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Palladium migrations and aryne annulations

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Palladium migrations and aryne annulations

by

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To my wife Yun and my daughter Yingling for everything

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LIST OF ABBREVIATIONS

Ac	acetyl
aq.	aqueous
Bn	benzyl
bp	boiling point
br	broad
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
BuLi	butyl lithium
ºC	degrees Celsius
cat.	catalytic amount
δ	chemical shift in ppm
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram
h	hour

Hz	hertz
IR	infrared (spectrum)
i-Pr	isopropyl
J	coupling constant
LDA	lithium diisopropylamide
m	multiplet or meta
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mp	melting point
MS	mass spectrometry
M. S.	molecular sieves
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
OAc	acetate
PPh_3	triphenylphosphine
py	pyridine
rt	room temperature

s	singlet
satd	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid

GENERAL INTRODUCTION

Introduction

Palladium-catalyzed reactions have found numerous applications in organic synthesis, especially in processes involving C-C bond or C-X bond formation. The Larock research group has developed numerous palladium-mediated annulation methodologies, which generally involve multiple bond formations, for instance, the *Larock indole synthesis*. These methodologies afford efficient and general protocols for the preparation of heterocyclic compounds, many of which exhibit remarkable biological activities. Usually, catalytic amounts of palladium catalysts are employed and moisture, oxygen and various functional groups can be readily tolerated.

Recently, during the course of investigating palladium-catalyzed reactions, the Larock group discovered a novel palladium rearrangement process, namely the through-space palladium migration, which has also been observed independently by other groups. This chemistry appears to be fairly general and occurs between a variety of different carbon atoms. This through-space shift of a palladium moiety is apparently mechanistically important, and it is also synthetically useful, because it provides an alternative way to introduce a palladium moiety into an organic molecule. At this point, palladium migration chemistry has been successfully employed to prepare numerous heterocycles and carbocycles.

The Larock group has also developed chemistry, that involves the facile coupling of nucleophiles and arynes readily generated from silylaryl triflates. The carbanion generated from nucleophilic attack on an aryne appears to be able to further attack a neighboring electrophile to afford cyclization products. These tandem coupling-cyclization reactions have been employed to prepare various heterocycles exhibiting interesting biological activities.

This dissertation is focused on palladium migration chemistry involving intramolecular C-H activation processes and the tandem aryne coupling-cyclization reaction. The contents described in this dissertation are published or will be published shortly.

Dissertation Organization

This dissertation is divided into four chapters. Each of the chapters is written according to the guidelines for a full paper in the *Journal of Organic Chemistry* and is composed of an abstract, introduction, results and discussion, conclusions, experimental section, acknowledgments and references.

Chapter 1 describes a novel synthesis of π-allylpalladium complexes from simple aryl iodides and alkynes via a consecutive aryl to vinylic to allylic palladium migration. This process presumably proceeds by carbopalladation of the alkyne, consecutive vinylic to aryl to allylic palladium migration, and subsequent displacement by a pivalate anion. This multiple migration process appears to involve an equilibrium between organopalladium(IV) hydrides and organopalladium(II) intermediates. The results from deuterium labeling experiments are consistent with the proposed mechanism. This chapter also reports an investigation of the reaction mechanism of the aryl to aryl palladium migration process. It appears that palladacycle(IV) hydrides or palladacycle(II) intermediates may both be involved, and a proton transfer mechanism is not favored.

Chapter 2 describes a synthesis of substituted carbazoles, indoles and dibenzofurans by the palladium-catalyzed cross-coupling of alkynes and appropriately substituted aryl iodides. This process proceeds by carbopalladation of the alkyne, a heteroatom-directed vinylic to aryl palladium migration, and ring closure via intramolecular arylation or a Mizoroki-Heck

reaction. Results from deuterium labeling experiments are consistent with the proposed mechanism.

Chapter 3 describes the preparation of biologically-interesting fluoren-9-one and xanth-9-one derivatives by a novel aryl to imidoyl palladium migration, followed by intramolecular arylation. The fluoren-9-one synthesis appears to involve both a palladium migration mechanism and a C-H activation mechanism through an unprecedented organopalladium(IV) hydride intermediate. The results from the deuterium labeling experiments are consistent with the proposed dual mechanism.

Chapter 4 reports the synthesis of xanthone, thioxanthone and acridone derivatives from the coupling-cyclization of silylaryl triflates and substituted benzoates. The reaction of silylaryl triflates, CsF and *ortho* heteroatom-substituted benzoates affords a general and efficient way to prepare biologically-interesting xanthones, thioxanthones and acridones. This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the benzoate with an aryne and subsequent intramolecular electrophilic cyclization.

Finally, all of the ^{1}H and ^{13}C NMR spectra of the starting materials and products are compiled in appendices A-D.

CHAPTER 1. CONSECUTIVE VINYLIC TO ARYL TO ALLYLIC PALLADIUM MIGRATION AND ARYL TO ARYL PALLADIUM MIGRATION

Based on a communication published in the *Angewandte Chemie International Edition* and a full paper accepted by the *Journal of the American Chemical Society*

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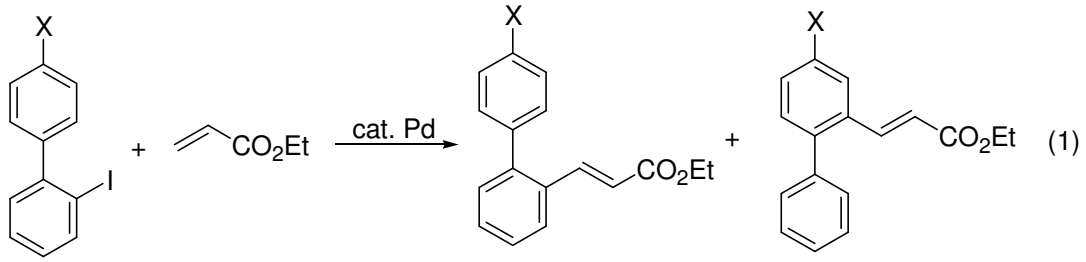
Abstract. A novel synthesis of π-allylpalladium complexes from simple aryl iodides and alkynes is disclosed. This process presumably proceeds by carbopalladation of the alkyne, consecutive vinylic to aryl to allylic palladium migration involving intramolecular C-H activation, and subsequent displacement by a pivalate anion. This migration process appears to involve an equilibrium between organopalladium(IV) hydrides and organopalladium(II) intermediates. The results from deuterium labeling experiments are consistent with the proposed mechanism. The reaction mechanism of an aryl to aryl palladium migration process has also been investigated. It appears that palladacycle(IV) hydrides or palladacycle(II) intermediates may both be involved, and a proton transfer mechanism is not favored.

Introduction

Palladium-catalyzed reactions have found numerous applications for constructing new bonds in organic synthesis. Organopalladium intermediates are often generated by oxidative addition of an organic halide or triflate, the transmetallation of an organometallic species, or

the direct C-H activation of an arene, but the former process is the most frequently used method to introduce a palladium moiety into an organic molecule. After the organic halide or triflate has undergone oxidative addition to Pd(0), the metal usually stays where the halogen or triflate originally resides, and subsequent bond formation occurs at this position too.

However, there are some examples in which the bond forming reaction does not occur at the position where oxidative addition takes place. The rearrangement of a palladium moiety along a saturated hydrocarbon chain by a sequence involving Pd-H elimination and subsequent readdition has been disclosed and developed into very useful methodology.[1] There are also a few reports of the "through-space" migration of palladium between remote carbons. The synthesis of 9-benzylidene-9*H*-fluorenes from diphenylacetylene and aryl halides has been reported by Larock, *et al*., and a mechanism involving facile 1,4-migration of palladium between a vinylic position and an arene has been proposed.[2] Larock *et al*. and Gallagher *et al*. both observed palladium migration between the *ortho* positions of biaryls in the Heck reaction of unsymmetrical *o*-halobiaryls with ethyl acrylate (eq. 1).[3] Aryl to benzylic[4] and alkyl to aryl[5] palladium migrations have also been reported.



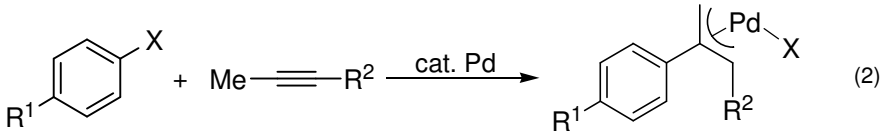
(1)

X = Me, OMe, NMe_2, CO_2Et, NO_2

π-Allylpalladium complexes are usually generated by the oxidative addition of allylic compounds bearing a good leaving group.[6] Alternatively, the reaction of organopalladium compounds with 1,3- and 1,2-dienes can also afford π-allylpalladium complexes.[7] Although

π-allylpalladium chemistry has been extensively investigated and become a very useful methodology in organic synthesis,[8] there have been few recent reports on developing new ways of generating π-allylpalladium complexes from simple starting materials.

Recently, we communicated a novel synthesis of π-allylpalladium complexes from the coupling of aryl halides and acetylenes (eq. 2).[9] We now wish to provide a full account of this consecutive vinylic to aryl to allylic palladium migration involving multiple C-H activation processes, which provides a new route to prepare π-allylpalladium intermediates. This chemistry presumably proceeds by carbopalladation of the alkyne, consecutive vinylic to aryl to allylic palladium migration, and subsequent displacement by a pivalate anion.



(2)

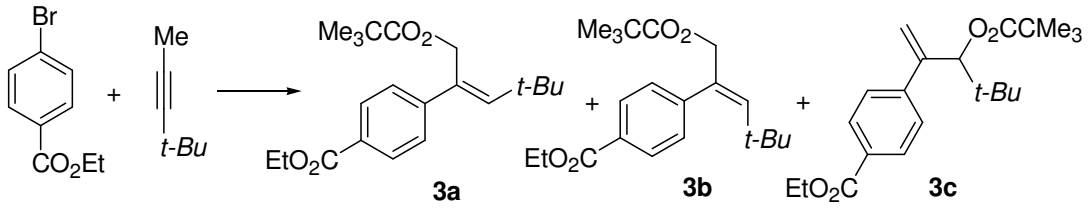
For the aryl to aryl palladium migration in biaryls, we have proposed a mechanism which proceeds via a palladacycle(II) or a palladacycle(IV) hydride involving C-H activation processes, and this mechanism is supported by calculations carried out by Jenks, *et al.*[10] However, an alternative mechanism which involves proton transfer has also been proposed and supported by other calculations.[2d] Since the theoretical calculations are apparently not conclusive, experimental evidence obtained from appropriately designed systems is highly desirable for a clear picture of the aryl to aryl palladium migration mechanism to emerge.

Results and Discussion

Optimization Studies. In order to obtain "optimal" reaction conditions for the consecutive vinylic to aryl to allylic palladium migration reaction, we first employed the reaction of methyl 4-bromobenzoate and 4,4-dimethyl-2-pentyne as our model system. All the

optimization results were summarized in Table 1. Methyl 4-bromobenzoate and 4,4-dimethyl-2-pentyne were first treated with 5 mol % $Pd(OAc)_2$, 5 mol % *bis*(diphenylphosphino)methane (dppm), 2 equiv of NaOAc in 10 mL of *N*,*N*-dimethylformamide (DMF) solvent at 100 °C. After 1 d of reaction, none of the desired product was observed (Table 1, entry 1). Repeating this reaction in the presence of *n*-Bu_4NCl (TBAC), a trace amount of the ester product was evident by GC-MS analysis (entry 2). When CsO_2CCMe_3 (CsPiv) was employed as the base, surprisingly, a 19% yield of an ester mixture was obtained (entry 3). Running the reaction in the presence of TBAC does not improve the yield (entry 4). The reaction using CsOAc as the base does not afford any product. Changing the ratio of aryl halide and alkyne decreased the reaction efficiency (entries 6 and 7). We also ran the reaction in the presence of water, which presumably should increase the solubility of the CsPiv base. However, the yield is lower (entry 10). Assuming the reaction efficiency could be improved by trapping the generated π-allylpalladium complex with good nucleophiles, we ran the reaction in the presence of morpholine and diethyl malonate. Unfortunately, we did not see any of the desired amine or ester products (entries 9 and 10). We then conducted the reaction in more dilute conditions, and a lower yield was observed (entry 11). When the reaction was run using 10 mol % $Pd(OAc)_2$ and 10 mol % dppm, a 27% yield of a mixture of esters was obtained (entry 12). Repeating the reaction under more concentrated conditions affords a 35% yield of the ester products (entry 13). We then increased the reaction temperature to 125 °C, and a slightly higher 42% yield was obtained (entry 14). Finally, we switched the solvent to *N*,*N*-dimethylacetamide (DMA) and a 50% yield of the ester mixture was isolated by flash chromatography (entry 15). Running the reaction at a higher temperature does not improve the reaction efficiency (entry

Table 1. Optimization Studies[a]



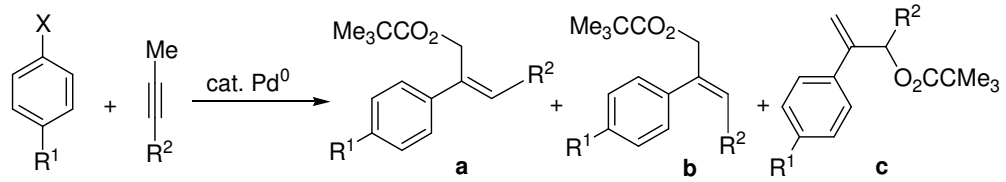
entry	ArX (equiv)	Alkyne (equiv)	% cat.	base	solvent	additive	temp. (°C)	% yield (**3a**:**3b**:**3c**)
1	1	1	5	2 NaOAc	DMF		100	-
2	1	1	5	2 NaOAc	DMF	1 TBAC	100	trace
3	1	1	5	2 CsPiv	DMF		100	19 (3:3:4)
4	1	1	5	2 CsPiv	DMF	1 TBAC	100	18 (3:3:4)
5	1	1	5	2 CsOAc	DMF		100	-
6	2	1	5	2 CsPiv	DMF		100	14 (3:3:4)
7	1	2	5	2 CsPiv	DMF		100	15 (3:3:4)
8	1	1	5	2 CsPiv	DMF	5 H_2O	100	5 (3:3:4)
9	1	1	5	2 CsPiv	DMF	5 morpholine	100	-
10	1	1	5	2 CsPiv	DMF	5 diethyl malonate	100	-
11	1	1	5	2 CsPiv	DMF		100	11 (3:3:4)[b]
12	1	1	10	2 CsPiv	DMF		100	27 (3:3:4)[c]
13	1	1	10	2 CsPiv	DMF		100	35 (1:1:2)[c]
14	1	1	10	2 CsPiv	DMF		125	42 (1:2:10)[c]
15	1	1	10	2 CsPiv	DMA		125	50 (1:2:18)[c]
16	1	1	10	2 CsPiv	DMA		140	45 (1:2:20)[c]

[a]All reactions were conducted on a 0.5 mmol scale in 10 mL of solvent for 24 h, and the ratio in parentheses was determined by ^{1}H NMR spectroscopy (sealed vial, under Ar). [b]This reaction was run in 20 mL of DMF solvent. [c]This reaction was conducted in 5 mL of DMA.

16). We also conducted the reaction under microwave heating conditions, but only a 44% yield of the product was obtained after 20 min. Therefore, the best conditions so far discovered for this transformation are: 10 mol % $Pd(OAc)_2$, 10 mol % dppm, 125 ^oC, and 5 mL of DMA in the presence of 2 equiv of CsO_2CCMe_3.

Reaction Scope and Limitations. After we had good reaction conditions in hand, we investigated the reaction scope and limitations as shown in Table 2. The reaction of *p*-iodoanisole and 1-phenyl-1-propyne under our usual palladium migration conditions using CsO_2CCMe_3 as the base has been observed to give a 20% yield of a 1:1 *E/Z*

Table 2. Multiple Palladium Migration[a]



entry	X	R^1	R^2	products	% yield (**a**:**b**:**c**)
1	I	OMe	Ph	**1a/b**	20 (1:1:0)[b]
2	Br	H	*t*-Bu	**2a/b, 2c**	35 (1:2:7)[c]
3	I	H	*t*-Bu	**2a/b, 2c**	44 (1:2:12)[c]
4	Br	CO_2Et	*t*-Bu	**3a/b, 3c**	50 (1:2:18)[c]
5	Br	Cl	*t*-Bu	**4a/b, 4c**	42 (1:2:20)[c]

[a]All reactions were conducted on a 0.5 mmol scale for 24 h, and the ratio of ArX to alkyne was 1:1 (sealed vial, under Ar). [b]This reaction was run using 5 mol % $Pd(OAc)_2$, 5 mol % dppm, 100 ^oC, 10 mL of DMF, and 2 equiv of CsO_2CCMe_3. [c]The reactions reported in entries 2-5 were run using 10 mol % $Pd(OAc)_2$, 10 mol % dppm, 125 ^oC, and 5 mL of DMA in the presence of 2 equiv of CsO_2CCMe_3.

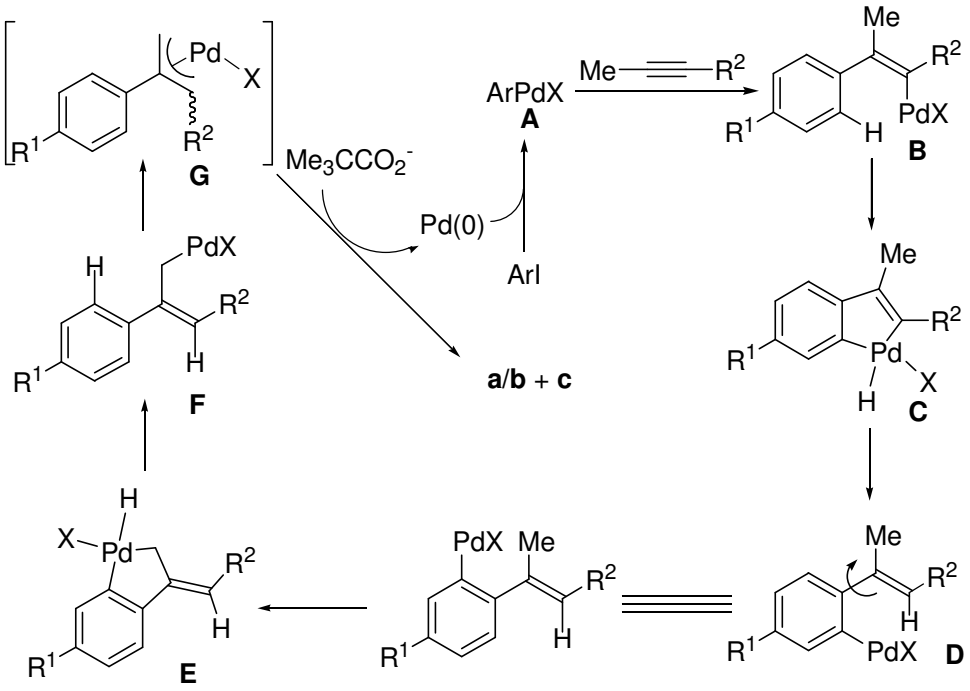
mixture of 2-(4-methoxyphenyl)-3-phenyl-2-propenyl pivalate (**1a/b**). The reaction of bromobenzene with 4,4-dimethyl-2-pentyne affords a 35% yield of a 1:2:7 mixture of three esters **2a**, **2b** and **2c** (entry 2). When iodobenzene was employed, a 44% yield of a mixture of

three esters **2a**, **2b** and **2c** was obtained in a 1:2:12 ratio (entry 3). The reaction using 4-chloro-bromobenzene affords a 42% yield of the products (entry 5). When R^2 is a Ph group, only two isomers are generated. When R^2 is a *t*-Bu group, the yield is higher and three isomers are generated. The ratio of the three isomers is dependent on the reaction time and temperature. It appears that longer times and higher temperatures generally favor the formation of isomer **c**.

Reaction Mechanism. Although these reactions only proceed in relatively low yields, and three isomers are usually obtained, which somewhat limits applications in synthesis, the mechanism of this unique transformation is fairly important and quite interesting. This process appears to involve palladium migration from a vinylic to an aryl to an allylic position and subsequent displacement by a pivalate anion (Scheme 3). Intermediate **A**, generated by oxidative addition of the aryl halide to Pd(0), adds to the alkyne to produce vinylic palladium intermediate **B**, which apparently then oxidatively adds the neighboring C-H bond to the palladium to form palladacycle **C**.[11] Subsequent reductive elimination affords **D**. This results in palladium migration from a vinylic to an aryl position via C-H activation, a process we have reported earlier.[3] To initiate a second C-H activation, the palladium moiety apparently rotates into the vicinity of the methyl group. Insertion of palladium into the neighboring C-H bond affords palladacycle **E**, which undergoes reductive elimination with transfer of the palladium moiety to the allylic position. This unprecedented migration process generates palladium intermediate **F**, which rapidly isomerizes to the corresponding π-allylpalladium species **G**. This unusual process provides a new route for the preparation of π- allylpalladium species, which have proven very versatile as intermediates in organic synthesis. The three isomeric ester products are presumed to arise by attack of the pivalate

anion on the palladium intermediate **G**. This proposed mechanism indicates that the migration of palladium is always accompanied by a simultaneous migration of hydrogen in the opposite direction. Thus, the observation of a hydrogen or deuterium shift should provide convincing evidence for the palladium migration, since the shift of palladium is technically difficult to observe.

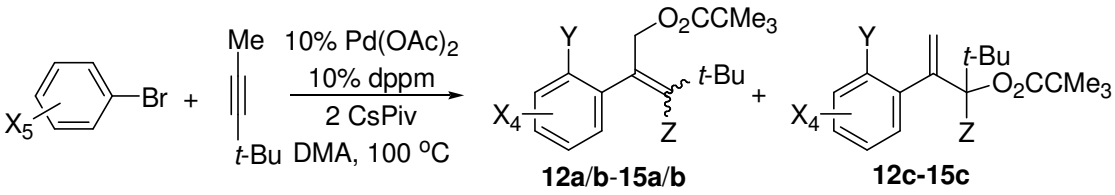
Scheme 3. Proposed Mechanism



Bromobenzene-d_5 (99% deuterium) and 4,4-dimethyl-2-pentyne were allowed to react with 10 mol % $Pd(OAc)_2$, 10 mol % *bis*(diphenylphosphino)methane (dppm), and 2 equiv of CsO_2CCMe_3 in DMA at 125 ^oC (Table 3, entry 1). *E* and *Z*-4,4-dimethyl-2-phenylpent-2-enyl pivalate (**12a/b**) and 1-*tert*-butyl-2-phenyl-2-propenyl pivalate (**12c**) were obtained in a ratio of 1:2:7. The formation of the deuterated product is proposed in Scheme 4. The ester **12c** was isolated in a 20% yield and found to contain 40% deuterium in the allylic position and 95% hydrogen in the *ortho* position of the aromatic ring. Since the ^1H NMR spectrum of

12c could result from the presence of a mixture of esters **18** and **19** in an appropriate ratio (Scheme 5), it was important to establish the exact nature of these products. A determination of the molecular weight of these ester products should clarify the situation. However, the vinylic position in **12a/b** and the allylic position in **12c** also contain either a hydrogen or a deuterium, which complicates the situation and makes the analysis more difficult.

Table 3. Deuterium Labeling Experiments[a]



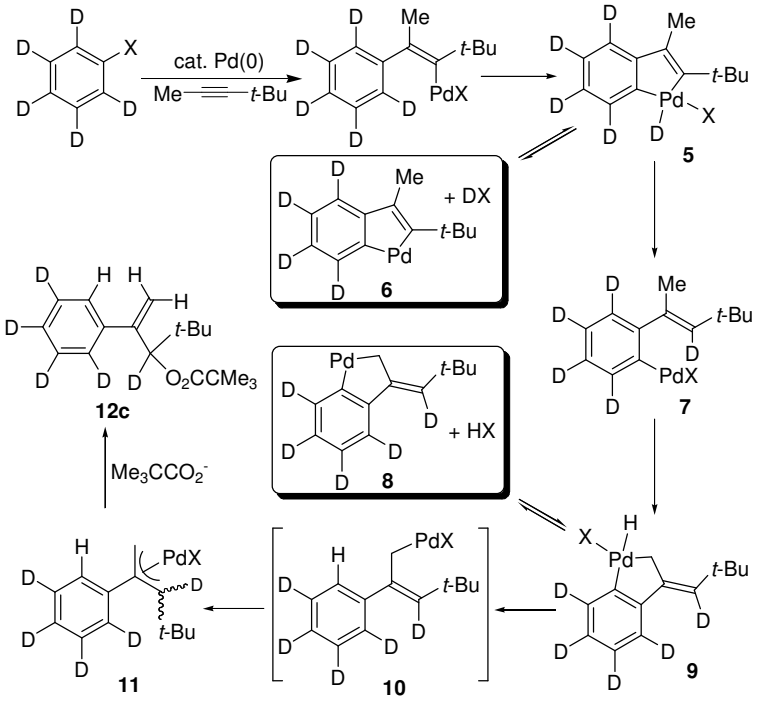
12a/b-15a/b **12c-15c**

entry	X	additive	product	Y	Z
1	D	-	**12c**	95% H	40% D
2	D	10 D_2O	**13c**	55% H	75% D
3	D	10 H_2O	**14c**	95% H	40% D
4	H	10 D_2O	**15c**	40% D	40% D

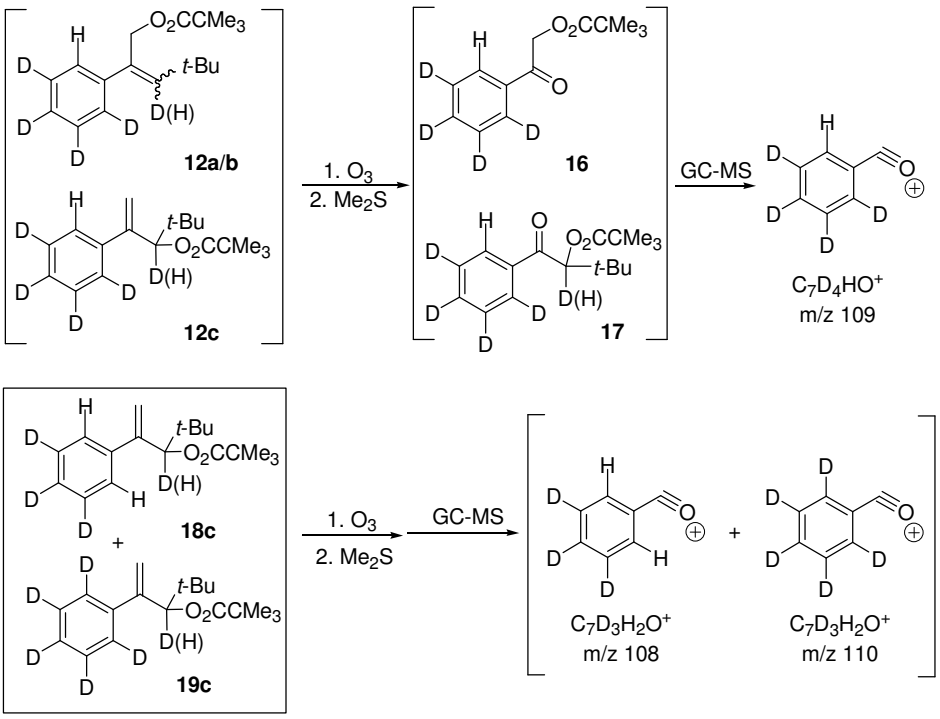
[a]The ratio of deuterium to hydrogen has been determined by ^1H NMR spectroscopy.

To eliminate the interference from the vinylic position, the mixture of ester products was treated with O_3 and Me_2S at -78 °C, and then the ketones **16** and **17** obtained were analyzed by GC-MS (Scheme 5). Presumably, ketones **16** and **17** will undergo fragmentation in the mass spectrum to afford the most stable oxonium cation (m/z 109), but a mixture of **18c** and **19c** would afford two different oxonium cations (m/z 108 and m/z 110), which should be easily detected by mass spectral analysis. Indeed, from the MS spectrum obtained, the intensity of the peaks m/z 108 ($C_7D_3H_2O^+$) and m/z 110 ($C_7D_5O^+$) are less than 5% of the

Scheme 4. Proposed Formation of the Deuterium Labeled Product



Scheme 5. Analysis of the Deuterated Esters

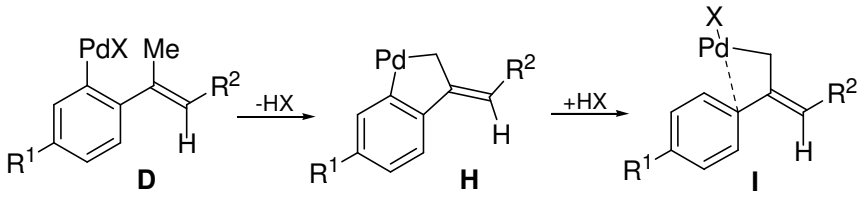


peak m/z 109 ($C_7D_4HO^+$), which indicates the former two species are not important. Thus, the hydrogen attached to the phenyl ring in compounds **12a**-**c** is only incorporated into one of the two *ortho* positions of the arene.

The results from this deuterium labeling experiment are consistent with the proposed mechanism, except for the fact that a relatively low allylic deuterium content is observed. However, the deuterium content can be increased by adding 10 equiv of D_2O to the reaction. (*E*/*Z*)-4,4-Dimethyl-2-phenylpent-2-enyl pivalate (**13a/b**) and 1-*tert*-butyl-2-phenyl-2-propenyl pivalate (**13c**) were obtained in a ratio similar to what was obtained from the reaction conducted in the absence of D_2O. The resulting ester **13c** contained 55% of one hydrogen in the *ortho* position of the arene and 75% deuterium in the allylic position (Table 3, entry 2). The product esters **13a**-**c** were treated with O_3 and Me_2S, and the ketones obtained were analyzed by GC-MS. The intensity of the peak m/z 110 ($C_7D_5O^+$) and the peak m/z 109 ($C_7D_4HO^+$) are almost the same, which is consistent with the ratio (about 1:1) of hydrogen and deuterium observed in the ^1H NMR spectrum. The loss of deuterium in the allylic position of **13c** presumably arises by deuterium/hydrogen exchange through an equilibrium between organopalladium(IV) intermediate **5** and palladacycle **6** or perhaps direct exchange of the metal hydride/deuteride in intermediate **5** (Scheme 4). The deuterium incorporation in the allylic position is dependant on the competition between H/D exchange and palladium migration, and it appears that neither one is dominant in this case. The reaction of bromobenzene-d_5 and 4,4-dimethyl-2-pentyne was repeated in the presence of 10 equiv of H_2O, and the esters (*E*/*Z*)-4,4-dimethyl-2-phenylpent-2-enyl pivalate (**14a/b**) and 1-*tert*-butyl-2-phenyl-2-propenyl pivalate (**14c**) obtained contain the same amount of vinylic deuterium incorporation and aryl hydrogen incorporation as esters **12a**-**c** (entry 3). A similar

exchange of hydrogen and deuterium has been observed in aryl-norbornyl palladacycles.[12] When bromobenzene-H_5 and 4,4-dimethyl-2-pentyne were allowed to react in the presence of 10 equivs of D_2O, the ester **15c**, which was obtained, had incorporated 40% deuterium in one of the *ortho* positions of the arene and 40% deuterium in the allylic position (entry 4). This experiment suggests that H-D exchange occurs during both of the two migration steps. Although the experimental data is consistent with the proposed aryl to allylic palladium migration mechanism, an alternative mechanism involving an organopalladium(II) palladacycle and an allylpalladium-arene complex stabilized by a π, η^1 interaction is also possible (Scheme 6).[13]

Scheme 6

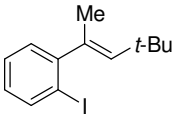
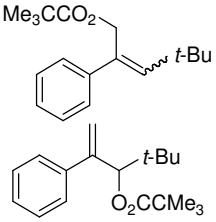
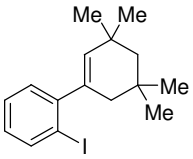
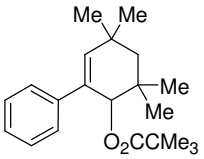
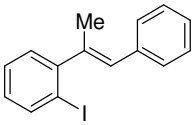
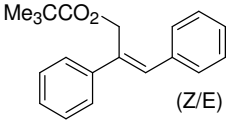
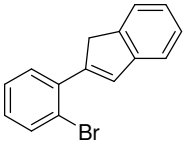
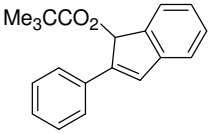
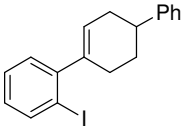
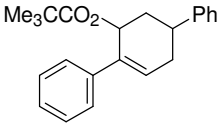


We have also carried out a palladium migration reaction using aryl iodide **20,** which would be expected to generate arylpalladium intermediate **D** (see Scheme 3) directly (Table 4, entry 1). This species should undergo palladium migration to produce the same mixture of pivalate esters as we obtained via the consecutive rearrangements discussed earlier. Under the same reaction conditions used previously, we have obtained a 65% yield of the anticipated product mixture **2a**, **2b** and **2c** in a 1:2:20 ratio. Although the ratio of the regioisomer **2c** to **2a/b** is a little higher than that observed in the consecutive migration process, the results are still consistent with our proposed mechanism.

We have also examined the reaction of aryl iodide **21** under our usual reaction conditions, but at 145 ^{o}C (entry 2). This reaction affords a 45% yield of the allylic pivalate **25**. Thus, it

appears that the arylpalladium intermediate corresponding to **21** is able to undergo migration to a secondary allylic position. Aryl iodide **22** was also prepared and treated in the same fashion. After one day of reaction, a 55% yield of two isomeric esters **26a/b** was obtained with a small amount of inseparable impurities (entry 3).

Table 4. Aryl to Allylic Palladium Migration[a]

entry	aryl iodide		product		% yield
1		**20**		**2a/2b** **2c**	65 (1:2:20)
2		**21**		**25**	45[b]
3		**22**		**26a/b**	55[c]
4		**23**		**27**	messy
5		**24**		**28**	0

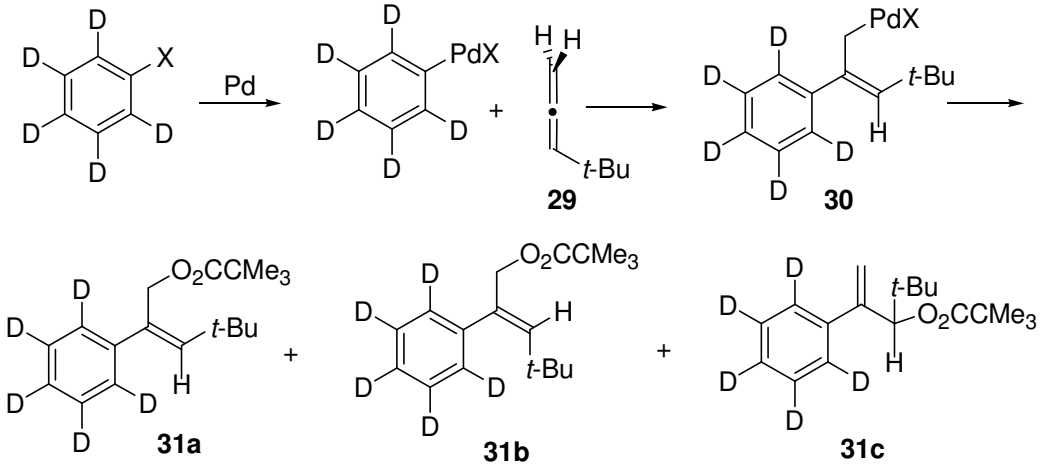
[a]The reaction was conducted on a 0.25 mmol scale using 10 mol % $Pd(OAc)_2$, 10 mol % dppm, 125 °C, and 5 mL of DMA in the presence of 2 equiv of CsO_2CCMe_3. [b]The reaction was conducted at 145 °C. [c]The yield was determined by ^1H NMR spectroscopy due to inseparable impurities.

When aryl bromide **23** was subjected to our standard migration conditions, the reaction was very messy and we did not observe any of the desired ester product for reasons that we still do not understand (entry 4). The reaction employing **24** does not afford the expected ester

28, but about 20% of [1,1';4',1"]terphenyl was obtained after one day of reaction, which presumably is due to facile *β*-H elimination in the π-allylpalladium intermediate and subsequent palladium-catalyzed dehydrogenation of the resulting cyclohexadiene (entry 5).

