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Palladium-catalyzed and electrophilic cyclization approaches to carbocycles and heterocycles

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Palladium-catalyzed and electrophilic cyclization approaches to carbocycles and heterocycles

by

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To my most beloved,

Parents, Arvind J. Worlikar and Smita A. Worlikar
Siblings, Mayura, Deepali and Amey Worlikar
Fiancé, Lalit K. Bohra

Dear folks
No words of gratitude come to my heart, because I have them reserved for god, for giving me such an awesome lot

TABLE OF CONTENTS

LIST OF ABBREVATIONS

Ac	acetyl
aq	aqueous
t-Bu	tert-butyl
^{o}C	degree Celsius
cat.	catalytic
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DME	Dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	Dimethyl Sulfoxide
dt	doublet of triplets
DEAD	diethyl azodicarboxylate
eq	equation
equiv	equivalent
E	electrophile
GC	gas chromatography
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
HPLC	high performance liquid chromatography
IR	infrared

LAH	Lithium aluminum hydride
m	multiplet
m	meta
Me	methyl
mg	milligram
mL	milliliter(s)
mol	mole(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho
OTf	trifluoromethanesulfonate
p	para
Ph	phenyl
q	quartet
s	singlet
satd	saturated
t	triplet
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

ABSTRACTS

Palladium-catalyzed and electrophilic cyclization reactions are among the most studied in synthetic organic chemistry. However, these methodologies cannot always be generally applied to obtain good yields of a desired class of compounds. Many factors, including the reaction conditions, the nature of the ligands, and the reactivity of the involved species determine the product and the yield. This thesis describes several useful and novel palladium-catalyzed and electrophilic cyclization methodologies that have been optimized to obtain biologically and industrially useful carbocycles and heterocycles in good to excellent yields. These methods are tolerant of a number of functional groups including, a halogen moiety, which is further subjected to palladium-catalyzed Sonogashira, Suzuki-Miyaura and CO insertion reactions.

Chapter 1 describes the synthesis of 3,4-disubstituted 2*H*-benzopyrans by the electrophilic cyclization of propargylic aryl ethers. Emphasis has been placed on the iodocyclization reactions of these ethers using I_2 and ICl as the electrophiles. The regioselectivity of unsymmetrical propargylic aryl ethers has also been studied.

An innovative one step palladium-catalyzed aminocarbonylative cyclization is explored in Chapter 2. Our method uses only one atmosphere of CO and requires no specialized equipment to obtain an important class of heterocycles called phthalimides, starting from commercially available primary amines and the corresponding *ortho*-halobenzoates.

Arynes and organopalladium species both are very reactive and, therefore, their coupling reactions are limited in the literature, particularly due to the harsh conditions generally required to obtain arynes. A novel palladium-catalyzed aryne annulation to obtain

the important class of carbocycles known as 9-fluorenylidenes from *ortho*-halostyrenes and *o*-silylaryl triflates in the presence of CsF is described in Chapter 3. The methodology has also been extended to the synthesis of 9,10-phenanthrenes from the corresponding *ortho*-halo allylic benzenes.

Obtaining a good sized library of important potential pharmacophores (*e.g.*, indoles) is desirable in medicinal or pharmaceutical fields. Chapter 4 describes the synthesis of highly substituted indoles in compliance with Lipinski rules. The palladium-catalyzed reactions employed have achieved substitution at the 3-position of the indole moiety, which is difficult due to the electron-rich nature of the C-I bond. The chemistry has been successfully transferred to a solid support and diversity has been achieved at the 5-position by various cleavage reactions.

GENERAL INTRODUCTION

The establishment of new or innovative synthetic methods for obtaining carbocycles and heterocycles is an area of active research in synthetic organic chemistry. Although numerous electrophilic cyclization and palladium-catalyzed methods are known, they cannot be generally applied to all organic systems and, therefore, there is a constant need for improved methods for a particular class of compounds or for new molecules. Introduction of a halogen moiety in a compound is highly desired as it provides a handle for further organic transformations. Also, mild reaction conditions, which are tolerant of a variety of functional groups, are desirable since they can be subjected to further organic transformations. Many times biologically active natural products are a good indicator of possible biologically active substrates. Good methods for the synthesis of a library of small molecules are therefore desirable to both synthetic chemists and biologists.

An efficient method for the synthesis of 2*H*-benzopyrans is described in Chapter 1. Substituted propargylic aryl ethers on electrophilic cyclization by I_2, ICl and PhSeBr give 3,4-disubstituted 2*H*-benzopyrans in good to excellent yields. The scope of the reaction has been studied using various substrates, and expanded by subsequent palladium-catalyzed Sonogashira and CO insertion reactions at the 3-position, using the iodine handle provided by this methodology.

The palladium-catalyzed aminocarbonylation is a highly desired reaction in organic chemistry, the major concern being the use of a high pressure of CO gas. Chapter 2 describes an efficient one step method of preparing 2-substituted isoindole-1,3-diones in good yields by the palladium-catalyzed aminocarbonylation of *ortho*-halobenzoates, which produces the corresponding *ortho*-amidocarboxylate, which further undergoes base-catalyzed

cyclization. This methodology provides this important class of heterocycles in good to excellent yields using only one atmosphere of CO. The methodology is tolerant of a halogen moiety, which is further subjected to palladium-catalyzed Sonogashira and Suzuki-Miyaura cross coupling reactions.

The use of arynes as reagents in synthetic organic chemistry has been somewhat limited, due to the harsh conditions needed to generate arynes and the often uncontrolled reactivity exhibited by these species. Recently *o*-silylaryl triflates have been used to generate the corresponding arynes under very mild reaction conditions, which then undergo palladium-catalyzed annulation to give important classes of compounds. An efficient route to a variety of 9-fluorenylidenes and 9,10-phenanthrenes is described in Chapter 3, which involves the reaction of *ortho*-halostyrenes and *ortho*-halo allylicbenzenes respectively, with *o*-silylaryl triflates in the presence of CsF.

Substituted indoles are prevalent in numerous natural products and are extremely important in medicinal chemistry. Chapter 4 describes the parallel synthesis of a library of highly substituted indoles. 3-Iodoindoles have been prepared in excellent yields by coupling terminal acetylenes with *N*,*N*-dialkyl-*o*-iodoanilines in the presence of a Pd/Cu catalyst, followed by electrophilic cyclization of the resulting *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines using I_2 in CH_2Cl_2. The iodine moiety at the 3-position is subjected to palladium-catalyzed Sonogashira and Suzuki-Miyaura reactions to obtain a library of highly substituted indoles. The coupling reactions have been successfully transferred to a solid-phase, facilitating the multistep synthesis and eliminating the cumbersome purification steps. Various substituents have been introduced at the 5-position by employing different methods of cleavage.

Dissertation Organization

This dissertation is organized into four chapters. Each of the first three chapters presented herein is written following the guidelines for a full paper in the *Journal of Organic Chemistry*, while the fourth chapter is written following the guidelines for a full paper in the *Journal of Combinatorial Chemistry*. Each chapter is composed of the abstract, introduction, results and discussion, conclusion, experimental section, and references.

Chapter 1 discusses an efficient method for the synthesis of 3,4-disubstituted 2*H*-benzopyrans in excellent yields by the electrophilic cyclization of substituted propargylic aryl ethers by I_2, ICl and PhSeBr.

Chapter 2 presents the Pd-catalyzed, one-step synthesis of a variety of isoindole-1,3-diones, commonly known as phthalimides, starting with the corresponding *ortho*-halobenzoates and commercially available primary amines.

Chapter 3 describes an efficient Pd-catalyzed method for the synthesis of 9-fluorenylidenes and 9,10-phenanthrenes by the reaction of the corresponding *ortho*-halostyrenes and *ortho*-halo allylicbenzenes with *o*-silylaryl triflates and CsF.

Chapter 4 discusses the solution phase and the solid phase synthesis of a highly substituted indole library by the Pd-catalyzed coupling reactions of various 3-iodoindoles with terminal alkynes and aryl boronic acids. This chemistry has afforded a 42-member indole library compliant with Lipinski's rules.

Finally, the ^{1}H and ^{13}C NMR spectra for all the new starting materials and products have been compiled in appendices A-D, following the general conclusions for this dissertation.

CHAPTER 1. SYNTHESIS OF 3,4-DISUBSTITUTED 2*H*-BENZOPYRANS THROUGH C-C BOND FORMATION VIA ELECTROPHILIC CYCLIZATION

Based on a paper published in the *Journal of Organic Chemistry*[35]

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Abstract

The electrophilic cyclization of substituted propargylic aryl ethers by I_2, ICl and PhSeBr produces 3,4-disubstituted 2*H*-benzopyrans in excellent yields. This methodology results in vinylic halides or selenides under mild reaction conditions, and tolerates a variety of functional groups, including methoxy, alcohol, aldehyde and nitro groups.

Introduction

2*H*-1-Benzopyrans, commonly known as 2*H*-benzopyrans or 2*H*-chromenes, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. The 2*H*-benzopyran Daurichromenic acid is known to exhibit anti-HIV properties,[1] while Coutareagenin possesses antidiabetic activity.[2] Derivatives of 3,4-diphenylchromans are known to have estrogenic activity.[3] Numerous derivatives of 2*H*-benzopyrans are useful for treatment of proliferative skin disorder and microbial infections[4] and show potent antifungal activity.[5] Derivatives of 2*H*-benzopyrans, like 2,4-diphenyl-2*H*-benzopyran and 2,2,4-triphenyl-2*H*-benzopyran, have been studied for their photochromic

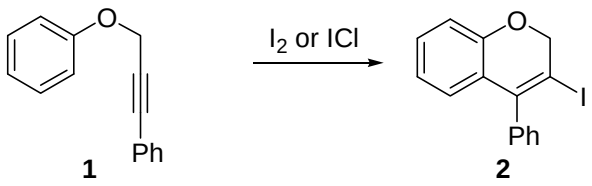
behavior.[6] Due to their biological and pharmaceutical importance, the isolation and synthesis of 2*H*-benzopyrans has received considerable attention in the literature.

Substituted 2*H*-benzopyrans have been synthesized in our laboratories by the Pd(II)-catalyzed cyclization of allylic aryl ethers,[7] while the palladium-catalyzed cross-coupling of 4-trifluoromethanesulfonyloxy-2*H*-benzopyrans with arylboronic acids has also been reported in the literature.[8] Syntheses of 2*H*-benzopyrans are also known using platinum and gold catalysis,[9] Hg(II)-mediated cyclizations,[10] Grignard reagents,[11] and microwave irradiation.[12]

A wide range of carbocycles and heterocycles have been constructed using the electrophilic cyclization of disubstituted alkynes[13] and transition metal-catalyzed cyclizations.[14,15] Many researchers, including those from our group, have utilized these cyclizations for the synthesis of benzofurans,[16] furans,[17] benzo[*b*]thiophenes,[18] thiophenes,[19] naphthols,[20] indoles,[21] quinolines,[22] isoquinolines,[23] isocoumarins,[24] isochromenes[25] and polycyclic aromatics.[26] Some methods are not compatible with functionality, while some require the use of costly metals as catalysts. Recently Barluenga and co-workers reported the synthesis of 2*H*-benzopyrans by the cyclization of aryl propargylic ethers using costly IPy_2BF_4 and HBF_4.[27] They also reported two examples of the iodocyclization of propargylic ethers using I_2 in water. We report herein many examples and a general synthesis of 2*H*-benzopyrans in good yields via electrophilic cyclization using the simple, inexpensive electrophiles I_2, ICl, and PhSeBr in nitromethane.

Results and Discussion

Our early studies mainly focused on the iodocyclization of substituted propargylic aryl ethers to give 3,4-disubstituted 2*H*-benzopyrans in excellent yields. Phenyl 3-phenyl-2-propynyl ether (**1)** was used as a model system for optimization of the reaction conditions using I_2 or ICl (eq 1).



1 **2** (1)

Early in this work, conditions similar to our previous iodocyclization reactions were used. For instance, the reaction was run with 0.25 mmol of **1**, 2 equiv of $NaHCO_3$ as the base, and 3 equiv of I_2 in 5 ml of CH_3CN at 25 ^oC to obtain a 61% isolated yield of the desired 3-iodo-4-phenyl-2*H*-benzopyran (**2)**[27] (Table 1, entry 1). Solvents, like CH_2Cl_2, CH_3OH and DMF, resulted in lower yields (entries 2-4), but CH_3NO_2 gave a yield of 77% (entry 5). No reaction was observed at 0 ^oC after 4 h (entry 6), while the reaction was messy and produced only a 42% yield at 40 ^oC (entry 7). Reducing the amount of I_2 to 2 equiv decreased the yield significantly to 53% (entry 8), while an increase in the number of equivalents of I_2 caused a slight decrease in the yield to 69% (entry 9). Reducing the reaction time to 12 h lowered the yield to 62% (entry 10), while there was no increase in yield when the reaction time was doubled to 48 h (entry 11). The presence of the base proved to be important for the reaction as the yield was reduced to 58% without the base and only 70% with one equiv of the base (entries 12 and 13). Several additional bases were examined in this reaction, but $NaHCO_3$ was found to give the best yield (entries 14-16).

Table 1. Optimization of the Cyclization of Phenyl 3-Phenyl-2-propynyl Ether using I_2 as the Electrophile (eq 1)[a]

entry	solvent	I_2 (equiv)	base (equiv)	time (h)	% isolated yield
1	CH_3CN	3	$NaHCO_3$ (2)	24	61
2	CH_2Cl_2	3	$NaHCO_3$ (2)	24	49
3	CH_3OH	3	$NaHCO_3$ (2)	24	41
4	DMF	3	$NaHCO_3$ (2)	24	52
5	CH_3NO_2	3	$NaHCO_3$ (2)	24	77
6	CH_3NO_2	3	$NaHCO_3$ (2)	4	0[b]
7	CH_3NO_2	3	$NaHCO_3$ (2)	24	42[c]
8	CH_3NO_2	2	$NaHCO_3$ (2)	24	53
9	CH_3NO_2	4	$NaHCO_3$ (2)	24	69
10	CH_3NO_2	3	$NaHCO_3$ (2)	12	62
11	CH_3NO_2	3	$NaHCO_3$ (2)	48	76
12	CH_3NO_2	3	-	24	58
13	CH_3NO_2	3	$NaHCO_3$ (1)	24	70
14	CH_3NO_2	3	NaOMe (2)	24	69
15	CH_3NO_2	3	Na_2CO_3 (2)	24	75
16	CH_3NO_2	3	KOH (2)	24	-

[a] Representative procedure: phenyl 3-phenyl-2-propynyl ether (0.25 mmol), I_2, a base and the solvent (5 mL) were placed in a 4 dram vial and stirred at 25 ^oC for the indicated time. [b] The reaction was run at 0 ^oC. [c] The reaction was run at 40 ^oC.

In our previous cyclizations, ICl has proven to be a better electrophile for some substrates. Therefore, with a view to obtaining better yields, the cyclization of phenyl 3-phenyl-2-propynyl ether (**1**) was optimized using ICl as the electrophile, starting with our previously developed conditions. Because of the importance of the solvent in such reactions, the reaction was carried out using CH_2Cl_2, diethyl ether, THF, hexane, CH_3OH and CH_3NO_2 at low temperatures (Table 2, entries 1-6). The solvent CH_3NO_2 gave the best yield of 69%,

but the temperature had to be raised to -25 ^{o}C. The reaction was run at -25 ^{o}C with the second best solvent for the reaction, namely CH_2Cl_2, to get a slightly lower yield of 65% (entry 7). In all of these reactions, $NaHCO_3$ was used as a base. The yield increased to 96% when the reaction was carried out without $NaHCO_3$ (entry 8). Increasing the temperature to 0 ^{o}C gave undetermined side products with the desired compound being formed in less than a 5% yield (entry 9). Decreasing or increasing the amount of ICl gave slightly lower yields

Table 2. Optimization of the Cyclization of Phenyl 3-Phenyl-2-propynyl Ether using ICl as the Electrophile (eq 1)[a]

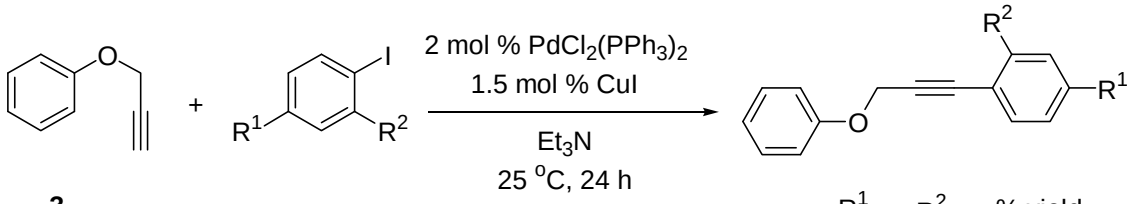
Entry	solvent	ICl (equiv)	temperature ^{o}C	time (h)	% yield
1	CH_2Cl_2	1.5	-78	2	63[b]
2	Ether	1.5	-78	2	51[b]
3	THF	1.5	-78	2	58[b]
4	Hexane	1.5	-78	2	49[b]
5	CH_3OH	1.5	-78	2	-[b]
6	CH_3NO_2	1.5	-25	2	69[b]
7	CH_2Cl_2	1.5	-25	2	65[b]
8	CH_3NO_2	1.5	-25	0.5	96
9	CH_3NO_2	1.5	0	0.5	<5
10	CH_3NO_2	1.2	-25	2	71
11	CH_3NO_2	2.0	-25	0.5	85

[a] Representative procedure: phenyl 3-phenyl-2-propynyl ether (0.25 mmol), ICl and the solvent (5 mL) were placed in a 4 dram vial and stirred at the indicated temperature for the indicated time. [b] $NaHCO_3$ (0.5 mmol) was added.

(entries 10 and 11). Thus, our optimized conditions using ICl are 0.25 mmol of **1**, 1.5 equiv of ICl and 5 ml of CH_3NO_2 at -25 ^oC.

After obtaining our best conditions using either I_2 or ICl, we decided to study the scope of this reaction on various substrates. Ethers **1**, **4**, **5** and **6** were obtained by standard Sonogashira chemistry[28] using commercially available starting materials (Scheme 1). Ethers **9** and **10** were obtained by a two step approach, the first step being the synthesis of the substituted aryl propargylic ethers **7** and **8**, followed by Sonogashira chemistry (Scheme 2). Ethers **11**, **12** and **13** were synthesized by a Mitsunobu reaction (Scheme 3), while ethers **14**,[29] **15**,[30] **16**,[30] **17**,[27] **18**,[31] **19**,[31] **20**,[31] **21**[32] and **22**[33] (refer to Table 3) were previously reported in the literature.

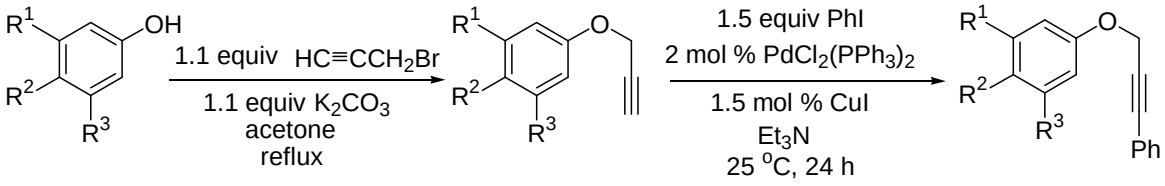
Scheme 1



3

	R^1	R^2	% yield
1	H	H	74
4	Me	H	75
5	OMe	H	85
6	H	OMe	79

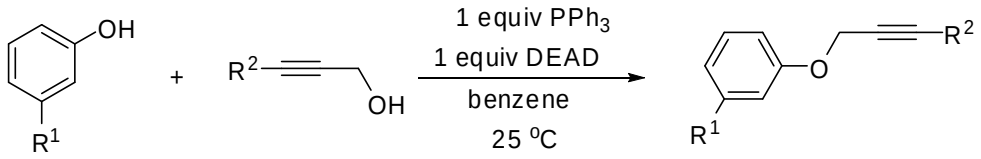
Scheme 2



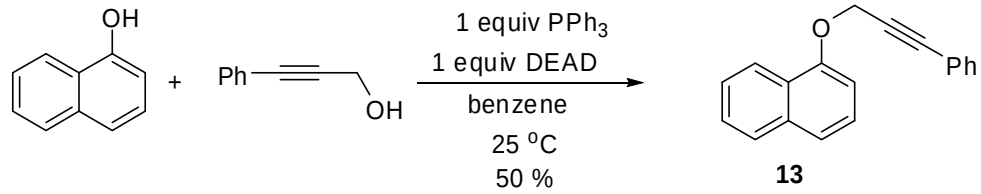
	R^1	R^2	R^3	%
7	H	CHO	H	67
8	*t*-Bu	H	*t*-Bu	70

	R^1	R^2	R^3	%
9	H	CHO	H	45
10	*t*-Bu	H	*t*-Bu	50

Scheme 3



	R^1	R^2	% yield
11	*t*-Bu	Ph	61
12	H	1-cyclohexyl	50



13

Cyclizations were then carried out using our optimized conditions for I_2 (conditions A) or ICl (conditions B). 3,4-Disubstituted 2*H*-benzopyrans were obtained in good yields using I_2 or ICl when the substituent on the propargylic alkyne was either a simple phenyl or an alkenyl group (Table 3, entries 1, 2, 32 and 33). An alkyl substituent on the alkyne terminus did not give the desired product with I_2 or ICl as the electrophile, but worked with PhSeBr (entries 34-36). However, an hydroxymethyl-substituted alkyne gave good yields with I_2, as well as ICl (entries 37 and 38). Simple phenyl propargyl ether **(3)** failed to give any of the desired product with I_2 or ICl (entries 30 and 31).

The introduction of substituents on the aryl groups has a considerable effect on the yield of the reaction. Substituents were first introduced onto the aromatic ring attached to the alkyne. Electron-donating groups, like Me and MeO in the *para* or *ortho* positions, gave good yields (entries 4-7, 10 and 11), while an electron-withdrawing group, like a NO_2 group, gave relatively poor yields of 59% with I_2 and 53% with ICl (entries 8 and 9). Introducing substituents onto the aromatic ring attached to the oxygen moiety also has a pronounced

effect. Electron-donating groups, like Me, *t*-Bu and MeO, on the phenyl ring *para* to the oxygen gave better yields with I_2 as the electrophile (entries 12, 14 and 16) than those obtained using ICl (entries 13, 15 and 17). Compound **30** was thus obtained in improved yields without the use of ion exchange resins as additives, as was reported by Barluenga.[27] The sterically-hindered ether **10** also gave good results (entries 23 and 24).

Placing an electron-withdrawing chlorine in the position *para* to the oxygen gave somewhat lower yields (entries 18 and 19) of the desired isomer. An aldehyde group in the position para to the oxygen gave a mixture of two inseparable regioisomers, the ratio of which depended on the electrophile used and the reaction temperature (entries 20 and21). The benzopyran isomer was favored when the reaction was carried out at -78 ^{o}C with CH_2Cl_2 as the solvent and ICl as the electrophile (entry 22).

Table 3. Synthesis of 3,4-Disubstituted 2*H*-Benzopyrans by Electrophilic Cyclization of Propargylic Aryl Ethers.[a]

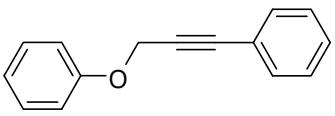
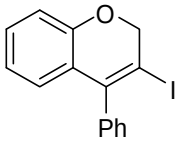
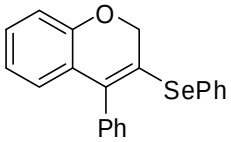
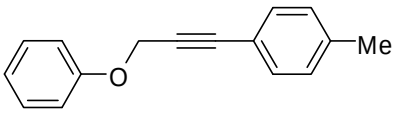
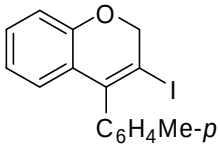
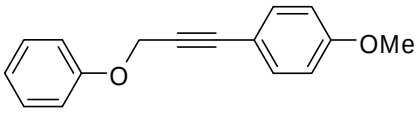
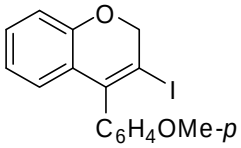
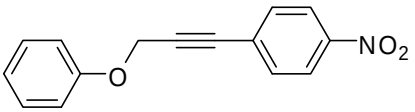
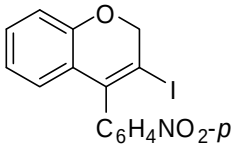
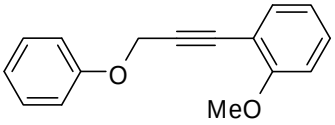
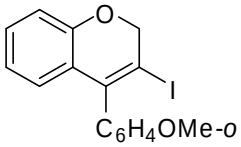
entry	ether	condition		product(s)	% isolated yield	
1		**1**	A		**2**	77
2		**1**	B		**2**	96
3		**1**	C		**23**	95
4		**4**	A		**24**	88
5		**4**	B		**24**	76

Table 3. Continued

entry	ether	condition	product(s)	% isolated yield
6		**5** A		**25** 89
7		**5** B		**25** 92
8		**14** A		**26** 59
9		**14** B		**26** 53
10		**6** A		**27** 85
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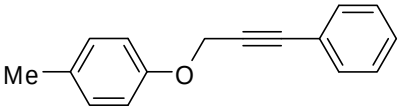
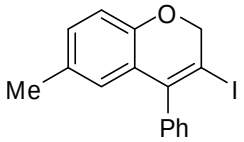
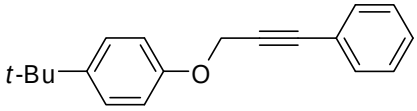
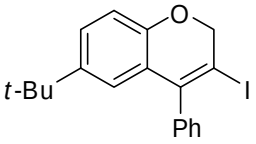
12		**15** A		**28** 79
13		**15** B		**28** 74
14		**16** A		**29** 82
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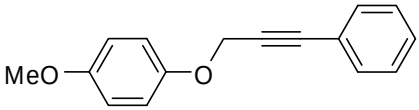
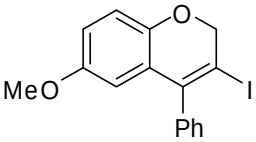
16		**17** A		**30** 92
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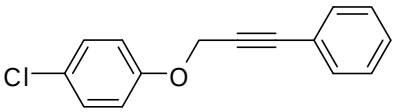
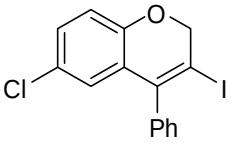
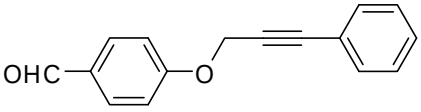
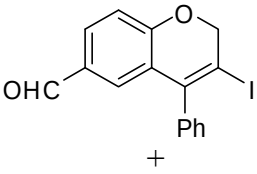
18		**18** A		**31** 52
19		**18** B		**31** 75
20		**9** A		**32** 76[b] [2:1]

Table 3. Continued

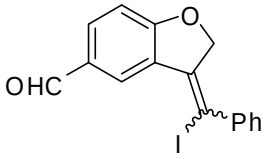
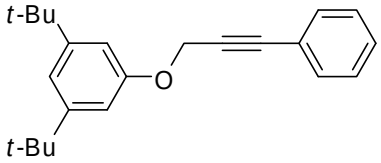
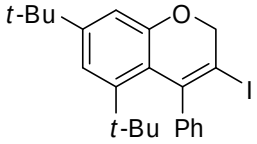
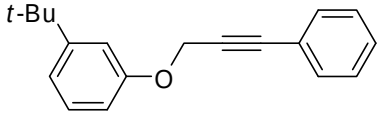
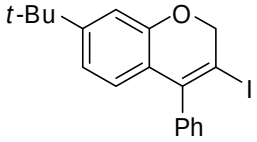
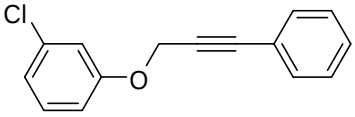
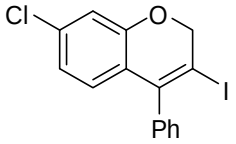
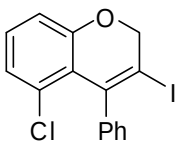
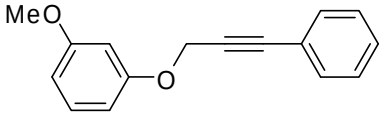
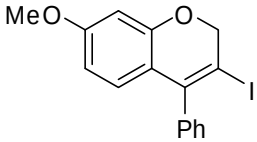
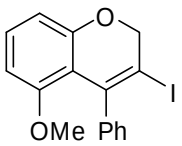
entry	ether	condition		product(s)		% isolated yield
					**33**	
21		**9**	B	**32** + **33**		78[b] [1:11]
22		**9**	D	**32** + **33**		77[b] [6:1]
23		**10**	A		**34**	93
24		**10**	B		**34**	77
25		**11**	A		**35**	72
26		**11**	B		**35**	79
27		**19**	A	 + 	**36** + **37**	21 28
28		**19**	B		**36** + **37**	27 42
29		**20**	B	 + 	**38** + **39**	82[b] [2:3]

Table 3. Continued

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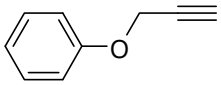
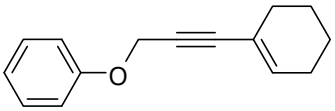
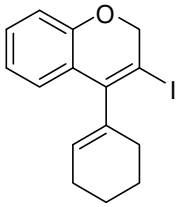
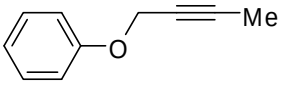
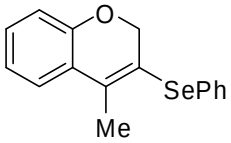
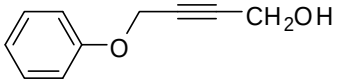
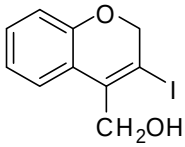
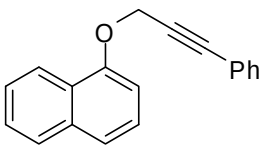
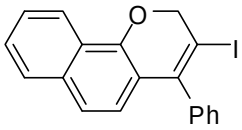
30		**3**	A		-
31		**3**	B		-
32		**12**	A		**40** 74
33		**12**	B		**40** 72
34		**21**	A		-
35		**21**	B		-
36		**21**	C		**41** 79
37		**22**	A		**42** 79
38		**22**	B		**42** 72
39		**13**	A		**43** 61
40		**13**	B		**43** 50

[a] Representative procedure for conditions A: ether (0.25 mmol), $NaHCO_3$ (0.50 mmol), I_2 (0.75 mmol) and CH_3NO_2 (5 mL) were placed in a 4 dram vial and stirred at 25 °C for 24 h. Conditions B: ether (0.25 mmol), ICl (0.375 mmol) and CH_3NO_2 (5 mL) were placed in a 4 dram vial and stirred at -25 °C for 30 min. Conditions C: ether (0.25 mmol), PhSeBr (1.2 equiv) and CH_2Cl_2 (5 mL) were placed in a 4 dram vial and stirred at 25 °C for the indicated time. Conditions D: CH_2Cl_2 was used as the solvent for conditions B at -78 °C. [b] The ratios were determined by ^1H NMR spectroscopy.

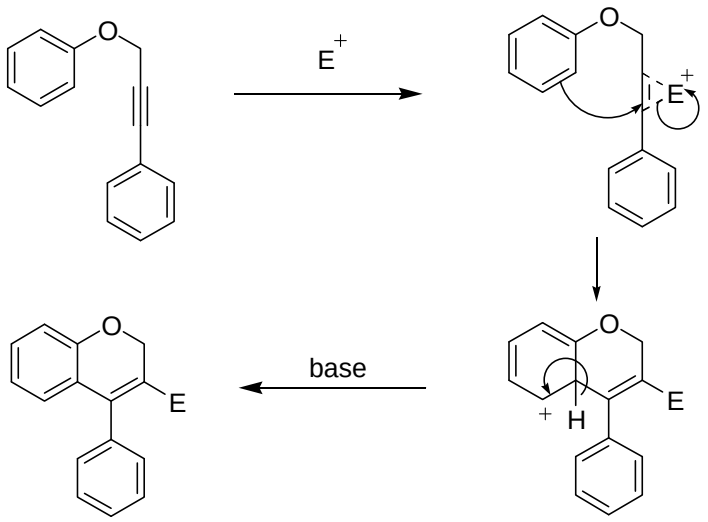
In order to study the regiochemistry of cyclization, the reaction was carried out with substituents *meta* to the oxygen moiety. A sterically bulky *t*-Bu group in the meta position gave selectively one product **35** (entries 25 and 26). A less bulky Cl in the meta position gave two regioisomers **36** and **37** (entries 27 and 28), while a MeO group gave a similar

mixture of two inseparable regioisomers **38** and **39** (entry 29). α-Naphthyl propargylic ether **13** also gave the desired compound **43** in modest yields (entries 39 and 40).

Phenyl 3-phenyl-2-propynyl ether (**3)** gave a 95% yield of the cyclized product **23** when PhSeBr was used as the electrophile (entry 3). Surprisingly, ether **21**, which failed to give the desired product with I_2 or ICl, gave a 79% yield of compound **41** with PhSeBr as the electrophile (entry 36).

We believe that the mechanism of these cyclizations involves initial formation of an iodonium or selenonium intermediate by attack of the electrophile on the triple bond, followed by electrophilic attack on the electron cloud of the aromatic ring. Loss of a proton gives the 2*H*-benzopyran (Scheme 4).

Scheme 4

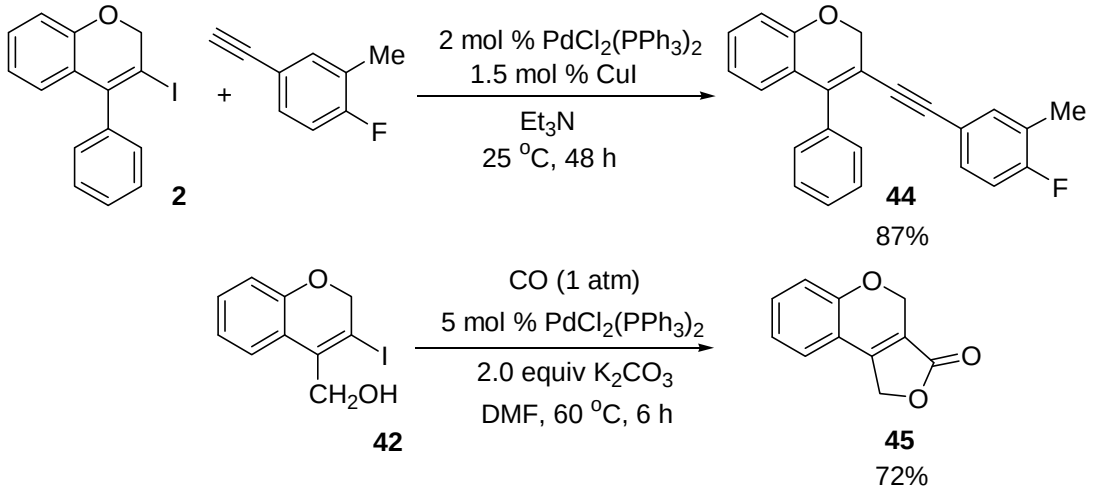


During our cyclization studies, ether **9** gave a mixture of two isomers, one being the expected benzopyran product and the other a possible five-membered ring dihydrofuran product. This encouraged us to confirm the structure of our cyclized product **2** using X-ray

crystallography (see the Supporting Information), which indeed proved to be a 2*H*-benzopyran.

The iodo-(*2H*)-benzopyrans obtained by iodocyclization appear highly promising as intermediates for the preparation of more highly substituted benzopyrans. Indeed 3-iodobenzopyrans, like the ones prepared here, have recently been further elaborated by palladium-catalysed cross-coupling reactions.[27] To further prove the utility of our methodology, we have carried out the palladium/copper-catalyzed reaction of our product **2** with 5-ethynyl-2-fluorotoluene to obtain **44** in an 87 % yield. Palladium catalysed CO insertion in our product **42** gave compound **45** in an overall 72 % yield (Scheme 5).

Scheme 5



Conclusions

3,4-Disubstituted 2*H*-benzopyrans have been obtained from starting materials that are easy to synthesize. The reaction conditions are mild and the products are easy to isolate in good yields. The iodine moiety in the products provides a useful handle for further functionalization of the resulting heterocycles. A polycyclic Sonogashira product **44** has

been obtained in a good yield. Our methodology tolerates functional groups, including alcohol, aldehyde, methoxy and nitro groups. In addition to I_2 and ICl, PhSeBr has also been used as the electrophile. The structure of 3-iodo-4-phenyl-2*H*-benzopyran (**2)** has been confirmed by X-ray crystallography.

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. Thin layer chromatography was performed using 60 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All high resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

Preparation of starting materials.

Substituted propargyl ether **7** was prepared according to a literature procedure.[34]

General procedure for the palladium/copper-catalyzed reaction of phenyl propargyl ether with aryl halides. To a solution of 2.5 mmol of the aryl halide in Et_3N (15 ml) was added $PdCl_2(PPh_3)_2$ (2 mol %), which was then stirred for 5 min. CuI (1.5 mol %) was then added and the flask was sealed and flushed with Ar. The reaction was stirred for 20 min. A solution of 3.0 mmol of phenyl propargyl ether 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 diluted with H_2O (10 ml) 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.

3,5-Di-*tert*-butylphenyl propargyl ether (8). To a solution of 2.06 g of 3,5-di-*tert*-butylphenol (10.0 mmol) in dry acetone (50 ml) was added propargyl bromide (11.0 mmol) and anhydrous K_2CO_3 (11.0 mmol). The resulting mixture was refluxed for 24 h. The reaction mixture was diluted with H_2O (20 ml) and extracted with diethyl ether (3 x 20 ml). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (7:1 hexane/EtOAc) to afford 1.68 g of the indicated compound **7** (69% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 18H), 2.42 (t, J = 2.5 Hz, 1H), 4.63 (d, J = 2.4 Hz, 2H), 6.83 (d, J = 1.6 Hz, 2H), 7.05 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 35.0, 55.7, 75.4, 79.1, 109.4, 115.7, 152.2, 157.3; IR (neat, cm^{-1}) 3298, 2939, 1588, 1424, 1285, 1050; HRMS m/z 244.18311 (calcd $C_{17}H_{24}O$, 244.18272).

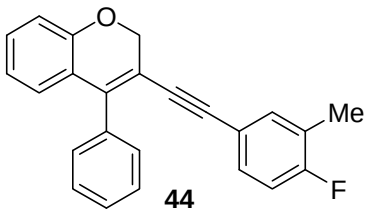
General procedure for the palladium/copper-catalyzed reaction of terminal alkynes with iodobenzene. To a solution of 4.5 mmol of iodobenzene in Et_3N (15 ml), was added $PdCl_2(PPh_3)_2$ (2 mol %), and CuI (1.5 mol %), and the mixture was stirred for 30 min under Ar. A solution of 3.0 mmol of the terminal alkyne 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 diluted with H_2O (10 ml) 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.

General procedure for the triphenylphosphine/diethyl azodicarboxylate-promoted formation of the substituted phenyl propargylic ethers. To a solution of 1.31 g of PPh_3 (5.0 mmol) in dry benzene (15 ml) was added the substituted propargylic alcohol (5.0 mmol) and the substituted phenol (5.0 mmol) under an inert atmosphere with stirring. Diethyl azodicarboxylate (0.87 g, 5.0 mmol) was then added slowly and the reaction mixture was stirred at r.t. for 18 to 36 h. After the reaction was complete, the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.

General procedure for iodocyclization. To a solution of 0.25 mmol of the ether and 3 mL of CH_3NO_2, 2.0 equiv of $NaHCO_3$ and 3.0 equiv of I_2 dissolved in 2 mL of CH_3NO_2 was added gradually. The reaction mixture was allowed to stir at room temperature for the desired time. Alternatively, to a solution of 0.25 mmol of the ether and 3 mL of CH_3NO_2 at -25 to -30 ^oC, 1.5 equiv of ICl dissolved in 2 mL of CH_3NO_2 was added gradually. The reaction mixture was allowed to stir at -25 to -30 ^oC 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 hexanes/ethyl acetate as the eluent.

General procedure for the PhSeBr cyclizations. To a solution of 0.25 mmol of the substituted phenyl propargylic ether and CH_2Cl_2 (3 mL), 0.375 mmol of PhSeBr 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

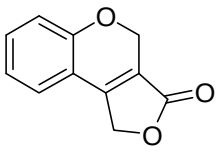
Na_2SO_4 and concentrated under vacuum to yield the crude product, which was further purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.



44

3-(4-Fluoro-3-methylphenylethynyl)-4-phenyl-2*H*-benzopyran (44). To a solution of 0.17 g of 3-iodo-4-phenyl-2*H*-benzopyran **(2)** (0.5 mmol) in Et_3N (5 ml), was added $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (1.5 mol %), and the mixture was stirred for 30 min under Ar. 0.6 Mmol of 5-ethynyl-2-fluorotoluene dissolved in 1 mL of Et_3N was then added dropwise and the reaction mixture was allowed to stir at room temperature for 24 h. The reaction was monitored by TLC and an additional 0.4 mmol of the 5-ethynyl-2-fluorotoluene dissolved in 1 mL of Et_3N was added slowly under an inert atmosphere and the reaction mixture was further allowed to stir at room temperature for another 24 h. After the reaction was over, the resulting solution was diluted with H_2O (5 ml) 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, which was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent to obtain the desired compound **44** in an 87% yield as a pale yellow solid: mp 79-80 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (d, J = 1.6 Hz, 3H), 4.88 (s, 2H), 6.81-6.93 (m, 4H), 6.97-7.05 (m, 2H), 7.10-7.21 (m, 1H), 7.39-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (d, J = 3.4 Hz), 68.0, 86.7 (d, J = 1.9 Hz), 95.1 (d, J = 0.8 Hz), 112.4, 115.3 (d, J = 9.4 Hz), 116.4, 118.9 (d, J = 3.8 Hz), 121.8, 124.3, 125.3 (d, J = 18.2 Hz), 126.8, 128.2 (d, J = 10.2 Hz), 129.8, 130.2,

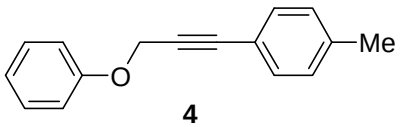
130.8 (d, J = 8.4 Hz), 134.7 (d, J = 5.7 Hz), 136.6, 140.8, 154.6, 160.1, 162.6; IR (neat, cm^{-1}) 3047, 2919, 2192, 1480, 1224, 1106; HRMS m/z 340.12694 (calcd $C_{24}H_{17}FO$, 340.12634).



45

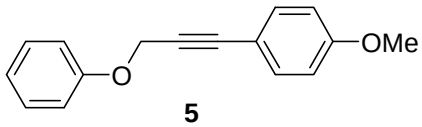
1,4-Dihydro-2,5-dioxacyclopenta[*a*]naphthalen-3-one (45). To a solution of 0.14 g of 4-hydroxymethyl-3-iodo-2*H*-benzopyran **(42)** (0.5 mmol) in DMF (5 ml) was added $PdCl_2(PPh_3)_2$ (5 mol %) and K_2CO_3 (2 equiv), and the mixture was stirred for 6 h under an atmosphere of CO at 60 ^oC. The reaction was monitored by TLC and, after completion of the reaction, the resulting solution was cooled to room temperature, diluted with ether (15 ml), and washed with brine (15 ml). The aqueous layer was 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, which was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent to obtain the desired compound **45** in an 72% yield as a brown solid: mp 151-152 ^oC; ^1H NMR (400 MHz, $CDCl_3$) 5.13-5.15 (m, 4H), 6.92-6.99 (m, 2H), 7.07 (dd, J = 7.5, 1.5 Hz, 1H), 7.34 (dt, J = 8.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.3, 68.8, 116.4, 117.2, 118.3, 122.0, 124.2, 133.8, 154.1, 154.8, 170.7; IR (neat, cm^{-1}) 2361, 1744, 1666, 1449, 1336, 1181, 1052; HRMS m/z 188.04776 (calcd $C_{11}H_8O_3$, 188.04743).

Characterization data:



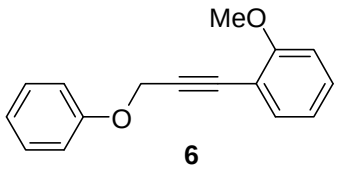
4

Phenyl 3-*p*-tolylprop-2-yn-1-yl ether (4). This compound was obtained as a white solid: mp 71-72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 4.86 (s, 2H), 6.94-7.08 (m, 5H), 7.18-7.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 56.9, 83.5, 87.5, 115.2, 119.5, 121.6, 129.3, 129.7, 132.0, 139.0, 158.1; IR (neat, cm^{-1}) 3032, 2914, 1598, 1490, 1214, 1029; HRMS m/z 222.10477 (calcd $C_{16}H_{14}O$, 222.10447).



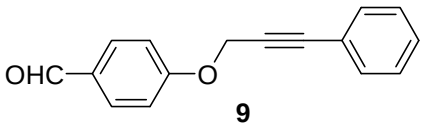
5

3-(4-Methoxyphenyl)prop-2-yn-1-yl phenyl ether (5). This compound was obtained as a light brown solid: mp 61-62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.88 (s, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.95-7.03 (m, 3H), 7.27-7.38 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 56.8, 82.7, 87.2, 114.0, 114.5, 115.1, 121.5, 129.6, 133.5, 158.0, 160.0; IR (neat, cm^{-1}) 3042, 2919, 1598, 1506, 1239, 1024; HRMS m/z 238.09979 (calcd $C_{16}H_{14}O_2$, 238.09938).



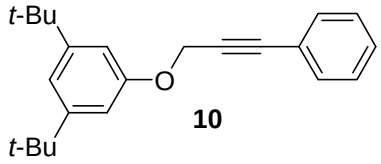
6

3-(2-Methoxyphenyl)prop-2-yn-1-yl phenyl ether (6). This compound was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.90 (s, 2H), 6.77-6.86 (m, 2H), 6.95 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 7.8 Hz, 2H), 7.20-7.30 (m, 3H), 7.36 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7, 56.9, 83.6, 88.1, 110.6, 111.4, 115.1, 120.4, 121.3, 129.4, 130.2, 133.8, 157.9, 160.2; IR (neat, cm^{-1}) 3057, 3032, 2934, 2243, 1603, 1270, 1024; HRMS m/z 238.09968 (calcd $C_{16}H_{14}O_2$, 238.09938).



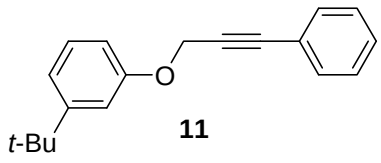
9

4-(3-Phenylprop-2-yn-1-yloxy)benzaldehyde (9). This compound was obtained as a brown solid: mp 86-87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.25-7.32 (m, 3H), 7.41-7.44 (m, 2H), 7.87 (d, J = 8.8 Hz, 2H), 9.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.0, 82.9, 88.1, 115.4, 122.0, 128.5, 129.1, 130.6, 132.0, 132.1, 162.8, 191.0; IR (neat, cm^{-1}) 3078, 2827, 1690, 1598, 1250, 1009; HRMS m/z 236.08409 (calcd $C_{16}H_{12}O_2$, 236.08373).



10

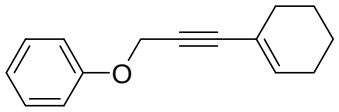
3,5-Di-*tert*-butylphenyl 3-phenylprop-2-yn-1-y1 ether (10). This compound was obtained as a light yellow solid: mp 54-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 18H), 4.91 (s, 2H), 6.91 (d, J = 1.6 Hz, 2H), 7.06 (t, J = 1.5 Hz, 1H), 7.26-7.31 (m, 3H), 7.41-7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.7, 35.2, 56.8, 84.5, 87.2, 109.6, 115.8, 122.6, 128.5, 128.8, 132.0, 152.4, 157.6; IR (neat, cm^{-1}) 3081, 2963, 1591, 1362, 1297, 1051; HRMS m/z 320.21446 (calcd $C_{23}H_{28}O$, 320.21402).



11

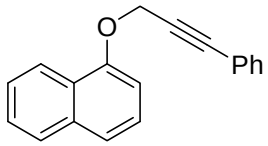
3-*tert*-Butylphenyl 3-phenylprop-2-yn-1-y1 ether (11). This compound was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 4.86 (s, 2H), 6.83 (dd, J = 8.0, 2.3 Hz, 1H), 6.96-7.02 (m, 1H), 7.08 (t, J = 1.9 Hz, 1H), 7.19-7.25 (m, 4H), 7.39-7.42

(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 34.8, 56.6, 84.3, 87.2, 111.2, 113.1, 118.6, 122.4, 128.4, 128.7, 129.1, 131.9, 153.0, 157.7; IR (neat, cm^{-1}) 3067, 2955, 2868, 1588, 1485, 1270, 1029; HRMS m/z 264.15187 (calcd $C_{19}H_{20}O$, 264.15142).



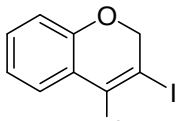
12

3-(Cyclohex-1-enyl)prop-2-yn-1-yl phenyl ether (12). This compound was obtained as a dark brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53-1.62 (m, 4H), 2.04-2.10 (m, 4H), 4.77 (s, 2H), 6.10-6.13 (m, 1H), 6.93-6.98 (m, 2H), 7.24-7.30 (m, 2H), 7.40-7.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 22.3, 25.7, 29.0, 56.7, 81.3, 89.1, 115.0, 120.0, 121.3, 129.5, 136.1, 157.9; IR (neat, cm^{-1}) 3032, 2919, 2217, 1593, 1485, 1219; HRMS m/z 212.12047 (calcd $C_{15}H_{16}O$, 212.12012).



13

1-Naphthyl 3-phenylprop-2-yn-1-yl ether (13). This compound was obtained as a light brown solid: mp 50-51 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (s, 2H), 6.99 (d, J = 7.4 Hz, 1H), 7.26-7.49 (m, 9H), 7.77-7.80 (m, 1H), 8.30-8.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.2, 84.2, 87.5, 105.9, 121.2, 122.4, 122.6, 125.6, 125.9, 126.0, 126.7, 127.7, 128.5, 128.9, 132.0, 134.8, 153.8; IR (neat, cm^{-1}) 3057, 2914, 1577, 1398, 1229, 1091; HRMS m/z 258.10497 (calcd $C_{19}H_{14}O$, 258.10447).



2

3-Iodo-4-phenyl-2*H*-benzopyran (2). This compound was obtained as a pale yellow solid: mp 99-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 2H), 6.61 (dd, J = 7.7, 1.6 Hz, 1H), 6.76 (dt, J = 7.7, 1.1 Hz, 1H), 6.85 (dd, J = 8.0, 1.0 Hz, 1H), 7.14 (dd, J = 7.9, 1.6 Hz, 1H), 7.18-7.22 (m, 2H), 7.39-7.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.1, 91.2, 116.1, 121.7, 124.2, 126.5, 128.3, 128.7, 129.5, 129.7, 140.0, 142.0, 153.3; IR (neat, cm^{-1}) 3062, 2904, 1475, 1219, 1029, 994; HRMS m/z 333.98600 (calcd $C_{15}H_{11}IO$, 333.98547).

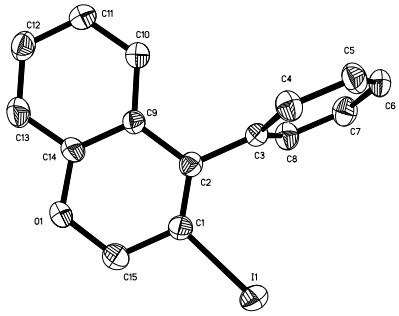
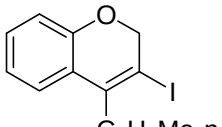


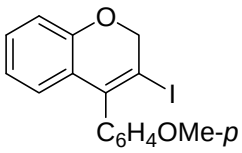
Figure 1. X-ray structure of compound **2**



24

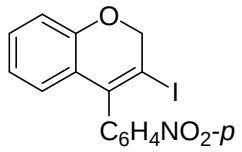
3-Iodo-4-(4-methylphenyl)-2*H*-benzopyran (24). This compound was obtained as a pale brown solid: mp 68-69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 4.87 (s, 2H), 6.46 (dd, J = 7.7, 1.6 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.89-6.98 (m, 3H), 7.07 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 75.2, 91.1, 116.1,

121.7, 124.4, 126.6, 129.4, 129.5, 129.7, 137.1, 138.1, 142.0, 153.5; IR (neat, cm^{-1}) 3032, 2914, 2842, 1475, 1219, 999; HRMS m/z 348.00051 (calcd $C_{16}H_{13}IO$, 348.00112).



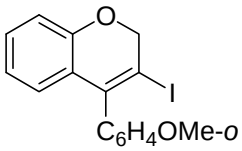
25

3-Iodo-4-(4-methoxyphenyl)-2*H*-benzopyran (25). This compound was obtained as a pale brown solid: mp 110-111 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.05 (s, 2H), 6.66 (dd, J = 7.7, 1.2 Hz, 1H), 6.77 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 7.11-7.17 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 75.2, 91.4, 114.1, 116.1, 121.7, 124.6, 126.6, 129.7, 130.8, 132.3, 141.7, 153.5, 159.5; IR (neat, cm^{-1}) 2955, 2918, 2833, 1505, 1244, 1171, 1037; HRMS m/z 363.99640 (calcd $C_{16}H_{13}IO_2$, 363.99603).



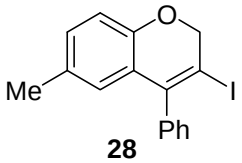
26

3-Iodo-4-(4-nitrophenyl)-2*H*-benzopyran (26). This compound was obtained as a yellow solid: mp 140-142 ^{o}C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 2H), 6.50 (dd, J = 7.7, 1.4 Hz, 1H), 6.79 (dt, J = 7.8, 0.9 Hz, 1H), 6.88 (dd, J = 8.2, 0.9 Hz, 1H), 7.19 (dt, J = 8.0, 1.4 Hz, 1H), 7.41 (dd, J = 6.9, 1.9 Hz, 2H), 8.32 (dd, J = 6.9, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.0, 91.8, 116.5, 122.0, 123.4, 124.1, 125.9, 130.4, 130.8, 140.4, 146.6, 147.8, 153.2; IR (neat, cm^{-1}) 3093, 2837, 1926, 1593, 1516, 1337, 1219; HRMS m/z 378.97119 (calcd $C_{15}H_{10}INO_3$, 378.97055).



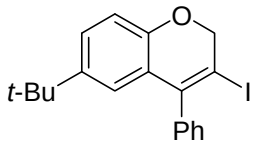
27

3-Iodo-4-(2-methoxyphenyl)-2*H*-benzopyran (27). This compound was obtained as a light brown solid: mp 111-113 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 5.01-5.13 (m, 2H), 6.57 (dd, J = 7.8, 1.5 Hz, 1H), 6.74 (dt, J = 7.6, 1.1 Hz, 1H), 6.83 (dd, J = 7.1, 1.0 Hz, 1H), 6.96-7.14 (m, 4H), 7.37-7.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 74.9, 92.7, 111.6, 116.0, 121.0, 121.7, 123.8, 126.1, 129.0, 129.5, 130.0, 131.0, 139.5, 153.2, 156.9; IR (neat, cm^{-1}) 2955, 2918, 1505, 1244, 1171, 1037; HRMS m/z 363.99644 (calcd $C_{16}H_{13}IO_2$, 363.99603).



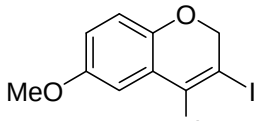
28

3-Iodo-6-methyl-4-phenyl-2*H*-benzopyran (28). This compound was obtained as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 5.01 (s, 2H), 6.41 (s, 1H), 6.75 (d, J = 8.2, Hz, 1H), 6.94 (d, J = 8.2, Hz, 1H), 7.17-7.20 (m, 2H), 7.40-7.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 75.1, 91.4, 115.8, 124.1, 126.8, 128.2, 128.6, 129.5, 130.2, 131.0, 140.1, 142.1, 151.1; IR (neat, cm^{-1}) 3052, 2914, 1741, 1485, 1229, 999; HRMS m/z 348.00155 (calcd $C_{16}H_{13}IO$, 348.00112).



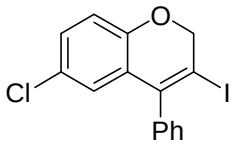
29

6-*tert*-Butyl-3-iodo-4-phenyl-2*H*-benzopyran (29). This compound was obtained as a pale yellow solid: mp 84-86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9H), 5.03 (s, 2H), 6.63 (d, J = 2.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.18-7.22 (m, 2H), 7.37-7.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 34.3, 75.2, 90.9, 115.4, 123.5, 123.8, 126.6, 128.3, 128.6, 129.5, 140.1, 142.4, 144.5, 151.1; IR (neat, cm^{-1}) 3052, 2950, 1485, 1357, 1229, 1004; HRMS m/z 390.04856 (calcd $C_{19}H_{19}IO$, 390.04807).



30

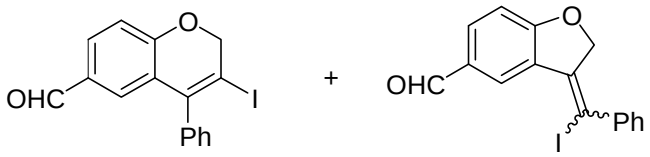
3-Iodo-6-methoxy-4-phenyl-2*H*-benzopyran (30). This compound was obtained as a pale brown solid: mp 81-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H), 4.99 (s, 2H), 6.19 (d, J = 2.9 Hz, 1H), 6.69 (dd, J = 8.7, 2.9 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 7.18-7.23 (m, 2H), 7.38-7.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 75.3, 92.4, 112.5, 114.4, 116.6, 125.1, 128.4, 128.8, 129.5, 140.0, 142.1, 147.4, 154.3; IR (neat, cm^{-1}) 2991, 2924, 2822, 1572, 1480, 1301, 1198; HRMS m/z 363.99663 (calcd $C_{16}H_{13}IO_2$, 363.99603).



31

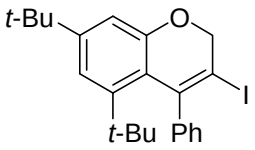
6-Chloro-3-iodo-4-phenyl-2*H*-benzopyran (31). This compound was obtained as a brown solid: mp 89-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 2H), 6.59 (d, J = 2.6 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.5 Hz, 1H), 7.19 (dd, J = 7.8, 1.9 Hz 2H), 7.43-7.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.3, 93.0, 117.4, 125.3, 126.1, 126.7,

128.6, 129.0, 129.4, 129.5, 139.4, 141.2, 151.9; IR (neat, cm^{-1}) 2919, 2848, 1477, 1403, 1093, 638; HRMS m/z 367.94723 (calcd $C_{15}H_{10}ClIO$, 367.94649).



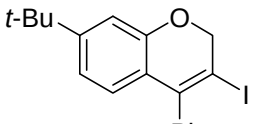
32 **33**

3-Iodo-4-phenyl-2*H*-benzopyran-6-carbaldehyde (32) and 3-(iodophenyl-methylene)-2,3-dihydrobenzofuran-5-carbaldehyde (33). These compounds were obtained as a light brown solid as a 2:1 mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 2H), 5.19 (s, 1H), 6.95 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 8.5 Hz, 3H), 7.19-7.23 (m, 3H), 7.31-7.40 (m, 4H), 7.47-7.49 (m, 2H), 7.70 (dd, J = 8.3, 1.9 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 9.68 (s, 1H), 9.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.5, 80.1, 92.7, 98.49, 99.4, 115.9, 116.9, 123.8, 128.1, 128.5, 128.7, 128.8, 129.0, 129.1, 129.3, 130.7, 130.9, 131.8, 132.2, 139.2, 141.0, 147.2, 158.6, 162.7, 190.7, 190.9; IR (neat, cm^{-1}) 3057, 2827, 1690, 1598, 1234, 1157; HRMS m/z 361.98090 (calcd $C_{16}H_{11}IO_2$, 361.98038).



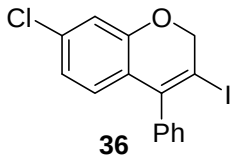
34

5,7-Di-*tert*-butyl-3-iodo-4-phenyl-2*H*-benzopyran (34). This compound was obtained as a yellow solid: mp 142-143 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.31 (s, 9H), 4.81 (s, 2H), 6.89 (d, J = 1.9 Hz, 1H), 7.12 (d, J = 2.1 Hz, 2H), 7.24-7.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.3, 32.1, 35.2, 36.8, 7.8, 85.0, 109.5, 119.9, 122.7, 127.6, 128.0, 131.1, 143.7, 143.9, 149.8, 152.5, 157.2; IR (neat, cm^{-1}) 2955, 2893, 1593, 1444, 1403, 1004; HRMS m/z 446.11117 (calcd $C_{23}H_{27}IO$, 446.11067).



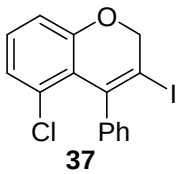
35

7-*tert*-Butyl-3-iodo-4-phenyl-2*H*-benzopyran (35). This compound was obtained as a light brown solid: mp 97-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 5.09 (s, 2H), 6.59 (d, J = 4.3 Hz, 1H), 6.83 (dd, J = 8.1, 1.8 Hz, 1H), 6.93 (d, J = 1.7 Hz, 1H), 7.21-7.25 (m, 2H), 7.40-7.44 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.3, 35.0, 75.3, 90.1, 113.3, 118.7, 121.8, 126.1, 128.3, 128.7, 129.5, 140.2, 142.0, 153.1, 153.8; IR (neat, cm^{-1}) 2965, 2904, 2356, 1603, 1485, 1004; HRMS m/z 390.04856 (calcd $C_{19}H_{19}IO$, 390.04807).



36

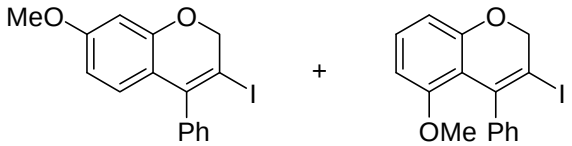
7-Chloro-3-iodo-4-phenyl-2*H*-benzopyran (36). This compound was obtained as a light brown solid: mp 90-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 2H), 6.52 (d, J = 8.3 Hz, 1H), 6.72 (dd, J = 8.4, 2.1 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 7.16-7.19 (m, 2H), 7.41-7.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.3, 91.2, 116.5, 121.9, 122.7, 127.4, 128.5, 128.8, 129.4, 134.7, 139.6, 141.3, 154.0; IR (neat, cm^{-1}) 2837, 1588, 1475, 1413, 1219, 999; HRMS m/z 367.94720 (calcd $C_{15}H_{10}ClIO$, 367.94649).



37

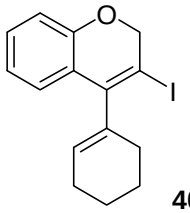
5-Chloro-3-iodo-4-phenyl-2*H*-benzopyran (37). This compound was obtained as a light brown solid: mp 73-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 2H), 6.88-6.91 (m, 2H), 7.10 (t, J = 8.0 Hz, 1H), 7.17-7.20 (m, 2H), 7.34-7.38 (m, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 76.0, 92.8, 115.2, 123.3, 125.0, 128.0, 128.1, 129.7, 129.9, 131.7, 140.4, 141.3, 156.6; IR (neat, cm^{-1}) 3052, 2937, 1588, 1444, 1239, 999; HRMS m/z 367.94725 (calcd $C_{15}H_{10}ClIO$, 367.94649).



38 **39**

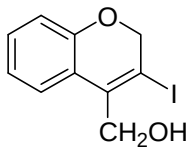
3-Iodo-7-methoxy-4-phenyl-2*H*-benzopyran (38) and 3-iodo-5-methoxy-4-phenyl-2*H*-benzopyran (39). These compounds were obtained as a light brown solid as a 2:3 mixture: ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 3H), 3.76 (s, 2H), 4.93 (s, 2H), 5.04 (s, 1H), 6.31 (dd, J = 8.6, 2.5 Hz, 1H), 6.37-6.47 (m, 2H), 6.50-6.62 (m, 2H), 7.12-7.21 (m, 4H), 7.28-7.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 55.8, 75.3, 75.8, 87.0, 89.0, 101.7, 106.1, 107.4, 109.2, 115.1, 117.8, 127.0, 127.6, 127.7, 128.2, 128.5, 128.6, 129.5, 130.2, 140.2, 140.5, 141.8, 143.4, 154.7, 156.0, 156.1, 161.0; IR (neat, cm^{-1}) 3016, 2934, 2827, 1608, 1465, 1270; HRMS m/z 363.99664 (calcd $C_{16}H_{13}IO_2$, 363.99603).



40

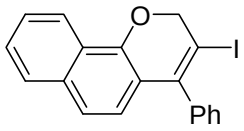
4-(1-Cyclohexenyl)-3-iodo-2*H*-benzopyran (40). This compound was obtained as a light brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.76 (m, 4H), 2.05 (m, 2H), 2.18-2.20 (m, 2H), 4.93 (s, 2H), 5.60-5.62 (m, 1H), 6.79 (dd, J = 8.0, 0.9 Hz, 1H), 6.86 (dt, J = 7.6, 1.1 Hz, 1H), 7.06 (dd, J = 7.7, 1.5 Hz, 1H), 7.13 (dt, J = 7.7, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 22.8, 25.3, 27.6, 74.7, 89.2, 116.1, 121.7, 122.8, 125.6, 129.3, 129.5, 137.5,

143.5, 153.6; IR (neat, cm^{-1}) 3027, 2914, 1598, 1475, 1209, 1034; HRMS m/z 338.01726 (calcd $C_{15}H_{15}IO$, 338.01677).



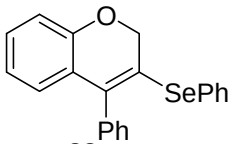
42

4-Hydroxymethyl-3-iodo-2*H*-benzopyran (42). This compound was obtained as a yellow solid: mp 62-63 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 1H), 4.64 (s, 2H), 4.86 (s, 2H), 6.82 (d, J = 8.0 Hz, 1H), 6.92-6.98 (m, 1H), 7.18 (dt, J = 8.0, 1.3 Hz, 1H), 7.41 (dd, J = 7.7, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.0, 75.0, 93.8, 116.4, 121.8, 122.1, 124.3, 129.9, 137.3, 153.7; IR (neat, cm^{-1}) 3334, 2934, 1480, 1444, 1219, 1009; HRMS m/z 287.96514 (calcd $C_{10}H_9IO_2$, 287.96473).



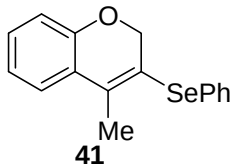
43

3-Iodo-4-phenyl-2*H*-benzo[*h*]chromene (43). This compound was obtained as a light brown solid: mp 104-105 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 2H), 6.77 (d, J = 8.5 Hz, 1H), 7.21-7.25 (m, 3H), 7.42-7.50 (m, 5H), 7.68-7.71 (m, 1H), 8.17-8.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.6, 88.1, 118.8, 120.8, 122.2, 124.0, 124.3, 126.0, 127.1, 127.7, 128.3, 128.7, 129.6, 134.3, 140.2, 142.7, 149.4; IR (neat, cm^{-1}) 3055, 2923, 2847, 1562, 1400, 1341; HRMS m/z 384.00158 (calcd $C_{19}H_{13}IO$, 384.00112).



23

4-Phenyl-3-phenylselenyl-2*H*-benzopyran (23). This compound was obtained as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 2H), 6.84-6.87 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 7.12-7.25 (m, 5H), 7.27-7.34 (m, 4H), 7.40-7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 71.1, 115.3, 121.4, 124.0, 128.2, 128.4, 128.8, 129.1, 129.2, 129.2, 129.3, 129.6, 134.6, 141.0, 158.4; IR (neat, cm^{-1}) 3052, 2919, 1582, 1480, 1224, 1024; HRMS m/z 364.03707 (calcd $C_{21}H_{16}OSe$, 364.03664).



41

4-Methyl-3-phenylselenyl-2*H*-benzopyran (41). This compound was obtained as a brown solid: mp 54-55 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.66 (s, 3H), 4.80 (s, 2H), 6.83 (d, J = 7.9 Hz, 2H), 6.92 (t, J = 7.3 Hz, 1H), 7.20-7.26 (m, 4H), 7.42-7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 72.1, 115.2, 121.3, 125.4, 127.6, 128.4, 129.5 (2C), 129.7, 130.2, 132.5, 158.5; IR (neat, cm^{-1}) 3057, 2914, 2847, 1593, 1485, 1229; HRMS m/z 302.02154 (calcd $C_{16}H_{14}OSe$, 302.02099).

Acknowledgements

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References

1. (a) Zhendong, J.; Ying, K. *PCT Int. Appl*. **2004**, *25* pp. (b) Iwata, N.; Wang, N.; Yao, X.; Kitanaka, S. *J. Nat. Prod.* **2004**, *67*, 1106. (c) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem*. **2004**, *69*, 3782.
2. Korec, R.; Sensch, K. H.; Zoukas, T. *Arzneim. Forsch.* **2000**, *50*, 122.
3. (a) Carney, R. W. J.; Bencze, W. L.; Wojtkunski, J.; Renzi, A. A.; Dorfman, L.; De Stevens, G. *J. Med. Chem*. **1966**, *9*, 516. (b) Gauthier, S.; Caron, B.; Cloutier, J.; Dory, Y. L.; Favre, A.; Larouche, D.; Mailhot, J.; Ouellet, C.; Schwerdtfeger, A.; Leblanc, G.; Martel, C.; Simard, J.; Merand, Y.; Belanger, A.; Labrie, C.; Labrie, F. *J. Med. Chem*. **1967**, *40*, 2117.
4. Bonadies, F.; Di Fabio, R.; Bonini, C. *J. Org. Chem*. **1984**, *49*, 1647.
5. Morandim, A. A.; Bergamo, D. C. B.; Kato, M. J.; Cavalheiro, A. J.; Bolzani, V. S.; Furlan, M. *Phytochem. Anal.* **2005**, *16*, 282.
6. (a) Martins, C. I.; Coelho, P. J.; Carvalho, L. M.; Oliveira-Campos, A. M. F.; Samat, A.; Guglielmetti, R. *Helv. Chim. Acta* **2003**, *86*, 570. (b) Kodama, Y.; Nakabayashi, T.; Segawa, K.; Hattori, E.; Sakuragi, M.; Nishi, N.; Sakuragi, H. *J. Phys. Chem. A.* **2000**, *104*, 11478. (c) Padwa, A.; Andrew, A.; Lee, G. A.; Owens, W. *J. Org. Chem*. **1975**, *40*, 1142.
7. Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522.
8. Eguchi, T.; Hoshino, Y.; Ayame, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 581.
9. (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (b) Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155.
10. Balasubramanian, T.; Balasubramanian, K. K. *Tetrahedron Lett*. **1991**, *32*, 6641.

11. Kirkiacharian, B. S.; Danan, A.; Koutsourakis, P. G. *Synthesis* **1991**, *10*, 879.

12. Dintzner, M. R.; Lyons, T. W.; Akroush, M. H.; Wucka, P.; Rzepka, A. T. *Synlett* **2005**, 1046.

13. (a) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622. (b) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 2859. (c) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857. (d) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193. (e) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798. (f) Knight, D. W.; Redfern, A. L.; Gilmore, *J. Chem. Commun.* **1998**, 2207. (g) Redfern, A. L.; Gilmore, J. *Synlett* **1998**, 731. (h) Ren, X. F.; Konaklieva, M. I.; Shi, H.; Dicy, H.; Lim, D. V.; Gonzales, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898. (i) Bew, S. P.; Knight, D. W. *Chem. Commun.* **1996**, 1007. (j) El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 5945.

14. For a review, see: Larock, R. C. *Top. Organomet. Chem.* **2005**, *14*, 147.

15. (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *4*, 553. (b) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (d) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (e) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (f) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (g) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39,* 5101. (h) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (i) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (j) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet.*

Chem. **1994**, *475,* 289. (k) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33,* 3915. (l) Cacchi, S. *J. Organomet. Chem.* **1999**, *576,* 42.

16. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (c) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687.
17. (a) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (c) Larock, R. C.; Liu, C. L. *J. Org. Chem.* **1983**, *48*, 2151.
18. (a) Hessian K. O.; Flynn B. L. *Org. Lett.* **2003**, *5*, 4377. (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (c) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42,* 6011.
19. Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341.
20. Zhang, X.; Sarkar, S.; Larock. R. C. *J. Org. Chem*. **2006**, *71*, 236.
21. (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (b) Yao, T.; Yue, D.; Larock, R. C. *J. Comb. Chem.* **2005**, *7*, 809. (c) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (d) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.
22. Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett* **2005**, *7*, 763.
23. Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.
24. Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.
25. Yue, D.; Della Cá, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581.

26. (a) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511. (b) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6,* 2677.

27. Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; Gonzalez, J. M. *Chem. Commun*. **2005**, 2008.

28. Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 5, pp 203-229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

29. Berg, T. C.; Bakken, V.; Gundersen, L.; Petersen, D. *Tetrahedron* **2006**, *62*, 6121.

30. Muldakhmetov, Z. M.; Agelmenev, M. E.; Sovetov, E. S. *Zh. Fiz. Khim.* **1999**, *73*, 2085.

31. Issei, W.; Junya, I. *Chem. Pharm. Bull*. **1963**, *11*, 1042.

32. Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett*. **2003**, *5*, 1055.

33. Tolstikov, G. A.; Tolstikov, A. G.; Miftakhov, M. S.; Spirikhin, L. V. *Zh. Org. Khim.* **1986**, *22*, 1620.

34. Pal, M.; Parasuraman, K.; Yeleswarapu, K. R. *Org. Lett*. **2003**, *5*, 349.

35. Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347.

CHAPTER 2. PALLADIUM-CATALYZED ONE STEP SYNTHESIS OF ISOINDOLE-1,3-DIONES BY CARBONYLATIVE CYCLIZATION OF *O*-HALOBENZOATES AND PRIMARY AMINES

Based on a paper accepted to the *Journal of Organic Chemistry*[46]

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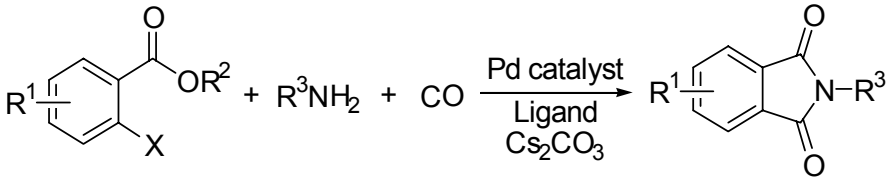
Abstract



The palladium-catalyzed aminocarbonylation of *ortho*-halobenzoates produces 2-substituted isoindole-1,3-diones in good yields. This methodology provides a good one step approach to this important class of heterocycles and tolerates a variety of functional groups, including methoxy, alcohol, ketone and nitro groups.

Introduction

Isoindole-1,3-diones, commonly known as phthalimides, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. The drug thalidomide [2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione], was originally developed as a sedative, an alternative to barbiturates, but was withdrawn from the market in the 1960s, because it displayed teratogenic properties.[1] Recently, interest in this compound has increased, because of its interesting anti-inflammatory and antiangiogenic[2]

properties and its possible use in the treatment of acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV),[3,4] leprosy[5] and other diseases.[6-8] The isoindole-1,3-dione *N*-phthaloyl-*L*-glutamic acid is a selective glutamate receptor agonist,[9] while 1,8-naphthalimide is known for its cytotoxicity against the growth of human cancer cultured cells.[10] Some isoindole-1,3-dione derivatives are active in reducing the growth of colon adenocarcinoma, osteosarcoma and KB nasopharynx.[11] Isoindole-1,3-diones are also known for their antiviral,[12] anti-inflammatory,[13] Chk1 inhibitory,[14] sedative,[15] bactericidal and fungicidal[16] properties. They also find important applications as synthetic intermediates in the dye,[17] pesticide[18] and polymer[19] industries.

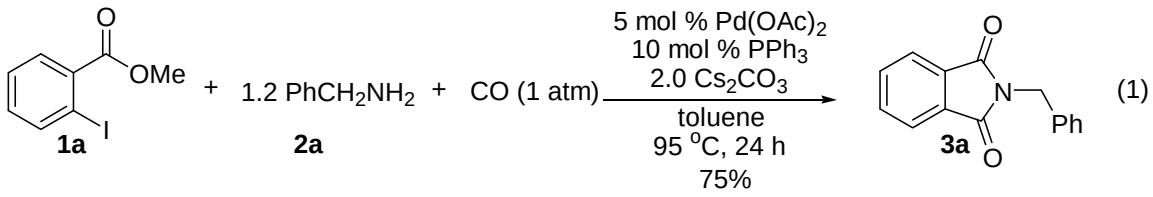
Due to their biological, pharmaceutical and industrial importance, the synthesis of isoindole-1,3-diones has received considerable attention in the literature. The most common method reported in the literature for the synthesis of isoindole-1,3-diones involves the reaction of a phthalic acid anhydride and a primary amine.[20] Syntheses of isoindole-1,3-diones have also been reported using other approaches, including the ammoxidation of *o*-xylenes by vanadium/titanium/oxygen catalysis and subsequent oxidation of intermediate *o*-tolunitriles,[21] microwave irradiation of *N*-hydroxymethylphthalimides with aryl amines or phthalic anhydrides with urea, the microwave-induced cleavage of solid-supported *o*-amidoesters,[22] the palladium-catalyzed carbonylation of *o*-haloamides, and a combination of carbonylation and nitrogenation of *o*-halophenyl alkyl ketones.[23]

The development of new methods for the simultaneous formation of both carbon-carbon and carbon-heteroatom bonds in a single step is quite advantageous to the organic chemist, since it allows the assembly of complex molecules from simple precursors. Transition metal-catalyzed reactions, especially palladium-catalyzed processes, which

involve the insertion of unsaturated molecules, such as carbon monoxide, alkynes and alkenes, into a carbon-metal bond are an important step towards this goal. In the past couple of years, we have developed in our laboratories the palladium-catalyzed annulation of dienes and internal alkynes by aromatic and vinylic halides bearing a neighboring nucleophilic substituent as an efficient way to synthesize a wide variety of carbocyclic and heterocyclic compounds,[24] including indoles,[25] isoquinolines,[26] benzofurans,[27] benzopyrans,[27] isocoumarins,[27,28] α-pyrones,[28,29] indenones,[30] naphthalenes,[31] and phenanthrenes.[32] CO insertion into the aryl-palladium bond to form an acylpalladium complex is a ubiquitous process in organic synthesis.[33] The resulting acylpalladium complexes react with various nucleophiles to give aryl carbonyl compounds. When nitrogen acts as the nucleophile, the process is aminocarbonylation,[34] which is an important method for the synthesis of amides. While many examples of such processes have been reported to form acyclic amides,[35] relatively few have been reported for the formation of cyclic amides. Ban *et al.* have reported the palladium-catalyzed formation of isoindole-1,3-diones from *o*-bromobenzamides and CO,[36] while Perry *et al.* have prepared isoindole-1,3-diones from *o*-dihaloarenes in the presence of CO, a primary amine, a catalytic amount of palladium, and a base in dipolar aprotic solvents.[37] However, these routes either limit the groups that can be introduced on the nitrogen of the isoindole-1,3-dione, because one first needs to prepare the starting benzamides, or they require high pressures of CO and specialized equipment, like pressure reactors. To the best of our knowledge, the synthesis of *N*-substituted isoindole-1,3-diones by the palladium-catalyzed aminocarbonylation of simple *ortho*-halobenzoates has not been reported previously. We report herein a number of examples of such a one step synthesis of this important class of heterocycles in good yields using readily available starting materials.

Results and Discussion

The focus of our early studies was the palladium-catalyzed aminocarbonylation of *ortho*-halobenzoates to give 2-substituted isoindole-1,3-diones in good yields. Methyl 2-iodobenzoate (**1a**) was used as a model system for optimization of the reaction conditions using benzylamine (**2a**) as the amine. Early in this work, the reaction was run with 0.5 mmol of **1a**, 1.2 equiv of benzylamine, 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, 2 equiv of Cs_2CO_3 as a base in 6 ml of toluene at 95 ^oC under one atmosphere of CO to obtain a 75% isolated yield of the desired 2-benzylisoindole-1,3-dione (**3a**) (eq. 1). The yield of the desired product **3a**



slightly increased to 76% when the amount of palladium catalyst and the triphenylphosphine ligand was increased to 10 mol % and 20 mol % respectively (Table 1, entry 1). No desired product was obtained when the reaction was carried out in the absence of the ligand PPh_3.

Table 1. Optimization of the Palladium-Catalyzed Carbonylative Cyclization of Methyl 2-Iodobenzoate and Benzylamine using various Phosphine Ligands (eq. 1)[a]

entry	ligand (20 mol %)	% isolated yield
1	PPh_3	76
2	P(*o*-tolyl)$_3$	14
3	Tri-(2-methoxyphenyl)phosphine	38

Table 1. Continued

entry	ligand (20 mol %)	% isolated yield
4	Tricyclohexylphosphine	82
5	Triethylphosphine	39
6	Tri-(2-furyl)phosphine	66
7	Diphenyl-2-pyridylphosphine	84
8	(2-Biphenyl)di-*tert*-butylphosphine	31
9	Tri-*t*-butylphosphine	53
10	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-PHOS)	66
11	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos)	64
12	(±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (BINAP)	19
13	2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthalene (Tol-BINAP)	71
14	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos)	78
15	1,1'-Bis(diphenylphosphino)ferrocene (dppf)	17
16	1,1-Bis(diphenylphosphino)methane (dppm)	34
17	1,2-Bis(diphenylphosphino)ethane (dppe)	~5
18	1,3-Bis(diphenylphosphino)propane (dppp)	91
19	1,4-Bis(diphenylphosphino)butane	81
20	1,5-Bis(diphenylphosphino)pentane	64

[a] Representative procedure: methyl 2-iodobenzoate (0.5 mmol), benzylamine (1.2 equiv), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), Cs_2CO_3 (2 equiv) and toluene (6 mL) were placed in a 4 dram vial. The vial was sealed and flushed with CO. The reaction was then stirred at 95 ^oC for 24 h with a CO balloon on top of the vial.

Noting the importance of the ligand in the reaction, various ligands were screened with the aim of increasing the yield of the imide. More sterically hindered triarylphosphines gave significantly lower yields (entries 2 and 3). More basic tricyclohexylphosphine gave a high yield (entry 4), but PEt_3 gave a poor yield (entry 5). Heterocyclic tri-(2-furyl)phosphine afforded a modest yield of imide (entry 6). Diphenyl-2-pyridylphosphine improved the yield dramatically to 84% (entry 7), but other bulky monodentate ligands gave only modest yields (entries 8-11).

Since the yields of imide are highly dependant on the ligands employed, we decided to screen bidentate ligands under similar reaction conditions. BINAP and dppf gave poor yields, while Tol-BINAP and Xantphos gave 71% and 78% yields respectively, which were close to those obtained with the parent triphenylphosphine (entries 12-15). The ligands dppm and dppe reduced the yields drastically to 34% and 5% respectively (entries 16 and 17), while dppp improved the yield to 91% (entry 18). With further elongation of the carbon chain of the bidentate ligand, the yields decreased. Thus, 1,4-bis(diphenylphosphino)butane and 1,5-bis(diphenylphosphino)pentane gave 81% and 64% yields respectively (entries 19 and 20).

With dppp as the ligand of choice, the reaction was carried out in various solvents. Reactions in the low boiling polar solvents CH_3CN and CH_3OH had to be carried out at lower temperatures and they did not give the desired product (Table 2, entries 1 and 2). The higher boiling polar solvents DMSO and DMF gave extremely poor yields at 95 ^oC (entries 3 and 4). Nitromethane gave a 10% yield of the desired product at 95 ^oC (entry 5), while THF gave a 42% yield of the desired product at the lower temperature of 60 ^oC (entry 6). Reaction in toluene as the solvent at the lower temperature of 80 ^oC reduced the yield to 79% (entry 7). A reduction in the amount of phosphine ligand to 10 mol % reduced the yield to 76% (entry 8). When the reaction was carried out with 10 mol % of the dppp ligand and 5 mol % of the palladium catalyst, the yield increased to 89% (entry 9), indicating that the ratio 1:2 of palladium catalyst to phosphine ligand works better than a ratio of 1:1. Maintaining the ratio of the palladium catalyst and phosphine at 1:2, but reducing the amount of palladium to 2 mol %, the yield dropped to 78% (entry 10). An excess of the ligand reduced

the yield further to 49% (entry 11). Excess ligand with 5 mol % of palladium also gave a poor yield of 53% (entry 12). The base Cs_2CO_3 proved to be very important for the reaction

Table 2. Optimization of the Palladium-Catalyzed Carbonylative Cyclization of Methyl 2-Iodobenzoate and Benzylamine with dppp as the Ligand (eq. 1)[a]

entry	$Pd(OAc)_2$ (mol %)	dppp (mol %)	Cs_2CO_3 (equiv)	solvent	time (h)	temp. (^oC)	% yield[b]
1	10	20	2.0	CH_3CN	24	75	0
2	10	20	2.0	CH_3OH	24	60	0
3	10	20	2.0	DMSO	24	95	~5[c]
4	10	20	2.0	DMF	24	95	~5[c]
5	10	20	2.0	CH_3NO_2	24	95	10
6	10	20	2.0	THF	24	60	42
7	10	20	2.0	$PhCH_3$	24	80	79
8	10	10	2.0	$PhCH_3$	24	95	76
9	5	10	2.0	$PhCH_3$	24	95	89
10	2	4	2.0	$PhCH_3$	24	95	78
11	2	10	2.0	$PhCH_3$	24	95	49
12	5	20	2.0	$PhCH_3$	24	95	53
13	5	10	1.5	$PhCH_3$	24	95	73
14	5	10	3.0	$PhCH_3$	24	95	90
15	5	10	2.0	$PhCH_3$	12	95	78

[a] Representative procedure: methyl 2-iodobenzoate (0.5 mmol), benzylamine (1.2 equiv), $Pd(OAc)_2$, dppp, Cs_2CO_3 and the solvent (6 mL) were placed in a 4 dram vial. The vial was sealed and flushed with CO. The reaction was then stirred at 95 ^oC for the indicated time with a CO balloon on top of the vial. [b] Isolated yields. [c] GC yields.

as the yield was reduced to 73% when using only 1.5 equiv of the base (compare entries 9 and 13). Increasing the amount of the base afforded no significant increase in the yield (entry 14). A reduced reaction time gave a lower yield of 78% (entry 15). Thus, our optimized conditions for the carbonylative cyclization are 0.5 mmol of **1a**, 1.2 equiv of **2a**, 5 mol % of $Pd(OAc)_2$, 10 mol % of dppp, 2 equiv of Cs_2CO_3 in 6 ml of toluene at 95 ^oC under one atmosphere of CO for 24 h.

After obtaining our best reaction conditions for aminocarbonylation, we examined the scope of this reaction on various substrates. The *ortho*-halo esters **1a**, **1b**, **1d** and **1e** were obtained from commercial sources, while **1c** was prepared according to a literature procedure.[38] The model system under our optimized conditions with benzylamine gave an 89% isolated yield of the desired product **3a** (Table 3, entry 1). Compound **3a** was obtained in a slightly lower 85% yield, when the reaction was carried out on a larger scale (entry 2). A reaction with methyl 2-bromobenzoate (**1b**) gave a reduced yield of 55% (entry 3). This is probably due to the fact that the oxidative insertion of Pd(0) into a C-Br bond is less facile than into a C-I bond. For similar reasons, when two electron-donating methoxy groups were placed on the *ortho*-iodobenzoate, the yield was reduced to 46% (entry 4). Electron donation by methoxy substituents is known to slow oxidative addition to aromatic halides. The presence of an inductively electron-withdrawing bromo-substituent *para* to the iodo group in the benzoate ester **1d** sharply lowered the yield to 51% when compared with the parent system (entry 5). The presence of a strong electron-withdrawing NO_2 group *para* to the bromo group in the benzoate ester **1e** increased the yield from 55% to 71% (compare entries 3 and 6).

We have also examined the reactivity of an ester bearing a vinylic halide. When methyl 2-bromocyclohept-1-enecarboxylate was subjected to aminocarbonylation under our optimized conditions using benzyl amine, the desired product was obtained in only a poor yield (<15%).

Table 3. Synthesis of Isoindole-1,3-diones by the Aminocarbonylative Cyclization of *ortho*-Halobenzoate Esters.[a]

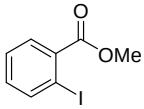
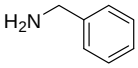
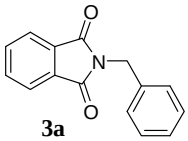
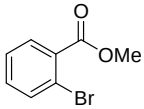
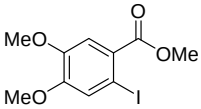
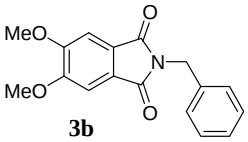
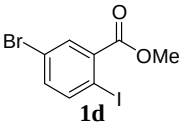
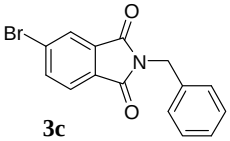
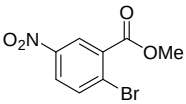
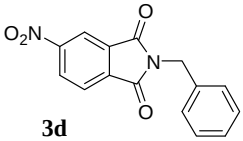
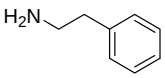
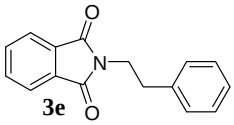
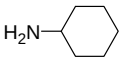
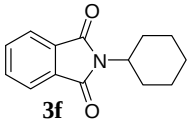
Entry	*o*-halo ester	amine	product	% isolated yield
1	 **1a**	 **2a**	 **3a**	89
2	**1a**	**2a**	**3a**	85[b]
3	 **1b**	**2a**	**3a**	55
4	 **1c**	**2a**	 **3b**	46
5	 **1d**	**2a**	 **3c**	51
6	 **1e**	**2a**	 **3d**	71
7	**1a**	 **2b**	 **3e**	81
8	**1a**	 **2c**	 **3f**	92

Table 3. continued

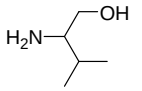
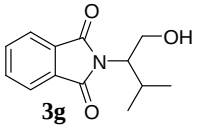
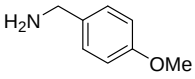
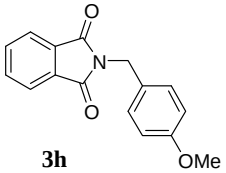
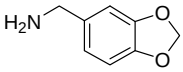
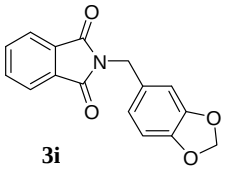
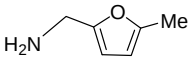
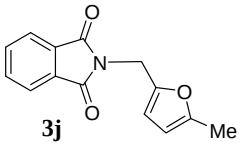
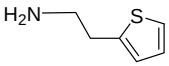
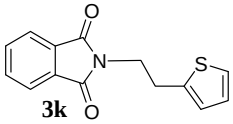
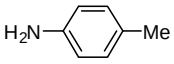
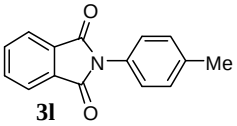
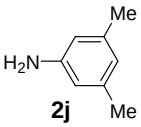
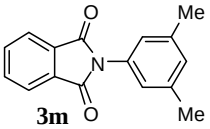
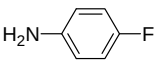
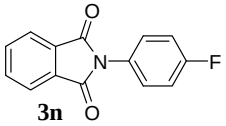
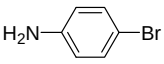
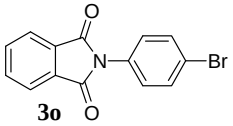
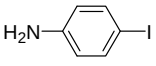
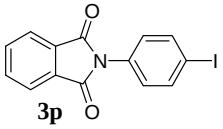
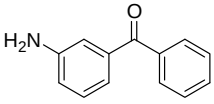
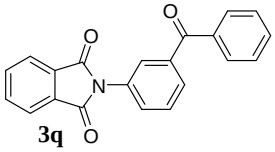
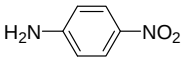
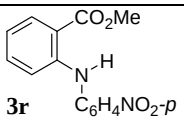
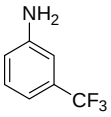
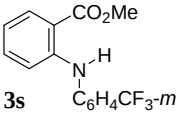
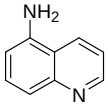
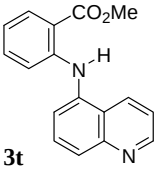
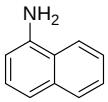
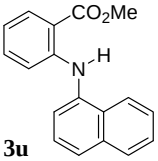
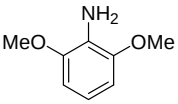
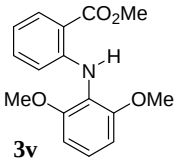
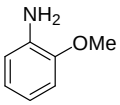
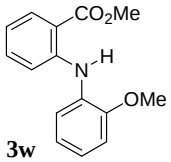
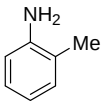
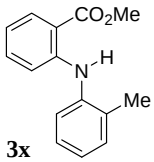
Entry	*o*-halo ester	amine	product	% isolated Yield
9	**1a**	 **2d**	 **3g**	25
10	**1a**	**2d**	**3g**	41[c]
11	**1a**	 **2e**	 **3h**	68
12	**1a**	 **2f**	 **3i**	61
13	**1a**	 **2g**	 **3j**	77
14	**1a**	 **2h**	 **3k**	71
15	**1a**	 **2i**	 **3l**	79
16	**1a**	 **2j**	 **3m**	77
17	**1a**	 **2k**	 **3n**	71
18	**1a**	 **2l**	 **3o**	68
19	**1a**	 **2m**	 **3p**	57
20	**1a**	 **2n**	 **3q**	25

Table 3. continued

Entry	*o*-halo ester	amine	product	% isolated yield
21	**1a**	 **2o**	 **3r**	62
22	**1a**	 **2p**	 **3s**	61
23	**1a**	 **2q**	 **3t**	57
24	**1a**	 **2r**	 **3u**	55
25	**1a**	 **2s**	 **3v**	61
26	**1a**	 **2t**	 **3w**	62
27	**1a**	 **2u**	 **3x**	55

[a] Representative procedure: *ortho*-halobenzoate ester **1** (0.5 mmol), amine **2** (1.2 equiv), $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), Cs_2CO_3 (2 equiv) and toluene (6 mL) were placed in a round bottom flask. The flask was sealed and flushed with CO. The reaction was stirred at 95 ^oC for 24 h with a CO balloon on top of the flask. [b] The reaction was scaled up to 2 mmol of halo ester. [c] The reaction was carried out using 10 equiv of amine.

