工學博士 學位論文

An adaptable one-carbon more and one-carbon less homologation of aliphatic aldehydes

지방족 알데히드의 탄소 개수를 간편하게 1개 늘리고 줄일 수 있는 동족체화 합성법

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An adaptable one-carbon more and one-carbon less homologation of aliphatic aldehydes

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
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by
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ABSTRACT

An adaptable one-carbon more and one-carbon less homologation of aliphatic aldehydes

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The one-carbon more and one-carbon less homologation of carbonyl compounds have been highly useful in organic chemistry for a long time because they could increase the synthetic value of the carbonyl compounds. Although various useful one-carbon more homologations and one-carbon less homologations have been respectively reported, they still have some drawbacks. They often require harsh reaction conditions that may be incompatible with several functional groups present in the compounds or suffer from difficulties in handling and the

large-scale preparation. First of all, there has been no homologation method to produce both one-carbon more and one-carbon less homologous compounds from the same synthon or the same intermediate.

We found that the mild proline-catalyzed reaction of aliphatic aldehydes with phenylsulfonylnitromethane under ultrasound irradiation could afford not α,β-unsaturated α-nitrosulfones but β,γ-unsaturated α-nitrosulfones in good yields through mild and tandem addition-elimination-isomerization.

We could develop a new concept of the adaptable one-carbon more and one-carbon less homologation of aliphatic aldehydes using β,γ-unsaturated α-nitrosulfones as key intermediates. While the ozonolysis of the key intermediates gave one-carbon less carbonyl homologs, the reduction of the double bond in the same key intermediates followed by the ozonolysis of the nitronate provided one-carbon more carbonyl homologs. Previously, one-carbon more homologation and/or one-carbon less homologation were required to be performed separately

using different homologation methods. But our homologation method to produce both one-carbon more and one-carbon less homologous compounds from the same intermediate can provide not only the more efficient synthesis but also the option to select a starting material with lower cost or better availability. We have also tried to design the homologation process to be milder and more practical by avoiding the use of strong base or rather reactive intermediates under anhydrous conditions. Moreover, we also prepared complementary one-carbon more homologation for the substrate having a functional group that is incompatible to ozonolysis and designed to obtain various carbonyl homologs such as aldehydes, acetals, carboxylic acids, esters, amides through simple modification of the reactions.

The two-way homologation was applied to the synthesis of the two key intermediates for biologically active histone deacetylases inhibitors, which was previously prepared respectively from 5-aminopentanoic acid and 7-aminoheptanoic acid. Both an 5-aminopentanoic acid derivative and an 7-aminoheptanoic acid derivative could be efficiently

prepared from readily available 6-aminohexanoic acid via the same intermediate (6 steps, 33-35% yields).

Our flexible homologation method could increase the synthetic availability of the carbonyl compounds and greatly diversify the choice of the chemical reactions for the construction of new carbon-carbon bonds.

***Keywords*: Homologation, Phenylsulfonylnitromethane, β,γ-unsaturated α-nitrosulfones**

***Student number*: 2008-30263**

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LIST OF ABBREVIATIONS

LDA	Lithium diisopropylamide
DMF	*N*,*N*-Dimethylformamide
THF	Tetrahydrofuran
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
m-CPBA	*meta*-Chloroperoxybenzoic acid
TFA	Trifluoroacetic acid
Bt	Benzotriazole
DMSO	Dimethylsulfoxide
TEA	Triethylamine
TBA	Tetrabutylammonium
Equiv or eq.	Equivalent
DMAP	4-Dimethylaminopyridine
KHMDS	Potassium bis(trimethylsilyl)amide
DCM	Dichloromethane
p-TsOH	*para*-Toluenesulfonic acid
TMS	Tetramethylsilane (NMR)
TMS	Trimethylsilyl
DBU	1,8-Diazabicycloundec-7-ene
MeOH	Methanol

Introduction

1. Homologation reaction

1.1. Introduction of homologation reaction

Efficient functional group transformations have been the target of organic chemists for many years. The conversion of the reactant with certain functional groups into the next member of the homologous series, which is called homologation reaction, is an important transformation that chemists have tackled from many different angles in the organic synthesis. In the narrow sense, a homologous series is a group of compounds that differ only by a constant unit, generally a (-CH_2-) group, and have the same functional group. But, it includes a group of compounds that differ by a constant unit, generally a (-CH_2-) group and have the similar functional group in the broad sense. Some reactions can increase the chain length by one carbon or more than one carbon, and other reactions can decrease the chain length by one carbon or more than one carbon as shown Figure 1.

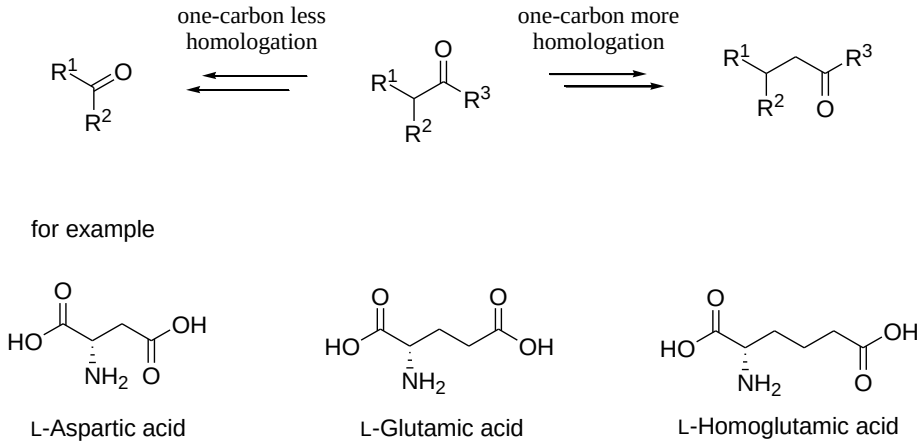


Figure 1. One-carbon more and one-carbon less homologation.

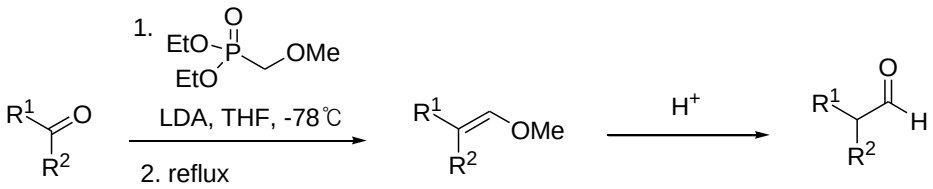
Carbonyl compounds such as aldehyde, ketone, carboxylic acid, ester, and amide are among the most important and fundamental compounds in organic chemistry. The homologation of carbonyl compounds is one of the important transformations that chemists have tackled from many different angles in the organic synthesis. Among them, one-carbon more or one-carbon less homologation of carbonyl compounds has been highly useful in organic and medicinal chemistry for a long time because they could increase the synthetic value of the carbonyl compounds.[1]

1.2. Previous studies on the one-carbon more homologation of carbonyl compounds

Various methods for the one-carbon more homologation with various one carbon synthons have been investigated and reported, but often require harsh conditions that may not be compatible with many functional groups present in the compounds or suffer from difficulties in handling and the large-scale preparation. The representative examples are as follows.

1) Wittig reaction of an aldehyde with methoxymethylene-triphenylphosphonate[2]

Scheme 1. Wittig reaction of an aldehyde with methoxymethylene-triphenylphosphonate



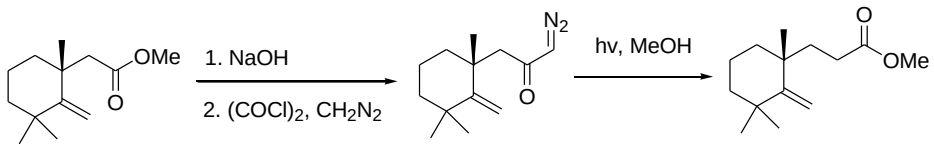
Enol ethers have been often used as an intermediate for the one-carbon homologation. Wittig reaction of an aldehyde with methoxymethylenetriphenylphosphonate followed by acidic hydrolysis can give a homologated aldehyde through simple reaction steps, but it requires a strong base such as LDA and alkoxide and shows low yields

with enolizable substrates.

2) Arndt-Eistert reaction[3]

The Arndt-Eistert reaction allows the formation of homologated carboxylic acids or their derivatives by reaction of the activated carboxylic acids with diazomethane and subsequent Wolff-rearrangement of the intermediate diazoketones in the presence of nucleophiles such as water, alcohols, or amines. It is widely used nowadays for the synthesis of β-amino acids from α-amino acids. But it required toxic and explosive diazomethane and safer alternative procedures has been developed such as the usage of ynolates (Kowalski ester homologation) or diazo(trimethylsilyl)methane.

Scheme 2. Arndt-Eistert reaction

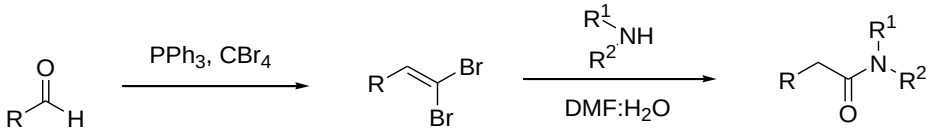


3) Homologation via 2-aryl-1,1-dibromo-1-alkenes[4]

The easily accessible 2-aryl-1,1-dibromo-1-alkenes can be converted to one-carbon more amides under mild conditions. The route of the

homologation is short and convenient but its substrate is unfortunately limited to aryl aldehydes. The toxic triphenylphosphine and tetrabromomethane should be also used in the homologation.

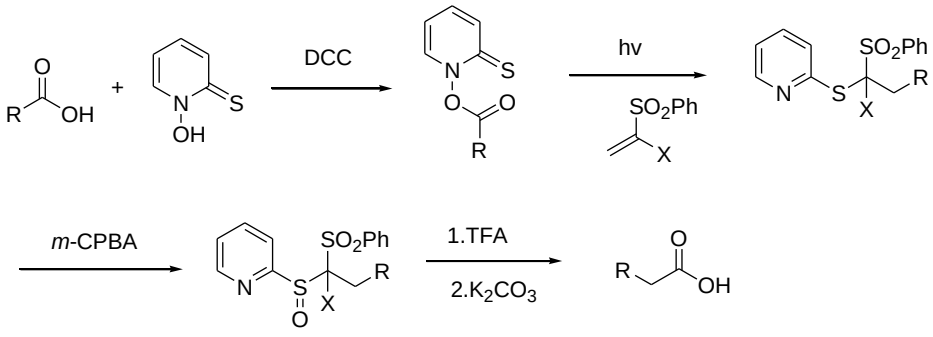
Scheme 3. Homologation via 2-aryl-1,1-dibromo-1-alkenes



4) Barton radical homologation[5]

This homologation is a kind of multistep reaction which employs the unstable intermediate *O*-acyl-*N*-hydroxylthiopyridone and two-carbon radical trap, phenyl vinyl sulfone.

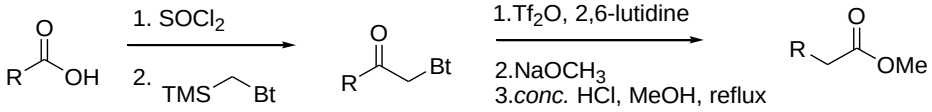
Scheme 4. Barton radical homologation



5) Homologation using 1-(trimethylsilylmethyl)benzotriazole[6]

This homologation uses available, versatile, and high-yielding reagent 1-(trimethylsilylmethyl)benzotriazole as an one-carbon synthon. Both aromatic and aliphatic carboxylic acids can be converted into one-carbon homologated acid derivatives. But, the procedure for the homologation is not simple and some substrates give only undesired allene compounds.

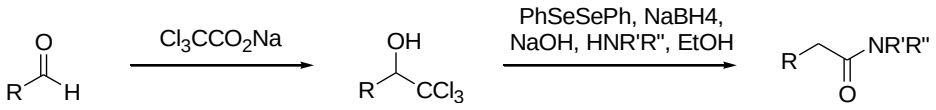
Scheme 5. Homologation using $TMSCH_2Bt$



6) Homologation via trichloromethyl carbinol[7]

This homologation provided one-carbon homologated primary, secondary, or tertiary amides in two steps via trichloromethyl carbinol. Deprotonation of the trichloromethyl carbinol in a protic solvent results in the formation of a reactive gem-dichloroepoxide intermediate. It has the advantage that it is compatible with even sensitive substrates, such as asymmetric α-amino aldehydes, enals and enolizable aldehydes.

Scheme 6. Homologation via trichloromethyl carbinol



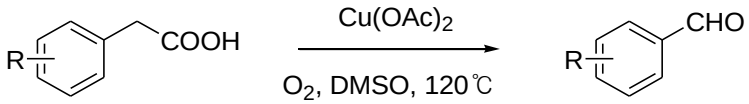
1.3. Previous studies on the one-carbon less homologation of carbonyl compounds

In contrast to one-carbon more homologation, only a few one-carbon less homologations using oxidative cleavage have been reported.

1) Copper-Catalyzed Aerobic Oxidative Decarboxylation[8]

This reaction involved a novel Cu(II)-catalyzed aerobic oxidative decarboxylation of phenylacetic acids in a one-pot protocol. This homologation desirably used oxygen as the sole terminal oxidant but unfortunately its substrates are limited to phenylacetic acids.

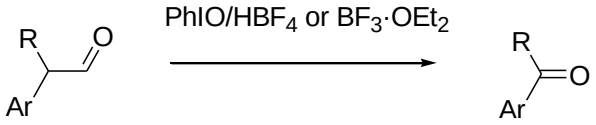
Scheme 7. Copper-catalyzed oxidative decarboxylation



2) Oxidative cleavage using Iodosylbenzene[9]

α-Aryl aldehydes can be cleaved to chain-shortened carbonyl compounds by using a combination of iodosylbenzene and strong acid HBF_4 or $BF_3{\cdot}OEt_2$. The oxidative cleavage proceeds most likely via the enol form and α-trialkyl acetaldehydes such as pivalaldehyde do not react in the reaction because they have no α-hydrogens. The substrate of this decarboxylation is also limited to α-aryl aldehydes.

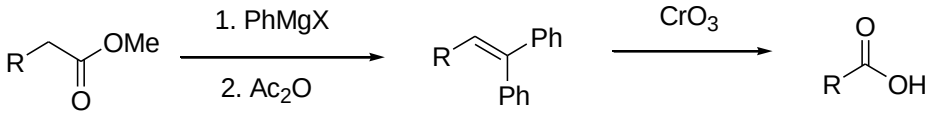
Scheme 8. Oxidative cleavage using Iodosylbenzene



3) Barbier–Wieland degradation[10]

The reaction sequence involves conversion of the carboxyl and alpha carbon into an alkene, which is then cleaved by oxidation to convert into one-carbon less carboxylic acid. It also requires reactive Grigmard reagent and chromium trioxide.

Scheme 9. Barbier–Wieland degradation



2. Phenylsulfonylnitromethane

α-Nitrosulfones have been known since the early 1900's but have only recently received much attention because of their potential as a useful intermediate or a synthon. Phenylsulfonylnitromethane can easily undergo deprotonation (p*K*a ≈ 5.7) to form a corresponding anion that can serve as a nucleophile in many chemical transformations. Moreover, phenylsulfonylnitro group can also be transformed to various functional groups.

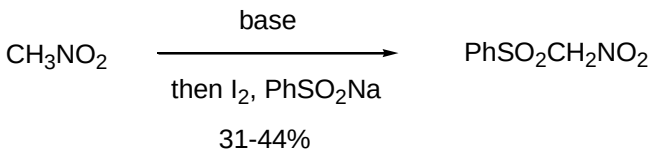
2.1. Preparation of phenylsulfonylnitromethane

Several methods for the preparation of phenylsulfonylnitromethane by three principal routes, sulfonylation of α-nitrohalide, oxidation of α-nitrosulfides, and nitration of sulfone, have been reported. But, the development of its facile preparative approach in a large scale is still required for its wider application.

(1) sulfonylation of α-nitrohalide [11]

This method has been usually used in the preparation of phenylsulfonylnitromethane despite the low yield. The reaction was reported to be able to proceed with various bases and solvents in a one-pot protocol even on the dozens of g scale but the practical preparation of phenylsulfonylnitromethane is still troublesome.

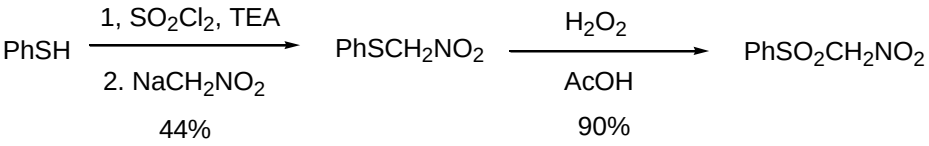
Scheme 10. Preparation of $PhSO_2CH_2NO_2$ via iodonitromethane



(2) oxidation of α-nitrosulfides[12]

Phenylsulfonylnitromethane can be prepared by the oxidation of α-nitrosulfides, which was derived from phenylsulfenyl chloride. But the preparation of the intermediate phenylsulfenyl chloride in a large scale is not easy because of the toxicity and the smell of thiophenol and sulfuryl chloride.

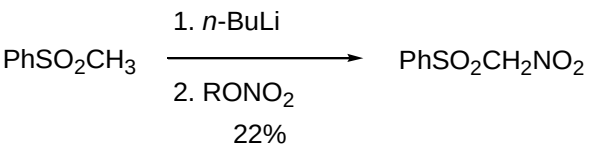
Scheme 11. Preparation of $PhSO_2CH_2NO_2$ via oxidation of $PhSCH_2NO_2$



(3) nitration of sulfone[13]

Phenylsulfonylnitromethane can be prepared by the nitration of phenylmethylsulfone. The use of a strong base such as *n*-BuLi for the formation of sulfone anion is required for the preparation of phenylsulfonylnitromethane. The reaction sometimes can also give an undesired side product.

Scheme 12. Preparation of $PhSO_2CH_2NO_2$ by nitration of sulfone



2.2. Transformation of phenylsulfonylnitromethane

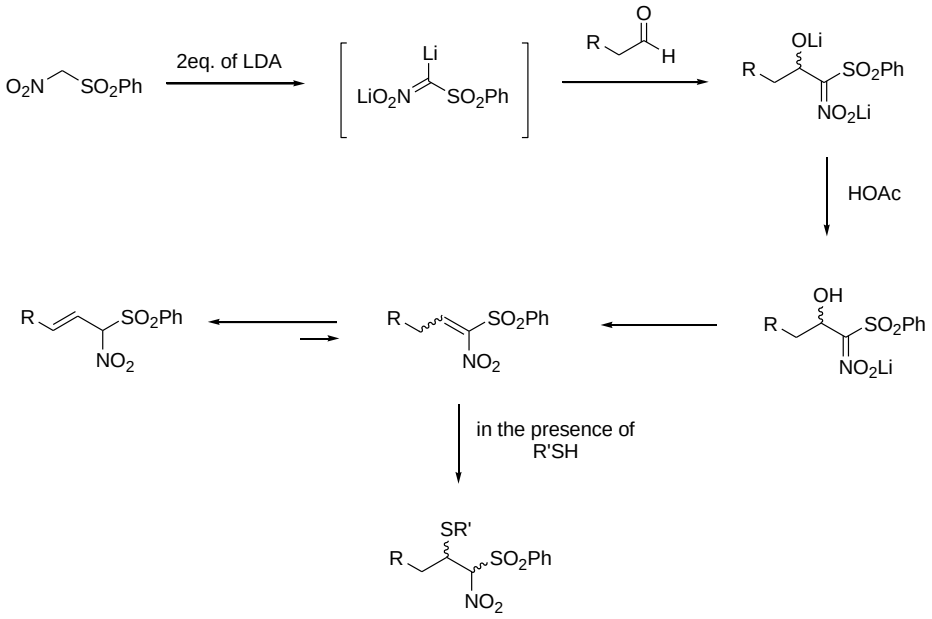
It was known that phenylsulfonylnitro group can also be transformed to several functional groups by the corresponding procedures. The

representative examples are as follows. Nevertheless, further studies on the transformation of phenylsulfonylnitro group are still required for the wider application of phenylsulfonylnitromethane.

(1) Tandem nitroaldol and dehydration[14]

Wade *et al.* reported its tandem nitroaldol-dehydration reactions of aliphatic unbranched aldehydes. The treatment of phenylsulfonyl-nitromethane with more than 2 molar equiv. of LDA could afford dianion of phenylsulfonylnitromethane. Unexpectedly its monoanion couldn't act as a nucleophile to aldehydes. Condensation of this dianion with unbranched aldehydes afford the initial nitroaldols, which was then dehydrated after the acidification and the storage at room temperature for 12-24h to give β,γ-unsaturated α-nitrosulfones. The author proposed that the formation of β,γ-unsaturated α-nitrosulfones by equilibration from initially-formed conjugated α,β-unsaturated α-nitrosulfones might be favored. The trapping of α,β-unsaturated α-nitrosulfones intermediates with thiol or diisopropylamine was reported when tandem reactions were carried out in the presence of thiols or diisopropylamine.

Scheme 13. Tandem nitroaldol and dehydration of $PhSO_2CH_2NO_2$



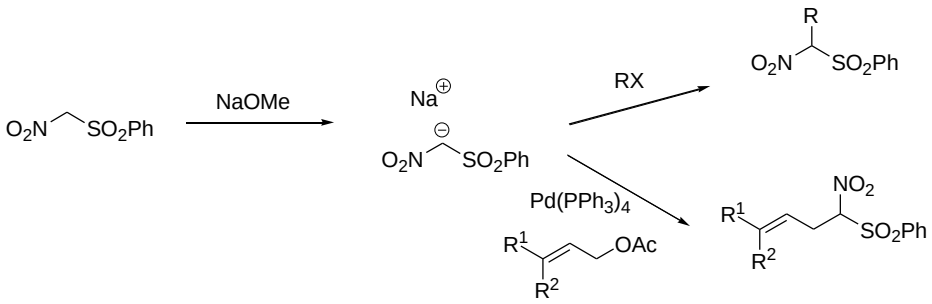
(2) Desulfonylation[15]

A sulfonyl group of α-nitrosulfones can be replaced by hydrogen on the treatment with *N*-benzyl-1,4-dihydronicotinamide (BNAH) by a free-radical process through one-electron transfer. 1,3-dimethyl-2-phenylbenzimidazolin(DMBI), which was found to be a more reactive electron-transfer reducing agent than BNAH, can be also used instead of BNAH.

(3) Alkylation[16]

Phenylsulfonylnitromethane contains a bulky phenylsulfonyl group adjacent to the carbanion center and presumably favors o-alkylation. When the excess of monoanion of phenylsulfonylnitromethane was treated with alkyl iodides or benzyl bromide, c-alkylation product could be obtained in moderate yields. In contrast, the reaction with allylic acetate in the presence of catalytic tetrakis(tripheny1phosphine)-palladium provided α -nitro sulfones in high yields.

Scheme 14. Alkylation of phenylsulfonylnitromethane

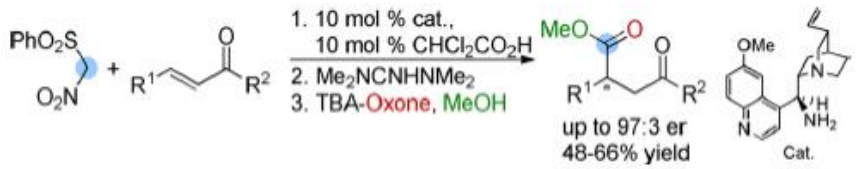


(4) Transformation to an ester[17]

The oxidative degradation of primary nitroalkanes and primary sulfones usually requires harsh reaction conditions, such as the use of strong bases and/or oxidants. In comparison, the oxidative achoholysis of the α-nitrosulfones moiety can be achieved under considerably milder conditions. For this reason, phenylsulfonylnitromethane could

be a better candidate of the acyl anion equivalent than other highly toxic acyl anion equivalents such as cyanide and malononitrile. Enantioselective Michael addition of α-nitrosulfones moiety and transformation into an ester was reported by several researcher groups as shown in Scheme 15.

Scheme 15. Transformation to an ester

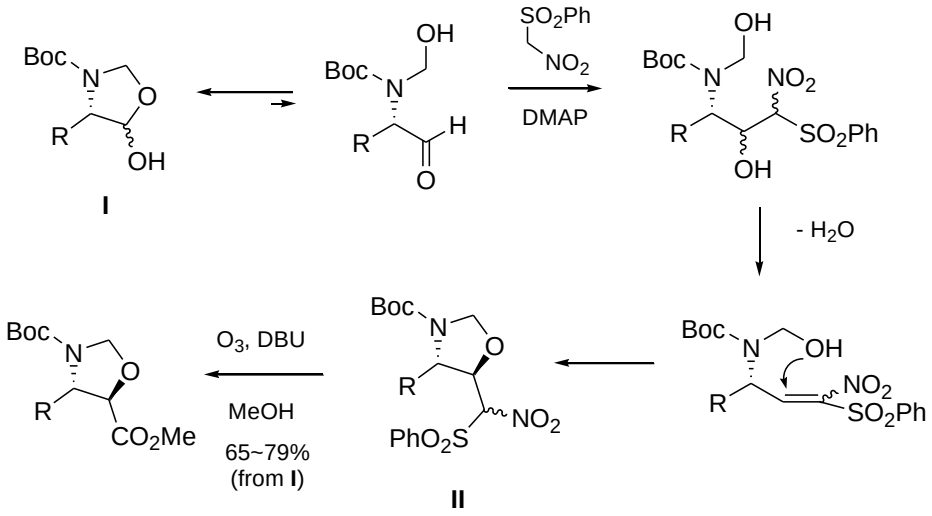


3. Our previous study

Our research started from the results of our previous study on the development of a novel and efficient synthetic method for preparing β-amino-α-hydroxy acids and their derivatives from the corresponding α-amino aldehydes by using an *N*-hydroxymethyl group as an internal nucleophile.[17a] We have found that the treatment of *N*-hydroxymethyl-α-amino aldehydes **I** with phenylsulfonylnitromethane in the mild reaction conditions produced the *trans*-oxazolidines **II** as a result of

three sequential reactions, i.e., the nitroaldol addition, the dehydration, and the intramolecular conjugate addition as shown in Scheme 16.

Scheme 16. Our previous study on preparing β-amino-α-hydroxy acids and their derivatives from the corresponding α-amino aldehydes



Contrary to the results of Wade *et al.*,[14] the reaction of aldehydes with monoanion of phenylsulfonylnitromethane afforded nitroaldol condensation products which were then reacted with internal nucleophile, *N*-hydroxymethyl group. We found the possibility of its application to a mild homologation reaction and decided to develop a new homologation method. But unfortunately this condition couldn't be applied to other normal aldehydes as reported by Wade *et al.* Further intramolecular conjugate addition of *N*-hydroxymethyl group to disfavored α,β-unsaturated α-nitrosulfones seemed to facilitate the

formation of the *trans*-oxazolidines **II** exceptionally. Anyway, this research on the reaction between aldehydes and phenylsulfonylnitromethane became a chance to discover a new synthetic method, proline-catalyzed tandem nitroaldol-dehydration reaction of aliphatic aldehydes.

Results and Discussion

1. Our strategy

1.1. The starting point of the research

After reviewing the previous studies on the one-carbon more homologation and one-carbon less homologation, we found that they often require harsh conditions such as the use of a strong base and may not be compatible with many functional groups present in the compounds or suffer from difficulties in handling and the large-scale preparation. So we started the research from finding an appropriate one-carbon synthon that can be deprotonated with a mild base and react with aldehydes. We have tried to find the convenient and mild reaction condition using an appropriate one-carbon synthon. It was desirable to find a method to give unsaturated products in one step because the addition of one-carbon synthon to aldehydes usually gives aldol products, which are followed by elimination through 1-2 steps to afford unsaturated products. Moreover, the approach to produce both one-carbon more and one-carbon less homologous compounds from the same intermediate has not been reported yet even though large numbers

of different approaches to produce either one-carbon more or one-carbon less carbonyl compounds using separate reaction pathways has been reported. So the intermediates and reagents used in one-carbon less homologations were different from those used in one-carbon more homologations. If we develop a new method for not only one-carbon more homologation but also one-carbon less homologation using the same intermediate, It could increase the synthetic availability of the carbonyl compounds and greatly diversify the choice of the chemical reactions for the construction of new carbon-carbon bonds. Moreover, it could provide the option to select the starting material with the cheaper price or ready availability from either one-carbon more or one-carbon less aldehydes to prepare the same target carbonyl compounds.

To enable not only one-carbon more homologation but also one-carbon less homologation using the same intermediate, we focused on the formation of not α,β-unsaturated products **3**' but β,γ-unsaturated products **4'** because oxidative cleavage of α,β-unsaturated products **3**' can result in the regeneration of starting aldehydes **2** but that of β,γ-unsaturated products **4'** can result in the formation of one-carbon less carbonyl homologs **5'**. Finally, the moiety from one-carbon synthon can be transformed into the carbonyl compound **7'**. If possible, multiple transformations into several carbonyl compounds are desirable to provide various options for the choice to organic chemists.

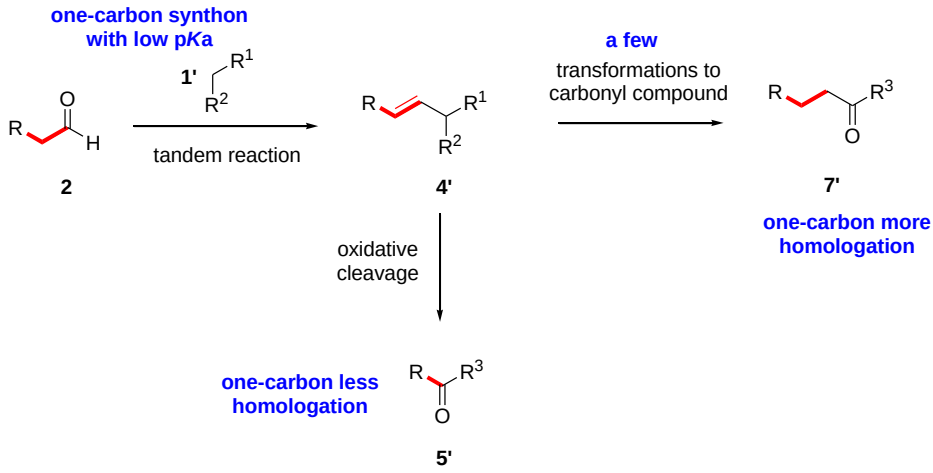


Figure 2. The initial version of our strategy for the one-carbon more and one-carbon less homologation.

1.2. Selection of a one-carbon synthon

As mentioned before, we have tried to find one-carbon synthons that fit our synthetic strategy. First, we were interested in mild reactions with one-carbon synthons with low p*K*a, which could easily deprotonated with a mild base. So one-carbon synthons having electron withdrawing groups were a good candidate. Because one-carbon synthon moiety could be transformed to homologous carbonyl compounds, various ideas were derived from aldehyde equivalents. The α-aminosulfone moiety was known to be an equivalent of an iminium ion which could be easily transformed to aldehyde by hydrolysis.[18]

Acetals or ketals of heteroatoms can be also transformed to carbonyl compounds. Therefore, we selected the candidates that could be transformed to α-aminosulfone moiety or acetals/ketals of heteroatoms as shown in Fig 3. We checked the possibility of candidates through the feasibility test.

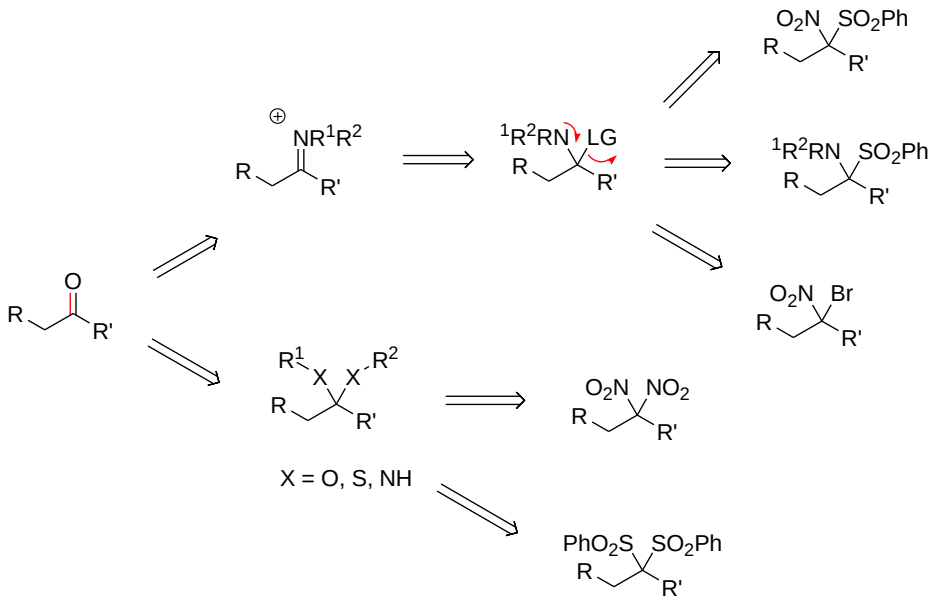


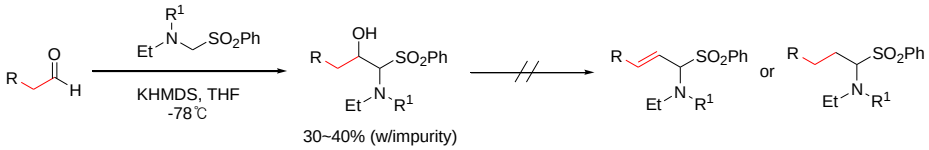
Figure 3. Ideation of candidates for an one-carbon synthons.

1.2.1. Amidosulfones

Amidosulfones was expected to be easily converted into aminosulfones by the deprotection of the *N*-protecting group. Moreover, the reaction condition for its deprotection could be chosen according to the *N*-protecting group.

N-alkyl substituted α-amidosulfones were prepared in good yields by the treatment of *N*-alkyl substituted carbamates with paraformaldehyde and benzenesulfinic acid sodium salt in the presence of an acid catalyst.[19] *N*-Alkyl substituted α-amidosulfones were used in the reactions because an acidic carbamate proton could interrupt the deprotonation of α-amidosulfones. But they required the treatment of strong base such as KHMDS for their aldol reactions and their transformation to β,γ-unsaturated nitroolefins or saturated nitroolefins was not successful.

Scheme 17. The feasibility test with amidosulfone as an one-carbon synthon

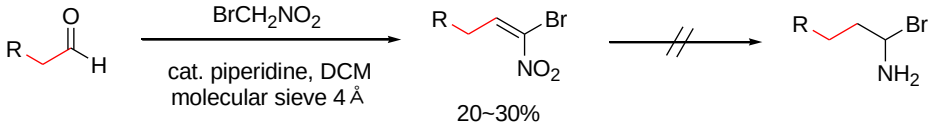


1.2.2. Bromonitromethane

Commercially available bromonitromethane was expected to be a good candidate as a one-carbon synthon for our homologation. The reactions of aldehydes with bromonitromethane showed different results from that with phenylsulfonylnitromethane. Interestingly the reactions of aliphatic aldehydes with bromonitromethane in the

presence of catalytic proline didn't afford the desired product in a reasonable yield. NaI-catalyzed reaction of aldehydes with bromonitromethane gave nitroaldol products in good yields but further elimination steps was required to obtain α,β-unsaturated nitroolefins. The reaction of octanal with bromonitromethane in the presence of catalytic piperidine and molecular sieve 4 Å gave the α,β-unsaturated nitroolefin as a major product although its yield was low. But the reduction of its nitro group was not successful in the presence of bromo group.

Scheme 18. The feasibility test with bromonitromethane as an one-carbon synthon



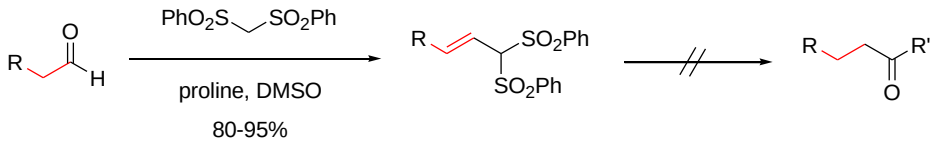
1.2.3. Dinitromethane

The preparation of dinitromethane was reported in literature but its synthesis in large scale was known to be dangerous. So it was not thought to be proper for our mild homologation.

1.2.4. Bissulfonylmethane

Bis(phenylsulfonyl)methane was commercially available and could be also prepared by the oxidation of bis(phenylthio)methane. Among the candidates for a one-carbon synthon, encouragingly bis(phenylsulfonyl)methane showed the similar results with phenylsulfonylnitromethane in the reaction with aliphatic aldehydes. Proline also catalyzed the reaction of aliphatic aldehydes with bis(phenylsulfonyl)methane in mild condition to afford β,γ-unsaturated bissulfones[20] in good yields. But we couldn't find the method for the transformation of a bissulfonyl group into a carbonyl group in a mild condition. For example, the reduction of sulfones to sulfides, which result in the formation of thioacetals, was not successful. I thought it could be a good one-carbon synthon if the methods for its transformation to other functional group would be developed.

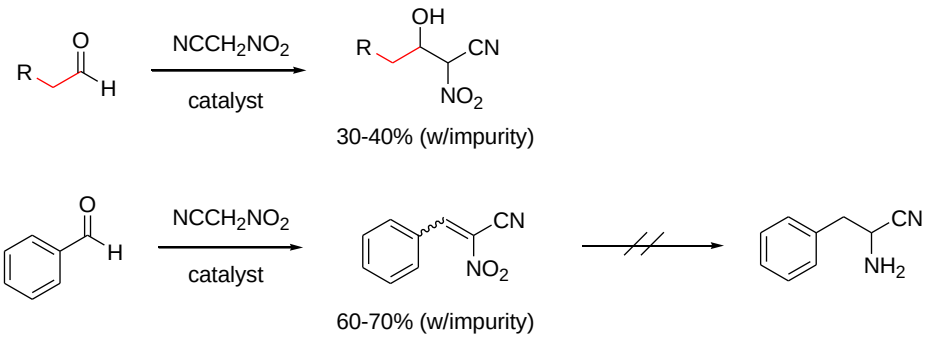
Scheme 19. The feasibility test with bissulfonylmethane as a one-carbon synthon



1.2.5. 2 cyanonitromethane

We also tested the possibilities of cyanonitromethane as a one-carbon synthon. In the case of aromatic aldehydes, tandem nitroaldol-dehydration occurred to give α,β-unsaturated nitroolefin. But in the case of aliphatic aldehydes, only nitroaldol reaction occurred and additional transformations to α,β-unsaturated nitroolefin were required. Moreover, selective reduction of nitro group in the presence of a labile cyano group was difficult.

Scheme 20. The feasibility test with 2-nitroacetonitrile as a one-carbon synthon



1.2.6. Phenylsulfonylnitromethane

After the feasibility tests with various one-carbon synthons, we were able to choose phenylsulfonylnitromethane as a possible one-carbon synthon that fit our synthetic strategy. Finally our studies have focused on the mild and convenient tandem nitroaldol-dehydration of aldehydes with phenylsulfonylnitromethane.

We have been interested in phenylsulfonylnitromethane as a one-carbon synthon in the one-carbon more homologation reaction because Wade *et al.* reported its tandem nitroaldol-dehydration reactions of aliphatic unbranched aldehydes to afford not α,β-unsaturated α-nitrosulfones but β,γ-unsaturated α-nitrosulfones as mentioned in 2.2. section in the introduction. The formation of β,γ-unsaturated α-nitrosulfones seemed to be very extraordinary because α,β-unsaturated α-nitrosulfones was expected to be stabilized by the conjugation with nitro group. The normally disfavored α,β-unsaturated α-nitrosulfones have been implicated in the formation of bis(α-nitrosulfones) **IIIb**, the further conjugate addition product of α,β-unsaturated α-nitrosulfones with phenylsulfonylnitromethane. Moreover, α,β-unsaturated α-nitrosulfones could be intercepted before isomerization to β,γ-unsaturated α-nitrosulfones **4** in the presence of nucleophile such as thiol or amine as shown in Figure 4.[11a] This phenomenon was also observed in our previous study on the development of a novel and efficient synthetic method for preparing β-amino-α-hydroxy acids and

their derivatives from the corresponding α-amino aldehydes by using an *N*-hydroxymethyl group as an internal nucleophile.[17a]

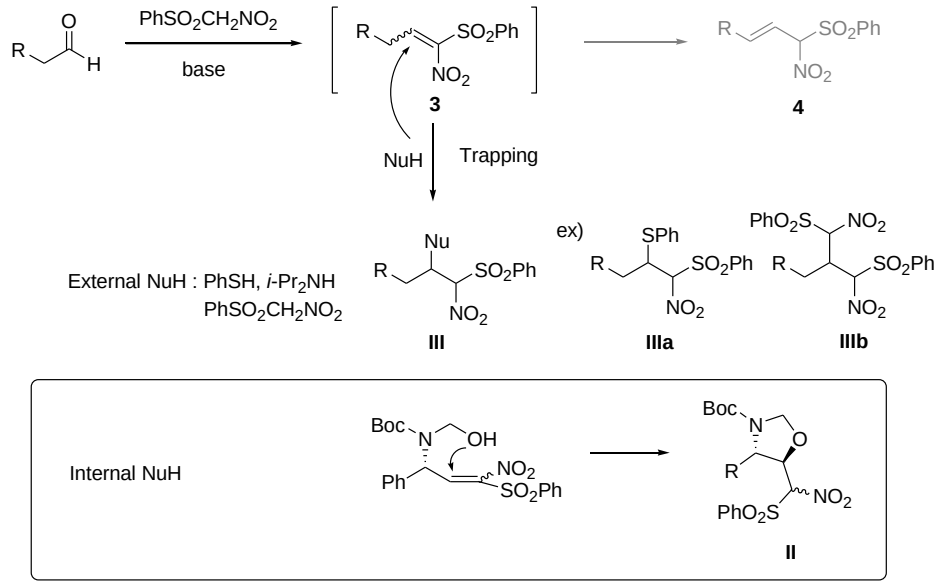


Figure 4. Trapping of α,β-unsaturated α-nitrosulfones intermediate with nucleophile.

Because the isomerization of α,β-unsaturated α-nitrosulfones to β,γ-unsaturated α-nitrosulfones **4** was critical to an adaptable one-carbon more and one-carbon less homologation, the further study on the isomerization was conducted. Whereas alkenes substituted with only one nitro or sulfonyl group were known to prefer α,β-unsaturated conjugate nitro compounds or sulfones, phenylsulfonylnitromethane or bis(phenylsulfonyl)methane with two large functional groups at α-

carbon gave exclusively β,γ-unsaturated non-conjugate nitro compounds or sulfones. So, we guess that the driving force for the non-conjugation may be to avoid the steric hindrance between the nitro group (or phenylsulfonyl group) and alkyl group in the trisubstituted alkenes as shown in Figure 5.

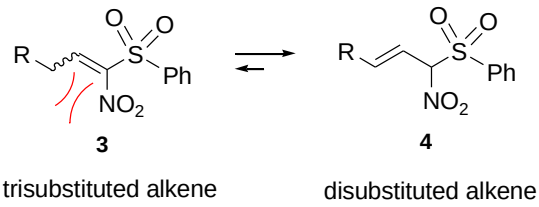
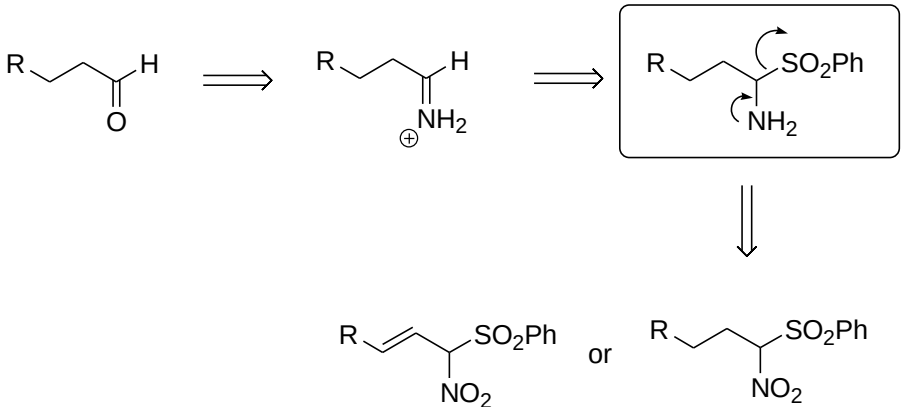


Figure 5. The equilibrium between α,β-unsaturated α-nitrosulfones **3** and β,γ-unsaturated α-nitrosulfones **4**.

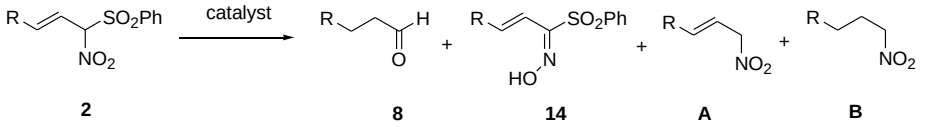
Our idea on the homologation was originated from the paper where it was reported that an α-aminosulfone moiety was an equivalent of an iminium ion which could be easily transformed to aldehyde by hydrolysis as shown in Scheme 21.[18] At first, we naively thought that α-aminosulfone moieties could be easily prepared by the reduction of α-nitrosulfone.

Scheme 21. α-Aminosulfone moiety as an equivalent of an aldehyde



Therefore, we initially focused on the selective reduction of nitro group in β,γ-unsaturated α-nitrosulfones using various reducing agents as shown in Table 1. But unfortunately all the trials for the selective reduction of α-nitrosulfone to α-aminosulfone were not successful. The desired product was not obtained under various conditions other than the conditions on the table. Unexpectedly even the reduction of the double bond in β,γ-unsaturated α-nitrosulfones also didn't afford the desired product in typical reduction conditions. In catalytic hydrogenation conditions, sulfonyl group seemed to be more easily reduced than a nitro group. In electron transfer methods for the nitro reduction, oxime **14** was usually obtained as a major product. Unfortunately only small amount of an aldehyde was observed in some cases.

Table 1. Feasibility test on reduction of β,γ-unsaturated α-nitrosulfone



2 **8** **14** **A** **B**

a : R = C_6H_{13}

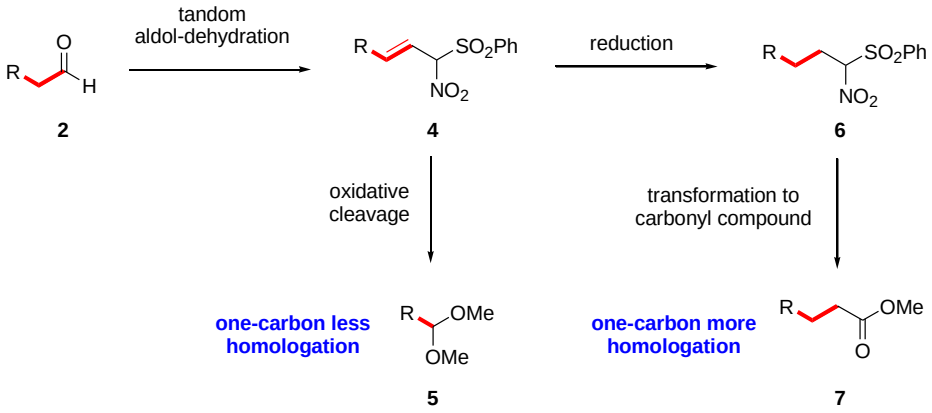
entry	catalyst	condition	Yield (%)
1	Pd/C	H_2(1atm), MeOH, RT	**A**+**B** (25)
2	Pd/C	H_2(1atm), DMAP, MeOH, RT	**B** (16)
3	Pd/C	H_2(1atm), 1*N* HCl, MeOH, RT	**14** (10)
4	PtO_2	H_2(50atm), THF, RT	**A**+**B** (23)
5	Raney nickel	H_2(3atm), EtOH, RT	**B** (15)
6	Raney nickel	HCOOH, reflux	-[a]
7	$SnCl_2$	EtOH, sonication	**14** (65)
8	Zn	$HCOON_2H_5$	-[a]
9	Fe	AcOH, EtOH-H_2O, sonication	**8**(10) + **14**(32)
10	SmI_2	*i*-$PrNH_2$, THF-H_2O	-[a]
11	LAH	THF, RT to reflux	-[a]
12	$LiBH_4$	THF, RT	-[a]
13	$NaCNBH_3$	AcOH, MeOH, reflux	-[b]
14	In	NH_4Cl, EtOH-H_2O, reflux	-[a]
15	$(NCOOK)_2$	AcOH, MeOH, RT	-[a]

a : unidentified products were observed.

b : most starting material was recovered.

We couldn't find a selective method of the reduction of nitro group but could find a method to transform a nitro group to an oxime through this research and it became a chance to discover a complementary one-carbon more homologation.

Scheme 22. Our plan for an adaptable one-carbon less and one-carbon more homologation using phenylsulfonylnitromethane



Finally, we modified our strategy on the homologation from the selective reduction of nitro group in β,γ-unsaturated α-nitrosulfones **4** to the selective reduction of double bond in β,γ-unsaturated α-nitrosulfones **4**. We thought that β,γ-unsaturated α-nitrosulfones **4** prepared by the tandem nitroaldol-dehydration reaction could be transformed not only to one-carbon more homologous esters **7** by the reduction followed by transformation to carbonyl group, but also to one-carbon less homologous aldehydes or acetals **5** by oxidative

cleavage as shown in Scheme 22.

2. Adaptable one-carbon more and one-carbon less homologation

2.1. Process development for the preparation of the one-carbon synthon, phenylsulfonylnitromethane

In spite of the vast potential of phenylsulfonylnitromethane, it is disadvantaged by its high cost and limited synthetic accessibility. To be widely used as a one-carbon synthons, it can be stably provided in homologation reactions. But several preparation methods that were previously reported had some limitations as mentioned in the introduction. To overcome this disadvantage, we decided to set up the synthetic procedure for phenylsulfonylnitromethane in a large scale. First, we checked the methods which were mentioned in 2.1. section but they didn't show good results in large scales. So it was necessary to develop the process for the stable preparation of phenylsulfonylnitromethane. Iodonitromethane, which is prepared by the reaction of nitromethane and iodine in the presence of the base, can react not only with benzenesulfinate to give a product but also with

extra iodine to give an undesired product, diiodonitromethane. This control was a key factor of the process development. After long efforts, we have developed a synthetic procedure that can reproducibly provide *ca*. 10g of phenylsulfonylnitromethane by modification of known procedures as follows.[11c] Removal of the dimethylformamide as much as possible in the extraction and washing step can facilitate the purification of phenylsulfonylnitromethane.

----------citation----------

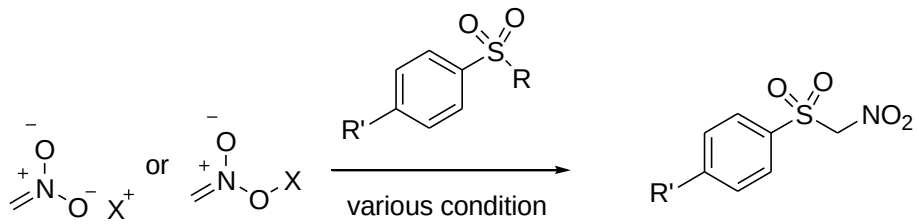
A 1-L, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar (40 x 20 mm) was charged with nitromethane (9.0 mL, 165.1 mmol, 1.00 equiv) and *N*,*N*-dimethylformamide (180 mL). After the reaction mixture was stirred for 10 min in an ice bath, 1,8-diazabicycloundec-7-ene (DBU, 27.4 mL, 181.7 mmol, 1.10 equiv) was added by syringe for 5 min. After further stirring for 20 min in an ice bath, benzenesulfinic acid sodium salt ($C_6H_5SO_2Na$, 22.50 g, 137.1 mmol, 0.83 equiv) and iodine (31.85 g, 125.5 mmol, 0.76 equiv) were added to the flask and the mixture was stirred for another 5 min at 0 ℃. Then, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was cooled again to 0 ℃ in an ice bath, and diluted with water (150 mL). A saturated aqueous solution of Na_2SO_3 was added to the reaction flask until the mixture turned from

dark brown to bright yellow. The mixture was then slowly acidified to *ca*. pH 1 at 0 ℃ with a conc. aqueous solution of HCl (ca. 45 mL). The acidified mixture was transferred to a 2-L separatory funnel and the reaction flask was rinsed with Et_2O (2 x 50 mL). The aqueous layer was extracted with Et_2O (4 x 300 mL). The combined organic layers were washed with an aqueous solution of HCl (0.1 M, 2 x 500 mL), dried over $MgSO_4$ (30 g), filtered, and concentrated under reduced pressure (25 ℃, 25 mmHg). The resulting crude product wass purified by silica gel column chromatography to afford 10.00 g (36%) as white powder.

Even though we have developed a synthetic procedure that can reproducibly provide *ca*. 10g of phenylsulfonylnitromethane, we also tried to find more practical preparation method of phenylsulfonyl-nitromethane. Theoretically, the most economic and simple synthetic method may be the reaction between a carbanion of nitromethane and an electrophile such as sulfonyl halide but it has not been reported yet. An anion of nitromethane can act as not only *C*-nucleophile but also *O*-nucleophile. Unfortunately *O*-sulfonylation may be predominant in this reaction. To find a condition for the selective *C*-sulfonylation, we tried the reaction of various anions of nitromethane with several

sulfonylating agents as shown in Table 2. The soft counter ion was known to prefer the action as a *C*-nucleophiles but the reaction with even quaternium ammonium salt of nitromethane also didn't afford the desired C-sulfonylation product. *N*-sulfonylbenzotriazoles was known as advantageous reagents for *C*-sulfonylation and the reaction of *N*-sulfonylbenzotriazoles with enolates of esters gave desired *C*-sulfonylation product, α-sulfonyl esters.[27] However, the reactions of *N*-Sulfonyl-benzotriazoles with nitronate ions didn't give the desired *C*-sulfonylation product, phenylsulfonylnitromethane. The reactions with silyl nitronate also didn't give the desired *C*-sulfonylation product. We have made a lot of efforts to solve this problem, but we have not found a solution yet. We thought that the availability of phenylsulfonylnitromethane and other sulfonyl compounds could be increased significantly if the solution for the *C*-sulfonylation of nitonates would be found.

Table 2. *C*-sulfonylation study of nitronate



entry	X	R	R’	Results
1	Li	Cl	H	No desired product
2	Na	Cl	H	No desired product
3	K	Cl	H	No desired product
4	Et_3NH	Cl	H	No desired product
5	Bu_4N	Cl	H	No desired product
6	TBS	Cl	H	No desired product
7	Bu_4N	I	H	No desired product
8	Na	Benzotriazole	H	No desired product
9	Bu_4N	Benzotriazole	H	No desired product
10	Na	imidazole	CH_3	No desired product
11	Bu_4N	imidazole	CH_3	No desired product
12	Na	OTs	CH_3	No desired product
13	Bu_4N	OTs	CH_3	No desired product
14	Na	SO_2Ph	H	No desired product
13	Bu_4N	SO_2Ph	H	No desired product

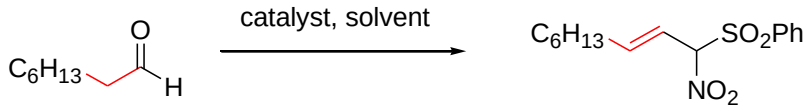
2.2. Mild tandem addition-elimination reaction

Initial our studies have focused on the mild and convenient tandem nitroaldol-dehydration with phenylsulfonylnitromethane to afford β,γ-unsaturated nitrosulfones, because more than 2 equiv. of strong base such as LDA was known to be required for the reaction. In comparison, three sequential reactions, that is, its nitroaldol, the dehydration, and the intramolecular conjugate addition of *N*-hydroxymethyl α-aminoaldehydes in the presence of DMAP was successfully conducted in our previous study.[17a] First, we tested the reaction with various amine bases including DMAP and common inorganic bases but unfortunately this condition were all not successful for other normal aldehydes to afford β,γ-unsaturated nitrosulfones **4** in good yields. Piperidine that could form iminium ion with aldehydes showed a better yield than other tertiary amine or aromatic amine such as TEA and DMAP. Fortunately, desired product **4** were obtained in low yields in the presence of the catalyst that can act as both acid catalyst and base catalyst such as ammonium acetate, quinidine, NH_2-functionalized silica, and proline.[21] Then, we tried to optimize tandem aldol-dehydration reaction with octanal **2a** in the presence of proline as a model study. As the amount of phenylsulfonylnitromethane in the reaction mixture increases, the formation of bis(α-nitrosulfones) **IIIb**,

the further conjugate addition product of α,β-unsaturated α-nitrosulfones with phenylsulfonylnitromethane tends to increase. On the contrary, the formation of self-aldol products of α-unbranched aldehyde tends to increase as the amount of aldehyde in the reaction mixture increases. Finally, 1.0 eq. and 0.3 eq. of aldehydes were added separately at the beginning and the middle of reaction to increase the yield of the reaction (Entry 9-10) because the monitoring of the reaction by ^{1}H NMR spectrum showed faster depletion of aldehyde than that of phenylsulfonylnitromethane. As the amount of catalyst or the temperature of the reaction increased, the reaction rate was increased but side reactions such as self-aldol reaction was also increased (Entry 10-12). Therefore, the control between our reaction and self-aldol reaction was an important hurdle to overcome. As a result, the reaction of 1.0 - 1.3 eq. of an aldehyde with 1.0 eq. of phenylsulfonylnitromethane in the presence of 0.05 eq. of proline in especially DMSO at room temperature showed better yields.

But it took still long time to complete the reaction. Moreover, α-branched aldehydes such as 2-ethylhexanal showed slower reaction rate than unbranched aldehydes and elevated temperature was required for the reaction. Fortunately, we found that sonication can help to reduce the reaction time dramatically from 48 hours to 4 hours without the significant decrease of the yield (Entry 13, Table 3).[22]

Table 3. Optimization of tandem nitroaldol, dehydration reaction



2a **4a**

entry	catalyst	eq.	solvent	Time(h)	Yield(%)
1	TEA	0.1~2.3	various	48	< 5
2	DMAP	0.1~2.3	various	48	< 5
3	NaOH	0.1~2.3	various	48	< 5
4	Piperidine	0.1	THF	48	18
5	Quinidine	0.1	THF	48	35
6	NH_2-functinalized silica	0.1	THF	48	25
7	NH_4OAc	0.1	DMSO	48	40
8	Proline	0.1	DMF	48	35
9	Proline	0.1	DMSO	48	53
10[a]	Proline	0.1	DMSO	48	78
11[a]	Proline	0.05	DMSO	48	87
12[a]	Proline	0.01	DMSO	72	81
13[a,b]	Proline	0.05	DMSO	4	86

[a] 1.0 eq. and 0.3 eq. of aldehydes were added separately at the beginning and the middle of reaction
[b] sonication was applied in the reaction

It is interesting that proline can catalyze the tandem addition-elimination reaction because it can also catalyze self-aldol reaction and has been rarely used for the nitroaldol reactions of α-unbranched aldehydes. Therefore, we were interested in the mechanism of proline-catalyzed tandem addition-elimination reaction of aliphatic aldehydes with phenylsulfonylnitromethane.

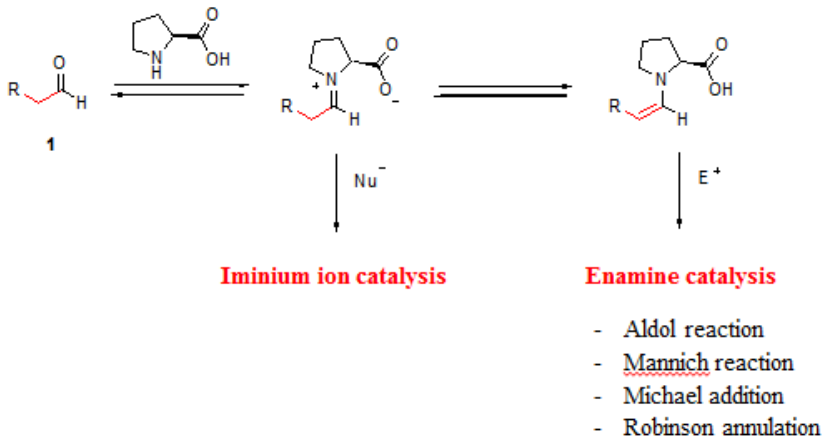


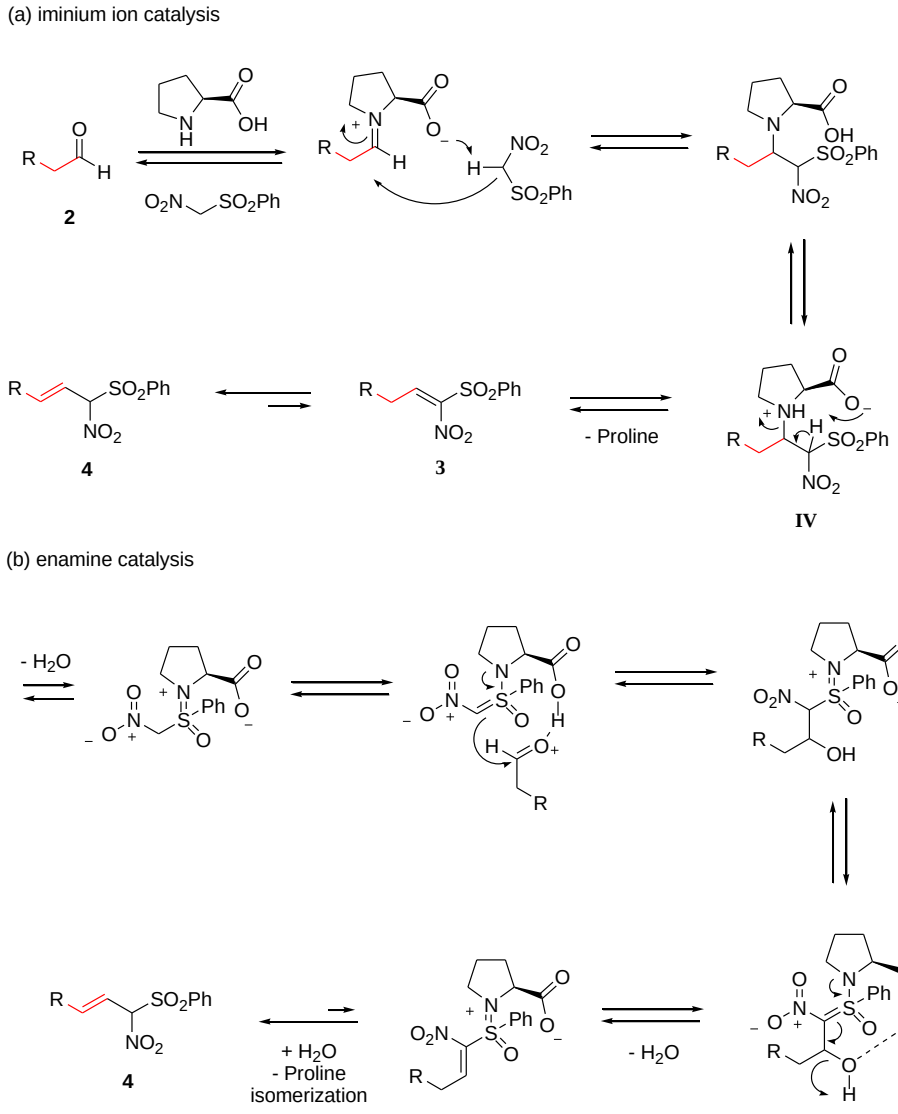
Figure 6. Catalysis modes of proline.

There are two possible proline-catalytic pathways, iminium ion catalysis and enamine catalysis. Iminium ion catalysis proceeds via conversion of a carbonyl compounds into iminium ions, facilitating a reaction with various nucleophiles. On the other hand, Enamine catalysis involves catalytically generated enamine intermediates, which can react with various electrophiles. Most well-known proline-

catalyzed reactions were known to proceed via enamine catalysis. In proline-catalyzed aldol reaction, it was known that aldol product was formed by enamine catalysis and only small amount of aldol condensation product was formed as a side product by iminium catalysis through Mannich reaction-elimination sequences.[23]

The mechanism of our proline-catalyzed reaction with phenylsulfonylnitromethane could be explained by not only iminium ion catalysis but also enamine catalysis (Scheme 23). The first mechanism is iminium ion catalysis. The reactions of iminium ions with nucleophiles usually give amines stoichiometrically. But in the case of low p*K*a of phenylsulfonylnitromethane, resulting intermediate **IV** could deprotonate an acidic proton on themselves. It might facilitate the elimination to afford α,β-unsaturated α-nitrosulfones **3**, which could isomerize to β,γ-unsaturated nitrosulfones **4**. Moreover, proline could be recycled. The second mechanism is enamine catalysis. A sulfonyl group in phenylsulfonylnitromethane might be reacted with proline to afford sulfoximinium ion, which make a proton positioned at the α-carbon to the nitro group more acidic and facilitate the formation of an enamine-like form. Therefore, it might be reacted more easily with an aldehyde that is activated by carboxylic acid group of proline. The resulting nitroaldol product could be also dehydrated and isomerized more easily with the help of proline catalyst.

Scheme 23. Proposed mechanism of proline-catalyzed tandem addition-elimination of aliphatic aldehydes



In comparison to the reactions with phenylsulfonylnitromethane, those with α-alkyl substituted phenylsulfonylnitromethane or

nitromethane didn't give the desired products. In the study with the similar one-carbon synthons, proline interestingly catalyzed the reaction with not bromonitromethane but bis(phenylsulfonyl)methane. The proline-catalyzed tandem addition-elimination reaction seems to be deeply dependent on the acidity of the one-carbon synthon.

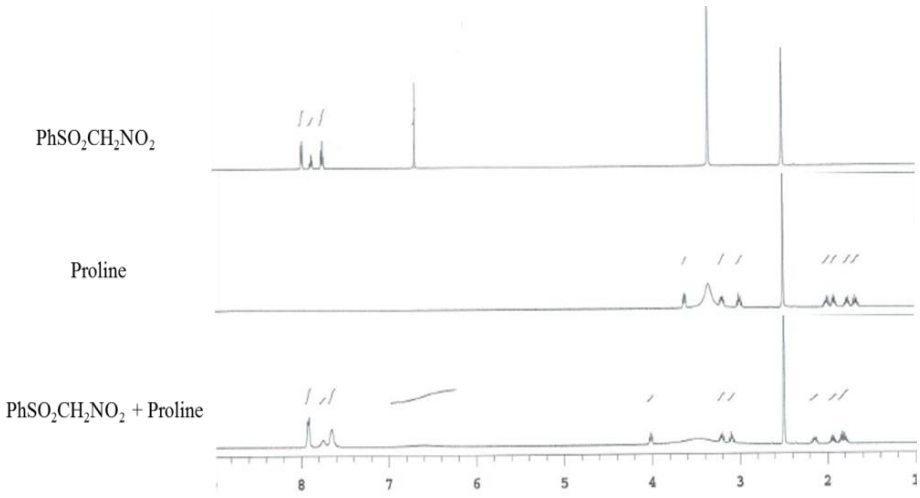


Figure 7. The NMR study on the interaction between phenylsulfonylnitromethane and proline.

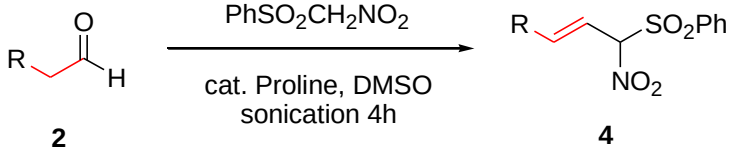
NMR experiments were conducted to confirm whether the mechanism of the proline-catalyzed tandem addition-elimination reaction follows iminium ion catalysis or enamine catalysis. On the NMR experiment, the representing peak of the enamine-like form was not observed and only broadening of the peak in the phenylsulfonylnitromethane was

observed when phenylsulfonylnitromethane and proline was mixed in DMSO-d_6 (Figure 7). So, we thought that iminium catalysis would be more reasonable mechanism of the reaction. In the iminium catalysis, no reaction with α-alkyl substituted phenylsulfonylnitromethane could be explained by the absence of α-proton in the intermediate **IV** for the elimination to afford α,β-unsaturated α-nitrosulfones **3**.

Next, we have tested tandem addition-elimination reaction with various aldehydes to show the scope and limitations of our homologation. The optimized reaction condition (entry 13 in Table 3) was applied to various aldehydes. Only aldehydes that have a proton at the α-carbon to the carbonyl group could give the desired β,γ-unsaturated nitrosulfones **4**. The reaction with aldehydes that have no proton at the α-carbon to the carbonyl group such as benzaldehyde and pivalaldehyde didn't afford desired products as mentioned in the mechanism. The reaction with α-branched aldehydes such as 2-ethylhexanal and 2-diphenylacetaldehyde showed slower reaction rate than unbranched aldehydes and elevated temperature was required when the reaction proceeded at room temperature. In some entries (**2c-2h**), remarkable decrease in yields was observed owing to the side reactions such as oxidation of starting materials or formation of polymeric unidentified substances. But β,γ-unsaturated α-nitrosulfones **4c-4h** was obtained in reasonable yields when DMSO which was

deoxygenated by purging with nitrogen or argon and antioxidant was introduced in the reaction. In the screening test with several antioxidants, significant differences between antioxidants were not observed. Among them, Tinogard TT® (Pentaerythritol tetrakis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate)[24] showed good results regardless of the type of the substrate. As mentioned above, the formation of β,γ-unsaturated α-nitrosulfones **4** through the isomerization of α,β-unsaturated nitrosulfones is critical to an adaptable one-carbon more and one-carbon less homologation. Fortunately, the significant formations of α,β-unsaturated nitrosulfones or γ,δ-unsaturated nitrosulfones were not observed in **4a-4k** under the reaction condition. In the case of the hydrocinnamaldehyde derivatives **2d-2g**, there might be another issue of further isomerization of the double bond in addition to the preference of β,γ-unsaturated α-nitrosulfone intermediates **4d-4g** over α,β-unsaturated nitrosulfone intermediates **3d-3g**, which was the isomerization of β,γ-unsaturated α-nitrosulfone intermediates **4d-g** to γ,δ-unsaturated α-nitrosulfone intermediates whose double bonds would be stabilized by the conjugation with the aromatic ring. However, the undesired isomerization was not observed.

Table 4. Tandem addition and elimination



2 **4**

entry	R	Yield (%)[a]
a	*n*-C_6H_{13}	86
b	*n*-$C_{10}H_{21}$	81
c	4-PrO-Ph	87[b]
d	$PhCH_2$	86[b]
e	3-Cl-$PhCH_2$	70[b]
f	4-MeO-$PhCH_2$	76[b]
g	Ph(Me)CH	75[b]
h	$CbzNHCH_2$	61[b]
i	$BnOCH_2CH_2$	83
j	$PhCH_2CH_2$	84
k	$MeO_2C(CH_2)_7$	70

[a] The yields based on $PhSO_2CH_2NO_2$ (**1**).

[b] 0.0025 eq. of Tinogard TT(antioxidant) was added in the reaction.

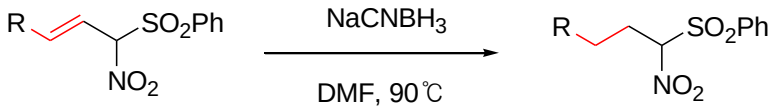
An aliphatic aldehyde with a nitrogen atom at the β-carbon to the aldehyde group (entry h) and an oxygen atom at the γ-carbon to the aldehyde group (entry i) provided the desired product **4** in good yields although the similar aldehydes with a nitrogen atom at the α-carbon

such as *N*-Cbz-aminoacetaldehyde or with an oxygen atom at the α- or β-carbon such as benzyloxyacetaldehyde and benzyloxypropionadehyde did not provide the desired product **4** in reasonable yields. The mild reaction condition with proline enable the CbzN-H proton to be compatible. With an ester group in the same substrate (entry k), phenylsulfonylnitromethane showed the chemoselectivity and selectively reacted with the aldehyde carbonyl group over the ester carbonyl group.

2.3. Reduction of β,γ-unsaturated nitrosulfones to saturated nitrosulfones

The reduction of β,γ-unsaturated α-nitrosulfones **4** has been investigated with various reductants. Unexpectedly, the reduction of their double bond in various catalytic hydrogenation conditions was not successful. But saturated nitrosulfones **6** was successfully obtained in good yields by the treatment of $NaCNBH_3$[25] in DMF at 90°C. According to our study with $NaCNBD_3$, it seemed to occur through double bond isomerization to α,β-unsaturated α-nitrosulfones at elevated temperature in polar solvent, followed by 1,4-addition of hydride (Scheme 24).[26]

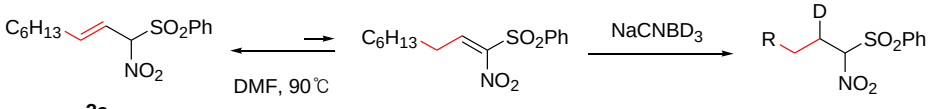
Table 5. Reduction to saturated nitrosulfones



4 **6**

entry	R	Yield (%)
a	*n*-C_6H_{13}	87
b	*n*-$C_{10}H_{21}$	86
c	4-PrO-Ph	45
d	$PhCH_2$	85
e	3-Cl-$PhCH_2$	72
f	4-MeO-$PhCH_2$	69
g	Ph(Me)CH	70
h	$CbzNHCH_2$	78
i	$BnOCH_2CH_2$	89
j	$PhCH_2CH_2$	84
k	$MeO_2C(CH_2)_7$	83

Scheme 24. Study on the mechanism using $NaCNBD_3$



2a **4a'**

For this reason, **4c** having a double bond conjugated with phenyl group showed a lower yield than other substrates, and α-branched aldehydes such as 2-ethylhexanal and diphenylacetaldehyde didn't afford the saturated nitrosulfones **6**. We presumed that the isomerization of β,γ-unsaturated α-nitrosulfone **4** into α,β-unsaturated α-nitrosulfone **3** would be more difficult for aliphatic aldehydes with one α-proton because of the larger steric hindrance between the nitro or phenylsulfonyl group and alkyl group as shown in Figure 8.

