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Studies in electrophilic cyclization, palladium migration and cationic polymerization

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by

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LIST OF ABBREVIATIONS

Aq	aqueous
br s	broad singlet
Bu	butyl
C	celsius
Cat.	catalytic
calcd	calculated
D	deuterium
D	days
D	doublets
Dd	doublet of doublets
DCM	dichloromethane
DMA	*N,N*-dimethylacetamide
DME	ethylene glycol dimethyl ether
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppm	1,2-bis(diphenylphosphino)methane
Dt	doublet of triplets
DVB	divinylbenzene
EI	electron ionization
Eq	equation
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate

eV	electron volt
G	gram
GC	gas chromatography
GC-MS	gas chromatograpgy-mass spectroscopy
CsPiv	cesium pivatae
H	hours
H	hydrogen
Hex	hexanes
HRMS	high-resolution mass spectroscopy
Hz	hertz
IR	infrared
M	multiplet
M	meta
Me	methyl
Mg	milligram
MHz	mega hertz
mL	milliliters
mmol	millimole(s)
mol	moles
Mp	melting point
Nm	nanometers
NMR	nuclear magnetic resonance
O	ortho
P	para

Pd(0)	palladium(0)
Ph	phenyl
PPh_3	triphenylphosphine
Q	quartet
rpm	rotation per minutes
S	singlet
satd	saturated
SEM	scanning electron microscopy
S_N1	substitution, nucleophilic, unimolecular
Soln	solution
T	triplets
Td	triplet of doublets
TEM	transmission electron microscopy
tert	tertiary
t-Bu	*tert*-butyl
temp	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet

GENERAL INTRODUCTION

In the last few years, electrophilic cyclizations of alkynes using halogens and organometallic reagents, particularly those derived from palladium and copper, have emerged as a useful tool for the synthesis of many heterocyclic ring systems. These methodologies have been applied to both carbon and heteroatom bond formation. These reactions have also been extensively used for the formation of C-C bonds, a particularly important bond formation in organic synthesis. Electrophilic cyclizations using iodine and bromine as electrophiles introduce a halide moiety into the heterocycle at positions which are difficult to obtain by other methodologies. These halide-containing heterocycles can then be subsequently functionalized using metal exchange reactions or transition metal-catalyzed coupling reactions.

Palladium- and other transition metal-catalyzed reactions have also been extensively applied in C-H bond activation reactions. Among transition metal-catalyzed reactions, those of palladium are the most extensively used due to their tolerance of many important functional groups and the metals low toxicity. Although palladium is a relatively expensive metal, it is still attractive in organic synthesis, since it can be used catalytically. Palladium-catalyzed C-H bond activation can occur by unique processes, such as the formation of a five- or six-membered ring palladacycle. These five- and six-membered ring palladacycles can undergo reductive elimination to form four- or five-membered heterocyclic ring systems or they can undergo 1,4- or 1,5-palladium migrations. These “through space” palladium migration reactions provide a unique way

to activate a carbon-hydrogen bond and introduce palladium at various positions in the molecule, which are difficult to achieve otherwise.

The Larock group has done extensive basic research on organopalladium methodologies and electrophilic cyclizations. Our group has utilized these methodologies for the formation of various heterocycles and carbocycles, such as indoles, benzofurans, furans, benzo[*b*]thiophenes, carbazoles, dibenzofurans, xanthones, naphthalenes and fluorenones. This dissertation not only serves to extend the scope and utility of these methodologies, but it also discusses a unique way to form fibrous and tubular carbon structures by the cationic polymerization of divinylbenzene and its copolymerization with styrene.

Dissertation Organization

This dissertation is divided into four chapters and each chapter is written as an independent paper following the guidelines of the *Journal of Organic Chemistry* for the first and third chapters, *Tetrahedron* for the second chapter, and *Chemistry of Materials* for the fourth chapter. The papers are composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgements and references.

Chapter 1 extends the earlier work of the Larock group on electrophilic cyclizations, which was previously applied to the synthesis of indoles, benzo[*b*]thiophenes and benzofurans, and now generates the benzo[*b*]selenophene ring system. The reaction has been optimized and the scope of the reaction has been studied by employing a number of different alkynes. The mechanism of the reaction has been

studied by isolating an intermediate and studying its decomposition using proton NMR spectroscopy.

Chapter 2 presents recent results on a novel palladium-catalyzed selective C-H activation of a benzylic position, whereas Chapter 3 presents the C-H activation of an acyl position. Both of these chapters give a detailed account of the methodology, which uses "through space" 1,4-palladium migration as a key step. Different substrates undergoing these new palladium migration reactions are investigated. Detailed mechanisms are proposed and studied by deuterium labeling experiments.

Chapter 4 gives a detailed account of the formation of organic nanotubes, one of the most versatile structures in nanotechnology. A method to prepare fibrous structures and hollow tubes is described using the cationic polymerization of commercially available starting monomers. The effect of temperature, stirring speed, stoichiometry and solvents on the morphological properties of the polymers has been studied. Various substituted monomers have also been employed and their effect on the morphology of the product has been investigated.

A general conclusion and appendices are included with supporting materials for the papers.

CHAPTER 1: SYNTHESIS OF 2,3-DISUBSTITUTED BENZO[*b*]SELENOPHENES VIA ELECTROPHILIC CYCLIZATION

Based on a paper published in the *Journal of Organic Chemistry*

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Abstract

2,3-Disubstituted benzo[*b*]selenophenes have been prepared by the electrophilic cyclization of various 1-(1-alkynyl)-2-(methylseleno)arenes by Br_2, NBS, I_2, ICl, PhSeCl, PhSeBr and $Hg(OAc)_2$. This method tolerates a wide variety of functional groups, including alcohol, ester, nitrile, nitro and silyl groups, and proceeds under exceptionally mild reaction conditions. A cationic intermediate in the cyclization with Br_2 has been isolated and studied, providing evidence for a stepwise cyclization process.

Introduction

The electrophilic cyclization of alkynes having a nucleophile in close proximity to the triple bond has proven to be an efficient way of constructing a wide array of carbocycles and heterocycles.[1] Recently our group and others have successfully utilized this approach to synthesize benzo[*b*]thiophenes,[2] benzofurans,[3] furans,[4] thiophenes,[5] indoles,[3c,6] isoquinolines,[7] quinolines,[8] isocoumarins,[9] and polycyclic aromatic hydrocarbons.[10] Similar cyclizations have also been reported using transition metal

catalysts.[11] However, some of these transition metal approaches are either incompatible with functionality or lack regioselectivity. Chalcogens, like sulfur, selenium and tellurium, have seldom been employed in such transition metal-catalyzed cyclizations due to their strong affinity for transition metals.

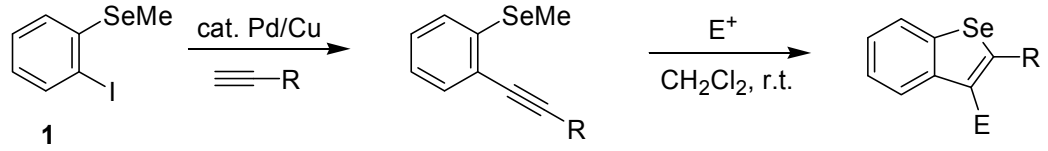
Benzo[*b*]selenophenes have received little attention as potential drugs, although their potent biological activity and synthetic utility have been discussed in the literature.[12] Recently Otsubo and co-workers have shown that high performance organic field effect transistors can be developed from benzodiselenophenes.[13] Their studies suggest that the replacement of sulfur atoms with selenium can enhance the optoelectronic properties of thiophene-containing molecules. Thus, we were encouraged to examine the synthesis of selenium analogs of benzo[*b*]thiophenes using acetylene cyclization chemistry.

Earlier syntheses of benzo[*b*]selenophenes have generally required harsh reaction conditions and suffer from poor reaction yields and intolerance of many functional groups.[14] Among the known protocols for the synthesis of 3-halobenzo[*b*]selenophenes,[15] the reaction of 1-aryl-1-alkynes with $SeBr_4$ or $SeCl_4$ is reported to give good yields.[16] Although iodides are more useful than bromides or chlorides for subsequent transition metal-catalyzed cross coupling reactions, no general method is known for the synthesis of 3-iodobenzo[*b*]selenophenes. Herein, we report a general, high yielding synthesis of 3-iodobenzo[*b*]selenophenes via iodocyclization, which also gives good yields with several other electrophiles.

Results and Discussion

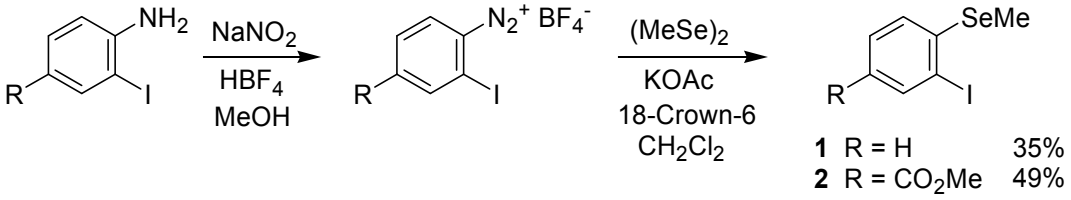
The expeditious synthesis of benzo[*b*]selenophenes have been achieved by a two step approach involving the Sonogashira coupling of 2-iodoselenoanisoles with terminal alkynes, followed by electrophilic cyclization using various electrophiles (Scheme 1). The required starting compounds **1** and **2** have been prepared by a two step approach developed by Christiaens and co-worker[17] in 35% and 49% overall yields respectively (Scheme 2).

Scheme 1



1

Scheme 2



1 R = H 35%
2 R = CO_2Me 49%

Various substituted selenium-containing alkynes have been prepared using standard Sonogashira coupling conditions[18] in order to study the scope and generality of our methodology (Table 1). Although selenium compounds **1** and **2** react slowly with terminal alkynes under standard Sonogashira reaction conditions, the required coupling products are obtained in good to excellent yields after 24-48 h. The slow reaction may be attributed to the strong coordination between selenium and palladium in the key arylpalladium intermediate. Terminal alkynes bearing simple alkyl groups have afforded

the expected internal alkynes in high yields (Table 1, entries 1 and 2). The reactions of alkylalkynes bearing cyano, ester and hydroxyl groups also proceed in excellent yields (entries 3-5). Alkynes bearing a triethylsilyl group (entry 6) and a vinylic group (entry 7) furnished the desired products in 79% and 96% yields respectively. The reaction of phenylacetylene was low yielding due to homocoupling of this alkyne (entry 8). Substituted aryl groups on the alkyne were also successfully employed in the coupling reaction (entries 9 and 10). Diyne **13** was prepared from coupling of **1** and 1,4-diethynylbenzene. However, the reaction proceeded rather slowly and afforded only a 47% yield (entry 11). The reaction of **2** and 3-cyclohexyl-1-propyne also proceeded smoothly to furnish the desired product **14** in an excellent yield (entry 12).

We have found that the electrophilic cyclization of 1-(1-decynyl)-2-(methylseleno)benzene (**3)** with I_2 in CH_2Cl_2 as the solvent at room temperature affords a near quantitative yield of the desired 2,3-disubstituted benzo[*b*]selenophene **15** after only 30 min reaction time (Scheme 3).

Scheme 3

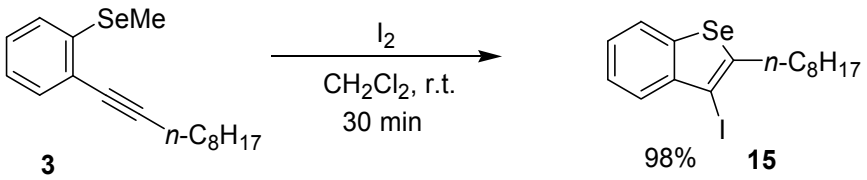
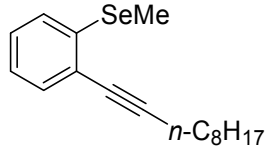
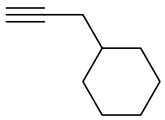
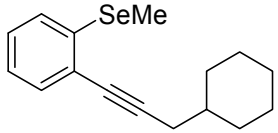
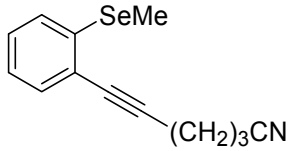
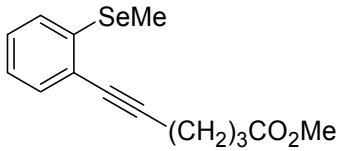
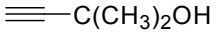
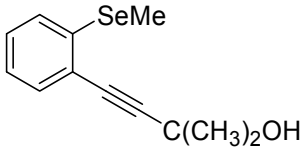
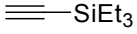
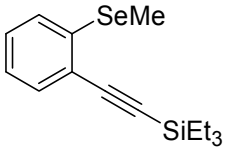
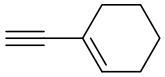
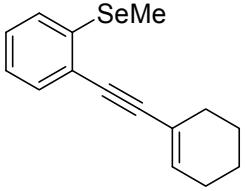
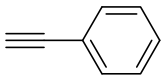
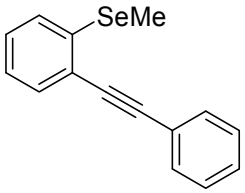
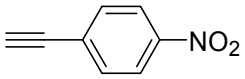
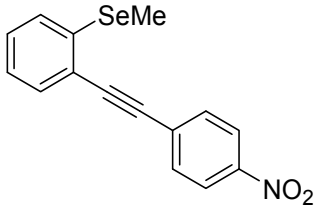
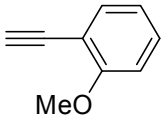
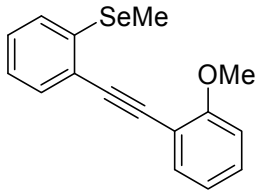
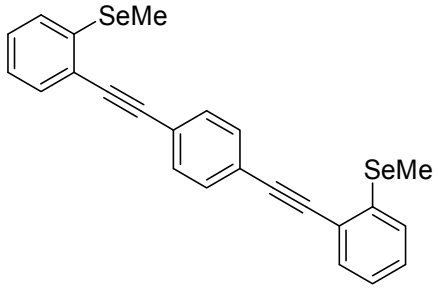
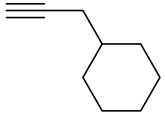
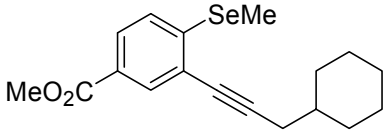


Table 1. Sonogshira coupling of 1-iodo-2-(methylseleno)arenes and terminal acetylenes.[a]

entry	substrate	Alkyne	time (h)	product		% isolated yield
1	**1**	≡—*n*-C_8H_{17}	24		**3**	82
2	**1**		24		**4**	88
3	**1**	≡—$(CH_2)_3CN$	24		**5**	86
4	**1**	≡—$(CH_2)_3CO_2Me$	48		**6**	90

5	**1**		24		**7**	95
6	**1**		24		**8**	79
7	**1**		24		**9**	96
8	**1**		24		**10**	68

9	**1**		48		**11**	85[b]
10	**1**		24		**12**	95
11	**1**		48		**13**	47[c]
12	**2**		48		**14**	92

[a] Unless otherwise stated, all reactions were carried out on a 2.0 mmol scale in 12 mL of Et_3N using 1.0 equiv of the 1-iodo-2-(methylseleno)arene, 1.5 equiv of alkyne, 2 mol % of $PdCl_2(PPh_3)_2$ and 1 mol % of CuI at room temperature for the desired time. [b] This reaction was carried out in a 1:1 mixture of DMF and Et_3N as the solvent for 48 h. [c] This reaction was performed using 2.2 equiv of 1-iodo-2-(methylseleno)benzene and 1.0 equiv of alkyne.

The yield of this reaction is not much affected when different solvents are employed (Table 2). THF, Et_2O, CH_3CN and hexanes gave **15** in greater than 90% yields, while the reaction proceeded more slowly and gave a lower yield in MeOH (entry 4). The mild reaction conditions, ease of product isolation and high yields encouraged us to broaden the scope of our methodology by using different 1-(1-alkynyl)-2-(methylseleno)arenes (Table 3).

Table 2. Effect of the solvent in the reaction of 1-(1-decynyl)-2-(methylseleno)benzene (**3**) with I_2.[a]

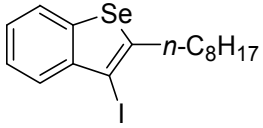
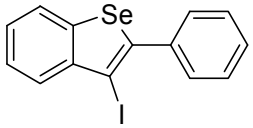
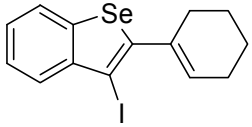
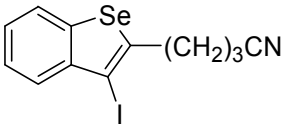
entry	solvent	I_2 equiv	time (min)	% yield
1	CH_2Cl_2	1.1	30	98
2	CH_2Cl_2	2.0	30	97
3	Et_2O	1.1	30	91
4	MeOH	1.1	60	82
5	THF	1.1	30	92
6	CH_3CN	1.1	30	95
7	Hexanes	1.1	30	90

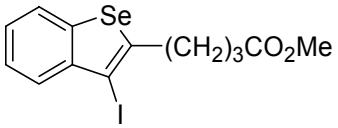
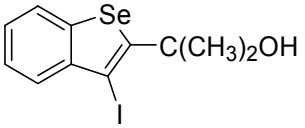
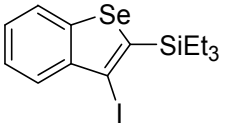
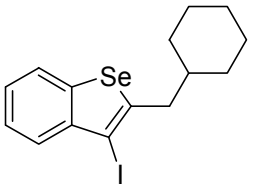
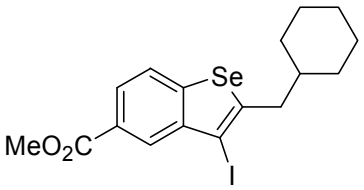
[a] All reactions were carried out on a 0.25 mmol scale in 5 mL of solvent using 1.0 equiv of 1-(1-decynyl)-2-(methylseleno)benzene (**3**) and the indicated amount of I_2 at room temperature.

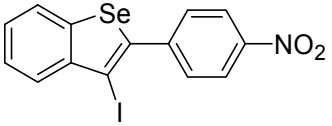
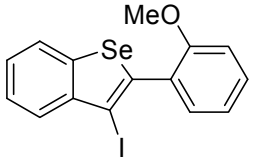
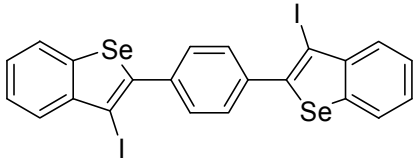
The yield of benzo[*b*]selenophenes was excellent whether the substituent on the alkyne was alkyl, aryl or vinylic (Table 3; entries 1, 3 and 5). In some of our earlier work on the iodocyclization of functionally-substituted alkynes ICl proved to be a better electrophile than I_2 for some substrates. In our current methodology, ICl gave somewhat lower yields compared to I_2 (see entries 2, 4 and 6). The higher yields with I_2 as the electrophile may be attributed to the higher nucleophilicity of an iodide ion than a chloride ion, which facilitates removal of the methyl group present in the cationic intermediate presumably generated during cyclization (see the later discussion of mechanism). Alternatively, the weaker electrophile I_2 may simply be less likely to react directly with the selenium moiety.

Iodocyclization also readily tolerates functionally-substituted alkyl groups (entries 7-9) with little effect on the reaction yield. The sterically hindered triethylsilylalkyne **8** also reacted rapidly to give benzo[*b*]selenophene **21** in a 91% yield (entry 10). The iodocyclization of **14** proceeded slowly when compared to that of compound **4** (entries 11 and 12); this observation can be attributed to the presence of an ester group *para* to the selenium, which reduces the electron density on selenium. No such effect is observed when varying the nature of the substituents on the remote aryl group. The presence of an electron-withdrawing nitro group or an electron-donating methoxy group did not make much of a difference and the reaction proceeded with ease giving the desired products in greater than 90% yields (entries 13 and 14). The iodocyclization of **13** resulted in the formation of the dicyclized product in a good yield of 88% (entry 15).

Table 3. Iodocyclization of various 1-(alkynyl)-2-(methylseleno)arenes.[a]

entry	alkyne	electrophile	time (min)	product		% isolated yield
1	**3**	I_2	30		**15**	98
2	**3**	ICl	60		**15**	78
3	**10**	I_2	30		**16**	90
4	**10**	ICl	60		**16**	79
5	**9**	I_2	30		**17**	92
6	**9**	ICl	60		**17**	76
7	**5**	I_2	60		**18**	87

8	**6**	I_2	60		**19**	83
9	**7**	I_2	30		**20**	93
10	**8**	I_2	30		**21**	91
11	**4**	I_2	30		**22**	91
12	**14**	I_2	60		**23**	82

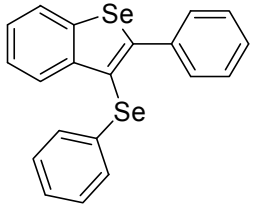
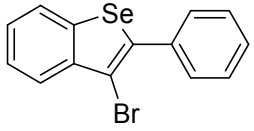
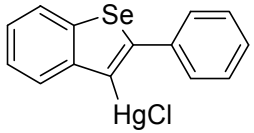
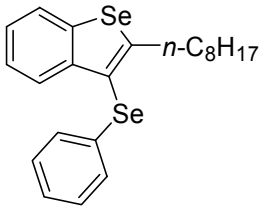
13	**11**	I_2	30		**24**	94
14	**12**	I_2	30		**25**	91
15	**13**	I_2	30		**26**	88[b]

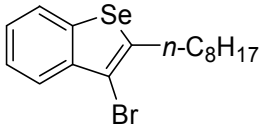
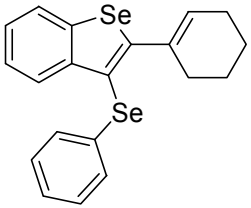
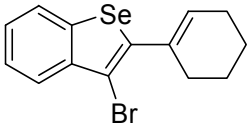
[a] Unless otherwise stated, all reactions were carried out on a 0.25 mmol scale in 5 mL of solvent using 1.0 equiv of 1-(1-alkynyl-2-(methylseleno)benzene and 1.1 equiv of I_2 or ICl at room temperature. [b] This reaction was carried out on a 0.25 mmol scale in 5 mL of solvent using 1.0 equiv of 1-(1-alkynyl)-2-(methylseleno)benzene and 2.2 equiv of I_2.

Electrophilic cyclization using other electrophiles, such as Br_2, NBS, PhSeBr, PhSeCl, $Hg(OAc)_2$ and *p*-$O_2NC_6H_4SCl$, has also been examined in order to extend the scope of our methodology (Table 4). The cyclization of alkyne **10** using PhSeBr resulted in a slightly higher yield of the desired product when compared to PhSeCl (entries 1 and 2). PhSeBr was then employed for the cyclization of alkynes bearing alkyl and vinylic groups (entries 6 and 9) and the yields were 84% and 87% respectively. With $Hg(OAc)_2$ as the electrophile, the reaction was quenched with an aqueous NaCl solution and the chloromercurio derivative **29** was isolated in 92% yield (entry 5). When *p*-$O_2NC_6H_4SCl$ was used as an electrophile on alkyne **10**, the corresponding cyclized product was not observed even after 2 d.

The cyclization of alkynes using Br_2 and NBS as electrophiles gave some interesting results. The use of NBS resulted in formation of the desired product in lower yields (entries 4, 8 and 10), contrary to our analogous efforts earlier in preparing benzo[*b*]thiophenes.[2b] Unlike the reactions using NBS, cyclizations employing Br_2 were slower and also resulted in lower yields in comparison with our earlier benzo[*b*]thiophene methodology[2b] (entries 3 and 7). When the bromocyclization of **10** was monitored by TLC, the disappearance of starting compound was observed soon after the addition of Br_2, but formation of the product was not observed. However, after 20 min, the product spot appeared and its intensity increased over a period of 2-3 h. A similar observation was made during the bromocyclization of **3**, indicating once again a possible intermediate.

Table 4. Other electrophilic cyclizations of 1-(1-alkynyl)-2-(methylseleno)arenes.[a]

entry	alkyne	electrophile (equiv)	time (h)	Product		% isolated yield
1	**10**	PhSeCl (1.5)	2		**27**	92
2	**10**	PhSeBr (1.5)	2		**27**	95
3	**10**	Br_2 (1.1)	12		**28**	75
4	**10**	NBS (2.2)	12		**28**	46
5	**10**	$Hg(OAc)_2$ (1.1)	1		**29**	92[b]
6	**3**	PhSeBr (1.5)	2		**30**	84

7	**3**	Br_2 (1.1)	12		**31**	78
8	**3**	NBS (2.2)	48		**31**	43
9	**9**	PhSeBr (1.5)	2		**32**	87
10	**9**	NBS (2.2)	48		**33**	48

[a] Unless otherwise stated, reactions were carried out on a 0.25 mmol scale in 5 mL of CH_2Cl_2 by using 1.0 equiv of 1-(1-alkynyl)-2-(methylseleno)benzene and 1.1 equiv of I_2 or ICl at room temperature. [b] This reaction was carried out on a 0.25 mmol scale in 5 mL of AcOH using 1.0 equiv of alkyne and 1.1 equiv of $Hg(OAc)_2$ at room temperature and quenched with satd aq NaCl solution.

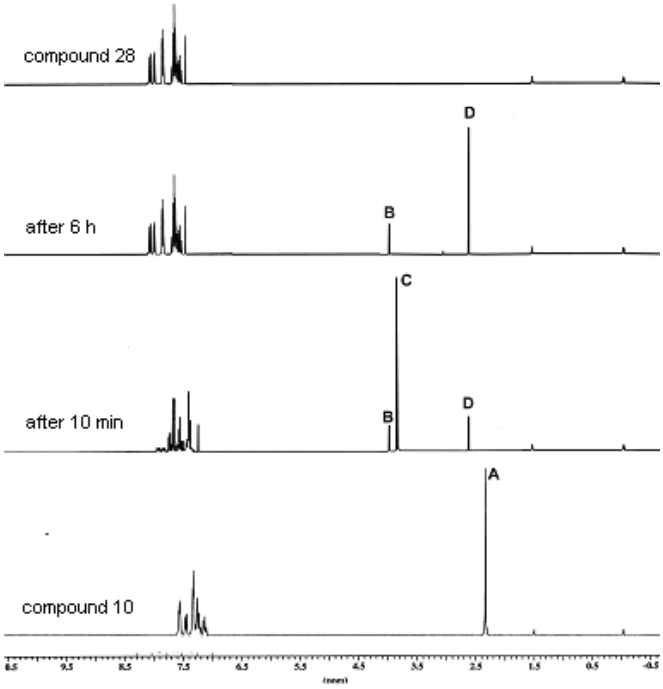
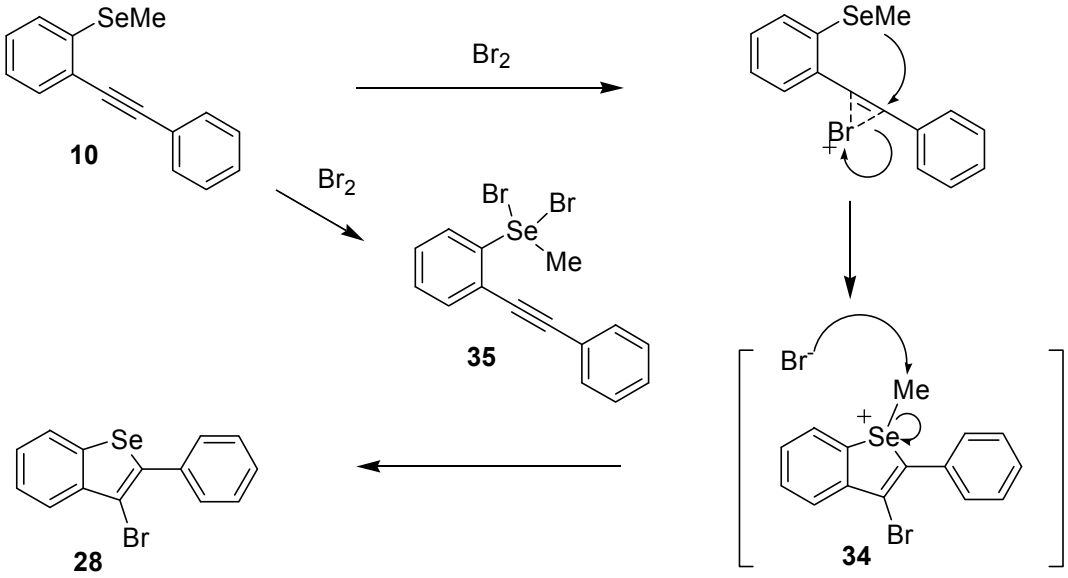


Figure 1. ^{1}H NMR spectra from the reaction of alkyne **10** in $CDCl_3$ before and after the addition of Br_2.

In an attempt to clarify these results, the cyclization of alkyne **10** by Br_2 was carried out in $CDCl_3$ as the solvent and the reaction was monitored by ^{1}H NMR spectroscopy. A small peak **D** was observed at δ 2.5 soon after the addition of Br_2. This peak corresponds to MeBr, the by-product of this overall process (Figure 1). Two more peaks were observed at approximately δ 4.0, which may correspond to a methyl group on an electron-deficient selenium. From the above ^{1}H NMR studies, a possible stepwise mechanism can be derived for bromocyclization by Br_2. In the first step, the electrophile coordinates with the triple bond, followed by nucleophilic attack by selenium to generate a cationic intermediate **34** (Scheme 4). The peak **B** (Figure 1) can be attributed to the methyl protons in **34**, while peak **C** corresponds to the methyl group in dibromo compound **35**. The formation of dibromo compounds of type **35** on addition of bromine

to selenides has been reported earlier.[19] The cationic intermediate **34** can then undergo a facile removal of the methyl group via S_N2 displacement by the counter ion bromide generated *in situ* during the cyclization (Scheme 4). Selenonium salts analogous to intermediate **34** are known in the literature and have been used for the alkylation of relative acidic carbon nucleophiles.[20]

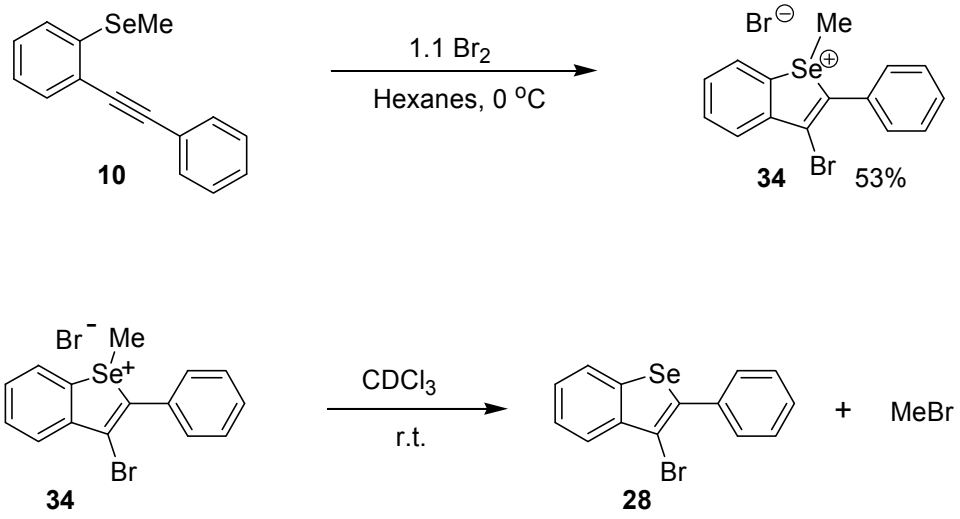
Scheme 4



To support this mechanistic hypothesis, we attempted to isolate intermediate **34**. The bromocyclization of **10** was performed in nonpolar hexanes at 0 ^oC, which resulted in the formation of a yellow precipitate soon after the addition of Br_2. The precipitate was filtered, washed with cold hexanes, and isolated in 53% yield (Scheme 5). This precipitate was then dissolved in $CDCl_3$ and monitored by ^1H NMR spectroscopy, which showed decomposition of this material, assumed to be intermediate **34** (Figure 2). Peak **C** slowly disappeared over a period of 6 h, which indicated the decay of intermediate **34**. The height of peak **D** increased over this same time period, supporting the formation of

methyl bromide. A noticeable change in the aromatic region was also observed, which matched the aromatic peaks of compound **28**. Reactions with I_2 as an electrophile proceed much faster, and similar experiments to trap the cationic intermediate failed even at a lower temperature.

Scheme 5



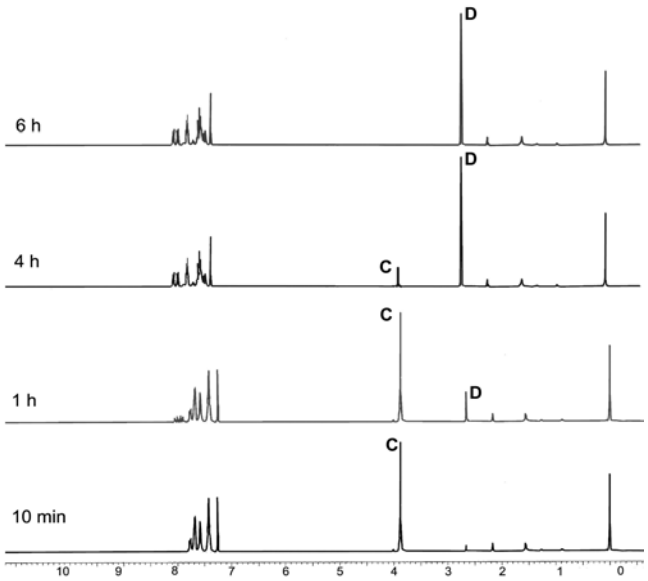
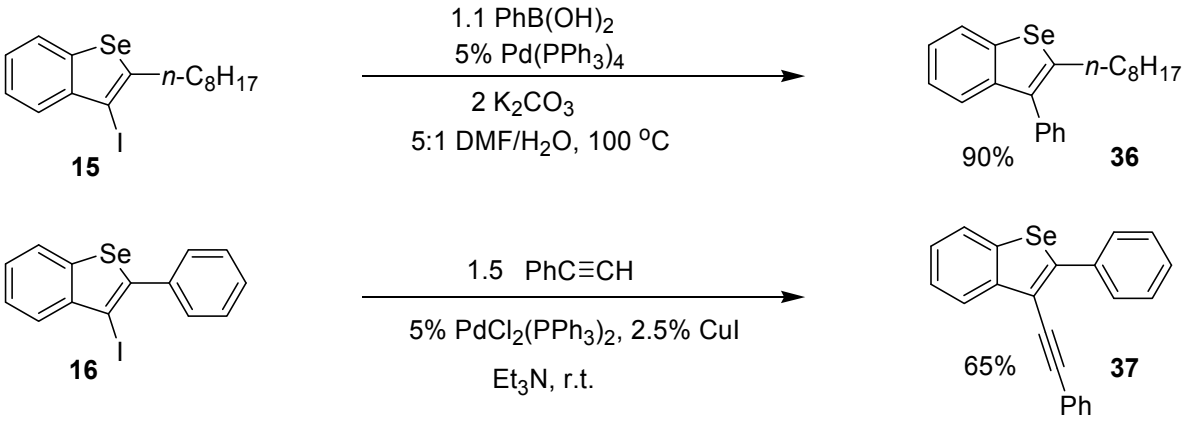


Figure 2. ^{1}H NMR spectra following the decomposition of **34** into **28** and MeBr

Our iodobenzo[*b*]selenophene products can be further functionalized by palladium-catalyzed coupling reactions. 2-(1-Octynyl)-3-phenylbenzo[*b*]selenophene (**36**) has been successfully obtained in a 90% isolated yield by the Suzuki cross-coupling of **15** with phenylboronic acid (Scheme 6). In a similar manner, the Sonogashira coupling of **16** with phenylacetylene gave alkyne **37** in 65% yield.

Scheme 6



Conclusions

2,3-Disubstituted benzo[*b*]selenophenes have been obtained in good yields from simple starting materials by the electrophilic cyclization of 2-(1-alkynyl)selenoanisoles by Br_2, NBS, I_2, ICl, PhSeCl, PhSeBr and $Hg(OAc)_2$. This method tolerates many functional groups, including nitrile, hydroxyl, silyl, nitro, methoxy and ester groups. An iodine moiety can be readily introduced into the heterocycle in a position not easily obtained previously. Subsequent functionalization of the resulting heterocycles by palladium-catalyzed coupling reactions leads to a number of interesting substituted

benzo[*b*]selenophenes. With respect to subsequent transition metal-catalyzed reactions, 3-iodobenzo[*b*]selenophenes are expected to be more effective than the corresponding bromo and chloro derivatives and that augurs well for this new approach to benzo[*b*]selenophenes. A cationic intermediate in the cyclization with Br_2 has been isolated and studied, providing evidence for a stepwise cyclization process.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

General preparation of 2-iodo(methylselenyl)arenes. To a stirred solution of methanol (30 mL) and 10 mmol of the 2-iodoaniline, 20 mmol of HBF_4 (36 mL, 48% solution) was added dropwise. After the addition was complete, the solution was allowed to cool to 0 ^{o}C. To this solution an aqueous solution of $NaNO_2$ (12 mmol in 5 mL of water) was added dropwise to the reaction mixture, which turned a pale yellow to red brown. The mixture was allowed to warm to room temperature and methanol was removed under vacuum at room temperature. The mixture was filtered and washed with cold methanol. The diazonium salt was dried under vacuum and used for the next step without purification. A suspension of 8 mmol of the crude diazonium salt in 25 mL of $CHCl_3$

containing 10 mol % of 18-crown-6 and 9 mmol of dimethyl diselenide was stirred at 0 ^{o}C. To this mixture, 16 mmol of KOAc was added in small portions over a period of 10 min and the resulting solution was allowed to stir for 4 h and then filtered. The solid residue was washed with chloroform and the resulting filtrate was washed with water (2 x 5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product obtained was then purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-Iodophenyl methyl selenide (1). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 6.89 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.17-7.20 (m, 1H), 7.28-7.34 (m, 2H), 7.74 (dd, *J* = 1.2, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.1, 100.0, 126.9, 128.2, 128.8, 139.4, 139.6; IR (neat, cm^{-1}) 3050, 2998, 2923, 1561, 1422; HRMS calcd for C_7H_7ISe 297.87575, found 297.87617.

Methyl 3-iodo-4-(methylselenyl)benzoate (2). The product was obtained as a orange semisolid: ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.89 (s, 3H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.35 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.4, 52.4, 98.3, 126.9, 128.3, 129.4, 140.0, 147.2, 165.7; IR (neat, cm^{-1}) 3060, 3010, 2954, 2920, 1719, 1290; HRMS calcd for $C_9H_9IO_2Se$ 355.88125, found 355.88200.

General procedure for the palladium/copper-catalyzed formation of 1-(1-alkynyl)-2-(methylselenyl)arenes. To a solution of Et_3N (10 mL), 2.0 mmol of the 2-iodo(methylselenyl)arene and $PdCl_2(PPh_3)_2$ (2 mol %) (stirring for 5 min beforehand), CuI (1 mol %) was added and the flask was sealed and flushed with Ar. 3.0 Mmol of

terminal acetylene dissolved in 2 mL of Et_3N was then added dropwise and the reaction mixture was allowed to stir at room temperature for the desired time. After the reaction was over, the resulting solution was filtered, washed with satd aq NaCl and extracted with diethyl ether (3 x 15 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-(1-Decynyl)phenyl methyl selenide (3). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.86-0.90 (t, *J* = 6.9 Hz, 3H), 1.28-1.30 (m, 8H), 1.43-1.51 (m, 3H), 1.60-1.69 (m, 2H), 2.31 (s, 1H), 2.45-2.49 (t, *J* = 6.9 Hz, 2H), 7.05-7.11 (m, 1H), 7.16-7.21 (m, 2H), 7.32-7.35 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.0, 14.3, 19.8, 22.9, 28.9, 29.1, 29.3, 29.4, 32.0, 79.2, 96.9, 124.4, 125.1, 127.0, 128.3, 132.3, 136.2; IR (neat, cm^{-1}) 3057, 2926, 2853, 2226, 1581, 1460; HRMS calcd for $C_{17}H_{24}Se$ 308.10432, found 308.10500.

2-(3-Cyclohexylprop-1-ynyl)phenyl methyl selenide (4). The product was obtained as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.05-1.35 (m, 5H), 1.56-1.78 (m, 4H), 1.89-1.93 (m, 2H), 2.32 (s, 1H), 2.37-2.39 (d, *J* = 6.6 Hz, 2H), 7.06-7.13 (m, 1H), 7.17-7.22 (m, 2H), 7.33-7.36 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.1, 26.4, 26.5, 27.7, 33.0, 37.7, 80.1, 95.8, 124.5, 125.2, 127.0, 128.3, 132.4, 136.2; IR (neat, cm^{-1}) 3058, 2923, 2850, 2227, 1460; HRMS calcd for $C_{16}H_{20}Se$ 292.07302, found 292.07347.

6-[2-(Methylselenyl)phenyl]hex-5-ynenitrile (5). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.96-2.03 (q, *J* = 5.3 Hz, 2H), 2.33 (s, 3H), 2.64-2.69 (m, 4H), 7.08-7.14 (m, 1H), 7.22-7.24 (m, 2H), 7.33-7.35 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.3, 16.5, 19.0, 24.9, 81.2, 93.2, 119.6, 123.5, 125.3, 127.2, 128.9, 132.4, 136.3; IR (neat, cm^{-1}) 3056, 3005, 2929, 2247, 1580, 1460; HRMS calcd for $C_{13}H_{13}NSe$ 263.02132, found 263.02180.

Methyl 6-[2-(methylselenyl)phenyl]hex-5-ynoate (6). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.94-2.01 (q, *J* = 5.3 Hz, 2H), 2.32 (s, 3H), 2.55-2.60 (m, 4H), 3.69 (s, 3H), 7.08-7.13 (m, 1H), 7.19-7.23 (m, 2H), 7.33-7.35 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.1, 19.3, 24.1, 33.1, 51.8, 80.1, 95.2, 124.0, 125.2, 127.1, 128.6, 132.4, 126.3, 173.8; IR (neat, cm^{-1}) 3056, 2997, 2948, 2841, 2226, 1735, 1581, 1460; HRMS calcd for $C_{14}H_{16}O_2Se$ 296.03155, found 296.03210.

2-Methyl-4-[2-(methylselenyl)phenyl]but-3-yn-2-ol (7). The product was obtained as a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 6H), 2.17 (s, 1H), 2.26 (s, 3H), 7.01-7.08 (m, 1H), 7.13-7.19 (m, 2H), 7.27-7.30 (m, 1H);^{13}C NMR ($CDCl_3$) δ6.1, 31.6, 65.9, 80.8, 99.8, 123.1, 125.3, 127.3, 129.1, 132.3, 136.7; IR (neat, cm^{-1}) 3419, 2977, 2868, 1642, 1444; HRMS calcd for $C_{12}H_{14}OSe$ 254.02099, found 254.02129.

Triethyl[(2-(methylselenyl)phenyl)ethynyl]silane (8). The product was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.66-0.74 (q, *J* = 8.4 Hz, 6H), 1.05-1.10 (t, *J* = 7.7 Hz, 9H), 2.23 (s, 3H), 7.07-7.13 (m, 1H), 7.22-7.24 (m, 2H), 7.40-7.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 4.68, 6.10, 7.82, 98.43, 104.19, 123.73, 125.11, 127.09, 129.16, 132.95,

136.91; IR (neat, cm^{-1}) 3017, 2955, 2931, 2874, 2152, 1457; HRMS calcd for $C_{15}H_{22}SeSi$ 310.06560, found 310.06610.

2-(Cyclohex-1-enylethynyl)phenyl methyl selenide (9). The product was obtained as a yellow liquid: ^1H NMR ($CDCl_3$) δ 1.57-1.72 (m, 4H), 2.12-2.24 (m, 2H), 2.25-2.31 (m, 5H), 6.24-6.26 (m, 1H), 7.04-7.14 (m, 1H), 7.16-7.22 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 5.9, 21.6, 22.4, 25.9, 29.2, 85.3, 97.2, 120.7, 124.0, 125.1, 127.0, 128.4, 131.9, 135.6, 136.2; IR (neat, cm^{-1}) 3054, 2927, 2856, 2197, 1578, 1458, 1433; HRMS calcd for $C_{15}H_{16}Se$ 276.04171, found 276.042303.

2-(Phenylethynyl)phenyl methyl selenide (10). The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 7.13-7.17 (m, 1H), 7.22-7.37 (m, 5H), 7.46-7.48 (d, *J* = 7.6 Hz, 1H), 7.56-7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 6.26, 88.01, 95.23, 123.26, 123.78, 125.37, 127.52, 128.53, 128.64, 129.02, 131.77, 132.34, 136.67; IR (neat, cm^{-1}) 3061, 3016, 2929, 2399, 1598, 1490; HRMS calcd for $C_{15}H_{12}Se$ 272.01042, found 272.01100.

Methyl 2-[(4-nitrophenyl)ethynyl]phenyl selenide (11). The product was obtained as a orange solid: mp 99-101 ^oC; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 7.17-7.22 (m, 1H), 7.31-7.33 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.69-7.73 (m, 2H), 8.21-8.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 6.4, 93.1, 93.2, 122.6, 123.9, 125.5, 127.7, 130.0, 130.2, 132.4, 132.7, 137.3, 147.3; IR (neat, cm^{-1}) 3018, 2933, 2214, 1595, 1518; HRMS calcd for $C_{15}H_{11}NO_2Se$ 316.99549, found 316.99602.

2-[(2-Methoxyphenyl)ethynyl]phenyl methyl selenide (12). The product was obtained as a pale yellow solid: mp 75-77 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.93 (s, 3H), 6.89-6.97 (m, 2H), 7.12-7.17 (m, 1H), 7.21-7.24 (m, 1H), 7.26-7.34 (m, 2H), 7.49-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 6.4, 56.1, 91.7, 92.0, 110.9, 112.6, 120.7, 124.3, 125.4, 127.7, 128.8, 130.1, 132.5, 133.8, 136.5, 160.2; IR (neat, cm^{-1}) 3013, 2962, 2932, 2836, 2212, 1596, 1494; HRMS calcd for $C_{16}H_{14}OSe$ 302.02099, found 302.02150.

1,4-*Bis*[(2-(methylselenyl)phenylethynyl]benzene (13). The product was obtained as a yellow solid: mp 159-161 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 6H), 7.14-7.16 (m, 2H), 7.24-7.32 (m, 4H), 7.48 (d, J = 7.3 Hz, 2H), 7.56 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 6.4, 89.9, 94.9, 123.3, 123.6, 125.5, 127.6, 129.3, 131.7, 132.5, 136.8; IR (neat, cm^{-1}) 3053, 2986, 2926, 2852, 2305, 1717, 1437, 1265; HRMS calcd for $C_{24}H_{18}Se_2$ 465.97387, found 465.97450.

Methyl 3-(3-cyclohexylprop-1-ynyl)-4-(methylselenyl)benzoate (14). The product was obtained as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.08-1.32 (m, 5H), 1.59-1.78 (m, 4H), 1.87-1.92 (m, 2H), 2.34-2.40 (m, 5H), 3.89 (s, 3H), 7.23 (d, J = 8.3 Hz, 1H), 7.83 (dd, J = 8.3, 1.9 Hz, 1H), 7.97 (d, J = 1.7 Hz, 1H) ; ^{13}C NMR ($CDCl_3$) δ 6.1, 26.3, 26.4, 27.6, 32.9, 37.6, 52.3, 79.2, 97.0, 124.0, 125.9, 126.8, 128.8, 132.9, 143.7, 166.8; IR (neat, cm^{-1}) 3058, 2923, 2850, 1710, 1460; HRMS calcd for $C_{18}H_{22}O_2Se$ 350.07850, found 350.07902.

General procedure for iodocyclization. To a solution of 0.25 mmol of the alkyne and 3 mL of CH_2Cl_2, 1.1 equiv of I_2 or ICl dissolved in 2 mL of CH_2Cl_2 was added gradually. The reaction mixture was allowed to stir at room temperature for the desired time. The

excess I_2 or ICl was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by diethyl ether (3 x 10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

3-Iodo-2-octylbenzo[*b*]selenophene (15). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3H), 1.31-1.48 (m, 10H), 1.71-1.79 (m, 2H), 3.02 (t, J = 7.8 Hz, 2H), 7.24-7.29 (m, 1H), 7.39-7.45 (m, 1H), 7.77-7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.9, 29.4, 29.5, 29.6, 31.6, 32.1, 36.1, 83.4, 125.3, 125.5, 125.7, 127.8, 139.1, 143.2, 148.2; IR (neat, cm^{-1}) 3056, 2953, 2923, 2852, 1450, 1432, 1242; HRMS calcd for $C_{16}H_{21}ISe$ 419.98532, found 419.98620.

3-Iodo-2-phenylbenzo[*b*]selenophene (16). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.34 (t, J = 5.5 Hz, 1H), 7.41-7.51 (m, 4H), 7.61-7.63 (m, 2H), 7.83-7.85 (d, J = 5.9 Hz, 1H), 7.93-7.95 (d, J = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 82.9, 125.3, 125.9, 126.0, 128.6, 128.9, 129.1, 130.2, 137.1, 140.7, 143.8, 144.7; IR (neat, cm^{-1}) 3052, 2926, 2919, 1481, 1430, 1239; HRMS calcd for $C_{14}H_9SeI$ 383.89142, found 383.89200.

2-(Cyclohex-1-enyl)-3-iodobenzo[*b*]selenophene (17). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.65-1.83 (m, 4H), 2.21-2.23 (m, 2H), 2.41-2.43 (m, 2H), 6.10-6.20 (m, 1H), 7.25 (t, J = 6.7 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.0, 25.8, 30.6, 80.9, 125.4, 125.5, 125.7, 128.5, 132.1, 134.7, 139.5, 143.5, 148.0; IR (neat, cm^{-1}) 3018, 2917, 2848, 1461, 1215; HRMS calcd for $C_{14}H_{13}ISe$ 387.92272, found 387.92340.

4-(3-Iodobenzo[*b*]selenophen-2-yl)butanenitrile (18). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.12 (q, *J* = 7.3 Hz, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 3.18 (t, *J* = 7.5 Hz, 2H), 7.25-7.33 (m, 1H), 7.41-7.45 (m, 1H), 7.77-7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.7, 27.0, 34.6, 85.1, 119.4, 125.6, 125.9, 126.0, 128.2, 139.3, 143.0, 144.0; IR (neat, cm^{-1}) 3053, 2931, 2851, 2245, 1449, 1432; HRMS calcd for $C_{12}H_{10}INSe$ 374.90232, found 374.90290.

Methyl 4-(3-iodobenzo[*b*]selenophen-2-yl)butanoate (19). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.08 (q, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 7.24-7.29 (m, 1H), 7.39-7.44 (m, 1H), 7.76-7.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.5, 33.2, 35.2, 51.9, 84.2, 125.5, 125.6, 125.8, 129.3, 143.1, 146.4, 173.7; IR (neat, cm^{-1}) 3058, 2918, 2843, 1730, 1431; HRMS calcd for $C_{13}H_{13}IO_2Se$ 407.91255, found 407.91320.

2-(3-Iodobenzo[*b*]selenophen-2-yl)propan-2-ol (20). The product was obtained as a pale yellow solid: mp 91-93 ^{o}C;^{1}H NMR ($CDCl_3$) δ 1.77 (s, 6H), 2.69 (s, 1H), 7.16-7.22 (m, 1H), 7.31-7.37 (m, 1H), 7.70-7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.8, 75.0, 76.0, 125.2, 125.4, 125.6, 128.1, 138.4, 145.1, 157.5; IR (neat, cm^{-1}) 3398, 2973, 2922, 2850, 1447, 1433, 1239; HRMS calcd for $C_{11}H_{11}IOSe$ 365.90197, found 365.90242.

2-(Triethylsilyl)benzo[*b*]selenophene (21). The product was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.99-1.08 (m, 15H), 7.24-7.34 (m, 1H), 7.41-7.47 (m, 1H), 7.87-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 4.2, 7.7, 90.2, 125.0, 125.4, 125.5, 128.2, 142.3, 142.4,

145.1; IR (neat, cm^{-1}) 3053, 2952, 2872, 1473, 1416, 1230; HRMS calcd for $C_{14}H_{19}ISiSe$ 421.94660, found 421.94720.

2-Cyclohexylmethyl-3-iodobenzo[*b*]selenophene (22). The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.07-1.25 (m, 6H), 1.67-1.84 (m, 5H), 2.92 (d, J = 7.0 Hz, 2H), 7.24 (t, J = 7.1 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.75-7.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.6, 33.3, 40.8, 43.5, 84.5, 125.4, 125.5, 125.6, 127.9, 139.4, 143.2, 146.8; IR (neat, cm^{-1}) 2920, 2849, 1446, 1432, 1242; HRMS calcd for $C_{15}H_{17}ISe$ 403.95402, found 403.95458.

Methyl 2-cyclohexylmethyl-3-iodobenzo[*b*]selenophene-5-carboxylate (23). The product was obtained as a white solid: mp 150-152 °C; ^1H NMR ($CDCl_3$) δ 1.08-1.26 (m, 5H), 1.61-1.84 (m, 6H), 2.95 (d, J = 7.0 Hz, 2H), 3.98 (s, 3H), 7.82-7.93 (m, 2H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.5, 33.3, 40.7, 43.5, 52.5, 84.6, 125.5, 125.7, 127.9, 129.3, 143.3, 144.8, 148.3, 167.3; IR (neat, cm^{-1}) 2976, 2928, 2859, 1726, 1444, 1382; HRMS calcd for $C_{17}H_{19}IO_2Se$ 461.95948, found 461.96021.

3-Iodo-2-(4-nitrophenyl)benzo[*b*]selenophene (24). The product was obtained as an orange solid: mp 147-149 °C; ^1H NMR ($CDCl_3$) δ 7.36-7.41 (m, 1H), 7.49-7.54 (m, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H), 8.30 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 84.8, 123.9, 125.5, 126.5, 126.7, 129.6, 131.3, 140.9, 141.5, 143.6, 143.7, 147.8; IR (neat, cm^{-1}) 3004, 2977, 2872, 1445, 1383; HRMS calcd for $C_{14}H_8INO_2Se$ 428.87648, found 428.87710.

3-Iodo-2-(2-methoxyphenyl)benzo[*b*]selenophene (25). The product was obtained as a yellow solid: mp 94-96 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.99-7.07 (m, 2H), 7.28-7.47 (m, 4H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.9, 86.0, 111.6, 120.6, 125.4, 125.7, 126.1, 128.8, 130.8, 132.4, 141.2, 141.7, 143.2, 156.9; IR (neat, cm^{-1}) 3056, 3004, 2934, 2843, 1597, 1482, 1432, 1249; HRMS calcd for $C_{15}H_{11}IOSe$ 413.90199, found 413.90260.

1,4-*Bis*(3-iodobenzo[*b*]selenophen-2-yl)benzene (26). The product was purified by washing the crude product with hexanes and recrystallizing it from benzene. The product was obtained as a yellow solid: mp >260 ^{o}C; IR (KBr, cm^{-1}) 3067, 3044, 1537, 1478, 1428, 1237; HRMS calcd for $C_{22}H_{12}Se_2I_2$ 689.73586, found 689.73730; Anal. Calcd for $C_{22}H_{12}Se_2I_2$: C, 38.31; H, 1.73. Found: C, 38.75; H, 1.72.

General procedure for bromocyclization. To a solution of 0.25 mmol of the alkyne and 3 mL of CH_2Cl_2, 1.1 equiv of Br_2 or 2.2 equiv of NBS dissolved in 2 mL of CH_2Cl_2 was added gradually. The reaction mixture was allowed to stir at room temperature for the desired time. The excess Br_2 or NBS was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by diethyl ether (3 x 10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

3-Bromo-2-phenylbenzo[*b*]selenophene (28). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.34-7.53 (m, 5H), 7.68-7.72 (m, 2H), 7.87 (d, *J* = 7.9 Hz, 1H),

7.95 (d, J = 7.5 Hz, 1H);^{13}C NMR ($CDCl_3$) δ 106.9, 125.4, 125.8, 125.9, 126.3, 128.8, 128.9, 130.1, 135.2, 139.2, 140.9, 141.2; IR (neat, cm^{-1}) 3059, 3016, 2925, 1484, 1216; HRMS calcd for $C_{14}H_9BrSe$ 335.90528, found 335.90562.

3-Bromo-2-octylbenzo[*b*]selenophene (31). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 6.3 Hz, 3H), 1.10-1.40 (m, 10H), 1.65 (quintet, J = 7.7 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H), 7.18-7.22 (m, 1H), 7.31-7.37 (m, 1H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.9, 29.3, 29.4, 29.6, 31.4, 32.1, 32.5, 107.6, 125.1, 125.2, 125.4, 125.6, 138.0, 140.5, 144.5; IR (neat, cm^{-1}) 3059, 2926, 2854, 1452, 1434, 1214; HRMS calcd for $C_{16}H_{21}BrSe$ 371.99918, found 371.99990.

3-Bromo-2(cyclohex-1-enyl)benzo[*b*]selenophene (33). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.60-1.85 (m, 4H), 2.20-2.30 (m, 2H), 2.45-2.55 (m, 2H), 6.22-6.28 (m, 1H), 7.30 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.1, 25.9, 30.3, 105.0, 125.3, 125.4, 125.5, 125.7, 132.1, 132.8, 137.9, 141.1, 144.2; IR (neat, cm^{-1}) 3018, 2932, 1450, 1215; HRMS calcd for $C_{14}H_{13}BrSe$ 339.93658, found 339.93720.

General procedure for the PhSeCl and PhSeBr cyclizations. To a solution of 0.25 mmol of the alkyne and CH_2Cl_2 (3 mL), 0.375 mmol of PhSeBr or PhSeCl dissolved in 2 mL of CH_2Cl_2 was added dropwise. The mixture was allowed to stir at room temperature for the desired time. The reaction mixture was washed with 20 mL of water and extracted with diethyl ether (3 x 10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was

further purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-Phenyl-3-(phenylselenyl)benzo[*b*]selenophene (27). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.07-7.17 (m, 5H), 7.29-7.41 (m, 5H), 7.55-7.58 (m, 2H), 7.89-7.97 (m, 2H);^{13}C NMR ($CDCl_3$) δ 118.6, 125.3, 125.5, 125.6, 126.1, 127.8, 128.4, 128.9, 129.2, 129.4, 130.3, 133.2, 136.4, 141.2, 144.1, 153.2 ; IR (neat, cm^{-1}) 3056, 2917, 2848, 1476, 1431, 1215; HRMS calcd for $C_{20}H_{14}Se_2$ 411.94547, found 411.94630.

2-Octyl-3-(phenylselenyl)benzo[*b*]selenophene (30). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 6.5 Hz, 3H), 1.23-1.37 (m, 10H), 1.69 (quintet, J = 7.3 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H), 7.08-7.14 (m, 5H), 7.21-7.34 (m, 2H), 7.83-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.9, 29.4, 29.6, 32.1, 32.7, 33.7, 118.8, 124.9, 125.3, 125.5, 126.0, 126.6, 129.0, 129.4,132.9, 139.9, 143.7, 157.8; IR (neat, cm^{-1}) 3058, 2925, 2853, 1577, 1476, 1215; HRMS calcd for $C_{22}H_{26}Se_2$ 448.03937, found 448.04010.

2-(Cyclohex-1-enyl)-3-(phenylselenyl)benzo[*b*]selenophene (32). The product was obtained as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.52-1.77 (m, 4H), 2.14-2.20 (m, 2H), 2.43-2.45 (m, 2H), 6.00-6.03 (m, 1H), 7.08-7.18 (m, 5H), 7.21-7.32 (m, 2H), 7.81-7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.1, 25.9, 31.1, 116.7, 125.1, 125.3, 125.9, 127.1, 129.2, 129.3, 131.9, 133.5, 134.0, 140.0, 143.9, 156.3; IR (neat, cm^{-1}) 3017, 2932, 2859, 1476, 1215; HRMS calcd for $C_{20}H_{18}Se_2$ 417.98082, found 417.98160.

(2-Phenylbenzo[*b*]selenophen-3-yl)mercury(II) chloride (29). To a solution of 0.25 mmol of **10** in glacial acetic acid (5 mL) was added 0.27 mmol of $Hg(OAc)_2$ at 0 °C. The resulting solution was stirred at 0 °C for 1 h and room temperature for an additional 1 h. The resulting mixture was poured into an ice cold satd NaCl solution (10 mL) with vigorous stirring. The resulting mixture was filtered and the residue was washed with water (5 mL) and hexane (10 mL). The residue was dried and recrystallized using $CHCl_3$ to give the pure product as a white solid: mp 207-209 ^oC: ^1H NMR ($CDCl_3$) δ 7.28 -7.43 (m, 2H), 7.39-7.52 (m, 4H), 7.63-7.66 (m, 2H), 7.87 (d, J = 7.3 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H); IR (KBr, cm^{-1}) 3063, 3015, 2989, 1583, 1477, 1441; Anal. Calcd for $C_{14}H_9SeHgCl$: C, 34.16; H, 1.84. Found: C, 34.01; H, 1.71.

2-Octyl-3-phenylbenzo[*b*]selenophene (36). To the stirred solution of 5:1 DMF/water (5 mL), 0.25 mmol of 3-iodo-2-octylbenzo[*b*]selenophene (**15**), $Pd(PPh_3)_4$ (5 mol %) and 0.50 mmol of K_2CO_3, 0.37 mmol of phenylboronic acid was added. The reaction flask was sealed and flushed with Ar. After overnight stirring at 100 ^oC, the resulting mixture was filtered, washed with satd aq NH_4Cl and extracted with diethyl ether (3 x 10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using hexanes as the eluent to furnish the desired product as colorless oil: ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.1 Hz, 3H), 1.20-1.34 (m, 10H), 1.67 (quintet, J = 7.6 Hz, 2H), 2.83 (t, J = 7.8 Hz, 2H), ; ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 29.3, 29.4, 29.5, 31.1, 32.1, 33.0, 124.2, 124.6, 124.9, 125.5, 127.5, 128.7, 130.4, 136.9, 137.1, 139.6, 143.4, 147.6 ; IR (neat, cm^-

^{1}) 3055, 2925, 2853, 1453, 1434, 1215; HRMS calcd for $C_{22}H_{36}Se$ 370.11997, found 370.12059.

2-Phenyl-3-(phenylethynyl)benzo[*b*]selenophene (37). To a solution of Et_3N (5 mL), 0.25 mmol of 3-iodo-2-phenylbenzo[*b*]selenophene (**16**) and $PdCl_2(PPh_3)_2$ (2 mol %) (stirring for 5 min beforehand), CuI (1 mol %) was added and the flask was sealed and flushed with Ar. 0.38 Mmol of phenylacetylene dissolved in 2 mL of Et_3N was then added dropwise and the reaction mixture was allowed to stir at room temperature for 24 h. After the reaction was over, the resulting solution was filtered, washed with satd aq NaCl and extracted with diethyl ether (3 x 10 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using hexanes as the eluent. The product was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.31-7.43 (m, 5H), 7.45-7.52 (m, 3H), 7.55-7.59 (m, 2H), 7.86 (d, J = 5.9 Hz, 1H), 7.99 (d, J = 5.7 Hz, 1H), 8.08 (d, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 85.6, 93.8, 116.9, 123.6, 125.3, 125.4, 125.6, 125.7, 128.6, 128.7, 128.9, 129, 129.2, 131.8, 136.0, 139.1, 143.3, 151.1; IR (neat, cm^{-1}) 3053, 2986, 2304, 1421, 1265; HRMS calcd for $C_{22}H_{14}Se$ 358.02062, found 358.02672.

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CHAPTER 2: BENZYLIC C-H ACTIVATION AND C-O BOND FORMATION VIA ARYL TO BENZYLIC 1,4-PALLADIUM MIGRATIONS

Based on a paper accepted in *Tetrahedron*

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Abstract

A procedure for benzylic C-H activation has been developed using a palladium 1,4 aryl to benzylic migration as a key step. Carboxylates and phenoxides readily trap the resulting benzylic palladium intermediates obtained from palladium "through space" migration. Aryl bromides and iodides have been successfully employed in this reaction, furnishing moderate to good yields. The mechanism of this reaction has been studied by deuterium labeling experiments, which suggest that the migration of palladium from an aryl to a benzylic position occur reversibly. The reaction conditions developed for the migration process also oxidize neighboring benzylic alcohols to the corresponding aldehydes and ketones

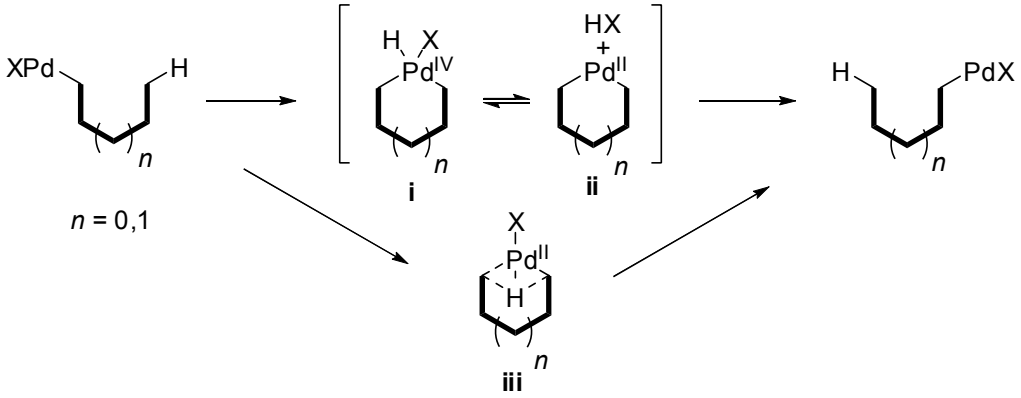
Introduction

Metal-catalyzed C-C bond forming reactions and C-H activation are well studied areas of growing interest.[1] These reactions have been increasingly applied to the synthesis of natural products.[1e-h] Among all of the transition metals known to undergo such processes, the C-C bond forming reactions of palladium have received the most attention. In recent years, palladium-catalyzed C-H activation has been used extensively in organic synthesis.[2] Many examples of cyclopalladation proceeding through alkyl/aryl palladacycles have been reported. They have proven to be a good model for C-H activation.[3] Lautens, Catellani and others have successfully employed these reactions for the formation of a variety of heterocyclic ring systems.[3]

Transition metal-catalyzed intramolecular C-H activation via "through space" migration of a metal has been recently disclosed.[4] It appears that the "through space" migration is quite a general reaction in the case of palladium, examples of vinylic to aryl,[5] aryl to aryl,[6] alkyl to aryl,[7] vinylic to aryl to allylic,[8] benzylic to aryl,[9] and aryl to imidoyl[10] migration having been recently reported. We have earlier demonstrated that in *o*-iodobiaryls, palladium can migrate from one ring to the other and the resulting palladium intermediate can be trapped by Heck, as well as Suzuki, cross-coupling reactions or direct arylation.[6] The arylpalladium intermediate formed by alkyl to aryl palladium migration can also be trapped by Heck olefination or arylation.[7] Cesium pivalate, a crucial base for these Pd migration reactions, can also be used for the trapping, as we have demonstrated in vinylic to aryl to allylic migrations to form the corresponding allylic esters.[8]

Metal migration reactions provide an alternate way to introduce a palladium moiety into a specific position in an organic molecule, which has proven to be a useful tool for the synthesis of many heterocyclic ring systems. Vinylic to aryl migrations have been employed for the synthesis of alkylidene fluorenes,[5a,b] dibenzofurans,[5c,d] carbazoles,[5c,d] and indoles,[5d] whereas alkyl to aryl and aryl to aryl migrations have proven useful for the synthesis of fused polycycles.[6,7] Recently, we have also utilized aryl to imidoyl palladium migrations for the synthesis of fluoren-9-ones and xanthones.[10] Dyker has successfully applied the C-H activation of a methoxy group for the synthesis of 6*H*-dibenzo[*b*,*d*]pyrans.[11]

Scheme 1



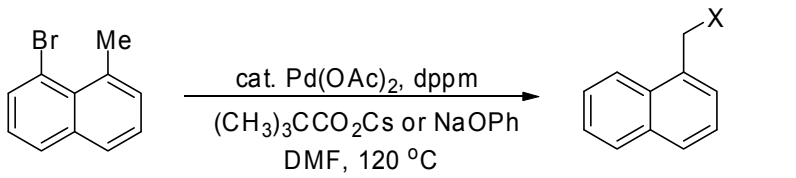
The reported palladium migration reactions are presumed to proceed through a five- or six-membered palladacycle. The mechanism suggested for these Pd migrations by our group involves a palladacycle(IV) hydride **i** or a palladacycle(II) intermediate **ii**.[5-8] In contrast to our observations, a theoretical study published by Bour and co-workers suggests the possibility of intermediate **iii,** which they suggest is energetically favored.[5e,f] However, this mechanism fails to account for H-D exchange processes observed in our present work, as well as many of our earlier migration reactions.[6a,8]

Wang and co-workers have reported the migration of palladium from a benzylic to an aryl position and subsequent trapping of the resulting intermediates by a Heck reaction.[9] Their reaction conditions required that relatively electron-rich alkenes be employed in order for the Pd migration to take place prior to the Heck reaction. A mixture of isomeric olefins was produced, reducing the synthetic utility of the overall process. Moreover, they did not demonstrate the actual migration of the palladium from an aryl to a benzylic position. Herein, we report a number of aryl to benzylic palladium migrations and subsequent trapping of the benzylic palladium intermediate by oxygen nucleophiles to form benzylic esters and ethers. The advantage of our methodology is that the benzylic position can be selectively activated, resulting in good clean reactions, producing a single product in good yields.

Results and discussion

We have found that 1-bromo-8-methylnaphthalene (**1**), prepared by the reduction of commercially available (8-bromonaphthalen-1-yl)methanol using $NaBH_3CN$ and $BF_3 \bullet Et_2O$,[12] when subjected to our standard palladium migration conditions employing cesium pivalate as a base furnished the corresponding benzylic ester **2** in 64% yield (Scheme 2; Table 1, entry 1). The reaction requires a shorter reaction time (6 h) compared with our earlier reported migration reactions and is very clean. Only a trace amount of the protodehalogenated by-product 1-methylnaphthalene was observed.

Scheme 2



1

X = O_2CCMe_3 (**2**) 64%
X = OPh (**3**) 40%

To study the scope of this migration process, different nucleophiles other than cesium pivalate have been employed as potential traps for the presumed benzylic palladium intermediate. It seemed most reasonable to try nucleophiles which have been used to trap π-benzylic[13] and π-allylic[14] intermediates. As mentioned earlier, cesium pivalate has proven crucial for migration of the palladium in our earlier work. However, we were surprised to observe that sodium phenoxide also allows the migration of palladium. Nucleophilic displacement of palladium by this nucleophile gave a 40% yield of the corresponding benzylic aryl ether **3** (Scheme 2; Table 1, entry 2). However, most other nucleophiles examined failed to give the desired product, including an alkoxide, amines, azide, malonate and a phthalimide anion (Table 1, entries 3-8).

Table 1. Effect of the nucleophile on the reaction in Scheme 2.[a]

entry	nucleophile	time (h)	product	yield (%)
1	$(CH_3)_3CCO_2Cs$	6	**2**	64
2	PhONa	12	**3**	40
3	EtONa	24	**4**	0
4	Ph_2NH	24	**5**	0

5	*n*-Bu_2NH	24	**6**	0
6	NaN_3	24	**7**	0
7	diethyl sodium malonate	24	**8**	0
8	sodium phthalimide	24	**9**	0

[a] Reaction conditions: all reactions were performed using 0.25 mmol of aryl halide **1a**, 5 mol % of $Pd(OAc)_2$, 5 mol % of dppm, 3 equiv of the nucleophile and 4 mL of DMF at 120 °C.

Since the cation present in such reactions can often have a profound effect on the overall yield, we have examined the effect of various alkali metal pivalates on the process shown in Scheme 2 (see Table 2). In contrast to cesium pivalate, sodium pivalate gave a poor yield of 27% (Table 2, compare entries 1 and 2). We also tried the corresponding potassium and lithium salts, but they also failed to give better yields when compared with cesium. Potassium pivalate only gave a 15% yield of the desired product and lithium pivalate failed to give any of the desired product even after 1 day (entries 3 and 4). No correlation is observed between the size of the cation and the yield of the reaction.

Table 2. Effect of the cation on the reaction in Scheme 2. [a]

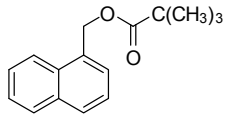
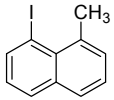
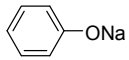
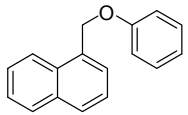
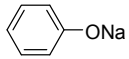
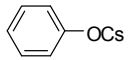
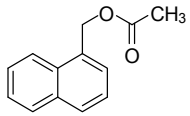
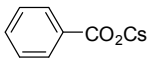
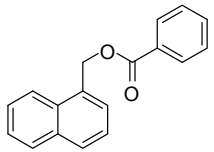
entry	base	time (h)	yield (%)
1	$(CH_3)_3CCO_2Cs$	6	64
2	$(CH_3)_3CCO_2Na$	12	27
3	$(CH_3)_3CCO_2K$	12	15
4	$(CH_3)_3CCO_2Li$	24	0

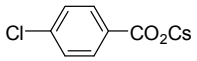
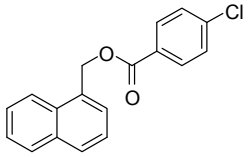
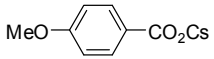
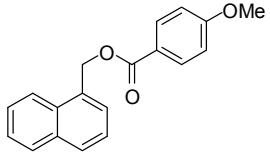
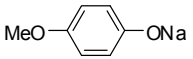
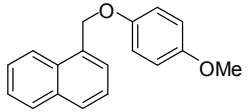
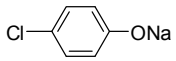
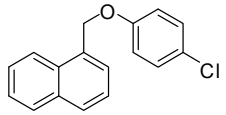
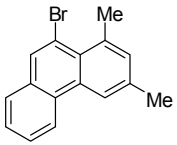
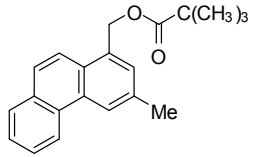
[a] Reaction conditions: all reactions were performed using 0.25 mmol of aryl halide **1a**, 5 mol % of $Pd(OAc)_2$, 5 mol % of dppm, 3 equiv of the base and 4 mL of DMF at 120 °C.

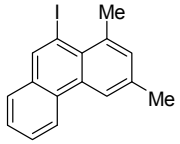
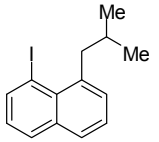
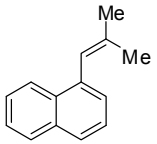
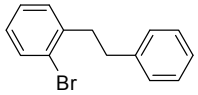
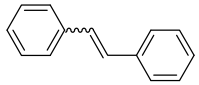
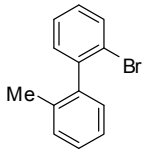
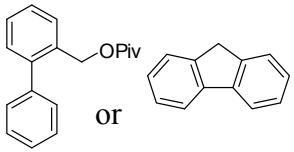
To further study the scope of this methodology, other aryl halides along with several other phenoxides and carboxylates have been subjected to our migration reaction conditions (Table 3). In the pivalate reactions, we have found that 1-iodo-8-methylnaphthalene (**10**) gives a better yield and a cleaner reaction than the corresponding bromide (Table 3, entries 1 and 2). Similar results have been obtained with phenoxide as the nucleophile. Thus, iodoarene **10** gave aryl ether **3** in a 52% yield, while the corresponding aryl bromide furnished the desired product in only a 40% yield (entries 3 and 4). Surprisingly, aryl bromide **1** when subjected to our migration conditions using cesium phenoxide as the nucleophile failed to give a higher yield of the desired aryl ether **3** (entry 5).

When cesium acetate was employed, instead of cesium pivalate, the yield of the reaction dropped from 81% to 64% (compare entries 2 and 6). Substituted cesium benzoates have also been successful in these benzylic C-H activation processes (entries 7-9). However, the yields are lower than those obtained using pivalate anion. Cesium *p*-chlorobenzoate (entry 8) produced a lower yield than cesium benzoate (entry 7). However, cesium *p*-methoxybenzoate resulted in a higher yield (entry 9). This observation can be attributed to the relative nucleophilicity of the corresponding anions. The nucleophilicity of the phenoxides has also been found to be a crucial factor in the yields of the reactions (compare entries 4, 10 and 11). Phenoxide gave a lower yield of ether **3** than *p*-methoxyphenoxide, which gave a 57% yield of the desired product **15** (entry 10). Whereas *p*-chlorophenoxide gave **16** in only a 44% yield (entry 11).

Table 3. Scope of the benzylic C-H activation.[a]

entry	aryl halide		base	time (h)	product		yield (%)[b]
1		**1**	$(CH_3)_3CCO_2Cs$	6		**2**	64
2		**10**	$(CH_3)_3CCO_2Cs$	4		**2**	81
3		**1**		12		**3**	40
4		**10**		12		**3**	52
5		**1**		12		**3**	39
6		**10**	CH_3CO_2Cs	4		**11**	64
7		**10**		4		**12**	61

8		**10**		4		**13**	38[c]
9		**10**		4		**14**	67
10		**10**		12		**15**	57
11		**10**		12		**16**	44
12		**17**	$(CH_3)_3CCO_2Cs$	6		**18**	37

13		**19**	$(CH_3)_3CCO_2Cs$	4		**18**	66
14		**20**	$(CH_3)_3CCO_2Cs$	4		**21**	75[c]
15		**22**	$(CH_3)_3CCO_2Cs$	24		**23**	0
16		**24**	$(CH_3)_3CCO_2Cs$	24		**25** or **26**	0

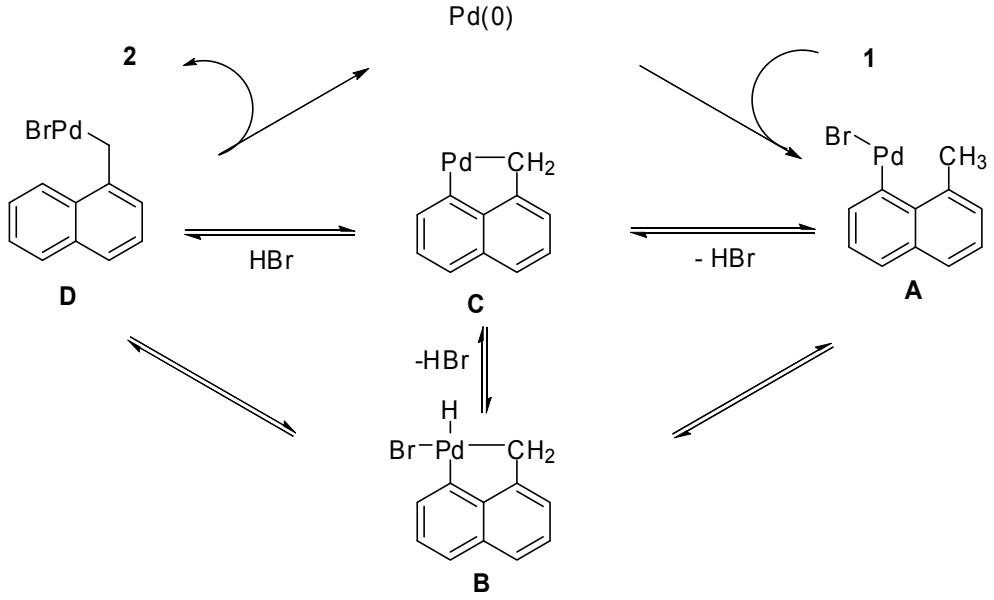
[a] Unless otherwise stated, all reactions were performed using 0.25 mmol of the aryl halide, 5 mol % of $Pd(OAc)_2$, 5 mol % of dppm, 3 equiv of the base and 4 mL of DMF at 120 °C.
[b] Isolated yield.
[c] The yield was determined by quantitative ^1H NMR spectroscopic analysis.

Our methodology has an advantage over typical benzylic oxidations or brominations as these latter reactions are usually not very selective if more than one benzylic group is present. Our methodology can be used for selective C-H activation as observed in the case of aryl halides **17** and **19,** where the benzylic C-H, which is in close proximity to the halide is selectively activated and furnishes only the corresponding ether (entries 12 and 13). Analogous to our earlier observation, aryl bromide **17** furnished the corresponding ester **18** in a lower yield (37%) than aryl iodide **19**, which gave a 66% yield of ester **18** (entries 12 and 13).

The benzylic palladium intermediate formed after palladium migration can also undergo facile β-hydride elimination when such hydrogens are available, as observed in the case of aryl iodide **20**, where the expected product **21** was formed in a good yield of 75% (entry 14). Our efforts to extend this methodology to a limited number of other systems have failed. For example, no migration/hydride elimination product **23** was observed when bibenzyl **22** was subjected to the usual migration reaction conditions (entry 15). In similar systems, Olivier and co-workers have demonstrated the C-H activation of an alkyl position.[15] However, the presence of a benzylic gem-dialkyl group in their systems reduces the bond angle and enhances the possibility of forming the necessary five-membered ring palladacycle. Our one attempt to activate a benzylic C-H bond by a 1,5-palladium migration also failed, as biphenyl derivative **24** failed to furnish any of the desired products **25** or **26**, instead producing only protodehalogenated product (entry 16).

Possible mechanisms for these reactions are depicted in Scheme 3. After oxidative addition of the aryl halide to Pd(0), the resulting intermediate **A** can insert into the neighboring C-H bond to form palladium(IV) intermediate **B** or a palladium(II) intermediate **C**. Intermediate **C** can also be produced by loss of HBr from palladacycle **B.** Palladacycles **B** and **C** both can form **D**, which results in migration of the palladium to the benzylic position. Previous work on benzylic to aryl palladium migrations reported by Wang and co-workers[9] suggested that the steps to obtain **D** from **A** could be reversible.

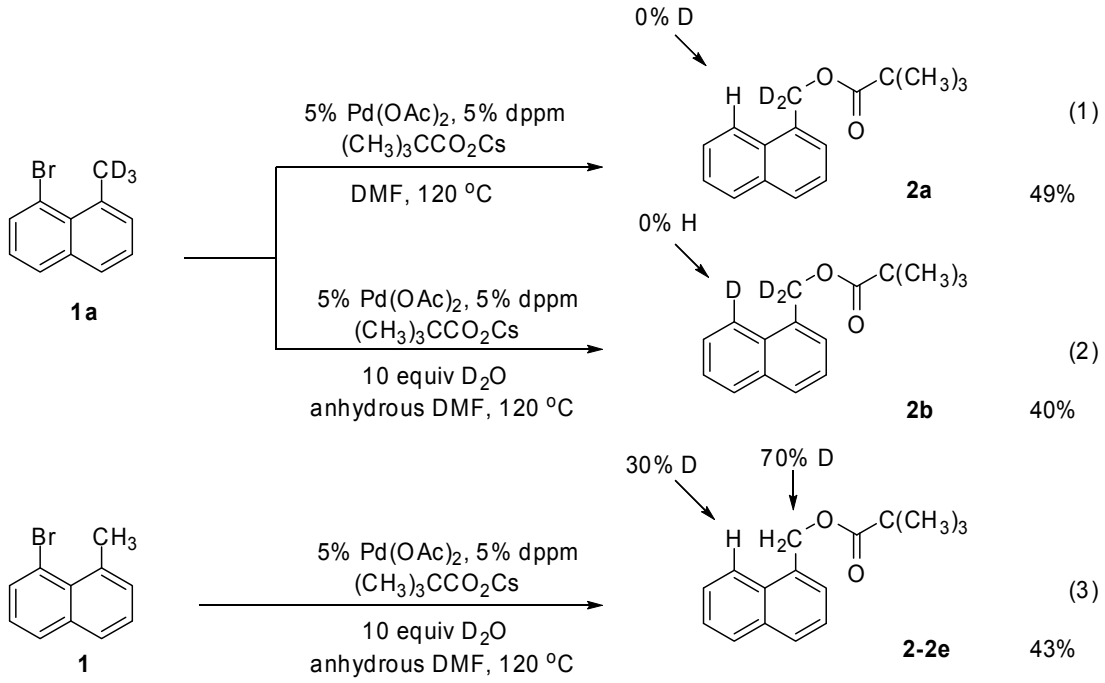
Scheme 3



To study the mechanism in detail, we decided to employ a deuterated version of compound **1** (**1a)** under our standard reaction conditions, since such reactions should result in the migration of deuterium from the benzylic position to the aryl position (Scheme 4). To our surprise, we did not see any deuterium incorporation in the aromatic

ring when **1a** was allowed to react with cesium pivalate in DMF straight from the bottle (Scheme 4, equation 1). This observation might be attributed to H-D exchange between the palladium(IV) deuteride or DBr formed in the reaction with spurious H_2O present in the reaction system. However, we observed 100% deuterium incorporation into one aryl position when the same reaction was performed with 10 equivalents of D_2O added to anhydrous DMF (Scheme 4, equation 2). The outcome of the above studies strongly suggests that the H-D exchange reactions arise by the equilibria indicated in Scheme 3. This encouraged us to check the reversibility of the steps that might exist between intermediates **D** and **A**.

Scheme 4



To do this, we decided to carry out the reaction with non-deuterated 1-bromo-8-methylnaphthalene in the presence of 10 equivalents of D_2O using anhydrous DMF

(Scheme 4, equation 3). Proton NMR spectroscopic analysis of the product showed that incorporation of the deuterium occurs not only in the aryl position (30% of one aromatic hydrogen), but also in the benzylic position (70% of two benzylic hydrogens). This provides strong evidence that the palladium migration occurs reversibly between the aryl and benzylic positions. Increasing the amount of D_2O from 10 equivalents to 20 equivalents did not change the amount of deuterium incorporation in either the aryl or the benzylic position. Interestingly, we have found that not only an M+ (MW = 242) peak was observed in the GC-MS, but also M+1, M+2 and M+3 peaks were also present in significant amounts.

These four peaks in the GC-MS suggest that six possible compounds have been formed as illustrated in Figure 1. Out of the six possible products formed, the mechanism for the formation of **2e** and **2c** is outlined in Scheme 5. As discussed earlier, palladacycles **B** and **C** could be obtained from **A** via cyclopalladation. These two cyclic intermediates can undergo H-D exchange to form **E**. Benzylic intermediate **F** can be obtained from reductive elimination of **E**, or from palladium(II) palladacycle **C** directly. Nucleophilic substitution of **F** ultimately produces the deuterated compound **2e**. Similar steps can be written for the formation of **2c** starting from **G**. The formation of **G** can take place from **E** via reductive elimination. **G**, which can also be obtained from **C** directly, can undergo benzylic C-H activation similar to that of **A**. The steps for the formation of **2c** from **G** are expected to be similar to those required for the formation of **2e**. Again, they may proceed through palladium(II) intermediate **H** or palladium(IV) intermediate **I**. Equivalent processes can be written starting from **H** and **J** for the formation of the other deuterated products.

Scheme 5

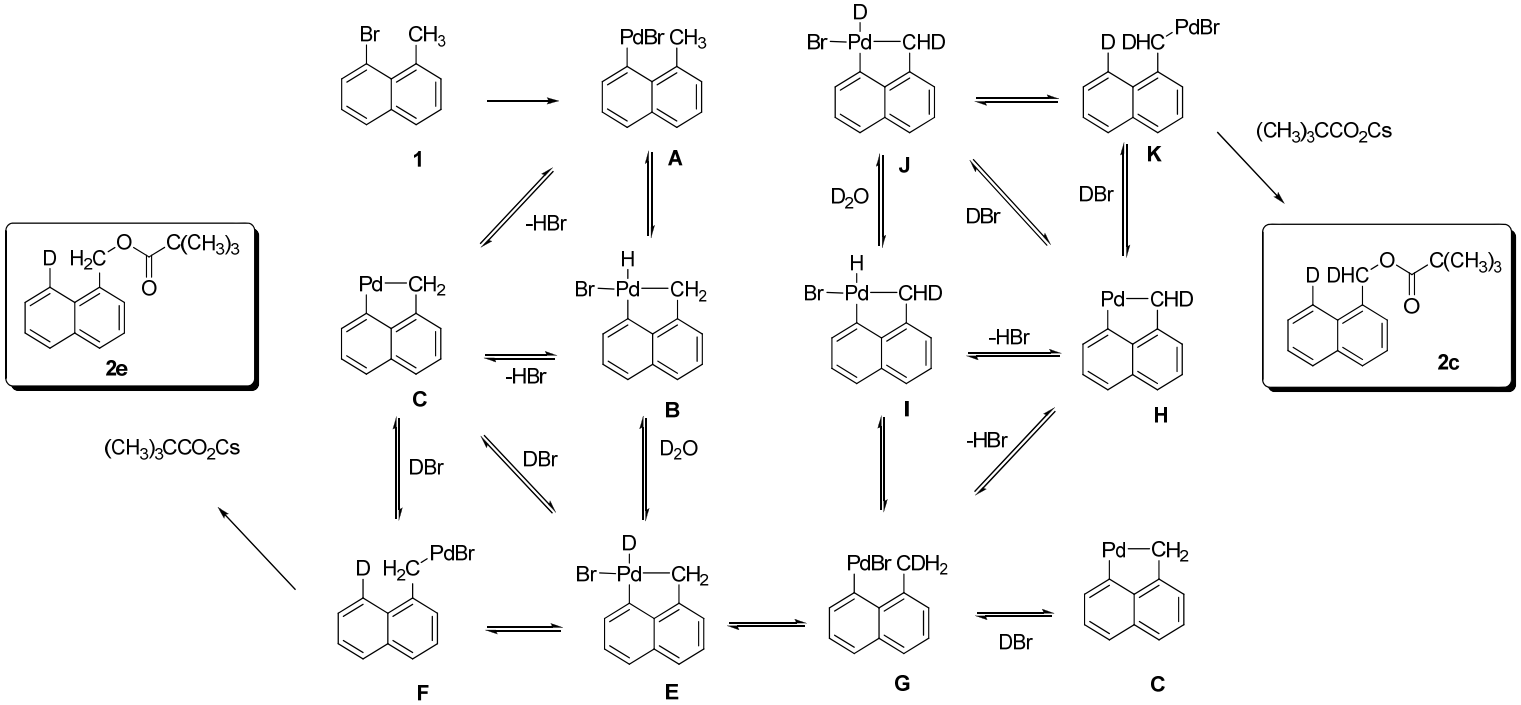
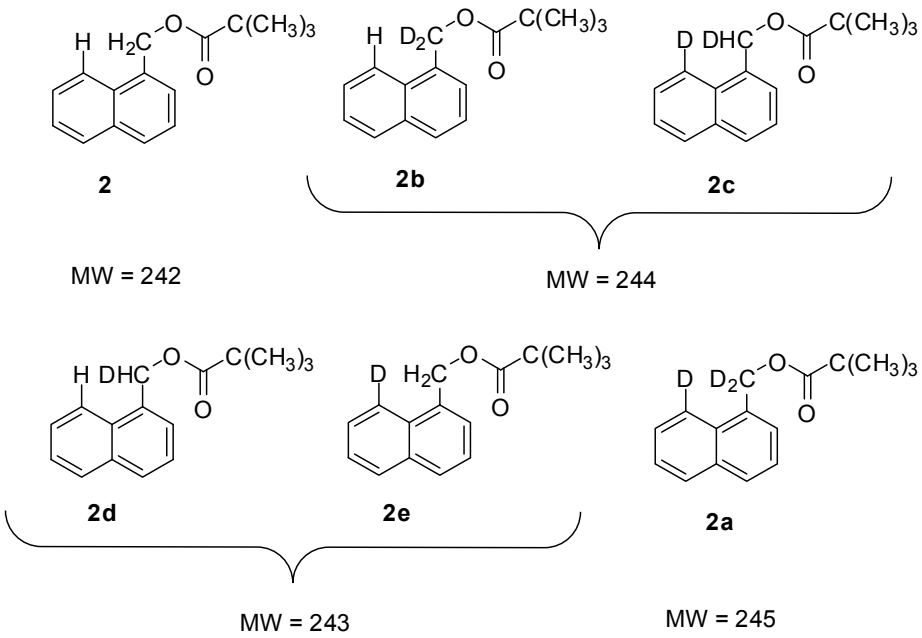
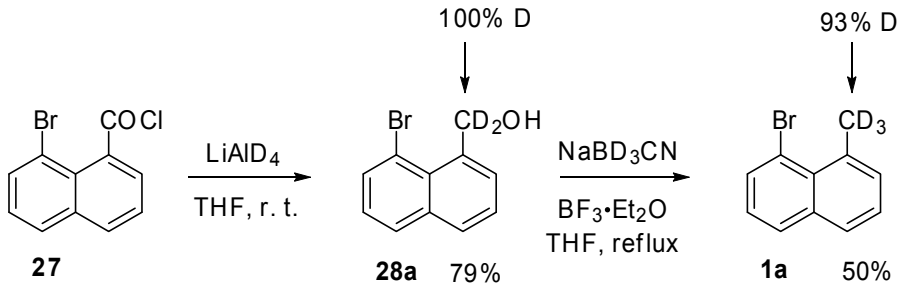


Figure 1



The deuterated compound **1a** used for the mechanistic study was prepared in two steps. We started from 8-bromo-1-naphthoyl chloride (**27)** (Scheme 6), which was prepared from 8-bromo-1-naphthoic acid using a literature procedure.[16] Reduction of the acid chloride **27** to the corresponding benzylic alcohol **28a** using $LiAlD_4$ resulted in a 79% yield of **28a** with 100% deuterium incorporation in both of the benzylic positions. The reduction of **28a** with $NaBD_3CN$ and $BF_3•Et_2O$ gave the desired deuterated compound **1a** in a 50% yield with 93% deuterium incorporation in the three benzylic positions.

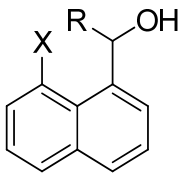
Scheme 6



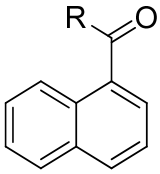
Oxidation of benzylic alcohols

The palladium-catalyzed oxidation of alcohols has been well studied.[17] Generally these reactions require a palladium catalyst with an aryl halide or O_2 as the oxidant.[17b-i] When aryl halide **28** was subjected to our standard palladium migration conditions, 1-naphthaldehyde (**29)** was obtained in a 71% yield (Scheme 7). Since the reaction was performed under argon, the absence of O_2 suggests that the aryl bromide present in the starting material must be acting as an oxidant. To check the involvement of the aryl bromide in the reaction, we performed the same reaction using 1-naphthylmethanol (**30)** (Scheme 7, entry 2), which did not give any aldehyde product. Aryl iodide **31** gave a cleaner reaction than **28** and a slightly higher yield of aldehyde when compared with the corresponding bromo derivative **28** (compare entries 1 and 3). We have also found that aryl halide-containing secondary benzylic alcohols can be oxidized to the corresponding ketones in good yields (entries 4 and 5). The relatively hindered alcohol **36** was also successfully oxidized, but in a lower yield of 52% (entry 6).

Scheme 7



5% $Pd(OAc)_2$, 5% dppm
3 $(CH_3)_3CCO_2Cs$
DMF, 120 °C, 2 h

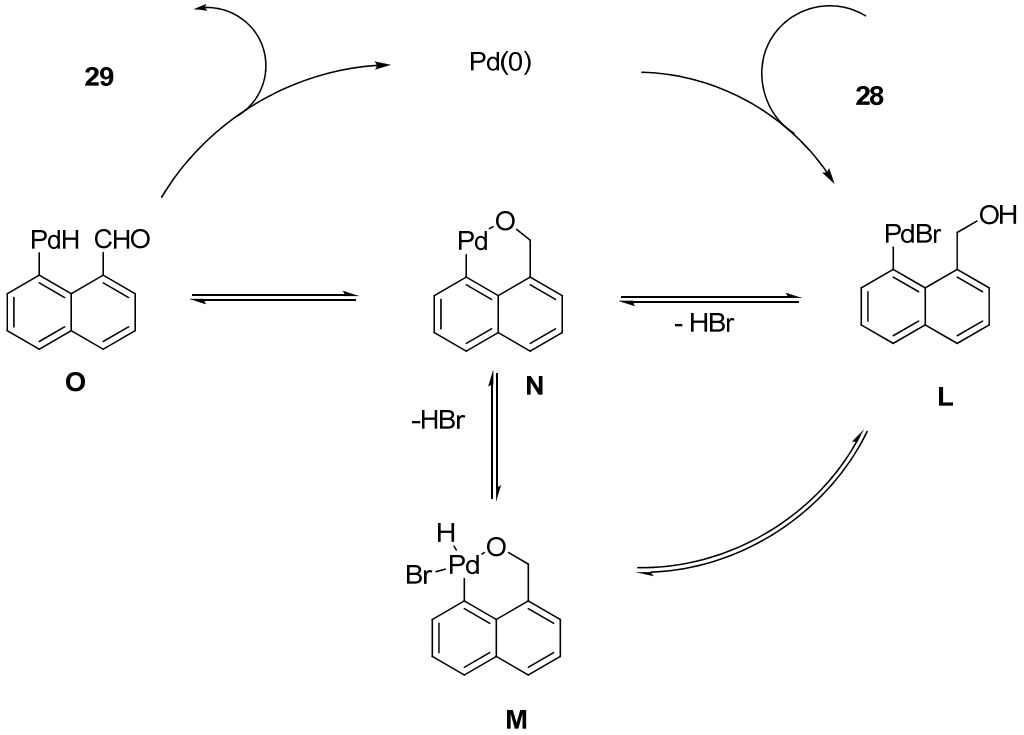


entry	aryl alcohol	X	R	product	yield (%)
1	**28**	Br	H	**29**	71
2	**30**	H	H	**29**	0
3	**31**	I	H	**29**	73
4	**32**	I	$PhCH_2CH_2$	**33**	70
5	**34**	Br	*n*-Hex	**35**	67
6	**36**	Br	Ph	**37**	52

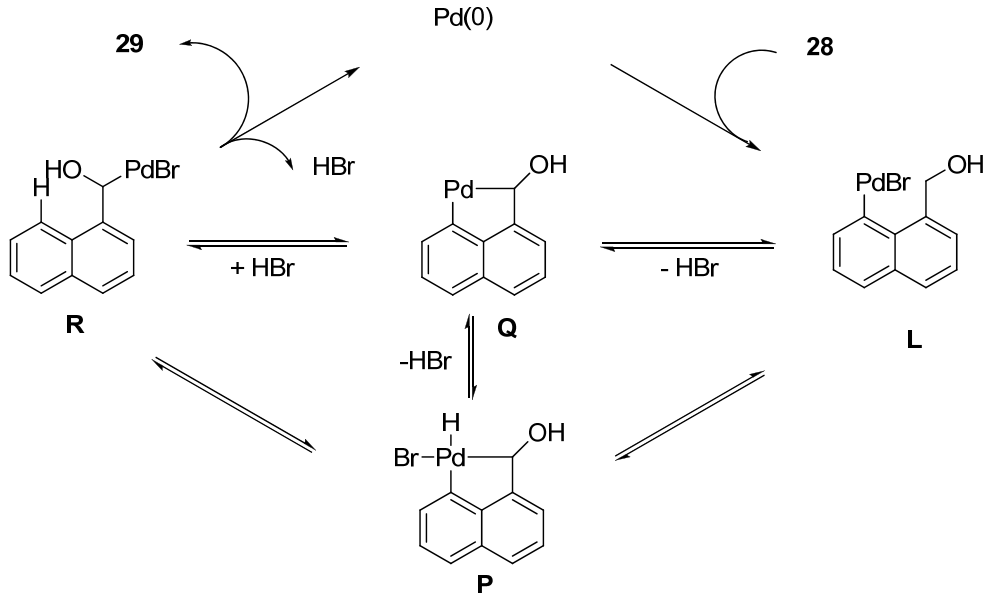
This redox chemistry could potentially occur via two different pathways. One possible route to the product could be the usual oxidation mechanism suggested by Turner and others (Scheme 8).[17c] Palladacycle **L** obtained after oxidative insertion of palladium into aryl halide **28**, can react with the neighboring alcohol group to form the Pd(IV) palladacycle **M** or Pd(II) intermediate **N**. Arylpalladium intermediate **O** can then be obtained via β-hydride elimination from **N** and can undergo reductive elimination to form the corresponding product **29**. A second possible route based upon a methoxy C-H activation process reported by Dyker[12] and our present aryl to benzylic palladium migration is outlined in Scheme 9. Arylpalladium intermediate **L** could also undergo benzylic C-H activation to form palladacycles **P** or **Q**. Intermediate **P** can also lead to the formation of **Q** via loss of HBr. Benzylic palladium intermediate **R**, which might be

obtained from **P** and/or **Q** could easily undergo *β*-hydride elimination to give aldehyde **29**.