We also studied the scope of the reaction using various amines. The reaction of **1a** with phenethylamine (**2b**) gave the desired product **3e** in an 81% yield (entry 7). The more hindered aliphatic amine cyclohexyl amine gave an excellent 92% yield of the desired

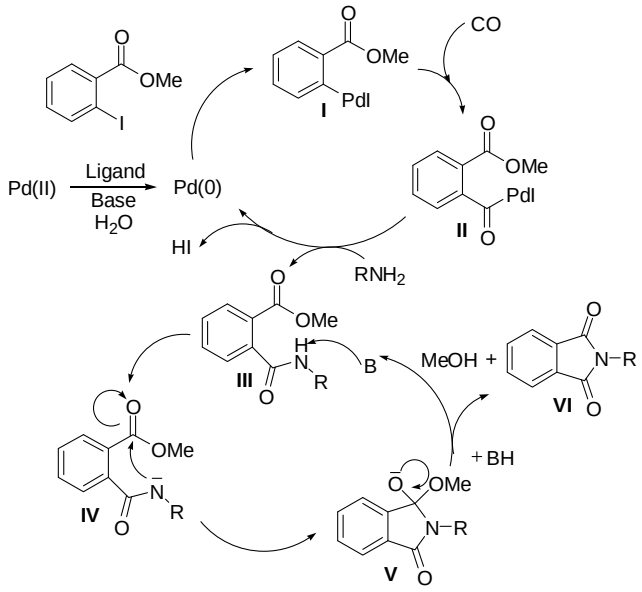
product **3f** (entry 8). The lower boiling alcohol-containing amine **2d** gave a poor yield of 25% (entry 9), but the yield was increased to 41% when the reaction was carried out with an excess of the amine (entry 10). The reaction using benzyl amine bearing an electron-donating *para* methoxy group gave a 68% yield of the desired product **3h** (entry 11). Oxygen- and sulfur-containing heterocyclic amines worked well under our optimized conditions (entries 12-14). The nitrogen-containing heterocyclic amines *N*-(3-aminopropyl)morpholine and *N*-(3-aminopropyl)imidazole failed to give the desired products under our reaction conditions for reasons not presently understood.

After screening the above-mentioned aliphatic amines, we decided to study the scope of the reaction with aromatic amines. Amines **2i** and **2j** with electron-donating methyl groups gave 79% and 77% yields of the desired products **3l** and **3m** respectively (entries 15 and 16). 4-Aminophenol failed to give the desired product apparently due to solubility problems. An electron-withdrawing fluoro group did not have much of an effect on the yield (entry 17). But the presence of a bromo or iodo substituent at the *para* position of the aniline gave somewhat lower yields of 68% and 57% respectively (entries 18 and 19). It is possible that the desired products are perhaps undergoing further reaction with palladium. The presence of an electron-withdrawing ketone group on the amine drastically reduced the yield of the desired product **3q** to 25% (entry 20). The presence of strong electron-withdrawing NO_2 and CF_3 groups on the amine failed to give the desired cyclic products. Instead these substrates formed **3r** and **3s** in 62% and 61% yields respectively (entries 21 and 22). Amine **2q** also failed to form the desired cyclic product (entry 23). In order to establish if the reason this substrate failed to cyclize was its slightly electron-deficient nature or its steric bulk, we studied the aminocarbonylation of 1-naphthylamine (**2r**). To our surprise, this substrate also

failed to cyclize. Instead we obtained ester **3u** in a 55% isolated yield (entry 24). We have also examined the reaction of amine **2s** to confirm that sterically hindered aromatic amines fail to give the desired cyclic isoindole-1,3-diones under our reaction conditions. Again an amino ester was obtained (entry 25). Even the simple mono *ortho*-substituted amines **2t** and **2u** failed to give the desired cyclic products, but afforded decent yields of the corresponding amino esters (entries 26 and 27).

We believe that the mechanism of these carbonylative cyclizations involves a two step process: (1) palladium-catalyzed formation of the corresponding *ortho*-amidocarboxylates, followed by (2) base-catalyzed cyclization of these *ortho*-amidocarboxylates to the cyclic isoindole-1,3-diones (Scheme 4). Palladium undergoes oxidative insertion into the carbon-halogen bond to give Pd(II) intermediate **I**, which then inserts CO to form the acylpalladium complex **II**. The acylpalladium complex then reacts with the amine to give the *ortho*-amidocarboxylate **III**. This species then participates in a base-catalyzed cyclization. The base extracts the amide proton to give anionic nitrogen species **IV**, which attacks the ester carbonyl to afford cyclic intermediate **V**, which results in formation of the final isoindole-1,3-dione **VI** by loss of a methoxy group. The insertion of CO in the Pd(II) intermediate **I** to form the acylpalladium complex **II** is a reversible process. We believe that the desired *ortho*-amidocarboxylate **III** is obtained in the presence of a more nucleophilic amine by trapping the acylpalladium intermediate **II**. Amines with strong electron-withdrawing groups, due to their poor nucleophilicity, fail to trap the acylpalladium complex **II** to form the corresponding *ortho*-amidocarboxylate **III**, but apparently they react with the Pd(II) intermediate **I** to form the corresponding amino ester (refer to Table 3, entries 21 and 22). Amino ester products **3t** to **3x** (refer to Table 3, entries 23 to 27) are apparently

Scheme 4



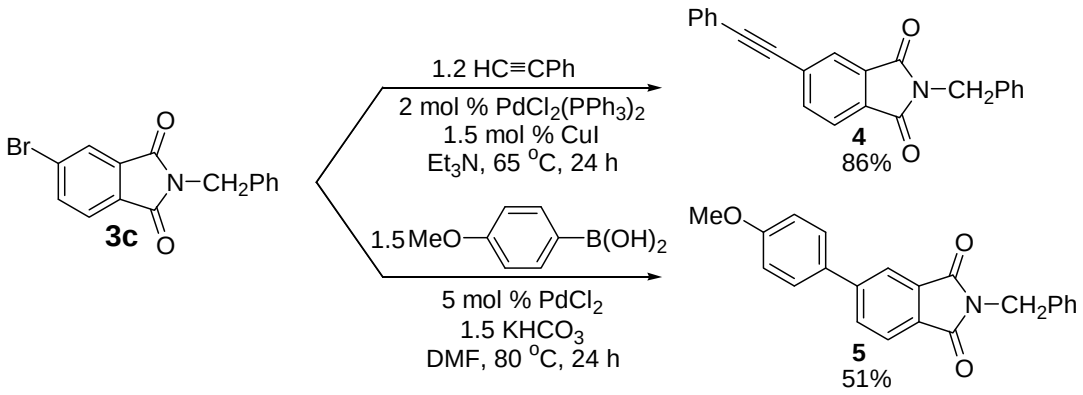
formed by more rapid reaction of the intermediate arylpalladium intermediate **I** directly with the more hindered amine rather than the acylpalladium intermediate **II**.

The isoindole-1,3-diones obtained by this simple palladium-catalyzed aminocarbonylation process appear to be promising intermediates for the preparation of more highly substituted isoindole-1,3-diones. To expand the scope of our chemistry, we subjected isoindole-1,3-dione **3c** to a palladium/copper-catalyzed Sonogashira reaction to obtain an excellent 86% isolated yield of the substituted isoindole-1,3-dione **4** (Scheme 5). The Suzuki coupling of **3c** with *p*-methoxyphenylboronic acid gave a 51% yield of the desired product **5**.

Conclusions

A range of isoindole-1,3-diones have been obtained by the one step palladium-catalyzed aminocarbonylation of simple *o*-halobenzoate esters starting materials that are

Scheme 5

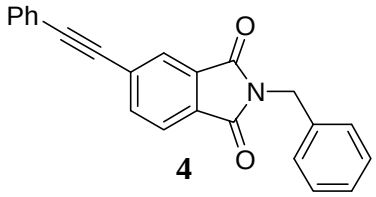


readily available or easily synthesized. The reaction conditions are mild and the products are easy to isolate in good yields. A halogen moiety can also be introduced into the products, which provides a useful handle for further functionalization of the resulting heterocycles. The Sonogashira and Suzuki products **4** and **5** have been obtained in good to excellent yields in this manner. Our methodology tolerates a number of functional groups, including alcohol, ketone, methoxy and nitro groups, and works well for both aliphatic and aromatic primary amines. The methodology provides a very convenient one step approach to this important class of heterocycles.

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. Thin layer chromatography was performed using 60 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All high resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

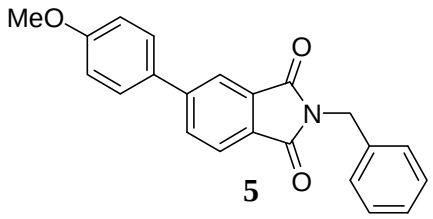
General procedure for the palladium-catalyzed carbonylative cyclization of *ortho*-halobenzoates and primary amines. To a solution of 0.5 mmol of the *ortho*-halobenzoate in $PhCH_3$ (6 ml) was added the primary amine (1.2 equiv), $Pd(OAc)_2$ (5 mol %), dppp (10 mol %) and Cs_2CO_3 (2.0 equiv). The flask was then sealed and flushed with CO. A balloon filled with CO was placed on the top of the flask and the reaction was stirred at 95 ^oC for 24 h. After the reaction was over, the resulting solution was diluted with EtOAc (10 ml) and filtered through celite. The celite was thoroughly washed with EtOAc (15 ml) to ensure complete extraction of the crude product. The combined EtOAc fractions 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. Solid products were further recrystallized from ethanol.



4

2-Benzyl-5-(phenylethynyl)isoindoline-1,3-dione (4). This compound was prepared by the following procedure. To a solution of 63 mg of 2-benzyl-5-bromoisoindoline-1,3-dione **(3c)** (0.2 mmol) in Et_3N (2 ml) was added $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (1.5 mol %), and the mixture was stirred for 10 min under Ar. 0.3 Mmol of phenylacetylene dissolved in 0.5 mL of Et_3N was then added dropwise and the reaction mixture was allowed to stir at 60 ^oC for 24 h. The reaction was monitored by TLC. After the reaction was over, the resulting solution was diluted with H_2O (5 ml) and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate fractions 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 hexanes/ethyl acetate as the eluent to obtain the desired compound **4** in an 86% yield as a pale brown solid: mp 166-167 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 2H), 7.25-7.44 (m, 8H), 7.54-7.56 (m, 2H), 7.81 (d, J = 0.6 Hz, 2H), 7.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.9, 87.9, 94.0, 122.2, 123.5, 126.3, 128.0, 128.7, 128.8, 128.9, 129.4, 129.7, 130.9, 132.0, 132.5, 136.3, 137.0, 167.5, 167.6; IR (neat, cm^{-1}) 2924, 1708, 1627, 1436, 1359, 1106, 955; HRMS m/z 337.11077 (calcd $C_{23}H_{15}NO_2$, 337.11028).

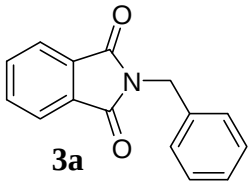


5

2-Benzyl-5-(4-methoxyphenyl)isoindoline-1,3-dione (5). This compound was prepared by the following procedure. To 63 mg of 2-benzyl-5-bromoisoindoline-1,3-dione **(3c)** (0.2 mmol) was added 46 mg (1.5 equiv) of 4-methoxyphenylboronic acid, $PdCl_2$ (5 mol %), $KHCO_3$ (1.5 equiv) and 4:1 DMF/H_2O (5 ml). The reaction mixture was stirred at 80 ^{o}C for 12 h. The resulting solution was cooled to room temperature, diluted with H_2O (5 ml) and extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate fractions were washed with brine, 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 hexanes/ethyl acetate as the eluent to obtain the desired compound **5** in a 51% yield as a white solid: mp 167-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.86 (s, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.24-7.34 (m, 3H), 7.44 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 0.8 Hz, 2H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.8, 55.6, 114.8,

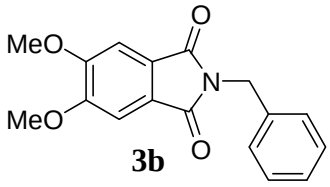
121.5, 123.9, 127.9, 128.6, 128.7, 128.8, 129.9, 131.5, 132.0, 133.2, 136.6, 147.2, 160.5, 168.2, 168.3; IR (neat, cm^{-1}) 2916, 1774, 1700, 1596, 1250, 1033; HRMS m/z 343.12126 (calcd $C_{22}H_{17}NO_3$, 343.12084).

Characterization data:



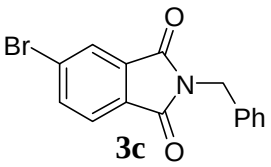
3a

2-Benzylisoindoline-1,3-dione (3a). This compound was obtained as a white solid: mp 119-121 ^oC (lit.[22d] 118-120 ^oC); ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 2H), 7.25-7.33 (m, 3H), 7.43 (d, J = 7.1 Hz, 2H), 7.67-7.70 (m, 2H), 7.82-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7, 115.4, 123.4, 127.9, 128.7, 132.2, 134.1, 136.5, 168.1; IR (neat, cm^{-1}) 2926, 2253, 1770, 1712, 1394, 909; HRMS m/z 237.07927 (calcd $C_{15}H_{11}NO_2$, 237.07898).



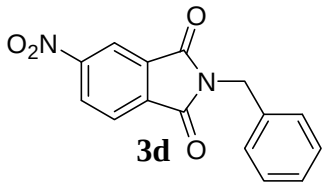
3b

2-Benzyl-5,6-dimethoxyisoindole-1,3-dione (3b). This compound was obtained as a white solid: mp 222-223 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 6H), 4.80 (s, 2H), 7.23-7.27 (m, 3H), 7.29-7.33 (m, 2H), 7.40-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7, 56.8, 105.5, 125.7, 127.8, 128.6, 128.8, 136.8, 153.9, 168.4; HRMS m/z 297.10057 (calcd $C_{17}H_{15}NO_4$, 297.10011).



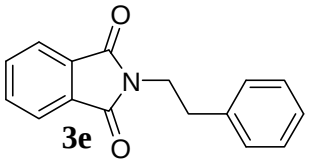
3c

2-Benzyl-5-bromoisoindole-1,3-dione (3c). This compound was obtained as a white solid: mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 2H), 7.24-7.33 (m, 3H), 7.41 (d, J = 6.8 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.83 (dd, J = 8.0, 1.5 Hz, 1H), 7.96 (d, J = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.0, 115.5, 124.8, 126.9, 128.1, 128.8, 128.9, 130.7, 133.9, 136.1, 137.1, 166.8, 167.3; HRMS m/z 314.99000 (calcd $C_{15}H_{10}O_2NBr$, 314.98949).



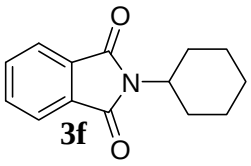
3d

2-Benzyl-5-nitroisoindole-1,3-dione (3d). This compound was obtained as a white solid: mp 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 2H), 7.26-7.32 (m, 3H), 7.43 (d, J = 6.7 Hz, 2H), 8.03 (d, J = 7.9 Hz, 1H), 8.58 (d, J = 7.8, 1H), 8.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.4, 118.9, 124.7, 128.3, 128.94, 128.99, 129.4, 133.6, 135.6, 136.6, 151.8, 165.7, 166.0; HRMS m/z 282.06060 (calcd $C_{15}H_{10}O_4N_2$, 282.06442).



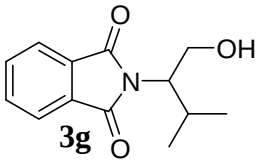
3e

2-(Phenethyl)isoindole-1,3-dione (3e). This compound was obtained as a white solid: mp 130-132 °C (lit.[39] 131-132 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (t, J = 7.6 Hz, 2H), 3.91 (t, J = 7.7 Hz, 2H), 7.18-7.29 (m, 5H), 7.67-7.70 (m, 2H), 7.80-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.7, 39.4, 123.3, 126.7, 128.6, 128.9, 132.1, 134.0, 138.1, 168.2; HRMS m/z 251.09493 (calcd $C_{16}H_{13}O_2N$, 251.09463).



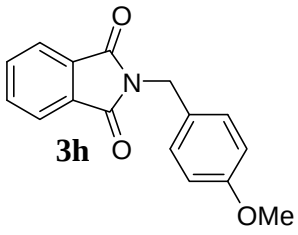
3f

2-Cyclohexylisoindole-1,3-dione (3f). This compound was obtained as a white solid: mp 170-172 °C (lit.[40] 169-171 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.42 (m, 3H), 1.68-1.74 (m, 3H), 1.86 (d, J = 13.2 Hz, 2H), 2.15-2.25 (m, 2H), 4.07-4.15 (m, 1H), 7.68-7.70 (m, 2H), 7.80-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 26.2, 30.0, 51.0, 123.1, 132.2, 133.8, 168.6; HRMS m/z 229.11047 (calcd $C_{14}H_{15}O_2N$, 229.11028).



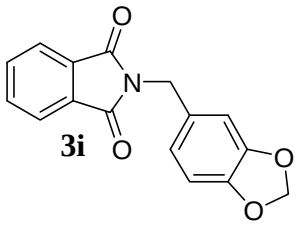
3g

2-(1-Hydroxymethyl-2-methylpropyl)isoindole-1,3-dione (3g). This compound was obtained as a colorless oil: ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 20.2, 27.1, 60.1, 62.4, 123.5, 131.7, 134.3, 169.5; HRMS m/z 233.10548 (calcd $C_{13}H_{15}O_3N$, 233.10519). The ^{1}H NMR spectrum matches the literature data.[41]



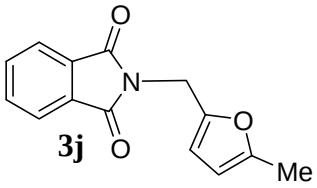
3h

2-(4-Methoxybenzyl)isoindole-1,3-dione (3h). This compound was obtained as a white solid: mp 129-131 °C; HRMS m/z 267.09005 (calcd $C_{16}H_{13}O_3N$, 267.08954). The ^{1}H and ^{13}C NMR spectra match the literature data.[22c]



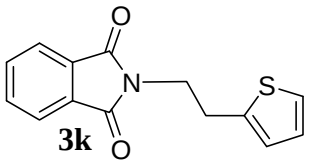
3i

2-(Benzo[1,3]dioxol-5-ylmethyl)isoindole-1,3-dione (3i). This compound was obtained as a white solid: mp 133-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 5.90 (s, 2H), 6.73 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 7.0 Hz, 2H), 7.68-7.70 (m, 2H), 7.81-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.5, 101.2, 108.3, 109.3, 122.4, 123.4, 130.2, 132.1, 134.0, 147.2, 147.8, 168.0; HRMS m/z 281.06930 (calcd $C_{16}H_{11}O_4N$, 281.06881).



3j

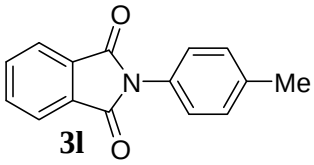
2-(5-Methyl-2-furanylmethyl)isoindole-1,3-dione (3j). This compound was obtained as a pale yellow solid: mp 80-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 4.79 (s, 2H), 5.87 (d, J = 2.1 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 7.69-7.71 (m, 2H), 7.83-7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 34.5, 106.5, 109.7, 123.4, 132.1, 134.0, 147.5, 152.2, 167.7; IR (neat, cm^{-1}) 3467, 2924, 1770, 1724, 1421, 1382; HRMS m/z 241.07434 (calcd $C_{14}H_{11}O_3N$, 241.07389).



3k

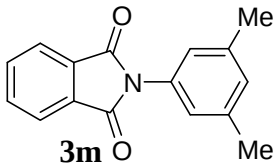
2-(2-Thiophen-2-ylethyl)isoindole-1,3-dione (3k). This compound was obtained as a white solid: mp 130-131 ^{o}C (lit.[42] 128-130 ^{o}C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 39.4,

123.3, 124.2, 125.7, 127.0, 132.0, 134.0, 140.0, 168.1; HRMS m/z 257.05140 (calcd $C_{14}H_{11}O_2NS$, 257.05105). The ^1H NMR spectrum matches the literature data.[42]



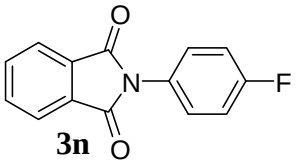
3l

2-*p*-Tolylisoindole-1,3-dione (3l). This compound was obtained as a colorless solid: mp 204-206 ^oC (lit.[43] 205-206 ^oC); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 123.8, 126.6, 129.1, 129.9, 131.9, 134.4, 138.3, 167.5; IR (neat, cm^{-1}) 2915, 2847, 1715, 1515, 1294, 1097; HRMS m/z 237.07927 (calcd $C_{15}H_{11}O_2N$, 237.07898). The ^1H NMR spectrum matches the literature data.[43]



3m

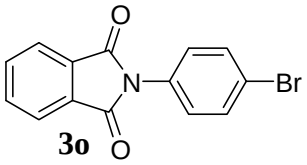
2-(3,5-Dimethylphenyl)isoindole-1,3-dione (3m). This compound was obtained as a white solid: mp 133-135 ^oC (lit.[44] 133 ^oC); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 123.7, 124.6, 130.2, 131.4, 131.9, 134.4, 139.0, 167.5; IR (neat, cm^{-1}) 2921, 1713, 1609, 1373, 1171, 714; HRMS m/z 251.09507 (calcd $C_{16}H_{13}O_2N$, 251.09463). The ^1H NMR spectrum matches the literature data.[44]



3n

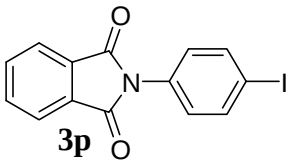
2-(4-Fluorophenyl)isoindole-1,3-dione (3n). This compound was obtained as a yellow solid: mp 166-168 ^oC; IR (neat, cm^{-1}) 1704, 1526, 1475, 1122, 1079, 831, 710;

HRMS m/z 241.05421 (calcd $C_{14}H_8FNO_2$, 241.05391). The ^1H and ^{13}C NMR spectra match the literature data.[45]



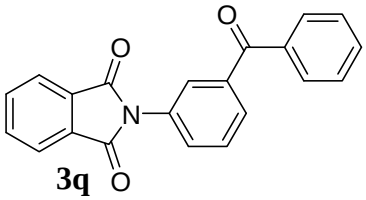
3o

2-(4-Bromophenyl)isoindole-1,3-dione (3o). This compound was obtained as a light brown solid: mp 206-208 °C (lit.[43] 205-206 °C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.9, 124.0, 128.1, 130.8, 131.7, 132.4, 134.7, 167.0; IR (neat, cm^{-1}) 1704, 1492, 1396, 1285, 1124, 818, 714; HRMS m/z 300.97434 (calcd $C_{14}H_8O_2NBr$, 300.97384). The ^1H NMR spectrum matches the literature data.[43]



3p

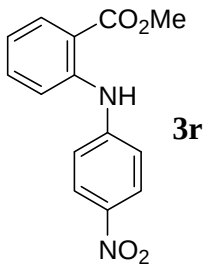
2-(4-Iodophenyl)isoindole-1,3-dione (3p). This compound was obtained as a white solid: mp 226-228 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.26 (m, 2H), 7.79-7.84 (m, 4H), 7.95-7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 93.5, 124.0, 128.3, 131.6, 131.7, 134.7, 138.4, 167.0; HRMS m/z 348.96046 (calcd $C_{14}H_8O_2NI$, 348.95998).



3q

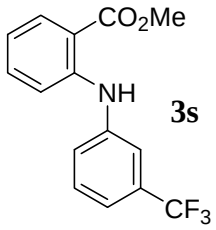
2-(3-Benzoylphenyl)isoindole-1,3-dione (3q). This compound was obtained as a white solid: mp 179-181 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.53 (m, 2H), 7.58-7.72 (m, 3H), 7.79-7.81 (m, 2H), 7.85-7.90 (m, 4H), 7.95-7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 124.1, 128.3, 128.6, 129.4, 129.6, 130.3, 130.4, 131.7, 131.9, 132.8, 134.8, 137.2, 138.5, 167.1, 195.5; HRMS m/z 327.09008 (calcd $C_{21}H_{13}O_3N$, 327.08954).



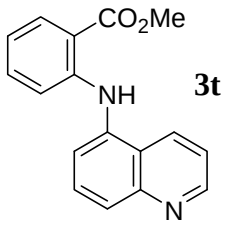
3r

Methyl 2-(4-nitrophenylamino)benzoate (3r). This compound was obtained as a orange solid: mp 130-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.96-6.99 (m, 1H), 7.22-7.24 (m, 2H), 7.44-7.55 (m, 2H), 8.02 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 9.0 Hz, 2H), 9.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 115.6, 116.9, 117.6, 120.8, 126.0, 132.1, 134.3, 141.5, 144.1, 147.9, 168.7; HRMS m/z 272.08005 (calcd $C_{14}H_{12}O_4N_2$, 272.07971).



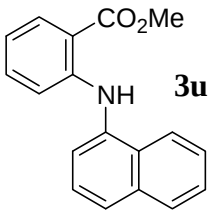
3s

Methyl 2-(3-trifluoromethylphenylamino)benzoate (3s). This compound was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.78-6.82 (m, 1H), 7.26-7.28 (m, 2H), 7.33-7.41 (m, 3H), 7.48 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 113.1, 114.4, 118.1 (d, J = 3.7 Hz), 118.5, 119.7 (d, J = 3.7 Hz), 122.8, 124.6 (d, J = 1.1 Hz), 125.5, 130.0, 131.9, 134.4, 141.8, 146.8, 169.0; IR (neat, cm^{-1}) 3318, 2953, 1693, 1517, 1268, 1087; HRMS m/z 295.08234 (calcd $C_{15}H_{12}O_2NF_3$, 295.08201).



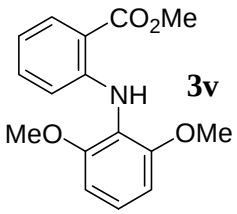
3t

Methyl 2-(quinolin-5-ylamino)benzoate (3t). This compound was obtained as a yellow solid: mp 92-94 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 6.74-6.77 (m, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.26 (t, J = 8.5 Hz, 1H), 7.39 (dd, J = 8.5, 4.1 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.70 (t, J = 10.7 Hz, 1H), 7.95-8.03 (m, 2H), 8.42 (d, J = 8.8 Hz, 1H), 8.94 (d, J = 2.7 Hz, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 111.9, 114.3, 117.5, 120.9, 121.2, 125.0, 126.4, 129.5, 131.5, 131.7, 134.5, 136.9, 149.0, 149.5, 150.8, 169.4; HRMS m/z 278.10611 (calcd $C_{17}H_{14}O_2N_2$, 278.10563).

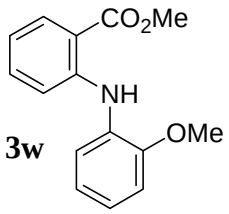


3u

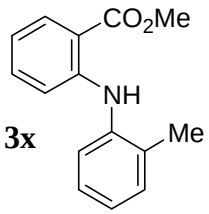
Methyl 2-(naphthalen-1-ylamino)benzoate (3u). This compound was obtained as a white solid: mp 112-114 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.74-6.77 (m, 1H), 6.99 (d, J = 8.5 Hz, 1H), 7.25-7.29 (m, 1H), 7.48-7.57 (m, 4H), 7.74 (d, J = 8.0 Hz, 1H), 7.91-7.93 (m, 1H), 8.05-8.07 (m, 1H), 8.15-8.17 (m, 1H), 9.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0, 111.5, 114.3, 116.8, 120.9, 122.8, 125.2, 125.9, 126.3, 126.4, 128.5, 129.8, 131.6, 134.3, 134.8, 136.7, 149.5, 169.3; HRMS m/z 277.11069 (calcd $C_{18}H_{15}O_2N$, 277.11028).



Methyl 2-(2,6-dimethoxyphenylamino)benzoate (3v). This compound was obtained as a pale yellow solid: mp 65-67 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 6.51 (dd, J = 8.8, 2.7 Hz, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 7.31-7.35 (m, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0, 55.8, 56.5, 106.4, 106.7, 111.9, 113.3, 114.9, 117.7, 131.2, 131.8, 134.0, 145.6, 146.7, 153.7, 168.7; IR (neat, cm^{-1}) 3323, 2947, 2833, 1692, 1524, 1455, 1262; HRMS m/z 287.11608 (calcd $C_{16}H_{17}O_4N$, 287.11576).



Methyl 2-(2-methoxyphenylamino)benzoate (3w). This compound was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87-3.89 (m, 6H), 6.70-6.74 (m, 1H), 6.89-6.94 (m, 2H), 7.00-7.04 (m, 1H), 7.31 (d, J = 3.4 Hz, 2H), 7.41-7.43 (m, 1H), 7.95 (d, J = 7.9 Hz, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 55.9, 111.3, 112.8, 114.4, 117.3, 120.6, 123.3, 130.2, 131.7, 134.0, 147.3, 151.5, 168.8; HRMS m/z 257.1040 (calcd $C_{15}H_{15}O_3N$, 257.1052).



3x

Methyl 2-(*o*-tolylamino)benzoate (3x). This compound was obtained as a dark yellow solid: mp 54-56 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.89 (s, 3H), 6.68 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 7.3 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.22-7.27 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.96 (dd, J = 8.0, 1.3 Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 51.9, 111.4, 113.9, 116.6, 124.0, 124.7, 126.7, 131.2, 131.7, 132.9, 134.3, 139.1, 148.8, 169.2; HRMS m/z 241.1096 (calcd $C_{15}H_{15}O_2N$, 241.1103).

Acknowledgements

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References

1. Karimi, F.; Kihlberg, T.; Langstrom, B. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1528.
2. Muller, G. W.; Konnecke, W. E.; Smith, A. M.; Khetani, V. D. *Org. Process Res. Dev.* **1999**, *3*, 139.

3. Makonkawkeyoon, S.; Limson-Pobre, R. N. R.; Moreira, A. L.; Schauf, V.; Kaplan, G. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5974.
4. Figg, W. D.; Raje, S.; Bauer, K. S.; Tompkins, A.; Venzon, D.; Bergan, R.; Chen, A.; Hamilton, M.; Pluda, J.; Reed, E. *J. Pharm.Sci.* **1999**, *88*, 121.
5. Atra, E.; Sato, E. I. *Clin. Exp. Rheumatol*. **1993**, *11*, 487.
6. Ochonisky, S.; Verroust, J.; Bastuji-Garin, S.; Gherardi, R.; Revuz, J. *Arch. Dermatol*. **1994**, *130*, 66.
7. Miyachi, H.; Azuma, A.; Ogasawara, A.; Uchimura, E.; Watanabe, N.; Kobayashi, Y.; Kato, F.; Kato, M.; Hashimoto, Y. *J. Med. Chem.* **1997**, *40*, 2858.
8. Parker, P. M.; Chao, N.; Nademanee, A.; O'Donnell, M. R.; Schmidt, G. M.; Snyder, D. S.; Stein, A. S.; Smith, E. P.; Molina, A.; Stepan, D. E.; Kashyap, A.; Planas, I.; Spielberger, R.; Somlo, G.; Margolin, K.; Zwingenberger, K.; Wilsman, K.; Negrin, R. S.; Long, G. D.; Niland, J. C.; Blume, K. G.; Forman, S. J. *Blood* **1995**, *86*, 3604.
9. Nagasawa, H. T.; Elberling, J. A.; Shirota, F. N. *J. Pharm. Sci.* **1980**, *196*, 1022.
10. Hall, I. H.; Chapman, J. M.; Wong, O. T. *Anti-Cancer Drugs* **1994**, *5*, 75.
11. Hall, I. H.; Wong, O. T.; Scovill, J. P. *Biomed. Pharmacother.* **1995**, *49*, 251.
12. Balzarini, J.; Clercq, E. D.; Kaminska, B.; Orzeszko, A. *Antiviral Chem. Chemother.* **2003**, *14*, 139.
13. Meng, X.-B.; Han, D.; Zhang, S.-N.; Guo, W.; Cui, J.-R.; Li, Z.-J. *Carbohydr. Res.* **2007**, *342*, 1169.
14. Henon, H.; Messaoudi, S.; Anizon, F.; Aboab, B.; Kucharczyk, N.; Leonce, S.; Golsteyn, R. M.; Pfeiffer, B.; Prudhomme, M. *Eur. J. Pharmacol.* **2007**, *554*, 106.

15. Eger, K.; Jalalian, M.; Verspohl, E. J.; Luepke, N. P. *Arzneim.-Forsch.* **1990**, *40*, 1073.

16. Lukevics, E.; Castro, I.; Popelis, J.; Dipans, I.; Rozhkova, N. G.; Andreeva, E. I.; Kukalenko, S. S. *Kimijas Serija* **1983**, *6*, 739.

17. (a) Kemmochi, H.; Kanda, T.; Hotta, H.; Akamatsu, T. Dyeing fibers with reactive dyes. Jpn. Tokkyo Koho JP 45029233 19700924, **1970**. (b) Steffanut, P.; Klein, C.; Graciet, J. C.; Luecke, L.; Winter, M. A. Uses of phthalimide based azo metal complex dyes in optical layers for optical data recording. PCT Int. Appl. WO 2007118784, **2007**.

18. Pawar, N. S.; Kapadi, U. R.; Hundiwale, D. G.; Kumbhar, P. P. *J. Sci. Ind. Res.* **2002**, *61*, 454.

19. (a) Chae, K. H.; Kim, Y. H. *Adv. Funct. Mater.* **2007**, *17*, 3470. (b) Chen, G.; Zhang, X.; Zhang, S.; Chen, T.; Wu, Y. *J. Appl. Polym. Sci.* **2007**, *106*, 2808.

20. (a) Kang, H. B.; Quan, L. G.; Lee, J. K.; Kim, S. Process for preparation of chiral glycidylphthalimide in highly optical purity. PCT Int. Appl. WO 2007132990, **2007**. (b) Han, T.; Chen, C. F. *J. Org. Chem.* **2007**, *72*, 7287. (c) Sani, M.; Fossati, G.; Huguenot, F.; Zanda, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3526. (d) Abdel-Aziz, A. A.-M. *Eur. J. Med. Chem.* **2007**, *42*, 614. (e) Kobrakov, K. I.; Zubkova, N. S.; Stankevich, G. S.; Shestakova, Y. S.; Stroganov, V. S.; Adrov, O. I. *Fibre Chemistry* **2006**, *38*, 183. (f) Sahu, S. K.; Mishra, S. K.; Mandal, S.; Choudhury, P.; Sutradhar, S.; Misro, P. K. *J. Ind. Chem. Soc.* **2006**, *83*, 832. (g) Barooah, N.; Sarma, R. J.; Baruah, J. B. *Eur. J. Inorg. Chem.* **2006**, *15*, 2942. (h) Lima, L. M.; Castro, P.; Machado, A. L.; Fraga, C. A. M.; Lugnier, C.; de Moraes, V. L. G.; Barreiro, E. J.

Bioorg. Med. Chem. **2002**, *10*, 3067. (i) Hellwinkel, D.; Lenz, R.; Laemmerzahl, F. *Tetrahedron* **1983**, *39*, 2073. (j) Sheehan, J. C.; Chapman, D. W.; Roth, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 3822. (k) Sheehan, J. C.; Frank, V. S. *J. Am. Chem. Soc.* **1949**, *71*, 1856. (l) Billman, J. H.; Parker, E. E. *J. Am. Chem. Soc.* **1943**, *65*, 761.

21. (a) Centi, G.; Pinelli, D.; Trifiro, F. *Gazz. Chim. Ital.* **1989**, *119*, 133. (b) Cavani, F.; Parrinello, F.; Trifiro, F. *J. Mol. Catal.* **1987**, *43*, 117.
22. (a) Sena, V. L. M.; Srivastava, R. M.; Simone, C. A. d.; Goncalves, S. M. d. C.; Silva, R. O.; Pereira, M. A. *J. Braz. Chem. Soc.* **2007**, *18*, 1224. (b) Mogilaiah, K.; Reddy, G. R. *Ind. J. Chem., Sect B* **2004**, *43B*, 882. (c) Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* **2003**, *5*, 1851. (d) Vidal, T.; Petit, A.; Loupy, A.; Gedye, R. N. *Tetrahedron* **2000**, *56*, 5473.
23. (a) Uozumi, Y.; Kawasaki, N.; Mori, E.; Mori, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 3725. (b) Wu, X.; Mahalingam, A. K.; Wan, Y.; Alterman, M. *Tetrahedron Lett.* **2004**, *45*, 4635.
24. (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (b) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.
25. (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
26. (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.
27. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.
28. Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

29. Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.

30. (a) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. (b) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238.

31. Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

32. Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536.

33. (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons, Ltd.: Chichester, U.K., 1995. (b) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York and London, 1991.

34. Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142.

35. (a) Takacs, E.; Varga, C.; Skoda-Foeldes, R.; Kollar, L. *Tetrahedron Lett.* **2007**, *48*, 2453. (b) Karimi, F.; Langstroem, B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2111. (c) Morera, E.; Ortar, G. *Tetrahedron Lett.* **1998**, *39*, 2835.

36. Mori, M.; Chiba, K.; Ohta, N.; Ban, Y. *Heterocycles* **1979**, *13*, 329.

37. Perry, R. J.; Turner, S. R. *J. Org. Chem.* **1991**, *56*, 6573.

38. Carme Pampin, M.; Estevez, J. C.; Estevez, R. J.; Maestro, M.; Castedo, L. *Tetrahedron* **2003**, *59*, 7231.

39. Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949.

40. Suau, R.; Garcia-Segura, R.; Sanchez-Sanchez, C.; Perez-Inestrosa, E.; Pedraza, A. M. *Tetrahedron* **2003**, *59*, 2913.

41. Humljan, J.; Gobec, S. *Tetrahedron Lett.* **2005**, *46*, 4069.

42. Othman, M.; Pigeon, P.; Decroix, B. *Tetrahedron* **1997**, *53*, 2495.

43. Li, H.; Zhang, J.; Zhou, Y.; Li, T. *Synth. Commun.* **2002**, *32*, 927.

44. Shibata, Y.; Sasaki, K.; Hashimoto, Y.; Iwasaki, S. *Chem. Pharm. Bull.* **1996**, *44*, 156.

45. Rasmussen, L. K.; Begtrup, M.; Ruhland, T. *J. Org. Chem.* **2004**, *69*, 6890.

46. Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* (accepted).

CHAPTER 3. PALLADIUM-CATALYZED SYNTHESIS OF 9-FLUORENYLIDENES AND 9,10-PHENANTHRENES THROUGH ARYNE ANNULATION

Based on a paper to be published in the *Journal of Organic Chemistry*[37]

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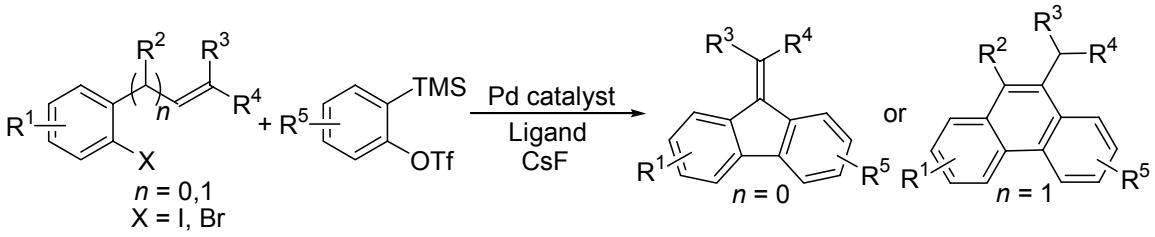
Abstract



The palladium-catalyzed annulation of arynes by substituted *ortho*-halostyrenes and *ortho*-halo allylicbenzenes produces substituted 9-fluorenylidenes and 9,10-phenanthrenes respectively in good yields. This methodology provides these important carbocyclic ring systems in a single step, which involves the generation of two new carbon-carbon bonds, occurs under relatively mild reaction conditions and tolerates a variety of functional groups, including cyano, ester, aldehyde and ketone groups.

Introduction

9-Fluorenylidenes and phenanthrenes are key structural units of many compounds possessing biological activity. Derivatives of 9*H*-fluoren-9-ylidenes, commonly known as 9-fluorenylidenes, are pharmaceutically and cosmetically significant. The 9-fluorenylidene

derivative Paranylene is used in dispersible formulations of anti-inflammatory agents,[1] while the 9-fluorenylidene derivative Lumefantrine is used in dermatological and photostable cosmetic compositions.[2] 3-Fluoren-9-ylidene-2'-hydroxy-3-phenylpropiophenone exhibits thermochromic properties.[3] 2,4,7-Trinitro-9-fluorenylmethacrylate (TNFMN) has been used to study the donor-acceptor interactions of poly(FIMA's) with different tacticities.[4] The phenanthrene derivative 3,7-dihydroxy-2,4,8-trimethoxyphenanthrene is known for its anti-inflammatory properties,[5] while the derivative Aristolochic acid exhibits tumor-inhibitory properties.[6] The phenanthrene derivatives 3-hydroxy-2,4-dimethoxy-7,8-methylenedioxyphenanthrene and 2,7-dihydroxy-1-methyl-5-vinylphenanthrene are cytotoxic.[7]

Due to the pharmaceutical and biological importance of these compounds, the synthesis of 9-fluorenylidenes and phenanthrenes is important. In the literature, 9-fluorenylidenes are mainly synthesized, either from 9*H*-fluoren-9-one derivatives using a Wittig reaction[8] or from 9*H*-fluorene derivatives.[9] Several methods have been reported for the synthesis of 9-phenanthrene derivatives or 9,10-phenanthrene derivatives. These approaches have several disadvantages, including the use of toxic chemicals, harsh reaction conditions or multistep reaction sequences.[10] The synthesis of phenanthrenes by the cocyclization of arynes and alkynes is known,[11] but in most cases the reactions are not regioselective.

Transition metal-catalyzed annulation reactions are very valuable from a synthetic point of view.[12] The Pd-catalyzed annulation of alkynes by substituted aryl and vinylic halides has been employed for the synthesis of a variety of carbocycles and heterocycles,[13] and some of these reactions have also been recently extended to arynes. The major difficulty

in employing arynes is the high reactivity of arynes[14] compared to alkynes, and the harsh reaction conditions often needed to generate arynes *in situ*. A common problem associated with the high reactivity of arynes is their Pd-catalyzed cyclotrimerization[15] to form polycyclic aromatic hydrocarbons. Also, the harsh reaction conditions often required to obtain arynes severely limit the functional group compatibility of the chemistry. It has been reported that the silylaryl triflate **2a** in the presence of CsF generates benzyne under very mild reaction conditions.[16] This method of aryne generation has been used in our research laboratories and reported in the literature for a variety of electrophilic and nucleophilic reactions,[17] Pd-catalyzed annulation reactions,[18] cycloaddition reactions[19] and insertion reactions.[20]

We have previously reported palladium-catalyzed alkyne annulations of ethyl (*E*)-4-(2-iodophenyl)-2-butenoate to obtain naphthalenes,[21] while the palladium-catalyzed alkyne annulation of methyl 3-(2-iodophenyl)acrylate has also been reported in the literature.[22] To the best of our knowledge, the palladium-catalyzed aryne insertion and subsequent cyclization of *ortho*-halostyrenes or *ortho*-halo allylicbenzenes, has not been reported previously. We report herein an efficient approach to 9-fluorenylidenes and phenanthrenes, which proceeds in good yields from starting materials that are readily available or easy to synthesize, and involves a palladium-catalyzed annulation of arynes.

Results and Discussion

The focus of our early studies on this project was the palladium-catalyzed aryne annulation of substituted *ortho*-halostyrenes to give substituted 9-fluorenylidenes in good yields. (*E*)-3-(2-Iodophenyl)acrylonitrile (**1a**) was used as a model system for optimization

of the reaction conditions using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) as the aryne precursor. Early in this work, the reaction was run with 0.3 mmol of **1a**, 2.0 equiv of **2a**, 5 mol % $Pd(dba)_2$, 5 mol % P(*o*-tolyl)$_3$, and 3 equiv of CsF as the base in 5 ml of 1:9 acetonitrile/toluene at 110 °C in a sealed vial to obtain a 28% isolated yield of the desired 2-(9*H*-fluoren-9-ylidene)acetonitrile (**3a**) (eq 1; Table 1, entry 1). Previously in our

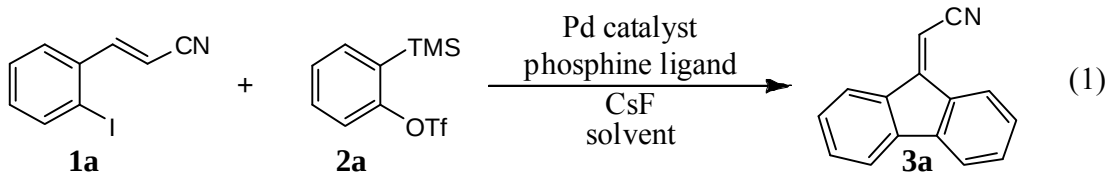


Table 1. Optimization of the Palladium-Catalyzed Benzyne Insertion into (*E*)-3-(2-Iodophenyl)acrylonitrile Using Various Solvents and Ligands (eq. 1)[a]

entry	$Pd(dba)_2$ mol %	phosphine ligand (mol %)	solvent (CH_3CN:$PhCH_3$)	% yield[b]
1	5	P(*o*-tolyl)$_3$ (5)	1:9	28[c]
2	5	P(*o*-tolyl)$_3$ (5)	1:7	36[c]
3	5	P(*o*-tolyl)$_3$ (5)	1:5	35[c]
4	5	P(*o*-tolyl)$_3$ (5)	1:3	35[c]
5	5	P(*o*-tolyl)$_3$ (5)	1:1	37[c]
6	5	P(*o*-tolyl)$_3$ (5)	1:0	25[c]
7	5	P(*o*-tolyl)$_3$ (5)	0:1	0[c]
8	10	P(*o*-tolyl)$_3$ (10)	1:1	39[c]
9	10	P(*o*-tolyl)$_3$ (20)	1:1	49[c]
10	15	P(*o*-tolyl)$_3$ (30)	1:1	48[c]
11	20	-	1:1	0[c]
12	10	Tris(2,4,6-trimethoxyphenyl)phosphine (20)	1:1	40[c]
13	10	Tris(2,6-dimethoxyphenyl)phosphine (20)	1:1	75
14	10	Tri(2-methoxyphenyl)phosphine (20)	1:1	84

Table 1. Continued

entry	$Pd(dba)_2$ mol %	phosphine ligand (mol %)	solvent (CH_3CN:$PhCH_3$)	% yield[b]
15	10	Tri-(2-furyl)phosphine (20)	1:1	30
16	10	$[(CH_3)_3P \cdot AgI]_4$ (20)	1:1	25[c]
17	10	Tri(*t*-butyl)phosphine (20)	1:1	<5[c,d]
18	10	2-(Di-*tert*-butylphosphino)biphenyl (20)	1:1	32
19	10	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (20)	1:1	35
20	10	1,3-Bis(diphenylphosphino)propane (dppp) (20)	1:1	<5[c,d]
21	10	1,1′-Bis(diphenylphosphino)ferrocene (dppf) (20)	1:1	<5[d]
22	10	1,1-Bis(diphenylphosphino)methane (dppm) (20)	1:1	91

[a] Representative procedure: (*E*)-3-(2-iodophenyl)acrylonitrile (0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2.0 equiv), $Pd(dba)_2$, ligand, CsF (3 equiv) and solvent (5 mL) were placed in a 4 dram vial. The vial was sealed with a screw cap. The reaction was then stirred at 110 °C for 24 h. [b] Isolated yields. [c] Some starting material **1a** was left. [d] GC yields.

laboratories, we have found that the polarity of the acetonitrile/toluene solvent system, greatly affects the yields of the products of the aryne chemistry under our experimental conditions, as it controls the rate of aryne formation. An increase in the polarity of the solvent system only slightly increases the yield of the desired product **3a** (entries 2-5). When the reaction was run in pure acetonitrile, the yield dropped to 25% (entry 6) with a simultaneous increase in the amount of the triphenylene side product resulting from palladium-catalyzed cyclotrimerization of the benzyne. None of the desired product was obtained when pure toluene was used as the solvent for the reaction, and both the starting *ortho*-halostyrene **1a** and the benzyne precursor **2a** remained unreacted under those conditions (entry 7). We believe that, this is due to the low solubility of the fluoride source in toluene, which hinders formation of the benzyne. With 1:1 acetonitrile/toluene as the optimized solvent system for the reaction, we tried to improve the yield of the desired

product **3a** by increasing the amount of the $Pd(dba)_2$ catalyst to 10 mol % and the P(*o*-tolyl)$_3$ ligand to 10 mol %. There was only a slight increase in the yield of the desired product **3a** to 39% (entry 8). An increase in the P(*o*-tolyl)$_3$ ligand to 20 mol % further increased the yield to 49% (entry 9). While maintaining a 1:2 ratio of the $Pd(dba)_2$ to the P(*o*-tolyl)$_3$, but further increasing the amount of the catalyst and the ligand, no significant increase in the yield was observed (entry 10). The reaction in the absence of P(*o*-tolyl)$_3$ did not yield the desired product **3a** (entry 11).

Noting the importance of the ligand in the reaction, various ligands have been screened with the aim of increasing the yield of the 9-fluorenylidene **3a**. Electron-rich tris(2,4,6-trimethoxyphenyl)phosphine gave a reduced yield of 40% (entry 12), while tris(2,6-dimethoxyphenyl)phosphine increased the yield to 75% (entry 13). Relatively unhindered tri(2-methoxyphenyl)phosphine improved the yield still further to 84% (entry 14). Along with steric factors, the electronic nature of the phosphine ligand seems to have an effect on the overall yield of the desired product **3a** (compare entries 12-14). To further study the effect on the yield of the desired product, in the presence of an oxygen moiety in the phosphine ligand (compare entries 9 and 14), the reaction was carried out with tri(2-furyl)phosphine ligand, which gave a poor 30% yield of **3a** (entry 15). The ligand trimethylphosphine obtained from $[(CH_3)_3P \cdot AgI]_4$ gave a poor 25% yield of the desired product **3a** (entry 16). The bulkier phosphine ligand tri(*t*-butyl)phosphine gave an extremely poor yield (<5%), while 2-(di-*tert*-butylphosphino)biphenyl gave only a 32% yield of the fluorenylidene (entries 17 and 18). We have also screened bidentate ligands with a view towards improving the yield of the desired 9-fluorenylidene **3a**. The bidentate Xantphos ligand did not improve the yield of the reaction (entry 19), affording only a 35% yield of **3a**.

The phosphine ligands dppp and dppf gave extremely poor yields (entries 20 and 21), but to our surprise dppm improved the yield to 91% (entry 22).

With dppm as the apparent ligand of choice, the reaction has been carried out at a lower temperature. At 85 ^{o}C, the desired product **3a** was obtained in a lower 52% yield (Table 2, entry 1), and the reaction did not go to completion. When the reaction was run at 100 ^{o}C, the yield increased to 68% (entry 2), while a further increase in the temperature to 120 ^{o}C did not have much effect on the yield of the product (compare Table 1, entry 22 and Table 2, entry 3). Reducing the amount of the benzyne precursor to 1.5 equiv did not effect the yield of the desired product **3a** (entry 4), but a further reduction of **2a** to 1.2 equiv decreased the yield of **3a** to 69% (entry 5). Either a decrease or an increase in the amount of the base CsF gave reduced yields of 78% and 86% respectively (compare entries 4, 6 and 7).

Table 2. Optimization of the Palladium-Catalyzed Benzyne Insertion into (*E*)-3-(2-Iodophenyl)acrylonitrile with dppm as the Ligand (eq. 1)[a]

entry	$Pd(dba)_2$ (mol %)	dppm (mol %)	precursor (equiv)	CsF	time (h)	temp. (^{o}C)	% yield[b] **3a**
1	10	20	2.0	3	24	85	52[c]
2	10	20	2.0	3	24	100	68[c]
3	10	20	2.0	3	24	120	92
4	10	20	1.5	3	24	110	91
5	10	20	1.2	3	24	110	69[c]
6	10	20	1.5	2	24	110	78
7	10	20	1.5	5	24	110	86
8	5	5	1.5	3	24	110	49[c]

Table 2. Continued

entry	$Pd(dba)_2$ (mol %)	dppm (mol %)	precursor (equiv)	CsF	time (h)	temp. (^oC)	% yield[b] **3a**
9	5	10	1.5	3	24	110	62[c]
10	10	10	1.5	3	24	110	69[c]
11	20	10	1.5	3	24	110	42
12	10	40	1.5	3	24	110	76
13	10	20	1.5	3	12	110	71[c,d]

[a] Representative procedure: (*E*)-3-(2-iodophenyl)acrylonitrile (0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, $Pd(dba)_2$, dppm, CsF and solvent (5 mL) were placed in a 4 dram vial. The vial was sealed with a screw cap. The reaction was then stirred at the desired temperature for the indicated time. [b] Isolated yields. [c] Some starting material **1a** was left. [d] GC yields.

This variation in yields probably reflects a variation in the rate of benzyne formation from the 2-(trimethylsilyl)phenyl trifluoromethanesulfonate. After optimization of the reaction conditions with respect to the solvent system, the phosphine ligand, the temperature, the amount of the aryne precursor and the base, we also studied if the reaction can be carried out at a lower catalyst loading with different palladium catalyst to phosphine ligand ratios. When the reaction was run with only 5 mol % of the $Pd(dba)_2$ catalyst and 5 mol % of the dppm ligand, the yield decreased to 49% (entry 8). An increase in the amount of the dppm ligand to 10 mol % increased the yield to 62% (entry 9), indicating that a ratio of $Pd(dba)_2$ to the dppm ligand of 1:2 works better than the ratio of 1:1, even at a lower catalyst loading. To cross check this finding, the reaction was carried out with 10 mol % of $Pd(dba)_2$ and 10 mol % of the dppm ligand which, afforded only a 69% yield of the desired product **3a** (compare entries 4 and 10). A higher $Pd(dba)_2$ to dppm ligand ratio or a further excess of the dppm ligand decreased the yield of **3a** to 42% and 76% respectively (entries 11 and 12). A reduced

reaction time gave a lower yield of 71% (entry 13). Thus, our optimized conditions for the palladium-catalyzed aryne annulation are 0.3 mmol of **1a**, 1.5 equiv of **2a**, 10 mol % of $Pd(dba)_2$, 20 mol % of dppm, 3 equiv of CsF in 5 ml of 1:1 acetonitrile/toluene at 110 ^oC in a sealed vial for 24 h.

After obtaining our best reaction conditions for the aryne annulation, we examined the scope of this reaction on various substrates. Aryl halides **1f**, **1i**, **1j**, and **1k** were prepared by standard Wittig chemistry (Scheme 1), using commercially available aldehydes **4a**, **4b** and **4d**, while **4c** was prepared according to a literature procedure.[23] The aryl halide **1t** was prepared by condensation of *o*-iodobenzaldehyde with diethyl malonate (Scheme 2). Aryl halides **1a**, **1h**, and **1r** were obtained from commercial sources, while **1b**,[24] **1c**,[24] **1d**,[25] **1e**,[26] **1g**,[27] **1l**,[28] **1m**,[28] **1n**,[21] **1o**,[28] **1p**,[28] **1q**,[29] and **1s**[30] were prepared according to literature procedures. The benzyne precursor **2a** is commercially available, while the aryne precursors **2b**,[19] **2c**,[19] **2d**[19] and **2e**[19] have been prepared according to literature procedures.

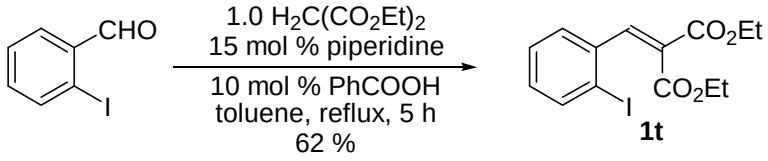
Scheme 1

	X	R^1	R^2, R^3	R^4
4a	I	H	H, H	CHO
4b	Br	H	OMe, OMe	CO_2Et
4c	I	H	OCH_2O	CN
4d	I	F	H, H	CN

	X	R^1	R^2, R^3	R^4	time (h)	%
1f	I	H	H, H	CHO	48	39
1i	Br	H	OMe, OMe	CO_2Et	12	36
1j	I	H	OCH_2O	CN	24	52
1k	I	F	H, H	CN	24	54

The model system **1a** under our optimized conditions with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) as the benzyne precursor gave an 91% isolated yield of the

Scheme 2



desired product **3a** (Table 3, entry 1). Compound **3a** was obtained in a slightly lower 79% yield, when the reaction was carried out using the corresponding aryl bromide, (*E*)-3-(2-bromophenyl)acrylonitrile (**1b**). The improved yield from the aryl iodide is no doubt a direct

Table 3. Synthesis of 9-Fluorenylidenes and Phenanthrenes by Palladium-Catalyzed Aryne Annulation of *ortho*-Halostyrenes and *ortho*-Halo Allylicbenzenes.[a]

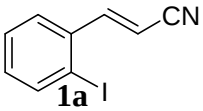
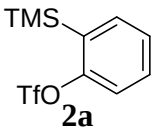
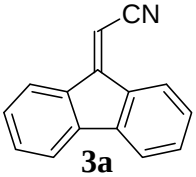
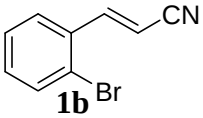
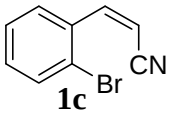
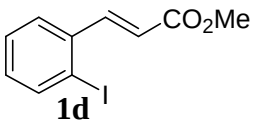
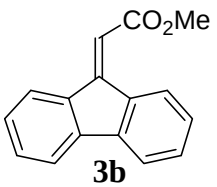
entry	unsaturated arene	benzyne precursor	product(s)	% isolated yield
1	 **1a**	 **2a**	 **3a**	91
2	 **1b**	**2a**	**3a**	79
3	 **1c**	**2a**	**3a**	72
4	 **1d**	**2a**	 **3b**	76

Table 3. Continued

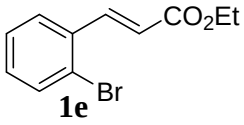
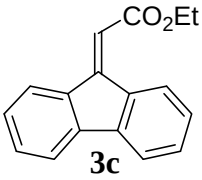
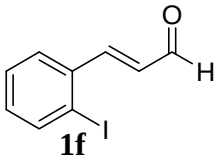
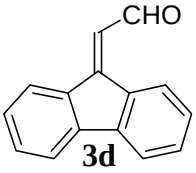
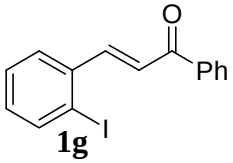
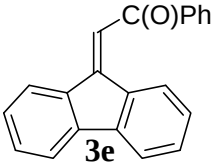
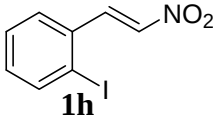
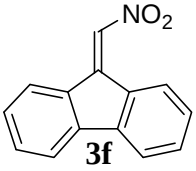
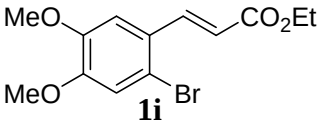
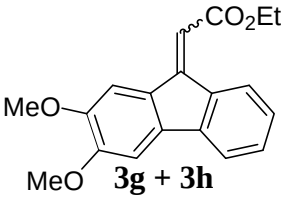
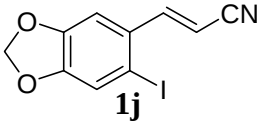
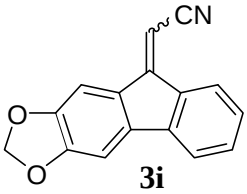
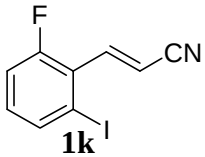
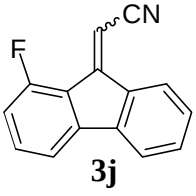
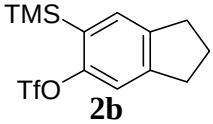
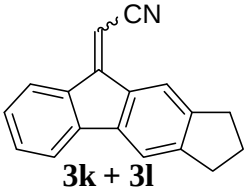
entry	unsaturated arene	benzyne precursor	product(s)	% isolated yield
5	 **1e**	**2a**	 **3c**	75
6	 **1f**	**2a**	 **3d**	76
7	 **1g**	**2a**	 **3e**	61
8	 **1h**	**2a**	 **3f**	0
9	 **1i**	**2a**	 **3g + 3h**	<5%[b]
10	 **1j**	**2a**	 **3i**	73[c]
11	 **1k**	**2a**	 **3j**	46[d,e]
12	**1a**	 **2b**	 **3k + 3l**	82[f] [11:1]

Table 3. Continued

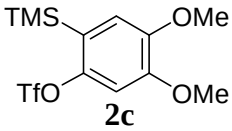
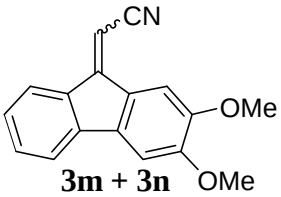
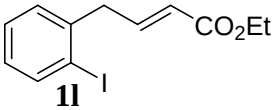
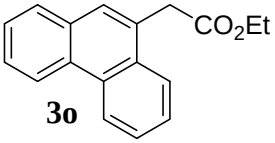
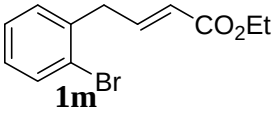
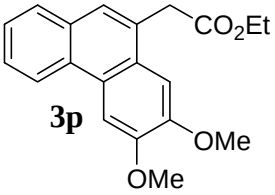
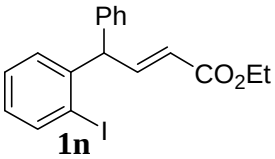
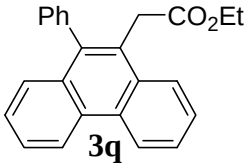
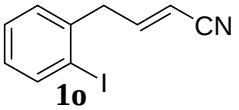
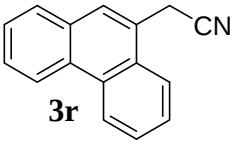
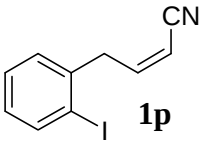
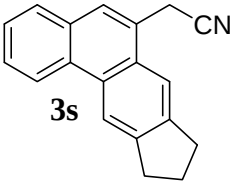
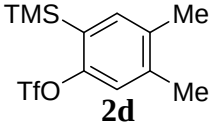
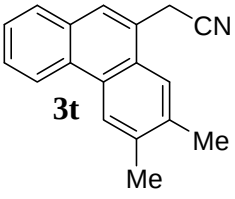
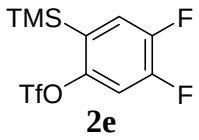
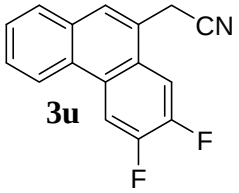
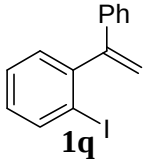
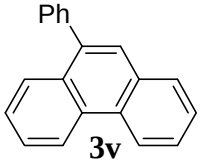
entry	unsaturated arene	benzyne precursor	product(s)	% isolated yield
13	**1a**	 **2c**	 **3m + 3n**	78[f] [4:1]
14	 **1l**	**2a**	 **3o**	62
15	 **1m**	**2a**	**3o**	49
16	**1l**	**2c**	 **3p**	45
17	 **1n**	**2a**	 **3q**	~20[b]
18	 **1o**	**2a**	 **3r**	58
19	 **1p**	**2a**	**3r**	47
20	**1o**	**2b**	 **3s**	52
21	**1o**	 **2d**	 **3t**	50

Table 3. Continued

entry	unsaturated arene	benzyne precursor	product(s)	% isolated yield
22	**1o**	 **2e**	 **3u**	0
23	 **1q**	**2a**	 **3v**	35[b]

[a] Representative procedure: aryl halide **1**(**a-r**) (0.3 mmol), silylaryl triflate **2**(**a-e**) (2.0 equiv), 10 mol % of $Pd(dba)_2$, 20 mol % of dppm, CsF (3 equiv) and 1:1 $CH_3CN/PhCH_3$ (5 mL) were placed in a 4 dram vial. The vial was sealed with a screw cap. The reaction was then stirred at 110 °C for 24 h. [b] GC yields. [c] Eight percent of a minor isomer is observed by GC analysis. [d] Some starting material **1l** was left. The reaction did not go to completion even at 140 °C. [e] Five percent of a minor isomer is observed by GC analysis. [f] The ratio was determined by H^1 NMR spectroscopy.

result of the more facile oxidative addition of aryl iodides over aryl bromides. The *cis* isomer (*Z*)-3-(2-bromophenyl)acrylonitrile (**1c**) gave a slightly lower yield of 72% than the corresponding *trans* isomer, (*E*) 3-(2-bromophenyl)acrylonitrile (**1b**) (compare entries 2 and 3). With a methyl ester as the electron-withdrawing group (EWG) on the double bond of the *ortho*-halostyrene **1d**, the yield dropped to 76% under our optimized conditions (compare entries 1 and 4). Similar results were obtained using the corresponding bromide-containing ethyl ester (entry 5). With an aldehyde as the EWG on the *ortho*-halostyrene **1f**, a 76% yield of the desired product **3d** was obtained (entry 6). The yield is comparable to that obtained with an ester group present on the double bond of the *ortho*-halostyrene. With a ketone present in the *ortho*-halostyrene **1g**, the yield dropped to 61% (entry 7). Previously aryl triflates have proved to work well in oxidative palladium insertion chemistry. Thus, we carried out a reaction with 2-(3-oxo-3-phenyl-propenyl)phenyl trifluoromethanesulfonate, but

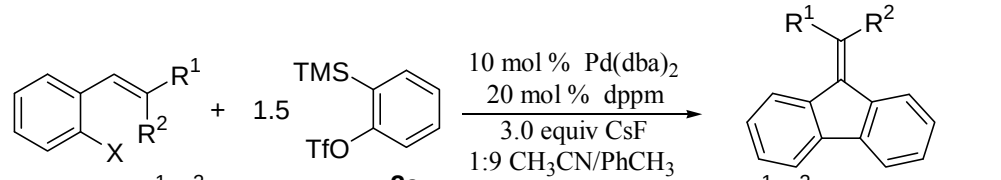
none of the desired product was obtained. When a stronger electron-withdrawing nitro group was placed on the *ortho*-halostyrene, the reaction also failed to give the desired product **3f** (entry 8). Instead, we got a polymeric residue in the reaction flask. We believe 2-(2-nitrovinyl)iodobenzene (**1h**) undergoes polymerization under our reaction conditions. Also, when an electron-donating methyl group was placed on the double bond of the *ortho*-halostyrene, as in 1-iodo-2-(1-propenyl)benzene, the reaction with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) failed to give the desired fluorenylidene under our reaction conditions. When electron-donating methoxy groups were placed on the *ortho*-halostyrene, we obtained an extremely poor yield (<5%), presumably because oxidative addition of palladium is unfavorable in such electron-rich aryl halides (compare entries 5 and 9). On the other hand, the electron-rich substrate **1j** with a carbon-iodine, instead of a carbon-bromine bond, gave the desired product in a 73% yield (entry 10). The *ortho*-halostyrene **1k**, reacted with **2a** to give a 46% yield of the fluorenylidene (entry 11). However, the reaction was slow and did not go to completion even at the higher temperature of 140 ^{o}C. The structure of the major product has not been rigorously established, but is assumed to be the less hindered *E*-isomer. Five percent of a minor isomer has also been observed.

We have also studied the scope of the reaction using various aryne precursors. The model system **1a** on reaction with the aryne precursor **2b** gave the desired compounds **3k** and **3l** as a 13:1 mixture of inseparable isomers in an 82% overall yield (entry 12). It is unclear as to which stereoisomer is the major product. The aryne precursor **2c** with two electron-rich methoxy groups gave a slightly lower yield of 78% when allowed to react with the model system **1a**; a 4:1 ratio of stereoisomers was obtained (entry 13). Again, the stereochemistry

of the major isomer is unknown. The slightly lower yield may be due to the slower rate of aryne formation from precursor **2c**, as observed previously by us.

When we carried out the palladium-catalyzed aryne annulation using aryne precursor 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) and *ortho*-halostyrene **1r**, bearing a trisubstituted double bond, under our optimized reaction conditions, the reaction was messy and the desired product **3w** was obtained in an extremely low (<5%) yield as determined by GC analysis (Scheme 3). We have also tried an analogous reaction with *ortho*-halostyrene **1s**, where the electron-withdrawing groups on the double bond of the styrene were ester groups, instead of cyano groups. The desired product **3x** was obtained in a low (<5%) yield as determined by GC analysis. A reaction with the corresponding aryl iodide **1t** only slightly improved the yield to ~5-10% and the reaction was cleaner when compared to that of aryl bromide **1s**.

Scheme 3



1r (X = Br; R^1,R^2 = CN)
1s (X = Br; R^1,R^2 = CO_2Et)
1t (X = I; R^1,R^2 = CO_2Et)

2a

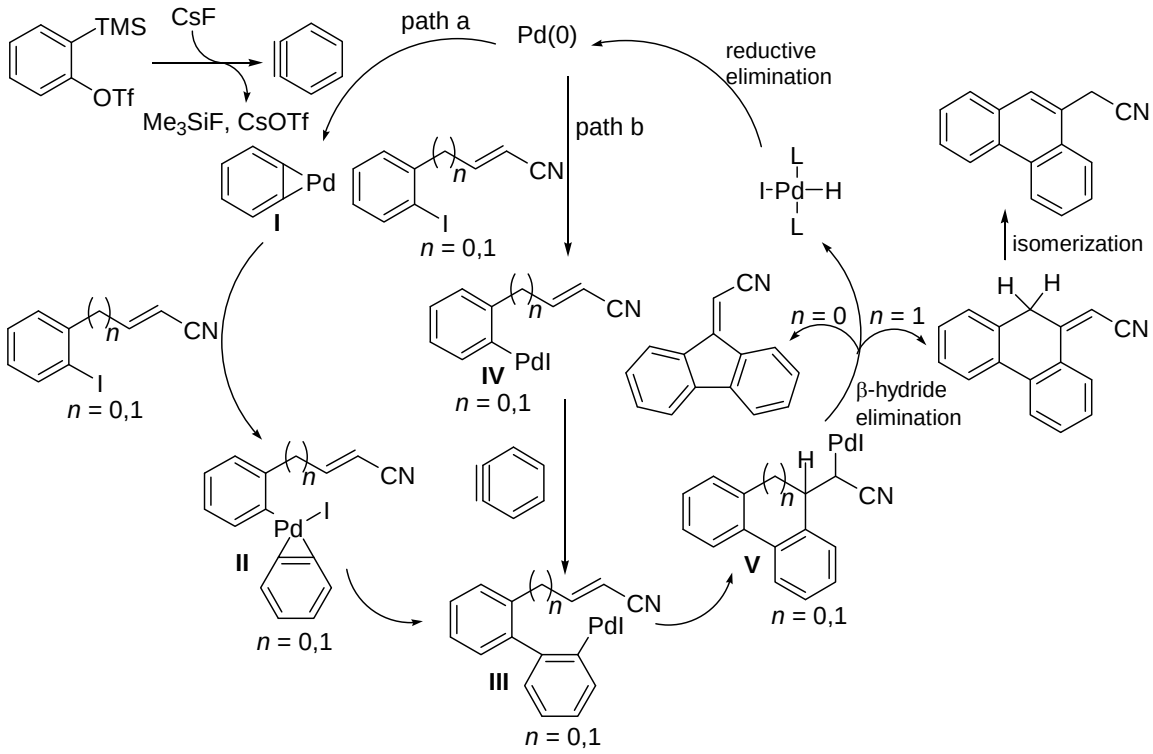
3w (R^1,R^2 = CN), <5%
3x (R^1,R^2 = CO_2Et),<10%

We have also been able to extend our methodology to the synthesis of phenanthrene derivatives from the corresponding *ortho*-halo allylicbenzenes. Ethyl (*E*)-4-(2-iodophenyl)but-2-enoate (**1l**) on reaction with **2a** gave a 62% yield of the desired 9-phenanthrene **3o** (entry 14). Ethyl (*E*)-4-(2-bromophenyl)but-2-enoate (**1m**) gave a slightly

lower yield of 49% of **3o**, presumably due to reasons mentioned previously. Ethyl (*E*)-4-(2-iodophenyl)but-2-enoate, when allowed to react with the electron-rich aryne precursor **2c**, gave a somewhat lower yield of 45% of the desired phenanthrene **3p** (compare entries 14 and 16). The *ortho*-halo allylicbenzene **1n** gave a poor ~20% yield of the desired phenanthrene **3q**, but the product could not be purified (entry 17). An electron-withdrawing cyano group on the *ortho*-halo allylicbenzene **1o**, instead of an ester group, gave a slightly lower 58% yield of the desired phenanthrene **3r**, contrary to our observations with the analogous fluorenylidenes (compare entries 14 and 18, and entries 1 and 4). (*Z)*-4-(2-Iodophenyl)-2-butenenitrile (**1p**) gave a 47% yield of the desired phenanthrene, which was slightly less than the (*E*)-isomer (compare entries 18 and 19). *ortho*-Halo allylicbenzene **1o**, when treated with the aryne precursors **2b** and **2d**, gave 52% and 50% yields respectively of the corresponding phenanthrenes **3s** and **3t** (entries 20 and 21). Thus, the yield of the reaction decreases when more electron-rich aryne precursors are used. When inductively electron-withdrawing fluorine atoms were placed on the aryne precursor **2e**, none of the desired product was obtained for reasons not known to us. The *ortho*-halostyrene **1q** gave the phenanthrene **3v** in a 35% yield. This product, however, could not be isolated from the corresponding triphenylene, which is the major side product in all of these reactions.

We propose the following possible mechanisms for these reactions based on the known reactions of organopalladium compounds with alkynes (Scheme 4).[13] The reaction can follow two pathways, path a or path b. In path a, the aryne generated from the triflate in the presence of the fluoride source coordinates with Pd(0), affording palladacycle **I**.[31] Oxidative addition of the aryl halide to **I** might generate an arylpalladium(IV) complex **II**. Upon reductive elimination, complex **II** could afford a new arylpalladium intermediate **III**.

Scheme 4



Alternatively, according to path b, Pd(0) might add oxidatively to the aryl halide to afford the arylpalladium(II) intermediate **IV**, which in turn might add to the aryne[32] to afford arylpalladium intermediate **III**. Regardless of how intermediate **III** is generated, the palladium-carbon bond in this intermediate can then add across the neighboring carbon-carbon double bond to afford intermediate **V**, which directly affords the fluorenylidene product by β-hydride elimination when $n = 0$. When $n = 1$, the phenanthrene is obtained by further isomerization of the resulting olefin. This isomerization may be promoted by the base present in the reaction or by the palladium hydride generated during the process.

Similar intramolecular palladium-catalyzed Heck reactions, followed by olefin isomerization, have been reported by us during the carbopalladation of alkynes to generate naphthalenes.[21]

Conclusions

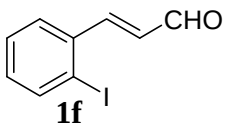
A range of fluorenylidenes and phenanthrenes have been obtained from simple starting materials that are readily available or easily synthesized, using a one step palladium-catalyzed aryne insertion of *o*-halostyrenes and *o*-halo allylbenzenes respectively. The arynes are obtained *in situ* under mild reaction conditions from the corresponding 2-(trimethylsilyl)aryl trifluoromethanesulfonates and CsF. Our methodology is tolerant of a variety of functional groups, including cyano, ester, aldehyde, ketone, and methoxy groups, which provide a handle for further organic transformations. A fluorine moiety can also be introduced into the products. This methodology provides a very convenient, general approach to these two important classes of aromatic hydrocarbons.

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. Thin layer chromatography was performed using 60 mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All high resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

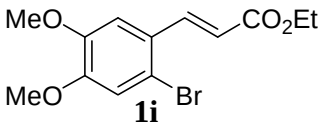
General procedure for the synthesis of the starting *ortho*-halostyrenes by a Wittig reaction. To a solution of triphenylphosphoranylidene (4.5 mmol) in 30 ml of

CH_2Cl_2 was added dropwise a solution of the aldehyde (3.0 mmol) in 6 ml of CH_2Cl_2 at 0 ^oC under an inert argon atmosphere. The resulting mixture was stirred at 25 ^oC until completion of the reaction, which was monitored by TLC. The solvent was then evaporated under reduced pressure. The solid residue was dissolved in 15 ml of hexanes and the mixture was stirred at 25 ^oC for 30 min. The Ph_3PO was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/ EtOAc as the eluent to afford the desired product.



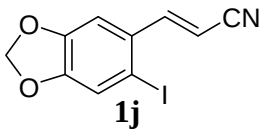
1f

(*E*)-3-(2-Iodophenyl)propenal (1f). This compound was obtained as a yellow solid: mp 79-80 $^\circ C$ (lit.[33] 78-79 $^\circ C$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.56-6.62 (m, 1H), 7.07-7.11 (m, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.60 (dd, J = 7.9, 1.5 Hz, 1H), 7.71 (d, J = 15.7 Hz, 1H), 7.92 (dd, J = 7.9, 0.9 Hz, 1H), 9.76 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.0, 127.7, 128.8, 130.8, 132.2, 136.9, 140.3, 155.4, 193.4.



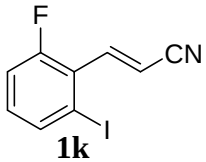
1i

(*E*)-Ethyl 3-(2-bromo-4,5-dimethoxyphenyl)propenoate (1i). This compound was obtained as a white solid: mp 112-114 $^\circ C$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.2 Hz, 3H), 3.89 (s, 6H), 4.27 (q, J = 7.1 Hz, 2H), 6.28 (d, J = 15.8 Hz, 1H), 7.04 (d, J = 13.7 Hz, 2H), 7.96 (d, J = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 56.0, 56.2, 60.5, 109.0, 115.4, 117.1, 118.5, 126.2, 142.6, 148.5, 151.2, 166.5; HRMS m/z 314.01596 (calcd $C_{13}H_{15}BrO_4$, 314.01537).



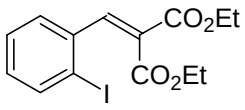
1j

3-(6-Iodobenzo[1,3]dioxol-5-yl)acrylonitrile (1j). This compound was obtained as a white solid: mp 104-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (d, J = 11.8 Hz, 1H), 5.97 (s, 2H), 7.18 (d, J = 11.9 Hz, 1H), 7.26 (s, 1H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 91.0, 96.4, 97.1, 102.5, 105.8, 108.6, 116.8, 119.2, 152.2, 153.5; HRMS m/z 298.94482 (calcd $C_{10}H_6INO_2$, 298.94433).



1k

3-(2-Fluoro-6-iodophenyl)acrylonitrile (1k). This compound was obtained as a white solid: mp 82-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, J = 16.8 Hz, 1H), 7.03-7.16 (m, 2H), 7.41 (d, J = 16.8 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 101.64, 101.66, 104.0, 104.2, 115.4, 116.8, 117.0, 117.8, 124.9, 125.0, 132.70, 132.79, 136.35, 136.39, 148.54, 148.57, 159.6, 162.1 (extra peaks due to splitting by fluorine); HRMS m/z 272.94554 (calcd C_9H_5FIN, 272.94508).

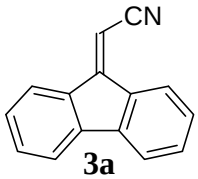


1t

Diethyl [(2-iodophenyl)methylene]propanedioate (1t). This compound was prepared by the following procedure. To a solution of 2-iodobenzaldehyde (10 mmol), diethyl malonate (10 mmol), and piperidine (1.5 mmol) in 60 mL of toluene, benzoic acid (1.0 mmol) was added. The reaction mixture was refluxed for 5 h using a Dean-Stark

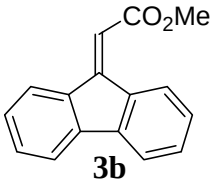
condenser for water removal. The mixture was cooled to room temperature and diluted with diethyl ether (100 mL) and EtOAc (100 mL). The organic layer was separated and washed two times each with 2 N HCl, saturated $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/ EtOAc as the eluent and further subjected to distillation to remove traces of diethyl malonate (bp: 195-196 ^oC) at ~200 ^oC to afford the desired product as a brown oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.33 (q, J = 7.0 Hz, 2H), 7.03-7.07 (m, 1H), 7.29-7.39 (m, 2H), 7.83 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.2, 61.6, 61.8, 99.6, 128.2, 128.6, 128.9, 131.1, 137.4, 139.4, 145.9, 163.5, 165.4; IR (neat, cm^{-1}) 3060, 2979, 1746, 1627, 1458, 1361; HRMS m/z 374.00220 (calcd $C_{14}H_{15}IO_4$, 374.00151).

General procedure for the palladium-catalyzed annulation of arynes by *ortho*-halostyrenes and *ortho*-halo allylicbenzenes. To 0.3 mmol of the aryl halide was added the *o*-silylaryl triflate (1.5 equiv), $Pd(dba)_2$ (10 mol %), dppm (20 mol %) and 1:1 $CH_3CN/PhCH_3$ (5 ml). CsF (3.0 equiv) was then added and the vial was sealed with a screw cap. The reaction mixture was then stirred at 110 ^oC for 24 h. After the reaction was complete, the resulting solution was washed with brine (25 mL) and extracted with EtOAc (25 mL). The combined EtOAc fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/ EtOAc as the eluent to afford the desired product.



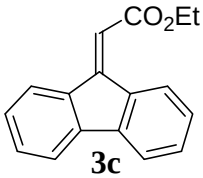
3a

2-(9*H*-Fluoren-9-ylidene)acetonitrile (3a). This compound was obtained as a yellow solid: mp 109-111 °C (lit.[34] 109-110 °C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.6, 120.3, 120.4, 121.7, 125.5, 128.0, 128.5, 131.9, 132; HRMS m/z 203.07381 (calcd $C_{15}H_9N$, 203.07350). The ^{1}H NMR spectrum matches the literature data.[34]



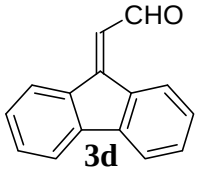
3b

Methyl 2-(9*H*-fluoren-9-ylidene)acetate (3b). This compound was obtained as a white solid: mp 60-62 °C (lit.[35] 59-62 °C); HRMS m/z 236.08397 (calcd $C_{16}H_{12}O_2$, 236.08373). The ^{1}H and ^{13}C NMR spectra match the literature data.[35]



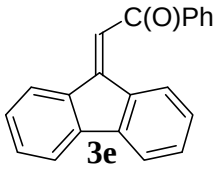
3c

Ethyl 2-(9*H*-fluoren-9-ylidene)acetate (3c). This compound was obtained as a yellow solid: mp 75-76 °C; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 60.9, 114.1, 119.7, 119.9, 121.4, 127.6, 128.2, 129.3, 130.7, 131.0, 135.3, 139.0, 140.9, 142.6, 148.4, 166.5. The ^{1}H NMR spectrum matches the literature data.[36]



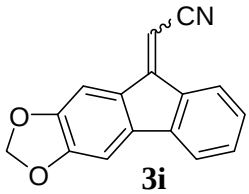
3d

2-(9*H*-Fluoren-9-ylidene)acetaldehyde (3d). This compound was obtained as a yellow solid: mp 115-117 °C (lit.[9a] 115.6-116.3 °C). The ^{1}H and ^{13}C NMR spectra match the literature data.[36]



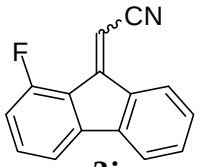
3e

2-(9*H*-Fluoren-9-ylidene)-1-phenylethanone (3e). This compound was obtained as a yellow solid: mp 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.24 (m, 1H), 7.29 (dt, J = 7.5, 0.8 Hz, 1H), 7.34-7.42 (m, 2H), 7.48-7.52 (m, 2H), 7.58-7.63 (m, 4H), 7.76 (d, J = 7.6 Hz, 1H), 8.09-8.11 (m, 2H), 8.33 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.6, 119.8, 120.0, 121.2, 127.6, 127.7, 128.1, 128.94, 128.98, 130.6, 130.9, 133.5, 135.5, 138.4, 138.9, 141.0, 142.4, 146.2, 192.6 ; HRMS m/z 282.10477 (calcd $C_{21}H_{14}O$, 282.10447).



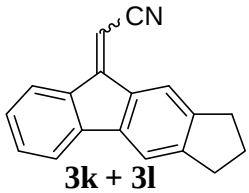
3i

(1,3-Dioxacyclopenta[*b*]fluoren-9-ylidene)acetonitrile (3i). This compound was obtained as a pale yellow solid: mp 193-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (s, 2H), 7.24-7.25 (m, 1H, merged $CDCl_3$ peak shows extra proton), 7.67-7.73 (m, 2H), 8.00 (s, 1H), 8.10 (s, 1H), 8.25-8.27 (m, 1H), 8.47-8.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.2, 102.2, 106.4, 107.5, 118.4, 123.0, 126.2, 126.5, 127.5, 127.9, 128.8, 129.2, 129.9, 134.7, 148.5, 150.9; HRMS m/z 247.0633 (calcd $C_{16}H_9NO_2$, 247.0633).



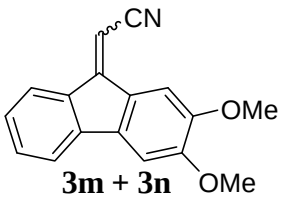
3j

(1-Fluorofluoren-9-ylidene)acetonitrile (3j). This compound was obtained as a yellow solid: mp 129-131 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, J = 3.4 Hz, 1H), 6.95-7.00 (m, 1H), 7.36-7.49 (m, 4H), 7.64 (d, J = 7.4 Hz, 1H), 8.43 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 93.6, 93.7, 115.6, 115.8, 116.4, 116.5, 117.5, 120.7, 125.5, 129.1, 131.8, 133.3, 133.4, 135.1, 141.23, 141.26, 143.3, 143.4, 150.8, 159.5, 162.0 (extra peaks due to fluorine splitting); HRMS m/z 221.0634 (calcd $C_{15}H_8FN$, 221.0641).



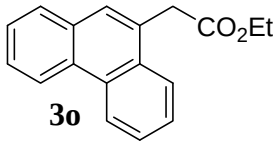
3k + 3l

(2,3-Dihydro-1*H*-cyclopenta[*b*]fluoren-9-ylidene)acetonitriles (3k + 3l). These compounds were obtained as a yellow oil as a 11:1 mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08-2.24 (m, 6H), 2.88-3.04 (m, 11H), 3.13-3.18 (m, 1H), 7.09-7.29 (m, 4H), 7.38-7.42 (m, 6H), 7.50-7.89 (m, 5H), 8.10-8.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 32.8, 32.9, 33.2, 33.3, 87.1, 87.2, 116.4, 117.7, 117.9, 119.7, 119.8, 121.51, 121.53, 125.3, 127.3, 127.8, 131.6, 131.7, 133.7, 135.2, 135.4, 137.0, 139.6, 140.9, 141.1, 142.3, 144.6, 145.0, 149.15, 149.18, 153.80, 153.84; HRMS m/z 243.10514 (calcd $C_{18}H_{13}N$, 243.10480).



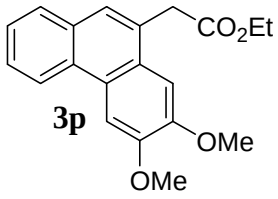
3m + 3n

(2,3-Dimethoxyfluoren-9-ylidene)acetonitriles (3m + 3n). These compounds were obtained as a orange solid as a 4:1 mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 12H), 4.01 (s, 12H), 4.10 (s, 3H), 4.13 (s, 3H), 5.92 (s, 4H), 7.07 (s, 4H), 7.16-7.20 (m, 4H), 7.35-7.39 (m, 4H), 7.44-7.50 (m, 8H), 7.57-7.63 (m, 2H), 7.74-7.78 (m, 1H), 7.91 (s, 5H), 7.98 (s, 1H), 8.14 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.3, 56.4, 63.6, 66.2, 86.6, 103.2, 103.5, 104.8, 105.9, 108.2, 115.5, 118.1, 118.6, 119.23, 119.29, 121.4, 122.5, 126.7, 127.0, 127.5, 127.7, 129.4, 129.5, 129.7, 131.7, 133.6, 134.1, 136.4, 137.0, 140.8, 149.4, 150.7, 152.6, 153.7; HRMS m/z 263.09505 (calcd $C_{17}H_{13}NO_2$, 263.09463).



3o

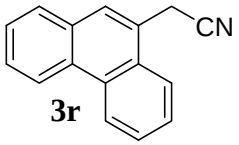
Ethyl (phenanthren-9-yl)acetate (3o). This compound was obtained as a yellow solid: mp 55-57 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H), 4.10 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 7.56-7.68 (m, 5H), 7.85 (d, J = 7.5 Hz, 1H), 8.02-8.04 (m, 1H), 8.66 (d, J = 8.1 Hz, 1H), 8.72-8.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 40.0, 61.2, 122.6, 123.3, 124.6, 126.6, 126.8, 126.9, 127.0, 128.5, 129.0, 129.3, 130.3, 130.8, 131.2, 131.7, 171.7; HRMS m/z 264.11547 (calcd $C_{18}H_{16}O_2$, 264.11503).



3p

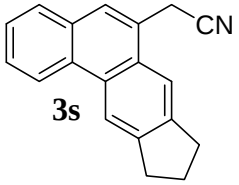
Ethyl (6,7-dimethoxyphenanthren-9-yl)acetate (3p). This compound was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 4.05-4.06 (m, 5H), 4.12-4.18 (m, 5H), 7.44 (s, 1H), 7.50-7.54 (m, 1H), 7.58-7.61 (m, 2H), 7.84 (d, J = 7.6 Hz,

1H), 8.04 (s, 1H), 8.50 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 40.7, 56.0, 56.1, 61.2, 103.9, 105.1, 122.1, 125.6, 125.9, 126.3, 126.4, 127.3, 128.5, 128.6, 129.8, 131.2, 149.2, 149.4, 171.8; HRMS m/z 324.13656 (calcd $C_{20}H_{20}O_4$, 324.13616).



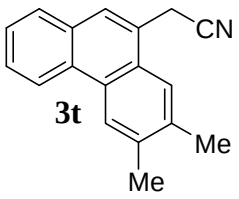
3r

(Phenanthren-9-yl)acetonitrile (3r). This compound was obtained as a yellow solid: mp 103-105 ^{o}C (lit.[10b] 104-106 ^{o}C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 117.8, 122.7, 123.2, 123.7, 124.3, 127.32, 127.39, 127.51, 127.58, 127.6, 128.8, 129.6, 130.5, 130.9, 131.2. The ^{1}H NMR spectrum matches the literature data.[10b]



3s

(9,10-Dihydro-8*H*-cyclopenta[*b*]phenanthren-6-yl)acetonitrile (3s). This compound was obtained as a pale yellow solid: mp 134-136 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19-2.26 (m, 2H), 3.13-3.20 (m, 4H), 7.56-7.66 (m, 2H), 7.72 (s, 1H), 7.81 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 8.60-8.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 26.2, 33.2, 33.3, 118.0, 118.2, 118.7, 122.6, 124.3, 126.6, 126.7, 127.2, 128.71, 128.78, 129.9, 130.7, 131.0, 144.6, 144.8; HRMS m/z 257.12093 (calcd $C_{19}H_{15}N$, 257.12045).