Mechanistically, an intermediate like **D** (Scheme 3) could also be generated by the carbopalladation of the allene 4,4-dimethyl-1,2-pentadiene (**29**), which might arise by isomerization of 4,4-dimethyl-2-pentyne (Scheme 7). However, this process when run with pentadeuterated bromobenzene in D_2O would not introduce a hydrogen into the *ortho* position of the arene or a deuterium into the allylic position of the final ester

Scheme 7. Possible Allene Mechanism

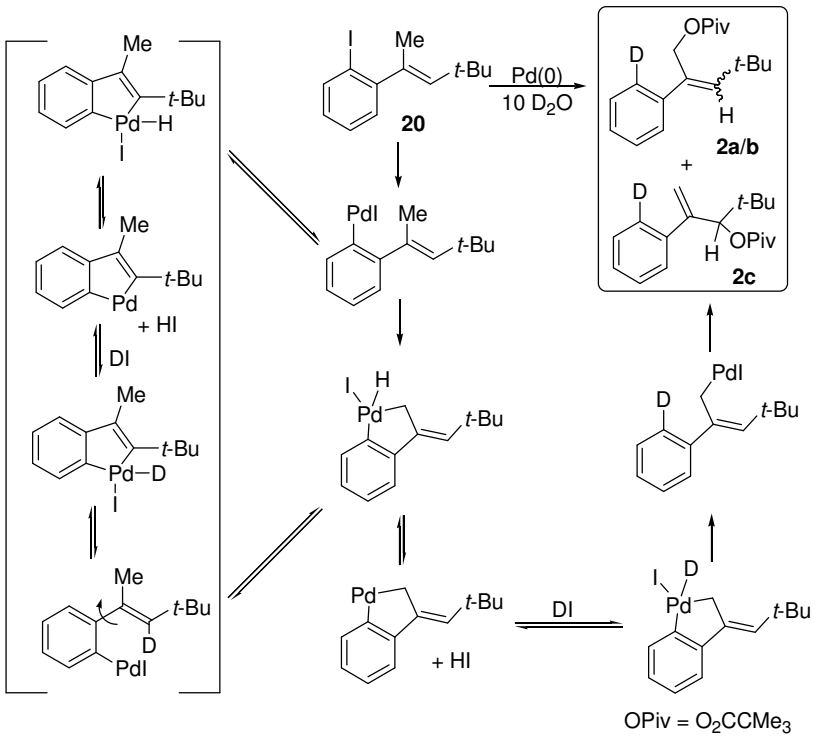


product, unless the palladium moiety could reversibly migrate from the allylic to the aryl to the vinylic position. Only then could one observe a hydrogen in the *ortho* position of the arene and a deuterium in the vinylic position, plus deuterium incorporation into the allylic position.

To test the reversibility of this palladium migration process, the reaction using aryl iodide **20** was conducted in the presence of 10 equiv of D_2O (Scheme 8). The isolated product **2c** contained 40% of deuterium in one of the *ortho* positions of the arene by GC-MS analysis,

and no deuterium in the vinylic or allylic positions. Ester **2c** was treated with O_3 and Me_2S, and the ketone obtained was analyzed by GC-MS. The peak m/z 105 ($C_7H_5O^+$) and the peak m/z 106 ($C_7DH_4O^+$) exhibited similar intensities, but the peak m/z 107 ($C_7D_2H_3O^+$) displayed less than 5% of the intensity of the peaks at m/z 105 and m/z

Scheme 8. Reversibility of Palladium Migration



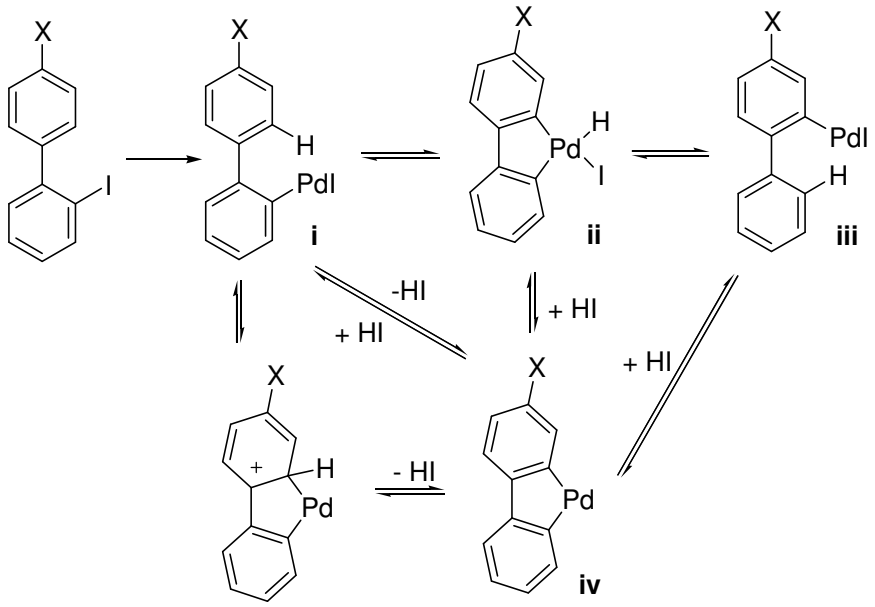
106, which indicates that deuterium is incorporated in only one of the two *ortho* positions of the arene. This suggests that the vinylic to aryl migration is not a reversible process. Because no deuterium incorporation in the methylene or allylic positions was observed, we can also rule out reversible palladium migration from the allylic to the aryl position.

Mechanistic Studies on Aryl to Aryl Palladium Migrations. Recently, we and others observed a palladium migration process between the *ortho* positions of unsymmetrical biaryls (eq. 1).[3] Heck and Suzuki reactions have been employed to trap the migrated palladium

moiety.[10] Plus, this aryl to aryl palladium migration process has been employed to prepare numerous heterocycles and carbocycles.[3c]

We propose a possible mechanism (Scheme 9) for the aryl to aryl palladium migration in the organopalladium intermediates derived from *o*-halobiaryls, which involves oxidative addition of the aryl halide to Pd(0) to generate intermediate **i**, which can either (a) undergo oxidative addition of a neighboring C-H bond to produce a hydridopallada(IV)cycle (**ii**), followed by reductive elimination of CH to generate either **iii** or **i**, or (b) electrophilic palladation to generate intermediate **iv**, followed by either protonolysis of a C-Pd bond to generate **i** or **iii** or oxidative addition of HX to generate **ii**. With regard to the mechanism, we would like to point out that not all ligands on palladium are shown for simplicity. We believe that the intermediacy of **iv** is unlikely for two main reasons. First, it is improbable that intermediate **iv** could react with HI under the basic reaction conditions we have employed. Second, Catellani and Chiusoli have demonstrated that pallada(II)cycles analogous to intermediate **iv**

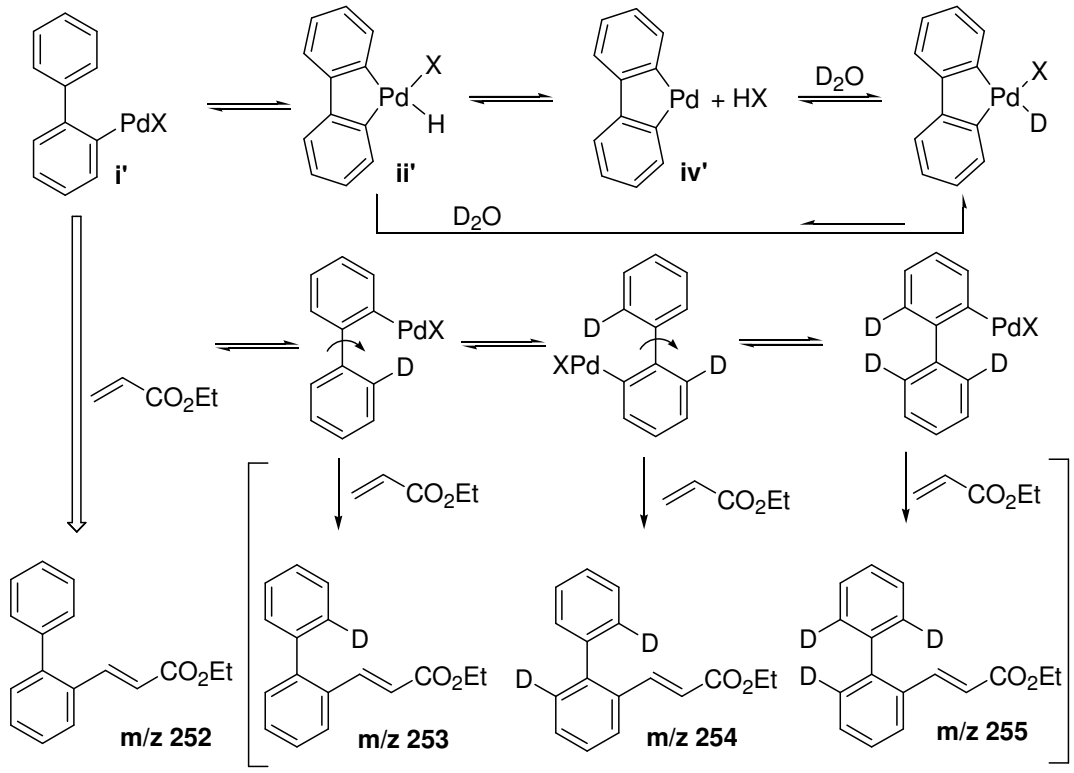
Scheme 9. Plausible Mechanism for Aryl to Aryl Palladium Migration



easily undergo oxidative addition to aryl and alkyl halides to generate palladium(IV) intermediates generating characteristic polycyclic compounds,[14] which have not been observed under our reaction conditions. As a result, we favor the reversible interconversion between **i** and **iii** via hydridopallada(IV)cycle **ii**. Organopalladium(IV) species are well known,[11] although no such hydride-containing species have ever been isolated. It is also important to realize that palladium migration involves intramolecular C-H activation, possibly through an electrophilic palladium species.

To better understand this aryl to aryl palladium migration process, we have carried out additional mechanistic studies. Our first experiments involved incorporation of deuterium into the product by running one of these migration reactions in the presence of a large excess

Scheme 10. Deuterium Labeling Experiments



of D_2O. In the presence of D_2O, deuterium incorporation in the *ortho* positions would be expected if the migration proceeds through formation of **iv**. In fact, if the equilibration is substantially faster than the reaction with an olefin (the Heck reaction), then virtually complete D incorporation would be expected in the three available *ortho* positions, as shown in Scheme 10. Lack of deuterium incorporation would, of course, imply that no intermediate with exchangeable hydrogen was involved, and thus eliminate **iv**. The rate of hydrogen exchange in an intermediate like **ii** is unknown. However, if it were slow enough, migration could occur without incorporation of deuterium.

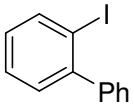
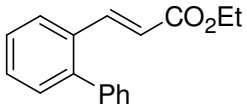
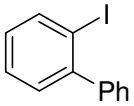
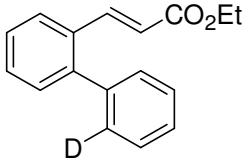
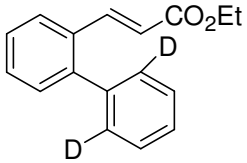
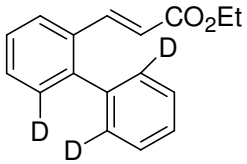
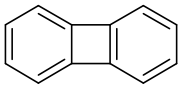
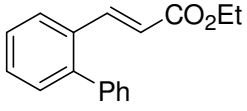
Thus, we first treated 2-iodobiphenyl and 4 equiv of ethyl acrylate with 5 mol % $Pd(OAc)_2$, 5 mol % dppm, 1 equiv of TBAC, 2 equiv of $NaHCO_3$ in 1 mL of DMF and 0.05 mL of D_2O (conditions A) (Table 5, entry 1), conditions under which migration has not previously been observed.[10] No deuterium incorporation in the *ortho* positions of the coupled product is expected, because only the original position of the iodide substituent is ever activated. This expectation was met for the ester product, as analyzed by ^1H NMR spectroscopy and GC-MS.

However, when this same reaction was conducted using 0.2 mL of D_2O instead of 0.2 mL of H_2O (condition B), approximately 2 of the *ortho* hydrogens on average were substituted by deuterium, as indicated by the ^1H NMR spectrum of the ester product obtained (entry 2). A broad peak in the ^2H NMR spectrum at 7.4 ppm was also observed, consistent with deuterium incorporation occurring at more than one carbon atom. Mass spectral data indicated that comparable amounts of the nondeuterated (m/z 252), monodeuterated (m/z 253), dideuterated (m/z 254), and trideuterated (m/z 255) esters were observed.

This result indicates that our "equilibrating" conditions (conditions B) are not such that the migration of the palladium species is orders of magnitude faster than the coupling step.

Otherwise, the overwhelming majority of material would be trideuterated. However, it does not clearly distinguish between the intermediacy of **ii** and **iv**, because, while it is obvious that H exchange would occur with formation of **iv**, it is also reasonable that H exchange could occur with **ii** as the key intermediate even if **iv** were never formed. A second experiment involving the formation of **iv** via an alternate synthetic pathway was carried out (Scheme 11). Biphenylene has been reported to react under some conditions with Pd(0) to generate

Table 5. Mechanistic Studies[a]

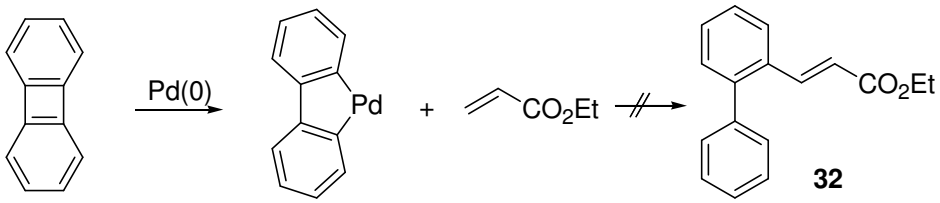
entry	ArI	% Pd	additive	product(s)	% yield	% d
1		5	10 D_2O		90[a]	0
2		5	10 D_2O	  	90[b]	67
3		5	10 D_2O		0[b]	-
4		5	10 D_2O 1 DCl		0[b]	-
5		100	10 D_2O		0[b]	-

[a]Conditions A: the reaction was run using 0.25 mmol of the iodobiaryl, 4 equivs of ethyl acrylate (EA), 2 equivs of $NaHCO_3$, and 1 equiv of *n*-Bu_4NCl (TBAC), where indicated, in 4 ml of DMF at 100 °C. [b]Conditions B: the reaction was run using 0.25 mmol of the iodobiaryl, 1 equiv of ethyl acrylate (EA), 2 equivs of CsPiv, in 4 ml of DMF at 100 °C.

iv (X = H), which can also undergo Heck and Suzuki couplings.[15] Assuming this process will occur under our "optimal" equilibration reaction conditions, the same ester products **32** should be observed from biphenylene as from 2-iodobiphenyl.

However, biphenylene was not an effective precursor under our standard palladium migration conditions. When biphenylene was allowed to react with 1 equiv of ethyl acrylate (0.25 mmol) in the presence of 5 mol % $Pd(OAc)_2$, 5 mol % dppm, 2 equiv of CsPiv in 3.8 mL of DMF and 0.2 mL of D_2O, GC-MS spectral analysis indicated that, after reaction for 1 day, none of the anticipated Heck product **32** was obtained and only the starting biphenylene was present (Table 5, entry 3). Since one equiv of HI acid is usually generated in our Heck palladium migration reactions, this reaction was repeated in the presence of 1 equiv of DCl. Again, none of the anticipated Heck product was obtained. This reaction was also conducted using 1 equiv of $Pd(OAc)_2$. After reaction for 1 day, only biphenylene was evident by GC-MS spectral analysis.

Scheme 11



This result is, again, mechanistically ambiguous regarding the palladium migration. The most likely cause of the problem may be that the conditions were not conducive to palladium insertion into the biphenylene C-C bond. Indeed, Gallagher has demonstrated a kinetic preference for palladium insertion into aryl bromides over biphenylene.[16] Alternatively, our failure to observe Heck-type products in these biphenylene reactions may occur because **iv** is reversibly formed, but unreactive, under our reaction conditions (and thus excluded

mechanistically from the palladium migration chemistry). However, without any other evidence for the formation of **iv**, such a conclusion cannot be drawn.

Conclusions

We have established an unusual consecutive vinylic to aryl to allylic palladium migration process, which affords a novel new way to generate π-allylpalladium complexes. This migration process appears to involve an equilibrium between organopalladium(IV) hydrides and organopalladium(II) intermediates, which undergo facile exchange with a H source in solution. However, we cannot rule out direct exchange of the palladium(IV) hydride. A mechanistic study of the aryl to aryl palladium migration process provides some new information. For example, the palladium shift is a reversible process and a proton shift mechanism is not favored. However, the results are still mechanistically ambiguous.

Experimental Section

General Procedures. All ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and a basic $KMnO_4$ solution. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI and 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of THF, DMF, DMA, diethyl ether, ethyl acetate, hexanes, and 4,4-dimethyl-2-pentyne were purchased from Lancaster Synthesis, Inc. Iodobenzene, bromobenzene, bromobenzene-d_5, *p*-iodoanisole, *p*-chloroiodobenzene**,** ethyl 4-

bromobenzoate, and 1-phenyl-1-propyne, were purchased from Aldrich Chemical Co., Inc. Cesium pivalate was prepared according to the procedure of Campo and Larock.[3b]

(*E*)-2-(2-Iodophenyl)-4,4-dimethyl-2-pentene (20).

(*E*)-2-Iodo-4,4-dimethyl-2-pentene was prepared by a literature procedure,[17] and subjected to a Suzuki reaction with 2-bromophenylboronic acid. The reaction employed 2.0 mmol of vinylic iodide, 2.5 mmol of arylboronic acid, 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and 2 equiv of Na_2CO_3 in 2 mL of water and 8 mL of DMF at room temperature for 12 h. The aryl bromide obtained was treated with 1.2 equiv of *n*-BuLi at -78 ^oC, and then 1.2 equiv of I_2 to afford aryl iodide **20**: ^1H NMR ($CDCl_3$) δ 1.23 (s, 9H), 2.02 (d, *J* = 1.5 Hz, 3H), 5.27 (q, *J* = 1.5 Hz, 1H), 6.90 (td, *J* = 7.5, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.27 (td, *J* = 7.5, 1.8 Hz, 1H), 7.81 (dd, *J* = 7.6, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 19.3, 30.9, 33.0, 99.0, 128.0, 128.2, 128.9, 138.2, 139.2, 141.1, 151.9; IR ($CDCl_3$) 2960, 2904, 2866, 1461 cm^{-1}; HRMS m/z 300.0379 (calcd for $C_{13}H_{17}I$, 300.0375).

1-(2-Iodophenyl)-3, 3, 5, 5-tetramethylcyclohexene (21).

The corresponding aryl bromide was prepared utilizing a Suzuki reaction of 1-iodo-3,3,5,5-tetramethylcyclohexene[18] and 2-bromophenylboronic acid, and the resulting aryl bromide was converted to the corresponding iodide by the *n*-BuLi procedure reported earlier: ^1H NMR ($CDCl_3$) δ 1.07 (s, 6H), 1.10 (s, 6H), 1.40 (s, 2H), 1.99 (d, *J* = 1.5 Hz, 2H), 5.33 (t, *J* = 1.5 Hz, 1H), 6.87 (td, *J* = 7.4, 1.7 Hz, 1H), 7.08 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.24 (td, *J* = 7.5, 1.2 Hz, 1H), 7.80 (dd, *J* = 7.5, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 30.5, 31.2, 31.4, 33.2, 43.5, 49.8, 98.8, 128.2, 128.3, 129.2, 136.5, 137.7, 139.5, 149.1; IR ($CDCl_3$) 2954, 2902, 2866, 1462 cm^{-1}; HRMS m/z 340.0696 (calcd for $C_{16}H_{21}I$, 340.0688).

Representative procedure for the palladium-catalyzed migration reactions. The appropriate aryl halide (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), *bis*(diphenylphosphino)methane (dppm) (9.6 mg, 0.025 mmol) and CsO_2CCMe_3 (CsPiv) (0.234 g, 1.0 mmol) in DMA (5 mL) were stirred under Ar at 125 ^oC for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (50 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (25 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel.

(*E*)- and (*Z*)-2-(4-Methoxyphenyl)-3-phenyl-2-propenyl pivalate (1a/b).

^1H NMR ($CDCl_3$) δ 1.13 (s, 9H), 1.15 (s, 9H), 3.81 (s, 3H), 3.84 (s, 3H), 4.89 (d, J = 1.4 Hz, 2H), 5.10 (s, 2H), 6.63 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 7.02-7.45 (m, 15H); ^{13}C NMR ($CDCl_3$) 27.3, 27.4, 39.0, 39.1, 55.4, 55.5, 62.2, 69.2, 114.0, 114.2, 127.2, 127.5, 127.8, 128.2, 128.5, 128.6, 129.1, 129.5, 130.2, 130.4, 131.6, 133.0, 136.0, 136.6, 137.0, 137.1, 159.2, 159.5, 178.3, 178.6; IR ($CDCl_3$) 2973, 2936, 1719 cm^{-1}; HRMS m/z 324.1731 (calcd for $C_{21}H_{24}O_3$, 324.1725).

When using 4,4-dimethyl-2-pentyne and ArX as the starting materials, GC-mass spectral analysis of the products indicated three close peaks with the same m/z values, corresponding to the three isomers reported, and the ratio of isomers was determined by ^1H NMR spectroscopy. Pure **2c**, **3c** and **4c** have been isolated from the respective product mixtures and fully characterized, but we were not able to separate and obtain the pure **a** and **b** stereoisomers from **2a/b**, **3a/b** and **4a/b**. After column chromatography, we obtained **2a/b** containing a minor amount of **2c** and **3a/b** containing a minor amount of **3c**. The ^1H NMR spectra reported for **2a/b** and **3a/b** were taken on those incompletely separated mixtures.

(*E*)- and (*Z*)-4,4-Dimethyl-2-phenylpent-2-enyl pivalate (2a/b).

^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9H), 1.08 (s, 9H), 1.11 (s, 9H), 1.23 (s, 9H), 4.60 (d, *J* = 1.2 Hz, 2H), 5.07 (s, 2H), 5.70 (s, 1H), 5.95 (s, 1H), 7.14-7.53 (m, 10H).

1-*tert*-Butyl-2-phenyl-2-propenyl pivalate (2c).

Product **2c** could be isolated from the product mixture: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 1.27 (s, 9H), 5.19 (s, 1H), 5.30 (s, 1H), 5.41 (s, 1H), 7.22-7.34 (m, 3H), 7.55 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) 26.6, 27.3, 35.7, 39.2, 81.7, 115.3, 127.2, 127.7, 128.6, 142.8, 148.6, 177.9; IR ($CDCl_3$) 2974, 2907, 2872, 1715, 1478 cm^{-1}; HRMS m/z 274.1936 (calcd for $C_{18}H_{26}O_2$, 274.1933).

Bromobenzene-d_5 (99.5% deuterium) and 4,4-dimethyl-2-pentyne were allowed to react using the reaction conditions reported in footnote c of Table 1 to afford product **12c**: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 1.27 (s, 9H), 5.19 (s, 1H), 5.30 (s, 1H), 5.41 (s, 0.6H), 7.55 (s, 0.95H).

The reaction of bromobenzene-d_5 and 4,4-dimethyl-2-pentyne conducted in the presence of 10 equiv of D_2O afforded product **13c**: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 1.27 (s, 9H), 5.19 (s, 1H), 5.30 (s, 1H), 5.41 (s, 0.27H), 7.55 (s, 0.55H). The product esters were treated with O_3 and Me_2S, and the ketones obtained were analyzed by GC-MS. The intensity of the peak m/z 110 ($C_7D_5O^+$) and the peak m/z 109 ($C_7D_4HO^+$) were almost the same, which is consistent with the ratio of hydrogen to deuterium (about 1:1) observed in the ^{1}H NMR spectrum.

Bromobenzene-H_5 and 4,4-dimethyl-2-pentyne were allowed to react under the same reaction conditions in the presence of 10 equiv of D_2O to afford product **15c**: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 1.27 (s, 9H), 5.19 (s, 1H), 5.30 (s, 1H), 5.41 (s, 0.60H), 7.55 (d, *J* = 6.8 Hz, 1.65H).

Aryl iodide **20** was also subjected to our standard migration conditions in the presence of 10 equiv of D_2O to afford product **12c**: ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 9H), 1.27 (s, 9H), 5.19 (s, 1H), 5.30 (s, 1H), 5.41 (s, 1H), 7.55 (d, *J* = 6.8 Hz, 1.55H).

(*E*)- and (*Z*)-Ethyl 4-[4,4-dimethyl-1-(pivaloyloxy)pent-2-en-2-yl]benzoate (3a/b).

^{1}H NMR ($CDCl_3$) δ 0.78 (s, 9H), 1.07 (s, 9H), 1.10 (s, 9H), 1.24 (s, 9H), 1.36-1.42 (m, 6H), 4.33-4.40 (m, 4H), 4.60 (s, 2H), 5.09 (s, 2H), 5.75 (s, 1H), 6.02 (s, 1H), 7.23-7.24 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.95-8.00 (m, 4H).

Ethyl 4-[4,4-dimethyl-3-(pivaloyloxy)pent-1-en-2-yl]benzoate (3c).

Product **3c** could be isolated from the product mixture: ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 9H), 1.27 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 5.27 (s, 1H), 5.37 (s, 1H), 5.38 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 8.00 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) 14.6, 26.5, 27.3, 35.8, 39.1, 61.1, 81.5, 116.8, 127.1, 129.7, 130.0, 147.2, 148.0, 166.7, 177.9; IR ($CDCl_3$) 2975, 1711, 1478 cm^{-1}; HRMS m/z 346.2150 (calcd for $C_{21}H_{30}O_4$, 346.2144).

1-*tert*-Butyl-2-(4-chlorophenyl)-2-propenyl pivalate (4c).

Product **4c** could be isolated from the product mixture: ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9H), 1.27 (s, 9H), 5.20 (s, 1H), 5.28 (d, *J* = 0.9 Hz, 1H), 5.31 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) 26.6, 27.3, 35.8, 39.2, 81.6, 116.0, 128.5, 133.5, 141.4, 147.7, 177.9; IR ($CDCl_3$) 2972, 2907, 2872, 1716, 1479, 1091 cm^{-1}; HRMS m/z 308.1547 (calcd for $C_{18}H_{25}ClO_2$, 308.1543).

4,4,6,6-Tetramethyl-2-phenylcyclohex-3-enyl pivalate (25).

^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.05 (s, 12H), 1.11 (s, 3H), 1.15 (s, 3H), 1.41 (d, *J* = 13.2 Hz, 1H), 1.64 (d, *J* = 13.2 Hz, 1H), 5.63 (s, 1H), 5.84 (s, 1H), 7.20-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) 26.0, 27.3, 27.31, 31.0, 32.5, 33.0, 35.3, 39.1, 45.8, 74.7, 126.4, 127.0, 128.4,

134.0, 138.9, 140.8, 178.1; IR ($CDCl_3$) 2959, 1712, 1478 cm^{-1}; HRMS m/z 314.2246 (calcd for $C_{21}H_{30}O_2$, 314.2250).

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CHAPTER 2. SYNTHESIS OF SUBSTITUTED CARBAZOLES, INDOLES AND DIBENZOFURANS BY DIRECTED VINYLIC TO ARYL PALLADIUM MIGRATION

Based on a communication published in *Organic Letters* and a full paper published in the *Journal of Organic Chemistry*

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Abstract. Substituted carbazoles, indoles and dibenzofurans are readily prepared in moderate to excellent yields by the palladium-catalyzed cross-coupling of alkynes and appropriately substituted aryl iodides. This process proceeds by carbopalladation of the alkyne, heteroatom-directed vinylic to aryl palladium migration, and ring closure via intramolecular arylation or a Mizoroki-Heck reaction. Results from the deuterium labeling experiments are consistent with the proposed mechanism.

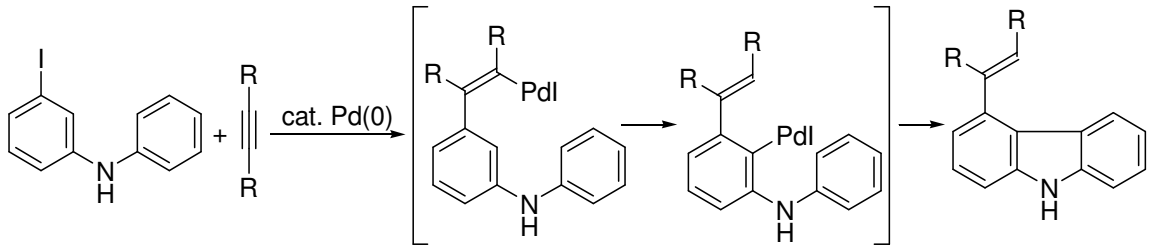
Introduction

The palladium-catalyzed activation of unfunctionalized C-H bonds is considered a highly atom-efficient and environmentally-friendly strategy for organic synthesis. Recently, a number of palladium migration examples involving intramolecular C-H activation have been disclosed by our group and others.[1] This through-space shift of palladium appears to be fairly general and can take place between a wide variety of carbon

atoms. Specifically, vinylic to aryl,[2] aryl to aryl,[3] alkyl to aryl,[4] and vinylic to aryl to allylic[5] palladium migration processes have been reported. These novel palladium migration processes are not only mechanistically important, but also synthetically useful, because they afford an alternative way to introduce a palladium moiety into an organic molecule.

Recently, we reported a nitrogen-directed vinylic to aryl palladium migration, which provides an efficient way to prepare biologically interesting carbazoles as shown in Scheme 1.[2c,6] This process proceeds by carbopalladation of the internal alkyne, and then the palladium moiety migrates from the vinylic position to the aryl position through an intramolecular C-H activation process. The arylpalladium intermediate generated subsequently undergoes intramolecular arylation to afford the carbazole products. Herein, we

Scheme 1. Synthesis of Substituted Carbazoles via Vinylic to Aryl Palladium Migration

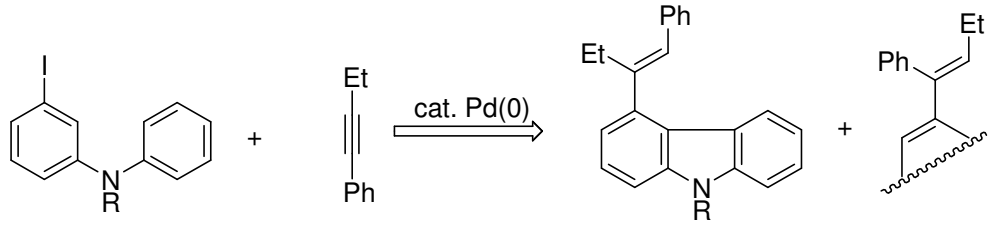


wish to report a complete account of this nitrogen-directed palladium migration, an extension of this methodology to the synthesis of biologically interesting dibenzofurans[7], and the synthesis of indoles[8] in which the arylpalladium intermediate is trapped by an intramolecular Mizoroki-Heck reaction. Furthermore, substrates labeled with deuterium have also been prepared and employed in this process to explore the mechanistic details of this rearrangement.

Results and Discussion

1. Optimization of Reaction Conditions. In our initial work on this carbazole synthesis, we treated *N*-phenyl-3-iodoaniline and 1 equiv of 1-phenyl-1-butyne with 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and 2 equiv of NaOAc in *N*,*N*-dimethylformamide (DMF) at 100 °C for 24 h (Table 1, entry 1). Unfortunately, only a trace of the desired carbazole product **1a** was observed by GC-MS analysis. This reaction was subsequently

Table 1. Optimization of the Carbazole Synthesis



1a **1b**

entry	R	base	ligand	additive	time (h)	% yield (**1a**:**1b**)[a]
1	H	2 NaOAc	10% PPh_3	-	24	trace
2	H	2 Na_2CO_3	10% PPh_3	-	24	0
3	H	2 NEt_3	10% PPh_3	-	24	0
4	H	2 NaOAc	10% PPh_3	1 TBAC	24	20 (10:1)
5	H	2 CsPiv	10% PPh_3	-	12	60[b] (10:1)
6	H	2 CsPiv	5% dppm	-	6	73 (10:1)
7	H	2 CsPiv	5% dppm	1 TBAC	6	71[b] (10:1)
8	Me	2 CsPiv	5% dppm	-	12	trace
9	Ph	2 CsPiv	5% dppm	-	12	0

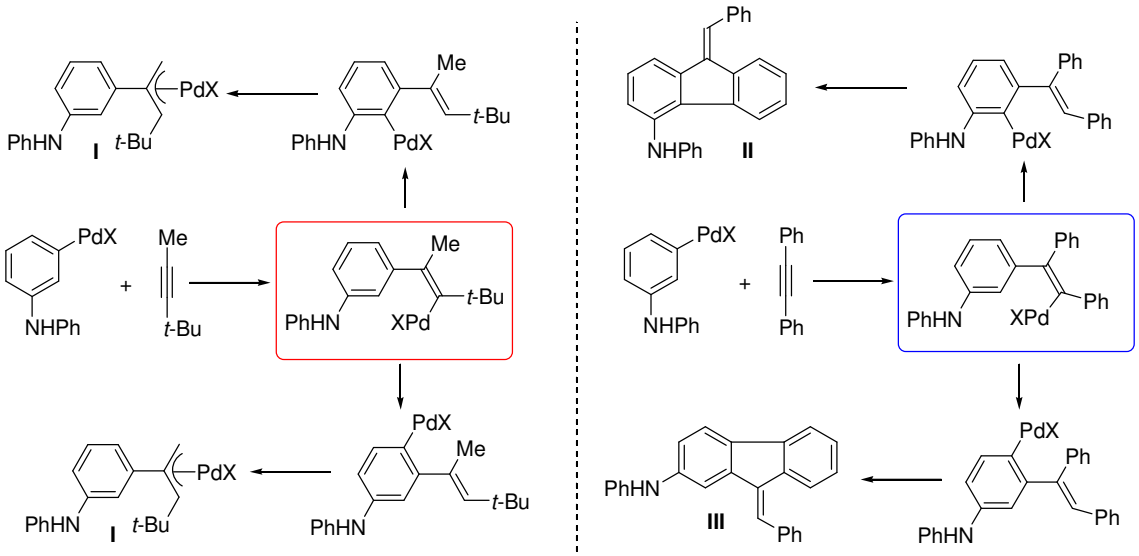
[a]All reactions were conducted on a 0.25 mmol scale at 100 °C in 4 mL of DMF, and the ratio of aryl iodide to alkyne was 1:1 (sealed vial, under Ar). The ratio of **1a** to **1b**, as determined by ^{1}H NMR spectroscopy, is reported in parentheses. [b]GC yield.

carried out using both an inorganic base Na_2CO_3 (entry 2) and an organic base NEt_3 (entry 3), but none of the desired carbazole product was observed. When 1 equiv of *n*-Bu_4NCl (TBAC) was added to the NaOAc reaction, a 20% yield of a 10:1 ratio of isomeric carbazoles **1a** and **1b** was obtained (entry 4). We next conducted the model reaction in the presence of 2 equiv of CsO_2CCMe_3 (CsPiv) because of its superior solubility in DMF. To our delight, a 60%

yield of the desired products was obtained (entry 5). By simply replacing PPh_3 with a bidentate ligand *bis*(diphenylphosphino)methane (dppm), a 73% yield of the two regioisomers was isolated by flash chromatography (entry 6). We then repeated the same reaction in the presence of 1 equiv of TBAC, but it appears that the presence of chloride source is unnecessary for this transformation (entry 7). The lack of a substitutent on the aniline nitrogen is also crucial, because the corresponding amines with Me and Ph substitutents produced none of the anticipated carbazoles (entries 8 and 9). In conclusion, the "optimal" reaction conditions for this nitrogen-directed vinylic to aryl palladium migration utilizes 5 mol % $Pd(OAc)_2$, 5 mol % *bis*(diphenylphosphino)methane (dppm), and 2 equiv of CsO_2CCMe_3 (CsPiv) in DMF at 100 ^oC.

