**) may occur by the superoxides forming a hydroperoxyl species (HOO•) on the surface and the formed radical on xanthene is relatively stabilized due to its position being doubly benzylic. The combination of xanthene radical (**24**) with the hydroperoxide would deliver the intermediate **25**. This intermediate can either directly convert to xanthone (**2**) by a dehydration step (**Figure 5b**, Path A) or through a secondary alcohol intermediate (**26**) which can be further oxidized to ketone since the number of oxidizing species is high in the reaction environment (**Figure 5b**, Path B).

Similar control experiments were performed with the optimized Ni_{0.6}Mn_{0.4}(OH)₂ catalyst as well. The reaction with no catalyst using fluorene (**3**) as the substrate at 80 °C, has also given <1% conversion expectedly, once again proving the role of catalyst for the activation of both the reactant and the molecular oxygen. Anaerobic experiments using two different batches resulted in average 11% conversion to fluorenone (**4**) and 3% conversion to the dimerization product (**27**) this time, showing the activation of C-H in fluorene as well while 87% of the starting material remained unreacted under the optimized conditions (**Scheme 7**). However, the details of the mechanism of Ni_{0.6}Mn_{0.4}(OH)₂ catalyzed oxidation reactions of alkylarenes and alcohols are currently unknown and further investigation is needed.



Scheme 7: Effects of catalyst and oxygen on the reaction results of $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ catalyzed oxidations.

1.2.5. Kinetic Studies

Time-dependent conversion of the reactant to the product was examined next. The mixtures of LMO-600 (100 mg), xanthene (0.5 mmol) and heptane (2 mL) were heated at 80 °C and conversion values were determined at 3, 6, 9 and 24 hours, sequentially. It was seen that the reaction proceeds in a fast manner up to 6 h and reaches 86% conversion, while it is more than 90% at the end of 9 h (**Figure 6a**). Likewise, $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ displays a similar behaviour when the reaction with 7 mg of catalyst, xanthene (0.5 mmol) and heptane (2 mL) was conducted, and conversion values were determined at 6, 12, 18

and 24 h. More than 80% conversion can be achieved in 6 hours this time (**Figure 6b**). This type of kinetic behaviour is known in the literature, and explained by Mars–van Krevelen mechanism where the surface plays an important role in the mechanism as proposed by our group and the substrate is oxidized by the active surface species.^{65, 66}

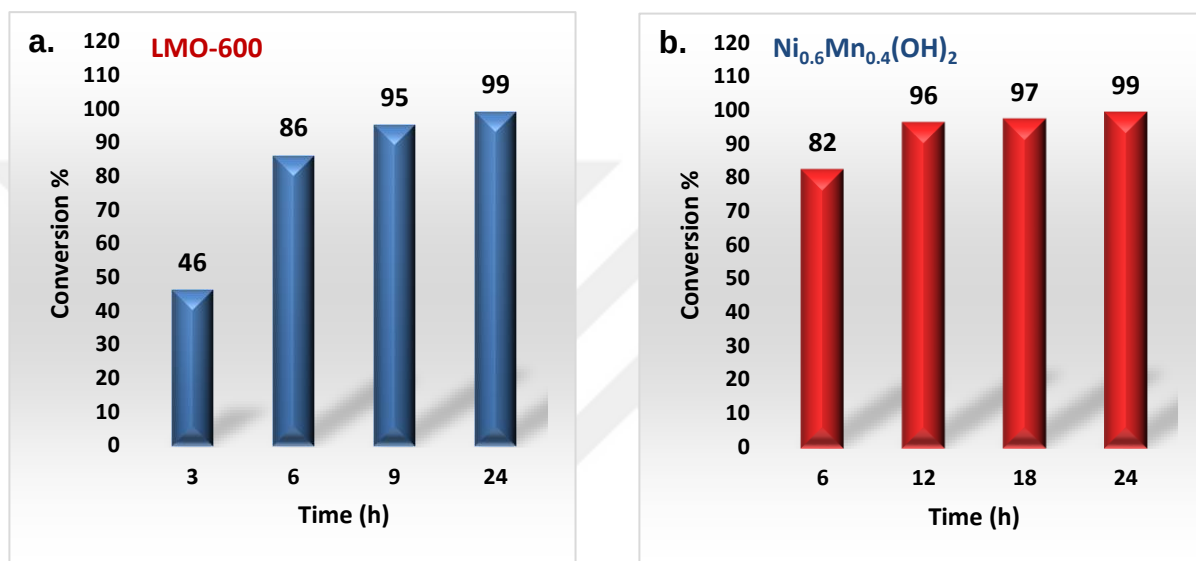


Figure 6: Dependence of conversion on reaction times: a) for LMO-600 b) for $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$

1.2.6. Studies on Catalyst Regeneration and Reusability

As the investigation for the best catalytic performance and other studies have been completed, the next step was to examine the reusability of the optimized catalysts. The transformation of xanthene (**1**) to xanthone (**2**) was used as the model reaction for LMO-600 tests while fluorene (**3**) was the model substrate for $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ catalyst. The reusability tests were conducted by running the first reaction using the optimum condition for each substrate/catalyst amount, separating the catalyst by centrifugation using an

appropriate solvent and then drying to conduct the second and the third cycles, sequentially.

Firstly, LMO-600 was studied in detail (**Table 8**). The mixtures at the end of each reaction were diluted with EtOAc and centrifuged three times to taken into evaporating dishes with methanol and dried in oven at 130 °C prior to the second cycle. The conversion to xanthone (**2**) decreased to 5% when the catalyst was used directly, showing an insufficient performance. This was justified by the XPS and ATR-IR results of the spent catalyst where the surface of the active catalyst is poisoned by carbon either be it unreacted starting, product or other carbon-based species formed during the reaction such as $-\text{CO}_3$, $-\text{CH}_x$ etc. This covering on the surface causes deactivation in the next cycles.

Therefore, the goal became the cleaning of the surface from these carbon-species before the second cycle. The first plan was to reduce the catalyst again with the same procedure applied at the beginning which was the reduction using 4% H_2 in argon at 600°C (Method A). Fortunately, the catalyst showed a better activity this time with a conversion value of 63% for the second cycle while it was 39% in the third (**Table 8**, entry 2). Then, the reduction time was extended to 6 hours with the expectation that it would clean more area and regain the first conversion value (entry 3). However, it decreased the activity to 16% instead, and decreasing the time to 1 h (entry 1) did not work either.

Afterwards, a different approach was undertaken. It was expected that the calcination in air or with oxygen would burn the carbon species to produce carbon dioxide, thus cleaning the surface (Method B). The activity was 18% in the second cycle after calcination at 700 °C in air for 5 h and reduction with 4% H_2 in argon at 600 °C for 3 h (entry 4). Decreasing the time and temperature of calcination did not cause any

improvement (entry 5). Burning the surface species in a flow furnace was also tried and the catalysts were exposed to continuous oxygen flow at 600 °C for 3 h before reduction with hydrogen (Method C) (entry 6). This technique gave 15% conversion for the second cycle. Finally, ozone as a more aggressive oxidant was used for cleaning by introducing it to the catalyst for approximately 2 h at room temperature before reduction (entry 7). This process did also not deliver a good activity (Method D).

Table 8: Details of the studies on catalyst regeneration and reusability for LMO

Entry	Method	Calcination Temp. (°C) / time(h)	Reduction Time (h)	Cycle I Conv.	Cycle II Conv.	Cycle III Conv.	Cycle IV Conv.
1	A	-	1	93	23	18	-
2	A	-	3	99	63	39	-
3	A	-	6	96	16	13	-
4	B	700/5	3	96	18	17	-
5 ^a	B	400/1	3	-	-	18	8
6 ^b	C	-	3	87	15	-	-
7 ^b	D	-	3	82	7	-	-

^a The separated catalyst from entry 1 cycle 3 was used for this experiment. ^b The low conversions of cycle 1 in these experiments are due to a technical problem with the flow furnace.

Different attempts for regeneration have been made for the $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ catalyst. Essentially, the second cycle gave 61% conversion to fluorenone (**4**) after the catalyst was separated by centrifugation using acetone and dried at room temperature prior to using, while the activity for the third cycle was only 19% (**Figure 7a**). ATR and XPS results showed a similar poisoning by carbon of the surface. However, reduction procedure was not used for this catalyst, since it would change the structure and the comparison of the activities would not be scientifically correct. Hence, cleaning the surface with argon emerged a plausible option. Fortunately, drying the catalyst under a continuous argon flow in a closed furnace at 300 °C for 6 h helped regaining the activity and caused a conversion of 97% in cycle 2. However, 6 h of treatment was not enough for the third cycle and the activity was 35%. But, when the time was increased to 12 h for the third cycle, the conversion value of 70% was obtained (**Figure 7b**).

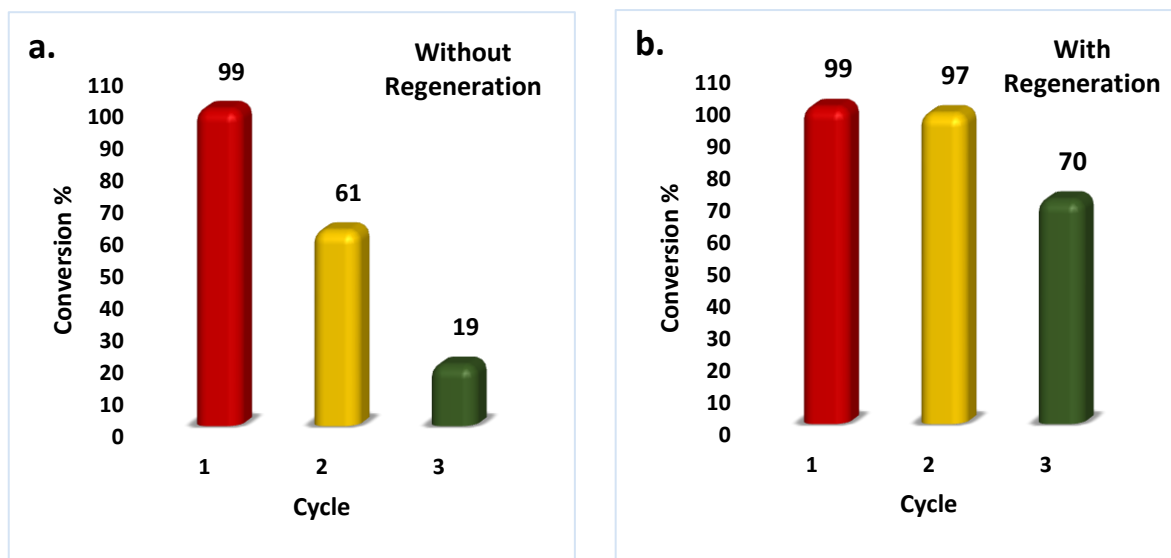


Figure 7: Conversion data for xanthene (**1**) oxidation by $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ a) With no regeneration, b) With regeneration of $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ using argon flow (100 SCCM) for 6 hours (Cycle 2) and for 12 hours (Cycle 3).

1.3. CONCLUSION

In this work, the catalytic abilities of two transition metal-based catalysts namely, LaMnO_3 and $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ was investigated in collaboration with the Ozensoy research group. The main focus was the heterogeneous aerobic C-H oxidation reactions in liquid phase.

We have developed a new methodology that uses a highly efficient reductive pretreatment system using 4% H_2 in argon to increase the activity of precious metal-free LaMnO_3 perovskites. This methodology includes careful optimization of structural and electronic properties of the catalyst as well as optimization of the reaction conditions of various substrates. As a result, it was found that treatment at 600 °C affords a perovskite with high catalytic ability (LMO-600) for aerobic oxidations of alkylarenes such as xanthene (**1**) and fluorene (**3**) with good yields at mild temperatures. Also, it was effective for the formation of BINOL (**8**) *via* oxidative dimerization of 2-naphthol (**7**). Detailed spectroscopic and mechanistic studies revealed the formation of superoxides (O_2^-) on the catalyst surface and a radical on organic compound *via* H-atom abstraction, then a mechanism was proposed for aerobic oxidation of alkylarenes. Another finding is that the catalyst is deactivated because of carbon poisoning after the first cycle and it can be re-activated using a proper regeneration method up to a degree.

Moreover, a novel bimetallic hydroxide ($\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$) was synthesized using nickel and manganese in basic conditions. Synthesis method was proven to be an important parameter and the calcination of the catalyst in high temperature decreases activity. It was also found that the elemental ratio of nickel to manganese has a serious impact on the catalytic activity and the catalyst with 0.6:0.4 (Ni:Mn) concentration gives

the best results with very small catalyst loading. Aerobic oxidations of both alkylarenes and alcohols was achieved in excellent yields. Similar to LMO, this catalyst too was deactivated due to carbon, however, a regeneration method that employs surface cleaning with argon flow was developed giving 70% recovery of the first activity. In comparison to the literature, this is the first time a bimetallic hydroxide is used for heterogeneous aerobic oxidation reactions and it holds the top places in terms of small catalyst loading.



CHAPTER 2: DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF FLUORANTHENE DERIVATIVES USING Pd-BASED CATALYSIS AND INTRAMOLECULAR DIELS-ALDER REACTIONS

2.1. INTRODUCTION

2.1.1. Fluoranthene Derivatives and Their General Applications

Fluoranthenes are an important subclass of polycyclic aromatic hydrocarbons (PAHs) and can be defined as the fused forms of naphthalene and benzene rings via a five-membered ring in between. They have numerous applications in medicine,⁶⁷ organic electronics⁶⁸ and material science⁶⁹ due to their planar structure, highly conjugated π -system and potential for modification. Several natural products that were derived from fungi also contain the fluoranthene core (**29**) in their structures. They have been investigated over the years and many of them show bioactivity such as Truncatone C⁷⁰ (**31**) and Daldinone B (**30**).⁷¹

Additionally, these π -conjugated polycyclic aromatic hydrocarbons are known to have unique thermal and air stability, thus gaining a significant place in material science and optoelectronics. They can be used in the preparation of organic semiconductors, transistors, light-emitting diodes or solar cells due to their fluorescent nature under the UV light.⁷² Recent examples (**32** and **33**) for the mentioned applications of fluoranthenes can be seen in **Figure 8**.

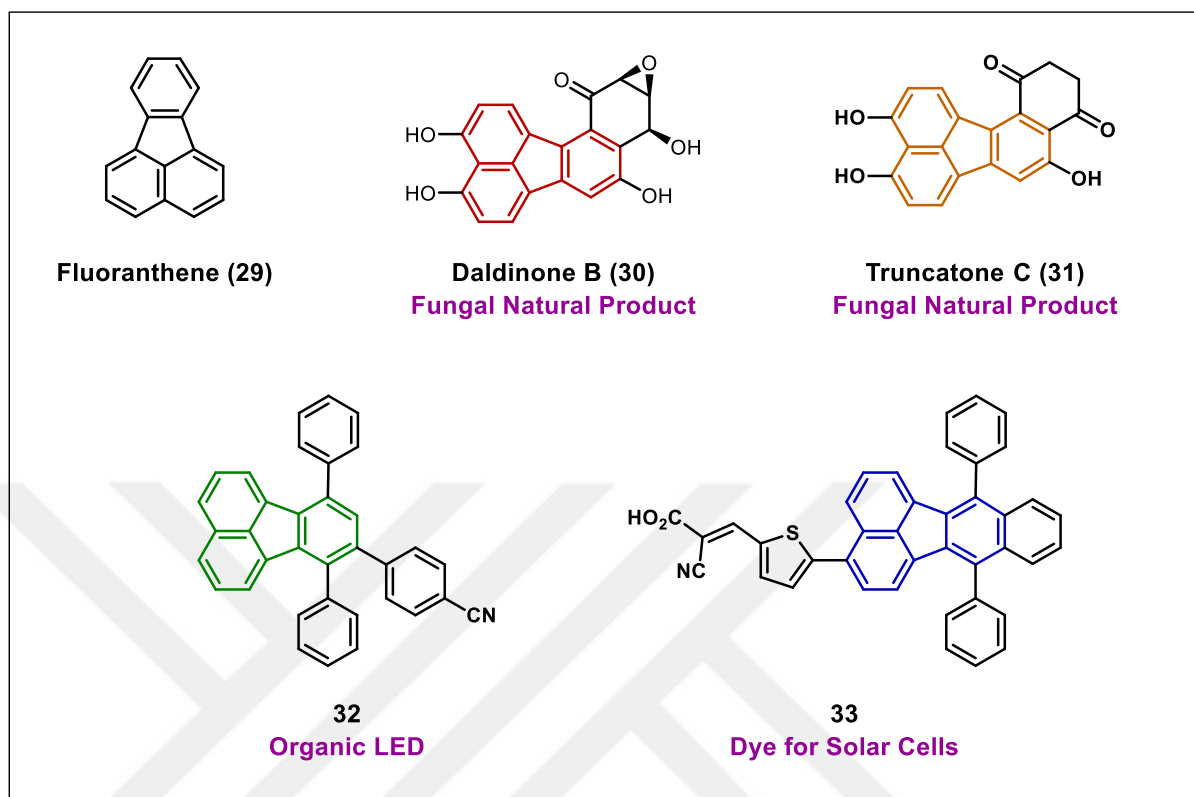


Figure 8: Examples of important fluoranthene analogues

2.1.2. Synthesis and Derivatization of Fluoranthenes

There are a number of ways that employ different approaches for the synthesis of fluoranthene derivatives from simple building blocks by mainly using C-H activation methods, transition metal catalysis or cyclization reactions.

Quimby et al.⁷³ and Yamaguchi et al. reported two examples that utilize Pd-catalyzed C-H activation reactions. Yamaguchi and co-workers developed a highly selective three-step sequence which involve intermolecular and intramolecular C-H arylation processes, and demonstrated the successful synthesis of more than ten fluoranthene analogues. However, the reaction conditions usually require a high loading

of [Pd] catalyst/ligand and the synthesized analogues were only mono-substituted (**Figure 9a**).⁷⁴

Another example of fluoranthene synthesis, which was reported by Chen et. al in 2011, is shown in **Figure 9b**.⁷⁵ This single step reaction includes the iodine-mediated electrophilic cyclization of 1,8-dialkynyl naphthalenes. The mechanism starts with the formation of an enyne from propargyl alkyne part and iodonium ion forms by the addition to one of the alkynes. The attack of the other triple bond to the iodonium forms the middle five membered-ring and a carbocation, which causes an intramolecular cyclization forming the final fluoranthene derivative (**Figure 9b**). The downsides of this method are that the regioselectivity of cyclization highly depends on the substrate, and that the resulting products are not synthetically very useful due to their highly specialized structures.

Further example of a cyclization reaction can be seen in **Figure 9c** where potassium bis(trimethylsilyl)amide (KHMDs) promotes a domino reaction and was used both as a base and a single-electron donor.⁷⁶ However, the syntheses of the biaryl substrates of this reaction require at least four steps, reducing the synthetic utility of this protocol.

In 2011, Echavarren and co-workers reported a method using highly electrophilic gold (I) complexes or gallium trichloride (GaCl_3) for the hydroarylation of alkynes.⁷⁷ A distinguishing feature of this method from the others is that the naphthalene core is not present initially in the structure of the reactants, but is formed during the reaction via the metal-catalyzed cyclization step (**Figure 9d**). Finally, our group recently developed a method in which either homogeneous or heterogeneous Pd catalysts were observed to

work effectively for the synthesis of substituted fluoranthene derivatives (**Figure 9e**).⁷⁸ This reaction involves a Suzuki-Miyaura cross-coupling followed by an intramolecular C-H arylation reaction, and operates with broad functional group tolerance on the benzene ring.



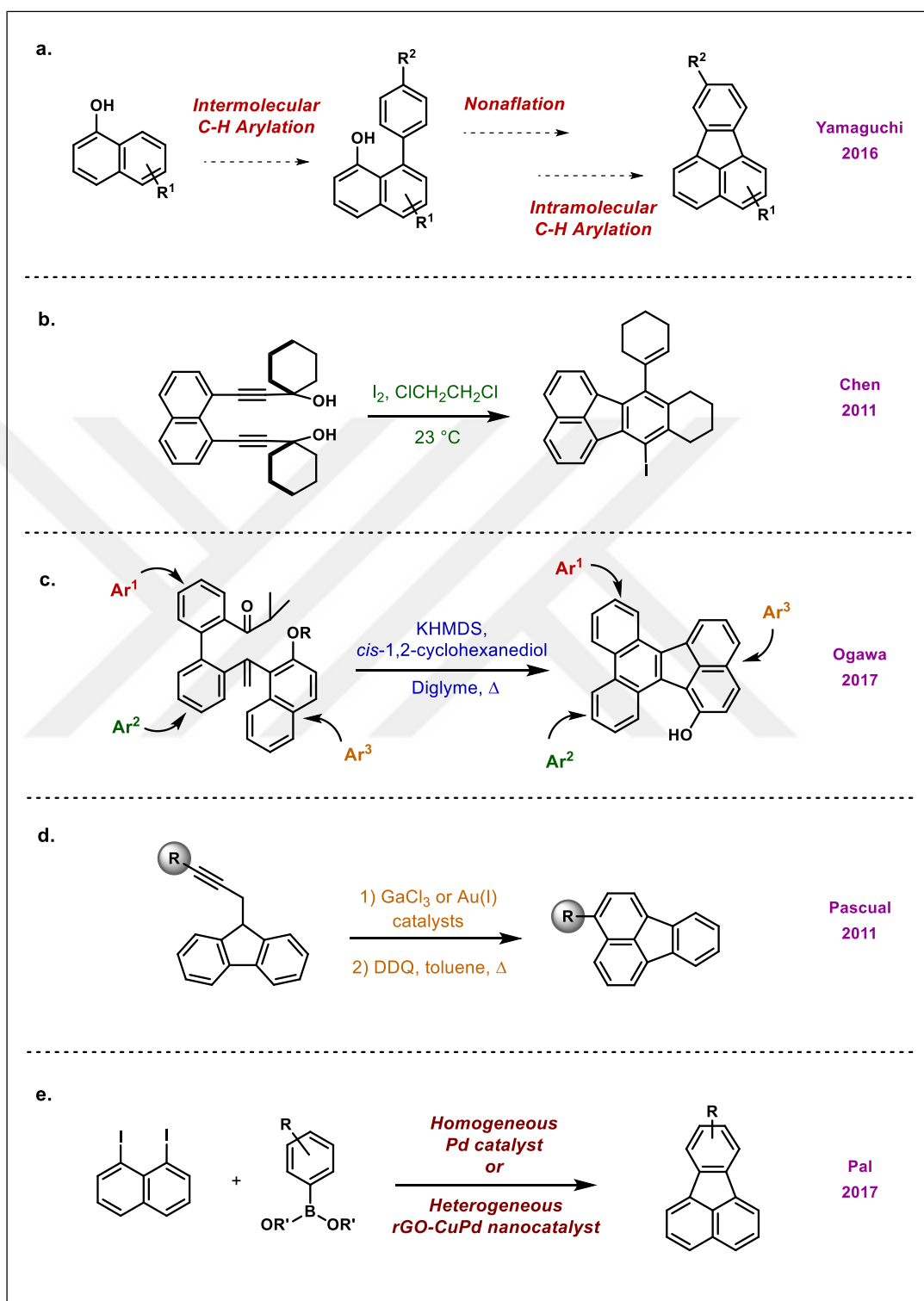
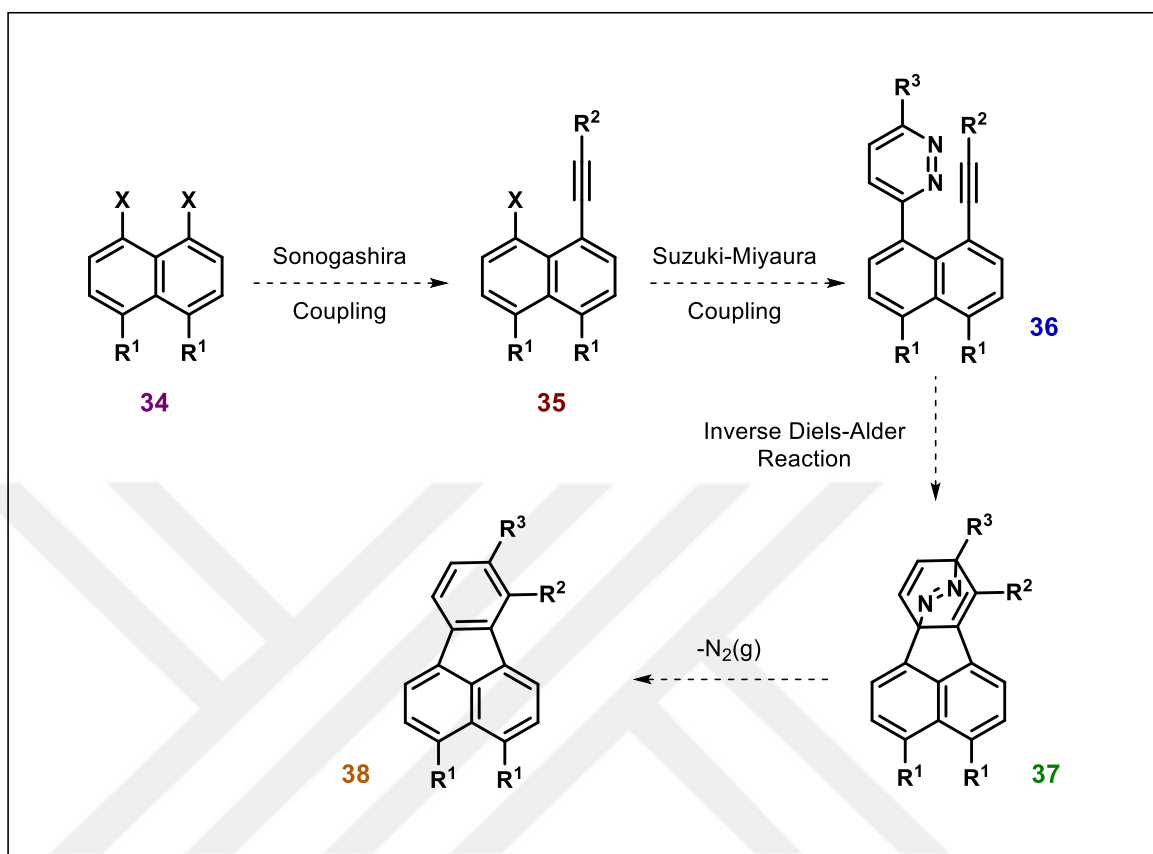


Figure 9: Various methods for the synthesis of fluoranthene derivatives

2.1.3. Aim of This Work

Since most of the methods mentioned above require either high catalyst loadings, exceedingly complex starting materials or multiple steps, a new method to synthesize substituted fluoranthenes in a practical and modular manner would be highly beneficial to the synthetic community. Therefore, the main purpose of this project was to develop two new methodologies for the synthesis of multi-substituted fluoranthene derivatives using intramolecular Diels-Alder reactions. These methods were designed to utilize a three-component system to form a complex polycyclic hydrocarbon skeleton which can be modified since all components are either commercially available or readily prepared. In both approaches, 1,8-dihalonaphthalene derivatives were planned to be used as the starting materials in Suzuki-Miyaura and Sonogashira cross-coupling reactions.

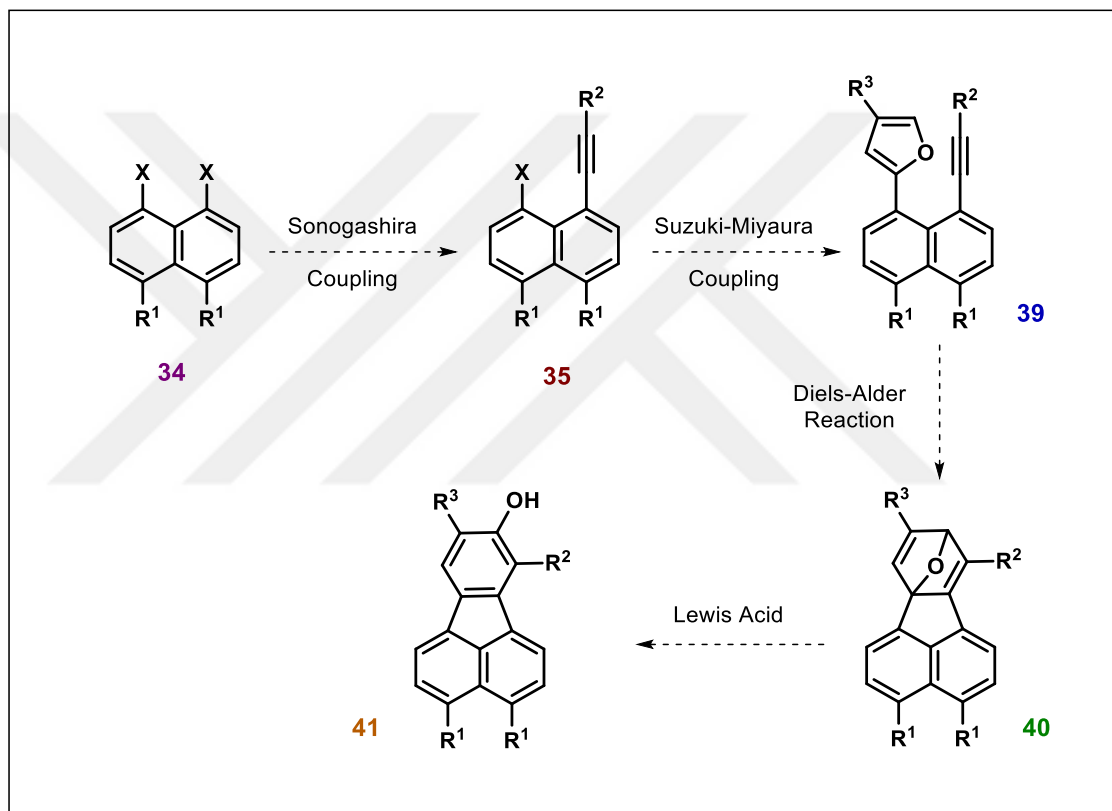
In the first method, the key step is the use of a 1,2-diazine group that participates as an electron-deficient diene in an inverse electron-demand Diels-Alder (IEDDA) reaction.⁷⁹ First, 1,8-dihalonaphthalene (**34**) would undergo a Sonogashira coupling with a terminal alkyne, and then the resulting product **35** would react with a diazineboronic ester derivative via a Suzuki-Miyaura coupling reaction to afford doubly-functionalized naphthalene **36**. An inverse electron-demand Diels-Alder (IEDDA) reaction between the electron-deficient azadiene and the electron-rich alkyne components is expected to afford adduct **37**, which would lead to the formation of the final fluoranthene product **38** after the loss of N₂ gas (**Scheme 8**). Considering the facile nature of *intramolecular* Diels-Alder reactions as well as the thermodynamic advantage of N₂(g) release, the possibility that the final product might be obtained spontaneously after the Suzuki-Miyaura coupling reaction was also considered during the reaction design.



Scheme 8: Consecutive Sonogashira, Suzuki-Miyaura cross-coupling and IEDDA reactions for fluoranthene synthesis

In the second stage of this study, an electron-rich furan was planned to be used as the diene in a Diels-Alder reaction after the consecutive coupling reactions to form the core fluoranthene structure. Since this reaction is designed as a normal electron-demand Diels-Alder reaction, electron-deficient alkynes are expected to give better results compared to electron-rich alkynes. In the designed reaction sequence, alkyne-containing intermediate **35**, which would be obtained by the Sonogashira coupling of **34** with a terminal alkyne, would be coupled with a furanboronic acid or ester by a Suzuki-Miyaura coupling to afford product **39** (**Scheme 9**). The intramolecular Diels-Alder reaction of **39**

is expected to give strained pentacyclic product **40** which would give fluoranthene product **41** either spontaneously or in the presence of a Lewis or Brønsted acid. As a difference from the previous method, fluoranthenes that are formed this way are expected to have a phenol moiety. As a result, synthesis of the phenol-containing fluoranthenes would become possible in three or four steps through this methodology.



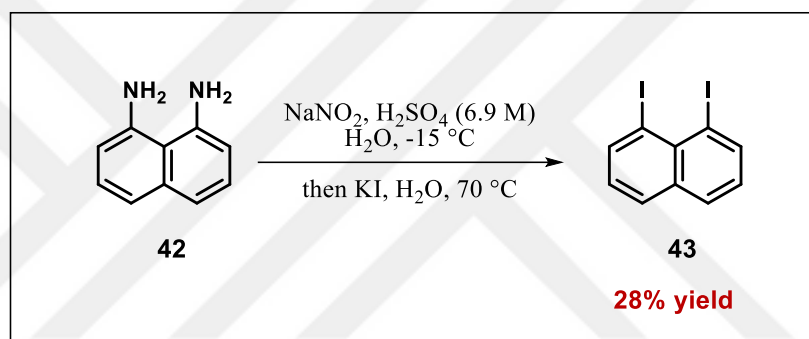
Scheme 9: Consecutive Sonogashira, Suzuki-Miyaura cross-coupling and Diels-Alder reactions for fluoranthene synthesis

2.2. RESULTS and DISCUSSION

2.2.1. Synthesis of 1,8-dihalonaphthalene Derivatives

In the beginning of this study, two 1,8-dihalonaphthalene derivatives were prepared to be used as the starting materials. First, 1,8-diiodonaphthalene (**43**) was

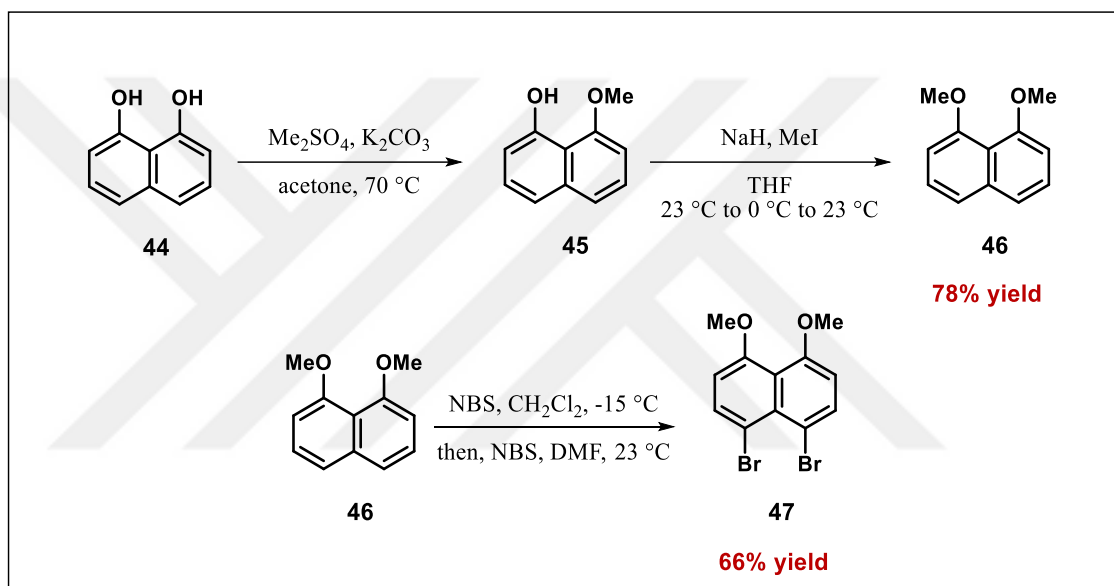
synthesized on gram scale from commercially available and inexpensive 1,8-diaminonaphthalene (**42**) by a Sandmeyer reaction.⁸⁰ With the addition of sodium nitrite and sulphuric acid, 1,8-diaminonaphthalene forms a bis-diazonium salt that was further iodinated with potassium iodide at 70 °C to afford 1,8-diiodonaphthalene (**43**) in 28% yield (**Scheme 10**). Although the procedure is known to be very effective for halogenation of anilines, the low yield was caused primarily by the difficulties in the purification process.



Scheme 10: Synthesis of 1,8-diiodonaphthalene (**43**) via Sandmeyer reaction.

The other naphthalene derivative, which was planned to be used as a substrate in this project, is 1,8-dibromo-4,5-dimethoxynaphthalene (**47**). Essentially, the commercially available 1,8-dihydroxynaphthalene (**44**) was methylated employing a known method that involves the treatment of 1,8-dihydroxynaphthalene with excess potassium carbonate (K_2CO_3) and dimethyl sulfate (Me_2SO_4) at 70°C.⁸¹ The reaction did not go to completion in the expected time, resulting in a mixture of mono- and dimethylation products **45** and **46**, respectively. Thus, the mixture was treated with NaH and MeI at room temperature in order to convert remaining 8-methoxy-1-naphthol (**45**) to 1,8-dimethoxynaphthalene (**46**). This two-step procedure afforded 1,8-dimethoxynaphthalene

(**46**) in 78% yield. The next step was the bromination of **46** at the para-positions of the two -OMe groups following a literature procedure.⁸² This reaction was accomplished by successive bromination reactions using *N*-bromosuccinimide first in CH₂Cl₂ and then in DMF, and 1,8-dibromo-4,5-dimethoxynaphthalene (**47**) was obtained in 66% yield after purification by column chromatography (**Scheme 11**).



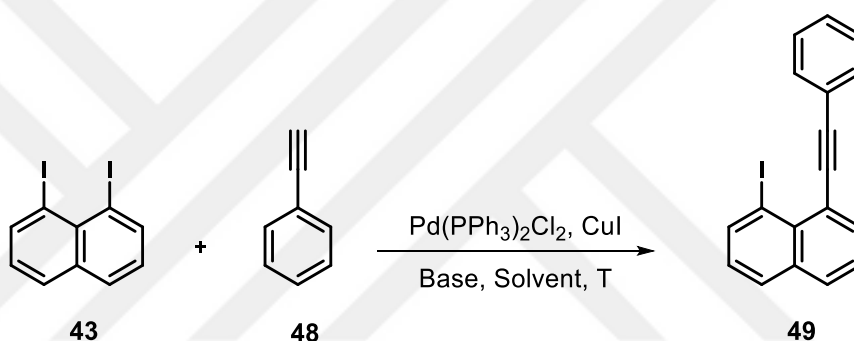
Scheme 11: Synthesis of 1,8-dibromo-4,5-dimethoxynaphthalene (**47**).

2.2.2. Optimization of the Sonogashira Cross-Coupling Reaction

In this part, the objective was to find the optimal conditions for the cross-coupling between an alkyne and the 1,8-dihalonaphthalene derivatives. Firstly, the reaction of 1,8-diiodonaphthalene (**43**) with phenylacetylene was investigated. The conditions that were used for this reaction are summarized in **Table 9**. Apart from the expected mono-alkynylation product (**49**), the formation of the di-alkynylation product (**50**) was also observed regardless of the equivalent of the alkyne used. This was surprising because the expectation was that the coupling of a second alkyne would be sterically disfavoured

caused by the volume of phenyl group in the used alkyne and it would be controlled relatively easily by using only one equivalent of the alkyne. It should also be noted that the oxidative homo-coupling product of the alkynes (**51**) in the presence of oxygen (Glaser coupling) was observed under conditions that involve the use of copper salts (**Figure 10**).

Table 9: Optimization of Sonogashira Coupling between 1,8-diiodonaphthalene (**43**) and phenylacetylene (**48**).



Entry	Alkyne Equiv.	Amount of Pd (Equiv.)	Amount of CuI (Equiv.)	Base	Temperature (°C)	Time (h)	Yield of 49 (%)
1	1.5	0.06	0.1	Et_3N	70	22	Mixture of 50 and 51
2^{a, b}	0.67	0.033	0.067	Et_3N	23	18	23%
3^{a, b}	0.67	0.033	0.067	Et_3N	23	18	52%
4^{a, b}	3.0	0.033	0.067	Et_3N	23	6	Di-alkynylation (50)
5	1.0	0.02	-	piperidine	70	0.5	51%
6	0.67	0.02	-	piperidine	70	0.5	38%

7	1.0	0.02	-	piperidine	70	0.5	33%
8	1.0	0.02	-	piperidine	23	23	24%

^a In these experiments, additional to Pd catalyst, 0.066 equiv. of. PPh₃ was used. ^b THF was used as the solvent.

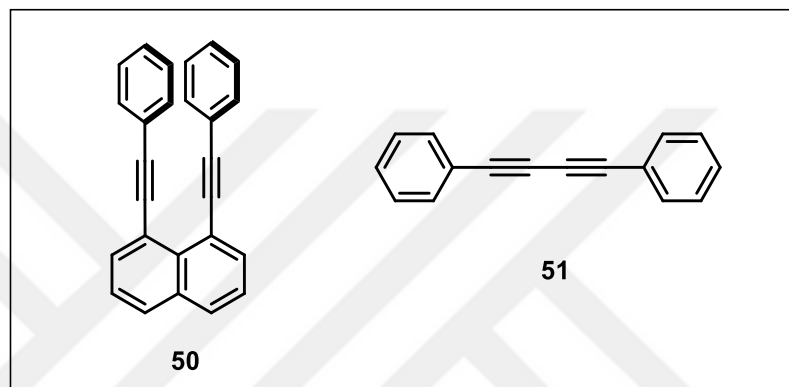


Figure 10: Di-alkynylation and Glaser coupling products

In the interest of decreasing the amount of Glaser coupling product, deoxygenation was carried out with different techniques, and it was observed that deoxygenation of the solvent led to an increase in the yield from 23% to 52% along with a decrease in the formation of homo-coupling of the alkyne effectively. Moreover, having the alkyne as the limiting reagent in the reaction caused an improvement on obtaining the mono-alkynylation product and provided the best result at room temperature affording product **49** in 52% yield.

Copper-free Sonogashira coupling reactions were investigated as well to overcome the oxidative alkyne homo-coupling problem. Pleasingly, it was found that mono-alkynylation product could be obtained in 51% yield in short reaction time by using a lower catalyst loading (2 mol%) and piperidine as the base without additional reagent or

solvent. As a result, conditions of entries 3 and 5 in **Table 9** were determined to give the desired product in a reproducible and easy way and therefore, these conditions were decided to be used for the synthesis of other alkyne-substituted naphthalene derivatives.

Alternative alkyne derivatives that were considered for use in this project are listed in **Figure 11**. The next alkyne to be used after phenyl acetylene was compound **52**, which could be synthesized by the methylation of propargyl alcohol in basic environment. This alkyne was tried to be prepared essentially by treating propargyl alcohol with sodium hydroxide (60% aqueous NaOH solution) or sodium hydride (NaH) and using dimethyl sulphate as the methylation agent. However, the resulting product was extremely volatile because of the weak intermolecular interactions, and could not be isolated purely even though the formation was observed through ^1H -NMR spectroscopy.