3t

(6,7-Dimethylphenanthren-9-yl)acetonitrile (3t). This compound was obtained as a pale yellow solid: mp 154-156 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 2.55 (s, 3H), 4.15 (s, 2H), 7.56-7.67 (m, 3H), 7.80 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 8.50 (s, 1H), 8.63 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 20.7, 22.4, 118.0, 122.5, 123.5, 123.9, 124.0, 126.6, 126.8, 127.2, 128.2, 128.7, 129.2, 130.3, 131.0, 136.7, 136.9; HRMS m/z 245.12075 (calcd $C_{18}H_{15}N$, 245.12045).

Acknowledgements

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References

1. Britten, N. J.; Burns, J. W.; Hallberg, J. W.; Waldron, N. A.; Watts, J. L. Dispersible formulations of an anti-inflammatory agent. PCT Int. Appl. WO 2004082588, 2004.
2. Mueller, S.; Herzog, B.; Quass, K. Photostable cosmetic or dermatological compositions containing sunscreens. PCT Int. Appl. WO 2006034968, 2006.
3. Schoenberg, A.; Singer, E. *Ber.* **1961**, *94*, 248.
4. Ishizawa, H.; Nakano, T.; Yade, T.; Tsuji, M.; Nakagawa, O.; Yamaguchi, T. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4656.

5. Bordat, P.; Tarroux, R.; Charveron, M.; David, B. Phenanthrene derivatives, their synthesis, anti-inflammatory activity, and use in treating inflammatory skin diseases. Fr. Demande WO 2006089881, 2006.

6. Kupchan, S. M.; Wormser, H. C. *J. Org. Chem.* **1965**, *30*, 3792.

7. (a) Kovacs, A.; Forgo, P.; Zupko, I.; Rethy, B.; Falkay, G.; Szabo, P.; Hohmann, J. *Phytochemistry* **2007**, *68*, 687. (b) Dellagreca, M.; Fiorentinob, A.; Isidorib, M.; Lavorgna, M.; Monaco, P.; Previtera, L.; Zarrelli, A. *Phytochemistry* **2002**, *60*, 633.

8. (a) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 2130. (b) Kendurkar, P. S.; Tewari, R. S. *Ind. J. Chem., Sect. B* **1977**, *15B*, 290. (c) Bestmann, H. J.; Schlosser, W. *Synthesis* **1979**, 201. (d) Wittig, G.; Schoch-Gruebler, U. *J. Liebigs Ann. Chem.* **1978**, *2*, 362. (e) Abdel-Malek, H. A. *Egypt. J. Chem.* **2005**, *48*, 129.

9. (a) Ye, J.; Ge, J.; Chen, X.; Zhao, Z.; Lu, P. *Tetrahedron* **2007**, *63*, 11040. (b) Cadierno, V.; Diez, J.; Garcia-Garrido, S. E.; Gimeno, J.; Nebra, N. *Adv. Synth. Catal.* **2006**, *348*, 2125. (c) Hudgens, D. P.; Taylor, C.; Batts, T. W.; Patel, M. K.; Brown, M. L. *Bioorg. Med. Chem.* **2006**, *14*, 8366. (d) Lukes, V.; Vegh, D.; Hrdlovic, P.; Stefko, M.; Matuszna, K.; Laurinc, V. *Synth. Met.* **2005**, *148*, 179.

10. (a) Fernandez, F.; Gomez, G.; Lopez, C.; Santos, A. *Synthesis* **1988**, 802. (b) Amin, S.; Balanikas, G.; Huie, K.; Hussain, N.; Geddie, J. E.; Hecht, S. S. *J. Org. Chem.* **1985**, *50*, 4642. (c) Tomioka, H.; Okuno, A.; Sugiyama, T.; Murata, S. *J. Org. Chem.* **1995**, *60*, 2344.

11. (a) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827. (b) Kanno, K. I.; Liu, Y.; Iesato, A.; Nakajima, K.; Takahashi, T. *Org. Lett.* **2005**, *7*,

5453. (c) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535. (d) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Eur. J. Org. Chem.* **2003**, *7*, 1238.

12. (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265.
13. (a) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435. (b) Larock, R. C. In *Topics in Organometallic Chemistry*; Springer: Berlin, Germany, 2005; p 147.
14. (a) For reviews on the use of arynes in organic synthesis, see: (a) Kessar, S. V. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, NY, 1991; Vol. 4, p 483. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.
15. (a) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **1999**, *1*, 1555. (c) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **2000**, *2*, 1629.
16. Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
17. (a) Yoshida, H.; Honda, Y.; Shirakawa, E.; Hiyama, T. *Chem. Commun.* **2001**, 1880. (b) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247. (c) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673. (d) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99.
18. (a) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (b) Zhang, X.; Larock, R. C. *Org. Lett.* **2005**, *7*, 3973. (c) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (d) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347.

19. Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219.

20. (a) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (b) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340.

21. Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 7342.

22. Grigg, R.; Kennewell, P.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 153.

23. Matveenko, M.; Kokas, O. J.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 3683.

24. Solodenko, W.; Kunz, U.; Jas, G.; Kirschning, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1833.

25. Grigg, R.; Inman, M.; Kilner, C.; Koppen, I.; Marchbank, J.; Selby, P.; Sridharan, V. *Tetrahedron* **2007**, *63*, 6152.

26. Métay, E.; Léonel, E.; Sulpice-Gaillet, C.; Nédélec, J. Y. *Synthesis* **2005**, 1682.

27. Davey, W.; Gwilt, J. R. *J. Am. Chem. Soc.* **1957**, *79*, 1015.

28. Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505.

29. Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804.

30. Ksander, G. M.; de Jesus, R.; Yuan, A.; Ghai, Y. R. D.; Trapani, A.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 495.

31. (a) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *Organometallics* **2005**, *24*, 156. (b) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5052.

32. Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589.

33. Rapson, W. S.; Shuttleworth, R. G. *J. Chem. Soc.* **1941**, 487.

34. Dibbiase, S. A.; Lipisko, B. A.; Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640.

35. Rivero, I. A.; Heredia, S.; Ochoa, A. *Synth. Commun.* **2001**, *31*, 2169.

36. Hayashi, T.; Ishigedani, M. *Tetrahedron* **2001**, *57*, 2589.

37. Worlikar, S. A.; Larock, R. C. (To be submitted to the *Journal of Organic Chemistry*)

CHAPTER 4. HIGHLY SUBSTITUTED INDOLE LIBRARY SYNTHESIS BY PALLADIUM-CATALYZED COUPLING REACTIONS IN SOLUTION AND ON A SOLID SUPPORT

Based on a paper to be submitted to the *Journal of Combinatorial Chemistry*[20]

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Abstract

3-Iodoindoles have been synthesized mainly by the iodocyclization of *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines, obtained by the Pd/Cu catalyzed coupling of terminal acetylenes with *N*,*N*-dialkyl-*o*-iodoanilines. These 3-iodoindoles undergo palladium-catalyzed Sonogashira and Suzuki coupling reactions to yield 1,2,3-trisubstituted indoles. These reactions have been applied to parallel library synthesis utilizing commercially available terminal acetylenes and boronic acids. The aforementioned chemistry has also been carried out on a chlorinated Wang resin as a solid support, affording 1,2,3,5-tetrasubstituted indoles after cleavage. A diverse 42-member library of highly substituted indoles has been synthesized.

Introduction

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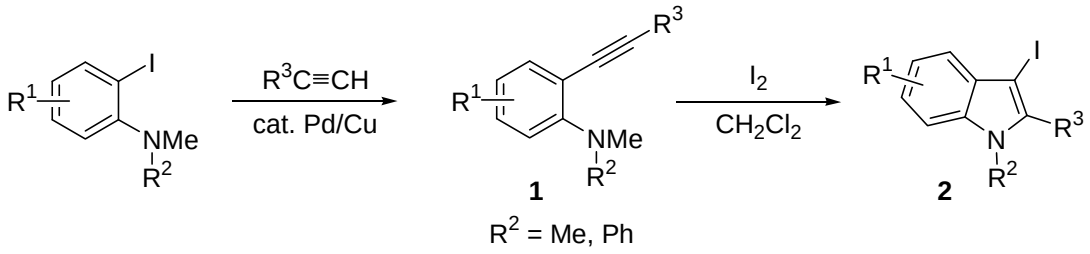
Indoles are very important in medicinal chemistry and the indole moiety is prevalent in numerous naturally-occurring and synthetic biologically active compounds.[1] It is one of the most important nitrogen-containing pharmacophores,[2] and is present in various drugs.[1b,1g] Due to the importance of the indole nucleus, many synthetic approaches to this ring system have been developed in our research group and reported in the literature for the synthesis of substituted indoles.[3] Biologically active natural products are a good indicator of lead structures that might possess biological activity. Due to the biological importance of compounds containing the indole nuclei, it is quite likely that the libraries of low molecular weight indoles will display similar activity and thus serve as valuable tools for drug development. Several methods are known for the synthesis of indoles in solution phase[4] and on a solid support[5] by combinatorial methods, but 3-iodoindoles have not previously been examined as key intermediates for indole library synthesis.

Yamanaka *et al.* have reported the coupling of 3-iodoindoles with terminal acetylenes, but satisfactory results were obtained only when the N atom of the indole was protected with an electron-withdrawing 1-methanesulfonyl group.[6] With an electron-donating group on the N atom of the 3-iodoindole, the C-I bond is electron-rich and this appears to limit further functionalization at the 3 position of the indole by palladium-catalyzed coupling reactions.

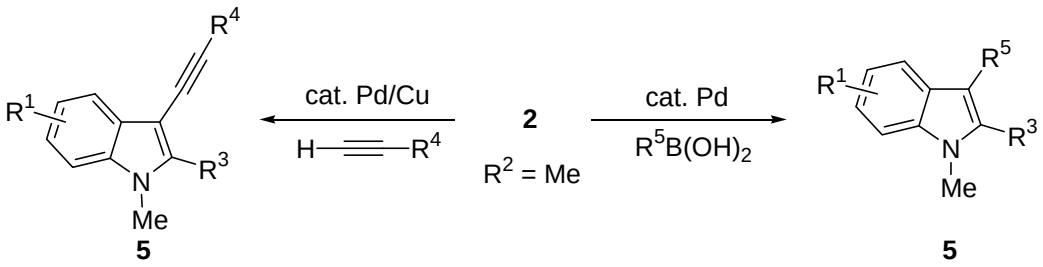
Previously, in our laboratory, we have synthesized *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines (**1**) by coupling terminal acetylenes with *N*,*N*-dialkyl-*o*-iodoanilines in the presence of a Pd/Cu catalyst, which on iodocyclization yield 3-iodoindoles (**2**) in excellent yields (Scheme 1).[7] We have previously reported individual examples of Sonogashira[8] and Suzuki-Miyaura[9]

cross-coupling reactions, which provide the corresponding 1,2,3-trisubstituted indoles in good yields (Scheme 2).[6b] We further optimized each of these processes in order to adapt

Scheme 1



Scheme 2

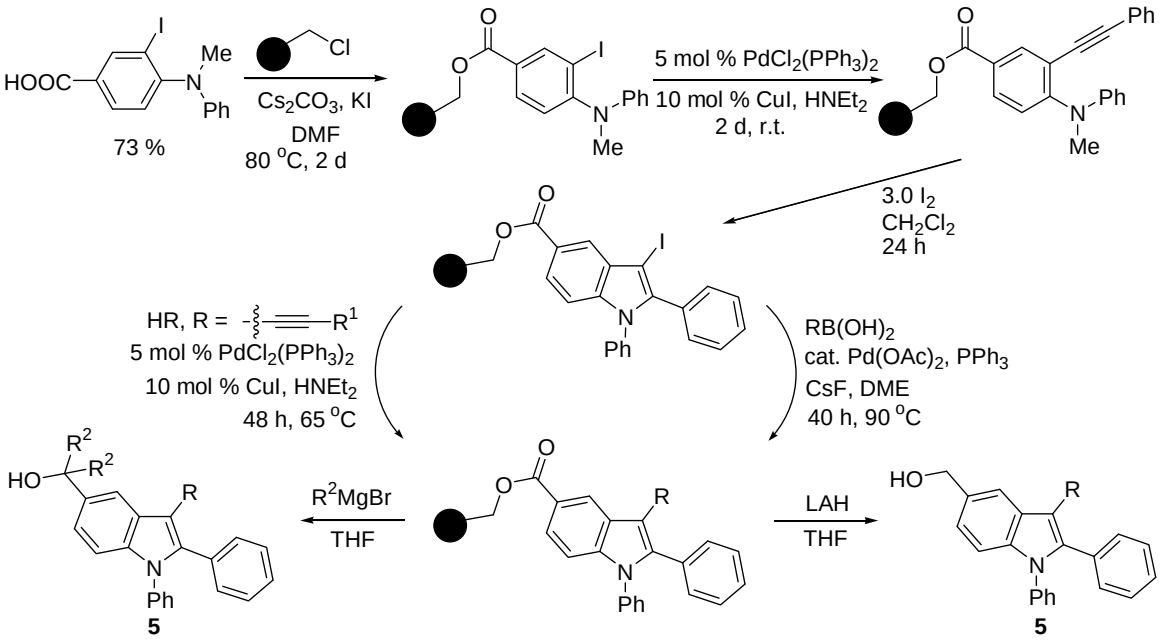


them for library generation. We have previously also reported individual examples of these two coupling reactions on a solid support, followed by cleavage by base.[10] The development of a solid phase version of this chemistry allows the multistep synthesis of highly substituted indoles and eliminates cumbersome purification steps. We herein report the successful synthesis of 1,2,3,5-tetrasubstituted indoles on a solid support by slight modifications of our earlier procedure and alternative cleavage reactions (Scheme 3).

Results and Discussion

Our previous work on 3-iodoindole synthesis reported good yields of single cyclization products if R^2 is a methyl or a phenyl group in the corresponding *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines (**1**). After the iodocyclization step in the former case, the N-atom of the

Scheme 3



3-iodoindole is protected by a methyl group, and, in the latter case, by a phenyl group. Our desire for a low molecular weight indole library led us to choose methyl as the *N*-protecting group. Therefore, our choice of R^2 was a methyl group in our solution phase library synthesis. 3-Iodoindole **2**{1} was synthesized as our basic scaffold by using our previous cyclization method.[7] The 3-iodoindoles **2**{2} and **2**{3} were similarly synthesized from the corresponding *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines **1**. Due to certain limitations in the types of R^1 and R^2 groups that can be employed in our iodocyclization methodology, we synthesized the 3-iodoindoles **2**{4}[11] and **2**{5}[12] by literature methods, while the 3-iodoindole **2**{6} was

obtained by treatment of **2**{5} with $NaBH_4$. Accordingly, we choose a subset of various 3-iodoindoles on the basis of the ease of synthesis from readily available starting materials and with different electron-donating and electron-withdrawing functionalities at the 2-position of the indoles (Figure 1).

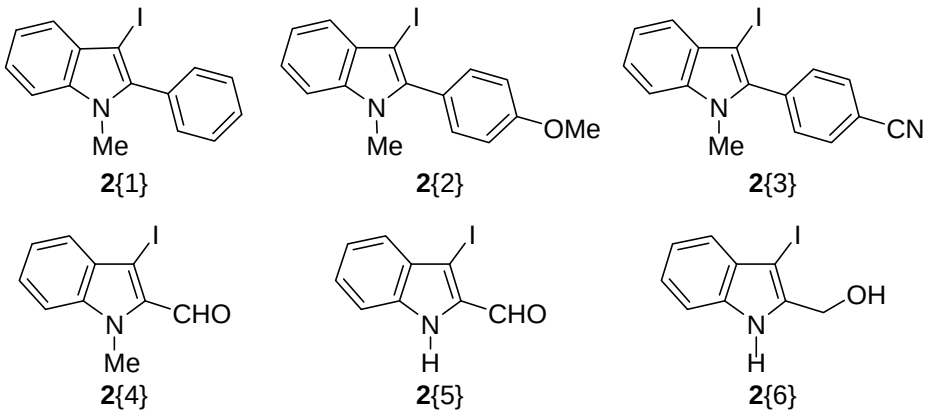


Figure 1. 3-Iodoindole sublibrary.

The terminal alkyne sublibrary was chosen on the basis of commercially available acetylenes. Attempts were made to include heteroatoms in the acetylenes that could impart drug-like, hydrogen bond donor and/or acceptor properties to the indoles after Sonogashira coupling (Figure 2). For similar reasons, acetylenes **3**{5} and **3**{8} were chosen due to the increasing popularity of fluorine[13] and sulfur[14] atoms in drug molecules.

The boronic acids for the Suzuki-Miyaura reactions were also chosen on the basis of their commercial availability and their ability to provide the requisite diversity and drug-like properties to the indole scaffold after subsequent cross-coupling reactions (Figure 3). For instance, the methoxy-containing boronic acids **4**{1} and **4**{2} were chosen with a view towards increasing the polarity of the substituted indole. The *N*-heterocyclic boronic acids

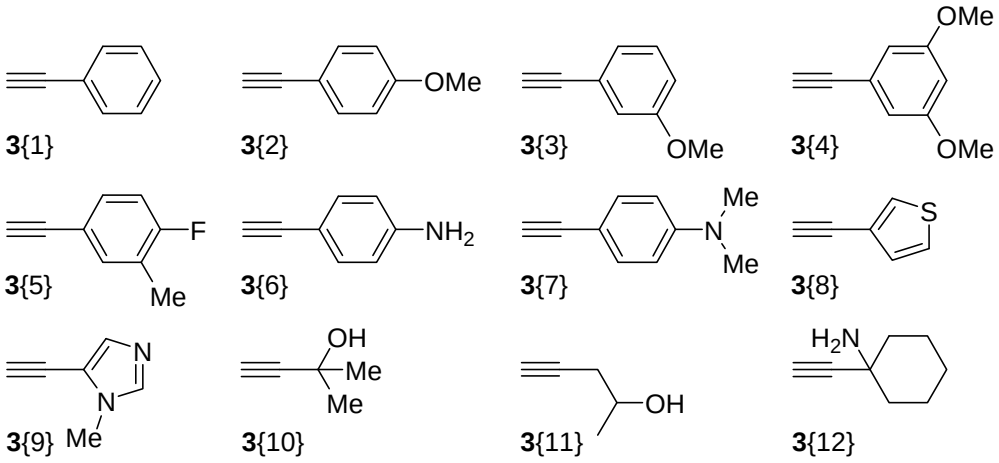


Figure 2. Terminal acetylene sublibrary.

4{3}, **4**{4} and the indolylboronic acid **4**{9}, were chosen to increase the drug-like nature of the corresponding indoles. The fluorine-containing acids **4**{8} and **4**{10} were desirable due to the importance of fluorine in medicinal chemistry.

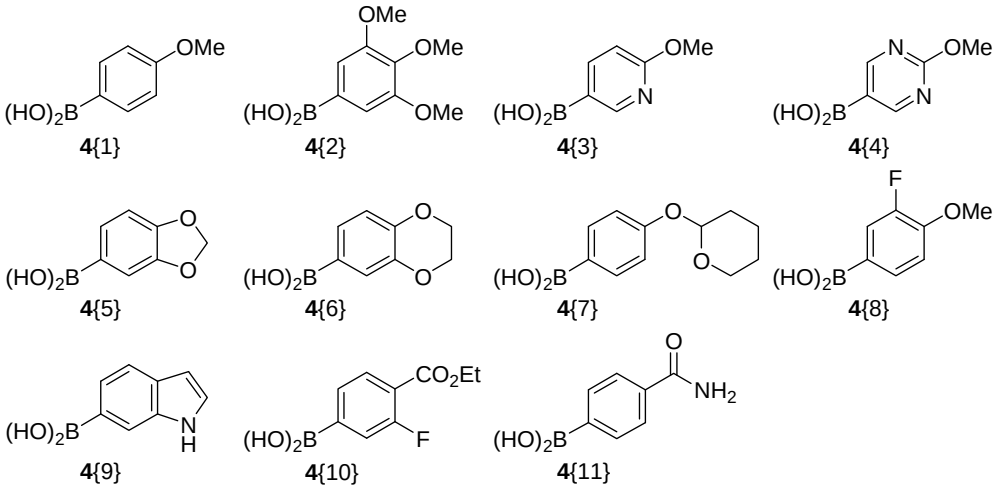
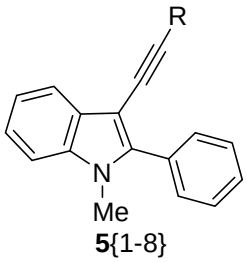


Figure 4. Boronic acid sublibrary.

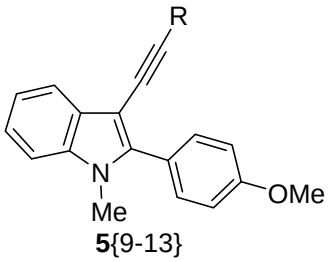
Having chosen these sublibraries, we proceeded to prepare a diverse library of 1,2,3-trisubstituted indoles via solution phase chemistry as outlined in Scheme 2 and 1,2,3,5-tetrasubstituted indoles using a chlorinated Wang resin as the solid support as depicted in Scheme 3. The crude products have been analyzed by LC/MS, followed by purification by preparative HPLC or flash chromatography.

A summary of the results of the library synthesis is provided in Tables 1-3. Most of the crude products were subjected to preparative HPLC. Purities in the range of 70-100% have been achieved after purification. Most of the Sonogashira coupling reactions proceeded well, except for those run with the terminal alkynes **3**{11} and **3**{12}. Suzuki-Miyaura

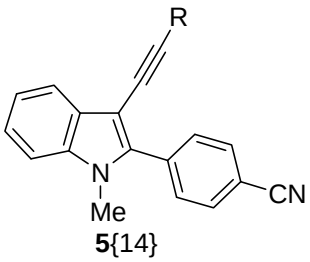
Table 1. Library Data for Compounds **5**{1-29}



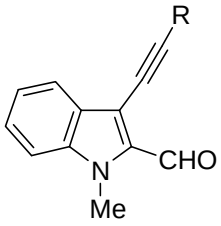
5{1-8}



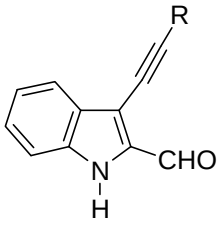
5{9-13}



5{14}



5{15-20}



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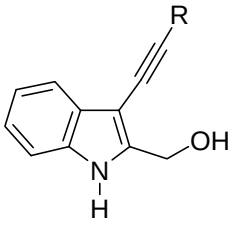


5{26-29}

compound	R	yield[a] (%)	purity[b] (%)
5{1}	4-$MeOC_6H_4$	12	97
5{2}	3,5-dimethoxyphenyl	38	94
5{3}	4-fluoro-3-methylphenyl	47	99
5{4}	4-$H_2NC_6H_4$	27	95

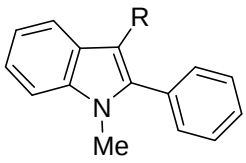
Table 1. Continued

compound	R	yield[a] (%)	purity[b] (%)
5{5}	4-$Me_2NC_6H_4$	30	79
5{6}	1-amino-1-cyclohexyl	-	-
5{7}	2-hydroxypropyl	-	-
5{8}	(1-hydroxy-1-methyl)ethyl	13	70
5{9}	C_6H_5	43	99
5{10}	3,5-dimethoxyphenyl	34	98
5{11}	4-$Me_2NC_6H_4$	59	97
5{12}	3-thiophenyl	20	93
5{13}	(1-hydroxy-1-methyl)ethyl	33	90
5{14}	C_6H_5	45	98
5{15}	C_6H_5	89	100
5{16}	4-$MeOC_6H_4$	90	97
5{17}	3-$MeOC_6H_4$	79	95
5{18}	3,5-dimethoxyphenyl	94	91
5{19}	1-methyl-1*H*-imidazol-5-yl	82	90
5{20}	(1-hydroxy-1-methyl)ethyl	77	95
5{21}	C_6H_5	52	100
5{22}	3,5-dimethoxyphenyl	52	90
5{23}	1-methyl-1*H*-imidazol-5-yl	36	98
5{24}	3-thiophenyl	76	93
5{25}	(1-hydroxy-1-methyl)ethyl	43	96
5{26}	4-$MeOC_6H_4$	21	86
5{27}	3-$MeOC_6H_4$	36	92
5{28}	3,5-dimethoxyphenyl	3	100
5{29}	(1-hydroxy-1-methyl)ethyl	13	95

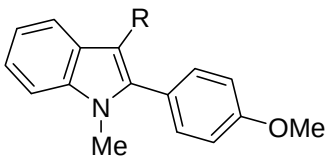
[a] Isolated yield after preparative HPLC.
[b] UV purities determined at 214 nm after preparative HPLC.

reactions with the boronic acids **4**{10} and **4**{11} with electron-withdrawing groups failed to give the desired coupling products. The boronic acids **4**{3} and **4**{8} gave decent yields of the coupling products **5**{32} and **5**{33} and excellent purities when reacted with 3-iodoindole **2**{2}, but failed to give the corresponding trisubstituted indoles when coupled with 3-iodoindole **2**{3}. On the solid support, the cleavage by MeMgBr was successful, but EtMgBr failed to give the anticipated products. Out of a total of 51 palladium-catalyzed processes attempted, around 80% were successful.

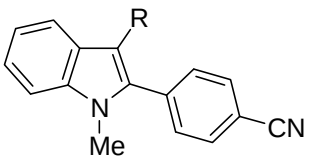
Table 2. Library Data for Compounds **5**{30-45}



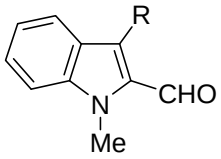
5{30}



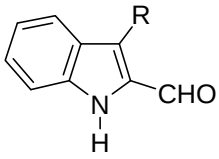
5{31-37}



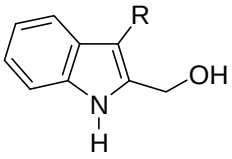
5{38-39}



5{40-42}



5{43-44}



5{45}

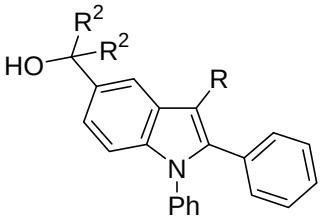
compound	Ar	yield[a] (%)	purity[b] (%)
5{30}	4-$MeOC_6H_4$	23	100
5{31}	3,4,5-trimethoxyphenyl	79	83
5{32}	3-fluoro-4-methoxyphenyl	42	100
5{33}	2-methoxy-5-pyridinyl	50	98
5{34}	benzo[1,3]dioxol-5-yl	39	99
5{35}	2-methoxy-5-pyrimidinyl	59	99
5{36}	4-$H_2NC(O)C_6H_4$	-	-
5{37}	4-EtO_2C-3-FC_6H_3	-	-
5{38}	3-fluoro-4-methoxyphenyl	-	-

Table 2. Continued

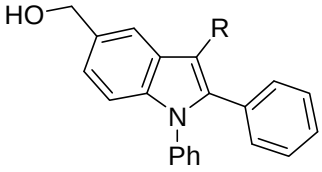
compound	Ar	yield[a] (%)	purity[b] (%)
5{39}	2-methoxy-5-pyridinyl	-	-
5{40}	2,3-dihydrobenzo[1,4]dioxin-6-yl	84	89
5{41}	2-methoxy-5-pyrimidinyl	2	100
5{42}	6-indolyl	25	94
5{43}	benzo[1,3]dioxol-5-yl	9	100
5{44}	6-indolyl	-	-
5{45}	4-(tetrahydropyran-2-yloxy)phenyl	9	91

[a] Isolated yield after preparative HPLC.
[b] UV purities determined at 214 nm after preparative HPLC.

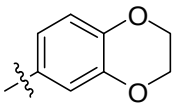
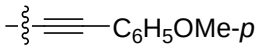
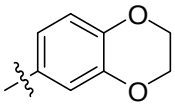
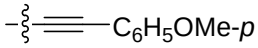
Table 3. Library Data for Compounds **5**{14-45}



5{46} : R^2 = Me
5{47-48} : R^2 = Et



5{49-51}

compound	R	yield[a] (%)	purity[b] (%)
5{46}	C_6H_5	69[c]	<90[d]
5{47}		-	
5{48}		-	
5{49}	C_6H_5	60[c]	<90[d]
5{50}		54	91
5{51}		64	95

[a] Isolated yield after preparative HPLC.
[b] UV purities determined at 214 nm after preparative HPLC.

[c] Isolated yield after flash chromatography.
[d] Purities determined by H^1 NMR spectroscopy after flash chromatography.

Our goal in synthesizing these low molecular weight heterocycles is for use in high-throughput screening projects. Therefore, we carried out an *in silico* evaluation of these library members to determine their agreement with Lipinski's[15] "rule of five" and Veber's rules.[16] The SYBYL[17] program was used for the calculation of molecular weight, clog P, the number of hydrogen bond donors and acceptors, and the number of rotatable bonds for each library member (Table 4). According to these rules a potential drug molecule is more drug-like and more bioavailable if the clog P value is not more than 5, the molecular weight is less than 500, the hydrogen bond acceptors are not more than 10, the hydrogen bond donors are not more than 5, and the rotatable bonds in the molecule are not more than 12. One Lipinski violation is allowed for potential drug design. All of the indole library members are Lipinski compliant and no molecule has more than one Lipinski violation. The only violation that a molecule in the library had was clog P, which points towards potential solubility and delivery issues.

Table 4. *In silico* parameters for gauging oral availability / drug-likeness

	Mean	St. Dev.	Range
Clog P	5.1	1.9	0.6 - 8.0
Mol. Weight	317	53	227-433
H-Bond Acceptors	2.0	0.9	0 - 4
H-Bond Donors	0.8	0.8	0 - 3
Rotatable Bonds	4.1	1.1	2 - 6

Conclusions

In conclusion, the synthesis of 4-iodoindoles and subsequent palladium-catalyzed Sonogashira and Suzuki-Miyaura cross-coupling reactions with various commercially available terminal alkynes and boronic acids have allowed the construction of a 42-member library of highly substituted indoles. The chemistry has been successfully transferred to a solid support and diversity has been achieved at the 5-position by different cleavage reactions. The average yield of the library was 46% and the average purity after purification was 94%.

Experimental Section

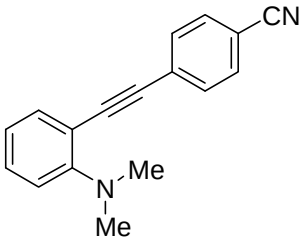
General The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All reagents were used directly as obtained commercially unless otherwise noted. THF and CH_2Cl_2 were distilled from sodium/benzophenone or CaH_2 respectively, under an atmosphere of argon prior to use. All glassware and stirring bars were oven dried prior to use.

HPLC analysis was carried out using an XBridge MS C-18 column (5 μM, 4.6 × 150 mm) with gradient elution (5% CH_3CN to 100% CH_3CN) on a Waters Alliance 2795 Separation Module with a Waters 2996 Photodiode Array UV detector and a Waters/Micromass LCT Premier (TOF) detector. Purification was carried out using an XBridge MS C-18 column (5 μM, 19 × 150 mm) with a gradient elution (a narrow CH_3CN gradient was chosen based on the targets retention time from the LCMS analysis of the crude

sample) on a Mass Directed Fractionation instrument with a Waters 2767 sample manager, a Waters 2525 HPLC pump, a Waters 2487 dual λ absorbance detector, and a Waters/Micromass ZQ (quadrupole) detector. Fractions were triggered using a MS and/or UV threshold determined by an LCMS analysis of the crude sample. One of three aqueous mobile phases were chosen for both analysis and purification to promote the targets neutral state (water, 0.05% formic acid or pH 9.8 1mM HCO_2NH_4). High resolution mass spectra (HRMS) were obtained using a Waters/Micromass LCT Premier (TOF instrument).

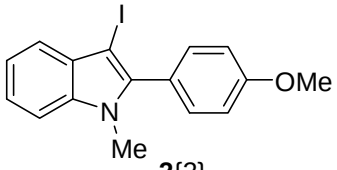
[2-(4-Methoxyphenylethynyl)phenyl]dimethylamine was prepared by literature procedure.[18]

General procedure for the palladium/copper-catalyzed synthesis of *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines.[7] In a 100 ml round bottom flask, $PdCl_2(PPh_3)_2$ (0.2 mmol, 140.2 mg) and CuI (0.1 mmol, 19.0 mg) was added to a solution of *N*,*N*-dimethyl-*o*-iodoaniline (10.0 mmol, 2.47 g) in Et_3N (15 ml). The flask was then sealed and flushed with Ar. The reaction mixture was stirred for 20 min at room temperature. A solution of the corresponding alkyne (12.0 mmol) in Et_3N (10 mL) and DMF (10 ml) was then added dropwise and the reaction mixture was allowed to stir at 50 ^oC till completion of the reaction which was monitored by TLC. After the reaction was over, the resulting solution was diluted with H_2O (25 ml) and extracted with EtOAc (3 x 20 mL). The combined EtOAc 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 to afford the desired *N*,*N*-dialkyl-*o*-(1-alkynyl)aniline.



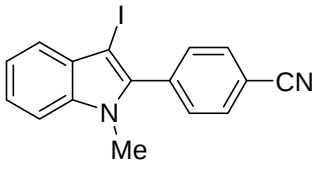
4-(2-Dimethylaminophenylethynyl)benzonitrile. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded 1.67 g (68%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.99 (s, 6H), 6.88-6.95 (m, *2*H), 7.25-7.31 (m, 1H), 7.47-7.49 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.58-7.63 (m, 4H); ^{13}C NMR δ 43.72, 93.20, 93.83, 111.21, 113.94, 117.22, 118.83, 120.65, 128.98, 130.35, 131.81, 132.19, 134.72, 155.23; HRMS Calcd for $C_{17}H_{14}N_2$: 246.11570. Found: 246.11610.

General procedure for iodocyclization. To a solution of *N*,*N*-dialkyl-*o*-(1-alkynyl)aniline (1.0 mmol) in CH_2Cl_2 (10 ml), I_2 (2 mmol, 508 mg) dissolved in CH_2Cl_2 (10 mL) was added gradually. The reaction mixture was allowed to stir at room temperature for the desired time. The reaction was monitored by TLC. After the completion of the reaction, the excess I_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by CH_2Cl_2 (3 x 10 mL). The combined CH_2Cl_2 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 hexanes/ethyl acetate as the eluent to afford the desired 3-iodoindole.



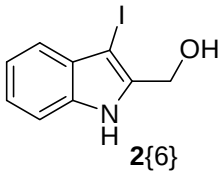
2{2}

3-Iodo-2-(4-methoxyphenyl)-1-methyl-1H-indole 2{2}. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded 0.28 g (79%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.65 (s, 3H), 3.87 (s, 3H), 7.01-7.04 (d, *J* = 8.6 Hz, 2H), 7.20-7.24 (m, 1H), 7.28-7.29 (d, *J* = 3.6 Hz, 2H), 7.36-7.39 (d, *J* = 8.7 Hz, 2H), 7.47-7.49 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 32.14, 55.53, 58.95, 109.96, 114.04, 120.79, 121.45, 122.88, 123.92, 130.47, 132.31, 137.81, 141.81, 160.05; HRMS Calcd for $C_{16}H_{14}ONI$: 363.01202. Found: 363.01253.



2{3}

4-(3-Iodo-1-methyl-1H-indol-2-yl)benzonitrile 2{3}. Purification by flash chromatography (20:1 hexanes/EtOAc) afforded 0.17 g (48%) of the product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 (s, 3H), 7.23-7.27 (m, 1H), 7.30-7.36 (m, 2H), 7.49-7.51 (d, *J* = 7.8 Hz, 1H), 7.56-7.59 (d, *J* = 8.2 Hz, 2H), 7.76-7.78 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR δ 32.40, 60.39, 110.20, 112.47, 118.65, 121.32, 121.96, 123.93, 130.44, 131.70, 132.32, 136.33, 138.23, 139.45; HRMS Calcd for $C_{16}H_{11}N_2I$: 357.99670. Found: 357.99728.



2{6}

Procedure for the preparation of (3-iodo-1H-indol-2-yl)methanol 2{6}. A modified literature procedure was used.[19] In a 100 mL flask to a solution of 3-Iodo-1H-indole-2-carbaldehyde (3.0 mmol, 0.825 g) in anhydrous THF (20 ml), $NaBH_4$ (6 mmol,)

was added and the reaction mixture was refluxed for 5h. After the completion of the reaction which was monitored by TLC, the reaction mixture was cooled to room temperature and the excess $NaBH_4$ was quenched by slow addition of water (20 ml). THF was removed under reduced pressure. The solid residue was filtered, washed with cold water and dried to afford 0.60 g (74%) of the desired (3-iodo-1H-indol-2-yl)methanol. : ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82 (s, 2H), 7.15-7.28 (m, 4H), 7.39-7.41 (d, *J* = 7.5 Hz, 1H), 8.84 (s, 1H); ^{13}C NMR δ 57.75, 59.18, 111.53, 120.96, 121.03, 123.50, 130.42, 136.15, 137.95; HRMS Calcd for C_9H_9ONI: 273.96507. Found: 273.96562.

General procedure for Sonogashira coupling in solution phase. To a 4-dram vial was added the appropriate 3-iodoindole (0.2 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol, 7.0 mg), CuI (0.005 mmol, 1.0 mg), Et_3N (1.5 mL), DMF (1.5 mL) and the acetylene (0.3 mmol). The reaction mixture was flushed with argon and stirred for 10 minutes at room temperature. It was then heated to 65 ^oC until TLC revealed complete conversion of the starting material. After the reaction was over, the resulting solution was diluted with H_2O (10 ml) and extracted with EtOAc (2 x 10 mL). The combined EtOAc fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The residue was purified by preparative HPLC.

General procedure for Suzuki-Miyaura cross-coupling in solution phase. To a 4-dram vial was added the appropriate 4-iodoindole (0.2 mmol), the aryl boronic acid (0.3 mmol), $Pd(PPh_3)_4$ (0.02 mmol, 23.1 mg) and KOH (1.6 mmol, 89.6 mg) in 5:1 $PhCH_3$:EtOH (3.0 mL). Few drops of water were added to the reaction mixture which was stirred at 90 ^oC

until TLC revealed complete conversion of the starting material. The reaction mixture was cooled, diluted with EtOAc (15 ml) and filtered through celite. The celite-bed was washed with EtOAc. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC.

General Procedure for Coupling the Acid to the Polymer-bound 4-(Benzyloxy)benzyl Chloride Resin. Chlorinated Wang resin (3.73 g, 0.75 mmol/g) was placed in dry DMF (40 mL) for 10 min. After addition of 3-iodo-4-[methyl(phenyl)amino]benzoic acid (1.25 g, 1.5 equiv), Cs_2CO_3 (2.8 g, 3.0 equiv) and KI (0.23 g, 0.5 equiv), the mixture was stirred at 80 °C for 2 d. The reaction mixture was allowed to cool to room temperature and the resin was then filtered, washed with water (4 ×), DMF (4 ×), methanol (4 ×) and DCM (4 ×), and dried under vacuum overnight.

General procedure for the palladium/copper-catalyzed synthesis of *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines on solid support. In a 100 mL round bottom flask were placed the acid coupled polymer-bound resin (1.0 g, 0.6 mmol), $PdCl_2(PPh_3)_2$ (23 mg, 5 mol %) and CuI (12.5 mg, 10 mol %). Toluene (13 mL) was added and the reaction mixture was shaken for 5 min. $HNEt_2$ (13 mL) and the terminal acetylene (5.0 equiv) were added and the mixture was shaken at room temperature for 2 d. The polymer was filtered, washed successively with DMF (4 ×), MeOH (4 ×) and DCM (4 ×), and dried under vacuum overnight.

General procedure for iodocyclization on solid support. The appropriate polymer bound *N*,*N*-dialkyl-*o*-(1-alkynyl)aniline (800 mg) was placed in DCM (20 mL) for 5 min. I_2

(0.52 g, 4.0 equiv) was added and the mixture was shaken at room temperature for 24 h. The polymer was filtered, washed successively with DMF (4 ×), MeOH (4 ×) and DCM (4 ×), and dried under vacuum overnight.

General procedure for Sonogashira cross-coupling on solid support. In a 100 mL round bottom flask were placed the appropriate polymer-bound 3-iodoindole (0.5 g, ~0.3 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 5 mol %) and CuI (6.0 mg, 10 mol %). Toluene (7 mL) was added and the reaction mixture was shaken for 5 min. $HNEt_2$ (7 mL) and the terminal acetylene (5.0 equiv) were added and the mixture was stirred at 65 ^oC for 2 d. The polymer was filtered, washed successively with DMF (4 ×), MeOH (4 ×) and DCM (4 ×), and dried under vacuum overnight.

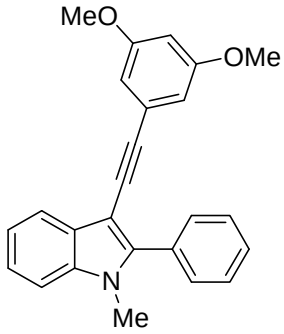
General procedure for Suzuki-Miyaura cross-coupling on solid support. In a 100 mL round bottom flask were placed the appropriate polymer-bound 3-iodoindole (0.5 g, ~0.3 mmol), $Pd(OAc)_2$ (7.3 mg, 10 mol %), PPh_3 (16.7 mg, 20 mol %), CsF (14.2 mg, 4.4 equiv) and arylboronic acid (2.5 equiv). DME (15 mL) was added and the reaction mixture was heated at 90 °C for 48 h. The polymer was filtered, washed successively with DMF (4 ×), MeOH (4 ×) and DCM (4 ×), and dried under vacuum overnight.

General procedure for cleavage by Lithium Aluminum Hydride. A solution of LAH in THF (1.0 M, 2 mL) was added to a stirred suspension of the appropriate resin-bound indole (200 mg) in THF (4 mL) at 0 ^oC under inert atmosphere. The mixture was stirred at 0 ^oC for 2 h, diluted with THF (2 mL), and quenched with a saturated solution of Na^+K^+ tartrate (8.0 mL). The reaction was warmed to room temperature and stirred vigorously for 2

h. The resulting mixture was filtered and the resin was washed with CH_2Cl_2. The biphasic filtrate was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified either by flash chromatography or by preparative HPLC to give the final isolated yield of product based upon the loading of resin.

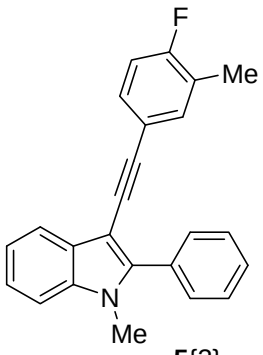
General procedure for cleavage by an alkyl magnesium bromide. A solution of alkyl magnesium bromide in THF (2.0 M, 1 mL) was added to a stirred suspension of the appropriate resin bound indole (200 mg) in THF (4 mL) at 0 ^oC under inert atmosphere. The mixture was gradually warmed to room temperature and stirred for 5 h. It was then quenched with satd solution of ammonium chloride (10 mL). The resulting mixture was filtered and the resin was washed with CH_2Cl_2. The biphasic filtrate was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified either by flash chromatography or by preparative HPLC to give the final isolated yield of product based upon the loading of resin.

Characterization data for representative library compounds.



5{2}

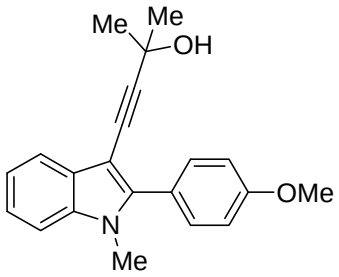
3-(3,5-Dimethoxyphenylethynyl)-1-methyl-2-phenyl-1*H*-indole 5{2}. Yield = 38%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 3H), 3.78 (s, 6H), 6.38-6.39 (t, *J* = 2.4 Hz, 1H), 6.59-6.596 (d, *J* = 2.4 Hz, 2H), 7.24-7.33 (m, 2H), 7.37-7.39 (m, 1H), 7.43-7.47 (m, 1H), 7.51-7.55 (m, 2H), 7.66-7.69 (m, 2H), 7.83-7.86 (m, 1H); ^{13}C NMR δ 31.89, 55.59, 84.22, 91.98, 96.83, 100.91, 109.10, 110.06, 120.27, 121.06, 123.14, 126.06, 128.58, 128.75, 128.94, 130.49, 130.96, 137.39, 144.27, 160.64.



5{3}

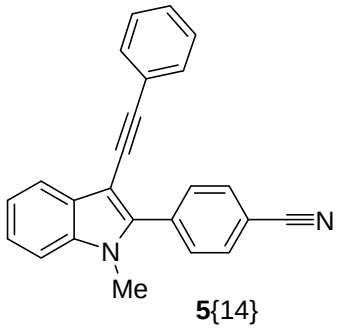
3-(4-Fluoro-3-methylphenylethynyl)-1-methyl-2-phenyl-1*H*-indole 5{3}. Yield = 47%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (d, *J* = 2.0 Hz, 3H), 3.75 (s, 3H), 6.89-6.94 (t, *J* = 9.6 Hz, 1H), 7.19-7.20 (m, 1H), 7.24-7.27 (m, 2H), 7.29-7.33 (m, 1H), 7.36-7.38 (m, 1H), 7.43-7.47 (m, 1H), 7.51-7.55 (m, 2H), 7.66-7.68 (m, 2H), 7.81-7.83 (m, 1H); ^{13}C NMR δ 14.61, 14.64, 31.87, 83.52, 91.01, 96.92, 110.05, 115.12, 115.35, 120.22, 120.39, 120.43,

121.00, 123.12, 125.02, 125.20, 128.59, 128.72, 128.97, 130.39, 130.46, 131.03, 134.34, 134.39, 137.38, 143.92, 159.58, 162.03 (extra peaks due to C-F splitting).



5{13}

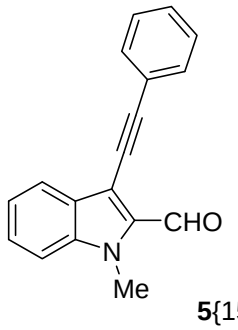
4-[2-(4-Methoxyphenyl)-1-methyl-1*H*-indol-3-yl]-2-methylbut-3-yn-2-ol 5{13}. Yield = 33%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59 (s, 6H), 3.71 (s, 3H), 3.88 (s, 3H), 7.01-7.04 (m, 2H), 7.18-7.29 (m, 3H), 7.32-7.34 (m, 1H), 7.52-7.55 (m, 2H), 7.69-7.71 (m, 1H); ^{13}C NMR δ 31.74, 31.93, 55.56, 66.16, 68.69, 95.61, 96.20, 109.86, 113.97, 119.85, 120.83, 122.76, 123.24, 129.01, 131.64, 137.15, 143.98, 159.94.



5{14}

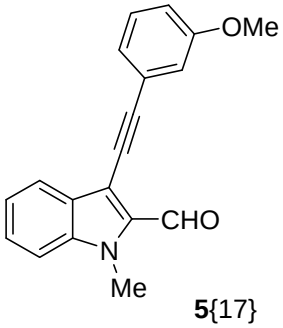
4-(1-Methyl-3-phenylethynyl-1*H*-indol-2-yl)benzonitrile 5{14}. Yield = 45%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.75 (s, 3H), 7.24-7.37 (m, 6H), 7.42-7.44 (m, 2H), 7.80 (s, 4H), 7.84-7.86 (dt, *J* = 7.6, 0.8 Hz, 1H); ^{13}C NMR δ 32.11, 83.38, 92.86, 98.73, 110.25, 112.03,

118.91, 120.65, 121.48, 124.10, 127.91, 128.56, 128.78, 130.85, 131.34, 132.34, 135.60, 137.91, 141.32.



5{15}

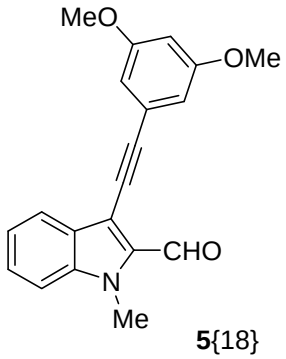
1-Methyl-3-phenylethynyl-1*H*-indole-2-carbaldehyde 5{15}. Yield = 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (s, 3H), 7.23-7.26 (m, 1H), 7.34-7.39 (m, 4H), 7.43-7.46 (m, 1H), 7.57-7.59 (m, 2H), 7.87-7.89 (m, 1H), 10.25 (s, 1H); ^{13}C NMR δ 31.96, 80.48, 97.08, 110.69, 111.97, 121.82, 122.32, 123.17, 127.72, 127.92, 128.64, 128.71, 131.68, 135.47, 139.62, 182.44.



5{17}

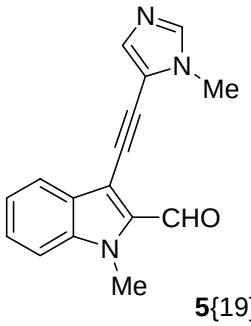
3-(3-Methoxyphenylethynyl)-1-methyl-1*H*-indole-2-carbaldehyde 5{17}. Yield = 79%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H), 4.07 (s, 3H), 6.91-6.93 (m, 1H), 7.09-7.10 (m, 1H), 7.17-7.19 (m, 1H), 7.23-7.30 (m, 3H)(one extra proton due to merger with $CDCl_3$ peak), 7.35-7.37 (d, J = 6.8 Hz, 1H), 7.44-7.47 (m, 1H), 7.88-7.90 (m, 1H), 10.2 (s, 1H); ^{13}C

NMR δ 31.98, 55.50, 80.32, 97.01, 100.93, 110.71, 111.89, 115.34, 116.32, 121.85, 122.34, 124.27, 127.74, 127.95, 129.73, 135.54, 139.64, 159.54, 182.46.



5{18}

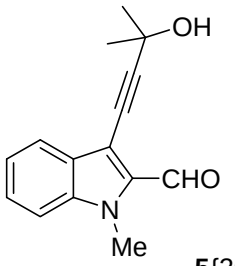
3-(3,5-Dimethoxyphenylethynyl)-1-methyl-1*H*-indole-2-carbaldehyde 5{18}. Yield = 94%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 6H), 4.06 (s, 3H), 6.48-6.49 (t, *J* = 2.0 Hz, 1H), 6.71-6.73 (m, 2H), 7.23-7.26 (m, 2H)(one extra proton due to merger with $CDCl_3$ peak), 7.35-7.36 (d, *J* = 6.8 Hz, 1H), 7.43-7.46 (m, 1H), 7.88-7.89 (d, *J* = 6.8 Hz, 1H), 10.25 (s, 1H); ^{13}C NMR δ 31.95, 55.62, 80.08, 97.08, 102.13, 109.34, 110.70, 111.76, 121.84, 122.31, 124.43, 127.71, 127.93, 135.57, 139.61, 160.74, 182.42.



5{19}

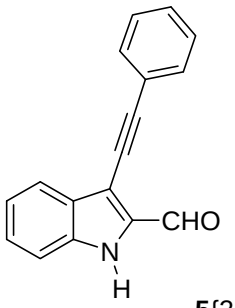
1-Methyl-3-(3-methyl-3*H*-imidazol-4-ylethynyl)-1*H*-indole-2-carbaldehyde 5{19}. Yield = 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H), 4.06 (s, 3H), 7.25-7.28 (m, 1H), 7.37-7.41 (m, 2H), 7.45-7.49 (m, 1H), 7.53 (s, 1H), 7.81-7.83 (m, 1H), 10.20 (s, 1H);

^{13}C NMR δ 31.96, 32.33, 84.29, 87.55, 110.79, 116.27, 122.03, 127.43, 128.02, 128.57, 132.11, 134.71, 135.28, 138.73, 139.50, 181.84.



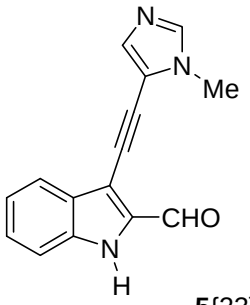
5{20}

3-(3-Hydroxy-3-methylbut-1-ynyl)-1-methyl-1*H*-indole-2-carbaldehyde 5{20}. Yield = 77%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 6H), 3.21 (broad s, 1H), 3.93 (s, 3H), 7.16-7.19 (m, 1H), 7.22-7.24 (d, *J* = 6.8 Hz, 1H), 7.36-7.39 (m, 1H), 7.72-7.74 (m, 1H), 10.08 (s, 1H); ^{13}C NMR δ 31.70, 65.89, 72.93, 98.43, 101.94, 110.52, 111.49, 121.61, 122.02, 127.55, 127.80, 135.35, 139.35, 182.51.



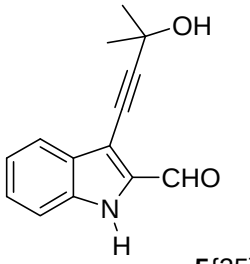
5{21}

3-Phenylethynyl-1*H*-indole-2-carbaldehyde 5{21}. Yield = 52%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.29 (m, 1H), 7.39-7.48 (m, 5H), 7.61-7.63 (m, 2H), 7.92-7.93 (dd, *J* = 6.4, 0.4 Hz, 1H), 9.43 (broad s, 1H), 10.16 (s, 1H); ^{13}C NMR δ 80.19, 96.88, 110.21, 112.90, 122.10, 122.48, 123.04, 128.39, 128.73, 128.80, 128.95, 131.87, 136.32, 137.17, 181.29.



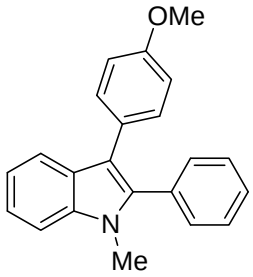
5{23}

3-(3-Methyl-3*H*-imidazol-4-ylethynyl)-1*H*-indole-2-carbaldehyde 5{23}. Yield = 36%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (s, 3H), 7.22-7.30 (m, 2H) (one extra proton due to merger with $CDCl_3$ peak), 7.45-7.47 (m, 3H), 7.58 (s, 1H), 7.86-7.87 (d, *J* = 6.4 Hz, 1H), 9.27 (broad s, 1H), 10.12 (s, 1H); ^{13}C NMR δ 68.20, 84.16, 98.66, 108.16, 112.94, 122.27, 122.39, 128.52, 128.59, 130.44, 135.17, 136.26, 136.95, 138.95, 180.74.



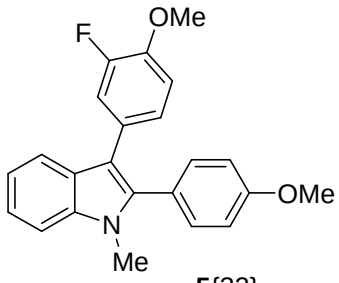
5{25}

3-(3-Hydroxy-3-methylbut-1-ynyl)-1*H*-indole-2-carbaldehyde 5{25}. Yield = 43%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 6H), 7.41-7.55 (m, 3H), 7.65-7.69 (m, 1H), 7.79-7.81 (dd, *J* = 6.4, 0.8 Hz, 1H), 9.29 (broad s, 1H), 10.03 (s, 1H); ^{13}C NMR δ 31.79, 66.17, 101.44, 108.16, 109.43, 112.80, 122.04, 128.31, 128.68, 132.27, 136.41, 136.96, 181.21.



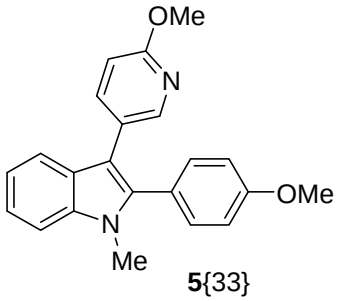
5{30}

3-(4-Methoxyphenyl)-1-methyl-2-phenyl-1*H*-indole 5{30}. Yield = 23%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 3H), 3.79 (s, 3H), 6.81-6.83 (m, 2H), 7.16-7.24 (m, 3H), 7.27-7.41 (m, 7H), 7.74-7.76 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 31.37, 55.30, 109.72, 113.96, 114.94, 119.80, 120.21, 122.33, 127.35, 127.76, 128.12, 128.59, 131.12, 131.43, 132.26, 137.64, 157.80, 167.48.



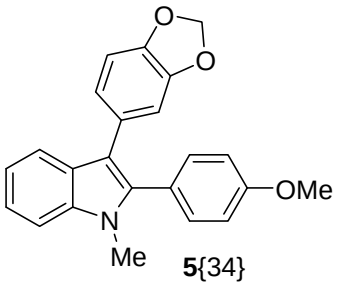
5{32}

3-(3-Fluoro-4-methoxyphenyl)-2-(4-methoxyphenyl)-1-methyl-1*H*-indole 5{32}. Yield = 42%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 6.84-6.93 (m, 3H), 6.99-7.04 (m, 2H), 7.15-7.282 (m, 3H), 7.285-7.30 (m, 1H), 7.37-7.39 (d, *J* = 8.0 Hz, 1H), 7.72-7.74 (m, 1H); ^{13}C NMR δ 31.02, 55.46, 56.41, 109.76, 113.44, 113.46, 113.57, 114.20, 117.39, 117.57, 119.37, 120.40, 122.27, 123.98, 125.61, 125.64, 127.03, 128.87, 128.94, 132.45, 137.29, 137.80, 145.55, 145.66, 151.15, 153.58, 159.70 (extra peaks due to fluorine splitting).



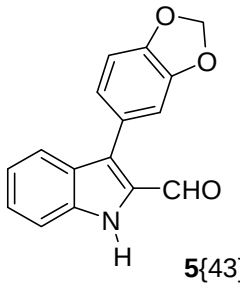
5{33}

2-(4-Methoxyphenyl)-3-(6-methoxypyridin-3-yl)-1-methyl-1*H*-indole 5{33}. Yield = 50%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 6.66-6.68 (dd, *J* = 8.8, 0.8 Hz, 1H), 6.91-6.93 (m, 2H), 7.16-7.28 (m, 3H), 7.29-7.31 (m, 1H), 7.39-7.41 (d, *J* = 8.0 1H), 7.45-7.47 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.70-7.72 (d, *J* = 8.0 1H), 8.17 (dd, *J* = 2.4, 0.4 Hz, 1H); ^{13}C NMR δ 31.05, 53.61, 55.47, 109.82, 110.58, 111.17, 114.29, 119.21, 120.50, 122.37, 123.76, 124.67, 127.10, 132.44, 137.34, 138.10, 140.37, 147.23, 159.77, 162.24.



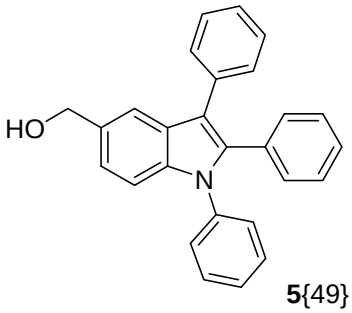
5{34}

3-Benzo[1,3]dioxol-5-yl-2-(4-methoxyphenyl)-1-methyl-1*H*-indole 5{34}. Yield = 39%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 3H), 3.84 (s, 3H), 5.92 (s, 2H), 6.75-6.77 (m, 3H), 6.91-6.93 (d, *J* = 8.8 Hz, 2H), 7.16-7.24 (m, 4H), 7.27-7.37 (m, 1H), 7.72-7.74 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 31.05, 55.46, 100.91, 108.47, 109.68, 110.55, 114.12, 114.64, 119.57, 120.24, 122.16, 123.39, 124.19, 127.26, 129.45, 132.47, 137.25, 137.58, 145.60, 147.56, 159.58.



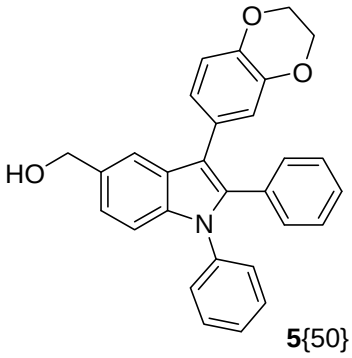
5{43}

3-Benzo[1,3]dioxol-5-yl-1*H*-indole-2-carbaldehyde 5{43}. Yield = 9%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.07 (s, 2H), 6.97-6.98 (d, *J* = 6.4 Hz, 1H), 7.04-7.09 (m, 2H), 7.18-7.22 (m, 1H), 7.41-7.48 (m, 2H), 7.79-7.81 (dd, *J* = 6.4, 0.8 Hz, 1H), 9.14 (broad s, 1H), 9.86 (s, 1H); ^{13}C NMR δ 101.62, 109.04, 110.77, 112.59, 121.61, 122.45, 124.55, 125.72, 127.01, 127.99, 129.46, 131.91, 137.30, 147.96, 148.37, 182.80.



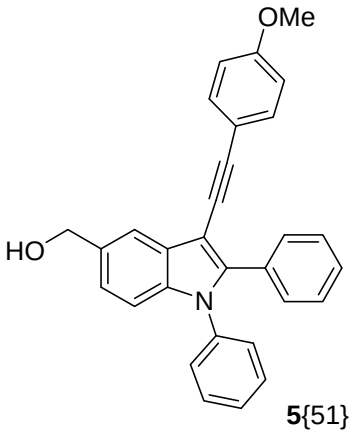
5{49}

(1,2,3-Triphenyl-1*H*-indol-5-yl)methanol 5{49}. Yield = 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.78 (s, 2H), 7.06-7.39 (m, 18H), 7.77 (s, 1H); ^{13}C NMR δ 66.47, 111.13, 117.00, 118.68, 122.79, 126.24, 127.43, 127.60, 127.86, 128.09, 128.39, 128.53, 129.30, 130.41, 131.32, 131.60, 133.89, 134.92, 137.76, 137.79, 138.23.



5{50}

[3-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,2-diphenyl-1*H*-indol-5-yl]methanol 5{50}. Yield = 54%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24-4.27 (m, 4H), 4.76 (s, 2H), 6.74-6.80 (m, 2H), 6.941-6.945 (d, *J* = 1.6 Hz, 1H), 7.07-7.09 (m, 2H), 7.13-7.15 (m, 3H), 7.18-7.20 (m, 3H), 7.22-7.25 (dd, *J* = 7.2, 1.6 Hz, 2H) (one extra proton due to merger with $CDCl_3$ peak, 7.29-7.30 (m, 2H), 7.33-7.36 (m, 2H), 7.75-7.76 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR δ 64.53, 66.33, 68.15, 108.10, 110.99, 116.36, 117.31, 118.67, 118.90, 122.72, 123.70, 127.32, 127.53, 127.90, 128.06, 128.33, 129.25, 131.25, 131.58, 133.79, 137.47, 137.56, 138.22, 142.14, 143.46.



5{51}

[3-(4-Methoxyphenylethynyl)-1,2-diphenyl-1*H*-indol-5-yl]methanol 5{51}. Yield = 64%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H), 4.80 (s, 2H), 6.83-6.85 (m, 2H), 7.18-

7.33 (m, 9H), 7.35-7.38 (m, 2H), 7.42-7.47 (m, 4H), 7.87 (s, 1H); ^{13}C NMR δ 55.44, 66.06, 82.26, 92.81, 99.18, 108.10, 111.14, 114.06, 116.52, 118.98, 123.39, 127.69, 128.01, 128.03, 128.07, 129.52, 130.20, 130.83, 132.81, 134.41, 137.43, 138.00, 142.75, 159.19.

Acknowledgments

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References

1. For reviews, see: (a) Sundberg, R. J. *Prog. Heterocycl. Chem.* **1989**, *1*, 111. (b) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996. (c) Saxton, J. E. *Nat. Prod. Rep.* **1986**, *3*, 357; **1987**, *4*, 591; **1989**, *6*, 1. (d) Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem*. **1996**, *61*, 5804. (e) Toyota, M.; Ihara, M. *Nat. Prod. Rep*. **1998**, *15*, 327. (f) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (g) Mori, H.; Yoshimi, N. *Mutat. Res.* **2001**, *480*, 201. (h) Tokuyama, H.; Fukuyama, T. *Kagaku Kogyo* **2001**, *52*, 416. (i) Xiong, W. N.; Yang, C. G.; Jiang, B. *Bioorg. Med.*

Chem. **2001**, *9*, 1773. (j) Lobo, A. M.; Prabhakar, S. *J. Heterocycl. Chem.* **2002**, *39*, 429.

2. (a) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2289. (b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (c) Loughlin, W. A. *Aust. J. Chem.* **1998**, *51*, 875.
3. (a) Hegedus, L. S. *Angew. Chem.* **1988**, *100*, 1147. (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (c) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (d) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (e) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (f) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem.* **1999**, *64*, 1137. (g) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (h) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem.*, *Int. Ed. Engl.* **2000**, *39*, 2488. (i) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662. (j) Pete, B.; Toke, L. *Tetrahedron Lett.* **2001**, *42*, 3373. (k) Kamijo, S.; Yamamoto, Y. *Angew. Chem.*, *Int. Ed.* **2002**, *41*, 3230. (l) Kamijo, S.; Yamamoto, Y. *J. Am. Soc. Chem.* **2002**, *124*, 11940. (m) Yasuhara, A.; Takeda, Y.; Suzuki, N.; Sakamoto, T. *Chem. Pharm. Bull.* **2002**, *50*, 235. (n) Rossiter, S. *Tetrahedron Lett.* **2002**, *43*, 4671. (o) Zhou, T.; Chen, Z. C. *Synth. Commun.* **2002**, *32*, 903. (p) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, UK, 2000; pp 73-187.
4. (a) Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G.; Gellerman, G. *Synlett* **2003**, 1411. (b) Jennings, L. D.; Foreman, K. W.; Rush Iii, T. S.; Tsao, D. H. H.; Mosyak, L.; Kincaid, S. L.; Sukhdeo, M. N.; Sutherland, A. G.; Ding, W.; Kenny, C. H.;

Sabus, C. L.; Liu, H.; Dushin, E. G.; Moghazeh, S. L.; Labthavikul, P.; Petersen, P. J.; Tuckman, M.; Ruzin, A. V. *Bioorg. Med. Chem.* **2004**, *12*, 5115.

5. (a) Nicolaou, K. C.; Roecker, A. J.; Hughes, R.; van Summeren, R.; Pfefferkorn, J. A.; Winssinger, N. *Bioorg. Med. Chem.* **2003**, *11*, 465. (b) Lee, S. H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Comb. Chem* **2003**, *5*, 188. (c) Tanaka, H.; Ohno, H.; Kawamura, K.; Ohtake, A.; Nagase, H.; Takahashi, T. *Org. Lett.* **2003**, *5*, 1159.
6. Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 2248.
7. (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62.
8. (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 5, pp 203. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
9. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
10. Yao, T.; Yue, D.; Larock, R. C. *J. Comb. Chem.* **2005**, *7*, 809.
11. Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083.
12. Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535.
13. (a) *Chemistry of Organic Fluorine Compounds II. A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington,

DC, 1995. (b) *Organofluorine Compounds. Chemistry and Applications*; Hiyama, T., Ed.; Springer-Verlag: New York, 2000.

14. (a) Rajbhoj, A. S.; Gaikwad, S. T.; Chondhekar, T. K. *J. Ind. Chem. Soc.* **2007**, *84*, 987. (b) Walash, M. I.; El-Brashy, A. M.; Metwally, M. S.; Abdelal, A. A. *Bull. Kor. Chem. Soc.* **2004**, *25*, 517. (c) Roopnarinesingh, E. S.; Steventon, G. B.; Harris, R. M.; Waring, R. H.; Mitchell, S. C. *Drug Metabolism and Drug Interactions* **2005**, *21*, 75. (d) Hiller, K. O.; Hodd, P. L.; Willson, R. L. *Chem. Biol. Interact.* **1983**, *47*, 293.
15. (a) Lipinski, C. A.; Lombardo, F.; Dominay, B. W.; Feeney, P. J. *Adv. Drug Del. Rev.* **1997**, *23*, 3. (b) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney P. J. *Adv. Drug Del. Rev*. **2001**, *46*, 3.
16. Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem*. **2002**, *45*, 2615.
17. *SYBYL*, version 8.0; The Tripos Associate: St. Louis, MO, 2007.
18. Koten, G.; ten Hoedt, R. W.; Noltes, J. G. *J. Org. Chem.* **1977**, *42*, 2705.
19. Bowyer, P. K.; Black, D. C.; Craig, D. C. *Tetrahedron* **2005**, *61*, 10781.
20. Worlikar, S. A.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. (To be submitted to the *Journal of Combinatorial Chemistry*)

GENERAL CONCLUSIONS

In this dissertation, novel and synthetically useful methods involving palladium catalysis and electrophilic cyclization have been employed for the synthesis of potential medicinally and industrially important carbocycles and heterocycles. A wide variety of 2*H*-benzopyrans, phthalimides, fluorenylidenes, phenanthrenes and indoles have been synthesized using these methods.

Chapter 1 describes an efficient and mild method to synthesize 2*H*-benzopyrans by iodocyclization of substituted propargylic aryl ethers in good yields. Successful palladium-catalyzed Sonogashira and CO insertion reactions have been achieved at the 3-position, demonstrating the importance of the iodine handle incorporated in the heterocycle in a position not easily achieved previously. The chemistry is tolerable of a number of functional groups.

Chapter 2 provides an efficient one step synthesis of phthalimides from readily available *ortho*-halobenzoates and primary amines. Palladium-catalyzed aminocarbonylation has been achieved using one atmosphere of CO without the use of specialized equipment. The reaction tolerates a halogen moiety in the heterocycle, which has been further successfully subjected to Songashira and Suzuki cross-coupling reactions to achieve decent yields of the highly-substituted heterocyles.

Chapter 3 describes a successful coupling reaction between two reactive species, arynes and organopalladium compounds. The arynes have been obtained *in situ* under mild reaction conditions from the corresponding *o*-silylaryl triflates in the presence of CsF. The reaction conditions have been optimized for the palladium-catalyzed aryne annulation of *ortho*-halostyrenes to 9-fluorenylidenes and the methodology extended to *ortho*-halo

allylicbenzenes to afford 9,10-phenanthrenes. The chemistry is tolerant of a number of functional groups.

Chapter 4 describes the successful synthesis of a 42-member library of highly substituted indoles by the palladium-catalyzed cross-coupling reactions of 3-iodoindoles and terminal alkynes or aryl boronic acids. The palladium-catalyzed reactions on the highly electron-rich 3-position of the indole have been achieved in decent yields and good purities, both in a solution phase and on a chlorinated Wang resin as the solid support. Variety has been achieved at the 5-position by different cleavage reactions. The potentially medicinally important indole library is totally in compliance with Lipinski rules.

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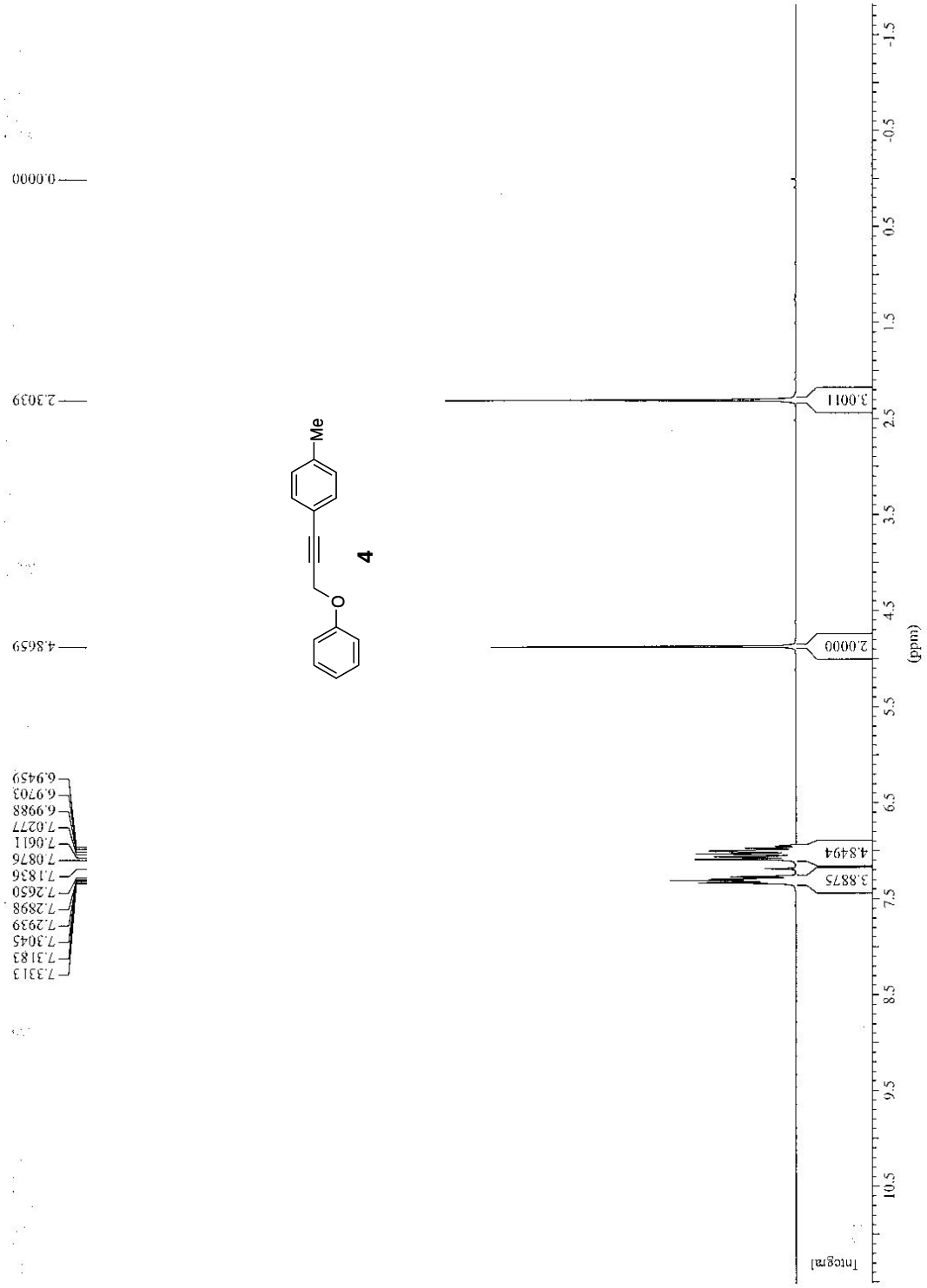
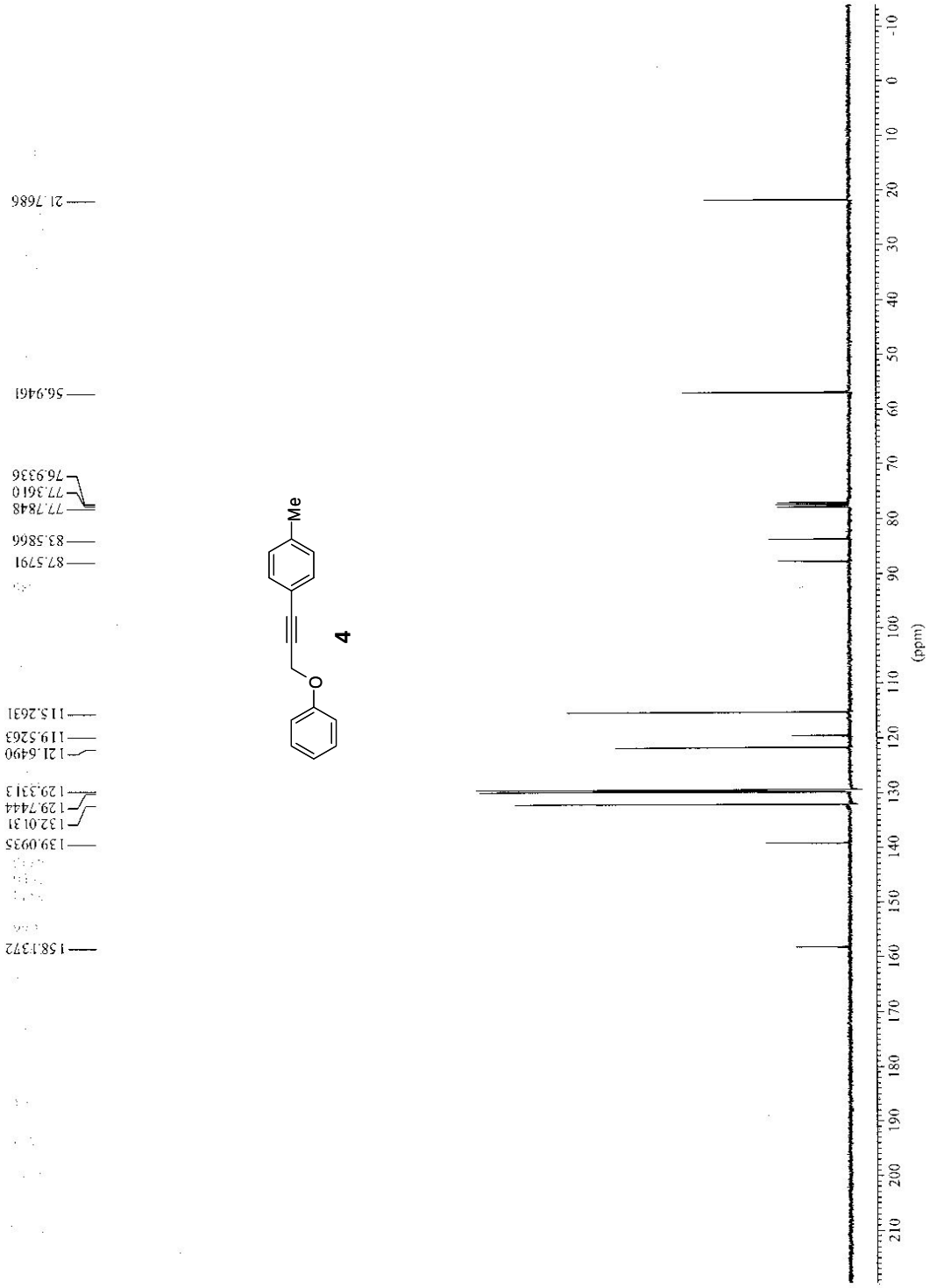
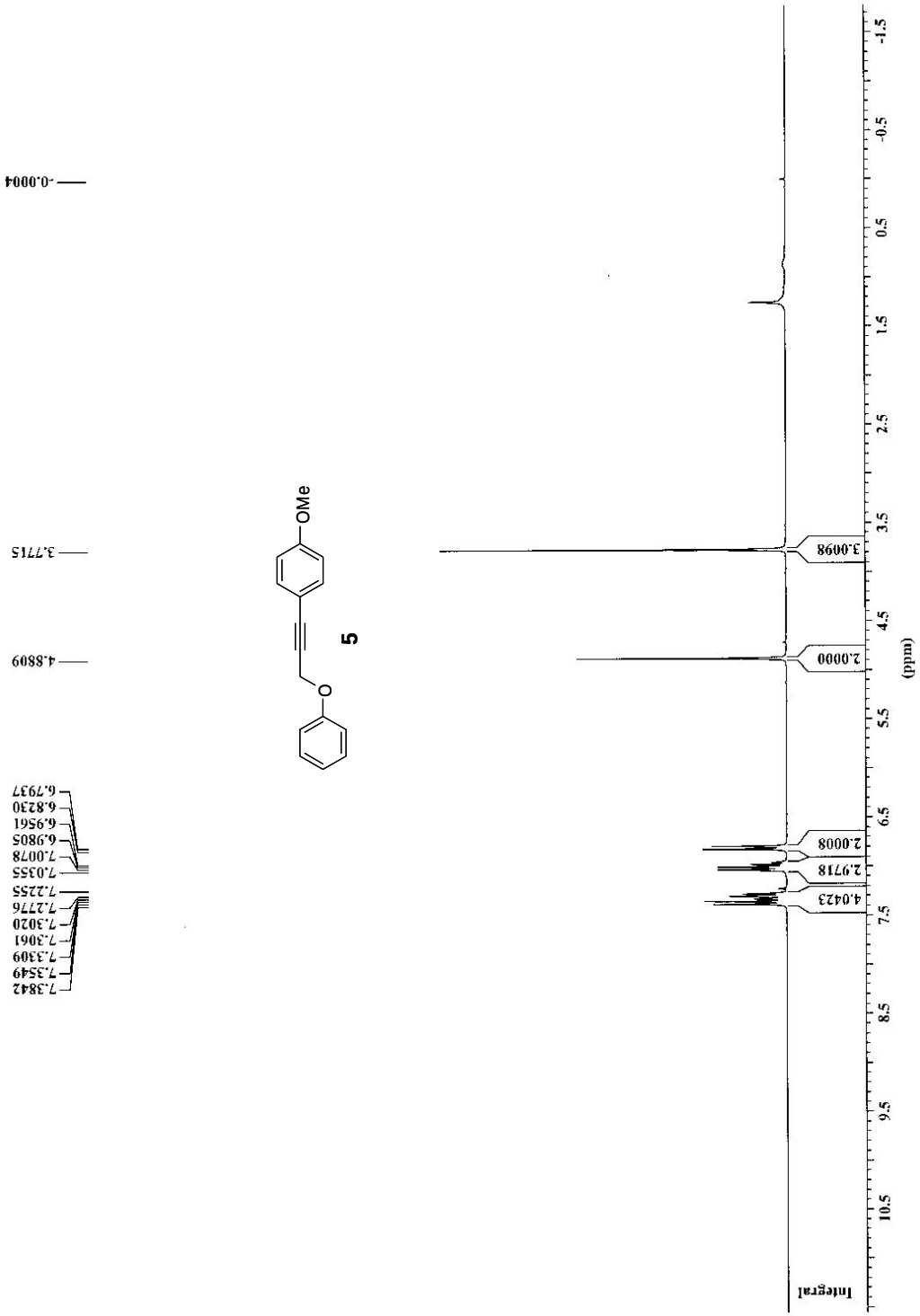
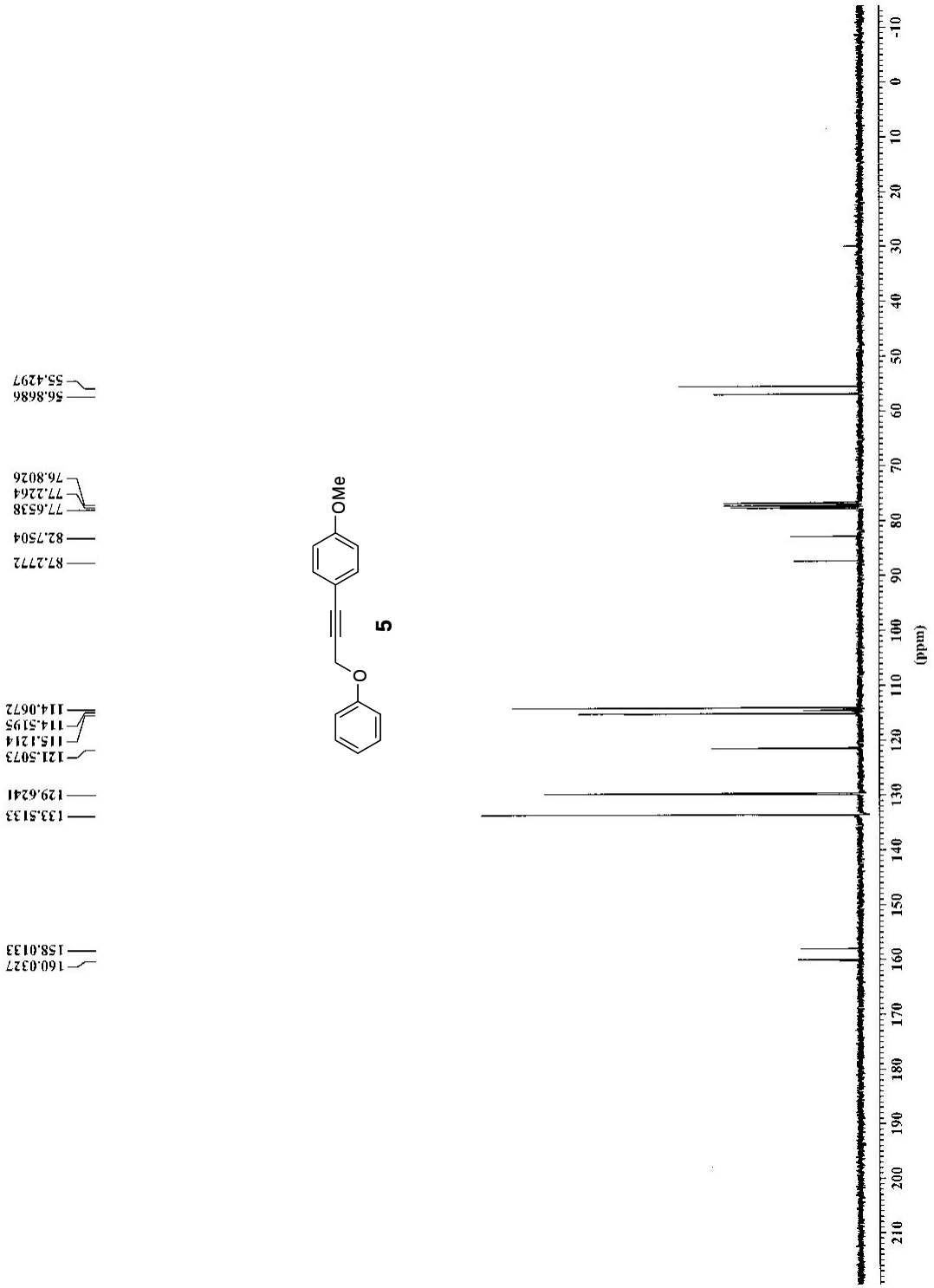
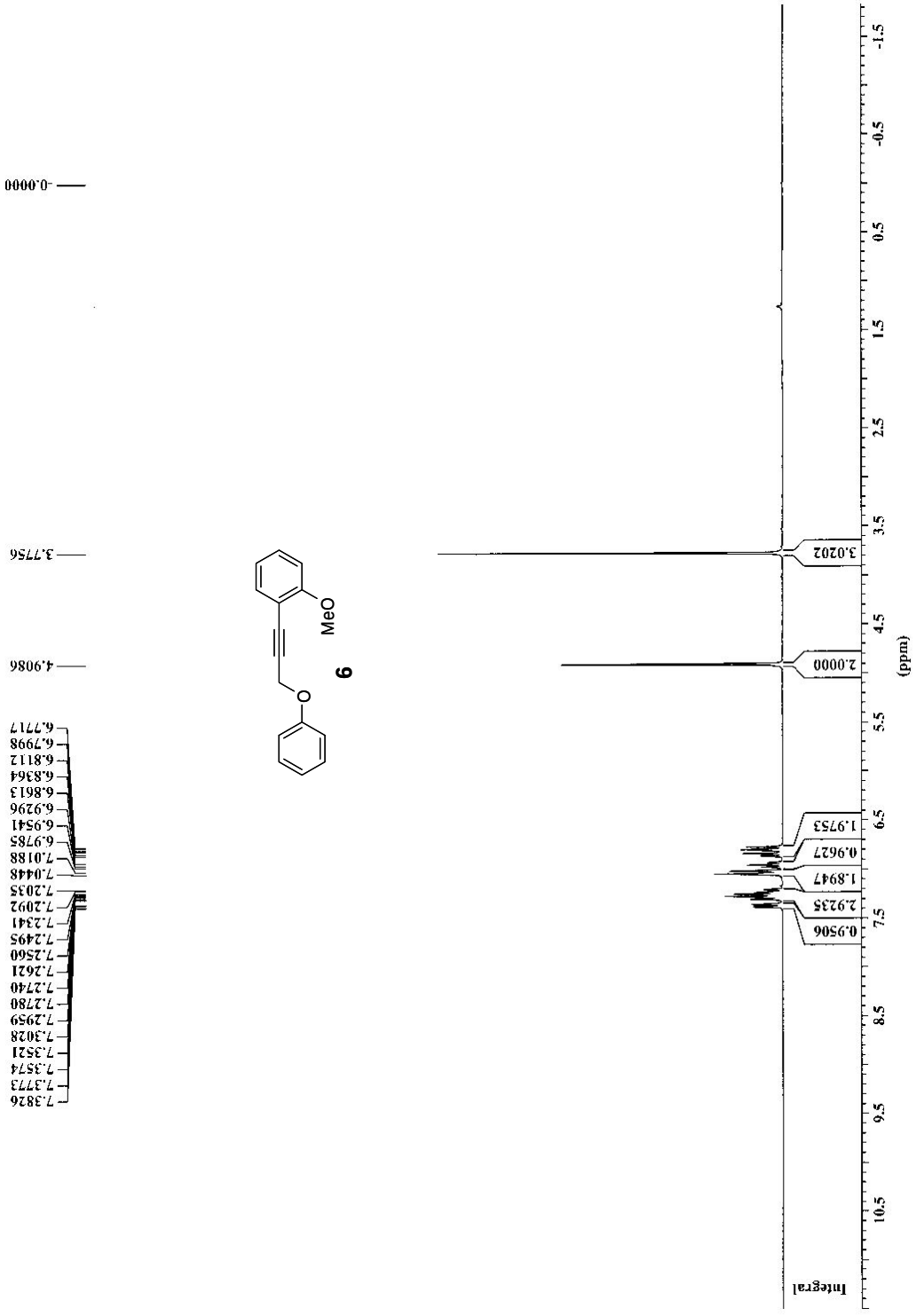
APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA

