Title

Part I, copper(I) iodide dimethyl sulfide catalyzed 1,4- addition of alkenyl groups from alkenylzirconium and alkenylzinc reagents and their application toward the total synthesis of azaspirene : Part II, aqueous Wittig chemistry employing stabilized...

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Part I: Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Addition of Alkenyl Groups From Alkenylzirconium and Alkenylzinc Reagents and Their Application Toward the Total Synthesis of Azaspirene

Part II: Aqueous Wittig Chemistry Employing Stabilized Ylides and Aldehydes

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Chemistry

by

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The dissertation of Amer Adnan El-Batta is approved, and is acceptable in quality and form for publication on microfilm:

Chair

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2007

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LIST OF ABBREVIATIONS

Ac	Acetyl
Bn	Benzyl
BOC	*t*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
dr	Diastereomeric ratio
DIBAL-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Et_2O	Ethyl ether
HMPA	Hexamethylphosphoramide
Im	Imidazole
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
Me	Methyl
Ms	Methanesulfonyl or mesyl
NaHMSD	Sodium hexamethyldisilazide
NIS	*N*-iodosuccinimide
$Ni(acac)_2$	Nickel(II) acetylacetonate
NMO	*N*-methylmorpholine *N*-oxide
PCC	Pyridinium chlorochromate
PDC	Pyridinium Dichromate
Ph	Phenyl
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl
Pyr	Pyridine
RCM	Ring closing metathesis
rt	Room temperature
SADH	Sharpless asymmetric dihydroxylation
SDS	Sodium dodecyl sulfate
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl

THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	Toluenesulfonyl

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El-Batta, A.; Hage, T.; Plotkin, S.; Bergdahl, M. Direct Copper(I) Iodide Dimethyl Sulfide Catalyzed Conjugate Addition of Alkenyl Groups From Vinylzirconocene Reagents. *Org. Lett.* **2004**, *6*, 107-110. (Chapter 2)

Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. Water as an Efficient Medium for Wittig Reactions Employing Stabilized Ylides and Aldehydes. *Tetrahedron Lett.* **2005**, *46*, 4473-4477. (Chapter 5)

El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. Wittig Reactions in Water Media Employing Stabilized Ylides with Aldehydes. Synthesis of α,β-Unsaturated Esters From Mixing Aldehydes, α-Bromoesters, and Ph_3P in Aqueous $NaHCO_3$. *J. Org. Chem.* **2007**, manuscript in press. (Chapter 5)

The above publications are also referenced at the end of the chapter in which their respective data appear.

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PUBLICATIONS

El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. Wittig Reactions in Water Media Employing Stabilized Ylides with Aldehydes. Synthesis of α,β-Unsaturated Esters From Mixing Aldehydes, α-Bromoesters, and Ph_3P in Aqueous $NaHCO_3$. *J. Org. Chem.* **2007**, manuscript in press.

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El-Batta, A.; Bergdahl, M. Copper(I) Iodide Dimethyl Sulfide Catalyzed Addition of a Vinylzirconium Reagent. Preparation of 4-Phenyl-5(*E*)-decen-2-one. *Org. Synth.* **2007**, *84*, 192-198.

Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. Water as an Efficient Medium for Wittig Reactions Employing Stabilized Ylides and Aldehydes. *Tetrahedron Lett.* **2005**, *46*, 4473-4477.

El-Batta, A.; Hage, T.; Plotkin, S.; Bergdahl, M. Direct Copper(I) Iodide Dimethyl Sulfide Catalyzed Conjugate Addition of Alkenyl Groups From Vinylzirconocene Reagents. *Org. Lett.* **2004**, *6*, 107-110.

ABSTRACT OF THE DISSERTATION

Part I: Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Addition of Alkenyl Groups From Alkenylzirconium and Alkenylzinc Reagents and Their Application Toward the Total Synthesis of Azaspirene

Part II: Aqueous Wittig Chemistry Employing Stabilized Ylides and Aldehydes

by

Amer Adnan El-Batta

Doctor of Philosophy in Chemistry

University of California, San Diego, 2007

San Diego State University, 2007

Professor B. Mikael Bergdahl, Chair

Hydrozirconation of alkynes, utilizing Schwartz's reagent, $\{Cp_2Zr(H)Cl\}$, is a superb protocol for making regioselective alkenylzirconocene reagents. We recently reported the direct conjugate addition of the alkenyl group in high yield from an alkenylzirconocene in the presence of a catalytic amount of the $CuI{\bullet}0.75SMe_2$ complex. Specifically, this Cu(I) additive is the most efficient when compared to several other copper(I) and copper(II) sources.

While organozirconocenes have been used in many applications for organic synthesis, the transmetallation from zirconium to zinc has been demonstrated to be a more efficient subsequent procedure in the synthesis of carbon-carbon bonds. The Zr→Zn transmetalation protocol illustrates that the 1,4-addition of mixed alkenyl-

alkyl*zincate* reagents to enones and enals is faster than the corresponding alkenyl*zirconocene* reagents using catalytic amount of the CuI•0.75DMS complex. This protocol was also applied to *N*-enoyl derived oxazolidinones and the stereoselectivity was measured. Quite remarkably, employing TMSOTf as a Lewis acid achieved the 1,4-products in high yields, with only 10 mol% of the CuI•0.75DMS catalyst was utilized.

Encouraged by the unique action of the mixed alkenyl-alkylzincate/CuI•0.75SMe$_2$ components, it is proposed that this protocol be used for the insertion of the hexadiene unit in the azaspirene structure. Azaspirene, a novel angiogenesis inhibitor, has biological activity that treats angiogenesis-related diseases such as cancer and rheumatoid arthritis. An efficient investigation for total synthesis of azaspirene was studied, aiming to achieve a concise stereocontrolled route to this unique anti-cancer agent as well as a small library thereof. Simple synthetic routes to achieve two key fragments in the target molecule were accomplished. The overall synthetic strategy proposed herein is of great economical use compared to few other reported synthetic studies toward the target molecule.

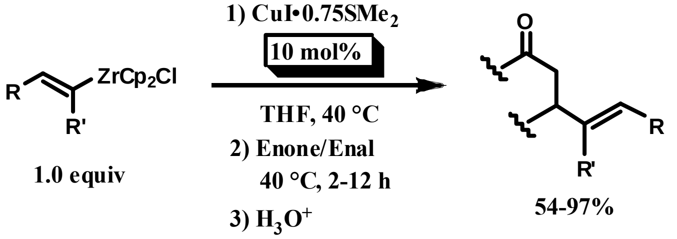
In addition, water is demonstrated to be an excellent medium for the synthesis of carbon-carbon double bonds. Excellent yields and *E/Z*-ratios were reported using a broad range of aldehydes and phosphoranes as well as *in situ* formed ylides. The rate of Wittig reactions in water is unexpectedly accelerated compared to conventional Wittig reactions in organic solvents, and water is the medium of choice for this type of chemistry. The role of water in Wittig reactions and its mechanism are discussed.

Chapter 1

Introduction

Copper is one of the oldest, most common transition metals to be used in organic synthesis. There is a plethora of literature published each year that highlights the advantage of this element for successful promotion, particularly the field of conjugate addition reactions. Copper-catalyzed 1,4-additions of alkenyl groups are among the most popular synthetic tools utilized in many total syntheses of natural products and target molecules. The ease of handling copper reagents as well as their chemo-, regio- and stereoselectivity characteristics make these reagents indispensable for many synthetic transformations, particularly in the 1,4-additions of various groups.

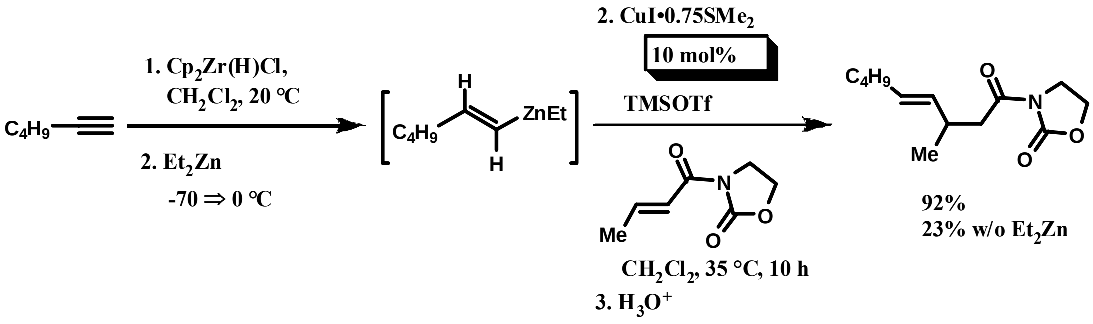
The main focus of the first part of this thesis is the development of an efficient direct method for the conjugate addition of alkenyl groups using copper catalysis. In Chapter 2, the 1,4-additions of vinyl groups to enones and enals using alkenylzirconocene reagents are discussed. These reagents are obtained from the hydrozirconation of alkynes utilizing the Schwartz's reagent (Scheme 1.1).



Scheme 1.1. Cu(I)-catalyzed 1,4-addition of alkenylzirconocene to enones and enals.

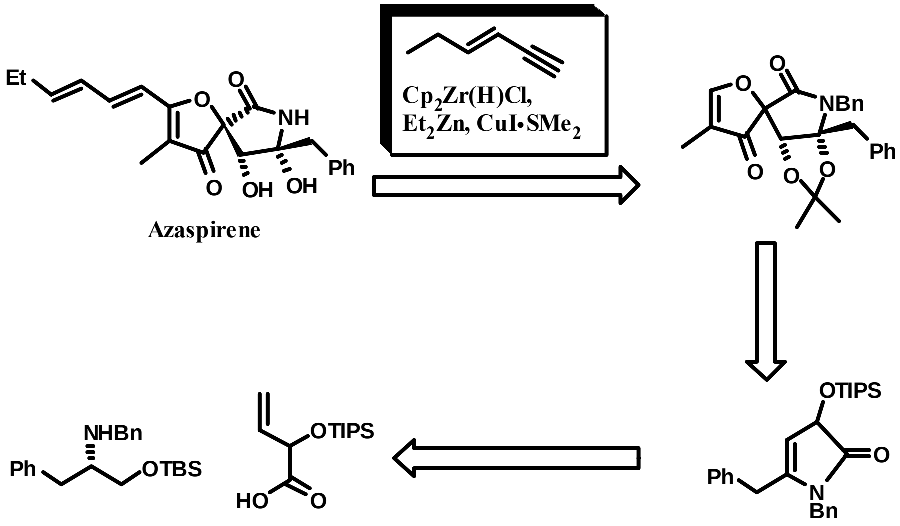
A wide range of substrates were employed and very good yields of the conjugate addition products were achieved in presence of catalytic amount of the copper iodide dimethyl sulfide complex ($CuI \cdot 0.75SMe_2$). This protocol has proven its efficiency compared to the use of vinylcopper reagents commonly originated from the corresponding organolithium and organomagnesium compounds. The high reactivity and the strongly basic character of the latter reagents occasionally complicate experimental procedure and limit functional group tolerance. Furthermore, the alkenylzirconocenes/$CuI \cdot 0.75SMe_2$ methodology is a reliable alternative for the 1,4-transfer of alkenyl groups that circumvents the use of extra additives, which are commonly used to sustain the catalytic efficiency of the copper complex.

In the course of expanding the scope of the alkenylzirconocenes/ $CuI \cdot 0.75SMe_2$ chemistry, a subsequent transmetalation step of zirconium to zinc is presented in Chapter 3 as an alternative in conjugate addition reactions. This mild manipulation has been proven in literature that the *in situ* formed *alkenyl-alkylzincate* intermediates are more reactive than their corresponding *alkenylzirconocene* intermediates in cross-coupling reactions as well as in 1,2-additions to aldehydes and ketones. In presence of one equivalent of TMSOTf, the mixed alkenyl-alkylzincates give high yields and very good diastereoselectivities of the 1,4-products when *N*-enoyl derived oxazolidinones are used as electrophiles (Scheme 1.2). This protocol was further investigated to include enones and enals substrates. The rate of the 1,4-addition reaction utilizing zincate intermediates is faster than when zirconocene intermediates are employed in the presence of catalytic amount of the CuI•0.75SMe$_2$ complex.



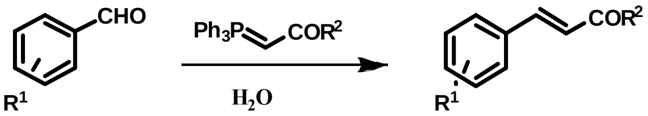
Scheme 1.2. TMSOTf-promoted Cu(I)-catalyzed conjugate addition of mixed alkenyl-alkylzincate reagents to α,β-unsaturated imides.

Zirconocene and zincate intermediates appear in fact to be a bimetallic combination that displays unique reactivity characteristics that are not shared by either of the parent compounds. Encouraged by the reports of the mixed alkenyl-alkylzincates/CuI•0.75SMe$_2$ chemistry, the strategy is to use this protocol for the insertion of the hexadiene unit in the azaspirene structure. Chapter 4 presents chemical studies carried out to achieve the total synthesis of azaspirene. In brief, this novel angiogenesis inhibitor will be synthesized via a highly convergent pathway utilizing two key subunits (Scheme 1.3). The amine and the acid fragments are easily obtained in high yields from readily available starting materials.



Scheme 1.3. Synthetic strategy toward azaspirene.

The second part of this thesis discusses the improvement of the Wittig reaction employing stabilized ylides and aldehydes in water as the single medium (Chapter 5). Although the solubility of the reactants appears very poor, the aqueous conditions gave very high yields and good to excellent *E*/*Z*-ratios of the α,β-unsaturated carbonyl products.



Scheme 1.4. Wittig reaction of aldehydes with stabilized ylides in water.

Future work and additional suggestions are discussed in Chapter 6, where the main focus is to expand the scope of the zirconocenes/zincates chemistry using copper catalysis. In addition, a proposed plan is presented to finalize the highly convergent enantioselective total synthesis of azaspirene.

All compounds are characterized accordingly in Chapter 7 using ^{1}H- and ^{13}C-NMR s33pectroscopy. For most of the compounds, HRMS, GC-MS and IR spectra are provided.

Part I

Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Addition of Alkenyl Groups From Alkenylzirconium and Alkenylzinc Reagents and Their Application Toward the Total Synthesis of Azaspirene

Chapter 2

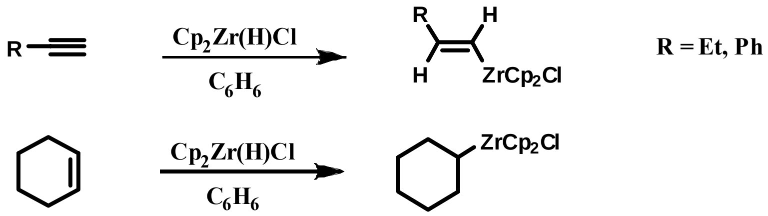
Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Addition of Alkenyl Groups From Alkenylzirconocene Reagents

2.1 Introduction

2.1.1 Background of Hydrozirconation

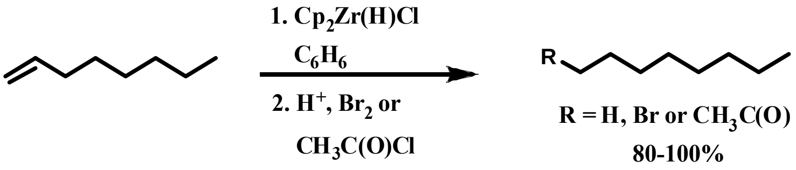
Zirconium (Zr) is the second member of the Group 4B Titanium triad. It occurs to the extent of 0.022% in the lithosphere. As such, it is as equally abundant as carbon and therefore readily available and relatively inexpensive compared to other transition metals.[1] In 1953, Birmingham prepared the first organozirconium compound, zirconocene dibromide.[2] Several years later, a more convenient recipe to yield zirconocene dichlorides appeared in literature.[3] Further than its characterization, no synthetic methodologies using zirconocene dichloride have been reported until 1960, when Breslow disclosed that the compound can be used to catalyze ethylene polymerization. At present, the most common use of organozirconium compounds is as polymerization catalysts.[1,4] These compounds have greatly improved olefin polymerization beyond what could be achieved with traditional Ziegler-Natta catalysts.

The first use of zirconium in organic synthesis began in the mid-1970s, when Schwartz and Hart[5] reported the first hydrozirconation reaction. This process, which had been discovered by Wailes and Weigold,[6] made alkyl- and alkenylzirconocene intermediates readily available simply by reacting zirconocene hydrochloride with alkenes or alkynes (Scheme 2.1).[7]



Scheme 2.1. Hydrozirconation of alkenes and alkynes using Schwartz's reagent.

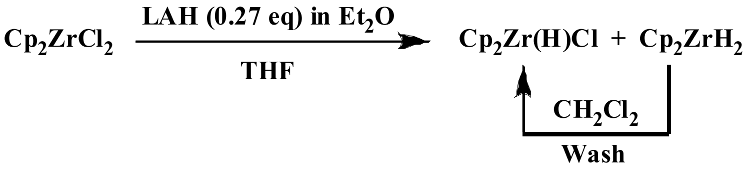
Because of the pioneering work by Schwartz and co-workers,[5,8] who described the hydrozirconation products for the functionalization of organic compounds (Scheme 2.2), zirconocene hydrochloride ($Cp_2Zr(H)Cl$) is now well known as the "Schwartz's reagent."



Scheme 2.2. First reports by Schwartz using zirconocene hydrochloride.

2.1.1.1 Preparation of Schwartz's Reagent {$Cp_2Zr(H)Cl$}

Although zirconium hydride is available commercially,[9] it is yet expensive. This reagent was first prepared by Wailes and Weigold who described the reduction of Cp_2ZrCl_2 using 0.25 equiv of $LiAlH_4$.[10] This procedure led to considerable over-reduction to the very insoluble Cp_2ZrH_2 and therefore, one equiv of LiAl(O-*t*-Bu)$_3$H was instead implemented. However, the high cost of the reducing agent and the difficulty in isolating the product by filtration due to impurities made Wailes' approach less attractive. As an alternative, Carr and Schwartz reported the use of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) as a reducing agent.[11] The material prepared in this way was reported to contain 30% sodium chloride. To prevent isolation problems resulting from impurities and over-reduction, Buchwald *et al.*[12] developed an experimentally simple procedure for large scale preparations of pure Schwartz's reagent (Scheme 2.3).



Scheme 2.3. Buchwald's protocol for the preparation of Schwartz's reagent.

Buchwald and co-workers introduced a washing step with CH_2Cl_2 which converts most of the zirconocene dihydride to the desired monohydride after the reduction. This development was based on the previous work by Wailes[10b] who discovered the relatively rapid reaction between Cp_2ZrH_2 and CH_2Cl_2 to form more of the $Cp_2Zr(H)Cl$. This methodology is dependent on the relatively slow reaction between Cp_2ZrHCl and CH_2Cl_2. In Buchwald's protocol, for the preparation of Schwartz's reagent, the use of filtered solutions of $LiAlH_4$ in Et_2O prevented contamination of salt impurities. This development also simplified product isolation via filtration of the precipitated reagent. Furthermore, because there are no salt impurities using Buchwald's procedure, the endpoint of the hydrozirconation reaction of alkenes and alkynes is always "signaled" when the heterogeneous reaction mixture turns clear. The $Cp_2Zr(H)Cl$ reagent is insoluble in most organic solvents whereas the colored alkyl- and alkenylzirconocene intermediates are highly soluble. It is important to emphasize that Schwartz's reagent is a moderately air-, moisture- and light-sensitive white solid. Nevertheless, the reagent can be handled and weighed easily on a balance. However, the hydrozirconation reaction should be handled under an inert atmosphere due to the high reactivity and sensitivity of the resulted zirconocene intermediates.

2.1.1.2 Applications of Hydrozirconation

The *syn*-addition of the Schwartz's reagent across alkenes and alkynes is still today a very frequently used manipulation in organic reactions and synthesis. Hydrozirconation of olefins proceeds similarly as BH_3 in that it places the zirconium moiety at the sterically least hindered position of the olefin chain.[5] Formation of this product involves either the regiospecific addition of Zr-H to a terminal double bond or Zr-H addition to an internal double bond followed by rapid rearrangement via Zr-H elimination and re-addition, placing the metal in each case at the less hindered position of the alkyl chain. Hydrozirconation of terminal alkynes proceeds with (C=C) *cis* stereochemistry, positioning the zirconium atom on the terminal carbon atom. When utilizing unsymmetrically substituted internal alkynes, the hydrozirconation reaction readily gives mixtures of regioisomers enriched in alkenylzirconocene, again placing the zirconium atom geminal to the sterically less demanding substituent. The initial selectivity is low, but excess $Cp_2Zr(H)Cl$ readily isomerizes the adduct to give improved thermodynamically controlled regioselectivity.[8b,13]

Since the reaction of Schwartz's reagent with alkynes is very fast and highly regioselective, the majority of synthetic applications utilize alkenylzirconocenes in further synthesis. The alkenes on the other hand are not as reactive, and the internal alkylzirconocenes are rapidly isomerized into terminal alkylzirconocenes.[14] Alkenylzirconocenes may be used in various ways to synthesize organic compounds (Figure 2.1). Those reactions could be classified based on the formation of carbon-hydrogen, carbon-heteroatom or carbon-carbon bond. Examples of these three types of reactions are: protonolysis and deuterolysis[8c] (a), halogenolysis[5,8b,e,f] (b), oxidation[8b] (c), replacement[15] with sulfur,[16] selenium,[17] SO_2[18] and tellurium[19] (d), carbonylation[8a,c] to form RCHO, RCO_2H, RCO_2R and RCOBr (e), acylation (f), Pd- or Ni-catalyzed cross-coupling[20] (g), and Cu- or Ni-promoted conjugate addition (h). The latter reaction (h) will be discussed in detail in this thesis (*vide infra*).

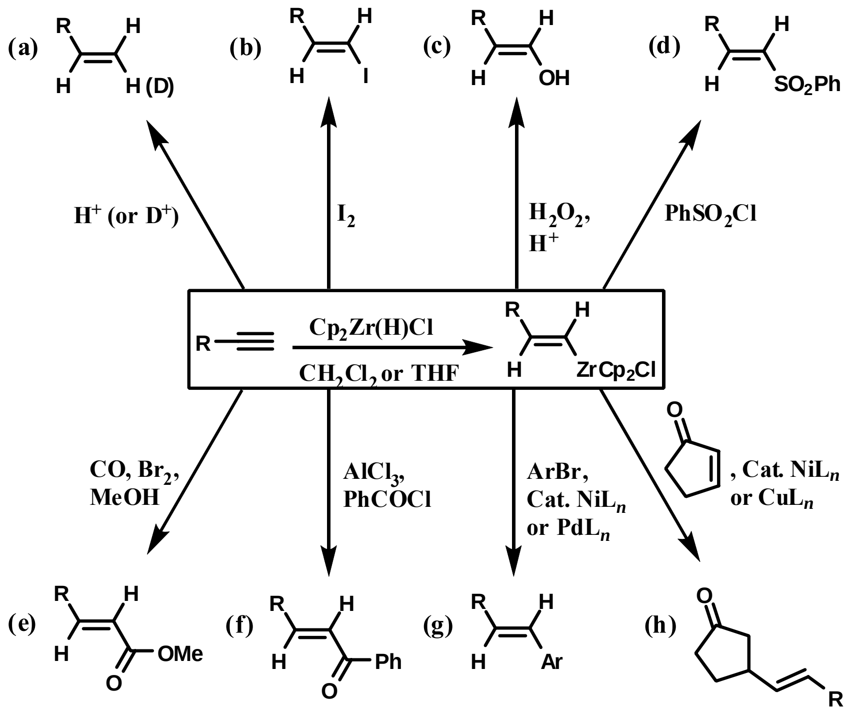
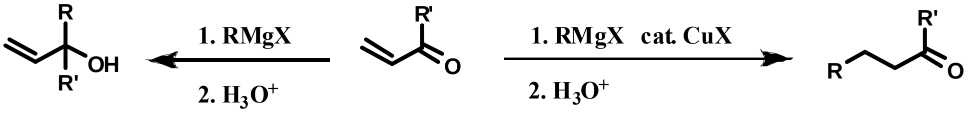


Figure 2.1. Applications of alkenylzirconocenes in organic synthesis.

It is important to mention that the chemoselectivity of Schwartz's reagent toward alkenes and alkynes is limited. In general, this reagent is not compatible with aldehydes, amides, enones, epoxides, isonitriles, ketones, nitriles or esters. Functional groups that are recovered unchanged after exposure to Schwartz's reagent include benzyl, *t*-butyl and silyl esters, carbamates, acetals, ethers, halides, sulfides and sulfonamides. Alcohols undergo an acid-base reaction with one equivalent of $Cp_2Zr(H)Cl$ and thereafter do not significantly interfere with alkene or alkyne hydrozirconation. Zirconocene hydrochloride has also been used as a reducing agent by Ganem and co-workers for the deoxygenation of β-ketoesters toward α,β-unsaturated esters,[21] and for the reduction of amides toward imines.[22] Schwartz's reagent also reduces *N*,*N*-disubstituted amides toward aldehydes,[23] and phosphine oxides toward phosphines.[24]

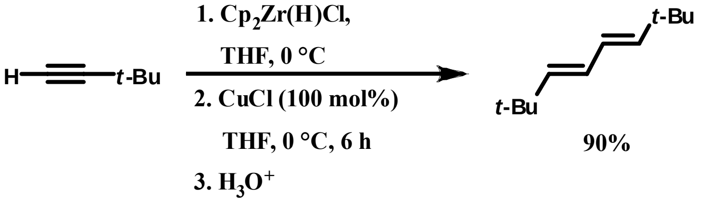
2.1.2 Cu- and Ni-Promoted Conjugate Additions

In the border between the transition metals and the main group elements, copper occupies a unique position in the periodic table. The key roles of copper have been widely recognized in various areas including superconductivity,[25] biological oxygenation,[26] and organic synthesis.[27] Since a wide range of organozirconium reagents has become readily available from the development of highly regio- and stereoselective hydrozirconation reaction of alkenes and alkynes, these intermediates have been used in a variety of carbon-carbon bond formations as indicated previously. However, both alkyl- and alkenylzirconium reagents are far less reactive toward organic electrophiles than the corresponding copper or magnesium species. Therefore, transmetalation procedures are often required in alkylation reactions. The observation by Kharasch and Tawney[28] that catalytic amount of copper halides favored 1,4-addition over the more traditionally observed 1,2-addition in the reaction between Grignard reagents and α,β-unsaturated ketones (Scheme 2.4) was of a crucial importance for the further development of organocopper reagents as synthetic tools in organic synthesis. The implication of organocopper species as the reactive intermediates in these copper-catalyzed Grignard reactions led to the development of a new area of organometallic chemistry; the stoichiometric organocopper reagents.[29] These were found to be useful species for conjugate addition of organic side chains to a variety of α,β-unsaturated carbonyl substrates, for coupling with organic halides,[30] and for other types of carbon-carbon bond formation processes.[31,32,33,34]

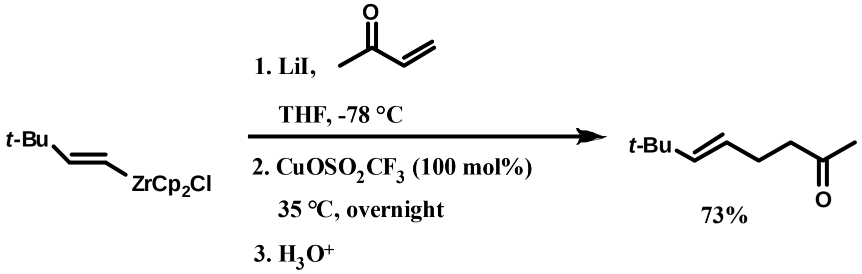


Scheme 2.4. Change of regioselectivity by the addition of copper(I).

In 1977, Schwartz and co-workers pioneered the transmetalation reactions of organozirconium compounds.[11] The first example reported by this group[35] was the addition of CuCl to alkenylzirconocene which leading to the formation of a copper mirror and the diene (Scheme 2.5). Conversion of the alkenylcopper(I) intermediates to the corresponding ate complexes in the presence of lithium iodide allowed conjugate addition reaction to α,β-unsaturated ketones (Scheme 2.6). However, in these examples, stoichiometric amount of copper(I) was necessary, and the 1,4-product was not achieved in high yield.[36]

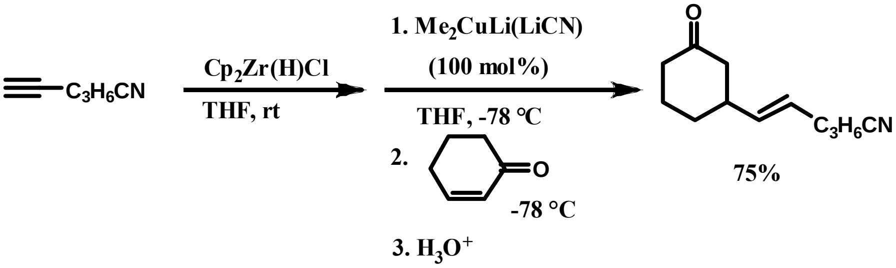


Scheme 2.5. Copper(I)-promoted formation of diene by Schwartz.



Scheme 2.6. First Cu(I)-promoted alkenylzirconocene addition to an enone.

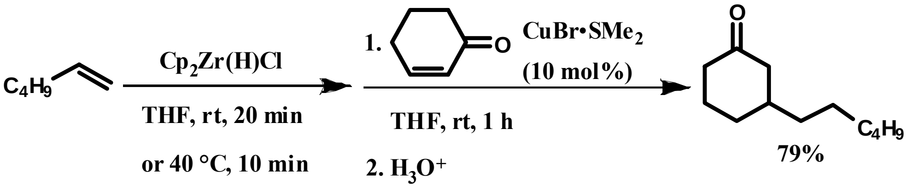
Modifications of this process were then developed by Lipshutz and co-workers using lithium dimethylcuprate derived from CuCN,[37] $Me_2CuLi(LiCN)$ (Scheme 2.7). Stoichiometric amount of the copper species was still needed. To circumvent this, MeLi[38a] and Me_3ZnLi[38b] as additives were utilized by the same group to obtain the 1,4-addition product using only 5 mol% of the copper complex.



Scheme 2.7. Using $Me_2CuLi(LiCN)$ in the 1,4-addition of alkenylzirconium reagents to α,β-unsaturated ketones.

Wipf and Smitrovich reported the first example of the use of alkylzirconocenes and catalytic copper(I) salts for conjugate addition reactions (Scheme 2.8).[39] In this protocol, enones were used as substrates and very good yields of the 1,4-alkyl transfer products were reported in the presence of 10 mol%

of CuBr(SMe$_2$). Organocopper decomposition and formation of a copper mirror is somewhat minimized by use of copper complexes, such as CuBr(SMe$_2$)[39] and CuCN.[40]



Scheme 2.8. First Cu(I)-catalyzed alkylzirconocene addition to an enone.

Mole[41] and Ashby[42] observed that Ni(acac)$_2$ also catalyzes the 1,4-addition of trimethylaluminum to various α,β-unsaturated ketones. Later, Schwartz and co-workers reported that catalytic amount of Ni(acac)$_2$ was utilized in the conjugate addition of alkenylzirconocenes to enones in low to moderate yields.[43]

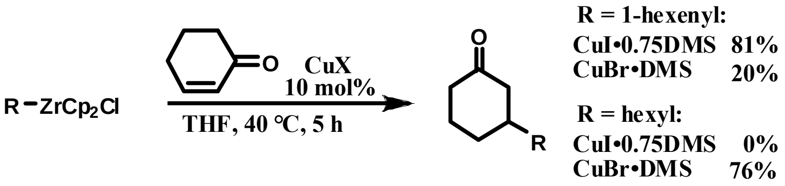
Due to the problems associated with copper catalysis in conjugate addition of alkenyl groups, additional research was required. Such problems are (1) generating alkenylcopper reagents without relying on organolithium or organomagnesium compounds, and (2) using only catalytic amount of copper source with no additives employed in order to achieve 1,4-products in high yields. The focus of this chapter is the development of a direct method for Cu(I)-catalyzed conjugate addition of alkenyl groups from alkenylzirconocene reagents to α,β-unsaturated aldehydes and ketones.

2.2 Results and Discussion

2.2.1 Additions to Enones and Enals

Hydrozirconation of alkynes, utilizing Schwartz's reagent,[35] {$Cp_2Zr(H)Cl$},[12] is a superb protocol for making regioselective vinylzirconocene reagents. Although the alkenylzirconium intermediates have been used in various coupling reactions as described earlier in this chapter (Figure 2.1), there is no reliable method available for utilizing a combination of the alkenylzirconocene and a catalytic amount of copper(I) source directly in the conjugate addition of vinyl groups. Taking advantage of copper(I) catalysis in promoting the 1,4-addition of alkenyl groups is not only a very useful transformation in synthetic chemistry, but it is also a complementary resource to the corresponding discrete alkenylcuprate reagents.[27] Moreover, applying a stoichiometric quantity of the copper(I) source makes the reaction less appealing, particularly for scale-up.

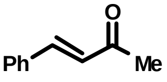
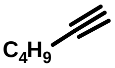
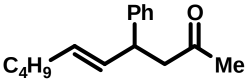
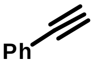
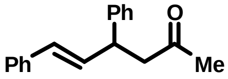
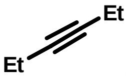
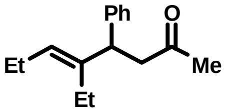
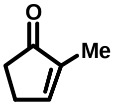
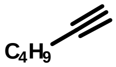
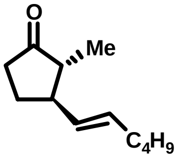
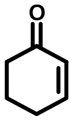
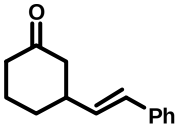
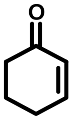
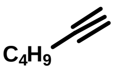
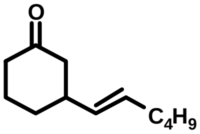
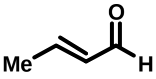
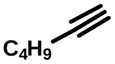
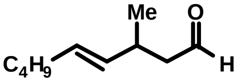
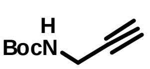
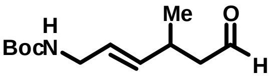
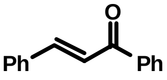
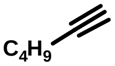
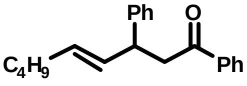
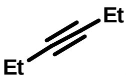
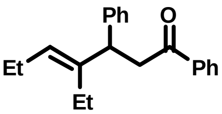
Inspired by Wipf's protocol[39] for the conjugate addition of alkylzirconocenes to enones (Scheme 2.8), the thought of transferring alkenyl groups in a 1,4-fashion to α,β-unsaturated carbonyl compounds was explored. The report by Dambacher *et al.*[44] for the conjugate addition of monosilylcopper reagents in presence of CuI•0.75DMS complex gave additional motivation for our investigation. In sharp contrast, the conjugate addition of *alkyl*zirconocenes to enones using CuBr•DMS produced a high yield of product, but the corresponding conjugate addition employing CuI•0.75DMS did not achieve the 1,4-addition product (Scheme 2.9). In the case of the *alkenyl*zirconocenes, CuBr•DMS failed to achieve a promising yield while CuI•0.75DMS produced a high yield of the conjugate addition product.



Scheme 2.9. Conjugate addition of alkyl- and alkenylzirconocene to enone.

Due to the unique properties on solubility and reactivity of the copper reagent obtained from CuI•0.75DMS,[44] a direct 1,4-transfer of alkenyl groups to enones and enals could be feasible. The conjugate addition of alkenyl groups from the alkenylzirconocene reagents is easily accomplished by adding 10 mol% of the CuI•0.75DMS complex to one equiv of the appropriate alkenylzirconocene reagent and enone/enal at +40 °C. Table 2.1 displays the results of this simple protocol that has a very good economy of alkenyl-transfer.

Table 2.1. CuI•0.75DMS-catalyzed conjugate addition of alkenyl groups.

entry	enone	alkyne^a	cond.^{b}	product		yield^c
1			12 h		1	97^d
2			12 h		2	79^d
3			12 h		3	86^d
4 5			5 h		4	54^d 87^e
6			5 h		5	78^d
7			5 h		6	81^d
8			2 h		7	90^d
9			2 h		8	88^d
10			10 h		9	84^d
11			10 h		10	71^d

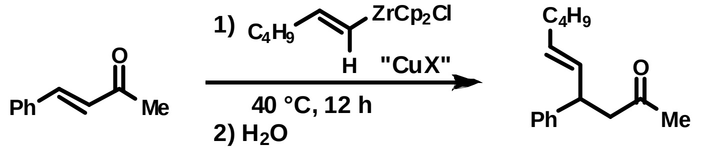
[a] 1.0 equiv alkyne *vs*. enone. [b] 40 °C. [c] Based on isolated and purified material (%). [d] 10 mol% CuI•0.75DMS *vs*. alkyne. [e] 100 mol% CuI•0.75DMS, *trans-cis* ratio, 20:1.

Reacting various alkynes with Schwartz's reagent, $Cp_2Zr(H)Cl$, in THF at +40 ºC for 10 minutes, afforded the corresponding alkenylzirconocenes, which subsequently were treated with 10 mol% CuI•0.75DMS and the substrates at +20 °C. Increasing the temperature of the resulting mixture to +40 ºC afforded the 1,4-adducts in high yields after the time indicated.[45] The results show that the conjugate addition works well for internal and terminal alkynes, as well as NHBoc substituted alkynes. It is worth mentioning that the 2-methyl substituted cyclopentenone gave lower yield of the 1,4-product in presence of catalytic amount of CuI•0.75DMS (Entry 4). The reactive β,β-disubstituted substrates are often challenging substrates in 1,4-addition reactions. This is might be the reason for the loss of product. However, applying stoichiometric quantity of the CuI•0.75DMS complex achieved 87% of the conjugate addition product (Entry 5). Furthermore, addition of the 1-hexenyl group to crotonaldehyde gave the corresponding product in 90% (Entry 8). High yield of the 1,4-product suggests that the oligomerization process, a zirconium enolate reacting with an aldehyde, is a very slow process compared to the 1,4-alkenyl transfer.

2.2.2 Efficiency of the $(CuI)_4(SMe_2)_3$ Complex

In order to expand this investigation, further exploration was carried out for the role of the CuI•0.75DMS complex in the conjugate addition of alkenylzirconium reagents. Benzalacetone was tested as a substrate to react with 1-hexenylzirconocene in presence of various copper sources (Table 2.2). The catalytic turn-over of the CuI•0.75DMS complex is most efficient when compared to various copper(I) and copper(II) sources in the conjugate addition of alkenylzirconocene reagents (Entries 1-4).

Table 2.2. Influence of the copper source on the conjugate addition.



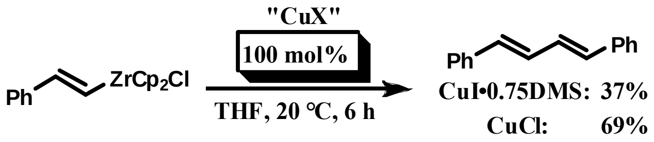
1

entry[a]	copper(I) source	mol. equiv Cu(I)	yield[b]
1	CuI·0.75DMS	1.00	97
2	CuI·0.75DMS	0.10	97
3	CuI·0.75DMS	0.05	89
4	CuI·0.75DMS	0.01	79
5	CuI[c]	0.10	34
6	CuI·DMS[d]	0.10	68
7	CuI·2PBu$_3$[e]	0.10	32
8	CuI·2PPh$_3$[e]	0.10	16
9	CuI·0.75S(*i*-Pr)$_2$[f]	0.10	52
10	CuBr·DMS	0.10	20
11	None	-	0
12	CuBr	0.10	0
13	LiCuBr$_2$	0.10	0
14	CuCl	0.10	2
15	CuCN	0.10	10
16	CuCN·2LiCl	0.10	10
17	CuOTf·PhMe	0.10	0

[a] 1.0 equiv alkyne *vs.* benzalacetone. [b] Based on isolated and purified material (%). [c] Aldrich ultrapure grade (99.999%). [d] 60 equiv DMS added to 99.999% grade CuI. [e] 2.0 equiv PR$_3$ added to 99.999% grade CuI. [f] CuI purified via CuI•S(*i*-Pr)$_2$ and used as the solid CuI•0.75S(*i*-Pr)$_2$ complex.

The efficiency of the CuI•0.75DMS catalyst is demonstrated (Entry 2) and compared to the yield obtained using a 99.999% grade CuI (Entry 5). The addition of excess methyl sulfide to the reaction gave a modest increase in yield of the 1,4-product (Entry 6). Substituting methyl sulfide with phosphines (Entries 7, 8) or diisopropyl sulfide (Entry 9) resulted in lower yields. The corresponding CuBr•DMS complex also failed to achieve high yield of the conjugate addition product (Entry 10). Copper salts purified via their DMS complex make these salts more soluble in THF or Et_2O, which in turn increases reactivity and stability, particularly in neat dimethyl sulfide.[46,47] Since there is a big difference in efficiency between CuI (99.999%) with DMS added and the purified CuI•0.75DMS complex, the reaction seems very sensitive toward impurities. The very low yielding reactions also included using CuBr, CuCl, CuCN and CuOTf. Not only were these copper catalysts less soluble and less efficient, but the formation of copper mirror precipitation was also noticed. This suggests that there is a less stable alkenylzirconocene/copper(I) intermediate formed under these conditions. The CuI•0.75DMS complex is also a more efficient catalyst in comparison to the reported[43] nickel(II) catalyst used in conjugate additions of vinylzirconocenes, product yields (97% *vs.* 34%).

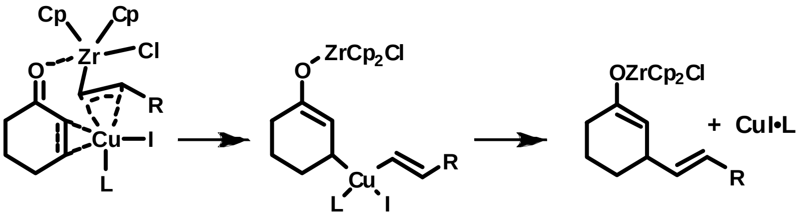
Treatment of a styrylzirconocene reagent with 100 mol% CuCl[35] at +20 °C in the absence of enone gave 69% of 1,4-diphenylbutadiene (Scheme 2.10). Under similar reaction conditions using 100 mol% CuI•0.75DMS, the rate of formation of the coupling product decreased. However, in the presence of 10 mol% CuI•0.75DMS and one equiv of 2-cycohexenone at +40 °C, formation of diene product did not occur based on ^{1}H-NMR data obtained from the crude reaction mixture. This suggests that the 1,4-addition reaction is faster than the formation of diene.



Scheme 2.10. Formation of diene product in presence of Cu(I) catalyst.

2.3 Mechanistic Postulate

Although the mechanism for the CuI•0.75DMS catalyzed conjugate addition of alkenyl groups is quite obscure and unknown, there is the possibility for a three-component interaction between the carbonyl oxygen of an enone, the zirconium atom of an alkenylzirconocene and the Cu(I) species (Scheme 2.11). The mechanism is closely related to the proposed CuBr•DMS catalyzed conjugate addition of *alkyl*zirconocenes to enones.[48]



Scheme 2.11. Proposed mechanism for the Cu(I)-catalyzed conjugate addition of *alkenyl*zirconocenes.

In addition, the π-base complexation of the Zr-alkene to Cu(I) is more favored with iodide present as a π-donor ligand compared to bromide and chloride. This could explain the failure of using CuBr•DMS in the 1,4-addition of *alkenyl*zirconocenes. The formation of a putative alkylvinyl-copper(III) intermediate[49] could next undergo a fast reductive elimination step to form the zirconium enolate product and then regenerate the copper(I) catalyst.

2.4 Conclusion

An efficient method for the conjugate addition of alkenyl groups to enones and enals has been developed using CuI•0.75DMS as a catalyst. While only catalytic amount of the copper(I) complex is required to achieve high yields of the 1,4-products, no additives or additional transmetalation steps are needed. In contrast to organolithium and organomagnesium compounds, high regioselectivity and chemoselectivity of the hydrozirconation step make this approach of alkenyl group transfer a better alternative for organic synthesis. Overall, the copper(I) iodide dimethyl sulfide complex is most efficient for the Cu-catalyzed conjugate addition of alkenylzirconocenes to α,β-unsaturated aldehydes and ketones when compared to other copper(I) and copper(II) sources as well as $Ni(acac)_2$ complex. Most important, this simple one-pot procedure has a very good economy of alkenyl group transfer.

This chapter contains material that appears in the following publications. The dissertation author was a co-author on both papers.

(1) El-Batta, A.; Hage, T.; Plotkin, S.; Bergdahl, M. Direct Copper(I) Iodide Dimethyl Sulfide Catalyzed Conjugate Addition of Alkenyl Groups From Vinylzirconocene Reagents. *Org. Lett.* **2004**, *6*, 107-110.

(2) El-Batta, A.; Bergdahl, M. Copper(I) Iodide Dimethyl Sulfide Catalyzed Addition of a Vinylzirconium Reagent. Preparation of 4-Phenyl-5(*E*)-decen-2-one. *Org. Synth.* **2007**, *84*, 192-198.

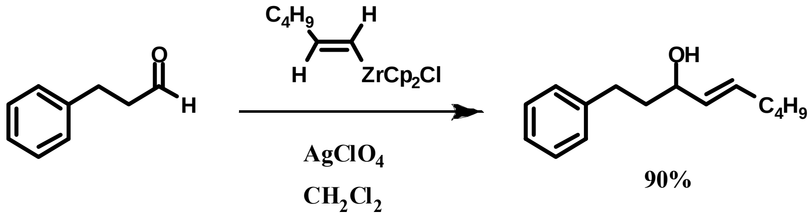
Chapter 3

Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Addition of Alkenyl Groups From Alkenyl-Alkylzinc Reagents

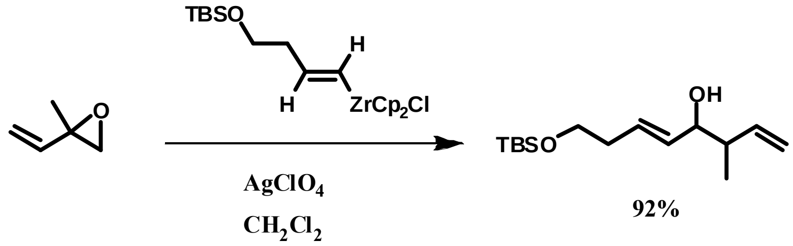
3.1 Introduction

Since the preparation of the first organochlorozirconium(IV) complex by Wailes, Weigold and Bell over 30 years ago,[6a] the application of these organometallics for carbon-carbon and carbon-heteroatom bond formations has become an integral part of synthetic strategies and tactics. A particularly attractive aspect of these early transition metal derivatives is their ease of preparation by hydrometalation of readily available alkenes and alkynes.[7,8f] A major advantage with zirconocenes is that they are compatible with many other functional groups such as benzyl, *t*-butyl and silyl esters, carbamates, acetals, ethers, halides, sulfides and sulfonamides (*vide supra*).

Although the ionic character of the polar covalent carbon-zirconium bond is almost equivalent to that of the carbon-magnesium bond, cyclopentadienyl-zirconocenes are weaker nucleophiles than the corresponding Grignard reagents. This is mostly due to steric shielding at the metal center by the two large cyclopentadienyl ligands.[7] Smaller electrophiles such as halogens, protons, dioxygen, CO,[8a] and isocyanides[50] can be directly added to the carbon-zirconium bond. The reactivity of alkenylzirconocenes towards organic electrophiles can be increased by reducing the steric congestion around zirconium via chloride abstraction. Suzuki and co-workers reported cationic zirconocenes prepared *in situ* that react rapidly with aldehydes to generate allylic alcohols (Scheme 3.1).[51] Wipf and co-workers reported cationic alkenylzirconocenes that promote epoxide rearrangement/[1,2]-hydrogen shift of terminal epoxides, followed by vinylation of the resulting aldehydes to afford secondary alcohols when catalytic amount of $AgClO_4$ was used (Scheme 3.2).[52]

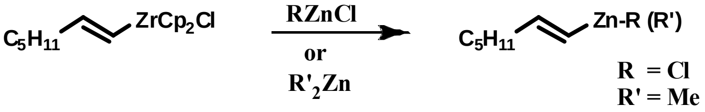


Scheme 3.1. $AgClO_4$-catalyzed addition of alkenylzirconocenes to aldehydes.



Scheme 3.2. Alkenylzirconocenes addition to epoxides catalyzed by $AgClO_4$.

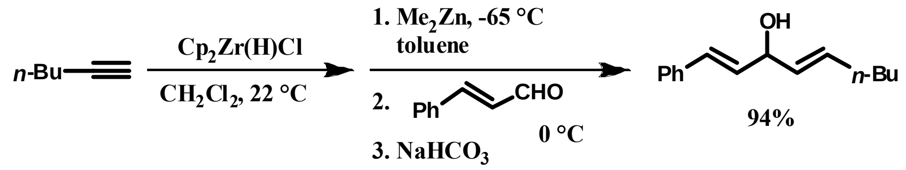
Transmetalation is another approach to increase the reactivity of alkenylzirconocenes toward organic electrophiles. Although many metals can be used for transmetalation from alkenylzirconocenes, the most synthetically useful metals are Pd, Ni, Cu and Zn. Since the early disclosure by Negishi and co-workers[20c] of zinc halide salts accelerating Pd(0)-catalyzed couplings between alkenylzirconocenes and alkenyl, aryl and alkynyl halides, several methods have been developed to extend the utility of this metathesis process from a zirconium chloride to the corresponding zinc chloride (Scheme 3.3). An organozinc species was postulated as an intermediate, and Hartner and Schwartz were indeed able to prepare an alkenylzincate intermediate from the corresponding chlorozirconocene.[53]



Scheme 3.3. Transmetalation of an alkenylzirconium to an alkenylzinc reagent.

Routes to more reactive diorganozinc intermediates, e.g., using Me_2Zn can alternatively be done. This would give the mixed species, alkenyl-alkylzinc, which selectively couple with various electrophiles.[7b,54] It is likely that transmetalation from the bulky zirconocenes to the sterically much more accessible zinc dichloride, and subsequent transmetalation from zinc to the palladium complex, is faster than the direct Zr/Pd exchange reaction. This process is an attractive alternative to the Suzuki-Miyaura cross coupling reaction. The versatility of this process has been demonstrated in the syntheses of complex molecules such as β-carotine,[55] eunicenone A,[56] microcystin,[57] (-)-motuporin,[58] pitiamide A,[59] reveromycin B,[60] 'FR901464',[61] xerulin,[62] discodermolide and callysatin A.[63]

A synthetically useful variant of the Zr→Zn transmetalation reaction was reported by Wipf and Xu.[64] Transmetalation of alkenylzirconocene to the corresponding alkenyl-alkylzinc compound occurs rapidly and at low temperature in the presence of commercially available dimethyl- or diethylzinc (Scheme 3.4). Subsequent addition of aldehydes to the reaction mixture afforded allylic alcohols in high yields. Wipf *et al.* later reported that in the presence of chiral amino alcohol or amino thiol ligands, high enantioselectivities of 1,2-addition products could be obtained.[65] It has also been described that the Me_2Zn reagent can be used in catalytic quantities.[66] Furthermore, this same 1,2-addition reaction has been shown to be mediated by both $ZnBr_2$[67] and MeLi.[68]

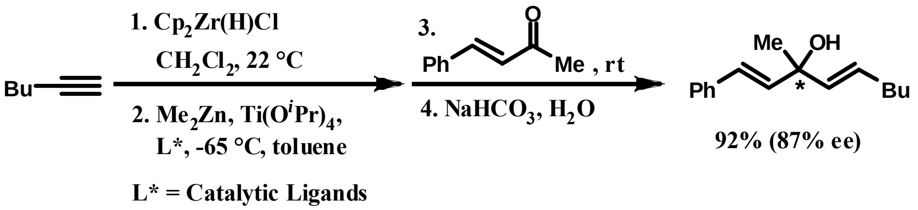


Scheme 3.4. Wipf's report on the vinylation of aldehydes using mixed alkenyl-alkylzincate reagents.

The high stereoselectivity of the crucial C-C bond formation contributes greatly to the synthetic versatility of the Zr→Zn transmetalation process,[27k] which combines the ease for the preparation of functionalized organometallics from alkynes via hydrozirconation with the broad range of reactivity of organozinc reagents.[69] Therefore, it has been used successfully in several natural product total syntheses such as asukamycin,[70] (+)-curacin A,[71] D-*erythro*- and *threo*-C_{18}-sphingosine,[72]

(+)-halichlorine,[73] laulimalide,[74] leucascandrolide A,[75] lobatamide C,[76] (±)-nisamycin,[77] and (-)-ratjadone.[78]

In addition, Li and Walsh have recently reported the catalytic asymmetric vinylation of ketones using the Zr→Zn transmetalation strategy (Scheme 3.5).[79] Although Walsh and co-workers previously did report a catalytic asymmetric vinylation of aldehydes using B→Zn transmetalation/aldehyde addition[80] in the presence of chiral amino alcohol (-)-MIB,[81] this approach failed when ketones were used as substrates. High levels of enantiocontrol as well as very good yields were obtained using a Zr→Zn transmetalation protocol and a catalytic quantity of chiral titanium complex prepared from Ti(O*i*-Pr)₄ and diol ligand.[82] Chavez and Jacobsen utilized the same Zr→Zn transmetalation methodology in the addition to ketones, specifically epoxyketone, in their total synthesis of fostriecin.[83] Furthermore, Wipf and co-workers have extended this transmetalation process to imines,[84] aldimines[85] and α-keto and α-imino esters.[86]



Scheme 3.5. Catalytic asymmetric Zr→Zn transmetalation/ketone addition.

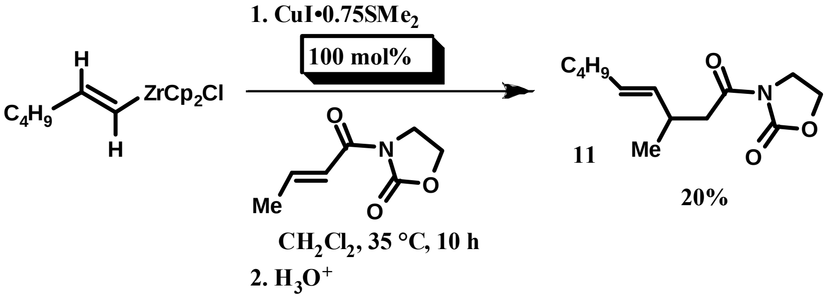
Zirconocenes and zinc appear, in fact, to be a bimetallic combination that displays unique reactivity characteristics that are not shared by either of the individual parent compounds. The goal of the research presented here was to develop a method for Cu(I)-catalyzed conjugate addition of alkenyl groups utilizing mixed alkenyl-alkylzincate reagents to *N*-enoyl derived oxazolidinones. In addition, the reactivity of mixed alkenyl-alkylzincate reagents versus their corresponding alkenylzirconocenes in the 1,4-addition to enones and enals was examined.

3.2 Results and Discussion

3.2.1 Additions to *N*-Enoyl Derived Oxazolidinones

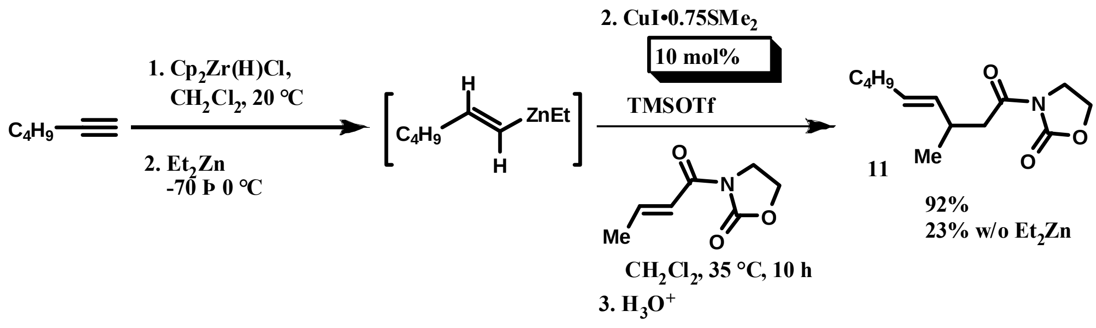
Motivated with the catalytic efficiency of the copper(I) iodide dimethyl sulfide complex in the direct 1,4-transfer of alkenyl groups to enones and enals using zirconocene chemistry,[45] we thought of applying this methodology to less reactive substrates such as *N*-enoyl derived oxazolidinones. The interest of this research avenue also stems from the fact that there was no efficient method available in literature for the 1,4-addition of alkenyl groups to α,β-unsaturated imides. The resulting products could also be further utilized as important building blocks in the synthesis of significant target molecules.

While employing stoichiometric quantity of the CuI•0.75DMS complex and 1.0 equiv of alkenylzirconocene reagent in CH_2Cl_2, the conjugate addition to *N*-butenoyl derived oxazolidinone achieved only 20% yield of the product (Scheme 3.6). Several attempts to utilize Lewis acids, such as BF_3•OEt_2, $ZnCl_2$, TMSI and $Al(O^{i-}Pr)_3$, were then conducted, but this approach failed to produce higher yield.[87]



Scheme 3.6. The first attempt of a Cu(I)-catalyzed conjugate addition of alkenylzirconocenes to α,β-unsaturated imides.

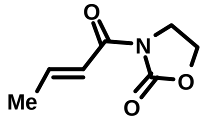
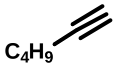
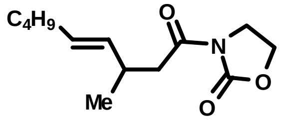
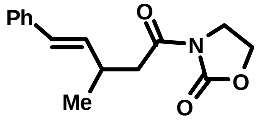
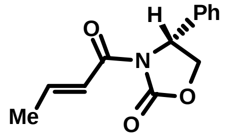
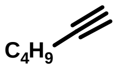
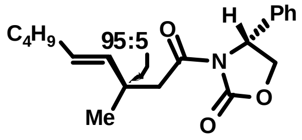
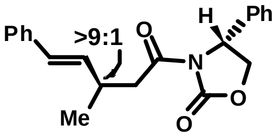
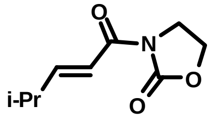
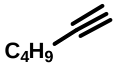
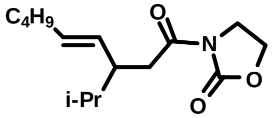
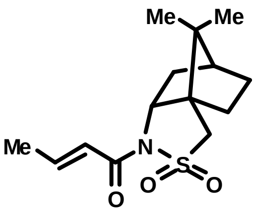
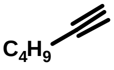
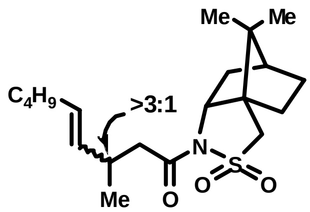
Transmetalation of zirconium to zinc has been demonstrated to be a more efficient subsequent procedure to form carbon-carbon bonds.[64,65,84-86,88] As discussed earlier in this chapter, this manipulation increases the reactivity of alkenylzirconocene intermediates and as a consequence achieves higher yields in cross coupling[20c] and vinylation of aldehydes[64,65] and ketones.[79] Applying the Zr→Zn transmetalation and subsequently adding a stoichiometric quantity of the CuI•0.75DMS complex in the conjugate reaction shown in Scheme 3.6, the 1,4-alkenyl transfer gave 86% of product. Furthermore, it was also found that the presence of TMSOTf[87] not only preserved the efficiency of the CuI•0.75DMS as a catalyst in the conjugate addition of mixed alkenyl-alkylzincate reagent to *N*-enoyl derived oxazolidinone,[89] but it also achieved the 1,4-product in higher yield (Scheme 3.7).



Scheme 3.7. TMSOTf-promoted Cu(I)-catalyzed conjugate addition of mixed alkenyl-alkylzincate reagents to α,β-unsaturated imides.

Results of the TMSOTf-promoted dimethyl sulfide-containing copper(I) iodide-catalyzed conjugate addition of mixed alkenyl-alkylzincate reagents to *N*-enoyl derived oxazolidinones are summarized in Table 3.1.[90] The protocol illustrates that TMSOTf promotes the formation of the 1,4-products in high yields as well as diastereomeric ratios of up to 95:5.

Table 3.1. TMSOTf-promoted Cu(I)-catalyzed conjugate addition of mixed alkenyl-alkylzincate in CH_2Cl_2 to α,β-unsaturated imides.

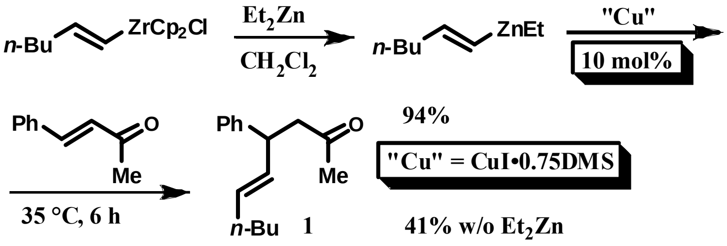
entry	substrate	alkyne[a]	reaction time[b]	product		yield[c,d]
1			10 h		11	92[e] (23)[e,f] 89[g]
2			12 h		12	84[e]
3			10 h		13	86[e] (27)[e,f] 87[g]
4			12 h		14	89[e]
5			12 h		15	85[e]
6			12 h		16	54[e] (0)[e,f]

[a] 1.0 molar ratio of alkyne:substrate:TMSOTf. [b] 35 °C in CH_2Cl_2. [c] Based on isolated and purified material (%). [d] Diastereomeric ratio (dr) determined on the crude material using ^{1}H-NMR spectroscopy. [e] 10 mol% CuI•0.75DMS *vs*. alkyne. [f] Reaction conducted with alkenylzirconocene reagent (absence of Et_2Zn). [g] Without TMSOTf. 100 mol% CuI•0.75DMS *vs*. alkyne.

When the reaction is applied to imides in the absence of TMSOTf, employing the mixed alkenyl-alkylzincate reagents, stoichiometric quantity of the CuI•0.75DMS is required in order to sustain a respectable yield of the 1,4-addition products. The results suggest that TMSOTf is most likely a more efficient Lewis acid with the imides than the mixed alkenyl-alkylzincate species. In the absence of Et_2Zn, the intermediate *alkenylzirconocene* reagent is much less reactive and will not undergo Cu(I)-catalyzed 1,4-transfer of the vinyl group to the imides, even with the presence of 1 equiv of TMSOTf (Entries 1, 3, 6). Nor is the TMSOTf powerful enough to assist in the 1,4-addition of the *alkenylzincate* reagent[91] in the absence of the CuI•0.75DMS catalyst, which underscores the crucial role of the Cu(I) species in these reactions.

3.2.2 Efficiency of the Zr→Zn Transmetalation Methodology in Cu(I)-Catalyzed 1,4-Additions of Alkenyl Groups to Enones and Enals

In order to examine the reactivity of the mixed alkenyl-alkylzincate reagents, a comparison study with the corresponding alkenylzirconocenes was conducted. The reaction of the *in situ* prepared alkenyl-alkylzincate intermediate with benzalacetone utilizing the CuI•0.75DMS complex (Scheme 3.8) providing the 1,4-product in 94% illustrates the efficiency of this specific Cu(I) catalyst. The protocol for this reaction is initiated by the hydrozirconation of an alkyne using $Cp_2Zr(H)Cl$ in CH_2Cl_2 at ambient temperature for 15 minutes, followed by an *in situ* transmetalation at -70 °C with Et_2Zn.[92] The corresponding alkenylzincate reagent was then allowed to warm to 0 °C and was subsequently exposed to 10 mol% of the CuI•0.75DMS complex, followed by the specific enone/enal. The reaction mixture was then heated to +35 °C for the time indicated and the corresponding 1,4-product was afforded.[90] In the presence of Cu(I), it is possible to completely circumvent the formation of the 1,2-addition product. The reaction rate is also faster than the corresponding alkenylzirconocene using benzalacetone as the substrate in CH_2Cl_2 as the medium. This suggests a higher reactivity of the alkenyl-alkylzincate reagent compared to the corresponding alkenylzirconocene. In addition, the addition of ethyl groups from the 1-hexenyl-ethylzincate reagents to enones and enals is not detected in presence of the CuI•0.75DMS complex.[93]



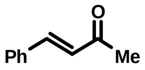
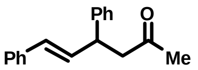
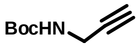
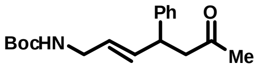
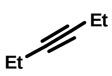
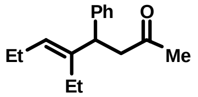
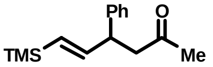
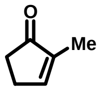
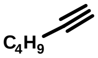
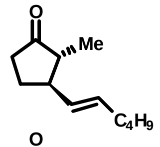
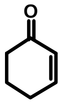
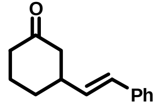
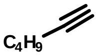
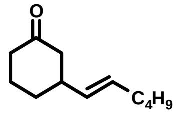
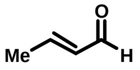
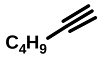
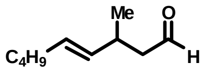
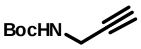
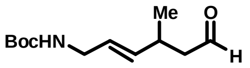
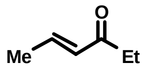
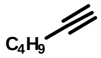
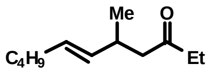
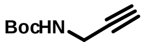
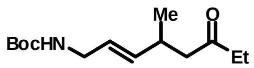
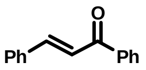
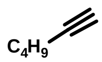
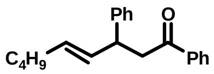
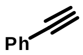
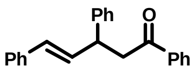
Scheme 3.8. CuI•0.75DMS-catalyzed conjugate addition to benzalacetone.

The reaction is in addition solvent dependent; when using the same reaction conditions, the 1,4-addition of 1-hexenyl-ethylzincate reagent is faster in CH_2Cl_2 than those conducted in THF or toluene where the yield at best was 60% of the conjugate product. This implies that a coordination effect by the more polar solvent could cause lower yields.

The unique efficiency of the dimethyl sulfide-containing copper(I) iodide complex in the conjugate addition of mixed alkenyl-alkylzincate reagents is demonstrated using a number of enones and enals (Table 3.2). It is important to note the efficiency of the Et_2Zn reagent. Applying the same system without the *in situ* transmetalation with the dialkylzinc reagent is also shown (Table 3.2). In the absence of Et_2Zn, the reaction resulted in lower yield of the desired products and with starting materials recovered (e.g. Entry 1, 33% vs. 82% with Et_2Zn).

The results exemplify the capability and the synthetic potential of this novel protocol. The methodology also works well for terminal and internal alkynes, as well as functional groups such as TMS and NHBoc substituted alkynes. Good chemical yields are obtained with enones and enals implies there is little, if any, oligomerization occurring. Normally, this is a common side reaction between aldehydes and the enolates generated from conventional Gilman type organocopper reagents.

Table 3.2. CuI•0.75DMS-catalyzed conjugate addition of mixed alkenyl-alkylzincate reagents in CH_2Cl_2 using enones and enals.

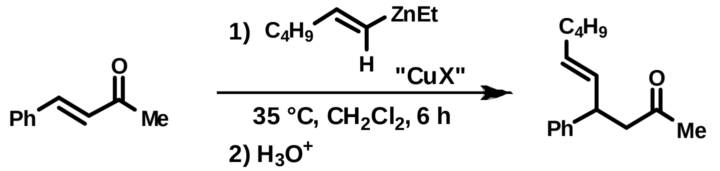
entry	substrate	alkyne[a]	reaction time[b]	product		yield[c,d]
1			6 h		2	82^{e} 33^{f}
2			6 h		17	89^{e} 29^{f}
3			6 h		3	82^{e}
4			6 h		18	84^{e}
5			2 h		4	$67^{e,g}$ 27^{f}
6			2 h		5	74^{e}
7			2 h		6	83^{e} 39^{f}
8			30 min		7	88^{e} 41^{f}
9			30 min		8	82^{e}
10			4 h		19	95^{e} 39^{f}
11			4 h		20	93^{e}
12			6 h		9	91^{e} 51^{f}
13			6 h		21	79^{e}

[a] 1.0 equiv alkyne *vs*. enone. [b] 35 °C in CH_2Cl_2. [c] Isolated and purified material (%). [d] 10 mol% CuI•0.75DMS *vs*. alkyne. [e] Reaction conducted with alkenyl-alkylzincate reagent. [f] Reaction conducted with alkenylzirconocene reagent (absence of Et_2Zn). [g] *trans-cis* ratio, ~20:1.

3.2.3 Efficiency of the $(CuI)_4(SMe_2)_3$ Complex

Studies on the efficiency of the CuI•0.75DMS complex were conducted and further discussed in this section. The CuI•0.75DMS complex[47] is unique when it is compared to other commonly used copper(I) and copper(II) sources employed in 1,4-additions. For instance, the 1,4-addition of a vinyl group utilizing a mixed vinylzincate reagent (Table 3.3) is best conducted in the presence of the CuI•0.75DMS complex.

Table 3.3. Influence of Cu and Ni additives on the 1,4-addition of alkenyl-alkylzincate reagents.



1

entry[a]	additive	mol. equiv "CuX"	yield[b]
1	CuI·0.75DMS	0.10	94 (0)
2	CuI[c]	0.10	64 (30)
3	CuBr·DMS	0.10	32 (60)
4	CuCl	0.10	0 (95)
5	CuOTf·PhMe	0.10	0 (95)
6	CuCN·2LiCl	0.10	10 (85)
7	$Cu(acac)_2$	0.10	0 (95)
8	$Cu(OTf)_2$	0.10	0 (95)
9	$Ni(acac)_2$	0.10	21 (70)
10	None	-	55[d] (0)

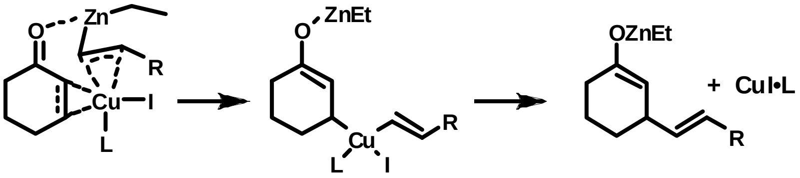
[a] 1.0 equiv alkyne *vs.* substrate. [b] Isolated and purified material. Recovered substrate in brackets (%). [c] Aldrich ultrapure grade (99.999%). [d] 24% of 1,2-addition product.

It is not entirely surprising that the mixed alkenyl-alkylzinc reagent displays both 1,4- and 1,2-addition pathways with benzalacetone in CH_2Cl_2 in the absence of a Cu(I) catalyst (Entry 10), however it is unexpected that both of these reaction pathways are shut down in the presence with most of the scrutinized copper catalysts. Moreover, the amount of the diene coupling product suggests that the Cu(I) species maintains its role as a catalyst in those side-reactions. On the other hand, the presence of only 10 mol% of the CuI•0.75DMS complex (Entry 1) circumvents the formation of this "Glaser-type"[94] coupling product and provides in its place a high yield of the conjugate addition product from benzalacetone.

3.3 Mechanistic Postulate

The Cu(I) catalyst is promoting the 1,4-addition of the vinyl group over the ethyl group[93] using the mixed alkenyl-ethylzinc reagent. This is presumably due to the pre-formation of a more favorable sp^2-hybridized carbon to copper bond during the reaction pathway. However, the mechanism for the CuI•0.75DMS catalyzed 1,4-addition of the alkenyl group is still unknown. Since there is no evidence for the formation of a discrete alkenylcopper species via the zinc to copper transmetalation, it is proposed that the reaction proceeds via an alkenyl-alkylcopper(III) intermediate as indicated in Scheme 3.9.[49] Subsequent reductive elimination would then provide the zinc enolate of the 1,4-addition product and regeneration of the essential Cu(I) species.

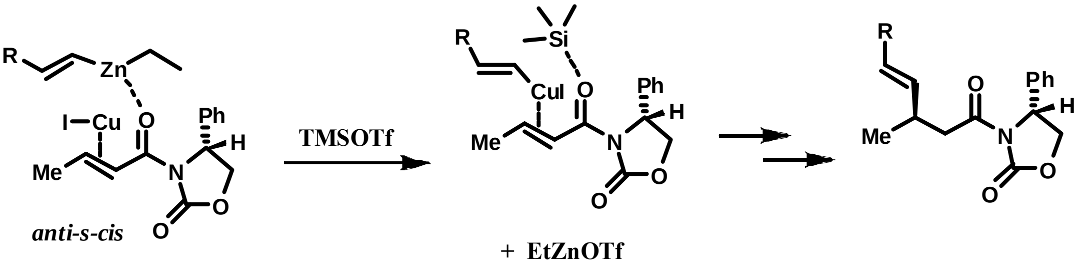
As in the case for alkenylzirconocenes discussed previously (section 2.3), it is possible for a π-base complexation of the alkene moiety of the Zn-alkene to Cu(I).



Scheme 3.9. Proposed mechanism for the Cu(I)-catalyzed conjugate addition of mixed alkenyl-alkylzincate reagents.

This complex seems more favorable with iodide present as a π-donor ligand compared to bromide and chloride. Moreover, it is possible for the iodide to aid further in the reductive elimination step compared to bromide or chloride. Thus, there is a greater efficiency of the CuI•0.75DMS complex compared to the CuBr•DMS complex in the conjugate addition of mixed alkenyl-alkylzincate reagents.

Although the presence of TMSOTf was crucial to achieve good results for the conjugate addition process using *N*-enoyl derived oxazolidinones, its precise role still remains uncertain. TMSOTf was used previously in our group in promoting copper(I)-catalyzed conjugate additions of alkyl groups to the same chiral *N*-enoyl amides.[95] The conclusion from this study was the major diastereomer being formed via the non-chelating conformational (*anti-s-cis*) transition state (entry 3).[95b] Furthermore, the same diastereomer was obtained in the absence of TMSOTf or Et_2Zn (entry 3), suggesting the zinc reagent is not acting as a chelating reagent in these reactions. Conducting the same reaction using $MgBr_2$ instead of TMSOTf influenced the diastereomeric ratio in the direction opposite to the TMSOTf-promoted 1,4-additions of mixed alkenyl-alkylzincate reagents to chiral α,β-unsaturated imides. This suggests that the *anti-s-cis* conformation is more favored than the chelated form (*syn-s-cis*) for the *N*-enoyl derived oxazolidinones (Scheme 3.10).



Scheme 3.10. Postulated interactions for the TMSOTf-promoted Cu(I)-catalyzed conjugate addition of mixed alkenyl-alkylzincate reagents to chiral imides.

3.4 Conclusion

Transmetalation of zirconium to zinc has proved to be a more efficient tool for the formation of the carbon-carbon bond. This manipulation gave high yield of the conjugate addition products of alkenyl groups to enals, enones and α,β-unsaturated imides. The Zr→Zn transmetalation protocol illustrates that the 1,4-addition of mixed alkenyl-alkyl*zincate* reagents to enones and enals is faster than the corresponding alkenyl*zirconocene* reagents in CH_2Cl_2 or THF. In this system, there is no evidence for the formation of a discrete alkenylcopper species via the zinc to copper transmetalation, therefore it is proposed the reaction proceeds via an alkenyl-alkylcopper(III) intermediate.

While TMSOTf maintained the efficiency of CuI•0.75DMS as a catalyst in the conjugate addition of alkenylzincates to *N*-enoyl derived oxazolidinones, the yields of 1,4-products as well as the diastereomeric ratios (dr) were very good (up to 95:5). It is demonstrated the zinc reagent is not acting as a chelating reagent. The non-chelating conformation (*anti-s-cis*) is more favored than the chelated form (*syn-s-cis*) for the *N*-enoyl derived oxazolidinones.

This chapter contains material that appears in the following publication. The dissertation author was a co-author on the paper.

(1) El-Batta, A.; Bergdahl, M. Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Addition of Alkenyl Groups From Alkenyl-Alkylzincate Reagents. *Tetrahedron Lett.* **2007**, *48*, 1761-1765.

Chapter 4

Chemical Studies Toward the Total Synthesis of Azaspirene, a Novel Angiogenesis Inhibitor

4.1 Introduction

4.1.1 Biological Significance of Angiogenesis in Cancer

Angiogenesis plays an important role in cancer from the initial stage of carcinogenesis to the end stage of metastatic disease.[96] The development of neovessels during angiogenesis provides two essential functions for the growth and metastasis of a cancer. Primarily, the neovessels provide a route for supply of nutrients and oxygen to sustain tumor growth, as well as excretion of metabolic waste. In addition, the neovessels provide access for tumor cells to enter the blood circulation.[97] The angiogenesis activity in the tumors has been shown to correlate with metastasis in many human cancers.[98] Figure 4.1 summarizes the role of angiogenesis in the various steps of tumor growth and metastasis.[99]

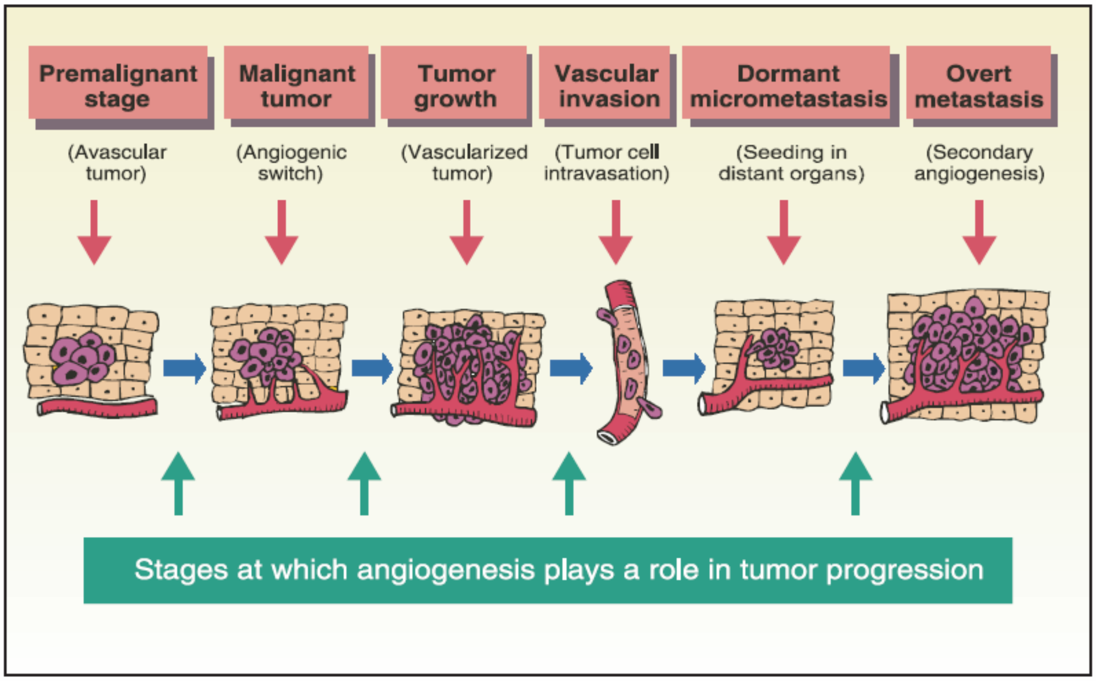


Figure 4.1. Role of angiogenesis in cancer development, growth and metastasis.

The process of angiogenesis is a complex multi-step process initiated by the release of angiogenic factors from tumor cells. The angiogenic factors bind to specific receptors of endothelial cells of pre-existing blood vessels and activate the endothelial cells, which then secrete enzymes to degrade the underlying basement membrane. Additional proteinases such as matrix metalloproteinases (MMPs) and plasminogen activators are secreted by the tumor cells to degrade the extracellular matrix in front of the sprouting vessels. The activated endothelial cells then proliferate, migrate and assemble into new capillary tubes, followed by the synthesis of a new basement membrane. It is widely accepted that angiogenesis by the sprouting of new blood vessels from pre-existing vessels in surrounding tissues plays the most important role in tumor growth and metastasis in most cancers.[100-102]

The extent of angiogenesis in a tumor is the result of complex interactions of factors released from tumor cells, capillary endothelial cells and infiltrating host cells such as macrophages and fibroblasts.[103-105] There are also negative regulators of angiogenesis known as antiangiogenic factors. Tumor angiogenesis is the net balanced result of actions of multiple angiogenic and antiangiogenic factors from both tumor cells and host cells in the tumor. Table 4.1 lists some of the relatively well-characterized angiogenic and antiangiogenic factors; only vascular endothelial growth factor will be discussed in further details later in this chapter.

Table 4.1. Examples of endogenous angiogenic and antiangiogenic factors that regulate angiogenesis.

Angiogenic factors	Antiangiogenic factors
Vascular endothelial growth factor	Thrombospondin-1,2
Acidic and basic fibroblast growth factors	Endostatin
Transforming growth factor-alpha/beta	Angiostatin
Platelet-derived endothelial cell growth factor	Interferon-alpha/beta
Hepatocycle growth factor	Interleukin-12
Tumor necrosis factor-alpha	Platelet factor 4 fragment
Epidermal growth factor	Tissue inhibitor of metalloproteinase-1/2
Placental growth factor	Human macrophage metalloelastase
Tissue factor	Anti-thrombin III fragment
Interleukin-6/8	Vascular endothelial growth inhibitor
Angiogenin	Vasostatin
Angiopoietin-1	
Cyclo-oxygenase-2	
Macrophage migration inhibitory factor	
Nitric oxide	

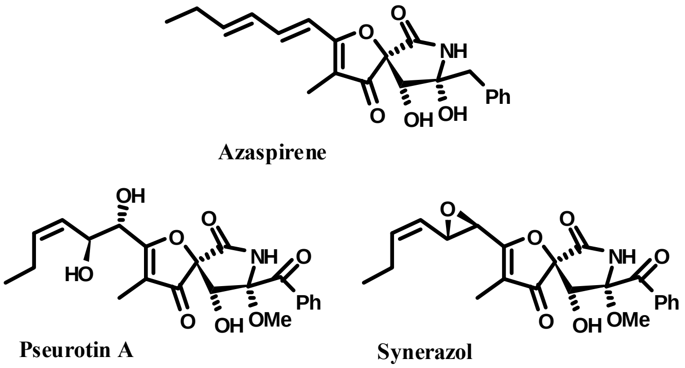
4.1.2 Mode of Action of Azaspirene

Azaspirene, isolated from the fungus *Neosartoya* species,[106] is a novel angiogenesis inhibitor. It was reported to inhibit endothelial migration induced by vascular endothelial growth factor (VEGF). VEGF is one of the first isolated angiogenic peptides, and is the most well-studied angiogenic factor thus far. It has a specific mitogenic effect on endothelial cells, increaseing vascular permeability, hence also known as a vascular permeability factor. VEGF also promotes extravasation of proteins from tumor vessels, leading to the formation of a fibrin matrix that supports the growth of endothelial cells and allows invasion of stromal cells into the developing tumor.[107] The effects of VEGF are mediated via its receptors, VEGF-1 (Flt-1) and VEGF-2 (KDR), by endothelial cells.[108,109]

In view of this, efficient inhibition of VEGF is a clever method of treating angiogenesis-related diseases such as cancer and rheumatoid arthritis.[96,110] Simply, the antiangiogenic drugs work by blocking the signals that tumors send out asking for a supply of nutrient and oxygen, which may be responded by the development of neovessels in the endothelial cells. Antiangiogenic therapy has some advantages over conventional cytotoxic chemotherapy: (1) the endothelial cells are genetically stable cells with a low mutation rate, and hence drugs targeted at endothelial cells are less likely to induce drug resistance compared to conventional cytotoxic drugs, (2) as antiangiogenic therapy targets the specific immature characteristics of tumor vasculature, which differs from normal quiescent vasculature, low toxicity has been demonstrated in pre-clinical studies, and (3) endothelial cells are directly exposed to blood borne agents, circumventing the problem of drug delivery to tumor cells, which is a major obstacle to conventional anticancer therapy.

4.2 Prior Total Syntheses of Azaspirene

The structure of azaspirene is a highly oxygenated *1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione* skeleton with benzyl and hexadiene substituents.[106] The interest in synthesizing azaspirene stems from the difficulty to isolate larger quantities of this structure enough to further investigate its properties and its mode of action. Also, chemical studies toward azaspirene synthesis will allow the construction of a library of analogs of this target molecule to possibly find more interesting biological candidates. The core structure of azaspirene is also found in pseurotin A[111] and synerazol[112] (Figure 4.2). However, these compounds were reported to have no antiangiogenic activity. Because of the unique structure of azaspirene that gives it a more opportune route for the synthesis of this series of compounds, Hayashi[113] and Tadano[114] groups have achieved asymmetric total syntheses of this angiogenesis inhibitor. Furthermore, several other synthetic studies on the pseurotins have been reported.[115]



Azaspirene

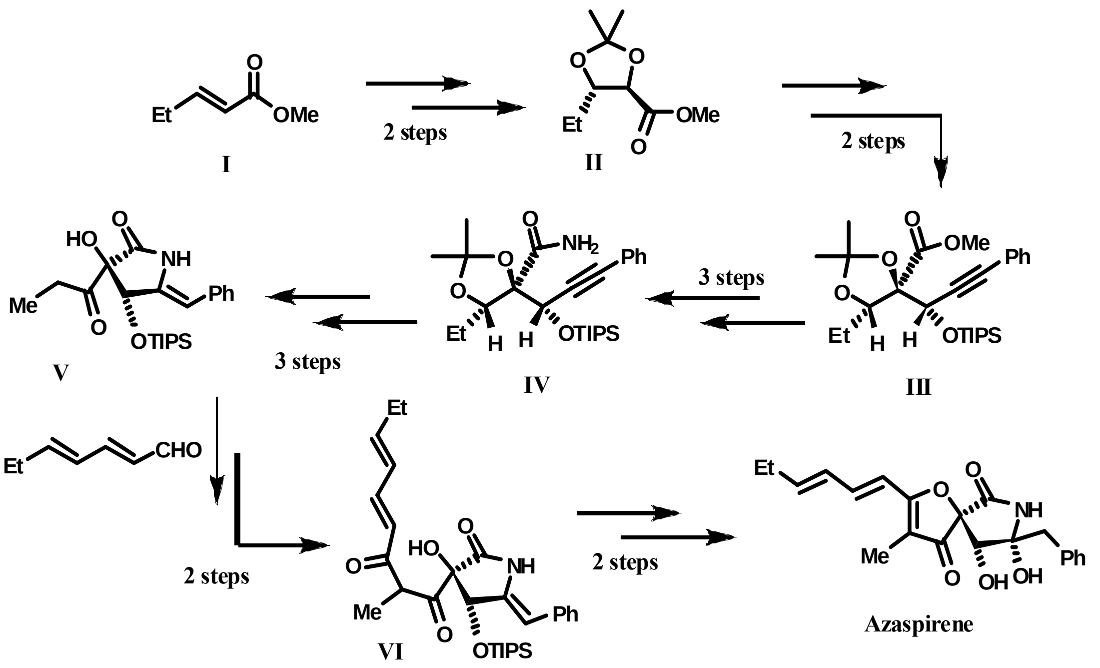
Pseurotin A

Synerazol

Figure 4.2. Structures of azaspirene, psuerotin A and synerazol.

4.2.1 Hayashi's Approach

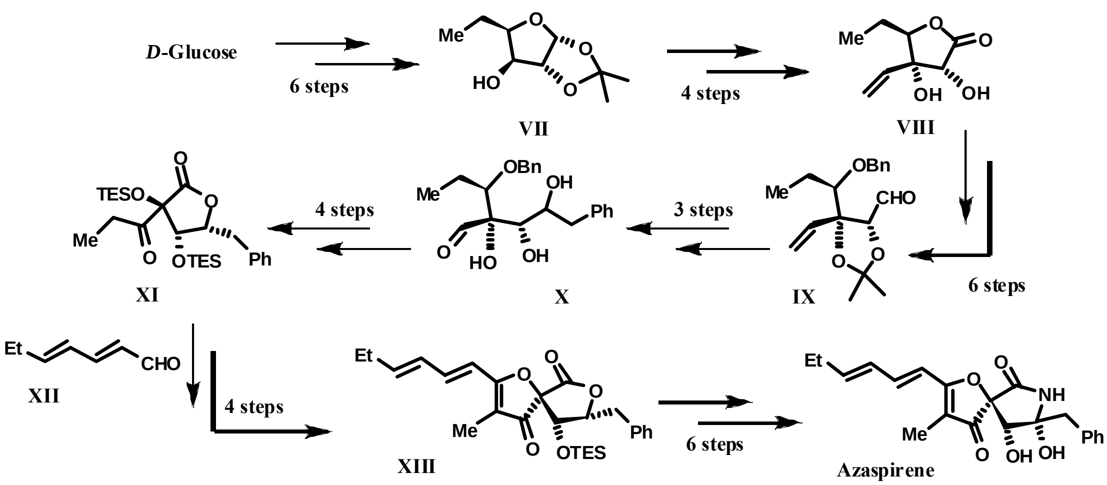
The first asymmetric total synthesis of (-)-azaspirene was reported by Hayashi's group in 2002, and the absolute stereochemistry for this target molecule was also determined.[113] The synthetic route started with the Sharpless asymmetric dihydroxylation of methyl 2-pentenoate (**I**) providing the *syn*-diol adduct, followed by the acetal formation to give intermediate **II** (Scheme 4.1). The next step, an aldol condensation of **II** with phenylpropargyl aldehyde in the presence of $MgBr_2{\bullet}OEt_2$ as a Lewis acid afforded the desired diastereomer as the major product. Protection of the resulted alcohol provided the silyl ether **III**. Hydrolysis of the methyl ester in **III**, conversion to its corresponding acid chloride and ammonolysis using NH_3 yielded amide **IV**. The reaction of **IV** with sodium hydride in DMF resulted in the formation of the *Z*-benzylidene γ-lactam as the major isomer. The *Z*-isomer was then treated with CF_3CO_2H/MeOH to cleave its acetal function, affording the diol intermediate. Oxidation of the resulted diol with Dess-Martin periodinane in the presence of water, according to the method by Schreiber's modified conditions, gave α-hydroxy ketone **V**. Aldol condensation of the lithium enolate of **V** and heptadienal in the presence of HMPA resulted in a mixture of diastereomers, followed by oxidation using Dess-Martin periodinane gave 1,3-diketone adduct **VI**. This diketone underwent cyclization when purified on thin-layer chromatography to provide the azaspiro[4.4]nonenedione bicycle. Acidic hydrolysis of the benzylidene group and deprotection of the TIPS group were done effectively to complete the synthesis of (-)-azaspirene.