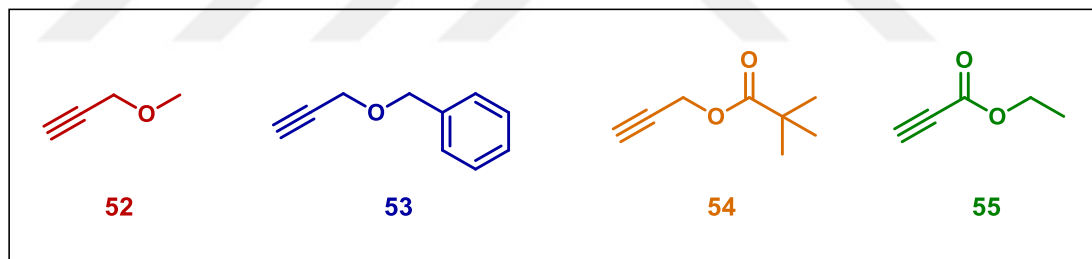
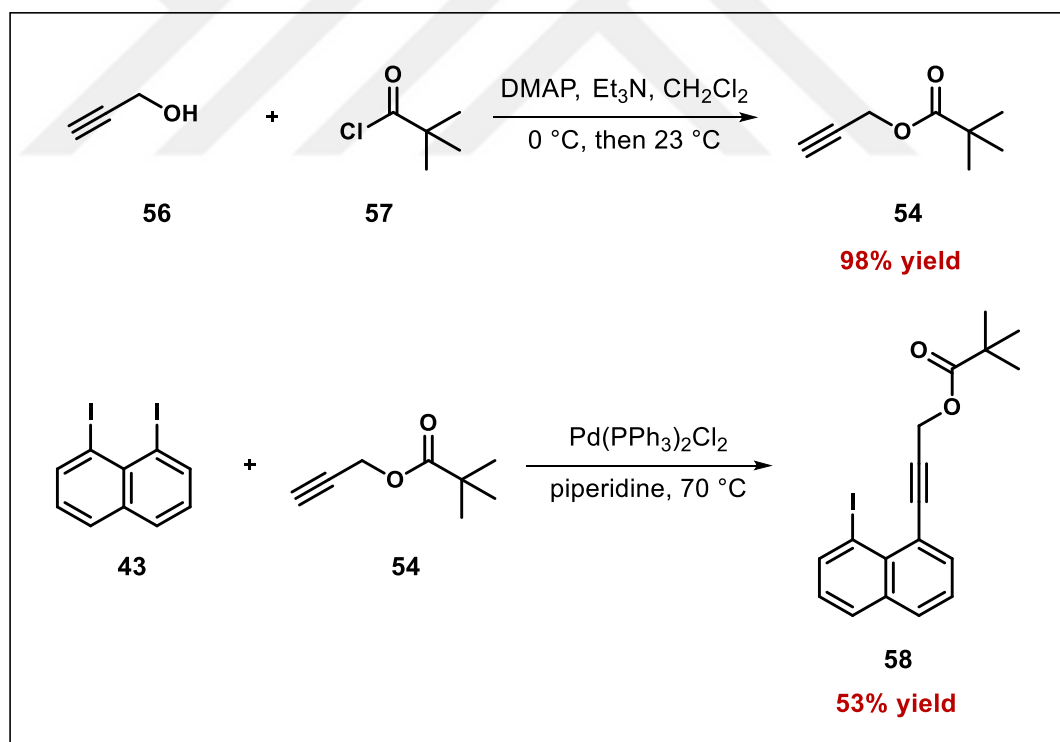


Figure 11: Alkyne derivatives to be used in the Sonogashira cross-coupling.

Thus, with this observation in mind, a terminal alkyne with a protecting group having high molecular weight was synthesized. Compound **53** contains a benzyl group which is useful to decrease the volatility and was synthesised in 73% yield by the reaction of propargyl alcohol with benzyl bromide under basic conditions. The Sonogashira coupling of this alkyne with 1,8-diiodonaphthalene (**43**) resulted in the mono-alkynylation product as analyzed by ^1H -NMR spectroscopy, but unfortunately, the compound could

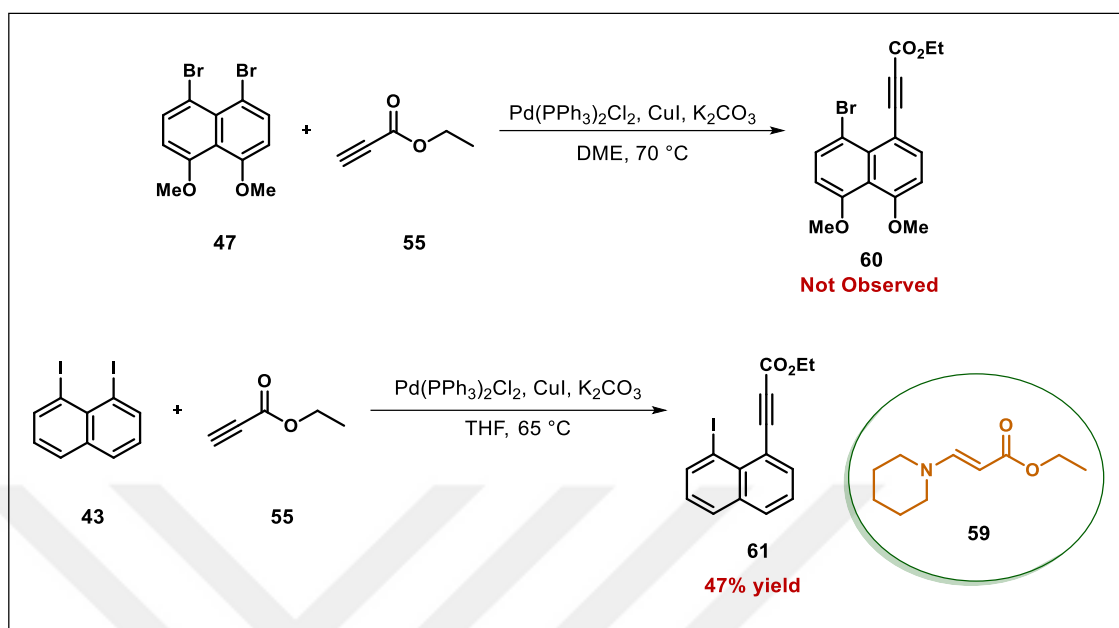
not be isolated in pure form in high yield. Additionally, the use of this benzyl propargyl ether (**53**) was expected to cause problems in the deprotection step in terms of selectivity after the synthesis of fluoranthene derivative. So, alkyne **54** with the pivaloyl protecting group has gained priority at this point.

Compound **54** was obtained in 98% yield when propargyl alcohol (**56**) was reacted with pivaloyl chloride (**57**) in the presence of a stoichiometric amount of triethylamine (Et_3N) and catalytic amount of *N,N*-dimethylaminopyridine (DMAP). The coupling of alkyne **54** with 1,8-diiodonaphthalene (**43**) under the optimized conditions gave mono-alkynylation product **58** in 53% yield (**Scheme 12**).



Scheme 12: The synthesis of terminal alkyne **54** and its use in the Sonogashira coupling

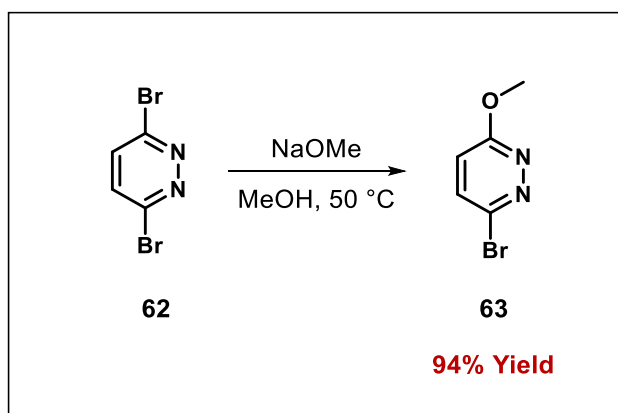
The next alkyne to be used was the commercially available ethyl propiolate (**55**). Unexpectedly, the optimized conditions that were used for the coupling of previous alkynes did not work for the Sonogashira coupling of ethyl propiolate (**55**). This difference in reactivity was attributed to the presence of an α,β -unsaturated carbonyl group in the structure of ethyl propiolate (**55**). In order to investigate further the reactivity of alkyne **55**, various reaction conditions were examined extensively, including its reaction with iodobenzene as the aryl halide model compound. It was seen that ethyl propiolate (**55**) did not react with the aryl halide and gave instead the nucleophilic addition (aza-Michael addition) product **59** when a secondary amine-type organic base (piperidine) was used. The olefin geometry of compound **59** was found to be *trans* by ^1H -NMR spectroscopy. Based on this result, we next decided to use an inorganic base. However, solubility of the inorganic bases in organic solvents was considered as a potential problem along with the possibility of hydrolysis of the ester group if H_2O /organic solvent mixtures were used. The reaction of alkyne with the dibromonaphthalene derivative **47** did not deliver the desired Sonogashira coupling product **60**. On the other hand, after numerous trials, product **61** was obtained in 47% yield when 1,8-diiodonaphthalene (**43**) was stirred with excess ethylpropiolate (4 equiv.) in the presence of potassium carbonate (3 equiv.) and catalytic amounts of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and CuI in THF at 65 °C (**Scheme 13**).



Scheme 13: The synthesis of compound **61** and the structure of the aza-Michael addition product **59**.

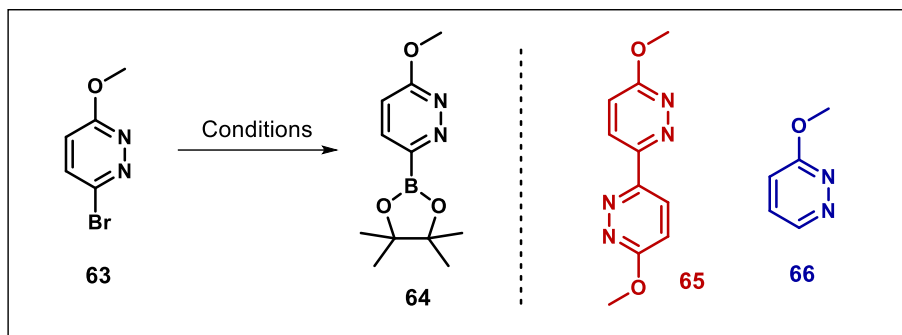
2.2.3. Studies on the Synthesis of Diazineboronic Esters

As the successful optimization of Sonogashira coupling for mono-alkynylation has been achieved, the next stage was the synthesis of diazineboronic esters for the second step of the fluoranthene synthesis sequence. For this purpose, the commercially available 3,6-dibromopyridazine (**62**) was initially used. It was reacted with sodium methoxide (NaOMe) in methanol (MeOH) for a nucleophilic aromatic substitution reaction and compound **63** was obtained in 94% yield (**Scheme 14**). The high yield and selectivity towards mono-substituted bromopyridazine may have resulted from the expectation that the second nucleophilic substitution reaction is much slower because of the addition of electron donating methoxy group to the para position of bromide.



Scheme 14: Synthesis of **63** from 3,6-dibromopyridazine (**62**)

The next focus was the borylation of compound **63** and several attempts were made for this purpose. Unfortunately, compound **64** could not be obtained in any of the conditions listed in **Table 10**. The main problem was the formation of the dimerization product **65**. One justification on why this compound became the major product in most conditions was that the borylation product reacted with the unreacted 3-bromo-6-methoxypyridazine (**63**) in the same medium and this Suzuki-Miyaura coupling reaction was faster than the first borylation reaction. When the -Bpin source was switched from B₂pin₂ to HBpin, protodeboration product **66** was mainly observed.

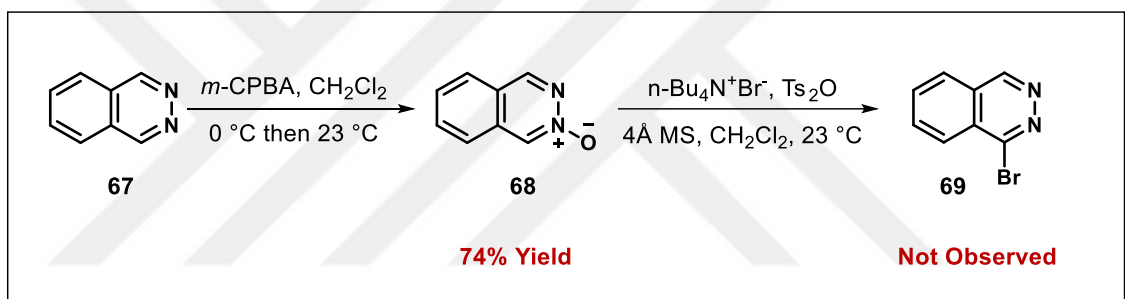
Table 10: Investigation of the borylation reaction of bromopyridazine derivative **63**.

Entry	Catalyst	Base	Solvent	Temperature (°C)	Time (h)	Result
1^a	Pd(dppf)Cl ₂	KOAc	DMSO	80	24	Major Product: 65
2^a	Pd(dppf)Cl ₂	KOAc	1,4-dioxane	80	3.5	63 + B ₂ pin ₂
3^a	Pd(dppf)Cl ₂	KOAc	1,4-dioxane	80	23	63 + 65 + B ₂ pin ₂
4^a	Pd(dppf)Cl ₂	KOAc	toluene	80	21	63 + 65 + B ₂ pin ₂
5^a	Pd(PPh ₃) ₄	KOAc	1,4-dioxane	80	4	63 + 65 + B ₂ pin ₂
6^a	Pd(PPh ₃) ₂ Cl ₂	KOAc	1,4-dioxane	80	21	63 + 65 + B ₂ pin ₂
7^b	Pd(OAc) ₂	Et ₃ N	1,4-dioxane	100	2	Major Product: 66
8^b	Pd(OAc) ₂	Et ₃ N	1,4-dioxane	23	1	Major Product: 66
9^a	XPhos Pd G3	KOAc	THF	23	9.5	63 + B ₂ pin ₂
10^a	XPhos Pd G3	K ₃ PO ₄	THF	23	9.5	63 + B ₂ pin ₂ + Decomposition

^a B₂pin₂ was used as the source of -Bpin. ^b HBpin was used as the source of -Bpin with DPEPhos ligand.

At this point, a different approach was undertaken to achieve the addition of diazine groups to the dihalonaphthalene derivatives, and phthalazine was used as the diazine component. The initial goal was to turn phthalazine into the corresponding

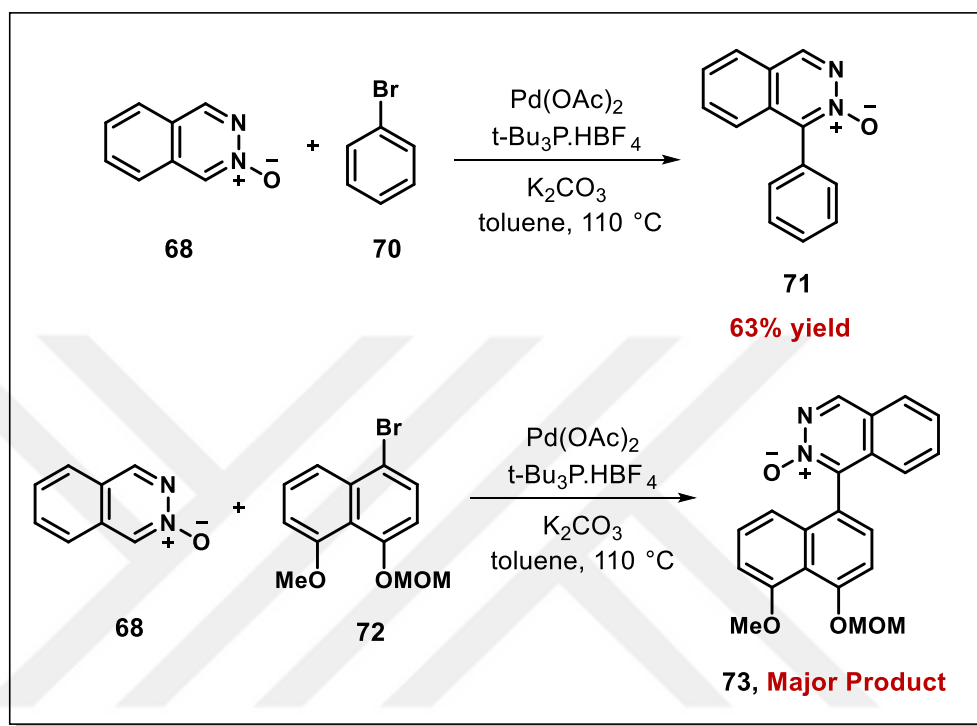
borylated derivative so that it may couple with the mono-alkynylation products through a Suzuki-Miyaura reaction. Therefore, a new method for the bromination of fused heterocyclic *N*-oxides developed by the Baran Group was tested.⁸³ Oxidation of phthalazine (**67**) with stoichiometric *m*-CPBA (1.1 equiv) in CH₂Cl₂ afforded phthalazine *N*-oxide (**68**) in 74% yield. However, the treatment of phthalazine *N*-oxide (**68**) with tetrabutylammonium bromide (n-Bu₄NBr) and *p*-toluenesulfonic anhydride (Ts₂O) in CH₂Cl₂ did not result in the formation of the desired product (**69**) (**Scheme 15**).



Scheme 15: Studies of the syntheses of phthalazine *N*-oxide (**68**) and 1-bromophthalazine (**69**).

Considering the ineffectiveness of this halogenation method, direct coupling of the *N*-oxide to aryl halide by C-H activation was attempted. A method developed by Fagnou Group for the direct arylation of *N*-oxides was adopted since it was reported to be compatible with various functional groups.⁸⁴ The first test reaction with bromobenzene (**70**) and *N*-oxide (**68**) afforded the expected product **71** in 63% yield showing the successful application of the method (**Scheme 16**). We next opted to test the effectiveness of this method with a more intricate substrate. To this end, we selected bromonaphthalene derivative **72** which was prepared by Dilgam Ahmadli for another project in our group. The reaction between phthalazine *N*-oxide (**68**) and bromonaphthalene **72** was observed

to work successfully providing the C-H arylation product **73** as judged by NMR spectroscopic analysis.

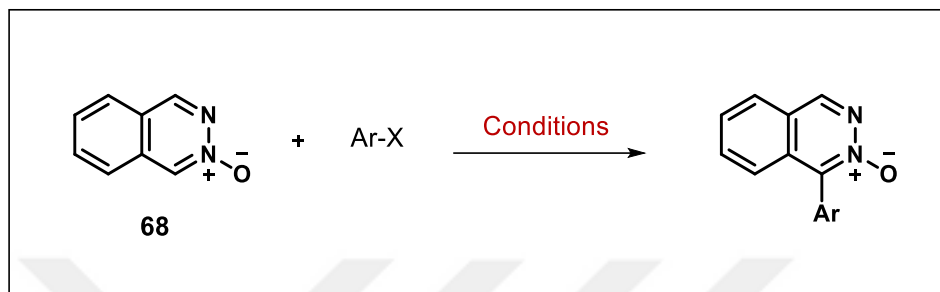


Scheme 16: Test reactions for the direct arylation of phthalazine *N*-Oxide (**68**).

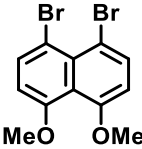
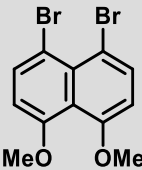
With these promising results in hand, the same conditions were applied with a few modifications to the dihalonaphthalene derivatives (**43** and **47**) and to the mono-alkynylation product **49** that were synthesized earlier. Surprisingly, the reactions of 1,8-dibromo-4,5-dimethoxynaphthalene (**47**) and 1,8-diiodonaphthalene (**43**) with phthalazine *N*-oxide (**68**) did not deliver the desired products **74** and **75**, respectively (**Figure 12**). First, the base used in the reaction was changed to cesium carbonate for iodinated compounds since it is known from the literature that this base works better. However, the investigated changes in the base, ligand or the temperature did not result in the expected improvement. The reason for these results is anticipated to be the steric

hindrance resulted from the additional iodine and bromine atoms at the peri positions in naphthalenes. Details of the investigation are listed in **Table 11**.

Table 11: Investigation of C-H arylation reactions of phthalazine *N*-Oxide (**68**)



Entry	Aryl Halide	N-oxide (equiv.)	Base (2 equiv.)	Solvent	Temp. (°C)	Time (h)	Result
1 ^a		2	Cs ₂ CO ₃	xylenes	135	11	NR
2 ^a		3	Cs ₂ CO ₃	xylenes	135	11	NR
3 ^a		3	K ₂ CO ₃	toluene	110	12	NR
4 ^a		2	K ₂ CO ₃	toluene	110	11	NR
5 ^a		2	K ₂ CO ₃	xylenes	135	6	NR

6 ^a		2	K ₂ CO ₃	mesitylene	160	7	NR
7 ^b		3	K ₂ CO ₃	toluene	110	10	NR

^a *t*-Bu₃P·HBF₄ was used as the ligand. ^b (C₆H₁₁)₃PHBF₄ was used as the ligand.

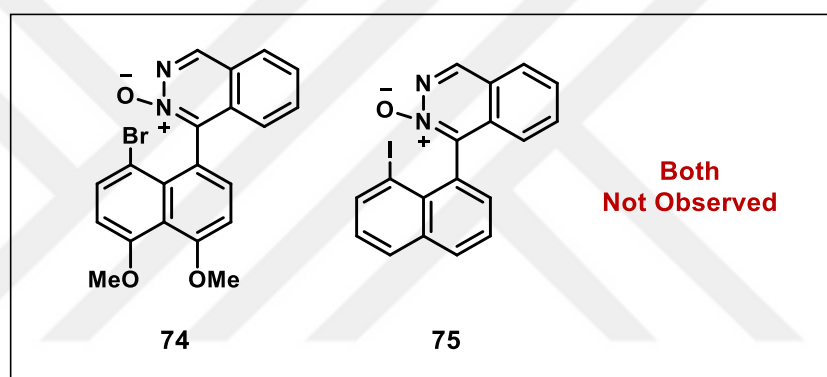
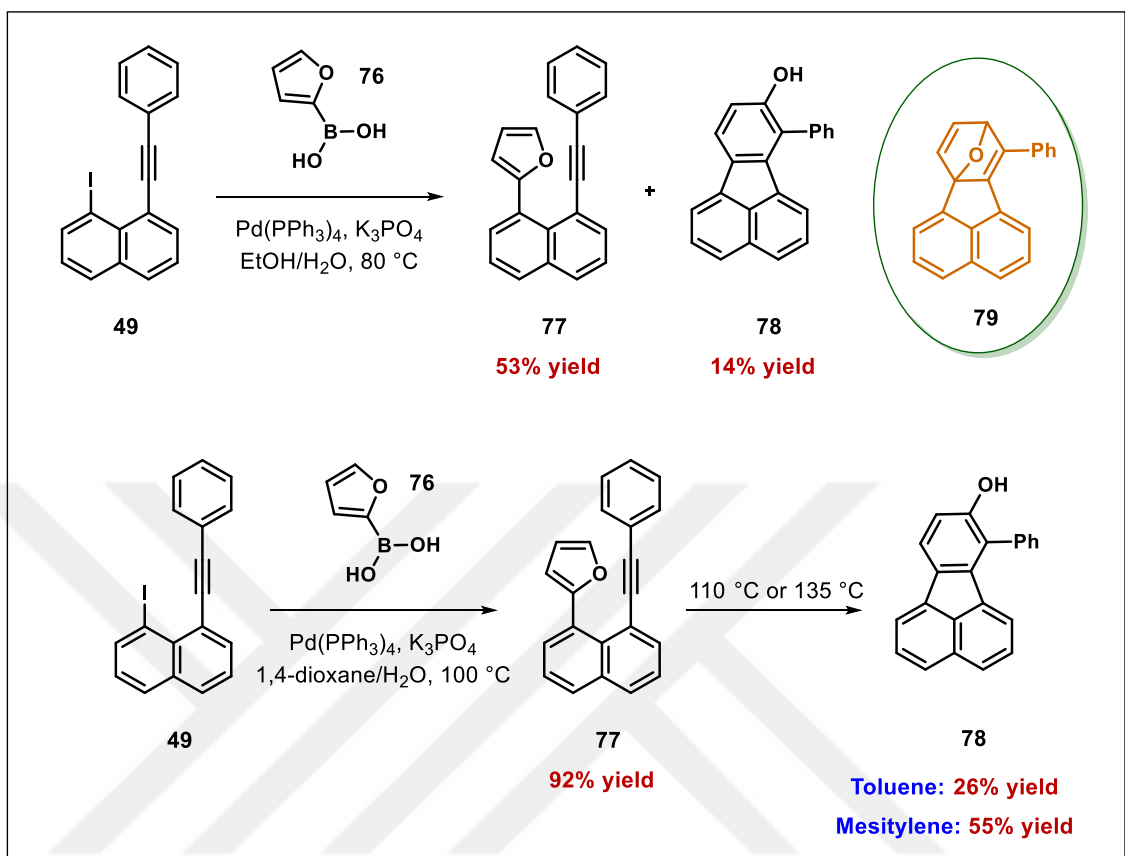


Figure 12: Expected C-H arylation products **74** and **75**.

2.2.4. Investigation of Suzuki-Miyaura Coupling Reactions

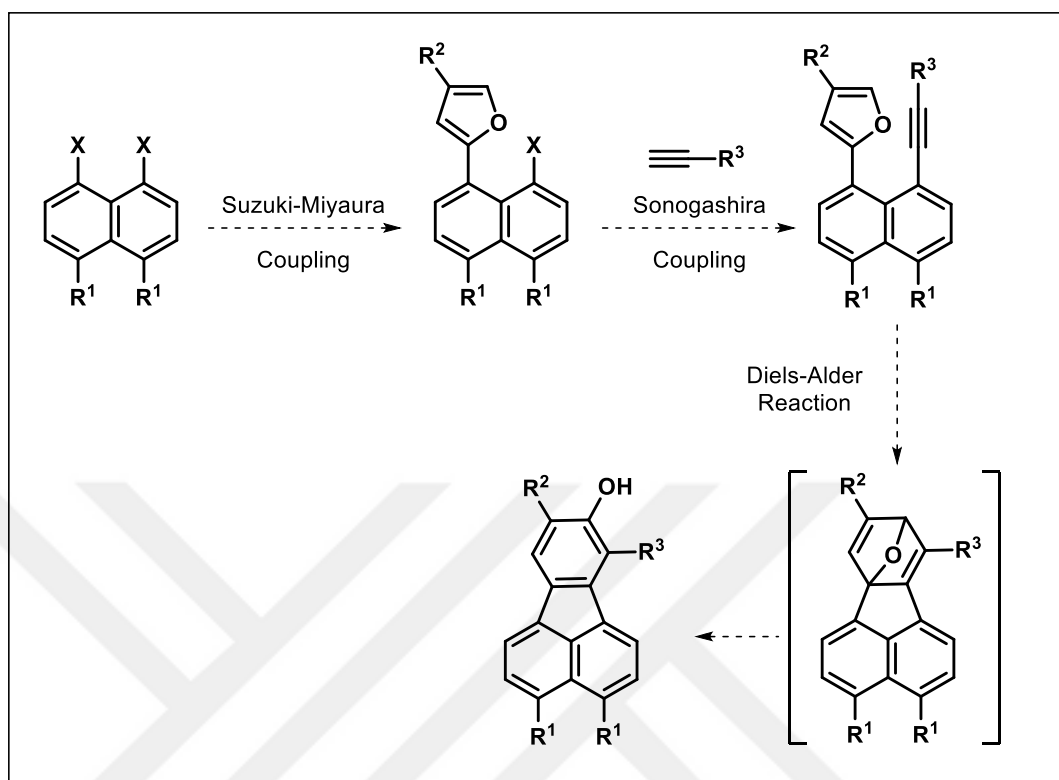
The difficulties in the use of diazines for fluoranthene synthesis led us to move forward to the second stage of the project, which is based on the addition of furanboronic acids or esters to the halonaphthalenes. For this objective, the Suzuki-Miyaura reaction of compound **49** with 2-furanboronic acid (**76**) was investigated in the first place. The two reactants were stirred in the presence of potassium carbonate and Pd(PPh₃)₄ in EtOH/H₂O mixture at 80 °C, and the targeted product **77** was obtained in 53% yield after purification by column chromatography (**Scheme 17**). Pleasingly, the final phenol-containing fluoranthene derivative **78** was also observed to form, and was isolated in 14% yield. This

fluoranthene is formed from the intermediate **79** after the alkyne and furan moieties undergo an intramolecular Diels-Alder reaction and the highly strained bicyclic intermediate opens without a need for additional Lewis acid activation. When the same reaction was carried out in 1,4-dioxane/H₂O solvent system at 100 °C, Suzuki-Miyaura product **77** was obtained in 92% yield in 4 hours. Moreover, the isolated Suzuki product was objected to heating in different solvents to prove that the alkyne and furan part of the molecule undergo the Diels-Alder reaction and the final product is constructed from the intermediate **79**. The expectation was that the use of a polar solvent like DMF would fasten the process and facilitate the opening of the bicyclic intermediate. However, the results showed the opposite where the reaction only proceeds in the non-polar solvents like toluene and mesitylene while only trace amount of fluoranthene forms in DMF. The yields of the corresponding fluoranthene product (**78**) were observed to be 26% and 55% in toluene and mesitylene, respectively. The fluoranthene derivative **78** was characterized by ¹H-NMR and ¹³C-NMR spectroscopy, ATR-IR spectroscopy and HRMS (high resolution mass spectrometry). The formation of the fluoranthene product **78** clearly supports the conceptual and mechanistic design principles of the project.



Scheme 17: Synthesis of fluoranthene (**78**)

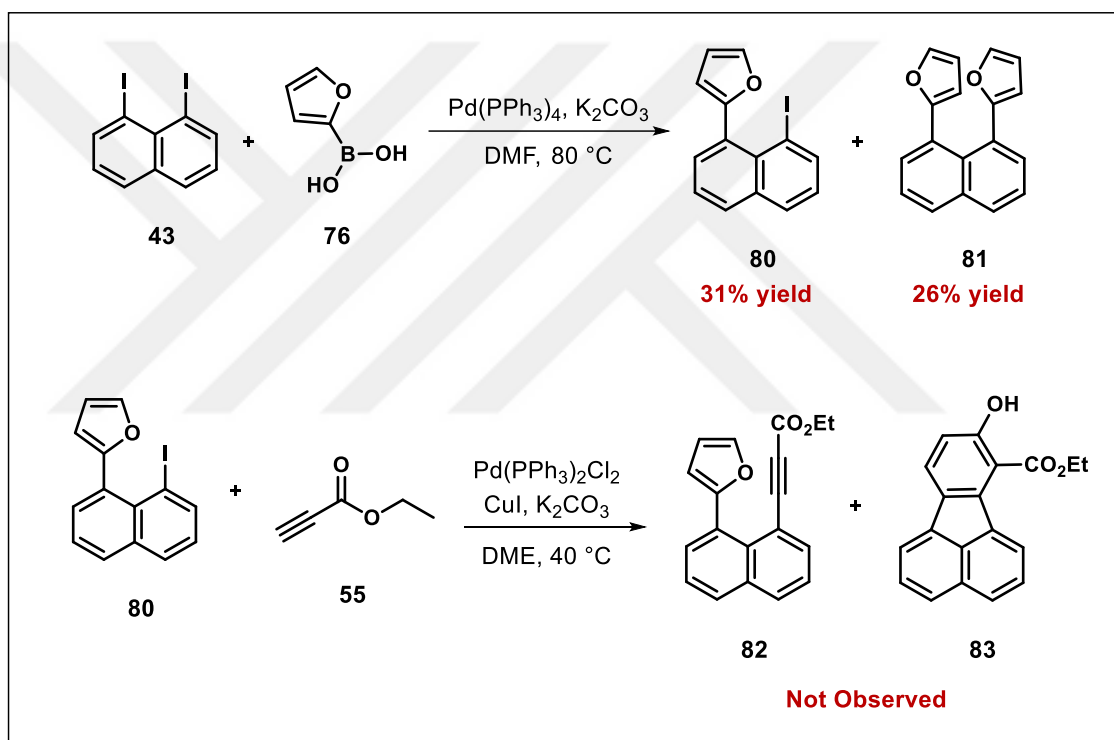
After seeing the accomplishment in the planned sequence, a separate approach was investigated next, which was based on the change in the order of the Sonogashira and Suzuki-Miyaura cross-coupling reactions (**Scheme 18**).



Scheme 18: Alternative synthesis plan for the fluoranthene derivatives

To this end, the first reaction was carried out using the previously optimized conditions with reactants 1,8-diiodonaphthalene (**43**) and 2-furanboronic acid (**76**) in the presence of potassium carbonate and $\text{Pd}(\text{PPh}_3)_4$ in EtOH/ H_2O mixture affording mono-furylnaphthalene product (**80**) in 24% yield along with formation of the undesired difurylnaphthalene derivative **81**. It was expected that the addition of second furan would be less as oppose to the alkyne coupling in Sonogashira reactions but still it appeared to be a serious problem. It should be noted that sequential and selective mono- and diarylation reactions of 1,8-dihalonaphthalenes with substituted phenylboronic acids were previously established in our group. However, 2-furanboronic acid was found to behave differently than phenylboronic acids, possible due its smaller size. When the same reaction

was conducted in DMF at 80 °C with the use of potassium carbonate as base, product **80** was isolated in 31% yield along with the formation of **81** in 26% yield. Then, Sonogashira coupling was tried with ethyl propiolate (**55**) at 40°C, yet no product formation was observed (**Scheme 19**). Hopefully, the addition of this specific alkyne might be achieved by the previously optimized conditions in future work.



Scheme 19: Synthesis of **80** and investigation of its Sonogashira coupling.

2.3. CONCLUSION

In summary, we have worked on the development of two new methodologies for the synthesis of fluoranthene derivatives in a practical manner using sequential Pd-catalyzed coupling reactions such as Sonogashira and Suzuki-Miyaura couplings as well as intramolecular Diels-Alder reactions. These methods provide an access to multi-substituted fluoranthene derivatives since they are designed as three-component synthetic pathways. Each component can either be found commercially or be prepared from simple building blocks in a few steps resulting in the versatile formation of a complex hydrocarbon skeleton.

The starting materials were 1,8-dihalonaphthalene derivatives and they can be used in Suzuki-Miyaura and Sonogashira cross-coupling reactions of both sequences. First, the synthesis of these halonaphthalene derivatives was conducted and the products were obtained in moderate to good yields. Then, the synthesis mono-alkynylation compounds was achieved using various alkynes that have different electronic, steric properties by Sonogashira coupling. The careful and detailed optimization reactions with parameters like temperature, equivalent, time, solvent etc. was conducted to achieve the best yield. Next step was the addition of a diazine for an inverse electron-demand Diels-Alder reaction *via* Suzuki-Miyaura cross-coupling. Although numerous ways have been tried, the addition product could not be obtained in high yield.

Moreover, furanboronic acid was used for a normal-demand Diels-Alder reactions and the addition of furan to mono-alkyne halonaphthalenes was successful. It was seen that once the Suzuki-product forms, it can spontaneously undergo a cycloaddition reaction forming a sterically hindered bicyclic intermediate. This intermediate then can open up to

form the final fluoranthene derivative containing a hydroxy group without the need for an external reagent than heat. The formation of fluoranthene derivative clearly supports the conceptual and mechanistic design principles of the project.



CHAPTER 3: EXPERIMENTAL SECTION

3.1. INSTRUMENTAL DETAILS

All the experiments in this work were conducted using oven-dried glassware. Chemicals for the experiments were purchased from Acros, Merck, TCI, MilliporeSigma, Alfa Aesar and Carlo Erba, and they were used without further purification unless stated otherwise. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed plates pre-coated with SiO₂ (Silicycle, F254). Visualization of TLC plates was carried out either with the help of UV light (254 and 365 nm) or with the use of KMnO₄ or PMA staining solutions. Flash column chromatography was performed using Silicycle 40-63 μ m (230-400 mesh) flash silica gel. All organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure.

¹H-NMR and ¹³C-NMR spectra were recorded on Bruker DPX 400 spectrometer in CDCl₃. For calibration of ¹H-NMR spectra, either the signal of internal standard, which is tetramethyl silane (TMS), as 0 ppm or the signal of CDCl₃ as 7.26 ppm was used. The signal resulting from CDCl₃ was calibrated as 77.16 ppm for ¹³C-NMR spectra. ¹H-NMR data are reported as follows: chemical shift (parts per million, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet), coupling constant (Hz).

Infrared (FTIR) spectra were recorded on a Bruker Alpha-Platinum-ATR spectrometer equipped with a diamond ATR crystal module, and a deuterated triglycine sulfate (DTGS) mid-IR detector. They were reported with only selected peaks from the spectra.

High resolution mass spectral analyses (HRMS) were performed on Agilent Technologies 6224 TOF LC/MS at UNAM-National Nanotechnology Research Center and Institute of Materials Science and Nanotechnology, Bilkent University and QTOF/LCMS analysis were performed at DAYTAM-East Anatolia High Technology Application and Research Center, Atatürk University.

3.2. EXPERIMENTAL DETAILS: CHAPTER 1

3.2.1. Synthesis of LMO and $\text{Ni}_x\text{Mn}_{1-x}(\text{OH})_2$ Catalysts

$\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$, $\text{Mn}(\text{NO}_3)_3$ and citric acid were purchased from MilliporeSigma and used as received. LaMnO_3 perovskites was prepared according to reported procedure that employs the citrate method.⁸⁵ A solution was prepared by dissolving $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (5.372 g, 0.0124 mole), $\text{Mn}(\text{NO}_3)_3$ (3.114 g, 0.0129 mole) and citric acid (5.735 g, 0.0298 mole) in 250 mL of de-ionized water and it was stirred at room temperature for 1 h. Then, the mixture was heated at 80 °C until the formation of a viscous gel was observed with the release of a brown gas (i.e., NO_2). The obtained gel was dried in an oven at 110 °C for 24 h. Finally, the dry sample was taken as powder and calcined in air at 700 °C for 5 h. LMO acronym corresponds to this specific LaMnO_3 catalyst. Reduced LMO catalysts were prepared by reducing LMO catalysts under 100 sccm 4% H_2 in Ar for 3 h at 400 °C, 500 °C, 600 °C, 700 °C and 800 °C in a flow furnace.

$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{MnCl}_2 \cdot 2\text{H}_2\text{O}$ and NaOH were purchased from MilliporeSigma and used as received. For $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ catalyst, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (2.937 g, 0.012 mole) and $\text{MnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.333 g, 0.008 mole) were dissolved in 20 ml deionized water and stirred (600 rpm) at 23 °C for 30 minutes. NaOH (9.885 g, 0.247 mole) was dissolved in 20 mL

of deionized water, separately and stirred (400 rpm) at 23 °C for 30 minutes. Nickel-manganese solution was poured into sodium hydroxide solution at 23 °C at 1500 rpm, then the mixture was stirred for 1 hour with 600 rpm. The resulting powders were centrifuged with deionized water 6 times (6000 rpm, 3 min). Finally, the obtained colloidal solutions were dried at 60 °C for 24 h. Similar procedure was used for the solvothermal method where the solutions after 1 hour stirring were transferred into a Teflon line, inserted into an autoclave and dried in oven at a targeted temperature, i.e., 130 °C for 12 h and 70 °C for 36 h.

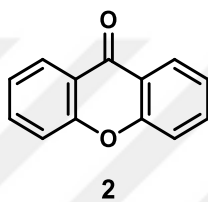
3.2.2. Synthesis and Characterization of Compounds

General Procedure for the Catalytic Aerobic Oxidation Reactions:

Xanthene, Fluorene and Diphenylmethane were purchased from MilliporeSigma. Diphenylmethanol, Isochroman, DL-*sec*-phenethyl alcohol were purchased from Acros while L-menthol was purchased from Alfa Aesar. All chemicals were used as received.

The catalytic oxidation of different substrates was performed in oven-dried 25-mL Schlenk tubes containing a magnetic stir bar. Reactant, catalyst (LMO or $\text{Ni}_x\text{Mn}_{(1-x)}(\text{OH})_2$), solvent, O_2 (1 bar) were charged into the flask. The sealed reaction mixture was stirred at the specified temperature for 24 h. After the reaction is stopped, the mixture was filtered through a Celite pad with a proper eluent, and concentrated under reduced pressure. The analytically pure products were isolated using flash silica gel column chromatography with appropriate separation systems. The products were identified by comparison of the ^1H -NMR and ^{13}C -NMR signals with the corresponding literature data.

For regeneration experiments, the catalysts were diluted with ethyl acetate (for LaMnO₃) or acetone (for Ni_xMn_{1-x}(OH)₂) separated by centrifugation (6000 rpm, 3 min). They were taken into evaporating dishes with methanol or acetone. After the evaporation of methanol or acetone at ambient conditions, the wet LMO catalysts were dried in oven (130 °C) for 2 h while Ni_xMn_{1-x}(OH)₂ catalysts were dried at room temperature before reuse.



9H-xanthene-9-one (**2**). A 25-mL Schlenk flask was charged with LMO-600 (100.0 mg), xanthene (**1**) (90.4 mg, 0.50 mmol) and 2.0 mL of heptane. The flask was filled with O₂ gas (1 bar) and sealed. The reaction mixture was stirred at 80 °C in an oil bath for 24 h. It was then cooled down to room temperature, diluted with EtOAc, and passed through a pad of Celite. Purification by flash column chromatography (SiO₂, EtOAc:hexanes = 1:3) gave pure xanthone (**2**) (95.1 mg, 97% yield) as a white solid. The spectral data were observed to be in agreement with the values reported in the literature.⁸⁶

R_f = 0.43 (EtOAc:hexanes 1:19)

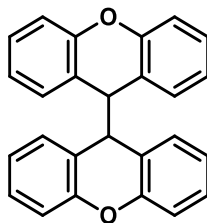
TLC Visualization: UV active.

¹H NMR (400 MHz, CDCl₃) δ: 8.35 (2H, dd, *J* = 7.8, 1.5 Hz), 7.73 (2H, ddd, *J* = 8.8, 7.1, 1.7 Hz), 7.50 (2H, dd, *J* = 8.5, 0.7 Hz), 7.38 (2H, ddd, *J* = 8.1, 7.1, 1.0 Hz).

¹³C NMR (100 MHz, CDCl₃) δ: 177.4, 156.3, 135.0, 126.9, 124.1, 122.0, 118.1.

IR ν_{max} (ATR, film)/cm⁻¹: 3080, 1655, 1606, 1479, 1457, 1331, 757.

HRMS (APCI+) Calcd for (C₁₃H₉O₂)⁺ (M+H)⁺: 197.0598, found: 197.0607



23

9,9'-Bixanthene (**23**). The compound was obtained as white solid when the oxidation reaction of xanthene (**1**) was tested under an atmosphere of N₂(g) instead of O₂(g). The spectral data were observed to be in agreement with the values reported in the literature.⁸⁶

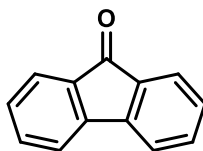
R_f = 0.57 (EtOAc:hexanes 1:19)

TLC Visualization: UV active.

¹H NMR (400 MHz, CDCl₃) δ : 7.20 (4H, dt, *J* = 8.2, 1.6 Hz), 6.93 (4H, dt, *J* = 7.5, 1.1 Hz), 6.87 (2H, dd, *J* = 8.1, 0.9 Hz), 6.66 (4H, dd, *J* = 7.6, 1.5 Hz), 4.20 (2H, s).

¹³C NMR (100 MHz, CDCl₃) δ : 153.2, 129.3, 128.3, 122.8, 122.0, 116.0, 49.7

IR ν_{max} (ATR, film)/cm⁻¹: 2923, 1601, 1574, 1481. 1458, 1257, 755.



4

9H-fluoren-9-one (**4**). A 25-mL Schlenk flask was charged with LMO-873K (150 mg), fluorene (**3**) (83.1 mg, 0.50 mmol) and 2.0 mL of heptane. The flask was filled with O₂ gas (1 bar) and sealed. The reaction mixture was stirred at 80 °C in an oil bath for 24 h. It was then cooled to room temperature, diluted with EtOAc, and passed through a pad of

Celite. Purification by flash column chromatography (SiO₂, gradual increase of polarity from hexanes to 30% EtOAc in hexanes) gave pure fluorenone (**4**) (86.9 mg, 96% yield) as a yellow solid.

R_f = 0.62 (EtOAc:hexanes 1:5)

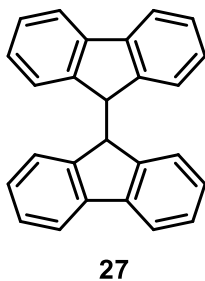
TLC Visualization: UV active.

¹H NMR (400 MHz, CDCl₃) δ : 7.66 (2H, d, J = 7.6 Hz), 7.53 (2H, d, J = 7.3 Hz), 7.49 (2H, dt, J = 7.4, 1.2 Hz), 7.30 (2H, dt, J = 7.3, 1.2 Hz).

¹³C NMR (100 MHz, CDCl₃) δ : 193.9, 144.4, 134.7, 134.1, 129.1, 124.2, 120.3.

IR ν_{max} (ATR, film)/cm⁻¹: 3042, 1715, 1610, 1598, 1450, 1298, 1190, 1147, 1097, 1013, 915, 733.

HRMS (APCI+) Calcd for (C₁₃H₉O)⁺ (M+H)⁺: 181.0648, found: 181.0657.



9,9'-Bifluorene (**27**). This compound was obtained as orange-yellow solid when N₂(g) was used instead of O₂(g) in the synthesis procedure for fluorenone (**4**) using Ni_{0.6}Mn_{0.4}(OH)₂ (20 mg), fluorene (83.1 mg, 0.50 mmol) and 2 mL heptane at 80 °C. The spectral data were observed to be in agreement with the values reported in the literature.⁸⁶

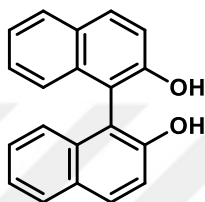
R_f = 0.61 (EtOAc:hexanes 1:19)

TLC Visualization: UV active.