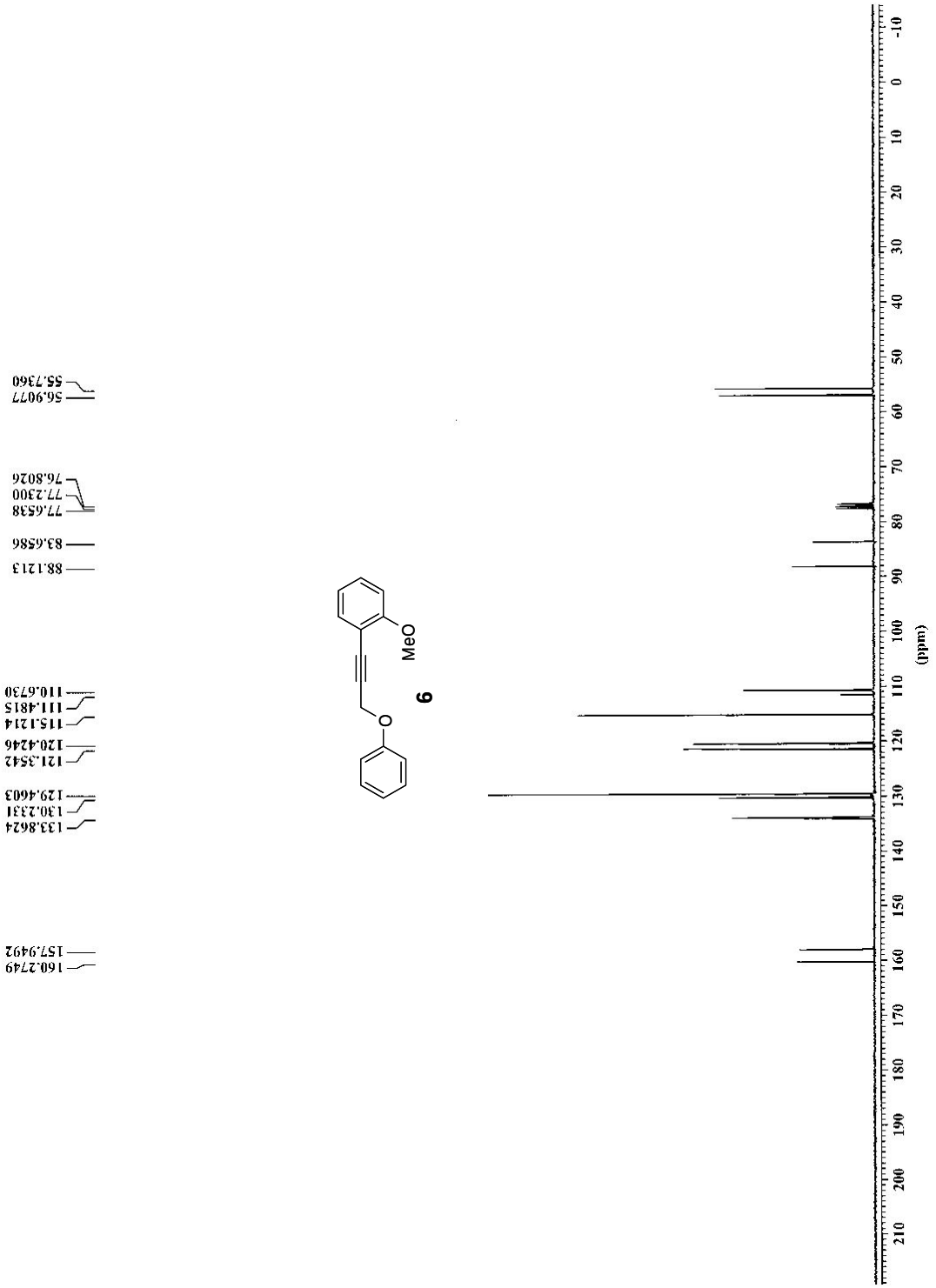


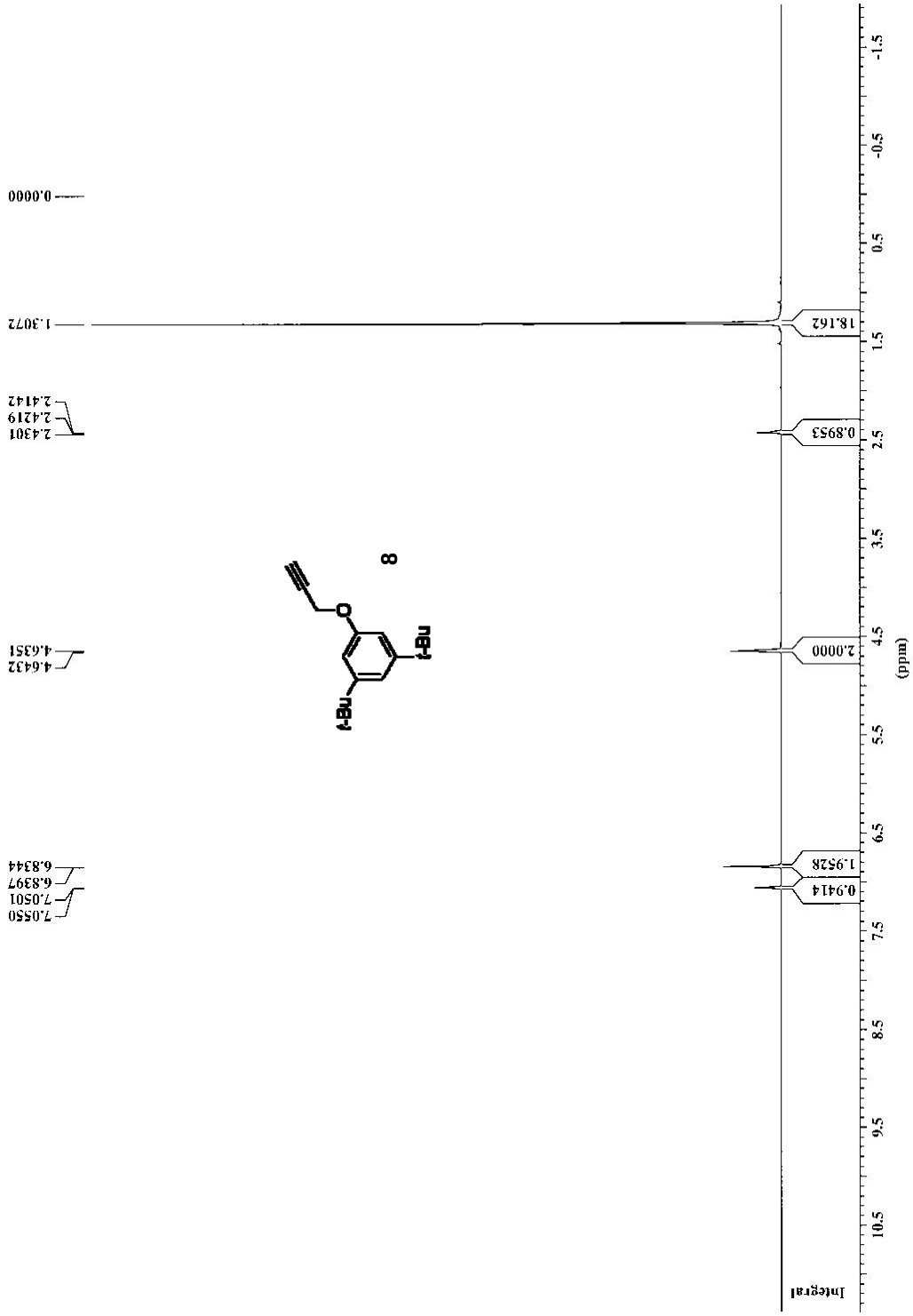


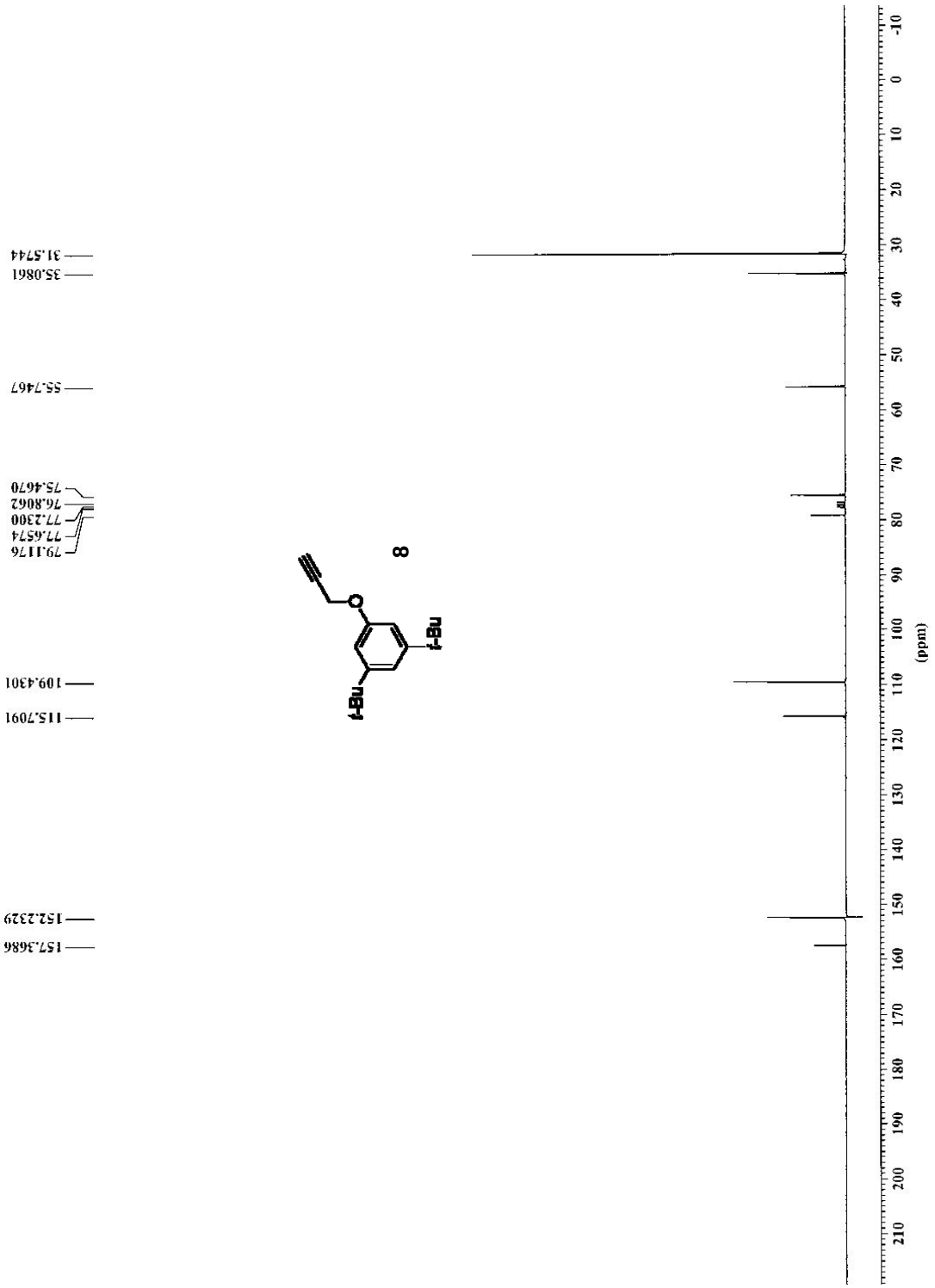


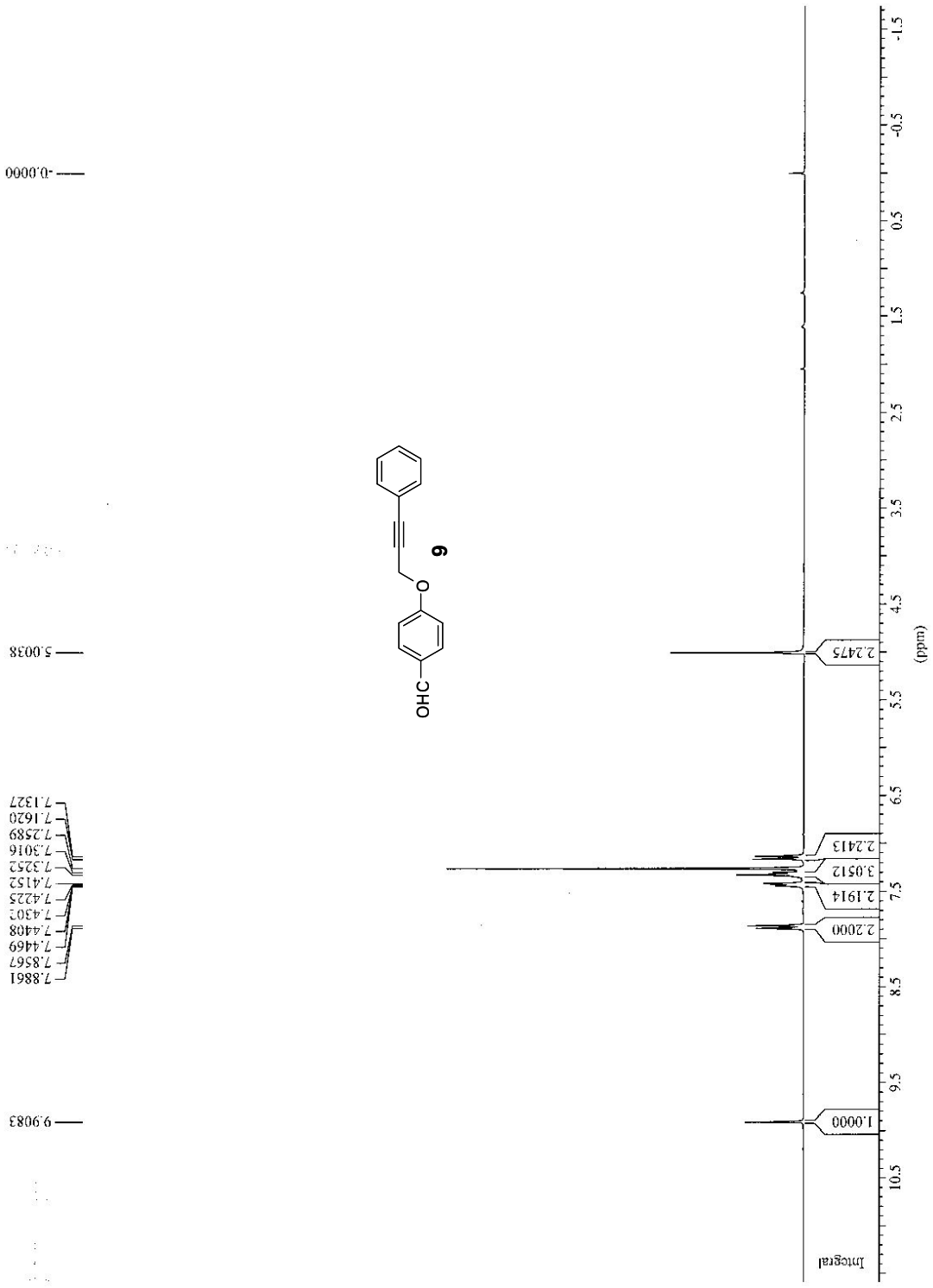


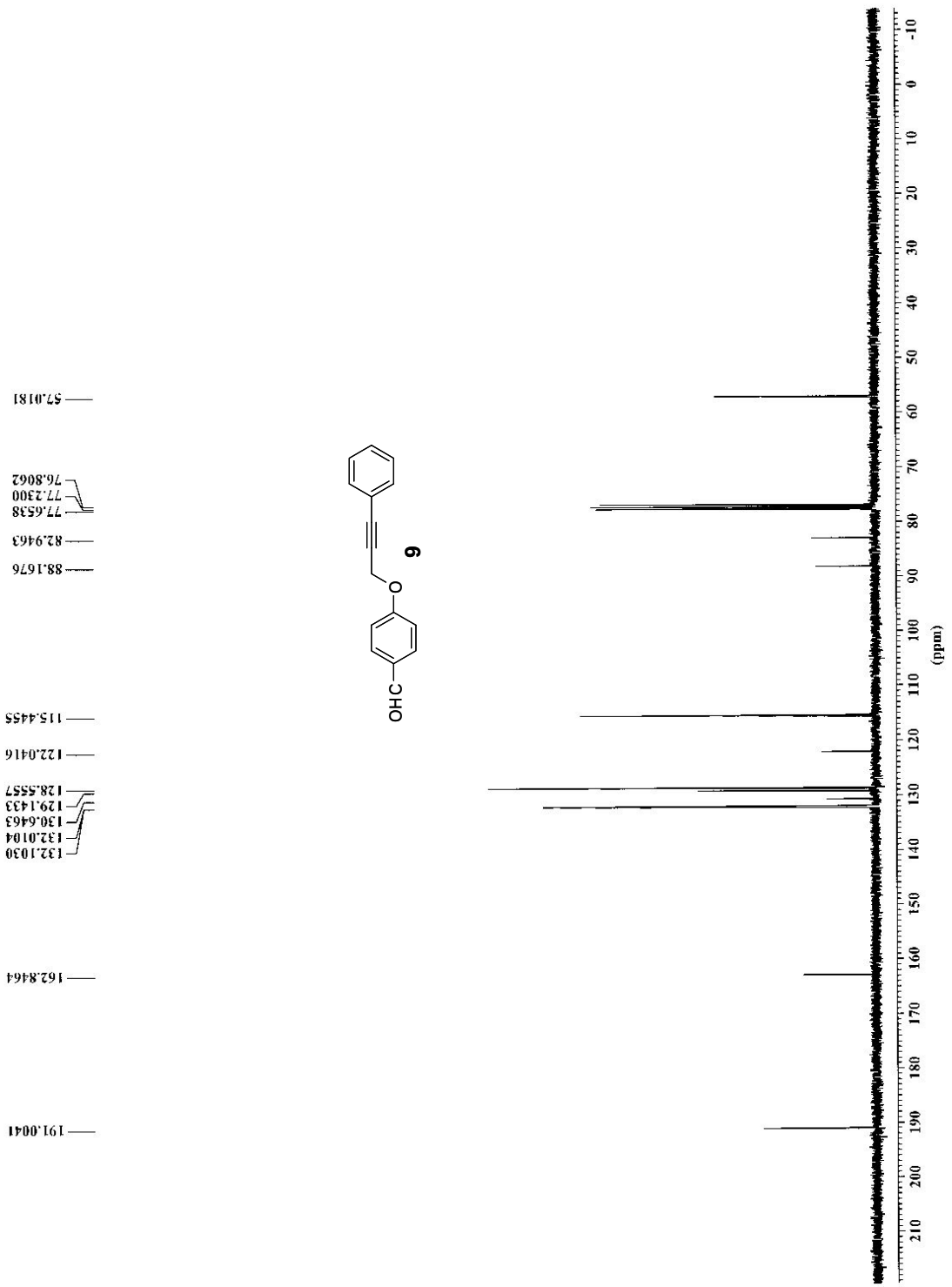


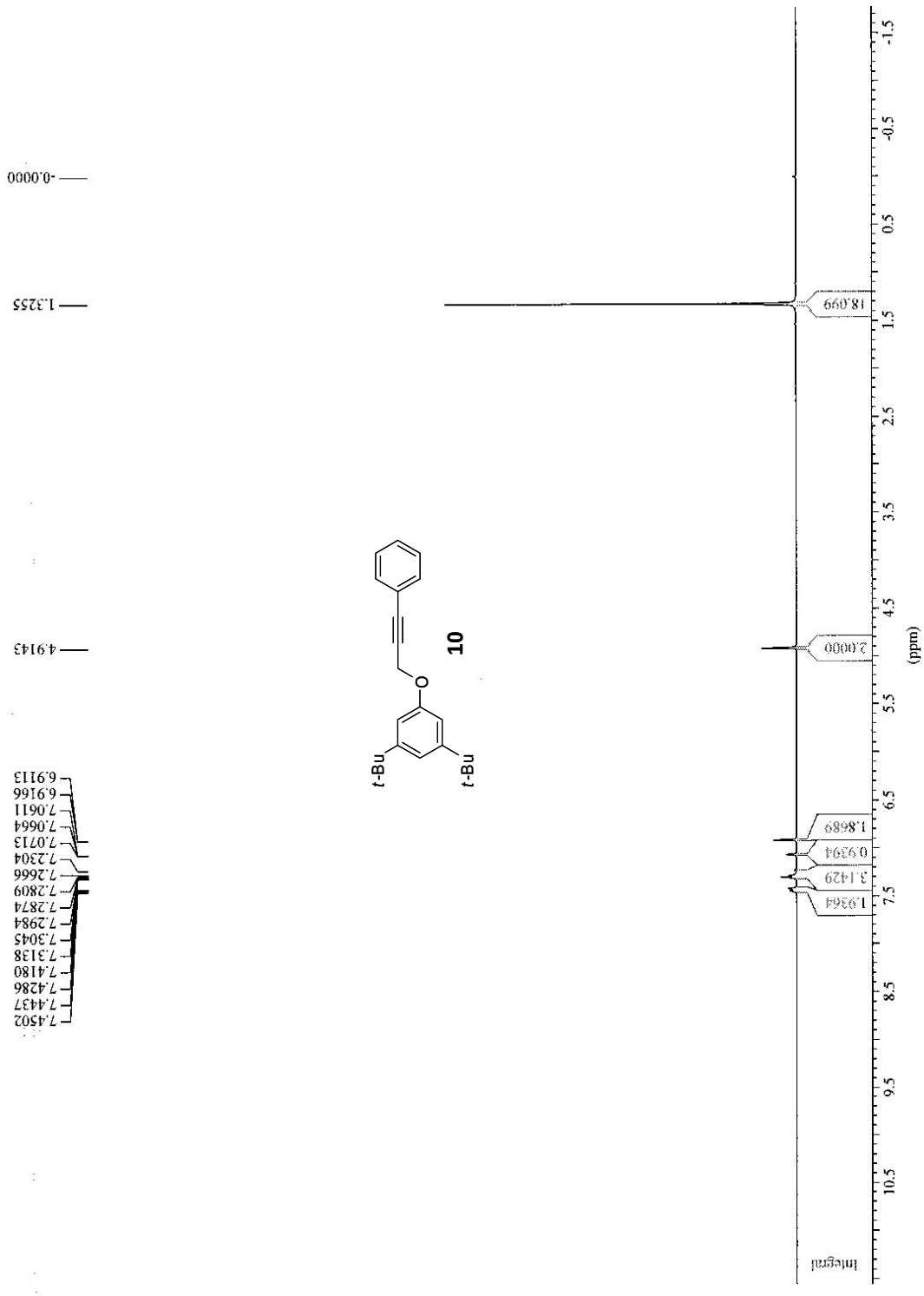


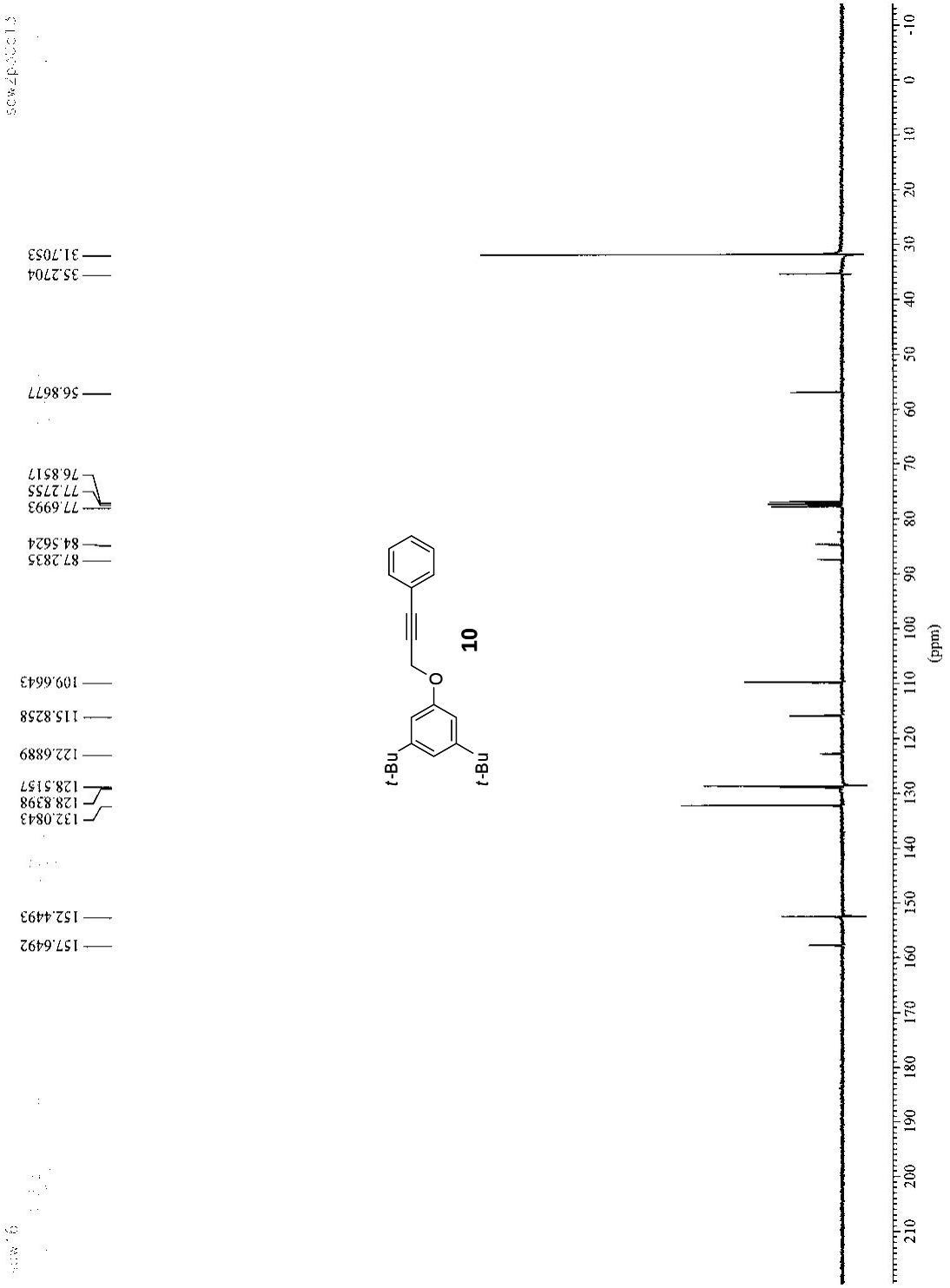


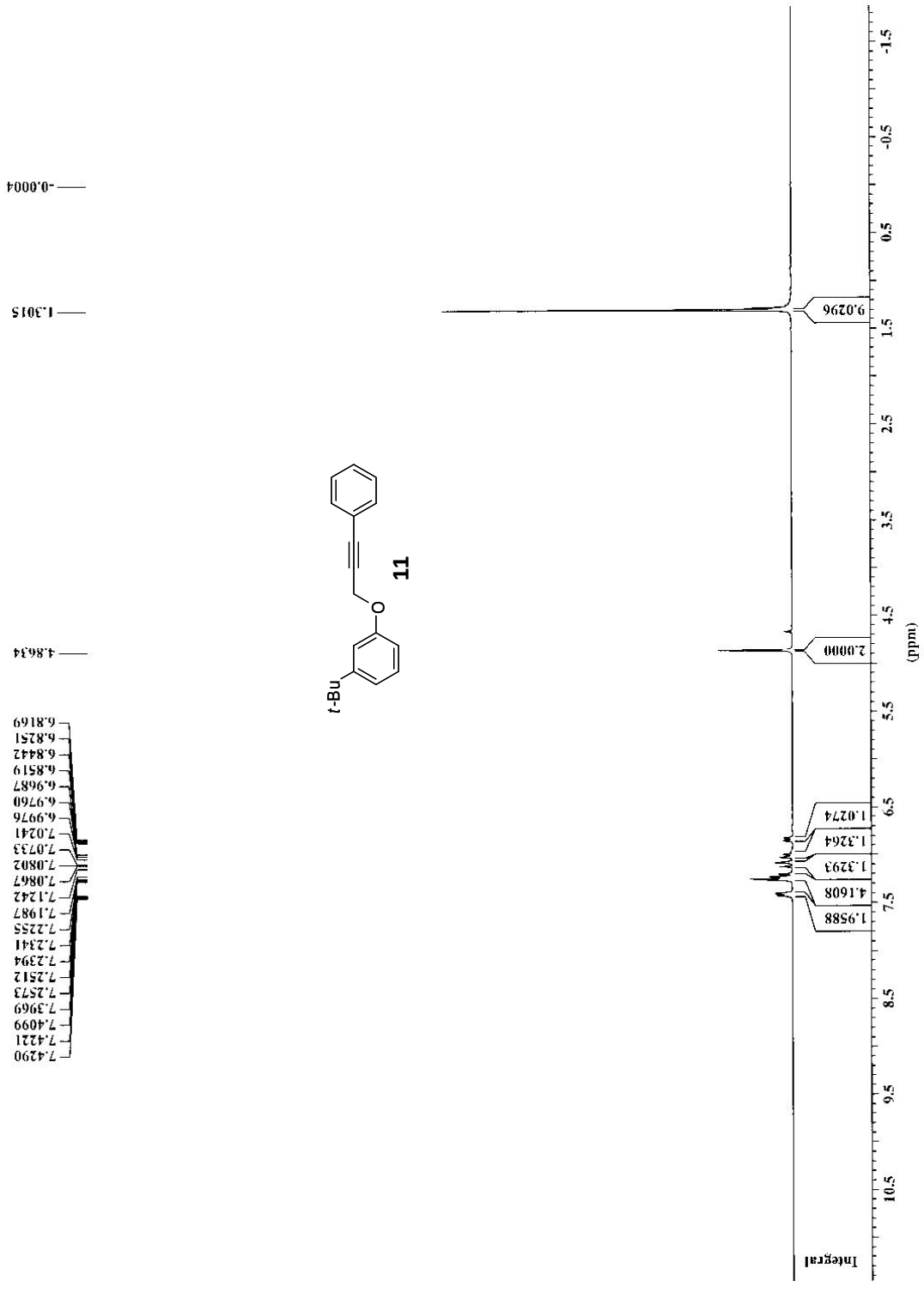


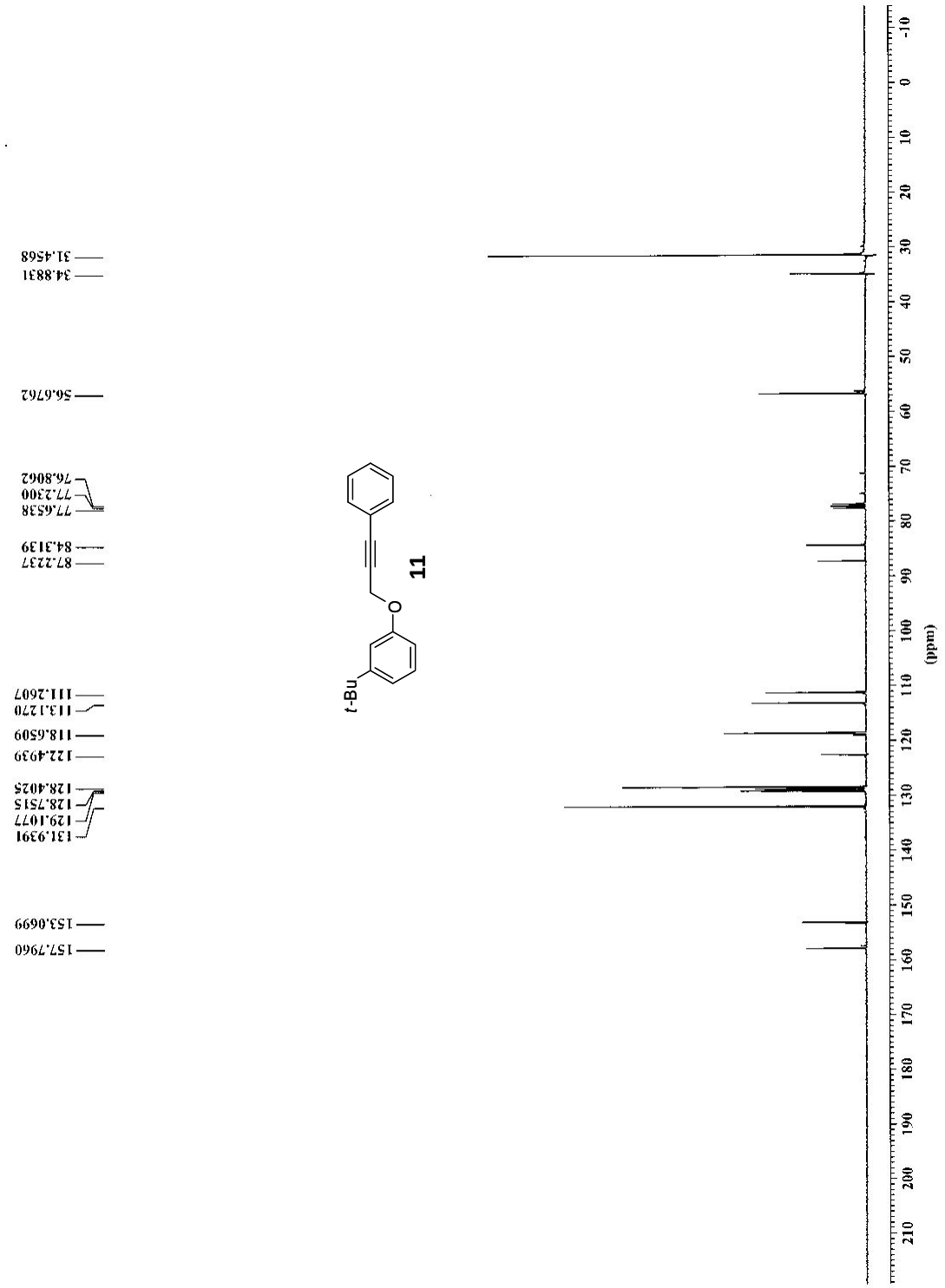


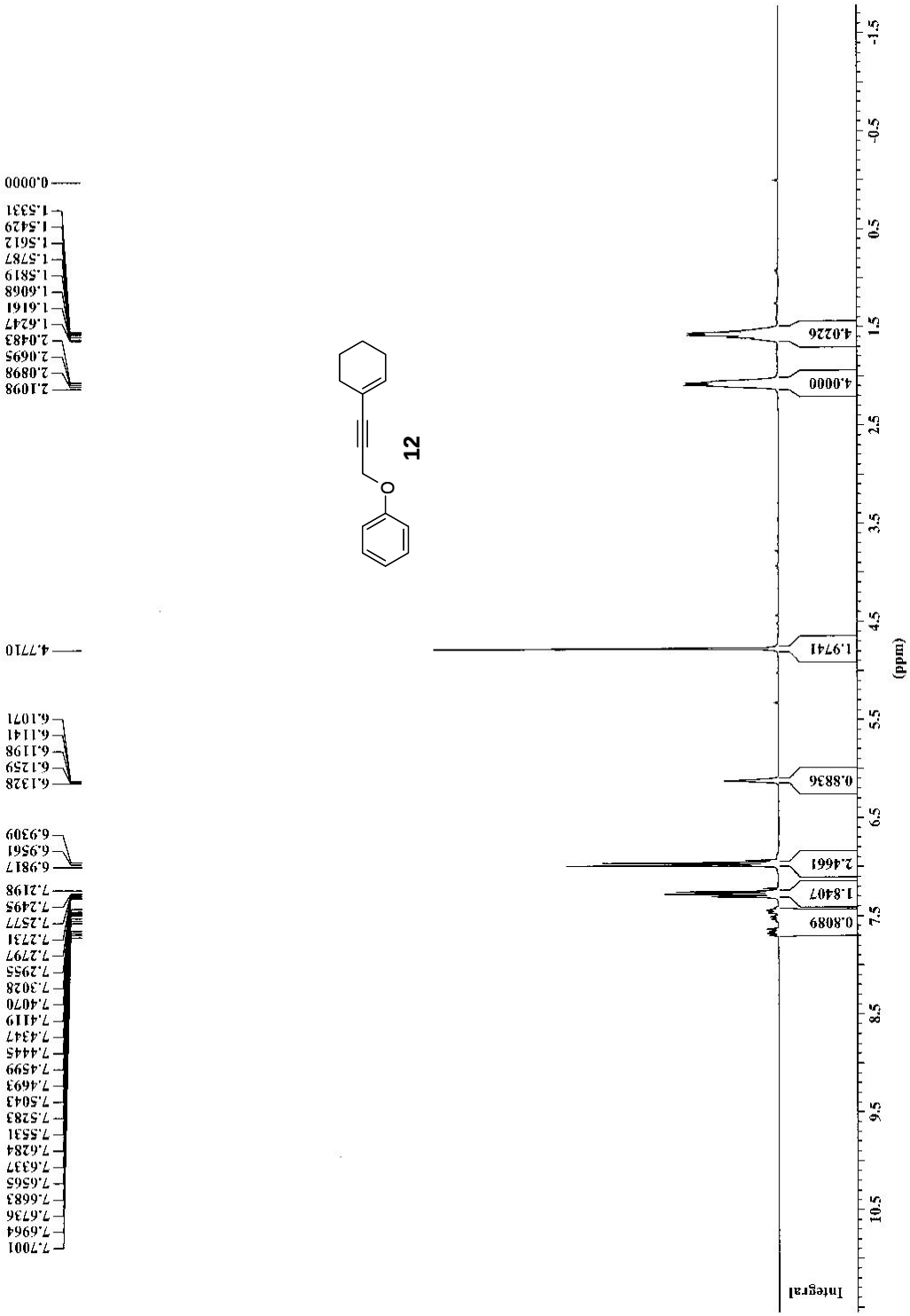


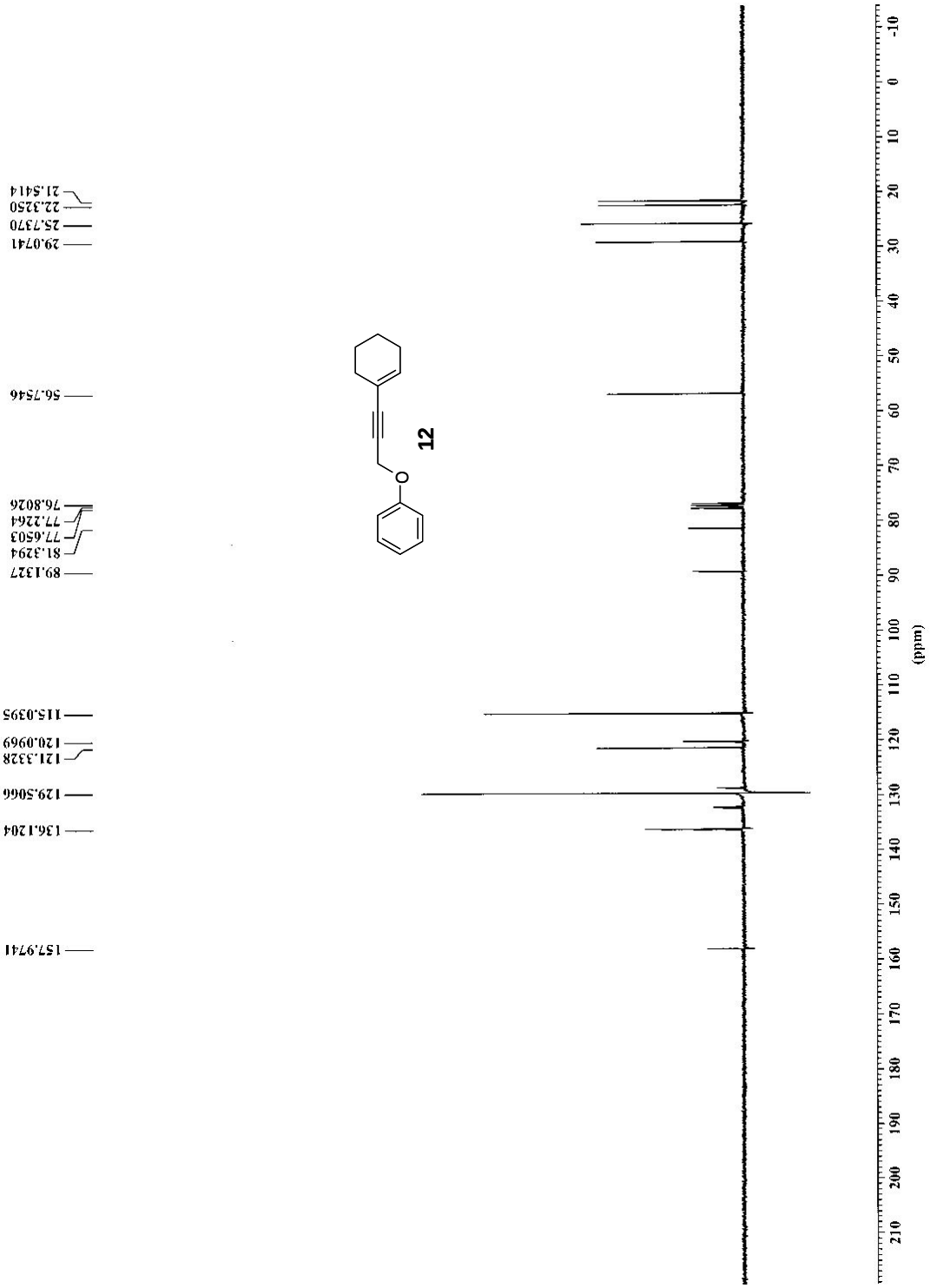


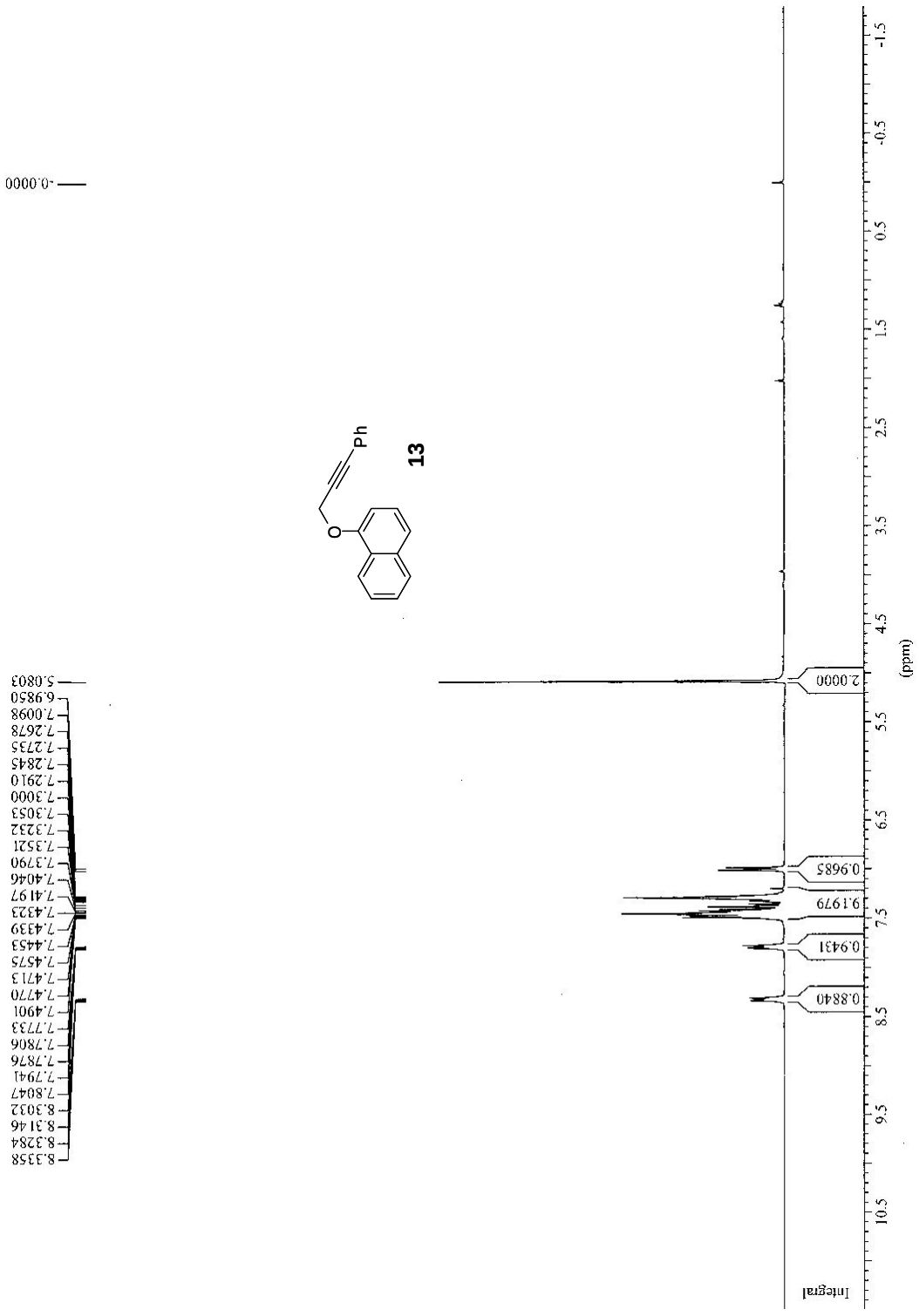


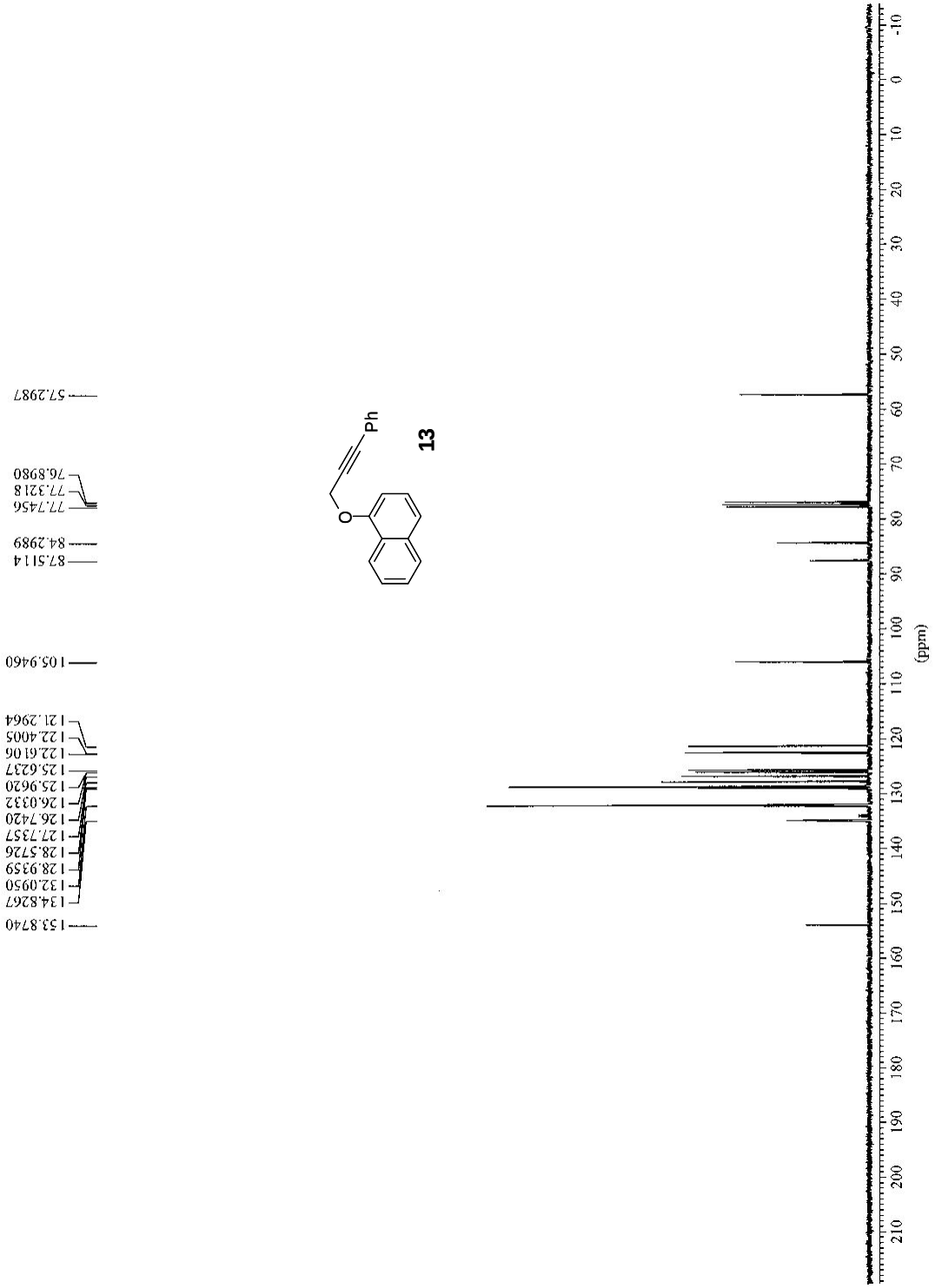


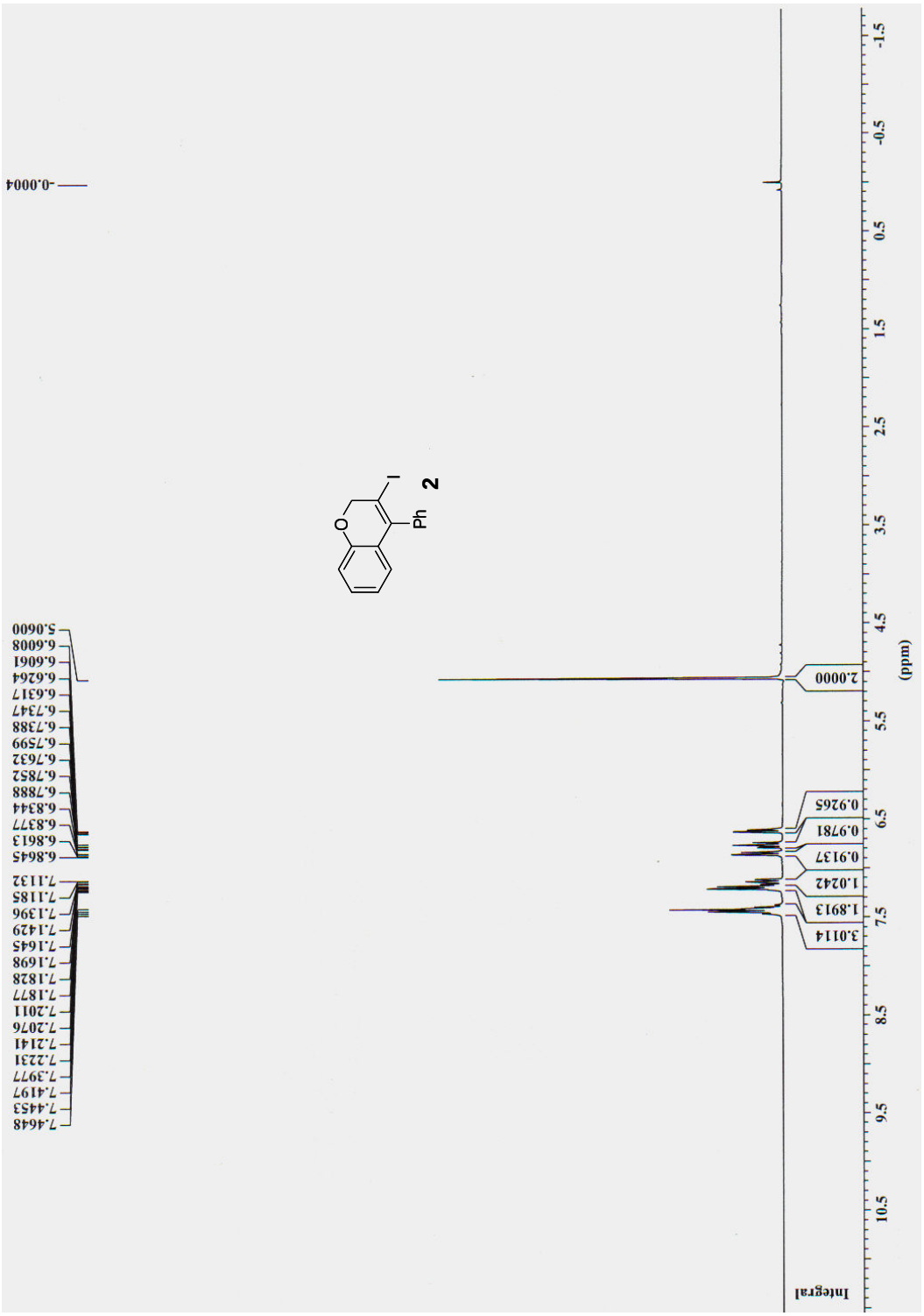


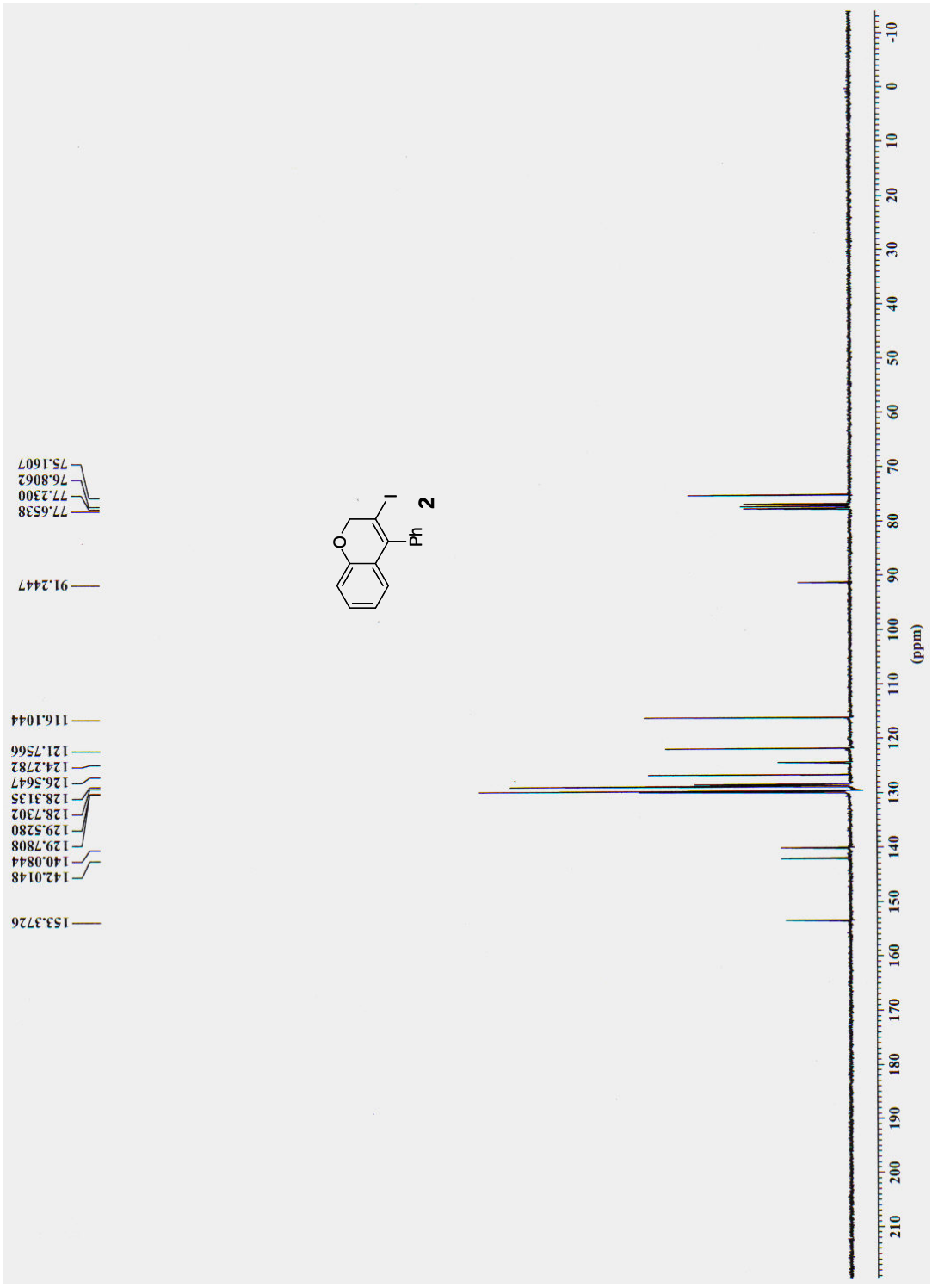


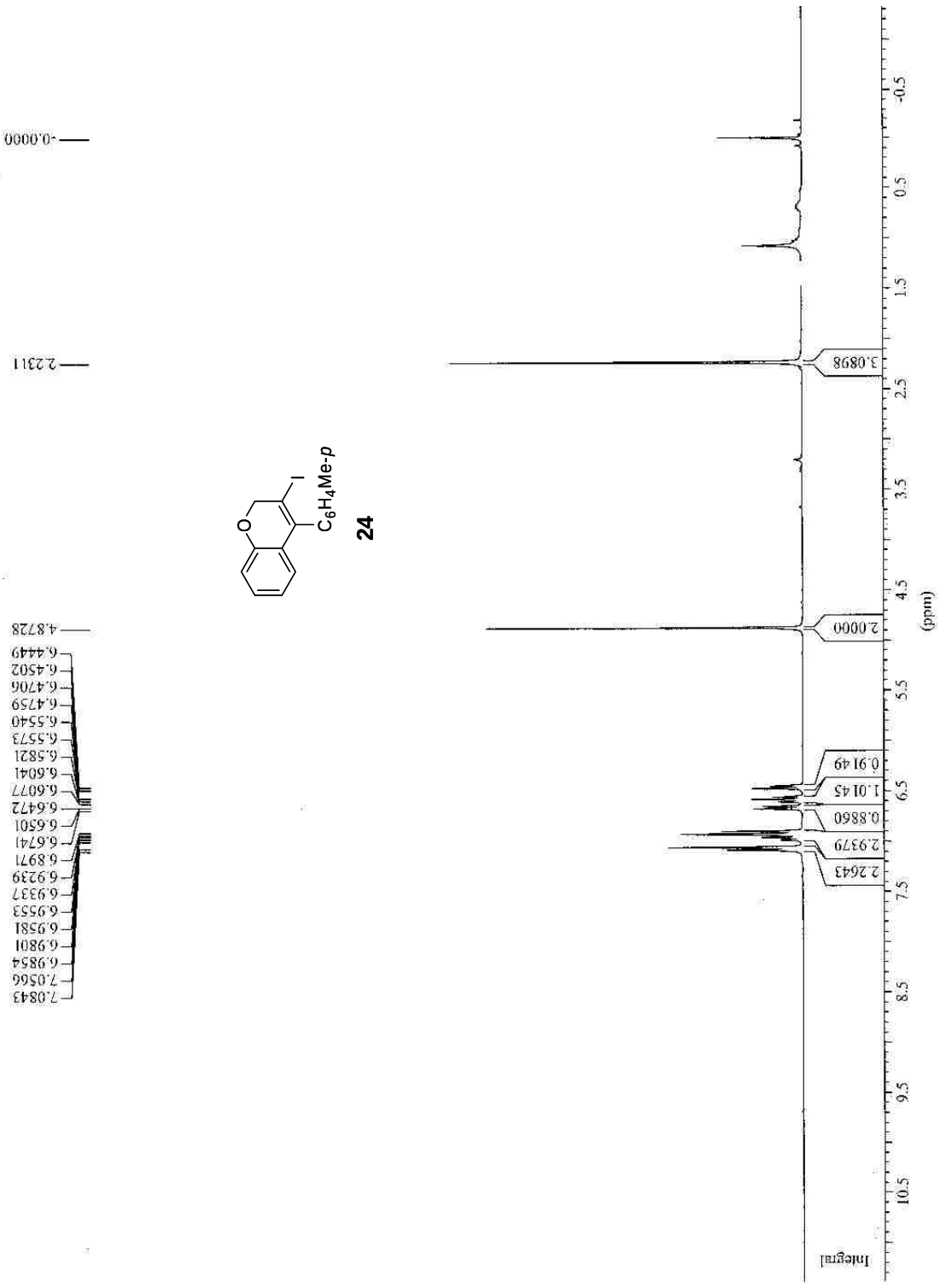


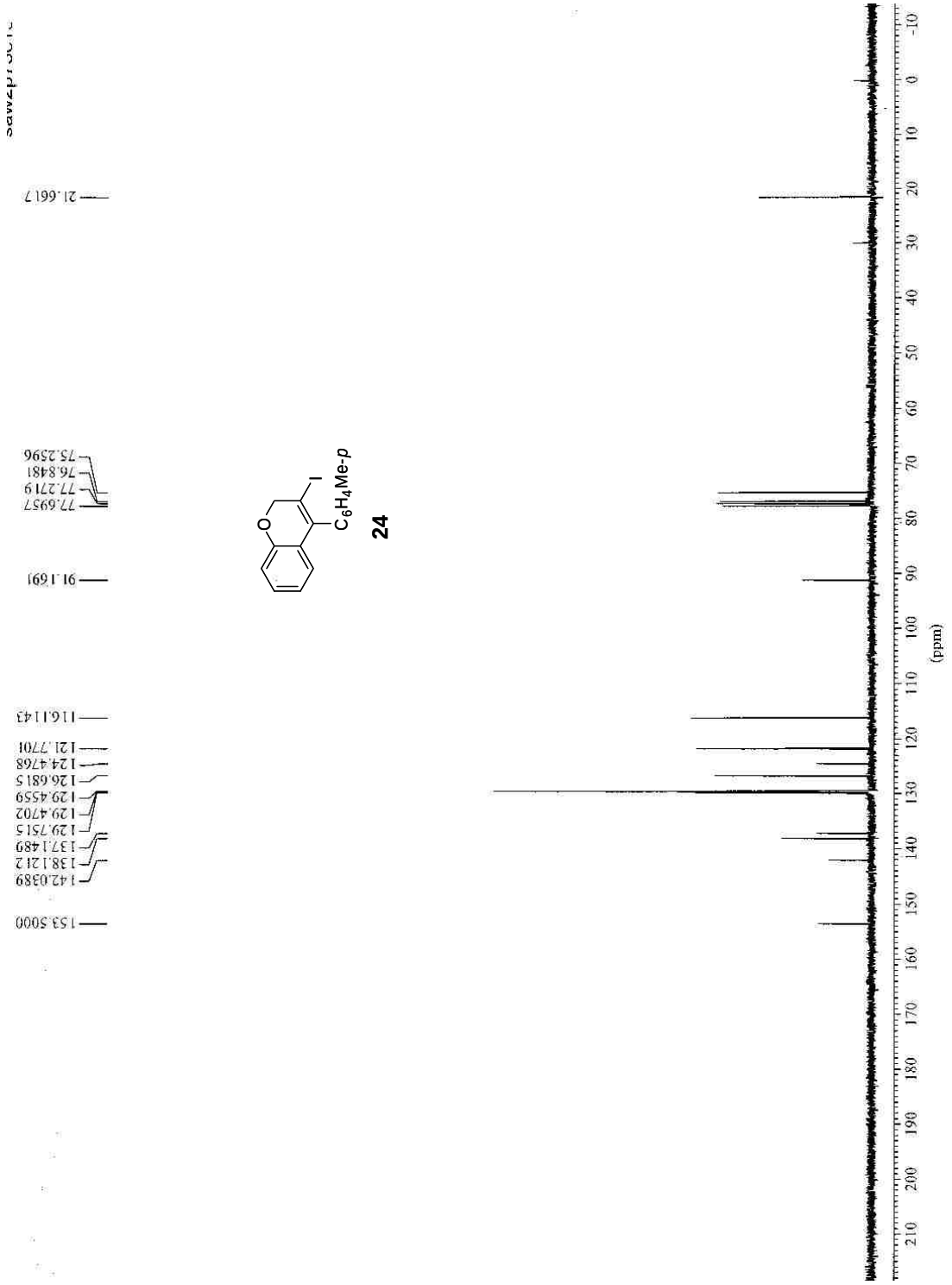


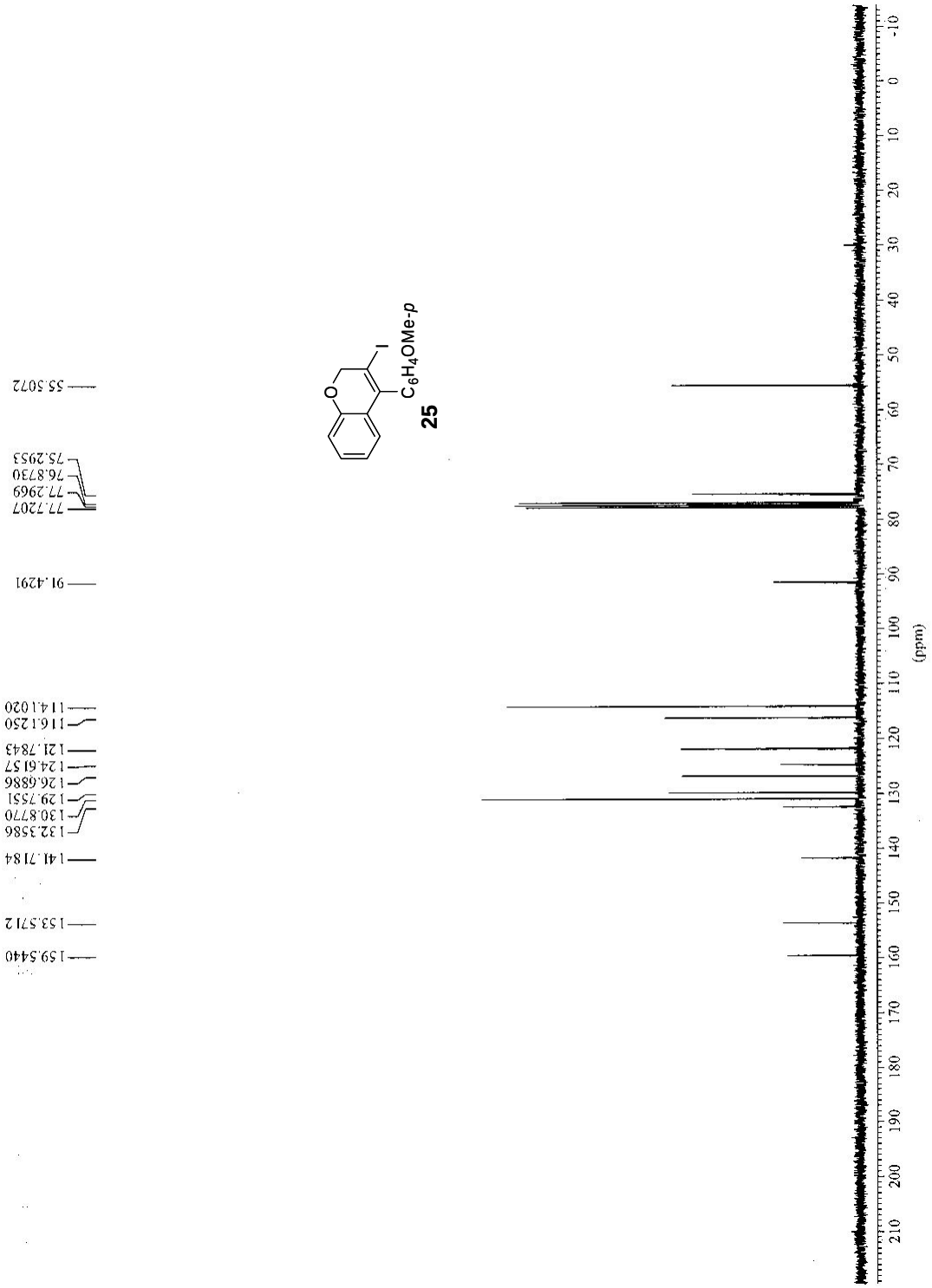


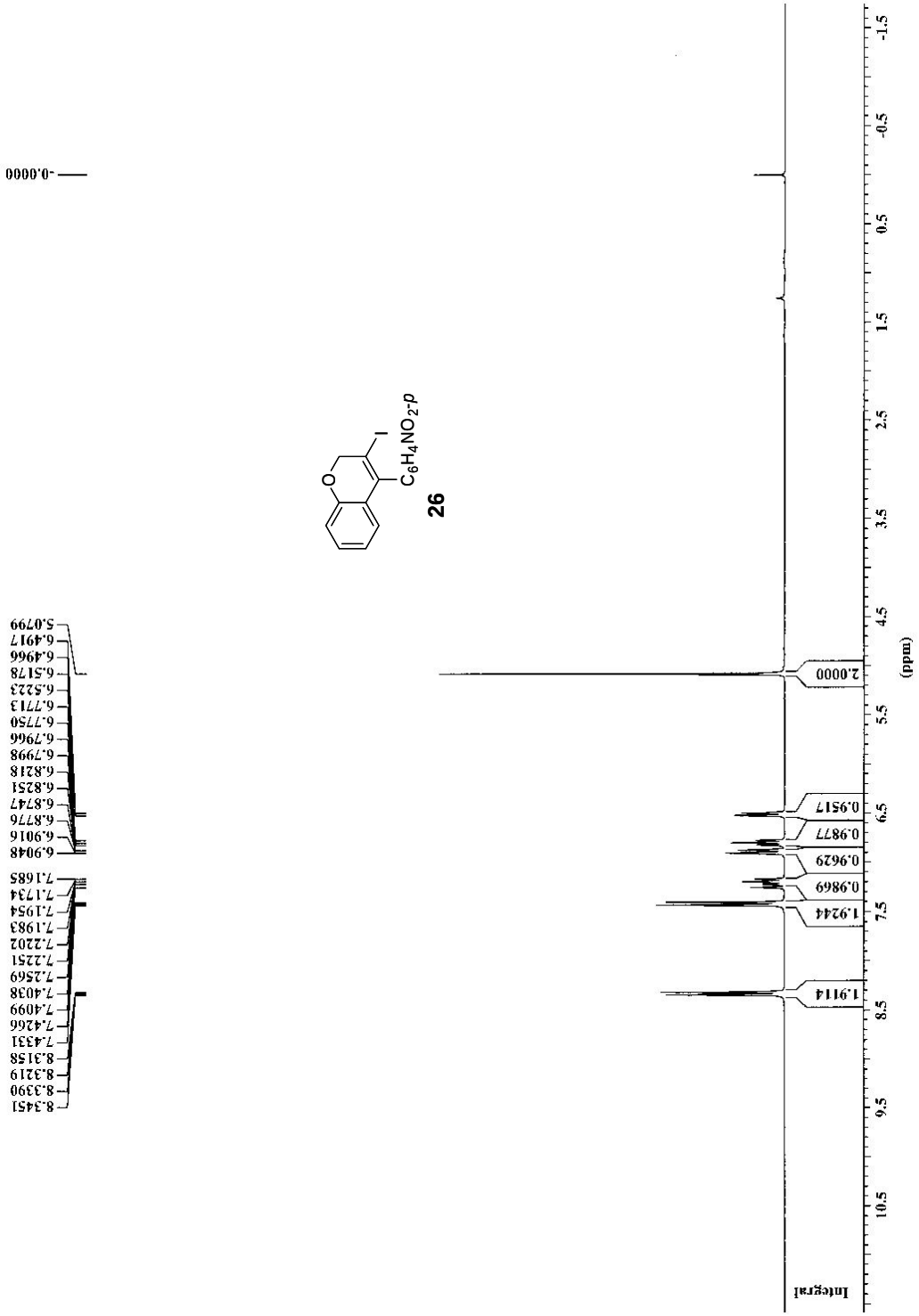


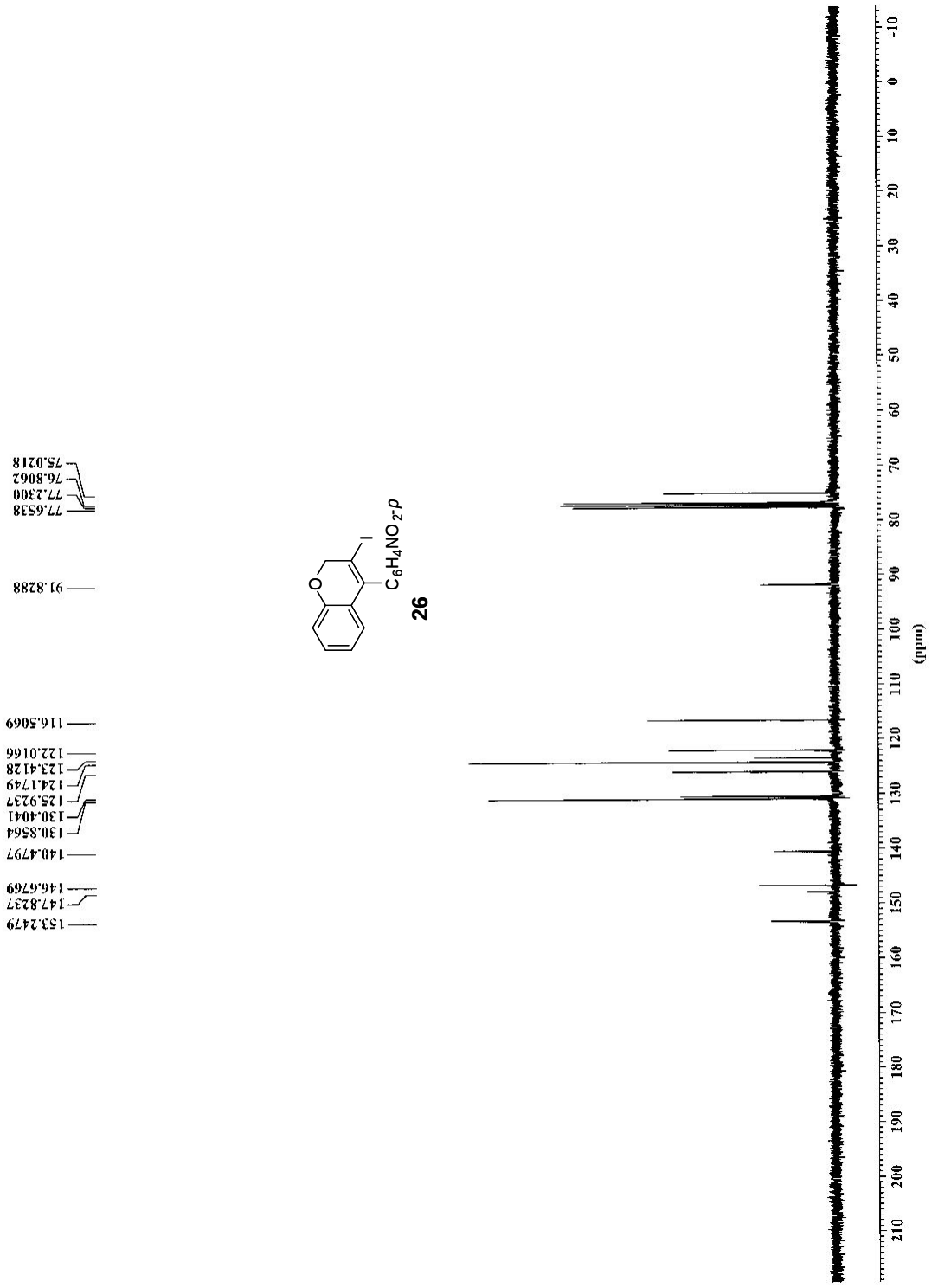


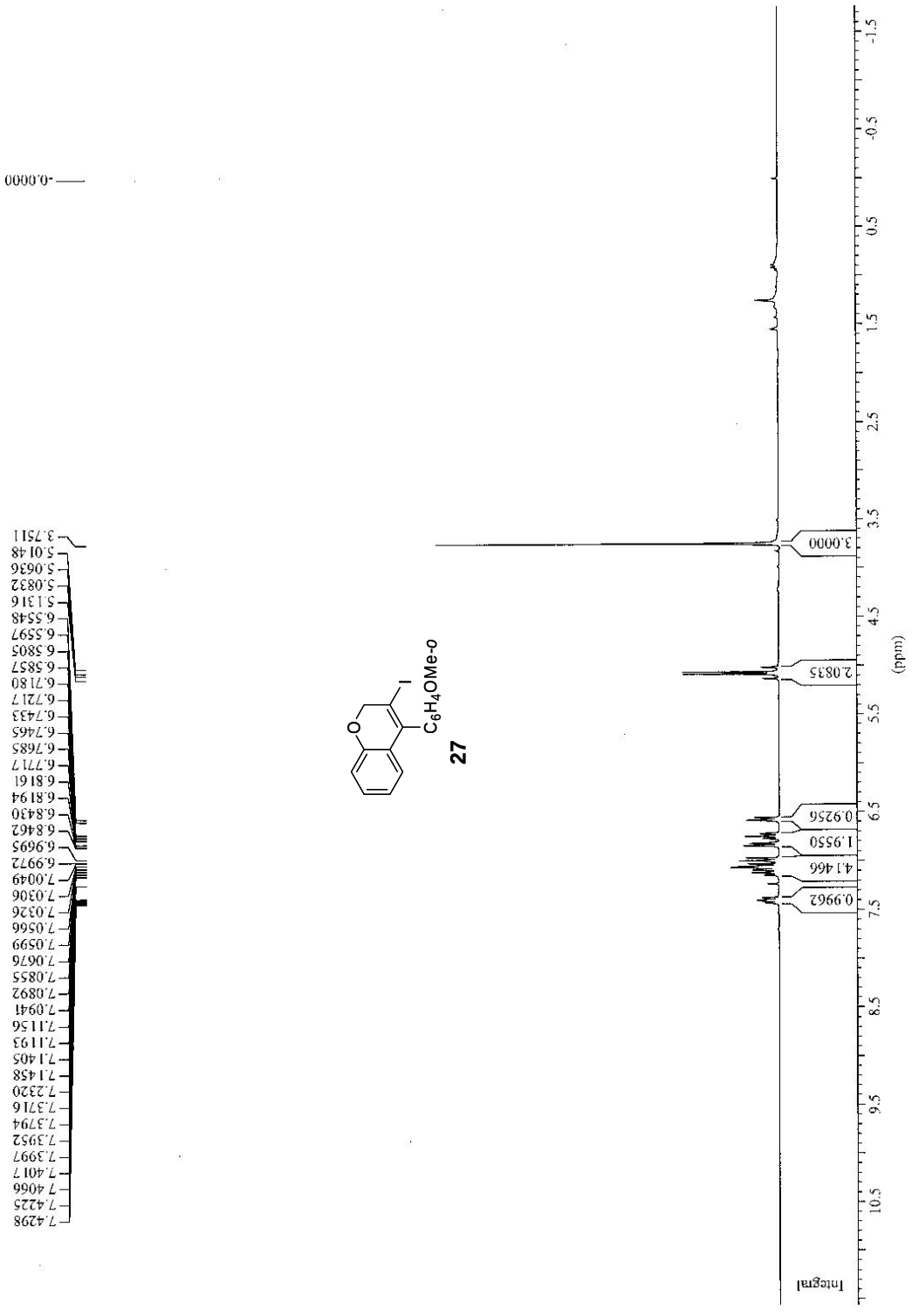


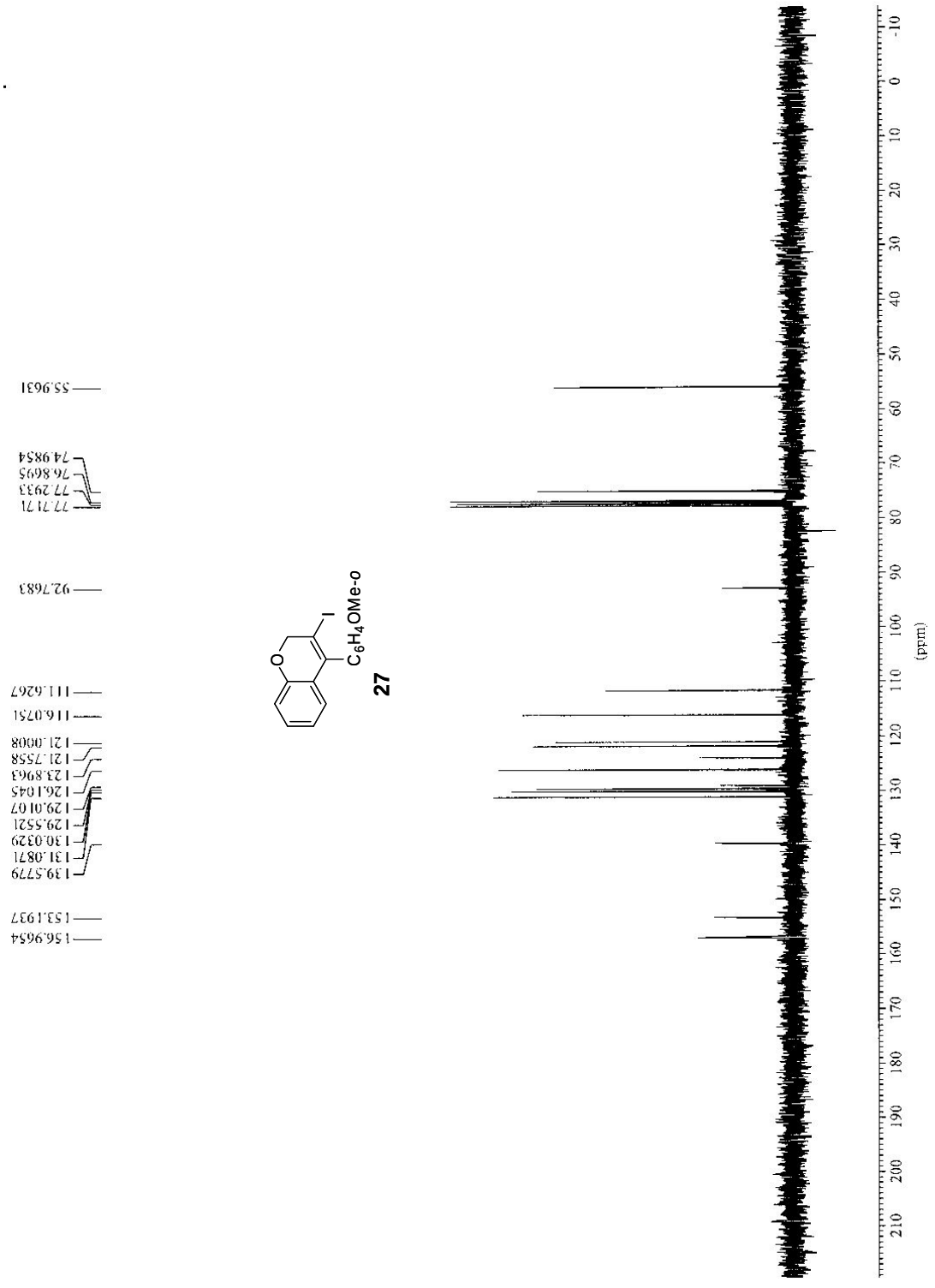


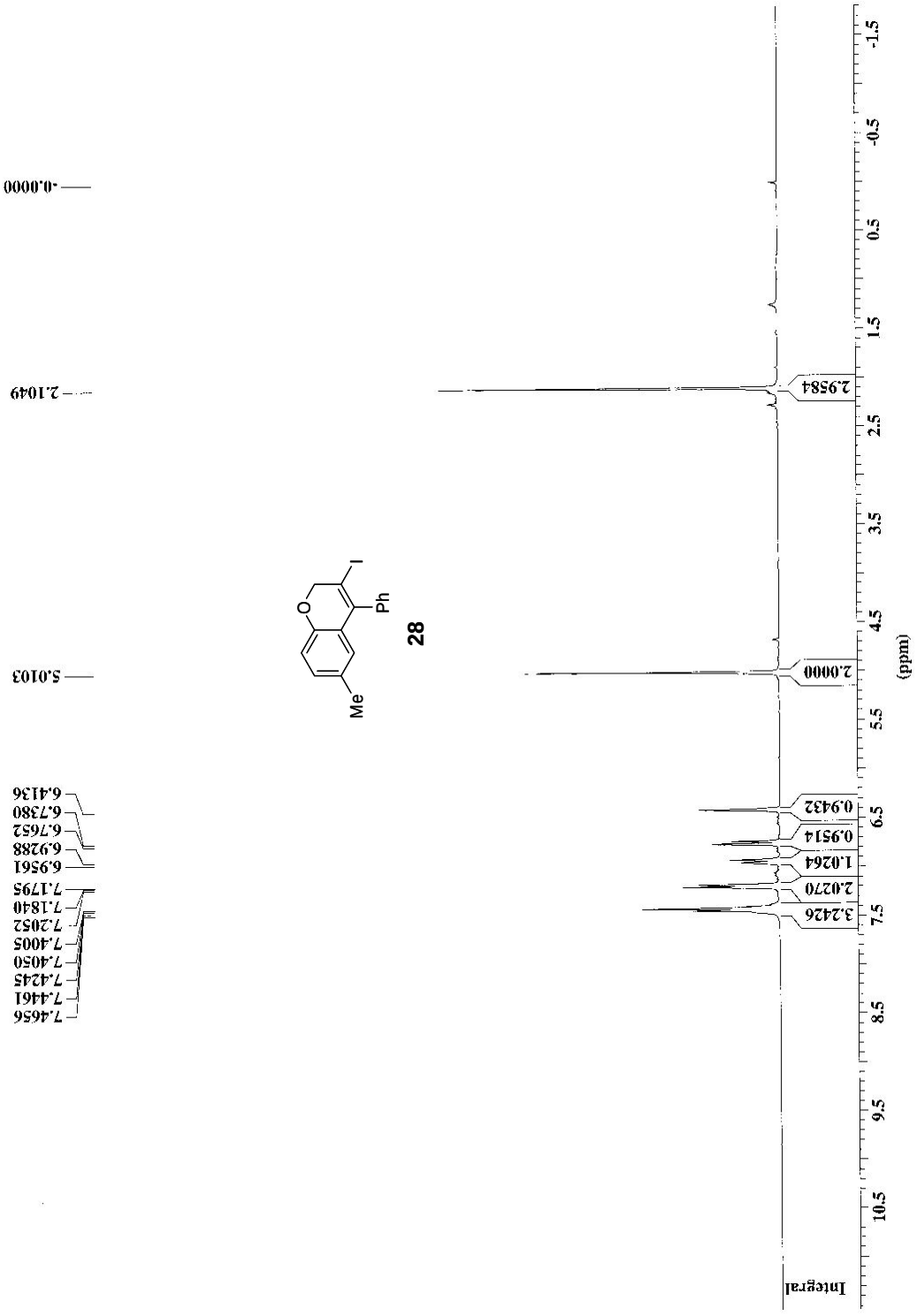












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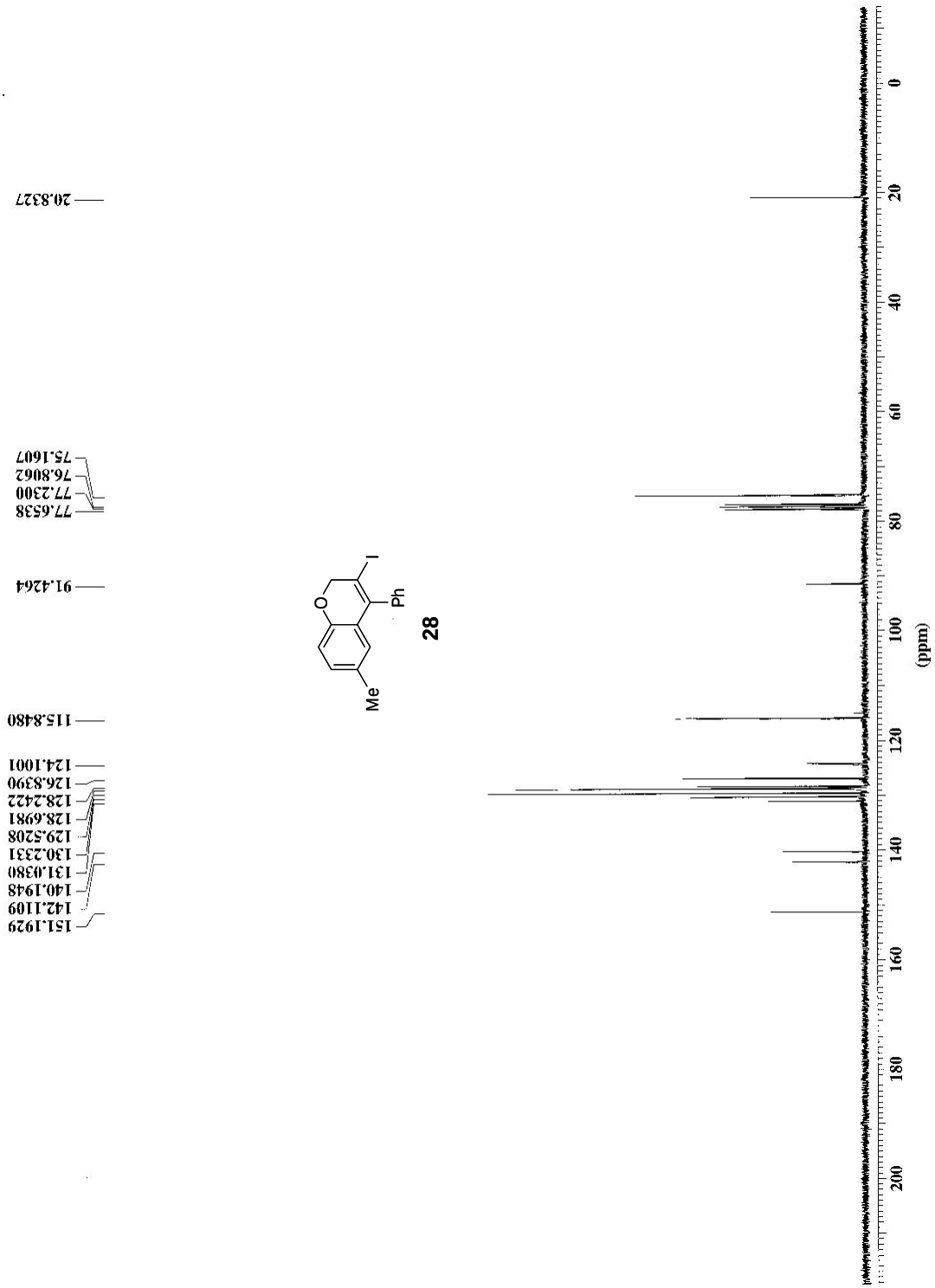
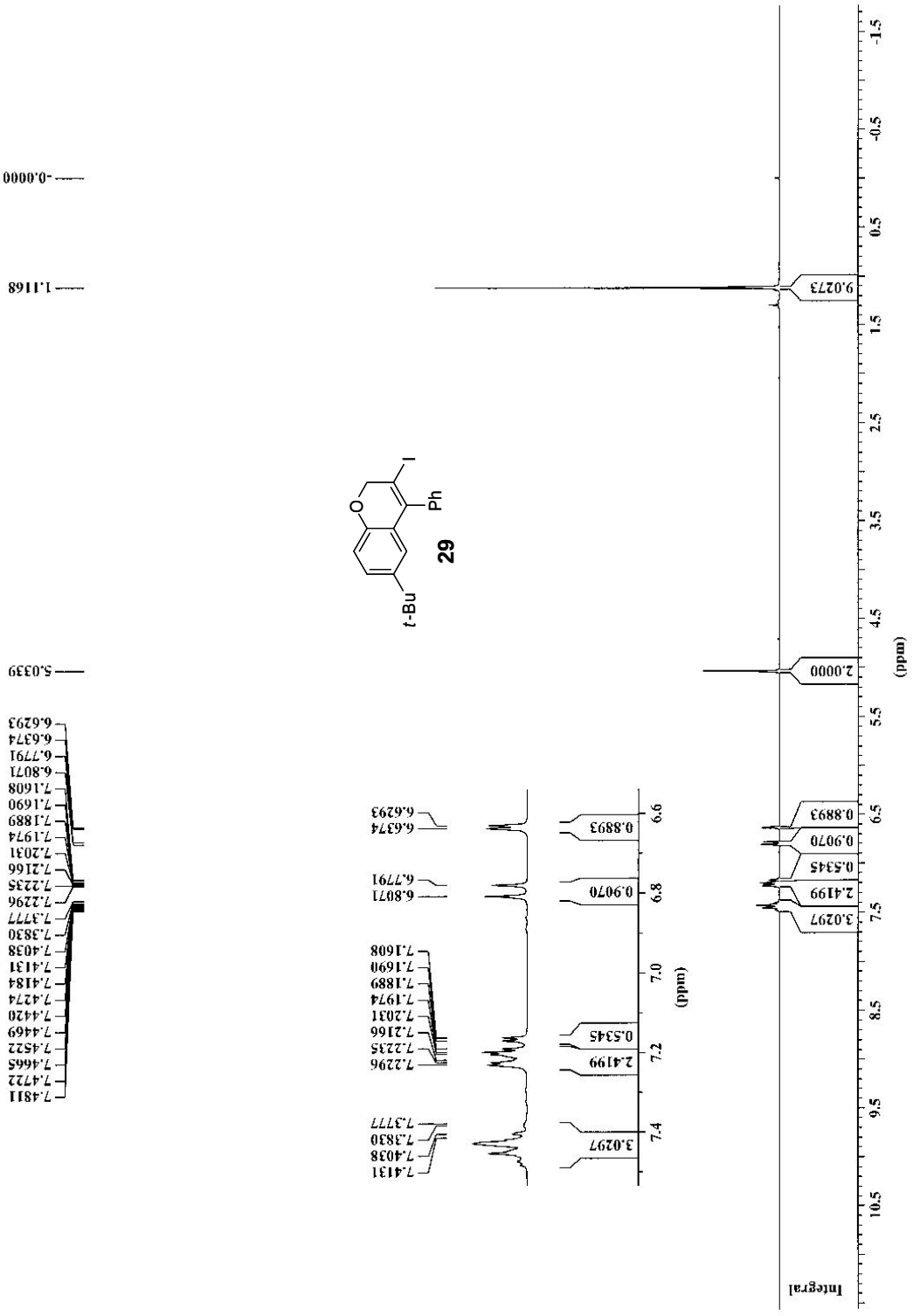
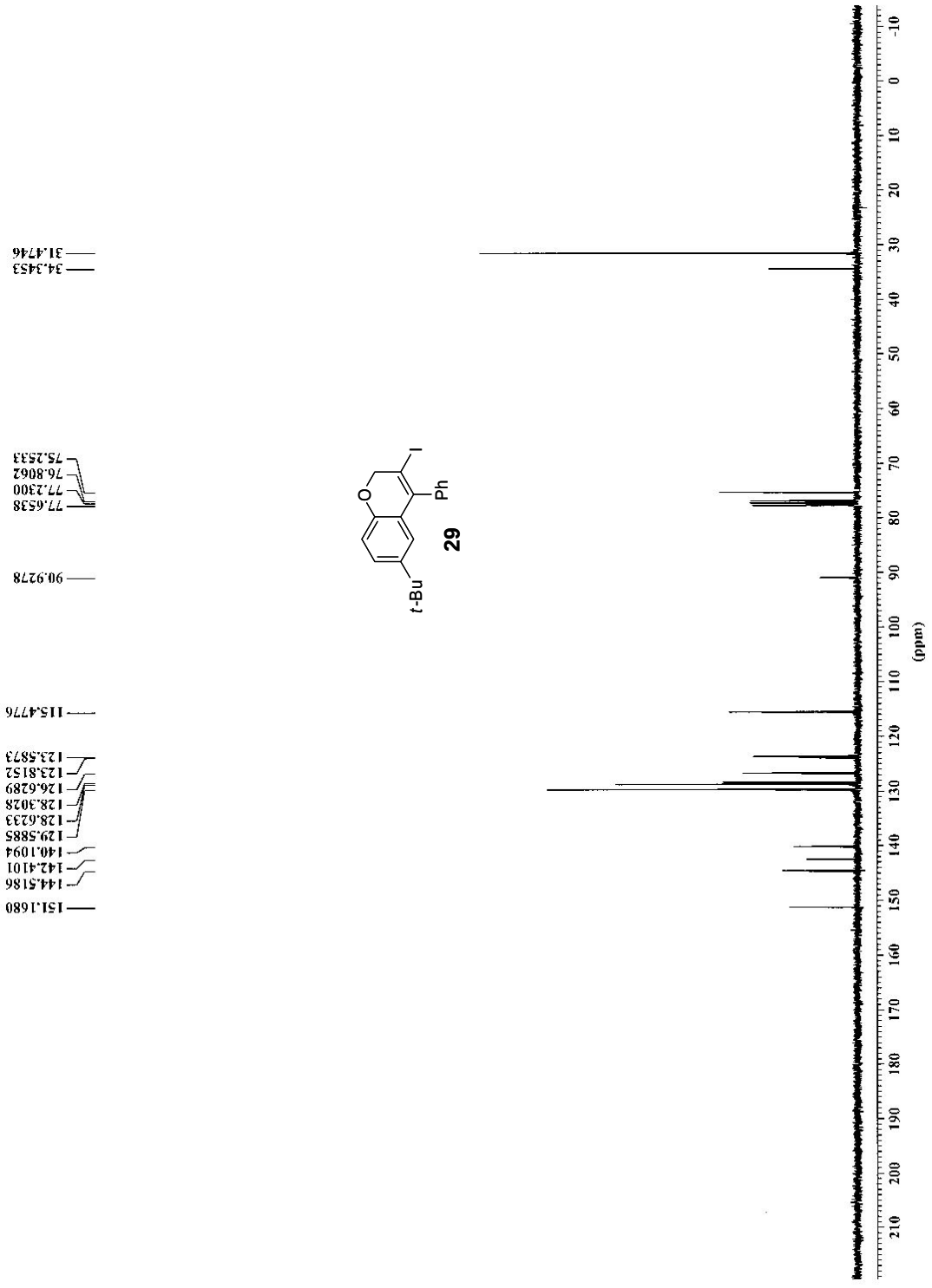
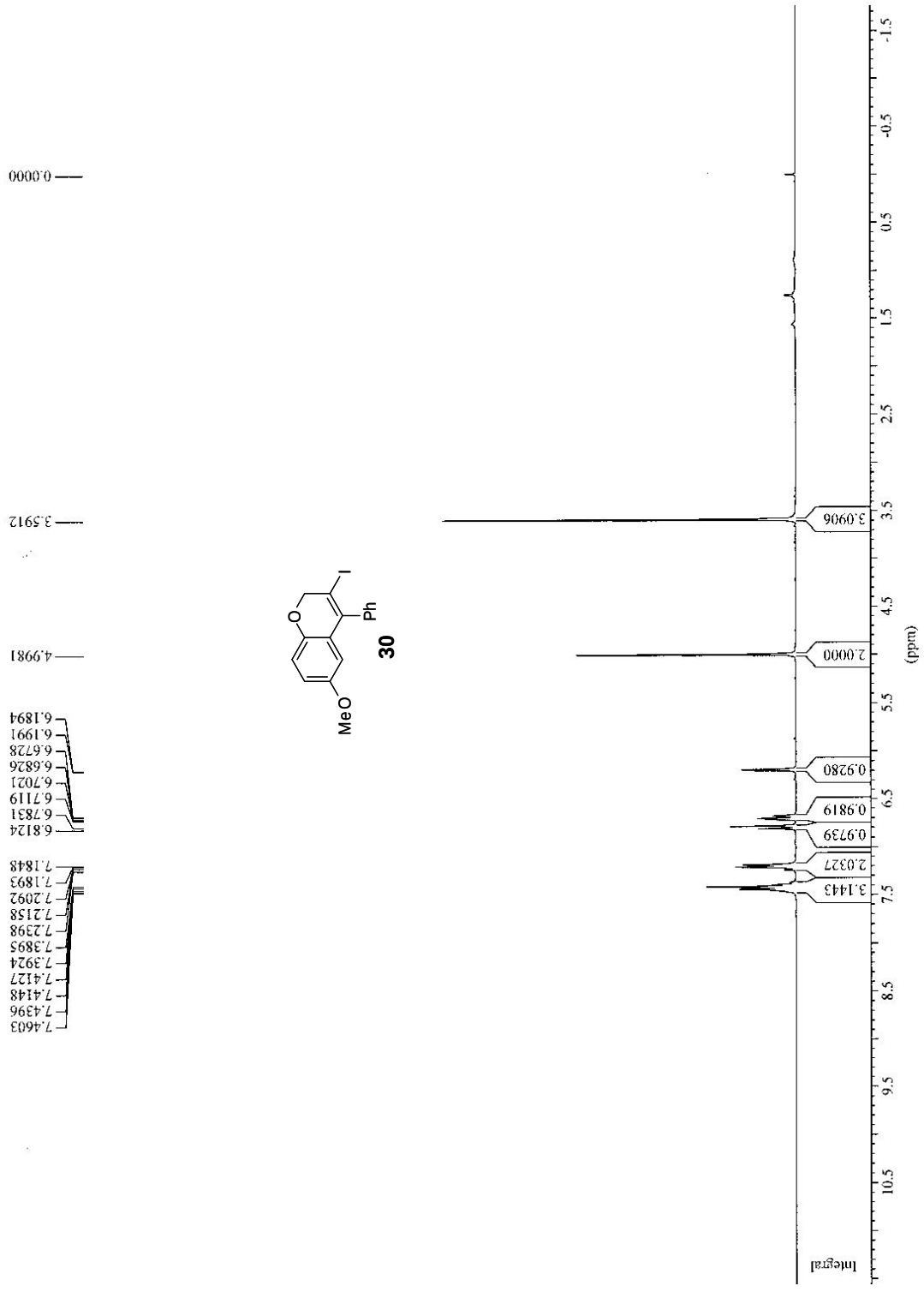
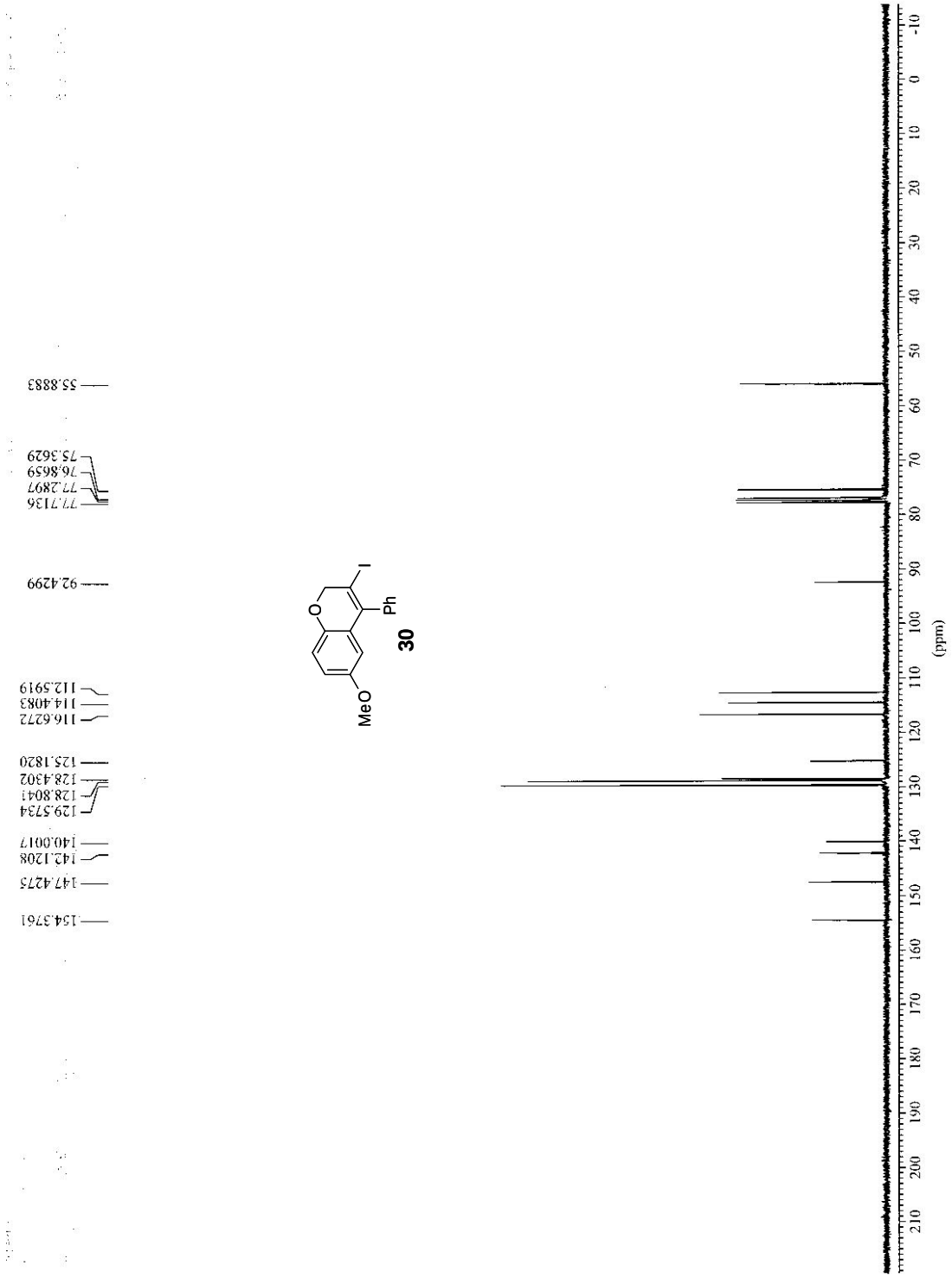
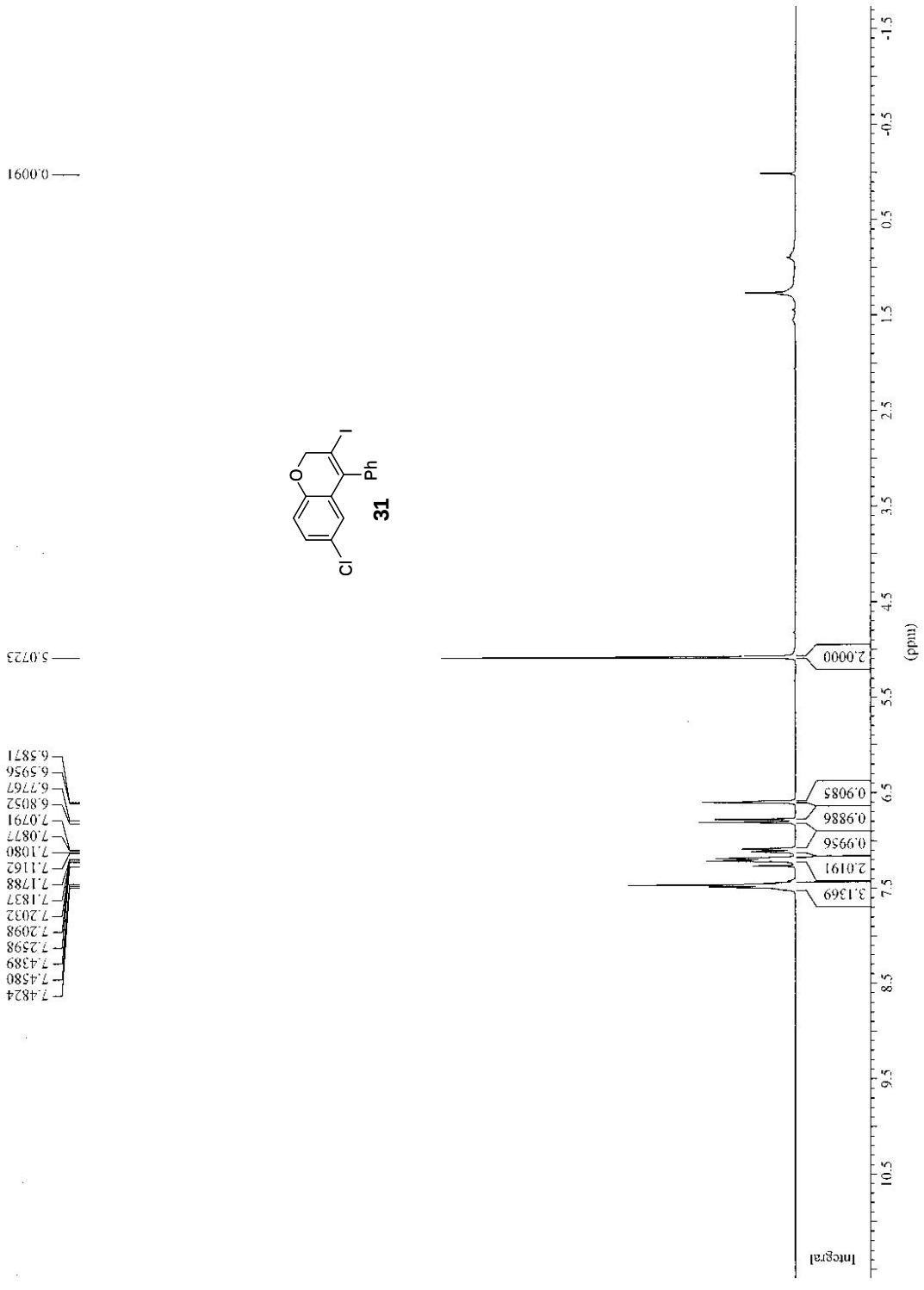