Scheme 4.1. Synthesis of azaspirene by Hayashi and his co-workers.

4.2.2 Tadano's Approach

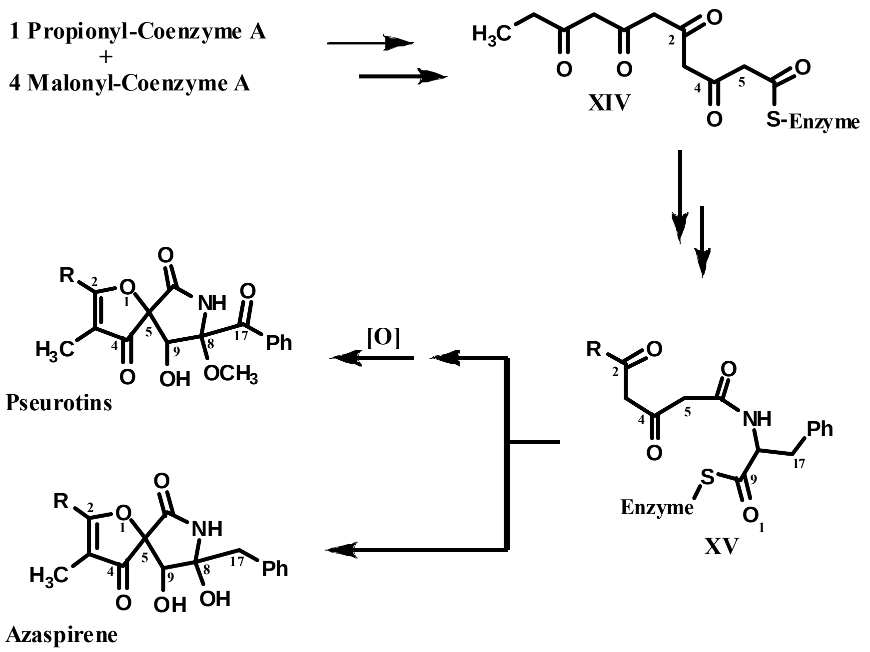
Tadano's group achieved the total syntheses of natural pseurotin A and F_2 in 2004.[114] This particular synthetic route was modified to complete the synthesis of azaspirene (Scheme 4.2). The synthesis started with *D*-glucose and in six convenient steps, 5,6-dideoxy-1,2-*O*-isopropylidene-α-*D*-*xylo*-hexofuranose (**VII**) was prepared elsewhere.[116] The oxidation of **VII** with PCC, followed by the insertion of a vinyl group via Grignard conditions afforded one single diastereomer. Acid hydrolysis of the acetal moiety, and subsequent chemoselective oxidation of the hemiacetal carbon with NIS in the presence of TBAI, provided γ-lactone-α,β-diol **VIII**. The *cis*-diol in **VIII** was protected as an isopropylidene acetal, which was then treated with $LiAlH_4$ to provide a ring-opened diol. A three-step protection/deprotection process from diol adduct via a trityl ether provided an acyclic protected secondary alcohol as its benzyl ether. Dess-Martin oxidation then produced aldehyde **IX**. This aldehyde underwent 1,2-addition using benzylmagnesium chloride in the presence of CuBr•DMS in a mixed solution of THF and DMS to afford the 1,2-benzyl addition product. After ozonolysis and successive hydrolytic removal of the acetal, intermediate **X** was achieved. The resultant γ-lactol adduct **X** underwent chemoselective oxidation using NIS, vicinal di-*O*-TES protection, debenzylation and subsequent oxidation via Dess-Martin to provide ethyl ketone intermediate **XI**. An aldol reaction was next conducted where **XI** was exposed to KHMDS in THF and then commercially available (2*E*,4*E*)-heptadienal **XII** was added to provide the product. After exposure of this adduct to a HF-pyridine solution, the tertiary TES group was selectively removed. Dess-Martin oxidation, followed by dehydration of the resultant γ-lactone hemiketal with thionyl chloride, provided the desired 1,7-dioxaspiro[4.4]non-2-ene-4,6-dione **XIII**. The spirocyclic γ-lactone **XIII** underwent several more steps; ammonolysis using saturated NH_3 in *i*-PrOH, followed by Dess-Martin oxidation and exposure to saturated aqueous Na_2CO_3 as the key steps, finalized the total synthesis of azaspirene.



Scheme 4.2. Synthesis of azaspirene by Tadano and his co-workers.

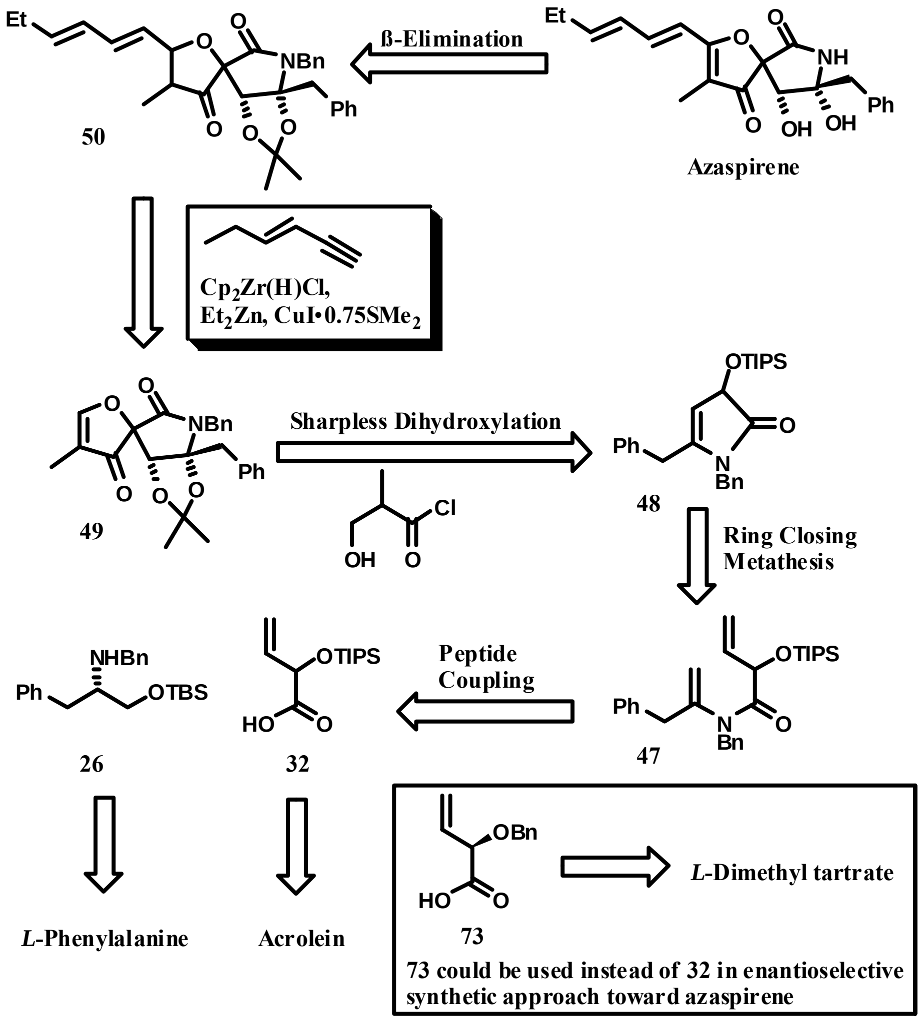
4.3 Retrosynthetic Strategy for Azaspirene

There have been reports that the building blocks of pseurotin A arise from one unit of propionate, four units of malonate, one unit of phenylalanine, and two units of methionine.[117] Since the culture broth of the azaspirene-producing strain contained pseurotin A, these compounds could share the same biosynthetic pathway. In particular, the structure of azaspirene with its benzyl group is the first example of this series of compounds and also indicates that oxidation at the benzyl group position occurs after the incorporation of phenylalanine. A possible biosynthetic pathway from the starter unit, propionyl-coenzyme A, for the production of azaspirene is shown in Scheme 4.3. The spiro-center in azaspirene could be formed via key intermediates **XIV** and **XV** accompanied by the incorporation of one unit of phenylalanine and one unit of methionine.



Scheme 4.3. Possible biosynthetic pathway for the production of azaspirene.

Due to the complex nature of the target molecule, we are proposing a number of synthetic methodologies or strategies to successfully complete the total synthesis of azaspirene. The proposed retrosynthetic plan for azaspirene is illustrated (Scheme 4.4). Among the key synthetic manipulations involved is the direct conjugate addition of either an alkenylzirconocene or a mixed alkenyl-alkylzincate reagent, recent methodologies developed in our laboratory using copper(I) catalysis.[45,90] Other notable features in this viable pathway are: i) Sharpless asymmetric dihydroxylation, ii) ring closing metathesis, and iii) peptide coupling of easily available intermediates from inexpensive precursors to build a key fragment in the target molecule.



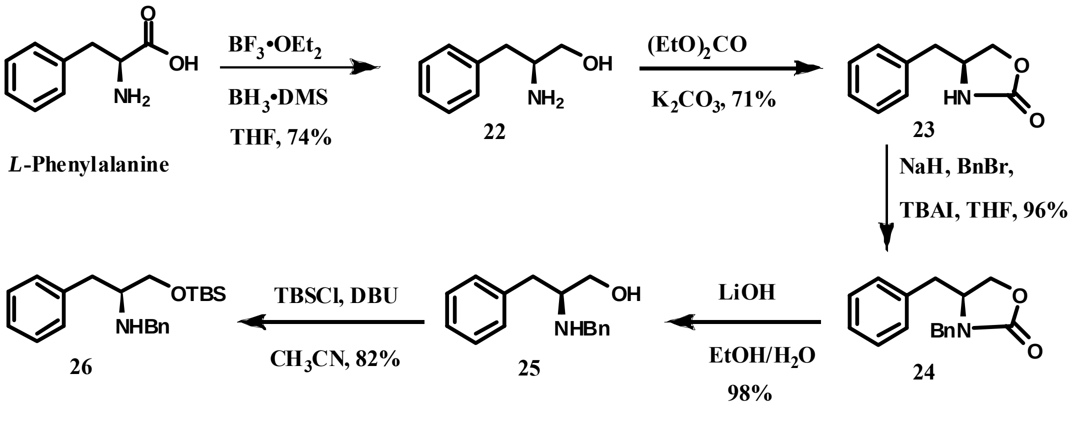
Scheme 4.4. Synthetic strategy toward azaspirene.

4.4 Results and Discussion

The convergent synthetic plan for azaspirene starts with the preparation of two key fragments, (2*S*)-(benzylamino)-3-phenyl-1-(*tert*-butyldimethylsilyloxy) propane (**26**) and 2-(triisopropylsilyloxy)-3-butenoic acid (**32**).

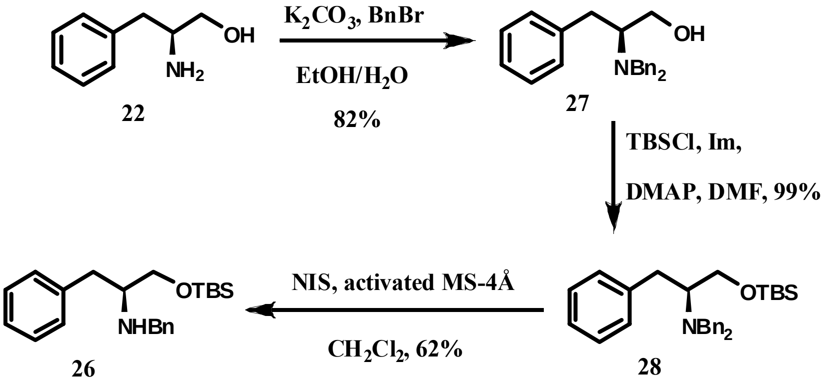
4.4.1 Synthesis of the Amine Fragment

The synthetic route toward amine **26** starts with *L*-phenylalanine, which was reduced using BH_3•DMS and BF_3•OEt_2 to give 74% of the corresponding alcohol (Scheme 4.5).[118] *L*-Phenylalaninol (**22**) was then exposed to diethyl carbonate and K_2CO_3 to afford the oxazolidinone **23** in 71%. This amide was deprotonated using NaH, and subsequently protected as its benzyl amide **24** in 96% yield.[119] The hydrolysis of oxazolidinone was conducted in the presence of lithium hydroxide and aqueous EtOH to give 98% of *N*-Bn-*L*-phenylalaninol (**25**).[120] The primary alcohol **25** next was protected as its *O*-(*t*-butyldimethylsilyl) ether using DBU and acetonitrile to finally achieve the amine fragment **26** in 82% yield.[121]



Scheme 4.5. Synthesis of amine fragment **26**.

It is important to mention the method using TBSCl, imidazole and DMAP in DMF, being the conventional way for protecting a primary alcohol as its silyl ether, was conducted first with intermediate **25** and failed to afford the product **26**. This is probably due to the consumption of the silyl reagent by reacting it with the amine nucleophilic substituent faster than the alcohol site. Before finding an alternative literature method utilizing TBSCl, DBU in MeCN to afford the protected primary alcohol as its silyl ether, another approach to achieve the amine fragment was planned and executed (Scheme 4.6).

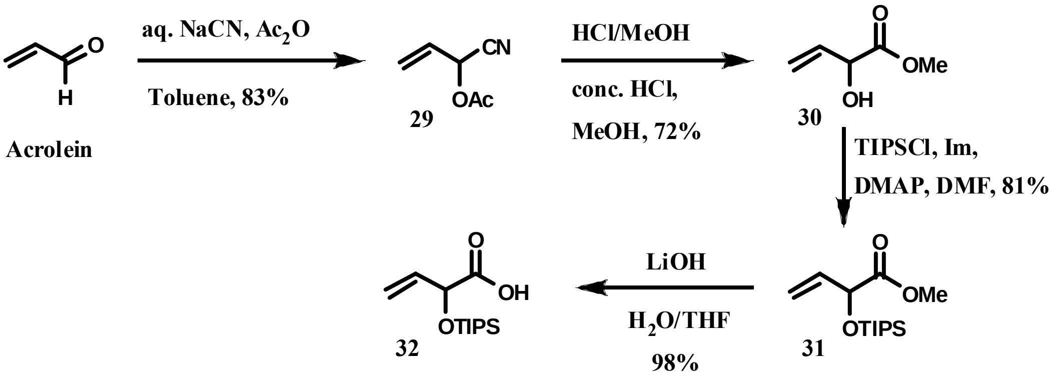


Scheme 4.6. Alternative approach for the synthesis of amine fragment **26**.

The second approach toward adduct **26** starts with *L*-phenylalaninol (**22**), which initially was protected as its dibenzyl amine **27** in 82% using potassium carbonate and aqueous EtOH.[122] The primary alcohol (**27**) was then treated with imidazole, DMAP and TBSCl in DMF to afford 99% of the silyl ether **28**.[123] Exposure of the dibenzyl amine to *N*-iodosuccinimide and molecular sieves (4Å) in methylene chloride finally achieved the monodebenzylation and gave 62% of the desired fragment **26**.

4.4.2 Synthesis of the Acid Fragment

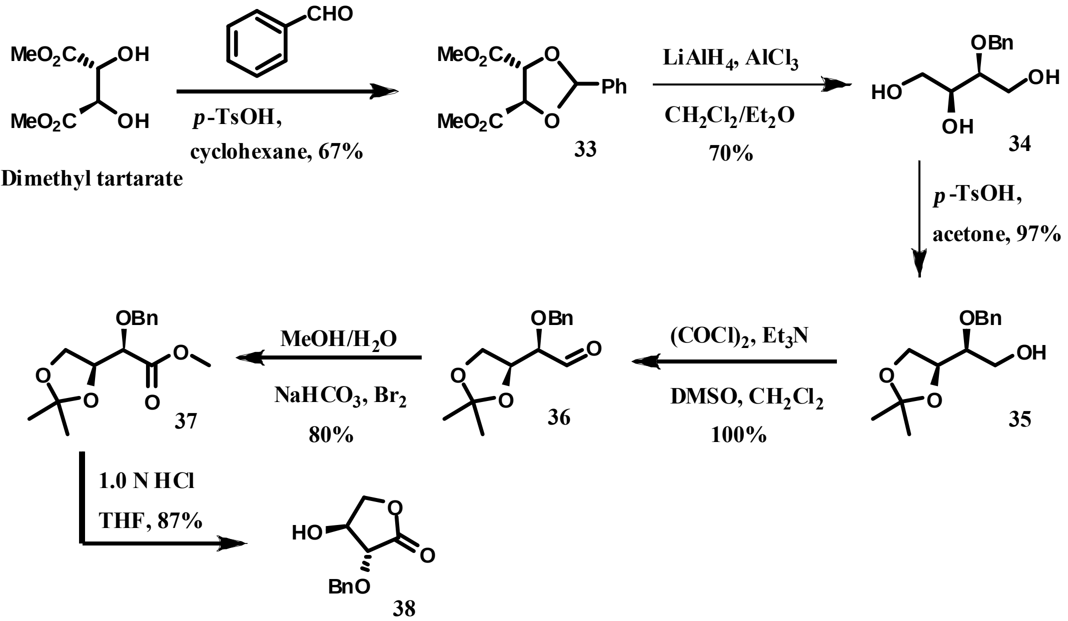
A simplified synthetic approach toward fragment **32** started with the commercially available acrolein (Scheme 4.7). Thus, the aldehyde was treated with aqueous sodium cyanide and acetic anhydride to give 1-acyloxy-1-cyano-2-propene (**29**) in 83% yield.[124] Cyanide **29** was then exposed to hydrochloric acid and MeOH affording 72% of the α-hydroxy-2-butenoic methyl ester (**30**). The secondary alcohol **30** was protected as its TIPS ether using imidazole, DMAP, TIPSCl in DMF to give 81% of the silyl ether **31**.[125] The methyl ester **31** was then hydrolyzed using aqueous LiOH in THF to achieve 98% of the racemic acid fragment **32**.



Scheme 4.7. Synthesis of acid fragment **32**.

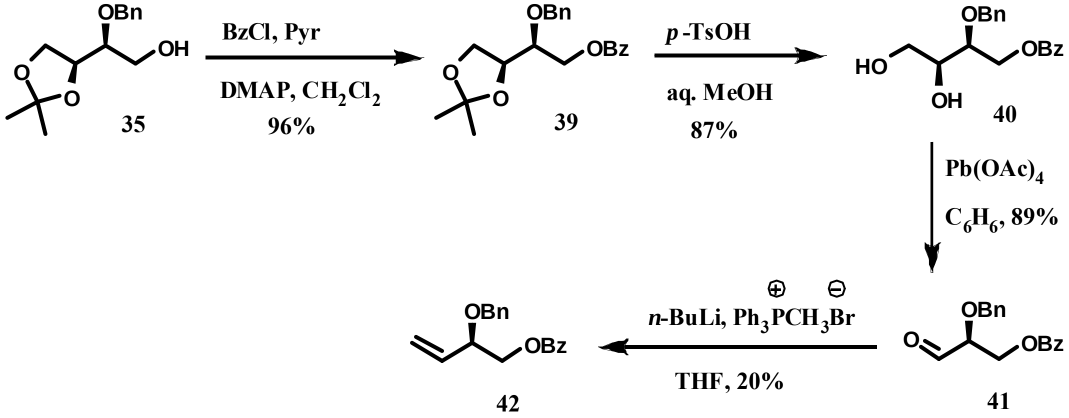
Using the racemic mixture of the acid **32** in the peptide coupling with the amine fragment **26** possibly complicates the ^{1}H- and ^{13}C-NMR spectra of the resulted amide product, making it hard to confirm the transformations thereafter. As a result, a synthetic route has been planned to achieve the pure enantiomer of (*R*)-α-hydroxy-2-butenoic acid.

The attempted synthesis of (*R*)-α-hydroxy-2-butenoic acid starts with the commercially available dimethyl *L*-tartrate, which was treated with benzaldehyde and a catalytic amount of *p*-toluenesulfonic acid monohydrate in cyclohexane to give 67% of the benzylidene adduct **33** (Scheme 4.8).[126] The benzylidene **33** was then reduced using lithium aluminum hydride and aluminum chloride to afford 2-*O*-benzyl-*L*-threitol (**34**) in 70%. Subsequently, protection of the adjacent hydroxyl groups was accomplished with *p*-toluenesulfonic acid monohydrate in acetone to give acetonide **35** in 97%.[127] Primary alcohol **35** was next oxidized under Swern conditions to give the aldehyde **36**, which readily was exposed to solid $NaHCO_3$ and bromine in aqueous methanol to give the methyl ester **37** in 80%.[128] After treating the acetonide with 1 N HCl in THF, the lactone **38** was formed in 87% instead of the free diol.[129]



Scheme 4.8. First synthetic attempt toward (*R*)-α-hydroxy-2-butenoic acid.

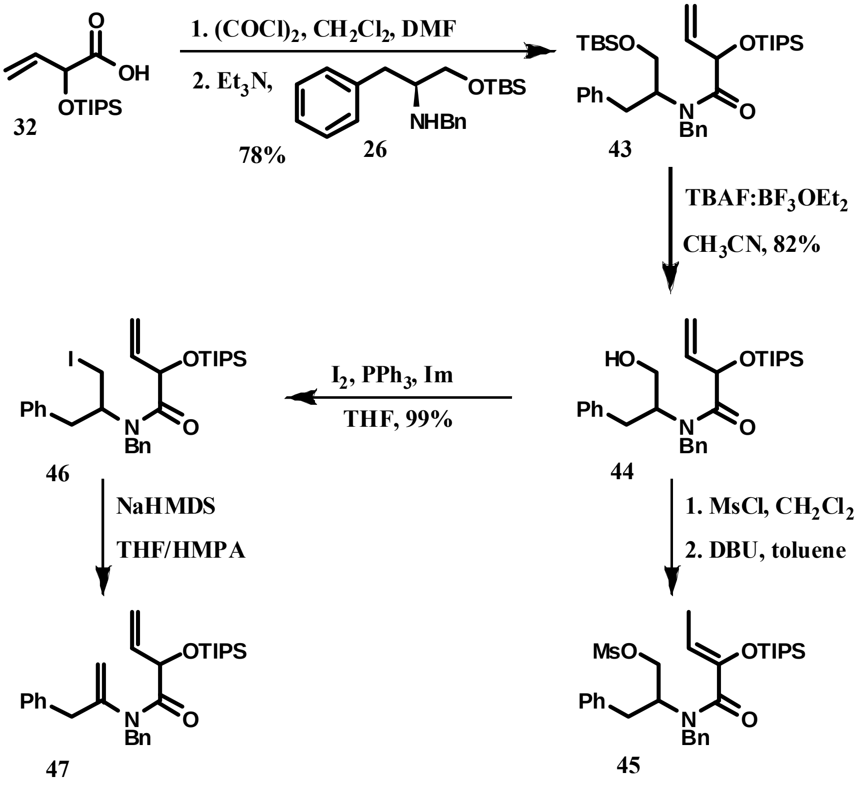
In addition, the attempted route toward (*R*)-α-hydroxy-2-butenoic acid was modified and started from the acetonide **35**, in which the primary alcohol was protected as its benzoyl ester **39** in 96% yield.[127] The acetonide **35** was then cleaved using *p*-toluenesulfonic acid monohydrate in aqueous methanol to give 87% yield of the free diol **40**. The diol **40** was treated with lead tetraacetate in benzene to afford the aldehyde **41** in 89% yield.[129] The Wittig reaction was then conducted using the aldehyde **41** with the *in situ* formed non-stabilized ylide in THF. However, an unsatisfactory yield of 20% of the desired olefination product **42** was formed.



Scheme 4.9. Second synthetic attempt toward (*R*)-α-hydroxy 2-butenoic acid.

4.4.3 Synthesis of Advanced Intermediate Toward Azaspirene

While the efforts are still conducted toward finding either better conditions or higher yielding approach toward (*R*)-α-hydroxy-2-butenoic acid, the focus is currently on the synthesis of azaspirene using racemic acid **32** and amine **26** fragments now in hand. Attempted coupling of the acid and the amine fragments using DCC and *N*-methylmopholine in CH_2Cl_2 did not afford the desired product **43** (Scheme 4.10). However, utilizing the acid chloride, obtained from fragment **32**, and amine **26** gave 78% of amide **43**. This intermediate was then treated with tetrabutylammonium floride/boron trifluoride-etherate complex in acetonitrile, which selectively removed the TBS group while the TIPS group was intact provided the primary alcohol **44** in 82%.[130] This alcohol was then protected as its mesylate using methanesulfonyl chloride in CH_2Cl_2. Subsequent treatment of the mesylate with DBU gave the isomerized side product **45** rather than the desired terminal alkene product **47**. Alcohol **44** instead was treated with I_2, imidazole and Ph_3P in THF to afford a quantitative conversion to its corresponding iodide adduct **46**. Iodide **46** was exposed next to NaHMDS in THF/HMPA. There is no confirmation whether the diolefinic product **47** was formed because of the complexity of NMR signals of the purified product.



Scheme 4.10. Synthesis toward an advanced intermediate of azaspirene.

4.5 Conclusion

The angiogenesis inhibition has proven to be a more efficient strategy than conventional chemotherapy in the treatment of cancer. Not only that antiangiogenic drugs are specific and low in toxicity in targeting tumor cells, but those drugs are less likely than cytotoxic drugs to induce drug resistance. Since azaspirene was found to inhibit endothelial migration induced by vascular endothelial growth factor (VEGF), this target molecule has shown promise in the treatment of angiogenesis-related diseases such as cancer and rheumatoid arthritis.

Although Hayashi's and Tadano's groups have reported asymmetric total syntheses for azaspirene, there is still a need for a less complex synthetic approach. Our proposed synthetic strategy toward azaspirene utilizes the direct conjugate addition of alkenylzirconocene and their corresponding mixed alkenyl-alkylzincate reagents. These developed methodologies using copper catalysis were discussed in earlier chapters. In addition, Grubbs ring closing metathesis and Sharpless dihydroxylation will be used in a few key manipulations toward the target structure.

Simple synthetic routes to achieve two key fragments in the target molecule were accomplished. 2-*O*-(Triisopropylsilyl)-3-butenoic acid (**32**) was obtained in its racemic form as well as the optically active *(2S)*-*N*-(benzyl)-1-*O*-(*tert*-butyldimethylsilyl)phenylalaninol (**26**). These intermediates were used to further prepare an advanced intermediate (**47**). Chapter 6 will discuss the future plan to progress our strategy to complete the total synthesis of azaspirene.

Part II

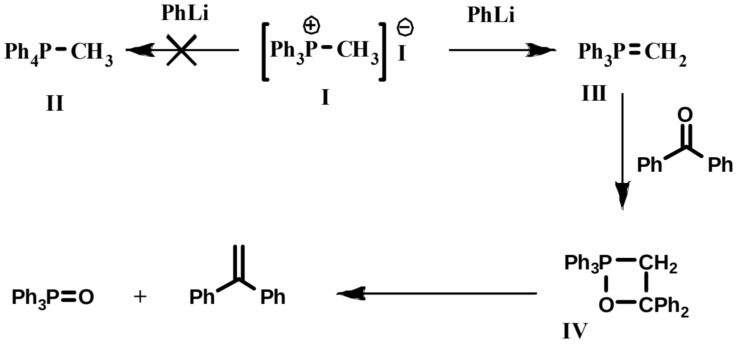
Aqueous Wittig Chemistry Employing Stabilized Ylides and Aldehydes

Chapter 5

Aqueous Wittig Reactions

5.1 Introduction

The carbonyl olefination by phosphorous ylides was in fact discovered rather incidentally in the course of experiments aimed at the study of pentaphenylphosphorane and the syntheses of new derivatives thereof by Wittig and Geissler in the early 1950's.[131] With the objective of synthesizing methyltetraphenylphosphorane (**II**), methyltriphenylphosphonium iodide (**I**) was reacted with phenyllithium, and the nucleophile was caught by the acidic protons of the methyl group and thus prevented from reaching the phosphorous center (Scheme 5.1). Instead, the known triphenylphosphinemethylene (**III**) was formed. At this point, everything was quite normal and could have been predicted from earlier investigations.[132] The crucial point, however, was reached when **III** was mixed with benzophenone. This resulted in the formation of the cyclic phosphorane **IV** which then collapsed to the olefination product and triphenylphosphonium oxide.



Scheme 5.1. Discovery of the olefination reaction by Wittig and Geissler.

Since then, the Wittig reaction of phosphonium ylides with aldehydes and ketones to form olefins quickly attracted the general attention of the chemical community. A major advantage for this powerful synthetic tool is the high level of regioselectivity at the carbon-carbon double bond.[133]

The stereochemistry of the Wittig reaction has been under extensive investigation by both NMR spectroscopy[134] and computational modeling.[135] Achieving high *E*- or *Z*-selectivity can depend on different factors such as the nature of the ylide, the carbonyl substrate, or the reaction conditions.[136] In term of ylides, the geometrical *Z*-alkene product is preferred for a non-stabilized ylide, while the *E*-alkene product is formed mainly when a stabilized ylide is employed. A semi-stabilized ylide is stabilized by weak electron donating substituents that can form resonance hybrids with the carbanion (e.g. Ph). These groups show little preference for one isomer over the other. Employing salts or additives, concentration, temperature and solvents are other factors that can play a role in the stereochemistry of the olefination reaction.[133b]

Traditional conditions that provide excess of the *E*-alkenes include the use of a stabilized ylide and an aldehyde often in solvents ranging from benzene or toluene to DMF or DMSO. It is well documented that when stabilized ylides are used, reactions proceed much slower, especially in non-polar solvents, and no reactions performed at all with ketones.[137] To overcome this problem, numerous reports have appeared in the literature that propose various efficient reaction conditions. Some of these include increasing temperature[138] or pressure,[139] using additives,[140] irradiation with microwaves[141] or light,[142] sonication,[143] silica gel,[137] and ionic solvents.[144] Few reports have also appeared describing the influence of aqueous lithium chloride[145] and a surfactant.[146] Furthermore, recent advances in synthetic aspects include generation of phosphorous ylides in solid-state reactions of phosphonium salts with anhydrous potassium carbonate and subsequent Wittig reaction in solid-state conditions.[147]

Since the discovery by Breslow[148] and Grieco[149] that hydrophobic interactions can play a significant role in the rate of organic reactions in water, it was not until recent that the use of water as a medium in organic transformations has gained a widespread attention.[150] The chemistry community before then was hesitant of using water, most likely due to inherent insolubility, obstructing catalytic activity and possible decomposition of reaction substrates. However, recent significant results highlighted by Sharpless have been achieved when using water as a medium in organic reactions. These results obtained focused on targeting the attraction between hydrophobic moieties of the reactants.[151] In addition, that water excludes non-polar functional groups minimizes the Gibbs energy of solvation.[152] Due to this effect, water does not only accelerate the reaction rate but it also improves the selectivity of the Diels-Alder [4+2] cycloaddition reaction regardless the reactants poor solublility in water. Besides the Diels-Alder cycloadditions,[153] Claisen re-arrangements,[154] ene reactions,[151] and Claisen/Diels-Alder cycloaddition[155] have been reported to undergo rate increases in spite of poor solubility of the reactants when conducting in water media. Although water has been used as a medium for Wittig reactions employing modified water-soluble phosphonium salts,[156,157] the application of water as the primary medium or solvent for performing Wittig reactions utilizing poorly water-soluble stabilized ylides is very limited in the literature.

In this chapter, an extensive study for the use of water as the single medium in Wittig reactions employing stabilized ylides and aldehydes will be presented.[158] An investigation has been included for the rate of the olefination reactions in water compared to these conducted in conventional organic solvents. Furthermore, the influence of additives will be reported. An extension to this work, the aqueous *in situ* preparation of stabilized ylides and their subsequent Wittig reaction in water will be highlighted herein.[159]

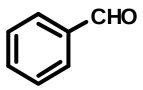
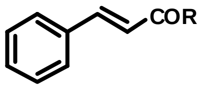
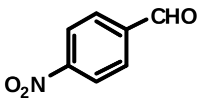
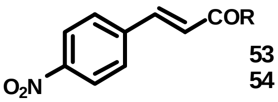
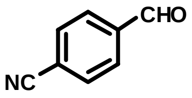
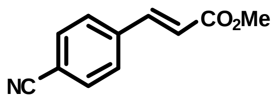
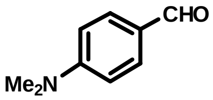
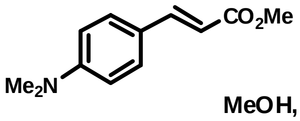
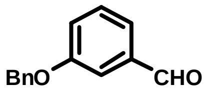
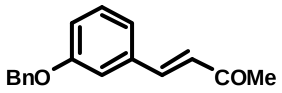
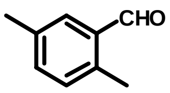
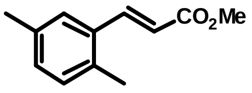
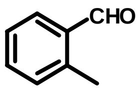
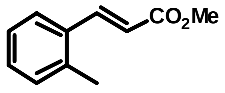
5.2 Results and Discussion

Since the reactants appear to be insoluble during the course of Wittig reactions conducted in water, the word 'medium' will be used instead of 'solvent' in the following context.[160] Indeed, the recent work by Sharpless using water as a medium for some organic transformations was a motivation to try the Wittig reaction in water media. Although the starting materials and products appear to be poorly soluble in the medium, the rate of the Wittig reaction using various stabilized ylides and wide range of aldehydes is unexpectedly fast in water.

5.2.1 Aqueous Wittig Reactions Employing Various Aromatic Aldehydes

The aqueous Wittig protocol was applied to aromatic aldehydes using various phosphoranes. Table 5.1 presents results with some aromatic aldehydes, and when applicable, comparisons are made to literature reactions conducted in conventional solvents. In fact, good yields as well as high *E*/*Z*-isomeric ratios of the olefination products were achieved.

Table 5.1. Wittig reactions of various aromatic aldehydes with stabilized ylides in water.

entry	substrate	cond.[a]	product			yield (%),[b] *E*:*Z*[c]
1		$\xrightarrow[\text{1 h}]{\text{A}}$		51	R = Ph	91, 90:10
2						C_6H_6, 80 °C , 3 d: 70[d]
3				52	R = OMe	88, 93:7
4						MeOH, rt, 1 h: 89, 3:1
5		$\xrightarrow[\text{1 h}]{\text{B}}$		53	R = Ph	93, 84:16
6				54	R = Me	96, 87:13
7		$\xrightarrow[\text{2 h}]{\text{B}}$		55		86, 87:13
8		$\xrightarrow[\text{2 h}]{\text{B}}$		56		81, 90:10
9						MeOH, 20 °C, 3 h: 78, 3:1
10						CH_2Cl_2, 40 °C, 4 h: 0[e]
11		$\xrightarrow[\text{2 h}]{\text{B}}$		57		98, 95:5
12		$\xrightarrow[\text{2 h}]{\text{A}}$		58		92, 94:6
13		$\xrightarrow[\text{2 h}]{\text{A}}$		59		89, 93:7

[a] The reactions were conducted on a 1 mmol scale in 5 mL deionized water. [b] Isolated purified material. [c] Crude reaction mixtures analyzed by 500 MHz ^{1}H-NMR. [d] Ref. 161. [e] Ref. 20a. **A** = 1.2 equiv ylide, 20 °C, **B** = 1.5 equiv ylide, 90 °C.

The reaction of benzaldehyde with the ylide in water for one hour at *ambient temperature* gave chalcone (**51**) in 91% and high *E/Z*-ratio (Entry 1). The same olefination reaction conducted in refluxing benzene was reported to form 70% of product after 3 days (Entry 2).[161] When benzaldehyde was subjected to aqueous Wittig conditions with methoxycarbonylmethylenetriphenylphosphorane, methyl cinnamate (**52**) was achieved in 88% (Entry 3). In comparison, the same reaction conducted in methanol resulted in virtually the same yield (89%), but the *E/Z*-ratio was significantly depleted to 3/1 (Entry 4).

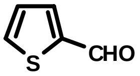
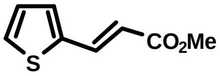
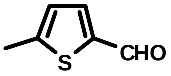
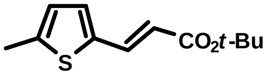
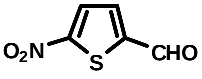
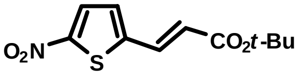
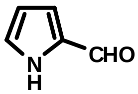
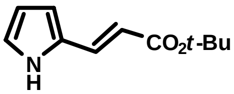
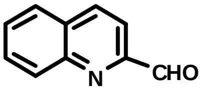
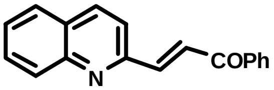
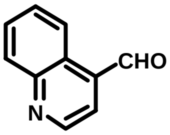
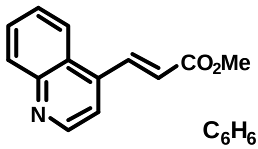
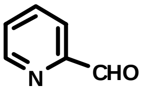
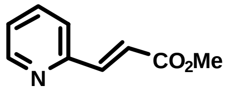
The protocol for the Wittig reaction works well and straightforward utilizing various stabilized ylides and a wide range of aromatic aldehydes having electron donating or electron withdrawing groups present. In general, solid aldehydes tend to react slower in water media than readily dispersed aldehydes. Thus, applying heat in the aqueous Wittig reaction conditions is an effective approach to achieve higher yields of the olefination products. Employing elevated temperature conditions when using *p*-nitro- (Entry 5 and 6) or *p*-cyanobenzaldehyde (Entry 7) provided high yields and good *E/Z*-ratios of the corresponding olefination products. The slowly reacting *p*-Me_2N-substituted benzaldehyde did not react with the ylide in water at 20 °C, but heating the reaction mixture to 90 °C afforded 81% of product **56** (Entry 8). In contrast, when MeOH was used instead of water, this reaction provided 78% of **56** (Entry 9) at *ambient temperature*, but the *E/Z*-ratio was significantly dropped to 3/1. This same reaction conducted in refluxing CH_2Cl_2 was reported fruitless (Entry 10).[139a] When 3-benzyloxybenzaldehyde was used in the aqueous Wittig reaction with the ylide, the corresponding product **57** was achieved in 98% and very high *E/Z*-

ratio after 2 h at 90 °C (Entry 11). Furthermore, employing the *o*-methyl substituted carboxyaldehydes provided excellent *E/Z*-ratios of the olefination products (**58**-**59**) as well as high yields (Entry 12 and 13). It is fascinating to observe that the methyl groups have no influence on the isomeric ratio of the products since the same *E/Z*-ratio was obtained without the methyl group present (Entry 3). These results demonstrate water as an efficient medium for the Wittig reaction employing stabilized ylides and various aromatic aldehydes. For more examples of aqueous Wittig reactions to aromatic aldehydes, refer to Dambacher *et al.*[158] and El-Batta *et al.*[159] It should also be mentioned that unprotected acidic functional groups (e.g. phenol and carboxylic acids) have no drawback on the Wittig reaction. The olefination products were achieved in excellent yields and high *E/Z*-ratios.

5.2.2 Aqueous Wittig Reactions Employing Various Heterocylic Aromatic Aldehydes

Motivated by the excellent yields and *E/Z*-ratios of the Wittig reactions obtained when using stabilized ylides and various aromatic aldehydes in water, an extension including heterocyclic aromatic aldehydes is presented (Table 5.2). Solid heterocyclic aromatic aldehydes required heat while performing the Wittig reaction with ylides to achieve higher yields of the corresponding products.

Table 5.2. Wittig reactions of various heterocyclic aromatic aldehydes with stabilized ylides in water.

entry	substrate	cond.[a]	product		yield (%),[b] *E*:*Z*[c]
1		$\xrightarrow[1\ h]{A}$		60	95, 92:8
2		$\xrightarrow[1\ h]{B}$		61	97, 90:10
3		$\xrightarrow[1\ h]{C}$		62	94, 86:14
4		$\xrightarrow[1\ h]{C}$		63	84, 99:1
5		$\xrightarrow[2\ h]{C}$		64	89, 99:1
6		$\xrightarrow[2\ h]{C}$		65	92, 99:1
7			C_6H_6, 80 °C, 19 h: 83[d]		
8		$\xrightarrow[1\ h]{B}$		66	88, 81:19
9			CH_2Cl_2, 40 °C, 4 h: 90[e]		

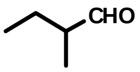
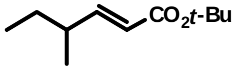
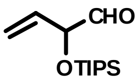
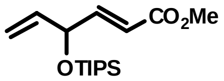
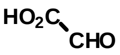
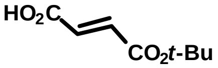
[a] The reactions were conducted on a 1 mmol scale in 5 mL deionized water. [b] Isolated purified material. [c] Crude reaction mixtures analyzed by 500 MHz ^{1}H-NMR. [d] Ref. 162. [e] Ref. 163. **A** = 1.2 equiv ylide, 20 °C, **B** = 1.5 equiv ylide, 20 °C, **C** = 1.5 equiv ylide, 90 °C.

Liquid thiophenecarboxaldehyde reacted with the phosphorane in water at *ambient temperature* to afford 95% of the olefination product **60** (Entry 1). While the Wittig reaction of methyl substituted thiophenecarboxaldehyde with the ylide in water gave a very high conversion to the corresponding α,β-unsaturated *t*-butyl ester **61** (Entry 2), the aqueous olefination reaction using nitro substituted thiophenecarboxaldehyde required elevated temperature conditions to achieve 94% of **62** (Entry 3). Employing pyrrole- and quinolinecarboxyaldehydes with stabilized ylides afforded very high yields and exceptional *E/Z*-ratios of the corresponding products (**63**-**65**) (Entry 4-6). The Wittig reaction conducted in refluxing benzene using 4-quinolinecarboxaldehyde achieved 83% of the olefination product after 19 h (Entry 7).[162] This result indicates again the advantage of using water as a medium and its efficiency in accelerating the Wittig reactions utilizing stabilized ylides compared to other conventional solvents. When 3-pyridinecarboxaldehyde was subjected to the aqueous Wittig conditions with the ylide, 88% of **66** was afforded after 1 h at 20 °C (Entry 8). The same reaction conducted in refluxing CH_2Cl_2 was reported to give 90% of **66** after 4 h (Entry 9).[163] For more examples of aqueous Wittig reactions to heterocylic aromatic aldehydes, refer to Dambacher *et al.*[158] and El-Batta *et al.*[159]

5.2.3 Aqueous Wittig Reactions Employing Various Aliphatic Aldehydes

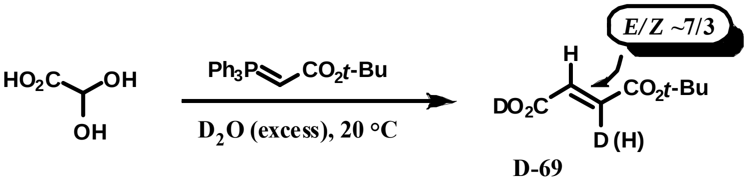
The aqueous Wittig reaction is also applicable to aliphatic aldehydes where various ylides were used to produce the corresponding α,β-unsaturated esters (Table 5.3). Thus, employing 2-methylbutyraldehyde (Entry 1) and the α-*O*(TIPS)-substituted 3-butenal[164] (Entry 2) achieved high yields and good *E/Z*-ratios of the Wittig products (**67**-**68**) in water media. It is interesting that glyoxylic acid underwent a fast Wittig reaction in water at 20 °C to afford 74% of **69** considering the aldehyde was commercially available only in its hydrate form.[165] Additional aliphatic aldehydes were subjected to the aqueous Wittig protocol and presented in Dambacher *et al.*[158] and El-Batta *et al.*[159]

Table 5.3. Wittig reactions of various aliphatic aldehydes with stabilized ylides in water.

entry	substrate	cond.[a]	product		yield (%),[b] *E*:*Z*[c]
1		$\xrightarrow[\text{1 h}]{\text{A}}$		67	77, 99:1
2		$\xrightarrow[\text{2 h}]{\text{B}}$		68	83, 88:12
3		$\xrightarrow[\text{30 min}]{\text{C}}$		69	74, 70:30[d]

[a] The reactions were conducted on a 1 mmol scale in 5 mL deionized water. [b] Isolated purified material. [c] Crude reaction mixtures analyzed by 500 MHz ^{1}H-NMR. [d] *E/Z*-ratio is sensitive to the silica gel (purification) applied; SiO_2 column gave ~50% (*E/Z* = 99:1). **A** = 1.5 equiv ylide, 20 °C, **B** = 1.5 equiv ylide, 90 °C, **C** = 1.0 equiv ylide, 20 °C.

The Wittig reaction of glyoxylic acid with phosphorane was also conducted in D_2O at 20 °C and monitored by ^{1}H-NMR spectroscopy (Scheme 5.2). The methine signal of the hydrate of glyoxylic acid (δ_{CH} = 5.2 ppm) slowly disappears in the presence of the ylide to afford the Wittig product (**69**) and triphenylphosphine oxide, which makes the reaction increasingly heterogeneous over time. Not only did the NMR analysis confirm the formation of the olefination product, but also the resultant incorporation of deuterium (*D/H* ~ 10/1) at the α-olefinic carbon of ester **69**. In a separate experiment, it was determined that the proton/deuterium exchange can easily occur if there is a high concentration of D_2O. These results show that, even if the aldehyde molecule is masked as its hydrate, the Wittig product is still obtained. This study also shows that ylides are basic in nature and can therefore easily abstract a deuterium from D_2O.



Scheme 5.2. Wittig reaction of glyoxylic acid and a stabilized ylide in water.

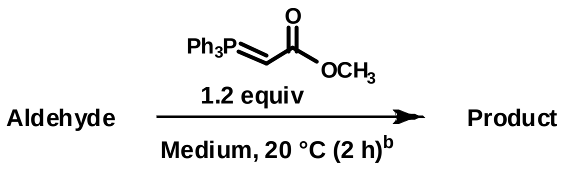
It is worthy to mention that the *trans*-**69** isomer of mono-*tert*-butyl fumarate is the major product of the aqueous Wittig reaction in its crude status. However, performing an acid-base extraction to purify the product caused partial isomerization to the corresponding *cis*-**69** isomer of mono-*tert*-butyl maleate. Thus, applying a short silica-gel column was the best method of purification to isolate the major *trans* isomer.

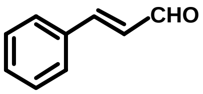
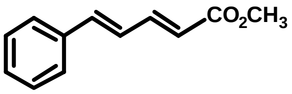
5.2.4 Role of Water in the Aqueous Wittig Reactions

Water has been used as a medium for many organic transformations with insoluble substrates, however the mechanism for how water accelerates the rate of the Wittig reaction in particular still remains obscure. Several explanations have been proposed, including the hydrophobic association of the reactants,[148a] micellar catalysis,[148b] solvophobicity,[166] Lewis acid-like catalysis by enhanced hydrogen bonding at the transition state,[167] cohesive energy density[168] and ground-state destabilization.[169] Nonetheless, Sharpless postulated the possibility of a role played by surface-tension energetics[170] or the unique properties of molecules at a macroscopic phase boundary between water and insoluble hydrophobic moieties in order to rationalize the “on water” phenomenon.[171] More experimental and theoretical work is needed in order to explain the mechanism behind this phenomenon.

Encouraged by the high impact using water as a medium in the Wittig reactions with stabilized ylides, an investigation was also carried out comparing the Wittig reaction in water to those conducted in conventional organic solvents (Table 5.4).

Table 5.4. Rate study of the Wittig reaction in different media.[a]



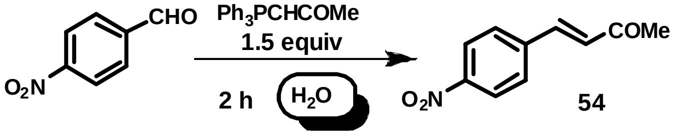
aldehyde	medium	yield[c]	*E*/*Z*[d]	product
	Water	88% (7%)	84/16	 70
	Methanol	94% (0%)	67/33	
	CH_2Cl_2	78% (14%)	84/16	
	Toluene	59% (35%)	91/9	
	CCl_4	71% (27%)	91/9	
	THF	33% (60%)	92/8	
	MeCN	41% (55%)	90/10	

[a] The reactions were conducted on a 1 mmol scale in 5 mL deionized water. [b] 5 mL 1.0 M HCl (aq) added after 2 h. [c] Isolated product yield and recovered aldehyde in brackets. [d] Determined using ^{1}H-NMR of crude reaction mixtures.

The Wittig reaction of cinnamaldehyde and methoxycarbonylmethylene-triphenylphosphorane in 5 mL of the appropriate medium was vigorously stirred for 2 h at 20 °C, and then quenched using 1.0 M HCl solution to ensure that the ylide was hydrolyzed and no further Wittig reaction was performed during the extraction step with organic solvent. In general, the trend is that the Wittig reaction was fastest in methanol and slowest in THF. The reactions in water, despite the low solubility of the reagents, are faster than all the scrutinized organic solvents, except methanol. On the other hand, the *E/Z*-ratio observed while using water or methanol as a medium is slightly lower than those obtained with organic solvents.

Several reports appear in literature including numerous means to improve the outcome of the Wittig reaction.[137-144] Some of these include the use of additives such as lithium halides,[140a,b] benzoic acid,[140c,g] and recently aqueous lithium chloride[145] and a surfactant.[146] In view of this, it became interesting to study the influence of those additives on the yield and the *E/Z*-ratio obtained when conducting the aqueous Wittig reaction (Table 5.5). During this study, *p*-nitrobenzaldehyde was utilized in the aqueous Wittig reaction with the ylide and the reaction was run for 2 h. Since this solid aldehyde reacts slowly at 20 °C, applying heat increases the reaction yield of the Wittig product.

Table 5.5. Influence of additives on the aqueous Wittig reaction.

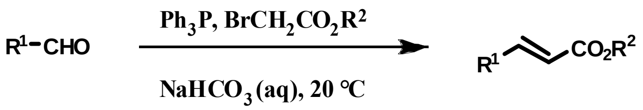


conditions[a]	yield (%)[b]	*E*:*Z* ratio[c]
20 °C	63	90:10
20 °C, 5% DMSO	89	80:20
80 °C	96	87:13
20 °C, $PhCO_2H$[d]	85	91:9
20 °C, LiCl[d]	76	92:8
20 °C, SDS[e]	63	89:11

[a] The reactions were conducted on a 1 mmol scale in 5 mL deionized water. [b] Isolated purified material. [c] Crude reaction mixtures analyzed by 500 MHz ^{1}H-NMR. [d] 10 mol% vs. aldehyde. [e] Sodium dodecyl sulfate, 30 mol%.

The presence of 5% DMSO had a positive influence on the rate of the olefination reaction, presumably due to the increased dispersion of the aldehyde in the aqueous media. Employing either aqueous lithium chloride or benzoic acid increased the yield as well as the *E*/*Z*-ratio. It is conceivable that LiCl perhaps has a stabilizing effect on the phosphoranes from not reacting with water.[145a] However, using SDS has no influence on the yield or the selectivity of the Wittig reaction.[146] Instead, it caused unpleasant problems during the work-up procedure and further complicated the isolation of the Wittig product.

Because of the initial data obtained, an extension for this efficient aqueous Wittig protocol to include the *in situ* formed stabilized ylides and their subsequent olefination reactions using saturated aqueous sodium bicarbonate solution as a medium was conducted (Scheme 5.3). Ph_3P and α–bromoesters are mixed in saturated aqueous $NaHCO_3$ solution, followed by the exposure to various aromatic and heterocylic aromatic carboxaldehydes. It is worthy to mention that elevated temperature conditions are inappropriate for these types of reactions. Presumably, the reactants are decomposed at high temperature in the basic medium. In addition, the research is still undergoing to explore the conditions using *in situ* formed ylides in saturated aqueous $NaHCO_3$ solution to employ aliphatic aldehydes. For a full account of the aqueous Wittig work conducted in saturated $NaHCO_3$ using water as the medium, refer to El-Batta *et al.*[159]

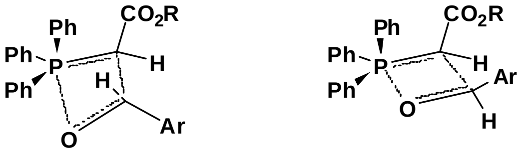


Scheme 5.3. Wittig reaction using Ph_3P and α-bromoesters in aqueous $NaHCO_3$.

5.3 Mechanistic Studies of the Aqueous Wittig Reaction

It is probable the protic nature of water which allows it to participate in the Wittig reaction via hydrogen bonding rationalizes the acceleration effect on the reaction rate. When a Wittig reaction with benzaldehyde and methyl (triphenylphosphoranylidene) acetate was conducted in D_2O, methyl cinnamate was produced in 90% yield with 90% deuterium incorporation at the α-carbon.[158] This implies a very fast deuterium exchange which is consistent with results reported by Bestmann utilizing EtOD.[172] It should be noted however the precise role of water in organic transformations with insoluble substrates is yet to be well understood.

Although several models have been proposed to explain the observed *E/Z*-ratio of the Wittig reaction depending on what types of ylides are employed,[173-175] Aggarwal and Harvey[135] reported calculations of the transition state for the salt-free Wittig reaction of stabilized ylides. Their model explains the high *E*-selectivity of product using a stabilized ylide by the considerably puckered oxaphosphetane-type transition state, which orients the dipole moments along the C=O bond in the aldehyde and along the C(ylide)-C(ester) bond within the ylide (Figure 5.1).



***Trans*-TS**
puckered
(yields E-alkene)
Favored

***Cis*-TS**
planar
(yields Z-alkene)

Figure 5.1. TS models to account for the *E/Z*-selectivity.

The dipole-dipole interaction can in part provide an explanation for the observed *E*-selectivity when different solvents are employed in the Wittig reaction using stabilized ylides. From the rate study conducted in various solvents (Table 5.4), the Wittig reactions conducted in protic media, e.g. methanol and water, give slightly lower *E*-selectivity. Since the electron density over the carbonyl group in aromatic aldehydes is mostly influenced by electron donating and electron withdrawing groups located in the *ortho*-position, it is expected the dipole moment would change for these aldehydes. As a result, this could provide a lower *E/Z*-ratio compared to benzaldehyde in the Wittig reactions. Although *ortho*-substituents in general could sterically influence the TS for the Wittig reaction, the *o*-methyl-substituted aldehydes provide very high *E*-selectivity. This could be due to a very weak change of the C=O dipole for the *o*-methyl-substituted benzaldehydes. However, the protic media surrounding the reactants must also be considered. There is most likely hydrogen bonding between the carbonyl oxygen and methanol or water, which could weaken the dipole-dipole interaction between the stabilized ylide and the aldehyde during the Wittig reaction, thereby lowering the *E*/*Z*-ratio. Although it is suspected that water molecules lower the energy of the transition state for the Wittig reaction, the exact role of water in accelerating the rate of the Wittig reactions is still not clear. Moreover, since there are no big relative differences between the *E/Z*-ratios using different aldehydes, this makes it more difficult to discuss various favored transition states in the aqueous Wittig reaction.

5.4 Conclusion

One of the important aspects of "green chemistry" is to reduce or eliminate the use of toxic and/or hazardous reagents in the chemical processes.[176] The use of water as a medium for organic reactions is therefore one of the latest challenges for modern organic chemists.[177] The desire to use water as a "medium" in organic chemistry stems from the fact that water is extremely inexpensive and straightforward, and represents no environmental concerns. Inspired by the earlier work of Breslow[148] and Grieco[149] and also recently the reports by Sharpless[151] and Nicolaou[155] in this field, an extensive study was carried out about Wittig reactions of stabilized ylides with different aromatic, heterocylic aromatic and aliphatic aldehydes in water. This discovery showed that water is an efficient medium compared to other conventional toxic organic solvents used in Wittig reactions. Excellent yields and *E/Z*-ratios of the desired products were achieved.

Although the starting materials and products appear to be poorly soluble in the medium, the rate of the reaction is unexpectedly fast in water. Using aromatic aldehydes, electron withdrawing groups increased the rate of the Wittig reactions conducted in water. Steric effects appear to be crucial for *ortho*-substituted aldehydes, but electronic effects cannot be ruled out. Furthermore, conducting the Wittig reaction in water using stabilized ylides is advantageous with substrates having unprotected acidic functional groups. When using solid aldehydes, heat will presumably disperse the aldehyde in water and increase the rate of the reaction to provide good yields and *E/Z*-ratios.

Recently, a protocol utilizing *in situ* formed stabilized ylides in water was developed. These ylides were generated *in situ* via reactions of triphenylphosphine with alkyl bromoacetate in saturated sodium bicarbonate solution and then reacted with aromatic and heterocyclic aromatic carboxaldehydes. As previously observed, the Wittig reactions in water are unexpectedly accelerated and water is the medium of choice for this type of chemistry.

Several proposals have been reported in literature to rationalize the observed *E/Z*-ratios of the olefination reactions. However, the dipole-dipole interaction between the stabilized ylide and the aldehyde during the Wittig reaction could fairly provide an explanation for the high *E*-selectivity. Indeed, the dipole-dipole interaction has already been used to rationalize the stereoselectivity in aldol reactions.[178]

This chapter contains material that appears in the following publications. The dissertation author was a co-author on both papers.

(1) Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. Water as an Efficient Medium for Wittig Reactions Employing Stabilized Ylides and Aldehydes. *Tetrahedron Lett.* **2005**, *46*, 4473-4477.

(2) El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. Wittig Reactions in Water Media Employing Stabilized Ylides with Aldehydes. Synthesis of α,β-Unsaturated Esters From Mixing Aldehydes, α-Bromoesters, and Ph_3P in Aqueous $NaHCO_3$. *J. Org. Chem.* **2007**, manuscript in press.

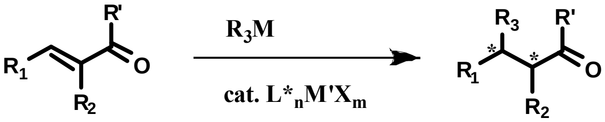
Chapter 6

Future Work

In the following chapter, new ideas will be presented as an extension of the work previously described in this thesis. The future objective is to accomplish efficient organic methodologies in the area of copper catalysis. In addition, a synthetic route will also be pursued in order to achieve an enantioselective total synthesis for azaspirene.

2.5 Asymmetric Conjugate Additions of Alkenyl Groups Using Copper Catalysis

The conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the most important reactions to form a carbon-carbon bond.[27] With optically active metal complexes, this transformation can be catalyzed enantioselectivitely (Scheme 6.1).



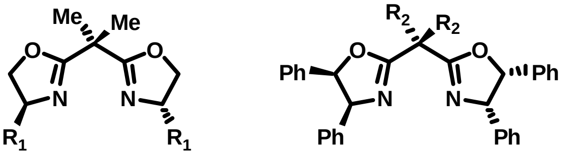
Scheme 6.1. Asymmetric conjugate addition of carbon nucleophile (R_3M) in presence of chiral metal complexes.

These catalytic enantioselective processes were reviewed exclusively in literature by Krause and Hoffmann-Röder[179] and recently by Christoffers *et al.*[180] Although there has been a broad range of metal complexes used in asymmetric conjugate additions, the catalysts with rhodium and copper complexes play a dominant role in this area up to this date.

6.1.1 Enantioselective Additions of Alkenylzirconium Reagents

The advantage of the alkenylzirconocene intermediates is that they are readily available through hydrozirconation of alkynes[35] with the Schwartz's reagent, $Cp_2Zr(H)Cl$.[12] These carbon nucleophiles have been applied in rhodium-catalyzed conjugate additions to enones using BINAP as the chiral ligand.[181] Recently, Nicolaou and his co-workers have used alkenylzirconocene species in the presence of the Rh-BINAP complex in their synthesis of the spirocyclic fragment of marine natural product vannusal A.[182] By taking advantage of the published methodology using catalytic amount of the CuI•0.75DMS complex, alkenylzirconium reagents undergo a direct conjugate addition to enones with no additives or extra manipulations.[45] Furthermore, this simple one-pot procedure produces higher yields of the 1,4-products than those reported using the more expensive rhodium catalyst.

Bisoxazolines (BOX) could also be utilized as chiral ligands in the copper-catalyzed asymmetric conjugate additions of alkenylzirconocenes to enones and enals (Scheme 6.2). Numerous reports appearing in literature show excellent stereoselectivities when the BOX ligands were used in both the 1,4-addition of ethyl groups from dialkylzinc reagents to enones[183] and the Michael reactions.[184]



R_1 = Ph, Bn, *t*-Bu, *i*-Pr **R_2 = H, Me**

Scheme 6.2. Examples of BOX ligands used in Cu-catalyzed conjugate additions.

6.1.2 Enantioselective Conjugate Additions of Mixed Alkenyl-Alkylzinc Reagents

An asymmetric version of the copper(I)-catalyzed 1,4-addition of alkenyl groups from mixed alkenyl-alkylzincates could be developed by utilizing chiral BOX ligand-copper(I) complexes as the catalysts. The vinylzincate nucleophiles have been shown to react faster and more efficient in the conjugate addition of alkenyl groups using catalytic amount of the CuI•0.75DMS complex than their corresponding zirconocene counterparts. In addition, the transmetalation of zirconium to zinc has provided an efficient access to the products of the asymmetric 1,4-addition of alkenyl groups to *N*-enoyl derived oxazolidinones.[90]

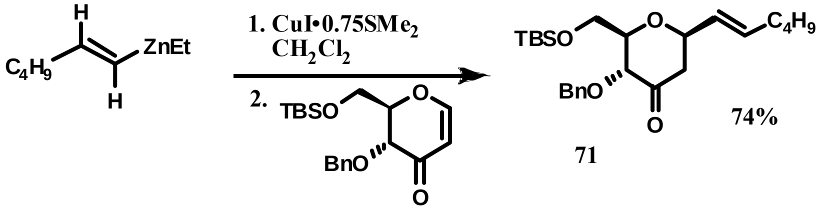
Encouraged by the catalytic efficiency of the CuI•0.75DMS complex[47] and the high reactivity of the mixed alkenyl-alkylzincate reagents, it is feasible to pursue an enantioselective 1,4-addition of alkenyl groups in the presence of C_2-symmetric ligands such as bisoxazolines[184a,185] or Feringa's phosphoramidite-based complexes.[186] Some work has been published on the mechanisms of these reactions.[183] Compared to the lithium or Grignard reagents, the corresponding zinc intermediates are less basic and often compatible with a wide range of functional groups.[69,88]

2.6 Expansion of the Methodology of Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Addition of Alkenyl Groups

6.2.1 Employing β-Oxy-Substituted α,β-Unsaturated Carbonyl Substrates

Hydrozirconation of alkynes to generate alkenylzirconocene reagents, followed by transmetalation with diethylzinc to yield the corresponding mixed alkenyl-alkylzincate intermediates is an efficient protocol for the 1,4-transfer of alkenyl groups when catalytic amount of the CuI•0.75DMS complex is utilized. Not only are the 1,4-products achieved in faster rate compared to the corresponding zirconocenes when enones or enals are employed, but the simple protocol has also been shown to give high yields as well as high diastereoselectivity ratios in presence of one equiv of TMSOTf when *N*-enoyl derived oxazolidinones are used as substrates (Chapter 3).[90] This methodology could be explored further to also include β-oxygen containing enones, esters, imides and amides to use as substrates in the Cu-catalyzed 1,4-additions.

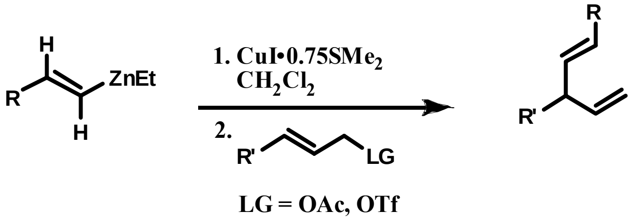
The presence of an oxygen atom on the β-position of α,β-unsaturated systems generally possess a challenge because (1) “O” is an electron donating group, and (2) RO^- is a good leaving group when strong bases are used, e.g. RMgBr. Such systems will be less reactive as electrophiles to be employed in the Cu-catalyzed conjugate additions. Hence, mixed alkenyl-alkylzincate intermediates could be potential useful nucleophiles to deliver alkenyl groups in 1,4-fasion to β-oxygenated enones, enoates, imides or amides in presence of the CuI•0.75DMS complex. An initial attempt was conducted using β-oxygen substituted enone obtained from the oxidation of glucals.[187] The 1,4-product was achieved in 74% yield using catalytic amount of the copper complex in CH_2Cl_2 as a solvent (Scheme 6.3).[188] This reaction could be further investigated to include similar α,β-unsaturated systems.



Scheme 6.3. An example of Cu(I)-catalyzed 1,4-addition of a mixed alkenyl-alkylzincate reagent to a β-oxygen containing enone.

6.2.2 Allylic Additions (S_N2')

Copper-catalyzed allylic addition (or S_N2') reactions are generally conducted in the presence of relatively reactive organolithium, -magnesium, or -titanium reagents. These reactions are most commonly executed at low temperature to avoid the competing S_N2 type pathways.[27j] The mixed alkenyl-alkylzincate reagent is a promising tool for allylic type addition reactions (Scheme 6.4).



Scheme 6.4. S_N2'-type reaction using the copper(I) iodide dimethyl sulfide complex.

In general, Gilman type reagents prefer the S_N2 pathway while the less reactive nucleophiles, such as RCu/LiI-BF_3•OEt_2, favor the allylic addition pathway (S_N2'). The milder alkenyl-alkylzinc/CuI•0.75DMS system is proposed to undergo S_N2'-type additions. Possibly, there will be a need for Lewis acids, such as BF_3•OEt_2 and $AgClO_4$[189] in order for the proposed system to give higher yields of the allylic addition products. This protocol, once developed, will provide access to highly desirable synthetic precursors for natural product synthesis.

6.2.3 Electrophilic Trapping of Zinc Enolates in α-Alkylation Type Reactions

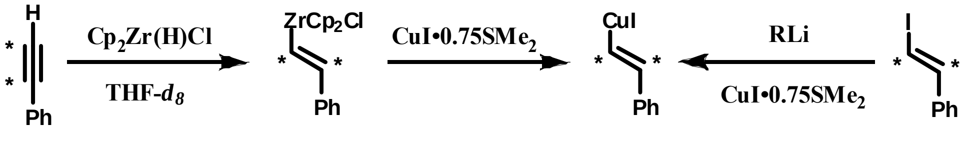
Trapping of zinc enolates with an electrophile in α-alkylation type reactions has rarely been reported.[36] The disconnection of a very favorable zinc-oxygen bond needed for an electrophilic trapping reaction seems to be a challenge to undertake. By taking advantage of more reactive electrophiles, such as using triflate electrophiles rather than iodides, could be a potential solution. The proposed avenue of research will not only serve as an efficient route for the Cu-catalyzed conjugate addition of alkenyl groups combined with α-alkylation, but it could also provide an answer on a long standing question using prostaglandin enolate to effectively achieve the synthesis of possibly analogs.[190]

2.7 Mechanistic Studies of the Copper(I) Iodide Dimethyl Sulfide Catalyzed 1,4-Additions of Alkenyl Groups

The detailed mechanism of the CuI•0.75DMS catalyzed conjugate addition of alkenyl groups from alkenylzirconocenes is rather obscure as indicated earlier (see

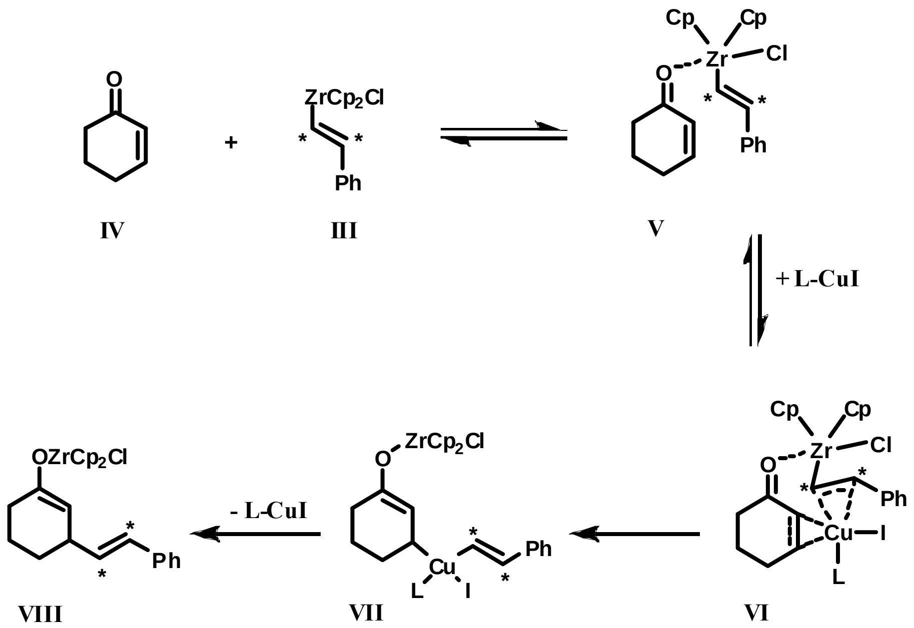
Chapter 2). Even though it could be some challenge to conduct studies to narrow down the mechanism, the current results will however facilitate further developments in this area of research. NMR experiments and computational studies could be performed in order to study plausible reaction intermediates obtained during the catalytic cycle of the 1,4-alkenyl group transfer of alkenylzirconium reagents in the presence of CuI•0.75DMS.

Organocopper reactions are very sensitive to oxygen atmosphere indeed.[27f,j,l] Therefore NMR studies must be conducted in glove boxes and/or sealable NMR tubes. Moreover, such experiments will possibly produce very reactive intermediates in low concentrations. Thus, in order to enhance the detection, ^{13}C-labeled precursors would be very useful for NMR studies of organocopper reagents or other intermediates in the copper-catalyzed reactions.[191] In details, an alkenylcopper (**I**) sample will be prepared via mixing alkenyliodide (**II**), *t*-BuLi and CuI•0.75DMS complex. In order to be able to answer the question whether the plausible alkenylcopper (**I**) intermediate is formed, alkenylzirconocene reagent (**III**) can be exposed to CuI•0.75DMS (Scheme 6.5).



Scheme 6.5. NMR studies for copper catalysis using ^{13}C-labeled precursors (Part I).

More challenging will be the detection of the very elusive copper(III) intermediate **VII**. By taking advantage of ^{13}C-labeled precursors in the protocol of CuI•0.75DMS catalyzed conjugate addition of an alkenyl group from an alkenylzirconocene reagent to an enone, this could aid in the detection of intermediate **VII**. The observation of the slower reaction in THF over more polar solvents (e.g. CH_2Cl_2) will help us better observe changes during the NMR analysis. ^{13}C labeled styrylzirconocene intermediate (**III**)[191] will be exposed to enone **IV** at low temperature (Scheme 6.6). The equilibrium position will be determined for the binding of carbonyl oxygen of **IV** to the zirconium atom in **III** using NMR integrations. Upon the exposure of the CuI•0.75DMS complex, intermediate **V** can be converted to the elusive Cu(III) intermediate (**VII**) via a possible transition state **VI**.[49,192] Intermediate **VII** will then undergo reductive elimination to yield the zirconium enolate product (**VIII**) and release the copper complex. Intermediate **VIII** will most likely be easy to see on NMR. The intermediates will be studied with variable temperature-NMR to determine the Cu-^{13}C in **VII** as well as ^{13}C=^{13}C coupling constants in **V**, **VII** or **VIII**.

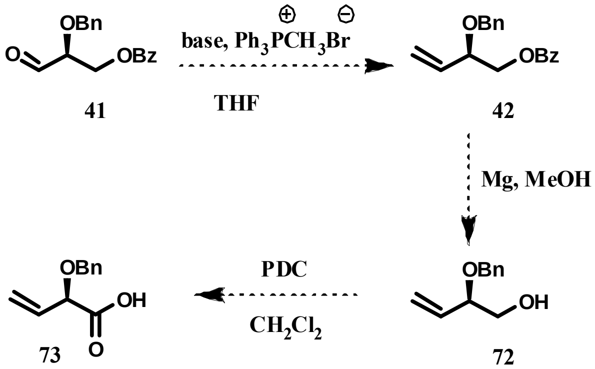


Scheme 6.6. NMR studies for copper catalysis using ^{13}C-labeled precursors (Part II).

Although the above experiments might have high risk involved, the results if obtained, will be the first direct spectroscopic evidence for a Cu(III) intermediate in 1,4-additions of organocopper reagents.[49e] Computational studies could also be used as an excellent tool to observe the intermediates for the copper reaction (**V-VIII**). The thermodynamic and the kinetic properties will be estimated using B3LYP density functional method[193] combined with effective core potential basis sets such as LANL2DZ.[194] The conductor-like screening method (COSMO) will be applied to observe solvent effects.[195] Furthermore, vibrational contributions to the free energy may be crudely estimated at the semi-empirical AM1 level to further improve the accuracy of the predictions.[196] Not only will the proposed calculations provide answers for the mechanistic studies of the organocopper reactions, but they will enhance further developments in the area of copper catalysis utilizing organozirconocene reagents.

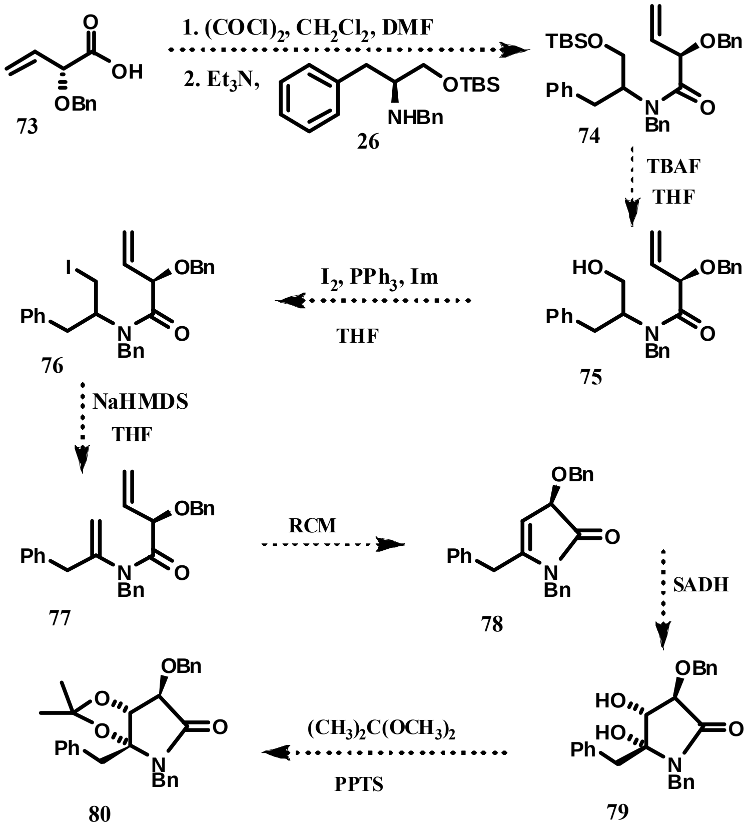
2.8 Completion of the Total Synthesis of Azaspirene

A proposed retrosynthetic route toward the total synthesis of azaspirene is described previously (Chapter 4). It is a considerable need to pursue an efficient synthetic strategy in order to eventually achieve an enantioselective synthesis for the target molecule. The Wittig reaction conducted using the aldehyde **41** and the *in situ* formed non-stabilized ylide in THF only gave 20% yield of the desired olefination product **42**. Therefore, modified conditions for this reaction are necessary to obtain higher yield of the olefin **42** probably by using other bases, such as $NaNH_2$ (Scheme 6.7). Once the product **42** is in hand, deprotection of the benzoyl group to free the primary alcohol **72**,[197] followed by an oxidation step using PDC in DMF to yield the corresponding carboxylic acid **73**.[198]



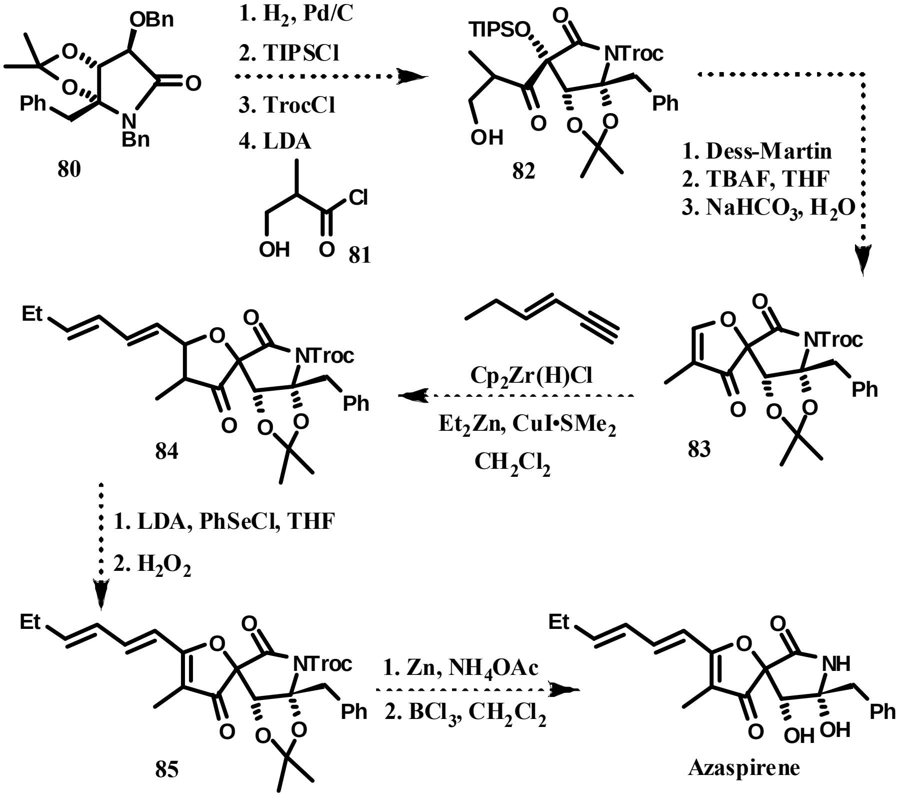
Scheme 6.7. Proposed synthetic route to obtain (*R*)-α-hydroxy-2-butenoic acid (**73**).

Coupling of the acid **73** and the amine **26** fragments will be conducted using the similar conditions employed in Scheme 4.10. After converting the acid fragment **73** *in situ* to its corresponding carboxylic acid chloride derivative, it will readily be used for the peptide coupling with the amine fragment **26** to give the amide **74**. This amide intermediate will then be exposed to tetrabutylammonium floride in THF to remove the TBS group and give the primary alcohol **75**. Alcohol **75** will subsequently be treated with I_2, imidazole and Ph_3P in THF to afford the corresponding iodide adduct **76**. After reacting iodide **76** with NaHMDS in THF/HMPA, the diolefinic product **77** can be achieved.



Scheme 6.8. Synthesis of an advanced intermediate toward the enantioselective total synthesis of azaspirene.

After applying ring closing metathesis using Grubbs' ruthenium catalyst,[199] followed by Sharpless dihydroxylation,[200] the diol intermediate **79** will then be protected to give acetonide **80**. Removal of the acidic α-proton in **80** using LDA and the corresponding enolate readily nucleophilic to attack the acid chloride **81** anti to the acetonide group already in place to give intermediate **82** (Scheme 6.9).



Scheme 6.9. Proposed strategy to complete the synthesis of azaspirene.

Exposing the latter fragment with the Dess-Martin reagent will oxidize the primary alcohol to the corresponding aldehyde. A subsequent deprotecting of the *O*-TIPS group and finally treating the aldol moiety with sodium bicarbonate solution will then achieve the β-oxygenated cyclic structure **83**. This substrate is then ready for the exposure of the newly developed copper(I)-catalyzed vinyl-addition methodology (Chapter 3). Thus, the mixed alkenyl-alkylzincate reagent in combination with 10 mol% CuI-0.75DMS complex should be sufficient to add directly to the α,β-unsaturated cyclic fragment **83** in a 1,4-fashion to give **84**. This intermediate will then be treated with LDA and phenyl selenium chloride to form the α-selenyl cyclic intermediate, which upon exposure to hydrogen peroxide, the β-elimination product **85** will be obtained. Deprotection of Troc and acetonide groups will finalize the total synthesis of azaspirene.

The proposed strategy herein is not only directed toward the synthesis of azaspirene, but it is also designed for the construction of a library of analogs. It is expected that this small library could provide more effective angiogenesis inhibitors for the community, which is in a desperate need for new drugs to battle cancer.

Chapter 7

Experimental Section

7.1 Chemicals and Instrumentals

General. All moisture-sensitive reactions were performed under an argon atmosphere. The glassware was oven dried overnight prior use. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60Å F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with PAA reagent (186 mL 95% EtOH, 7 mL conc. H_2SO_4, 2 mL conc. AcOH and 5 mL *p*-anisaldehyde to yield 200 mL of PAA) and PMA reagent (20% phosphomolybdic acid in EtOH). Flash chromatography was conducted using silica gel (Whatman, 60Å, 230-400 mesh). Chemical yields are based on purified material (>98% by ^{1}H NMR spectroscopy). All compounds were fully characterized using ^{1}H and ^{13}C-NMR, IR and MS. ^{1}H (500 MHz) and ^{13}C (125 MHz, standard: $^{13}CDCl_3$, $\delta = 77.23$ ppm) NMR spectra were recorded on a Varian 500-MHz spectrometer using TMS as internal standard ($\delta = 0$ ppm) at ambient temperature unless stated otherwise. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), J = coupling constants (Hz), and integration. Proton assignments were obtained from COSY and DEPT spectra. Mass spectra were obtained using a VG-ZAB or a VG 7070 spectrometer. IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. Elemental analysis and mass spectra were performed by Numega, San Diego. HRMS were performed by the University of California, Riverside.

Chemicals. $Cp_2Zr(H)Cl$ was prepared according to Buchwald *et al.*[12] and Et_2Zn in toluene was purchased from the Aldrich Chemical Company and used as received. The CuI•0.75DMS complex was prepared from commercially available 98% pure copper(I) iodide and methyl sulfide, purchased from Aldrich, according to the procedure described by House.[47] CH_2Cl_2 was dried by distillation over CaH_2. Et_2O and THF were distilled from sodium-benzophenone ketyl and were collected when the indicator became deep blue or purple. The aldehydes employed in the Wittig reactions were commercially available except 2-*O*-(triisopropylsilyl)-3-butenal.[164] Due to the relative sensitivity of some of the aldehydes, they were analyzed with ^1H-NMR spectroscopy prior use in the aqueous Wittig reactions. The ylides are generally hygroscopic and sensitive for hydrolysis in water. Hence, newly opened bottles or freshly prepared ylides were always used. Deionized water was used as a medium for the Wittig reactions. All other reagents and solvents were purchased from Aldrich or Fisher Scientific unless otherwise specified.

7.2 Experimental Procedures

Preparation of the CuI•0.75DMS complex. Copper(I) iodide (98%) was purified via its dimethyl sulfide complex following the House protocol.[47] Copper(I) iodide (26 mmol, 5.0 g) in anhydrous Et_2O (15 mL) was mixed with (380 mmol, 20 mL) of DMS. The resulting yellow solution was filtered through a cotton plug to remove heterogeneous material. The filtrate was diluted with cold hexanes (50 mL). The crystalline material obtained was filtered with suction using a büchner funnel and washed with cold hexanes (3 x 50 mL) to afford 5.1 g of the copper complex as white prisms. The CuI•DMS complex was subsequently dried under vacuum (ca. 0.1 mbar) at room temperature where it rapidly lost DMS and reached a constant weight within two hours to afford 4.5 of white crystals. Elemental analysis of this material indicated a stoichiometry of CuI•0.75DMS.[45b] Anal. Calcd. for $(CuI)_4$•$(SMe_2)_3$: C, 7.60; H, 1.91; S, 10.15. Found: C, 7.53; H, 1.72; S, 10.13.

Typical procedure for copper(I)-catalyzed conjugate addition of alkenylzirconocene reagents to enones and enals.[45] **Preparation of compounds 1-10.** A reflux condenser was connected to an oven-dried 25-mL 2-necked round bottom flask containing an egg-shaped stir bar. The alkyne (2.38 mmol, 1.0 equiv) was added under an argon atmosphere to the round bottom flask containing a suspension of Schwartz's reagent, $Cp_2Zr(H)Cl$ (2.61 mmol, 1.1 equiv) in anhydrous THF (10 mL) at ambient temperature (+20 °C). The reaction flask was then immersed in an oil-bath and carefully heated at +40 °C under stirring for 10 min. The temperature of the reaction was then cooled to +20 °C, and under a slow flow of argon, CuI•0.75DMS complex (0.24 mmol, 0.10 equiv) and enone or enal (2.38 mmol, 1.0 equiv) were added as a solid or via micro syringe. The reaction flask was then immediately capped with a septum, immersed in an oil-bath and carefully heated at +40 °C under stirring for the indicated time. The reaction was subsequently quenched by the addition of H_2O (2 mL) and diluted with Et_2O (25 mL) at ambient temperature (+20 °C). The heterogenous reaction mixture was then vacuum filtered through a glass fritted büchner funnel containing a 1 cm layer of Celite®. The mixture was transferred to a separatory funnel and the organic layer was washed with saturated $NaHCO_3$ (2 × 15 mL) and brine (15 mL) and then dried over anhydrous $MgSO_4$. After vacuum filtration and removal of the solvents, the crude product was purified by flash chromatography using the appropriate solvent system.

Typical procedure for copper(I)-catalyzed 1,4-transfer of alkenyl groups from mixed alkenyl-alkylzincate reagents to enones and enals.[90] **Preparation of compounds 1-9, 17-21.** A reflux condenser was connected to an oven-dried 25-mL 2-necked round bottom flask containing an egg-shaped stir bar. The alkyne (0.50 mmol, 1.0 equiv) was added under an argon atmosphere to the round bottom flask containing a suspension of Schwartz's reagent, $Cp_2Zr(H)Cl$ (0.55 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (3 mL) at ambient temperature (+20 °C). The reaction mixture was stirred for 15 min, cooled to -70 °C and then exposed to Et_2Zn [0.50 mmol, 1.0 equiv, 15 wt. % (1.1 M) solution in toluene]. The temperature of the reaction mixture was then increased to 0 °C using an ice-water bath. Under a slow flow of argon, CuI•0.75DMS complex (0.050 mmol, 0.10 equiv) and enone or enal (0.50 mmol, 1.0 equiv) were added as a solid or via micro syringe. The reaction flask was then immediately capped with a septum, the reaction mixture was warmed to ambient temperature (+20 °C) and then immersed in an oil-bath. The reaction mixture was then carefully heated under stirring at +35°C for the indicated time while stirring. The reaction was subsequently quenched after the time indicated by the addition of H_2O (1 mL) and diluted with Et_2O (10 mL) at ambient temperature (+20 °C). The heterogenous reaction mixture was then vacuum filtered through a glass fritted büchner funnel containing a 1 cm layer of Celite®. After washing the solids with Et_2O (3 × 5 mL), the ethereal phase was diluted with EtOAc (60 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (10 mL) and then dried over anhydrous $MgSO_4$. After vacuum filtration and removal of the solvents, the crude product was purified by flash chromatography using the appropriate solvent system.

Typical Procedure for TMSOTf-promoted Cu(I)-catalyzed conjugate addition of mixed alkenyl-alkylzincate reagents to *N*-enoyl derived oxazolidinones.[90] **Preparation of compounds 11-16.** A reflux condenser was connected to an oven-dried 25-mL 2-necked round bottom flask containing an egg-shaped stir bar. The alkyne (0.50 mmol, 1.0 equiv) was added under an argon atmosphere to the round bottom flask containing a suspension of Schwartz's reagent, $Cp_2Zr(H)Cl$ (0.55 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (3 mL) at ambient temperature (+20 °C). The reaction mixture was stirred for 15 min, cooled to -70 °C and treated with Et_2Zn [0.50 mmol, 1.0 equiv, 15 wt. % (1.1 M) solution in toluene]. The temperature of the reaction was then increased to 0 °C using an ice-water bath and under a slow flow of argon, TMSOTf (0.50 mmol, 1.0 equiv), CuI•0.75DMS complex (0.050 mmol, 0.10 equiv) and imide (0.50 mmol, 1.0 equiv) were added as a solid or via micro syringe. The reaction flask was then immediately capped with a septum, warmed to ambient temperature (+20 °C), immersed in an oil-bath and carefully heated at +35°C for the indicated time while stirring. The reaction was subsequently quenched after the time indicated by the addition of H_2O (1 mL) and diluted with Et_2O (10 mL) at ambient temperature (+20 °C). The heterogenous reaction mixture was then vacuum filtered through a glass fritted büchner funnel containing a 1 cm layer of Celite®. After washing the solids with Et_2O (3 × 5 mL), the ethereal phase was diluted with EtOAc (60 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 10 mL) and brine (10 mL) and then dried over anhydrous $MgSO_4$. After vacuum filtration and removal of the solvents, the crude product was purified by flash chromatography using the appropriate solvent system.

Reduction of amino acid to its corresponding alcohol.[118] **Preparation of compound 22.** An oven-dried 100-mL 2-necked round bottom flask was equipped with a stir bar and a reflux condenser connected to a bubbler. (*S*)-Phenylalanine (60.54 mmol, 10 g, 1.0 equiv) was added under argon to the flask, followed by anhydrous THF (30 mL) and dropwise addition of $BF_3•OEt_2$ (60.54 mmol, 7.7 mL, 1.0 equiv). The mixture was heated at reflux for 2 h resulting in a colorless homogenous solution. While refluxing, $BH_3•SMe_2$ (69.62 mmol, 6.6 mL, 1.15 equiv) was added dropwise to the solution. The solution was then heated at reflux for 12 h and cooled to ambient temperature (+20 °C). The excess borane was quenched by slow addition of THF:water (1:1, 10 mL), followed by aqueous NaOH (5.0 M, 60 mL). The resulting two-phase mixture was heated at reflux for an additional 12 h, cooled to ambient temperature and the mixture filtered through a coarse fritted Büchner funnel containing a 1 cm layer of Celite®. The solids were washed with THF (2 × 10 mL), and the filtrate was concentrated to remove the bulk of THF. The resulting slurry was extracted with CH_2Cl_2 (3 × 20 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified via recrystallization from EtOAc to give 74% (6.8 g) of **22** as a white solid.