2. Synthesis of Carbazoles by Nitrogen-directed Vinylic to Aryl Palladium Migration. We next examined the reaction using various internal alkynes in order to determine the scope and limitations of this process. The results are shown in Table 2. Theoretically, when 4,4-dimethyl-2-pentyne was allowed to react with *N*-phenyl-3-iodoaniline, the previously reported consecutive vinylic to aryl to allylic palladium migration could also occur, and a π-allylpalladium complex **I** would be generated as shown in Scheme 2. [5] However, as determined by GC-MS analysis, only the expected carbazole product was found, and a 44% yield of one regioisomer **2a** was isolated (Table 2, entry 2). When 4-octyne was employed as the starting material, the reaction was very messy, and only a 35% yield of the carbazole **3** was obtained (entry 3). In this system, the vinylpalladium intermediate generated from carbopalladation may undergo *β*-H elimination to afford an allene, which may account for the low yield of carbazole in this reaction. To avoid loss of the volatile alkyne (the boiling point of 4,4-dimethylpentyne is only 70 ^oC) or possible *β*-H elimination, 2,2-dimethyl-3-octyne

Scheme 2. Other Possible Palladium Migration Reactions



was prepared and allowed to react with our diarylamine. However, only a 48% yield of the desired product **4a** was isolated (entry 4). 1-Phenyl-1-propyne afforded a 65% yield of two regioisomers **5a** and **5b** in a 12:1 ratio (entry 5). In the case of diphenyl acetylene, the arylpalladium intermediate formed by vinylic to aryl Pd migration might be expected to undergo direct arylation of one of the phenyl groups of the diphenyl acetylene, affording phenylamino-substituted benzylidenefluorenes **II** or **III** (Scheme 2).[2] Surprisingly, a 69% yield of a single isomer **6** was isolated from this reaction (entry 6), and no benzylidenefluorene products were observed. We have also examined the reaction of this aniline with a couple of other aryl acetylenes bearing diverse functionalities on the arene. When 1-(4-nitrophenyl)-1-butyne was employed in our carbazole synthesis, a very messy reaction was observed and none of the desired product was evident by GC-MS analysis (entry 7). However, when a moderate electron-withdrawing ester group (CO_2Et) was present on the phenyl ring of the alkyne, a 71% yield of a single regioisomer **7a** was isolated by flash chromatography (entry 8). Presumably, the improved regioselectivity is due to the fact that

Table 2. Synthesis of Substituted Carbazoles[a]

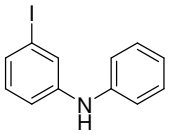
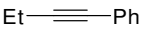
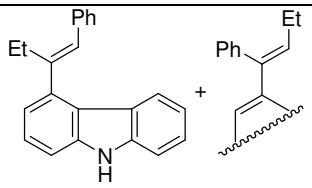
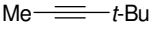
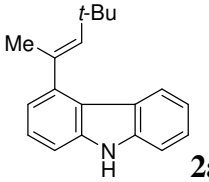
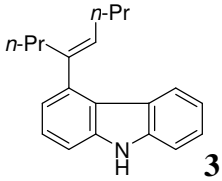
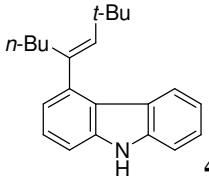
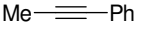
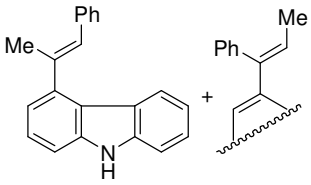
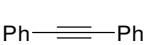
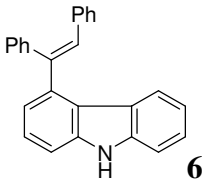
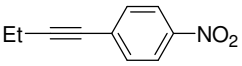
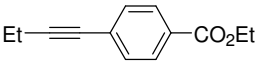
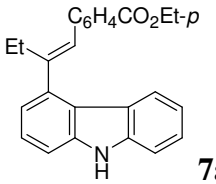
entry	aryl iodide	alkyne	product(s)	% yield (**a**:**b**)[b]
1			 **1a** **1b**	73 (10:1)
2			 **2a**	44
3			 **3**	35[c]
4			 **4a**	48
5			 **5a** **5b**	65 (12:1)
6			 **6**	69
7			-	0
8			 **7a**	71

Table 2. (Continued)

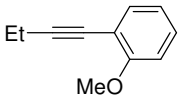
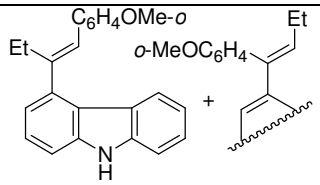
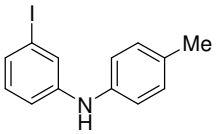
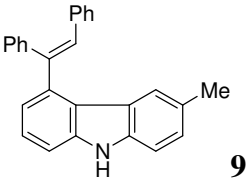
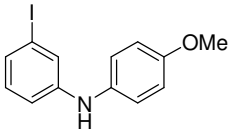
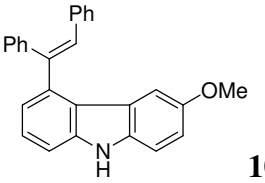
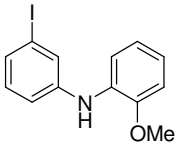
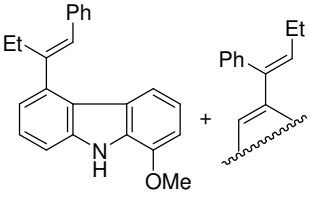
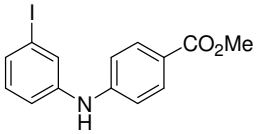
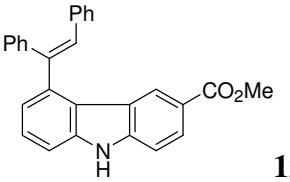
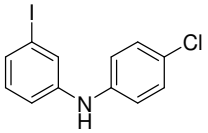
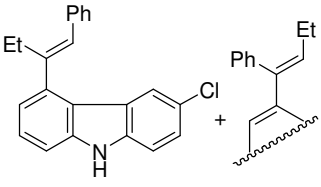
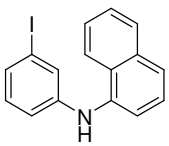
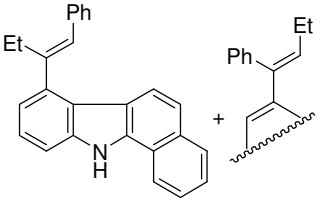
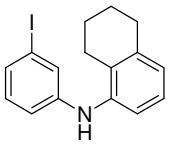
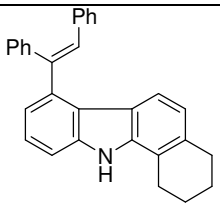
entry	aryl iodide	alkyne	product(s)	% yield (**a**:**b**)[b]
9			 **8a** **8b**	68 (10:1)
10		MeO_2C—≡—Ph	**-**	0
11		Ph—≡—Ph	 **9**	61
12		Ph—≡—Ph	 **10**	75
13		Et—≡—Ph	 **11a** **11b**	77 (10:1)
14		Ph—≡—Ph	 **12**	71
15		Et—≡—Ph	 **13a** **13b**	65 (10:1)
16		Et—≡—Ph	 **14a** **14b**	64 (10:1)

Table 2. (Continued)

entry	aryl iodide	alkyne	product(s)	% yield (**a**:**b**)[b]
17			 **15**	68

[a]All reactions were conducted on a 0.25 mmol scale at 100 °C, using 5 mol % $Pd(OAc)_2$, 5 mol % *bis*(diphenylphosphino)methane (dppm), and 2 equiv of CsO_2CCMe_3 (CsPiv) in DMF (4 mL), and the ratio of aryl iodide to alkyne was 1:1 (sealed vial, under Ar). [b]The ratio of **a** to **b**, as determined by ^{1}H NMR spectroscopy, is reported in parentheses. [c]The isolated products contain impurities, which cannot be separated by flash chromatography, thus the yield has been determined by GC analysis.

the electron-withdrawing group tends to stabilize the vinylpalladium intermediate generated,[9] and thus enhances the regioselectivity of carbopalladation. We can only surmise that the presence of the NO_2 group stabilizes the resulting vinylpalladium intermediate so much that it no longer undergoes palladium migration and side reactions ensue, consuming all starting materials. An analogous alkyne bearing an *ortho*-methoxy group on the arene afforded a 68% yield of the anticipated 10:1 mixture of carbazoles **8a** and **8b**, respectively (entry 9). When methyl phenylpropynoate was employed in this process, after a 24 h reaction, none of the desired carbazole product was evident (entry 10).

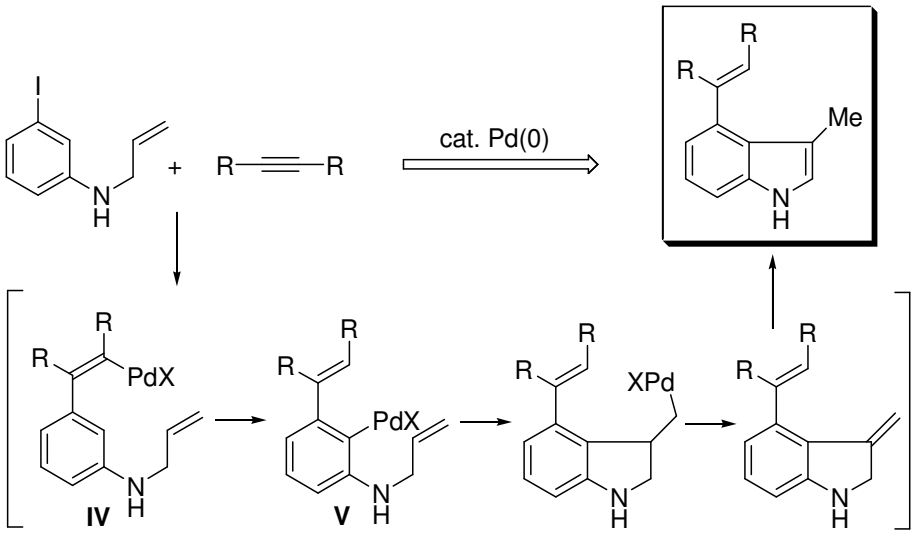
We have also examined the reaction of a number of anilines bearing functionality on the aromatic ring undergoing substitution by the arylpalladium intermediate generated by the vinylic to aryl palladium migration (see the later mechanistic discussion). The reaction of *N*-(4-methylphenyl)-3-iodoaniline and diphenyl acetylene afforded a 61% yield of carbazole **9** (entry 11). A more electron-rich substrate bearing a methoxy group afforded a 75% yield of a single carbazole product **10** (entry 12). The reaction of *N*-(2-methoxyphenyl)-3-iodoaniline and 1-phenyl-1-butyne was also studied (entry 13). Statistically, the methoxy group *ortho* to

the nitrogen would be expected to reduce the opportunities for intramolecular arylation, plus, the favored molecular configuration for the arylpalladium intermediate is expected to be one in which the aromatic ring is perpendicular to the other aromatic ring, which should disfavor intramolecular arylation. However, a 77% yield of a 10:1 mixture of regioisomeric carbazoles was obtained, probably because the oxygen atom of the methoxy group coordinates to the palladium moiety and perhaps stabilizes the arylpalladium intermediate generated. Substrates bearing either an electron-withdrawing 4-methoxycarbonyl or 4-chloro group also afforded a 71% yield of carbazole **12** and a 65% yield of two isomeric carbazoles **13a** and **13b** in a 10:1 ratio, respectively (entries 14 and 15). We have also examined the regioselectivity of ring closure by employing *N*-(3-iodophenyl)naphthalen-1-amine (entry 16). Here, cyclization might occur at either the 2 position or the 8 position of the naphthalene ring. However, the only products observed are those formed by ring closure at the 2 position of the naphthalene by the presumed intermediacy of a 6-membered ring palladacycle, as opposed to the analogous 7-membered ring palladacycle required to generate the product of attack at the 8 position of the naphthalene. A tetrahydronaphthylamine compound was also prepared and allowed to react with diphenyl acetylene, and a 68% yield of carbazole **15** was isolated by flash chromatography (entry 17).

3. Synthesis of Substituted Indoles by Vinylic to Aryl Palladium Migration Followed by Intramolecular Mizoroki-Heck Reaction. The arylpalladium intermediates generated by aryl to aryl palladium migration have been shown to undergo an intermolecular Mizoroki-Heck reaction and a Suzuki-Miyaura reaction,[10] and the arylpalladium species generated from alkyl to aryl palladium migration have also been shown to be easily trapped by an intermolecular Mizoroki-Heck reaction.[4] An arylpalladium species generated from vinylic to

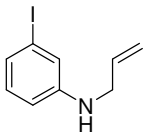
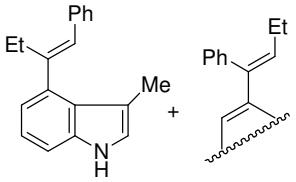
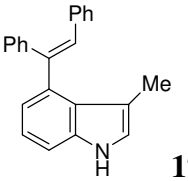
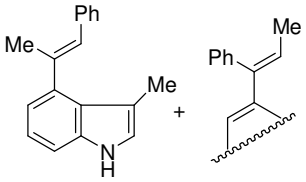
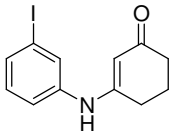
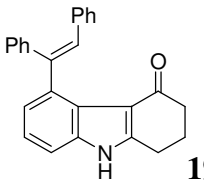
aryl palladium migration has also been trapped by a Stille coupling reaction.[2c] Since the intramolecular Mizoroki-Heck reaction is a very powerful method for C-C bond formation in organic synthesis, and a plethora of natural products and biologically interesting compounds have been synthesized employing this methodology,[11] we were encouraged by our carbazole synthesis to

Scheme 3. Synthesis of Substituted Indoles



examine possible intramolecuar Heck reactions as a trap for the arylpalladium intermediate generated. As shown in Scheme 3, after carbopalladation, vinylpalladium intermediate **IV** is generated. Once the palladium moiety undergoes nitrogen-directed vinylic to aryl migration to afford arylpalladium species **V**, an intramolecular Heck reaction, followed by aromatization, should generate indole derivatives. *N*-Allyl-3-iodoaniline and 1 equiv of 1-phenyl-1-butyne were allowed to react with 5 mol % $Pd(OAc)_2$, 5 mol % dppm, and 2 equiv of CsO_2CCMe_3 in 4 mL DMF at 100 ^oC. After 3 h, the aryl iodide was completely consumed and a 45% yield of two isomeric indoles **16a** and **16b** was obtained in a 10:1 ratio (Table 3, entry 1). Two equiv of *N*-allyl-3-iodoaniline was allowed to react with this alkyne.

Table 3. Synthesis of Substituted Indoles[a]

entry	aryl iodide	alkyne	product	% yield (**a**:**b**)[b]
1			 **16a** **16b**	45 (10:1)
2			 **17**	31
3			 **18a** **18b**	26 (15:1)
4			 **19**	40[c]

[a]These reactions were conducted on a 0.25 mmol scale at 100 °C for 3 h, using 5 mol % $Pd(OAc)_2$, 5 mol % *bis*(diphenylphosphino)methane (dppm), and 2 equiv of CsO_2CCMe_3 (CsPiv) in DMF (4 mL), and the ratio of aryl iodide to alkyne was 1:1 (sealed vial, under Ar). [b]The ratio of **a** to **b**, as determined by ^{1}H NMR spectroscopy, is reported in parentheses. [c]The reaction was conducted at 125 °C, using 10 mol % $Pd(OAc)_2$, 10 mol % *bis*(diphenylphosphino)methane (dppm), and 2 equiv of CsO_2CCMe_3 (CsPiv) in DMF (2 mL) for 24 h.

However, a lower yield was obtained. We have been very reluctant to dramatically change the reaction conditions, because the palladium migration chemistry is generally very sensitive to variations in the reaction conditions, especially the base. However, we did try a few things to optimize the reaction conditions in order to achieve higher yields. The reaction was conducted at both 80 °C and 125 °C, in more concentrated or diluted solutions, in the presence of TBAC or Ag_2CO_3, and using electron-rich ligands, like P(*t*-Bu)$_3$. Unfortunately,

none of our efforts were fruitful. A set of other alkynes and imine starting materials have been screened, and only moderate yields (26-40%) have been obtained (entries 2-4). The major problem in this process is probably the fact that the arylpalladium intermediate generated by oxidative addition, the vinylpalladium intermediate **IV**, and the arylpalladium intermediate **V** can all react with *N*-allyl-3-iodoaniline. Although the desired process is an intramolecular reaction, which should have some advantage over those intermolecular processes, at this time we are unable to get higher yields. An additional complication is that the vinylic to aryl palladium migration is presumably the slow step in this domino process, which leaves plenty of time for side reactions.

4. Synthesis of Substituted Dibenzofurans. After having investigated the nitrogen-directed vinylic to aryl palladium migration, we wondered if we could expand this protocol to the synthesis of substituted dibenzofurans, although Pd-O coordination would be expected to be much weaker than Pd-N coordination. 3-Iodophenyl phenyl ether and 1-phenyl-1-butyne were treated with 5 mol % $Pd(OAc)_2$, 5 mol % dppm, and 2 equiv of CsO_2CCMe_3 in DMF at 100 ^oC, but the reaction was very messy, and only a 30% yield of an 8:1 mixture of two isomeric dibenzofurans **20a** and **20b** was observed by GC-MS analysis (Table 4, entry 1). Previous aryl to aryl palladium migration studies in our group have indicated that palladium tends to reside on the more electron-rich aromatic ring. Thus, we felt that an increase in electron density in the arene undergoing vinylic to aryl palladium migration should facilitate this through-space migration. Indeed, the reaction of 1-iodo-3,5-diphenoxybenzene with 1-phenyl-1-butyne afforded a 75% yield of a 9:1 mixture of two regioisomeric dibenzofurans **21a** and **21b** (entry 2). The increased reaction efficiency could be a result of the increased electron density of the arene favoring Pd migration. However, this process may also be more

Table 4. Synthesis of Substituted Dibenzofurans[a]

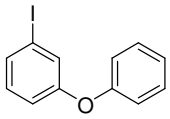
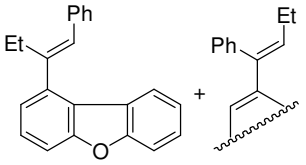
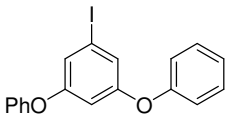
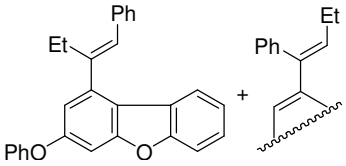
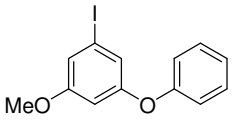
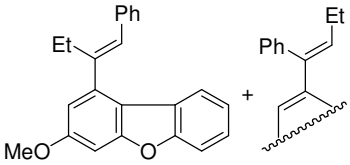
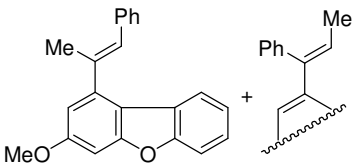
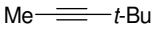
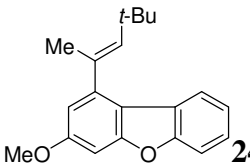
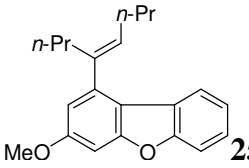
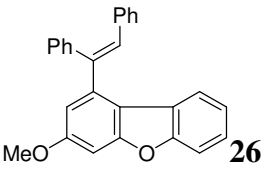
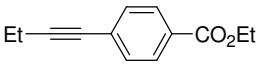
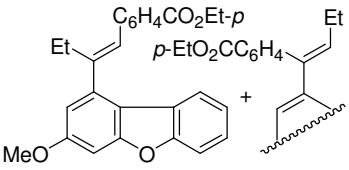
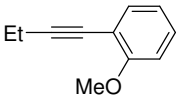
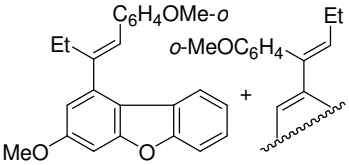
entry	aryl iodide	alkyne	product(s)	% yield (**a**:**b**)[b]
1			 **20a** **20b**	30
2			 **21a** **21b**	75 (9:1)
3			 **22a** **22b**	80 (9:1)
4			 **23a** **23b**	78 (9:1)
5			 **24a**	42
6			 **25**	44

Table 4. (Continued)

entry	aryl iodide	alkyne	product(s)	% yield (**a**:**b**)[b]
7			 **26**	76
8			 **27a** **27b**	60 (15:1)
9			 **28a** **28b**	37 (7:1)

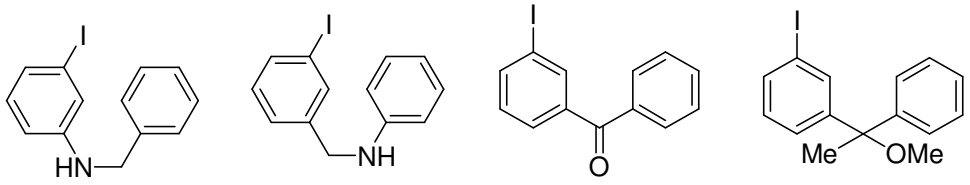
[a]All reactions were conducted on a 0.25 mmol scale at 100 °C for 12 h, using 5 mol % $Pd(OAc)_2$, 5 mol % *bis*(diphenylphosphino)methane (dppm), and 2 equiv of CsO_2CCMe_3 (CsPiv) in DMF (4 mL), and the ratio of aryl iodide to alkyne was 1:1 (sealed vial, under Ar). [b]The ratio of **a** to **b**, as determined by ^{1}H NMR spectroscopy, is reported in parentheses.

efficient, because migration to either of the two *ortho* positions of the arene is now possible, doubling the probability of intramolecular arylation. To further examine the effect of an electron-rich substituent, 3-iodo-5-phenoxyanisole was prepared and allowed to react with 1-phenyl-1-butyne. A 78% yield of two isomeric dibenzofurans **22a** and **22b** was obtained (entry 3), which clearly suggests that an increase in the electron-density of the arene is the major reason for the improved reaction efficiency. Several other internal alkynes have been allowed to react with this iodoarene, and moderate to excellent yields have generally been obtained. 1-Phenyl-1-propyne afforded a 78% yield of two regioisomers **23a** and **23b** in a 9:1 ratio (entry 4). 4,4-Dimethyl-2-pentyne afforded a 42% yield of a single regioisomer **24**,

as expected (entry 5). 4-Octyne afforded a 44% yield of dibenzofuran **25** (entry 6). When employing diphenyl acetylene, a 76% yield of a single isomer **26** was obtained (entry 7). When methyl 4-(but-1-ynyl)benzoate was employed in this reaction, a 60% yield of two isomeric dibenzofurans **27a** and **27b** was obtained in a 15:1 ratio (entry 8). An analogous alkyne bearing an *ortho*-methoxy group afforded a 37% yield of a 7:1 mixture of dibenzofuran products **28a** and **28b** (entry 9).

To further extend this protocol to the synthesis of other heteroatom-containing rings, we also prepared several heteroatom-containing aryl iodides as shown in Chart 1. The reactions of aryl iodides **29** and **30** with 1-phenyl-1-butyne were very messy and the anticipated dihydrophenanthridines were not evident by GC-MS. An electron-poor aryl iodide **31** was also allowed to react with 1-phenyl-1-butyne. However, the reaction was sluggish, and, after 24 h, none of the desired fluoren-9-one product was generated. In the case of the moderately electron-rich ring system **32**, none of the expected palladium migration product was observed.

Chart 1. Other Heteroatom-containing Aryl Iodides

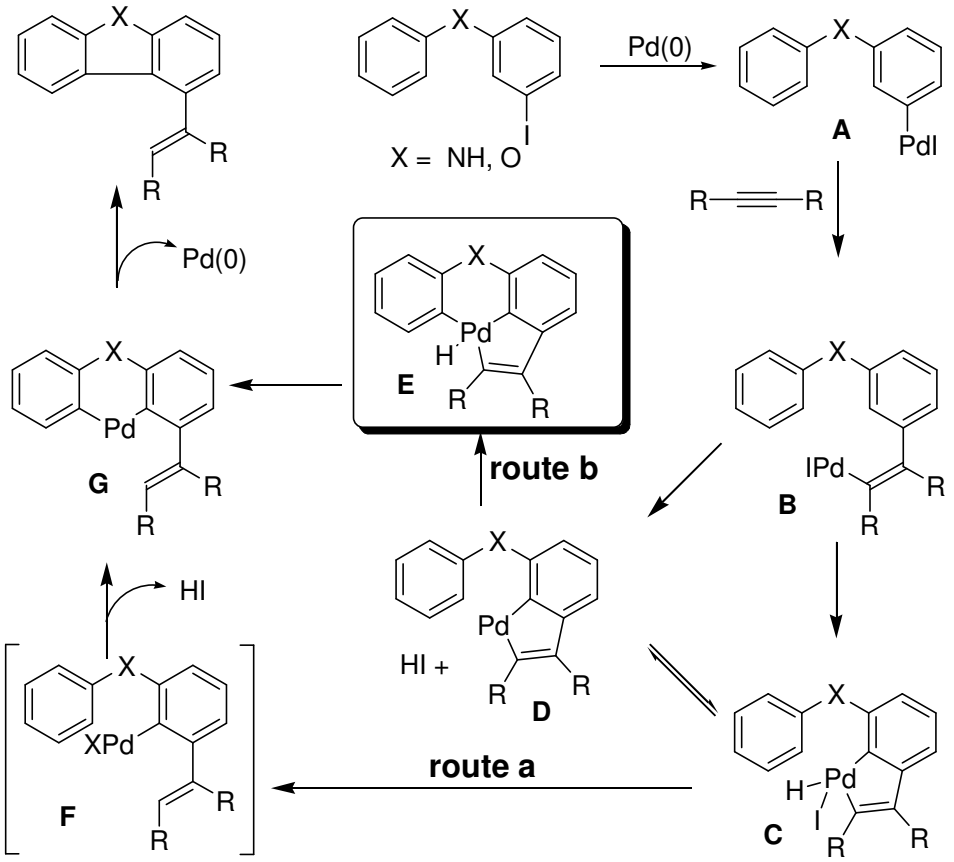


29 **30** **31** **32**

5. Mechanism. A plausible mechanism for this palladium rearrangement is proposed in Scheme 4. Intermediate **A** is first generated by oxidative addition of the aryl iodide to Pd(0). Subsequent intermolecular carbopalladation would be expected to afford intermediate **B**. The resulting vinylic palladium intermediate **B** might then undergo palladium migration from the

vinylic position to an aryl position to generate intermediate **F**, possibly through an organopalladium(IV) hydride **C** (route a), although such Pd(IV)hydride intermediates have not previously been reported.[12] An equilibrium between organopalladium(IV) hydride **C** and organopalladium(II) intermediate **D** is also possible, although palladacycle **D** could also be generated directly from intermediate **B**. Intermediate **F** eventually undergoes either palladium insertion into the C-H bond of the neighboring arene or electrophilic aromatic substitution to afford the six-membered ring palladacycle **G**. Alternatively, intermediate **D** can undergo intramolecular C-H activation to generate an interesting organopalladium(IV)

Scheme 4. Proposed Mechanism

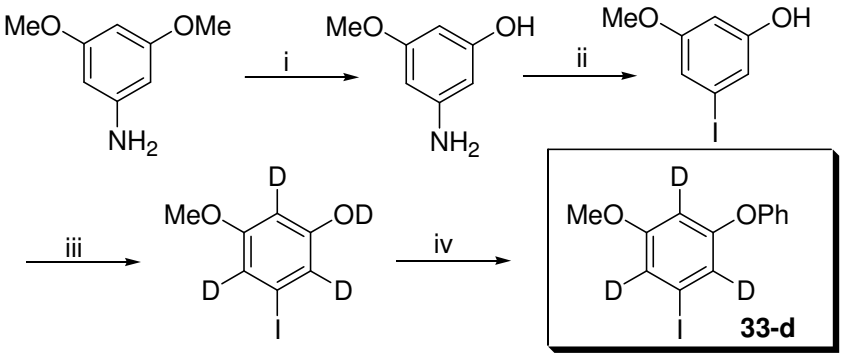


hydride **E**; subsequent reductive elimination could also generate intermediate **G** (route b). When R is a phenyl group, the palladium moiety can migrate to either of two *ortho* positions

of the arene originally bearing the iodo group and then be trapped by arylation to generate either the observed carbazole (dibenzofuran) or a fluorene. While we have previously reported such a fluorene synthesis,[2] only the carbazole (dibenzofuran) products are observed, which suggests that the palladium only migrates to the position *ortho* to the heteroatom. This interesting selectivity may be due to coordination between the *ortho* heteroatom and the palladium moiety, which is not available if the palladium migrates to the position *para* to the heteroatom. Alternatively, the palladium may prefer the position *ortho* to the heteroatom due to stabilization of the arylpalladium intermediate by inductive electron withdrawal, as suggested by recent results in our laboratories, which are supported by calculations.[10]

6. Deuterium Labeling Experiments. In order to clarify the ambiguities in the mechanism, we prepared the deuterium labeled starting material **33-d** (90% deuterium incorporation in each position of the arene, as shown in Scheme 5)[13] and allowed this compound to react with diphenyl acetylene under our usual palladium migration conditions. According to the proposed mechanism shown in Scheme 6, if the reaction

Scheme 5. Synthesis of Deuterated Compound **33-d**

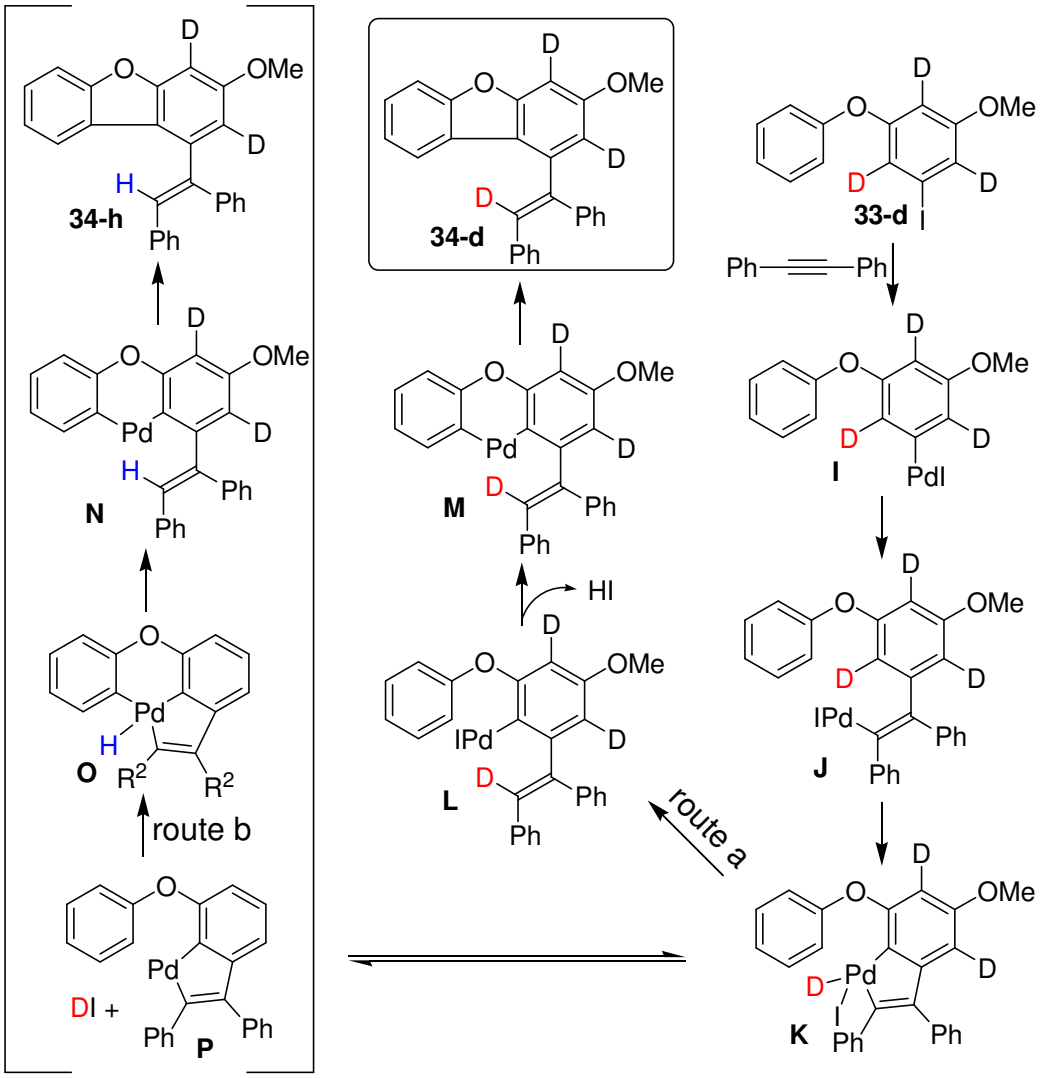


(i) NaSMe, DMA, 140 °C (ii) (a) $NaNO_2$, HCl (b) KI; (iii) CF_3CO_2D, reflux; (iv) 4 CsF,1.1 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, MeCN.

only proceeds through route a, the deuterium originally *ortho* to the oxygen atom and the iodine atom will shift to the vinylic position after the vinylic to aryl palladium migration.

Thus, we should obtain dibenzofuran **34-d**. On the other hand, if this reaction only goes through the mechanism described in route b, product **34-h** should be obtained. Indeed, an 80% yield of dibenzofuran **34-d** was isolated by flash chromatography, with 70% deuterium incorporation in the vinylic position (determined by ^{1}H NMR spectroscopy). This result clearly suggests the involvement of route a. The loss of deuterium could be due to H-D exchange through an equilibrium between palladacycle **K** and palladacycle **P** or the direct H-

Scheme 6. Deuterium Labeling Experiment



D exchange between intermediate **K** and an H source in the reaction solution. Alternatively, it could be due to the involvement of route b, because the aryl deuterium presumably would be washed out upon formation of intermediate **P**. To address these issues, we conducted the same reaction in the presence of 10 equiv of D_2O, and 85% deuterium incorporation was observed in the vinylic position of the isolated dibenzofuran product **34-d**, which suggests that the previous deuterium loss is probably the result of H-D exchange in intermediate **K**, instead of the alternative mechanistic route b.

Conclusions

In conclusion, we have established the scope and limitations of a mechanistically important palladium migration process, which affords an efficient way to prepare biologically interesting carbazoles, indoles and dibenzofurans. The advantage of this chemistry is that an alkenyl substituent can be efficiently incorporated into the heterocyclic ring during the course of the cyclization, which can be still further modified to other functional groups. This reaction is quite general for the synthesis of carbazoles, but only moderate yields can be obtained in the synthesis of indoles, and excellent yields can be achieved in the synthesis of dibenzofurans only if electron-rich aryl iodides are employed. The relatively modest regiochemistry of alkyne insertion also presents problems. The results of deuterium labeling experiments showed a high degree of deuterium incorporation in the vinylic position of the dibenzofuran product obtained, affording convincing evidence for the proposed palladium migration mechanism. The H-D exchange also suggests that the migration process involves an equilibrium between Pd(II) and Pd(IV) intermediates, which is consistent with a previously reported consecutive vinylic to aryl to allylic palladium migration[5] and does not favor the direct Pd-H shift mechanism reported elsewhere.[2d]

Experimental Section

I. General Procedures.

All ^{1}H and ^{13}C NMR spectra were collected in $CDCl_3$ unless noted otherwise. Thin layer chromatography was performed using 60-mesh silica gel plates, and visualization was affected using short wavelength UV light (254 nm) and a basic $KMnO_4$ solution. All high resolution mass spectra were recorded using EI.

All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of acetonitrile, DMF, diethyl ether, ethyl acetate, hexanes, and 4,4-dimethyl-2-pentyne were purchased from Lancaster Synthesis, Inc. 3-Iodoaniline, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, cesium fluoride, 1,3-diiodobenzene, 1,1'-bis(diphenylphosphino)ferrocene (dppf), sodium *tert*-butoxide, *p*-toluidine, *p*-anisidine, *p*-chloroaniline, *o*-methoxyaniline, methyl 4-aminobenzoate, 1-naphthylamine, 5,6,7,8-tetrahydronaphthalen-1-ylamine, 1-phenyl-1-butyne, 1-phenyl-1-propyne, 4-octyne, diphenyl acetylene, 3,5-dimethoxyaniline, sodium thiomethoxide, and trifluoroacetic acid-*d* were purchased from Aldrich Chemical Co., Inc. Cesium pivalate was prepared according to the procedure of Campo and Larock.[14] The substituted alkynes were prepared by the Sonogashira coupling of aryl iodides with 1-butyne using 5 mol % of $PdCl_2(PPh_3)_2$, 2 mol % of CuI in Et_3N solvent at room temperature.[15]

II. Noncommercial compounds.

***N*-Phenyl-3-iodoaniline**.

This compound was prepared according to the reported procedure.[16] ^{1}H NMR ($CDCl_3$) δ 5.67 (s, 1H), 6.94-7.10 (m, 5H), 7.23-7.41 (m, 4H); ^{13}C NMR ($CDCl_3$) 95.2, 116.5, 119.1,

122.3, 125.9, 129.7, 129.8, 131.1, 142.2, 145.1; IR ($CDCl_3$) 3427, 3061, 3034, 1584 cm^{-1}; HRMS m/z 294.9858 (calcd for $C_{12}H_{10}NI$, 294.9863).

Other aniline starting materials were prepared through a palladium-catalyzed amination reaction.[17] The typical yield is ~30%.

***N*-*p*-Tolyl-3-iodoaniline**.

^1H NMR ($CDCl_3$) δ 2.34 (s, 3H), 5.58 (s, 1H), 6.93-7.26 (m, 7H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$) 21.1, 95.3, 115.7, 120.2, 124.9, 129.0, 130.3, 131.0, 132.3, 139.3, 145.9; IR ($CDCl_3$) 3427, 3028, 2922, 1587 cm^{-1}; HRMS m/z 309.0018 (calcd for $C_{13}H_9IN$, 309.0015).