¹H NMR (400 MHz, CDCl₃) δ: δ 7.65 (4H, d, *J* = 7.5 Hz), 7.29 – 7.26 (4H, m), 7.09 (4H, t, *J* = 7.5 Hz), 6.96 (4H, d, *J* = 7.1 Hz), 4.85 (1H, s).

¹³C NMR (100 MHz, CDCl₃) δ: 144.8, 141.7, 127.4, 126.9, 124.2, 119.8, 50.0.

IR ν_{max} (ATR, film)/cm⁻¹: 2923, 2850, 1446, 779, 754. 666, 619.



8

1,1'-binaphthyl-2,2'-diol (BINOL) (**8**). A 25-mL Schlenk flask was charged with LMO-873K (50 mg), 2-naphthol (**7**) (36.0 mg, 0.25 mmol) and 1.0 mL of heptane. The flask was filled with O₂ gas (1 bar) and sealed. The reaction mixture was stirred at 60 °C in an oil bath for 24 h. It was then cooled to room temperature, diluted with EtOAc, and passed through a pad of Celite. Purification by flash column chromatography (SiO₂, first chromatography with EtOAc:hexanes = 1:9; second chromatography with EtOAc:hexanes = 1:4) gave pure BINOL (**8**) (23.6 mg, 66% yield) as a red solid.

R_f = 0.58 (EtOAc:hexanes 1:3)

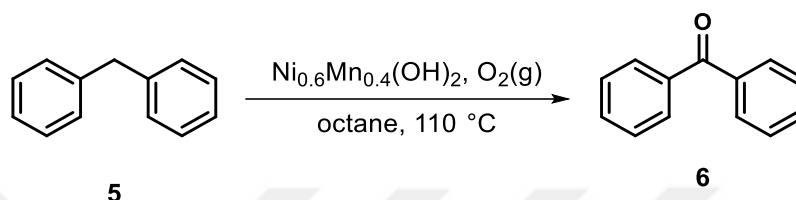
TLC Visualization: UV active, KMnO₄ stains.

¹H NMR (400 MHz, CDCl₃) δ: 7.97 (2H, d, *J* = 8.9 Hz), 7.89 (2H, d, *J* = 8.0 Hz), 7.39-7.37 (4H, m), 7.30 (2H, t, *J* = 7.6 Hz), 7.15 (2H, d, *J* = 8.4 Hz), 5.05 (2H, s).

¹³C NMR (100 MHz, CDCl₃) δ: 152.9, 133.6, 131.6, 129.6, 128.6, 127.6, 124.4, 124.2, 117.9, 111.0.

IR ν_{max} (ATR, film)/ cm^{-1} : 3485, 3409, 3058, 2924, 2854, 1618, 1513, 1382, 1271, 1212, 1178, 1143, 977, 816, 749.

HRMS (-APCI) Calcd for $(\text{C}_{20}\text{H}_{13}\text{O}_2)^-$ (M-H) $^-$: 285.0921, found: 285.0929.



Benzophenone (6). A 25-mL Schlenk flask was charged with $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ (20 mg), diphenylmethane (5) (84.1 mg, 0.50 mmol) and 2.0 mL of octane. The flask was filled with O_2 gas (1 bar) and sealed. The reaction mixture was stirred at 110 °C in an oil bath for 24 h. It was then cooled to room temperature, diluted with EtOAc, and passed through a pad of Celite. Purification by flash column chromatography (SiO_2 , EtOAc:hexanes = 1:19) gave pure benzophenone (6) (85.4 mg, 94% yield) as a colourless oil.

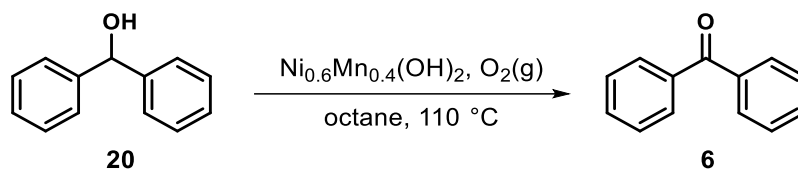
R_f = 0.49 (EtOAc:hexanes 1:19)

TLC: UV active.

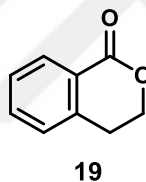
^1H NMR (400 MHz, CDCl_3) δ : 7.81 (4H, m), 7.58 (2H, t, J = 7.4 Hz), 7.48 (4H, t, J = 7.6 Hz).

^{13}C NMR (100 MHz, CDCl_3) δ : 196.8, 137.7, 132.5, 130.1, 128.4.

IR ν_{max} (ATR, film)/ cm^{-1} : 3058, 1655, 1620, 1446, 1273, 941, 763, 693.



Benzophenone (**6**). A 25-mL Schlenk flask was charged with $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ (10 mg), diphenylmethanol (**20**) (92.1 mg, 0.50 mmol) and 2.0 mL of heptane. The flask was filled with O_2 gas (1 bar) and sealed. The reaction mixture was stirred at 80 °C in an oil bath for 24 h. It was then cooled to room temperature, diluted with EtOAc, and passed through a pad of Celite. Purification by flash column chromatography (SiO_2 , EtOAc:hexanes = 1:5) gave pure benzophenone (**6**) (90.4 mg, 99% yield) as a colourless oil.



Isochromanone (**19**). A 25-mL Schlenk flask was charged with $\text{Ni}_{0.6}\text{Mn}_{0.4}(\text{OH})_2$ (20 mg), isochroman (**18**) (67.1 mg, 0.50 mmol) and 2.0 mL of octane. The flask was filled with O_2 gas (1 bar) and sealed. The reaction mixture was stirred at 110 °C in an oil bath for 24 h. It was then cooled to room temperature, diluted with EtOAc, and passed through a pad of Celite. Purification by flash column chromatography (SiO_2 , EtOAc:hexanes = 1:2) gave pure isochromanone (**19**) (71.4 mg, 96% yield) as a yellowish oil.

R_f = 0.37 (EtOAc:hexanes 1:2)

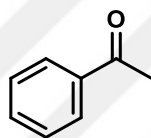
TLC Visualization: UV active.

¹H NMR (400 MHz, CDCl₃) δ: 8.05 (1H, dd, *J* = 7.8, 1.0 Hz), 7.51 (1H, td, *J* = 7.5, 1.4 Hz), 7.36 (1H, m), 7.24 (1H, d, *J* = 7.6 Hz), 4.50 (2H, t, *J* = 6.0 Hz), 3.03 (2H, t, *J* = 6.0 Hz).

¹³C NMR (100 MHz, CDCl₃) δ: 165.2, 139.6, 133.7, 130.4, 127.7, 127.3, 125.3, 67.4, 27.8.

IR ν_{max} (ATR, film)/cm⁻¹: 2953, 2901, 1715, 1292, 1241, 1119, 1028, 744.

HRMS (ESI⁺) Calcd for (C₉H₉O₂)⁺ (M+H)⁺: 1149.0598, found: 149.0597.



22

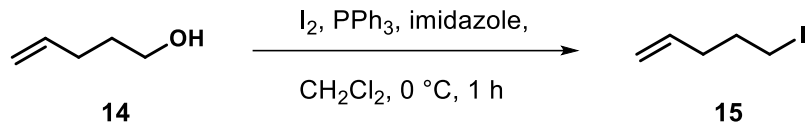
Acetophenone (**22**). A 25-mL Schlenk flask was charged with Ni_{0.6}Mn_{0.4}(OH)₂ (30 mg), DL-sec-phenethyl alcohol (**21**) (61.1 mg, 0.50 mmol) and 2.0 mL of heptane. The flask was filled with O₂ gas (1 bar) and sealed. The reaction mixture was stirred at 80 °C in an oil bath for 24 h. It was then cooled to room temperature, diluted with CH₂Cl₂, and passed through a pad of Celite. Purification by flash column chromatography (SiO₂, EtOAc:hexanes = 1:5) gave pure acetophenone (**22**) (55.6 mg, 93% yield) as a yellowish oil.

R_f = 0.58 (EtOAc:hexanes 1:7)

¹H NMR (400 MHz, CDCl₃) δ: 7.96-7.93 (2H, m), 7.57-7.53 (1H, m), 7.46-7.43 (2H, m), 2.59 (3H, s).

¹³C NMR (100 MHz, CDCl₃) δ: 198.2, 137.2, 133.2, 128.6, 128.4, 26.6.

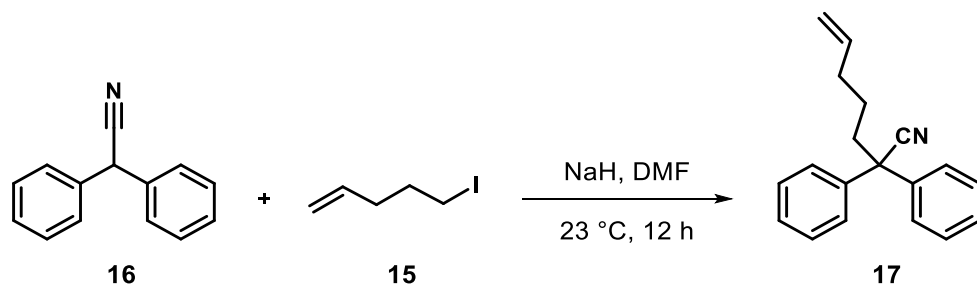
IR ν_{max} (ATR, film)/cm⁻¹: 3062, 1680, 1599, 1582, 1358, 1263, 955, 757, 688, 587.



To a solution of 4-penten-1-ol (**14**) (500 mg, 5.81 mmol), triphenylphosphine (1.83 g, 6.97 mmol) and imidazole (592.8 mg, 8.71 mmol) in 12 mL DCM at 0 °C was added I₂ (1.77 g, 6.97 mmol) slowly under an atmosphere of nitrogen. The resulting mixture was stirred at 23 °C for 1 h. Afterwards, the reaction mixture was quenched with 10 mL of saturated aqueous NH₄Cl solution, and the aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, only hexanes) gave compound **15** as a thick colourless oil (318.0 mg, 28% yield). Even though the TLC analysis showed full conversion of the starting material, product was lost due to volatility.

¹H NMR (400 MHz, CDCl₃) δ : 5.74 (1H, ddt, J = 17.1, 10.3, 6.8 Hz), 5.10 – 4.99 (2H, m), 3.18 (2H, t, J = 6.9 Hz), 2.16 (2H, app q, J = 6.8 Hz), 1.90 (2H, quint, J = 7.0 Hz).

¹³C NMR (100 MHz, CDCl₃) δ : 136.6, 116.0, 34.4, 32.5, 6.3.



To a suspension of NaH (20.0 mg, 0.83 mmol, 60% dispersion in mineral oil) in 2.2 mL DMF was added slowly diphenylacetonitrile (**16**) (124 mg, 0.64 mmol) at 0 °C. After 30 minutes of stirring at 23 °C, the mixture was cooled down to 0 °C, and 5-

iodopent-1-ene (**15**) (176 mg, 0.89 mmol) was added. The resulting mixture was warmed to 23 °C and stirred at this temperature for 12 h. The reaction mixture was quenched with water, and the aqueous phase was extracted with CH₂Cl₂ (3'5 mL). The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, EtOAc:hexanes = 1:2) gave compound **17** as yellow oil (164 mg, 98% yield). The spectral data were observed to be in agreement with the values reported in the literature.⁸⁷

R_f = 0.56 (EtOAc:hexanes 1:5)

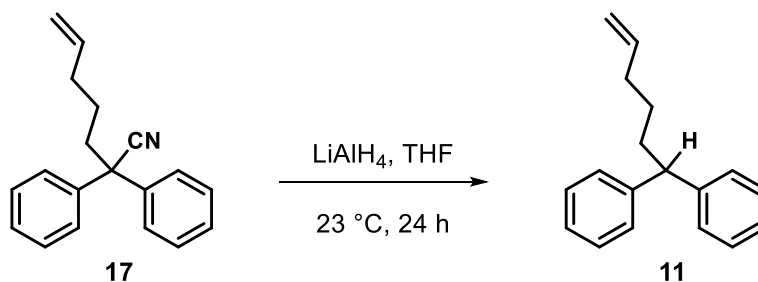
TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz, CDCl₃) δ : 7.40-7.33 (8H, m), 7.31-7.27 (2H, m), 5.75 (1H, ddt, J = 16.9, 10.2, 6.7 Hz), 5.04-4.96 (2H, m), 2.39-2.35 (2H, m), 2.12 (2H, q, J = 7.1 Hz), 1.58 – 1.50 (2H, m).

¹³C NMR (101 MHz, CDCl₃) δ : 140.4, 137.8, 129.0, 128.0, 127.0, 122.6, 115.6, 51.9, 39.2, 33.5, 24.9.

IR ν_{max} (ATR, film)/cm⁻¹: 3062, 2931, 1640, 1598, 1493, 1448, 751, 697.

HRMS (+APCI) Calcd for (C₁₉H₂₀N)⁺ (M-H)⁺: 262.1590, found: 262.1593.



An oven dried 25-mL Schlenk flask was charged with LiAlH₄ (83.2 mg, 2.19 mmol) and 0.6 mL anhydrous THF. The resulting mixture was cooled down to 0 °C.

Compound **17** (164 mg, 0.63 mmol) was dissolved in 1.0 mL dry THF, and this solution was added to the hydride suspension slowly under an atmosphere of nitrogen. The mixture was warmed to 23 °C and stirred at this temperature for 23 h. The reaction mixture was then quenched with 2 mL of water, 1 mL of 15% (w/v) aqueous NaOH solution. The aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, EtOAc:hexanes = 1:19) gave compound **11** as a yellow oil (64.9 mg, 44% yield). The spectral data were observed to be in agreement with the values reported in the literature.⁸⁷

R_f = 0.69 (only hexanes)

TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz, CDCl₃) δ : 7.29-7.22 (8H, m), 7.18-7.15 (2H, m), 5.76 (1H, ddt, J = 16.9, 10.1, 6.7 Hz), 5.00-4.91 (2H, m), 3.89 (1H, t, J = 7.8 Hz), 2.10- 2.02 (4H, m), 1.40-1.32 (2H, m).

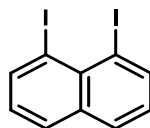
¹³C NMR (101 MHz, CDCl₃) δ : 145.3, 138.8, 128.5, 128.0, 126.2, 114.7, 51.4, 35.3, 33.9, 27.5.

IR $\nu_{\max}$ (ATR, film)/cm⁻¹: 3026, 2929, 1640, 1599, 1493, 1450, 909, 745, 696.

HRMS (+APCI) Calcd for (C₁₈H₂₁)⁺ (M-H)⁺: 237.1638, found: 237.1612.

3.3. EXPERIMENTAL DETAILS: CHAPTER 2

3.3.1. Synthesis and Characterization of Compounds



43

1,8-Diiodonaphthalene (**43**). A 250 mL 3-neck round-bottomed flask was charged with 1,8-diaminonaphthalene (**42**) (1.00 g, 6.32 mmol) and placed in an ice/NaCl bath. Then it was dissolved in 11.6 mL 6.9 M H₂SO₄(aq). To this solution, NaNO₂ (1.308 g, 18.96 mmol, dissolved in 5 mL H₂O) was added resulting in the formation of a brown/orange gas. Afterwards, KI (6.029 g, 37.92 mmol, dissolved in 5 mL H₂O) was added slowly at -15°C. The resulting solution was first warmed to room temperature, then heated at 70 °C for 1 h. After cooling down to rt, 100 mL of EtOAc was added, and the mixture was stirred at rt for 28 h. Solids in the mixture were filtered off, and the remaining solution was washed sequentially with 1 M NaOH solution, saturated aqueous Na₂S₂O₃ solution and brine. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure giving a black/brown crude product. Purification by flash column chromatography (SiO₂, only hexanes) afforded 1,8-diiodonaphthalene (**43**) as a yellow solid (674 mg, 28% yield).

R_f = 0.41 (Only hexanes)

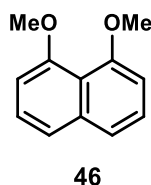
TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz; CDCl₃) δ : 8.39 (2H, d, J = 7.3 Hz), 7.79 (2H, d, J = 7.9 Hz), 7.03 (2H, t, J = 7.7 Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 144.1, 135.8, 132.1, 131.1, 127.0, 96.2.

IR ν_{max} (ATR, solid)/ cm^{-1} : 3051, 2923, 2853, 1532, 1488, 1417.

HRMS (APCI+) calculated: $\text{C}_{10}\text{H}_6\text{I}_2$ $[\text{M}]^+$: 379.8554, found: 379.8562.



An oven dried 250 mL round-bottomed flask was charged with a magnetic stir bar and evacuated/filled with nitrogen 3 times. 1,8-dihydroxynaphthalene (**44**) (2.0 g, 12.5 mmol) was added as a dark-grey solid. It was dissolved in 100 mL acetone, then K_2CO_3 (17.3 g, 125 mmol) and Me_2SO_4 (15.75 g, 11.9 mL, 125 mmol) were added sequentially at 23 °C. The resulting purple-black gel-like solution was placed in a pre-heated oil bath at 70 °C. The mixture was refluxed at this temperature for 48 hours. At the end of this period, extra 6 mL of Me_2SO_4 (5 equiv.) was added to the reaction. After 7 hours, the reaction mixture was cooled down to room temperature and acetone was evaporated under reduced pressure. The solid obtained was washed dissolved again in DCM until a clear solution forms and 40 mL of 2M $\text{NaOH}_{(\text{aq})}$ was added. The resulting mixture was stirred for 2 hours. Then extraction was done with DCM 4 times. The combined organic phase was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. 2.355 g of brownish white crude mixture was obtained. ^1H -NMR analysis showed 25% impurity of mono-methylation product (**45**). So, the mixture was dissolved in 30 mL of THF and cooled down to 0 °C. NaH (152.9 mg, 3.83 mmol, 60% dispersion in oil) was added at this temperature. After the gas evolution stopped, MeI was added at 0 °C and it was warmed up to room temperature. The resulting grey solution was stirred at 23 °C for 25 hours. At the end, it was cooled down to 0 °C, quenched with water and extracted with

EtOAc 3 times. The combined organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexanes 1:19 to 1:5) afforded product **46** as a yellowish solid in 78% yield (1.77 g).

R_f = 0.46 (EtOAc:hexanes, 1:9)

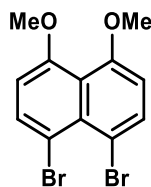
TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz; CDCl₃) δ : 7.41 (2H, dd, J = 8.2, 1.4 Hz), 7.39-7.35 (2H, m), 6.86 (2H, dd, J = 7.4, 1.2 Hz), 3.99 (6H, s).

¹³C NMR (100 MHz; CDCl₃) δ : 157.2, 137.5, 126.5, 121.0, 117.8, 106.3, 56.6

IR ν_{maks} . (ATR, solid)/cm⁻¹ 3001, 2956, 2836, 1580, 1460, 1427, 1386, 1348, 1273, 1237.

HRMS (APCI+) calculated: C₁₂H₁₃O₂ [M+H]⁺: 189.0911, found: 189.0917.



47

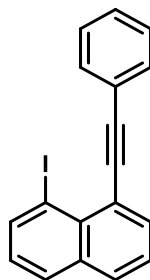
This compound was prepared according to reported procedures.⁸²

¹H NMR (400 MHz; CDCl₃) δ : 7.80 (2H, d, J = 8.8 Hz), 6.69 (2H, d, J = 8.4 Hz), 3.91 (6H, s).

¹³C NMR (100 MHz; CDCl₃) δ : 157.8, 135.9, 131.6, 121.7, 110.3, 107.8, 56.9

IR ν_{maks} . (ATR, solid)/cm⁻¹: 3010, 2965, 2916, 2837, 1583, 1508, 1462, 1448, 1369, 1351, 1293, 1231

HRMS (APCI+) calculated: C₁₂H₁₁⁷⁹Br₂O₂ [M+H]⁺: 344.9121, found: 344.9122.



49

To a glass tube, 1,8-diiodonaphthalene (**43**) (50 mg, 0.13 mmol), phenylacetylene (**48**) (13.4 mg, 14 μ L, 0.13 mmol), piperidine (34 mg, 39 μ L, 0.39 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.9 mg, 0.0026 mmol) were added sequentially. The mixture was stirred at 70 $^\circ\text{C}$ for 35 min. At the end of this time, the reaction mixture was cooled down to room temperature, and 5 mL of EtOAc was added. The resulting solution was washed with %15 (v/v) aqueous HCl solution and then with water. The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , only hexanes) afforded product (**49**) as a yellow oil (23.7 mg, 51% yield).

$R_f = 0.43$ (EtOAc:hexanes = 1:49)

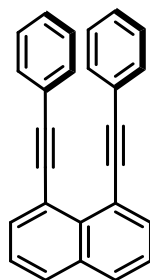
TLC Visualization: UV active; stains with KMnO_4 staining solution.

^1H NMR (400 MHz; CDCl_3) δ : 8.31 (1H, dd, $J = 7.3, 1.3$ Hz), 7.93 (1H, dd, $J = 7.2, 1.4$ Hz), 7.84 (1H, dd, $J = 8.2, 1.1$ Hz), 7.81 (1H, dd, $J = 8.2, 1.3$ Hz), 7.68-7.65 (2H, m), 7.45 (1H, dd, $J = 8.0, 7.4$ Hz), 7.42-7.36 (3H, m), 7.11 (1H, t, $J = 7.8$ Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 142.8, 136.1, 135.0, 132.0, 131.0, 130.5, 130.3, 128.6, 128.5, 127.2, 125.6, 124.2, 123.0, 101.0, 93.1, 89.4.

IR ν_{max} (ATR, film)/ cm^{-1} : 3054, 2923, 2851, 1597, 1551, 1489, 1441.

HRMS (APCI+) Calculated: $\text{C}_{18}\text{H}_{12}\text{I}$ $[\text{M}+\text{H}]^+$ 354.9979, Found: 354.9973.



50

A 25 mL Schlenk tube was charged with 1,8-diiodonaphthalene (**43**) (100 mg, 0.26 mmol), PPh_3 (4.6 mg, 0.017 mmol), Et_3N (1.6 mL) and anhydrous THF (1.6 mL). The mixture was deoxygenated with the application of “freeze-pump-thaw” technique for 3 cycles. Then, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (6.0 mg, 0.0086 mmol), CuI (3.3 mg, 0.018 mmol) and phenylacetylene (**8**) (80.6 mg, 87 μL , 0.79 mmol) were added quickly under nitrogen. The resulting mixture was stirred at 23 °C for 6 h. At the end of this time, the reaction mixture was quenched with water, and the aqueous phase was extracted three times with CHCl_3 . The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , only hexanes, then EtOAc :hexanes = 1:19) afforded product (**50**) as a dark yellow solid (46.1 mg, 53% yield).

R_f = 0.59 (EtOAc :hexanes = 1:19)

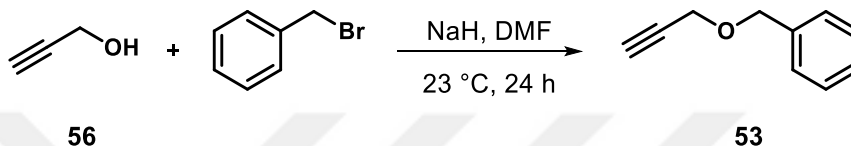
TLC Visualization: UV active (both 254 and 365 nm); stains with KMnO_4 staining solution.

^1H NMR (400 MHz; CDCl_3) δ : 7.89 (2H, dd, J = 7.2, 1.3 Hz), 7.84 (2H, dd, J = 8.4, 1.2 Hz), 7.47 (2H, dd, J = 8.2, 7.2 Hz), 7.39-7.36 (4H, m), 7.21 (2H, tt, J = 7.4, 1.3 Hz), 7.13 (4H, tt, J = 7.4 Hz, 1.5 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 135.0, 134.3, 131.7, 131.6, 129.7, 128.1, 128.0, 125.7, 123.9, 121.0, 96.8, 89.9.

IR ν_{max} (ATR, film)/cm⁻¹: 3054, 2924, 2853, 1597, 1567, 1489, 1441, 1376.

HRMS (APCI+) Calculated: C₂₆H₁₇ [M+H]⁺ 329.1325, Found: 329.1323.



An oven-dried 100 mL round-bottomed flask was charged with NaH (470.7 mg, 19.62 mmol, 60% dispersion in mineral oil), and the flask was evacuated and filled with nitrogen three times. Then, 16 mL of anhydrous DMF was added forming a suspension. The mixture was cooled down to 0 °C in an ice bath, and then propargyl alcohol (**56**) (1.00 g, 1.04 mL, 17.8 mmol) was added slowly releasing H₂(g). After the gas release ceased, benzyl bromide (3.36 g, 2.34 mL, 19.6 mmol) was added dropwise. The resulting mixture was warmed to 23 °C and stirred at this temperature for 24 h. At the end of this time, the reaction mixture was quenched with water and diluted with EtOAc. The two phases were partitioned, and the organic phase was washed with small amount of concentrated HCl. The organic phase was then dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, EtOAc:hexanes 1:49 to 1:19) afforded product (**53**) as a colourless liquid (1.90 g, 73% yield).

R_f = 0.49 (EtOAc:hexanes = 1:7)

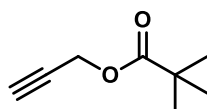
TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz; CDCl₃) δ: 7.40-7.30 (5H, m), 4.64 (2H, s), 4.20 (2H, d, *J* = 2.5 Hz), 2.49 (1H, t, *J* = 2.4 Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 137.3, 128.3, 128.0, 127.8, 79.7, 74.7, 71.3, 56.9.

IR ν_{max} (ATR, film)/ cm^{-1} : 3291, 2856, 2116, 1496, 1354, 1072, 1027, 737, 696, 632.

HRMS (APCI+) Calculated: $\text{C}_{10}\text{H}_{11}\text{O}^+$ $[\text{M}+\text{H}]^+$ 147.0804, Found: 147.0823.



54

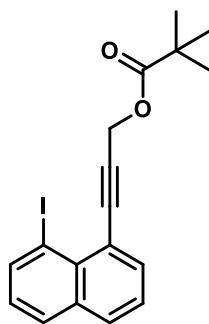
DMAP (109 mg, 0.89 mmol), propargyl alcohol (**56**) (1.00 g, 1.04 mL, 17.8 mmol) and distilled Et_3N (2.35 g, 3.23 mL, 23.2 mmol) were dissolved in 20 mL anhydrous CH_2Cl_2 , then cooled down to 0 °C in an ice bath. After 5 minutes of stirring, pivaloyl chloride (**57**) (2.80 g, 2.86 mL, 23.2 mmol) was added slowly under nitrogen. Then, the mixture was stirred at 23 °C for 2 h. At the end of this period, the reaction mixture was cooled down to 0 °C again and quenched with water. The aqueous phase was extracted four times with CH_2Cl_2 . The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , 5% to 10% CH_2Cl_2 in pentane) afforded product (**54**) as a colourless liquid (2.46 g, 98% yield). The spectral data were observed to be in agreement with the values reported in the literature.⁸⁸

R_f = 0.49 (EtOAc :hexanes = 1:2)

TLC Visualization: Stains with KMnO_4 staining solution.

^1H NMR (400 MHz; CDCl_3) δ : 4.65 (2H, d, J = 2.4 Hz), 2.44 (1H, t, J = 2.5 Hz), 1.22 (9H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 177.8, 78.1, 74.6, 52.1, 38.9, 27.2.



58

A 20-mL vial was charged with 1,8-diiodonaphthalene (**43**) (50 mg, 0.13 mmol) and alkyne **54** (18.5 mg, 0.13 mmol). To this mixture, piperidine (67 mg, 78 μ L, 0.79 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.9 mg, 0.0026 mmol) were added, and the resulting mixture was stirred at 70 $^\circ\text{C}$ for 2 h. At the end of this period, the mixture was cooled down to room temperature, and EtOAc was added. The two phases were partitioned, and the organic phase was washed with 15% (v/v) aqueous HCl solution and then with water. The organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , only hexanes) afforded product (**58**) as an orange oil (27.6 mg, 53% yield).

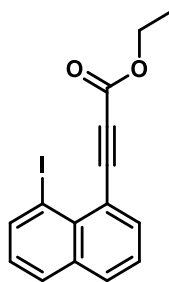
R_f = 0.39 (EtOAc:hexanes = 1:19)

TLC Visualization: UV active; stains with KMnO_4 staining solution.

^1H NMR (400 MHz; CDCl_3) δ : 8.28 (1H, dd, J = 7.4, 1.2 Hz), 7.84-7.79 (3H, m), 7.40 (1H, dd, J = 8.0, 7.4 Hz), 7.09 (1H, t, J = 7.8 Hz), 5.01 (2H, s), 1.27 (9H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 178.1, 142.9, 136.5, 134.9, 132.2, 131.0, 130.3, 127.3, 125.5, 121.9, 95.6, 92.8, 85.8, 53.9, 39.1, 27.4.

IR ν_{max} (ATR, film)/ cm^{-1} : 2968, 2929, 2870, 1729, 1554, 1478.



61

An oven-dried 25 mL Schlenk tube (evacuated and filled with nitrogen) was charged with 1,8-diiodonaphthalene (**43**) (100 mg, 0.26 mmol), ethyl propiolate (**55**) (103.3 mg, 107 μ L, 1.05 mmol) and 1 mL of anhydrous THF. To this solution, Pd(PPh₃)₂Cl₂ (3.7 mg, 0.0056 mmol), CuI (2.0 mg, 0.011 mmol) and K₂CO₃ (146 mg, 1.05 mmol) were added quickly under an atmosphere of nitrogen. The resulting mixture was stirred at 65 °C for 6 h. At the end of this time, the reaction mixture was cooled down to room temperature and quenched with water. The aqueous phase was extracted three times with EtOAc. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, EtOAc:hexanes 1:19) afforded product **61** as a bright yellow oil (43.1 mg, 47% yield).

R_f = 0.39 (EtOAc:hexanes 1:19)

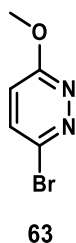
TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz; CDCl₃) δ : 8.29 (1H, dd, J = 7.4, 1.2 Hz), 7.98 (1H, dd, J = 7.3, 1.3 Hz), 7.89 (1H, dd, J = 8.2, 1.1 Hz), 7.83 (1H, dd, J = 8.1, 0.9 Hz), 7.44 (1H, t, J = 7.7 Hz), 7.13 (1H, t, J = 7.8 Hz), 4.33 (2H, q, J = 7.1 Hz), 1.37 (3H, t, J = 7.1 Hz).

¹³C NMR (100 MHz; CDCl₃) δ : 154.4, 143.3, 138.7, 134.9, 133.0, 132.9, 130.3, 127.7, 125.5, 119.5, 92.8, 92.4, 85.63, 62.0, 14.3.

IR ν_{max} (ATR, film)/cm⁻¹: 2980, 2198, 1696, 1283, 1204, 817, 756.

HRMS (ESI+) Calcd for (C₁₅H₁₂O₂I)⁺ (M+H)⁺: 350.9877, found: 350.9877.



The commercially available 3,6-dibromopyridazine (**62**) (1.00 g, 4.20 mmol) was dissolved in 10 mL of THF and 10 mL of MeOH, and the resulting solution was cooled to 0 °C. To this solution, NaOMe (250 mg, 4.62 mmol) was added, and the resulting mixture was stirred at 23 °C for 2 h. As the progress of the reaction was observed to be incomplete by TLC analysis, the solution was stirred at 50 °C for an additional period of 2 h. At the end of this time, the reaction mixture was cooled down to room temperature and quenched with water. The aqueous phase was extracted three times with EtOAc. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Nucleophilic substitution product (**63**) was obtained as a pale-yellow solid (746 mg, 94% yield) without further purification.

R_f = 0.55 (EtOAc:hexanes = 1:1)

M.P. 104-106 °C (CHCl₃).

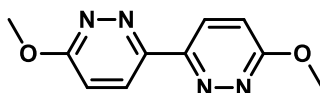
TLC Visualization: UV activity is low but still can be observed.

¹H NMR (400 MHz; CDCl₃) δ: 7.47 (1H, d, *J* = 9.1 Hz), 6.86 (1H, d, *J* = 9.1 Hz), 4.10 (3H, s).

¹³C NMR (100 MHz; CDCl₃) δ: 164.8, 141.7, 134.0, 120.0, 55.3.

IR ν_{max} (ATR, film)/cm⁻¹: 3058, 3033, 2950, 2871, 1678, 1584, 1573, 1460, 1395.

HRMS (APCI+) Calculated: C₅H₆⁷⁹BrN₂O [M+H]⁺ 188.9659, Found: 188.9663;
Calculated: C₅H₆⁸¹BrN₂O [M+H]⁺ 190.9638, Found: 190.9648.



65

An oven-dried Schlenk tube was assembled while hot, cooled under vacuum and evacuated and filled with nitrogen three times. 3-bromo-6-methoxypyridazine (**63**) (30 mg, 0.16 mmol) was added to the Schlenk flask and dissolved in 1.5 mL of DMSO. B₂pin₂ (42.3 mg, 0.17 mmol) and Pd(dppf)Cl₂ (6.48 mg, 0.0079 mmol) were added sequentially under nitrogen. After the addition of KOAc (46.7 mg, 0.48 mmol), the system was sealed with a glass stopper, and the solution was stirred at 80 °C for 24 h. At the end of this period, the brown-colored reaction mixture was cooled down to room temperature and quenched with water. The aqueous phase was extracted three times with EtOAc. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, EtOAc:hexanes 1:3) afforded product (**65**) as a white solid.

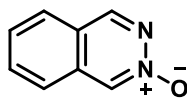
R_f = 0.36 (EtOAc:hexanes 1:2)

¹H NMR (400 MHz; CDCl₃) δ: 8.61 (2H, d, *J* = 9.3 Hz), 7.12 (2H, d, *J* = 9.1 Hz), 4.21 (6H, s).

¹³C NMR (100 MHz; CDCl₃) δ: 165.6, 152.7, 127.5, 118.3, 55.2. Signal at 29.85 ppm is resulted from grease.

IR ν_{max} (ATR, film)/cm⁻¹: 2922, 2852, 1597, 1465, 1403, 1312, 1285, 1003, 845.

HRMS (ESI+) Calcd for (C₁₀H₁₁N₄O₂)⁺ (M+H)⁺: 219.0877, found: 218.0977.



68

A 250 mL round-bottomed flask was charged with phthalazine (**67**) (1.50 g, 0.012 mol) and 60 mL of CH₂Cl₂. The solution was cooled down to 0 °C, and *m*-CPBA (2.19 g, 0.013 mol, 73% purity) was added slowly forming an orange solution. The resulting clear solution was stirred at 23 °C for 22 h. At the end of this time, the reaction mixture was quenched with saturated aqueous Na₂CO₃ solution, and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification with flash column chromatography (SiO₂, 1:2 to 1:1 *i*-PrOH:EtOAc) afforded product (**68**) as a pale yellow solid (1.25 g, 74% yield).

M.P. 150-152 °C (EtOAc, hexanes).

R_f = 0.34 (*i*-PrOH:EtOAc = 1:3)

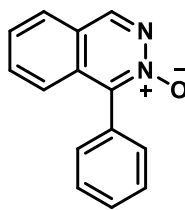
TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz; CDCl₃) δ: 9.01 (1H, s), 8.52 (1H, s), 7.87 (1H, dd, *J* = 8.2, 0.8 Hz), 7.74 (1H, ddd, *J* = 8.2, 7.0, 1.1 Hz), 7.63 (1H, d, *J* = 8.0 Hz), 7.59 (1H, ddd, *J* = 8.1, 7.1, 1.0 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 152.6, 134.0, 132.7, 129.6, 127.4, 127.1, 123.3, 120.8

IR ν_{max} (ATR, solid)/cm⁻¹ 3080, 3048, 2983, 1618, 1564, 1436, 1333.

HRMS (ESI+) Calcd for (C₈H₇N₂O)⁺ (M+H)⁺: 147.0553, found: 147.0553.



71

A 25 mL round-bottomed flask was charged with phthalazine *N*-oxide (**68**) (84 mg, 0.57 mmol), K₂CO₃ (53 mg, 0.38 mmol), *t*Bu₃P·HBF₄ (5.5 mg, 0.019 mmol) and Pd(OAc)₂ (2.1 mg, 0.0096 mmol). The flask was evacuated and filled with nitrogen three times. Bromobenzene (**70**) (30 mg, 20 μ L, 0.19 mmol) was then added via a microsyringe under nitrogen. In another 10 mL round-bottomed flask, toluene was deoxygenated by purging with nitrogen gas for 10 min, and sealed with a septum. This solvent was transferred to the flask containing *N*-oxide (**68**) forming a heterogeneous mixture. The reaction mixture was refluxed at 110 °C for 6 h. Then, it was cooled down to room temperature, quenched with water and extracted three times with CH₂Cl₂. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, EtOAc:*i*-PrOH 3:1) afforded product (**71**) as a pale-yellow solid (26.7 mg, 63% yield).

R_f = 0.56 (EtOAc:*i*-PrOH = 3:1)

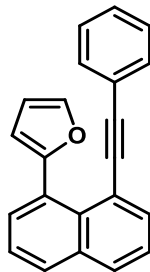
TLC Visualization: UV active (both 254 and 365 nm).

¹H NMR (400 MHz; CDCl₃) δ : 9.10 (1H, s), 7.94 (1H, d, *J* = 8.1 Hz), 7.73-7.62 (2H, m), 7.61-7.51 (m, 5H), 7.47 (1H, d, *J* = 8.4 Hz).

¹³C-NMR (100 MHz; CDCl₃) δ : 151.9, 137.7, 133.7, 132.8, 130.2, 129.9, 129.8, 129.0, 128.9, 127.3, 124.4, 121.3.

IR ν_{maks} (ATR, film)/cm⁻¹: 3059, 3039, 1615, 1553, 1350, 1328, 756.

HRMS (APCI+) Calculated: $C_{14}H_{11}N_2O^+$ $[M+H]^+$ 223.0866, Found: 223.0876



77

In a 25 mL round-bottomed flask, iodonaphthalene derivative (**49**) (33.4 mg, 0.09 mmol) was dissolved in 3 mL of 1,4-dioxane/ H_2O (2:1) mixture. Afterwards, 2-furanylboronic acid (**76**) (21.1 mg, 0.19 mmol) and K_3PO_4 (60.1 mg, 0.028 mmol) were added. The mixture was stirred at 23 °C for 5 min, and then $Pd(PPh_3)_4$ (5.5 mg, 0.0047 mmol) was added. The resulting mixture was stirred at 100 °C for 4 h. At the end of this period, the reaction mixture was cooled down to room temperature and quenched with water. The aqueous phase was extracted three times with CH_2Cl_2 . The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , EtOAc:hexanes gradual polarity increase from 1:19 to 1:7) afforded product (**77**) as an orange oil (25.7 mg, 92% yield).

R_f = 0.54 (EtOAc:hexanes = 1:19)

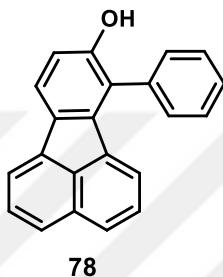
TLC Visualization: UV active (blue fluorescent at 365 nm); stains with $KMnO_4$ staining solution.

^1H NMR (400 MHz; $CDCl_3$) δ : 7.93 (1H, d, J = 8.1 Hz), 7.89 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 7.1 Hz), 7.59 (1H, d, J = 7.0 Hz), 7.53-7.47 (3H, m), 7.37-7.35 (2H, m), 7.30-7.26 (3H, m), 6.58 (1H, dt, J = 3.2, 0.8 Hz), 6.48-6.47 (1H, m).

^{13}C NMR (100 MHz; CDCl_3) δ : 154.7, 142.3, 135.0, 134.6, 131.9, 131.2, 130.4, 129.4, 129.3, 128.1, 128.0, 127.8, 125.6, 125.4, 124.1, 120.7, 111.9, 109.0, 95.0, 88.8.

IR ν_{max} (ATR, film)/ cm^{-1} : 3055, 2924, 1489, 1369, 1272, 1009, 828, 769, 755.

HRMS (APCI+) Calculated: $\text{C}_{22}\text{H}_{15}\text{O}^+$ $[\text{M}+\text{H}]^+$ 295.1117, Found: 295.1106



An oven dried 25 mL round-bottomed flask was charged with compound **77** (18.8 mg, 0.064 mmol) and dissolved in 1 mL of toluene. The forming orangish-yellow solution was stirred at 110 °C with a condenser under inert atmosphere for 51 hours. The crude mixture was directly loaded to a column. Purification by flash column chromatography (EtOAc:hexanes 1:19 to 1:9) afforded **78** as a yellow solid in 26% yield (4.8 mg).

R_f = 0.41 (EtOAc:hexanes = 1:4)

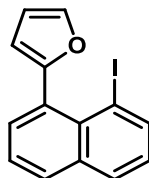
TLC Visualization: UV active (yellow fluorescent at 365 nm); stains with KMnO_4 staining solution.

^1H NMR (400 MHz; CDCl_3) δ : 7.87 (1H, d, J = 6.9 Hz), 7.83 (1H, d, J = 8.1 Hz), 7.75 (1H, d, J = 8.1 Hz), 7.73 (1H, d, J = 8.0 Hz), 7.67-7.55 (m, 6H), 7.30 (1H, t, J = 7.6 Hz), 7.03 (1H, d, J = 8.2 Hz), 6.74 (1H, d, J = 7.1 Hz), 4.98 (1H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 153.1, 138.8, 136.73, 136.71, 134.4, 133.0, 132.6, 130.4, 130.1, 130.0, 129.2, 128.1, 127.8, 126.9, 125.8, 124.9, 122.7, 122.1, 119.1, 114.2. (Grease is the source of the signal at 29.9 ppm)

IR ν_{max} (ATR, film)/ cm^{-1} : 3508, 3432, 3058, 2923, 1603, 1443, 1267, 1207, 1198, 1173, 816, 774, 712.

HRMS (APCI+) Calculated: $\text{C}_{22}\text{H}_{13}\text{O}^-$ $[\text{M}-\text{H}]^-$ 293.0972, Found: 293.0977



80

A 25 mL Schlenk tube was charged with 1,8-diiodonaphthalene (**43**) (70 mg, 0.18 mmol) and 2 mL of anhydrous DMF. Then, 2-furanboronic acid (**76**) (20.6 mg, 0.18 mmol), $\text{Pd}(\text{PPh}_3)_4$ (10.6 mg, 0.0092 mmol) and K_2CO_3 (102 mg, 0.74 mmol) were added quickly. The tube was sealed with a glass stopper, and the resulting mixture was stirred at 80 °C for 24 h. At the end of this period, the mixture was cooled down to room temperature and quenched with water. The aqueous phase was extracted three times with CH_2Cl_2 . The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , only hexanes) afforded mono-furylnaphthalene product **80** as a colourless oil in 31% yield (18.1 mg) and di-furylnaphthalene product **81** as orange oil in 26% yield (12.5 mg).

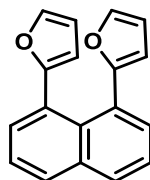
R_f = 0.49 (only hexanes)

TLC Visualization: UV active; stains with KMnO_4 staining solution.

^1H NMR (400 MHz; CDCl_3) δ : 8.27 (1H, d, J = 7.3 Hz), 7.89 (2H, d, J = 8.1 Hz), 7.63 (2H, dd, J = 7.0, 1.4 Hz), 7.49 (1H, t, J = 7.6 Hz), 7.12 (1H, t, J = 7.7 Hz), 6.58 (1H, dd, J = 3.2, 1.8 Hz), 6.49 (1H, d, J = 3.2 Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 151.6, 142.2, 141.9, 135.5, 132.9, 132.6, 131.1, 130.6, 129.8, 126.9, 125.2, 112.3, 111.4, 91.5.

FTIR ν_{max} (ATR, film)/ cm^{-1} : 3114, 3053, 2923, 1554, 1500, 1356.