Chiral oxazolidinone from amino alcohol.[118] **Preparation of compound 23.** An oven-dried 100-mL one-necked round bottom flask was equipped with a stir bar, distillation head and a 20-mL receiver flask connected to an argon source. The flask was charged with *S*-phenylalaninol (**22**) (37 mmol, 5.58 g, 1.0 equiv), potassium carbonate (3.7 mmol, 511 mg, 0.10 equiv) and diethyl carbonate (76.22 mmol, 9.23 mL, 2.06 equiv). The reaction flask was heated to 110-120 °C and the ethanol was collected (~ 2-3 h). After the light yellow solution was cooled to ambient temperature, it was diluted with CH_2Cl_2 (150 mL), transferred to a separatory funnel and washed with water (150 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was then purified via recrystallization from EtOAc:hexanes (2:1) to give 71% (4.7 g) of **23** as a white solid.

Benzylation of chiral oxazolidinone.[119] **Preparation of compound 24.** To an oven-dried 25-mL 2-necked round bottom flask equipped with a stir bar and connected to a condenser and an argon inlet, NaH (1.28 mmol, 51 mg, 1.5 equiv, 60% dispersion in oil) was added. The flask was then charged with anhydrous THF (5 mL) at 0 °C under argon. 4(*S*)-Benzyl-2-oxazolidinone (**23**) (0.85 mmol, 151 mg, 1.0 equiv) was slowly added to the reaction flask at 0 °C. The flask was then allowed to stir at ambient temperature for 20 min. Benzyl bromide (1.7 mmol, 202 μL, 2.0 equiv) and tetrabutylammonium iodide (0.85 mmol, 314 mg, 1.0 equiv) were added under a slow flow of argon. The reaction mixture was then allowed to stir at ambient temperature for 24 h. The reaction mixture was slowly quenched with a saturated NH_4Cl solution and carefully monitored because of the vigorous bubbling. The mixture was then partitioned between water and Et_2O (30 mL, 1:1) and the phases were separated. The aqueous portion was extracted with Et_2O (20 mL) and the combined organics were washed with aqueous sodium thiosulfate (10.0 M, 10 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography using petroleum ether: Et_2O (1:1); R_f 0.22) to give 96% (218 mg) of **24** as a colorless oil.

Hydrolysis of oxazolidinone to its corresponding amino alcohol.[120] **Preparation of compound 25.** To a 50-mL one-necked round bottom flask equipped with a stir bar were added oxazolidinone (**24**) (0.813 mmol, 217 mg, 1.0 equiv), lithium hydroxide (24.4 mmol, 584 mg, 30 equiv), H_2O (6.4 mL) and ethanol (15 mL). The reaction flask was heated at reflux for 20 h. The mixture was then concentrated to ~7-10 mL and the residue was extracted with CH_2Cl_2 (3 × 60 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was then purified using flash chromatography (95% EtOAc in methanol; R_f 0.52) to give 98% (192 mg) of **25** as a colorless oil.

Silylation of primary alcohol.[121] **Preparation of compound 26.** To an oven-dried 25-mL 2-necked round bottom flask equipped with a stir bar were added *N*-benzyl-*S*-

phenylalaninol (**25**) (0.85 mmol, 206 mg, 1.0 equiv), dry acetonitrile (3 mL) and *t*-butyldimethylsilylchloride (1.28 mmol, 193 mg, 1.5 equiv) at ambient temperature under argon. The flask was allowed to stir for few minutes and a suspension was formed. After immersing the flask in an ice-bath, DBU (1.28 mmol, 192 μL, 1.5 equiv) was added slowly and the reaction mixture turned to clear yellow. The flask content was allowed to stir at ambient temperature for 18 h (based on disappearance of starting material, TLC using 5% MeOH in EtOAc; R_f 0.52) and diluted with CH_2Cl_2 (150 mL). The organics were washed with saturated $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified using flash chromatography (10% EtOAc in hexanes; R_f 0.40) to give 82% (248 mg) of **26** as a colorless oil.

Dibenzylation of amino alcohol.[122] **Preparation of compound 27.** To a 250-mL 2-necked round bottom flask equipped with a stir bar were added a mixture of *S*-phenylalaninol (**22**) (25 mmol, 3.78 g, 1.0 equiv), potassium carbonate (50 mmol, 6.91 g, 2.0 equiv) in H_2O (10 mL) and ethanol (50 mL). Benzyl bromide was added dropwise and the vigorously stirred mixture was heated at reflux for an additional 30 min. The flask was cooled to ambient temperature and water (30 mL) was added. The reaction mixture was extracted with Et_2O (3 × 100 mL) and the combined organics were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified via recrystallization from hexanes to give 82% (6.8 g) of **27** as a white solid.

Silylation of primary alcohol.[123] **Preparation of compound 28.** To an oven-dried 250-mL 2-necked round bottom flask equipped with a stir bar, *N,N*-dibenzyl-(*S*)-phenylalaninol (**27**) (9.05 mmol, 3.0 g, 1.0 equiv), imidazole (63.8 mmol, 4.34 g, 7.05 equiv) and 4-dimethylaminopyridine (0.49 mmol, 60 mg, 0.054 equiv) were added under a slow flow of argon. Dry DMF (40 mL) was added, followed by slow addition of *t*-butyldimethylsilylchloride (36.2 mmol, 5.46 g, 4.0 equiv) at ambient temperature. The reaction mixture was stirred for 18 h. The mixture then was diluted with Et_2O (500 mL). The organics were washed with water (4 × 500 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (5% EtOAc in hexanes; R_f 0.60) to give 99% (4.0 g) of **28** as a colorless oil.

Mono-debenzylation of *N,N*-dibenzyl amino alcohol.[123] **Preparation of compound 26.** To an oven-dried 500-mL 2-necked round bottom flask equipped with a stir bar were added *N*-iodosuccinamide (9.7 mmol, 2.17 g, 3.0 equiv) and molecular sieves-4Å (7.52 g) under argon. A solution of **28** (3.22 mmol, 1.43 g, 1.0 equiv) in dry CH_2Cl_2 (100 mL) was added and the reaction mixture was allowed to stir at ambient temperature for few minutes to give a dark red suspension. After 3 h, TLC (10% EtOAc in hexanes) showed disappearance of starting material. The reaction mixture was diluted with CH_2Cl_2 (200 mL), and washed with aqueous sodium thiosulfate (150 mL), saturated $NaHCO_3$ (150 mL), water (150 mL), and brine (150 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated.

The crude product was then purified by flash chromatography (5% EtOAc in hexanes then 10% EtOAc in hexanes; R_f 0.40) to give 62% (709 mg) of **26** as a colorless oil.

Cyanation followed by acylation of aldehyde.[124] **Preparation of compound 29.** To an oven-dried 500-mL 2-necked round bottom flask equipped with a stir bar was added acrolein (177.4 mmol, 11.9 mL, 1.0 equiv) in dry toluene (40 mL) under argon, then vigorously stirred at -10 °C. Acetic anhydride (177.4 mmol, 16.8 mL, 1.0 equiv) was added at -10 °C, followed by dropwise addition of aqueous sodium cyanide solution (257 mmol, 12.6 g, 1.45 equiv, 86 mL water). After 3 h stirring at -10 °C, the toluene phase was separated and the aqueous phase was extracted with toluene (3 × 30 mL). The combined organics were washed with aqueous AcOH (1.0 M, 15 mL), saturated $NaHCO_3$ (15 mL) and water (15 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified via simple distillation (140 °C/17-20 mmHg) to give 83% (18.4 g) of **29** as a colorless oil.

Esterification of cyanide followed by deacetylation.[124] **Preparation of compound 30.** To an oven-dried 500-mL 2-necked round bottom flask equipped with a stir bar was dissolved 1-acyloxy-1-cyano-2-propene (**29**) (119.9 mmol, 15 g, 1.0 equiv) in anhydrous methanol (528 mmol, 21.4 mL, 4.4 equiv). The flask was heated at reflux and a drying tube was attached. While refluxing, HCl/MeOH mixture (45 mL) was added dropwise, followed by slow addition of concentrated HCl (5.62 mL). The reaction mixture was allowed to stir at reflux for 2 h and then cooled to 0 °C. The resulted NH_4Cl was precipitating and removed by filtration. The solution was diluted with Et_2O (200 mL) and the organic phase was washed with saturated $NaHCO_3$ (2 × 30 mL) and H_2O (2 × 30 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified via simple distillation (60 °C/20 mmHg) to give 72% (10 g) of **30** as a colorless oil.

Silylation of secondary alcohol.[125] **Preparation of compound 31.** To an oven-dried 50-mL 2-necked round bottom flask equipped with a stir bar was dissolved 2-hydroxy-3-butenyl methyl ester (**30**) (2.4 mmol, 279 mg, 1.0 equiv) in dry DMF (15 mL) under argon. At 0 °C, imidazole (4.8 mmol, 327 mg, 2.0 equiv), DMAP (0.132 mmol, 16.1 mg, 0.055 equiv) and triisopropylsilylchloride (2.64 mmol, 565 μL, 1.1 equiv) were added and the reaction was allowed to warm to ambient temperature. The mixture was then stirred for 42 h. The reaction was quenched by adding 5% aqueous citric acid and the mixture was extracted with Et_2O (3 × 60 mL). The organics were washed with water (4 × 30 mL), brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (5% EtOAc in hexanes; R_f 0.42) to give 81% (536 mg) of **31** as a colorless oil.

Hydrolysis of methyl ester. Preparation of compound 32. To a 50-mL one-necked round bottom flask equipped with a stir bar was dissolved 2-*O*-(triisopropylsilyl)-3-butenyl methyl ester (**31**) (1.24 mmol, 337 mg, 1.0 equiv) in THF (6.2 mL), followed by addition of aqueous lithium hydroxide solution (6.2 mmol, 149 mg, 5.0 equiv, 6.2 mL water) at ambient temperature. The reaction mixture was allowed to stir overnight before it was quenched with 1 M HCl and extracted with Et_2O (3 × 60 mL). The combined organics were washed with water (2 × 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then used for the next step without further purification. The yield obtained was 98% (314 mg) of **32** as a colorless oil.

Benzylidene acetal formation using benzaldehyde.[126] **Preparation of compound 33.** An oven-dried 500-mL one-necked round bottom flask equipped with a stir bar and a Dean-Stark trap was charged with dimethyl *L*-tartrate (168.4 mmol, 30 g, 1.0 equiv), cyclohexane (200 mL), benzaldehyde (168.4 mmol, 17.2 mL, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (5 mmol, 95 mg, 0.03 equiv). The stirred mixture was heated with azeotropic removal of water for 12 h. The solution was allowed to cool to ambient temperature, then concentrated. The residual yellow was dissolved in Et_2O (150 mL), transferred to a separatory funnel, and washed with aqueous bisulfate solution (60 mL) and water (2 × 60 mL). The organics were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was then collected via vacuum filtration and was triturated using 50 mL of hexanes to give 67% (30 g) of **33** as a white solid.

Reduction of Dimethyl 2,3-*O*-benzylidene-*L*-tartrate.[126] **Preparation of compound 34.** An oven-dried 1-L 3-necked round bottom flask was flushed with argon, equipped with a stir bar, an addition funnel, a condenser and a bubbler. The flask was charged with lithium aluminum hydride (225.6 mmol, 8.6 g, 2.02 equiv) and cooled to -30 °C. Then, anhydrous Et_2O (86 mL) was added with vigorous stirring, and a solution of aluminum chloride (225.6 mmol, 30.1 g, 2.02 equiv) in anhydrous Et_2O (69 mL) was added dropwise. Dry CH_2Cl_2 (69 mL) was placed in the addition funnel and added rapidly while the temperature is allowed to rise to 0 °C. A solution of **33** (111.7 mmol, 28.8 g, 1.0 equiv) in dry CH_2Cl_2 (69 mL) was added dropwise. The mixture was stirred for 1 h at ambient temperature and heated to reflux for an additional 2 h. The mixture was cooled to -20 °C, and water (7.5 mL) was added cautiously, followed by aqueous potassium hydroxide solution (16 g in 23.4 mL water) and THF (100 mL). The reaction flask was heated to reflux overnight while stirring efficiently. The mixture was then cooled, filtered through a glass fritted Büchner funnel containing a 2 cm layer of Celite®, washed with EtOAc and concentrated. The crude product was dissolved in CH_2Cl_2 (300 mL) and extracted via Soxhlet apparatus, and then recrystallized from CH_2Cl_2 to give 70% (16.6 g) of **34** as a white solid.

Acetonide protection of diol.[127] **Preparation of compound 35.** To a 100-mL one-necked round bottom flask equipped with a stir bar was dissolved 2-*O*-benzyl-*L*-threitol (**34**) (2.44 mmol, 517 mg, 1.0 equiv) in dry acetone (25 mL) at ambient temperature. *p*-Toluenesulfonic acid monohydrate (0.244 mmol, 26 mg, 0.10 equiv) was then added and the reaction flask was allowed to stir at ambient temperature for 12 h. Solid $NaHCO_3$ (1 spatula) was added and the mixture was then allowed to stir for 10 min. The reaction mixture was filtered, concentrated and the residue dissolved in EtOAc (100 mL). The organics were washed with saturated $NaHCO_3$ (15 mL), brine (15 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then used for the next step without further purification. The yield obtained was 97% (600 mg) of **35** as a colorless oil.

Oxidation of primary alcohol to aldehyde "Swern oxidation".[128] **Preparation of compound 36.** To an oven-dried 50-mL 2-necked round bottom flask equipped with a stir bar was added oxalyl chloride (3.24 mmol, 283 μL, 1.5 equiv) to dry CH_2Cl_2 (10 mL) under argon. At -60 °C, DMSO (5.4 mmol, 383 μL, 2.5 equiv) was added slowly. The mixture was allowed to stir at -60 °C for 45 min. Then, a solution of **35** (2.16 mmol, 544 mg, 1.0 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was then stirred at -60 °C for 1 h. Anhydrous triethylamine (10.8 mmol, 1.5 mL, 5.0 equiv) was added dropwise to the reaction mixture, which then was allowed to warm to -20 °C. Excess base was neutralized by adding aqueous HCl (1 M, 60 mL). The mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with saturated $NaHCO_3$ (20 mL) and water (20 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then used in the next step without further purification. The yield obtained was 100% (541 mg) of **36**.

Esterification of aldehyde.[128] **Preparation of compound 37.** To a one-necked round bottom flask equipped with a stir bar was dissolved aldehyde **36** (1.92 mmol, 482 mg, 1.0 equiv) in aqueous methanol (2 mL water in 12 mL MeOH). Solid $NaHCO_3$ (30.34 mmol, 2.6 g, 15.8 equiv) was added, followed by the dropwise addition of bromine (6.24 mmol, 320 μL, 3.25 equiv). The reaction was allowed to stir for 2 h at ambient temperature. The excess bromine was then quenched by adding solid sodium thiosulfate, diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (10% EtOAc in hexanes; R_f 0.12) to give 80% (430 mg) of **37** as a colorless oil.

Removal of the acetonide.[129] **Preparation of compound 38.** To a 100-mL one-necked round bottom flask equipped with a stir bar was dissolved methyl (2*R*,3*S*)-2-benzyloxy-3,4-isopropylidenedioxybutanoate (**37**) (1.53 mmol, 430 mg, 1.0 equiv) in THF (15 mL). Hydrochloric acid (1 M, 15 mL) was then added dropwise at 0 °C, and the reaction flask was allowed to stir for 12 h. The mixture was diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (2 × 25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (2:1 EtOAc in hexanes; R_f 0.53 to give 87% (277 mg) of **38** as a colorless oil.

Benzoylation of primary alcohol.[127] **Preparation of compound 39.** To an oven-dried 100-mL one-necked round bottom flask equipped with a stir bar were dissolved 3-*O*-benzyl-1,2-isopropylidene-*L*-threitol (**35**) (5.44 mmol, 1.37 g, 1.0 equiv) and DMAP (0.544 mmol, 67 mg, 0.10 equiv) in dry CH_2Cl_2 (20 mL) under argon. Pyridine (10.88 mmol, 880 μL, 2.0 equiv) was added slowly at 0 °C, followed by slow addition of freshly distilled benzoyl chloride (5.98 mmol, 695 μL, 1.1 equiv). The reaction mixture was allowed to stir for 12 h at ambient temperature and monitored using TLC (starting material R_f 0.21 using 20% EtOAc in hexanes). Pyridine was removed from the reaction mixture using 5% aqueous copper(II) sulfate solution. The organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (20% EtOAc in hexanes; R_f 0.50) to give 96% (1.87 g) of **39** as a colorless thick oil.

Removal of the acetonide.[127] **Preparation of compound 40.** To a 100-mL one-necked round bottom flask equipped with a stir bar was added **39** (5.25 mmol, 1.87 g, 1.0 equiv) in 5% aqueous methanol (25 mL), followed by the addition of *p*-toulenesulfonic acid monohydrate (0.53 mmol, 101 mg, 0.10 equiv) at ambient temperature. The mixture was allowed to stir for 12 h at ambient temperature. The reaction mixture was monitored by TLC (starting material R_f 0.50 using 20% EtOAc in hexanes). The solvent was evaporated and the mixture was diluted with Et_2O (100 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ solution (2 × 25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (60% EtOAc in hexanes; R_f 0.30) to give 87% (1.45 g) of **40** as a white flaky crystals.

Oxidative cleavage of diol.[129] **Preparation of compound 41.** To a 50-mL one-necked round bottom flask equipped with a stir bar was dissolved 4-*O*-benzoyl-3-*O*-benzyl-*L*-threitol (**40**) (0.955 mmol, 302 mg, 1.0 equiv) in dry benzene (15 mL). Lead tetraacetate (1.0 mmol, 443 mg, 1.05 equiv) was added slowly in two portions at ambient temperature and the reaction mixture was allowed to stir for 5 h (TLC was monitored using 60% EtOAc in hexanes, starting material R_f 0.30 and product R_f 0.67). The reaction mixture was diluted with Et_2O (80 mL) and filtered through a glass fritted Büchner funnel containing a 2 cm layer of Celite®. The organic layer was washed with saturated $NaHCO_3$ (3 × 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then run through a silica-plug, and used subsequently as is for the next step. The yield obtained was 89%, (243 mg) of **41**.

Preparation of compound 42. Olefination reaction with aldehyde 41. To an oven-dried 100-mL 2-necked round bottom flask equipped with a stir bar was added *n*-BuLi (1.11 mmol, 444 µL, 1.3 equiv) slowly to a solution of methyltriphenylphosphoniumbromide (1.03 mmol, 368 mg, 1.2 equiv) in dry THF (10 mL) at -78 °C under argon. A solution of 3-*O*-benzoyl-2-*O*-benzyl-*L*-glyceraldehyde (**41**) (0.855 mmol, 243 mg, 1.0 equiv) in dry THF (2 mL) was then added and the reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The reaction mixture was diluted with EtOAc (80 mL), washed with brine (2 × 20 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (5% EtOAc in hexanes; R_f 0.31) to give 20% (48 mg) of **42** as a colorless oil.

Peptide coupling of carboxylic acid with secondary amine. Preparation of compound 43. To an oven-dried 2-necked round bottom flask equipped with a stir bar was dissolved 2-*O*-triisopropylsilyl-3-butenoic acid (**32**) (1.22 mmol, 332.4 mg, 1.0 equiv) in dry CH_2Cl_2 (5 mL) and DMF (2 drops) under argon. A solution of oxalyl chloride (3.72 mmol, 325 μL, 3.05 equiv) in dry CH_2Cl_2 (2 mL) was then added at 0 °C under a slow flow of argon. The reaction mixture was warmed to ambient temperature and allowed to stir for 2 h. The solvent then was evaporated under reduced pressure. The residue was treated with dry CH_2Cl_2 (5 mL) and concentrated under vacuum. This fraction was dissolved in dry THF (8 mL) and the resulting solution was added to a mixture of amine **26** (1.59 mmol, 567 mg, 1.3 equiv) and Et_3N (1.59 mmol, 221 μL, 1.3 equiv) in dry THF (6 mL) under argon at ambient temperature. After the reaction mixture was stirred for 4 h, it was quenched with water (5 mL). The layers were separated and the aqueous layer was treated with Et_2O (3 × 50 mL). The combined organics were washed with 10% aqueous hydrochloric acid (10 mL), water (10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (5% EtOAc in hexanes; R_f 0.30).

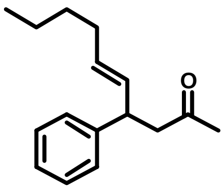
Selective desilylation of TBS over TIPS.[130] **Preparation of compound 44.** To an oven-dried 2-necked round bottom flask equipped with a stir bar was dissolved amide **43** (0.606 mmol, 361.3 mg, 1.0 equiv) in acetonitrile (6 mL) under argon. $BF_3•OEt_2$ (6.06 mmol, 770 μL, 10 equiv) was then added, followed by slow addition of TBAF (6.10 mmol, 6.10 mL, 10 equiv, 1 M in THF) at ambient temperature under a slow flow of argon. The reaction mixture was allowed to stir for 15 min. TLC was taken and showed disappearance of starting material (5% EtOAc in hexanes; R_f 0.30). The reaction was quenched with water (3 mL) and diluted with Et_2O (150 mL). The organics were washed with saturated $NaHCO_3$ (50 mL), water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (5% EtOAc in hexanes) then flushed with EtOAc.

Iodination of primary alcohol. Preparation of compound 46. To a dry 25-mL 2-necked round bottom flask equipped with a stir bar, filled with argon were charged with alcohol **44** (0.279 mmol, 134.4 mg, 1.0 equiv), triphenylphosphine (0.837 mmol, 220 mg, 3.0 equiv), imidazole (0.837 mmol, 57 mg, 3.0 equiv) and iodine (0.837 mmol, 212 mg, 3.0 equiv) in freshly distilled THF (5 mL). The reaction flask was allowed to stir for 12 h, then quenched with water (2 mL) and diluted with EtOAc (100 mL). The organic layer was washed with aqueous sodium thiosulfate (2 × 30 mL), brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was then used for the next step without further purification.

Elimination of primary iodide. Preparation of compound 47. To a dry 25-mL 2-necked round bottom flask equipped with a stir bar was dissolved iodide **46** (0.279 mmol, 165 mg, 1.0 equiv) in freshly distilled THF (2 mL) and dry HMPA (5 mL) under argon at -78 °C. Sodium hexamethyldisilazide (0.42 mmol, 420 μL, 1.5 equiv) was then added dropwise. The reaction was allowed to stir for 12 h at ambient temperature. The reaction was then quenched with water (2 mL) and diluted with EtOAc (150 mL). The organic layer was washed with water (3 × 60 mL), brine (60 mL), dried over anhydrous $MgSO_4$ and concentrated. The crude product was not confirmed using ^{1}H- and ^{13}C-NMR.

Typical procedure for aqueous Wittig reactions.[158,159] **Preparation of compounds 51-70.** A 20-ml scintillation vial, fitted with a magnetic stirring bar, was charged with ylide (1.2-1.8 mmol, 1.2-1.8 equiv), the appropriate aldehyde (1.0 mmol, 1.0 equiv) and deionized water (5 mL). The vial was capped and the content was stirred for the time indicated. In some cases, the vial was heated to 90 °C at 1 atm for the time indicated. The heterogeneous reaction mixture was cooled to ambient temperature, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The *E*/*Z*-ratio of the obtained residue was analyzed using ^{1}H-NMR spectroscopy. The crude material was subsequently purified by flash chromatography using the appropriate solvent system.

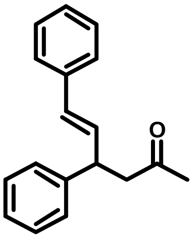
7.3 Compounds Characterized



$C_{16}H_{22}O$

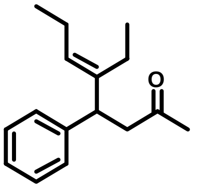
4-Phenyl-5(*E*)-decen-2-one (1).[201] The crude product was purified by flash chromatography (30% EtOAc in hexane; R_f 0.40) to give **1** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31-7.25 (m, Ar*H*, 2H), 7.21-7.16 (m, Ar*H*, 3H), 5.55 (ddt,

$CH_2CH=CH$-CHPh, *J* = 15.3, 7.1, 1.0 Hz, 1H), 5.44 (ddt, $CH_2CH=CH$-CHPh, *J* = 15.3, 6.5, 0.8 Hz, 1H), 3.84 (q, PhC*H*, *J* = 7.2 Hz, 1H), 2.82 (dd, $COCH_2CH$, *J* = 15.7, 7.2 Hz, 1H), 2.78 (dd, $COCH_2CH$, *J* = 15.7, 7.2 Hz, 1H), 2.07 (s, $COCH_3$, 3H), 1.98 (q, $CH_2CH=CH$, *J* = 6.5 Hz, 2H), 1.35-1.22 (m, $(CH_2)_2$, 4H), 0.87 (t, CH_3CH_2, *J* = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 207.6, 144.0, 132.3, 131.3, 128.8, 127.7, 126.6, 50.1, 44.2, 32.4, 31.7, 30.9, 22.4, 14.1; FTIR (film, cm^{-1}) 1717, 1602, 1494, 1453, 970, 700. HRMS (El) calculated for $C_{16}H_{22}O$: 230.1671, found: 230.1668.



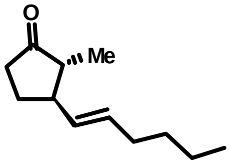
$C_{18}H_{18}O$

4,6-Diphenyl-5(*E*)-hexen-2-one (2).[202] The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.30) to give **2** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32-7.13 (3m, Ar*H*, 10H), 6.36 (d, PhC*H*=CH, *J* = 15.9 Hz, 1H), 6.31 (dd, PhCH=C*H*CH, *J* = 15.9, 6.7 Hz, 1H), 4.06 (q, PhC*H*, *J* = 7.1 Hz, 1H), 2.93 (dd, $COCH_2CH$, *J* = 16.2, 7.4 Hz, 1H), 2.89 (dd, $COCH_2CH$, *J* = 16.2, 7.0 Hz, 1H), 2.06 (s, $COCH_3$, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 206.7, 143.0, 137.1, 132.4, 130.0, 128.7, 128.5, 127.6, 127.3, 126.7, 126.2, 49.4, 43.9, 30.6; FTIR (film, cm^{-1}) 1716, 1599, 1494, 967, 746, 699; MS *m/z* = 250 (M$^+$, 100%), 207 (M-$COCH_3$, 90%), 129 (63%).



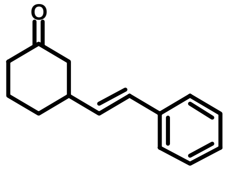
$C_{16}H_{22}O$

5-Ethyl-4-Phenyl-5(*E*)-octen-2-one (3). The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.40) to give **3** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.28-7.23 (m, Ar*H*, 2H), 7.21-7.15 (m, Ar*H*, 3H), 5.24 (dd, C=C*H*CH$_2$, *J* = 7.1 Hz, 1H), 3.85 (dd, PhC*H*CH$_2$, *J* = 7.6 Hz, 1H), 2.90 (dd, COC*H*$_2$CH, *J* = 15.9, 7.5 Hz, 1H), 2.77 (dd, COC*H*$_2$CH, *J* = 15.9, 7.8 Hz, 1H), 2.11-2.02 (m, C*H*$_2$, "partly hidden", 3H total), 2.04 (s, COC*H*$_3$, 3H), 1.73 (m, C*H*$_2$, 1H total), 0.99, 0.86 (2t, C*H*$_3$CH$_2$, *J* = 7.6 Hz, 3H each); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 207.6, 143.4, 141.8, 128.3, 128.0, 126.4, 126.3, 48.7, 46.4, 30.5, 23.3, 21.0, 14.6, 13.5; FTIR (film, cm^{-1}) 1717, 1601, 1452, 967, 755, 701; MS *m/z* = 231 ([M+H]$^+$, 100%), 230 (M$^+$, 30%), 213 (30%), 172 (23%).



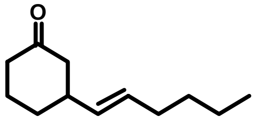
$C_{12}H_{20}O$

3-[1(*E*)-Hexenyl]-2-methyl-cyclohexan-1-one (4). The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.50) to give **4** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.53 (dt, CH$_2$C*H*=CH, *J* = 15.3, 6.7 Hz, 1H), 5.36 (dd, CH=C*H*CH, *J* = 15.3, 7.6 Hz, 1H), 2.41-2.34 (m, α-C*H*$_2$, 1H), 2.22-2.00 (3m, "complex", 5H), 1.80 (m, α-C*H*CH$_3$, 1H), 1.63-1.55 (m, 1H), 1.40-1.27 (m, (C*H*$_2$)$_2$, 4H), 1.03 (d, C*H*$_3$CH, *J* = 6.9 Hz, 3H), 0.90 (t, C*H*$_3$CH$_2$, *J* = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 220.4, 131.85, 131.79, 50.2, 48.4, 37.2, 32.2, 31.7, 28.0, 22.2, 13.9, 12.0; FTIR (film, cm^{-1}) 1740, 1456, 969, 734; MS *m/z* = 180 (M$^+$, 37%), 100 (78%), 67 (100%). HRMS (ESI) calcd for [$C_{12}H_{20}O$+H]$^+$ 181.1587, found 181.1579. HRMS (ESI) calcd for [$C_{12}H_{20}O$+Na]$^+$ 203.1406, found 203.1413.



$C_{14}H_{16}O$

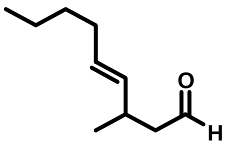
3(*E*)-Styrylcyclohexan-1-one (5).[203] The crude product was purified by flash chromatography (10% EtOAc in hexane; *R*$_f$ 0.30) to give **5** as a yellow oil. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.37-7.19 (m, Ar*H*, 5H), 6.34 (d, PhC*H*=CH, *J* = 16.1 Hz, 1H), 6.15 (dd, CHC*H*=CH, *J* = 15.9, 6.7 Hz, 1H), 2.68 (m, methine, 1H), 2.53 (m, α-C*H*$_2$, 1H), 2.40 (m, 1H), 2.36-2.25 (m, 2H), 2.10, 2.01, 1.74, 1.62 (4m, 1H each); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 211.0, 137.4, 133.2, 129.4, 128.8, 127.6, 126.4, 47.6, 42.1, 41.5, 31.6, 25.2; FTIR (film, cm^{-1}) 1716, 1494, 1448, 966, 748, 695; MS *m/z* = 200 (M$^+$, 100%), 128 (27%), 91 (38%).



$C_{12}H_{20}O$

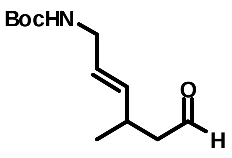
3-[1(*E*)-Hexenyl]cyclohexan-1-one (6).[204] The crude product was purified by flash chromatography (10% EtOAc in hexane; *R*$_f$ 0.30) to give **6** as a yellow oil. ^{1}H-NMR

(500 MHz, $CDCl_3$) δ 5.43 (dt, CH=C*H*CH_2, *J* = 15.3, 6.2 Hz, 1H), 5.36 (dd, C*H*=CHCH_2, *J* = 15.3, 5.9 Hz, 1H), 2.50-2.38 (2m, methine & α-CH_2, "partly hidden", 1H each), 2.38-2.12 (3m, 1H each), 2.08-1.94 (m, 3H), 1.92-1.85 (m, 1H), 1.73-1.62 (m, 1H), 1.53-1.42 (m, 1H), 1.36-1.24 (m, 2 × CH_2, 4H), 0.88 (t, C$H_3$$CH_2$, J = 6.6 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.6, 133.2, 130.2, 48.0, 41.8, 41.5, 32.4, 31.9, 31.8, 25.2, 22.4, 14.1; FTIR (film, cm^{-1}) 1716, 1448, 1222, 968; MS *m/z* = 180 (M^+, 25%), 163 (55%), 110 (M-C_5H_{10}, 100%), 97 (M-C_6H_{11}, 37%), 81 (67%).



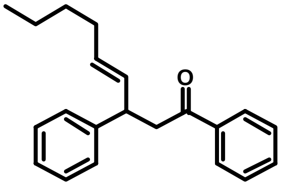
$C_{10}H_{18}O$

3-Methyl-4(*E*)-nonenal (7).[205] The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.40) to give **7** as a light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.72 (t, C*H*O, *J* = 2.4 Hz, 1H), 5.44 (dt, CH_2C*H*=CH, *J* = 15.6, 6.1 Hz, 1H), 5.34 (ddt, CH_2CH=C*H*, *J* = 15.6, 7.0, 1.1 Hz, 1H), 2.72 (m, methine, 1H), 2.40 (ddd, COCH_2, *J* = 16.0, 7.3, 2.4 Hz, 1H), 2.33 (ddd, COCH_2, *J* = 16.0, 6.6, 2.4 Hz, 1H), 1.98 (bq, CH_2CH=CH, *J* = 6.8 Hz, 2H), 1.36-1.25 (m, 2 × CH_2, 4H), 1.06 (d, CH_3CH, *J* = 6.8 Hz, 3H), 0.88 (t, C$H_3$$CH_2$, *J* = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 202.7, 133.8, 130.0, 50.6, 32.1, 31.7, 31.6, 22.1, 20.8, 13.9.



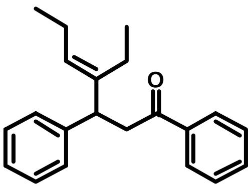
$C_{12}H_{21}NO_3$

6-(*N*-Boc)amino-3-methyl-4(*E*)-hexenal (8). The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.40) to give **8** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.72 (t, C*H*O, *J* = 2.0 Hz, 1H), 5.55 (dd, $CH_2CH=CH$, *J* = 15.5, 6.8 Hz, 1H), 5.48 (dt, CH_2CH=CH, *J* = 15.5, 5.6 Hz, 1H), 4.50 (bs, N*H*, 1H), 3.69 (bs, $NHCH_2$, 2H), 2.77 (m, methine, 1H), 2.44 (ddd, $COCH_2$, *J* = 16.4, 7.0, 2.0, 1H), 2.37 (ddd, $COCH_2$, *J* = 16.4, 7.0, 2.1, 1H), 1.45 (s, *t*-Bu, 9H), 1.07 (d, CH_3CH, *J* = 6.8 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 202.1, 155.9, 136.3, 126.2, 79.6, 50.4, 42.6, 31.2, 28.6, 20.4.



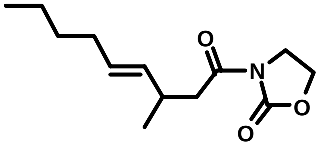
$C_{21}H_{24}O$

1,3-Diphenyl-4(*E*)-nonen-1-one (9).[206] The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.50) to give **9** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.93-7.89 (m, Ar*H*, 2H), 7.55-7.51 (m, Ar*H*, 1H), 7.46-7.41 (m, Ar*H*, 2H), 7.31-7.23 (m, Ar*H*, 4H), 7.20-7.15 (m, Ar*H*, 1H), 5.61 (ddt, $CH_2CH=CH$, *J* = 15.3, 7.2, 1.3 Hz, 1H), 5.43 (ddt, CH_2CH=CH, *J* = 15.3, 6.7, 1.1 Hz, 1H), 4.05 (bq, PhC*H*, *J* = 7.2 Hz, 1H), 3.38 (dd, α-CH_2CO, *J* = 16.1, 7.8 Hz, 1H), 3.31 (dd, α-CH_2CO, *J* = 16.1, 6.6 Hz, 1H), 1.96 (m, CH_2CH=CH, 2H), 1.31-1.19 (m, 2 × CH_2, 4H), 0.84 (t, CH_3CH_2, *J* = 7.2 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 198.7, 144.2, 137.4, 132.9, 132.2, 131.2, 128.54, 128.52, 128.1, 127.6, 126.3, 44.9, 44.0, 32.2, 31.5, 22.1, 13.9; FTIR (film, cm^{-1}) 1686, 1598, 1449, 971, 750, 699; MS *m/z* = 292 (M$^+$, 13%), 221 (18%), 173 (M-C_8H_7O, 20%), 105 (100%), 77 (28%).



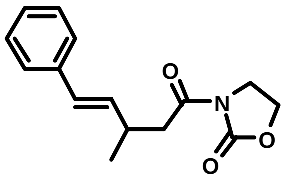
$C_{21}H_{24}O$

1,3-Diphenyl-4(*E*)-nonen-1-one (10).[206] The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.50) to give 71% (494 mg) of **10** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.91-7.88 (m, Ar*H*, 2H), 7.54-7.50 (m, Ar*H*, 1H), 7.44-7.40 (m, Ar*H*, 2H), 7.26-7.23 (m, Ar*H*, 4H), 7.18-7.14 (m, Ar*H*, 1H), 5.27-5.23 (t, olefinic, 1H), 4.08 (t, PhC*H*, 1H), 3.52-3.44 (dd, α-C*H*$_2$CO, *J* = 16.5, 7.5 Hz, 1H), 3.32-3.26 (dd, α-C*H*$_2$CO, *J* = 16.5, 7.3 Hz, 1H), 2.18-2.00 (m, CH=CC*H*$_2$, 1H), 1.80-1.74 (m, C*H*$_2$CH=CC*H*$_2$, 3H), 0.94 and 0.87 (2 × t, C*H*$_3$CH$_2$, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 198.9, 143.7, 141.9, 137.6, 132.8, 128.5, 128.3, 128.1, 128.0, 126.3, 126.3, 46.4, 43.6, 23.5, 20.9, 14.6, 13.4; FTIR (film, cm^{-1}) 1686, 1598, 1449, 896, 739, 704; MS *m/z* = 292 (M$^+$, 13%), 220 (18%), 172 (M-C_8H_7O, 20%), 105 (100%), 77 (28%).



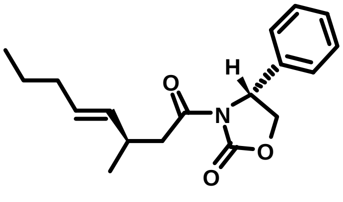
$C_{13}H_{21}NO_3$

***N*-(3’-Methyl-4’(*E*)-nonenoyl)-1,3-oxazolidin-2-one (11)**. The crude product was purified by flash chromatography (20% EtOAc in hexane; R_f 0.30) to give 92% (110 mg) of **11** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.44 (dt, CH_2CH=CH, *J* = 15.4, 6.6 Hz, 1H), 5.36 (ddt, CH_2CH=C*H*, *J* = 15.4, 7.2, 1.1 Hz, 1H), 4.42-4.36 (m, OCH_2, 2H), 4.03-3.97 (m, NCH_2, 2H), 3.00 (dd, α-CH_2CO, *J* = 15.8, 7.4 Hz, 1H), 2.84 (dd, α-CH_2CO, *J* = 15.8, 6.8 Hz, 1H), 2.72 (m, methine, 1H), 2.00-1.92 (m, CH_2CH=CH, 2H), 1.34-1.25 (m, 2 × CH_2, 4H), 1.06 (d, CH_3CH, *J* = 6.7 Hz, 3H), 0.88 (t, CH_3CH_2, *J* = 7.2 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.4, 153.5, 134.0, 129.7, 61.9, 42.5, 42.1, 33.3, 32.1, 31.7, 22.1, 20.6, 13.9; FTIR (film, cm^{-1}) 1782, 1700, 1386, 1223, 1040, 970, 761. HRMS (ESI) calcd for $[C_{13}H_{21}NO_3+H]^+$ 240.1594, found 240.1550. HRMS (ESI) calcd for $[C_{13}H_{21}NO_3+Na]^+$ 262.1414, found 262.1415.



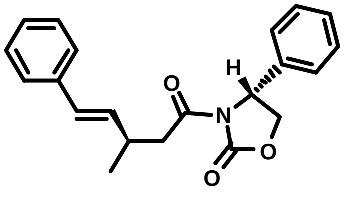
$C_{15}H_{17}NO_3$

***N*-[3’-Methyl-5’-phenyl-4’(*E*)-pentenoyl]-1,3-oxazolidin-2-one (12)**. The crude product was purified by flash chromatography (20% EtOAc in hexane; R_f 0.30) to give 84% (109 mg) of **12** as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, Ar*H*, 2H), 7.31-7.26 (m, Ar*H*, 2H), 7.22-7.19 (m, Ar*H*, 1H), 6.42 (d, PhC*H*=CH, *J* = 15.9 Hz, 1H), 6.18 (dd, PhCH=C*H*, *J* = 15.9, 7.4 Hz, 1H), 4.40-4.30 (m, OCH_2, 2H), 4.03-3.94 (m, NCH_2, 2H), 3.21-3.13 (m, methine, 1H), 3.00-2.92 (m, α-CH_2O, 2H), 1.19 (d, CH_3CH, *J* = 6.6 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.1, 153.6, 137.4, 134.3, 129.0, 128.5, 127.1, 126.1, 62.0, 42.5, 41.9, 33.7, 20.4; FTIR (film, cm^{-1}) 1782, 1701, 1387, 1267, 750, 697. HRMS (ESI) calcd for $[C_{15}H_{17}NO_3+H]^+$ 260.1281, found 260.1284. HRMS (ESI) calcd for $[C_{15}H_{17}NO_3+Na]^+$ 282.1101, found 282.1102.



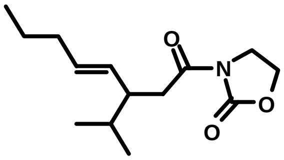
$C_{18}H_{23}NO_3$

***N*-[3′(*R*)-Methyl-4’(*E*)-nonenoyl]-4(*R*)-phenyl-1,3-oxazolidin-2-one [13(*R*)]**. The diasteromeric ratio (dr = 95:5) was analyzed based on the crude ^{1}H-NMR spectrum. The crude product was then purified by flash chromatography (20% EtOAc in hexane; R_f 0.30) to give 86% (136 mg, 95:5 dr) of **13** as a colorless oil. ^{1}H-NMR (500 MHz, CDCl3) “Major diastereomer (95%)” δ 7.39-7.25 (m, Ar*H*, 5H), 5.42 (dd, NC*H*CH$_2$, *J* = 8.8, 3.7 Hz, 1H), 5.36 (dt, CH$_2$C*H*=CH, *J* = 15.4, 5.6 Hz, 1H), 5.32 (dd, CH$_2$CH=C*H*, *J* = 15.4, 5.8 Hz, 1H), 4.66 (dd, NCHC*H*$_2$, *J* = 8.8, 8.8 Hz, 1H), 4.25 (dd, NCHC*H*$_2$, *J* = 8.8, 3.7 Hz, 1H), 3.04 (dd, α-C*H*$_2$CO, *J* = 15.9, 6.7 Hz, 1H), 2.80 (dd, α-C*H*$_2$CO, *J* = 15.9, 7.4 Hz, 1H), 2.67 (m, methine, 1H), 1.95-1.86 (m, C*H*$_2$CH=CH, 2H), 1.30-1.22 (m, 2 × C*H*$_2$, 4H), 0.98 (d, C*H*$_3$CH, *J* = 6.7 Hz, 3H), 0.87 (t, C*H*$_3$CH$_2$, *J* = 7.1 Hz, 3H). “Minor diastereomer (5%)” *distinct signals*: δ 5.45 (dd, NC*H*CH$_2$, *J* = 8.8, 3.7 Hz, 1H), 4.71 (dd, NCHC*H*$_2$, *J* = 8.8, 8.8 Hz, 1H), 4.31 (dd, NCHC*H*$_2$, *J* = 8.8, 3.7 Hz, 1H), 3.58 (dd, α-C*H*$_2$CO, *J* = 17.0, 9.0 Hz, 1H), 3.20 (dd, α-C*H*$_2$CO, *J* = 17.0, 4.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ; 171.7, 153.7, 139.2, 133.9, 129.5, 129.1, 128.6, 125.9, 69.9, 57.6, 42.4, 32.9, 32.1, 31.6, 22.2, 20.4, 13.9; FTIR (film, cm^{-1}) 1782, 1705, 1385, 1326, 1200, 762, 708. HRMS (ESI) calcd for $[C_{19}H_{25}NO_3+H]^+$ 316.1907, found 316.1909. HRMS (ESI) calcd for $[C_{19}H_{25}NO_3+Na]^+$ 338.1727, found 338.1731.



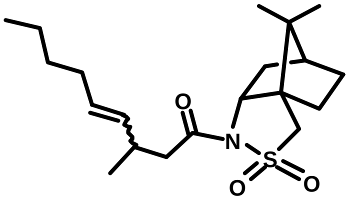
$C_{21}H_{21}NO_3$

***N*-[3′(*R*)-Methyl-5’-phenyl-4’(*E*)-pentenoyl]-4(*R*)-phenyl-1,3-oxazolidin-2-one [14(*R*)]**. The diasteromeric ratio (dr >9:1) was analyzed based on the crude ^{1}H-NMR spectrum. The crude product was then purified by flash chromatography (20% EtOAc in hexane; R_f 0.24) to give 89% (149 mg) of **14(*R*)** as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) “Major diastereomer” δ 7.29-7.26 (m, Ar*H*, 4H), 7.25-7.19 (m, Ar*H*, 6H), 6.29 (d, PhC*H*=CH, *J* = 15.9 Hz, 1H), 6.15 (dd. PhCH=C*H*, *J* = 15.9, 7.4 Hz, 1H), 5.41 (dd, NC*H*CH$_2$, *J* = 8.8, 3.8 Hz, 1H), 4.65 (dd, NCHC*H*$_2$, *J* = 8.8, 8.8 Hz, 1H), 4.22 (dd, NCHC*H*$_2$, *J* = 8.8, 3.8 Hz, 1H), 3.28 (dd, α-C*H*$_2$CO, *J* = 14.9, 6.5 Hz, 1H), 2.89 (m, CH$_3$C*H*, “partly hidden”, 1H), 2.86 (dd, α-C*H*$_2$CO, *J* = 14.9, 6.8 Hz, 1H), 1.12 (d, C*H*$_3$CH, *J* = 6.6 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.5, 153.7, 138.9, 137.4, 134.0, 129.1, 129.0, 128.6, 128.4, 127.1, 126.2, 125.8, 69.9, 57.7, 42.0, 33.9, 20.3; FTIR (film, cm^{-1}) 1778, 1698, 1456, 1384, 1317, 1198, 752, 697. HRMS (ESI) calcd for $[C_{21}H_{21}NO_3+H]^+$ 336.1594, found 336.1599. HRMS (ESI) calcd for $[C_{21}H_{21}NO_3+Na]^+$ 358.1414, found 358.1418.



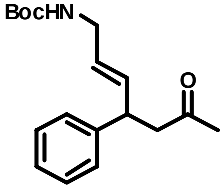
$C_{14}H_{23}NO_3$

***N*-(3′-isopropyl-4’(*E*)-nonenoyl)-1,3-oxazolidin-2-one (15)**. The crude product was purified by flash chromatography (20% EtOAc in hexane; R_f 0.30) to give 85% (114 mg) of **15** as a colorless oil. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 5.40 (dt, CH$_2$C*H*=CH, *J* = 15.3, 6.7 Hz, 1H), 5.26 (ddt, CH$_2$CH=C*H*, *J* = 15.3, 9.2, 1.2 Hz, 1H), 4.41-4.33 (m, OC*H*$_2$, 2H), 4.00-3.95 (m, NC*H*$_2$, 2H), 3.07 (dd, α-C*H*$_2$CO, *J* = 15.0, 9.8 Hz, 1H), 2.91 (dd, α-C*H*$_2$CO, *J* = 15.0, 4.9 Hz, 1H), 2.41 (m, C*H*CH=CH, 1H), 1.98 (m, C*H*$_2$CH=CH, 2H), 1.65 (m, Me$_2$C*H*, 1H), 1.34-1.24 (m, 2 × C*H*$_2$, 4H), 0.90 (d, C*H*$_3$CH$_2$, *J* = 6.8 Hz, 3H), 0.88 (t, C*H*$_3$CH$_2$, “partly hidden”, *J* = 7.3 Hz, 3H), 0.86 (d, C*H*$_3$CH, *J* = 6.8 Hz, 3H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 173.0, 153.5, 132.4, 130.2, 61.9, 45.7, 42.6, 38.1, 32.2, 31.9, 31.8, 27.1, 20.5, 19.0, 13.9; FTIR (film, cm^{-1}) 1782, 1698, 1387, 1224, 1040, 972, 760. HRMS (ESI) calcd for $[C_{15}H_{25}NO_3+H]^+$ 268.1907, found 268.1903. HRMS (ESI) calcd for $[C_{15}H_{25}NO_3+Na]^+$ 290.1727, found 290.1724.



$C_{20}H_{33}NO_3S$

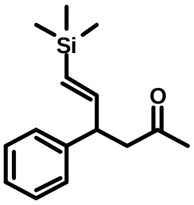
Sultam derivative 16.[207] The diasteromeric ratio (dr ~3:1) was analyzed based on the crude ^{1}H-NMR spectrum. The crude product was then purified by flash chromatography (20% EtOAc in hexane; R_f 0.30) to give 54% (110 mg) of **16** as a colorless oil. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 5.42 (dt, CH$_2$C*H*=CH, *J* = 15.4, 6.6 Hz, 1H), 5.34 (ddt, CH$_2$CH=C*H*, *J* = 15.4, 7.1, 1.2 Hz, 1H), 3.87 (m, NC*H*, 1H), 3.48 (d, SO$_2$C*H*$_2$, *J* = 13.8 Hz, 1H), 3.41 (d, SO$_2$C*H*$_2$, *J* = 13.8 Hz, 1H), 2.83 (dd, α-C*H*$_2$O, *J* = 14.9, 7.9 Hz, 1H), 2.76 (m, C*H*CH=CH, 1H), 2.53 (dd, α-C*H*$_2$O, *J* = 14.9, 5.9 Hz, 1H), 2.10-1.80 (2m, alkyl, 4H), 1.41-1.23 (3m, alkyl + 2 × C*H*$_2$, 8H), 1.15 (s, C*H*$_3$, 3H), 1.04 (d, C*H*$_3$CH, *J* = 6.7 Hz, 3H), 0.97 (s, C*H*$_3$, 3H), 0.89 (m, C*H*, "partly hidden", 1H), 0.88 (t, C*H*$_3$CH$_2$, *J* = 7.2 Hz, 3H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 171.1, 133.8, 129.7, 65.2, 53.1, 48.2, 47.7, 44.8, 42.6, 38.6, 33.8, 32.9, 32.1, 31.6, 26.5, 22.2, 20.8, 20.7, 19.9, 14.0; FTIR (film, cm^{-1}) 1697, 1457, 1332, 988. HRMS (ESI) calcd for $[C_{20}H_{33}NO_3S+H]^+$ 368.2254, found 368.2259. HRMS (ESI) calcd for $[C_{20}H_{33}NO_3S+Na]^+$ 390.2073, found 390.2077.



$C_{18}H_{25}NO_3$

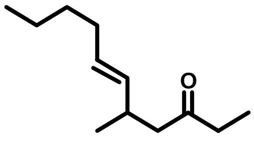
7-(*N*-Boc)amino-phenyl-5(*E*)-hepten-2-one (17). The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.30) to give 89% (135 mg) of **17** as a yellow oil. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.31-7.26 (m, Ar*H*, 2H), 7.21-7.15 (m, Ar*H*, 3H), 5.72 (dd, CHC*H*=CH, *J* = 15.4, 7.2 Hz, 1H), 5.44 (dt, CH$_2$C*H*=CH, *J* = 15.4, 5.8 Hz, 1H), 4.58 (bs, N*H*, 1H), 3.88 (q, PhC*H*, *J* = 7.2 Hz, 1H), 3.67 (bs, NHC*H*$_2$, 2H), 2.84 (dd, COC*H*$_2$CH, *J* = 19.5, 7.5 Hz, 1H), 2.80 (dd, COC*H*$_2$CH, *J* = 19.5, 7.1 Hz, 1H), 2.06 (s, C*H*$_3$CO, 3H), 1.42 (s, *t*-Bu, 9H); ^{13}C-NMR (125 MHz,

$CDCl_3$) δ 206.8, 155.7, 142.9, 134.5, 128.6, 127.5, 126.9, 126.6, 79.5, 49.3, 43.3, 42.3, 30.6, 28.4; FTIR (film, cm^{-1}) 3356, 1716, 1514, 1249, 1170, 701. HRMS (ESI) calcd for $[C_{18}H_{25}NO_3+Na]^+$ 326.1727, found 326.1725.



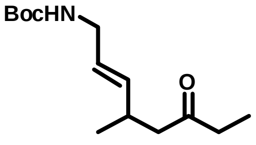
$C_{15}H_{22}OSi$

4-Phenyl-6-trimethylsilyl-5(*E*)-hexen-2-one (18). The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.50) to give 84% (104 mg) of **18** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, Ar*H*, 2H), 7.29-7.24 (m, Ar*H*, 3H), 6.22 (dd, $Me_3SiCH{=}CH$, J = 18.7, 6.2 Hz, 1H), 5.73 (dd, $Me_3SiCH{=}CH$, J = 18.7, 1.5 Hz, 1H), 4.00 (m, PhC*H*, 1H), 2.96 (dd, $COCH_2$, J = 16.1, 7.3 Hz, 1H) 2.88 (dd, $COCH_2$, J = 16.1, 7.3 Hz, 1H), 2.13 (s, CH_3CO, 3H), 0.12 (s, Me_3Si, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 206.9, 147.8, 142.8, 129.6, 128.5, 127.7, 126.4, 48.9, 46.8, 30.5, -1.3; FTIR (film, cm^{-1}) 1717, 1612, 1600, 1358, 1248, 866, 838, 700. HRMS (ESI) calcd for $[C_{15}H_{22}OSi+H]^+$ 247.1513, found 247.1514. HRMS (ESI) calcd for $[C_{15}H_{22}OSi+Na]^+$ 269.1332, found 269.1335.



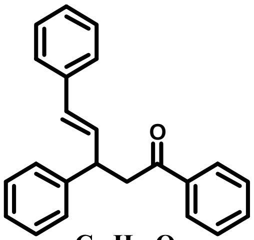
$C_{12}H_{22}O$

5-Methyl-6(*E*)-undecen-3-one (19). The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.30) to give 95% (87 mg) of **19** as a light yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.39 (ddt, $CH_2CH{=}CH$, $J = 15.4, 6.6, 0.9$ Hz, 1H), 5.30 (ddt, $CH_2CH{=}CH$, $J = 15.3, 7.2, 1.1$ Hz, 1H), 2.66 (m, methine, 1H), 2.40 (dd, $COCH_2CH$, "partly hidden", $J = 15.4, 7.1$ Hz, 1H), 2.38 (q, $COCH_2CH_3$, $J = 7.3$ Hz, 2H), 2.30 (dd, $COCH_2CH$, $J = 15.4, 7.2$ Hz, 1H), 1.95 (bq, $CH_2CH{=}CH$, $J = 6.8$ Hz, 2H), 1.33-1.26 (m, 2 × CH_2, 4H), 1.03 (t, CH_3CH_2, $J = 7.3$ Hz, 3H), 0.98 (d, CH_3CH, $J = 6.7$ Hz, 3H), 0.88 (t, CH_3CH_2, $J = 7.1$ Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.0, 134.4, 129.3, 49.8, 36.6, 32.9, 32.2, 31.7, 22.1, 20.6, 13.9, 7.7; FTIR (film, cm^{-1}) 1716, 1459, 1377, 969. HRMS (ESI) calcd for $[C_{12}H_{22}O+H]^+$ 183.1743, found 183.1740.



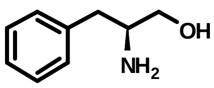
$C_{14}H_{25}NO_3$

5-Methyl-8-(*N*-Boc)amino-6(*E*)-octen-3-one (20). The crude product was purified by flash chromatography (20% EtOAc in hexane; R_f 0.30) to give 93% (119 mg) of **20** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.52 (ddt, $CH_2CH{=}CH$, $J = 15.5, 6.8, 0.9$ Hz, 1H), 5.42 (ddt, $CH_2CH{=}CH$, $J = 15.5, 5.6, 0.5$ Hz, 1H), 4.53 (bs, NH, 1H), 3.66 (bs, CH_2NH, 2H), 2.72 (m, methine, 1H), 2.42 (dd, α-CH_2CH, $J = 16.0, 6.8$, 1H), 2.39 (q, CH_2CH_3, $J = 7.3$ Hz, 2H), 2.34 (dd, α-CH_2CH, $J = 16.0, 7.2$, 1H), 1.44 (s, *t*-Bu, 9H), 1.04 (t, CH_3CH_2, $J = 7.3$ Hz, 3H), 0.99 (d, CH_3CH, $J = 6.7$ Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 210.4, 155.7, 136.9, 125.3, 79.2, 49.2, 42.4, 36.5, 32.1, 28.4, 20.1, 7.7; FTIR (film, cm^{-1}) 3365, 1712, 1518, 1366, 1172. HRMS (ESI) calcd for $[C_{14}H_{25}NO_3+Na]^+$ 278.1727, found 278.1724.



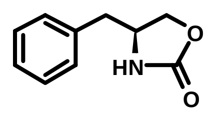
$C_{23}H_{20}O$

1,3,5-Triphenyl-4(*E*)-penten-1-one (21).[208] The crude product was purified by flash chromatography (10% EtOAc in hexane; R_f 0.40) to give 79% (123 mg) of **21** as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.96-7.91 (m, Ar*H*, 2H), 7.70-7.10 (m, Ar*H*, “complex”, 13H), 6.45-6.36 (m, *H*C=C*H*, 2H), 4.30 (bq, PhC*H*, 1H), 3.52 (dd, α-C*H*$_2$CO, *J*= 16.6, 7.5 Hz, 2H), 3.47 (dd, α-C*H*$_2$CO, *J*= 16.6, 6.8 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 198.2, 143.3, 133.1, 132.6, 130.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.1, 127.8, 127.2, 126.6, 126.3, 44.6, 44.0; FTIR (film, cm^{-1}) 1731, 1686, 1449, 1265, 744, 698.



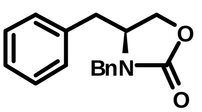
$C_9H_{13}NO$

(*S*)-Phenylalaninol (22).[118] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (m, Ar*H*, 2H), 7.25-7.18 (m, Ar*H*, 3H), 3.65-3.61 (dd, HC*H*OH, *J* = 10.5, 4 Hz, 1H), 3.40-3.36 (dd, *H*CHOH, *J* = 10.5, 7 Hz, 1H), 3.15-3.09 (m, C*H*NH$_2$, 1H), 2.82-2.77 (dd, HC*H*C$_6$H$_5$, *J* = 13.6, 5.2 Hz, 1H), 2.56-2.50 (dd, *H*CHC$_6$H$_5$, *J* = 13.6, 5 Hz, 1H), 1.7 (bs, N*H*$_2$, O*H*, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.7, 129.2, 128.6, 126.4, 66.5, 54.2, 41.1.



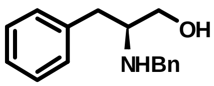
$C_{10}H_{11}NO_2$

4(*S*)-Benzyl-2-oxazolidinone (23).[118] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, Ar*H*, 2H), 7.30-7.26 (m, Ar*H*, 1H), 7.19-7.16 (m, Ar*H*, 2H), 5.06 (bs, N*H*, 1H), 4.50-4.46 (dd, HC*H*O, *J* = 8.4, 8.3 Hz, 1H), 4.17-4.14 (dd, *H*CHO, *J* = 5.62, 3.1 Hz, 1H), 4.12-4.05 (m, *H*CNH, 1H), 2.92-2.82 (dd, $\mathrm{C}H_2\mathrm{C_6H_5}$, *J* = 12, 8 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 158.9, 136.0, 129.1, 129.0, 127.4, 69.7, 53.8, 41.6.



$C_{17}H_{17}NO_2$

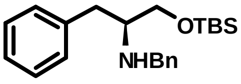
***N*-Benzyl-4(*S*)-Benzyl-2-oxazolidinone (24).**[119] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37-7.21 (m, Ar*H*, 8H), 7.05-7.02 (m, Ar*H*, 2H), 4.87-4.83 (d, $\mathrm{C_6H_5C}H_2\mathrm{N}$, *J* = 15 Hz, 1H), 4.14-4.08 (m, $\mathrm{CHC}H_2\mathrm{O}$ and $\mathrm{C_6H_5C}H_2\mathrm{N}$, 2H), 4.02-3.97 (dd, $\mathrm{CHC}H_2\mathrm{O}$, *J* = 9, 6 Hz, 1H), 3.83-3.77 (m, $\mathrm{C}H\mathrm{CH_2O}$, 1H), 3.12-3.06 (dd, $H\mathrm{CHC_6H_5}$, *J* = 13.6, 4.6 Hz, 1H), 2.66-2.60 (dd, $\mathrm{HC}H\mathrm{C_6H_5}$, *J* = 13.6, 9 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 158.3, 135.8, 135.5, 128.9, 128.8, 128.8, 128.1, 128.0, 127.1, 66.9, 55.3, 46.3, 38.4.



$C_{16}H_{19}NO$

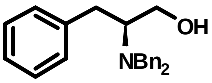
2*(S)*-Benzylamino-3-phenyl-propan-1-ol (25).[120] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29-7.12 (m, Ar*H*, 10H), 3.75 (s, $\mathrm{C_6H_5C}H_2\mathrm{NH}$, 2H), 3.63-3.59 (dd, $\mathrm{C}H_2\mathrm{OH}$, *J* = 10.7, 3.9 Hz, 1H), 3.35-3.31 (dd, $\mathrm{C}H_2\mathrm{OH}$, *J* = 10.7, 5.4 Hz, 1H), 2.96-2.90 (m, C*H*NH, 1H), 2.82-2.78 (dd, $\mathrm{C_6H_5C}H_2$, *J* = 13.6, 6.8 Hz, 1H), 2.76-2.71 (dd, $\mathrm{C_6H_5C}H_2$, *J* = 13.6, 6.8 Hz, 1H), 2.3-2.2 (bs, O*H* + N*H*, 2H); ^{13}C-NMR (125 MHz,

$CDCl_3$) δ 139.9, 138.4, 129.1, 128.5, 128.4, 128.0, 127.0, 126.4, 62.4, 59.4, 51.0, 38.0.



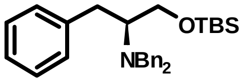
$C_{22}H_{33}NOSi$

2*(S)*-(Benzylamino)-3-phenyl-1-(*tert*butyldimethylsilyloxy)propane (26).[121] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.28-7.13 (m, Ar*H*, 10H), 3.78 (bs, $C_6H_5CH_2NH$, 2H), 3.55-3.52 (dd, CH_2OH, J = 10, 4.9 Hz, 1H), 3.50-3.46 (dd, CH_2OH, J = 10, 5.7 Hz, 1H), 2.90-2.85 (m, C*H*NH, 1H), 2.76 (dd, $C_6H_5CH_2$, J = 13.6, 6.2 Hz, 1H), 2.73 (dd, $C_6H_5CH_2$, J = 13.5, 7.3 Hz, 1H), 1.8 (bs, N*H*, 1H), 0.88 (s, $(CH_3)_3CSi$, 9H), 0.01 and 0.00 (2 × s, $(CH_3)_2Si$, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 140.6, 139.4, 129.3, 128.3, 128.3, 128.0, 126.8, 126.0, 64.2, 60.0, 51.5, 38.0, 26.0, 18.2, -5.39, -5.40.



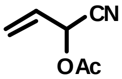
$C_{23}H_{25}NO$

2*(S)*-(*N,N*-Dibenzylamino)-3-phenyl-1-propanol (27).[122] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (m, Ar*H*, 12H), 7.21-7.17 (m, Ar*H*, 1H), 7.10 (m, Ar*H*, 2H), 3.92 (d, $C_6H_5CH_2N$, J = 13.3, 2H), 3.54-3.48 (t, CH_2OH, 1H), 3.5 (d, $C_6H_5CH_2N$, J = 13.3, 2H), 3.37-3.32 (m, HC*H*O, 1H), 3.14-3.04 (m, *H*CNBn$_2$ and HC*H*C$_6$H$_5$, 2H), 2.96 (m, *H*CHO, 1H), 2.47-2.40 (dd, *H*CHC$_6$H$_5$, J = 12.7, 3.7 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 139.2, 139.1, 129.0, 128.9, 128.6, 128.5, 127.3, 126.2, 60.9, 60.5, 53.3, 31.8.



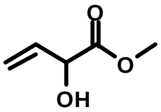
$C_{29}H_{39}NOSi$

2*(S)*-(*N,N*-Dibenzylamino)-3-phenyl-1-(*tert*butyldimethylsilyloxy)propane (28).[123] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26-7.15 (m, Ar*H*, 13H), 7.08-7.05 (m, Ar*H*, 2H), 3.78 (bs, $(C_6H_5CH_2)_2N$, 4H), 3.76-3.72 (dd, *H*CHO, *J* = 10.4, 4.4 Hz, 1H), 3.70-3.66 (dd, HC*H*O, *J* = 10.4, 5.2 Hz, 1H), 3.01-2.96 (m, C*H*CH_2O, 1H), 2.88-2.86 (m, $CH_2C_6H_5$, 2H), 0.89 (s, $(CH_3)_3CSi$, 9H), 0.01 and 0.00 (2 × s, $(CH_3)_2Si$, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 140.7, 140.6, 129.5, 128.6, 128.0, 128.0, 126.6, 125.7, 62.7, 60.5, 54.5, 34.2, 26.0, 18.2, -5.48, -5.54.



$C_6H_7NO_2$

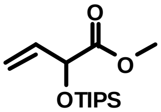
1-Acyloxy-1-cyano-2-propene (29).[124] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.94-5.88 (m, *H*C=CH_2, 1H), 5.87-5.85 (d, HC=CH_2 "*cis*", *J* = 5.6 Hz, 1H), 5.75-5.70 (d, HC=CH_2 "*trans*", *J* = 15.8 Hz, 1H), 5.56-5.54 (d, *H*CCN, *J* = 8.9 Hz, 1H), 2.16 (s, CH_3CO, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.8, 128.1, 122.4, 115.1, 61.5, 20.3.



$C_5H_8O_3$

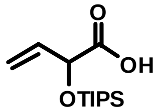
2-Hydroxy-3-butenyl methyl ester (30).[124] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.98-5.90 (ddd, *H*C=CH_2, *J* = 17.1, 10.4, 5.1 Hz, 1H), 5.53-5.48 (dt, HC=CH_2 "*trans*", *J* = 17.1 Hz, 1H), 5.30-5.26 (dt, HC=CH_2 "*cis*", *J* = 10.4 Hz, 1H), 4.68 (dt, *H*COH, *J* = 4.5, 1

Hz, 1H), 3.81 (s, CH_3O, 3H), 3.03 (bd, O*H*, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.6, 134.2, 117.1, 71.5, 52.8.



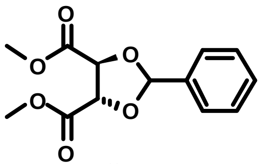
$C_{14}H_{28}O_3Si$

2-(Triisopropylsilyloxy)-3-butenoic methyl ester (31).[125] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.00-5.92 (ddd, *H*C=CH_2, *J* = 17.1, 10.4, 5.1 Hz, 1H), 5.53-5.47 (dt, HC=CH_2 "*trans*", *J* = 17.1 Hz, 1H), 5.26-5.23 (dt, HC=CH_2 "*cis*", *J* = 10.4 Hz, 1H), 4.83 (dt, *H*CCOTIPS, *J* = 5.1, 1.6 Hz, 1H), 3.73 (s, CH_3O, 3H), 1.17-1.05 (bm, Si(*i*-Pr)$_3$, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.3, 135.5, 116.6, 73.6, 52.0, 18.0, 17.8, 12.2.



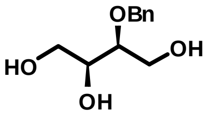
$C_{13}H_{26}O_3Si$

2-(Triisopropylsilyloxy)-3-butenoic acid (32). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.4-8.6 (bs, COOH, 1H), 6.00-5.93 (ddd, *H*C=CH_2, *J* = 17.1, 10.4, 5.1 Hz, 1H), 5.57-5.51 (dt, HC=CH_2 "*trans*", *J* = 17.1 Hz, 1H), 5.33-5.30 (dt, HC=CH_2 "*cis*", *J* = 10.4 Hz, 1H), 4.84 (dt, *H*CCOTIPS, *J* = 5.2, 2 Hz, 1H), 1.20-1.04 (bm, Si(*i*-Pr)$_3$, 21H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.5, 134.6, 117.6, 73.4, 17.8, 11.9.



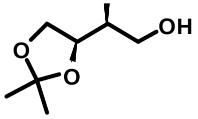
$C_{13}H_{14}O_6$

Dimethyl 2,3-*O*-benzylidene-*L*-tartrate (33).[126] ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 7.59-7.56 (m, Ar*H*, 2H), 7.42-7.38 (m, Ar*H*, 3H), 6.14 (s, *H*CC$_6$H$_5$, 1H), 4.98 (d, C*H*O, *J* = 4.2 Hz, 1H), 4.86 (d, C*H*O, *J* = 4 Hz, 1H), 3.87 (s, OC*H*$_3$, 3H), 3.82 (s, OC*H$_3$*, 3H); ^{13}C-NMR (CDCl$_3$, 125 MHz) δ 170.1, 169.4, 135.3, 130.0, 128.4, 127.2, 106.8, 52.9.



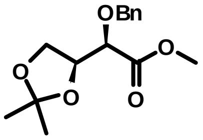
$C_{11}H_{16}O_4$

2-*O*-Benzyl-*L*-threitol (34).[126] ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 7.39-7.30 (m, Ar*H*, 5H), 4.72 (d, HC*H*C$_6$H$_5$, *J* = 11.6 Hz, 1H), 4.59 (d, *H*CHC$_6$H$_5$, *J* = 11.5 Hz, 1H), 3.91-3.82 (m, *H*$_2$C-4, 2H), 3.80-3.72 (m, *H*C-3 and *H*COBn, 2H), 3.71-3.55 (m, *H*$_2$C-1, 2H), 2.86, 2.56, 1.67 (bs, 3 O*H*, 3H); ^{13}C-NMR (CDCl$_3$, 125 MHz) δ 137.6, 128.7, 128.2, 128.0, 79.2, 72.5, 71.7, 63.0, 60.9.



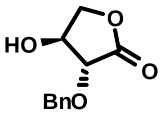
$C_{14}H_{20}O_4$

3-*O*-Benzyl-1,2-*O*-isopropylidene-*L*-threitol (35).[127] ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 7.37-7.28 (m, Ar*H*, 5H), 4.79-4.68 (AB q, C$_6$H$_5$C*H*$_2$O, *J* = 11.8 and 7.1 Hz, 2H), 4.33-4.29 (dd, BnOC*H*, *J* = 12.8, 6.7 Hz, 1H), 4.03-3.99 (dd, *H*$_2$C-1, *J* = 8.4, 6.6 Hz, 1H), 3.84-3.79 (dd, *J* = 8.4 and 7 Hz, H_2C-1, 1H), 3.76-3.70 (m, *H*C-2, 1H), 3.63-3.56 (m, CH_2OH, 2H), 2.12 (bt, O*H*, 1H), 1.44, 1.45 (2 × s, 2 CH_3, 6H); ^{13}C-NMR (CDCl$_3$, 125 MHz) δ 138.2, 128.5, 127.9, 127.8, 109.5, 79.2, 76.6, 72.8, 65.6, 61.8, 26.4, 25.3.



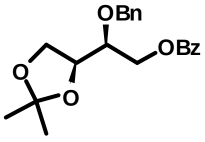
$C_{15}H_{20}O_5$

Methyl (2*R*,3*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidenebutanoate (37).[128] ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 7.37-7.26 (m, Ar*H*, 5H), 4.77, 4.51 (2 × d, C_6H_5CH_2O, *J* = 12 and 7.1 Hz, 2H), 4.41-4.37 (dd, *H*C-3, *J* = 12.1, 6.1 Hz, 1H), 4.02-4.00 (dd, H_2C-4, *J* = 8.5, 6.8 Hz, 1H), 4.00-3.99 (d, BnOC*H*, *J* = 12.6, 6.7 Hz, 1H), 3.98-3.94 (dd, H_2C-4, *J* = 8.7, 6.1 Hz, 1H), 3.75 (s, OCH_3, 3H), 1.39, 1.34 (2 × s, 2 CH_3, 6H); ^{13}C-NMR (CDCl$_3$, 125 MHz) δ 170.5, 137.0, 128.3, 128.1, 127.9, 109.8, 78.4, 75.8, 72.8, 65.4, 51.9, 26.2, 25.2.

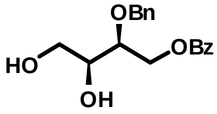


$C_{11}H_{12}O_4$

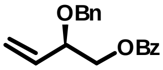
2(*R*)-Benzyloxy-3(*S*)-hydroxyfuran-2-one (38). ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 7.40-7.30 (m, Ar*H*, 5H), 5.0, 4.72 (2xd, C_6H_5CH_2O, *J* = 11.6 and 7.1 Hz, 2H), 4.50.4.45 (m, *H*COH, 1H), 4.43-4.39 (dd, H_2CO, J = 9.3, 2.6 Hz, 1H), 4.07 (d, *H*COBn, *J* = 6.1 Hz, 1H), 3.98-3.94 (dd, H_2CO, J = 9.3, 2.9 Hz, 1H), 2.71 (bd, O*H*, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 173.4, 136.7, 128.6, 128.3, 128.2, 79.1, 72.7, 72.1, 70.2.


$C_{21}H_{24}O_5$

4-*O*-Benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-*L*-threitol (39).[127] ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.02-7.99 (m, Ar*H*, 2H), 7.56-7.51 (m, Ar*H*, 1H), 7.43-7.23 (m, Ar*H*, 7H), 4.81-4.72 (AB q, $C_6H_5CH_2O$, *J* = 12, 4.5 Hz, 2H), 4.52-4.47 (dd, H_2COBz, *J* = 11.8, 4 Hz, 1H), 4.46-4.39 (dd, H_2COBz, *J* = 11.8, 5.7 Hz, 1H), 4.34-4.30 (dd, BnOC*H*, *J* = 12.6, 6.6 Hz, 1H), 4.06-4.02 (dd, H_2C-1, *J* = 8.3, 6.7 Hz, 1H), 3.90-3.86 (dd, H_2C-1, *J* = 8.3, 7 Hz, 1H), 3.84-3.79 (m, *H*C-2, 1H), 1.45, 1.37 (2 × s, 2 CH_3, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 166.1, 138.0, 133.0, 129.8, 129.5, 128.3, 128.2, 127.8, 127.6, 109.4, 77.0, 76.0, 72.8, 65.5, 64.0, 26.3, 25.2.

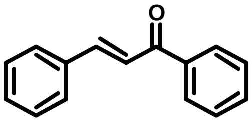

$C_{18}H_{20}O_5$

4-*O*-Benzoyl-3-*O*-benzyl-*L*-threitol (40).[127] ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.02 (m, Ar*H*, 2H), 7.58 (m, Ar*H*, 1H), 7.44 (m, Ar*H*, 2H), 7.34-7.27 (m, Ar*H*, 5H), 4.84-4.81 (d, $C_6H_5CH_2$, *J* = 11.4 Hz, 1H), 4.64-4.59 (dd, H_2COBz, *J* = 11.8, 4.6 Hz, 1H), 4.62-4.59 (d, $C_6H_5CH_2$, *J* = 11.5, 1H), 4.51-4.47 (dd, H_2COBz, *J* = 11.8, 5 Hz, 1H), 3.87-3.81 (m, *H*C-2, 2H), 3.75-3.68 (m, H_2C-1, 2H), 2.77 (bd, *H*OC-2, 1H), 2.28 (bt, *H*OC-1, 1H); ^{13}C-NMR (CDCl$_3$, 125 MHz) δ 166.4, 137.5, 133.2, 129.8, 129.6, 128.6, 128.5, 128.2, 128.1, 73.1, 71.5, 63.6, 63.5.



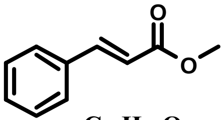
$C_{18}H_{18}O_3$

1-*O*-Benzoyl-2-*O*-benzyl-3-butene (42). ^{1}H-NMR (CDCl$_3$, 500 MHz) δ 8.3 (m, Ar*H*, 2H), 7.58-7.54 (m, Ar*H*, 1H), 7.46-7.42 (m, Ar*H*, 2H), 7.38-7.24 (m, Ar*H*, 5H), 5.90-5.82 (ddd, *H*C=CH$_2$, *J* = 17.1, 10.4, 5.1 Hz, 1H), 5.45-5.34 (dt, HC=C*H$_2$* "*trans*", *J* = 17.1, 10.4 Hz, 1H), 4.70 (d, C$_6$H$_5$C*H$_2$*, *J* = 11.4 Hz, 1H), 4.48 (d, C$_6$H$_5$C*H$_2$*, *J* = 11.5 Hz, 1H), 4.38 (m, *H*$_2$COBz, 2H), 4.18 (m, *H*COBn, 1H).



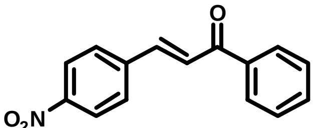
$C_{15}H_{12}O$

1,3-Diphenyl-2(*E*)-propenone {*trans*-chalcone} (51).[209] The crude product was purified by flash chromatography (10% EtOAc in hexanes; R_f 0.40) to give 91% (190 mg) of **51** as a yellow solid (*E/Z* ratio = 90/10). ^{1}H-NMR (500 MHz, CDCl$_3$) δ 8.00 (m, Ar*H*, 2H), 7.78 (d, CH^{β}=CH$^{\alpha}$, *J* = 15.8 Hz, 1H), 7.59 (m, Ar*H*, 2H), 7.54 (m, Ar*H*, 1H), 7.50 (d, CH$^{\beta}$=CH^{α}, *J* = 15.8 Hz, 1H), 7.46 (m, Ar*H*, 2H), 7.36 (m, Ar*H*, 3H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 144.6, 132.6, 130.4, 128.8, 128.5, 128.4, 128.3, 122.0.



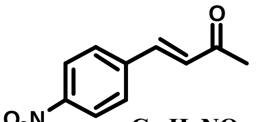
$C_{10}H_{10}O_2$

3-Phenyl-2(*E*)-propenoic acid methyl ester (52). The crude product was purified by flash chromatography (15% ethyl ether in pentane; R_f 0.40) to give 88% yield of **52** as a clear oil (*E/Z* ratio = 93/7). ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.70 (d, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 16.0 Hz, 1H), 7.54-7.50 (m, Ar*H*, 2H), 7.40-7.36 (m, Ar*H*, 3H), 6.44 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 16.0 Hz, 1H), 3.80 (s, OCH_3, 3H); ^{13}C-NMR (125MHz, $CDCl_3$) δ 167.4, 144.9, 134.5, 130.3, 128.9, 128.1, 117.9, 51.7; FTIR (film, cm^{-1}) 2950, 1717, 1637, 1171; MS: 162 (M+), 131 (M-OCH_3), 103 (Ph-CH=CH), 77 (Ph).



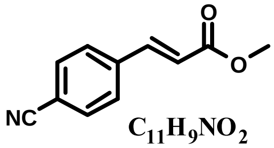
$C_{15}H_{11}NO_3$

3-(4'-Nitrophenyl)-1-phenyl-2(*E*)-propenone (53). The crude product was purified by flash chromatography (10% EtOAc in hexanes; R_f 0.40) to give 93% (235 mg) of **53** as a yellow solid (*E/Z* ratio = 84/16). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.10 (m, Ar*H*, 2H), 7.96 (m, Ar*H*, 2H), 7.59-7.51 (m, Ar*H*, 3H), 7.47-7.42 (m, Ar*H*, 2H), 7.06 (d, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 12.8 Hz, 1H), 6.87 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 12.8 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 193.5, 141.7, 136.9, 133.8, 130.3, 130.0, 129.0, 128.8, 128.6, 126.0, 124.2, 123.5; FTIR ($CHCl_3$, cm^{-1}) 1666, 1522, 1422, 1346, 1265, 736.



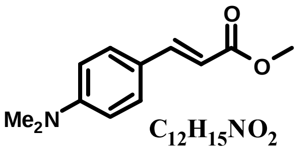
$C_{10}H_9NO_3$

4-(4’-Nitrophenyl)-3(*E*)-buten-2-one (54).[210] The crude product was purified by flash chromatography (10% EtOAc in hexanes; R_f 0.40) to give 96% (183 mg) of **54** as a yellow solid; mp 101–106 °C (*E/Z* ratio = 87/13) {lit.[208] mp 104–105 °C}. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 8.26 (m, Ar*H*, 2H), 7.70 (m, Ar*H*, 2H), 7.52 (d, C*H*$^\beta$=CH$^\alpha$, *J* = 16.3 Hz, 1H), 6.81 (d, CH$^\beta$=C*H*$^\alpha$, *J* = 16.3 Hz, 1H), 2.42 (s, C*H*$_3$CO, 3H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 197.4, 148.6, 140.7, 140.0, 130.4, 128.8, 124,2, 28.0.



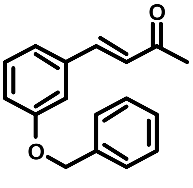
$C_{11}H_9NO_2$

3-(4’-Cyanophenyl)-2(*E*)-propenoic acid methyl ester (55).[211] The crude product was purified by flash chromatography (10% EtOAc in hexanes; R_f 0.40) to give 86% (161 mg) of **55** as a white solid; mp 98–103 °C (*E/Z* ratio = 87/13). ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.70-7.59 (multiplets, Ar*H* and C*H*$^\beta$=CH$^\alpha$, 5H), 6.53 (d, CH$^\beta$=C*H*$^\alpha$, *J* = 16 Hz, 1H), 3.83 (s, OCH$_3$, 3H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 166.4, 142.3, 138.6, 132.6, 128.3, 121.4, 118.2, 113.4, 51.9; FTIR (CHCl$_3$, cm^{-1}) 1720, 1641, 731.



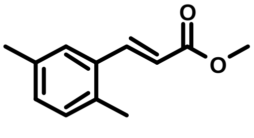
$C_{12}H_{15}NO_2$

3-(4’-Dimethylaminophenyl)-2(*E*)-propenoic acid methyl ester (56).[212] The crude product was purified by flash chromatography (10% EtOAc in hexanes; R_f 0.40) to give 81% (166 mg) of **56** as a yellow solid (*E/Z* ratio = 90/10); {lit.[210] mp 134–135 °C}. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.63 (d, C*H*$^\beta$=CH$^\alpha$, *J* = 15.9 Hz, 1H), 7.41 (m, Ar*H*, 2H), 6.66 (m, Ar*H*, 2H), 6.22 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 15.9 Hz, 1H), 3.77 (s, OC*H*$_3$, 3H), 3.01 (s, (C*H*$_3$)$_2$N, 6H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 168.3, 151.8, 145.4, 129.8, 122.3, 112.2, 111.9, 51.4, 40.1; FTIR (CH$_2$Cl$_2$, cm^{-1}) 1701, 1600, 1265, 735.



$C_{17}H_{16}O_2$

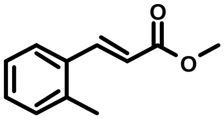
4-(3'-Benzyloxyphenyl)-3(*E*)-buten-2-one (57). The crude product was purified by flash chromatography (10% EtOAc in hexanes; R_f 0.40) to give 98% (247 mg) of **57** as a clear oil (*E/Z* ratio = 95/5). ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.47 (d, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 16.2 Hz, 1H), 7.45-7.42 (m, Ar*H* "partly hidden," 2H), 7.42-7.37 (m, Ar*H*, 2H), 7.36-7.29 (m, Ar*H*, 2H), 7.16-7.13 (m, Ar*H*, 2H), 7.02 (m, Ar*H*, 1H), 6.68 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 16.2 Hz, 1H), 5.09 (s, OC*H*$_2$Ph, 2H), 2.37 (s, C*H*$_3$O, 3H); ^{13}C-NMR (50 MHz, CDCl$_3$) δ 198.3, 159.2, 143.3, 136.7, 135.9, 130.0, 128.7, 128.1, 127.50, 127.47, 121.3, 117.3, 114.2, 70.2, 27.5; FTIR (film, cm^{-1}) 1669, 1610, 1257, 697. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H 6.39. Found: C, 80.55; H, 6.59.



$C_{12}H_{14}O_2$

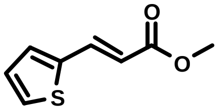
3-(2',5'-Dimethylphenyl)-2(*E*)-propenoic acid methyl ester (58).[213] The crude product was purified by flash chromatography (10% EtOAc in hexanes; R_f 0.47) to give 92% (175 mg) of **58** as a clear oil (*E/Z* ratio = 94/6). ^{1}H-NMR (500 MHz,

$CDCl_3$) δ 7.95 (d, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 15.9 Hz, 1H), 7.34 (s, Ar*H*, 1H), 7.07 (m, Ar*H*, 2H), 6.34 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 15.9 Hz, 1H), 3.80 (s, OC*H*$_3$, 3H), 2.38, 2.31 (2 × s, 2 C*H*$_3$Ar, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.4, 142.6, 135.7, 134.6, 133.1, 130.8, 130.7, 126.9, 118.5, 51.5, 20.8, 19.2.



$C_{11}H_{12}O_2$

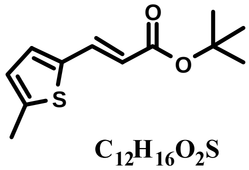
3-(2'-Methylphenyl)-2(*E*)-propenoic acid methyl ester (59).[214] The crude product was purified by flash chromatography (10% EtOAc in hexanes; *R*$_f$ 0.44) to give 89% (157 mg) of **59** as a clear liquid (*E/Z* ratio = 93/7). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.97 (d, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 15.9 Hz, 1H), 7.53 (d, Ar*H*, *J* = 7.4 Hz, 1H), 7.29-7.23 (m, Ar*H*, 1H), 7.22-7.16 (m, Ar*H*, 2H), 6.35 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 15.9 Hz, 1H), 3.80 (s, OC*H*$_3$, 3H), 2.43 (s, C*H*$_3$Ar, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.4, 142.5, 137.6, 133.4, 130.8, 130.0, 126.39, 126.31, 118.9, 51.6, 19.7.



$C_8H_8O_2S$

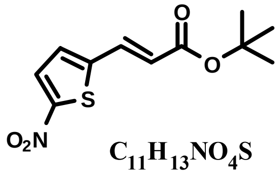
3-(2'-Thiophenyl)-2(*E*)-propenoic acid methyl ester (60).[215] The crude product was purified by flash chromatography (15% Et_2O in pentane, *R*$_f$ 0.40) to give 95% (160 mg) of **60** as a light yellow solid; mp 45-47 °C (*E/Z* ratio = 92/8). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.79 (d, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 15.7 Hz, 1H), 7.36 (d, Ar*H*, *J* = 5.1 Hz, 1H), 7.25 (d, Ar*H*, *J* = 3.6 Hz, 1H), 7.04 (dd, Ar*H*, *J* = 5.1, 3.6 Hz, 1H), 6.24 (d,

CH^{β}=CH^{α}, *J* = 15.7 Hz, 1H), 3.79 (s, OCH_3, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.2, 139.5, 137.2, 130.9, 128.4, 128.1, 116.6, 51.6; FTIR (CH_2Cl_2, cm^{-1}) 1701, 1635, 1205, 742; HRMS (DEI) calcd for [$C_8H_8O_2S$] 168.0245, found 168.0241.



$C_{12}H_{16}O_2S$

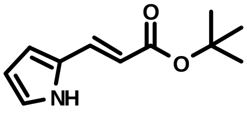
3-(5'-Methyl-2'-thiophenyl)-2(*E*)-propenoic acid *tert*-butyl ester (61). The crude product was purified by flash chromatography (10% EtOAc in hexanes, R_f 0.40) to give 97% (217 mg) of **61** as a clear oil (*E/Z* ratio = 90/10). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (d, CH^{β}=CH^{α}, *J* = 15.6 Hz, 1H), 7.01 (d, Ar*H*, *J* = 3.4 Hz, 1H), 6.68 (dq, Ar*H*, *J* = 3.4, 1.0 Hz, 1H), 6.02 (d, CH^{β}=CH^{α}, *J* = 15.6 Hz, 1H), 2.48 (d, CH_3Ar, *J* = 1.0 Hz, 3H), 1.51 (s, $OC(CH_3)_3$, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.4, 143.4, 137.8, 136.4, 131.1, 126.4, 117.6, 80.3, 28.2, 15.8; FTIR (CH_2Cl_2, cm^{-1}) 1701, 1624, 1147, 799; MS *m/z* 224 (M^+, 100%), 168 (M-C_4H_8, 45%), 151 (M-C_4H_9O, 35%), 135 (38%). Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.24; H, 7.19; S, 14.29. Found: C, 64.23; H, 7.36; S, 14.15.



$C_{11}H_{13}NO_4S$

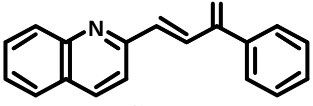
3-(5'-Nitro-2'-thiophenyl)-2(*E*)-propenoic acid *tert*-butyl ester (62). The crude product was purified by flash chromatography (10% EtOAc in hexanes, R_f 0.40) to give 94% (240 mg) of **62** as an orange solid; mp 87–92 °C (*E/Z* ratio = 86/14). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.84 (d, Ar*H*, *J* = 4.3 Hz, 1H), 7.56 (d, CH^{β}=CH^{α}, *J* =

15.8 Hz, 1H), 7.16 (d, Ar*H*, J = 4.3 Hz, 1H), 6.35 (d, CH$^{\beta}$=C*H*$^{\alpha}$, J = 15.8 Hz, 1H), 1.53 (s, OC(CH_3)$_3$, 9H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 164.6, 145.8, 134.0, 128.9, 128.3, 124.1, 114.9, 81.5, 28.0; FTIR (CH$_2$Cl$_2$, cm^{-1}) 1707, 1631, 1265, 739. Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H 5.13; N 5.49; S 12.56. Found: C, 51.75; H, 5.33; N, 5.53; S, 12.62.