***N*-(2-Methoxyphenyl)-3-iodoaniline**.

^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.15 (s, 1H), 6.92-7.01 (m, 4H), 7.09-7.12 (m, 1H), 7.26-7.35 (m, 2 H), 7.51 (t, *J* = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 55.9, 95.2, 111.0, 116.2, 117.2, 121.1, 121.3, 126.5, 129.9, 131.0, 131.9, 144.7, 149.0; IR ($CDCl_3$) 3418, 3060, 2962, 1244 cm^{-1}; HRMS m/z 324.9969 (calcd for $C_{13}H_9INO$, 324.9964).

***N*-(4-Methoxyphenyl)-3-iodoaniline**.

^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.51 (s, 1H), 6.82-7.23 (m, 8H); ^{13}C NMR ($CDCl_3$) 55.9, 95.5, 114.7, 115.1, 123.5, 123.9, 128.3, 131.1, 134.7, 147.1, 156.1; IR ($CDCl_3$) 3425, 3006, 2957, 1245 cm^{-1}; HRMS m/z 324.9967 (calcd for $C_{13}H_9INO$, 324.9964).

Methyl *N*-(3-iodophenylamino)benzoate.

^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.10 (s, 1H), 6.98-7.13 (m, 4H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 52.1, 95.0, 115.6, 119.1, 122.2, 128.6, 131.1, 131.8, 131.9, 142.7, 147.3, 167.1; IR ($CDCl_3$) 3340, 2945, 1694, 1580 cm^{-1}; HRMS m/z 352.9913 (calcd for $C_{14}H_{12}INO_2$, 352.9918).

***N*-(4-Chlorophenyl)-3-iodoaniline**.

^{1}H NMR ($CDCl_3$) δ 5.64 (s, 1H), 6.96-7.00 (m, 4H), 7.23-7.28 (m, 3H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$) 95.3, 116.8, 120.1, 126.1, 126.8, 129.7, 130.2, 131.2, 140.9, 144.6; IR ($CDCl_3$) 3427, 3061, 3034, 1583 cm^{-1}; HRMS m/z 328.9473 (calcd for $C_{12}H_9ClIN$, 328.9468).

***N*-(3-Iodophenyl)naphthalen-1-amine**.

^{1}H NMR ($CDCl_3$) δ 5.83 (s, 1H), 6.85-6.97 (m, 2H), 7.21 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.30 (t, *J* = 1.9 Hz, 1H), 7.37-7.56 (m, 4H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.88-8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) 95.2, 115.9, 118.2, 122.1, 124.5, 125.3, 126.2, 126.6, 128.6, 128.8, 129.1, 131.0, 134.9, 137.7, 146.9; IR ($CDCl_3$) 3415, 3060, 1574 cm^{-1}; HRMS m/z 345.0018 (calcd for $C_{18}H_{12}IN$, 345.0015).

***N*-(3-Iodophenyl)-5,6,7,8-tetrahydronaphthalen-1-amine**.

^{1}H NMR ($CDCl_3$) δ 1.79-1.90 (m, 4H), 2.60 (t, *J* = 6.1 Hz, 2H), 2.84 (t, *J* = 6.1 Hz, 2H), 5.31 (s, 1H), 6.87-6.90 (m, 2H), 6.96 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 4.3 Hz, 2H), 7.20-7.22 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$) 23.0, 23.3, 25.0, 30.2, 95.3, 116.1, 117.6, 124.4, 125.5, 126.1, 128.9, 129.0, 131.0, 139.1, 140.0, 146.1; IR ($CDCl_3$) 3396, 3054, 2927, 1578 cm^{-1}; HRMS m/z 349.0331 (calcd for $C_{16}H_{16}IN$, 349.0328).

***N*-Allyl-3-iodoaniline**.

This compound was prepared according to the reported procedure.[18] ^{1}H NMR ($CDCl_3$) δ 3.74 (d, *J* = 5.1 Hz, 2H), 3.81 (s, 1H), 5.19-5.33 (m, 2H), 5.87-5.99 (m, 1H), 6.57 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.89 (t, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 1.6 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 46.5, 95.6, 112.5, 116.9, 121.7, 126.6, 130.9, 135.0, 149.5; IR ($CDCl_3$) 3417, 3076, 2847, 1590 cm^{-1}; HRMS m/z 258.9862 (calcd for $C_9H_{10}NI$, 258.9858).

3-(3-Iodophenylamino)cyclohex-2-enone.

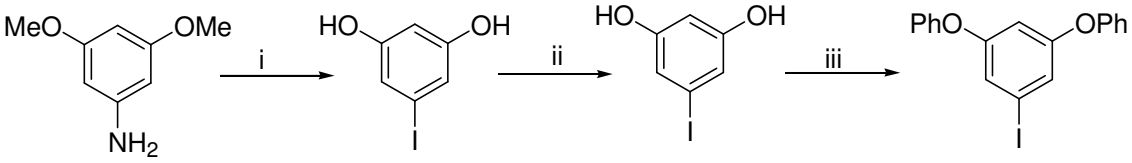
3-Iodoaniline (2 mmol) and cyclohexane-1,3-dione (2 mmol) were dissolved in 10 mL of toluene and then the mixture was heated at 100 °C in the presence of 8 mmol of anhydrous $MgSO_4$ and a catalytic amount of TsOH. After 12 h, the reaction mixture was filtered, and the toluene was removed from the filtrate. The residue obtained was purified by flash chromatography to afford a 90% yield of the imine product: ^{1}H NMR ($CDCl_3$) δ 1.96-2.02 (m, 2H), 2.32 (t, *J* = 6.2 Hz, 2H), 2.50 (t, *J* = 6.2 Hz, 2H), 5.51 (s, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.40-7.48 (m, 3H); ^{13}C NMR ($CDCl_3$) 22.0, 29.8, 36.7, 123.3, 130.9, 132.8, 134.6, 139.8, 162.8, 198.9; IR ($CDCl_3$) 3247, 3056, 2945, 1566 cm^{-1}; HRMS m/z 312.9968 (calcd for $C_{12}H_{12}INO$, 312.9964).

1-Iodo-3-(phenoxy)benzene.

This compound was prepared by the reported procedure.[19] ^{1}H NMR ($CDCl_3$) δ 6.96-7.07 (m, 4H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.35-7.44 (m, 4H); ^{13}C NMR ($CDCl_3$) 94.5, 118.2, 119.5, 124.2, 127.8, 130.2, 131.3, 132.4, 156.6, 158.3; IR ($CDCl_3$) 3075, 2965, 1582 cm^{-1}; HRMS m/z 295.9702 (calcd for $C_{12}H_9IO$, 295.9698).

Iodo-3,5-diphenoxybenzene.

This compound was prepared by the sequence shown below:

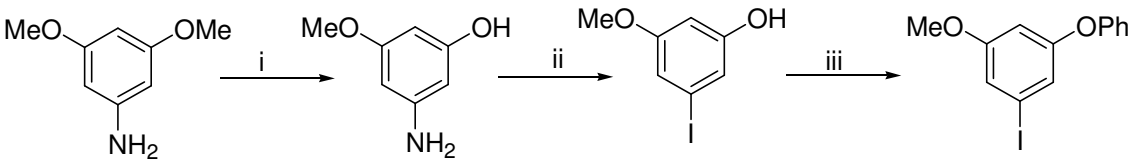


(i) (a) $NaNO_2$, HCl (b) KI; (ii) BBr_3; (iii) 6 CsF, 2.2 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, MeCN.

^{1}H NMR ($CDCl_3$) δ 6.63 (t, *J* = 2.2 Hz, 1H), 7.02-7.04 (m, 6H), 7.13-7.17 (m, 2H), 7.35-7.39 (m, 4H); ^{13}C NMR ($CDCl_3$) 94.1, 108.7, 119.8, 122.0, 124.5, 130.2, 156.1, 159.4; IR ($CDCl_3$) 3073, 3039, 1575 cm^{-1}; HRMS m/z 387.9964 (calcd for $C_{18}H_{13}IO_2$, 387.9960).

1-Iodo-3-methoxy-5-(phenoxy)benzene.

This compound was prepared by the sequence shown below.[13] ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 6.57 (t, *J* = 2.2 Hz, 1H), 6.97 (t, *J* = 1.5 Hz, 1H), 7.03-7.09 (m, 3H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.36-7.42 (m, 2H); ^{13}C NMR ($CDCl_3$) 55.9, 94.4, 104.9, 118.3, 119.8, 120.2, 124.3, 130.2, 156.4, 159.3, 161.5; IR ($CDCl_3$) 3074, 2960, 1586 cm^{-1}; HRMS m/z 325.9808 (calcd for $C_{13}H_{11}IO_2$, 325.9804).



(i) NaSMe, DMA, 140 °C; (ii) (a) $NaNO_2$, HCl; (b) KI; (iii) 4 CsF, 1.1 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, MeCN.

Compound **29-d**: ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 6.52 (s, 0.08H), 6.92 (s, 0.11H), 6.99-7.04 (m, 2H), 7.15 (t, *J* = 7.32 Hz, 1H), 7.34-7.39 (m, 2H).

III. Experimental Procedures.

The aryl halide (0.25 mmol), alkyne (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), *bis*(diphenylphosphino)methane (dppm) (4.8 mg, 0.0125 mmol) and CsO_2CCMe_3 (CsPiv) (0.117 g, 0.5 mmol) in 4 mL of DMF were stirred under Ar at 100 °C for 6 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (25 mL) and washed with 5% Na_2CO_3 (25 mL). The aqueous layer was re-extracted with diethyl ether (25 mL) twice. The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel.

For the products reported in entries 1, 5, 9, 13, 15 and 16 of Table 2; entry 1 in Table 3; and entries 2-4, 8, and 9 in Table 3, GC-mass spectral analysis shows two regioisomers,

which cannot be separated by flash chromatography. The ratio of these isomers was determined by ^{1}H NMR spectroscopy.

(*E*)-4-(1-Phenylbut-1-enyl)-9*H*-carbazole (1a).

^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.4 Hz, 3H), 2.94 (q, *J* = 7.4 Hz, 2H), 6.74 (s, 1H), 7.11-7.20 (m, 2H), 7.35-7.53 (m, 9H), 8.05 (s, 1H), 8.20 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 25.9, 109.4, 110.7, 119.6, 120.2, 120.9, 123.0, 123.3, 125.7, 125.8, 126.9, 128.7, 128.9, 129.0, 138.2, 139.9, 139.9, 140.1, 144.6; IR ($CDCl_3$) 3471, 3056, 2968, 2934, 1599 cm^{-1}; HRMS m/z 297.1522 (calcd for $C_{22}H_{19}N$, 297.1518).

(*E*)-4-(4,4-Dimethylpent-2-en-2-yl)-9*H*-carbazole (2).

^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 2.28 (d, *J* = 1.3 Hz, 3H), 5.67 (d, *J* = 1.4 Hz, 1H), 6.96 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.19-7.42 (m, 5H), 8.06 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 19.2, 31.2, 33.1, 108.8, 110.6, 119.4, 119.7, 120.2, 123.0, 123.2, 125.6, 125.9, 134.8, 139.6, 139.8, 139.9, 143.3; IR ($CDCl_3$) 3473, 2960, 2867, 1600 cm^{-1}; HRMS m/z 263.1679 (calcd for $C_{19}H_{21}N$, 263.1674).

4-[1-(2,2-Dimethylpropylidene)pentyl]-9*H*-carbazole (4a).

^{1}H NMR ($CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 1.22-1.40 (m, 13H), 2.71-2.78 (m, 2H), 5.62 (s, 1H), 6.97 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.19-7.42 (m, 5H), 8.01 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) 14.2, 23.4, 31.4, 31.7, 32.4, 33.2, 108.7, 110.6, 119.3, 120.5, 120.7, 123.2, 123.4, 125.5, 139.3, 139.8, 139.9, 140.1, 141.9; IR ($CDCl_3$) 3410, 2957, 2866, 1599 cm^{-1}; HRMS m/z 305.2148 (calcd for $C_{22}H_{27}N$, 305.2144).

(*E*)-4-(1-Phenylprop-1-enyl)-9*H*-carbazole (5a).

^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 6.78 (s, 1H), 7.12-7.20 (m, 2H), 7.33-7.54 (m, 9H), 8.10 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 19.9, 109.4, 110.7, 119.4, 119.6, 120.2,

122.9, 123.1, 125.8, 125.9, 126.8, 128.6, 129.3, 129.4, 138.3 (2C), 139.9, 140.1, 141.4; IR ($CDCl_3$) 3471, 3060, 3026, 1601, 1456 cm^{-1}; HRMS m/z 283.1367 (calcd for $C_{18}H_{19}N$, 283.1361).

(*E*)-4-(1,2-Diphenylvinyl)-9*H*-carbazole (6).

^1H NMR ($CDCl_3$) δ 7.03-7.14 (m, 3H), 7.23-7.42 (m, 14H), 8.03 (s, 1H), 8.37 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) 109.8, 110.8, 119.6, 121.3, 121.7, 123.0, 123.39, 125.7, 125.9, 127.3, 127.7, 128.5, 128.7, 129.8, 130.2, 131.1, 137.6, 140.0, 140.3, 140.4, 140.7, 141.3; IR ($CDCl_3$) 3414, 3054, 1599, 1455 cm^{-1}; HRMS m/z 345.1522 (calcd for $C_{26}H_{19}N$, 345.1518).

(*E*)-Ethyl 4-[1-(9*H*-carbazol-4-yl)but-1-enyl]benzoate (7a).

^1H NMR ($CDCl_3$) δ 1.90 (t, *J* = 7.5 Hz, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.91 (q, *J* = 7.5 Hz, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 6.73 (s, 1H), 7.10 (dd, *J* = 6.7, 1.7 Hz, 1H), 7.15 (td, *J* = 6.8, 1.5 Hz, 1H), 7.37-7.46 (m, 4H), 7.53 (d, *J* = 8.1 Hz, 2H), 8.10-8.20 (m, 4H); ^{13}C NMR ($CDCl_3$) 13.3, 14.6, 26.0, 6.19, 109.6, 110. 8, 119.6, 119.9, 120.8, 122.8, 123.1, 125.6, 125.8, 128.2, 128.8, 128.9, 130.0, 139.4, 139.9, 140.1, 142.8, 146.7, 166.8; IR ($CDCl_3$) 3472, 2968, 2873, 1710 cm^{-1}; HRMS m/z 369.1736 (calcd for $C_{25}H_{23}NO_2$, 369.1729).

(*E*)-4-[1-(2-Methoxyphenyl)but-1-enyl]-9*H*-carbazole (8a).

^1H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 3H), 2.80 (q, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 6.77 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.97-7.17 (m, 3H), 7.29-7.53 (m, 6H), 8.11 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 26.1, 55.5, 109.1, 110.5, 110.8, 118.3, 119.3, 120.2, 120.4, 121.2, 123.5, 124.7, 125.5, 125.6, 127.3, 128.3, 130.1, 139.9, 140.1, 144.0, 157.8; IR ($CDCl_3$) 3472, 2966, 2934, 1245 cm^{-1}; HRMS m/z 327.1628 (calcd for $C_{23}H_{21}NO$, 327.1623).

(*E*)-5-(1,2-Diphenylvinyl)-3-methyl-9*H*-carbazole (9).

^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 7.02-7.05 (m, 2H), 7.20-7.40 (m, 14H), 7.95 (s, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) 21.8, 109.8, 110.4, 121.3, 121.6, 123.1, 123.5, 125.5, 127.2, 127.2, 127.6, 128.5, 128.5, 128.6, 129.7, 130.3, 131.1, 137.8, 138.2, 140.2, 140.5, 140.7, 141.4; IR ($CDCl_3$) 3413, 3053, 3022, 1599, 1491 cm^{-1}; HRMS m/z 359.1678 (calcd for $C_{27}H_{21}N$, 359.1674).

(*E*)-5-(1,2-Diphenylvinyl)-3-methoxy-9*H*-carbazole (10).

^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H), 7.02-7.07 (m, 3H), 7.22-7.42 (m, 13H), 7.81 (d, *J* = 2.5 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$) 55.8, 105.2, 110.1, 111.5, 115.8, 121.5, 121.6, 123.6, 125.6, 127.3, 127.8, 128.7, 129.7, 130.3, 131.3, 134.8, 137.7, 140.1, 140.5, 141.1 (2C), 153.5; IR ($CDCl_3$) 3415, 3054, 2949, 1582, 1478 cm^{-1}; HRMS m/z 375.1629 (calcd for $C_{27}H_{21}NO$, 375.1623).

(*E*)-5-(1-Benzylidenepropyl)-1-methoxy-9*H*-carbazole (11a).

^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J* = 7.5 Hz, 3H), 2.91 (q, *J* = 7.5 Hz, 2H), 4.0 (s, 3H), 6.7 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.06-7.10 (m, 2H), 7.30-7.50 (m, 7H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 25.9, 55.8, 105.8, 109.7, 115.6, 119.7, 120.0, 124.2, 125.5, 126.8, 128.6, 128.9, 129.0, 130.3, 138.2, 139.8, 139.9, 144.5, 145.8; IR ($CDCl_3$) 3421, 2964, 2932, 1598 cm^{-1}; HRMS m/z 327.1625 (calcd for $C_{23}H_{21}NO$, 327.1623).

(*E*)-Methyl 5-(1,2-diphenylvinyl)-9*H*-carbazole-3-carboxylate (12).

^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 7.03 (s, 1H), 7.09 (t, *J* = 4.2 Hz, 1H), 7.20-7.42 (m, 13H), 8.07 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.41 (s, 1H), 9.00 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 51.9, 110.1, 110.2, 121.4, 121.6, 122.6, 122.9, 125.6, 126.4, 127.2, 127.5, 127.7, 128.3, 128.5, 129.8, 130.4, 131.5, 137.5, 140.0, 140.5, 140.7, 140.9, 142.7, 167.9; IR ($CDCl_3$) 3323, 3021, 2947, 1691 cm^{-1}; HRMS m/z 403.1578 (calcd for $C_{28}H_{21}NO_2$, 403.1572)

(*E*)-3-Chloro-5-(1-phenylbut-1-enyl)-9*H*-carbazole (13a).

^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.5 Hz, 3H), 2.91 (q, *J* = 7.5 Hz, 2H), 6.73 (s, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.29-7.52 (m, 10H), 8.08 (s, 1H), 8.19 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 25.7, 109.6, 111.7, 120.5, 122.6, 124.5, 124.9, 125.9, 126.4, 127.1, 128.8, 129.2, 129.7, 137.9, 138.2, 140.0, 140.6, 144.0; IR ($CDCl_3$) 3471, 2944, 2833 cm^{-1}; HRMS m/z 331.1132 (calcd for $C_{22}H_{18}NCl$, 331.1128).

(*E*)-7-(1-Phenylbut-1-enyl)-11*H*-benzo[*a*]carbazole (14a).

^{1}H NMR ($CDCl_3$) δ 1.10 (t, *J* = 7.6 Hz, 3H), 2.95 (q, *J* = 7.6 Hz, 2H), 6.75 (s, 1H), 7.16 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.26-7.60 (m, 10H), 7.98 (d, *J* = 7.5 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 26.1, 109.8, 118.5, 120.1, 120.6 (2C), 121.1, 121.8, 121.9, 124.7, 125.5, 125.7, 126.9, 128.7, 129.0, 129.1 (2C), 132.3, 135.3, 138.2, 139.1, 139.3, 144.5; IR ($CDCl_3$) 3472, 3060, 2969, 1572 cm^{-1}; HRMS m/z 347.1682 (calcd for $C_{26}H_{21}N$, 347.1674).

(*E*)-7-(1,2-Diphenylvinyl)-2,3,4,11-tetrahydro-1*H*-benzo[*a*]carbazole (15).

^{1}H NMR ($CDCl_3$) δ 1.91-2.03 (m, 4H), 2.93 (m, 4H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.07 (s, 1H), 7.23-7.40 (m, 12H), 8.01 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 23.1, 13.6, 24.6, 29.9, 109.8, 119.1, 120.0, 120.4, 121.2, 121.6, 122.0, 124.9, 127.2, 127.6, 128.4, 128.6, 129.8, 130.2, 131.0, 134.9, 137.7, 139.1, 139.9, 140.2, 140.8, 141.3; IR ($CDCl_3$) 3434, 3053, 2929, 1601 cm^{-1}; HRMS m/z 399.1993 (calcd for $C_{30}H_{25}N$, 399.1987).

(*E*)-3-Methyl-4-(1-phenylbut-1-en-2-yl)-*1H*-indole (16a).

^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.2 Hz, 3H), 2.36 (s, 3H), 2.77 (q, *J* = 7.2 Hz, 2H), 6.47 (s, 1H), 6.96-6.99 (m, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.27-7.32 (m, 2H), 7.41 (d, *J* = 4.1 Hz, 4H),

7.93 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.2, 13.4, 27.1, 110.0, 112.5, 119.7, 121.7, 122.9, 125.6, 126.6, 128.5, 128.9, 129.0, 137.3, 137.9, 138.4, 144.4; IR ($CDCl_3$) 3418, 3021, 2964, 1598 cm^{-1}; HRMS m/z 261.1518 (calcd for $C_{19}H_{19}N$, 261.1521).

(*E*)-4-(1,2-Diphenylvinyl)-3-methyl-1*H*-indole (17).

^{1}H NMR ($CDCl_3$) δ 2.24 (d, *J* = 0.8 Hz, 3H), 6.68 (s, 1H), 6.89 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.99 (d, *J* = 1.0 Hz, 1H), 7.11-7.32 (m, 12H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.7, 110.4, 112.8, 121.7, 121.8, 123.2, 126.8, 127.3, 128.3 (2C), 128.4, 129.6, 130.5, 137.6, 137.9, 138.1, 141.3, 141.4; IR ($CDCl_3$) 3422, 3053, 3021, 1695 cm^{-1}; HRMS m/z 309.1522 (calcd for $C_{23}H_{19}N$, 309.1518).

(*E*)-3-Methyl-4-(1-methyl-2-phenylvinyl)-1*H*-indole (18a).

^{1}H NMR ($CDCl_3$) δ 2.34-2.35 (m, 6H), 6.51 (d, *J* = 1.0 Hz, 1H), 6.96-6.99 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.26-7.31 (m, 3H), 7.39-7.43 (m, 4H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$) 12.8, 21.8, 110.1, 112.4, 119.1, 121.9, 122.8, 126.5, 128.4, 129.2, 129.4, 137.3, 138.5 (2C), 139.8; IR ($CDCl_3$) 3416, 3051, 2919, 1597 cm^{-1}; HRMS m/z 247.1365 (calcd for $C_{18}H_{17}N$, 247.1361).

(*E*)-5-(1,2-Diphenylvinyl)-1,2,3,9-tetrahydrocarbazol-4-one (19).

^{1}H NMR ($CDCl_3$) δ 2.05-2.12 (m, 2H), 2.48 (t, *J* = 6.1 Hz, 2H), 2.80 (t, *J* = 6.2 Hz, 2H), 6.51 (s, 1H), 7.02-7.34 (m, 13H), 9.72 (s, 1H); NMR ($CDCl_3$) 23.4, 23.8, 38.8, 110.8, 113.9, 123.9, 124.4, 125.4, 126.2, 126.8, 127.2, 127.3, 127.9, 128.0, 129.5, 134.0, 137.0, 138.5, 143.4, 144.2, 191.9; IR ($CDCl_3$) 3168, 3052, 2952, 1621 cm^{-1}; HRMS m/z 363.1631 (calcd for $C_{26}H_{21}NO$, 363.1623).

(*E*)-1-(1-Benzylidenepropyl)-3-(phenoxy)dibenzofuran (21a).

^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.5 Hz, 3H), 7.87 (q, *J* = 7.5 Hz, 2 H), 6.76 (s, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 7.04-7.58 (m, 14H), 8.01 (dd, *J* = 7.7, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 25.6, 100.9, 111.7, 114.5, 117.8, 119.3, 122.2, 123.0, 123.9, 124.2, 126.4, 127.3, 128.4, 128.8, 129.8, 130.2, 137.6, 140.9, 142.5, 156.9, 157.4, 157.5; IR ($CDCl_3$) 3023, 2966, 1628 cm^{-1}; HRMS m/z 390.1624 (calcd for $C_{28}H_{22}O_2$, 390.1620).

(*E*)-1-(1-Benzylidenepropyl)-3-methoxydibenzofuran (22a).

^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.6 Hz, 3H), 2.88 (q, *J* = 7.6 Hz, 2H), 3.94 (s, 3H), 6.73 (s, 1H), 6.87 (s, 1H), 7.05 (s, 1H), 7.21-7.57 (m, 8H), 7.82 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.2, 25.6, 56.0, 95.2, 111.0, 111.5, 115.5, 121.9, 122.8, 124.6, 125.7, 127.2, 128.7, 129.5, 137.7, 140.6, 142.9, 156.7, 158.0, 159.7; IR ($CDCl_3$) 3056, 3022, 2964, 1627 cm^{-1}; HRMS m/z 328.1468 (calcd for $C_{23}H_{20}O_2$, 328.1463).

(*E*)-3-Methoxy-1-(1-methyl-2-phenylvinyl)dibenzofuran (23a).

^{1}H NMR ($CDCl_3$) δ 2.45 (d, *J* = 1.3 Hz, 3H), 3.9 (s, 3H), 6.81 (s, 1H), 6.88 (d, *J* = 2.2 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 7.25-7.57 (m, 8H), 7.93 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 19.6, 56.0, 95.2, 110.6, 111.5, 114.7, 121.9, 122.8, 124.4, 125.8, 127.1, 128.7, 129.3, 130.2, 130.2, 136.5, 137.8, 142.2, 156.7, 158.0, 159.9; IR ($CDCl_3$) 3054, 2938, 2835, 1627 cm^{-1}; HRMS m/z 314.1311 (calcd for $C_{22}H_{18}O_2$, 314.1307).

(*E*)-3-Methoxy-1-(1,3,3-trimethylbut-1-enyl)dibenzofuran (24a).

^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.23 (d, *J* = 1.0 Hz, 1H), 3.90 (s, 1H), 5.68 (d, *J* = 1.0 Hz, 1H), 6.69 (d, *J* = 1.7 Hz, 1H), 6.97 (d, *J* = 1.7 Hz, 1H), 7.25-7.38 (m, 3H), 7.51 (d, *J* = 6.1 Hz, 1H), 7.88 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) 18.9, 31.2, 56.0, 94.5, 110.7, 111.4, 121.8, 122.6, 124.5, 125.5, 130.1, 133.2, 140.5, 143.8, 156.5, 157.8, 159.8; IR ($CDCl_3$) 2956, 2865, 1628 cm^{-1}; HRMS m/z 294.1624 (calcd for $C_{20}H_{22}O_2$, 294.1620).

(*E*)-3-Methoxy-1-(1-propylpent-1-enyl)dibenzofuran (25).

^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H), 1.32-1.45 (m, 2H), 1.48-1.60 (m, 2H), 2.31 (q, *J* = 7.3 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 3.90 (s, 3H), 5.67 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 7.22-7.38 (m, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) 14.3, 14.4, 22.0, 23.2, 30.6, 33.6, 55.9, 94.5, 111.3, 111.4, 115.2, 121.9, 122.6, 124.7, 125.5, 130.9, 138.8, 141.4, 156.6, 157.8, 159.6; IR ($CDCl_3$) 2957, 2930, 2869 cm^{-1}; HRMS m/z 308.1781 (calcd for $C_{21}H_{24}O_2$, 308.1776).

(*E*)-1-(1,2-Diphenylvinyl)-3-methoxydibenzofuran (26).

^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.72 (s, 1H), 7.06-7.37 (m, 14H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) 56.0, 95.7, 111.5, 112.8, 115.8, 122.0, 122.8, 124.5, 125.9, 127.5, 127.9, 128.5, 128.8, 129.8, 130.3, 131.6, 137.1, 140.0, 140.1, 140.9, 156.8, 158.2, 159.6; IR ($CDCl_3$) 3054, 3022, 2958, 1629 cm^{-1}; HRMS m/z 376.1470 (calcd for $C_{27}H_{20}O_2$, 376.1463).

(*E*)-1-(2-Deutero-1,2-diphenylvinyl)-2,4-dideutero-3-methoxydibenzofuran (26-d).

This compound contains 70% deuterium in the vinylic position: ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.72 (s, 0.30H), 7.09-7.37 (m, 12H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H). Compound **26-d** obtained from the reaction conducted in the presence of 10 equiv of D_2O: ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.72 (s, 0.13H), 7.37-7.37 (m, 12H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H).

(*E*)-Ethyl 4-[2-(3-methoxydibenzofuran-1-yl)but-1-enyl]benzoate (27a).

^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.4 Hz, 3H), 1.43 (t, *J* = 7.1 Hz, 3H), 2.86 (q, *J* = 7.4 Hz, 2H), 3.93 (s, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 6.72 (s, 1H), 6.83 (d, *J* = 2.2 Hz, 1H), 7.06 (d, *J*

= 2.1 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.33-7.55 (m, 4 H), 7.87 (d, *J* = 7.7 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) 13.2, 14.6, 25.7, 56.0, 61.2, 95.4, 111.0, 111.6, 115.3, 121.7, 122.8, 124.4, 125.8, 128.8, 128.8, 129.1, 129.9, 140.0, 142.2, 145.0, 156.7, 158.0, 159.7, 166.7; IR ($CDCl_3$) 2969, 2935, 2873, 1716 cm^{-1}; HRMS m/z 400.1679 (calcd for $C_{26}H_{24}O_4$, 400.1675).

(*E*)-3-Methoxy-1-[1-(2-methoxybenzylidene)propyl]dibenzofuran (28a).

^{1}H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.6 Hz, 3H), 2.77 (q, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 3.93 (s, 3H), 6.79 (s, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 7.03-7.08 (m, 2H), 7.19-7.25 (m, 1H), 7.30-7.38 (m, 2H), 7.47-7.54 (m, 2H), 8.14 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 13.3, 25.8, 55.5, 56.0, 95.0, 110.8, 110.9, 111.3, 115.7, 120.5, 122.4, 122.6, 124.7, 125.6, 126.8, 128.6, 130.0, 140.5, 142.3, 156.6, 157.7, 157.9, 159.6; IR ($CDCl_3$) 2962, 2933, 2834, 1627 cm^{-1}; HRMS m/z 358.1573 (calcd for $C_{24}H_{22}O_3$, 358.1569).

Acknowledgments

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CHAPTER 3. AN ARYL TO IMIDOYL PALLADIUM MIGRATION PROCESS INVOLVING INTRAMOLECULAR C-H ACTIVATION

Based on a full paper submitted to the *Journal of American Chemical Society*

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Abstract. Biologically-interesting fluoren-9-one and xanthen-9-one derivatives have been prepared by a novel aryl to imidoyl palladium migration, followed by intramolecular arylation. The fluoren-9-one synthesis appears to involve both a palladium migration mechanism and a C-H activation process proceeding through an unprecedented organopalladium(IV) hydride intermediate. The results from deuterium labeling experiments are consistent with the proposed duel mechanism.

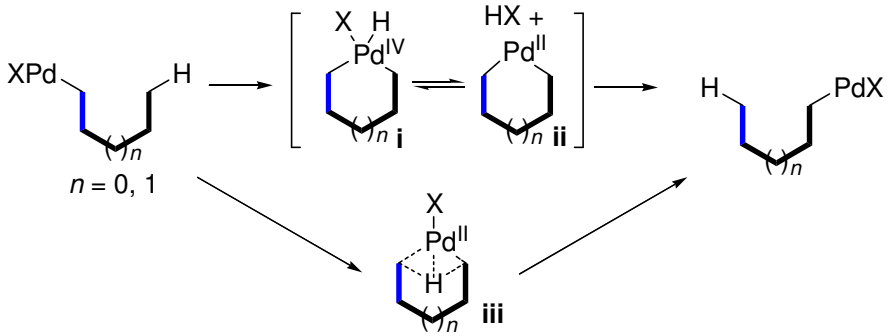
Introduction

Transitional-metal catalyzed reactions are widely used in organic synthesis. Recently, the through-space shift of a metal has been disclosed for both palladium- and rhodium-catalyzed reactions.[1] It appears that palladium migration is a fairly general rearrangement that has been observed to occur in a wide variety of systems. The through-space shift of palladium generally involves an intramolecular C-H activation process.[2] Specifically, vinylic to aryl,[3] aryl to aryl,[4] alkyl to aryl,[5] vinylic to aryl to allylic,[6] and aryl to benzyl[7] palladium migration

processes have been reported. Palladium migration is synthetically useful, because it affords an alternative way to introduce a palladium moiety into a specific position of an organic molecule, which may not be readily accessible by conventional methods. Indeed, palladium migration chemistry has been utilized to prepare a number of structurally diverse fused polycycles.[3-5]

In the reported palladium migration processes, a 5- or 6-membered palladacycle intermediate is generally involved, as shown in Scheme 1. Although the mechanism of palladium migration is still under investigation, the evidence obtained from our previous work on the vinylic to aryl to allylic palladium migration appears to favor a mechanism which involves a palladacycle(IV) hydride **i** or a palladacycle(II) intermediate **ii**, which also successfully explains the H-D exchange observed.[6] A recent theoretical study suggests a one-step proton transfer mechanism for a related palladium migration process in which an energetically favored transition state **iii** is presumably involved.[3d] However, this mechanism fails to account for the hydrogen-deuterium exchange observed in many of our migration processes, when such processes are run in the presence of D_2O.

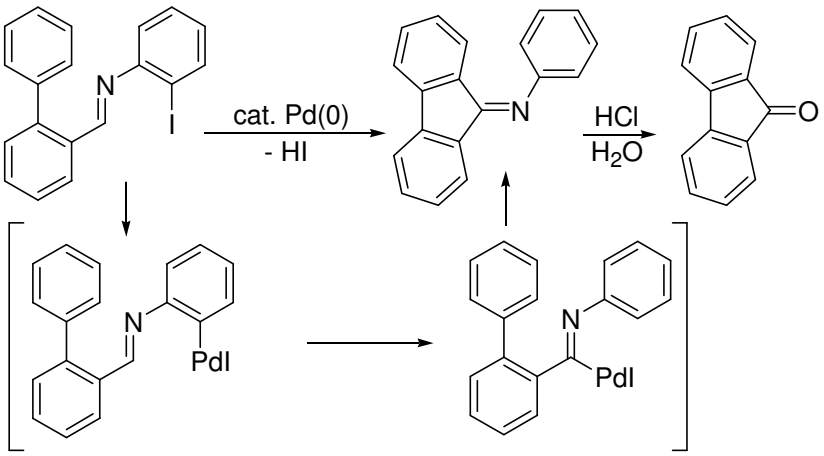
Scheme 1.



We recently briefly communicated the synthesis of fluoren-9-ones by an aryl to imidoyl palladium migration process (Scheme 2).[8] Herein, we wish to report a full account of this

novel palladium migration process, which affords a fairly general and efficient synthesis of biologically-interesting fluoren-9-ones and xanthen-9-ones, plus we also wish to provide evidence with regard to the reaction mechanism, which appears to involve both the usual palladium migration mechanism and an unprecedented mechanism proceeding through an organopalladium(IV) hydride intermediate. To the best of our knowledge, although imines have been widely employed in Pd-mediated reactions, especially chelation-assisted reactions, the direct activation of imidoyl C-H bonds by catalytic palladium is unknown. In the past, imidoyl palladium complexes have generally been obtained by the oxidative addition of imidoyl halides to Pd(0) species.[9]

Scheme 2



Results and Discussion

Synthesis of Fluoren-9-ones via Aryl to Imidoyl Palladium Migration. Fluoren-9-ones are the core structures of many biologically-interesting and pharmaceutically-important compounds.[10] The most useful syntheses of fluoren-9-ones include Friedel-Crafts ring closures of biarylcarboxylic acids,[11] intramolecular [4 + 2] cycloaddition reactions of conjugated enynes,[12] the oxidation of fluorenes,[13] the remote metalation of 2-

biphenylcarboxamides or 2-biphenyloxazolines,[14] and the palladium-catalyzed cyclocarbonylation of *o*-halobiaryls.[15] Those methods generally suffer from the use of strong acids, strong bases, toxic CO gas or harsh reaction conditions.