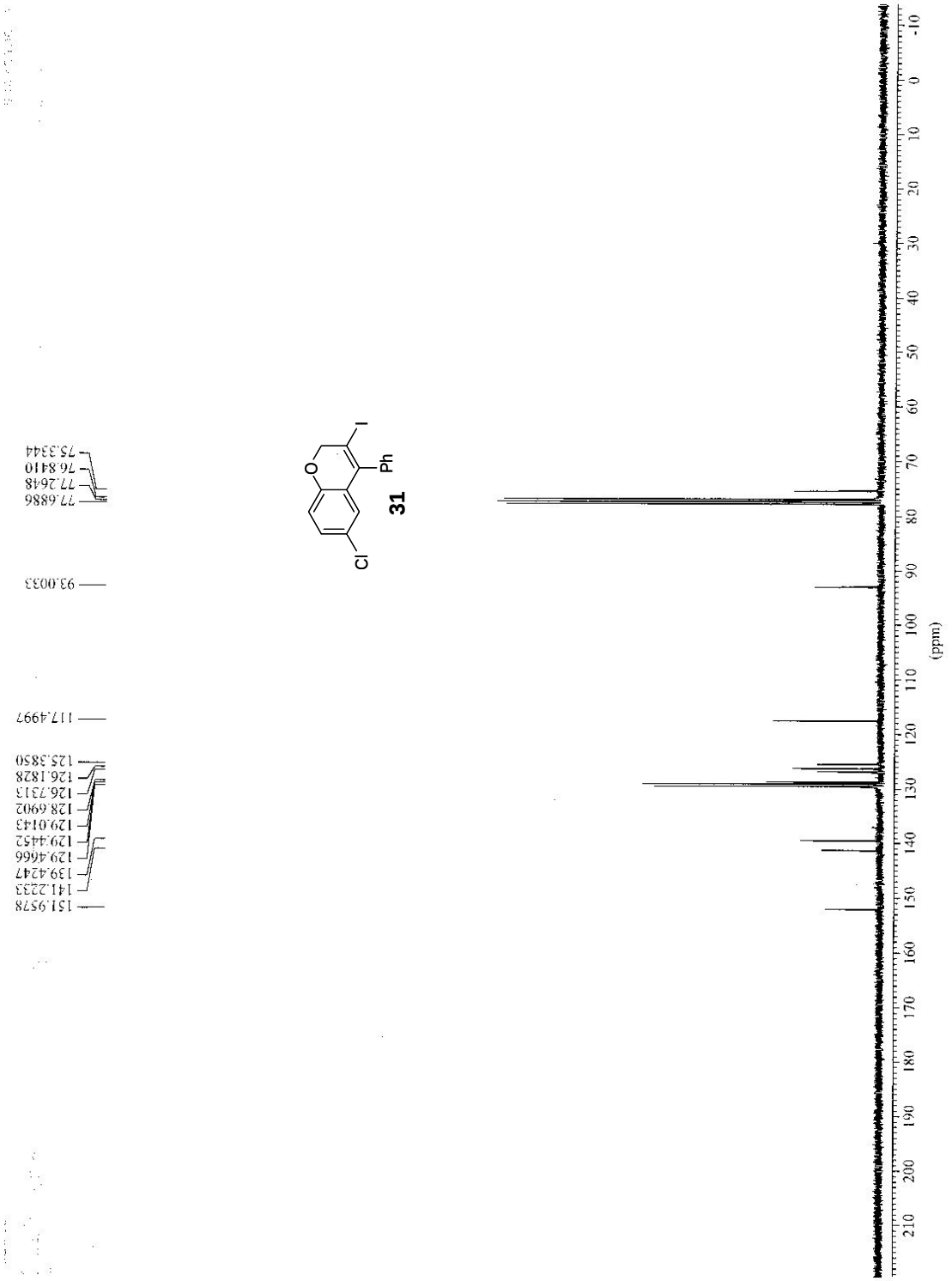


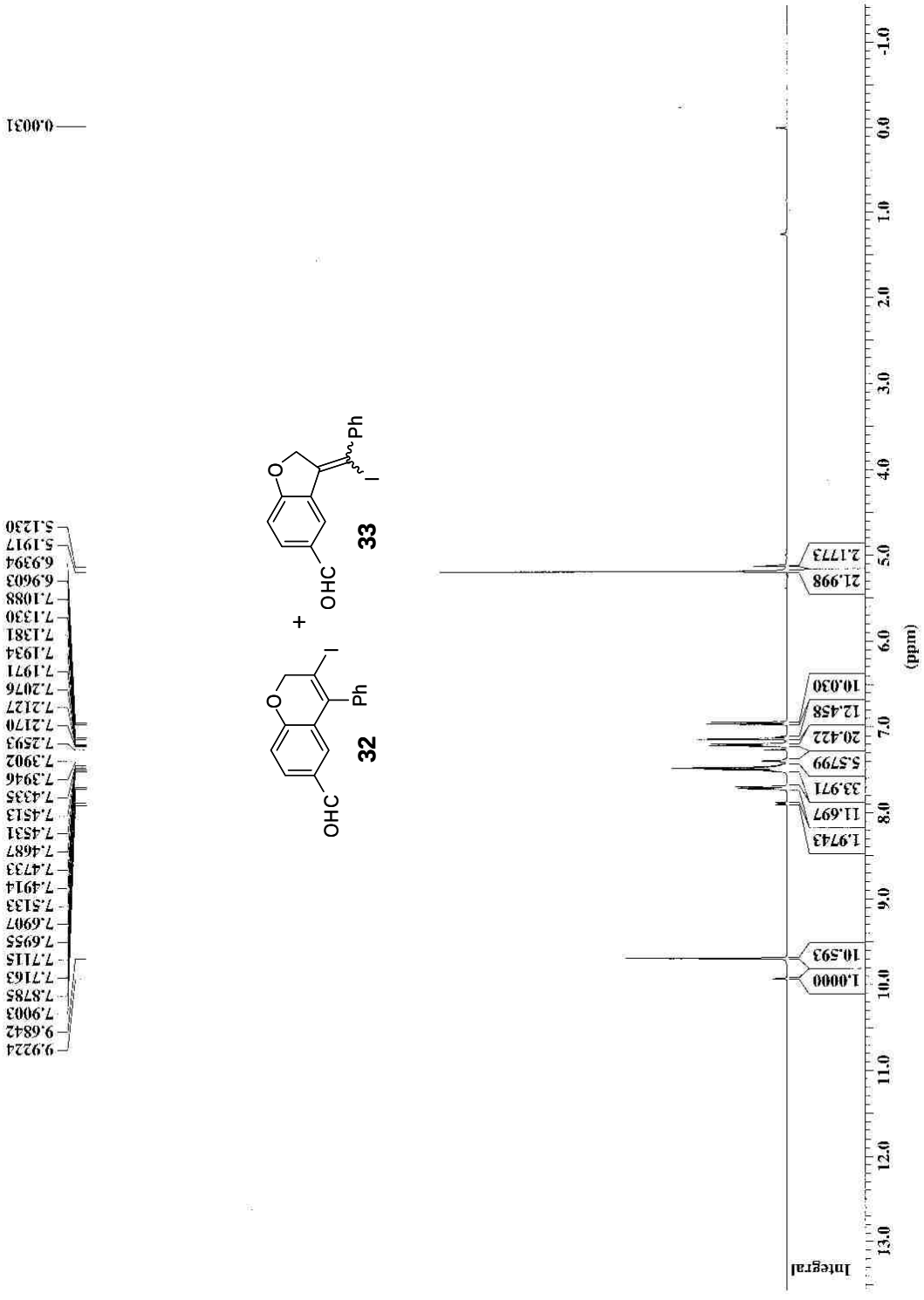


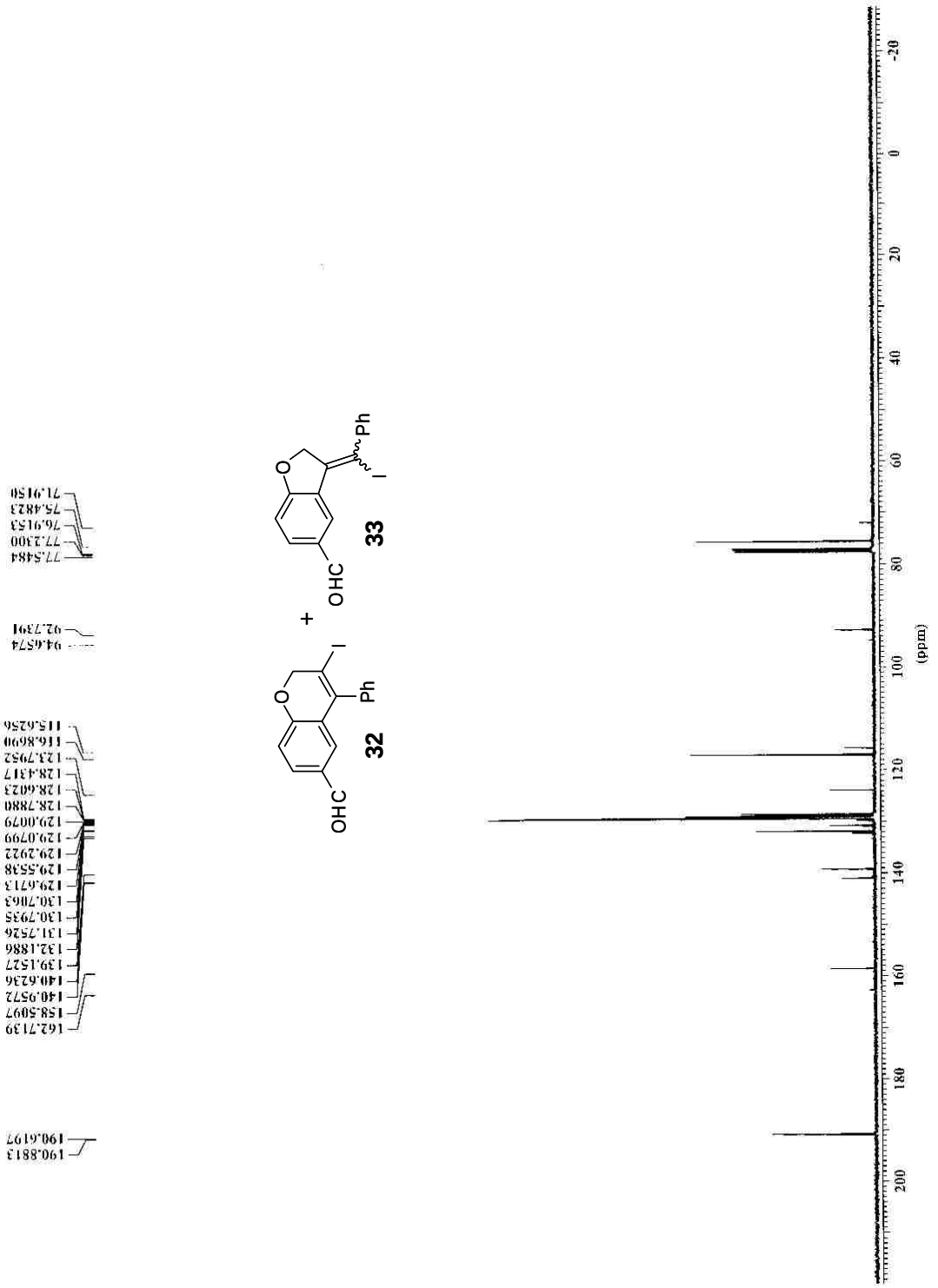


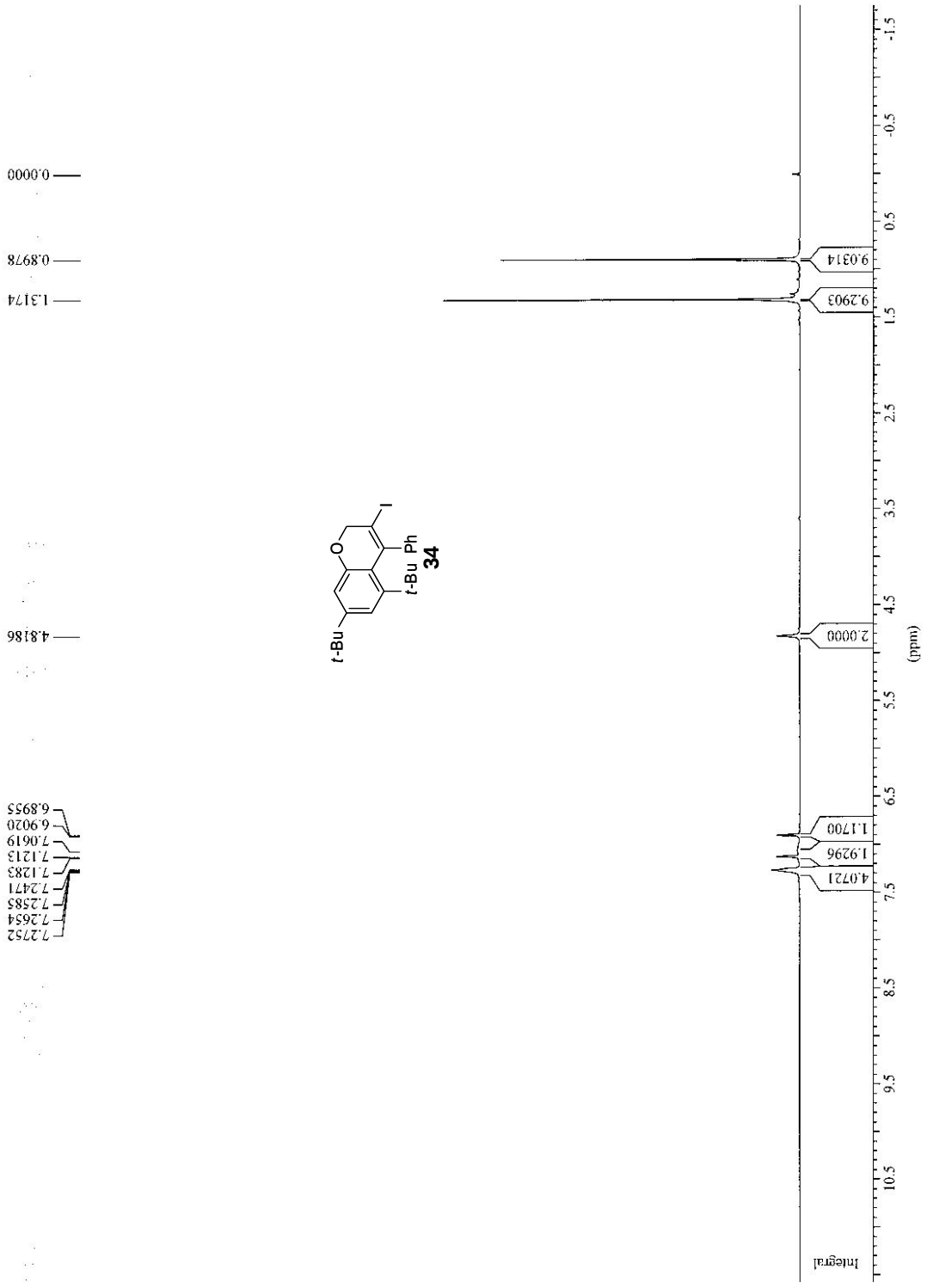


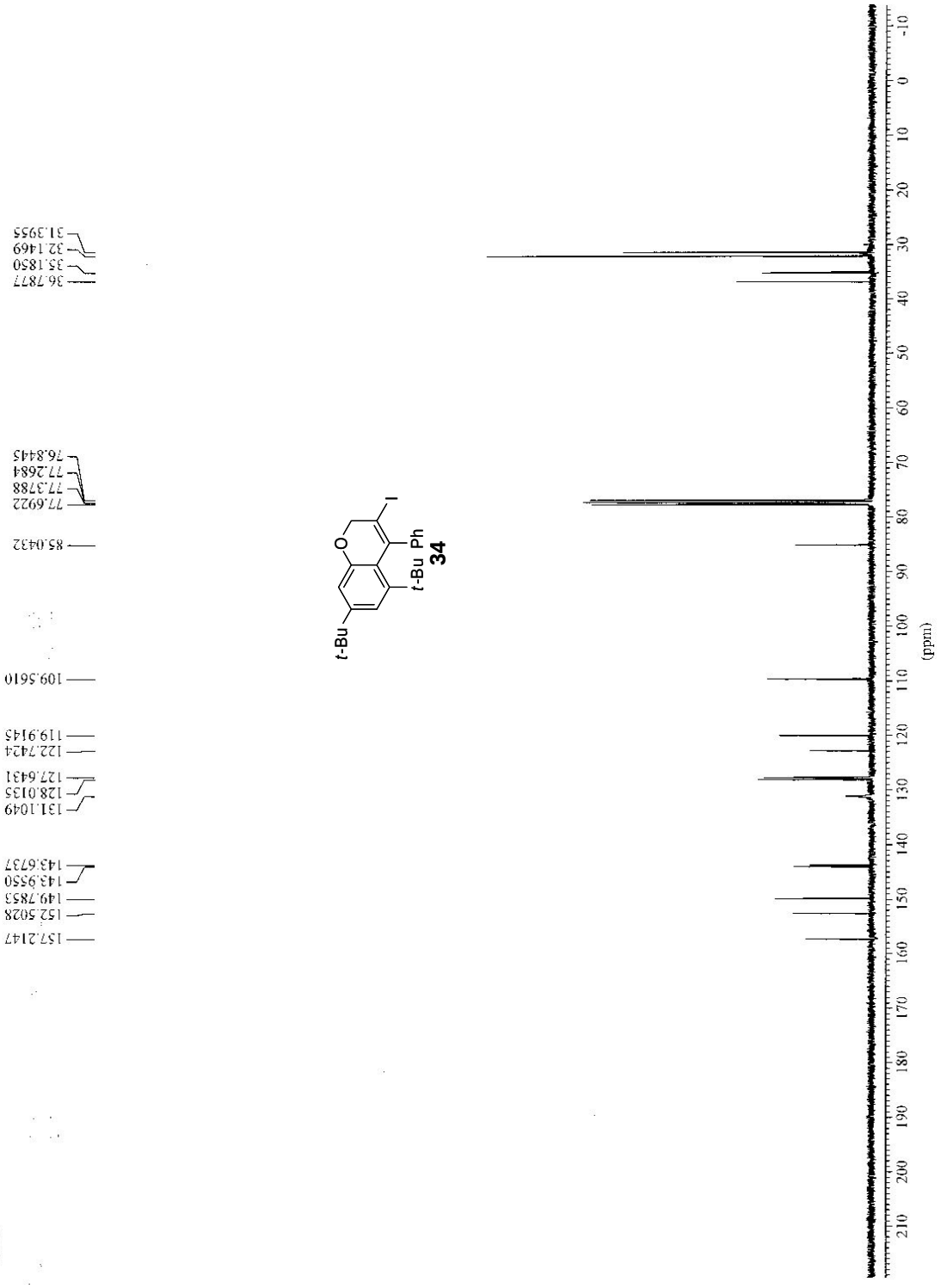


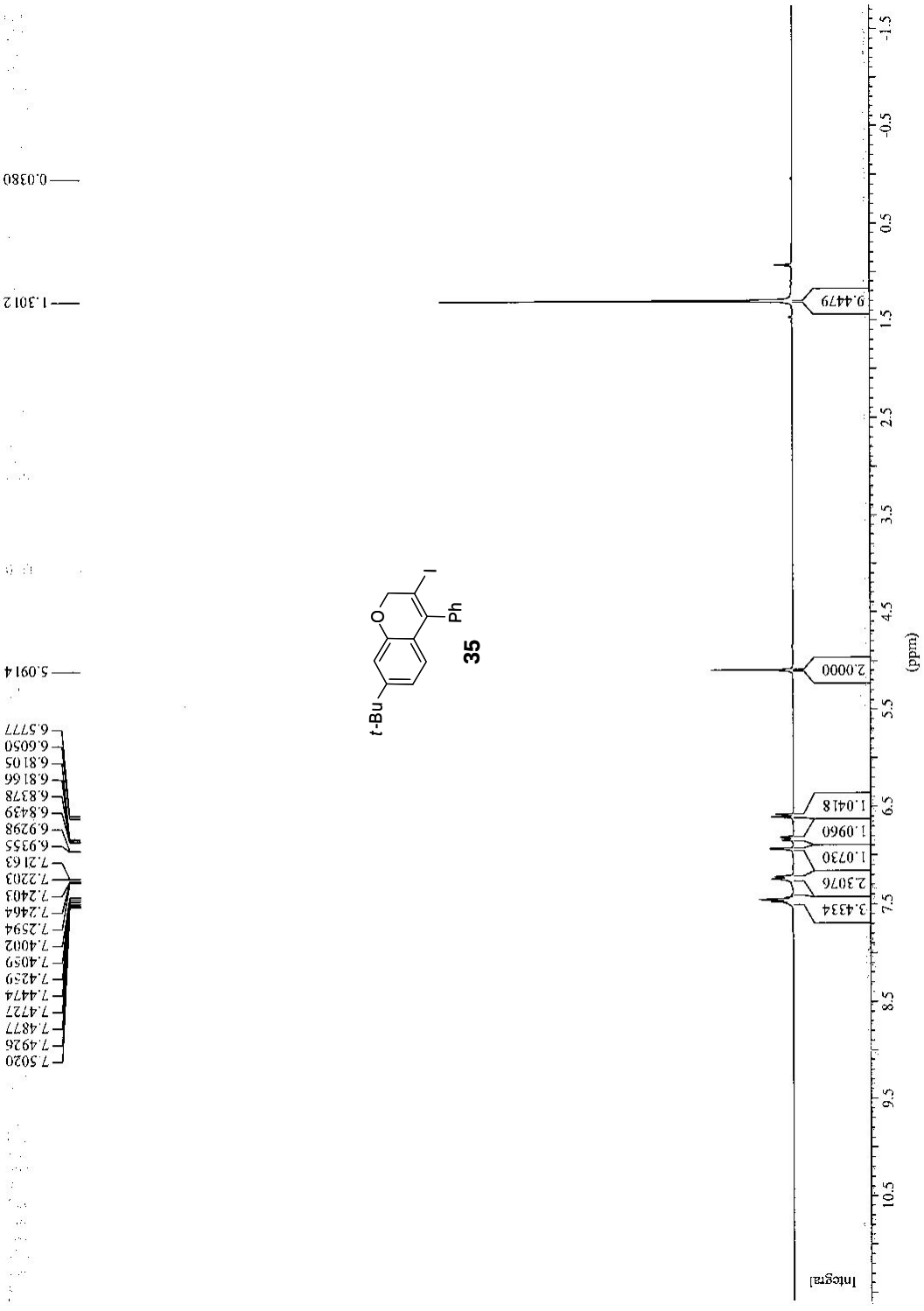


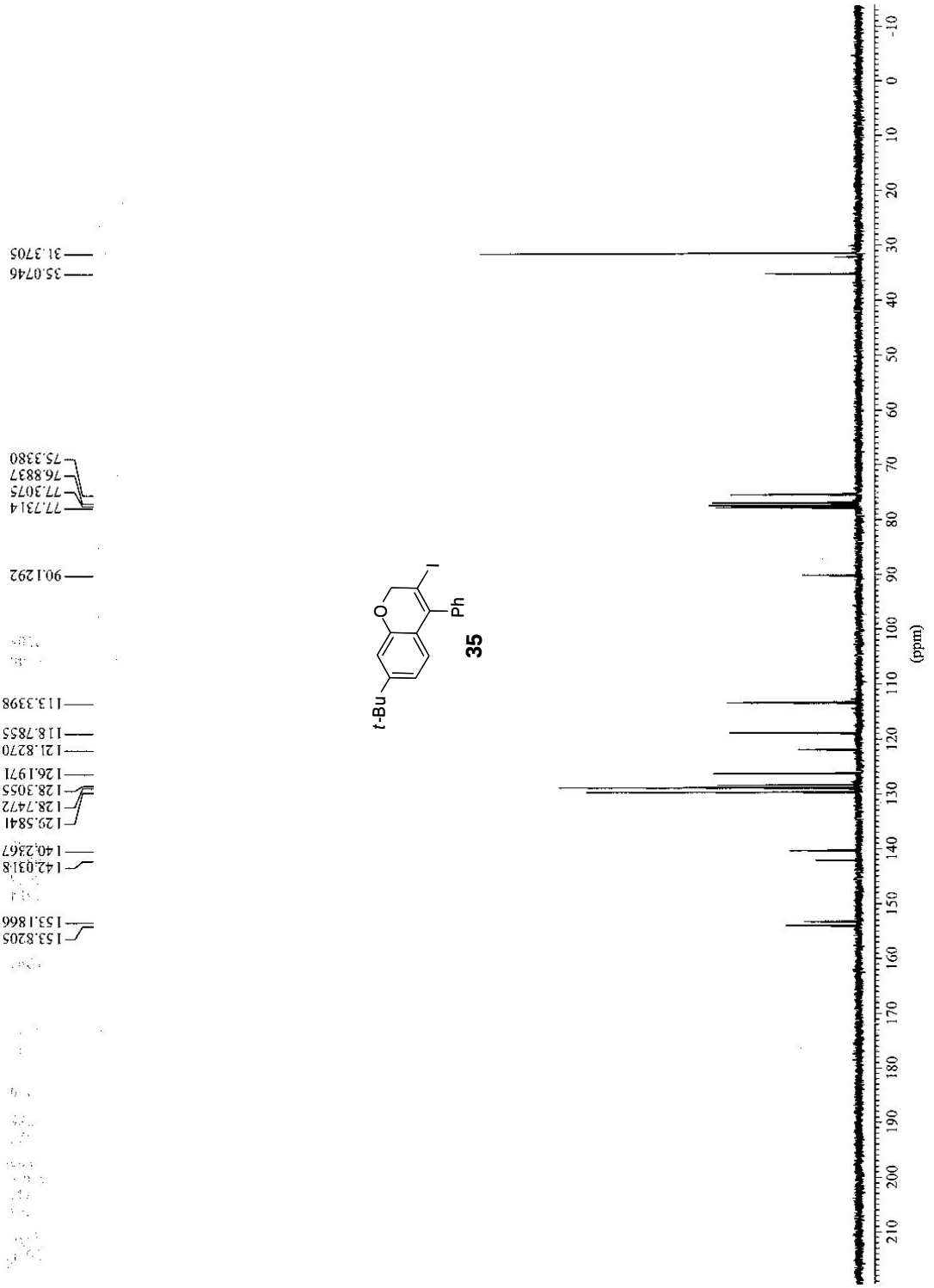


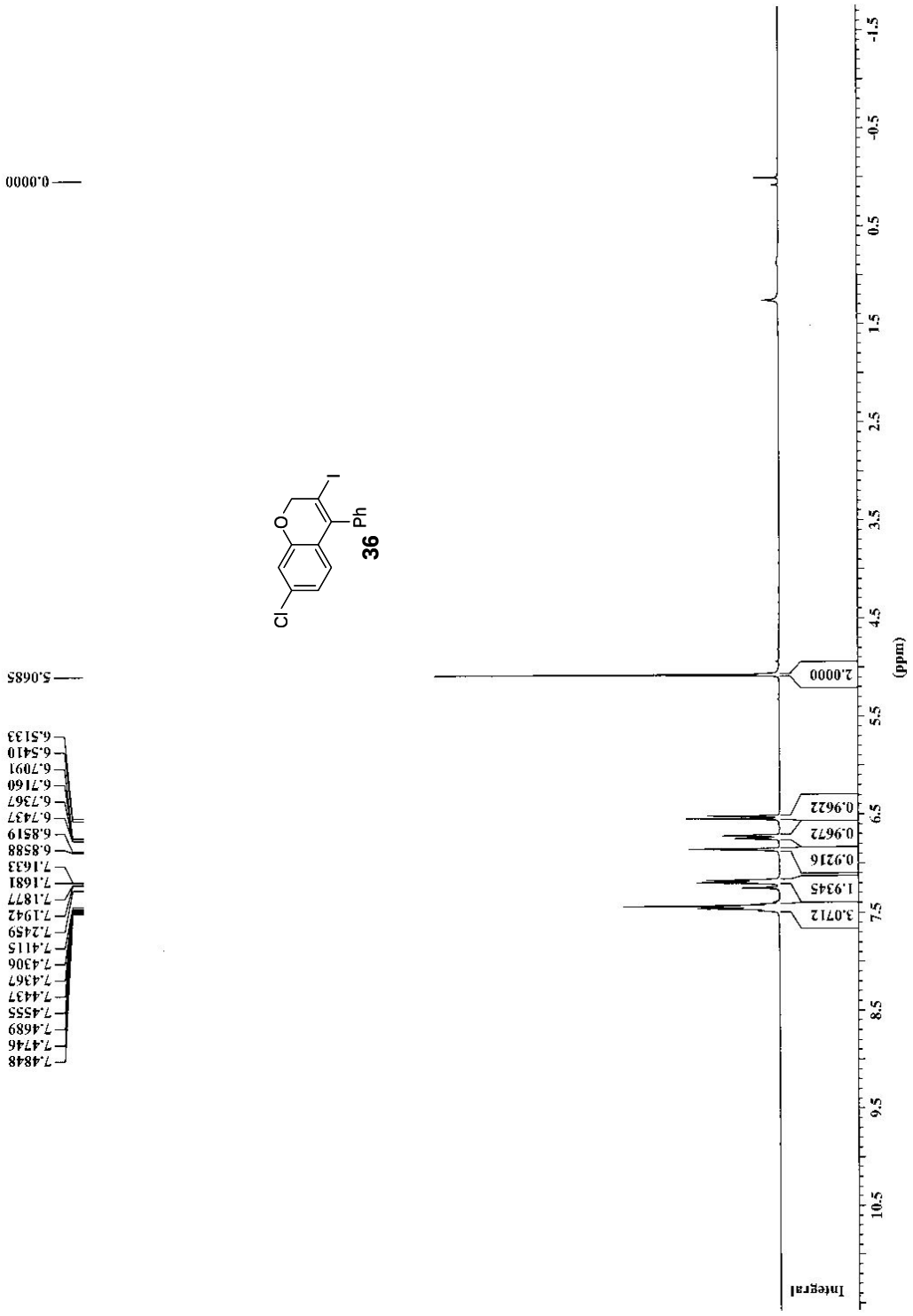


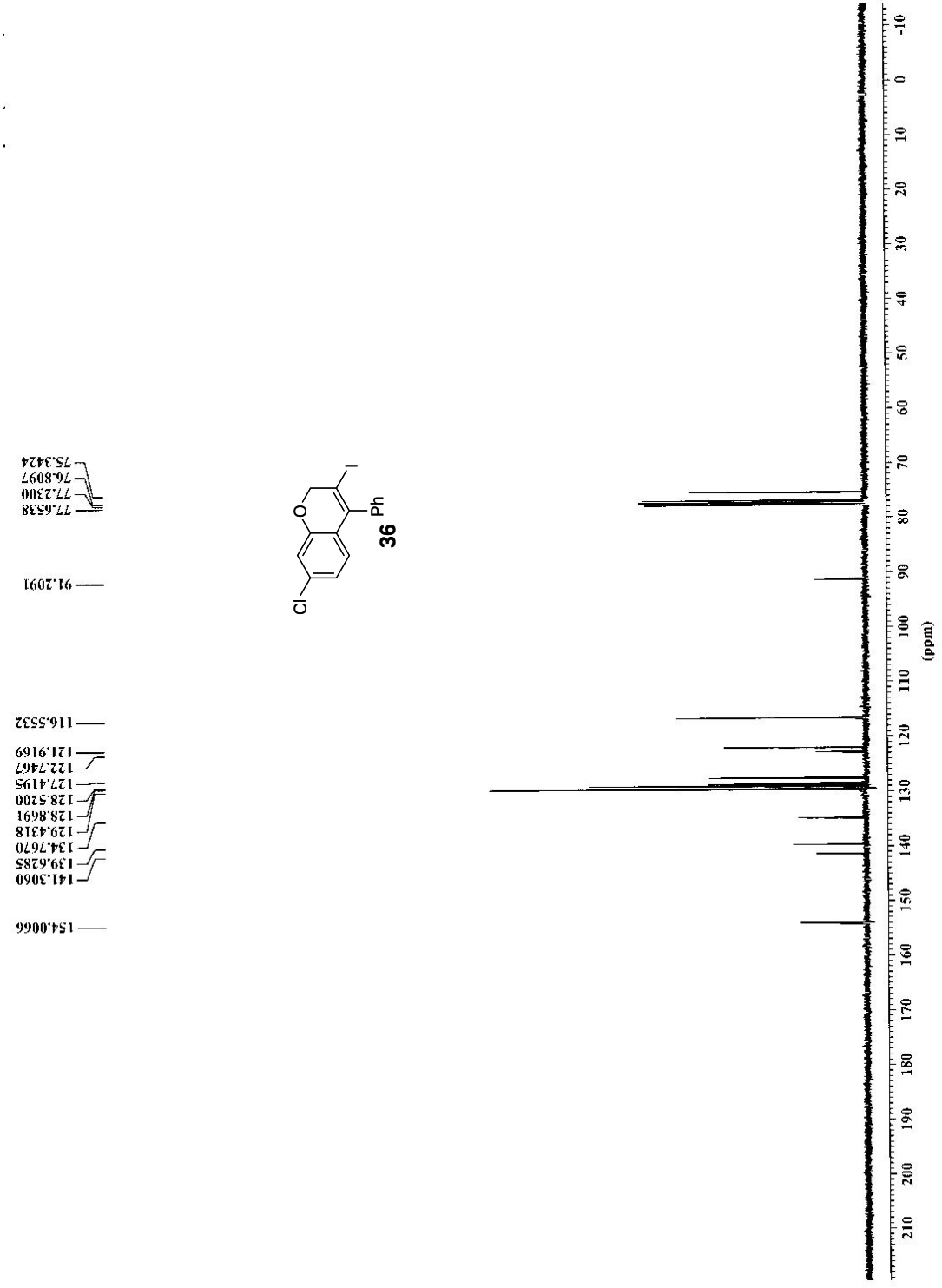


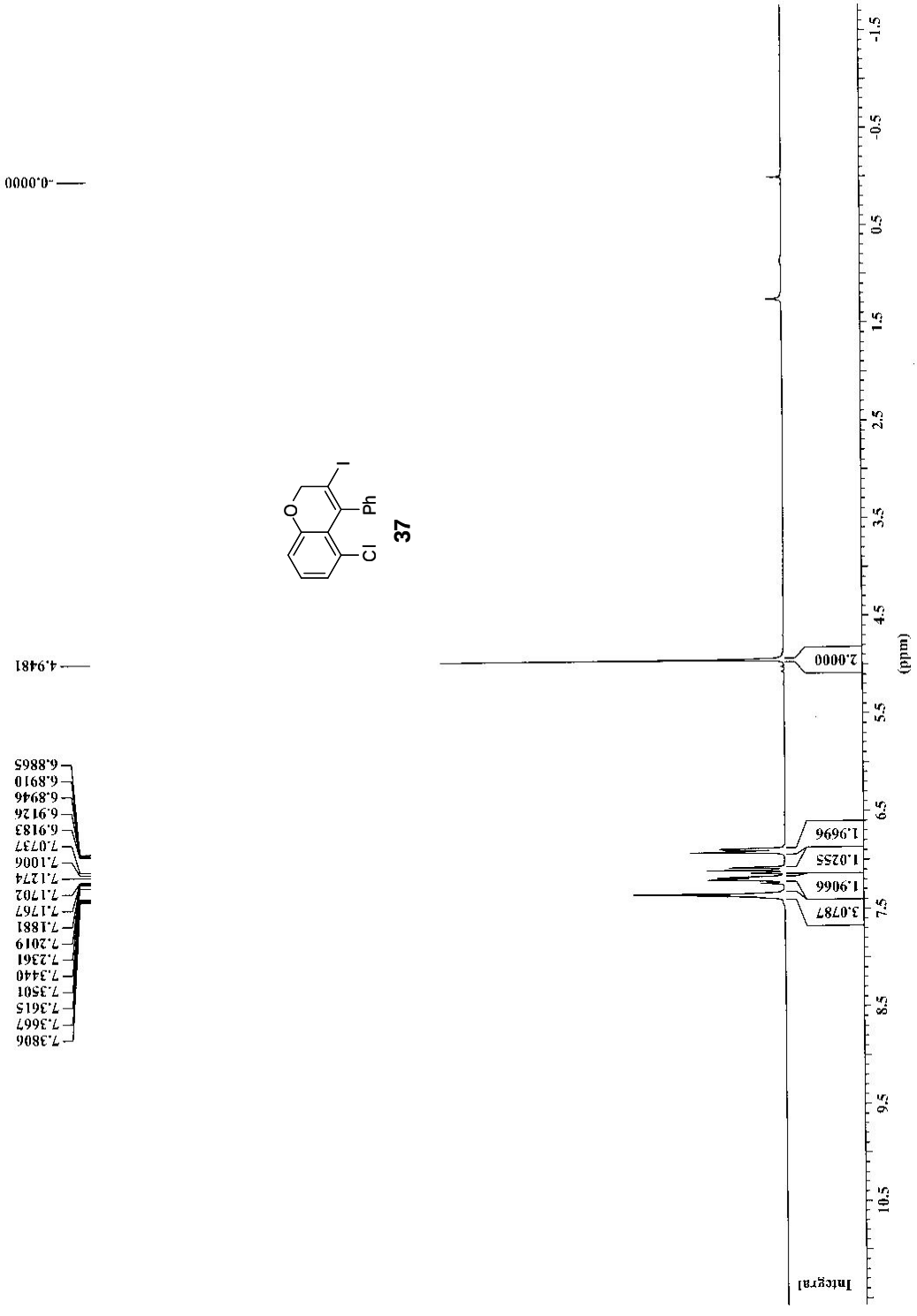


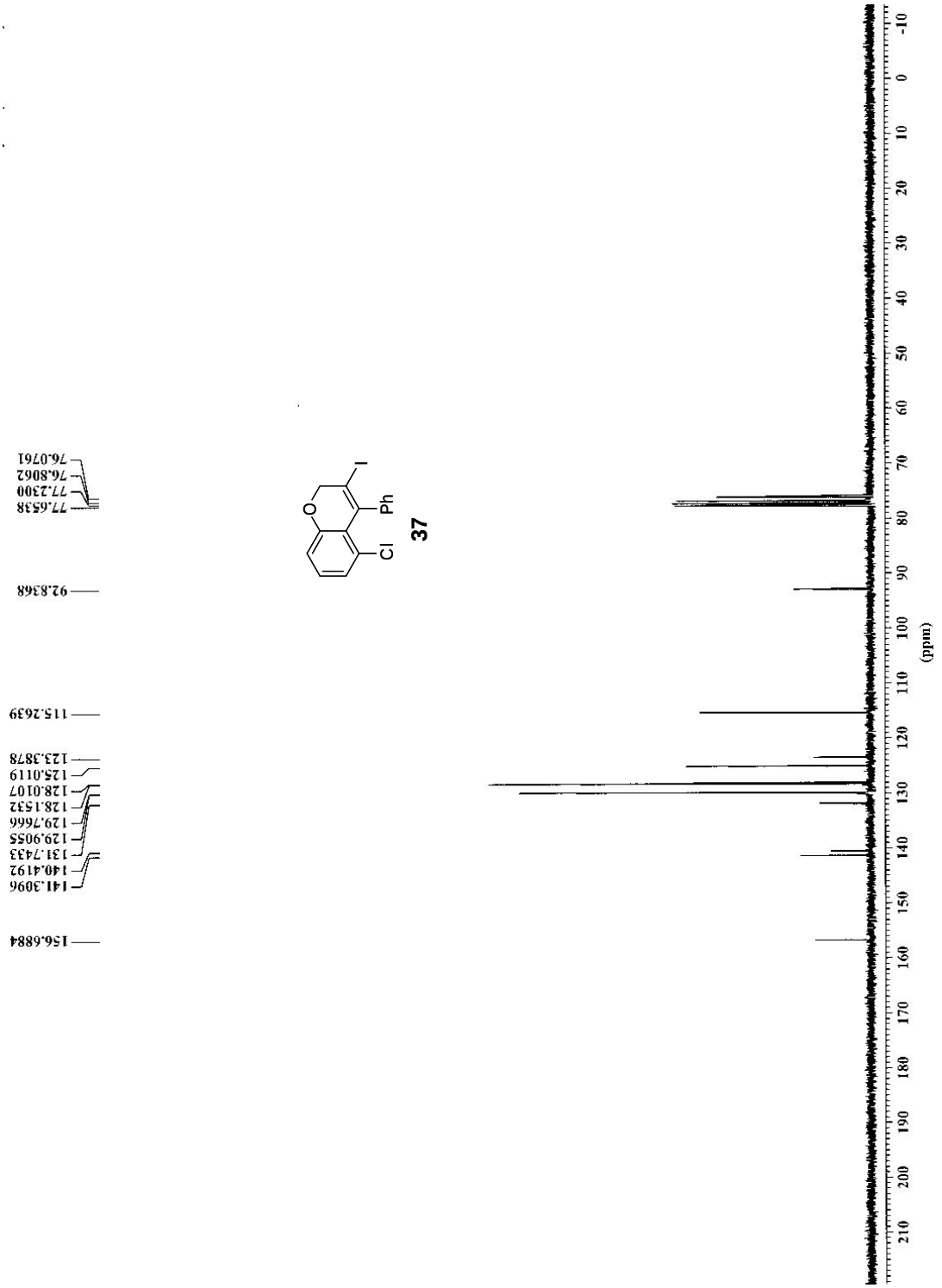


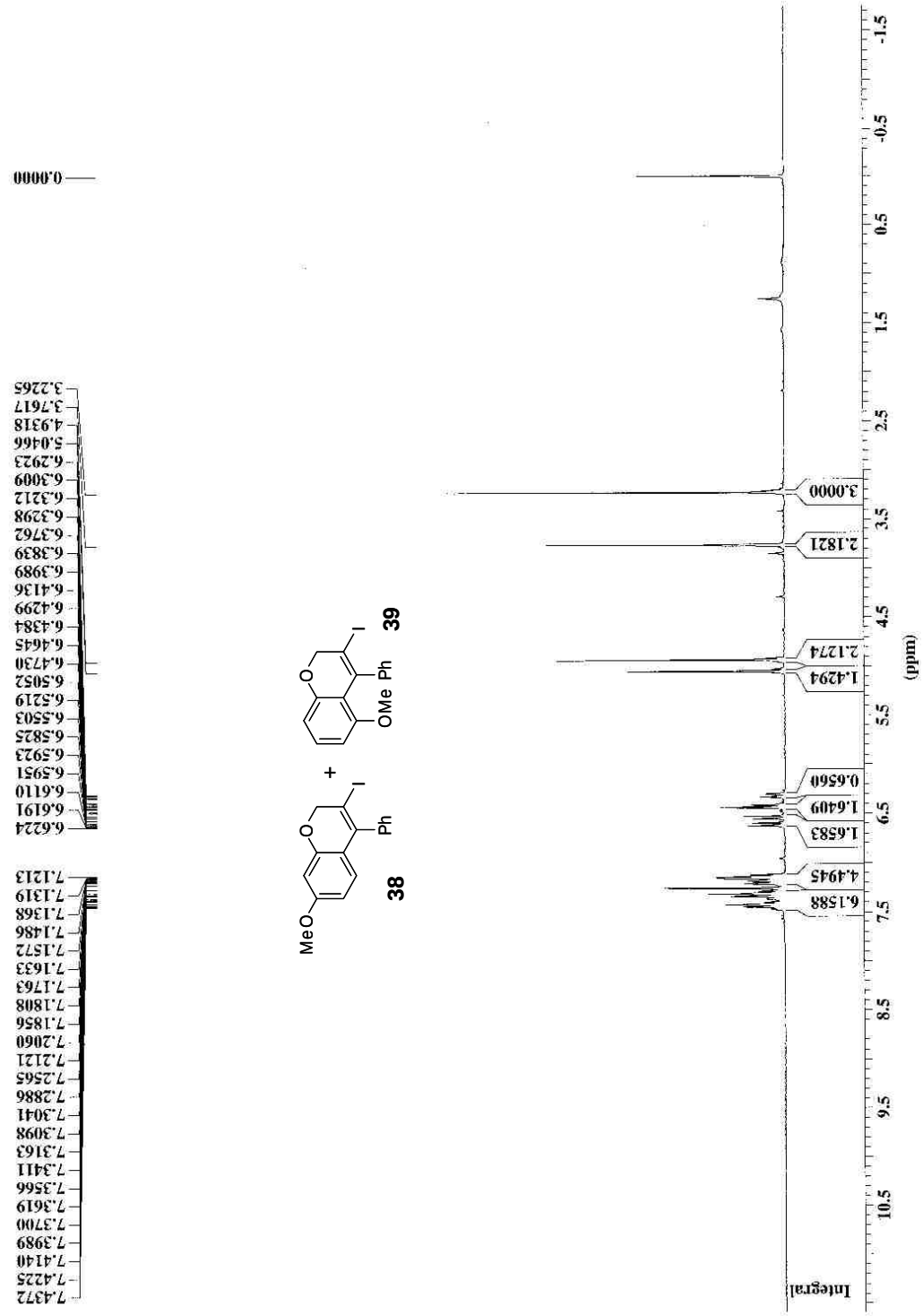


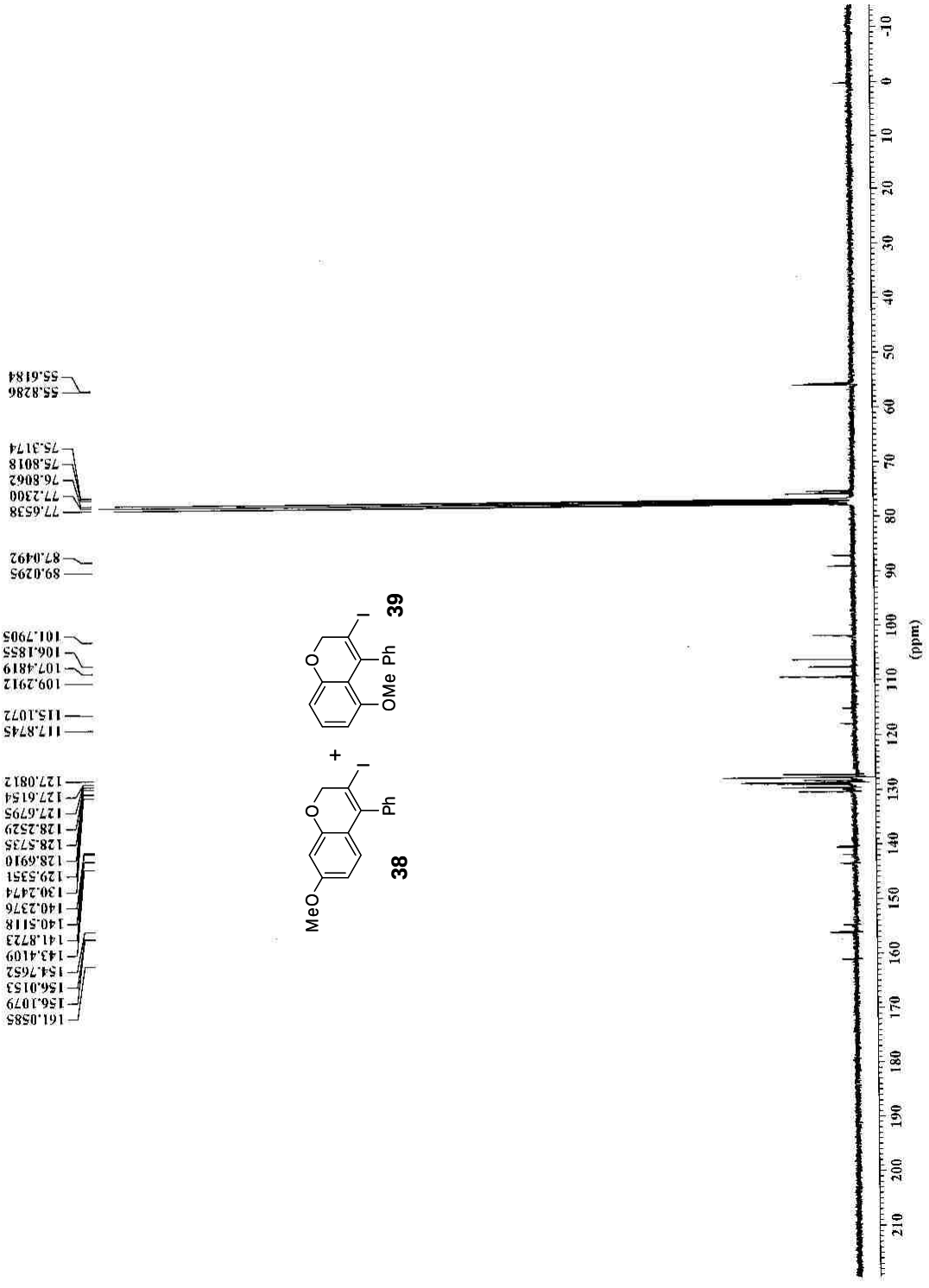


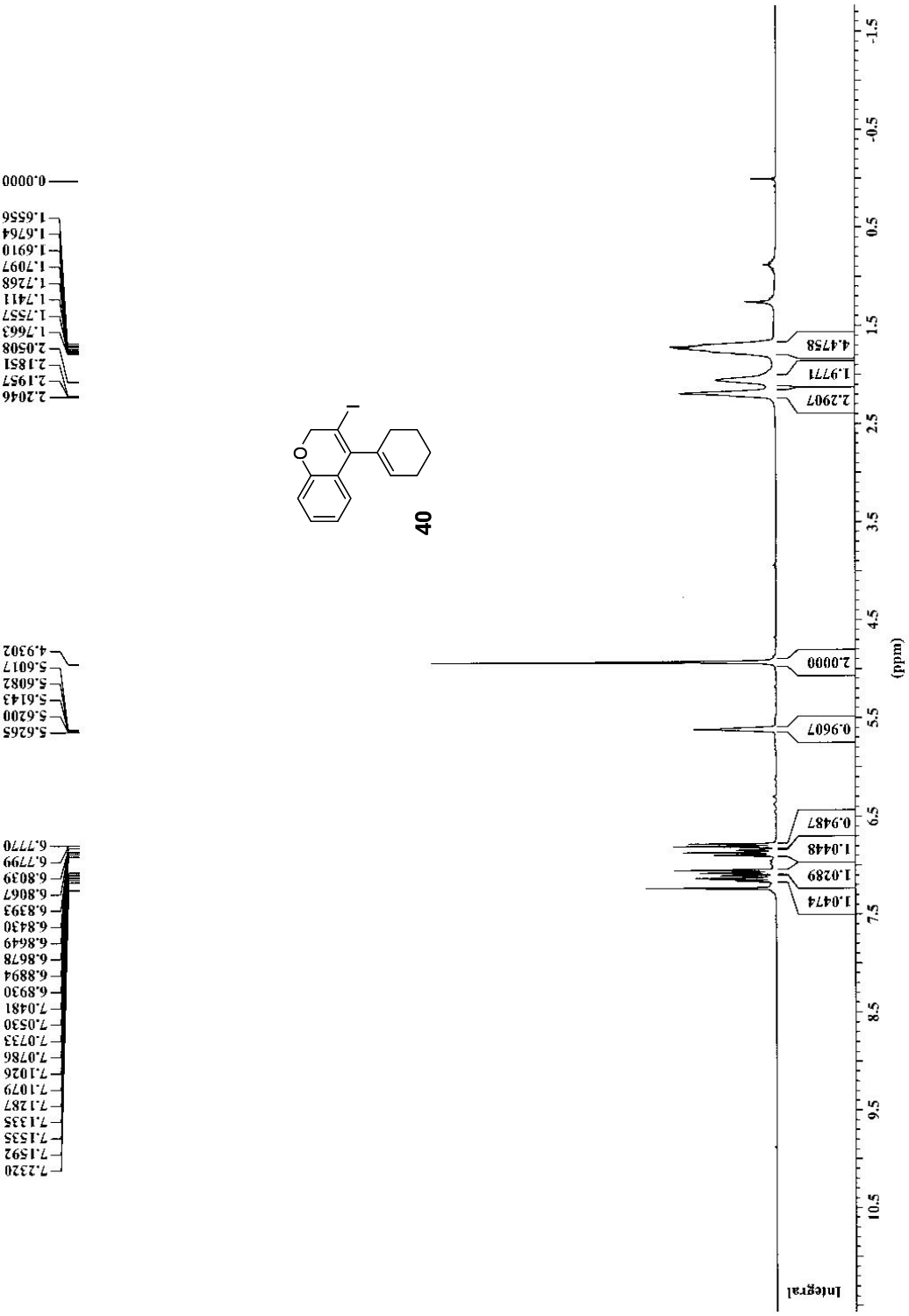


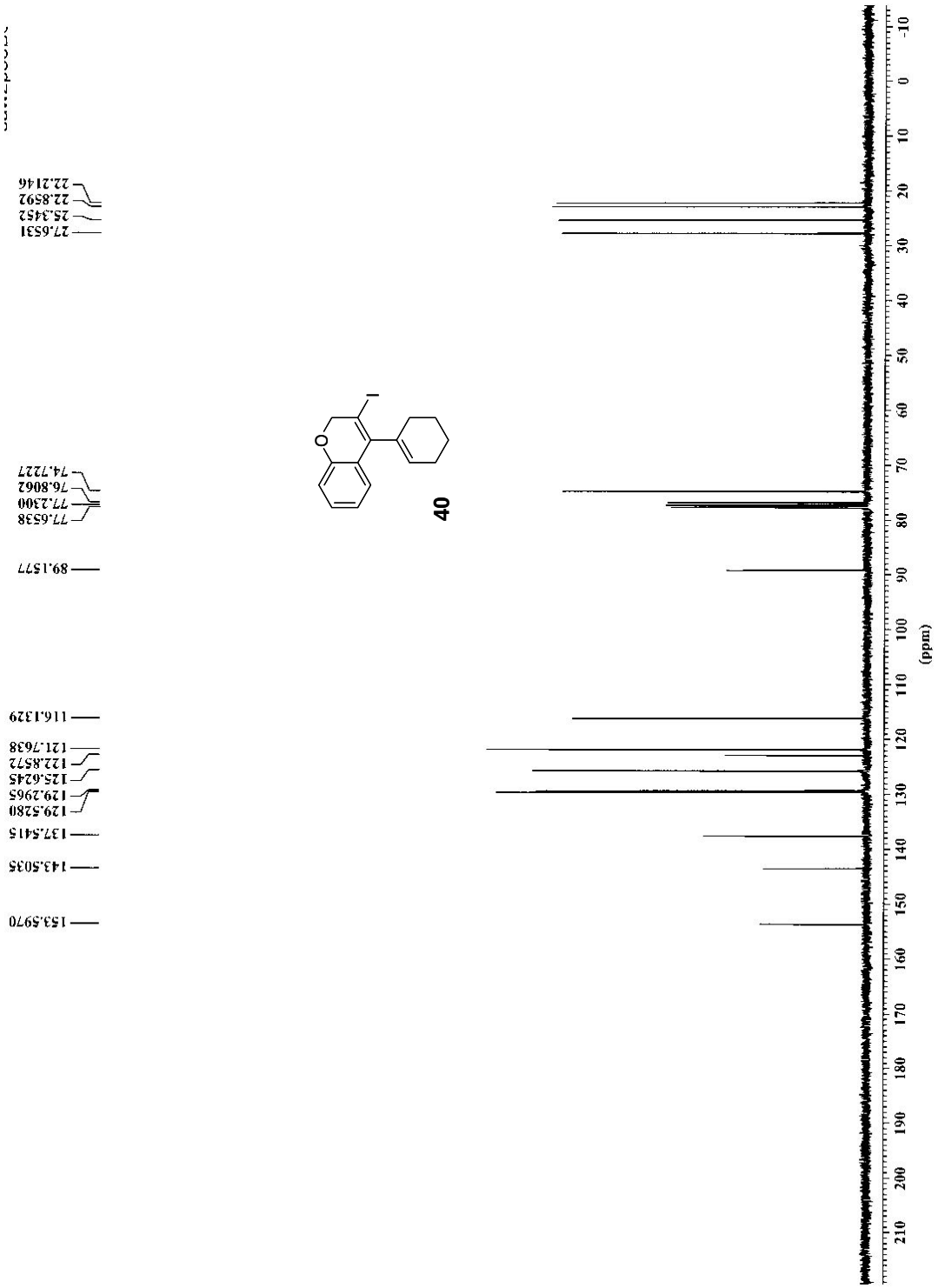


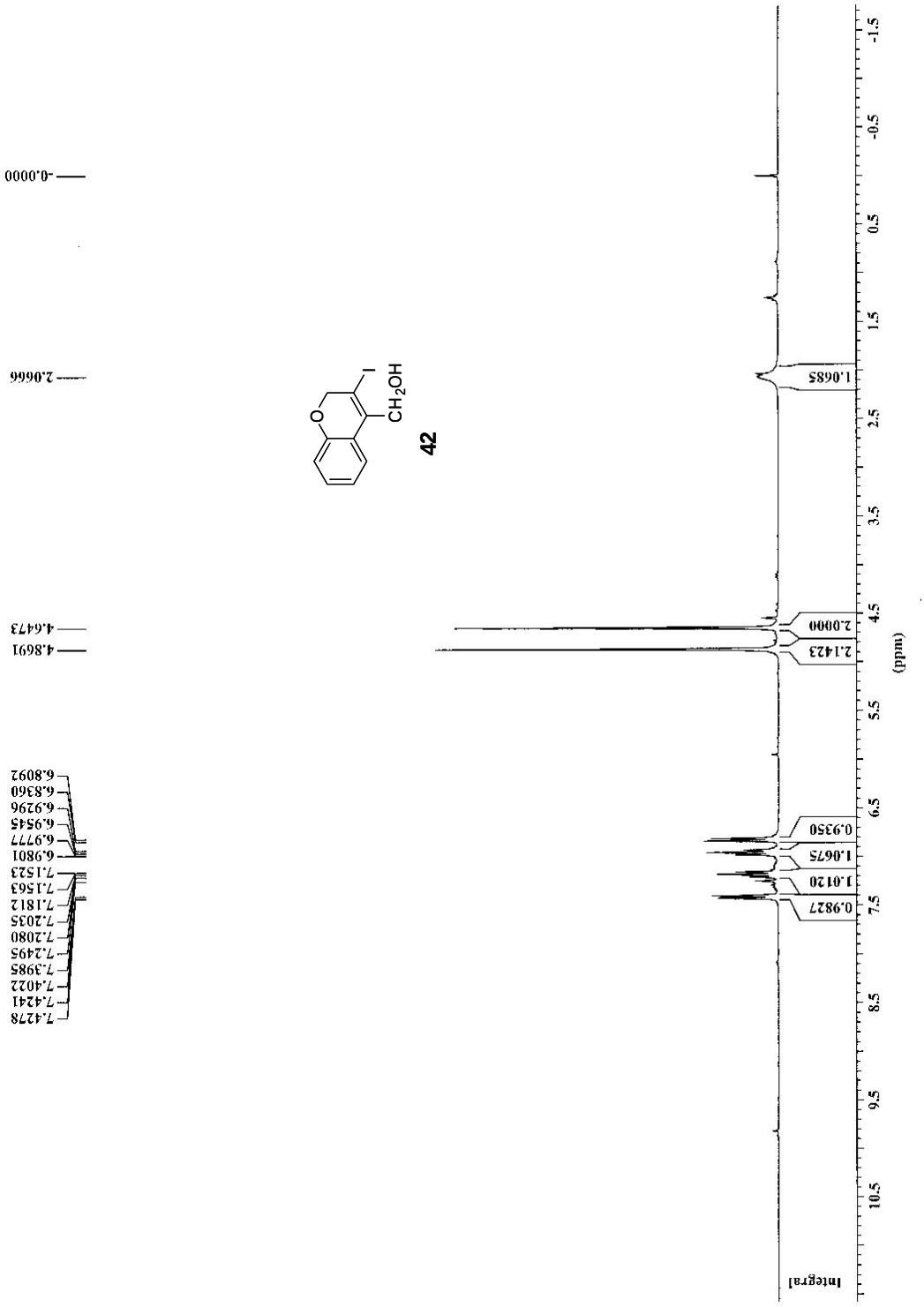


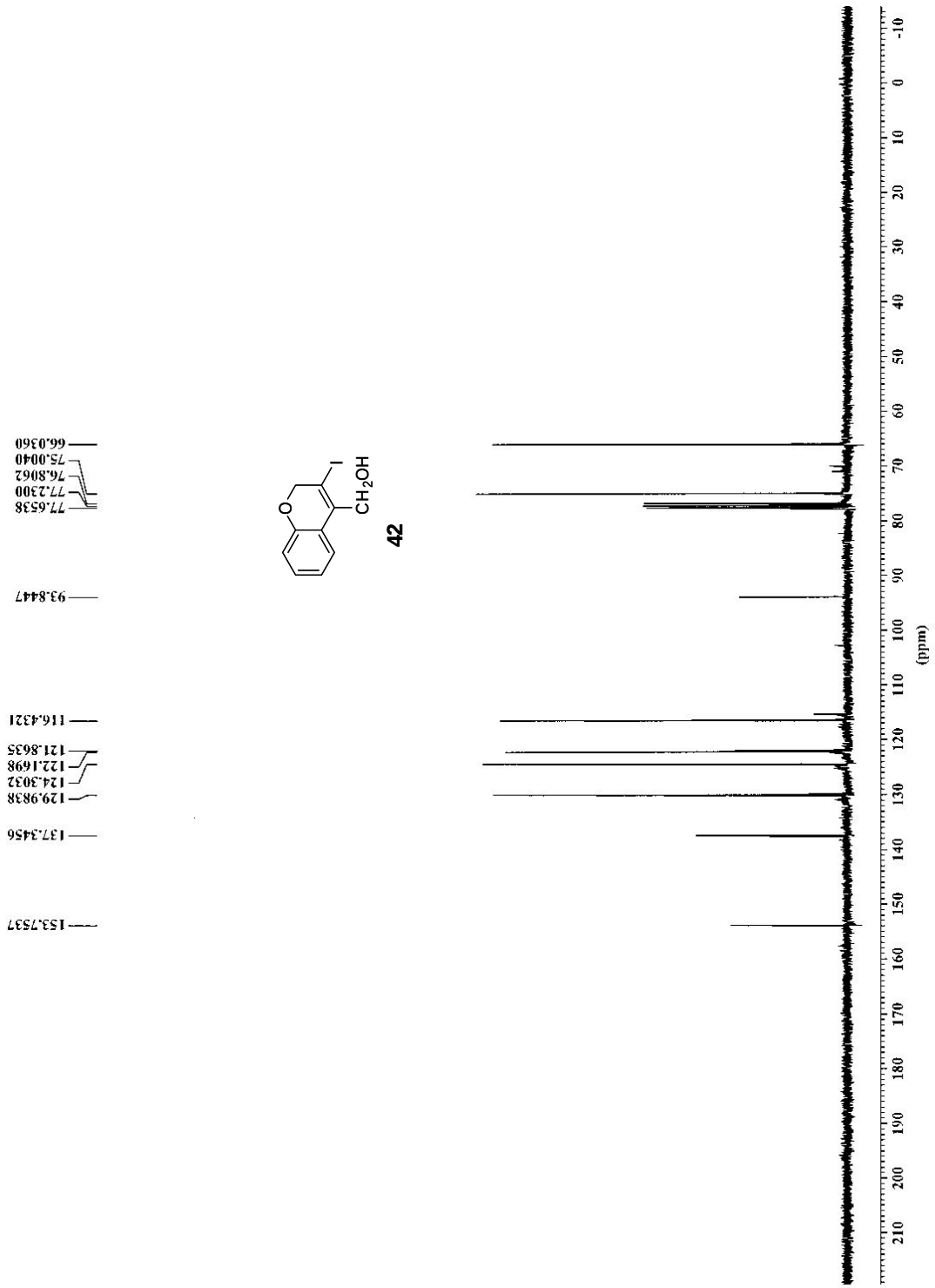


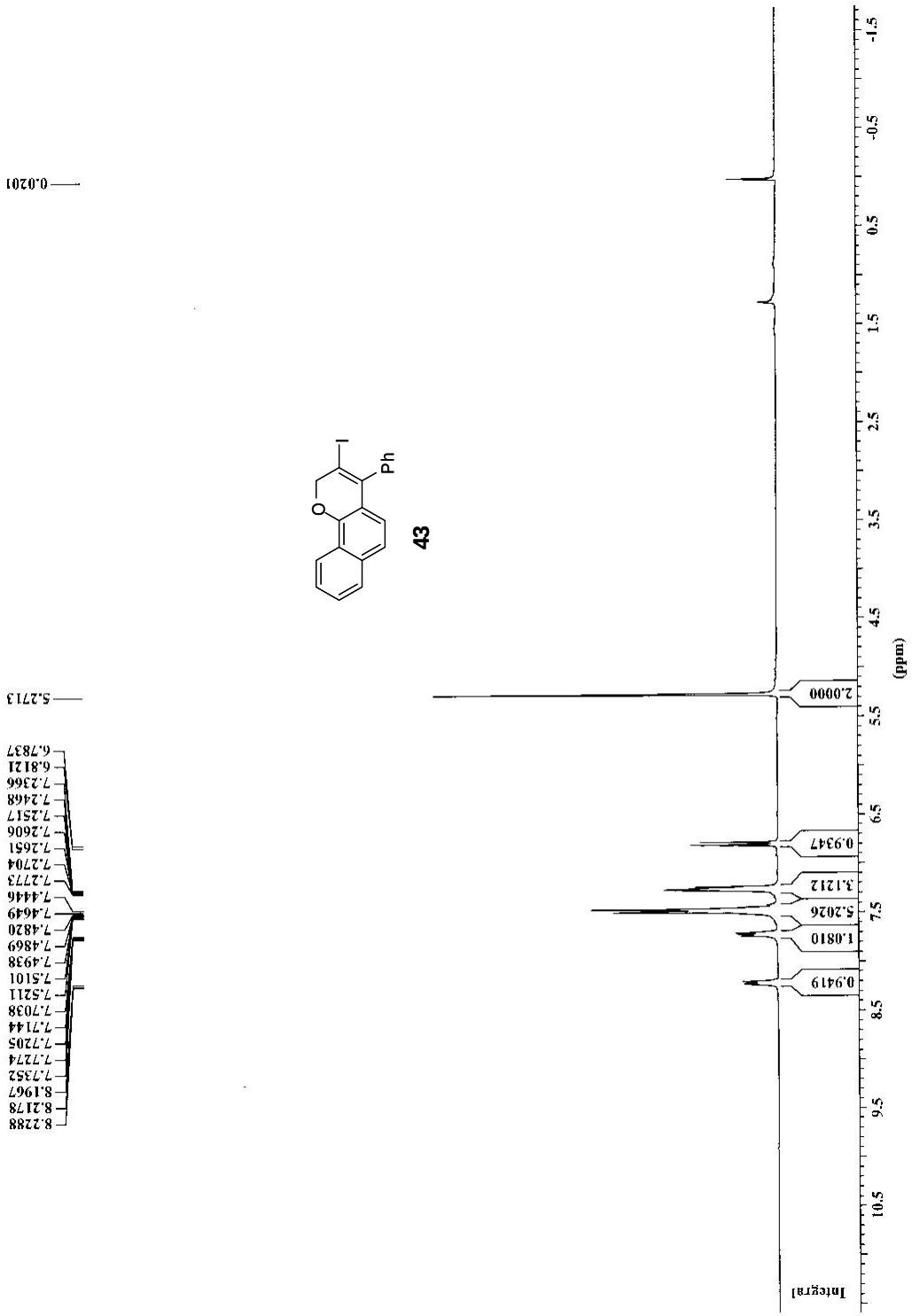


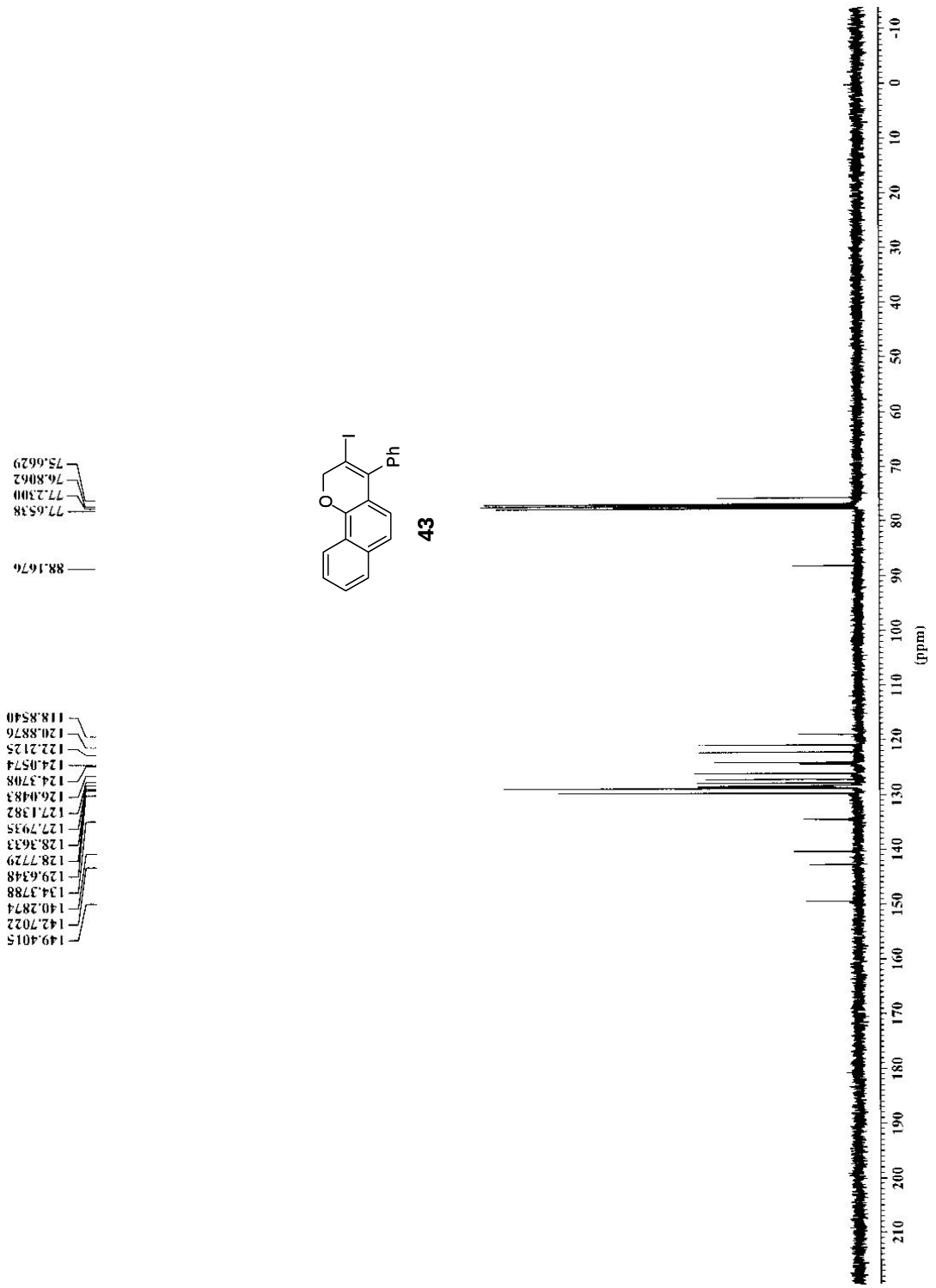


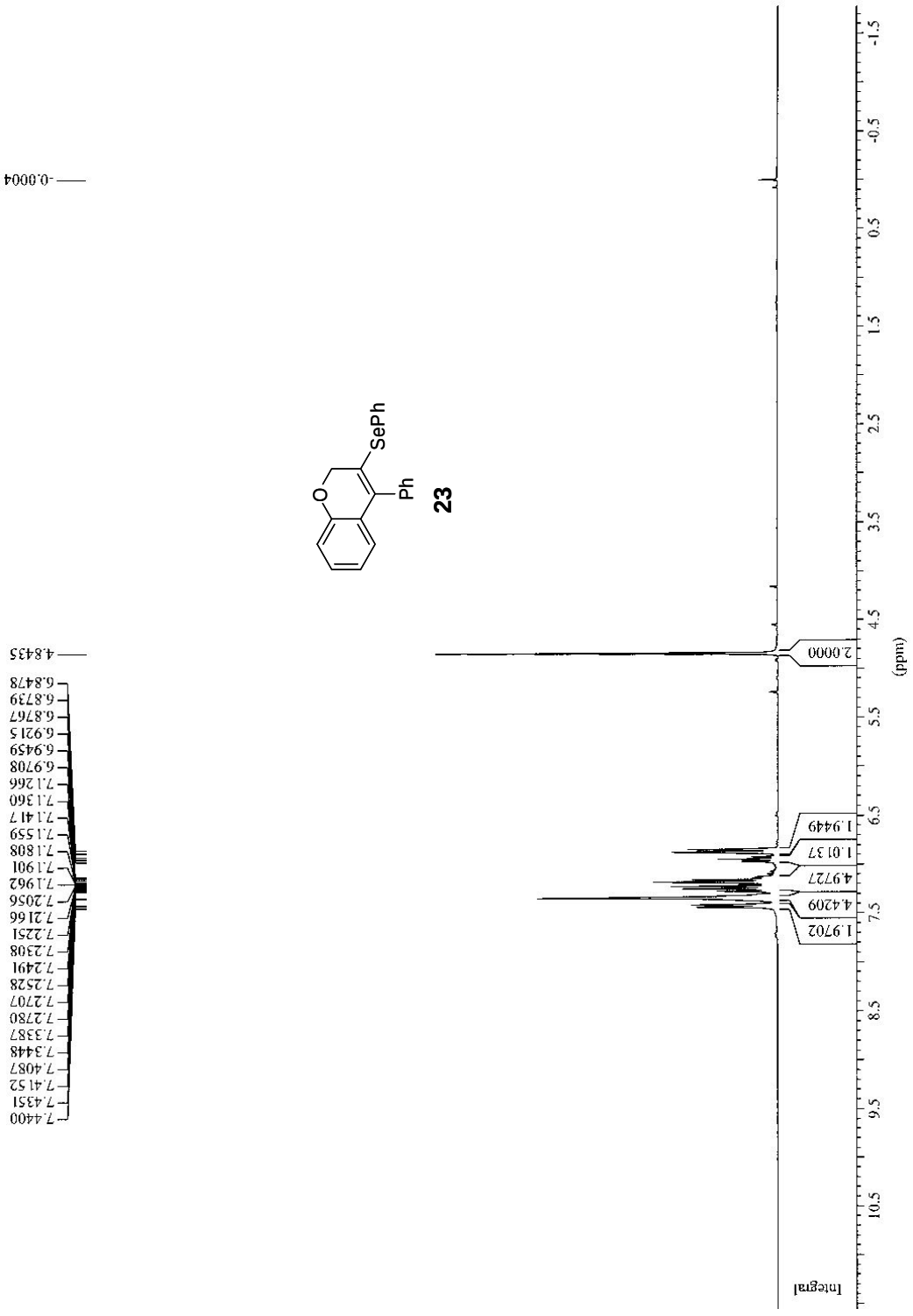


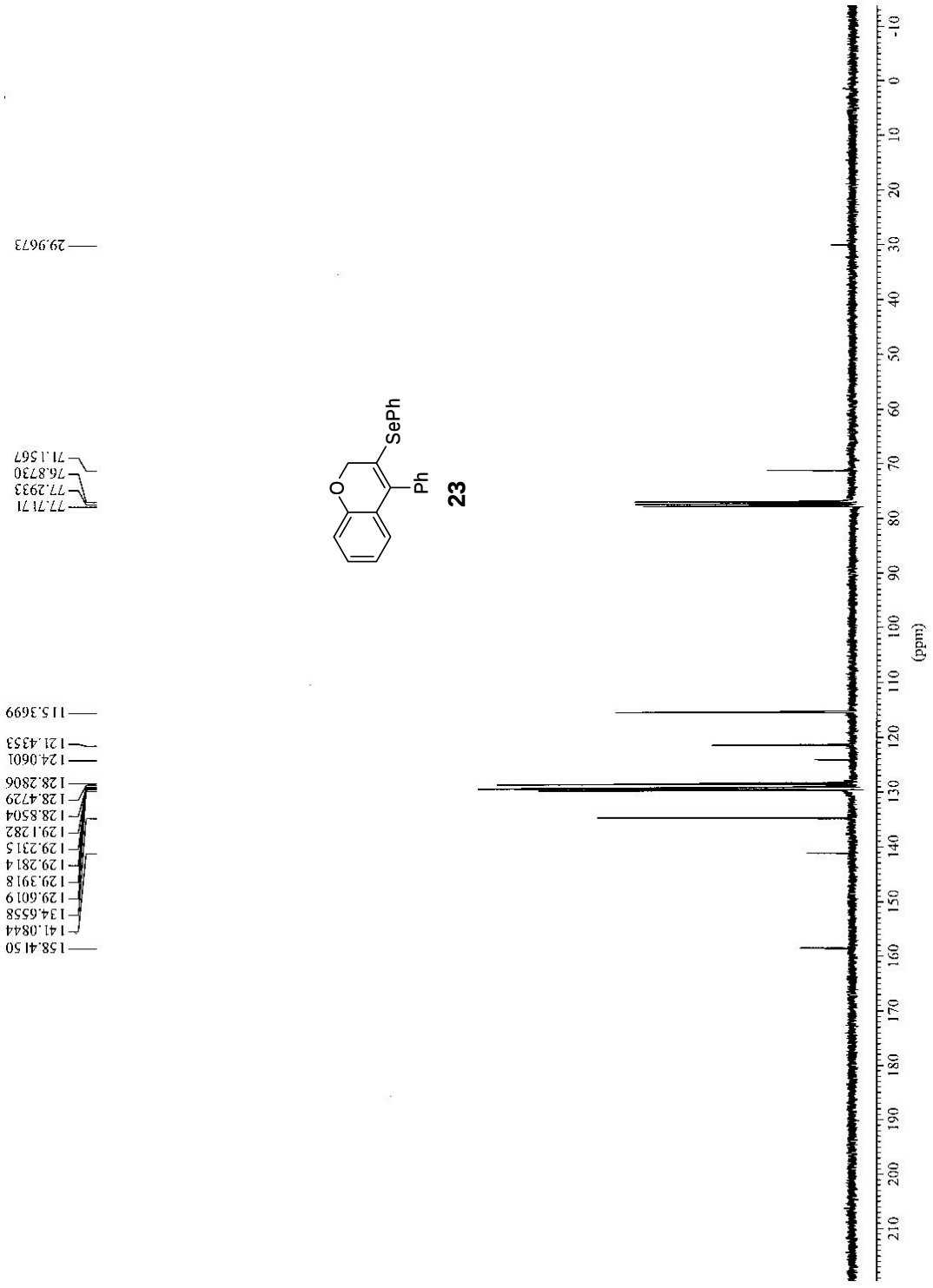


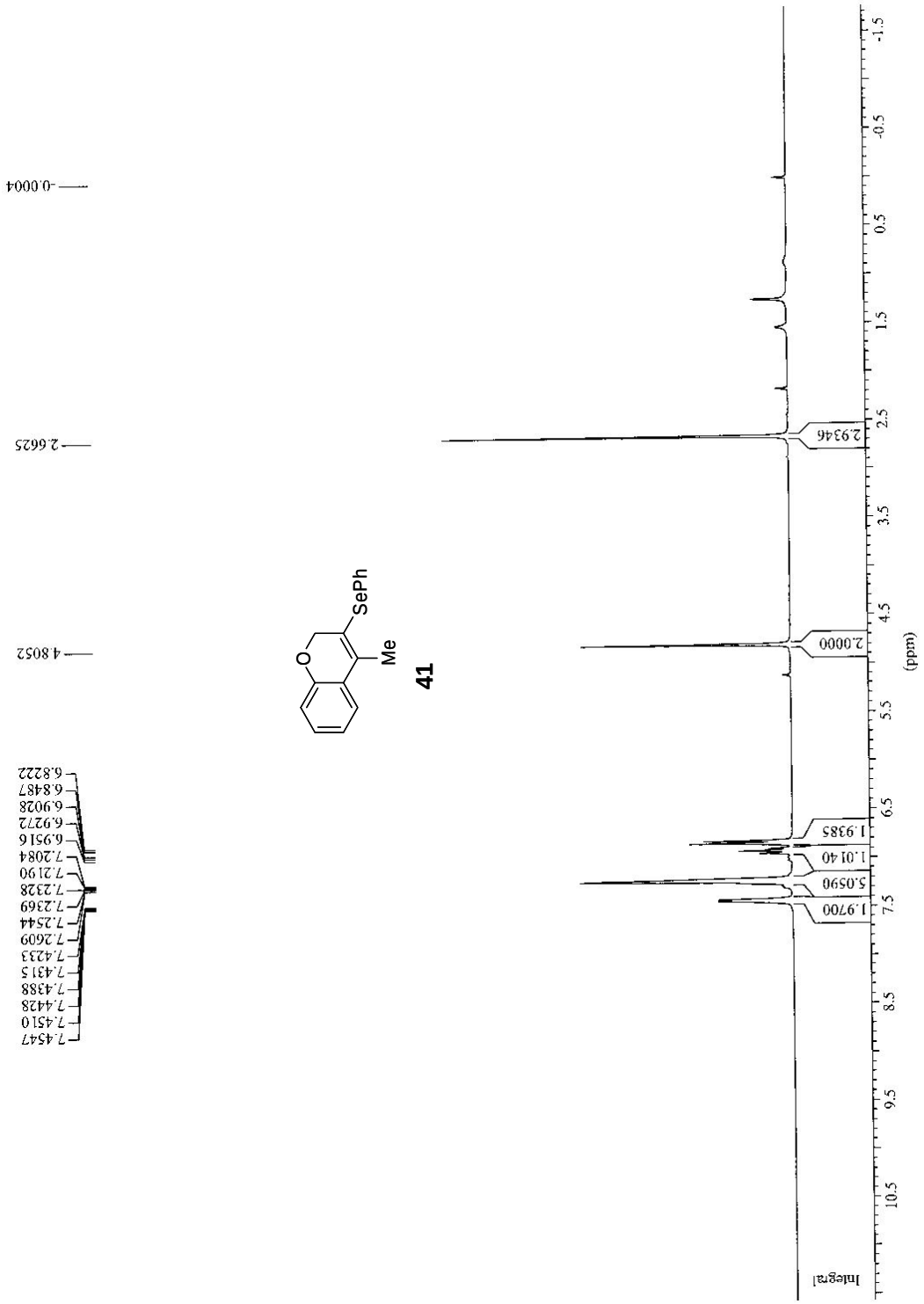


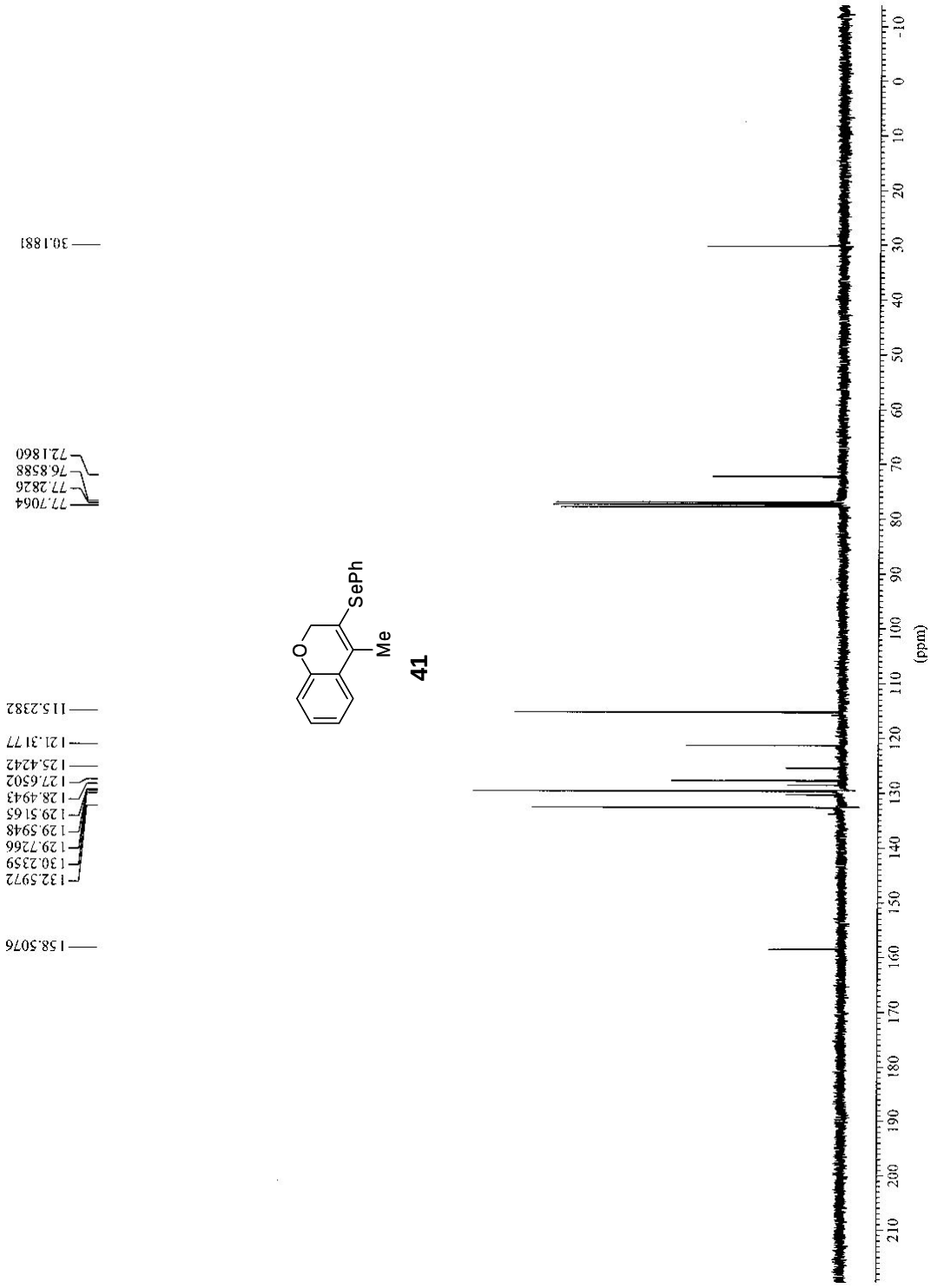


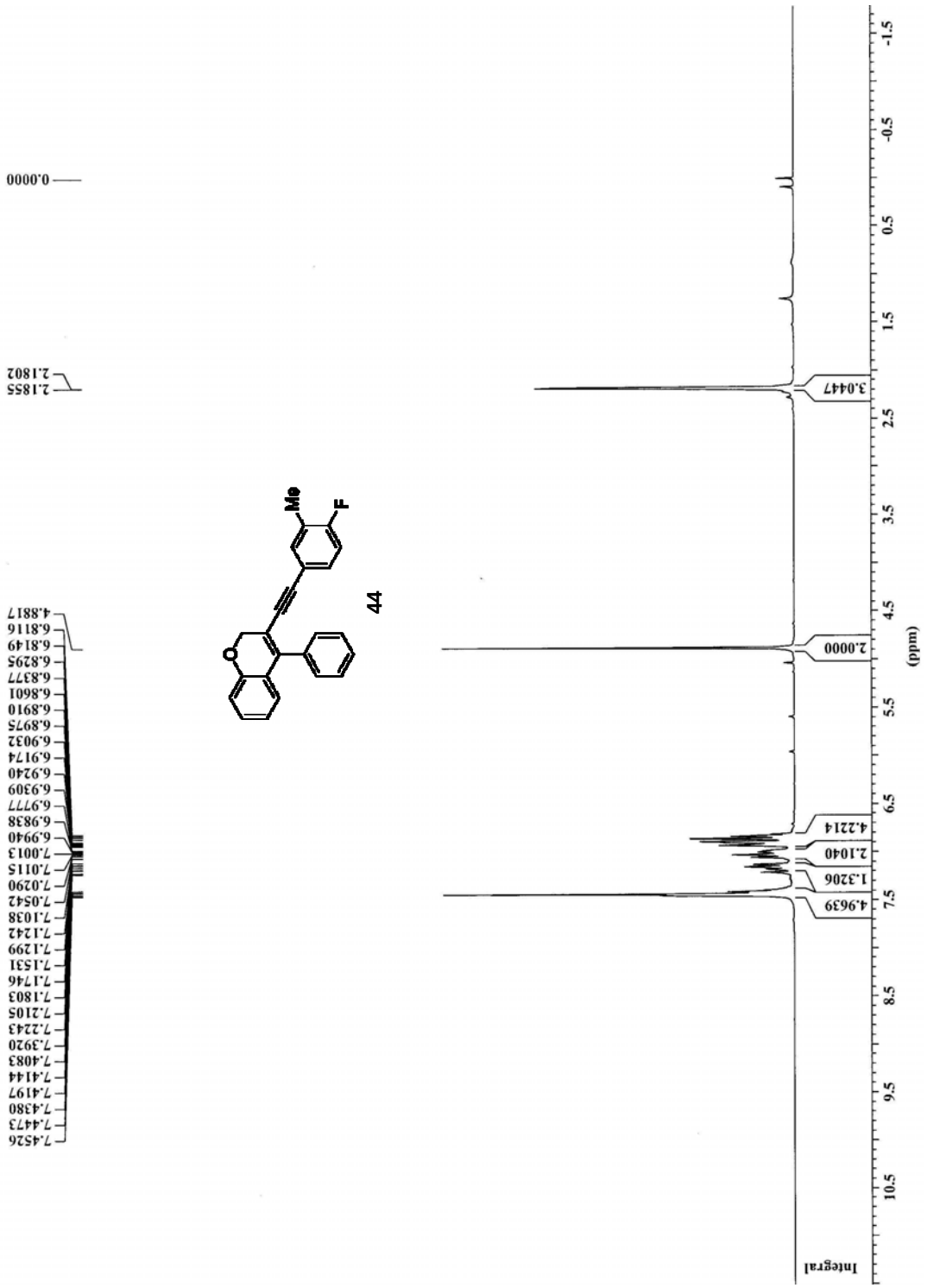


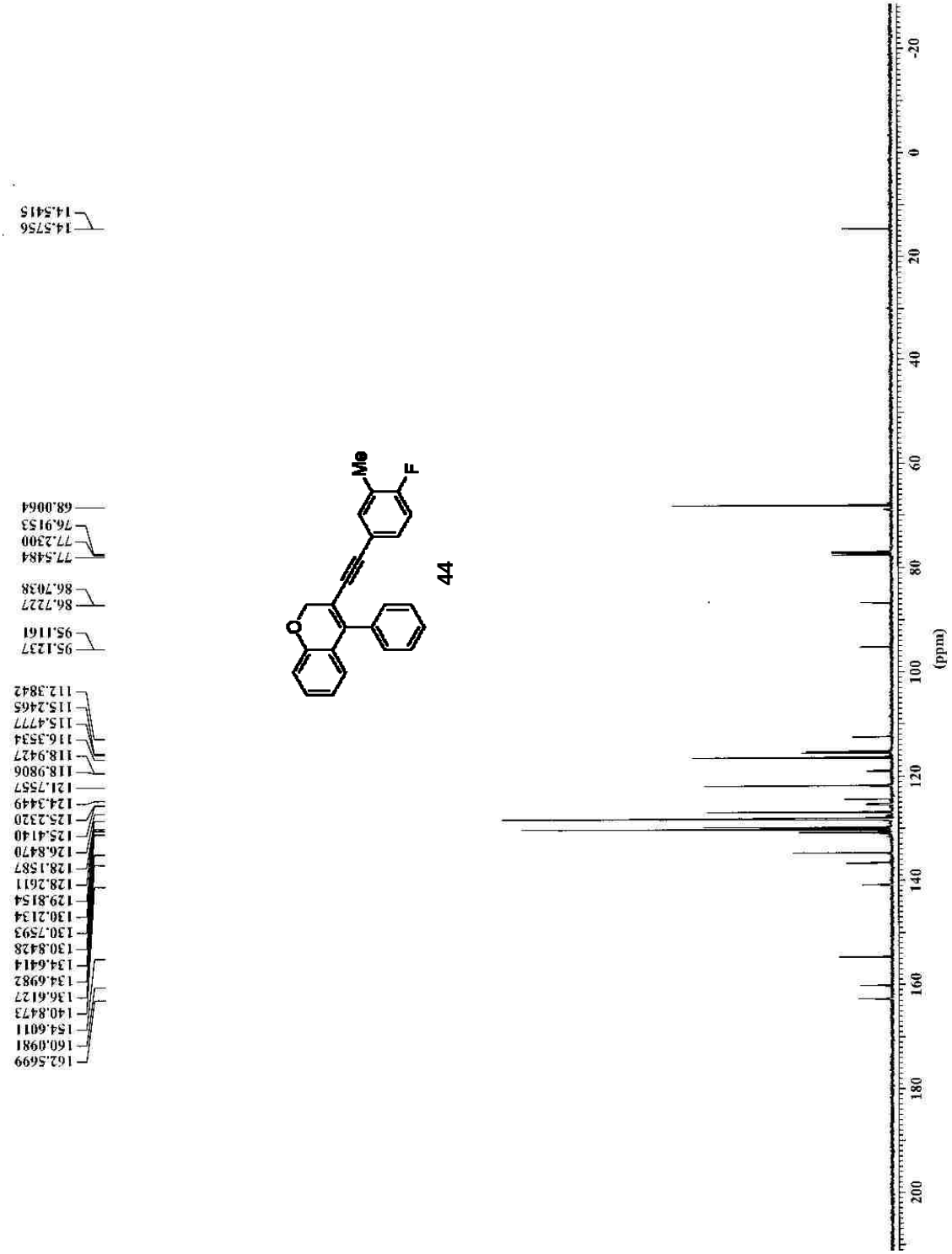


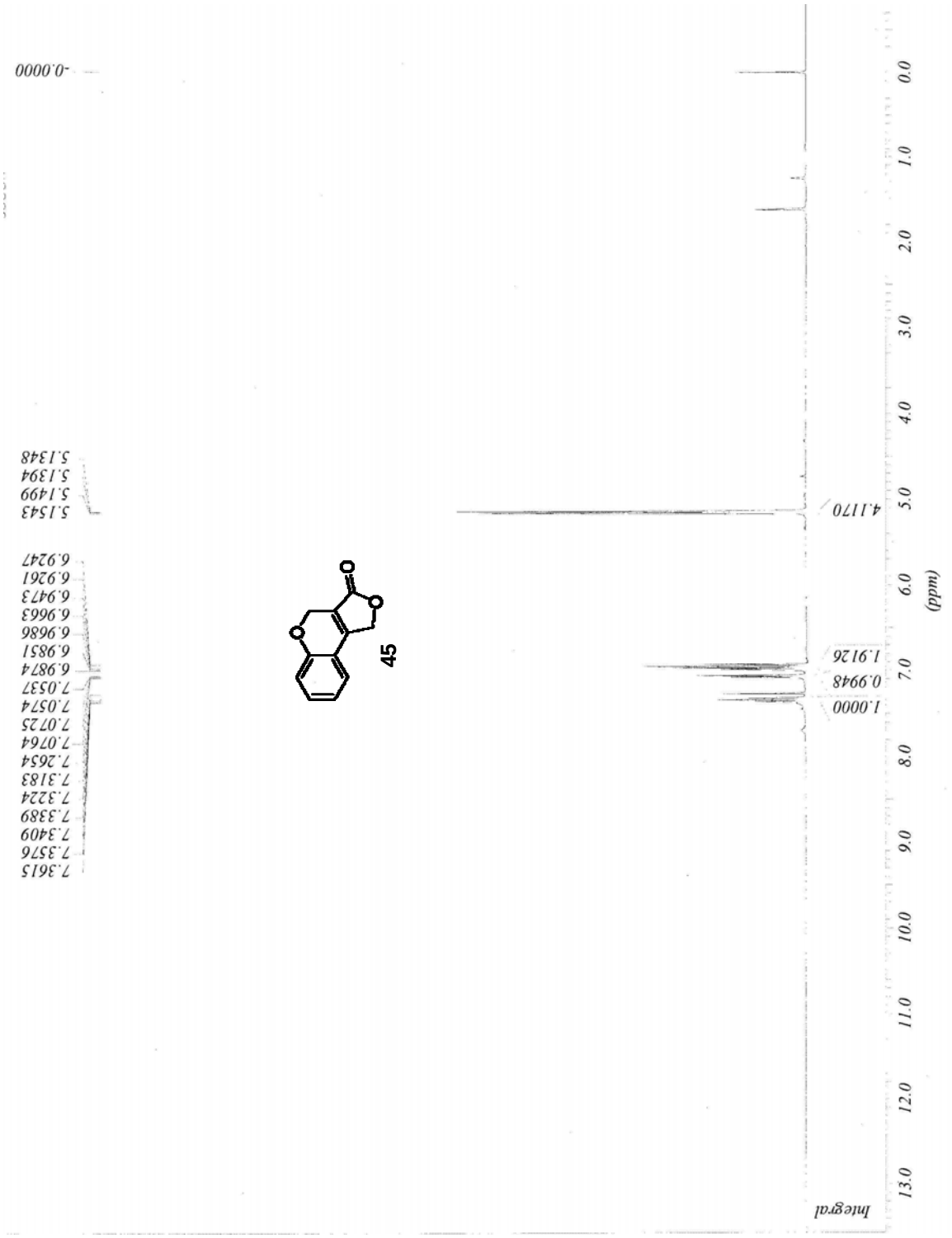


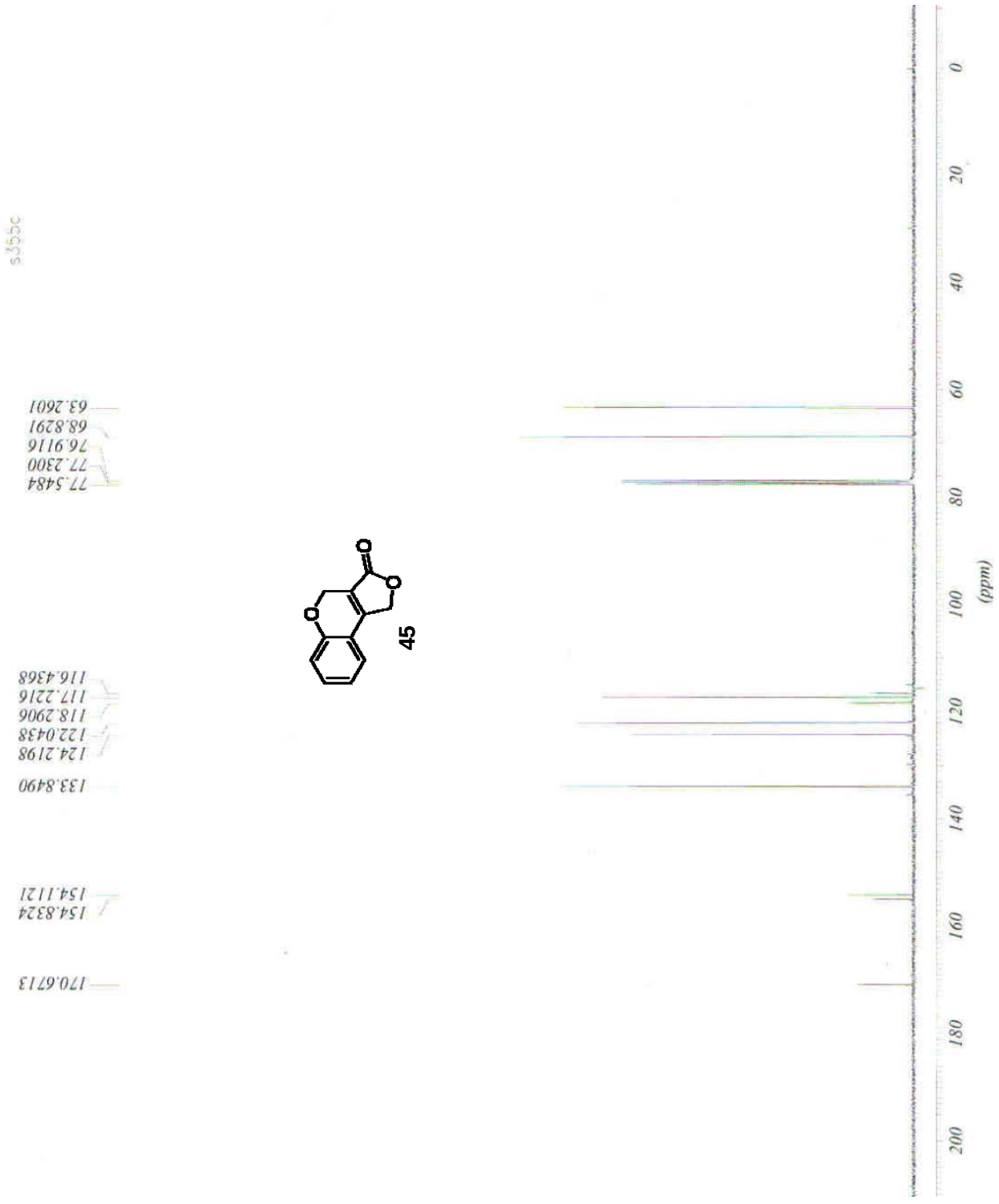




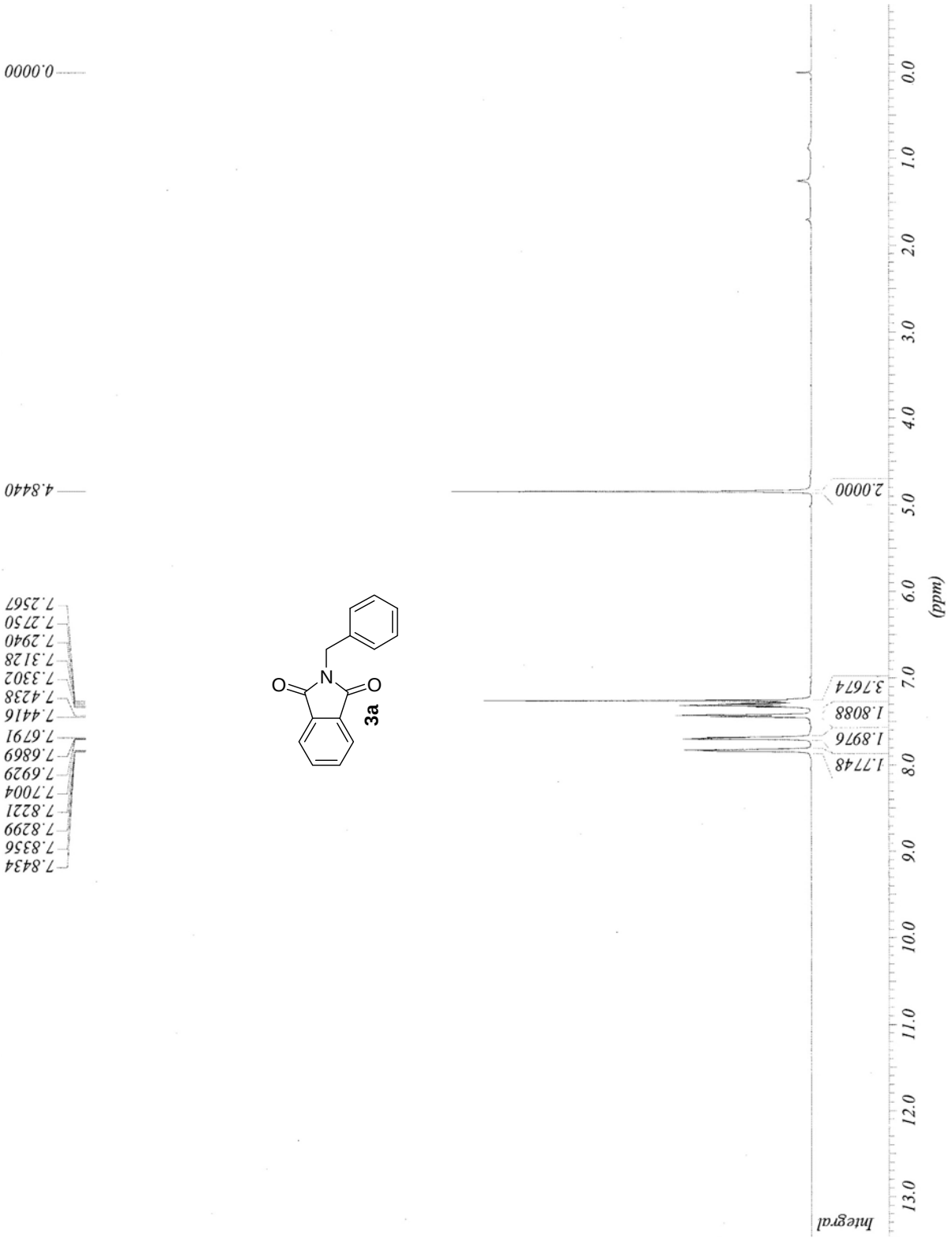


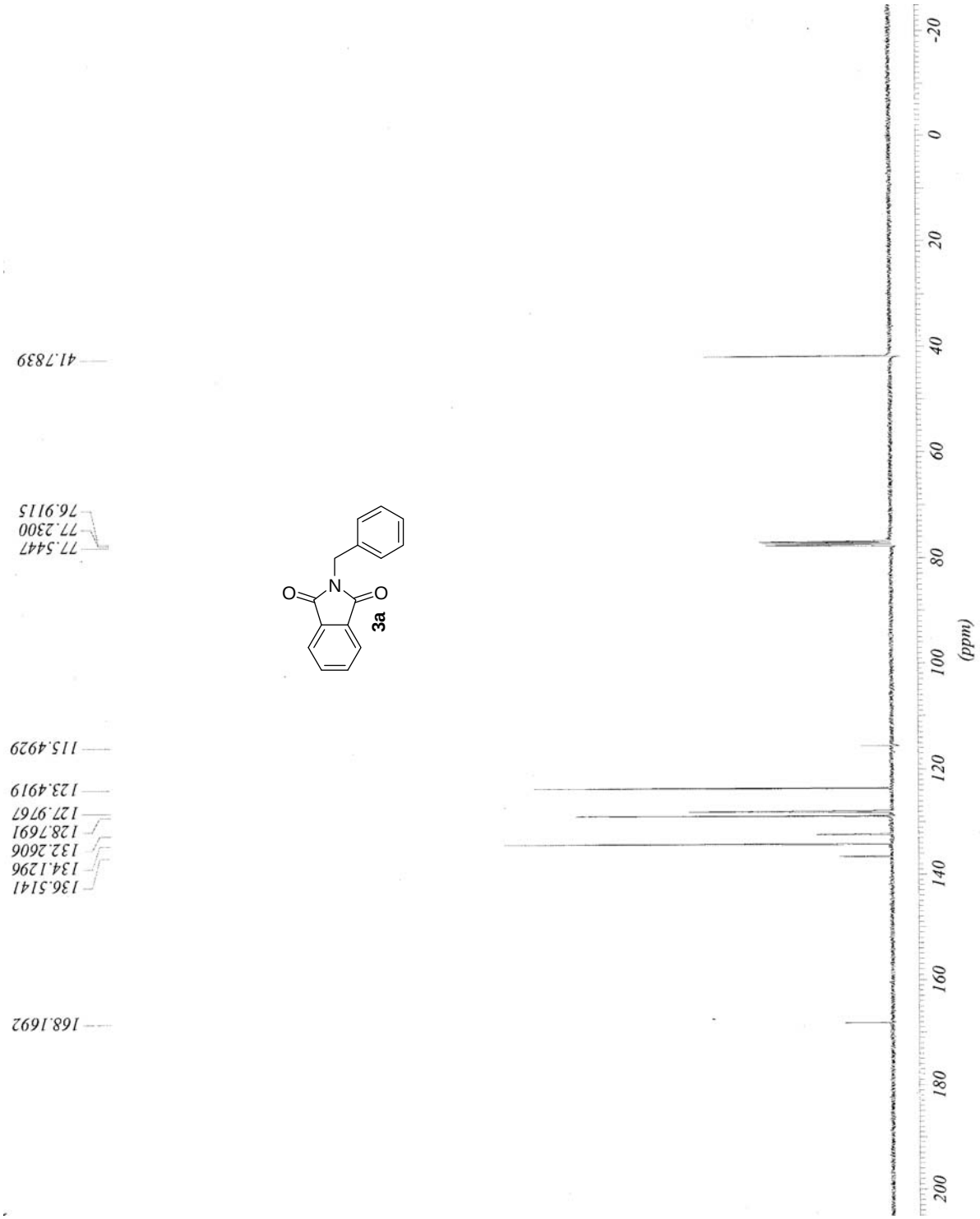


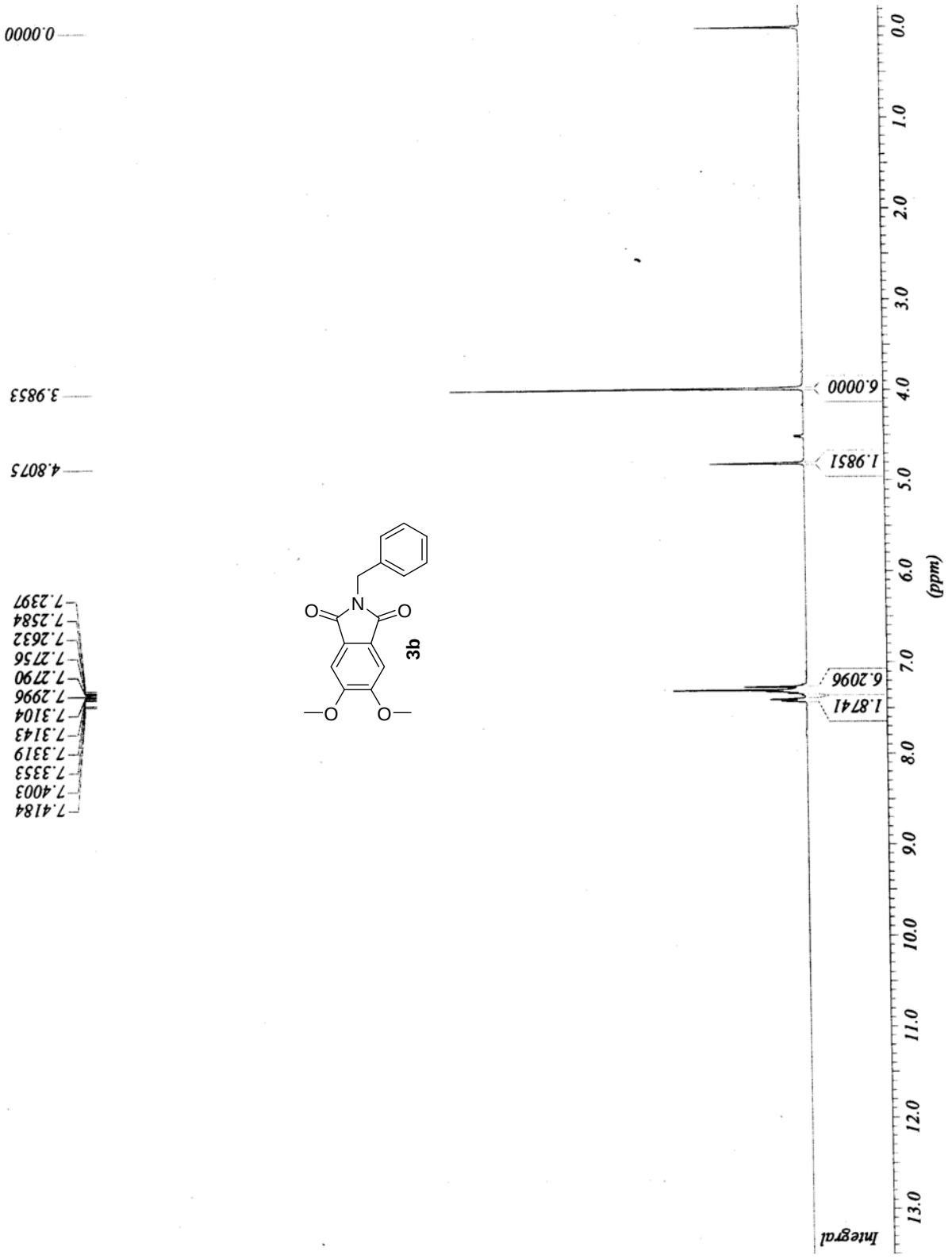


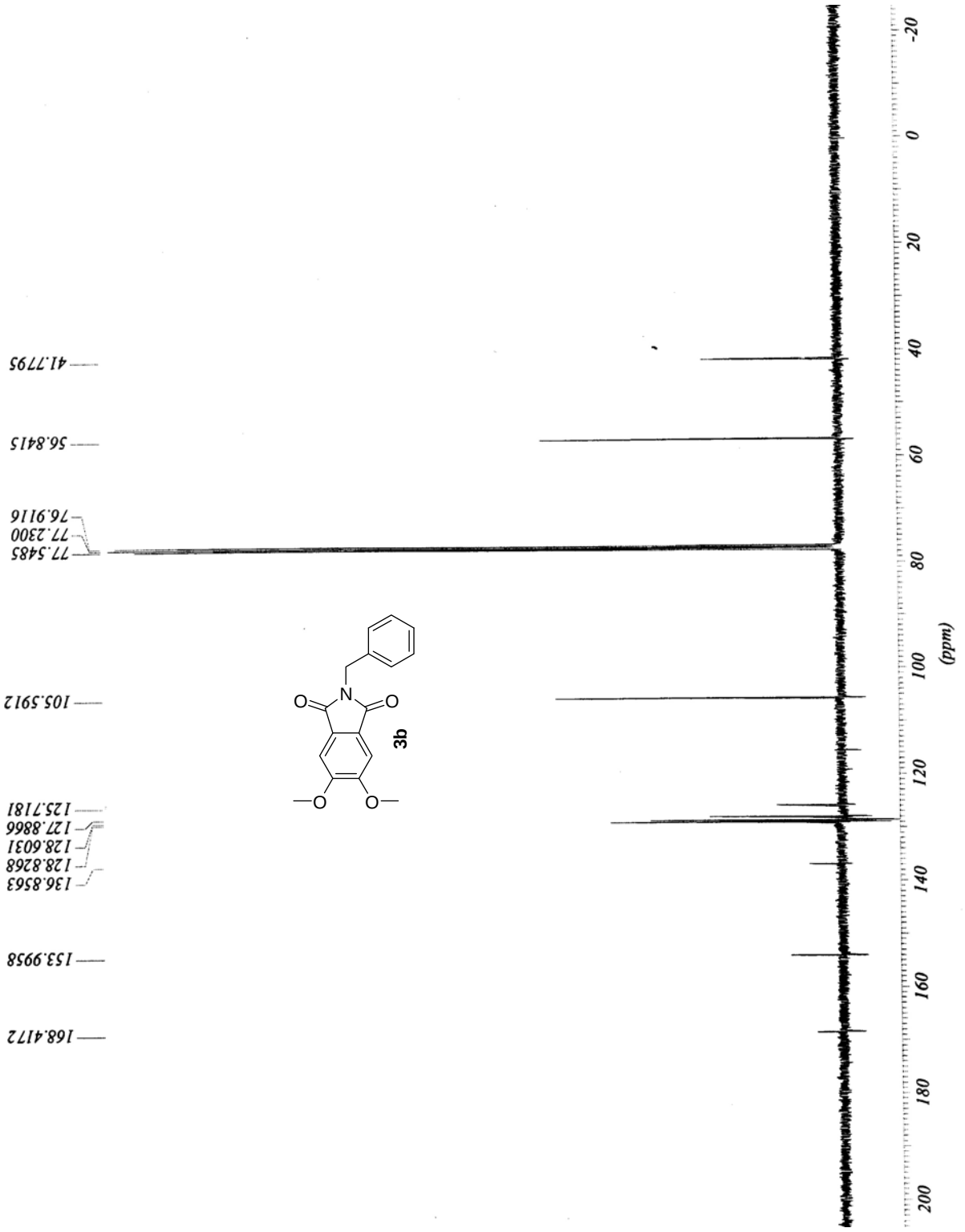


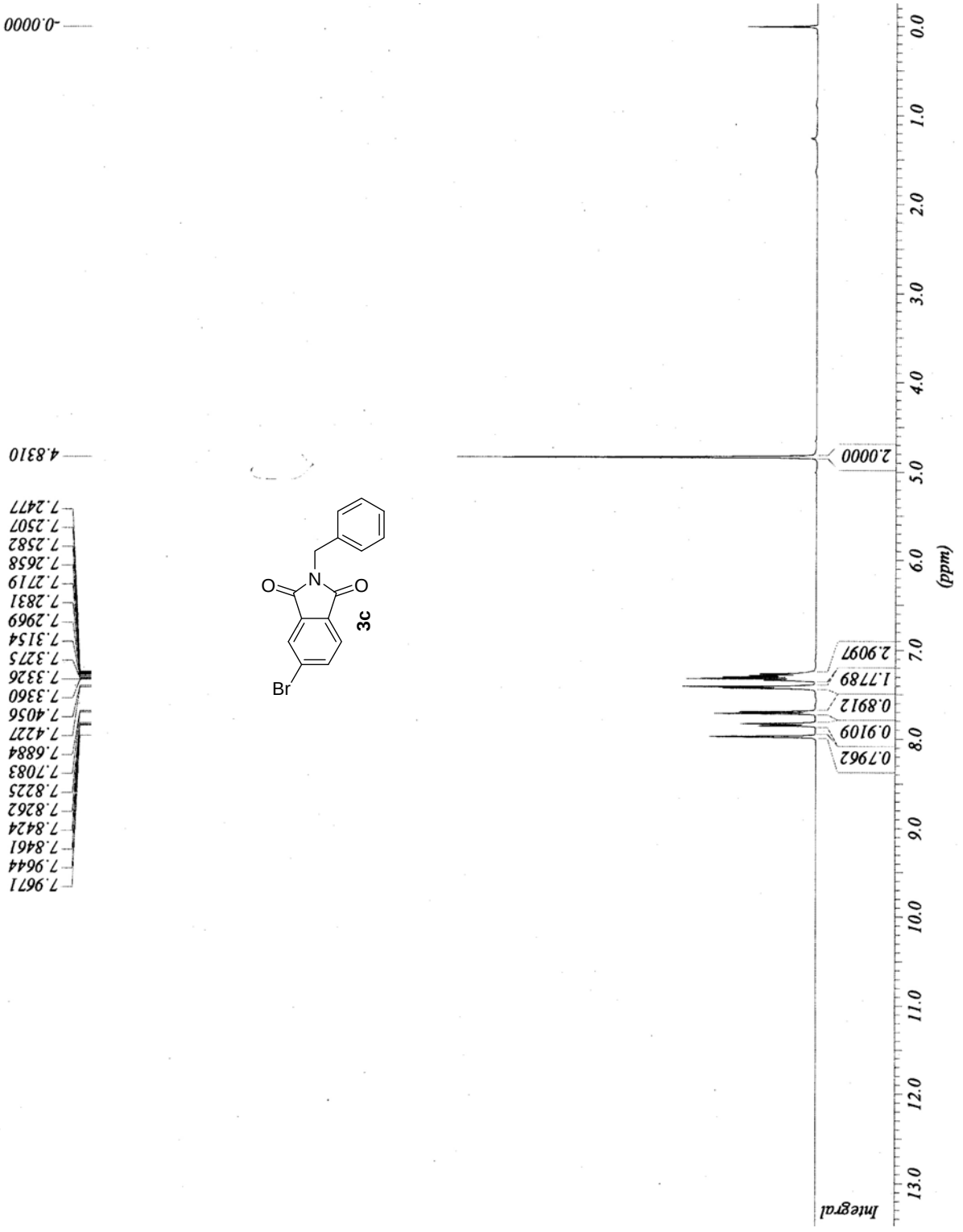
APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