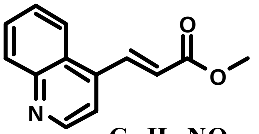
$C_{11}H_{15}NO_2$

3-(2'-Pyrrole)-2(*E*)-propenoic acid *tert*-butyl ester (63). The crude product was purified by flash chromatography (10% EtOAc in hexanes, R_f 0.20) to give 84% (162 mg) of **63** as a clear oil (*E/Z* ratio = 99/1). ^{1}H-NMR (500 MHz, CDCl$_3$) δ 12.27 (bs, N*H*, 1H), 6.99 (m, Ar*H*, 1H), 6.68 (d, C*H*$^{\beta}$=CH$^{\alpha}$, J = 12.6 Hz, 1H), 6.46 (m, Ar*H*, 1H), 6.24 (m, Ar*H*, 1H), 5.45 (d, CH$^{\beta}$=C*H*$^{\alpha}$, J = 12.6 Hz, 1H), 1.52 (s, OC(CH_3)$_3$, 9H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 168.8, 133.8, 129.3, 122.5, 118.0, 110.0, 109.9, 80.5, 28.2; FTIR (film, cm^{-1}) 3265, 1684, 1600, 1233, 754. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.40; H, 7.67; N, 6.98.

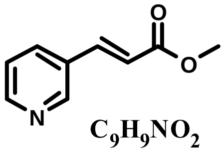


$C_{18}H_{13}NO$

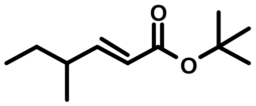
1-Phenyl-3-(2'-quinolinyl)-2(*E*)-propenone (64).[216] The crude product was purified by flash chromatography (10% EtOAc in hexanes, R_f 0.40) to give 89% (231 mg) of **64** as a orange solid; mp 114–116 °C (E/Z ratio = 99/1) {lit.[214] mp 113–115 °C}. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 8.18 (d, Ar*H*, J = 8.4 Hz, 1H), 8.15 (d, C*H*$^{\beta}$=CH$^{\alpha}$ 'partly hidden', *J* = 15.5 Hz, 1H), 8.15-8.09 (m, Ar*H*, 3H), 7.94 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 15.5 Hz, 1H), 7.81 (m, Ar*H*, 1H), 7.74 (m, Ar*H*, 1H), 7.65 (d, Ar*H*, *J* = 8.4 Hz, 1H), 7.62-7.49 (m, Ar*H*, 4H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 190.6, 153.5, 148.4, 143.5, 137.9, 136.8, 133.0, 130.1, 129.9, 128.8, 128.7, 128.2, 127.6, 127.3, 127.1, 121.4; FTIR (CH$_2$Cl$_2$, cm^{-1}) 1621, 1265, 737.


$C_{13}H_{11}NO_2$

3-(4'-Quinolinyl)-2(*E*)-propenoic acid methyl ester (65).[217] The crude product was purified by flash chromatography (10% EtOAc in hexanes, *R*$_f$ 0.40) to give 92% (196 mg) of **65** as a white solid; mp 47–49 °C (*E/Z* ratio = 99/1) {lit.[215] mp 48-50 °C}. ^{1}H-NMR (500 MHz, CDCl$_3$) δ 8.92 (d, Ar*H*, *J* = 4.5 Hz, 1H), 8.41 (d, C*H*$^{\beta}$=CH$^{\alpha}$, *J* = 15.9 Hz, 1H), 8.15 (m, Ar*H*, 2H), 7.78-7.74 (m, Ar*H*, 1H), 7.64-7.60 (m, Ar*H*, 1H), 7.52 (d, Ar*H*, *J* = 4.5 Hz, 1H), 6.64 (d, CH$^{\beta}$=C*H*$^{\alpha}$, *J* = 15.9 Hz, 1H), 3.88 (s, OC*H*$_3$, 3H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 166.4, 150.0, 148.7, 139.9, 139.3, 130.2, 129.7, 127.3, 126.0, 124.2, 123.2, 118.1, 52.0; FTIR (CH$_2$Cl$_2$, cm^{-1}) 1720, 1644, 1176, 732.

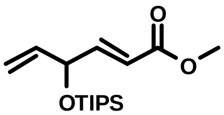

$C_9H_9NO_2$

3(3'-Pyridinyl)-(*E*)-propionic acid methyl ester (66).[215] The crude product was purified by flash chromatography (10% EtOAc in hexanes, *R*$_f$ 0.40) to give 88% (143 mg) of **66** as a orange solid; mp 37–41 °C (*E/Z* ratio = 81/19). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.75 (d, Ar*H*, *J* = 2.2 Hz, 1H), 8.61 (dd, Ar*H*, *J* = 4.8, 1.6 Hz, 1H), 7.84 (m, Ar*H*, 1H), 7.68 (d, CH^{β}=CH^{α}, J = 16.1 Hz, 1H), 7.32 (dd, Ar*H*, J = 7.9, 4.8 Hz, 1H), 6.51 (d, CH^{β}=CH^{α}, J = 16.1 Hz, 1H), 3.82 (s, OCH_3, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.7, 151.0, 149.7, 141.1, 134.2, 130.2, 123.7, 120.1, 51.9; FTIR (CH_2Cl_2, cm^{-1}) 1718, 1641, 1172, 807.



$C_{11}H_{20}O_2$

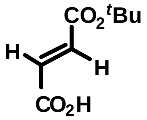
4-Methyl-2(*E*)-hexenoic acid *tert*-butyl ester (67).[218] The crude product was purified by flash chromatography (20% EtOAc in hexanes, R_f 0.40) to give 77% (153 mg) of **67** as a clear oil (*E/Z* ratio = 99/1). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.76 (dd, CH^{β}=CH^{α}, *J* = 15.6, 7.7 Hz, 1H), 5.70 (dd, CH^{β}=CH^{α}, *J* = 15.6, 1.1 Hz, 1H), 2.19 (m, methine, 1H), 1.48 (s, OC(CH_3)$_3$, 9H), 1.45-1.35 (m, methylene, 2H), 1.03 (d, CH_3CH, *J* = 6.7 Hz, 3H), (t, CH_3CH$_2$, *J* = 7.4 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.3, 153.1, 121.4, 79.9, 37.9, 28.8, 28.1, 18.9, 11.6; FTIR (film, cm^{-1}) 1716, 1652, 1153, 985; MS *m/z* 185 (M+1, 55%), 184 (M$^+$, 30%), 129 (95%), 111 (100%).



$C_{16}H_{30}O_3Si$

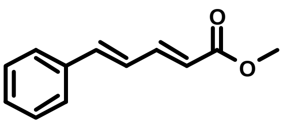
4-Triisopropyloxy-2(*E*),5-hexadieneoic acid methyl ester (68). The crude product was purified by flash chromatography (5% EtOAc in hexanes, R_f 0.43) to give 83%

(128 mg) of **68** as a clear oil (*E/Z* ratio = 88/12). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.89 (dd, C*H*$^\beta$=CH$^\alpha$, *J* = 15.6, 4.6 Hz, 1H), 6.06 (dd, CH$^\beta$=C*H*$^\alpha$, *J* = 15.6, 1.7 Hz, 1H), 5.76 (m, CH_2=C*H*, 1H), 5.28 (ddd, CH_2=CH, *J* = 17.1, 1.3, 1.3 Hz, 1H), 5.14 (ddd, CH_2=CH, *J* = 10.3, 1.3, 1.3 Hz, 1H), 4.87 (m, C*H*OSi, 1H), 3.74 (s, OCH_3, 3H), 1.13-1.04 (bm, Si(*i*-Pr)$_3$, 21H) ; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.1, 149.8, 138.6, 119.2, 115.3, 73.4, 51.6, 18.0, 12.3; FTIR (CH_2Cl_2, cm^{-1}) 2946, 1731, 1165, 883; MS *m/z* 298 (M, 0.5%), 255 (M-^{i}Pr, 100%), 145 (43%).



$C_8H_{12}O_4$

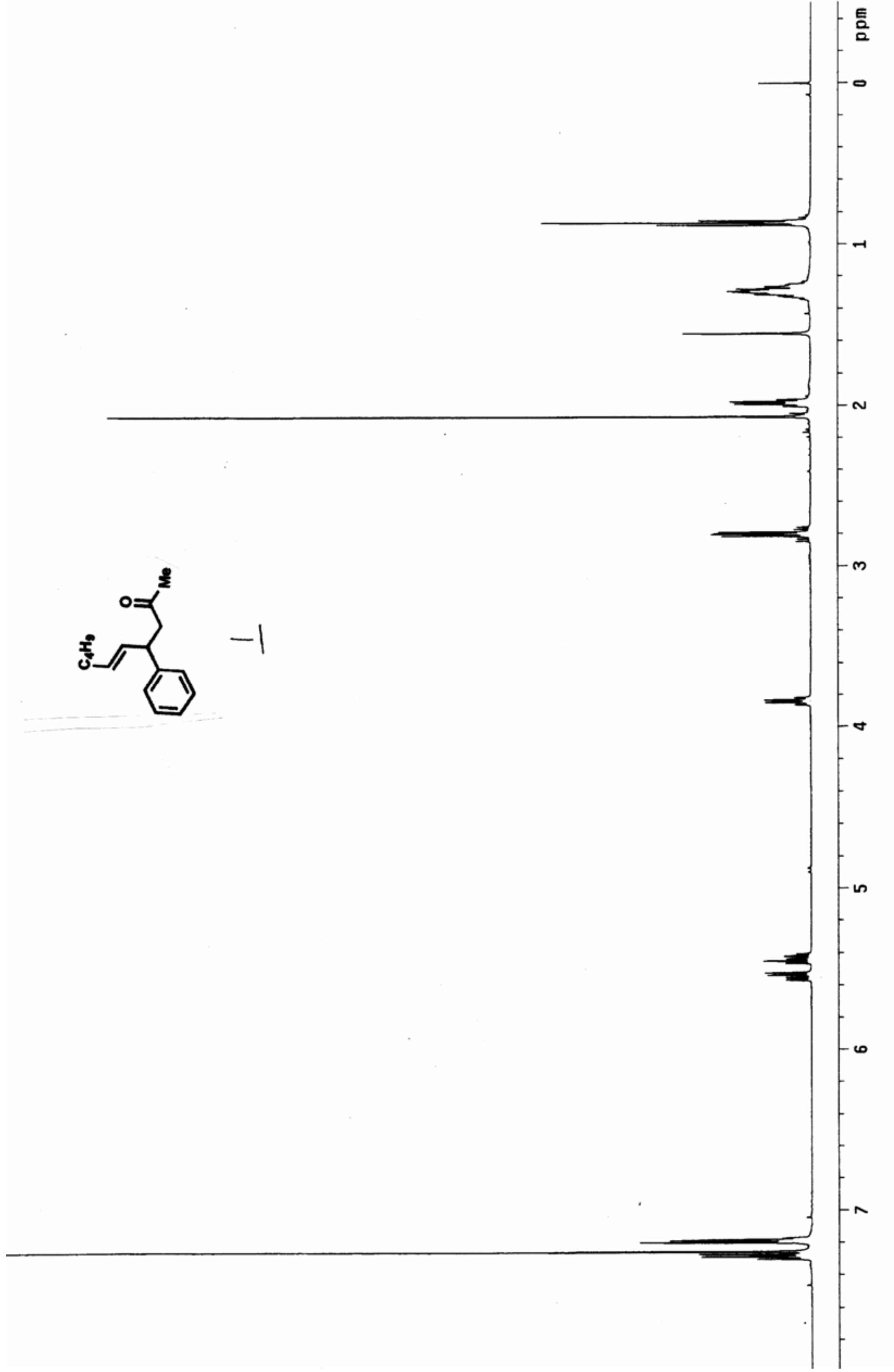
2(*E*)-Butenedioic acid mono-*tert*-butyl ester (69).[219] The crude product (est. 75%, 175 mg; *E/Z* ratio = ~70:30) was purified through a silica-gel plug (25% EtOAc in hexanes, *R*$_f$ 0.20) to give 30-50% (117 mg) of fumaric acid mono-*tert*-butyl ester (***E*-69**) as a white solid; mp 65–68 °C (*E/Z* ratio = 99/1). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.86 (d, olefinic, *J* = 15.8 Hz, 1H), 6.76 (d, olefinic, *J* = 15.8 Hz, 1H), 1.52 (s. OC(CH_3)$_3$, 9H); ^{1}H-NMR (DMSO-*d$_6$*) δ 13.1 (b, CO$_2$*H*, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 169.6, 163.9, 137.7, 131.6, 82.3, 28.0; FTIR (CH_2Cl_2, cm^{-1}) 2983, 1707, 1154, 908; MS *m/z* 172 (M$^+$, 28%), 57 (C_4H_9, 100%).

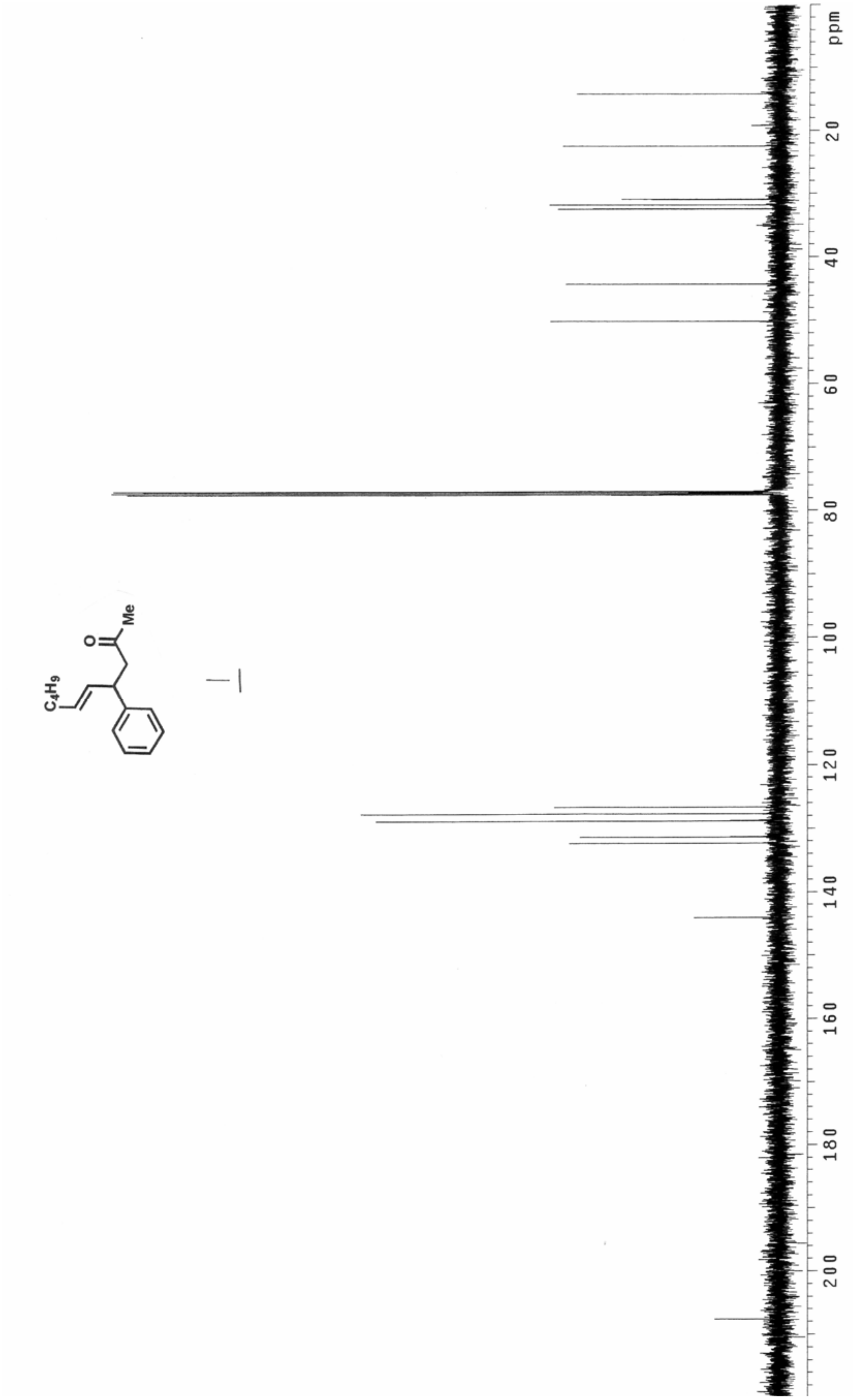


$C_{12}H_{12}O_2$

5-Phenyl-2(*E*),4(*E*)-pentadienoic acid methyl ester (70).[220] The crude product was purified by flash chromatography (15% Et_2O/pentane, R_f 0.50) to give 98% (184 mg) of **70** as a white solid; mp 64–67 °C (*E/Z*–ratio: 85/15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (m, Ar*H* and olefinic, 3H), 7.35, 7.30 (2 × m, Ar*H* and olefinic, 3H), 6.92-6.84 (m, olefinic, 2H), 5.99 (d, olefinic, *J* = 15.3 Hz, 1H), 3.77 (s, OCH_3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 144.8, 140.6, 136.0, 129.1, 128.8, 127.2, 126.2, 120.8, 51.6; FTIR (CH_2Cl_2, cm^{-1}) 1716, 1628, 996, 760.

Appendix

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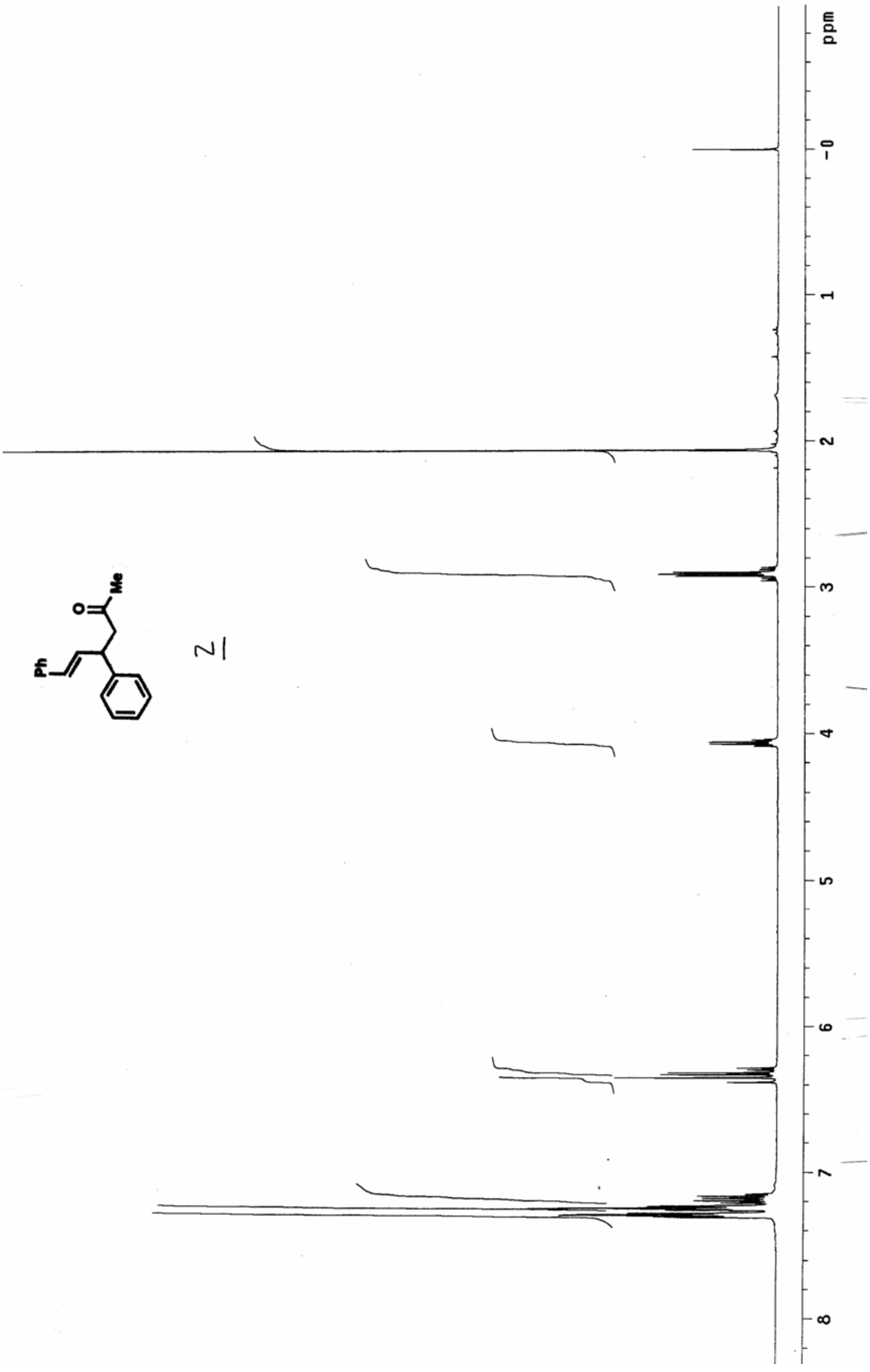

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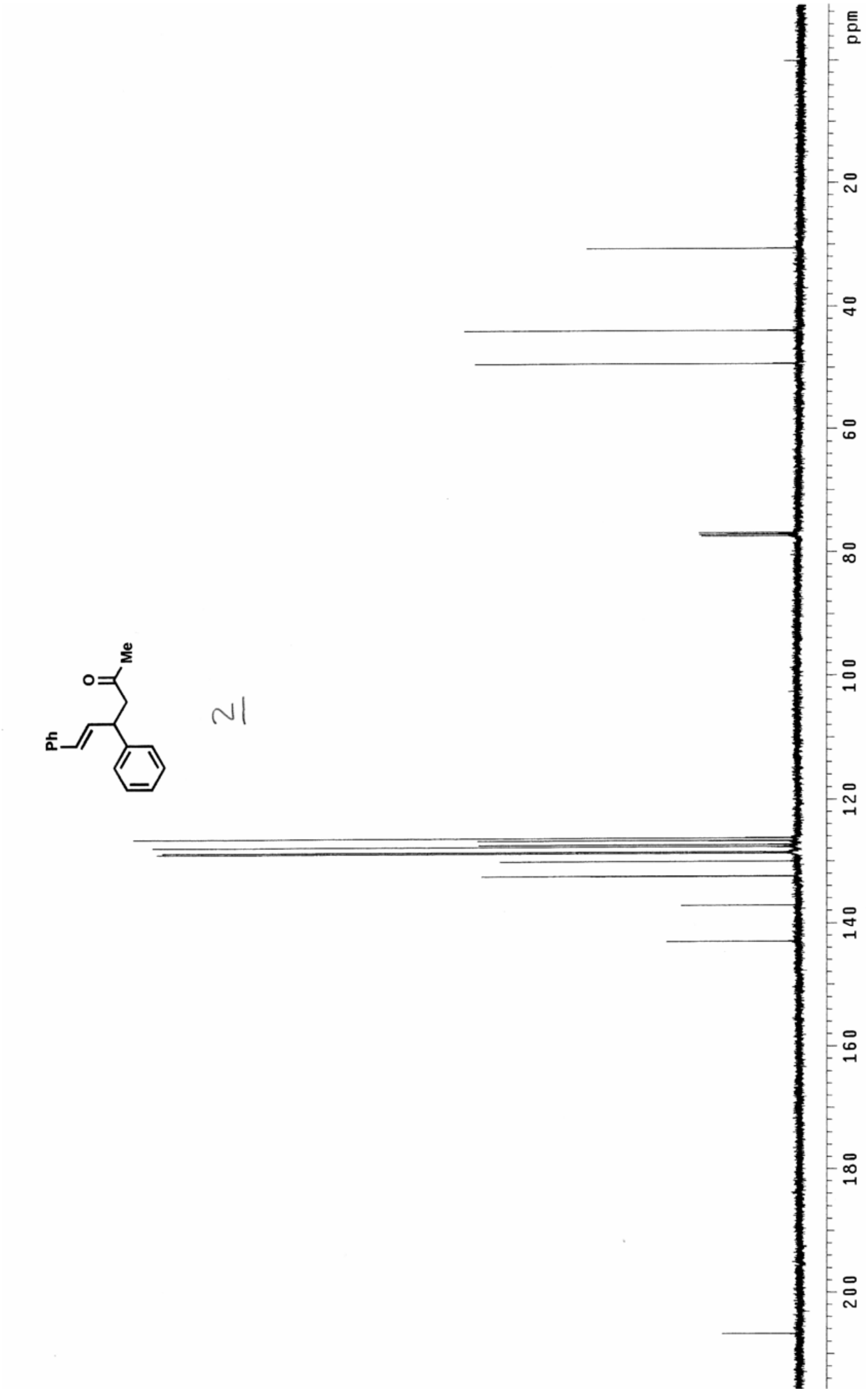

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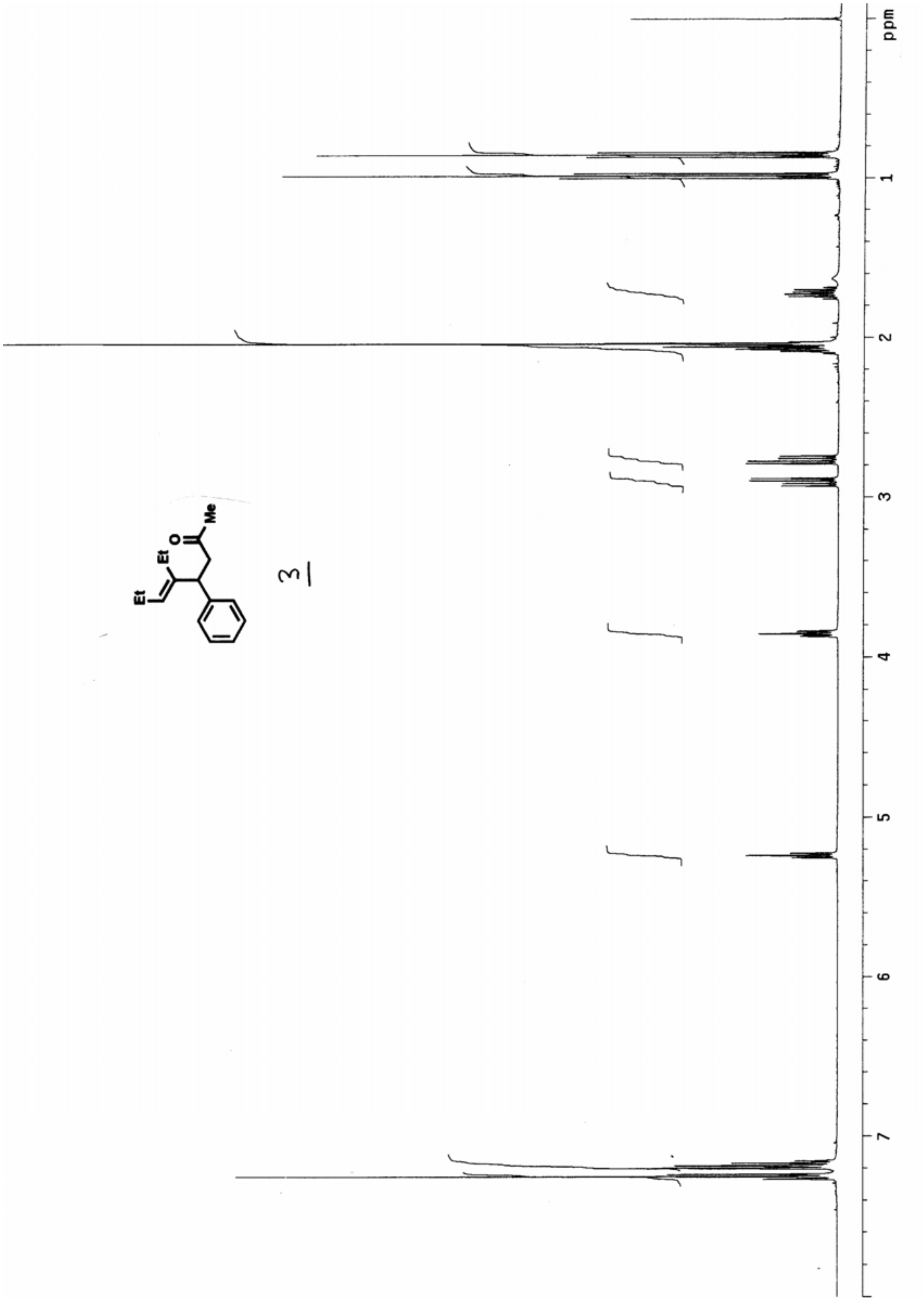

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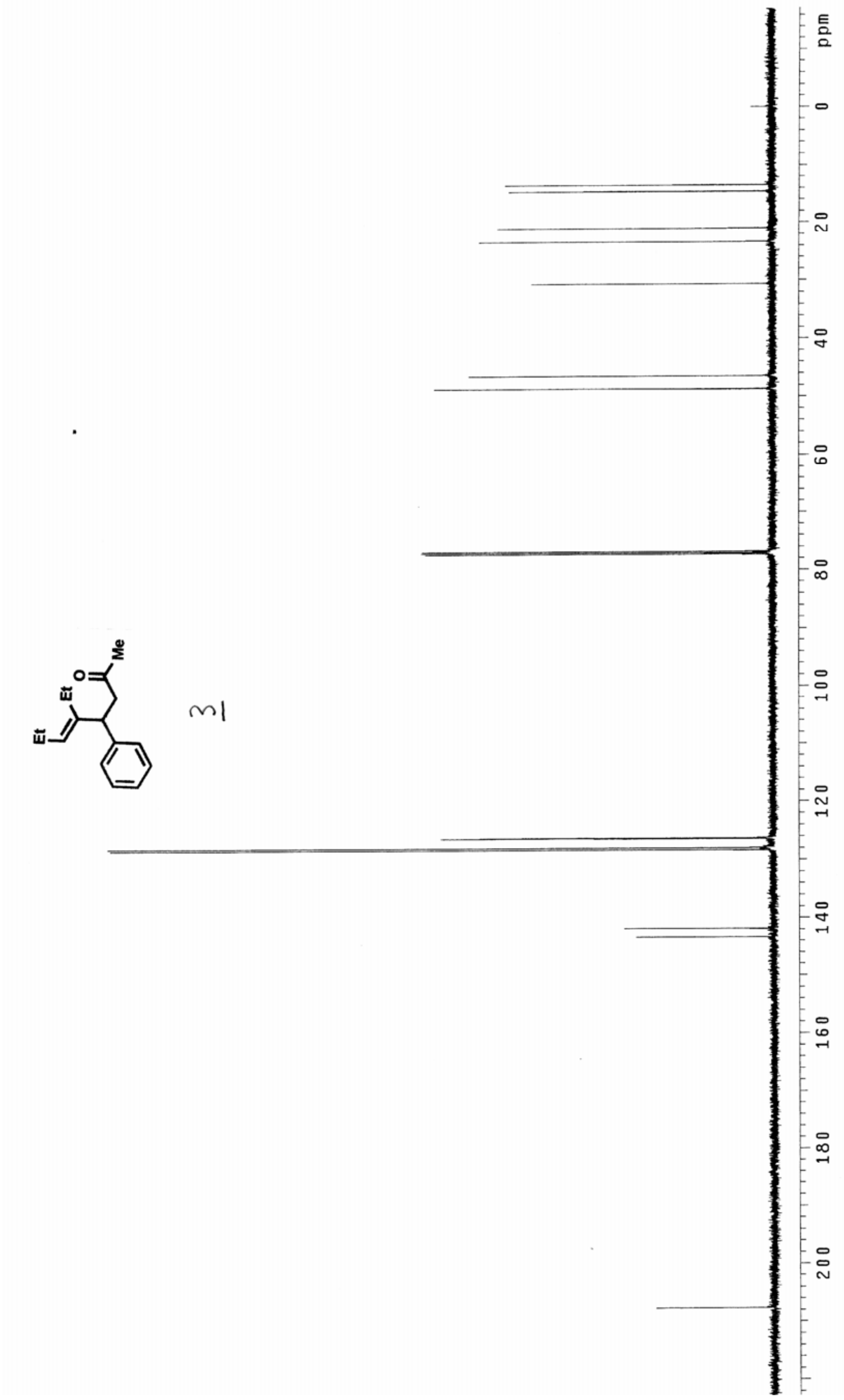

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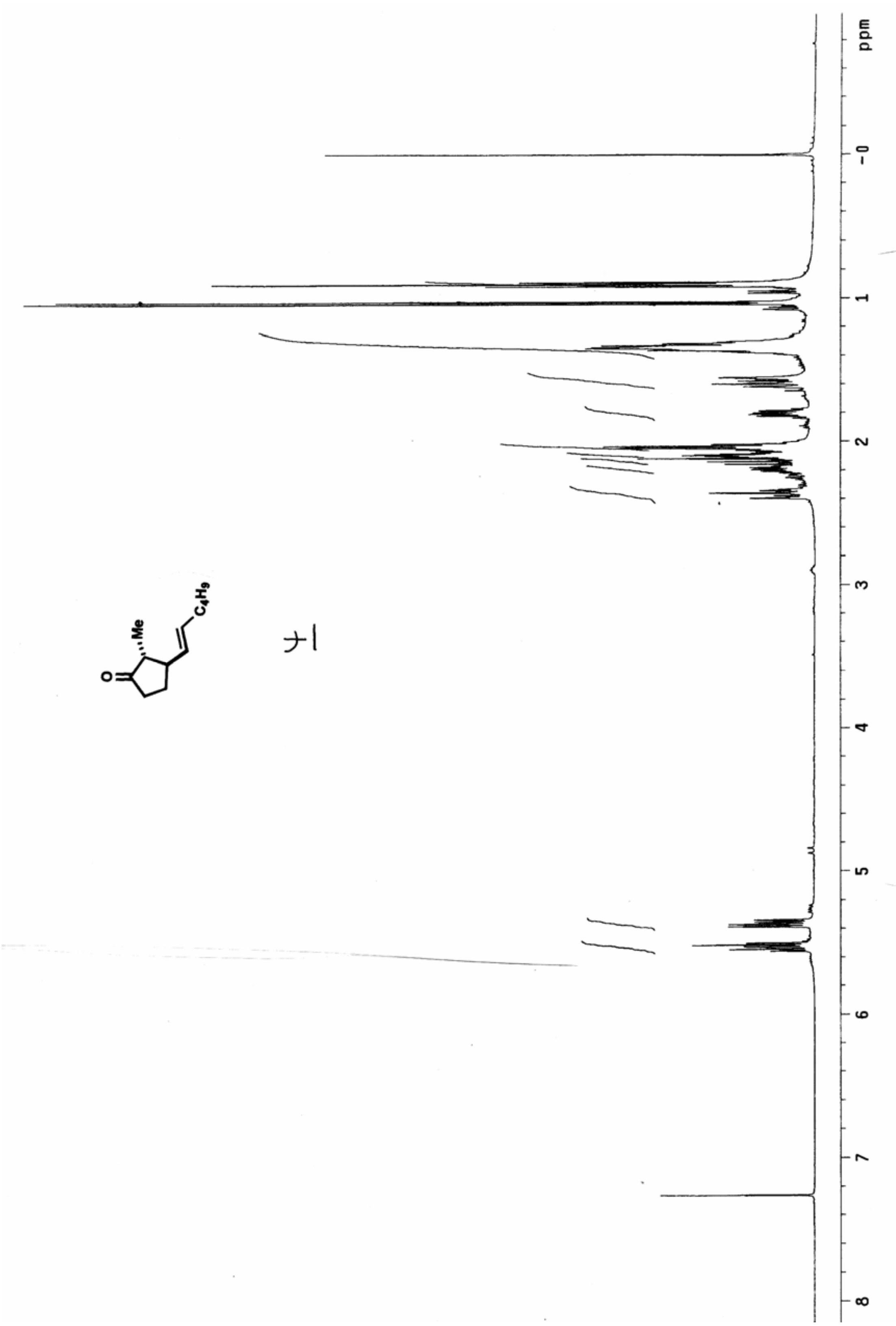

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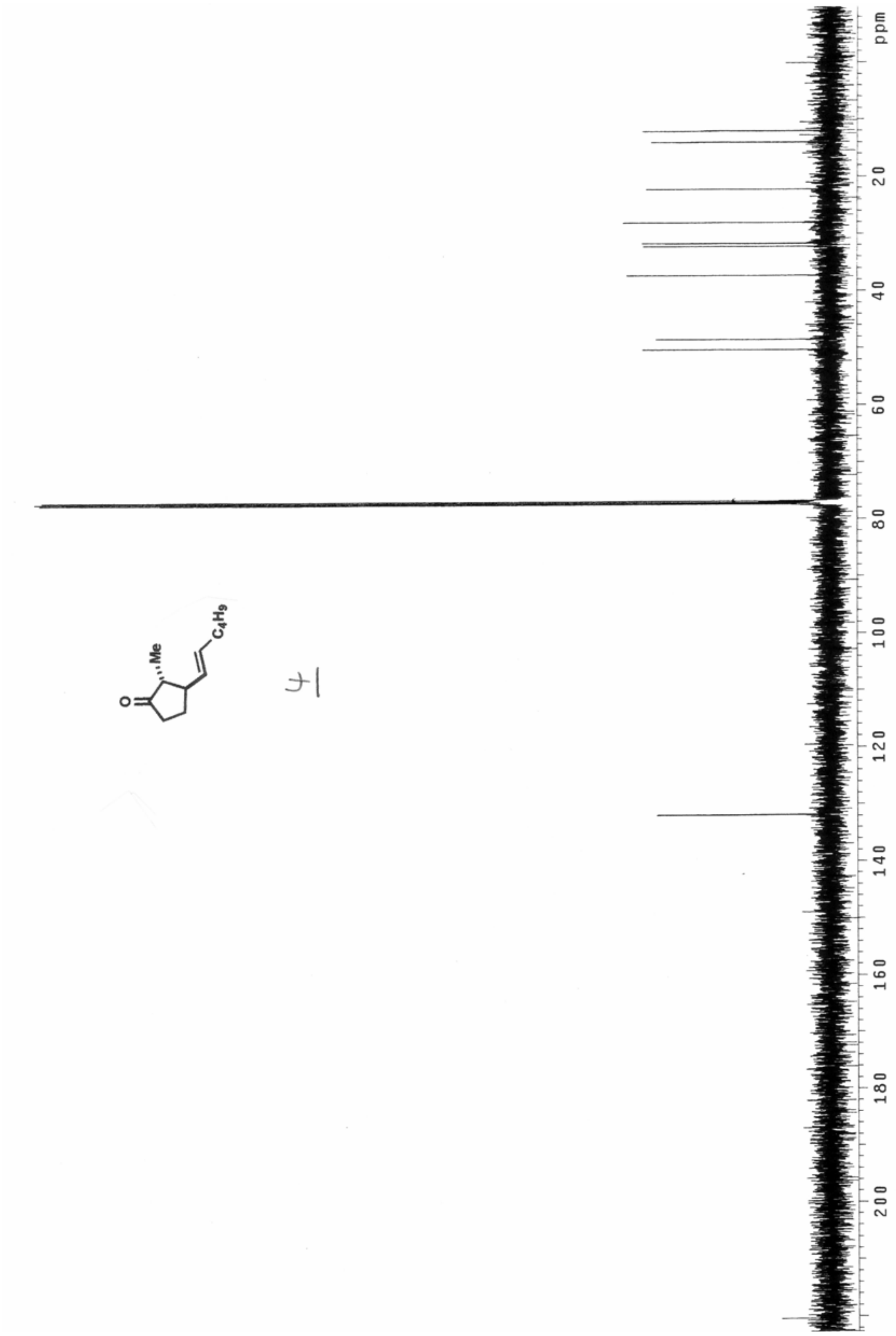

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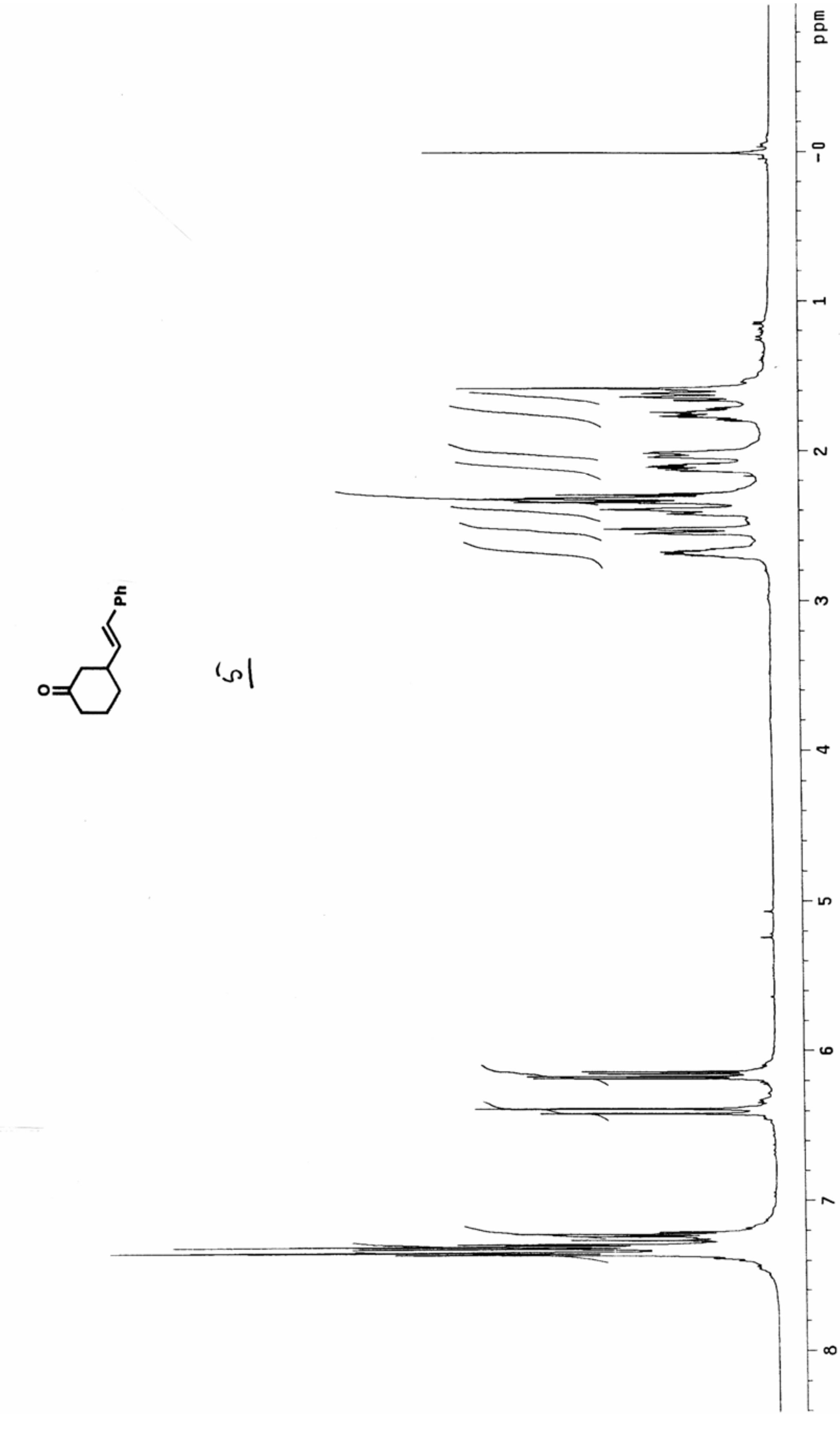

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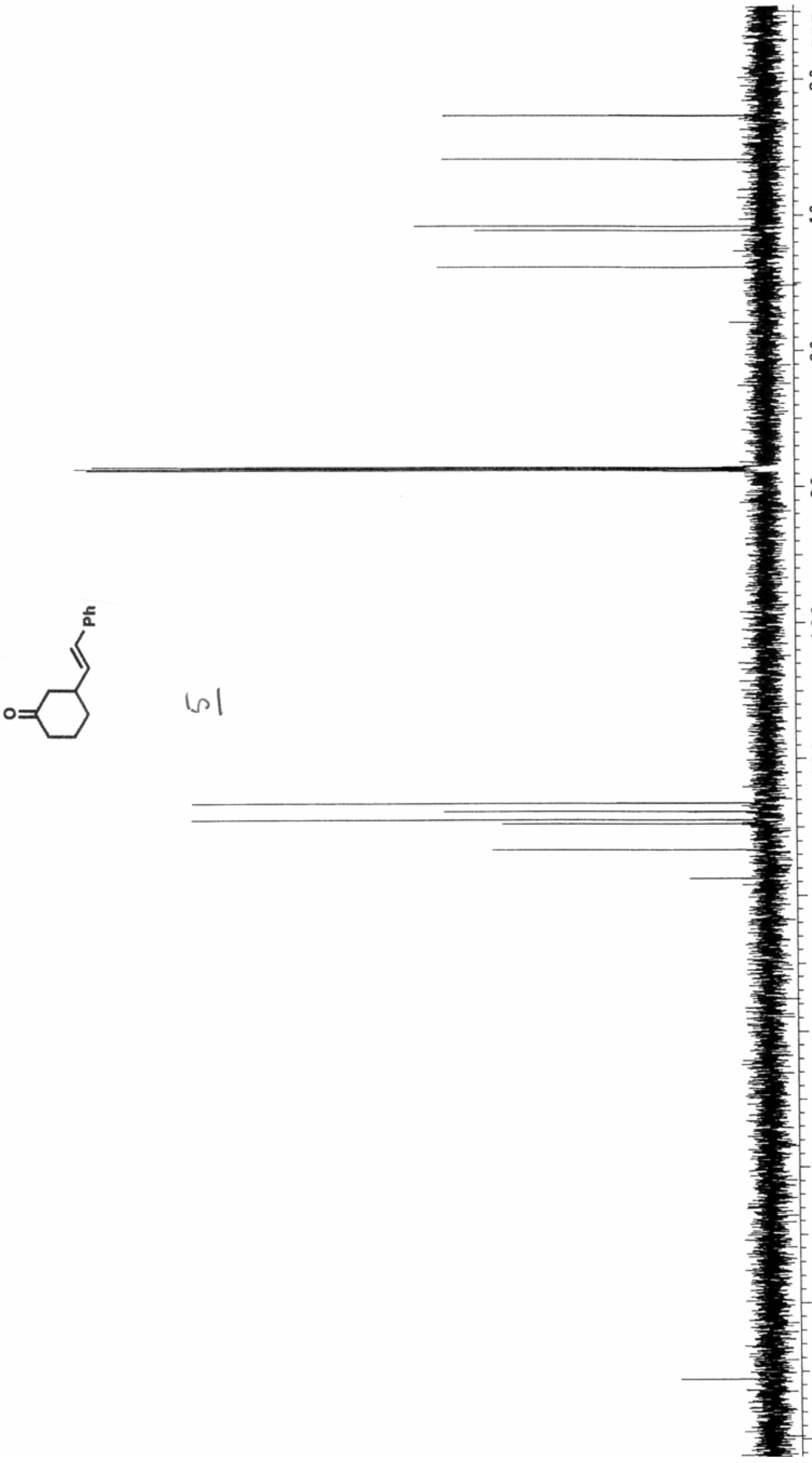

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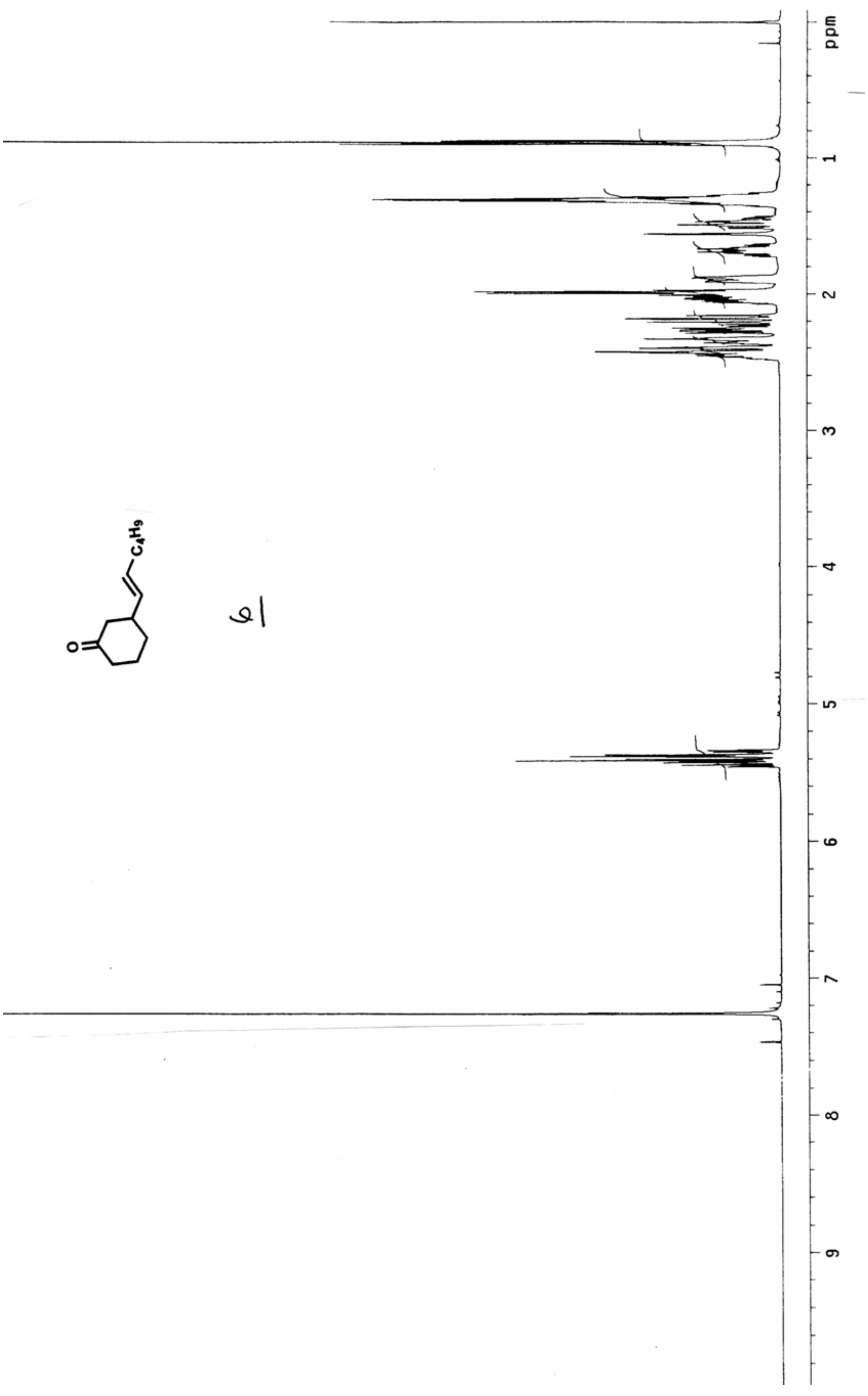

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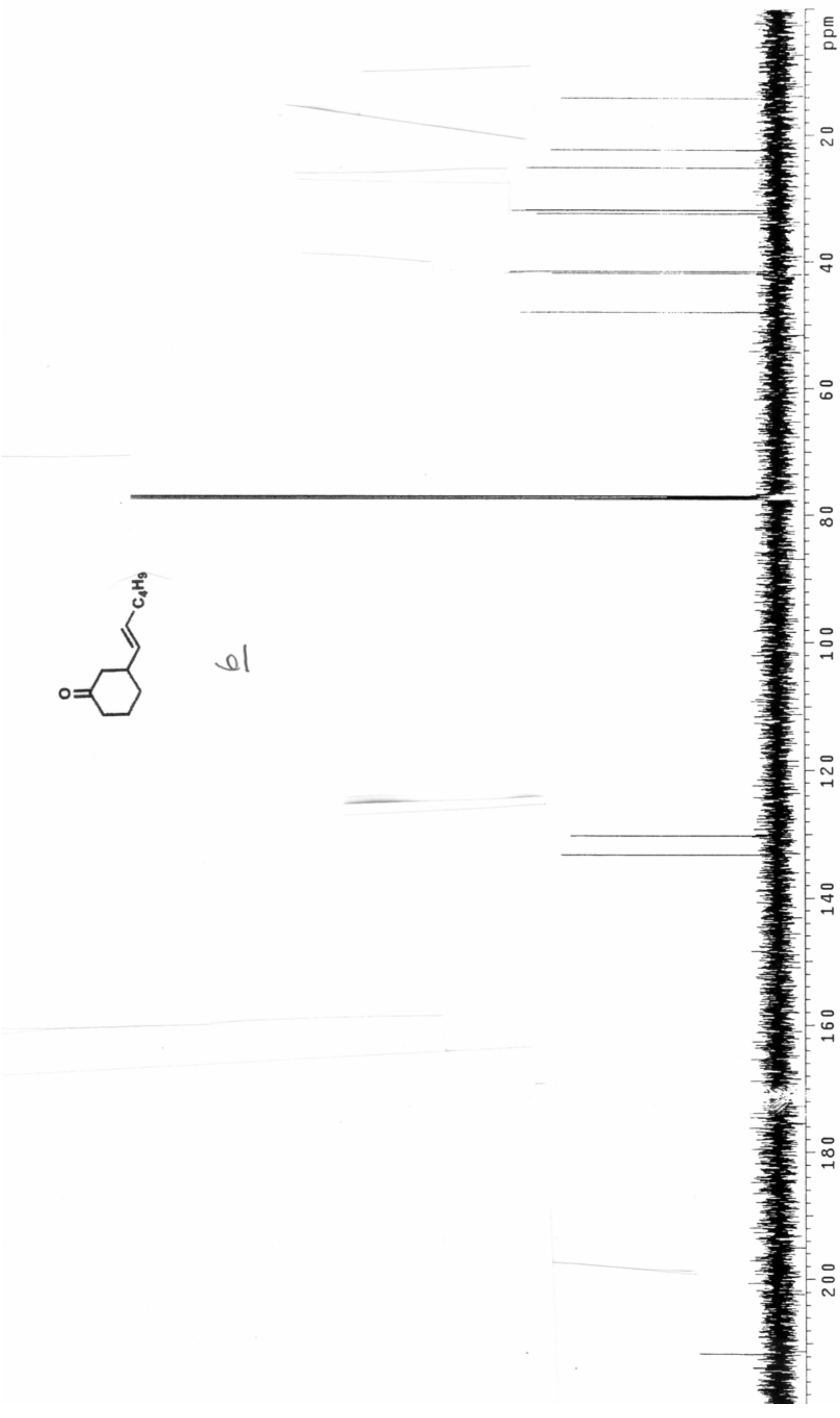

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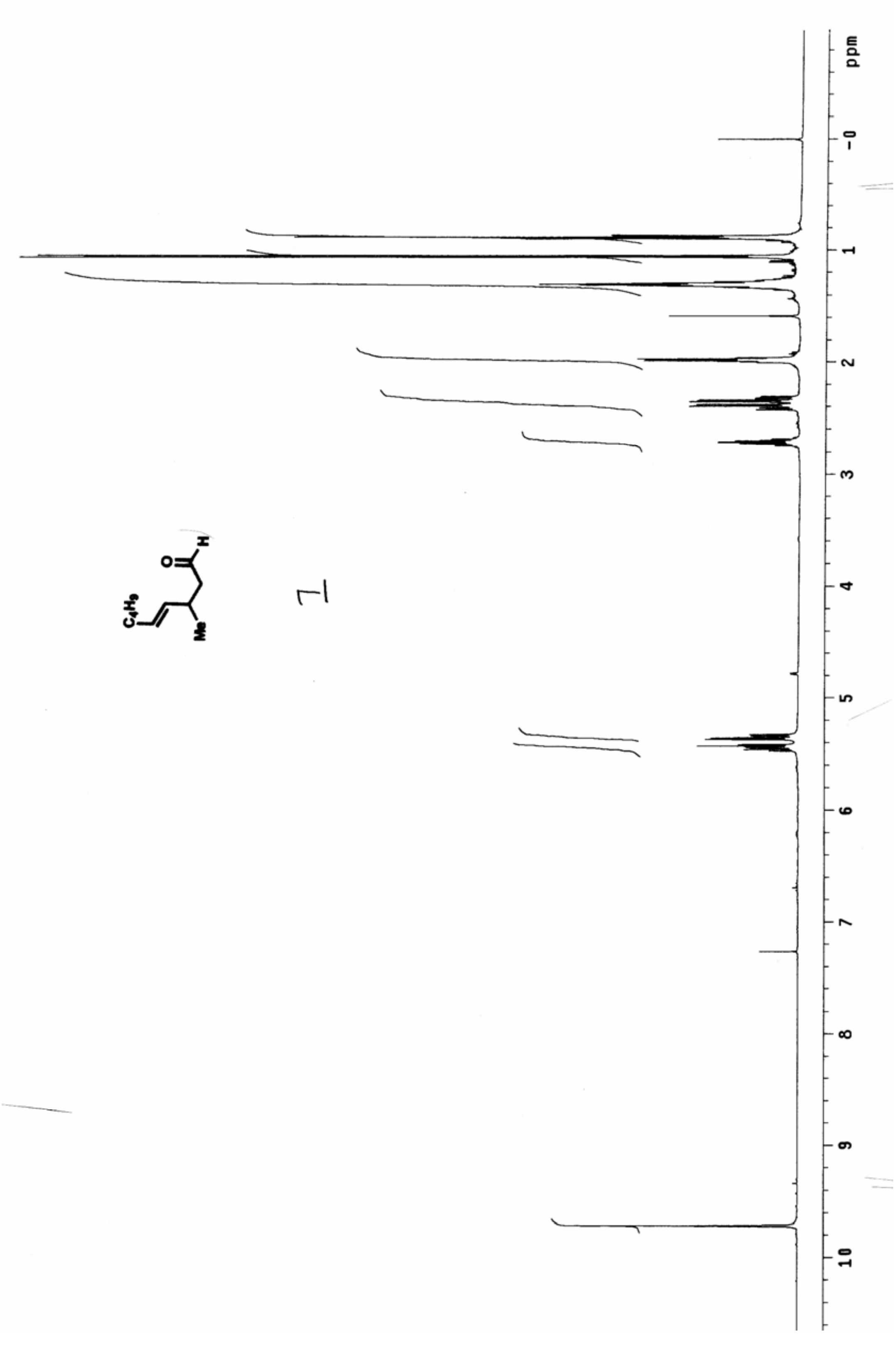

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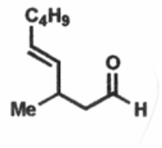

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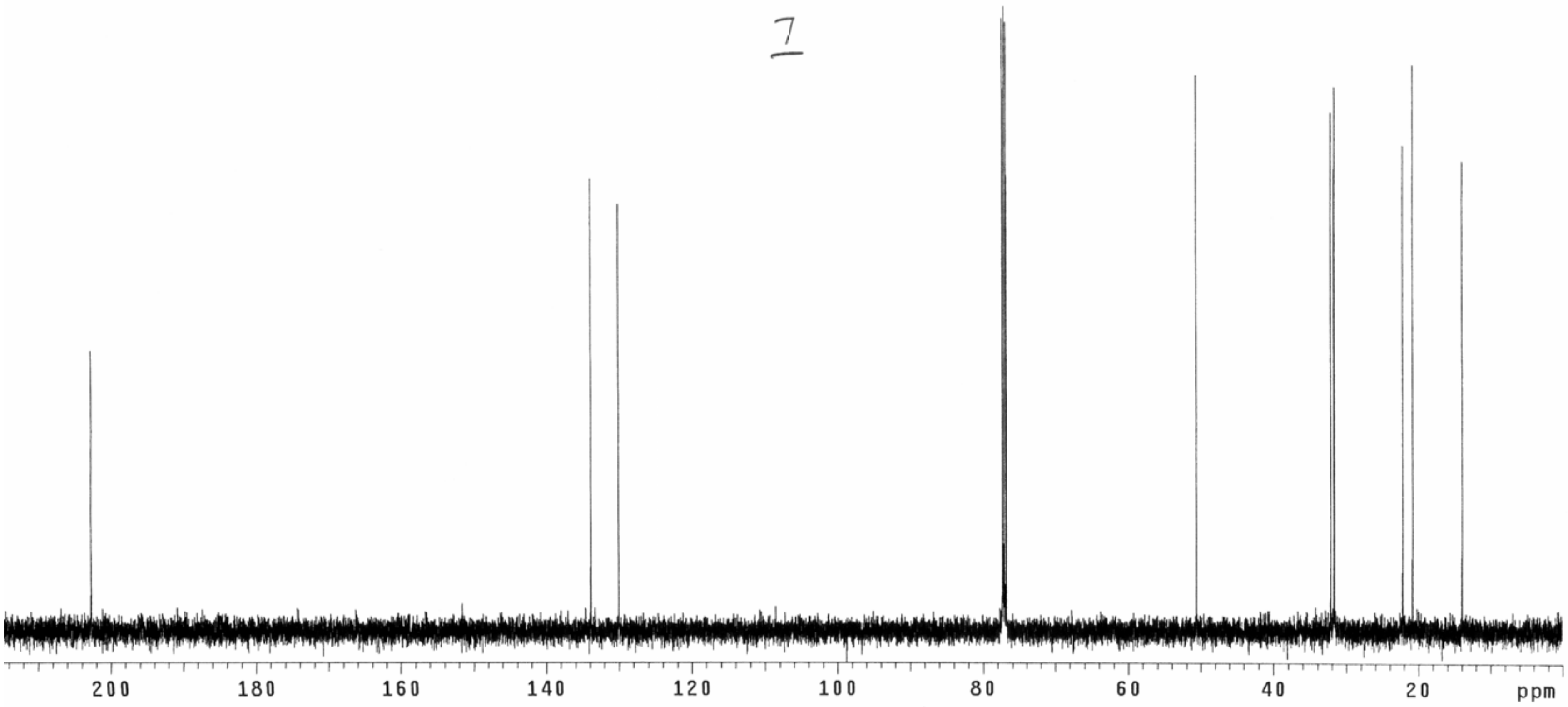

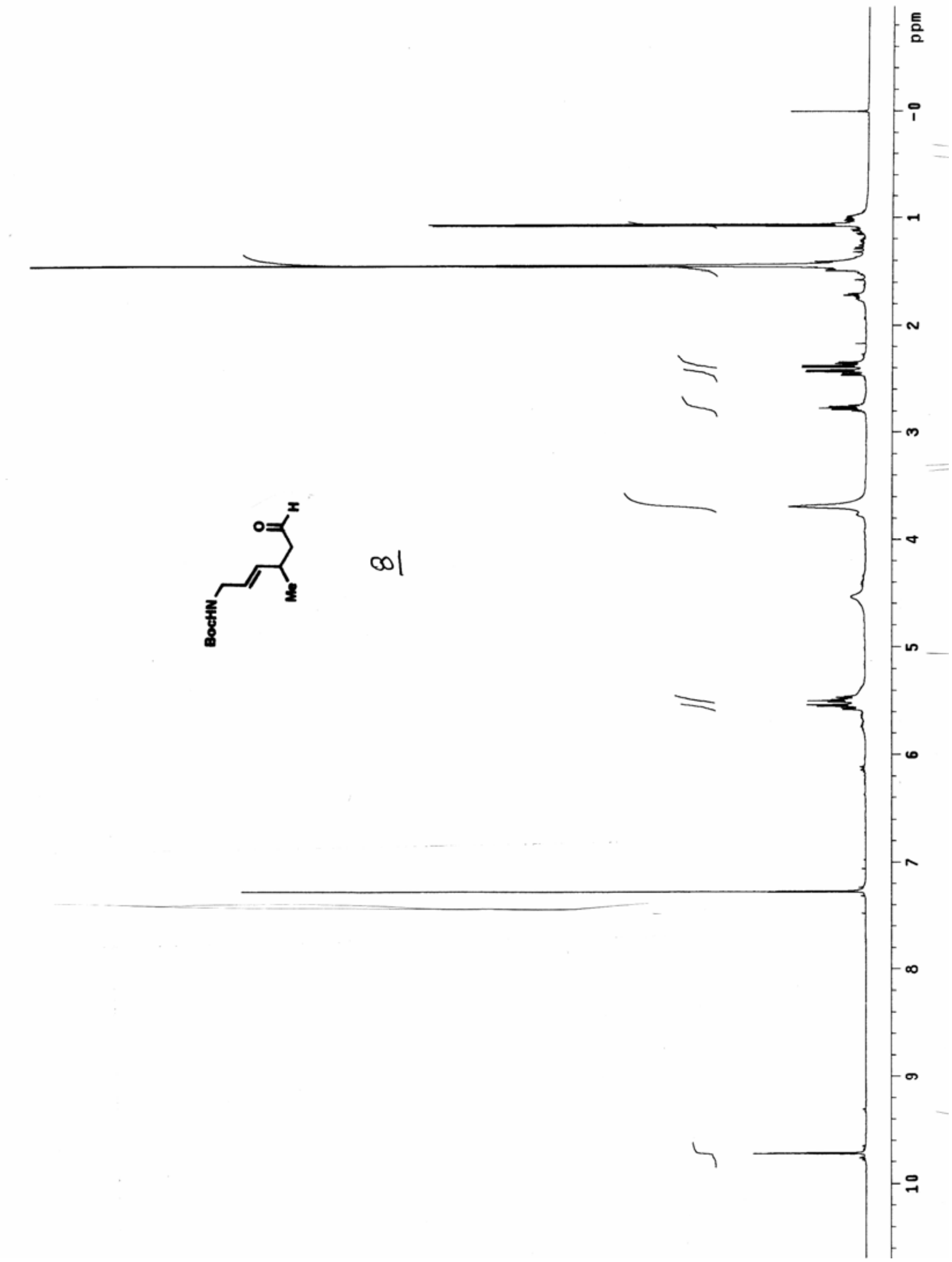

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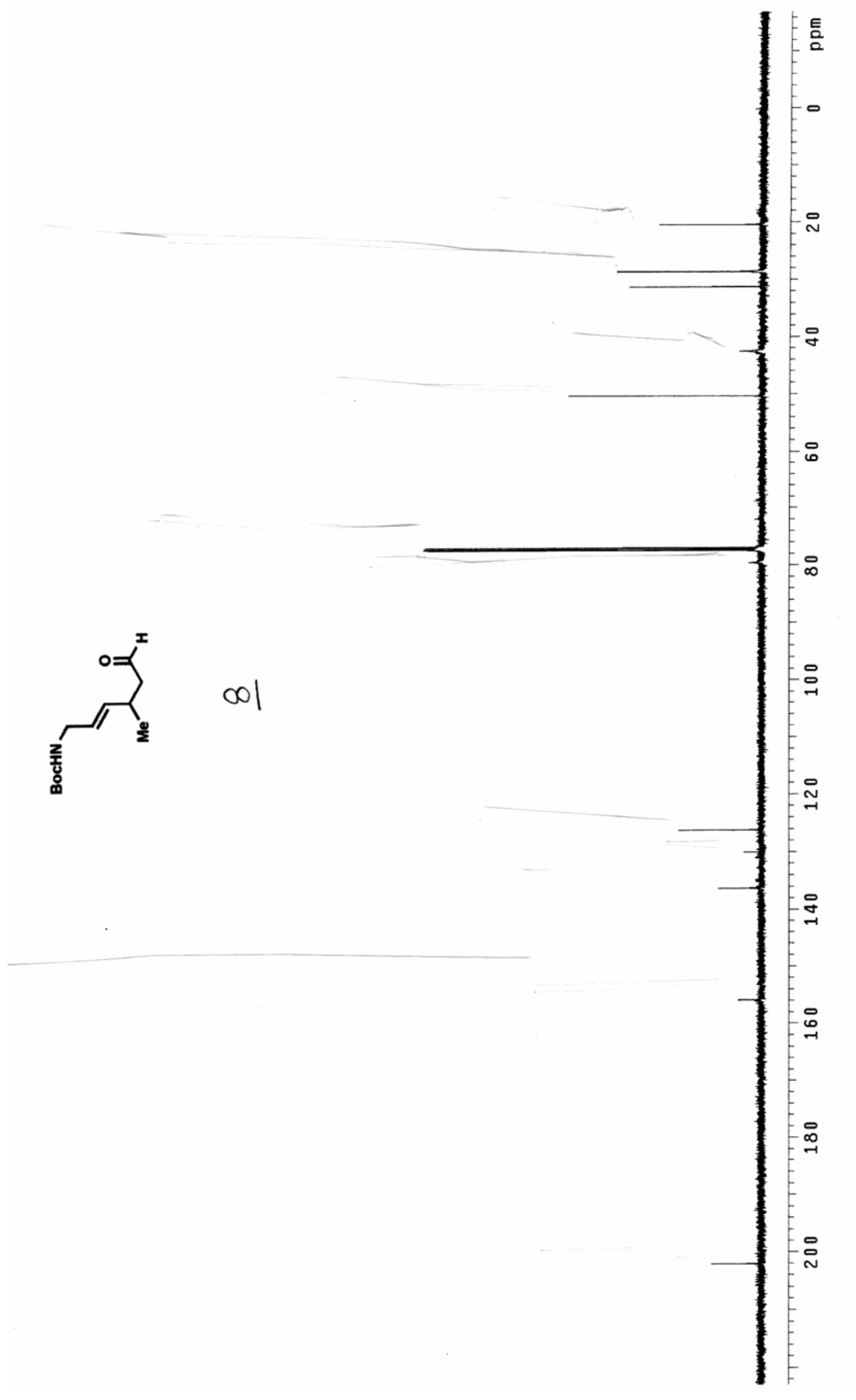

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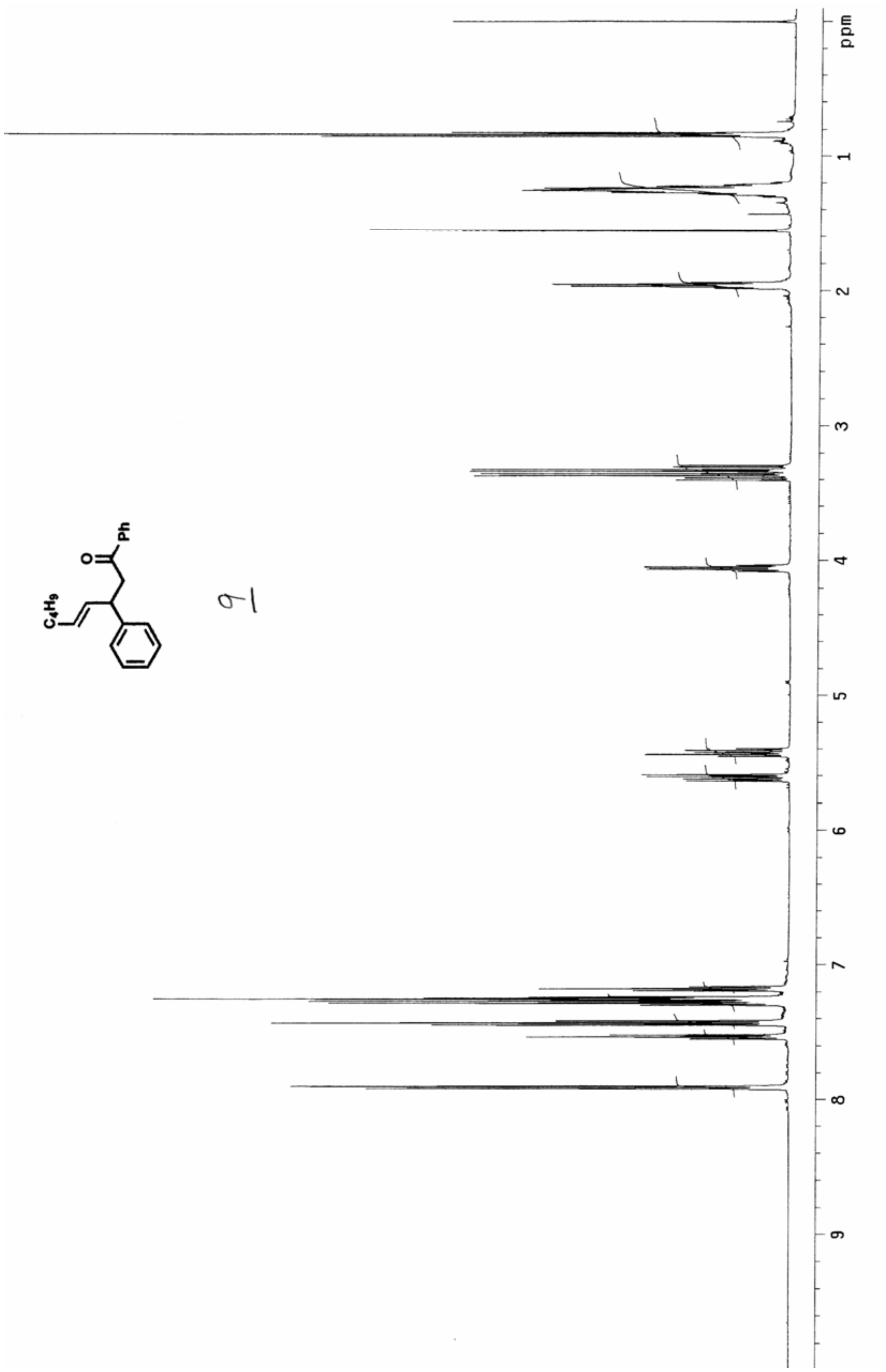

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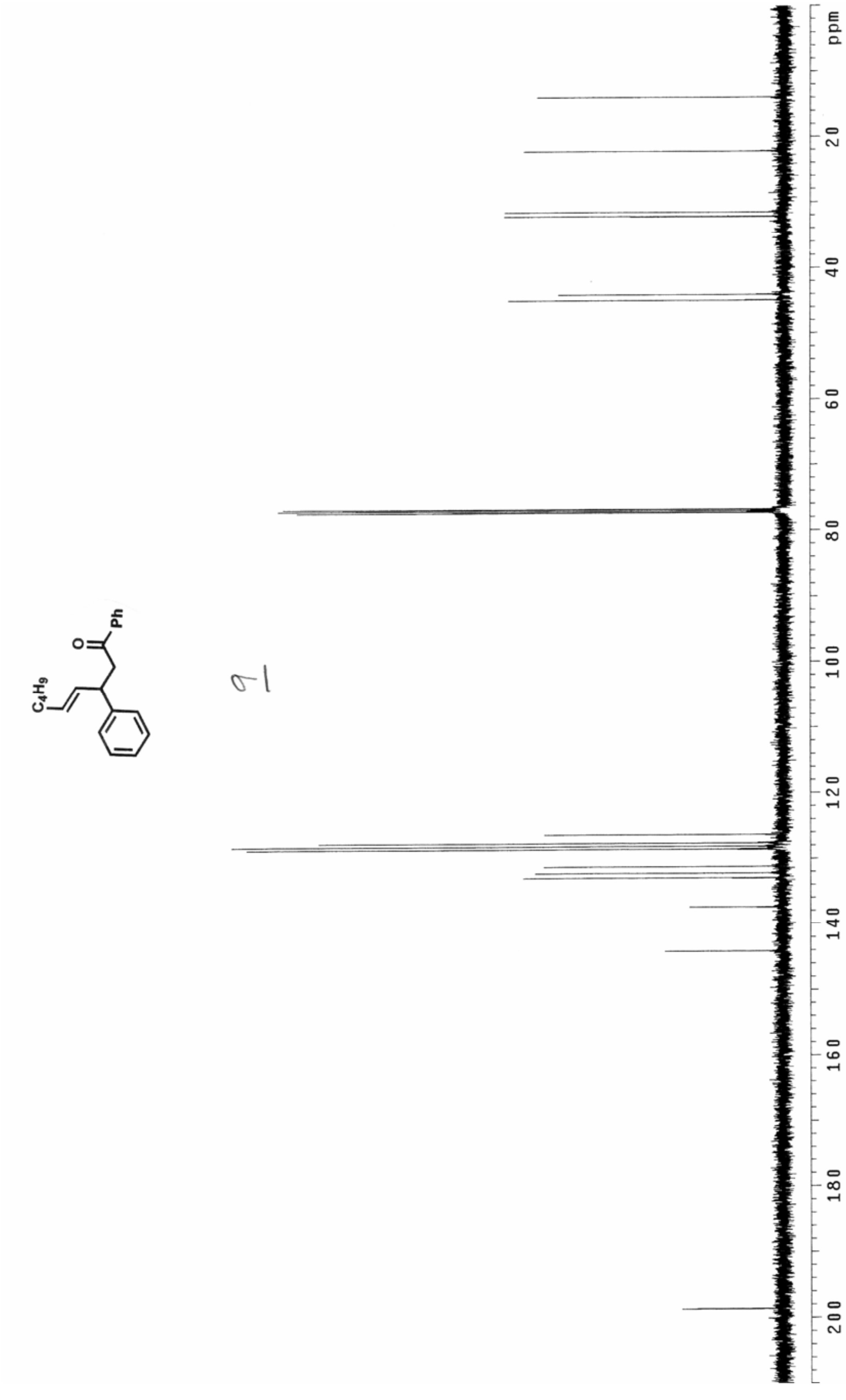

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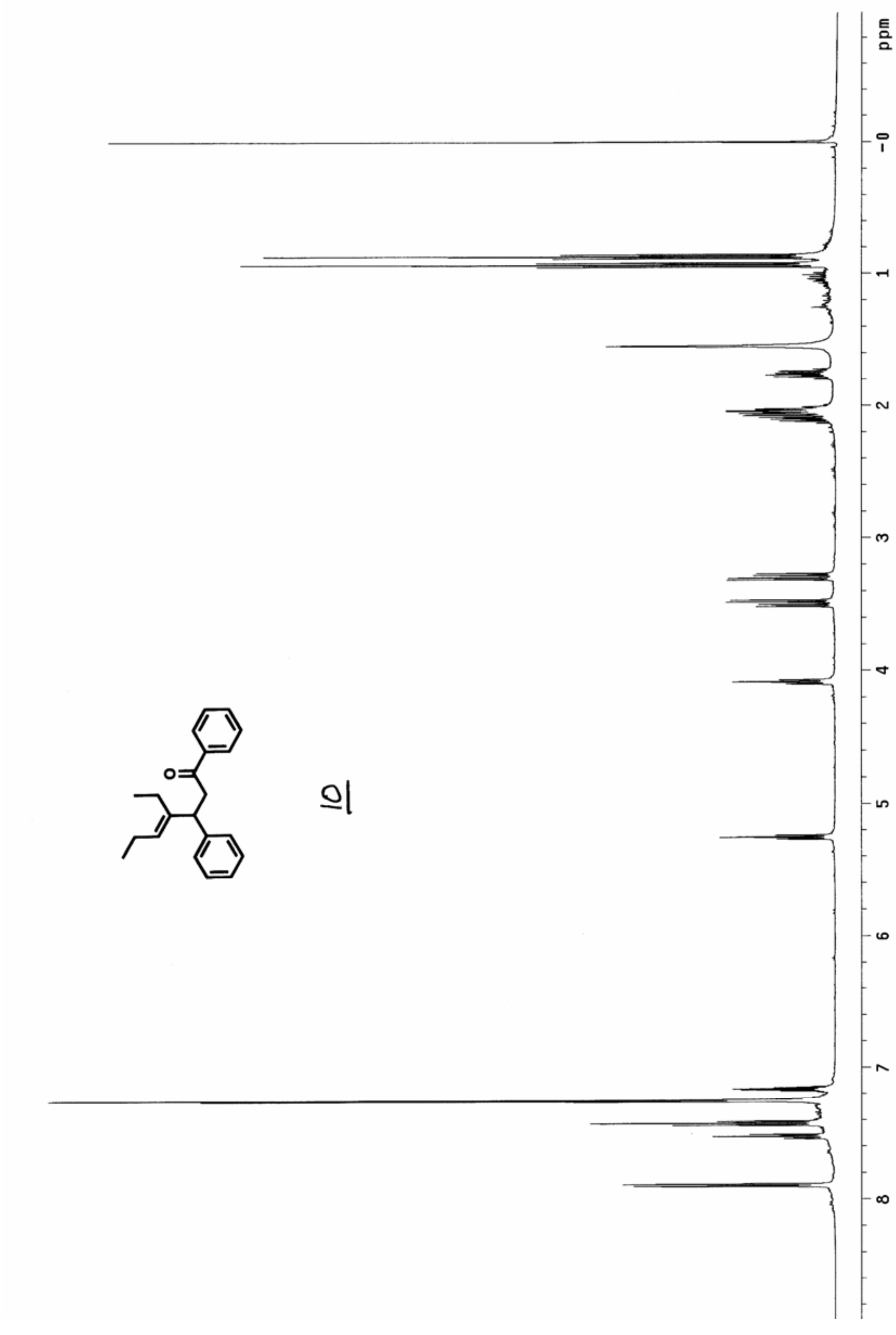

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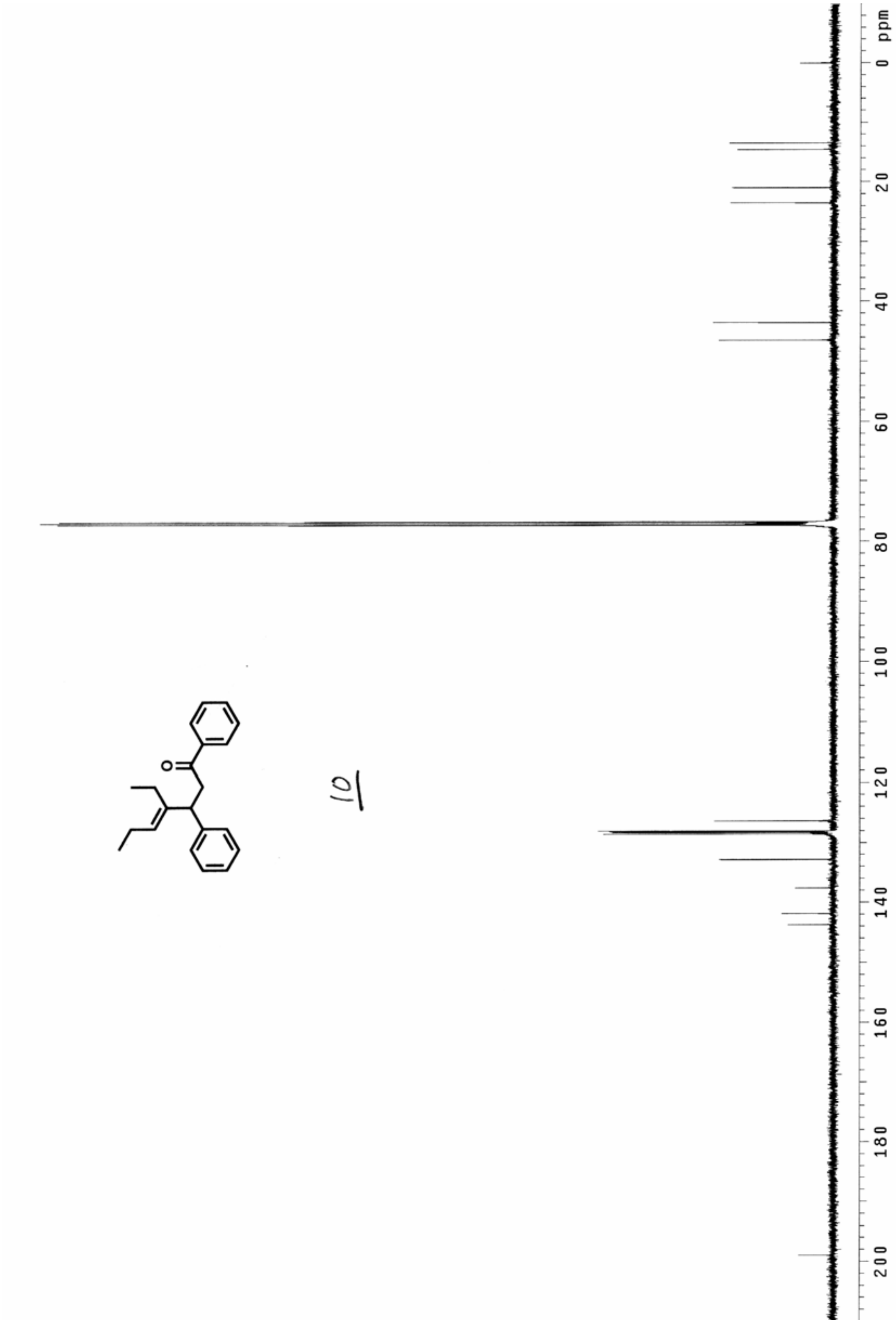

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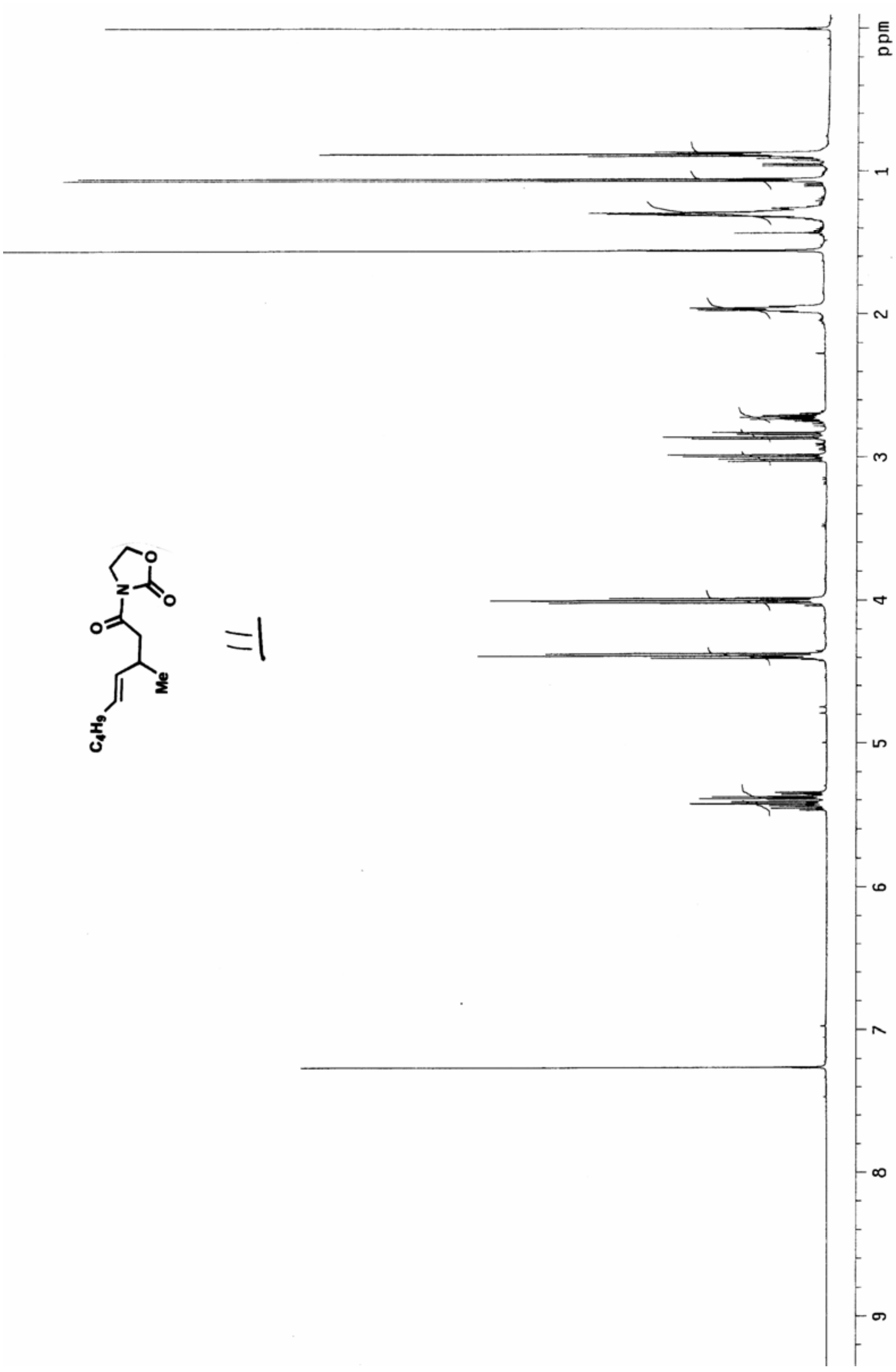

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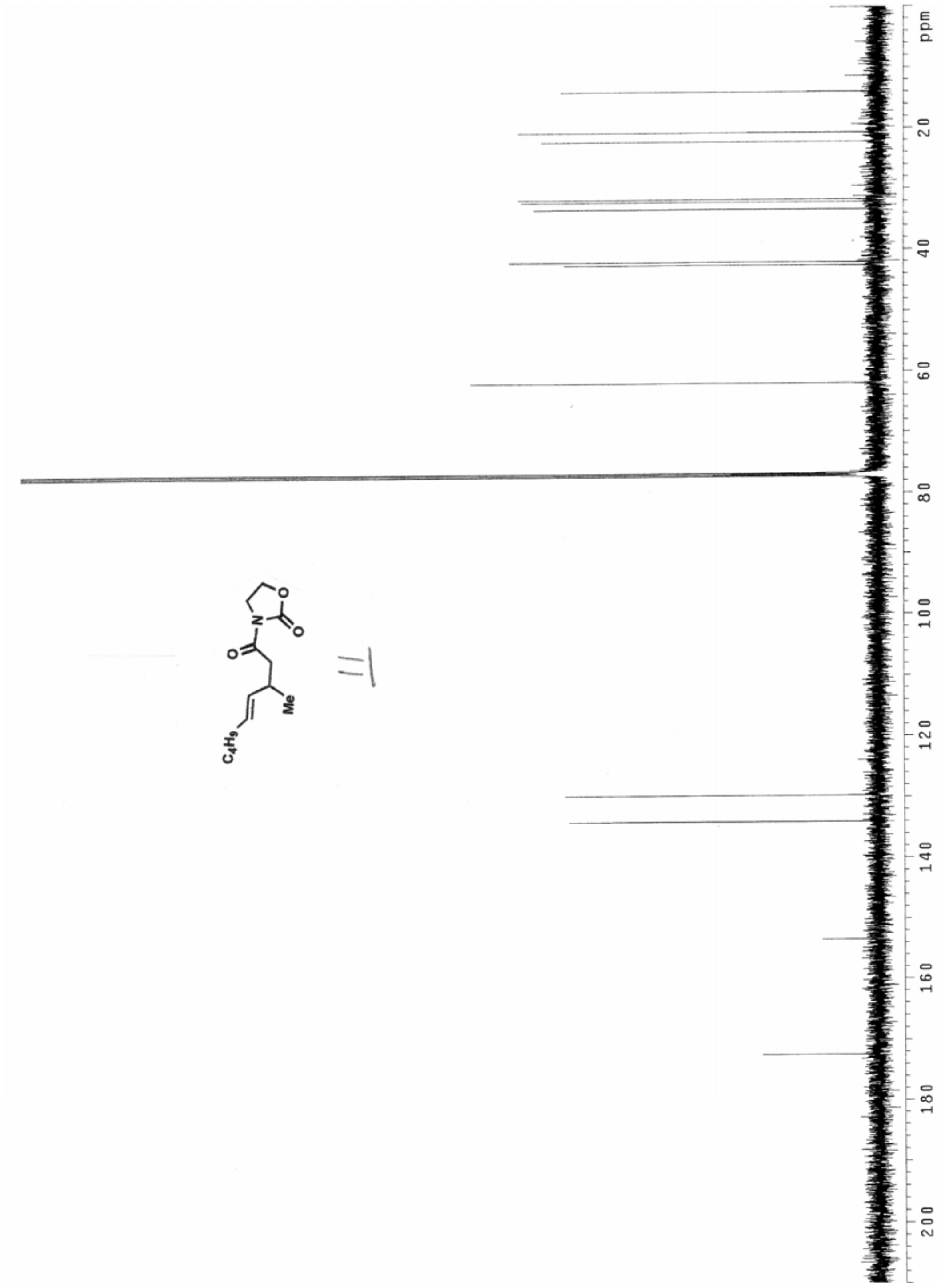