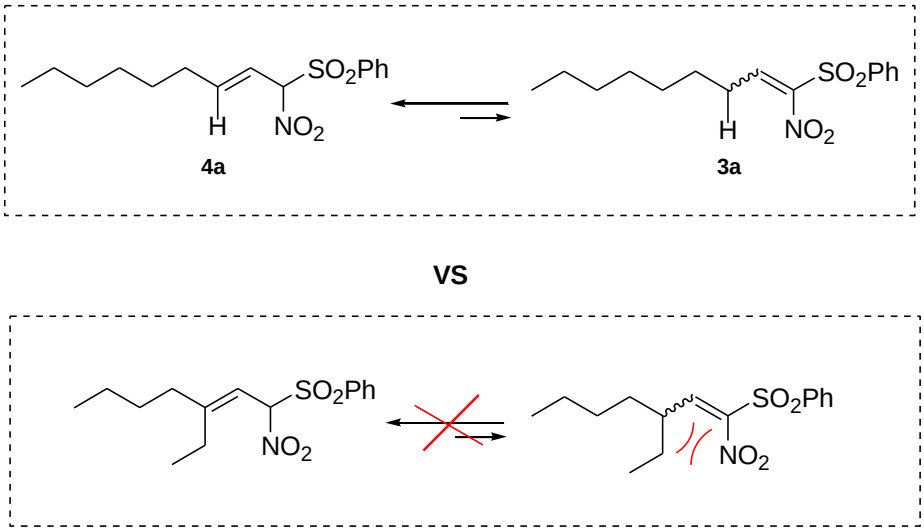
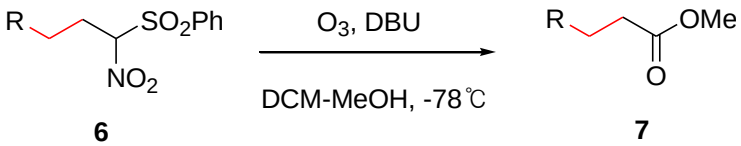


Figure 8. The tendency of isomerization to α,β-unsaturated α-nitrosulfone **3** according to the substrates.

2.4. Transformation to one-carbon more homologous carbonyl compounds

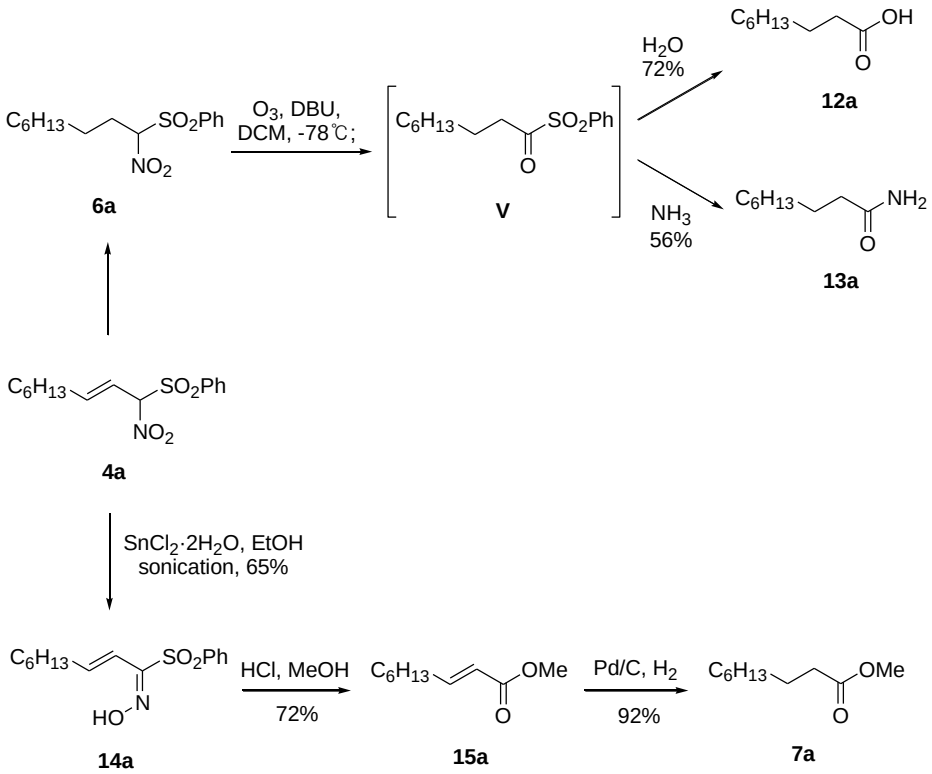
Table 6. Transformation to one-carbon more homologous esters



6 **7**

entry	R	Yield (%)
a	*n*-C_6H_{13}	73
b	*n*-$C_{10}H_{21}$	80
c	4-PrO-Ph	68
d	$PhCH_2$	78
e	3-Cl-$PhCH_2$	74
f	4-MeO-$PhCH_2$	73
g	Ph(Me)CH	80
h	$CbzNHCH_2$	88
i	$BnOCH_2CH_2$	66
j	$PhCH_2CH_2$	88
k	$MeO_2C(CH_2)_7$	71

Scheme 25. Functional group transformations of **4a** to other one-carbon longer carbonyl homologs



One-carbon more homologation was established after the oxidation of the anion of phenylsulfonylnitromethyl group in saturated nitrosulfones **6** into the methyl ester group (Table 6). It was known that the anion of nitrosulfone produced under the basic conditions could be oxidized with O_3 to give an α-keto phenylsulfonyl group and the following its solvolysis by methanol afforded the corresponding methyl ester.

One-carbon more carboxylic acid **12a** or amide **13a** could be also obtained by the simple change of the nucleophile from methanol to

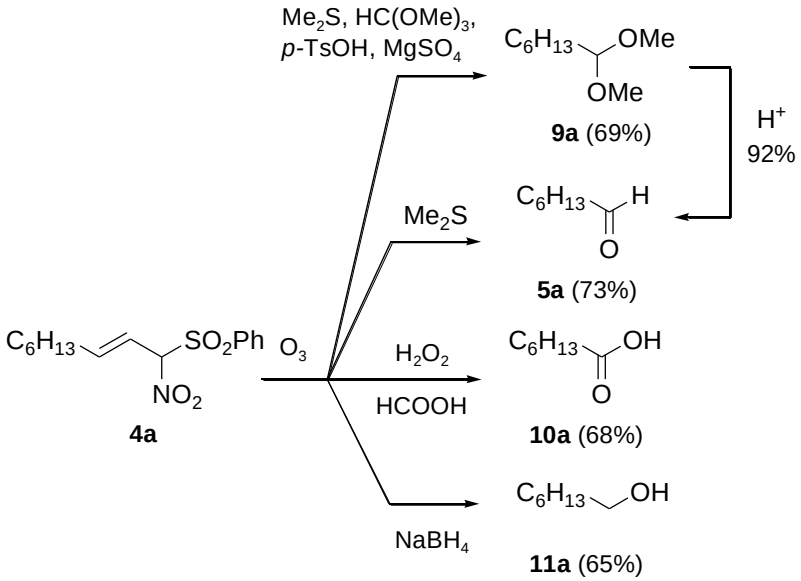
water or amine in the oxidation reactions, respectively, because the nitronate produced in-situ under the basic conditions from **6a** was mildly oxidized with ozone to give the intermediate **V** with the α-keto phenylsulfonyl group as shown in Scheme 25.

Unfortunately this homologation can't be applied to the substrate having a functional group that is incompatible to ozonolysis such as olefin. Therefore, we also have investigated complementary one-carbon more homologation via reduction of nitro group in β,γ-unsaturated α-nitrosulfones **4** or saturated nitrosulfones **6**.[26] As mentioned in 1.2.6 section, the reduction of their nitro group in various conditions provided only desulfonylated products or their oximes as a major product. The treatment of **4a** with tin(II) chloride dehydrate gave oxime **14a** in a reasonable yield, which was hydrolyzed in acidic condition to give a homologous methyl ester 1**5a**. This complementary method for the one-carbon more homologation can provide an alternative one-carbon more homologation for the substrates having a functional group that is incompatible to ozonolysis. Moreover, synthetically more useful α,β-unsaturated esters could be obtained. A homologation method to one-carbon more α,β-unsaturated esters from aldehydes is not common although two-carbon more α,β-unsaturated esters can be easily prepared from aldehydes by the reaction with several two carbon synthons. Finally, the catalytic hydrogenation of the C-C double bond

in **15a** yielded **7a** in a good yield.

2.5. Transformation to one-carbon less homologous carbonyl compounds

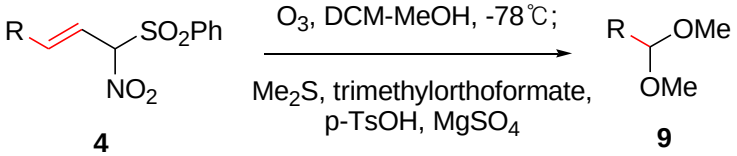
Scheme 26. Functional group transformations of **4a** to other one-carbon less carbonyl homologs



One-carbon less homologation was successfully conducted by ozonolysis of β,γ-unsaturated α-nitrosulfones **4**. The merit of ozonolysis is that various carbonyl compounds and their derivatives can be obtained according to its work-up method.[27] Reductive work-up conditions are far more commonly used. The use of triphenylphosphine,

thiourea, zinc dust, or dimethyl sulfide as a reductant produces aldehydes or ketones while the use of sodium borohydride produces alcohols. The use of hydrogen peroxide in the presence of formic acid produces carboxylic acids as shown in Scheme 26.

Table 7. Transformation to one-carbon less homologous acetals



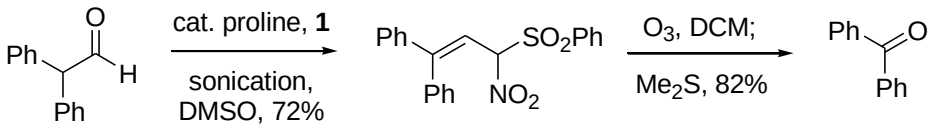
4 **9**

entry	R	Yield (%)
a	*n*-C_6H_{13}	69
b	*n*-$C_{10}H_{21}$	78
c	4-PrO-Ph	53
d	$PhCH_2$	53
e	3-Cl-$PhCH_2$	74
f	4-MeO-$PhCH_2$	63
g	Ph(Me)CH	67
h	$CbzNHCH_2$	-
i	$BnOCH_2CH_2$	73
j	$PhCH_2CH_2$	73
k	$MeO_2C(CH_2)_7$	79

In our study, homologous one-carbon less aldehydes was isolated as a more stable and less volatile dimethylacetal form **9** in reasonable yields after the treatment of trimethylorthoformate in the presence of *p*-TsOH and $MgSO_4$ (Table 7).[28] Dimethylacetals **9** can be easily converted into aldehydes **5** by the acid hydrolysis.

To check if the one-carbon less homologation of aliphatic aldehydes having one-α protone is possible, we have also performed the one-carbon shortening reaction of a derivative of diphenylacetaldehyde and the corresponding benzophenone was obtained in a 82% yield as shown below.

Scheme 27. One-carbon less homologation of diphenylacetaldehyde

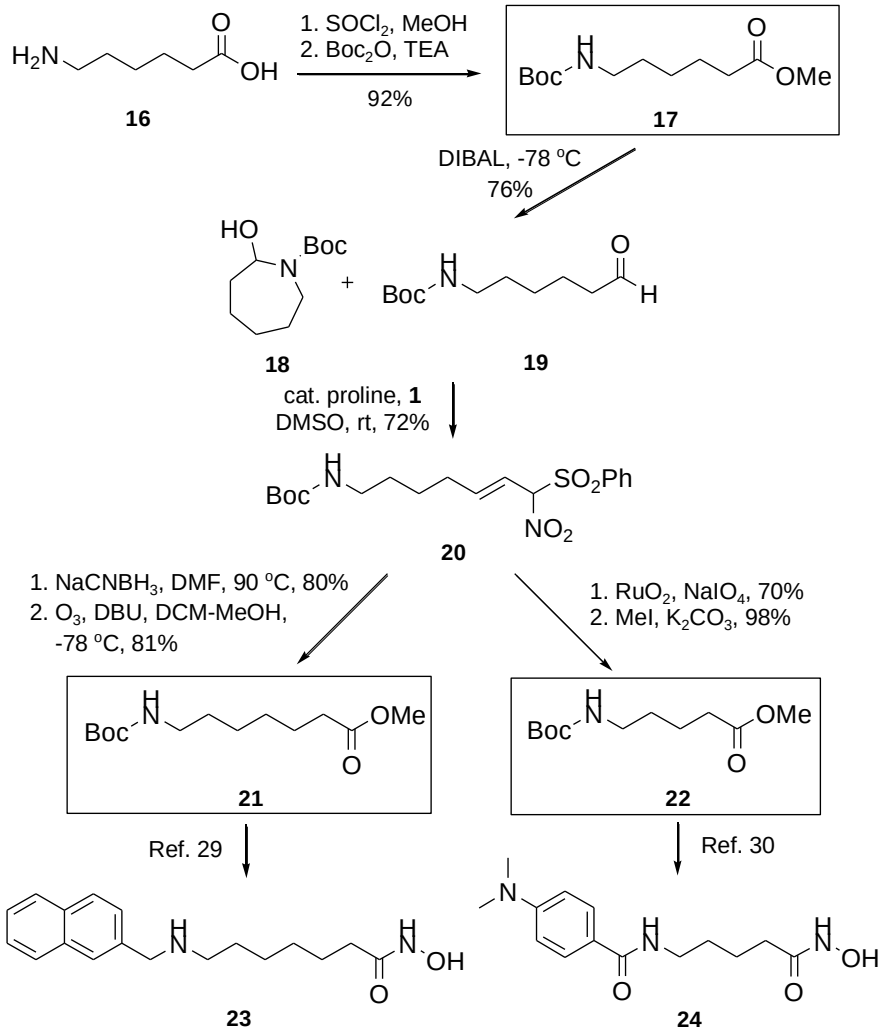


2.6. The application of our homologation

To demonstrate the synthetic utility of the our homologation, we decided to synthesize two key intermediates, **21** and **22**, for biologically active histone deacetylase inhibitors **23** and **24** from readily available common starting material, 6-aminohexanoic acid (**16**), in Scheme 27. In the previous reports, the two different amino acid derivatives, a C_7-amino acid derivative **21**[29] and a C_5-amino acid derivative **22**,[30] were obtained from rather expensive 7-aminoheptanoic acid and 5-aminopentanoic acid, respectively. We tried to produce both compounds, **21** and **22**, from the common intermediate **20** that was derived in a few steps from a cheap starting compound **16**, a monomer of Nylon 6®. A precursor to the common intermediate **20** was prepared, as a mixture of a cyclic and an acyclic form of amino aldehydes **18** and **19**, from the DIBAL reduction of an intermediate, methyl *N*-Boc-6-aminohexanoate (**17**). Compound **17** was prepared from the esterification of **16** followed by the *N*-Boc protection. The ratio of a cyclic and an acyclic form of amino aldehydes **18** and **19** was changed according to the reaction conditions. The mixture of a cyclic and an acyclic form of amino aldehydes **18** and **19** could be also prepared from caprolactam but a cyclic form **18** existed predominantly in the mixture, which resulted in the decrease of the reaction rate with

phenylsulfonylnitromethane (**1**). The precursor as a mixture of amino aldehydes **18** and **19** was reacted with phenylsulfonylnitromethane (**1**) at room temperature to afford β,γ-unsaturated α-nitrosulfones **20** in a good yield. C_7-amino acid derivative **21** was successfully obtained as described above by following the same reduction and oxidation protocol. But the ozonolysis of β,γ-unsaturated α-nitrosulfones **20** to obtain one-carbon less carboxylic acid was not successful. The acid-labile *N*-Boc group in the intermediate **20** was probably not compatible with formic acid used in the oxidative work-up after the ozonolysis. So, we tried to find an alternative functional group transformation of the intermediate **20** to one-carbon less homologous carboxylic acid. Finally C_5-amino acid derivative **22** was prepared by a modified oxidative cleavage reaction of the C-C double bond with catalytic RuO_4, followed by the esterification.

Scheme 28. Application of our homologation for the synthesis of two key intermediates, **21** and **22**, of biologically active histone deacetylase inhibitors, **23** and **24**



Conclusion

We found that the mild proline-catalyzed reaction of aliphatic aldehydes with phenylsulfonylnitromethane under ultrasound afforded β,γ-unsaturated α-nitrosulfones **4** in good yields through tandem addition-elimination-isomerization. Using this reaction, we have developed a new concept of the adaptable one-carbon more and one-carbon less homologation of aliphatic aldehydes via same intermediate, β,γ-unsaturated α-nitrosulfones **4**. While the ozonolysis of the key intermediates gave one-carbon less carbonyl homologs, the reduction of the double bond in the same key intermediates followed by the ozonolysis of the nitronate provided one-carbon more carbonyl homologs. The desired one-carbon more and one-carbon less homologous carbonyl compounds was obtained from various aliphatic aldehydes in good yields under mild conditions. Moreover, we also prepared complementary one-carbon more homologation for the substrate having a functional group that is labile in the ozonolysis reaction. Its synthetic value was demonstrated by the synthesis of the two key intermediates, a C7-amino acid derivative **21** and a C5-amino acid derivative **22**, for biologically active histone deacetylase inhibitors **23** and **24**. The two different amino acid derivatives, a C_7-amino acid derivative **21** and a C_5-amino acid derivative **22**, which were previously

obtained from rather expensive 7-aminoheptanoic acid and 5-aminopentanoic acid respectively, have been prepared using our homologation from the common intermediate **20** that was derived in a few steps from cheap and readily available 6-aminohexanoic acid (**16**) (C6-amno acid). Our flexible homologation method could increase the synthetic availability of the carbonyl compounds and greatly diversify the choice of the chemical reactions for the construction of new carbon-carbon bonds. We expect this homologation method to provide one of effective solutions for the problems on the homologation during the synthesis of target compounds.[31]

Experimental Details

1. General

All reagents were purchased from commercial suppliers and used without further purification unless otherwise mentioned. Aldehydes were used after purification by vacuum distillation or column chromatography. Dimethyl sulfoxide and *N*,*N*-dimethylformamide was stored over 4Å molecular sieves before use. All experimental glassware, syringes, and magnetic stirring bars were oven-dried and stored in a desiccator before use. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} glass plates pre-coated with a 0.25-mm thickness of silica gel, which were visualized by UV florescence quenching (254 nm), PMA, $KMnO_4$, cerium molybdate staining solution. Solvents were evaporated by using a rotary evaporator. Column chromatography was performed on kiesel gel 60 (70-230 mesh) silica gel. The ultasonic treatment was performed in ultrasonic cleaner bath for laboratory (Branson 5210, 140 W, 47 kHz). Water was exchanged to control the temperature of the water bath less than 40℃. NMR spectra were measured on commercially available spectrometers at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra,

^{1}H spectra were calibrated from internal standard TMS (δ 0.0). ^{13}C spectra were calibrated from solvent resonance ($CHCl_3$: 77.23). NMR data are reported as: chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. Infrared spectra were recorded on a Bruker TENSOR 27 FT-IR spectrometer and reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were measured by the electron ionization (EI), the chemical ionization (CI), and fast atom bombardment (FAB) ionization method. Melting points were determined with an open capillary melting point apparatus.

2. General Procedure of homologation

2.1. General Procedure for the preparation of β,γ-unsaturated α-nitrosulfones 4

To a solution of phenylsulfonylnitromethane (**1**) (402 mg, 2.00 mmol) in DMSO (2.0 mL) were added at room temperature aldehyde **2** (2.00 mmol) and proline (12 mg, 0.10 mmol). If necessary, pentaerythritol tetrakis(3,5-di-tert-butyl-4-hydroxy-hydrocinnamate) (6 mg, 0.005

mmol) was added or deoxygenated DMSO by purging with argon gas for several minutes before use. The reaction flask was placed in a sonicator for 2 h. Then, aldehyde **2** (0.60 mmol) was added again to the reaction mixture, which was then placed in the sonicator for further 2 h. The mixture was diluted with ether (20 mL) and aqueous 0.1 *N* HCl solution (20 mL) and extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **4** in 61 - 88% yields. The yields were calculated based on the amount of phenylsulfonylnitromethane (**1**).

*1-Benzenesulfonyl-1-nitronon-2-ene (**4a**):*

Colorless oil; yield 88%; ^{1}H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.22-1.34 (m, 6H), 1.36-1.44 (m, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 5.64 (dd, *J* = 9.5, 15.0 Hz, 1H), 5.87 (d, *J* = 9.5 Hz, 1H), 6.14 (dt, *J* = 7.0, 15.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 14.3, 22.7, 28.2 28.9, 31.7, 32.9, 103.8, 115.0, 129.5, 130.5, 134.5, 135.6, 147.6 ppm; IR (film): 2956, 1561, 1341, 1157 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{15}H_{22}NO_4S$: 312.1270, Found: 312.1269.

*1-Benzenesulfonyl-1-nitrotridec-2-ene (**4b**):*

Colorless oil; yield 81%; ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.21-

1.33 (m, 14H), 1.35-1.43 (m, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 5.64 (dd, *J* = 9.5, 14.5 Hz, 1H), 5.87 (d, *J* = 9.5 Hz, 1H), 6.14 (dt, *J* = 7.0, 14.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 14.3, 22.9, 28.3 29.3, 29.5, 29.5, 29.7, 29.8, 32.1, 32.9, 103.7, 114.9, 129.5, 130.5, 134.4, 135.6, 147.6 ppm; IR (film): 2926, 1562, 1343, 1157 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{19}H_{30}NO_4S$: 368.1896, Found: 368.1890.

*1-(3-Benzenesulfonyl-3-nitropropenyl)-4-propoxybenzene (**4c**):*

Yellowish oil; yield 87%; ^{1}H NMR δ 1.04 (t, *J* = 7.0 Hz, 3H), 1.82 (sex, *J* = 7.0 Hz, 2H), 3.94 (t, *J* = 7.0 Hz, 2H), 6.02-6.04 (m, 1H), 6.04 (dd, *J* = 9.5, 15.5 Hz, 1H), 6.83 (dt, *J* = 5.5, 15.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 10.6, 22.6, 69.8, 104.3, 109.7, 115.0, 126.7, 129.2, 129.5, 130.5, 134.5, 135.6, 142.9, 160.9 ppm; IR (film): 1559, 1511, 1337, 1256, 1155 cm^{-1}; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{18}H_{19}NO_5S$: 361.0984, Found: 361.0979.

*(4-Benzenesulfonyl-4-nitrobut-2-enyl)benzene (**4d**):*

Yellowish oil; yield 86%; ^{1}H NMR δ 3.49 (d, *J* = 6.5 Hz, 2H), 5.67 (dd, *J* = 10.0, 15.0 Hz, 1H), 5.90 (d, *J* = 10.0 Hz, 1H), 6.28 (dt, *J* = 6.5, 15.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.22-7.28 (m, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 2H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.82 (d, *J*

= 8.0 Hz, 2H) ppm; ^{13}C NMR δ 39.0, 103.3, 116.3, 127.0, 128.8, 129.0, 129.5, 130.4, 134.2, 135.6, 137.4, 145.4 ppm; IR (film): 1561, 1338, 1155 cm^{-1}; HRMS (CI, [M-H]$^{+}$) *m/z* calcd for $C_{16}H_{14}NO_4S$: 316.0644, Found: 316.0648.

*1-(4-Benzenesulfonyl-4-nitrobut-2-enyl)-3-chlorobenzene (**4e**):*

Yellowish oil; yield 70%; ^{1}H NMR 3.47 (d, *J* = 7.0 Hz, 2H), 5.67 (dd, *J* = 9.5, 15.5 Hz, 1H), 5.90 (d, *J* = 9.5 Hz, 1H), 6.25 (dt, *J* = 7.0, 15.5 Hz, 1H), 7.01 (d, *J* = 6.0 Hz, 1H), 7.10 (s, 1H), 7.22-7.28 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) 38.6, 103.2, 116.9, 127.1, 127.4, 129.0, 129.6, 130.3, 130.5, 134.2, 134.8, 135.7, 139.4, 144.3 ppm; IR (film): 1562, 1339, 1156 cm^{-1}; HRMS (CI, [M+H]$^{+}$) *m/z* calcd for $C_{16}H_{15}ClNO_4S$: 352.0410, Found: 352.0413.

*1-(4-Benzenesulfonyl-4-nitrobut-2-enyl)-4-methoxybenzene (**4f**):*

Yellowish oil; yield 76%; ^{1}H NMR δ 3.43 (d, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 5.64 (dd, *J* = 9.5, 15.5 Hz, 1H), 5.89 (d, *J* = 9.5 Hz, 1H), 6.27 (dt, *J* = 7.0, 15.5 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 38.2, 55.5, 103.4, 114.4, 115.9, 129.4, 129.5, 129.9, 130.5, 134.3, 135.6, 145.9, 158.7 ppm; IR (film): 1561, 1512, 1338, 1247, 1156 cm^{-1}; HRMS (EI, [M]$^{+}$) *m/z* calcd for $C_{17}H_{17}NO_5S$: 347.0827, Found: 347.0824.

*(4-Benzenesulfonyl-1-methyl-4-nitrobut-2-enyl)benzene (**4g**):*

Yellowish oil; yield 75%; ^{1}H NMR δ 1.39 (t, *J* = 6.5 Hz, 3H), 3.57 (q, *J* = 6.5 Hz, 1H), 5.57-5.69 (m, 1H), 5.89 (d, *J* = 10.0 Hz, 1H), 6.27 (td, *J* = 6.5, 16.5 Hz, 1H), 7.13 (t, *J* = 6.0 Hz, 2H), 7.22-7.28 (m, 1H), 7.32 (q, *J* = 6.0 Hz, 2H), 7.52 (t, *J* = 7.0 Hz, 1H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.69-7.78 (m, 2H), 7.85 (d, *J* = 7.0 Hz, 1H) ppm; ^{13}C NMR δ 20.4, 20.4, 42.7, 42.8, 103.5, 114.2, 114.4, 127.2, 127.4, 129.0, 129.5, 129.6, 130.5, 130.6, 134.3, 134.4, 135.5, 135.6, 143.0, 143.1, 150.6, 150.8 ppm; IR (film): 1561, 1340, 1156 cm^{-1}; HRMS (CI, $[M-H]^{+}$) *m/z* calcd for $C_{17}H_{16}NO_4S$: 330.0800, Found: 330.0797.

*(4-Benzenesulfonyl-4-nitrobut-2-enyl)carbamic acid benzyl ester (**4h**):*

Yellowish oil; yield 61%; ^{1}H NMR δ 3.95 (s, *2*H), 4.91 (br s, 1H), 5.13 (s, 2H), 5.84 (dd, *J* = 9.0, 15.5 Hz, 1H), 5.91 (d, *J* = 9.0 Hz, 1H), 6.16 (d, *J* = 15.5 Hz, 1H), 7.31-7.40 (m. 5H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 42.2, 67.3, 102.8, 115.8, 128.3, 128.5, 128.8, 129.6, 130.6, 134.0, 135.8, 136.3, 142.4, 156.3 ppm; IR (film): 1708, 1562, 1339, 1246, 1156 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z* calcd for $C_{18}H_{19}N_2O_6S$: 391.0964, Found: 391.0963.

*(5-Benzenesulfonyl-5-Nitropent-3-enyloxymethyl)benzene (**4i**):*

Yellowish oil; yield 83%; ^{1}H NMR δ 2.47 (q, *J* = 6.5 Hz, 2H), 3.55 (t, *J* = 6.5 Hz, 2H), 4.50 (s, 2H), 5.72 (dd, *J* = 9.5, 15.0 Hz, 1H), 5.88 (d, *J*

= 9.5 Hz, 1H), 6.19 (dt, *J* = 6.5, 15.0 Hz, 1H), 7.28-7.38 (m, 5H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 33.3, 68.3, 73.3, 103.6, 116.8, 127.9, 128.0, 128.7, 129.5, 130.6, 134.3, 135.6, 138.1, 143.9 ppm; IR (film): 1562, 1340, 1157, 1083 cm^{-1}; HRMS (FAB, $[M+H]^+$) *m/z* calcd for $C_{18}H_{20}NO_5S$: 362.1062, Found: 362.1067.

*(5-Benzenesulfonyl-5-nitropent-3-enyl)benzene (**4j**):*

White solid; yield 84%, mp 84-85 ℃; ^{1}H NMR δ 2.46-2.54 (m, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 5.63 (dd, J = 10.0, 15.0 Hz, 1H), 5.85 (d, *J* = 10.0 Hz, 1H), 6.17 (dt, J = 6.5, 15.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.21-7.28 (m, 1H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 2H), 7.72-7.79 (m, 3H) ppm; ^{13}C NMR δ 34.6, 103.5, 115.8, 126.5, 128.6, 128.8, 129.5, 130.5, 134.3, 135.6, 140.5, 146.2 ppm; IR (film): 1560, 1338, 1155 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{17}H_{18}NO_4S$: 332.0957, Found: 332.0958.

*11-Benzenesulfonyl-11-nitroundec-9-enoic acid methyl ester (**4k**):*

Colorless oil; yield 70%; ^{1}H NMR δ 1.25=1.35 (m, 6H), 1.36-1.44 (m, 2H), 1.59-1.66 (m, 2H), 2.16 (q, *J* = 7.0 Hz, 2H), 2.31 (t, *J* = 7.0 Hz, 2H), 3.67 (s, 3H), 5.65 (dd, *J* = 10.0, 15.0 Hz, 1H), 5.86 (d, *J* = 10.0 Hz, 1H), 6.14 (dt, *J* = 7.0, 15.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 25.1, 28.2,

29.0, 29.1, 29.2, 32.8, 34.2, 51.7, 103.7, 115.0, 129.5, 130.5, 134.5, 135.6, 147.5, 174.4 ppm; IR (film): 2929, 1731, 1561, 1339, 1156 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{18}H_{26}NO_6S$: 384.1481, Found: 384.1484.

2.2. Procedure for the preparation of heptanal (5a)

β,γ-Unsaturated α-nitrosulfone **4a** (280 mg, 0.90 mmol) was dissolved in dichloromethane (10 mL) and cooled to -78 ℃ in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ℃. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.5 mL, 6.5 mmol) at -78 ℃. The reaction mixture was allowed to warm up to room temperature, and stirred for 4h. Then, the reaction mixture was concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **5a**.

Colorless liquid; yield 73%; ^{1}H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.24-1.37 (m, 6H), 1.63 (quin, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 9.77 (s, 1H) ppm; ^{13}C NMR δ 14.2, 22.2, 22.6, 29.0, 31.7, 44.1, 203.1 ppm; IR (film): 2956, 1716, 1463 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_7H_{13}O$: 113.0966, Found: 113.0968.

2.3. General Procedure for the preparation of saturated α-nitrosulfones 6 or 6'

To a solution of **4** (2.00 mmol) in DMF (10 mL) was added at room temperature sodium cyanoborohydride or sodium cyanoborodeuteride (6.0 mmol). The reaction mixture was stirred overnight at 90 ºC and quenched with aqueous 0.1 *N* HCl solution (20 mL). Then, the reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **6** in 45 - 89% yields.

*1-Benzenesulfonyl-1-nitrononane (**6a**):*

White solid; yield 87%; mp 48-49 ºC; ^{1}H NMR δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.19-1.30 (m, 8H), 1.31-1.42 (m, 4H), 2.16-2.30 (m, 2H), 5.48 (dd, *J* = 4.0, 10.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 14.3, 22.8, 25.6, 28.0 28.8, 29.2, 29.2, 31.9, 102.6, 129.7, 130.2, 134.2, 135.7 ppm; IR (film): 2928, 1562, 1340, 1158 cm^{-1}; HRMS (FAB, $[M+H]^+$) *m/z* calcd for $C_{15}H_{24}NO_4S$: 314.1426, Found: 314.1427.

*Deuterated 1-benzenesulfonyl-1-nitrononane (**6a'**):*

White solid; yield 87%; mp 48-49 ºC; ^{1}H NMR δ 0.87 (t, *J* = 6.5 Hz,

3H), 1.19-1.30 (m, 8H), 1.31-1.41 (m, 4H), 2.16-2.28 (m, 1H), 5.48 (t, *J* = 6.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 14.3, 22.8, 25.5, 27.7 (t, *J* = 20.0 Hz), 28.8, 29.2, 29.2, 31.9, 102.5, 129.7, 130.2, 134.2, 135.7 ppm; IR (film): 2928, 1561, 1339, 1157 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{15}H_{23}DNO_4S$: 315.1489, Found: 315.1492.

*1-Benzenesulfonyl-1-nitrotridecane (**6b**):*

White solid; yield 86%; mp 57-58 ℃; ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.20-1.42 (m, 20H), 2.17-2.31 (m, 2H), 5.48 (dd, *J* = 4.0, 11.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 2H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR 14.3, 22.9, 25.6, 28.0 28.8, 29.2, 29.5, 29.5, 29.7, 29.8, 29.8, 32.1, 102.6, 129.7, 130.2, 134.2, 135.7 ppm; IR (film): 2926, 1562, 1341, 1158 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{19}H_{32}NO_4S$: 370.2052, Found: 370.2054.

*1-(3-Benzenesulfonyl-3-nitropropyl)-4-propoxybenzene (**6c**):*

Colorless oil; yield 45%; ^{1}H NMR δ 1.04 (t, *J* = 7.5 Hz, 3H), 1.80 (sex, J = 7.5 Hz, 2H), 2.48-2.56 (m, 3H), 2.7-2.81 (m, 1H), 3.90 (t, *J* = 6.5 Hz, 2H), 5.41 (dd, *J* = 6.0, 7.5 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 10.7, 22.8, 29.9, 30.6, 69.7, 101.5, 115.1, 129.6, 129.7, 130.2, 134.1, 135.7, 158.4 ppm; IR (film): 1561, 1511, 1338, 1246, 1157 cm^{-1}; HRMS (EI, $[M]^+$) *m/z* calcd for

$C_{18}H_{21}NO_5S$: 363.1140, Found: 363.1138.

*(4-Benzenesulfonyl-4-nitrobutyl)benzene (**6d**):*

Colorless oil; yield 85%; ^{1}H NMR (400 MHz) δ 1.64-1.76 (m, 2H), 2.23-2.32 (m, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 5.46 (dd, *J* = 5.6, 9.6 Hz, 1H), 7.09 (d, *J* = 6.8 Hz, 2H), 7.19 (tt, *J* = 1.2 Hz, 6.8 Hz, 1H), 7.23-7.29 (m, 2H), 7.59 (td, *J* = 1.2, 7.6 Hz, 2H), 7.75 (tt, *J* = 1.2, 7.6 Hz, 1H), 7.84 (dd, *J* = 1.2, 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz) δ 27.0, 27.5. 34.8, 102.2, 126.4, 128.4, 128.7, 129.6, 130.0, 134.1, 135.6, 140.3 ppm; IR (film): 1561, 1338, 1157 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{16}H_{18}NO_4S$: 320.0957, Found: 320.0954.

*1-(4-Benzenesulfonyl-4-nitrobutyl)-3-chlorobenzene (**6e**):*

Colorless oil; yield 72%; ^{1}H NMR δ 1.64-1.77 (m, 2H), 2.23-2.32 (m, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 5.47 (dd, *J* = 5.0, 10.0 Hz, 1H), 7.00 (d, *J* = 6.5 Hz, 1H), 7.10 (s, 1H), 7.18-7.23 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 27.0, 27.5. 34.6, 102.2, 126.7, 126.9, 128.6, 129.8, 130.1, 130.2, 134.1, 134.6, 135.8, 142.3 ppm; IR (film): 1561, 1338, 1157 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{16}H_{17}ClNO_4S$: 354.0567, Found: 354.0568.

*1-(4-Benzenesulfonyl-4-nitrobutyl)-4-methoxybenzene (**6f**):*

Colorless oil; yield 69%; ^{1}H NMR δ 1.63-1.72 (m, 2H), 2.20-2.32 (m, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 5.46 (dd, *J* = 5.0, 9.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.5

Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 27.4, 27.5, 34.0, 55.5, 102.3, 114.2, 129.4, 129.7, 130.2, 132.3, 134.1, 135.7, 158.3 ppm; IR (film): 1561, 1513, 1338, 1246, 1178 cm^{-1}; HRMS (EI, [M]$^{+}$) *m/z* calcd for $C_{17}H_{19}NO_5S$: 349.0984, Found: 349.0984.

*5-Benzenesulfonyl-5-nitro-2-phenylpentane (**6g**):*

Colorless oil; yield 70%; ^{1}H NMR δ 1.25 (dd, *J* = 3.0, 7.0 Hz, 3H), 1.58-1.74 (m, 2H), 2.03-2.15 (m, 1H), 2.15-2.26 (m, 1H), 2.70 (dq, *J* = 7.0 Hz, 21.0 Hz, 1H), 5.30 (dd, *J* = 3.0, 11.0 Hz, 0.5H), 5.44 (dd, *J* = 3.0, 11.0 Hz, 0.5H), 7.11 (dd, *J* = 7.5, 14.0 Hz, 2H), 7.22 (quin, *J* = 7.0 Hz, 1H), 7.26-7.34 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.75 (dd, *J* = 7.5,11.5 Hz, 1H), 7.81 (dd, *J* = 7.5,11.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz) δ 21.9, 22.1, 26.1, 26.5, 33.4, 33.8, 39.1, 39.7, 102.2, 126.7, 126.8, 128.7, 129.5, 129.9, 134.0, 134.1, 135.4, 145.0, 145.3 ppm; IR (film): 1561, 1339, 1157 cm^{-1}; HRMS (CI, [M+H]$^{+}$) *m/z* calcd for $C_{17}H_{20}NO_4S$: 334.1113, Found: 334.1111.

*(4-Benzenesulfonyl-4-nitrobutyl)carbamic acid benzyl ester (**6h**):*

Colorless oil; yield 78%; ^{1}H NMR δ 1.52-1.72 (m, 2H), 2.24-2.42 (m, 2H), 3.17-3.32 (m, 2H), 4.81 (br s, 1H), 5.09 (s, 2H), 5.64 (dd, *J* = 2.0, 10.5 Hz, 1H), 7.30-7.40 (m, 5H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz) δ 24.8, 25.8, 39.4, 66.8, 101.4, 128.0, 128.1, 128.5, 129.5, 129.8, 133.9, 135.4,

136.3, 156.5 ppm; IR (film): 1703, 1560, 1337, 1249, 1156 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{18}H_{21}N_2O_6S$: 393.1120, Found: 393.1119.

*(5-Benzenesulfonyl-5-Nitropentyloxymethyl)benzene (**6i**):*

Colorless oil; yield 89%; ^1H NMR δ 1.44-1.55 (m, 2H), 1.60-1.70 (m, 2H), 2.22-2.36 (m, 2H), 3.45 (t, *J* = 6.0 Hz, 2H), 4.46 (s, 2H), 5.52 (dd, *J* = 4.0, 10.5 Hz, 1H), 7.28-7.32 (m, 3H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 22.8, 27.9, 28.9, 69.5, 73.3, 102.5, 127.9, 128.6, 129.7, 130.2, 134.2, 135.7, 138.4 ppm; IR (film): 1560, 1337, 1158, 1083 cm^{-1}; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{18}H_{21}NO_5S$: 363.1140, Found: 363.1140.

*(5-Benzenesulfonyl-5-nitropentyl)benzene (**6j**):*

White solid; yield 84%; mp 66-67 ℃; ^1H NMR δ 1.34-1.48 (m, 2H), 1.62-1.72 (m, 2H), 2.23-2.31 (m, 2H), 2.53-2.66 (m, 2H), 5.46 (dd, *J* = 5.0, 9.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.26-7.30 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 25.1, 27.9, 30.5, 35.4, 102.4, 126.2, 128.5, 128.7, 129.7, 130.2, 134.1, 135.7, 141.5 ppm; IR (film): 1560, 1338, 1157 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{17}H_{20}NO_4S$: 334.1113, Found: 334.1114.

*11-Benzenesulfonyl-11-nitroundecanoic acid methyl ester (**6k**):*

White solid; yield 83%; mp 62-63 ºC; ^{1}H NMR δ 1.20-1.45 (m, 12H), 1.60 (quin, *J* = 7.0 Hz, 2H), 2.19-2.27 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 5.48 (dd, *J* = 3.5, 11.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 25.1, 25.6, 28.1, 28.8, 29.2, 29.3, 34.3, 51.7, 102.6, 129.8, 130.3, 134.2, 135.7, 174.5 ppm; IR (film): 2930, 1735, 1561, 1340, 1158 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z* calcd for $C_{18}H_{28}NO_6S$: 386.1637, Found: 386.1635.

2.4. General Procedure for the preparation of one-carbon longer homologous methyl esters 7

Method A: To a solution of **6** (1.00 mmol) in dichloromethane (5 mL) and MeOH (5 mL) was added in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3 mmol). The reaction mixture was stirred for 10 min and replaced in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ºC. After the ozonolysis was completed, the reaction mixture was quenched with dimethyl sulfide (0.1 mL, 1.3 mmol) and acetic acid (1.0 mL) at -78 ºC, allowed to warm up to room temperature, and stirred for 1 h. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The

resulting crude oil was purified by silica gel column chromatography to afford **7** in 66 - 88% yields.

Method B: To a solution of α β-unsaturated ester **15a** (200 mg, 1.17 mmol) in ethyl acetate (20 mL) was added 5% Pd/C (20 mg). The mixture was stirred at room temperature under H_2 (2-3 atm) atmosphere for 2 h. After the reaction was completed, the reaction mixture was filtered through a bed of Celite. The filtrate was concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **7a** in a 92% yield.

*Nonanoic acid methyl ester (**7a**):*

Colorless liquid; yield 73%; ^{1}H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20-1.36 (m, 10H), 1.62 (quin, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H) ppm; ^{13}C NMR δ 14.3, 22.8, 25.2, 29.3, 29.4, 29.4, 32.0, 34.3, 51.6, 174.5 ppm; IR (film): 2928, 1743, 1168 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{10}H_{21}O_2$: 173.1542, Found: 173.1541.

*Tridecanoic acid methyl ester (**7b**):*

Colorless liquid; yield 80%; ^{1}H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.22-1.34 (m, 18H), 1.62 (quin, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H) ppm; ^{13}C NMR δ 14.3, 22.9, 25.2, 29.4 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.1, 34.3, 51.6, 174.6 ppm; IR (film): 2925, 1743, 1171 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{14}H_{29}O_2$: 229.2168,

Found: 229.2171.

*3-(4-Propoxyphenyl)propionic acid methyl ester (**7c**):*

Colorless liquid; yield 68%; ^{1}H NMR δ 1.03 (t, *J* = 7.0 Hz, 3H), 1.79 (sex, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 3.89 (t, *J* = 7.0 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR δ 10.7, 22.8, 30.3, 36.2, 51.8, 69.7, 114.7, 129.4, 132.6, 157.8, 173.6 ppm; IR (film): 1738, 1513, 1244 cm^{-1}; HRMS (EI, $[M]^{+}$) *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256, Found: 222.1259.

*4-Phenylbutyric acid methyl ester (**7d**):*

Colorless liquid; yield 78%; ^{1}H NMR (400 MHz) δ 2.01 (quin, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 3.70 (s, 3H), 7.20-7.28 (m, 3H), 7.33 (t, *J* = 7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz) δ 26.5, 33.4, 35.2, 51.5, 126.0, 128.4, 128.5, 141.4, 173.9 ppm; IR (film): 1738, 1204 cm^{-1}; HRMS (FAB, $[M+H]^{+}$) *m/z* calcd for $C_{11}H_{15}O_2$: 179.1072, Found: 179.1068.

*4-(3-Chloro-phenyl)butyric acid methyl ester (**7e**):*

Colorless liquid; yield 74%; ^{1}H NMR δ 1.95 (quin, *J* = 7.5 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.15-7.19 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR δ 26.4, 33.4, 35.0, 51.8, 126.4, 126.9, 128.8, 129.8, 134.3, 143.6, 173.9 ppm; IR (film): 1738, 1435, 1205 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z*

calcd for $C_{11}H_{14}ClO_2$: 213.0682, Found: 213.0676.

*4-(4-Methoxyphenyl)butyric acid methyl ester (**7f**):*

Colorless liquid; yield 73%; ^{1}H NMR δ 1.92 (quin, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 3.66 (s, 3H), 3.79 (s, 3H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR δ 26.9, 33.5, 34.4, 51.7, 55.4, 114.0, 129.6, 133.6, 158.0, 174.2 ppm; IR (film): 1737, 1513, 1247 cm^{-1}; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{12}H_{16}O_3$: 208.1099, Found: 208.1098.

*4-Phenylpentanoic acid methyl ester (**7g**):*

Colorless liquid; yield 80%; ^{1}H NMR δ 1.27(d, *J* = 7.0 Hz, 3H), 1.84-1.98 (m, 2H), 2.13-2.26 (m, 2H), 2.71 (sex, *J* = 7.0 Hz, 1H), 3.63 (s, 3H), 7.15-7.22 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 22.4, 32.5, 33.4, 39.6, 51.7, 126.4, 127.2, 128.6, 146.4, 174.3 ppm; IR (film): 1738, 1166 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{12}H_{17}O_2$: 193.1229, Found: 193.1228.

*4-Benzyloxycarbonylaminobutyric acid methyl ester (**7h**):*

Colorless oil; yield 88%; ^{1}H NMR δ 1.85 (quin, *J* = 7.0 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 3.25 (q, *J* = 7.0 Hz, 2H), 3.66 (s, 3H), 4.87 (br s, 1H), 5.09 (s, 2H), 7.28-7.38 (m, 5H) ppm; ^{13}C NMR δ 25.3, 31.4, 40.6, 51.9, 66.9, 128.3, 128.7, 136.7, 156.6, 173.9 ppm; IR (film): 1723, 1712, 1531, 1254 cm^{-1}; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{13}H_{17}NO_4$: 251.1158, Found: 251.1155.

*5-Benzyloxypentanoic acid methyl ester (**7i**):*

Colorless oil; yield 66% ^{1}H NMR δ 1.65 (quin, *J* = 7.5 Hz, 2H), 1.73 (quin, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 3.66 (s, 3H), 4.50 (s, 2H), 7.26-7.30 (m, 1H), 7.31-7.37 (m, 4H) ppm; ^{13}C NMR δ 22.0, 29.4, 34.0, 51.7, 70.0, 73.1, 127.7, 127.8, 128.6, 138.7, 174.2 ppm; IR (film): 1738, 1168, 1099 cm^{-1}; HRMS (EI, $[M]^{+}$) *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256, Found: 222.1256.

*5-Phenylpentanoic acid methyl ester (**7j**):*

Colorless liquid; yield 88%; ^{1}H NMR δ 1.62-171 (m, 4H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 3.66 (s, 3H), 7.15-7.20 (m, 3H), 7.27-7.30 (m, 2H) ppm; ^{13}C NMR δ 24.8, 31.1, 34.1, 35.8, 51.7, 126.0, 128.5, 128.6, 142.3, 174.3 ppm; IR (film): 1739, 1200, 1173 cm^{-1}; HRMS (EI, $[M]^{+}$) *m/z* calcd for $C_{12}H_{16}O_2$: 192.1150, Found: 192.1151

*Undecanedioic acid dimethyl ester (**7k**):*

Colorless liquid; yield 71%; ^{1}H NMR δ 1.25-1.34 (m, 10H), 1.61 (t, *J* = 7.5 Hz, 4H), 2.30 (t, *J* = 7.5 Hz, 4H), 3.67 (s, 6H) ppm; ^{13}C NMR δ 25.1, 29.3, 29.3, 29.4, 34.3, 51.6, 174.5 ppm; IR (film): 2930, 1740, 1172 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z* calcd for $C_{13}H_{25}O_4$: 245.1753, Found: 245.1755.

2.5. Procedure for the preparation of Nonanal (8a):

A solution of ester **7a** (258 mg, 1.50 mmol) in anhydrous

dichloromethane (20 mL) was cooled to -78 ºC in a dry ice/acetone bath. To the reaction mixture was slowly added 1 M solution of DIBAL in dichloromethane (2.0 mL, 2.0 mmol) under nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred at -78 ºC for 30 min and then quenched by addition of MeOH (1.0 mL) and aqueous saturated solution of Rochelle salt (20 mL). Then, the reaction mixture was allowed to warm up to room temperature and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **8a**.

Colorless liquid; yield 88%; ^{1}H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.21-1.37 (m, 10H), 1.63 (quin, *J* = 7.5 Hz, 2H), 2.42 (td, *J* = 2.0, 7.5 Hz, 2H), 9.77 (t, *J* = 2.0 Hz, 1H) ppm; ^{13}C NMR δ 14.3, 22.3, 22.8, 29.3, 29.4, 29.5, 32.0, 44.1, 203.2 ppm; IR (film): 2927, 1728, 1461 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_9H_{17}O$: 141.1279, Found: 141.1277.

2.6. General Procedure for the preparation of one-carbon shorter homologous acetals 9

A solution of **4** (1.00 mmol) in dichloromethane (5 mL) and MeOH (5 mL) was cooled to -78 ºC in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min. After the reaction was

completed, the reaction mixture was quenched with dimethyl sulfide (0.5 mL, 6.5 mmol) at -78 ℃, and then *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol), $MgSO_4$ (1.0 g), and trimethyl orthoformate (3.0 mL) were added to the reaction mixture. The reaction mixture was allowed to warm up to room temperature, and stirred for overnight. Then, the reaction mixture was filtered and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **9** in 48 - 79% yields.

*1,1-Dimethoxyheptane (**9a**):*

Colorless liquid; yield 69%; ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.24-1.38 (m, 8H), 1.56-1.62 (m, 2H), 3.31 (s, 6H), 4.36 (t, *J* = 6.0 Hz, 1H) ppm; ^{13}C NMR δ 14.3, 22.8, 24.8, 29.4, 32.0, 32.7, 52.8, 104.8 ppm; IR (film): 2929, 1458 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_9H_{19}O_2$: 159.1385, Found: 159.1385.

*1,1-Dimethoxyundecane (**9b**):*

Colorless liquid; yield 78%; ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.20-1.37 (m, 16H), 1.54-1.63 (m, 2H), 3.31 (s, 6H), 4.36 (t, *J* = 6.0 Hz, 1H) ppm; ^{13}C NMR δ 14.3, 22.9, 24.8, 29.6, 29.7, 29.8, 29.8, 32.1, 32.7, 52.8, 104.8 ppm; IR (film): 2926, 1464, 1127, 1057 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_{13}H_{27}O_2$: 215.2011, Found: 215.2015.

*1-Dimethoxymethyl-4-propoxybenzene (**9c**):*

Colorless liquid; yield 53%; ^{1}H NMR δ 1.03 (t, *J* = 7.0 Hz, 3H), 1.81 (sex, *J* = 7.0 Hz, 2H), 3.31 (s, 6H), 3.92 (t, *J* = 7.0 Hz, 2H), 5.35 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR δ 10.7, 22.8, 52.8, 69.7, 103.3, 114.3, 128.1, 130.3, 159.4 ppm; IR (film): 1510, 1260, 1161 cm^{-1}; HRMS (EI, [M]$^{+}$) *m/z* calcd for $C_{12}H_{18}O_3$: 210.1256, Found: 210.1259.

*(2,2-Dimethoxyethyl)benzene (**9d**):*

Colorless liquid; yield 53%; ^{1}H NMR (400 MHz) δ 2.91 (d, *J* = 5.6 Hz, 2H), 3.33 (s, 6H), 4.54 (t, *J* = 5.6 Hz, 1H), 7.17-7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz) δ 39.7, 53.3, 105.4, 126.4, 128.3, 129.4, 137.1 ppm; IR (film): 1122, 1063 cm^{-1}.

*1-Chloro-3-(2,2-dimethoxyethyl)benzene (**9e**):*

Colorless liquid; yield 74%; ^{1}H NMR δ 2.88 (d, *J* = 5.5 Hz, 2H), 3.35 (s, 6H), 4.52 (t, *J* = 5.5 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 1H), 7.18-7.25 (m, 3H) ppm; ^{13}C NMR δ 39.5, 53.7, 105.1, 126.8, 127.9, 129.7, 129.8, 134.2, 139.2 ppm; IR (film): 1121, 1075 cm^{-1}; HRMS (CI, [M-H]$^{+}$) *m/z* calcd for $C_{10}H_{12}ClO_2$: 199.0526, Found: 199.0523.

*1-(2,2-Dimethoxyethyl)-4-methoxybenzene (**9f**):*

Colorless liquid; yield 48%; ^{1}H NMR δ 2.85 (d, *J* = 5.5 Hz, 2H), 3.34 (s, 6H), 3.79 (s, 3H), 4.50 (t, *J* = 5.5 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H) ppm; ^{13}C NMR δ 38.9, 53.6, 55.4, 105.7, 113.9,

129.3, 130.5, 158.4 ppm; IR (film): 1514, 1248, 1121, 1067, 1039 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{11}H_{17}O_3$: 197.1178, Found: 197.1183.

*(2,2-Dimethoxy-1-methylethyl)benzene (**9g**):*

Colorless liquid; yield 67%; ^1H NMR δ 1.28 (d, *J* = 7.0 Hz, 3H), 3.01 (quin, *J* = 7.0 Hz, 1H), 3.24 (s, 3H), 3.38 (s, 3H), 4.37 (d, *J* = 7.0 Hz, 1H), 7.19-7.27 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 17.1, 43.1, 54.2, 54.7, 108.8, 126.6, 128.1, 128.5, 143.3 ppm; IR (film): 1453, 1071 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_{11}H_{15}O_2$: 179.1072, Found: 179.1075.

*(2,2-Dimethoxyethyl)carbamic acid benzyl ester (**9h**):*

Colorless liquid; yield 59%; ^1H NMR δ 3.34 (t, *J* = 5.0 Hz, 2H), 3.39 (s, 6H), 4.38 (t, *J* = 5.0 Hz, 1H), 4.94 (br s, 1H), 5.11 (s, 2H), 7.29-7.39 (m, 5H) ppm; ^{13}C NMR δ 42.7, 54.6, 67.0, 103.0, 128.3, 128.7, 128.8, 136.6, 156.6 ppm; IR (film): 1717, 1532, 1251, 1129, 1065 cm^{-1}; HRMS (EI, $[M]^+$) *m/z* calcd for $C_{12}H_{17}NO_4$: 239.1158, Found: 239.1157.

*3-Benzyloxy-1,1-dimethoxypropane (**9i**):*

Colorless liquid; yield 73%; ^1H NMR δ 1.92 (q, *J* = 6.0 Hz, 2H), 3.33 (s, 6H), 3.55 (t, *J* = 6.0 Hz, 2H), 4.51 (s, 2H), 4.56 (t, *J* = 6.0 Hz, 1H), 7.26-7.31 (m, 1H), 7.31-7.36 (4H) ppm; ^{13}C NMR δ 33.4, 53.3, 66.5, 73.3, 102.5, 127.8, 127.8, 128.6, 138.6 ppm; IR (film): 1453, 1275,

1104 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_{12}H_{17}O_3$: 209.1178, Found: 209.1179.

*(3,3-Dimethoxypropyl)benzene (**9j**):*

Colorless liquid; yield 73%; ^1H NMR δ 1.88-1.96 (m, 2H), 2.68 (t, *J* = 8.0 Hz, 2H), 3.33 (s, 6H), 4.37 (t, *J* = 6.0 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 3H), 7.24-7.31 (m, 2H) ppm; ^{13}C NMR δ 31.1, 34.3, 52.9, 104.0, 126.1, 128.6, 128.7, 141.8 ppm; IR (film): 1454, 1125, 1055 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_{11}H_{15}O_2$: 179.1072, Found: 179.1074.

*9,9-Dimethoxynonanoic acid methyl ester (**9k**):*

Colorless liquid; 79%; ^1H NMR δ 1.26-1.37 (m, 8H), 1.58-1.65 (m, 4H), 2.30 (t, *J* = 8.0 Hz, 2H), 3.31 (s, 6H), 3.67 (s, 3H), 4.35 (t, *J* = 5.5 Hz, 1H) ppm; ^{13}C NMR δ 24.7, 25.1, 29.2, 29.4, 29.5, 32.7, 34.3, 51.6, 52.8, 104.7, 174.5 ppm; IR (film): 2936, 1740, 1438, 1127, 1056 cm^{-1}; HRMS (CI, $[M-H]^+$) *m/z* calcd for $C_{12}H_{23}O_4$: 231.1596, Found: 231.1590.

2.7. Procedure for the preparation of Heptanoic acid (10a):

A solution of **4a** (280 mg, 0.90 mmol) in dichloromethane (10 mL) and THF (10 mL) was cooled to -78 ℃ in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min. After the reaction was completed, aqueous hydrogen peroxide solution (2.0 mL) and formic acid (5.0 mL) were added to the reaction mixture, which

was then refluxed for 4h. Then, the solution was concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **10a**.

Colorless liquid; yield 68%; ^{1}H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.24-1.39 (m, 6H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR δ 14.2, 22.7, 24.9, 29.0, 31.6, 34.3, 180.3 ppm; IR (film): 2930, 1710, 1415, 1284 cm^{-1}.

2.8. Procedure for the preparation of Heptanol (11a):

A solution of **4a** (311 mg, 1.00 mmol) in dichloromethane (20 mL) was cooled to -78 ℃ in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min. After the reaction was completed, sodium borohydride (76 mg, 2.0 mmol) in methanol solution (5 mL) was added to the reaction mixture. The reaction mixture was stirred for overnight. Then, the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford an alcohol **11a**.

Colorless liquid; yield 65%; ^{1}H NMR δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.23-1.39 (m, 8H), 1.57 (quin, *J* = 7.0 Hz, 2H), 3.64 (t, *J* = 7.0 Hz, 2H) ppm; ^{13}C NMR δ 14.3, 22.8, 25.9, 29.3, 32.0, 33.0, 63.2 ppm; IR (film): 3331,

2929, 1460, 1057 cm^{-1}.

2.9. Procedure for the preparation of Nonanoic acid (12a):

To a solution of **6a** (313 mg, 1.00 mmol) in dichloromethane (5 mL) and THF (5 mL) was added in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3.0 mmol). The reaction mixture was stirred for 10 min and replaced in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ℃. After the reaction was completed, the reaction mixture was quenched with dimethyl sulfide (0.1 mL, 1.3 mmol), acetic acid (1.0 mL), and water (10 mL) at -78 ℃, which was allowed to warm up to room temperature, and stirred for 1 hr. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford a carboxylic acid **12a**.

Colorless liquid; yield 72%; ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.20-1.38 (m, 10H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 14.3, 22.9, 24.9, 29.3, 29.3, 29.4, 32.0, 34.3, 180.3 ppm; IR (film): 3034, 2926, 1710, 1415, 1287 cm^{-1}.

2.10. Procedure for the preparation of Nonanoic acid amide (13a):

To a solution of **6a** (313 mg, 1.00 mmol) in dichloromethane (10 mL) was added in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3.0 mmol). The reaction mixture was stirred for 10 min and replaced in a dry ice/acetone. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ℃. After the raction was completed, the reaction mixture was quenched with dimethyl sulfide (0.10 mL, 1.3 mmol) at -78 ℃ and 0.5 M ammonia solution in 1,4-dioxane (5.0 mL) was added to the reaction mixture, which was allowed to warm up to room temperature, and stirred for 1 hr. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford an amide **13a**.

White solid; yield 56%; mp 98.5-99.5 ℃; ^{1}H NMR δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.21-1.37 (m, 10H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 5.32 (br d, 2H) ppm; ^{13}C NMR δ 14.3, 22.8, 25.7, 29.3, 29.4, 29.5, 32.0, 36.2, 176.2 ppm; IR (film): 3358, 2920, 1659, 1633 cm^{-1}.

2.11. Procedure for the preparation of 1-Benzenesulfonylnon-2-en-1-one oxime (14a):

To a solution of **4a** (622 mg, 2.00 mmol) in ethanol (10 mL) was

added $SnCl_2.2H_2O$ (1.13 g, 5.00 mmol). The reaction mixture was treated with ultrasonic irradiation for 2 h until the reaction was complete as indicated by TLC analysis. The solvent was removed under reduced pressure and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **14a**.

White solid; yield 65%; mp 72-73 ℃; ^{1}H NMR (400 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.20-1.34 (m, 6H), 1.42 (quin, *J* = 7.2 Hz, 2H), 2.21 (q, *J* = 7.2 Hz, 2H), 6.35 (d, *J* = 16.4 Hz, 1H), 7.11 (dt, *J* = 7.2, 16.4 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 9.73 (br s, 1H) ppm; ^{13}C NMR (100 MHz) δ 13.9, 22.4, 28.0 28.6, 31.4, 34.1, 112.5, 128.5, 129.1, 133.9, 138.4, 147.7, 155.2 ppm; IR (film): 3326, 2956, 1633, 1311, 1149 cm^{-1}; HRMS (FAB, $[M+H]^+$) *m/z* calcd for $C_{15}H_{22}NO_3S$: 296.1320, Found: 296.1322.

2.12. Procedure for the preparation of Non-2-enoic acid methyl ester (15a):

Oxime **14a** (177 mg, 0.60 mmol) was dissolved in 1*N* HCl in MeOH (10 mL). Then, the reaction mixture was heated to reflux for overnight and concentrated on a rotary evaporator under reduced pressure. The

resulting crude oil was purified by silica gel column chromatography to afford **15a**.

Colorless liquid; yield 72%; ^{1}H NMR δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.23-1.35 (m, 6H), 1.45 (quin, *J* = 7.5 Hz, 2H), 2.20 (q, *J* = 7.5 Hz, 2H), 3.73 (s, 3H), 5.82 (d, *J* = 15.5 Hz, 1H), 6.97 (dt, *J* = 7.5, 15.5 Hz, 1H) ppm; ^{13}C NMR δ 14.3, 22.8, 28.2, 29.0, 31.8, 32.4, 51.6, 121.0, 150.0, 167.4 ppm; IR (film): 2930, 1727, 1270 cm^{-1}; HRMS (EI, [M]$^{+}$) *m/z* calcd for $C_{10}H_{18}O_2$: 170.1307, Found: 170.1311.

2.13. Procedure for the preparation of 6-tert-butoxycarbonyl-aminohexanoic acid methyl ester (17):

6-Aminohexanoic acid (**16**) (13.12 g, 100.0 mmol) was dissolved in methanol (200 mL). The solution was cooled down to 0 ºC in an ice bath, and thionyl chloride (8.7 mL, 120 mmol) was added dropwise into the stirred solution. Then, the reaction mixture was warmed to room temperature and stirred for overnight. Then it was concentrated on a rotary evaporator under reduced pressure and dissolved in dichloromethane (200 mL) and triethylamine (34.8 mL, 250 mmol). Di-*tert*-butyldicarbonate (22.91 g, 105.0 mmol) in dichloromethane (50 mL) was added dropwise into the reaction mixture, which was stirred for overnight. Then, the reaction mixture was extracted with dichloromethane (3 x 200 mL). The combined organic layers were

dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **17**.

Colorless liquid; yield 92%; ^{1}H NMR δ 1.34 (quin, *J* = 7.5 Hz, 2H), 1.44 (s, 9H), 1.46-1.53 (quin, *J* = 7.5 Hz, 2H), 1.64 (quin, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 3.07-3.15 (m, 2H), 3.67 (s, 3H), 4.52 (br s, 1H) ppm; ^{13}C NMR δ 24.8, 26.5, 28.6, 29.9, 34.1, 40.6, 51.7, 79.2, 156.2, 174.2 ppm; IR (film): 2936, 1738, 1712, 1522, 1171 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{12}H_{24}NO_4$: 246.1705, Found: 246.1697.

2.14. Procedure for the preparation of a mixture of a cyclic and an acyclic form of 6-tert-butoxycarbonylaminohexanal (18 + 19):

To a solution of **17** (3.46 g, 14.1 mmol) in 30 mL of anhydrous dichloromethane at -78 ℃ in a dry ice/acetone bath was slowly added DIBAL-H (1 M solution in dichloromethane, 19.7 mL, 19.7 mmol) under nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred at -78 ℃ for 0.5 h and then quenched by adding MeOH (1.0 mL) and aqueous saturated solution of Rochelle salt (20 mL). Then, the reaction mixture was allowed to warm up to room temperature and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford the mixture of **18** and **19**.

Colorless oil; yield 76%; ^{1}H NMR (major **19**) δ 1.30-1.40 (m, 2H), 1.44 (s, 9H), 1.46-1.53 (m, 2H), 1.65 (qin, *J* = 7.5 Hz, 2H), 2.44 (td, *J* = 1.0, 7.5 Hz, 2H), 3.12 (d, *J* = 6.0 Hz, 2H) 4.52 (br s, 1H), 9.77 (s, 1H) ppm; ^{13}C NMR (a mixture of **18** and **19**) δ 21.9, 24.6, 26.4, 28.5, 29.9, 30.0, 34.0, 40.5, 44.0, 79.3, 156.2, 177.3, 202.7 ppm; IR (film): 1700, 1522, 1169 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z* calcd for $C_{11}H_{22}NO_3$: 216.1600, Found: 216.1598.

2.15. Procedure for the preparation of (7-Benzenesulfonyl-7-nitro-hept-5-enyl)carbamic acid tert-butyl ester (20):

To a solution of phenylsulfonylnitromethane (**1**) (402 mg, 2.00 mmol) in deoxygenated DMSO (2.0 mL) were added at room temperature a mixture of a cyclic and an acyclic form of an amino aldehyde **18 + 19** (2.00 mmol), proline (12 mg, 0.10 mmol), and pentaerythritol tetrakis(3,5-di-*tert*-butyl-4-hydroxyhydro-cinnamate) (6 mg, 0.005 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, a mixture of a cyclic and an acyclic form of an amino aldehyde **18 + 19** (0.60 mmol) was added again to the reaction mixture, which was then stirred at room temperature for 24 h. The mixture was diluted

with ether (20 mL) and aqueous NH_4Cl solution (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **20**. The yield was calculated based on the amount of phenylsulfonylnitromethane (**1**).

Colorless oil; yield 72%; ^{1}H NMR (400 MHz) δ 1.38-1.57 (m, 13H), 2.20 (q, *J* = 6.8 Hz, 2H), 3.10-3.17 (m, 2H), 4.54 (br s, 1H), 5.69 (dd, *J* = 9.6, 15.2 Hz, 1H), 5.89 (d, *J* = 9.6 Hz, 2H), 6.15 (dt, *J* = 6.8, 15.2 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 2H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 2H) ppm; ^{13}C NMR δ 25.4, 28.6, 29.6, 32.4, 40.3, 79.3, 103.5, 115.3, 129.6, 130.4, 134.3, 135.6, 146.9, 156.2 ppm; IR (film): 1697, 1562, 1340, 1159 cm^{-1}; HRMS (CI, $[M+H]^+$) *m/z* calcd for $C_{18}H_{27}N_2O_6S$: 399.1590, Found: 399.1589.

2.16. Procedure for the preparation of 7-tert-Butoxycarbonyl-aminoheptanoic acid methyl ester (21):

To a solution of **20** (797 mg, 2.00 mmol) in DMF (10 mL) was added cyanoborohydride (377 mg, 6.0 mmol). The reaction mixture was stirred for 12 h at 90 ℃ and quenched with aqueous NH_4Cl solution. Then, the reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **SI-1**.

White solid; yield 80%; mp 80-81 ℃; ^{1}H NMR δ 1.24-1.33 (m, 2H), 1.33-1.40 (m, 4H), 1.40-1.48 (m, 11H), 2.17-2.30 (m, 2H), 3.08 (q, *J* = 7.0 Hz, 2H), 4.48 (br s, 1H), 5.48 (dd, *J* = 4.0, 10.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR δ 25.5, 26.4, 27.9, 28.5, 28.6, 30.0, 40.5, 79.3, 102.5, 129.7, 130.2, 134.2, 135.7, 156.2 ppm; IR (film): 1698, 1562, 1339, 1160 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z* calcd for $C_{18}H_{29}N_2O_6S$: 401.1746, Found: 401.1742.

To a solution of **SI-1** (400 mg, 1.00 mmol) in dichloromethane (5 mL) and MeOH (5 mL) was added in an ice bath 1,8-diazabicycloundec-7-ene (DBU, 0.45 mL, 3.0 mmol). The reaction mixture was stirred for 10 min and replaced in a dry ice/acetone bath. Then, ozone was bubbled through the reaction mixture for 10 min at -78 ℃. After the reaction was completed, the reaction mixture was quenched with dimethyl sulfide (0.10 mL, 1.3 mmol) and acetic acid (1.0 mL) at -78 ℃, allowed to warm up to room temperature, and stirred for 1 hr. Then, the reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The

resulting crude oil was purified by silica gel column chromatography to afford **21**.

Colorless oil; yield 81%; ^{1}H NMR δ 1.28-1.38 (m, 4H), 1.44 (s, 9H), 1.44-1.51 (m, 2H),1.63 (quin, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.10 (q, J = 7.5 Hz, 2H), 3.67 (s, 3H), 4.50 (br s, 1H) ppm; ^{13}C NMR δ 25.0, 26.6, 28.5, 28.9, 30.0, 34.1, 40.6, 51.6, 79.1, 156.1, 174.3 ppm; IR (film): 1738, 1712, 1521, 1250, 1171 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z* calcd for $C_{13}H_{26}NO_4$: 260.1862, Found: 260.1860.

2.17. Procedure for the preparation of 5-tert-Butoxycarbonyl-aminopentanoic acid methyl ester (22):

A solution of **20** (199 mg, 0.50 mmol) in acetone (15 mL) was stirred in an ice bath, and a solution containing $NaIO_4$ (802 mg, 3.75 mmol) and 51% RuO_2 (8 mg) in H_2O (5 mL) was added. After the ice bath was removed, the reaction mixture was stirred for 20 min while adjusting its pH to *ca*. 4 by adding aqueous saturated $NaHCO_3$ solution. Then, 2-propanol (1.0 mL) was added to the reaction mixture, which was additionally stirred for 10 min. The reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **SI-2**.

White solid; yield 70%; mp 49-50 ℃; ^{1}H NMR δ 1.44 (s, 9H), 1.54 (quin, *J* = 7.5 Hz, 2H), 1.67 (quin, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.05-3.19 (m, 2H), 4.58 (br s, 1H) ppm; ^{13}C NMR δ 22.1, 28.6, 29.6, 33.8, 40.3, 79.5, 156.3, 178.9 ppm; IR (film): 3342, 1708, 1525, 1251, 1169 cm^{-1}.

To a solution of **SI-2** (100 mg, 0.46 mmol) and K_2CO_3 (190 mg, 1.38 mmol) in DMF (10 mL) was added iodomethane (57 μL, 0.92 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting crude oil was purified by silica gel column chromatography to afford **22**.