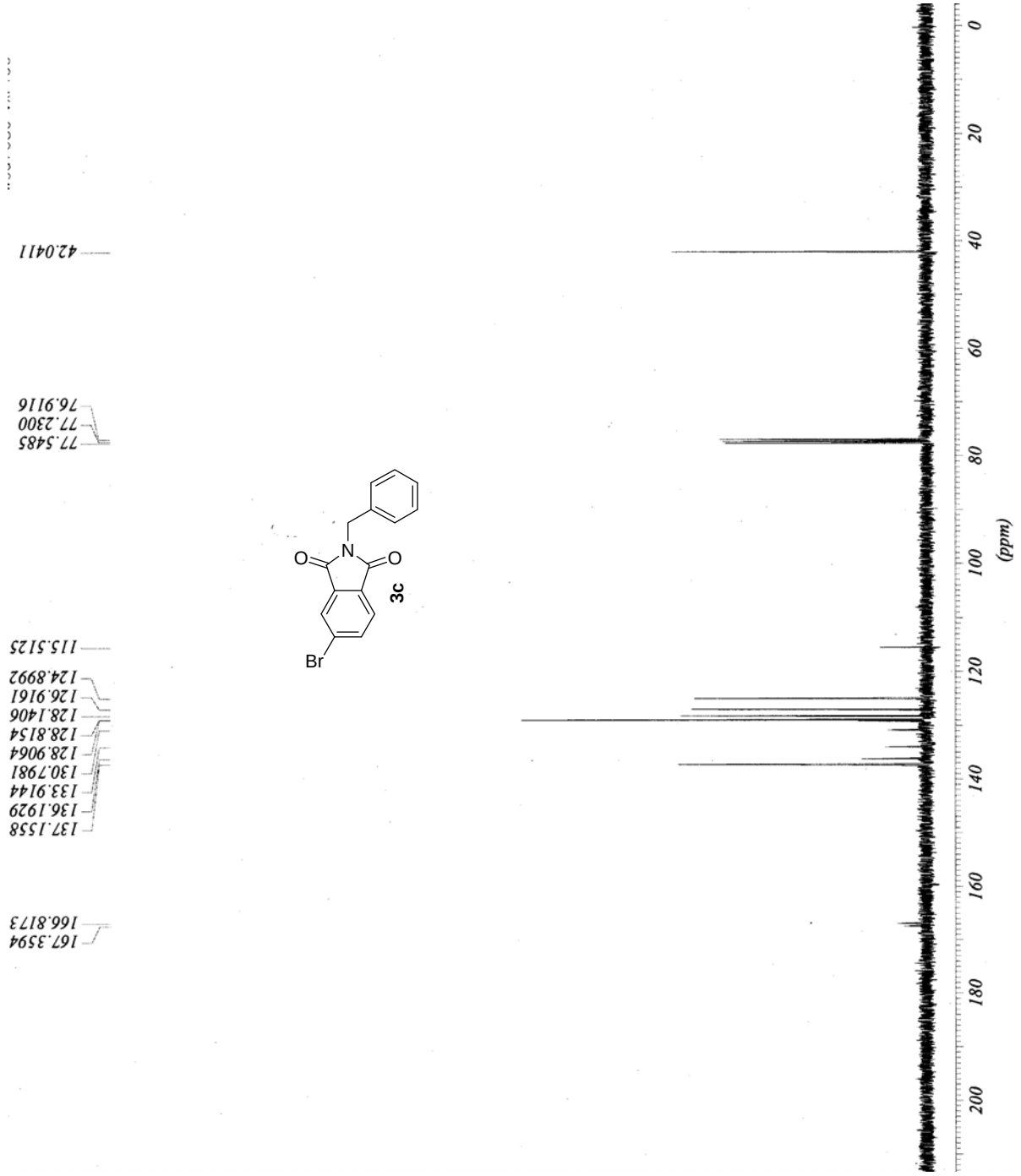


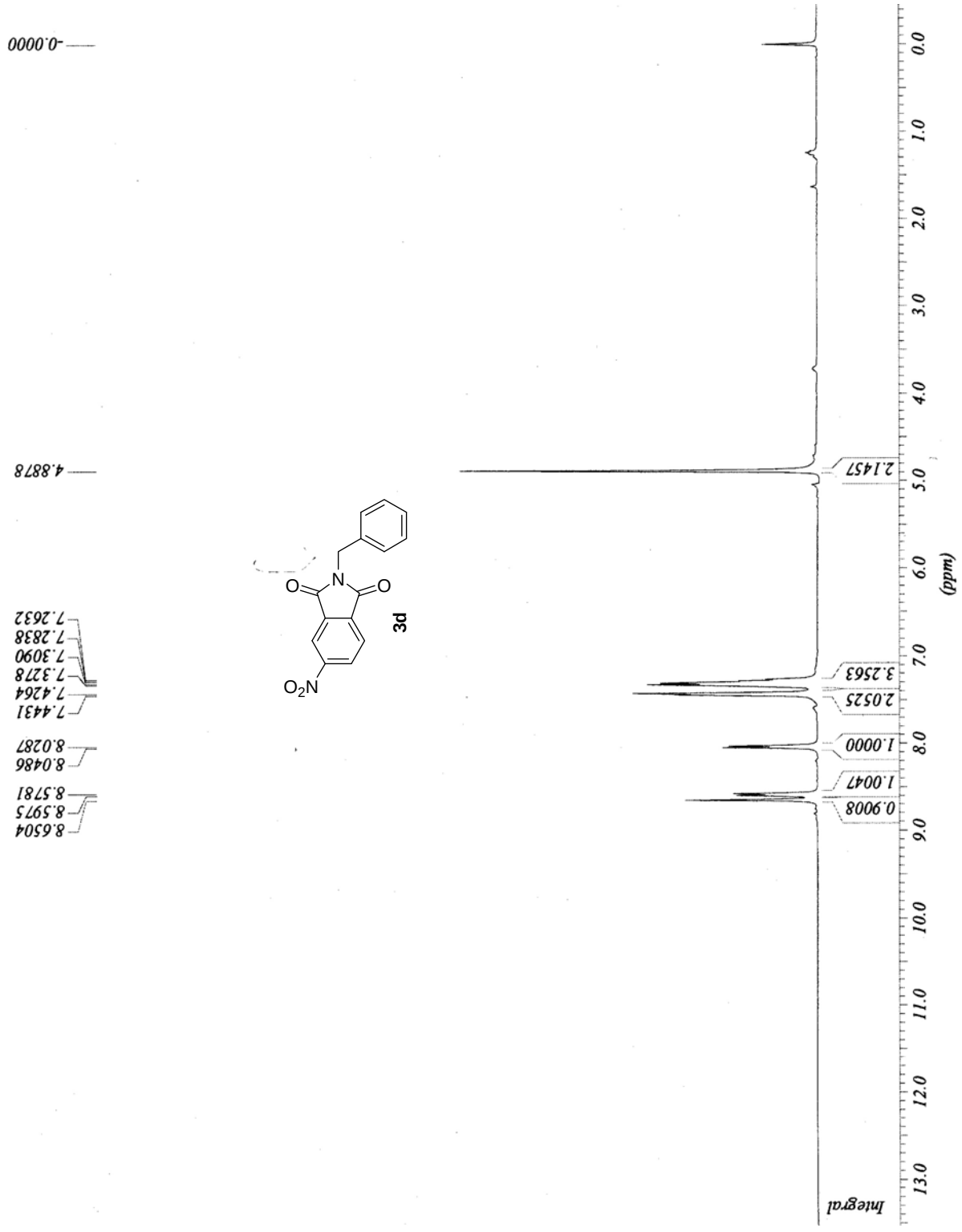


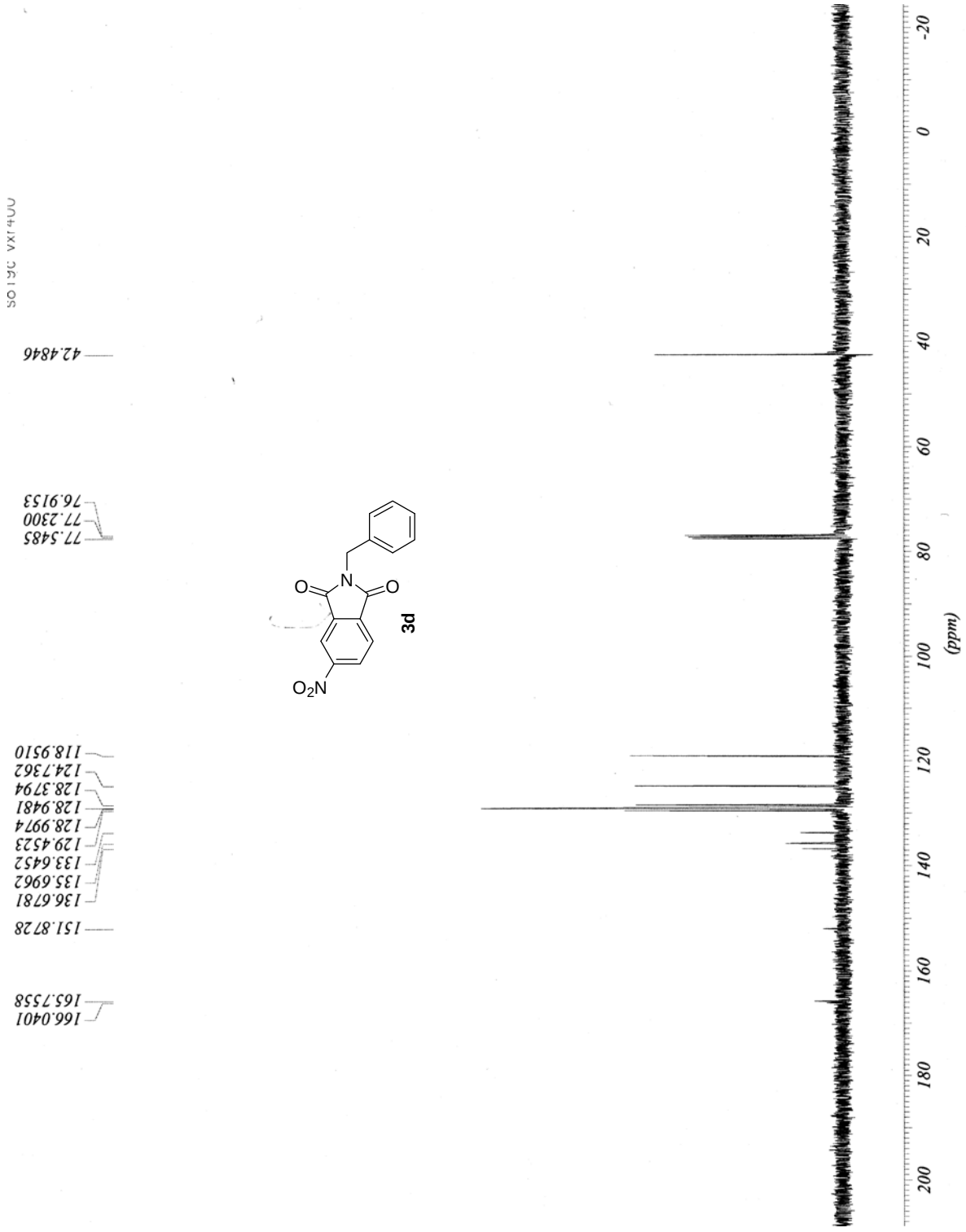


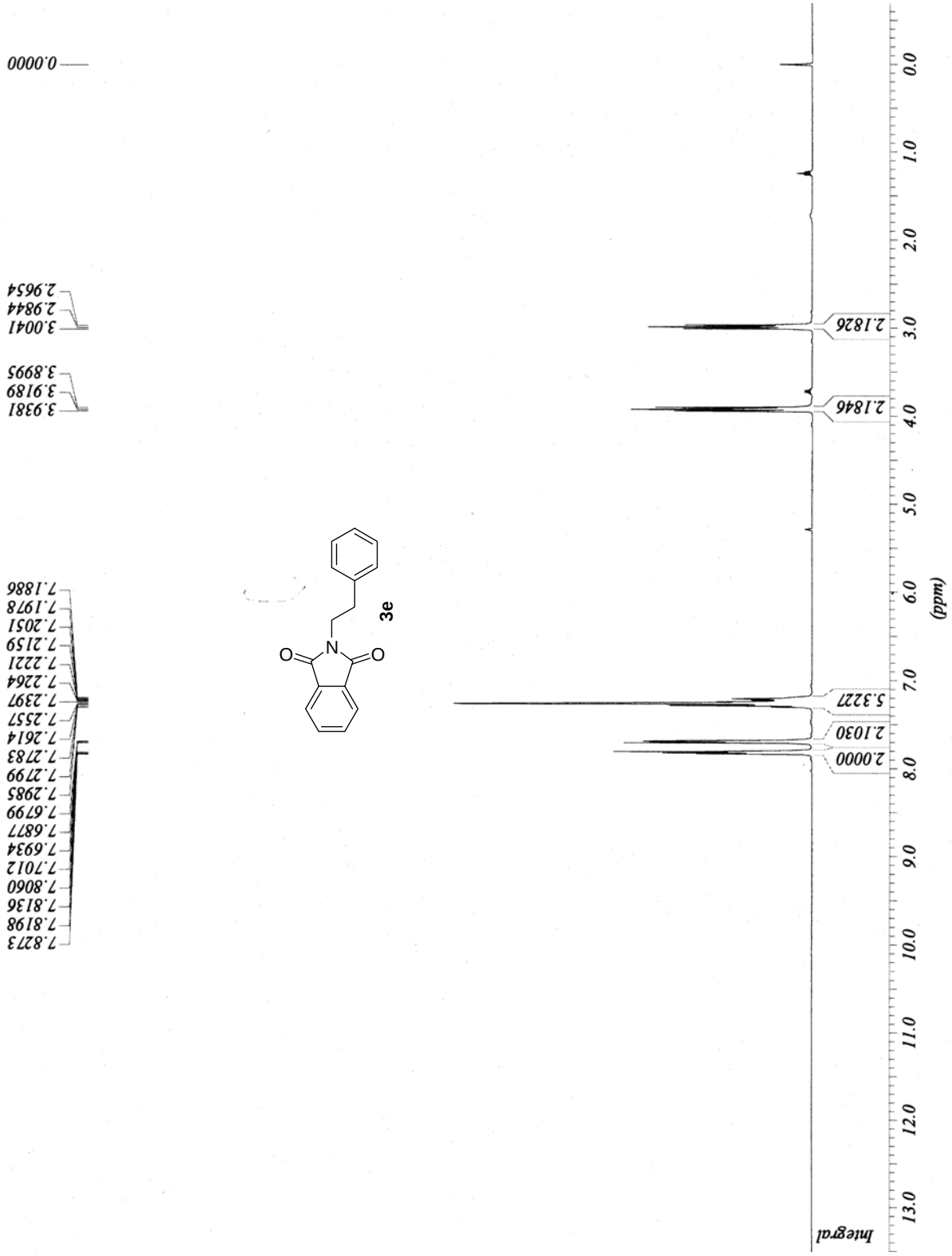


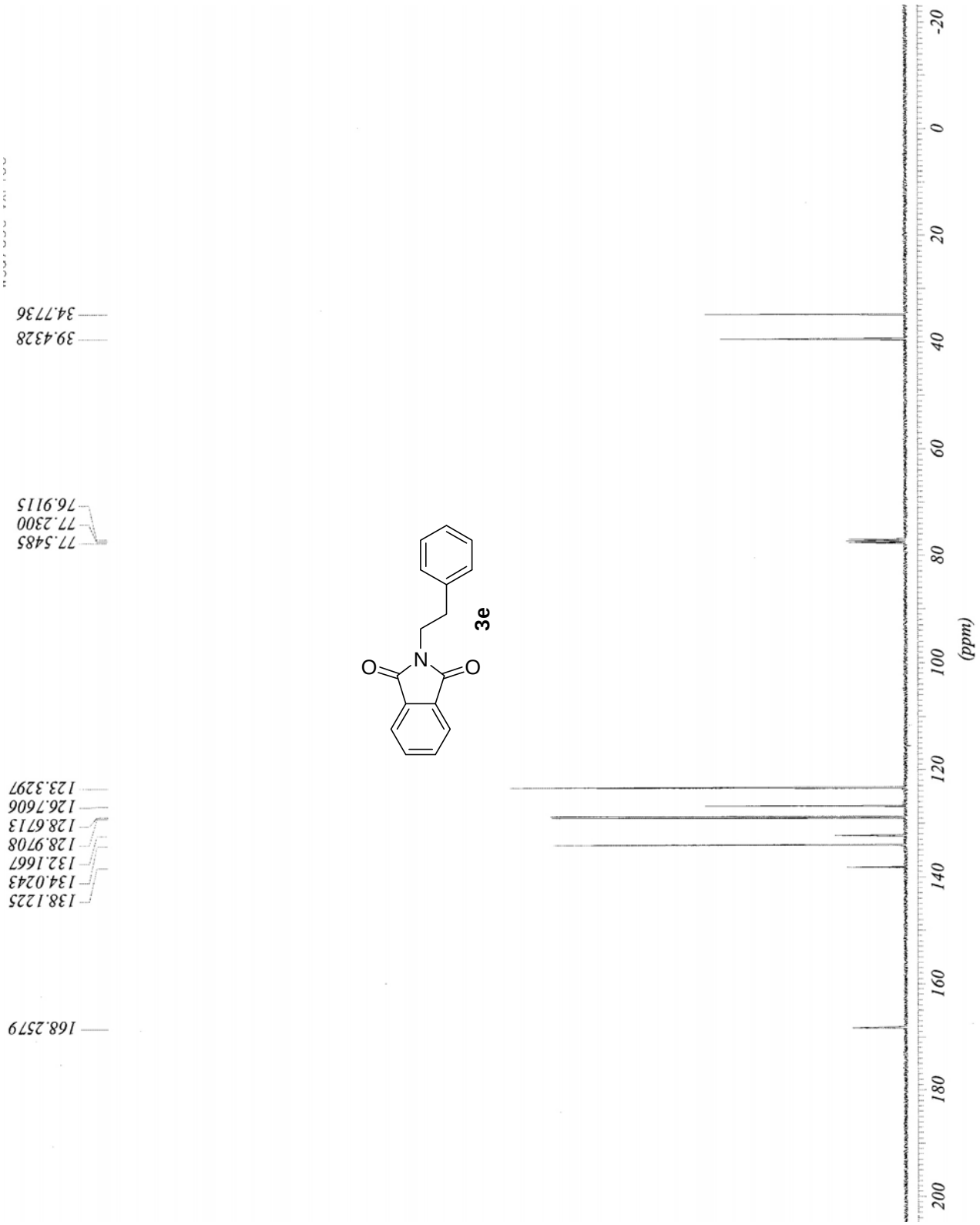


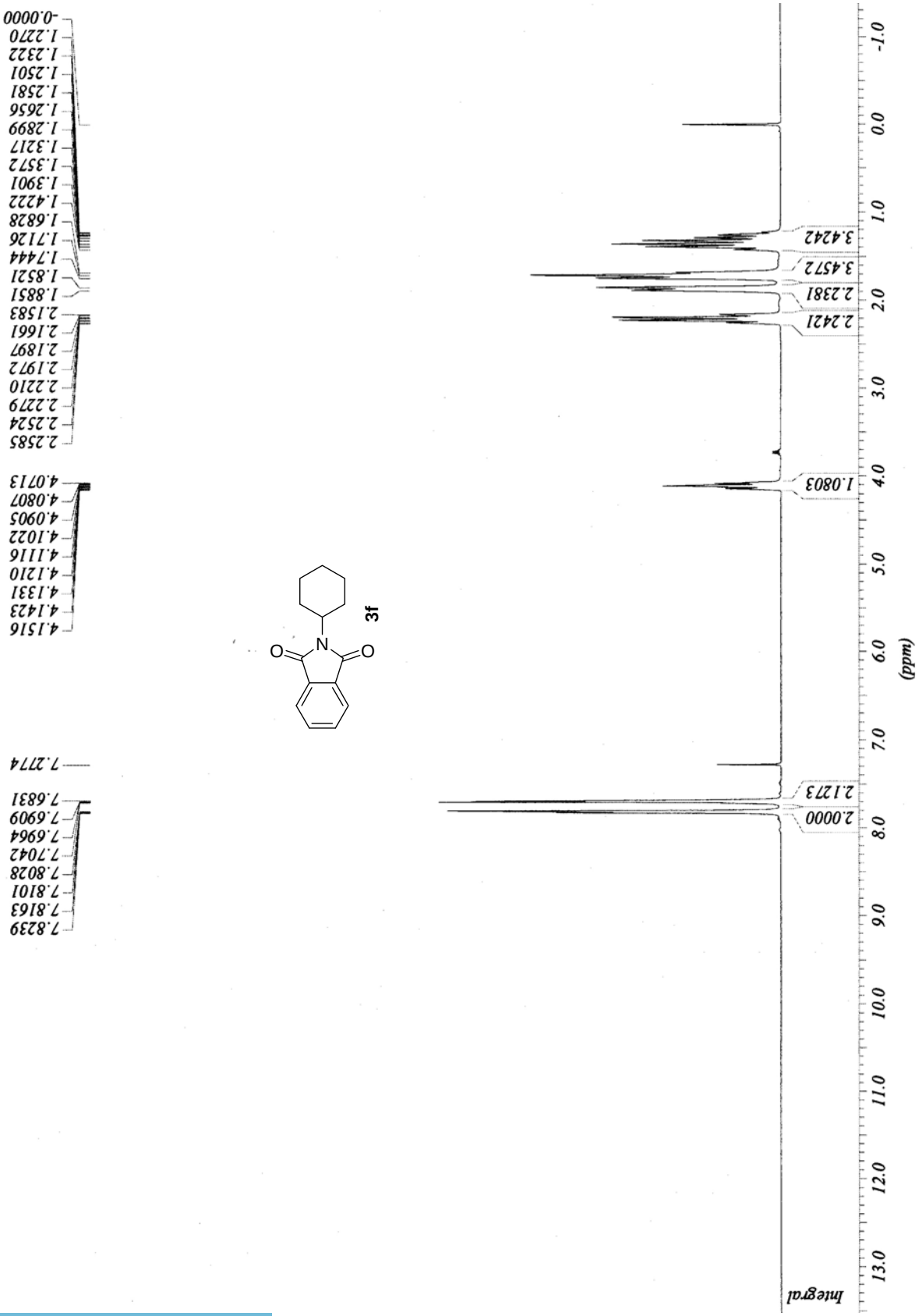


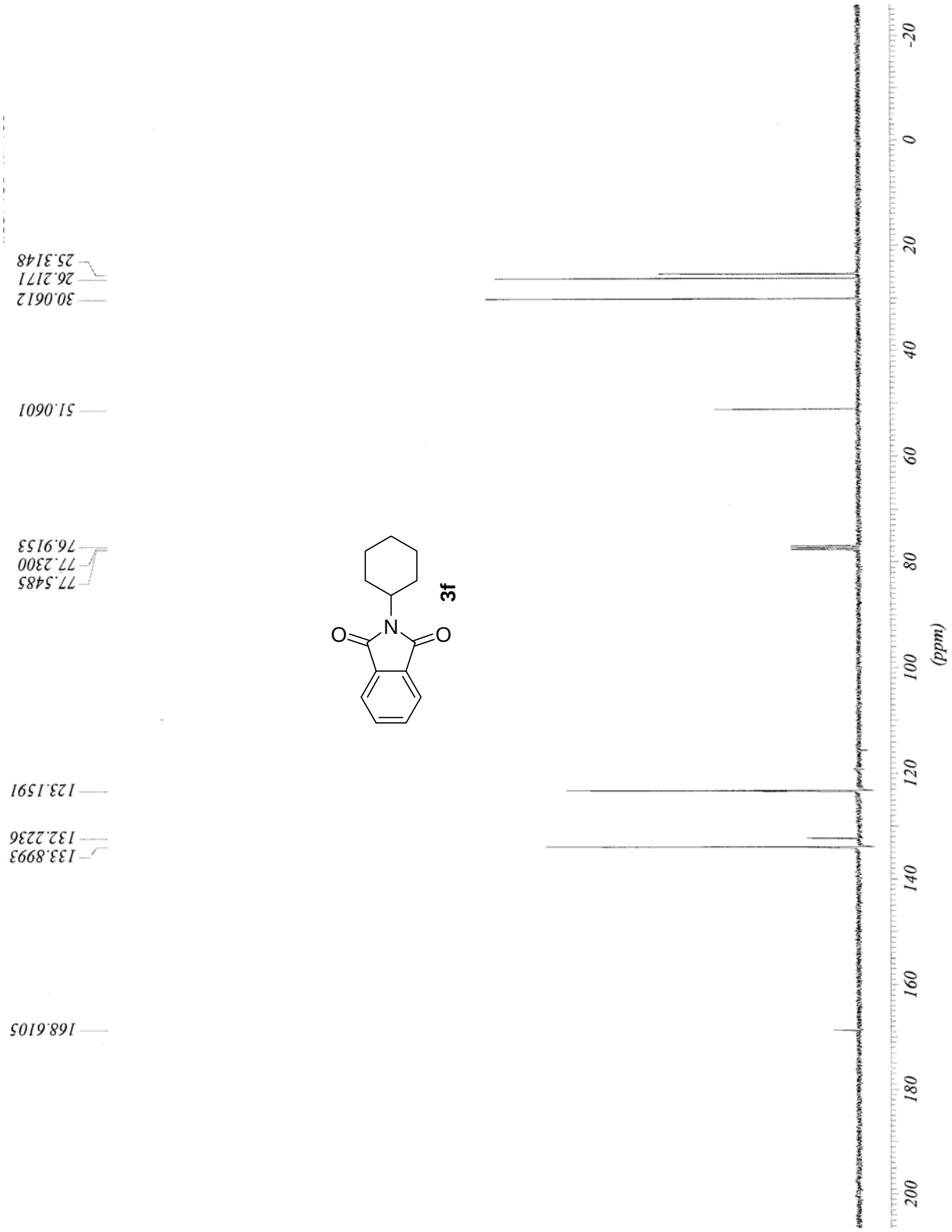


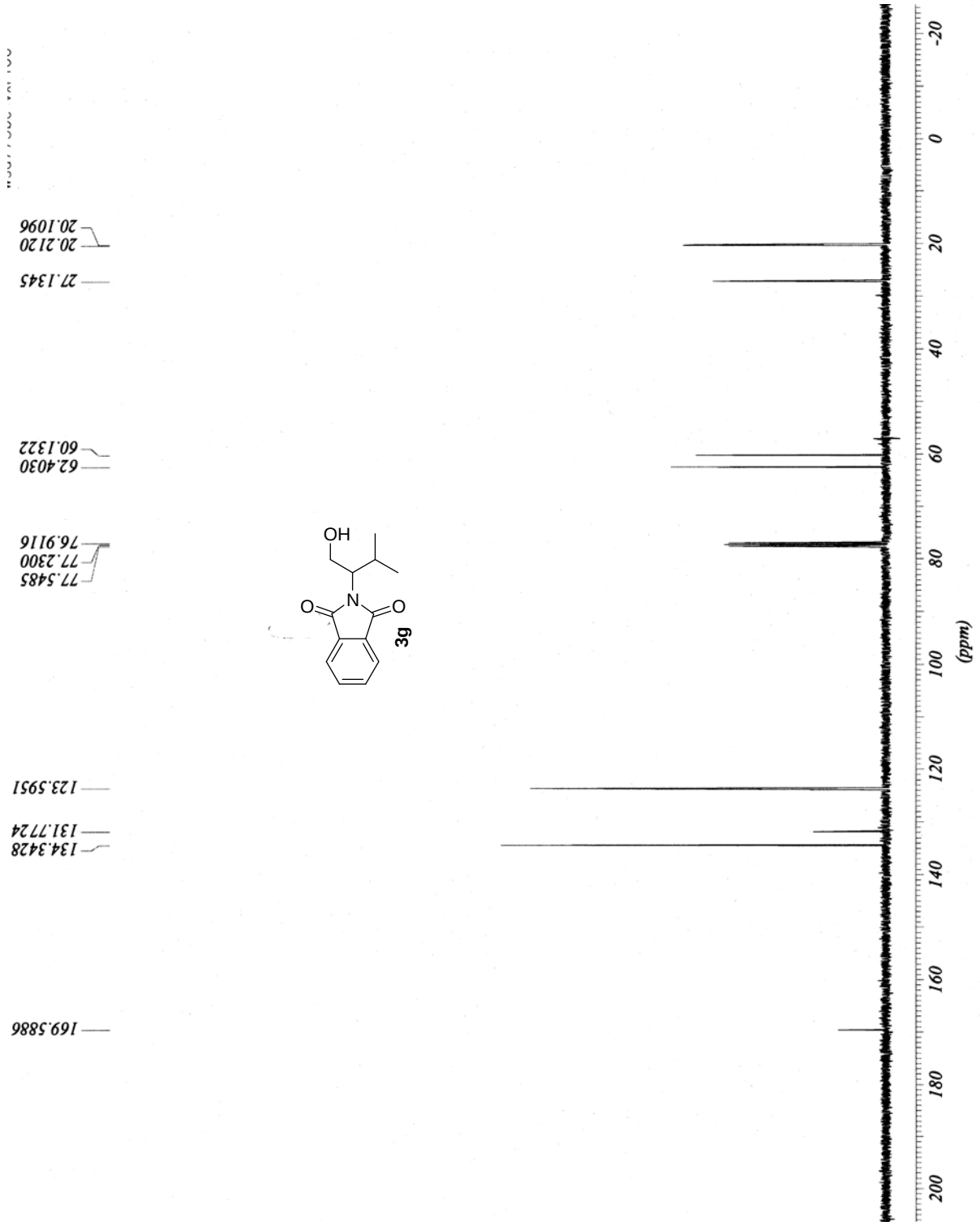


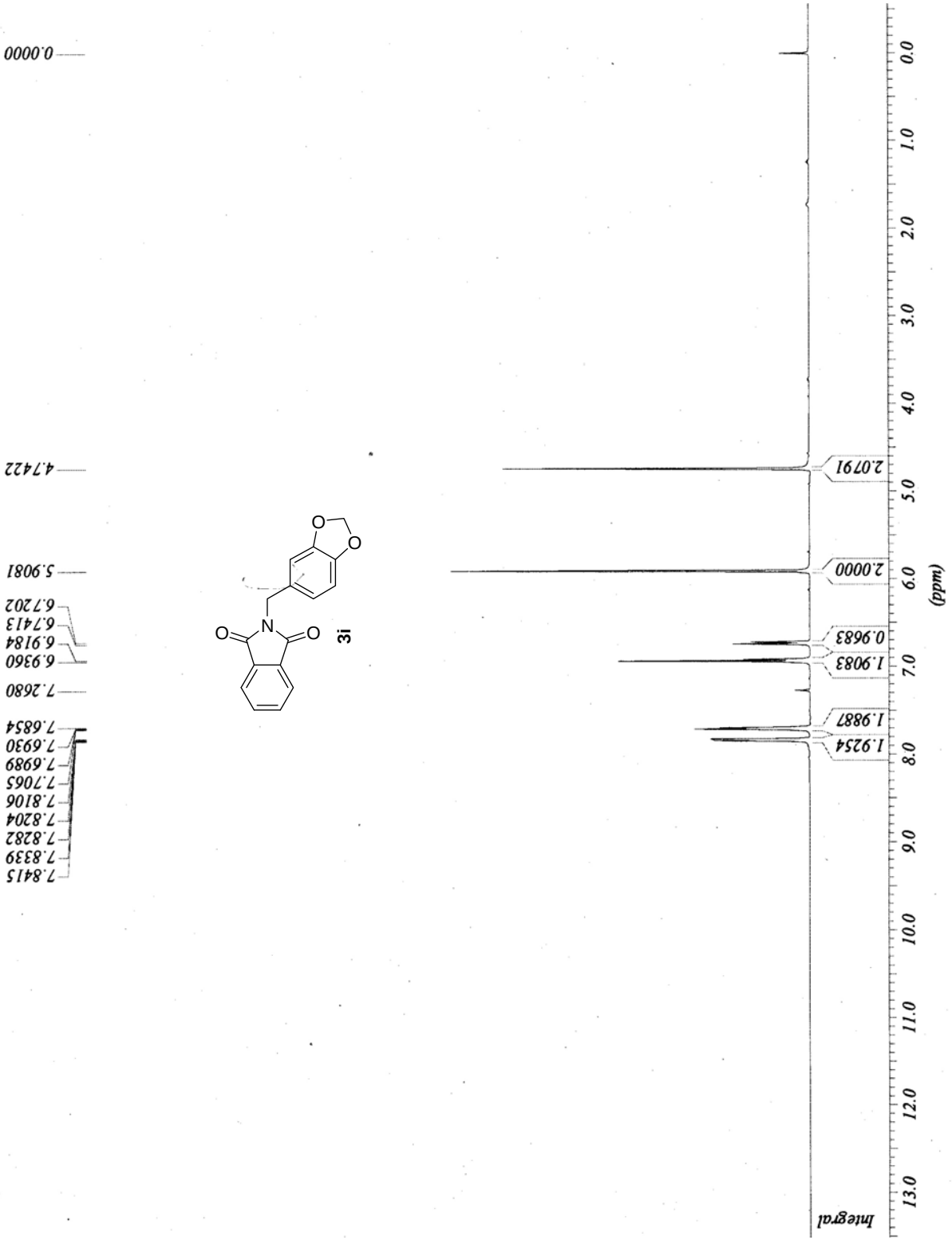


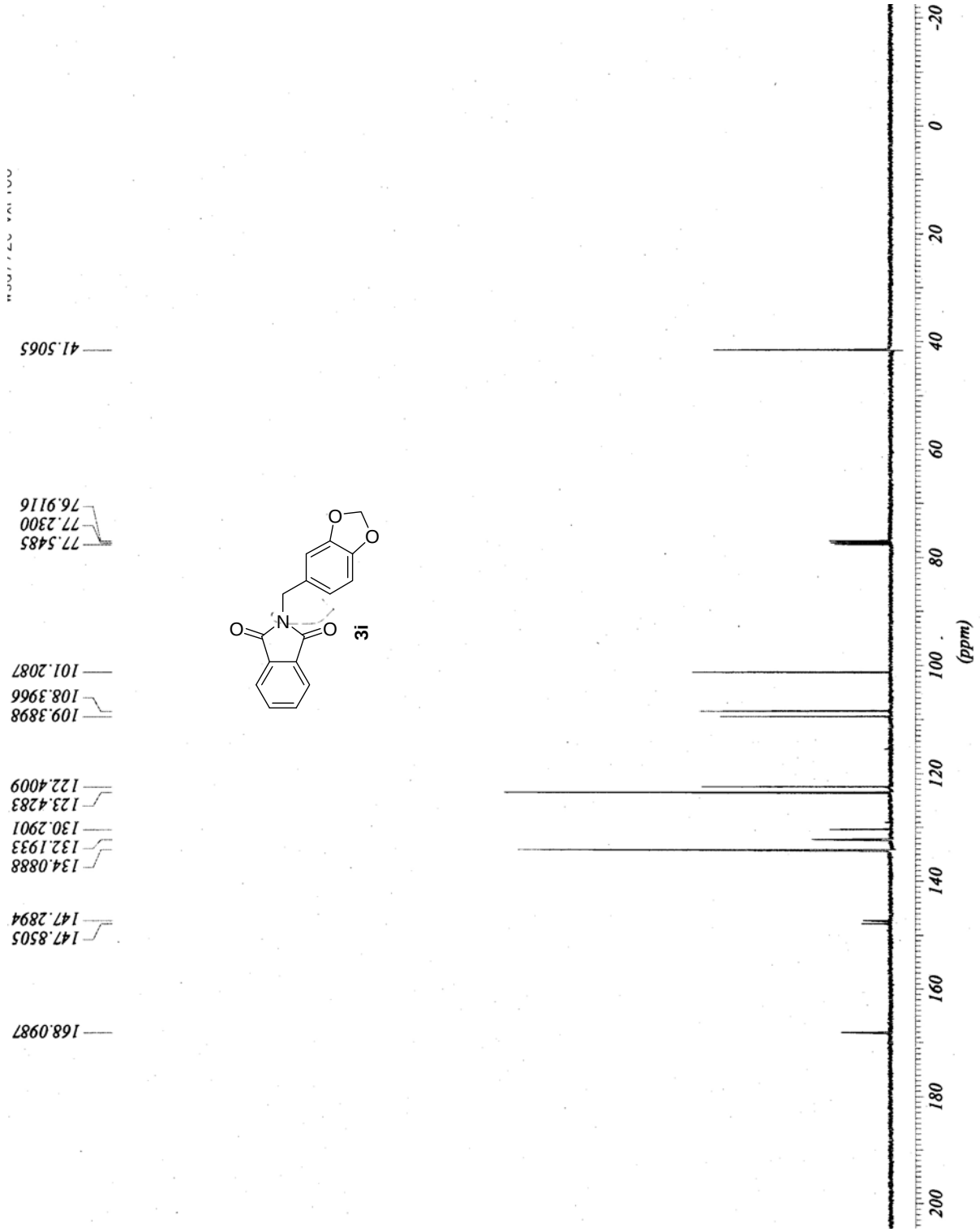


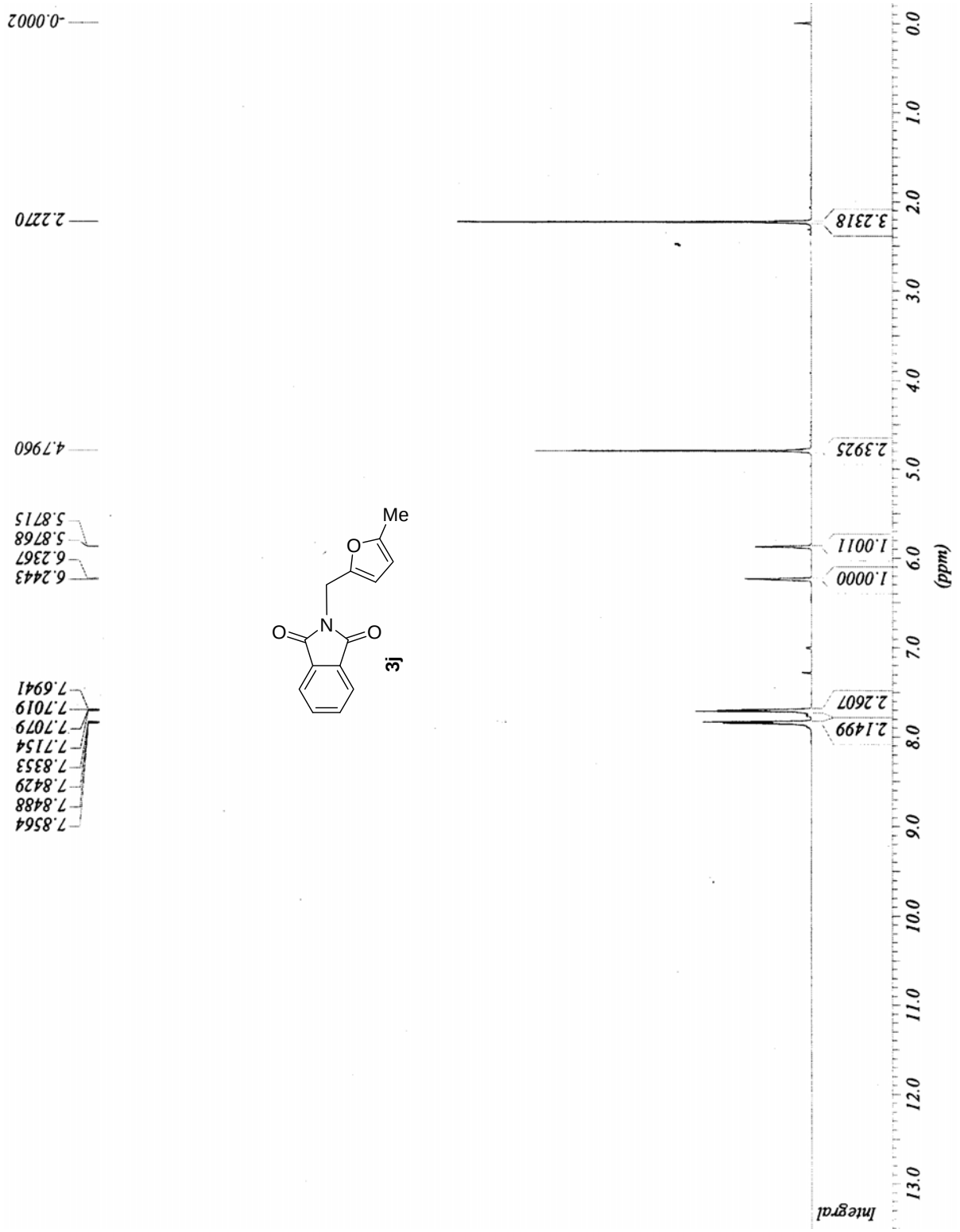


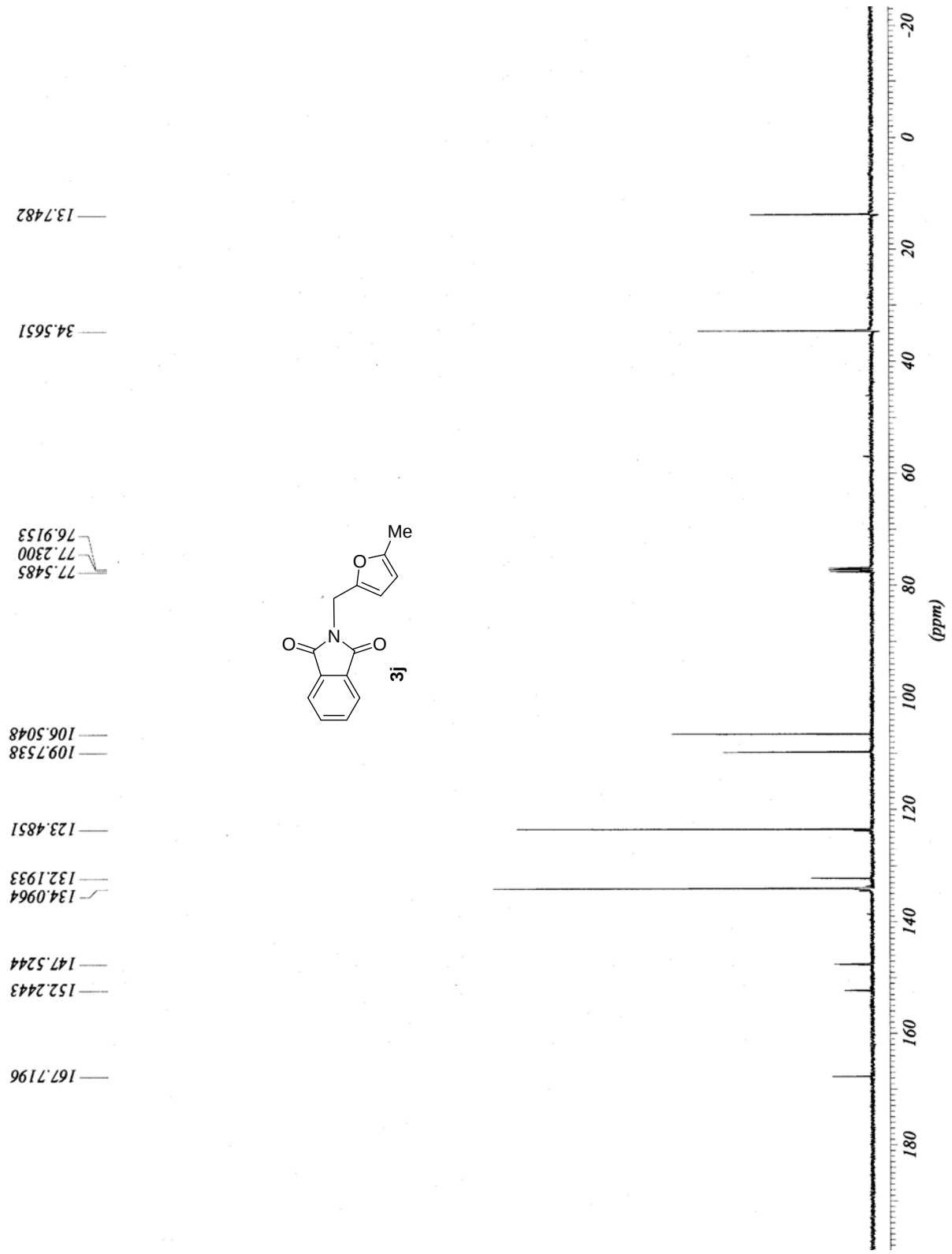


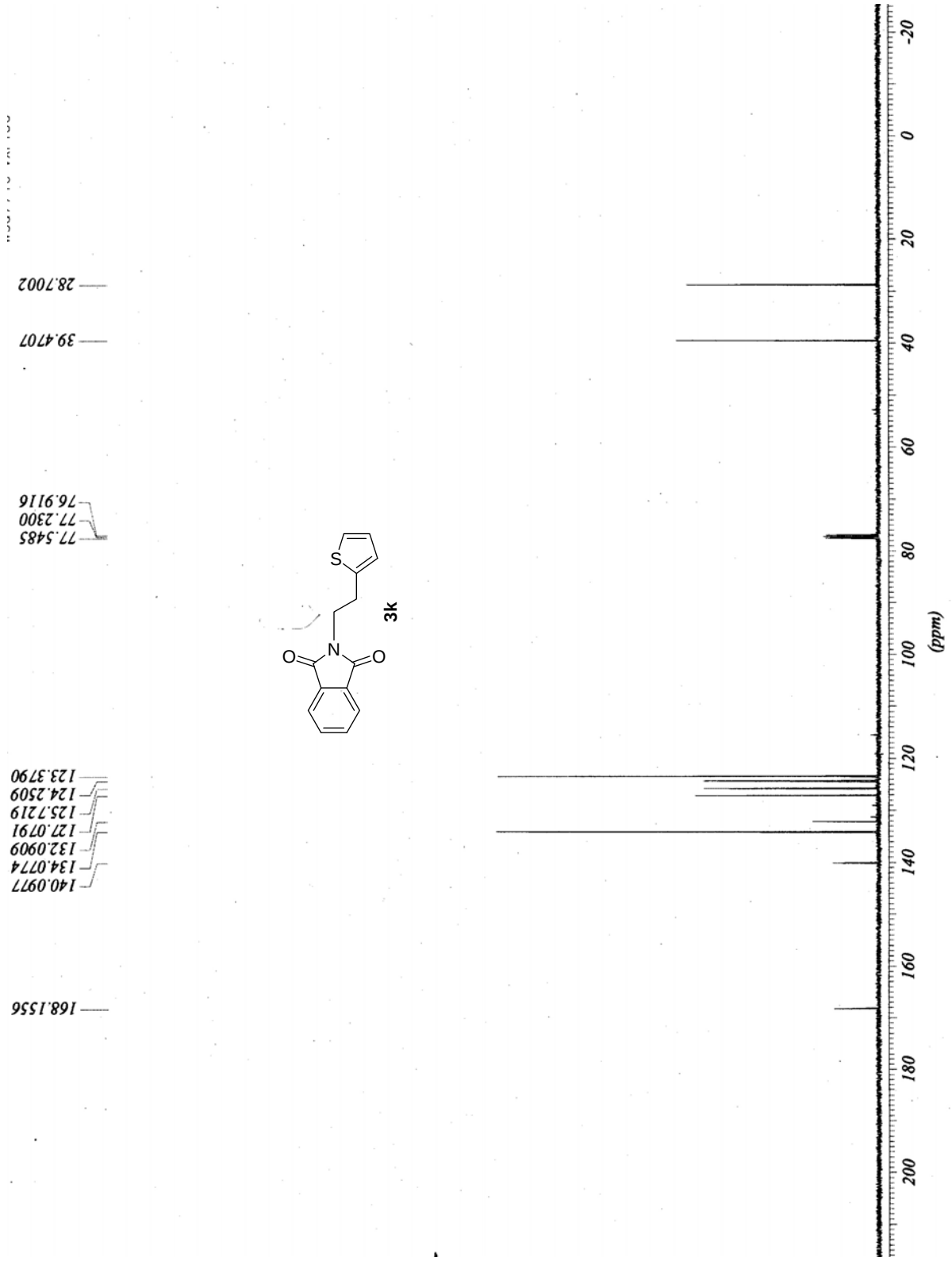


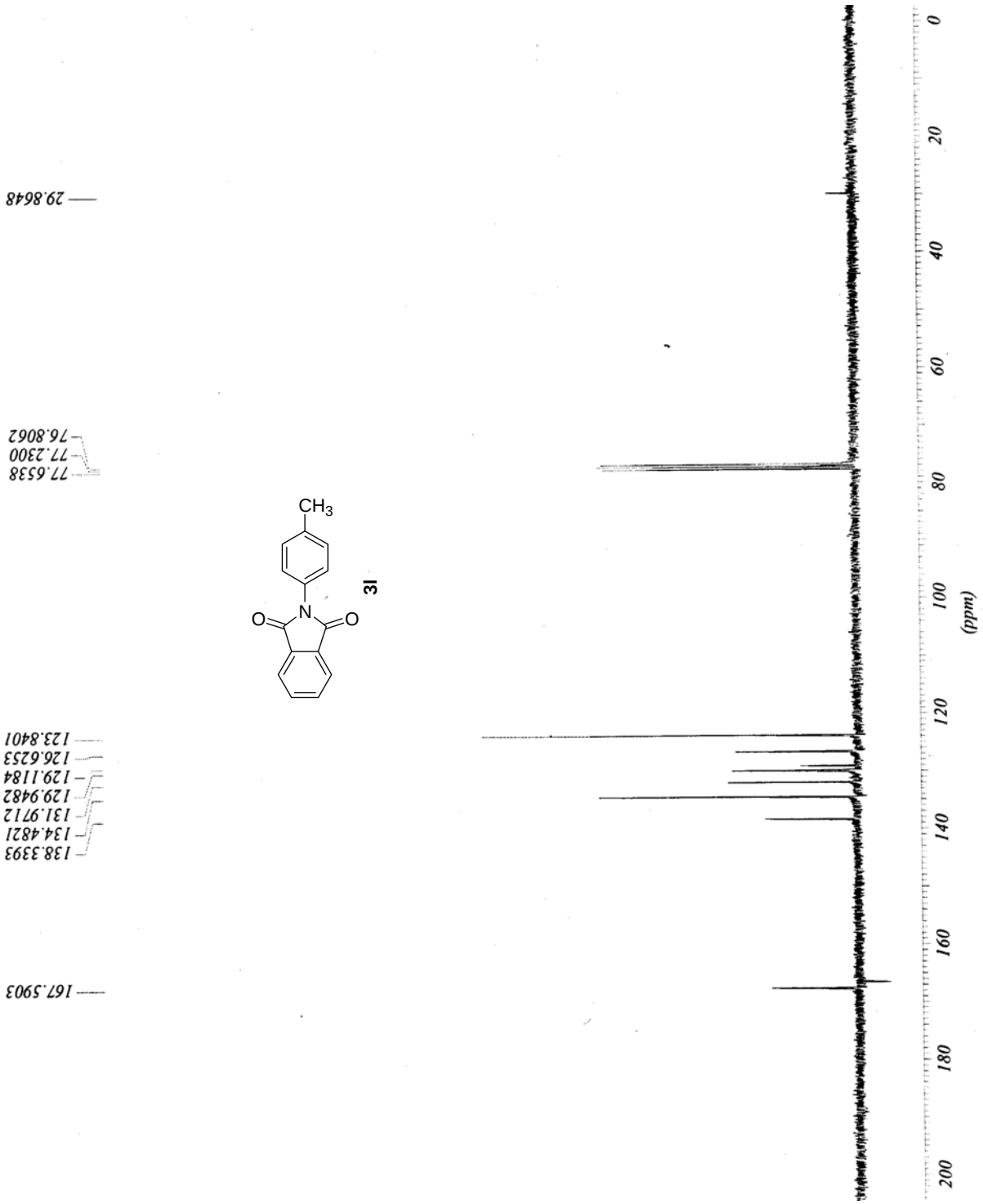


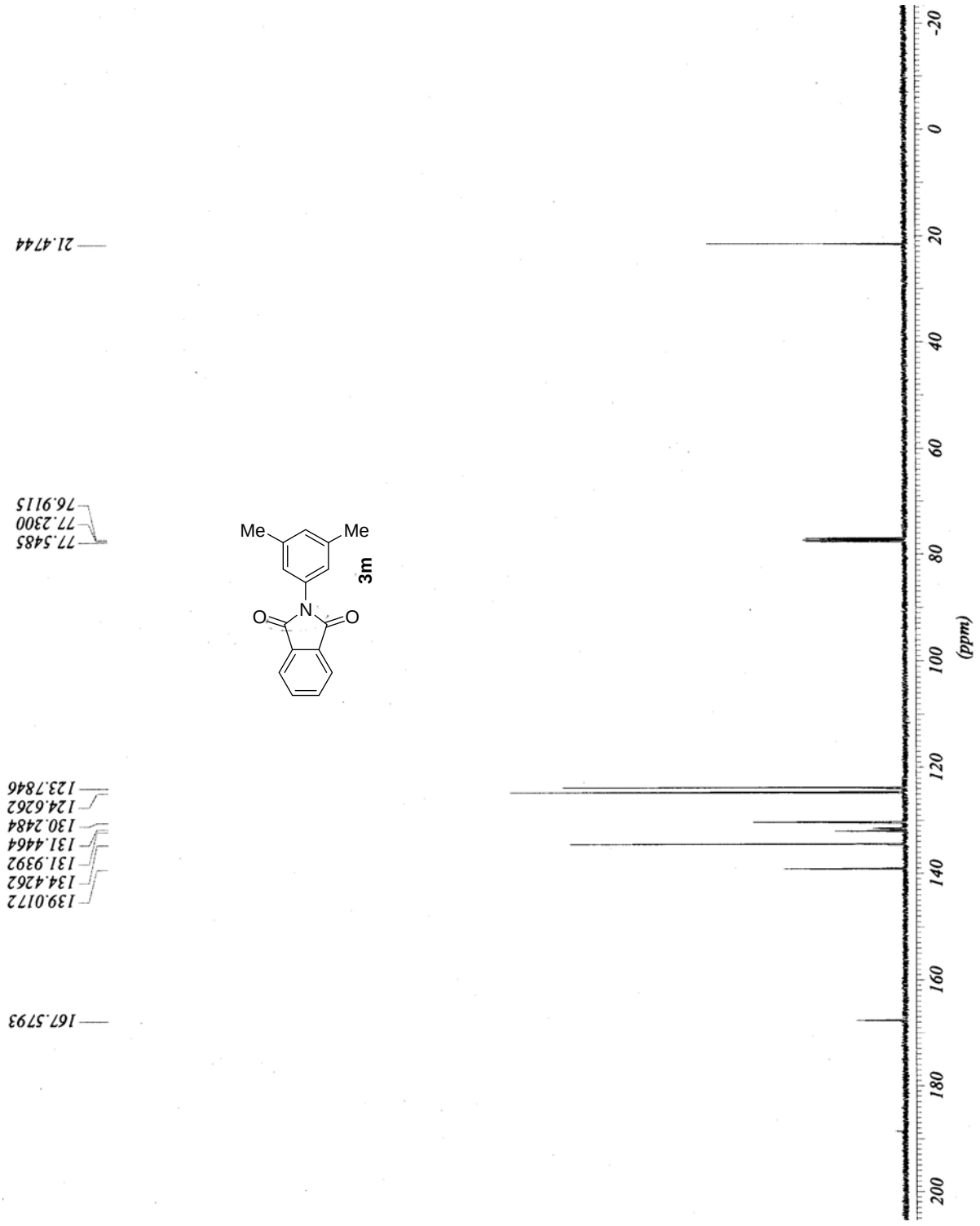


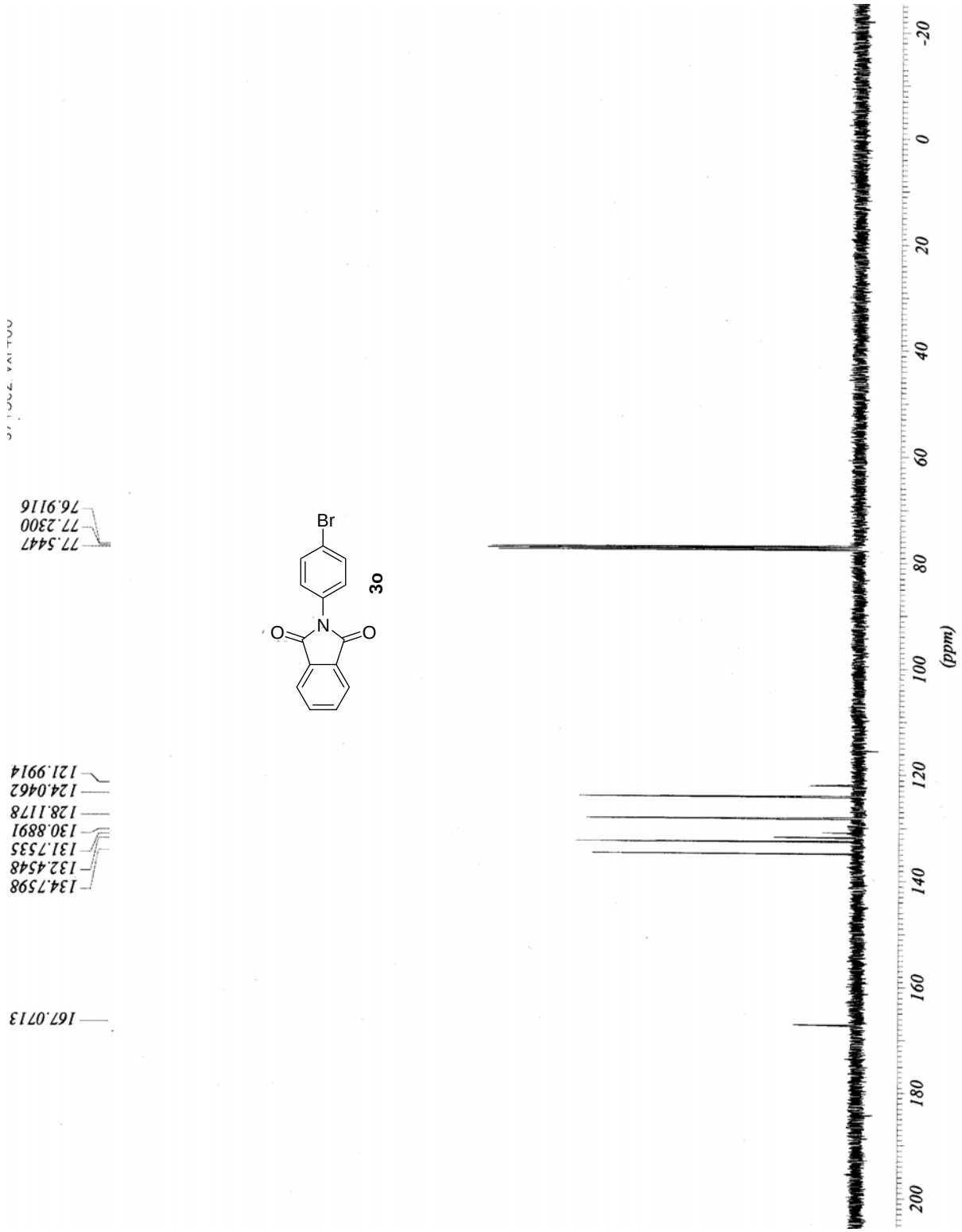


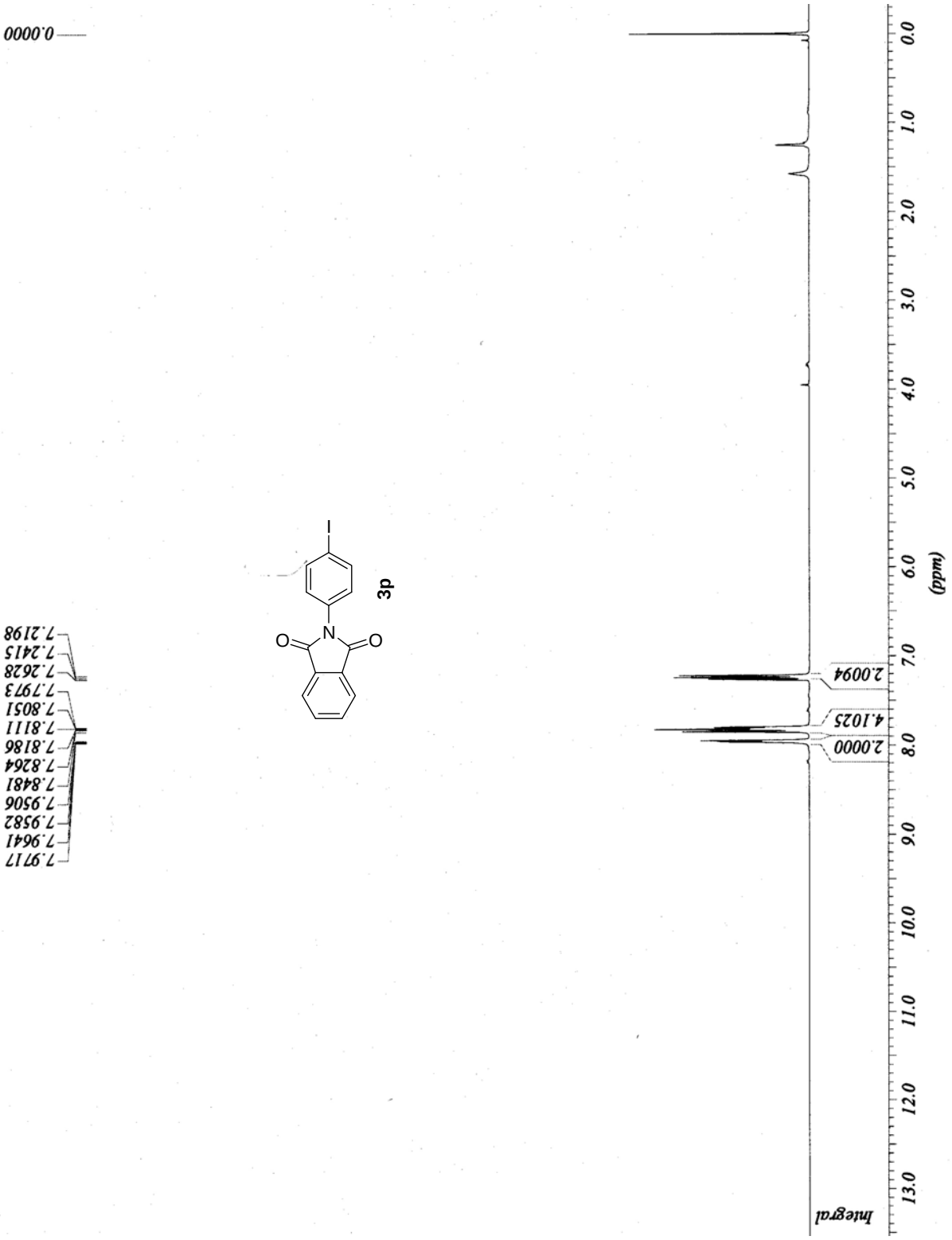


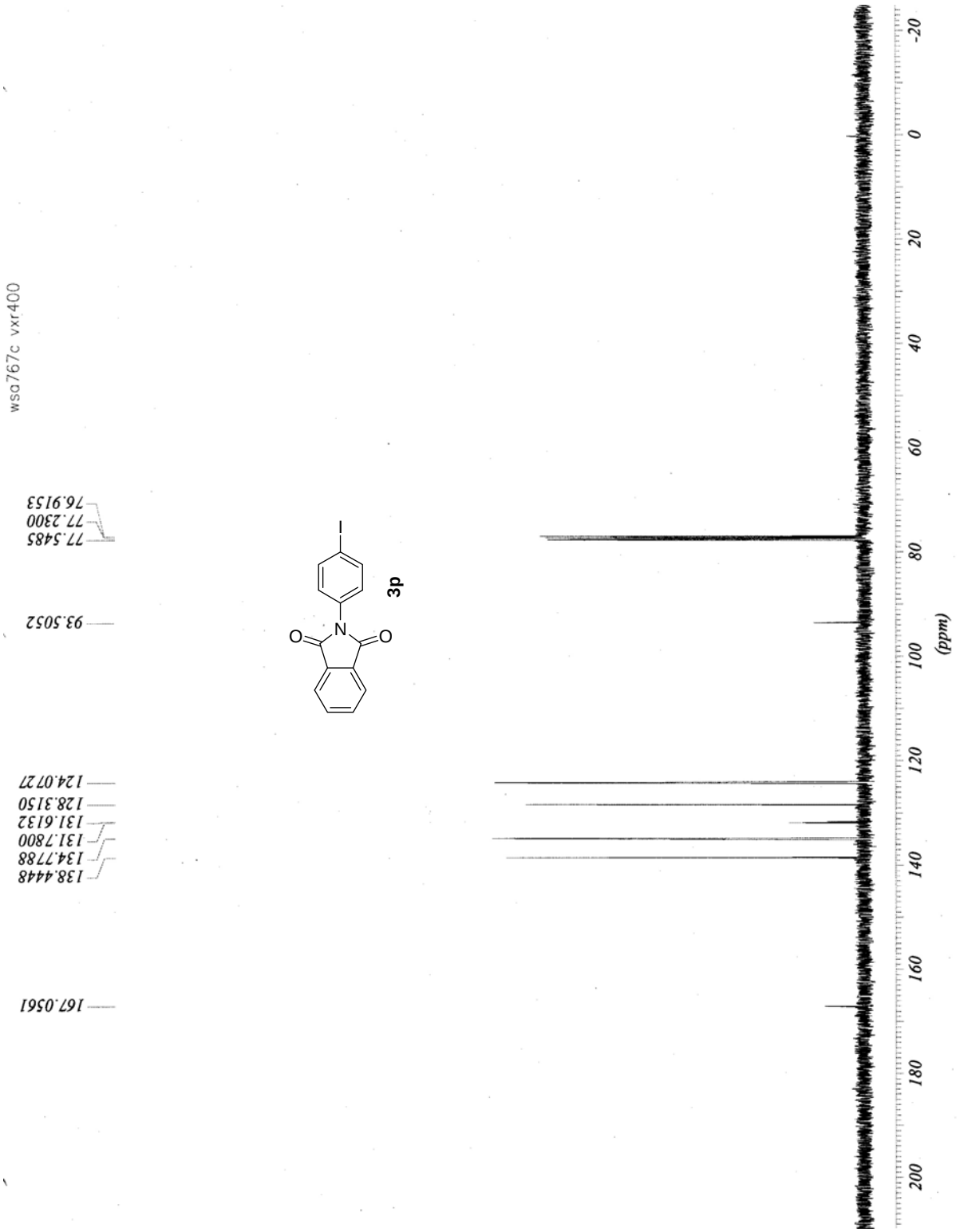


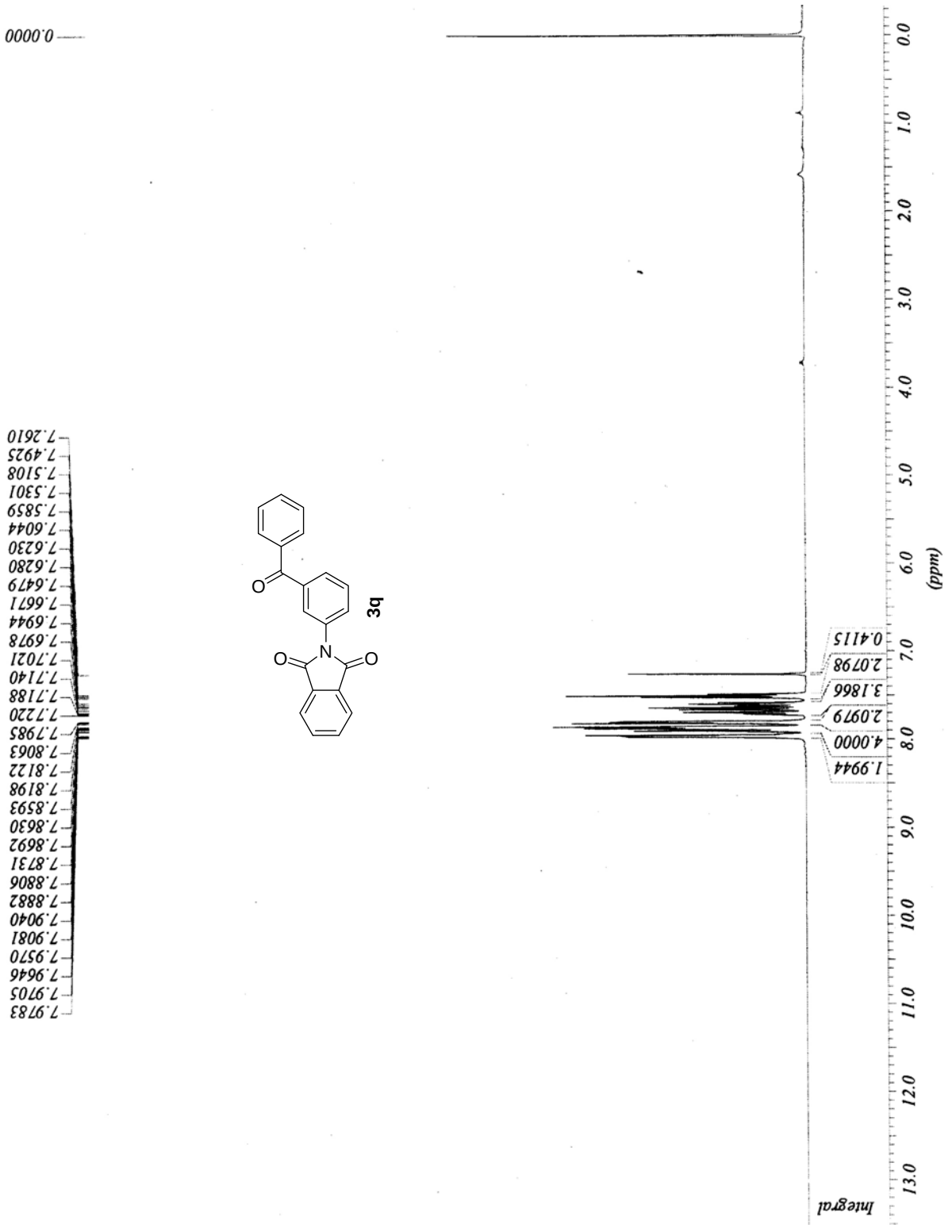


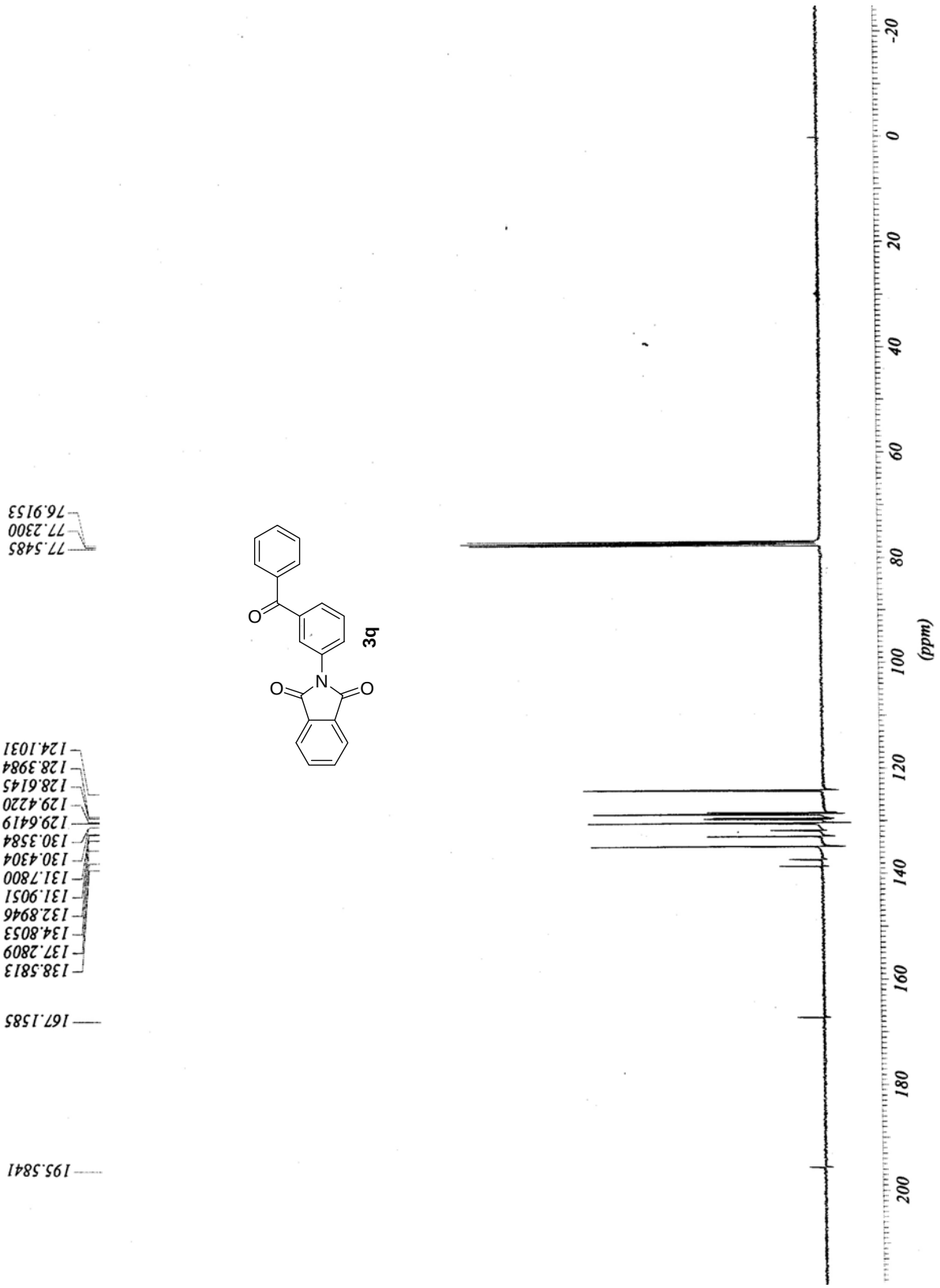