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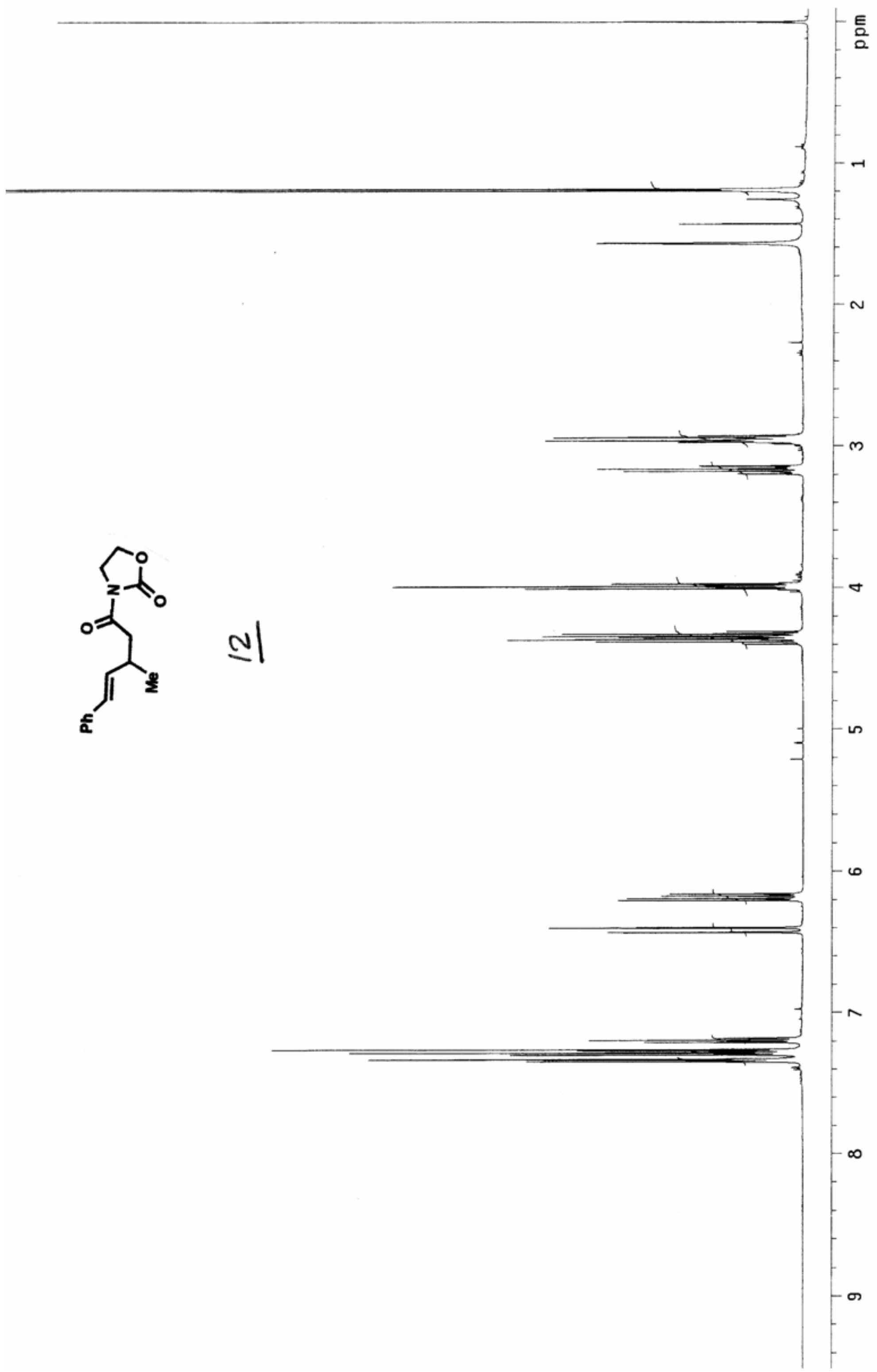

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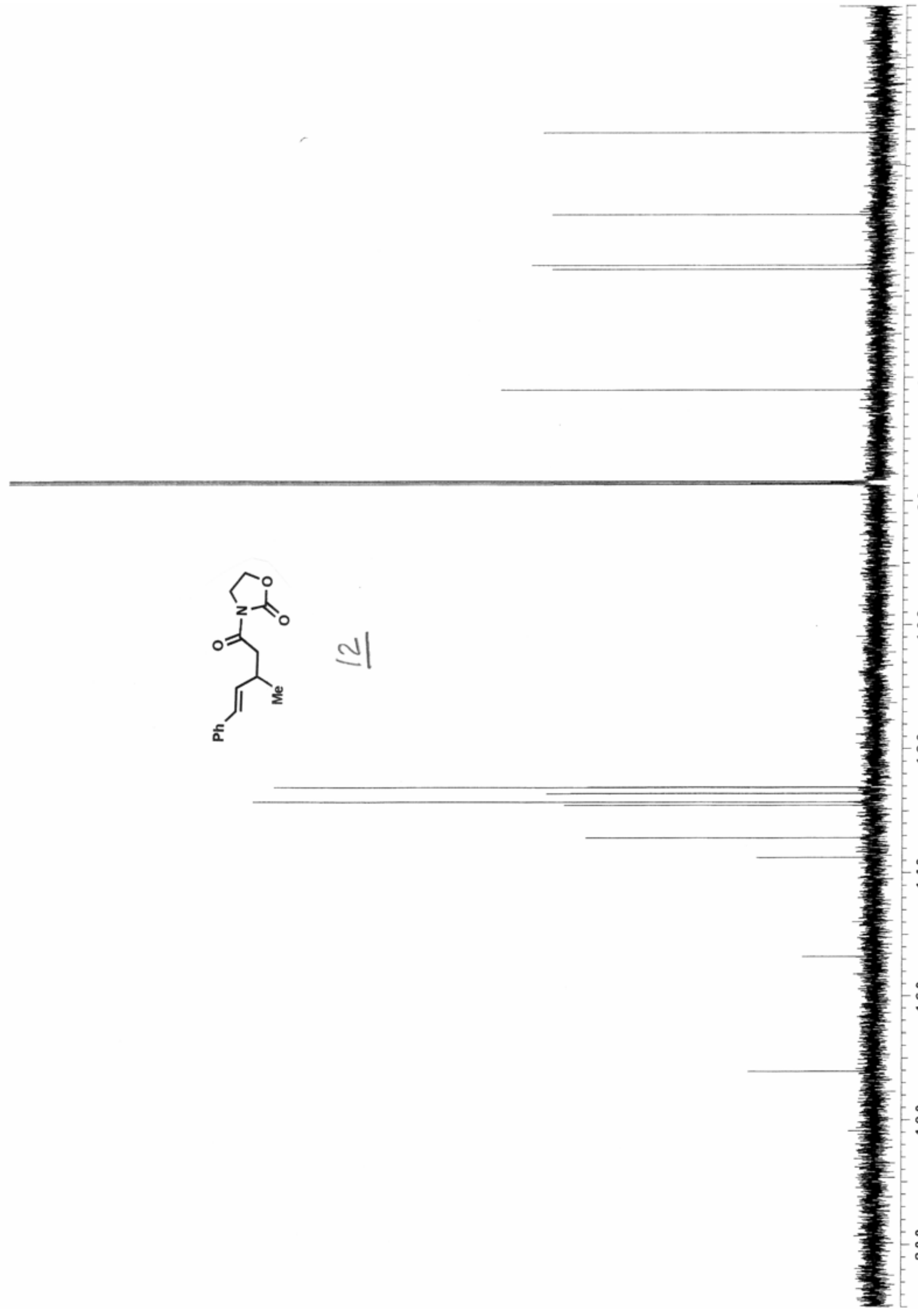

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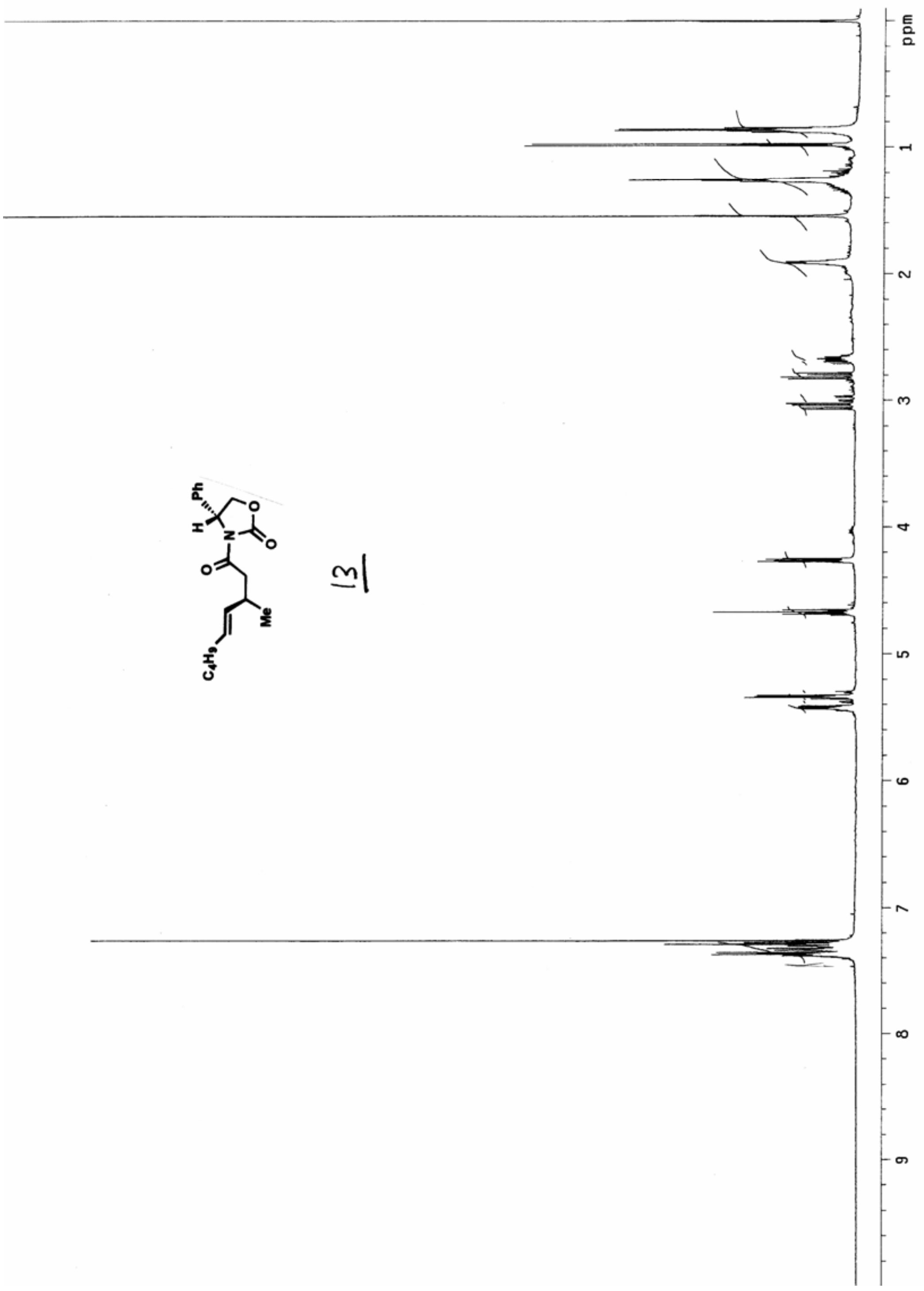

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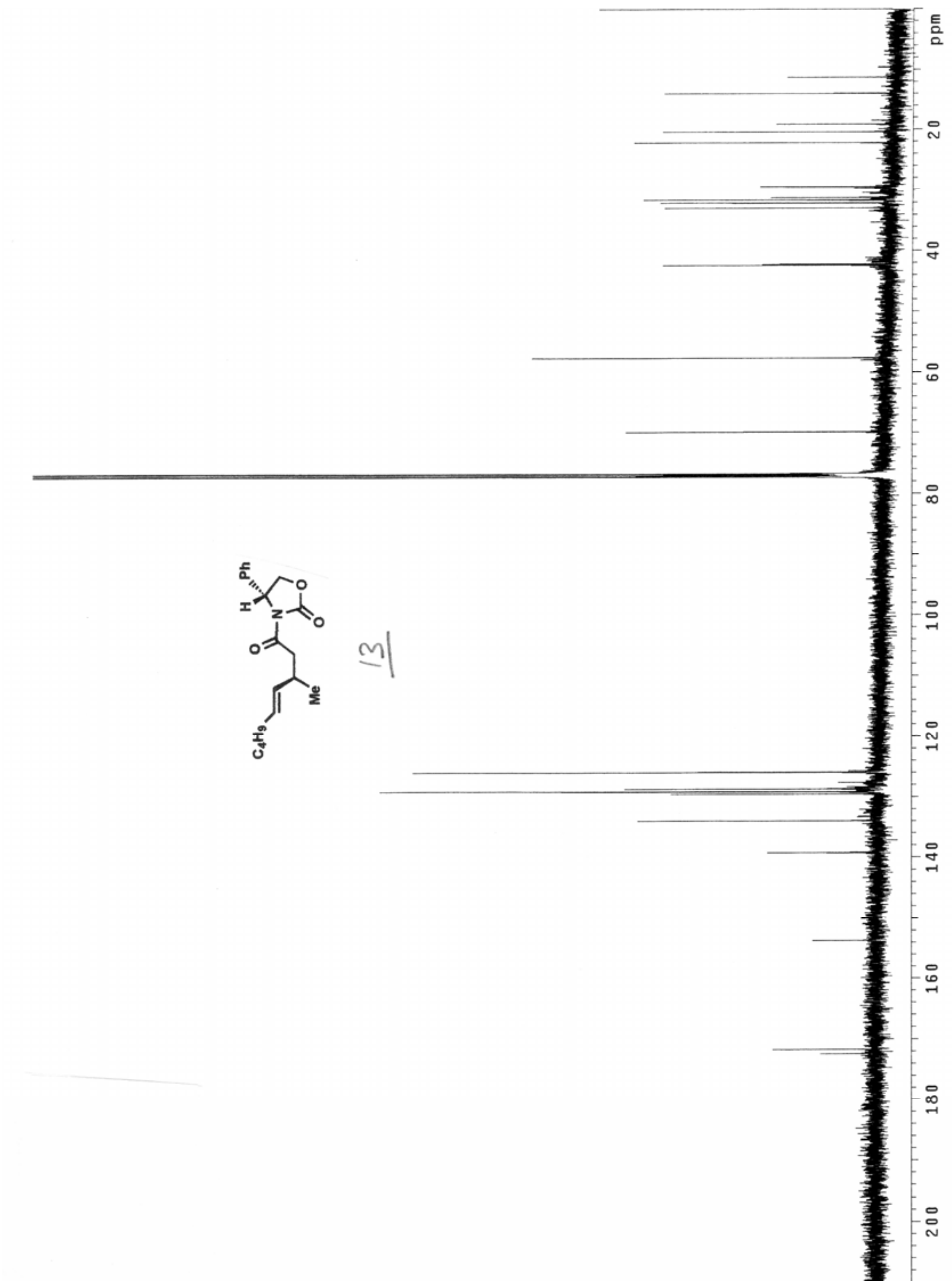

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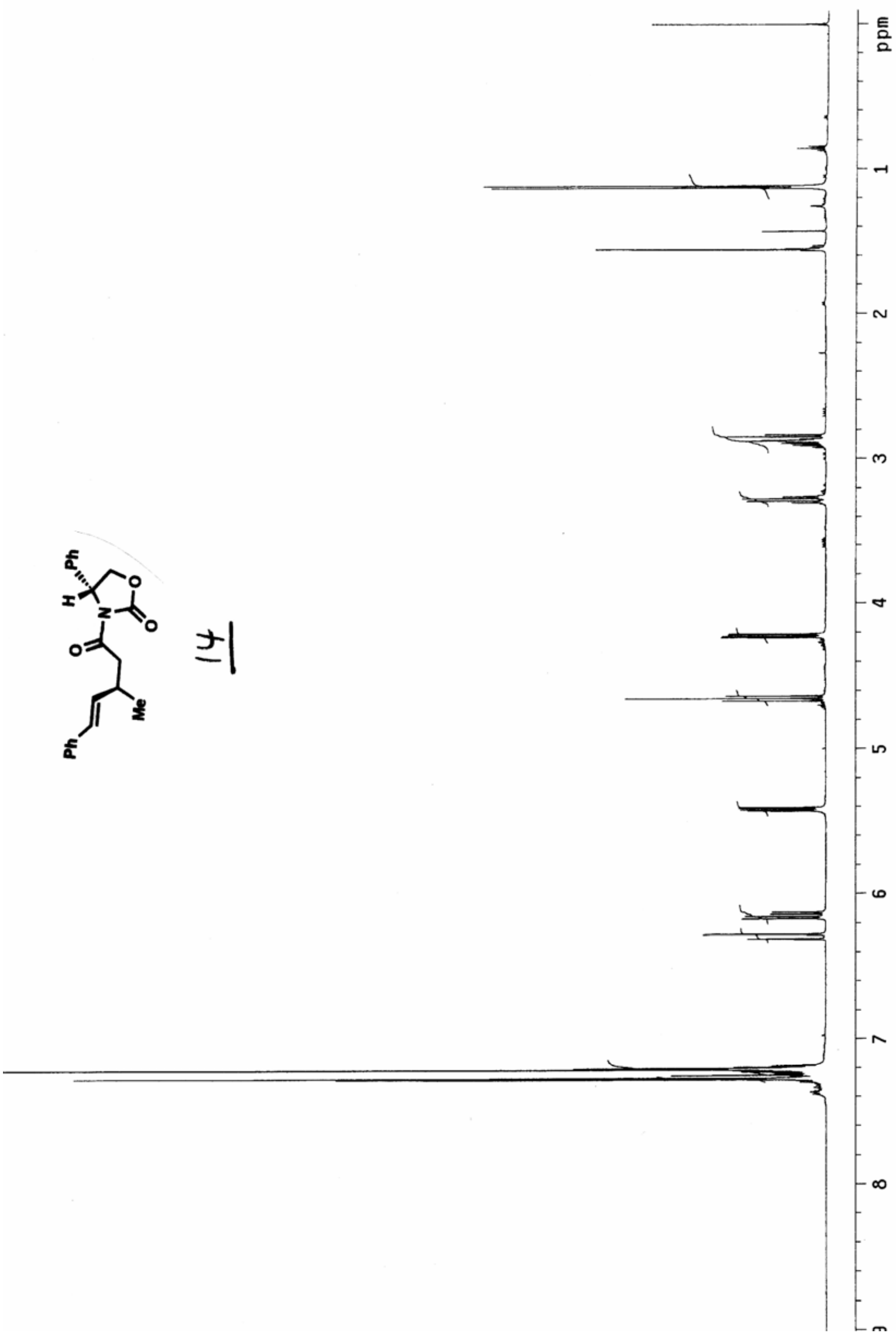

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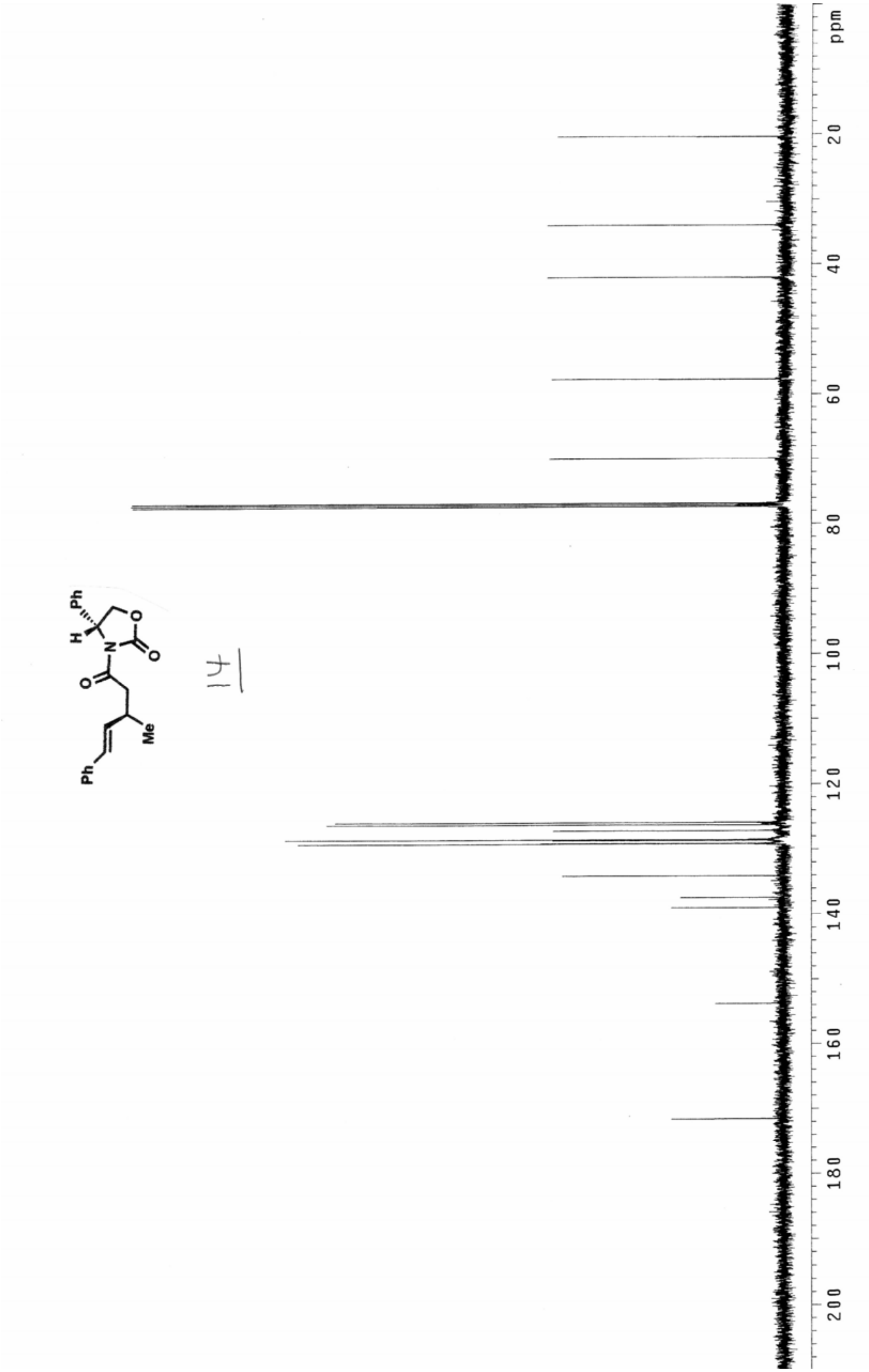

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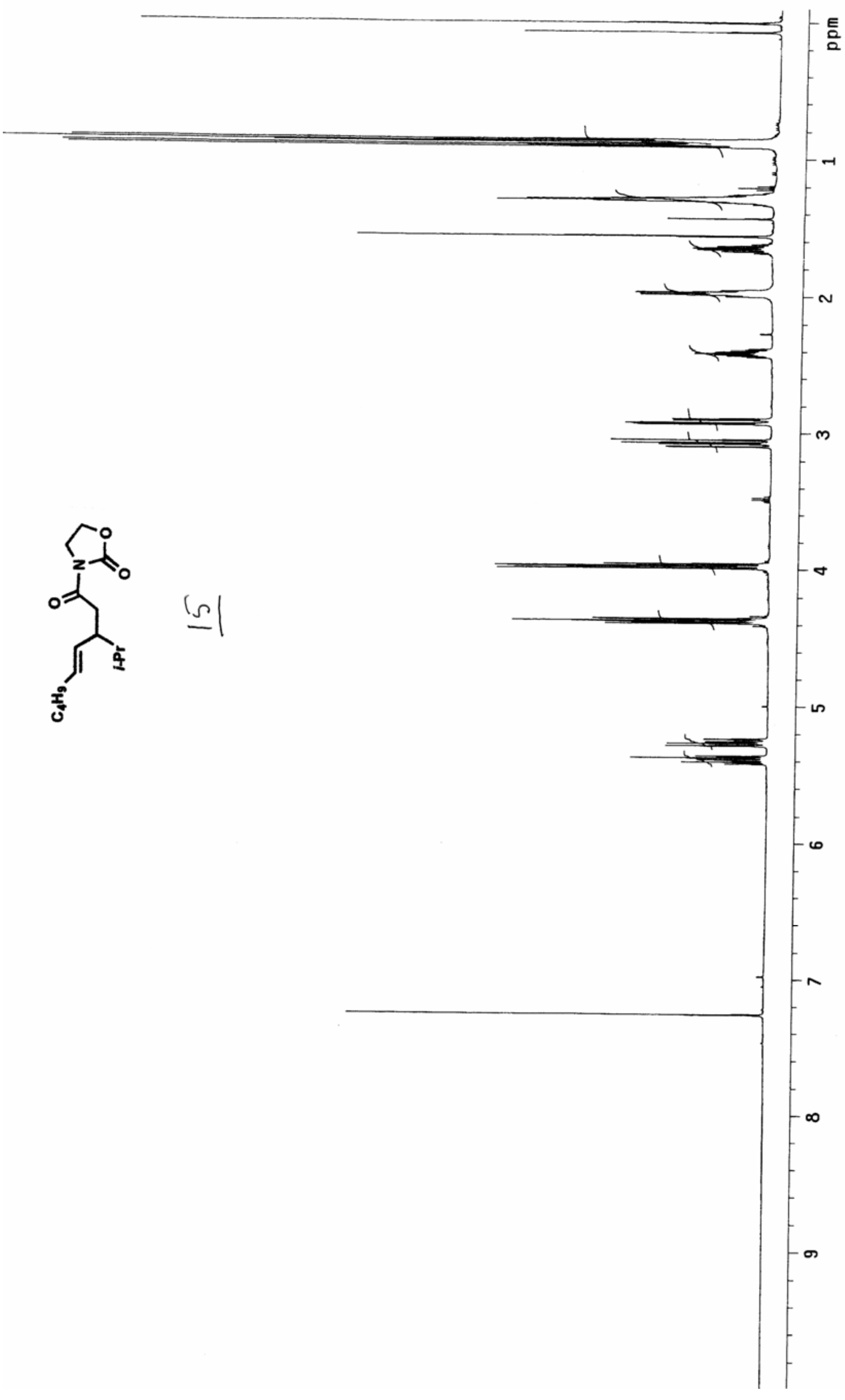

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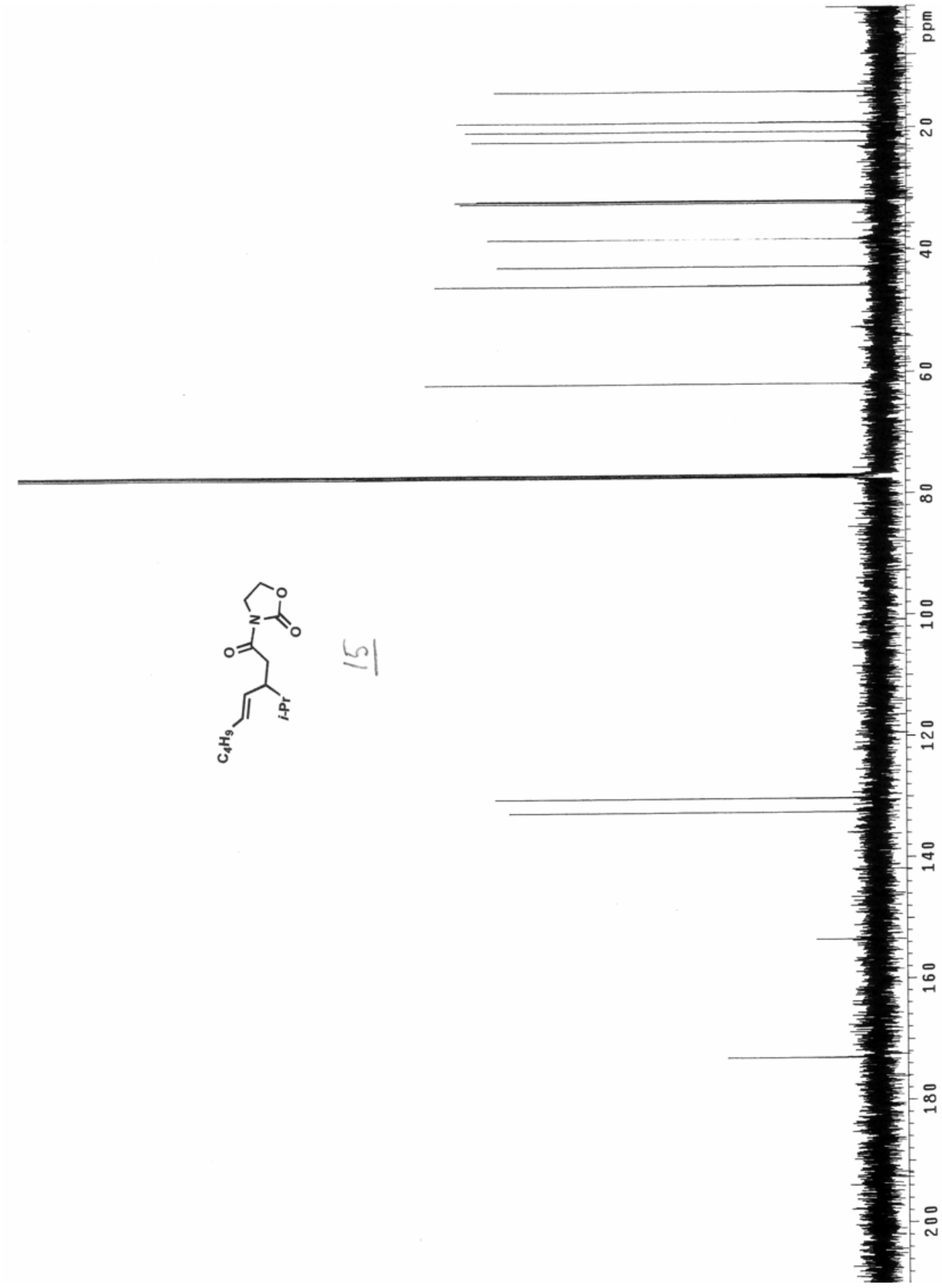

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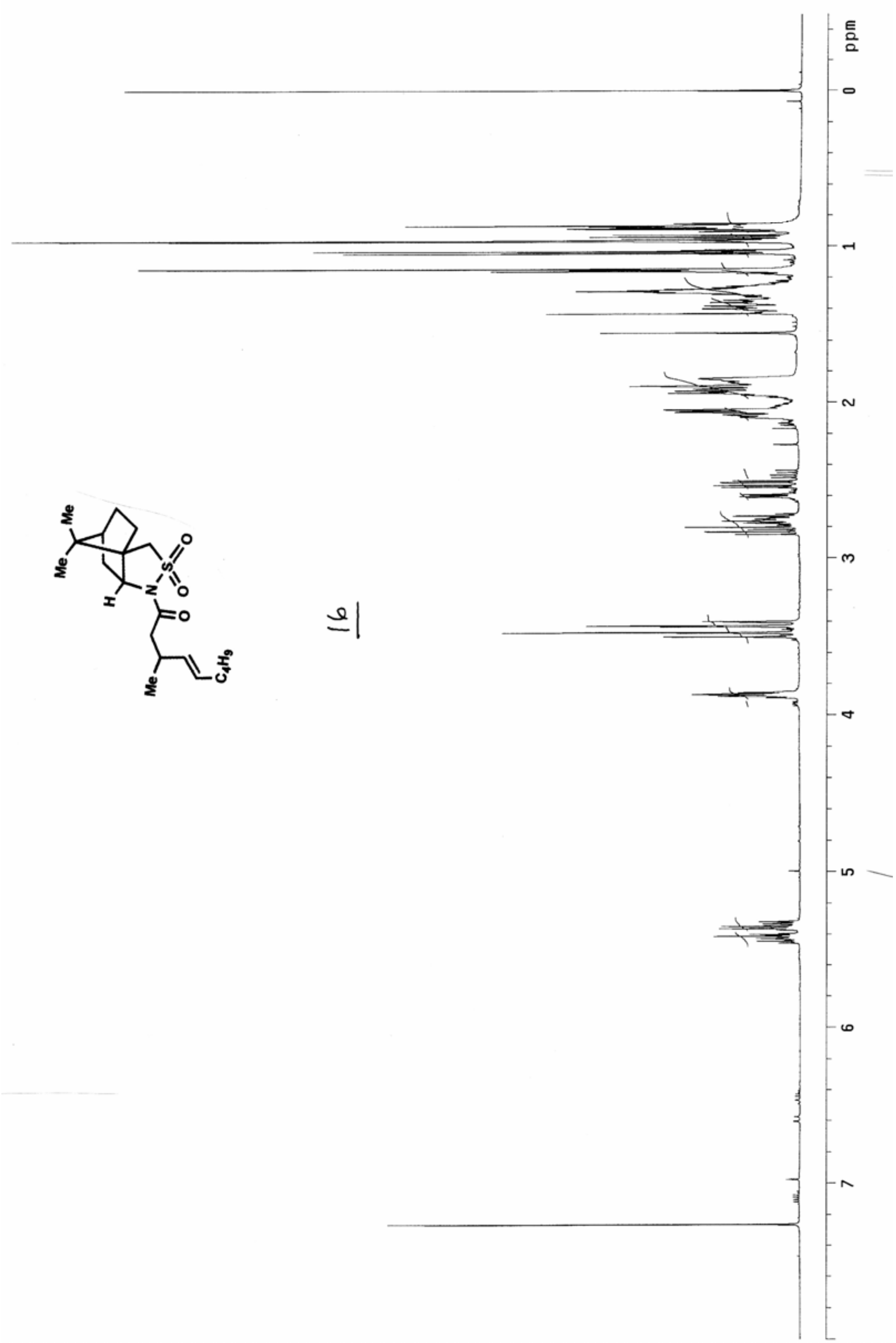

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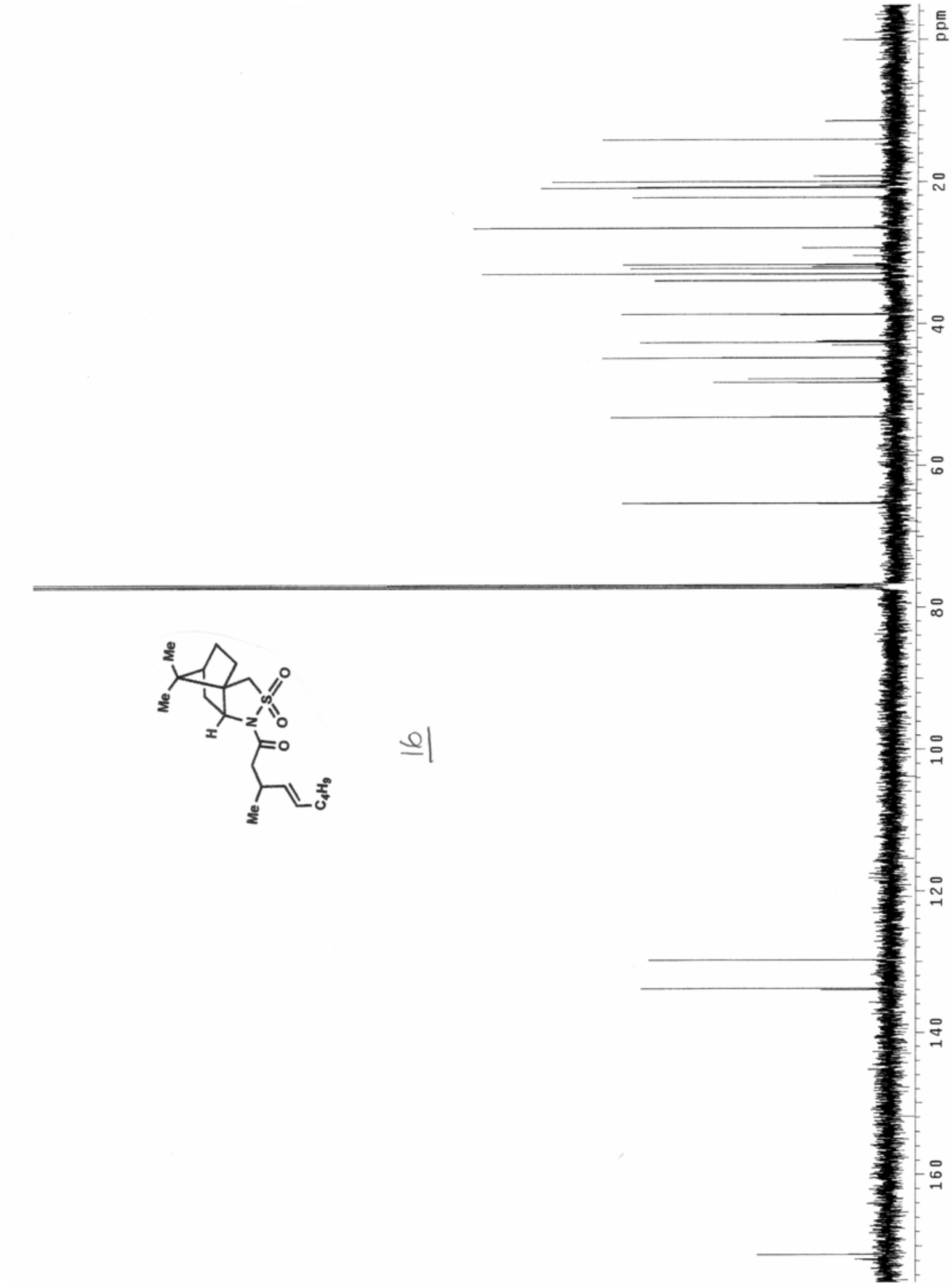

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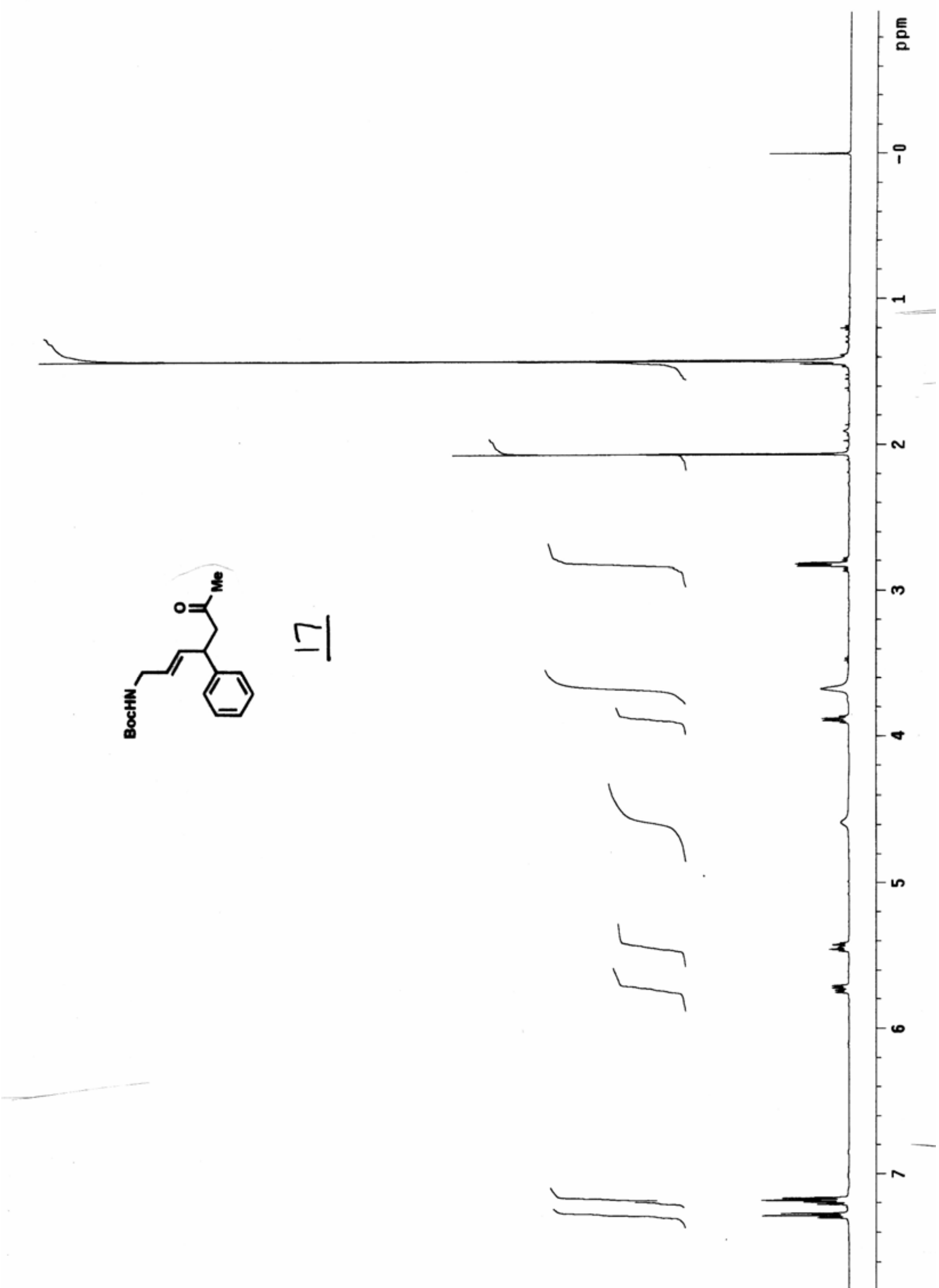

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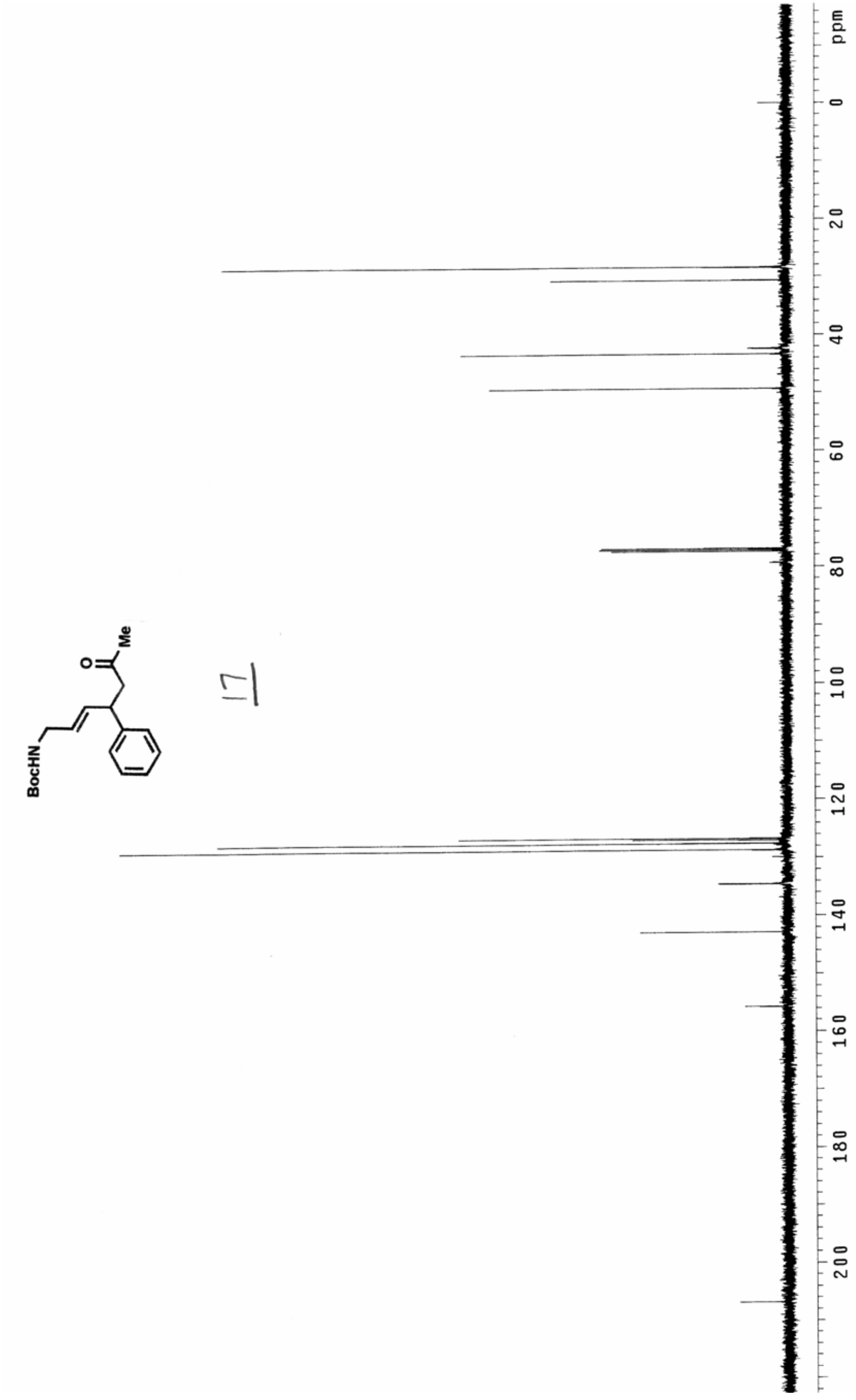

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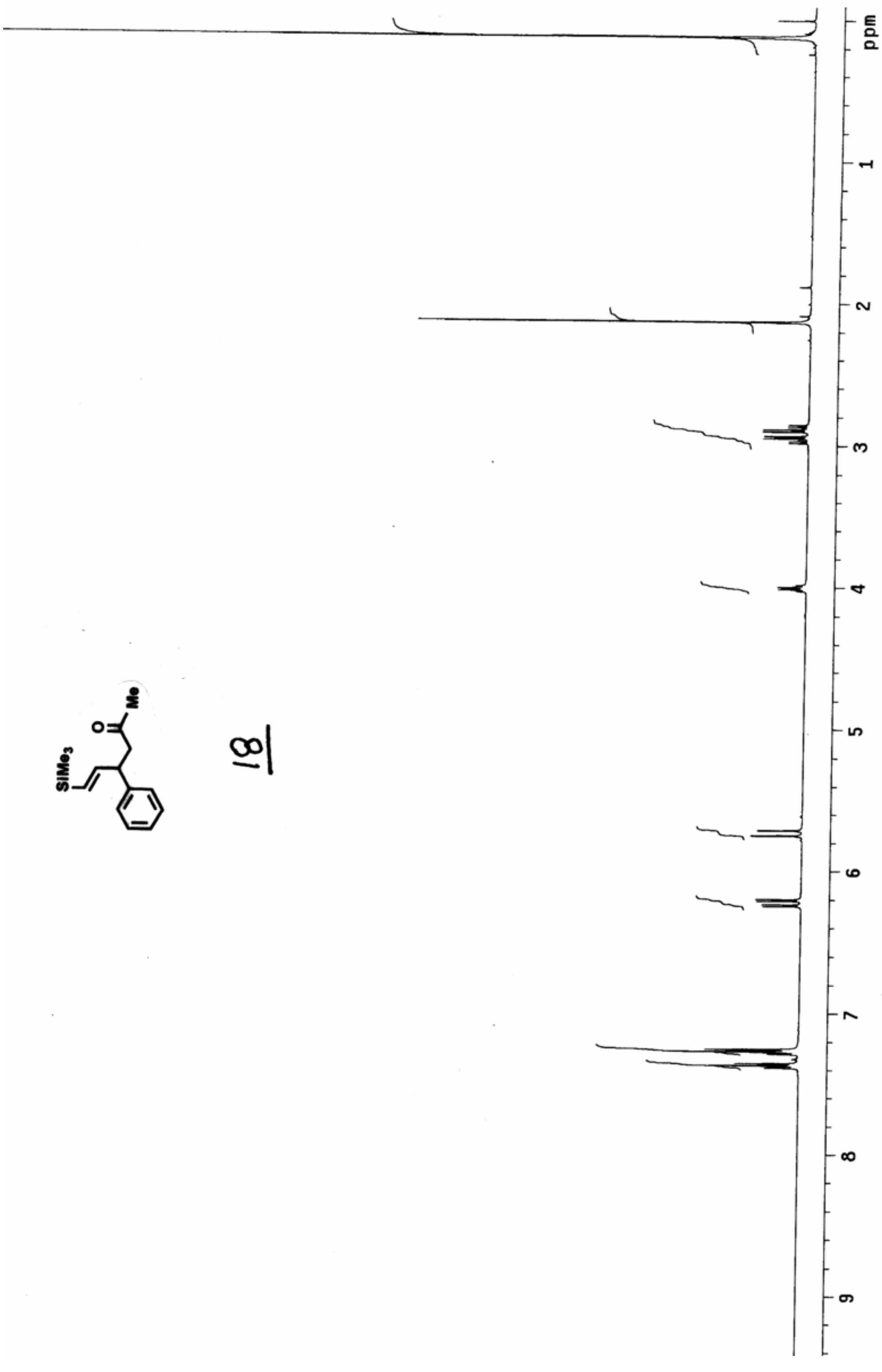

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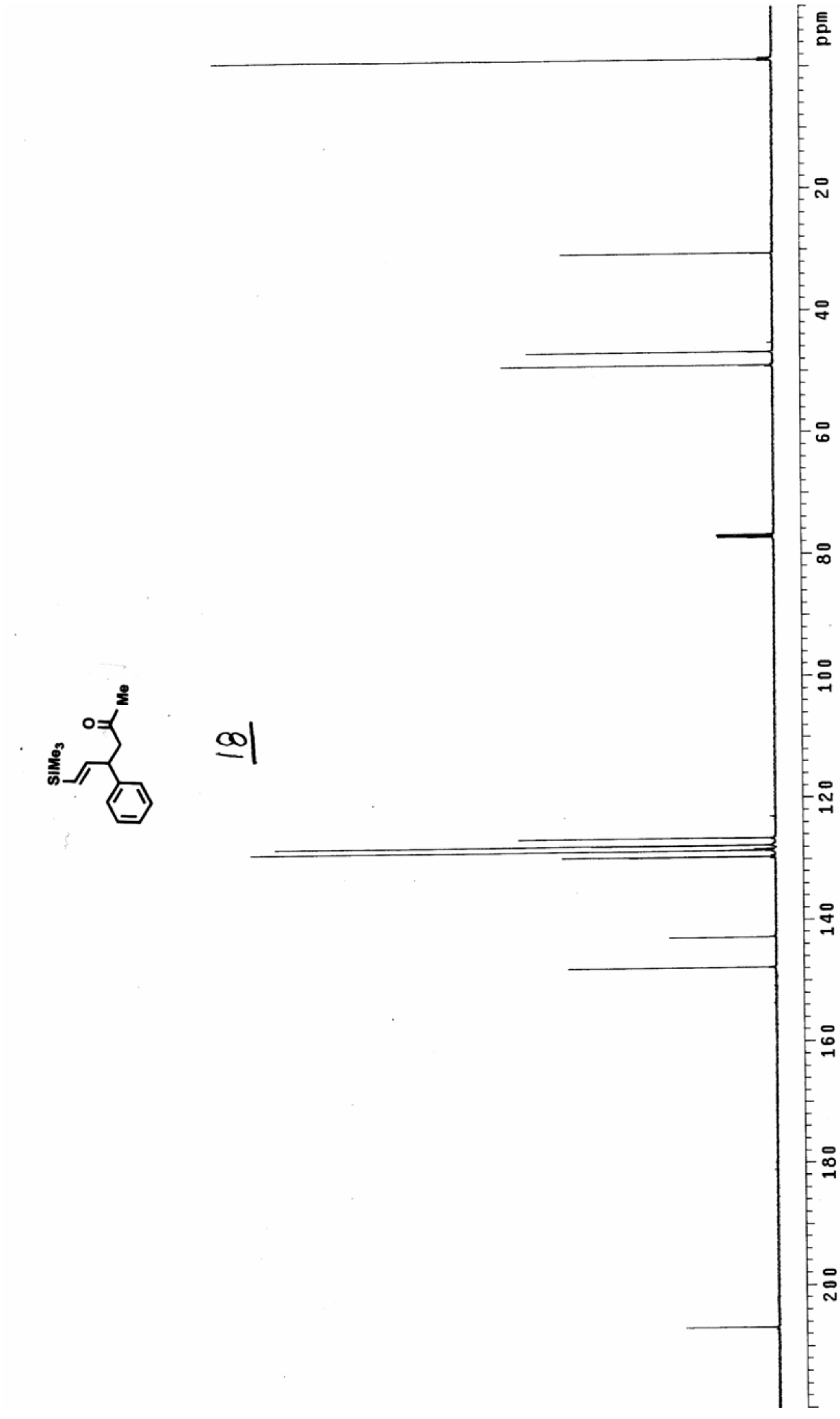

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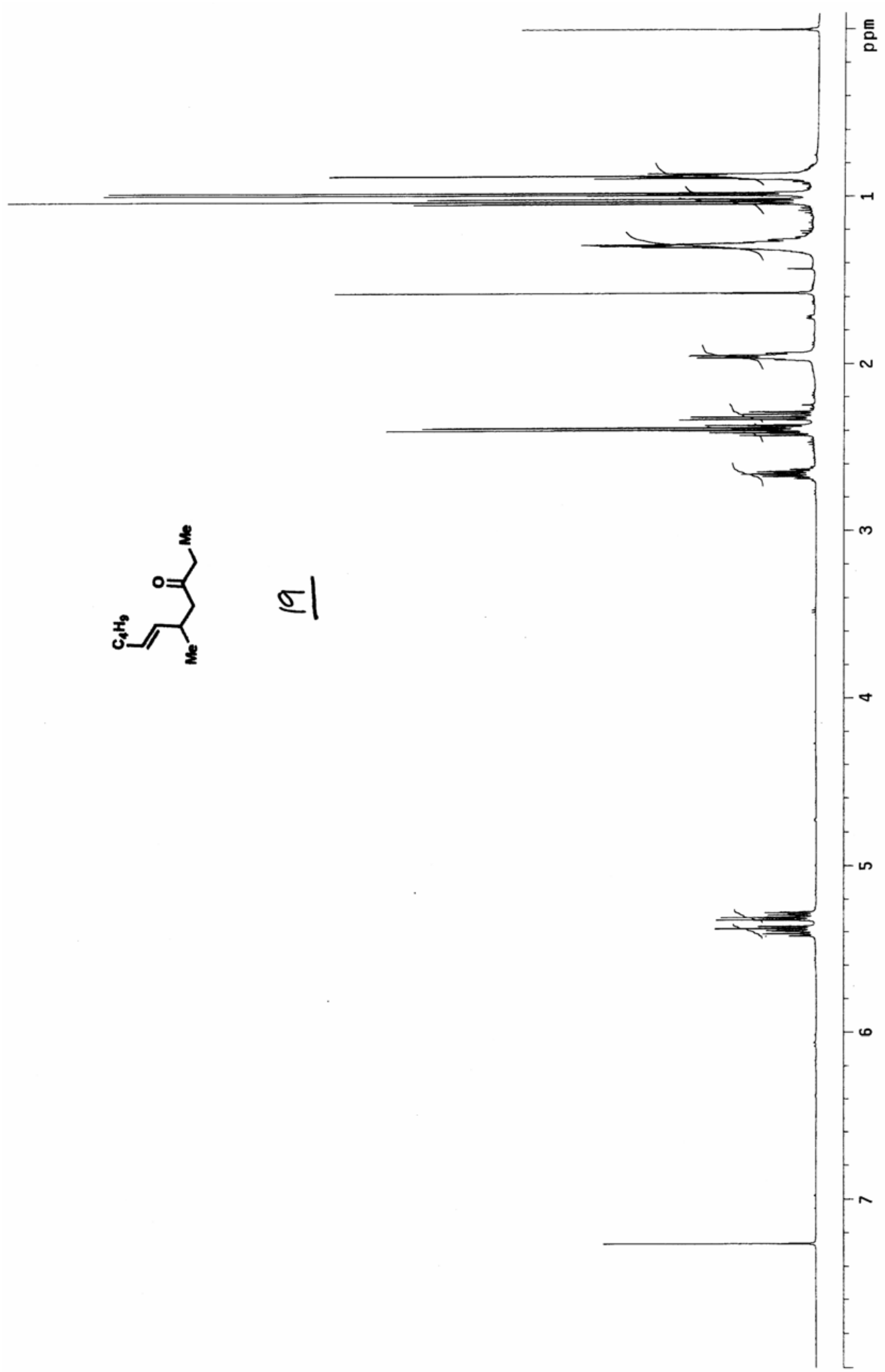

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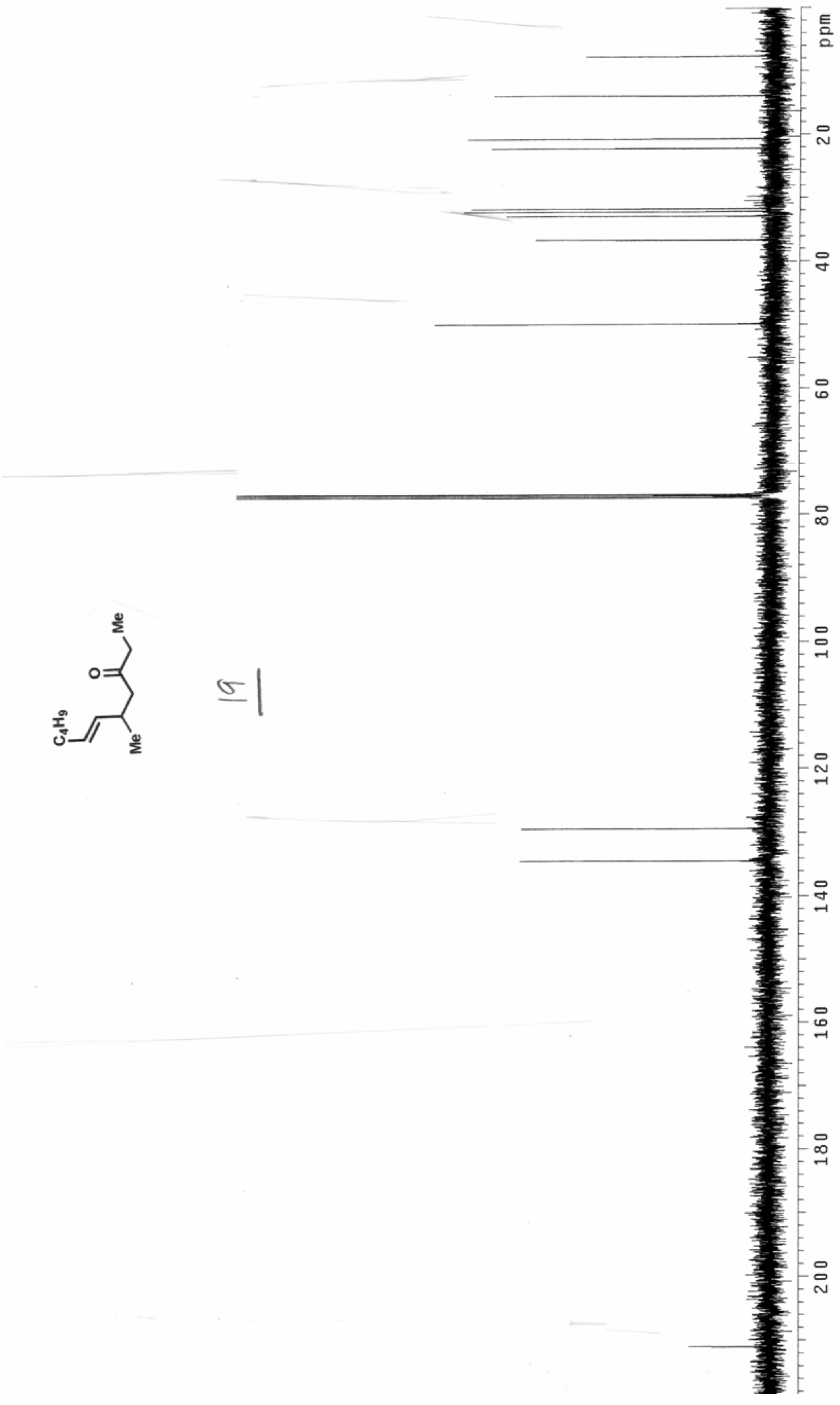

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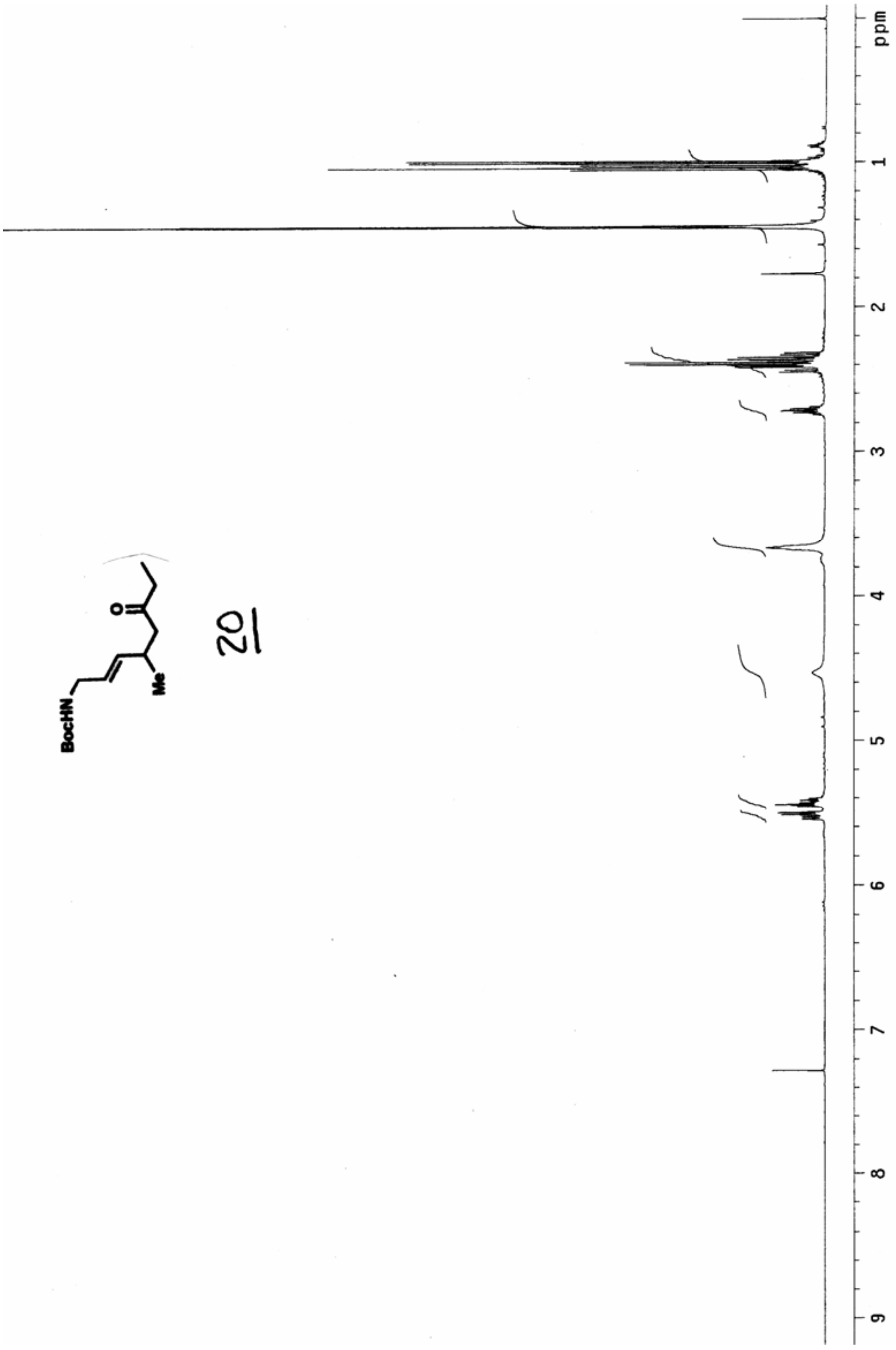

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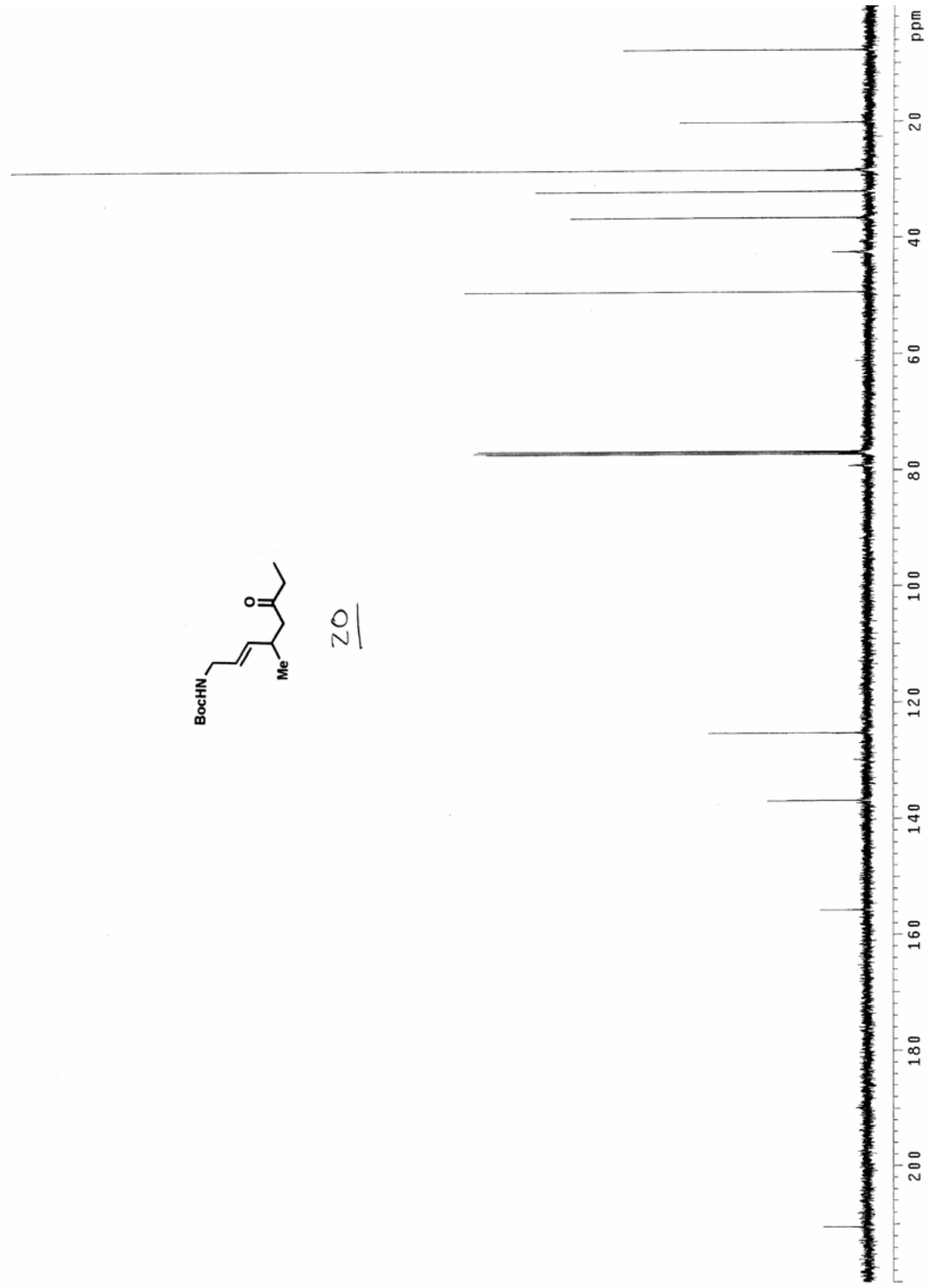

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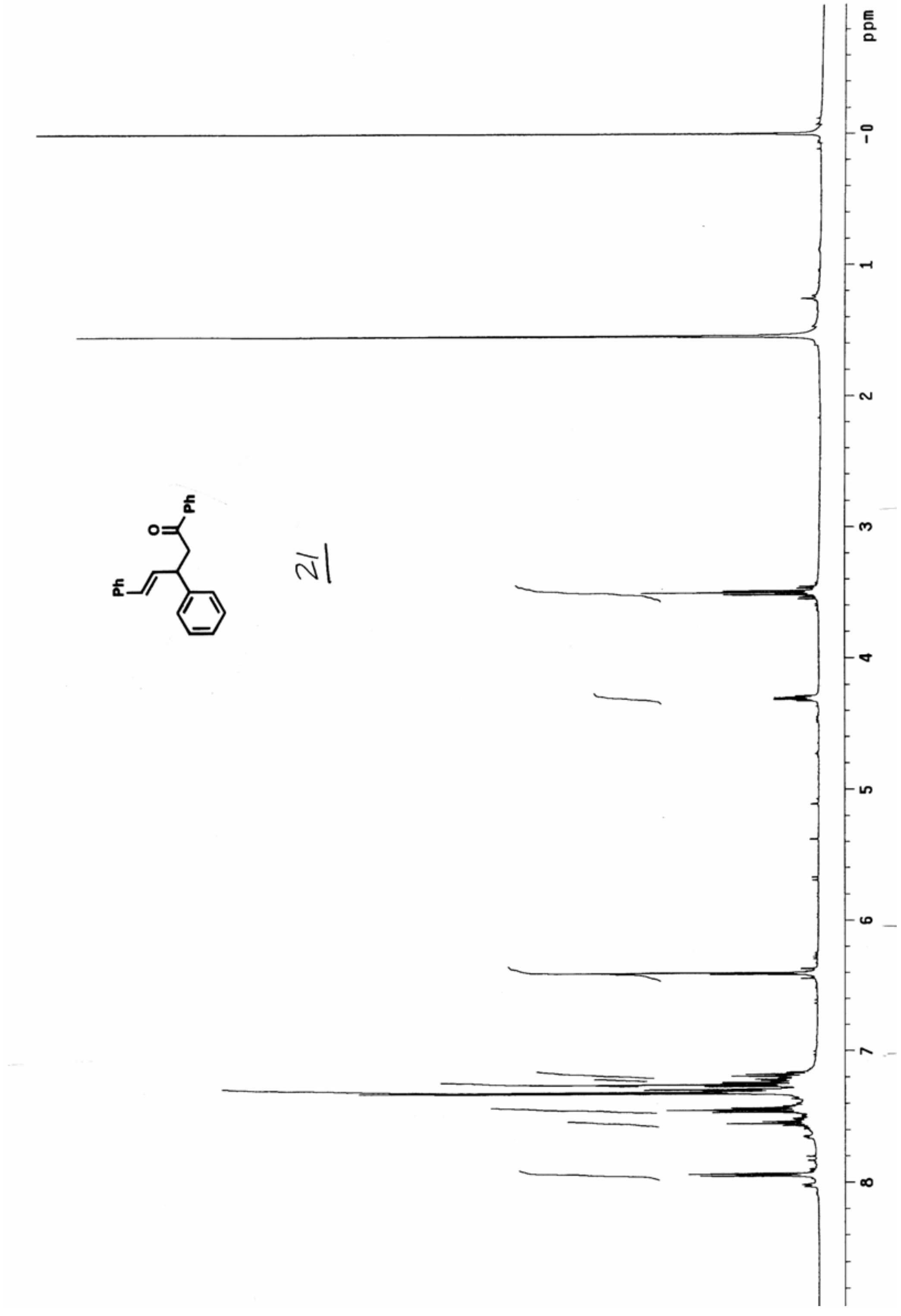
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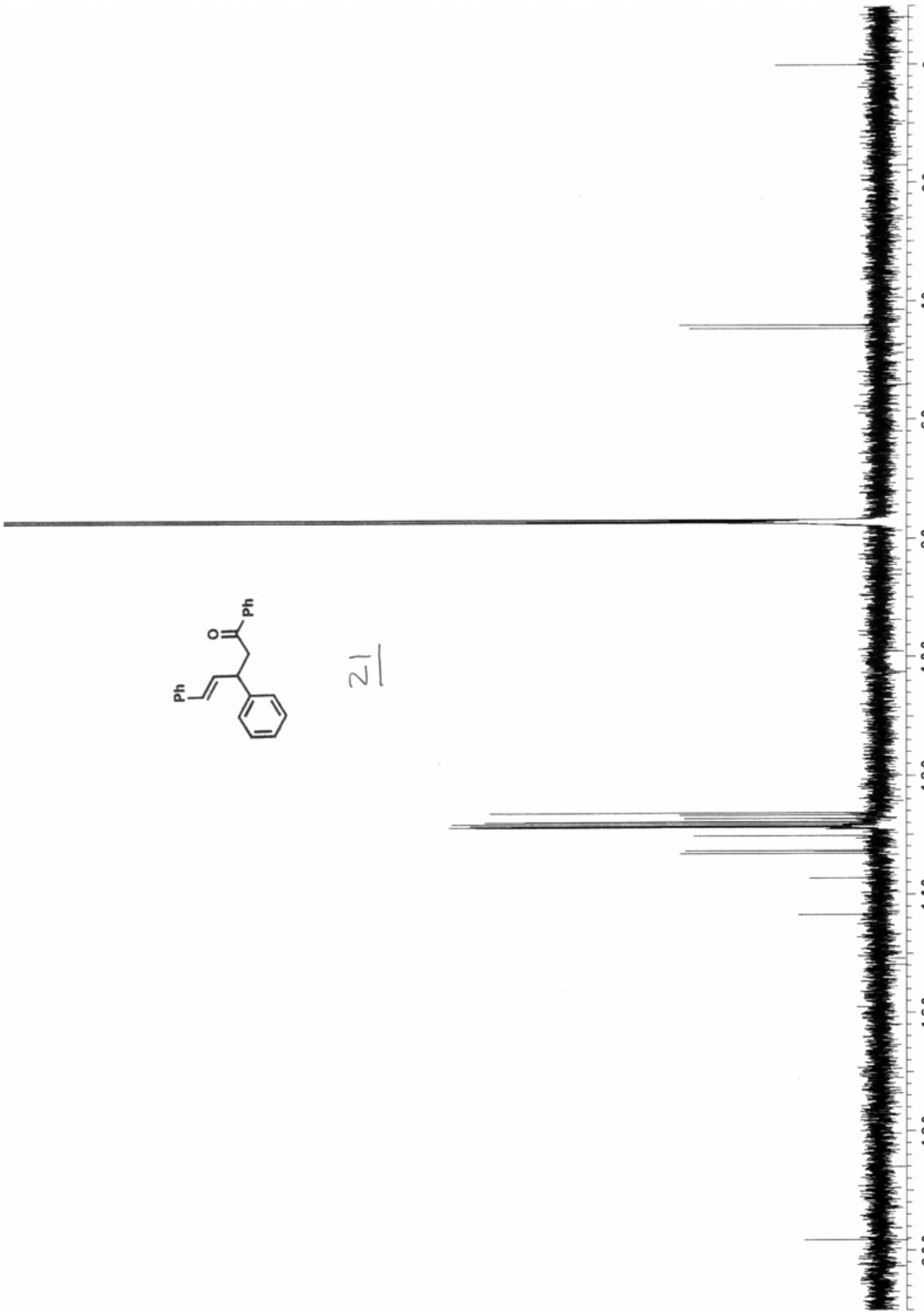

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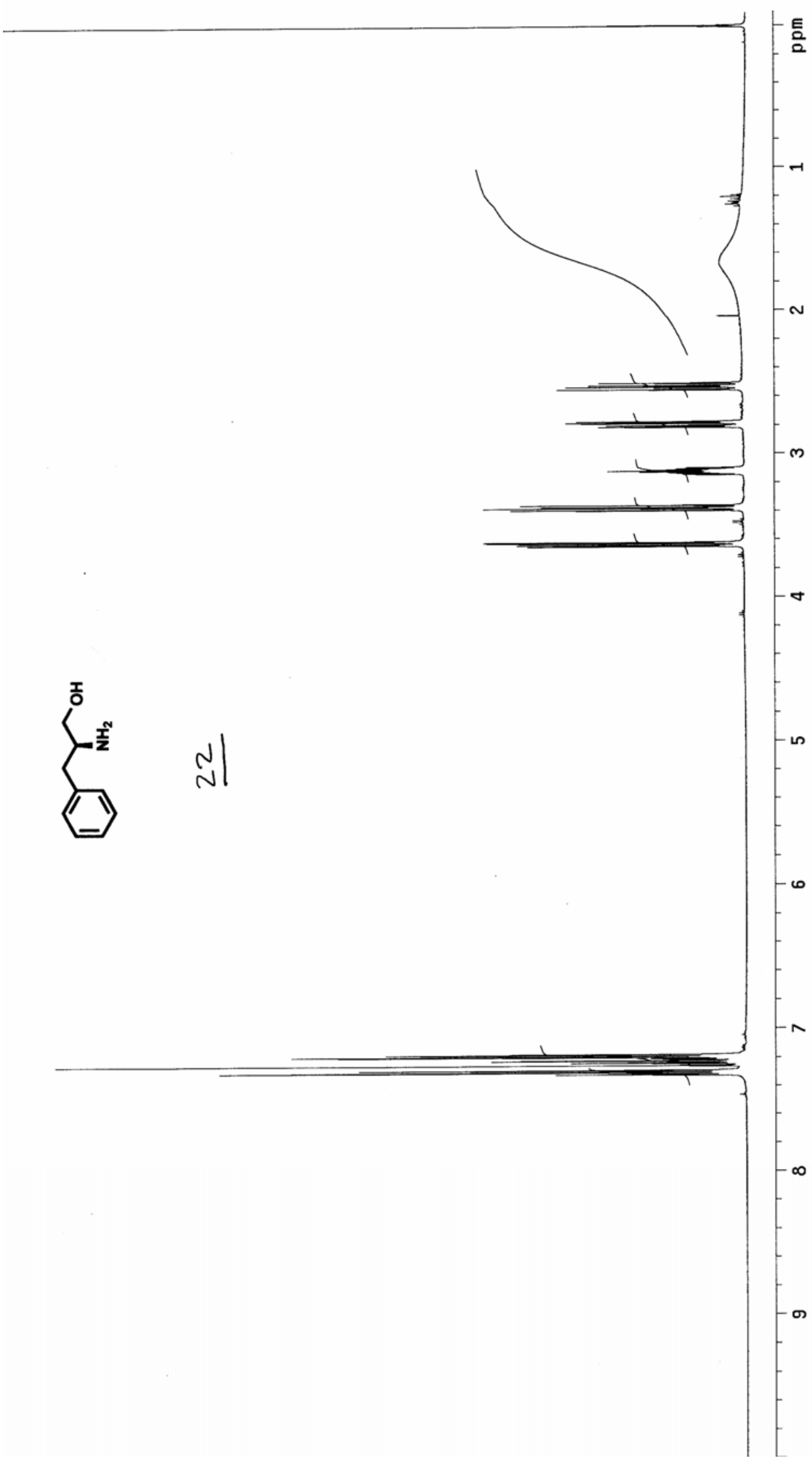
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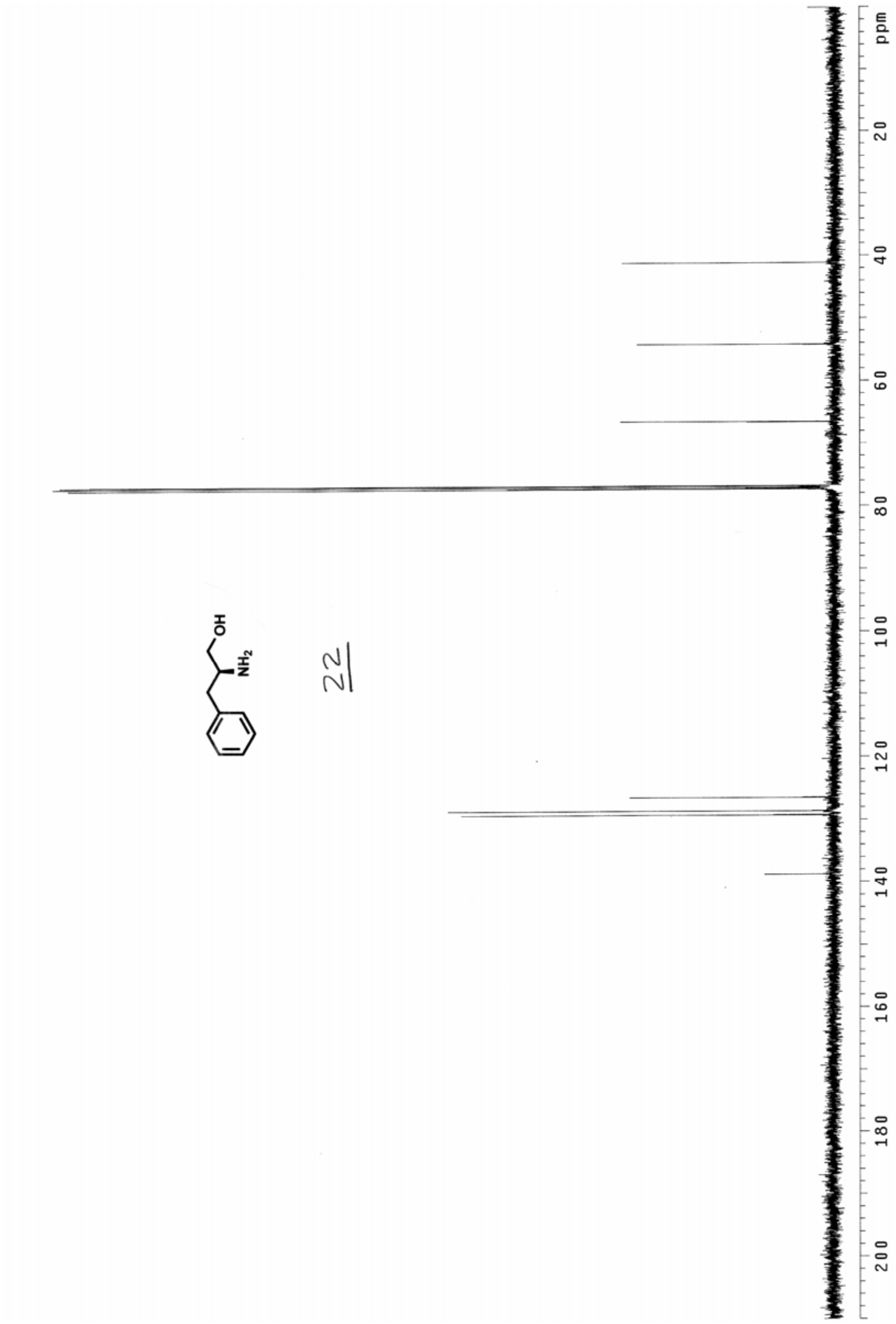

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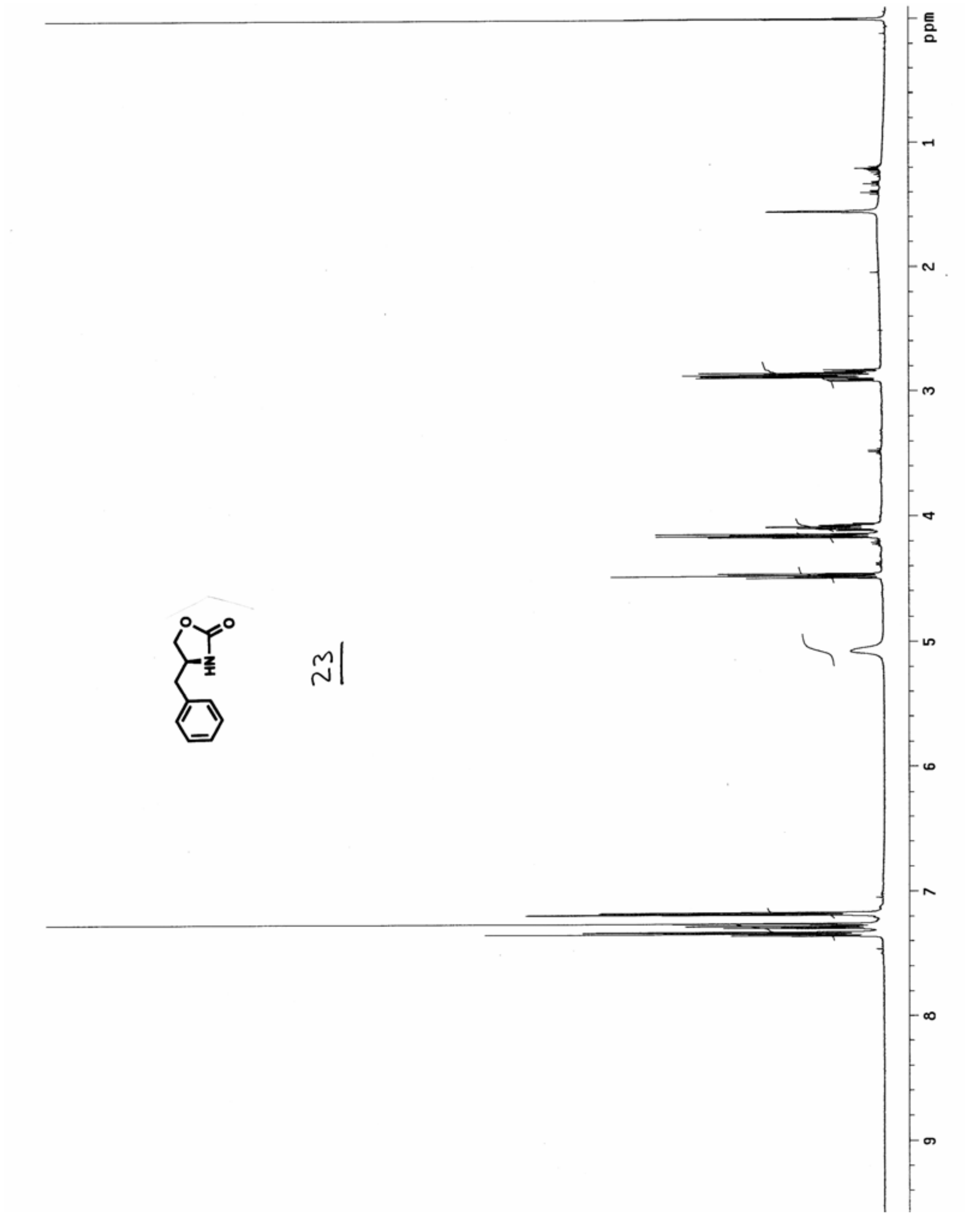

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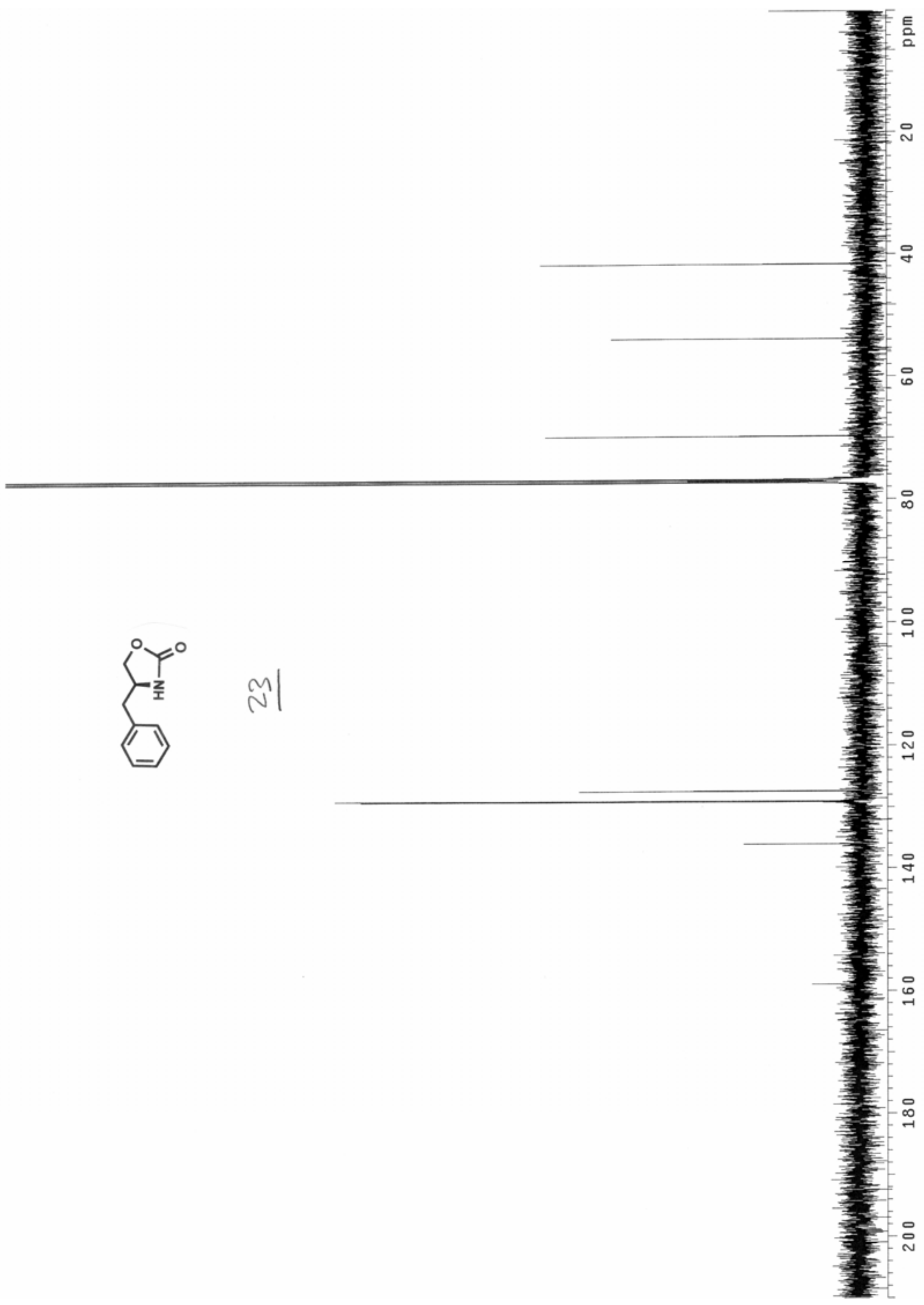