Our previous work indicated that the aryl-[3,4] or alkylpalladium[5] intermediates generated by palladium migration processes can be readily trapped by intramolecular arylation to afford a variety of polycyclic structures. Therefore, we envisioned that an imidoyl palladium intermediate generated from an aryl to imidoyl palladium migration process might also undergo facile intramolecular arylation to afford biologically-interesting fluoren-9-one derivatives. To examine this possibility, we first treated imine **1a** (0.25 mmol) with 5 mol % $Pd(OAc)_2$, 5 mol % *bis*(diphenylphosphino)methane (dppm), and 2 equivs of CsO_2CCMe_3 (CsPiv) in DMF (4 mL) at 100 ^oC (Table 1, entry 1). After 12 h reaction, the crude imine product obtained was hydrolyzed by aqueous HCl in acetone to afford a 95% yield of the desired fluoren-9-one **2a** after flash chromatography. It appears that the "optimal" palladium migration conditions, which have been successfully employed in a number of previously reported palladium migration reactions, work well in this fluoren-9-one synthesis.

We next investigated the scope and limitations of this process, as shown in Table 1. The effect of substituents on the arene which would bear the imidoyl palladium moiety was first examined. A 5- methoxy-substituted imine **1b** was prepared and allowed to react in the usual fashion, and a 90% yield of the fluoren-9-one **2b** was obtained (entry 2). However, imine **1c** bearing a methyl group on the 4 position of the arene, only affords a 56% yield of the desired product **2c** (entry 3). In this case, the electron density on the imidoyl group is presumably increased by the *para* methyl group, which apparently retards imidoyl C-H activation. The 5-fluoro-substituted imine **1d** affords an 80% yield of the fluoren-9-one

Table 1. Synthesis of Fluoren-9-ones[a]

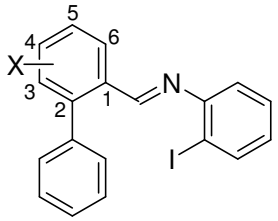
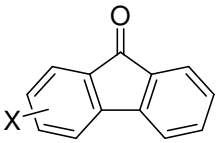
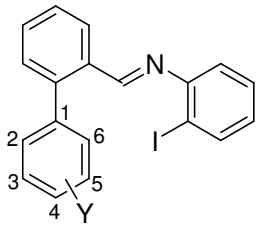
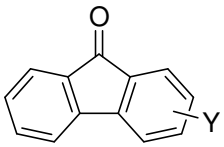
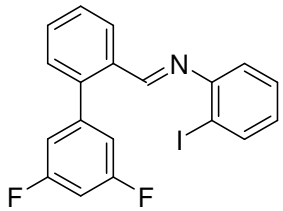
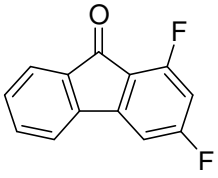
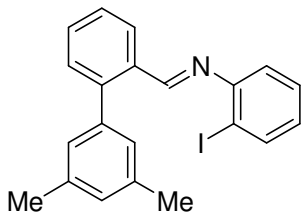
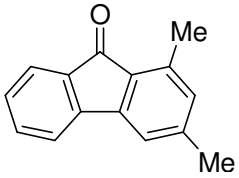
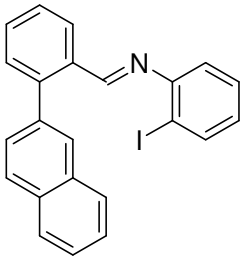
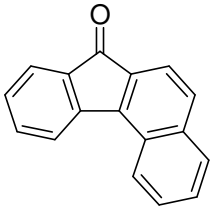
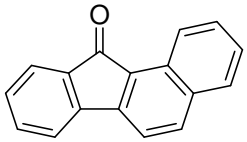
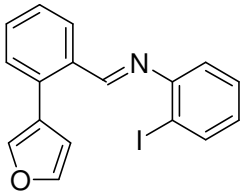
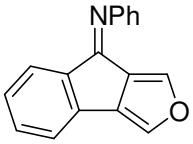
entry	imine		time (h)	product(s)		% yield
						
1	X = H	**1a**	12		**2a**	95
2	5-OMe	**1b**	12		**2b**	90
3	4-Me	**1c**	24		**2c**	56
4	5-F	**1d**	12		**2d**	80
						
5	Y = 4-Me	**1e**	4		**2e**	97
6	4-OMe	**1f**	2		**2b**	100
7	4-CO_2Me	**1g**	12		**2f**	100
8	4-NO_2	**1h**	12		**2g**	100
9	2-Cl	**1i**	48		**2h**	65
10		**1j**	6		**2i**	95
11		**1k**	24		**2j**	92

Table 1. (Continued)

entry	imine		time (h)	product(s)		% yield
12		**1l**	4		**2k**	91 (9:1)[b]
					**2l**	
13		**1m**	2		**2m**	82[c]

[a]The reaction was carried out employing 0.25 mmol of the imine, 5 mol % $Pd(OAc)_2$, 5 mol % $(Ph_2P)_2CH_2$ (dppm) and 2 equivs of CsO_2CCMe_3 (CsPiv) in DMF (4 mL) at 100 ^oC unless otherwise noted. [b]The ratio of products **2k**:**2l** was determined by GC analysis. [c]The reaction was run at 110 ^oC. [d]Compound **2m** is not stable under our usual hydrolysis conditions; omitting the hydrolysis step, the imine intermediate **2m** was isolated in an 82% yield.

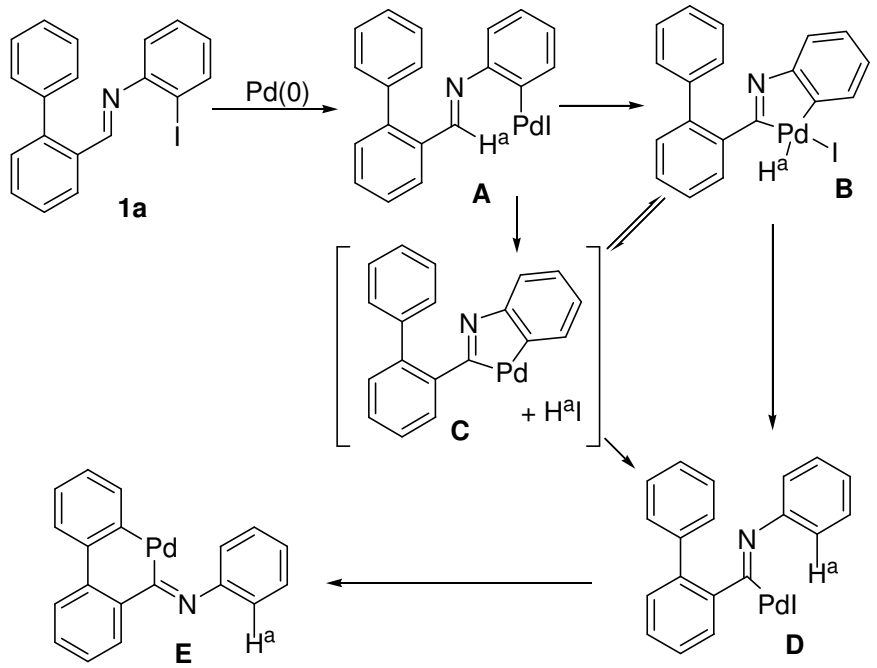
product **2d** (entry 4).

We then investigated the effect of substituents on the arene, which undergoes the cyclization reaction. Surprisingly, almost quantitative yields of fluoren-9-ones have been obtained for both electron-rich and electron-poor functionally-substituted substrates, which raises some question as to whether the intramolecular arylation step proceeds via electrophilic aromatic substitution as usually assumed (entries 5-8). These results also suggest that the palladium migration could be the rate-determining step in this overall transformation. The only exception to the high yields was the reaction employing the substrate **1i** with a 2-chloro group, where only a 65% yield of the fluoren-9-one **2j** was

obtained, possibly due to competing oxidative addition of the aryl chloride or perhaps hindered reaction of the aromatic ring or simply reduction in the number of *ortho* positions available for reaction (entry 9). Imines **1j** and **1k** afforded 95% and 92% yields of the expected fluoren-9-ones, respectively (entries 10 and 11). Once again neither electron-donating nor electron-withdrawing groups on the ring undergoing substitution seem to have a significant effect on the yield. When the naphthalene substrate **1l** was prepared and allowed to react under our usual reaction conditions, arylation took place in both the 3 and 1 positions of the naphthalene in a 91% overall yield, with the less hindered product **2k** predominant (9:1) (entry 12). The furan- containing ring present in imine **1m** facilitates electrophilic aromatic substitution and within 2 h the reaction was complete (entry 13). However, because the resulting 8*H*-indeno[2,1-*b*]furan-6-one was not stable under our hydrolysis conditions, we were only able to isolate a 50% yield of the ketone. Omitting the hydrolysis step, the corresponding imine **2m** was obtained in an 82% yield.

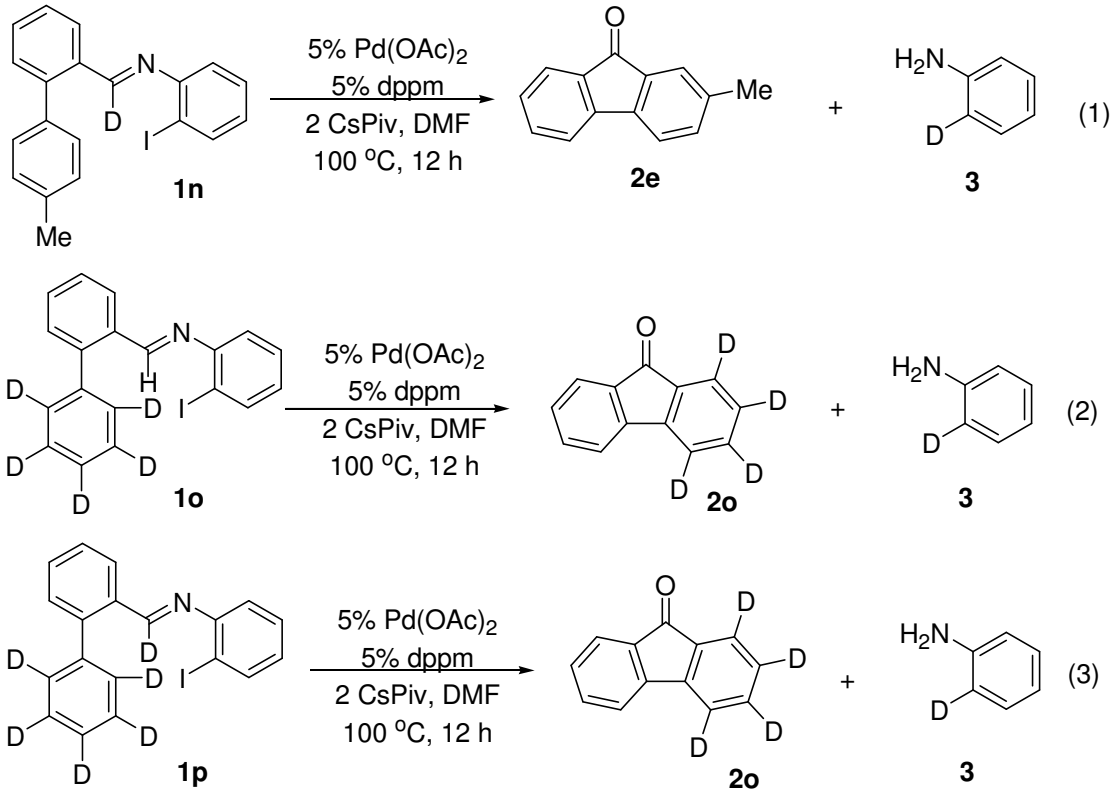
Mechanistic Studies of the Fluoren-9-one Synthesis. After we investigated the reaction scope and limitations, we examined the reaction mechanism of this fascinating process. In fact, it appears that this reaction proceeds through a rather unusual mechanism. Presumably, Pd(0) first undergoes oxidative addition to the aryl iodide **1a** to generate intermediate **A**. The palladium moiety may then undergo further oxidative addition of the imidoyl C-H bond to afford a palladacycle(IV) intermediate **B**, which can undergo reductive elimination to form palladacycle(II) **C** or the imidoyl palladium intermediate **D**. Alternatively, palladacycle(II) **C** may be directly generated from **A** or it may be formed through the intermediacy of **B**, where an equilibrium between **B** and **C** may be involved. A similar equilibrium has been demonstrated in a previously reported example of a consecutive vinylic to aryl to allylic

Scheme 3. Plausible Palladium Migration Mechanism (Route A).



palladium migration.[6] Intermediate **C** can also lead to intermediate **D**, which then undergoes intramolecular arylation to afford the cyclization product **E**, and the imine product after reductive elimination. According to this proposed mechanism, the imidoyl hydrogen (H^a) shifts to the *ortho* position of the aniline, when the palladium moiety migrates from the aryl position to the imidoyl position. By observing the movement of H^a, we should be able to detect the through-space shift of the palladium moiety. This proton shift should be readily determined by an appropriate isotope labeling experiment (Scheme 4). Indeed, deuterium-substituted imine **1n** was allowed to react under our "optimal" reaction conditions, and the aniline (**3**) obtained upon hydrolysis of the resulting imine was isolated (eq. 1). Thirty five percent deuterium incorporation was observed in one of the two *ortho* positions of the aniline as determined by ^1H NMR spectroscopy and GC-MS analysis. This reaction was repeated in the presence of 10 equiv of D_2O hoping that higher deuteriumincorporation could be

Scheme 4. Deuterium Labeling Experiments.

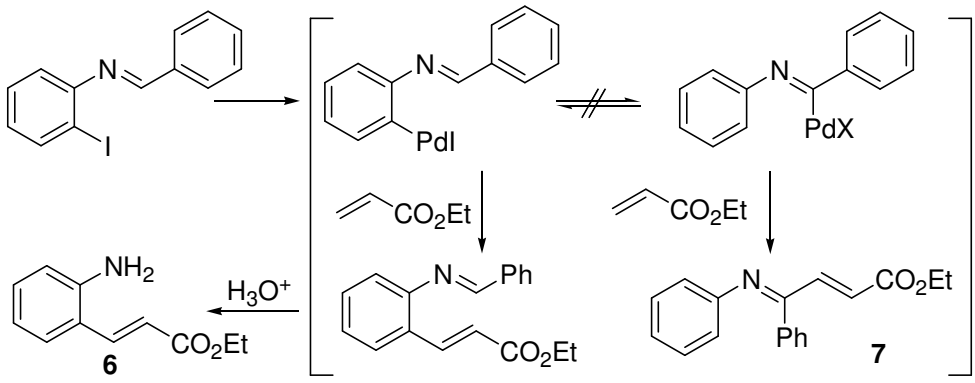


observed in the aniline (**3**). However, only slightly higher 45% deuterium incorporation was observed, which is apparently inconsistent with the proposed mechanism (route A). If the aryl to imidoyl palladium migration is a reversible process as observed with the analogous aryl to aryl palladium migrations,[4,16] we should be able to observe deuterium incorporation in both of the *ortho* positions when the reaction is conducted in the presence of a deuterium source. However, incorporation of only one deuterium was observed.

We have also attempted to trap the aryl and imidoyl palladium intermediates by a Heck reaction (Scheme 5) as we did in our aryl to aryl palladium migration chemistry.[4,16] Analogous Heck reactions of acylpalladium intermediates are well known.[17] However, after a 24 h reaction, only ester **6** was observed by GC-MS analysis, and ester **7**, which presumably should be generated from the Heck reaction of the postulated imidoyl palladium intermediate

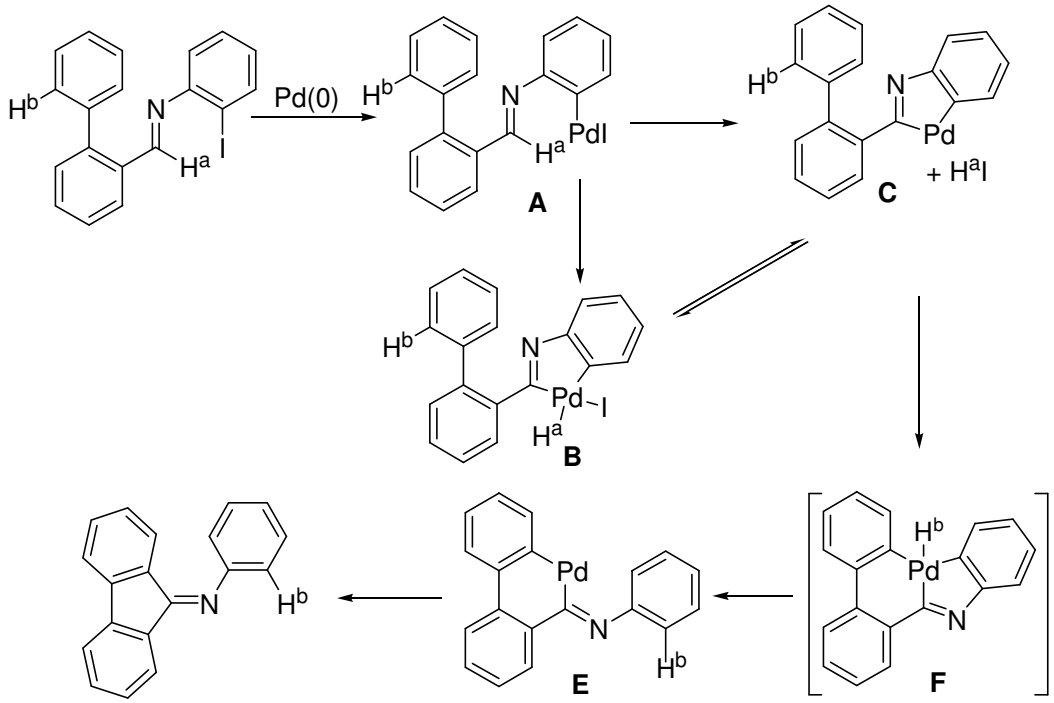
was not evident. These results indicate that the aryl to imidoyl palladium migration process is probably not a reversible process in the absence of intramolecular arylation as a driving force. Indeed, the whole process appears to be rather unusual compared with previously reported examples of palladium migration. Although H-D exchange occurs during the course of the palladium migration, this leads to low deuterium incorporation. It is difficult to attribute all of the deuterium loss to H-D exchange, since the yield of deuterated product was only slightly improved when the reaction was conducted in the presence of an additional deuterium source.

Scheme 5



An alternative pathway for generation of the fluoren-9-one product without invoking an imidoyl hydrogen shift is proposed in Scheme 6. In this mechanism, the arylpalladium intermediate **A** undergoes intramolecular C-H activation to afford palladacycle(IV) **B**; subsequent reductive elimination could generate palladacycle(II) **C**. It is also possible that palladacycle(II) **C** could be generated directly from arylpalladium intermediate **A**. At this point, the palladium moiety might insert into the C-H bond of the neighboring arene to afford an unprecedented palladacycle(IV) intermediate **F**. Such a palladacycle might be expected to undergo reductive elimination to afford palladacycle **E**, which after a second reductive

Scheme 6. Plausible C-H Activation Mechanism (Route B).

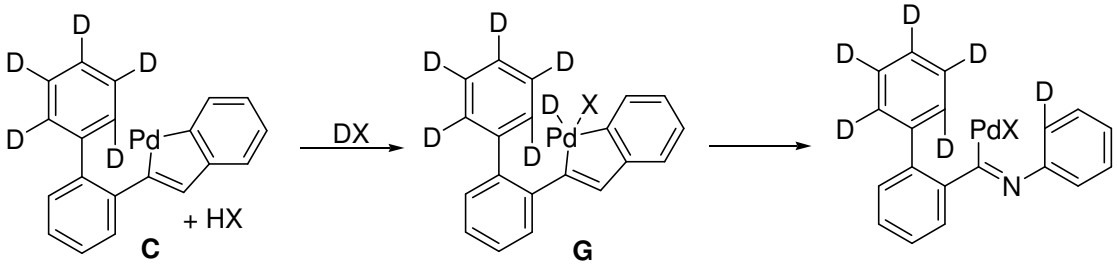


elimination would generate the expected imine product. In this mechanism, H^a is lost to the solution when forming intermediate **C**, but H^b shifts from the biphenyl moiety to one of the two *ortho* positions of the aniline. Deuterium labeled substrate **1o** (Scheme 4, eq. 2) was prepared and allowed to react under the standard reaction conditions. If this mechanism is in force, we expect to see some deuterium at one of the two *ortho* positions of the resulting aniline if the reaction goes through route B. Indeed, we observed 35% deuterium incorporation in one of the two *ortho* positions of the resulting aniline. At this point, we reasoned that this fluoren-9-one synthesis actually goes through a duel mechanism, a palladium migration mechanism (Scheme 3, route A) and an unprecedented intramolecular C-H activation mechanism (Scheme 6, route B). Based on this assumption, one would expect that higher deuterium incorporation would be obtained if both H^a and H^b are labeled with deuterium. Indeed, when substrate **1p** (Scheme 4, eq. 3) was employed in this reaction, 75%

deuterium incorporation in the aniline ring was observed, which is consistent with our hypothesis.

The final intramolecular arylation step of route A (Scheme 3) would release one equivalent of HX or DX into solution, which might add to palladacycle(II) **C** to afford a new palladacycle(IV) intermediate **G**. Subsequent reductive elimination could afford the *ortho* deuterated aniline product (Scheme 7). This can also explain the deuterium incorporation into the aniline observed in the experiment described in Scheme 4, eq. 2. However, if one equiv of DX can afford as much as 35% deuterium incorporation, even when the concentration of DX is quite low because it is gradually released into the solution, the analogous reaction run in the presence of 10 equiv of D_2O should afford very high deuterium incorporation, at least comparable to the results obtained from the experiments described in Scheme 4, eq. 3 in which two equiv of DX are released. However, we did not observe a significant increase in deuterium incorporation when 10 equiv of D_2O was present; only 45% deuterium incorporation was observed. Remember that these migration reactions have been conducted in the presence of 2 equiv of CsPiv

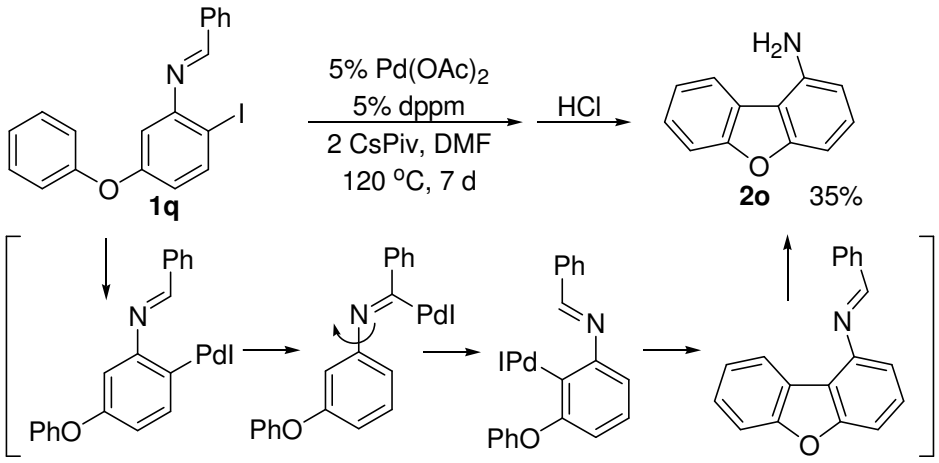
Scheme 7



base, which should quickly neutralize the DX acid generated by the final arylation step. Thus, this pathway for the introduction of deuterium into the aniline in the reaction reported in Scheme 3, eq. 2, is highly unlikely.

It has been shown previously that palladium can migrate more than once in these migration reactions.[4,6] Thus, an interesting question is whether the imidoyl palladium intermediate can migrate the palladium to a second aryl position. As shown in Scheme 8, imine **1q** was prepared and allowed to react under our usual reaction conditions, but this reaction failed to afford any of the desired product. By heating the reaction to 120 °C, after 7 days, we were able to obtain a 35% yield of the desired 1-aminodibenzo[*b,d*]furan (**2o**).[8] In this case, palladium must have migrated from the aryl to the imidoyl position

Scheme 8

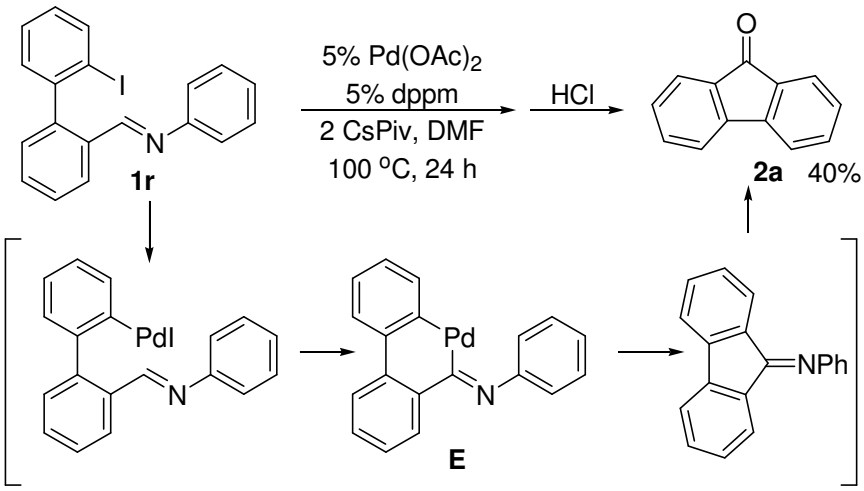


solely through the migration mechanism shown in Scheme 3. According to our study of the vinylic to aryl palladium migration chemistry,[3a] the palladium moiety tends to migrate to the more electron-rich arene during the course of the migration. The palladium migration from the phenoxy-substituted arene to the imidoyl position is probably not a very favorable process, but palladium migration from the imidoyl position back to the aryl position of this arene, which is *ortho* to the phenoxy group is quite possibly a favorable process.

Activation of the imidoyl C-H bond in this fluoren-9-one synthesis proceeds through a 5-membered ring intermediate. One might wonder whether palladium can activate an imidoyl

C-H bond by a 6-membered ring intermediate. Indeed, substrate **1r** has been prepared and allowed to react under our usual reaction conditions. After 24 h of reaction at 100 °C, only a 40% yield of the desired fluoren-9-one product was obtained (Scheme 9). Although it appears that 6-membered ring activation is feasible, the reaction efficiency is not high.

Scheme 9



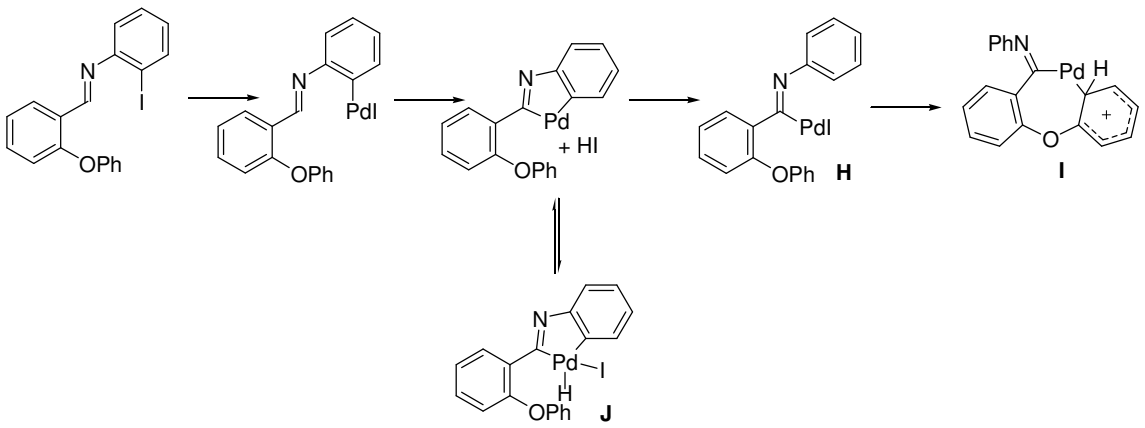
Synthesis of Xanthones via Aryl to Imidoyl Palladium Migration. After developing a general and efficient synthesis of fluoren-9-one derivatives, we attempted to extend this protocol to the synthesis of 6-membered ring heterocycles, such as xanthones, thioxanthones and acridones. Xanthones are secondary metabolites found in higher plant families, fungi and lichens exhibiting interesting pharmaceutical properties.[18] Most common syntheses of the xanthone skeleton typically involve a multi-step procedure, which generally proceeds through the intermediacy of a benzophenone or a diaryl ether.[19] Recently, we reported a one-step synthesis of xanthones by a tandem coupling-cyclization of 2-hydroxybenzoates and arynes.[20]

In our fluoren-9-one synthesis, palladium migrates from an aryl position to an imidoyl position and then undergoes intramolecular arylation through a 6-membered ring intermediate. We envisioned that an imidoylpalladium intermediate might also undergo

intramolecular arylation by a 7-membered ring intermediate to afford 6-membered ring heterocycles, as shown in Scheme 10. Indeed, imine **4a** was allowed to react under our "optimal" conditions and a 72% yield of the xanthone product **5a** was obtained by flash chromatography.

The reaction scope and limitations of this new xanthone synthesis are shown in Table 2. We first investigated the effect of the substituent on the arene bearing the imine group. Methyl-substituted substrate **4b** affords an 80% yield of the xanthone **5b** (entry 2), and methoxy-substituted imine **4c** affords a 77% yield of product **5c** (entry 3). Imines bearing an electron-withdrawing group have also been prepared and subjected to the usual reaction conditions. The imines **4d** and **4e** substituted with NO_2 and CF_3 groups afforded 56% and 38% yields of the xanthone products **5d** and **5e**, respectively (entries 4 and 5). Note that a higher temperature is required here. Substrates bearing a functional group Y on the arene

Scheme 10. Plausible Mechanism for the Synthesis of Xanthones.



which undergoes substitution have also been prepared. The methoxy-, chloro-, alkyl-, and aryl-substituted imines **4f-j** have been allowed to react under our usual reaction conditions, and 56-77% yields of the substituted xanthones **5f-j** have been obtained (entries 6-10). However, the reaction was very sluggish when imine **4k** bearing an electron-withdrawing

Table 2. Synthesis of Xanthones[a]

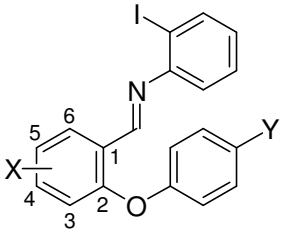
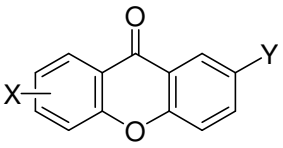
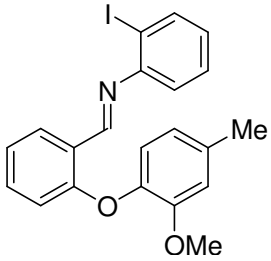
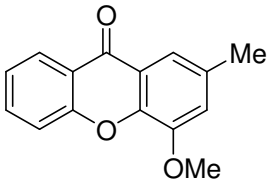
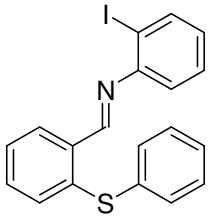
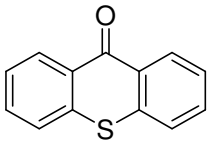
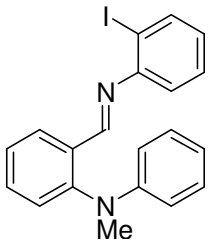
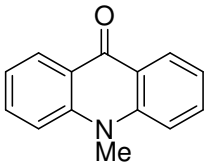
entry	imine			temp (°C)	product		% yield
							
	X	Y					
1	H	H	**4a**	100		**5a**	72
2	5-Me	H	**4b**	100		**5b**	80
3	5-OMe	H	**4c**	100		**5c**	77
4	5-CF_3	H	**4d**	120		**5d**	56
5	5-NO_2	H	**4e**	120		**5e**	38
6	H	OMe	**4f**	100		**5c**	77
7	H	Cl	**4g**	100		**5f**	73
8	H	*i*-Pr	**4h**	100		**5g**	56
9	H	Ph	**4i**	100		**5h**	63
10	H	*t*-Bu	**4j**	100		**5i**	61
11	H	CO_2Me	**4k**	120		**5j**	10
12			**4l**	100		**5k**	79
13			**4m**	120		**5l**	0[b]

Table 2. (Continued)

entry	imine		temp (°C)	product		% yield
14		**4n**	100		**5m**	20

[a]The reaction was carried out employing 0.25 mmol of the imine, 5 mol % $Pd(OAc)_2$, 5 mol % $(Ph_2P)_2CH_2$ (dppm) and 2 equivs of CsO_2CCMe_3 (CsPiv) in DMF (4 mL) under Ar for 24 h. [b]Starting materials were recovered.

ester group was allowed to react. After 1 d of reaction at 120 °C, only about 10% of the desired product was observed by GC-MS analysis (entry 11). This intramolecular arylation presumably proceeds via an electrophilic aromatic substitution,[21] although some evidence points towards a proton transfer mechanism.[22] Thus, an electron-withdrawing substituent might be expected to disfavor the cyclization step, especially for this cyclization proceeding by a difficult 7-membered ring intermediate **I**. Note, however, that cyclization to form a fluoren-9-one was not impeded by the presence of strong electron-withdrawing groups (see Table 1, entries 7 and 8). Introducing a methoxy group *ortho* to the oxygen atom of the phenoxy group could facilitate electrophilic aromatic substitution, but might introduce some steric hindrance at the same time, as well as reducing statistically the number of positions available for cyclization. In fact, the reaction of imine **4l** affords a 79% yield of the xanthone product, which indicates that electronic factors apparently predominate (entry 12). We have also attempted to extend this protocol to the synthesis of thioxanthones, an important class of potential anti-cancer drugs.[23] When imine **4m** was treated under the reaction conditions used in our xanthone synthesis, we did not observe any cyclization

product, and we recovered most of the starting material (entry 13). Repeating this reaction at 120 ^{o}C afforded similar results. The presence of the larger sulfur atom apparently disfavors cyclization through the now larger 7-membered ring intermediate or perhaps the sulfur chelates the intermediate imidoyl palladium species preventing cyclization.

Acridones are also naturally-occurring compounds exhibiting a variety of interesting biological activities. They are important anti-leishmanial, anti-fungal, anti-tumor and DNA-intercalating anti-cancer drugs.[24] We prepared imine **4n** from the corresponding aldehyde and treated it under our standard palladium migration conditions. After 1 d of reaction at 100 ^{o}C, a 20% yield of the acridone **5m** was obtained (entry 14). We have also conducted this reaction at 120 ^{o}C, but failed to observe any improvement in the reaction efficiency.

Conclusions

In summary, we have established a novel 1,4-Pd migration from an aryl position to an imidoyl position, which affords a general synthesis of the biologically-interesting fluoren-9-one and xanth-9-one ring systems. Both electron-rich and electron-poor substrates have been screened in this process, and generally good yields of the desired product have been obtained. The fluoren-9-one synthesis appears to involve both a standard palladium migration mechanism (route A) and a C-H activation mechanism (route B), which proceeds through an unprecedented organopalladium(IV) hydride intermediate. The results from the deuterium labeling experiments are consistent with the proposed duel mechanism.

Experimental Section

I. General Procedures.

All ^{1}H and ^{13}C spectra were collected in $CDCl_3$ unless noted otherwise. Thin layer chromatography was performed using 60-mesh silica gel plates, and visualization was affected using short wavelength UV light (254 nm) and a basic $KMnO_4$ solution. All high resolution mass spectra were recorded using EI.

All reagents were used directly as obtained commercially unless otherwise noted. Cesium pivalate was prepared according to the procedure of Campo and Larock.[25]

II. Noncommercial compounds.

General procedure for synthesis of the biarylcarboxaldehydes. To 10 mL of a 2:1 DMF/H_2O solution containing 5.0 mmol of 2-bromobenzaldehyde and 5.0 mmol of Na_2CO_3 were added 5.0 mmol of arylboronic acid and the reaction mixture was stirred for 2 min. $Pd(OAc)_2$ (5 mol %) was then added and the flask was flushed with Ar, sealed and allowed to stir at 25 ^{o}C for 12 h. The reaction mixture was extracted with ethyl ether (2 x 10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as eluent.

4-Methoxybiphenyl-2-carboxaldehyde.

^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.20 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.34-7.47 (m, 6H), 7.51 (d, *J* = 2.84 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8, 110.1, 121.6, 128.0, 128.6, 130.5, 132.3, 134.7, 137.7, 139.3, 159.3, 192.5; IR ($CDCl_3$) 3028, 2936, 2850, 1686 cm^{-1}; HRMS m/z 212.0841 (calcd for $C_{14}H_{12}O_2$, 212.0837).

5-Methylbiphenyl-2-carboxaldehyde.

^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 7.24 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.41-7.47 (m, 3H), 7.95 (d, *J* = 8.0 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1,

127.9, 128.3, 128.6, 128.9, 130.3, 131.6, 131.7, 138.1, 144.8, 146.4, 192.3; IR ($CDCl_3$) 3027, 2848, 1690 cm^{-1}; HRMS m/z 196.0891 (calcd for $C_{14}H_{12}O$, 196.0888).

4-Fluorobiphenyl-2-carboxaldehyde.