81

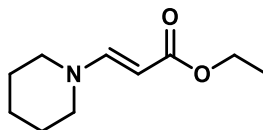
R_f = 0.34 (only hexanes)

TLC Visualization: UV active; stains with KMnO_4 staining solution.

^1H NMR (400 MHz; CDCl_3) δ : 7.92 (2H, dd, J = 8.2, 1.2 Hz), 7.67 (2H, dd, J = 7.1, 1.3 Hz), 7.54 (2H, t, J = 7.6 Hz), 7.17 (2H, dd, J = 1.7, 0.7 Hz), 6.22 (2H, dd, J = 3.3, 1.8 Hz), 6.13 (2H, dd, J = 3.3, 0.7 Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 154.7, 141.7, 135.3, 130.4, 129.5, 129.1, 129.0, 125.4, 111.1, 107.5.

IR ν_{max} (ATR, film)/ cm^{-1} 3114, 3055, 2925, 1509, 1496, 1363.



59

In an oven-dried 25 mL round-bottomed flask, furan-substituted naphthalene derivative **80** (18.1 mg, 0.06 mmol) was dissolved in 1 mL of anhydrous 1,4-dioxane. Then, ethyl propiolate (**55**) (11.1 mg, 11.6 μL , 0.11 mmol), piperidine (14.4 mg, 16.8 μL , 0.17 mmol)

and Pd(PPh₃)₂Cl₂ (4.0 mg, 0.0057 mmol) were added quickly under an atmosphere of nitrogen. The resulting mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled down to room temperature, and quenched with water. The aqueous phase was extracted three times with EtOAc. The combined organic phase was washed with 1 M aqueous HCl solution and water. The final organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, EtOAc:hexanes 1:19) afforded the unexpected aza-Michael addition product **59** as a brownish yellow oil (16.3 mg, 52% yield).

R_f = 0.32 (EtOAc:hexanes 1:5)

TLC Visualization: UV active; stains with KMnO₄ staining solution.

¹H NMR (400 MHz; CDCl₃) δ: 7.38 (1H, d, *J* = 13.1 Hz), 4.61 (1H, d, *J* = 13.1 Hz), 4.12 (2H, q, *J* = 7.1 Hz), 3.18 (4H, d, *J* = 5.3 Hz), 1.63-1.54 (6H, m), 1.24 (3H, t, *J* = 7.1 Hz).

HRMS (ESI+) Calcd for (C₁₀H₁₈NO₂)⁺ (M+H)⁺: 184.1313, found: 184.1334.

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APPENDIX

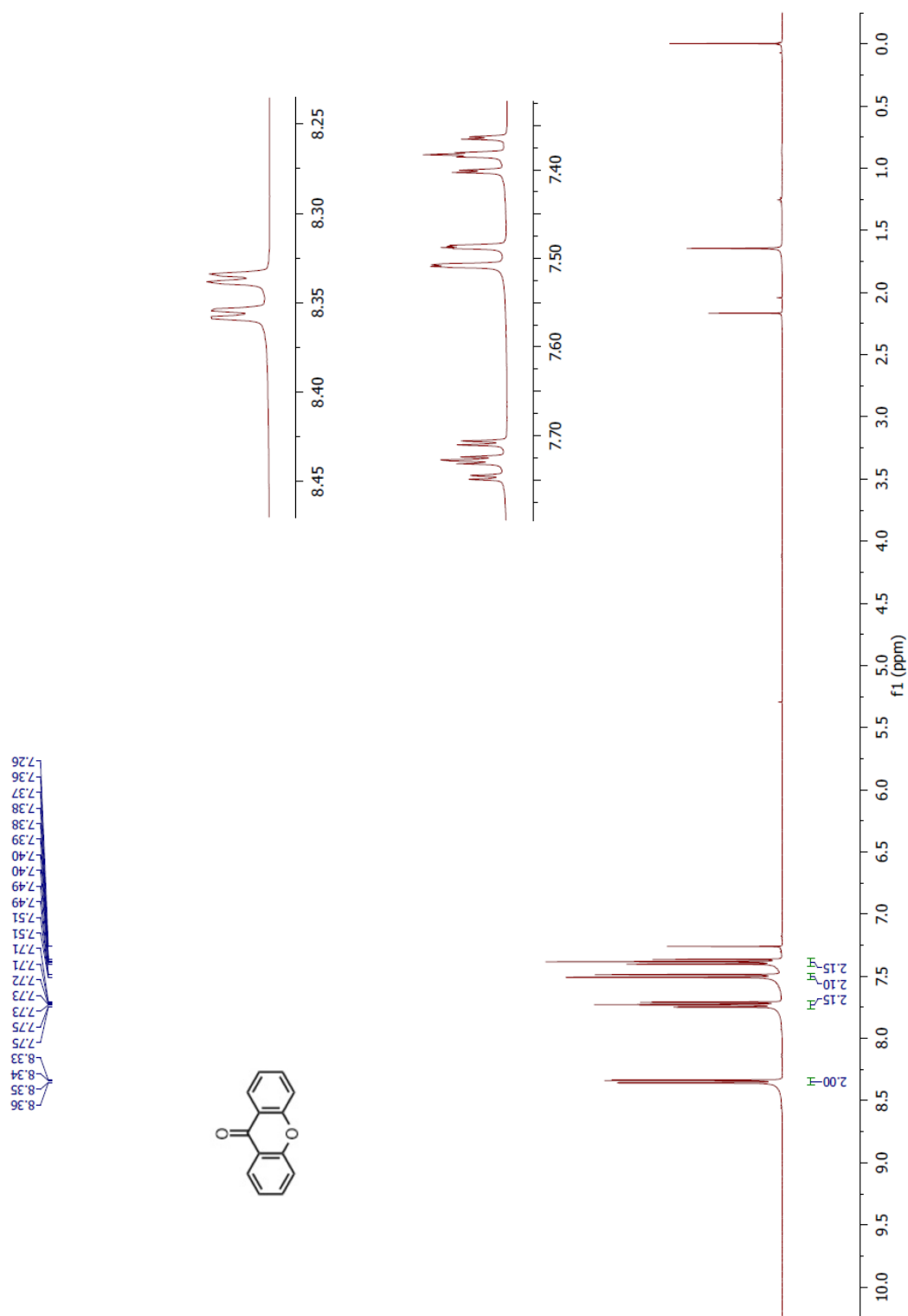


Figure 13: ^1H -NMR spectrum of **2** in CDCl_3 .

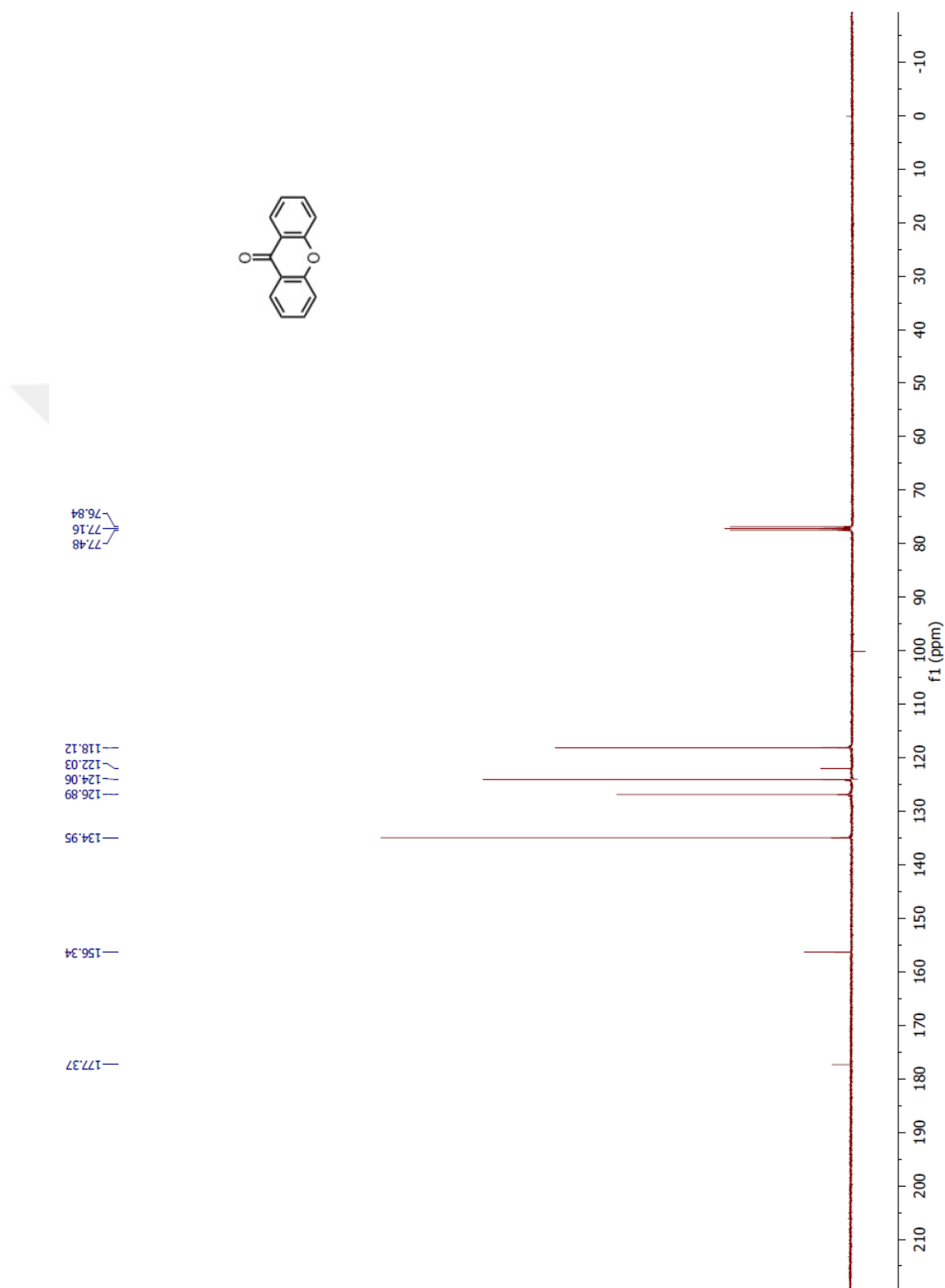


Figure 14: ^{13}C -NMR spectrum of **2** in CDCl₃.

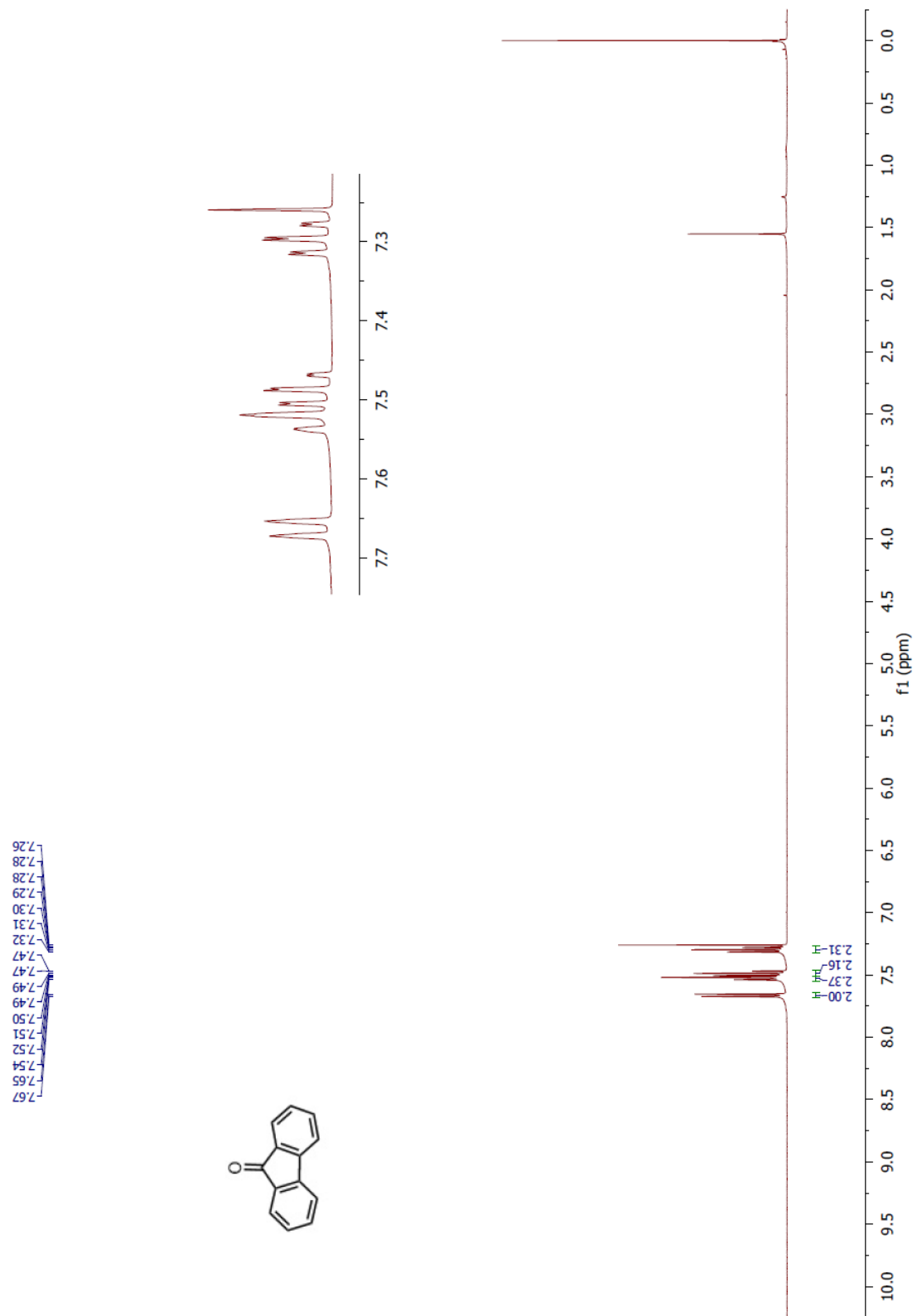


Figure 15: ^1H -NMR spectrum of **4** in CDCl_3 .

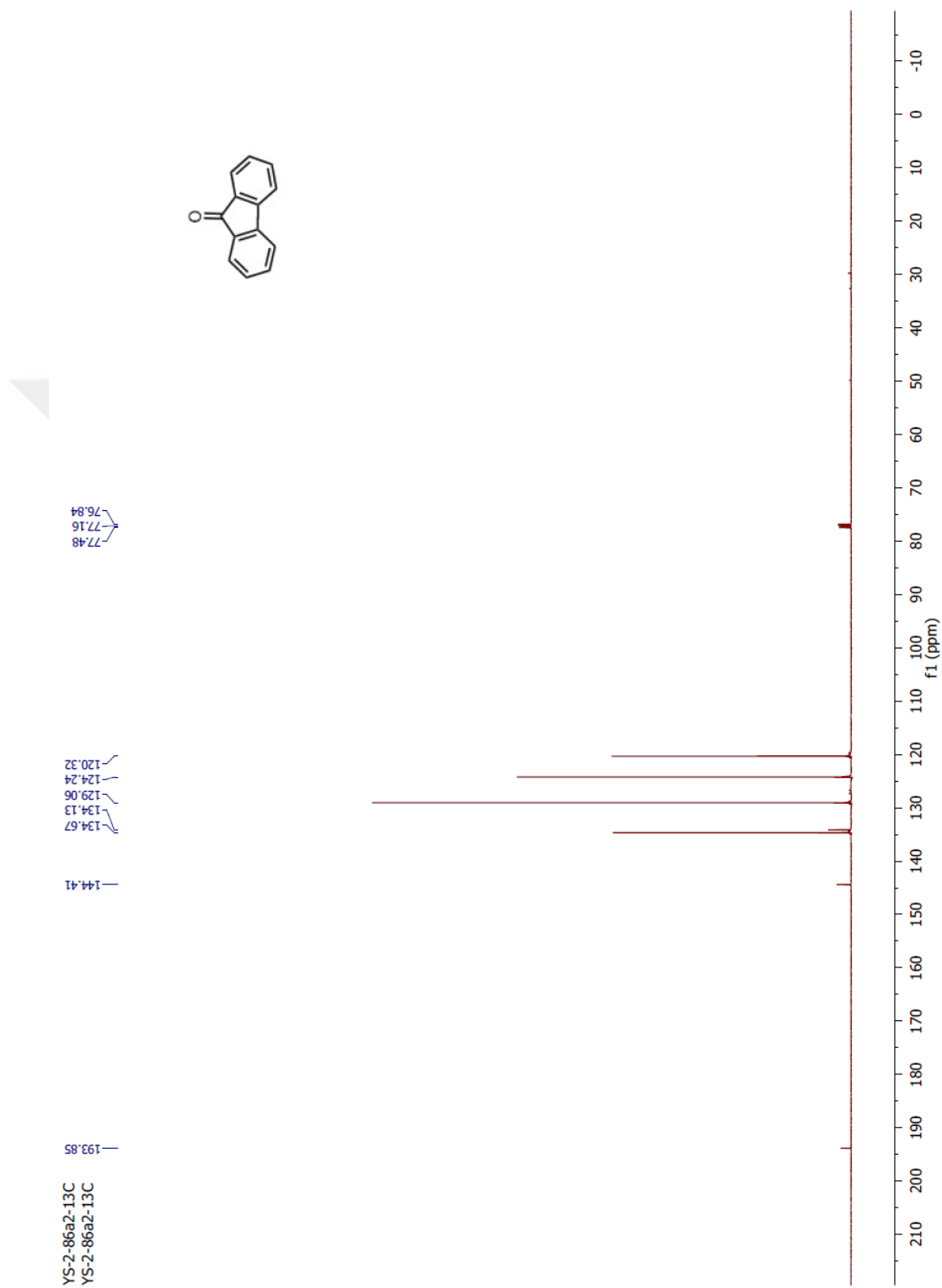


Figure 16: ¹³C-NMR spectrum of **4** in CDCl₃.

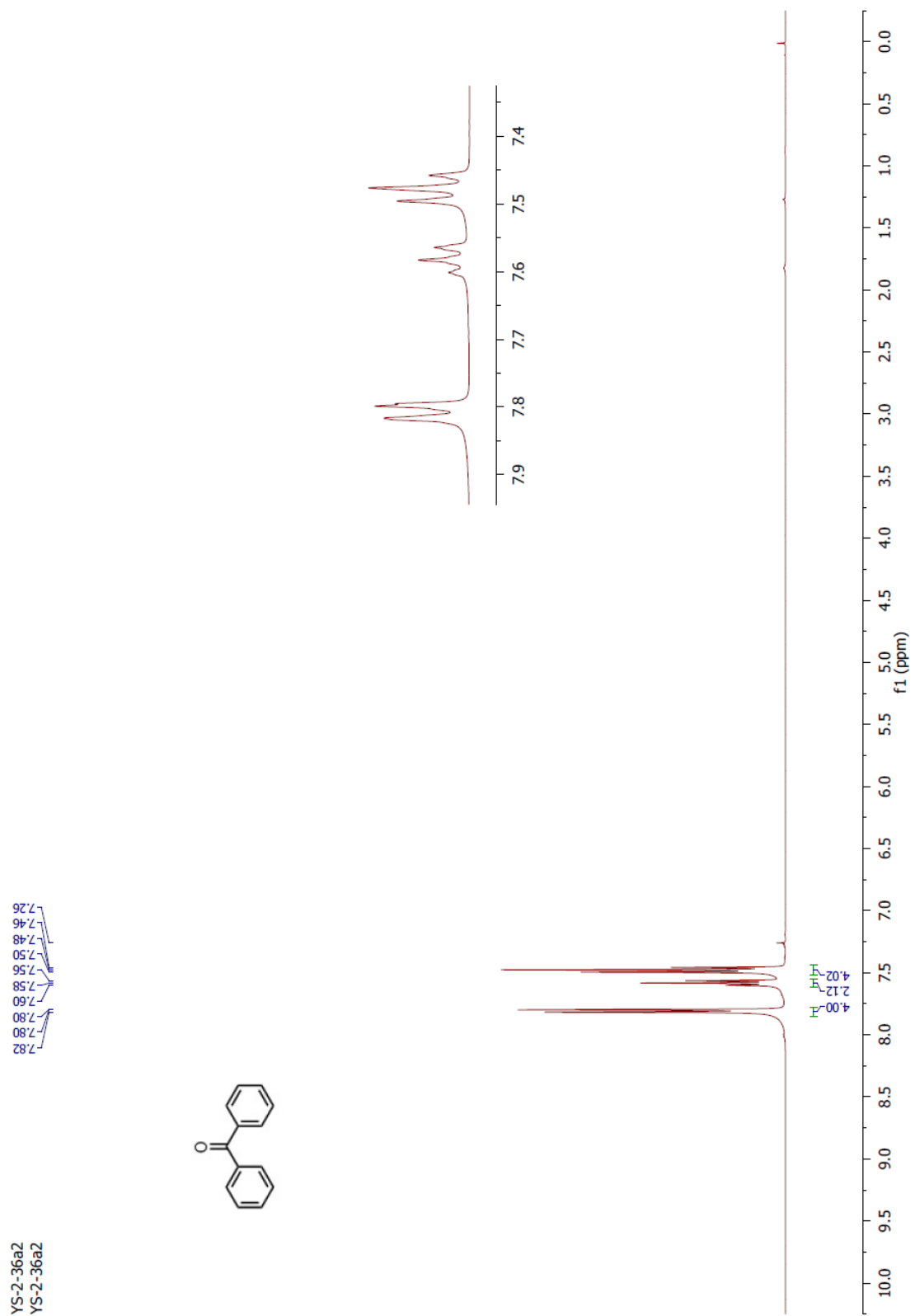


Figure 17: ^1H -NMR spectrum of **6** in CDCl_3 .

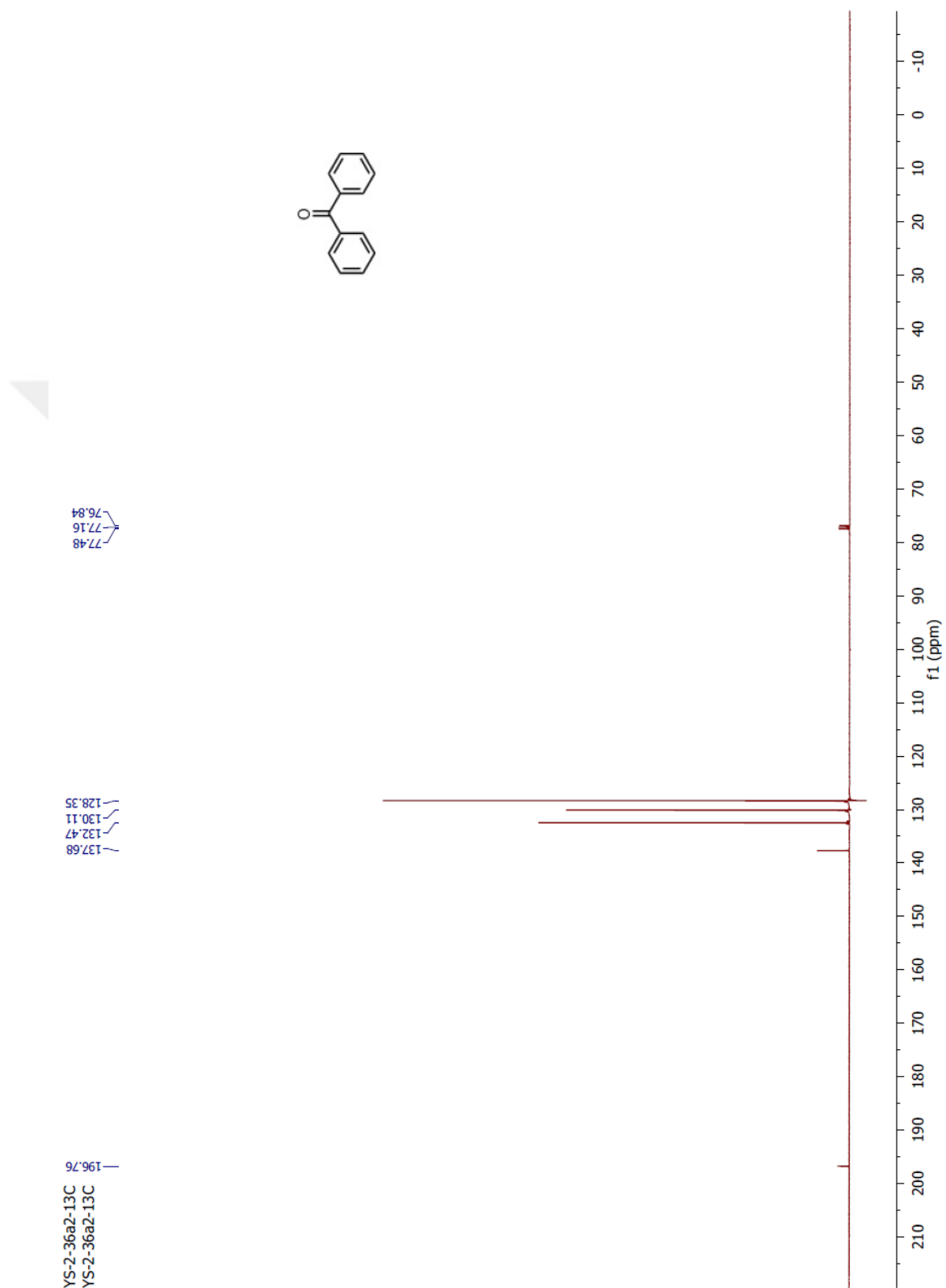


Figure 18: ^{13}C -NMR spectrum of **6** in CDCl_3 .

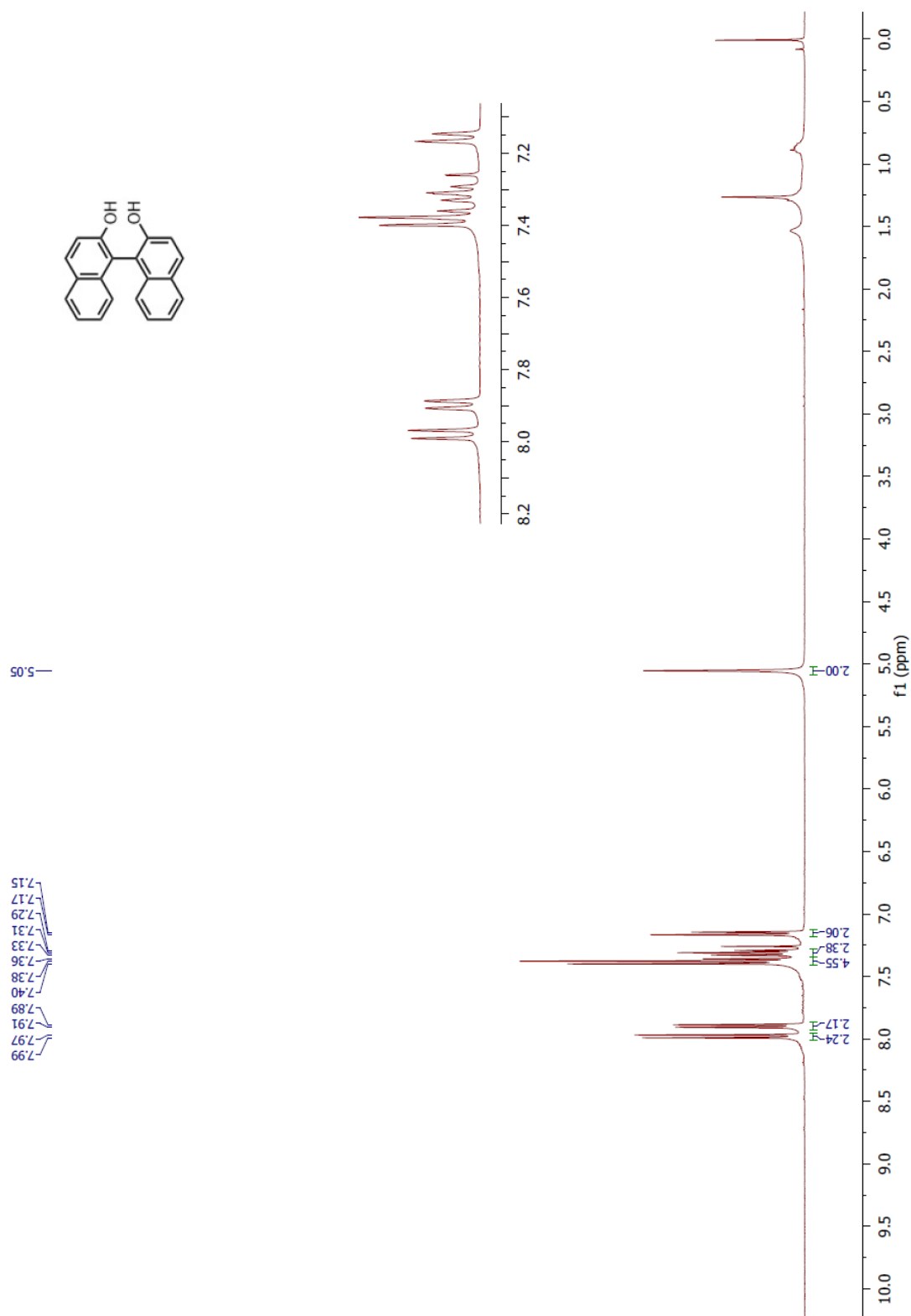


Figure 19: ¹H-NMR spectrum of **8** in CDCl₃.

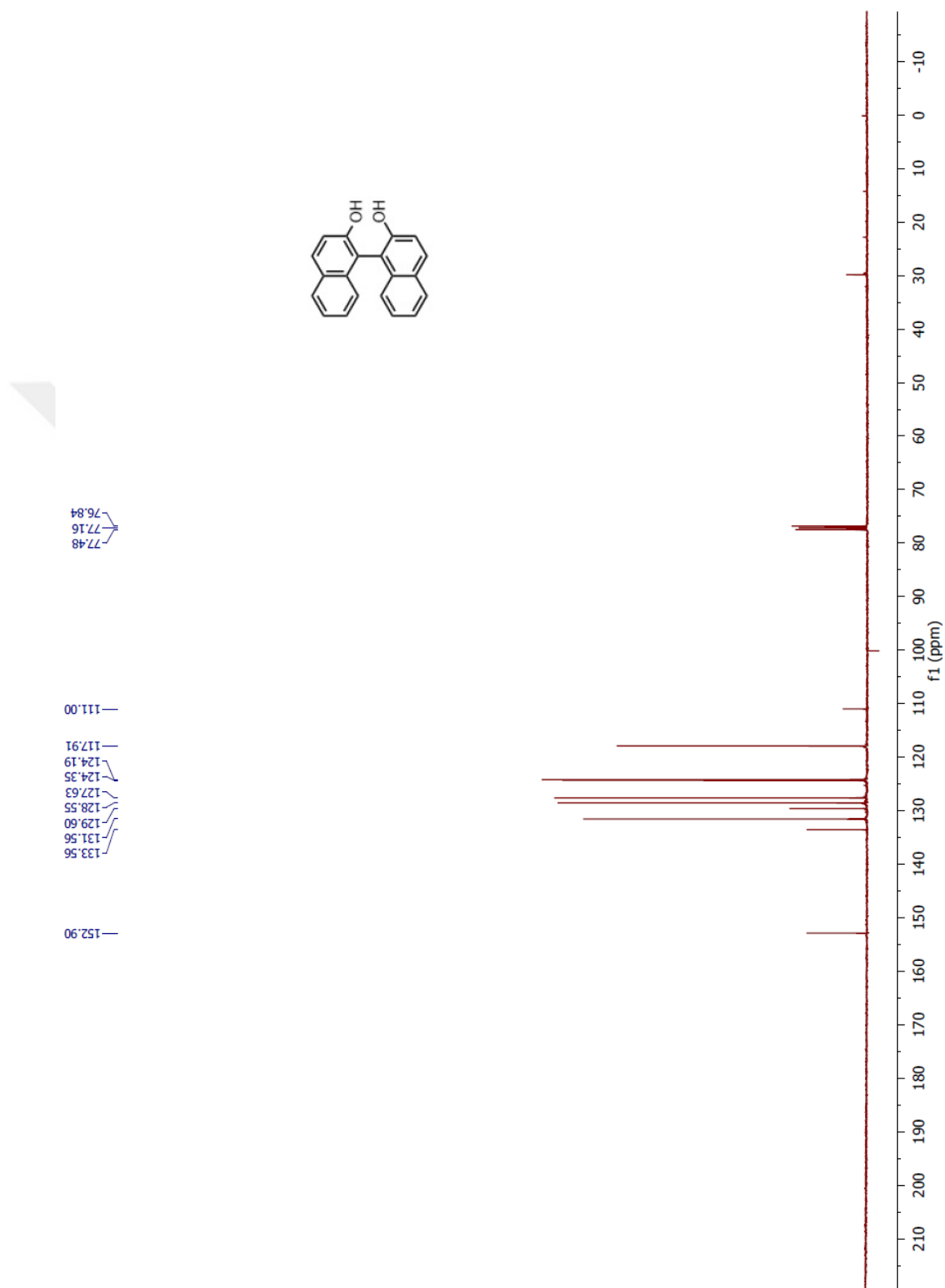


Figure 20: ^{13}C -NMR spectrum of **8** in CDCl_3 .

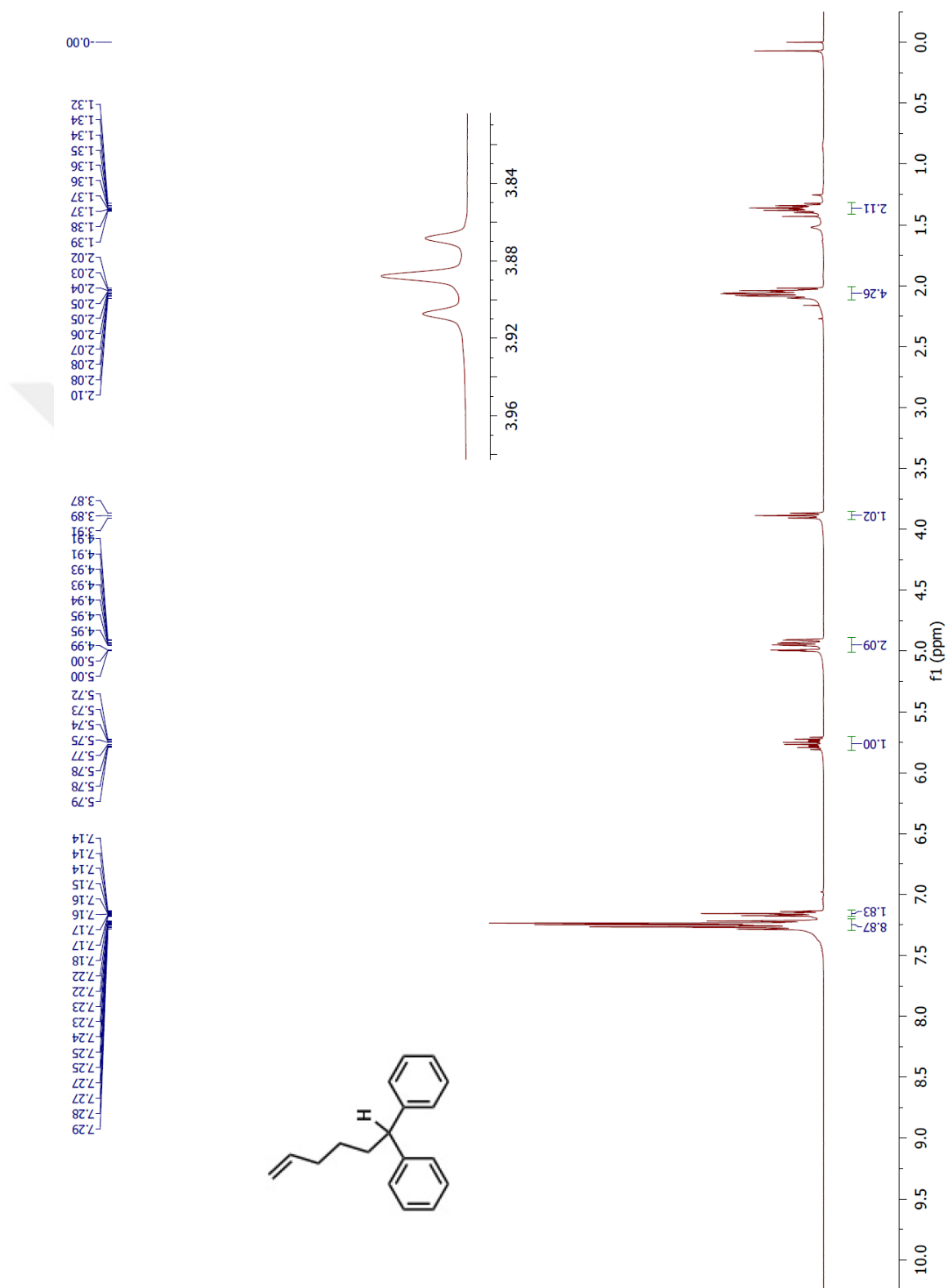


Figure 21: ^1H -NMR spectrum of **11** in CDCl_3 .

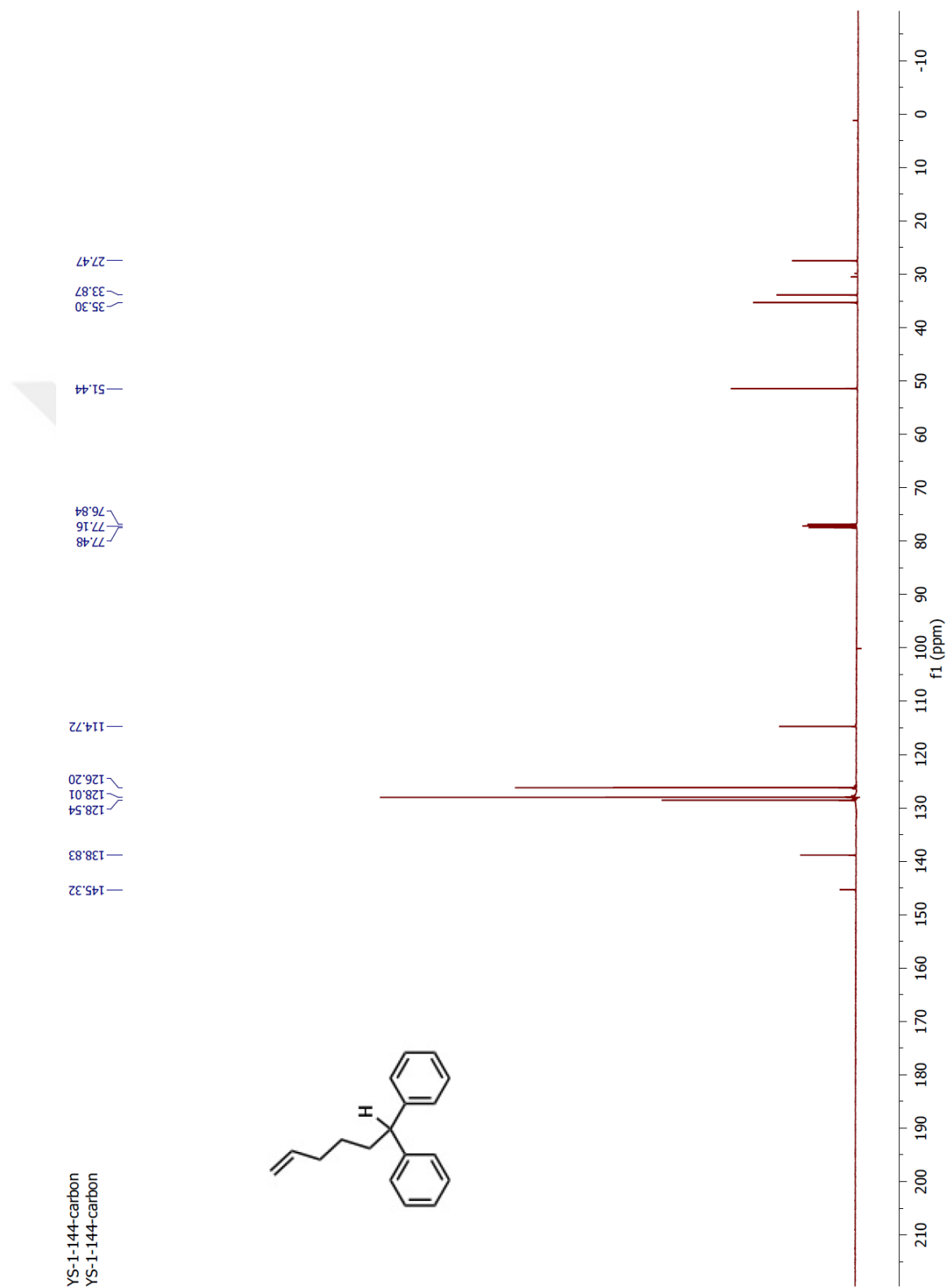


Figure 22: ^{13}C -NMR spectrum of **11** in CDCl_3 .

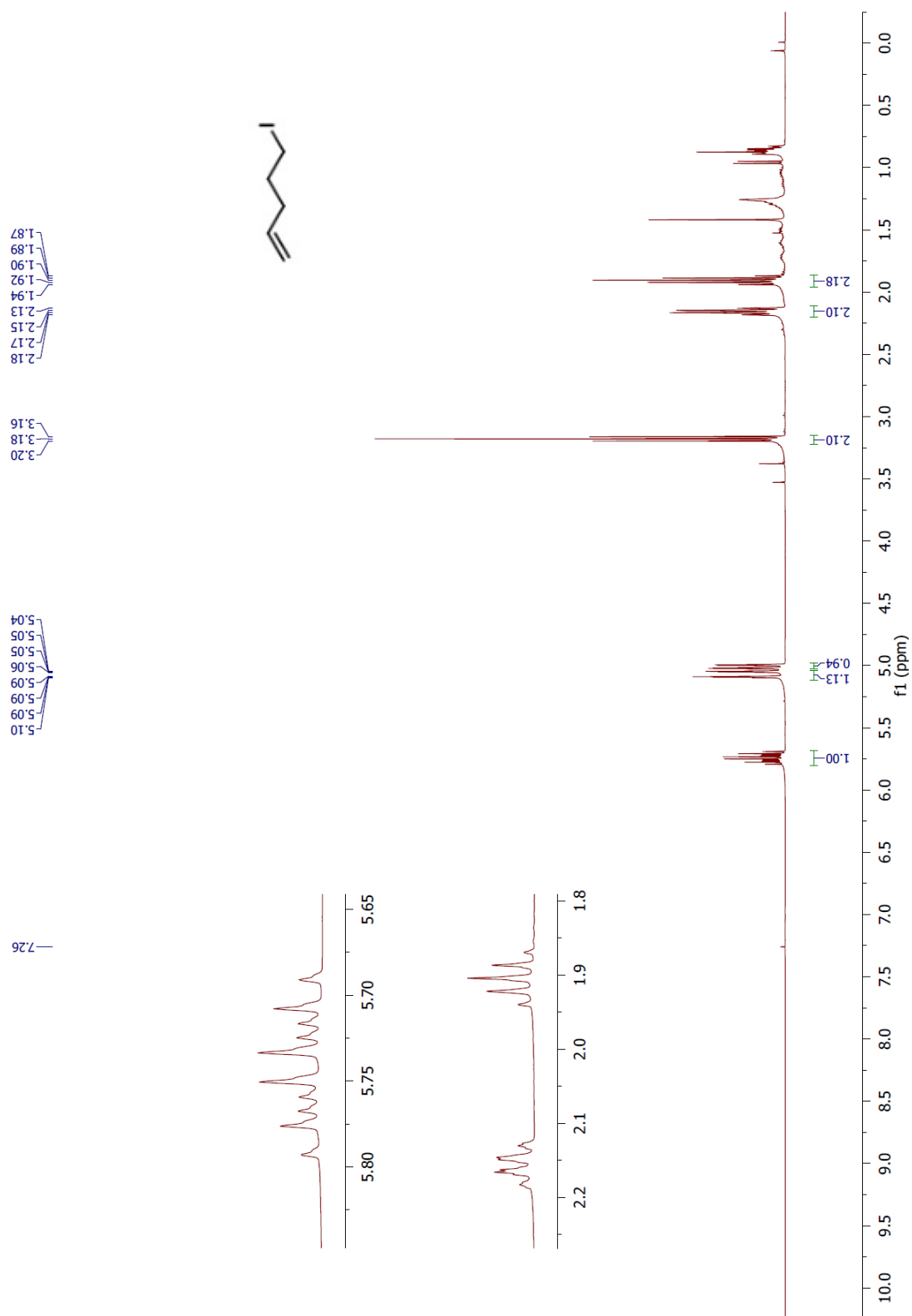


Figure 23: ¹H-NMR spectrum of **15** in CDCl₃.