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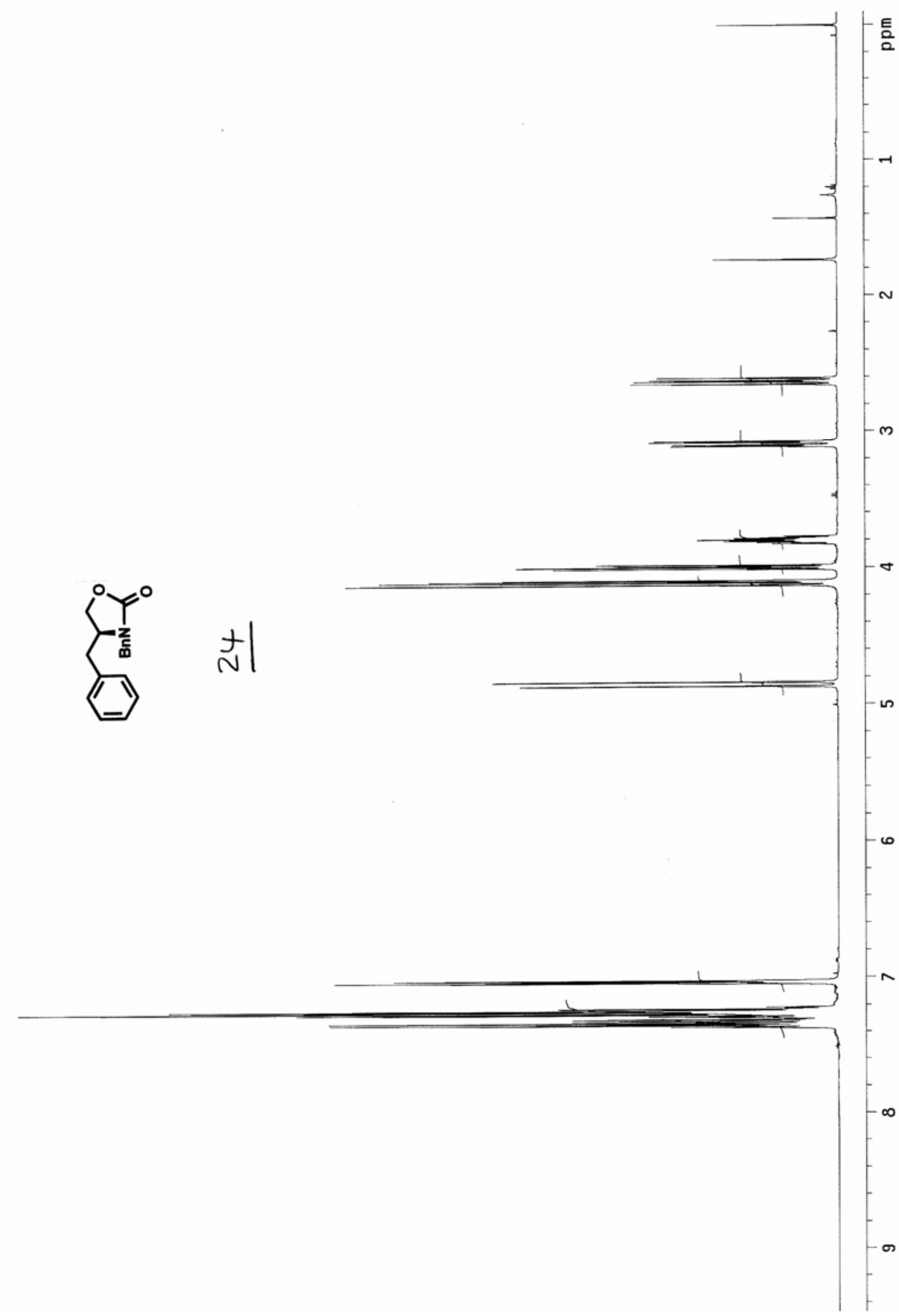

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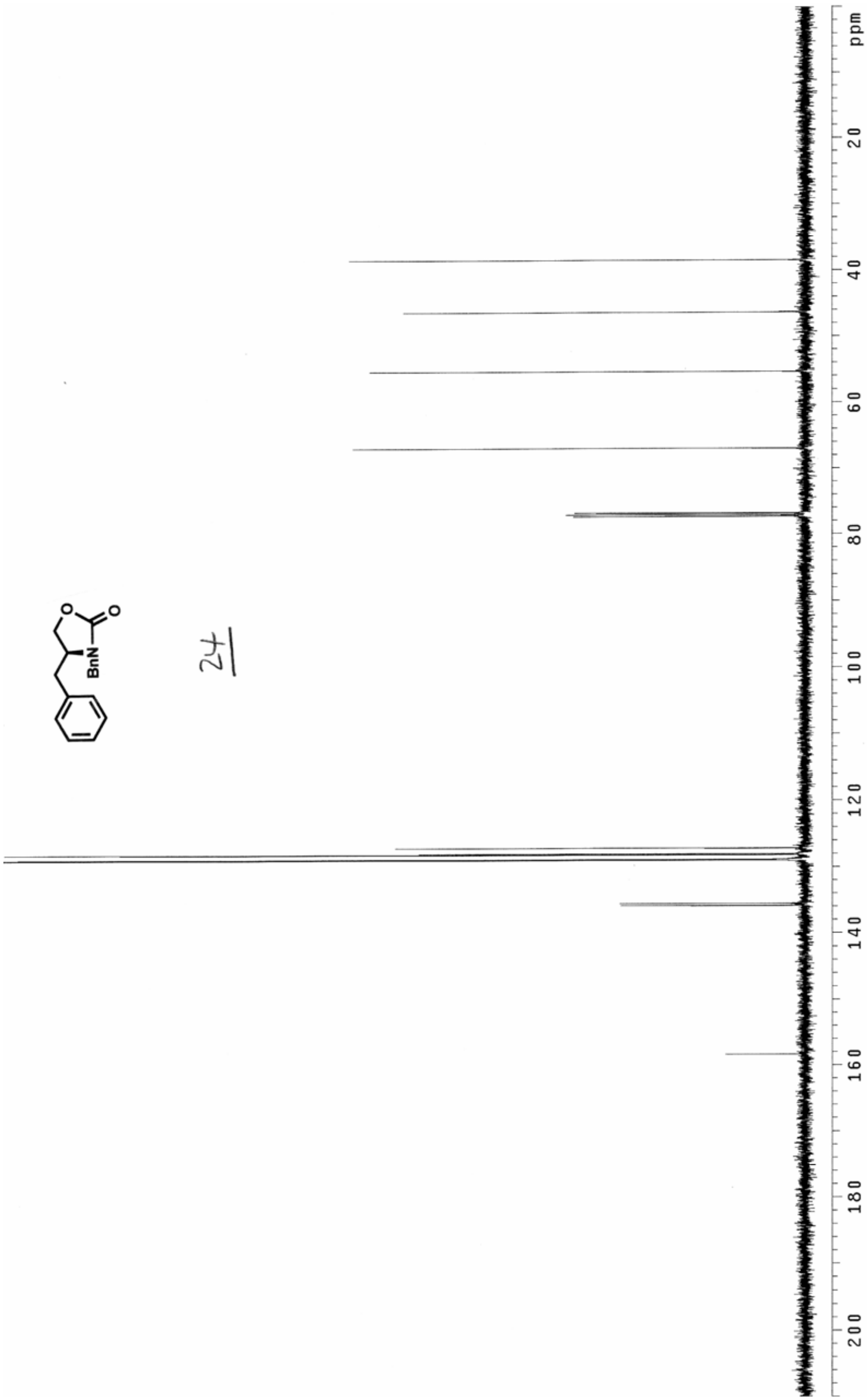

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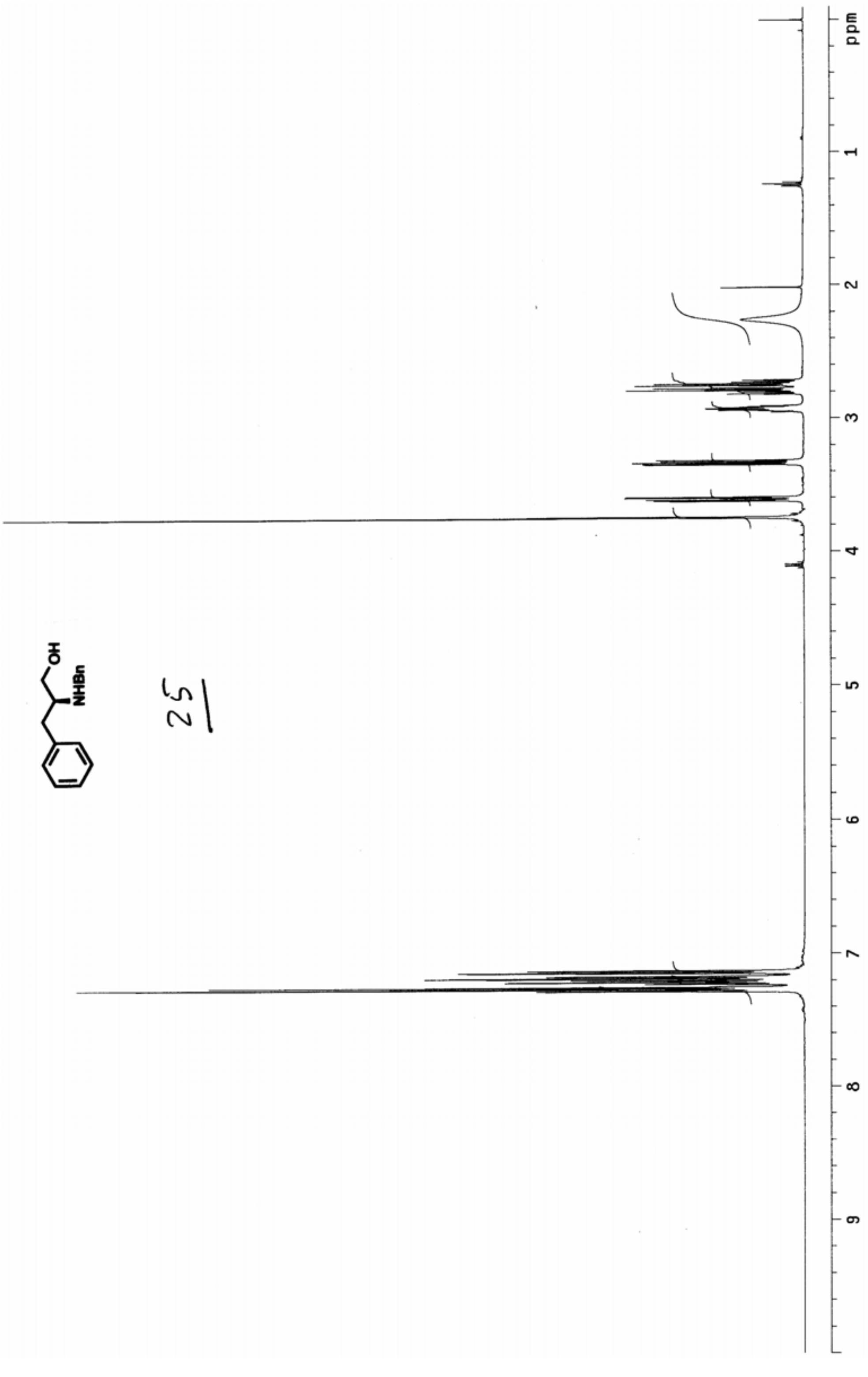

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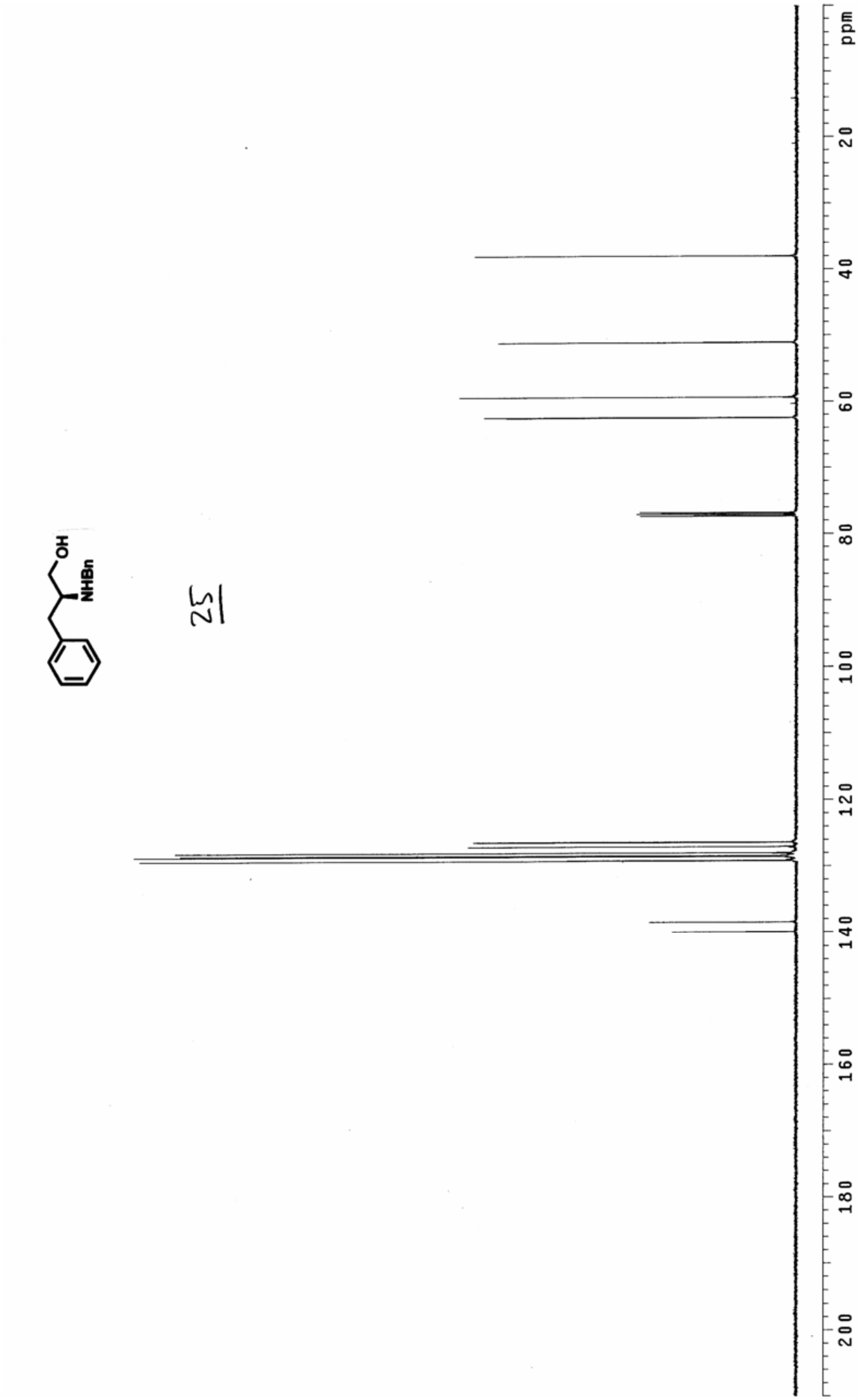

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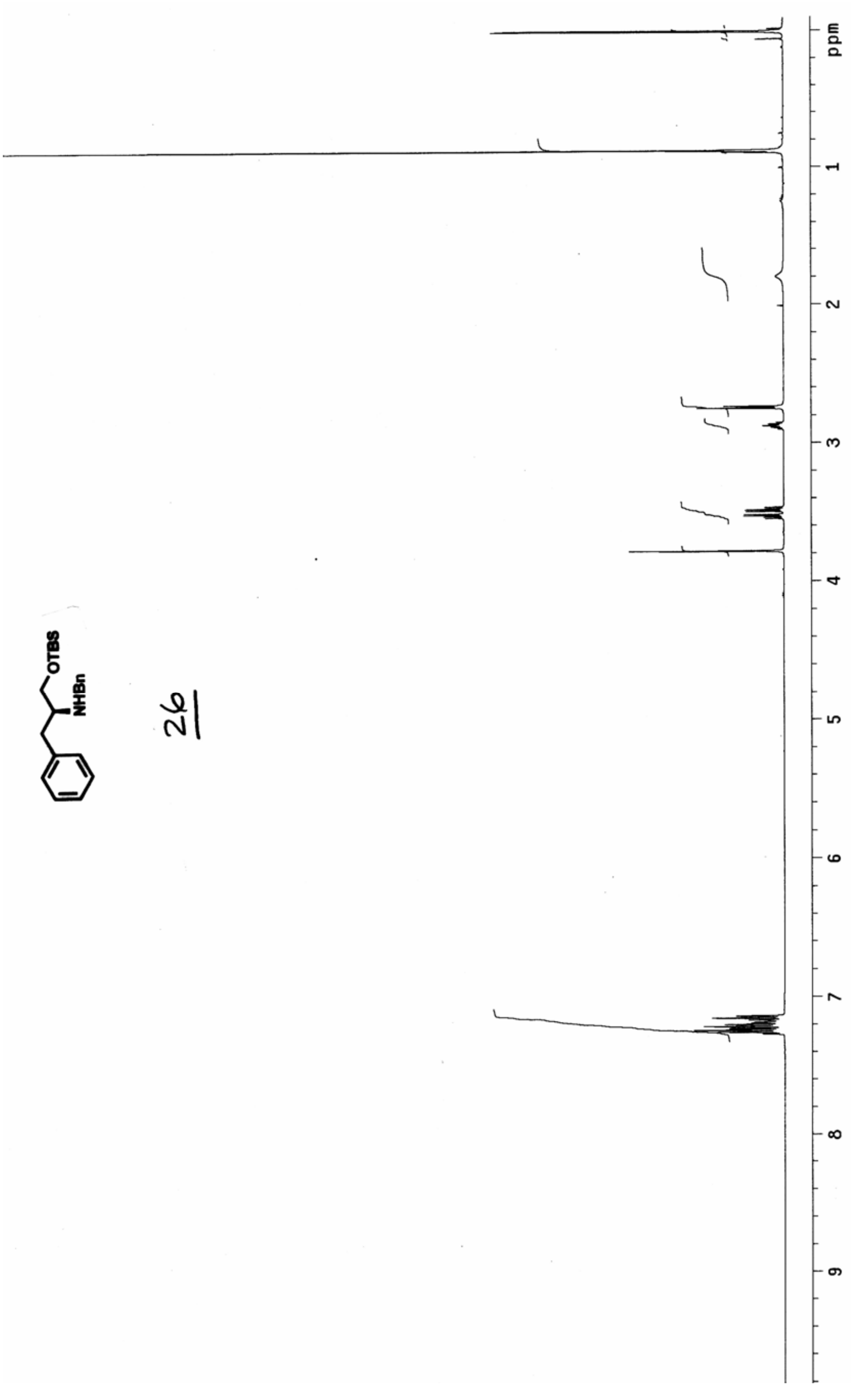

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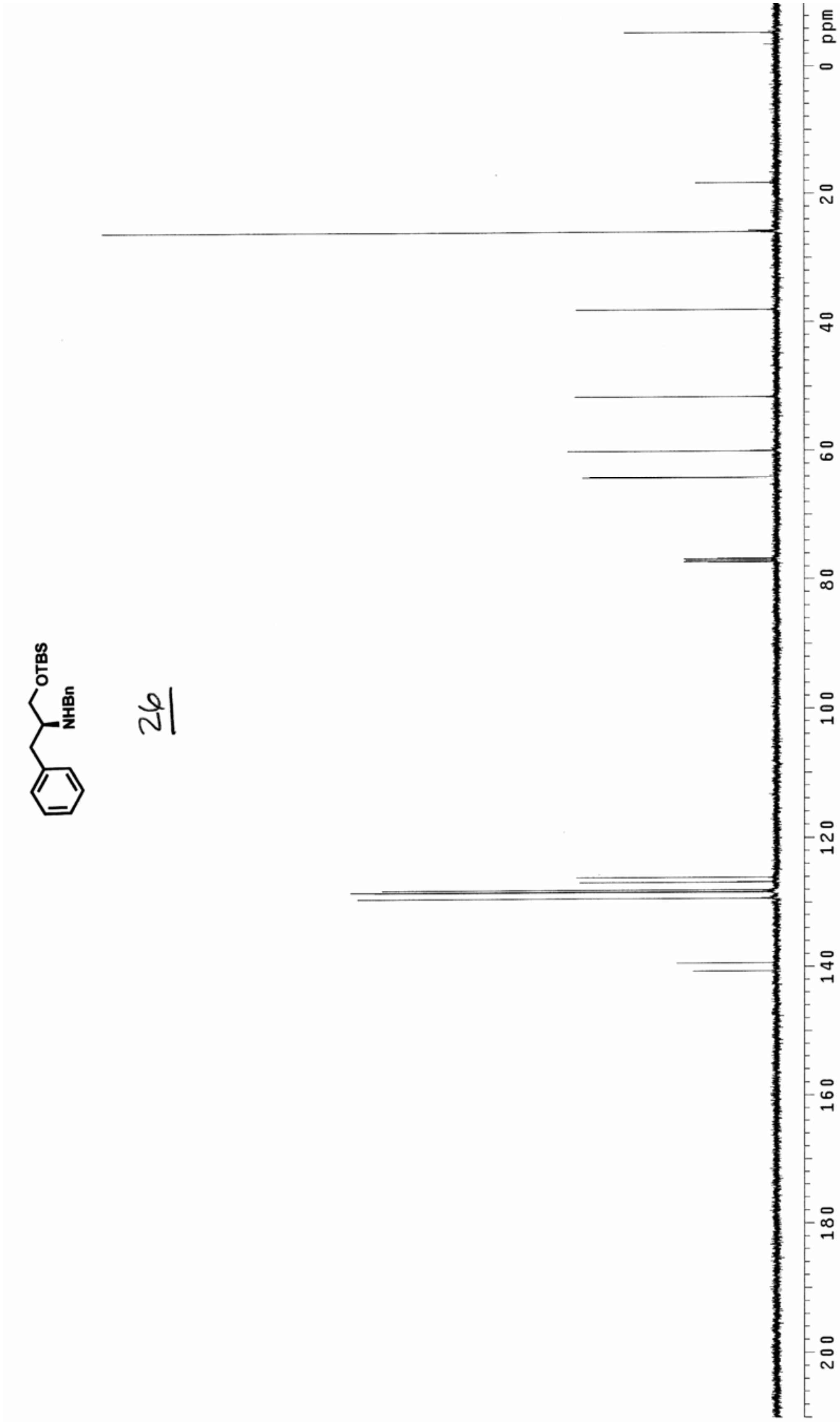

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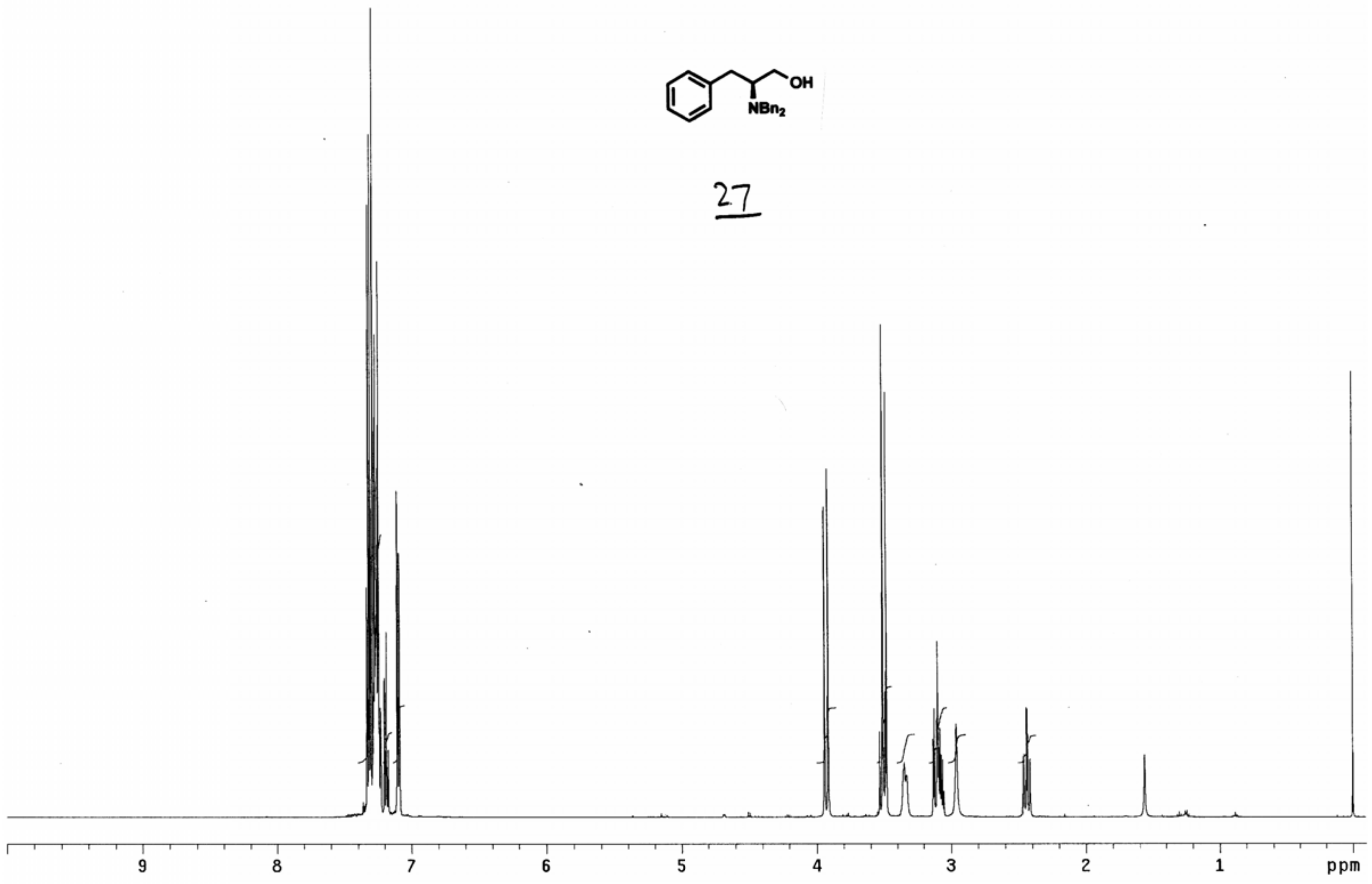

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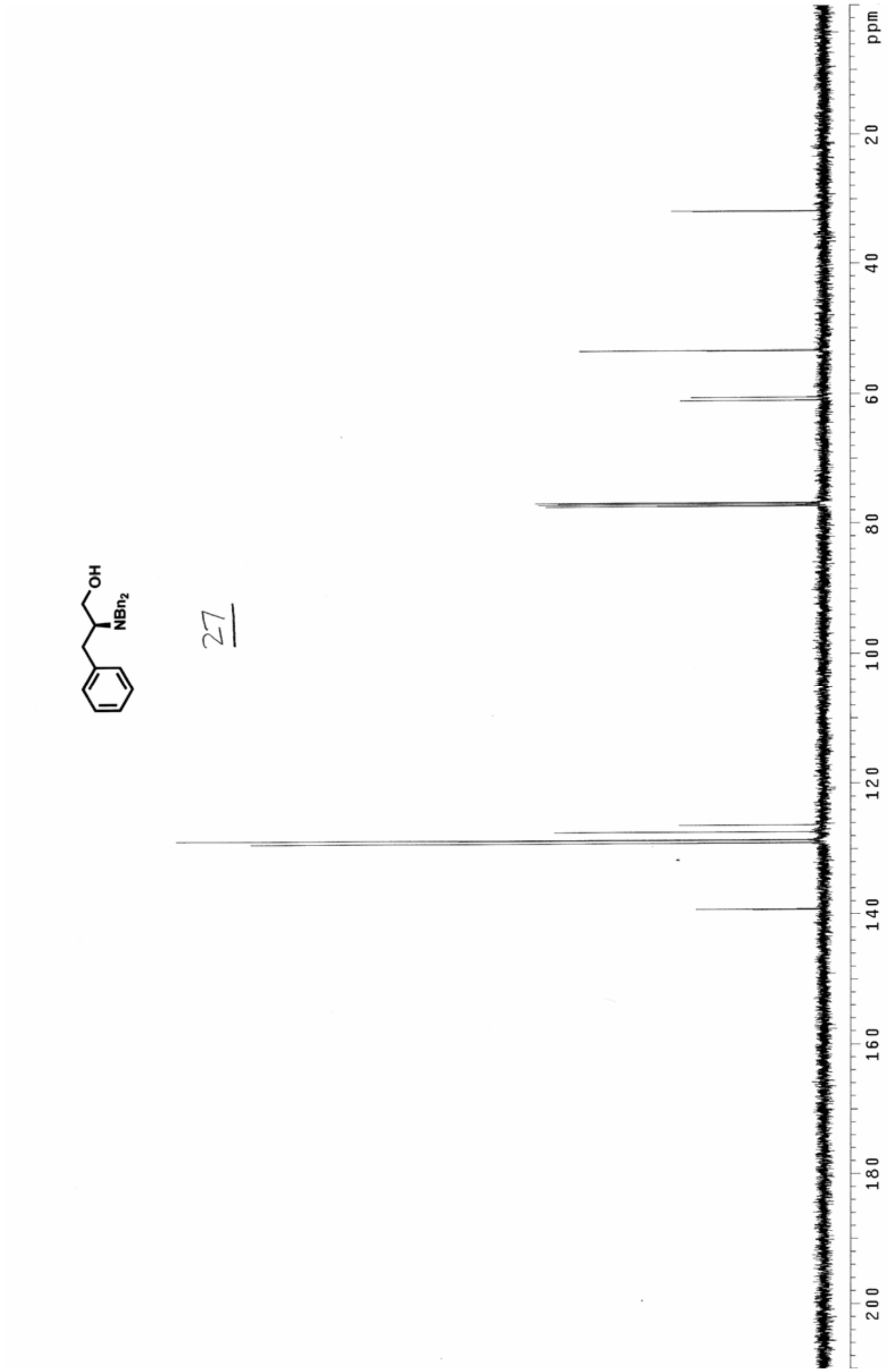

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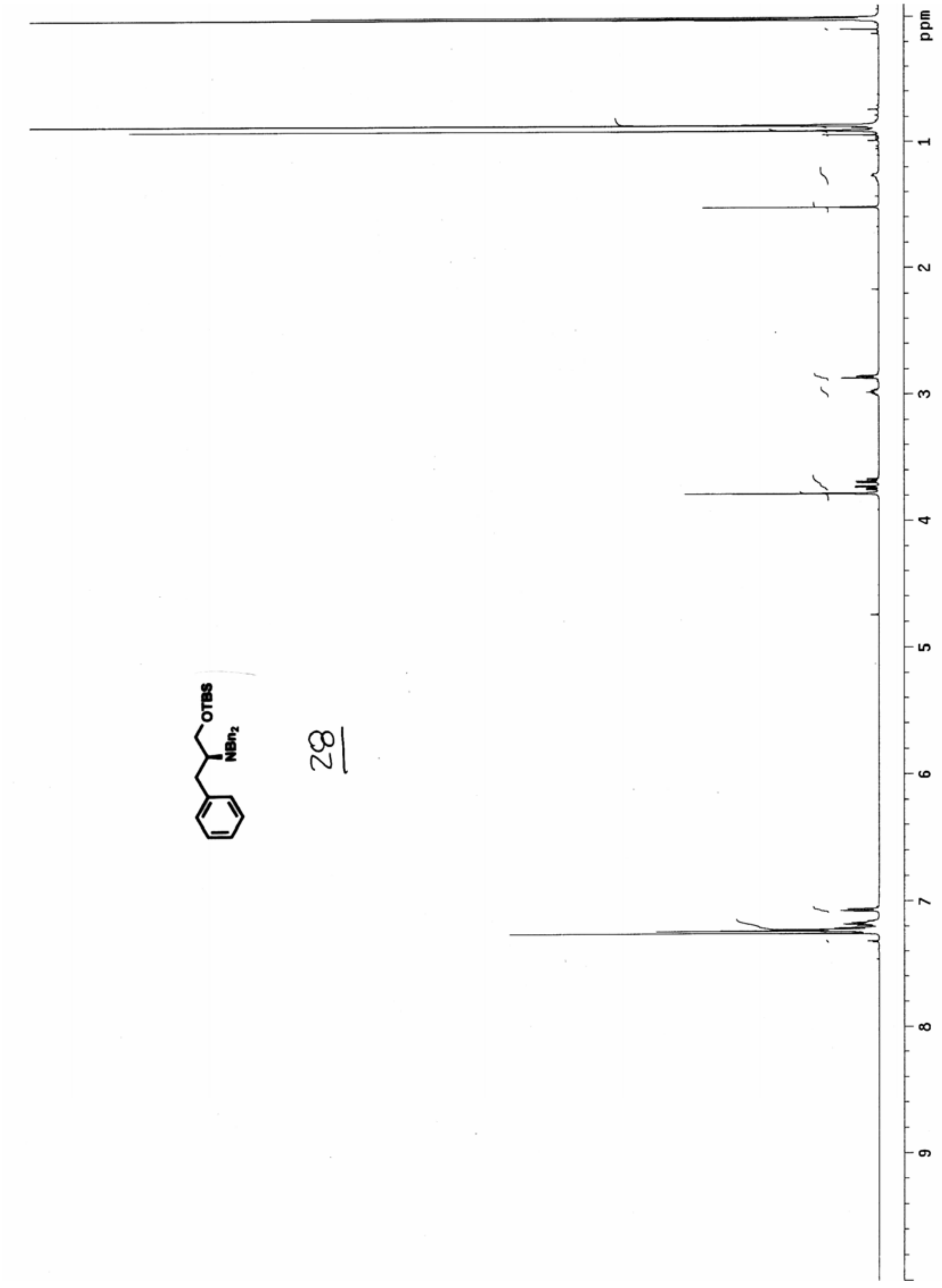

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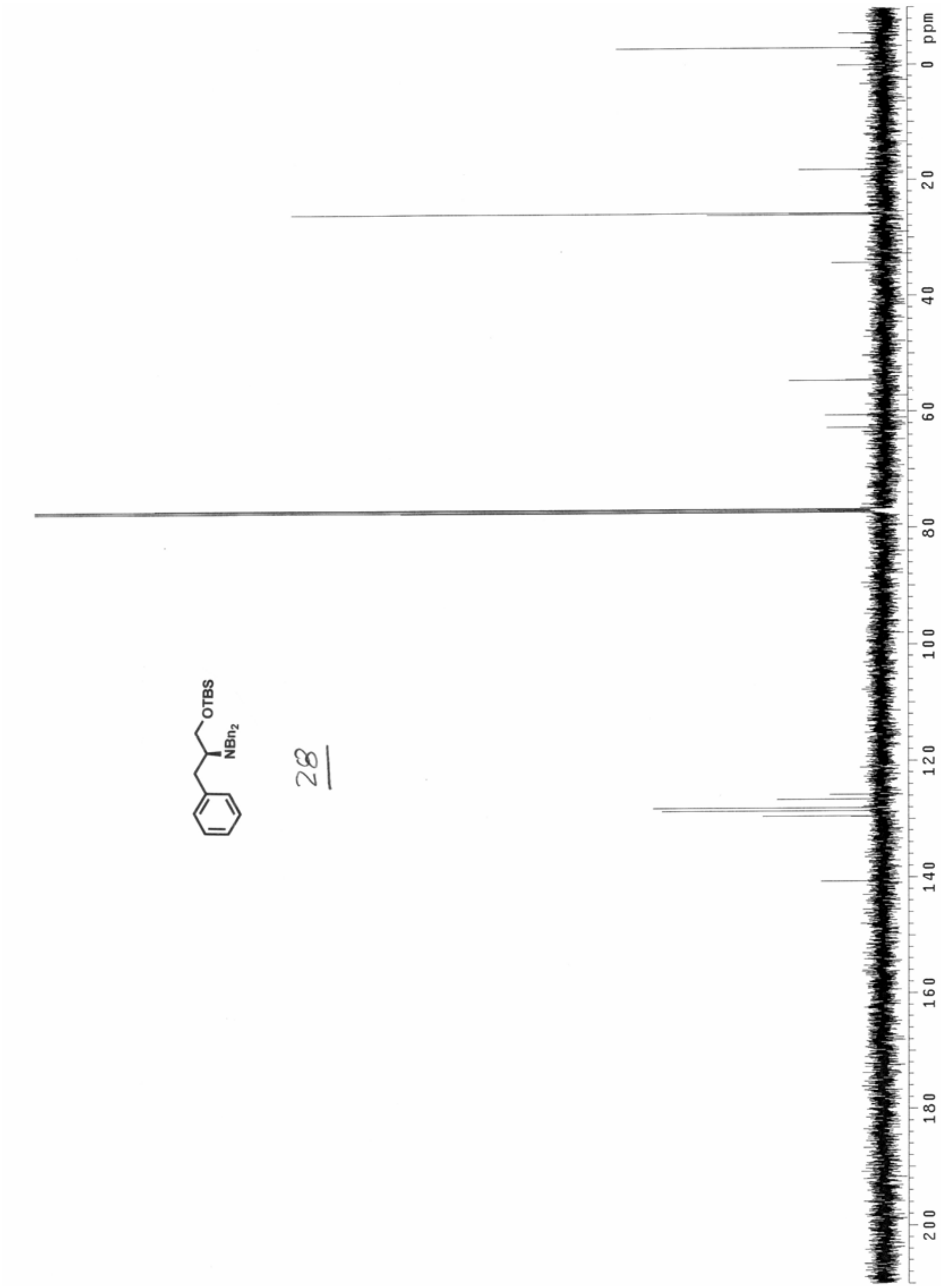

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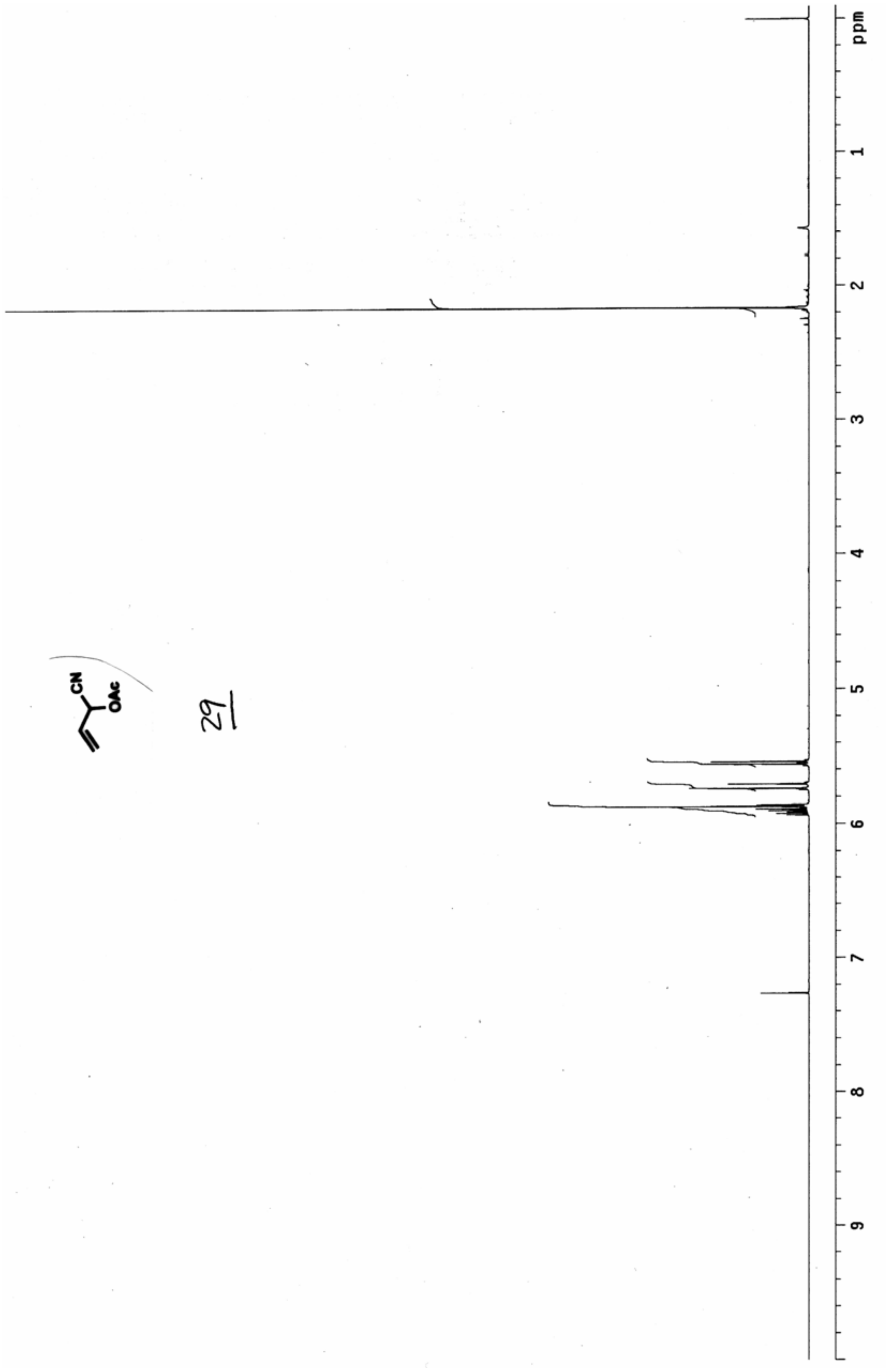

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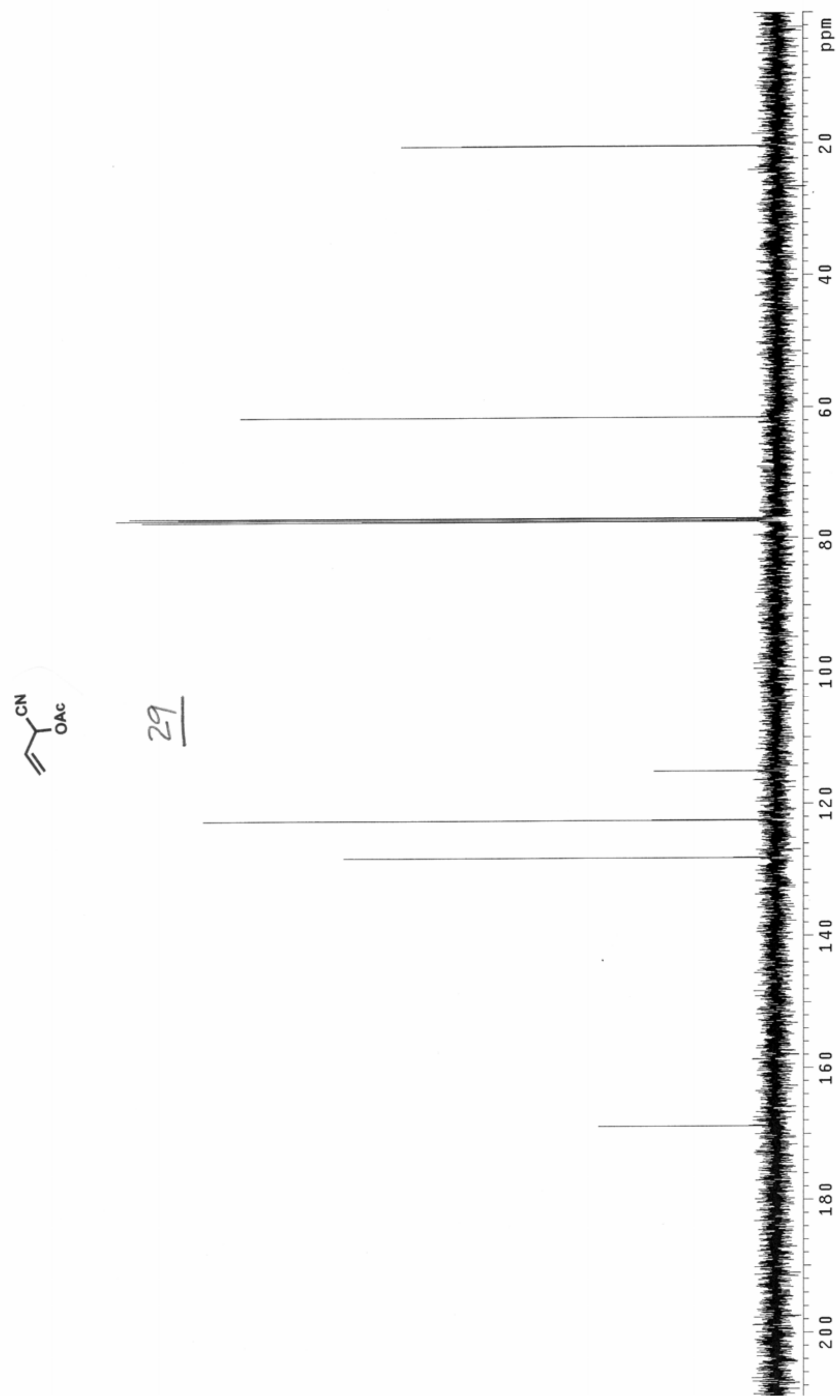

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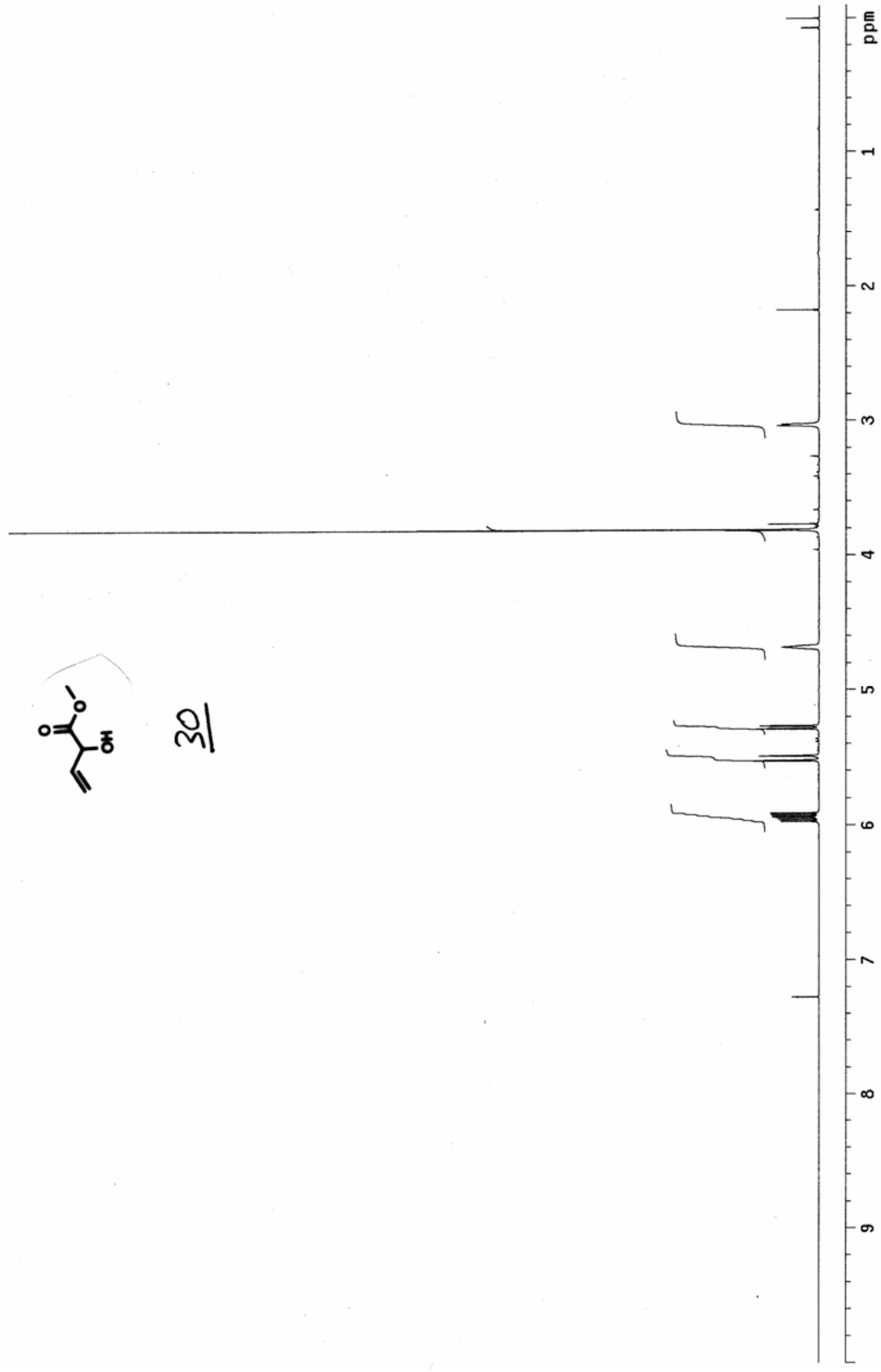
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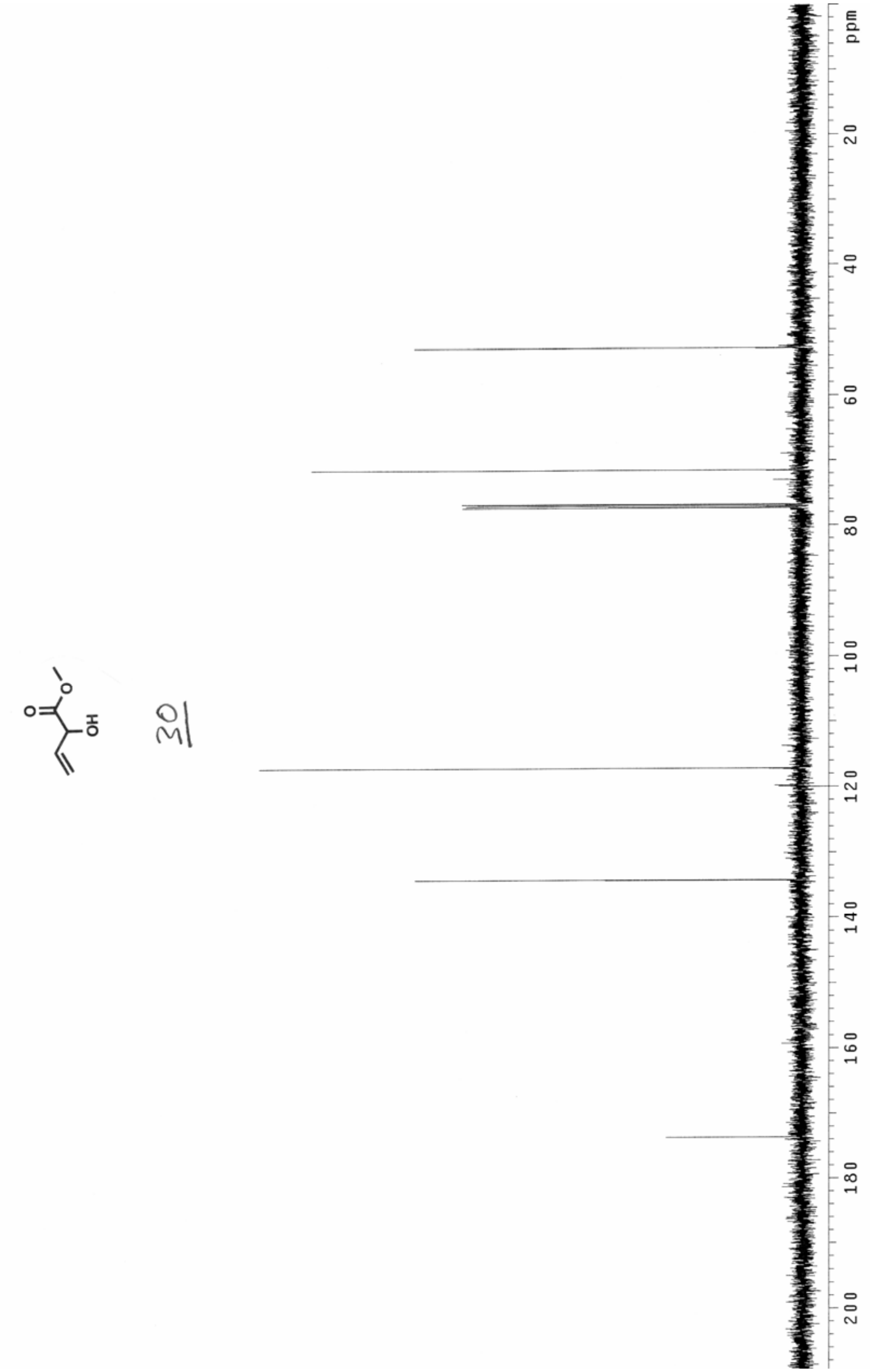

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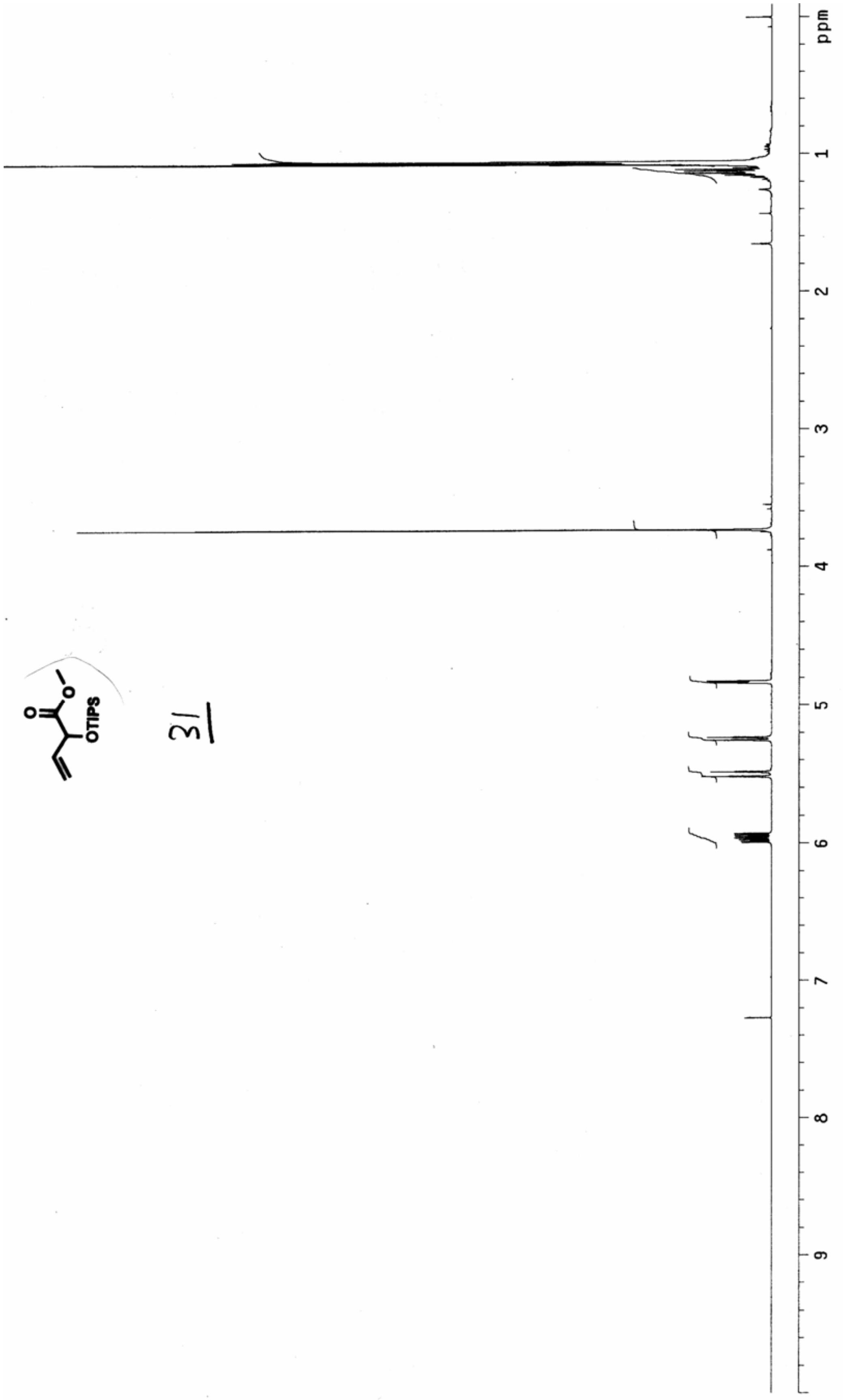

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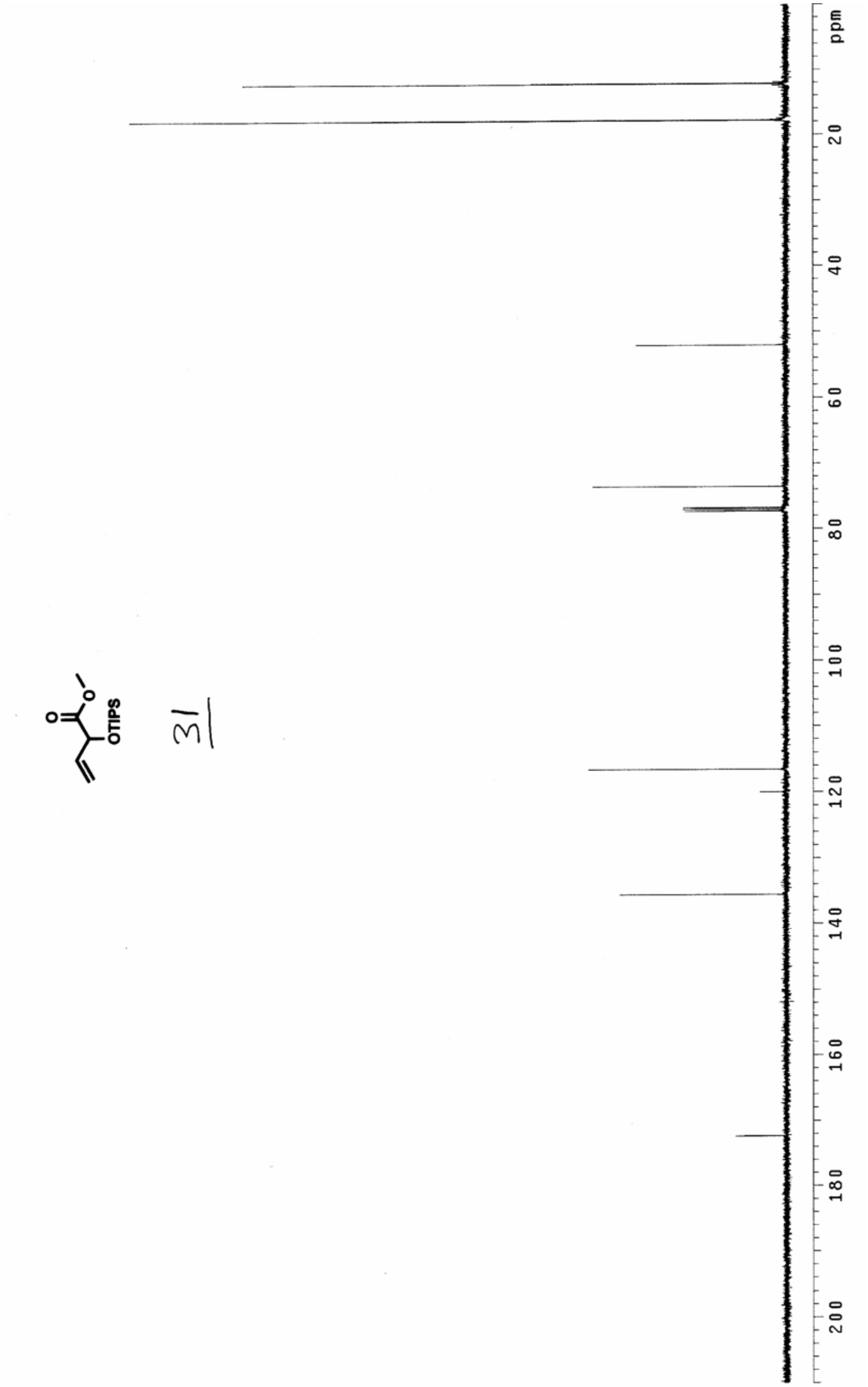

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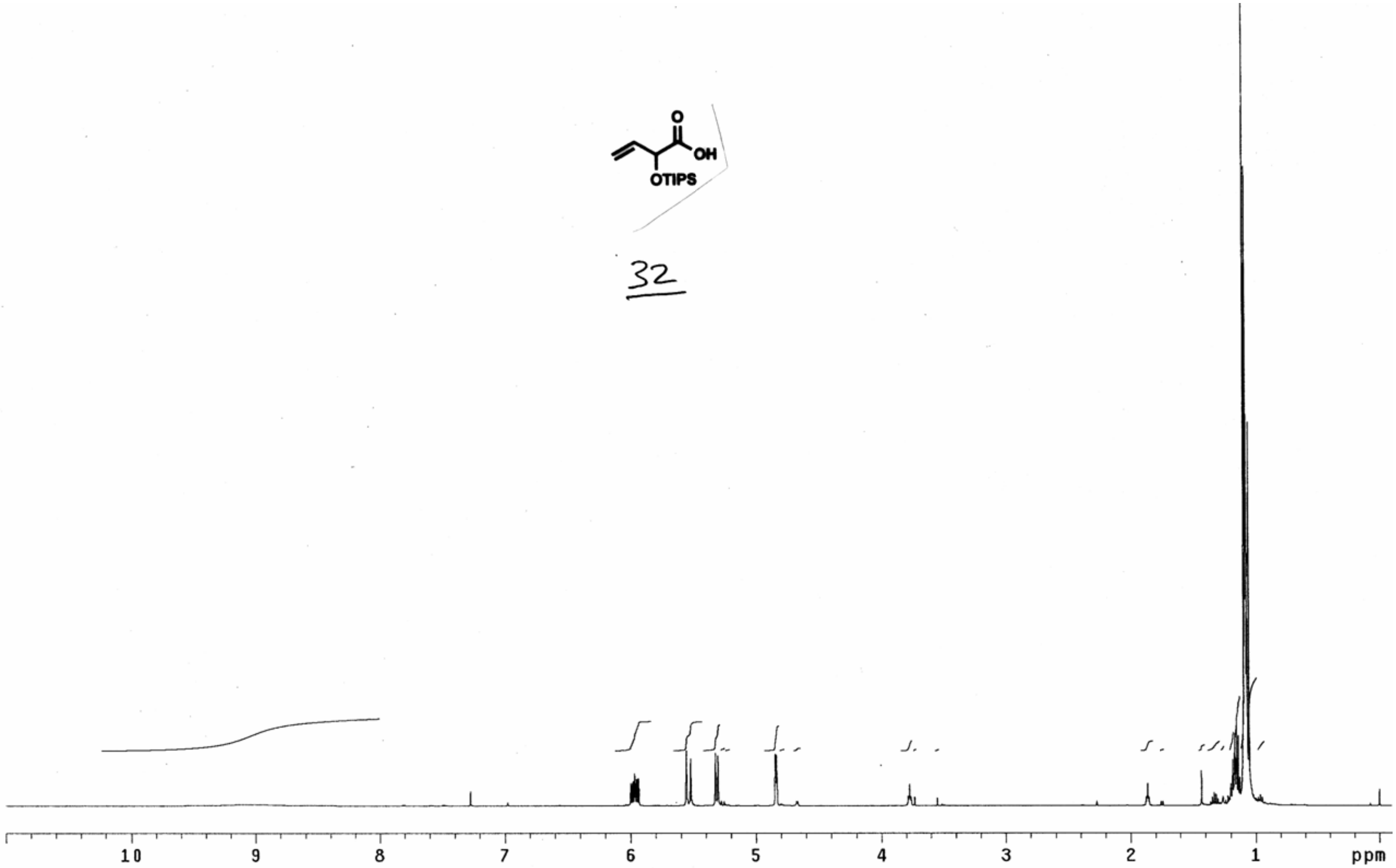

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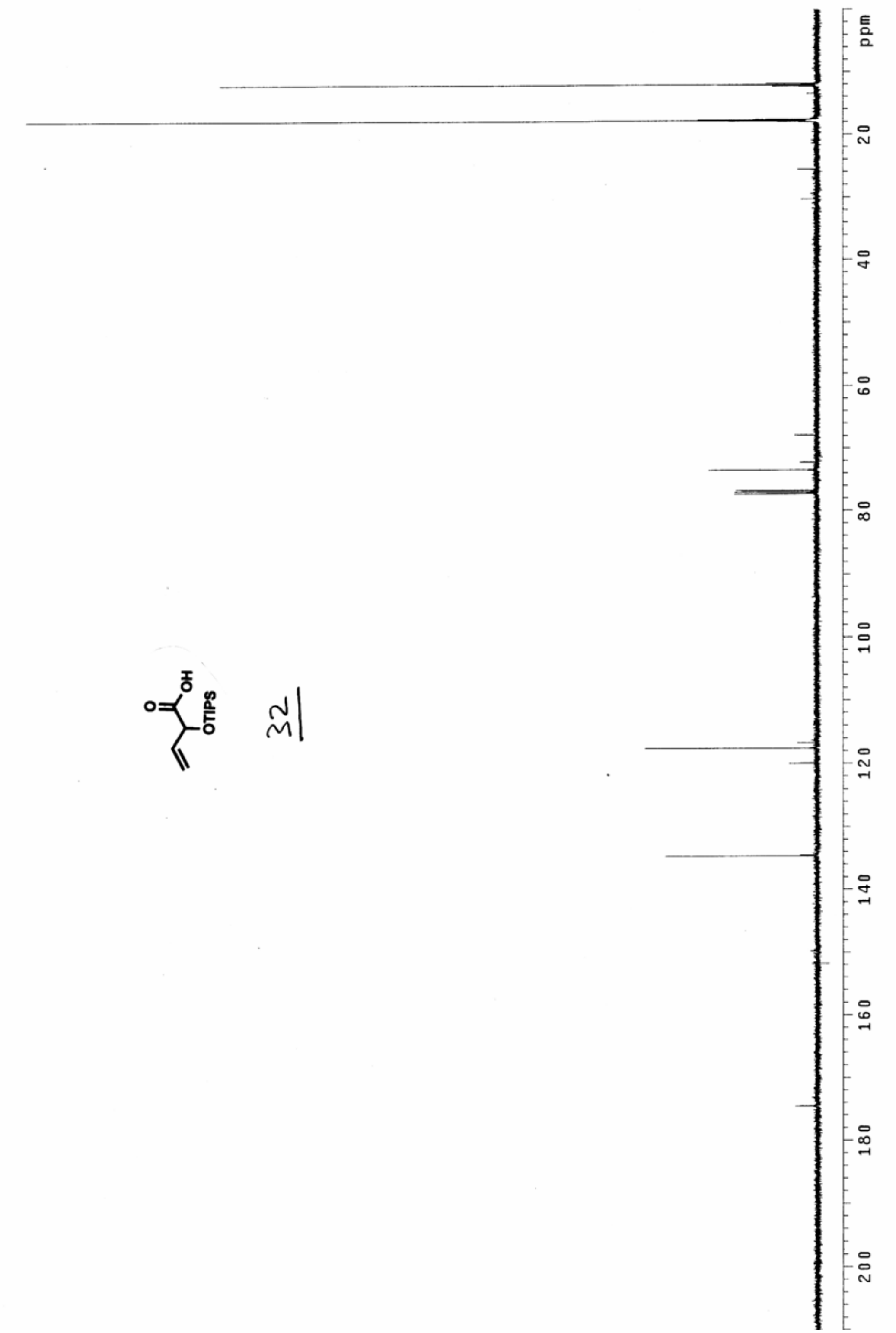

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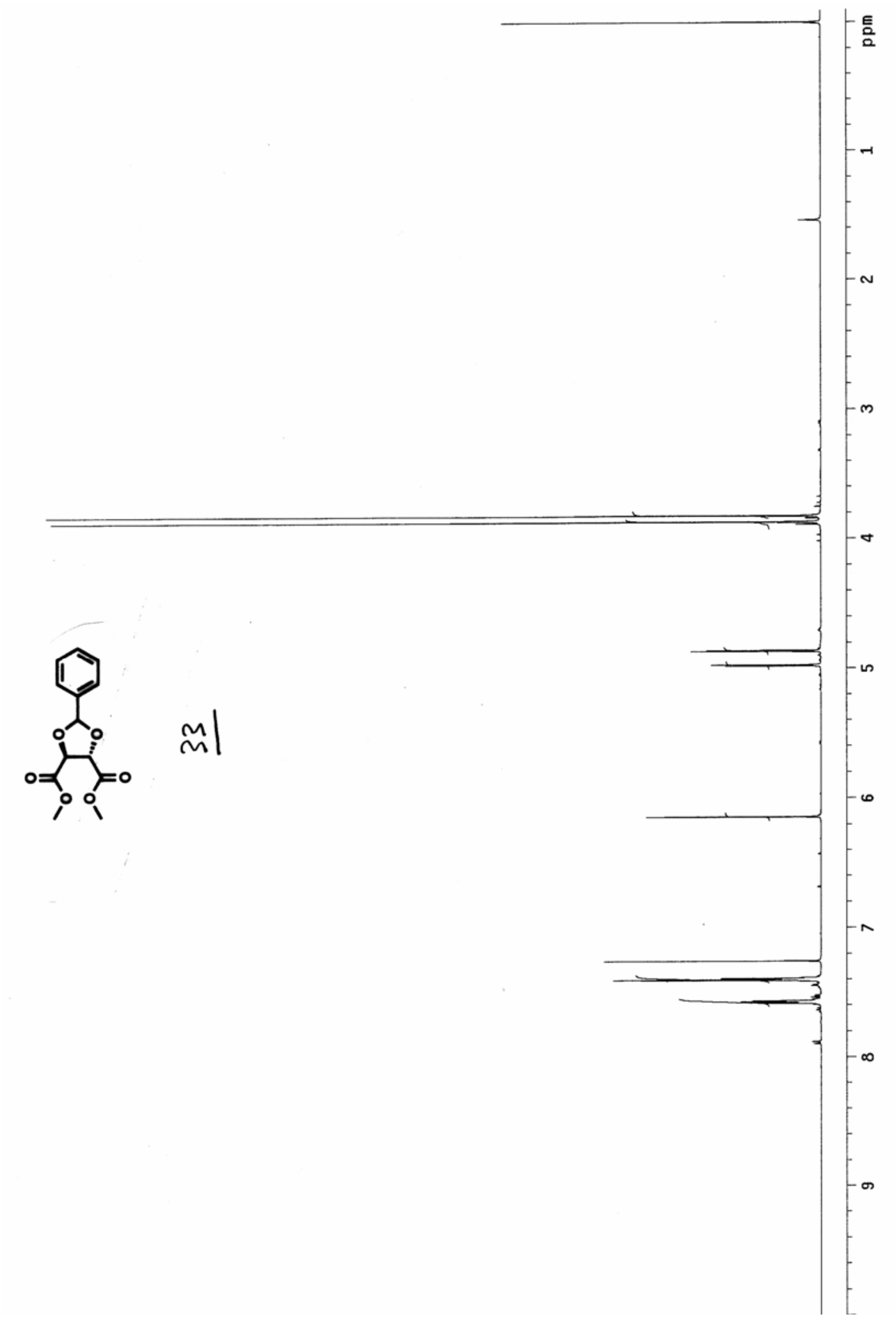

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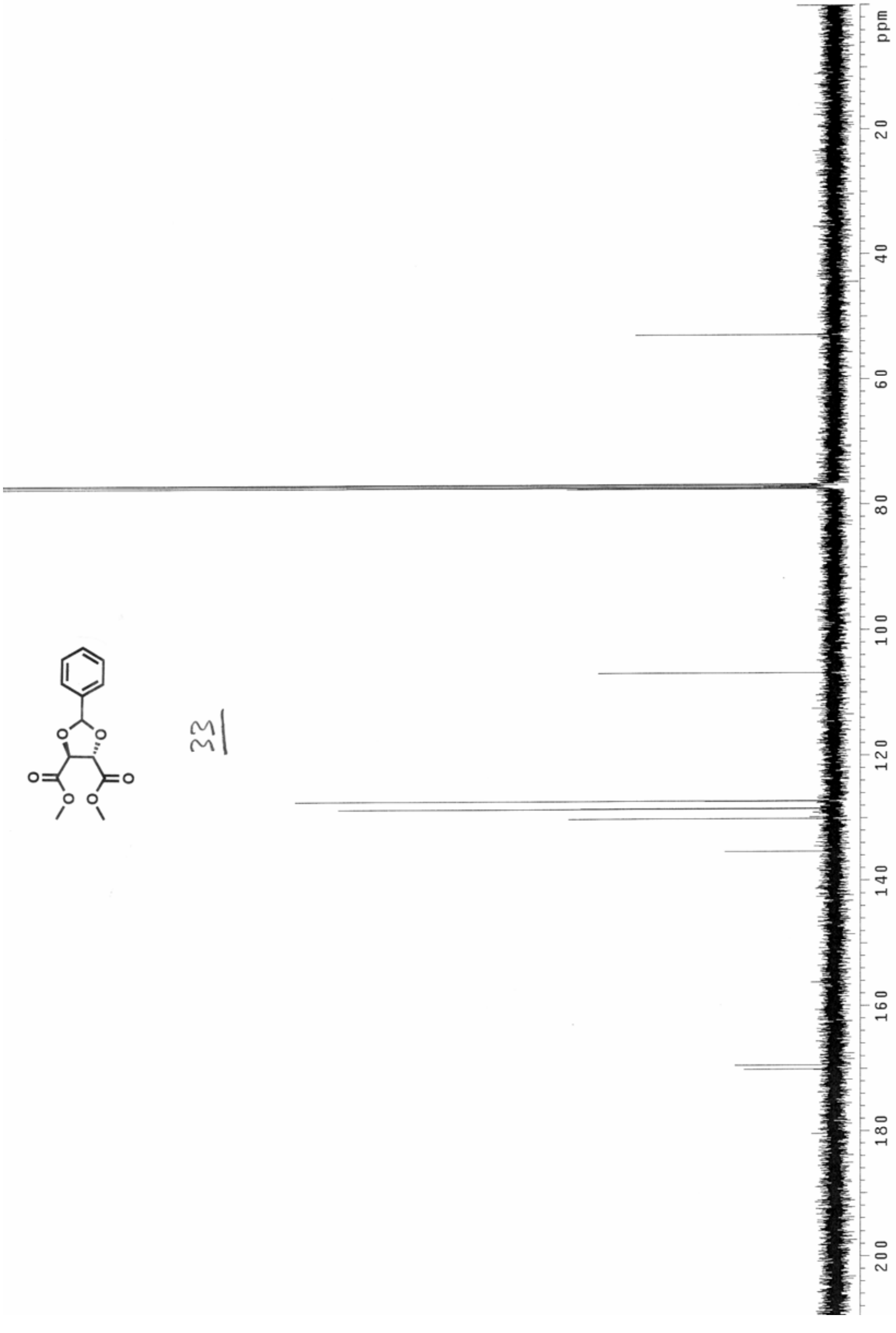

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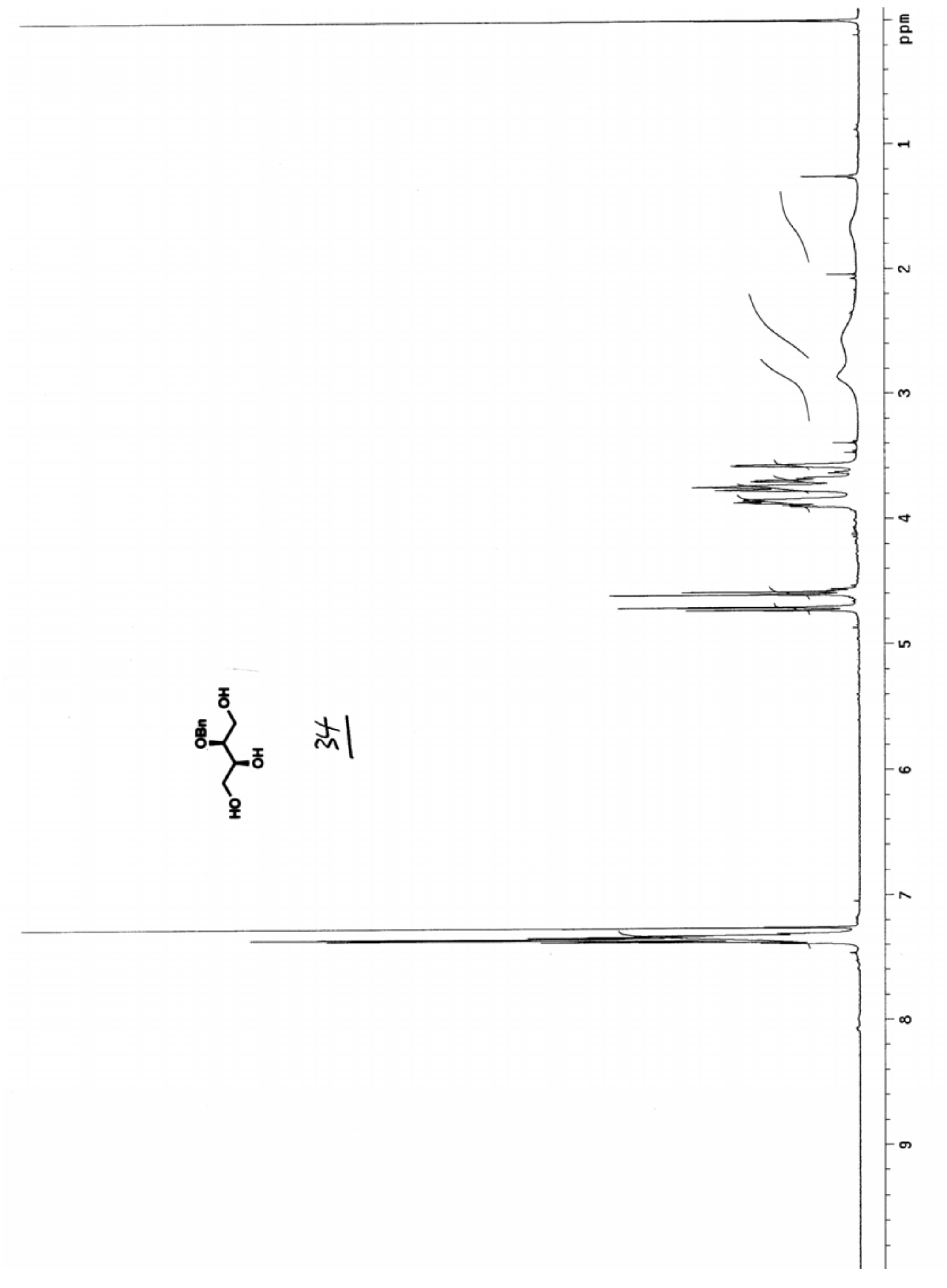

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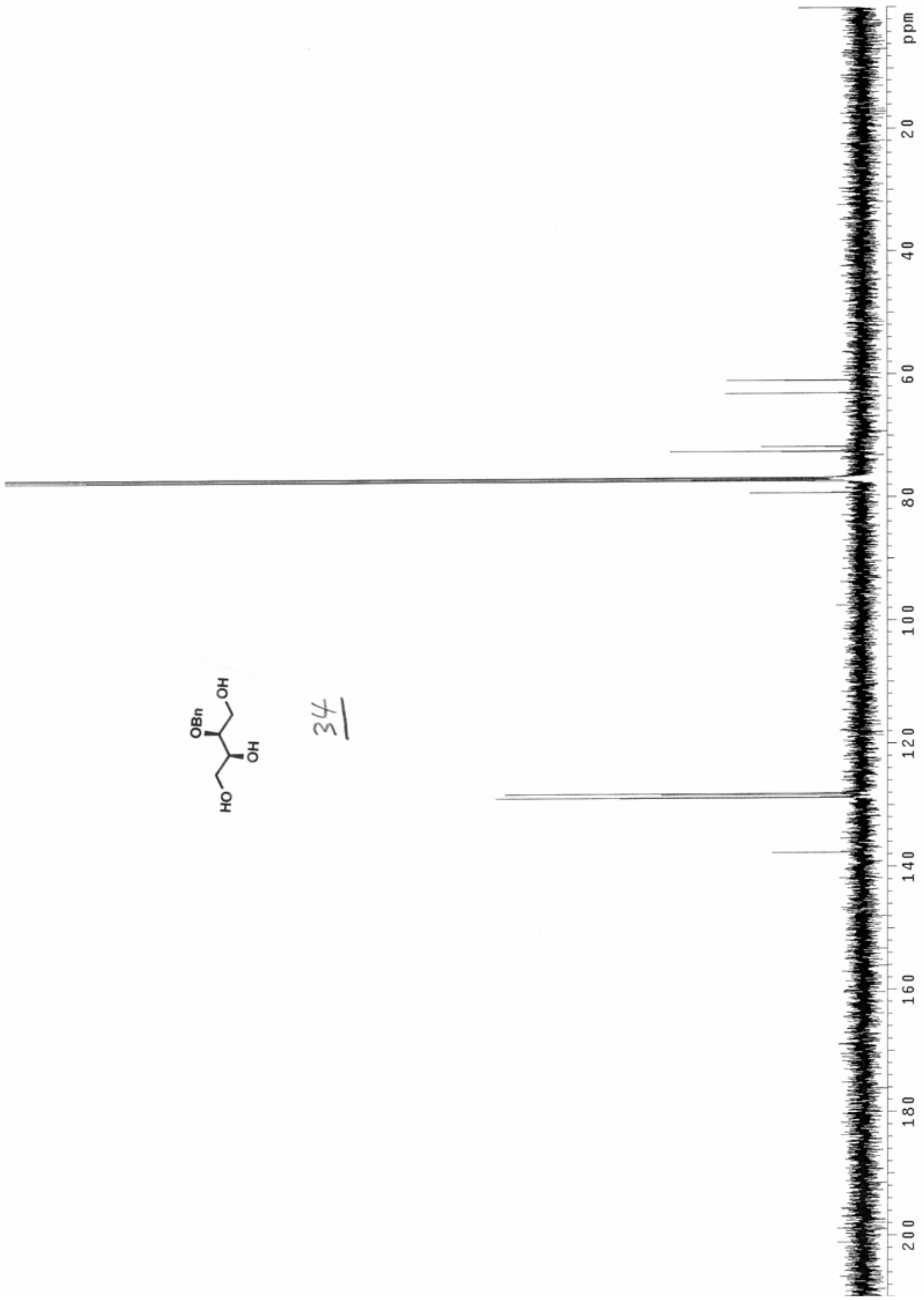

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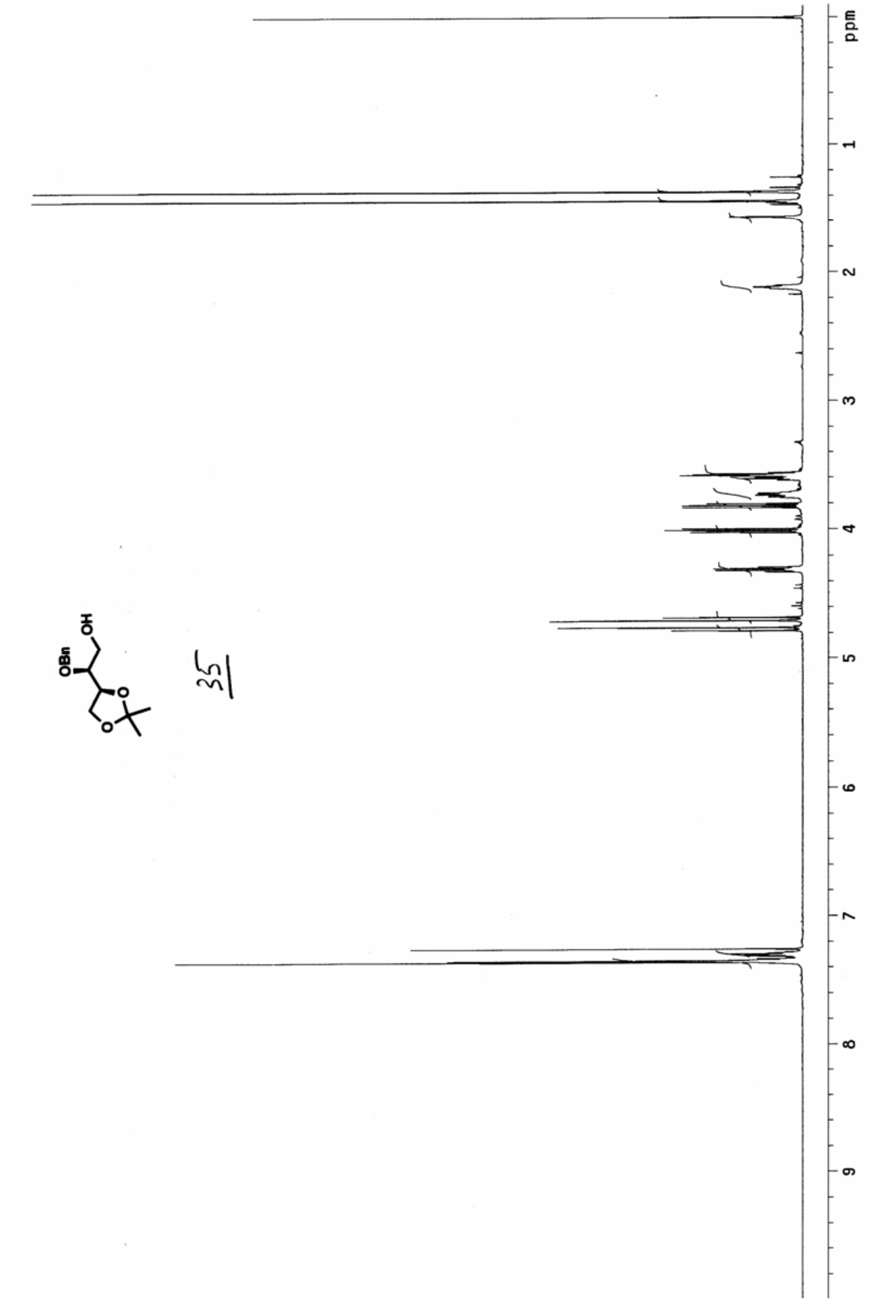

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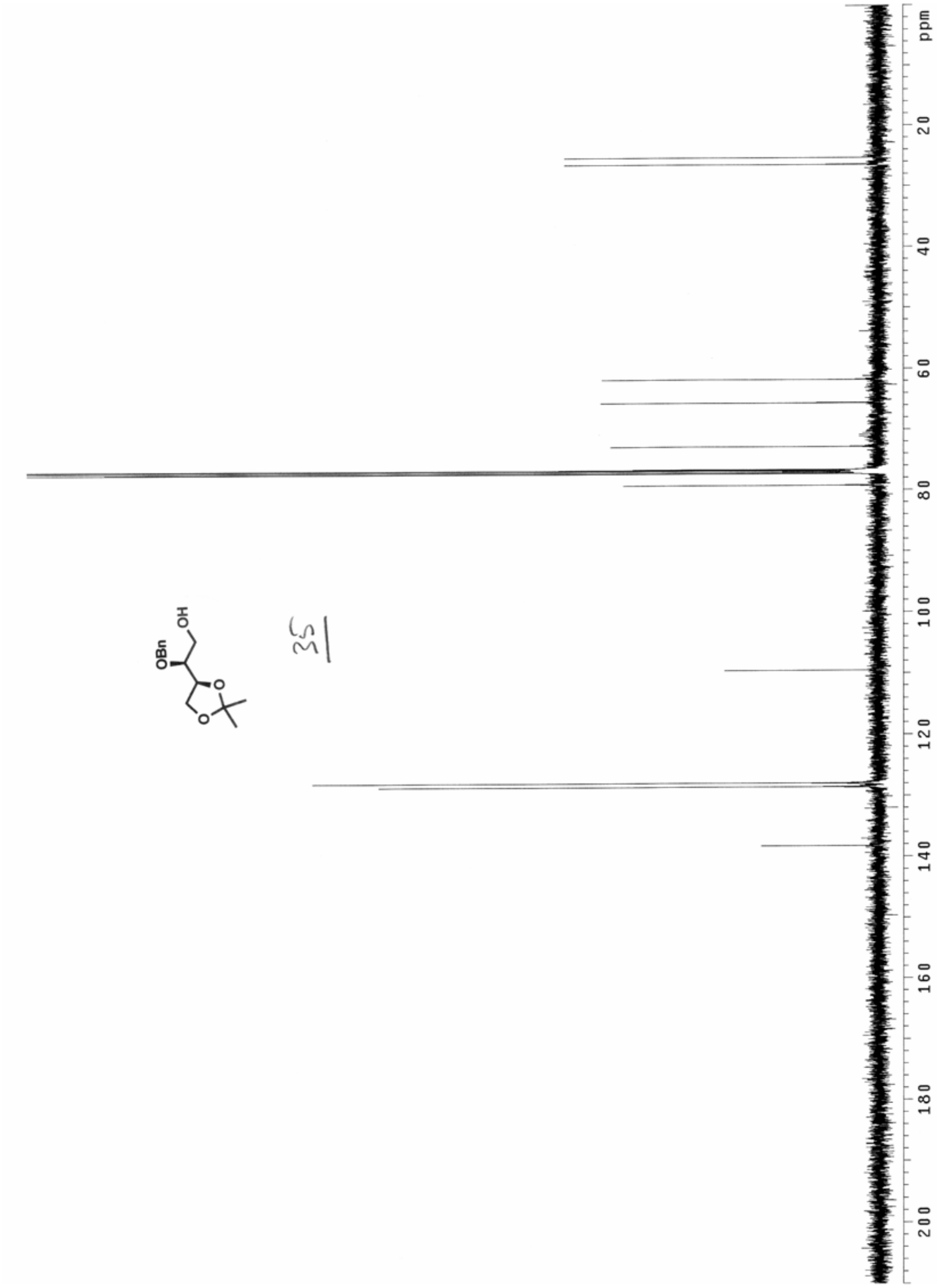