Due to C-F coupling, the ^{13}C NMR showed more peaks than carbon numbers. ^1H NMR ($CDCl_3$) δ 7.30-7.35 (m, 3H), 7.41-7.49 (m, 4H), 7.67 (dd, *J* = 8.9, 2.84 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 113.7, 113.9, 115.6, 120.9, 121.1, 128.5, 128.8, 130.4, 133.0, 135.4, 136.9, 142.3, 142.3, 161.1, 163.6, 191.3; IR ($CDCl_3$) 3066, 2855, 1691 cm^{-1}; HRMS m/z 200.0639 (calcd for $C_{13}H_9FO$, 200.0637).

4'-Methylbiphenyl-2-carboxaldehyde.

^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 7.24-7.29 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.2 Hz, 1H), 9.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 127.7, 129.3, 130.2, 130.9, 133.7, 133.9, 134.9, 138.2, 146.1, 192.7 ; HRMS m/z 196.0891 (calcd for $C_{14}H_{12}O$, 196.0888).

4'-Methoxybiphenyl-2-carboxaldehyde.

^1H NMR ($CDCl_3$) δ 3.87 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.41-7.48 (m, 2H), 7.61 (td, *J* = 7.5, 1.2 Hz, 1H), 8.00 (dd, *J* = 7.5, 1.2 Hz, 1H), 9.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.6, 114.1, 127.5, 127.8, 130.2, 131.0, 131.5, 133.7, 133.9, 145.8, 159.9, 192.8; HRMS m/z 212.0839 (calcd for $C_{14}H_{12}O_2$, 212.0837).

Methyl 2'-formylbiphenyl-4-carboxylate.

^1H NMR ($CDCl_3$) δ 3.97 (s, 3H), 7.43-7.48 (m, 3H), 7.54 (t, *J* = 9.0 Hz, 1H), 7.70 (td, *J* = 7.5, 1.5 Hz, 1H), 8.05 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.13-8.17 (m, 2H), 9.96 (s, 1H); ^{13}C NMR

($CDCl_3$) δ 52.5, 128.1, 128.6, 129.8, 130.1, 130.3, 130.8, 133.8, 133.9, 142.6, 144.8, 166.8, 191.9; HRMS m/z 240.0789 (calcd for $C_{15}H_{12}O_3$, 240.0786).

4'-Nitrobiphenyl-2-carboxaldehyde.

^{1}H NMR ($CDCl_3$) δ 7.44 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.55-7.63 (m, 3H), 7.71 (td, *J* = 7.6, 1.6 Hz, 1H), 8.06 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.34 (d, *J* = 6.8 Hz, 2H); 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.8, 129.1, 129.3, 130.8, 131.0, 133.8, 134.1, 143.2, 145.0, 147.9, 191.3; HRMS m/z 227.0592 (calcd for $C_{13}H_9NO_3$, 227.0582).

2'-Chlorobiphenyl-2-carboxaldehyde.

^{1}H NMR ($CDCl_3$) δ 7.31-7.39 (m, 4H), 7.48-7.54 (m, 2H), 7.66 (td, *J* = 7.5, 1.5 Hz, 1H), 8.04 (dd, *J* = 7.5, 1.5 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 127.0, 127.6, 128.7, 129.8, 129.9, 131.1, 131.9, 133.7, 133.9, 134.0, 137.0, 142.9, 191.7; HRMS m/z 216.0348 (calcd for $C_{13}H_9ClO$, 216.0345).

3',5'-Difluorobiphenyl-2-carboxaldehyde.

^{1}H NMR ($CDCl_3$) δ 6.78-6.81 (m, 3H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.55 (td, *J* = 7.5, 1.5 Hz, 1H), 7.91 (dd, *J* = 7.8, 1.5 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 103.7 (t), 113.3 (q), 128.3, 128.9 (t), 130.5, 133.7 (t), 141.3 (m), 143.3 (t), 161.2 (d), 164.5 (d), 191.4; HRMS m/z 218.0547 (calcd for $C_{13}H_8F_2O$, 218.0543).

3',5'-Dimethylbiphenyl-2-carboxaldehyde.

The spectral properties were identical to those previously reported.[26]

2-(Furan-3-yl)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 6.57 (s, 1H), 7.41-7.46 (m, 2H), 7.52-7.62 (m, 3H), 7.97 (dd, *J* = 7.8, 1.2 Hz, 1H), 10.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 112.3, 112.6, 122.6, 127.8, 127.9, 130.6,

133.9, 134.0, 136.4, 141.4, 143.6, 192.2; HRMS m/z 172.0528 (calcd for $C_{11}H_8O_2$, 172.0524).

5-Phenoxy-2-iodoaniline.

3-Phenoxyaniline (7.8 mmol) was added to a mixture of I_2 (7.9 mmol) and AgOAc (7.9 mmol) in ethanol (50 mL) at room temperature. The mixture was stirred for 14 h after which the solid was removed by filtration and the filtrate was evaporated under vacuum to afford a black residue, which was dissolved in ethyl ether and washed with satd aq $Na_2S_2O_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent. The compound was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 2H), 6.17 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.37 (d, *J* = 3.0 Hz, 1H), 6.98-7.01 (m, 2H), 7.10 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.29-7.34 (m, 2H), 7.51 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 76.4, 104.9, 110.9, 119.4, 123.8, 129.9, 139.7, 148.1, 156.8, 159.1; HRMS m/z 310.9811 (calcd for $C_{12}H_{10}INO$, 310.9808).

***N*-Phenylmethylene-2-iodo-5-phenoxyaniline**.

This compound was prepared following the procedure used for the preparation of the *N*-(biaryl-2-ylmethylene)-2-iodoanilines. The resulting imine was used for the next step without further characterization.

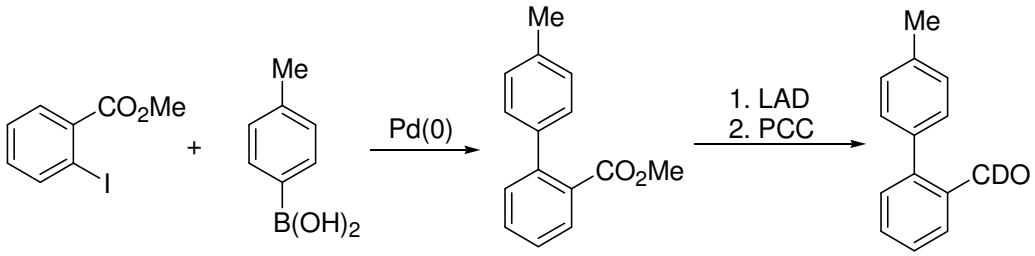
1-Aminodibenzo[*b,d*]furanamine (2o).

The spectral properties were identical to those previously reported.[27]

4'-Methylbiphenyl-2-carboxaldehyde-d.

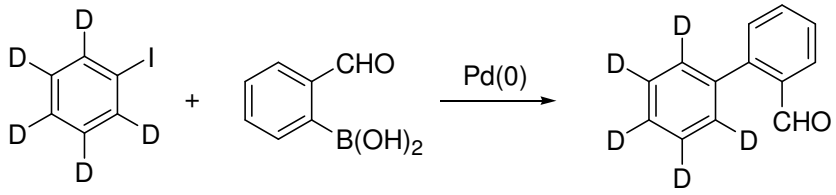
This compound was prepared through the strategy shown below. ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 7.24-7.29 (m, 4H), 7.40-7.47 (m, 2H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 8.02 (dd, *J* =

8.0, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.43, 127.77, 127.78, 129.42, 130.28, 131.02, 133.75, 135.04, 138.23, 146.20, 192.24 (t, *J* = 27 Hz).



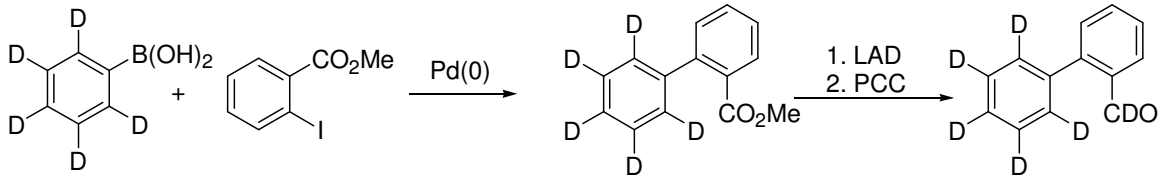
2-(Phenyl-d_5)-benzaldehyde.

This compound was prepared through the strategy shown below. ^{1}H NMR ($CDCl_3$) δ 7.44-7.52 (m, 2H), 7.63 (td, *J* = 7.4 Hz, 1.3 Hz, 1H), 8.04 (dd, *J* = 7.7 Hz, 1.2 Hz, 1H), 9.99 (d, *J* = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 127.80, 128.00, 121.02, 122.80, 137.79, 146.15.



2-(Phenyl-d_5)-benzaldehyde-d.

This compound was prepared through the strategy shown below. ^{1}H NMR ($CDCl_3$) δ 7.44-7.52 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 8.04 (dd, *J* = 7.7 Hz, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 127.79, 128.01, 131.01, 133.84, 137.76, 146.16.



General procedure for synthesis of the 2-(aryloxy)benzaldehydes. To 10 mL of a DMA solution containing 5.0 mmol of 2-fluorobenzaldehyde and 5.0 mmol of phenol were added 5.0 mmol of K_2CO_3 and the reaction mixture was stirred for 2 h at 170 °C under an Ar

atmosphere. The reaction mixture was cooled to room temperature and worked up using the procedure described previously.

2-(Phenoxy)benzaldehyde.

The spectral properties were identical to those previously reported.[28]

5-Methyl-2-(phenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 6.83 (d, *J* = 8.5 Hz, 1H), 7.02-7.04 (m, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.32-7.38 (m, 3H), 7.74 (d, *J* = 2.0 Hz, 1H), 10.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 119.0, 119.3, 124.1, 127.1, 128.5, 130.2, 133.5, 136.8, 157.3, 157.9, 189.7; IR ($CDCl_3$) 3039, 2857, 1689 cm^{-1}; HRMS m/z 212.0841 (calcd for $C_{14}H_{12}O_2$, 212.0837).

5-Methoxy-2-(phenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 2H), 7.07-7.12 (m, 2H), 7.29-7.35 (m, 2H), 7.39 (d, *J* = 3.2 Hz, 1H), 10.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0, 110.1, 118.2, 121.8, 123.7, 123.9, 128.2, 130.2, 153.6, 156.1, 158.2, 189.2; IR ($CDCl_3$) 2940, 2858, 1686 cm^{-1}; HRMS m/z 228.0789 (calcd for $C_{14}H_{12}O_3$, 228.0786).

5-Trifluoromethyl-2-(phenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 6.93 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H); 7.68 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.19 (d, *J* = 1.8 Hz, 1H), 10.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 117.8, 120.5, 125.8, 126.1, 126.2 (q), 126.3, 130.7, 132.4 (q), 155.0, 162.8, 188.2; IR ($CDCl_3$) 3068, 2870, 1695 cm^{-1}; HRMS m/z 266.0559 (calcd for $C_{14}H_9F_3O_2$, 266.0555).

5-Nitro-2-(phenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 6.90 (d, *J* = 9.3 Hz, 1H), 7.15-7.17 (m, 2H), 7.29-7.33 (m, 1H), 7.45-7.49 (m, 2H), 8.23 (dd, *J* = 9.2, 2.9 Hz, 1H), 8.64 (d, *J* = 2.9 Hz, 1H), 10.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 117.1, 121.0, 124.6, 125.6, 126.6, 130.5, 130.9, 142.7, 154.1, 164.8, 187.5; IR ($CDCl_3$) 3077, 2878, 1695, 1580 cm^{-1}; HRMS m/z 243.0535 (calcd for $C_{13}H_9NO_2$, 243. 0532).

2-(4-Methoxyphenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 6.78 (dd, *J* = 8.4, 0.6 Hz, 1H), 6.90-6.92 (m, 2H), 6.91 (dd, *J* = 6.8, 2.5 Hz, 2H), 7.09 (tt, *J* = 7.3, 0.9 Hz, 1H), 7.42-7.46 (m, 1H), 7.89 (dd, *J* = 7.7, 1.8 Hz, 1H), 10.55 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.9, 115.4, 117.2, 121.4, 122.7, 126.3, 128.5, 136.0, 149.3, 156.8, 161.3, 189.7; IR ($CDCl_3$) 2953, 2836, 1689 cm^{-1}; HRMS m/z 228.0789 (calcd for $C_{14}H_{12}NO_3$, 228.0786).

2-(4-chlorophenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 6.88 (d, *J* = 8.4 Hz, 1H), 6.98-7.01 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.32-7.35 (m, 2H), 7.50-7.55 (m, 1H), 7.92 (dd, *J* = 7.8, 1.7 Hz, 1H), 10.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 118.7, 120.8, 124.0, 127.2, 128.9, 129.7, 130.2, 136.1, 155.3, 159.7, 189.2; IR ($CDCl_3$) 3073, 2856, 1691 cm^{-1}; HRMS m/z 232.0294 (calcd for $C_{13}H_9ClO_2$, 232.0291).

2-(4-*i*-Propylphenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 1.27 (d, *J* = 7.0 Hz, 6H), 2.88-2.99 (m, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.99-7.02 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.46-7.50 (m, 1H), 7.93 (dd, *J* = 7.8, 1.8 Hz, 1H), 10.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.4, 33.8, 118.3, 119.7, 123.2, 126.9, 128.2, 128.5, 135.9, 145.3, 154.3, 160.7, 189.6; IR ($CDCl_3$) 2960, 2869, 1690 cm^{-1}; HRMS m/z 238.0997 (calcd for $C_{16}H_{14}O_2$, 238.0994).

2-(4-Phenylphenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 7.00 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.15-7.18 (m, 2H), 7.21-7.25 (m, 1H), 7.37-7.41 (m, 1H), 7.46-7.50 (m, 2H), 7.53-7.57 (m, 1H), 7.60-7.66 (m, 4H), 7.99-8.02 (m, 1H), 10.59 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 118.9, 119.9, 123.8, 127.2, 127.2, 127.6, 128.8, 129.0, 129.2, 136.1, 137.7, 140.4, 156.2, 160.1, 189.5; IR ($CDCl_3$) 3046, 3032, 1689 cm^{-1}; HRMS m/z 274.0999 (calcd for $C_{19}H_{14}O_2$, 274.0994).

2-(4-*t*-Butylphenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 6.89-6.91 (m, 1H), 6.98-7.02 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.39-7.50 (m, 3H), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 10.54 (d, *J* = 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.8, 34.7, 118.4, 119.3, 123.2, 126.9, 127.2, 128.5, 136.0, 147.6, 154.0, 160.6, 189.6; IR ($CDCl_3$) 3038, 2962, 1868, 1691 cm^{-1}; HRMS m/z 254.1307 (calcd for $C_{17}H_{18}O_2$, 254.1307).

Methyl 4-(2-formylphenoxy)benzoate.

^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.94-7.01 (m, 3H), 7.20-7.24 (m, 1H), 7.50-7.55 (m, 1H), 7.88-8.00 (m, 3H), 10.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.3, 118.1, 120.2, 124.9, 125.8, 127.8, 129.0, 132.1, 136.1, 158.4, 161.1, 166.4, 188.8; IR ($CDCl_3$) 3075, 2999, 2856, 1722, 1691 cm^{-1}; HRMS m/z 256.0740 (calcd for $C_{15}H_{12}O_4$, 256.0736).

2-(2-Methoxy-4-methylphenoxy)benzaldehyde.

^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.78 (s, 3H), 6.68-6.83 (m, 3H), 6.95 (d, *J* = 7.9 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.38-7.44 (m, 1H), 7.89 (dd, *J* = 7.8, 1.8 Hz, 1H), 10.65 (s, 1H); ^{13}C NMR ($CDCl_3$) 21.6, 56.1, 114.1, 116.2, 121.8, 122.1, 122.3, 125.7, 128.2, 135.8, 136.3,

141.6, 151.5, 161.4, 189.9; IR ($CDCl_3$) 2937, 2857, 1691 cm^{-1}; HRMS m/z 242.0946 (calcd for $C_{15}H_{14}O_3$, 242.0943).

2-(Phenylsulfanyl)benzaldehyde.

This compound was prepared using a literature procedure.[29]

2-(Methylphenylamino)benzaldehyde.

This compound was prepared using a literature procedure.[30]

III. Experimental Procedures.

General procedure for synthesis of the biaryl-2-ylmethyleneanilines. To a solution of biarylcarboxaldehyde (0.25 mmol) and 2-iodoaniline (0.25 mmol) in toluene (3 mL) under N_2 was added anhydrous $MgSO_4$ (0.50 mmol). The reaction mixture was stirred at 100 ^oC until TLC analysis indicated the disappearance of the starting aldehyde. The reaction mixture was then filtered and the resulting solvent was evaporated under reduced pressure to afford the crude product, which was used without further characterization.

General procedure for the palladium-catalyzed migration reaction. The appropriate imine (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), 1,1-*bis*(diphenylphosphino)methane (dppm) (4.8 mg, 0.0125 mmol), and CsO_2CCMe_3 (CsPiv) (0.117 g, 0.5 mmol) in DMF (4 mL) under Ar at 100 ^oC were stirred for the specified length of time. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (35 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford the crude imine product, which was used for the hydrolysis without further characterization.

General procedure for hydrolysis of the imines. To an acetone (5 mL) solution of the crude imine product, 1.0 N HCl (2 mL) was added. The resulting reaction mixture was stirred until disappearance of the starting material as indicated by thin layer chromatography. The mixture was then diluted with H_2O and extracted with diethyl ether (2 x 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the crude fluoren-9-one, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

IV. Characterization Data for Selected Compounds.

Fluoren-9-one (2a).

The spectral properties were identical to those previously reported.[25]

2-Methoxyfluoren-9-one (2b).

^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.94 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.14-7.18 (m, 2H), 7.34-7.41 (m, 3H), 7.56 (d, *J* = 7.6 Hz, 1H); IR (CH_2Cl_2) 1717 cm^{-1}; HRMS m/z 210.0684 (calcd for $C_{14}H_{12}O_2$, 210.0681).

3-Methylfluoren-9-one (2c).

^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 7.08 (dq, *J* = 8.7, 0.6 Hz, 1H), 7.26-7.30 (m, 1H), 7.32-7.33 (m, 1H), 7.44-7.50 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.63 (dt, *J* = 7.4, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 120.3, 121.5, 124.4, 124.5, 129.2, 129.8, 132.1, 124.6, 124.9, 144.5, 145.0, 146.0, 193.9; IR ($CDCl_3$) 3044, 2919, 1711 cm^{-1}; HRMS m/z 194.0734 (calcd for $C_{14}H_{10}O$, 194.0732).

3-Fluorofluoren-9-one (2d).

Due to C-F coupling, the ^{13}C NMR exhibited more peaks than the number of carbons present. ^{1}H NMR ($CDCl_3$) δ 7.12-7.17 (m, 1H), 7.24-7.28 (m, 1H), 7.31-7.33 (m, 1H), 7.44-

7.48 (m, 3H), 7.62-7.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 112.1, 112.3, 120.3, 120.4, 121.0, 121.2, 121.8, 121.9, 124.8, 129.0, 135.3, 140.3, 140.4, 144.1, 162.5, 165.0, 192.7; IR ($CDCl_3$) 3064, 2923, 1715 cm^{-1}; HRMS m/z 198.0483 (calcd for $C_{13}H_7FO$, 198.0481).

2-Methylfluoren-9-one (2e).

^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 7.19-7.24 (m, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.04-7.41 (m, 3H), 7.58 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 120.0, 120.2, 124.2, 125.0, 128.6, 134.3, 134.4, 134.7, 135.1, 139.3, 141.8, 144.7, 194.2. The other spectral properties were identical to those previously reported.[7]

Methyl fluorenone-2-carboxylate (2f).

^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 8.21 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.6, 120.4, 121.4, 124.8, 125.6, 130.4, 131.3, 134.4, 135.0, 135.2, 136.5, 143.5, 148.6, 166.3, 192.9; IR ($CDCl_3$) 2920, 2848, 1718 cm^{-1}; HRMS m/z 238.0634 (calcd for $C_{15}H_{10}O_3$, 238.0630).

2-Nitrofluoren-9-one (2g).

^{1}H NMR ($CDCl_3$) δ 7.46 (td, *J* = 7.6, 1.2 Hz, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.67-7.71 (m, 2H), 7.77 (d, *J* = 7.2 Hz, 1H), 8.42 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.47 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 119.8, 120.9, 122.0, 125.3, 130.1, 131.2, 135.2, 135.3, 135.7, 142.5, 149.0, 149.9, 191.1; IR ($CDCl_3$) 3096, 1712, 1518 cm^{-1}; HRMS m/z 225.0429 (calcd for $C_{13}H_7NO_3$, 225.0426).

Benzo[*b*]fluoren-11-one (2k).

^{1}H NMR ($CDCl_3$) 7.35 (dt, *J* = 7.4, 0.9 Hz, 1H), 7.47 (td, *J* = 8.1, 1.2 Hz, 1H), 7.55 (td, *J* = 8.1, 1.3 Hz, 1H), 7.56 (td, *J* = 7.4, 1.1 Hz, 1H), 7.72 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.75 (dt, *J* = 8.2, 0.7 Hz, 1H), 7.83 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.87 (s, 1H), 7.89 (dt, *J* = 8.1, 0.6 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$) 119.5, 121.4, 124.9, 126.1, 127.4, 129.2, 129.4, 129.6, 131.2, 133.2, 134.1, 135.4, 136.6, 137.4, 138.8, 145.3, 193.5; IR ($CDCl_3$) 3043, 1699 cm^{-1}; HRMS m/z 230.0734 (calcd for $C_{17}H_{10}O$, 230.0732).

1,3-Dimethylfluoren-9-one (2j).

The spectral properties were identical to those previously reported.[32]

1,3-Difluorofluoren-9-one (2i).

^{1}H NMR ($CDCl_3$) δ 6.66 (td, *J* = 9.2, 1.6 Hz, 1H), 7.05 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.38 (td, *J* = 7.6, 1.6 Hz, 1H), 7.50-7.55 (m, 2H), 7.68 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 104.9, 105.2 (q), 116.7 (d), 121.0, 124.7, 130.6, 134.6, 134.9, 142.1, 148.5 (q), 158.8 (d), 161.3, 166.8 (d), 169.4 (d), 188.8; IR (CH_2Cl_2) 3054, 2930, 1711 cm^{-1}; HRMS m/z 216.0390 (calcd for $C_{13}H_6F_2O$, 216.0387).

4-Chlorofluoren-9-one (2h).

^{1}H NMR ($CDCl_3$) δ 7.24 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 122.8, 124.3, 124.7, 129.7, 129.8, 130.2, 134.3, 135.2, 136.4, 136.6, 140.9, 143.4, 192.8; IR (CH_2Cl_2) 1718 cm^{-1}; HRMS m/z 214.0192 (calcd for $C_{13}H_7ClO$, 214.0189).

***N*-(Indeno[1,2-*d*]furan-6-ylidene)aniline (2m)**.

^{1}H NMR ($CDCl_3$) δ 6.51 (d, *J* = 2.0 Hz, 1H), 7.15-7.25 (m, 5H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$)

δ 106.2, 119.8, 121.5, 123.4, 125.6, 127.3, 128.9, 131.1, 134.8, 138.9, 141.0, 150.1, 150.5, 150.8, 152.4; HRMS m/z 245.0843 (calcd for $C_{17}H_{11}NO$, 245.0841).

Aniline (3).

The extent of deuterium incorporation was determined by ^{1}H NMR spectroscopy and mass spectral analysis. Aniline **3** obtained from the reaction illustrated in eq. 1, Scheme 4: ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2H), 6.68-6.80 (m, 2.68H), 7.17 (t, *J* = 7.5 Hz, 2H); peak intensity of m/z 93 is 100%, peak intensity of m/z 94 is 55%. Aniline **3** obtained from the reaction illustrated in eq. 2, Scheme 4: ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2H), 6.68-6.80 (m, 2.63H), 7.17 (t, *J* = 7.5 Hz, 2H); peak intensity of m/z 93 is 100%, peak intensity of m/z 94 is 60%. Aniline **3** obtained from the reaction illustrated in eq. 3, Scheme 4: ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2H), 6.68-6.80 (m, 2.28H), 7.17 (t, *J* = 7.5 Hz, 2H); peak intensity of m/z 93 is 50%, peak intensity of m/z 94 is 100%.

Xanthen-9-one (5a).

^{1}H NMR ($CDCl_3$) δ 7.37 (t, *J* = 6.0 Hz, 2H), 7.48 (d, *J* = 6.4 Hz, 2H), 7.70-7.74 (m, 2H), 8.33 (dd, *J* = 6.0, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) 118.2, 122.1, 124.1, 126.9, 135.0, 156.4, 177.4; IR ($CDCl_3$) 2914, 2874, 1654, 1456 cm^{-1}; HRMS m/z 196.0527 (calcd for $C_{13}H_8O_2$, 196.0524).

2-Methylxanthen-9-one (5b).

^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 7.32-7.52 (m, 4H), 7.66-7.72 (m, 1H), 8.10 (s, 1H), 8.32 (dd, *J* = 7.9, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 21.1, 117.9, 119.2, 121.7, 122.0, 123.9, 126.2, 126.9, 133.9, 134.8, 136.3, 154.6, 156.4, 177.5; IR ($CDCl_3$) 3060, 2921, 2862, 1657 cm^{-1}; HRMS m/z 210.0684 (calcd for $C_{14}H_{10}O_2$, 210.0681).

2-Methoxyxanthen-9-one (5c).

^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.30-7.49 (m, 4H), 7.68-7.73 (m, 2H), 8.34 (dd, *J* = 7.9, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 56.1, 106.0, 118.2, 119.6, 121.4, 122.3, 123.9, 125.1, 126.9, 134.8, 151.2, 156.2, 156.3, 177.3; IR ($CDCl_3$) 3014, 2980, 1664 cm^{-1}; HRMS m/z 226.0633 (calcd for $C_{14}H_{10}O_3$, 226.0630).

2-(Trifluoromethyl)xanthen-9-one (5d).

^{1}H NMR ($CDCl_3$) δ 7.40-7.44 (m, 1H), 7.50-7.52 (m, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.74-7.79 (m, 1H), 7.92 (dd, *J* = 8.8, 2.2 Hz, 1H), 8.33 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.62 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) 115.6, 118.3, 119.3, 121.8, 124.9, 125.0, 125.1, 127.1, 131.3, 135.7, 156.2, 176.4; IR ($CDCl_3$) 3083, 2961, 1666 cm^{-1}; HRMS m/z 264.0403 (calcd for $C_{14}H_7F_3O_2$, 264.0398).

2-Nitroxanthen-9-one (5e).

^{1}H NMR ($CDCl_3$) δ 7.46-7.50 (m, 1H), 7.56 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.65 (dd, *J* = 9.2, 0.3 Hz, 1H), 7.80-7.84 (m, 1H), 8.34-8.37 (m, 1H), 8.56 (dd, *J* = 9.1, 2.8 Hz, 1H), 9.21-9.22 (m, 1H); ^{13}C NMR ($CDCl_3$) 118.4, 119.9, 121.6, 121.9, 123.8, 125.5, 127.2, 129.3, 136.1, 156.1, 159.4, 175.9; IR ($CDCl_3$) 3077, 1667, 1611 cm^{-1}; HRMS m/z 241.0379 (calcd for $C_{13}H_7NO_4$, 241.0375).

2-Chloroxanthen-9-one (5f).

^{1}H NMR ($CDCl_3$) δ 7.37-7.41 (m, 1H), 7.43-7.49 (m, 2H), 7.64 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.72-7.76 (m, 1H), 8.27-8.32 (m, 2H); ^{13}C NMR ($CDCl_3$) 118.3, 120.0, 121.7, 122.9, 124.5, 126.2, 127.0, 129.9, 135.1, 135.4, 154.7, 156.2, 176.3; IR ($CDCl_3$) 3079, 1662 cm^{-1}; HRMS m/z 230.0137 (calcd for $C_{13}H_7ClO_2$, 230.0135).

2-*i*-Propylxanthen-9-one (5g).

^{1}H NMR ($CDCl_3$) δ 1.32 (d, *J* = 6.8 Hz, 6H), 2.98-3.12 (m, 1H), 7.34-7.49 (m, 3H), 7.60 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.68-7.74 (m, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 8.35 (dd, *J* = 7.9, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 24.2, 33.9, 118.1, 121.8, 122.0, 123.7, 123.9, 127.0, 134.0, 134.8, 144.9, 154.8, 156.4, 177.6; IR ($CDCl_3$) 2960, 2869, 1661 cm^{-1}; HRMS m/z 238.0997 (calcd for $C_{16}H_{14}O_2$, 238.0994).

2-Phenylxanthen-9-one (5h).

^{1}H NMR ($CDCl_3$) δ 7.37-7.41 (m, 2H), 7.46-7.52 (m, 3H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.67-7.76 (m, 3H), 7.96 (dd, *J* = 8.7, 2.4 Hz, 1H), 8.36 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.55 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 118.6, 118.7, 122.0, 122.1, 124.2, 124.8, 127.0, 127.3, 127.9, 129.2, 133.2, 133.9, 135.1, 137.3, 139.6, 155.8, 156.4, 177.4; IR ($CDCl_3$) 3062, 3034, 1661 cm^{-1}; HRMS m/z 272. 0842 (calcd for $C_{19}H_{12}O_2$, 272.0837).

2-*t*-Butylxanthen-9-one (5i).

^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 7.35-7.39 (m, 1H), 7.43-7.49 (m, 2H), 7.67-7.73 (m, 1H), 7.79 (dd, *J* = 8.8, 2.6 Hz, 1H), 8.32-8.36 (m, 2H); ^{13}C NMR ($CDCl_3$) 31.6, 35.0, 117.8, 118.1, 121.3, 122.0, 122.6, 123.9, 127.0, 133.0, 134.8, 147.3, 154.5, 156.4, 177.7; IR ($CDCl_3$) 2963, 2869, 1661 cm^{-1}; HRMS m/z 252.1154 (calcd for $C_{17}H_{16}O_2$, 252.1150).

4-Methoxy-2-methylxanthen-9-one (5k).

^{1}H NMR ($CDCl_3$) δ 2.44 (d, *J* = 0.6 Hz, 3H), 4.00 (s, 3H), 7.03 (d, *J* = 1.9 Hz, 1H), 7.34-7.38 (m, 1H), 7.57-7.59 (m, 1H), 7.67-7.73 (m, 2H), 8.32-8.33 (m, 1H); ^{13}C NMR ($CDCl_3$) 21.7, 56.6, 117.0, 117.1, 118.5, 121.9, 122.5, 124.1, 126.8, 133.7, 134.8, 144.9, 148.5, 156.1, 177.4; IR ($CDCl_3$) 2971, 2918, 1658 cm^{-1}; HRMS m/z 240.0790 (calcd for $C_{15}H_{12}O_3$, 240.0786).

10-Methyl-10*H*-acridin-9-one (5m).

^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.69-7.73 (m, 2H), 8.55 (dd, *J* = 8.0, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) 33.9, 115.0, 121.5, 122.7, 128.0, 134.0, 142.8, 178.3; IR ($CDCl_3$) 2917, 2850, 1637 cm^{-1}; HRMS m/z 209.0843 (calcd for $C_{14}H_{11}NO$, 209.0841).

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CHAPTER 4. SYNTHESIS OF XANTHONES, THIOXANTHONES AND ACRIDONES BY THE COUPLING OF ARYNES AND SUBSTITUTED BENZOATES

Based on a communication published in *Organic Letters* and a full paper published in the *Journal of Organic Chemistry*

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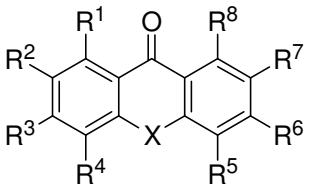
Abstract. The reaction of silylaryl triflates, CsF and *ortho* heteroatom-substituted benzoates affords a general and efficient way to prepare biologically-interesting xanthones, thioxanthones and acridones. This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the benzoate with an aryne and subsequent intramolecular electrophilic cyclization.

Introduction

Xanthones are secondary metabolites found in higher plant families, fungi and lichens.[1] This class of compounds exhibits interesting pharmaceutical properties; specifically, anti-bacterial, anti-inflammatory, anti-cancer, and anti-viral activities have been observed.[2] Some xanthone-containing plants, for example, *cratoxylum cochinchinense* (Lour.) Blume, have been used as traditional medicines to treat fever, coughing, diarrhea, itching, ulcers and abdominal complaints.[3] Thioxanthone derivatives also exhibit interesting anti-cancer

activities.[4] Xanthones are usually synthesized through the intermediacy of benzophenones or diaryl ethers under harsh reaction conditions and/or in the presence of



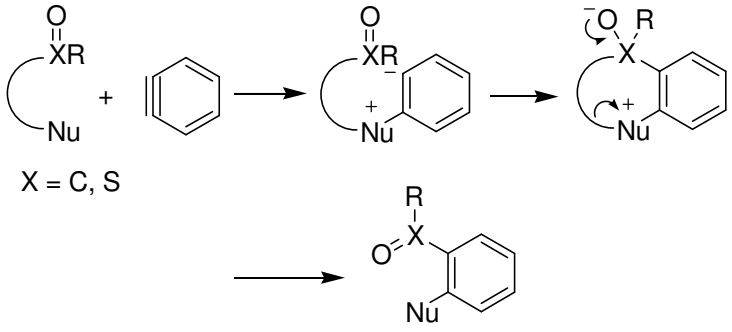
X = O Xanthones
X = S Thioxanthones
X = NR Acridones

strong acids or toxic metals.[5] Acridones are naturally-occurring compounds exhibiting a variety of biological activities. They are important anti-leishmanial, anti-fungal, anti-tumor and DNA-intercalating anti-cancer drugs.[6] Acridones are usually prepared by the acid-induced ring closure of *N*-phenyl anthranilic acids, which are usually obtained from Ullmann condensation of anilines with *ortho* halogen-substituted benzoic acids. However, harsh reaction conditions and tedious workup procedures are generally required.[7] An efficient and general synthesis of each of these heterocycles is thus highly desirable.

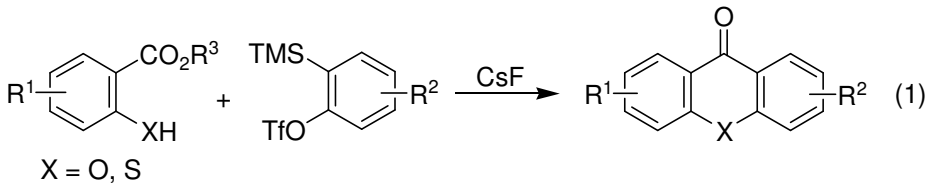
Benzyne, a highly reactive intermediate, was first proposed by Wittig in 1942,[8] and the structure was confirmed by Roberts in 1956 using ^{14}C isotope labeling.[9] Since then, many methods have been developed to generate benzynes, for example, the base-promoted elimination of hydrogen halide from aryl halides,[10] the elimination of *o*-dihaloaromatics with lithium amalgam or magnesium,[11] or the recently reported decomposition of 2-magnesiated aryl sulfonates.[12] In 1983, Kobayashi first reported a novel way to generate arynes from silylaryl triflate precursors in the presence of CsF.[13] Later, nucleophiles bearing neighboring electrophiles, such as ureas,[14] trifluoroacetanilides and sulfinamides,[15] and β-keto esters[16] have been shown to react with these aryne precursors to afford the C-N bond or C-C bond insertion products (Scheme 1). These nucleophiles first undergo intermolecular nucleophilic

attack on the aryne. Subsequent intramolecular electrophilic cyclization, followed by fragmentation, affords the final insertion product.

Scheme 1. Aryne Insertion Reactions.



Recently, we communicated a novel annulation reaction utilizing readily accessible salicylates and silylaryl triflates plus CsF, which affords an efficient one-step synthesis of biologically-interesting xanthones and thioxanthones (eq. 1).[17] This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the benzoate and aryne, and subsequent intramolecular electrophilic cyclization. A fragmentation step, which is inevitable in the insertion examples, is not involved in this annulation process, because the intermediate obtained from the cyclization is a stable 6-membered ring system. Herein, we provide a full account of this efficient synthesis of xanthones and thioxanthones, plus, we also wish to report an extension of this coupling-cyclization strategy to the synthesis of biologically-interesting acridones.



Results and Discussion

Optimization Studies. The reaction of methyl salicylate (**1a**) and the commercially available aryne precursor *o*-(trimethylsilyl)phenyl triflate (**2a**) was first conducted in the presence of 4 equiv of CsF in 5 mL of MeCN. After 12 h reaction at room temperature, an 80% combined yield of methyl 2-phenoxybenzoate (**3a**) and xanthone (**4a**) was obtained in a 40:60 ratio (Table 1, entry 1). Presumably, this reaction proceeds through the key intermediate **B** generated by nucleophilic coupling of the aryne and the aryloxide **A** (Scheme 2). The carbanion **B** can either undergo H abstraction to afford benzoate **3a** or intramolecular electrophilic cyclization to generate the xanthone (**4a**). The major problem here is the proton abstraction process, which could be suppressed by adjusting the reaction conditions, for example, using different solvents and concentrations. Thus,

Table 1. Optimization Studies.