Scheme 8

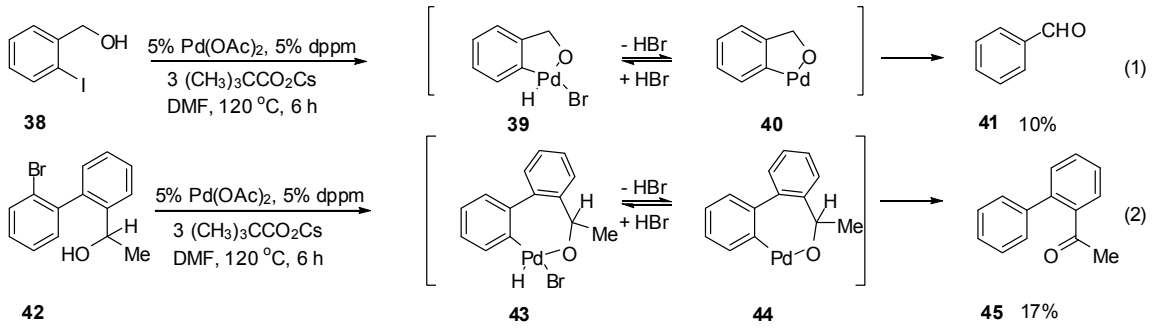


Scheme 9



If the reaction proceeds through the pathway mentioned in Scheme 8, then it should also be possible to oxidize aryl iodide **38** under these conditions (Scheme 10, eq 1). Moreover, the formation of five-membered ring palladacycles similar to **M** and **N** might be favored. However, we observe only a 10% yield of benzaldehyde (**41**) from this reaction. Even though the formation of five-membered rings is more favorable than six-membered ring formation, it is not a favorable geometry for the *β*-hydride elimination. Analogous to our above observation, the aryl bromide **42** also failed to furnish the desired product in a good yield, affording only a 17% yield of ketone **45** (Scheme 10, eq 2). In this case, the formation of a seven-membered ring palladacycle is not very favorable, even though it is probably a more favorable geometry for *β*-hydride elimination.

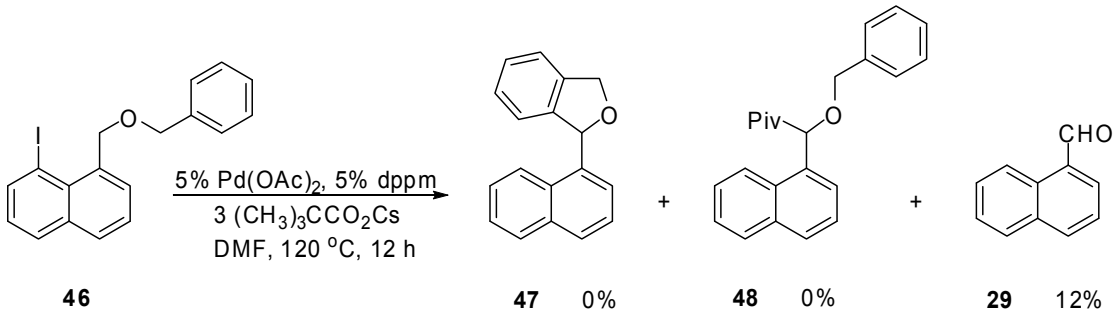
Scheme 10



We have also subjected aryl halide **46** to our standard migration conditions hoping to perhaps see heterocycle **47** or pivalate **48,** the formation of which would suggest the possibility of benzylic C-H activation next to the electron-withdrawing oxygen (Scheme 11). Cyclization of the resulting benzylic palladium intermediate onto the remote aryl group would lead to heterocycle **47**, whereas nucleophilic substitution of the benzylic palladium by pivalate anion should produce compound **48**. To our surprise, only 1-naphthaldehyde (**29)** was formed in a poor 12% yield. This observation suggests the

possible formation of **48**, which has hydrolyzed to give the observed aldehyde or perhaps Pd-benzyl elimination from an intermediate formed by benzylic C-H activation. However, all attempts to isolate **48** have failed.

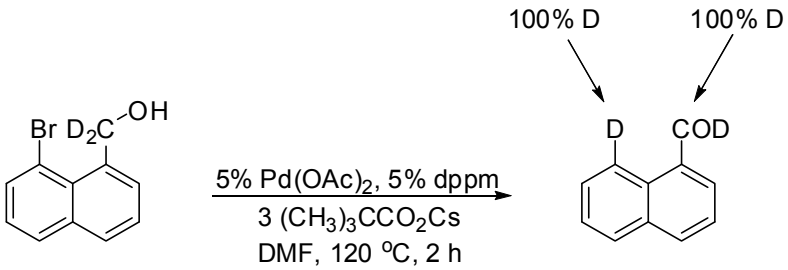
Scheme 11



46 **47** 0% **48** 0% **29** 12%

When the deuterium-labeled compound **28a** was subjected to our usual palladium migration conditions, 100% migration of one deuterium to the aryl position was observed (Scheme 12). This reaction was unaffected by H-D exchange with solvent, even when H_2O is added. This would presumably not be the case if the reaction is taking place by the mechanism depicted in Scheme 9. The deuterium-labeling experiments and the possibility of strong coordination between palladium and oxygen suggest that the pathway outlined in Scheme 8 is more favorable for this particular reaction.

Scheme 12



28a **29a** 66 %

Conclusions

A benzylic C-H activation procedure has been developed using "through space" migration of palladium as a key step. This process is not only very interesting from the point of view of mechanism, but it is also very useful for selective C-H activation. Carboxylates and phenoxides have been employed to prepare the corresponding benzylic esters and ethers in moderate to good yields. It is observed that the more nucleophilic aromatic phenoxides and carboxylates give better yields. The mechanism of the reaction involving palladium(II) or palladium(IV) intermediates have been discussed. Deuterium-labeling experiments suggest that the key step is reversible. That is aryl to benzylic and benzylic to aryl migrations are both possible. The reaction conditions developed for these migration processes also oxidize aryl-containing benzylic alcohols to the corresponding aldehydes and ketones in good yields with simultaneous reduction of halogen. Two possible mechanisms for the oxidation of these alcohols are discussed.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. (8-Bromonaphthalen-1-yl)methanol (**28**), **30**, (8-iodonaphthalen-1-yl)methanol (**31**), and **38** were obtained commercially. All reagents were used directly as obtained commercially unless otherwise noted. The following starting materials were made

according to literature procedures: 8-bromo-1-naphthoyl chloride (**27**),[16] 10-bromo-1,3-dimethylphenanthrene (**17**),[18] 1-bromo-2-(phenethyl)benzene (**22**),[19] and 1,8-diiodonaphthalene.[20]

Preparation of 1-bromo-8-methylnaphthalene (1). To a stirred solution of (8-bromonaphthalen-1-yl)methanol (472 mg, 2.0 mmol) and BF_3•Et_2O (2.39 ml, 6.0 mmol) in dry THF (10 mL), sodium cyanoborohydride (240 mg, 4.0 mmol) was added. The reaction mixture was allowed to reflux for 2 days and was monitored by TLC. After completion of the reaction, 20 ml of ether were added and the solution was washed with saturated aqueous $NaHCO_3$ and brine. The resulting mixture was dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the crude mixture on silica gel afforded the desired product **1** (234 mg, 53%) as a white solid: mp 78-80 ^oC (lit.[21] 79-80 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 3.14 (s, 3H), 7.23 (t, J = 7.6 Hz, 1H), 7.34-7.41 (m, 2H), 7.70-7.76 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 120.0, 125.6, 126.0, 128.1, 129.3, 131.0, 131.3, 133.4, 135.4, 136.6; IR (neat, cm^{-1}) 3055, 2968, 2930, 2861, 1563, 1497, 1441, 1381, 1357, 1248, 1192, 1070, 893, 807, 756; HRMS calcd for $C_{11}H_9Br$ 219.98876, found 219.98916.

Bromo-8-(trideuteromethyl)naphthalene (1a). 8-Bromo-1-naphthoyl chloride[16] (525 mg, 2.0 mmol) in anhydrous THF (2 mL) was added to lithium aluminum hydride (92.4 mg, 2.2 mmol) suspended in anhydrous THF (3 mL). After addition was complete, the mixture was stirred at room temperature for 1 h and hydrolyzed with saturated aqueous sodium sulfate. The resulting solution was extracted with ethyl ether (2 x 10 mL). The ether layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue

was obtained as a pale yellow solid, which was further purified using column chromatography to furnish deuterated alcohol **28a** (376 mg, 79%) as a white solid: mp 83-85 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (br s, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.66 (dd, J = 1.6, 7.2 Hz, 1H), 7.77-7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.4 (m), 118.1, 125.9, 126.2, 129.8, 129.9, 130.2, 130.3, 133.8, 136.7, 136.8; IR (neat, cm^{-1}) 3048, 2961, 1738, 1364, 1227, 1023, 798, 776; HRMS calcd for $C_{11}H_7D_2BrO$ 237.99623, found 237.99655. The deuterated aryl bromide **1a** was prepared using the procedure described for the preparation of **1**, but using alcohol **28a** and $NaBD_3CN$, and was obtained as a white solid: mp 78-80 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 7.6 Hz, 1H), 7.32-7.42 (m, 2H), 7.68-7.75 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (m), 120.0, 125.7, 126.0, 128.1, 129.4, 131.0, 131.3, 133.4, 135.3, 136.6; IR (neat, cm^{-1}) 3055, 2968, 2930, 2861, 1563, 1497, 1441, 1381, 1357, 1248, 1192, 1070, 893, 807, 756; HRMS calcd for $C_{11}H_9D_3Br$ 223.00759, found 223.00802.

1-Iodo-8-methylnaphthalene (10). Trifluoroacetic acid (1.3 gm, 12 mmol) was added to a solution of (8-iodonaphthalen-1-yl)methanol (568 mg, 2.0 mmol) and 5 mL of dry CH_2Cl_2 at 0 °C. A solution of triethylsilane (277 mg, 4.4 mmol) in 1 mL of anhydrous CH_2Cl_2 was added to the reaction. The reaction was allowed to reach room temperature and stirred overnight under nitrogen. After completion of the reaction, the CH_2Cl_2 was removed under reduced pressure and the resulting solution was diluted with 20 mL of ether and washed with saturated aqueous sodium bicarbonate solution. The resulting organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent

under reduced pressure and purification of the crude mixture using column chromatography furnished the desired product **10** (219 mg, 41% yield) as a white solid: mp 62-64 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (s, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.32-7.44 (m, 2H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 90.4, 125.8, 126.2, 128.7, 130.3, 131.0, 133.1, 135.0, 135.9, 142.2 ; IR (neat, cm^{-1}) 3051, 2964, 2927, 2860, 1558, 1494, 1440, 1380, 1191, 1038, 805, 756; HRMS calcd for $C_{11}H_9I$ 267.97490, found 267.97553.

10-Iodo-1,3-dimethylphenanthrene (19). To a stirred solution of **17**[18] (284 mg, 1.0 mmol) in THF (5 mL) at -78 ºC, *n*-BuLi (2.5 M in hexanes, 0.4 mL, 1.0 mmol) was added. The resulting solution was stirred for 15 min. To the resulting solution, I_2 (508 mg, 2.0 mmol) in THF (1 mL) was slowly added by syringe over a period of 5 min. The solution was then allowed to reach room temperature and treated with a saturated aqueous $Na_2S_2O_3$ solution. The resulting mixture was extracted with diethyl ether (2 x 10 mL). The extracted organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash chromatography to provide **19** as a brown solid (209 mg, 63%): mp 65-67 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.19 (s, 3H), 7.32 (s, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 8.41 (s, 1H), 8.55-8.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 27.1, 88.8, 121.8, 123.3, 127.0, 127.2, 127.4, 128.7, 130.3, 132.5, 132.7 133.6, 135.8, 136.2, 142.1; IR (neat, cm^{-1}) 3076, 3052, 2966, 2926, 1613, 1566, 1453, 1378, 11,64, 1033, 901, 874, 779; HRMS calcd for $C_{16}H_{13}I$ 332.00620, found 332.00662.

1-Iodo-8-isobutylnaphthalene (20). A 100 mL round bottom flask containing 1,8-diiodonaphthalene[20] (1.14 gm, 3.0 mmol) was flushed with argon and charged with 50 mL of anhydrous Et_2O. The pale yellow solution was cooled to -30 °C and *n*-BuLi (1.2 mL of 2.5 M solution in hexane, 3.0 mmol) was added over a period of 3 min. After 30 min, isobutyraldehyde (324 mg, 4.5 mmol) in 5 mL of anhydrous Et_2O was added by a syringe. The reaction mixture was allowed to warm to room temperature overnight and was then poured into 30 mL of 10% aqueous HCl. The aqueous layer was separated and extracted with three 10 mL portions of Et_2O. The combined organic layer was washed with 30 mL of aqueous NaCl. After drying over Na_2SO_4, the organic layer was concentrated to afford a yellow oil. Without purification this crude alcohol was added to a stirred solution of trifluoroacetic acid (975 mg, 9.0 mmol) and 5 mL of dry CH_2Cl_2 at 0 °C. A solution of triethylsilane (415 mg, 6.6 mmol) in 1 mL of anhydrous CH_2Cl_2 was added to the reaction. The reaction was allowed to warm to room temperature and stirred overnight under nitrogen. After completion of the reaction, the CH_2Cl_2 was removed under reduced pressure. The resulting solution was diluted with 30 mL of ether and washed with saturated aqueous sodium bicarbonate solution. The separated organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the crude mixture using column chromatography furnished the desired product **20** (130 mg, 14%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 6H), 2.08 (q, J = 6.4 Hz, 1H), 3.44 (d, J = 7.2 Hz, 2H), 7.03 (t, J = 7.6 Hz, 1H), 7.33-7.45 (m, 2H), 7.74 (dd, J = 2.0, 7.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.56 (dd, J = 1.2, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 31.0, 44.5, 89.9, 125.5, 126.1, 129.0, 130.8, 131.9, 132.4, 136.5, 138.4, 142.9; IR (neat, cm^{-1}) 3054, 2951,

2927, 2864, 1558, 1364, 1191, 1009, 801, 762; HRMS calcd for $C_{14}H_{15}I$ 310.021845, found 310.02887.

2-Bromo-2'-methylbiphenyl (22). 2-Bromophenylboronic acid (220 mg, 1.1 mmol) was added to a solution of *o*-iodotoluene (218 mg, 1.0 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol), K_2CO_3 (276 mg, 2.0 mmol), 4 mL of DMF and 1 mL of H_2O. The reaction vial was sealed and flushed with argon and then allowed to stir at room temperature for 24 h. The resulting reaction mixture was diluted with 20 ml of Et_2O and washed several times with water to remove DMF. The resulting organic solution was dried with Na_2SO_4, concentrated in vacuum and purified by column chromatography using hexanes as the eluent to furnish the desired product **22** (189 mg, 77%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 7.12 (d, J = 7.6 Hz, 1H), 7.17-7.40 (m, 6H), 7.66 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 123.8, 125.5, 127.2, 127.9, 128.8, 129.3, 129.8, 130.9, 132.6, 136.0, 141.2, 142.7; IR (neat, cm^{-1}) 3055, 3017, 2941, 2882, 1466, 1403, 1119, 1064, 1004, 779; HRMS calcd for $C_{11}H_9D_3Br$ 246.00441, found 246.00481.

1-(8-Iodonaphthalen-1-yl)-3-phenylpropan-1-ol (32). A 100 mL round bottom flask containing 1,8-diiodonaphthalene[20] (1.14 gm, 3.0 mmol) was flushed with argon and charged with 50 mL of anhydrous Et_2O. The pale yellow solution was cooled to -30 °C and *n*-BuLi (1.2 mL of 2.5 M solution in hexane, 3.0 mmol) was added over a period of 3 min. After 30 min, a solution of 3-phenylpropanal (603 mg, 4.5 mmol) in 5 mL of anhydrous Et_2O was added by a syringe. The reaction mixture was allowed to warm to room temperature overnight and then poured into 30 mL of 10% aqueous HCl. The

aqueous layer was separated and extracted with three 10 mL portions of Et_2O. The combined organic layer was washed with 30 mL of H_2O and 30 mL of saturated aqueous NaCl. After drying over Na_2SO_4, the organic layer was concentrated and the crude product was purified by column chromatography to give the desired alcohol **32** (453 mg, 39%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98-2.10 (m, 1H), 2.11-2.25 (br s, 1H), 2.28-2.41 (m, 1H), 2.95 (t, *J* = 8.8 Hz, 2H), 7.84 (dd, *J* = 2.8, 9.6 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 7.13-7.32 (m, 5H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.74 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 8.29 (dd, *J* = 1.2, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.5, 41.8, 67.6, 87.7, 125.8, 125.9, 126.0, 126.1, 128.4, 128.6, 129.6, 130.7, 131.2, 136.0, 141.3, 142.2, 143.0; IR (neat, cm^{-1}) 3320, 3056, 2951, 2924, 2854, 1563, 1463, 1035, 802, 761; HRMS calcd for $C_{19}H_{17}IO$ 388.03242, found 388.03309.

1-(8-Bromonaphthalen-1-yl)heptan-1-ol (34). Manganese(IV) oxide (352 mg, 4.0 mmol) was added to a solution of the alcohol (8-bromonaphthalen-1-yl)methanol (470 mg, 2.0 mmol) in chloroform (10 mL) and the stirred mixture was allowed to reflux for 24 h. The suspension was filtered through celite and washed with chloroform. The filtrate was washed with water (5 mL), dried with Na_2SO_4 and concentrated in vacuum to give 8-bromo-1-naphthaldehyde (369 mg, 79% yield) as a white solid: mp 81-83 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.81-7.96 (m, 3H), 8.22 (d, *J* = 7.6 Hz, 1H), 11.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.9, 126.0, 127.8, 129.8, 130.2, 133.7, 134.3, 135.7, 136.5, 141.4, 191.7; IR (neat, cm^{-1}) 2878, 2861, 1672, 1609, 1553, 1493, 1335, 1234, 1197, 1063, 824, 790, 747; HRMS calcd for

$C_{11}H_7BrO$ 233.96803, found 233.96836. At 0 °C, a 1 M solution of hexylmagnesium bromide (1.5 mL, 1.5 mmol) was added dropwise to a solution of 8-bromo-1-naphthaldehyde (233 mg, 1.0 mmol) in THF (10 mL). The mixture was stirred for 4 h at room temperature and then hydrolyzed with H_2O (3 mL). The organic phase was separated and the water phase was extracted with ether (2 x 10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was further purified by flash chromatography on silica gel to give the required alcohol **34** (153 mg, 48% yield) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.20-1.45 (br m, 6H), 1.50-1.75 (m, 3H), 1.98-2.18 (m, 2H), 6.60-6.67 (m, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.79-7.88 (m, 2H), 8.02 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.8, 26.5, 29.6, 32.0, 40.7, 69.8, 117.9, 125.6, 125.8, 126.2, 129.2, 129.3, 129.9, 134.4, 136.7, 142.5; IR (neat, cm^{-1}) 3388 (broad), 3056, 2951, 2924, 2854, 1563, 1463, 1192, 1059, 818, 761; HRMS calcd for $C_{17}H_{21}BrO$ 320.07758, found 320.07806.

(8-Bromonaphthalen-1-yl)(phenyl)methanol (36). The compound **36** was prepared as described for the synthesis of **34** using 8-bromo-1-naphthaldehyde and phenylmagnesium bromide and was obtained as a colorless liquid (240 mg, 77% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50-2.80 (br s, 1H), 7.25-7.32 (m, 2H), 7.33-7.42 (m, 4H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.68 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.80-7.94 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.9, 117.9, 125.9, 126.1, 127.4, 127.6, 128.4, 129.5, 130.0, 130.1, 130.2, 134.7, 136.7, 140.1, 144.1; IR (neat, cm^{-1}) 3319, 3083, 3057, 3028, 1561, 1450, 1193, 1035, 761; HRMS calcd for $C_{17}H_{13}BrO$ 312.01498, found 312.01548.

1-(2'-Bromobiphenyl-2-yl)ethanol (42). 2-Bromophenylboronic acid (440 mg, 2.2 mmol) was added to a solution of *o*-iodobenzaldehyde (462 mg, 1.0 mmol), $Pd(PPh_3)_4$ (48 mg, 0.04 mmol), K_2CO_3 (552 mg, 4.0 mmol), 8 mL of DMF and 2 mL of H_2O. The reaction vial was sealed and flushed with argon and allowed to stir at room temperature for 24 h. The resulting reaction mixture was diluted with 30 ml of Et_2O and washed several times with water to remove DMF. The resulting organic solution was dried with Na_2SO_4 and concentrated in vacuum. The crude product was further purified by column chromatography using hexanes as the eluent to furnish the desired product 2'-bromobiphenyl-2-carbaldehyde (848 mg, 82%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.38 (m, 3H), 7.42 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.63-7.73 (m, 2H), 8.05 (dd, *J* = 1.2, 8 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.0, 127.5, 127.6, 128.7, 130.0, 131.0, 131.8, 132.9, 133.8, 133.9, 139.0, 144.6, 191.7; IR (neat, cm^{-1}) 3058, 2916, 2847, 2750, 1693, 1597, 1464, 1393, 1268, 1196, 1003, 826, 754; HRMS calcd for $C_{13}H_9BrO$ 259.98368, found 259.98402. At 0 ^oC, a 1 M solution of methylmagnesium bromide (1.5 mL, 1.5 mmol) was added dropwise to a solution of 2'-bromobiphenyl-2-carbaldehyde (259 mg, 1.0 mmol) in THF (10 mL). The mixture was stirred for 4 h at rt and then hydrolyzed with H_2O (3 mL). The organic phase was separated and the water phase was extracted with ether (2 x 10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was further purified by flash chromatography on silica gel to give alcohol **42** (184 mg, 67% yield) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.4 Hz, 3H), 1.42 (d, *J* = 6.4 Hz, 3H), 2.01 (br s, 2H), 4.64-4.78 (m, 2H),

7.09 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.20-7.42 (m, 8H), 7.44-7.53 (m, 2H), 7.63-7.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.6, 66.9, 67.2, 123.7, 124.2, 125.3, 125.4, 127.2, 127.3, 127.3, 127.5, 128.7, 128.9, 129.2, 129.2, 129.3, 129.9, 131.1, 131.5, 132.6, 132.8, 138.8, 139.4, 141.6, 141.7, 143.0, 144.0; IR (neat, cm^{-1}) 3350 (broad), 3055, 3023, 2971, 2924, 1464, 1444, 1080, 1001, 754; HRMS calcd for $C_{14}H_{13}BrO$ 276.01498, found 276.01531.

1-(Benzyloxymethyl)-8-iodonaphthalene (46). NaH (54 mg, 2.2 mmol) was added in small portions to a stirred solution of (8-iodonaphthalen-1-yl)methanol (566 g, 2.0 mmol) in dry DMF (50 ml) at 0 °C. After 20 min, benzyl bromide (0.42 ml, 4.0 mmol) was added dropwise to the solution at 0 °C, and stirring was continued for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was diluted with Et_2O (30 ml). The organic layer was washed with water and brine, and then dried over $MgSO_4$. Evaporation of the solvent in vacuum afforded a residue, which was purified by column chromatography to furnish ether **46** (658 mg, 88%) as a yellow solid: mp 76-78 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (s, 2H), 5.50 (s, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.28-7.53 (m, 6H), 7.74-7.84 (m, 2H), 7.85 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.6, 72.3, 125.6, 126.3, 127.6, 128.0, 128.4, 129.6, 130.3, 130.3, 132.7, 133.9, 136.2, 138.3, 142.6; IR (neat, cm^{-1}) 3055, 3024, 2971, 2868, 1495, 1483, 1451, 1351, 1212, 1193, 1064, 1001, 815, 767, 757; HRMS calcd for $C_{18}H_{15}IO$ 374.01676, found 374.01709.

General procedure for the C-H activation chemistry. To a stirred solution of 0.25 mmol of the aryl halide, $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), dppm (4.8 mg, 0.012 mmol)

and 4 mL of DMF, 3 equiv of the desired base was added. The reaction vial was sealed, flushed with argon, heated at 120 °C, and monitored by TLC. After completion of the reaction, the mixture was diluted with 20 mL of Et_2O and washed several times with small amounts of water to remove DMF. The resulting organic solution was dried with Na_2SO_4, concentrated in vacuum, and purified by column chromatography using hexanes and ethyl acetate as the eluent.

Naphthalen-1-ylmethyl pivalate (2). The product was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 5.58 (s, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.51-7.60 (m, 3H), 7.83-7.94 (m, 2H), 8.01 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 39.2, 64.8, 123.8, 125.4, 126.1, 126.6, 127.2, 128.9, 129.2, 131.8, 132.0, 133.9, 178.6; IR (neat, cm^{-1}) 3049, 2972, 2934, 2871, 1726, 1599, 1479, 1397, 1281, 1148, 963, 795; HRMS calcd for $C_{16}H_{18}O_2$ 242.13068, found 242.13116.

1-(Phenoxymethyl)naphthalene (3). The product was obtained as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 2H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.45-7.62 (m, 3H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.85-7.96 (m, 2H), 8.09 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.8, 115.1, 121.3, 123.9, 125.5, 126.1, 126.6, 126.8, 128.9, 129.2, 129.8, 131.7, 132.5, 134.0, 159.1; IR (neat, cm^{-1}) 3053, 2986, 1598, 1495, 1421, 1265, 1173, 1029, 739; HRMS calcd for $C_{17}H_{14}O$ 234.10447, found 234.10483.

Naphthalen-1-ylmethyl acetate (11). The product was obtained as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 5.59 (s, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.51-7.64

(m, 3H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H). Other physical and spectral data are consistent with those reported in the literature.[22]

Naphthalen-1-ylmethyl benzoate (12). The product was obtained as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.47-7.63 (m, 4H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.90 (d, *J* = 9.6 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 8.15 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.3, 123.8, 125.5, 126.2, 126.8, 127.7, 128.6, 128.9, 129.5, 129.9, 130.3, 131.7, 131.9, 133.2, 133.9, 166.7; IR (neat, cm^{-1}) 3061, 3010, 2961, 2900, 1923, 1719, 1600, 1511, 1451, 1314, 1270, 957, 710; HRMS calcd for $C_{18}H_{14}O_2$ 262.09938, found 262.09974.

Naphthalen-1-ylmethyl 4-chlorobenzoate (13). The product was obtained as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.47-7.63 (m, 3H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.87-7.95 (m, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.5, 123.7, 125.4, 126.2, 126.8, 127.8, 128.6, 128.8, 128.9, 129.6, 131.3, 131.4, 131.9, 133.9, 139.6, 165.7; IR (neat, cm^{-1}) 3048, 2962, 1720, 1594, 1478, 1400, 1268, 1171, 1100, 1014, 792, 758; HRMS calcd for $C_{17}H_{13}ClO$ 296.06041, found 296.06080.

Naphthalen-1-ylmethyl 4-methoxybenzoate (14) The product was obtained as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.81 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.45-7.62 (m, 3H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 64.9, 113.7, 122.5, 123.7, 125.4, 126.0, 126.6, 127.4, 128.8, 129.3, 131.8, 131.8, 133.8, 163.5, 166.3; IR

(neat, cm^{-1}) 3050, 3007, 2960, 2934, 2838, 1710, 1605, 1511, 1256, 1167, 1100, 1028, 770; HRMS calcd for $C_{19}H_{16}O_3$ 292.10994, found 292.11036.

1-[(4-Methoxyphenoxy)methyl]naphthalene (15). The product was obtained as a white solid: mp 72-74 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.46 (s, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.52-7.65 (m, 3H), 7.84-7.94 (m, 2H), 8.08 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 69.6, 114.9, 116.1, 123.9, 125.5, 126.0, 126.6, 126.7, 128.8, 129.1, 131.7, 132.7, 133.9, 153.2, 154.3; IR (neat, cm^{-1}) 3051, 3001, 2954, 2911, 2834, 1507, 1465, 1265, 1227, 1037, 826, 738; HRMS calcd for $C_{18}H_{16}O_2$ 264.11503, found 264.11547.

1-[(4-Chlorophenoxy)methyl]naphthalene (16). The product was obtained as a pale yellow solid: mp 83-85 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48 (s, 2H), 5.58 (s, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 9.2 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.52-7.63 (m, 3H), 7.85-7.95 (m, 2H), 8.05 (dd, *J* = 2.4, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.2, 116.4, 123.8, 125.5, 126.2, 126.7, 126.8, 128.9, 129.4, 129.6, 131.6, 132.1, 134.0, 157.6; IR (neat, cm^{-1}) 3055, 2924, 2872, 1592, 1509, 1468, 1377, 1279, 1236, 1007, 917, 797; HRMS calcd for $C_{17}H_{13}ClO$ 268.06549, found 268.06583.

(3-Methylphenanthren-1-yl)methyl pivalate (18). The product was obtained as a brown solid: mp 74-76 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.63 (s, 3H), 5.57 (s, 2H), 7.49 (s, 1H), 7.55-7.70 (m, 2H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.85-7.95 (m, 2H), 8.52 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.4, 39.1, 65.2, 122.3, 123.0, 123.4, 126.7, 126.7, 126.8, 128.5, 128.7, 130.0, 130.4, 131.0, 131.9, 132.4,

135.8, 178.6; IR (neat, cm^{-1}) 2967, 2920, 2852, 1725, 1478, 1281, 1147, 1033, 950, 864, 819, 750; HRMS calcd for $C_{21}H_{22}O_2$ 306.16198, found 306.16244.

1-(2-Methylprop-1-enyl)naphthalene (21). The product was obtained as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.04 (s, 3H), 6.68 (s, 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.48-8.05 (m, 6H). The other physical and spectral data are consistent with those reported in the literature.[23]

General procedure for the alcohol oxidations. To the stirred solution of 0.25 mmol of the aryl halide, $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), dppm (4.8 mg, 0.012 mmol) and 4 mL of DMF, cesium pivalate (175 mg, 0.75 mmol) was added. The reaction vial was sealed, flushed with argon, heated at 120 °C, and monitored using TLC. After completion of the reaction, the mixture was diluted with 20 mL of Et_2O and washed several times with small amounts of water to remove the DMF. The resulting organic solution was dried with Na_2SO_4, concentrated in vacuum and purified by column chromatography using hexanes and ethyl acetate as the eluent.

1-Naphthaldehyde (29). The product was obtained as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.67 (t, J = 8.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 9.25 (d, J = 8.5 Hz, 1H), 10.36 (s, 1H). The other physical and spectral data are consistent with those reported in the literature.[24]

(8-Deuteronaphthalen-1-yl)deuterocarbaldehyde (29a). The product was obtained as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.68 (m, 2H), 7.71 (d, J = 6.8 Hz, 1H), 7.94 (dd, J = 1.2, 8.0 Hz, 1H), 8.01 (dd, J = 1.2, 6.8 Hz, 1H), 8.11 (d, J = 8.0 Hz,

1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.6, 124.9, 127.0, 128.5, 129.0, 130.5, 131.3 (m), 133.7, 135.4, 136.7, 193.3 (m); IR (neat, cm^{-1}) 3054, 2951, 2927, 2864, 1558, 1364, 1191, 1009, 801, 762; HRMS calcd for $C_{11}H_6D_2O$ 158.07007, found 158.07033.

1-(Naphthalen-1-yl)-3-phenylpropan-1-one (33). The product was obtained as a light brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (t, *J* = 7.6 Hz, 2H), 3.37 (t, *J* = 7.6, Hz, 2H), 7.10-7.36 (m, 6H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.48-7.60 (m, 2H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 44.0, 124.5, 125.9, 126.3, 126.6, 127.6, 128.1, 128.6, 128.6, 128.7, 130.3, 132.7, 134.1, 136.1, 141.3, 203.7; IR (neat, cm^{-1}) 3056, 3020, 2937, 2908, 1679, 1497, 1362, 1275, 1156, 1100, 945, 782; HRMS calcd for $C_{19}H1_6O$ 260.12012, found 260.12055.

1-(Naphthalen-1-yl)heptan-1-one (35). The product was obtained as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.20-1.45 (m, 6H), 1.79 (quintet, *J* = 7.2 Hz, 2H), 3.05 (t, *J* = 7.2 Hz, 2H), 7.46-7.65 (m, 3H), 7.81-7.92 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.55 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 24.8, 29.1, 31.7, 42.4, 124.4, 125.8, 126.4, 127.2, 127.8, 128.4, 130.1, 132.3, 134.0, 136.5, 205.2; IR (neat, cm^{-1}) 2953, 2926, 2855, 1677, 1507, 1462, 1278, 1233, 1171, 1086, 799, 775; HRMS calcd for $C_{17}H_{20}O$ 240.15142, found 240.15173.

Naphthalen-1-yl(phenyl)methanone (37). The product was obtained as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.51 (m, 2H), 7.51-7.56 (m, 3H), 7.56-7.63 (m, 2H), 7.86-7.89 (q, *J* = 3.3 Hz, 2H), 7.92-7.94 (t, *J* = 4.8 Hz, 1H), 8.00-8.02 (d, *J* = 8.0

Hz, 1H), 8.09-8.11 (d, J = 8.0 Hz, 1H). The other physical and spectral data are consistent with those reported in the literature.[25]

1-(Biphenyl-2-yl)ethanone (45). The product was obtained as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 7.35-7.47 (m, 7H), 7.53 (dt, J = 1.4, 7.5 Hz, 1H), 7.58 (dd, J = 1.2, 7.6 Hz, 1H). The other physical and spectral data are consistent with those reported in the literature.[26]

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CHAPTER 3: STUDIES IN ACYL C-H ACTIVATION VIA ARYL TO ACYL THROUGH SPACE MIGRATION OF PALLADIUM

Based on a paper to be submitted to the *Journal of Organic Chemistry*

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Abstract

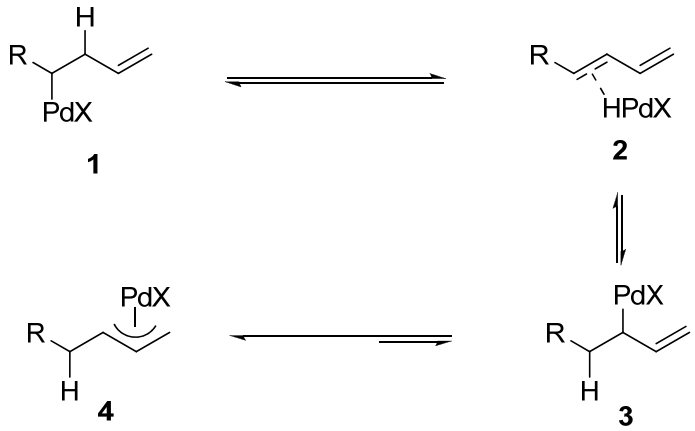
A procedure for acyl C-H activation has been developed using palladium-catalyzed 1,4-aryl to acyl migration as a key step. After migration, the corresponding acylpalladium species can undergo decarbonylation. Alcohols can also be used to trap the acylpalladium species to furnish the corresponding esters. Acyl C-H activation of both aldehydes and formamides has been achieved. Aryl bromides and iodides have been successfully employed in this chemistry. The mechanism of the palladium migration/decarbonylation/β-hydride elimination process has been studied by deuterium labeling experiments, which suggest the migration of palladium from an aryl to an acyl position.

Introduction

Palladium has proven to be one of the most widely used catalysts in organic

synthesis, because of the wide variety of useful synthetic processes it can affect, its compatibility with many functional groups, and its non-toxic nature.[1] The migration of palladium along an alkyl chain has been employed by our group for the synthesis of long chain compounds and heterocycles.[2] This chemistry involves migration of palladium down a saturated carbon chain by a palladium hydride elimination/addition sequence until a stable palladium intermediate is formed. One such elimination/addition sequence is depicted in Scheme 1, where an alkylpalladium species **1** undergoes *β*-hydride elimination to form an olefin complex **2**. The palladium hydride then reversibly adds to the carbon-carbon double bond with the opposite regiochemistry to form **3**, effectively migrating down the carbon chain to form a stable π-allylpalladium species **4**.

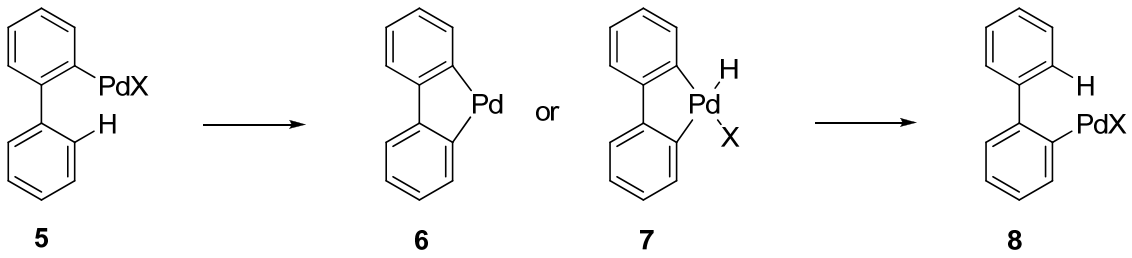
Scheme 1



C-H Activation reactions via cyclopalladation, which proceed through an alkyl or aryl palladacycle, have proven to be a good model for transition metal C-H activation in general. Such processes have been employed by several groups for the synthesis of a wide variety of heterocyclic ring systems.[3] Recently, our group discovered the "through space" migration of palladium in *o*-iodobiaryls, where palladium migrates from one ring

to the other by formation of a five-membered ring palladacycle **6** or **7** (Scheme 2).[4] Among the known transition metal-catalyzed C-H activation processes involving "through space" migration of the metal, palladium-catalyzed reactions have been the most widely studied. In fact, they have been found to be quite general reactions. Examples of aryl to aryl,[4,5] vinylic to aryl,[6] alkyl to aryl,[7] aryl to alkyl,[8] vinylic to aryl to allylic,[9] benzylic to aryl,[10] aryl to benzylic,[11] and aryl to imidoyl[12] migration have recently been reported by our group and others.

Scheme 2

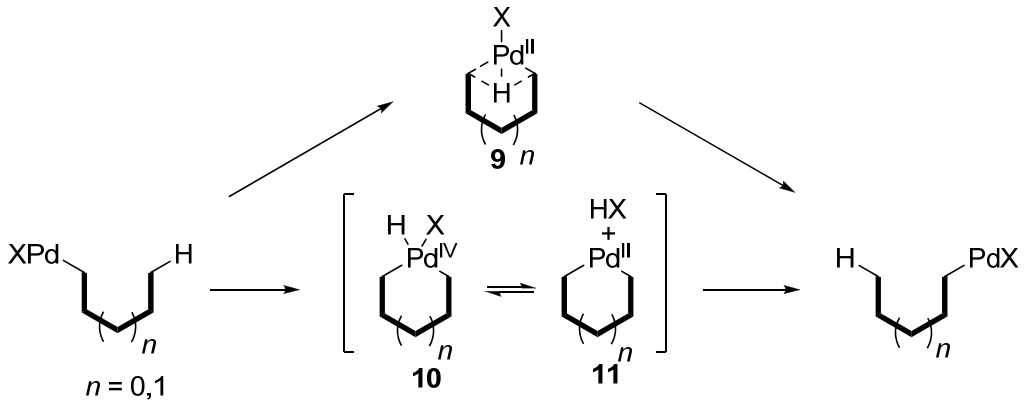


We earlier demonstrated that in the case of aryl to aryl palladium migrations, the arylpalladium species formed after the migration can be trapped via Heck, as well as Suzuki, cross-coupling reactions or direct arylation.[4,5] In the case of alkyl to aryl palladium migrations, only Heck olefination and arylation have been reported.[7] In vinylic to aryl to allylic palladium migrations, the resulting allylic palladium species have been trapped by cesium pivalate, a crucial base for these migration reactions.[9] To our surprise, not only cesium pivalate, but also cesium benzoates and sodium phenoxides can be employed as trapping agents in aryl to benzylic palladium migrations to afford the corresponding benzylic products.[11]

These migration reactions provide an alternate way to introduce a palladium moiety into organic molecules. They have proven to be a useful tool for the synthesis of many heterocyclic ring systems. For example, alkylidenefluorenes,[6a,b] dibenzofurans,[6c,d] carbazoles,[6c,d] and indoles[6d] have been synthesized by vinylic to aryl palladium migrations, whereas fluoren-9-ones[12] and xanthones[12] have been synthesized using aryl to imidoyl palladium migrations. Alkyl to aryl[7] and aryl to aryl[5] palladium migrations have also been used for the synthesis of fused polycycles. Dyker has successfully synthesized 6*H*-dibenzo[*b,d*]pyrans by C-H activation of a methoxy group using migration of palladium as a key step.[13]

The reported palladium migration reactions are presumed to go through five- or six-membered ring palladacycles. Intermediate **9** was suggested by Bour and co-workers[6e,f] in their theoretical study and was found to be energetically favored over palladacycle(IV) hydride **10** or palladacycle(II) **11**. However, this process fails to account for the H-D exchange processes observed in many of our processes.[9,11,12]

Scheme 3

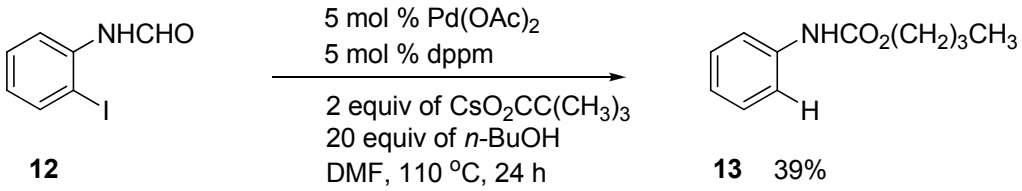


In this chapter, we report the migration of palladium from an aryl position to an acyl position. Our standard palladium migration reaction conditions can also be used to activate an acyl C-H bond. The C-H activation of both aldehydes and formamides can be achieved. The acylpalladium species can not only undergo decarbonylation, but can also be trapped using an alcohol as a nucleophile.

Results and Discussion

A few years ago, we found that an acyl C-H bond can also be activated using our novel palladium migration reaction conditions to form carbamates when starting from formamide **12** (Scheme 4). Although there are currently more efficient routes for the synthesis of carbamates, this migration chemistry provides a unique new route to acylpalladium intermediates of value in organic synthesis. Thus, we decided to explore the scope of this new C-H activation process.

Scheme 4

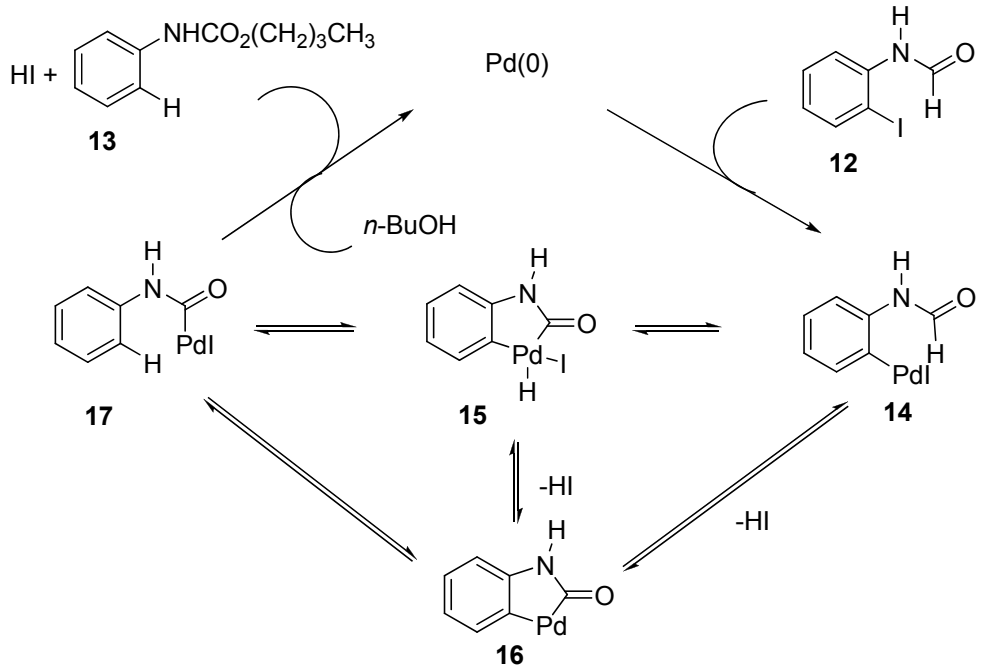


12 **13** 39%

A possible mechanism for this palladium migration reaction is outlined in Scheme 5. After oxidative addition of the aryl halide **12** to Pd(0), the resulting intermediate **14** can insert palladium into the neighboring acyl C-H bond to form palladium(IV)intermediate **15** or a palladium(II) intermediate **16**. Intermediate **16** can also be formed by the loss of HI from intermediate **15**. Acylpalladium species, which can

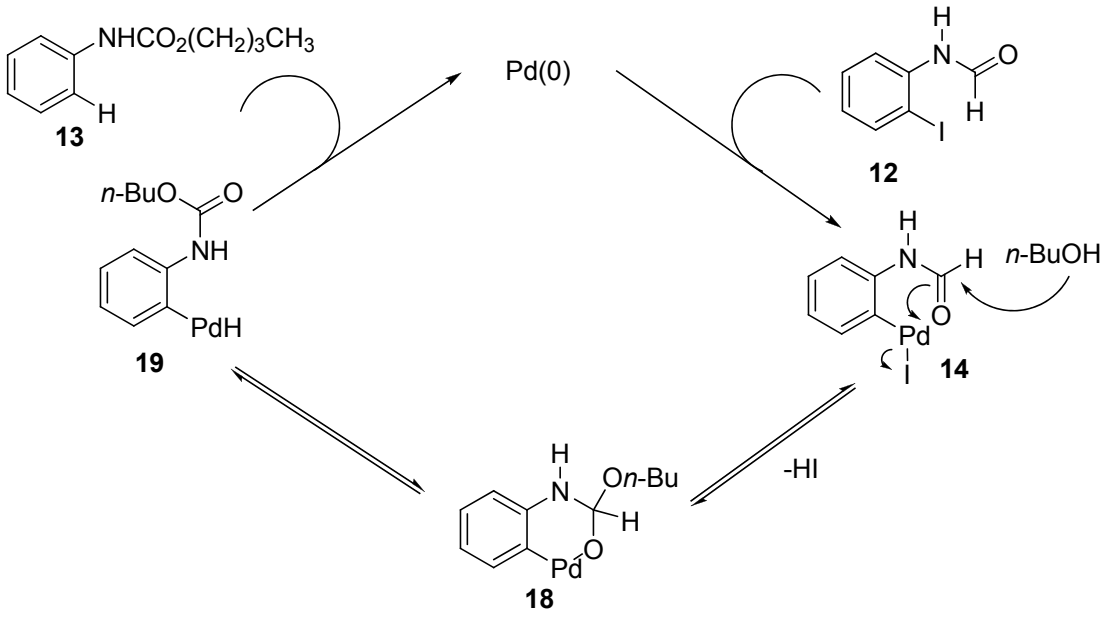
be formed from both **15** and **16**, can be trapped by a butanol molecule to furnish the corresponding carbamate **13**.

Scheme 5



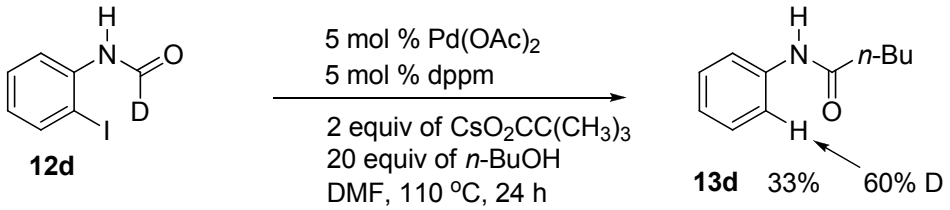
The formation of carbamate **13** can also be explained by a different mechanism, which is similar to one proposed by Wei and co-workers[14] in their esterification-hydroarylation reaction of 2-(1-alkynyl)benzaldehydes (Scheme 6). The intermediate **14** formed by oxidative insertion of Pd(0) into aryl halide **12** can produce six-membered ring palladacycle **18** by attack of an alcohol on the acyl carbon and nucleophilic displacement of the halide on palladium. Intermediate **18** can undergo β-hydride elimination to form arylpalladium intermediate **19**, which then can undergo reductive elimination to give carbamate **13**.

Scheme 6



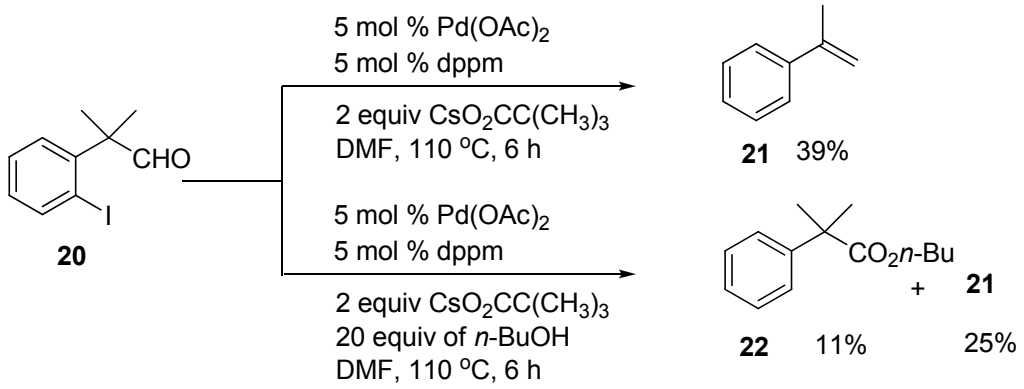
To further study the mechanism of this reaction, deuterium-labeled compound **12d** was synthesized with greater than 98% deuterium incorporation. Compound **12d**, when subjected to our standard palladium migration conditions, afforded 60% incorporation of deuterium in carbamate **13d**, which was obtained in a 33% yield (Scheme 7). This experiment illustrates the migration of deuterium from an acyl position to an aryl position; however, it fails to account for the differences between the two proposed mechanisms. H-D Exchange, presumably with the solvent, accounts for the fact that there is less than 100% deuterium incorporation in the product.

Scheme 7



To better understand the mechanism of these reactions, we decided to examine the reaction of aldehyde **20** in the absence of an alcohol nucleophile. If the reaction proceeds through the mechanism described in Scheme 5, then an acylpalladium intermediate analogous to **17** should be formed. In the absence of a nucleophile, the acylpalladium intermediate should undergo decarbonylation, followed by *β*-hydride elimination, to give the corresponding styrene derivative **21** (Scheme 8). Indeed, we were pleased to see the formation of styrene **21** in a 39% yield. This strongly suggests the formation of an acylpalladium species, which in turn implies the migration of palladium from an aryl position to an acyl position. Performing the same reaction in the presence of butanol furnishes not only the styrene in a 25% yield, but also the corresponding ester **22** in a poor yield of 11%.

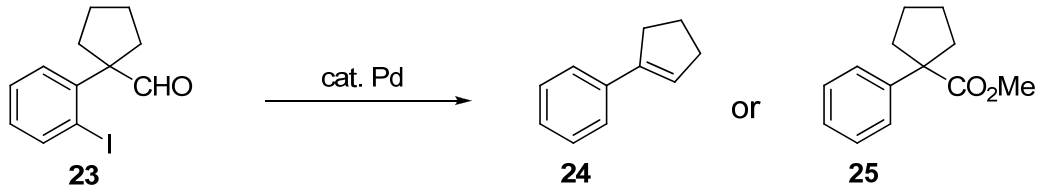
Scheme 8



The α-methylstyrene (**21**) formed after the migration/decarbonylation reaction sequence is a volatile compound, which could result in a lower yield of the product. Therefore, cyclic aldehyde **23** was employed, instead of aldehyde **20**, in similar migration reactions (Table 1). Besides our standard migration conditions, reaction conditions developed by other groups for similar reactions have also been employed to see if they

give a better yield of product **24**. Our migration conditions resulted in the formation of **24** in 47% yield (Table 1, entry 1). All other reaction conditions employed resulted in lower yields of this decarbonylation product. The conditions developed by Wang and co-workers[10] for a benzylic to aryl palladium migration resulted in formation of the product in only an 11% yield (entry 2), while the reaction conditions for aryl to alkyl palladium migration developed by Baudoin and co-workers[8] resulted in a 23% yield (entry 3). Changing the ligand from P(*o*-tol)$_3$ to dppm, while otherwise employing Baudoin and co-workers reaction conditions, gave a higher yield of 35% (entry 4). To our surprise, Wei and co-worker's esterification/hydroarylation reaction conditions[14] gave ester **25** in a synthetically useful yield of 82%, and did not furnish any decarbonylation product (entry 5).

Table 1. Examination of various palladium migration reaction conditions[a]



23 **24** **25**

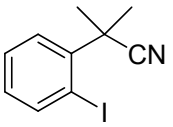
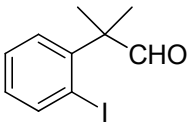
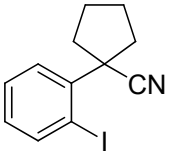
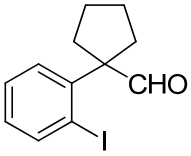
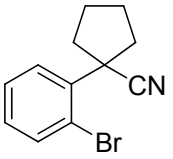
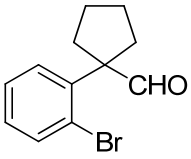
entry	reaction conditions	reference	product	% yield[b]
1	5 mol % $Pd(OAc)_2$, 5 mol % dppm, 2 equiv of CsPiv, DMF, 110 °C	4	**24**	47
2	5 mol % $Pd(OAc)_2$, 2 equiv of *n*-Bu_3N, DMF, 110 °C	10	**24**	11
3	10 mol % $Pd(OAc)_2$, 20 mol % of P(*o*-tol)$_3$, 2 equiv of Cs_2CO_3, DMF, 110 °C	8	**24**	23

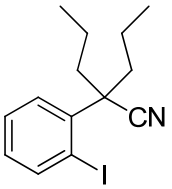
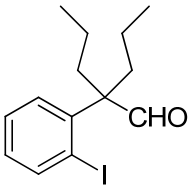
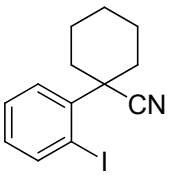
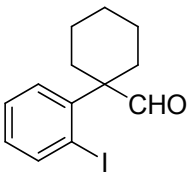
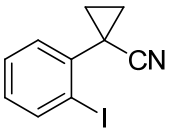
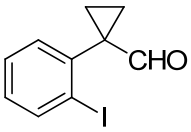
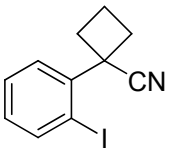
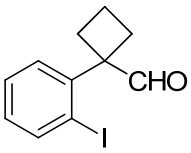
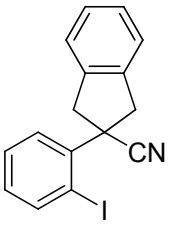
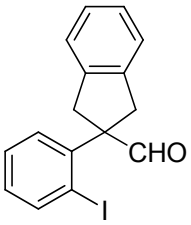
4	5 mol % $Pd(OAc)_2$, 5 mol % dppm, 2 equiv of Cs_2CO_3, DMF, 110 ^oC		**24**	35
5	5 mol % $Pd(OAc)_2$, 1.5 equiv of K_2CO_3, MeOH, 65 ^oC	14	**25**	82[c]

[a] Unless otherwise stated, all reactions were performed using 0.5 mmol of aldehyde **23** with the indicated amount of base, catalyst and ligand in 4 mL of the solvent at the indicated temperature for 24 h. [b] Isolated yields. [c] The reaction was performed using 8 mL of MeOH.

To further study the scope of our palladium migration conditions, several additional aldehydes have been prepared and employed in this migration/decarbonylation reaction. The aldehydes **20**, **23** and **26-31** were prepared from the corresponding nitriles by DIBAL reduction. The preparation of these aldehydes is summarized in Table 2. These reductions required 2 equiv of DIBAL and proceeded with ease at -78 ^oC to room temperature over 24 h, affording the corresponding aldehydes in yields ranging from 38-61%.

Table 2. Reduction of nitriles to aldehydes[a]

entry	nitrile		product		% yield[b]
1		**32**		**20**	39
2		**33**		**23**	57
3		**34**		**26**	61

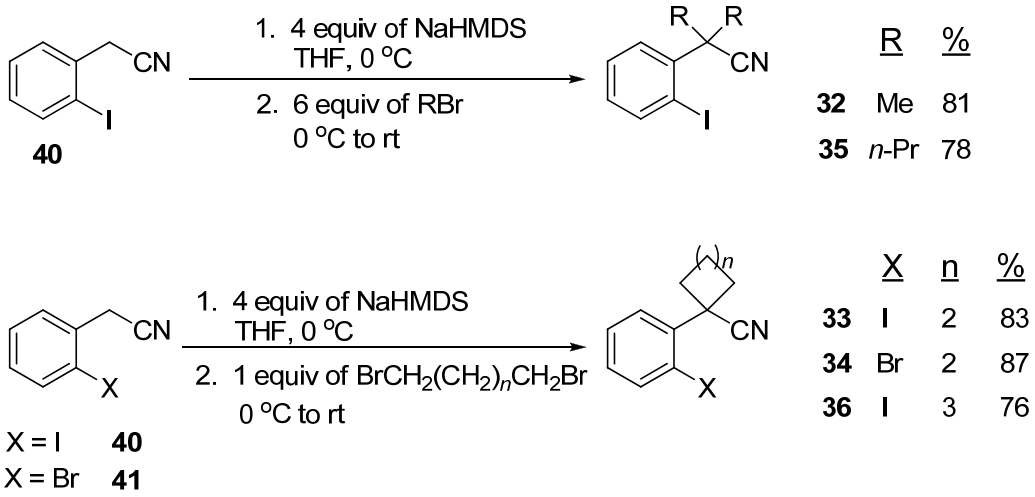
4		**35**		**27**	45
5		**36**		**28**	53
6		**37**		**29**	38
7		**38**		**30**	42
8		**39**		**31**	55

[a] Unless otherwise stated, all reactions were performed using 3 mmol of nitrile in 9 mL of anhydrous THF and 6 equiv of DIBAL at -78 °C to room temperature for 24 h. [b] Isolated yields.

The nitriles **32-39** used for the synthesis of the various aldehydes were prepared from 2-halobenzonitriles **40** and **41** by dialkylation (Scheme 9). Acyclic and cyclic nitriles **32-36** were prepared by using the reaction conditions developed by Papahatjis and co-workers,[15] which employ an excess of NaHMDS, followed by an excess of alkyl halide or equivalent amounts of dihaloalkanes as electrophiles. This reaction procedure gave nitriles **32-36** cleanly and in excellent yields ranging from 76-87%. However, this

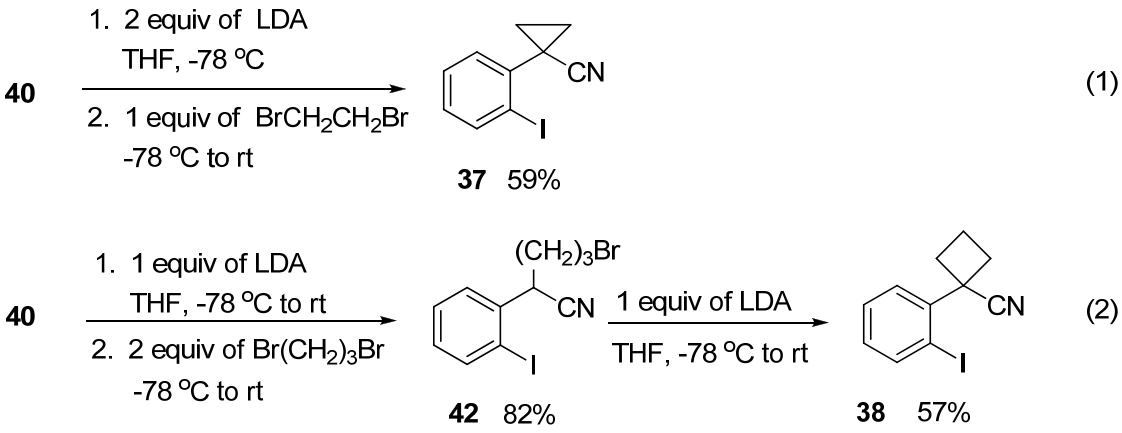
method failed to give a clean reaction for the preparation of cyclic nitriles **37-39**, affording instead inseparable mixtures of products.

Scheme 9



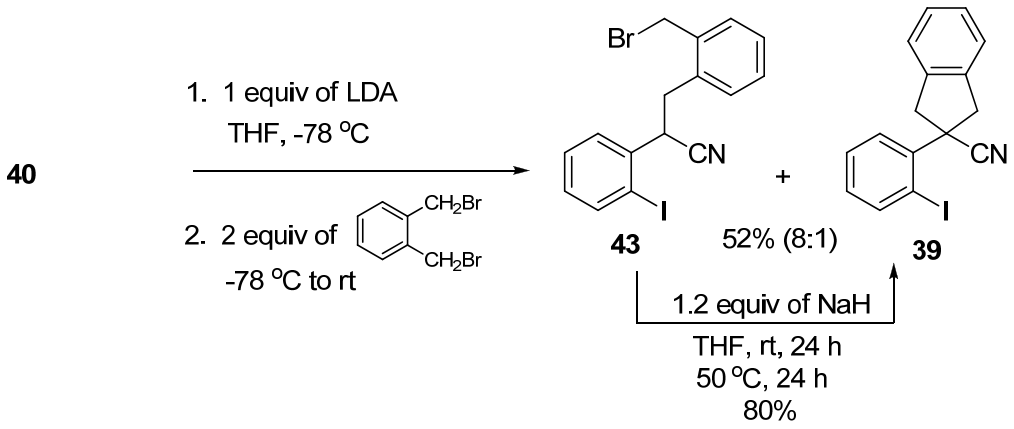
Cyclopropane carbonitrile **37** was prepared instead by a one-step procedure using LDA, instead of NaHMDS, as the base at a lower temperature of -78 °C (Scheme 10, eq 1), whereas carbonitrile **38** was prepared by a two-step protocol using LDA as the base, which afforded an overall yield of 46% for the two steps (Scheme 10, eq 2).

Scheme 10



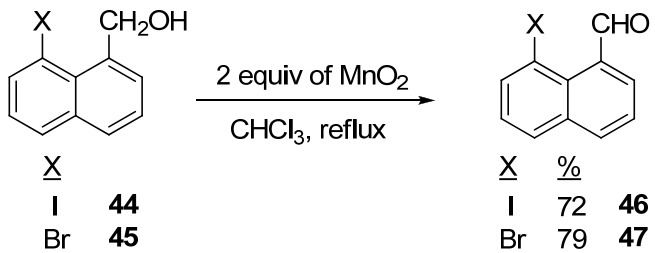
When one equivalent of LDA and α,α'-dibromo-*o*-xylene was employed with 2-iodophenylacetonitrile (**40**), a mixture of nitriles **43** and **39** were formed in a ratio of 8:1 (Scheme 11). Unfortunately, these nitriles could not be separated using column chromatography. Using two equiv of LDA gave a complex reaction mixture and we were again unable to separate the desired product. We attempted to convert **43** into **39** using the required amount of LDA or NaHMDS, but this also failed to give a clean reaction. Finally, NaH was employed in this conversion, which resulted in complete conversion of **43** into carbonitrile **39**.

Scheme 11



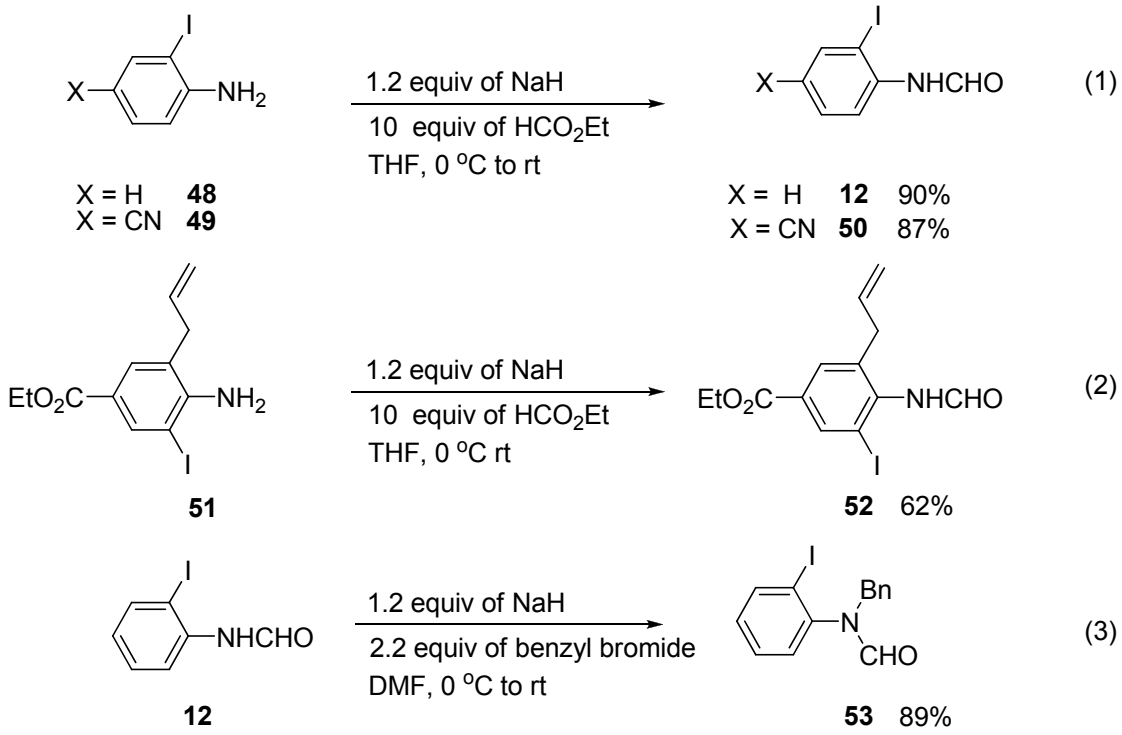
Aldehydes **46** and **47** were prepared by MnO_2 oxidation of the corresponding alcohols, which are commercially available (Scheme 12).

Scheme 12



Formamides **12** and **50** were prepared using a known procedure (Scheme 13, eq 1).[16] Iodoaniline **51,** which was obtained by a known procedure,[17] resulted in the formation of **52** in a 62% yield using 1.2 equiv of NaH and an excess of ethyl formate (Scheme 13, eq 2). The *N*-benzylation of **12** using NaH and benzyl bromide gave formamide **53** in a good yield of 89% (Scheme 13, eq 3).

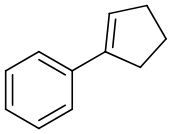
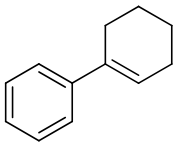
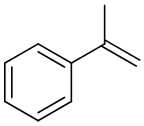
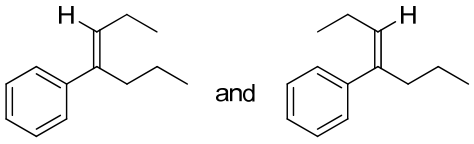
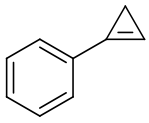
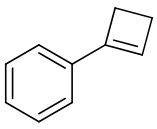
Scheme 13

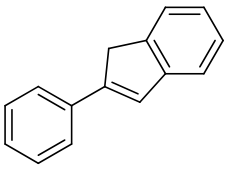
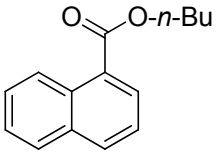
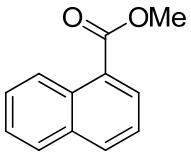
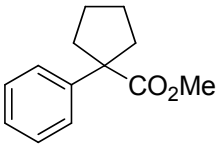
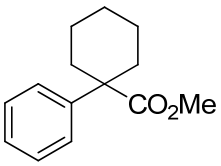
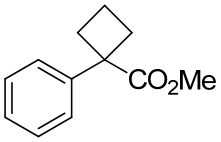
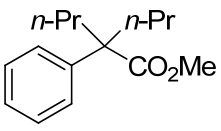


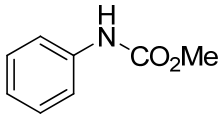
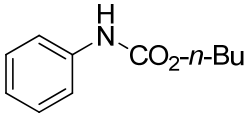
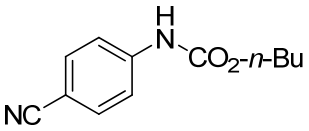
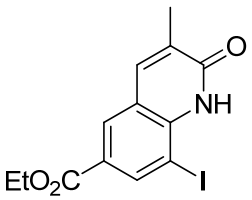
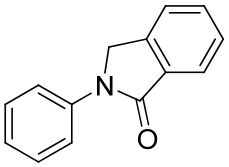
The scope of these apparent palladium migration reactions has been studied using several additional aldehydes and formamides. The results of these studies are summarized in Table 3. Three different reaction conditions have been employed. Reaction conditions A are our standard migration/decarbonylation conditions using 5 mol % $Pd(OAc)_2$ along with 2 equiv of cesium pivalate in DMF at 110 °C plus the indicated carbonyl substrate. Reaction conditions B are the same as those of A, except 20 equiv of *n*-BuOH have been

added to trap the acylpalladium intermediate. We have also employed Wei and co-workers reaction conditions,[14] since their reaction conditions are synthetically useful to convert aldehydes to esters.

Table 3. Scope of the aryl to acyl palladium migration

entry	aldehyde	reaction conditions[a]	product	% yield [b]
1	**23**	A		**24** 47
2	**26**	A		**24** 33
3	**28**	A		**54** 42
4	**20**	A		**21** 39
5	**27**	A		**55:56** 9:1 41[c]
6	**29**	A		**57** 0
7	**30**	A		**58** 36

8	**31**	A		**59**	32
9	**46**	B		**60**	38
10	**46**	C		**61**	76
11	**47**	C		**61**	55
12	**23**	C		**25**	82
13	**28**	C		**62**	80
14	**30**	C		**63**	84
15	**27**	C		**64**	56
16	**12**	C		**65**	0

					
17	**12**	B		**13**	39
18	**50**	B		**66**	45
19	**52**	A		**67**	0
20	**53**	A		**68**	0

[a] Reaction conditions A: unless otherwise stated, all reactions were performed using 0.5 mmol of aldehyde, 5 mol % $Pd(OAc)_2$, 5 mol % of dppm and 2 equiv of cesium pivalate in 6 mL of DMF at 110 °C for 12 h. Reaction conditions B: unless otherwise stated, all reactions were performed using 0.5 mmol of aldehyde, 5 mol % $Pd(OAc)_2$, 5 mol % of dppm, 20 equiv of *n*-BuOH and 2 equiv of cesium pivalate in 6 mL of DMF at 110 °C for 24 h. Reaction conditions C: unless otherwise stated, all reactions were performed using 0.5 mmol of aldehyde, 5 mol % $Pd(PPh_3)_4$, 1.5 equiv of K_2CO_3 in 8 mL of MeOH at 65 °C for 24 h. [b] Isolated yields. [c] The yield was determined by using ^1H NMR spectroscopy.

We have found that aryl bromide **26** also works for our migration/decarbonylation reaction, but gives a lower yield of 33% when compared to aryl iodide **23** (Table 3, compare entries 1 and 2). Cyclohexanecarboxaldehyde **28** resulted in the formation of olefin **54** in a 42% yield (entry 3). Acyclic carboxaldehyde **20** afforded a 39% yield of **21** (entry 4), whereas **27** gave a mixture of two stereoisomeric olefins **55** and **56** in the ratio

of 9:1 (*E*:*Z*) (entry 5). Cyclopropane carboxaldehyde **29** gave a very complex reaction mixture, which can be attributed to the instability of the expected 1-phenylcyclopropene (**57**) formed after decarbonylation/*β*-hydride elimination (entry 6). Other cyclic carboxaldehydes also afforded modest yields of decarbonylation products. Thus, we obtained olefins **58** and **59** in 36 and 32% yields respectively from the corresponding aldehydes (entries 7 and 8).

When aldehyde **46** was subjected to the reaction conditions B, using 20 equiv of *n*-BuOH, ester **60** was formed in a 38% yield (entry 9). When this same aldehyde **46** was subjected to reaction conditions C developed by Wei and co-workers,[14] ester **61** was obtained in a much higher yield of 76% (entry 10). Analogous to our earlier observation, aryl bromide **47** resulted in a lower yield of 55% when compared to aryl iodide **46** (compare entries 10 and 11). Carboxaldehydes **23**, **28** and **30** also afforded the corresponding esters in 82, 80 and 84% yields respectively (entries 12-14). Acyclic aldehyde **27** formed the corresponding ester product in a lower yield of 56% and did not result in a clean reaction (entry 15).

The reaction conditions employed on the various aldehydes failed on formamides. For example, formamide **12** failed to form any of the carbamate **65** when the reaction was run in methanol using reaction conditions C (entry 16)**.** Compound **12**, when subjected to our standard migration conditions with added *n*-BuOH, gave the corresponding carbamate **13** in a 39% yield (entry 17). Formamide **50**, having a nitrile group in the *para* position, gave the desired product **66** in a higher yield of 45% (entry 18). This improvement in yield can be attributed to the presence of the relatively electron-poor aryl

ring, which presumably facilitates the migration of palladium to the acyl position by stabilizing the resulting organopalladium product.

We attempted to trap the anticipated acylpalladium intermediate from formamide **52** by an intramolecular Heck reaction, but none of the product **67** was observed (entry 19). Formamide **53** also failed to give the lactam **68**, expected from an intramolecular arylation, but resulted instead in a complex reaction mixture (entry 20).

Conclusions

In summary, we have found a unique way of activating an acyl C-H bond. "Through space" migration of palladium from an aryl position to an acyl position via a five-membered ring palladacycle results in an acylpalladium species. The acylpalladium species can be trapped by an alcohol to form esters. In the absence of an alcohol, olefin products resulting from decarbonylation, followed by β-hydride elimination, are observed. The mechanism of these reactions has been studied by deuterium-labeling experiments, which unfortunately fail to distinguish either of the two anticipated mechanisms. However, the migration/decarbonylation reaction sequence strongly suggests the formation of an acylpalladium species in these processes and thus supports a process involving the migration of palladium. Aryl iodides and bromides have been successfully employed in these palladium migration reactions. Our efforts to trap the anticipated acylpalladium intermediates using Heck and direct arylation processes have, however, failed for reasons we do not presently understand.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

General procedure for the preparation of nitriles 32-36. A 250 mL round bottom flask containing 2-iodophenylacetonitrile (2.43 gm, 10.0 mmol) was flushed with argon and charged with 50 mL of anhydrous THF. The reaction mixture was then cooled to 0 ^{o}C and a solution of NaHMDS (2.0 M in THF, 20 mL, 40.0 mmol) was added dropwise over a period of 20 min. The resulting mixture was allowed to stir for an additional 1 h. To this solution, the dihaloalkane (10.0 mmol) or alkyl halide (40.0 mmol) was added and the resulting mixture was allowed to stir for 2 d at room temperature. The reaction was then quenched with 10 mL of H_2O and the THF was removed using a rotary evaporator. The resulting solution was extracted using Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over $NaSO_4$, filtered, and concentrated to give the crude product, which was purified by column chromatography using ethyl acetate and hexanes as the eluent.

2-(2-Iodophenyl)-2-methylpropanenitrile (32). The product was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 6H), 6.99 (td, *J* = 1.6, 7.6 Hz, 1H), 7.38 (td, *J* = 1.2, 7.2 Hz, 1H), 7.46 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.03 (dd, *J* = 0.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 39.2, 96.1, 123.4, 126.9, 128.8, 129.8, 140.6, 143.4; IR (neat, cm^{-1}) 3060, 2983, 2936, 2880, 2231, 1581, 1462, 1431, 1277, 1190, 1009, 911, 759, 721; HRMS calcd for $C_{10}H_{10}IN$ 270.98580, found 270.99609.

1-(2-Iodophenyl)cyclopentanecarbonitrile (33). The product was obtained as a white solid: mp 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83-1.97 (m, 2H), 1.97-2.10 (m, 2H), 2.10-2.25 (m, 2H), 2.75-2.88 (m, 2H), 6.95-7.05 (m, 1H), 7.32-7.42 (m, 2H), 8.01 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 38.7, 49.4, 97.6, 123.0, 127.7, 128.4, 129.7, 140.4, 142.8; IR (neat, cm^{-1}) 3051, 2971, 2877, 2230, 1580, 1463, 1431, 1263, 1010, 956, 741; HRMS calcd for $C_{12}H_{12}NI$ 297.00145, found 297.00181.

1-(2-Bromophenyl)cyclopentanecarbonitrile (34). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83-1.98 (m, 2H), 1.98-2.12 (m, 2H), 2.15-2.28 (m, 2H), 2.70-2.81 (m, 2H), 7.19 (td, *J* = 1.6, 7.6 Hz, 1H), 7.32 (td, *J* = 1.2, 7.6 Hz, 1H), 7.42 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.67 (dd, *J* = 1.2, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 38.4, 47.8, 123.2, 123.9, 127.7, 127.9, 129.7, 135.4, 137.7; IR (neat, cm^{-1}) 3065, 2960, 2876, 2230, 1586, 1468, 1435, 1023, 957, 756; HRMS calcd for $C_{12}H_{12}BrN$ 249.01531, found 249.01559.

2-(2-Iodophenyl)-2-propylpentanenitrile (35). The product was obtained as a white solid: mp 71-73 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 6H), 1.05-1.20 (m, 2H), 1.35-1.50 (m, 2H), 1.85-2.00 (m, 2H), 2.65-2.78 (m, 2H), 6.96 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.0, 39.3, 51.4, 92.3, 123.3, 128.4, 129.5, 131.8, 137.7, 143.9; IR (neat, cm^{-1}) 3055, 2961, 2931, 2872, 2227, 1582, 1464, 1423, 1325, 1266, 1193, 1008, 737; HRMS calcd for $C_{14}H_{18}IN$ 327.0478, found 327.0484.

1-(2-Iodophenyl)cyclohexanecarbonitrile (36). The product was obtained as a pale yellow solid: mp 67-69 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.38 (m, 1H), 1.72-2.02 (m, 7H), 2.58-2.68 (m, 2H), 6.95-7.05 (m, 2H), 7.35-7.45 (m, 2H), 8.04 (dd, J = 0.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.9, 35.3, 45.4, 96.5, 120.8, 127.2, 128.7, 129.6, 140.5, 143.4; IR (neat, cm^{-1}) 3054, 2938, 2859, 2302, 2230, 1581, 1453, 1430, 1264, 1197, 1016, 1004, 896, 742, 702; HRMS calcd for $C_{13}H_{14}IN$ 311.01709, found 311.01724.

1-(2-Iodophenyl)cyclopropanecarbonitrile (37). A 100 mL round bottom flask containing dry diisopropylamine (3.52 mL, 25.0 mmol) was flushed with argon and charged with 30 mL of anhydrous THF. To this solution, *n*-BuLi (2.5 M in hexanes, 8.8 mL, 22.0 mmol) was added dropwise over a period of 10 min and the resulting reaction mixture was stirred for an additional 15 min. This reaction mixture was cooled to -78 ^{o}C and a solution of 2-iodophenylacetonitrile (2.43 gm, 10.0 mmol) in 5 mL of dry THF was added over a period of 10 min by a syringe. After 1 h, 1,2-dibromoethane (0.92 mL, 11.0 mmol) was added dropwise. The resulting reaction mixture was allowed to stir at room

temperature overnight. The reaction was then quenched with 10 mL of H_2O and the THF was removed using a rotary evaporator. The resulting solution was extracted using Et_2O (3 x 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The mixture was dried over $NaSO_4$, filtered, and concentrated. The resulting crude mixture was purified by column chromatography using ethyl acetate and hexanes as the eluent. The product was isolated as a white solid: mp 84-86 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.39 (m, 2H), 1.78-1.87 (m, 2H), 7.01-7.10 (m, 1H), 7.29-7.39 (m, 2H), 7.91 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 19.3, 101.9, 121.7, 128.6, 130.4, 131.7, 138.3, 140.1; IR (neat, cm^{-1}) 3096, 3053, 3008, 2226, 1582, 1464, 1432, 1314, 1248, 1038, 1011, 947, 861, 751; HRMS calcd for $C_{10}H_8IN$ 268.97015, found 268.97074.

5-Bromo-2-(2-iodophenyl)pentanenitrile (42). A 50 mL round bottom flask containing diisopropylamine (1.69 mL, 12.0 mmol) was flushed with argon and charged with 30 mL of anhydrous THF. To this solution, *n*-BuLi (2.5 M in hexanes, 4.4 mL, 11.0 mmol) was added dropwise over a period of 10 min and the resulting reaction mixture was stirred for an additional 15 min. The reaction mixture was cooled to -78 ^oC and allowed to stir for an additional 30 min at this temperature. To this solution, 2-iodophenylacetonitrile (2.43 gm, 10.0 mmol) dissolved in 5 mL of dry THF was added over a period of 10 min, and the mixture was allowed to stir for an additional 1 h. To this solution, 1,3-dibromopropane (2.03 mL, 20.0 mmol) was added dropwise. The resulting reaction mixture was allowed to warm to room temperature overnight. The reaction was then quenched with H_2O (10 mL) and the THF was removed using a rotary evaporator. The resulting solution was

extracted using Et_2O (3 x 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The mixture was dried over $NaSO_4$, filtered, and concentrated. The resulting crude mixture was purified by column chromatography using ethyl acetate and hexanes as the eluent. The product was obtained as a light brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90-2.03 (m, 1H), 2.03- 2.18 (m, 3H), 3.45 (t, J = 6.4 Hz, 2H), 4.18-4.24 (m, 1H), 7.03 (td, J = 1.6, 8.0 Hz, 1H), 7.41 (td, J = 0.8, 7.6 Hz, 1H), 7.56 (dd, J = 1.6, 7.6 Hz, 1H), 7.85 (dd, J = 0.8, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 32.2, 33.4, 41.4, 98.9, 120.1, 128.3, 129.3, 130.1, 138.1, 140.2; IR (neat, cm^{-1}) 3057, 2959, 2934, 2861, 2243, 1565, 1466, 1436, 1249, 1012, 909, 754, 733; HRMS calcd for $C_{11}H_{11}BrIN$ 362.91196, found 362.91264.

1-(2-Iodophenyl)cyclobutanecarbonitrile (38). A 50 mL round bottom flask containing diisopropylamine (1.26 mL, 9.0 mmol) was flushed with argon and charged with 25 mL of anhydrous THF. To this solution, *n*-BuLi (2.5 M in hexanes, 3.52 mL, 8.8 mmol) was added dropwise over a period of 10 min and the resulting reaction mixture was stirred for an additional 15 min. The reaction mixture was cooled to -78 ^{o}C and allowed to stir for an additional 30 min at this temperature. To this solution, **42** (2.9 gm, 8.0 mmol) dissolved in 5 mL of dry THF was added dropwise and the resulting reaction mixture was allowed to stir at room temperature overnight. The reaction was then quenched with 5 mL of H_2O and the THF was removed using a rotary evaporator. The resulting solution was extracted using Et_2O (3 x 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The mixture was dried over $NaSO_4$, filtered, and concentrated. The resulting crude mixture was purified by column chromatography using ethyl acetate and

hexanes as the eluent. The product was obtained as a white solid: mp 77-79 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86-1.98 (m, 1H), 2.40-2.54 (m, 1H), 2.58-2.70 (m, 2H), 3.03-3.15 (m, 2H), 7.01 (td, *J* = 1.6, 7.6 Hz, 1H), 7.24 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.38 (td, *J* = 1.6, 8.0 Hz, 1H), 7.92 (dd, *J* = 1.2, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 34.6, 44.2, 95.6, 123.1, 127.9, 128.5, 129.8, 141.4, 141.8; IR (neat, cm^{-1}) 3067, 2996, 2949, 2925, 2855, 2220, 1740, 1581, 1562, 1460, 1430, 1263, 1175, 1010, 944, 745; HRMS calcd for $C_{11}H_{10}IN$ 282.98580, found 282.98625.

2-(2-Iodophenyl)-2,3-dihydro-1*H*-indene-2-carbonitrile (39). A 100 mL round bottom flask containing diisopropylamine (1.69 mL, 12.0 mmol) was flushed with argon and charged with 40 mL of anhydrous THF. To this solution, *n*-BuLi (2.5 M in hexanes, 4.4 mL, 11.0 mmol) was added dropwise over a period of 10 min and the resulting reaction mixture was stirred for an additional 15 min. The reaction mixture was cooled to -78 ^{o}C and allowed to stir for an additional 30 min at this temperature. To this solution, 2-iodophenylacetonitrile (2.43 gm, 10.0 mmol) dissolved in 5 mL of dry THF was added over a period of 10 min. The mixture was allowed to stir for an additional 1 h and 1,2-*bis*(bromomethyl)benzene (6.60 gm, 25.0 mmol) in 15 mL of dry THF was added dropwise. The resulting reaction mixture was allowed to warm to room temperature overnight. The reaction was then quenched with 10 mL of H_2O and the THF was removed using a rotary evaporator. The resulting solution was extracted using Et_2O (3 x 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The mixture was dried over $NaSO_4$, filtered, and concentrated. The resulting crude mixture was purified by column chromatography using ethyl acetate and hexanes as the

eluent. The product was obtained as an inseparable mixture of **43** and **39** (8:1). This mixture was added to a 25 mL round bottom flask, which was flushed with argon, charged with 15 mL of anhydrous THF, and cooled to 0 ^{o}C. To this solution, NaH (115 mg, 5.0 mmol) was added in small portions. The resulting mixture was allowed to stir at room temperature for 24 h and at 50 ^{o}C for an additional 24 h and cooled to 0 ^{o}C. The reaction was then quenched with 2 mL of H_2O and the THF was removed using a rotary evaporator. The resulting solution was extracted using Et_2O (3 x 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL). The mixture was dried over $NaSO_4$, filtered, and concentrated. The resulting crude mixture was purified by column chromatography using ethyl acetate and hexanes as the eluent. The product was obtained as a white solid: mp 143-145 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (d, J = 16.0 Hz, 2H), 3.93 (d, J = 16.0 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 7.18-7.35 (m, 5H), 7.43 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.4, 49.6, 96.8, 123.2, 124.6, 127.8, 128.5, 128.6, 129.9, 138.7, 139.1, 143.2; IR (neat, cm^{-1}) 3066, 2969, 2908, 2847, 2221, 1578, 1476, 1460, 1427, 1280, 1224, 1046, 1013, 756, 721; HRMS calcd for $C_{16}H_{12}ION$ 345.0011, found 345.0015.

General procedure for the preparation of aldehydes 20, 23 and 26-39. A 25 mL round bottom flask containing the desired aldehyde (3.0 mmol) was flushed with argon and charged with 10 mL of anhydrous CH_2Cl_2. This solution was cooled to -78 ^{o}C and a solution of DIBAL (1.0 M in CH_2Cl_2, 6 mL, 6.0 mmol) was added dropwise over a period of 5 min. The resulting reaction mixture was allowed to stir at room temperature for 12 h and was monitored by TLC. After the starting aldehyde was consumed, the reaction

mixture was cooled to -78 ^{o}C, quenched with 0.5 M H_2SO_4 (6 mL), and allowed to stir at room temperature overnight. The reaction mixture was diluted with 10 mL of water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL). This organic layer was dried over $NaSO_4$, filtered, and concentrated. The resulting crude mixture was purified by column chromatography using ethyl acetate and hexanes as the eluent.

2-(2-Iodophenyl)-2-methylpropanal (20). The product was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 6H), 7.01 (td, J = 1.2, 6.8 Hz, 1H), 7.36-7.45 (m, 2H), 7.94 (d, J = 7.6 Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 53.2, 98.2, 128.7, 128.8, 129.4, 142.1, 145.5, 203.9; IR (neat, cm^{-1}) 2976, 2931, 2798, 2701, 1719, 1462, 1430, 1236, 1008, 838, 755; HRMS calcd for $C_{10}H_{11}IO$ 273.98547, found 273.98573.

1-(2-Iodophenyl)cyclopentanecarboxaldehyde (23). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60-1.80 (m, 4H), 2.01-2.11 (m, 2H), 2.31-2.42 (m, 2H), 6.87-6.96 (m, 1H), 7.22-7.35 (m, 2H), 7.88 (dd, J = 1.2, 8.0 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 35.0, 65.3, 99.5, 128.3, 128.9, 129.2, 142.0, 145.0, 202.5; IR (neat, cm^{-1}) 2954, 2869, 1700, 1580, 1555, 1460, 1429, 1266, 1009, 755; HRMS calcd for $C_{12}H_{13}IO$ 300.00112, found 300.00162.

1-(2-Bromophenyl)cyclopentanecarboxaldehyde (26). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.85 (m, 4H), 2.15-2.20 (m, 2H), 2.34-2.48 (m, 2H), 7.16 (dt, J = 1.2, 8.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.6 Hz,

1H), 7.61 (d, J = 7.6 Hz, 1H), 9.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 34.1, 63.9, 124.6, 127.6, 128.9, 129.1, 134.6, 141.6, 201.9; IR (neat, cm^{-1}) 3065, 2953, 2870, 2800, 2716, 1721, 1466, 1435, 1102, 1023, 754; HRMS calcd for $C_{12}H_{13}BrO$ 252.01498, found 252.01528.

2-(2-Iodophenyl)-2-propylpentanal (27). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.4 Hz, 3H), 0.96-1.12 (m, 2H), 1.18-1.32 (m, 2H), 1.92-2.15 (m, 4H), 6.99 (td, J = 1.6, 8.0 Hz, 1H), 7.29 (dd, J = 1.6, 8.0 Hz, 1H), 7.38 (td, J = 1.6, 7.2 Hz, 1H), 7.96 (dd, J = 1.6, 8.0 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 17.0, 35.8, 59.8, 98.3, 128.1, 129.1, 130.5, 142.6, 143.0, 205.2; IR (neat, cm^{-1}) 3065, 2949, 2870, 2925, 2802, 2716, 1718, 1586, 1562, 1466, 1430, 1263, 1102, 1022, 944, 754; HRMS calcd for $C_{14}H_{19}IO$ 330.04807, found 330.04856.

1-(2-Iodophenyl)cyclohexanecarboxaldehyde (28). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.56 (m, 1H), 1.58-1.82 (m, 5H), 1.98-2.10 (m, 2H), 2.25-2.38 (m, 2H), 5.84 (s, 2H), 6.96 (td, J = 1.6, 7.6 Hz, 1H), 7.39 (td, J = 1.6, 7.2 Hz, 1H), 7.44 (dd, J = 1.6, 8.0 Hz, 1H), 7.94 (dd, J = 1.2, 8.0 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 25.7, 32.3, 55.7, 97.7, 128.3, 129.1, 129.8, 142.6, 145.6, 204.9; IR (neat, cm^{-1}) 2923, 2856, 2795, 1721, 1455, 1416, 1122, 1060, 1043, 1004, 876, 754, 736; HRMS calcd for $C_{13}H_{15}IO$ 314.01677, found 314.01736.

1-(2-Iodophenyl)cyclopropanecarboxaldehyde (29). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35-1.41 (m, 2H), 1.72-1.79 (m, 2H), 7.05 (td, J = 1.6, 7.6 Hz, 1H), 7.24 (dd, J = 2.0, 7.6 Hz, 1H), 7.36 (td, J = 1.2, 7.6 Hz, 1H),

7.92 (dd, J = 0.8, 7.6 Hz, 1H), 9.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 41.4, 103.4, 128.5, 129.8, 132.4, 139.8, 140.8, 200.2; IR (neat, cm^{-1}) 3062, 2988, 2861, 2742, 1714, 1462, 1435, 1263, 1175, 1002, 853, 752, 730; HRMS calcd for $C_{10}H_9IO$ 271.96982, found 271.97016.

1-(2-Iodophenyl)cyclobutanecarboxaldehyde (30). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.91 (m, 1H), 2.00-2.19 (m, 1H), 2.45-2.60 (m, 2H), 2.85-2.98 (m, 2H), 6.99 (td, J = 1.6, 7.6 Hz, 1H), 7.21 (dd, J = 1.6, 7.6 Hz, 1H), 7.40 (td, J = 1.2, 8.0 Hz, 1H), 7.89 (dd, J = 1.2, 8.0 Hz, 1H), 9.77(s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 30.1, 60.8, 96.3, 128.4, 129.1, 129.2, 141.0, 144.1, 200.2; IR (neat, cm^{-1}) 3058, 2982, 2941, 2853, 2709, 1716, 1462, 1429, 1263, 1157, 1009, 856, 755, 732; HRMS calcd for $C_{11}H_{11}OI$ 285.9844, found 285.9855.

2-(2-Iodophenyl)-2,3-dihydro-1*H*-indene-2-carboxaldehyde (31). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 3.43 (d, J = 16.0 Hz, 2H), 7.78 (d, J = 16.0 Hz, 2H), 6.98 (dt, J = 2.0, 8.0 Hz, 1H), 7.12-7.32 (m, 6H), 9.67 (dd, J = 1.2, 8.0 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7, 65.9, 98.6, 124.6, 127.4, 128.4, 129.4, 129.8, 140.3, 142.1, 143.9, 201.8; IR (neat, cm^{-1}) 3062, 3023, 2955, 2904, 1719, 1484, 1460, 1264, 1002, 859, 754, 735; HRMS calcd for $C_{16}H_{13}IO$ 348.00112, found 348.00173.

General procedure for the preparation of aldehydes 46 and 47. Manganese(IV) oxide (352 mg, 4.0 mmol) was added to a solution of the alcohol (8-halonaphthalen-1-yl)methanol (2.0 mmol) in chloroform (10 mL) and the stirred mixture was allowed to

reflux for 24 h. The suspension was filtered through celite and washed with chloroform. The filtrate was washed with water (5 mL), dried with Na_2SO_4, and concentrated under a vacuum to give crude aldehyde, which was purified by column chromatography.

8-Iodo-1-naphthaldehyde (46). The product was obtained as a white solid: mp 81-82 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.81-7.96 (m, 3H), 8.22 (d, J = 7.6 Hz, 1H), 11.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.9, 126.0, 127.8, 129.8, 130.2, 133.7, 134.3, 135.7, 136.5, 141.4, 191.7; IR (neat, cm^{-1}) 2878, 2861, 1672, 1609, 1553, 1493, 1335, 1234, 1197, 1063, 824, 790, 747; HRMS calcd for $C_{11}H_7IO$ 281.95416, found 281.95458.

8-Bromo-1-naphthaldehyde (47). The product was obtained as a white solid: mp 88-89 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, J = 8.0 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.95-8.30 (m, 3H), 8.37 (d, J = 7.6 Hz, 1H), 11.32 (s, 1H). The other physical and spectral data are consistent with those reported in the literature.[18]

Ethyl 3-allyl-4-amino-5-iodobenzoate (51).[17] A 25 mL round bottom flask containing ethyl 4-amino-3,5-diiodobenzoate (662 mg, 2.0 mmol) was flushed with argon, charged with 6 mL of anhydrous THF, and cooled to -30 °C. PhMgCl (1.4 mL, 1.4 M in THF, 2.0 mmol) was slowly added at -30 °C. The reaction mixture color changes from yellow orange to dark red. After 5 min, *i*-PrMgCl (1.04 mL, 2.1 M solution in ether, 2.2 mmol) was added below -20 °C and the reaction mixture was stirred for 0.3 h at -30 °C. A solution of CuCN (178 mg, 2.0 mmol) and LiCl (168 mg, 4.0 mmol, dried at 150 ^oC for 1 h) in 2 mL of THF was rapidly added. The resulting solution was stirred at -30 ^oC for 1.5

h and allyl bromide (288 mg, 0.2 ml, 2.4 mmol) was added. The reaction was allowed to stir at room temperature overnight and quenched with satd aq NH_4Cl solution. After extraction with CH_2Cl_2, drying (Na_2SO_4), filtration, and evaporation of the solvents, the residue was purified by flash chromatography, yielding the desired product as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 3.35 (d, *J* = 6.0 Hz, 3H), 4.31 (q, *J* = 6.8 Hz, 2H), 4.61 (s, 2H), 5.08-5.23 (m, 2H), 5.81-5.98 (m, 1H), 7.70 (s, 1H), 8.25 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 37.6, 60.8, 83.9, 117.4, 121.4, 122.7, 131.9, 134.6, 139.4, 149.1, 165.6 ; IR (neat, cm^{-1}) 3067, 2996, 2949, 2925, 2855, 1710, 1740, 1581, 1562, 1460, 1430, 1263, 1175, 1010, 944, 745; HRMS calcd for $C_{12}H_{14}INO_2$ 331.00692, found 331.00723.

General procedure for the preparation of formamides 12, 50 and 52. At 0 °C under anhydrous conditions, a solution of the appropriate aniline (1.0 mmol) was added to a solution of ethyl formate (0.83 mL, 10.0 mol) in anhydrous THF (5 mL). After stirring for 10 min, the mixture was treated with portions of NaH (29.0 mg, 1.2 mmol). The mixture was allowed to stir overnight. After the reaction was over, a few drops of H_2O were slowly added before diluting with EtOAc. The organic phase was washed successively with H_2O and brine, and dried ($MgSO_4$). After removal of the solvents under reduced pressure, the crude product was purified using column chromatography.

***N*-(2-Iodophenyl)formamide (12).** The product was obtained as a light pink solid: mp 110-111 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (m, 2H), 7.19 (m, 1H), 7.78 (m, 1H), 8.28 (d, *J* = 8.3 Hz, 1H), 8.49 (s, 1H), 8.64 (d, *J* = 11.0 Hz, 1H). The other physical and spectral data are consistent with those reported in the literature.[19]

***N*-(4-Cyano-2-iodophenyl)formamide (50).** The product was obtained as a white solid: mp 173-175 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (dd, J = 2.0, 8.5 Hz, 1H), 8.14 (br s, 1H), 8.35 (d, J = 2.0 Hz, 1H), 8.46 (s, 1H), 9.72 (br s, 1H). The other physical and spectral data are consistent with those reported in the literature.[16]

Ethyl 3-allyl-4-formamido-5-iodobenzoate (52). The product was obtained as a white solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.31 (t, J = 7.2 Hz, 3H), 3.39 (br s, 2H), 4.31 (q, J = 6.8 Hz, 2H), 5.02-5.12 (m, 2H), 5.80-5.92 (m, 1H), 7.82 (d, J = 1.6 Hz, 1H), 8.27 (d, J = 1.6 Hz, 1H), 8.31 (br s, 1H), 9.99 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1, 36.4, 61.2, 101.0, 117.1, 117.2, 130.1, 135.6, 137.4, 139.3, 141.8, 159.7, 164.0; IR (neat, cm^{-1}) 3058, 3012, 2926, 1710, 1678, 1578, 1474, 1410, 1250, 1212, 1199, 1020, 942, 764, 722; HRMS calcd for $C_{13}H_{14}INO_3$ 359.00184, found 359.00184.