Yellowish oil; yield 98%; ^{1}H NMR δ 1.44 (s, 9H), 1.51 (quin, *J* = 7.5 Hz, 2H), 1.66 (quin, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.13 (q, *J* = 7.5 Hz, 2H), 3.67 (s, 3H), 4.55 (br s, 1H) ppm; ^{13}C NMR δ 22.2, 28.6, 29.6, 33.7, 40.2, 51.6, 79.2, 156.1, 174.0 ppm; IR (film): 1737, 1711, 1522, 1250, 1170 cm^{-1}; HRMS (CI, $[M+H]^{+}$) *m/z* calcd for $C_{11}H_{22}NO_4$: 232.1549, Found: 232.1549.[31]

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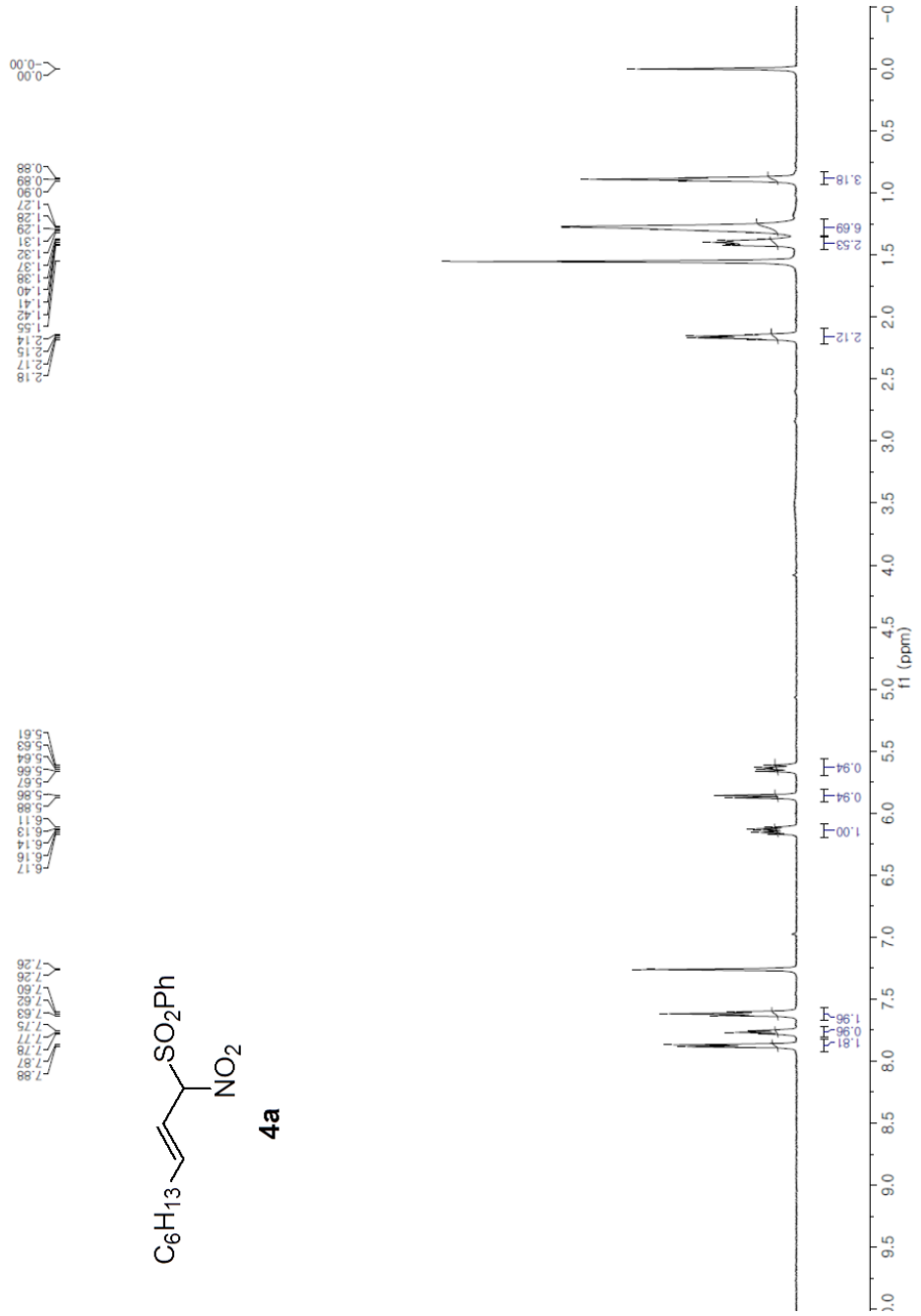
APPENDICES

List of ^{1}H NMR Spectra and ^{13}C NMR Spectra of Selected Compounds

Compound 4a ^{1}H NMR



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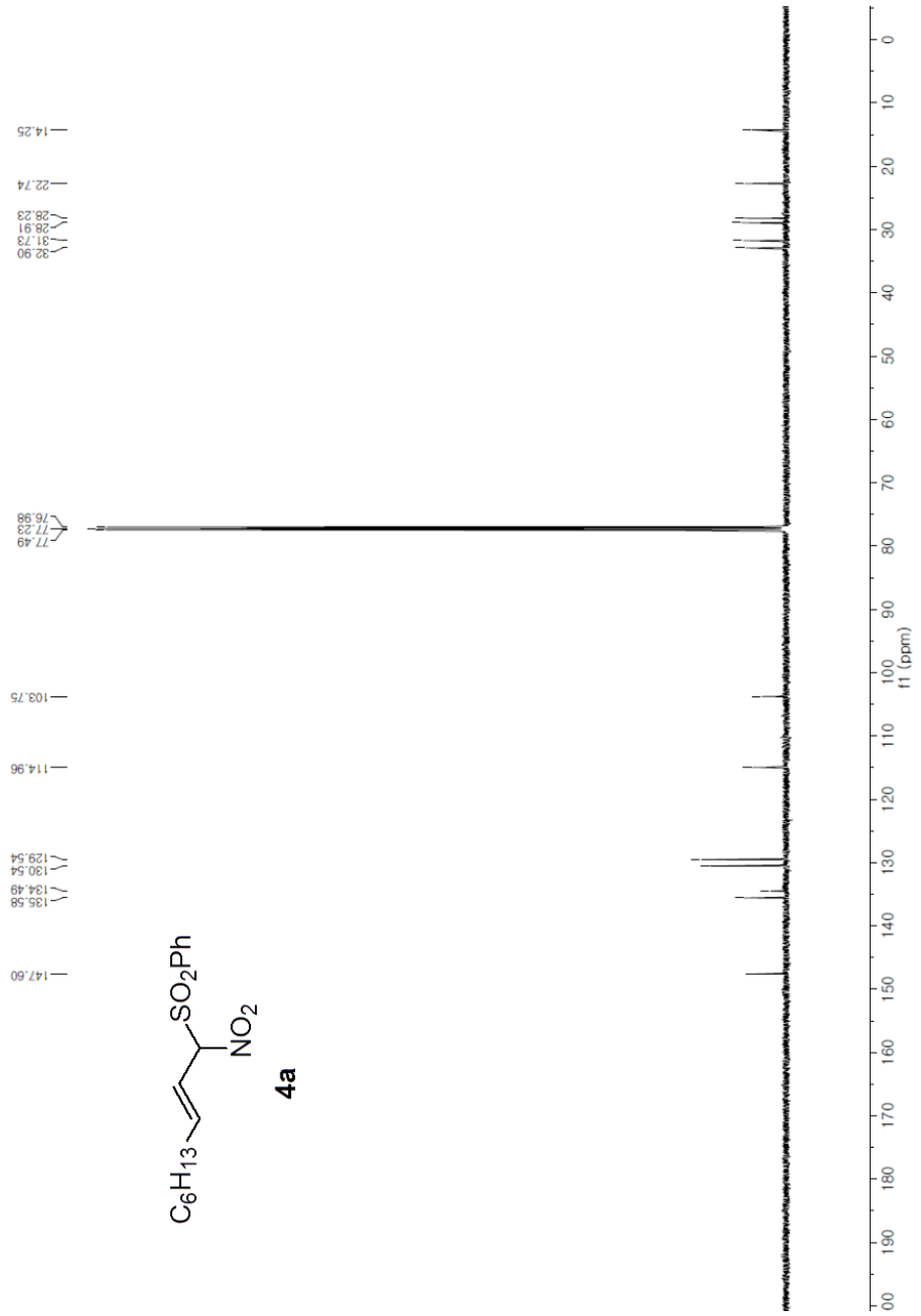

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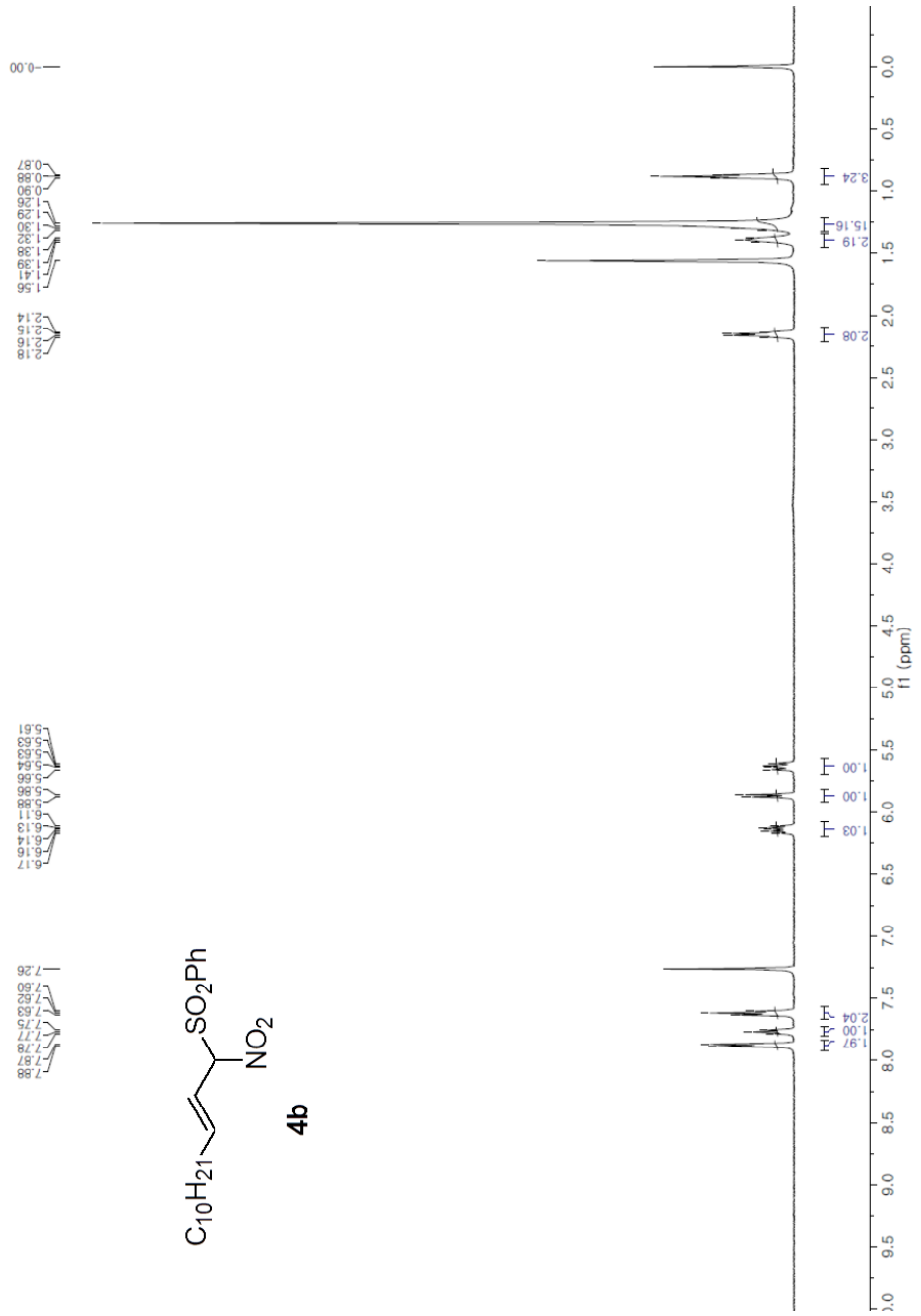

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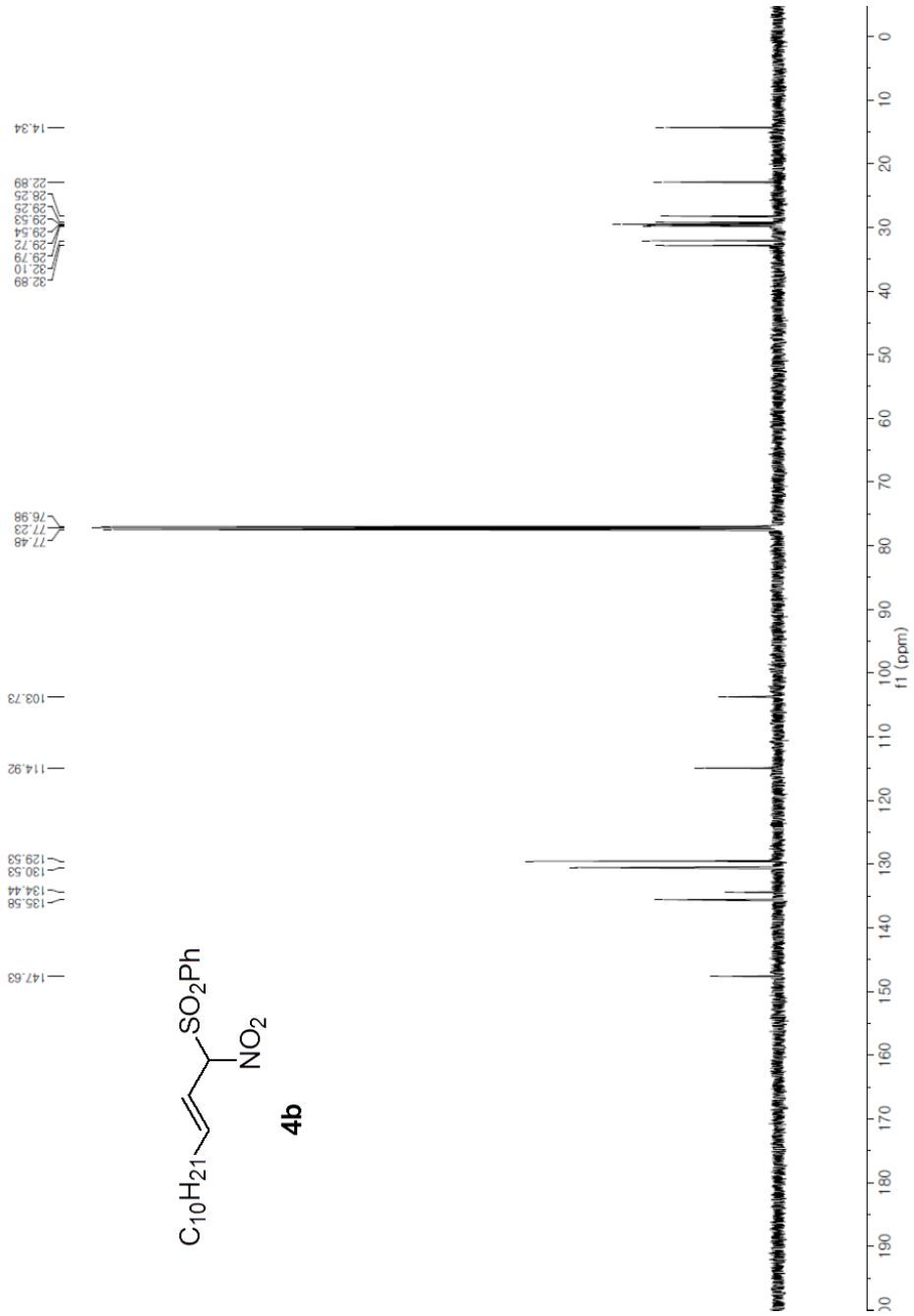

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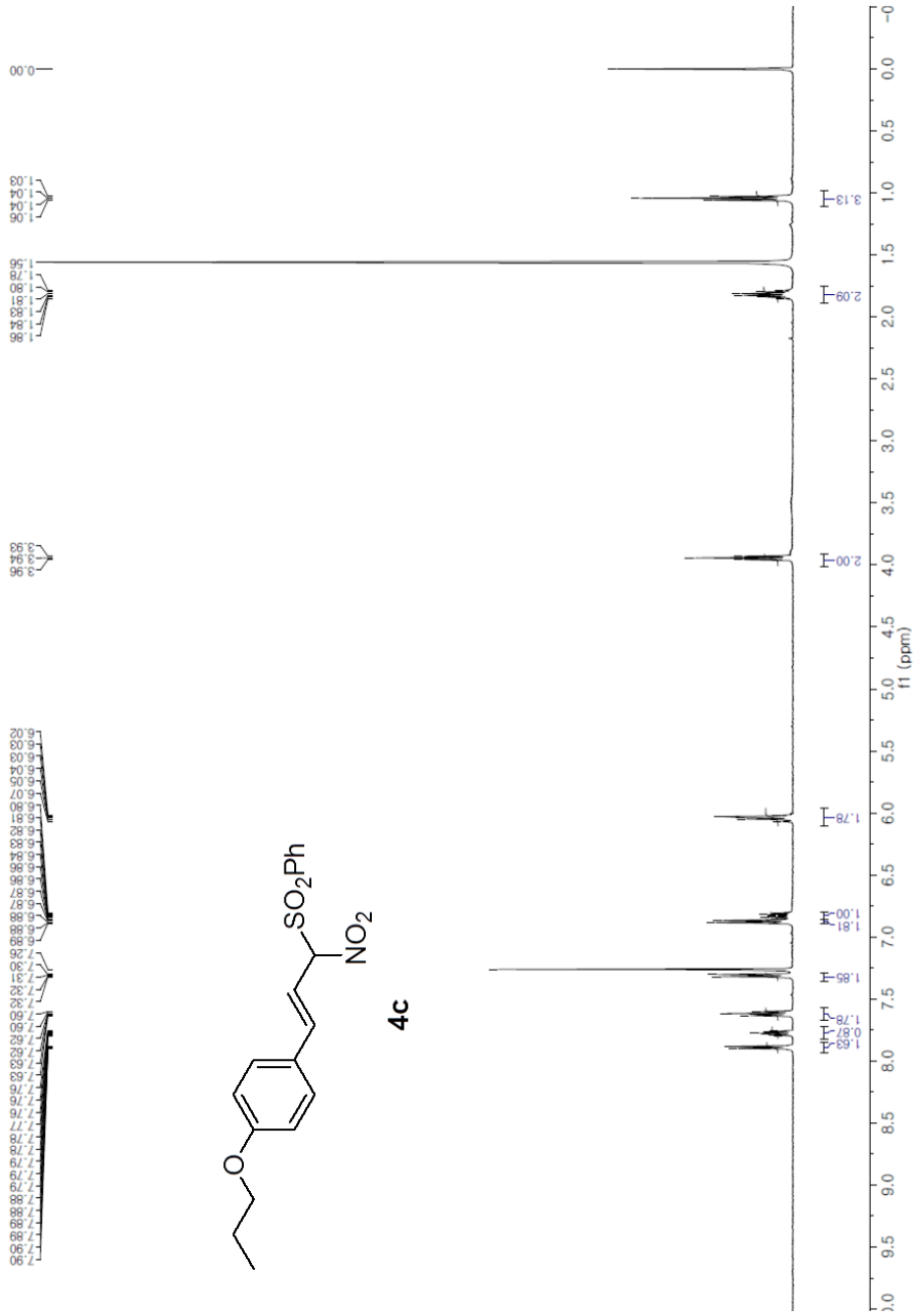

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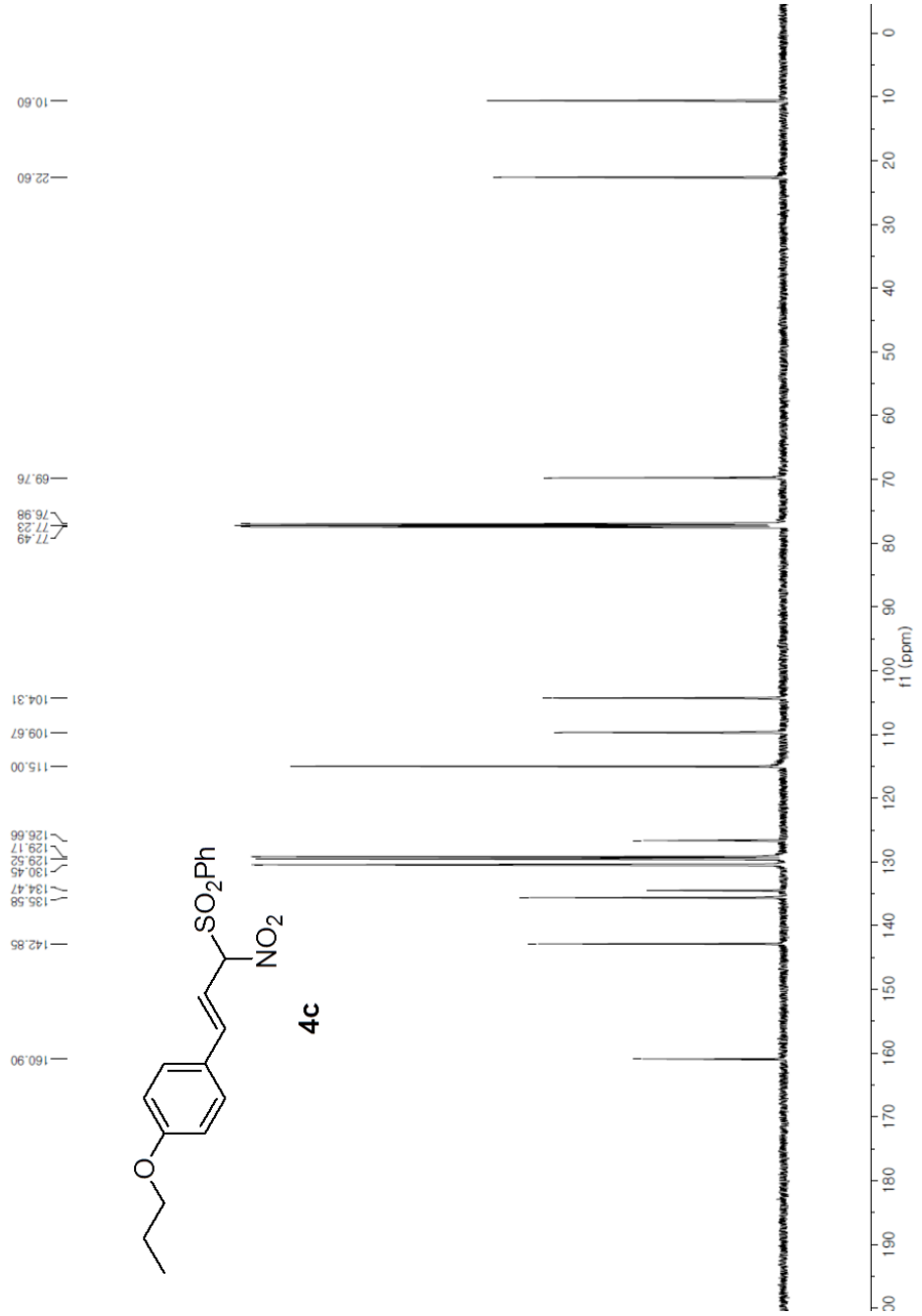

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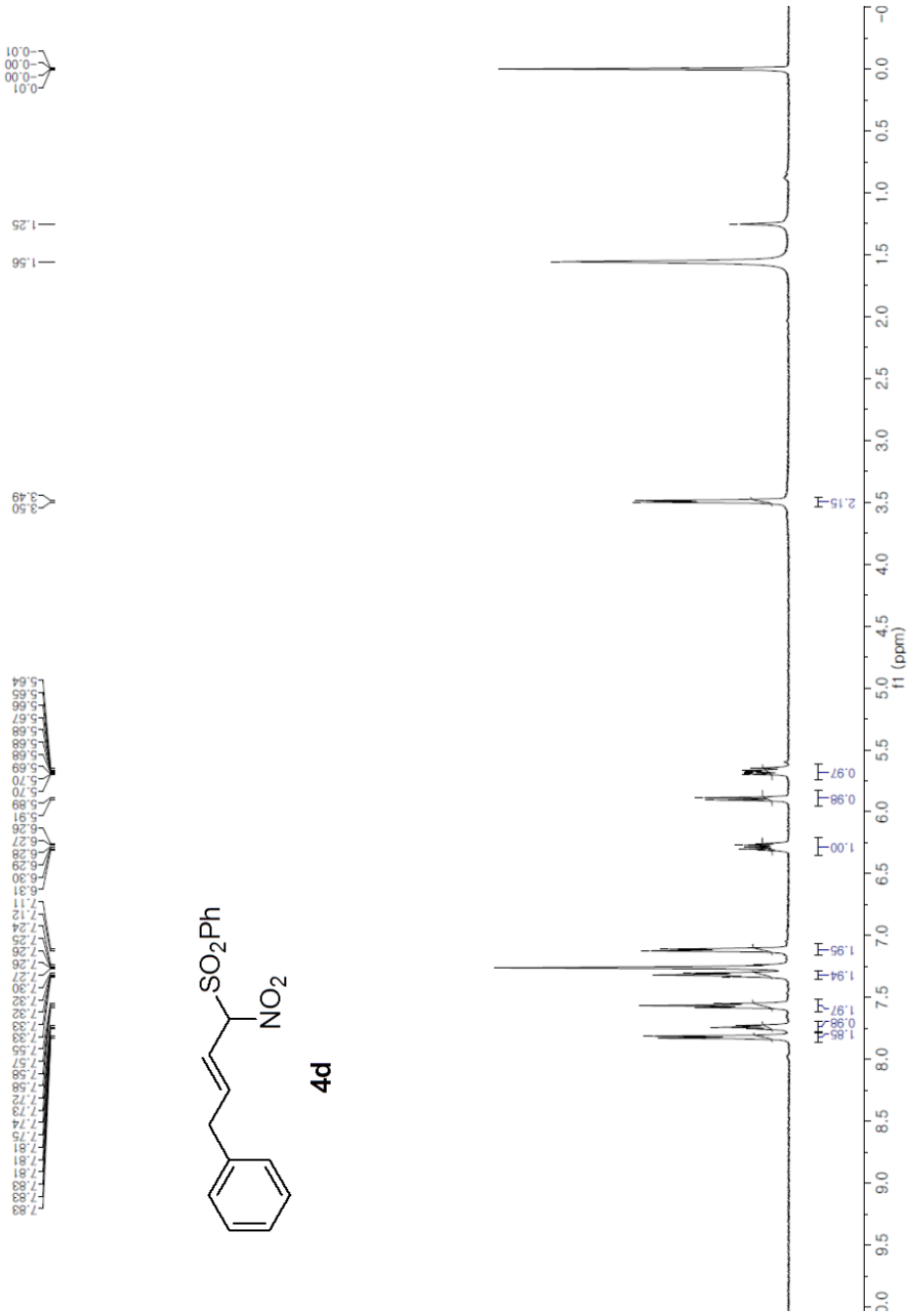

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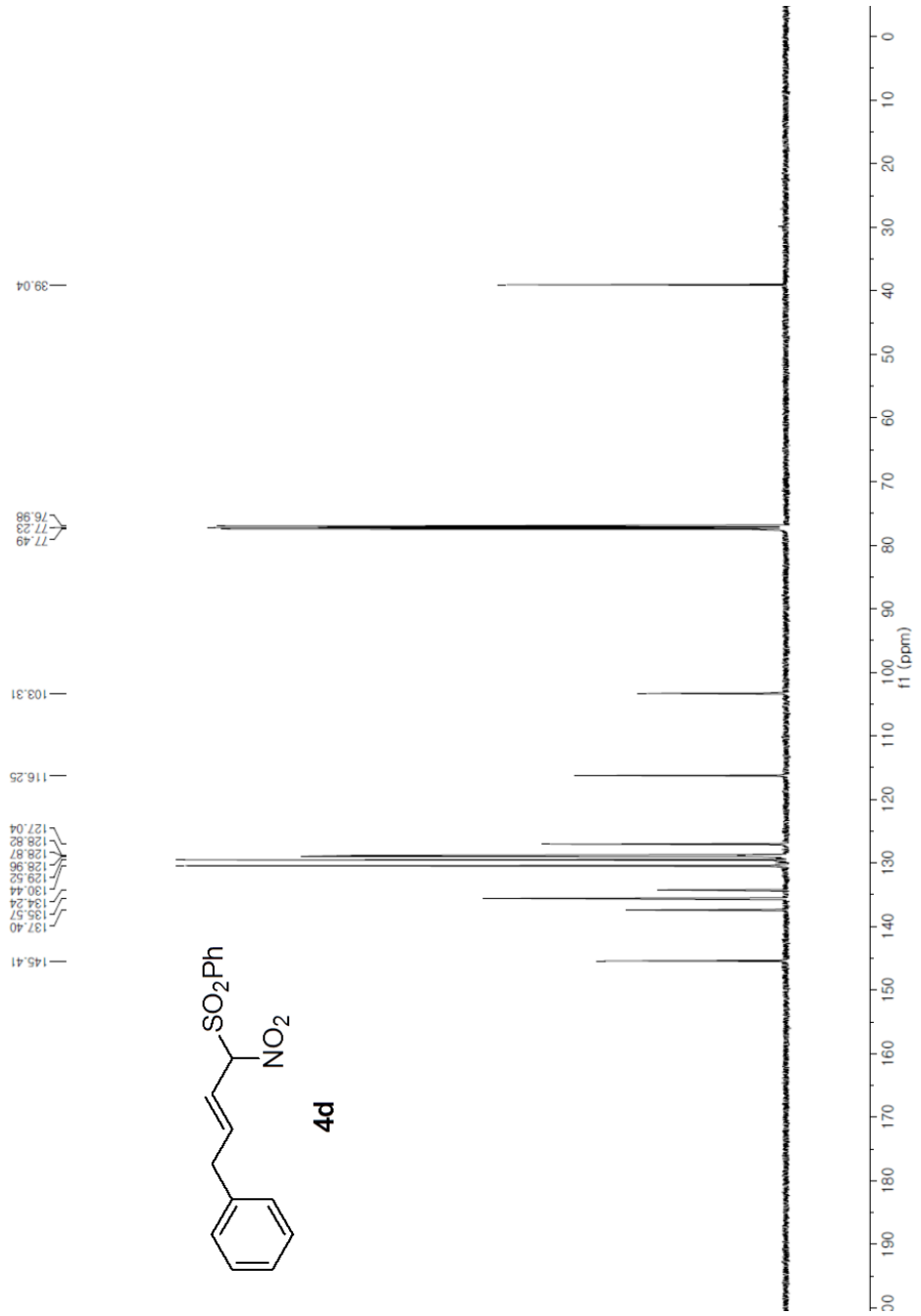

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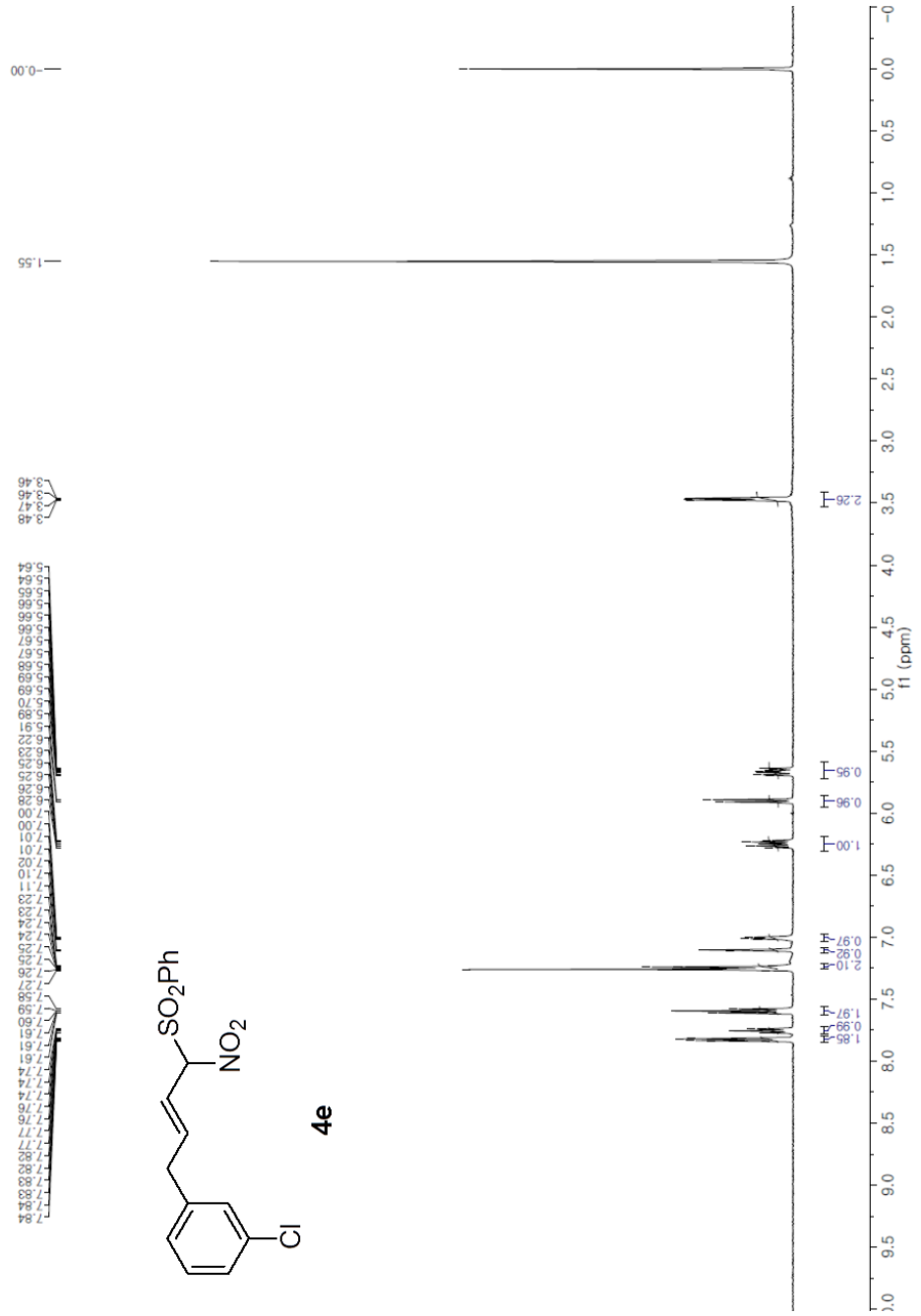

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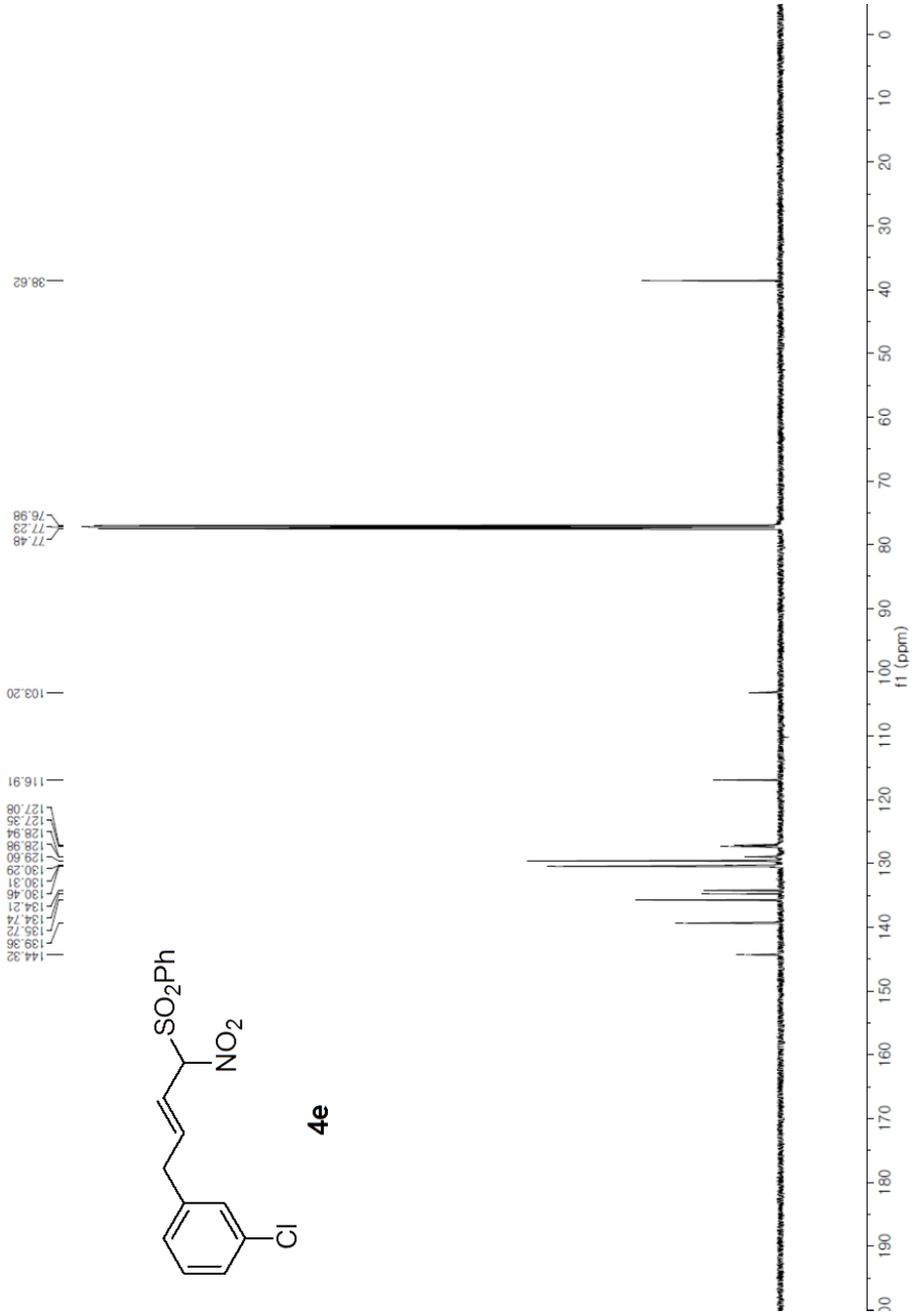

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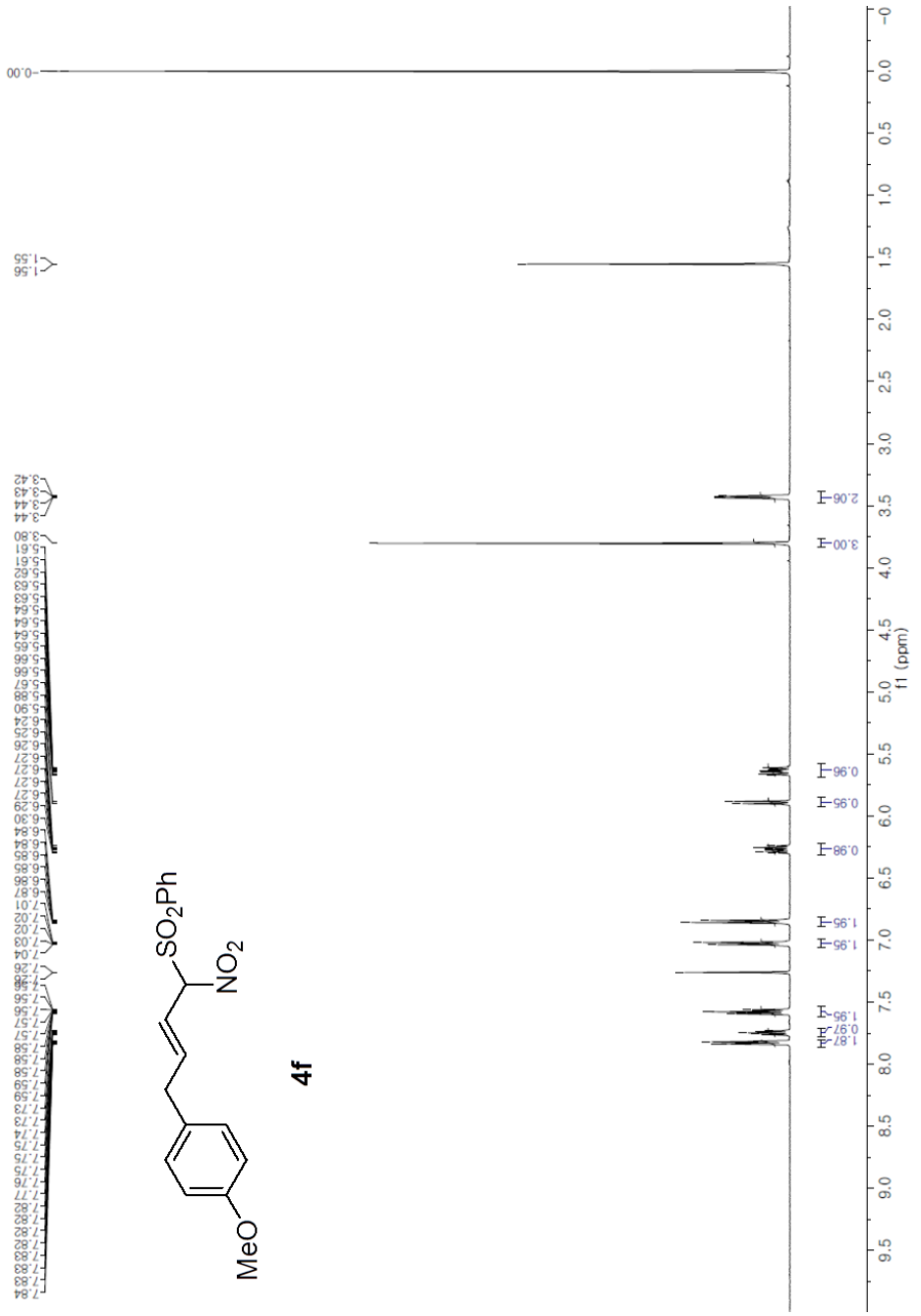

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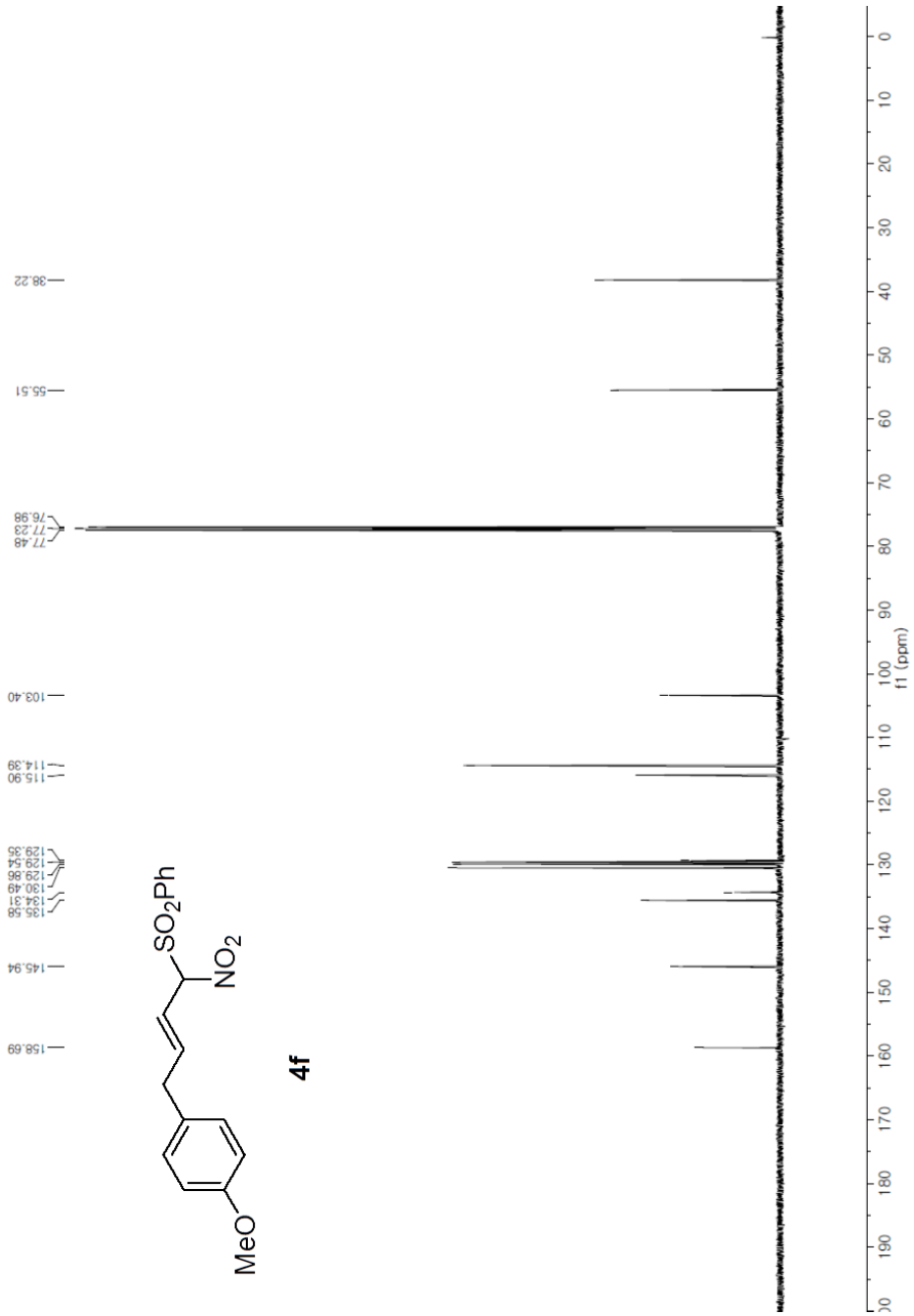

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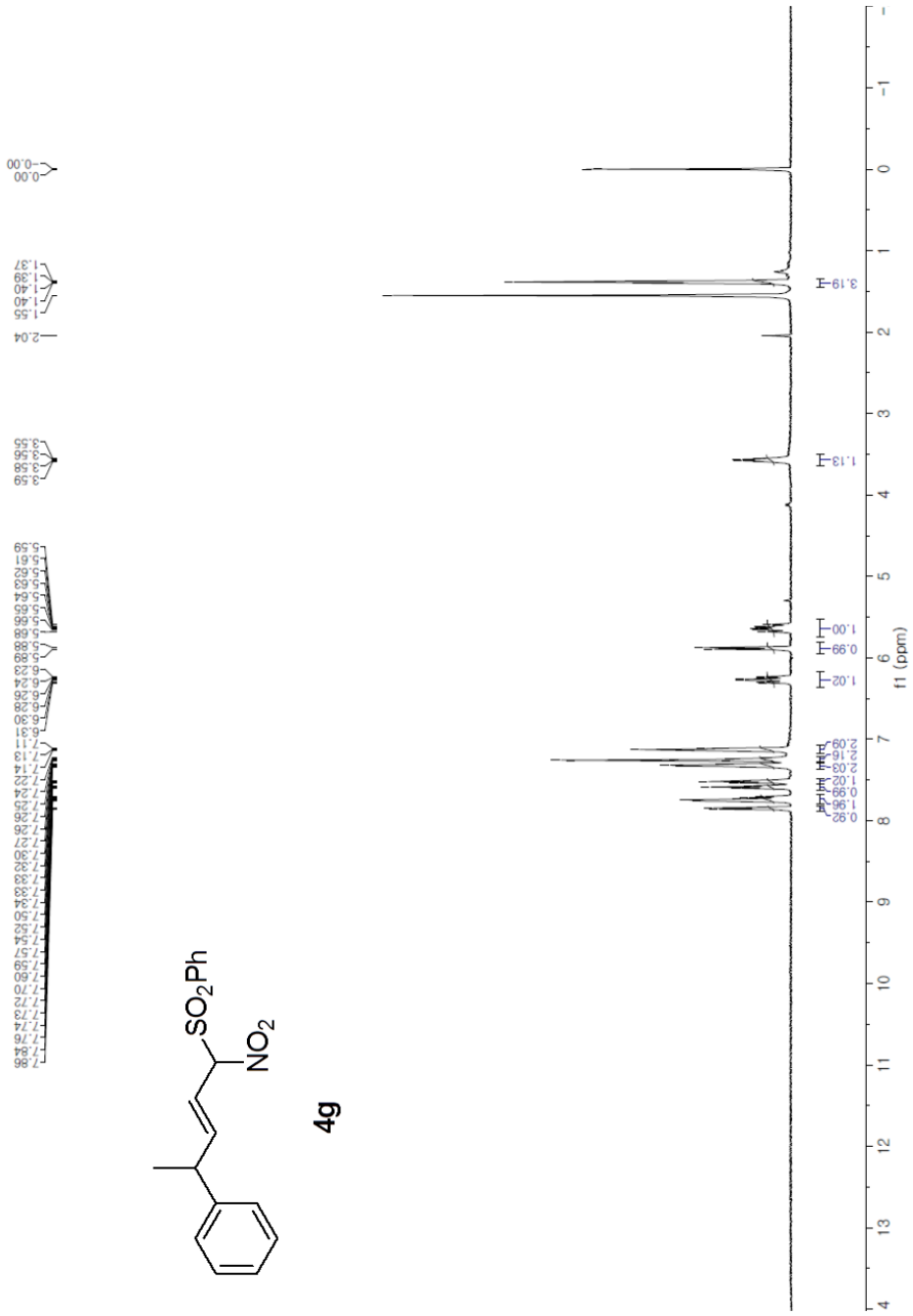

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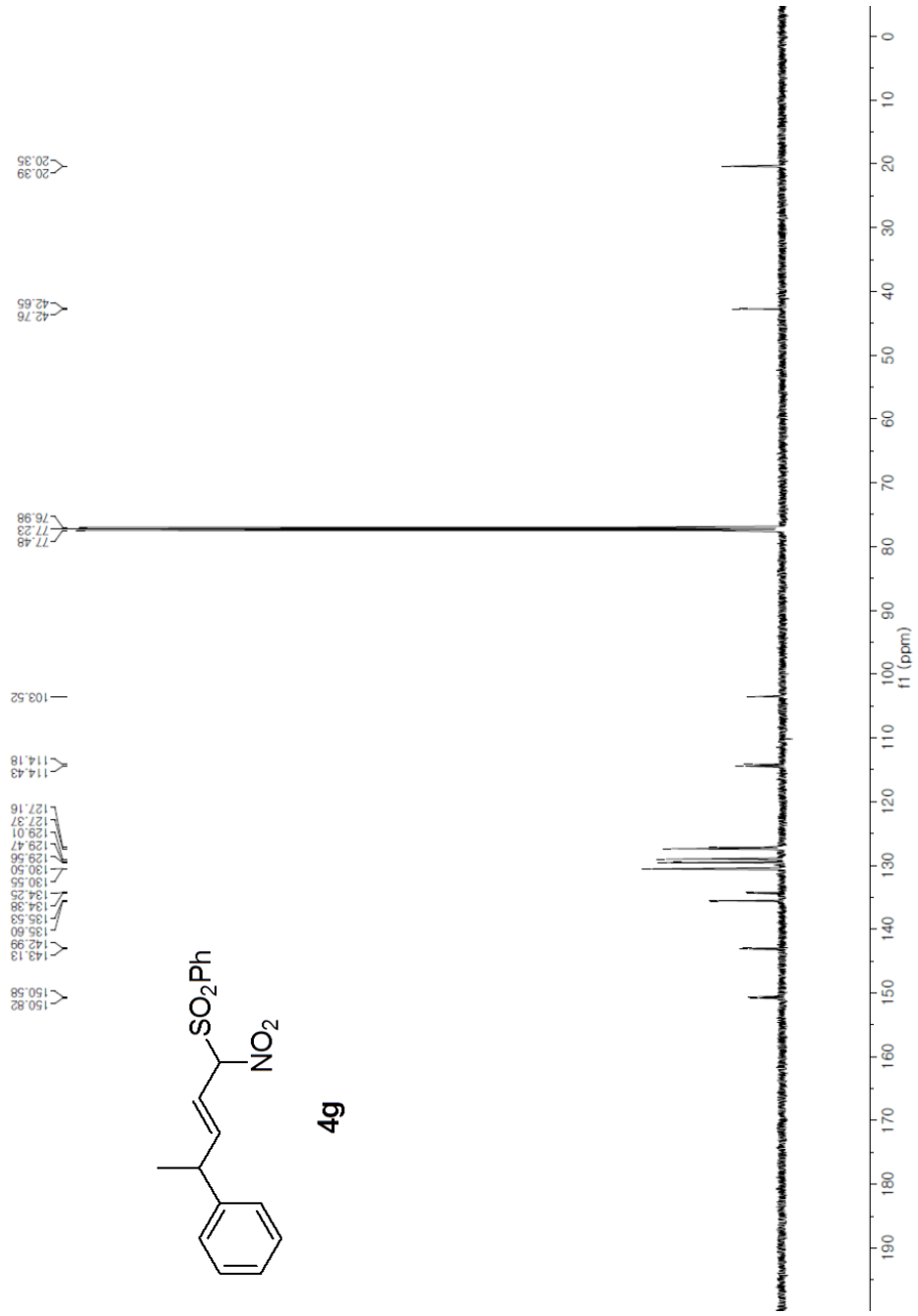

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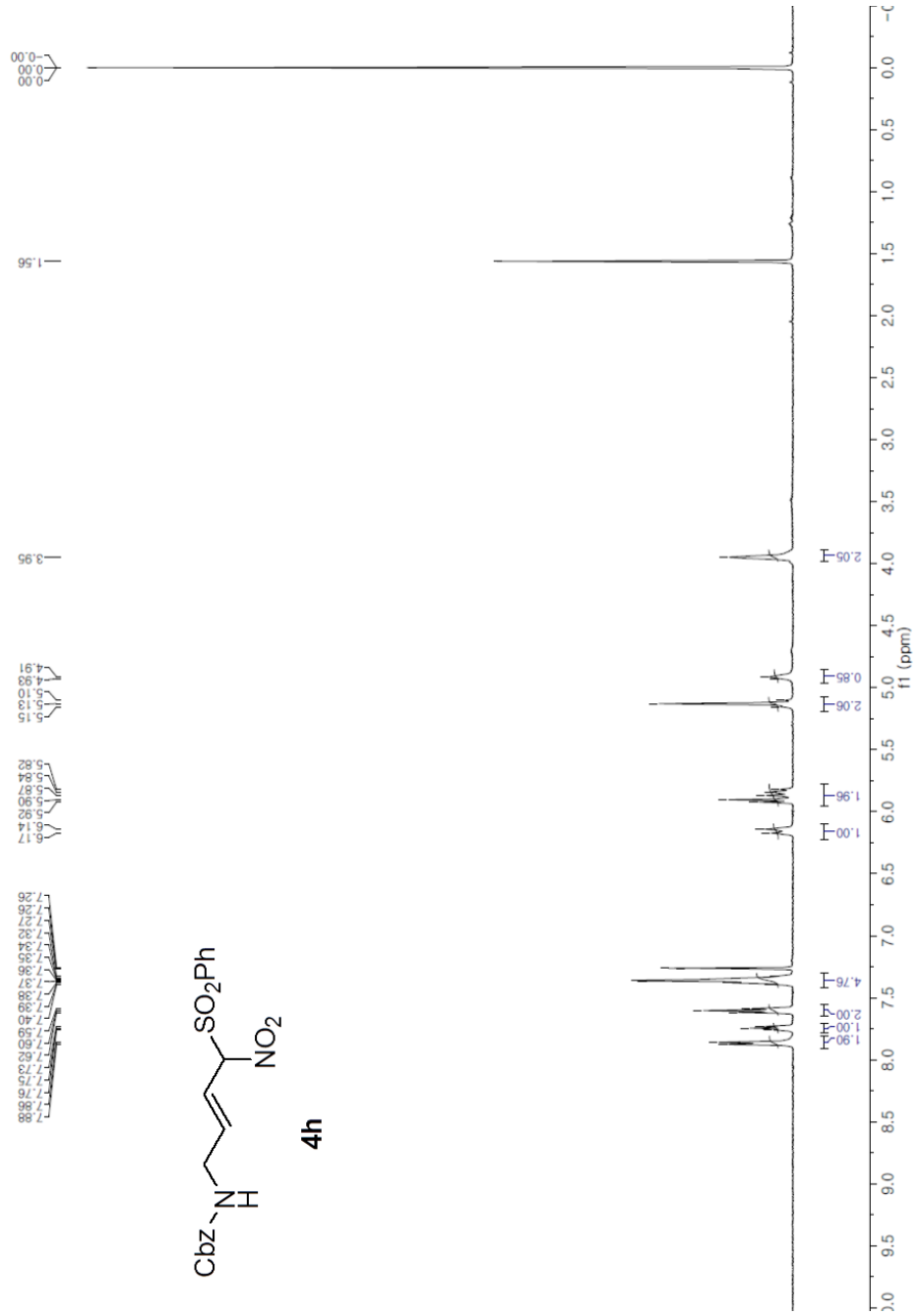

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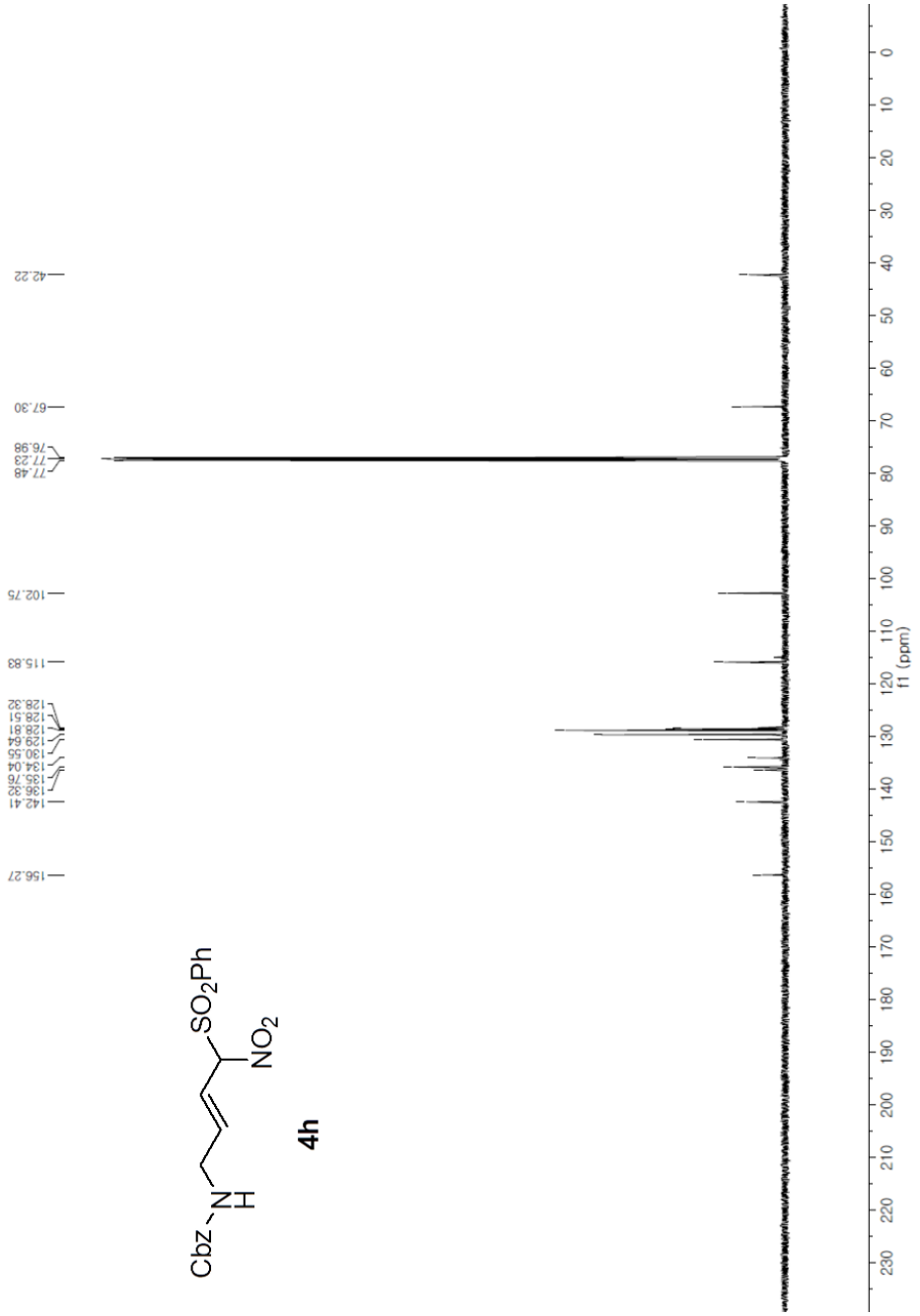

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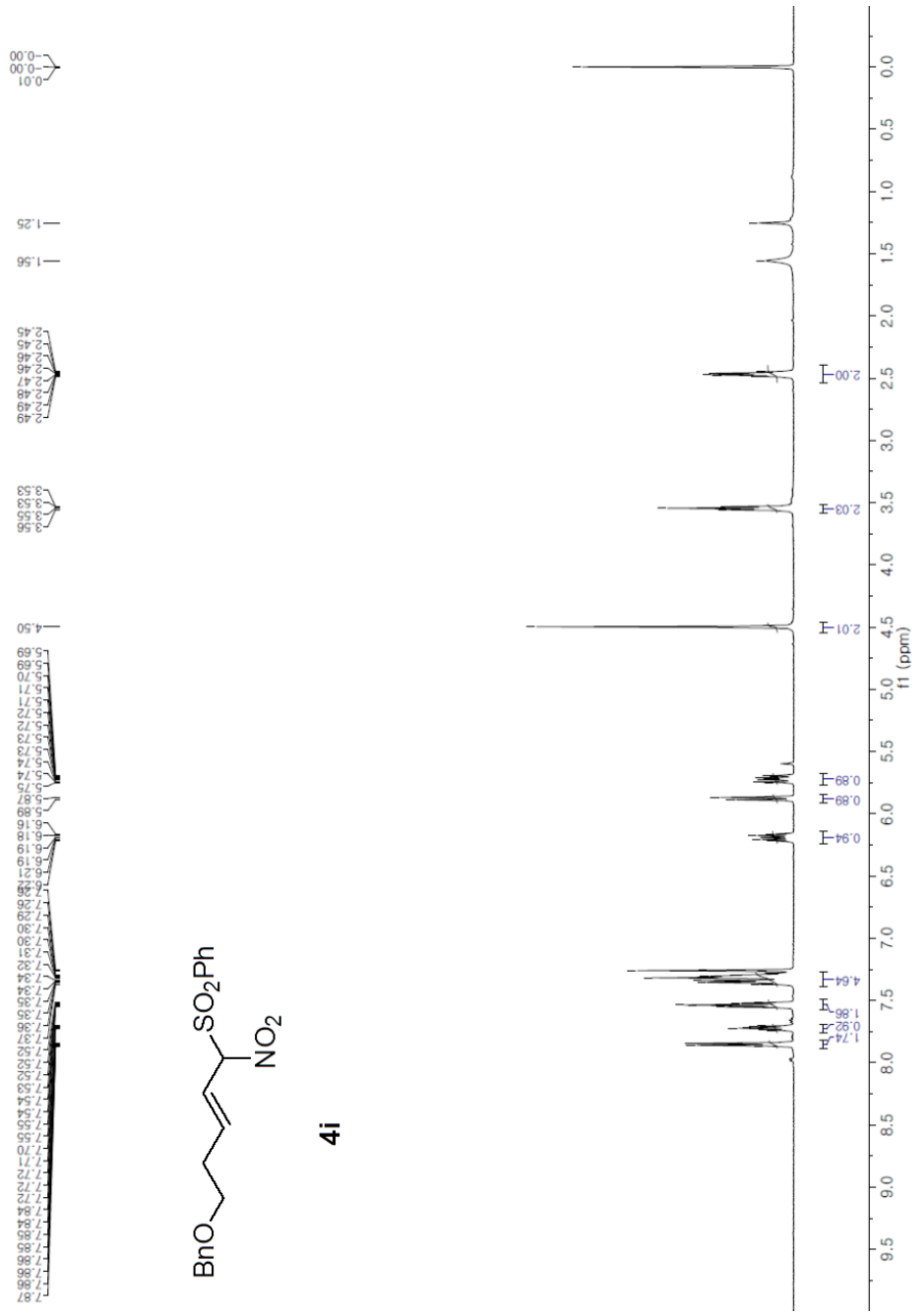

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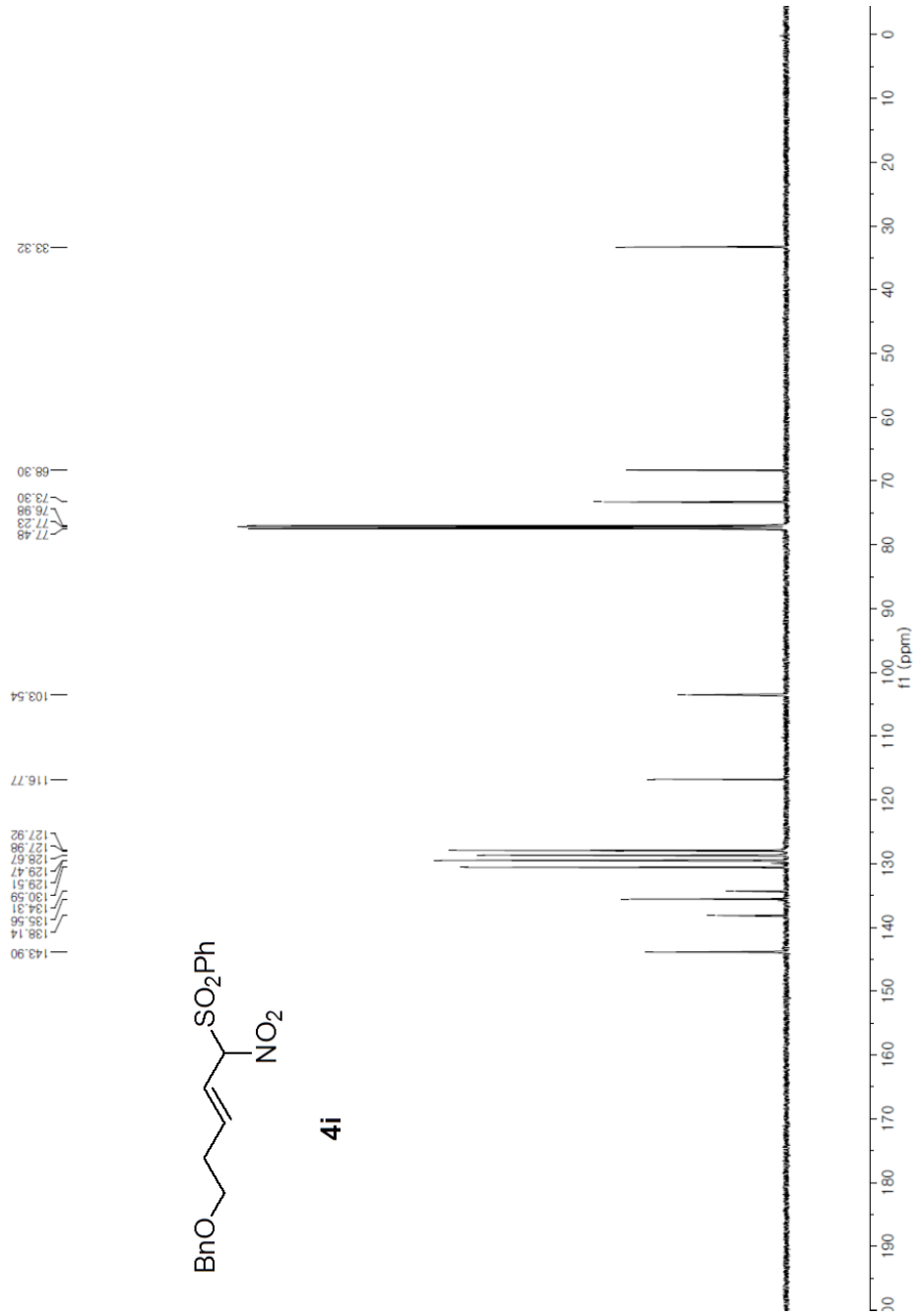

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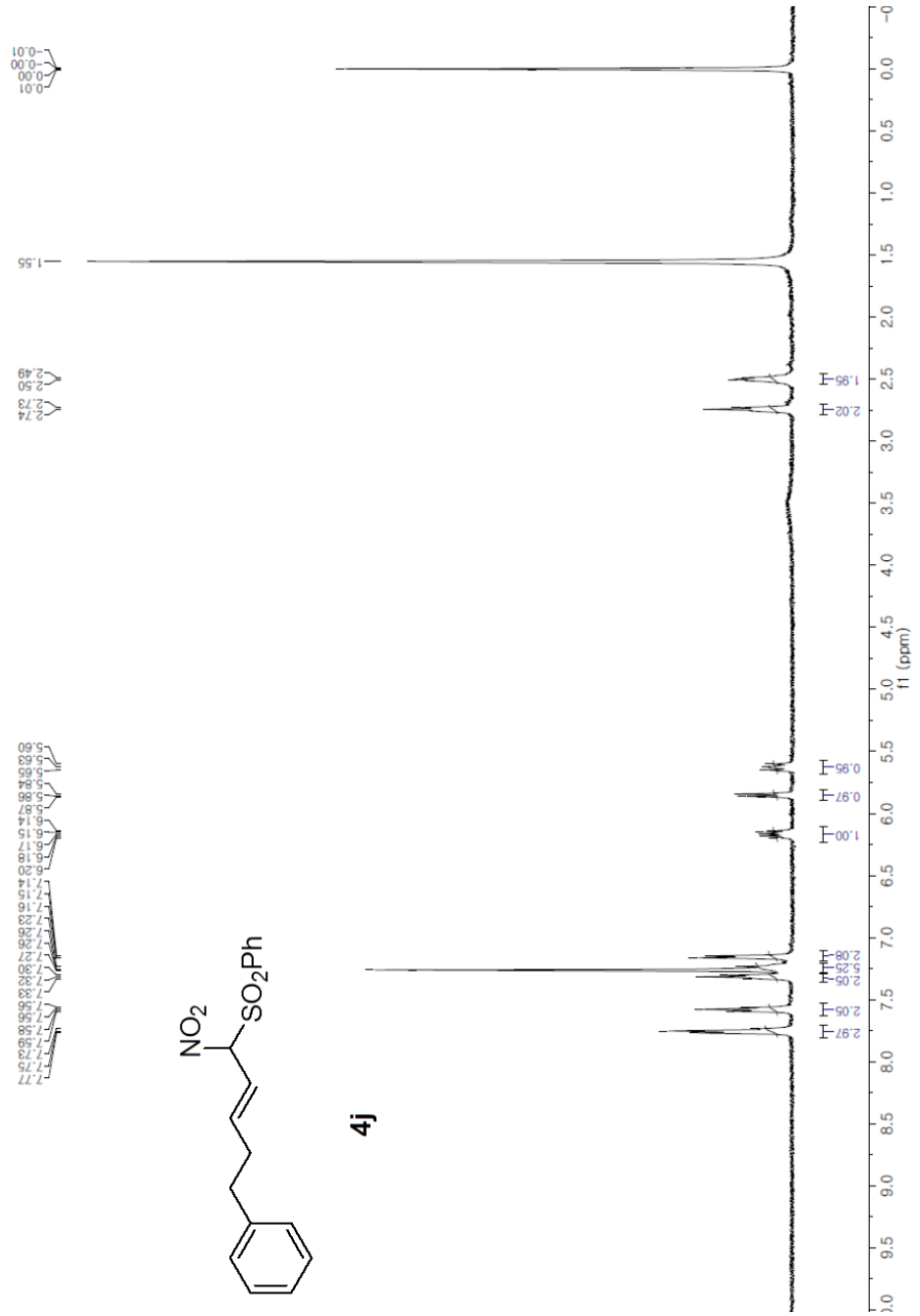

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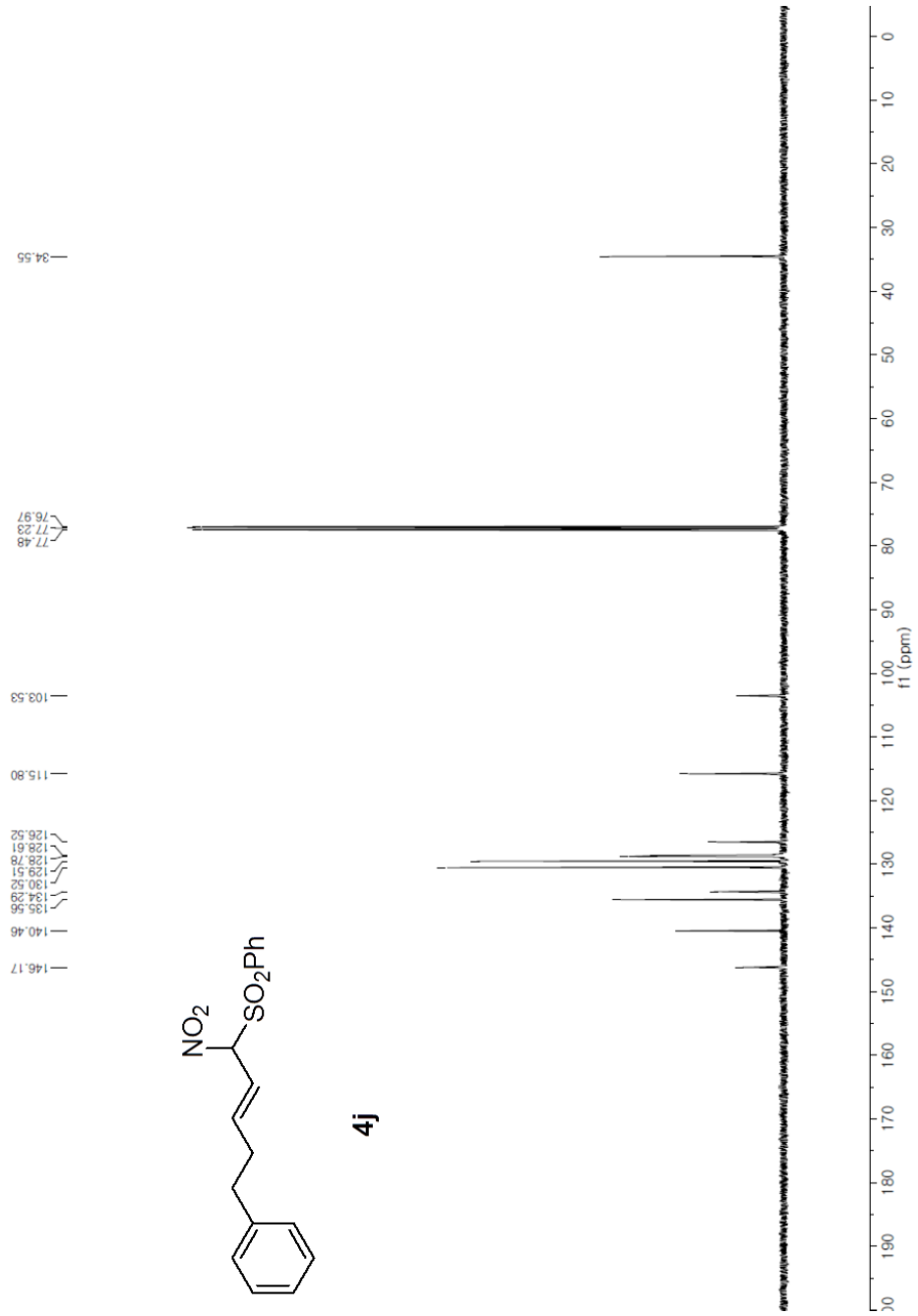
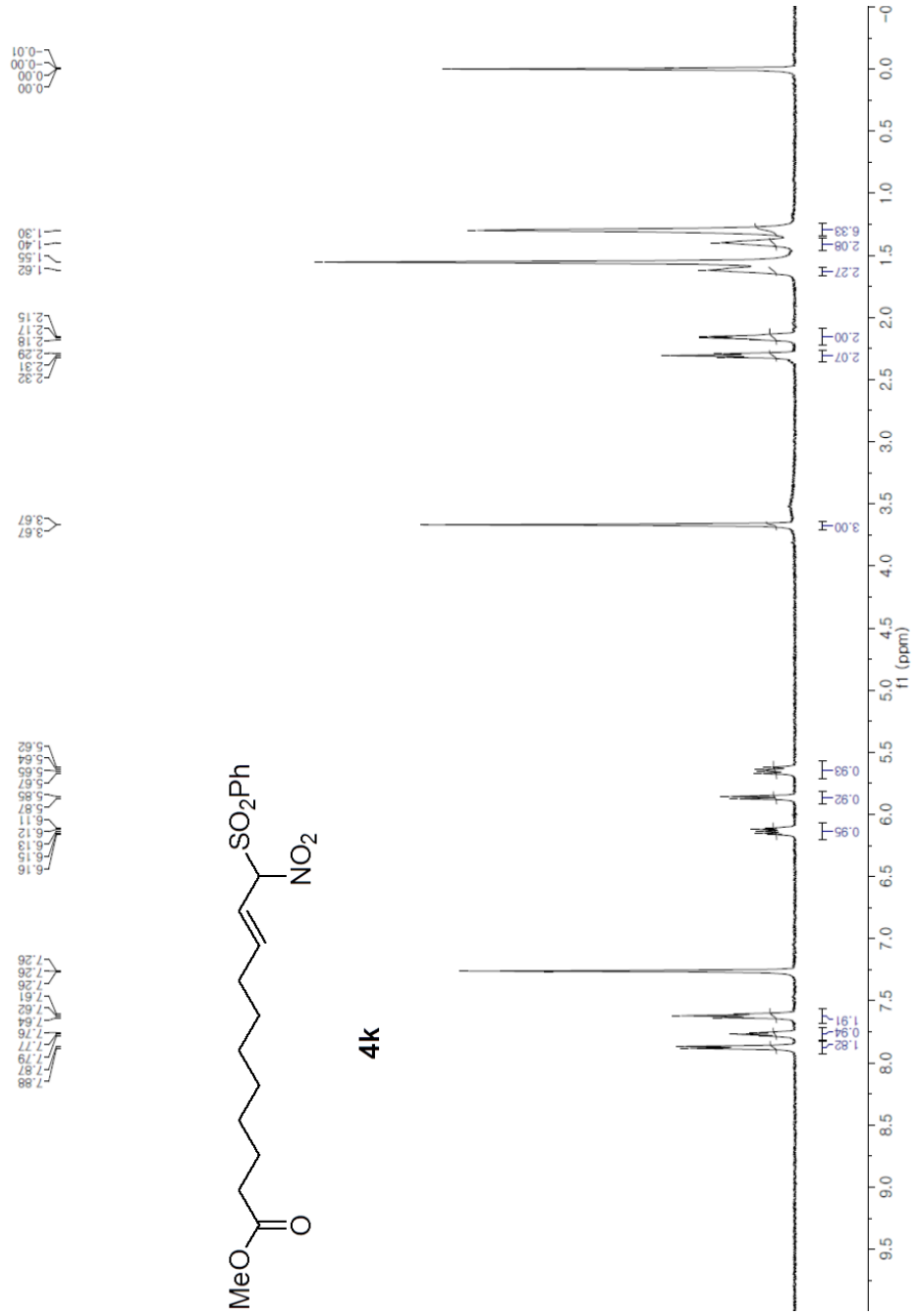
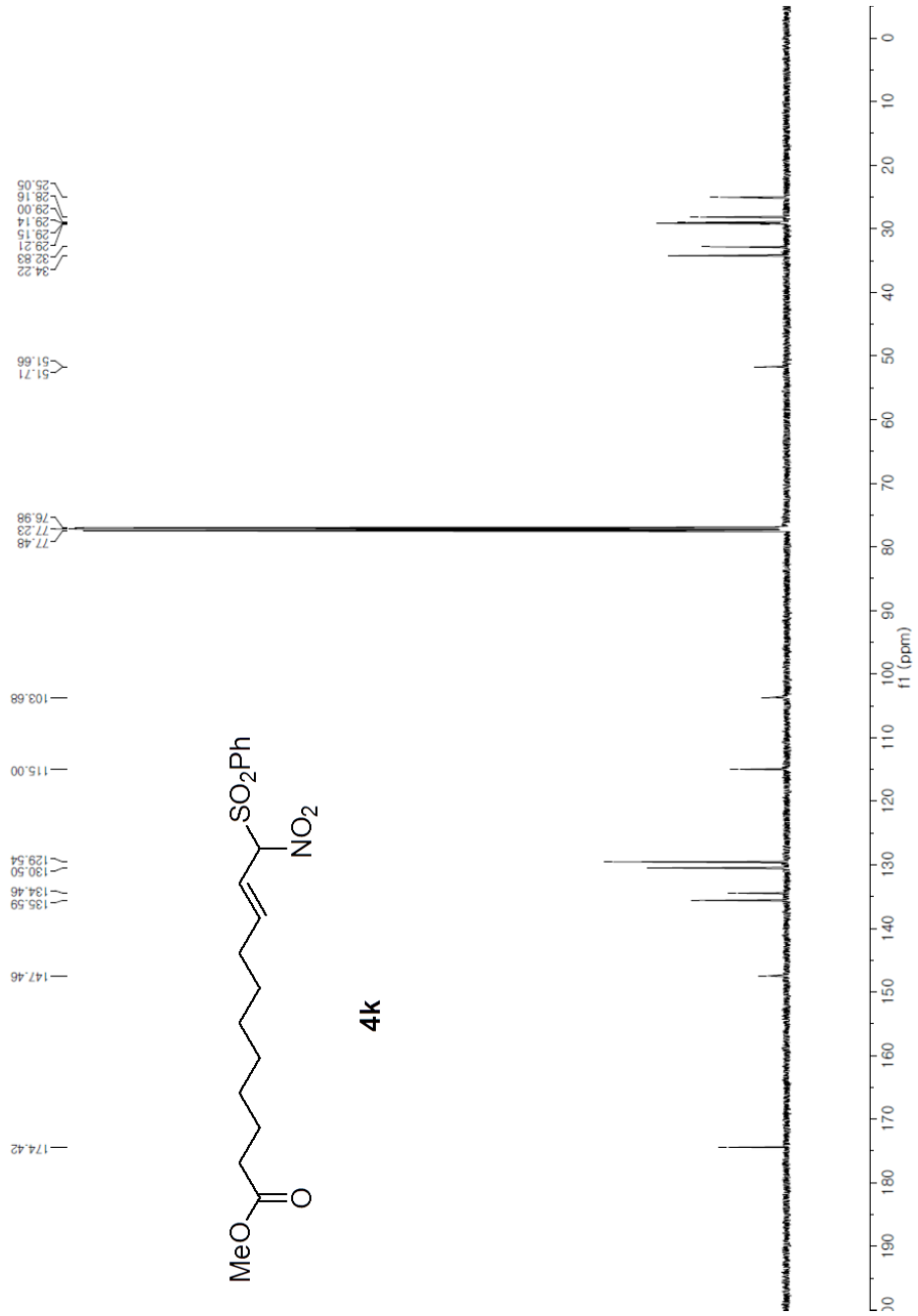