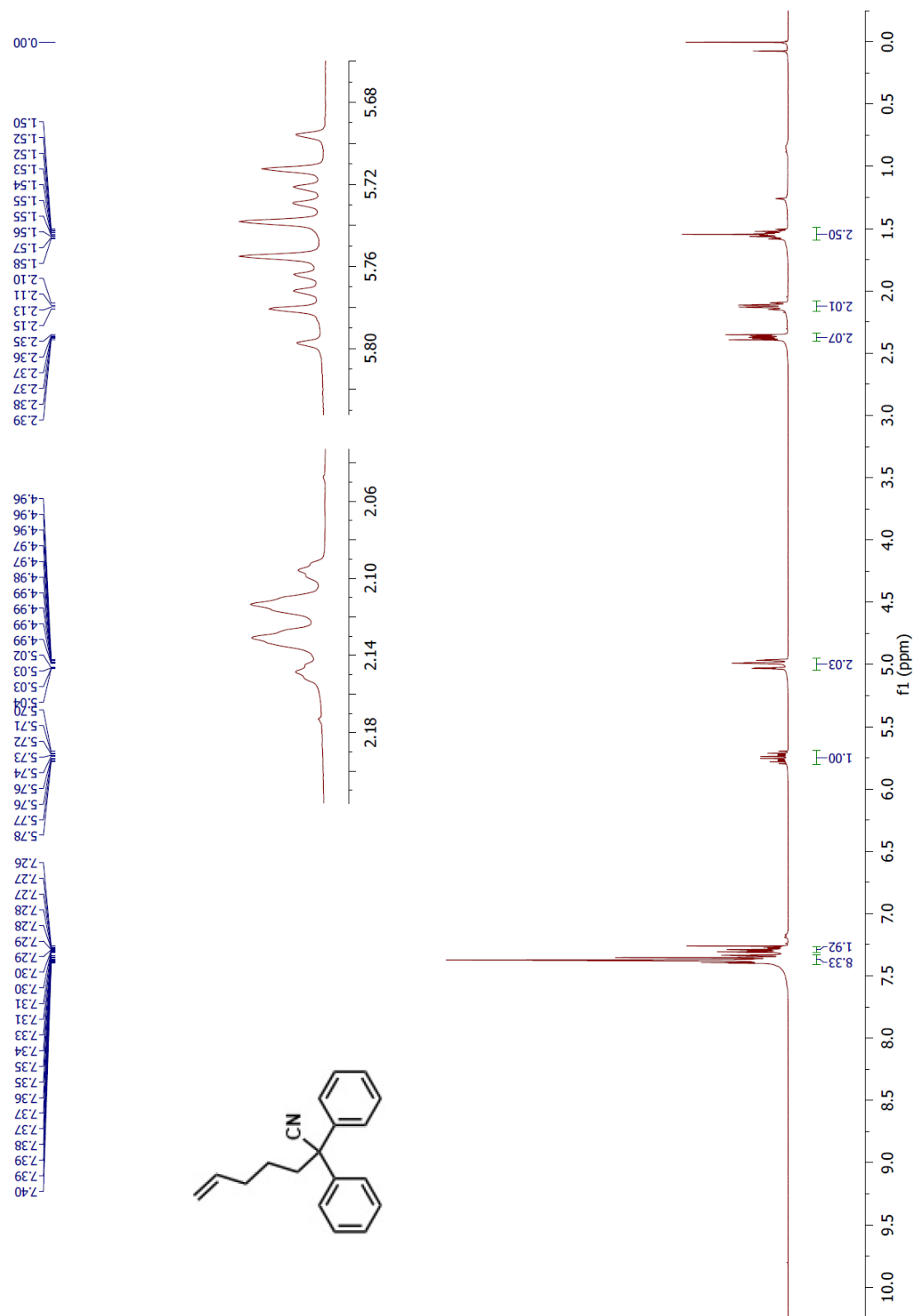


Figure 24: ^1H -NMR spectrum of **17** in CDCl_3 .

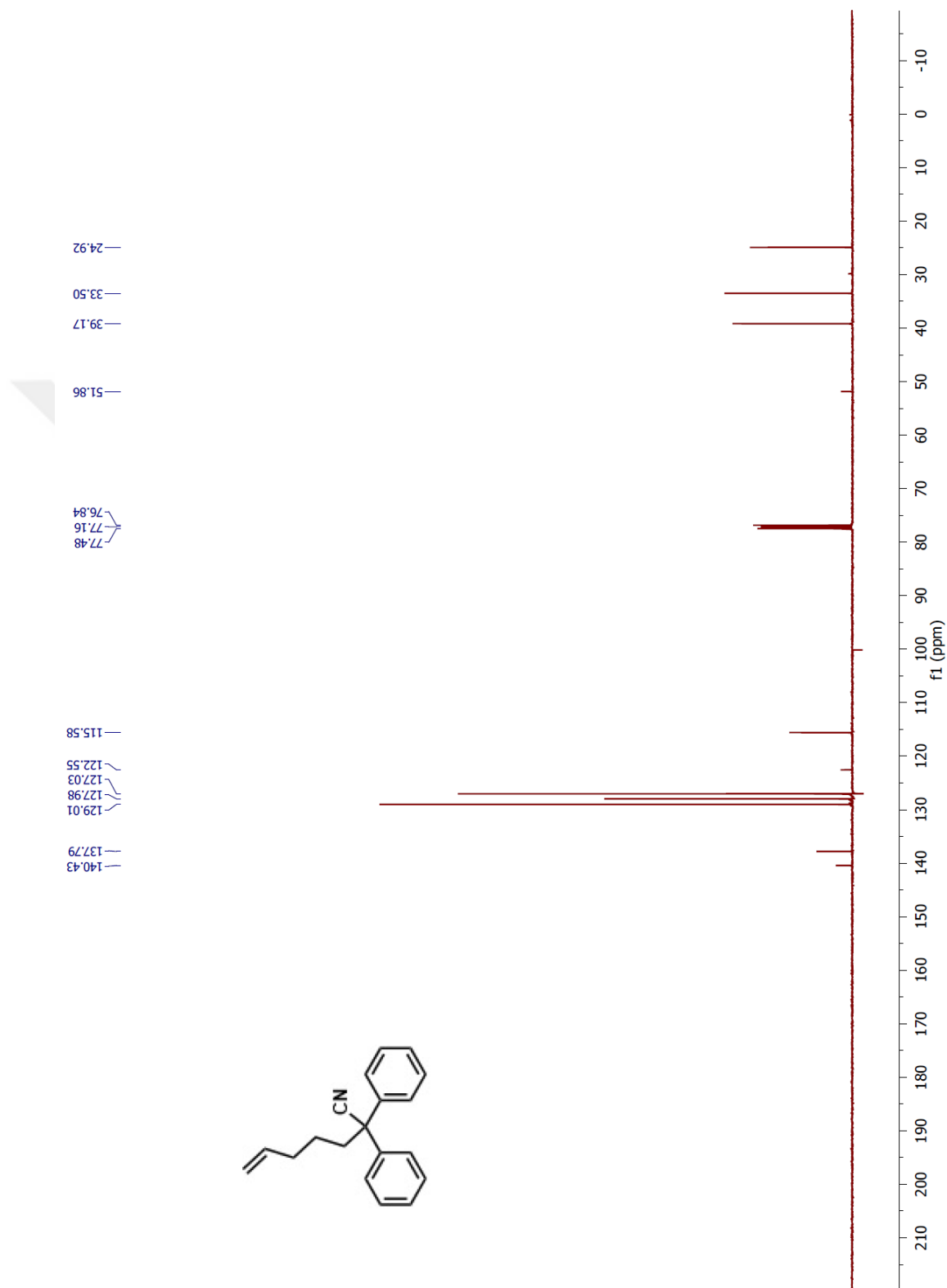


Figure 25: ^{13}C -NMR spectrum of **17** in CDCl_3 .

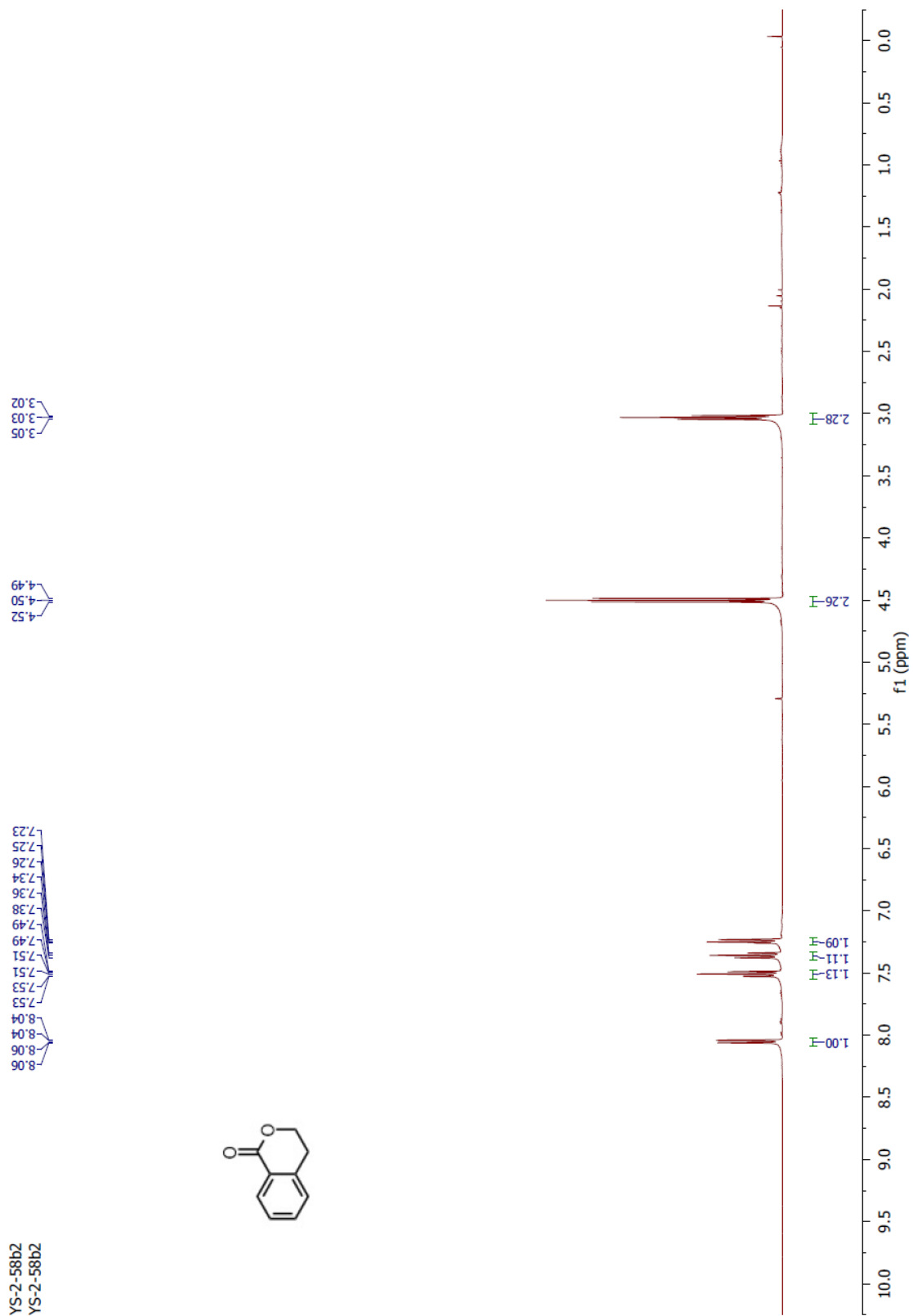


Figure 26: ¹H-NMR spectrum of **19** in CDCl₃.

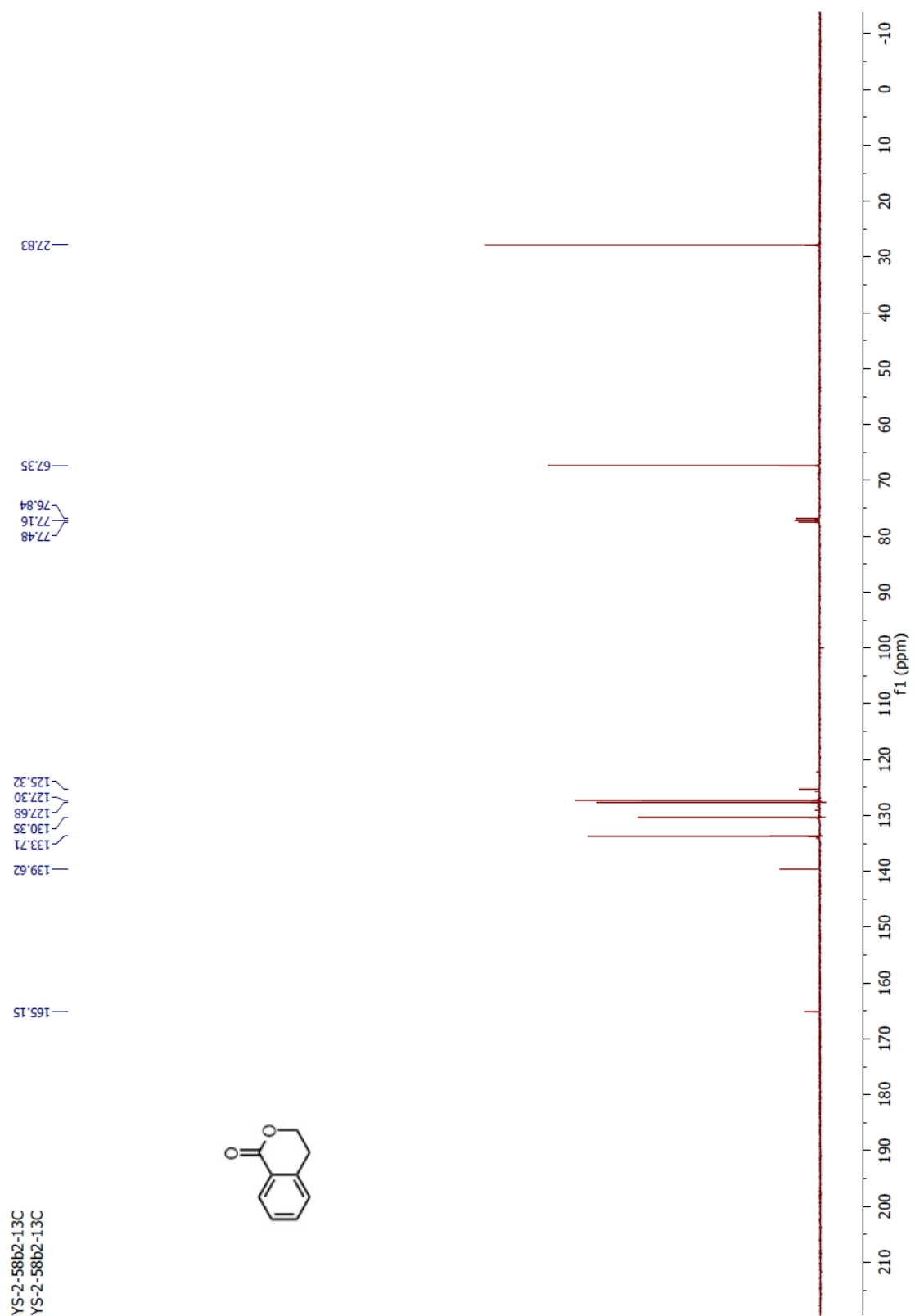


Figure 27: ^{13}C -NMR spectrum of **19** in CDCl₃.

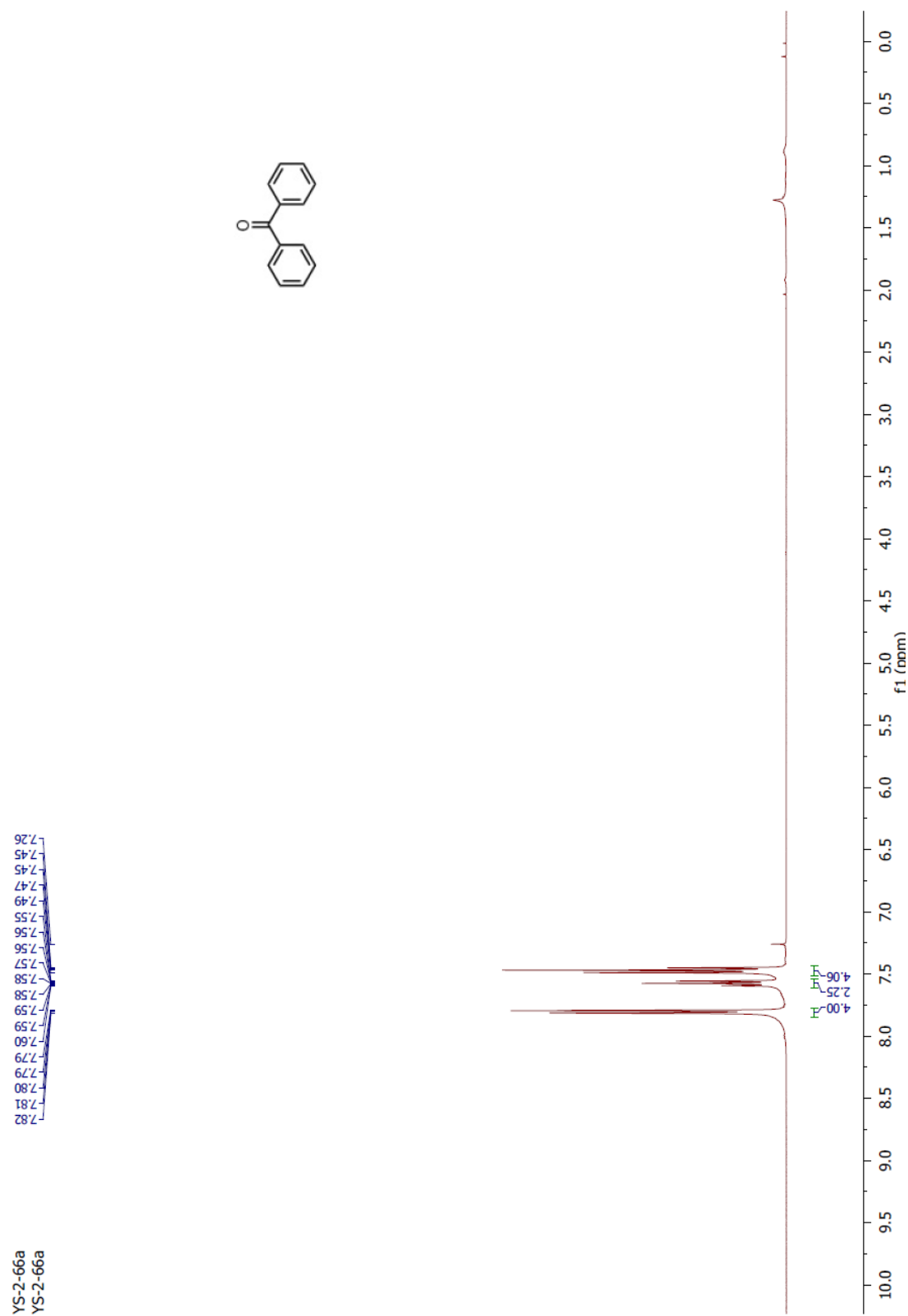


Figure 28: ¹H-NMR spectrum of **6** in CDCl₃. (synthesized from **20**)

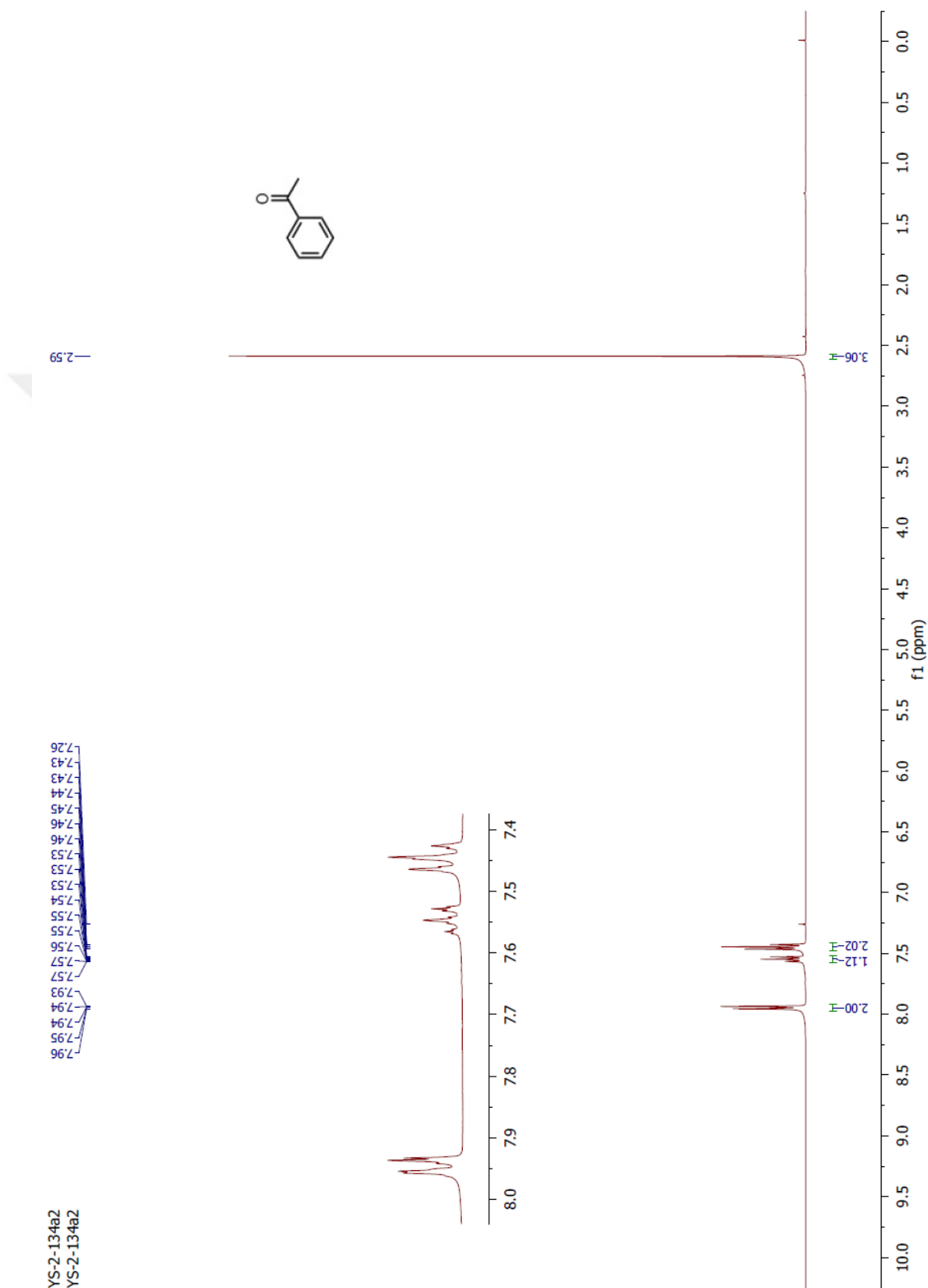


Figure 29: ^1H -NMR spectrum of **22** in CDCl_3 .

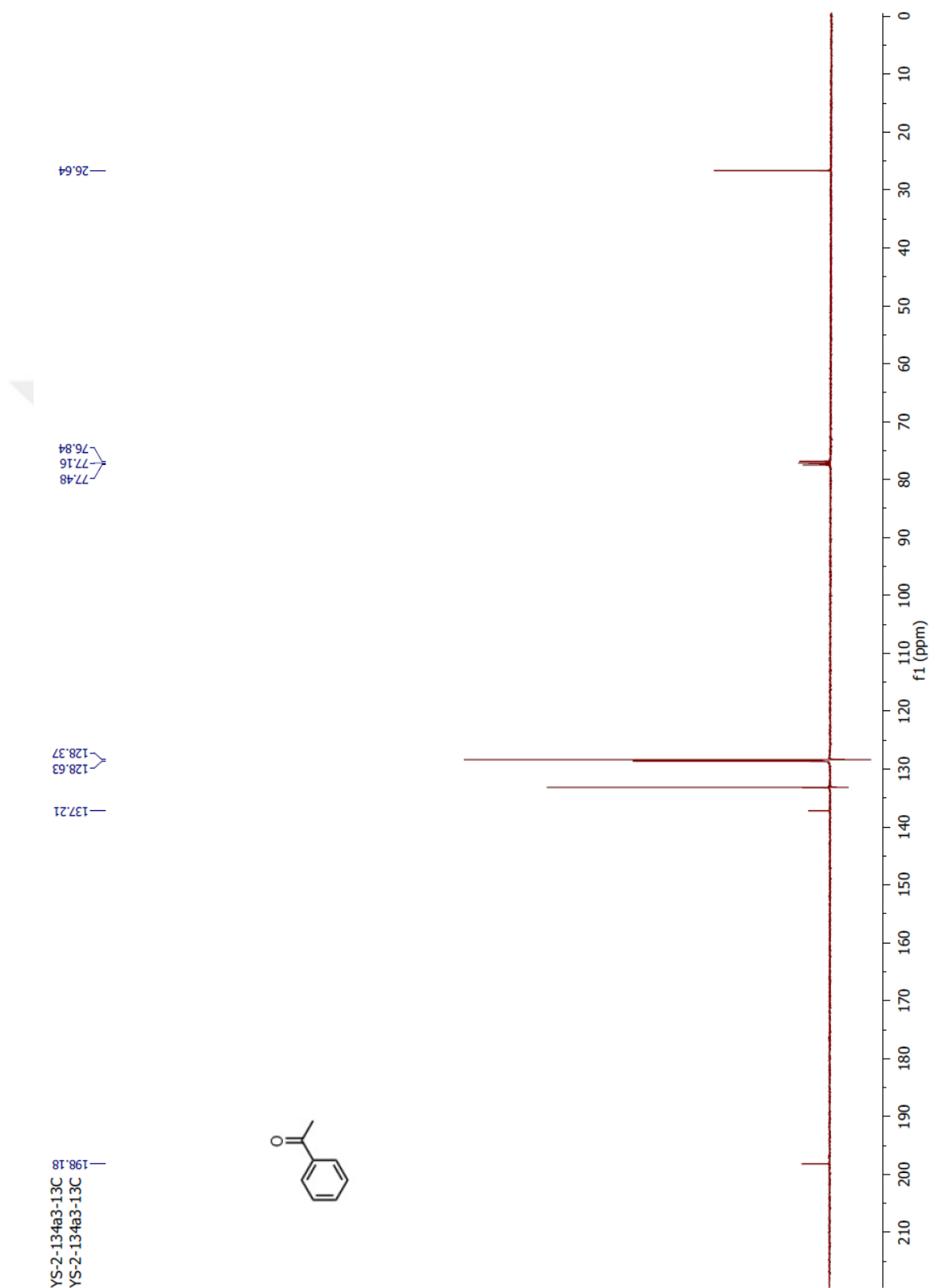


Figure 30: ^{13}C -NMR spectrum of **22** in CDCl_3 .

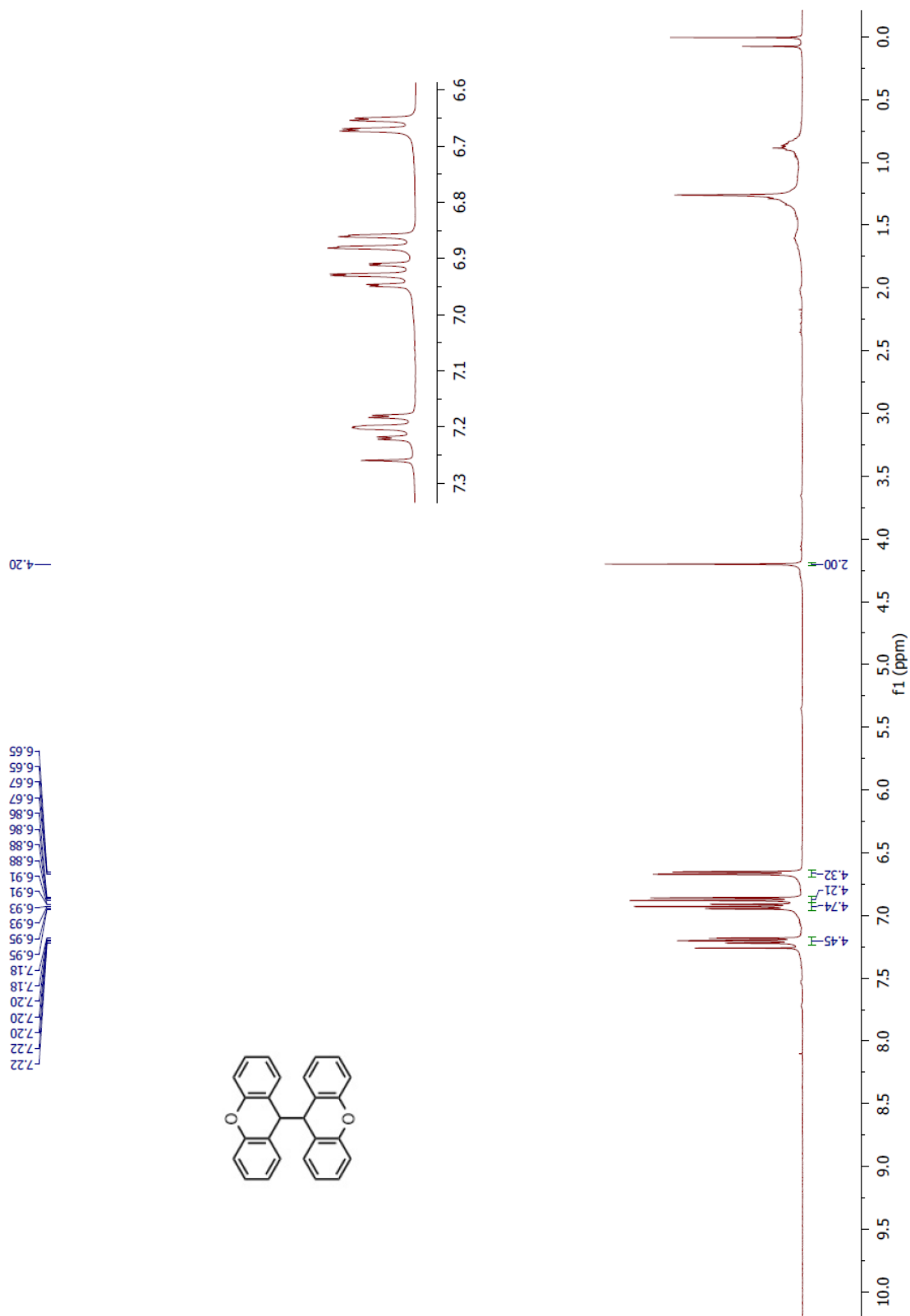
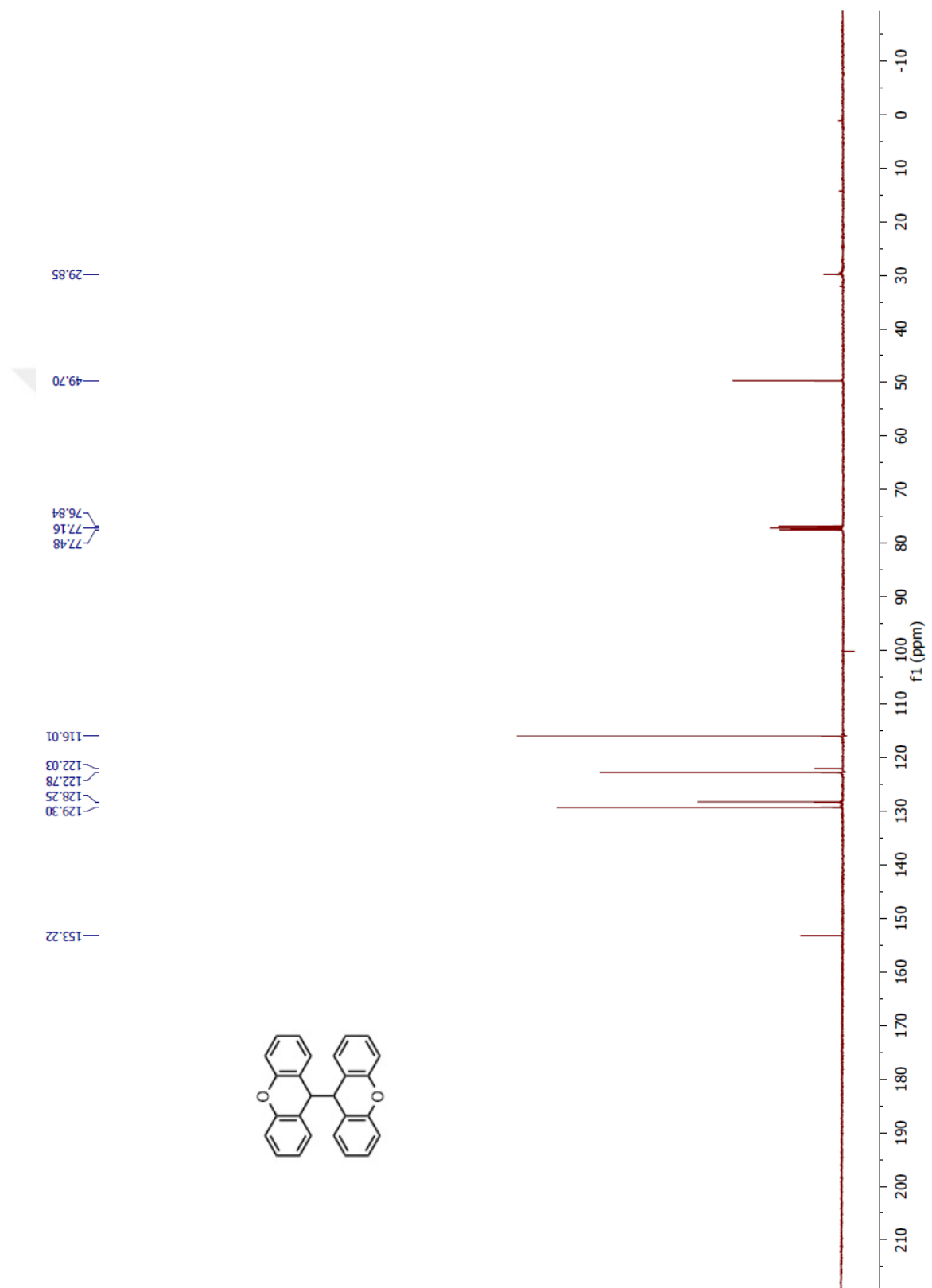


Figure 31: ^1H -NMR spectrum of **23** in CDCl_3 .



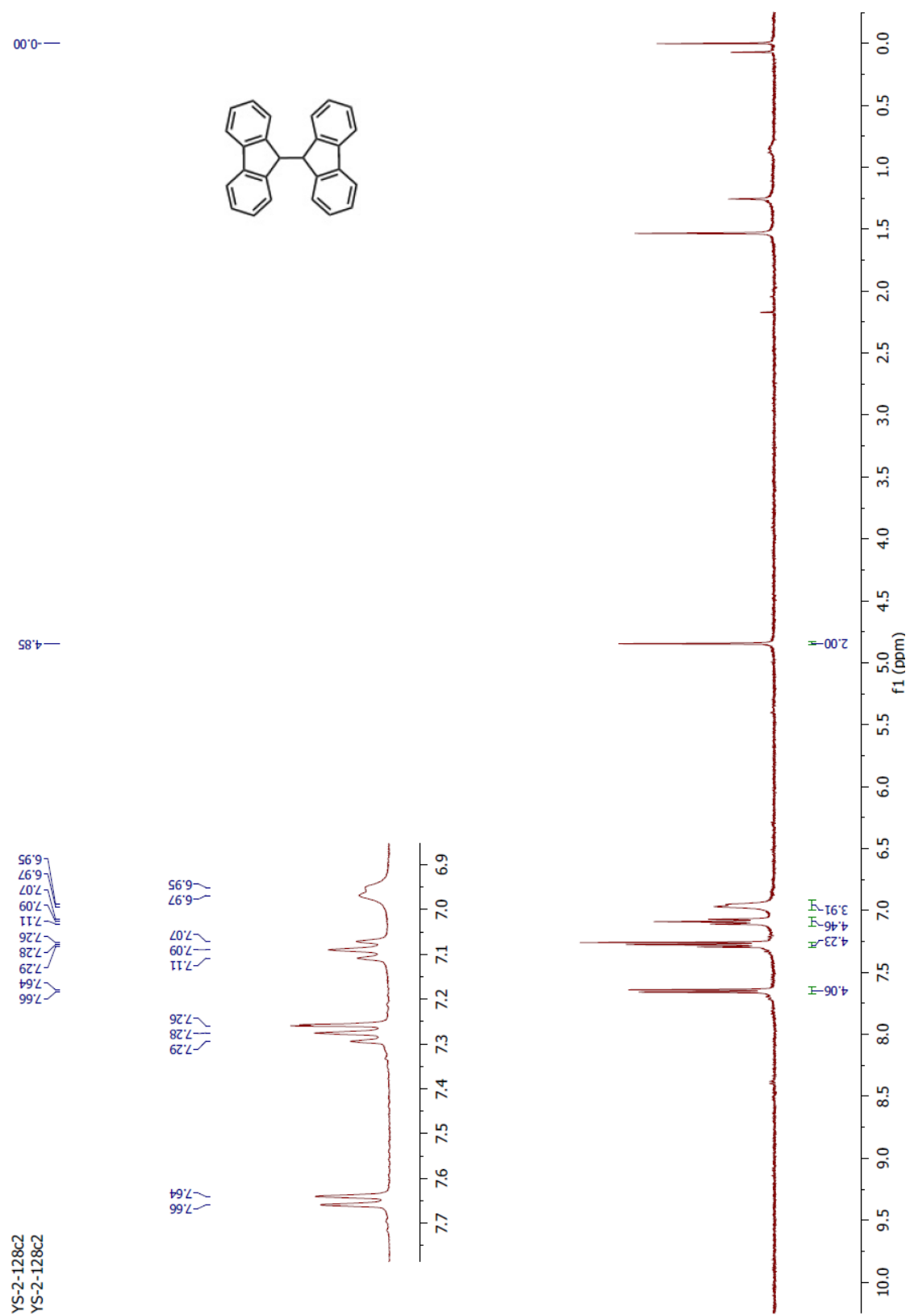


Figure 33: ¹H-NMR spectrum of 27 in CDCl₃.

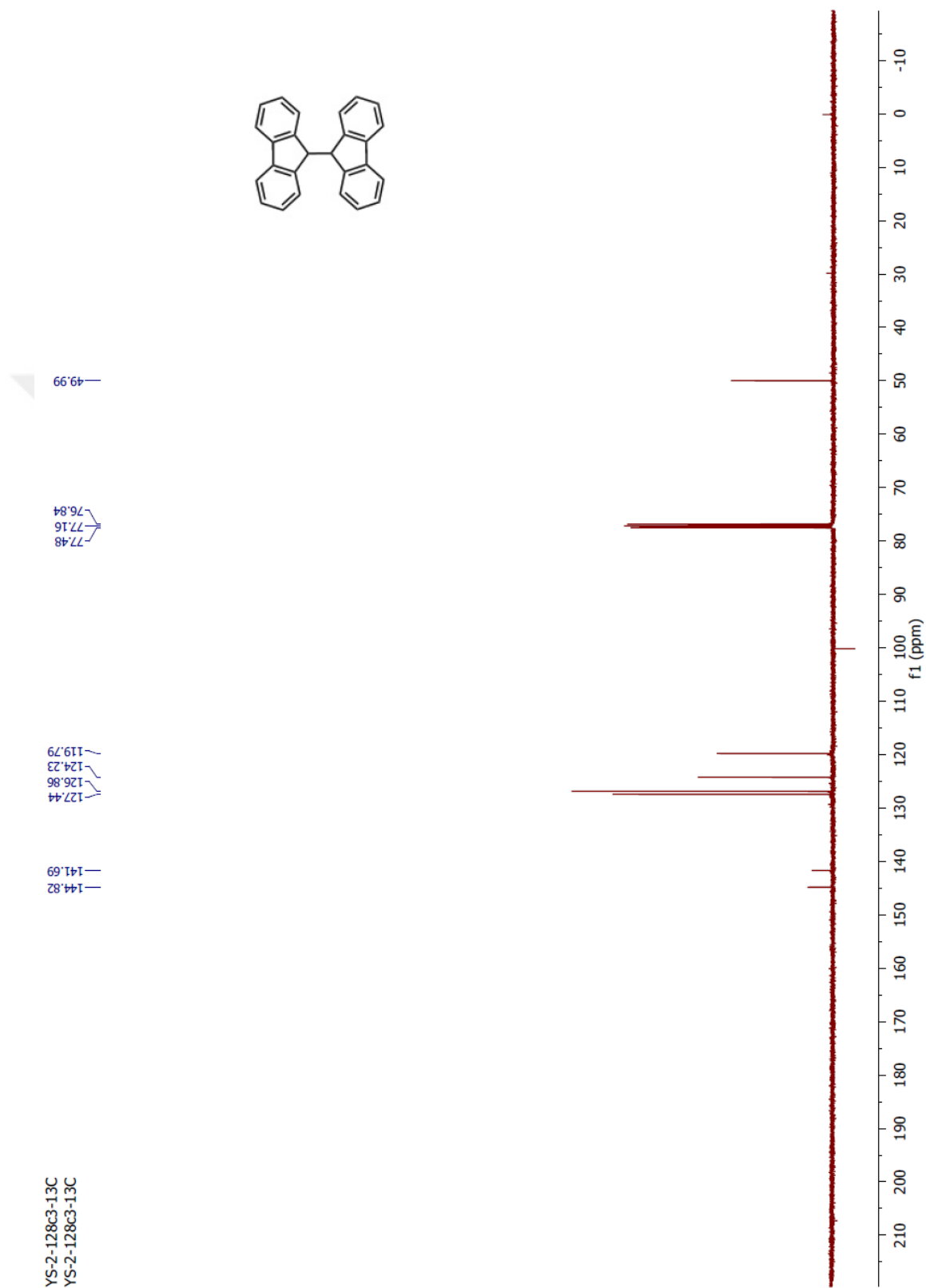


Figure 34: ^{13}C -NMR spectrum of **27** in CDCl_3 .