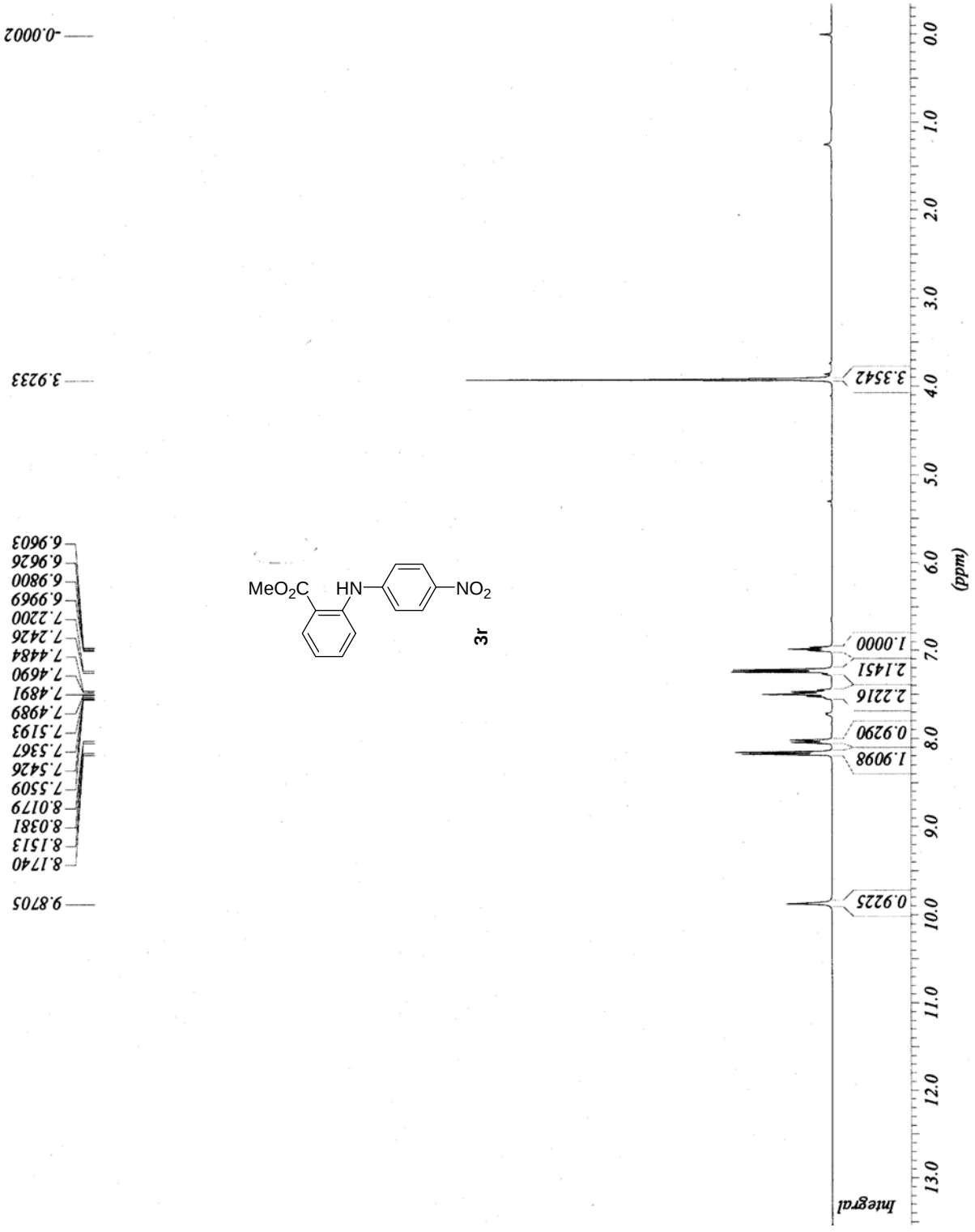


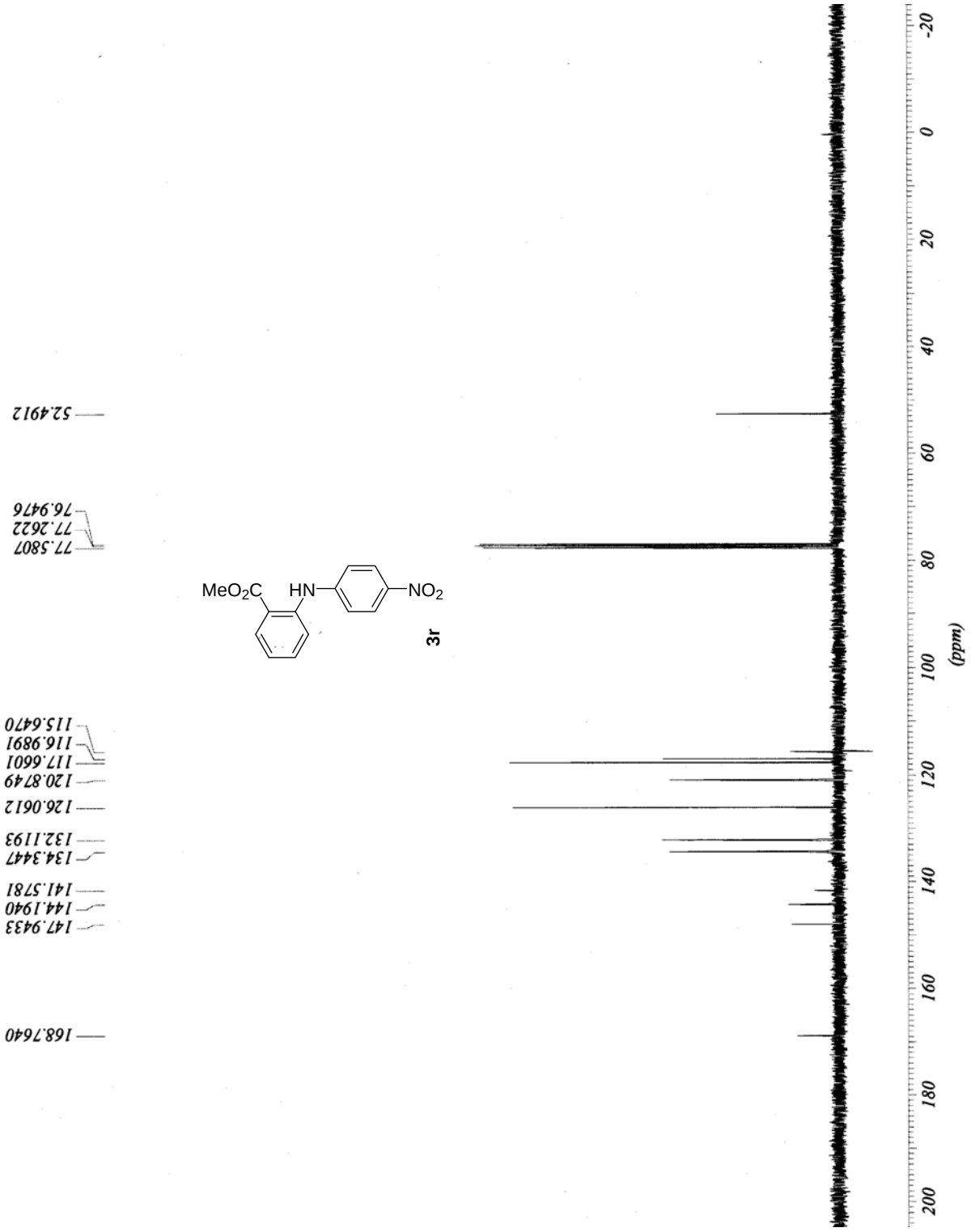


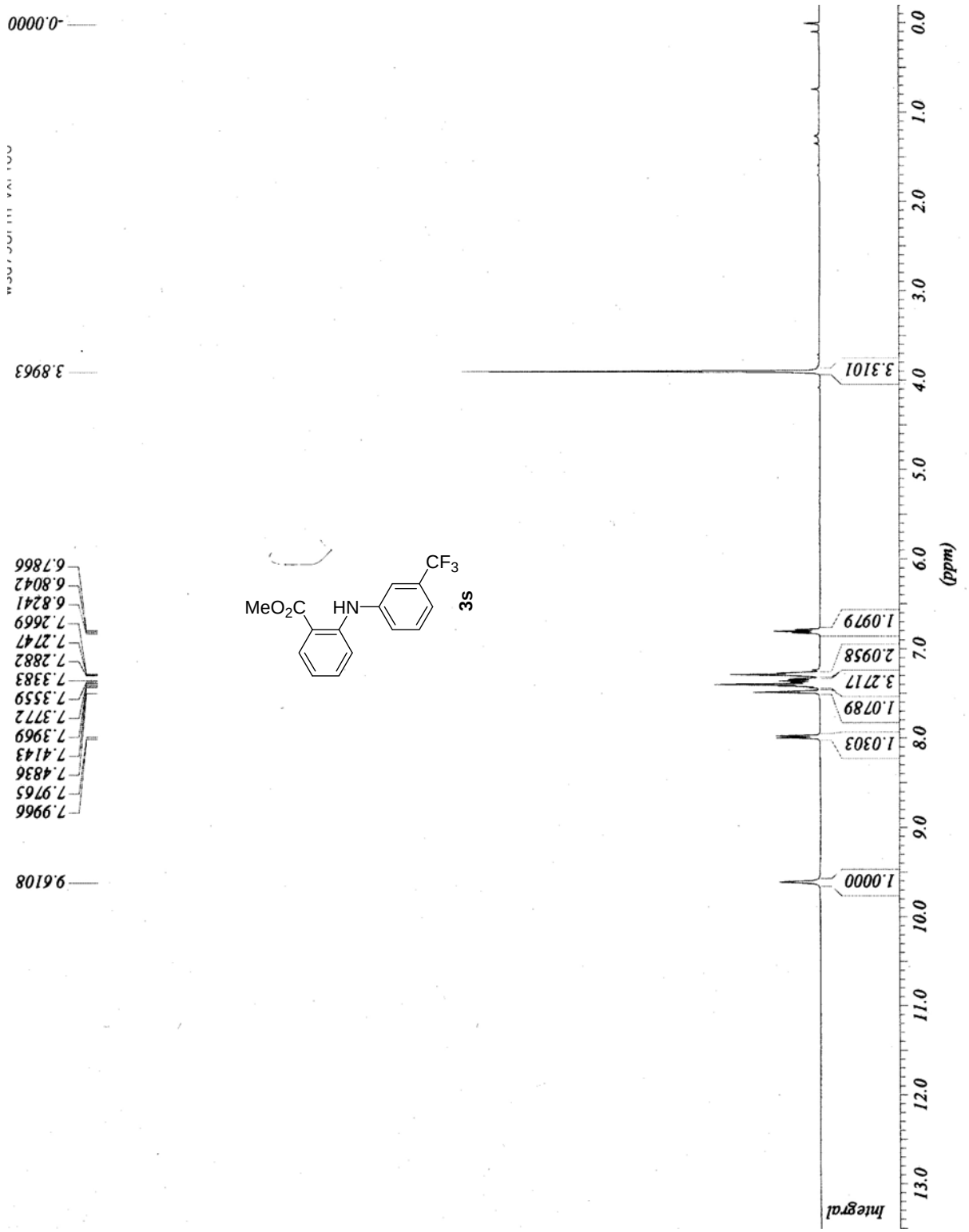


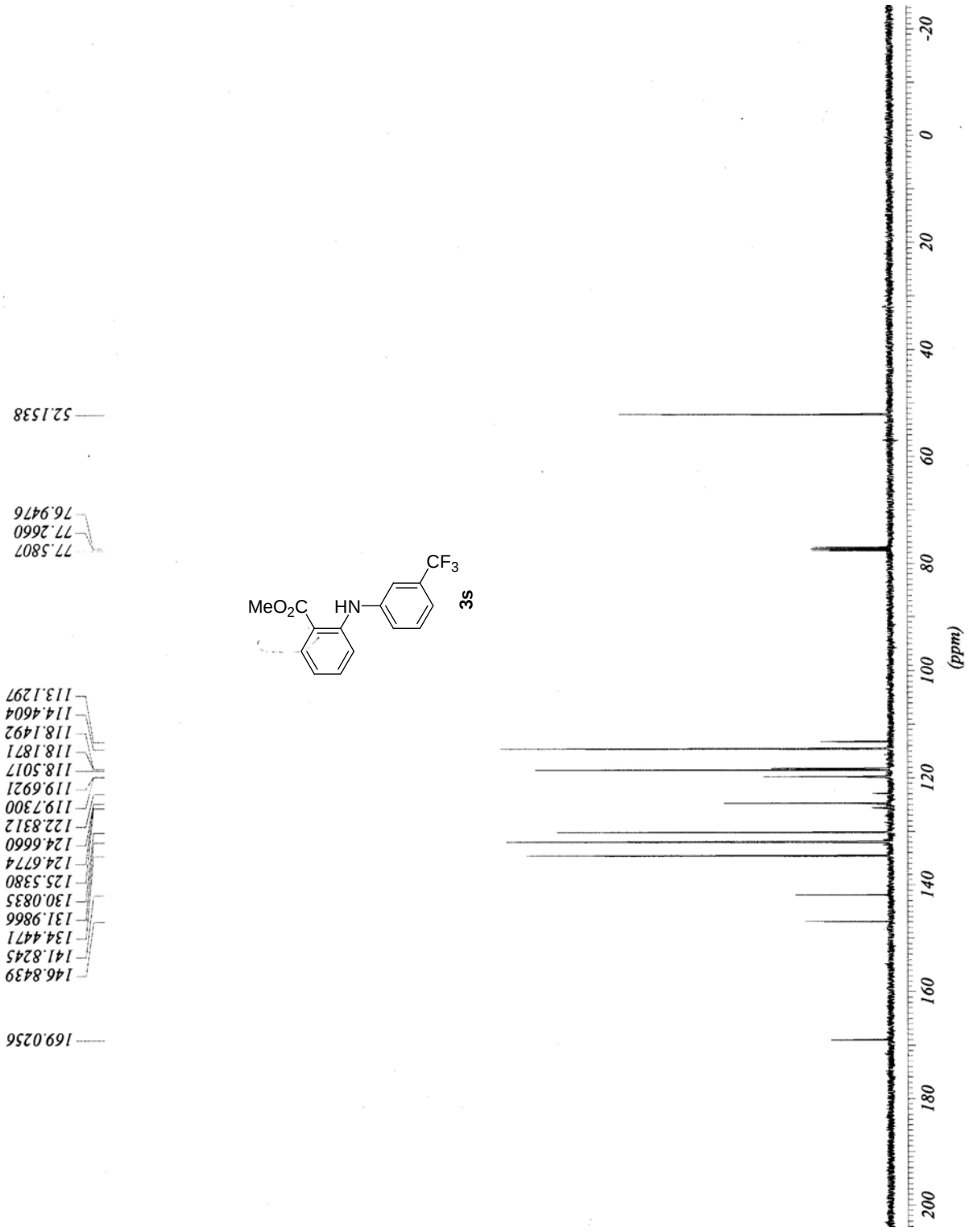


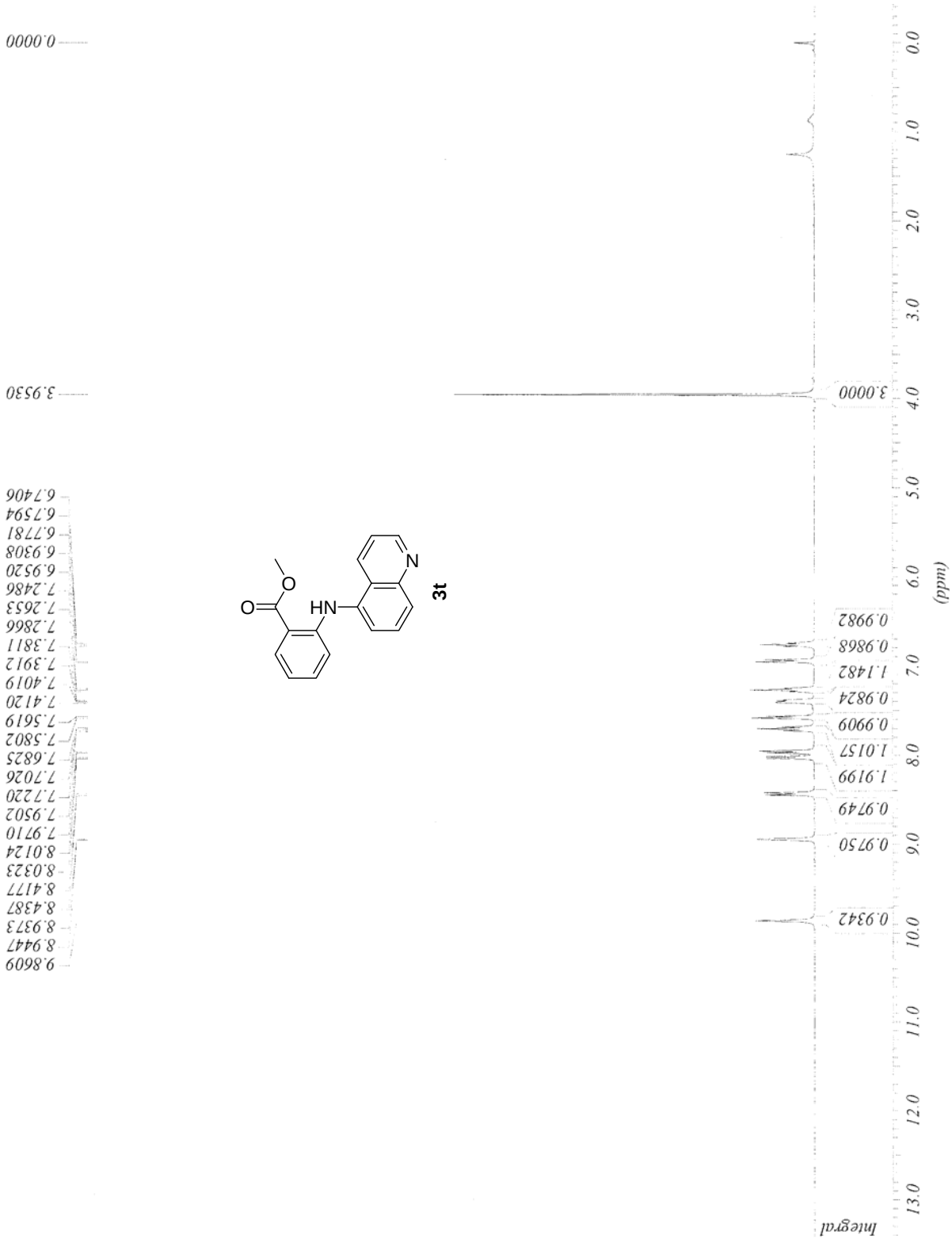


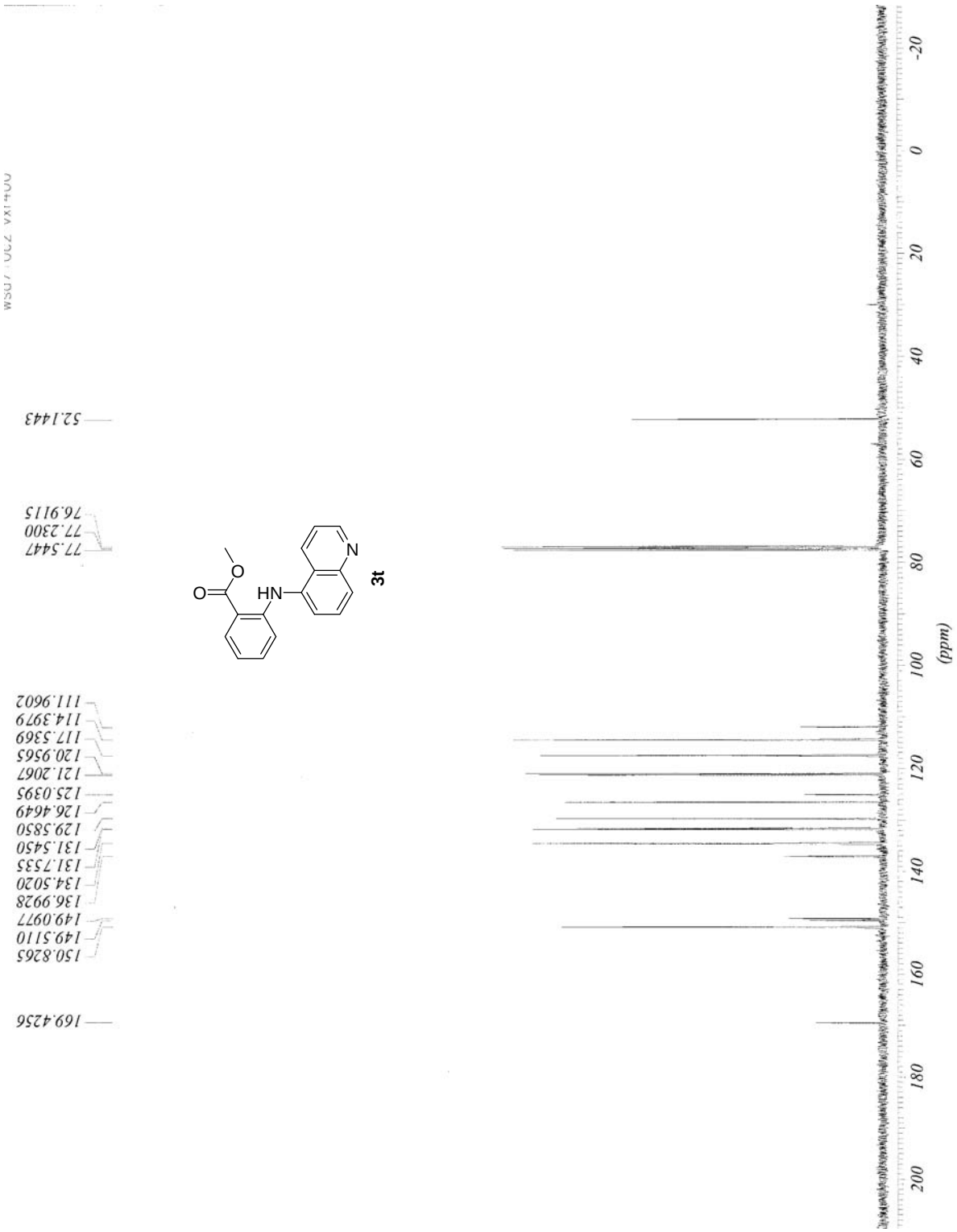


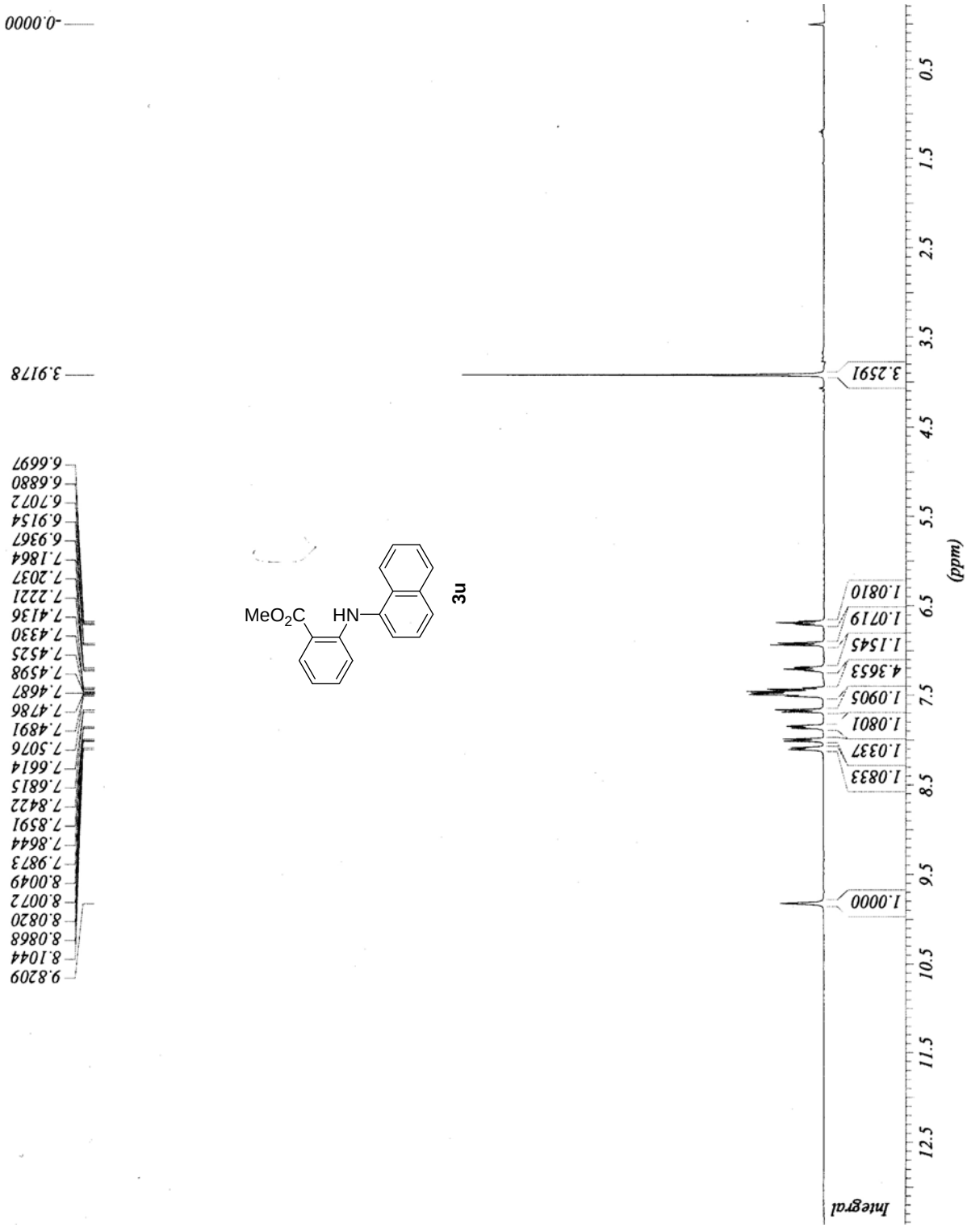


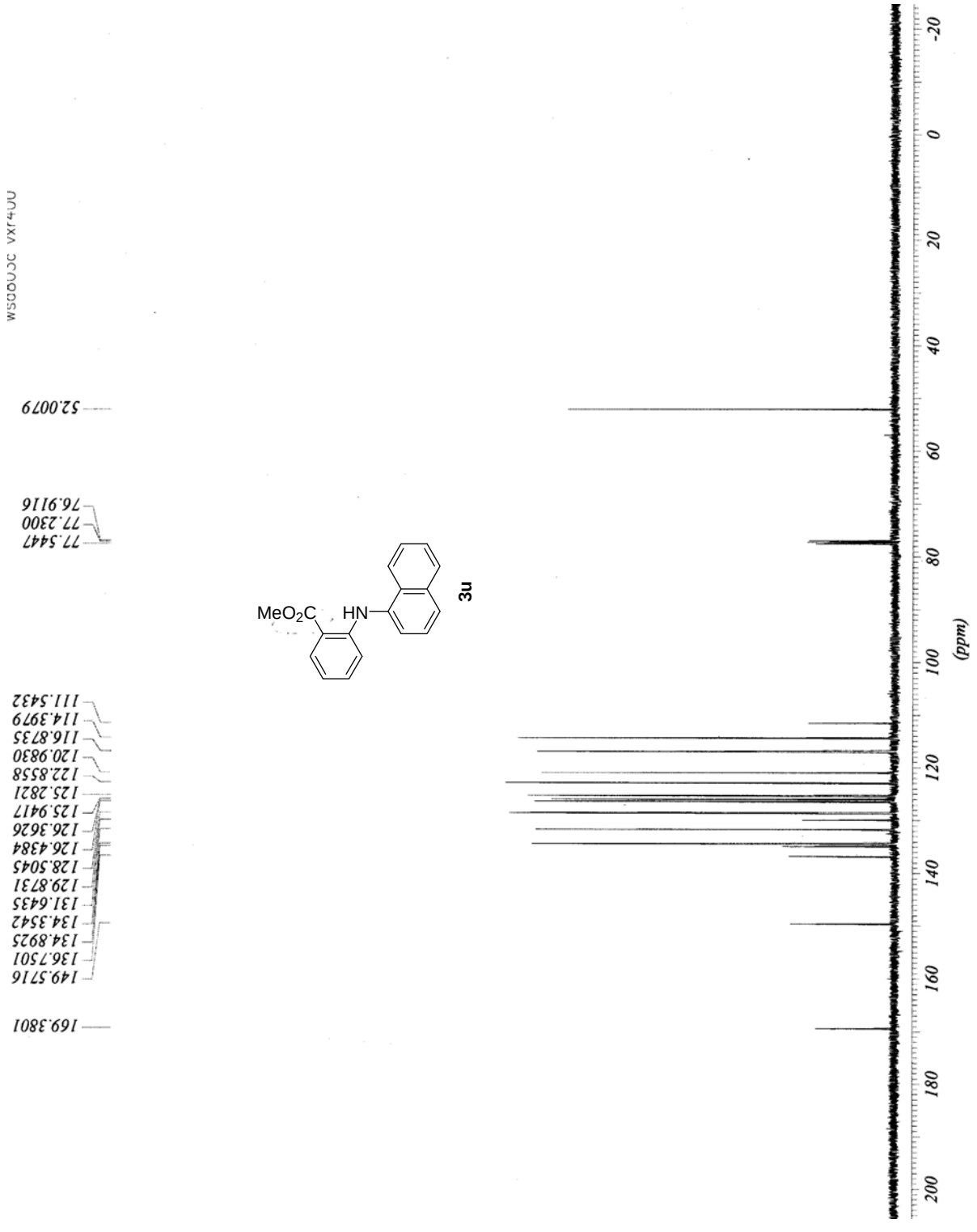


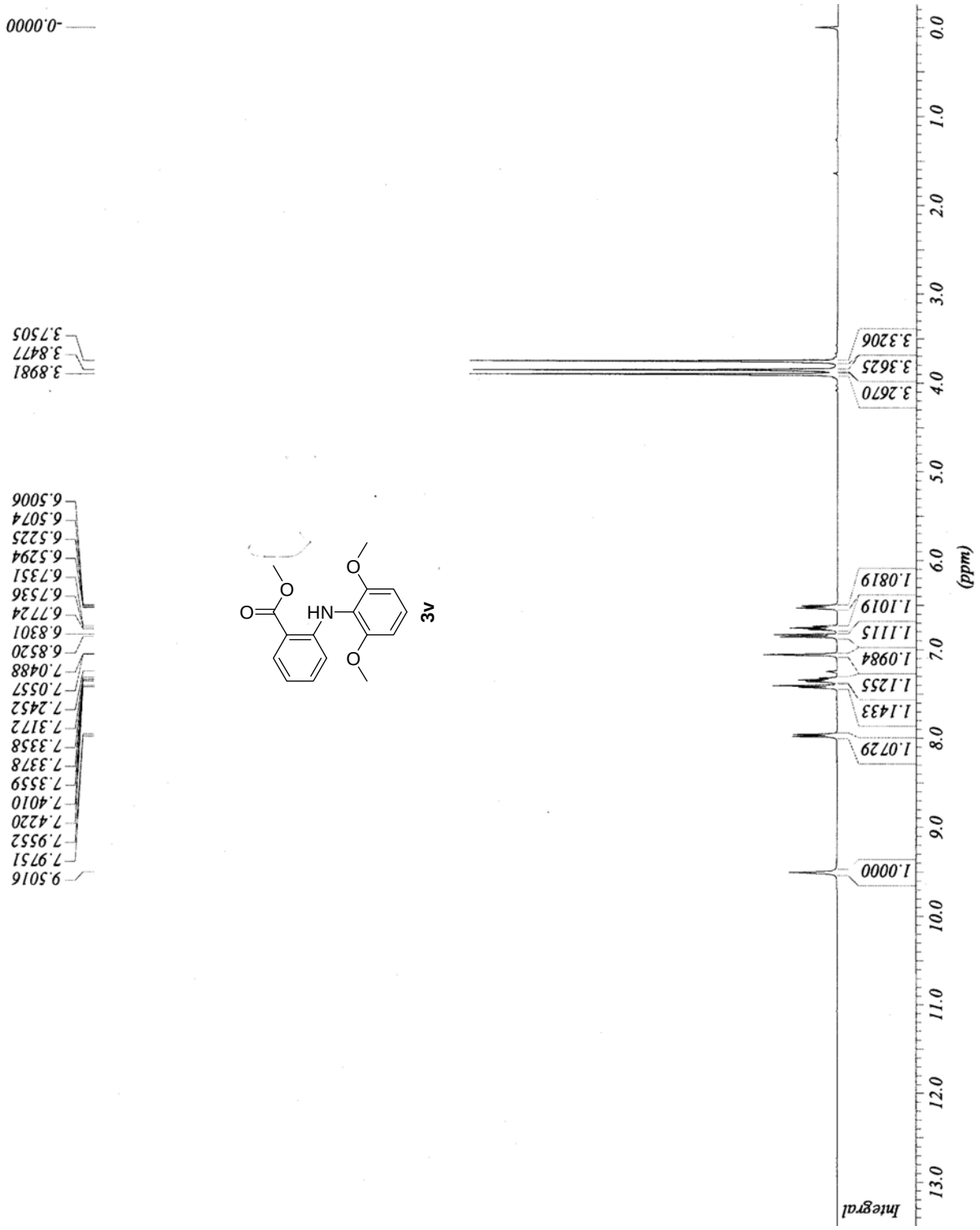


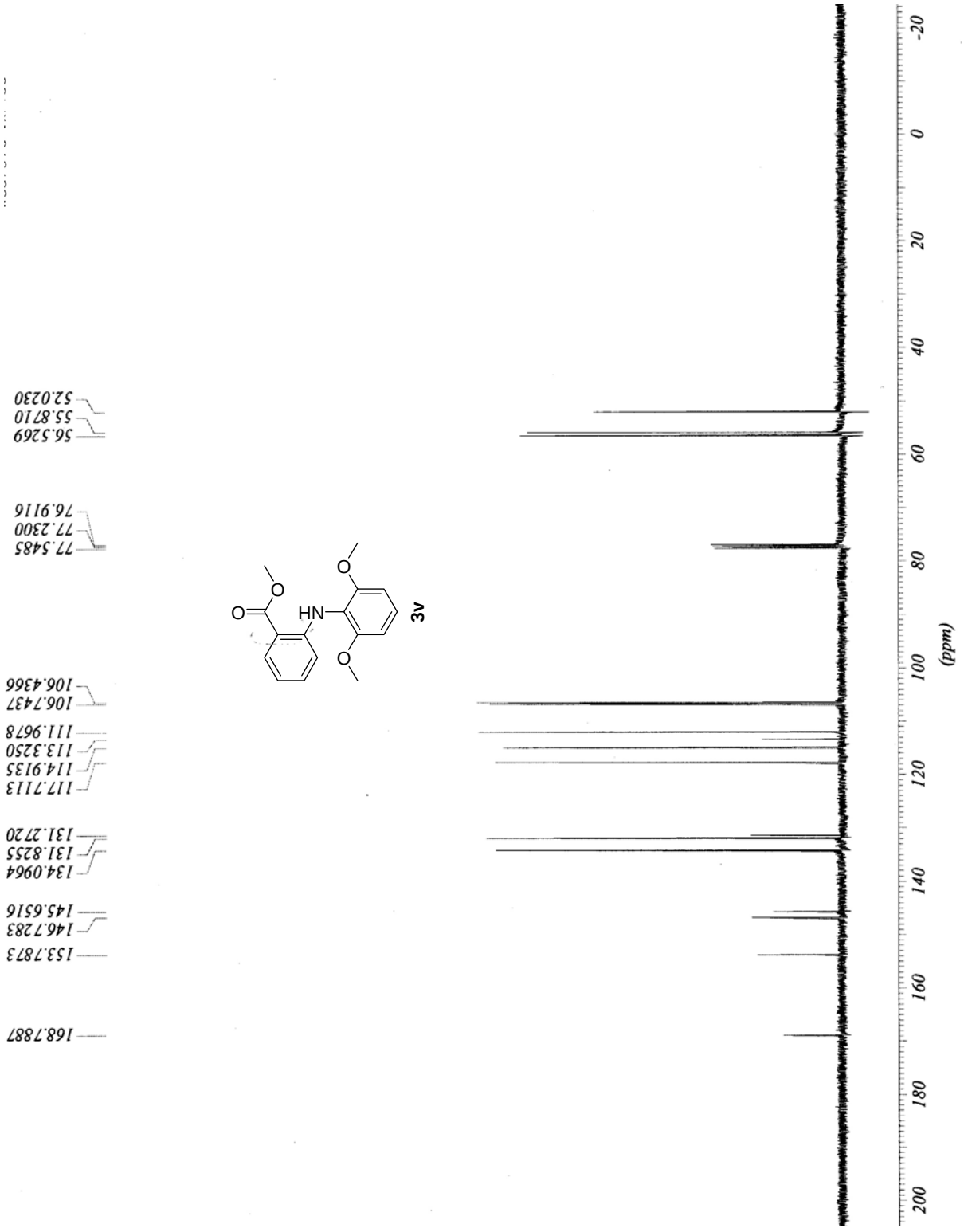


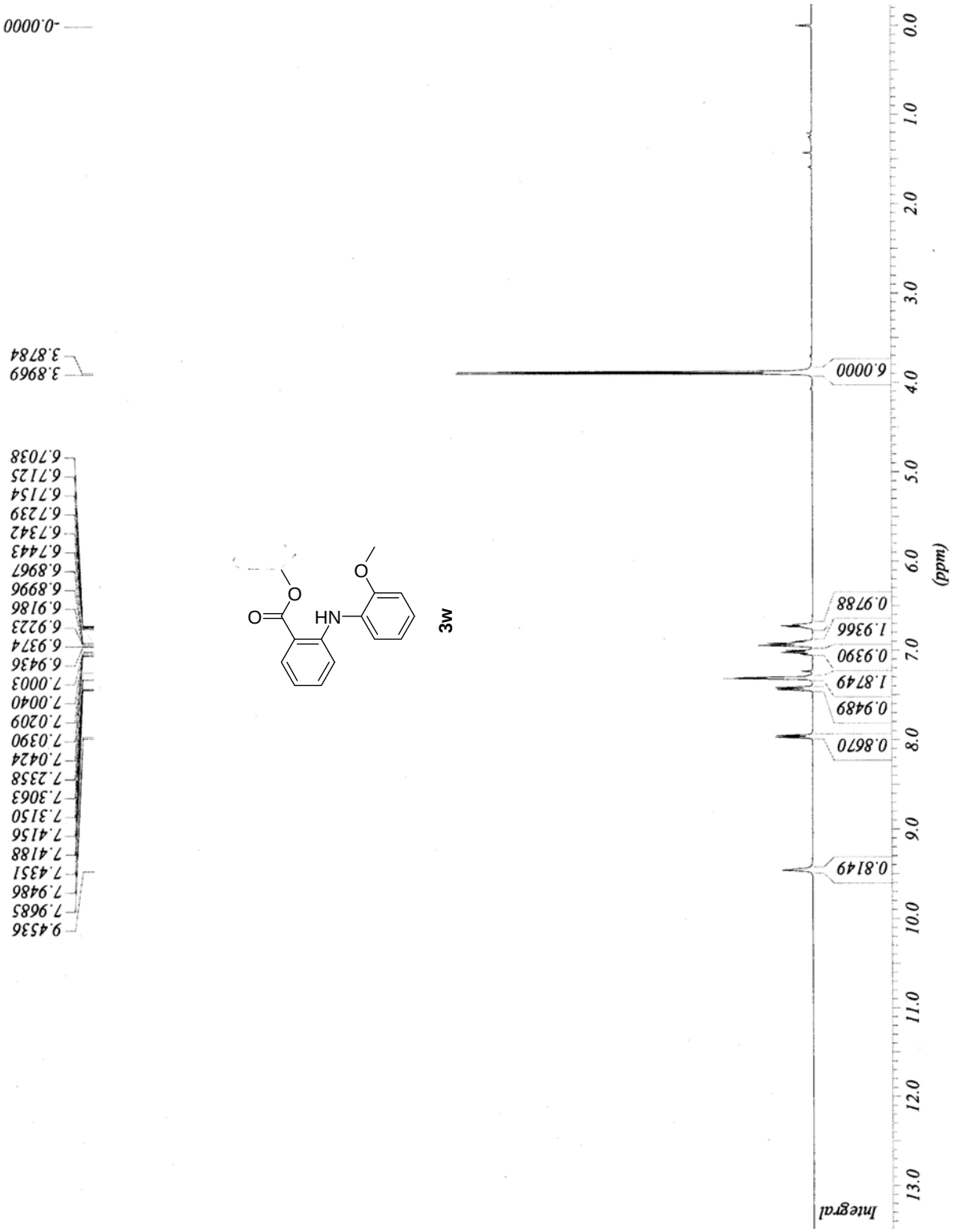


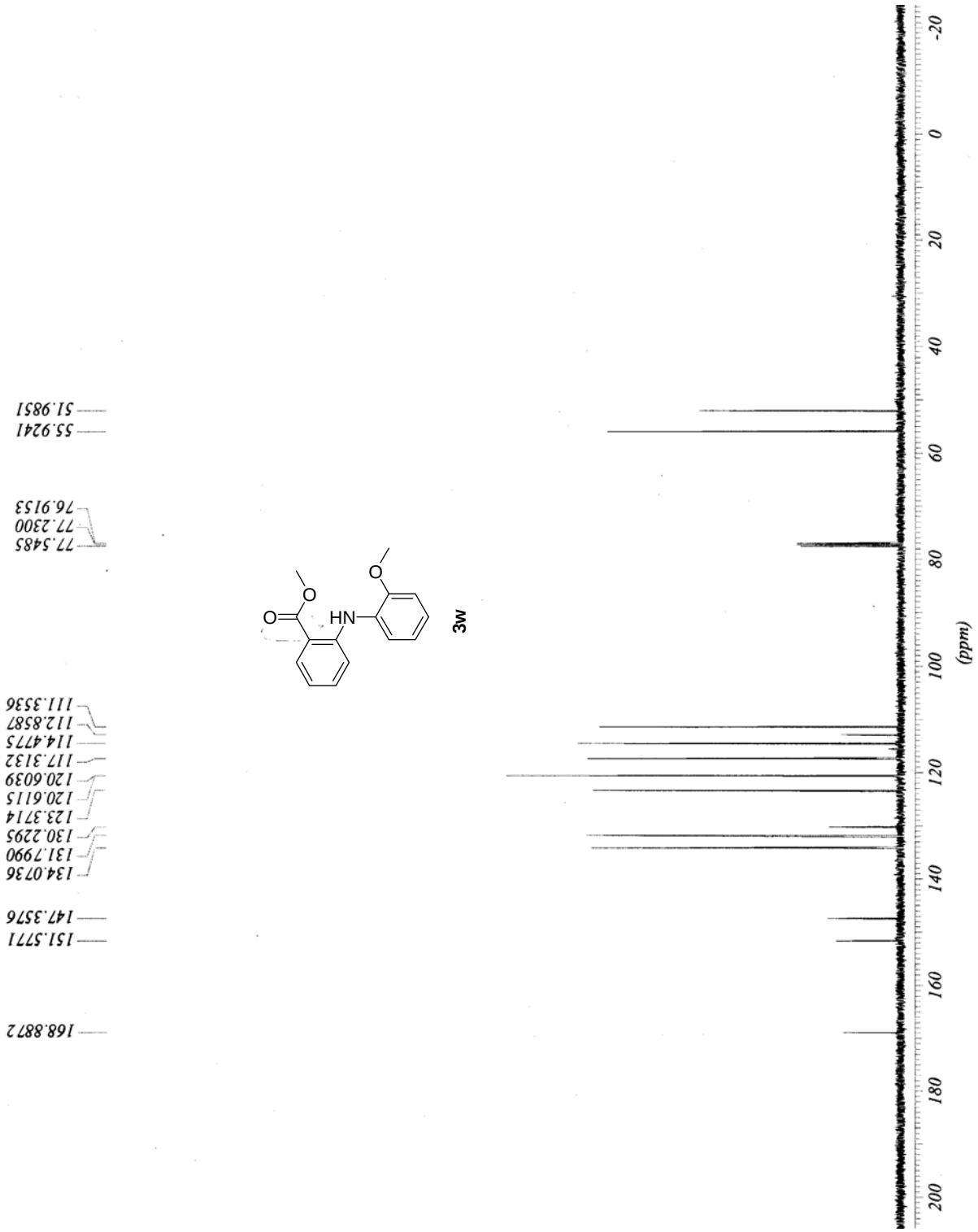


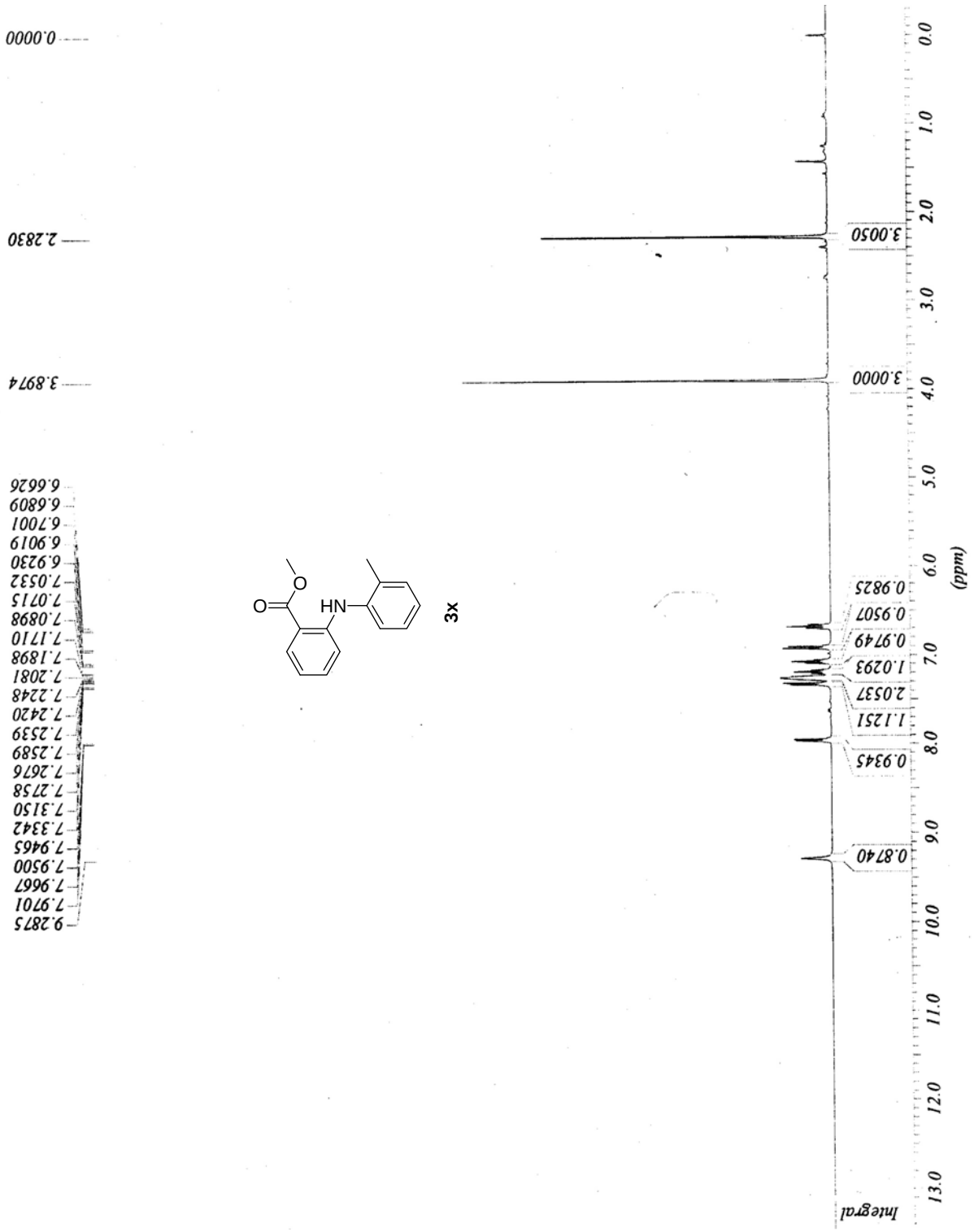


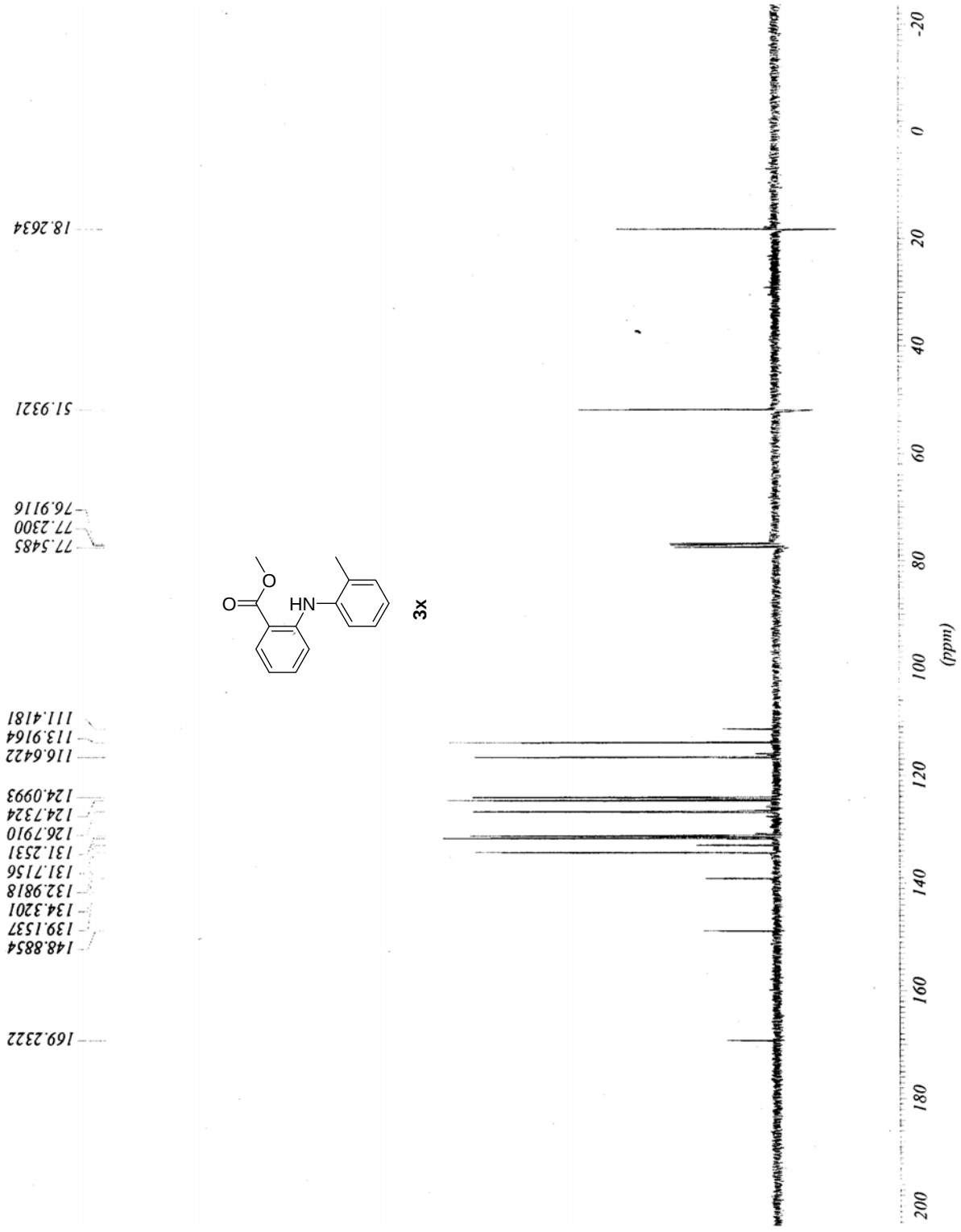




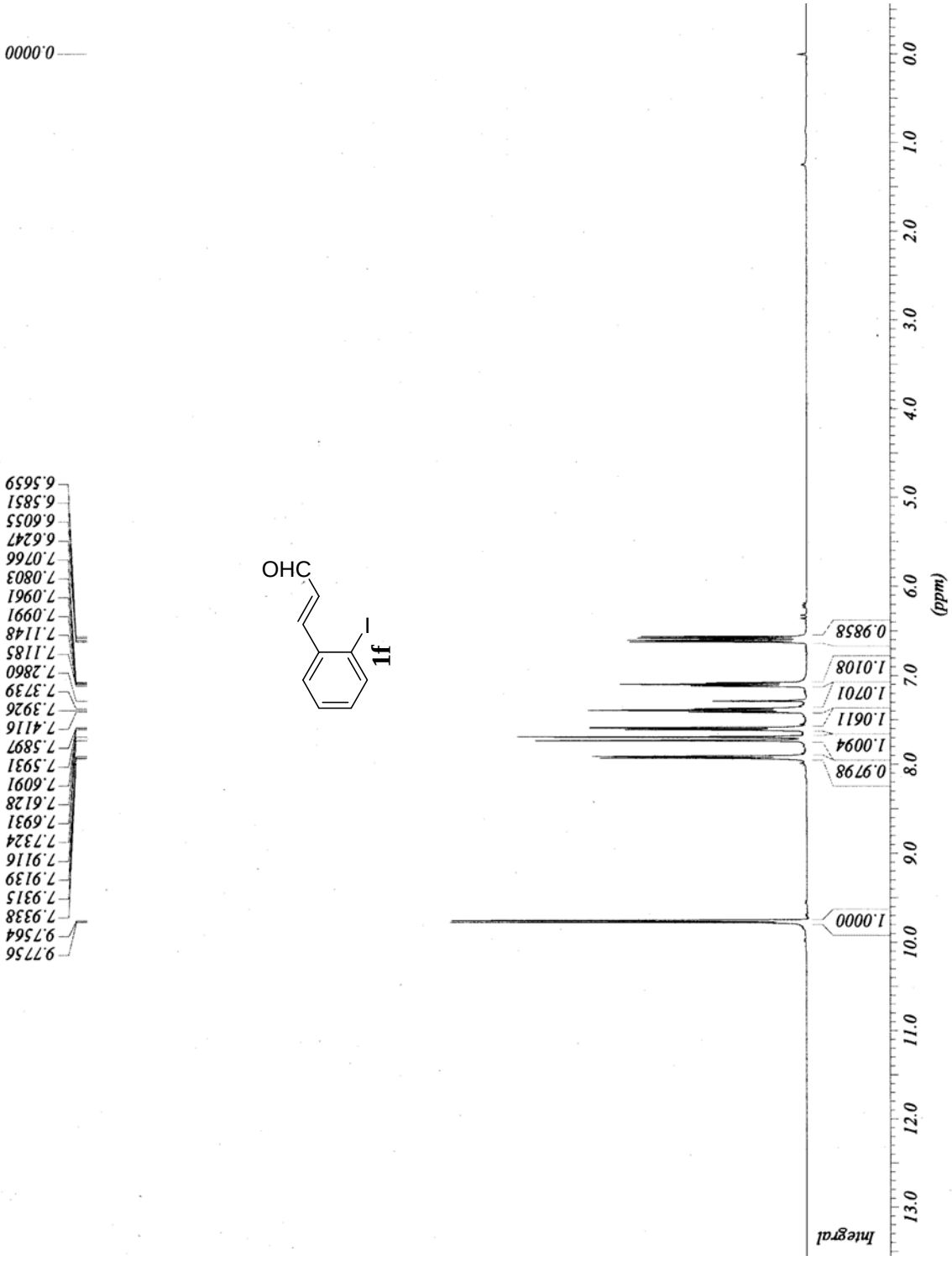


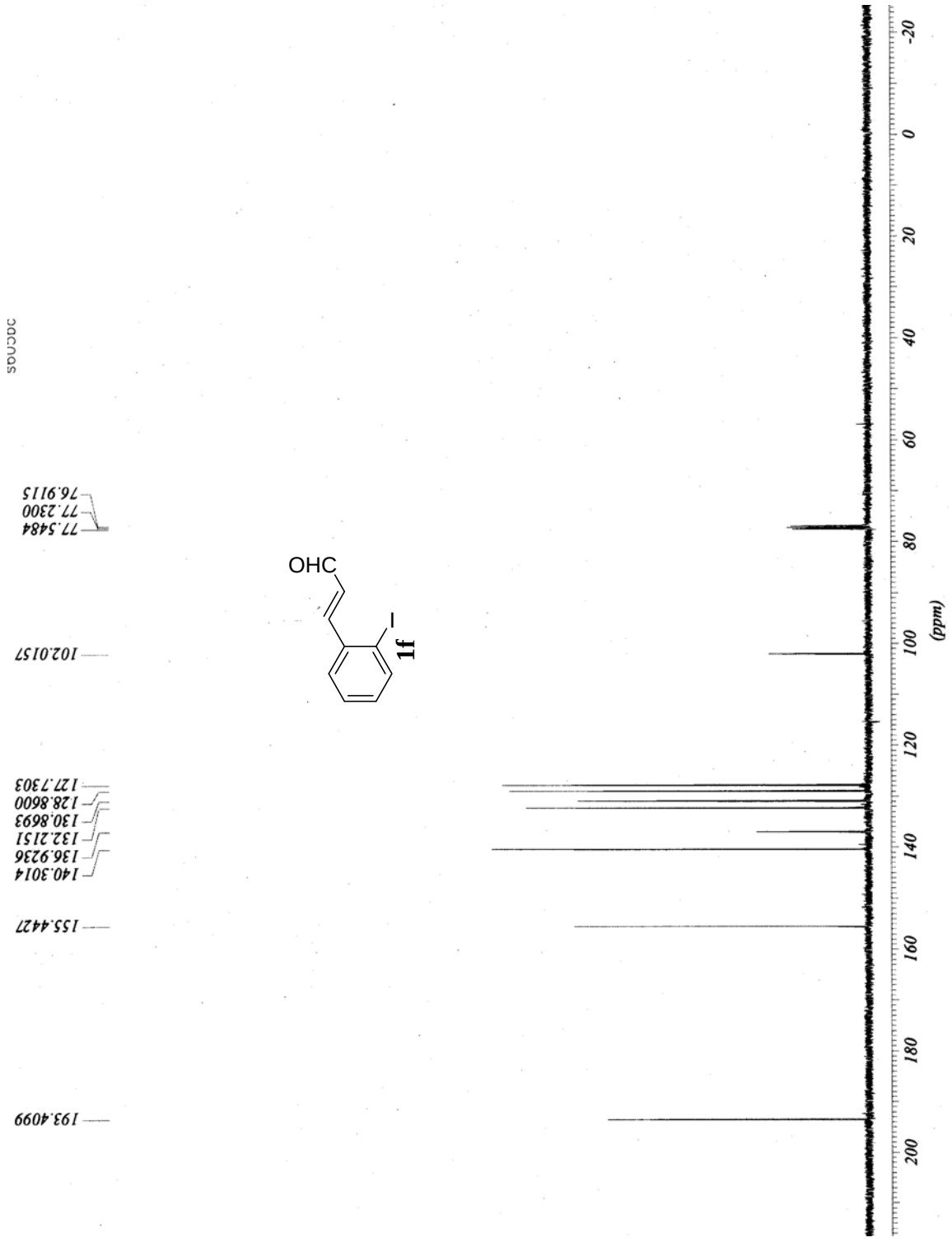


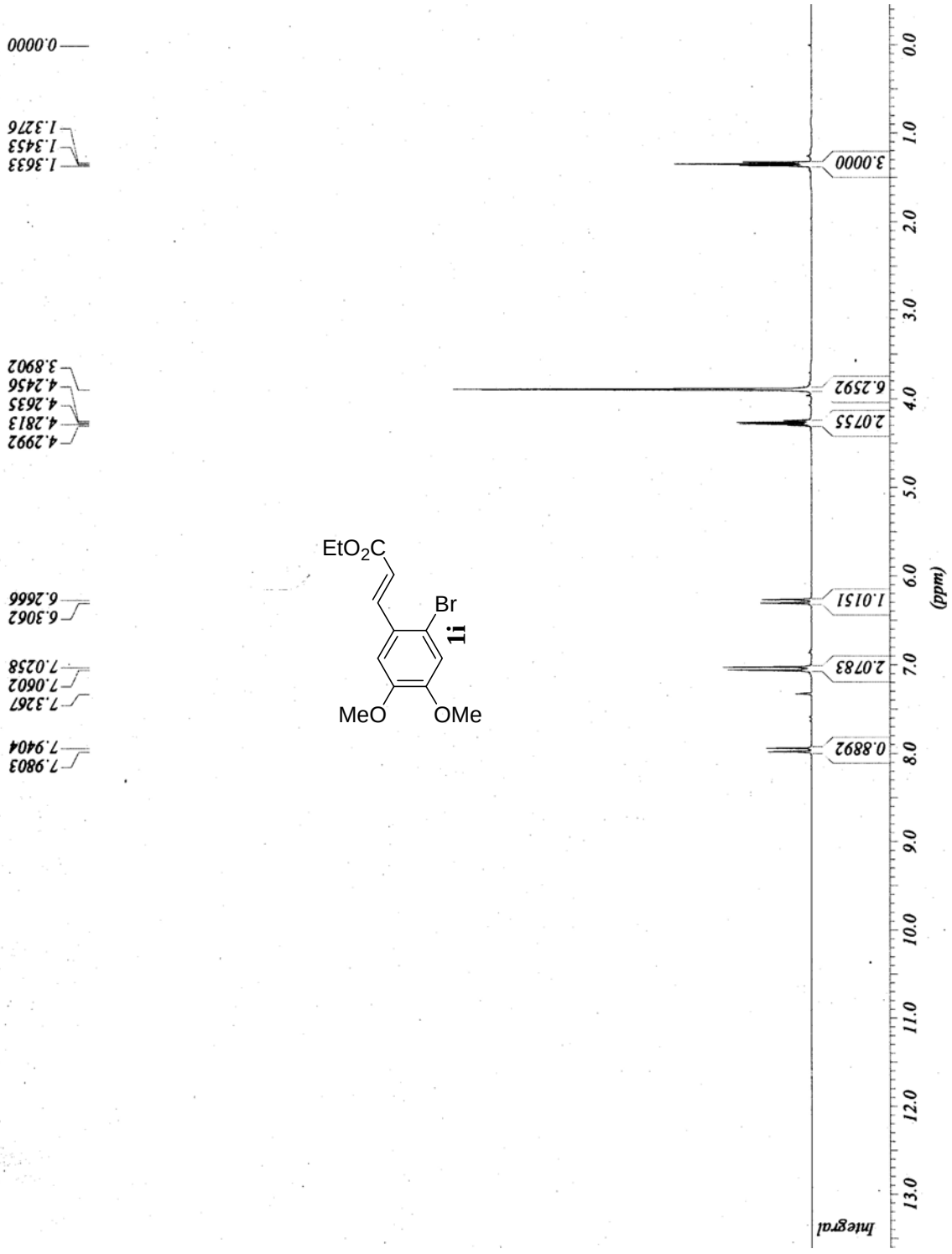


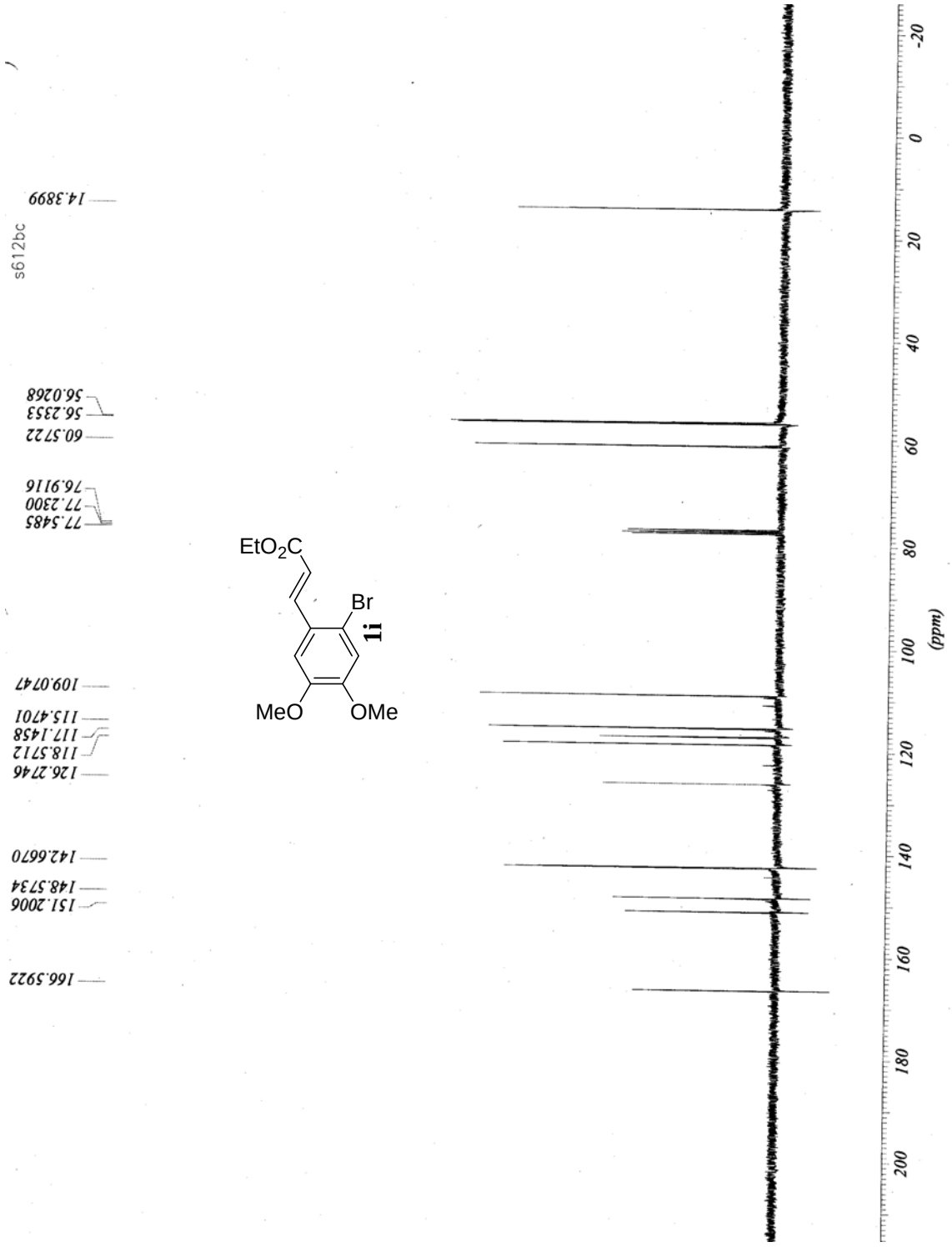


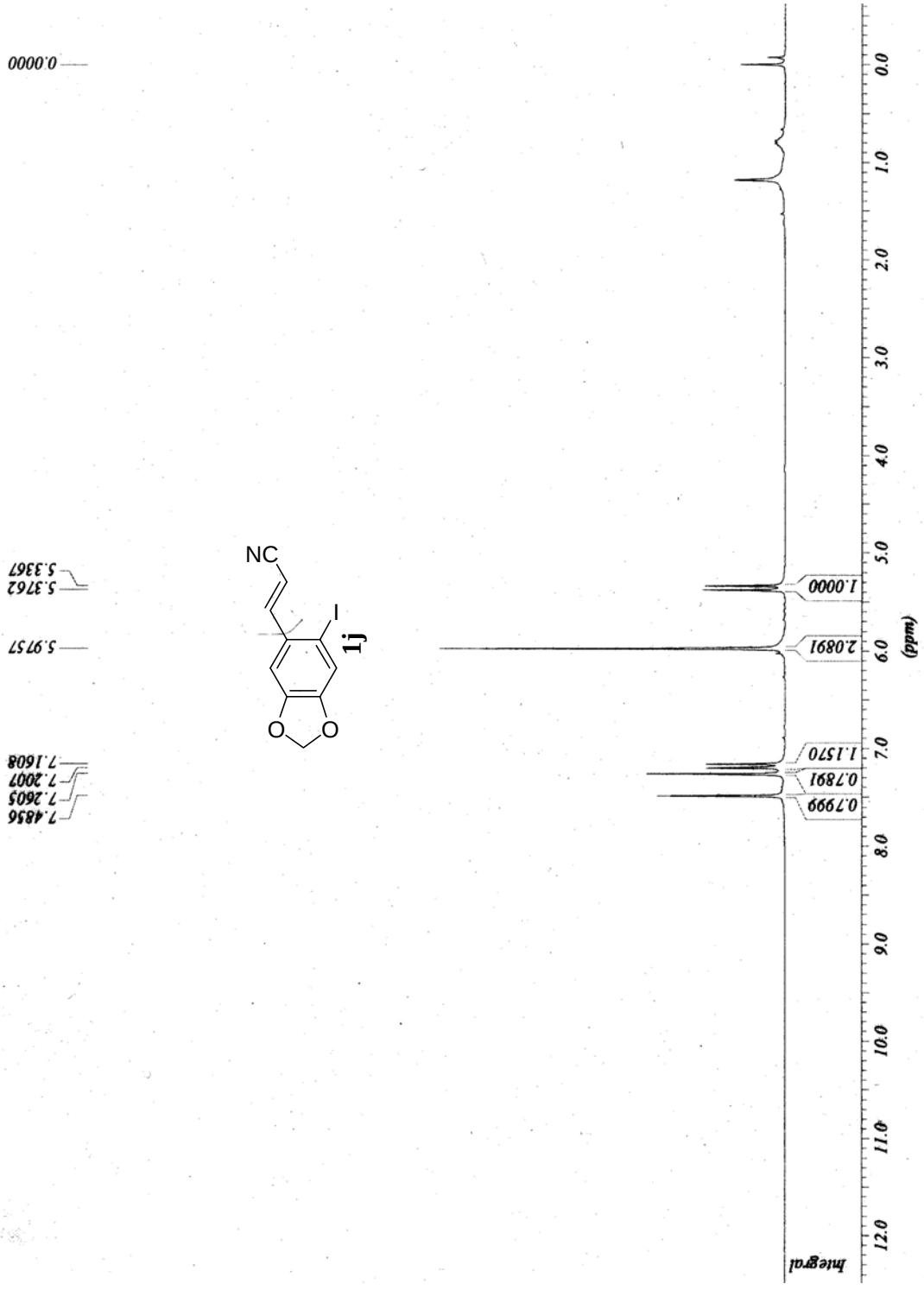
APPENDIX C. CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA