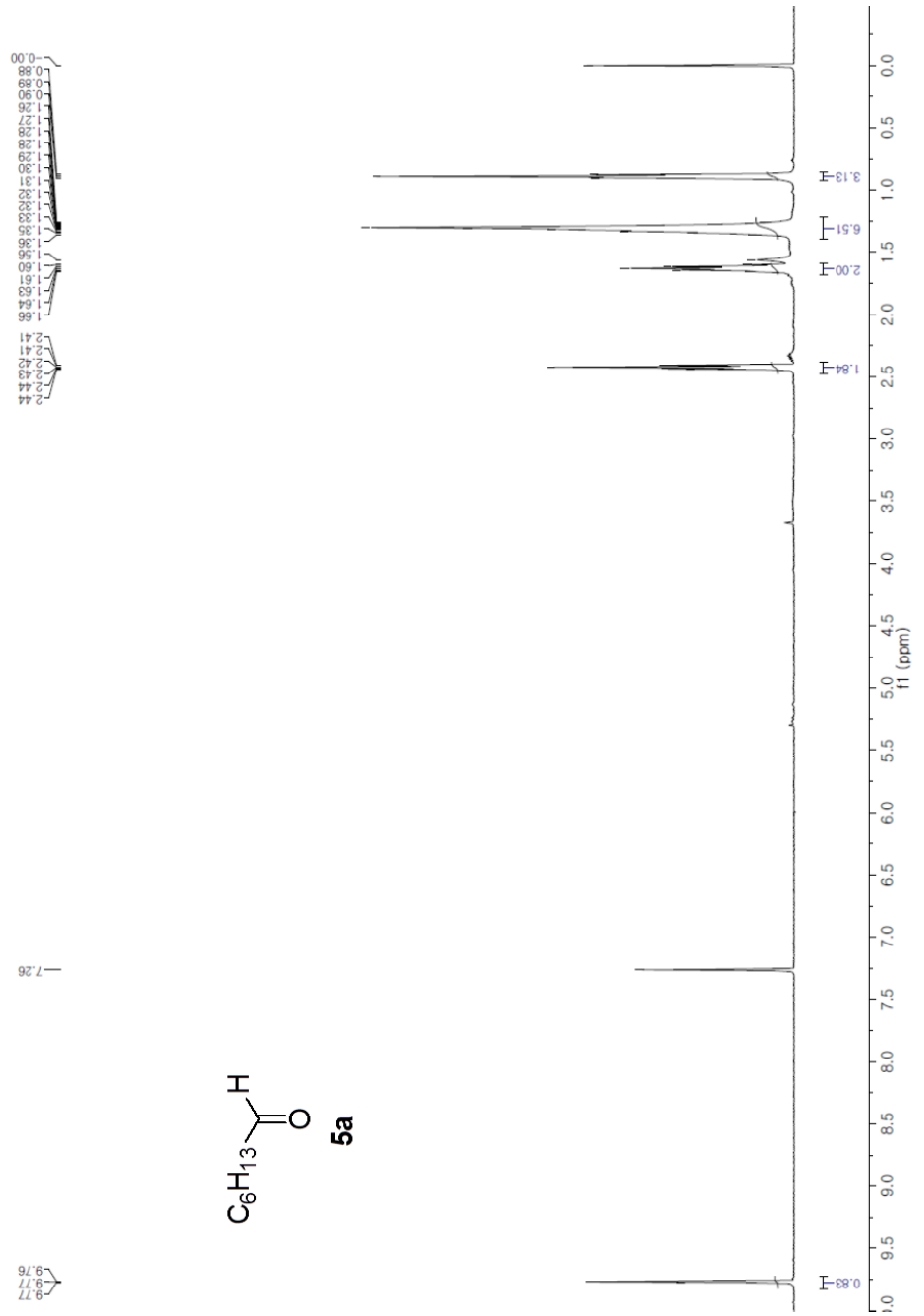
Compound 4k ^{1}H NMR



Compound 4k ^{13}C NMR



Compound 5a ^{1}H NMR



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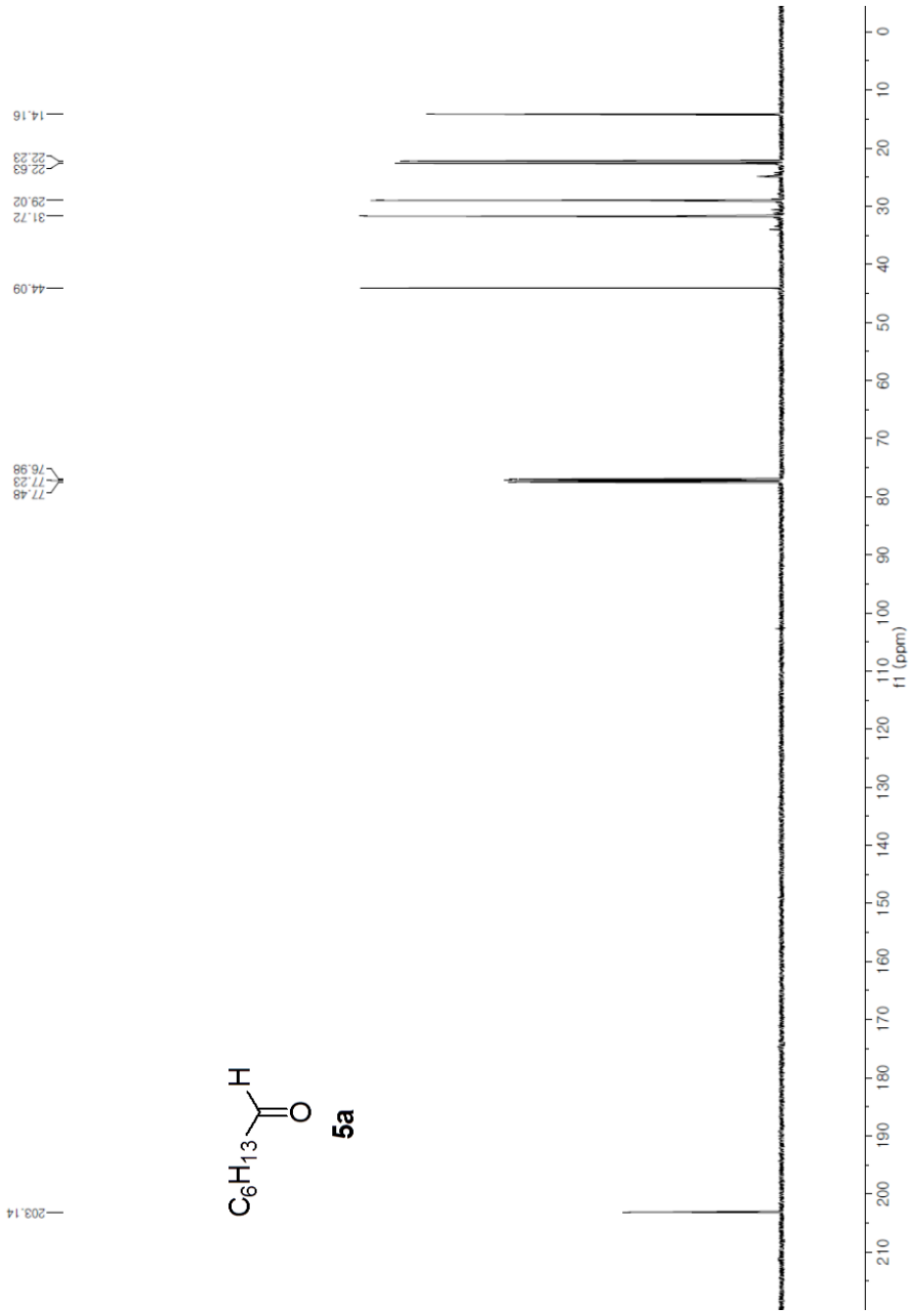

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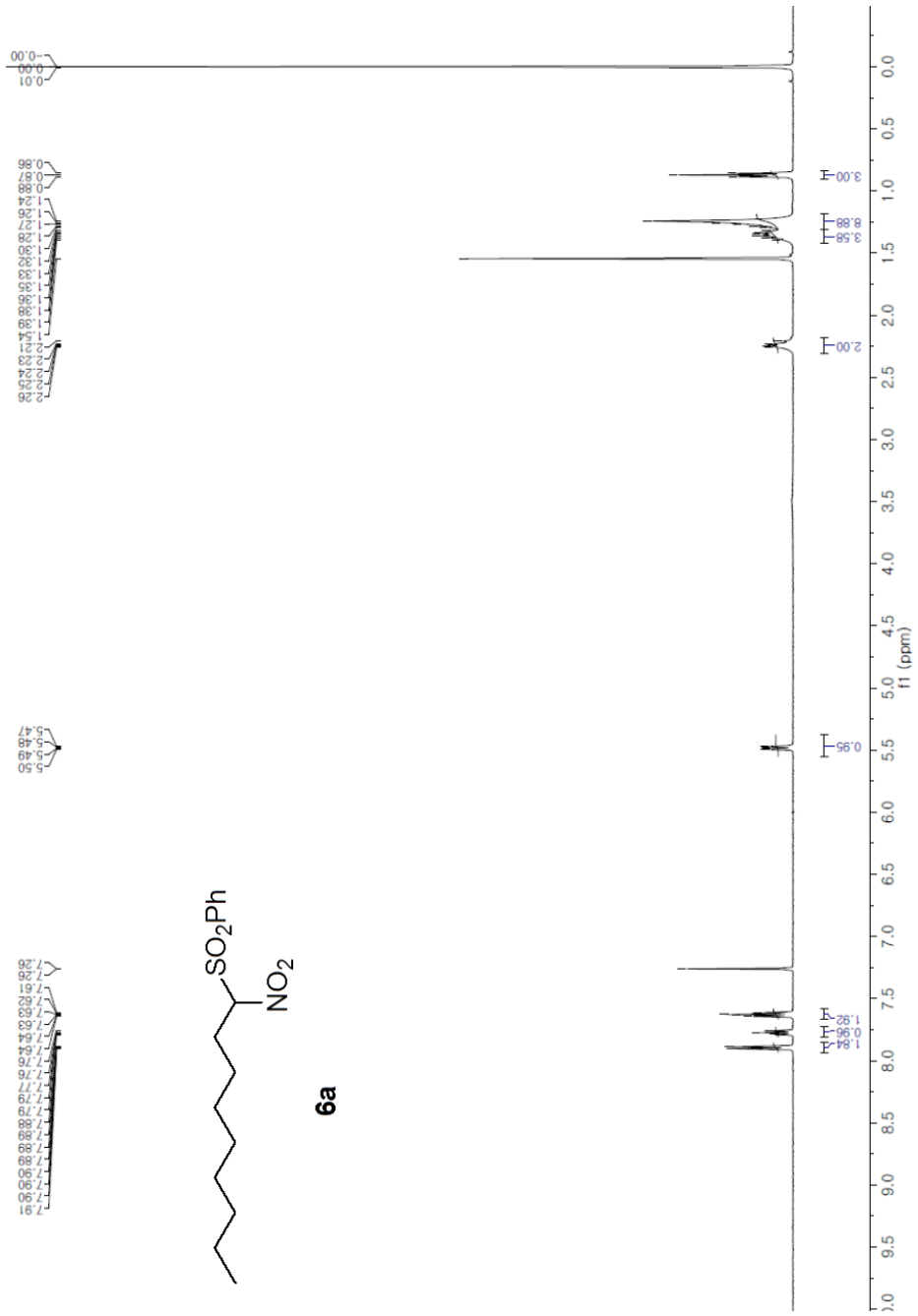

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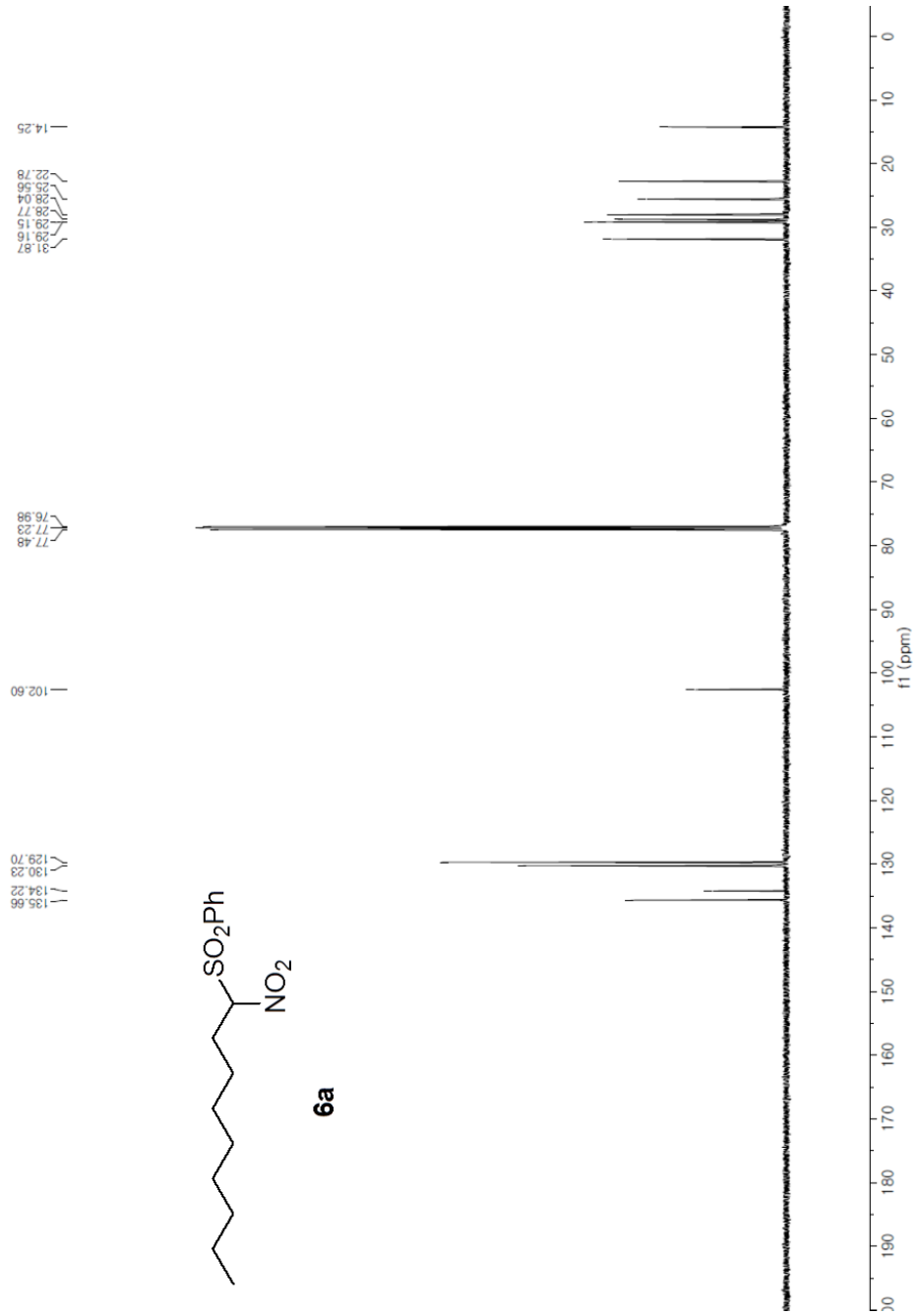
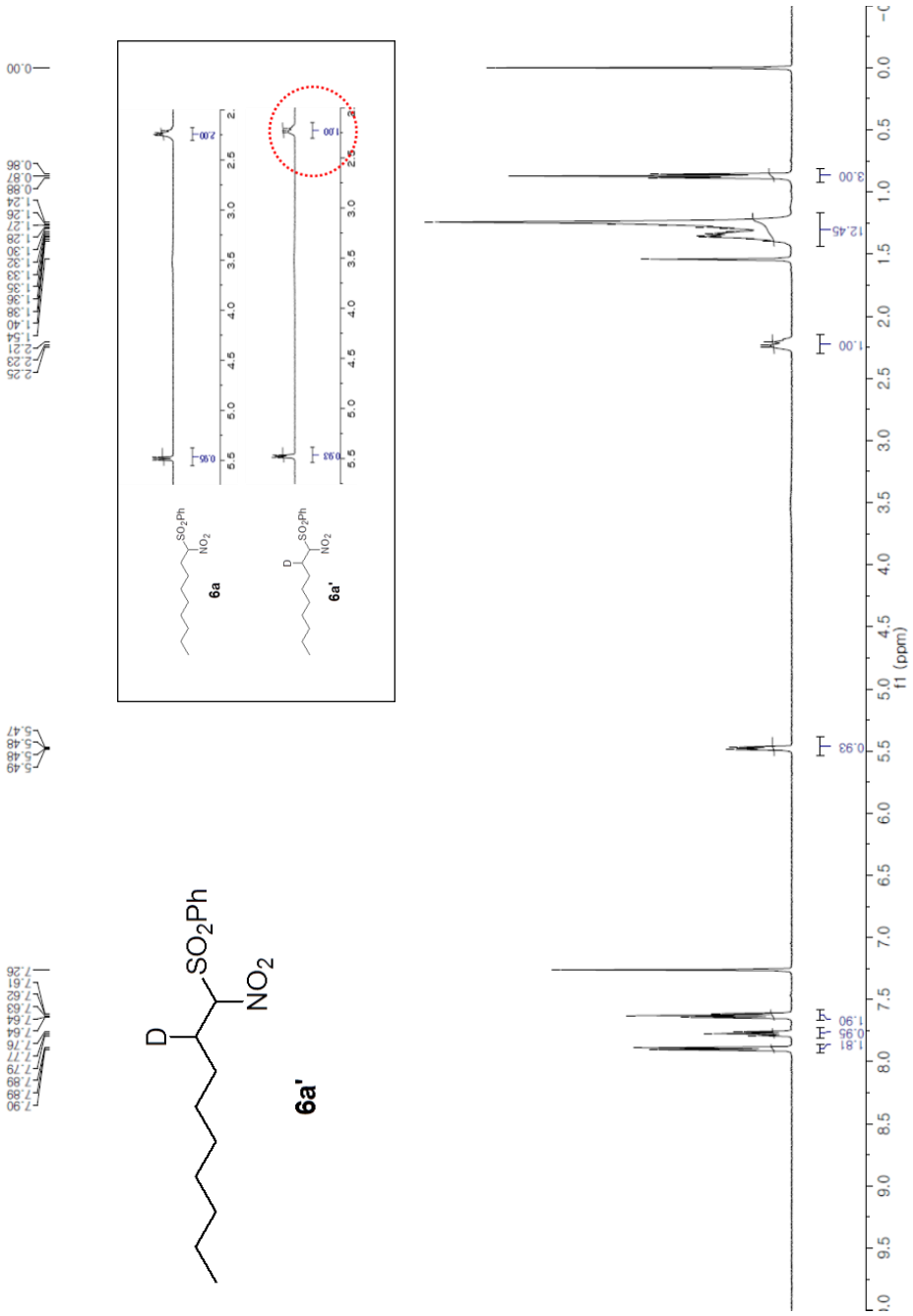
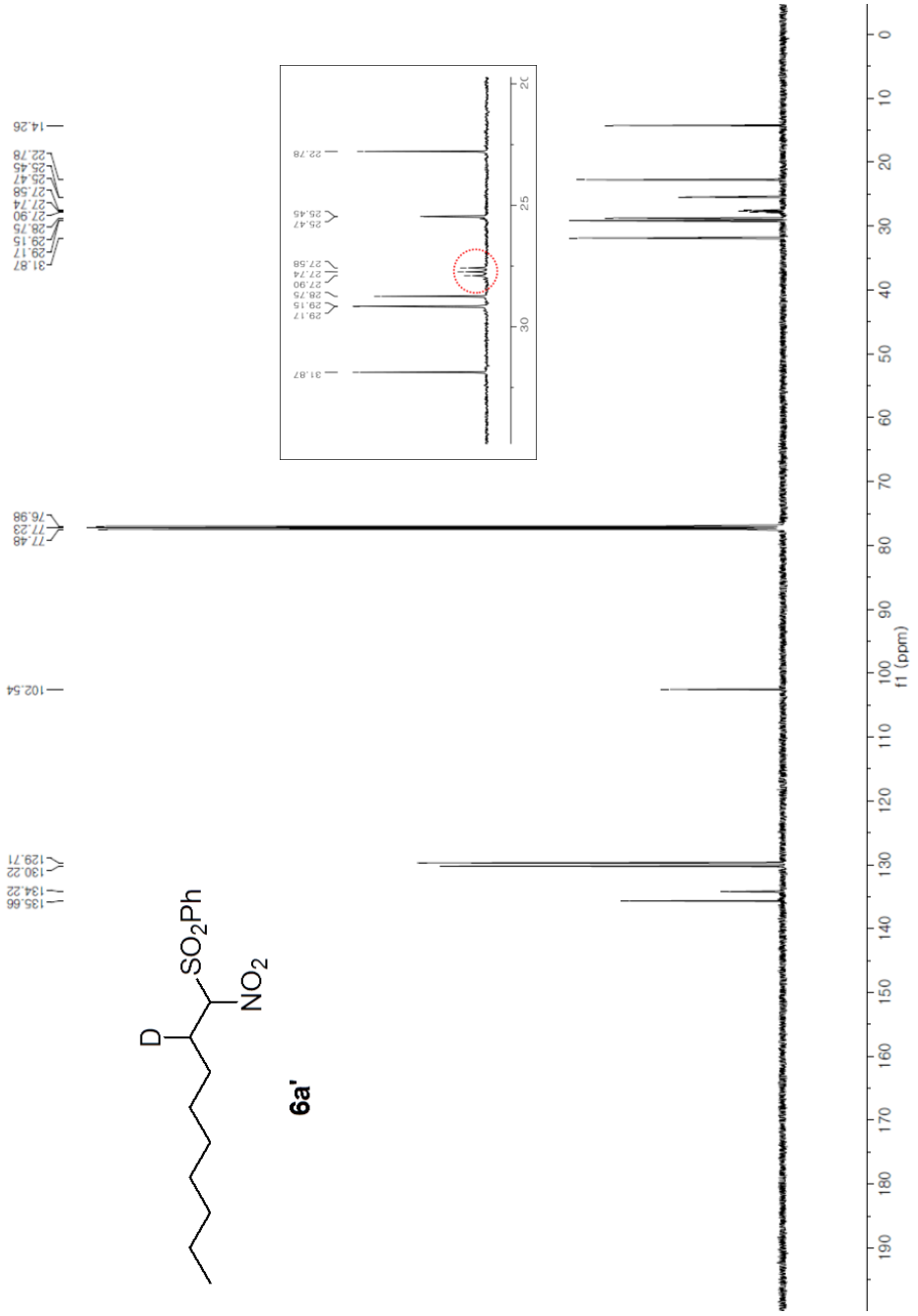


Compound 6a‘ ^{1}H NMR



Compound 6a‘ ^{13}C NMR



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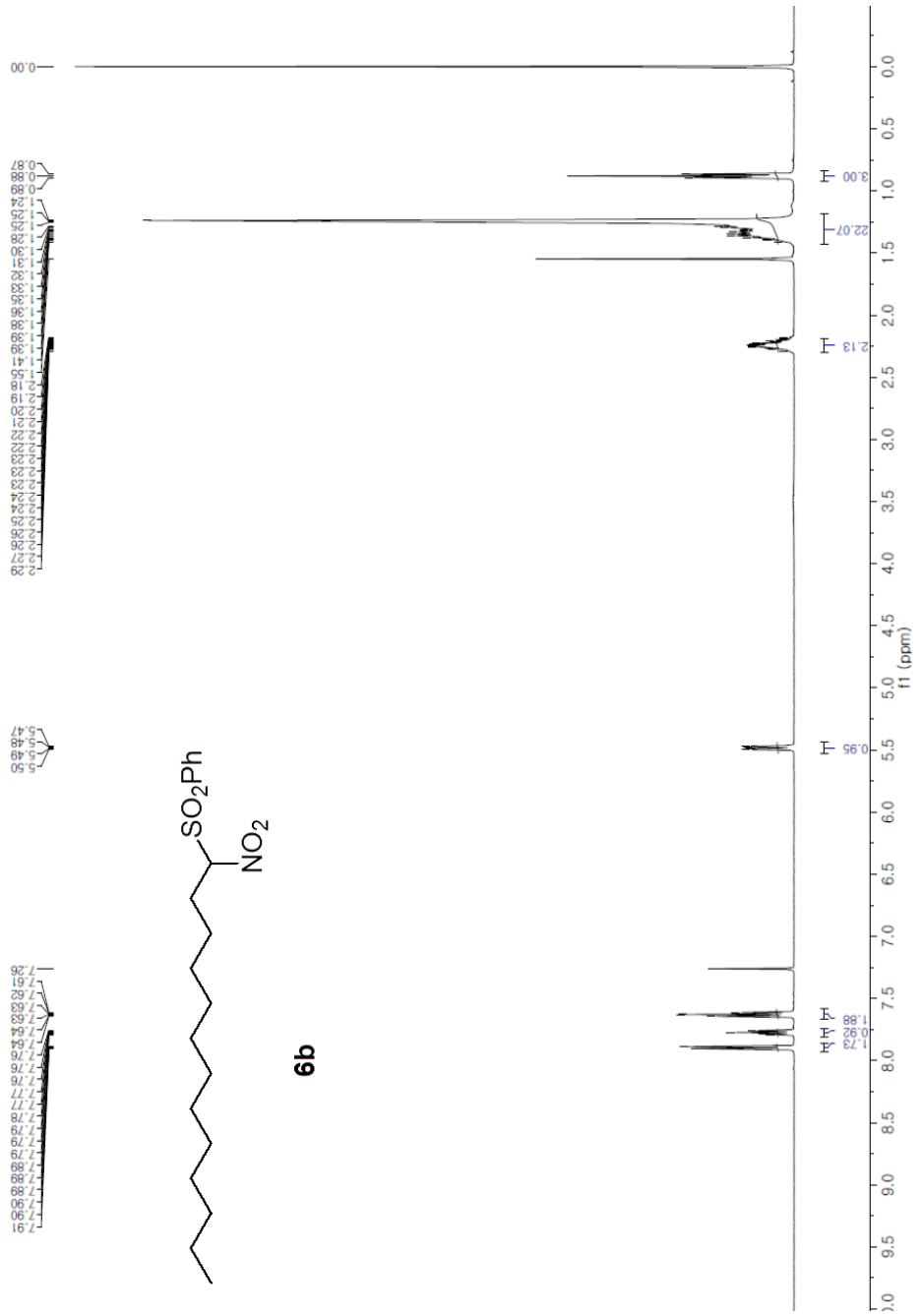

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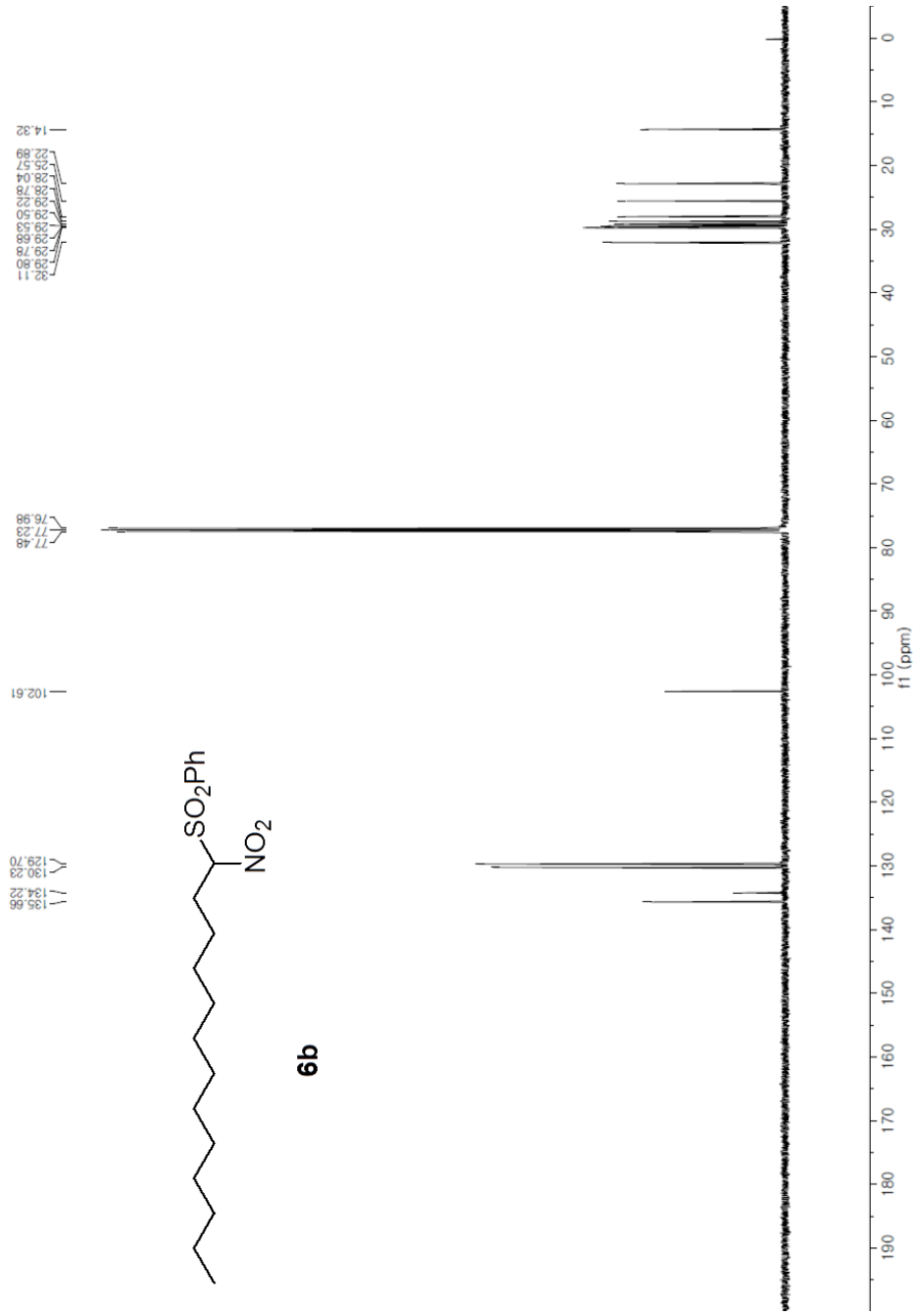
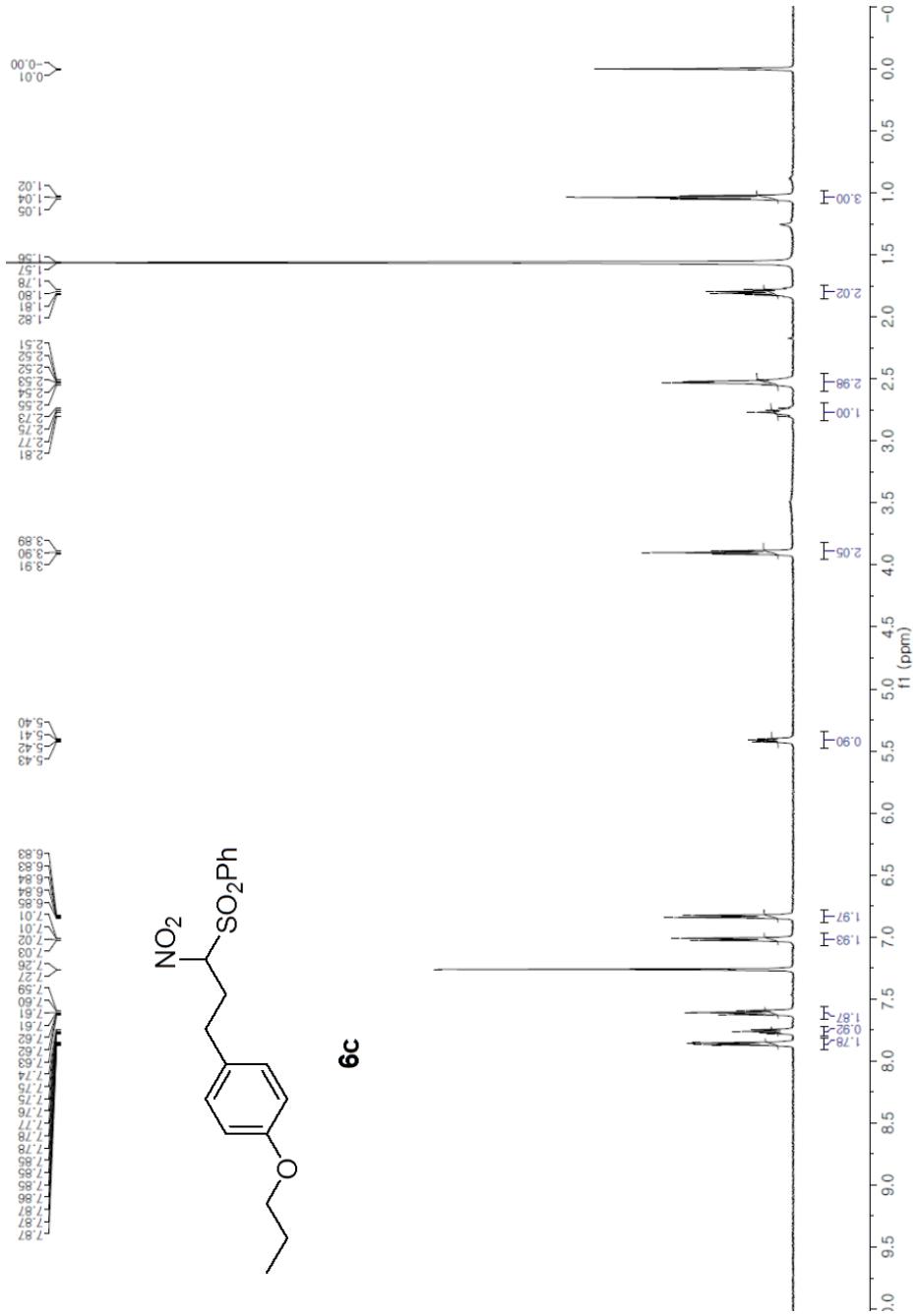


Compound 6c ^{1}H NMR



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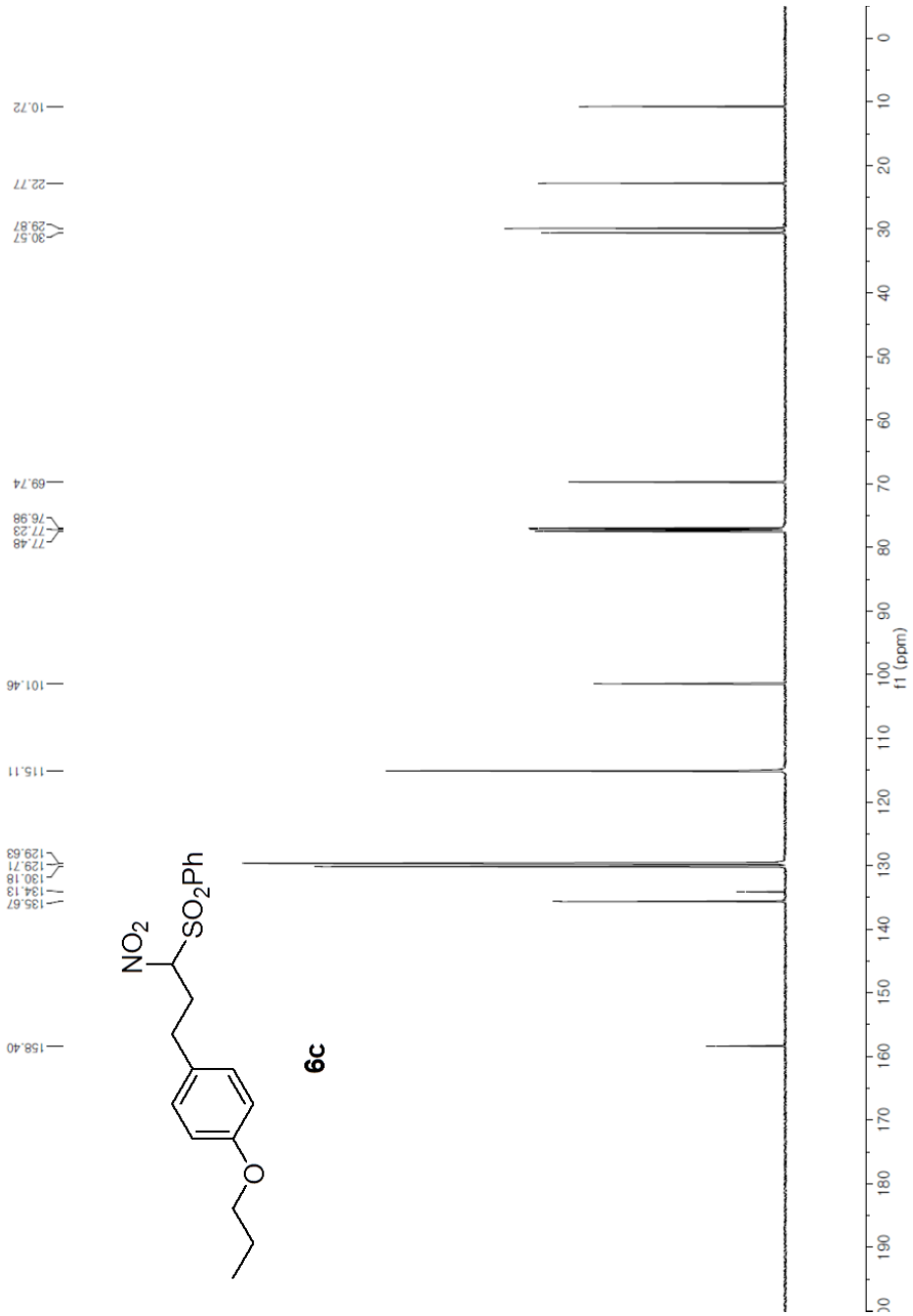

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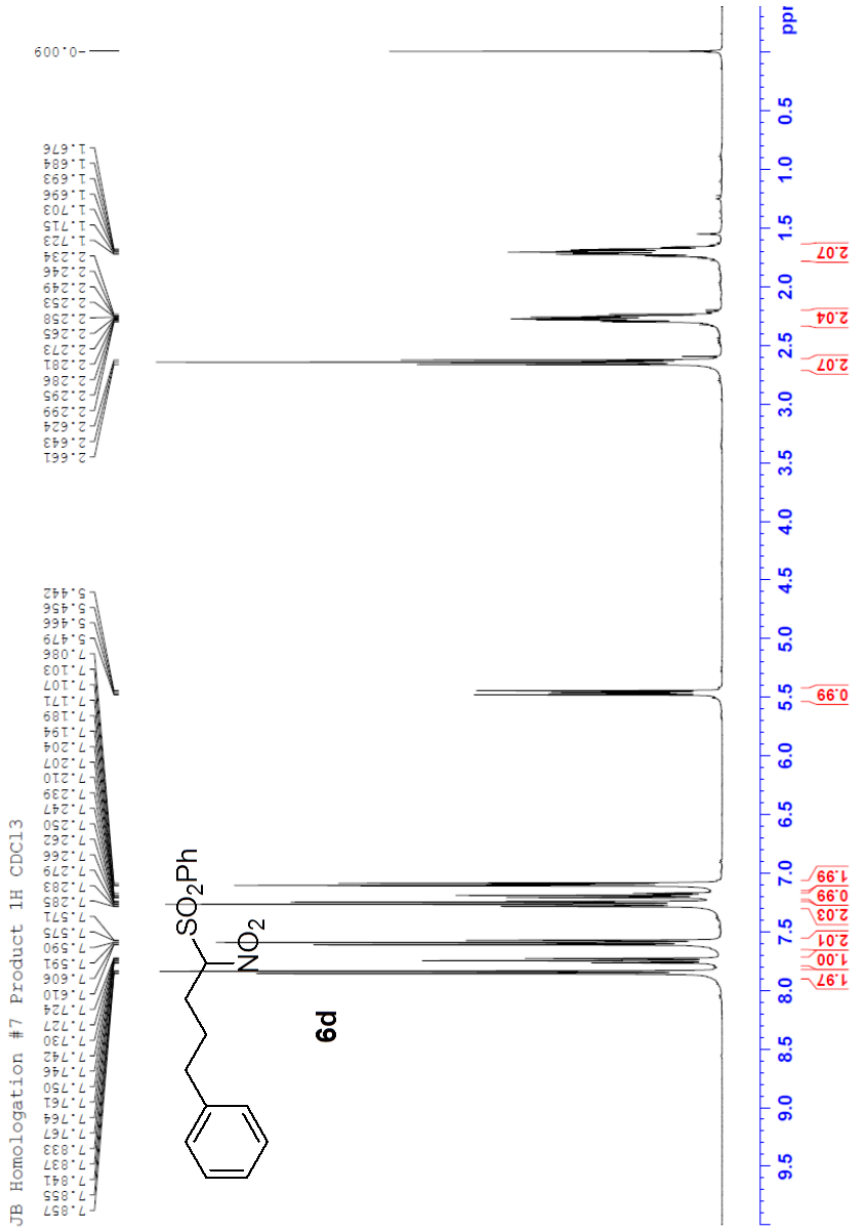

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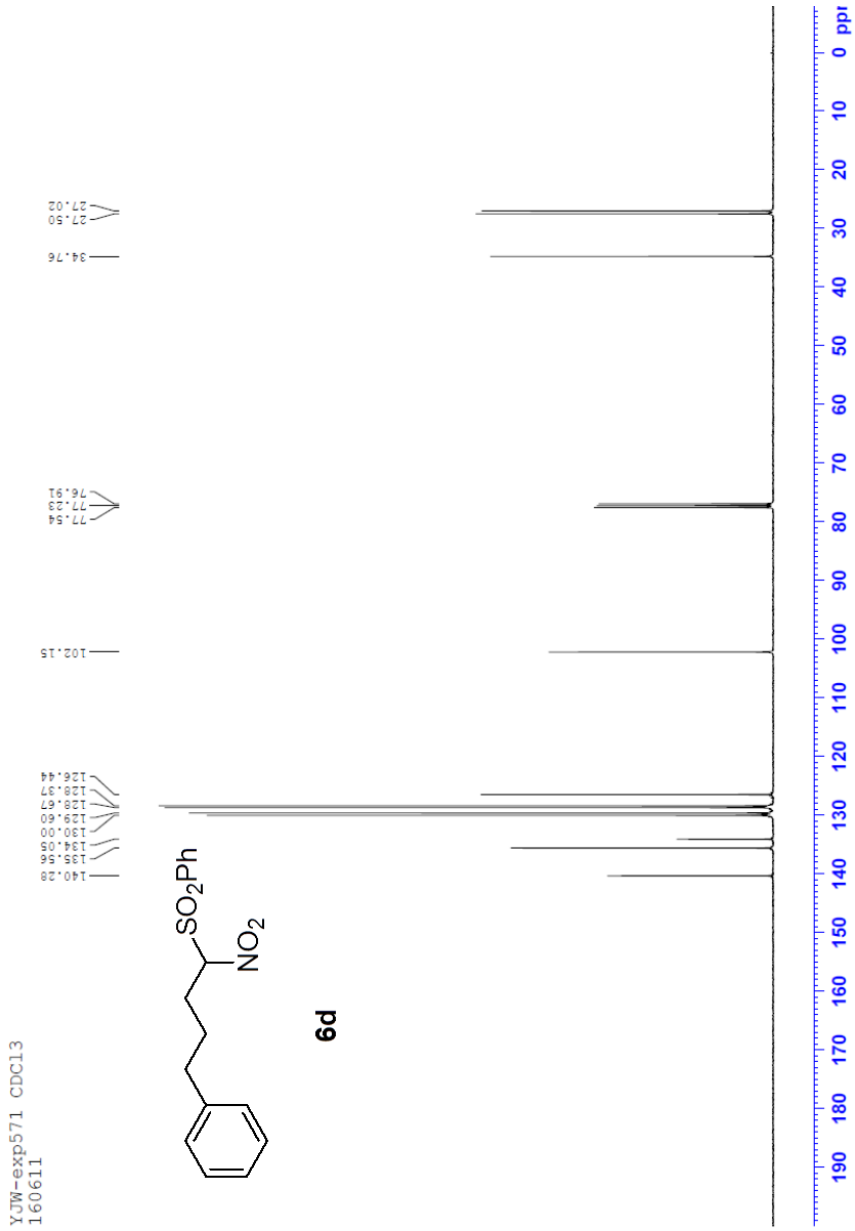

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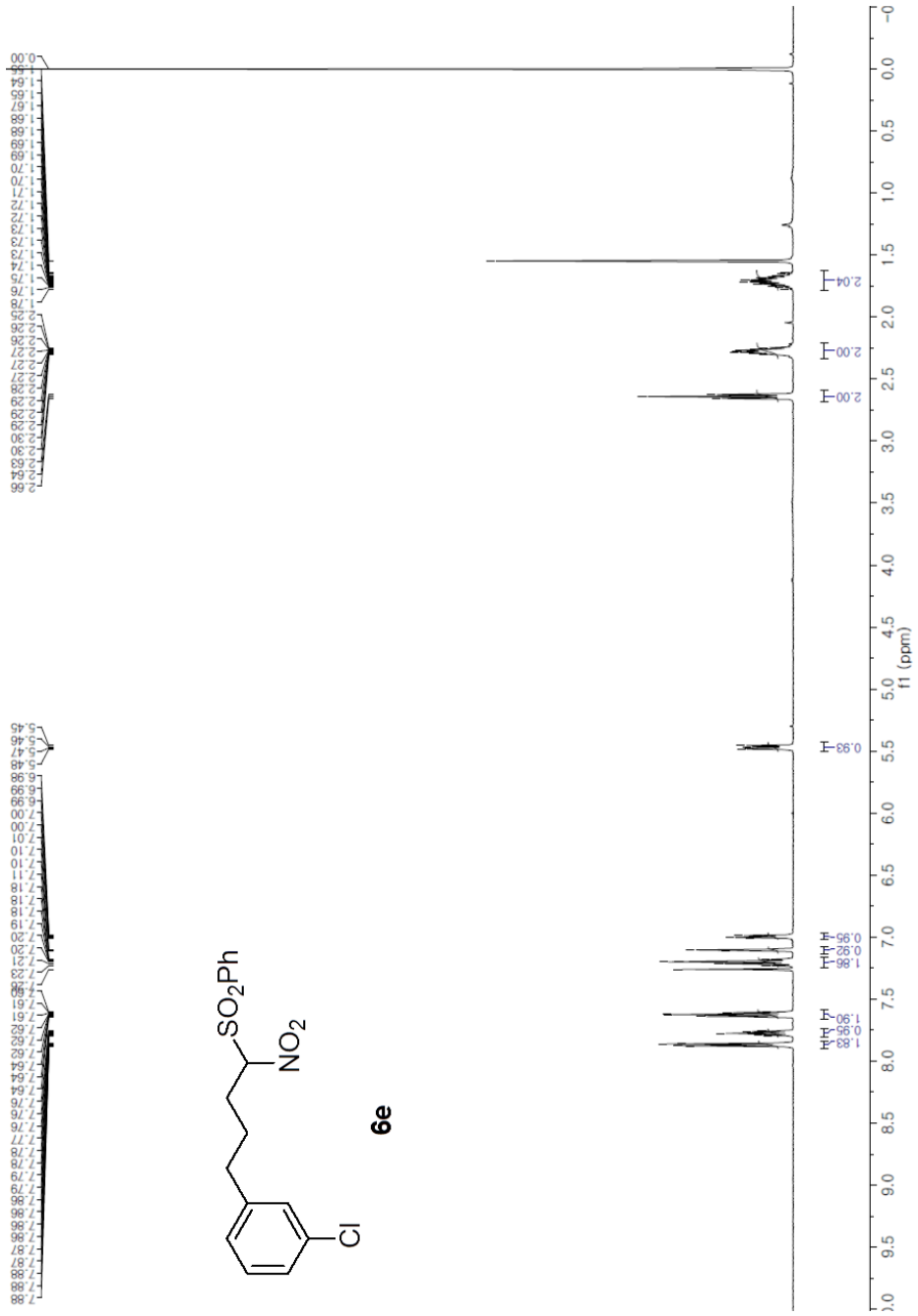

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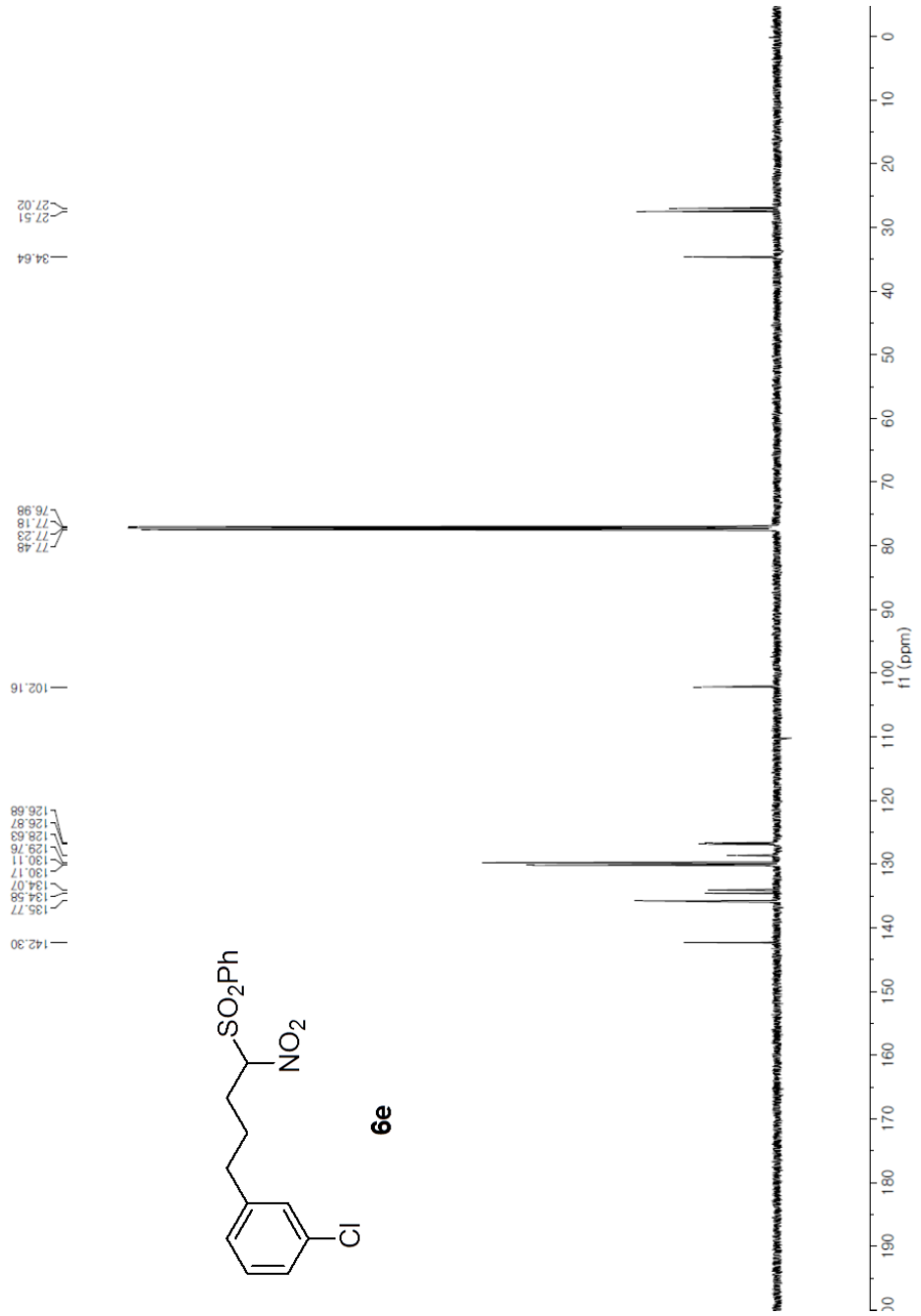
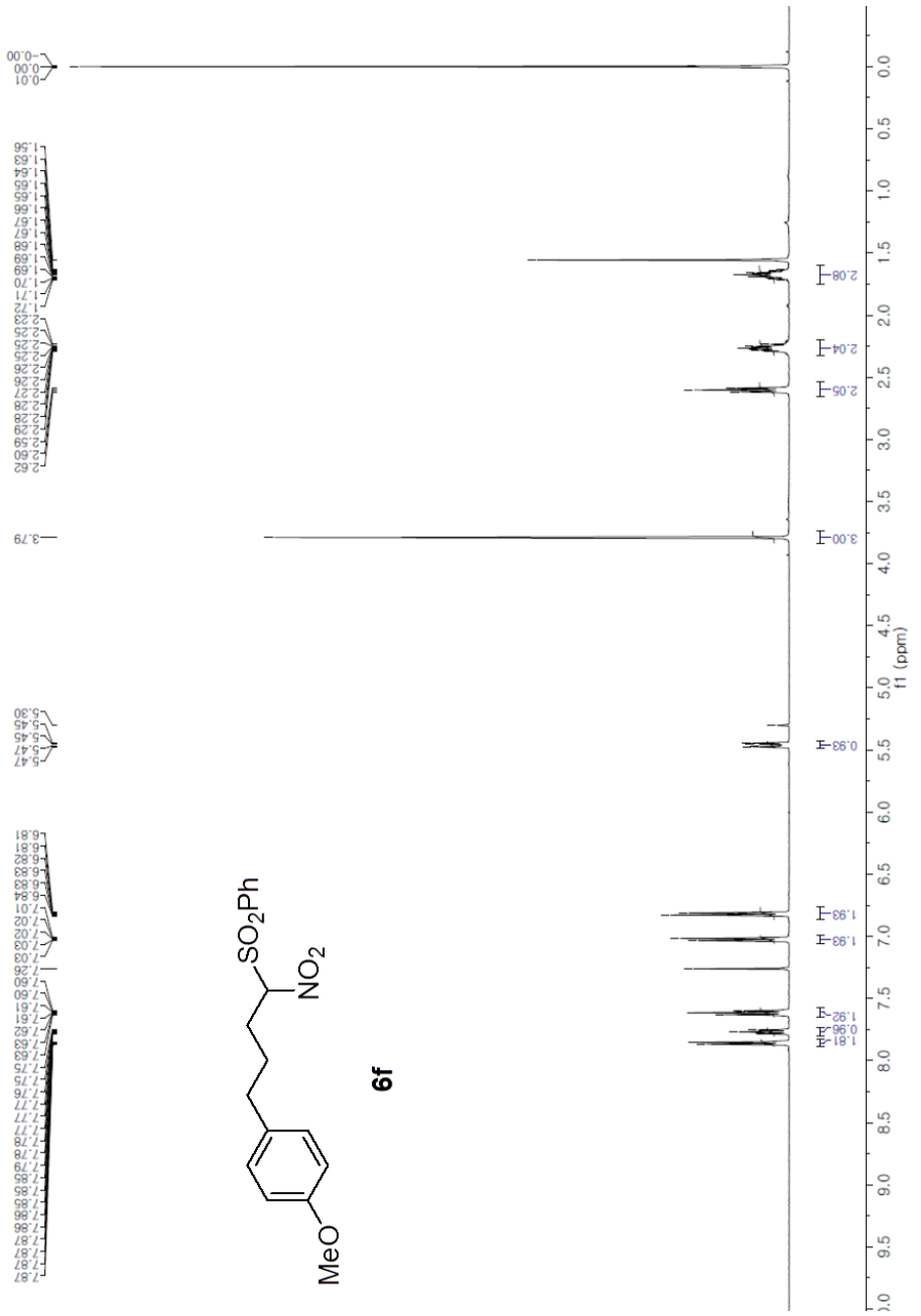
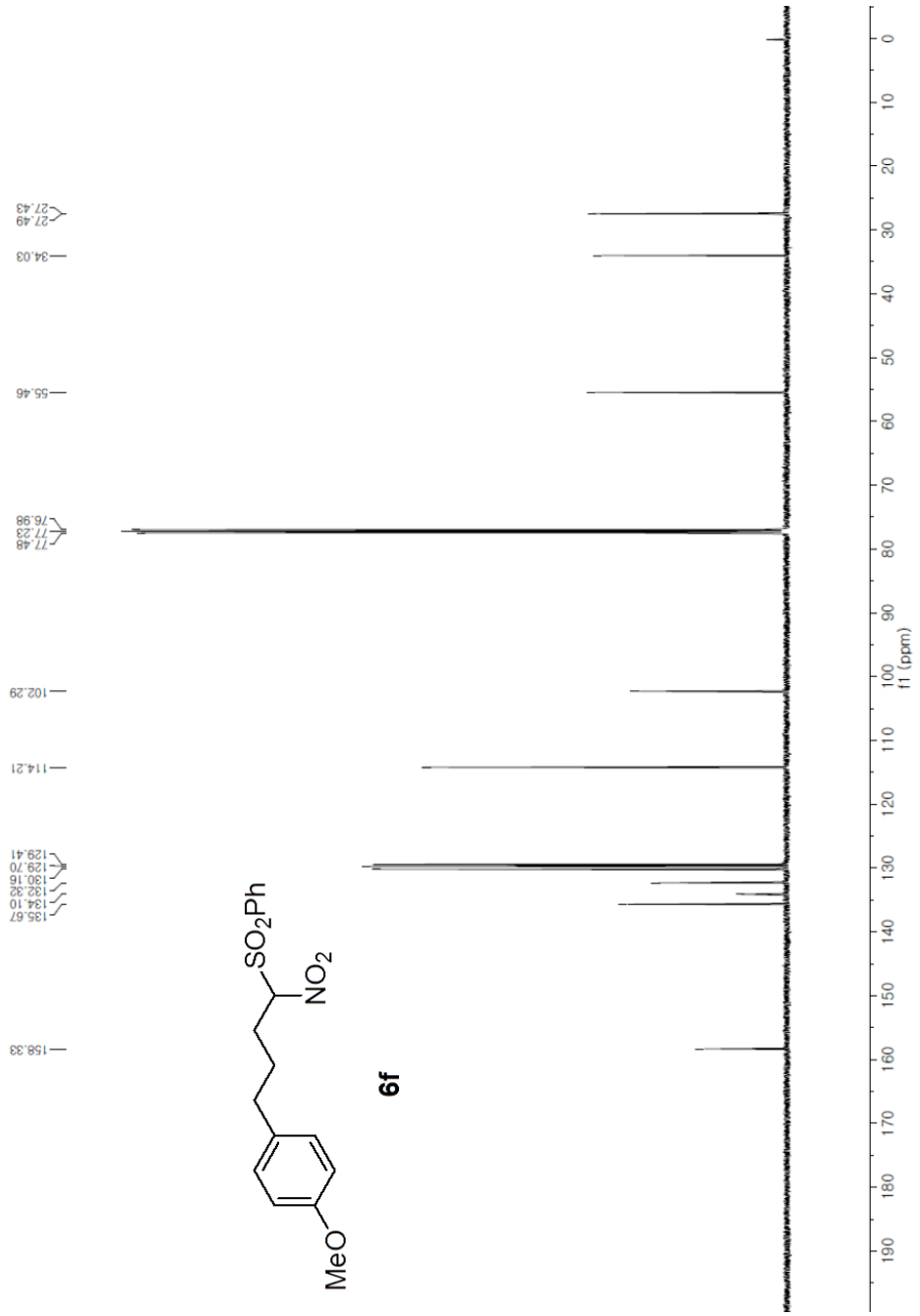


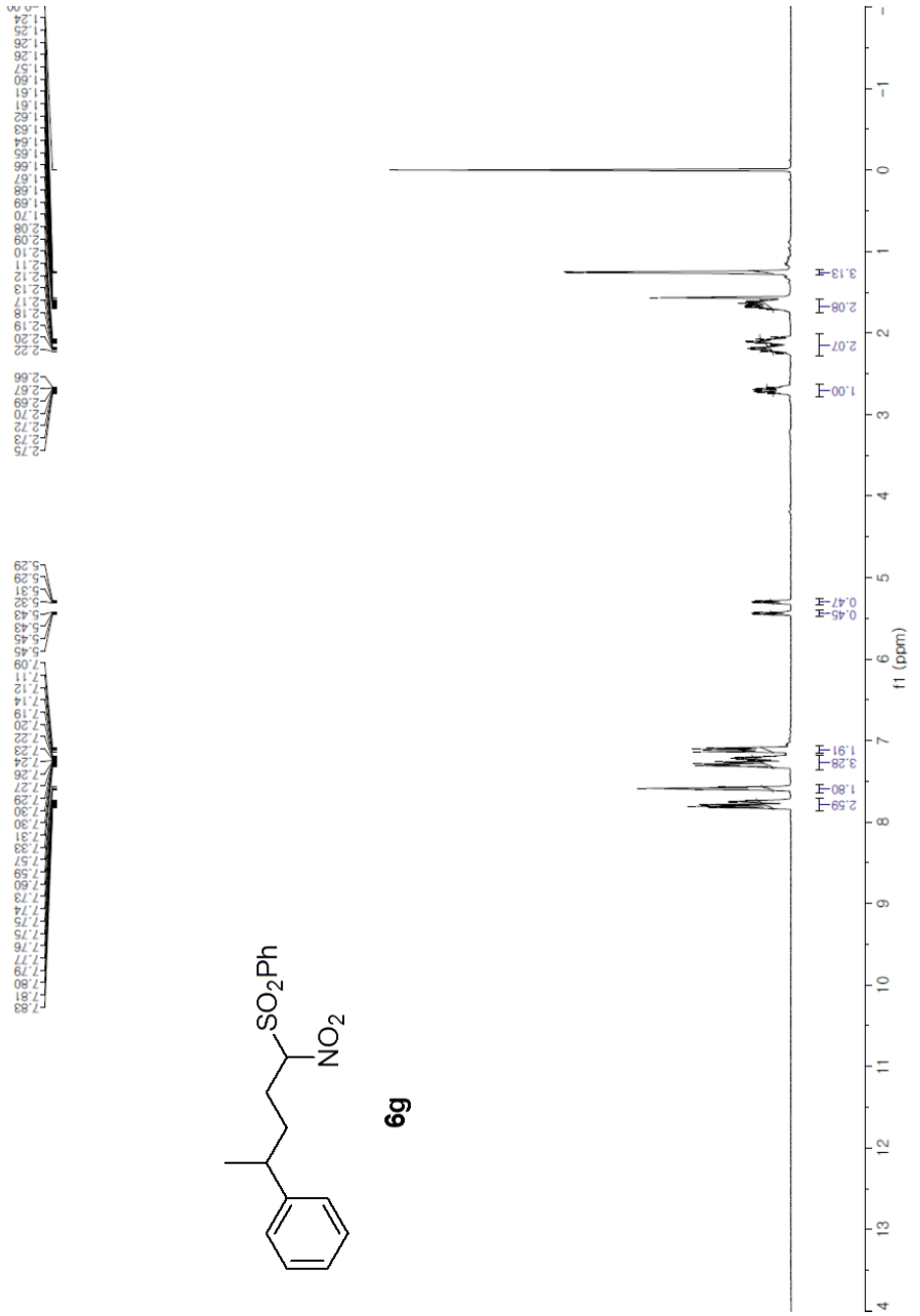
Compound 6f ^{1}H NMR



Compound 6f ^{13}C NMR



Compound 6g ^{1}H NMR



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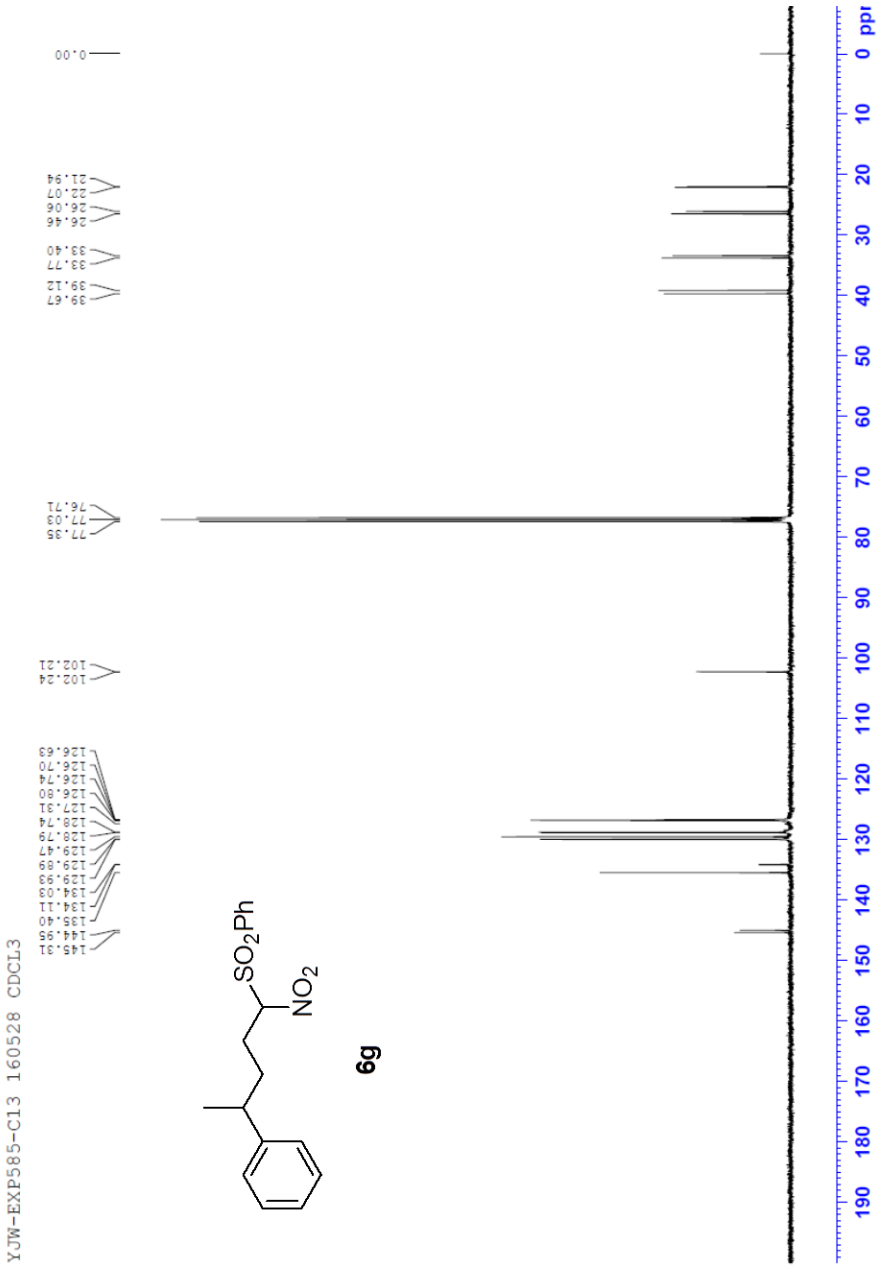

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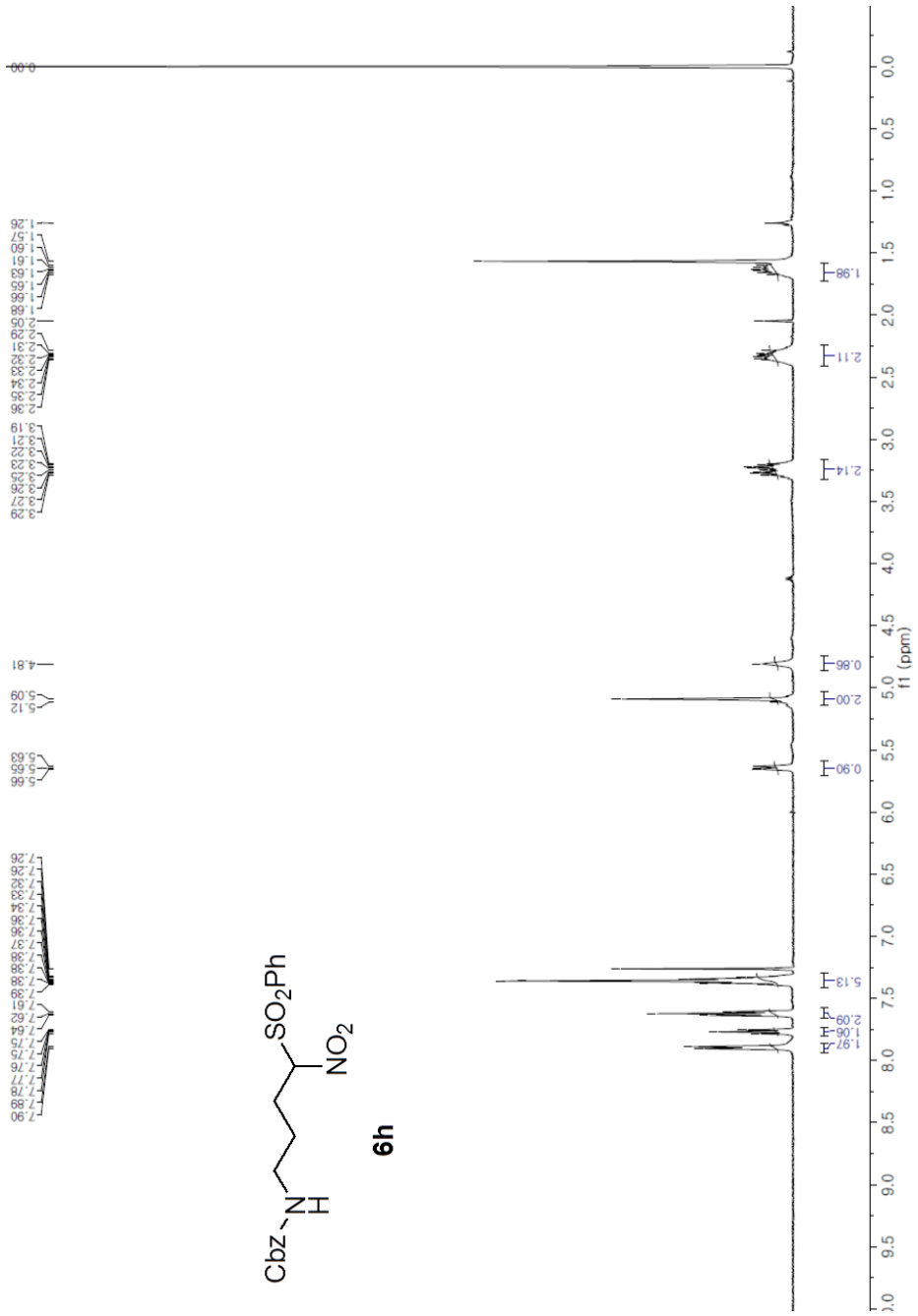