***N*-Benzyl-*N*-(2-iodophenyl)formamide (53).** At 0 °C under anhydrous conditions, a solution of *N*-(2-iodophenyl)formamide (247 mg, 1.0 mmol) in anhydrous DMF (5 mL) was treated portionwise with NaH (29.0 mg, 1.2 mmol). To this solution, benzyl bromide (0.14 mL, 1.2 mmol) was added via syringe. The mixture was allowed to stir overnight at room temperature. After the reaction was over, a few drops of H_2O were slowly added before diluting with EtOAc. The organic phase was washed successively with H_2O and brine, and dried ($MgSO_4$). After removal of the solvents under reduced pressure, the crude product was purified using column chromatography. The product was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.81 (br s, 8H), 6.78 (d, J = 7.6 Hz, 1H), 7.00-7.41 (m, 31H), 7.90 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 3H), 8.20 (s, 3H),

8.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.3, 52.6, 99.1, 99.8, 127.2, 127.6, 128.1, 128.2, 128.5, 128.6, 129.0, 129.3, 129.9, 135.8, 135.9, 139.3, 139.6, 141.2, 141.8, 162.0, 162.5; IR (neat, cm^{-1}) 3060, 3028, 2931, 2859, 1678, 1578, 1470, 1438, 1351, 1316, 1280, 1250, 1199, 1020, 942, 764, 722; HRMS calcd for $C_{14}H_{12}INO$ 336.99636, found 336.99699.

General procedure for reaction conditions A. To a stirred solution of 0.50 mmol of the aryl halide, $Pd(OAc)_2$ (5.6 mg, 0.024 mmol), dppm (9.6 mg, 0.024 mmol) and 6 mL of DMF, cesium pivalate (234 mg, 1.0 mmol) were added. The reaction vial was sealed, flushed with argon, heated at 110 °C, and monitored by TLC. After completion of the reaction, the mixture was diluted with 20 mL of Et_2O and washed several times with small amounts of water to remove DMF. The resulting organic solution was dried with Na_2SO_4, concentrated under a vacuum, and purified by column chromatography using hexanes and ethyl acetate as the eluent.

***α*-Methylstyrene (21).** The product was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 4.96-5.04 (m, 1H), 5.28 (s, 1H), 7.12-7.28 (m, 3H), 7.35-7.42 (m, 2H). The other physical and spectral data are consistent with those reported in the literature.[20]

1-Phenylcyclopentene (24). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99-2.09 (m, 2H), 2.52-2.57 (m, 2H), 2.73-2.76 (m, 2H), 6.20 (quintet, J = 2.0 Hz, 1H), 7.22-7.35 (m, 3H), 7.46 (d, J = 7.2 Hz, 2H). The other physical and spectral data are consistent with those reported in the literature.[21]

1-Phenylcyclohexene (54). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 2H), 1.82 (m, 2H), 2.24 (m, 2H), 2.43 (m, 2H), 6.15 (m, 1H), 7.19-7.42 (m, 5H). The other physical and spectral data are consistent with those reported in the literature.[22]

(*E*)-4-Phenyl-3-heptene (55). The product was obtained as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7.6 Hz, 3H), 1.03 (t, J = 7.6 Hz, 3H), 1.30-1.43 (m, 2H), 2.18 (quintet, J = 7.6 Hz, 2H), 2.45 (t, J = 7.6 Hz, 2H), 5.63 (t, J = 7.2 Hz, 1H), 7.20-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.6, 22.0, 22.1, 31.8, 126.5, 126.6, 128.3, 131.1, 139.6, 143.6; IR (neat, cm^{-1}) 3023, 2932, 2910, 2852, 1476, 1460, 1421, 1255, 1210, 1042, 1013, 755; HRMS calcd for $C_{13}H_{18}$ 174.14085, found 174.14131.

1-Phenylcyclobutene (58). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (t, J = 3.0 Hz, 2H), 2.83 (t, J = 3.0 Hz, 2H), 6.31 (s, 1H), 7.22-7.40 (m, 5H). The other physical and spectral data are consistent with those reported in the literature.[23]

2-Phenyl-1*H*-indene (59). The product was obtained as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 2H), 7.17 (td, J = 1.0, 7.5 Hz, 1H), 7.21 (t, J = 0.5 Hz, 1H), 7.24-7.28 (m, 2H), 7.35-7.40 (m, 3H), 7.46 (dd, J = 1.0, 7.5 Hz, 1H), 7.61-7.63 (m, 2H). The other physical and spectral data are consistent with those reported in the literature.[24]

General procedure for reaction conditions B. To a stirred solution of 0.50 mmol of the aryl halide, $Pd(OAc)_2$ (5.6 mg, 0.024 mmol), dppm (9.6 mg, 0.024 mmol), cesium pivalate (234 mg, 1.0 mmol) and 6 mL of DMF, *n*-BuOH (0.91 mL, 10.0 mmol) was added. The reaction vial was sealed, flushed with argon, heated at 110 °C, and monitored by TLC. After completion of the reaction, the mixture was diluted with 20 mL of Et_2O and washed several times with small amounts of water to remove DMF. The resulting organic solution was dried with Na_2SO_4, concentrated in vacuum, and purified by column chromatography using hexanes and ethyl acetate as the eluent.

***n*-Butyl *N*-phenylcarbamate (13).** This compound was isolated as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.38 (m, 2H), 1.59 (m, 2H), 4.15 (t, J = 6.6 Hz, 2H), 6.59 (br s, 1H), 7.03 (m, 1H), 7.27 (m, 2H), 7.37 (m, 2H). The other physical and spectral data are consistent with those reported in the literature.[25]

***n*-Butyl naphthalene-1-carboxylate (60)**. This compound was isolated as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, J = 5.6 Hz, 3H), 1.50 (m, 2H), 1.80 (m, 2H), 4.41 (t, J = 5.0 Hz, 2H), 7.48 (m, 3H), 7.87 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 6.2 Hz, 1H) , 8.17 (d, J = 5.6 Hz, 1H), 8.89 (d, J = 6.2 Hz, 1H). The other physical and spectral data are consistent with those reported in the literature.[26]

General procedure for reaction conditions C. To a stirred solution of 0.50 mmol of the aryl halide, K_2CO_3 (138 mg, 2.0 mmol) and 8 mL of MeOH, $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) was added. The reaction vial was sealed, flushed with argon, heated at 70 °C, and monitored by TLC. After the completion of the reaction, the mixture was concentrated.

The crude product was diluted with 20 mL of Et_2O. The resulting solution was washed with water (5 mL) and brine (5 mL), and dried over $NaSO_4$. After filtration, the organic solution was concentrated and purified by column chromatography using hexanes and ethyl acetate as the eluent.

Methyl 1-phenylcyclopentanecarboxylate (25). The product was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.66-2.70 (m, 8H), 3.60 (s, 3H), 7.19-7.39 (m, 5H). The other physical and spectral data are consistent with those reported in the literature.[27]

Methyl 1-naphthoate (61). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.52 (q, J = 7.8 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 7.2 Hz, 1H), 8.91 (d, J = 8.6 Hz, 1H). The other physical and spectral data are consistent with those reported in the literature.[28]

Methyl 1-phenylcyclohexanecarboxylate (62). The product was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.20-1.38 (m, 1H), 1.42-1.57 (m, 2H), 1.65-1.80 (m, 5H), 2.45-2.52 (m, 2H), 3.65 (s, 3H), 7.20-7.45 (m, 5H). The other physical and spectral data are consistent with those reported in the literature.[29]

Methyl 1-phenylcyclobutanecarboxylate (63). The product was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81-1.94 (m, 1H), 1.98-2.12 (m, 1H), 2.47-2.59 (m, 2H), 2.80-2.91 (m, 2H), 3.65 (s, 3H), 7.22-7.27 (m, 1H), 7.29-7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 32.6, 52.5, 52.6, 126.5, 126.8, 128.5, 143.8, 176.7; IR (neat, cm^{-1}) 3083, 2989, 2949, 2888, 1729, 1599, 1493, 1445, 1280, 1247, 1201, 1123, 733, 698; HRMS calcd for $C_{12}H_{14}O_2$ 190.09938, found 190.09963.

Methyl 2-phenyl-2-propylpentanoate (64). The product was obtained as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 6H), 1.02-1.84 (m, 4H), 1.90-2.28 (m, 4H), 3.42-3.84 (m, 3H), 7.27-7.80 (m, 5H). The other physical and spectral data are consistent with those reported in the literature.[30]

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CHAPTER 4: NANOSCALE MORPHOLOGICAL SCAFFOLDS BY CATIONIC POLYMERIZATION

Based on a paper to be submitted to *Chemistry of the Materials*

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Abstract

In this study, several interesting nanoscale materials have been synthesized by the cationic polymerization of divinylbenzene (DVB) and styrene (ST) using BF_3•Et_2O as an initiator. The structures of the polymer have been analyzed using SEM and TEM microscopic techniques. Polymerization of DVB alone produces nanowires. However, using ST as a copolymer produces nanotubes. The morphological properties of the polymers are not only dependent upon the composition of ST and DVB, but also upon the solvent, reaction time, temperature and rotational speed. Several substituted styrenes have also been employed in this polymerization. However, they failed to furnish the desired structures.

Introduction

The miniaturization of electronic devices has attracted major attention in recent years and has been a driving force for development of the nanosciences.[1] Two major scientific hurdles need to be addressed in order to connect the nanoscopic structure of such materials to the outer macroscopic world. First, one must generate the specific shape required, preferably using self-assembly,[2] and, second, one needs to integrate the functional nanostructure into an actual electronic device.

Tubular structures[3] are the most versatile module for electronic devices due to their ability to transport neutral, ionic and chiral species.[4] Transport processes can also be coupled to chemical transformations, i.e., catalysis, affording a flow-through nanoreactor for high-end analytical applications.[5] Tubular structures are also useful for the site isolation of the conducting and emitting core.[6]

The synthesis of a tubular structure with a specific diameter remains a challenging task and can be divided into two different approaches. The first one is based on artificial growth, template and shape transformation processes,[7] whereas the second approach uses covalent and non-covalent interactions and is a purely bio-inspired molecular synthesis.[8] The first category gives rise to the efficient synthesis of carbon and inorganic nanotubes, which are more promising building blocks for the miniaturization of electronic devices, because of their exceptional properties and commercial availability.[9] However, the separation and purification issues make them expensive and hinder their practical utility in electronic devices. The peripheral functionalization of tubes is solely statistical and not regioselective, reducing their further utility.[10]

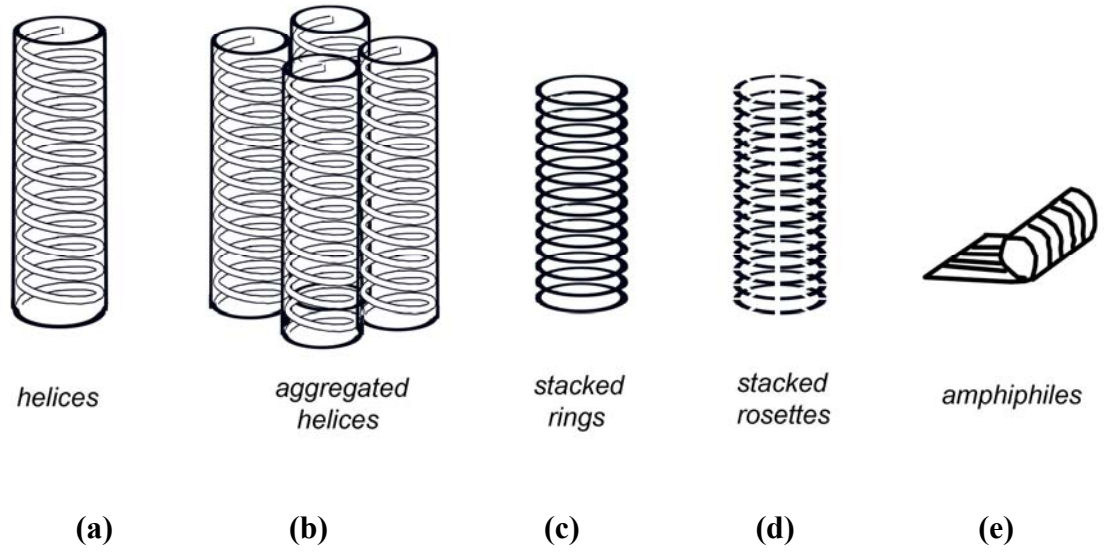


Figure 1. General strategies for the design of organic nanotubes

Five possible strategies for the molecular assembly of organic materials are depicted in Figure 1. The first two approaches employ a helical backbone to synthesize nanotubes (Figures 1a and 1b), whereas the third and fourth techniques utilize stacking of the rings (Figures 1c and 1d). The helical backbone approach has the maximum covalent character for generating tubular structures (Figure 1a).[11] These helical backbones can also lead to the formation of secondary helical structures, which are controlled by non-covalent interactions. Multiple helical entities can be organized in different modes, which can form multi-strand helices, which can stack along their axis in a continuous fashion to form tubes or can assemble in a barrel-stave fashion to form molecular bundles (Figure 1b).[12] In the third approach, macrocycles are stacked in such a manner that their centers are aligned in one common axis (Figure 1c).[13] The formation of macrocycles requires covalent interactions, whereas the stacking of these macrocycles requires non-covalent

interactions, such as π-π stacking or hydrogen bonding. The fourth approach is similar to the third one, except in this approach the formation of macrocycles takes place through non-covalent interactions of rosettes (Figure 1d).[14] Tubular structure formation by cylindrical micelles or rolled sheets arising from curved bilayers of certain amphiphiles falls into the fifth category (Figure 1e) and utilizes mostly non-covalent interactions. These linear amphiphiles can simplify the synthesis of tubular structures, but suffer from limited predictability of their shape.[15]

As mentioned earlier, all of these approaches use a combination of covalent and non-covalent interactions for the formation of tubular structures. The defined chemical bonds provide increased stability and control over molecular conformations, whereas supramolecular interactions allow their facile synthesis and repair of defects. These advantages are usually accompanied by significant challenges concerning predictability of structure and efficiency of large-scale production.

A radical simplification of the design of tubular structures is achieved by the use of linear amphiphiles. Their ease of synthesis and commercial availability makes this approach very attractive. However, it suffers from a disadvantage due to a limited predictability of the self assembly process. The reasons for this limited predictability are the high flexibility and ill-defined shapes of the building blocks. The two principle aggregation modes that lead to tubular structures involve rolled lamellar sheets and cylindrical micelles.

Tubular structures can be synthesized by using di- and triblock copolymers as amphiphiles. Diblock copolymer amphiphiles, such as polystyrenes-block-poly(ethylene oxide) [16] or poly(ethylene oxide)-block-poly(ethylethylene),[17] are observed to form

tubular bilayer aggregates in solution under appropriate conditions. Another sophisticated approach to tubular structure developed by Liu and co-workers involves block polymerization of polyisoprene, poly(2-cinnamoylethyl methacrylate) (PCMA), and poly(*tert*-butyl acrylate) (P*t*BA) to form cylindrical micelles in solution.[18] The ratios of blocks determine the size and shape of the assemblies. Ratios of approximately 1:1:6 (130:130:800 repeating units) lead to cylindrical micelles having dimensions 79 nm in diameter and a few micrometers in length. Polyisoprene forms the core surrounded by a PCMA shell, which is further surrounded by a PtBA core. Photo-crosslinking of the methacrylate shell and subsequent removal of the polyisoprene core by ozonolysis affords a hollow polyacrylate tube.

As mentioned earlier, polymerization is not a preferred process for the synthesis of nanotubes due to the limited predictability of the shape. Yan and co-workers have recently reported stable and soluble tubes by self assembly of a hyper-branched, multi-arm copolymer.[19] Herein, we report a new and simple method for the preparation of nanoscale fibers and tubes by the room temperature cationic polymerization of divinylbenzene and its copolymerization with styrene.

Results and Discussion

When we attempted the cationic polymerization of DVB using hexanes as the solvent and 5% BF_3•Et_2O as the initiator, we found that the polymerization furnished pale yellow solid particles in a good yield of about 80%. Washing the solid particles with acetone gave pure white solids. The surface analysis of these particles using SEM showed a long fibrous material with closed ends (Figures 2a and 2b). Upon TEM analysis, we

found that most of the single strands were not hollow (Figures 2c and 2d). However, some of them showed very narrow openings with a diameter of around 4-5 nm (Figure 2c). The diameter of these nanorods ranges from 300 to 500 nm.

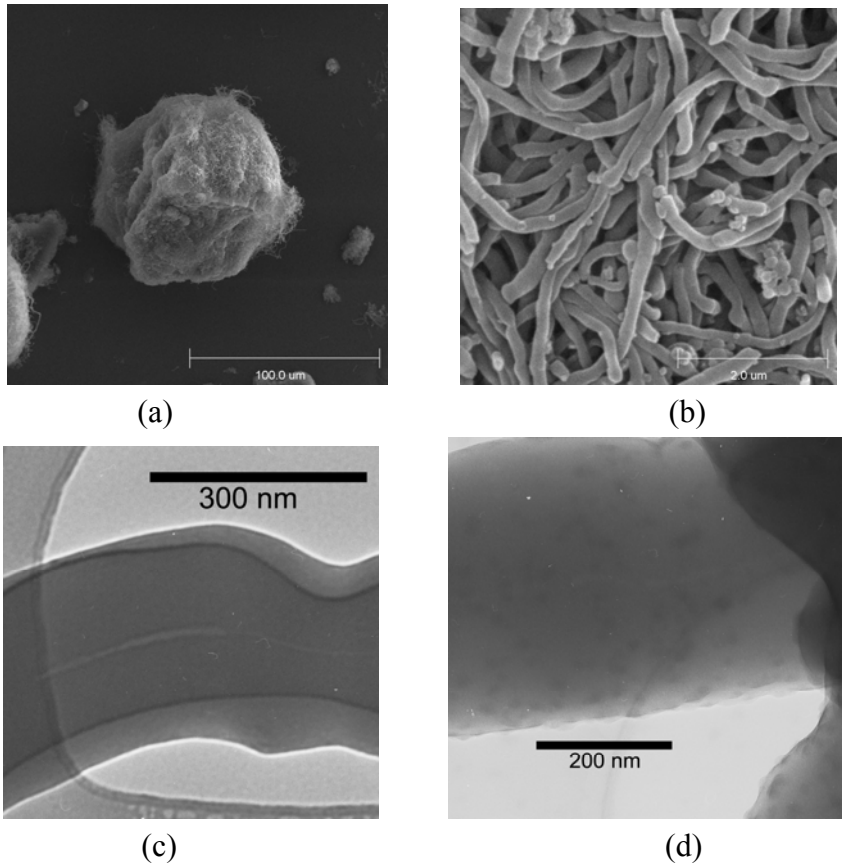


Figure 2. SEM (a and b) and TEM (c and d) images of fibers obtained from the polymerization of DVB in hexanes at 25 ^{o}C.

Commercially available DVB contains around 20 % of *o*- and *p*-ethylvinyl-benzene. We thought that this could be the reason for the formation of tubular structures. Therefore, we examined the cationic polymerization of styrene as a co-monomer along with the commercially available DVB. We found that when 70 wt % of DVB was employed with 30 wt % of styrene, the SEM of the polymer remained unchanged (Figures 3a and 3b) and did not show any opening at the end of the fiber. The thickness

of the fibers were also unchanged and were found to be in the same range as we obtained previously with pure DVB, i.e. 300-500 nm. Also, TEM showed that the majority of the structure was a solid rod with no opening. However, some of the fibrous strands have openings with diameters ranging from 20-40 nm, which is higher than the observed diameter in the case of 100% DVB (Figures 3c and 3d).

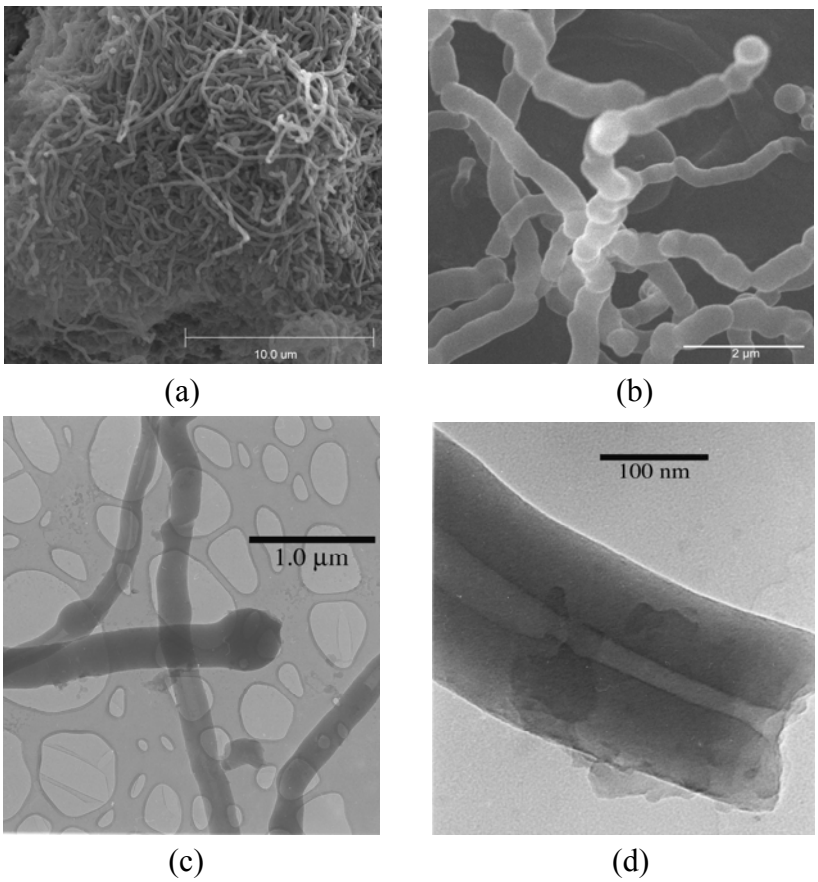
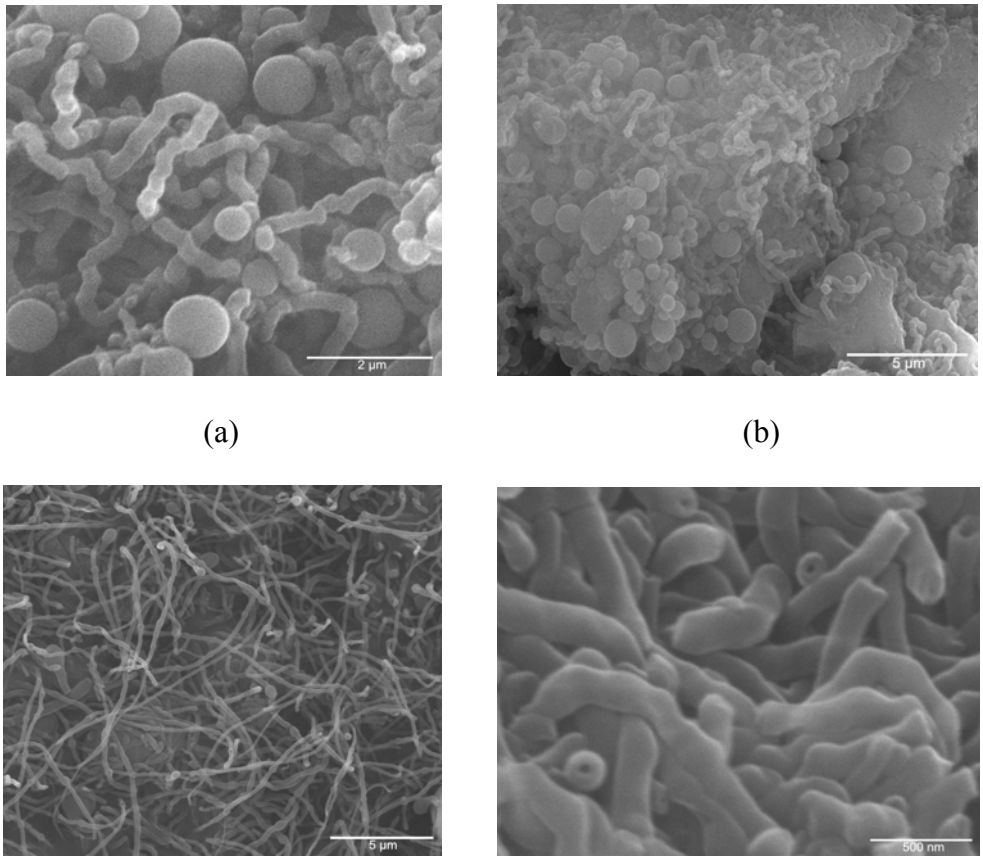


Figure 3. SEM (a and b) and TEM (c and d) images of fibers obtained from the polymerization of 70 wt % DVB and 30 wt % of ST in hexanes at 25 ^{o}C.

After the encouraging observation obtained with 30% ST, we decided to increase the amount of ST to see what further changes in the morphology of the polymer might occur. Increasing the amount of styrene from 30% to 40% decreased the morphological control in the resulting structure and gave a mixture of fibers and particles (Figures 4a

and 4b). To our surprise, increasing the amount of ST further to 45% resulted in a polymer with very good morphological control as observed in the SEM (Figures 4c and 4d). The TEM of these polymeric solid particles showed almost all the tubes to be hollow (Figure 5). The diameter of the tube ranges from 20-40 nm and the thickness of the tubes was found to be in the range of 200-300 nm.



(a) (b)

(c) (d)

Figure 4. SEM images of fibers obtained from the polymerization of 60 wt % DVB and 40 wt % of ST (a and b) and 55 wt % DVB and 45 wt % of ST (c and d) in hexanes at 25 ^{o}C.

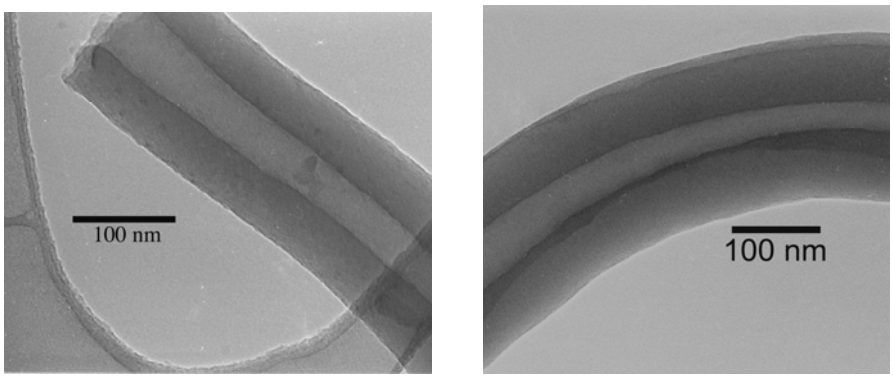
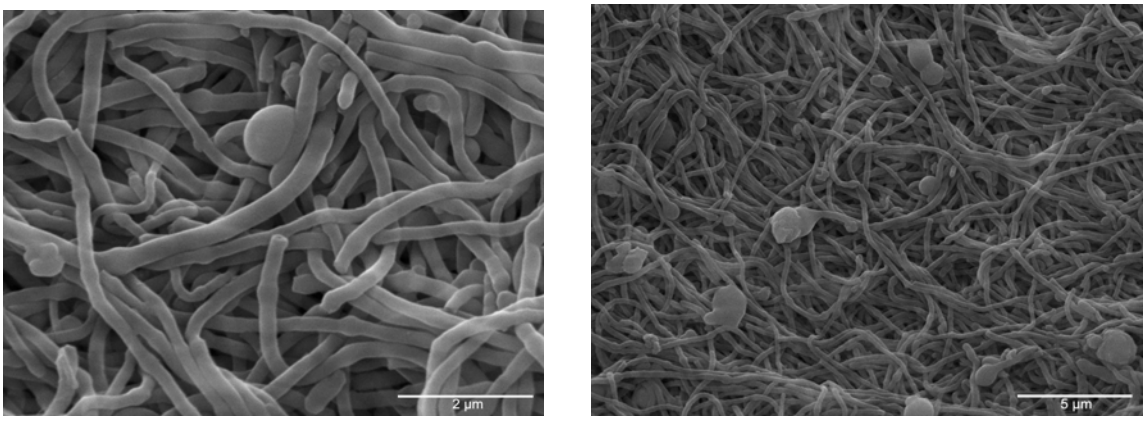
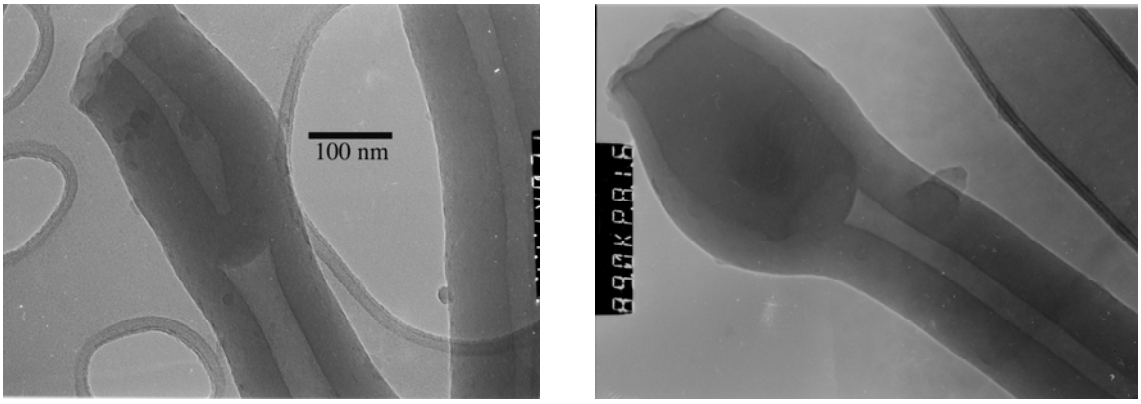


Figure 5. TEM images of fibers obtained from the polymerization of 55 wt % DVB and 45 wt % of ST in hexanes at 25 ^{o}C.

Using 50 wt % of ST gave similar results (Figure 6). However, no indication of a hollow opening was observed by SEM and the ends of the strands were mostly blocked or showed some indentations (Figure 6a). The TEM analysis of these elongated polymers, however, showed a hollow channel ranging from 20-30 nm (Figure 6b). Some blockage at the ends of the tubes and in between the tubes was also seen. This might be the reason for not observing a hollow channel in the SEM analysis.



(a)



(b)

Figure 6. SEM (a) and TEM (b) images of fibers obtained from the polymerization of 50 wt % DVB and 50 wt % of ST in hexanes at 25 ^{o}C.

Table 1. Effect of stoichiometry on the polymerization of ST and DVB.[a]

entry	ST	DVB	observation
1	0	100	solid fibers
2	30	70	mostly solid fibers and some hollow tubes
3	40	60	mixtures of solid fibers and particles
4	45	55	hollow tubes
5	50	50	hollow tubes
6	55	45	mixtures of solid fibers and particles
7	60	40	mixtures of solid fibers and particles
8	70	30	mostly particles
9	100	0	no polymer

[a]All reactions were performed using the indicated wt % of DVB and ST, while keeping the concentration of the solution constant at 16.6 g/L in 250 mL of hexanes at 25 ^{o}C for 6 h.

Further attempts to fine tune the structure using greater amounts of ST failed. Increasing the percentage of ST to 55 and above resulted in loss of the tubular structure

or in some cases only particles were observed, instead of fibers. A summary of all these attempts is given in Table 1 and the SEM images are shown in Figure 7. When 55 wt % of ST was allowed to react with 45 wt % of DVB, a mixture of fibers and particles was obtained (Figure 7a). Further increasing the amount of ST to 60 and 70 wt % gave only nanoparticles (Figures 7b and 7c).

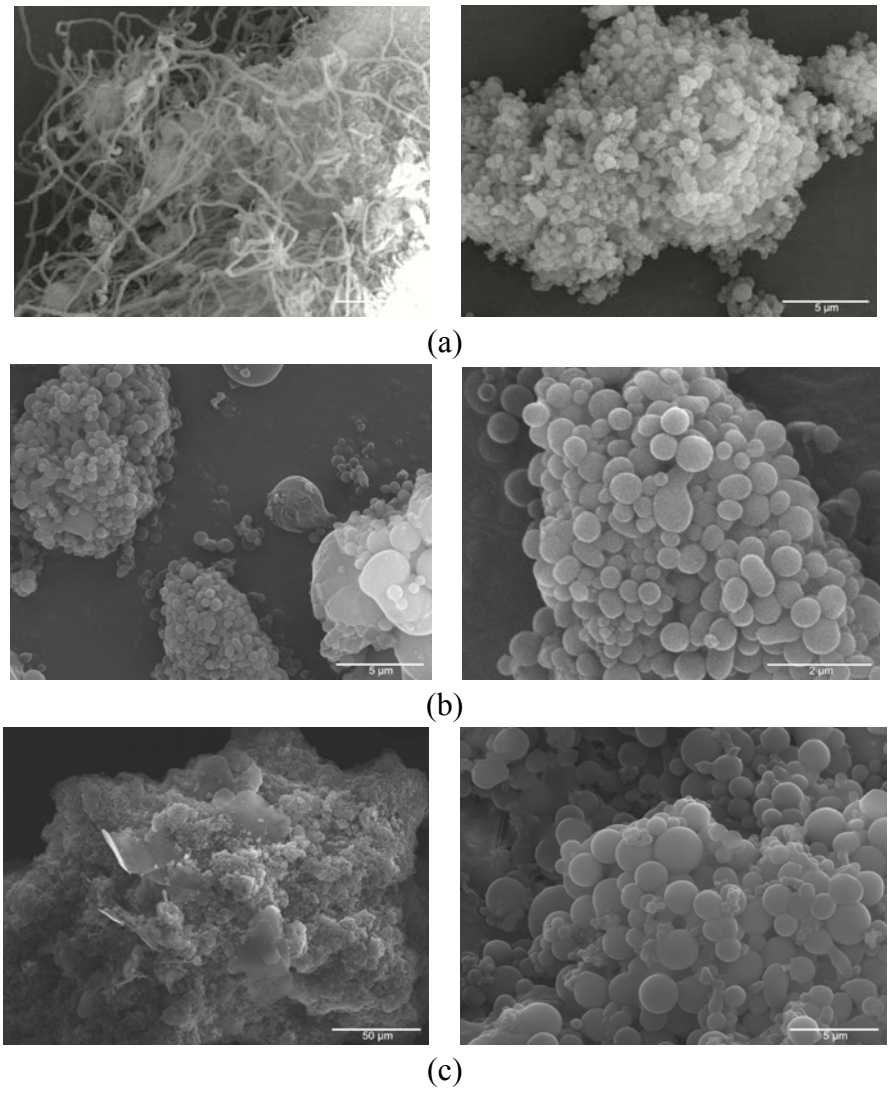


Figure 7. SEM images of fibers obtained from the polymerization of 45 wt % DVB and 55 wt % of ST (a), 40 wt % DVB and 60 wt % of ST (b), and 30 wt % DVB and 70 wt % of ST (c) in hexanes at 25 ^{o}C.

Effect of the solvent

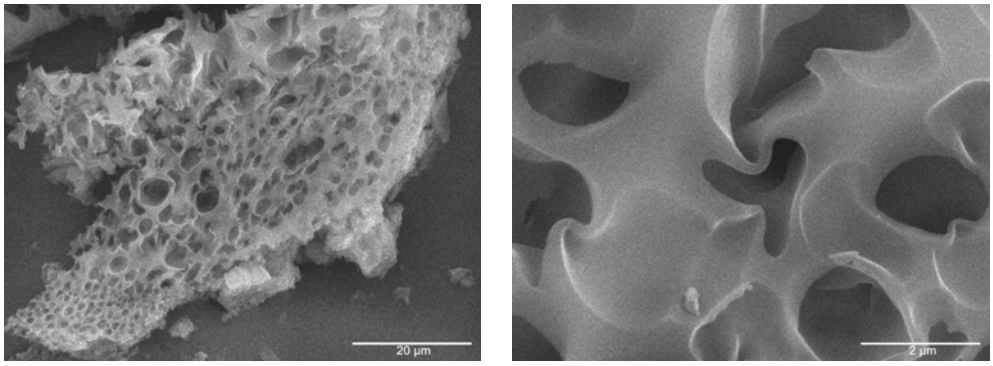
The effect of solvents on the morphology of the polymers has also been studied. A summary of the results is given in Table 2. When using 50 wt % of DVB and 50 wt % of ST, THF, DMF, acetonitrile, toluene, ethyl acetate and acetone failed to furnish any polymeric solid materials. Toluene gave a sticky product, which was semi-solid. No precipitate was observed in the case of DCM and ethyl ether, but, upon evaporation of the solvent, these reactions furnished solid products. The SEM of the polymer obtained from DCM indicated the formation of a sponge-like material (Figure 8a), whereas ethyl ether gave a massive solid material having no defined shape (Figure 8b). Using pentane as the solvent furnished elongated fibers similar to hexanes. However, no opening was observed at the ends of the fibrous structures (Figure 8c). Cyclohexane gave a mixture of particles and elongated fibers, and did not form any hollow channels (Figure 8d).

Table 2. Effect of the solvent on the polymerization of ST and DVB.[a]

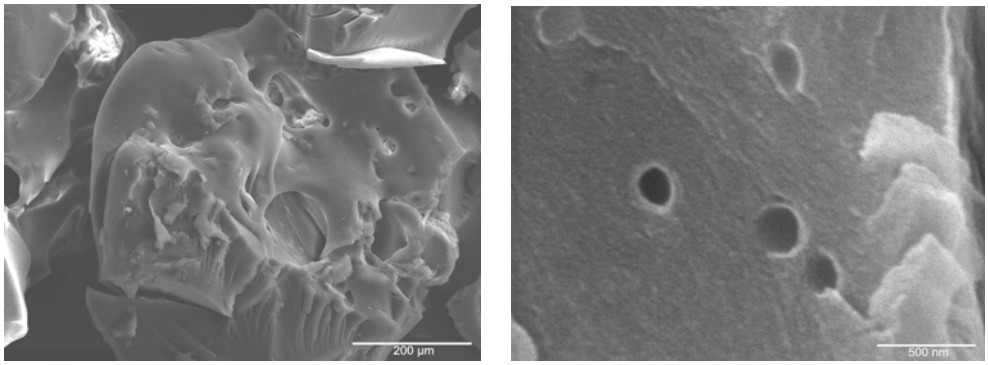
entry	solvent	time (h)	observations
1	DCM	6	solid particles with a sponge-like structure
2	diethyl ether	6	massive solid particles
3	cyclohexane	6	mixture of fibers and solid particles
4	pentane	6	elongated fibers with hollow channels
5	DMF	24	no product
6	toluene	24	sticky semi-solid
7	ethyl acetate	24	no product

8	THF	24	no product
9	acetonitrile	24	no product
10	acetone	24	no product

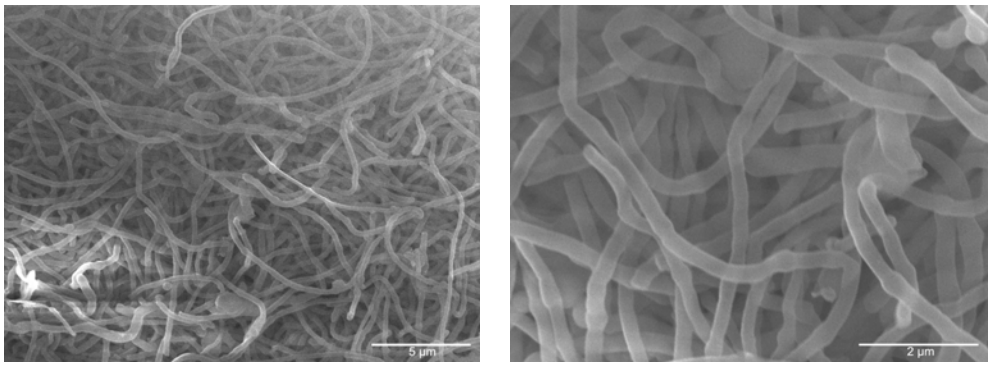
[a]All reactions were performed using 50 wt % of DVB and 50 wt % of ST, while keeping the concentration constant at 16.6 g/L in 250 mL of hexanes at 25 ^{o}C for 6 h.



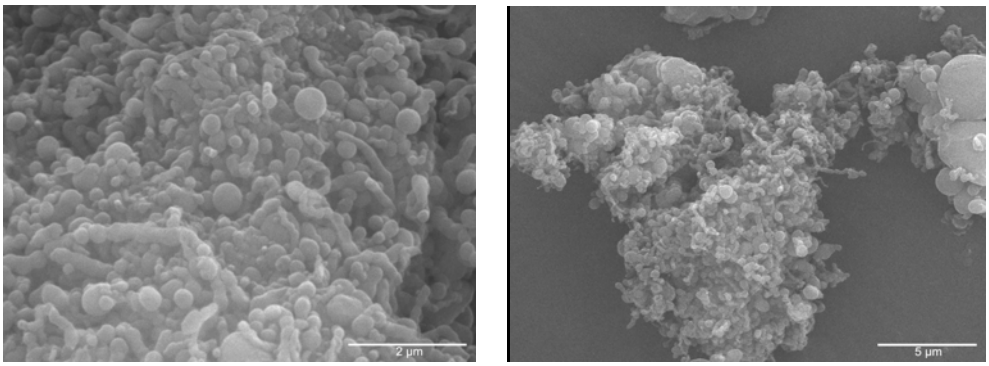
(a)



(b)



(c)

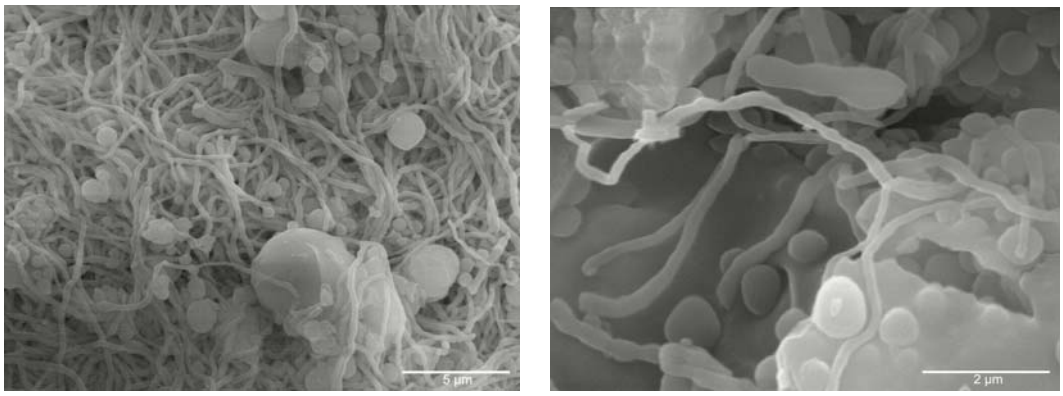


(d)

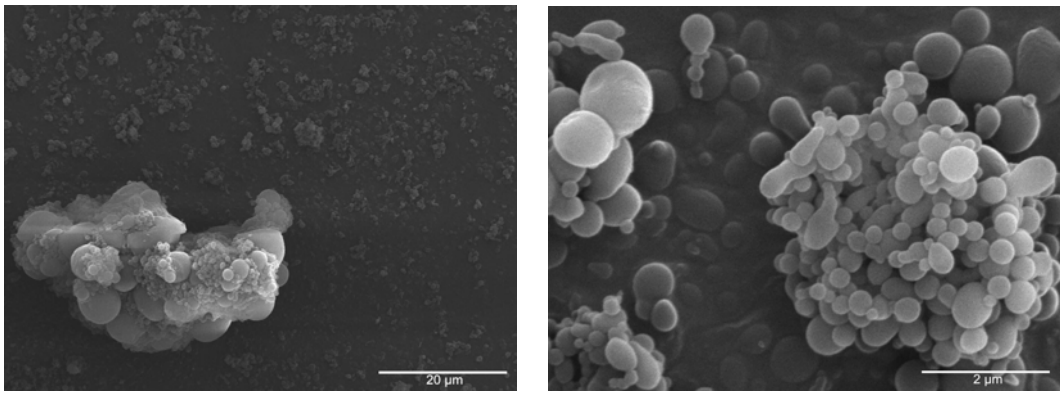
Figure 8. SEM images of fibers obtained from the polymerization of 55 wt % DVB and 45 wt % of ST using DCM (a), Et_2O (b), pentane (c) and cyclohexane (d) at 25 ^oC.

Effect of the temperature and stirring speed

We have also tried to change the reaction rate to see if we could get better morphological control of the polymeric material. When we ran the polymerization of 55 wt % DVB and 45 wt % ST at the higher temperature of 50 ^oC, we found that the products were mostly elongated fibers. However, the material was highly branched and networked (Figure 9a). This process also produced some spherical solid chunks (Figure 9b). Reducing the temperature to 0 ^oC resulted in the complete loss of fibrous structure and led to the formation of clumps of spherical particles (Figures 9c and 9d).



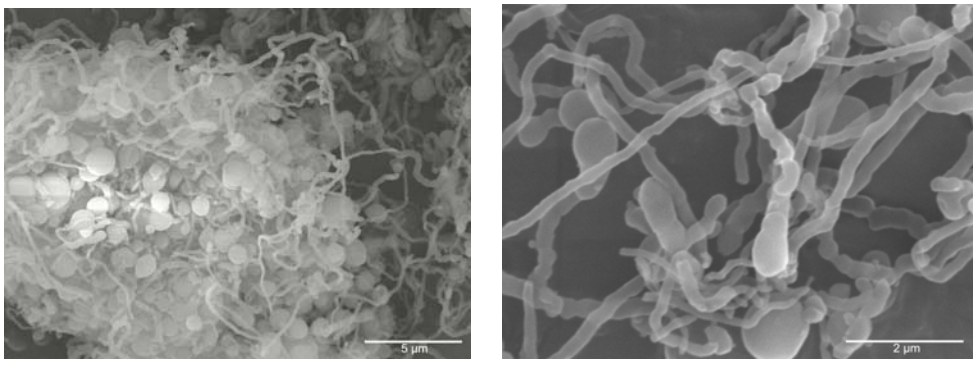
(a) (b)



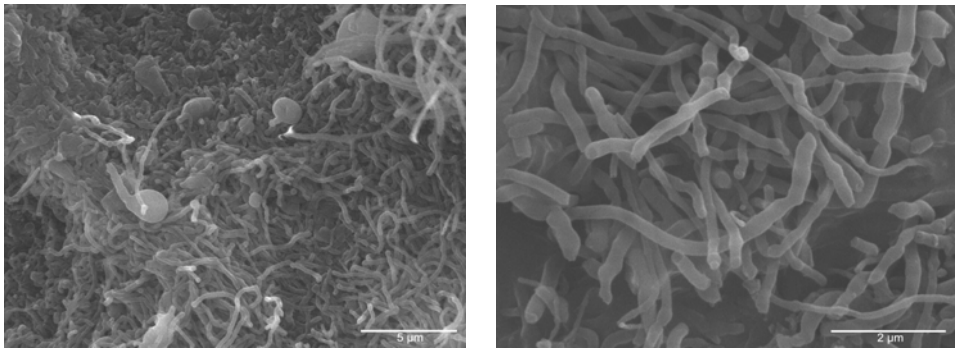
(c) (d)

Figure 9. SEM images of fibers obtained from the polymerization of 55 wt % DVB and 45 wt % of ST using hexanes as the solvent at 50 ^{o}C (a and b) and 0 ^{o}C (c and d).

Altering the stirring speed also resulted in a loss of morphological control. When the speed was reduced to 250 rpm from 500 rpm, the formation of some fibers and solid chunks was observed (Figure 10a). Increasing the rpm to 1000 did not make much of a difference and produced similar fibrous structures. However, they were more networked (Figure 10b). Increasing the rpm to 1500 rpm resulted in the formation of polymeric materials with fibers, which were sticking to or interpenetrating one another. There were also spherical structures at the ends of the fibers (Figure 10c).



(a)



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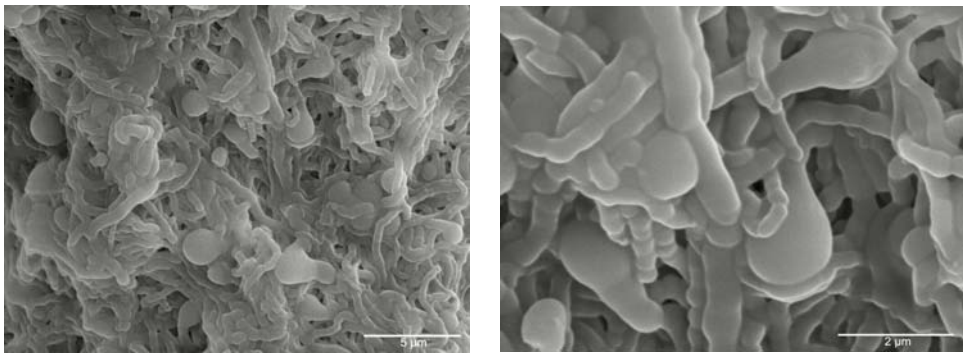


(c)

Figure 10. SEM images of fibers obtained from the polymerization of 55 wt % DVB and 45 wt % of ST using hexanes as the solvent, and a stirring speed of 250 rmp (a), 1000 rpm (b) or 1500 rmp (c) at 25 ^{o}C.

Substituted Styrenes

After optimizing the stoichiometry, solvents, stirring speed and temperature, we employed several substituted styrenes in this polymerization using our standardized conditions. Since we conducted the earlier experiments using a certain wt % of the substrates, we employed the same number of moles of the substituted styrene as styrene (0.0196 moles) and kept all other parameters constant. *p*-Methylstyrene led to the formation of spherical particles (Figure 11a). Using *p*-acetoxystyrene produced a massive material with large pores as if a volatile substance was being released (Figure 11b). *p*-Methoxystyrene gave mostly an elongated material with a diameter of about 200 nm

(Figure 11c). However, we did not find any hollow openings in this material. This result was similar to that obtained when we employed only DVB in the polymerization.

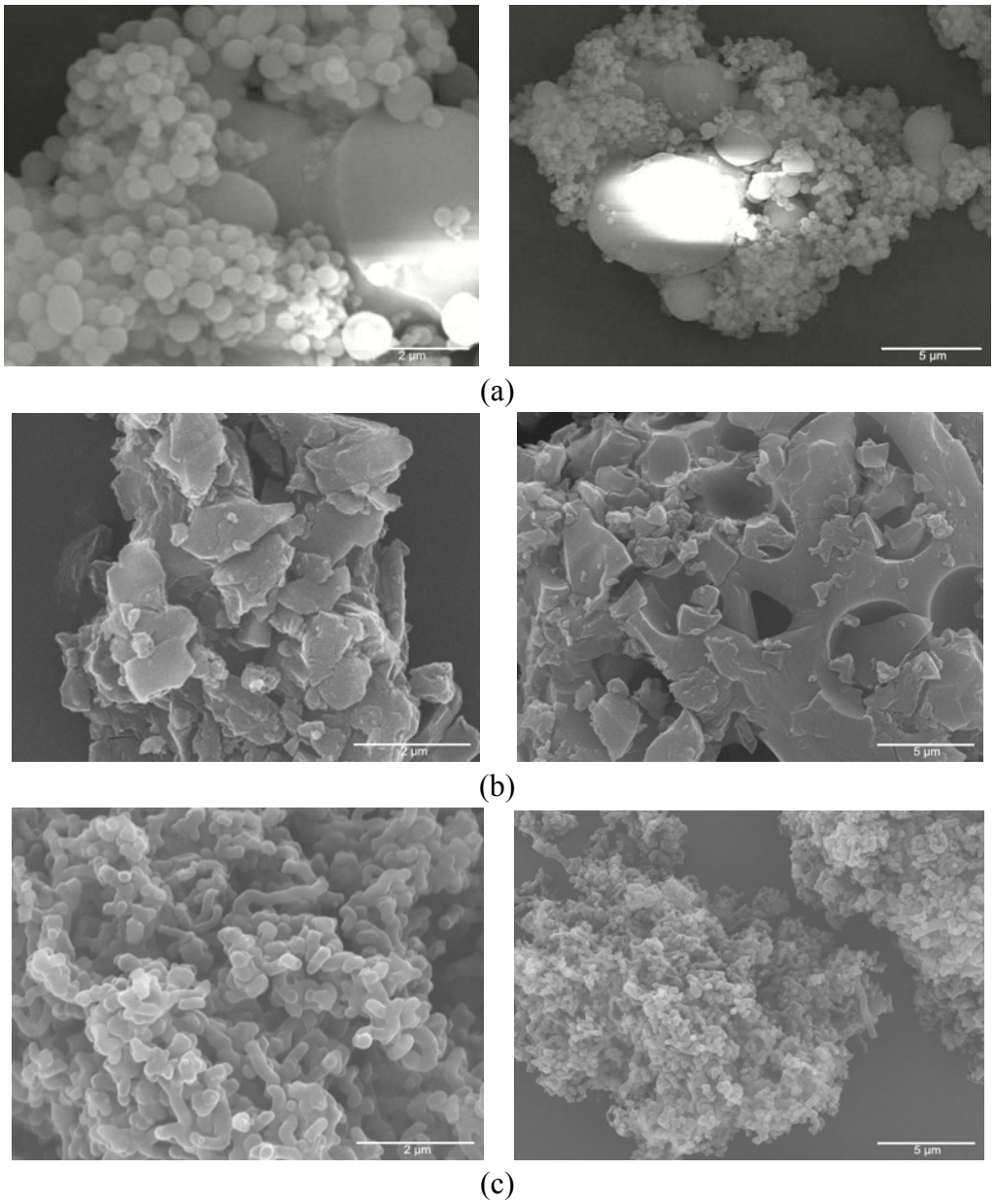
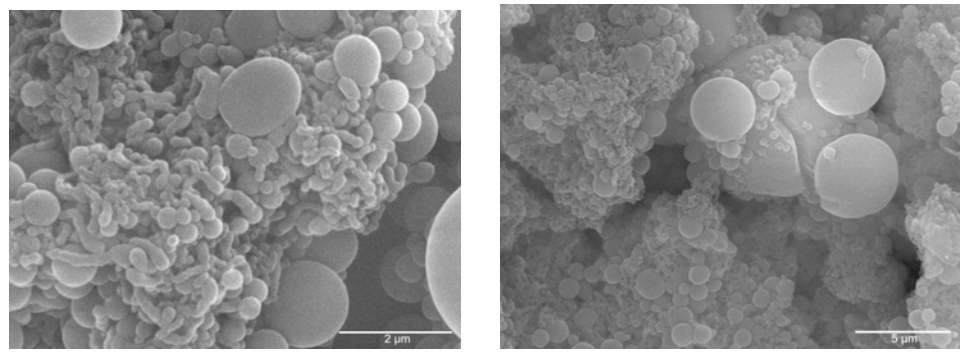
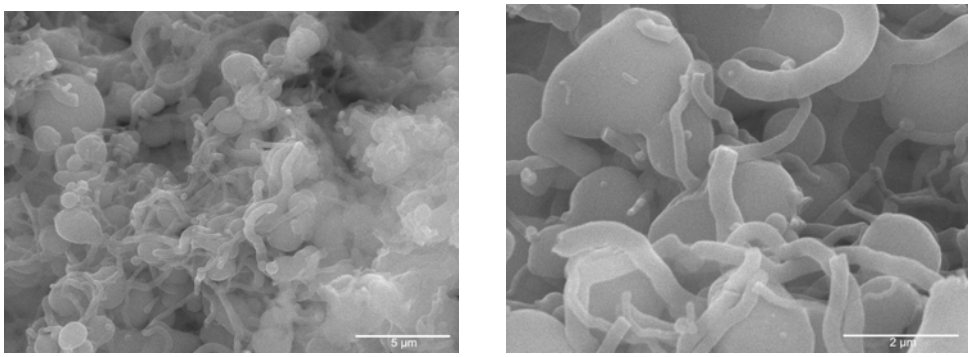


Figure 11. SEM images of fibers obtained from the polymerization of DVB with *p*-methylstyrene (a), *p*-acetoxystyrene (b), and *p*-methoxystyrene (c) using hexanes as the solvent at 25 ^{o}C.

p-Fluorostyrene mostly gave large spherical particles along with a small fraction of elongated structures with diameters ranging from 100-200 nm (Figure 12a). Some of the material was branched and networked. In the case of *p*-nitrostyrene, a mixture of spherical and elongated materials was obtained (Figure 12b). The elongated structures were about 200 nm in diameter. We did not find a clear indication of hollow channels inside the elongated structures even at a high magnification.



(a)



(b)

Figure 12. SEM images of fibers obtained from the polymerization of DVB with *p*-fluorostyrene (a) and *p*-nitrostyrene (b) using hexanes as the solvent at 25 ^{o}C.

Conclusions

The simple approach presented here offers great potential for the design and preparation of nanometer scale polymeric materials. The cationic polymerization of DVB in hexanes produces nanofibers with a diameter of 300-500 nm. The copolymerization of

DVB with styrenes produces nanotubes with internal diameters ranging from 30-50 nm. This provides an exciting opportunity for the facile preparation of novel and useful nanomaterials. Attempts have been made to further fine tune the morphologies of the resulting polymers by varying the solvent, stoichiometry, stirring speed, and the reaction temperature. Several substituted styrenes have also been employed in the polymerization, but they failed to produce the desired hollow fibrous structures. The failure of these styrenes reduces the chances for further functionalization of the tubular structure.

Experimental Section

General. The particle morphology was studied using a JEOL 840A scanning electron microscope with a 10 kV acceleration voltage. For transmission electron microscopy measurements, an aliquot of the polymer was sonicated in acetone for 30 min. A single drop of this suspension was placed on a lacey carbon-coated copper TEM grid and dried in air. The TEM experiments were performed on a Philips CM-30 electron microscope operated at 300 kV using electron optical magnifications of 69,000 to 340,000.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

General procedure for the cationic polymerization of styrene and divinylbenzene. A 500 mL round bottom flask was charged with 250 mL of hexanes and the required amount of ST and DVB was added dropwise. The concentration of the solution was kept constant at 16.6 g/L. Distilled grade boron trifluoride diethyl etherate initiator (Aldrich)

was added to the solution dropwise using a syringe. Typically, 5 parts initiator per 100 parts of reactants were used. Solid particle-like polymers appeared during addition of the initiator and they were suspended in the stirring solution. The resulting polymer particles were observed to grow in numbers with time. The reaction was terminated after 6 h by stopping the stirring, and the resulting materials were allowed to settle to the bottom of the flask and collected by filtration. The original yellow polymeric materials turned white upon washing with acetone. The isolated polymer was dried under a vaccum for 12 h prior to analysis.

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GENERAL CONCLUSIONS

In this dissertation, the scope and limitations of an electrophilic cyclization, palladium-catalyzed C-H activation processes, and cationic polymerization to produce nanotubes are discussed in detail. We have developed new methodology for the formation of benzo[*b*]selenophenes using an electrophilic cyclization of alkynes. The palladium-catalyzed C-H bond activation of benzylic and acyl positions has also been explored. Lastly, an investigation into the cationic polymerization of ST and DVB for the formation of tubular structures is discussed.

In Chapter 1, an efficient synthesis of benzo[*b*]selenophenes is discussed. The two step process starting from 2-iodo(methylseleno)benzene, a simple starting compound, has proven to be one of the best methods known for preparation of the benzoselenophene ring system. The effect of different substitutents has been studied and the reaction is found to be very general. Further functionalization of the products has been carried out using palladium-catalyzed coupling reactions, which increases the overall utility of this methodology. The mechanism of this reaction has also been investigated. The anticipated intermediate has been isolated and its decomposition investigated using proton NMR spectroscopy in order to establish a possible mechanism.

In Chapter 2, we report an efficient methodology for benzylic C-H activation using "through space" migration of palladium. Selective C-H and C-O bond forming reactions have been developed, which have an advantage over typical benzylic oxidations or brominations in terms of selectivity. The key to the success of these reactions is the nucleophilicity of the carboxylates and phenoxides used as nucleophiles. The more

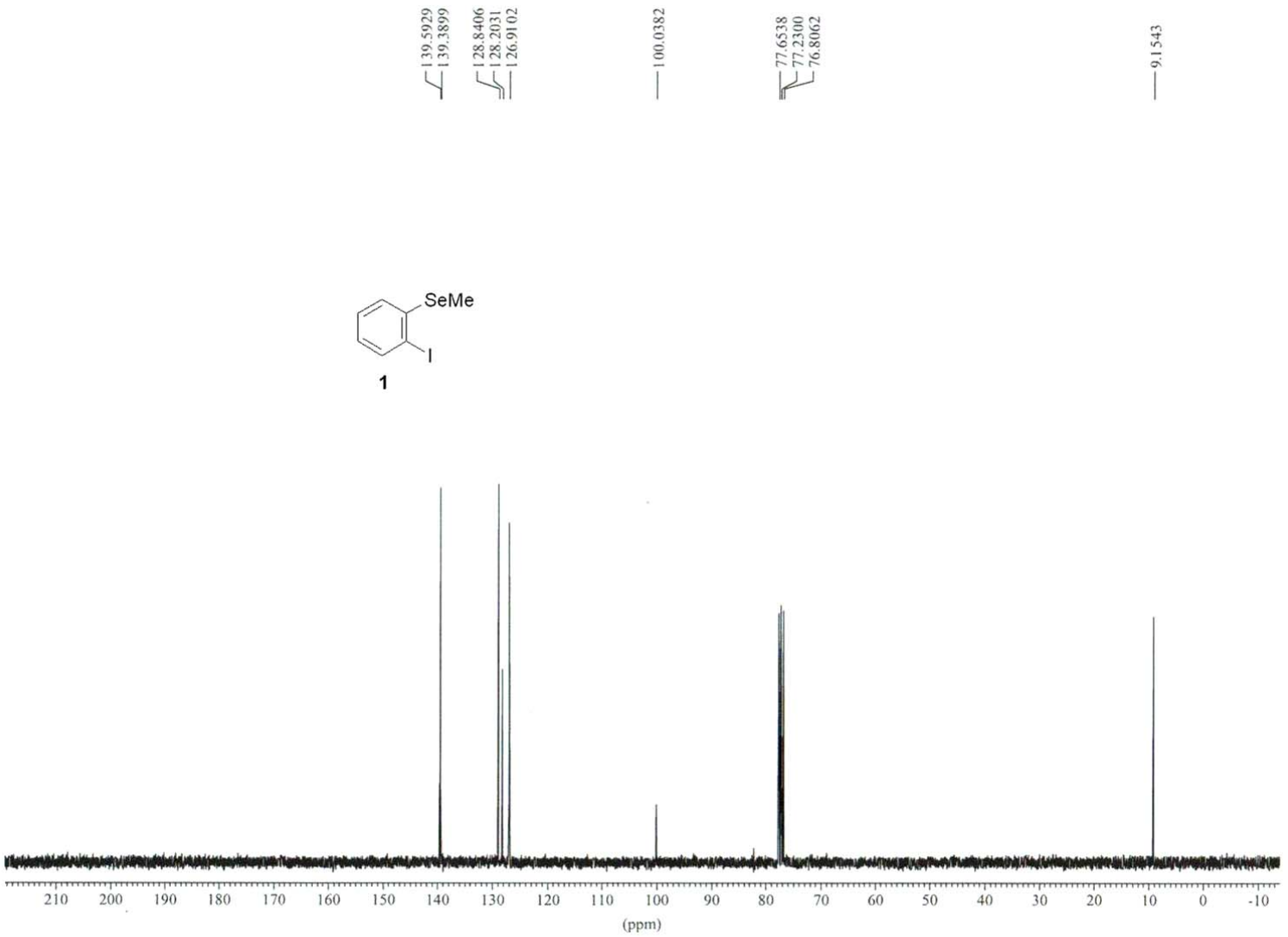
nucleophilic the base, the better the yields of the process. Additionally, the mechanism of these reactions, which may involve palladium(II) or palladium(IV) intermediates, are discussed. Deuterium-labeling experiments suggest that the key step is reversible. The reaction conditions developed for these migration processes also oxidize neighboring benzylic alcohols to the corresponding aldehydes and ketones in good yields with simultaneous reduction of the halogen.

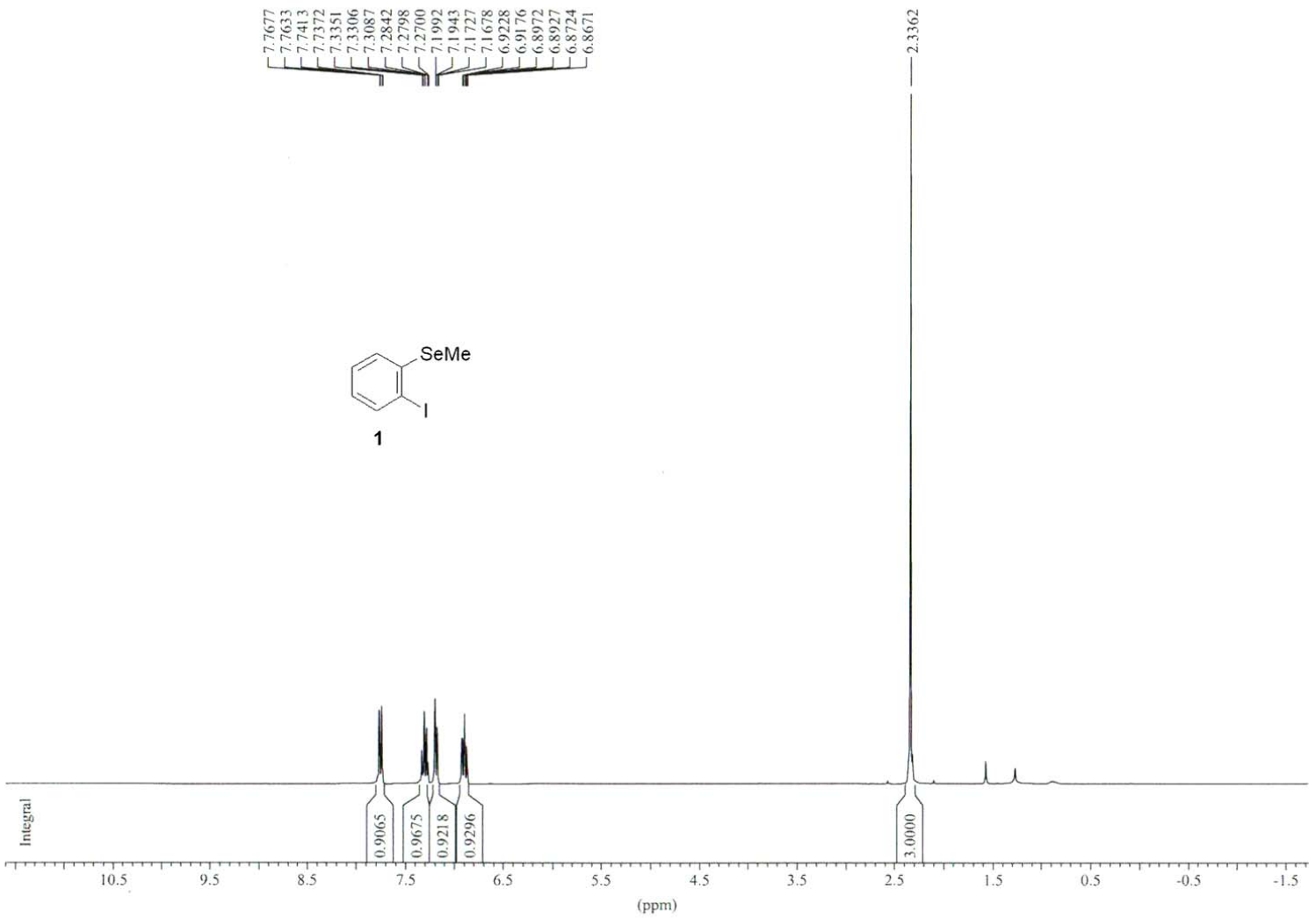
Chapter 3 gives a detailed account of a unique way to activate acyl C-H bonds via "through space" migration of palladium from an aryl to an acyl position. The acylpalladium species formed after migration of palladium from an aryl position has been trapped by an alcohol. Aryl iodides and aryl bromides are readily employed in this migration reaction. Under the proper reaction conditions, when the possibility for decarbonylation exits, the acylpalladium species undergoes decarbonylation, followed by β-hydride elimination, with the formation of olefins. The mechanism of this reaction has been studied by deuterium-labeling experiments, which establish the migration of deuterium from an aryl to an acyl position. Unfortunately, these labeling studies fail to differentiate between the two most likely mechanisms. However, the migration/decarbonylation/ β-hydride elimination reaction sequence strongly suggests the formation of acylpalladium species.

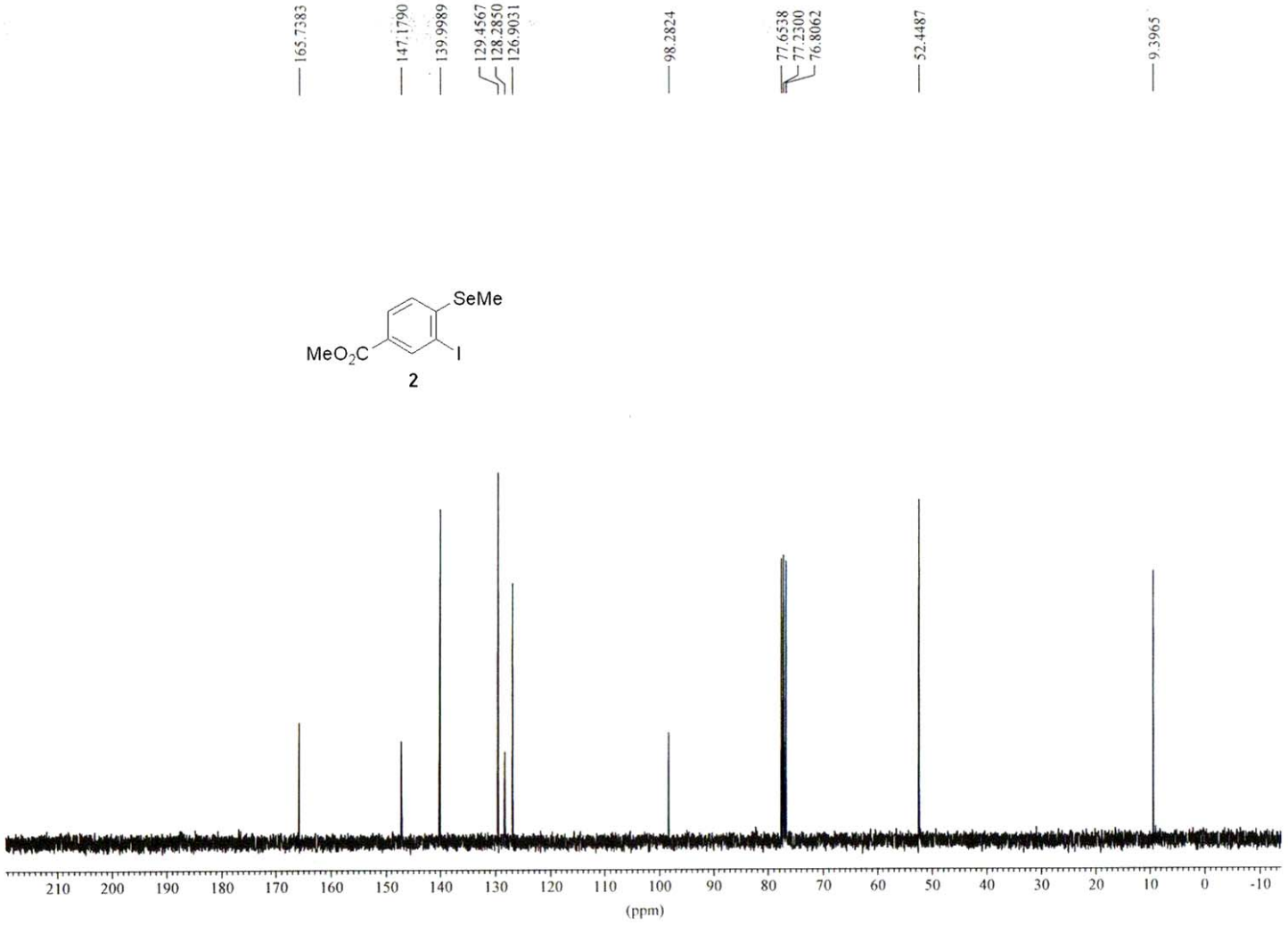
In Chapter 4, preliminary results on the formation of hollow tubular structures are described. The desired tubular structures have been synthesized by the cationic copolymerization of ST and DVB. Attempts have been made to further fine tune the morphologies of the resulting polymers by varying the solvent, stoichiometry, stirring speed, and the reaction temperature. Several substituted styrenes have also been

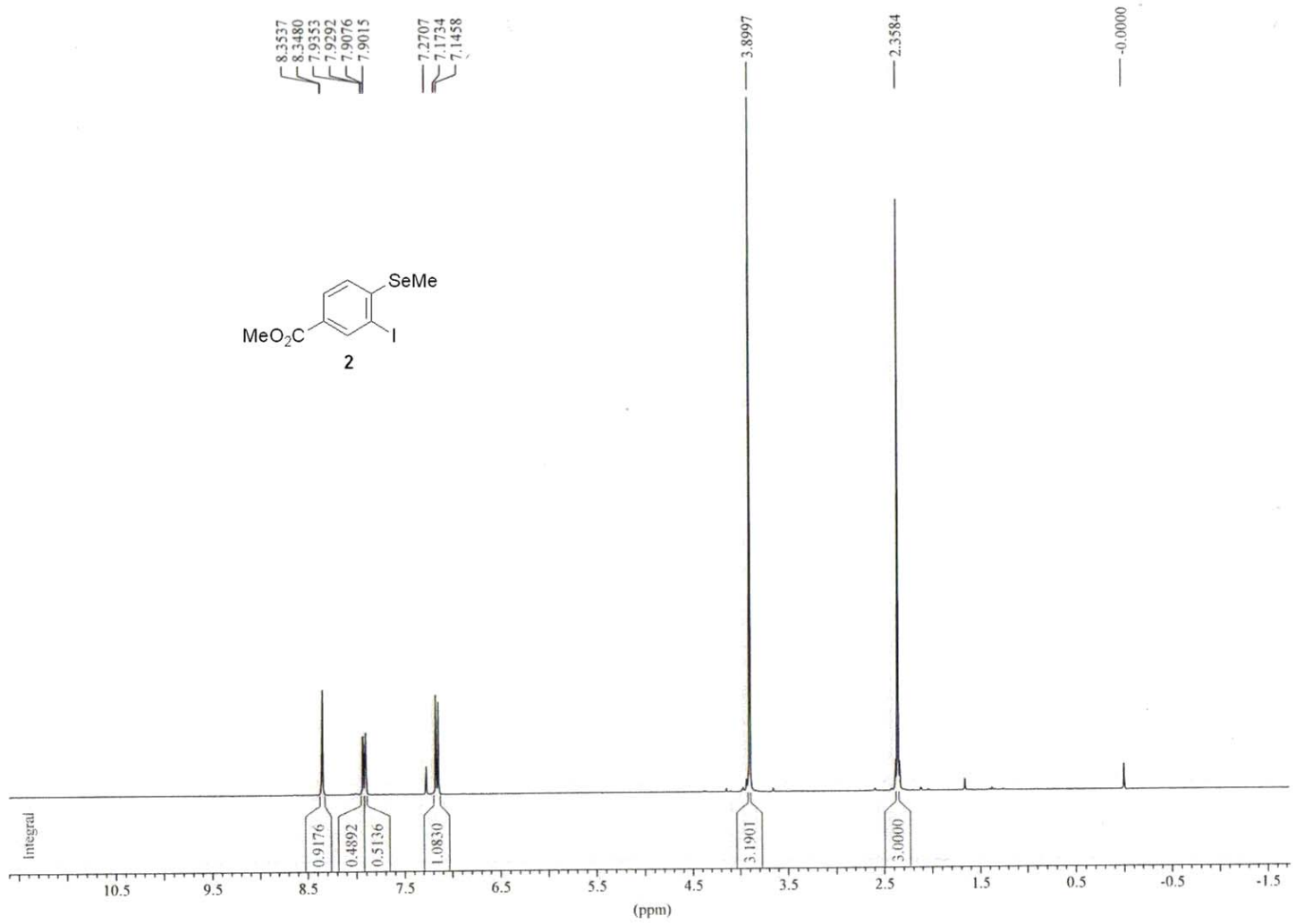
employed in these polymerization processes, but they have failed to produce the desired hollow fibrous structures.

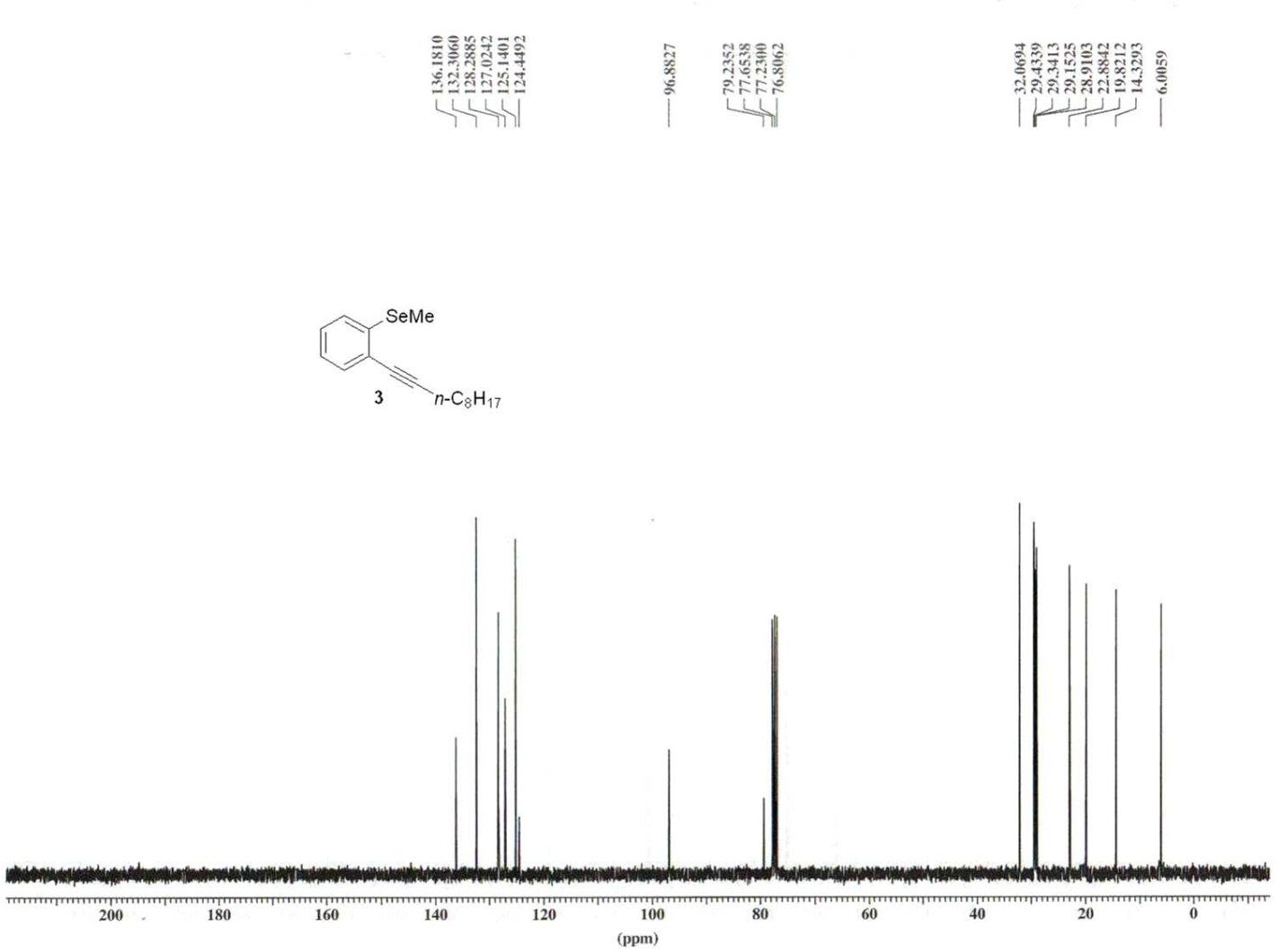
APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA