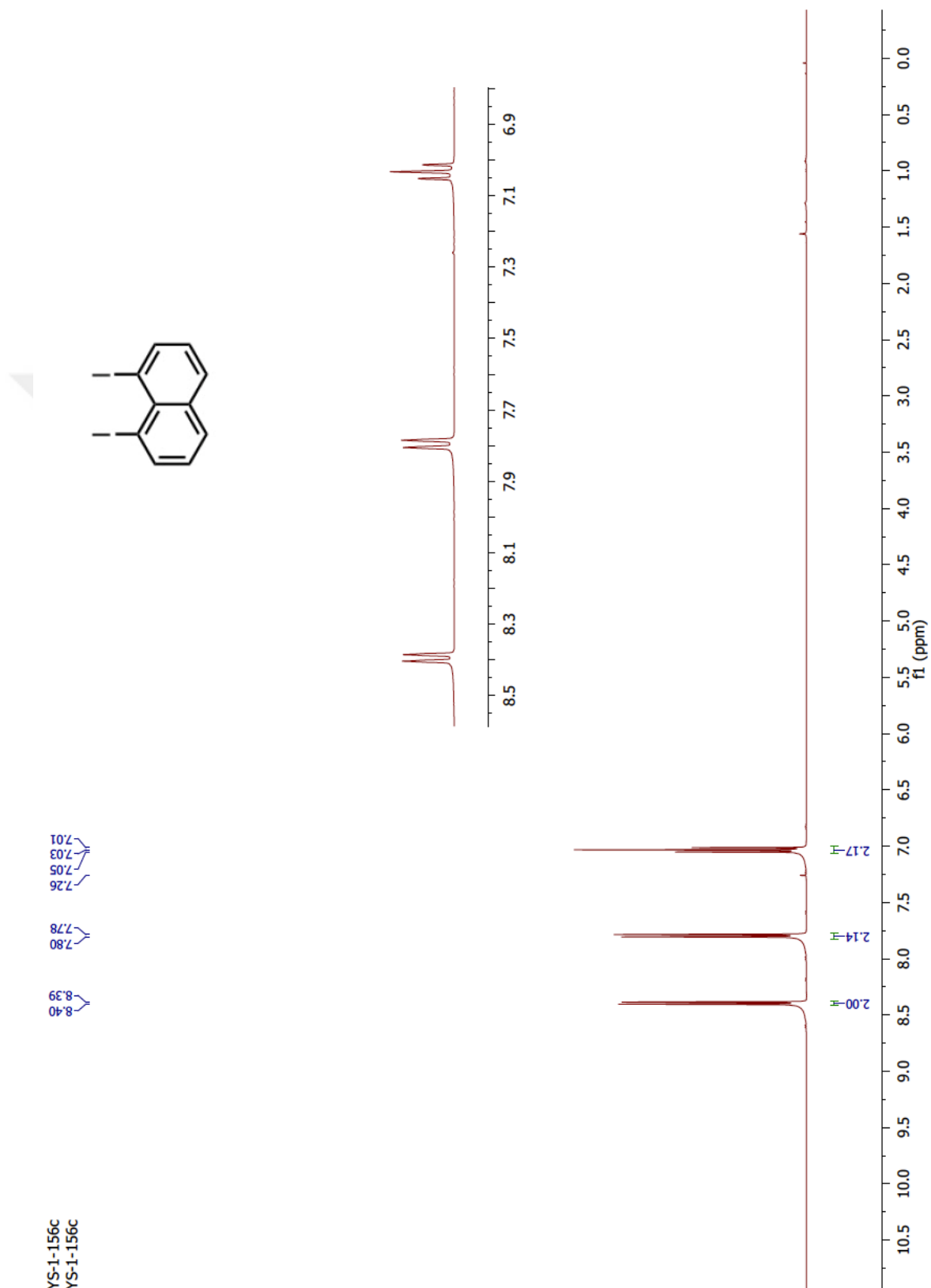


Figure 35: $^1\text{H-NMR}$ spectrum of **43** in CDCl₃.

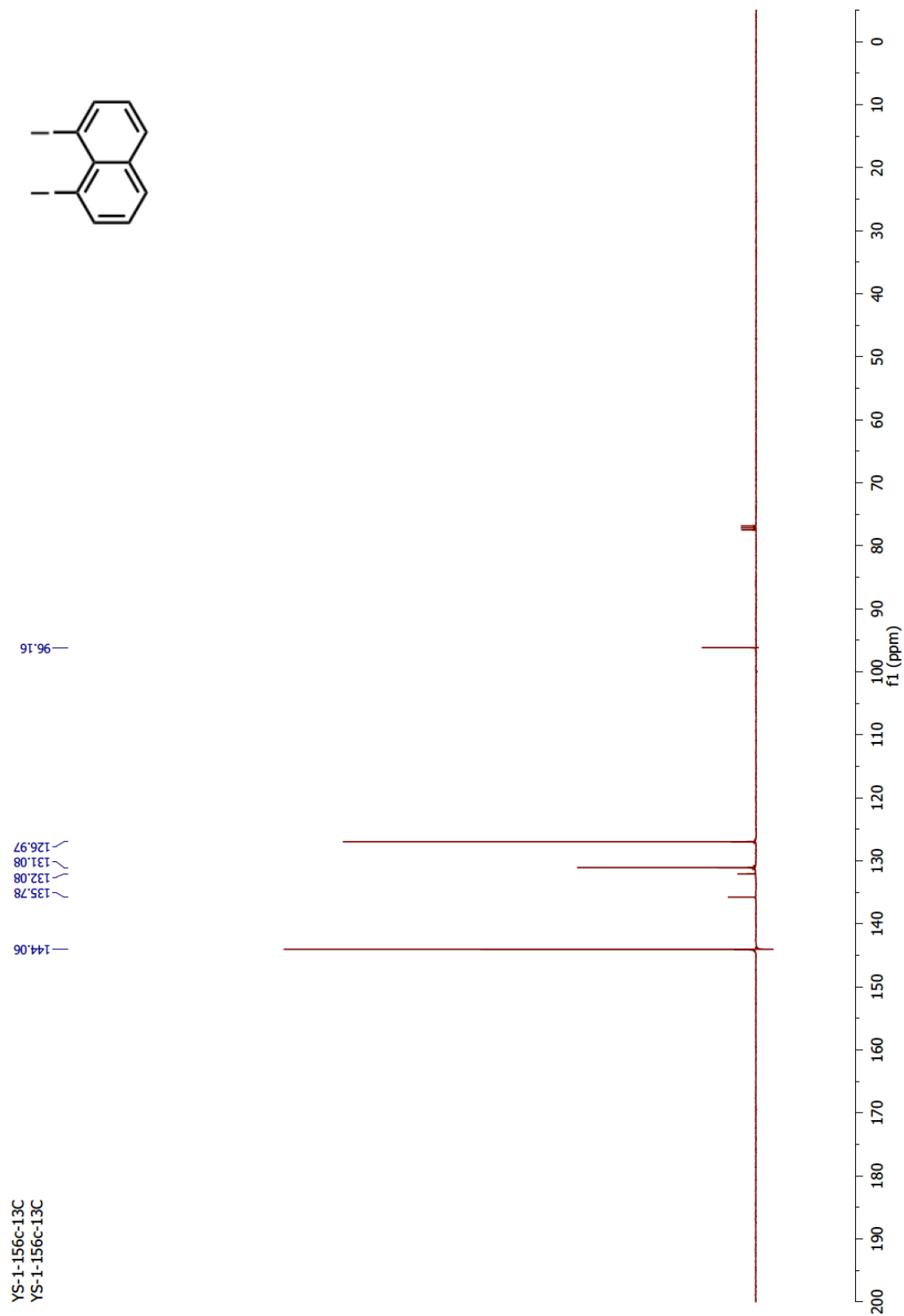


Figure 36: ^{13}C -NMR spectrum of **43** in CDCl_3 .

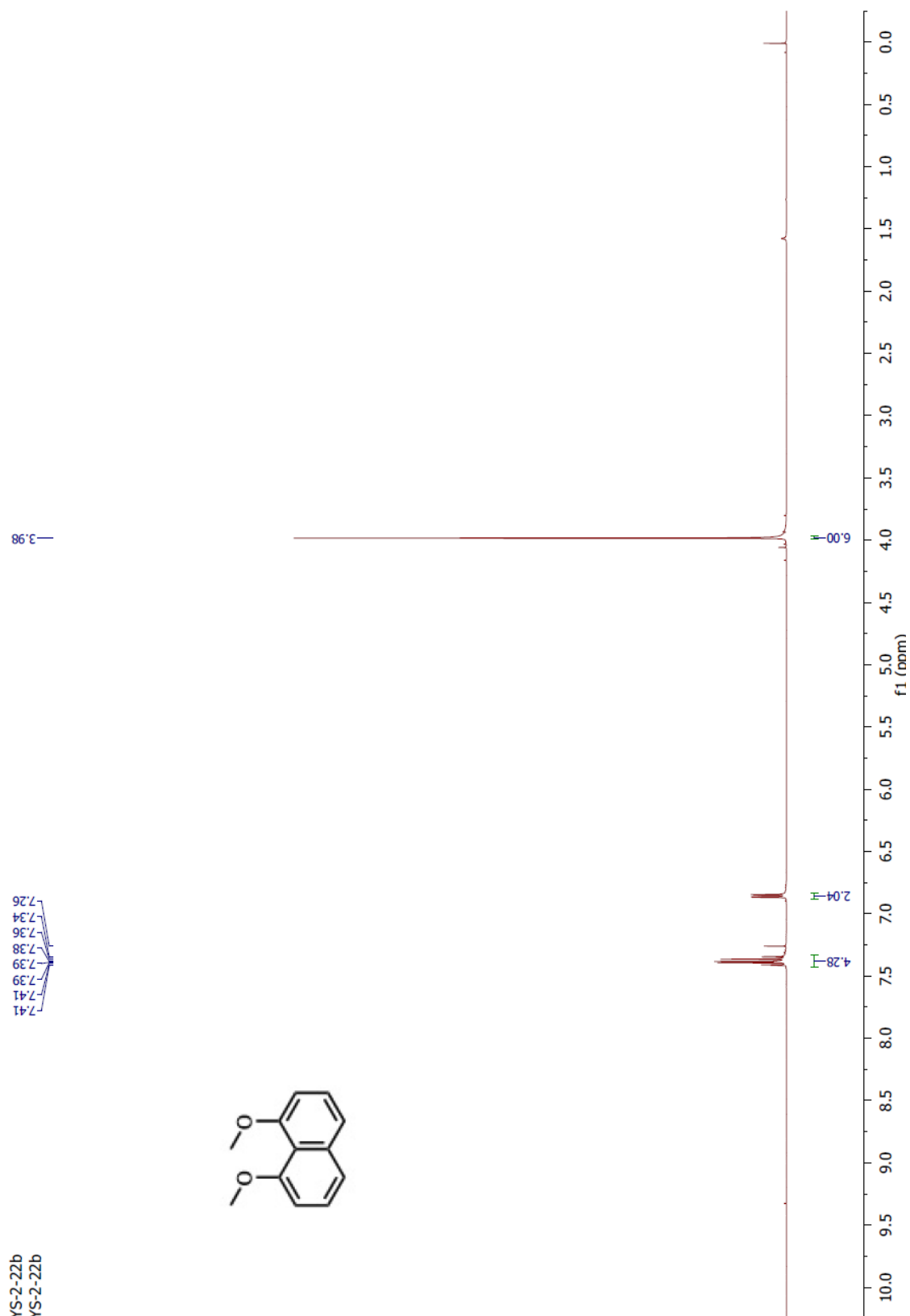


Figure 37: ^1H -NMR spectrum of **46** in CDCl_3 .

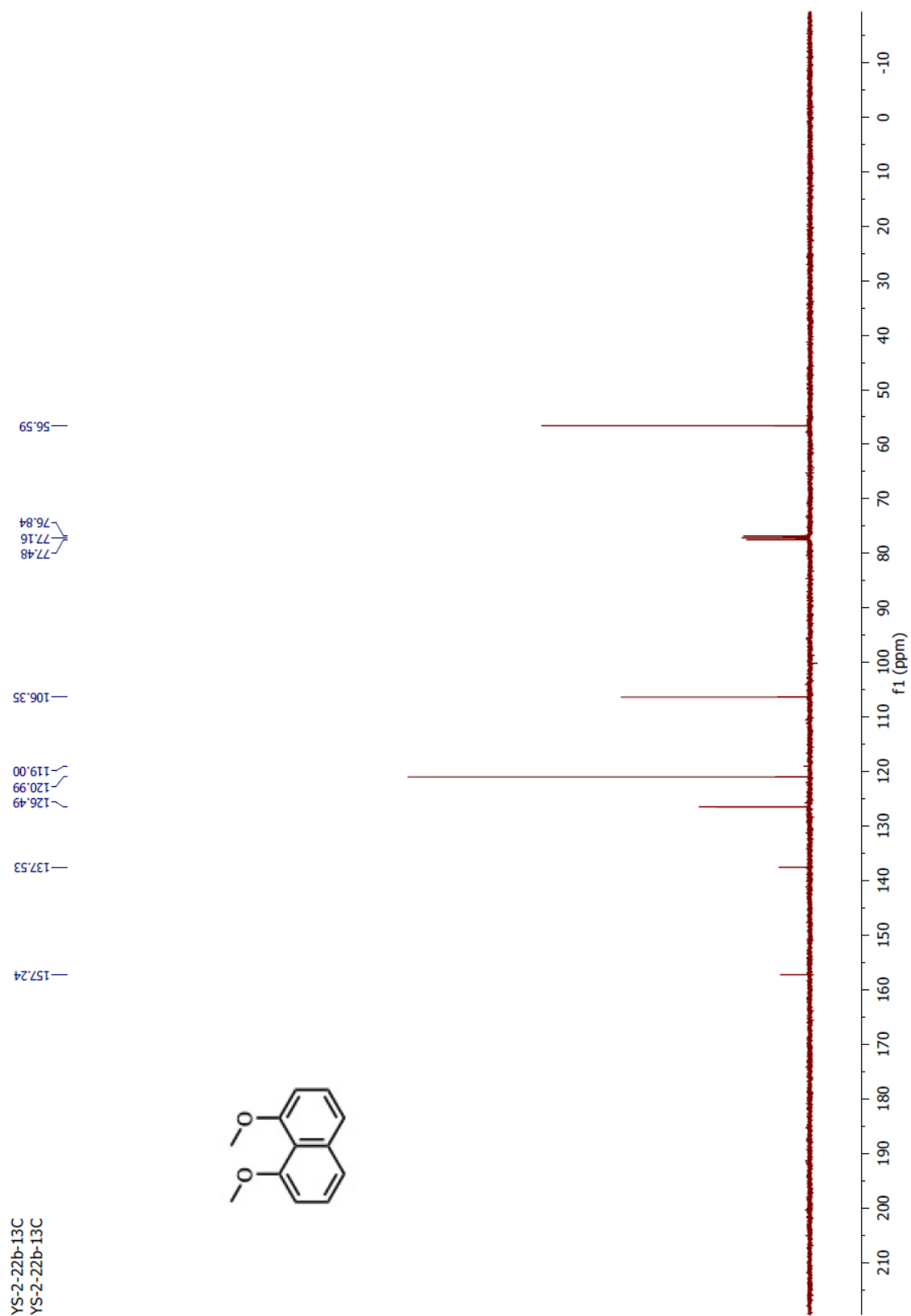


Figure 38: ^{13}C -NMR spectrum of **46** in CDCl_3 .

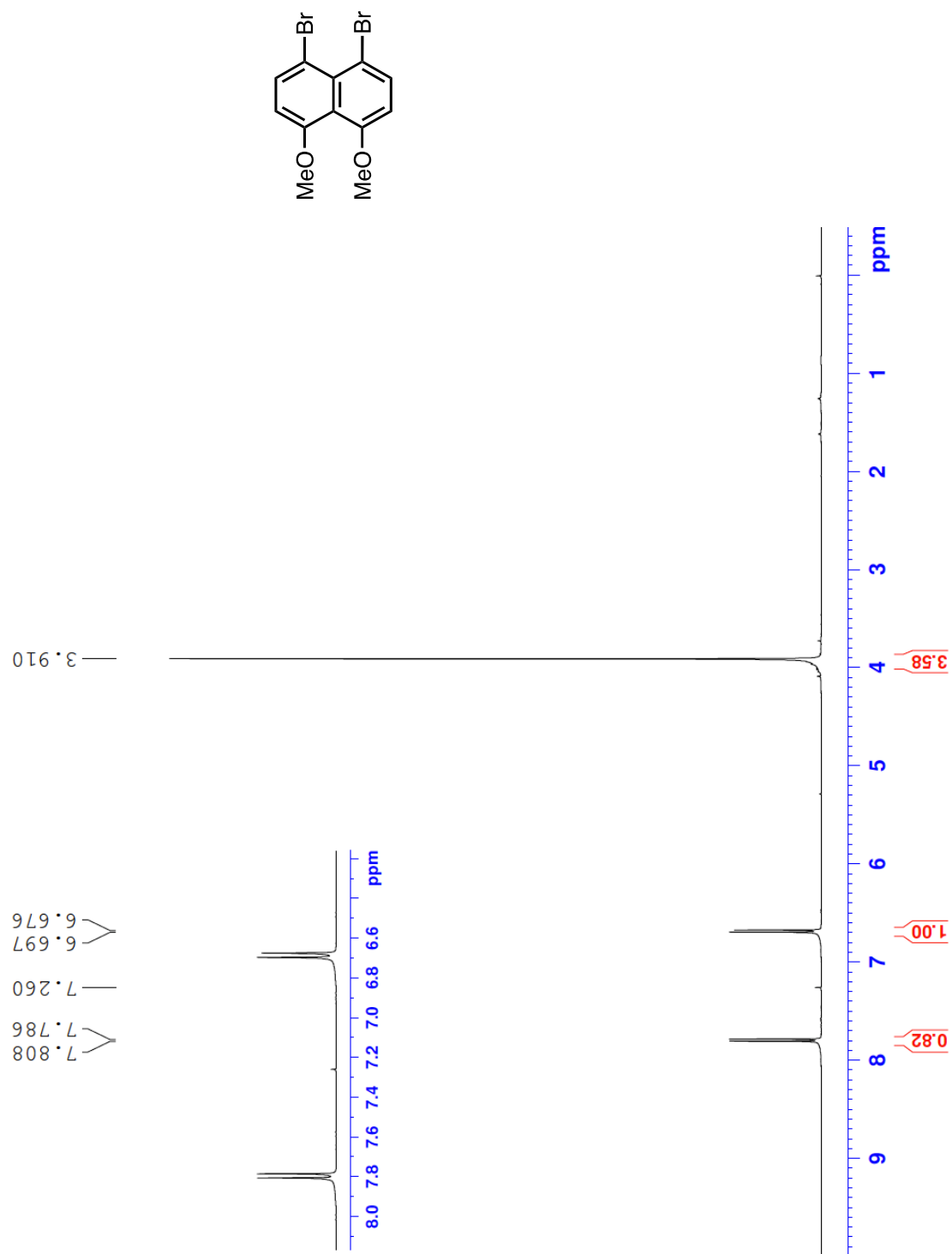


Figure 39: ^1H -NMR spectrum of **47** in CDCl₃.

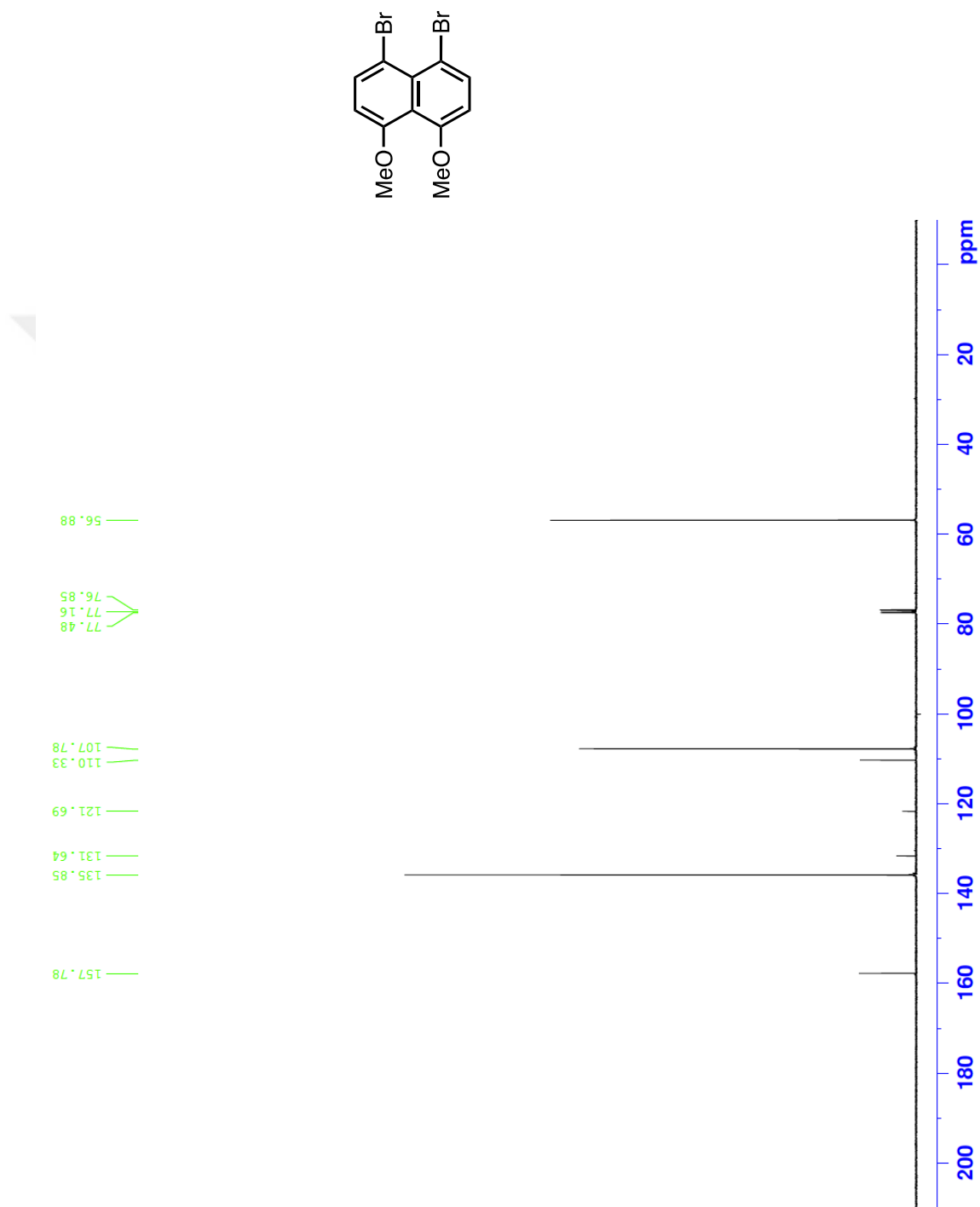


Figure 40: ^{13}C -NMR spectrum of **47** in CDCl₃.

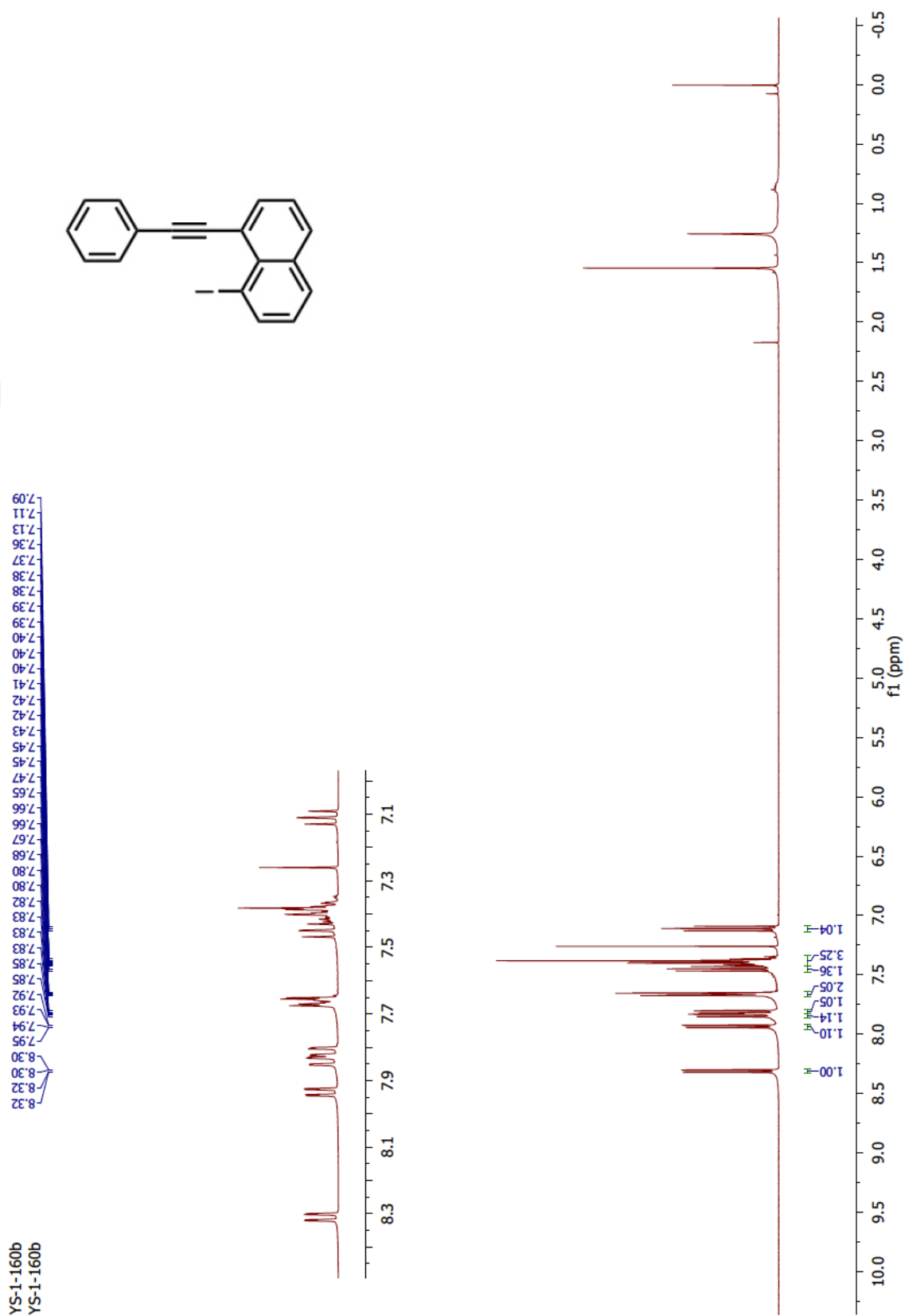


Figure 41: ¹H-NMR spectrum of **49** in CDCl₃.

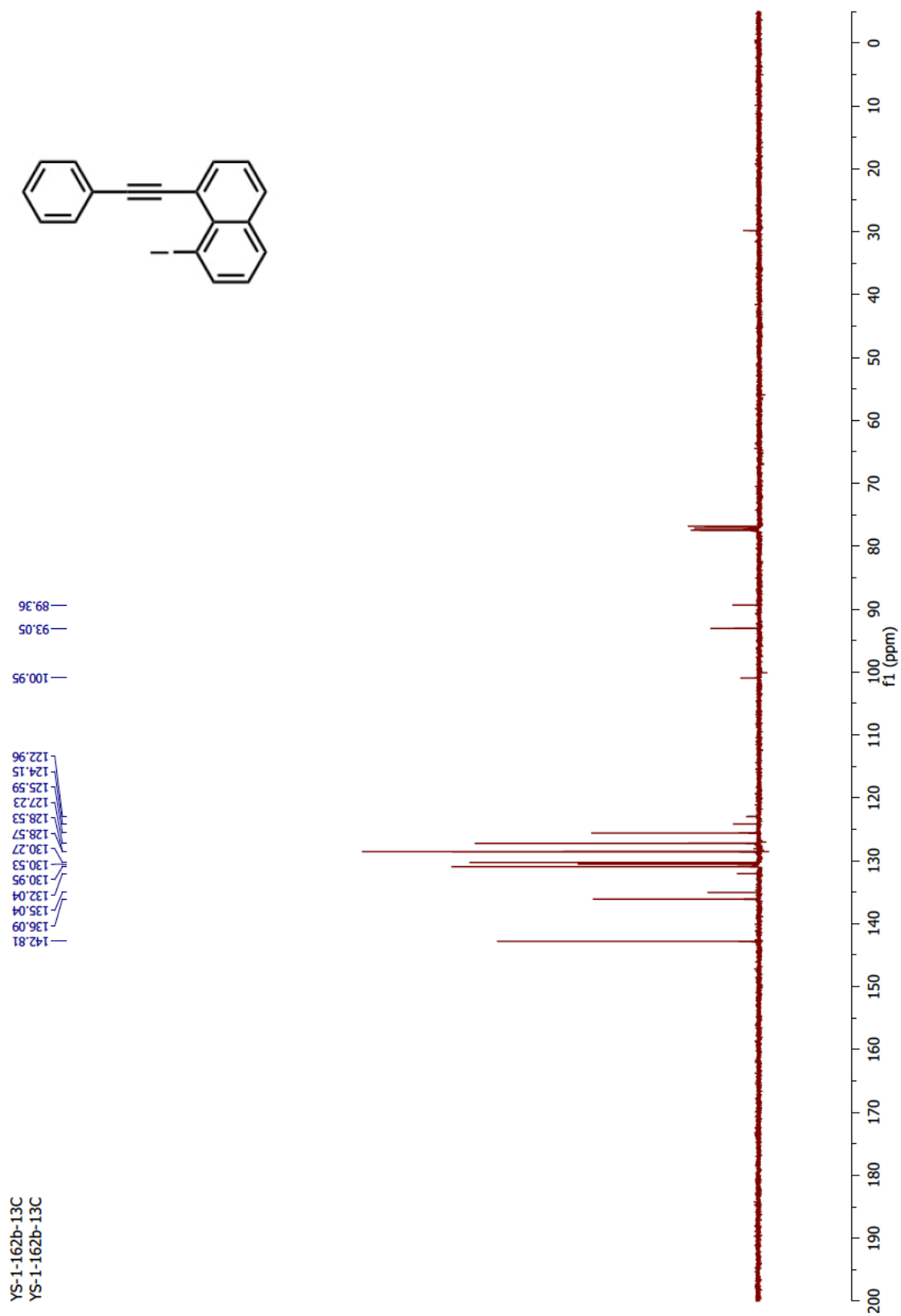


Figure 42: ^{13}C -NMR spectrum of **49** in CDCl_3 .

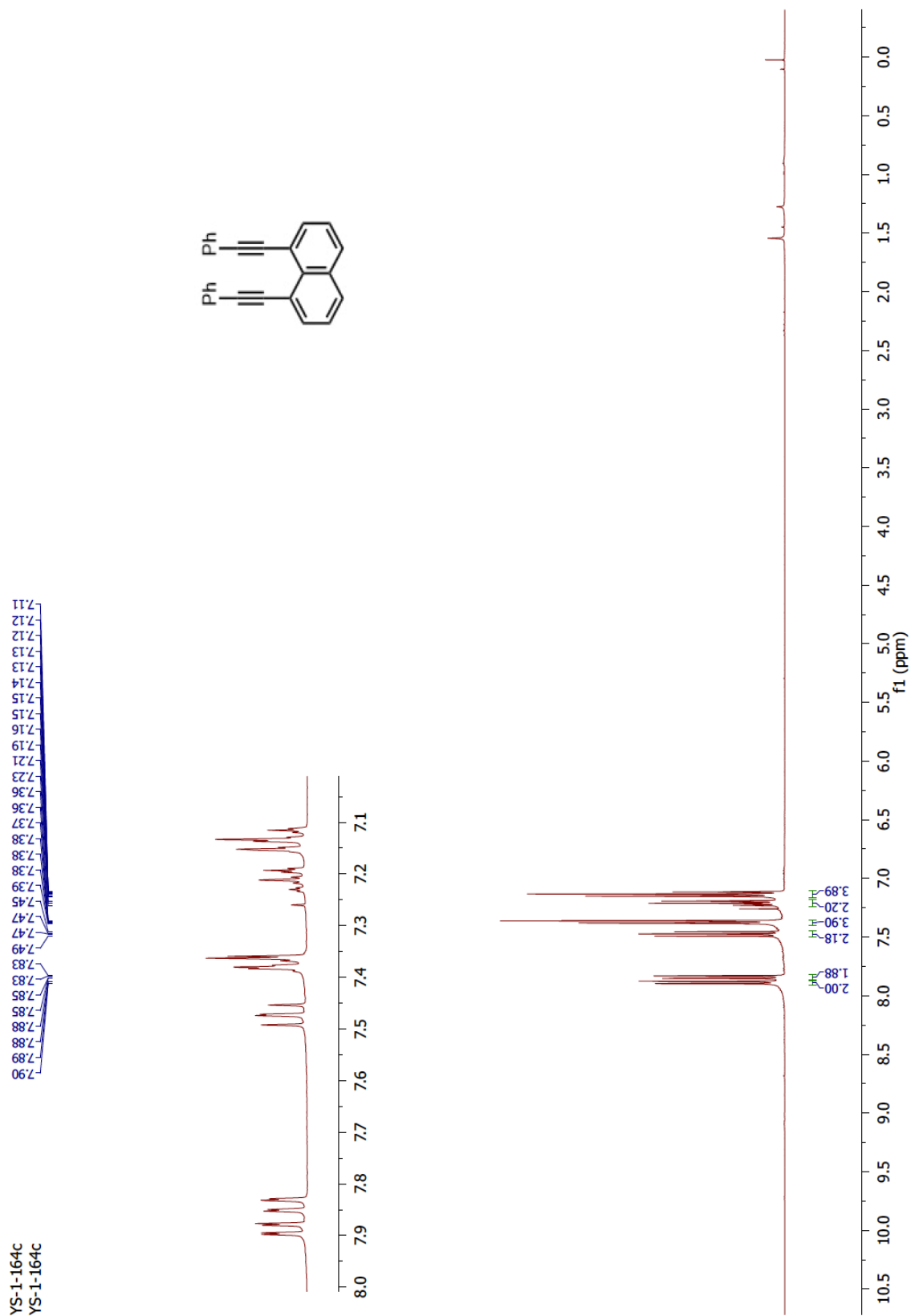


Figure 43: ¹H-NMR spectrum of **50** in CDCl₃.

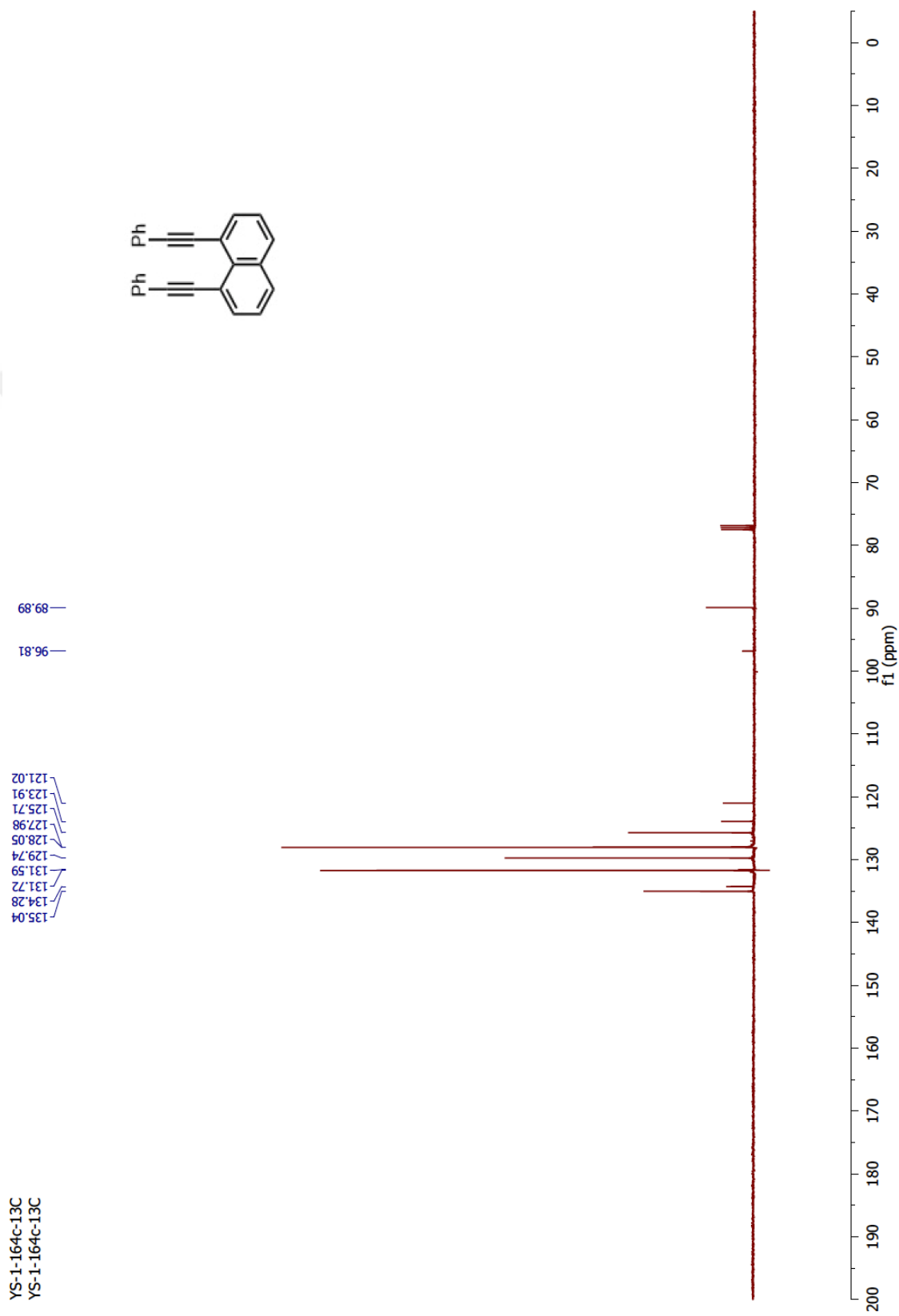


Figure 44: ^{13}C -NMR spectrum of **50** in CDCl_3 .

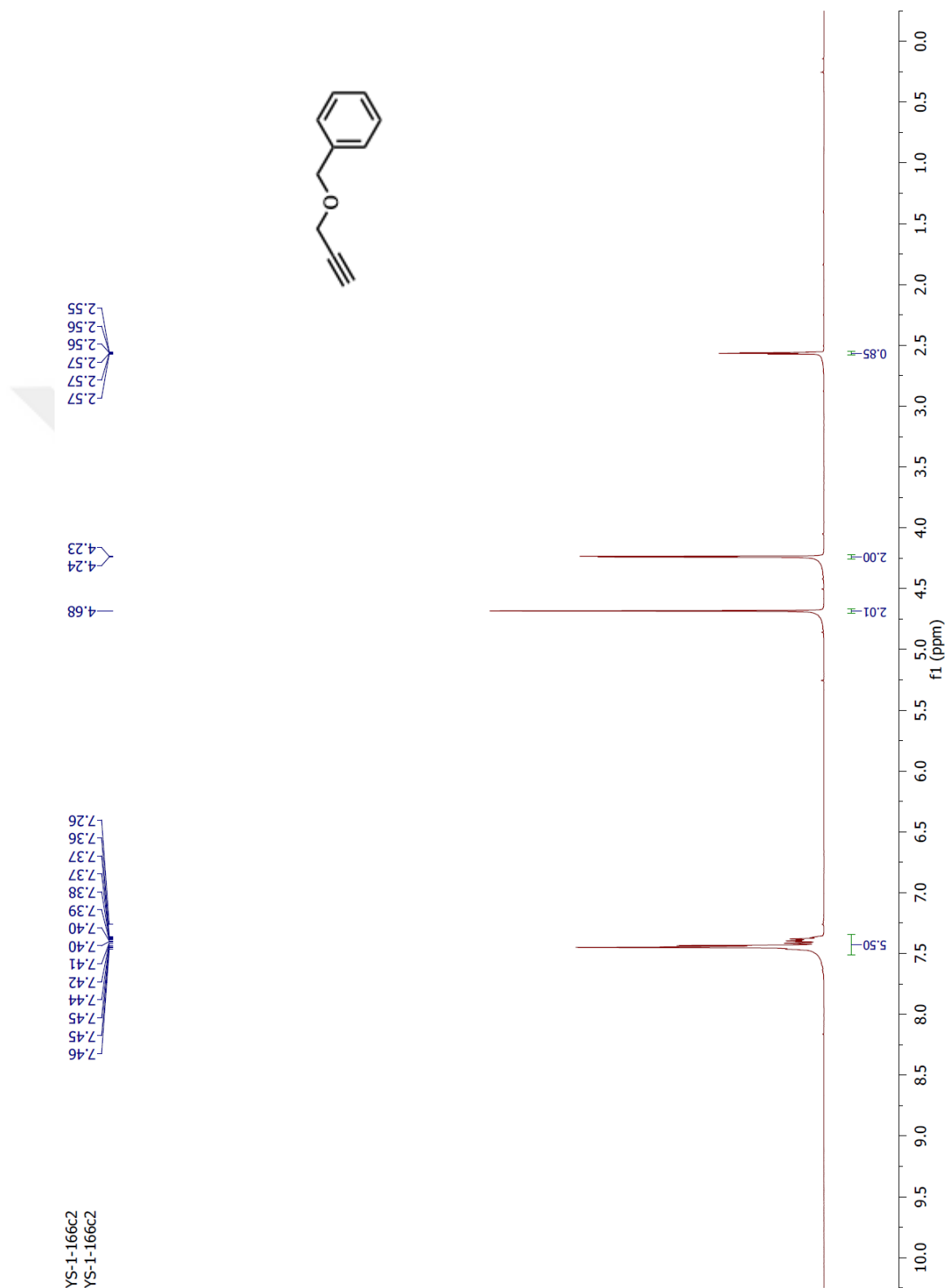


Figure 45: ¹H-NMR spectrum of **53** in CDCl₃.

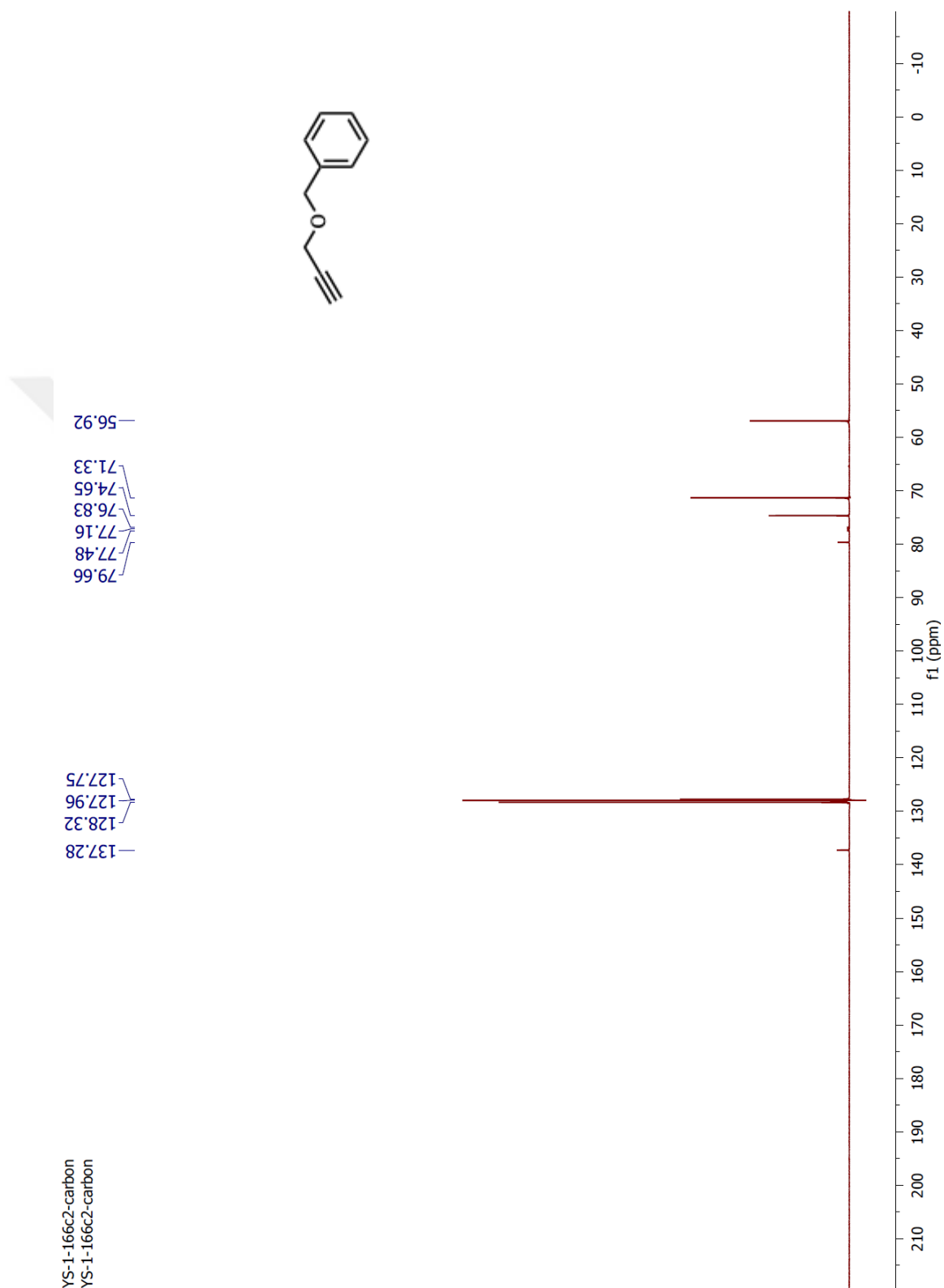


Figure 46: ¹³C-NMR spectrum of **53** in CDCl₃.