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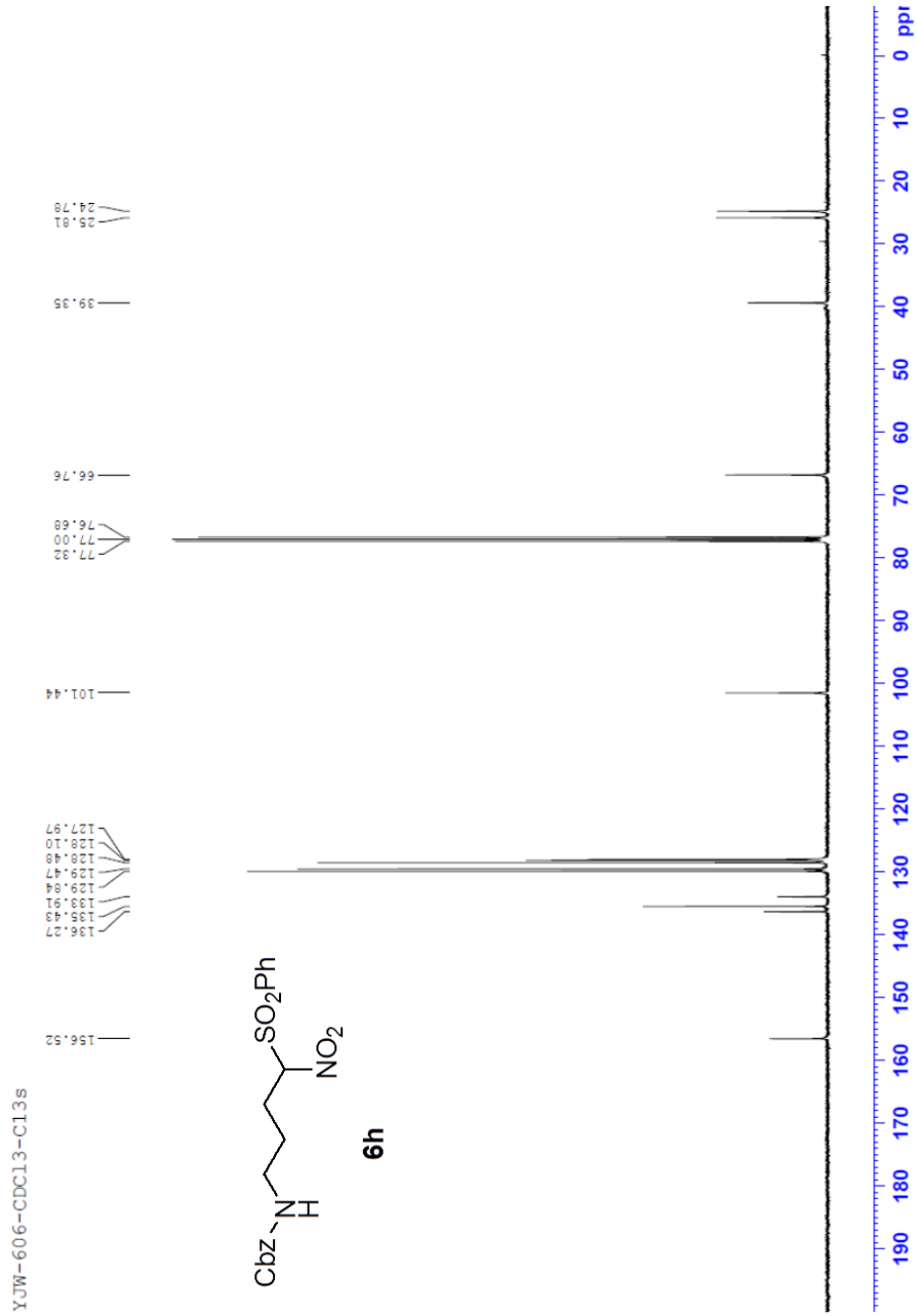
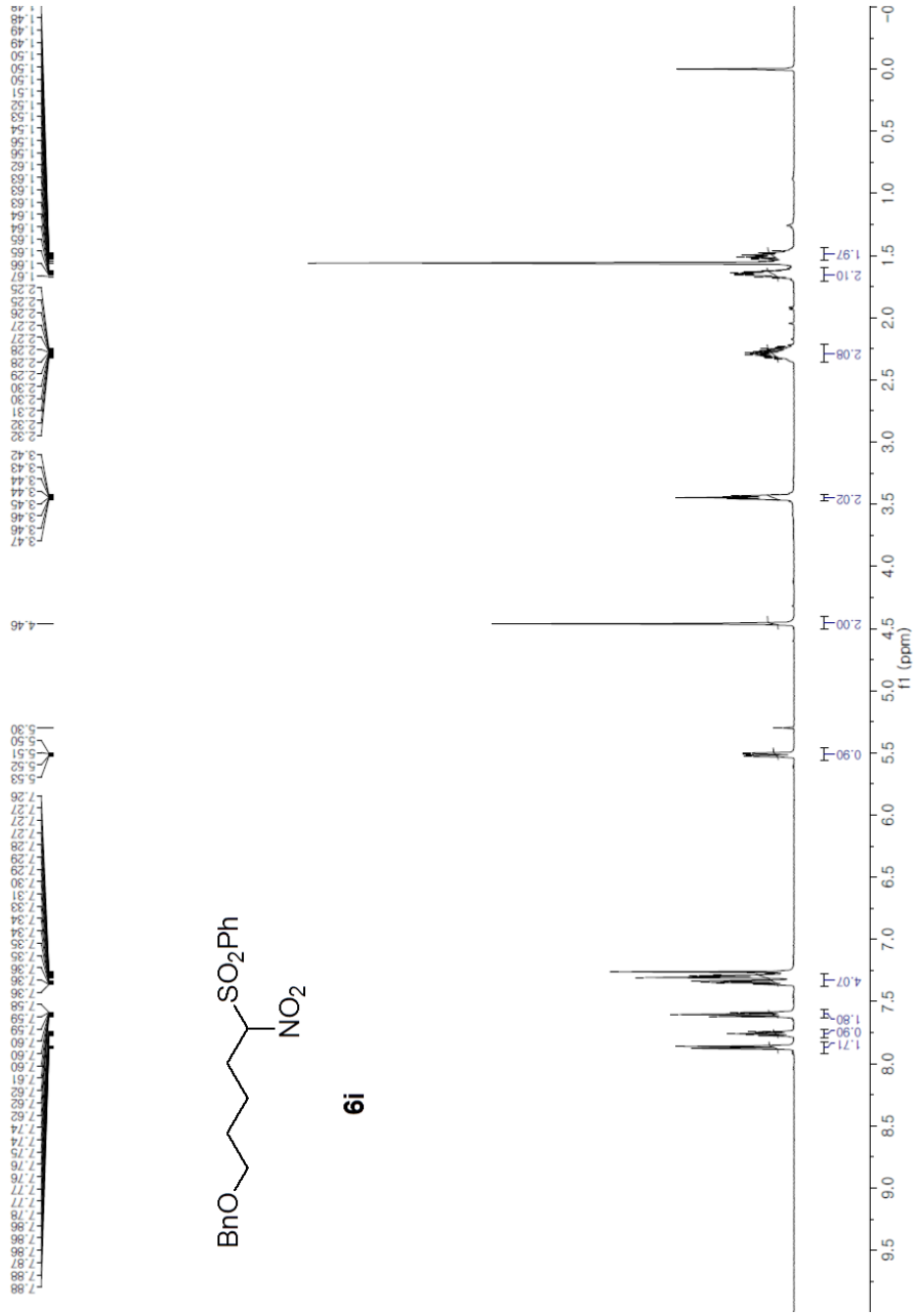
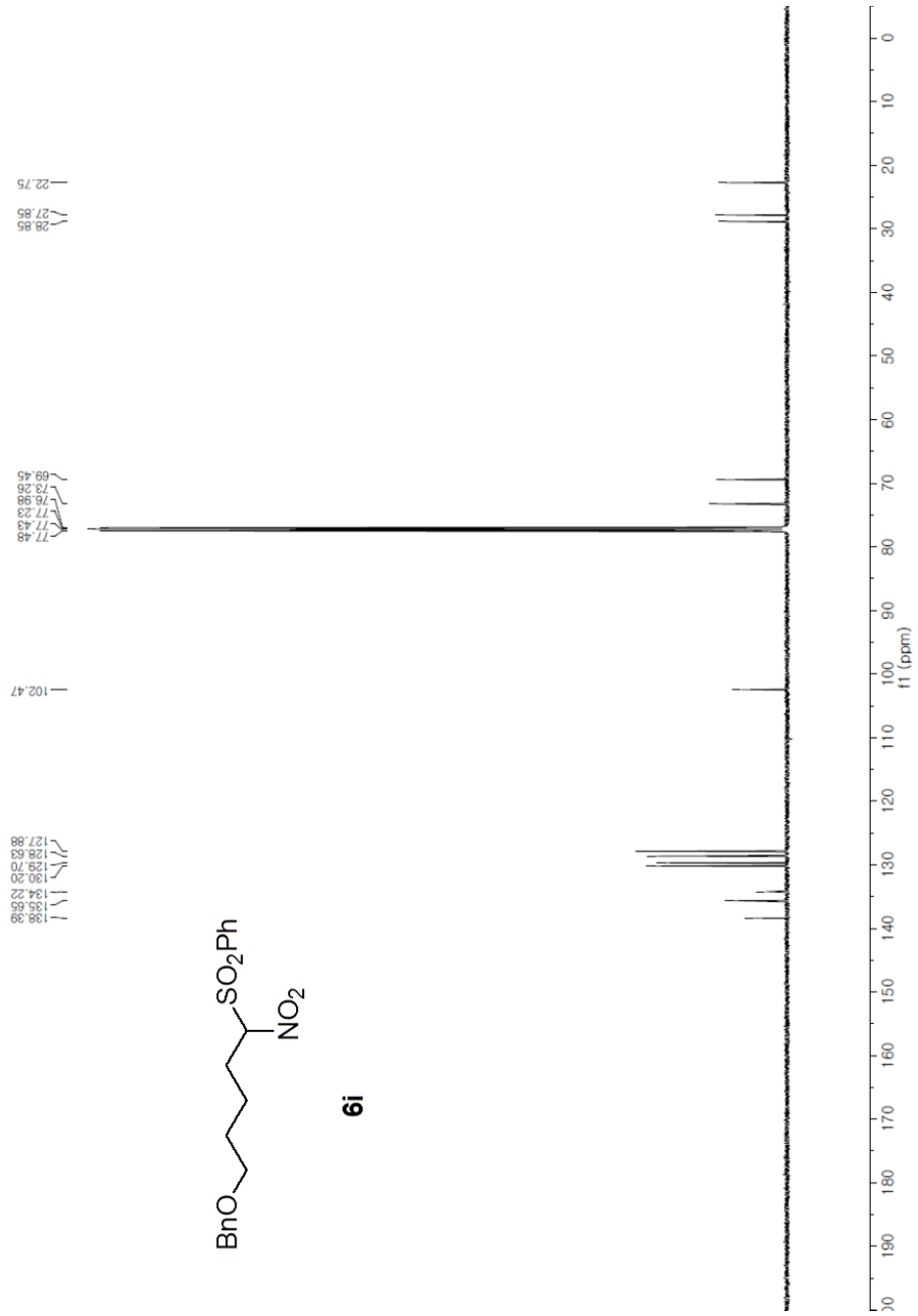


Compound 6i ^{1}H NMR



Compound 6i ^{13}C NMR



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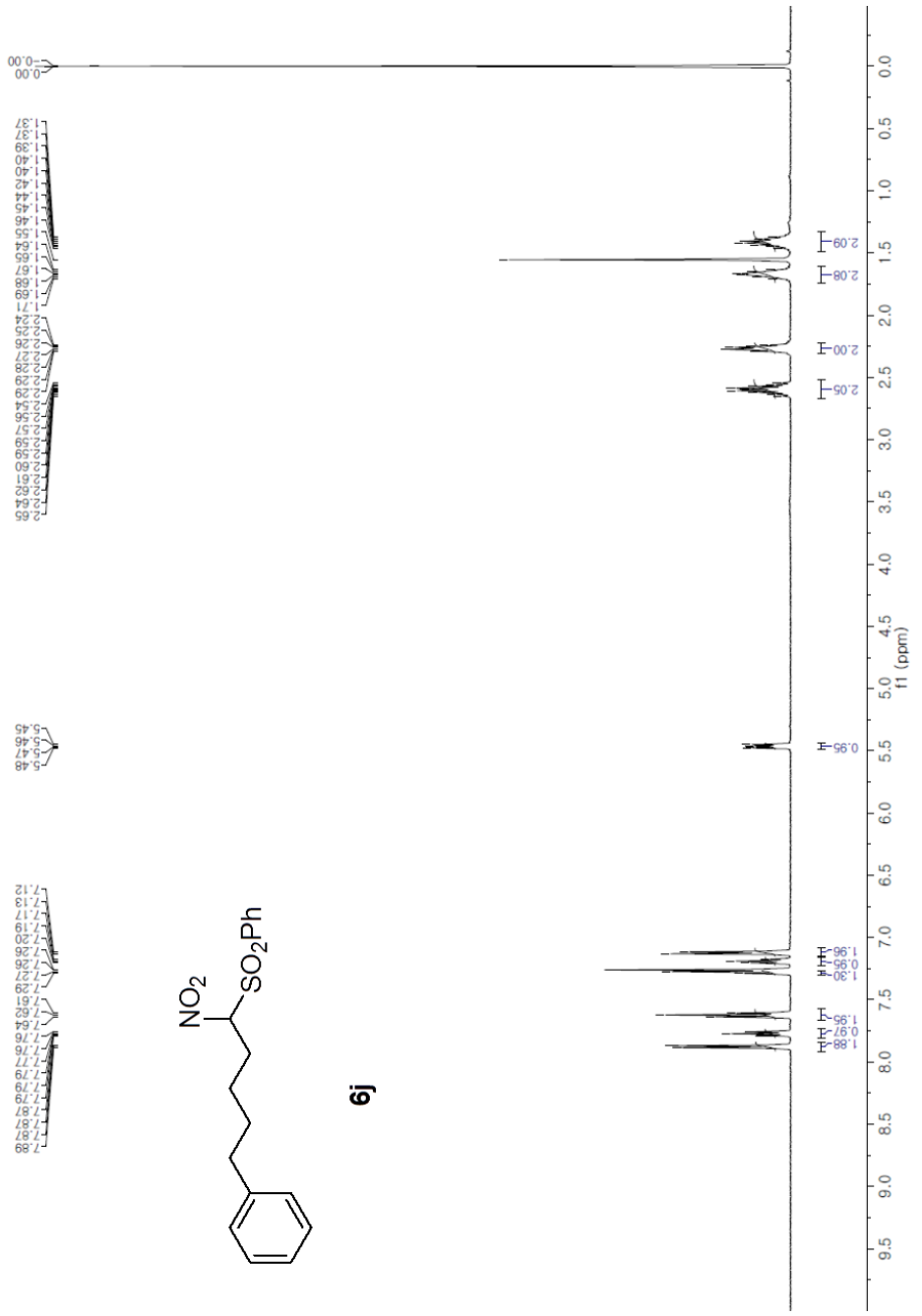

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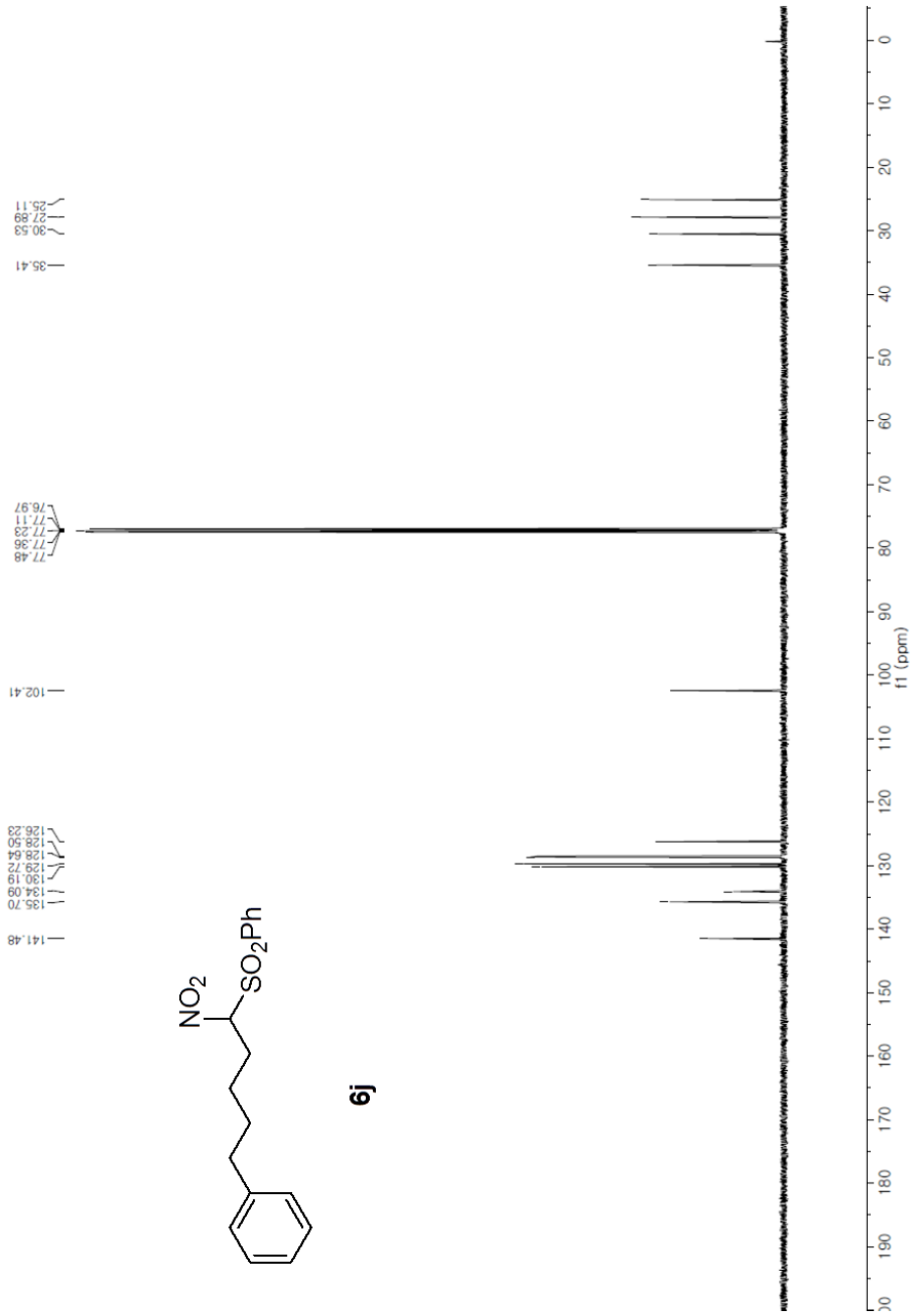

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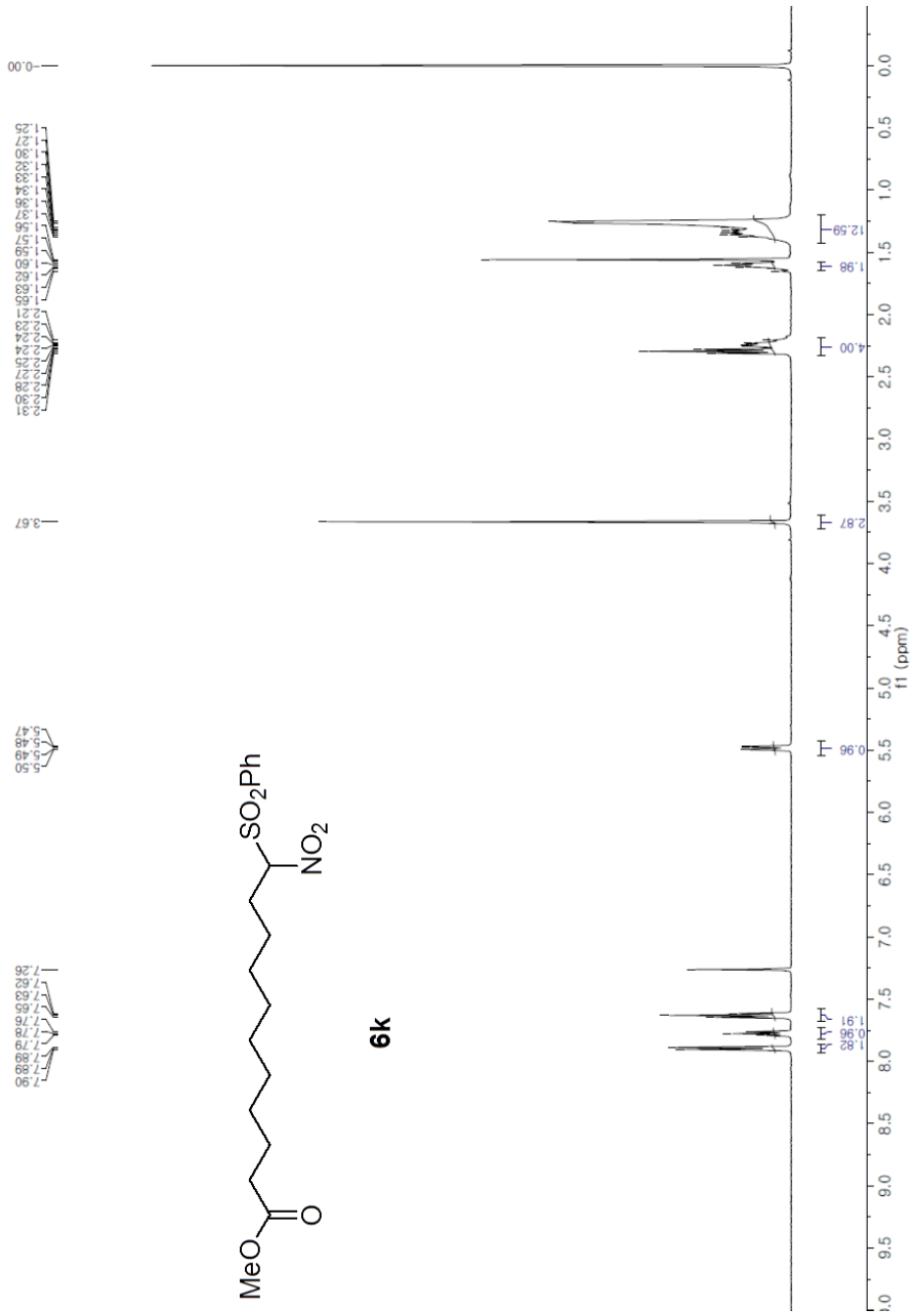

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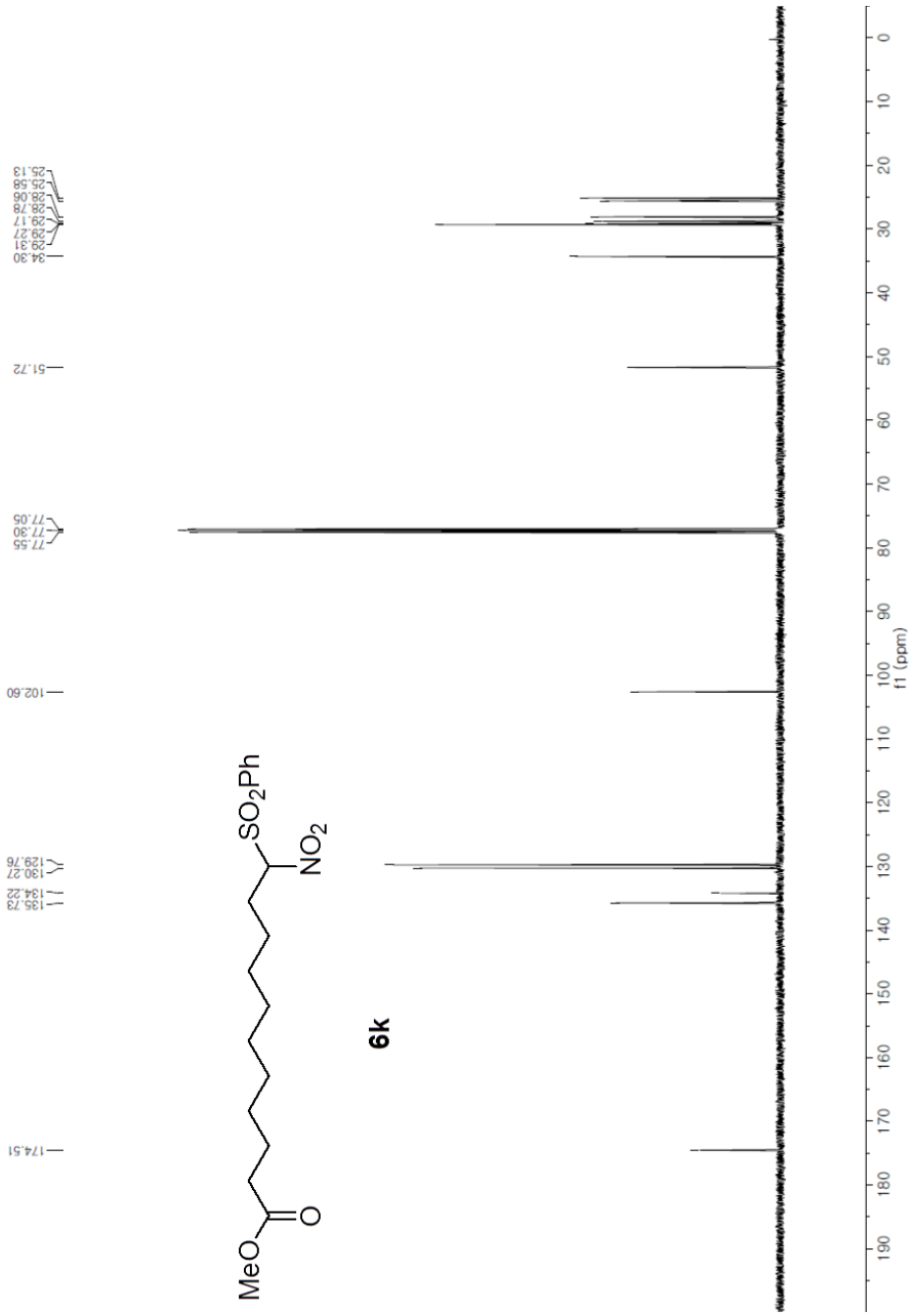
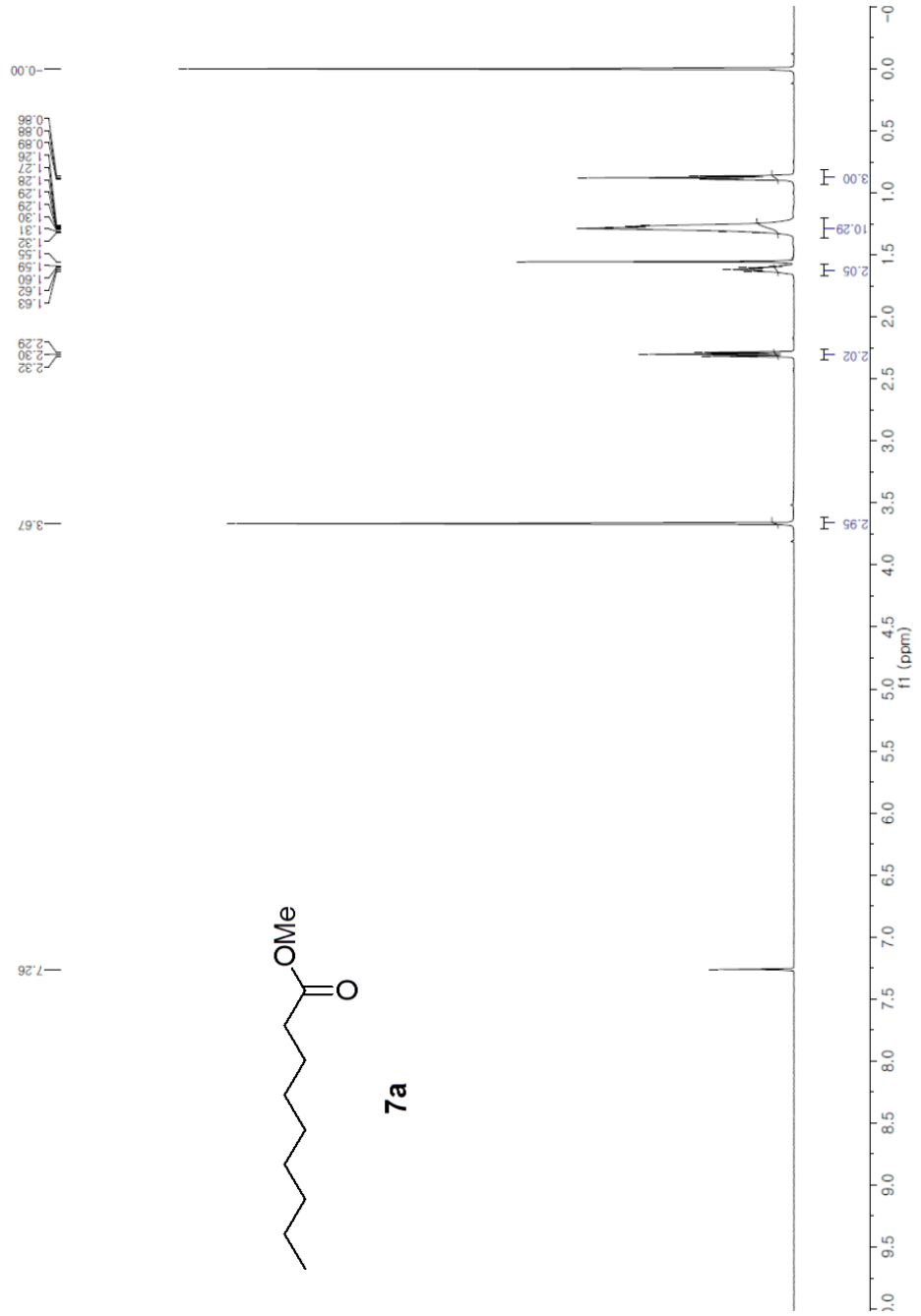


Compound 7a ^{1}H NMR



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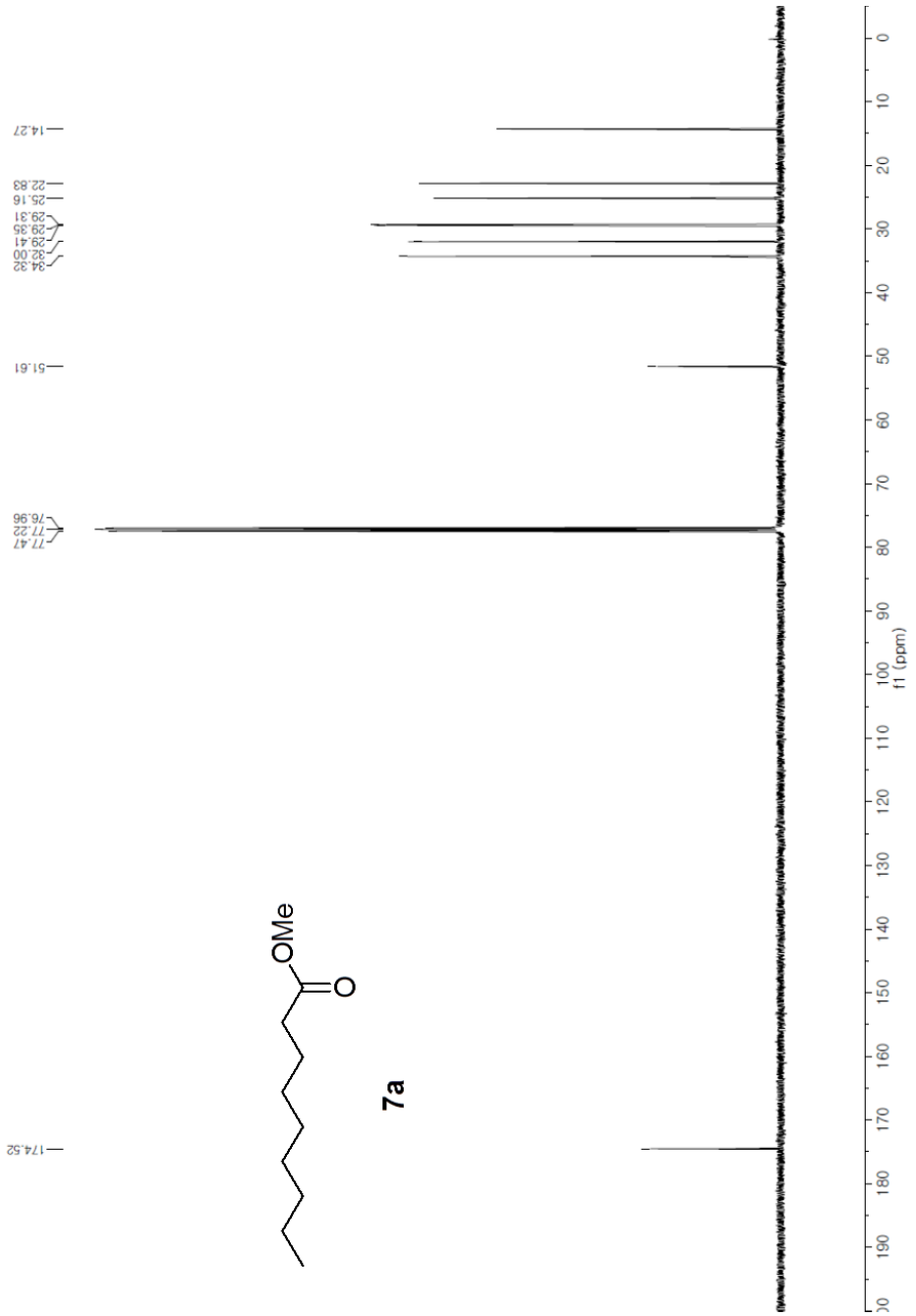

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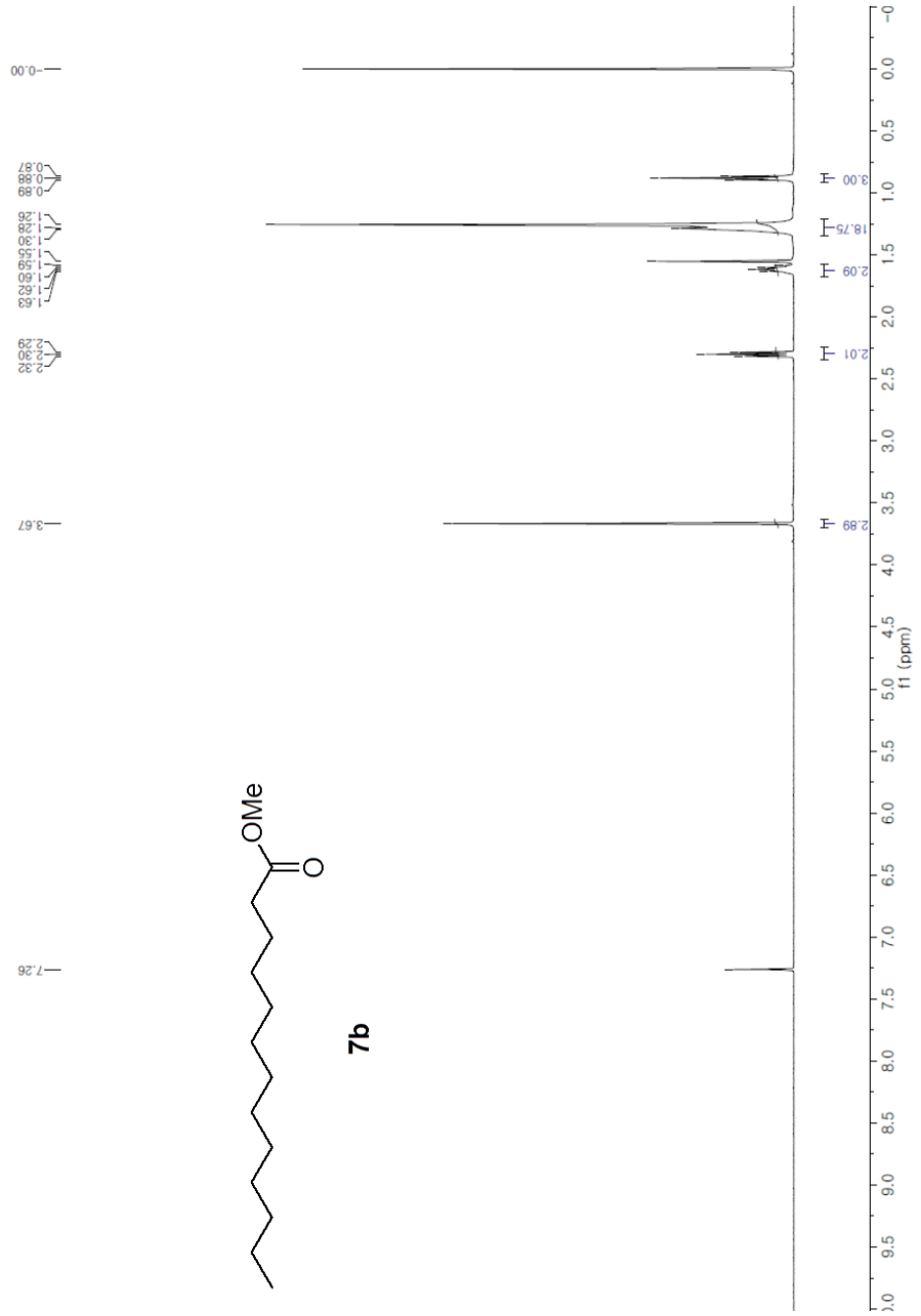

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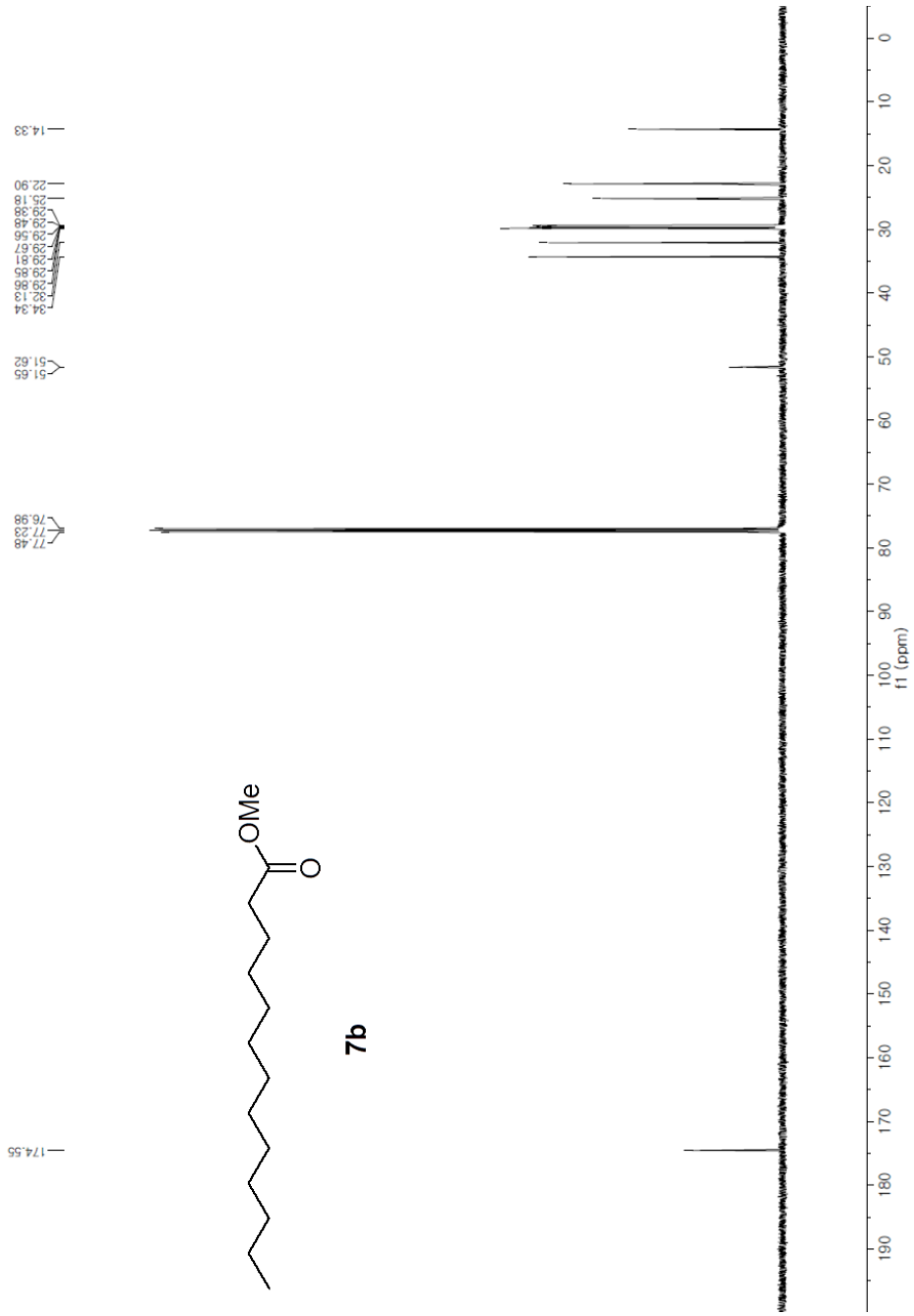

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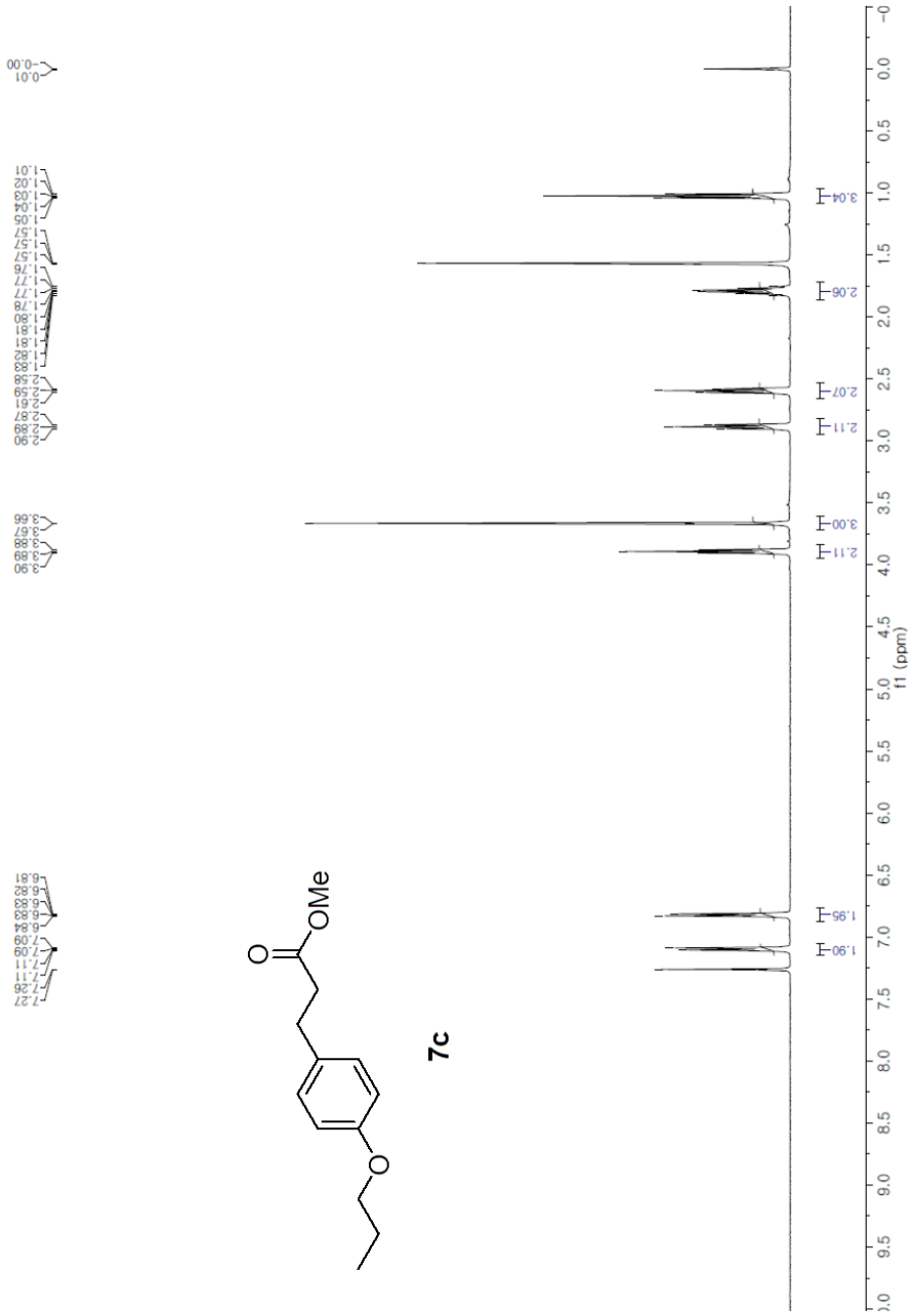
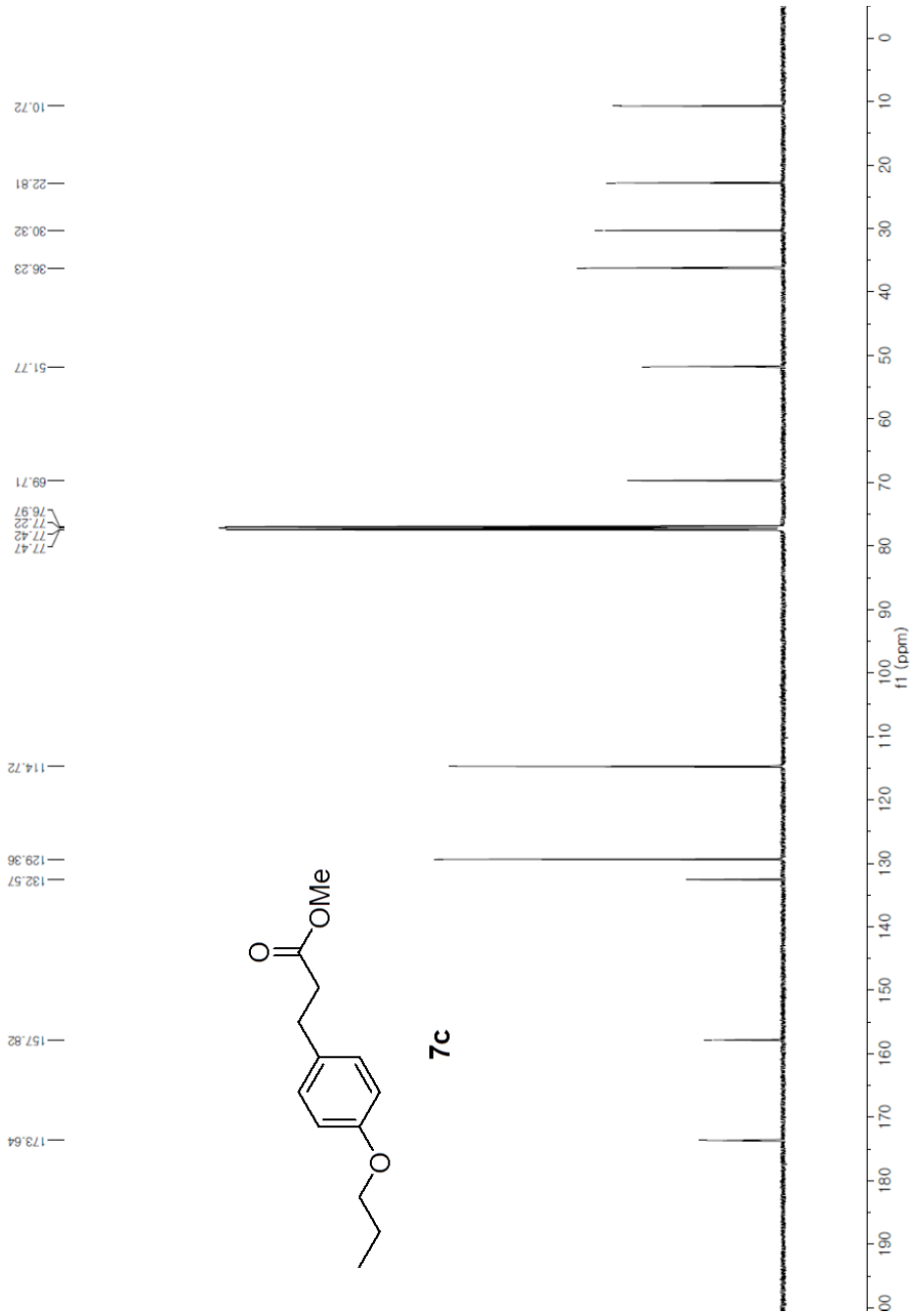
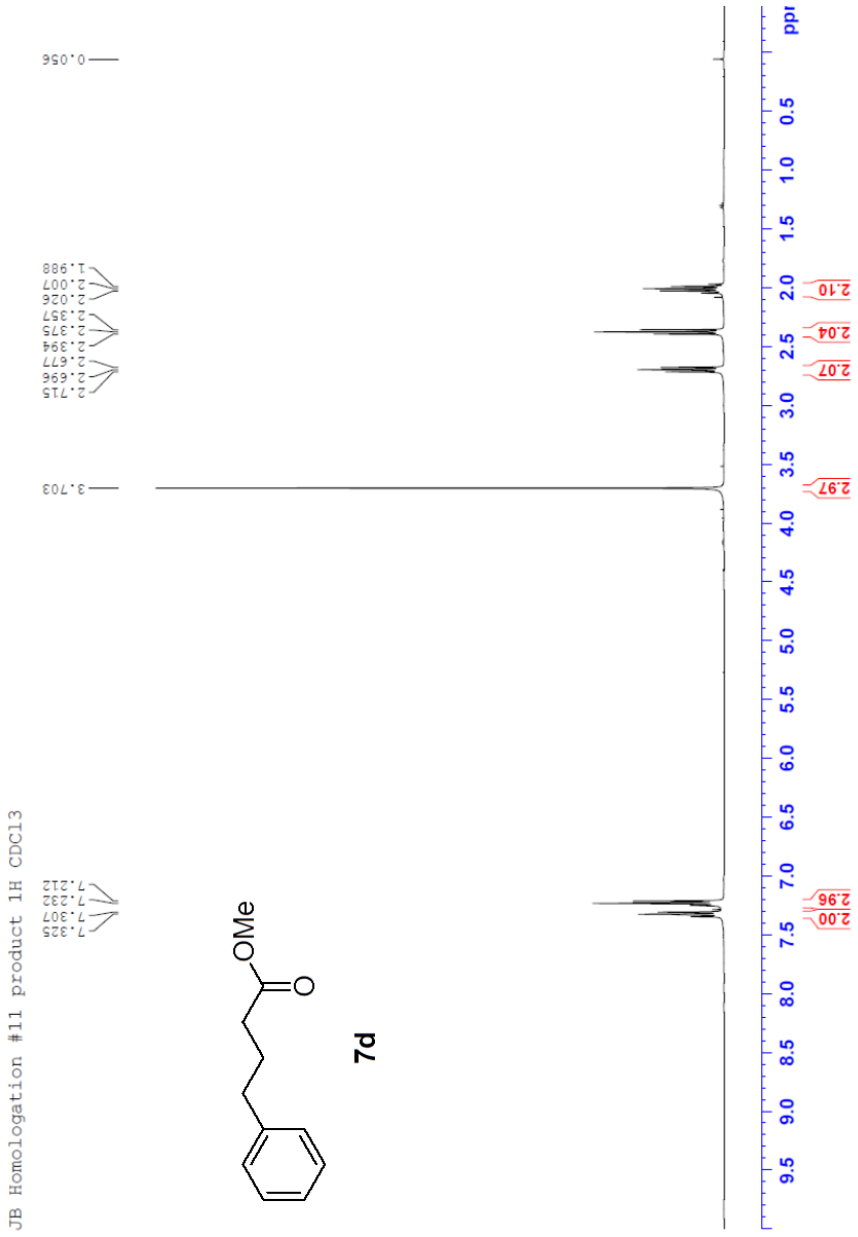


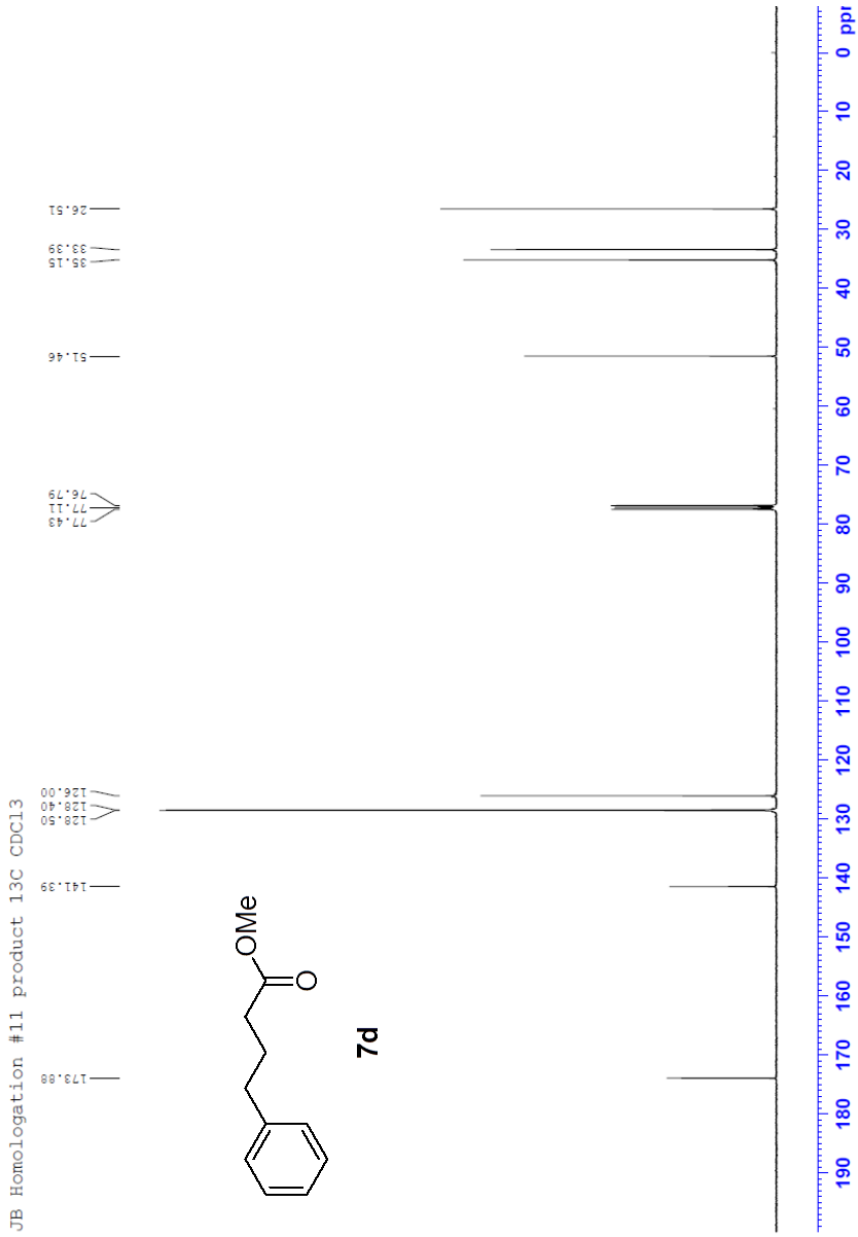
Compound 7c ^{13}C NMR



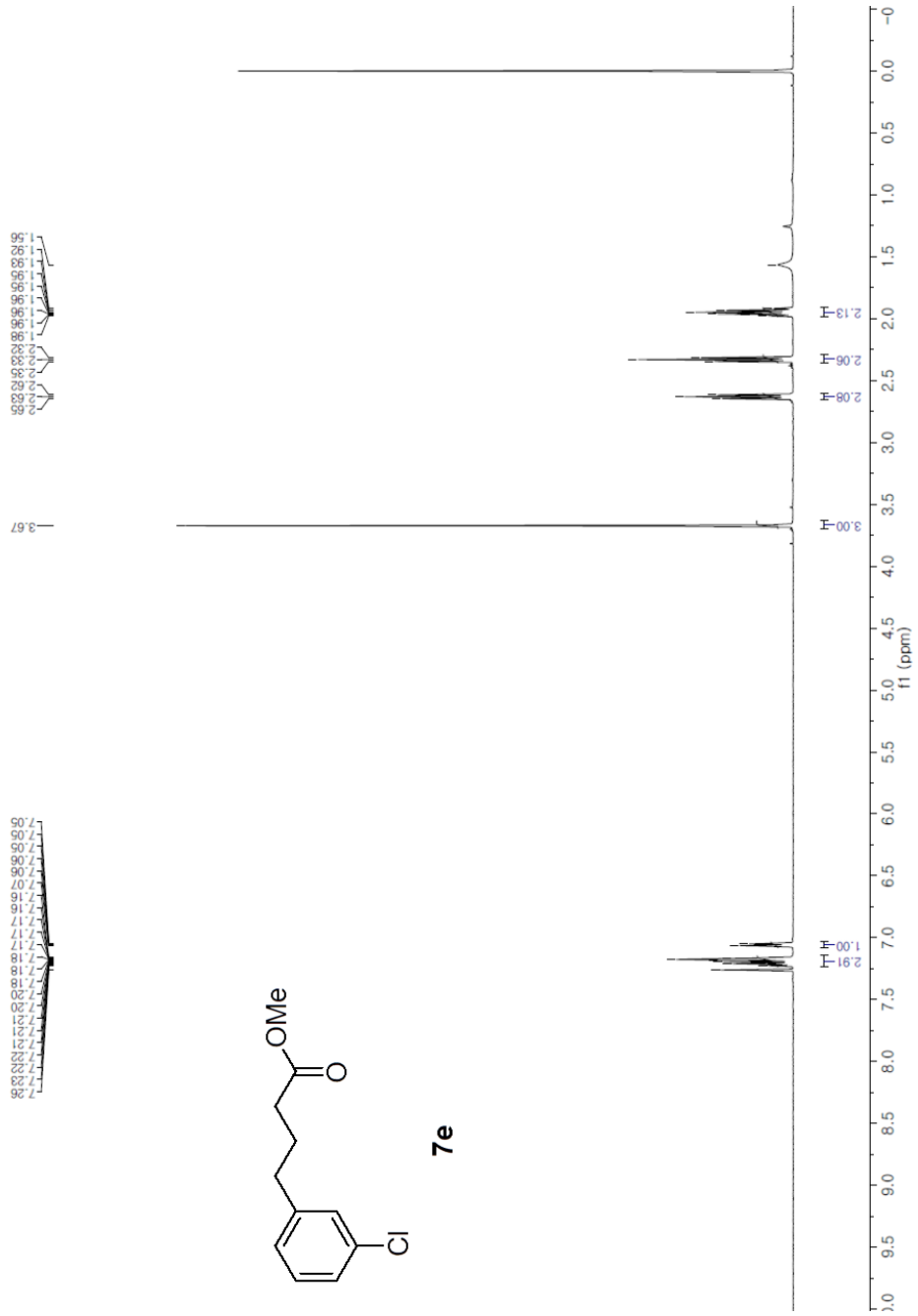
Compound 7d ^{1}H NMR



Compound 7d ^{13}C NMR



Compound 7e ^{1}H NMR



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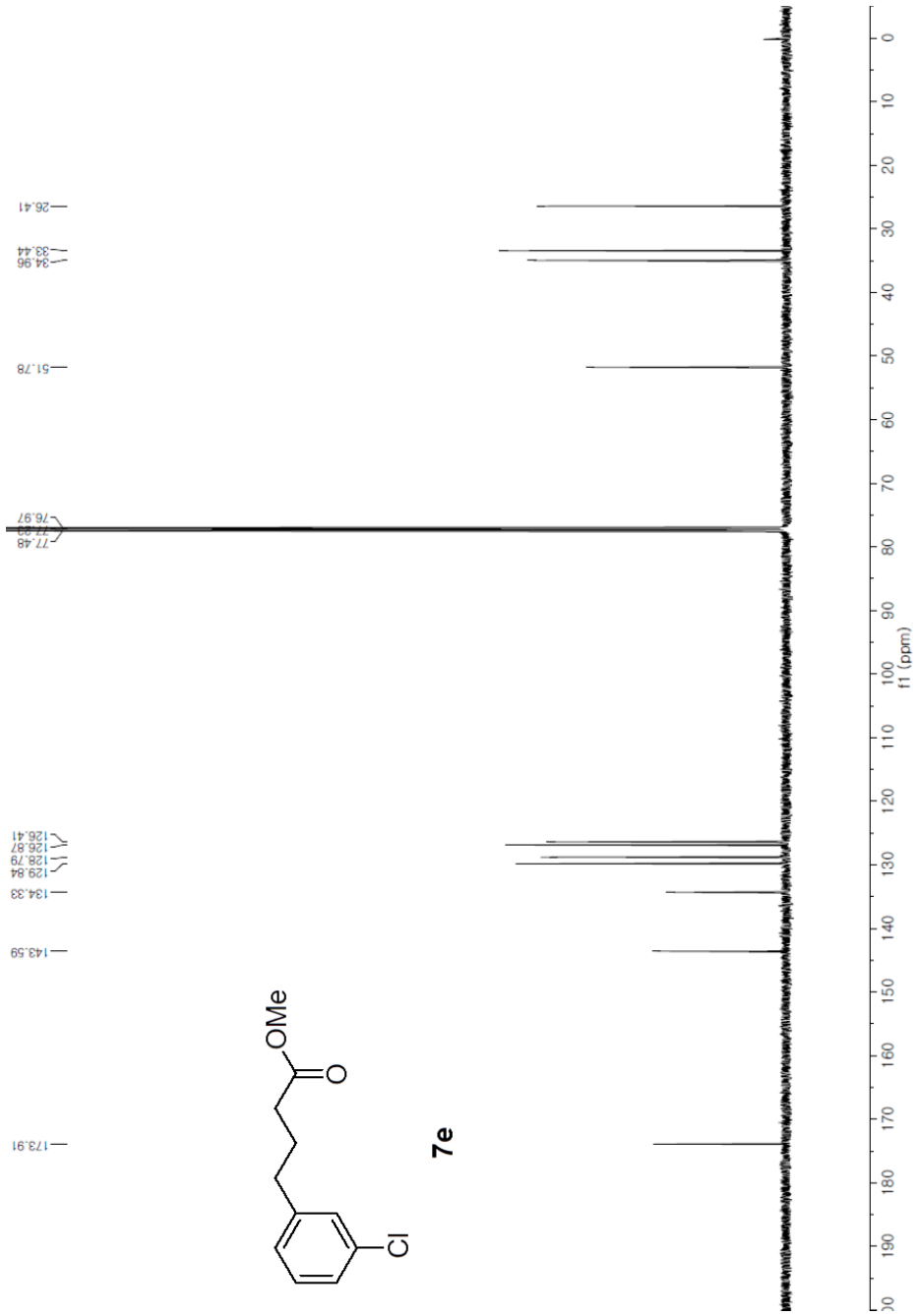

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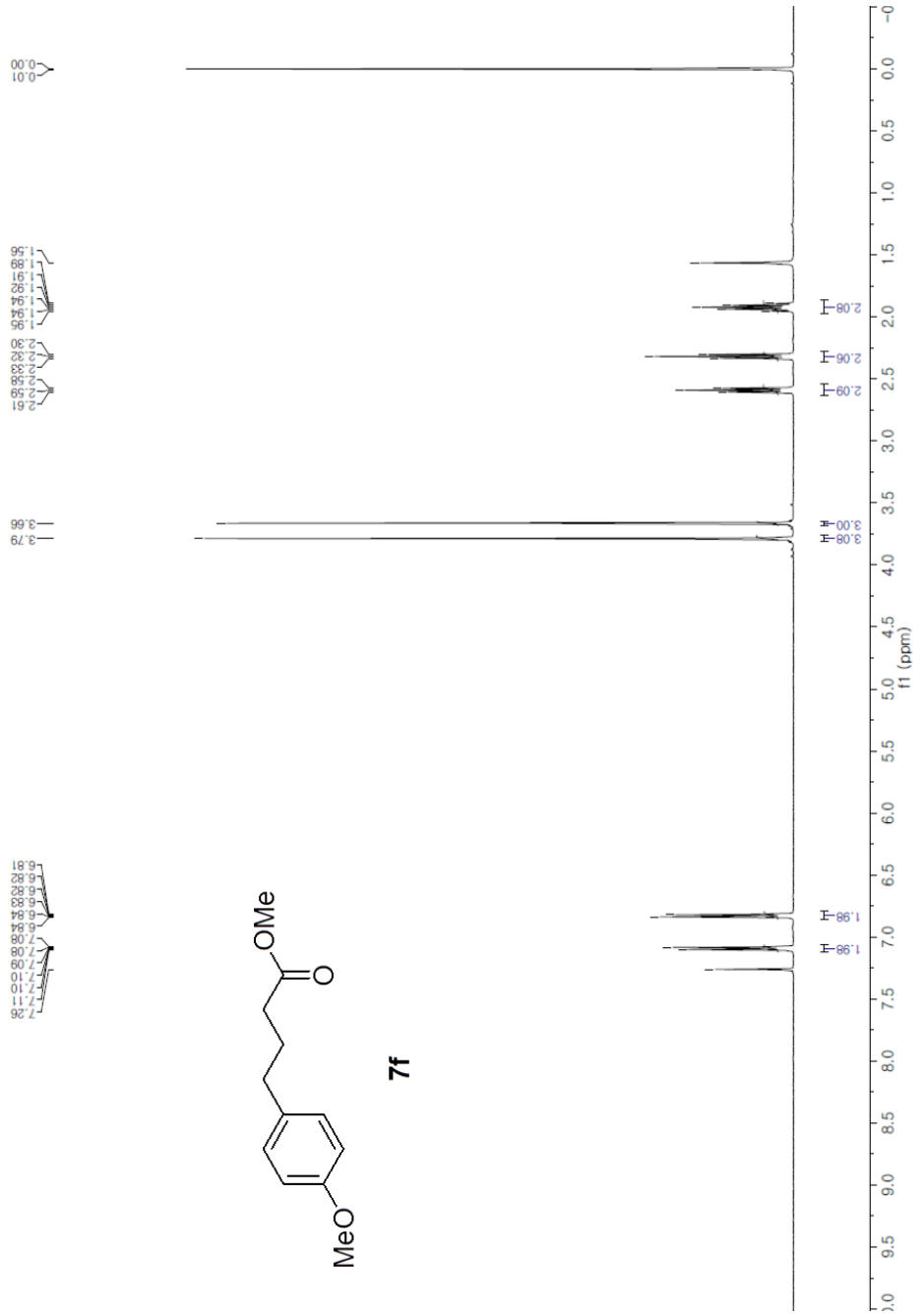

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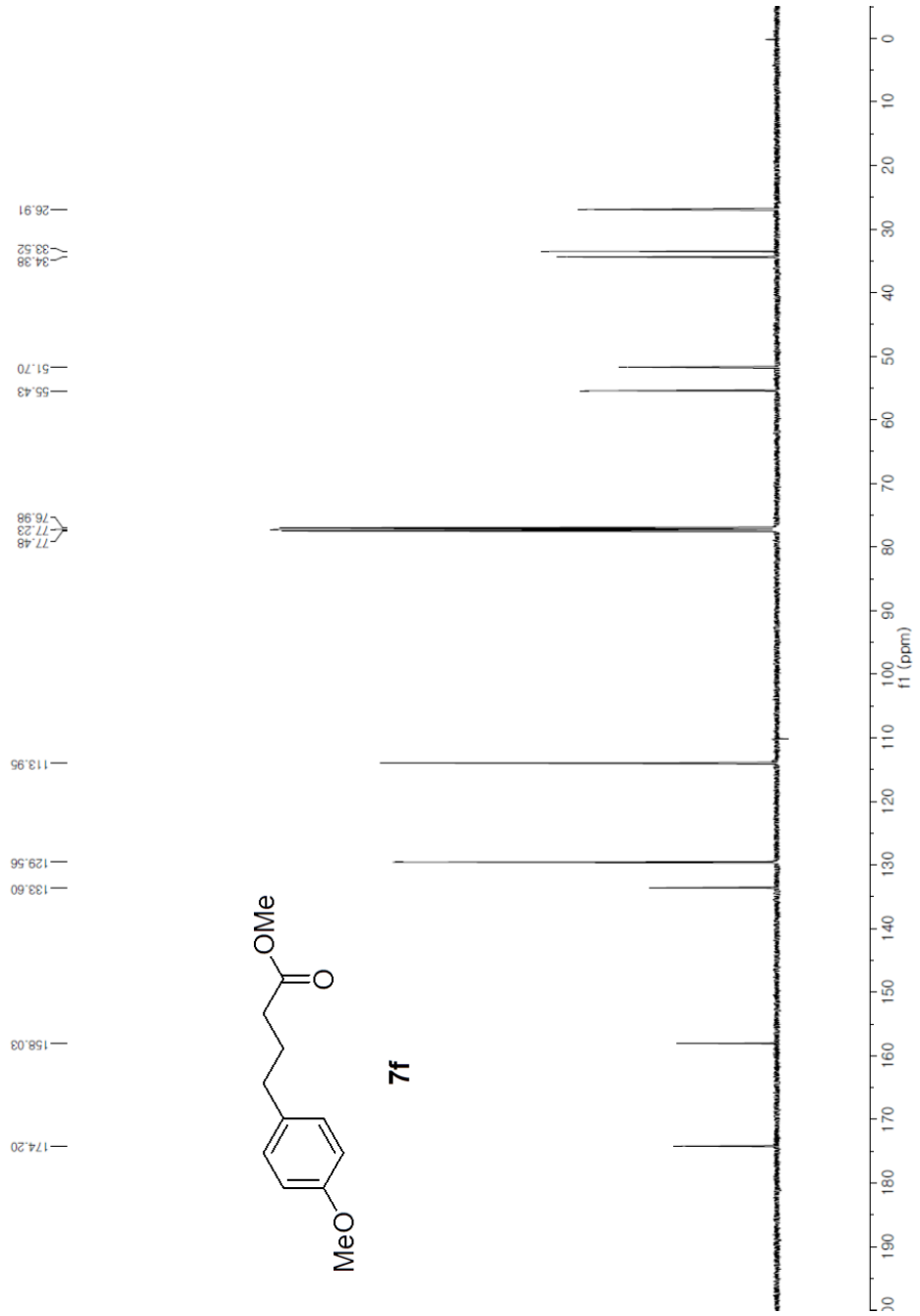

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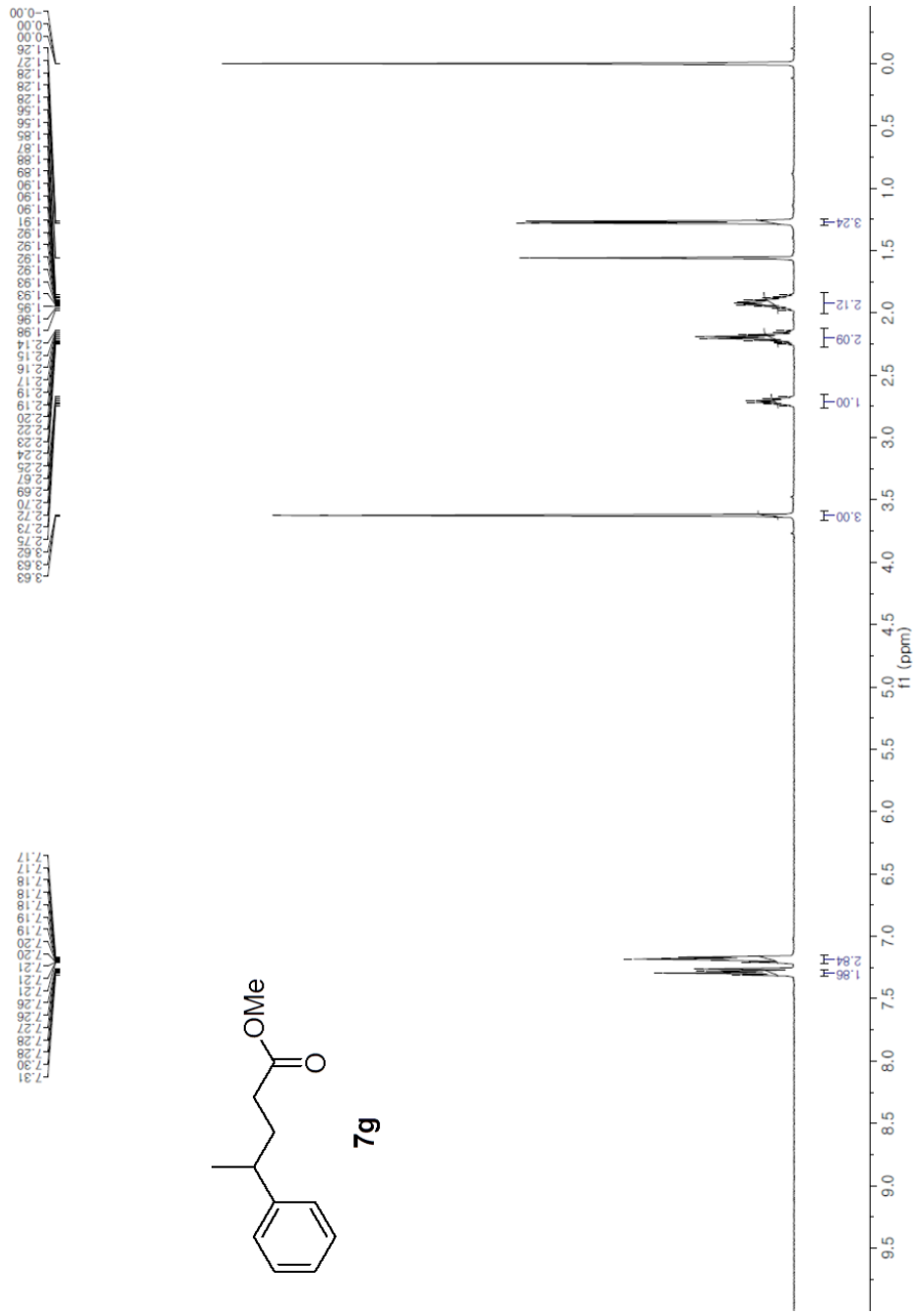
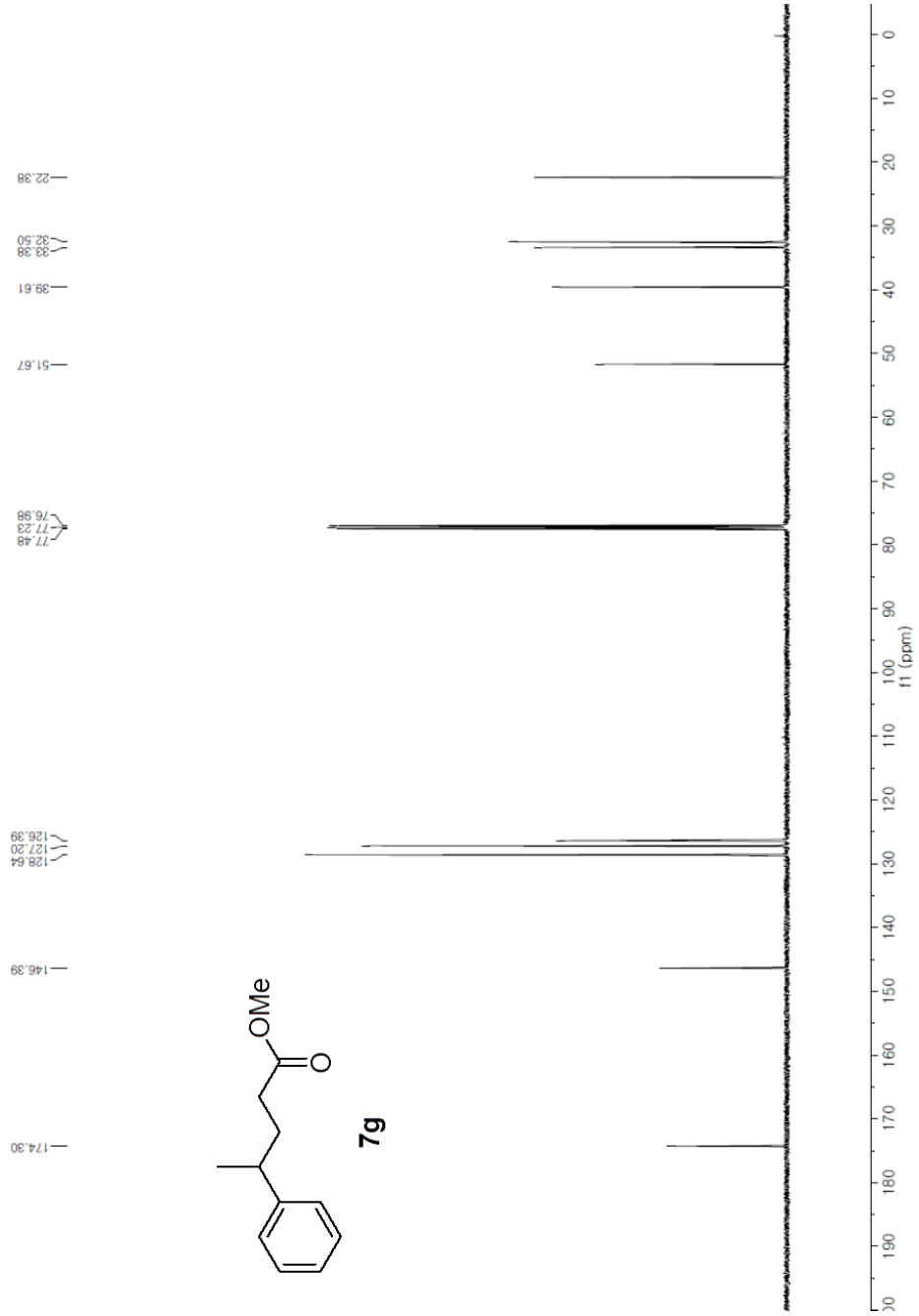