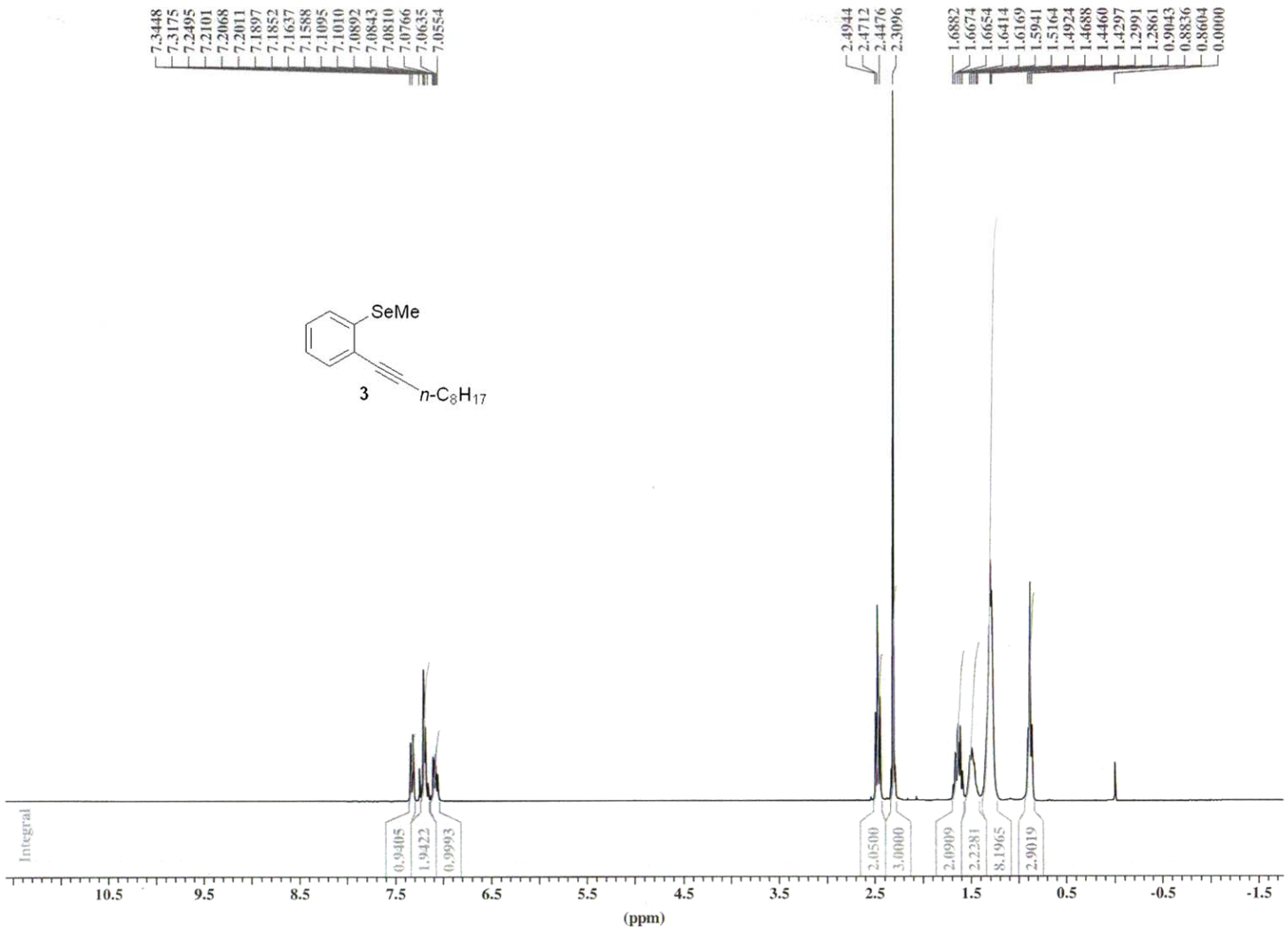


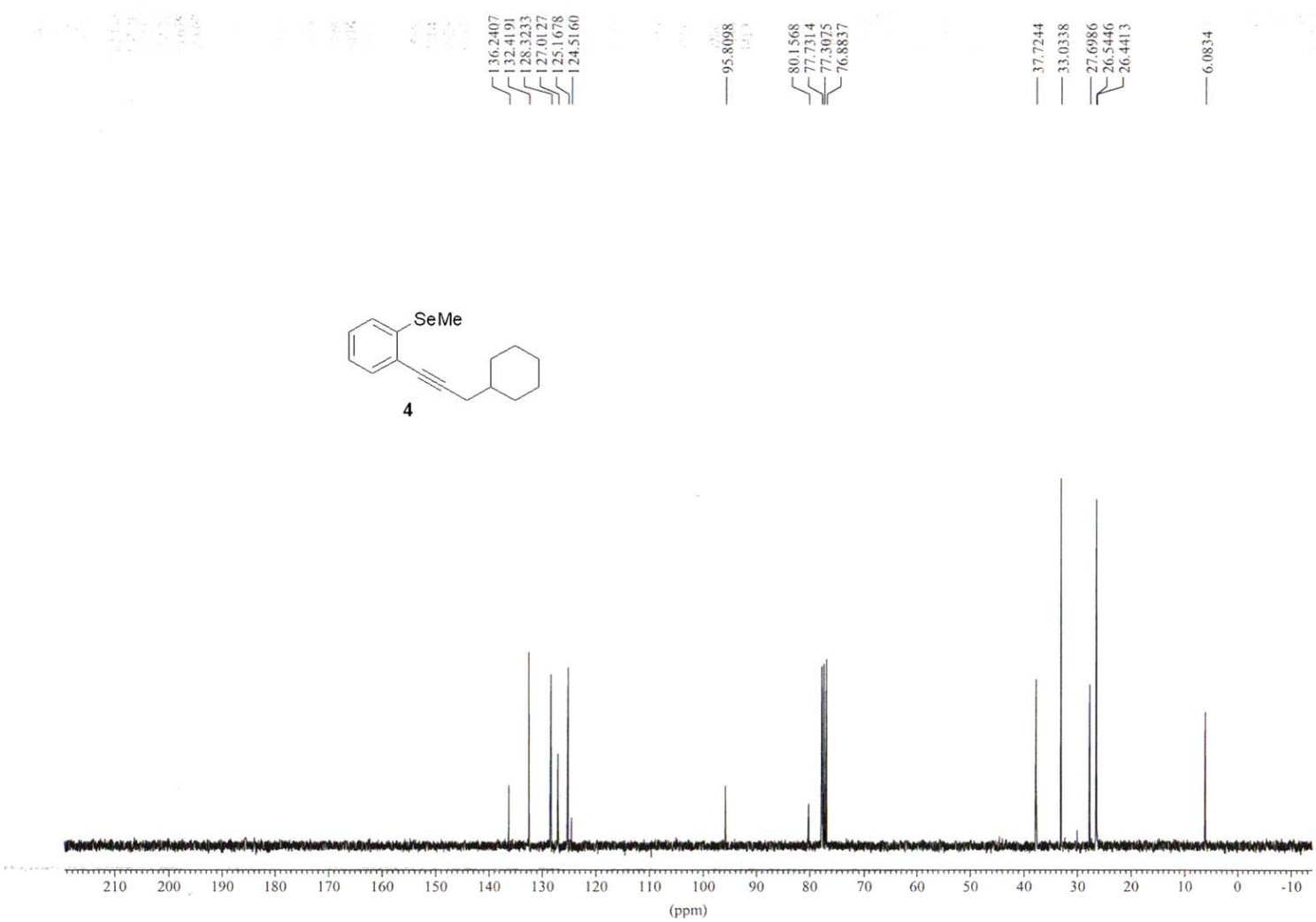


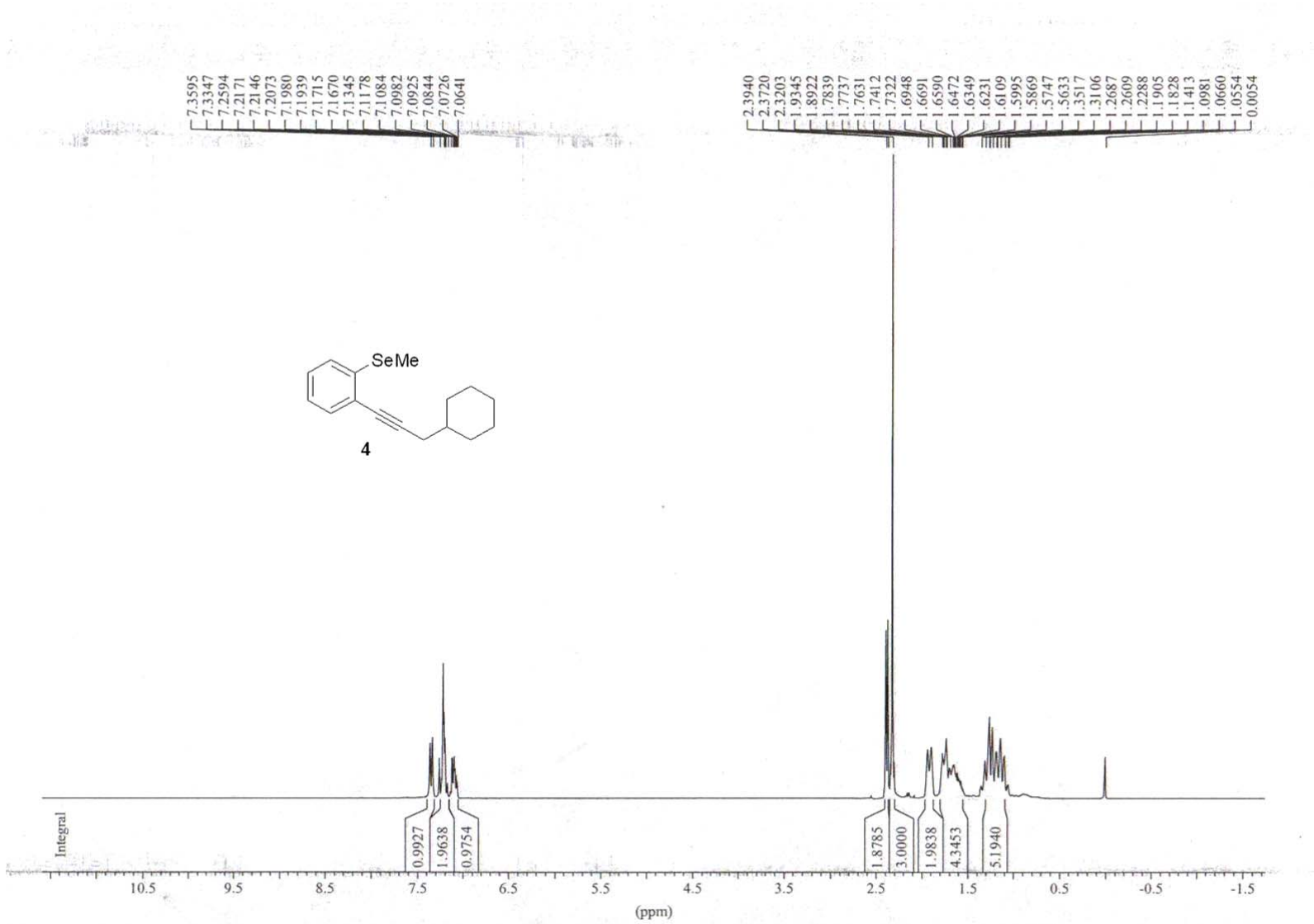


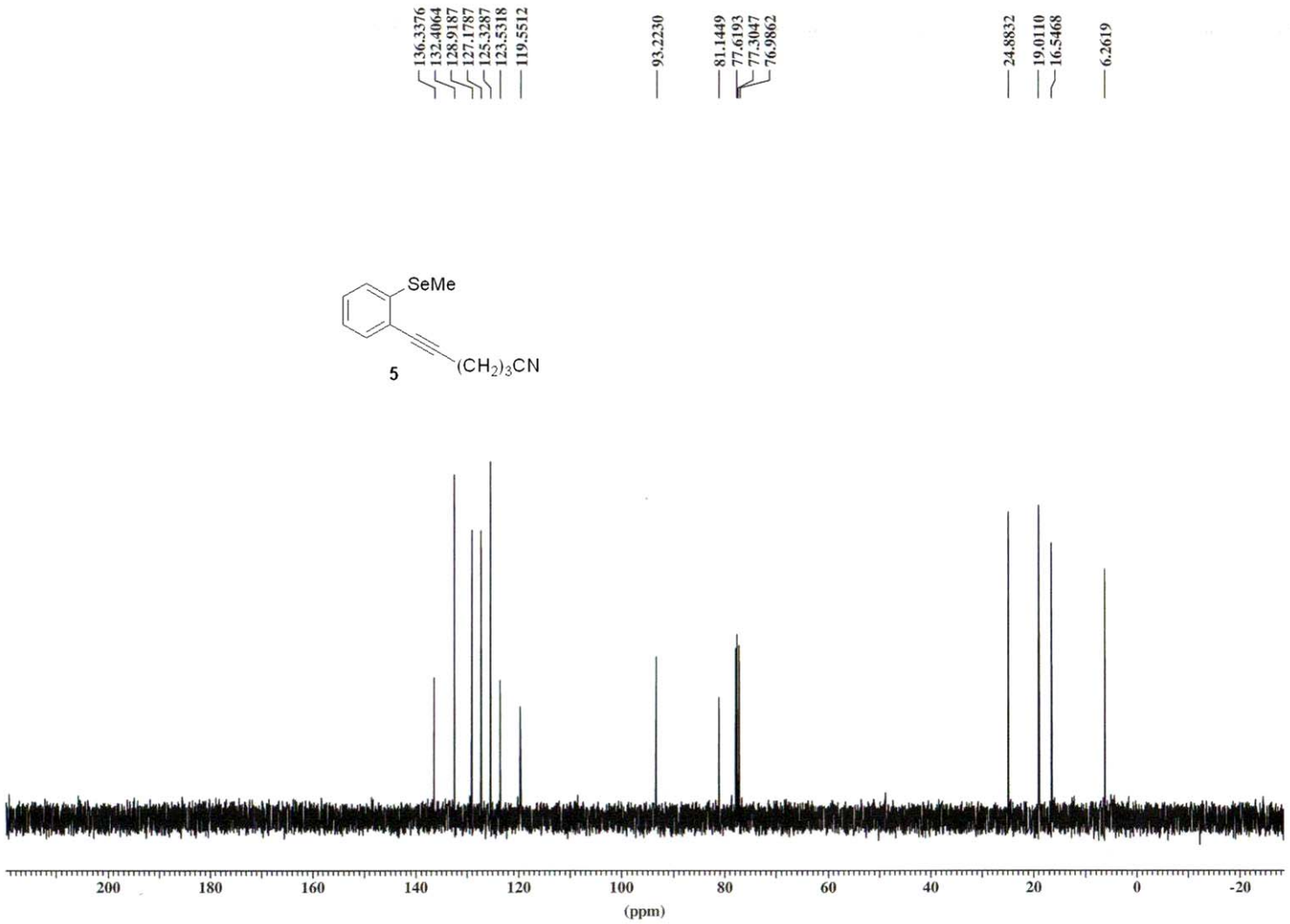


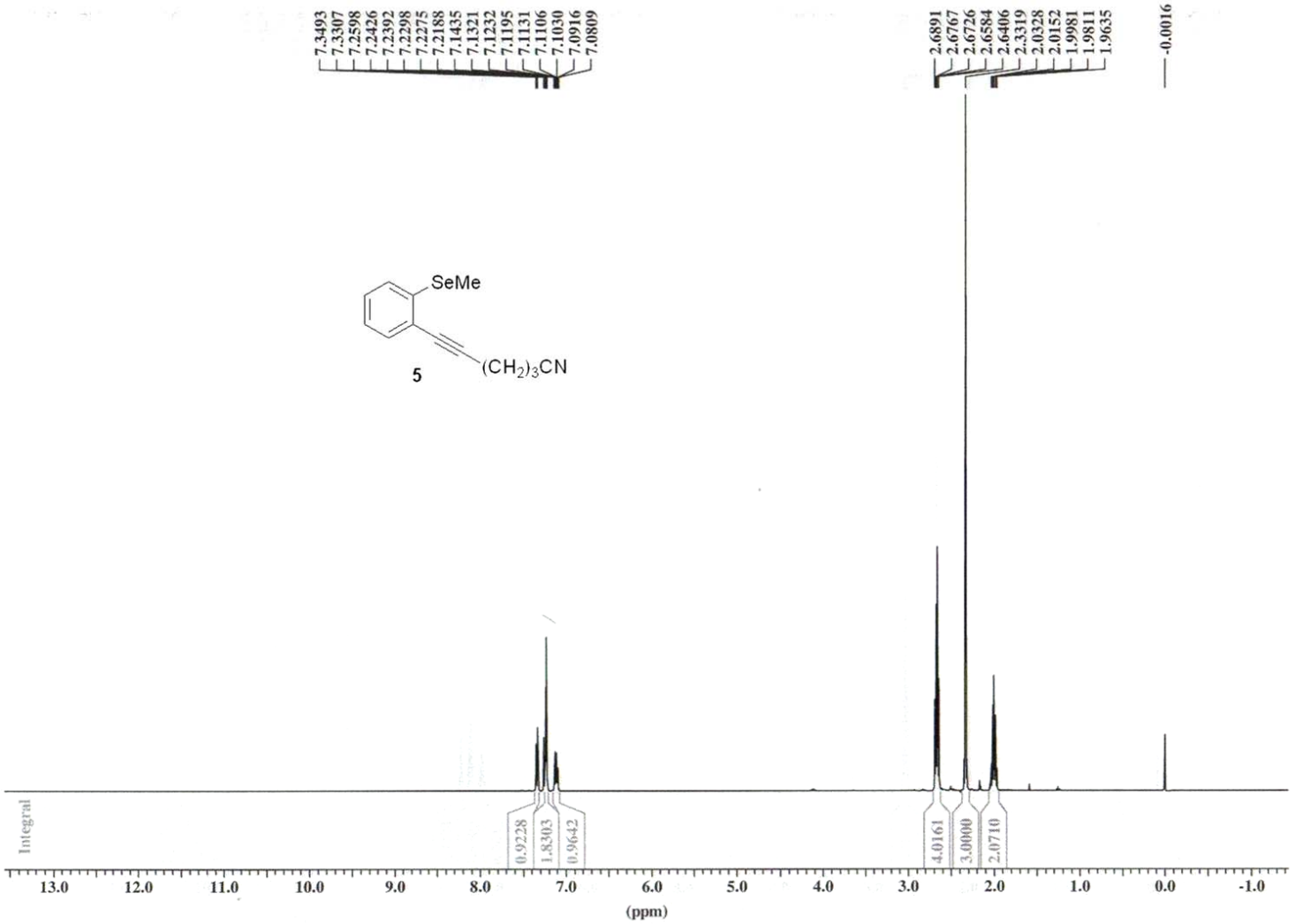


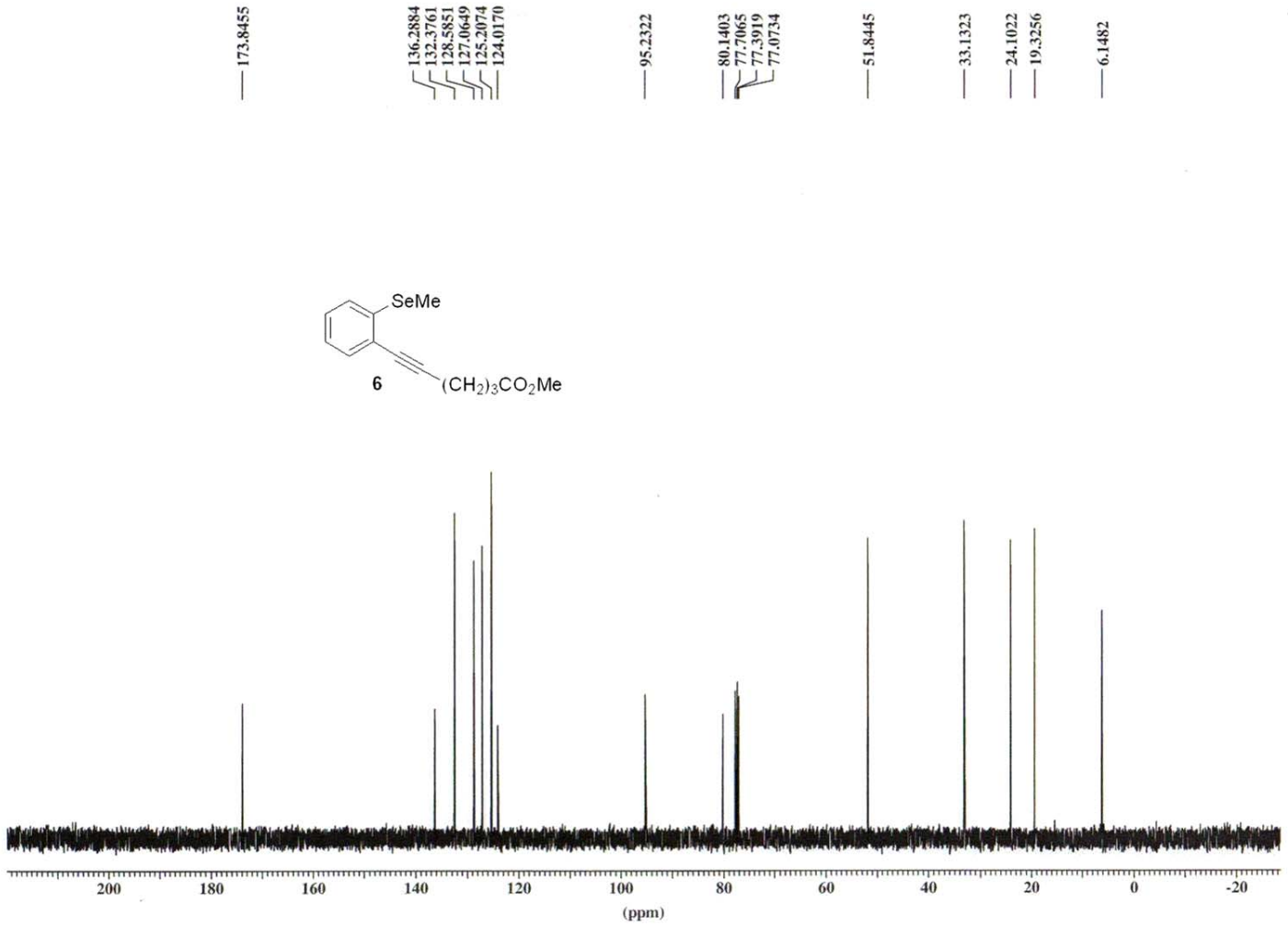


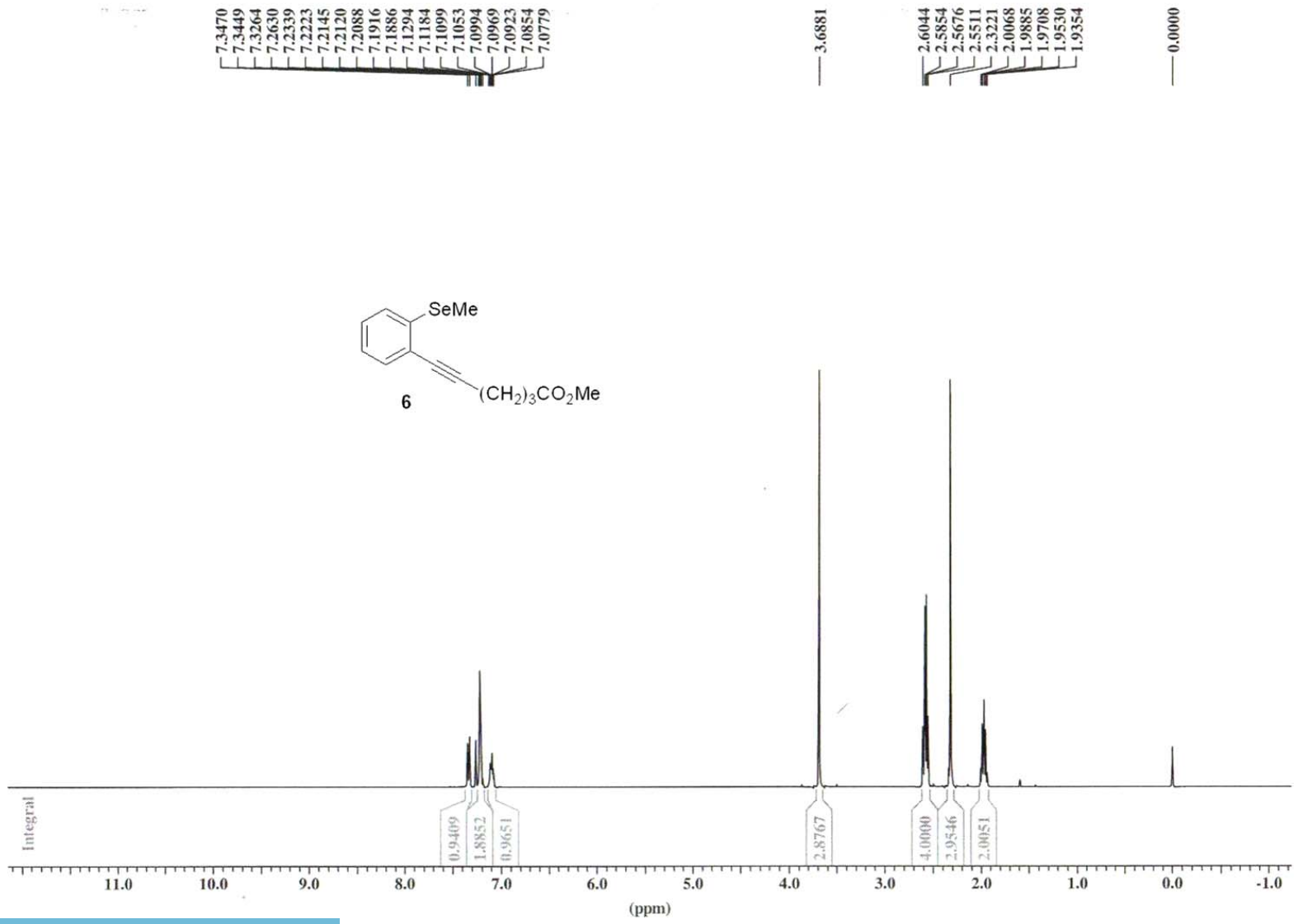


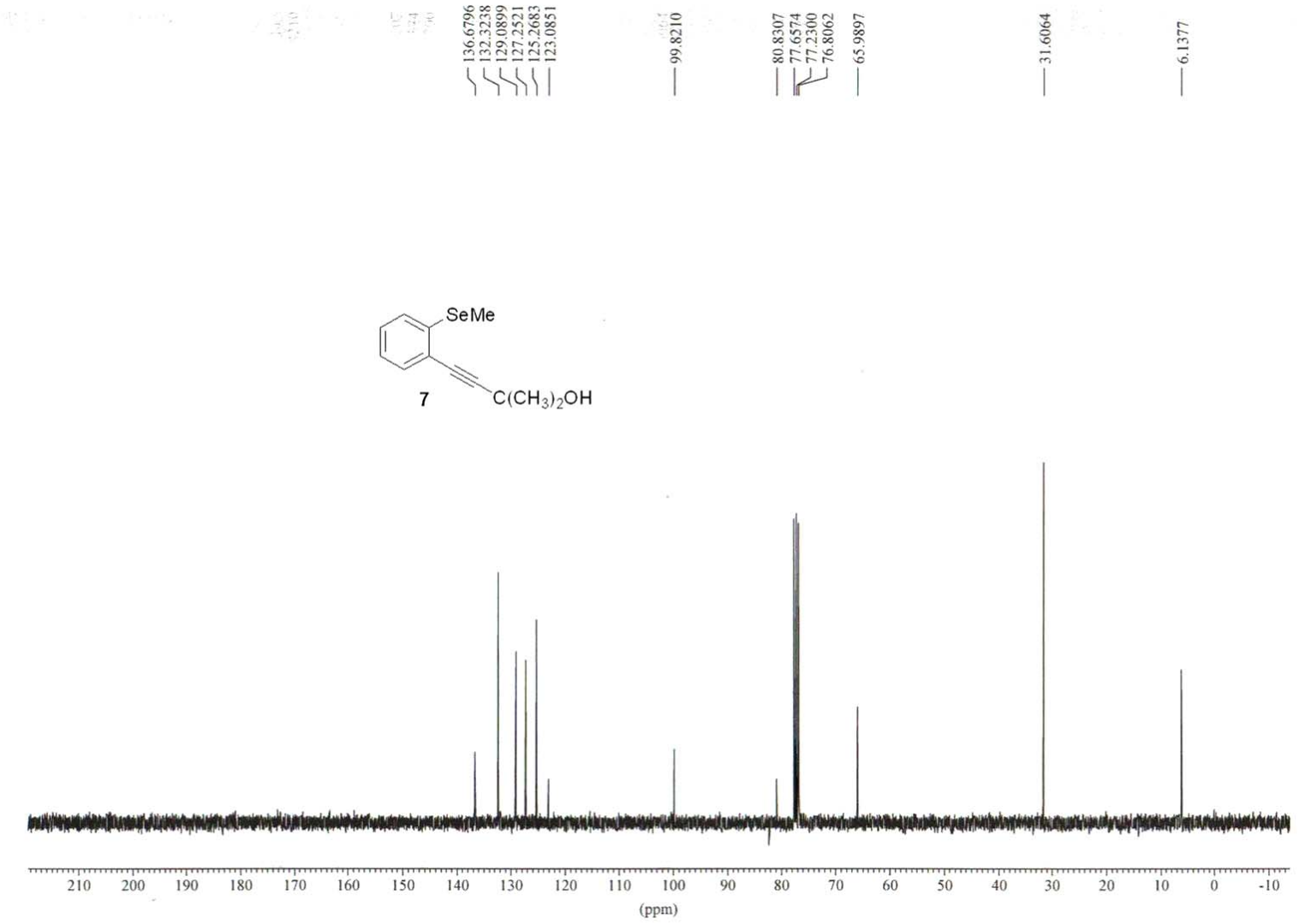


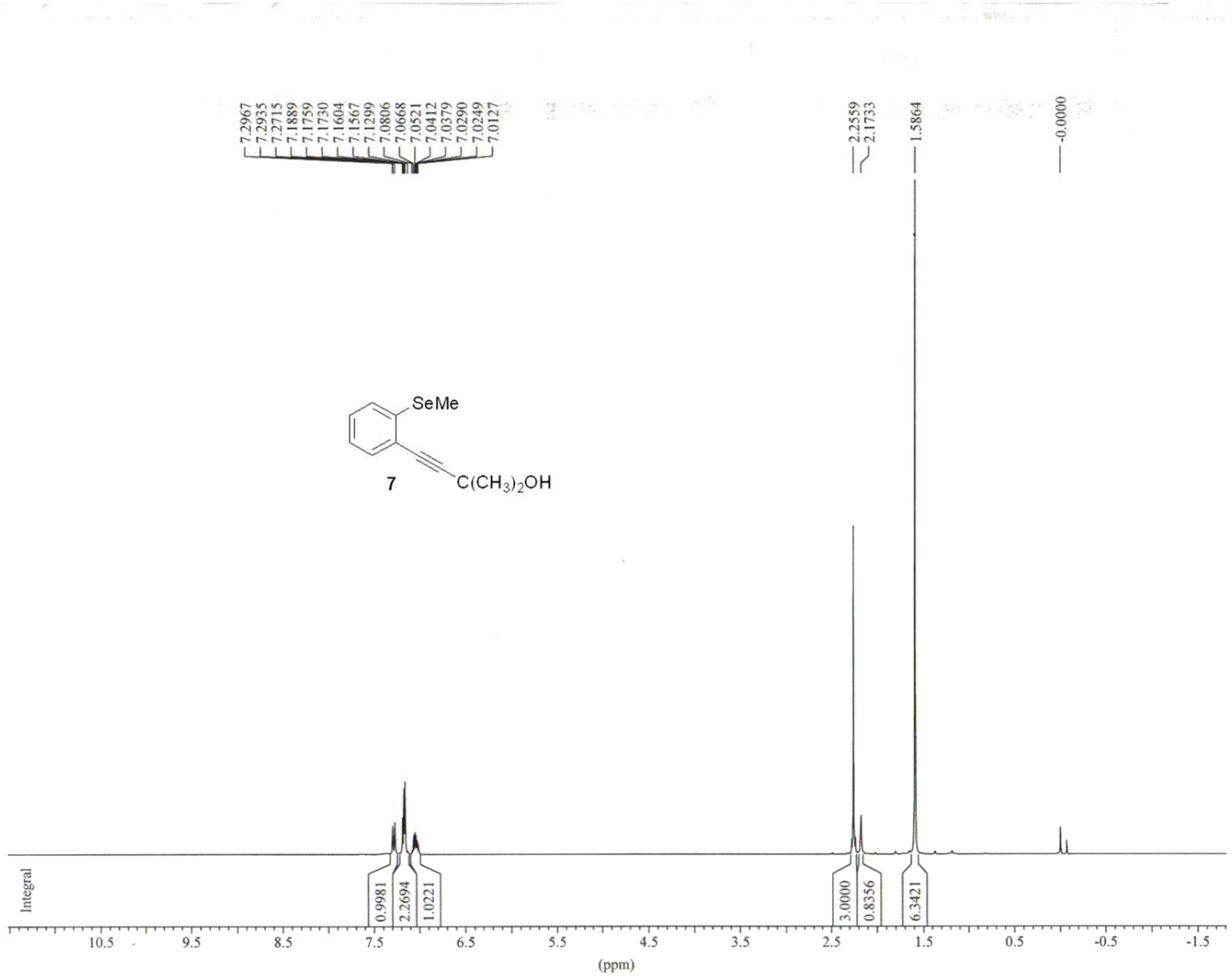


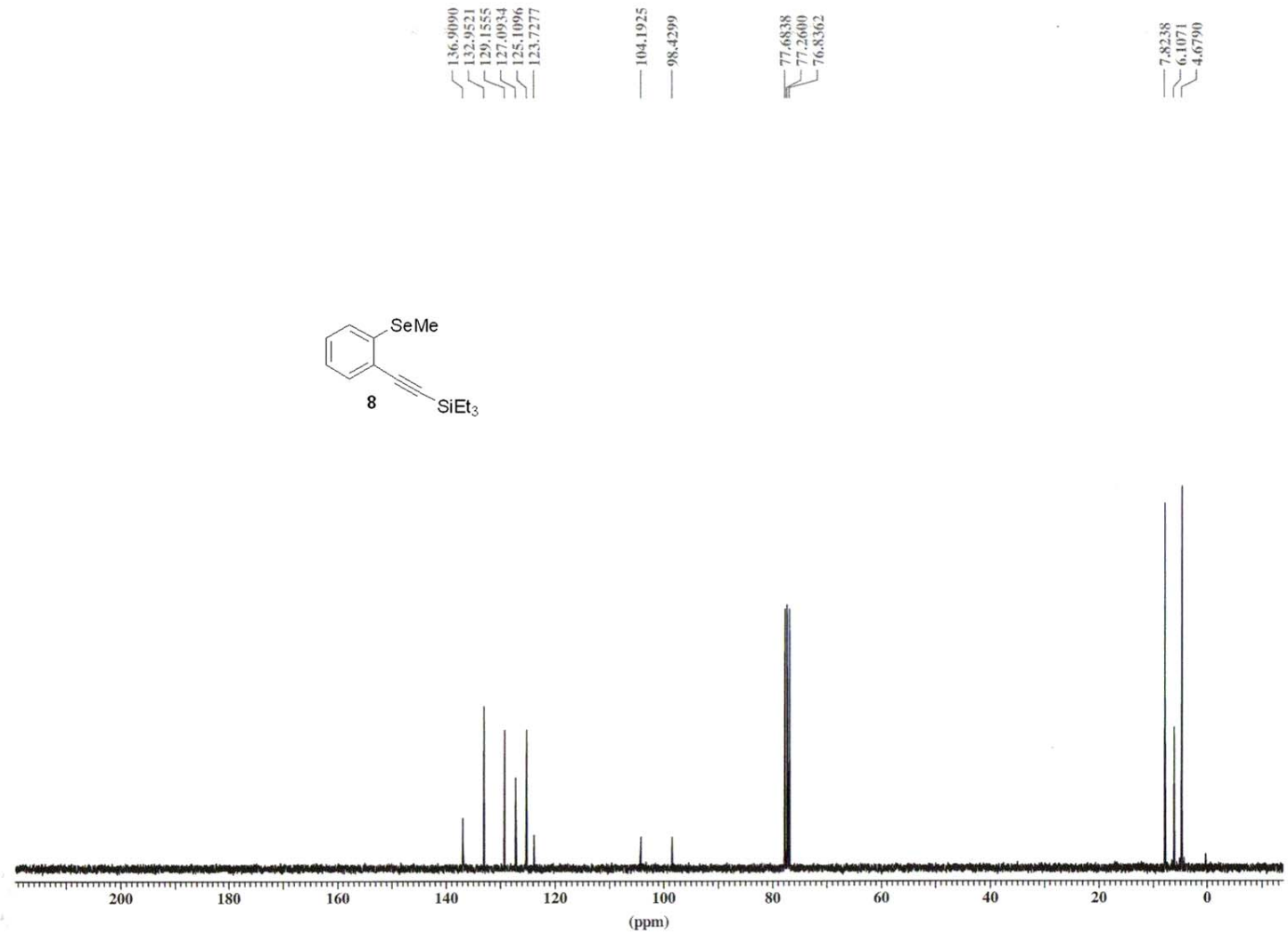


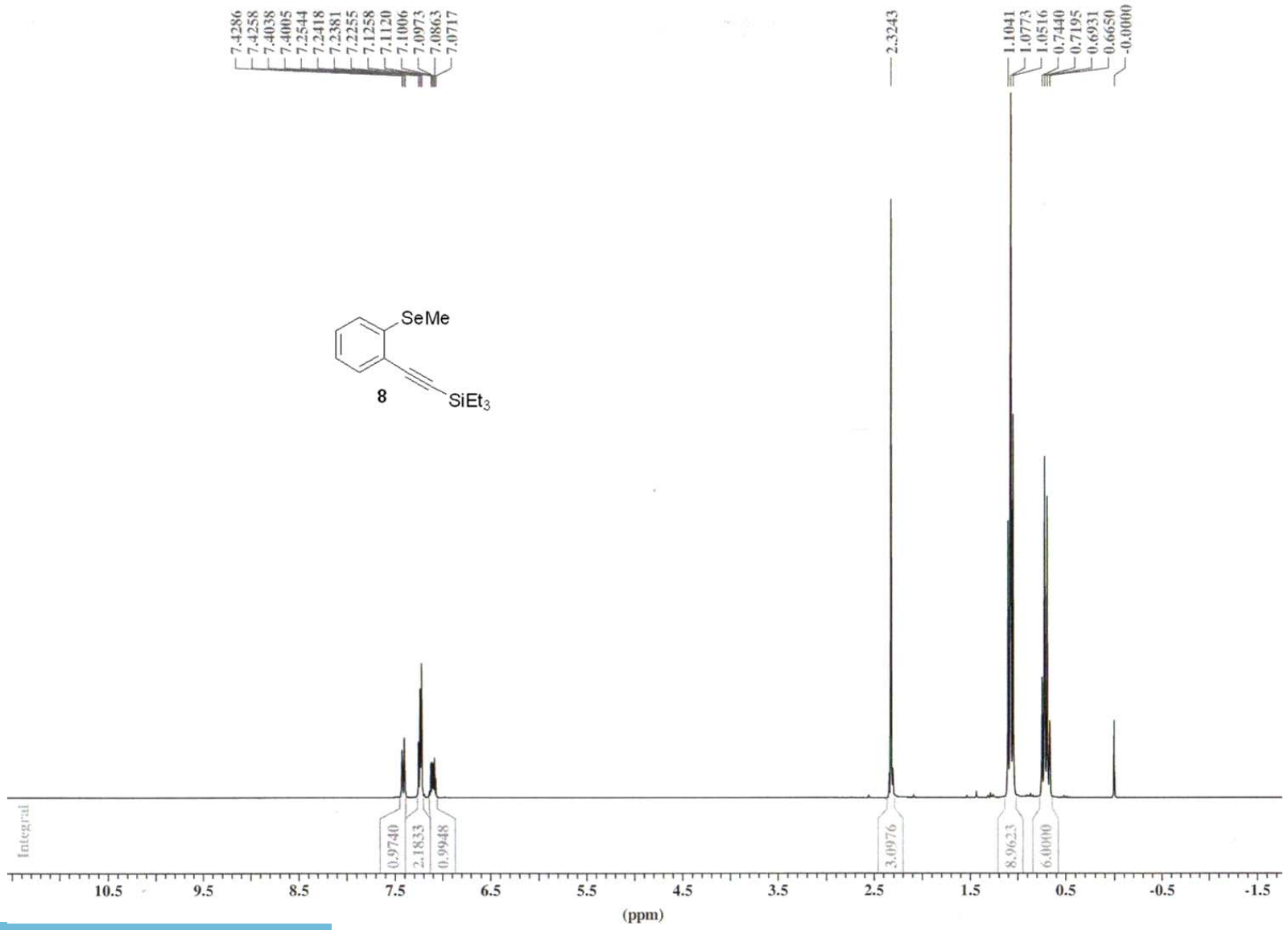


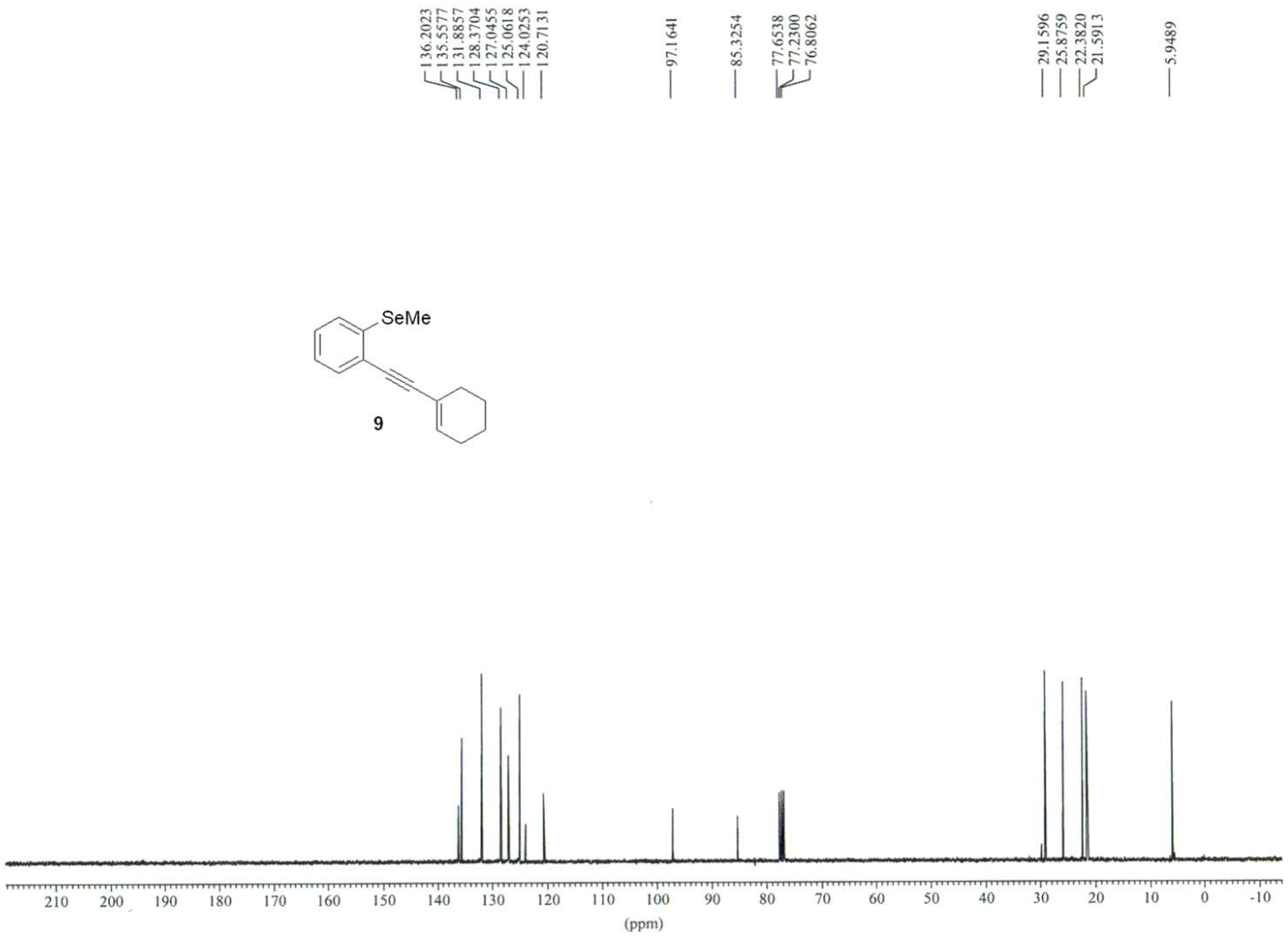


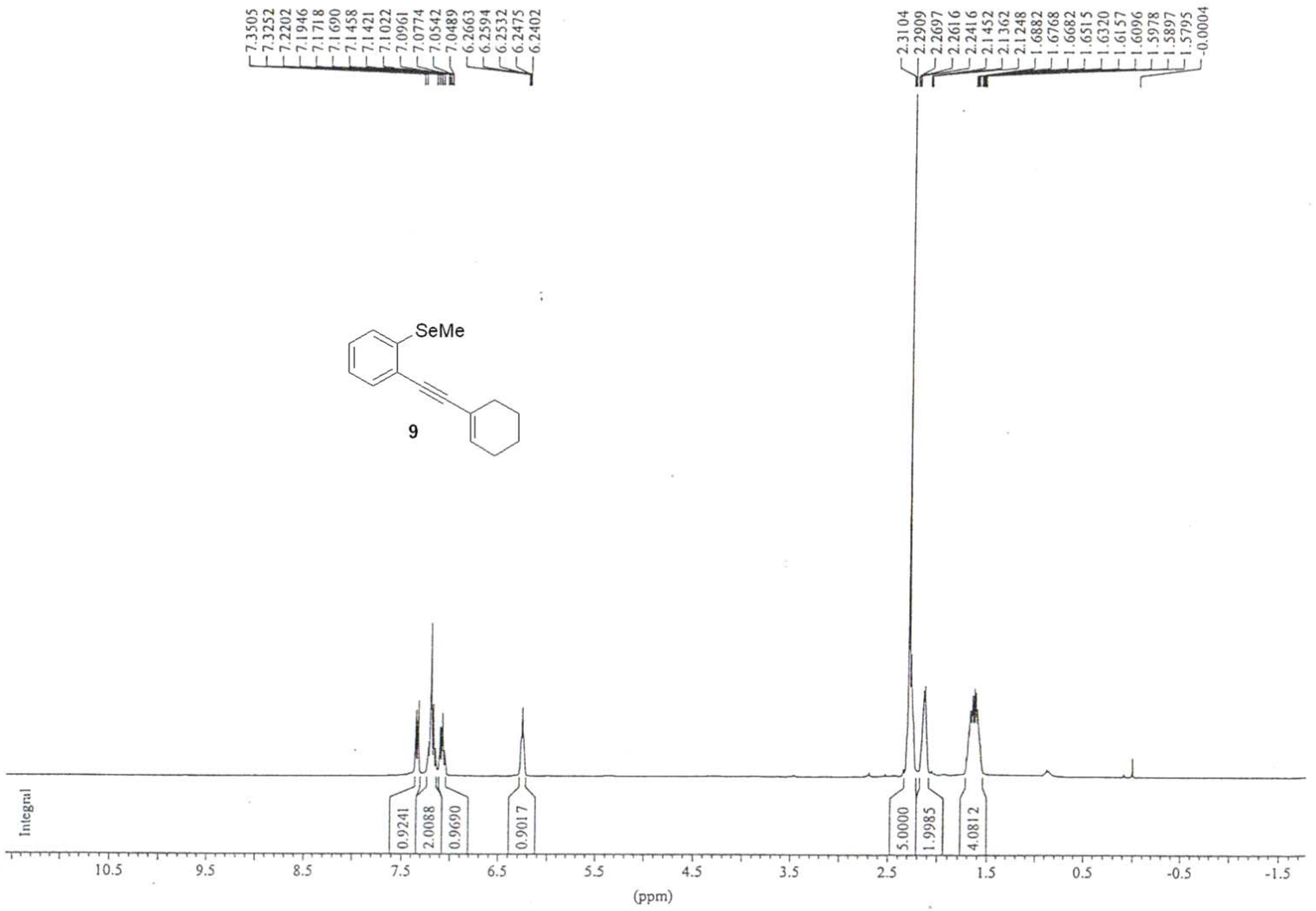


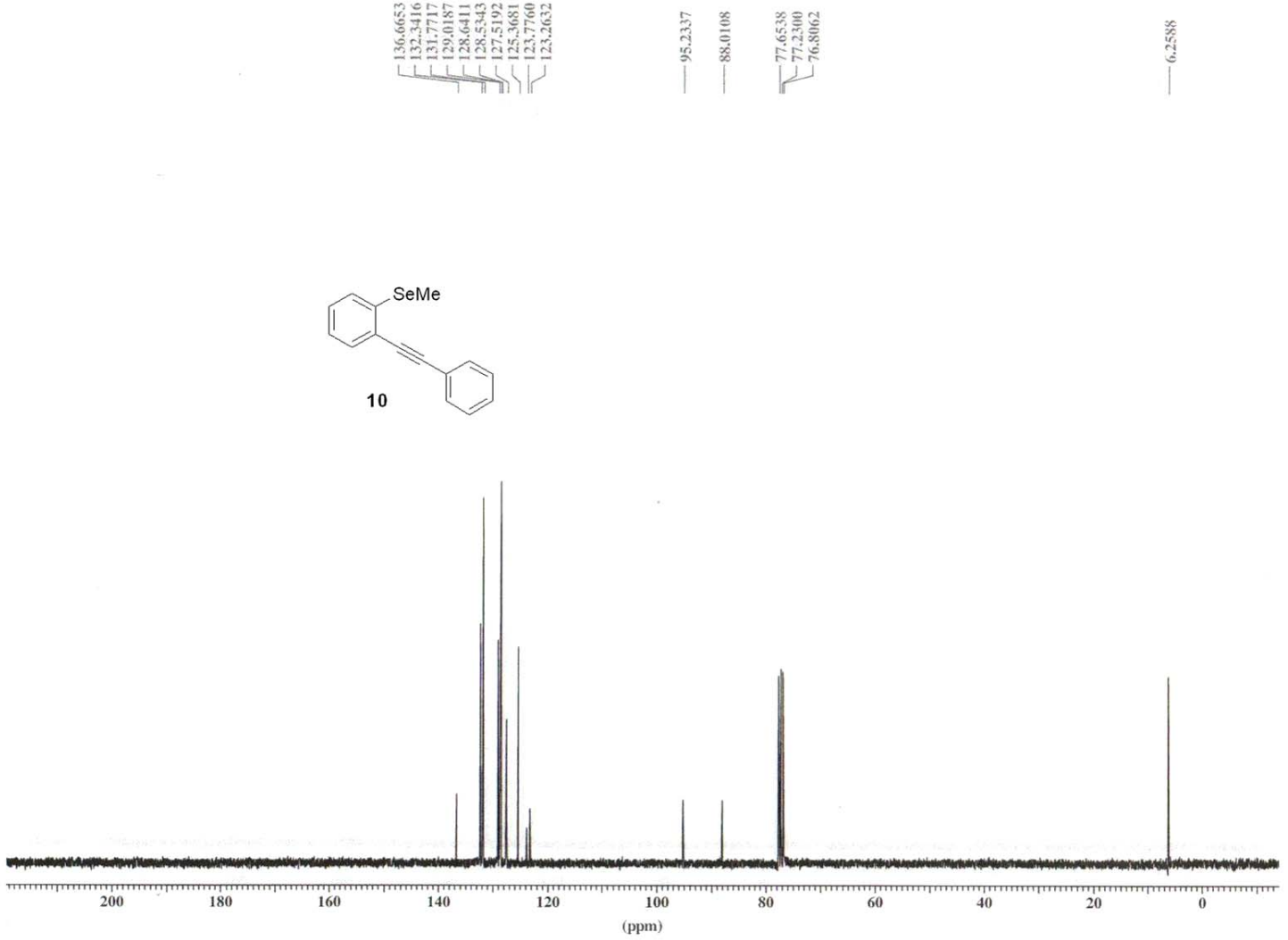


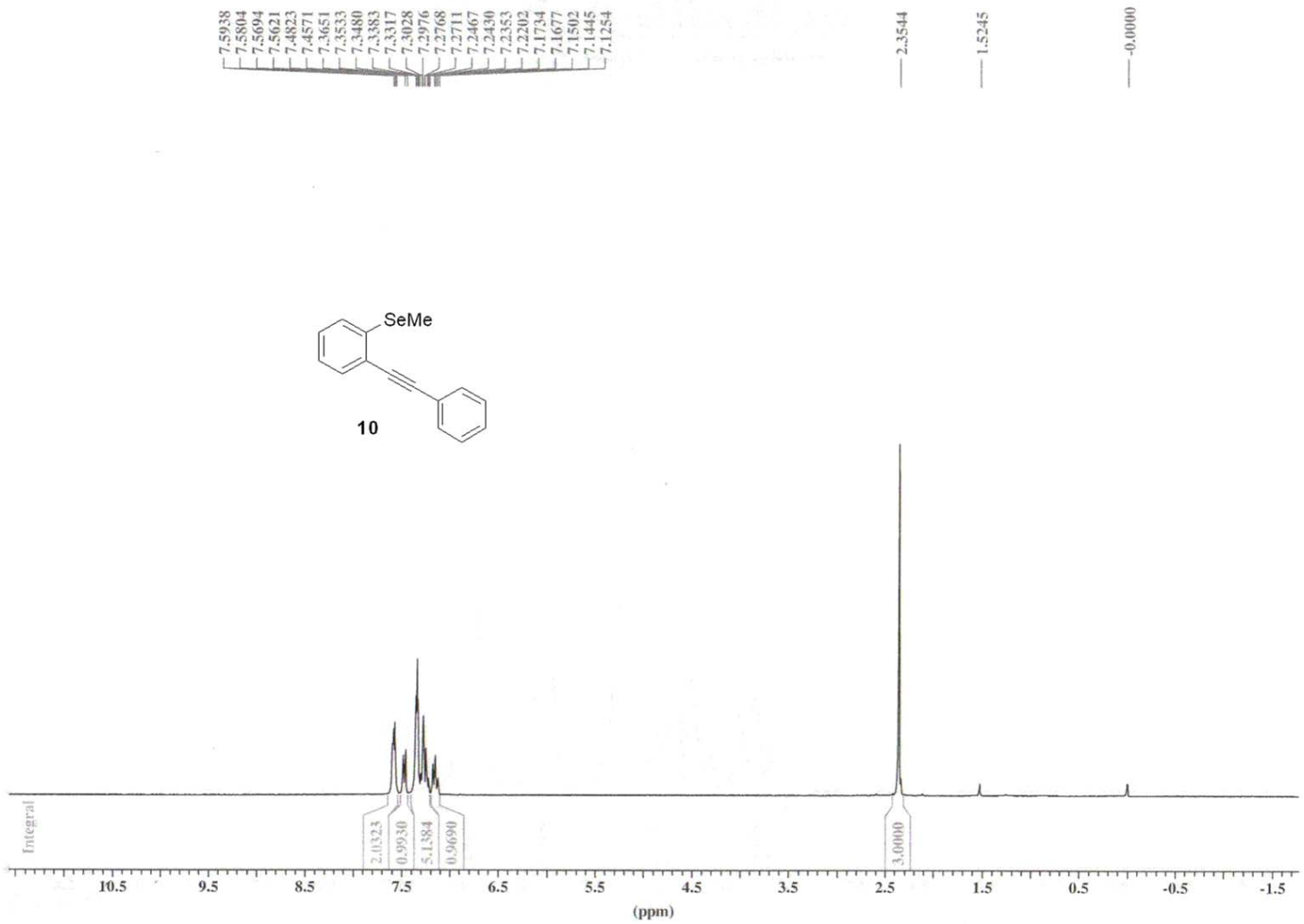


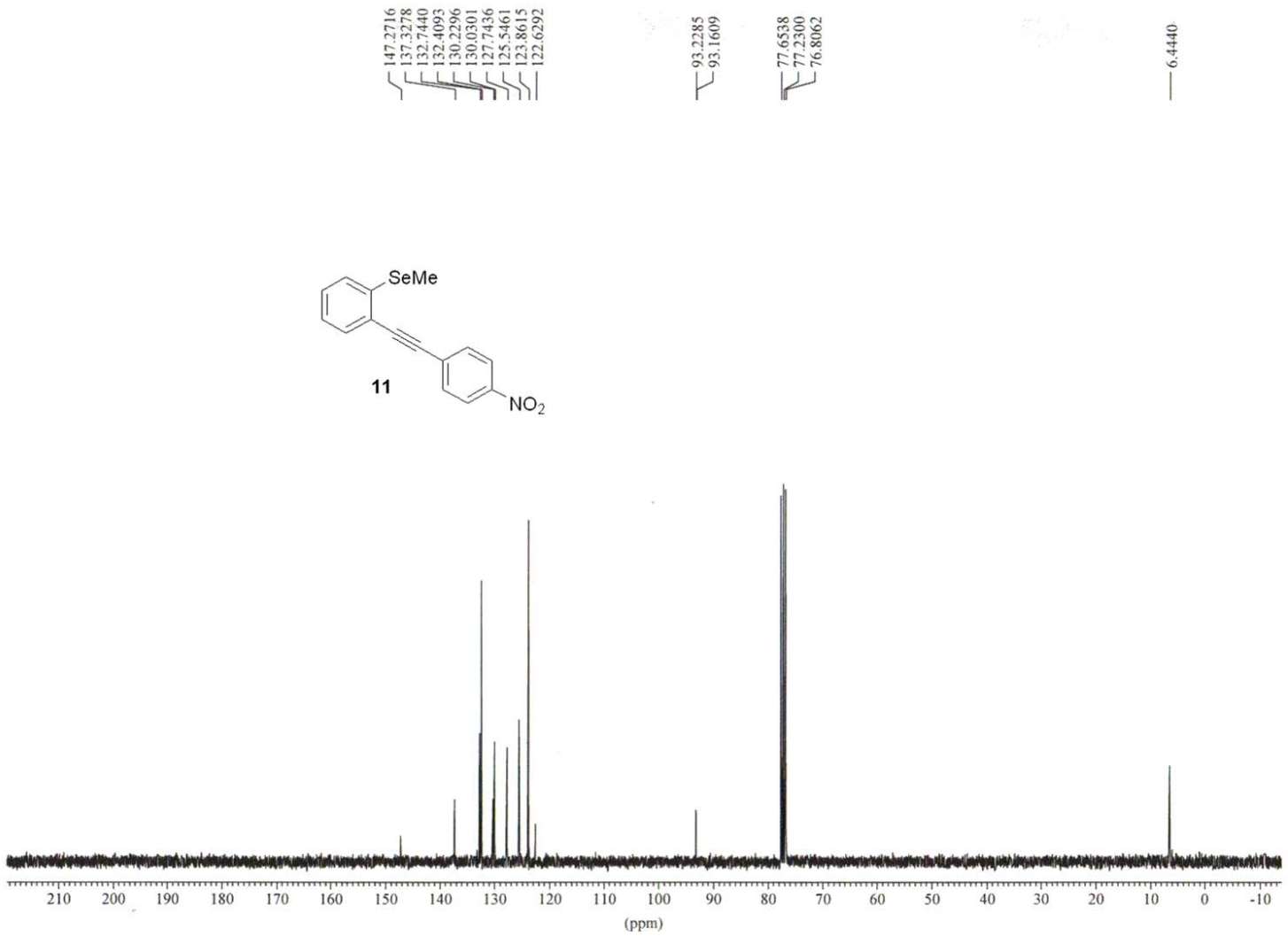


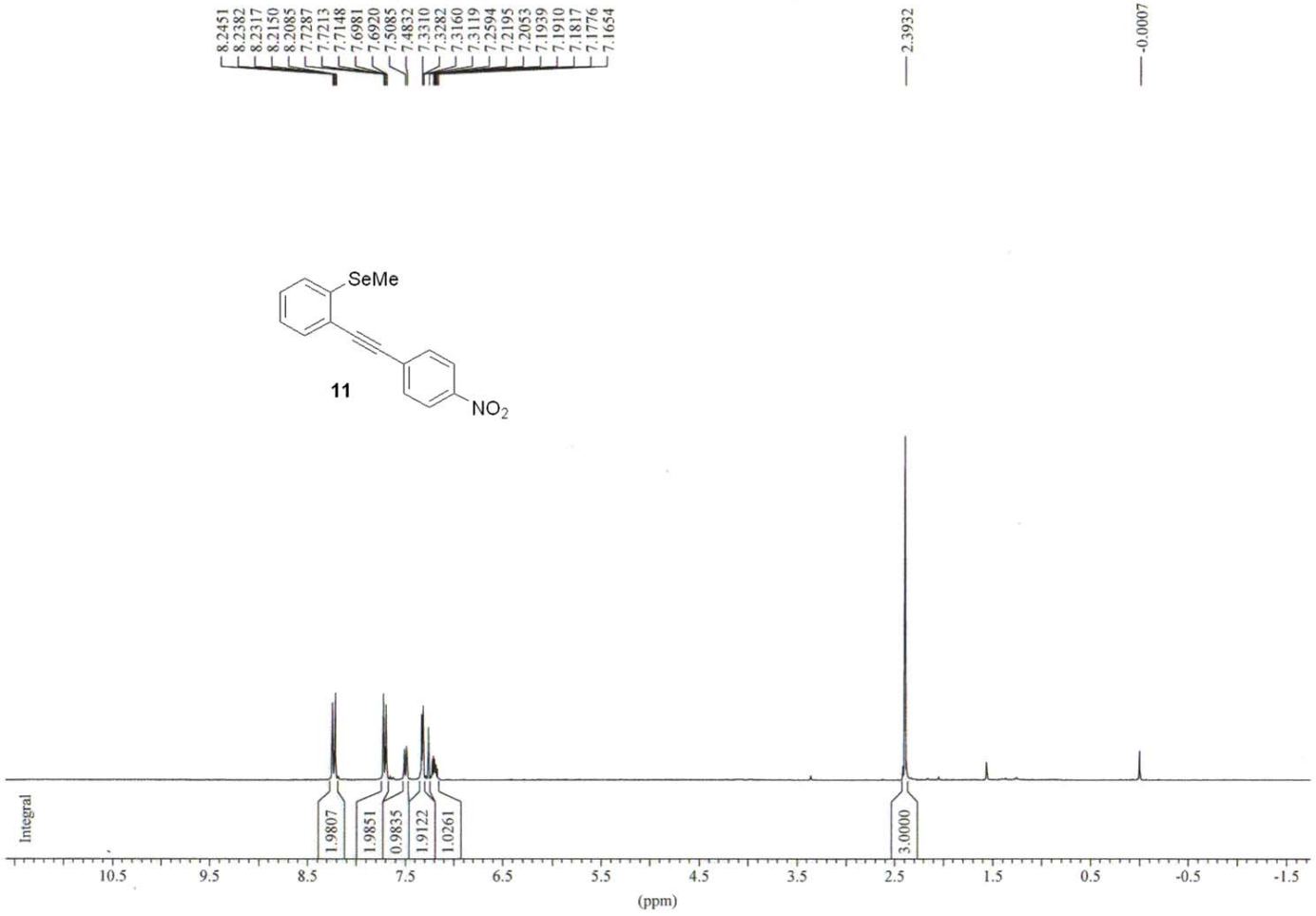


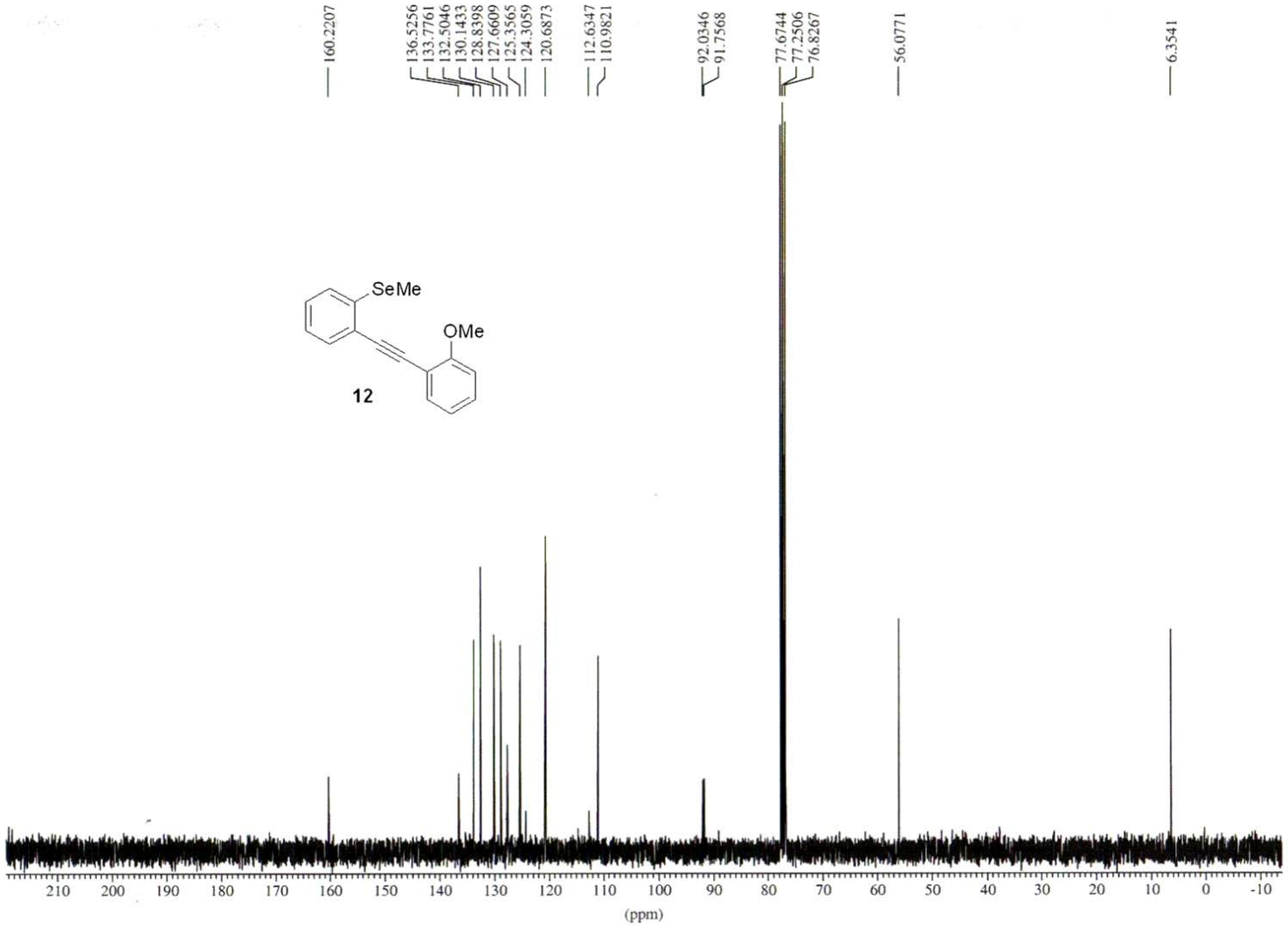


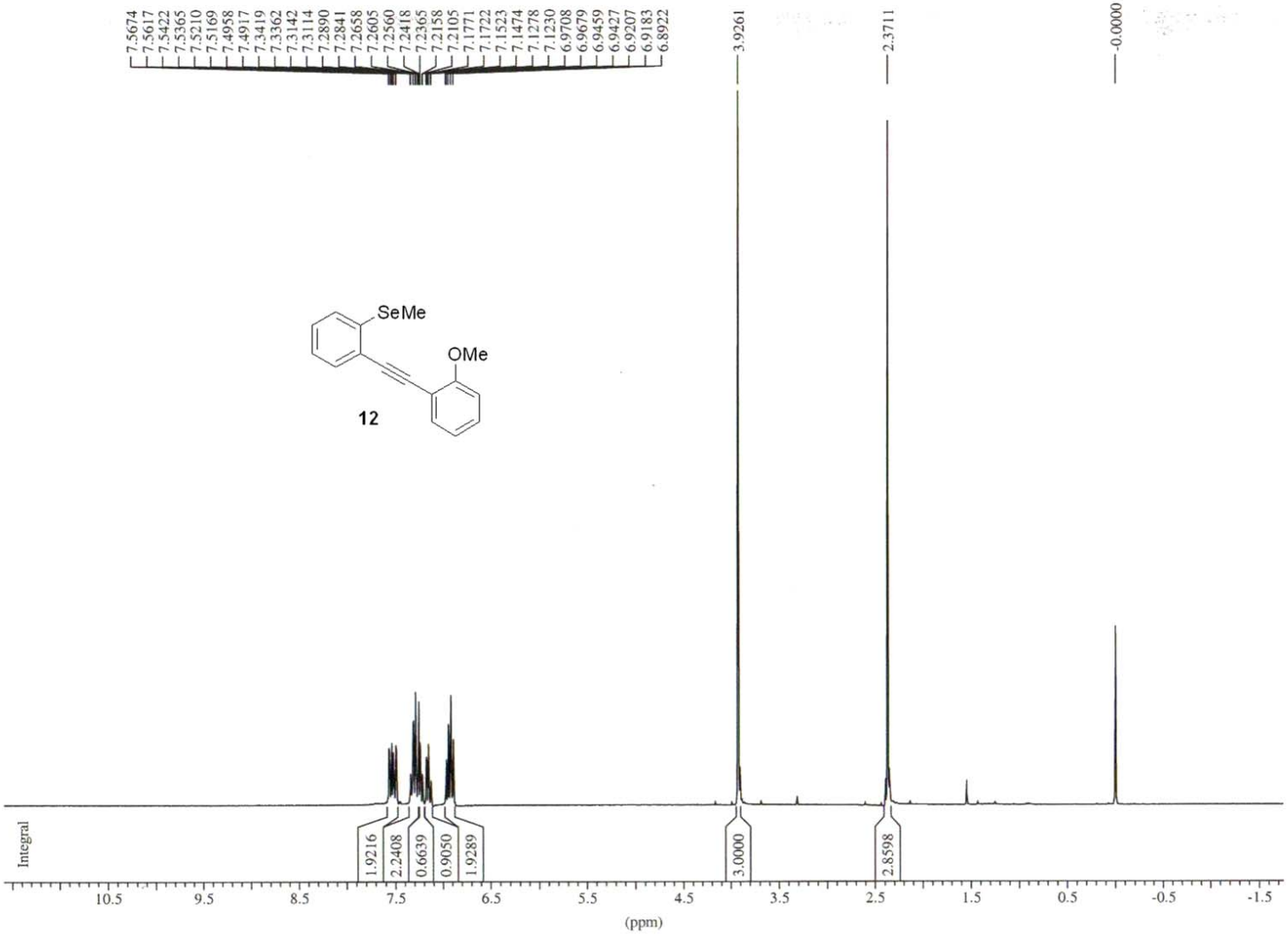


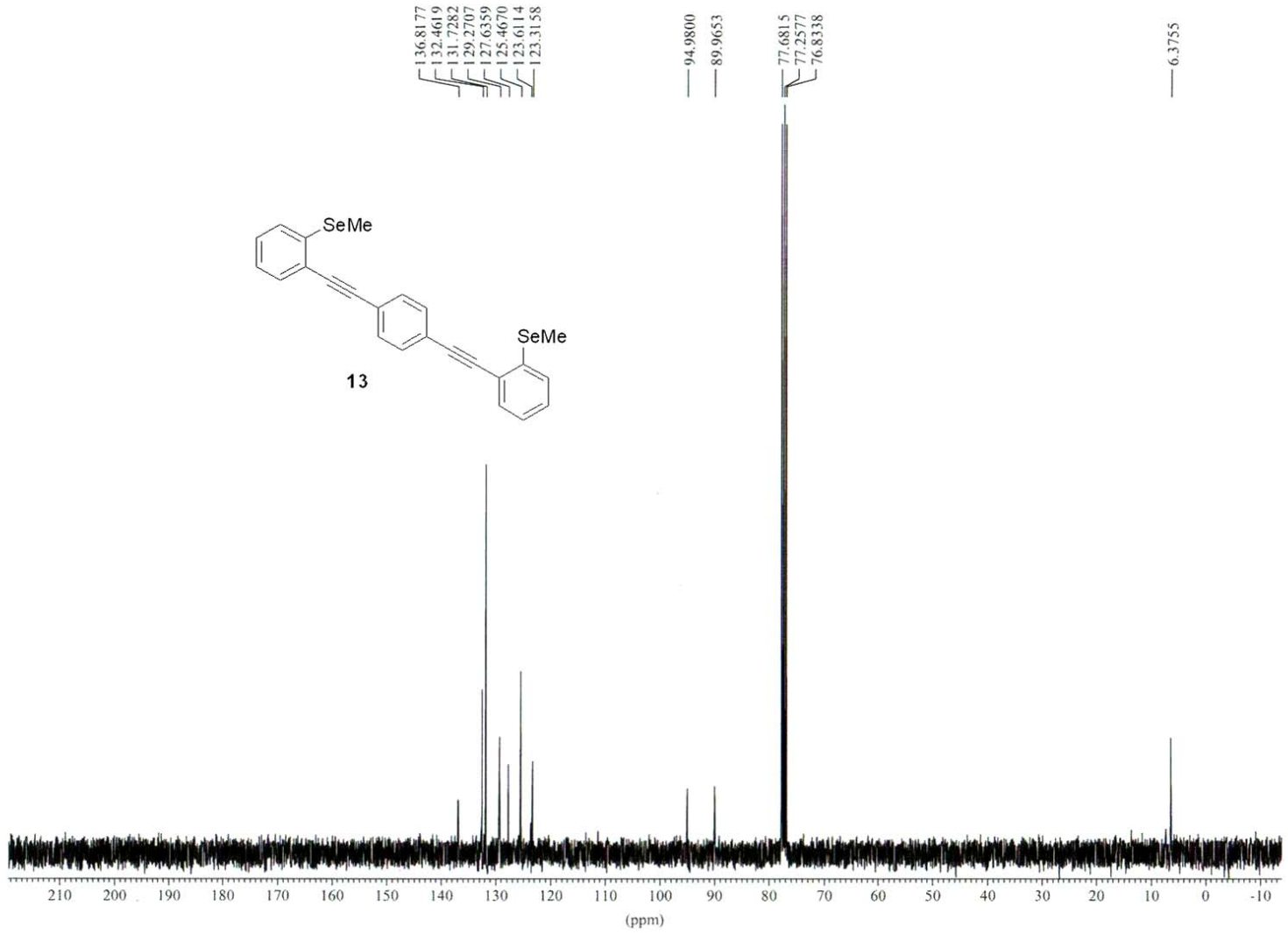


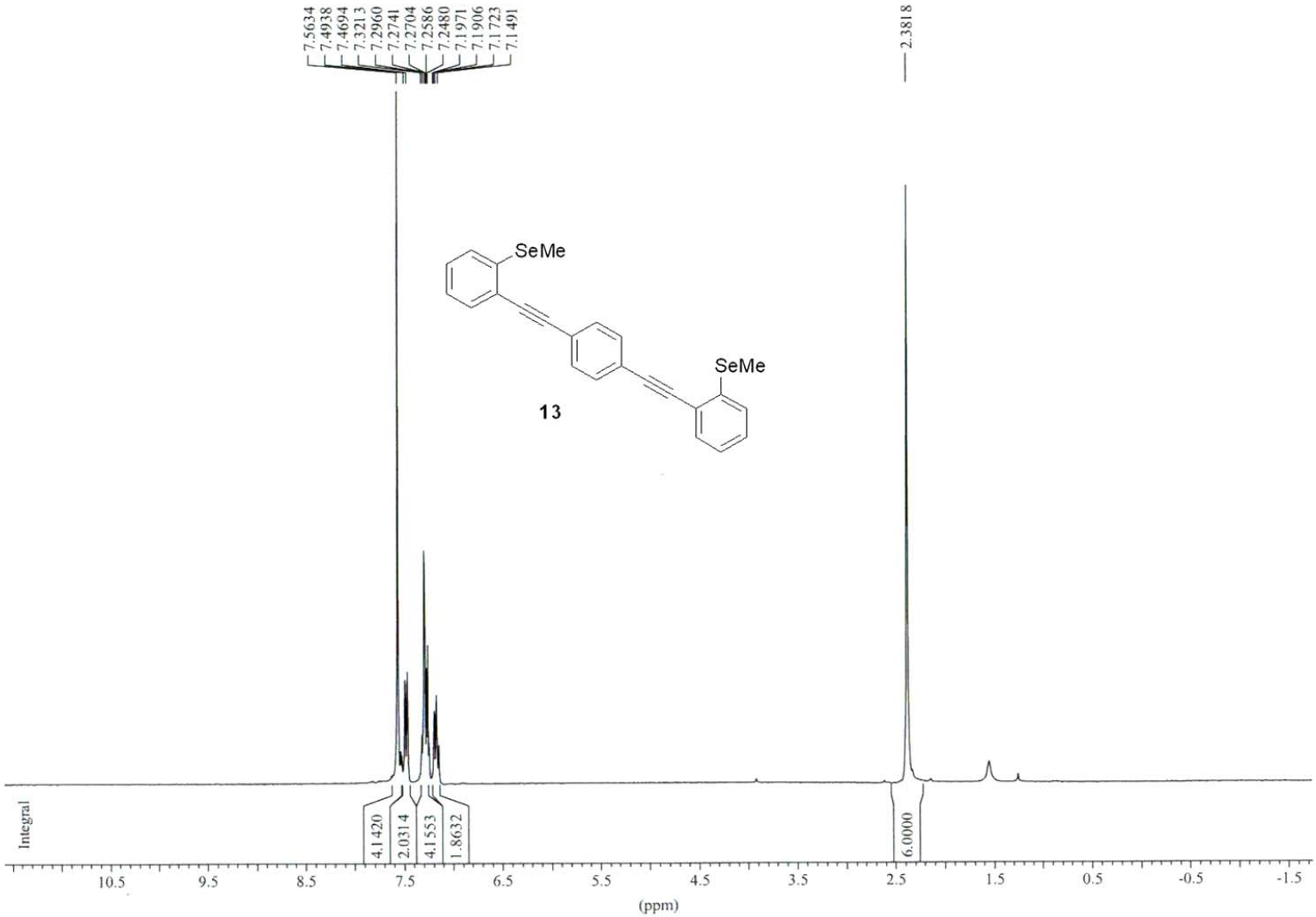


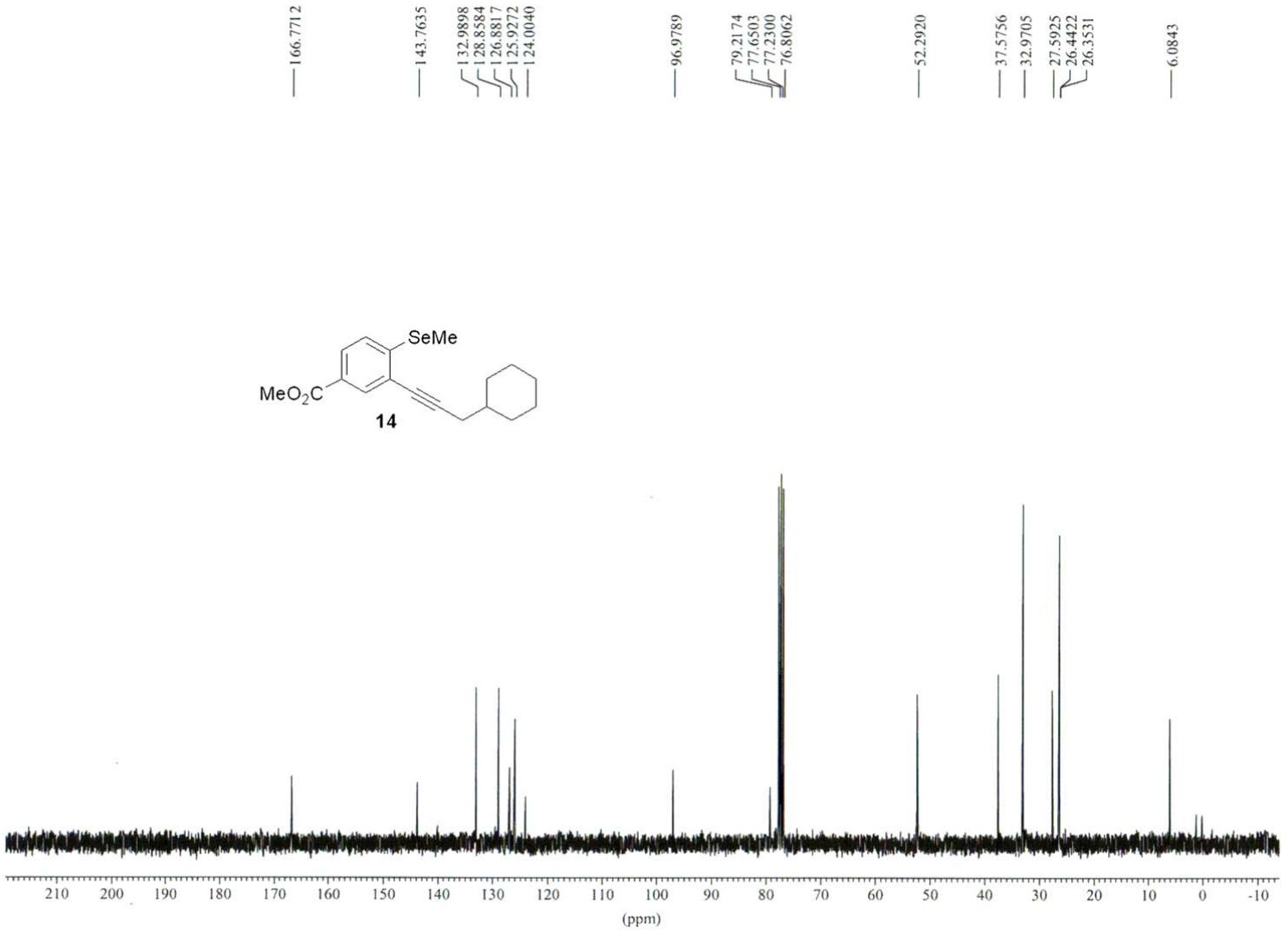


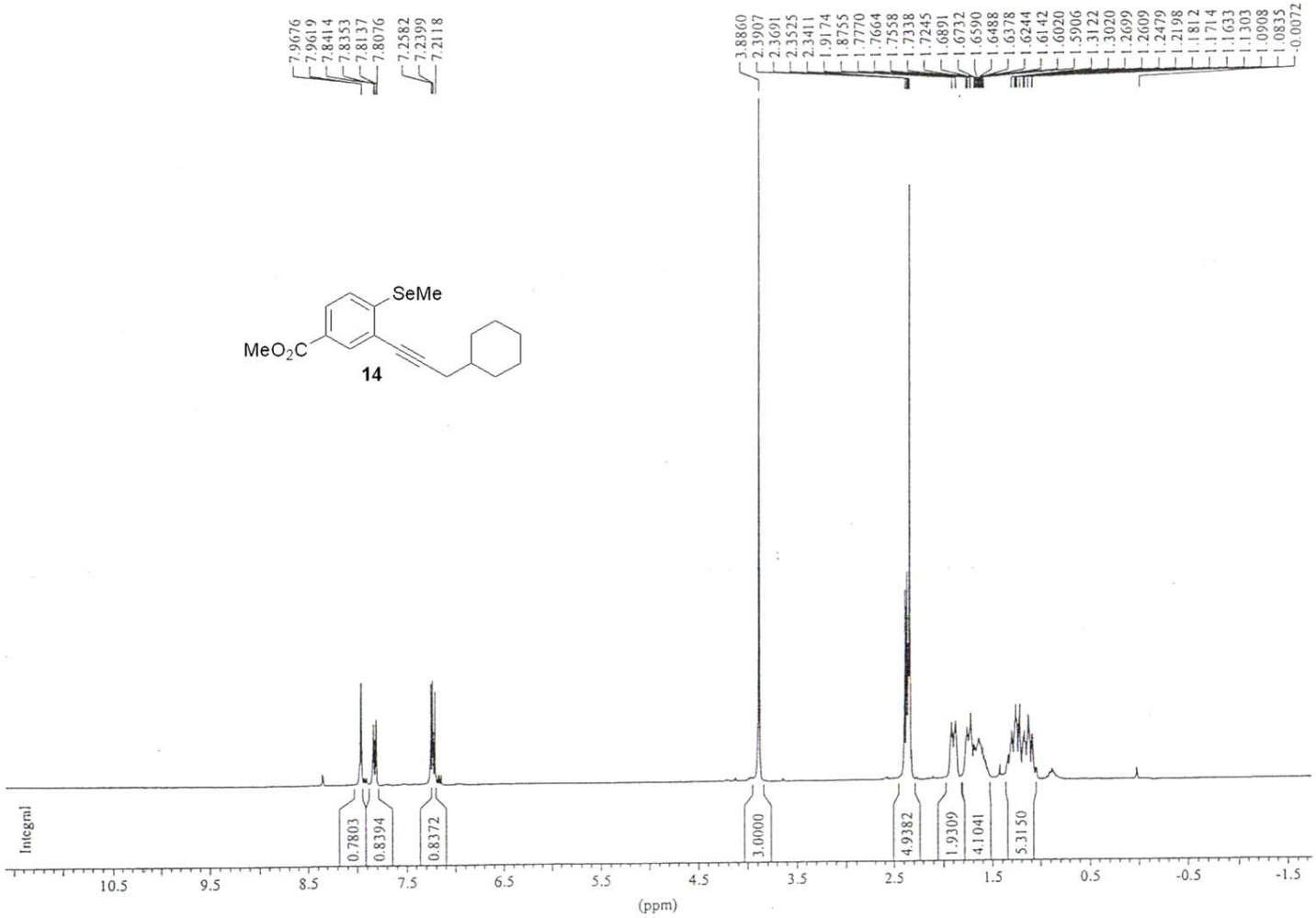


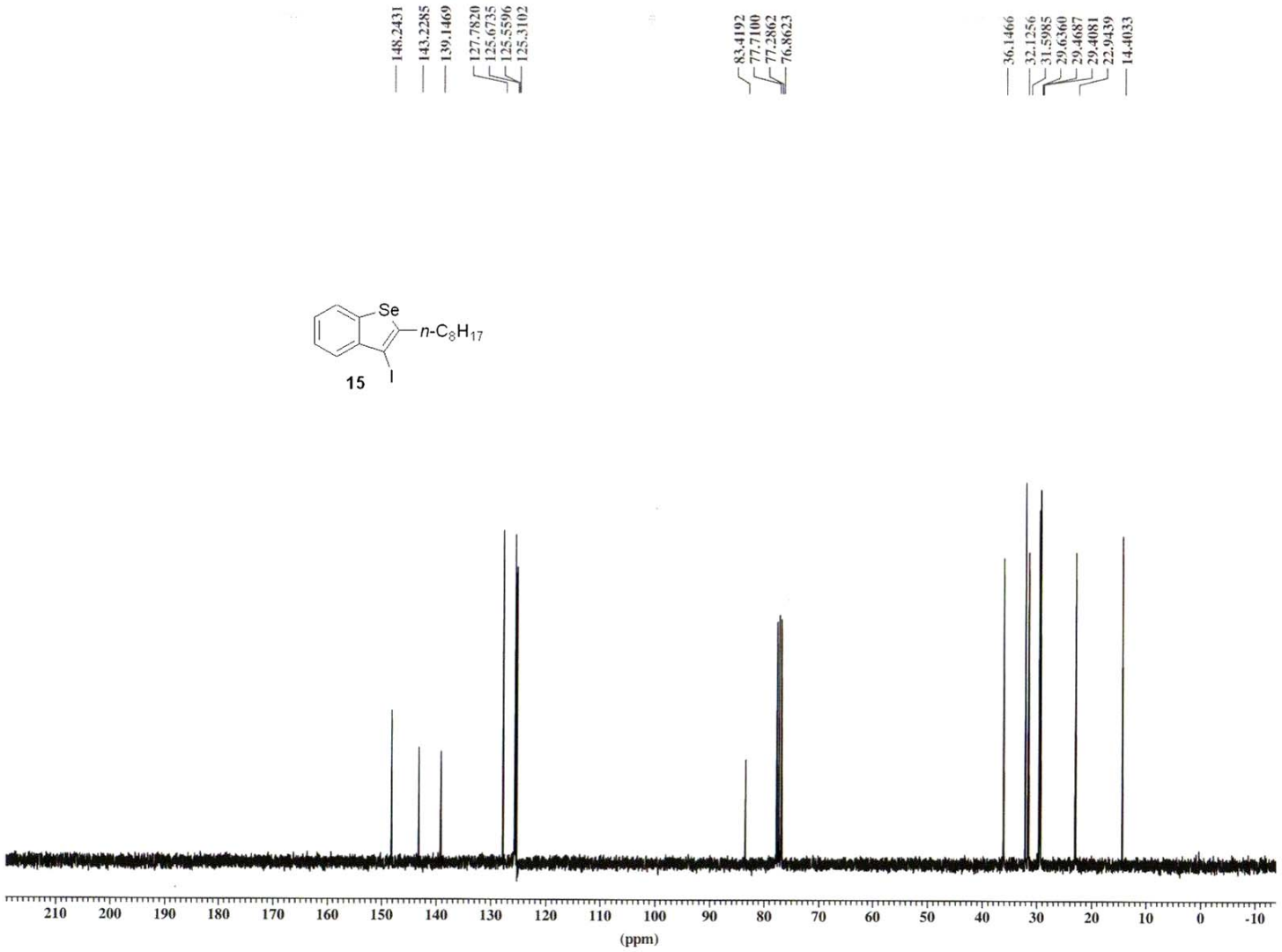


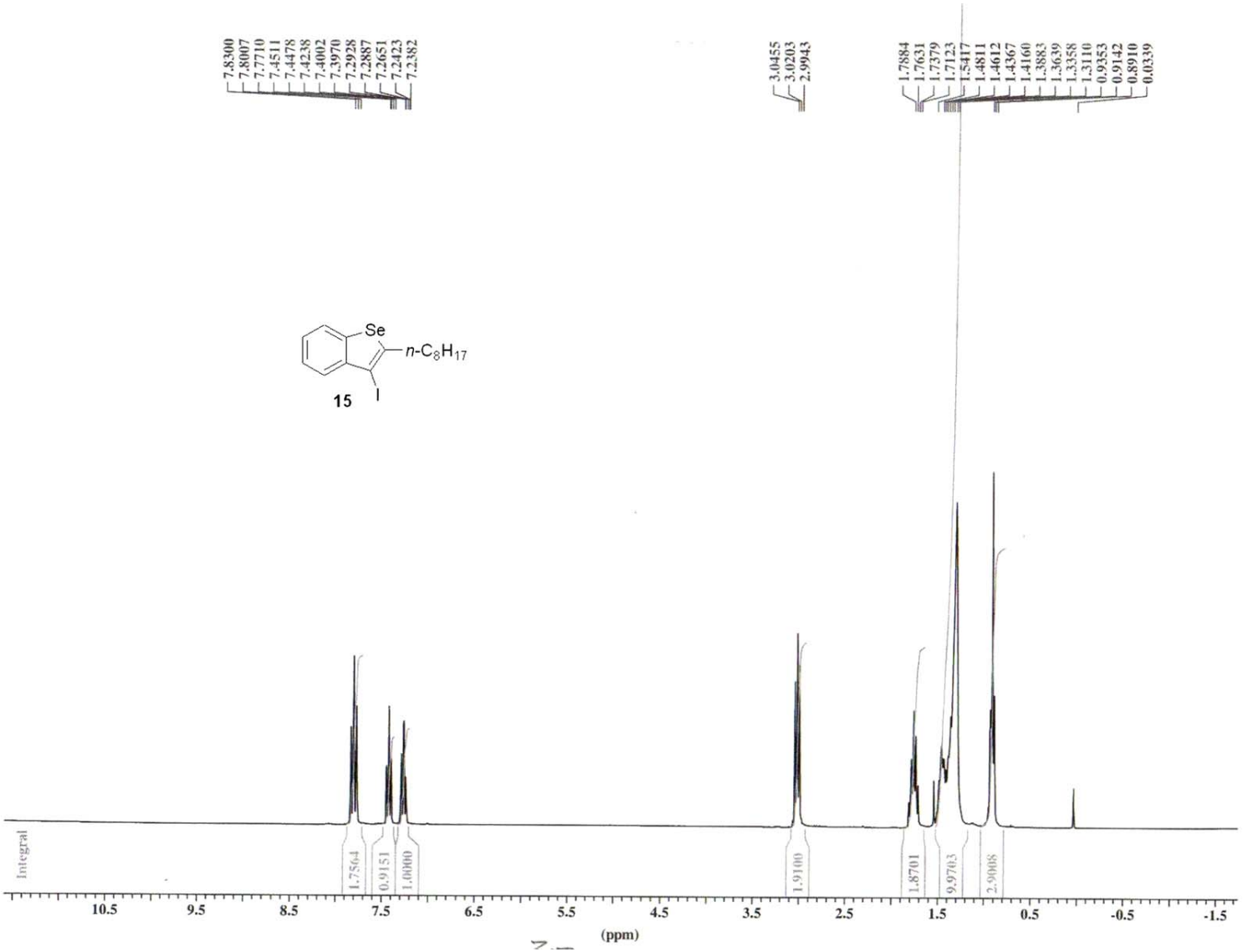


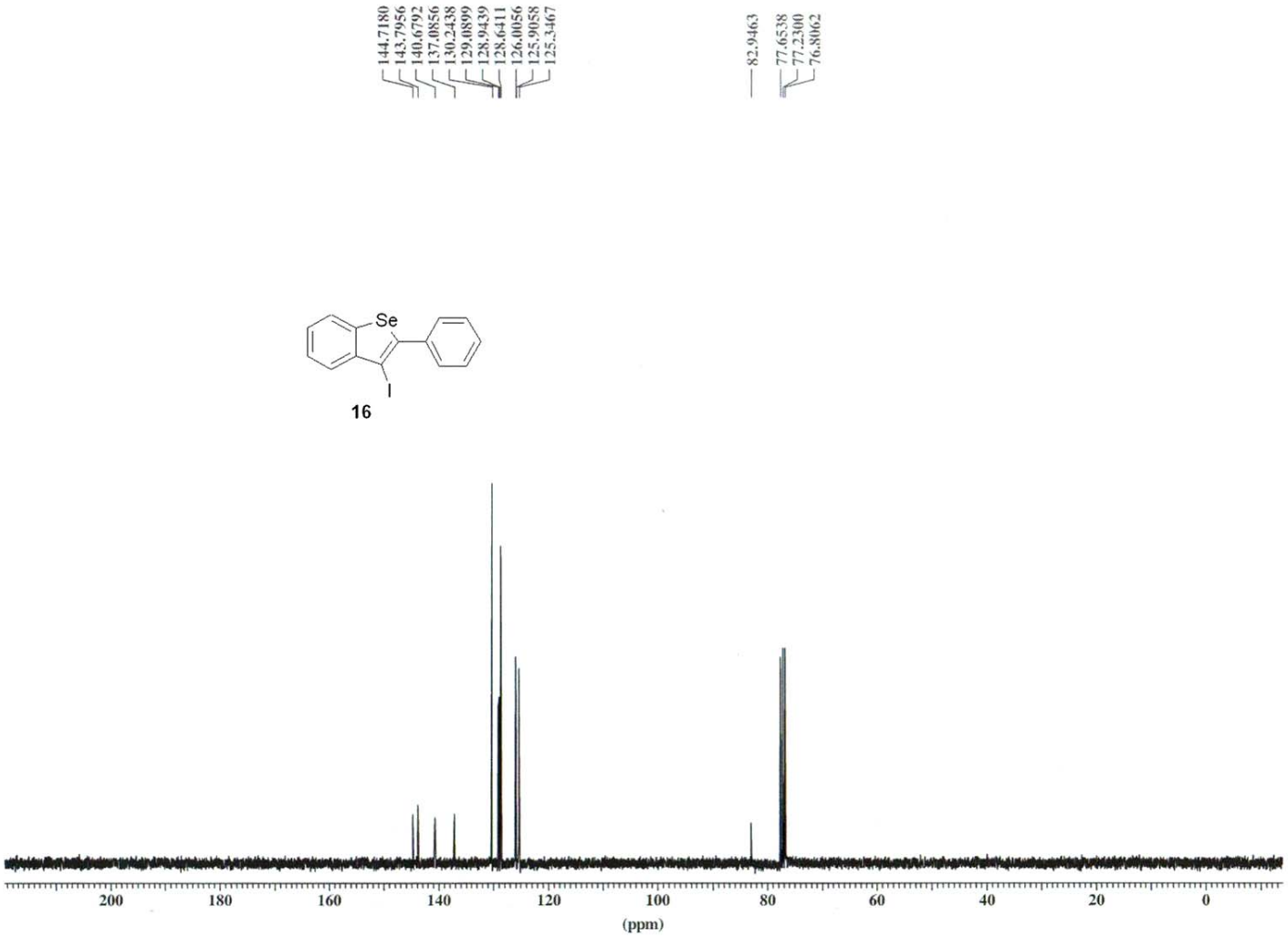


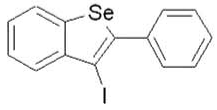












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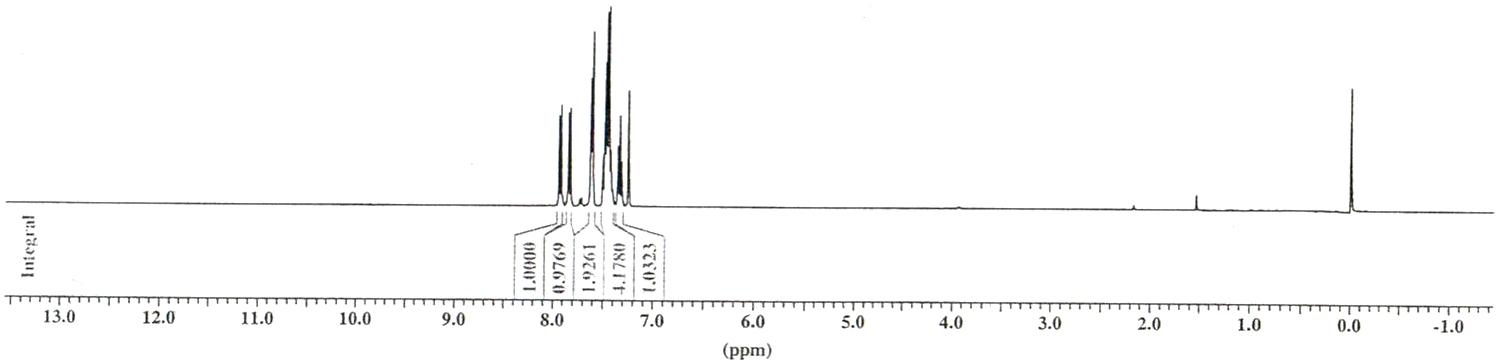

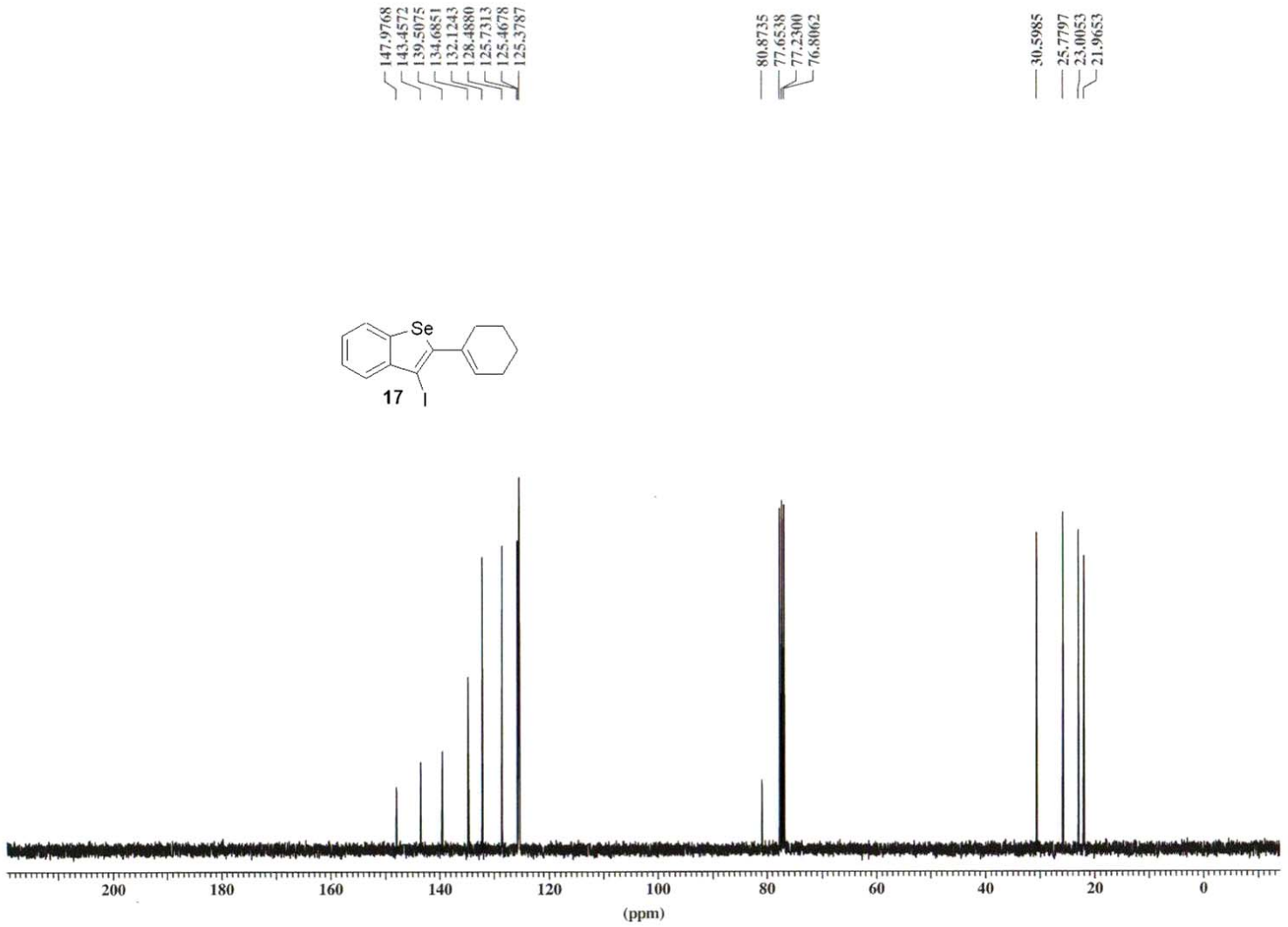

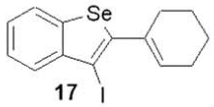

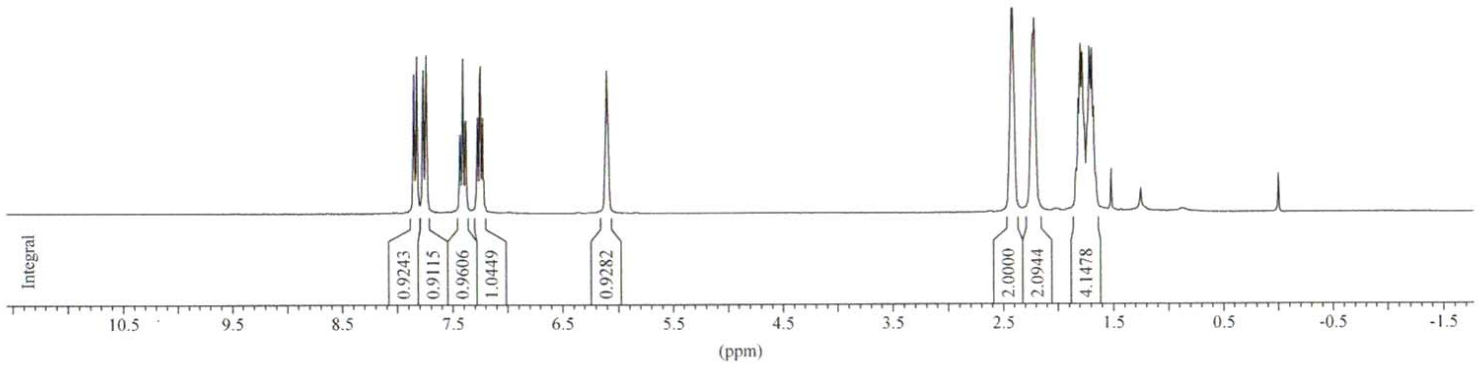

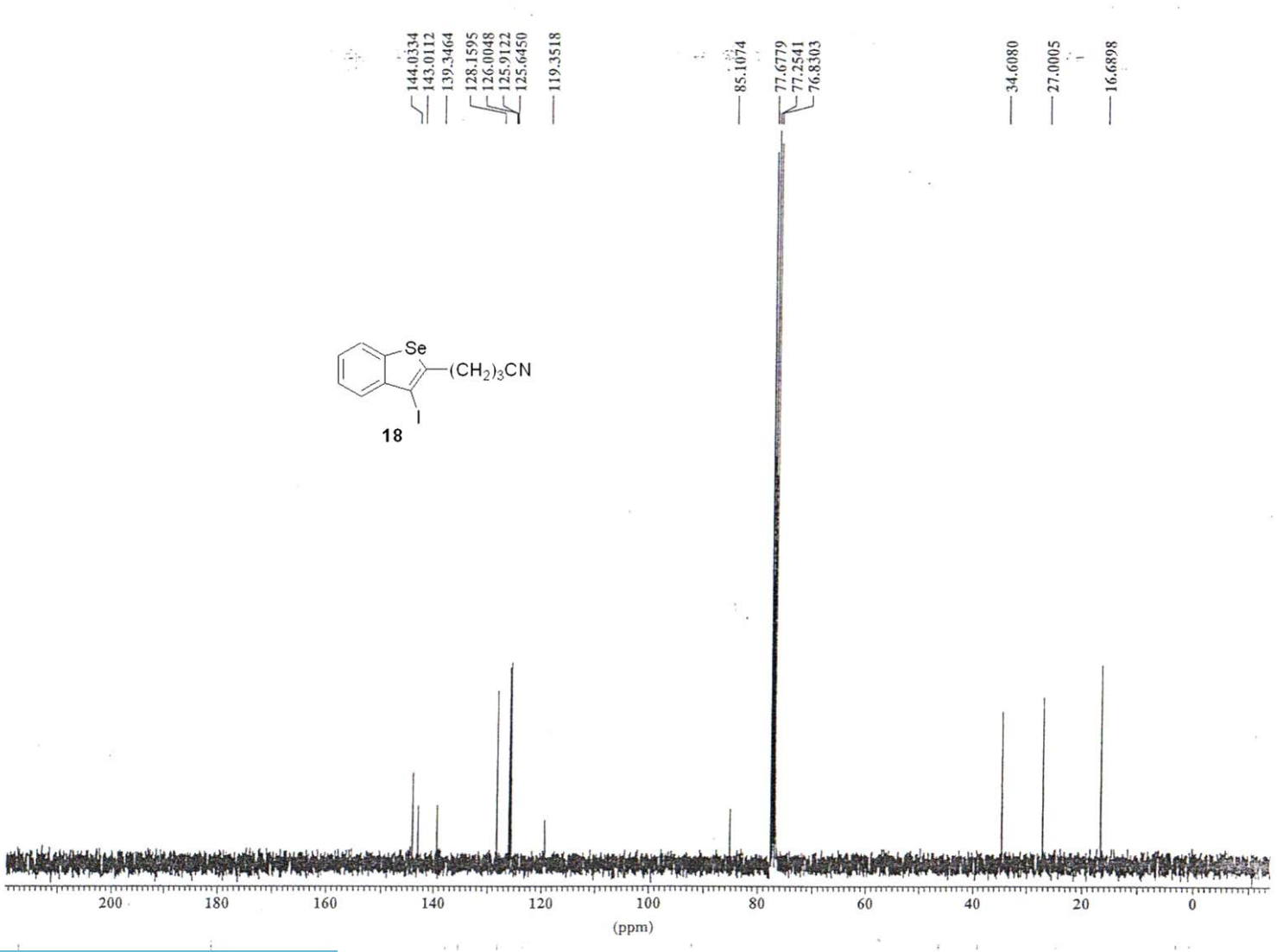

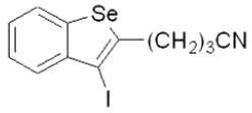

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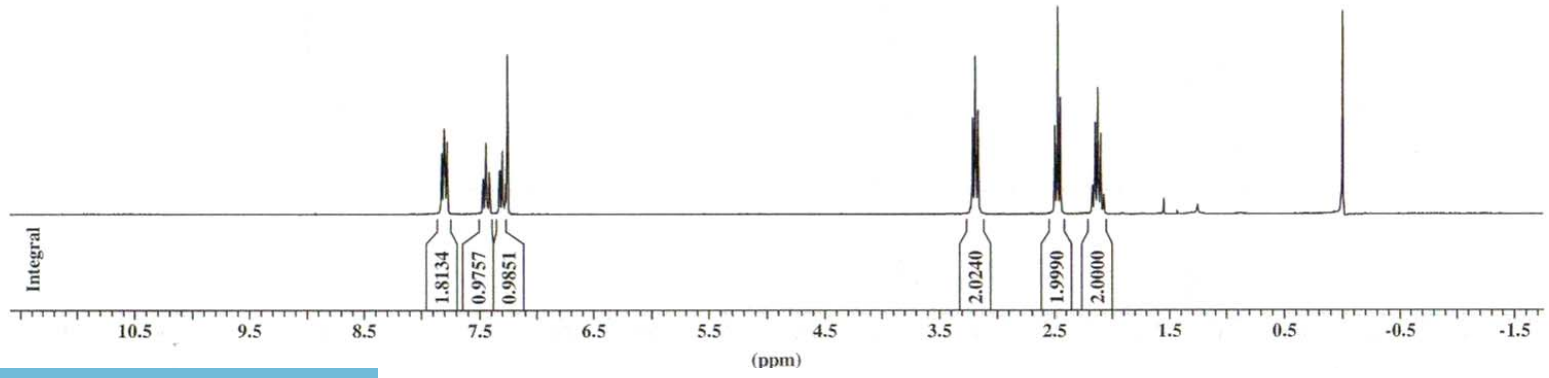

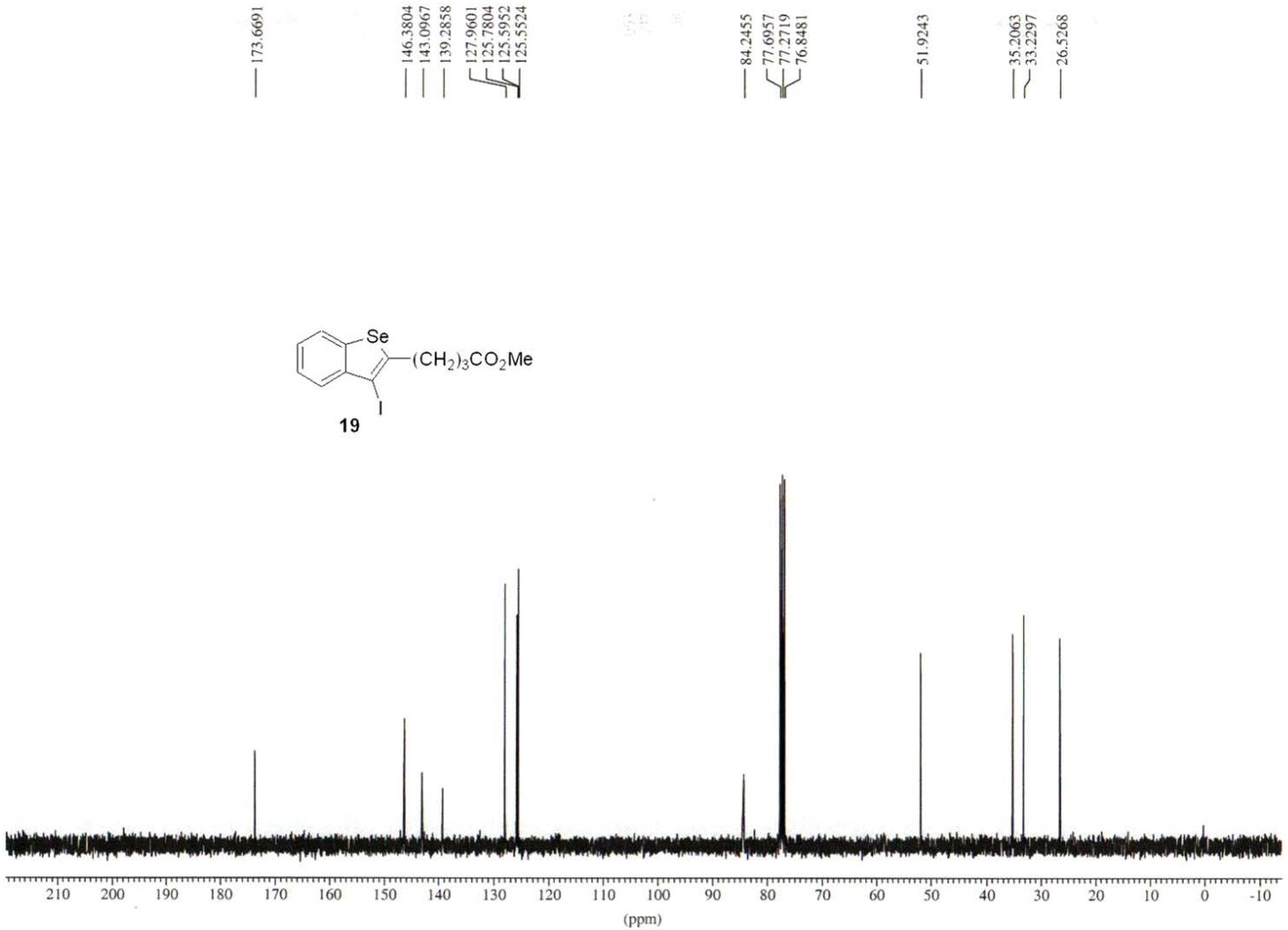

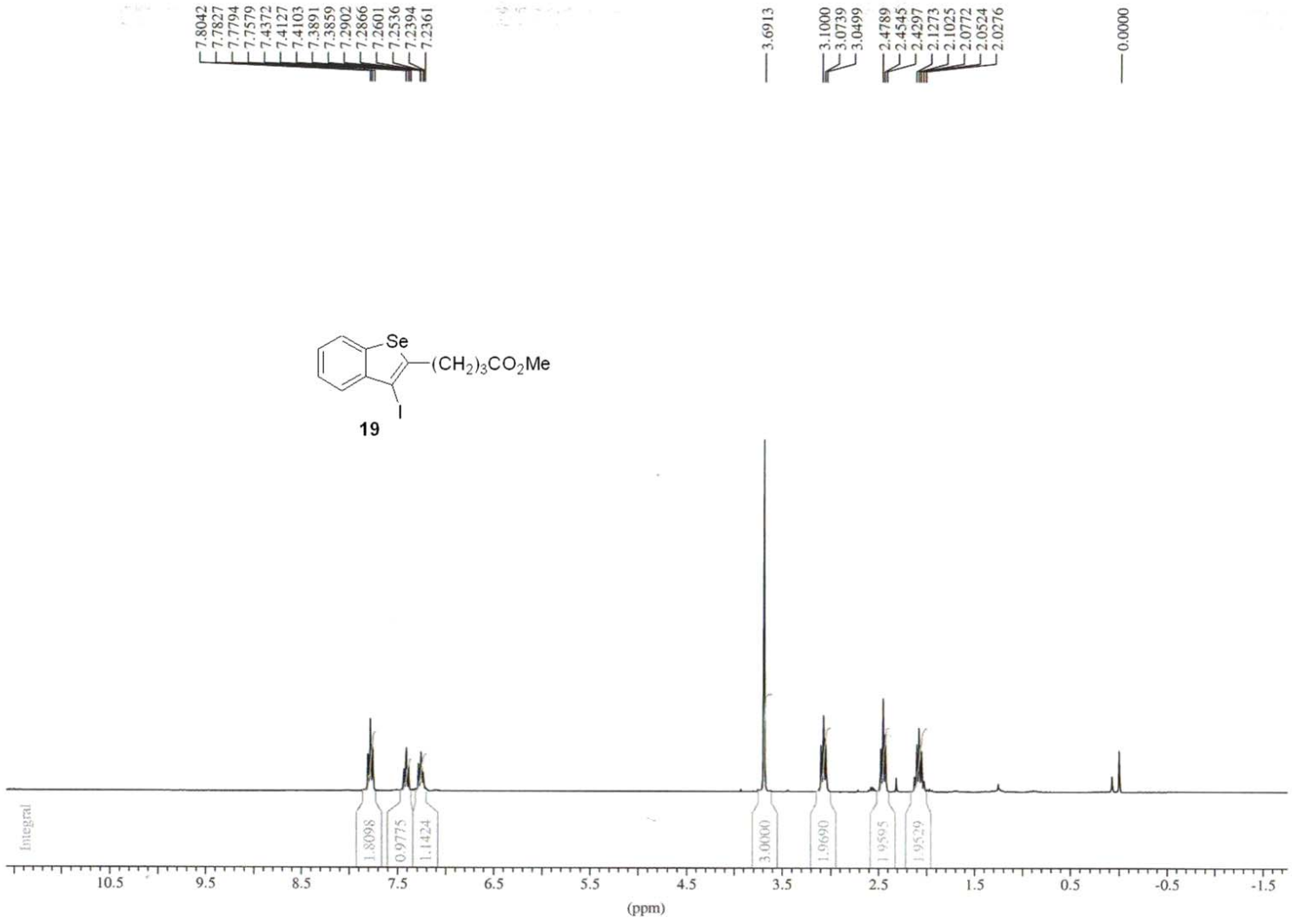

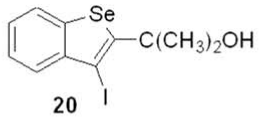

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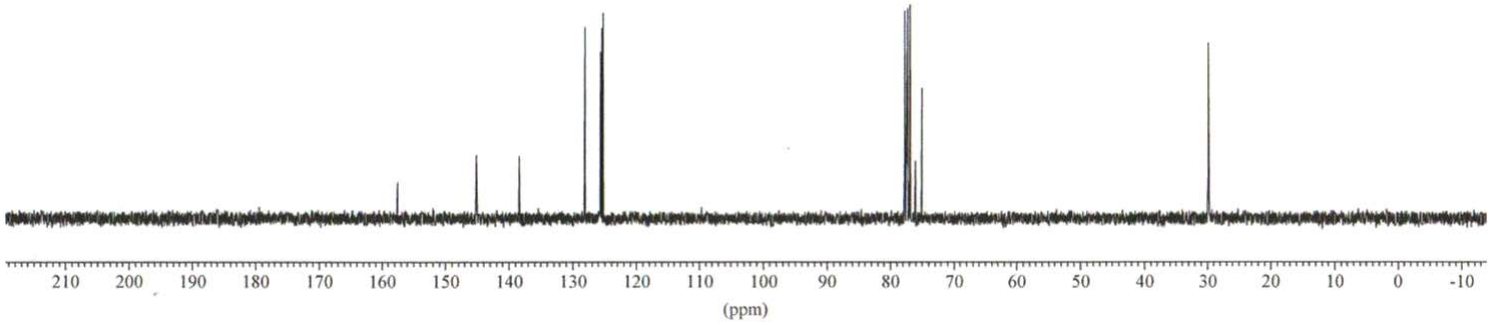