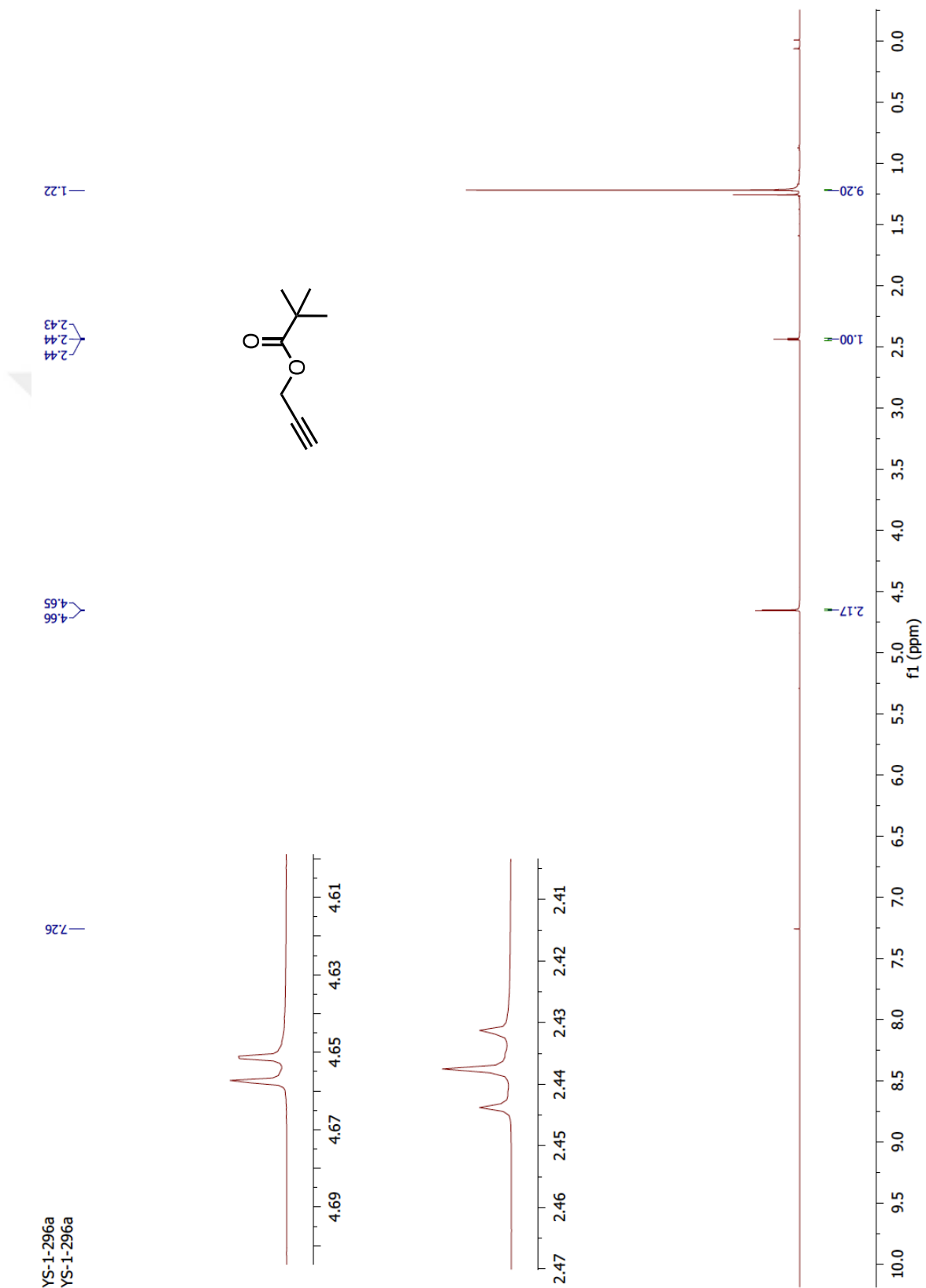


Figure 47: ¹H-NMR spectrum of **54** in CDCl₃.

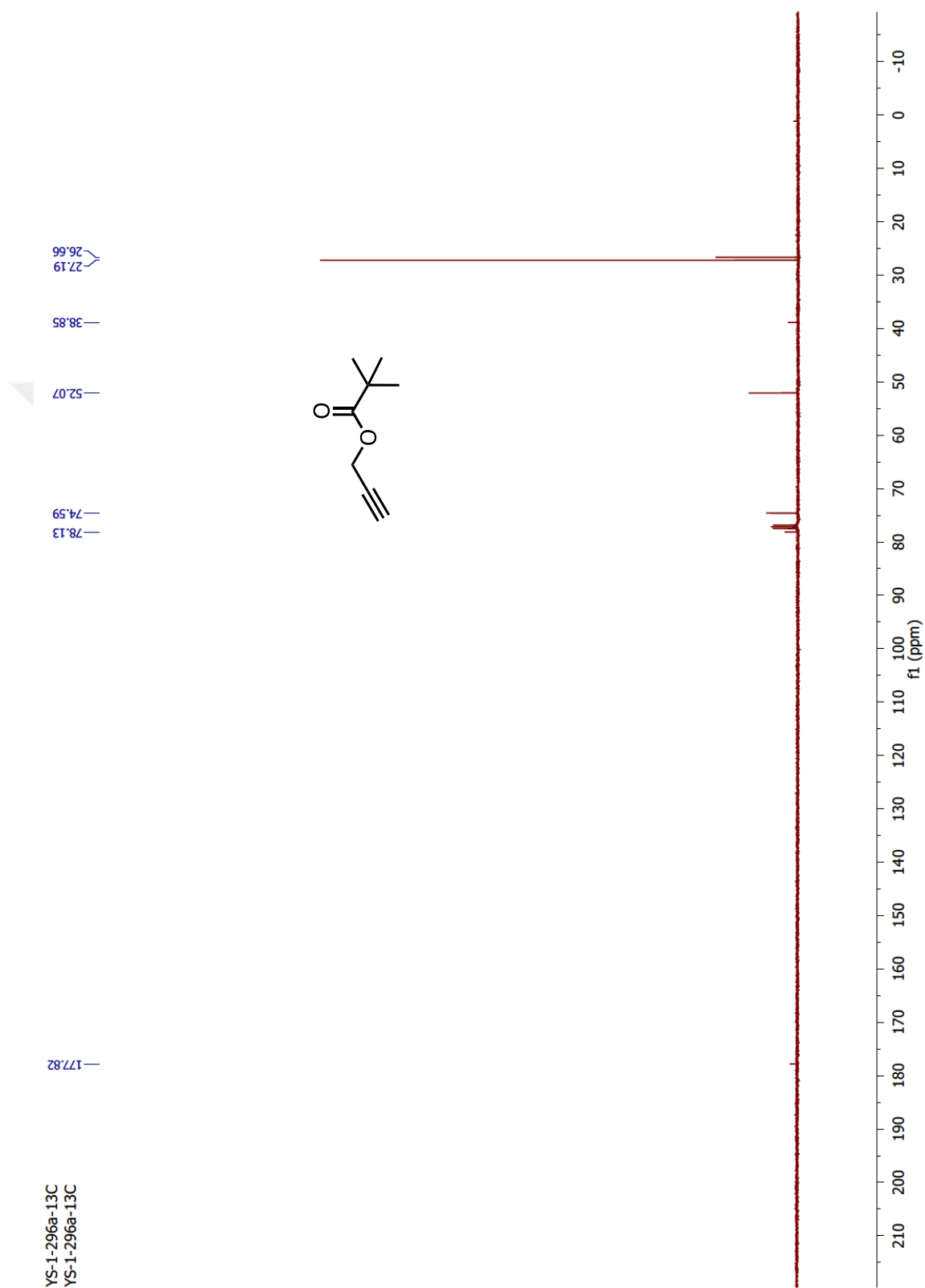


Figure 48: ¹³C-NMR spectrum of **54** in CDCl₃.

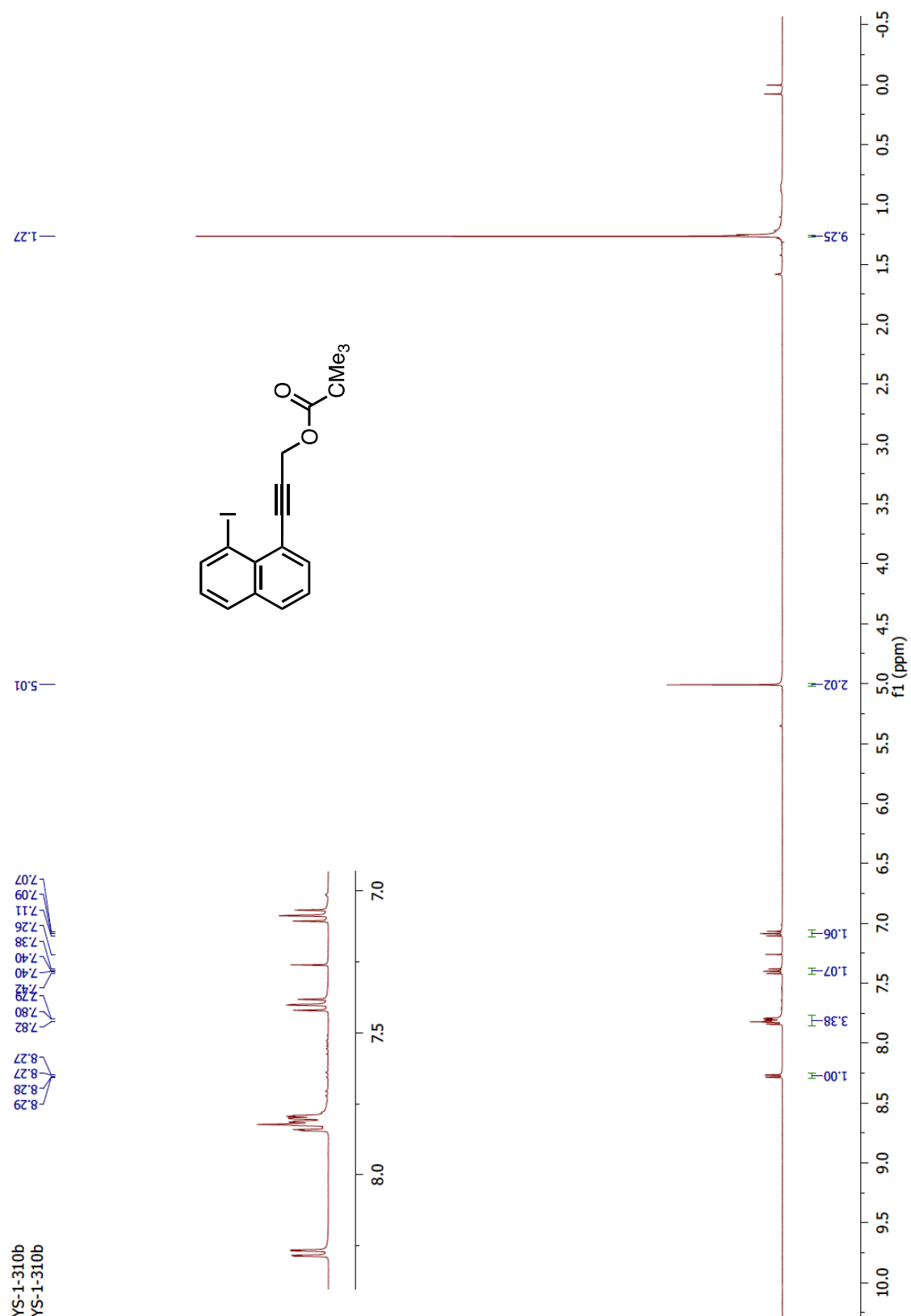


Figure 49: ¹H-NMR spectrum of **58** in CDCl₃.

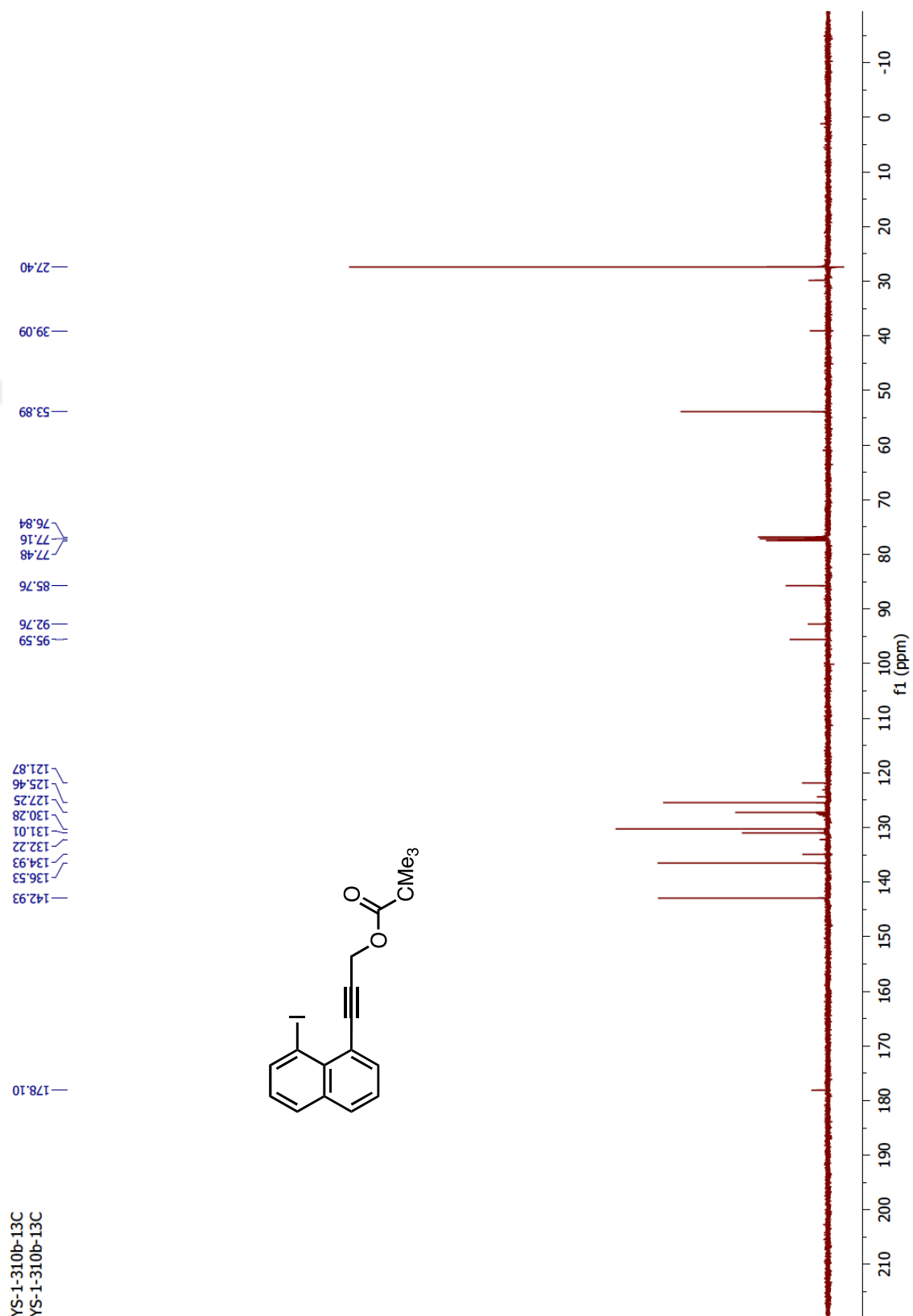


Figure 50: ¹³C-NMR spectrum of **58** in CDCl₃.

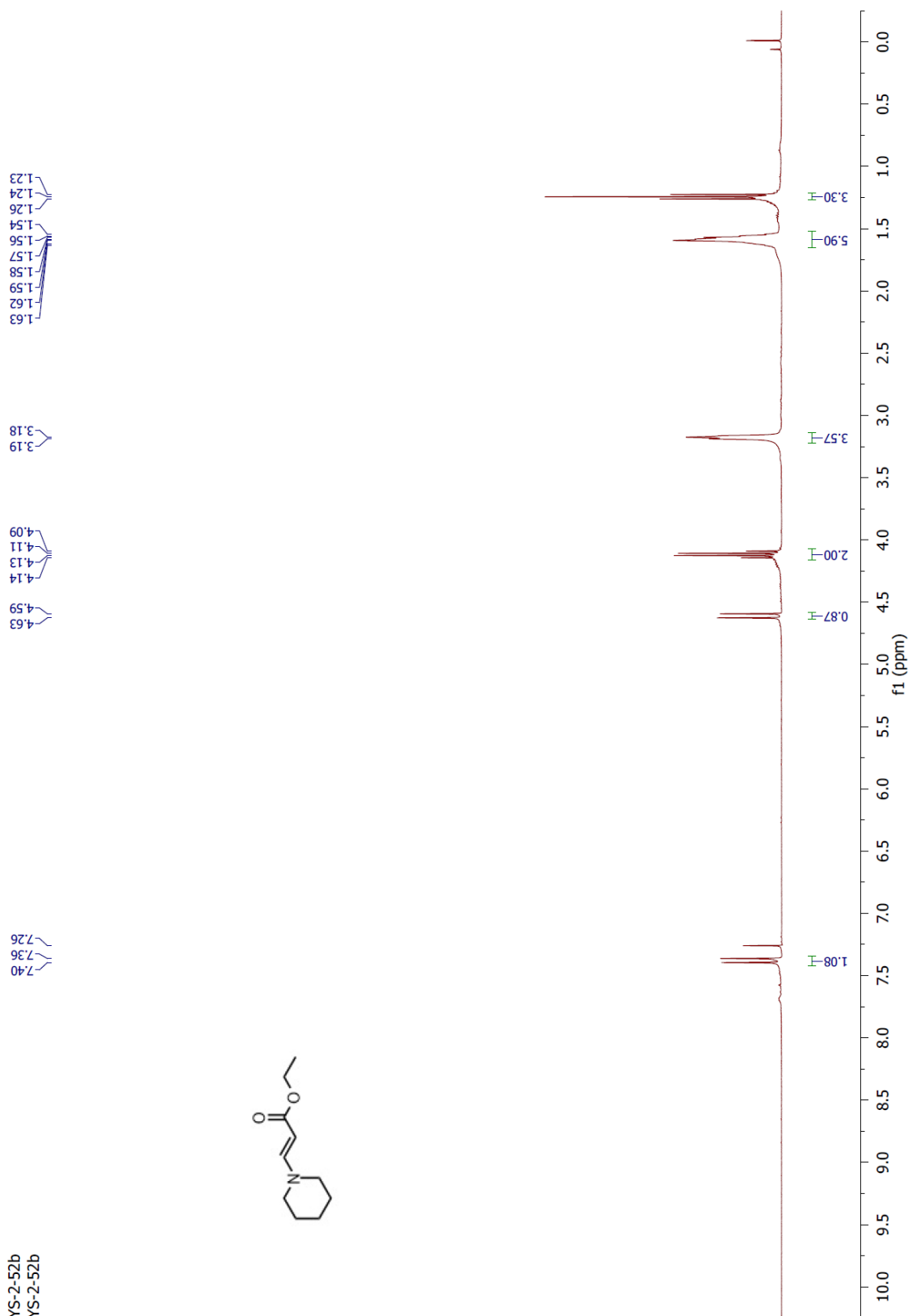


Figure 51: ¹H-NMR spectrum of **59** in CDCl₃.

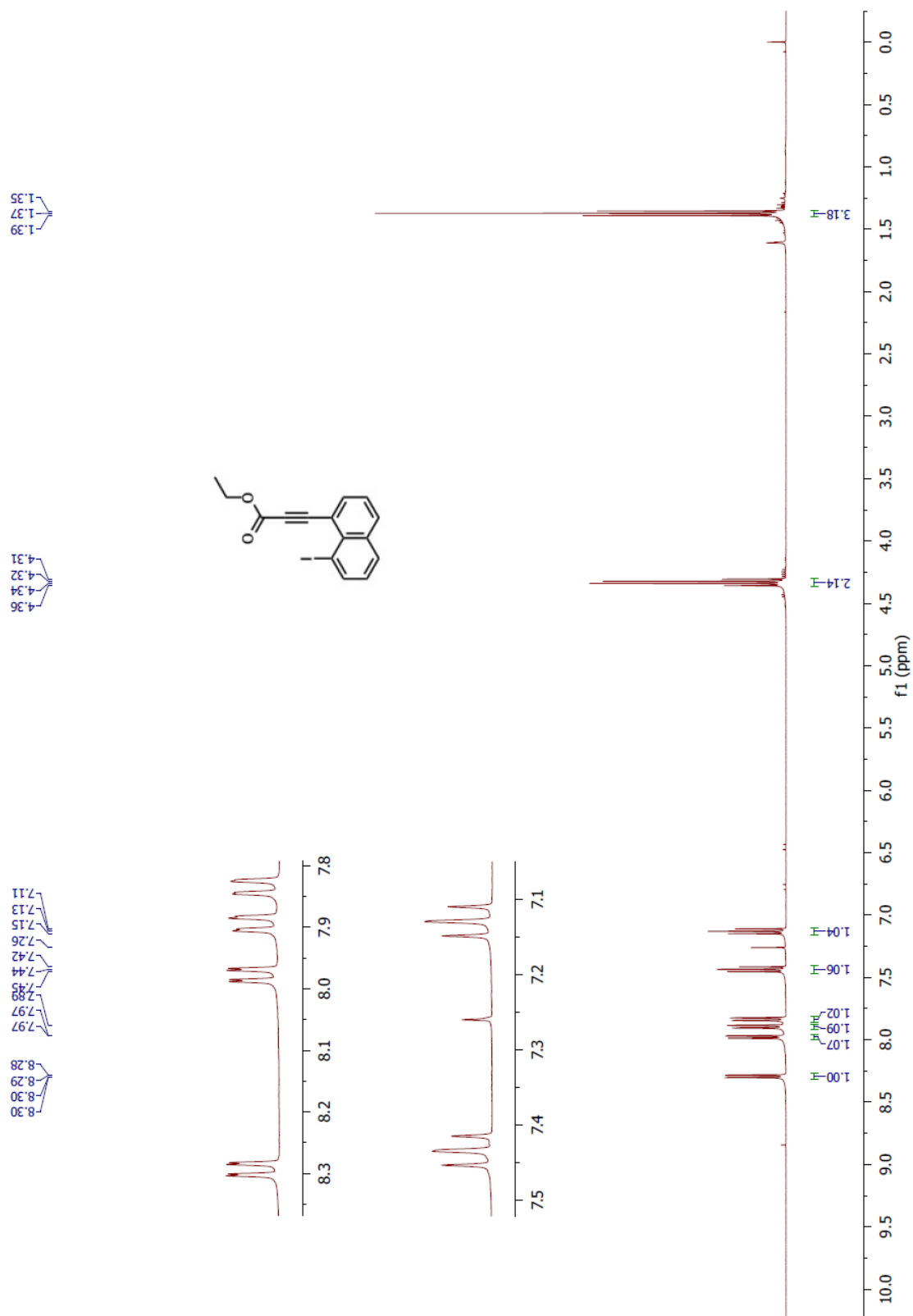


Figure 52: ¹H-NMR spectrum of **61** in CDCl₃.

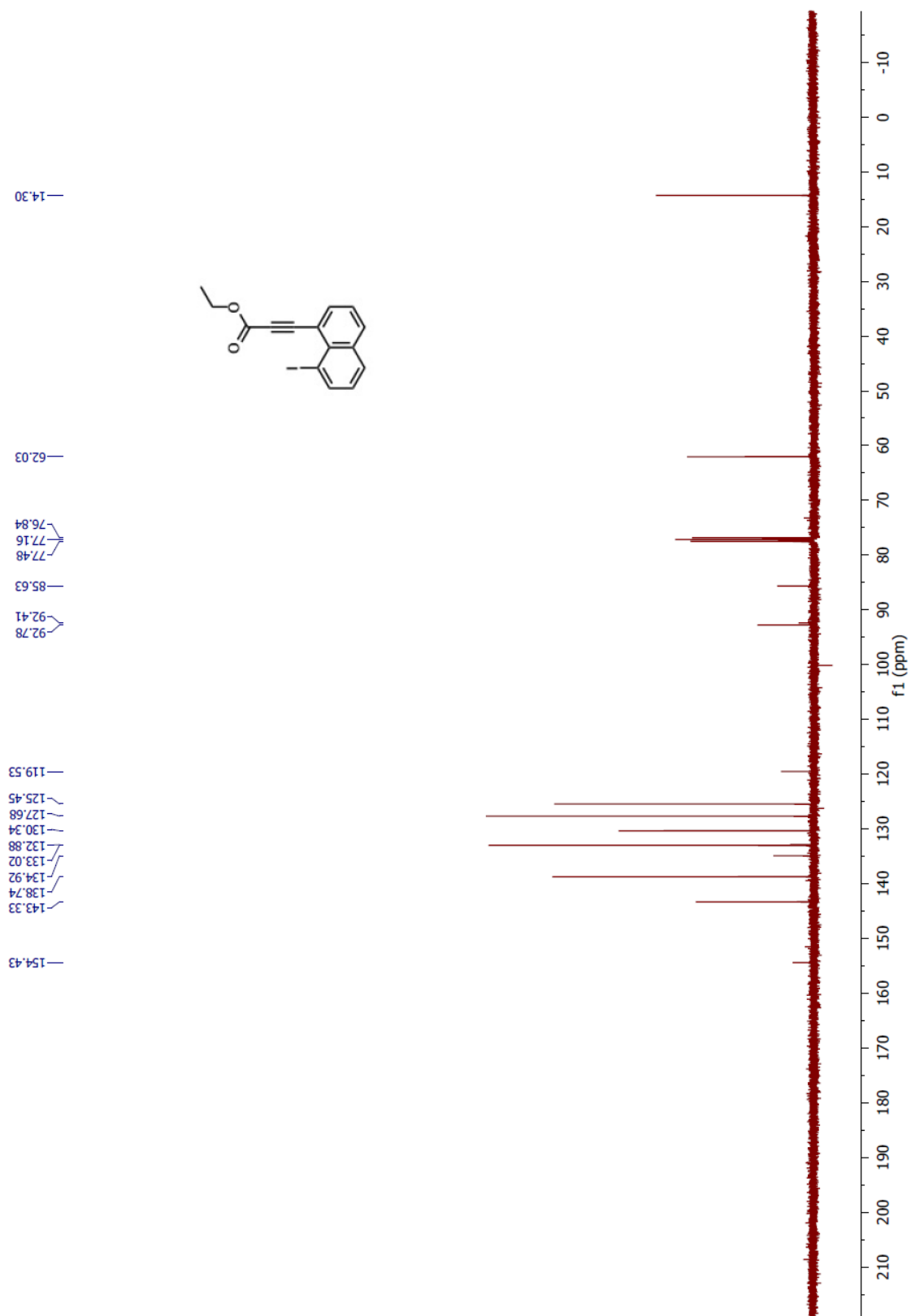


Figure 53: ¹³C-NMR spectrum of **61** in CDCl₃.

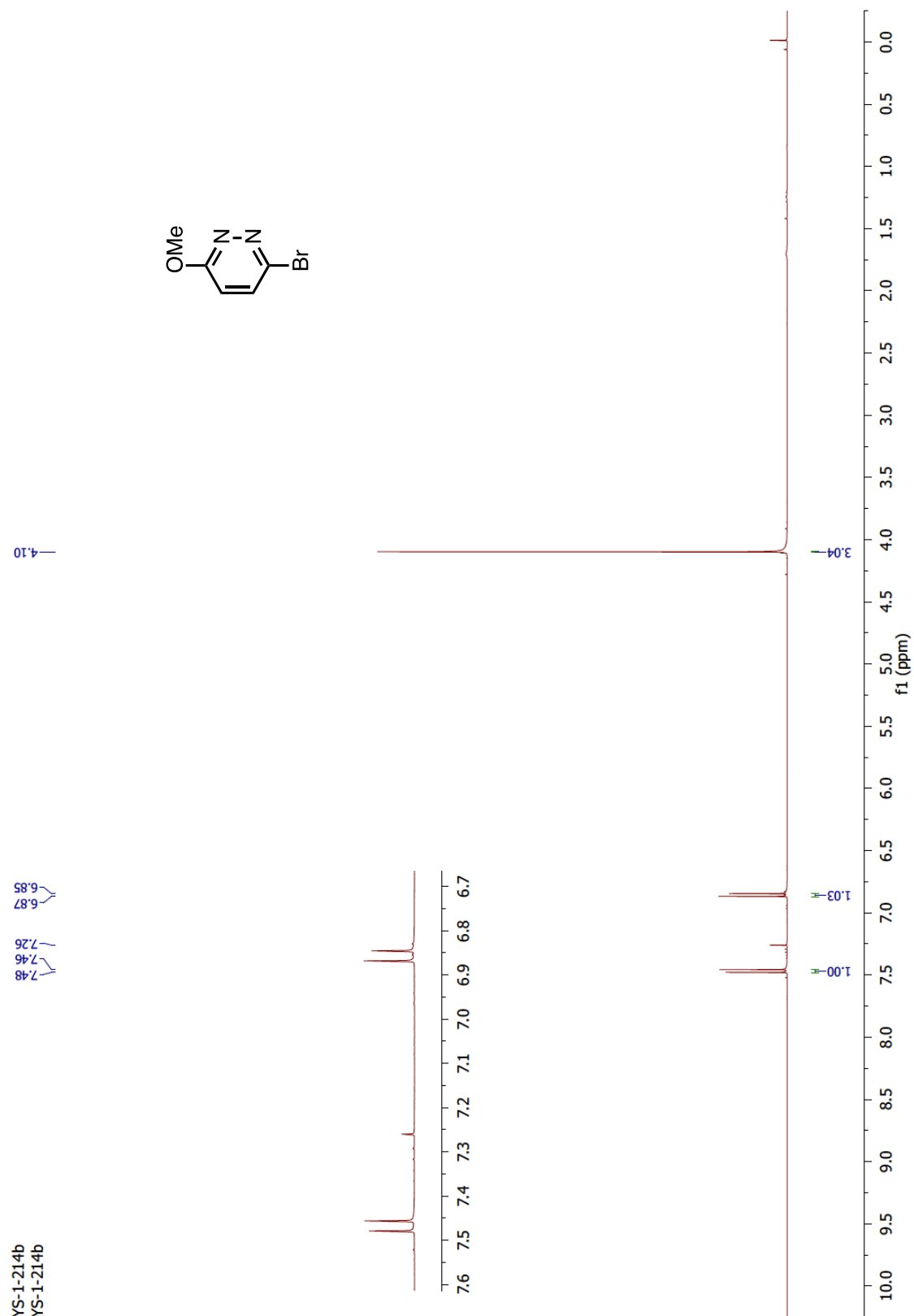


Figure 54: ^1H -NMR spectrum of **63** in CDCl_3 .

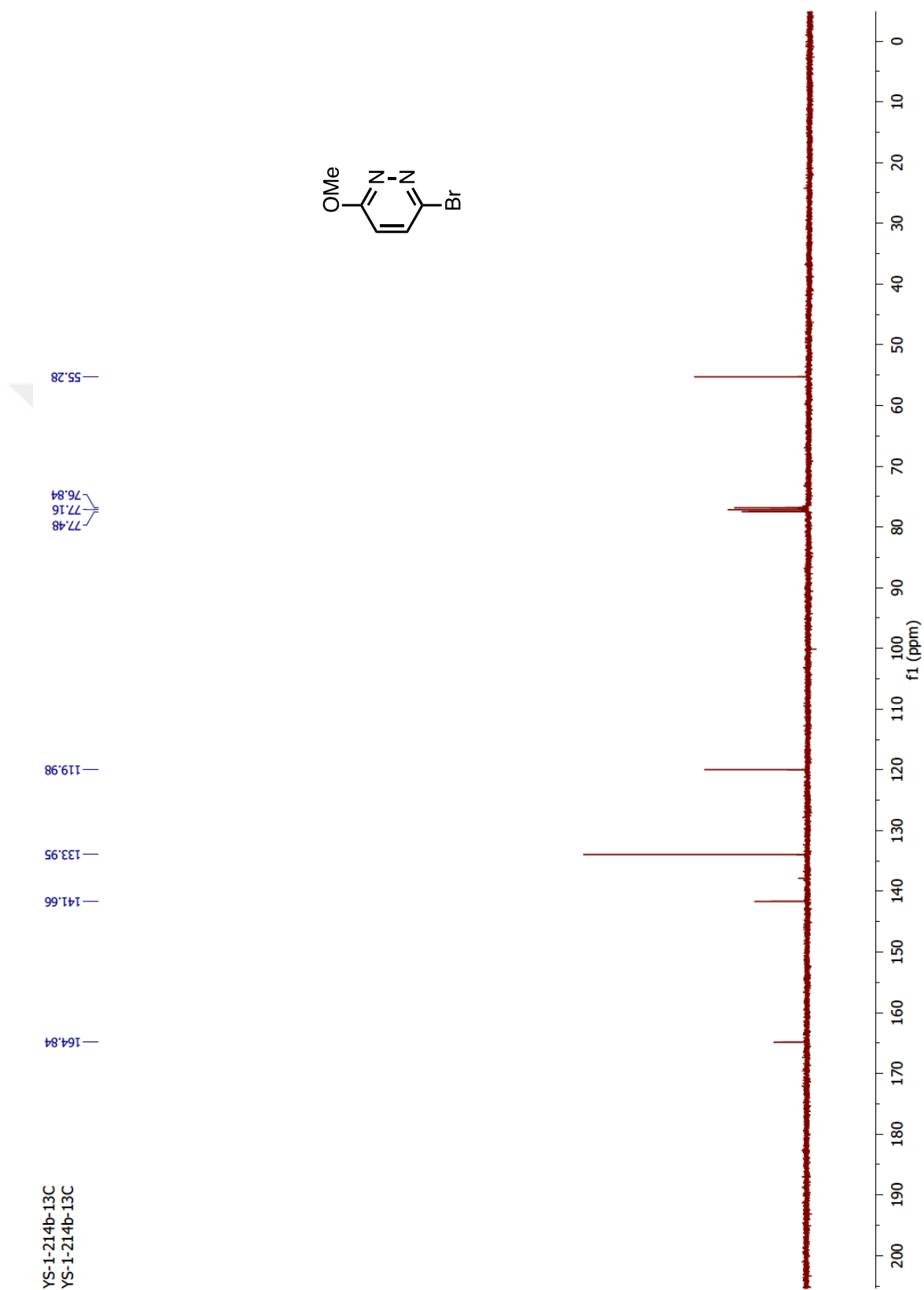


Figure 55: ^{13}C -NMR spectrum of **63** in CDCl_3 .

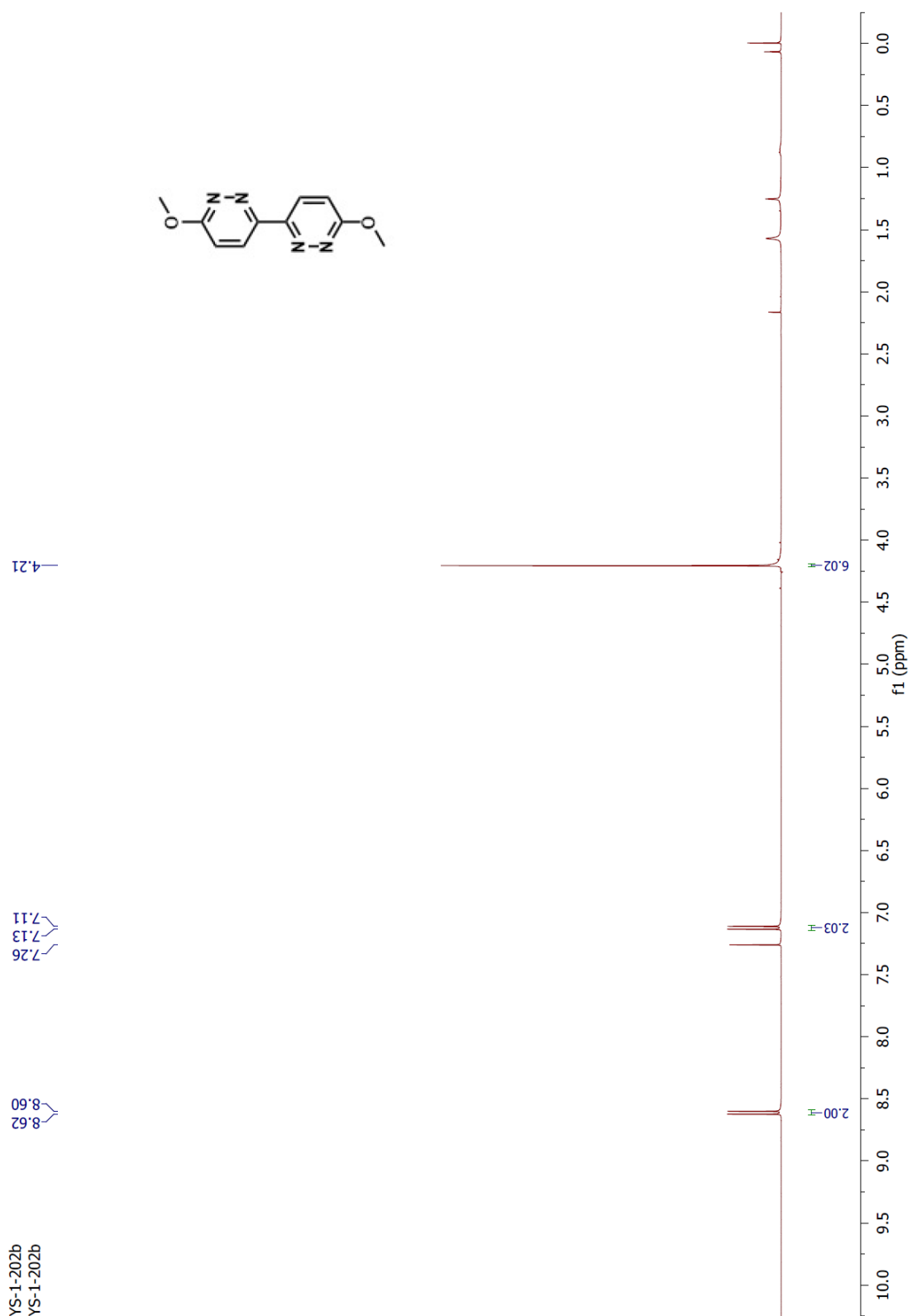


Figure 56: ¹H-NMR spectrum of **65** in CDCl₃.

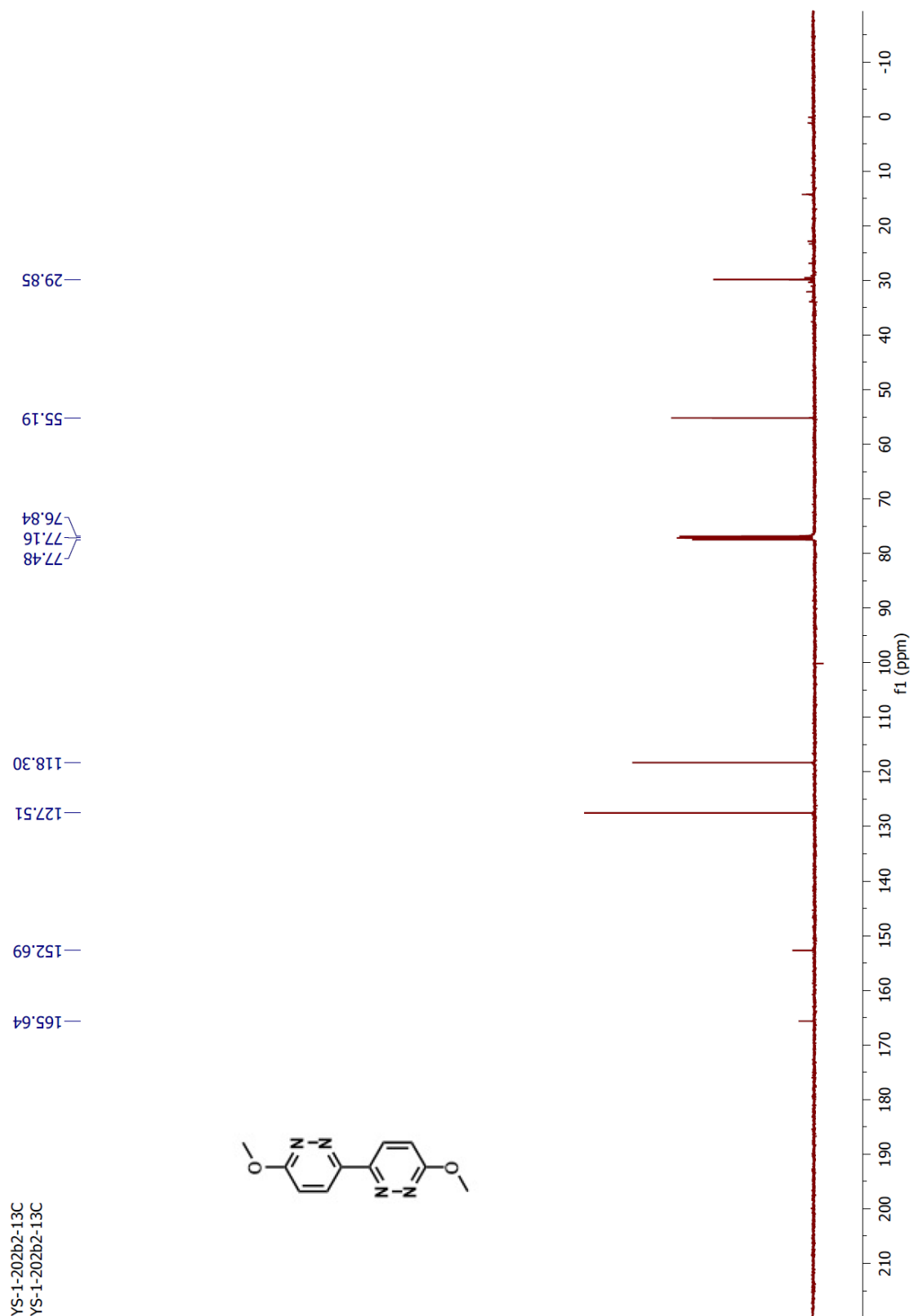


Figure 57: ^{13}C -NMR spectrum of **65** in CDCl_3 .