Compound 7g ^{13}C NMR



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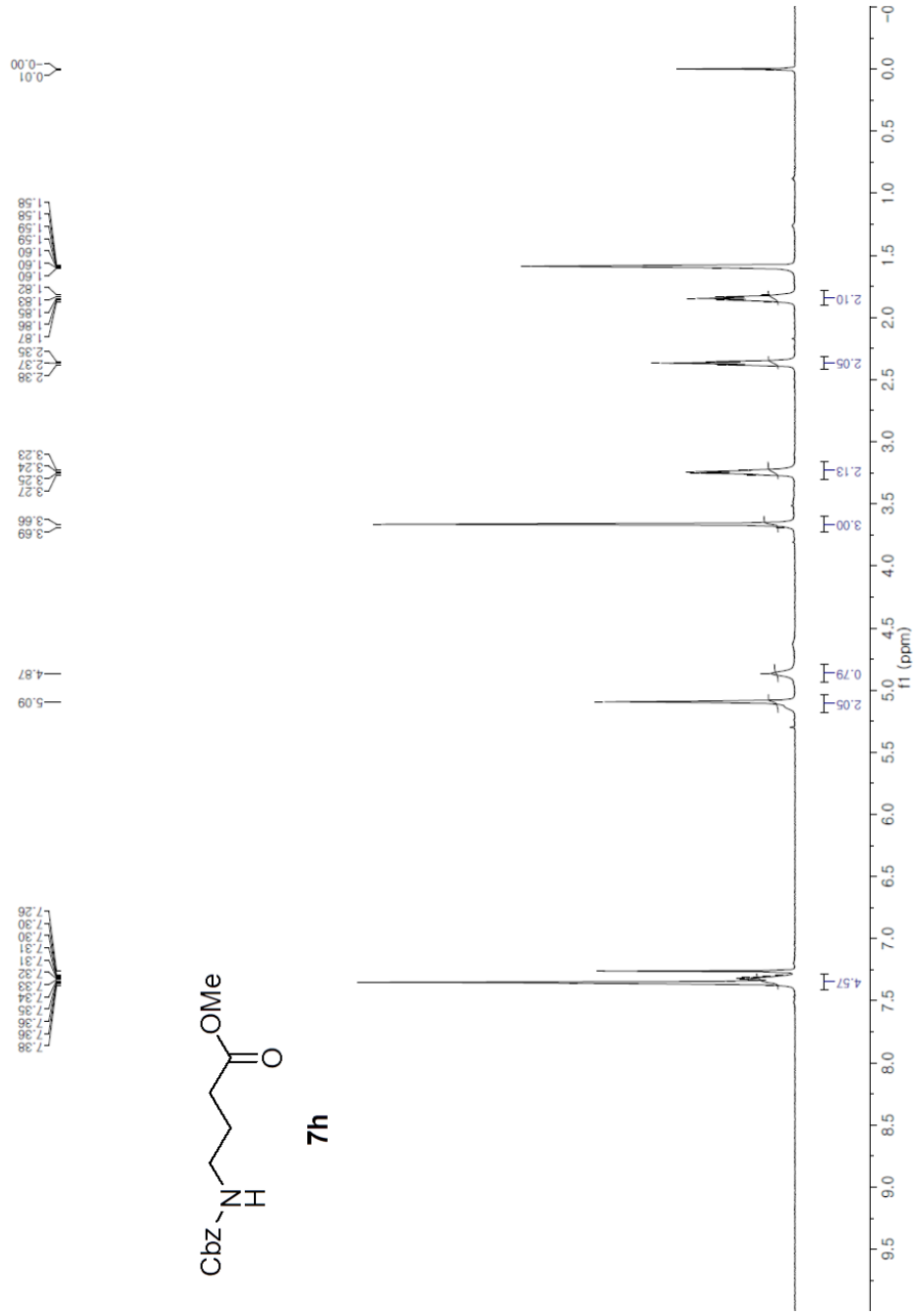
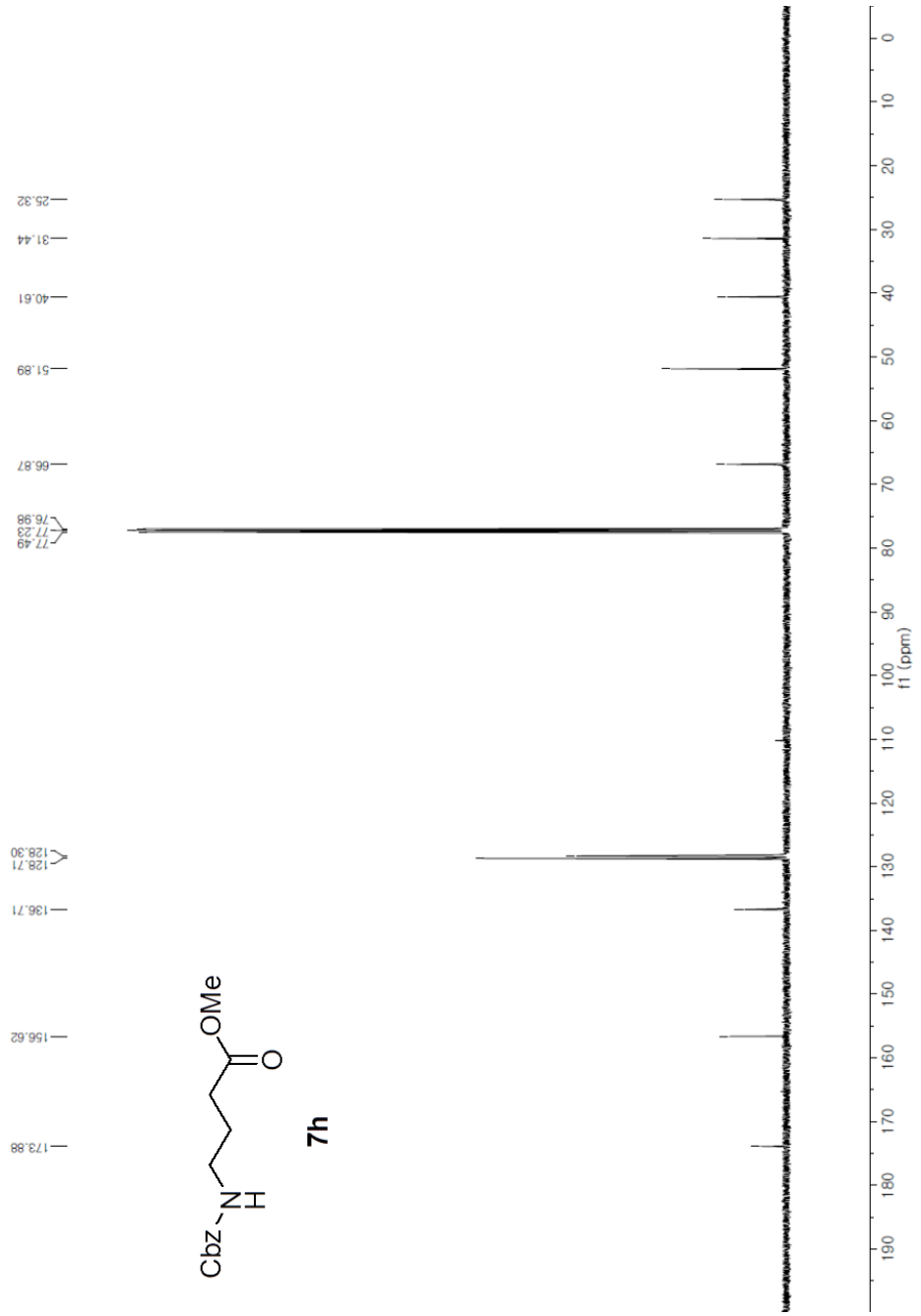
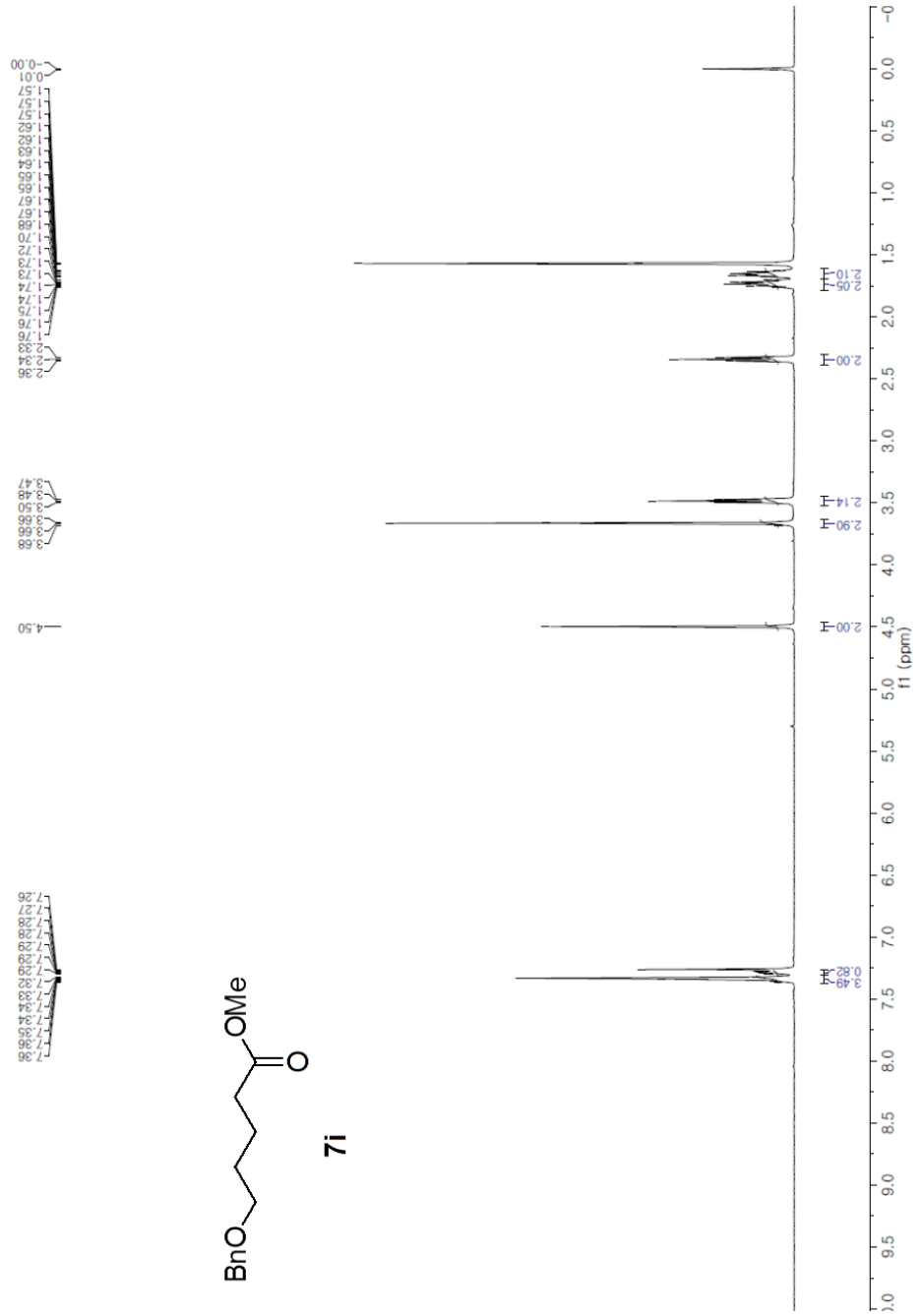


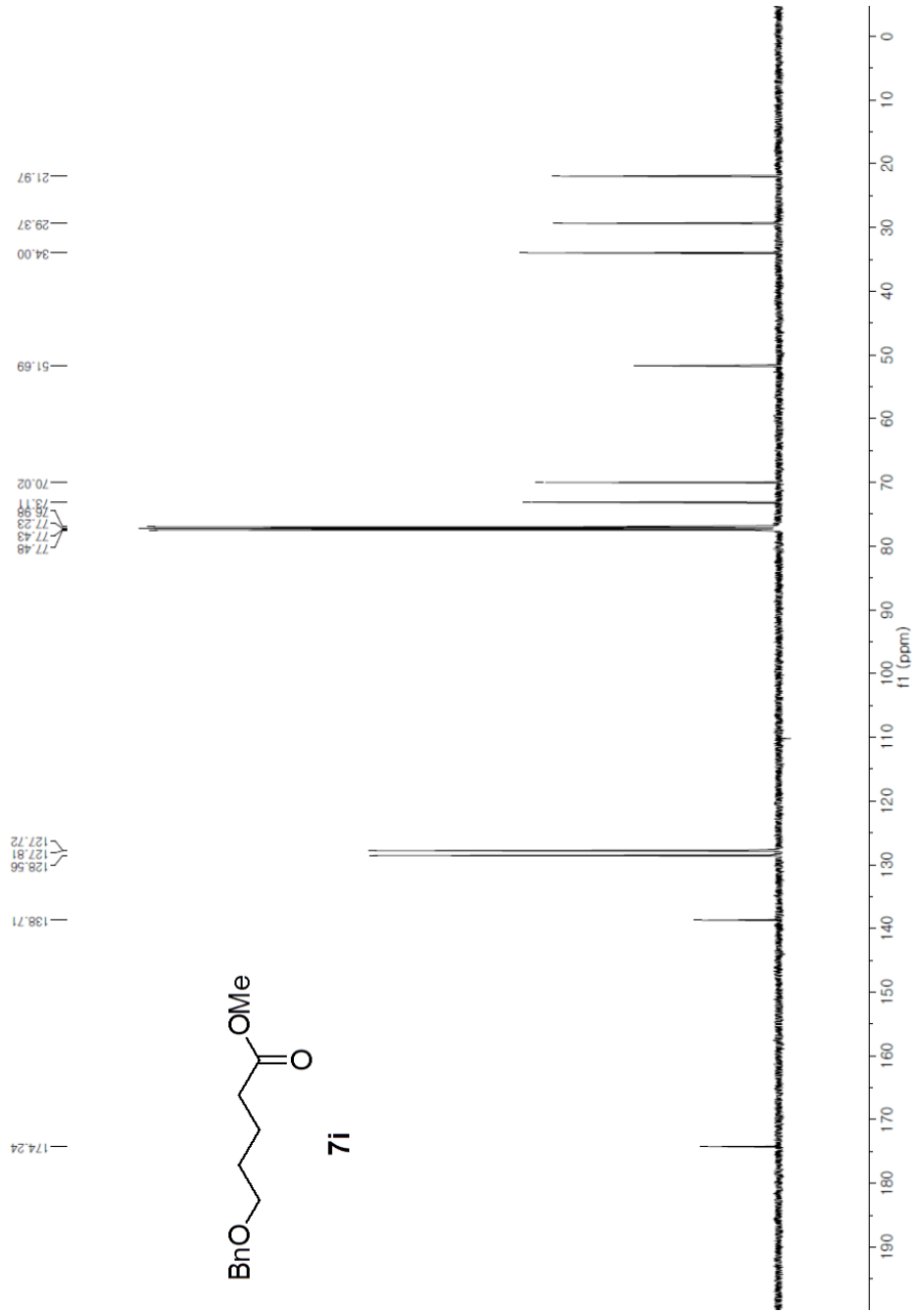
Compound 7h ^{13}C NMR



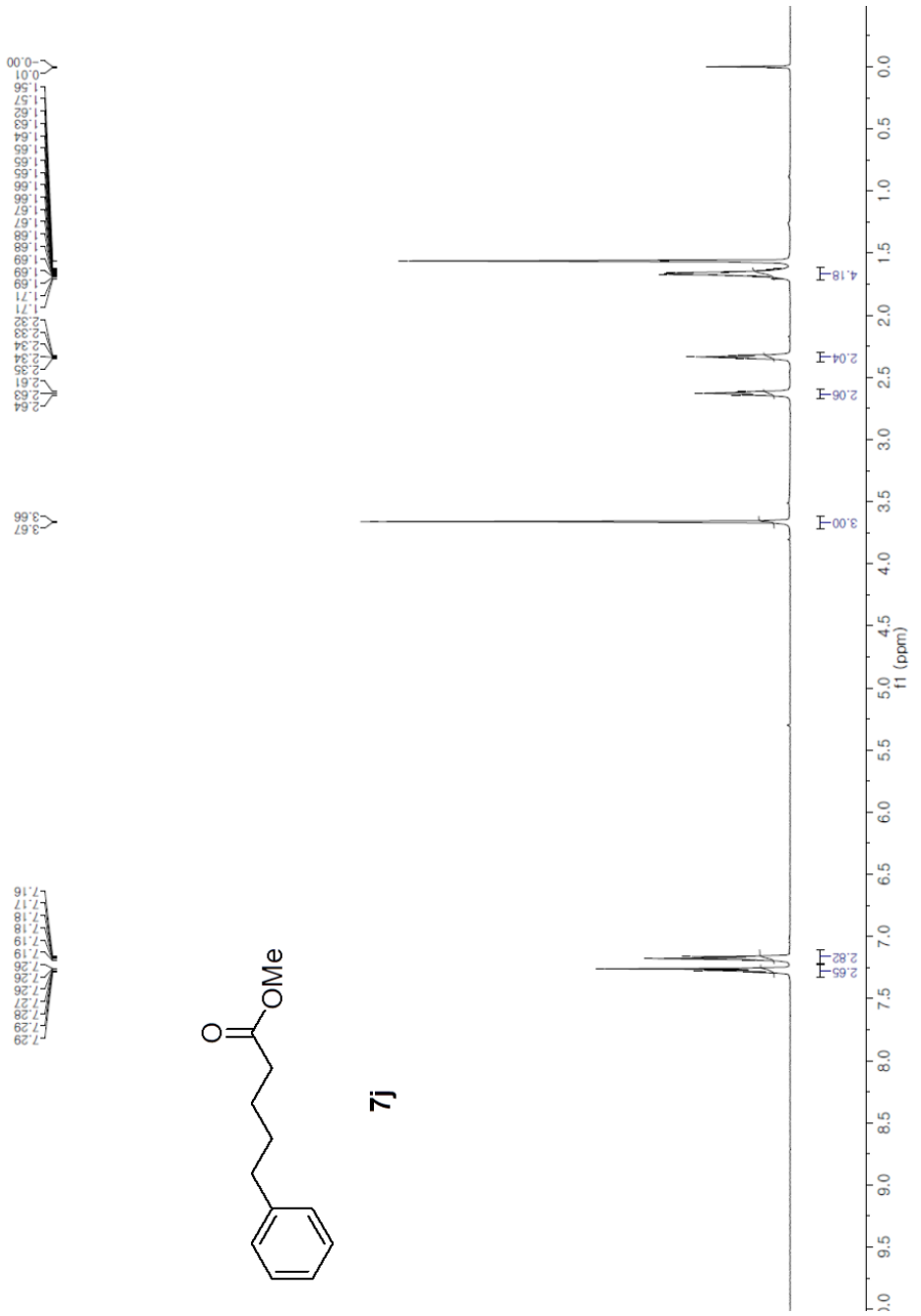
Compound 7i ^{1}H NMR



Compound 7i ^{13}C NMR



Compound 7j ^{1}H NMR



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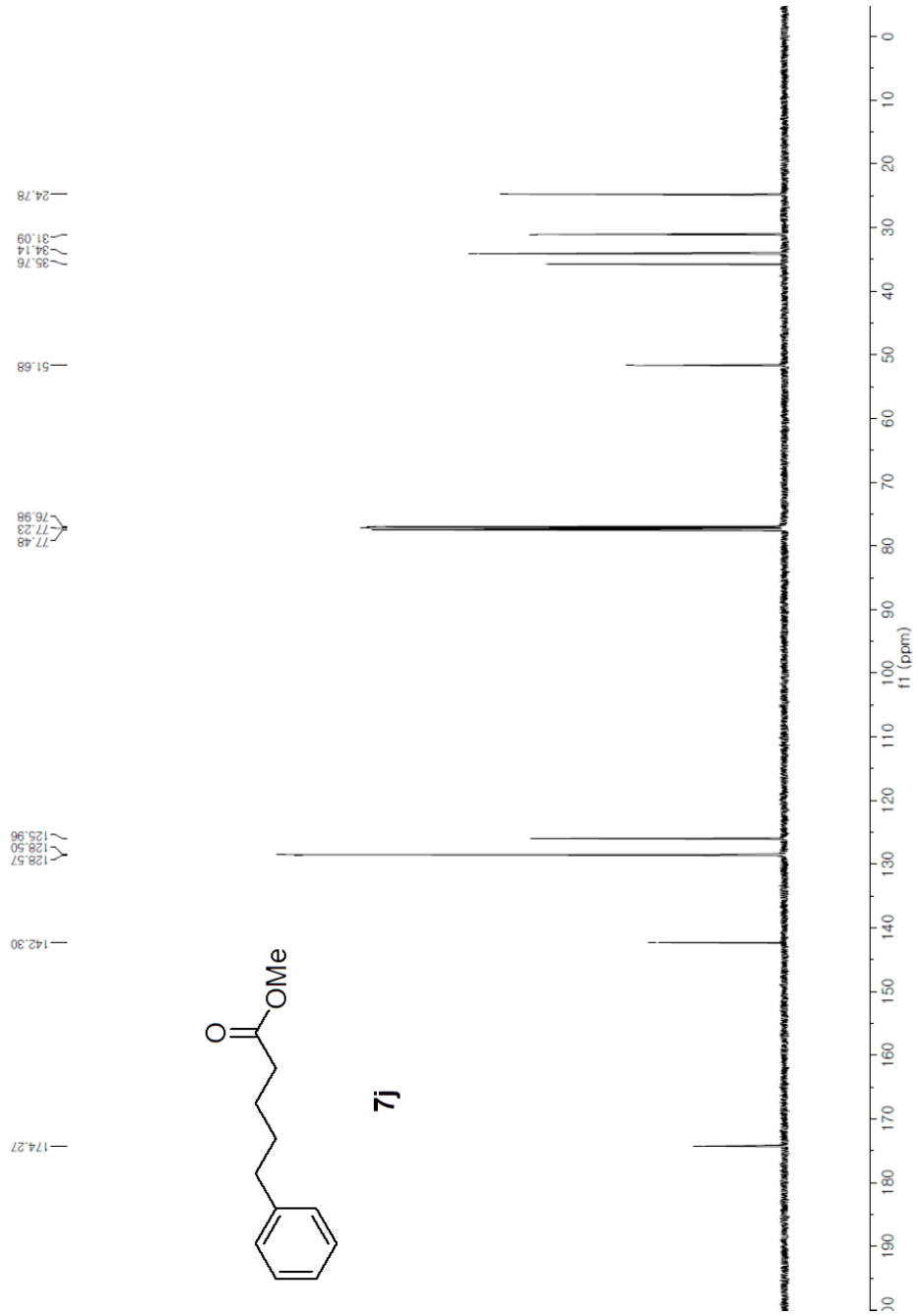
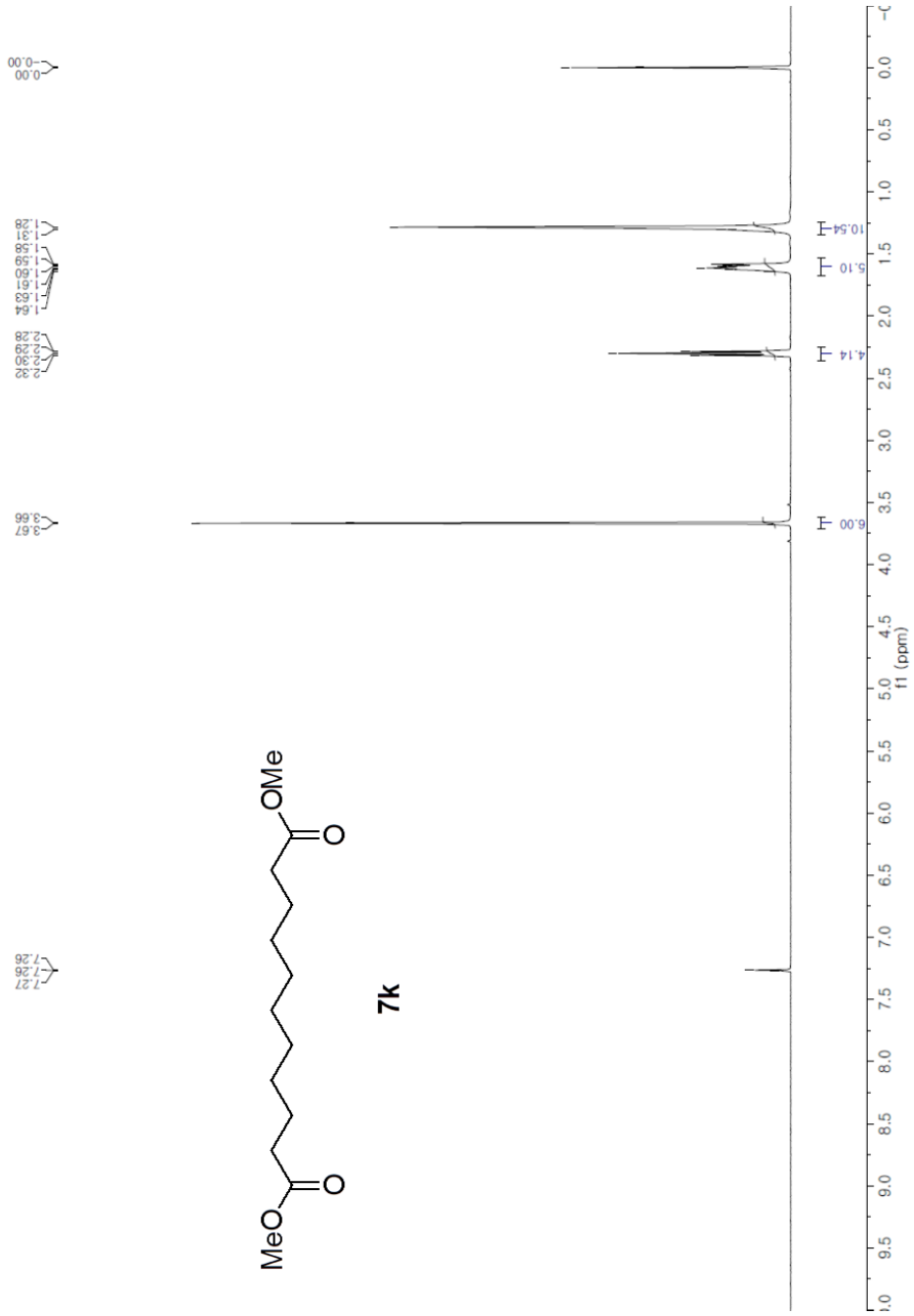
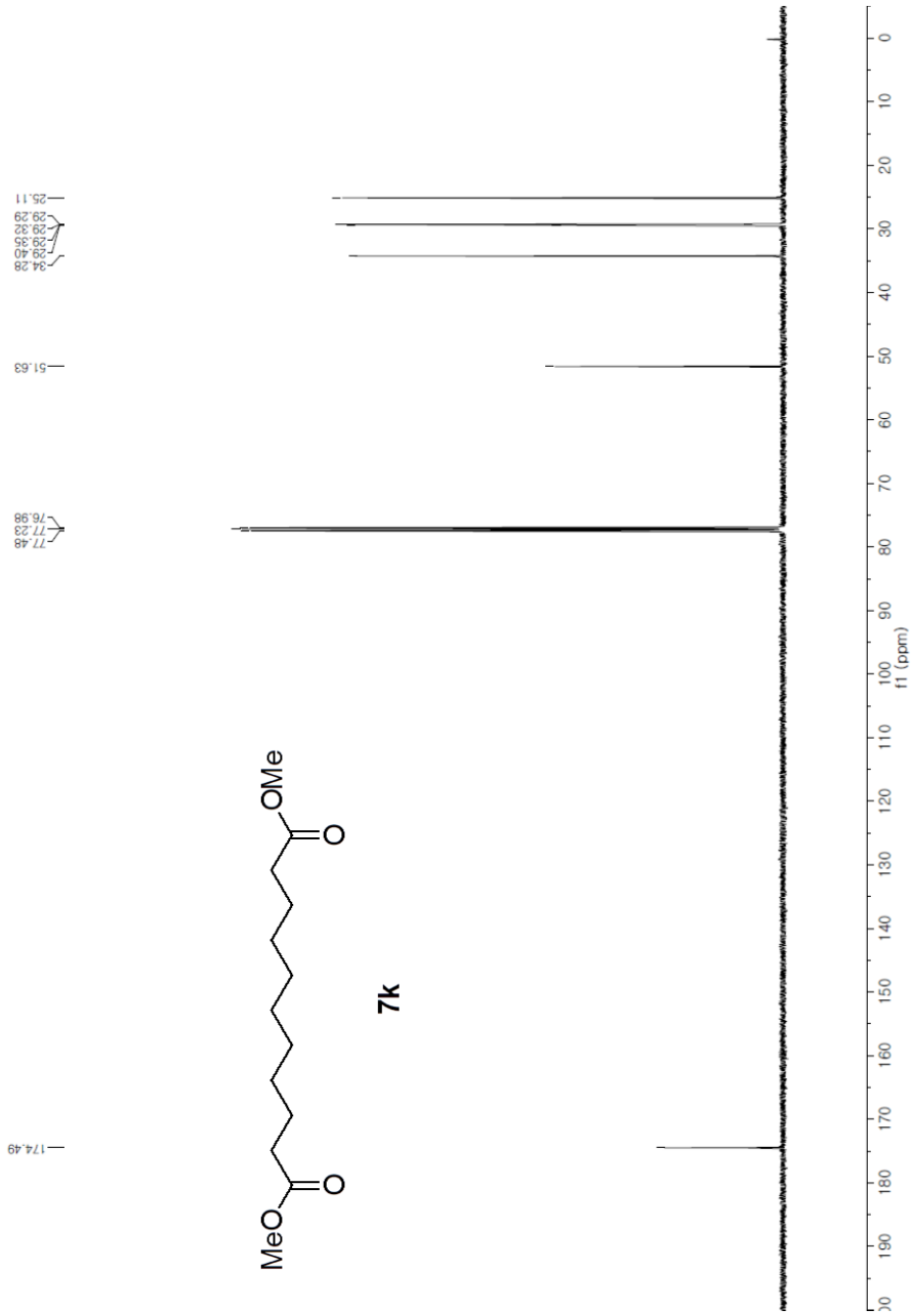


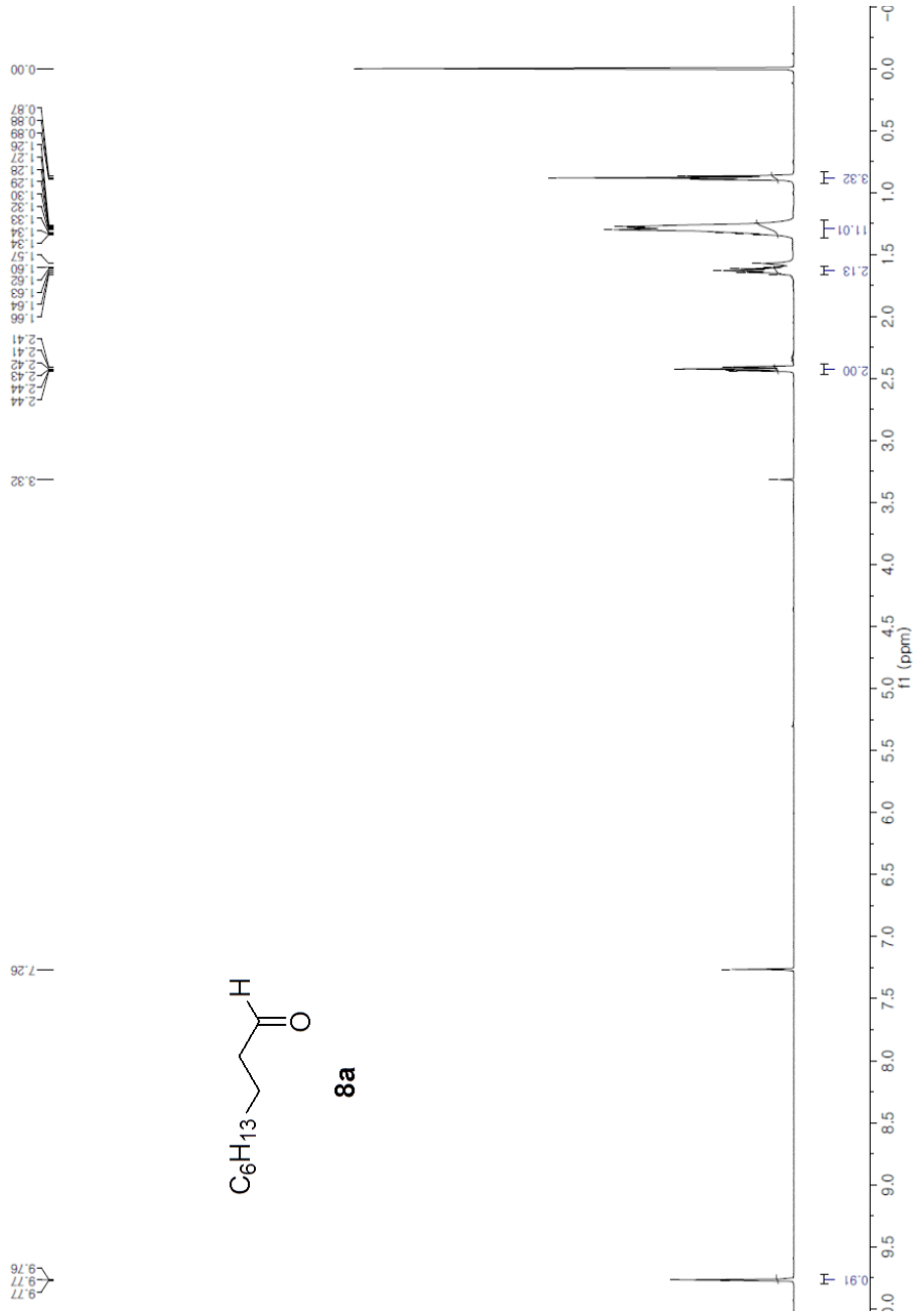
Compound 7k ^{1}H NMR



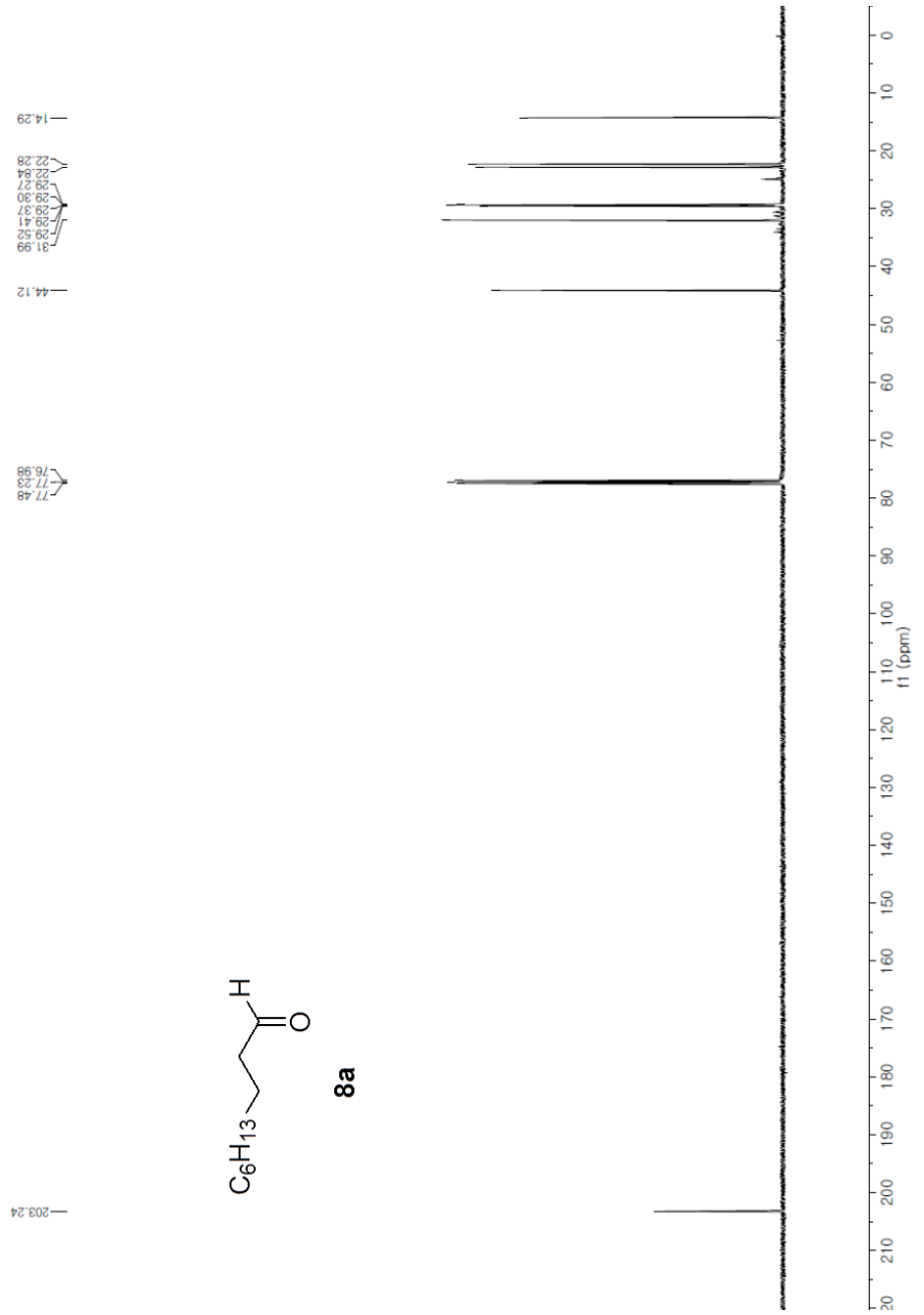
Compound 7k ^{13}C NMR



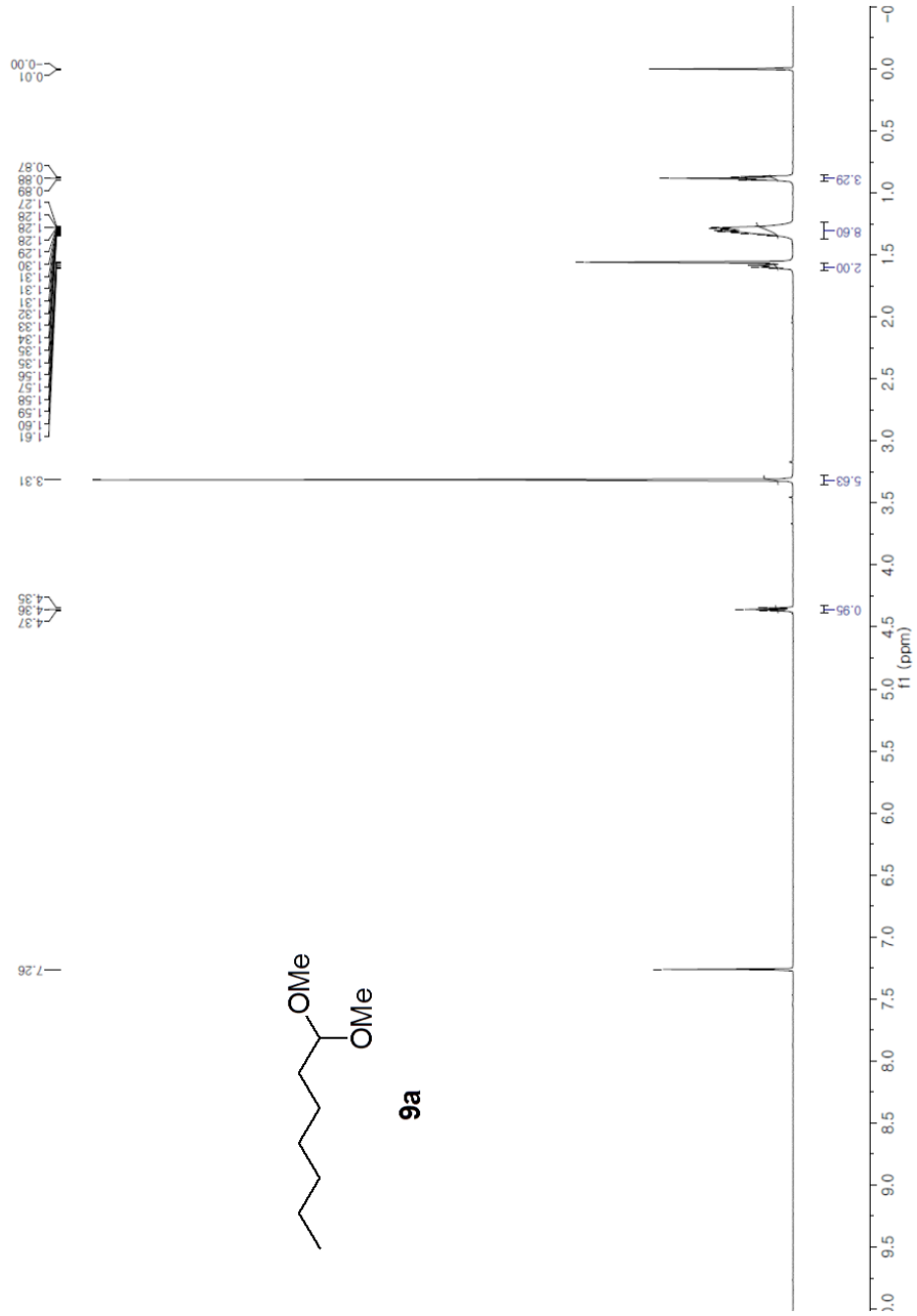
Compound 8a ^{1}H NMR



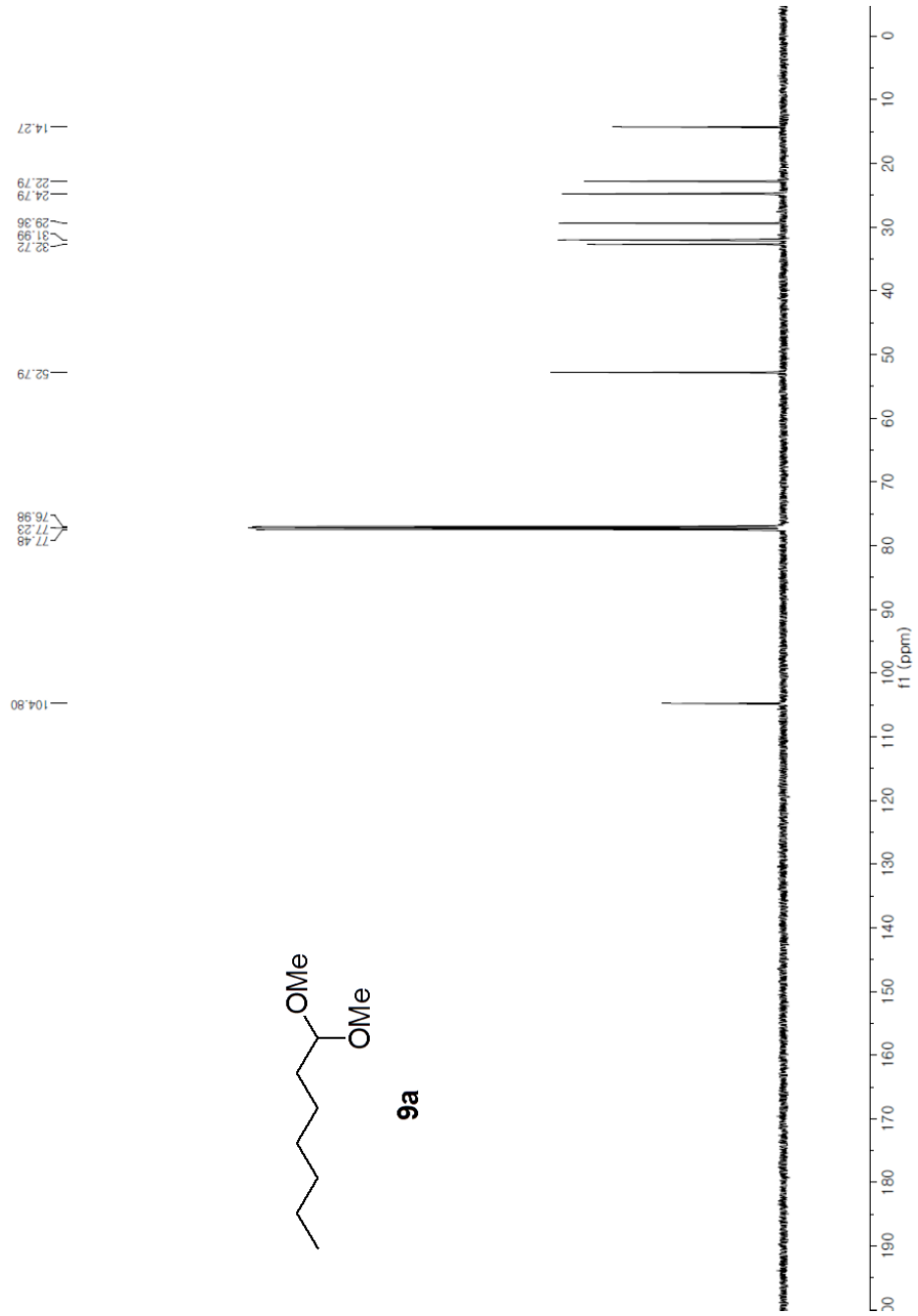
Compound 8a ^{13}C NMR



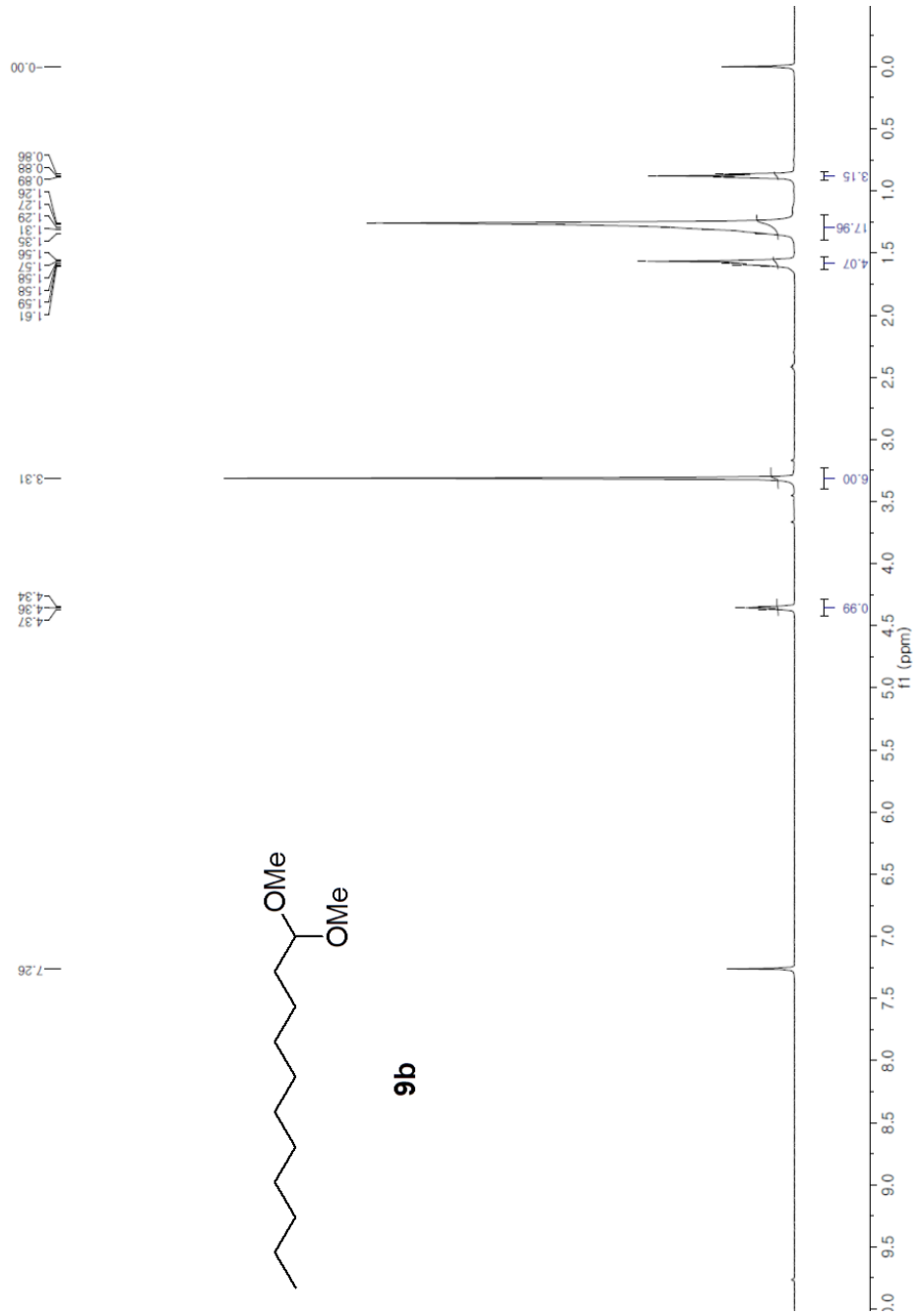
Compound 9a ^{1}H NMR



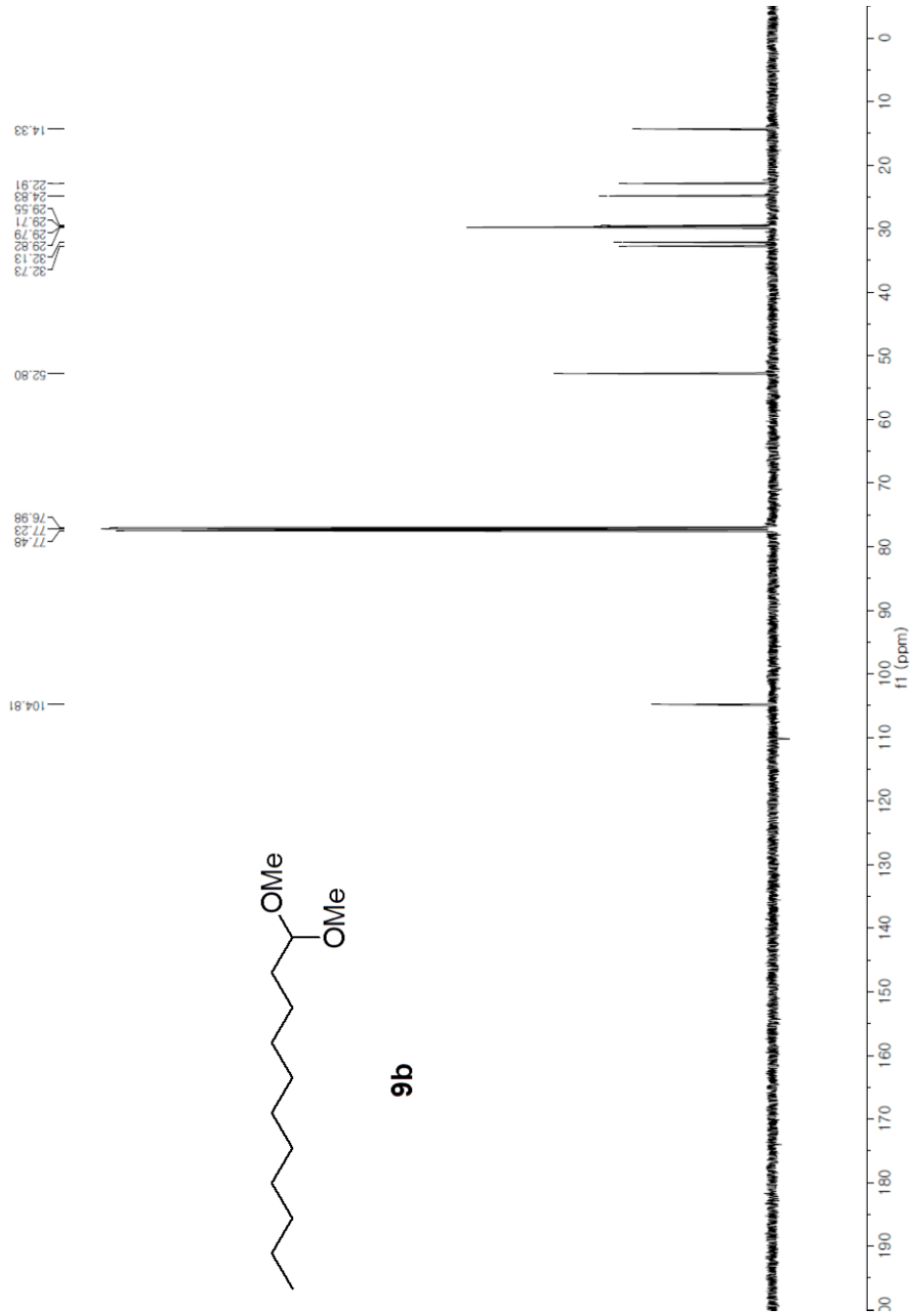
Compound 9a ^{13}C NMR



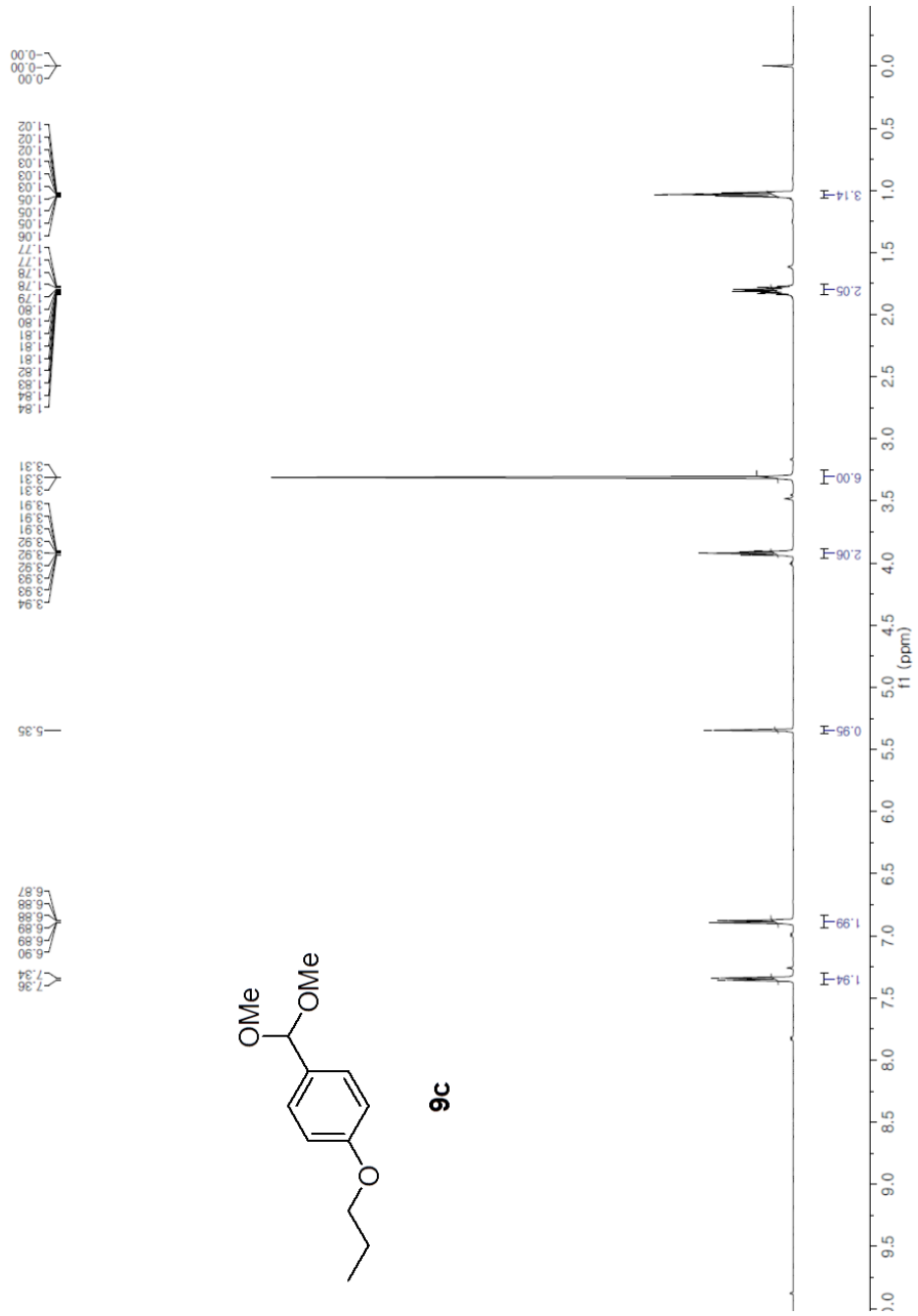
Compound 9b ^{1}H NMR



Compound 9b ^{13}C NMR



Compound 9c ^{1}H NMR



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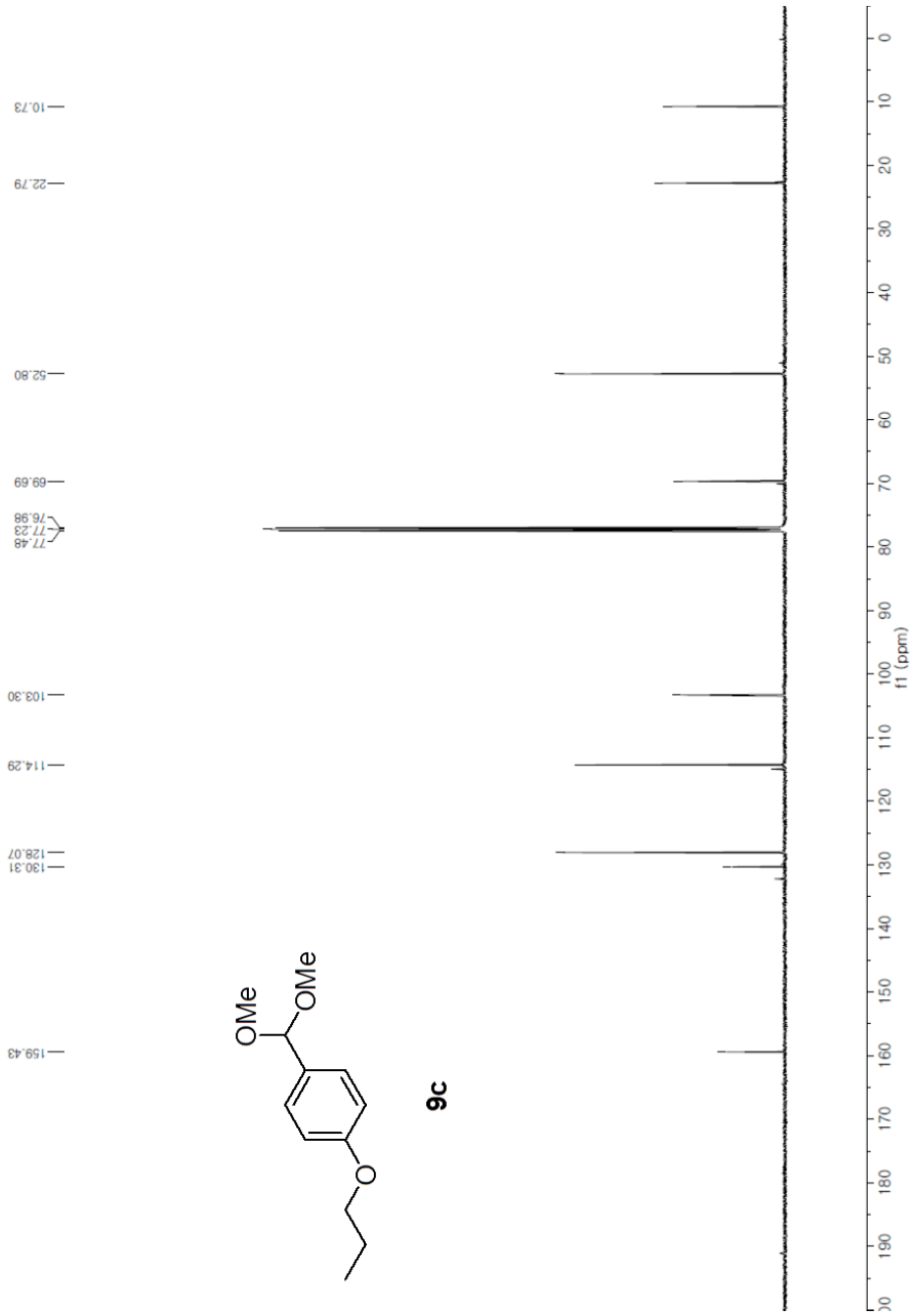

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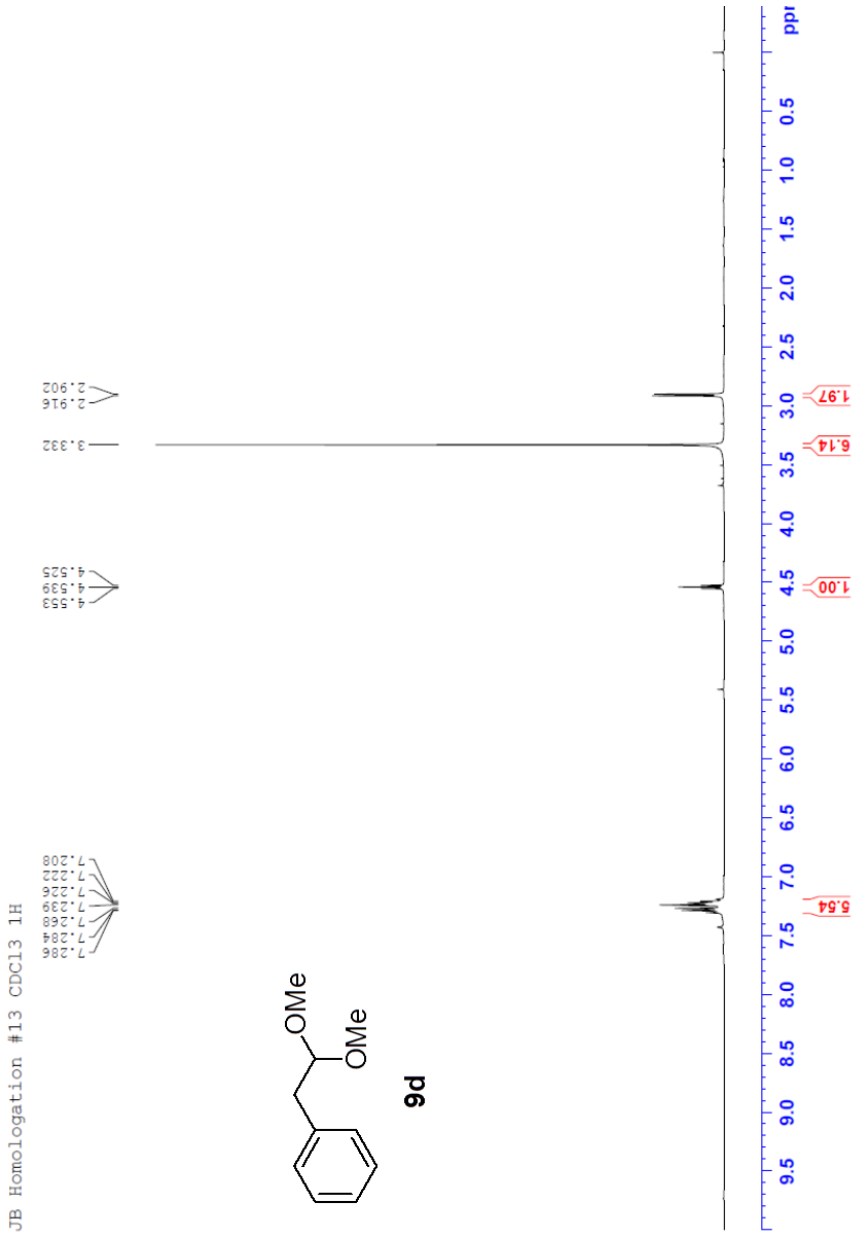

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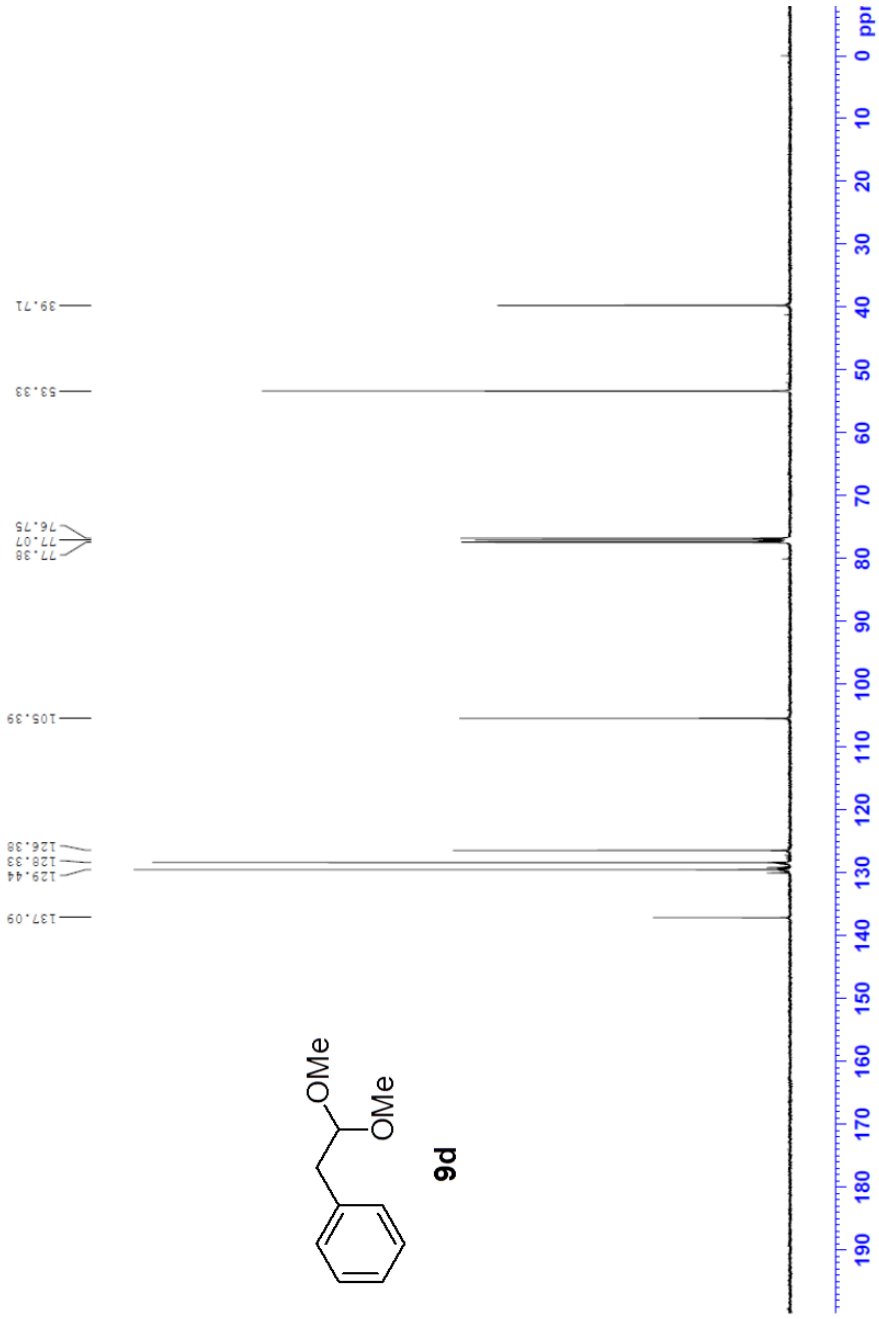