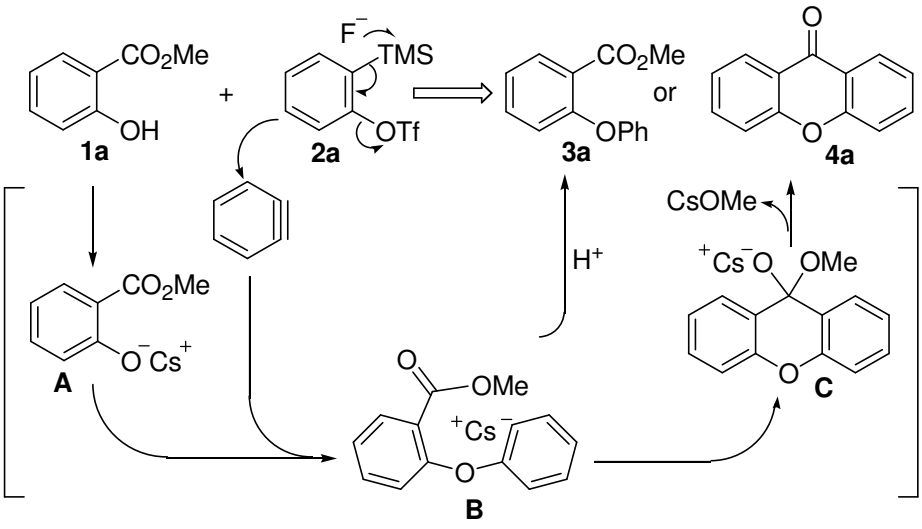
entry	fluoride source	solvent	temp (^{o}C)	time (h)	% yield (**3a**:**4a**)[a]
1	4 CsF	MeCN	rt	12	80 (40:60)
2	4 CsF	acetone	rt	4	75 (38:62)
3	4 CsF	CH_2Cl_2	rt	24	trace
4	4 CsF	THF	rt	24	20 (5:95)
5	4 CsF	toluene	100	48	trace
6	4 CsF	$MeNO_2$	rt	24	-
7	4 CsF	THF	65	24	82 (8:92)
8	4 CsF	THF	90	12	80 (14:86)
9	4 CsF	THF	50	24	30 (6:94)
10	4 CsF	DME	65	24	70 (25:75)
11	4 TBAF	THF	65	3	60 (83:17)
12	2 CsF	THF	65	24	65 (8:92)

[a]All reactions were conducted on a 0.25 mmol scale in 5 mL of solvent (sealed vial). The ratio of methyl salicylate to aryne precursor is 1 to 1.1. The ratio of **3a** to **4a** in parentheses has been determined by GC-MS analysis.

we next conducted the coupling-cyclization reaction in acetone, and a 75% yield of diaryl ether **3a** and xanthone (**4a**) was obtained in a 38:62 ratio (entry 2), which suggests that a less

polar solvent should be examined. We then performed the reaction in CH_2Cl_2. However, only a trace of the xanthone (**4a**) was observed by GC-MS analysis after 24 h (entry 3). When THF was used as the solvent at room temperature, after 24 h reaction, a 20% yield of products **3a** and **4a** was obtained, and a lot of the starting materials **1a** and **2a** was observed by GC-MS analysis. However, the ratio of **3a** to **4a** was 5:95, suggesting that proton abstraction has been almost completely suppressed (entry 4). When this reaction was conducted in toluene, only a trace of the product was evident by GC-MS analysis (entry 5). $MeNO_2$ also turned out to be an unsuitable solvent for this reaction (entry 6). At this point, THF seemed to be the best solvent, at least as far as the reaction selectivity was concerned. The same reaction was then carried out at 65 ^oC in THF for 24 h. A 75% yield of xanthone (**4a**) was isolated by flash chromatography and GC-MS analysis indicated only a trace of the diaryl ether **3a** was obtained (entry 7).

Scheme 2



Further investigation indicated that a reaction temperature of 90 ^oC or 50 ^oC reduces the amount of xanthone product (entries 8 and 9). When DME was used as the solvent, the

reaction afforded only a 70% yield of two isomers formed in a 25:75 ratio (entry 10). The effect of the fluoride source has also been examined in this process. When tetrabutylammonium fluoride (TBAF) was used as the fluoride source, the reaction proceeded much faster. After 3 h, all of the starting materials were consumed and the proton abstraction product **3a** predominated (entry 11). A 65% yield of an 8:92 ratio of **3a** and **4a** was obtained when this reaction was carried out in the presence of 2 equiv of CsF (entry 12). In conclusion, the "optimal" reaction conditions for this one-step synthesis of xanthone utilize 4 equiv of CsF in THF solvent at 65 ^{o}C for 24 h (entry 7).

Synthesis of Xanthones. Employing our "optimal" reaction conditions, we have investigated the reaction scope and limitations of this process. These results are summarized in Table 2. We first examined the effect of a methoxy substituent on the salicylate ring to determine which position on the salicylate ring affords the best yield of xanthone. Thus, salicylates **1b**, **1c**, **1d** and **1e** were employed, and 35-69% yields of substituted xanthones **4b**-**4e** were obtained (entries 2-5). Having an electron-donating methoxy group in the 5 position of the salicylate ring gave the highest yield (entry 4). The yields of xanthones from the 3- and 4-methoxy starting materials were only slightly lower, but the 6-methoxy isomer gave a much lower yield. When methyl 5-acetylsalicylate (**1f**) with an electron-withdrawing group in the 5 position was used as the starting material, a 58% yield of xanthone **4f** was isolated by flash chromatography (entry 6). On the other hand, the reaction of methyl 5-fluorosalicylate (**1g**) and aryne precursor **2a** affords an 83% yield of xanthone **4g** (entry 7). The reaction of methyl 5- bromosalicylate (**1h**) with aryne **2a** affords a 75% yield of the product **4h** (entry 8). The phenyl- and methyl-substituted salicylates **1i** and **1j** afforded 64% and 71% yields of the corresponding xanthone products respectively (entries 9 and 10). When methyl 5-

Table 2. Synthesis of Xanthones.[a]

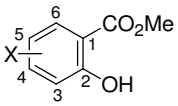
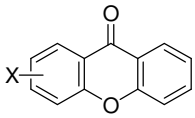
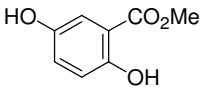
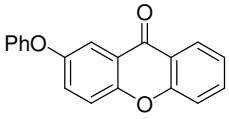
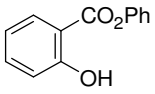
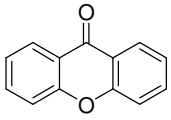
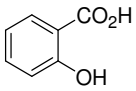
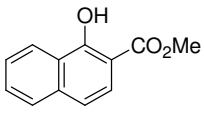
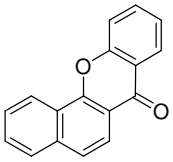
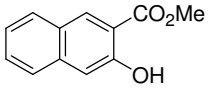
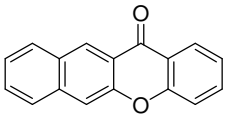
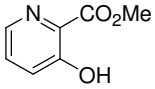
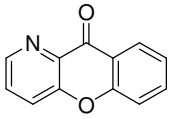
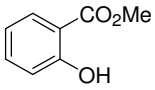
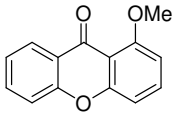
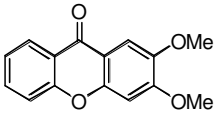
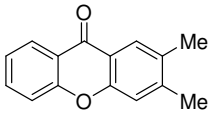
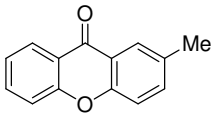
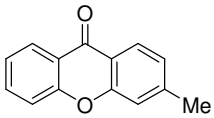
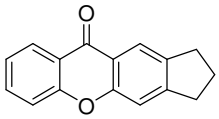
entry	salicylate		aryne	product(s)		% yield
						
	X					
1	H	**1a**	**2a**		**4a**	75
2	3-OMe	**1b**	**2a**		**4b**	59
3	4-OMe	**1c**	**2a**		**4c**	62[b]
4	5-OMe	**1d**	**2a**		**4d**	69
5	6-OMe	**1e**	**2a**		**4e**	35
6	5-COMe	**1f**	**2a**		**4f**	58
7	5-F	**1g**	**2a**		**4g**	83
8	5-Br	**1h**	**2a**		**4h**	75
9	5-Ph	**1i**	**2a**		**4i**	64
10	5-Me	**1j**	**2a**		**4j**	71
11		**1k**	**2a**		**4k**	52
12		**1l**	**2a**		**4a**	81
13		**1m**	**2a**		**4a**	0
14		**1n**	**2a**		**4l**	73

Table 2. (Continued)

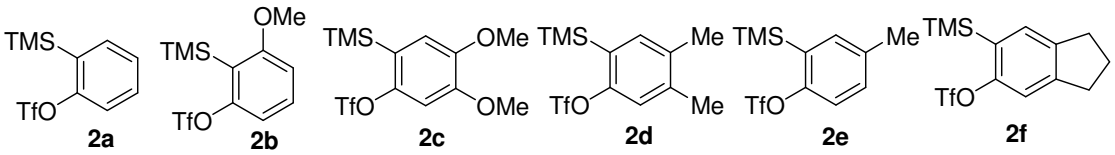
entry	salicylate		aryne	product(s)		% yield
15		**1o**	**2a**		**4m**	46[c]
16		**1p**	**2a**		**4n**	0
17		**1a**	**2b**		**4e**	62[b]
18		**1a**	**2c**		**4o**	57[b]
19		**1a**	**2d**		**4p**	51[b]
20		**1a**	**2e**		**4j**	59[b] (1:1)
					**4q**	
21		**1a**	**2f**		**4r**	45[b]

[a]All reactions were conducted on a 0.25 mmol scale in the presence of 4 equiv of CsF and 1.1 equiv of silylaryl triflate in 5 mL of THF at 65 °C for 24 h (sealed vial) unless otherwise stated. [b]The reaction was conducted in 5 mL of THF at 90 °C. [c]The yield has been determined by GC analysis due to the impurities in the product.

hydroxysalicylate (**1k**) is allowed to react with 2.5 equiv of aryne precursor **2a**, the *O*-arylated xanthone product **4k** was isolated in a 52% yield (entry 11). We have previously reported the

facile arylation of phenols by these same aryne precursors.[18] From these results with 5-substituted salicylates, there is no obvious correlation between the electronic properties of the substituent and the yield. Phenyl salicylate (**1l**) has been employed in this reaction and an 81% yield of xanthone **4a** was obtained (entry 12). Assuming that 2-hydroxybenzoic acid would first form the corresponding phenyl ester **1l**,[18] which should then afford the corresponding xanthone (**4a**), we treated 2 equiv of benzyne precursor **2a** and 2-hydroxybenzoic acid (**1m**) in the usual fashion. Unfortunately, none of the desired product was observed for reasons we do not really understand at this time (entry 13). Interestingly, the cross coupling of methyl 1-hydroxy-2-naphthoate (**1n**) with silylaryl triflate **2a** affords a 73% yield of xanthone **4l**, but the reaction using methyl 2-hydroxy-3-naphthoate (**1o**) only generates a 48% yield of the product **4m** (entries 14 and 15). This latter reaction produced several side products which have not been identified. The annulation of **1p**, which contains a pyridine ring, afforded none of the xanthone product under our "optimal" conditions (entry 16). Again, we are uncertain why this latter reaction failed.

Scheme 3. Aryne Precursors.

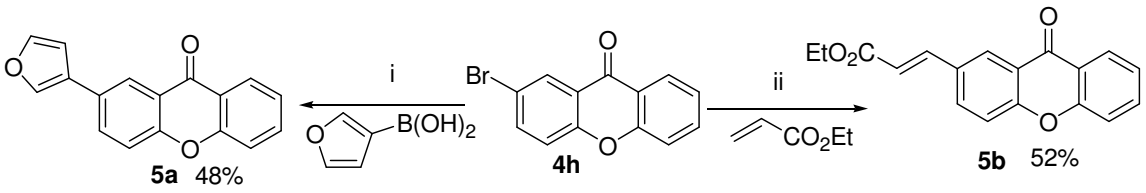


After investigating the effect of varying the salicylate structure, we examined the reaction efficiency using different aryne precursors (Scheme 3). A 62% yield of a single isomeric methoxyxanthone **4e** was obtained from the reaction of methyl salicylate **1a** with aryne precursor **2b** after 24 h at 90 ^{o}C (entry 17). Note that a somewhat higher temperature was required to get a good yield. The regioselectivity of this reaction is due to the steric and

electronic effects in the step involving nucleophilic attack on the aryne, which has been seen in several previous reactions involving this aryne.[18] When the dimethoxysilylaryl triflate **2c** was employed, a 57% yield of xanthone **4o** was isolated (entry 18). Again a higher temperature was required. The reaction of aryne precursor **2d** with methyl salicylate (**1a**) afforded a 51% yield of xanthone **4p** (entry 19). When aryne precursor **2e** was employed, a 59% yield of two isomeric xanthones **4j** and **4q** was obtained in a 1:1 ratio (entry 20). This is consistent with the intermediacy of an unsymmetrical methyl-substituted benzyne. Aryne precursor **2f** afforded a 45% yield of a single xanthone product **4r** (entry 21).

One of the major advantages of this methodology is that halogen atoms can be tolerated, which provides access to more structurally diverse xanthone skeletons via metal-catalyzed cross-coupling reactions. As illustrated in Scheme 4, the halogen-substituted xanthone product **4h** can be further modified by Heck[19] and Suzuki[20] reactions, affording interesting xanthone derivatives **5a** and **5b** for further biological examination.

Scheme 4. Diversification of Halogen-substituted Xanthones.

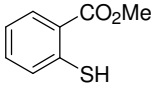
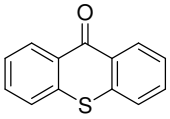
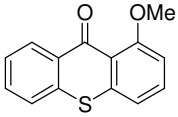
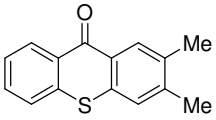
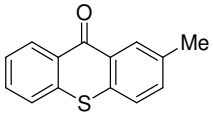
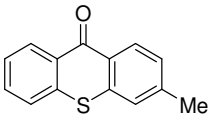
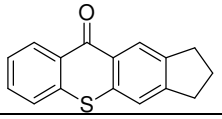


(i) 5% $Pd(PPh_3)_4$, 1 Na_2CO_3, 1:4 MeOH/Toluene, 80 °C, 12 h; (ii) 5% $Pd(OAc)_2$, 2 $NaHCO_3$, 1 TBAC, DMF, 100 °C, 24 h.

Synthesis of Thioxanthones. Biologically-interesting thioxanthone derivatives have also been prepared by this same methodology. All of the results are summarized in Table 3. Methyl thiosalicylate (**6a**) and 1.1 equiv of benzyne precursor **2a** were treated with 4 equiv of CsF in 5 mL of THF at 65 °C, after 24 h, a 35% yield of thioxanthone (**7a**) was isolated. The lower yield in this example is presumably due to oxidative homocoupling of the thiols, since

thiols are known to afford disulfides in the presence of CsF on a celite solid support in air.[21] In order to suppress this undesired homocoupling process, the same reaction was repeated under an Ar atmosphere, and a 55% yield of thioxanthone (**7a**) was obtained. Further optimization indicated that a 64% yield of product **7a** could be obtained under more dilute conditions, although a small amount of disulfide product and *S*-arylation product were present (Table 3, entry 1). The reaction of this thiol with benzyne precursor **2b** afforded a 45% yield of the desired thioxanthone **7b** (entry 2). When **2d** was employed as the aryne precursor in this reaction, a 40% yield of the product **7c** was isolated (entry 3). The reaction of **2e** afforded a 56% yield of two regioisomers **7d** and **7e** in a 1:1 ratio (entry 4). Finally,

Table 3. Synthesis of Thioxanthones.[a]

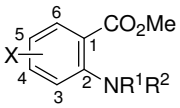
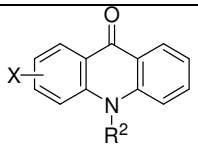
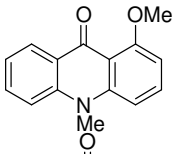
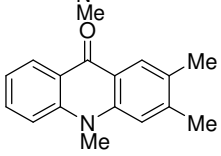
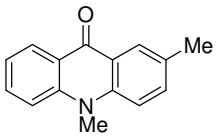
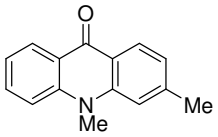
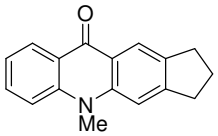
entry	thiosalicylate	aryne	product(s)	% yield
1	 **6a**	**2a**	 **7a**	64
2	**6a**	**2b**	 **7b**	45[b]
3	**6a**	**2d**	 **7c**	40[b]
4	**6a**	**2e**	 **7d**	56[b,c] (1:1)
			 **7e**	
5	**6a**	**2f**	 **7f**	62[b]

[a]All reactions were conducted on a 0.25 mmol scale in the presence of 4 equiv of CsF and 1.1 equiv of silylaryl triflate in 10 mL of THF at 65 °C under Ar. [b]The reaction was conducted in 10 mL of THF at 90 °C under Ar (sealed tube). [c]The ratio in parentheses has been determined by ^{1}H NMR spectroscopy.

aryne precursor **2f** was allowed to react with thiosalicylate **6a**, and a 62% yield of thioxanthone **7f** was isolated by flash chromatography (entry 5).

Synthesis of Acridones. After we had a general and efficient synthesis of xanthones and thioxanthones in hand, we attempted to expand this methodology to the synthesis of acridones, a well-known class of anti-fungal, anti-tumor and anti-cancer compounds.[6] Acridones have been prepared by the coupling of 3-halogeno-4-methoxybenzynes generated from 5-(3-halogeno-4-methoxyphenyl)thianthrenium perchlorates and LDA in THF at reflux with 2-aminobenzoate.[22] However, this protocol employs a fairly unusual aryne precursor, and it also suffers from the moisture-sensitive reagents and conditions. Methyl 2-aminobenzoate (**8a**) was first prepared and allowed to react with aryne precursor **2a**, and a 50% yield of the acridone product **9a** was obtained (Table 4, entry 1). Methyl 2-(*N*-methylamino)benzoate (**8b**) was then allowed to react with aryne precursor **2a**. After 1 day of reaction, a 72% yield of acridone **9b** was isolated by flash chromatography(entry 2). However, the reaction employing methyl 2-(*N*-phenylamino)benzoate (**8c**) was very sluggish; after 2 days of reaction, only a 7% yield of the desired product **9c** was observed by GC-MS analysis. The low yield is presumably due to the steric hindrance introduced by the presence of the phenyl substituent (entry 3). Interestingly, the reaction of methyl 2-(*N*,*N*-dimethylamino)benzoate (**8d**) affords a 65% yield of acridone product **9b**, which indicates that even tertiary amines can be successfully employed in this transformation (entry 4). Apparently the anticipated ammonium-containing product undergoes demethylation under the reaction conditions. Several halogen-substituted benzoates (**8e**-**8g**) have also been prepared from the corresponding acids and employed in this process (entries 5-7). Yields of 48-71% of the corresponding acridone products (**9d**-**9f**) have been obtained. We have not employed

Table 4. Synthesis of Acridones.[a]

entry	benzoate				aryne	product(s)		% yield
								
	R^1	R^2	X					
1	H	H	H	**8a**	**2a**		**9a**	50
2	H	Me	H	**8b**	**2a**		**9b**	72
3	H	Ph	H	**8c**	**2a**		**9c**	7[b]
4	Me	Me	H	**8d**	**2a**		**9b**	65
5	H	Me	4-F	**8e**	**2a**		**9d**	48
6	H	Me	5-F	**8f**	**2a**		**9e**	71
7	H	Me	5-Br	**8g**	**2a**		**9f**	61
8	H	Me	H	**8b**	**2b**		**9g**	trace[c]
9	H	Me	H	**8b**	**2d**		**9h**	27[c]
10	H	Me	H	**8b**	**2e**		**9i**	51[c] (1:1)
							**9j**	
11	H	Me	H	**8b**	**2f**		**9k**	35[c]

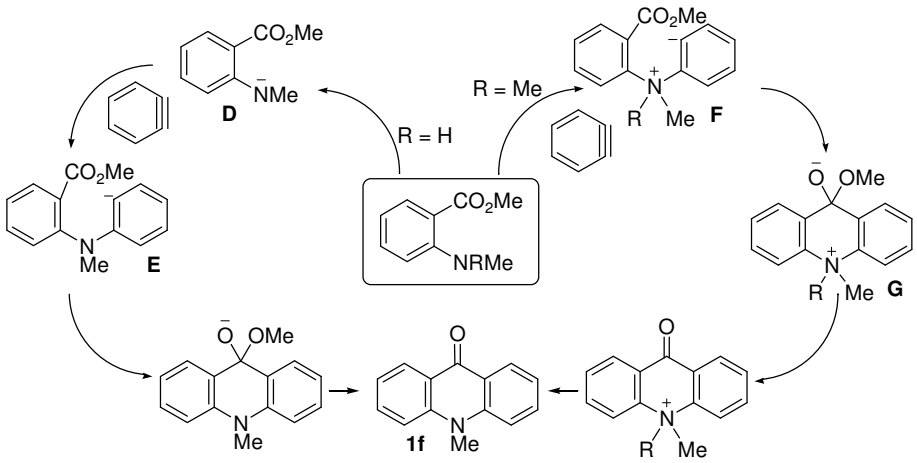
[a]All reactions were conducted on a 0.25 mmol scale in the presence of 4 equiv of CsF and 1.1 equiv of the silylaryl triflate in 10 mL of THF at 65 °C. [b]The yield was determined by GC-MS analysis. [c]The reaction was conducted in 10 mL of THF at 90 °C (sealed tube). The ratio in parentheses has been determined by ^{1}H NMR spectroscopy.

protecting groups on nitrogen since that could well lead to C-N insertion products.[14,15]

At this point, we examined the effect of the aryne structure on the yield of acridone. When silylaryl triflate **2b** was employed with benzoate **8b**, the reaction was very sluggish and only a trace amount of the desired acridone product **9g** was observed by GC-MS analysis (entry 8). Aryne precursor **2d** afforded only a 27% yield of the product **9h** and this reaction had to be run at 90 ^{o}C (entry 9). The reaction of aryne precursor **2e** with benzoate **8a** afforded a 51% yield of two isomeric acridones, **9i** and **9j**, in a 1:1 ratio (entry 10). A 35% yield of acridone product **9k** was obtained when aryne precursor **2f** was employed (entry 11). These last two reactions also had to be run at 90 ^{o}C.

A plausible mechanism for these aminobenzoate reactions is proposed in Scheme 4. The benzoate bearing an amino group presumably first undergoes nucleophilic attack on the aryne generated *in situ* from the silylaryl triflate. When R is a proton, the actual nucleophile involved could be either the neutral amine or the anionic intermediate **D** generated by

Scheme 4. Plausible Mechanism for the Acridone Synthesis.



hydrogen abstraction from the amine by CsF. However, when the tertiary amine **8d** is employed, although no proton is available for abstraction, this reaction still works well,

suggesting that the neutral amine itself is nucleophilic enough for this transformation. Therefore, the reaction mechanism which proceeds via intermediates **F** and **G** seems more likely, although we cannot rule out possible anionic nucleophilic attack on the aryne, which proceeds via intermediates **D** and **E**. Subsequent intramolecular cyclization should afford the final acridone products.

Conclusions

A general one-pot synthesis of biologically-interesting xanthones, thioxanthones and acridones has been developed. This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the substituted benzoates and arynes and subsequent intramolecular electrophilic cyclization. The mild reaction conditions and generally high reaction efficiency provide advantages over previously reported multi-step procedures. In generally, this strategy tolerates both electron-donating and electron-withdrawing functionalities on the benzoate ring, but substituents on the aryne ring appear to lower the yields of the desired products.

Experimental Section

I. General Procedures.

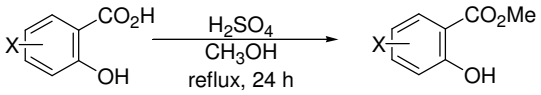
All ^{1}H and ^{13}C NMR spectra were collected in $CDCl_3$ unless noted otherwise. Thin layer chromatography was performed using 60-mesh silica gel plates, and visualization was affected using wavelength UV light (254 nm) and a basic $KMnO_4$ solution. All high resolution mass spectra were recorded using EI.

All reagents were used directly as obtained commercially unless otherwise noted. MeCN was dried by CaH_2, and THF solvent was dried over Na/benzophenone. The salicylates **1a**-**d**,

1f, **1g** and **1j**-**o**, the salicylic acids used to prepare salicylates **1e**, **1h**, **1i** and **1p**, the thiosalicylate **6a**, the anthranilic acids used to prepare amino esters **8a**-**g**, and the aryne precursor **2a** and CsF are commercially available. Aryne precursors **2b**-**f** were prepared according to literature procedures.[15]

II. Non-commercial compounds.

Non-commercial methyl salicylates were prepared from the corresponding salicylic acids by the following procedure. The salicylic acid (5.0 mmol) was dissolved in 50 mL of methanol, and 1 mL of concentrated H_2SO_4 was cautiously added to the mixture. The reaction mixture was refluxed for 24 h.



Methyl 6-methoxysalicylate (1e).

^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 3.92 (s, 3H), 6.38 (d, *J* = 8.3 Hz, 1H), 6.57 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.30 (t, *J* = 8.3 Hz, 1H), 11.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.7, 56.4, 102.4, 103.3, 110.3, 135.3, 161.0, 163.8, 171.8; IR ($CDCl_3$) 3250, 3010, 2956, 1654 cm^{-1}; HRMS m/z 182.0581 (calcd for $C_9H_{10}O_4$, 182.0579).

Methyl 5-bromosalicylate (1h).

^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 6.87 (d, *J* = 8.9 Hz, 1H), 7.52 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.94 (d, *J* = 2.5 Hz, 1H), 10.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.9, 110.0, 114.0, 119.8, 132.4, 138.6, 160.8, 169.7; IR ($CDCl_3$) 3177, 2954, 2854, 1678 cm^{-1}; HRMS m/z 229.9582 (calcd for $C_8H_7BrO_3$, 229.9579).

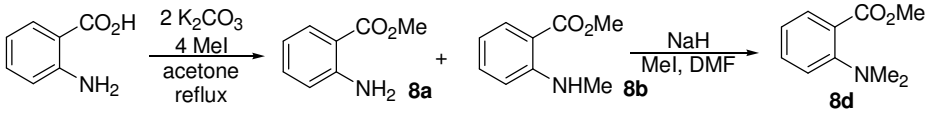
Methyl 5-phenylsalicylate (1i).

^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H), 7.07 (d, J = 8.6 Hz, 1H), 7.32-7.36 (m, 1H), 7.42-7.46 (m, 2H), 7.55-7.57 (m, 2H), 7.71 (dd, J = 8.7, 2.4 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H), 10.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.7, 112.7, 118.3, 126.9, 127.3, 128.4, 129.1, 132.7, 134.7, 140.1, 161.2, 170.8; IR ($CDCl_3$) 3220, 2960, 1675 cm^{-1}; HRMS m/z 228.0784 (calcd for $C_{14}H_{12}O_3$, 228.0786).

Methyl 3-hydroxypyridine-2-carboxylate (1p).

^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 7.12-7.22 (m, 2H), 8.04 (s, 1H), 10.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 53.2, 126.2, 129.6, 130.0, 141.4, 158.7, 169.8; IR ($CDCl_3$) 3106, 2956, 1678 cm^{-1}; HRMS m/z 153.0428 (calcd for $C_7H_7NO_3$, 153.0426).

The amino esters were prepared from the corresponding anthranilic acids by the following procedure. Anthranilic acid (5.0 mmol), K_2CO_3 (10.0 mmol), and MeI (20.0 mmol) were added to 50 mL of acetone and refluxed for 3 h. Esters **8a** and **8b** were separated by flash chromatography, and **8b** was converted to **8d** by treating it with NaH and MeI in DMF for 24 h.



Methyl 2-aminobenzoate (8a).

^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 5.78 (s, 2H), 6.61-6.64 (m, 2H), 7.22-7.26 (m, 1H), 7.84-7.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 51.8, 110.8, 116.4, 116.9, 131.4, 134.3, 150.8, 168.8; IR ($CDCl_3$) 3481, 3372, 2950, 2903, 1695 cm^{-1}; HRMS m/z 151.0635 (calcd for $C_8H_9NO_2$, 151.0633).

Methyl 2-(*N*-methylamino)benzoate (8b).

^{1}H NMR ($CDCl_3$) δ 2.91 (d, *J* = 5.0 Hz, 3H), 3.8 (s, 3H), 6.57-6.68 (m, 2H), 7.36-7.42 (m, 1H), 7.67 (s, 1H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 51.6, 110.1, 110.9, 114.6, 131.8, 134.9, 152.2, 169.3; IR ($CDCl_3$) 3368, 2990, 2871, 1685 cm^{-1}; HRMS m/z 165.0792 (calcd for $C_9H_{11}NO_2$, 165.0790).

Methyl 2-(*N*-phenylamino)benzoate (8c).

^{1}H NMR ($CDCl_3$) δ 3.9 (s, 3H), 6.77-6.81 (m, 1H), 7.15 (t, *J* = 5.1 Hz, 1H), 7.31-7.42 (m, 6H), 8.02-8.05 (m, 1H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.1, 112.2, 114.3, 117.4, 122.7, 123.8, 129.7, 131.9, 134.4, 141.0, 148.2, 169.2; IR ($CDCl_3$) 3365, 2965, 1667 cm^{-1}; HRMS m/z 227.0966 (calcd for $C_{14}H_{13}NO_2$, 227.09463).

Methyl 2-(*N*,*N*-dimethylamino)benzoate (8d).

^{1}H NMR ($CDCl_3$) δ 2.79 (s, 6H), 3.84 (s, 3H), 6.79 (t, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 7.29 (m, 1H), 7.62 (dd, *J* = 7.8, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.8, 52.2, 116.8, 118.8, 121.1, 131.8, 132.4, 152.5, 169.1; IR ($CDCl_3$) 2986, 2948, 1717 cm^{-1}; HRMS m/z 179.0949 (calcd for $C_{10}H_{13}NO_2$, 179.0946).

Methyl 4-fluoro-2-(*N*-methylamino)benzoate (8e).

^{1}H NMR ($CDCl_3$) δ 2.86 (s, 3H), 3.82 (s, 3H), 6.24 (m, 2H), 7.8 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.8, 51.7, 97.0, 97.2, 102.1, 102.4, 106.7, 134.3, 134.4, 154.3, 154.4, 166.3, 168.5, 168.8; IR ($CDCl_3$) 3373, 2994, 2951, 1689 cm^{-1}; HRMS m/z 183.0698 (calcd for $C_9H_{10}FNO_2$, 183.0696).

Methyl 5-fluoro-2-(*N*-methylamino)benzoate (8f).

^{1}H NMR ($CDCl_3$) δ 2.85 (s, 3H), 3.82 (s, 3H), 6.52 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.07-7.12 (m, 1H), 7.41 (s, 1H), 7.55 (dd, *J* = 9.7, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0, 51.8, 109.6, 109.7, 111.8, 111.9, 115.6, 116.7, 122.3, 122.5, 149.0, 151.9, 154.2, 168.3, 168.4; IR

($CDCl_3$) 3392, 2957, 2915, 1684 cm^{-1}; HRMS m/z 183.0698 (calcd for $C_9H_{10}FNO_2$, 183.0696).

Methyl 5-bromo-2-(*N*-methylamino)benzoate (8g).

^1H NMR ($CDCl_3$) δ 2.87 (d, *J* = 4.2 Hz, 3H), 3.83 (s, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 7.40 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.63 (s, 1H), 7.97 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 51.9, 105.8, 111.4, 112.8, 133.9, 137.4, 151.0, 168.2; IR ($CDCl_3$) 3377, 2948, 2909, 1689 cm^{-1}; HRMS m/z 242.9898 (calcd for $C_9H_{10}BrNO_2$, 242.9895).

III. Experimental Procedures.

Representative procedure for the coupling-cyclization of arynes and salicylates. CsF (1.0 mmol), the salicylate (0.25 mmol), and the silylaryl triflate (0.28 mmol) in 5 mL of anhydrous THF were stirred at 65 or 90 °C for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (25 mL) and washed with brine (25 mL). The aqueous layer was re-extracted with diethyl ether (2 x 25 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel.

Representative procedure for the coupling-cyclization of arynes and thiosalicylates. CsF (1.0 mmol), the thiosalicylate (0.25 mmol) and the silylaryl triflate (0.28 mmol) were added to 10 mL of anhydrous THF, and the reaction vial was flushed with Ar. The whole reaction solution was then stirred at 65 or 90 °C for 24 h and worked up as described previously.

Representative procedure for the coupling-cyclization of arynes and 2-aminobenzoates. CsF (1.0 mmol), the 2-aminobenzoate (0.25 mmol), and the silylaryl

triflate (0.28 mmol) in 10 mL of anhydrous THF were stirred at 65 or 90 °C for 24 h and worked up as described previously.

9*H*-Xanthen-9-one (4a).

^{1}H NMR ($CDCl_3$) δ 7.37 (t, *J* = 6.0 Hz, 2H), 7.48 (d, *J* = 6.4 Hz, 2H), 7.70-7.74 (m, 2H), 8.33 (dd, *J* = 6.0, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 118.2, 122.1, 124.1, 126.9, 135.0, 156.4, 177.4; IR ($CDCl_3$) 2914, 2874, 1654, 1456 cm^{-1}; HRMS m/z 196.0527 (calcd for $C_{13}H_8O_2$, 196.0524).

4-Methoxy-9*H*-xanthen-9-one (4b).

^{1}H NMR ($CDCl_3$) δ 4.03 (s, 3H), 7.22-7.31 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.71-7.75 (m, 1H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.33 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.7, 115.5, 117.8, 118.5, 121.9, 122.9, 123.7, 124.3, 126.9, 135.0, 146.7, 148.8, 156.2, 177.4; IR ($CDCl_3$) 3026, 2951, 2849, 1660 cm^{-1}; HRMS m/z 226.0632 (calcd for $C_{14}H_{10}O_3$, 226.0630).

3-Methoxy-9*H*-xanthen-9-one (4c).

^{1}H NMR ($CDCl_3$) δ 3.92 (s, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.34-7.38 (m, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.66-7.70 (m, 1H), 8.27 (d, *J* = 8.9 Hz, 1H), 8.31 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.1, 100.4, 113.5, 116.0, 117.9, 122.2, 124.1, 126.9, 128.5, 134.5, 156.4, 158.3, 165.3, 176.5; IR ($CDCl_3$) 3068, 2950, 2843, 1650 cm^{-1}; HRMS m/z 226.0634 (calcd for $C_{14}H_{10}O_3$, 226.0630).

2-Methoxy-9*H*-xanthen-9-one (4d).

^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.26-7.49 (m, 4H), 7.69-7.72 (m, 2H), 8.33 (dd, *J* = 5.9, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.2, 106.0, 118.2, 119.6, 121.4, 122.3, 123.9, 125.1,

126.9, 134.8, 151.2, 156.2, 156.3, 177.3; IR ($CDCl_3$) 3014, 2981, 1666, 1467 cm^{-1}; HRMS m/z 226.0633 (calcd for $C_{14}H_{10}O_3$, 226.0630).

1-Methoxy-9*H*-xanthen-9-one (4e).

^1H NMR ($CDCl_3$) δ 4.00 (s, 3H), 6.77 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 7.26-7.40 (m, 2H), 7.55-7.67 (m, 2H), 8.29 (dd, *J* = 8.0, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.7, 105.6, 110.2, 112.8, 117.5, 123.2, 124.0, 127.0, 134.4, 135.0, 155.2, 158.4, 161.0, 176.7; IR ($CDCl_3$) 2971, 2946, 1666, 1474 cm^{-1}; HRMS m/z 226.0633 (calcd for $C_{14}H_{10}O_3$, 226.0630).

2-Acetyl-9*H*-xanthen-9-one (4f).

^1H NMR ($CDCl_3$) δ 2.71 (s, 3H), 7.42 (td, *J* = 5.3, 0.7 Hz, 1H), 7.51-7.56 (m, 2H), 7.76 (td, *J* = 6.2, 1.3 Hz, 1H), 8.33-8.36 (m, 2H), 8.86 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.9, 118.4, 119.1, 121.4, 121.9, 124.9, 127.1, 128.6, 133.1, 134.1, 135.6, 156.2, 159.1, 176.9, 196.6; IR ($CDCl_3$) 3066, 2972, 1665, 1652 cm^{-1}; HRMS m/z 238.0632 (calcd for $C_{15}H_{10}O_3$, 238.0630).