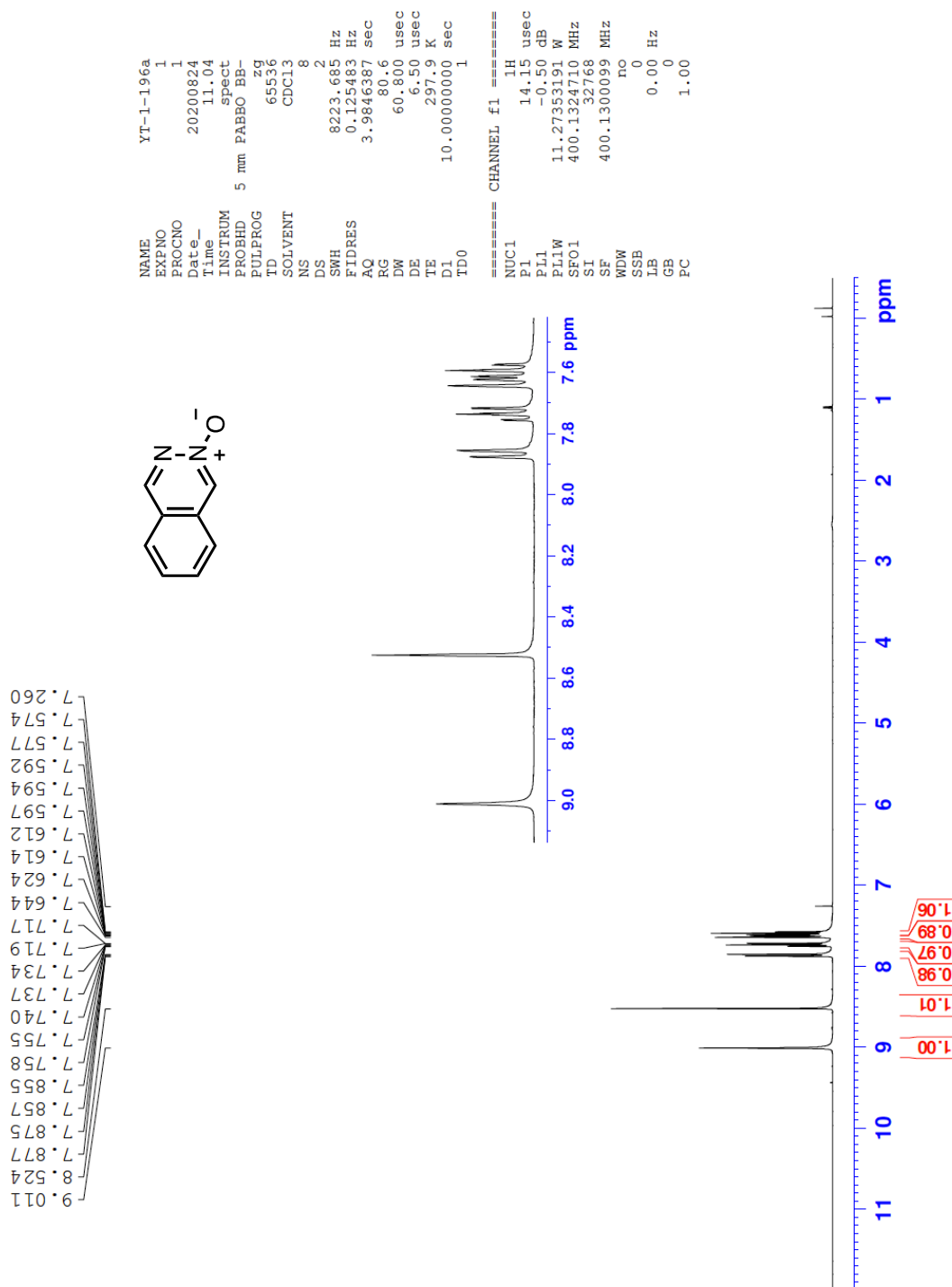


Figure 58: ¹H-NMR spectrum of **68** in CDCl₃.

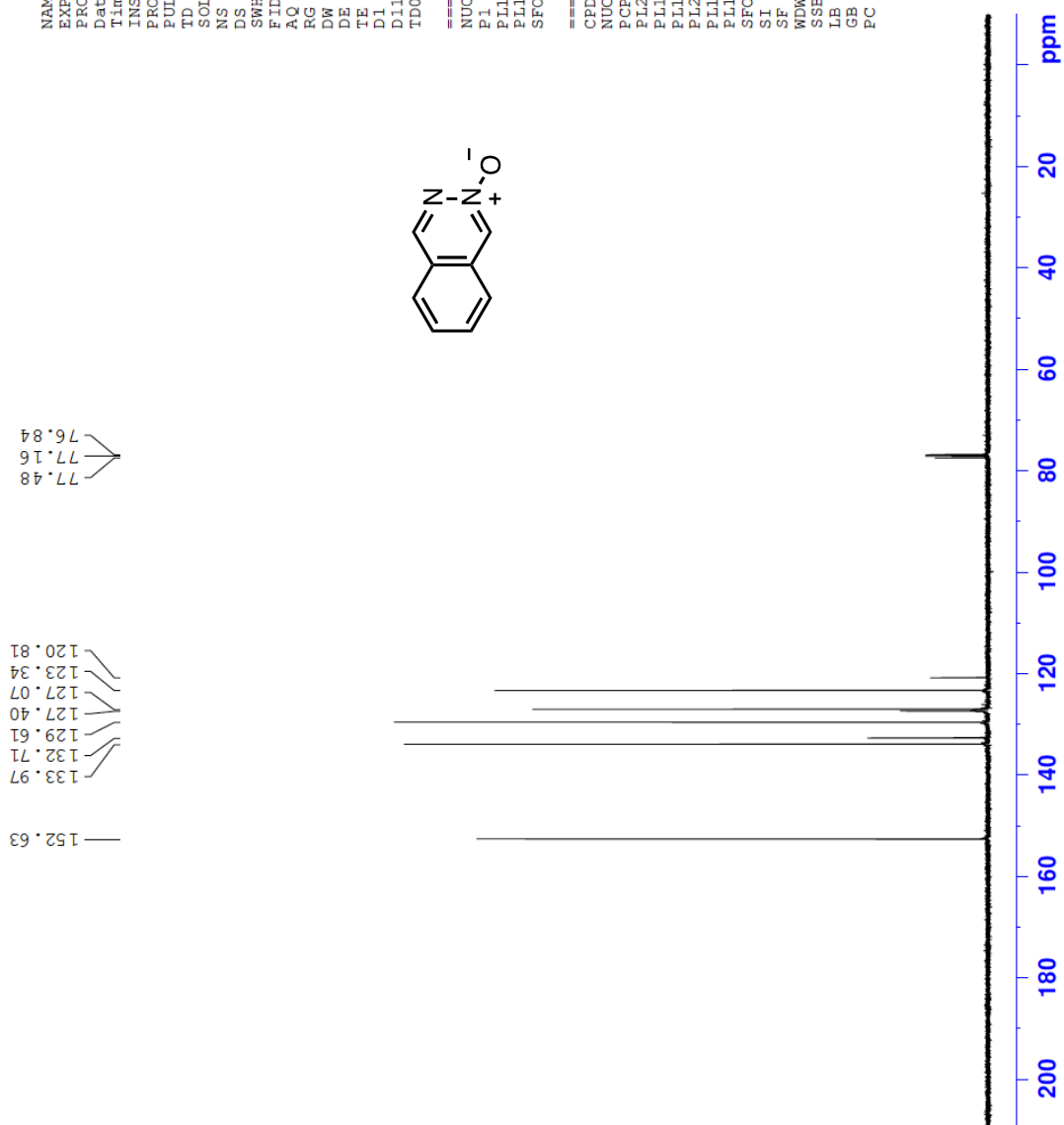


Figure 59: ^{13}C -NMR spectrum of **68** in CDCl_3 .

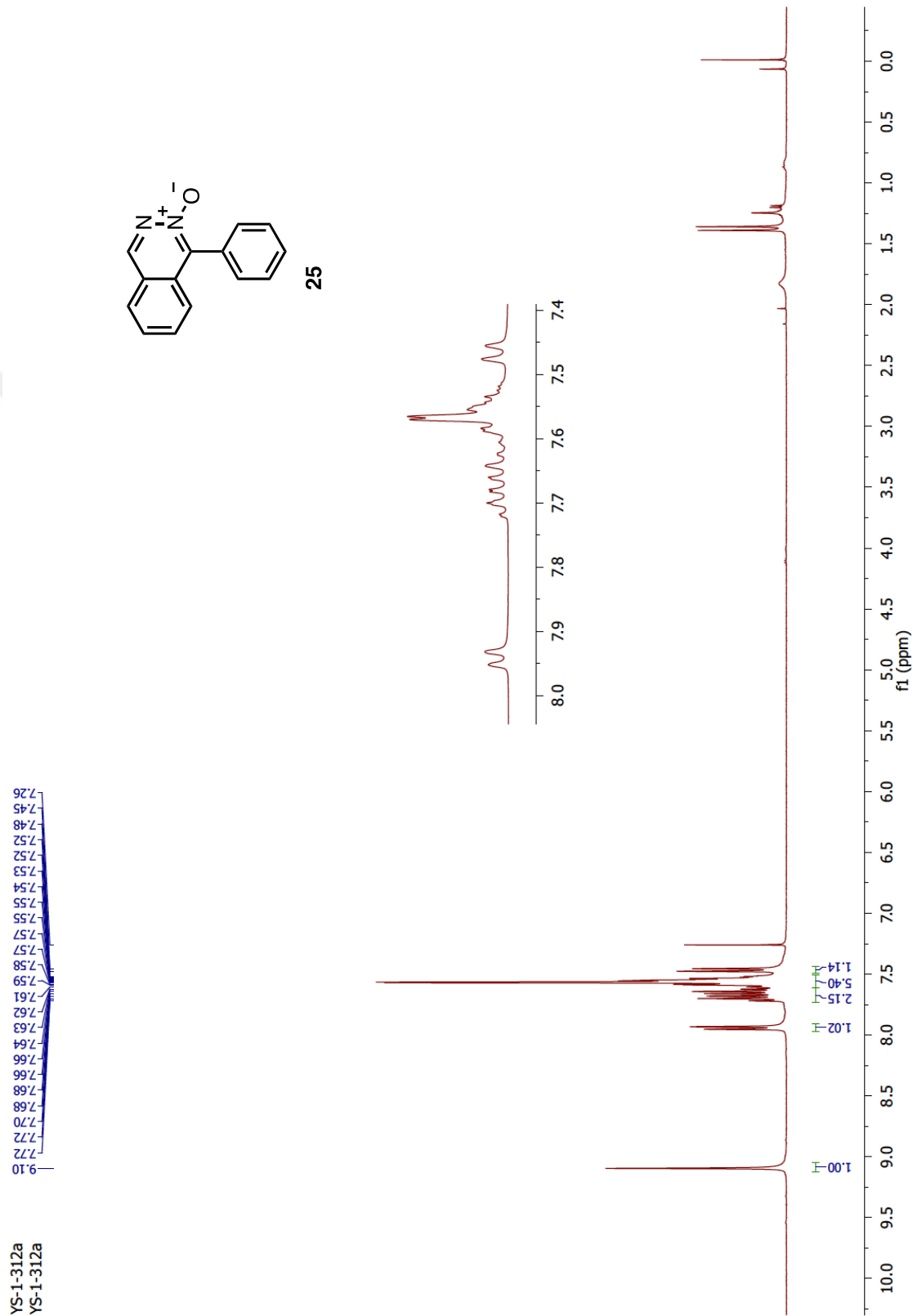


Figure 60: ^1H -NMR spectrum of **71** in CDCl_3 .

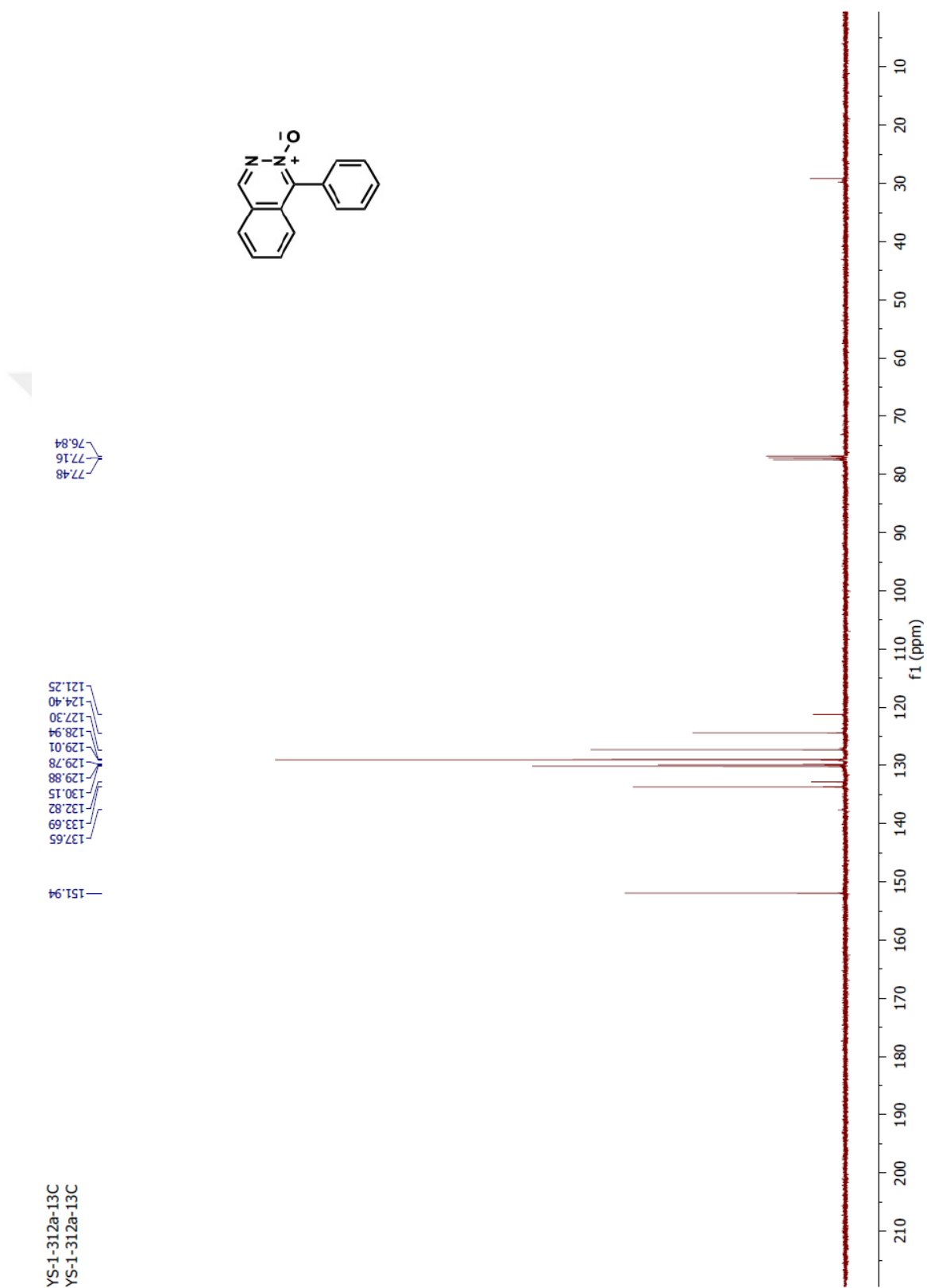


Figure 61: ^{13}C -NMR spectrum of **71** in CDCl_3 .

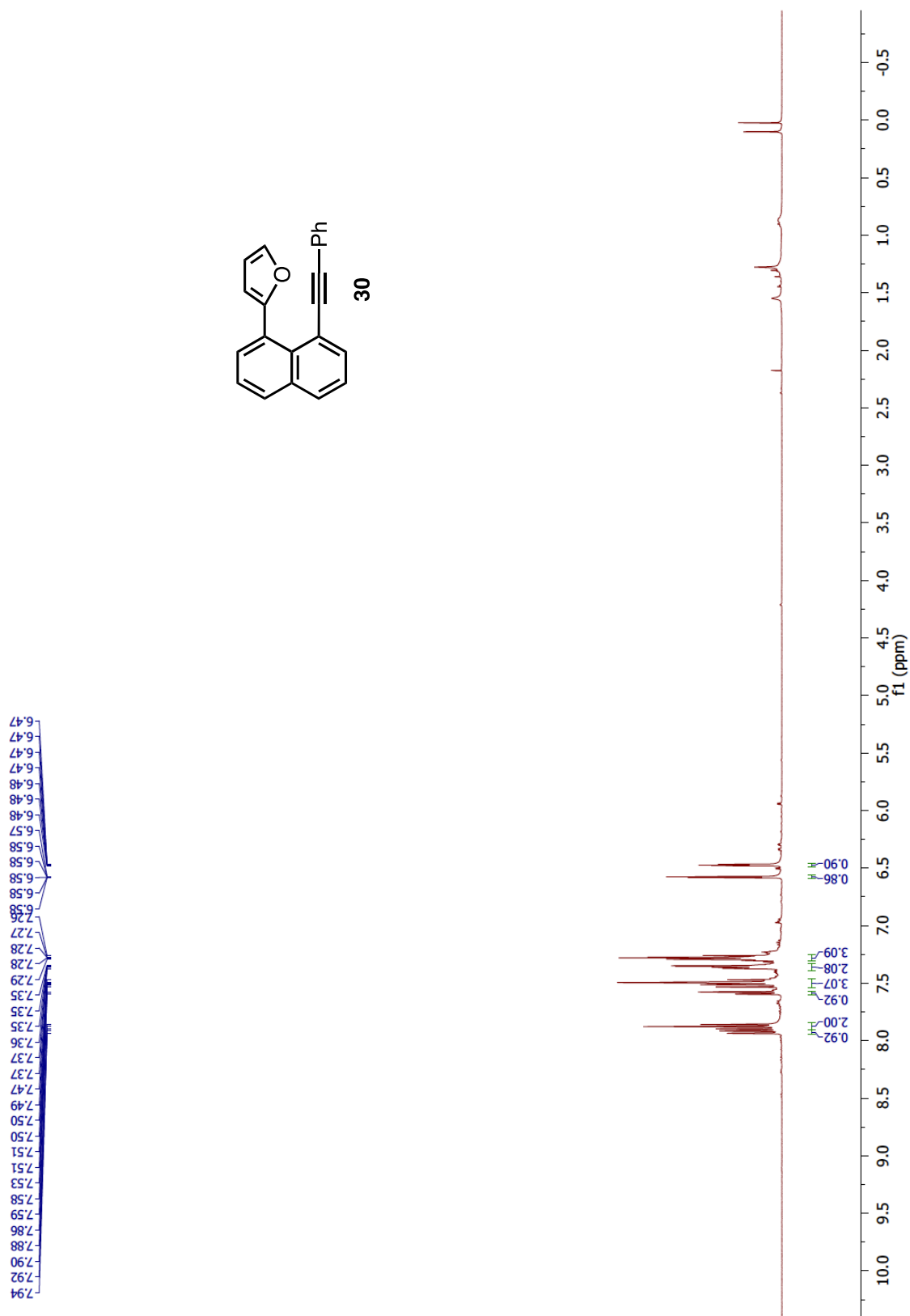


Figure 62: ¹H-NMR spectrum of 77 in CDCl₃.

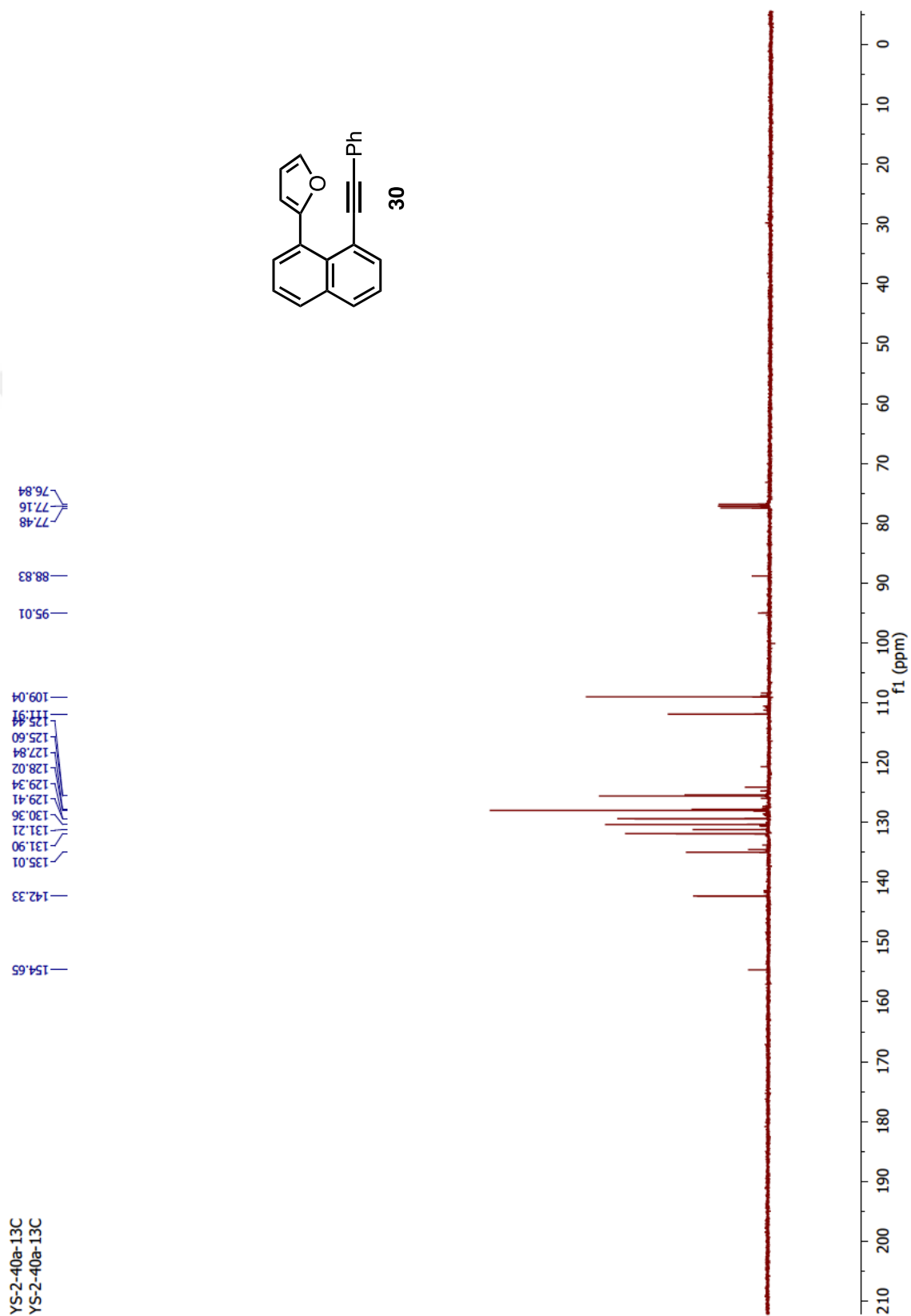


Figure 63: ^{13}C -NMR spectrum of 77 in CDCl_3 .

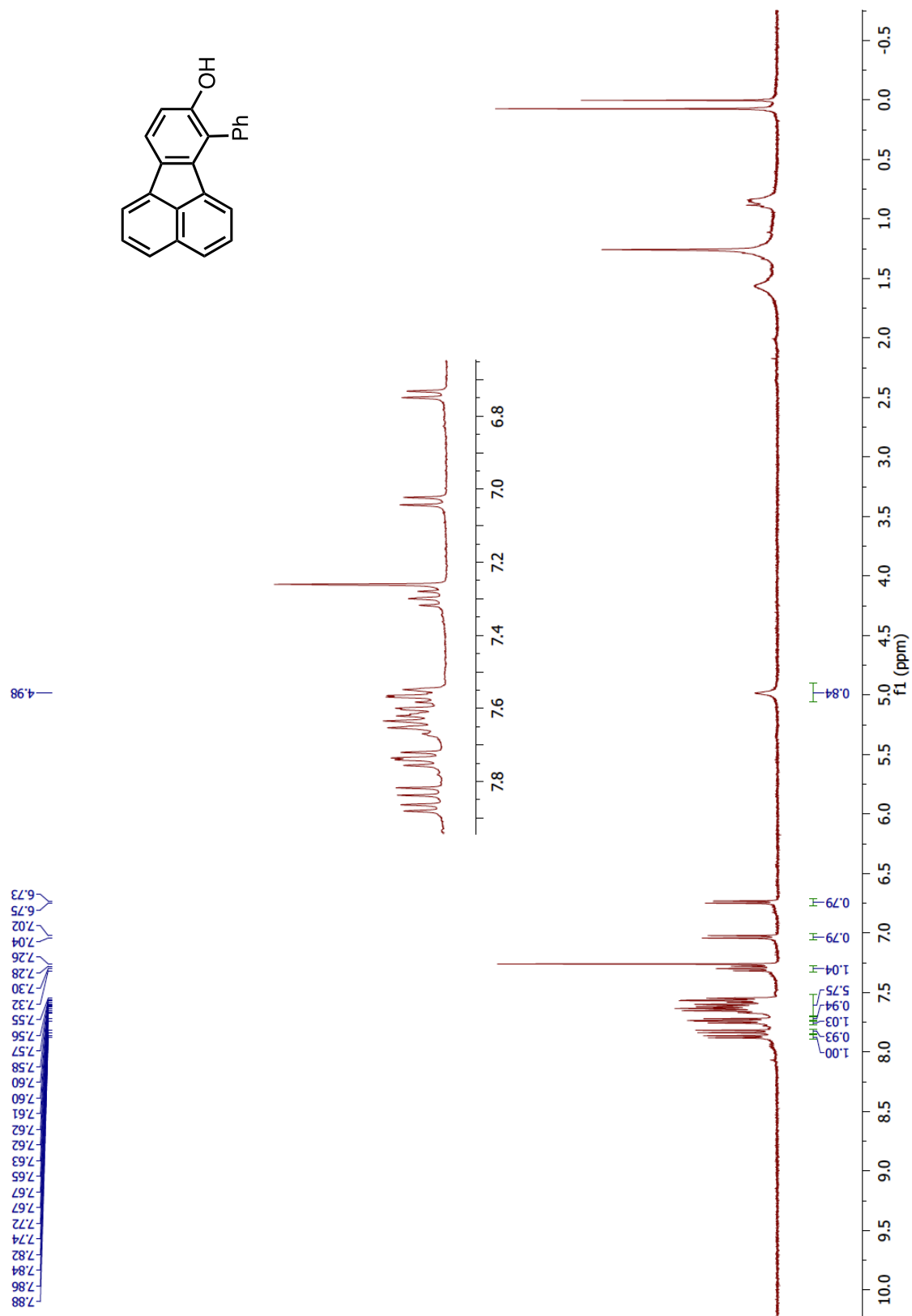


Figure 64: ^1H -NMR spectrum of **78** in CDCl₃.

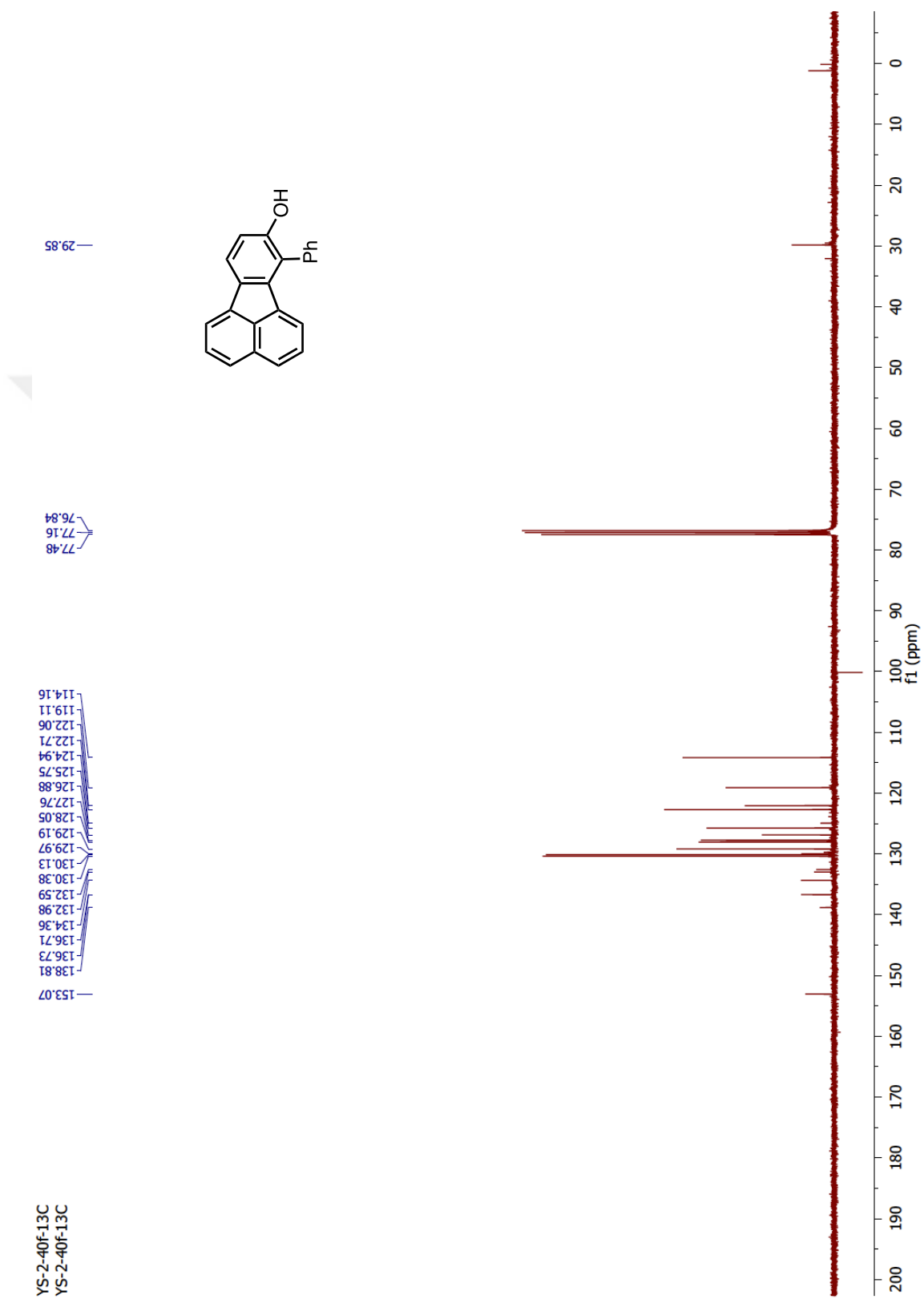


Figure 65: ^{13}C -NMR spectrum of **78** in CDCl₃.

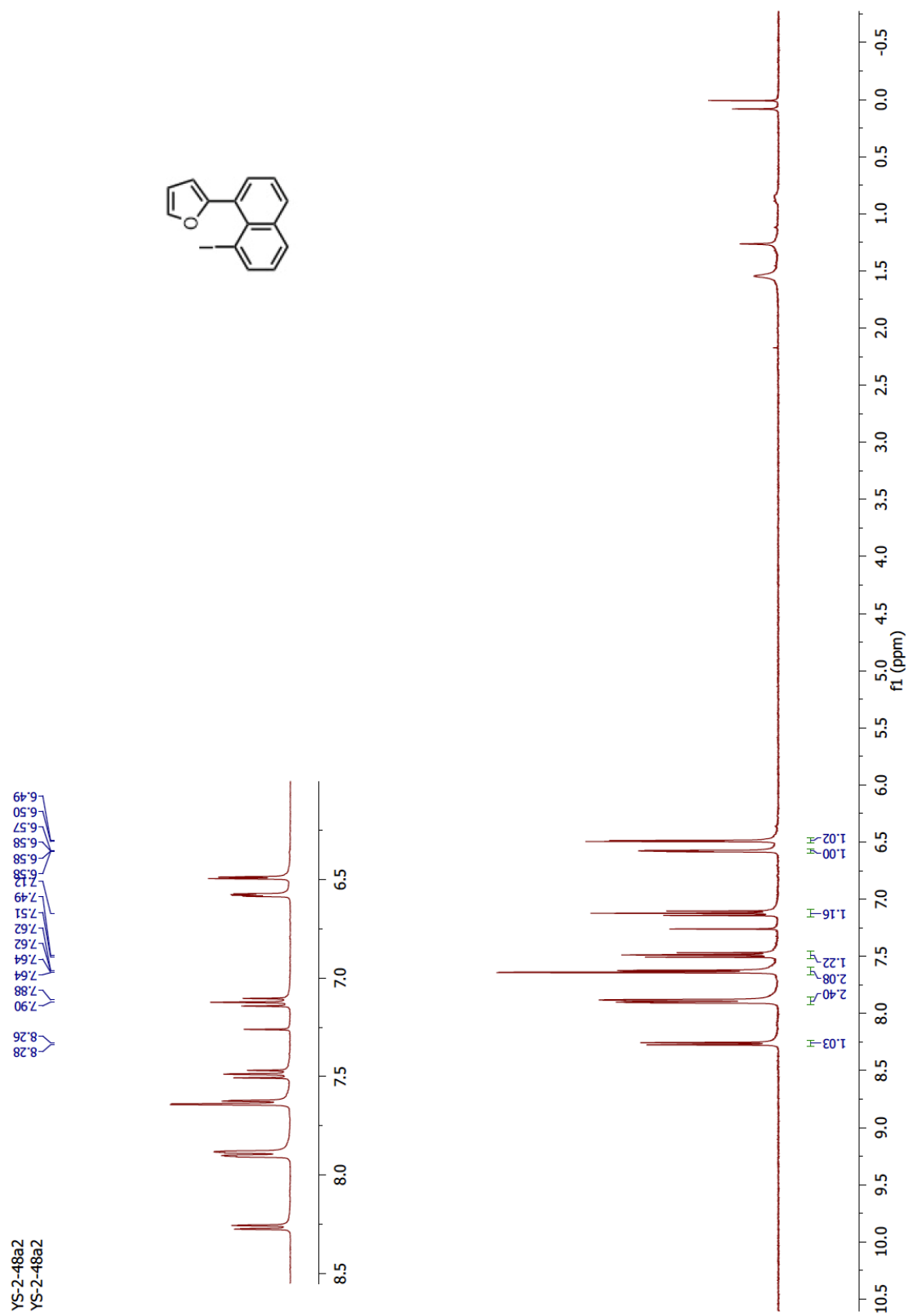


Figure 66: ^1H -NMR spectrum of **80** in CDCl_3 .

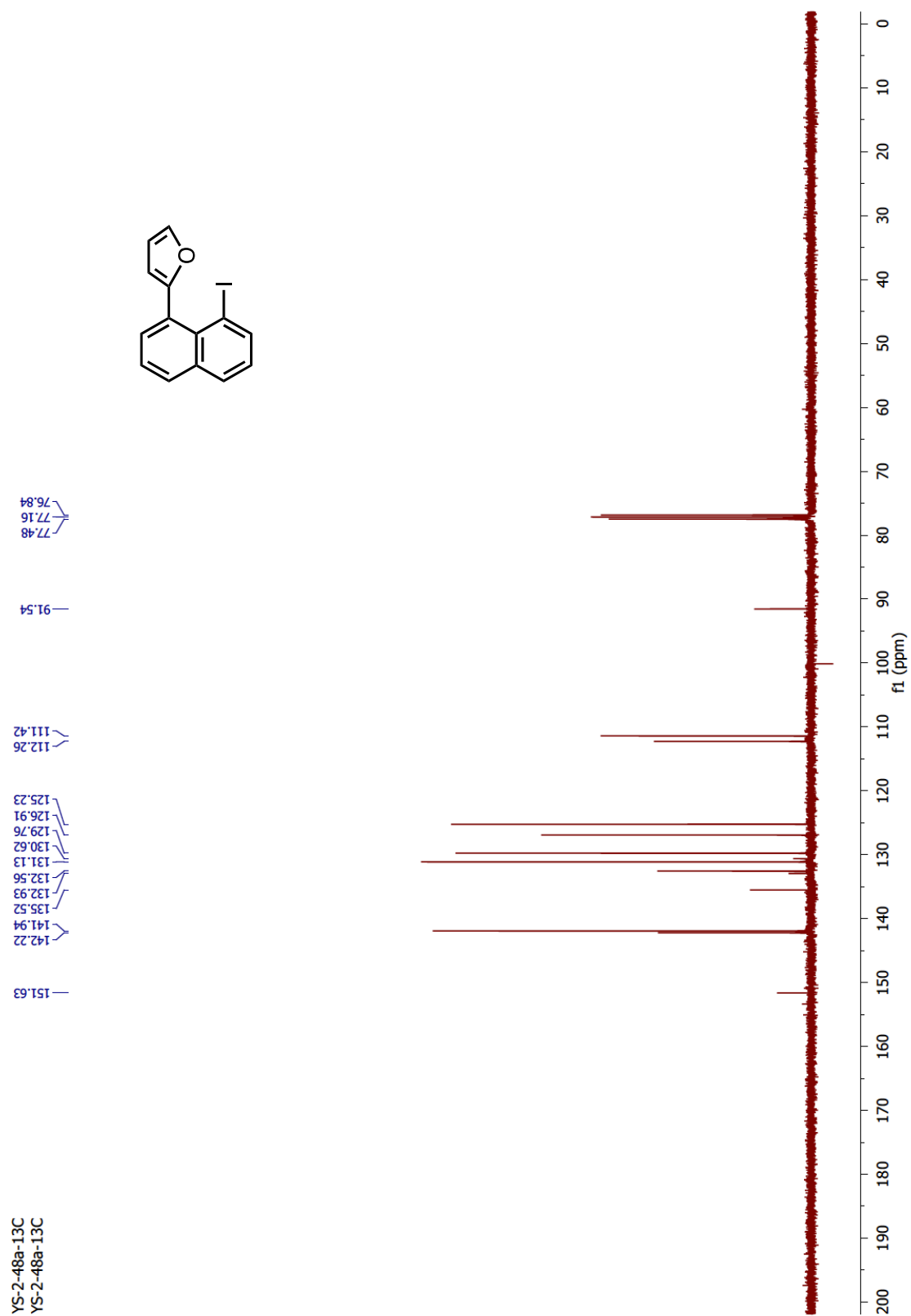


Figure 67: ^{13}C -NMR spectrum of **80** in CDCl_3 .

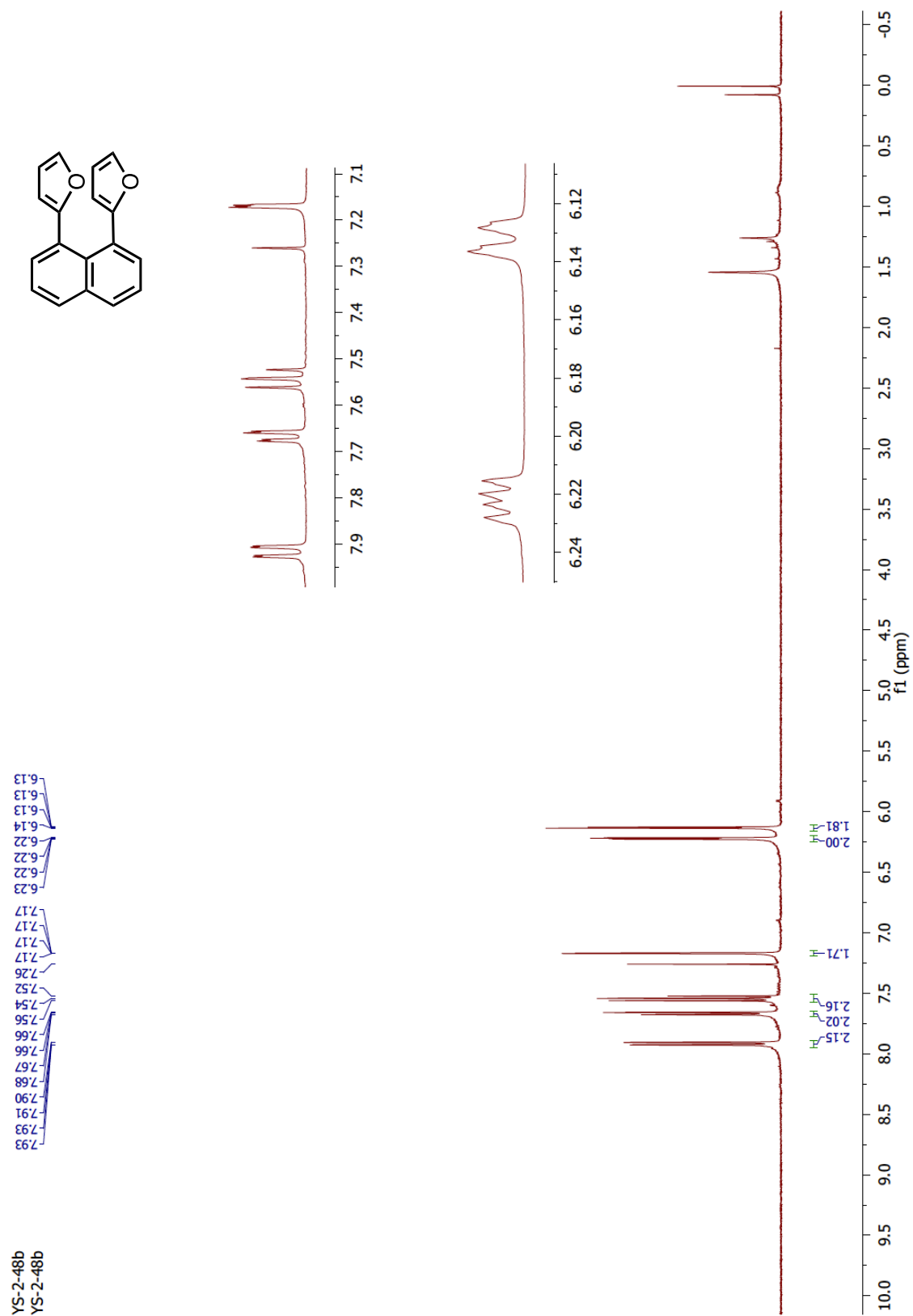


Figure 68: ¹H-NMR spectrum of **81** in CDCl₃.

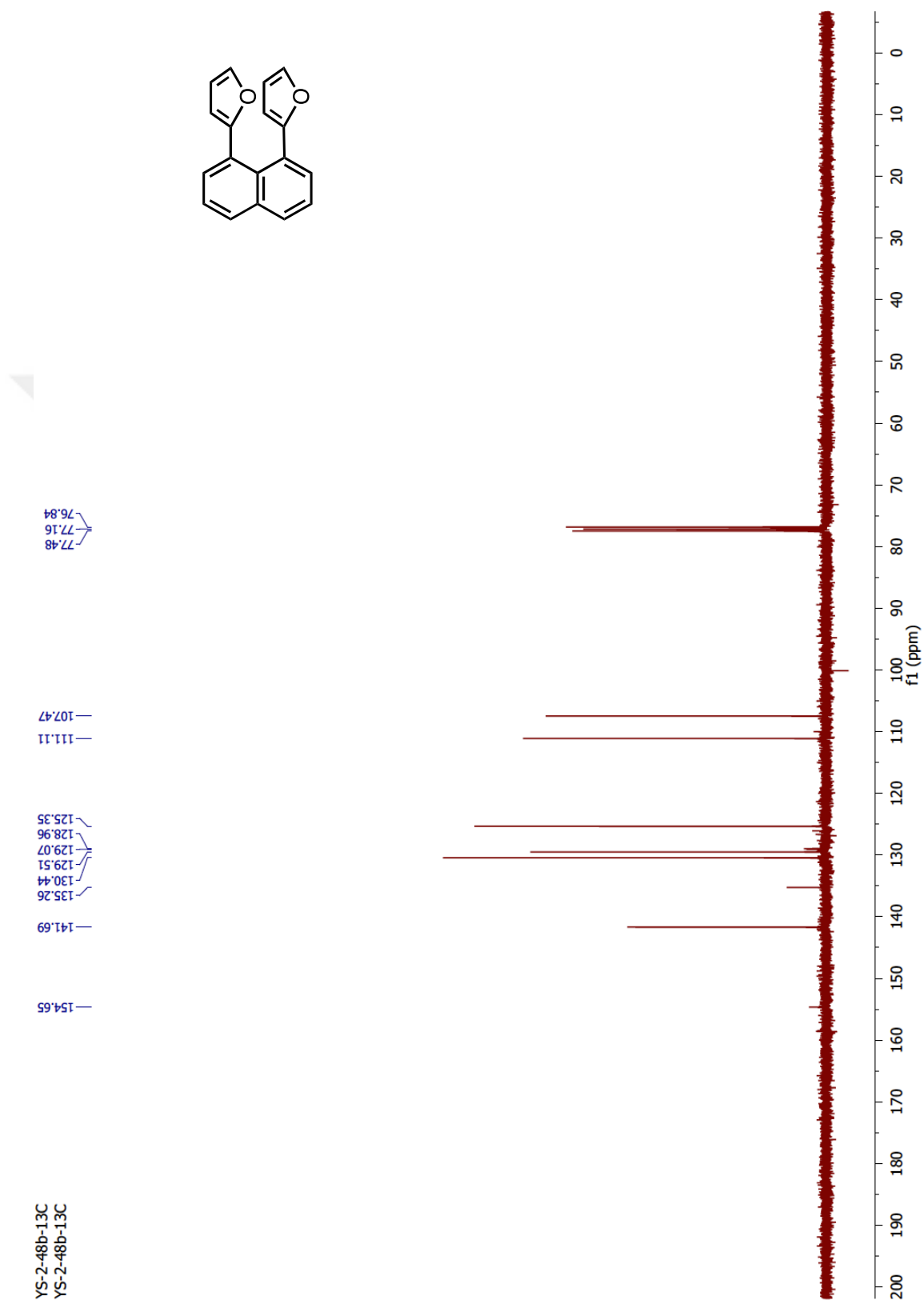


Figure 69: ^{13}C -NMR spectrum of **81** in CDCl₃.