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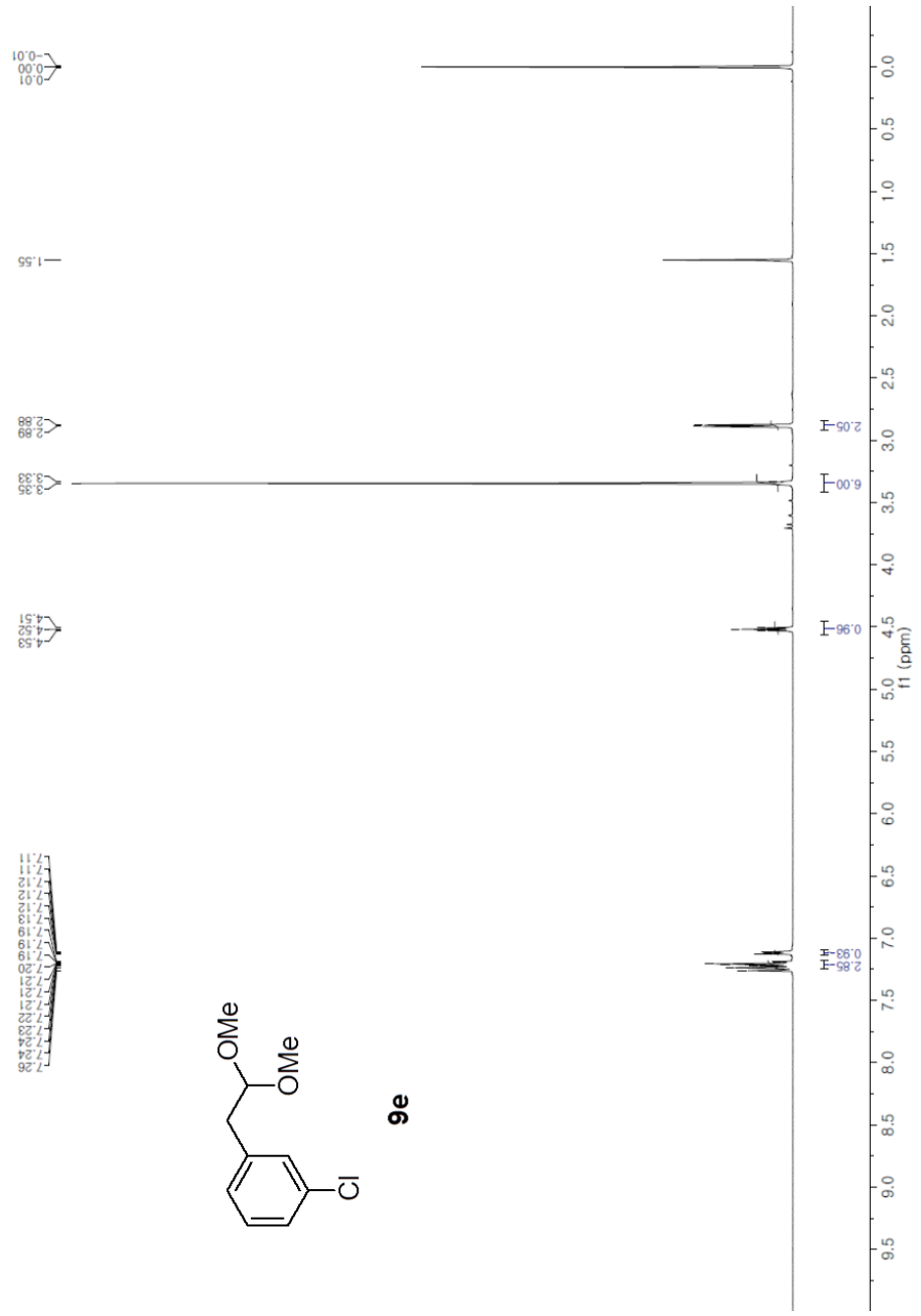
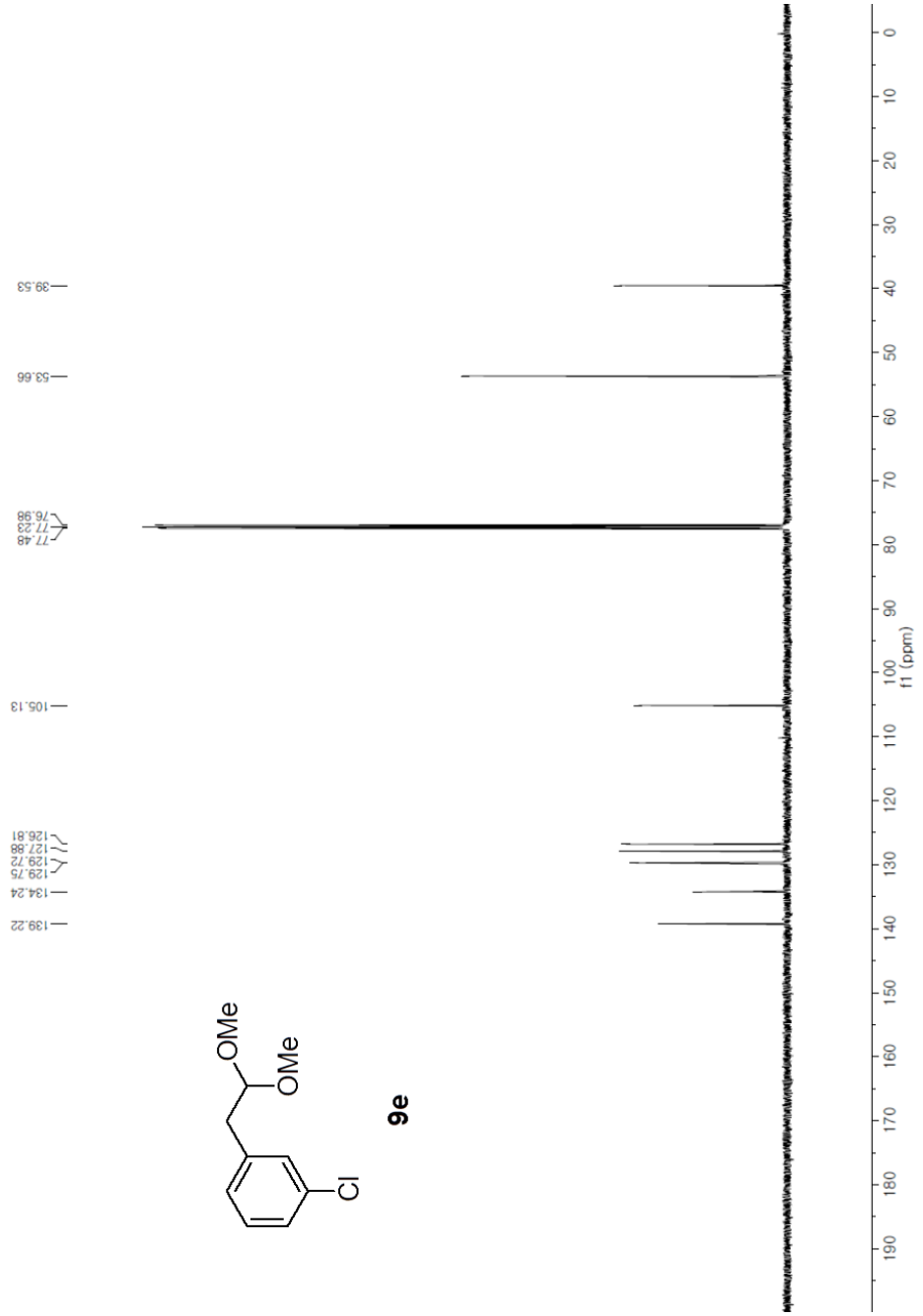
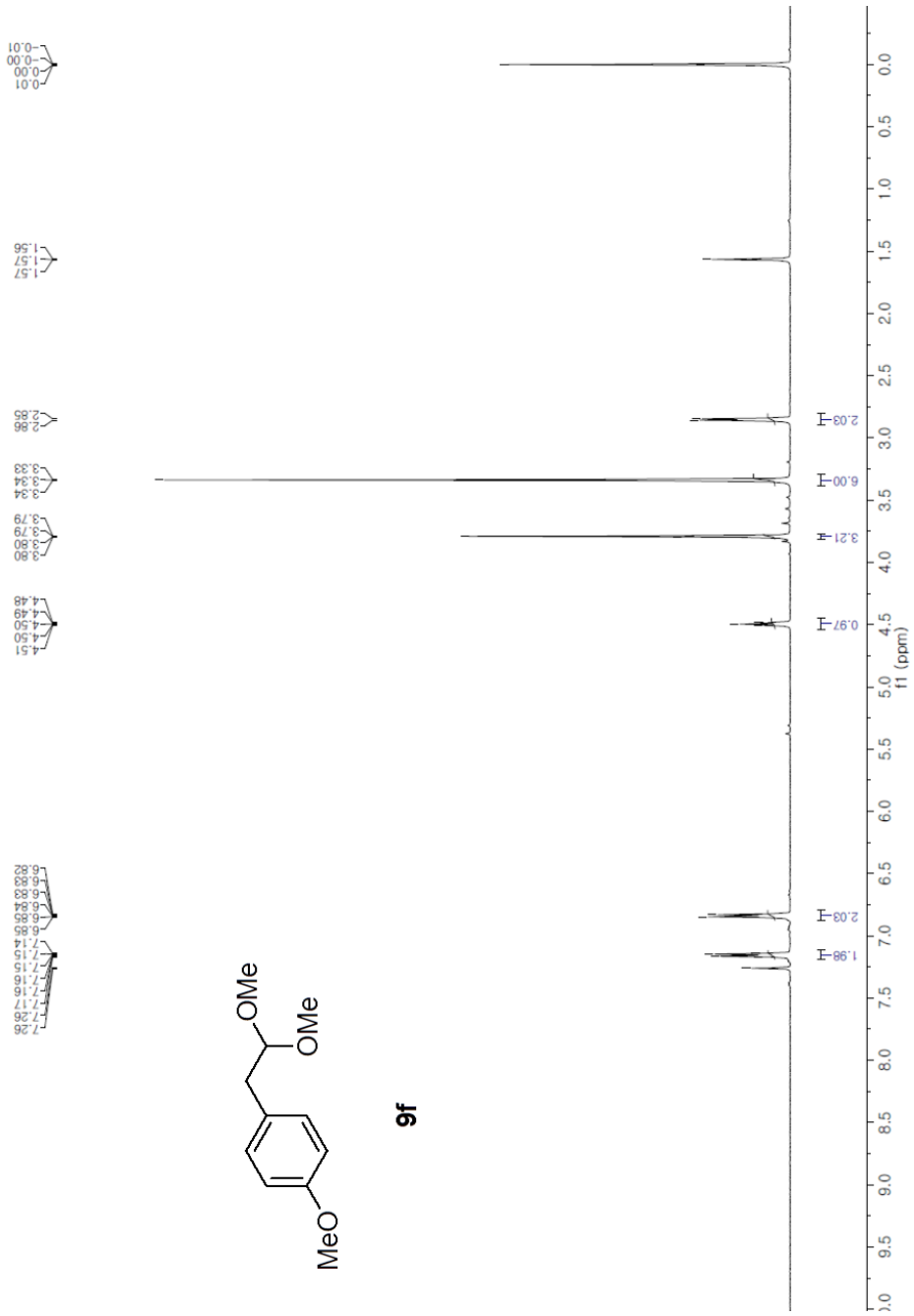


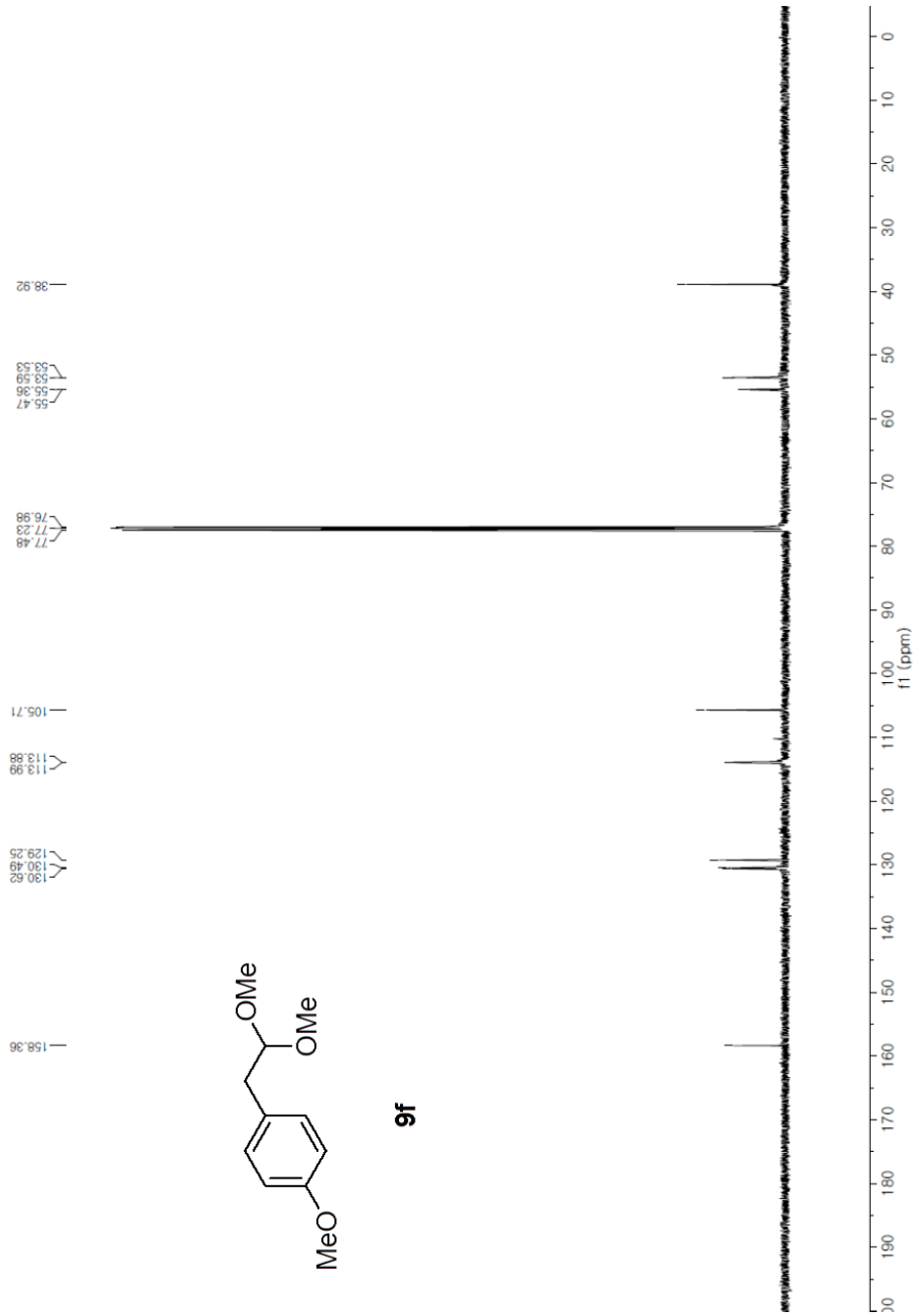
Compound 9e ^{13}C NMR



Compound 9f ^{1}H NMR

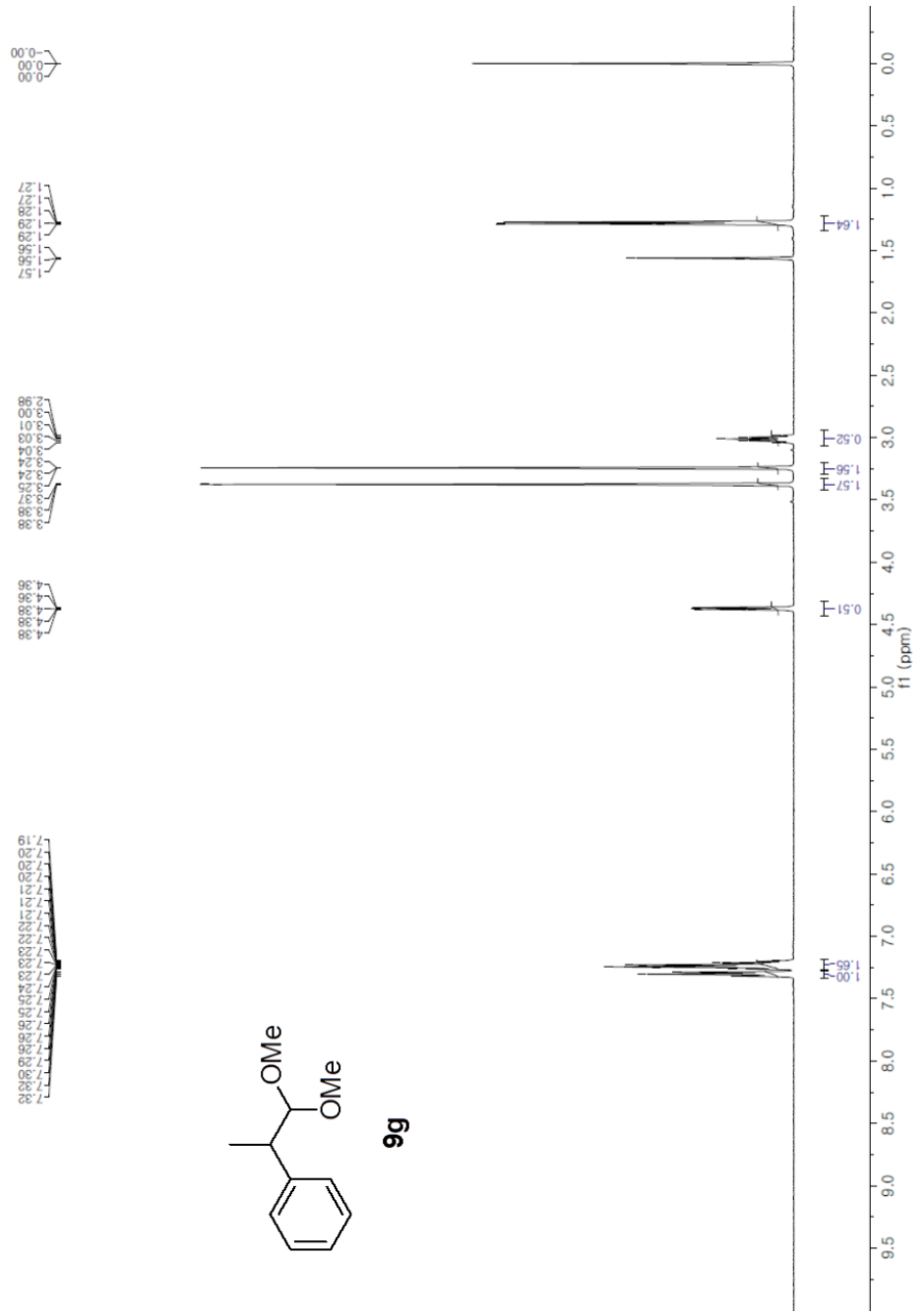


Compound 9f ^{13}C NMR

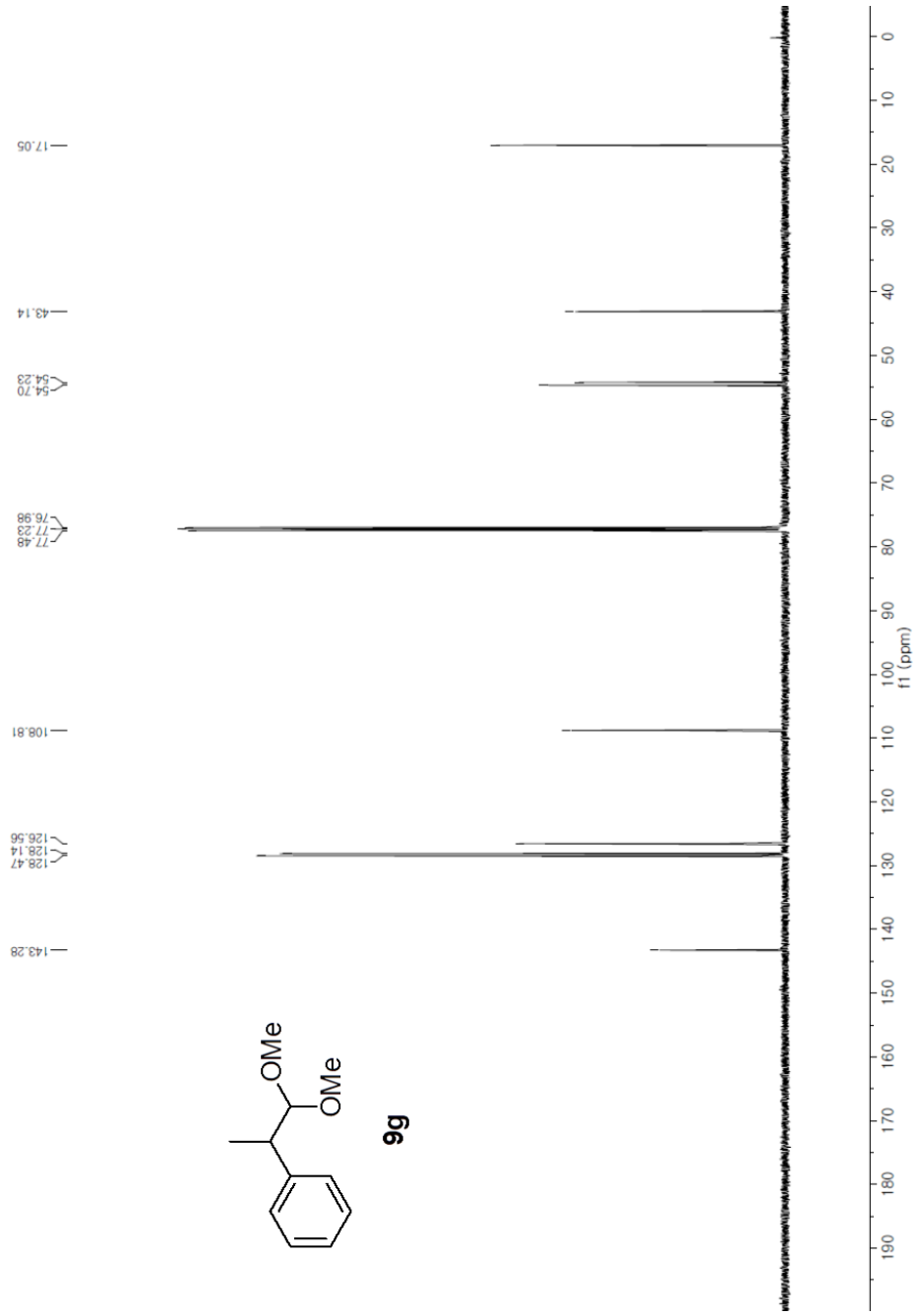


9f

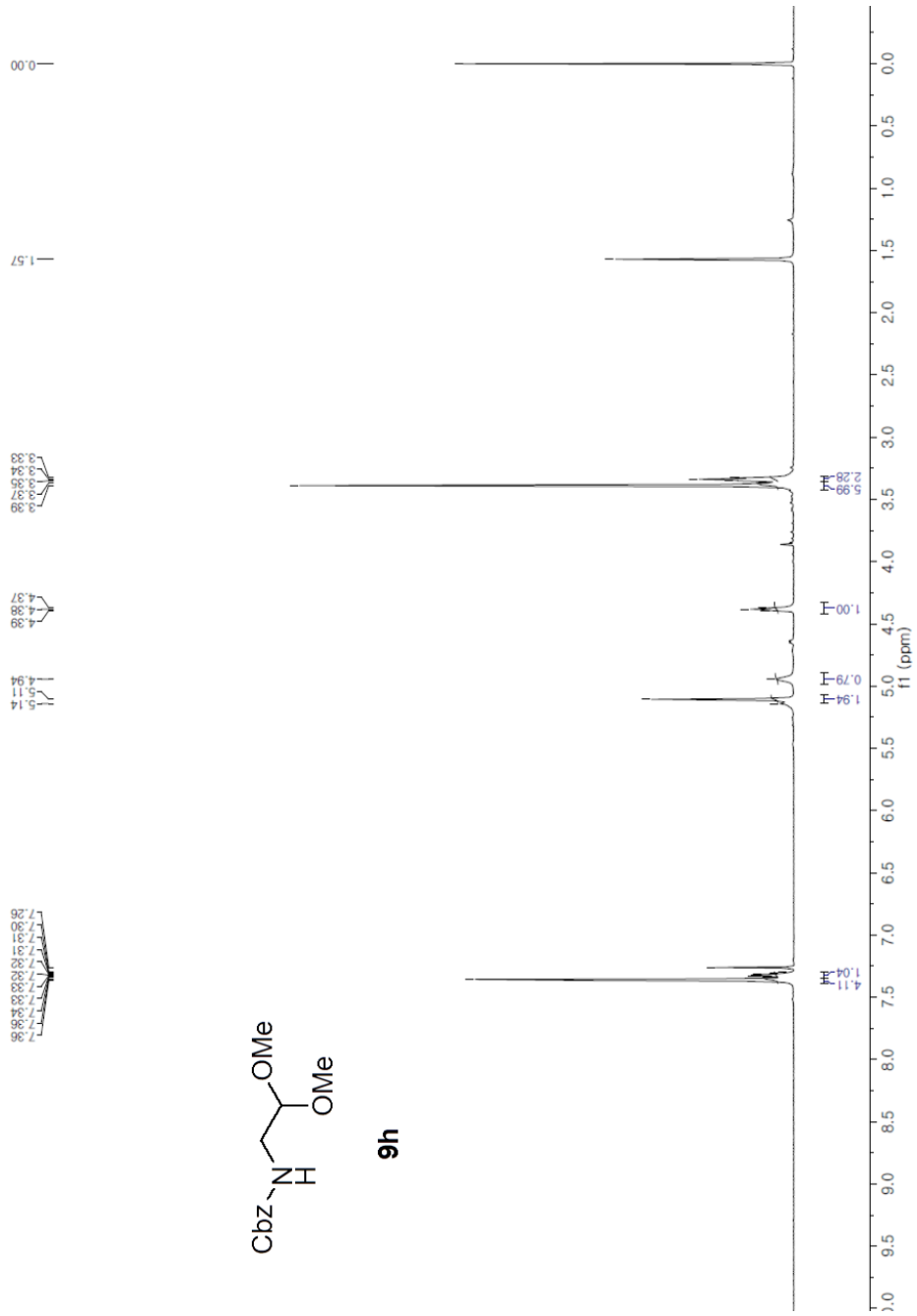
Compound 9g ^{1}H NMR



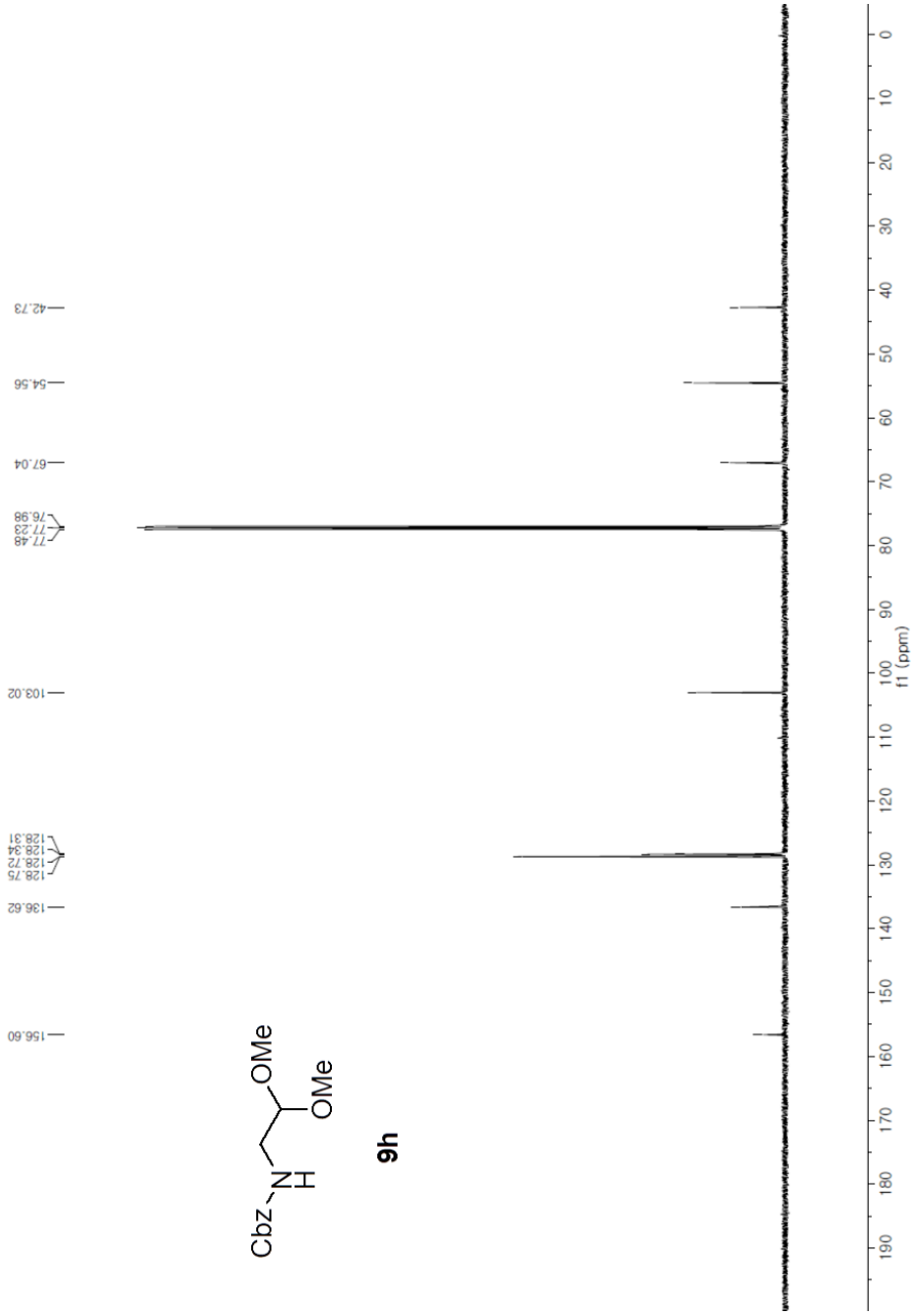
Compound 9g ^{13}C NMR



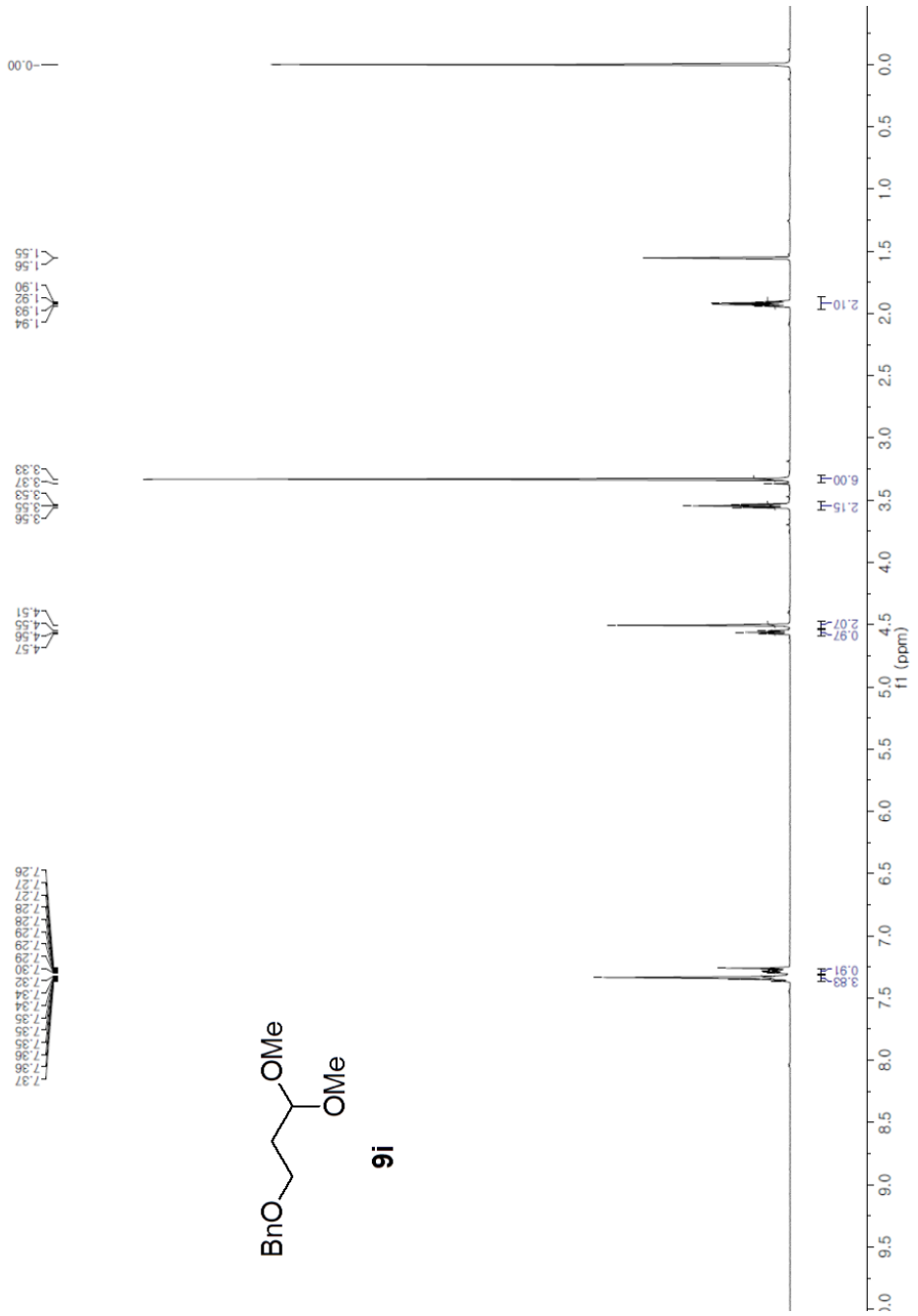
Compound 9h ^{1}H NMR



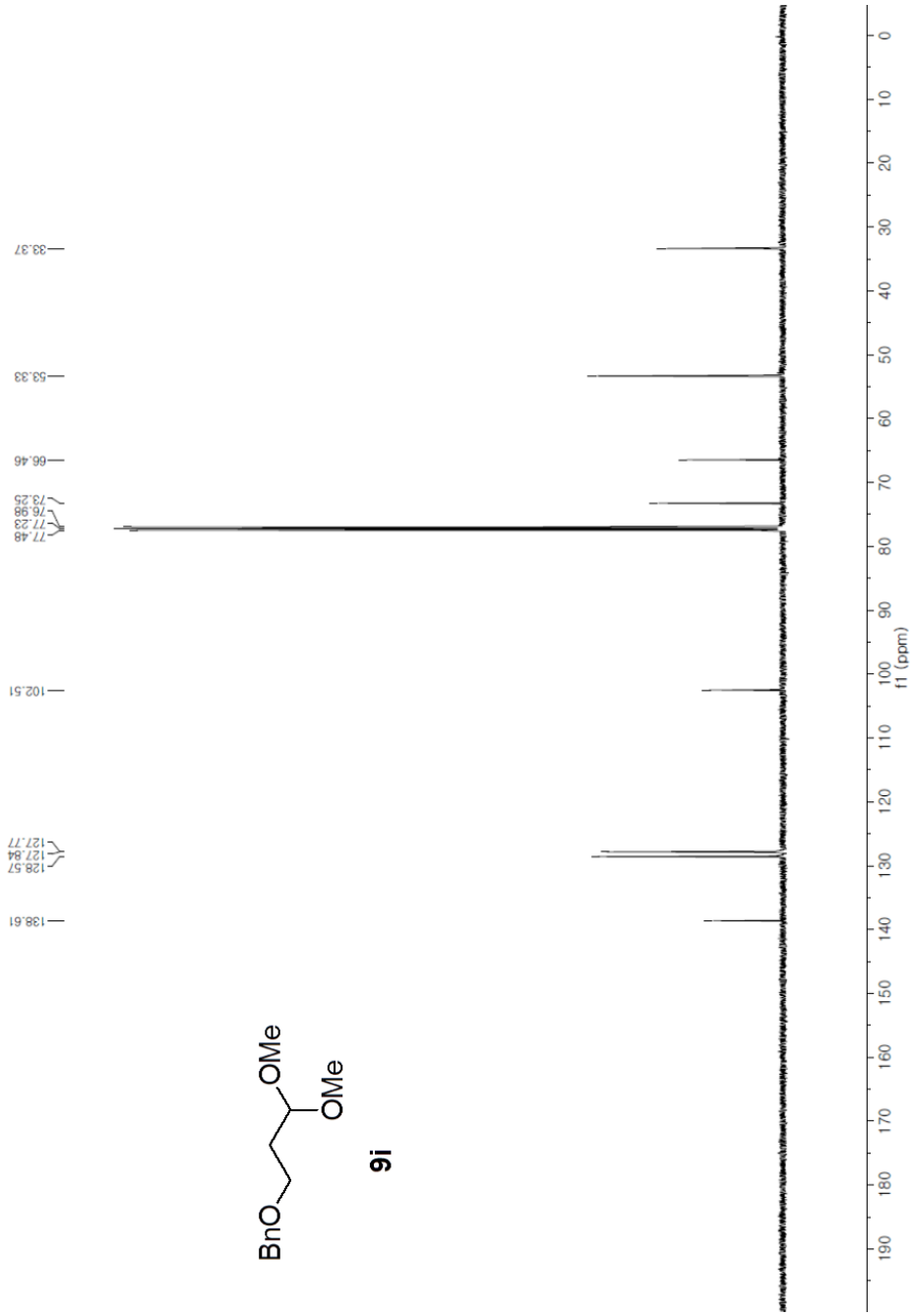
Compound 9h ^{13}C NMR



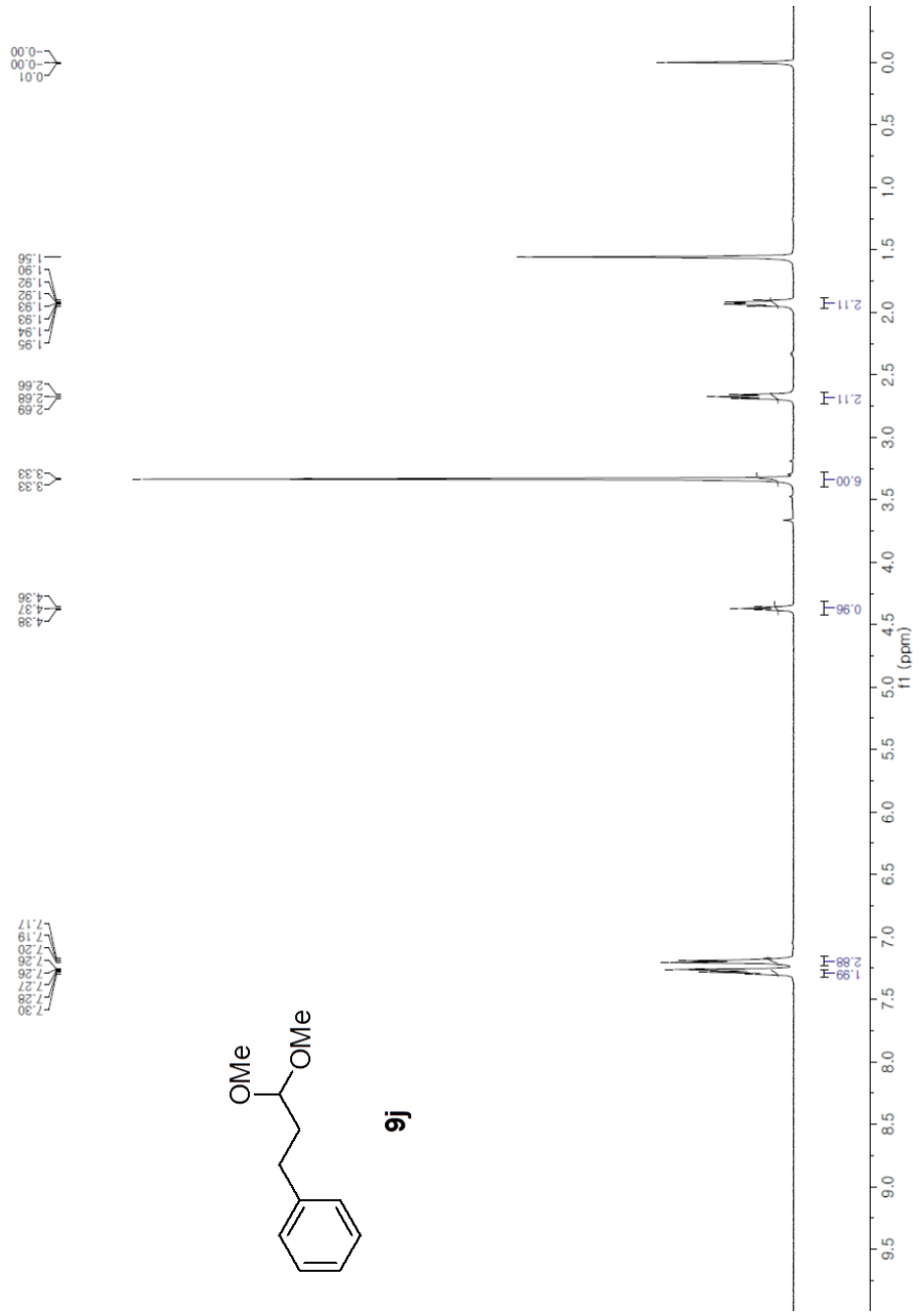
Compound 9i ^{1}H NMR



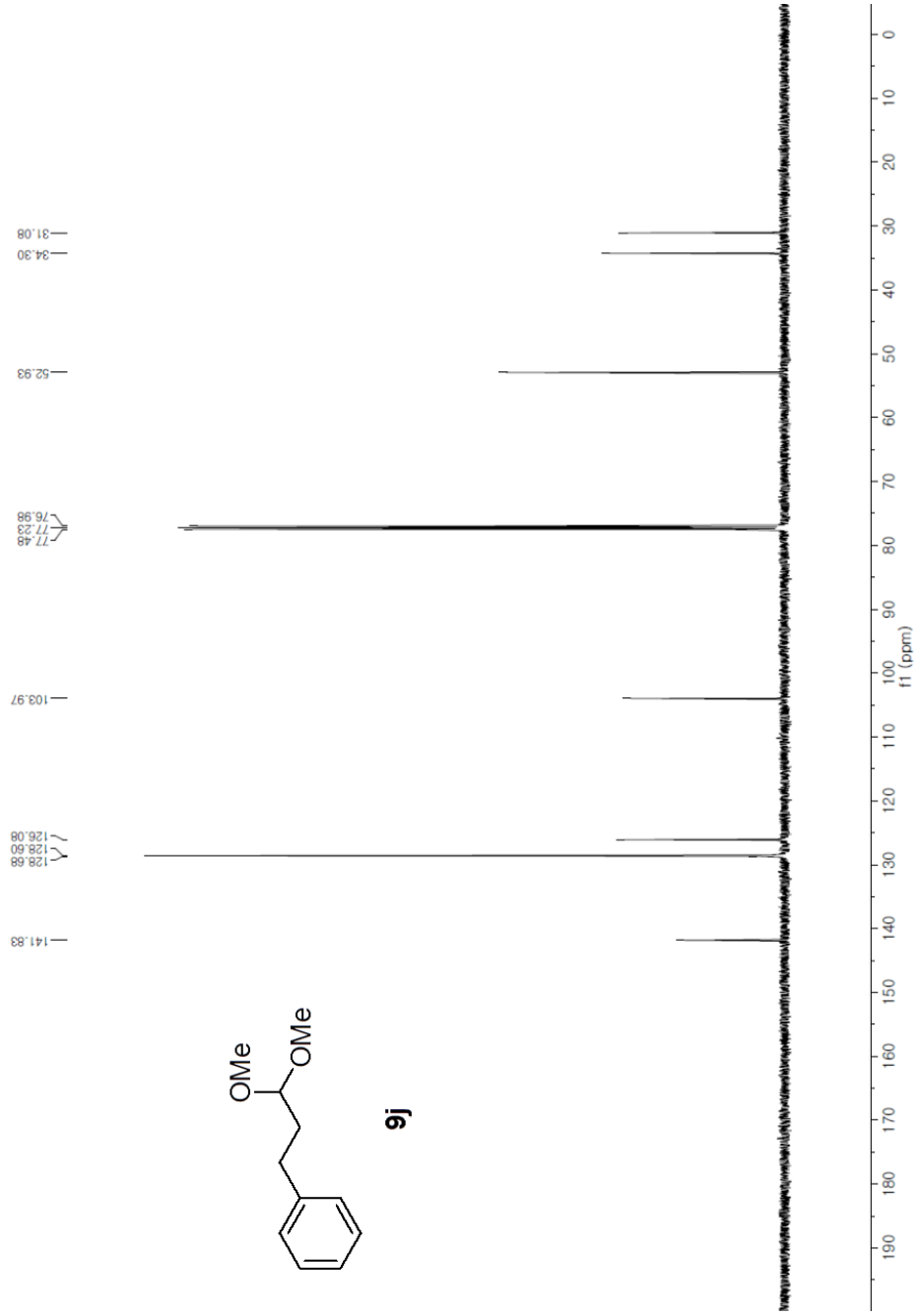
Compound 9i ^{13}C NMR



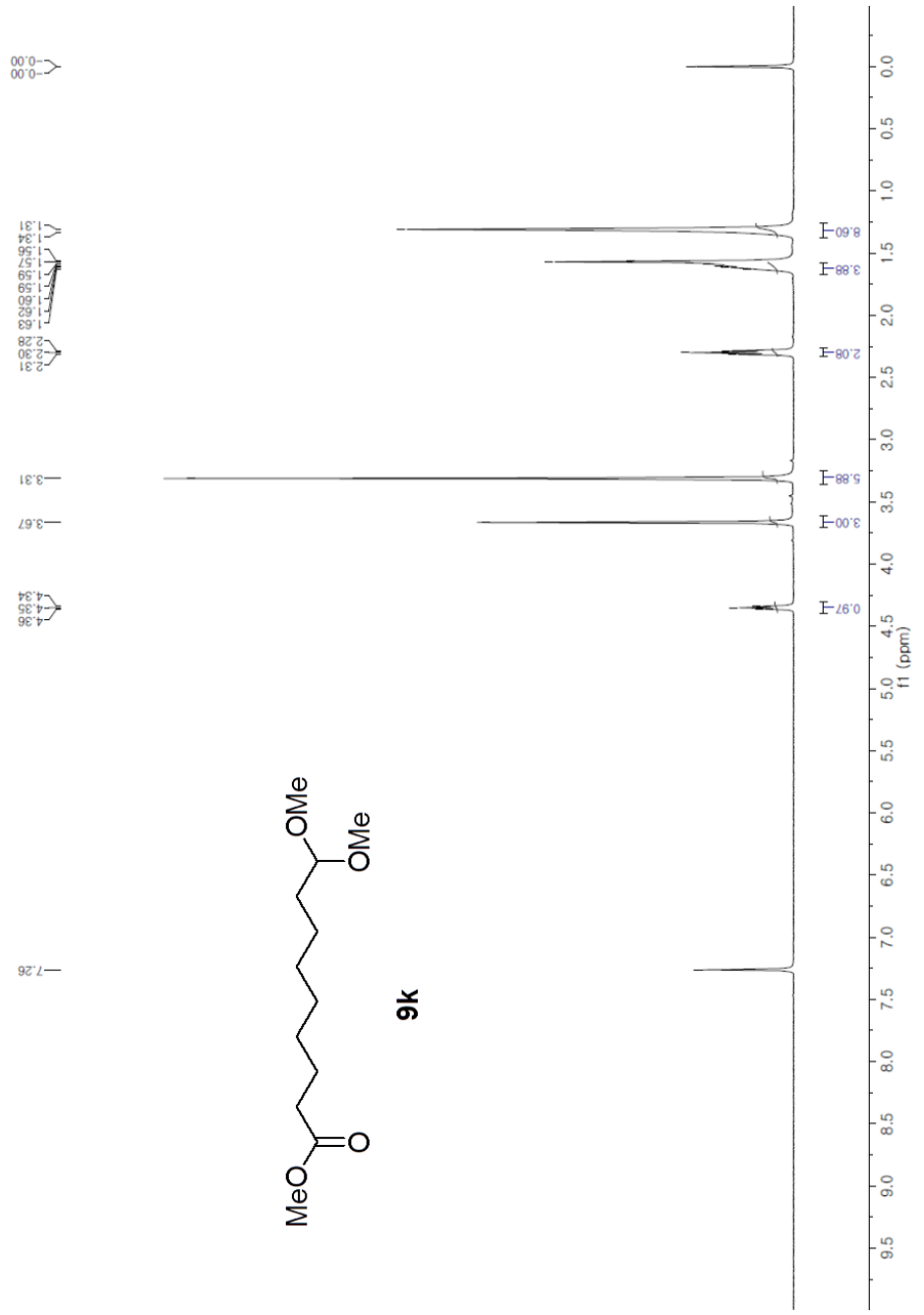
Compound 9j ^{1}H NMR



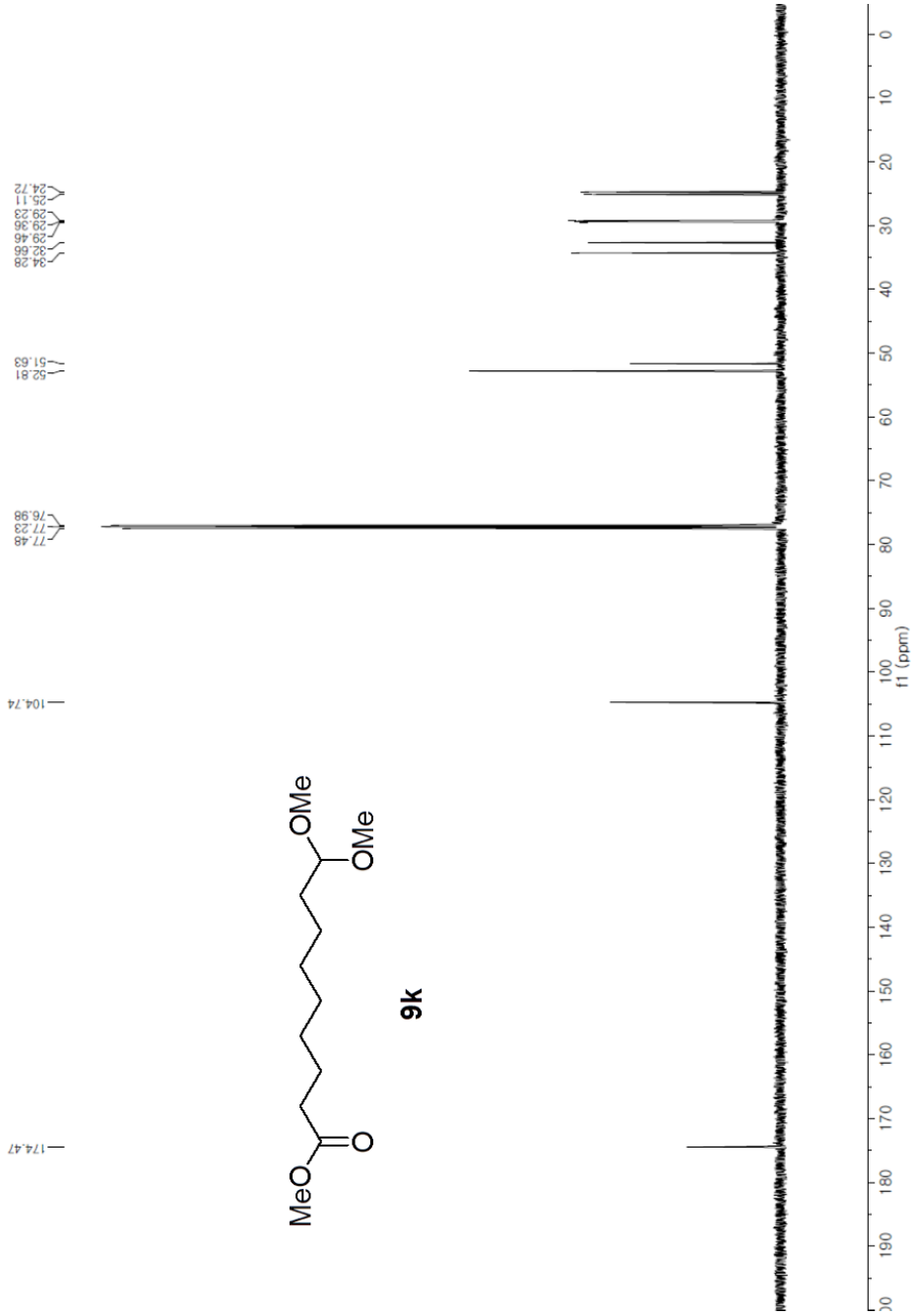
Compound 9j ^{13}C NMR



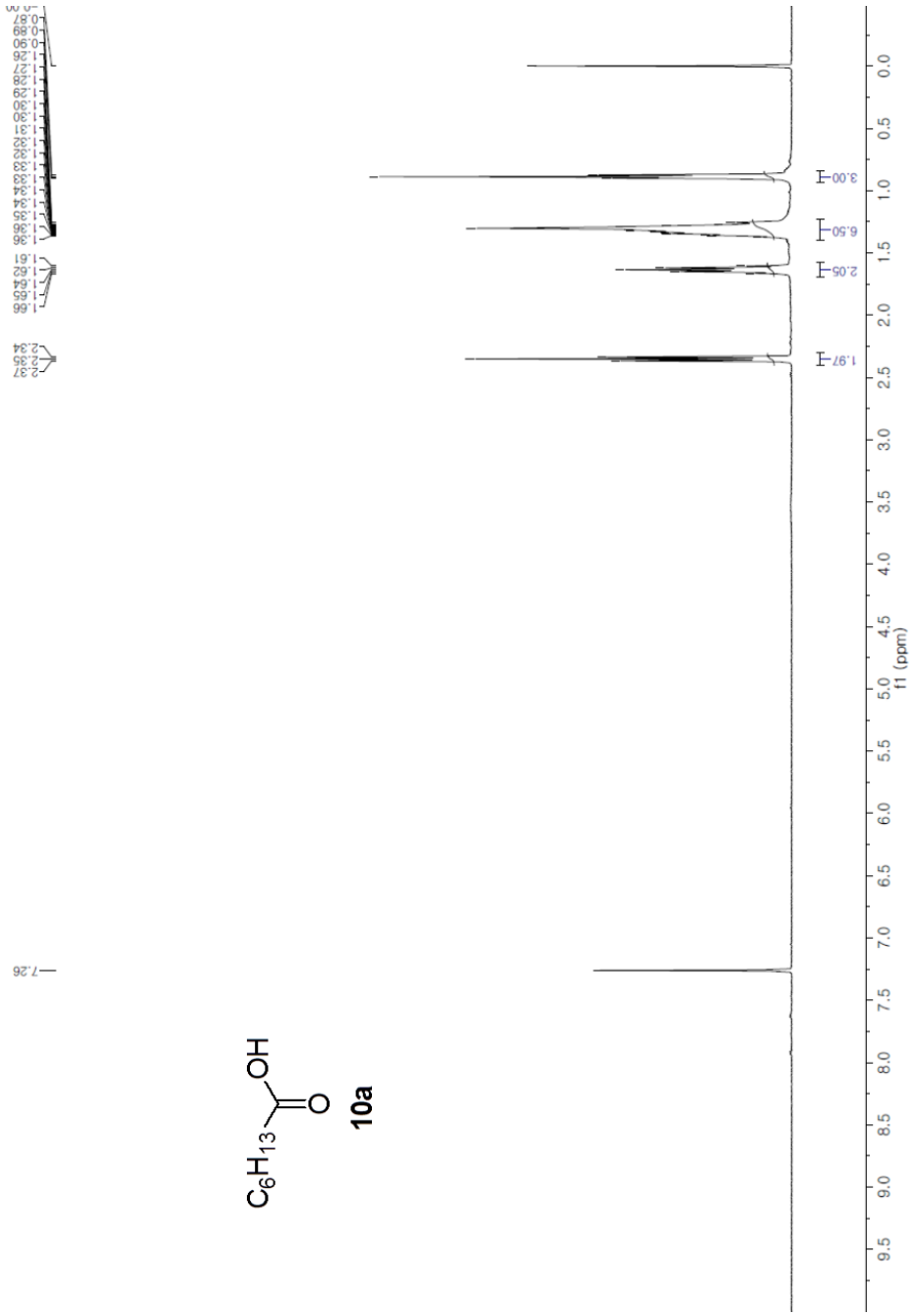
Compound 9k ^{1}H NMR



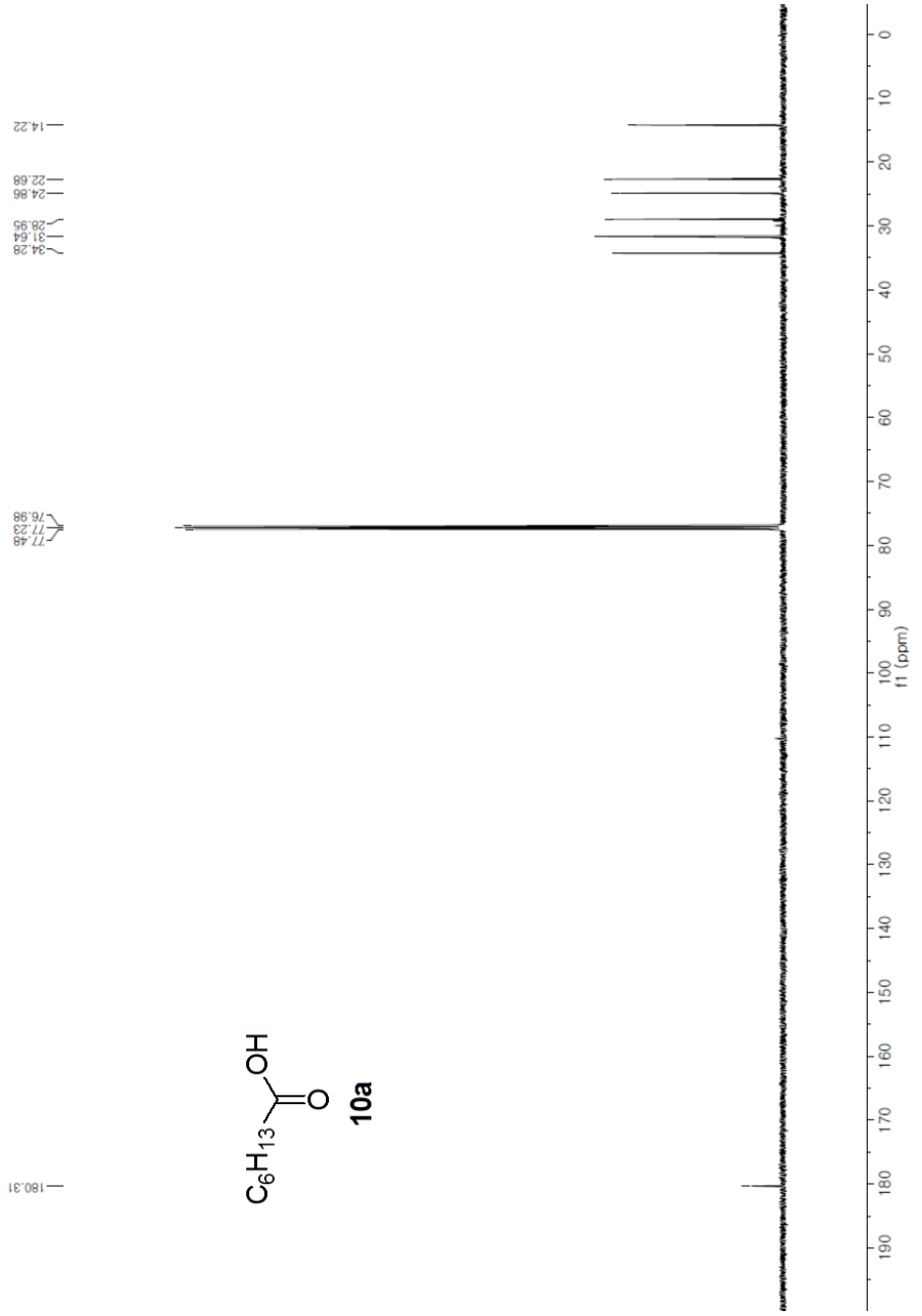
Compound 9k ^{13}C NMR



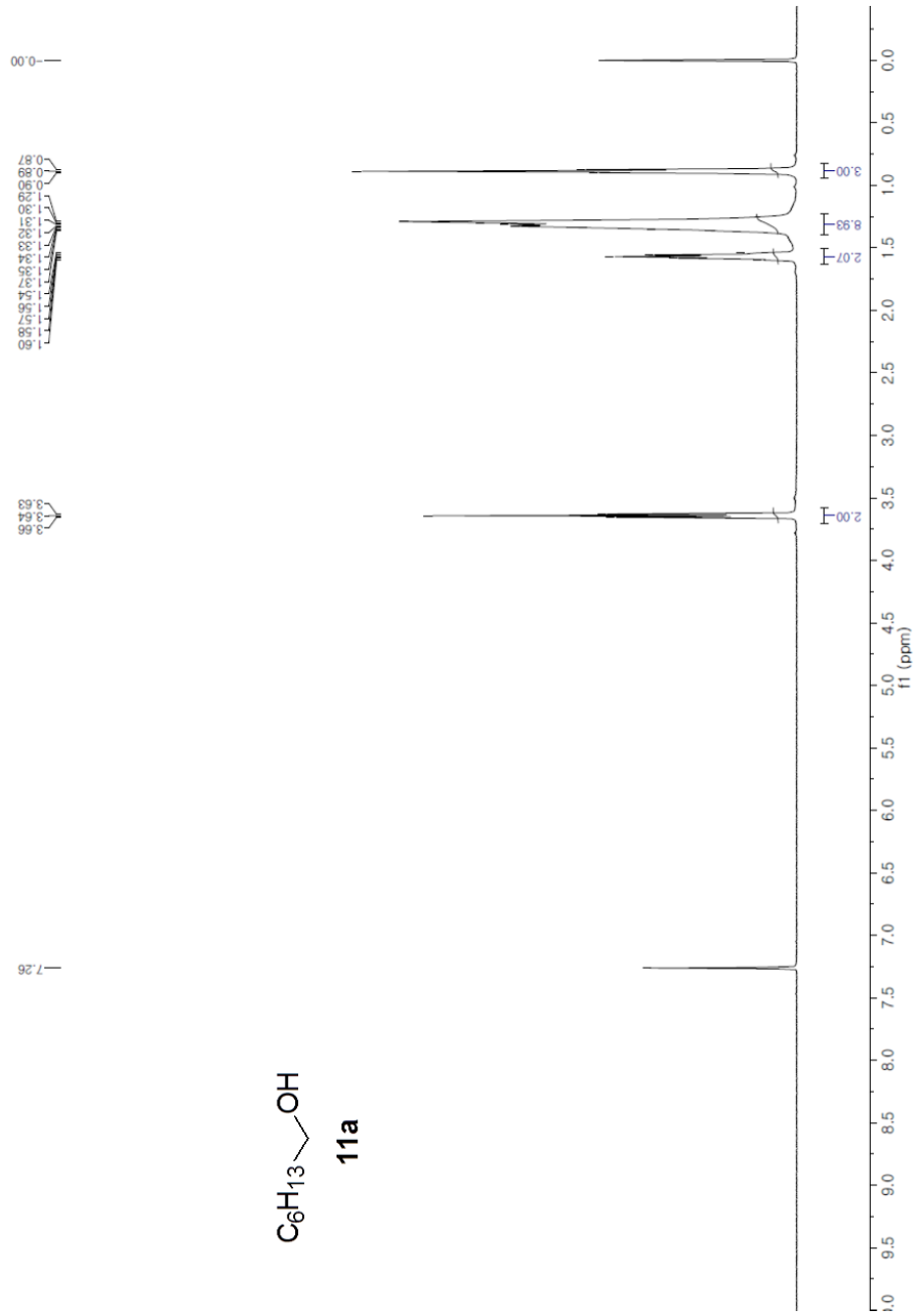
Compound 10a ^{1}H NMR



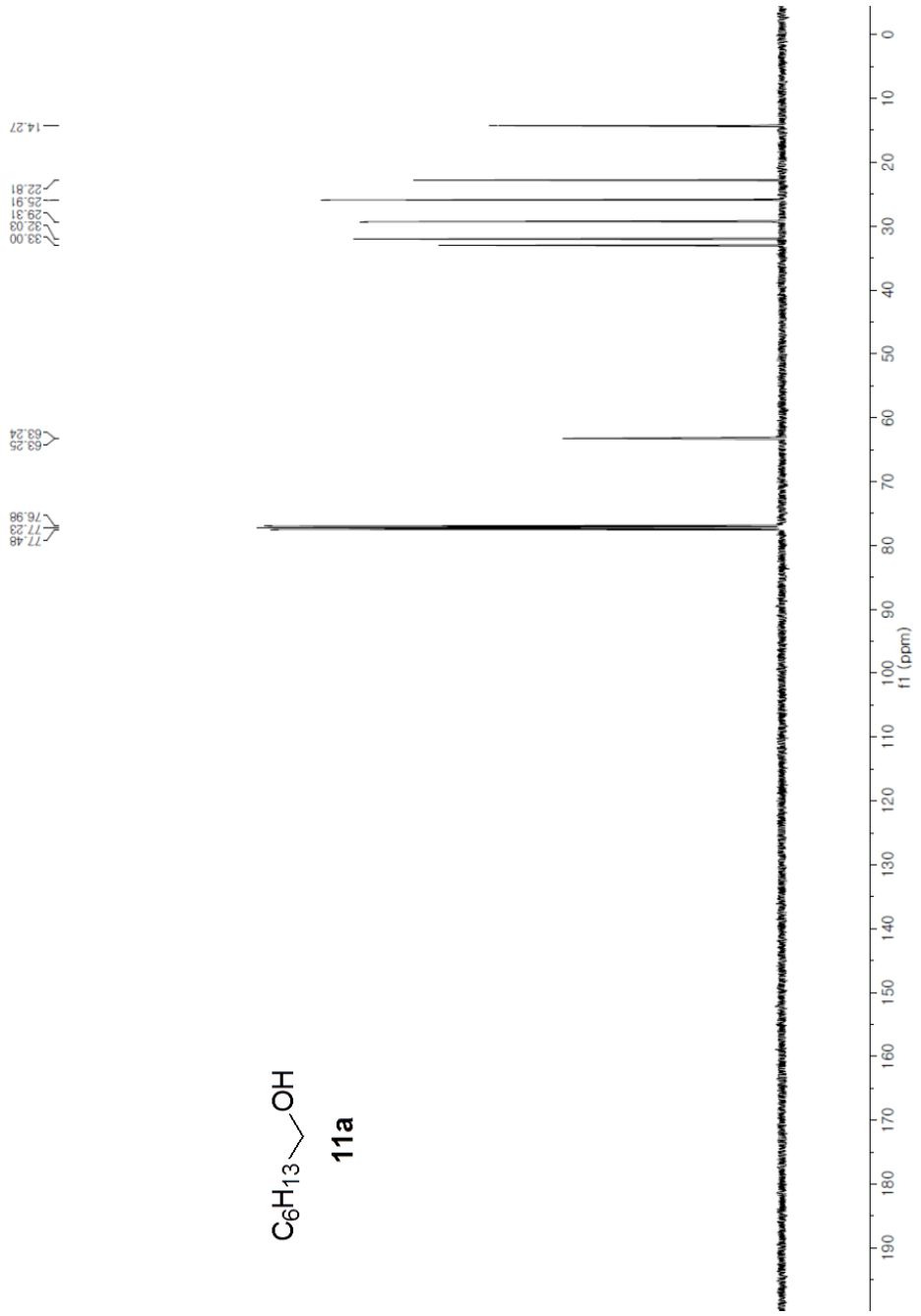
Compound 10a ^{13}C NMR



Compound 11a ^{1}H NMR



Compound 11a ^{13}C NMR



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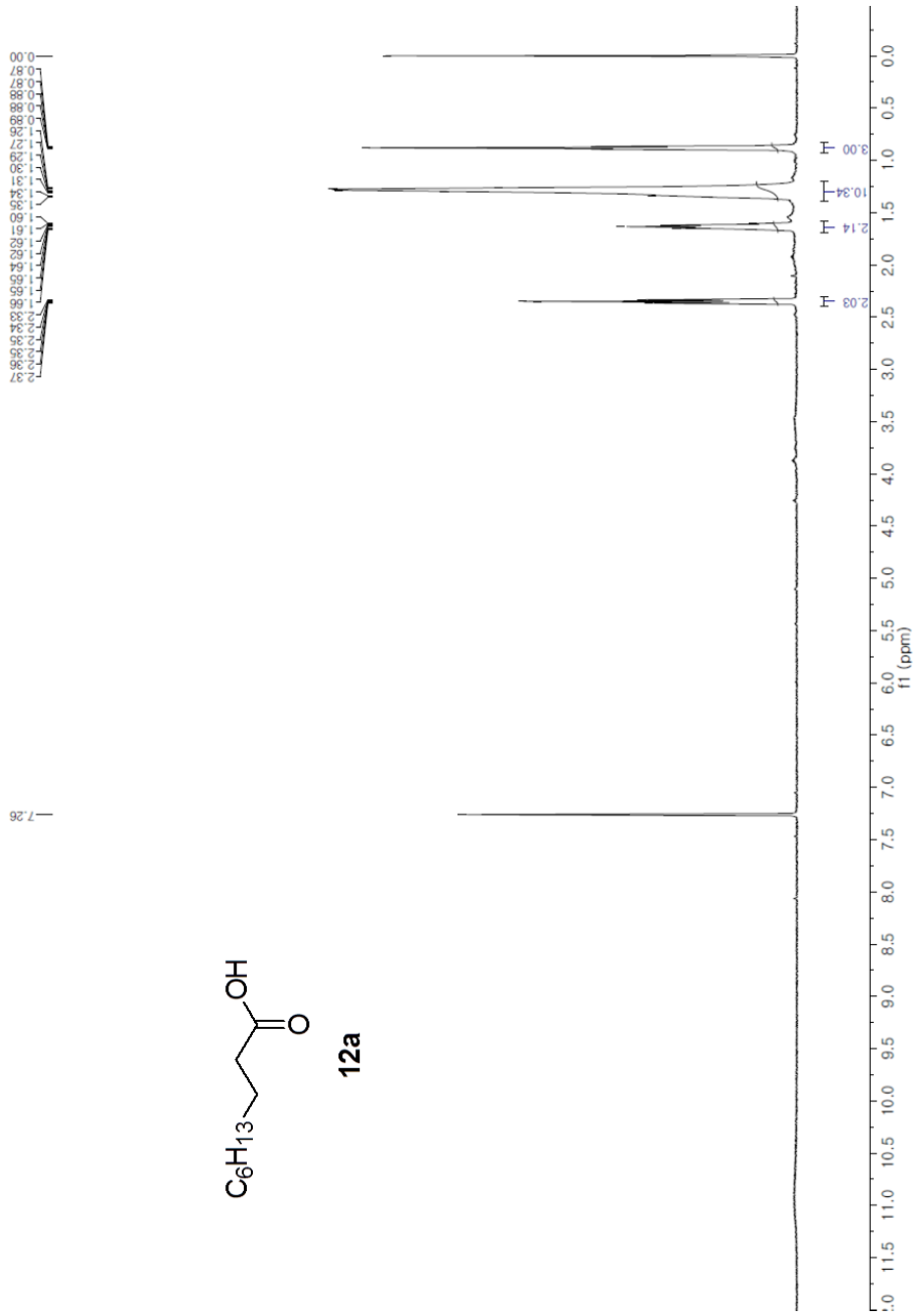
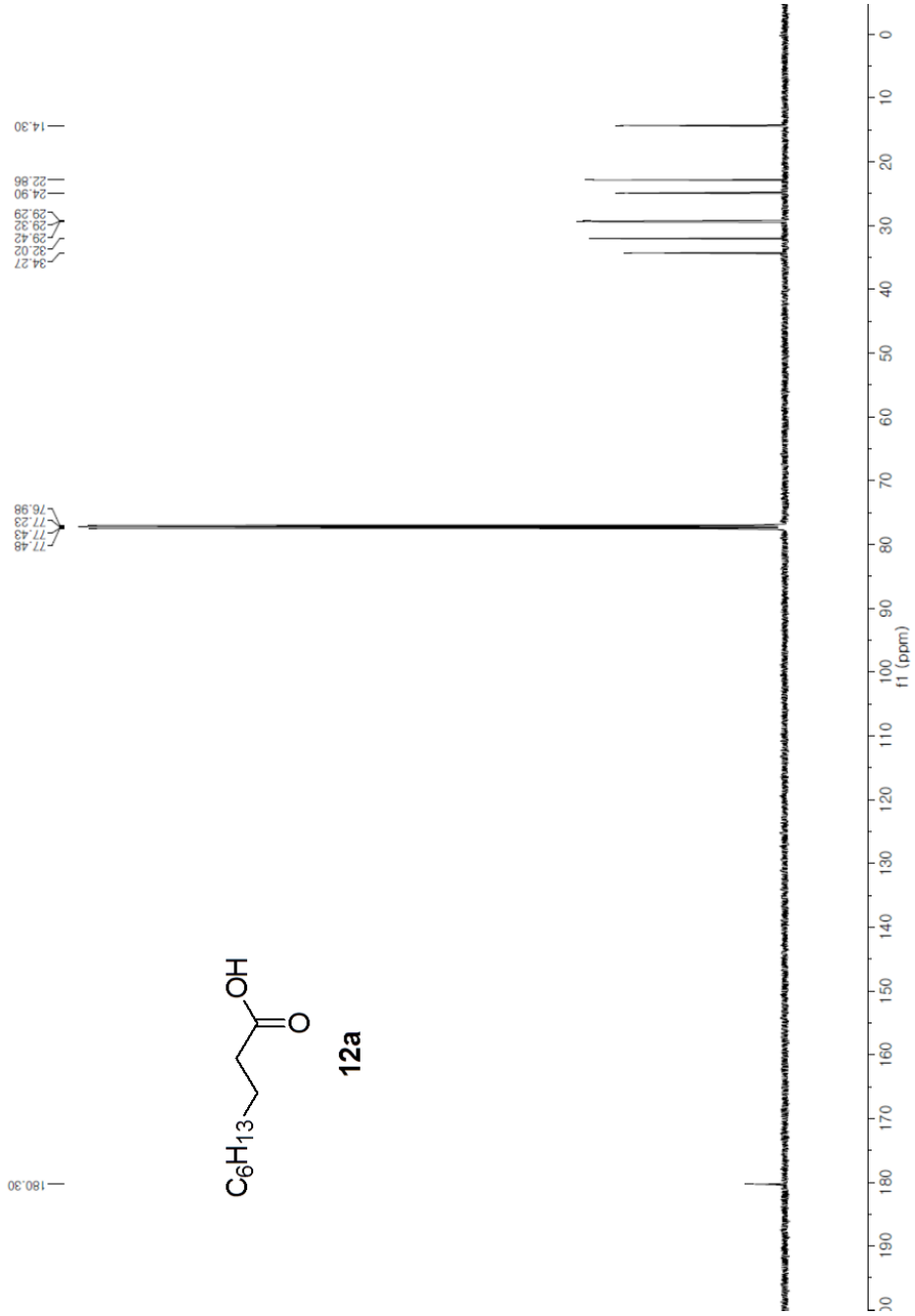
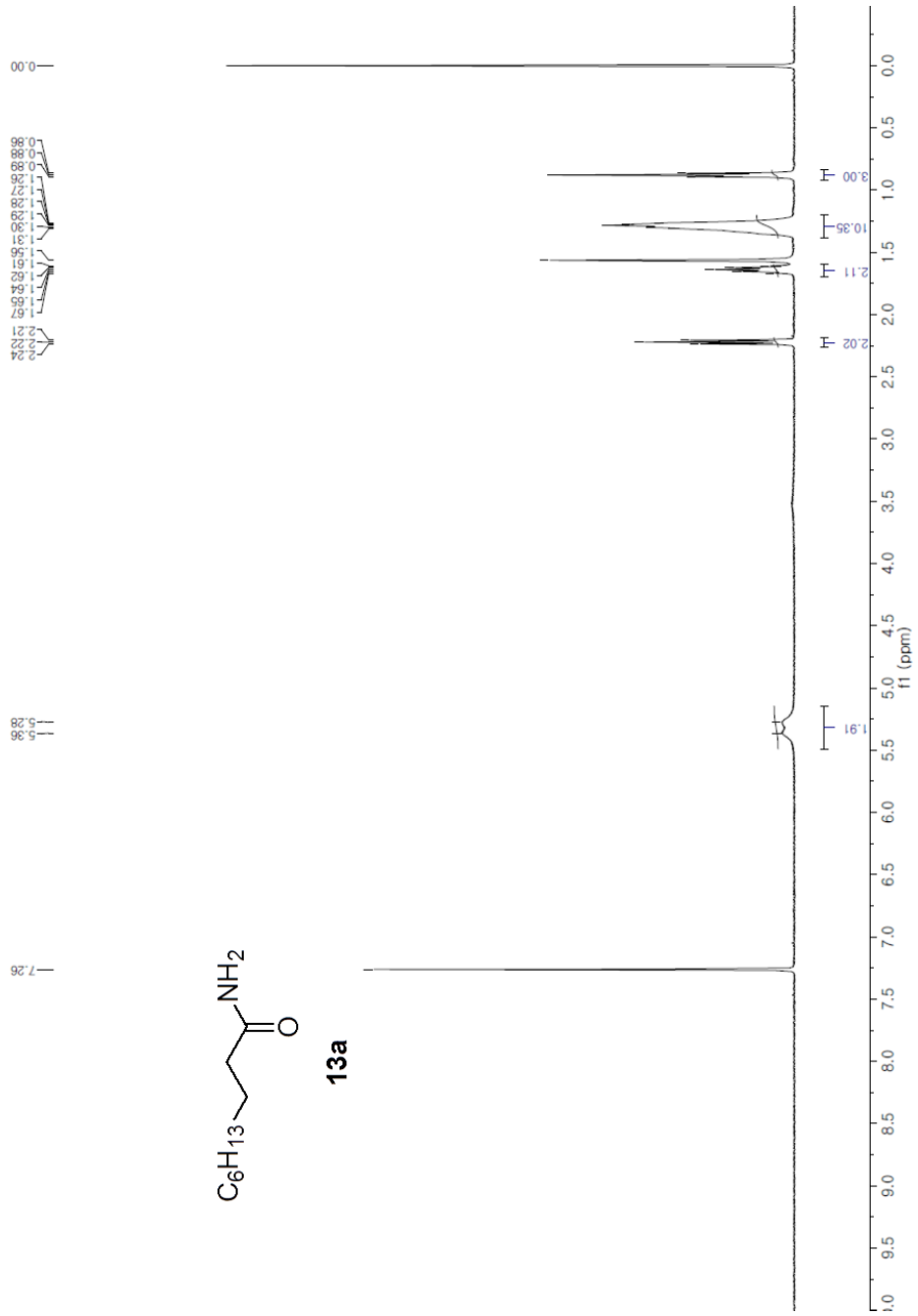