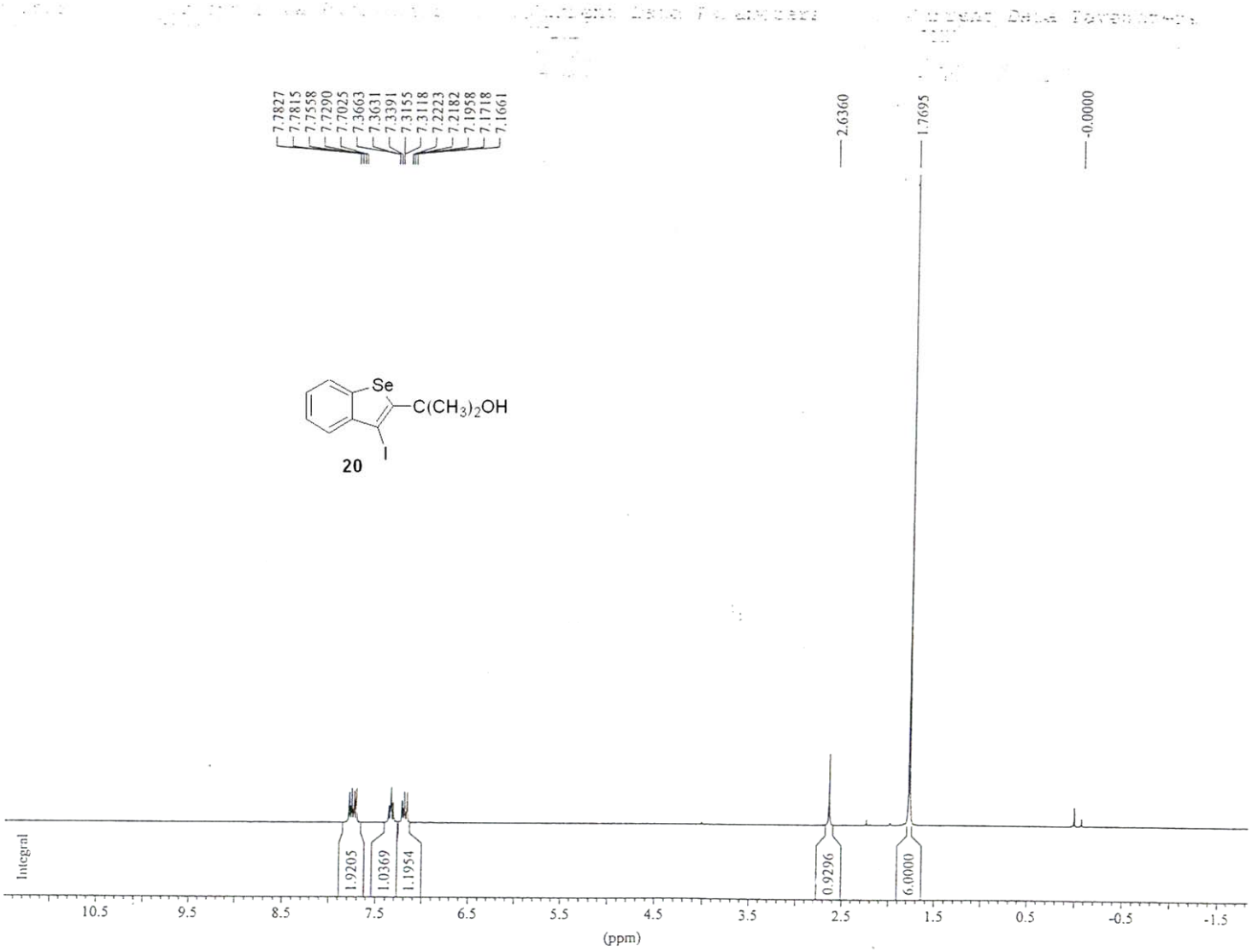

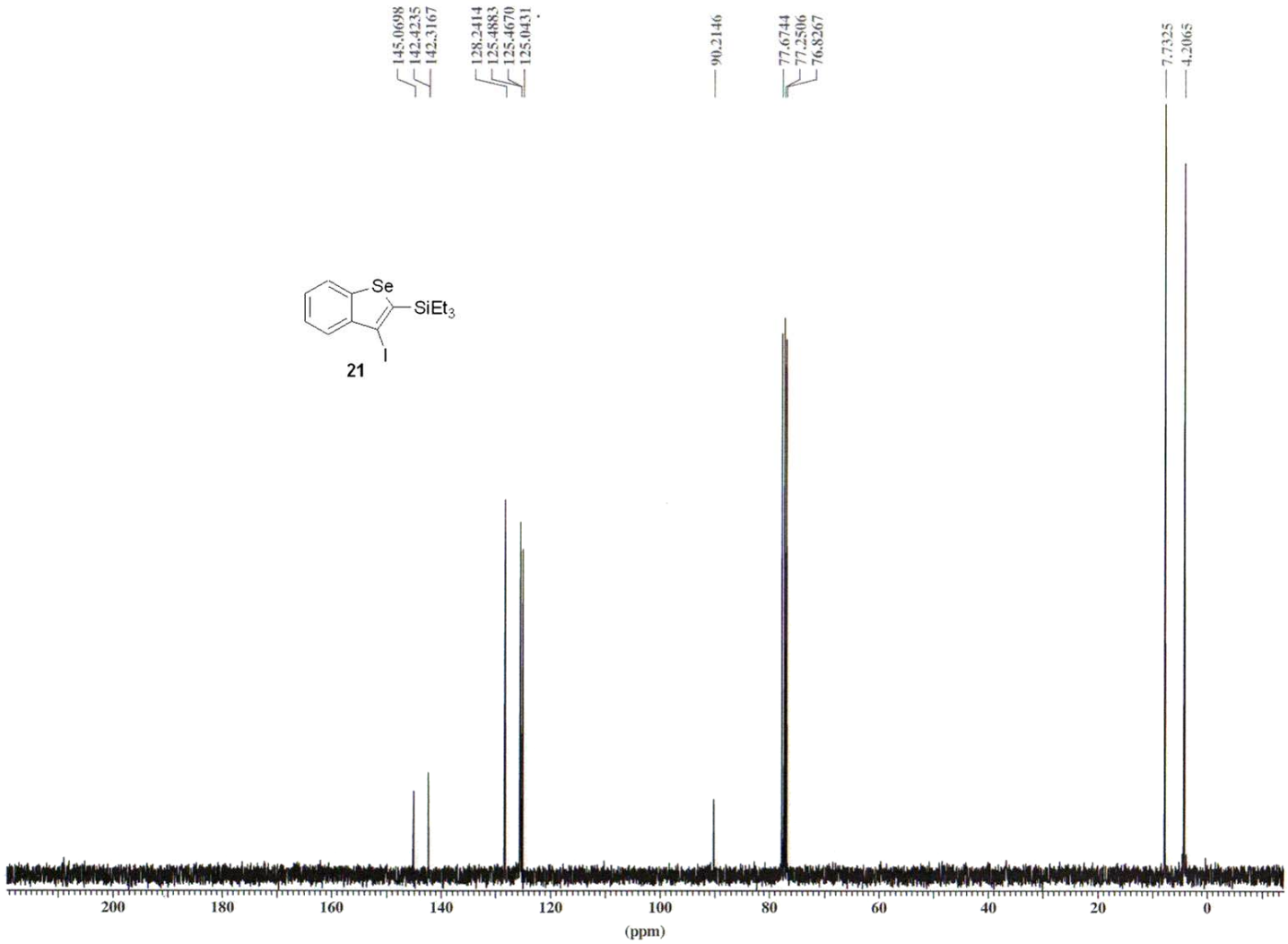

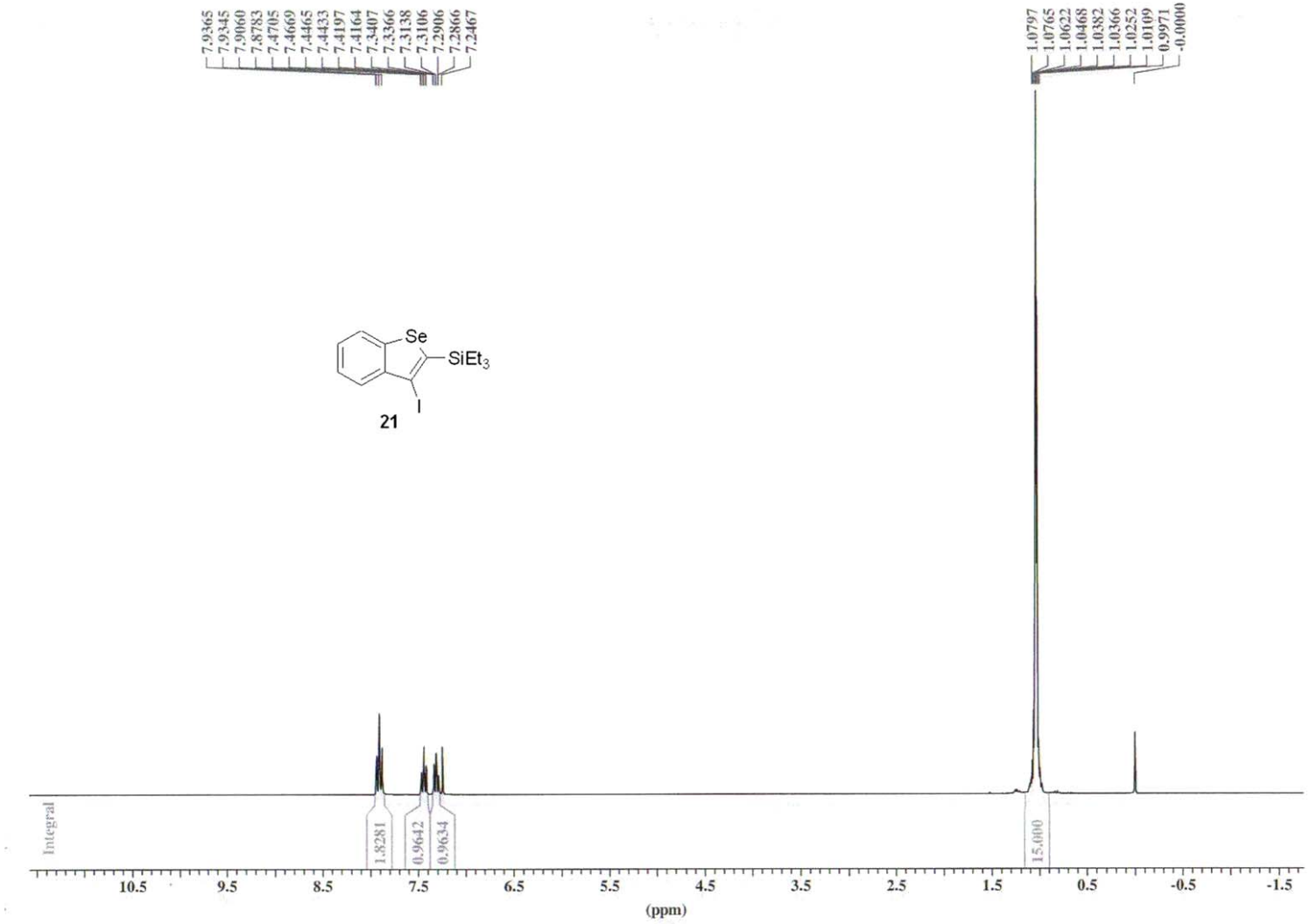

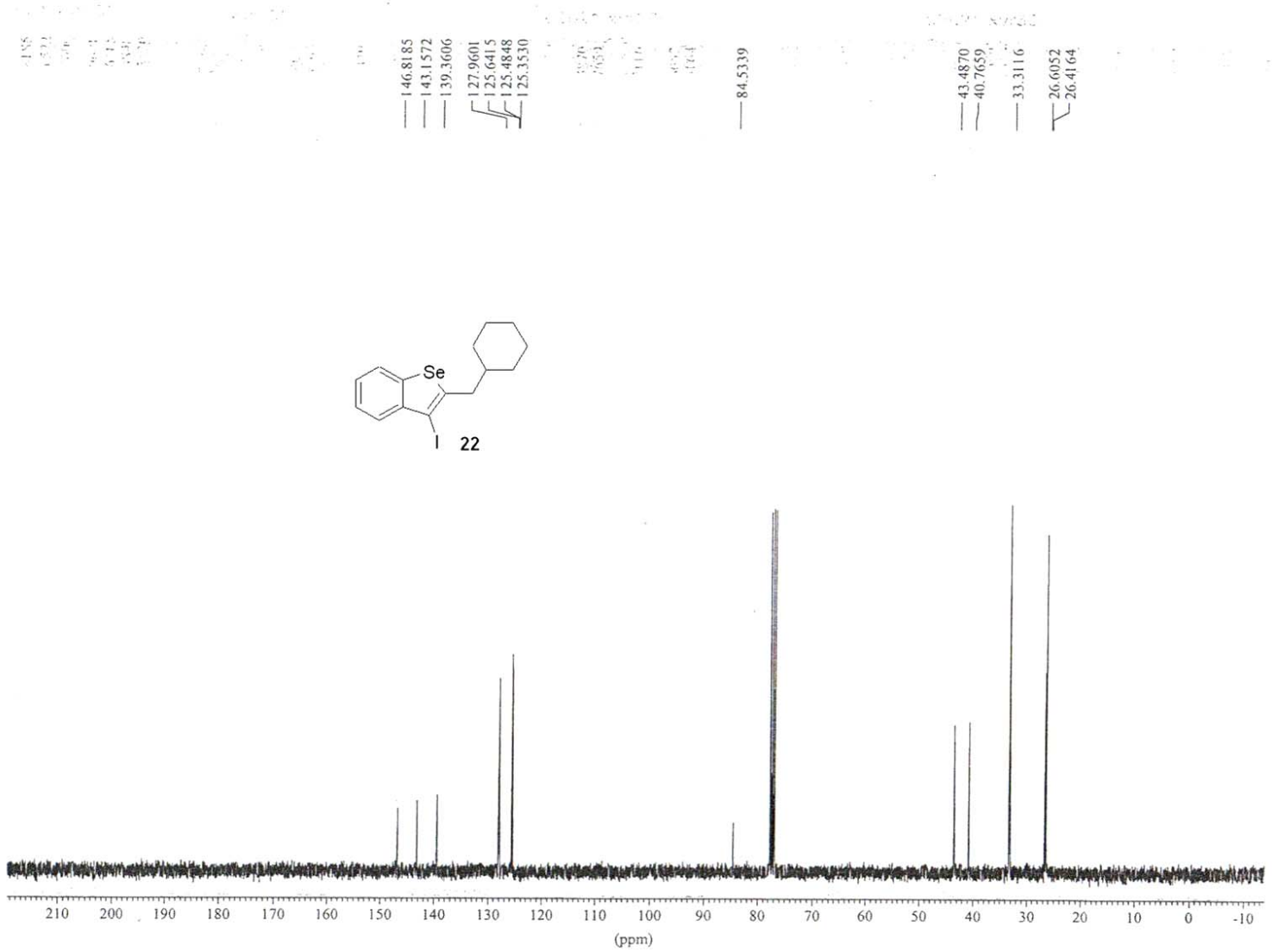

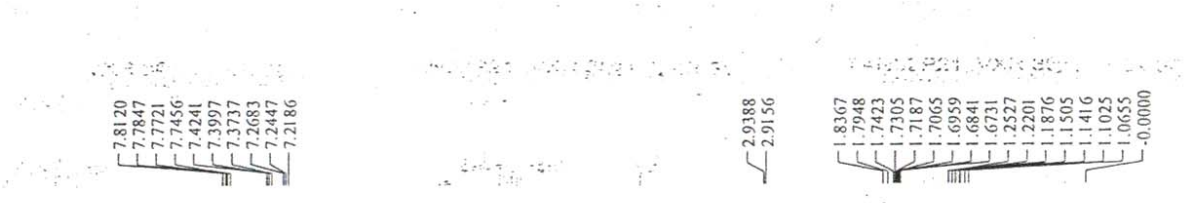

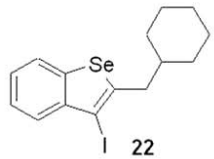

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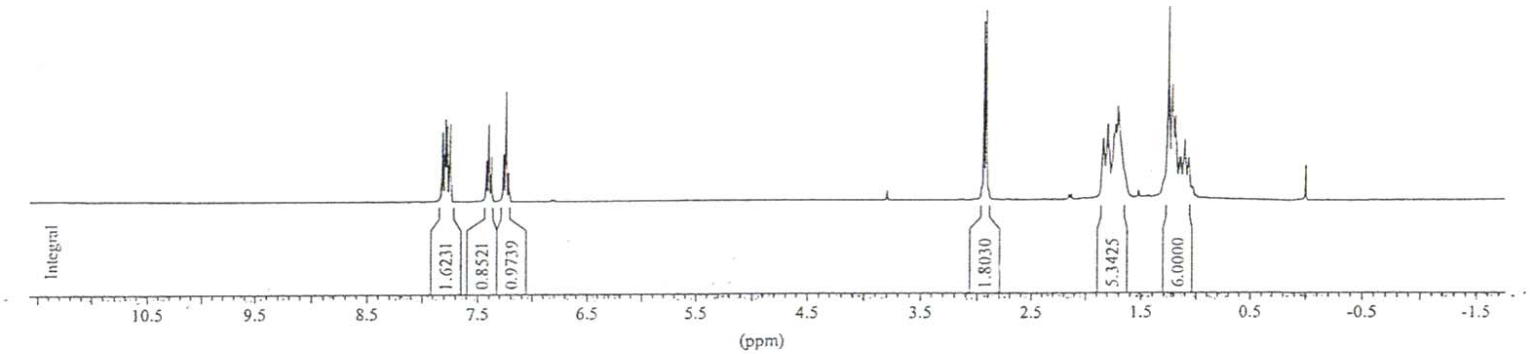

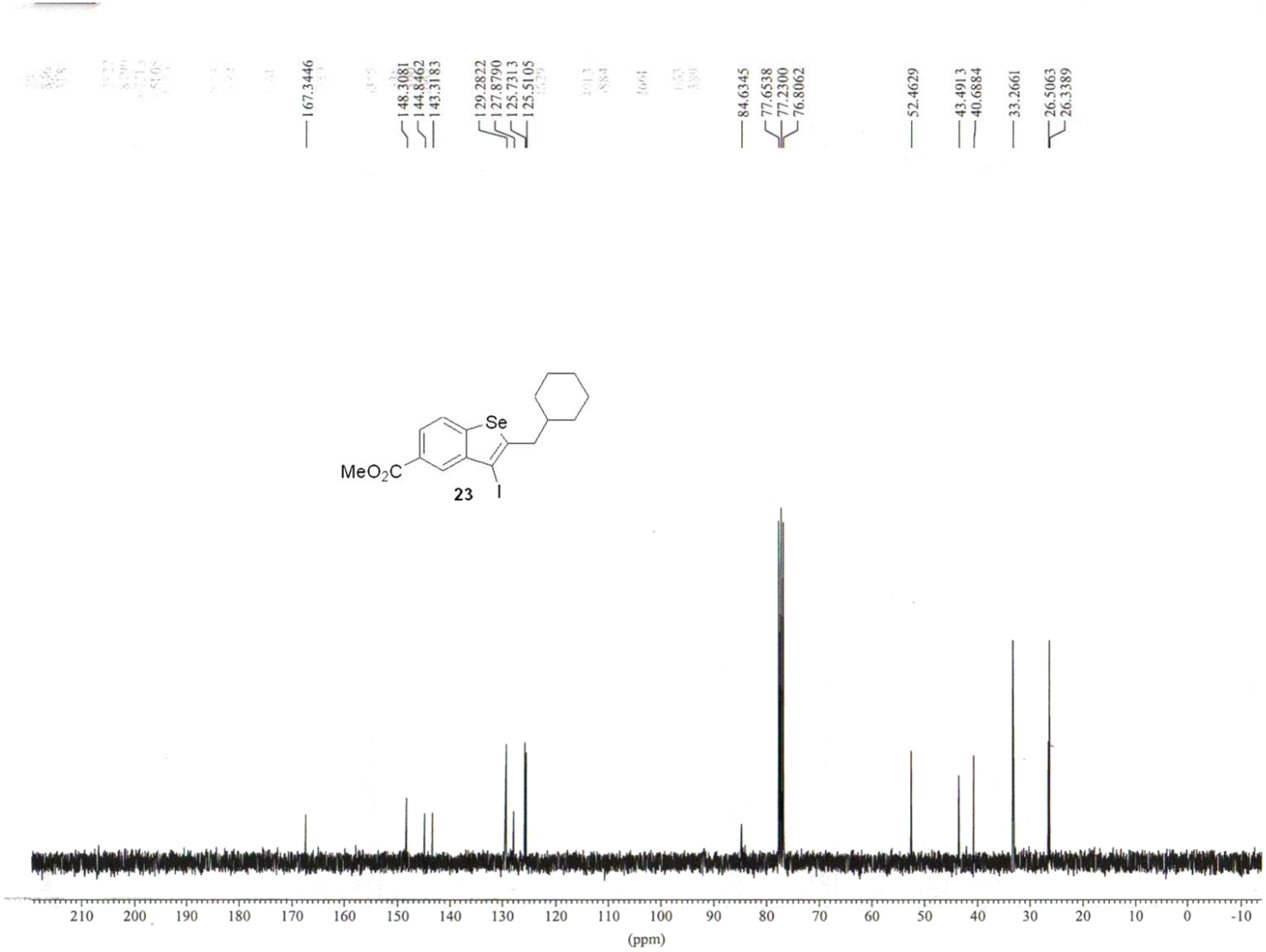

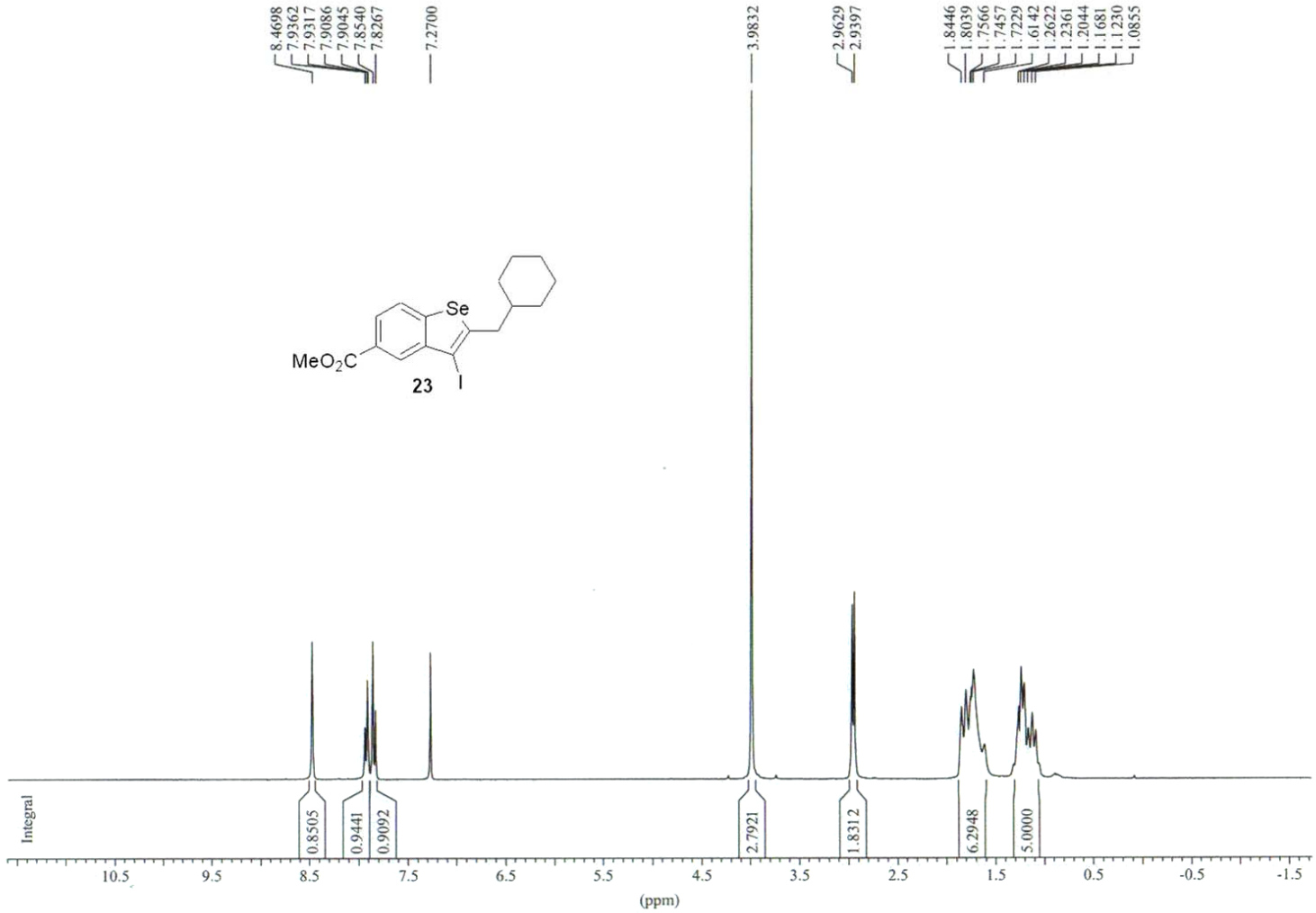

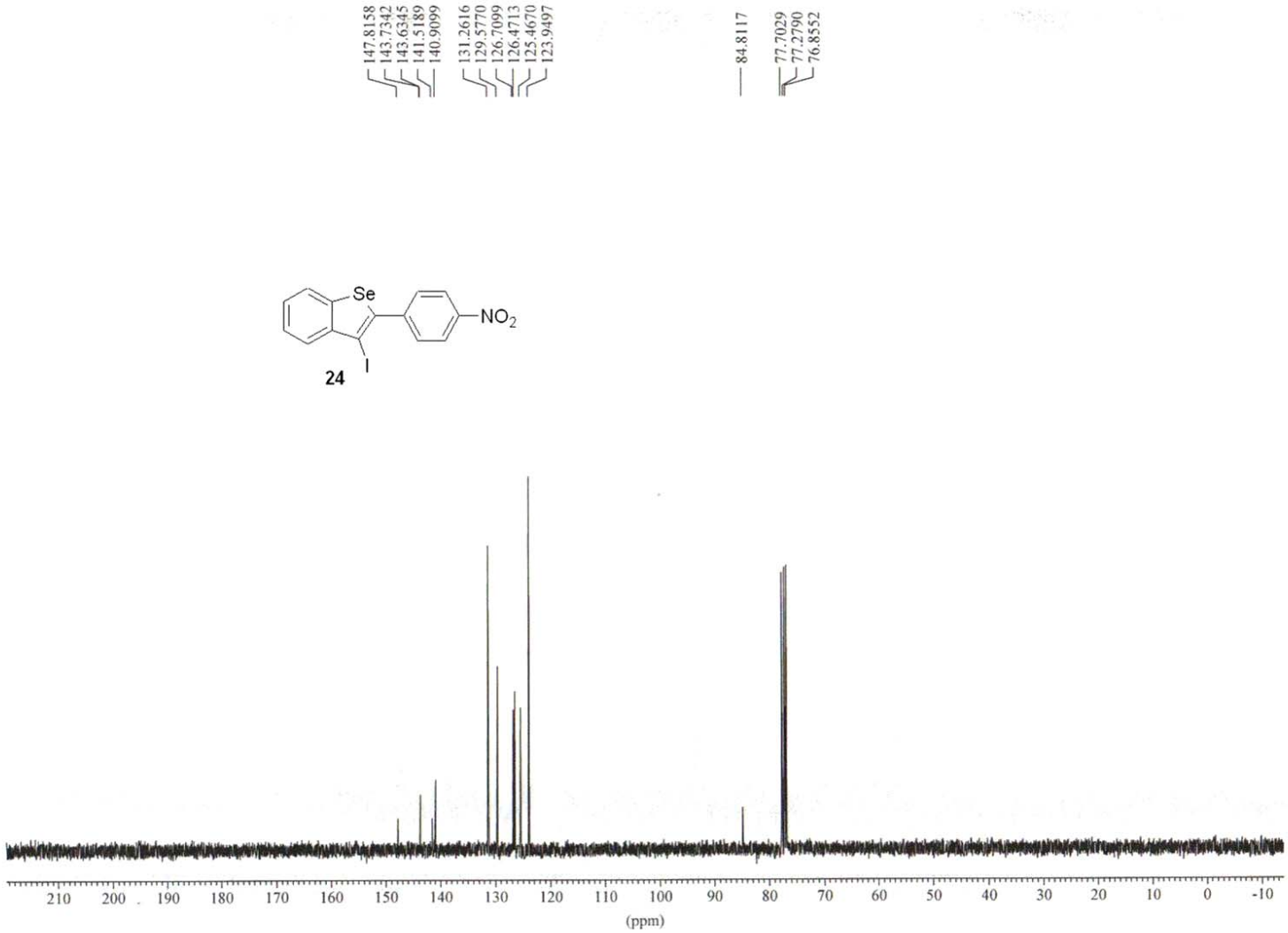

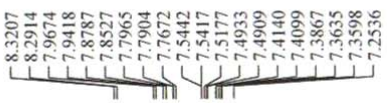

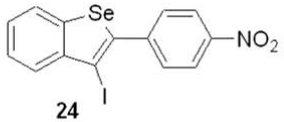

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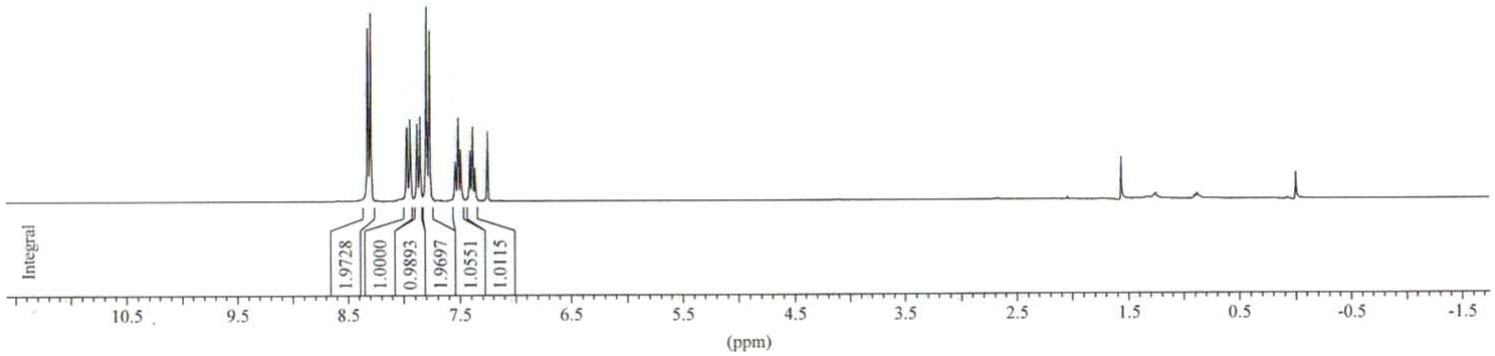

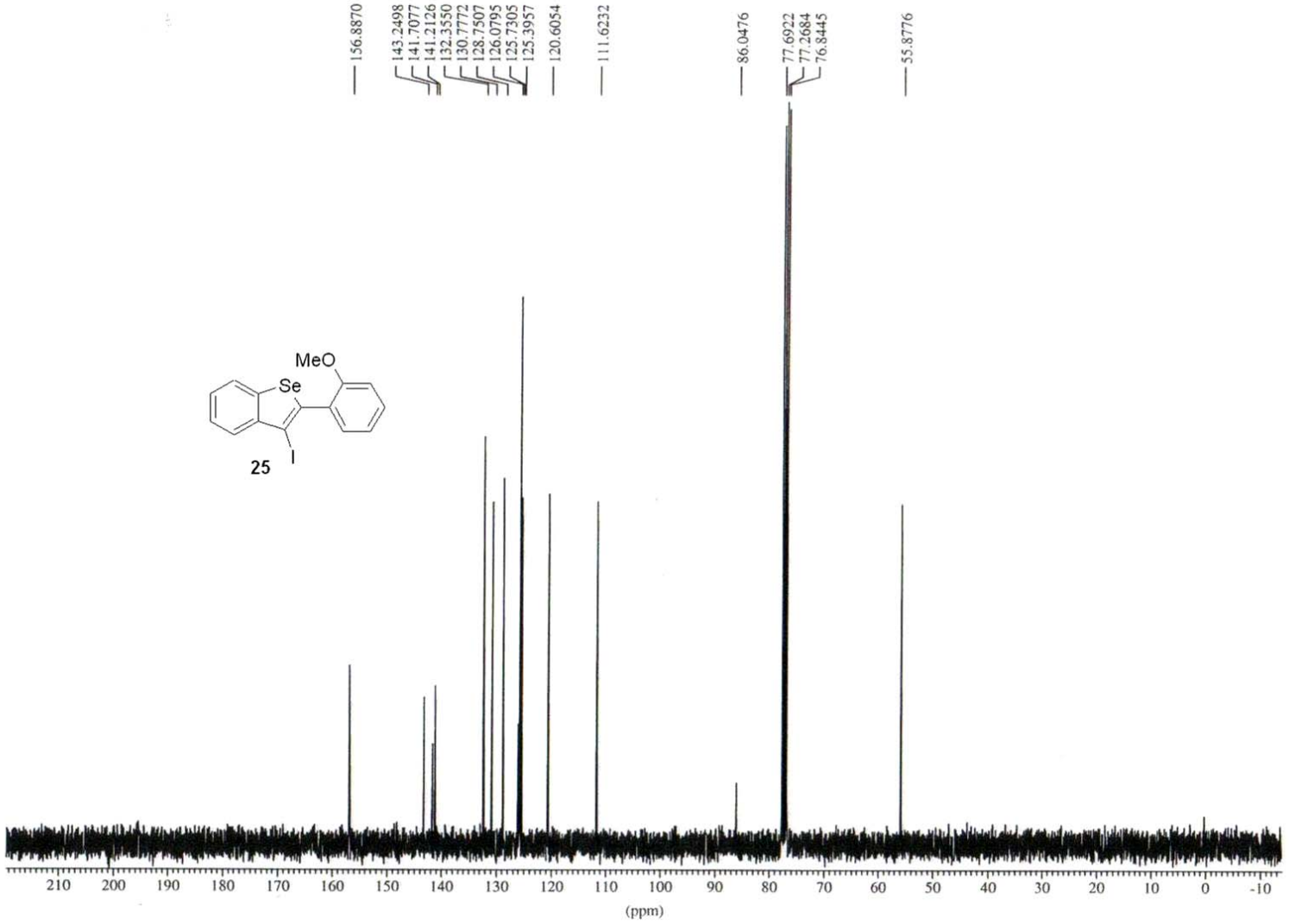

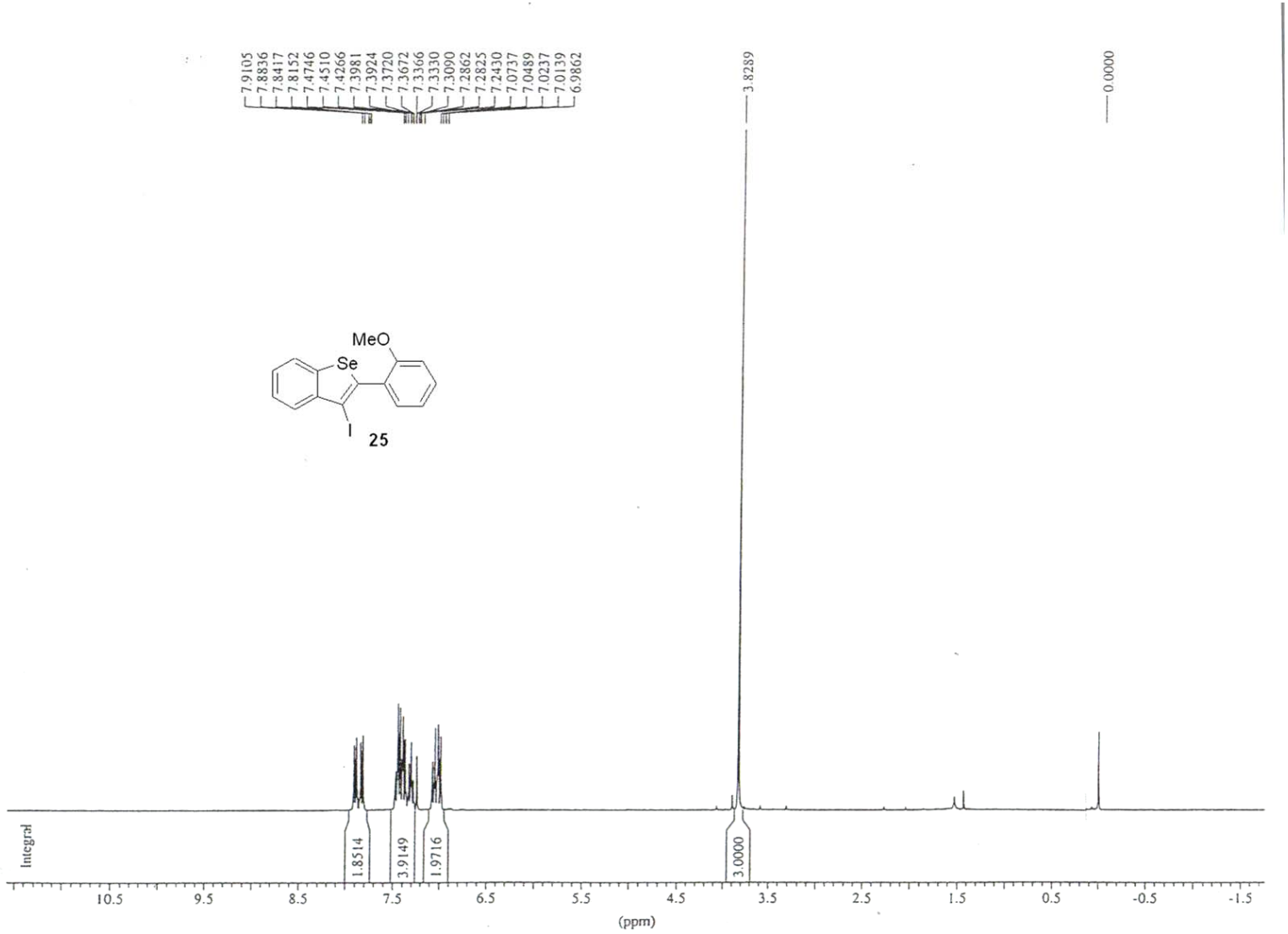

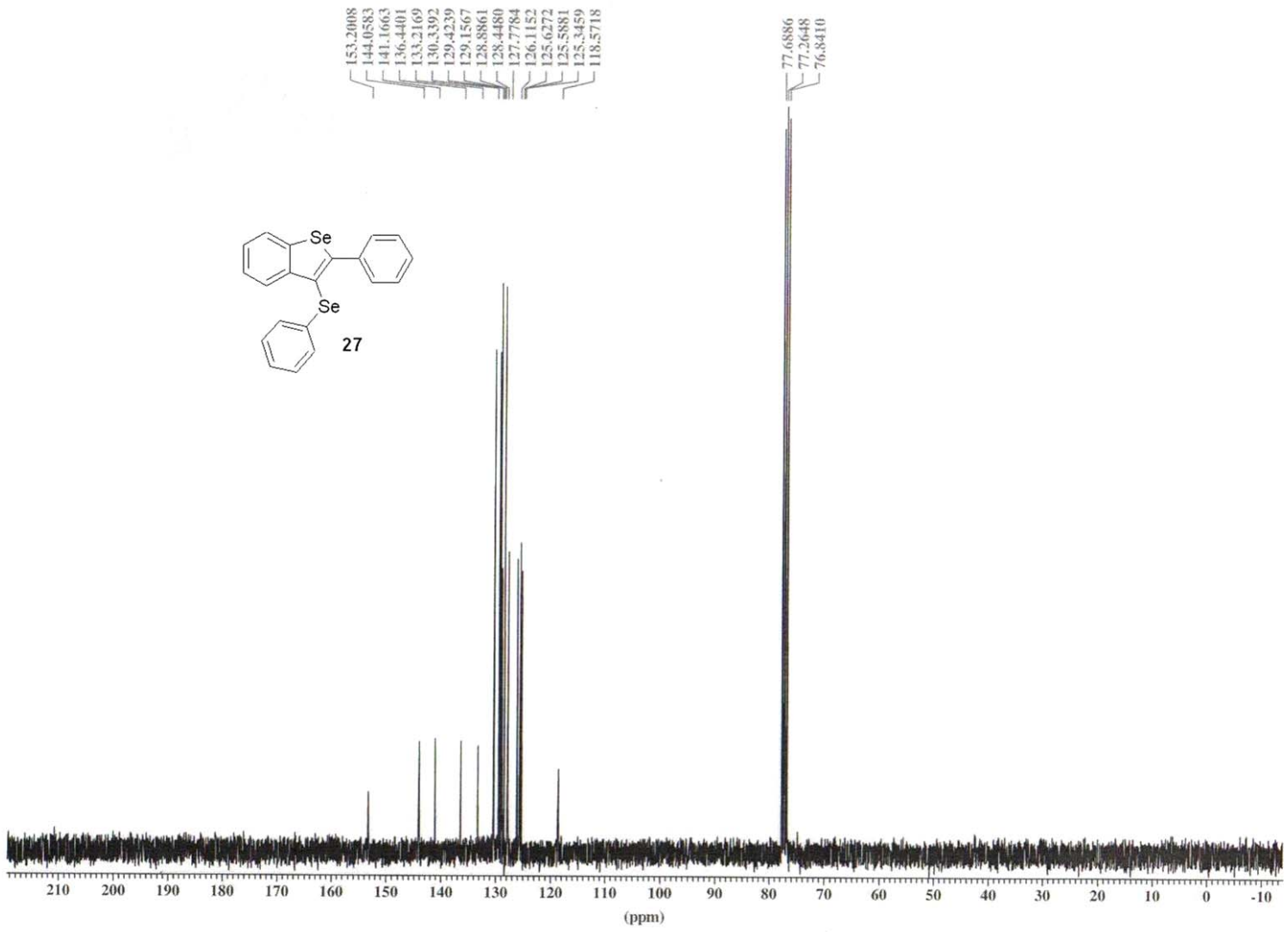

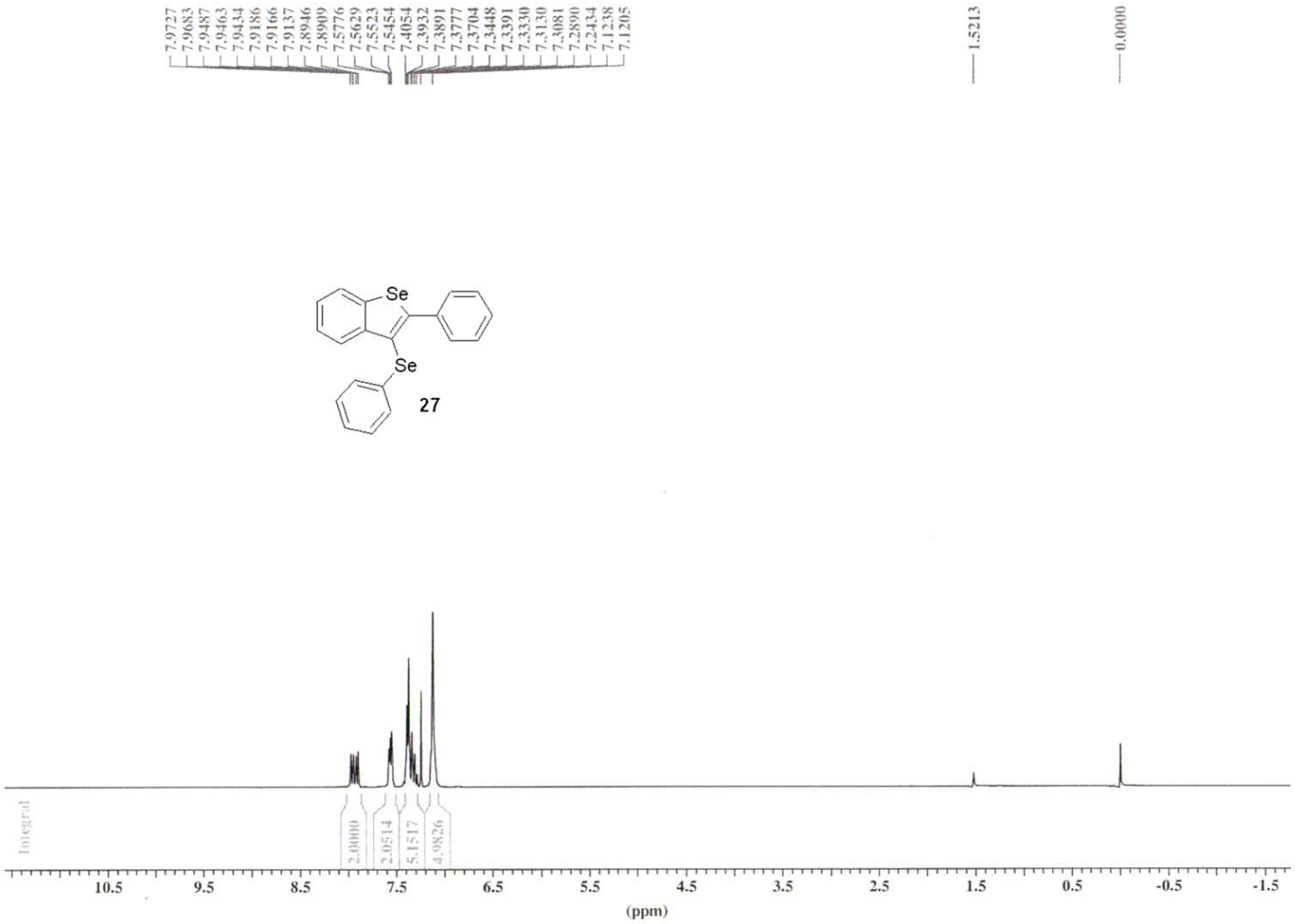

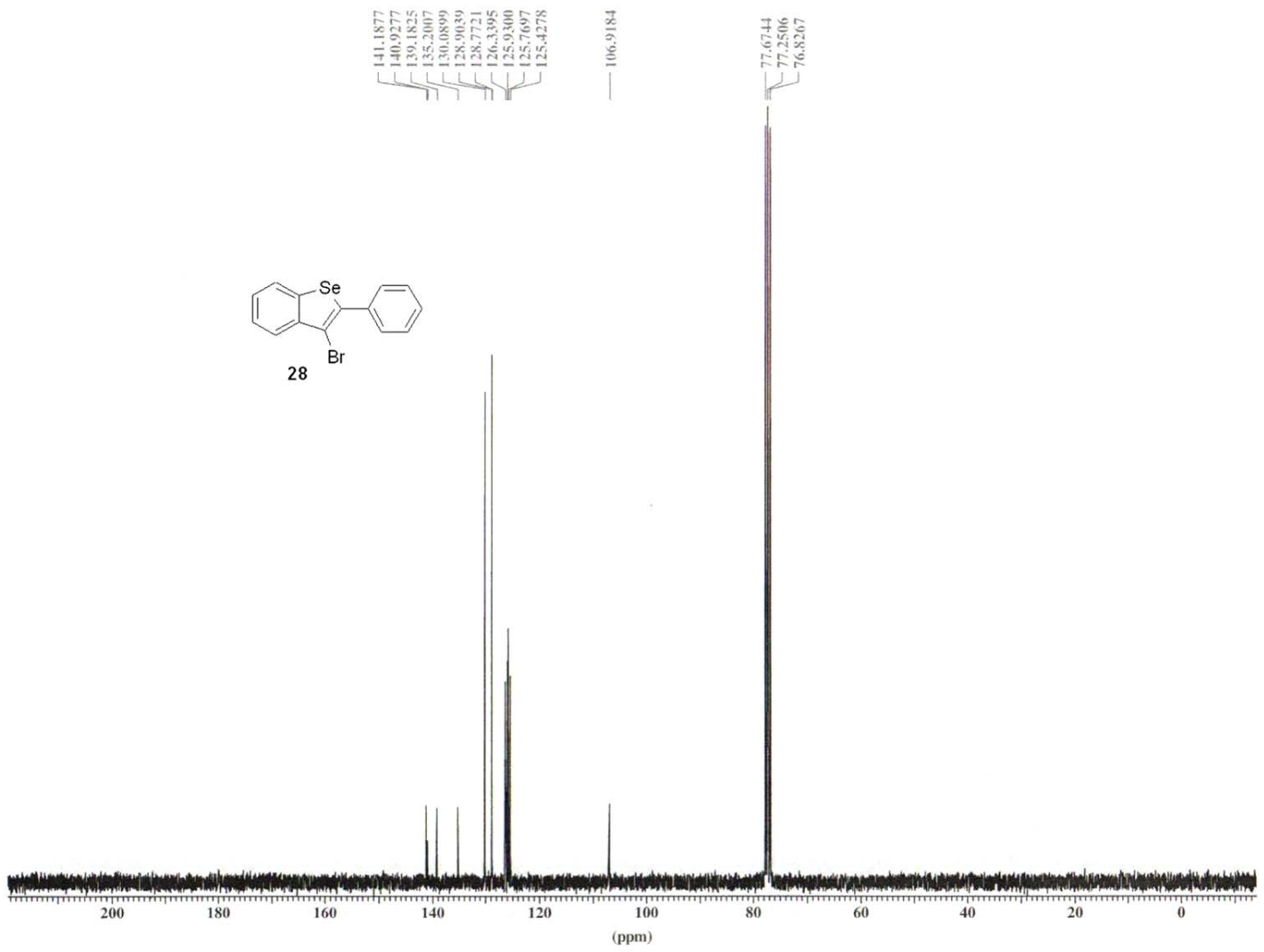

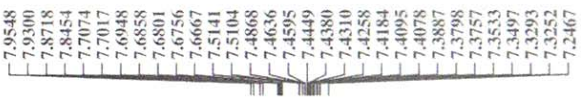

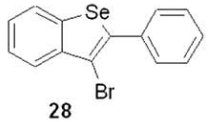

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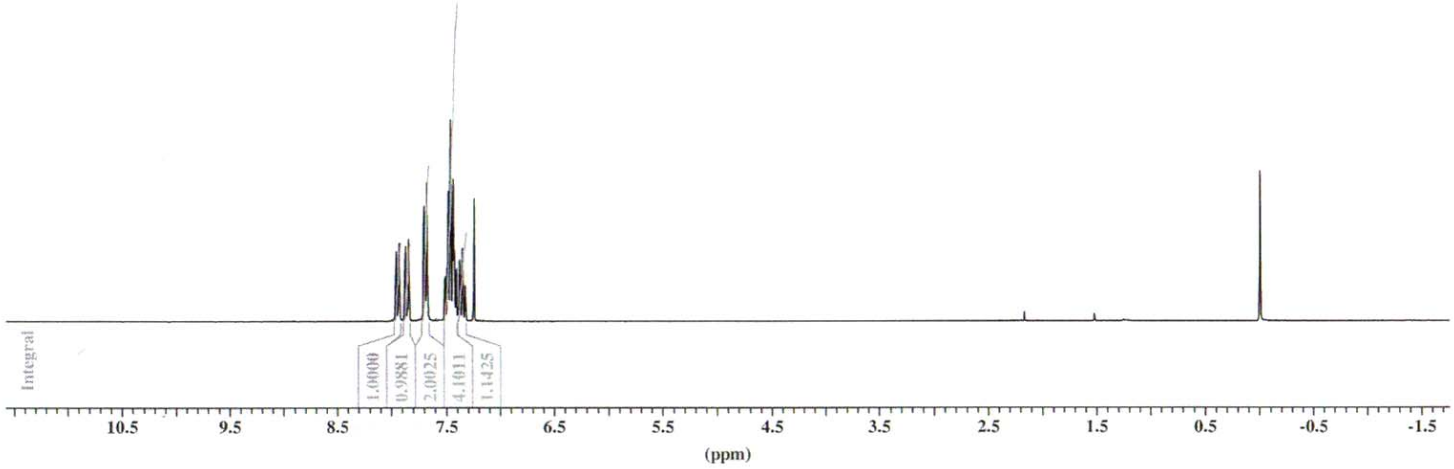

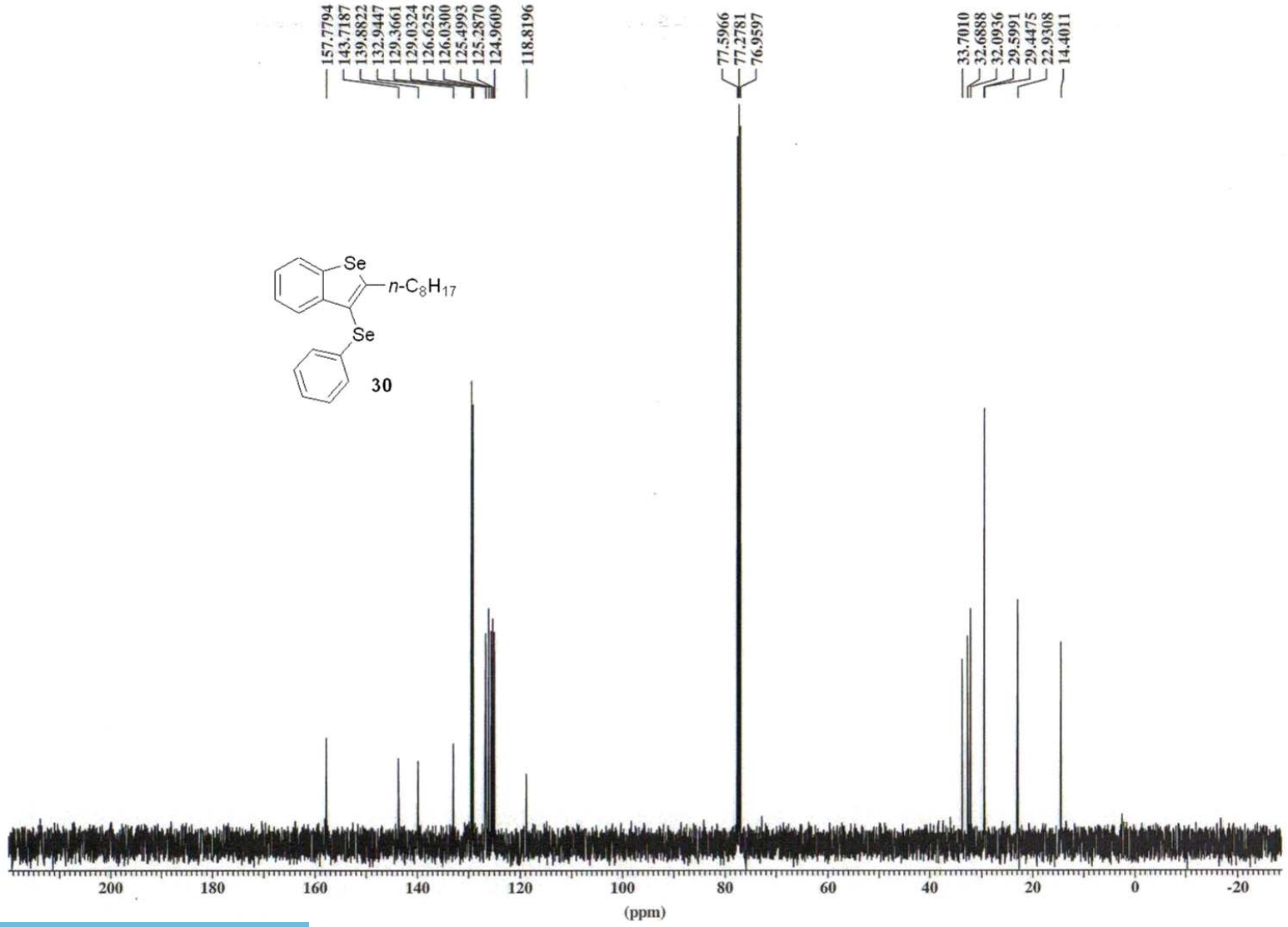

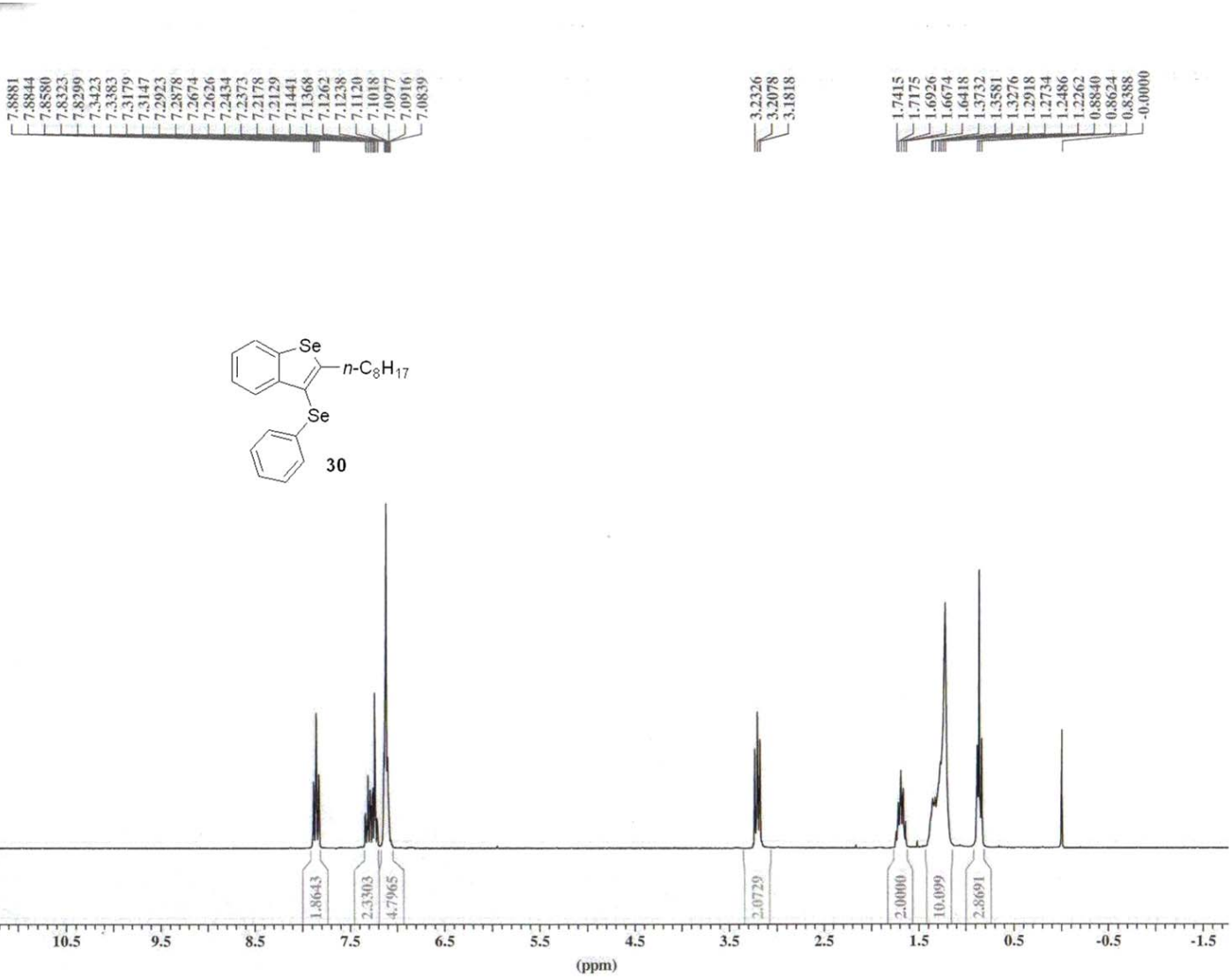

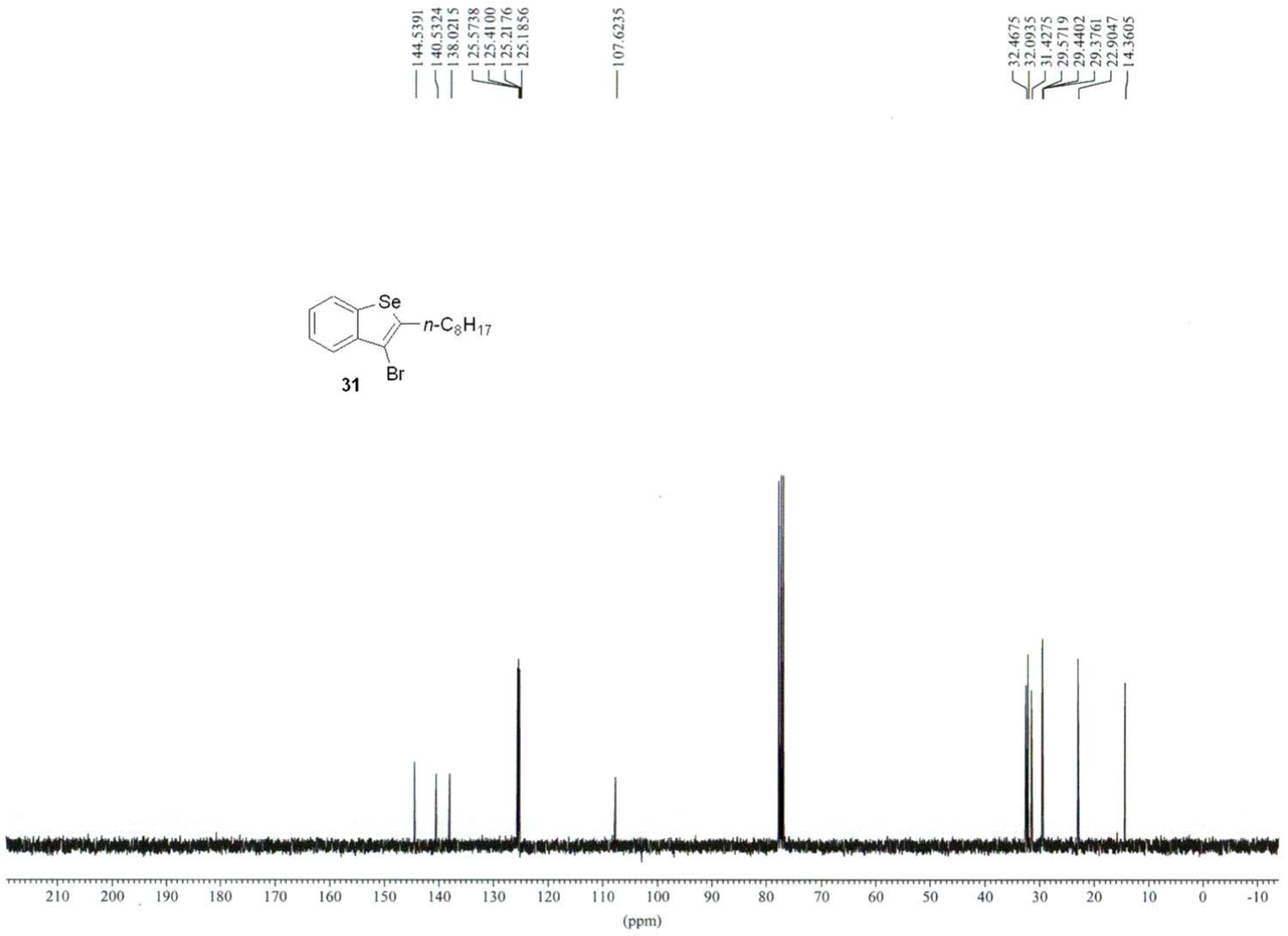

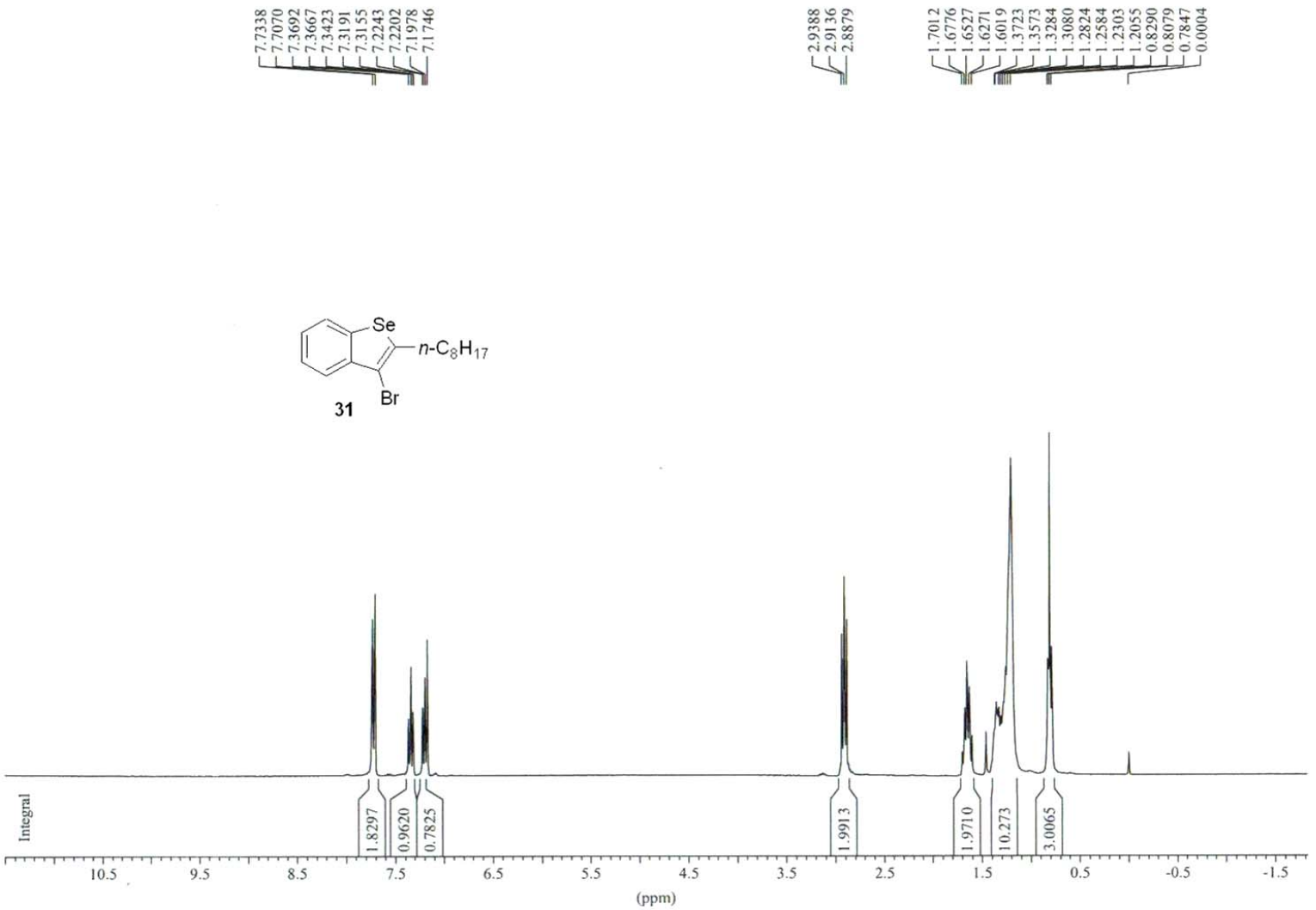

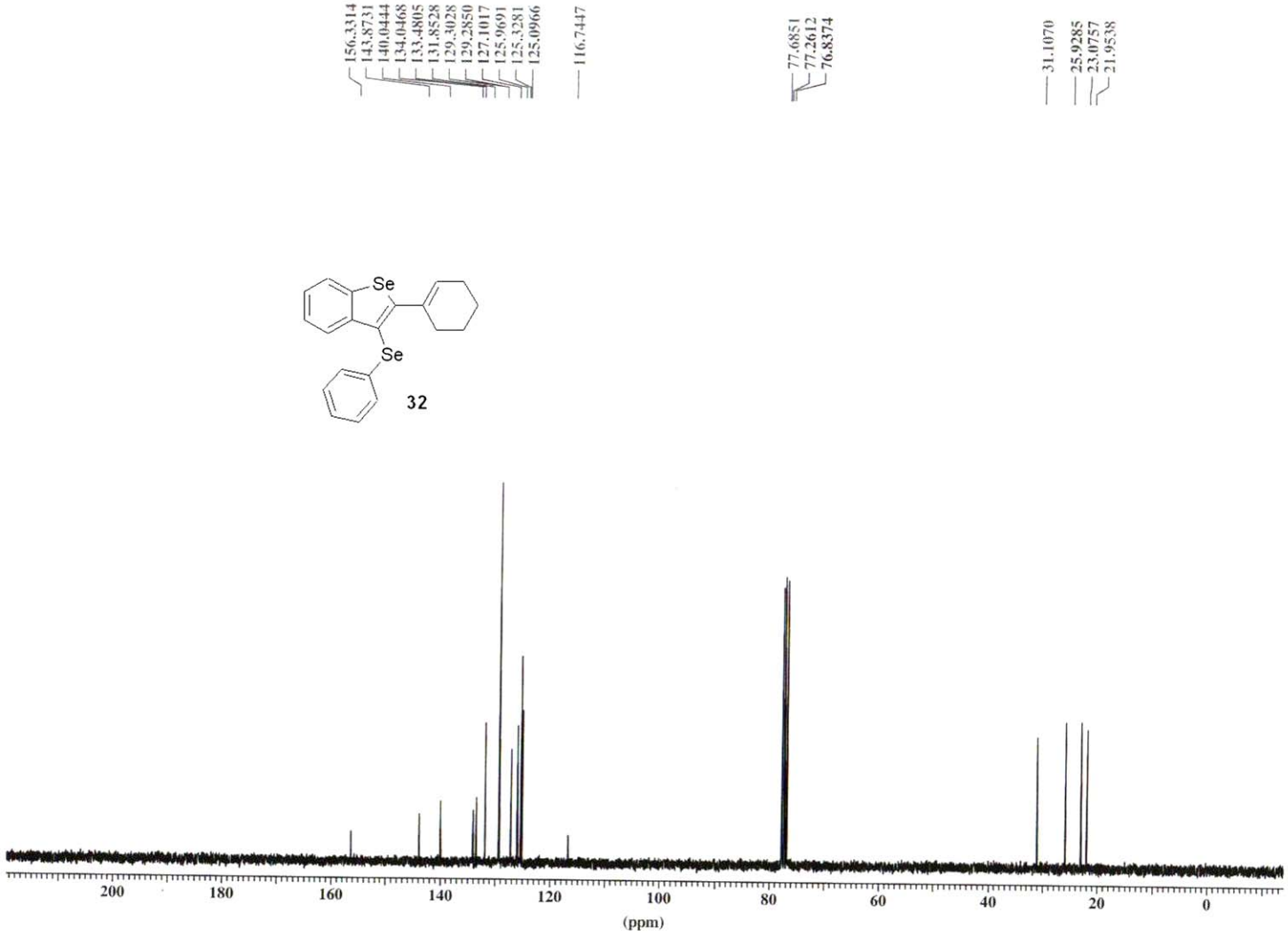

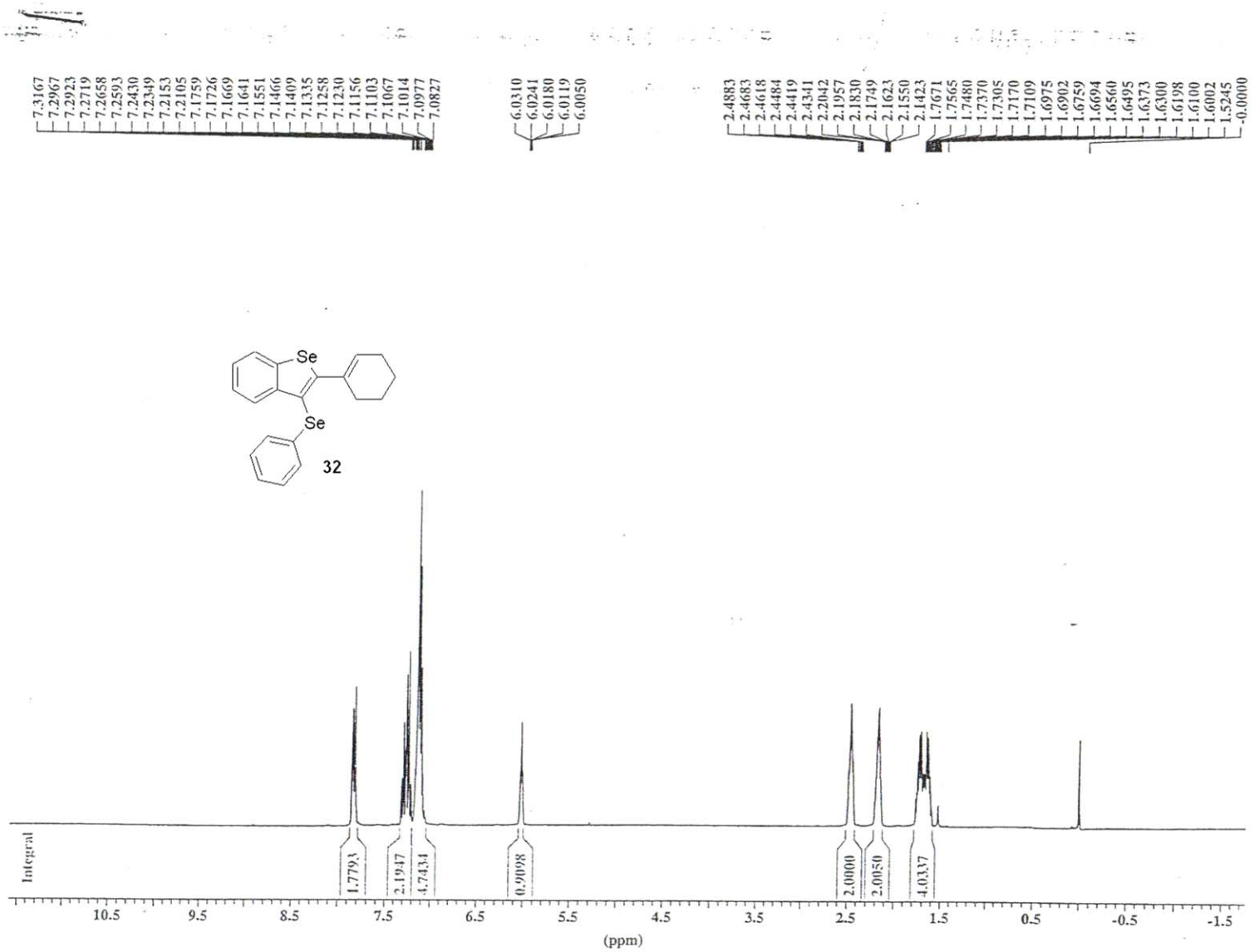

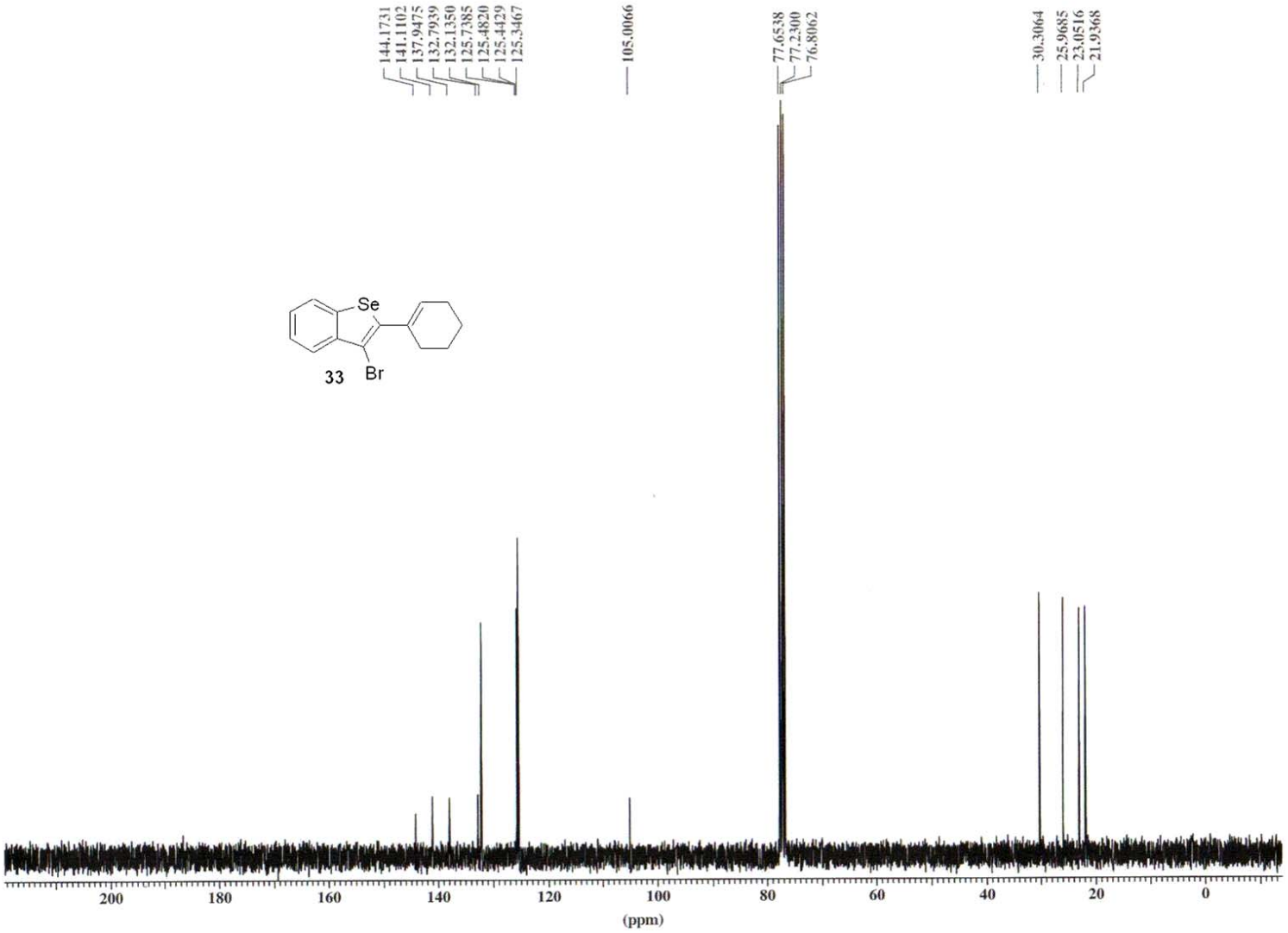

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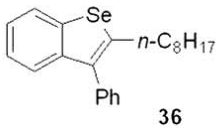

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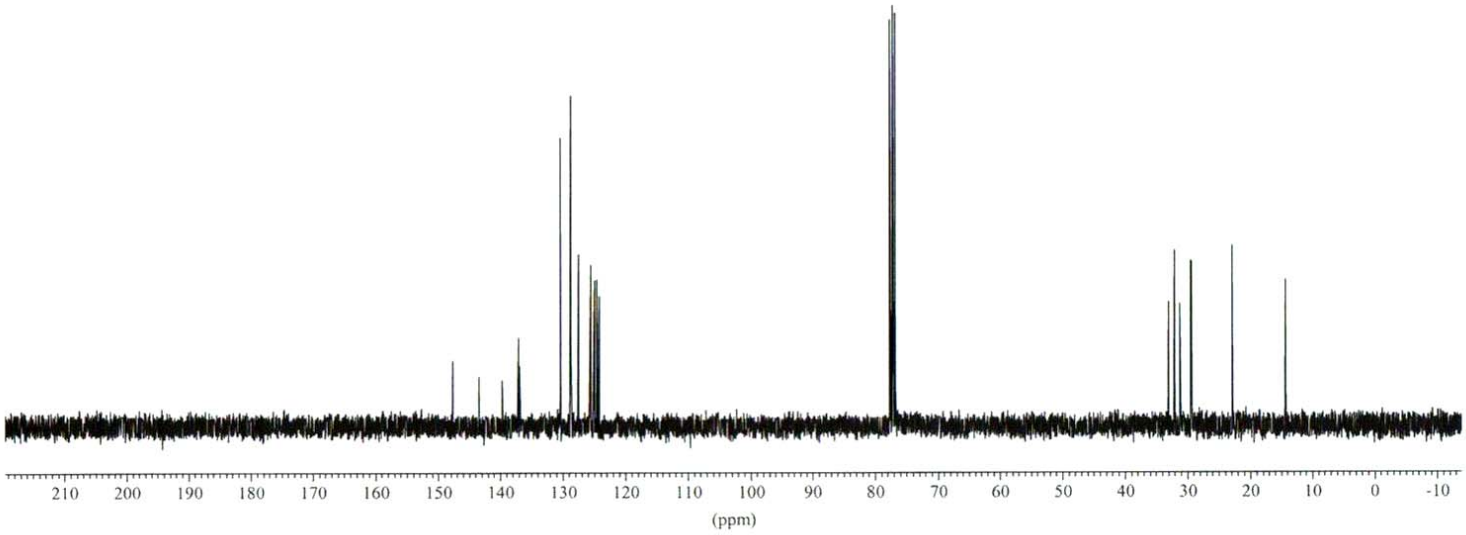

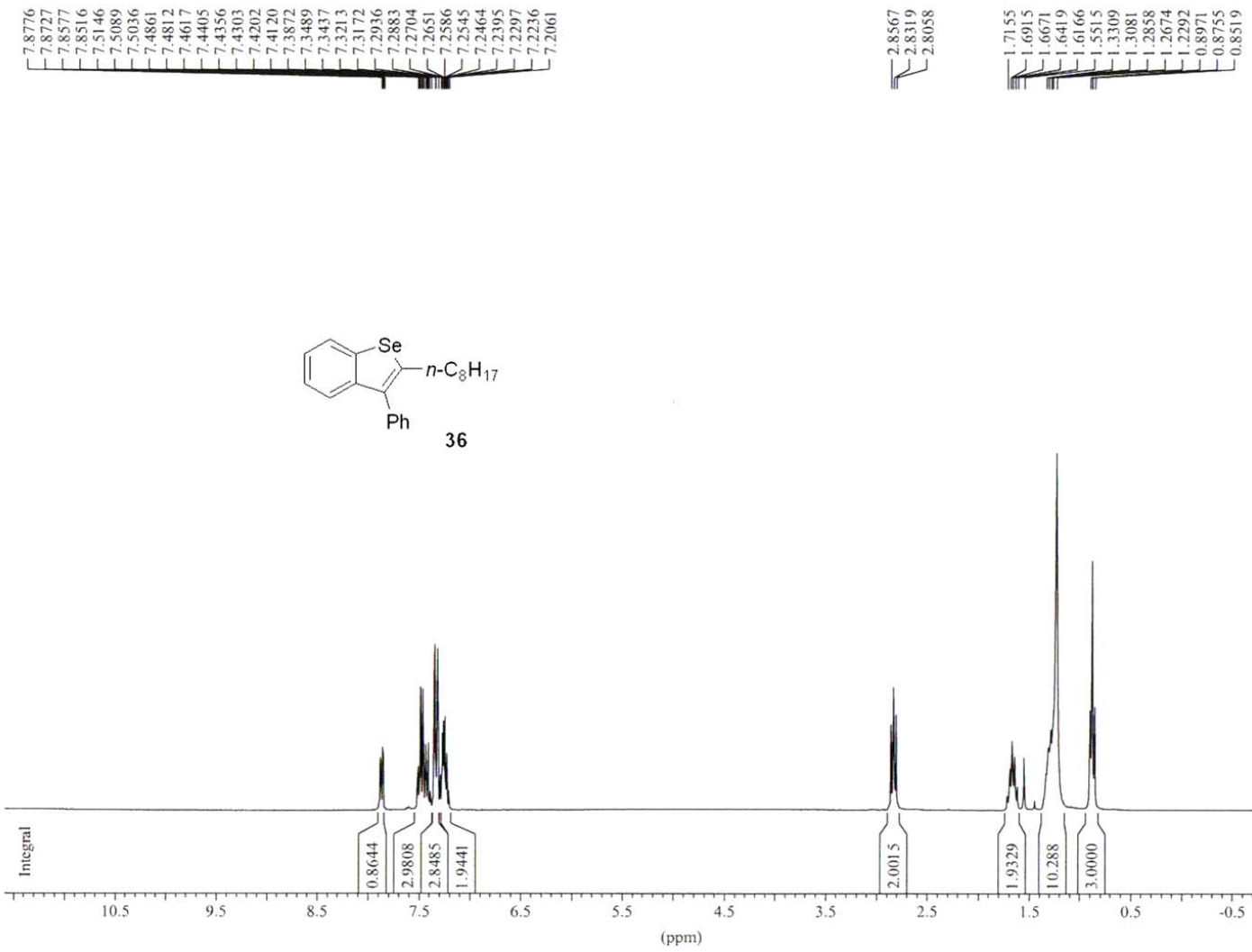

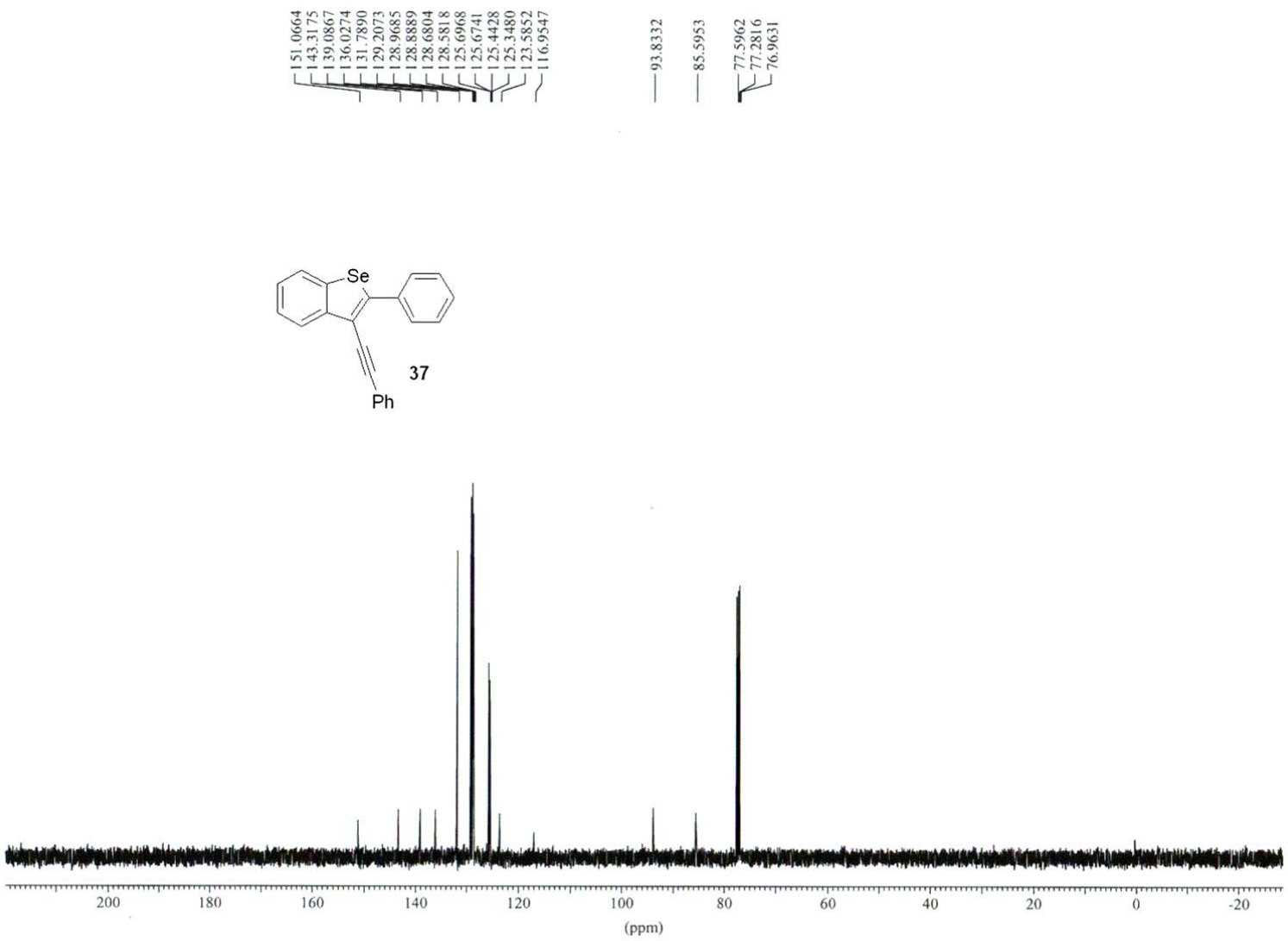

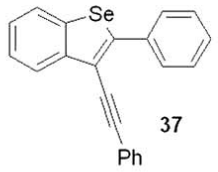

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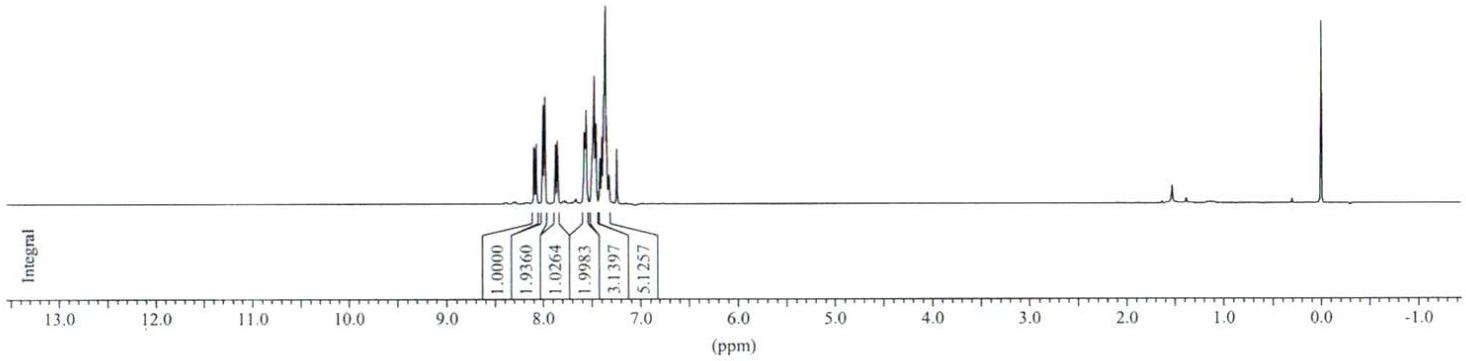
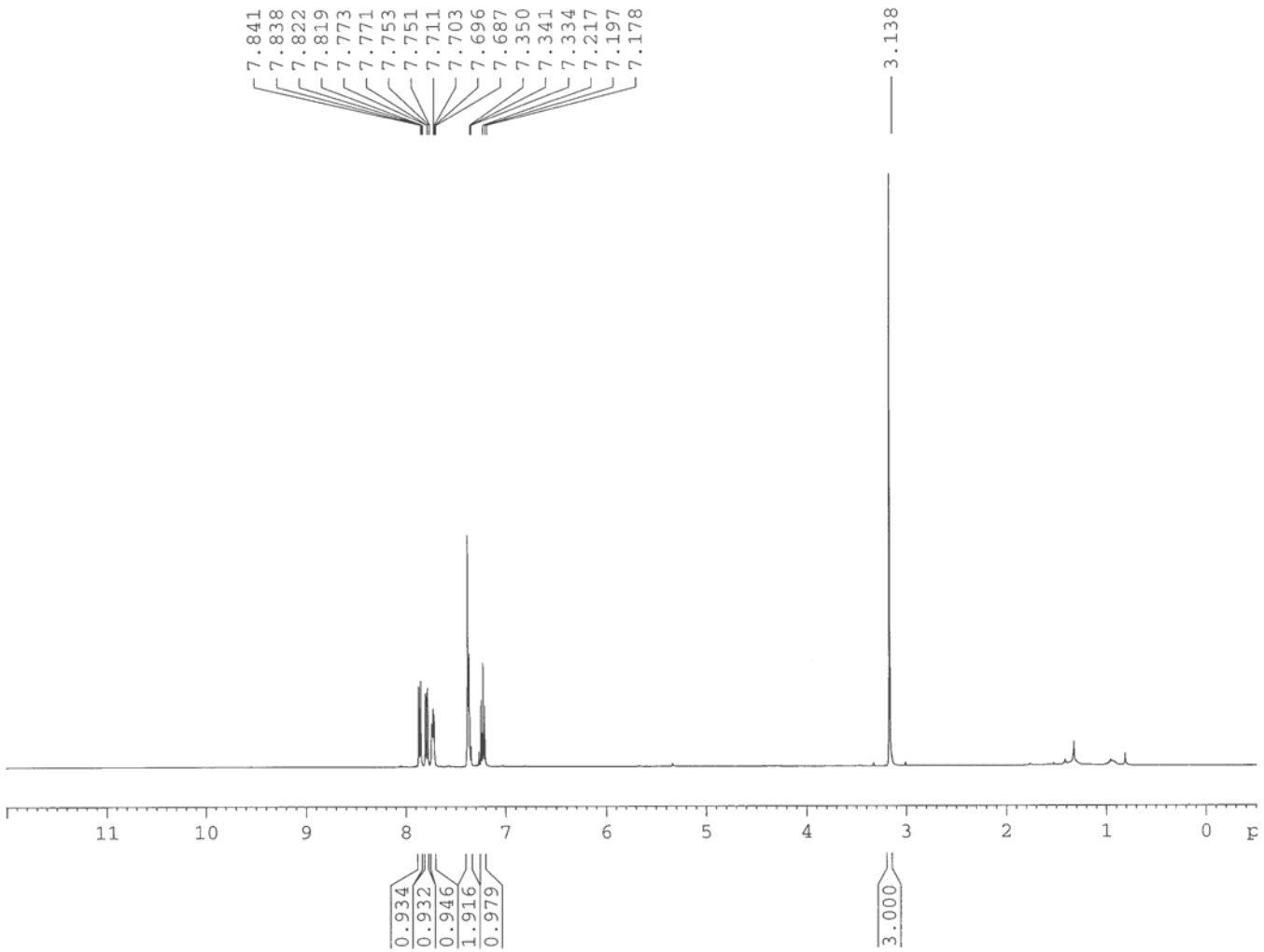
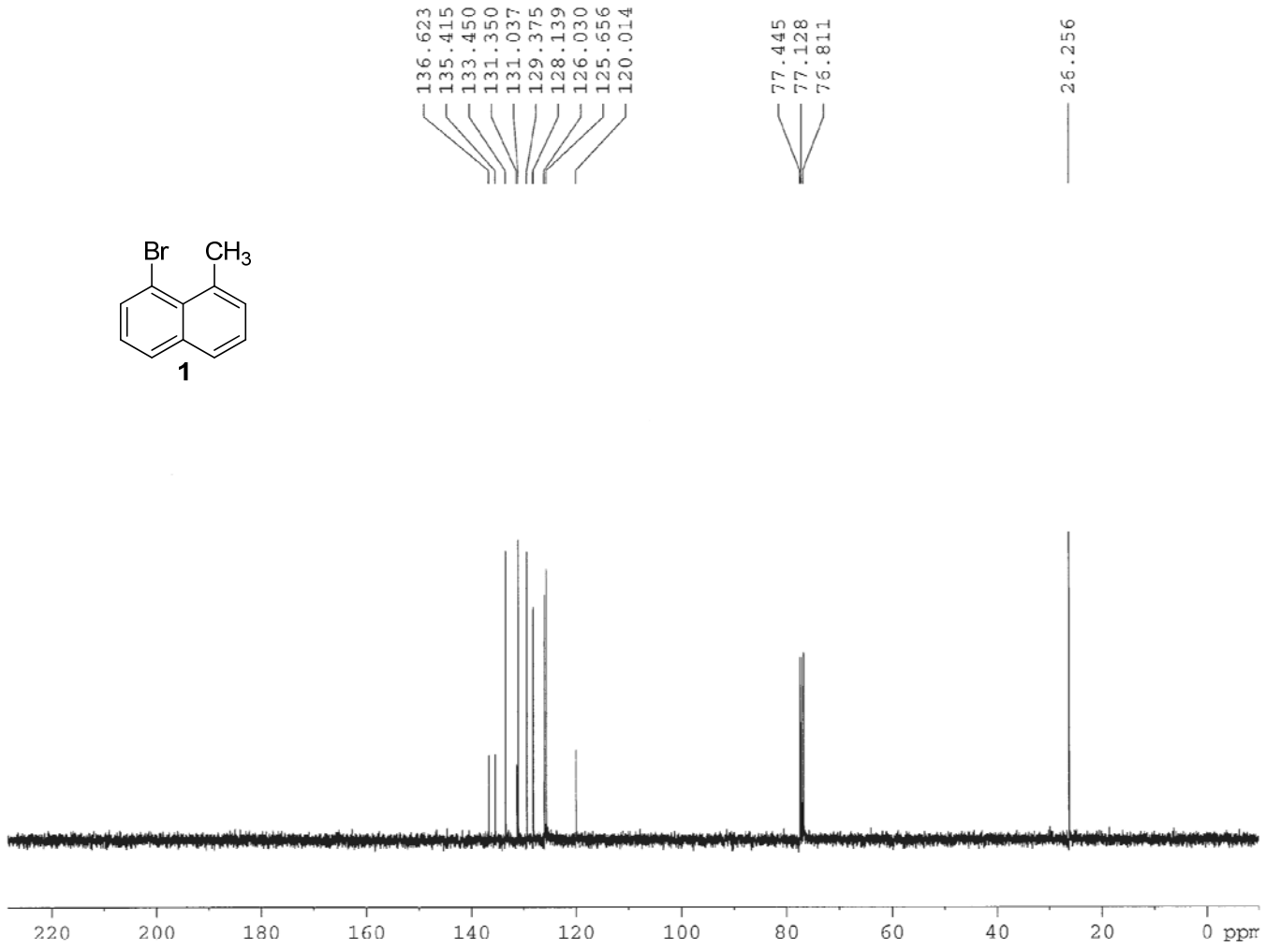
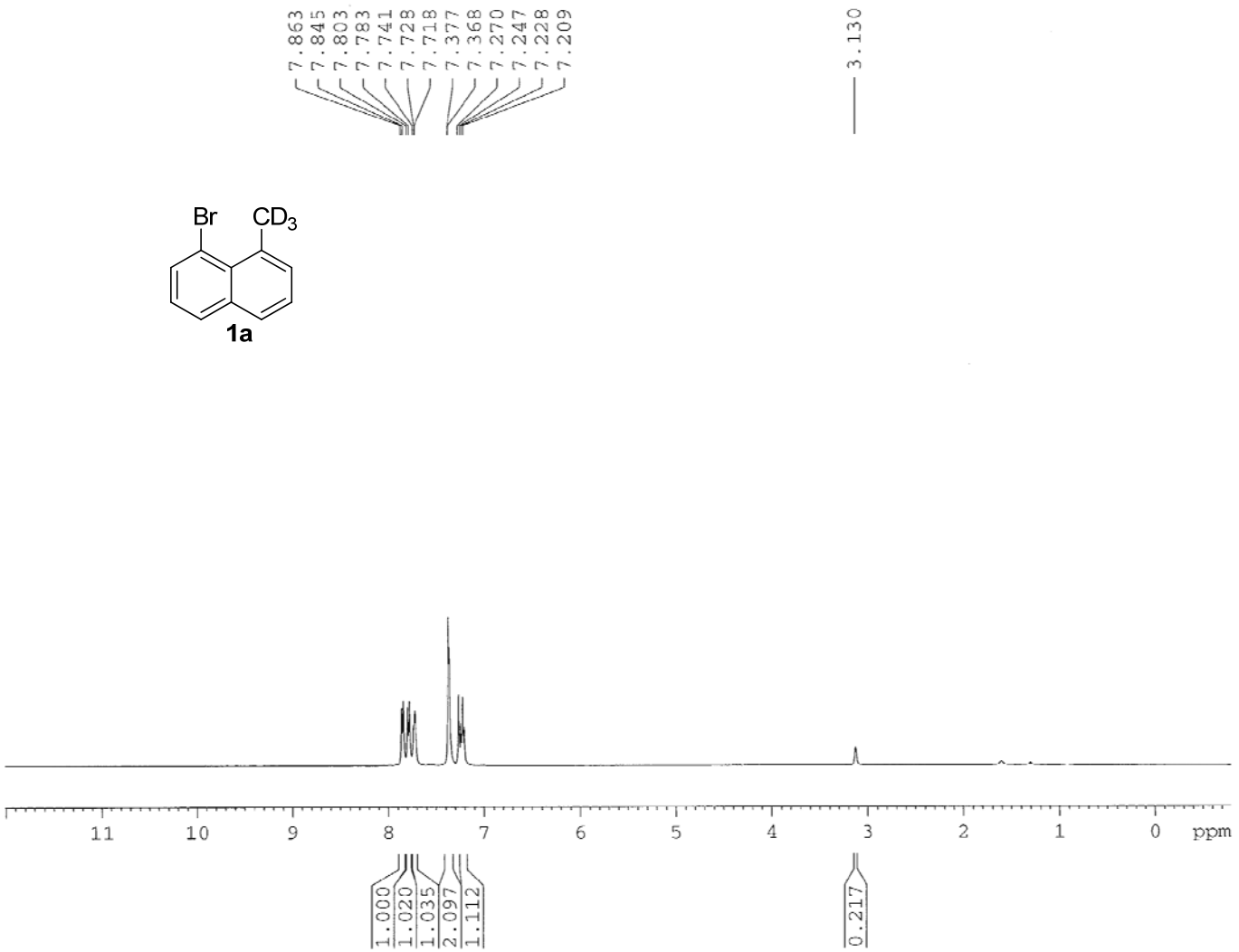
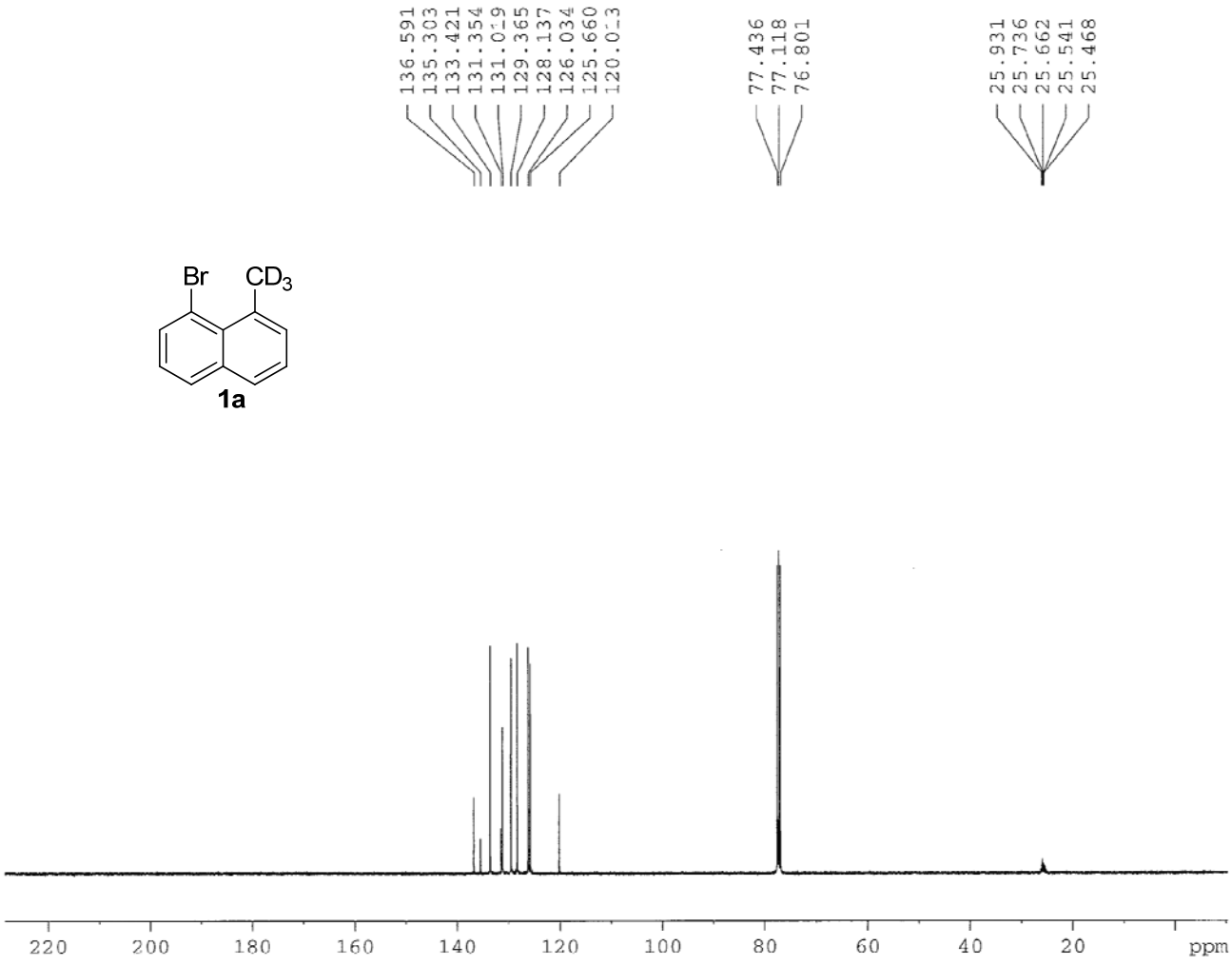