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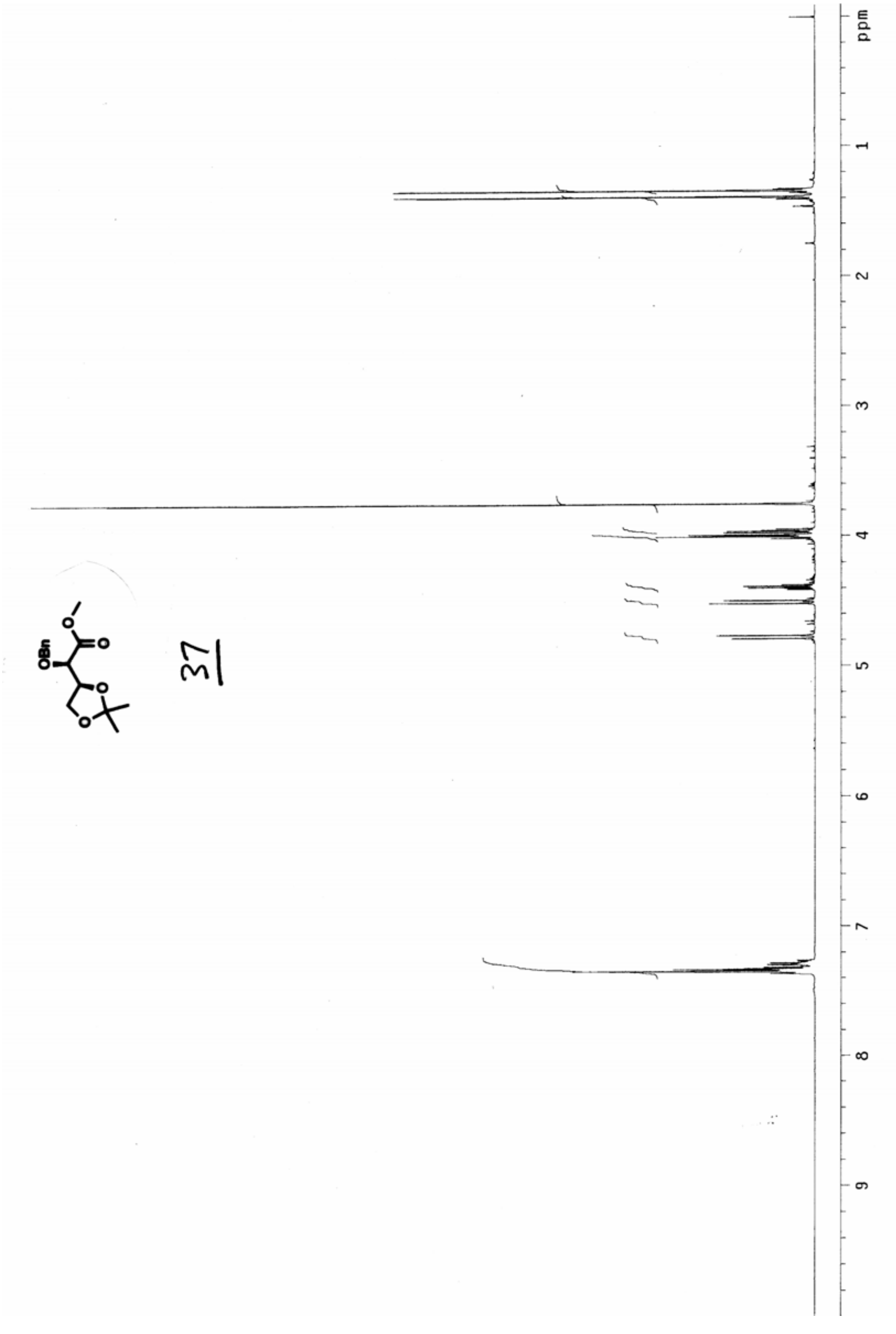

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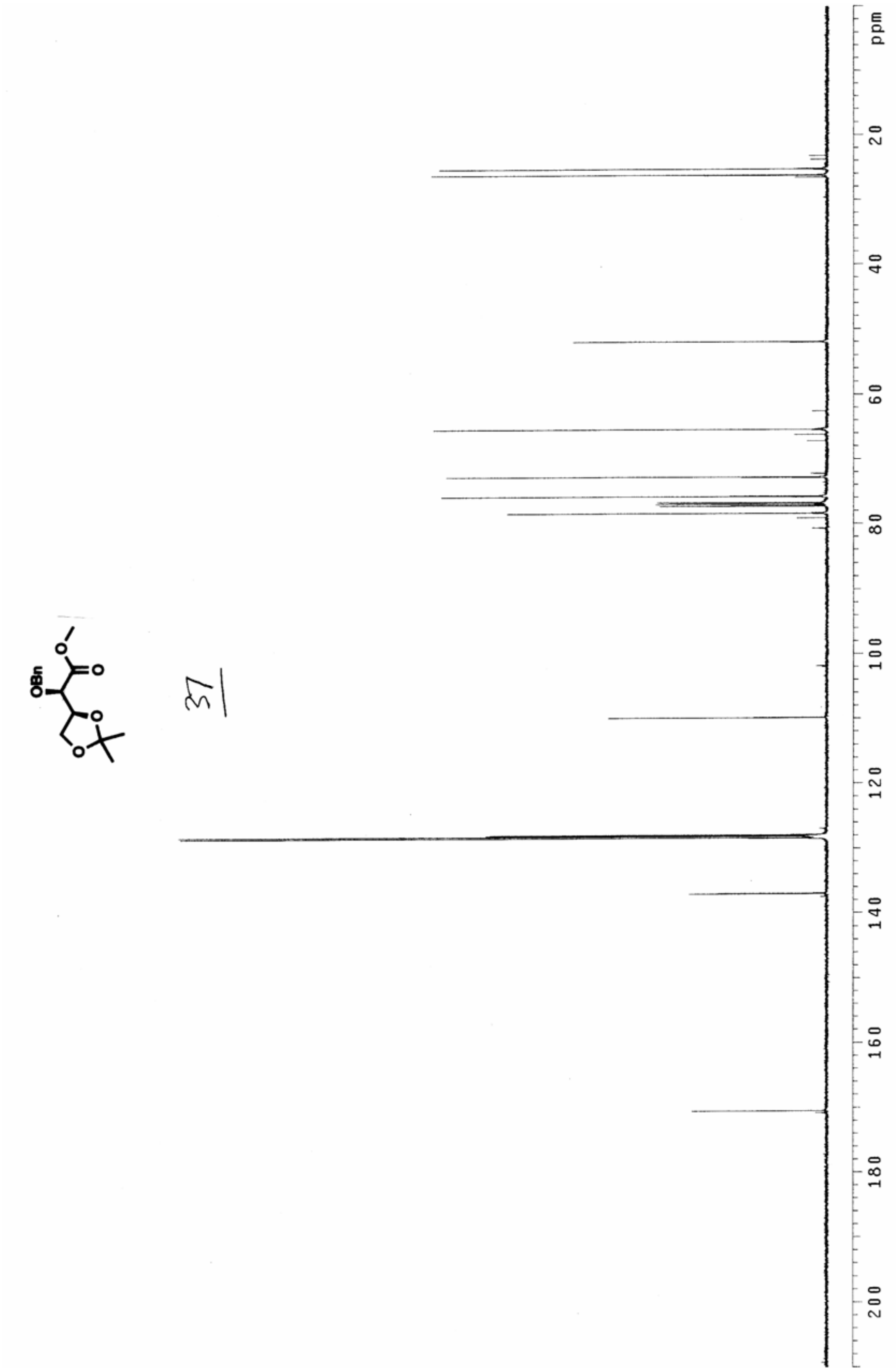

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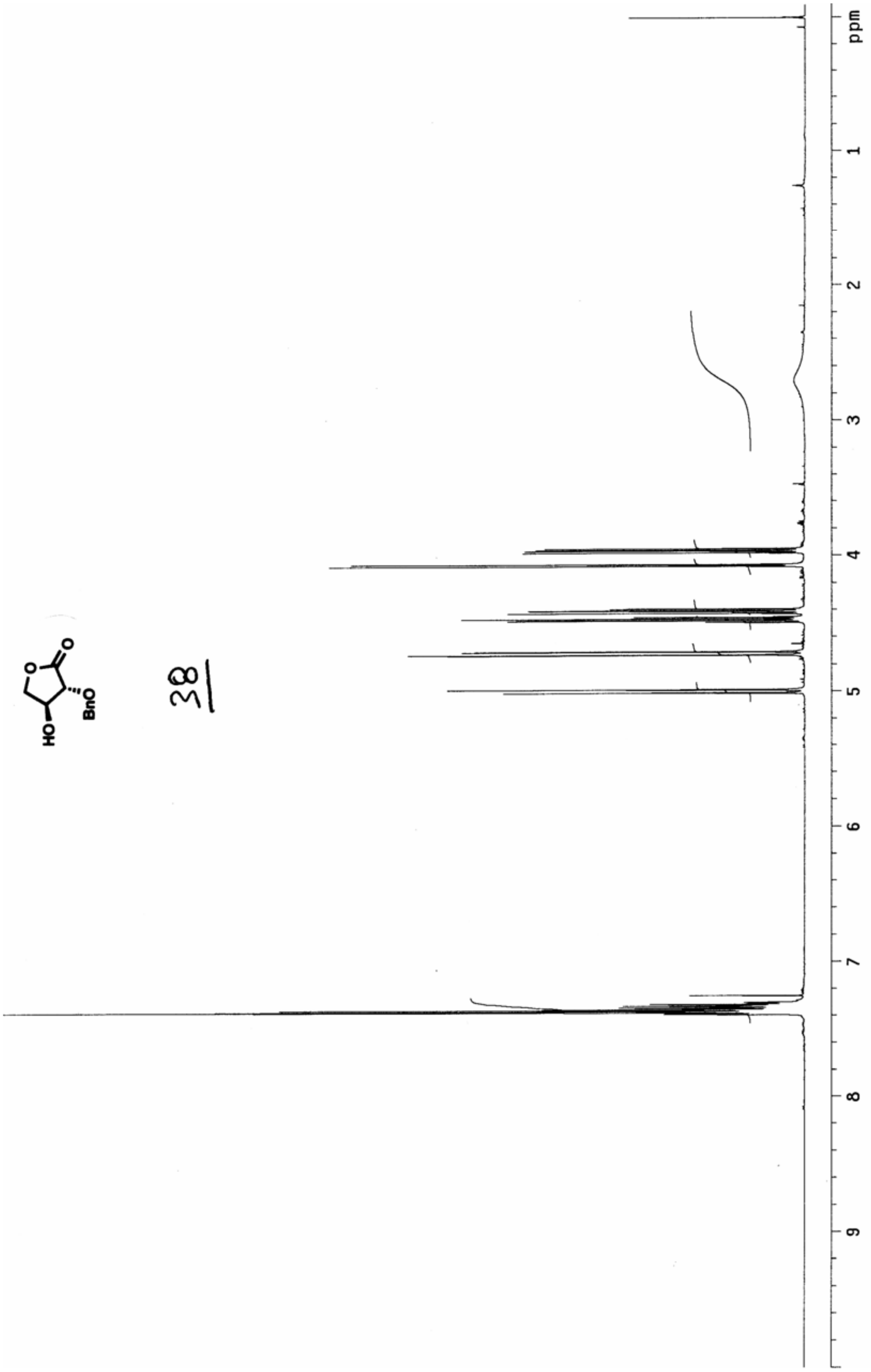

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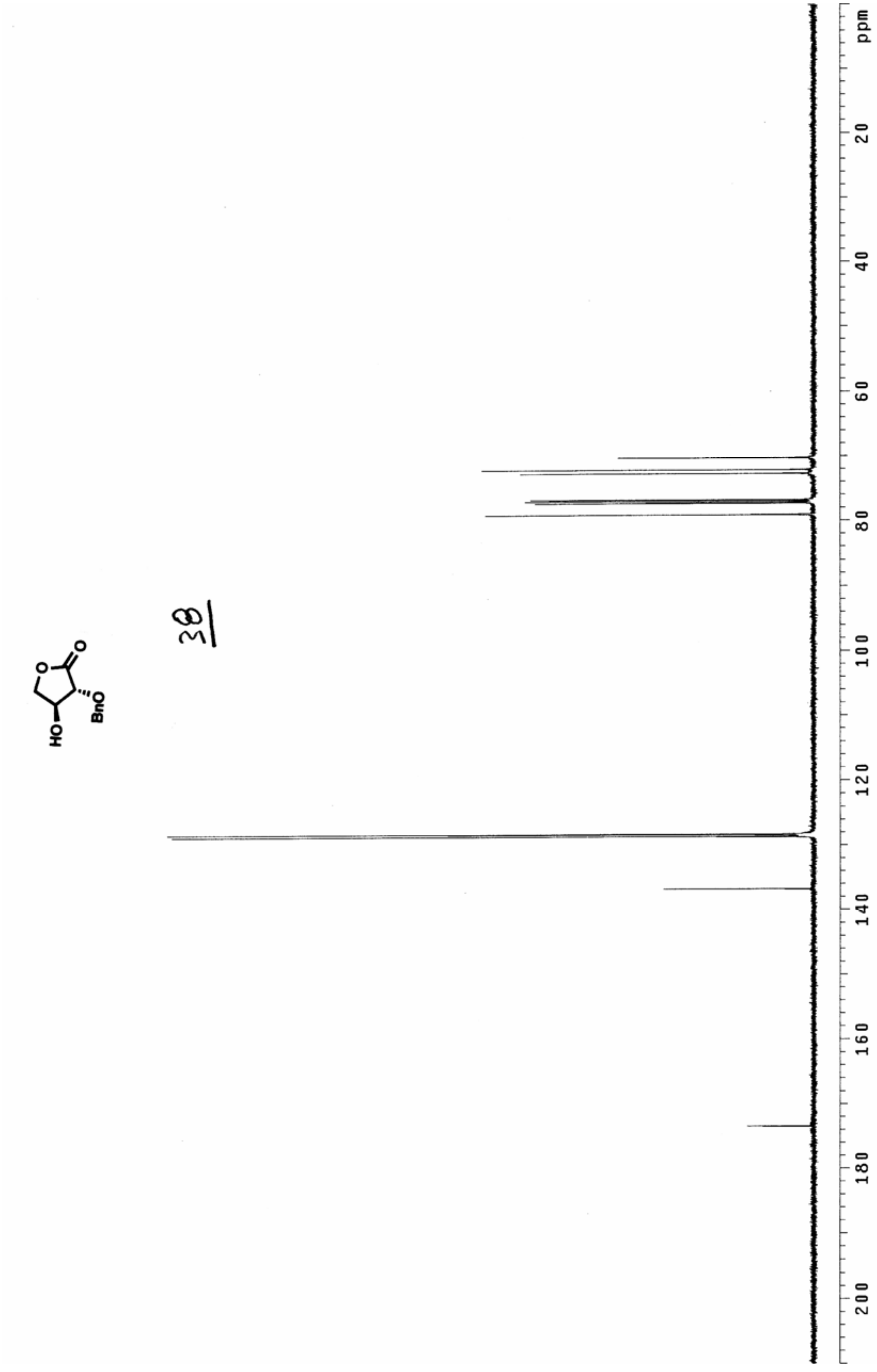

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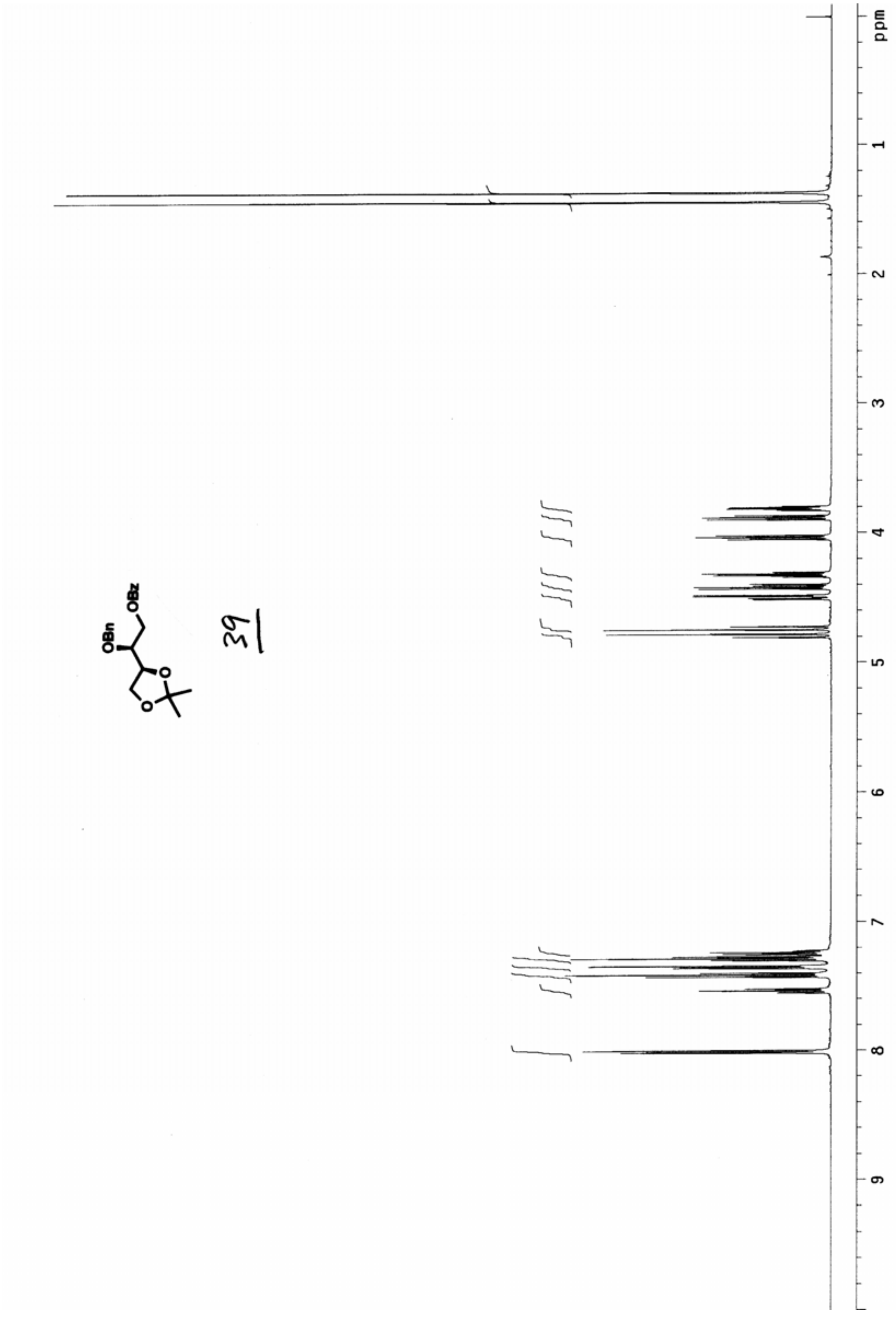

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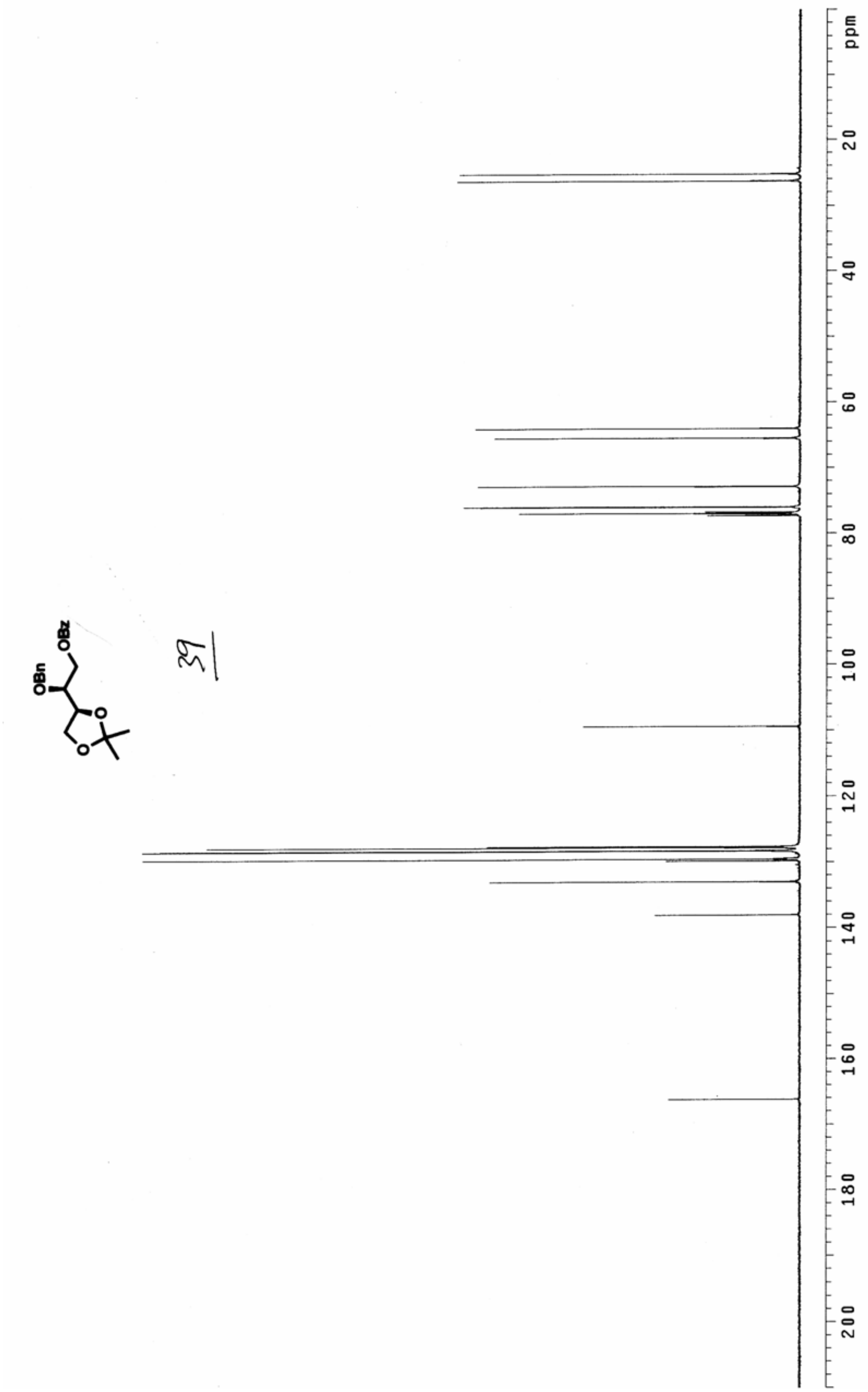

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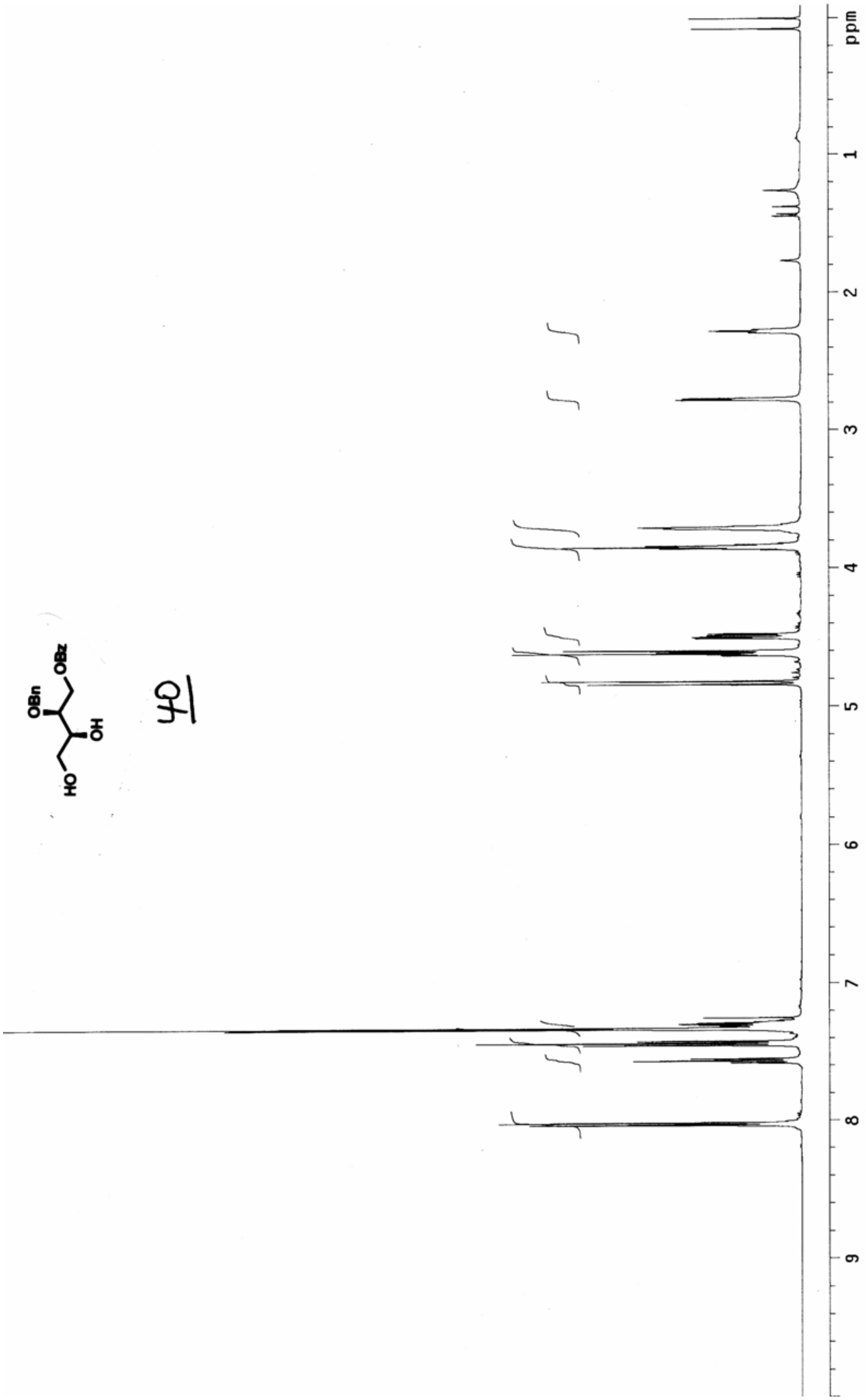

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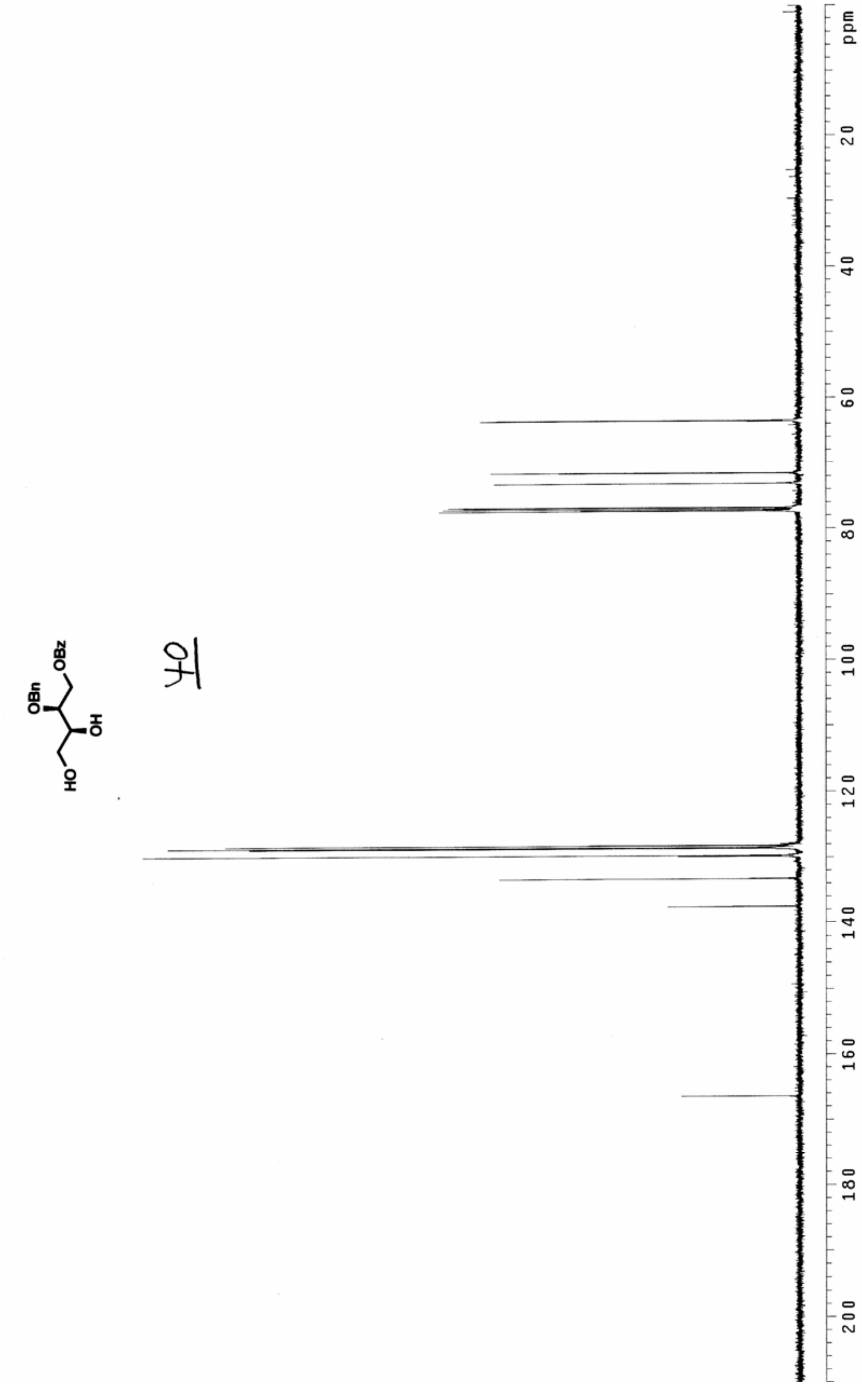

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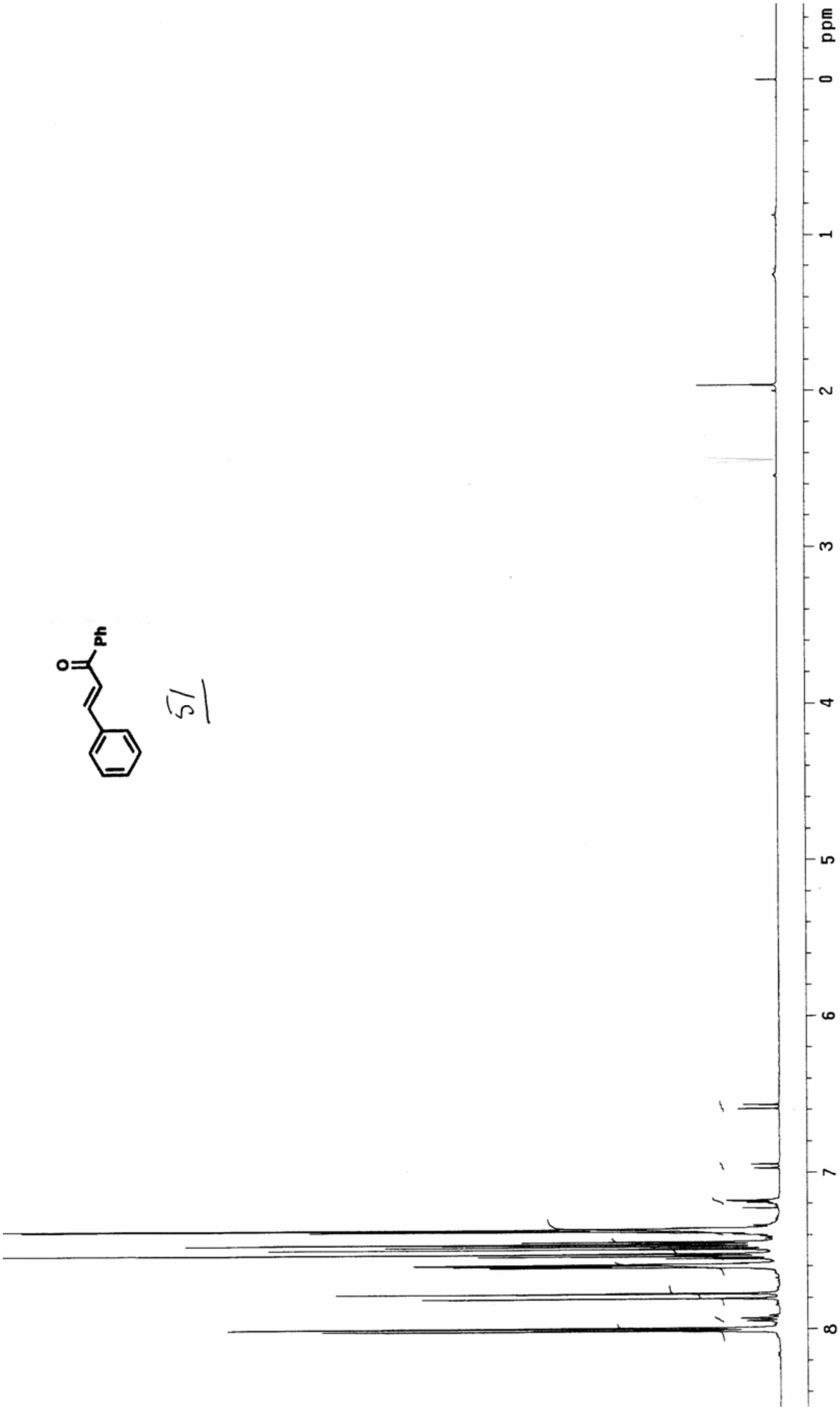

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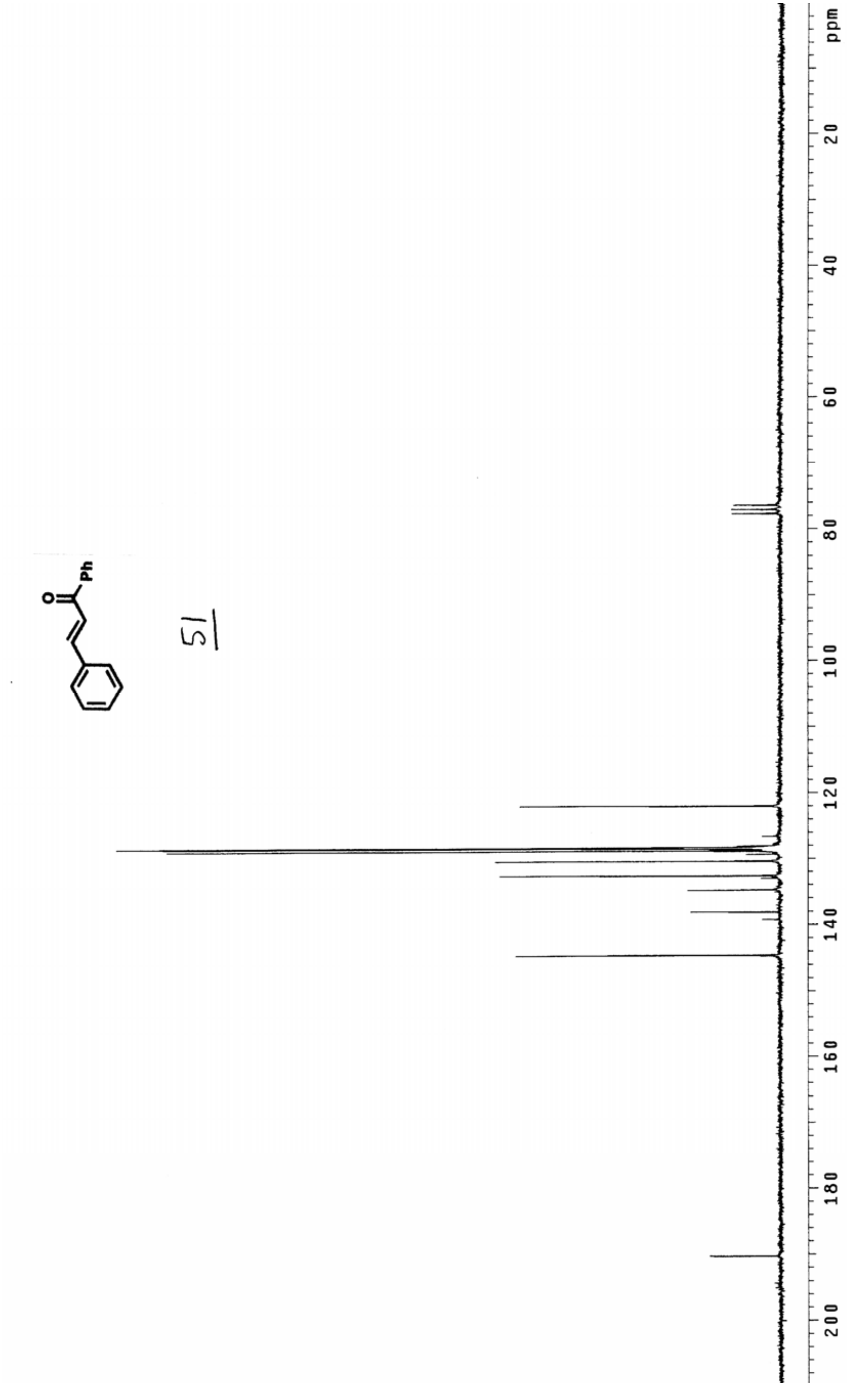

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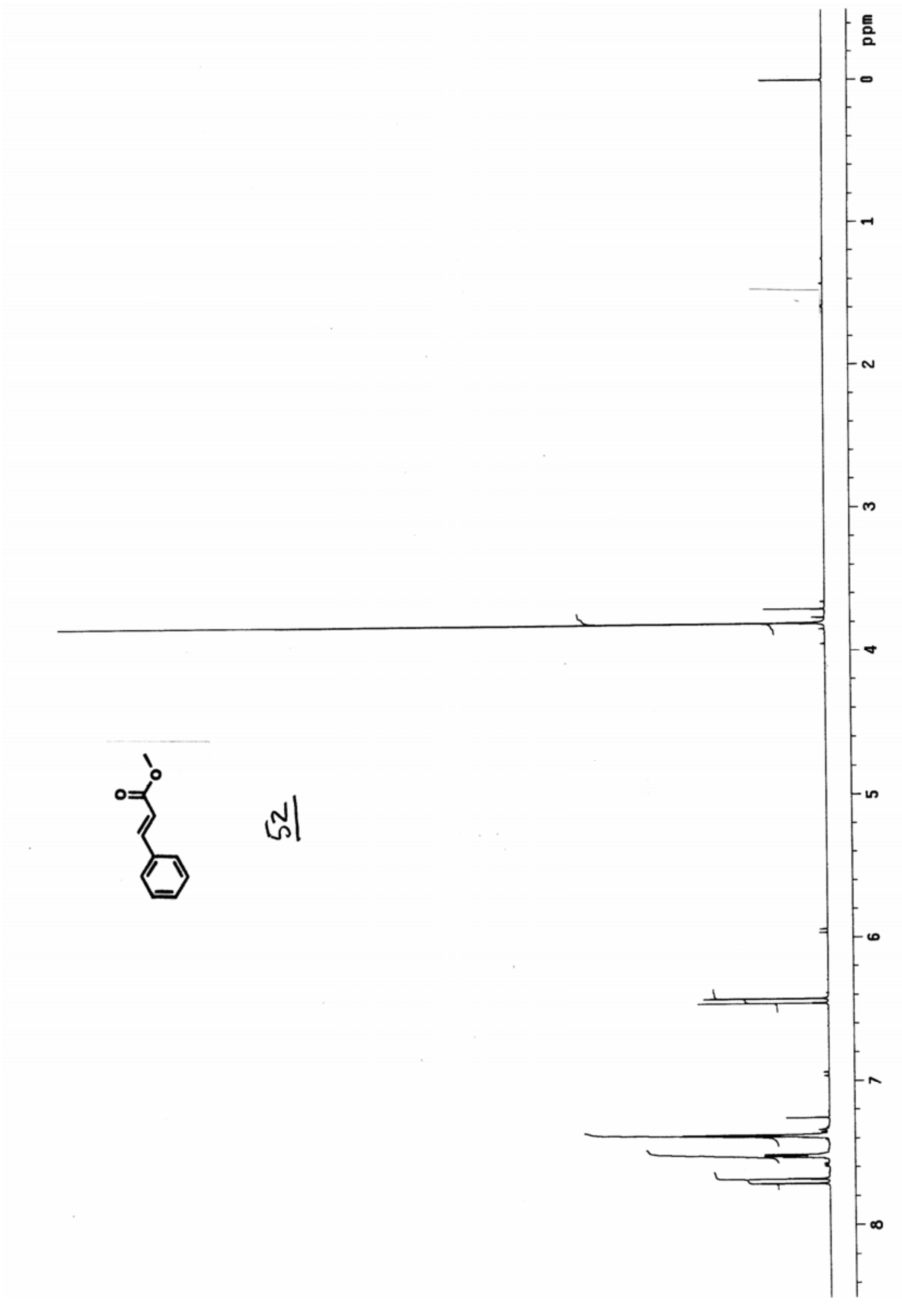

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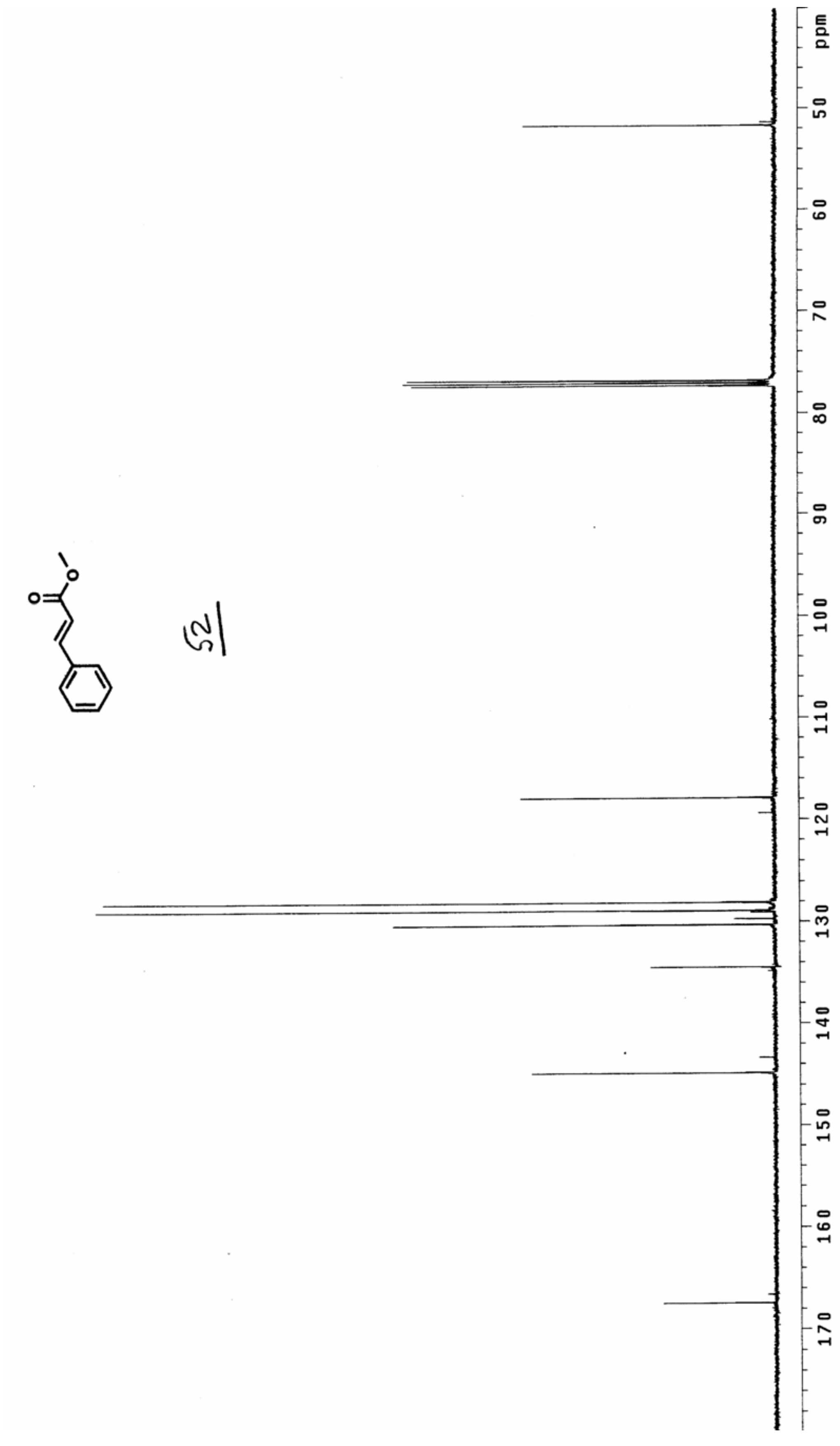
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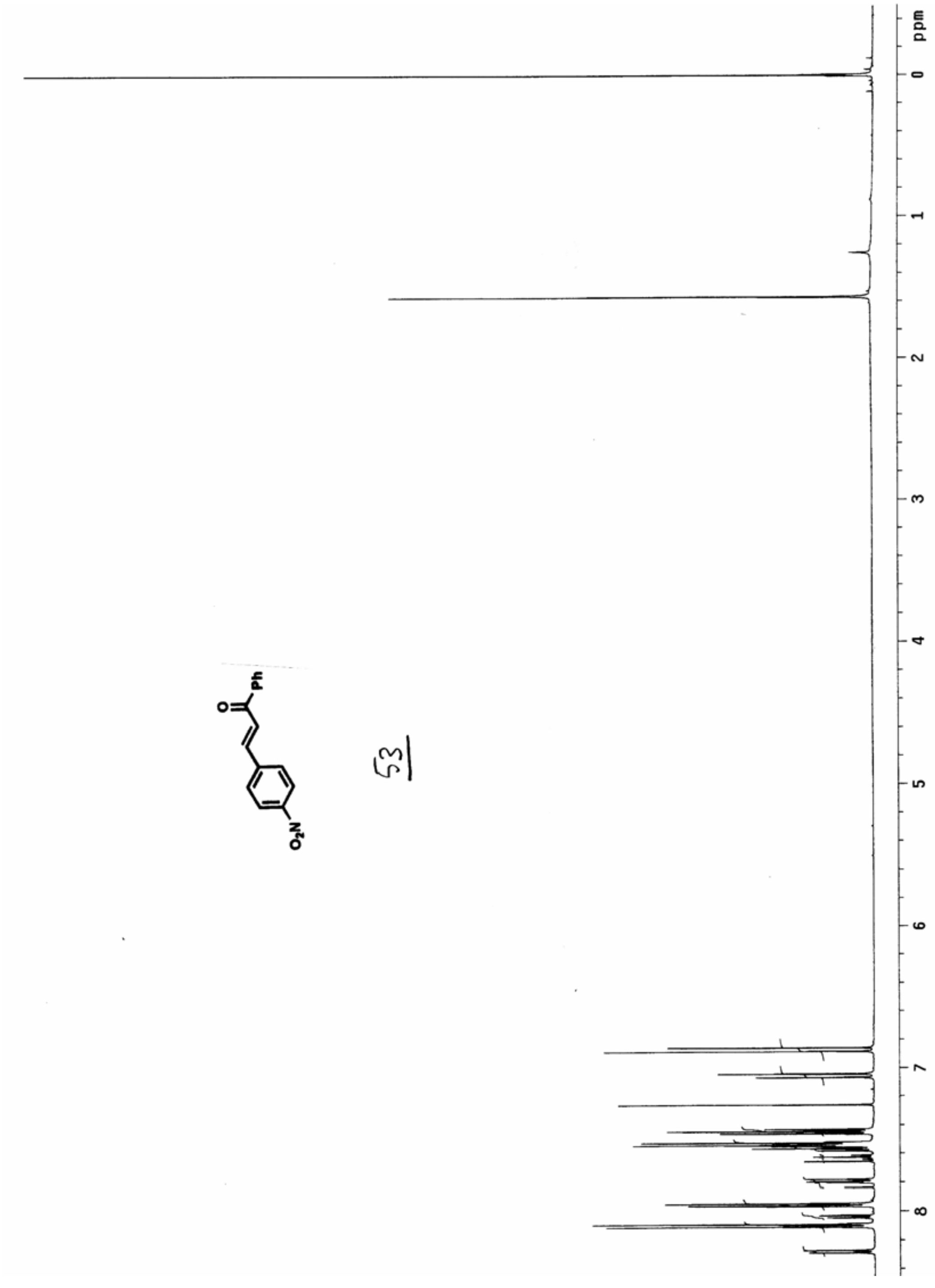

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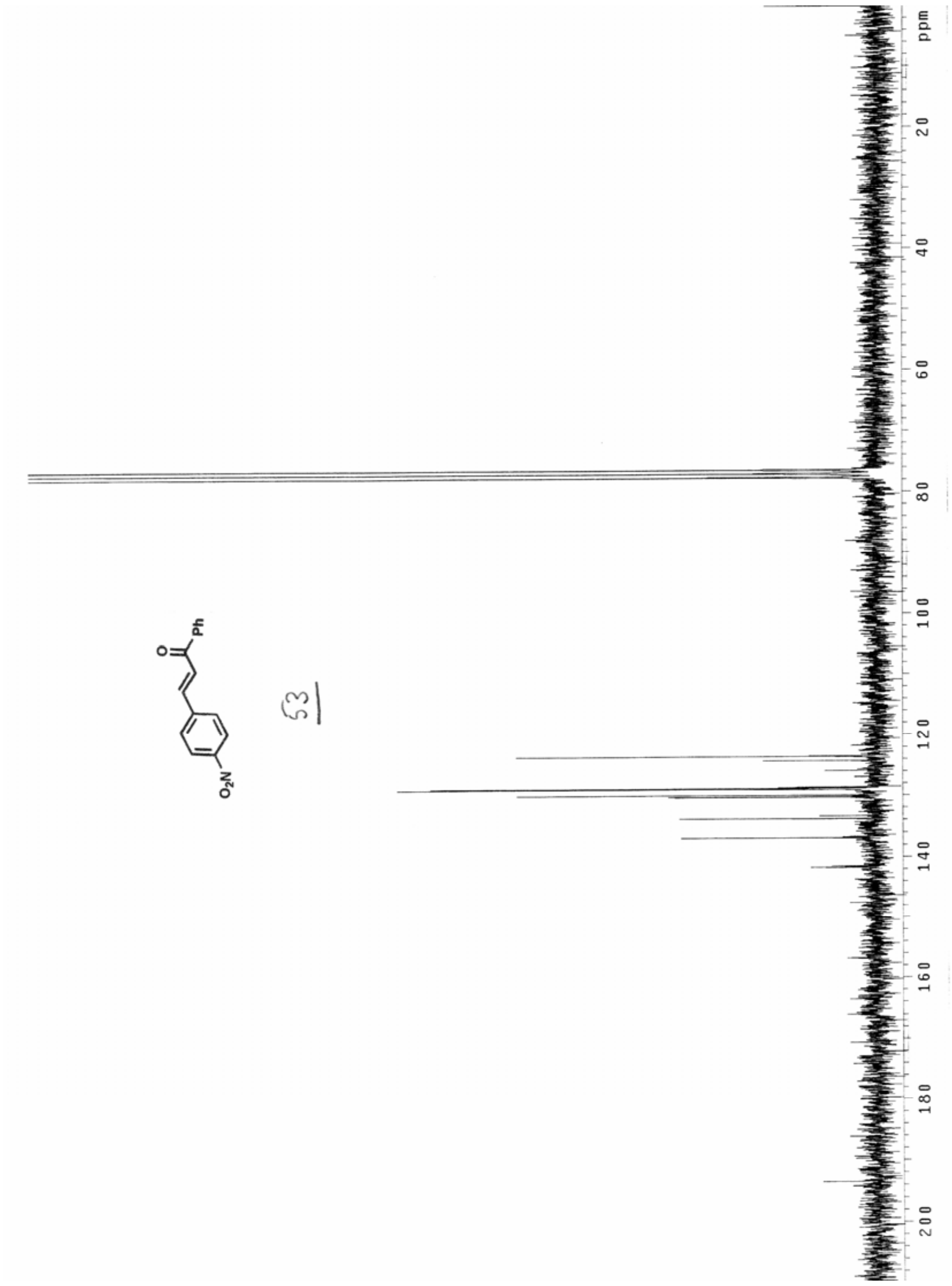

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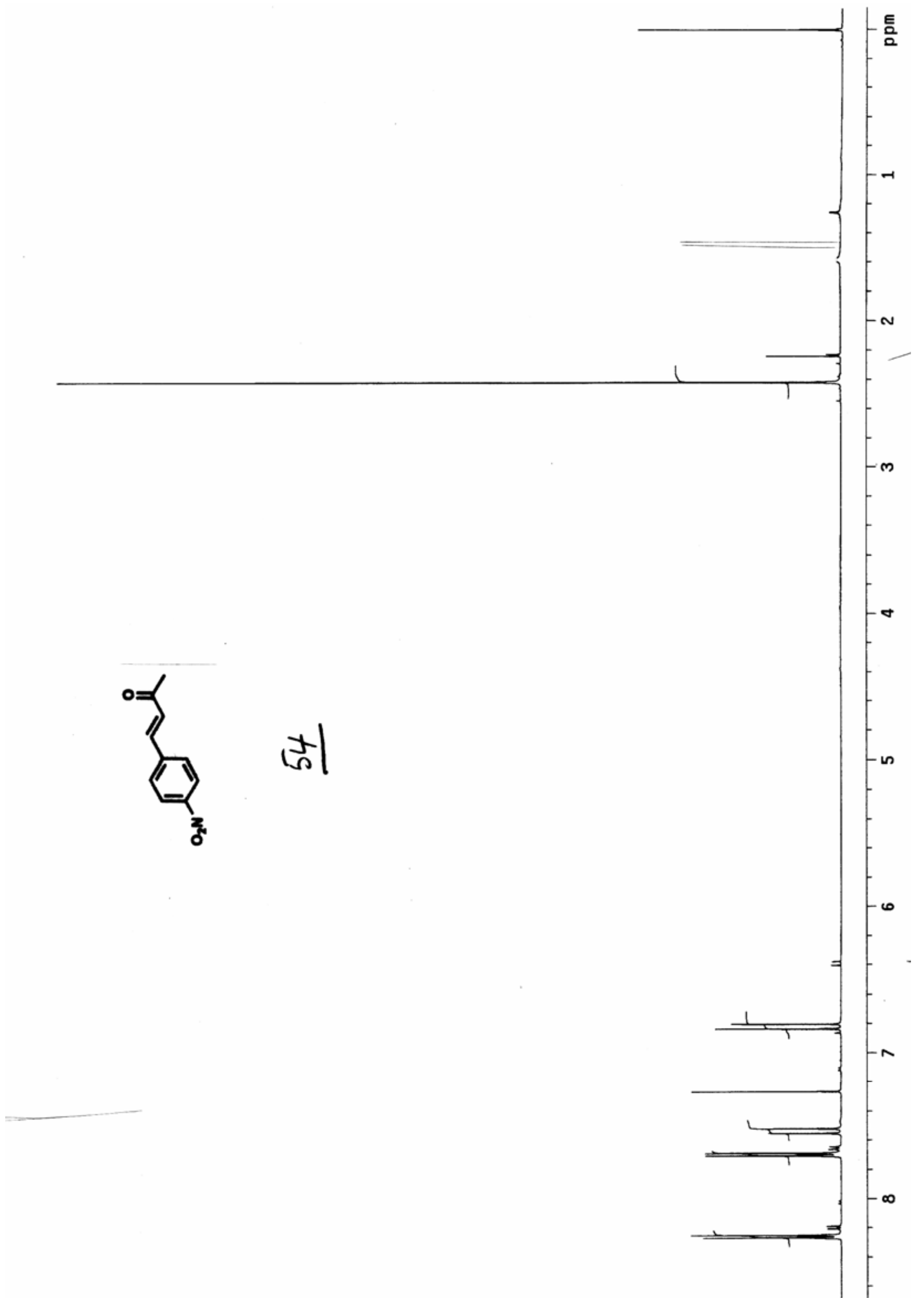

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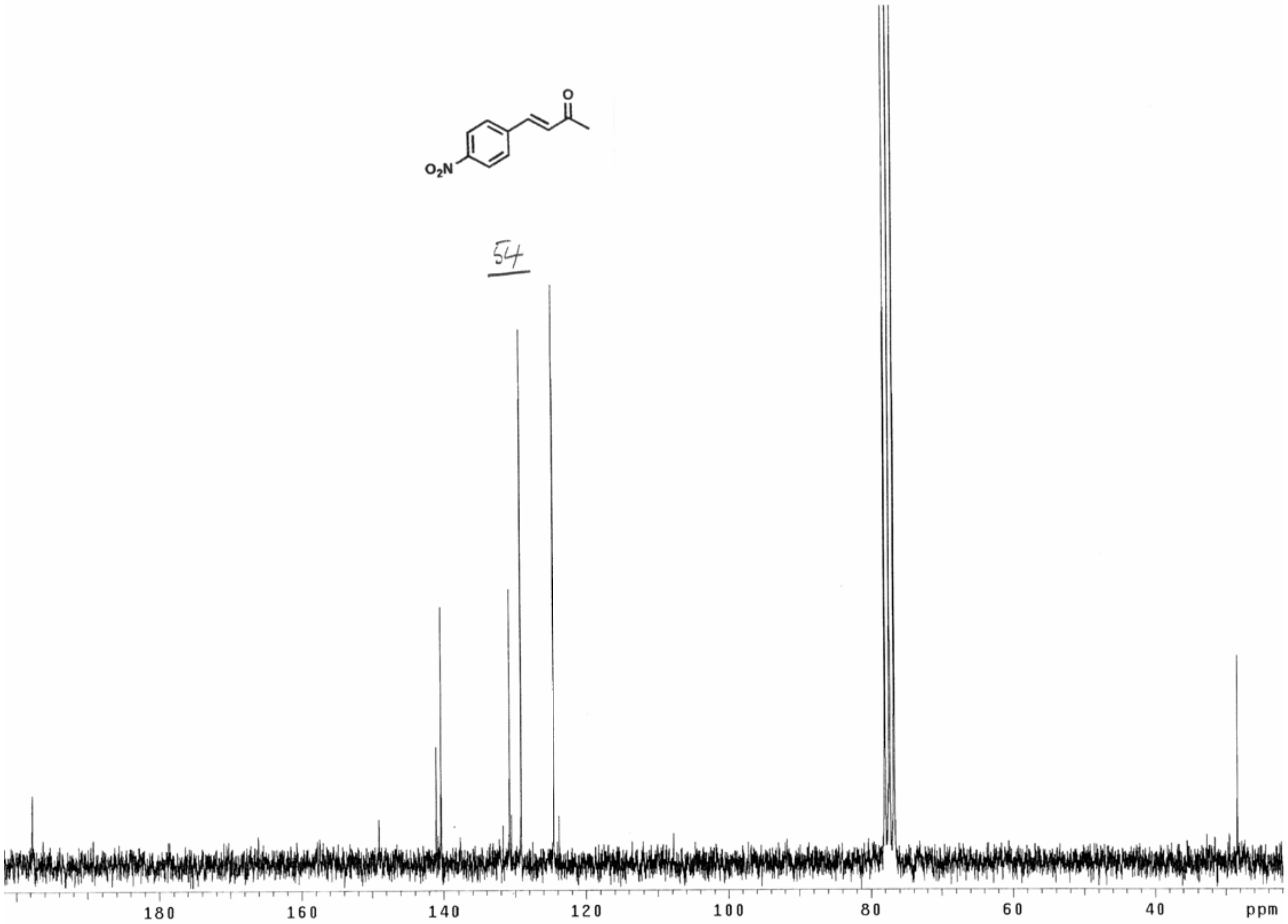

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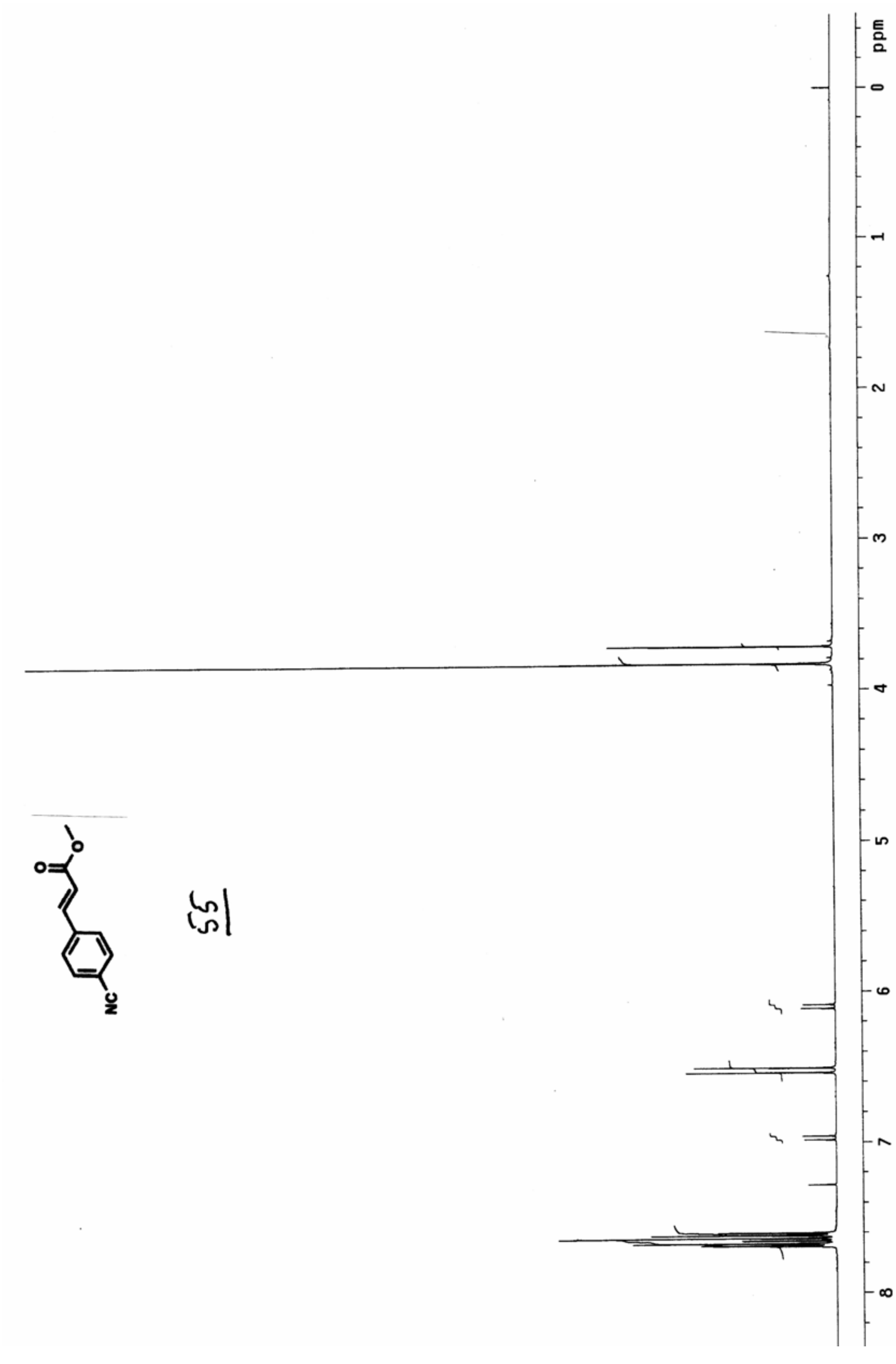

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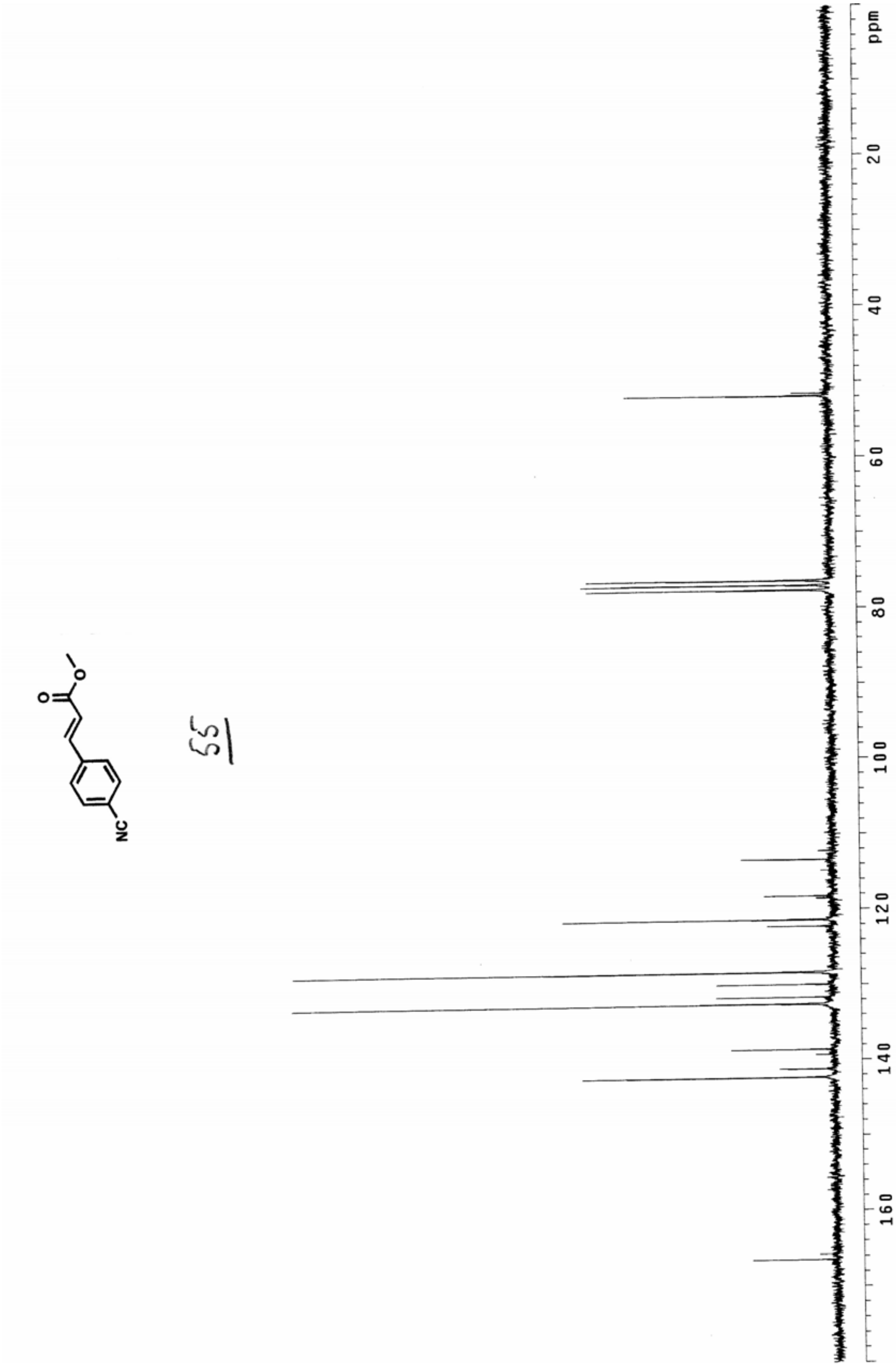

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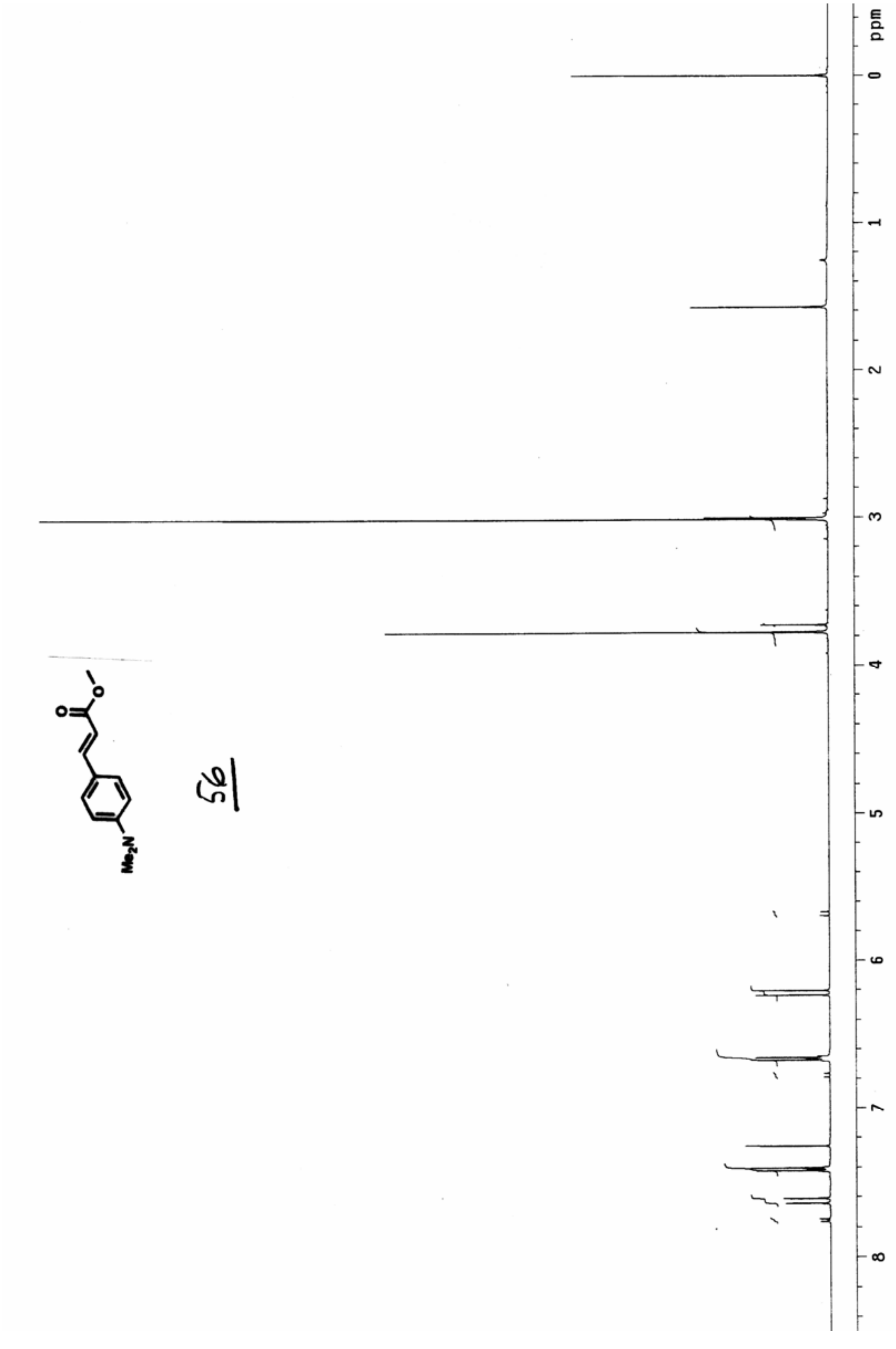

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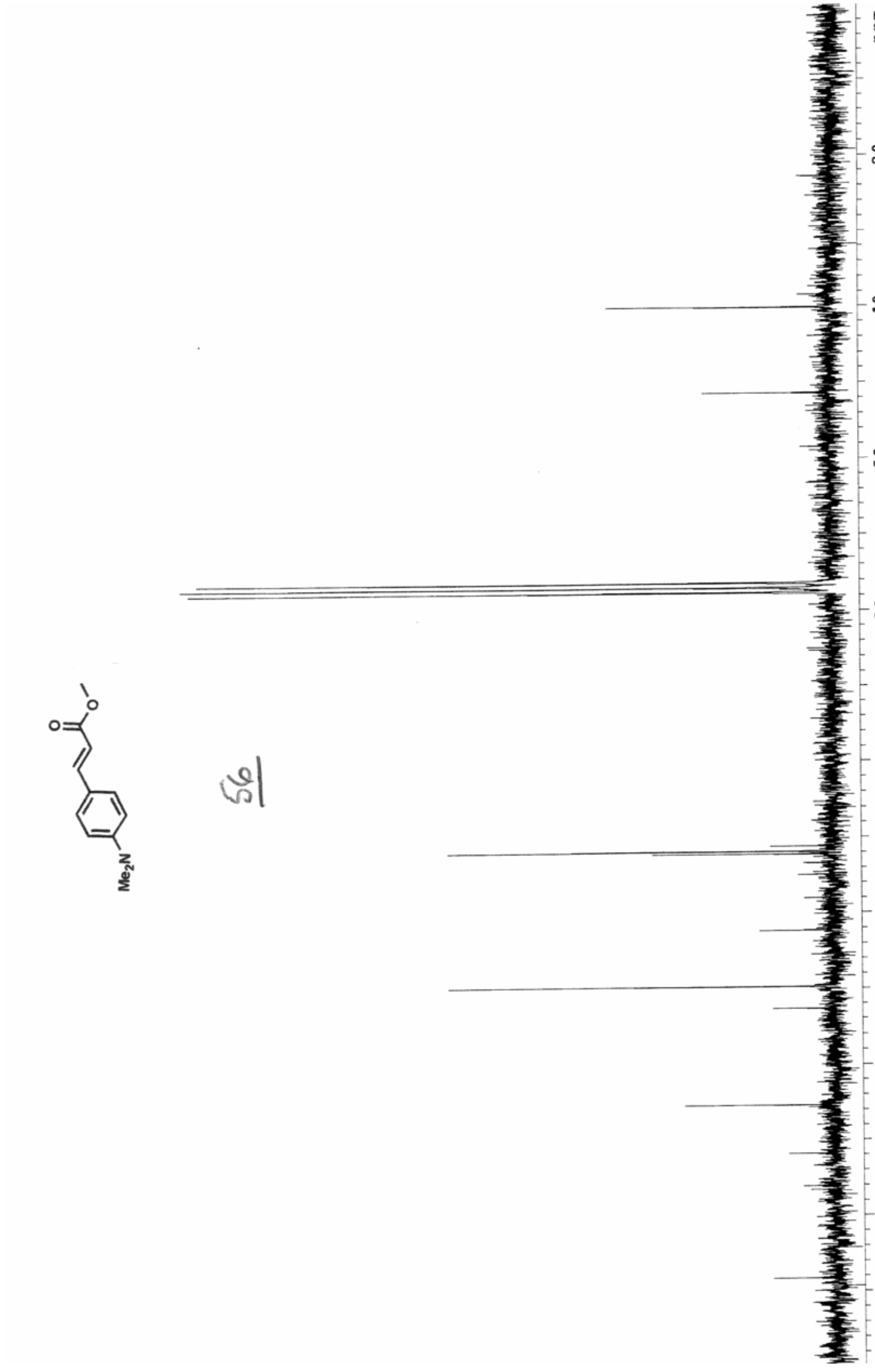

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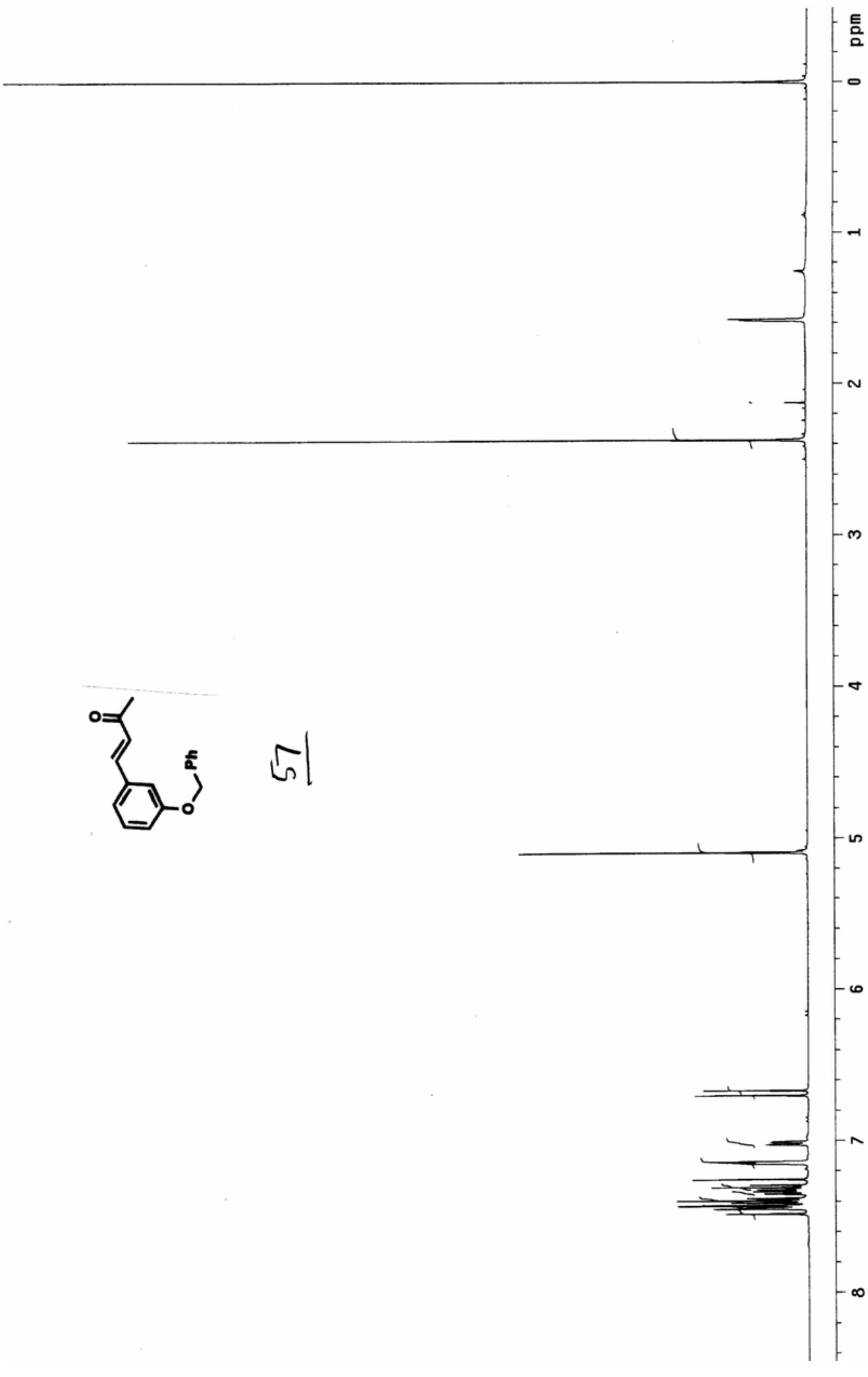

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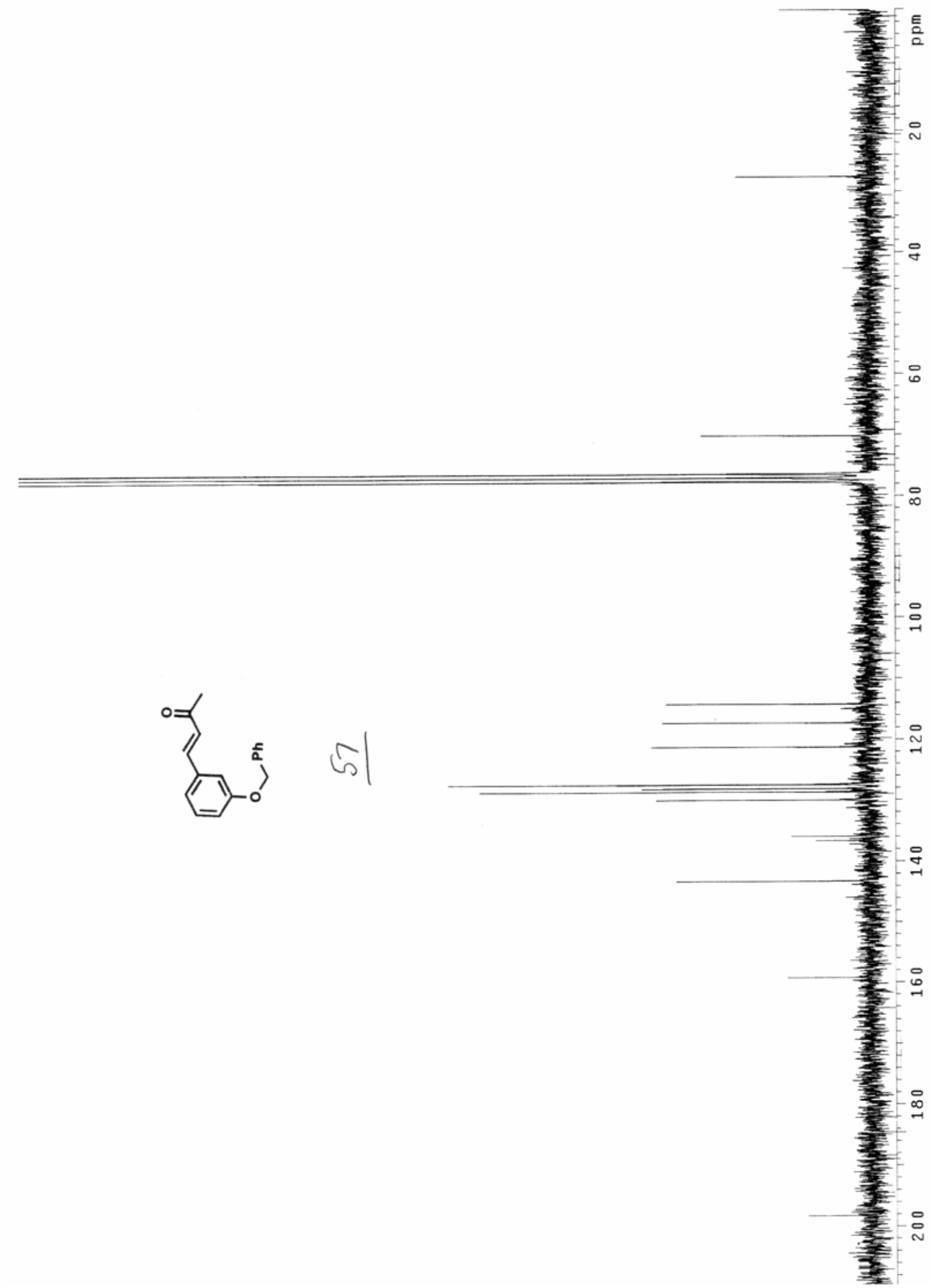
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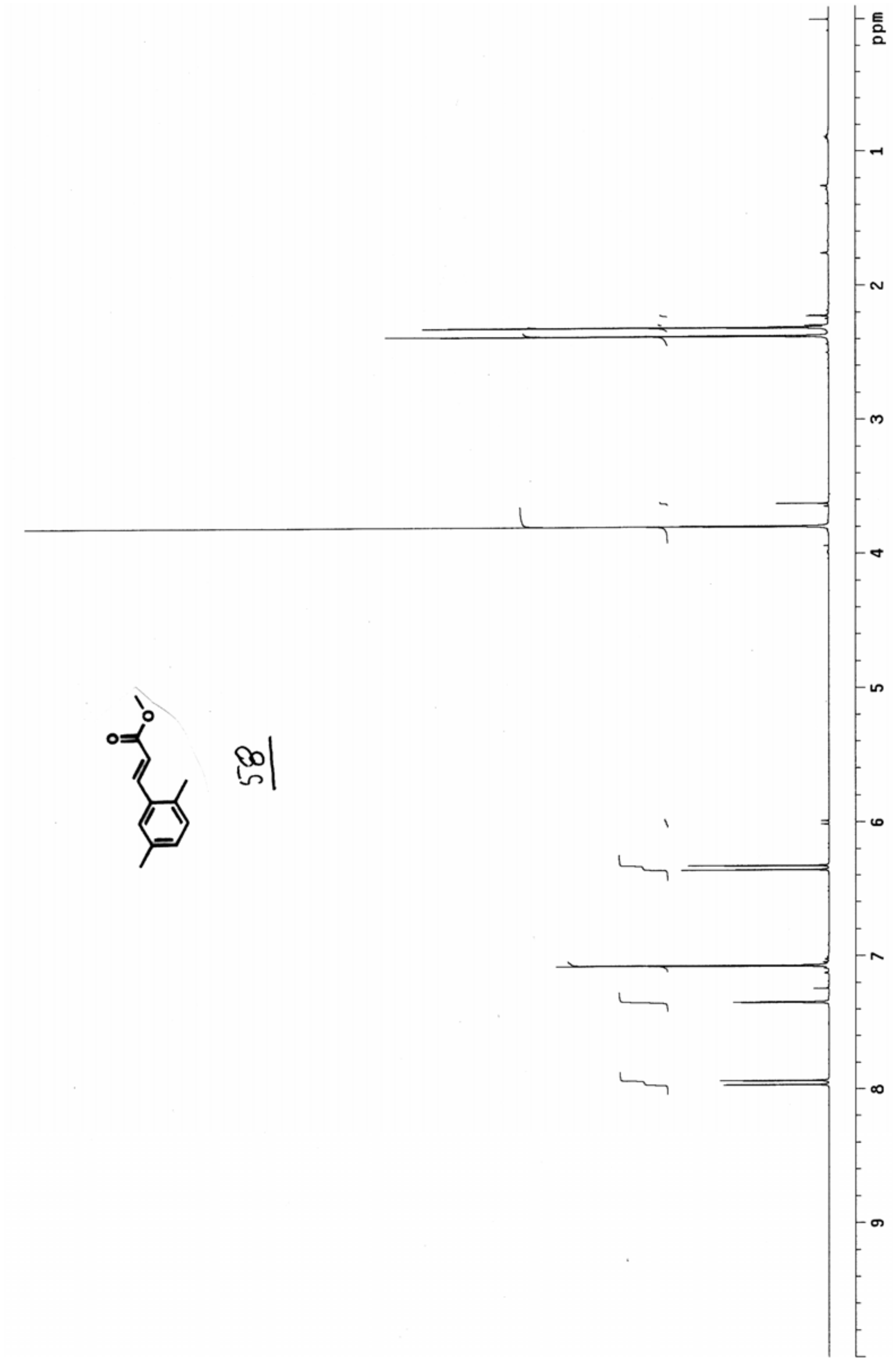

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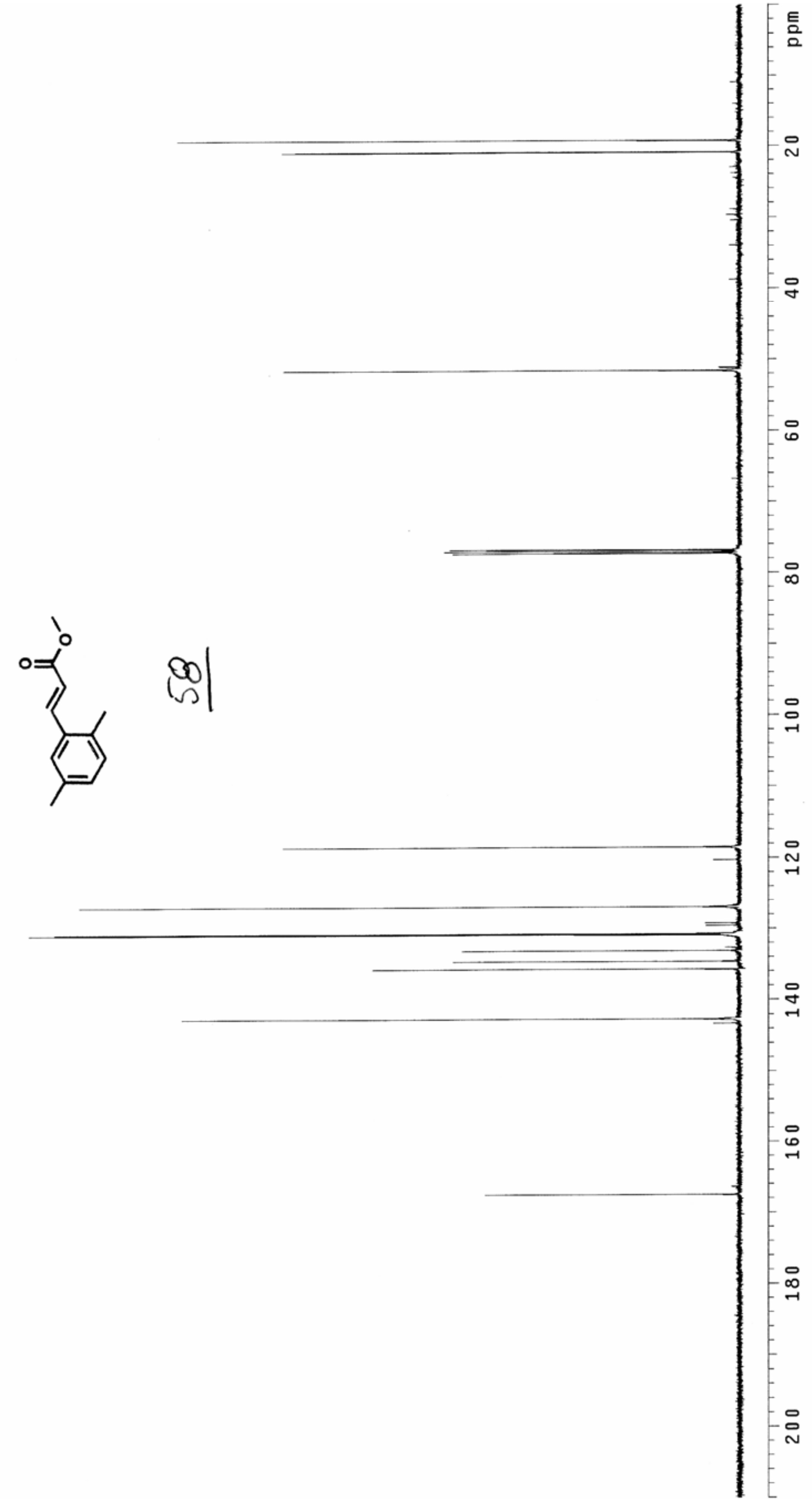