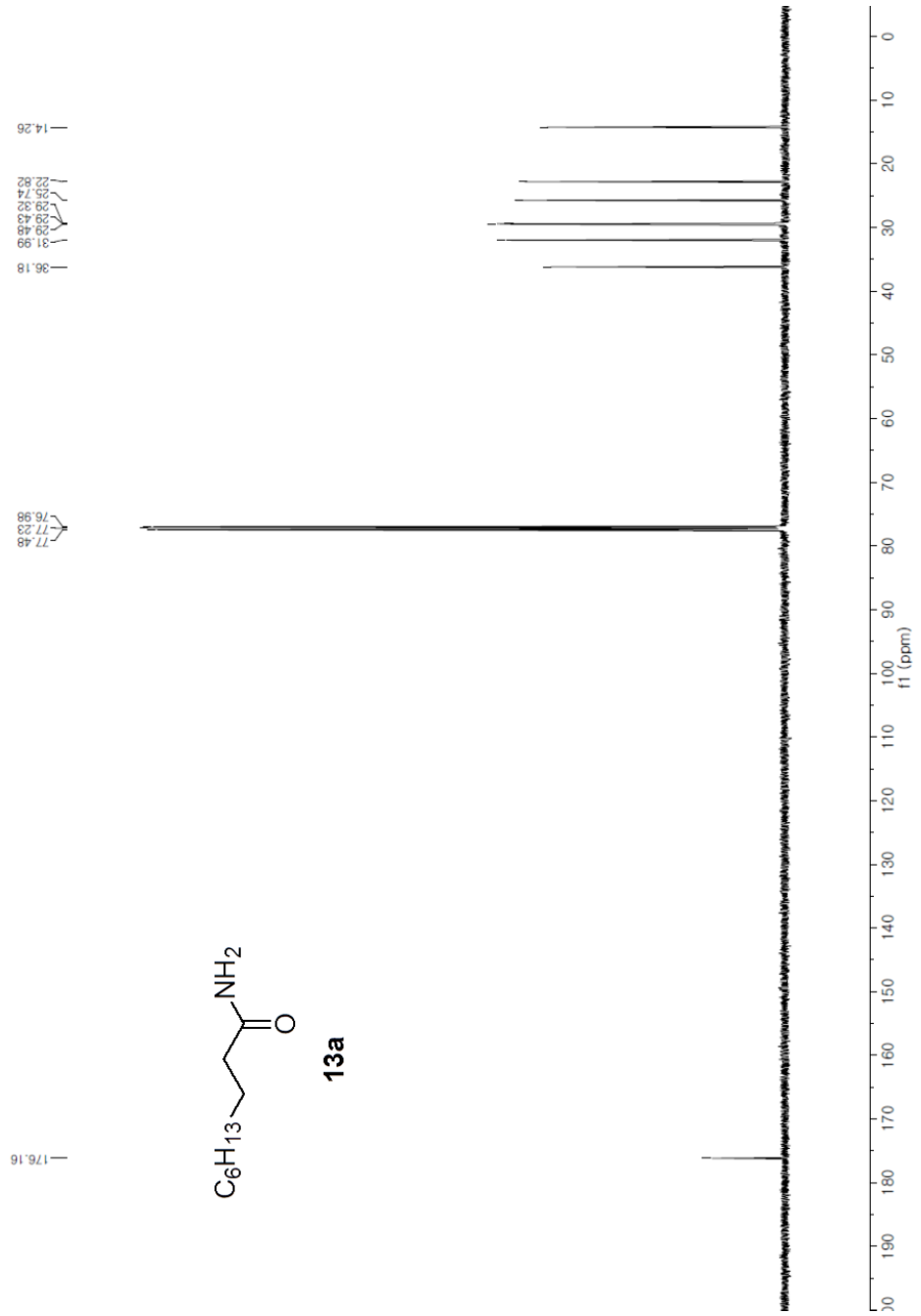
Compound 12a ^{13}C NMR



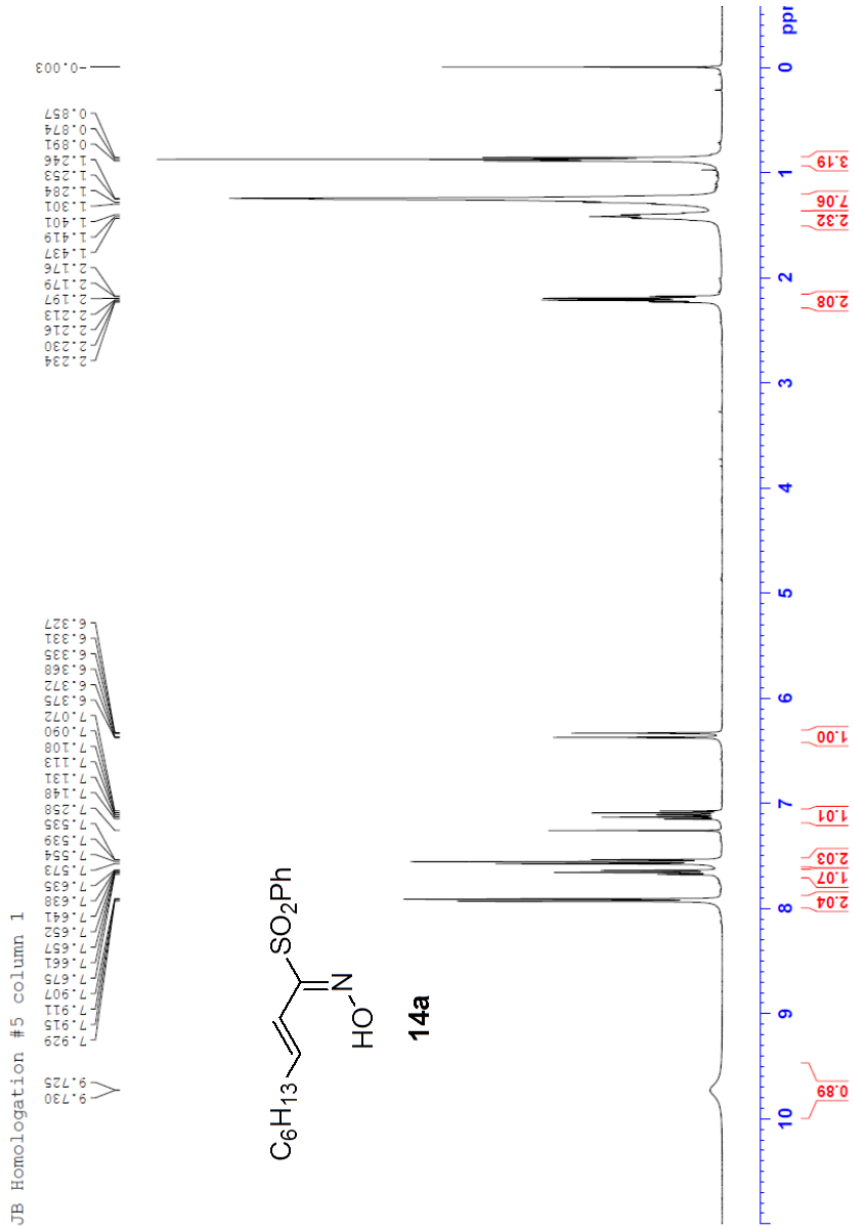
Compound 13a ^{1}H NMR



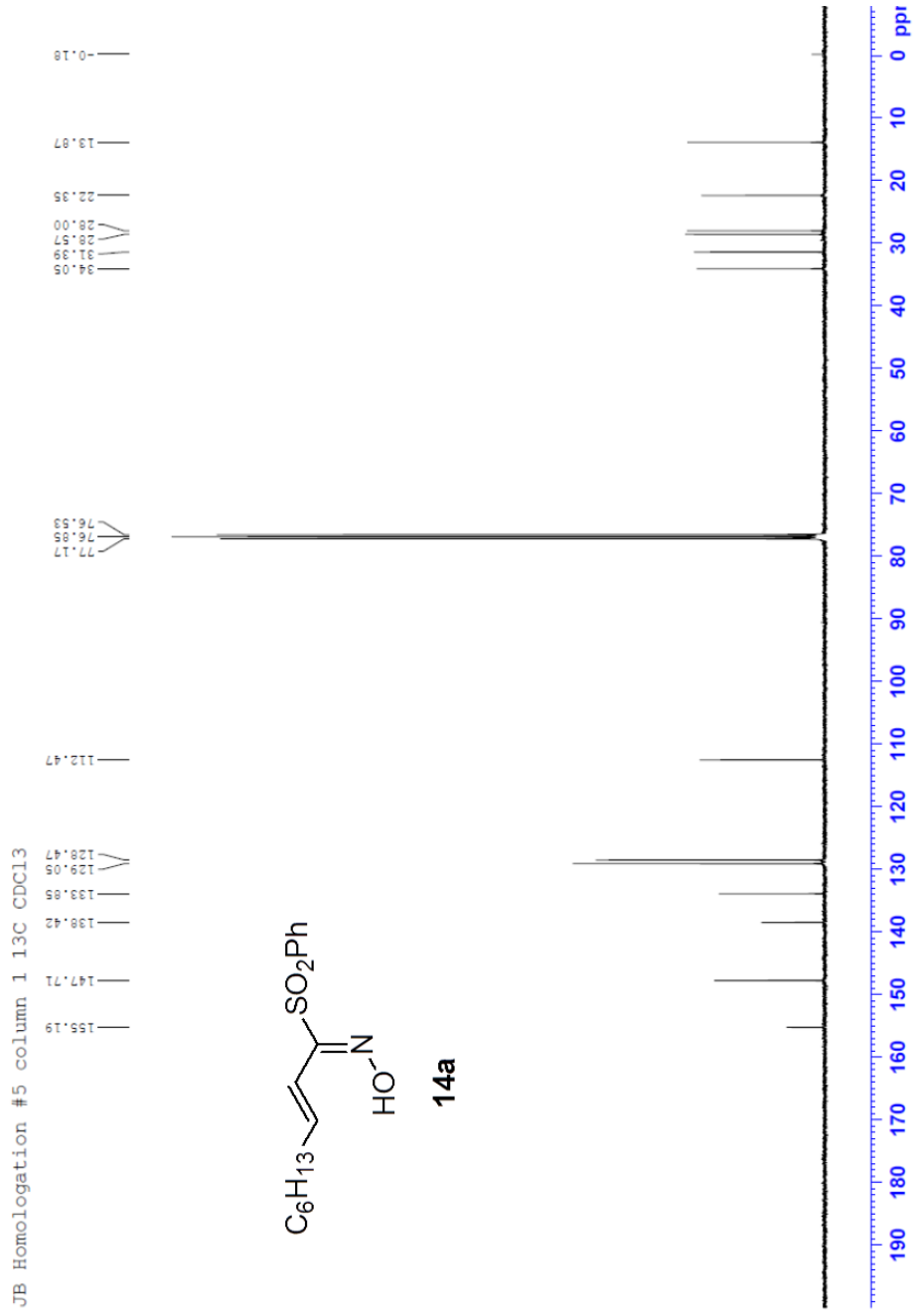
Compound 13a ^{13}C NMR



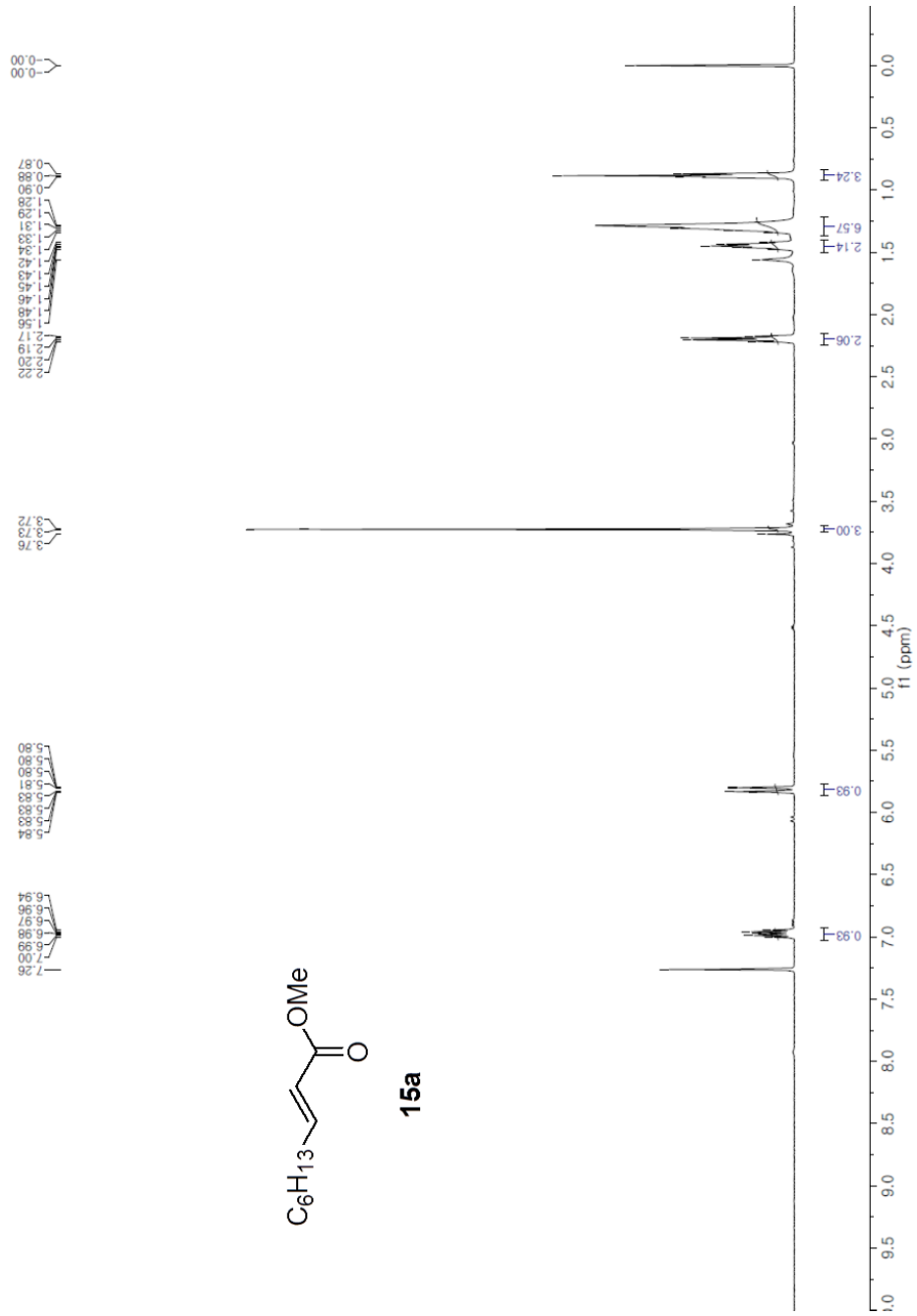
Compound 14a ^{1}H NMR



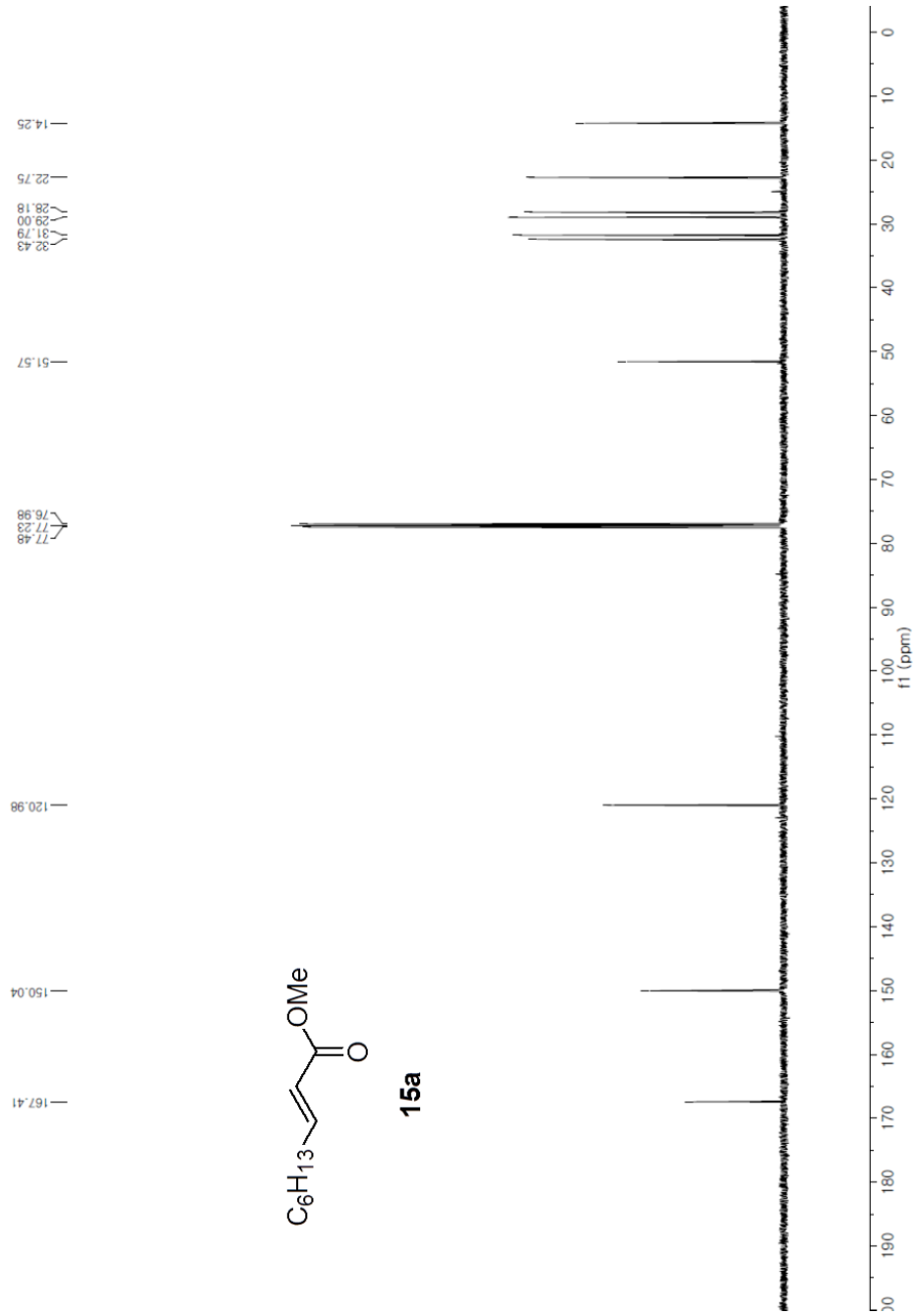
Compound 14a ^{13}C NMR



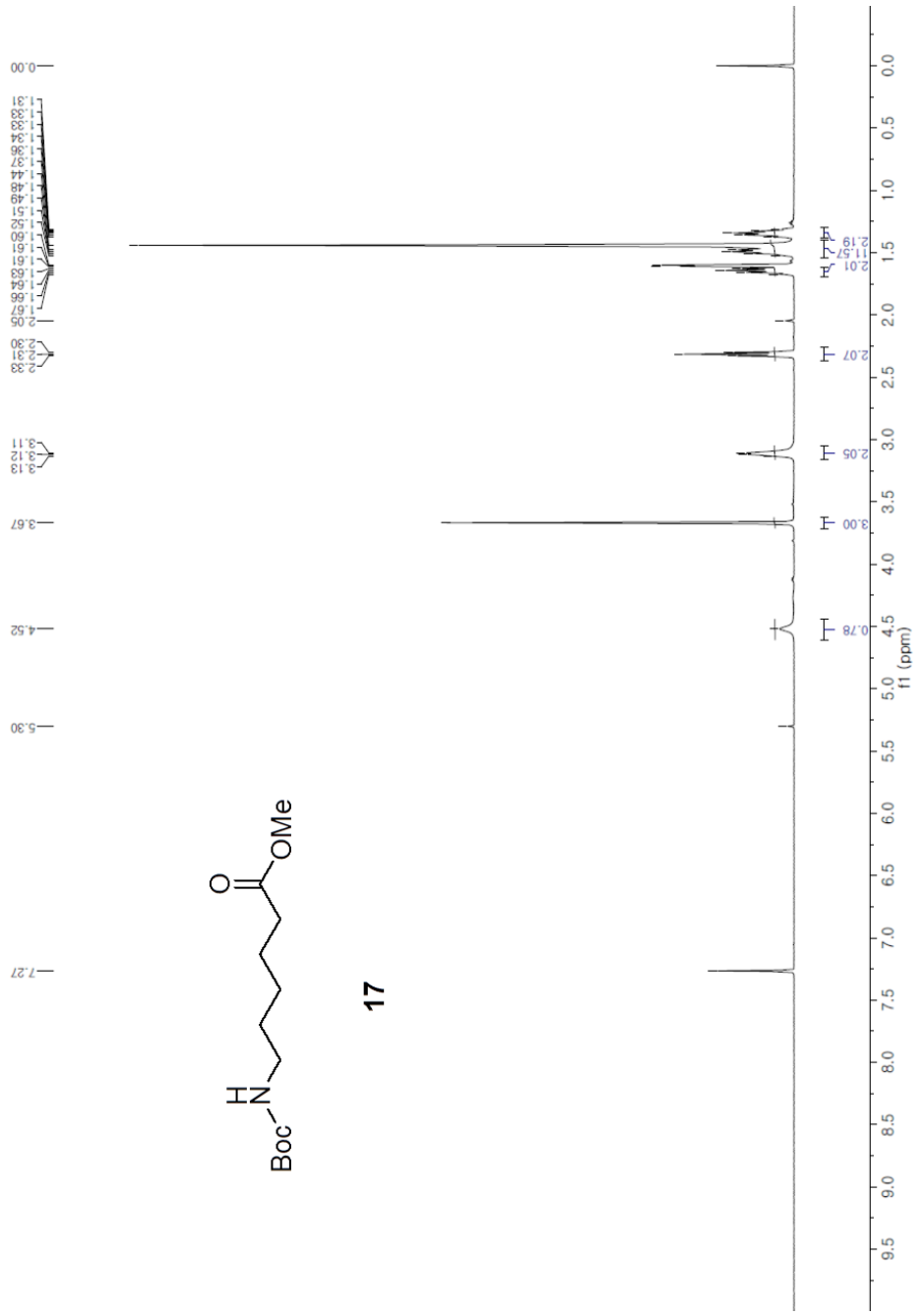
Compound 15a ^{1}H NMR



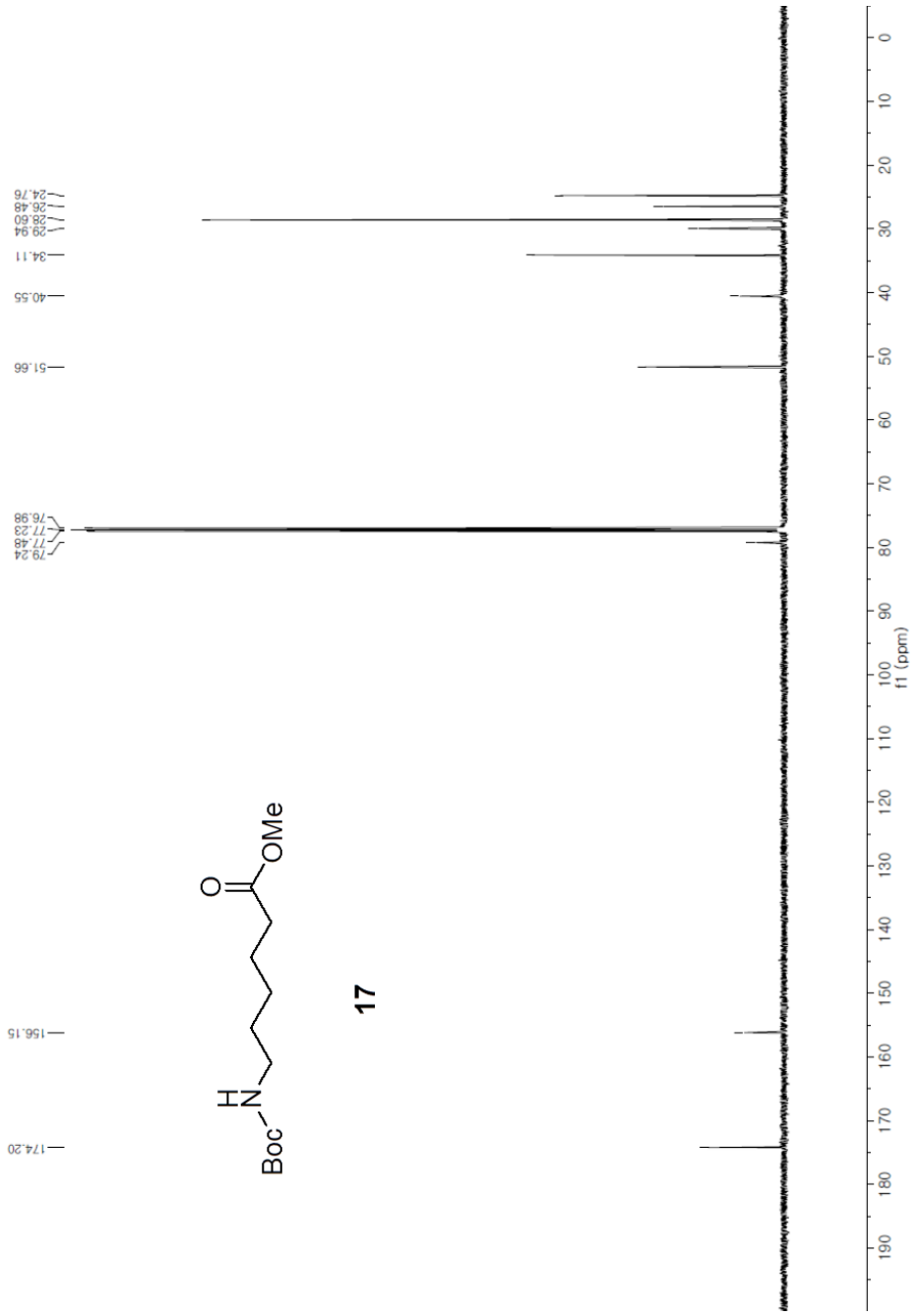
Compound 15a ^{13}C NMR



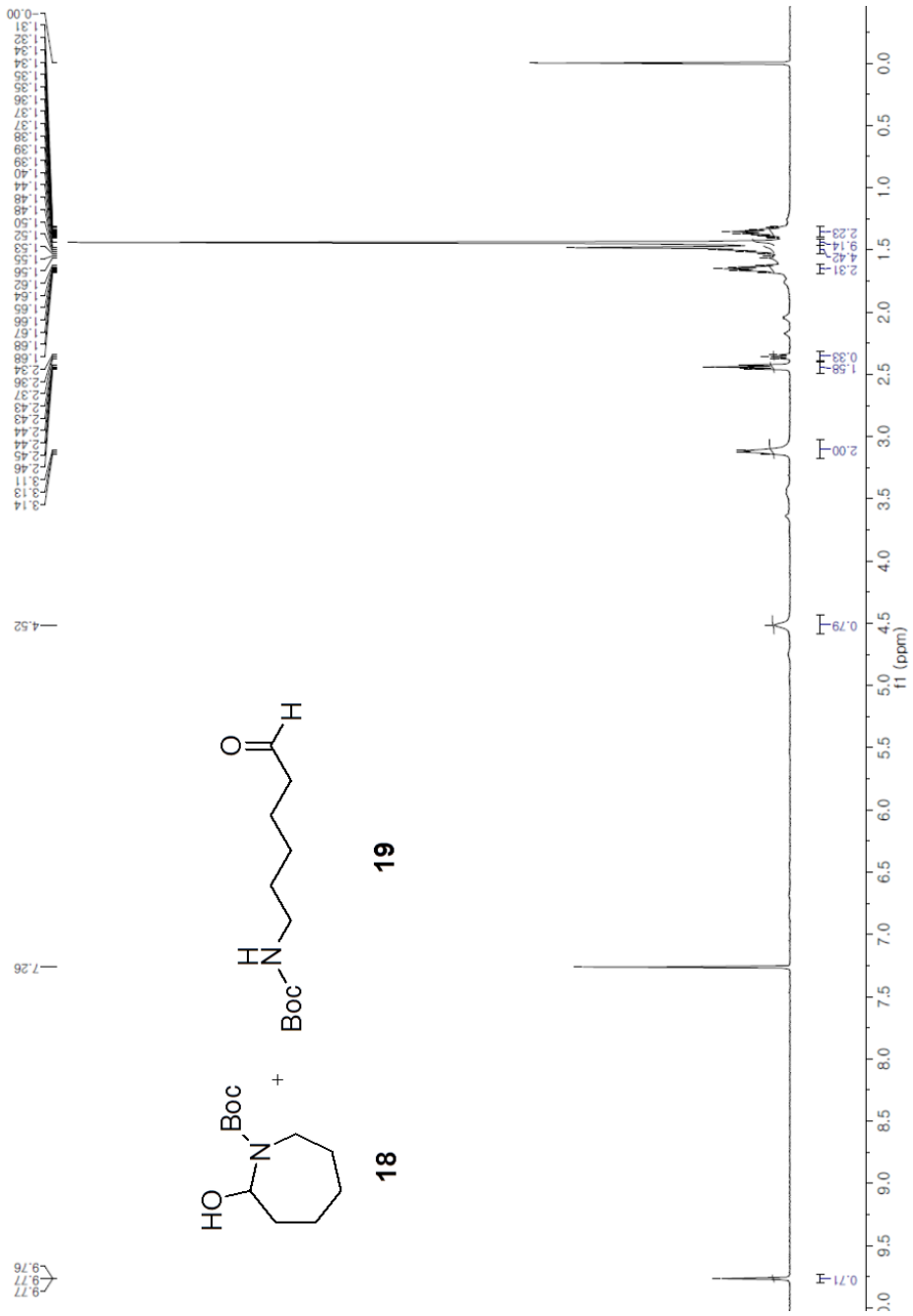
Compound 17 ^{1}H NMR



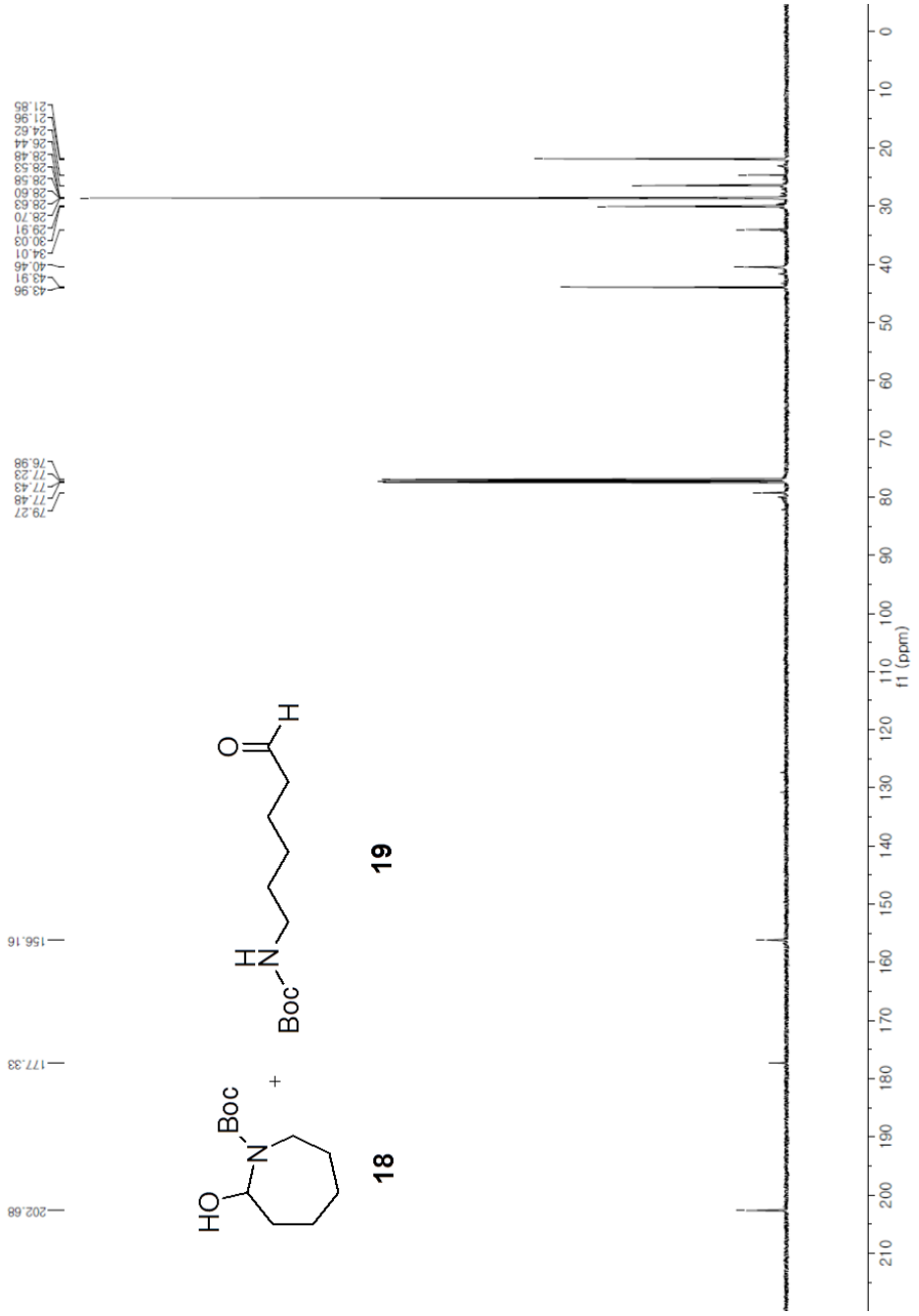
Compound 17 ^{13}C NMR



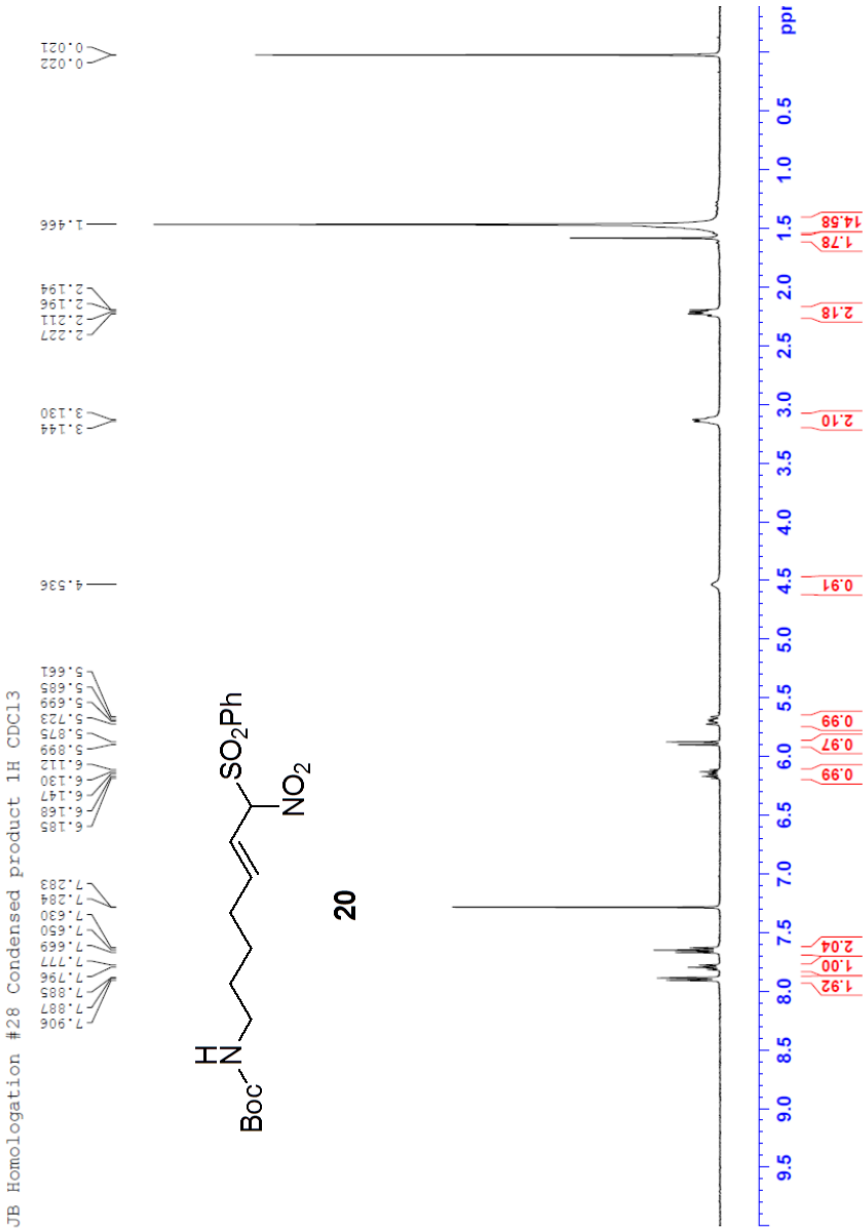
Compound 18 + 19 ^{1}H NMR



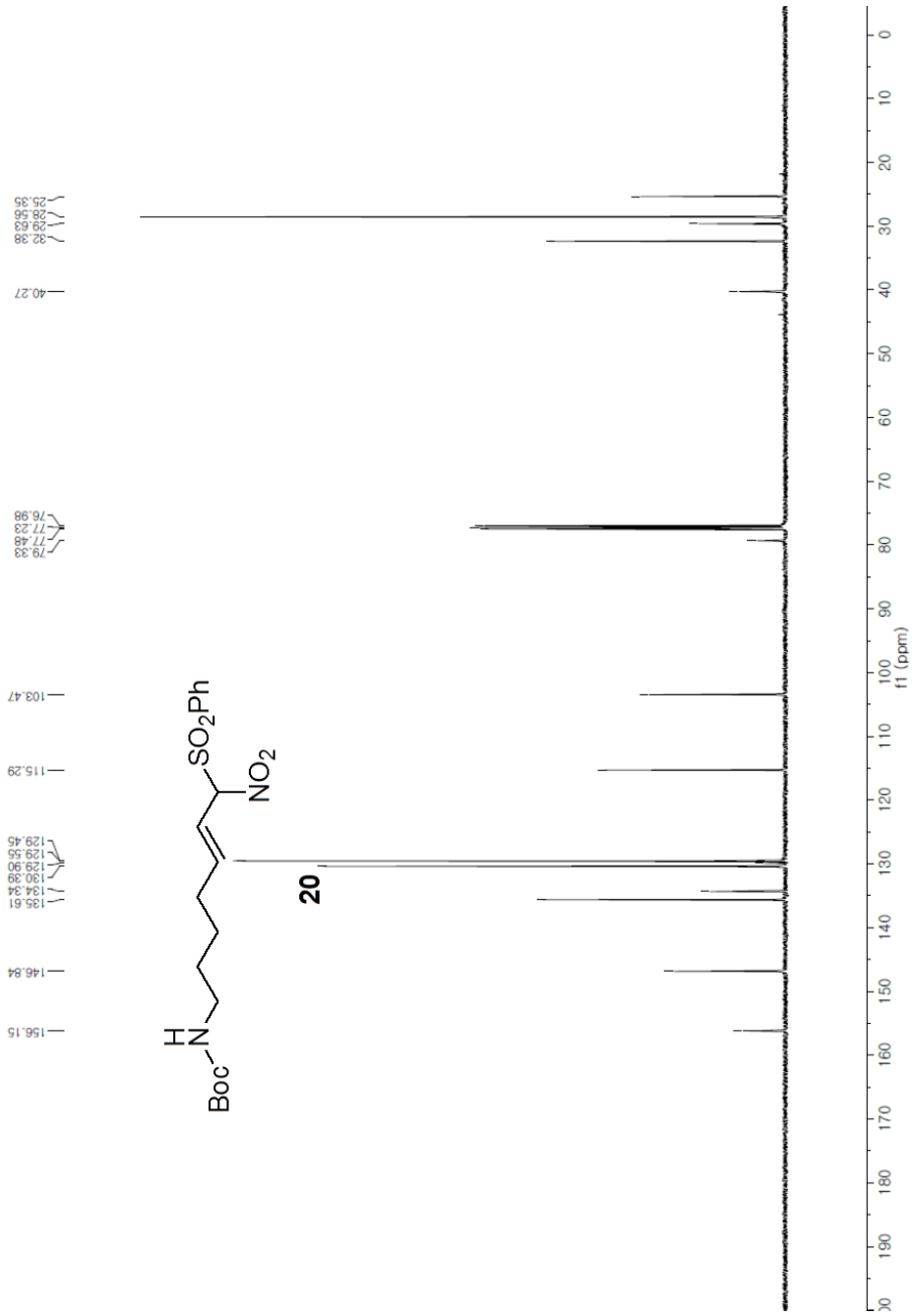
Compound 18 + 19 ^{13}C NMR



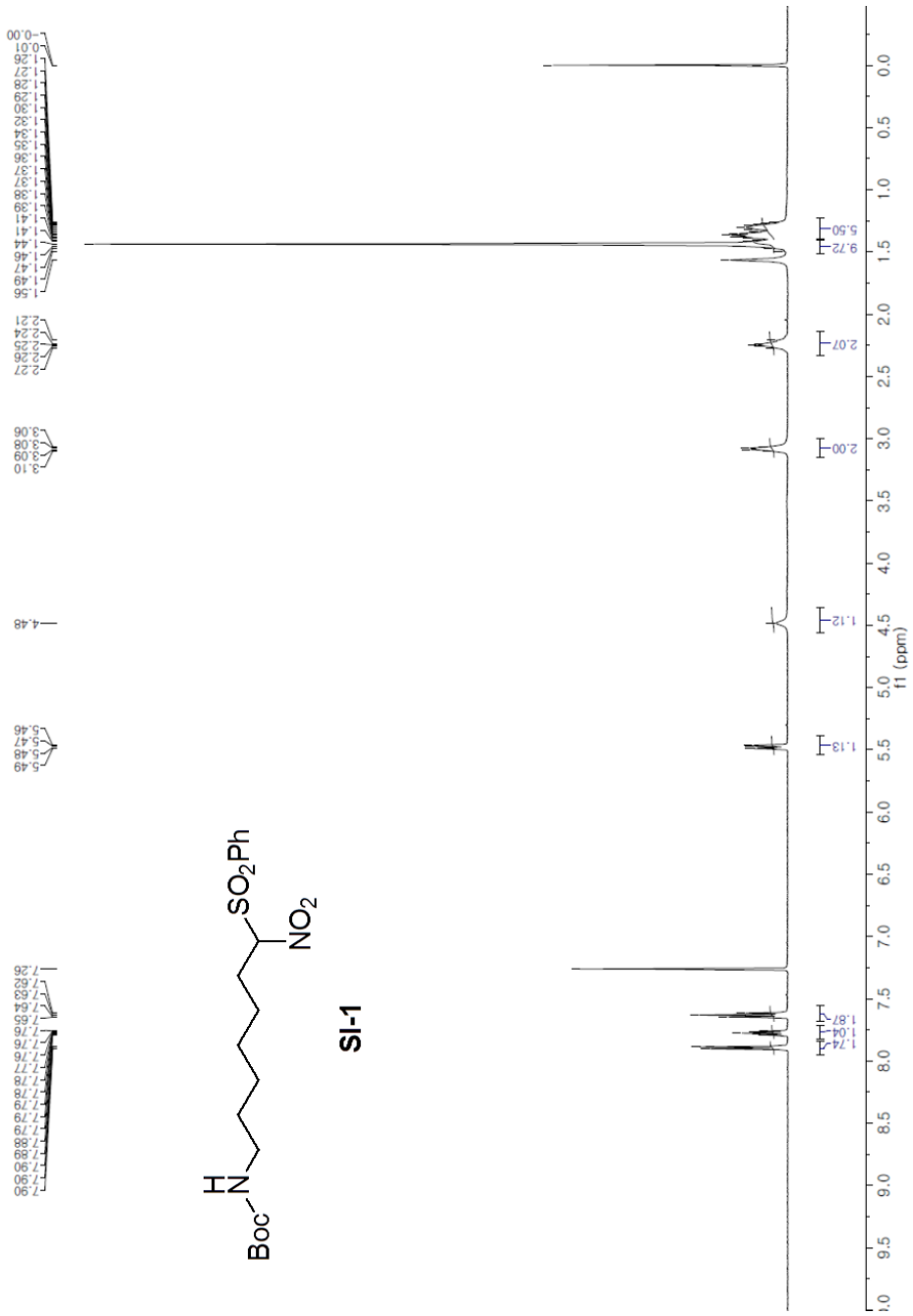
Compound 20 ^{1}H NMR



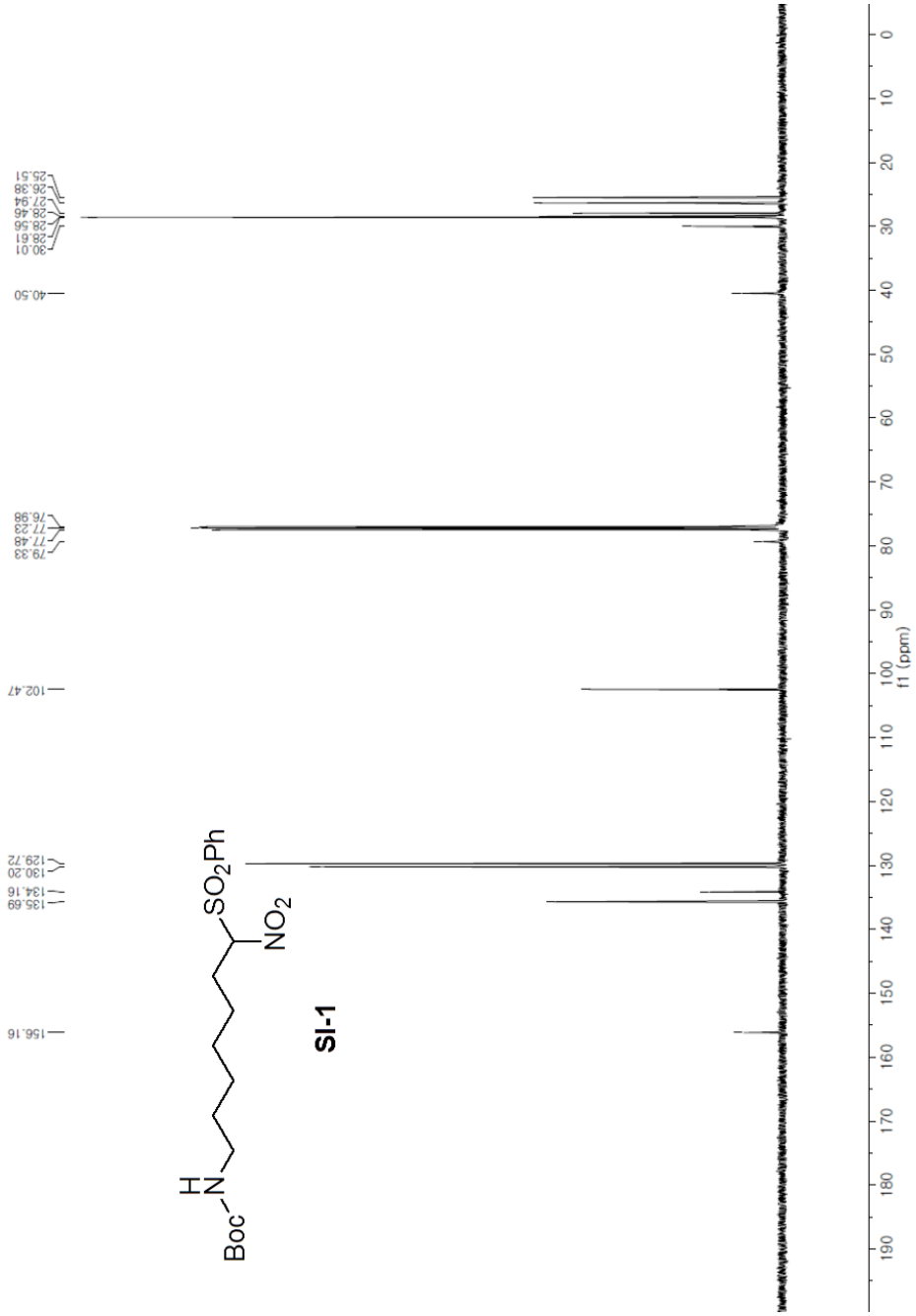
Compound 20 ^{13}C NMR



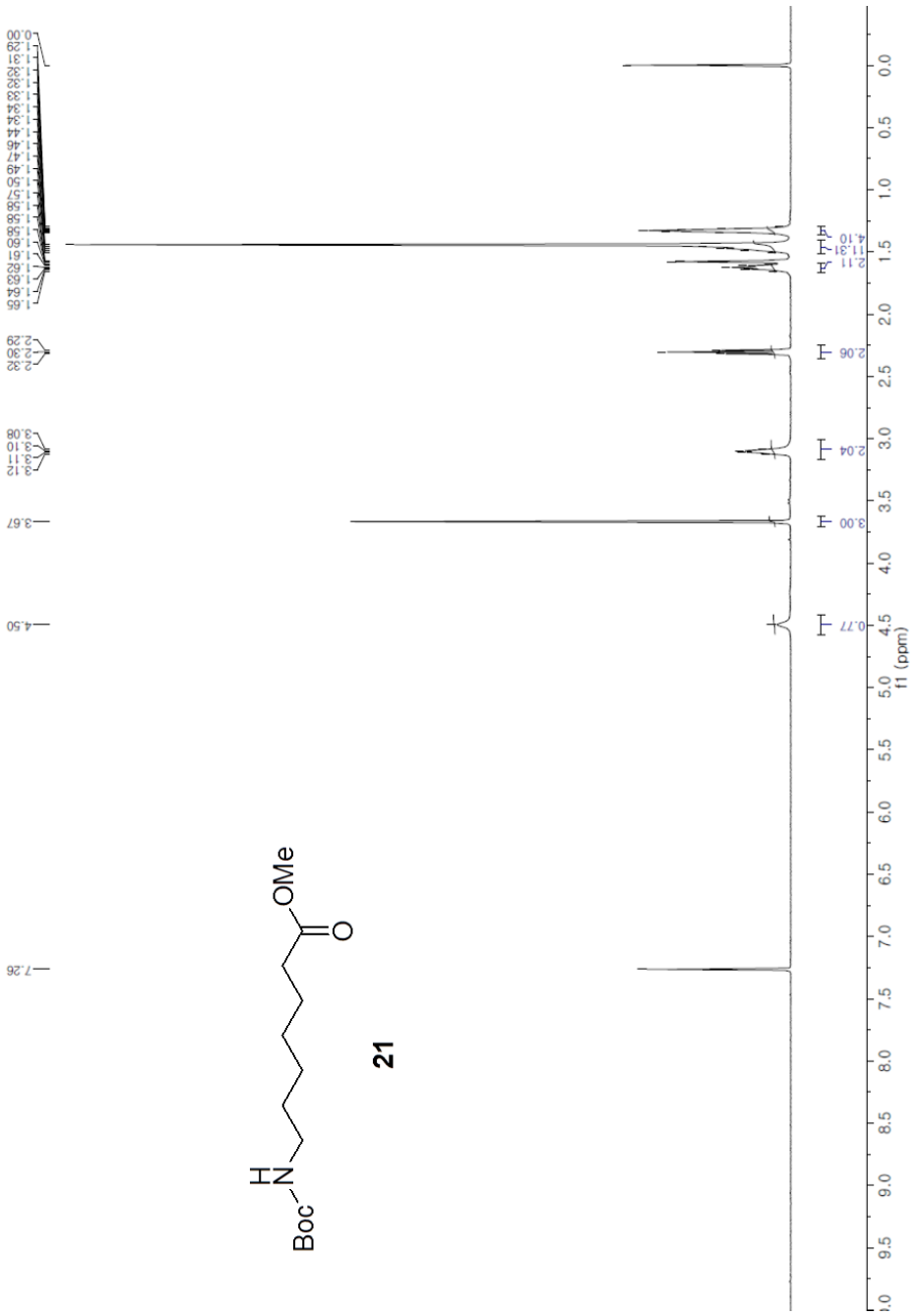
Compound SI-1 ^{1}H NMR



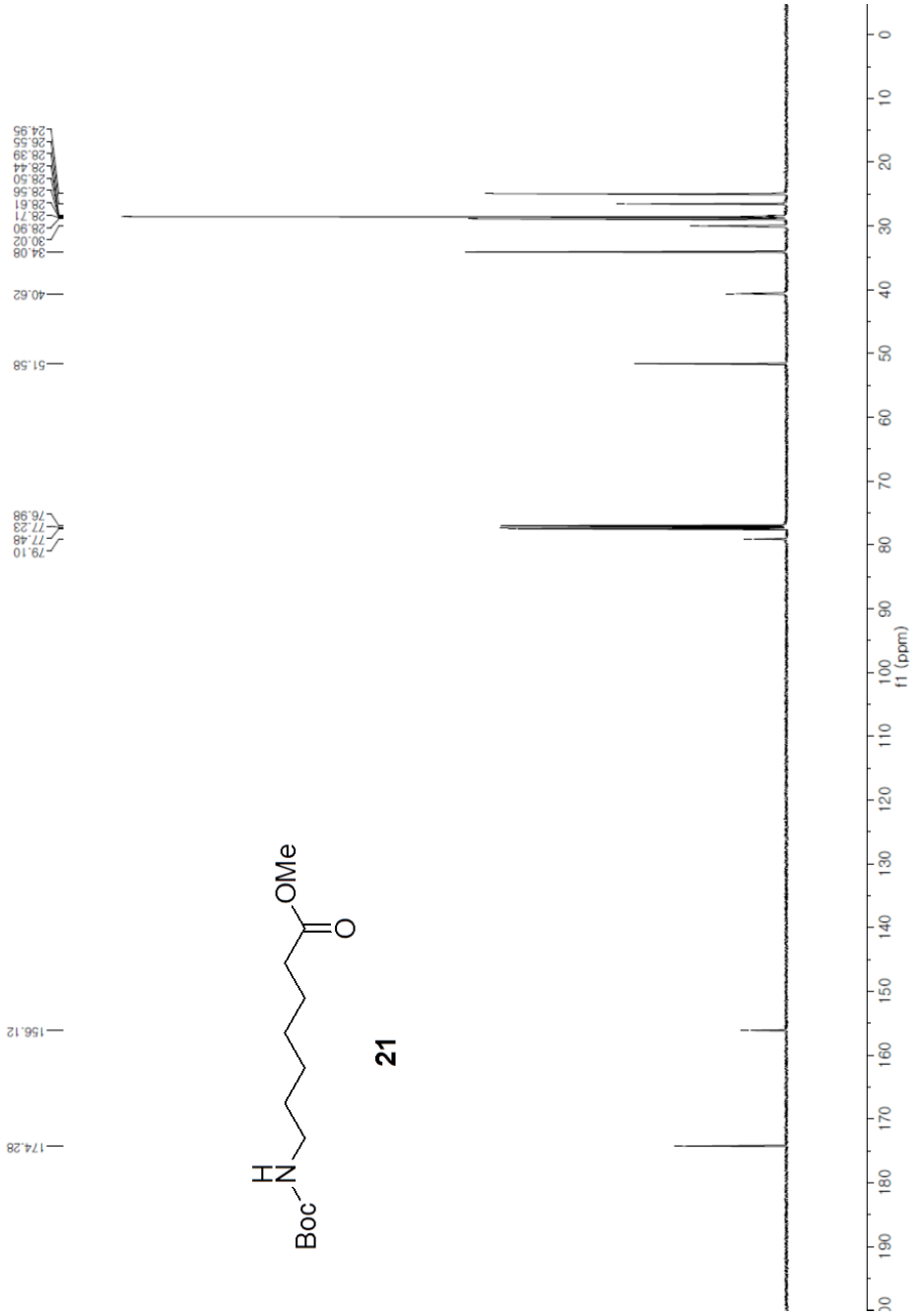
Compound SI-1 ^{13}C NMR



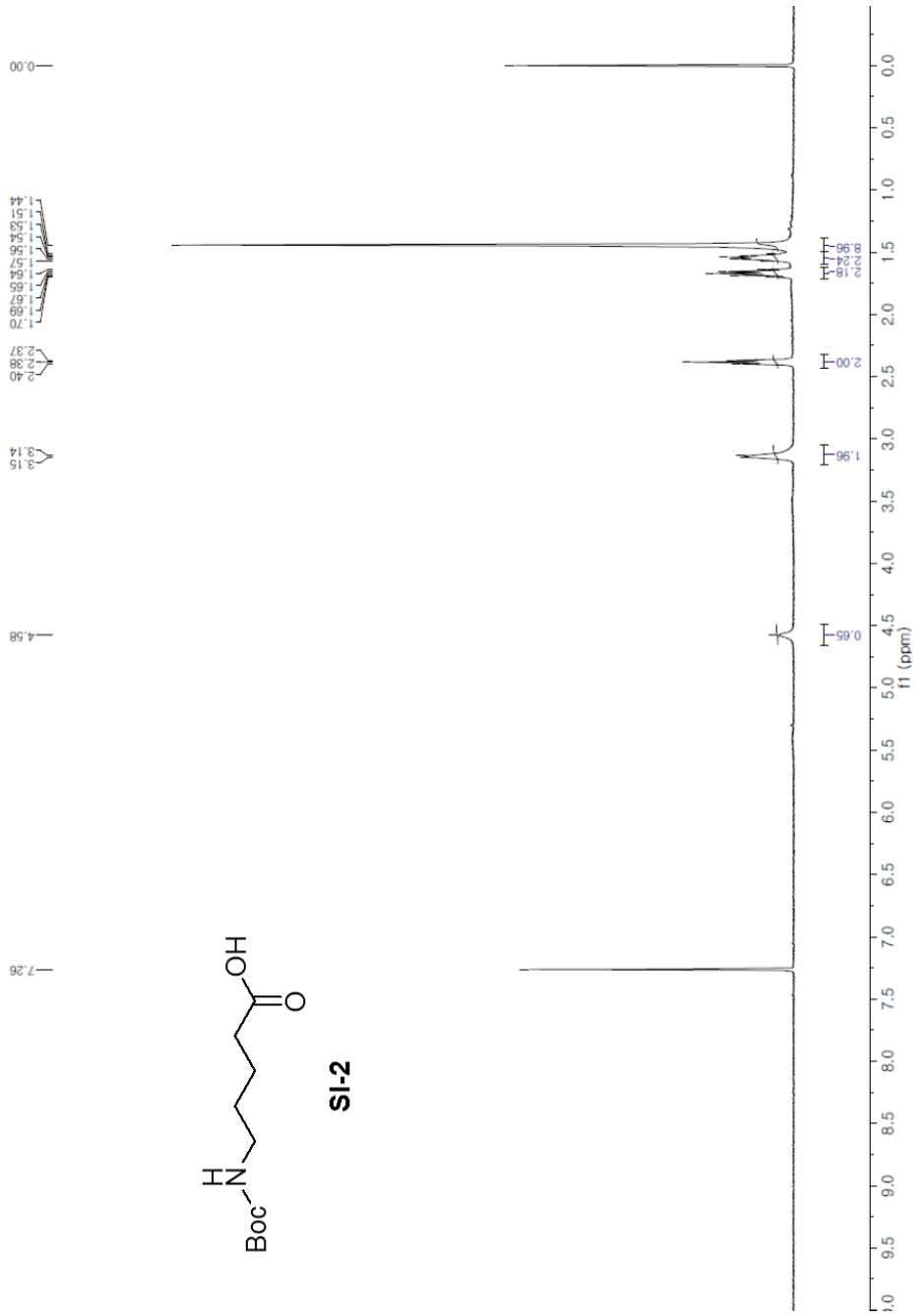
Compound 21 ^{1}H NMR



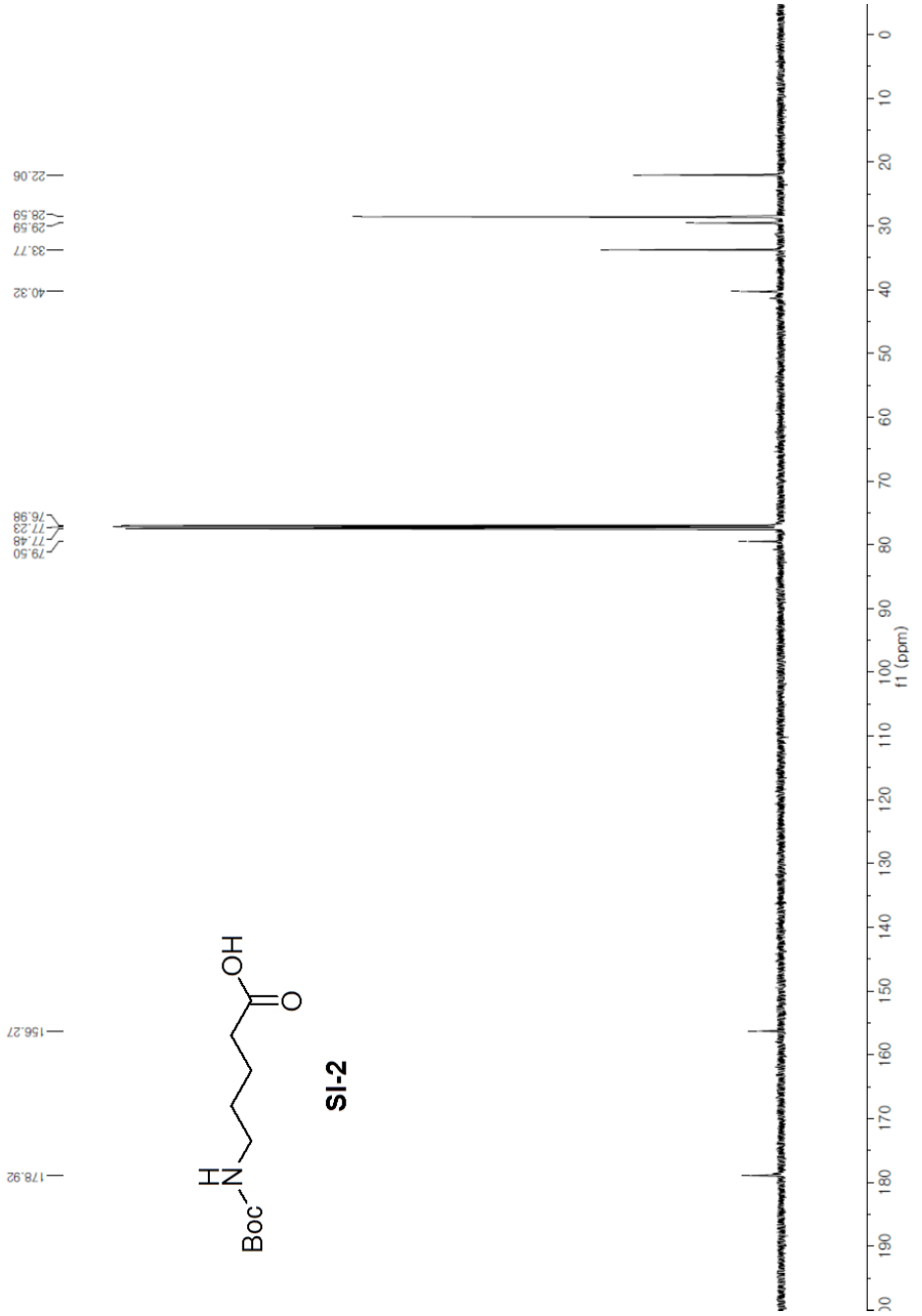
Compound 21 ^{13}C NMR



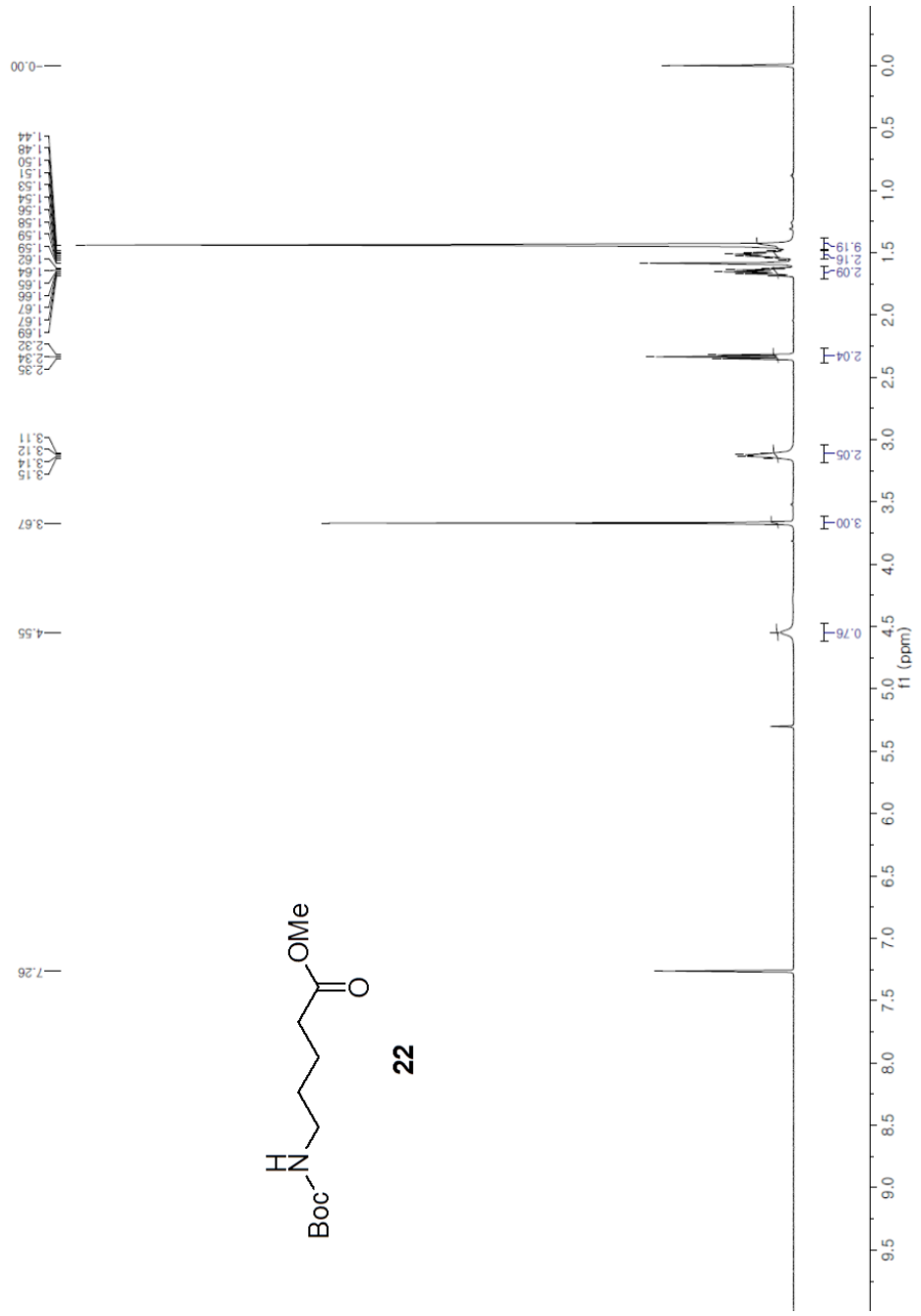
Compound SI-2 ^{1}H NMR



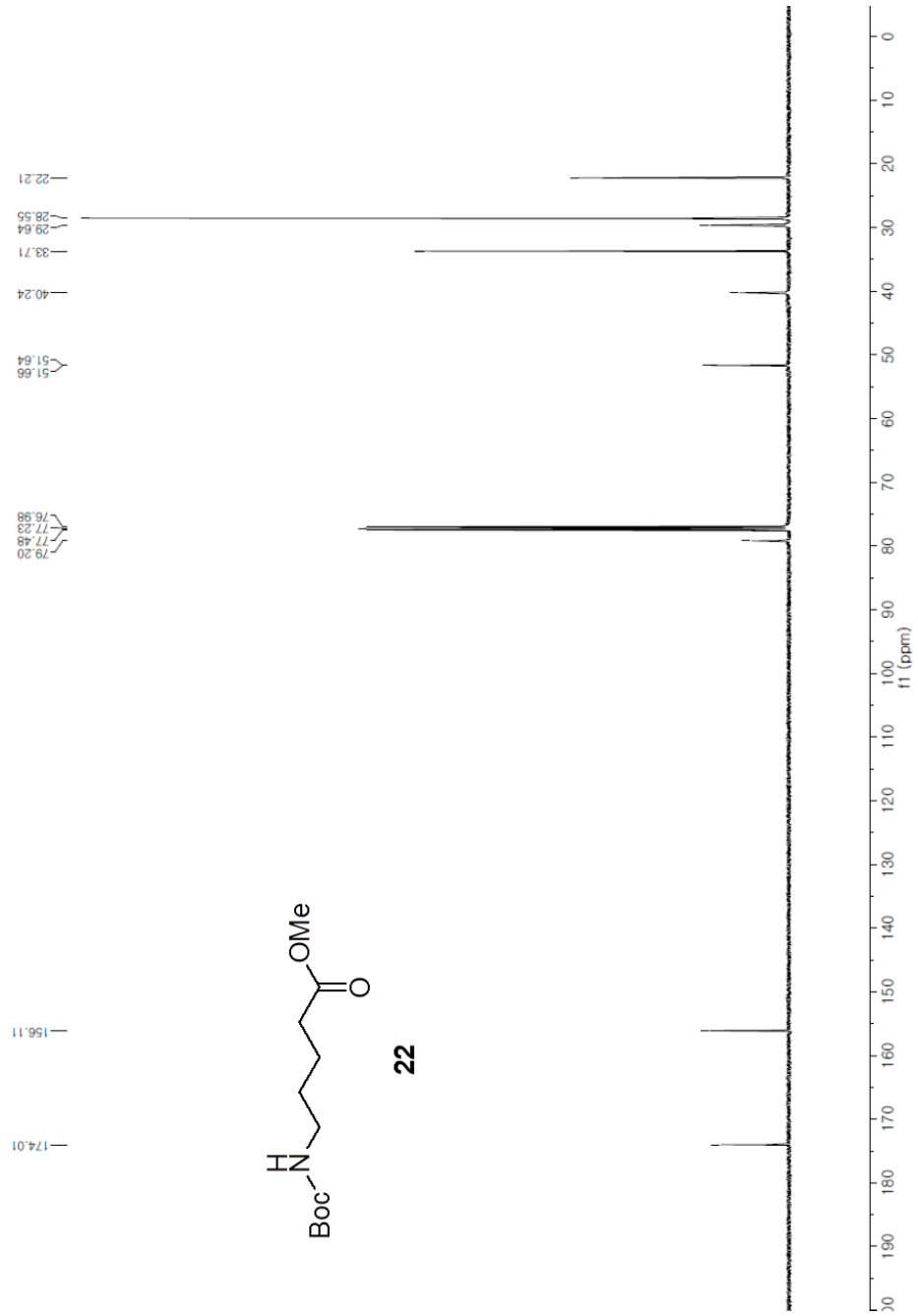
Compound SI-2 ^{13}C NMR



Compound 22 ^{1}H NMR



Compound 22 ^{13}C NMR



초록

쉽고 효율적인 작용기 변환은 오랫동안 유기 화학자들의 주요 연구 분야이자 목표였습니다. 그 중에서 카르보닐 화합물의 동족체화 합성법은 유기 화학자들이 이러한 목표를 달성하는 데 있어서 다양한 측면에서 접하게 되는 어려움들 중의 하나였습니다. 탄소 개수를 1개 증가시키는 동족체화 합성법과 탄소 개수를 1개 감소시키는 동족체화 합성법들이 다양하게 보고되었지만 여전히 몇 가지 단점들을 가지고 있습니다. 보고된 방법들은 종종 화합물에 존재하는 다양한 작용기와 양립할 수 없는 격렬한 반응 조건을 사용하여 적용 가능한 기질이 제한적이거나, 취급하기 어려운 시약이나 합성법이 사용되어 많은 양, 심지어는 적은 양을 합성할 때도 어려움을 겪는 경우가 있습니다. 무엇보다도 탄소 개수를 1개 증가시키는 동족체화 합성법과 탄소 개수를 1개 감소시키는 동족체화 합성법을 동일한 합성 단위체 또는 동일한 중간체를 사용하여 동시에 수행된 경우는 없었습니다. 우리는 지방족 알데히드와 페닐술포닐니트로메탄을 프롤린 촉매 존재 하에서 반응시켜 부가 반응, 제거 반응, 이성질체화의 연속적인

반응을 통해 β,γ-불포화 α-니트로술폰을 좋은 수율로 얻을 수 있음을 발견하였고, 이 반응을 활용하여 β,γ-불포화 α-니트로술폰을 중간체로 사용하여 지방족 알데히드의 탄소 개수를 1개 증가시키는 동족체화와 탄소 개수를 1개 감소시키는 동족체화를 동시에 할 수 있는 합성법을 개발했습니다. 온화한 조건 하에서도 다양한 지방족 알데히드로부터 탄소 개수가 1개 증가되거나 탄소 개수가 1개 감소된 동족 계열의 카르보닐 화합물을 양호한 수율로 얻을 수 있었습니다. 그리고 이 합성법을 활용하여 히스톤 탈아세틸화 효소 저해제 합성에 필요한 두 개의 중간체를 6단계를 거쳐 각각 33%, 35%의 수율로 효율적으로 합성할 수 있었습니다. 더 나아가 이 동족체화 합성법을 적용하기 어려운 작용기를 가지고 있는 기질들을 위하여 대체적인 동족체화 합성법도 마련했습니다. 이러한 합성법은 상황에 따라 유연하게 적용이 가능하여 카르보닐 화합물의 합성 가능성을 증가시키고 탄소-탄소 결합을 형성시키는 화학 반응의 선택성을 다양화할 수 있을 것으로 생각됩니다.

주요어: 동족체화 합성법, 페닐술포닐니트로메탄, β,γ-불포화 α-니트로술폰

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