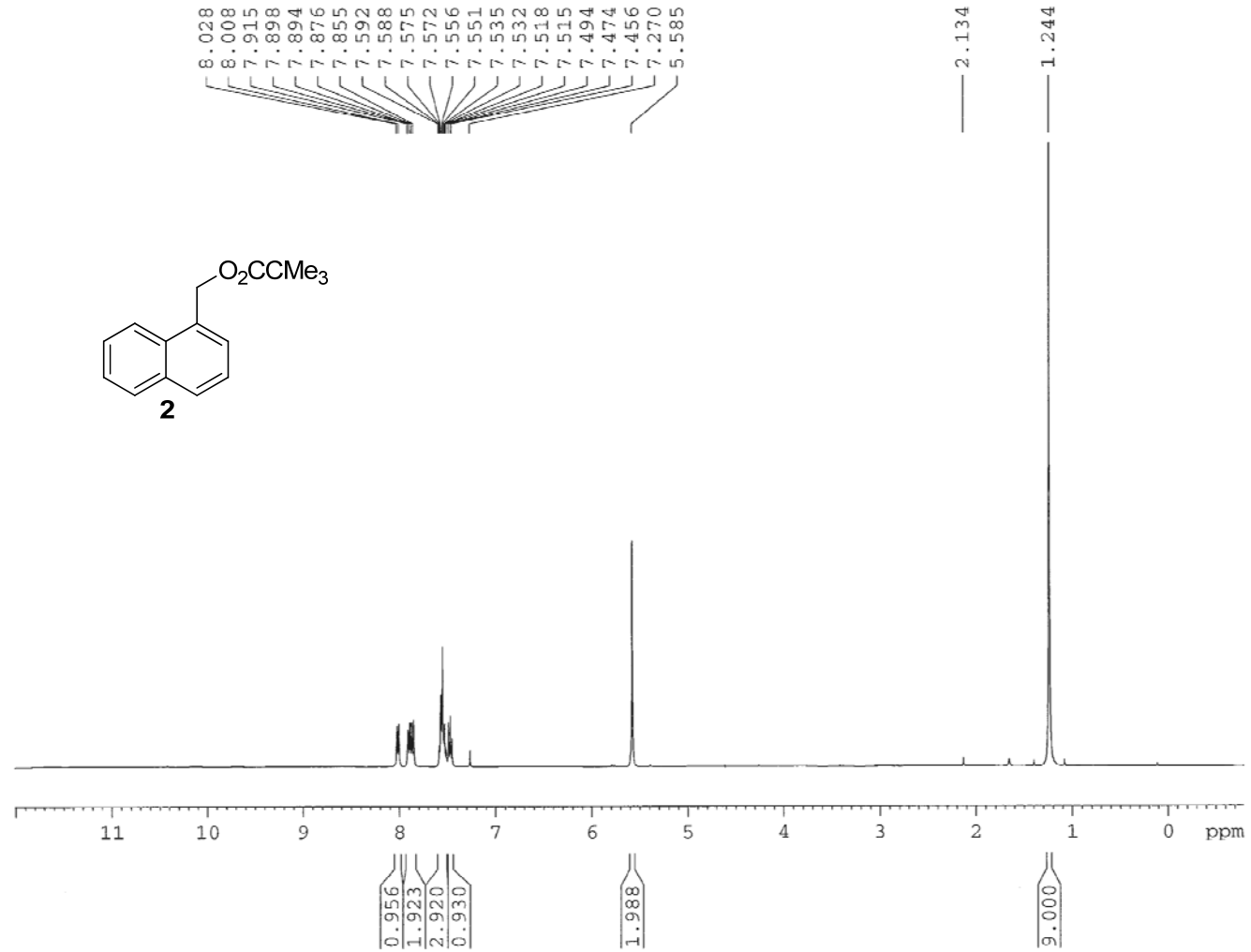
APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

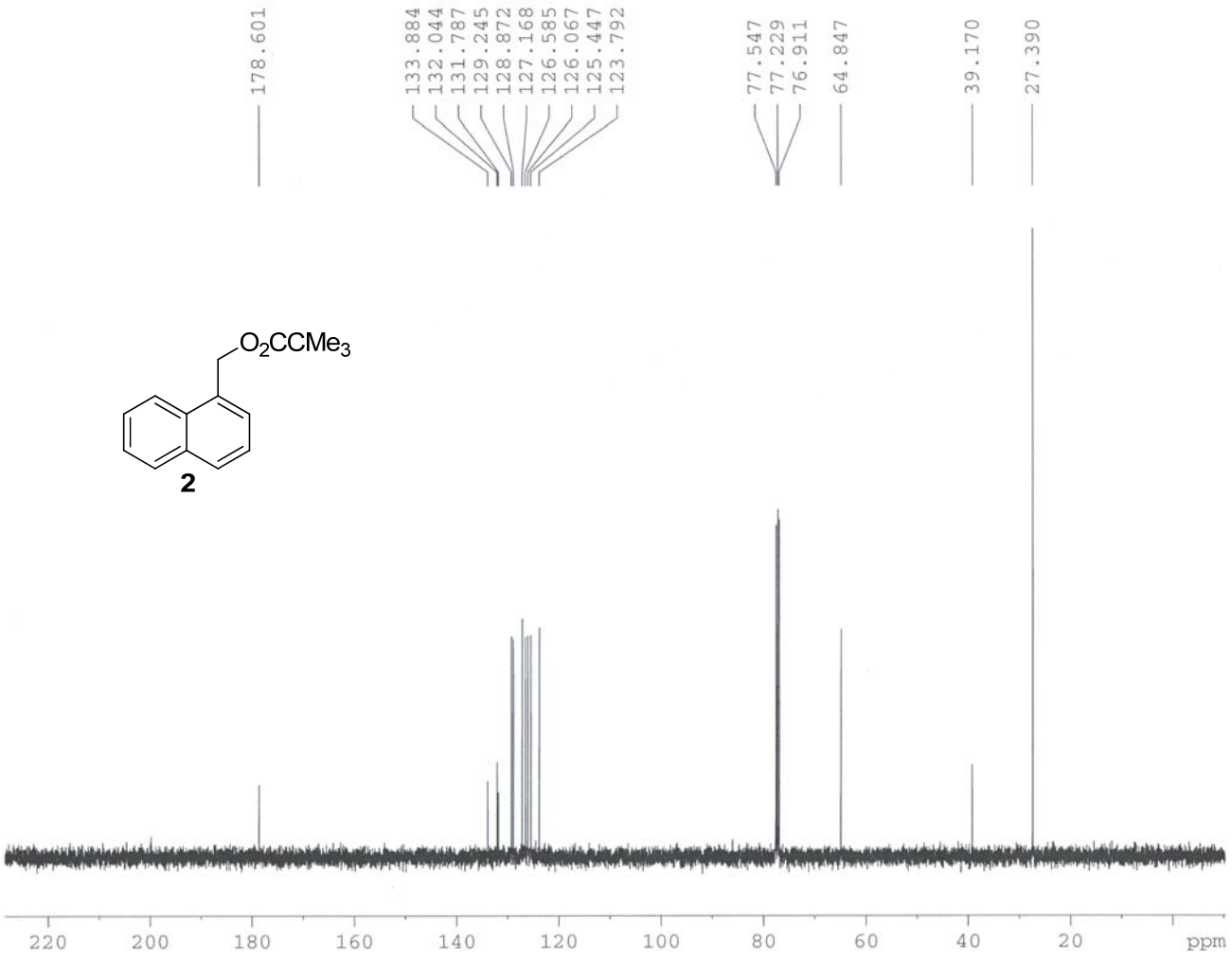


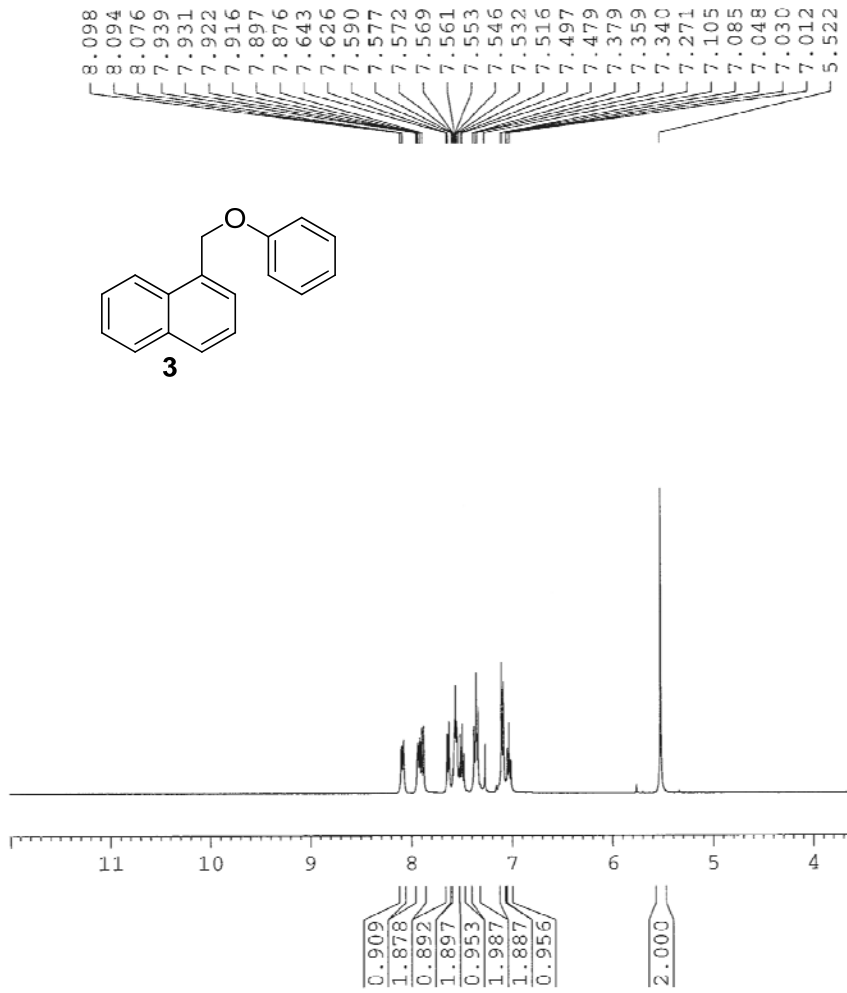


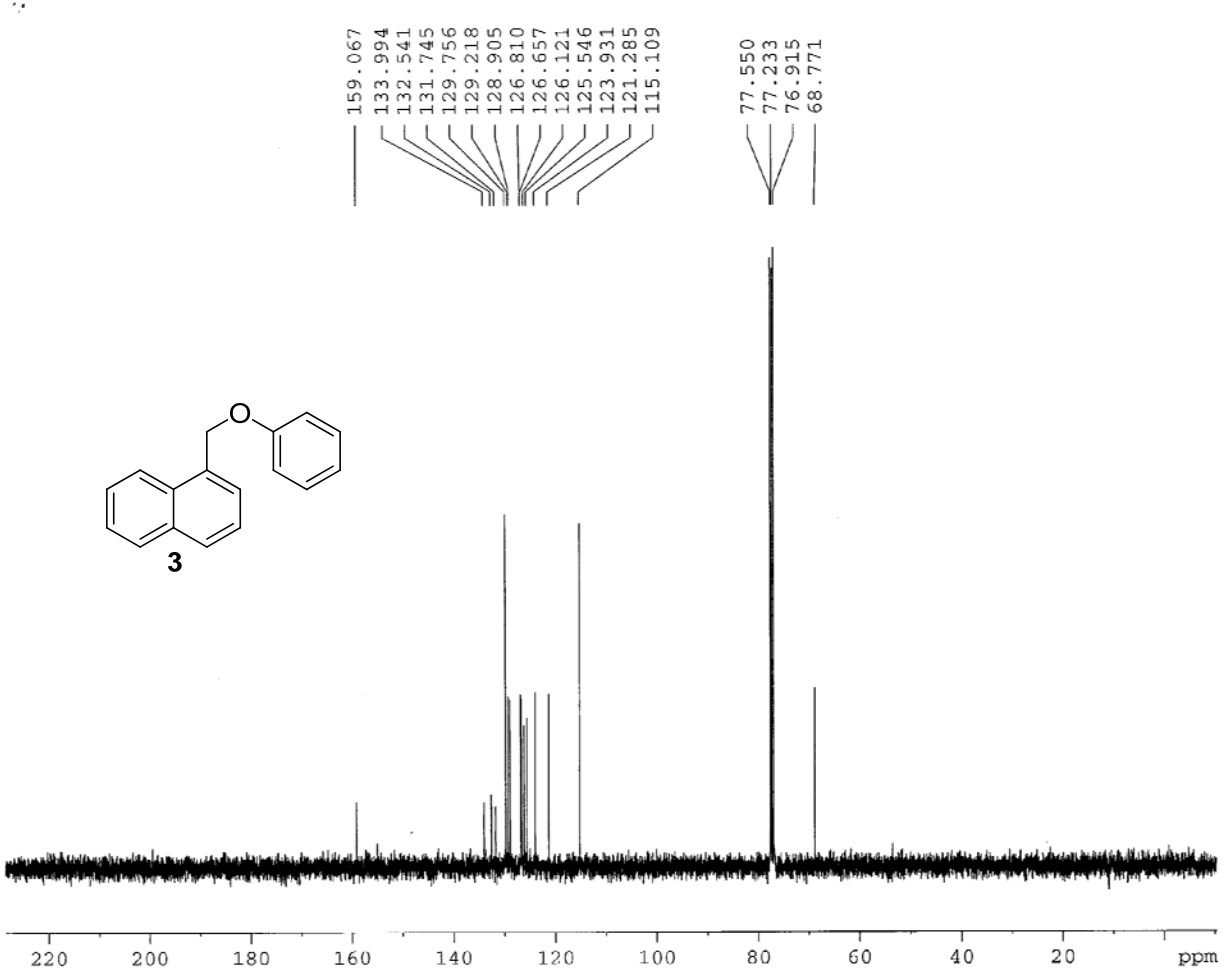


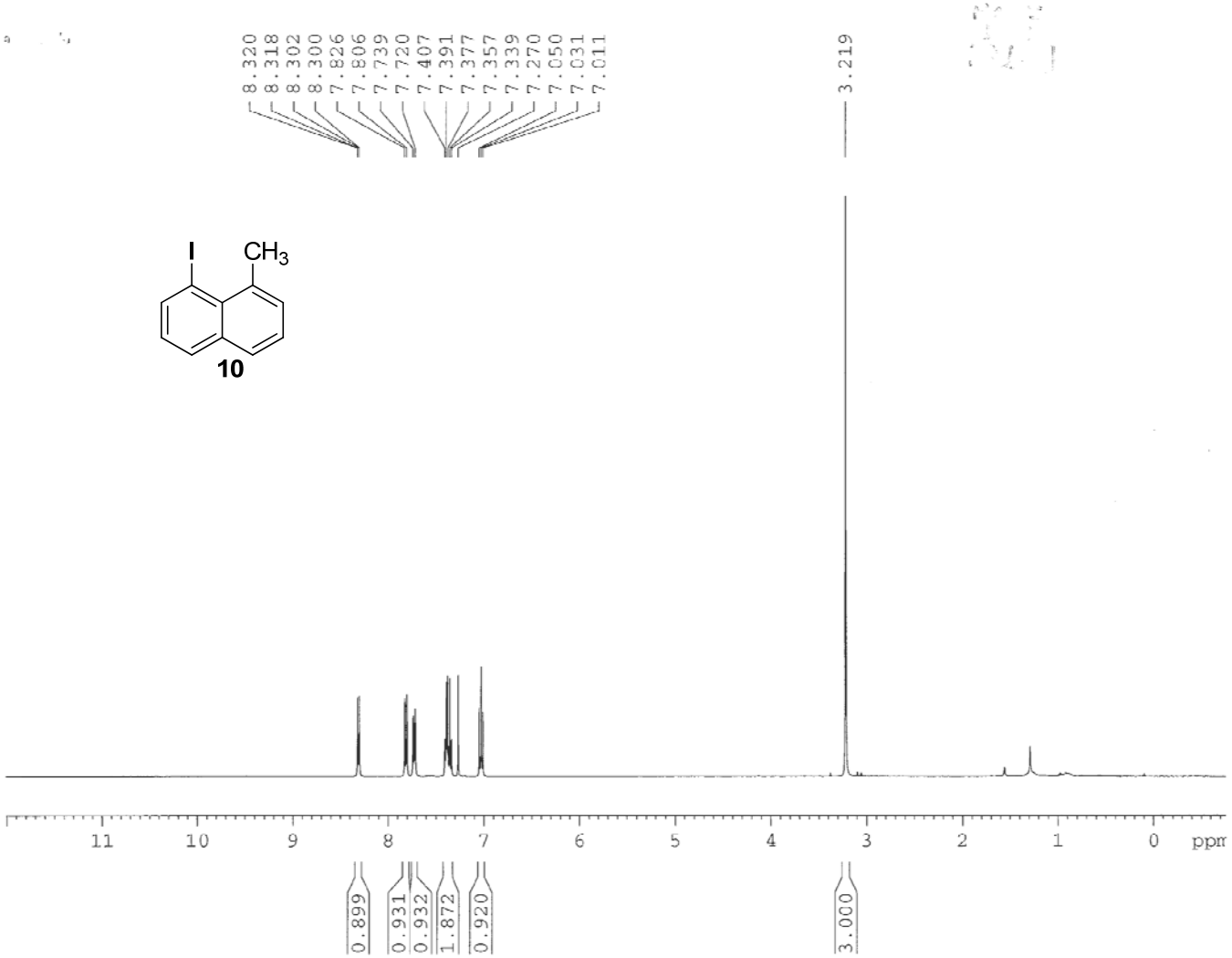


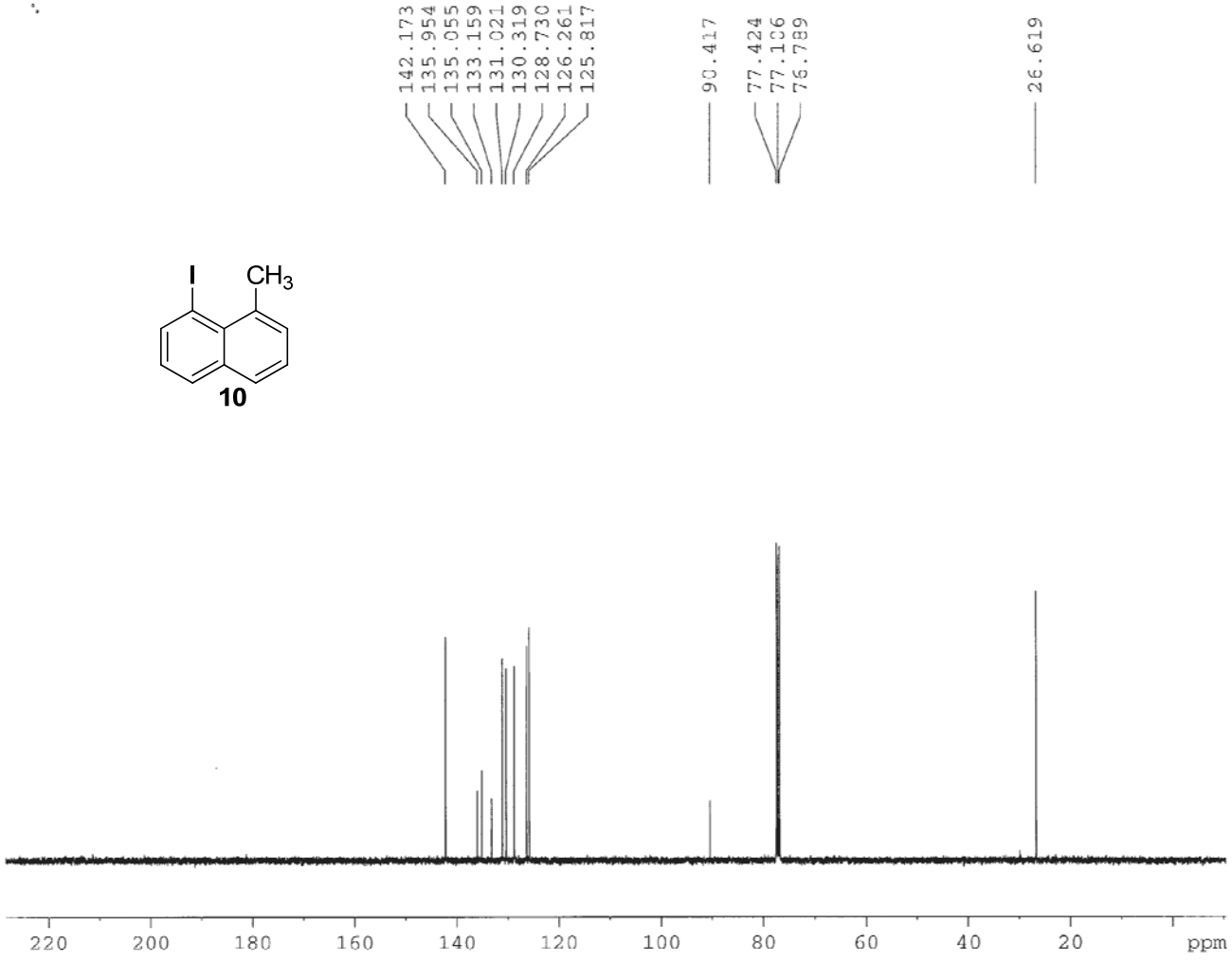


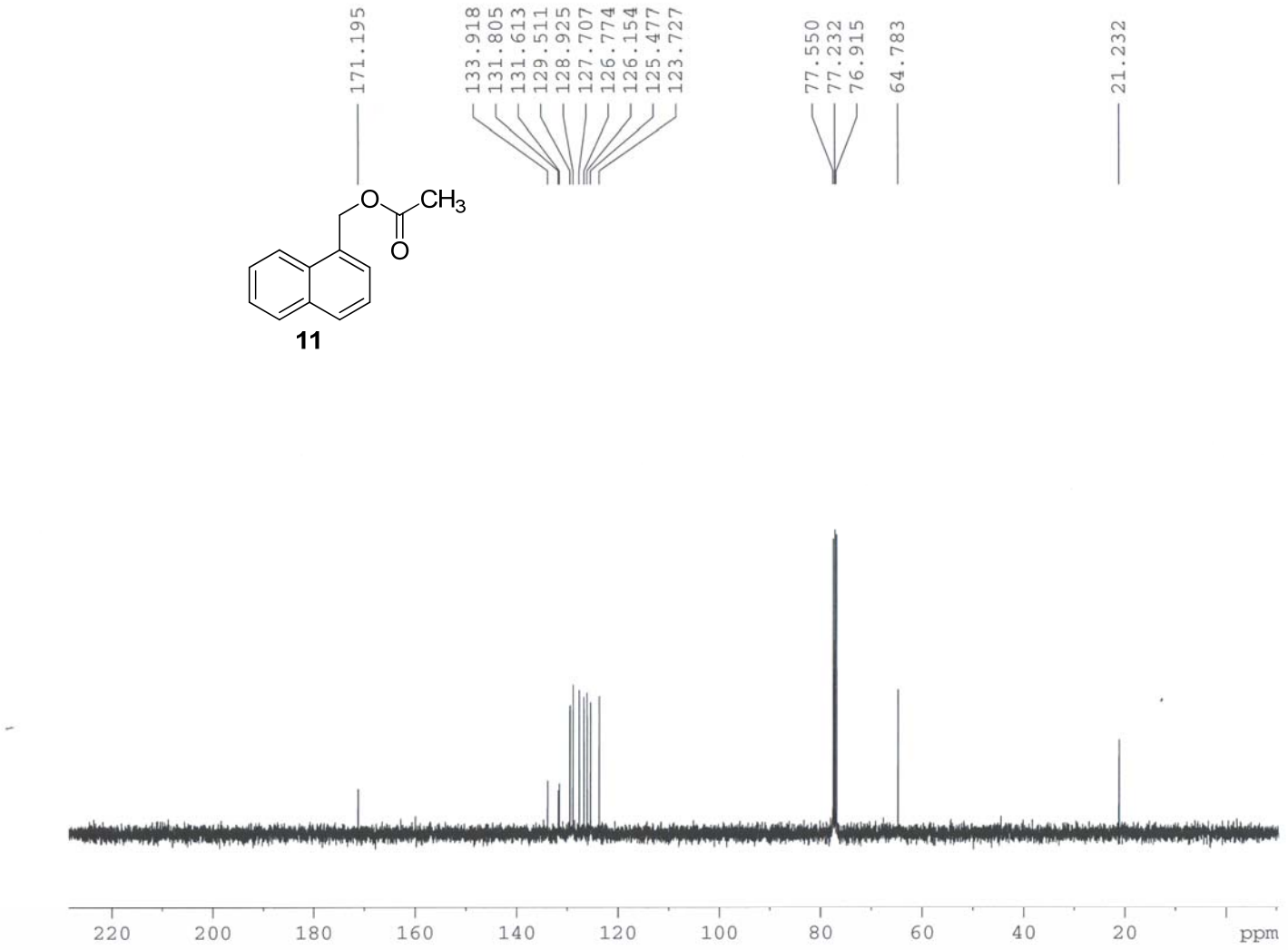


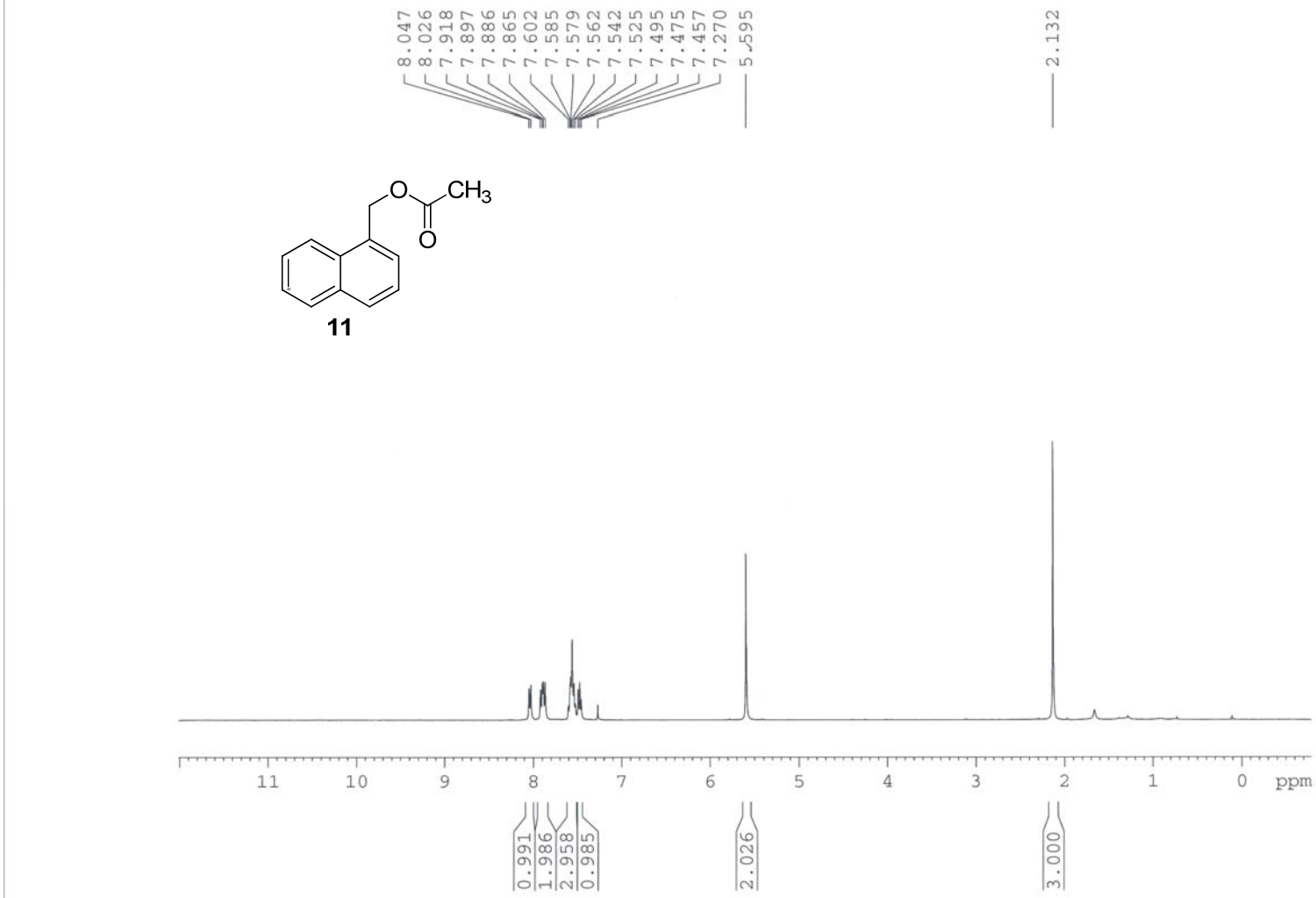


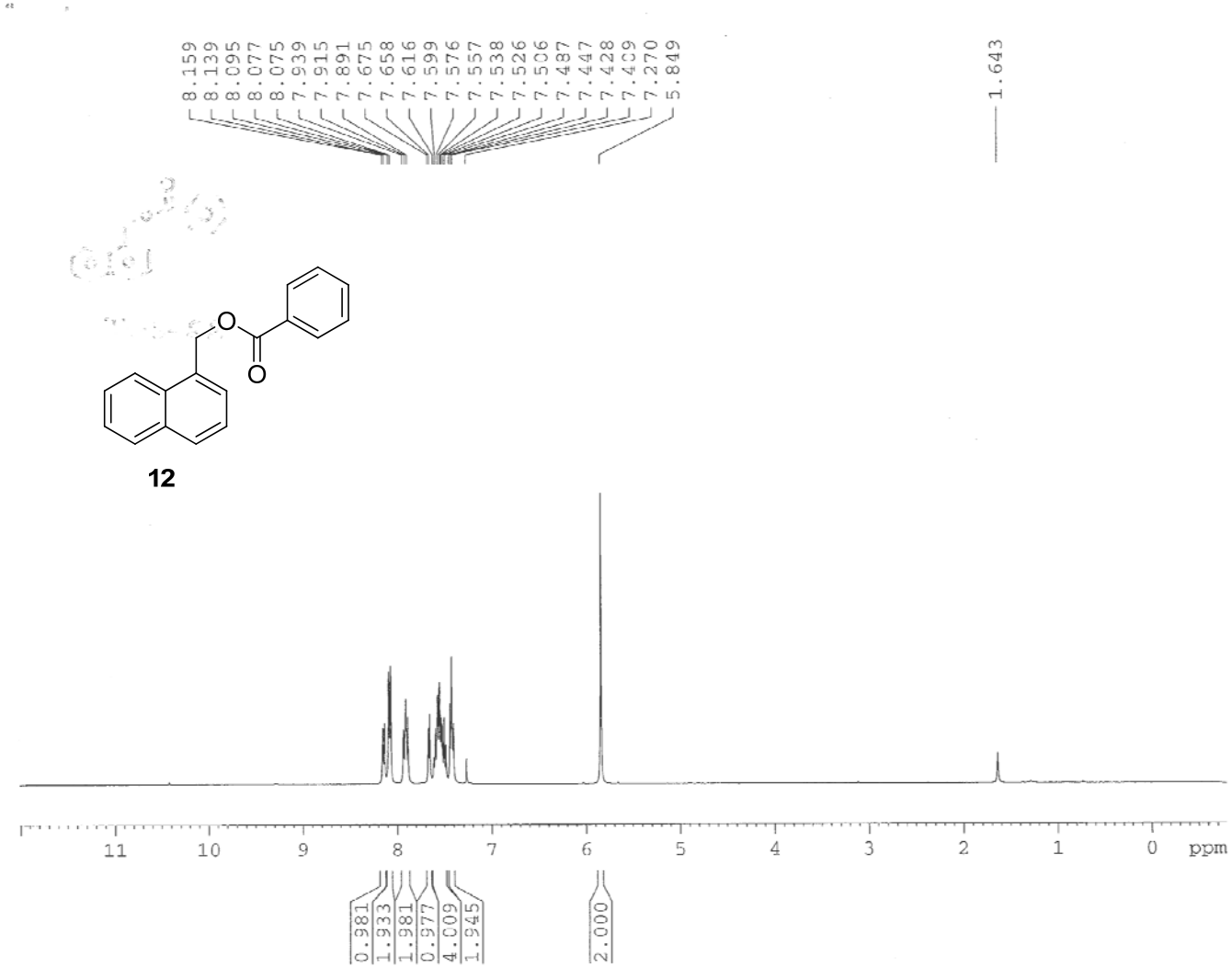












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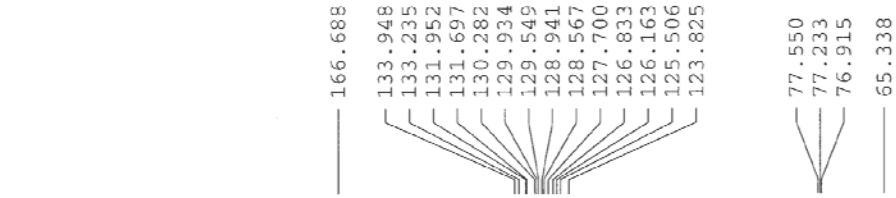

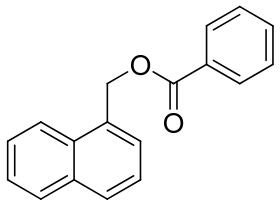

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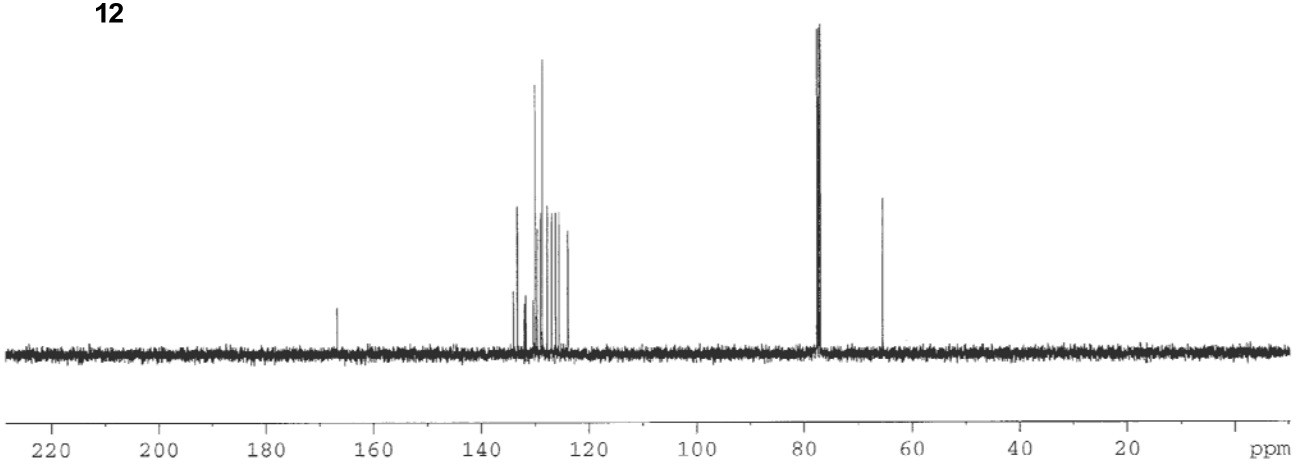

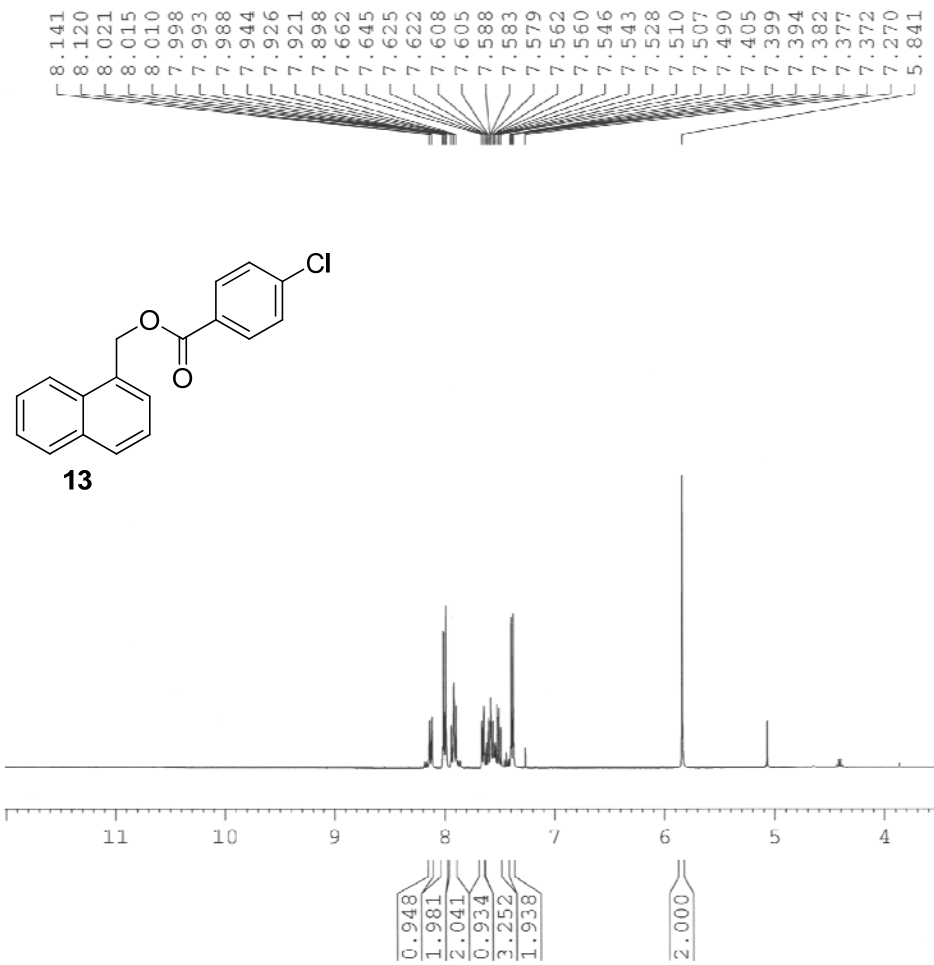

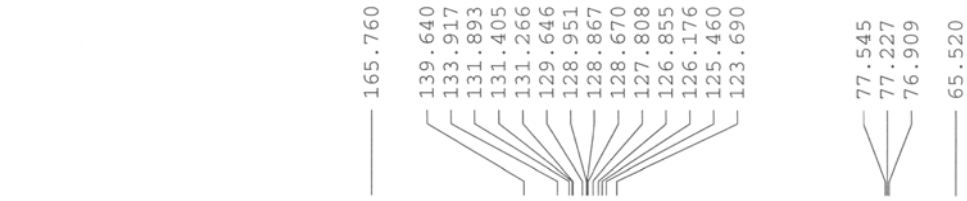

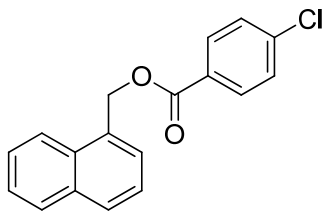

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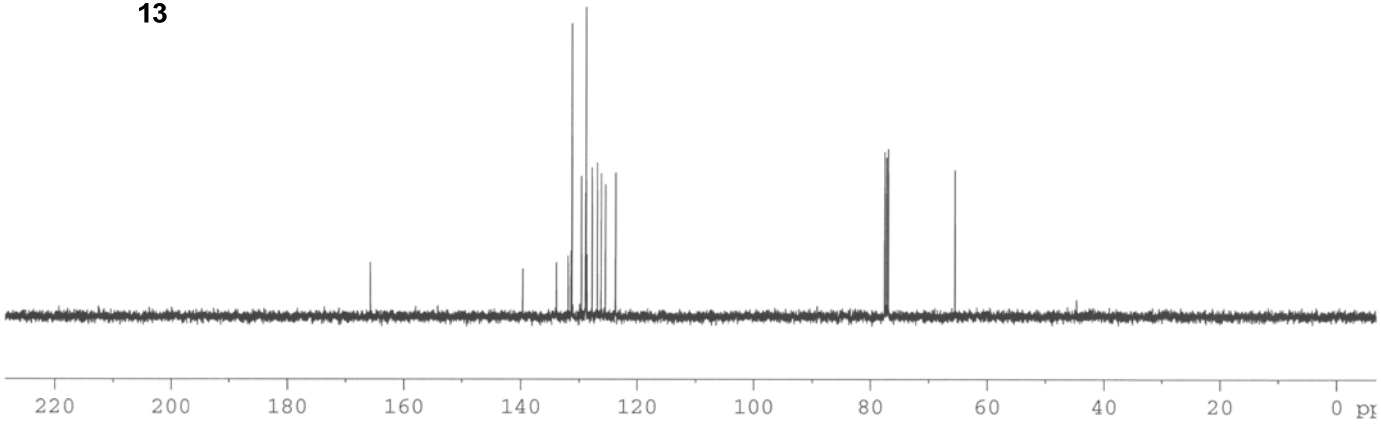

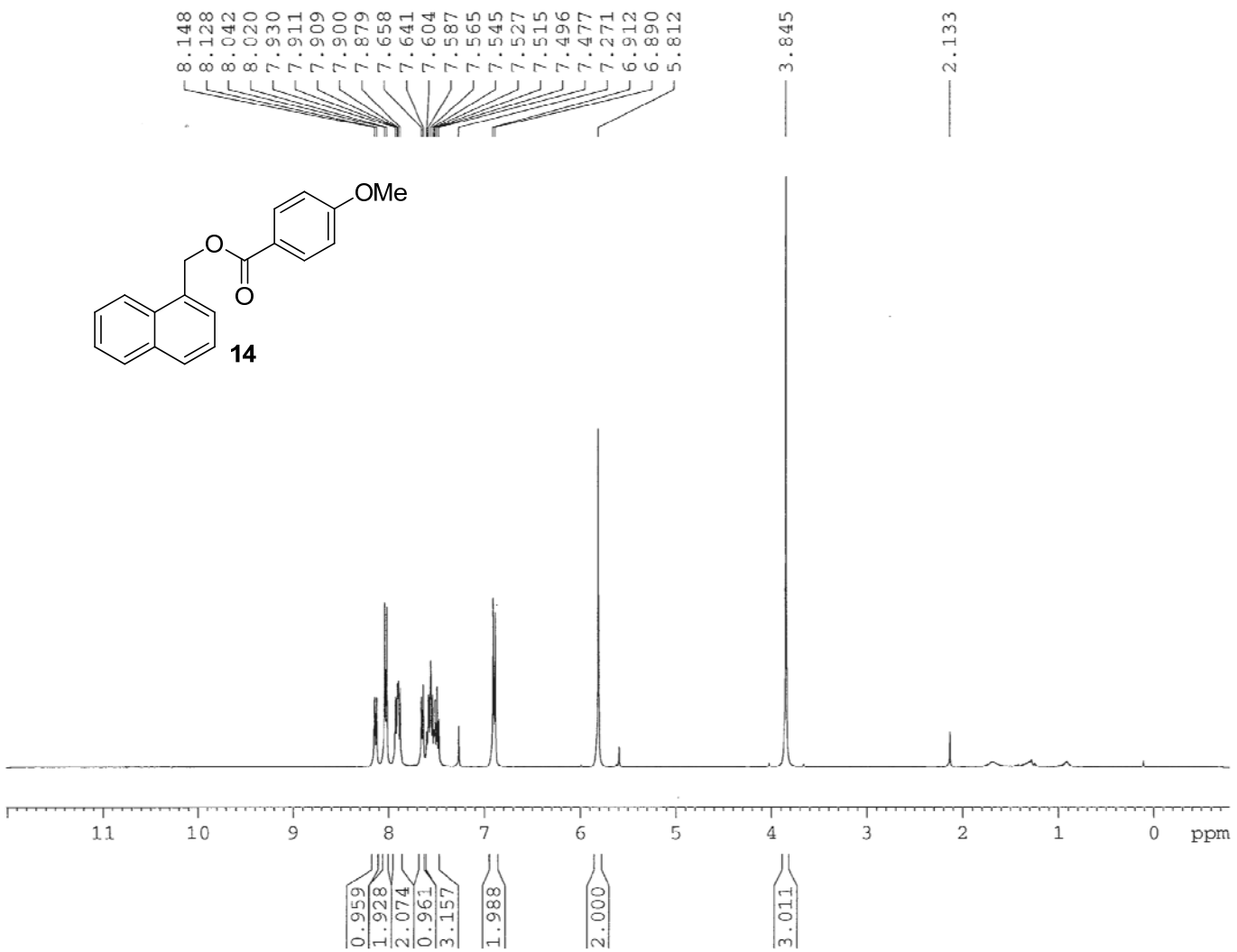

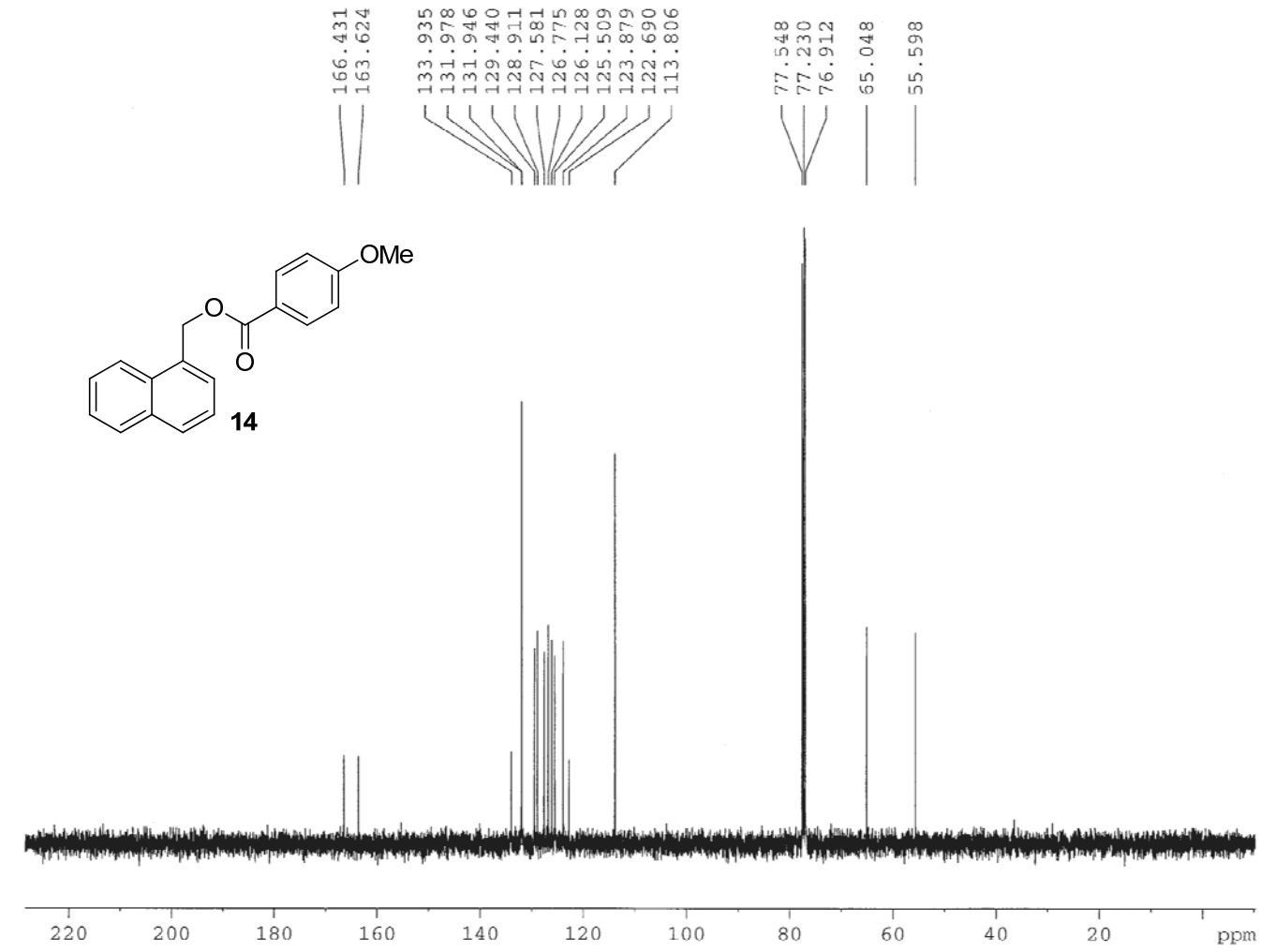

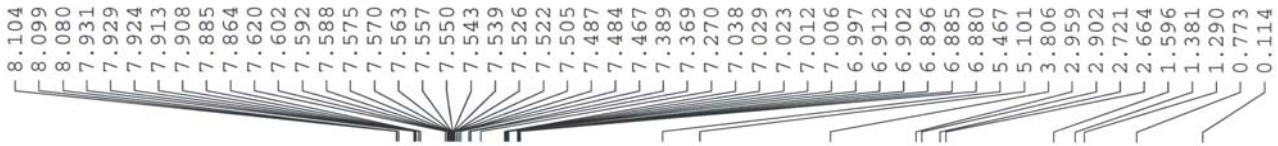

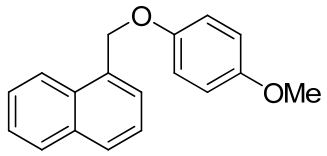

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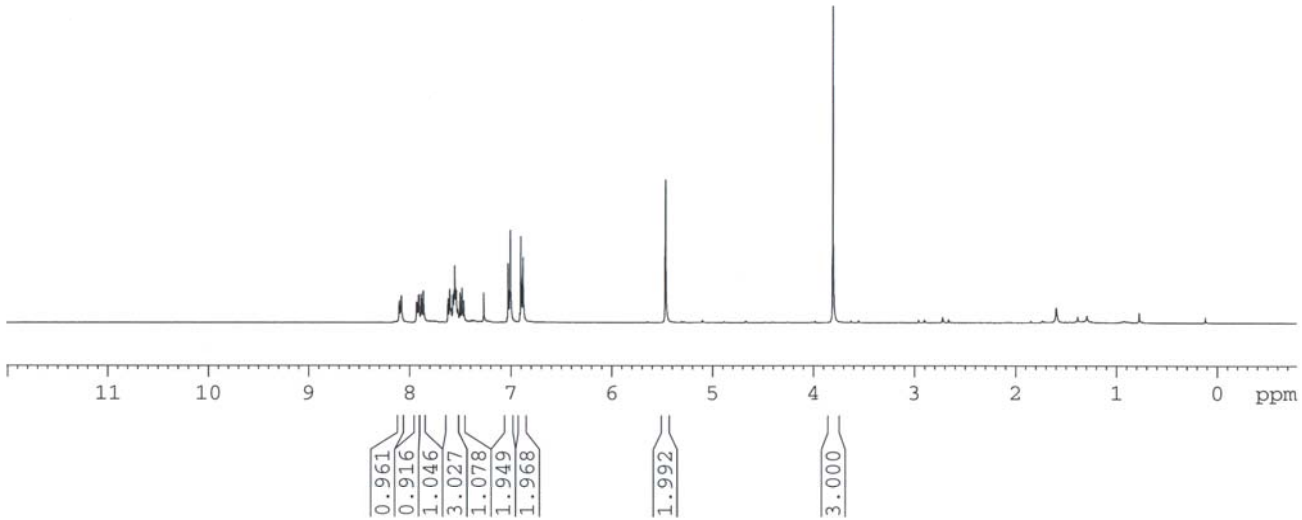

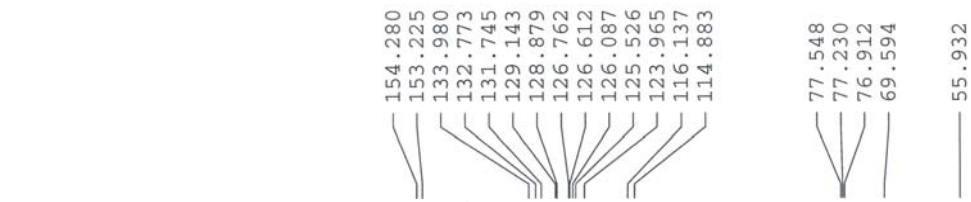

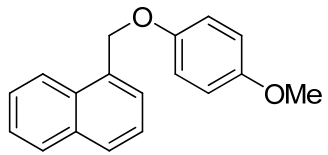

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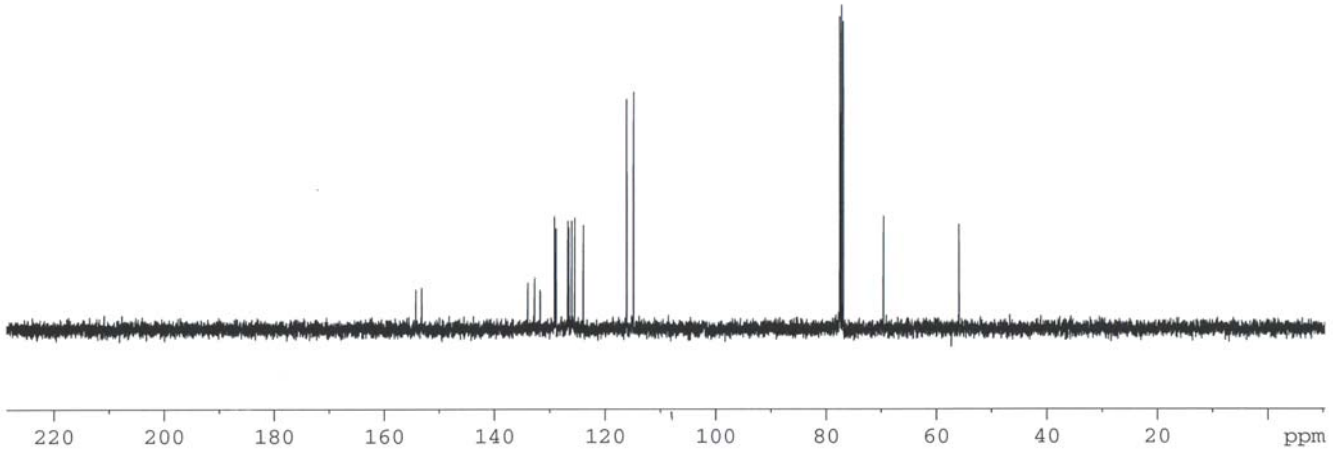

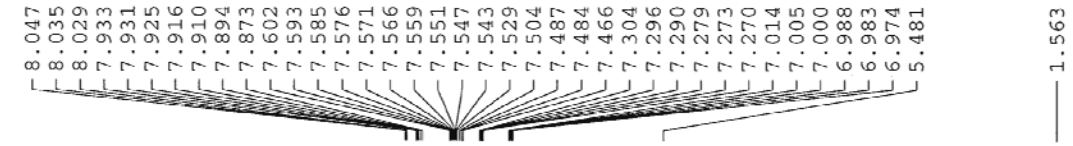

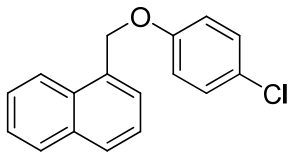

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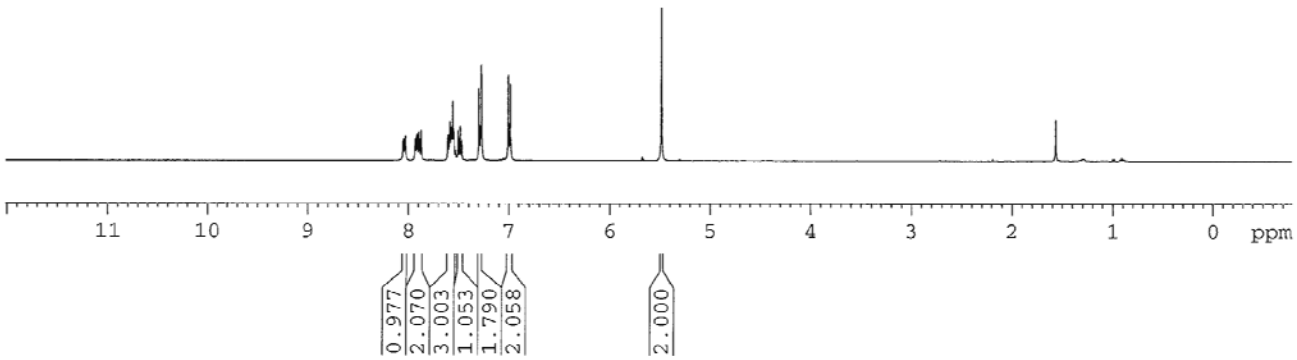

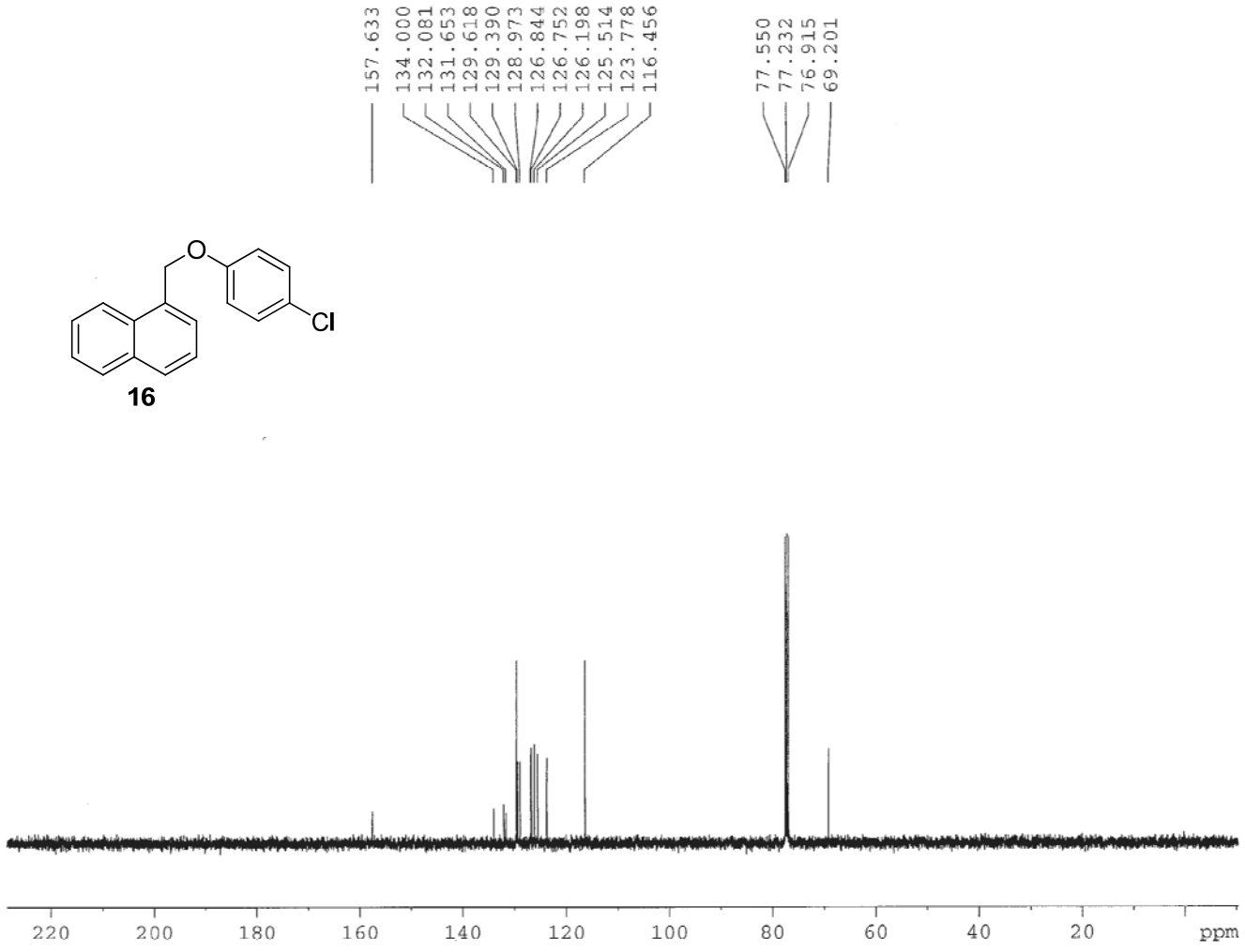

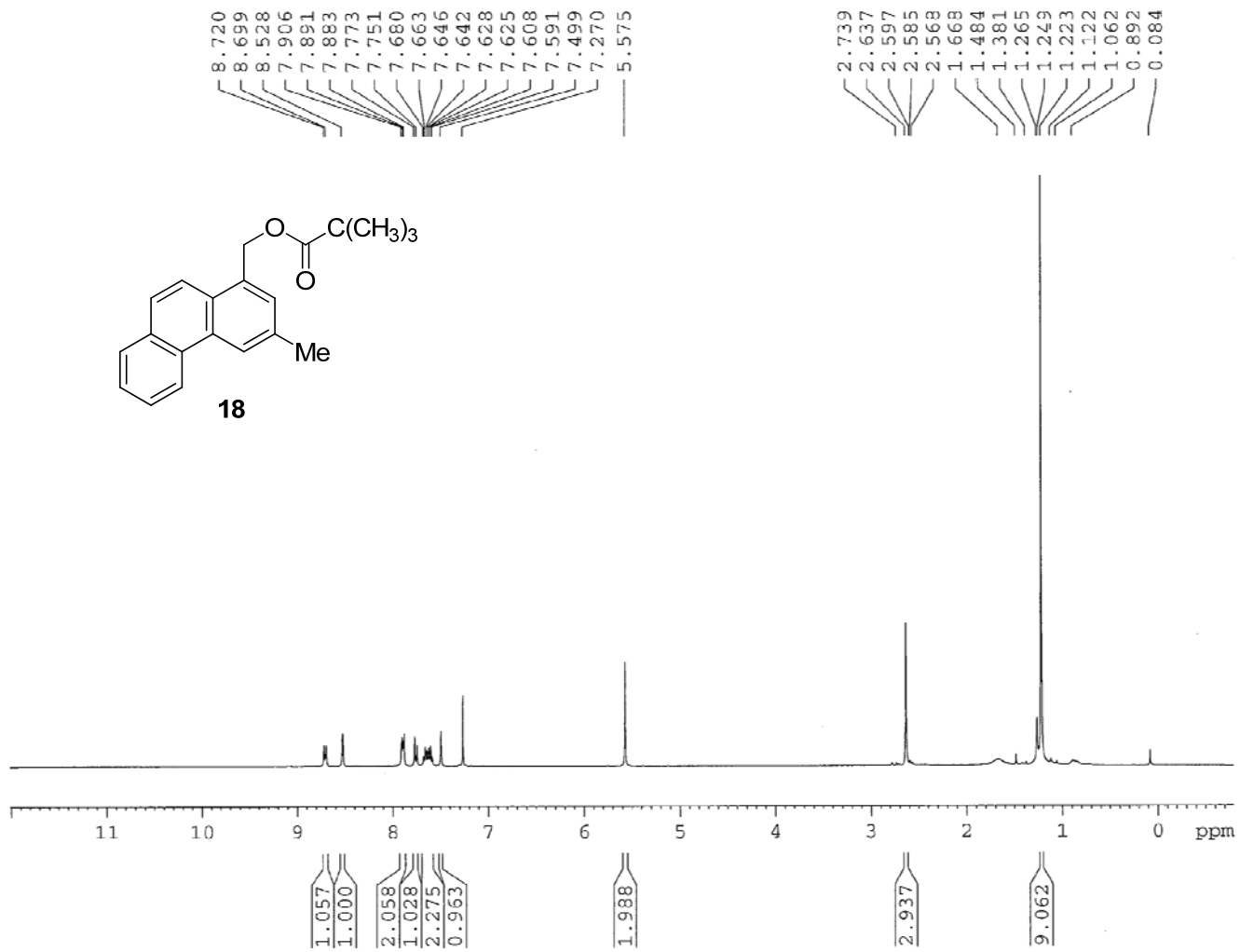

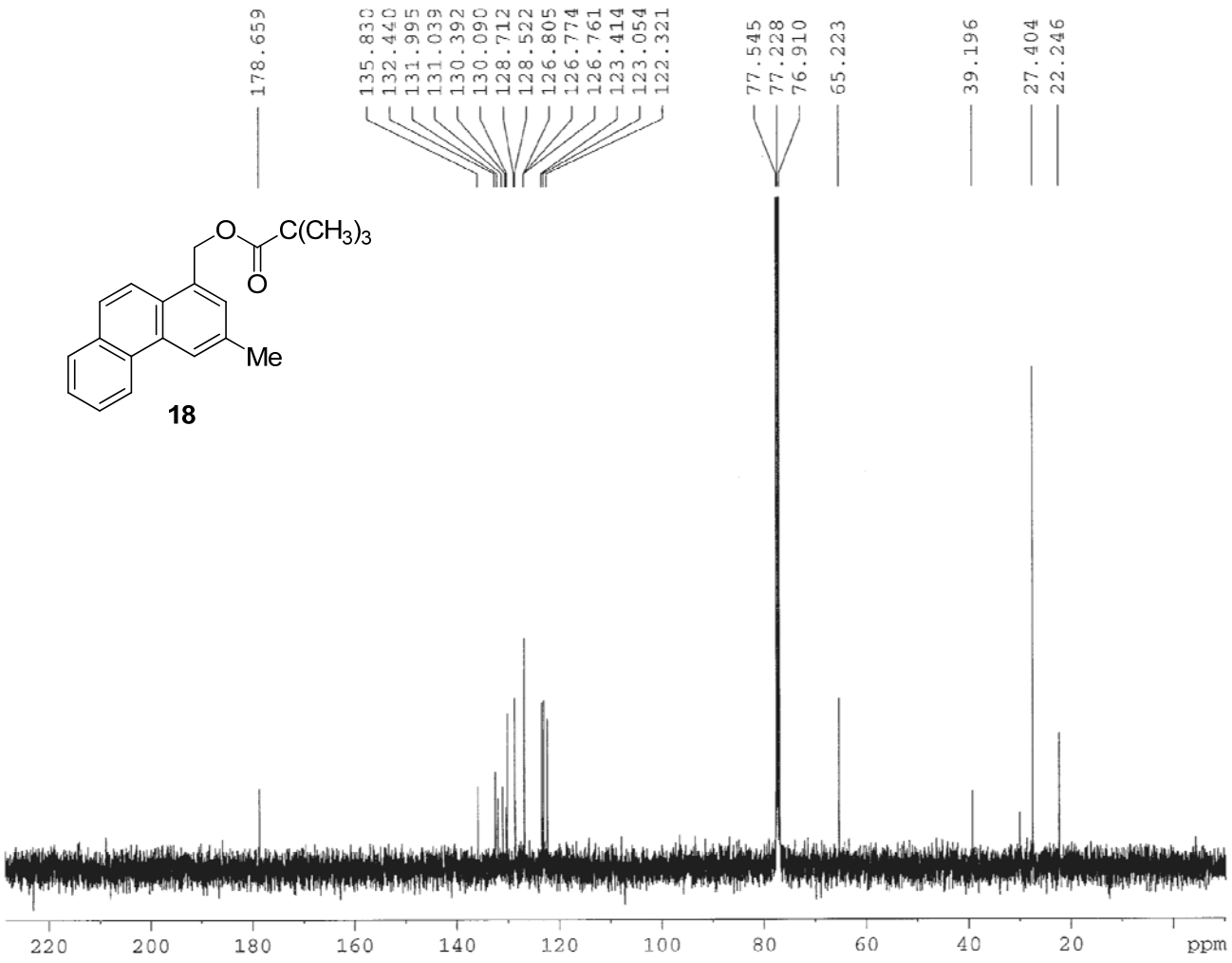

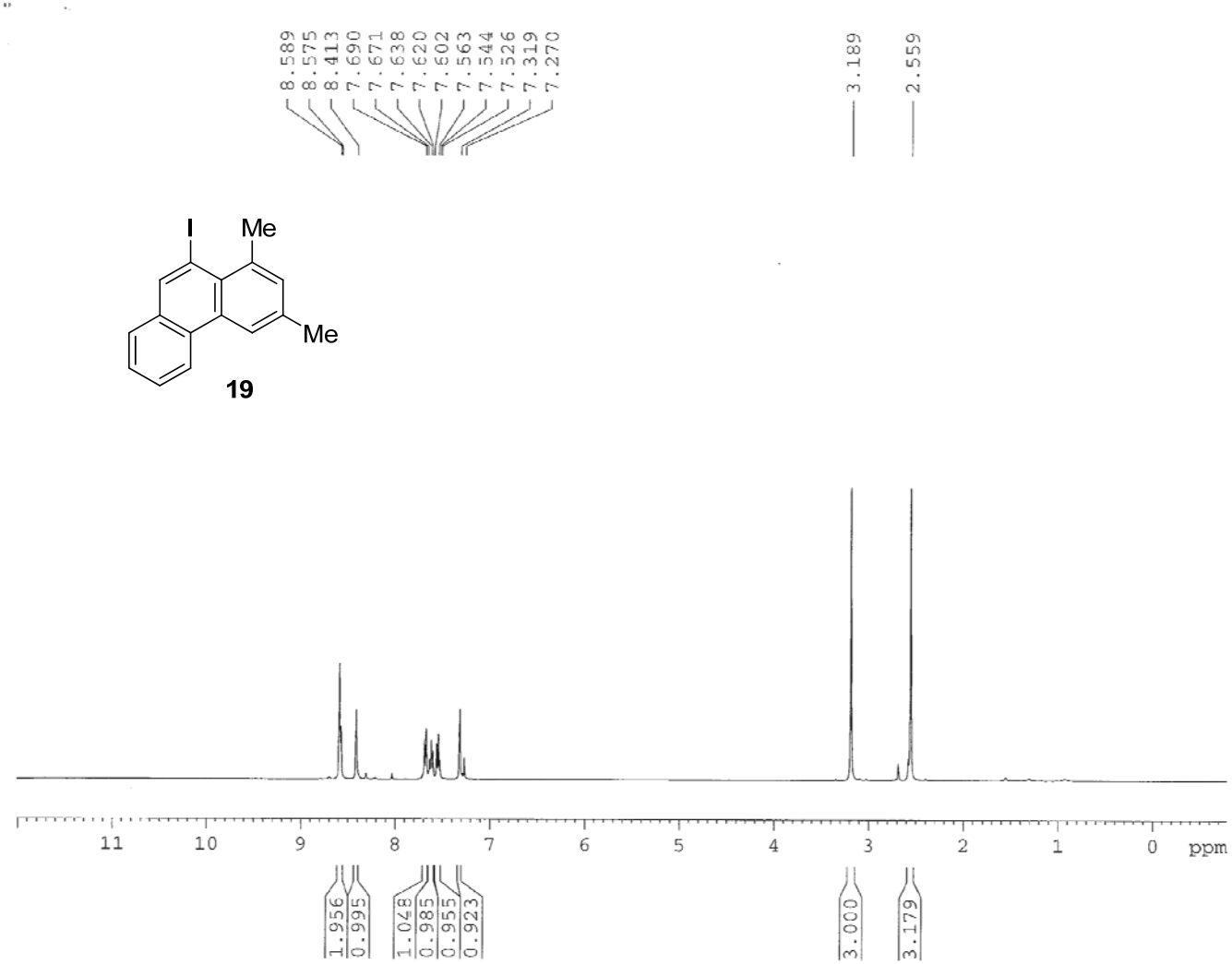

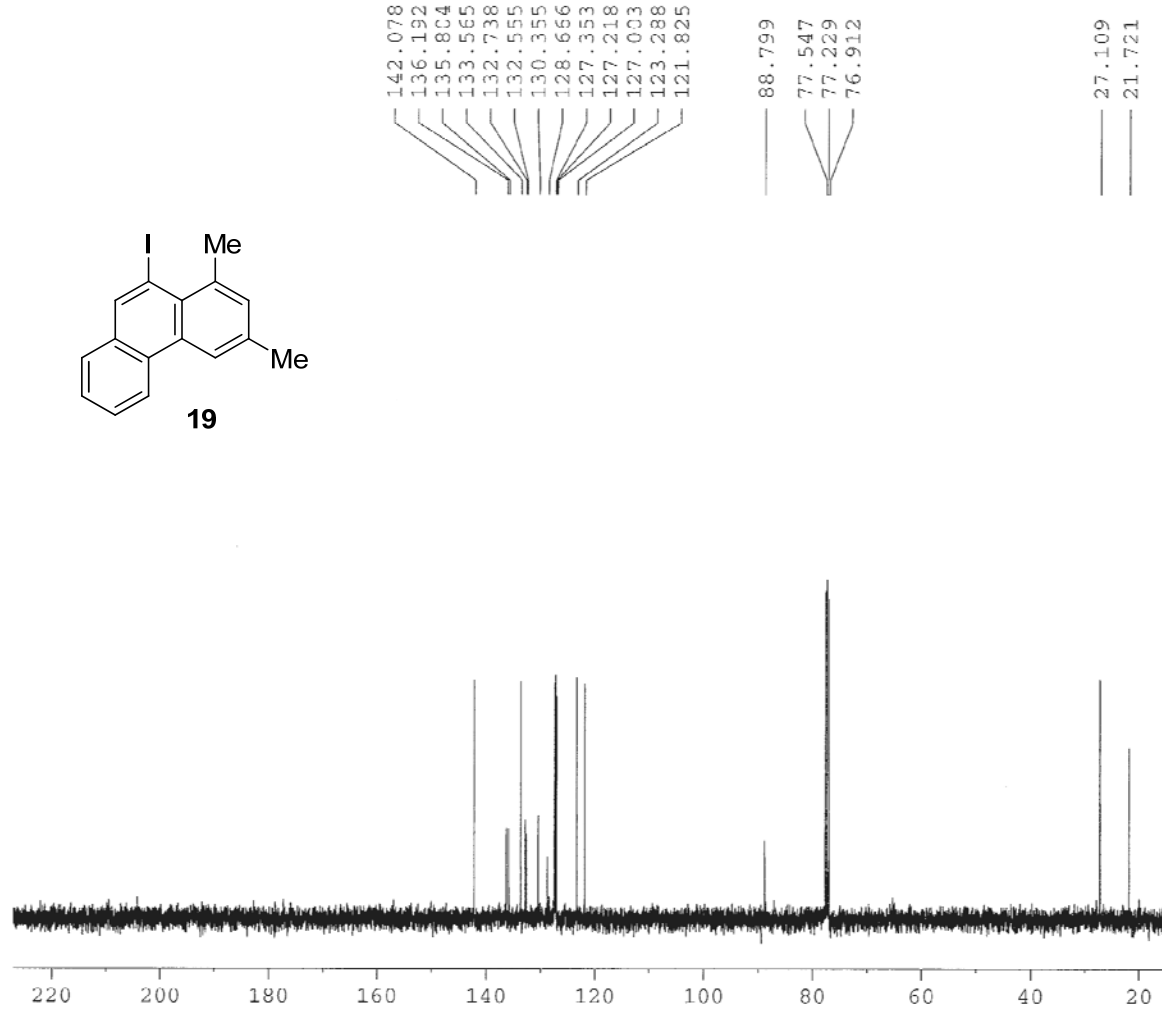

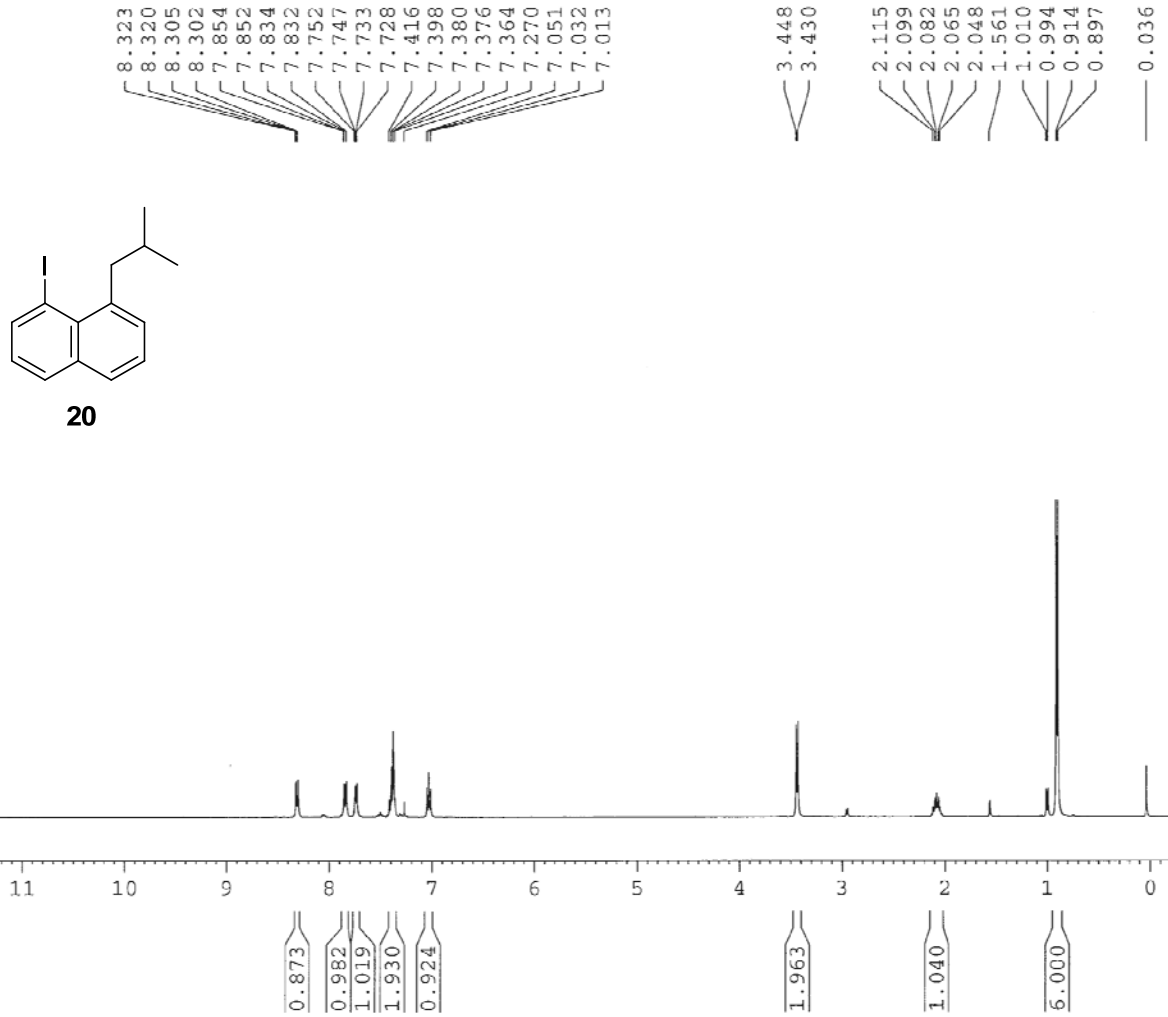

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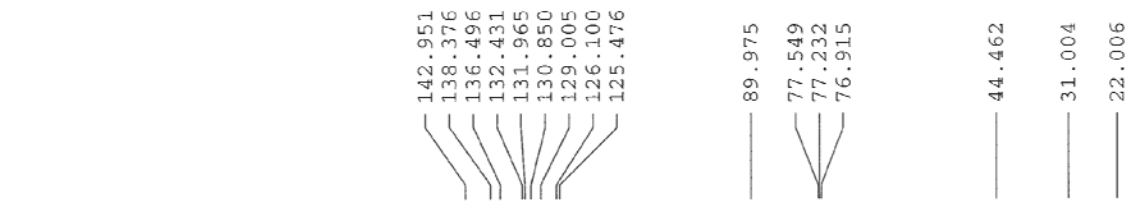

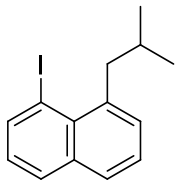

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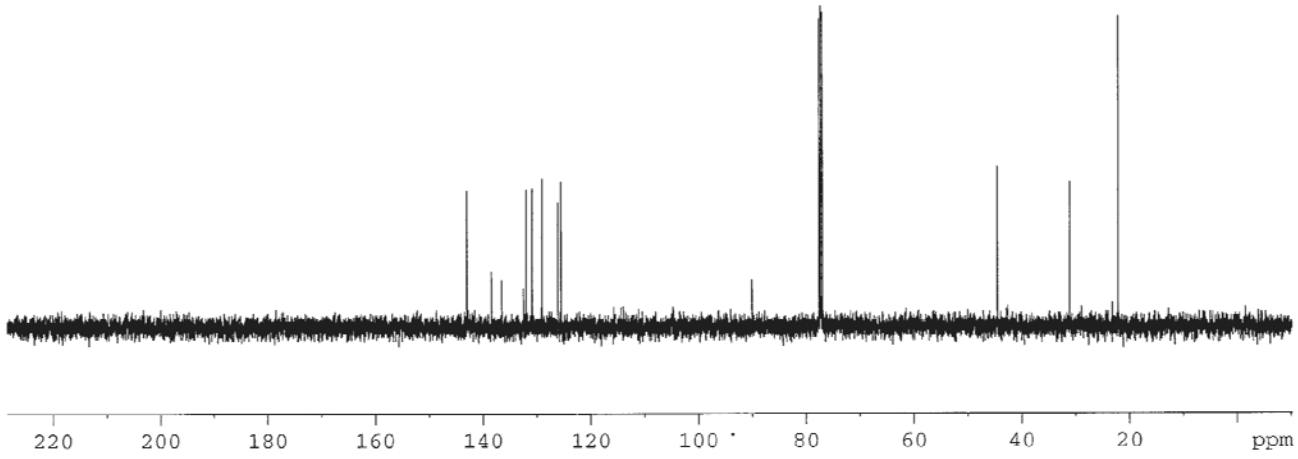

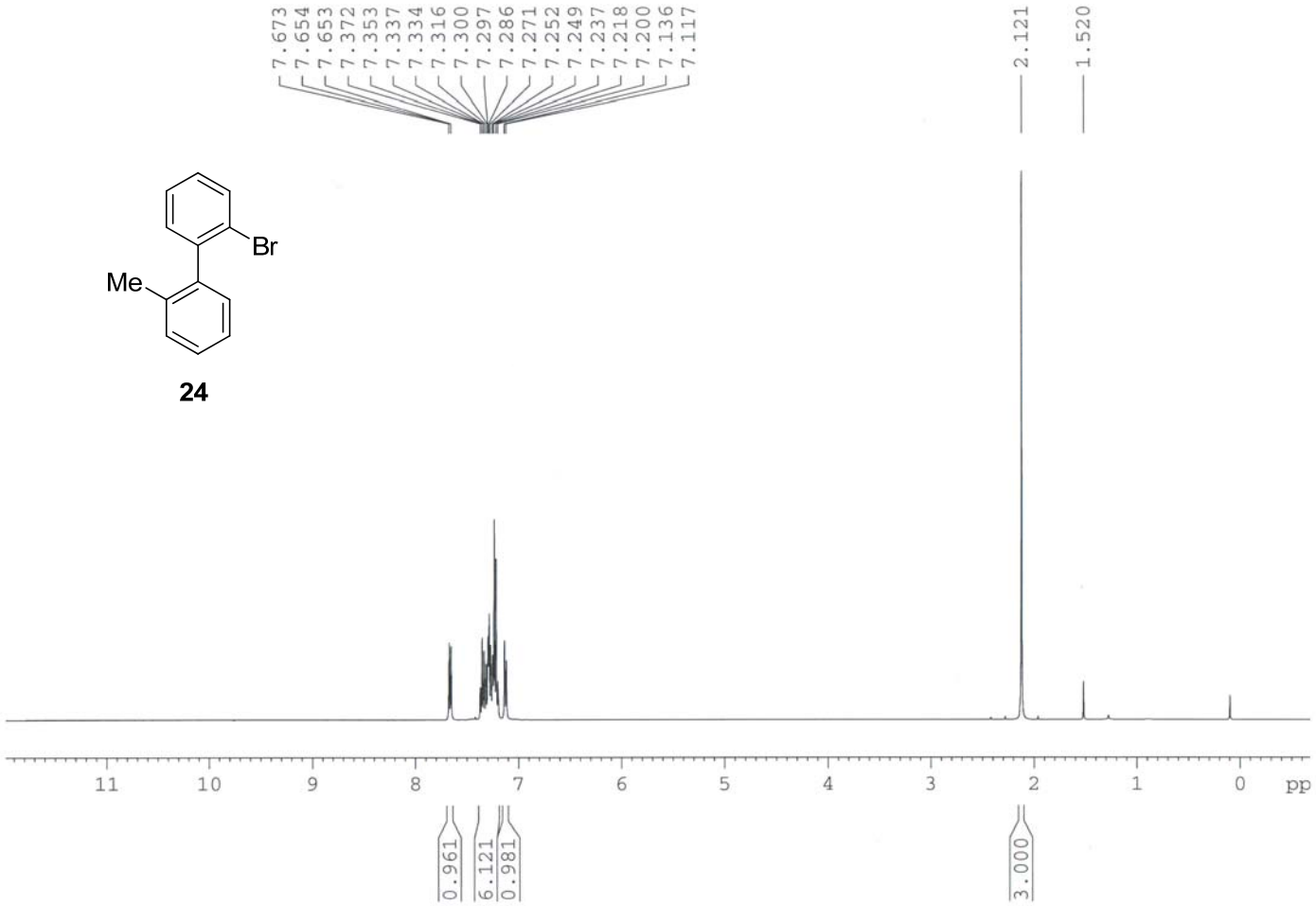

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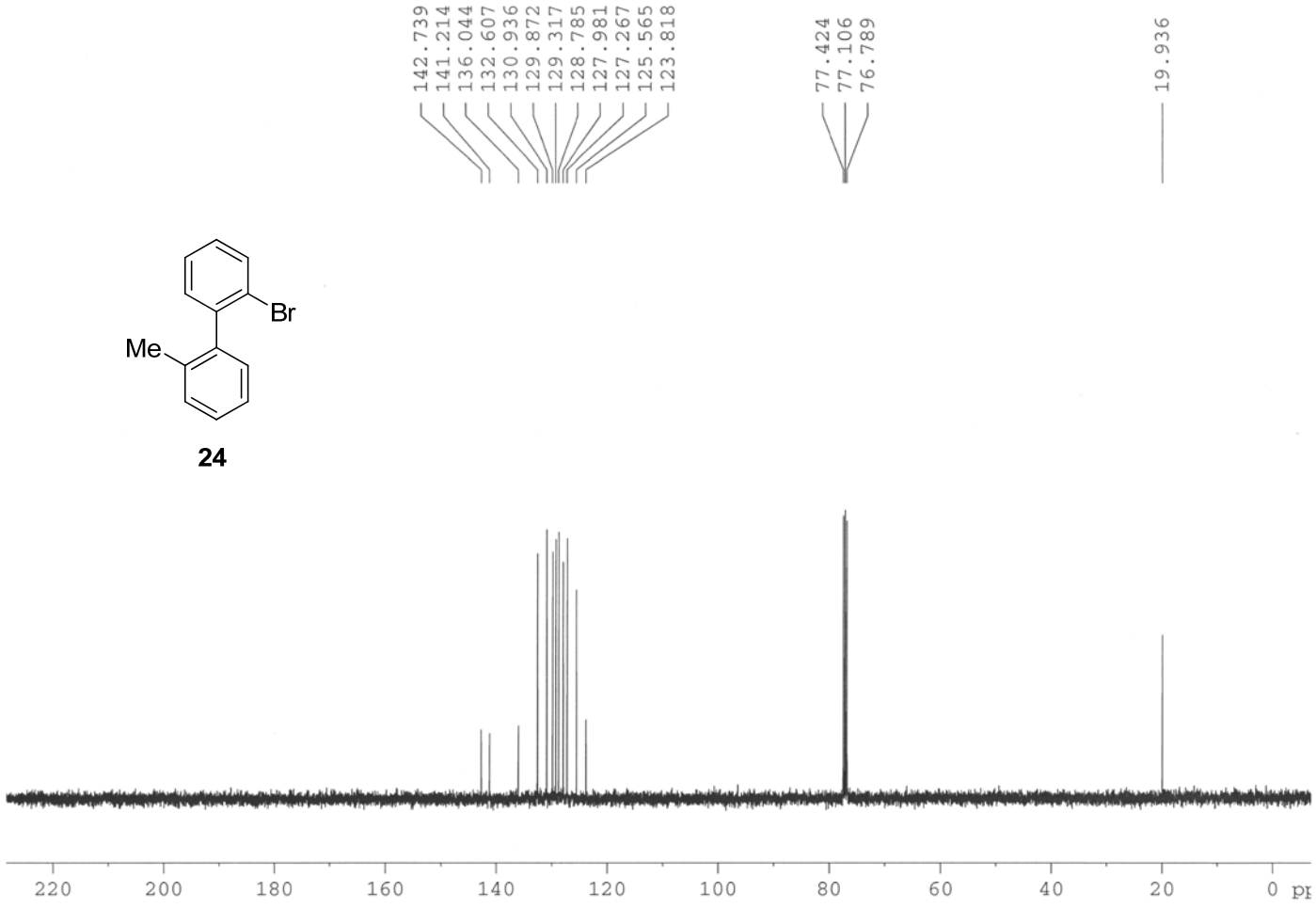

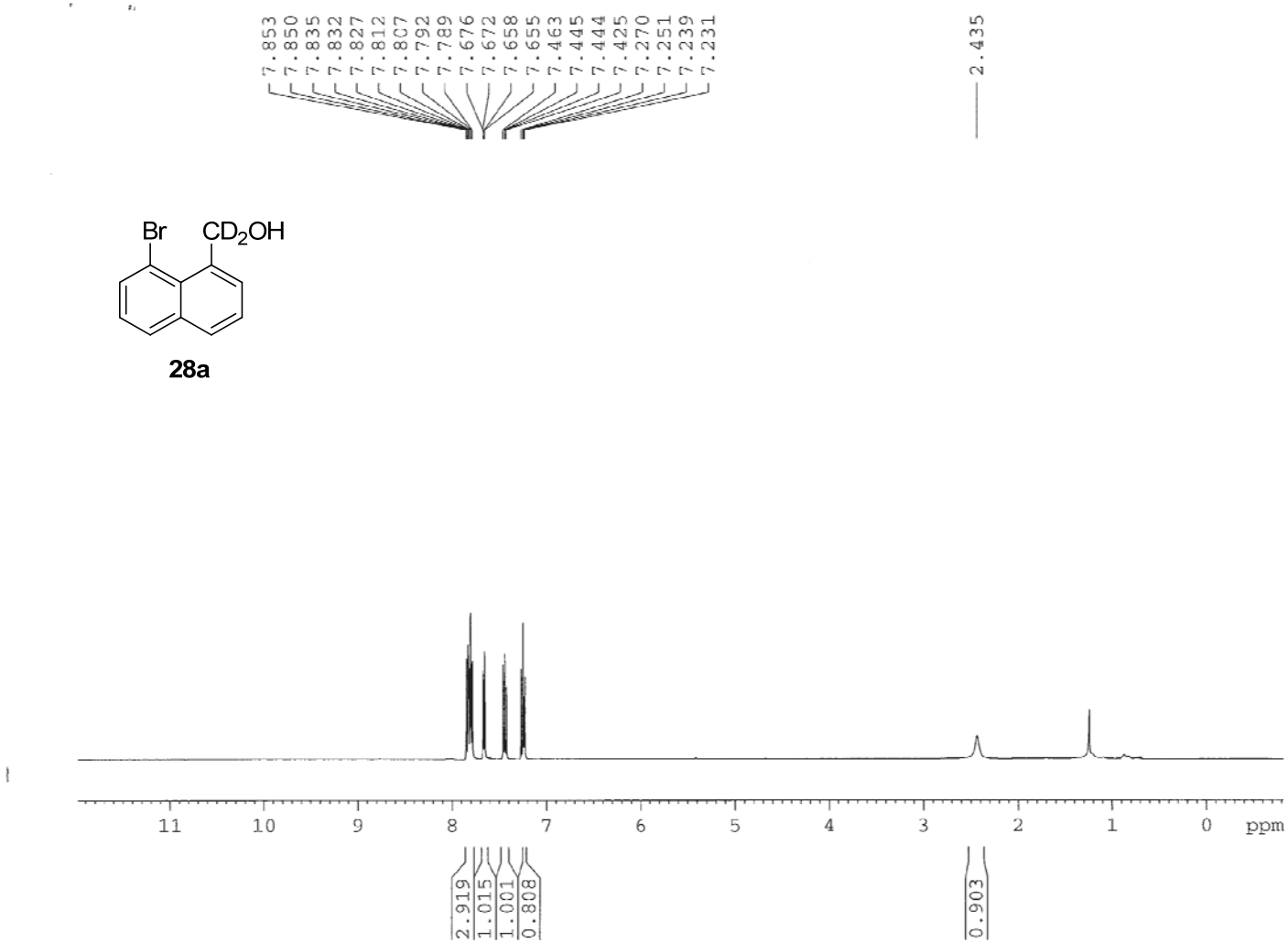

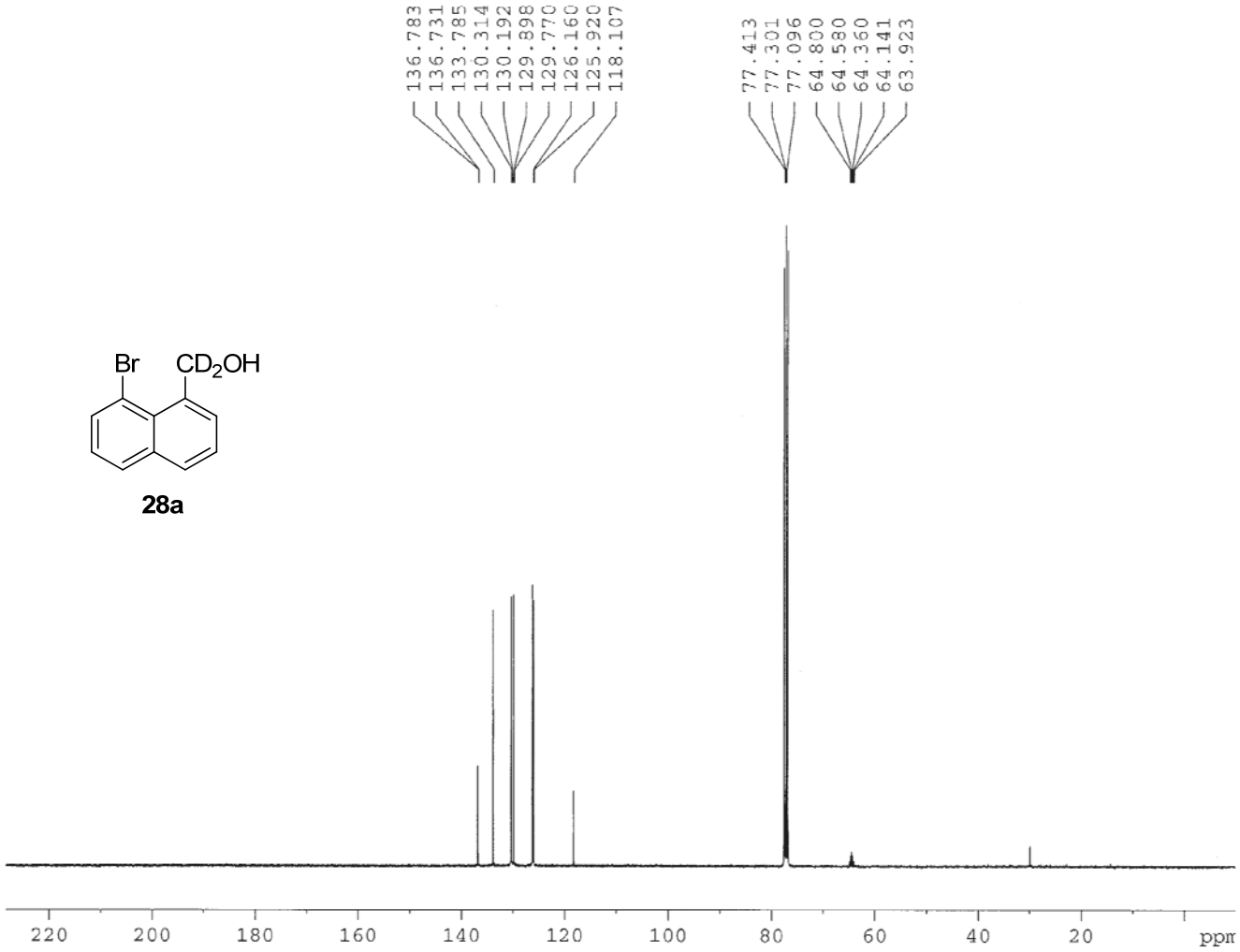

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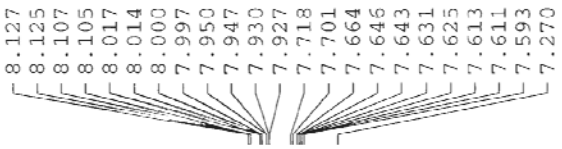