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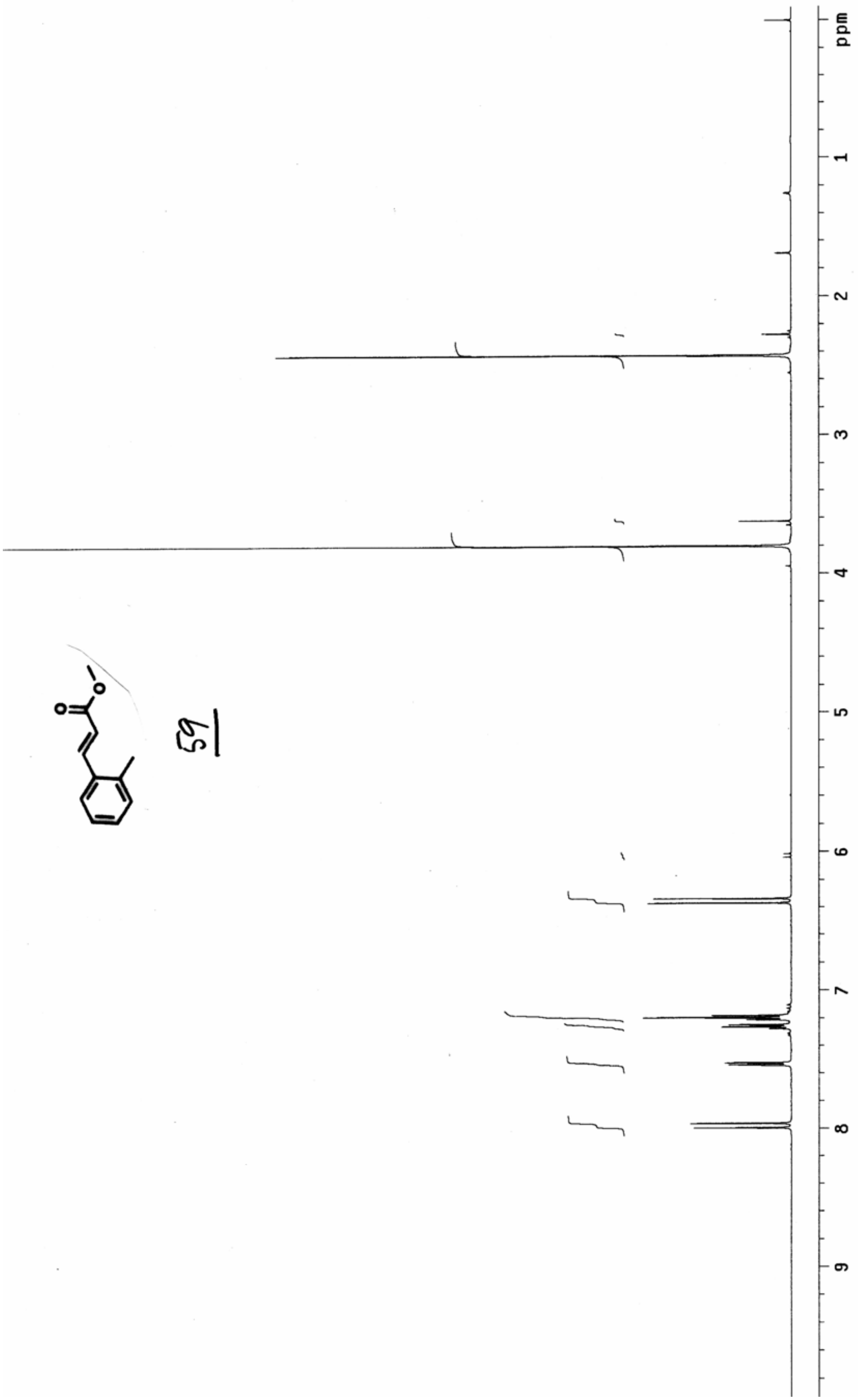

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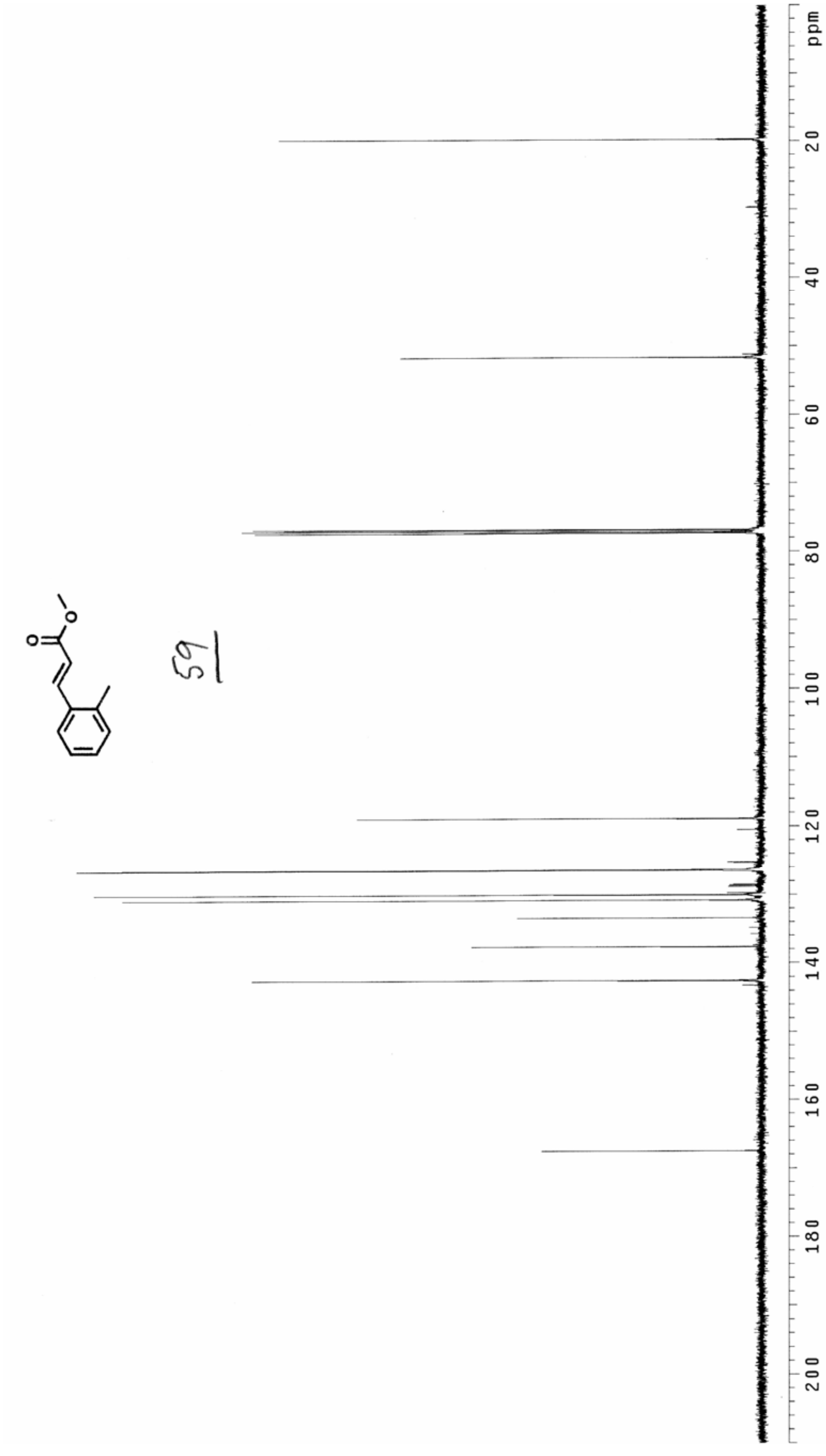

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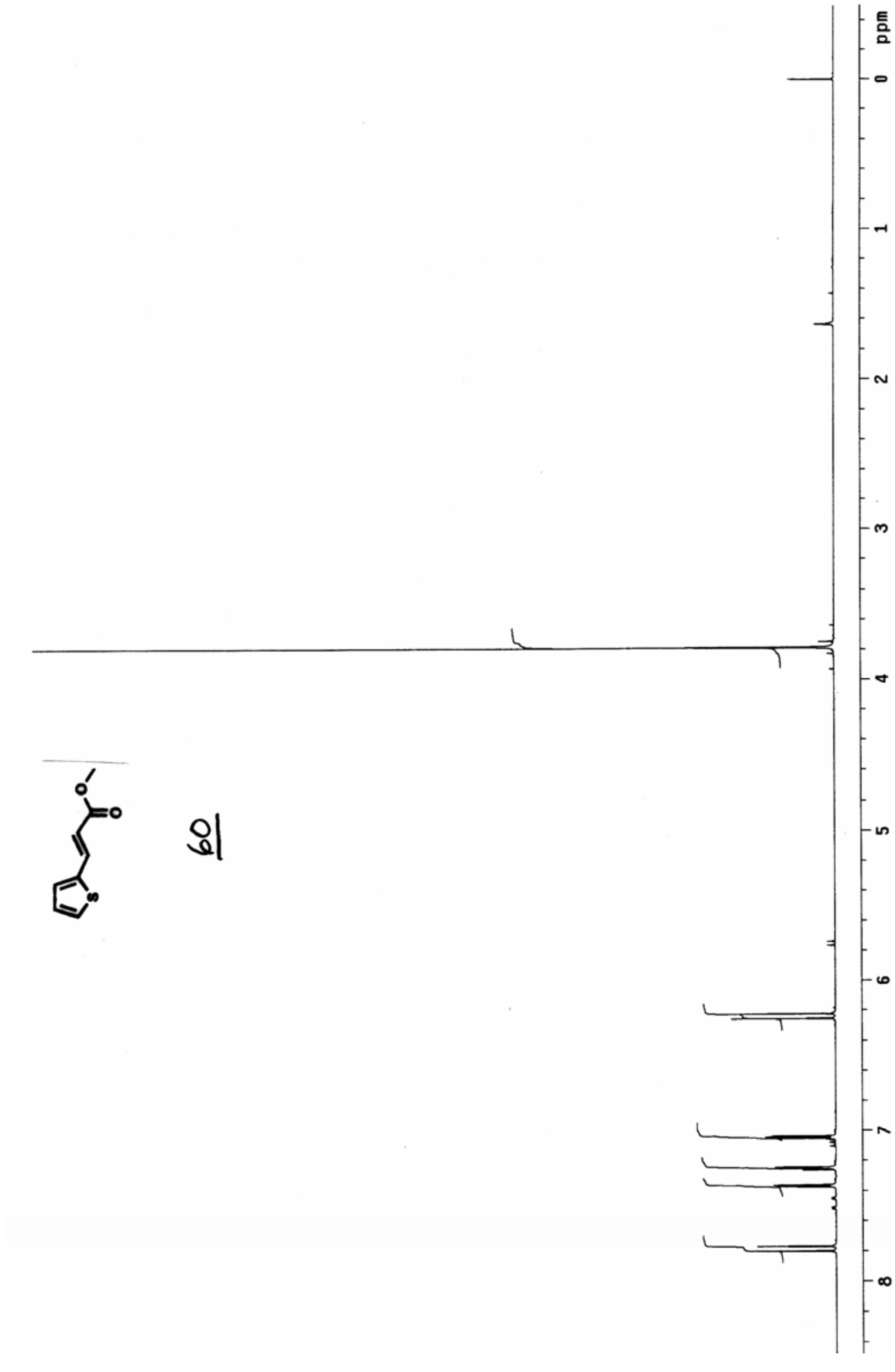

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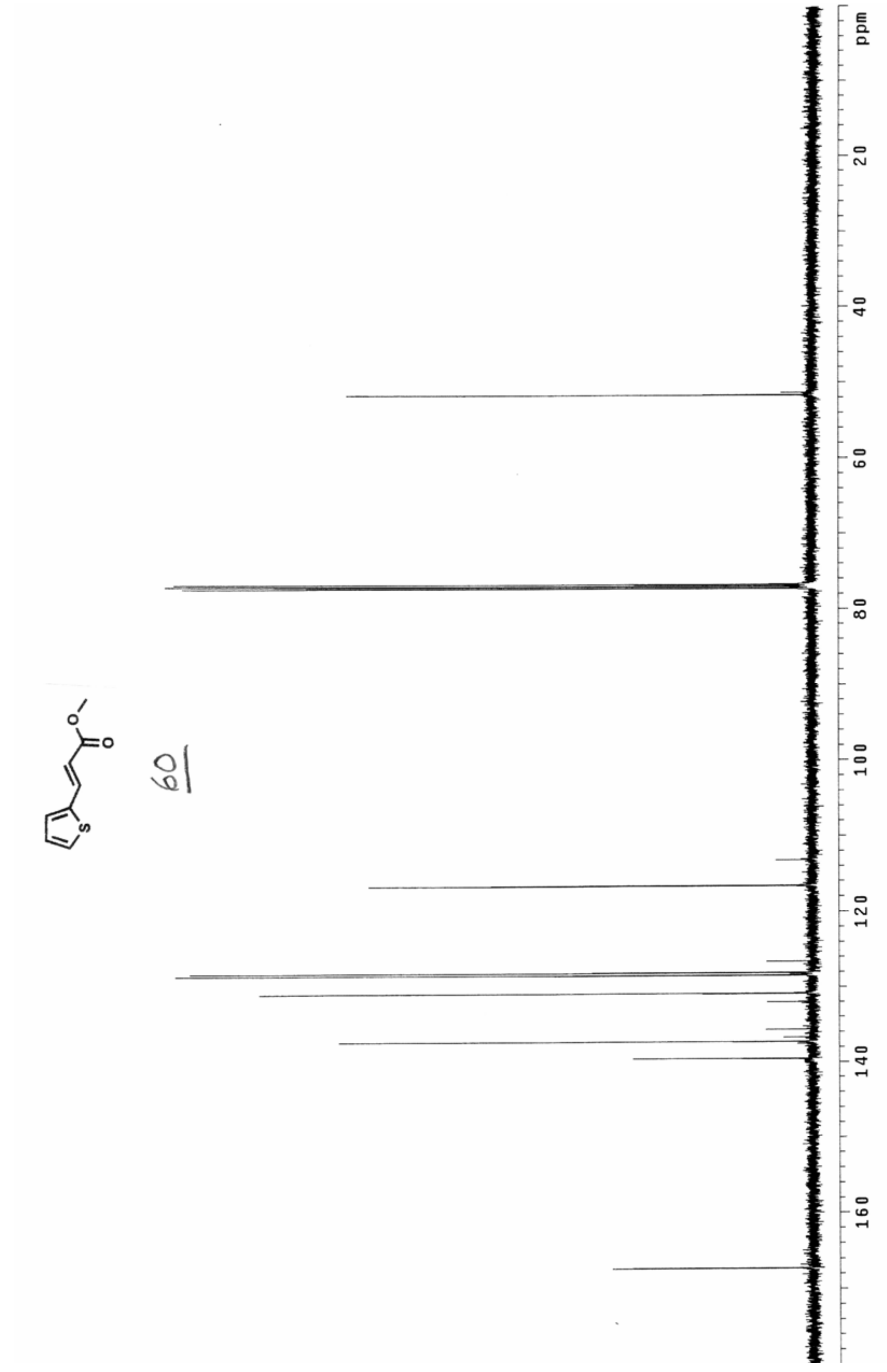

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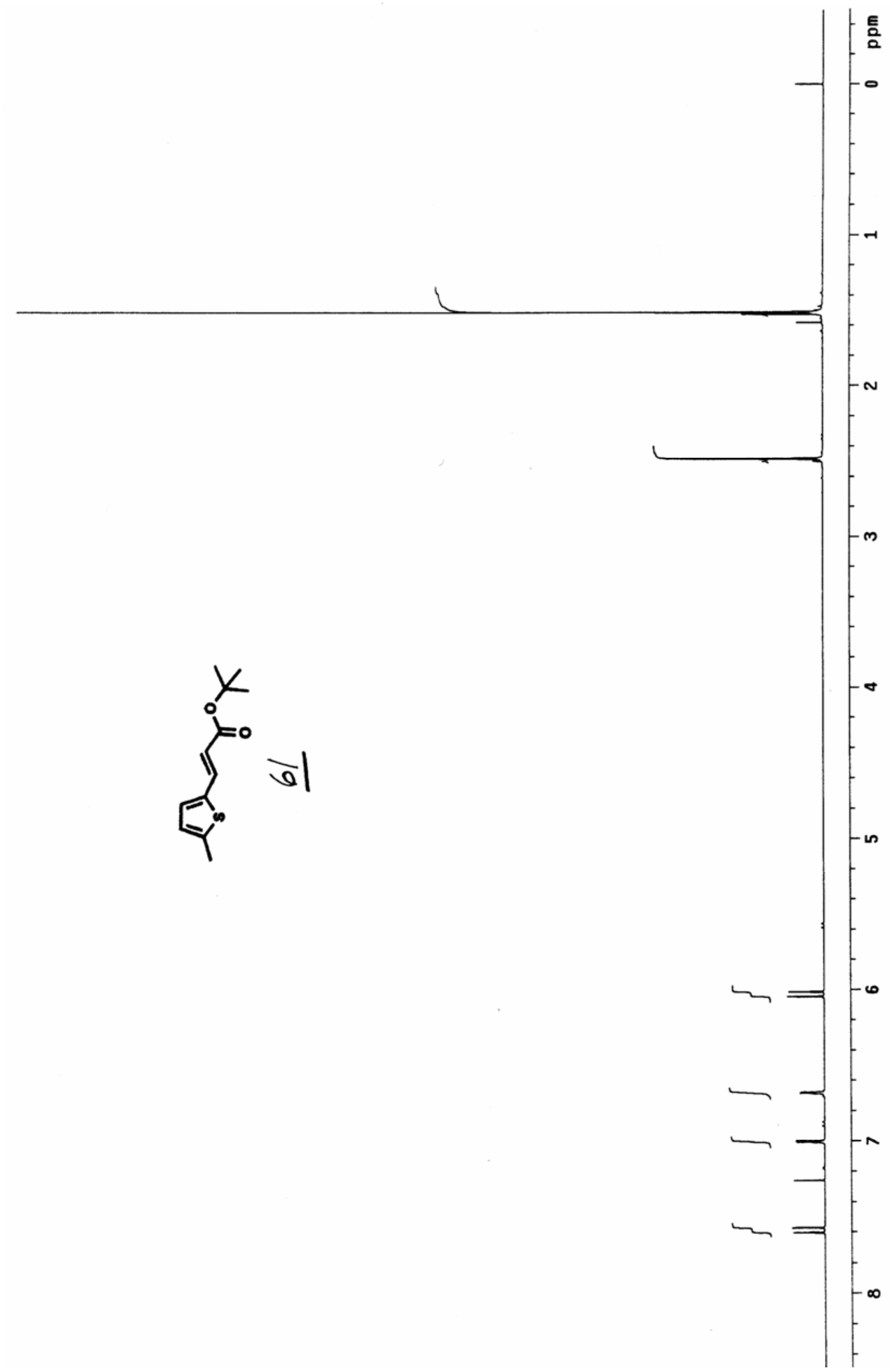

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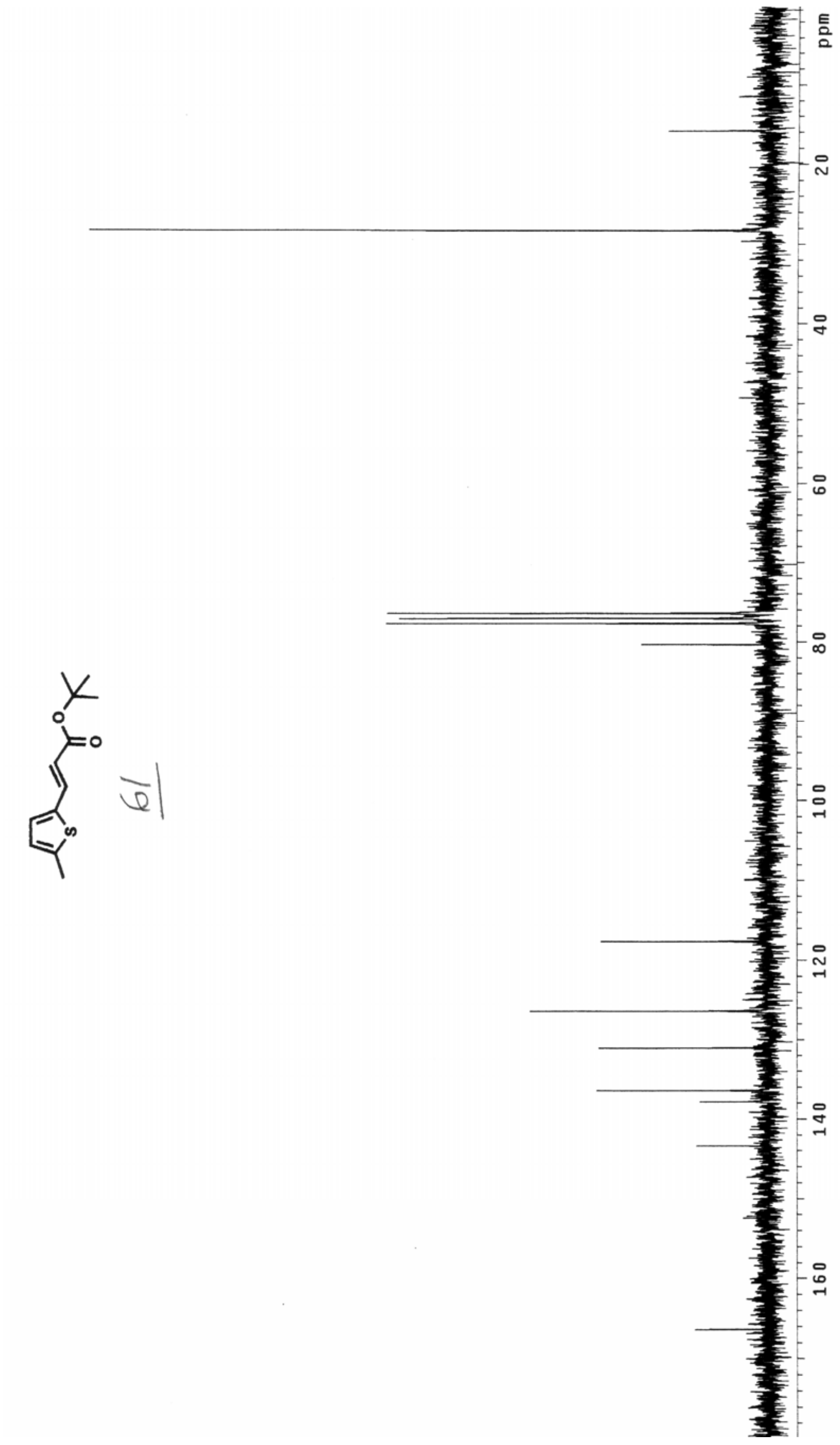

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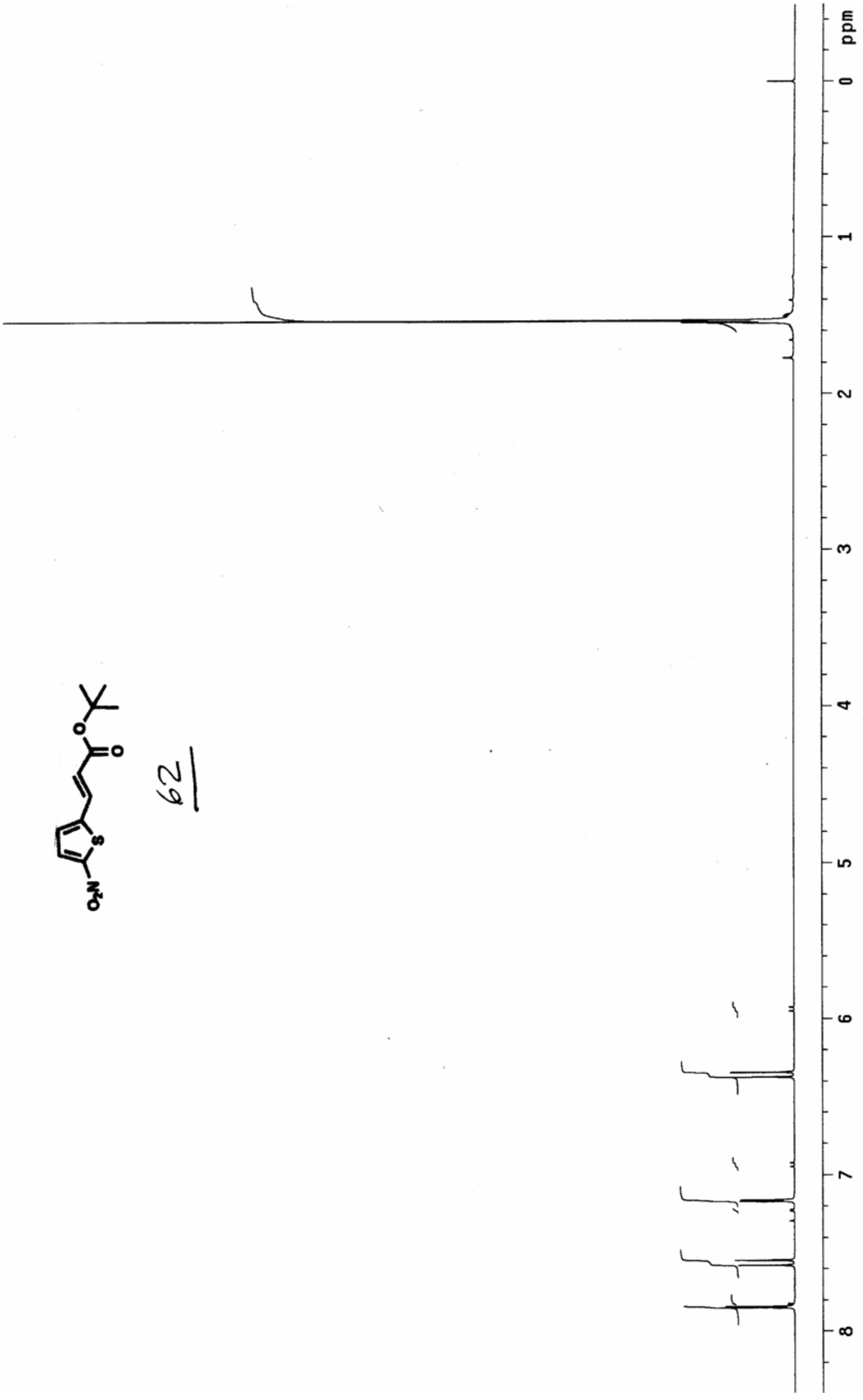

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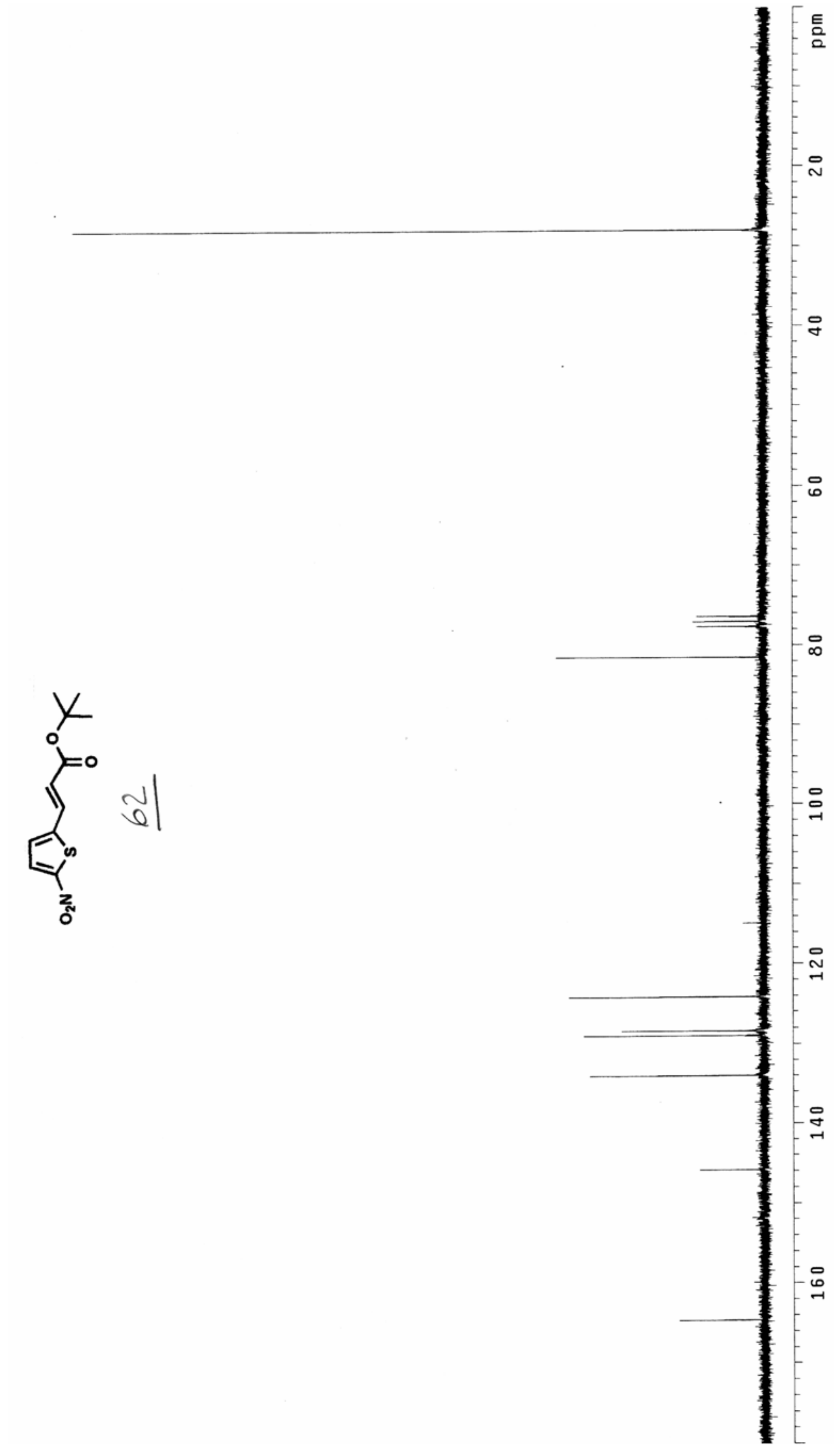

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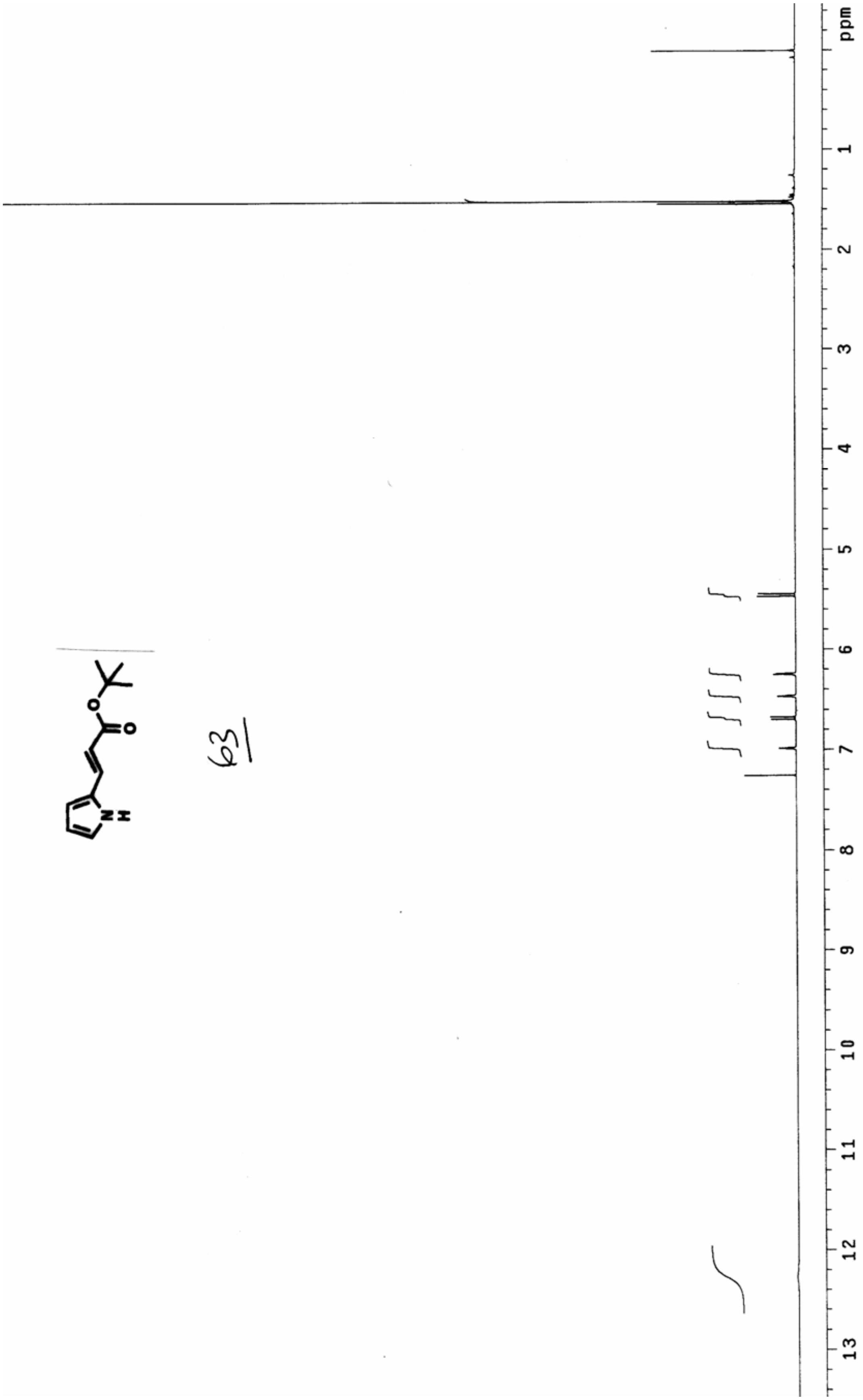

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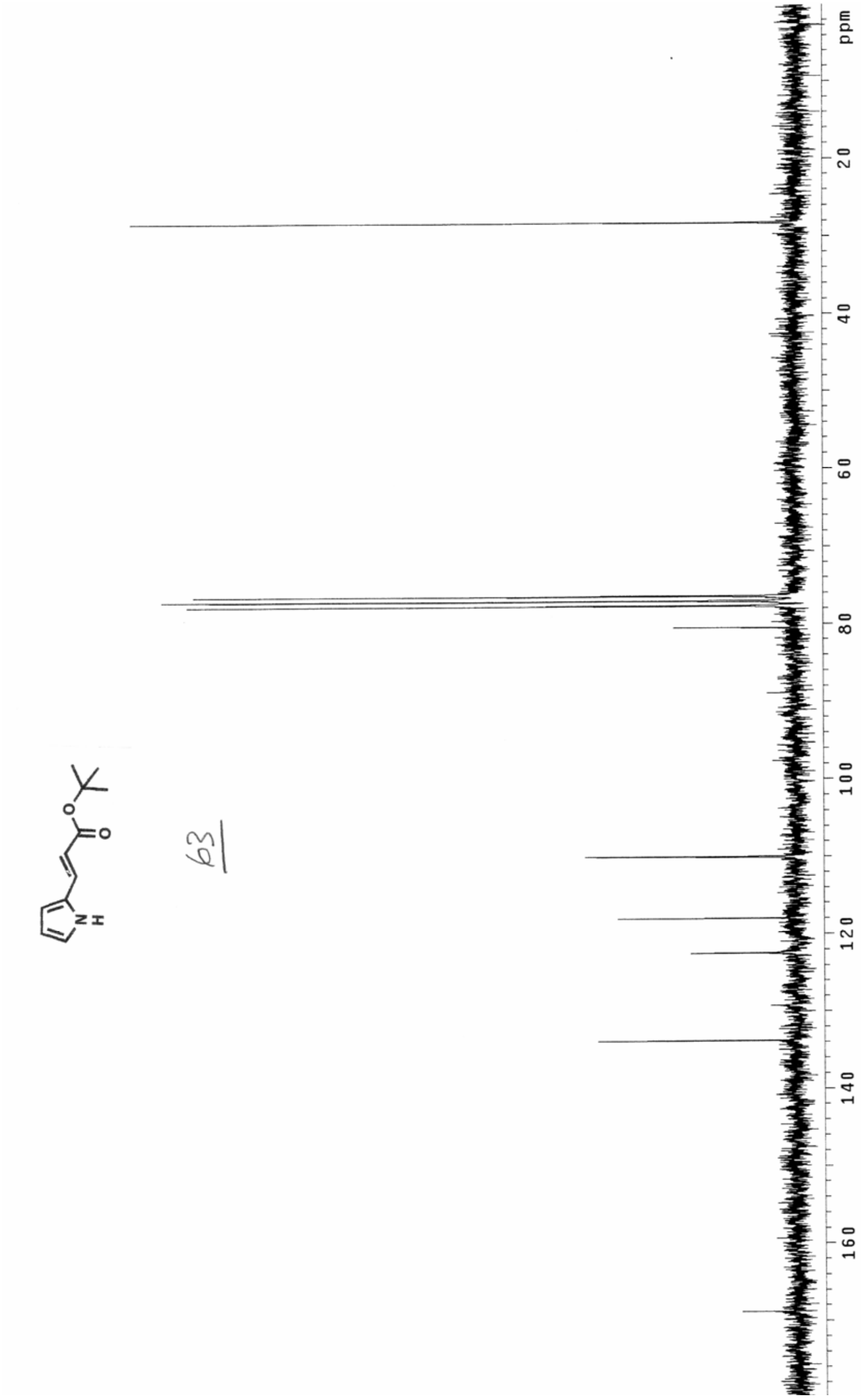

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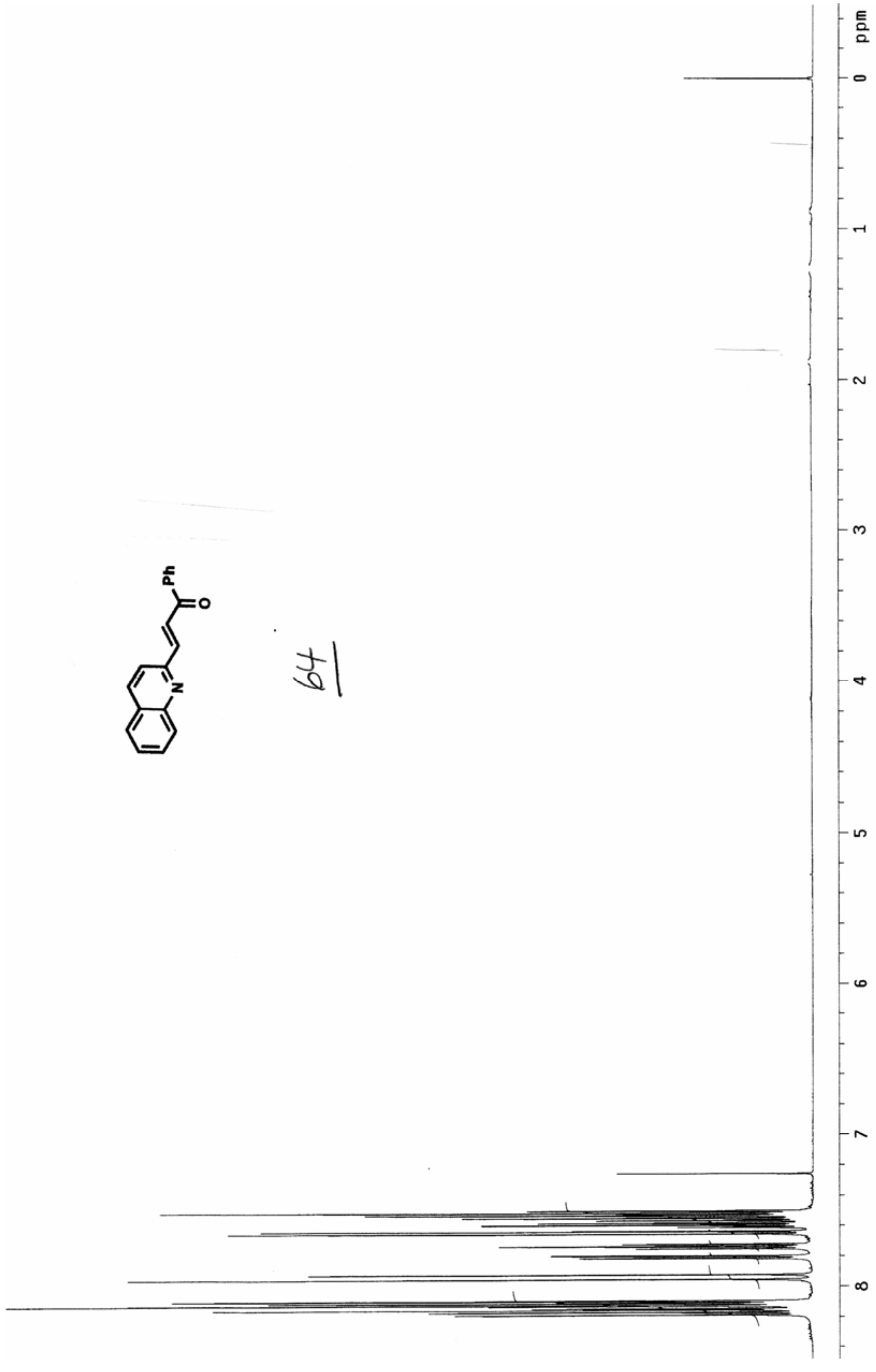

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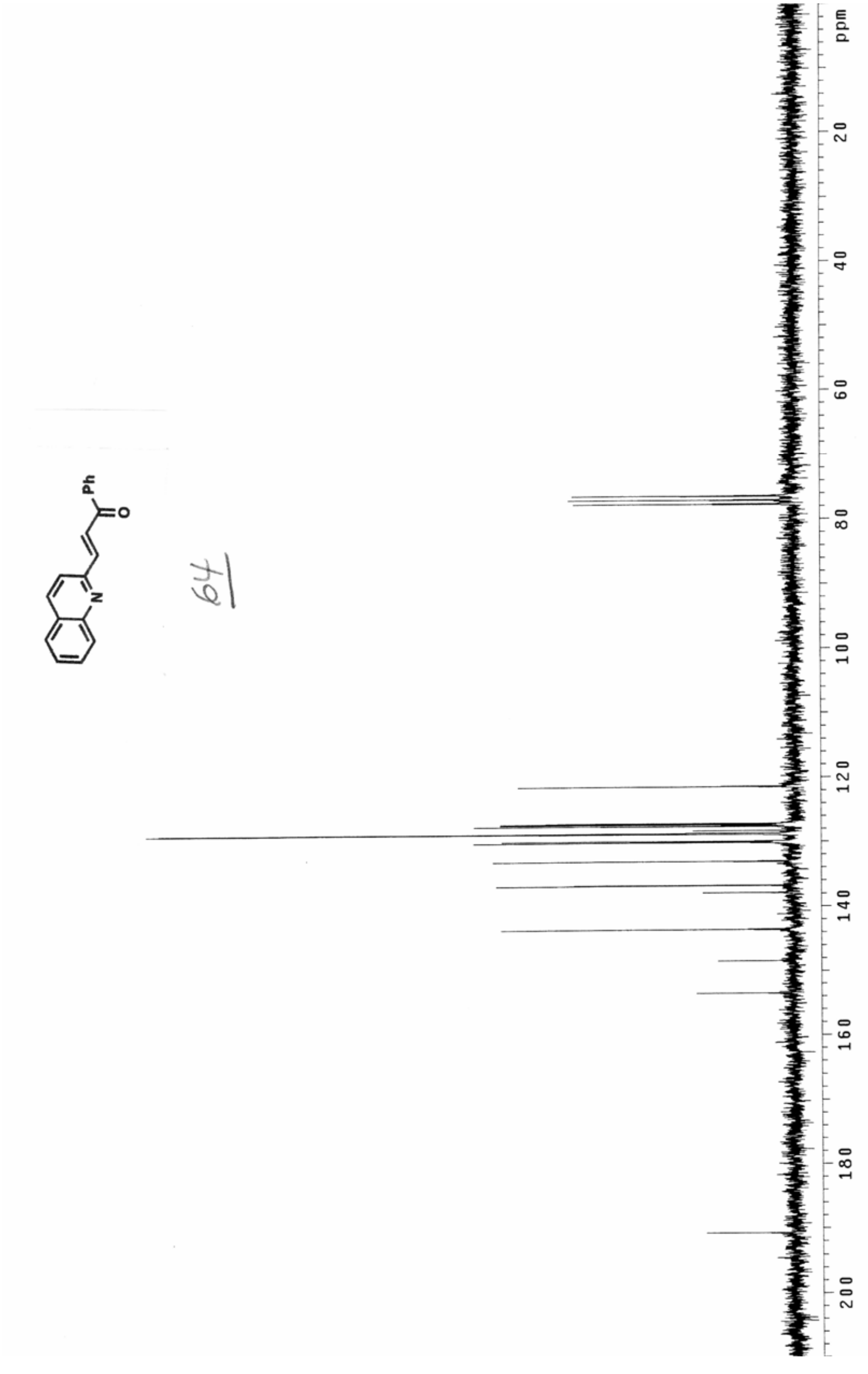

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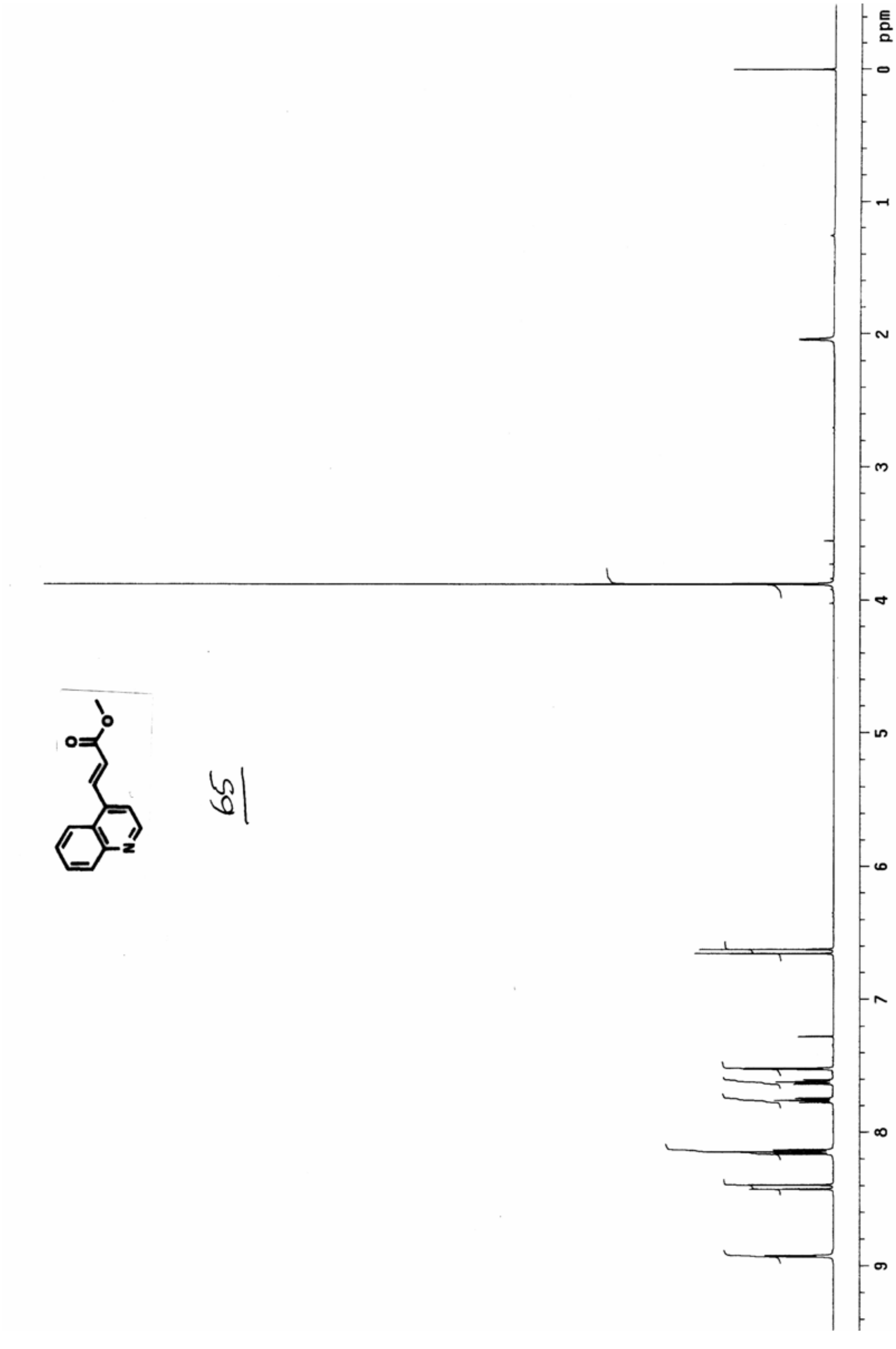

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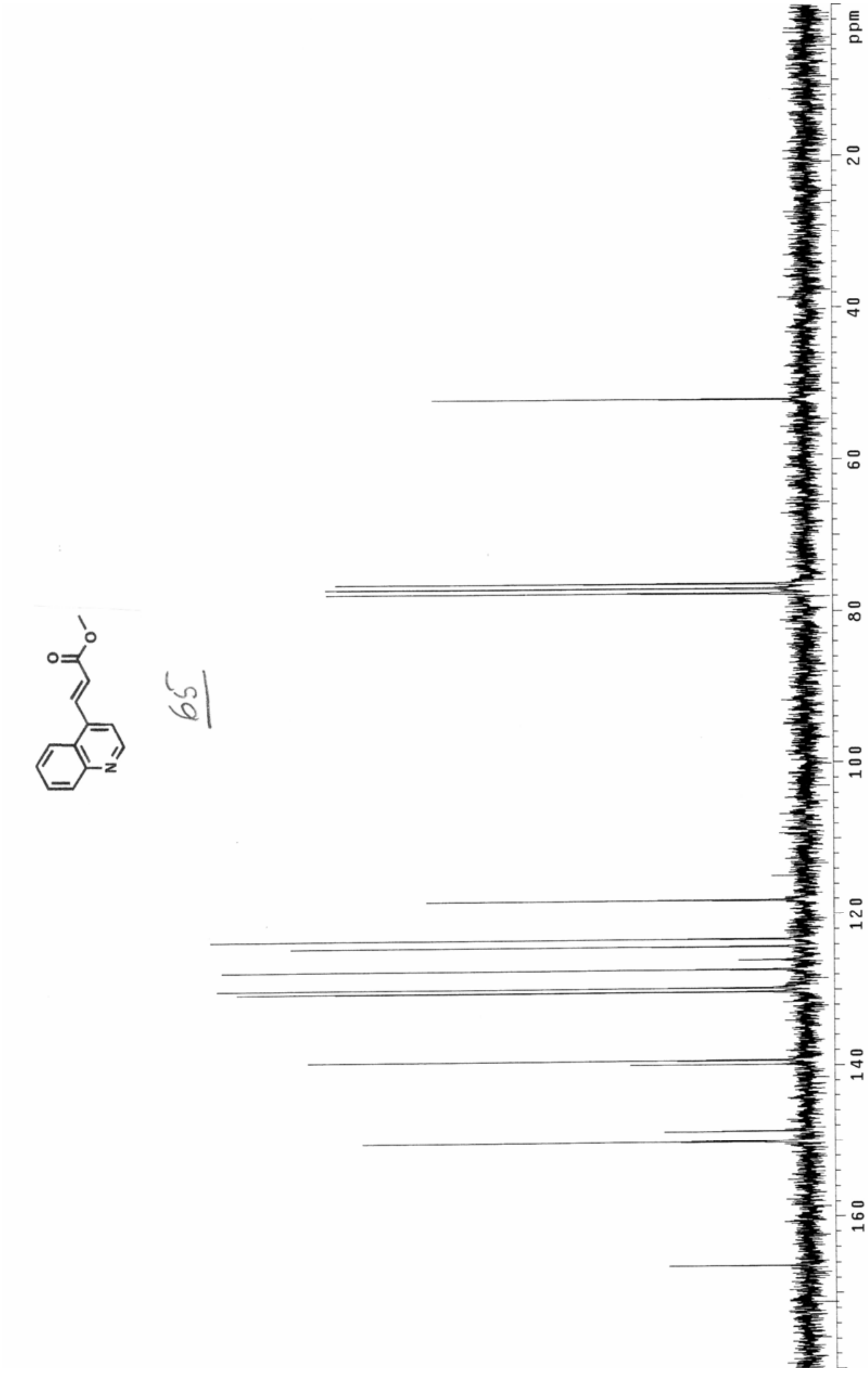

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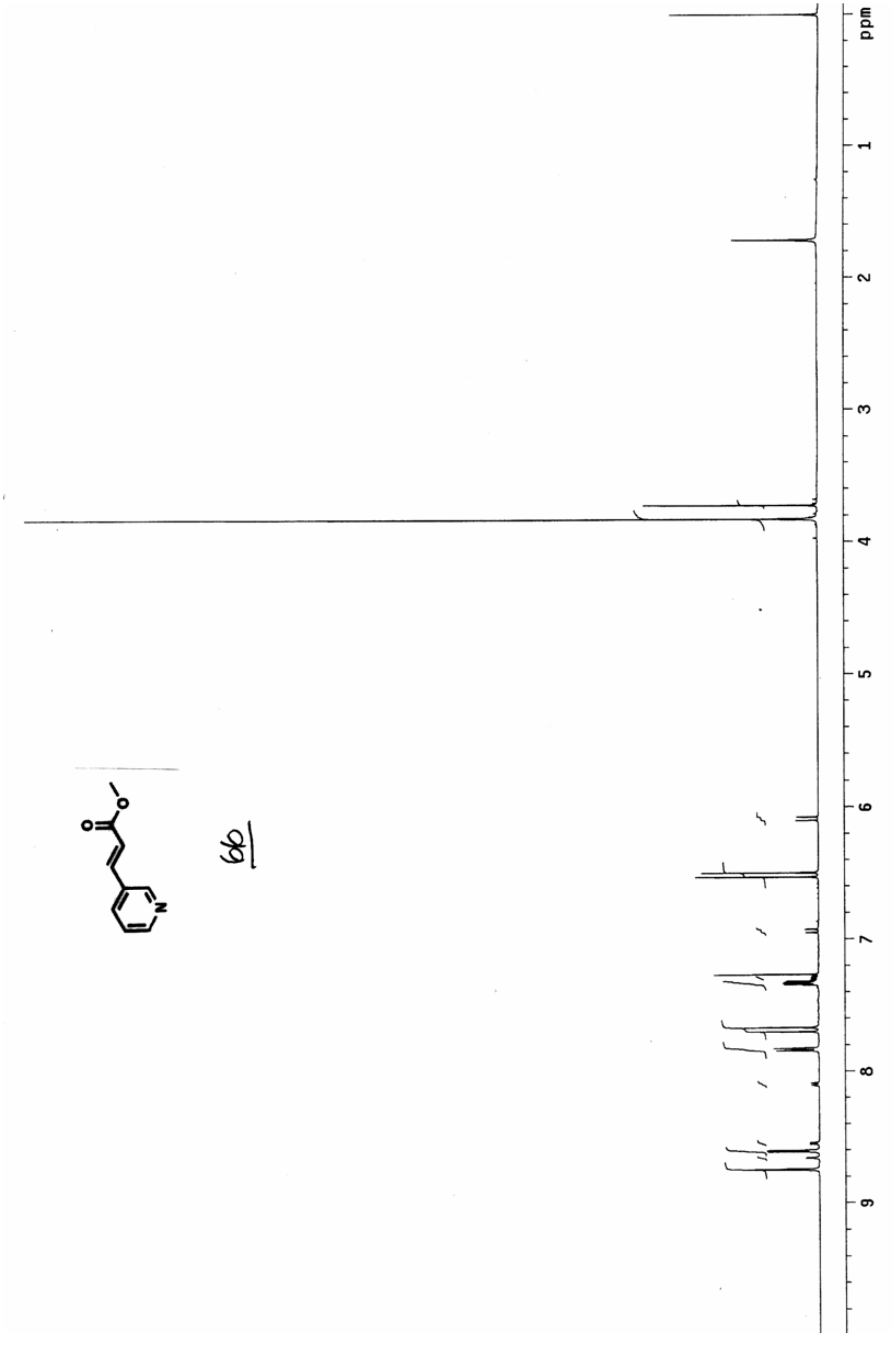

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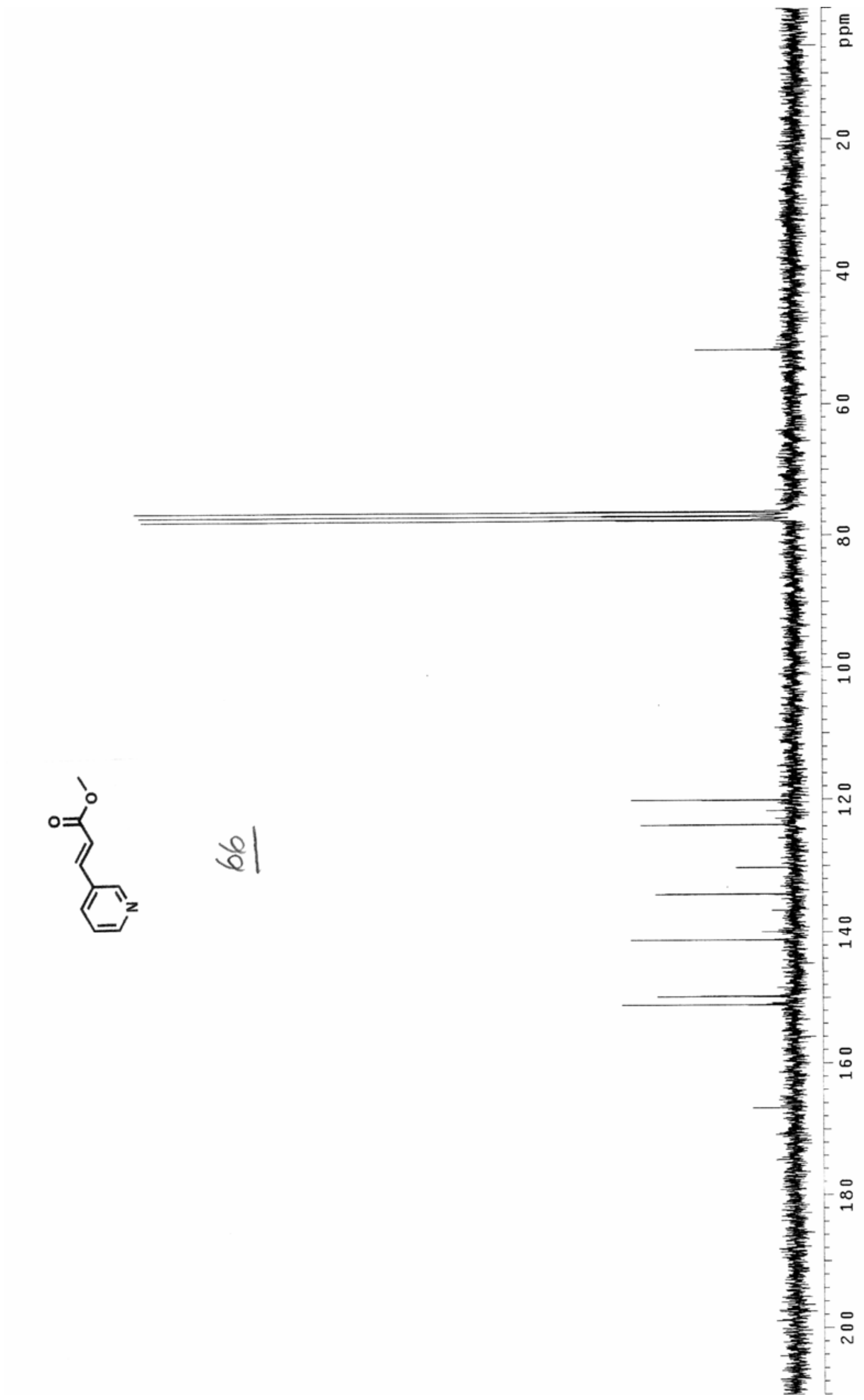

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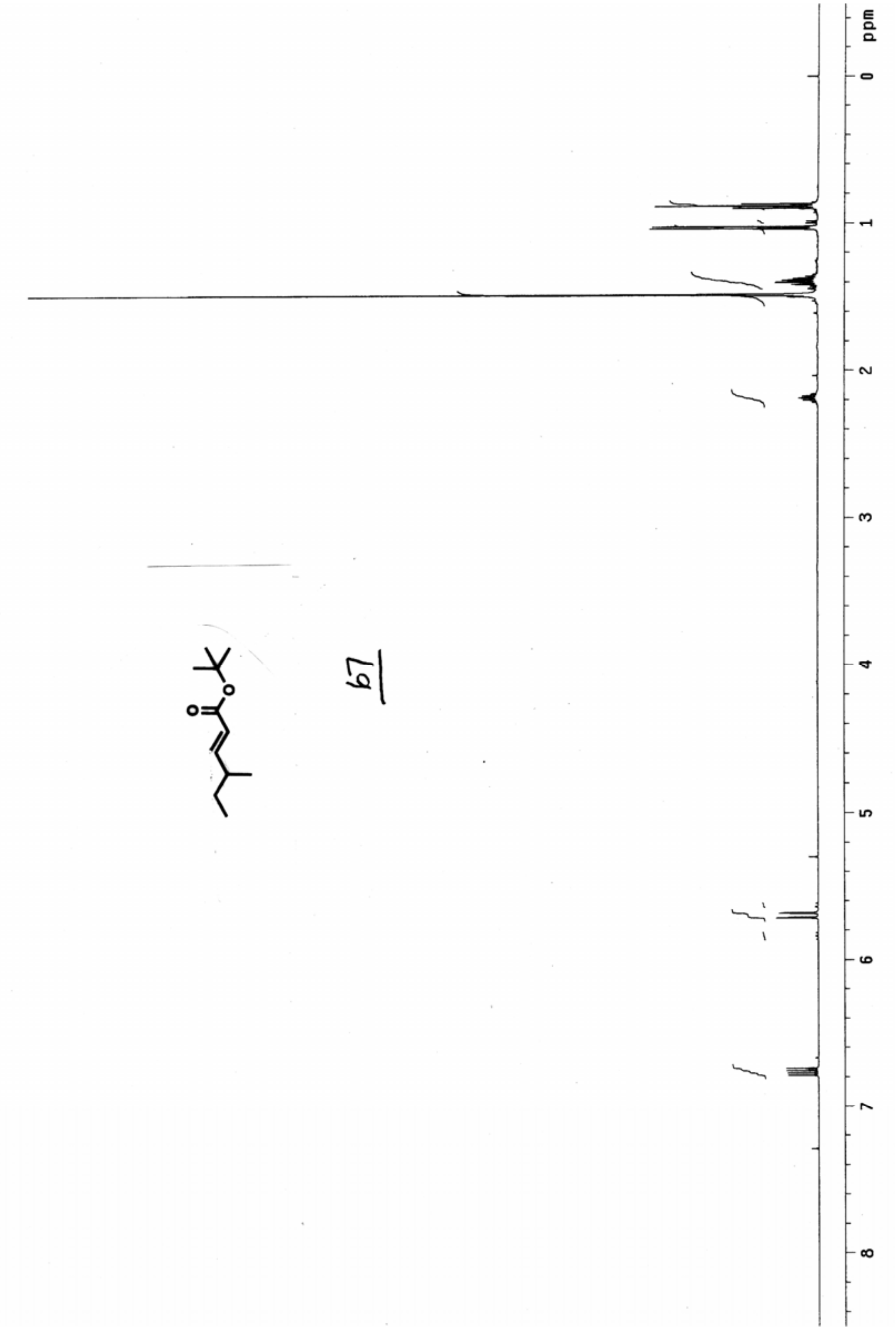

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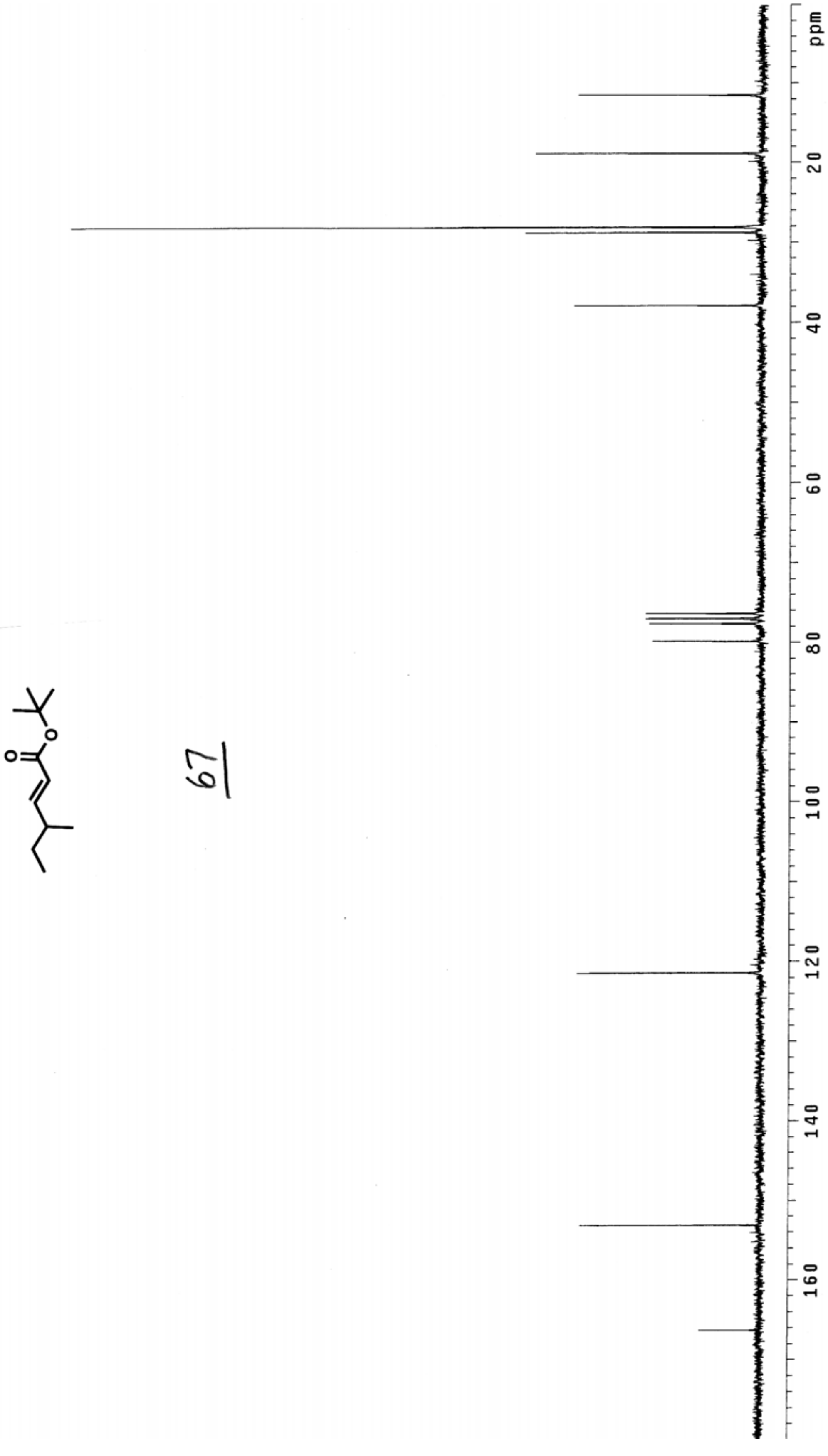

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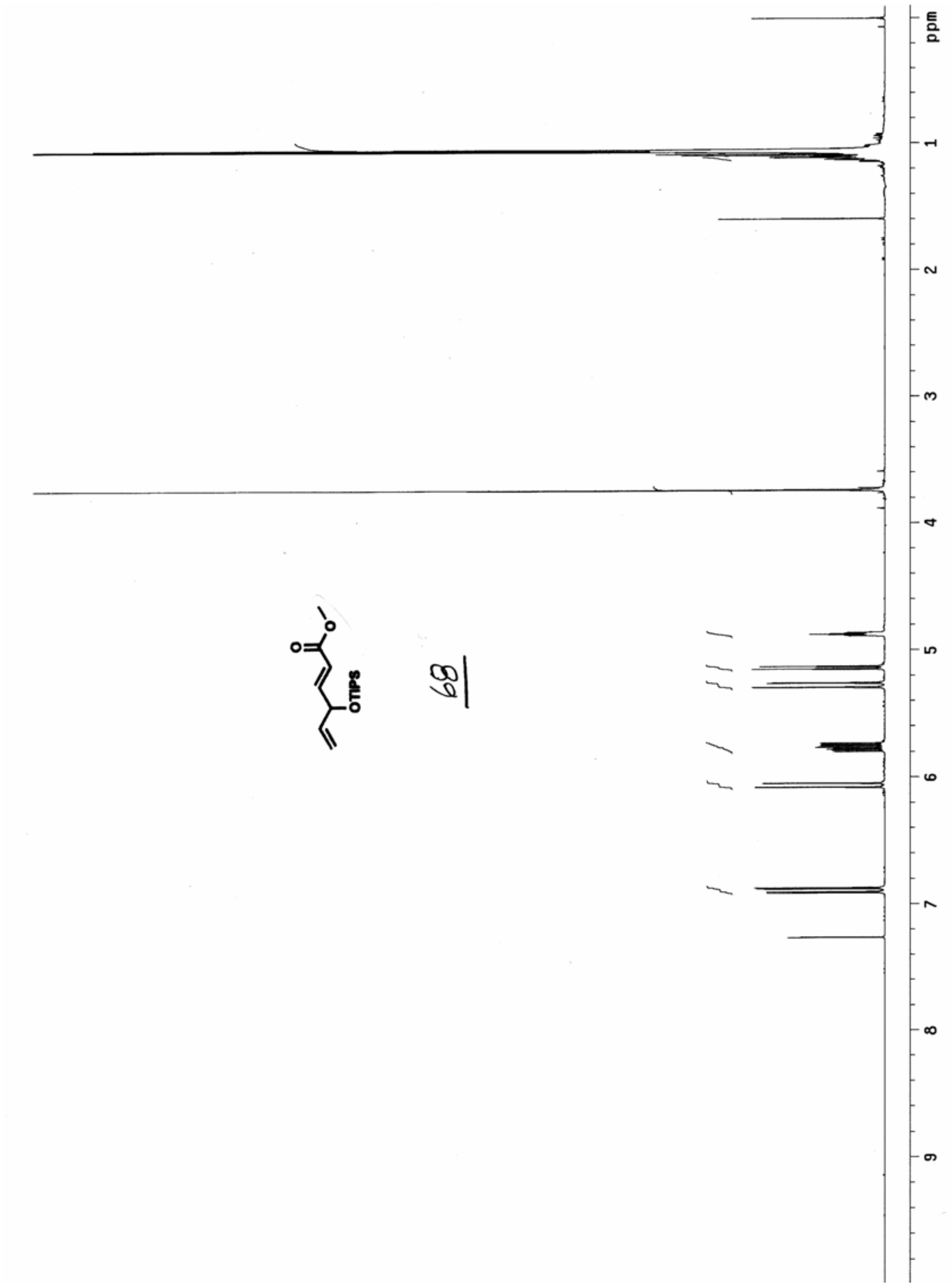

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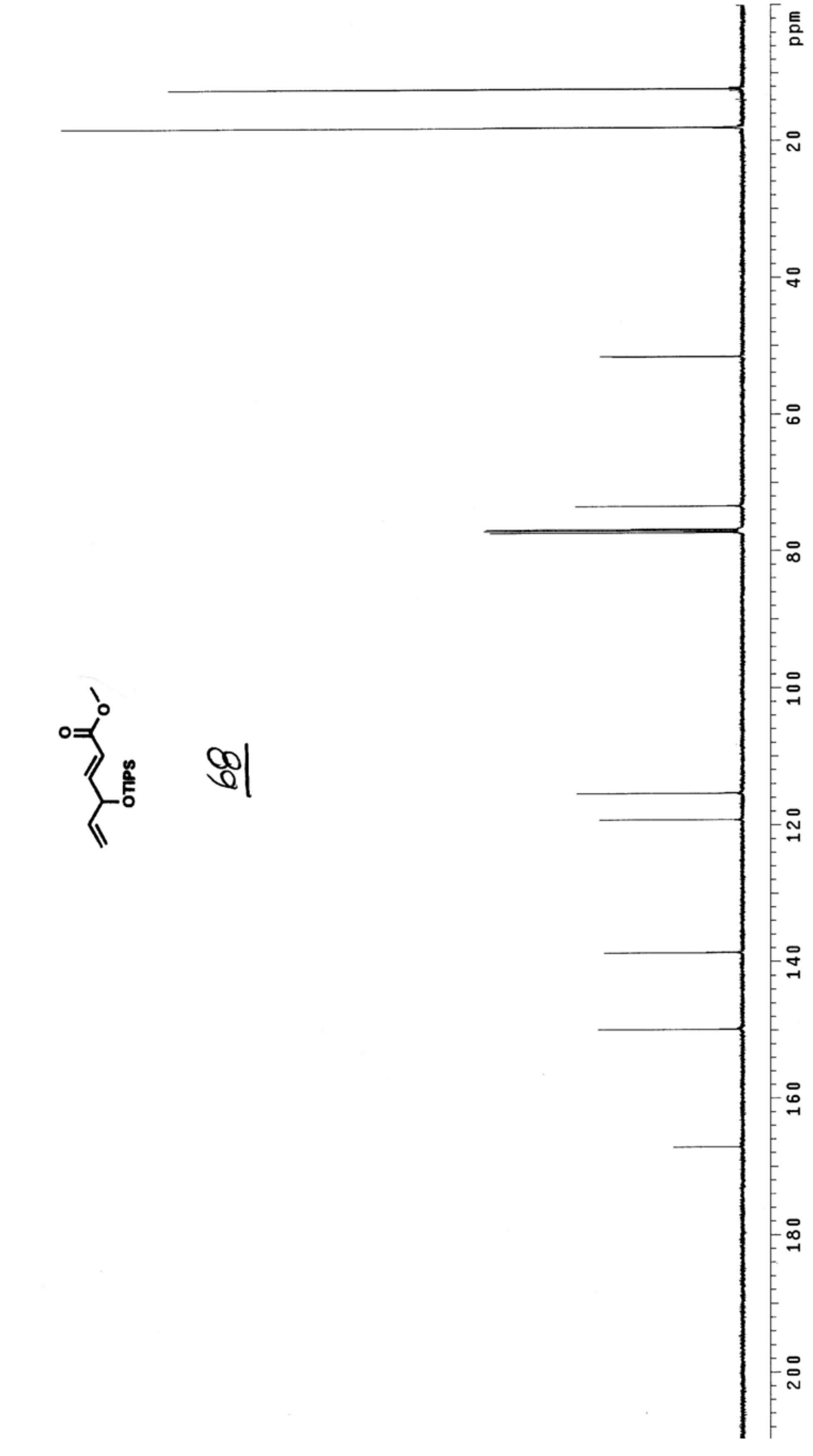

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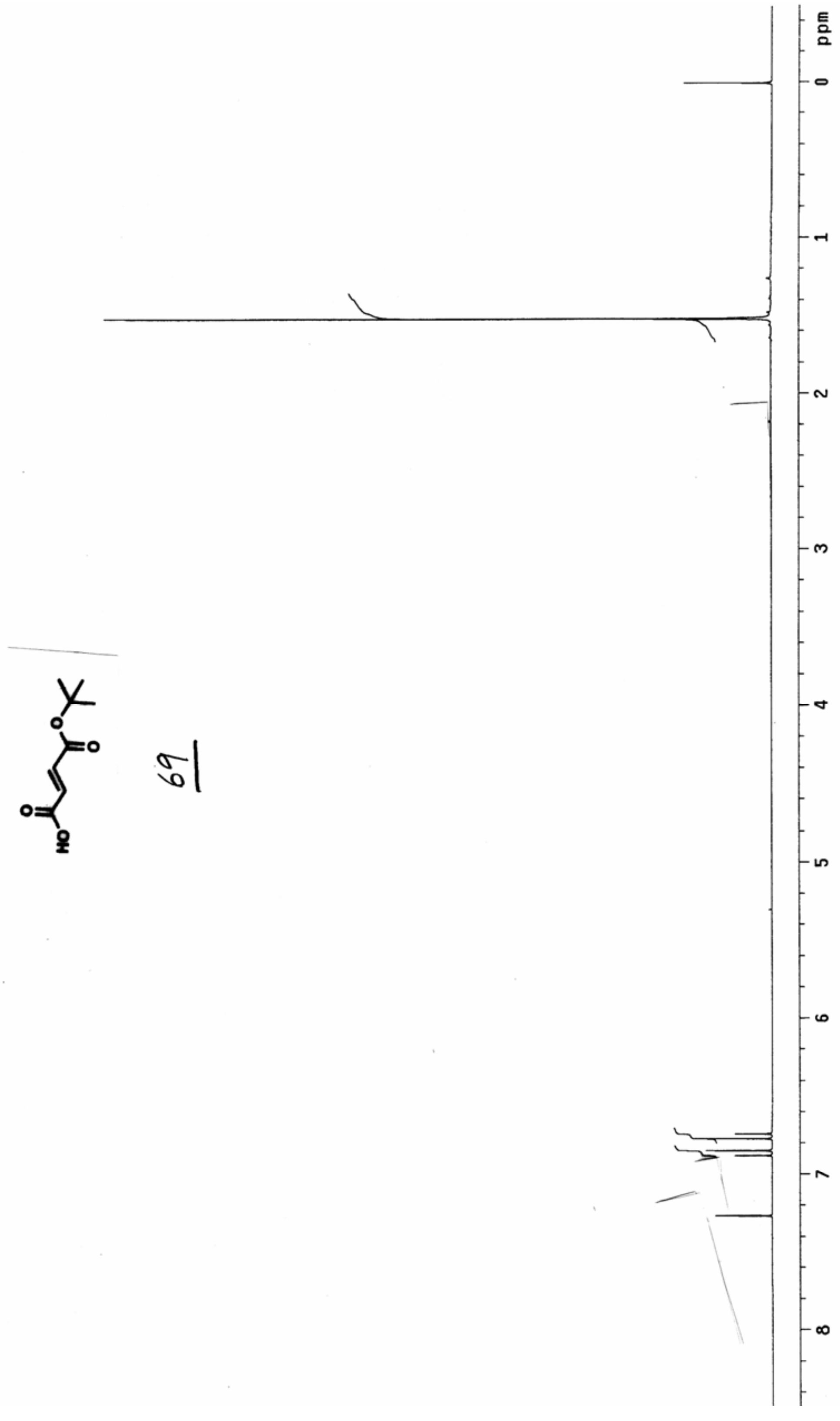

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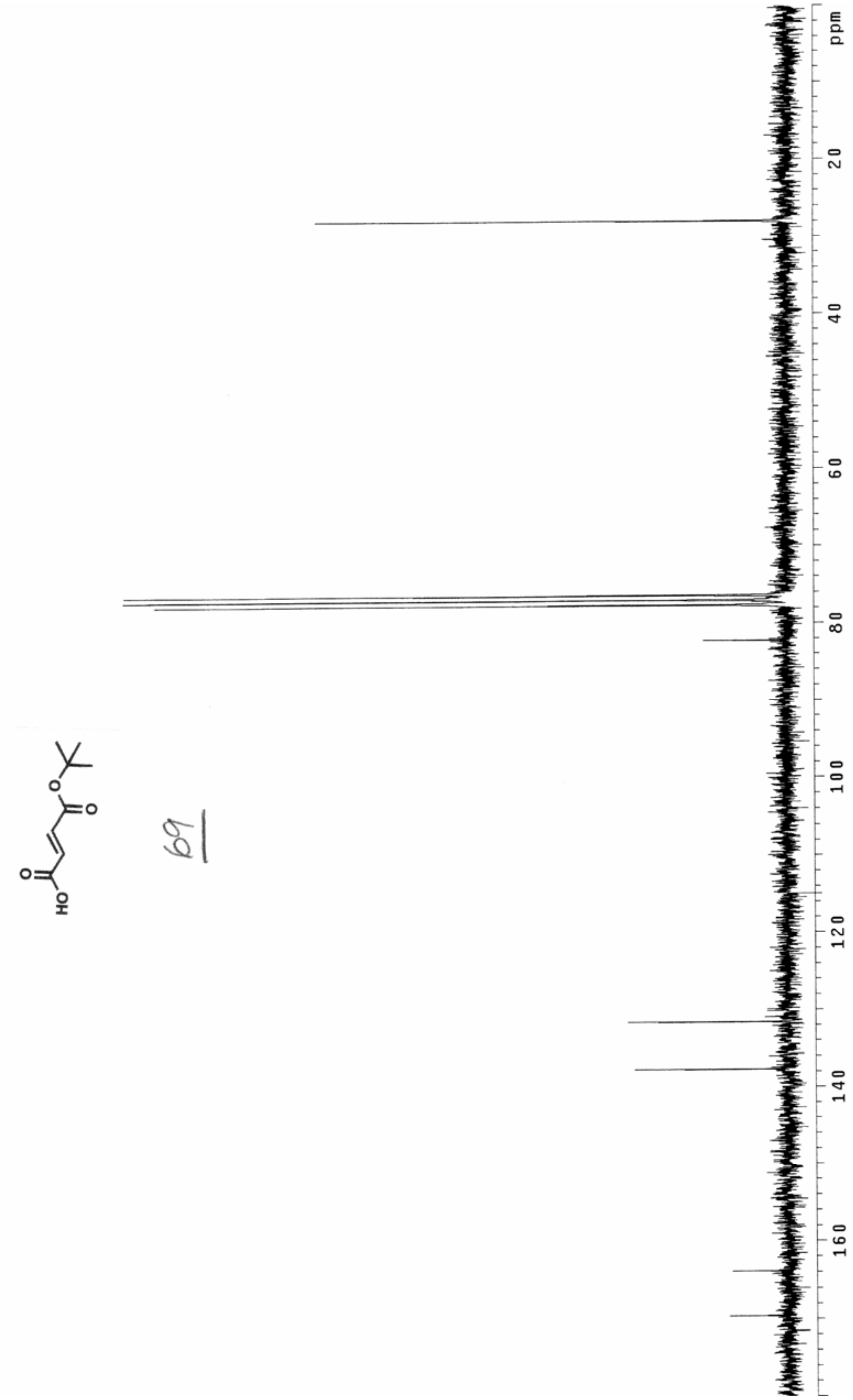

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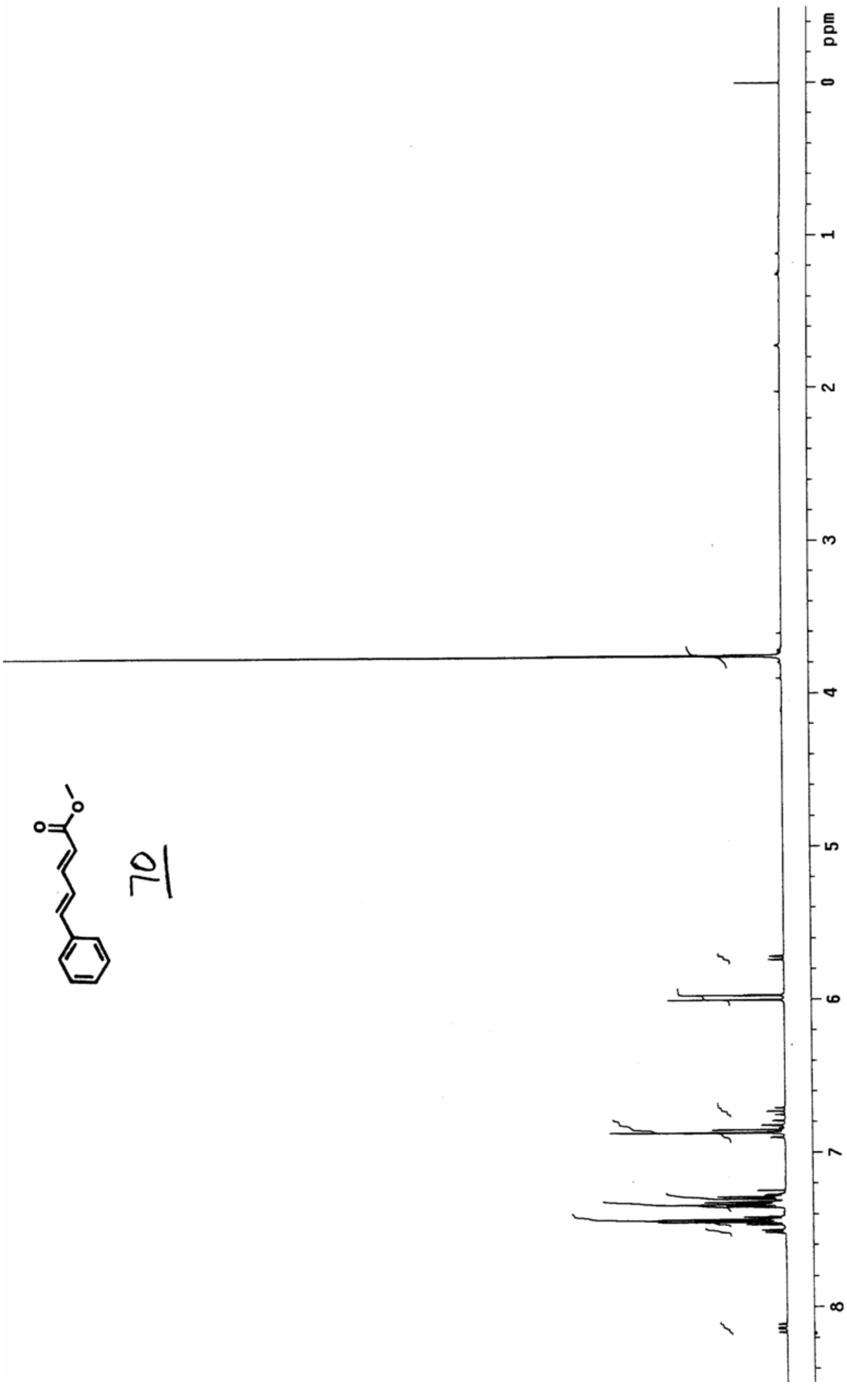
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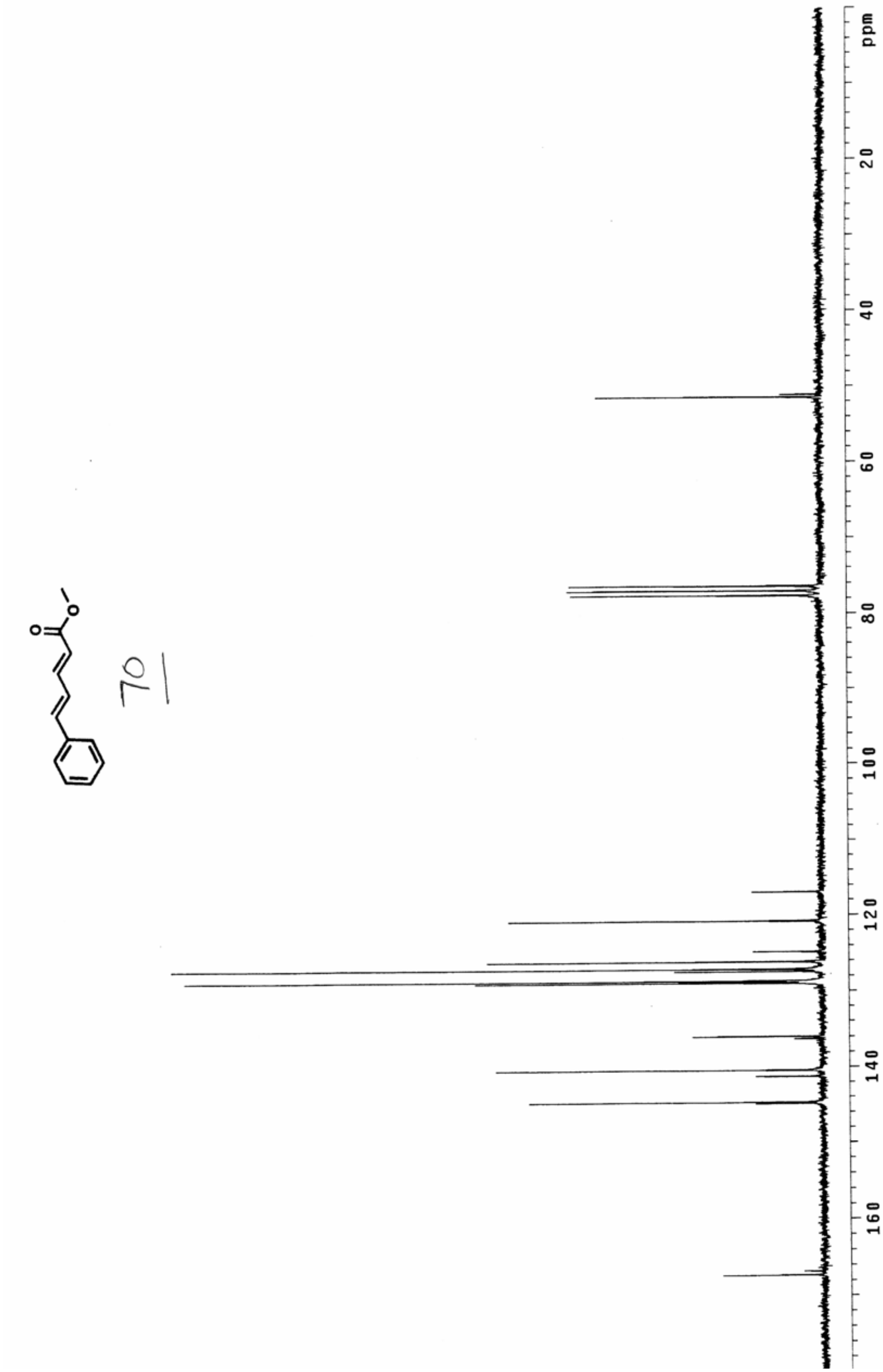

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