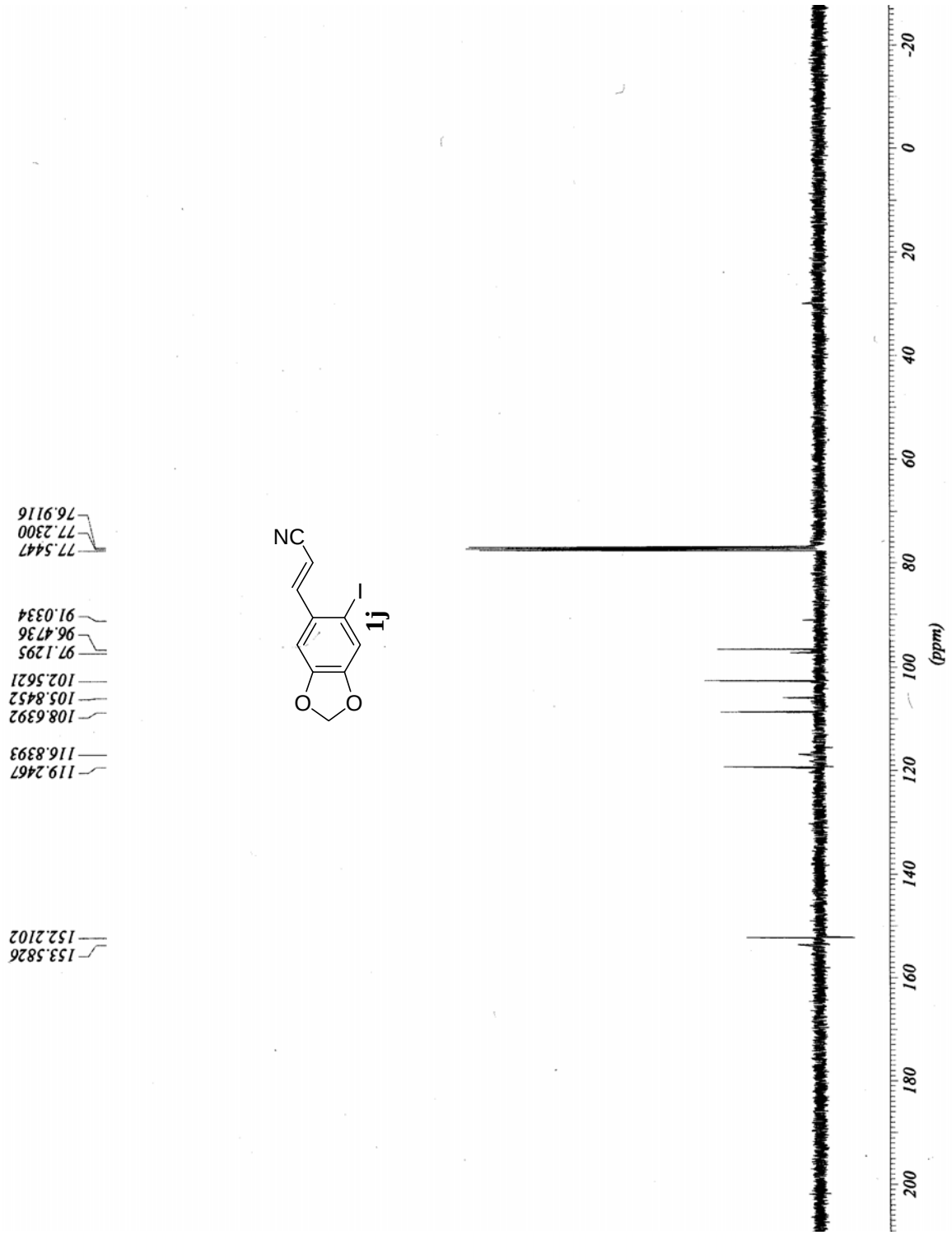


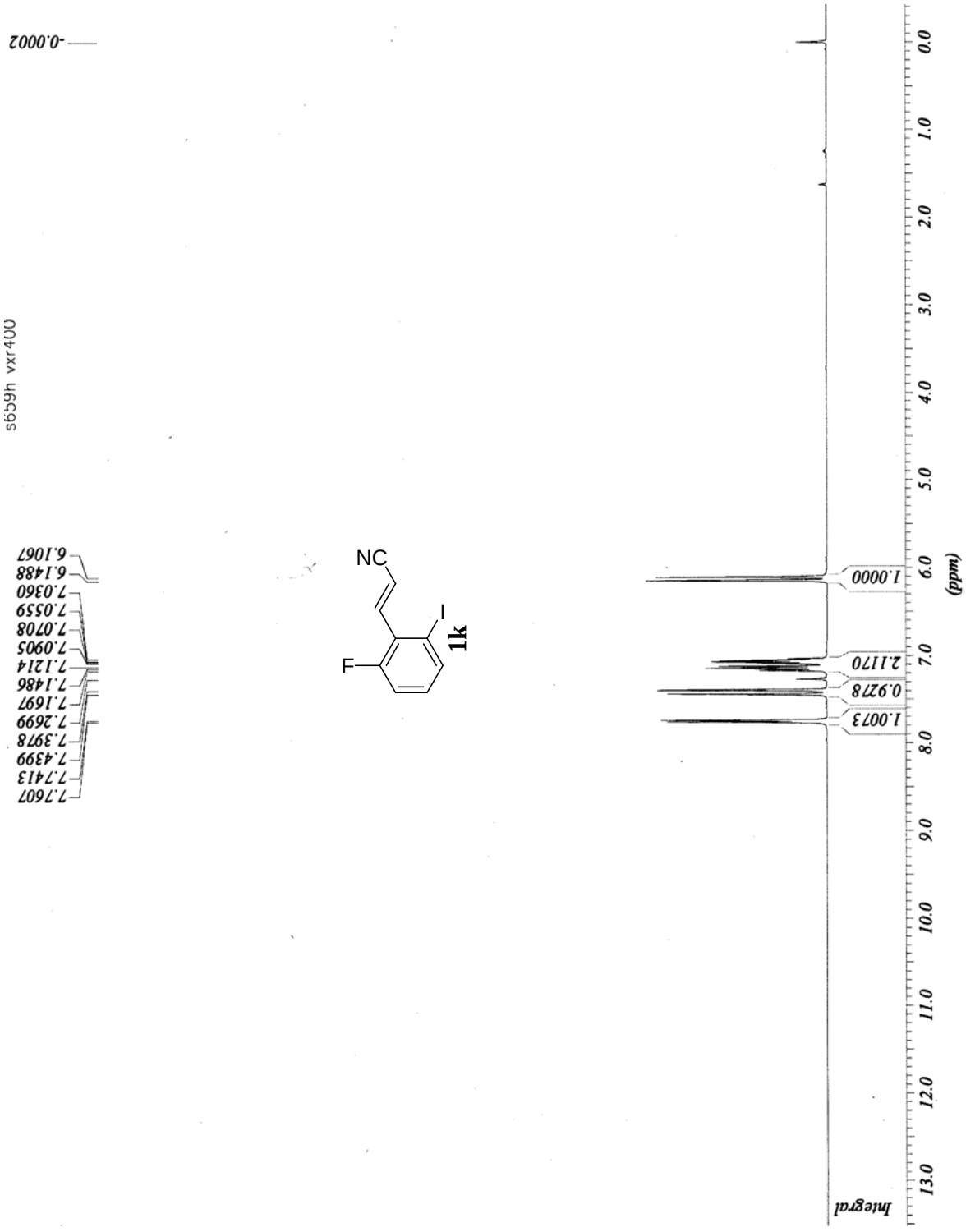


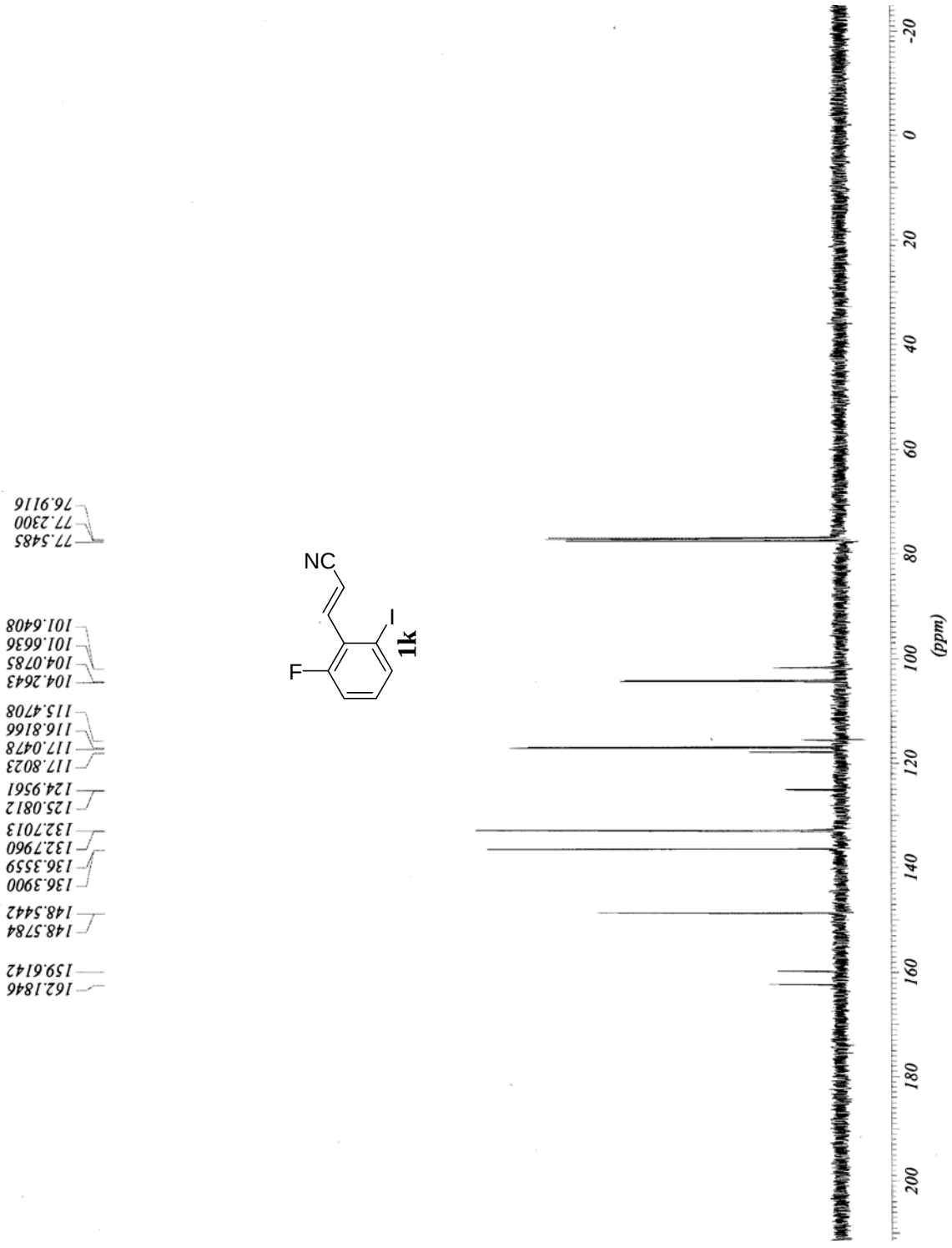


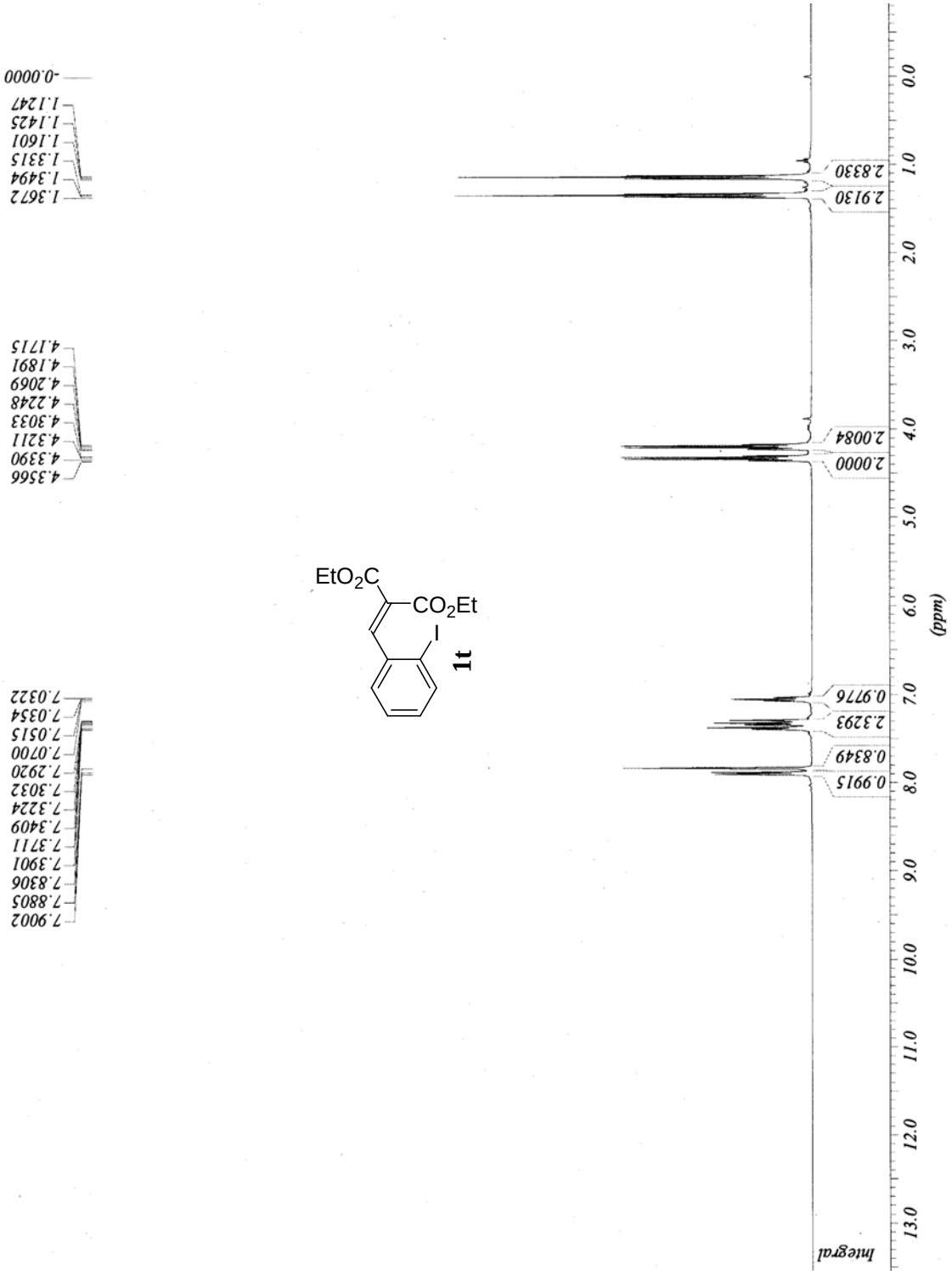


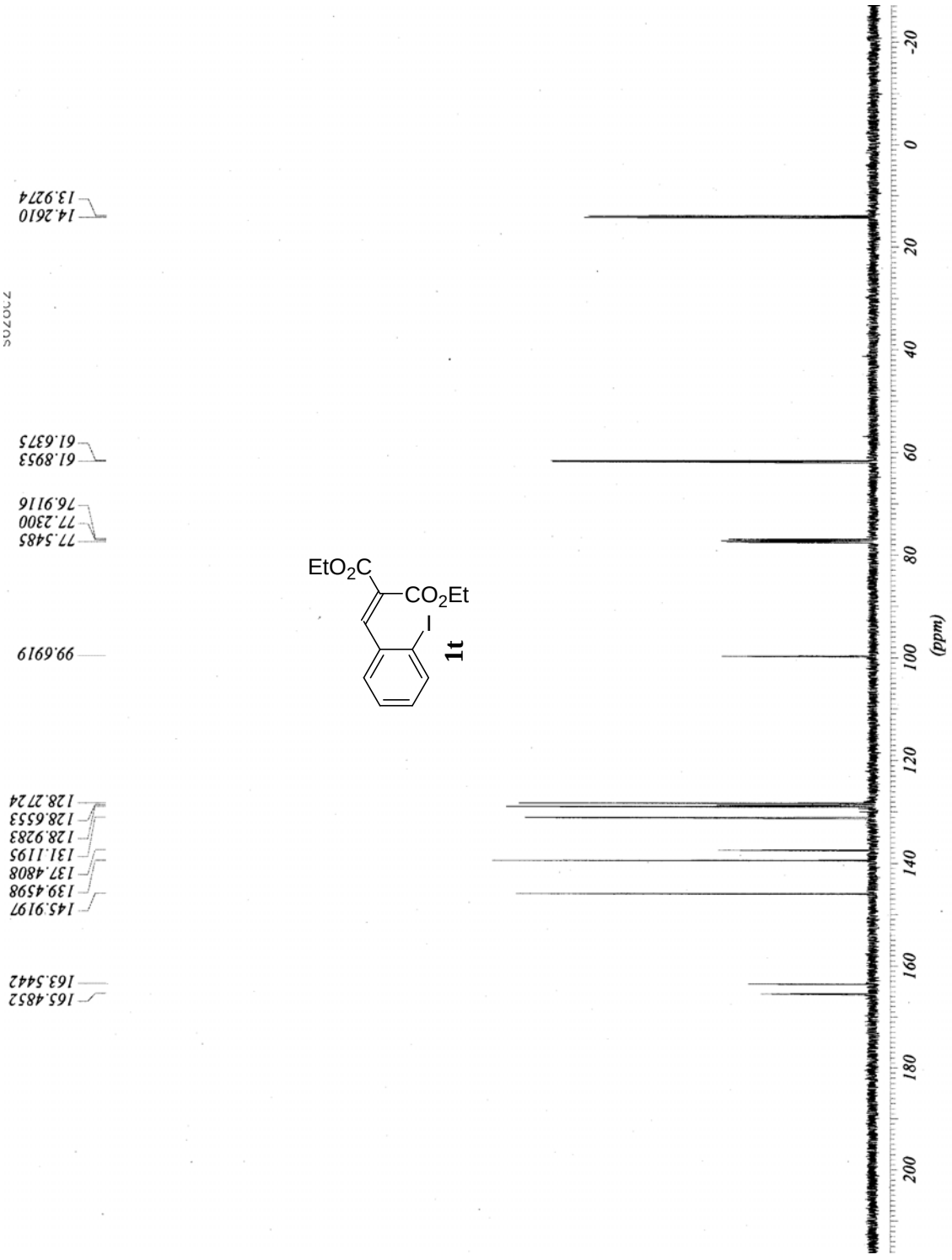


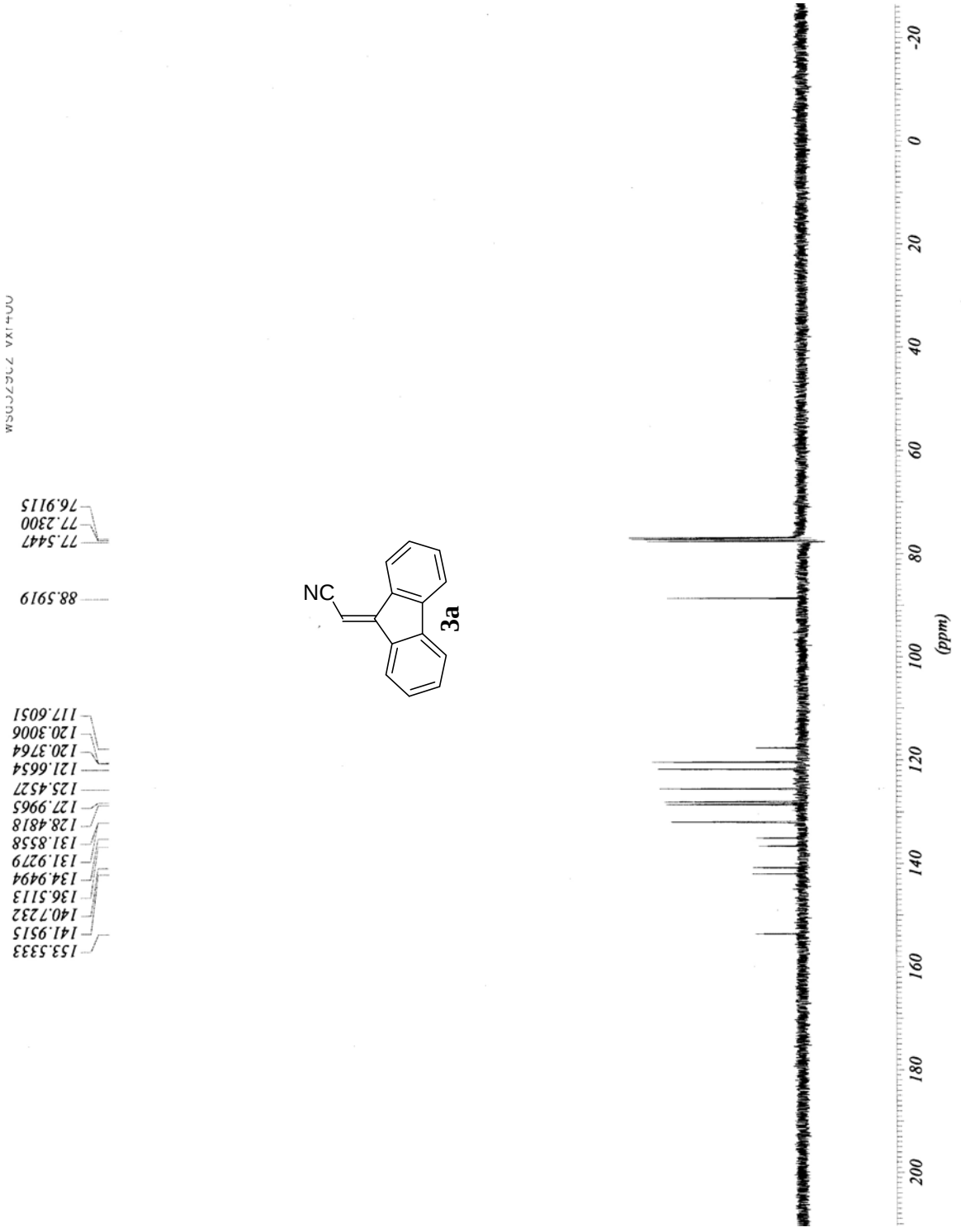


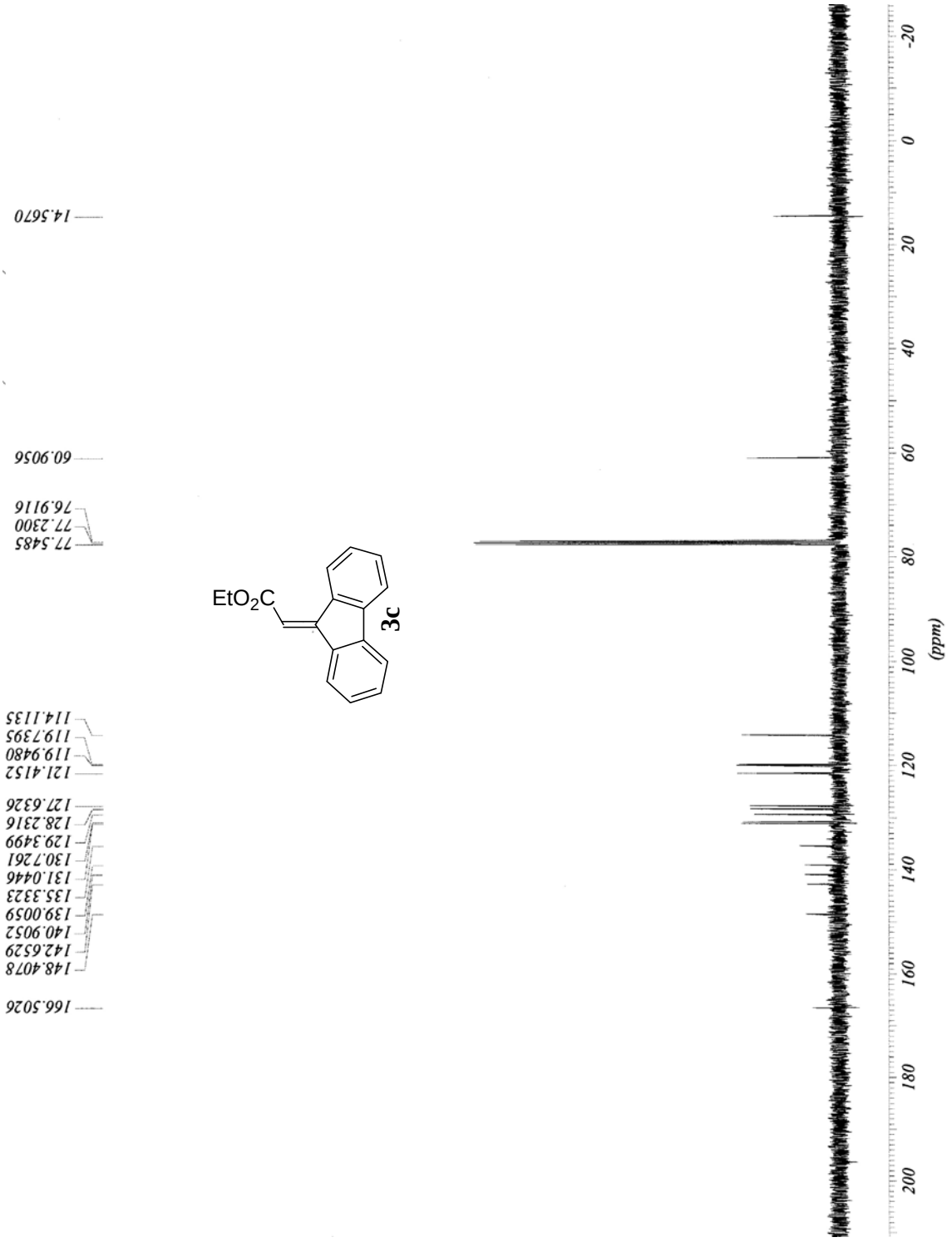


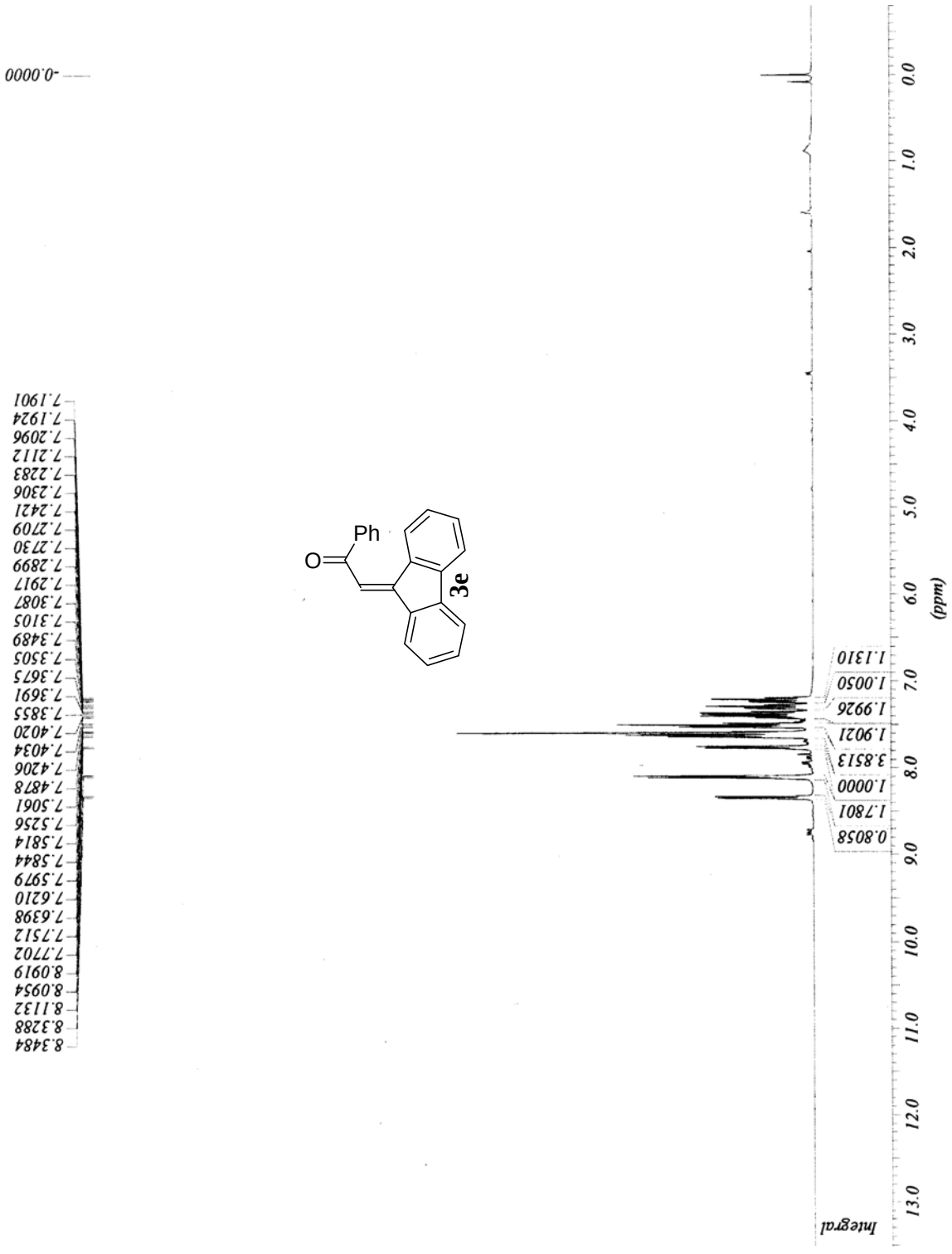


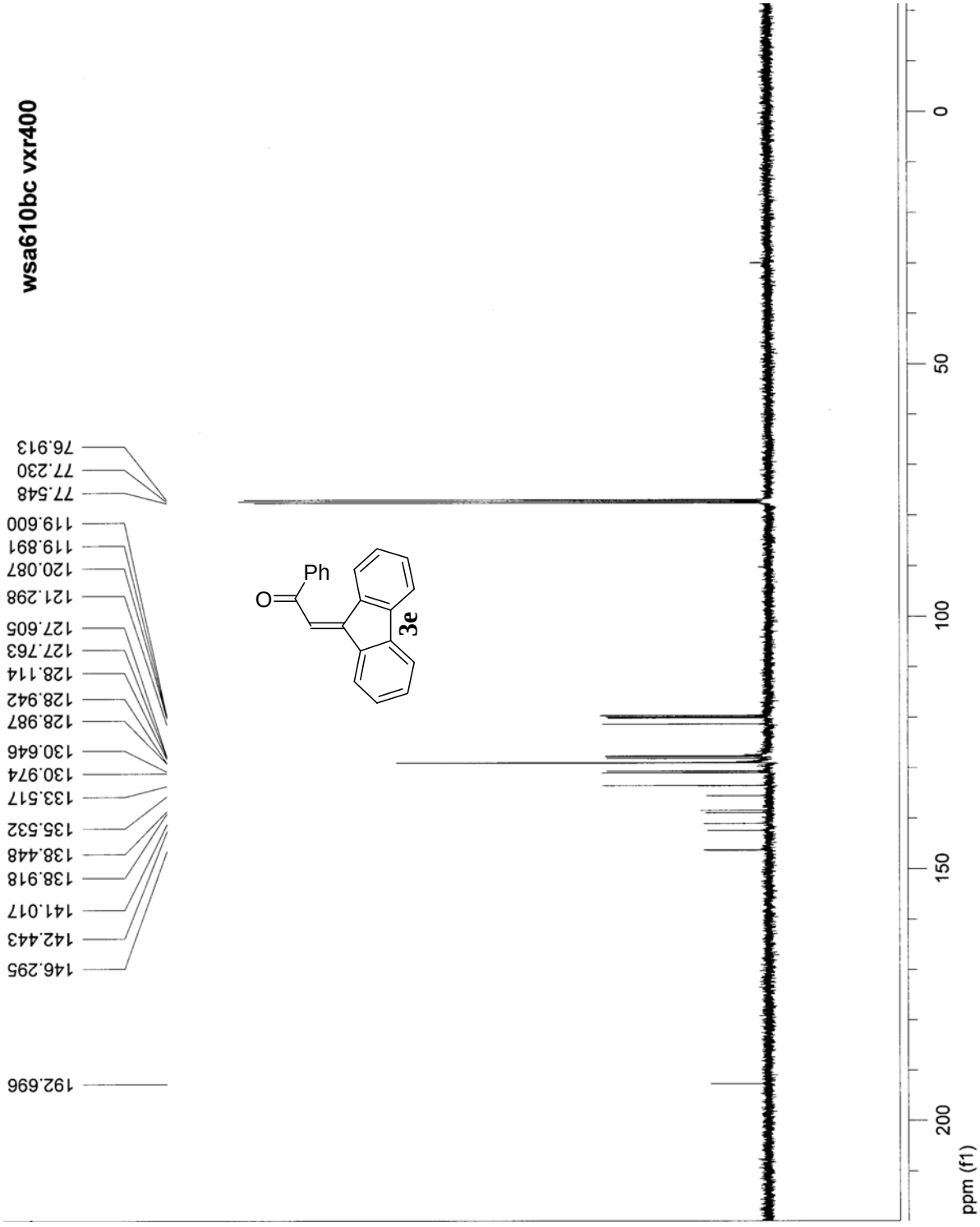


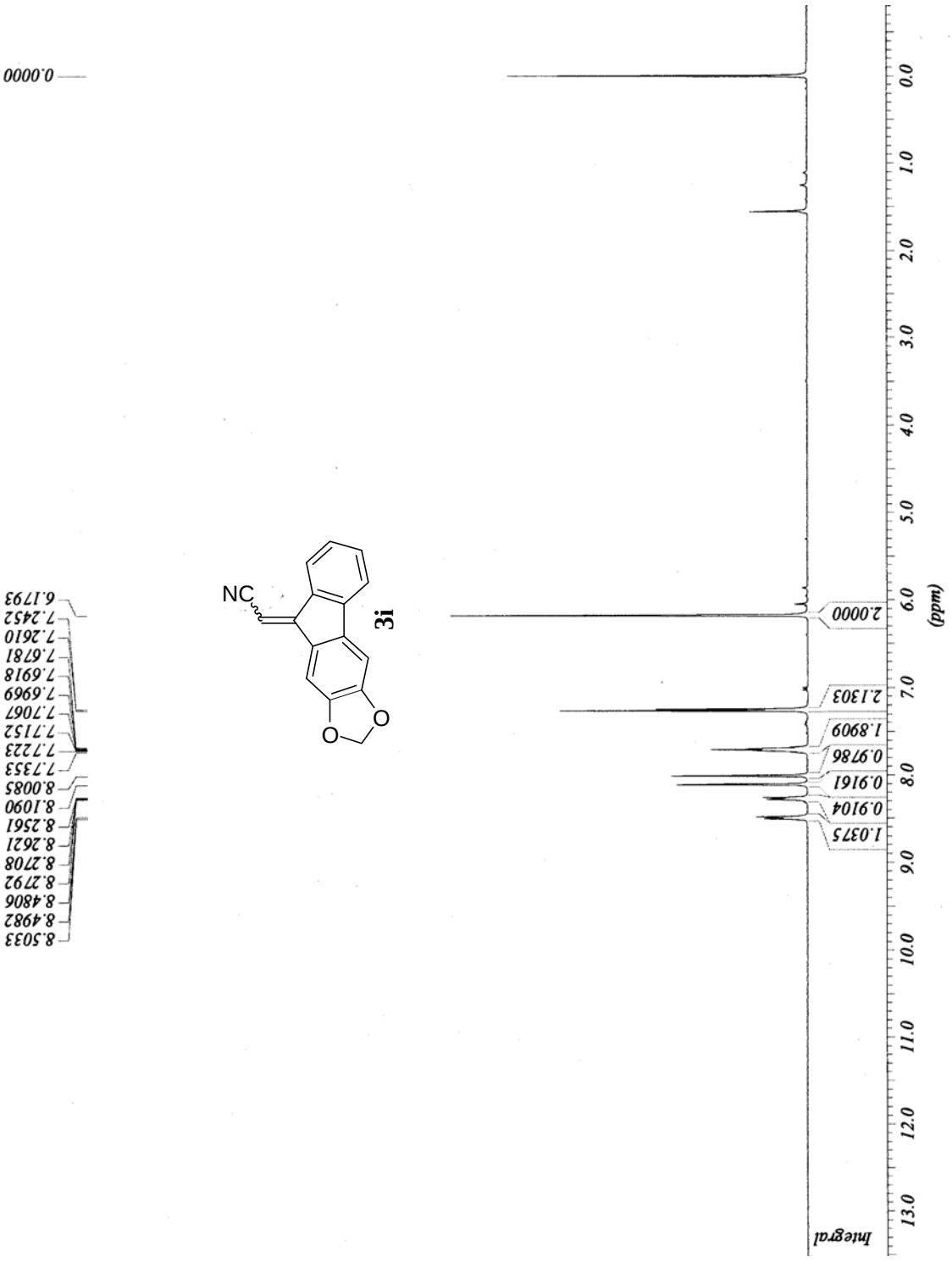


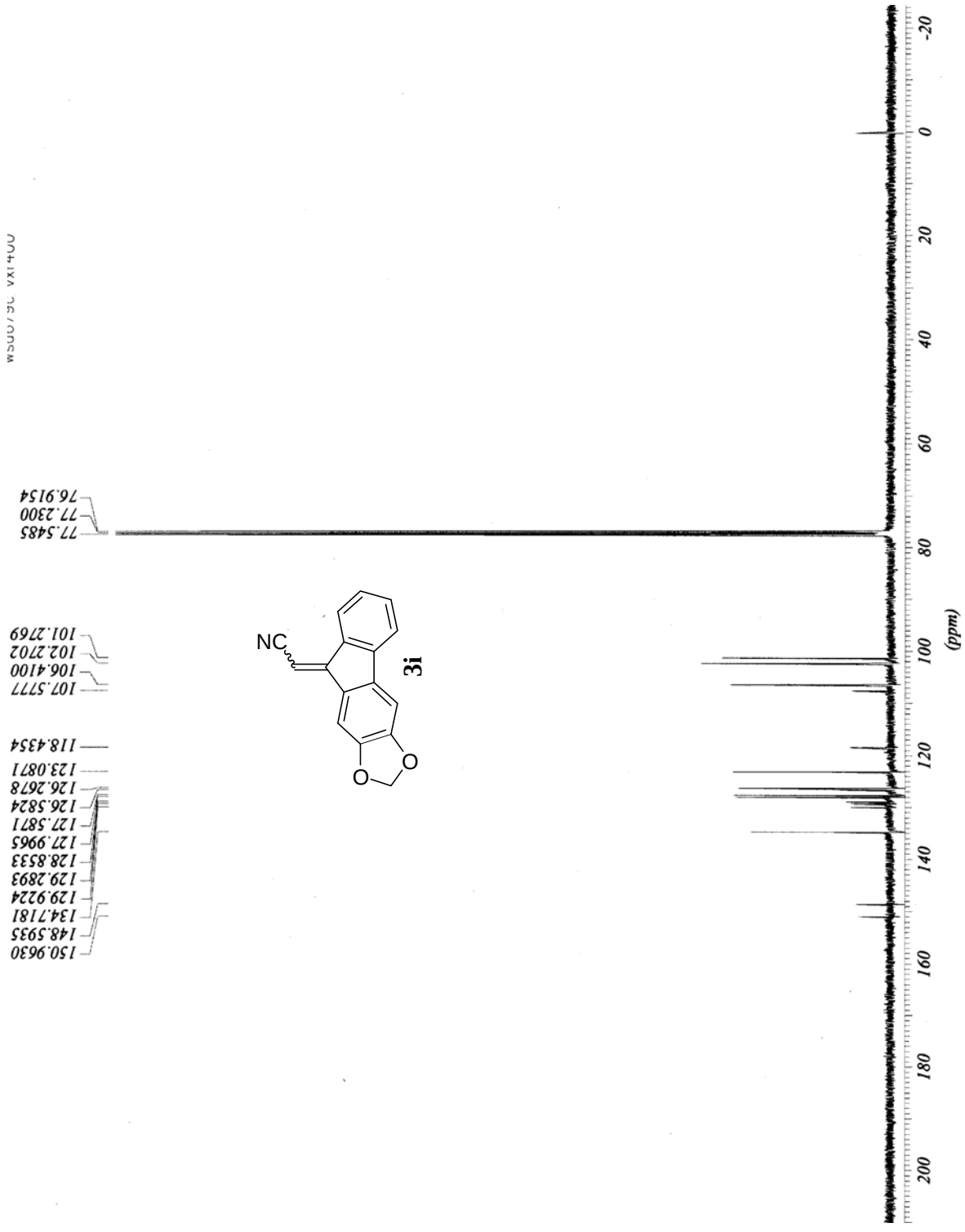


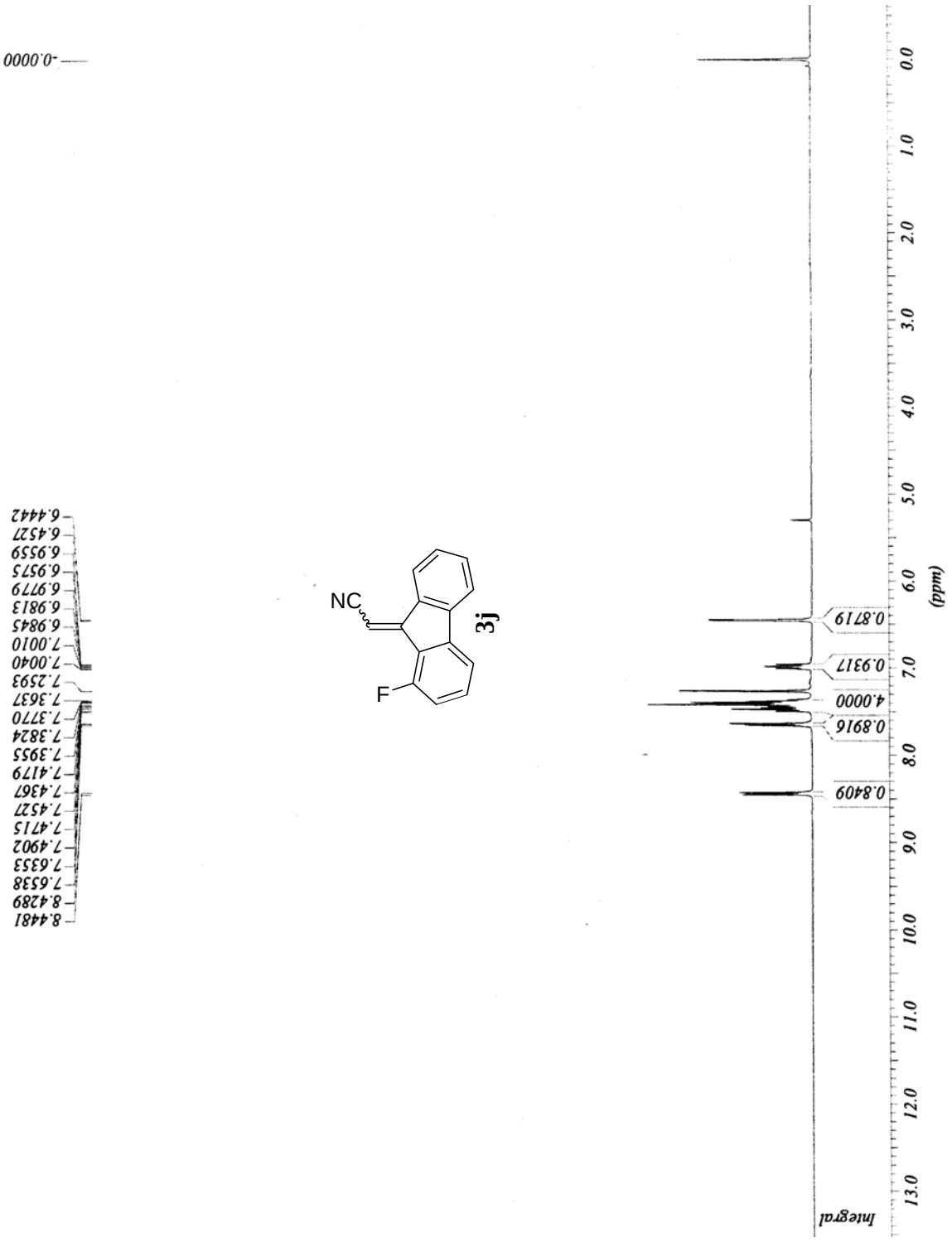


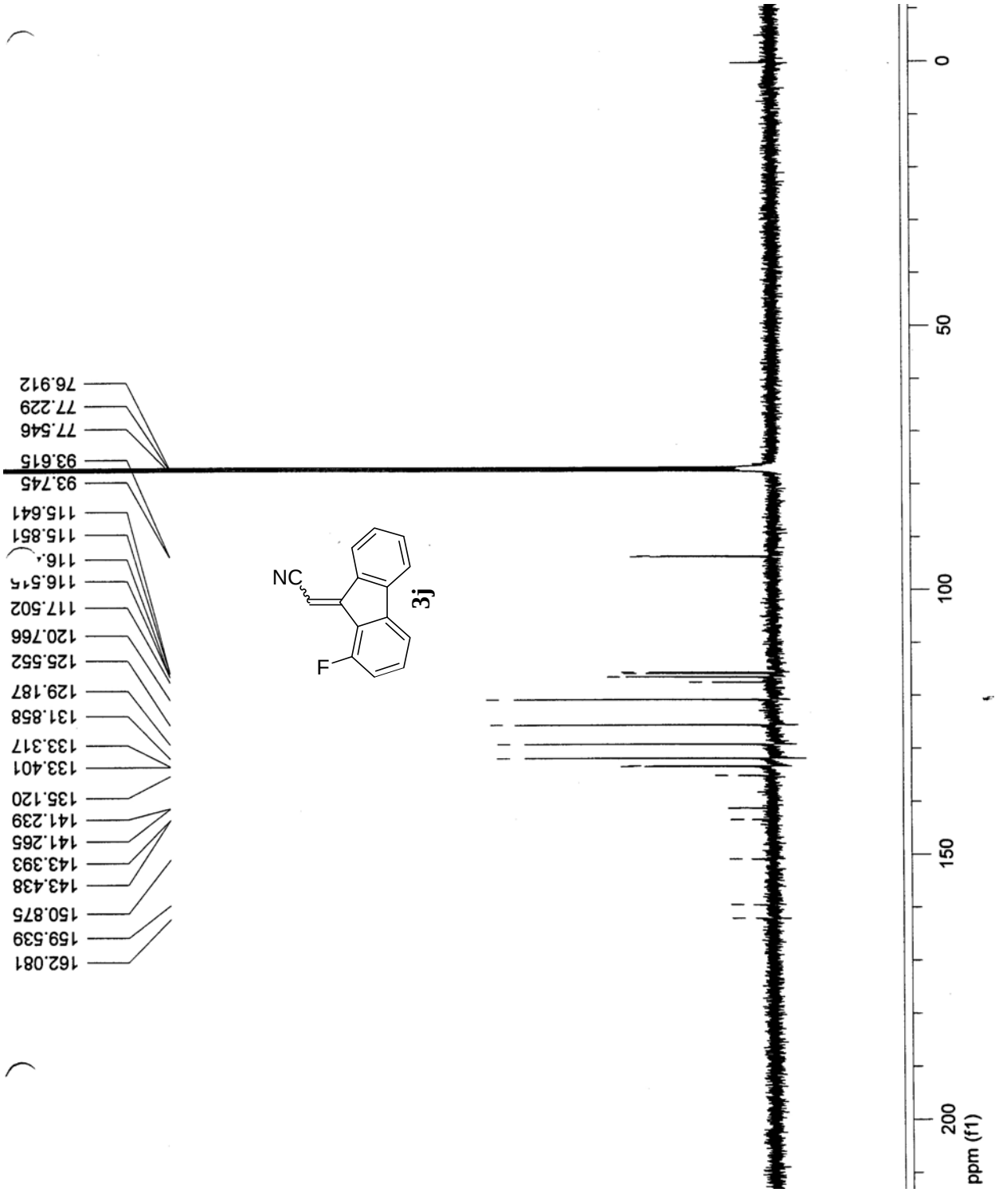


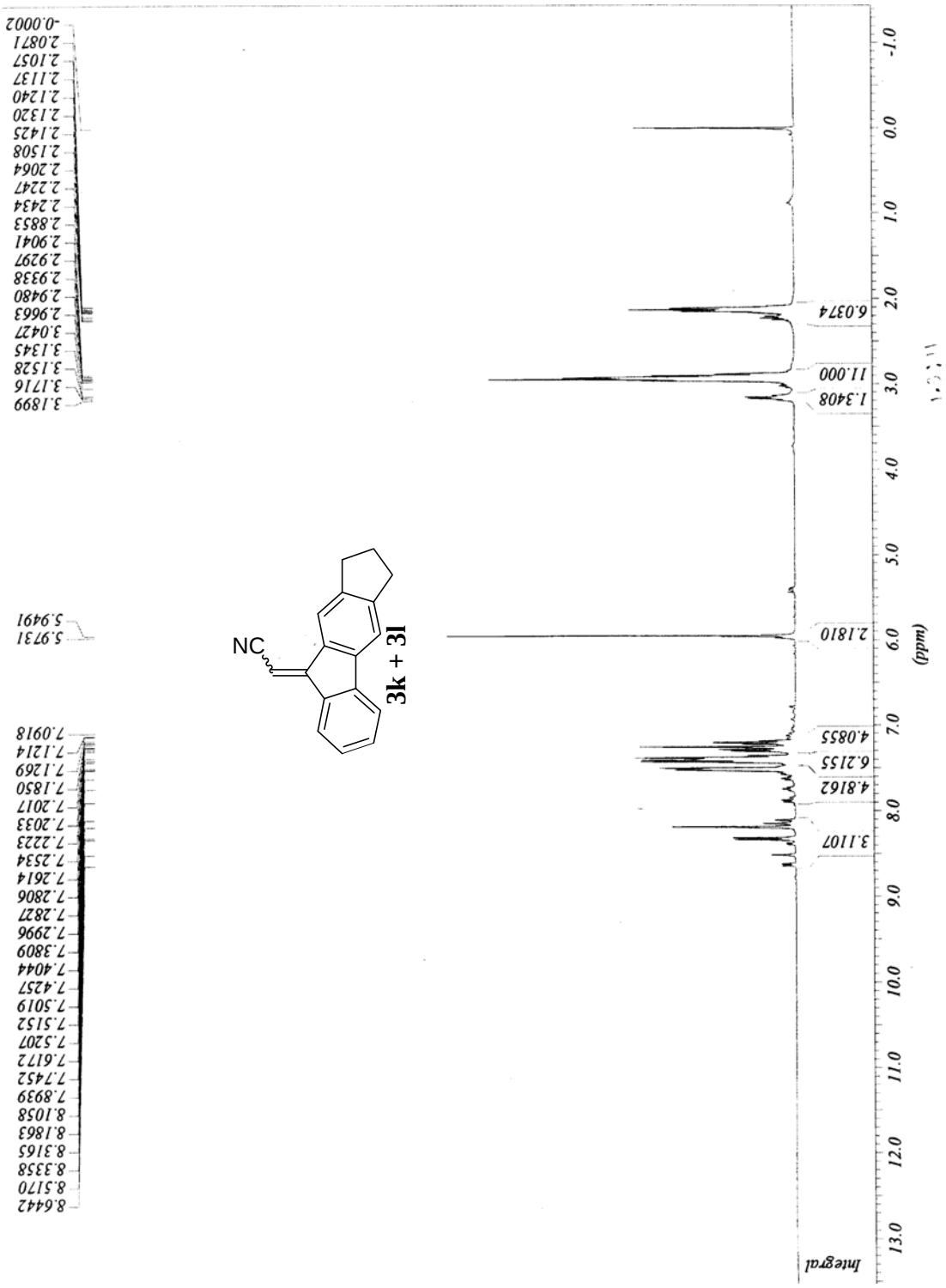


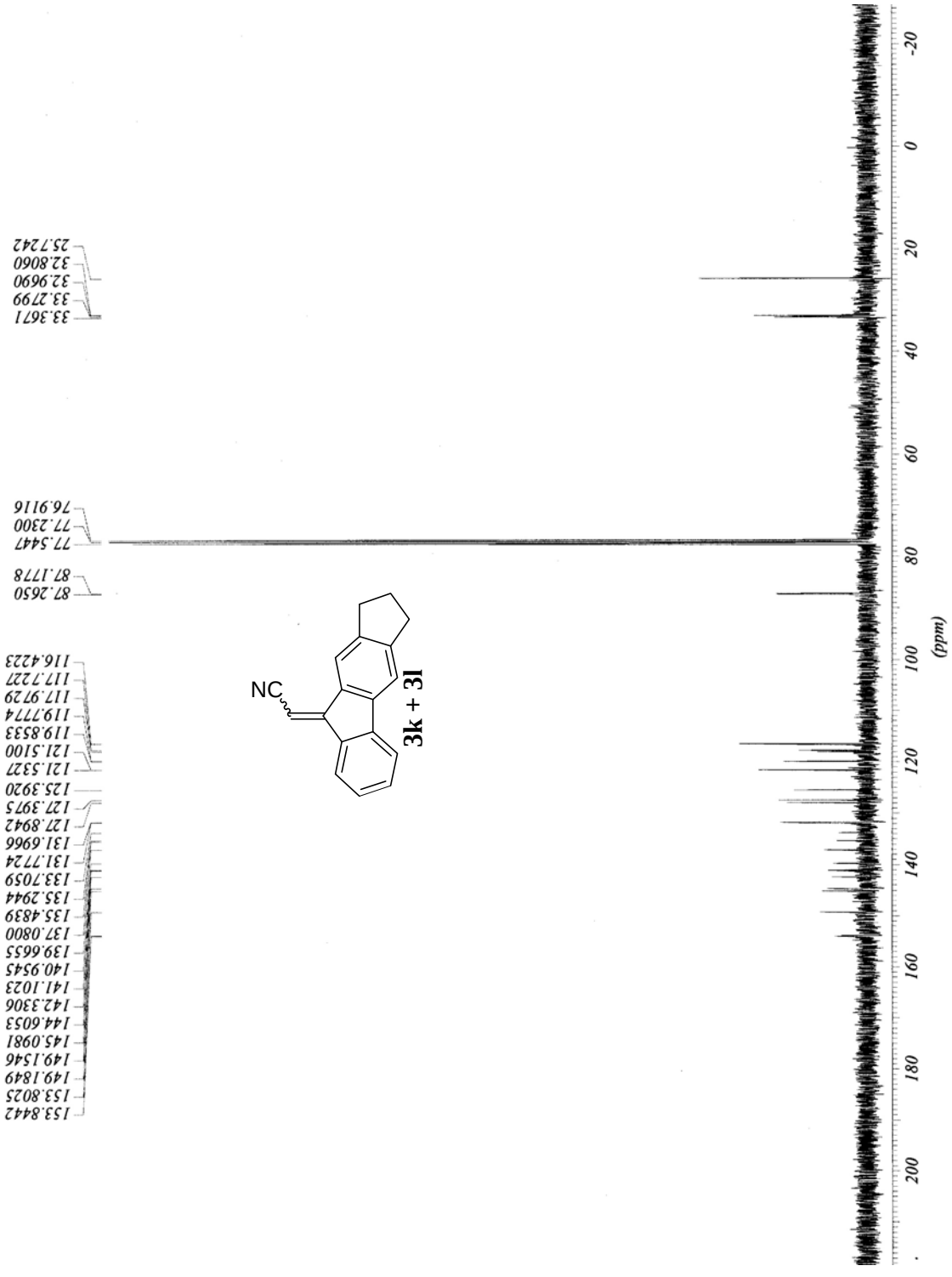


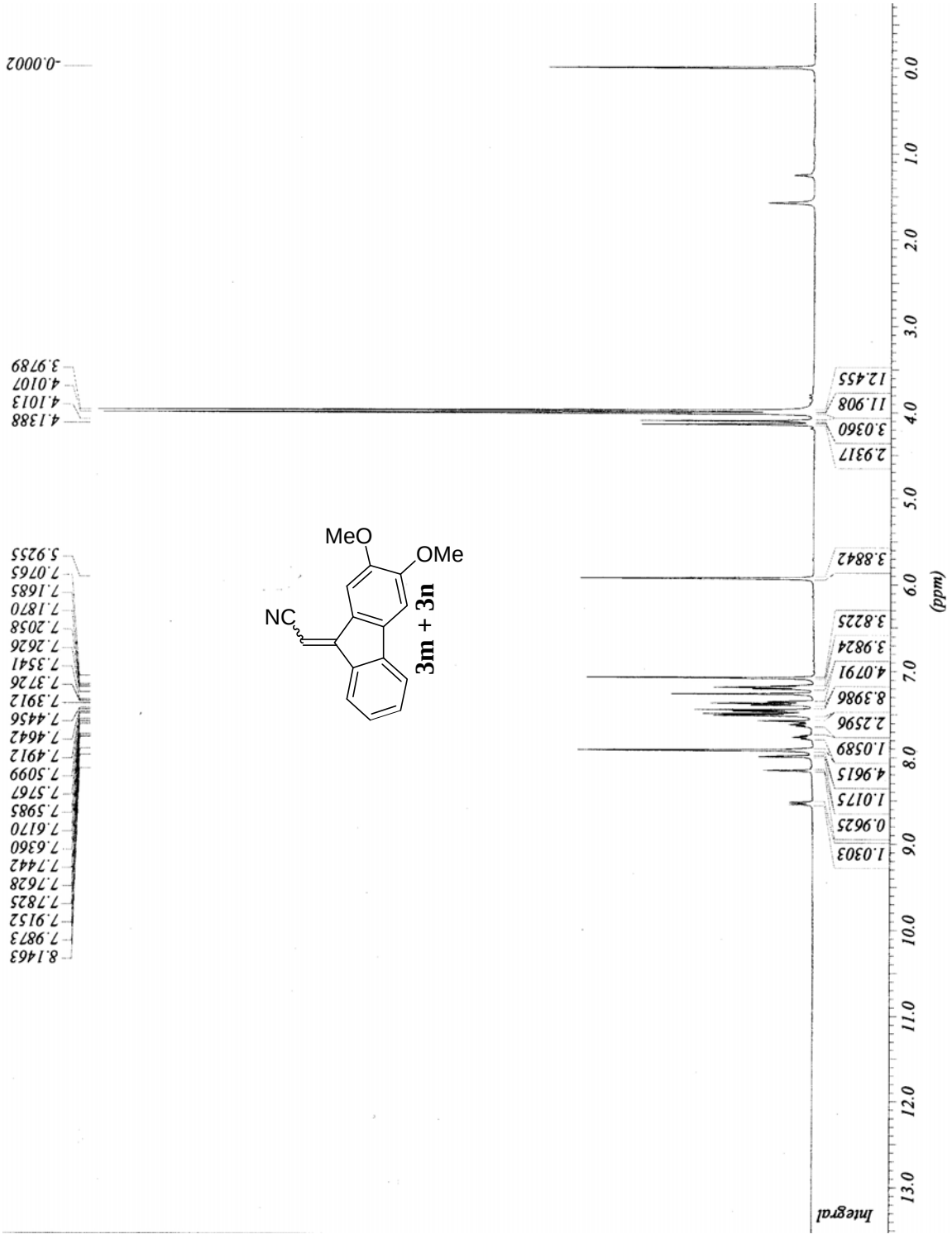


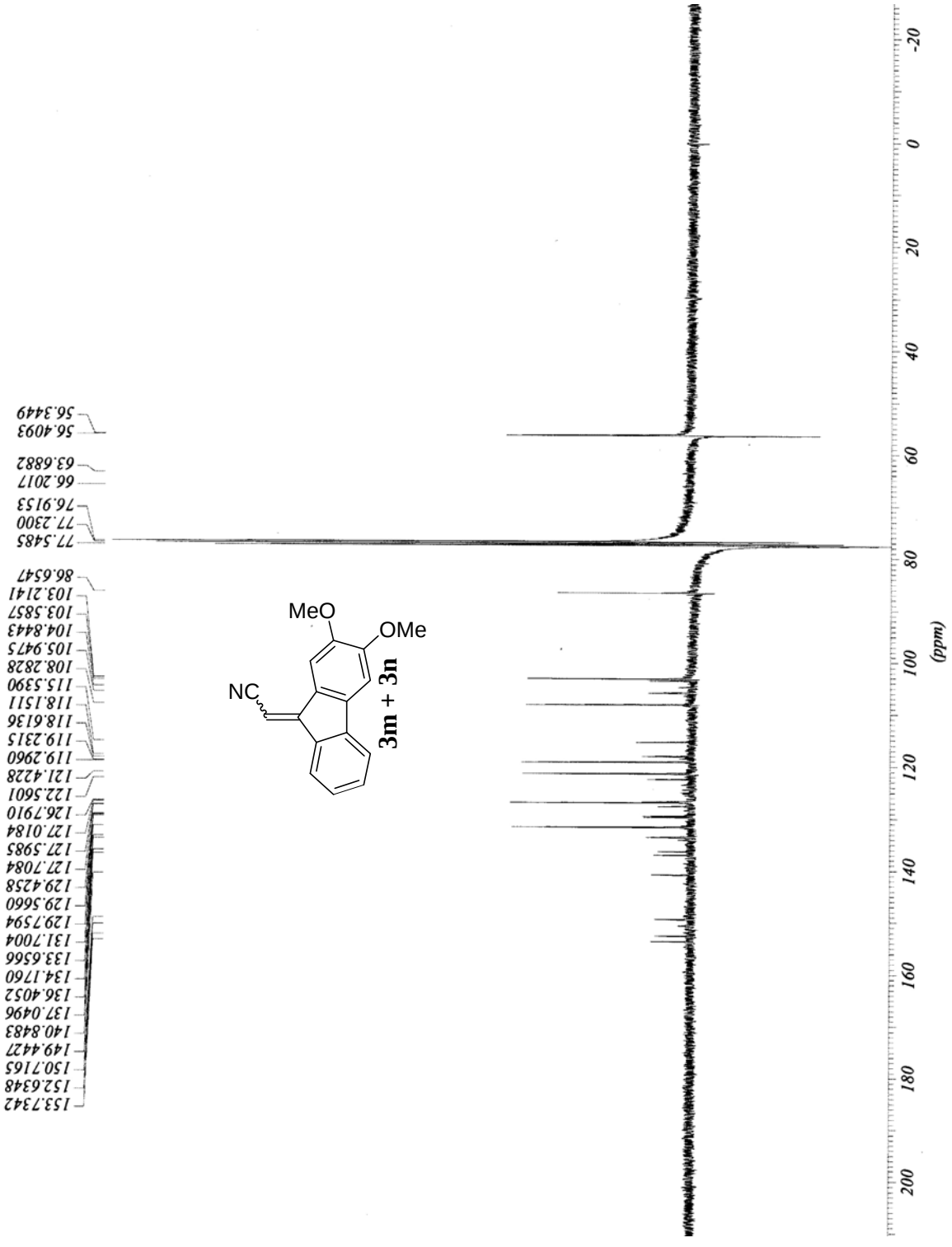


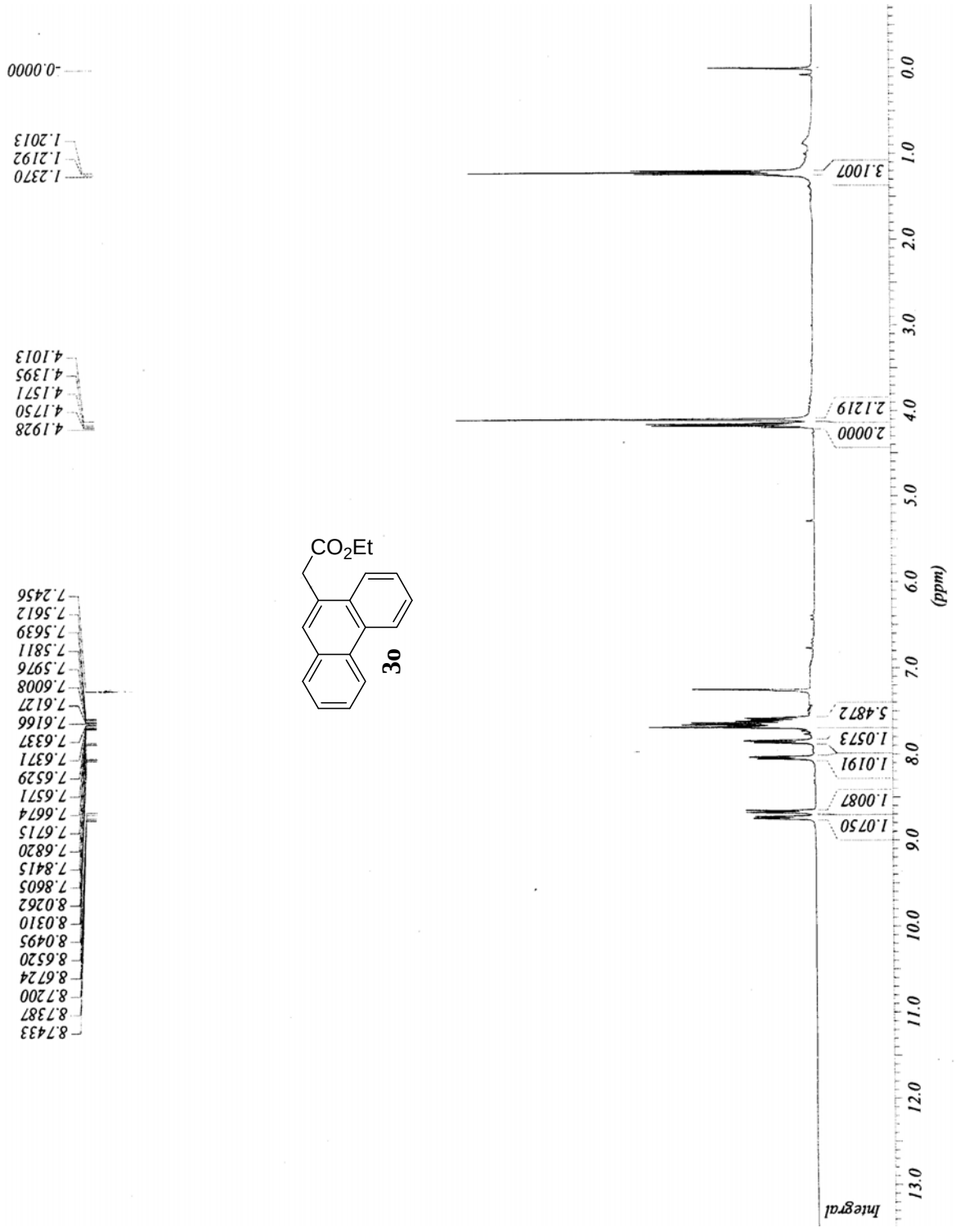


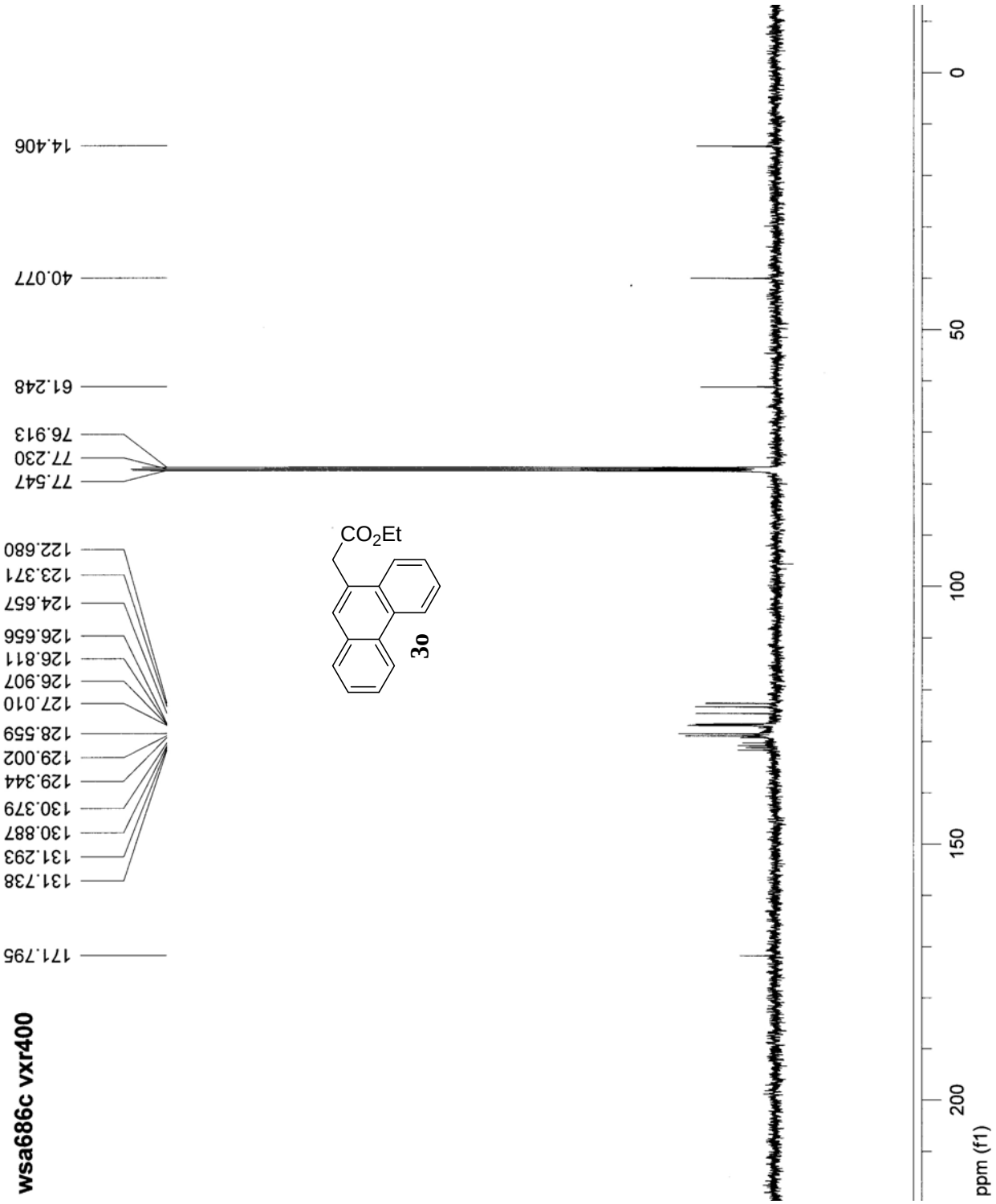


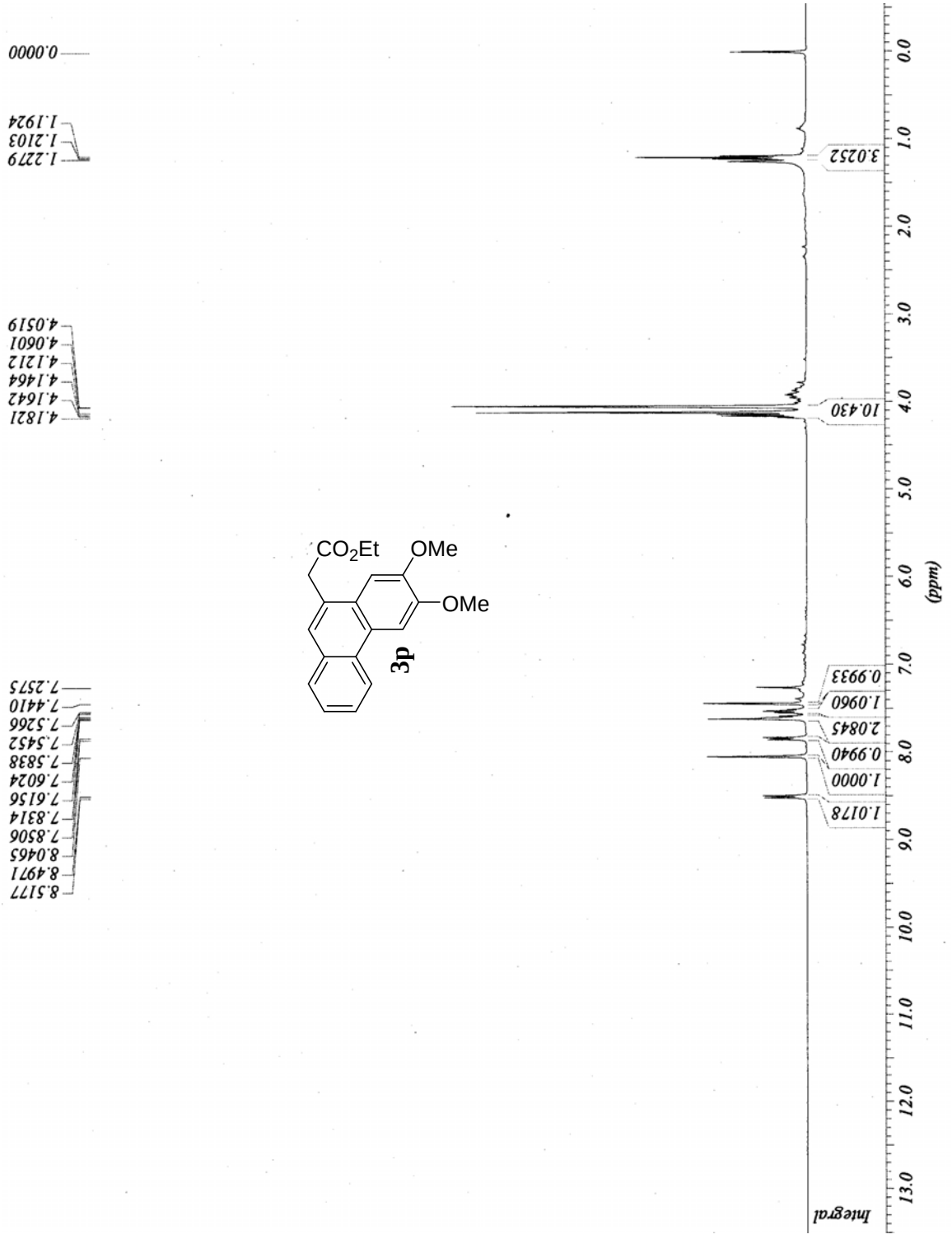


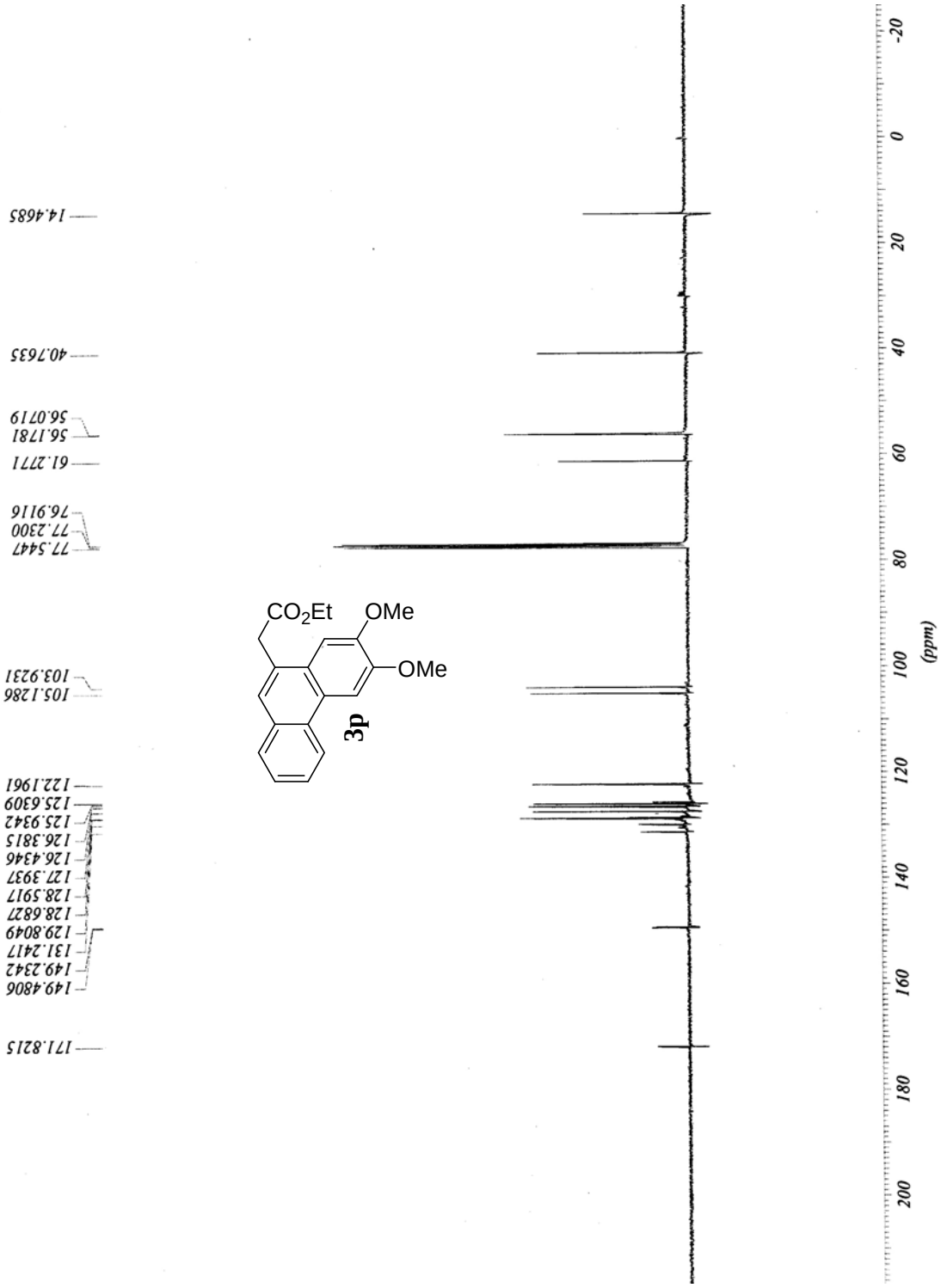


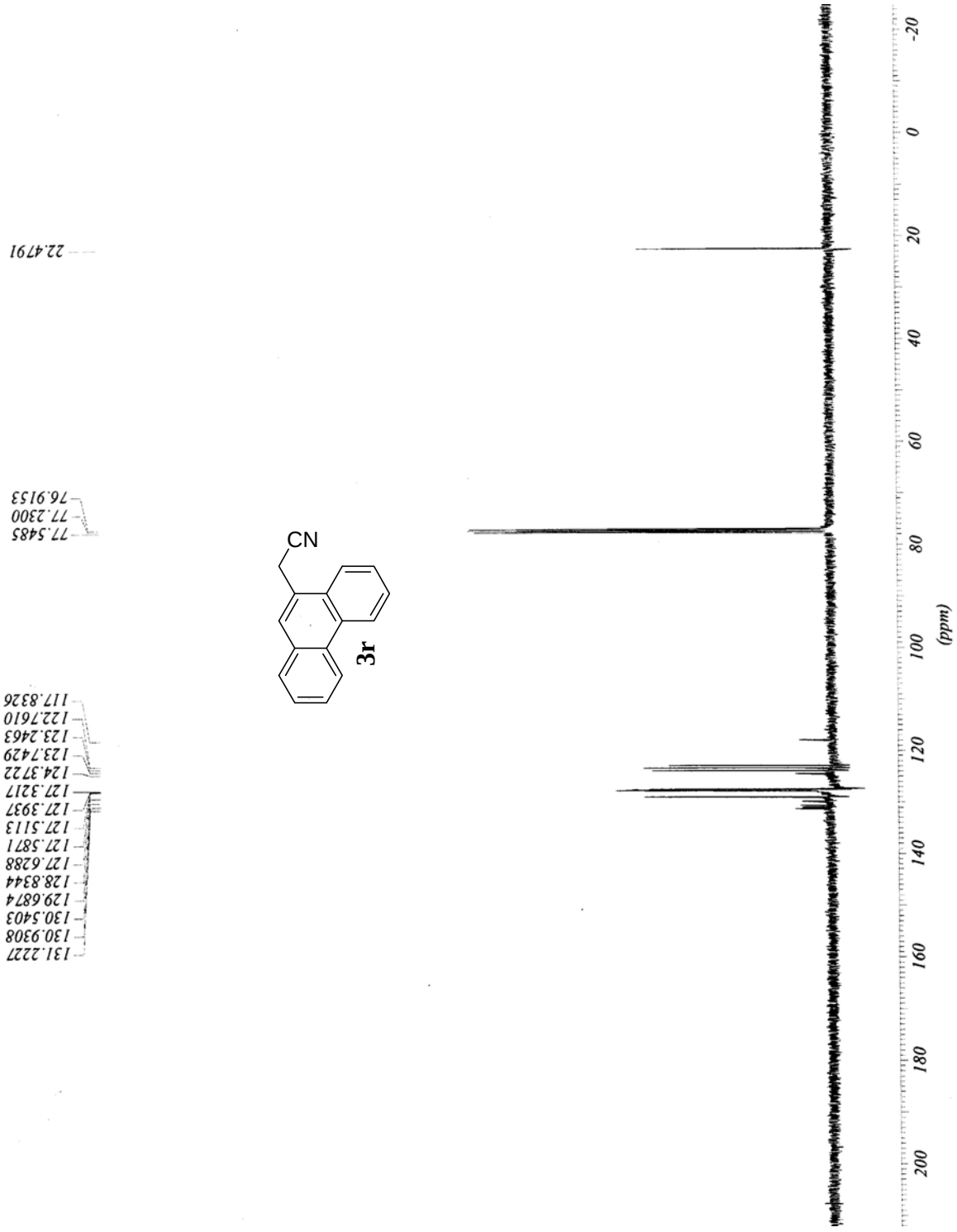


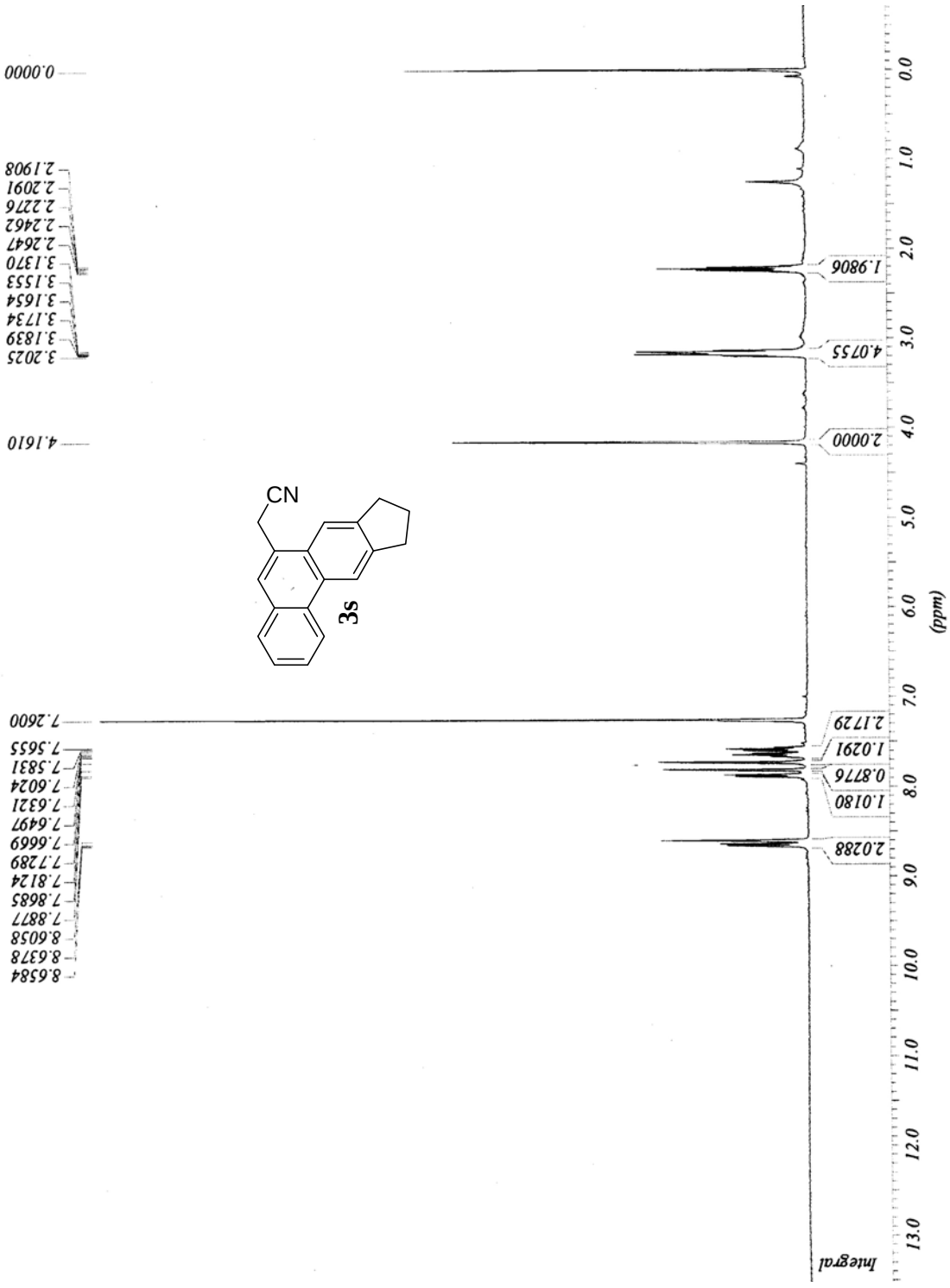


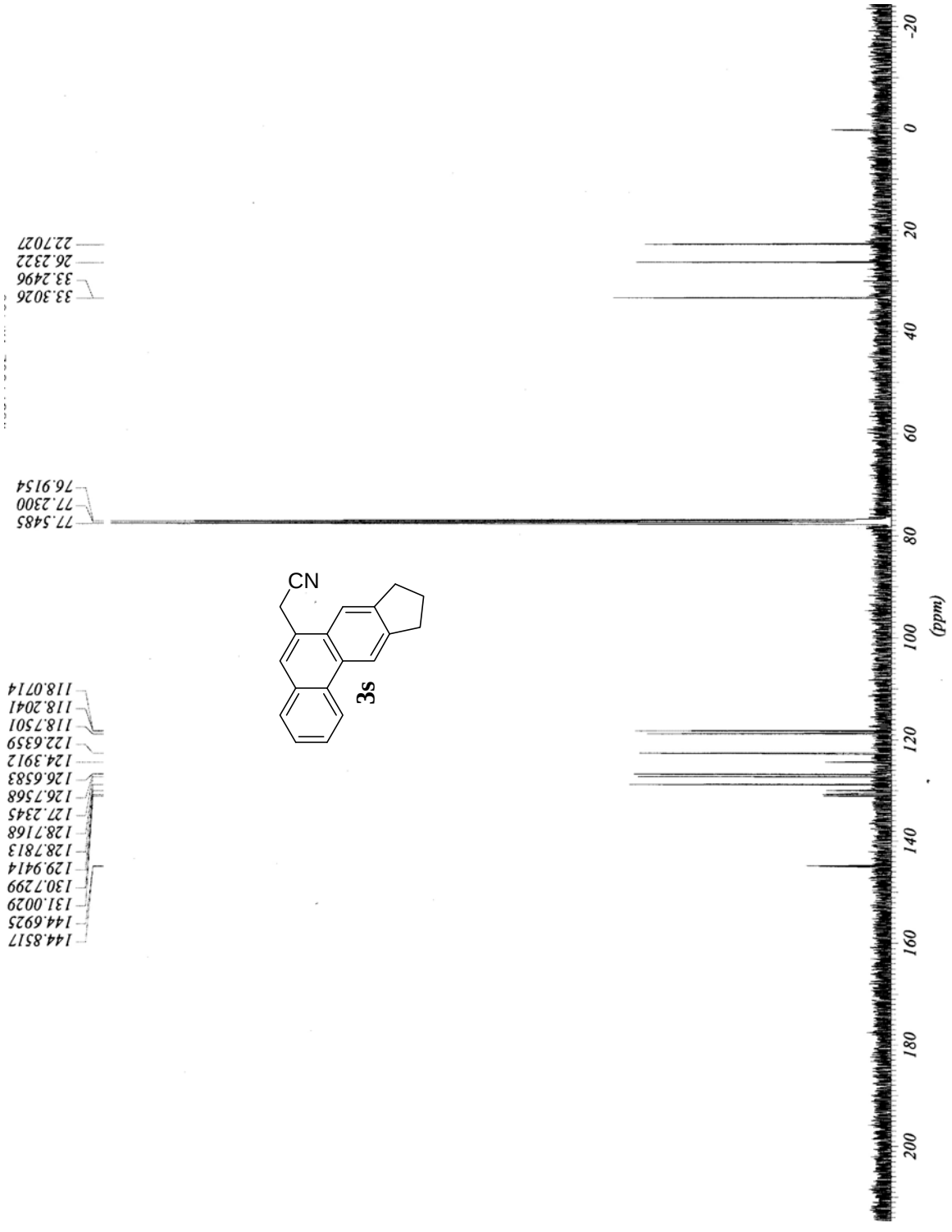


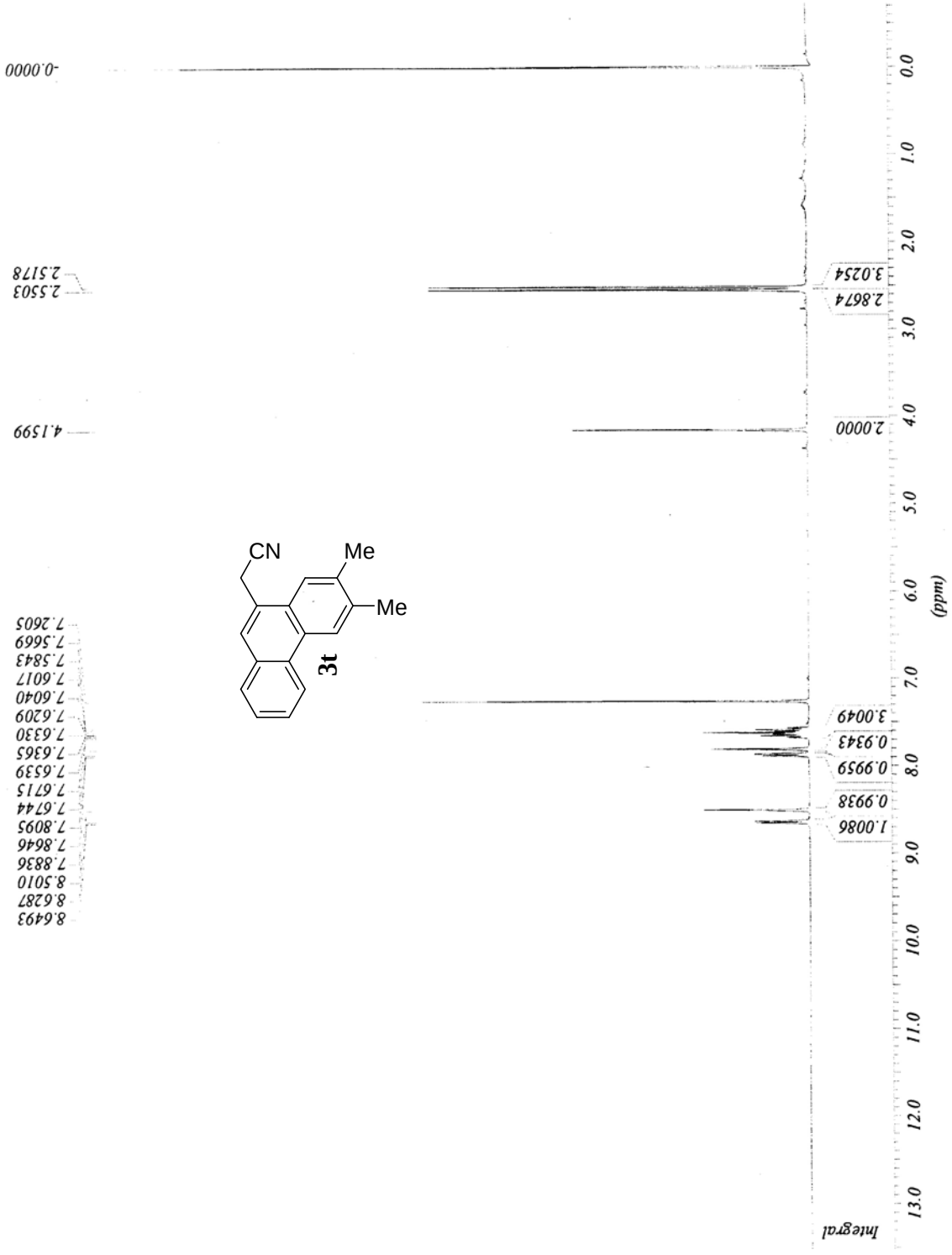


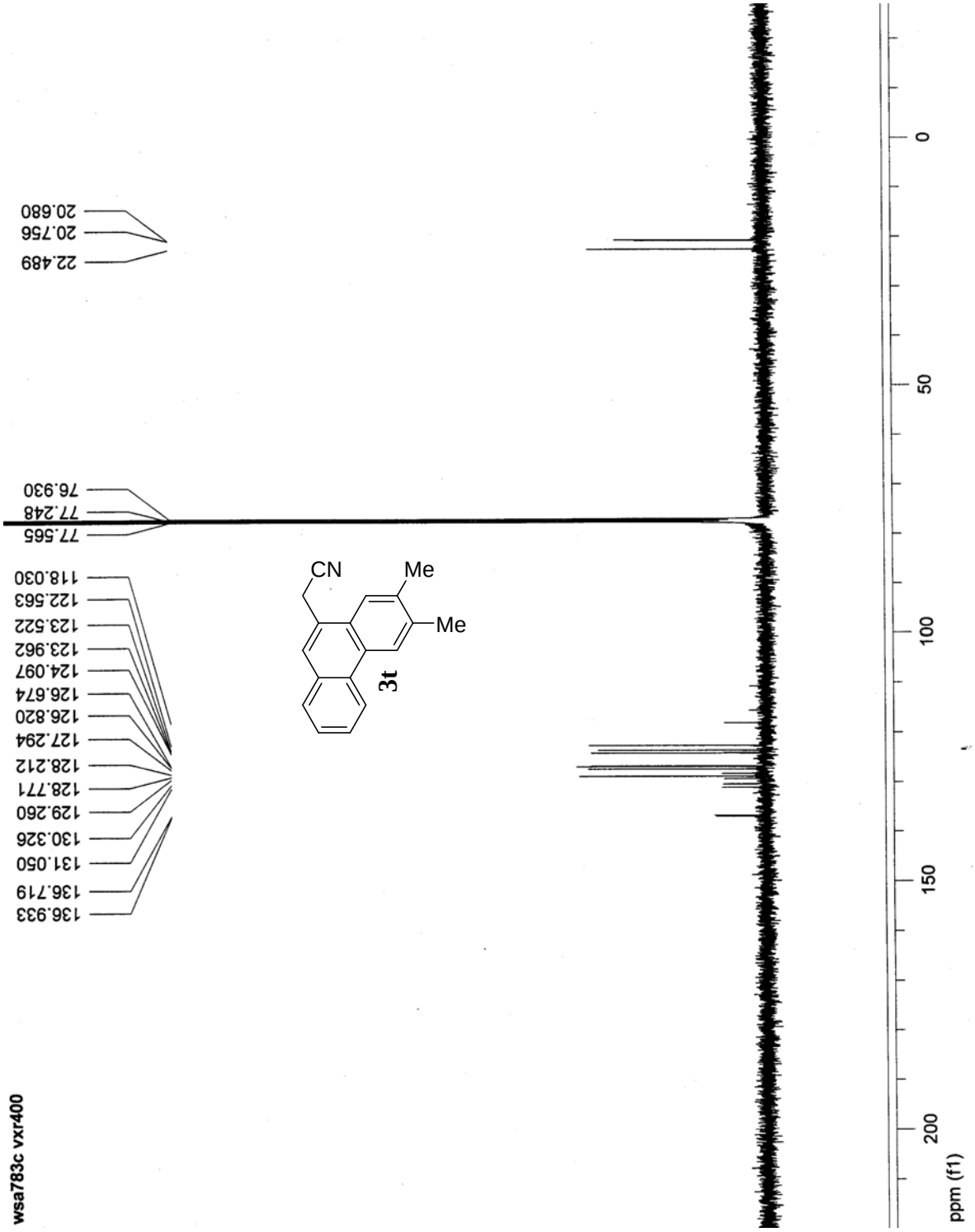












APPENDIX D. CHAPTER 4 ^{1}H AND ^{13}C NMR SPECTRA