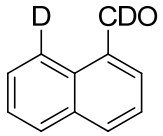

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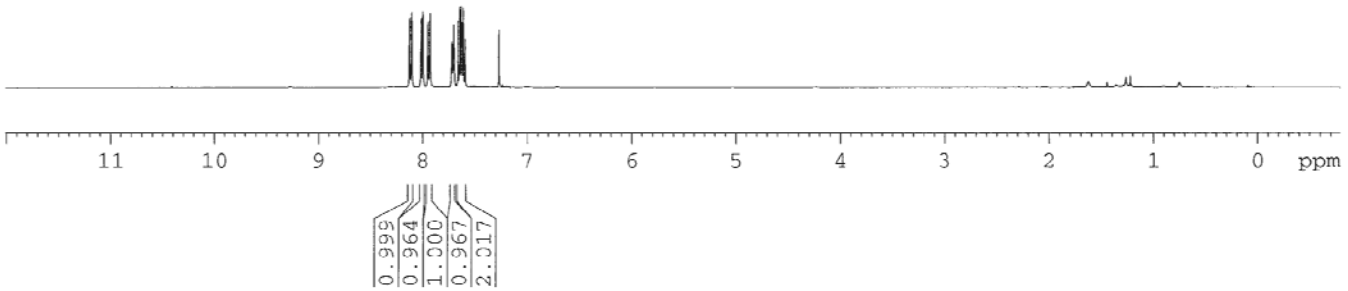

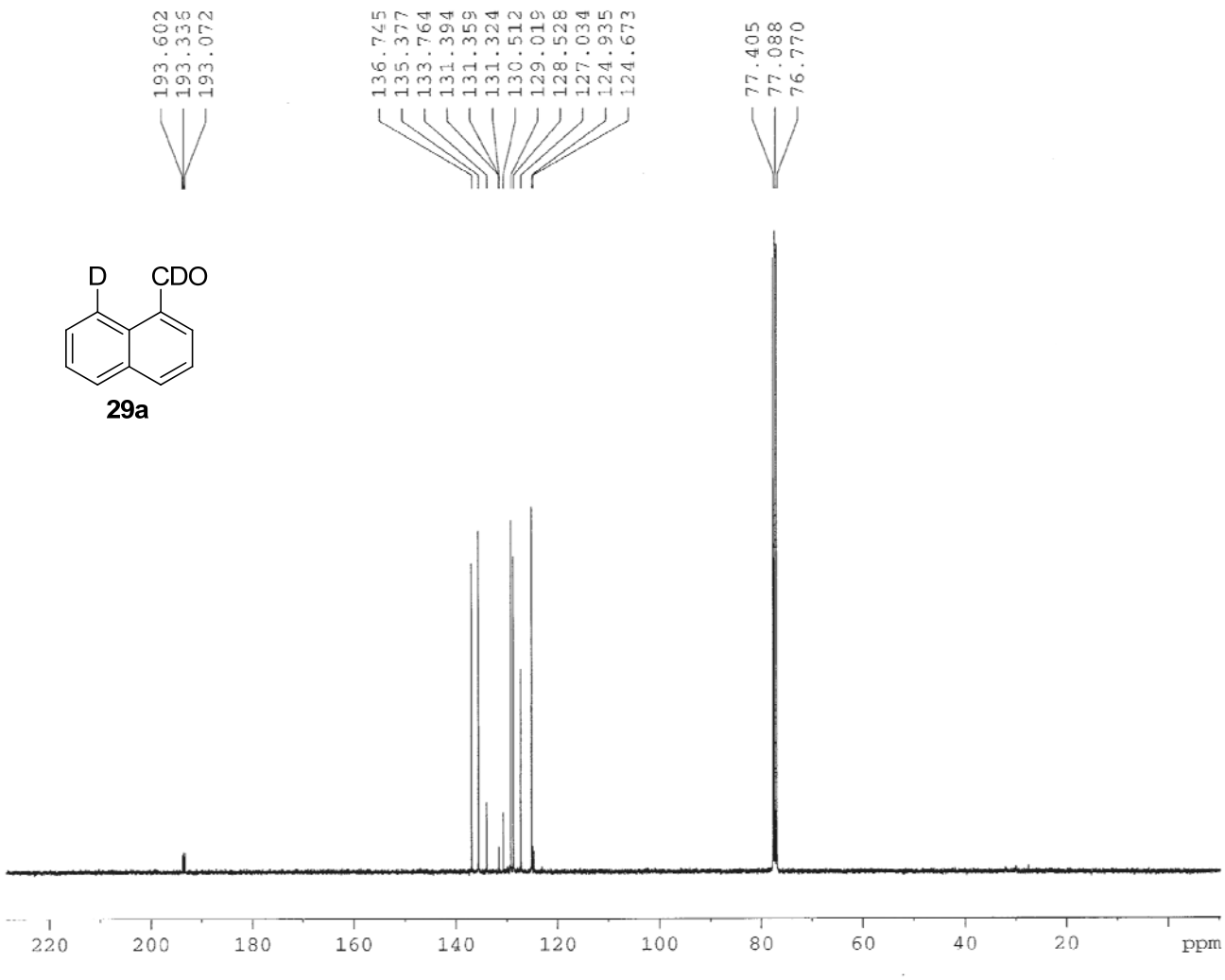

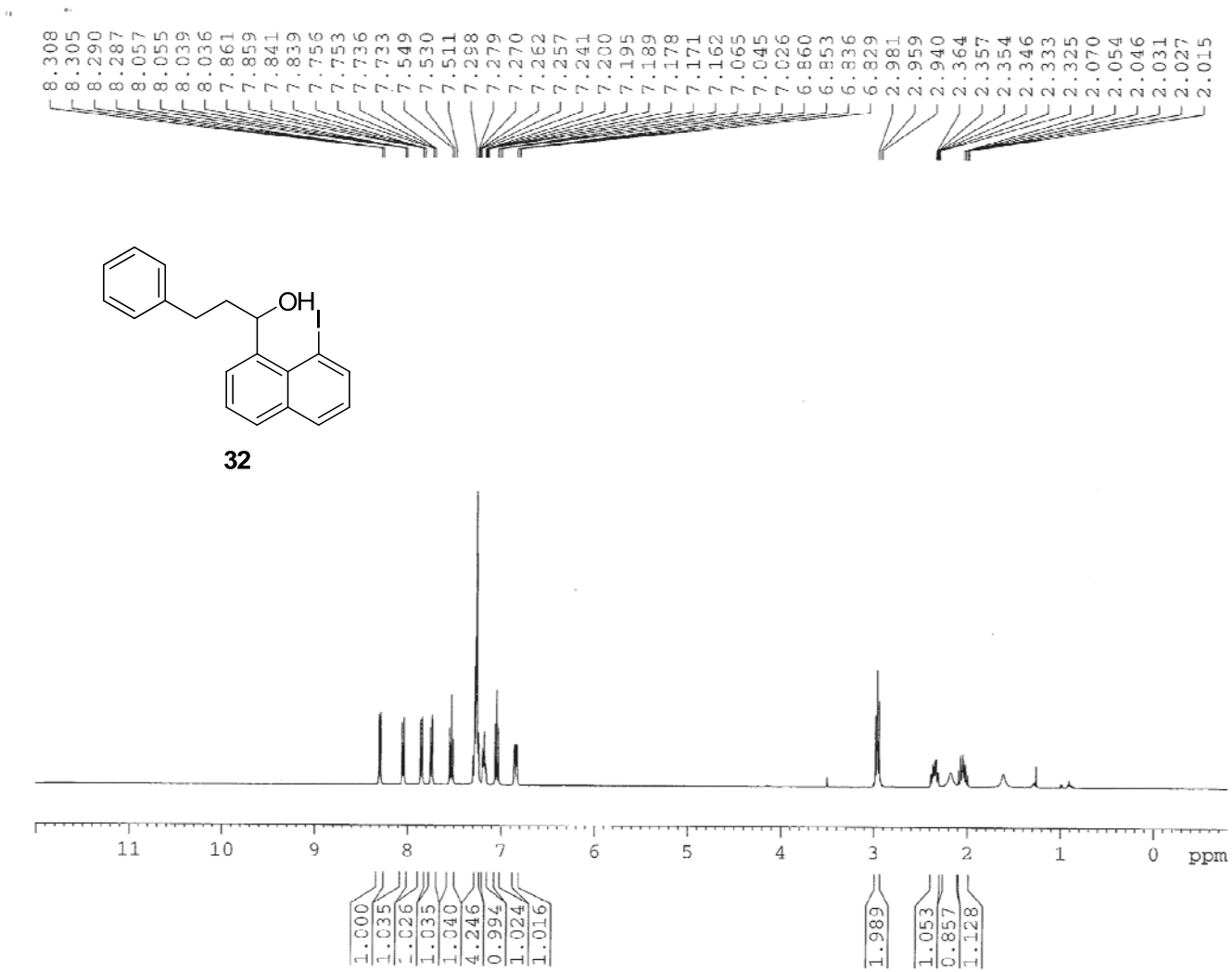

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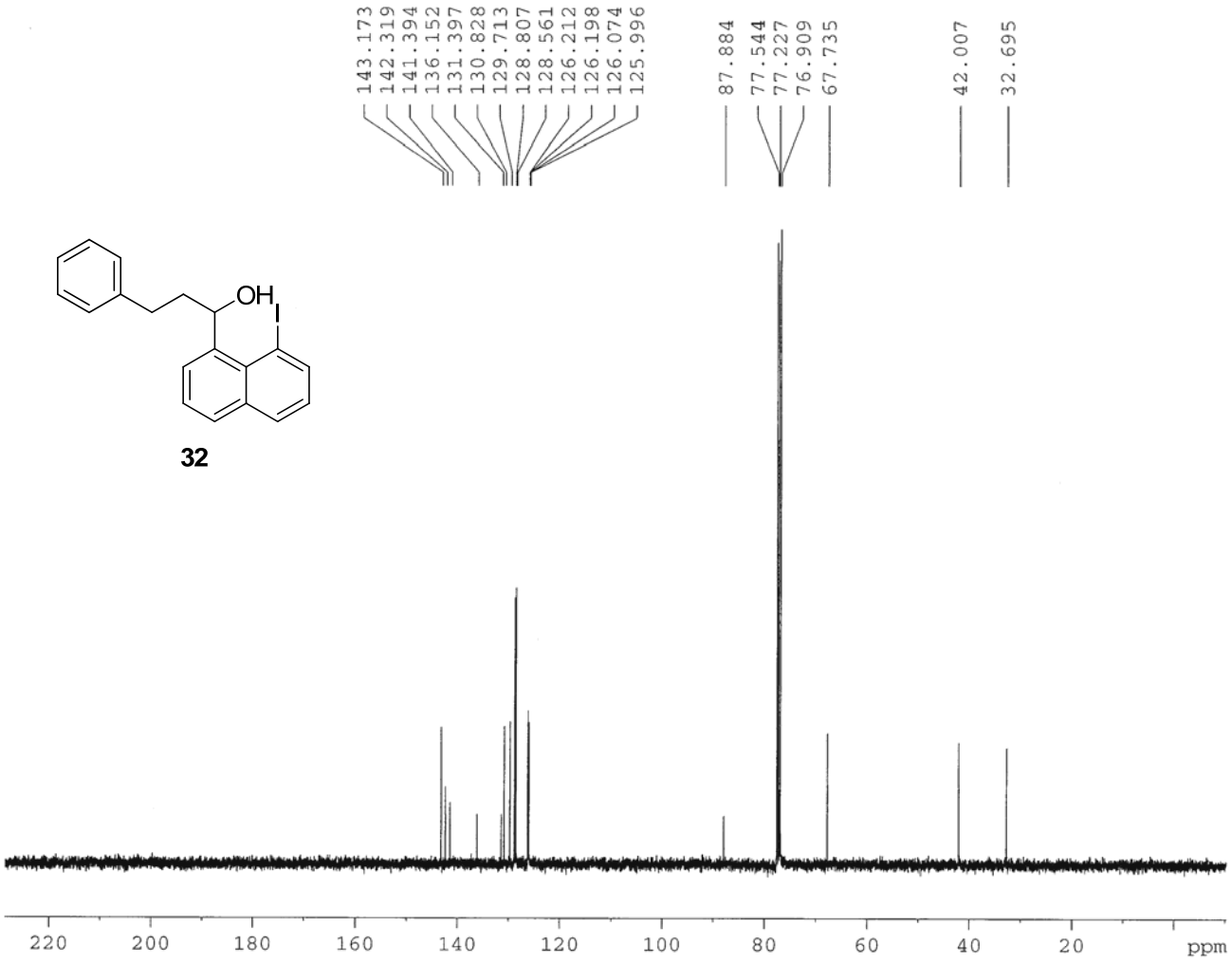

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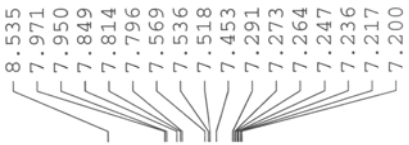

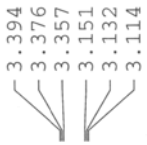

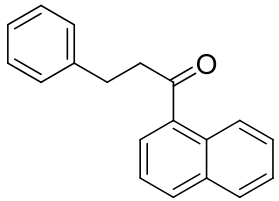

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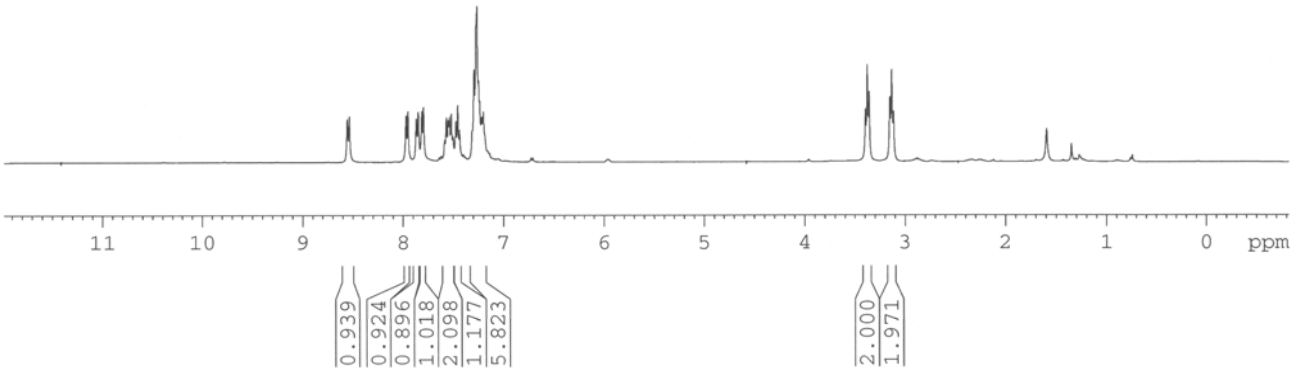

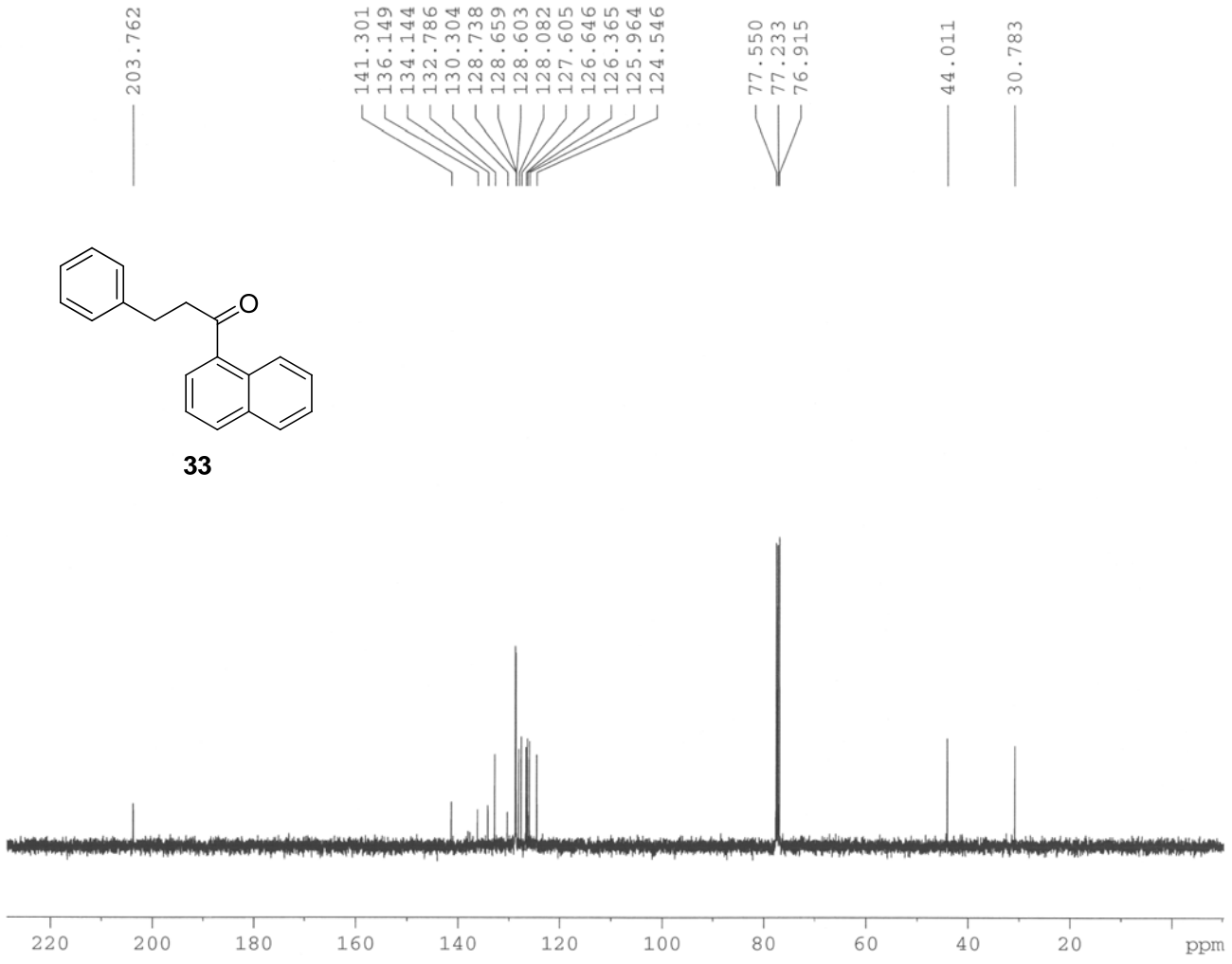

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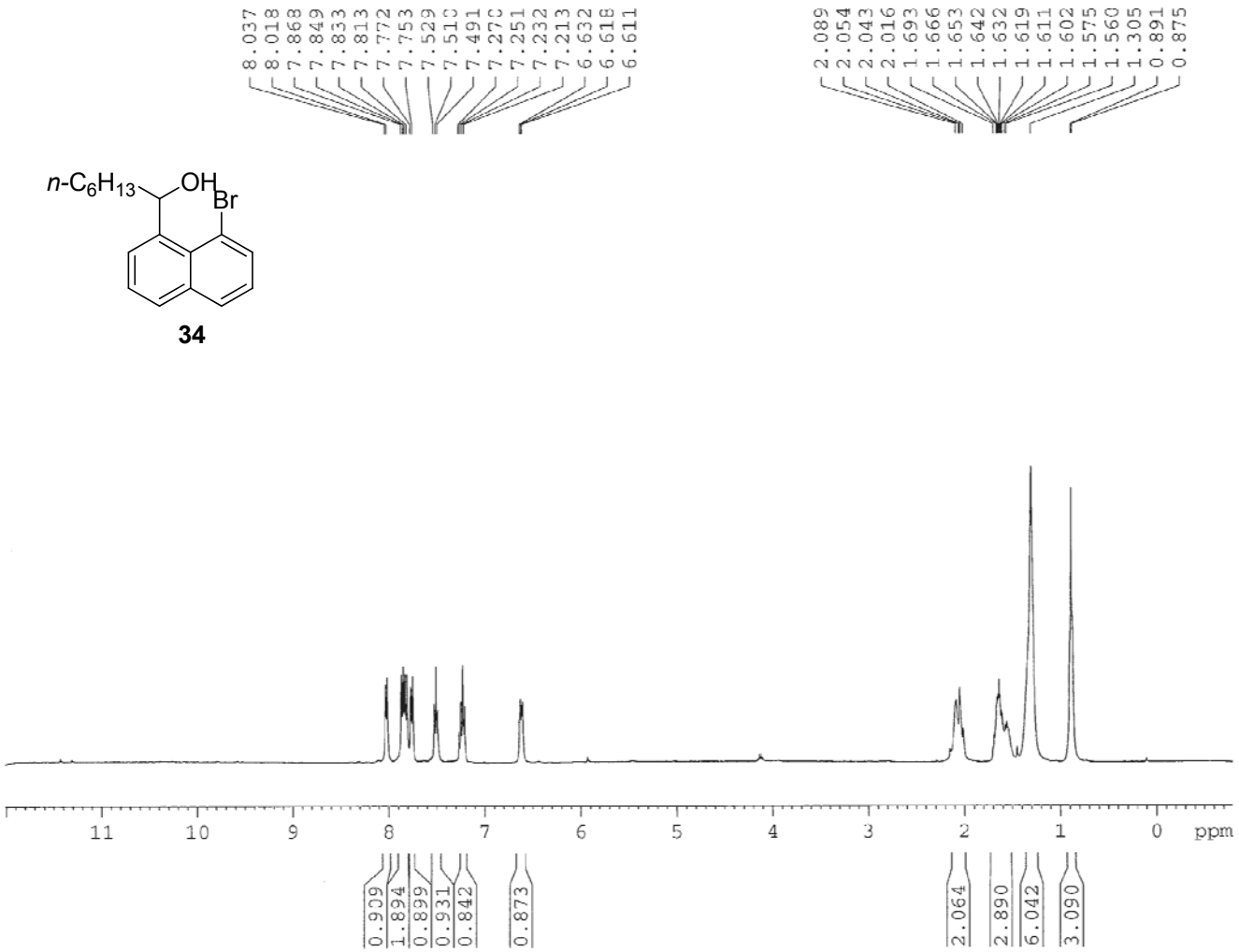

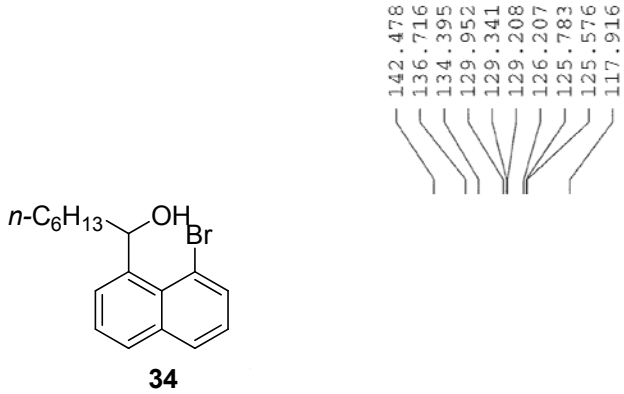

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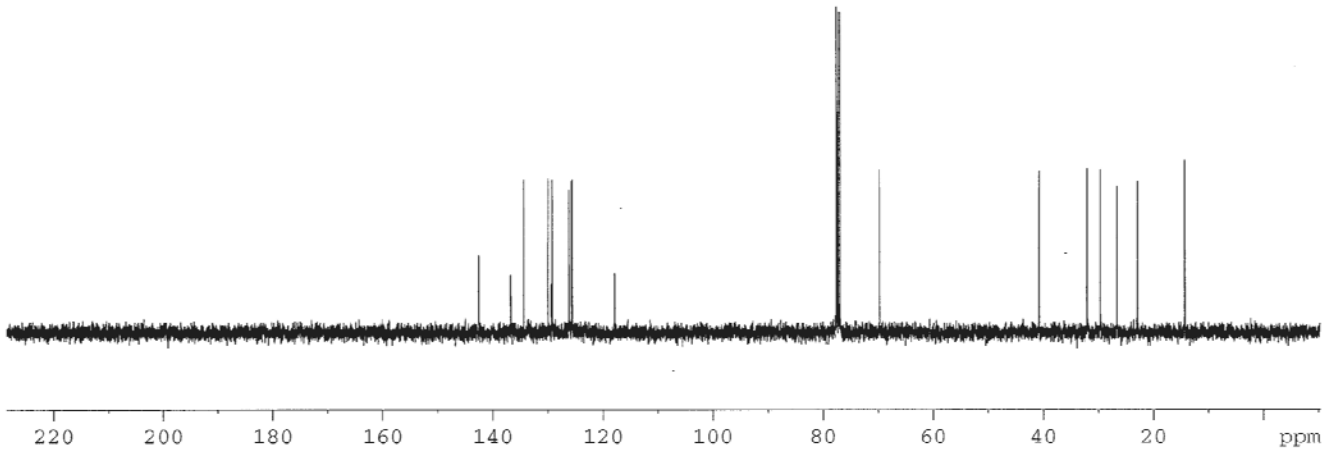

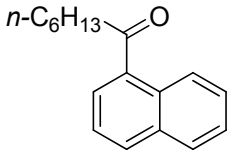

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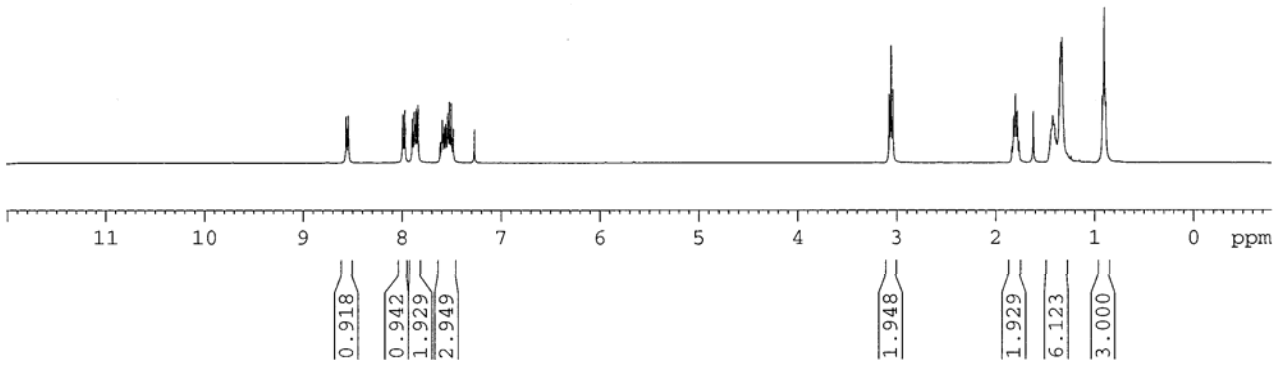

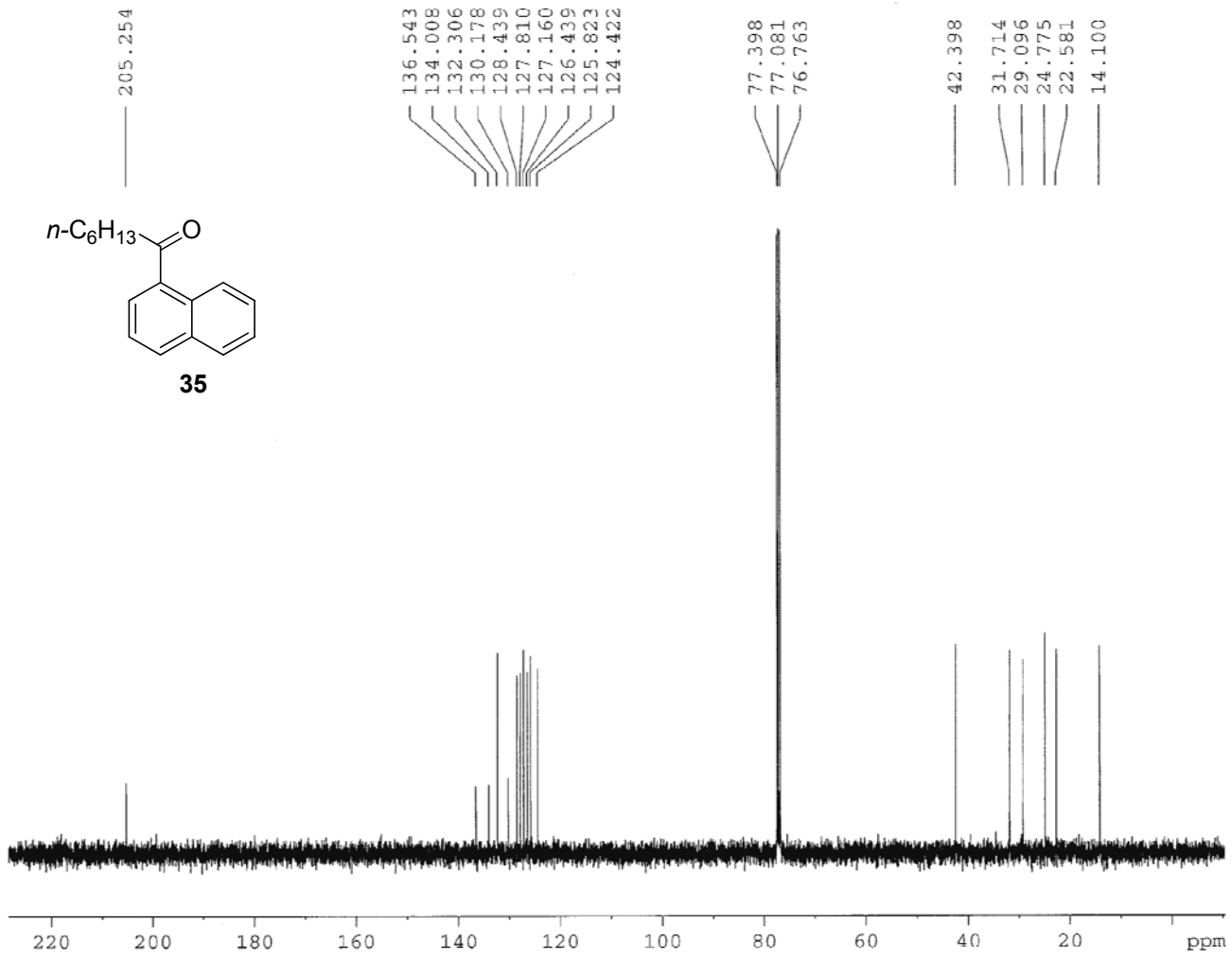

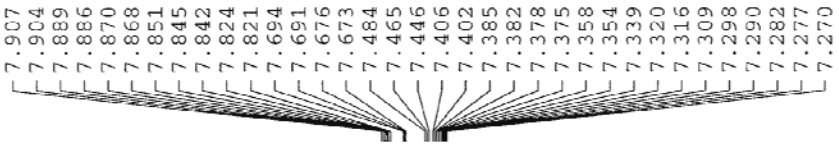

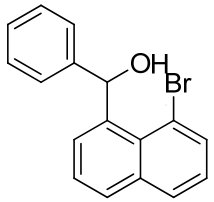

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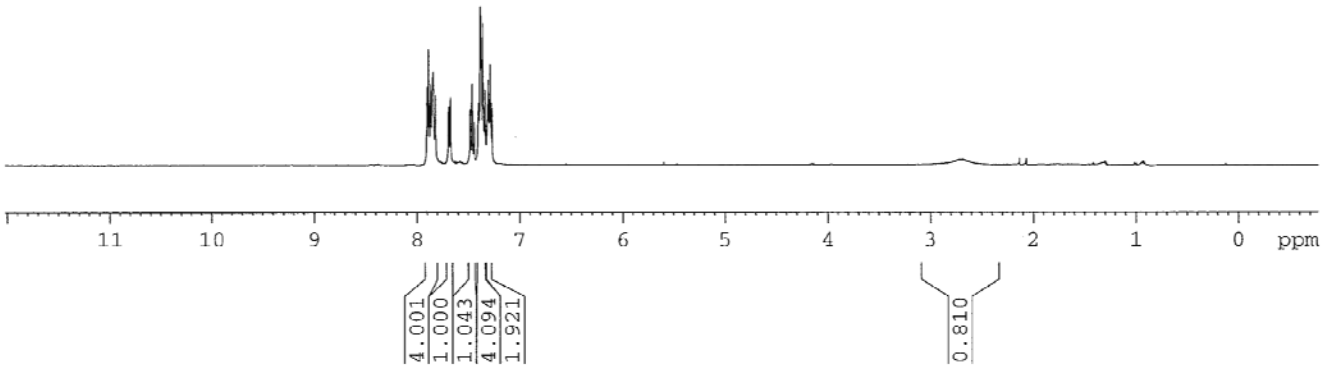

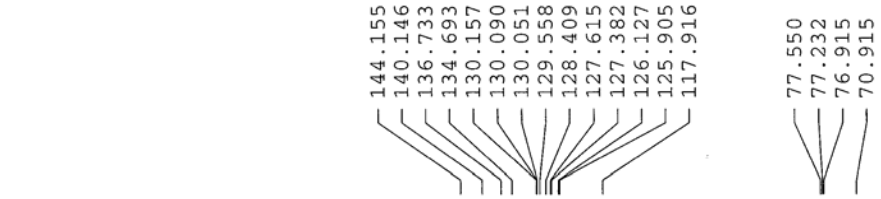

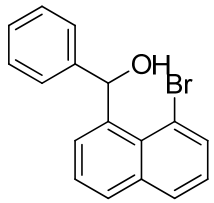

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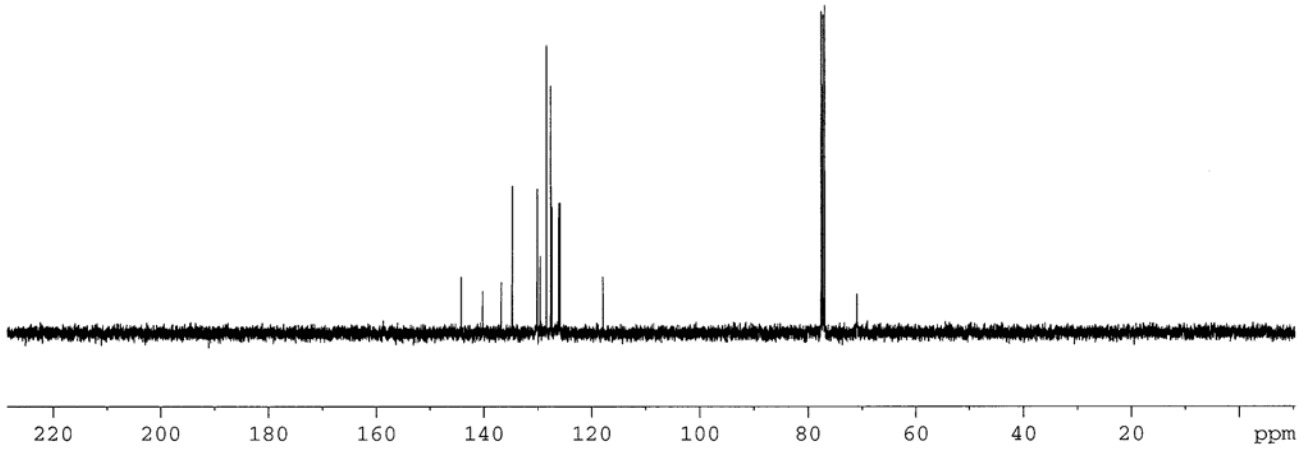

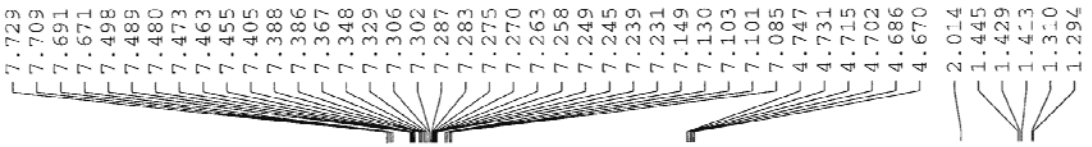

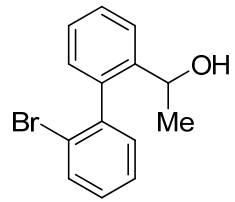

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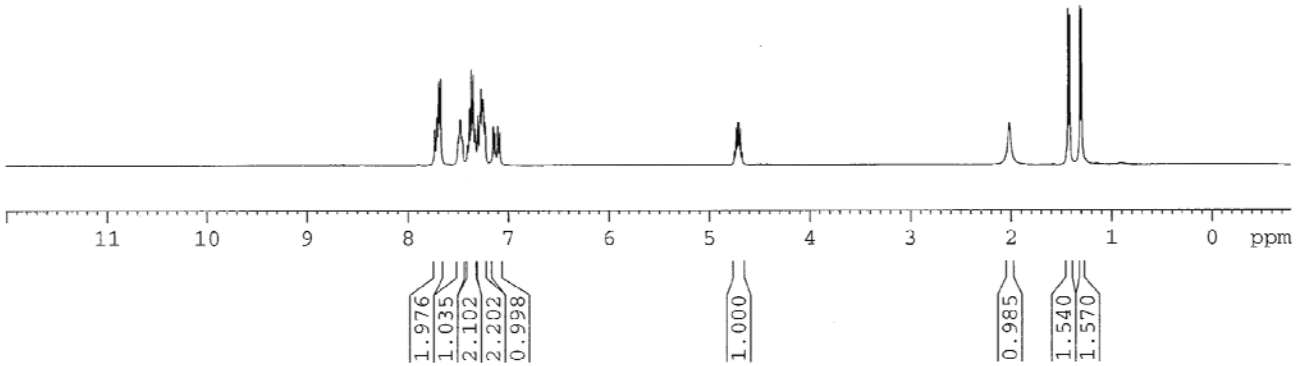

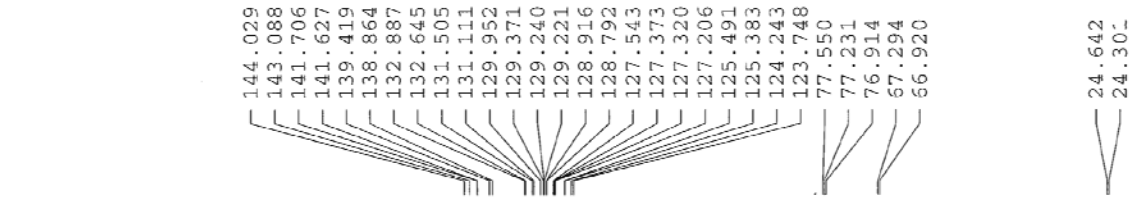

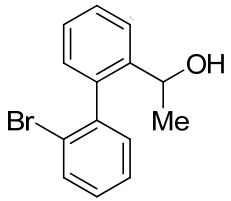

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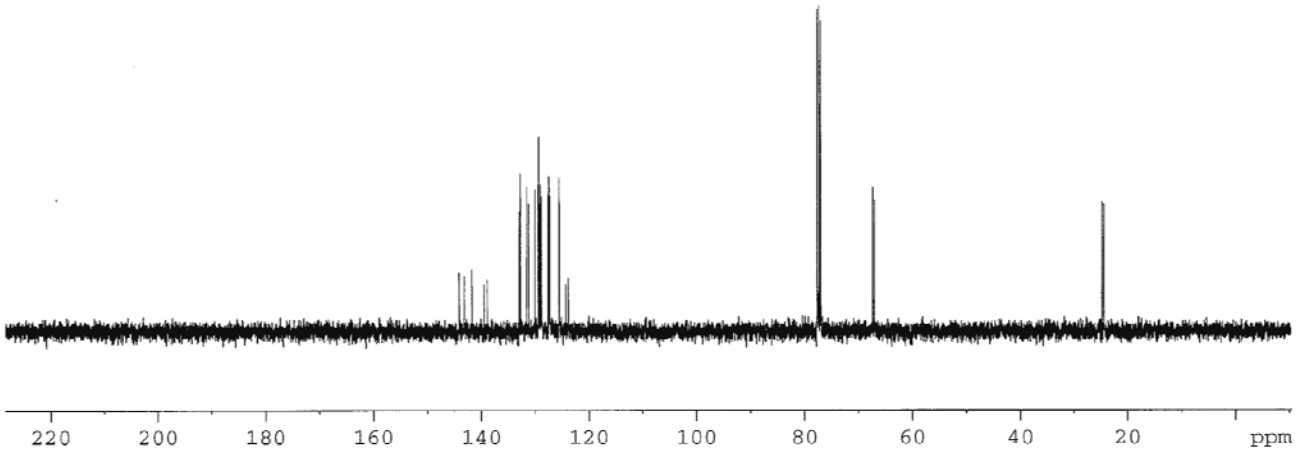

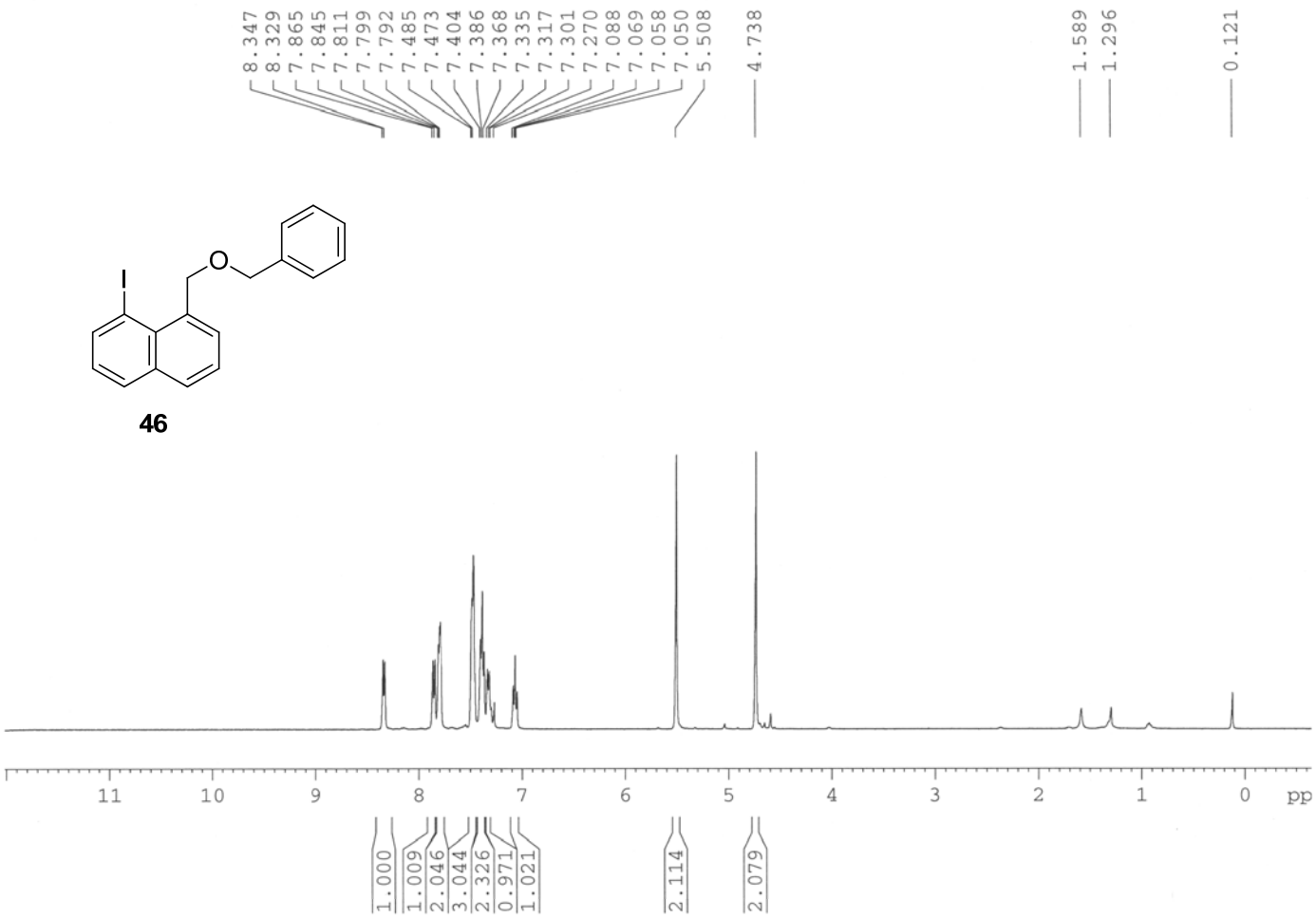

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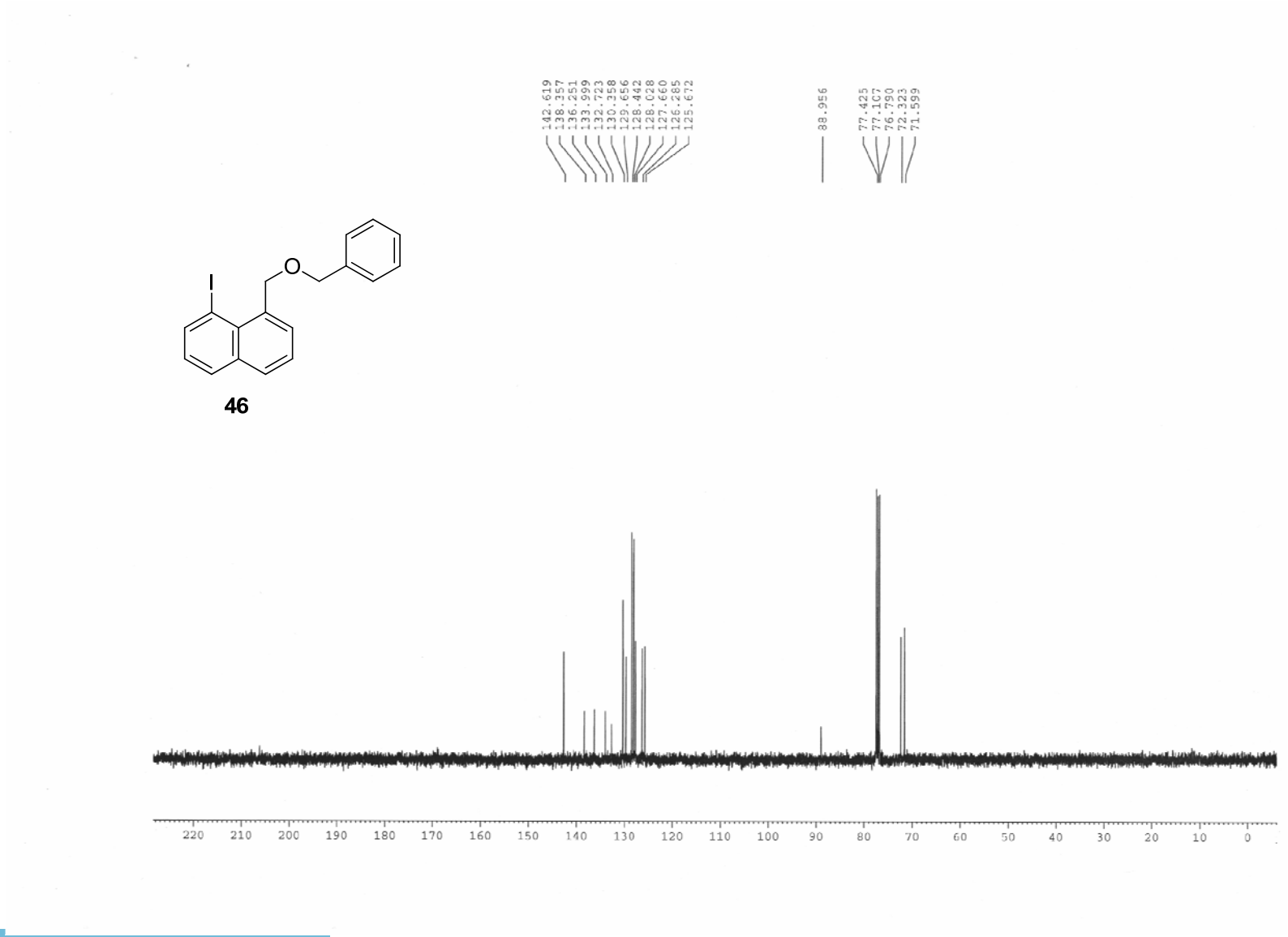

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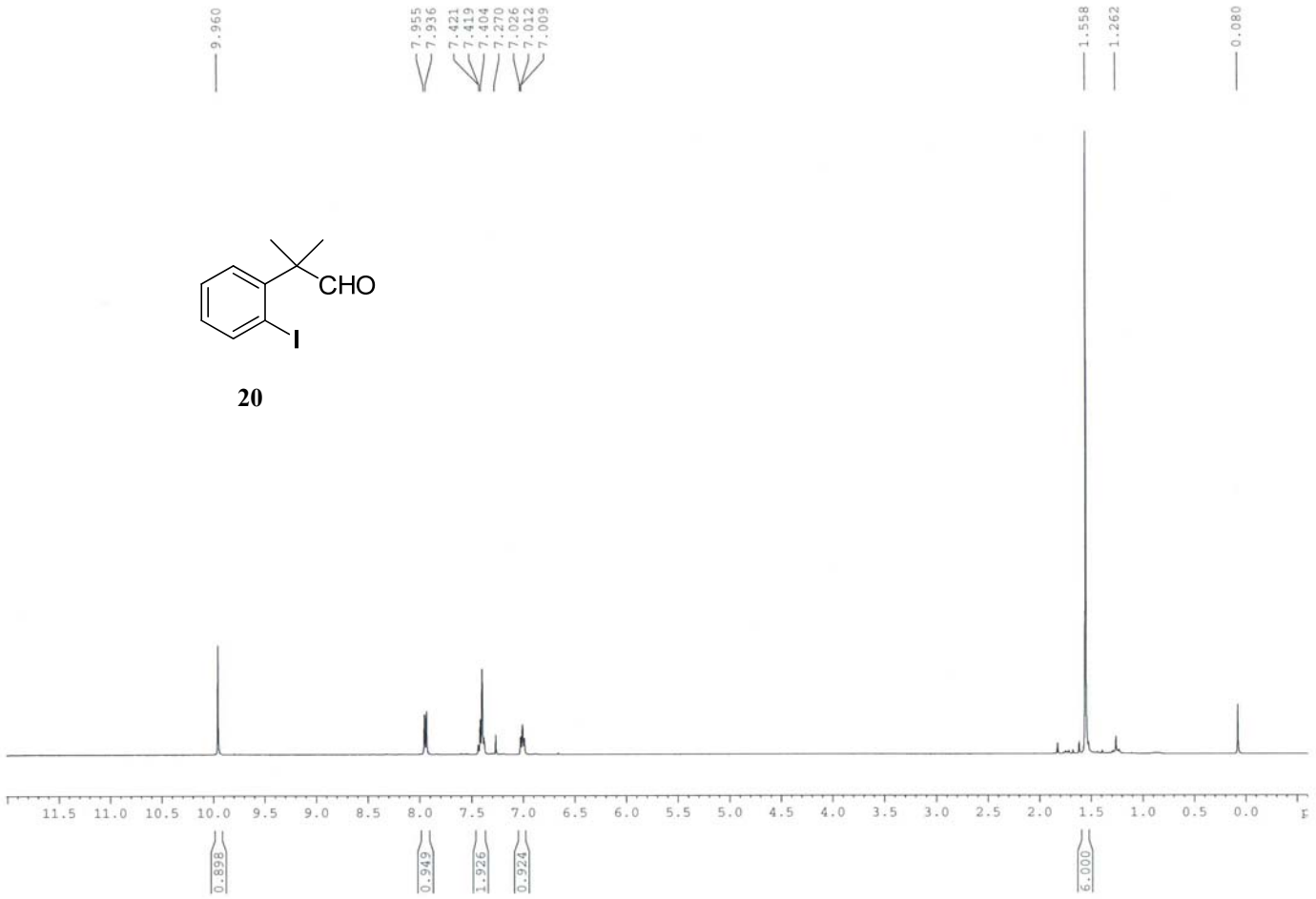
APPENDIX C. CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA



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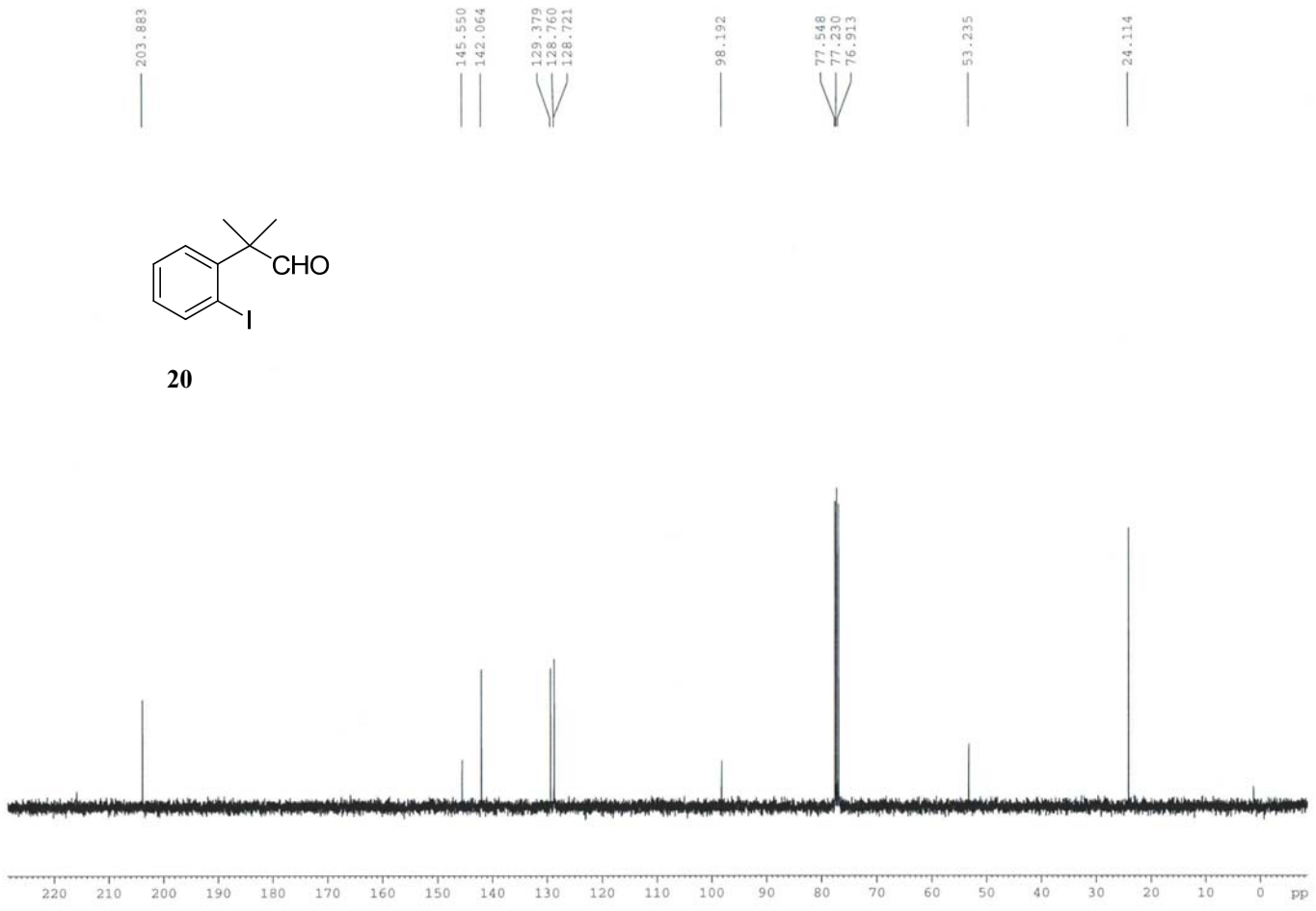

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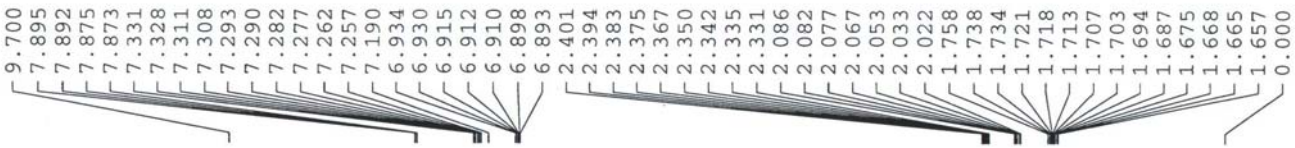

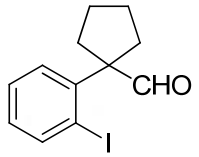

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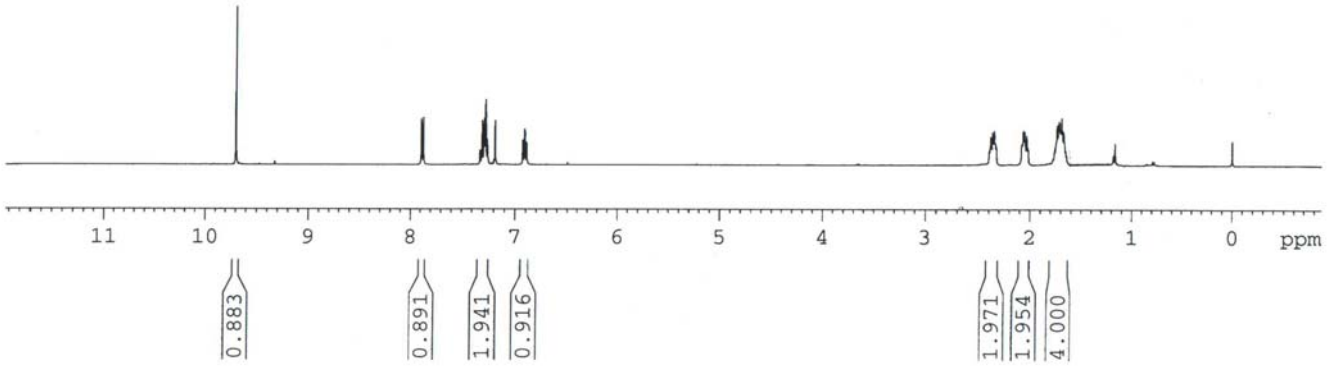

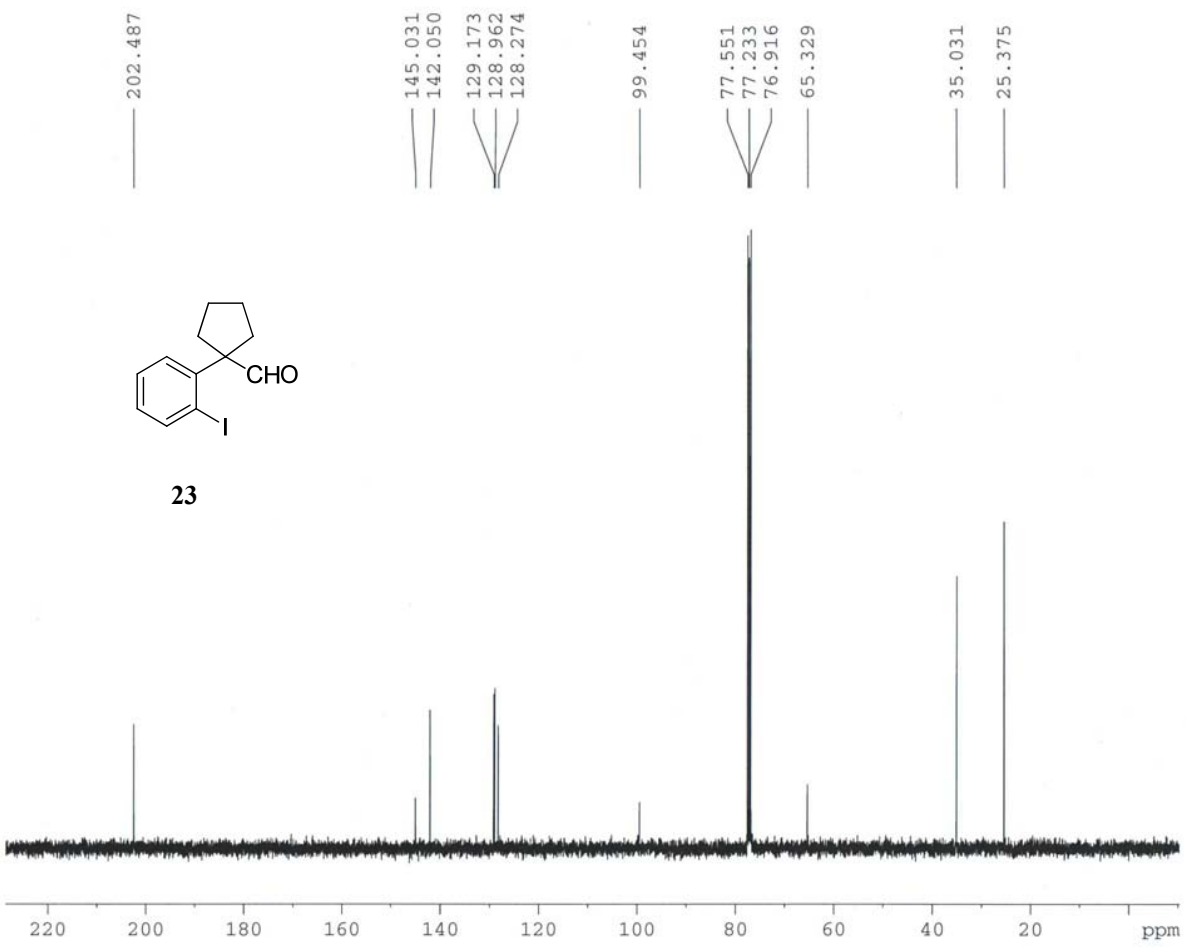

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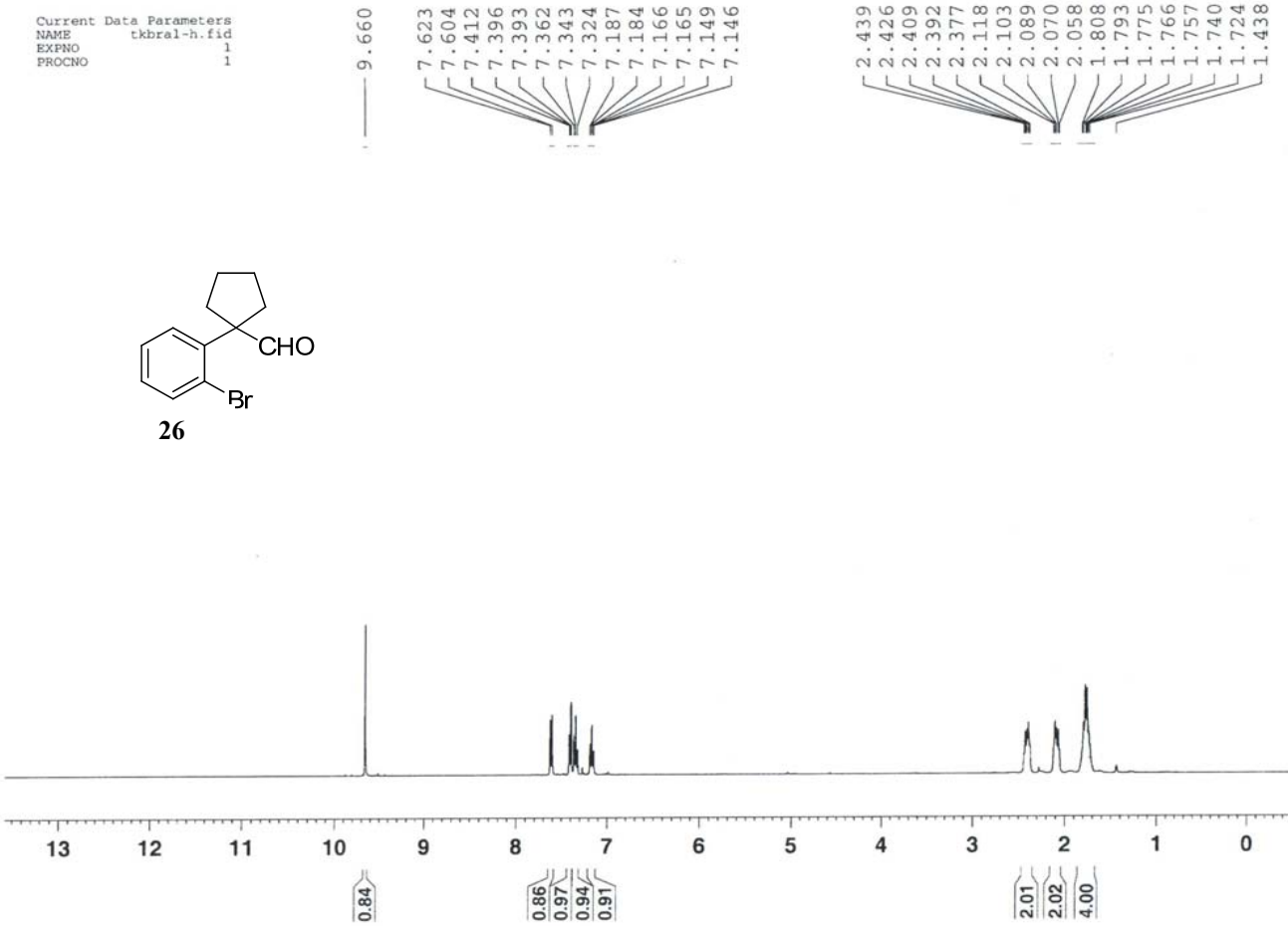

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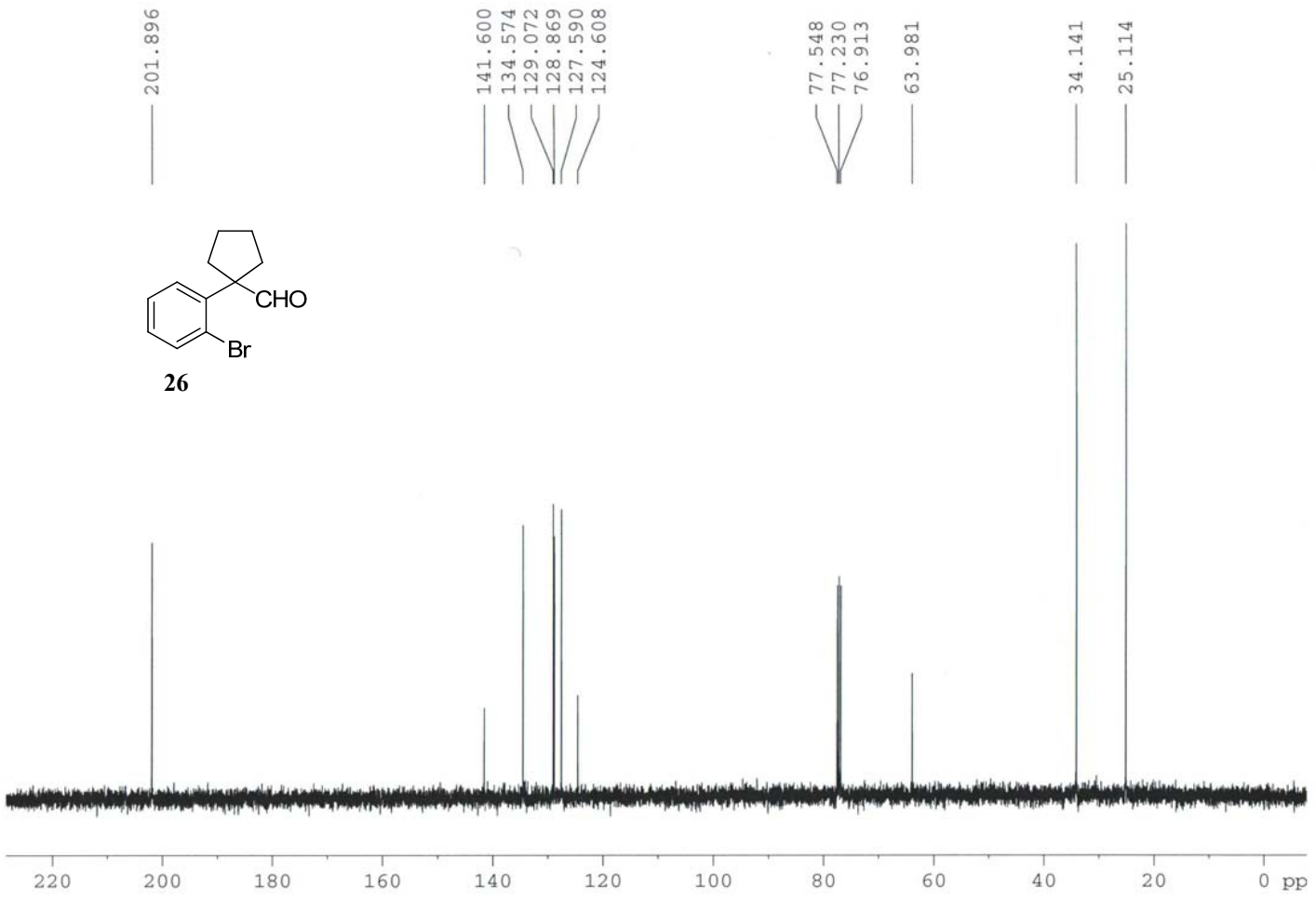

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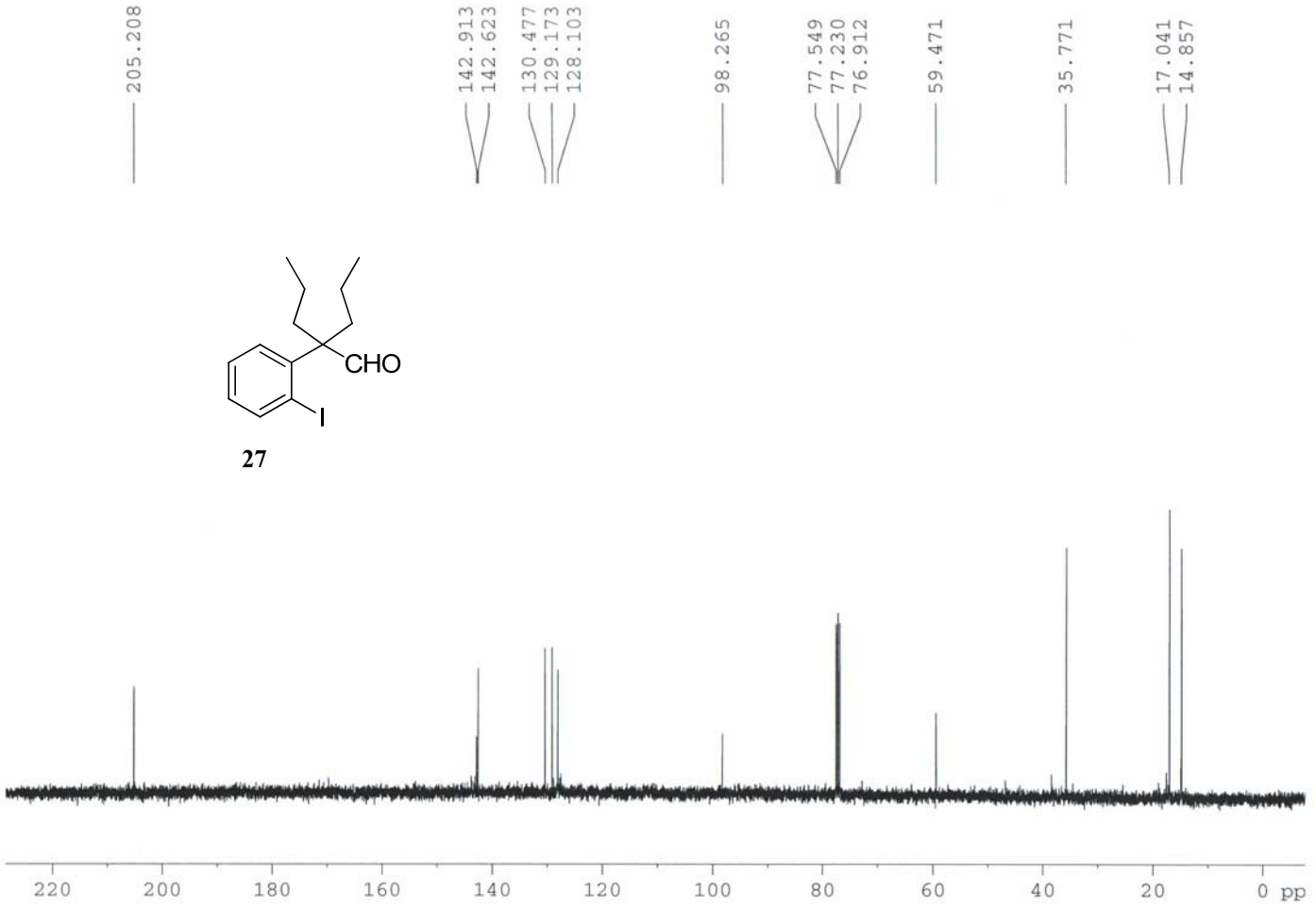

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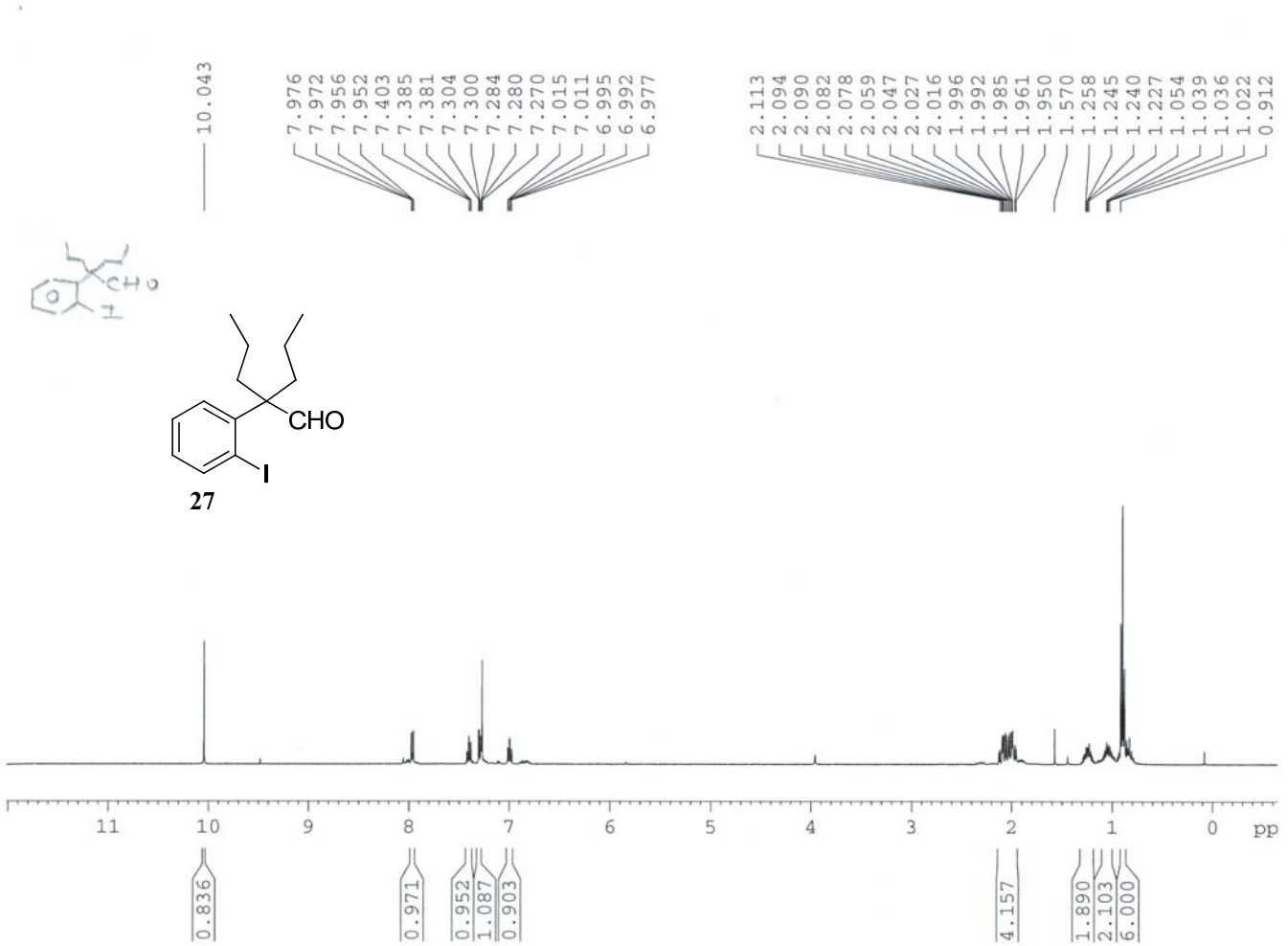

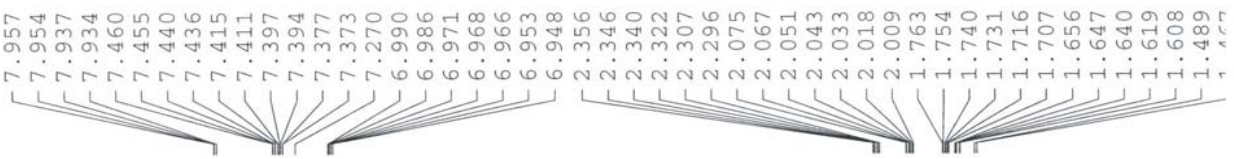

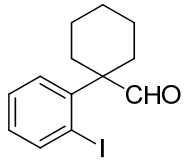

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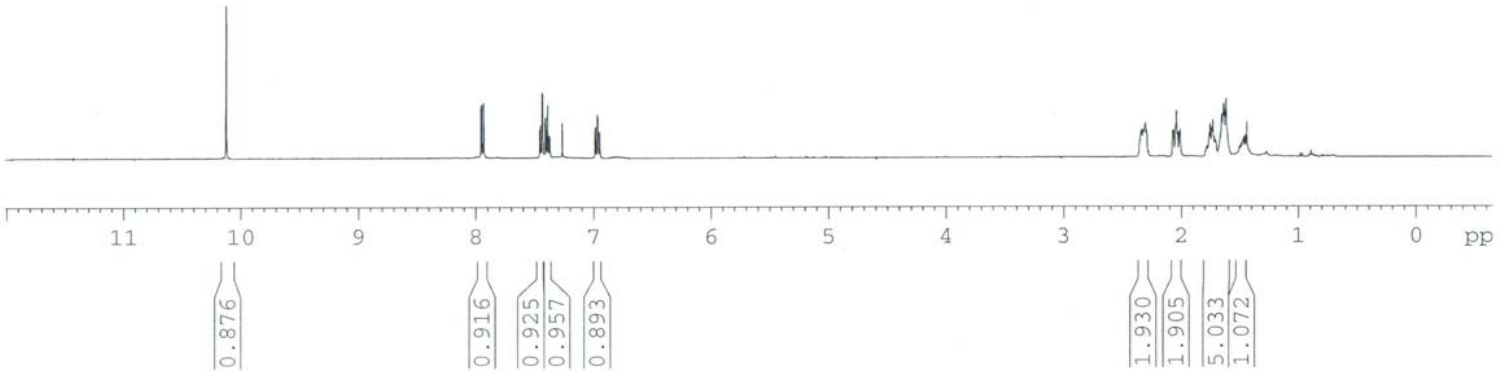

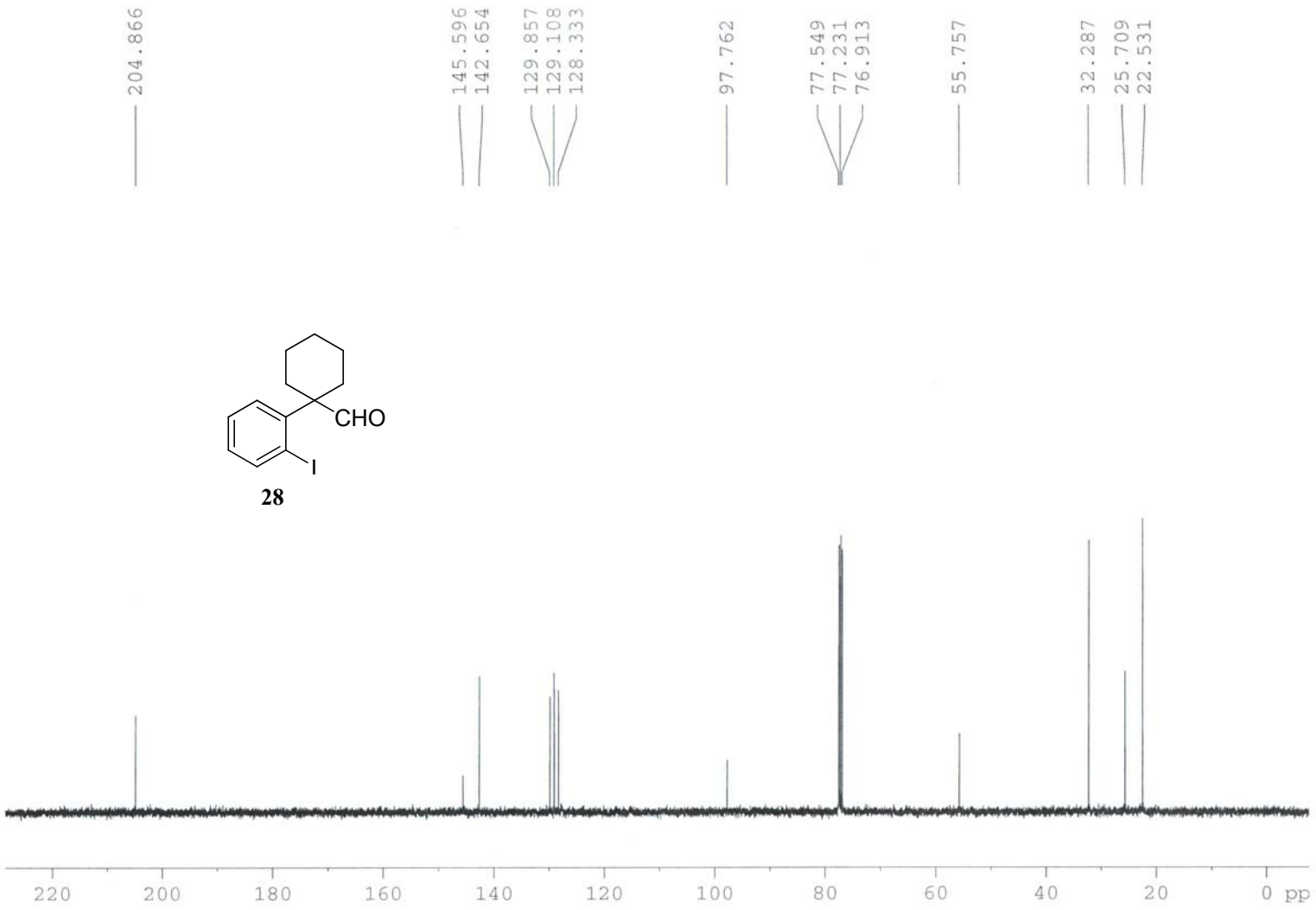

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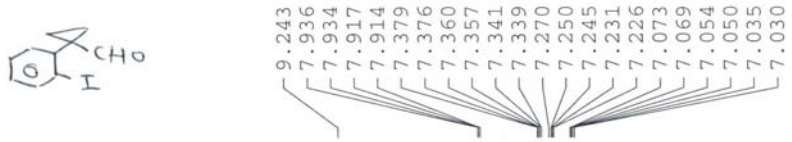

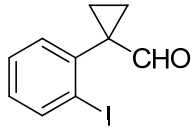

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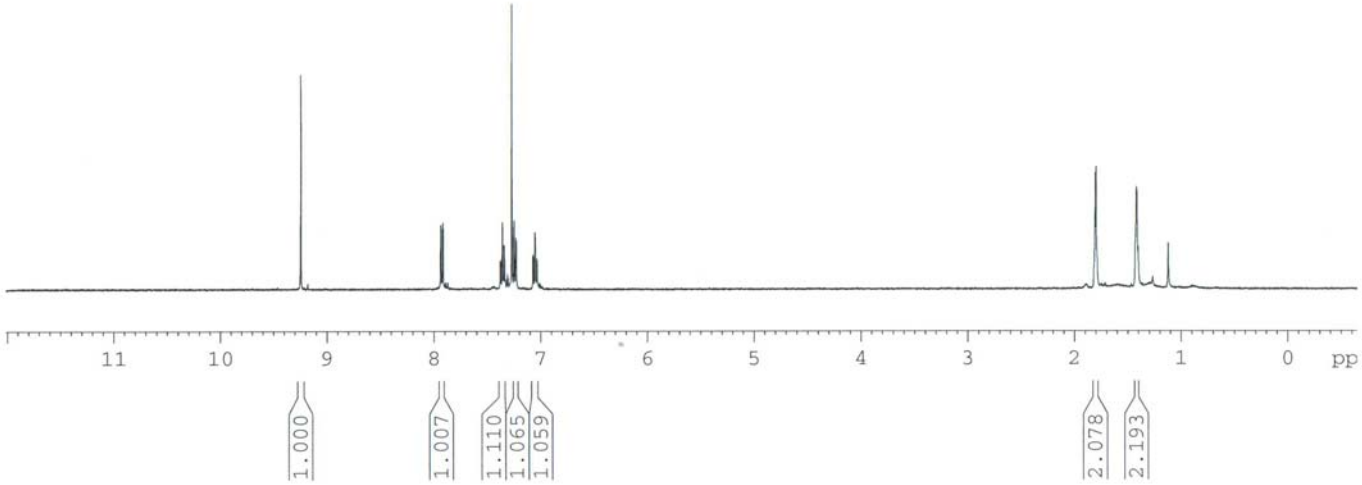

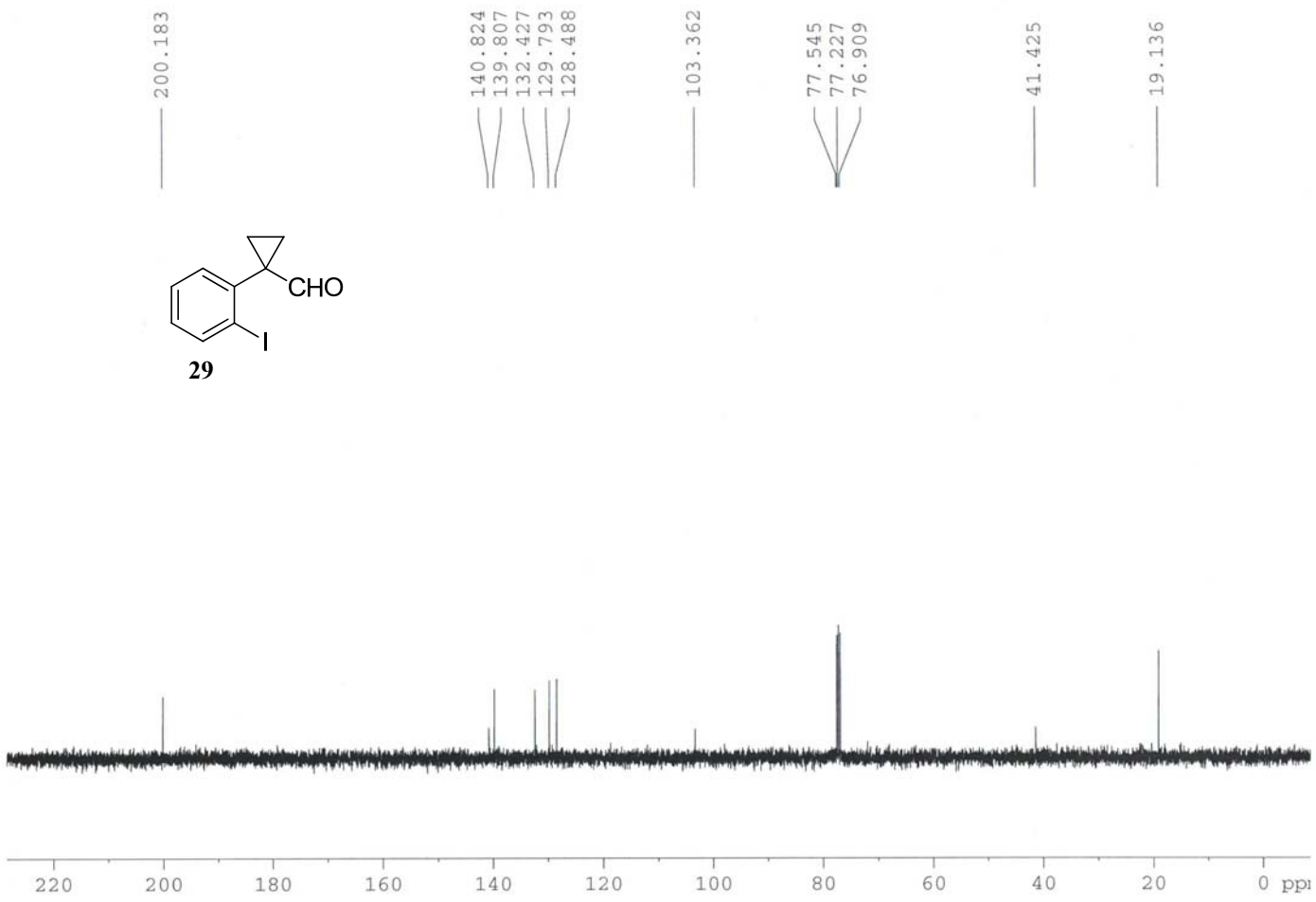

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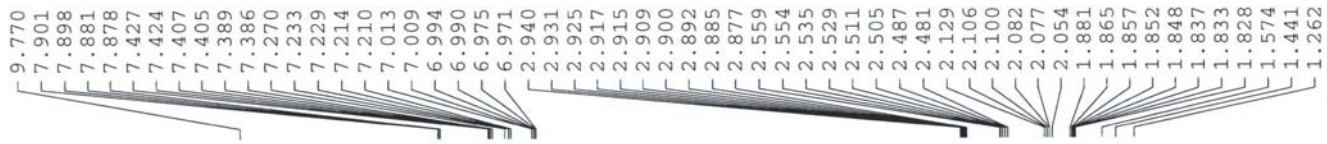

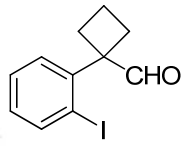

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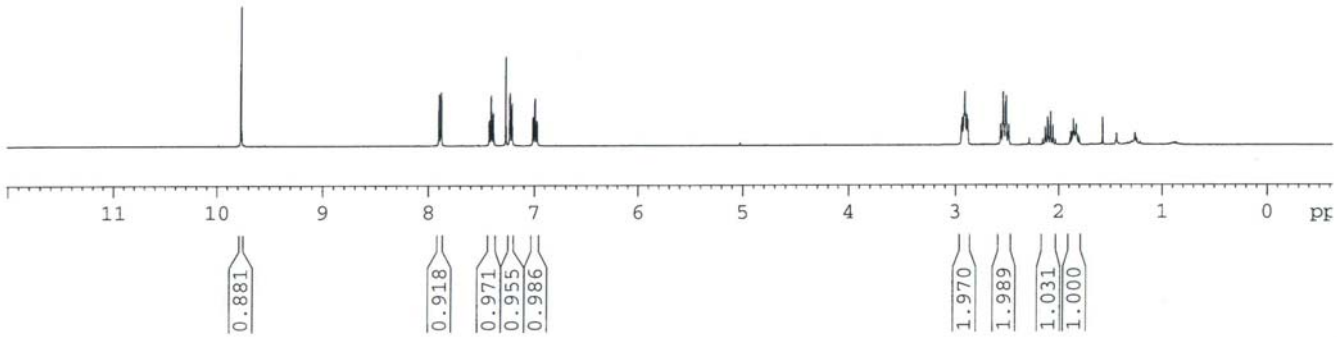

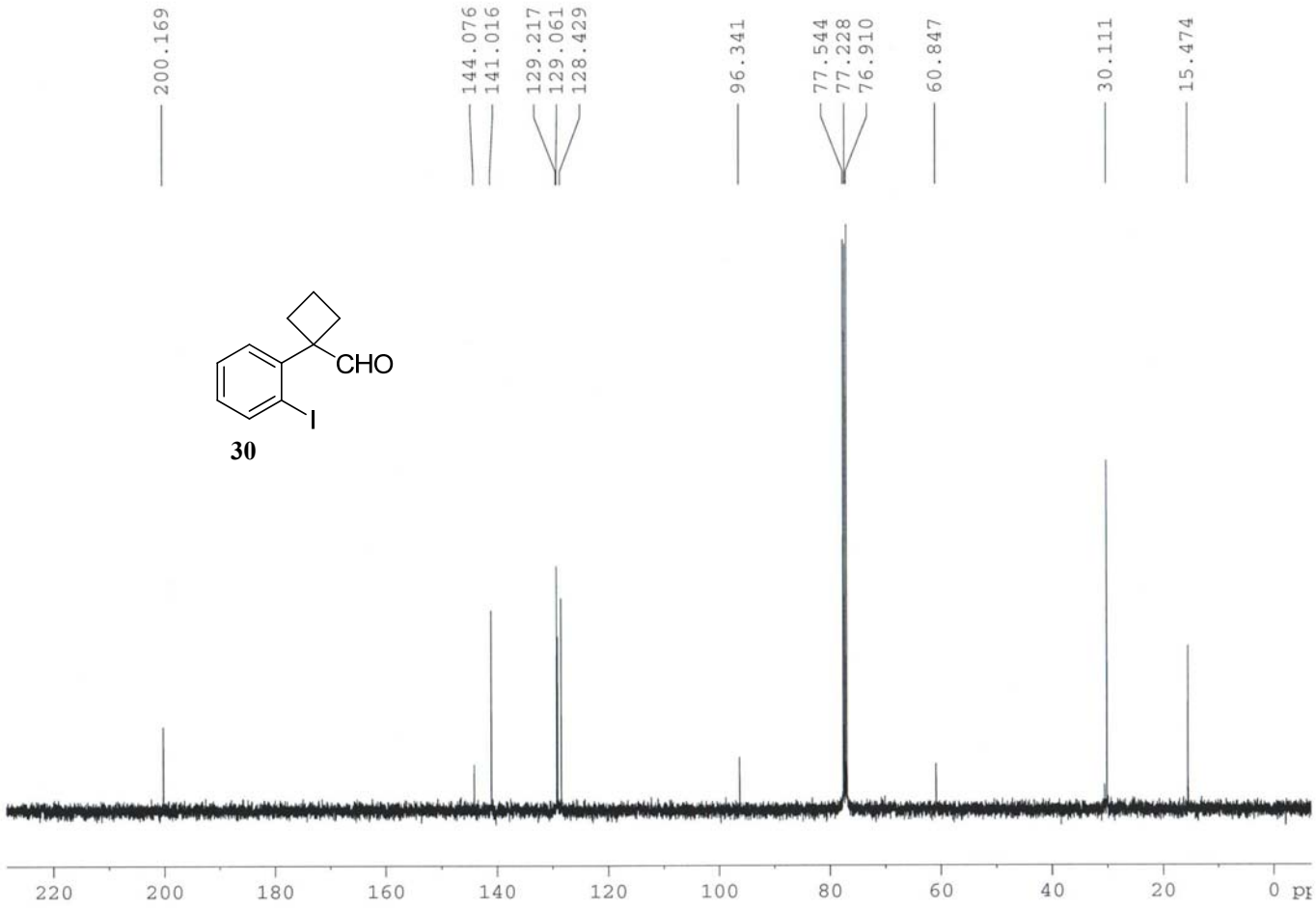

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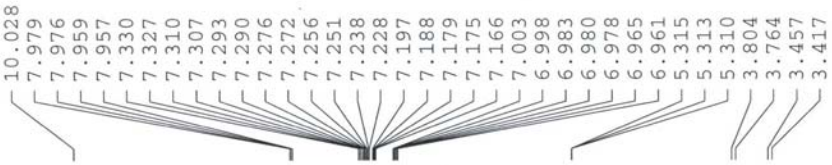

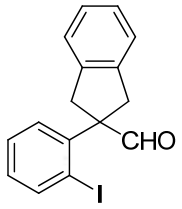

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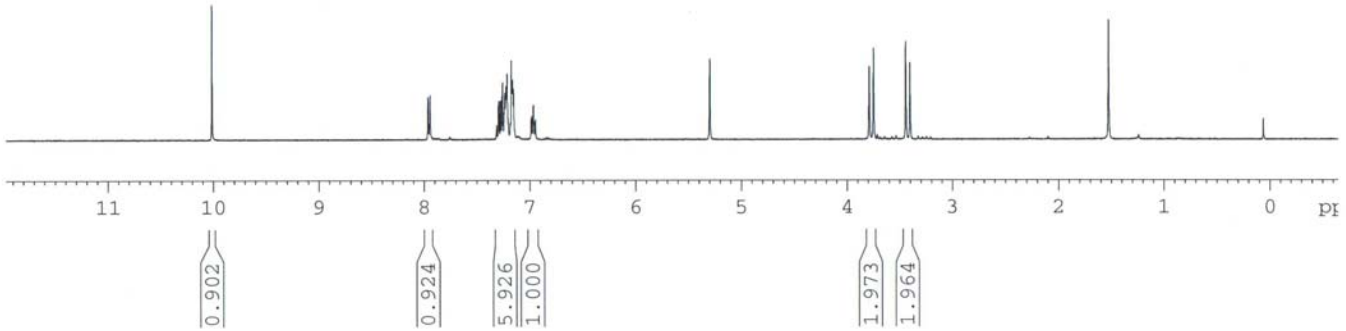

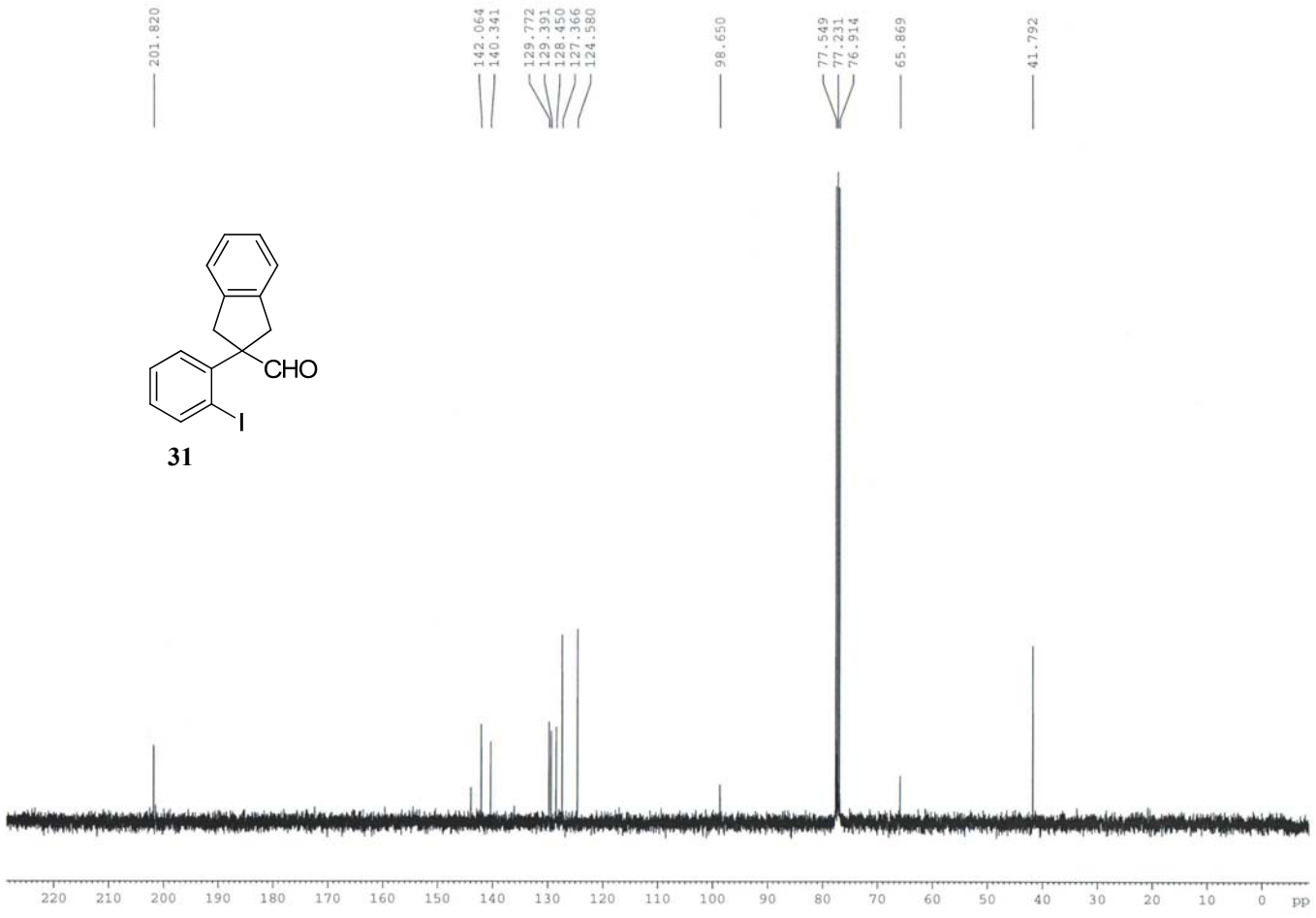

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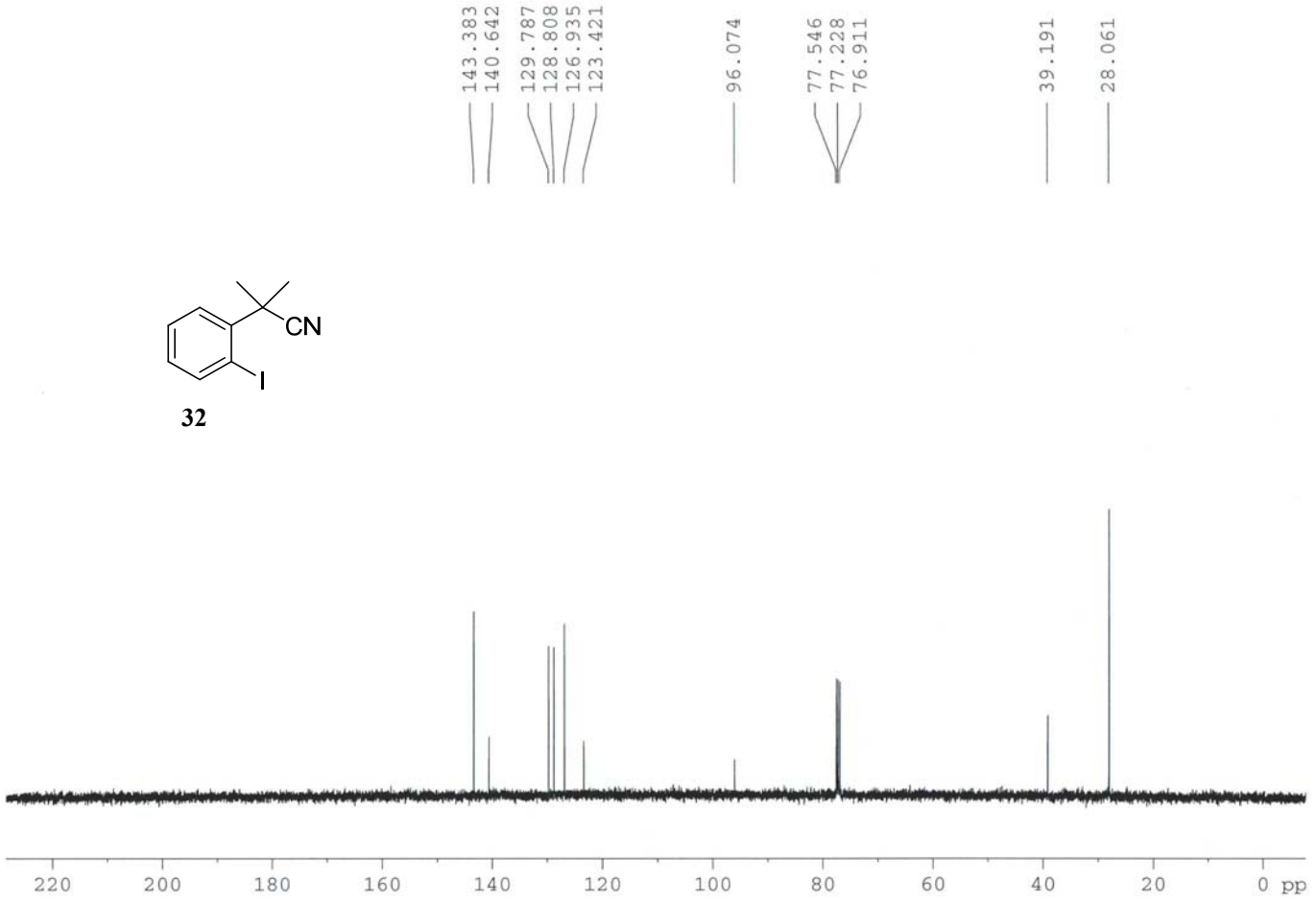

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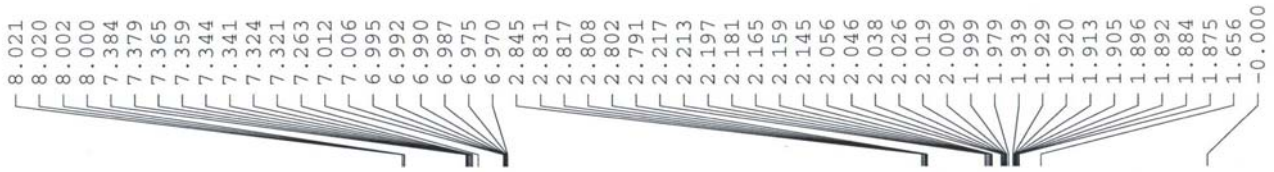

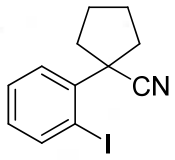

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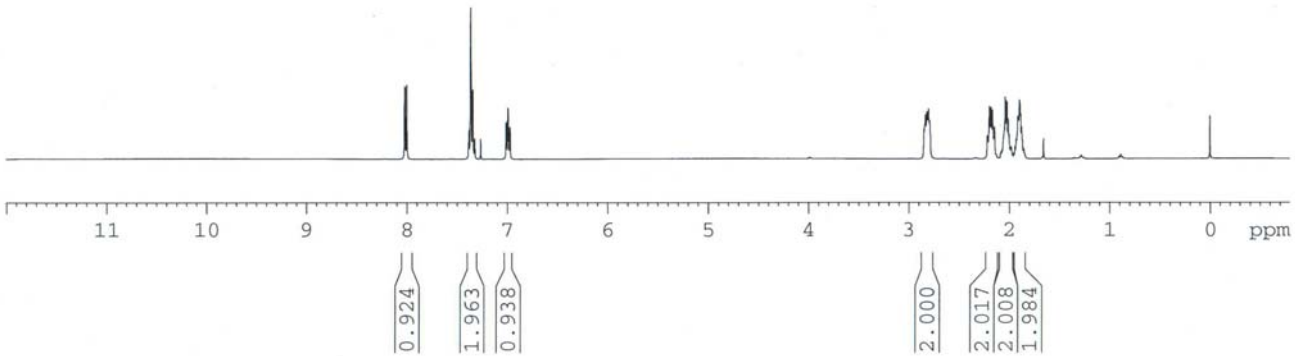

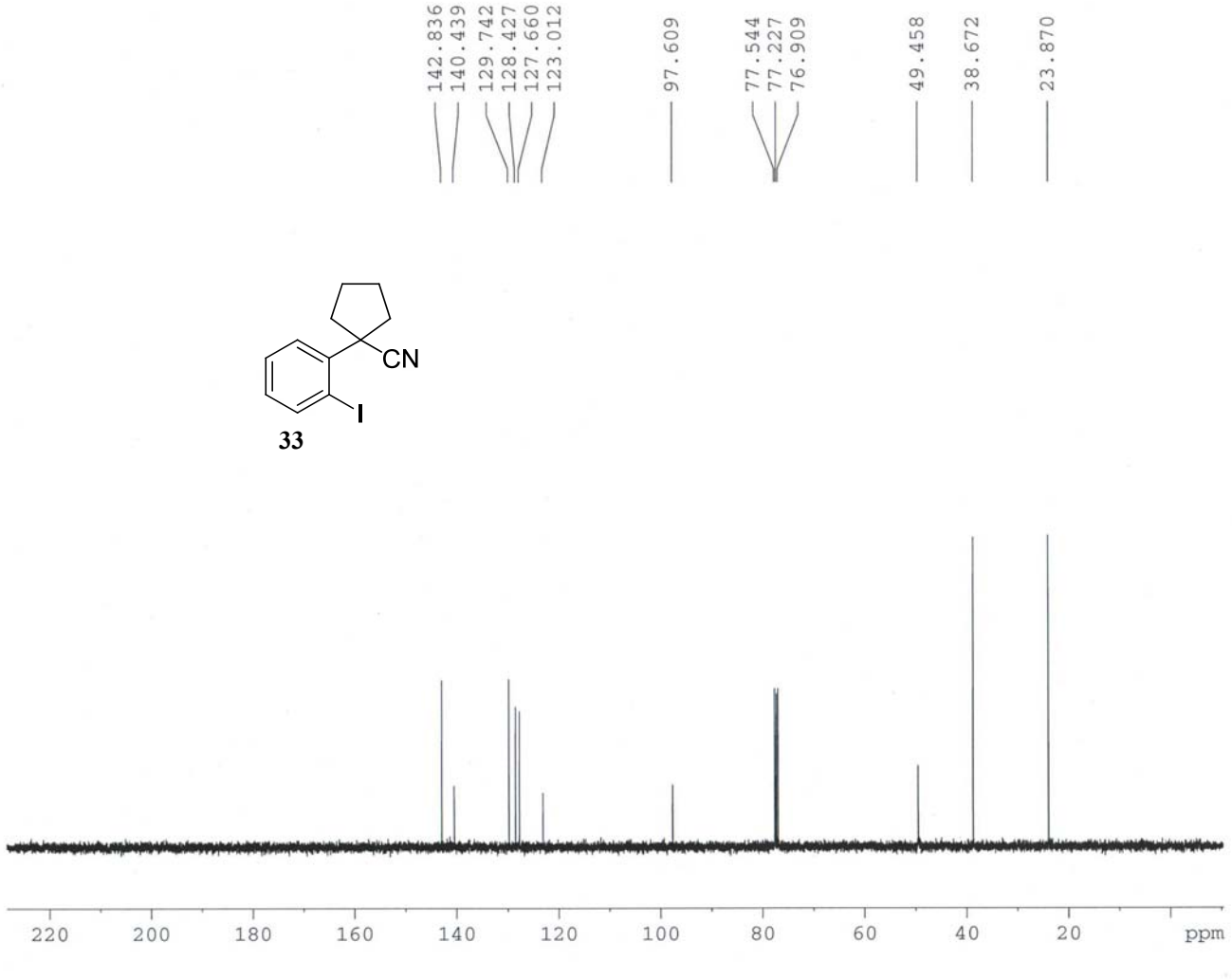

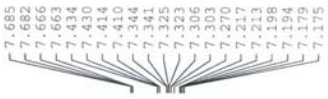

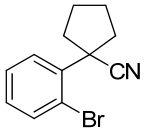

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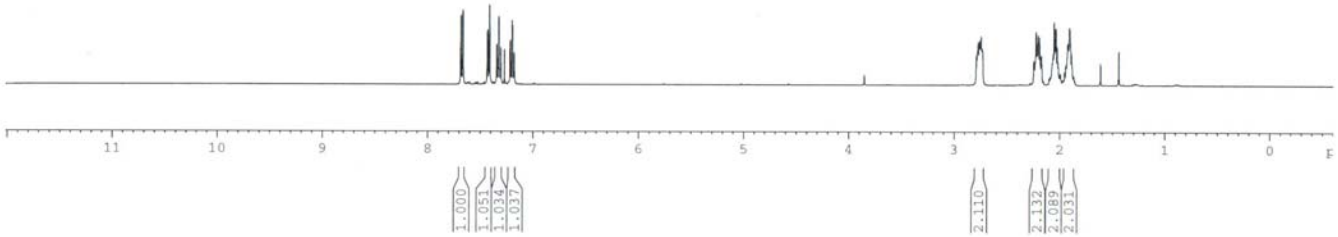

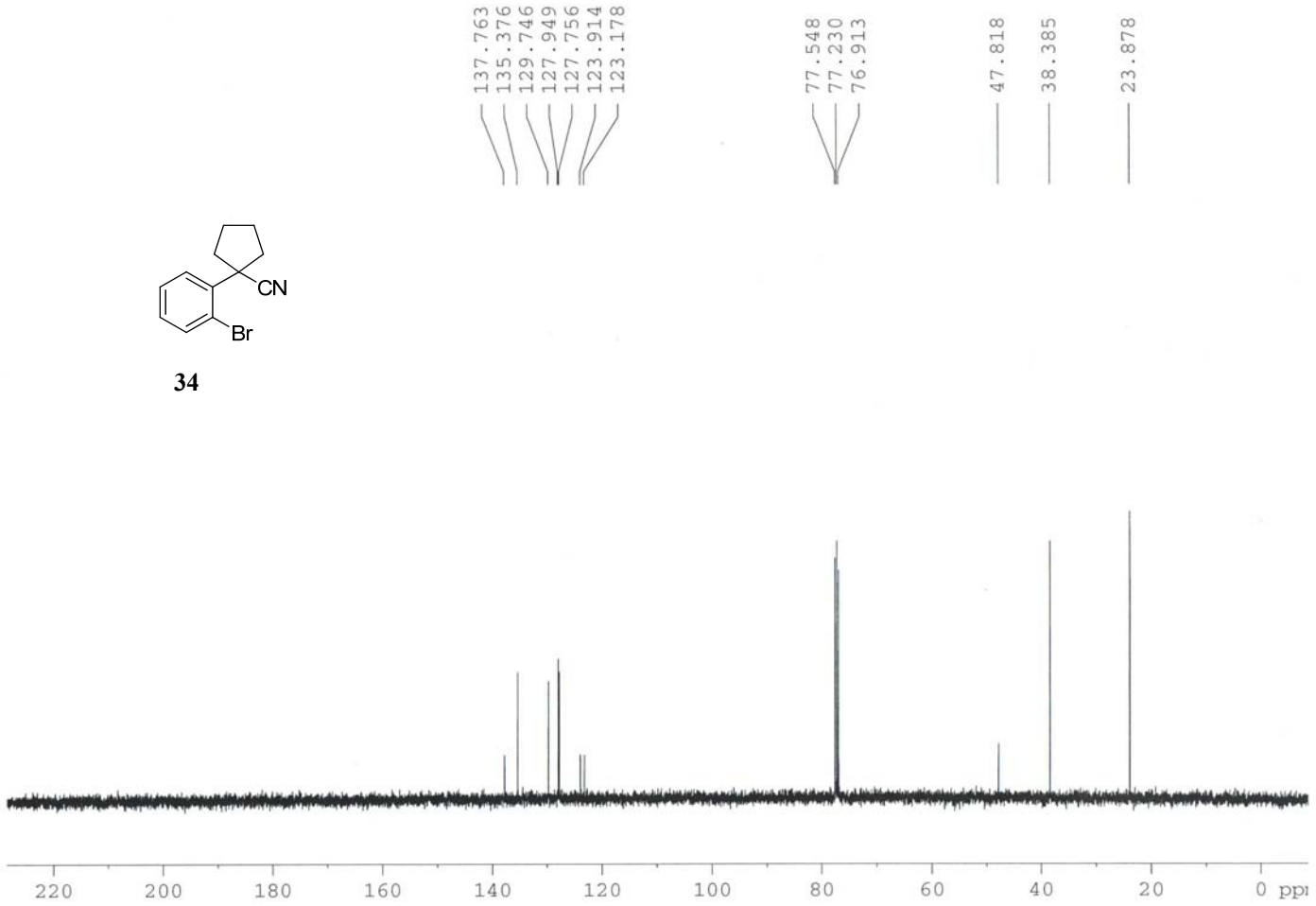

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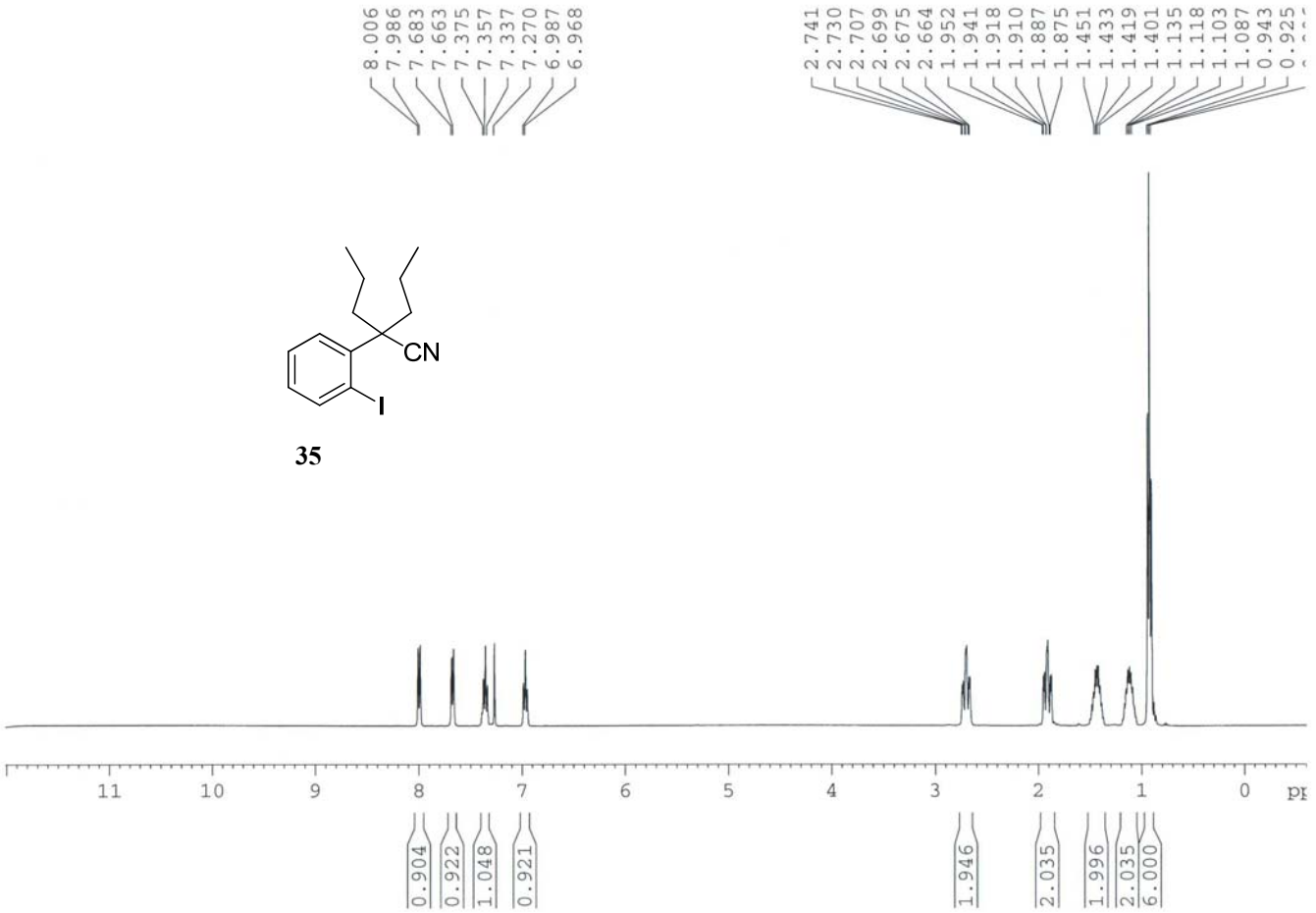

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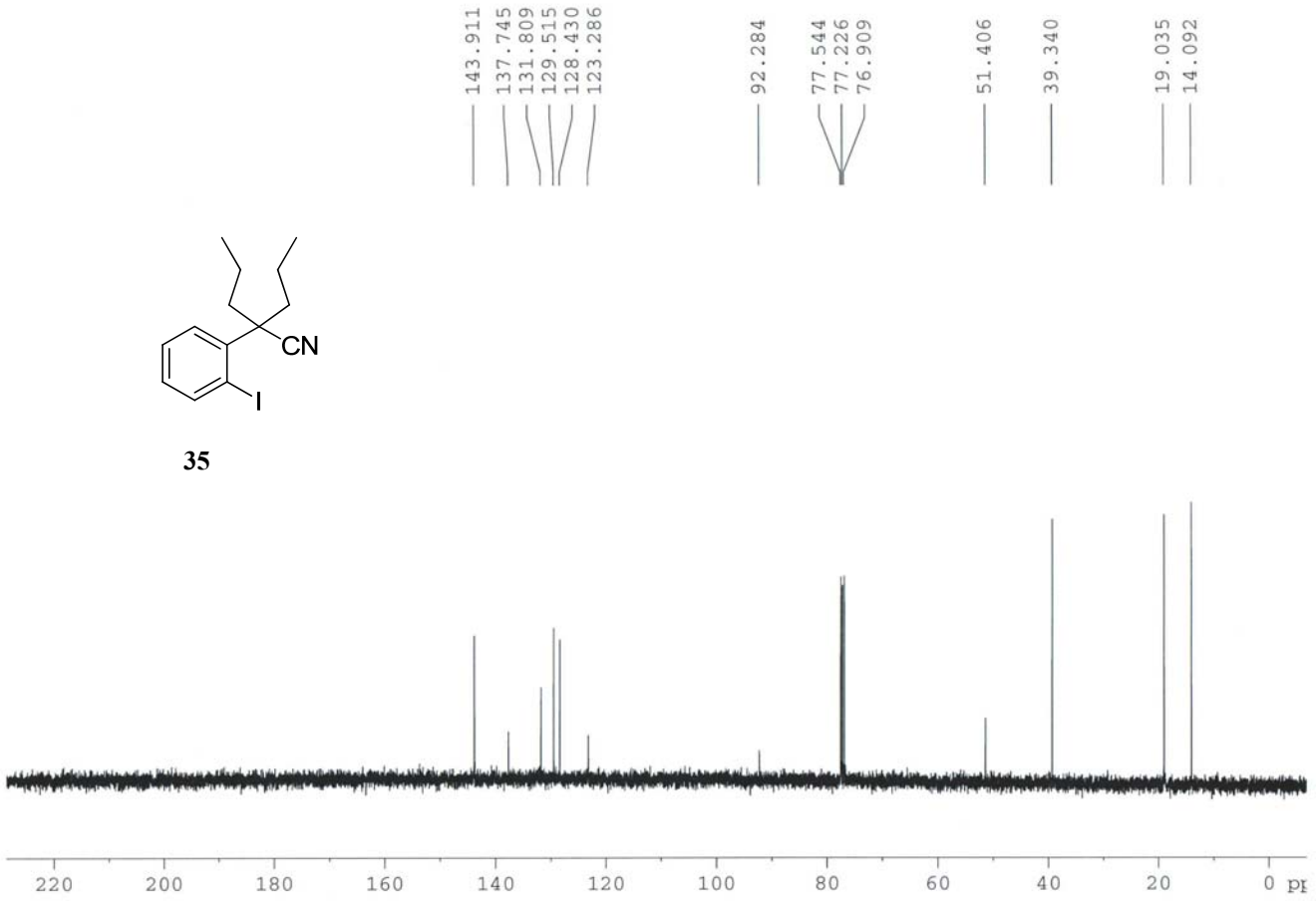

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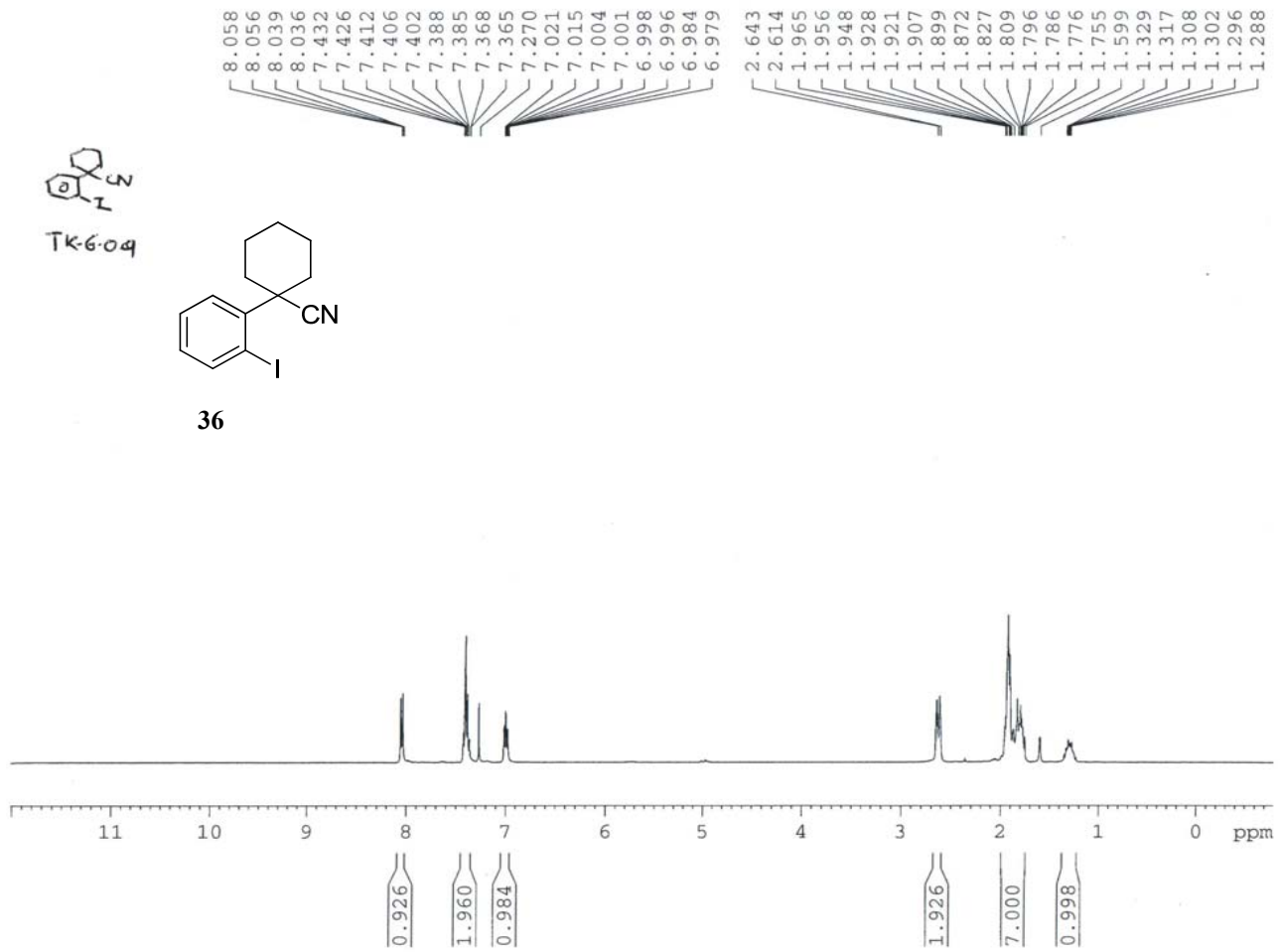

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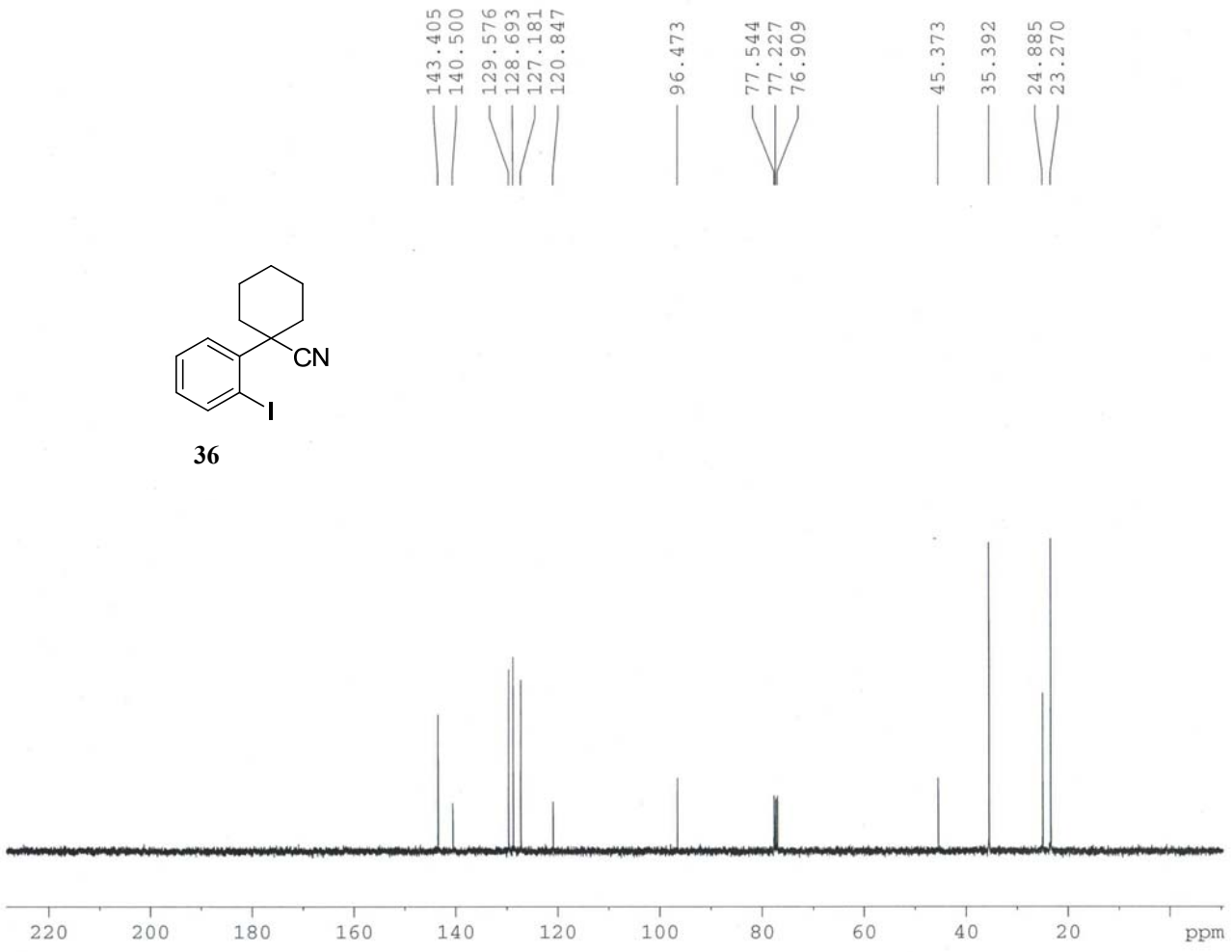

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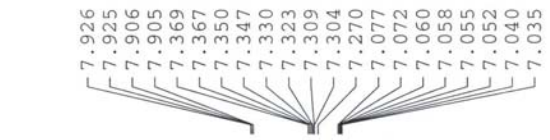

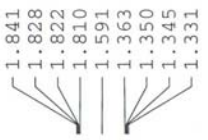

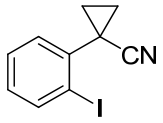

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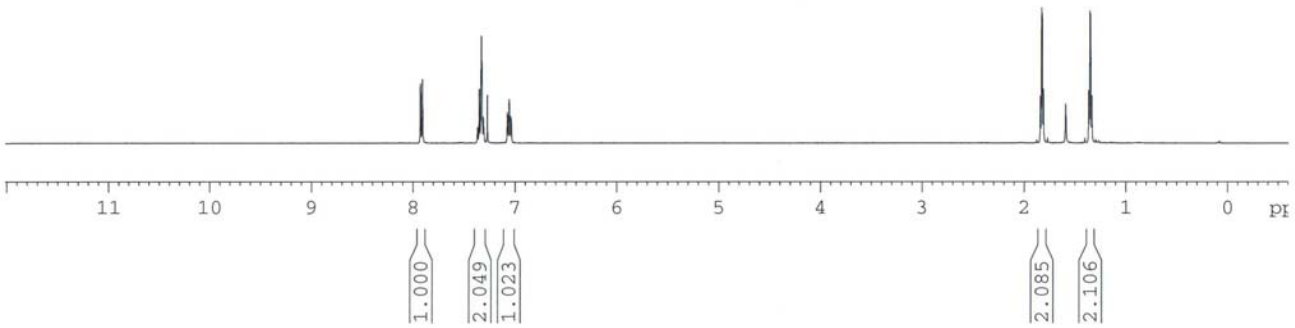

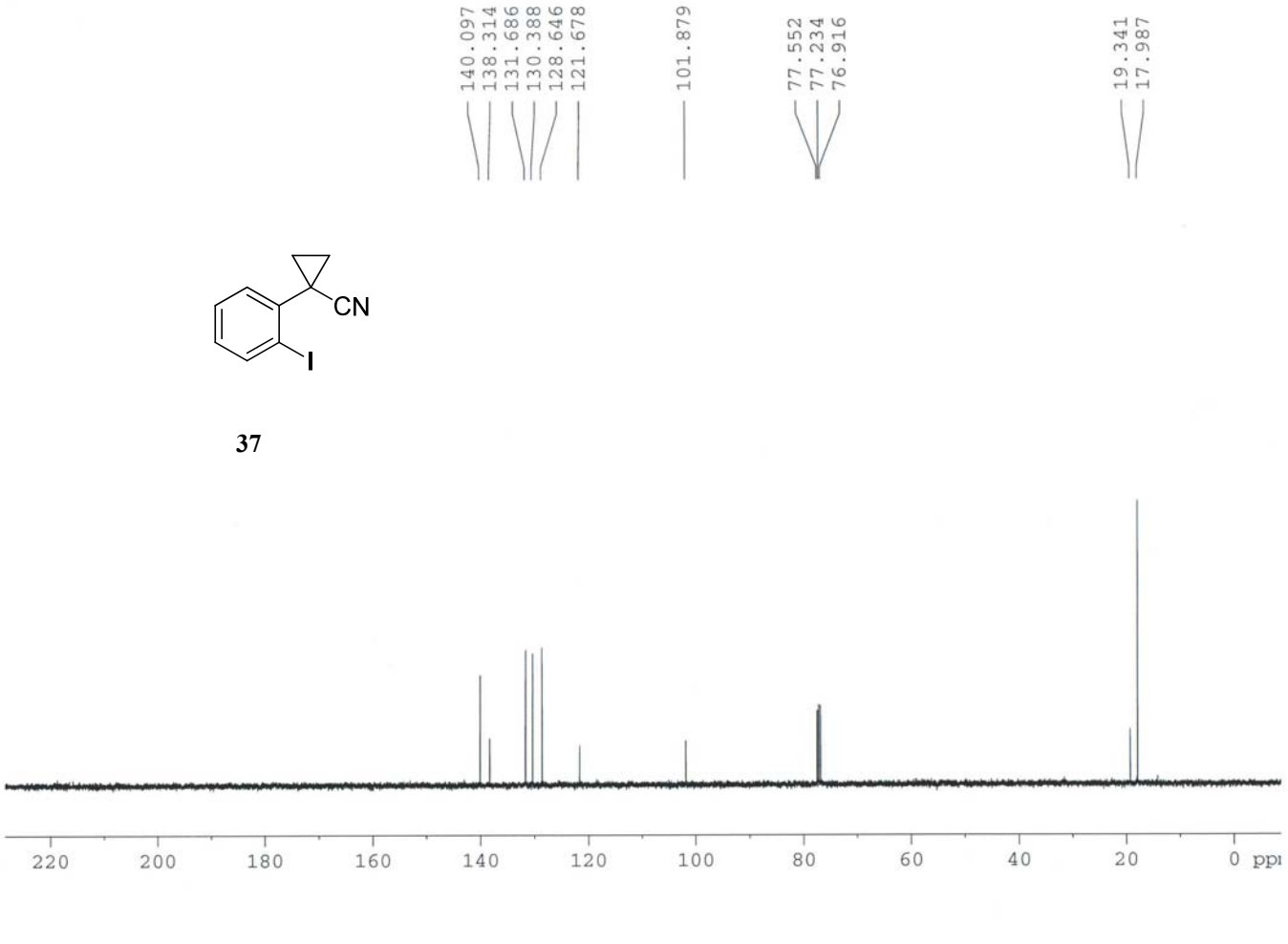

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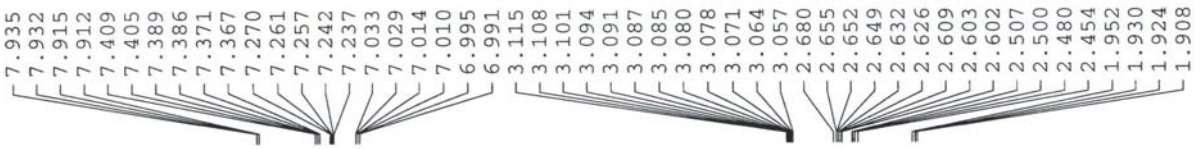

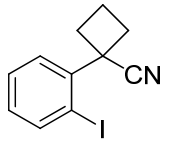

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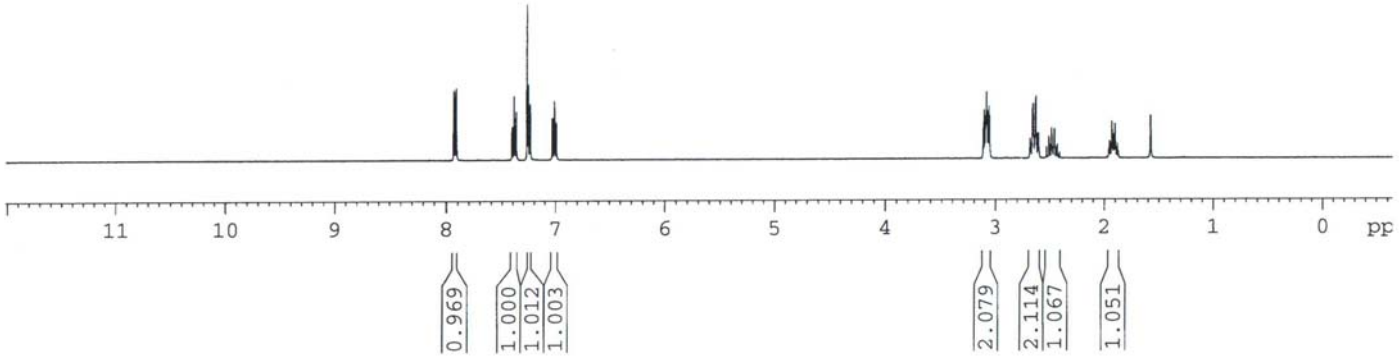

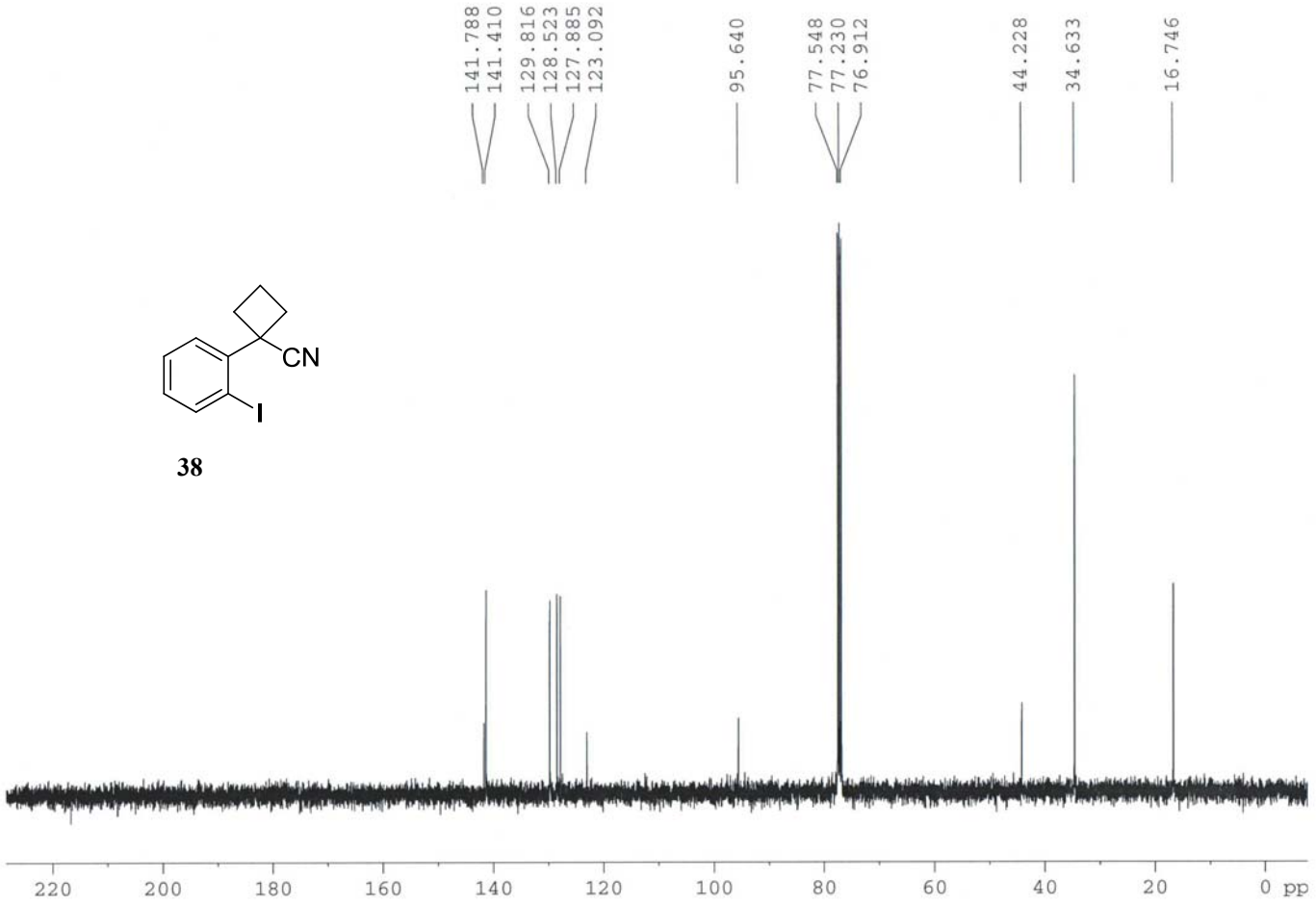

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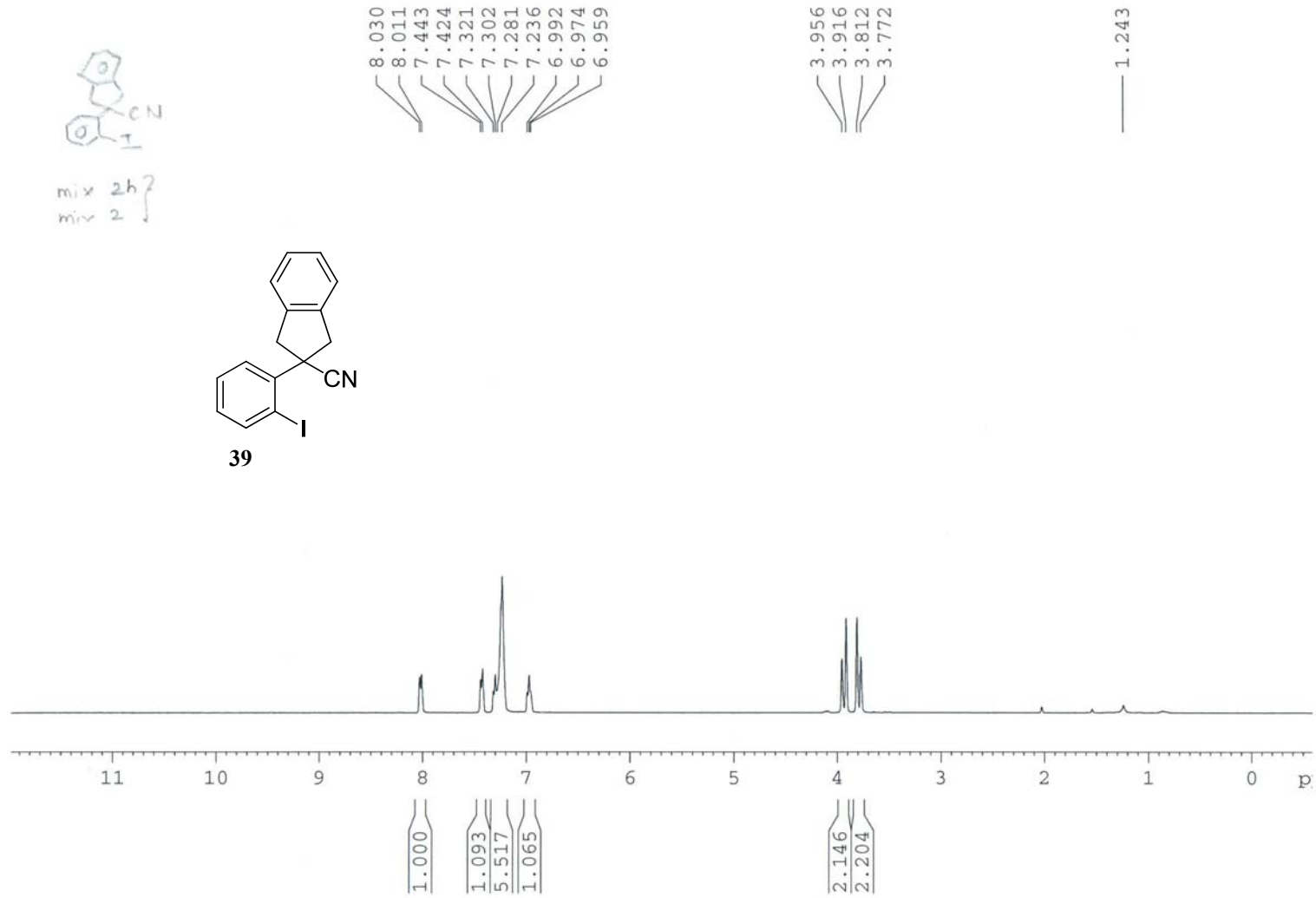

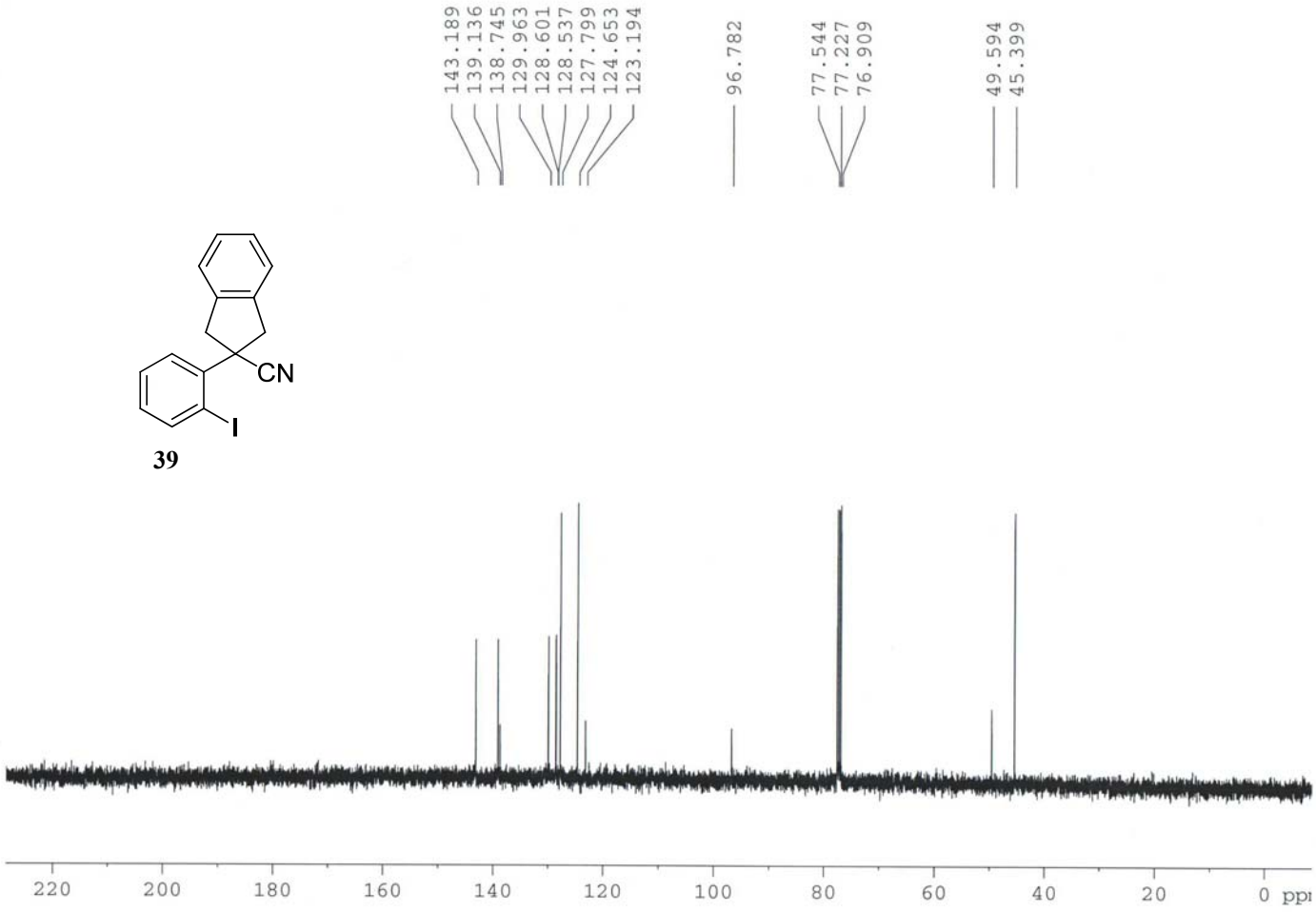

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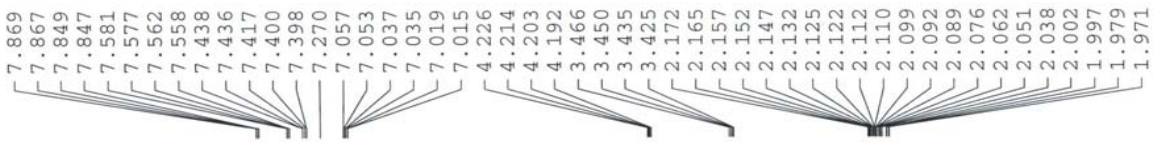

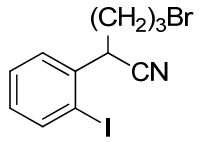

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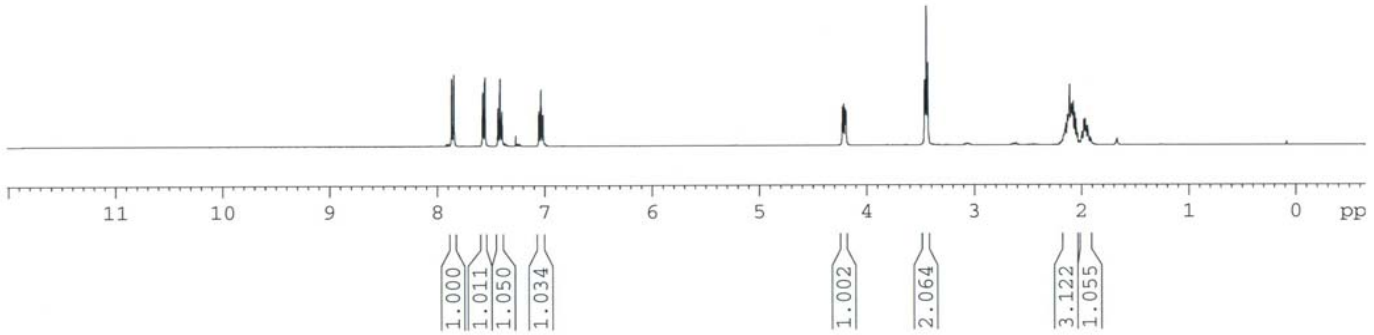

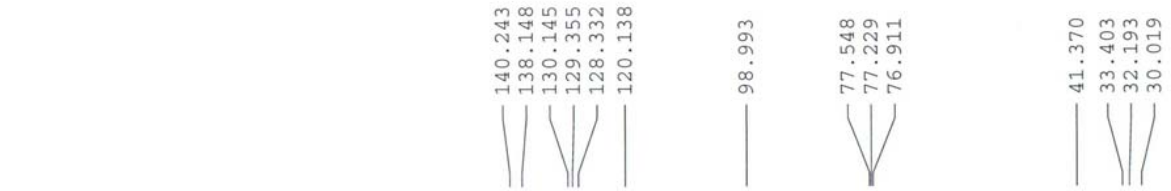

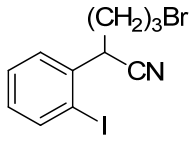

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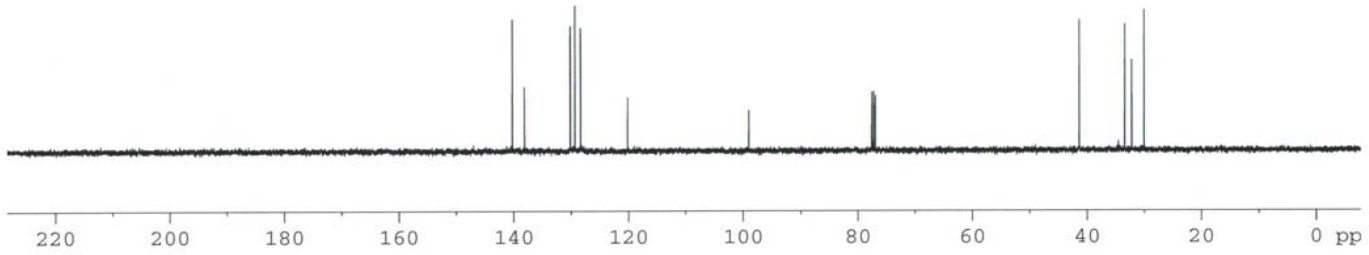

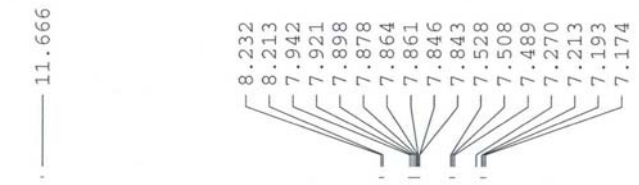

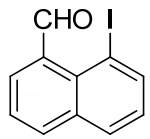

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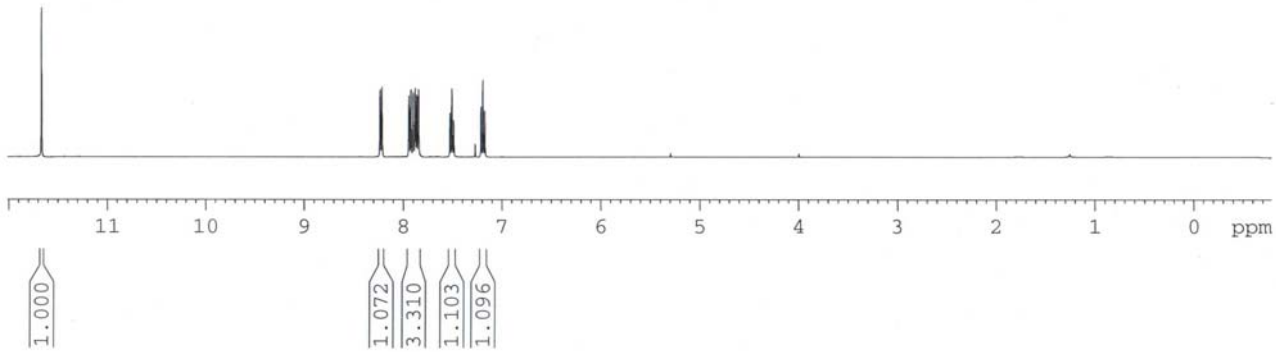

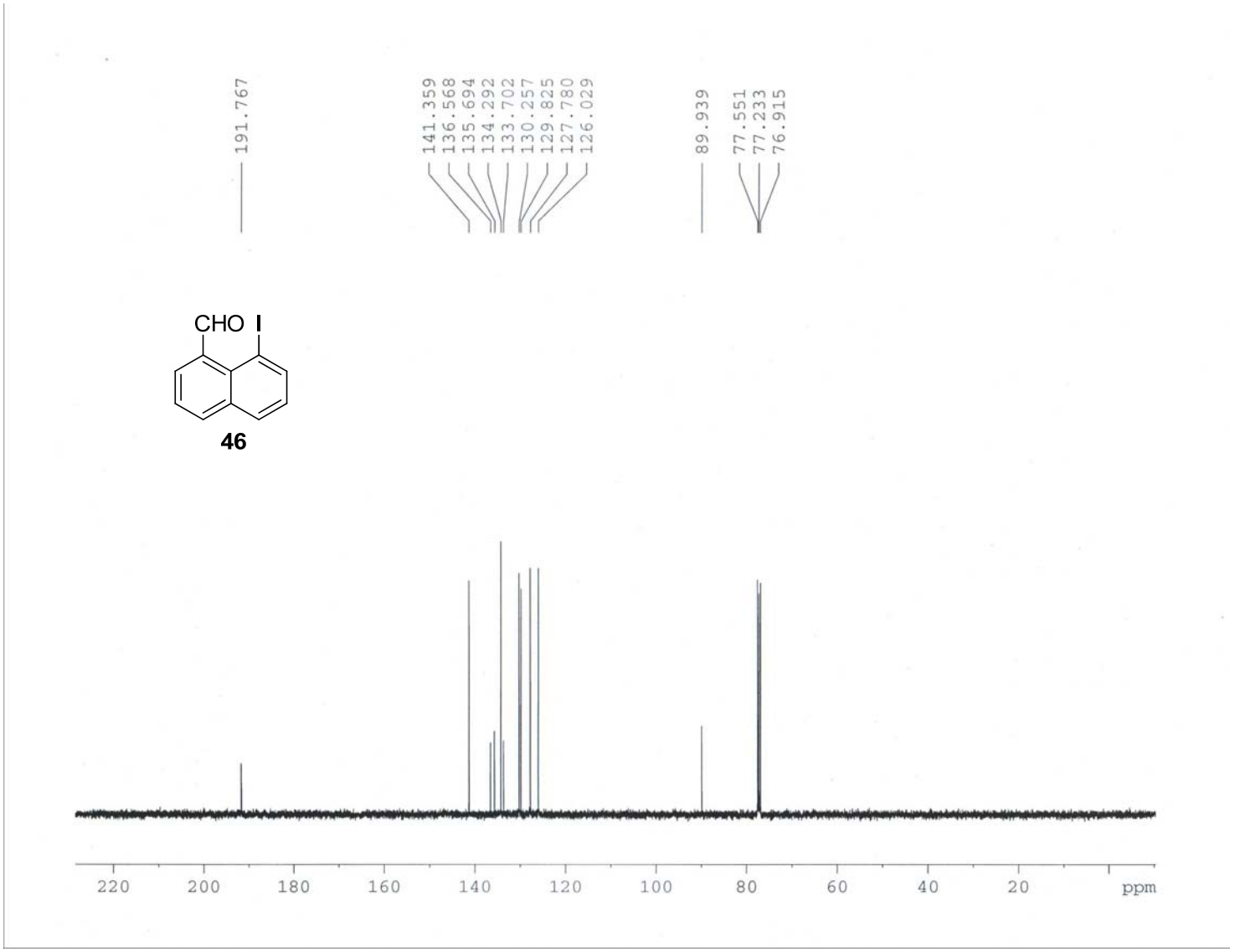

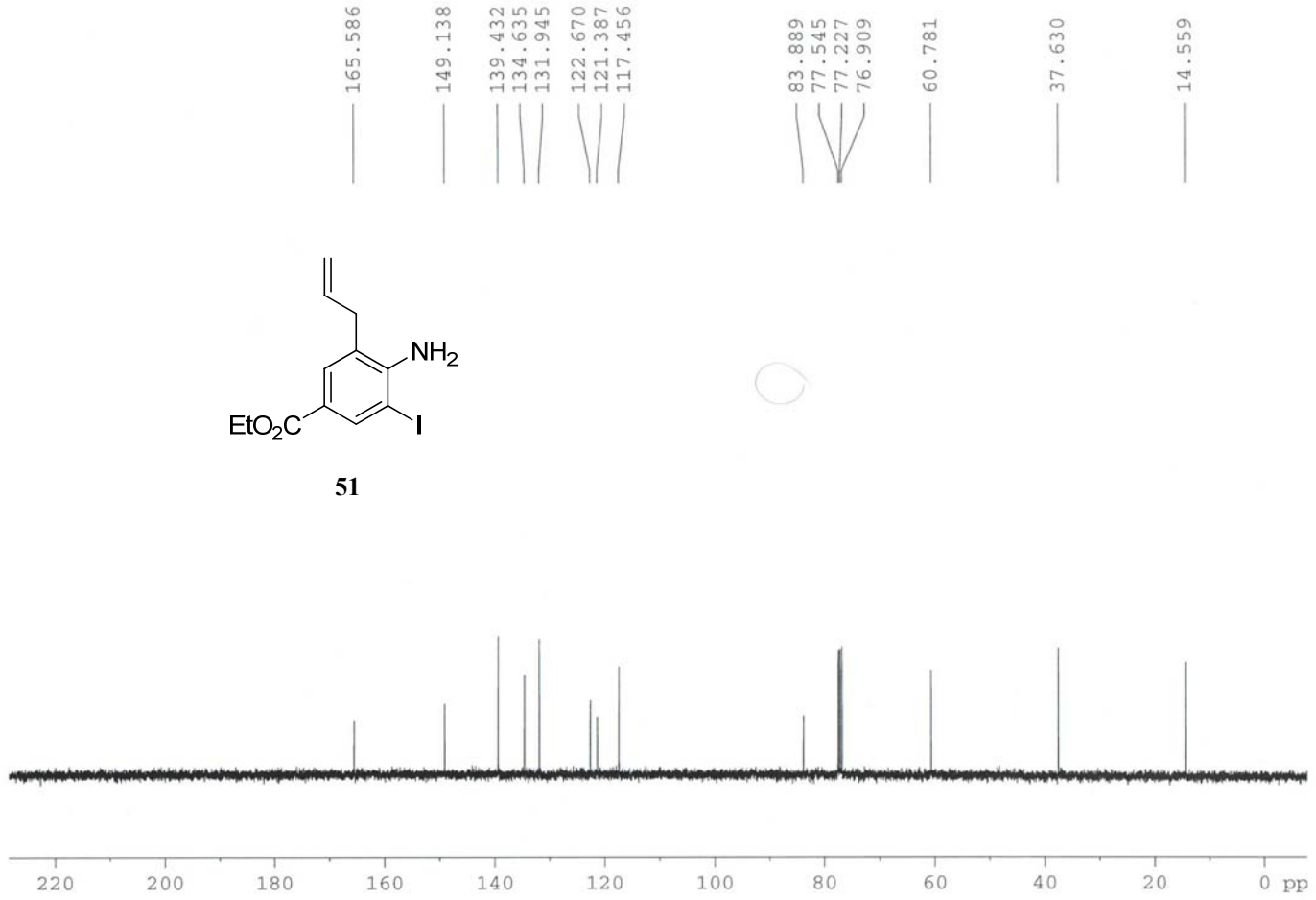

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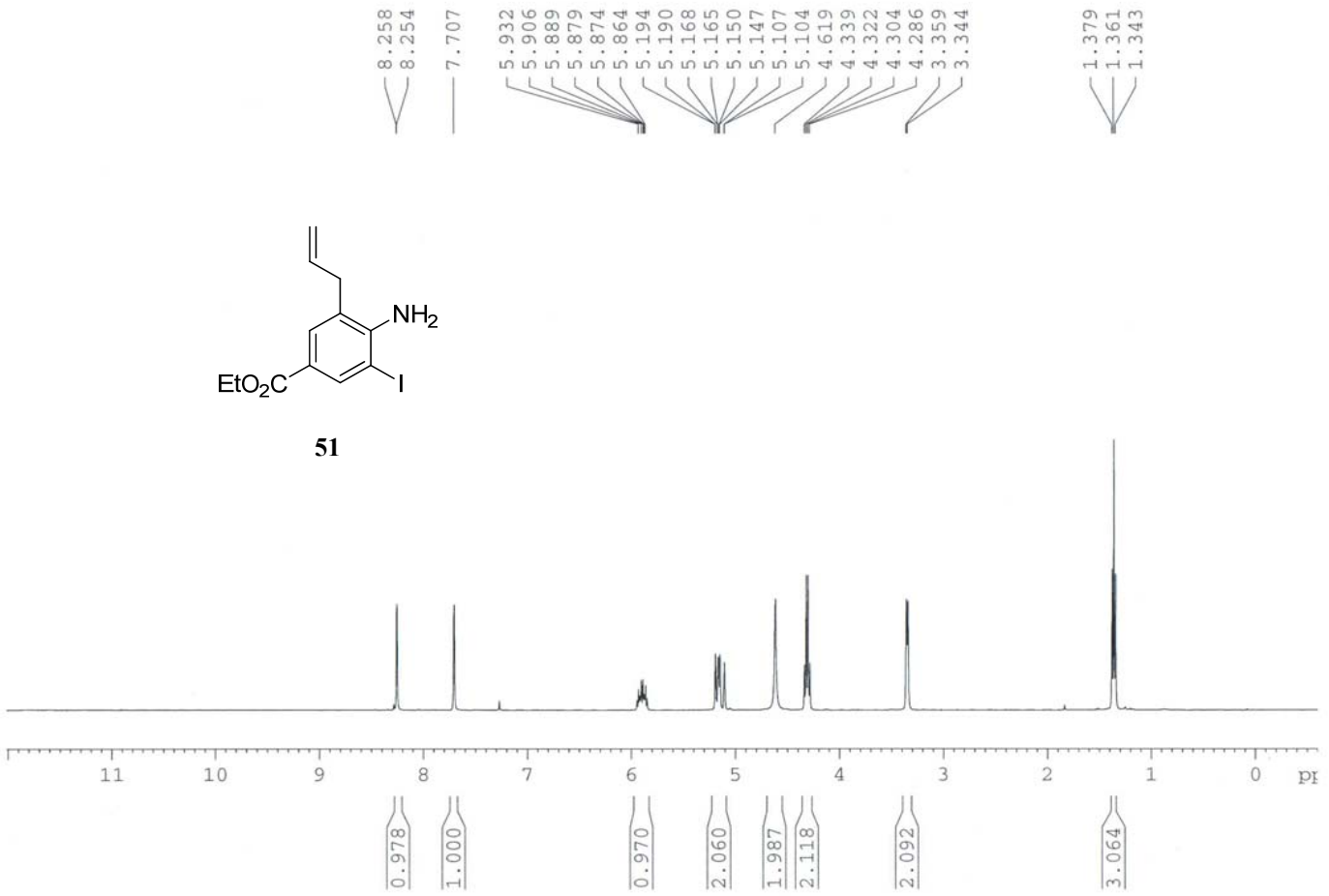

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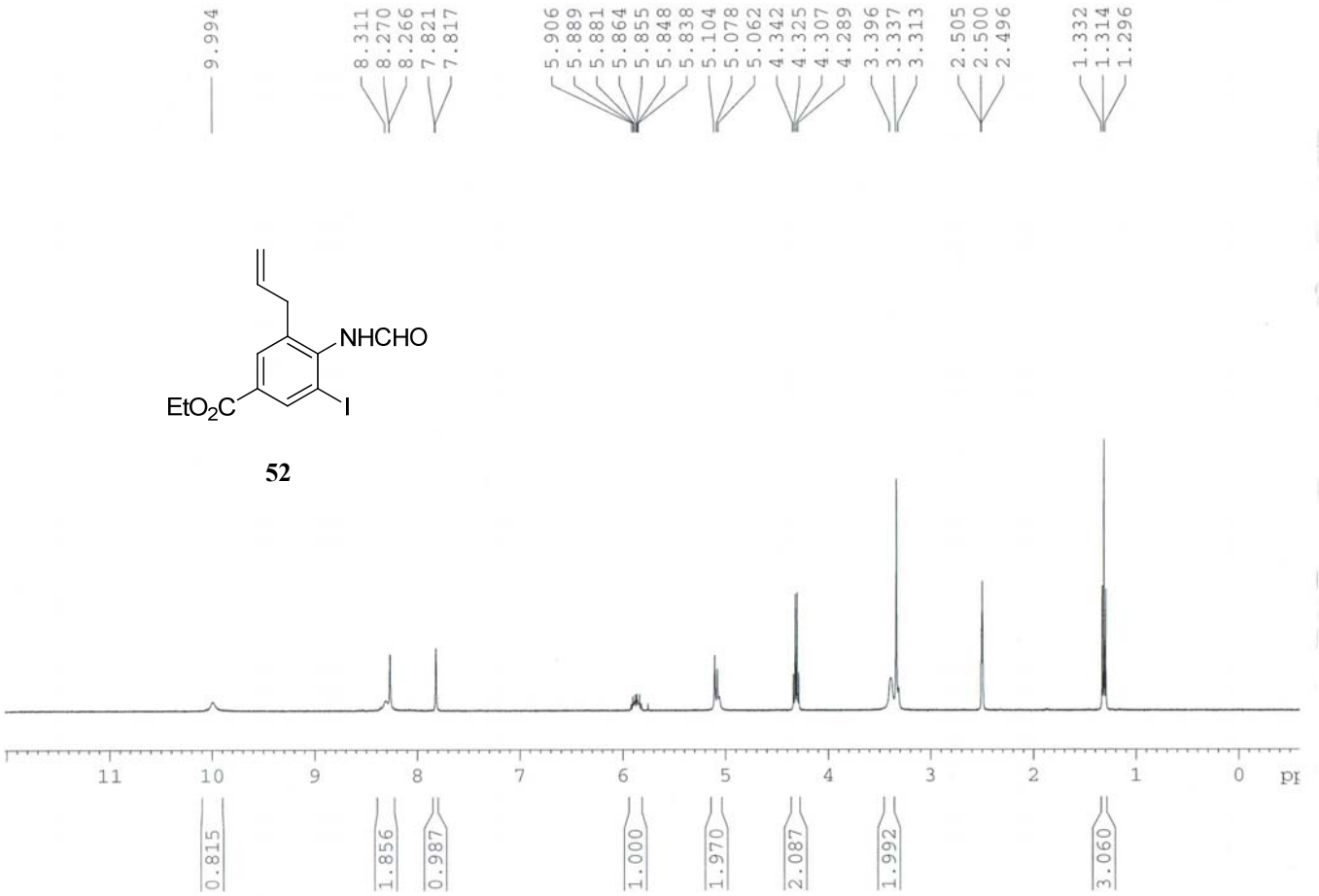

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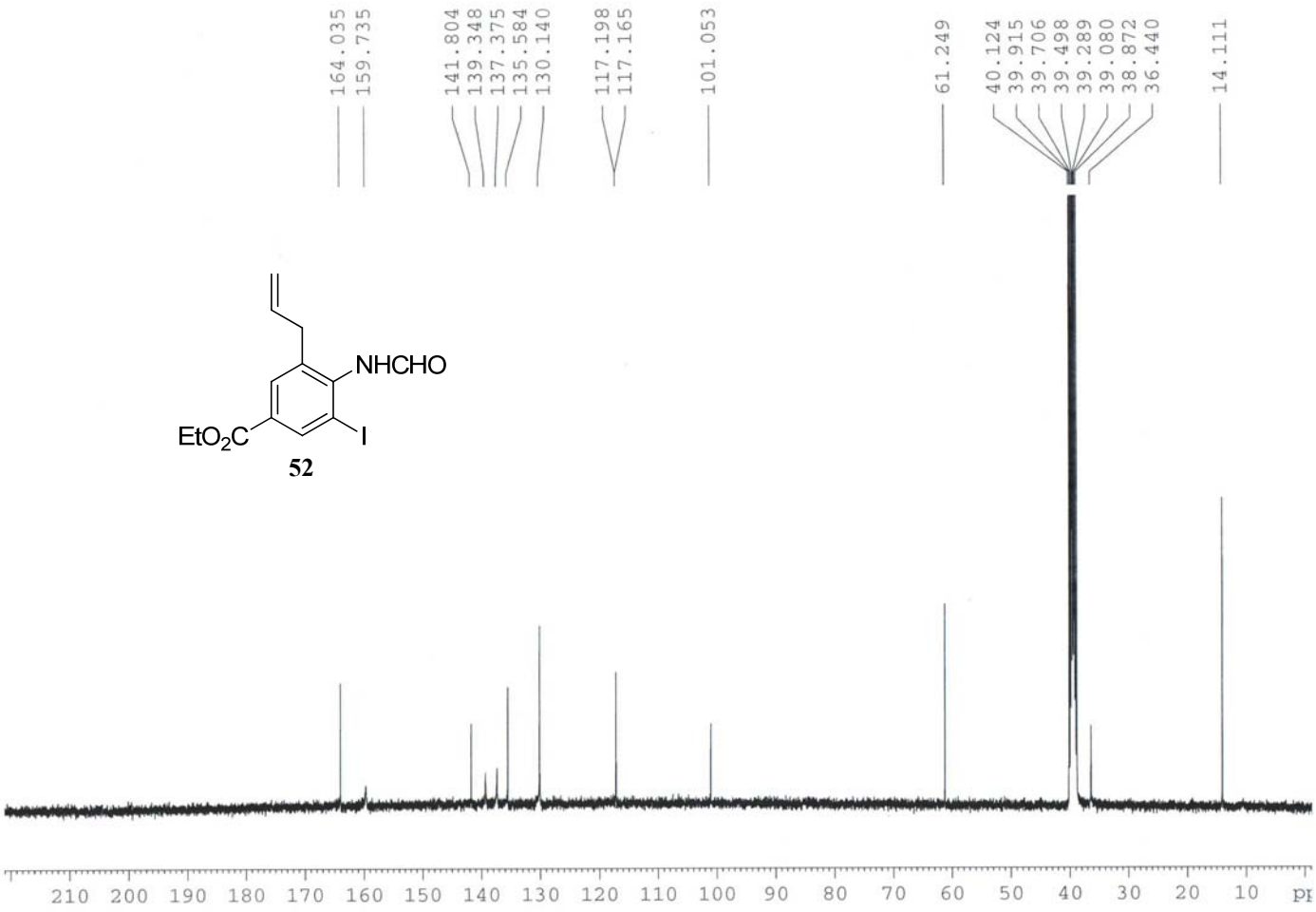

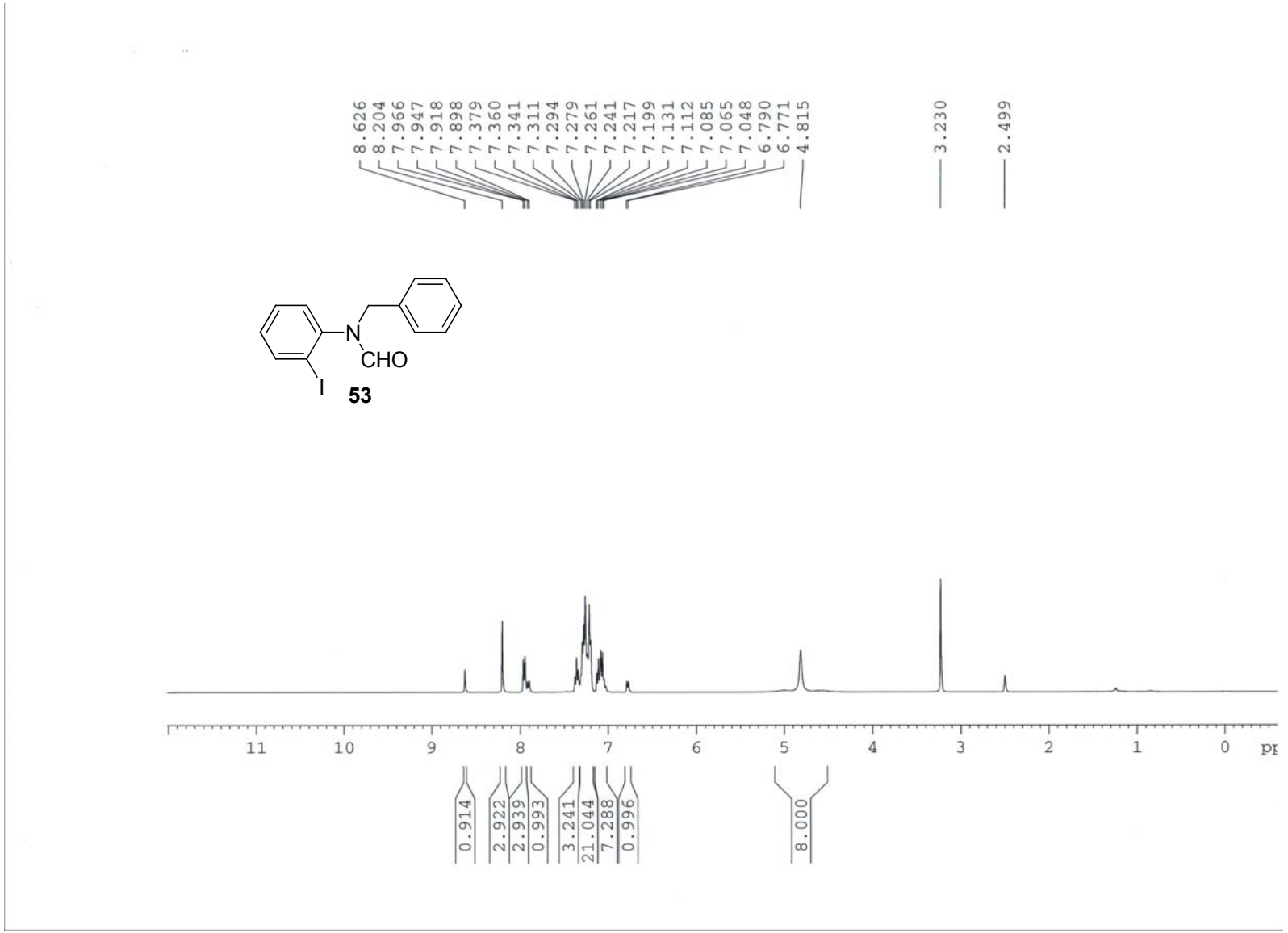

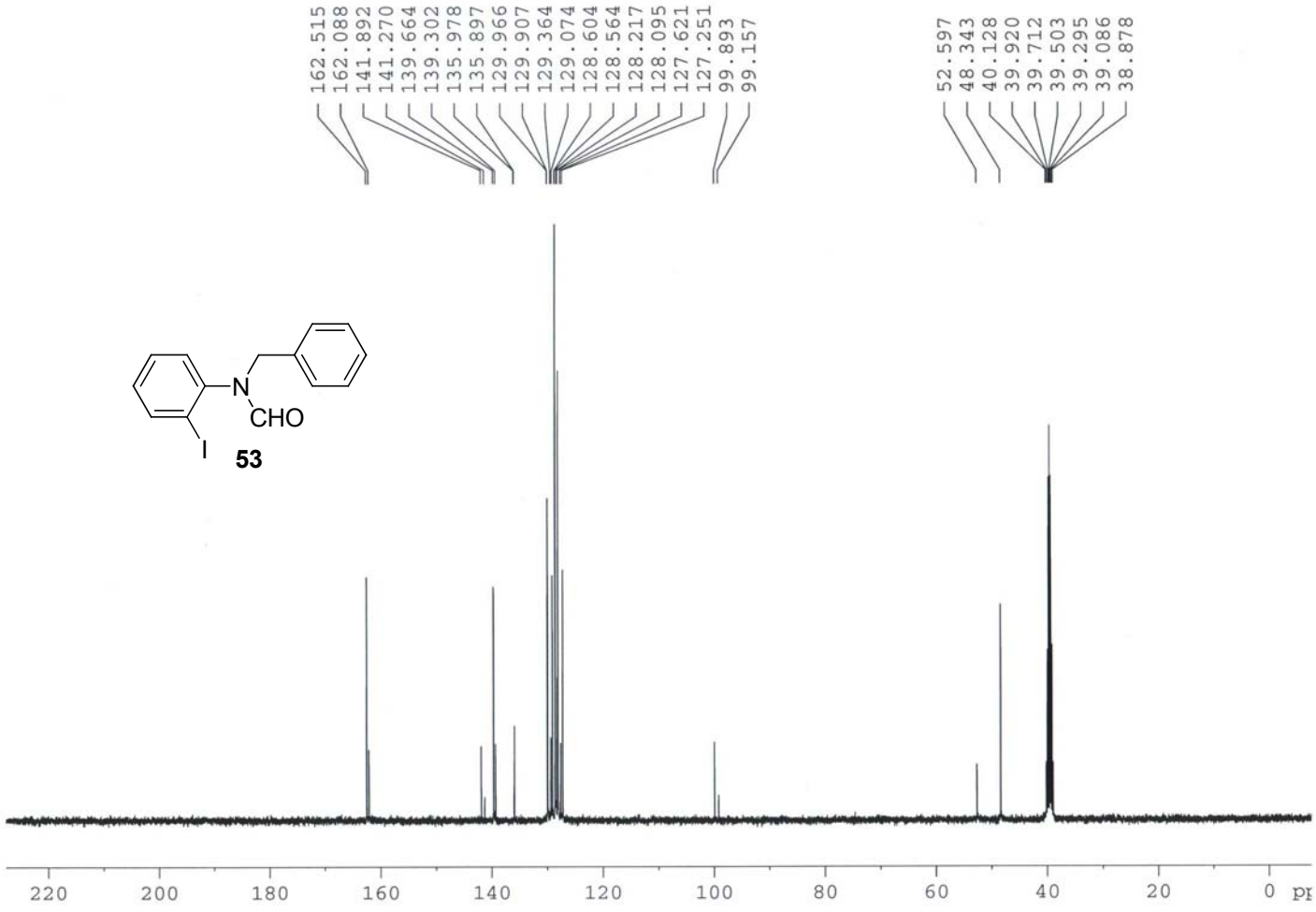

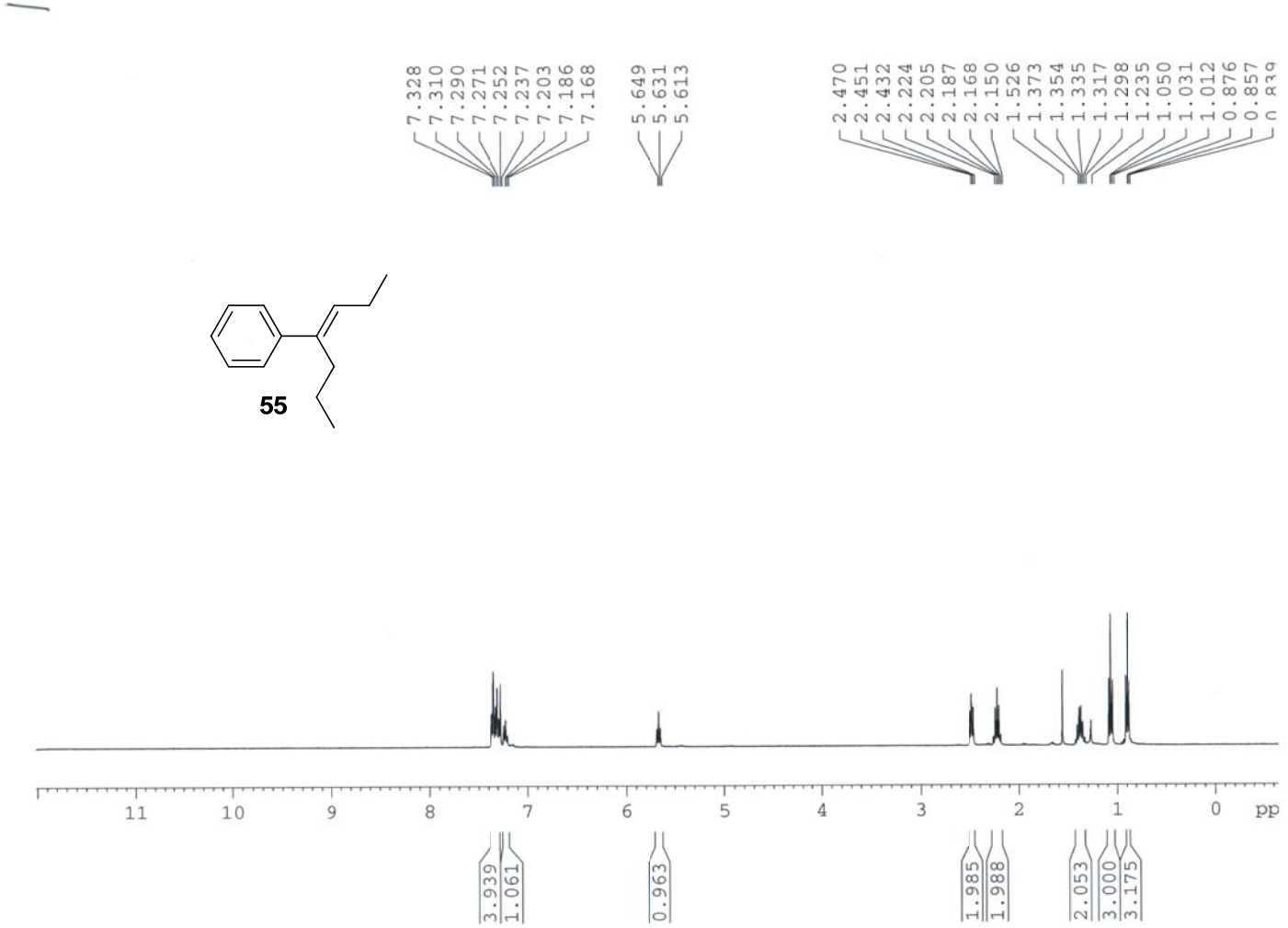

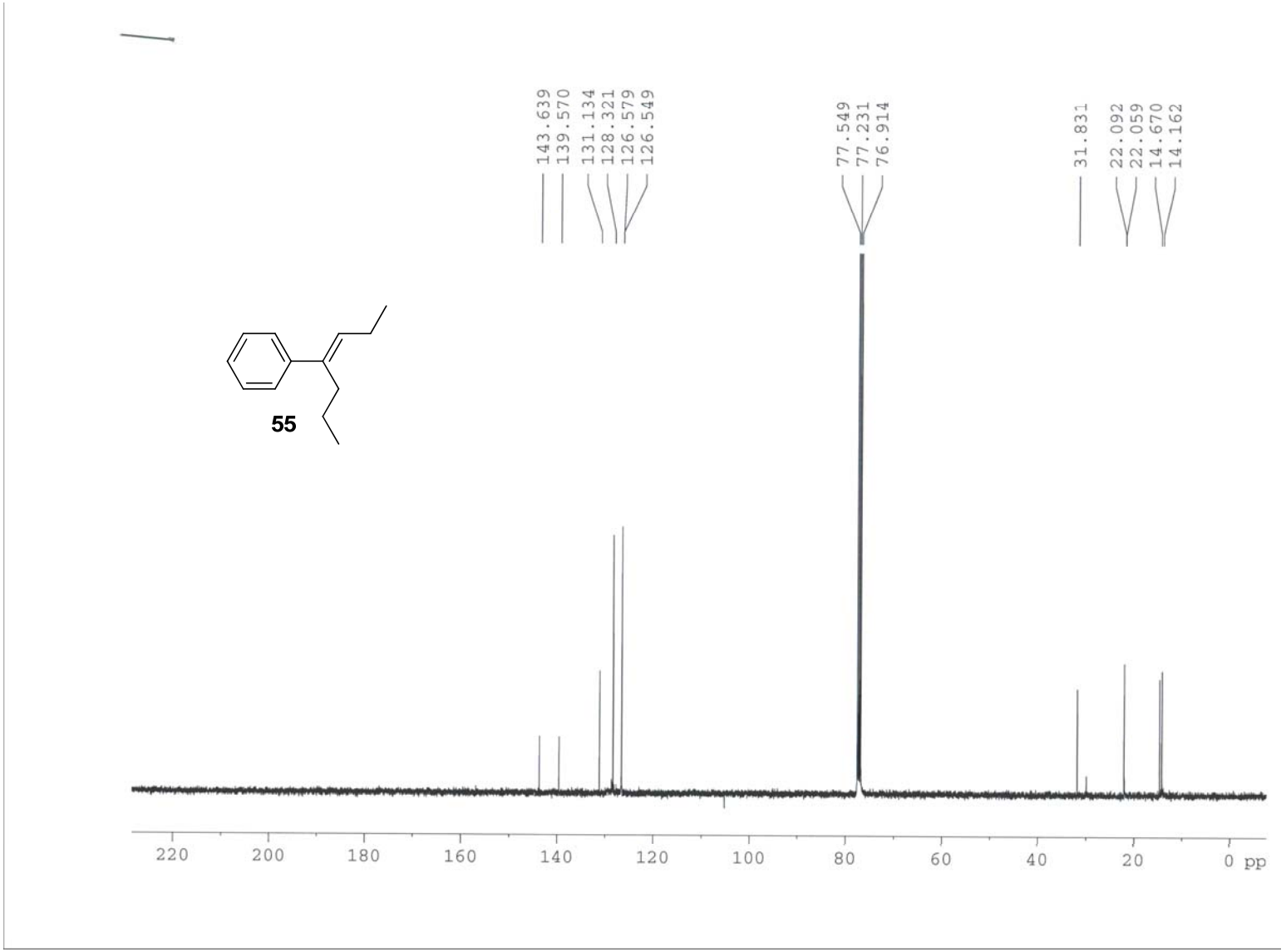

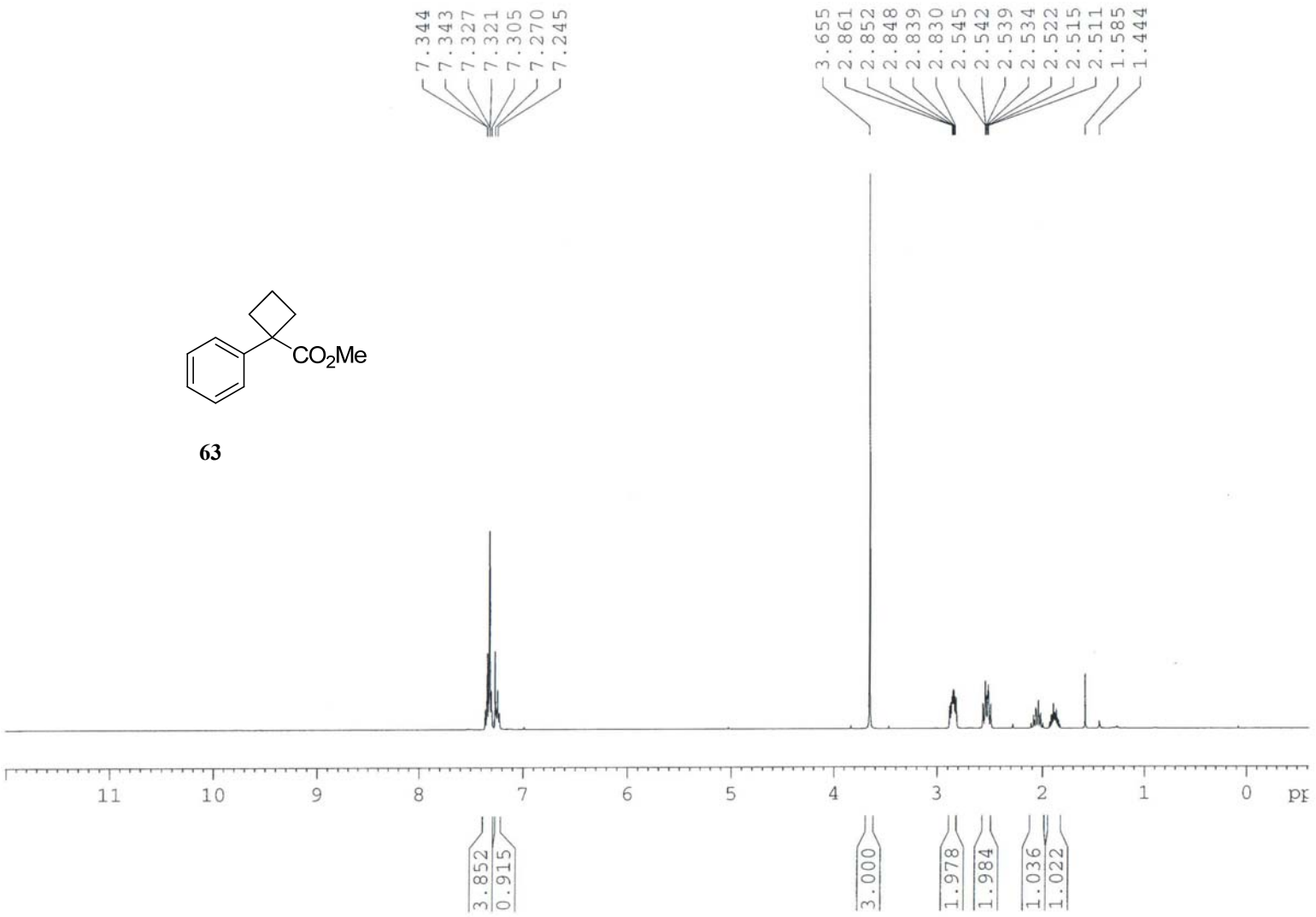

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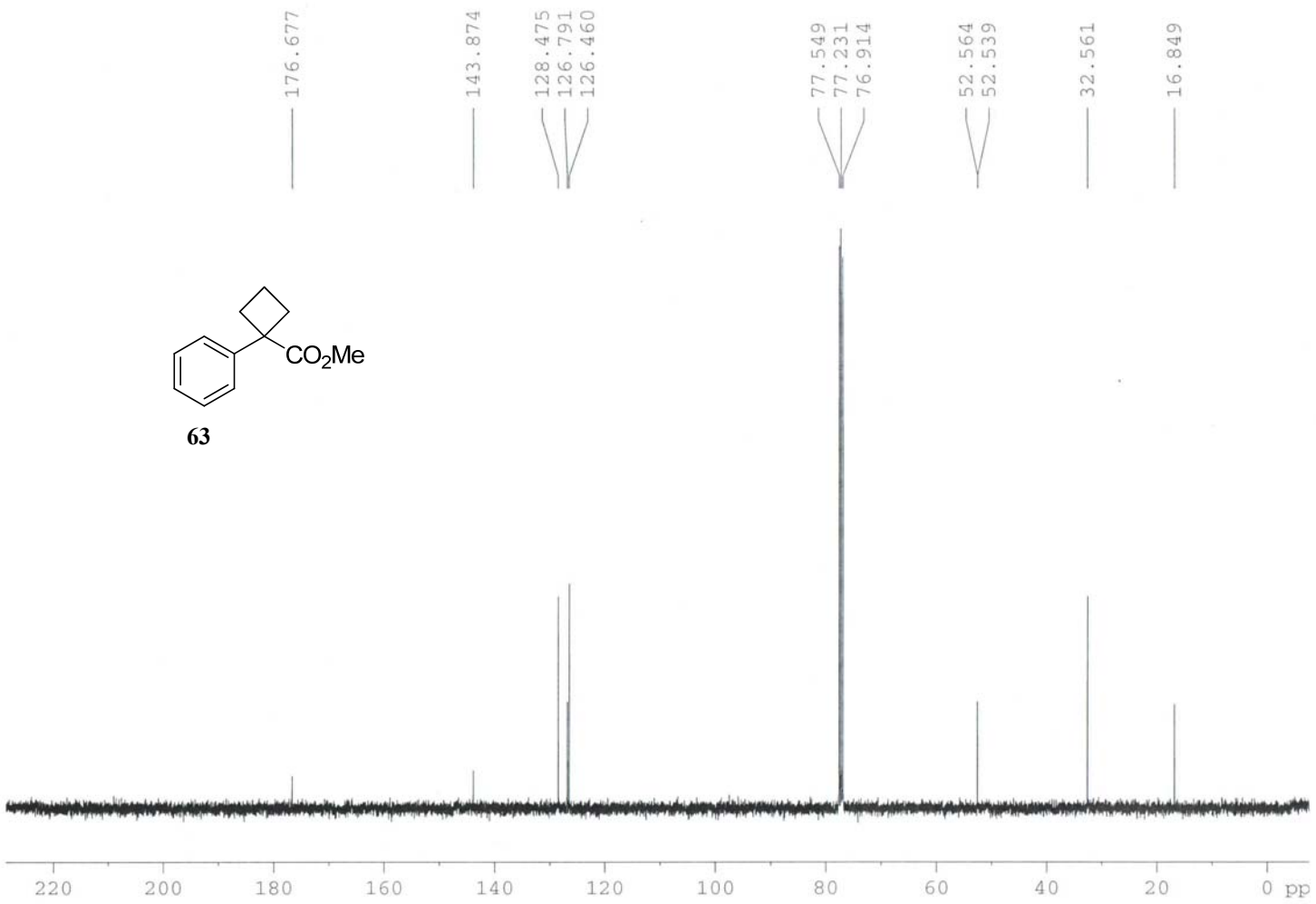

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