2-Fluoro-9*H*-xanthen-9-one (4g).

^1H NMR ($CDCl_3$) δ 7.35-7.51 (m, 4H), 7.73 (td, *J* = 7.2, 1.7 Hz, 1H), 7.95 (dd, *J* = 8.2, 2.8 Hz, 1H), 8.30 (dd, *J* = 7.9, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 111.6 (d, *J* = 13.7 Hz), 118.2, 120.20 (d, *J* = 8.1 Hz), 121.2, 122.8 (d, *J* = 7.0 Hz), 123.1 (d, *J* = 25.3 Hz), 124.3, 126.9, 135.3, 152.5 (d, *J* = 1.6 Hz), 156.3, 158.9 (d, *J* = 245.5 Hz), 176.7 (d, *J* = 2.4 Hz); IR ($CDCl_3$) 3087, 1664, 1157 cm^{-1}; HRMS m/z 214.0433 (calcd for $C_{13}H_7FO_2$, 214.0430).

2-Bromo-9*H*-xanthen-9-one (4h).

^1H NMR ($CDCl_3$) δ 7.36-7.40 (m, 2H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.71-7.79 (m, 2H), 8.30 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.42 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 117.3, 118.3, 120.2,

121.7, 123.3, 124.5, 127.0, 129.4, 135.4, 137.8, 155.1, 156.2, 176.2; IR ($CDCl_3$) 3075, 2919, 1663 cm^{-1}; HRMS m/z 273.9634 (calcd for $C_{13}H_7BrO_2$, 273.9630).

2-Phenyl-9*H*-xanthen-9-one (4i).

^1H NMR ($CDCl_3$) δ 7.37-7.42 (m, 2H), 7.47-7.52 (m, 3H), 7.55-7.58 (m, 1H), 7.67-7.77 (m, 3H), 7.96-7.99 (m, 1H), 8.36-8.39 (m, 1H), 8.56-8.57 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 118.3, 118.7, 122.1, 124.2, 124.8, 127.0, 127.3, 127.9, 129.2, 133.9, 135.1, 137.3, 139.6, 155.8, 156.4, 177.4; IR ($CDCl_3$) 3070, 3034, 1656 cm^{-1}; HRMS m/z 272.0842 (calcd for $C_{19}H_{12}O_2$, 272.0837).

2-Methyl-9*H*-xanthen-9-one (4j).

^1H NMR ($CDCl_3$) δ 2.46 (s, 3H), 7.34-7.40 (m, 2H), 7.47 (dd, *J* = 8.4, 0.5 Hz, 2H), 7.53-7.54 (m, 1H), 7.68-7.73 (m, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 8.33 (dd, *J* = 8.0, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 115.6, 118.0, 118.2, 121.7, 123.9, 126.2, 126.9, 133.9, 134.9, 136.3, 154.6, 156.4, 177.5; IR ($CDCl_3$) 3061, 2918, 2862, 1657 cm^{-1}; HRMS m/z 210.0684 (calcd for $C_{14}H_{10}O_2$, 210.0681).

2-Phenoxy-9*H*-xanthen-9-one (4k).

^1H NMR ($CDCl_3$) δ 7.04-7.06 (m, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.35-7.53 (m, 6H), 7.71-7.75 (m, 1H), 7.87 (d, *J* = 2.8 Hz, 1H), 8.32 (dd, *J* = 8.0, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 114.4, 114.7, 118.2, 119.9, 124.1, 124.2, 126.9, 127.0, 129.7, 130.2, 130.5, 135.1, 152.3, 153.8, 156.3, 157.1, 177.0; IR ($CDCl_3$) 3066, 2951, 2872, 1660 cm^{-1}; HRMS m/z 288.0790 (calcd for $C_{19}H_{12}O_3$, 288.0786).

7*H*-Benzo[*c*]xanthen-7-one (4l).

^1H NMR ($CDCl_3$) δ 7.43 (t, *J* = 7.7 Hz, 1H), 7.64-7.77 (m, 5H), 7.88-7.92 (m, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 8.39 (dd, *J* = 6.8, 1.5 Hz, 1H), 8.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 117.8,

118.3, 121.7, 122.7, 123.1, 124.2, 124.3, 124.6, 126.8, 127.1, 128.3, 129.8, 134.6, 136.7, 153.8, 156.0, 177.1; IR ($CDCl_3$) 3061, 1654, 1439 cm^{-1}; HRMS m/z 246.0684 (calcd for $C_{17}H_{10}O_2$, 246.0681).

2,3-Dimethoxy-9*H*-xanthen-9-one (4o).

^1H NMR ($CDCl_3$) δ 3.99 (m, 6H), 6.88 (t, *J* = 3.7 Hz, 1H), 7.33-7.45 (m, 2H), 7.63-7.69 (m, 2H), 8.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6, 56.7, 99.8, 105.5, 115.1, 117.9, 121.7, 124.0, 126.7, 134.2, 146.9, 152.6, 155.6, 156.2, 176.3; IR ($CDCl_3$) 2940, 2834, 1648, 1466 cm^{-1}; HRMS m/z 256.0740 (calcd for $C_{15}H_{12}O_4$, 256.0736).

2,3-Dimethyl-9*H*-xanthen-9-one (4p).

^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.38 (s, 3H), 7.23-7.45 (m, 3H), 7.68 (m, 1H), 8.04 (s, 1H), 8.32 (dd, *J* = 7.9, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.4, 20.8, 118.1, 118.3, 119.9, 122.1, 123.8, 126.5, 126.9, 133.3, 134.6, 145.7, 154.9, 156.4, 177.3; IR ($CDCl_3$) 2971, 2921, 1656, 1462 cm^{-1}; HRMS m/z 224.0840 (calcd for $C_{15}H_{12}O_2$, 224.0837).

2-Methyl-9*H*-xanthen-9-one (4j) and 3-methyl-9*H*-xanthen-9-one (4q).

These compounds were obtained as an inseparable mixture and characterized as a mixture. ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 2.51 (s, 3H), 7.19 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.29 (s, 1H), 7.35-7.41 (m, 3H), 7.48 (dd, *J* = 8.3, 2.1 Hz, 2H), 7.53 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.69-7.73 (m, 2H), 8.12 (d, *J* = 1.0 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 8.32-8.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1, 22.3, 118.0, 118.1, 119.8, 121.7, 122.0, 122.1, 123.9, 124.0, 125.7, 126.2, 126.7, 126.9, 127.0, 133.9, 134.8, 134.9, 136.3, 146.6, 154.6, 156.3, 156.4, 156.5, 177.3, 177.5; IR ($CDCl_3$) 3066, 2923, 1661, 1608 cm^{-1}; HRMS m/z 210.0684 (calcd for $C_{14}H_{10}O_2$, 210.0681).

1,2,3,5-Tetrahydrocyclopenta[*b*]thioxanthen-9-one (4r).

^{1}H NMR ($CDCl_3$) δ 2.11-2.19 (m, 2H), 2.98-3.05 (m, 4H), 7.30 (s, 1H), 7.33-7.37 (m, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.67-7.71 (m, 1H), 8.13 (s, 1H), 8.33 (dd, *J* = 8.0, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.1, 32.2, 33.7, 113.4, 115.6, 118.1, 120.5, 121.4, 123.8, 126.9, 134.6, 140.8, 153.3, 155.7, 156.3, 177.5; IR ($CDCl_3$) 2962, 2839, 1654 cm^{-1}; HRMS m/z 236.0841 (calcd for $C_{16}H_{12}O_2$, 236.0837).

Ethyl 3-(9-oxo-9*H*-xanthen-2-yl)acrylate (5a).

^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 6.49 (d, *J* = 1.6 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.71-7.76 (m, 2H), 7.85 (dd, *J* = 8.7, 2.1 Hz, 1H), 8.31 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.43 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 60.9, 118.3, 119.1, 119.4, 121.9, 122.1, 124.6, 127.0, 130.7, 133.7, 135.3, 142.9, 156.2, 157.1, 166.9, 176.9; IR ($CDCl_3$) 3034, 2981, 1714, 1657 cm^{-1}; HRMS m/z 294.0897 (calcd for $C_{18}H_{14}O_4$, 294.0892).

2-(Furan-3-yl)-9*H*-xanthen-9-one (5b).

^{1}H NMR ($CDCl_3$) δ 6.8 (q, *J* = 0.9 Hz, 1H), 7.36-7.40 (m, 1H), 7.47-7.51 (m, 3H), 7.70-7.74 (m, 1H), 7.81-7.84 (m, 2H), 8.34 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.39 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 109.0, 118.2, 118.8, 121.9, 122.1, 123.2, 124.2, 125.4, 127.0, 128.8, 132.7, 135.1, 139.0, 144.2, 155.3, 156.3, 177.3; IR ($CDCl_3$) 3069, 2924, 1660 cm^{-1}; HRMS m/z 262.0635 (calcd for $C_{17}H_{10}O_3$, 262.0630).

9*H*-Thioxanthen-9-one (6a).

^{1}H NMR ($CDCl_3$) δ 7.48 (td, *J* = 6.7, 1.5 Hz, 2H), 7.56-7.65 (m, 4H), 8.62 (dd, *J* = 7.4, 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 126.2, 126.5, 129.5, 130.1, 132.5, 137.5, 180.2; IR ($CDCl_3$) 2971, 2919, 1684, 1459 cm^{-1}; HRMS m/z 212.0299 (calcd for $C_{13}H_8OS$, 212.0296).

1-Methoxy-9*H*-thioxanthen-9-one (6b).

^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H), 6.90 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.39-7.56 (m, 4H), 7.45 (dd, *J* = 7.8, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6, 109.2, 118.3, 119.8, 125.2, 126.5, 129.9, 131.8, 132.2, 133.0, 135.5, 140.0, 162.4, 180.9; IR ($CDCl_3$) 3057, 2943, 1639, 1456 cm^{-1}; HRMS m/z 242.0404 (calcd for $C_{14}H_{10}O_2S$, 242.0402).

2,3-Dimethylthioxanthen-9-one (6c).

^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.40 (s, 3H), 7.34 (d, *J* = 0.5 Hz, 1H), 7.44-7.49 (m, 1H), 7.55-7.62 (m, 2H), 8.38 (d, *J* = 0.4 Hz, 1H), 8.61-8.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.4, 126.2, 127.5, 129.5, 130.0, 130.2, 132.2, 134.8, 136.0, 137.6, 143.0, 180.0; IR ($CDCl_3$) 2916, 2848, 1631 cm^{-1}; HRMS m/z 240.0613 (calcd for $C_{15}H_{12}OS$, 240.0609).

2-Methylthioxanthen-9-one (6d) and 3-methylthioxanthen-9-one (6e).

These compounds were obtained as an inseparable mixture and characterized as a mixture. ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 2.49 (s, 3H), 7.27-7.30 (m, 1H), 7.36-7.37 (m, 1H), 7.44-7.63 (m, 8H), 8.43-8.47 (m, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 8.60-8.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.0, 126.0, 126.1, 126.2, 126.3, 126.4, 127.3, 128.1, 129.2, 129.4, 129.5, 129.8, 130.0, 130.1, 132.3, 134.0, 136.6, 137.4, 137.5, 137.6, 143.5, 178.0; IR ($CDCl_3$) 3059, 2920, 1638, 1602 cm^{-1}; HRMS m/z 226.0456 (calcd for $C_{14}H_{10}OS$, 226.0452).

1,2,3,5-Tetrahydrocyclopenta[*b*]thioxanthen-9-one (7f).

^{1}H NMR ($CDCl_3$) δ 2.11-2.18 (m, 2H), 2.99-3.05 (m, 4H), 7.41-7.48 (m, 2H), 8.46 (s, 1H), 8.61-8.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 32.6, 33.3, 121.4, 125.2, 126.1, 126.2, 128.0, 129.6, 130.0, 132.1, 135.5, 137.6, 144.0, 150.5, 180.2; IR ($CDCl_3$) 2964, 2840, 1658 , 1630 cm^{-1}; HRMS m/z 252.0612 (calcd for $C_{16}H_{12}OS$, 252.0609).

10-Methyl-10*H*-acridin-9-one (9b).

^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.69-7.73 (m, 2H), 8.55 (dd, *J* = 8.0, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 33.9, 115.0, 121.5, 122.7, 128.0, 134.0, 142.8, 178.3; IR ($CDCl_3$) 2917, 2850, 1637 cm^{-1}; HRMS m/z 209.0843 (calcd for $C_{14}H_{11}NO$, 209.0841).

3-Fluoro-10-methyl-10*H*-acridin-9-one (9d).

^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 6.93-6.99 (m, 1H), 7.09 (dd, *J* = 15.6, 3.0 Hz, 1H), 7.24-7.29 (m, 1H), 7.43 (d, *J* = 11.6 Hz, 1H), 7.65-7.71 (m, 1H), 8.47-8.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.0, 101.0, 101.4, 110.0, 110.3, 115.0, 119.4, 122.0, 122.7, 127.9, 131.0, 131.1, 134.1, 142.8, 144.3, 144.5, 164.9, 168.2, 177.3; IR ($CDCl_3$) 2928, 1637, 1614 cm^{-1}; HRMS m/z 227.0744 (calcd for $C_{14}H_{10}FNO$, 227.0746).

2-Fluoro-10-methyl-10*H*-acridin-9-one (9e).

^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 7.21 (t, *J* = 6.9 Hz, 1H), 7.35-7.41 (m, 3H), 7.64 (t, *J* = 6.3 Hz, 1H), 8.06 (d, *J* = 5.8 Hz, 1H), 8.42 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.1, 111.9, 112.1, 114.9, 115.6, 117.1, 117.2, 121.5, 121.7, 122.1, 122.3, 127.7, 134.2, 139.1, 142.4, 156.4, 158.8, 177.3; IR ($CDCl_3$) 2924, 1617, 1599 cm^{-1}; HRMS m/z 227.0749 (calcd for $C_{14}H_{10}FNO$, 227.0746).

2-Bromo-10-methyl-10*H*-acridin-9-one (9f).

^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 7.23-7.27 (m, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 10.8 Hz, 1H), 7.65-7.71 (m, 2H), 8.44 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.55 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0, 114.7, 115.1, 117.0, 121.8, 122.5, 123.7, 127.9, 130.1, 134.3, 136.6, 141.3, 142.4, 176.9; IR ($CDCl_3$) 2926, 1628, 1608 cm^{-1}; HRMS m/z 286.9950 (calcd for $C_{14}H_{10}BrNO$, 286.9946).

2,3,10-Trimethyl-10*H*-acridin-9-one (9h).

^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.42 (s, 3H), 3.84 (s, 3H), 7.23-7.27 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.66-7.70 (m, 1H), 8.27 (s, 1H), 8.54 (dd, *J* = 8.1, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3, 21.4, 33.7, 114.8, 115.5, 120.9, 121.0, 122.6, 127.7, 127.9, 130.6, 133.6, 141.3, 142.6, 144.3, 177.9; IR ($CDCl_3$) 2918, 1638, 1614 cm^{-1}; HRMS m/z 237.1157 (calcd for $C_{16}H_{15}NO$, 237.1154).

2,10-Dimethyl-10*H*-acridin-9-one (9i) and 3,10-dimethyl-10*H*-acridin-9-one (9j).

These compounds were obtained as an inseparable mixture and characterized as a mixture. ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.49 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 7.05 (d, *J* = 8.1 Hz, 1H), 7.22-7.26 (m, 3H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.43-7.40 (m, 3H), 7.64-7.68 (m, 2H), 8.30 (d, *J* = 0.9 Hz, 1H), 8.50-8.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.8, 33.7, 33.8, 114.8, 114.9, 120.6, 121.1, 121.3, 122.4, 122.5, 122.6, 123.1, 127.1, 127.8, 127.9, 131.0, 133.7, 133.8, 135.4, 140.8, 142.7, 142.8, 144.9, 178.0, 178.2; IR ($CDCl_3$) 2917, 2851, 1632, 1611 cm^{-1}; HRMS m/z 223.0998 (calcd for $C_{15}H_{13}NO$, 223.0997).

5-Methyl-1,2,3,5-tetrahydrocyclopenta[*b*]acridin-10-one (9k).

^{1}H NMR ($CDCl_3$) δ 2.10-2.17 (m, 2H), 2.97-3.05 (m, 4H), 3.83 (s, 3H), 7.22-7.26 (m, 1H), 7.33 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.64-7.69 (m, 1H), 8.34 (s, 1H), 8.53 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0, 32.1, 34.0, 110.2, 114.8, 121.0, 121.6. 122.4. 127.9, 133.5, 138.3, 142.1, 142.5, 152.2, 178.1; IR ($CDCl_3$) 2948, 2840, 1617, 1595 cm^{-1}; HRMS m/z 249.1158 (calcd for $C_{17}H_{15}NO$, 249.1154).

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GENERAL CONCLUSIONS

In this dissertation, several novel palladium migration processes and a coupling-cyclization reaction of silylaryl triflates and substituted benzoates have been investigated. The scope, limitations, and applications of these reactions are presented in detail.

Chapter 1 investigated an unusual consecutive vinylic to aryl to allylic palladium migration process, which affords a novel way to generate π-allylpalladium complexes. This migration process appears to involve an equilibrium between organopalladium(IV) hydrides and organopalladium(II) intermediates. A mechanistic study of the aryl to aryl palladium migration process provides some new information.

Chapter 2 describes a synthesis of substituted carbazoles, indoles and dibenzofurans by the palladium-catalyzed cross-coupling of alkynes and appropriately substituted aryl iodides. Results from deuterium labeling experiments are consistent with the proposed mechanism.

Chapter 3 describes the preparation of biologically-interesting fluoren-9-one and xanth-9-one derivatives by a novel aryl to imidoyl palladium migration, followed by intramolecular arylation. The results from the deuterium labeling experiments are consistent with the proposed duel mechanism.

Chapter 4 reports the synthesis of xanthone, thioxanthone and acridone derivatives from the coupling-cyclization of silylaryl triflates and substituted benzoates. The scope and limitations of this methodology and elaboration of the halogen-substituted xanthone obtained have been investigated.

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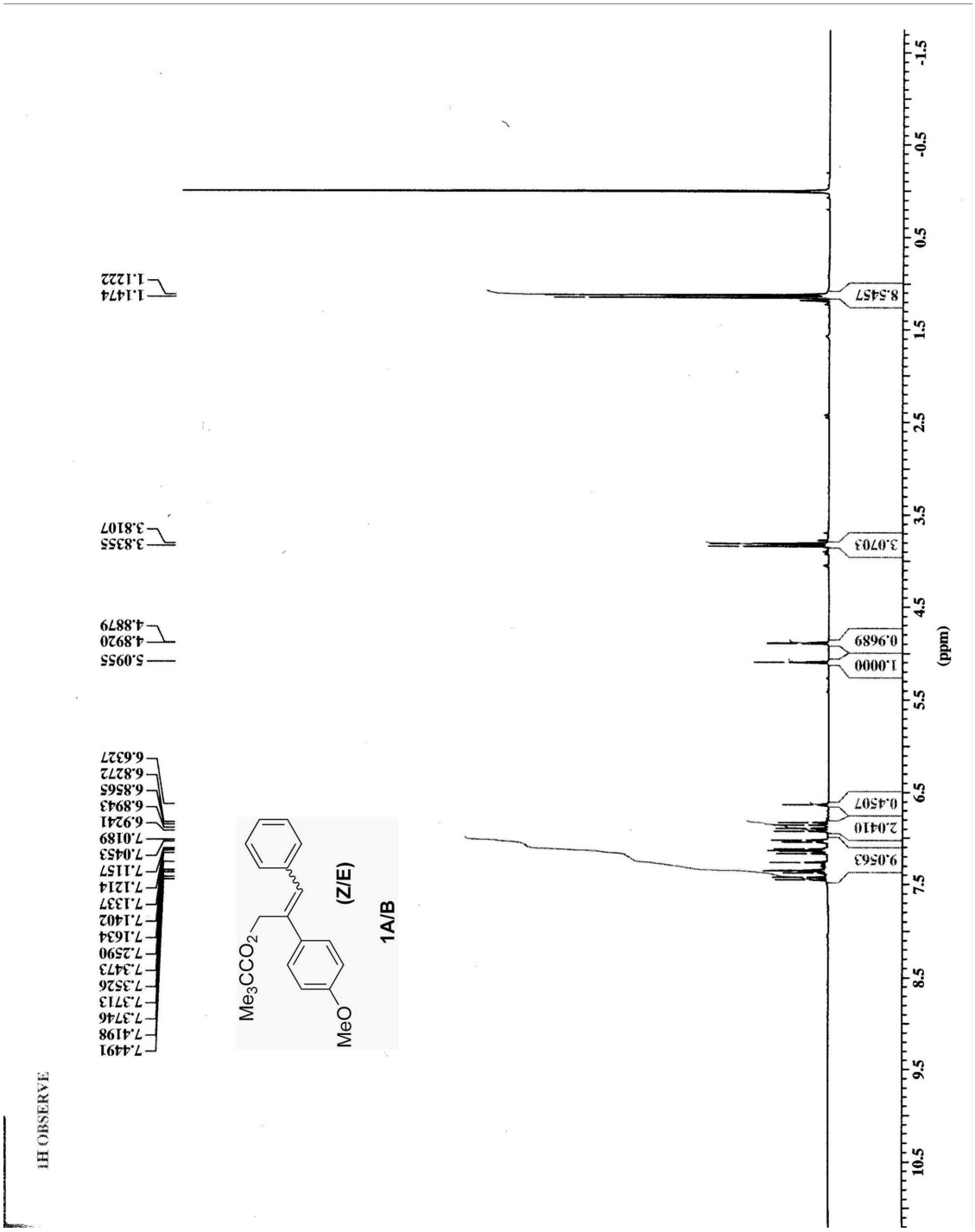
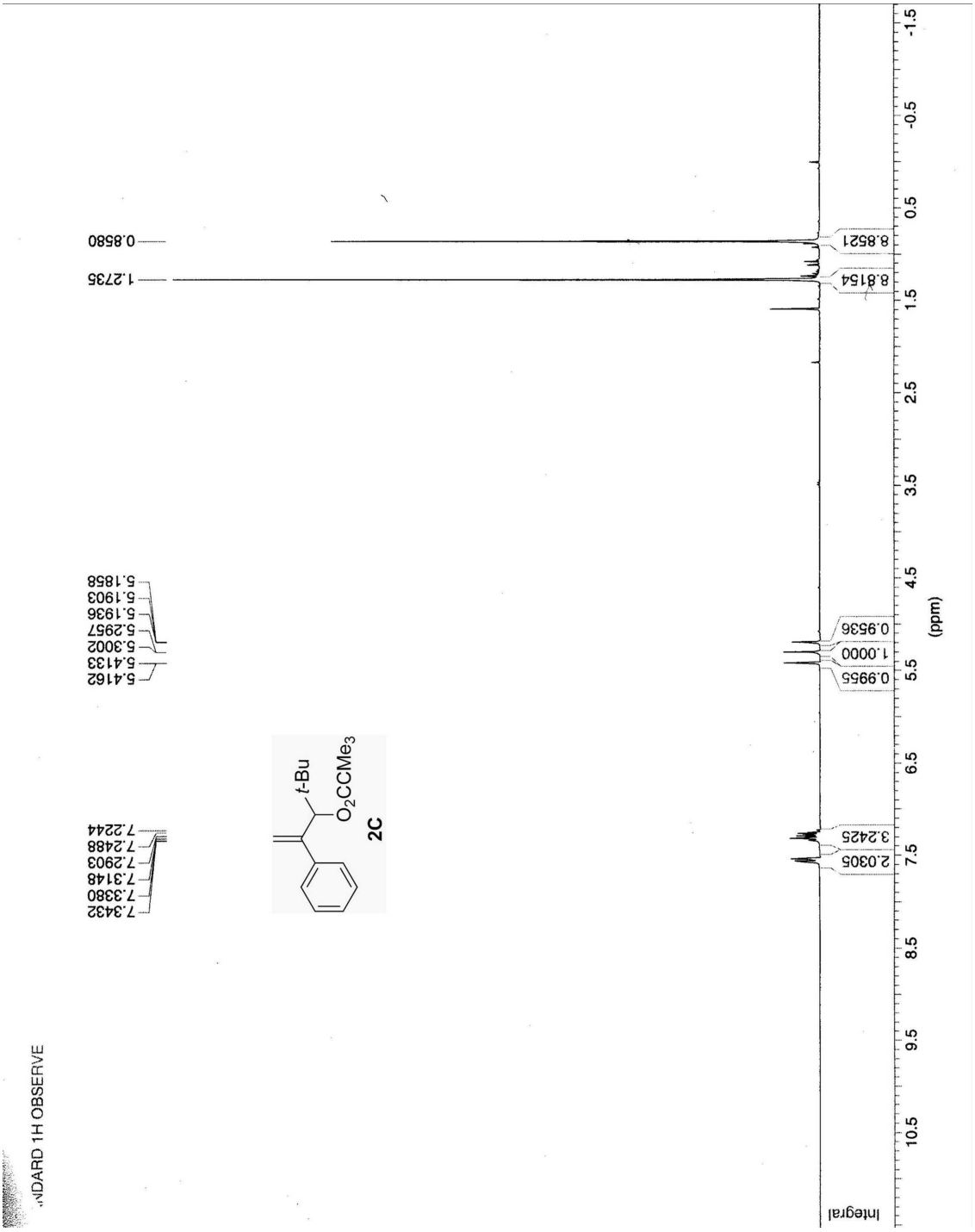
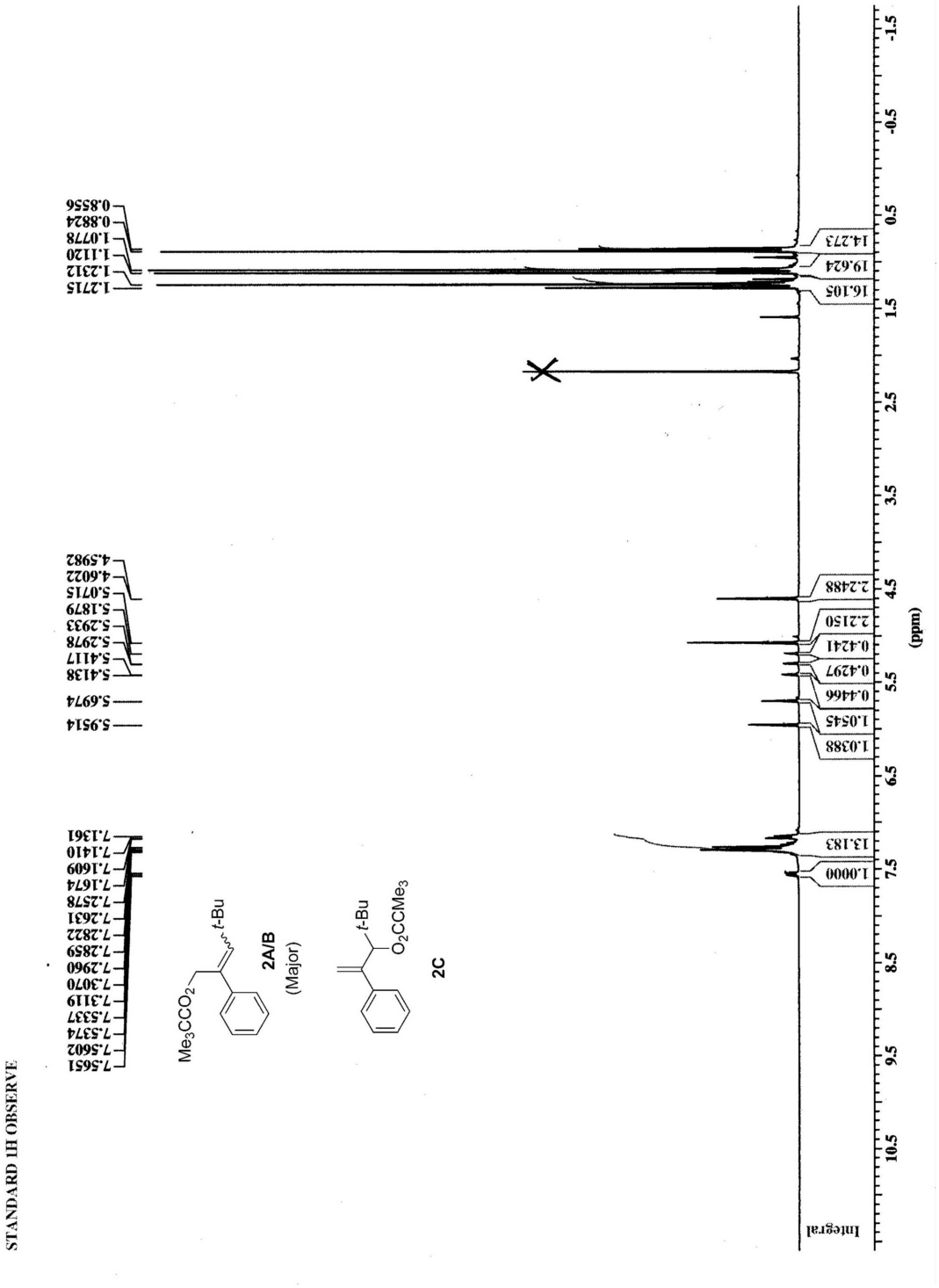
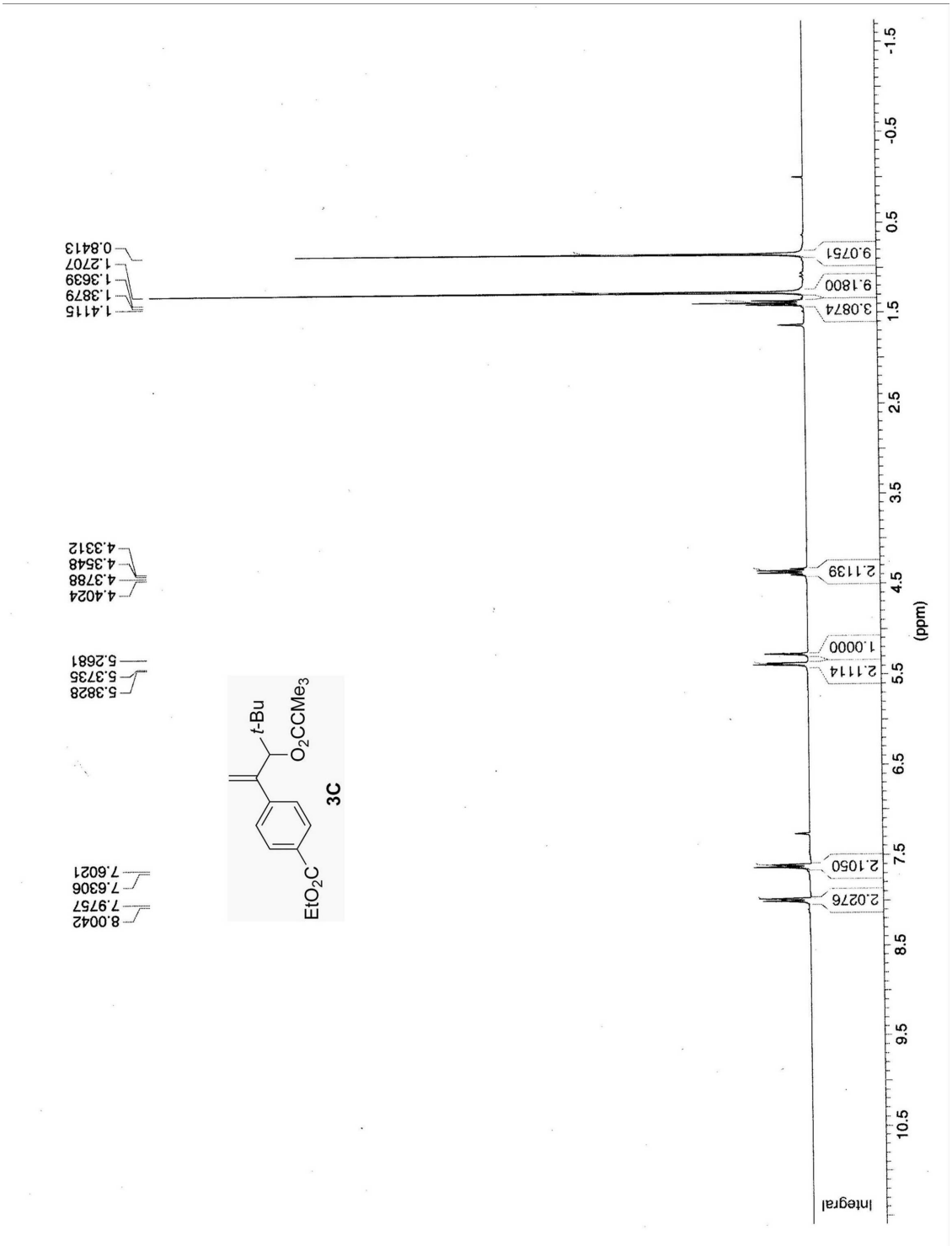
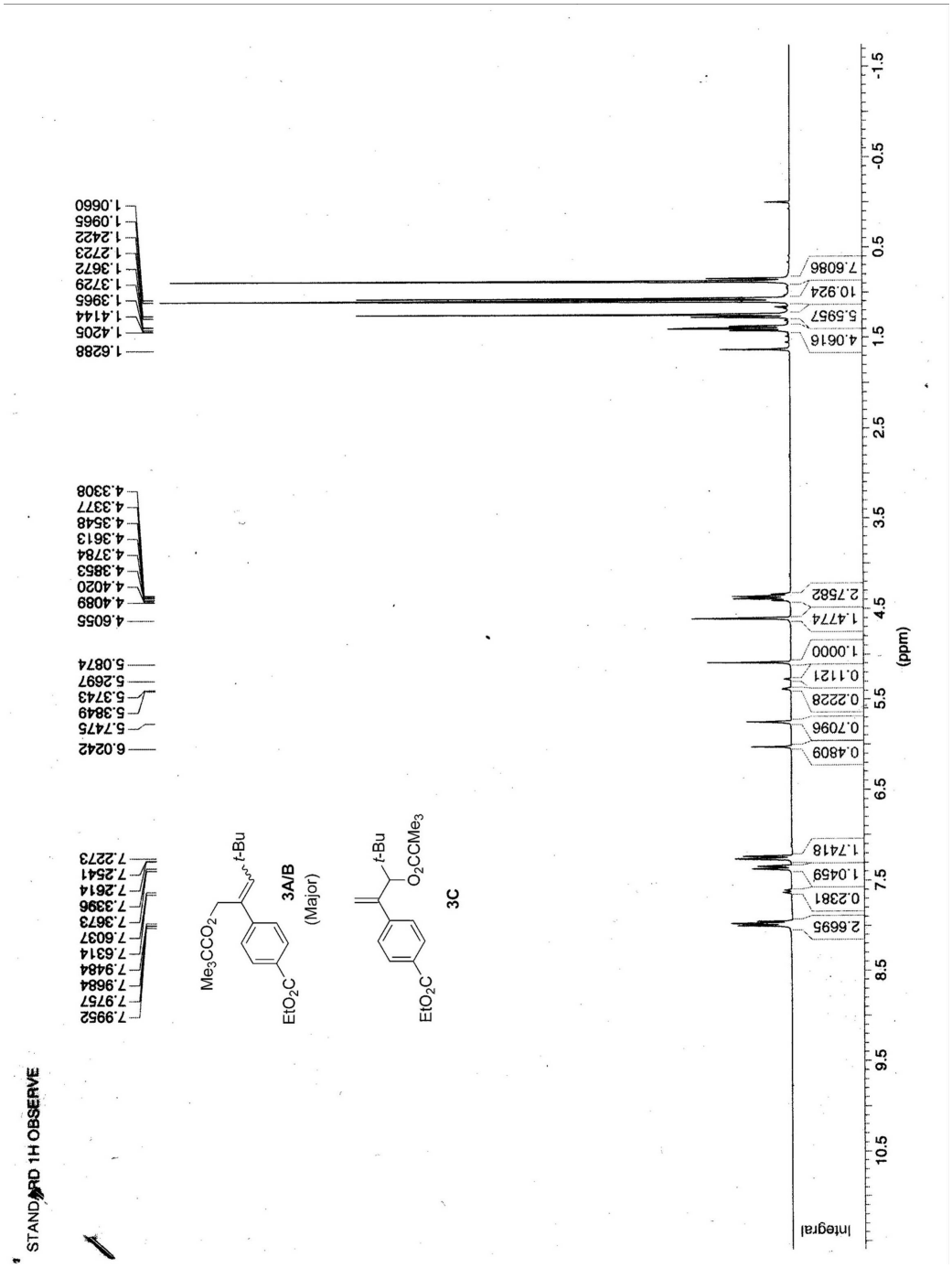
APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA

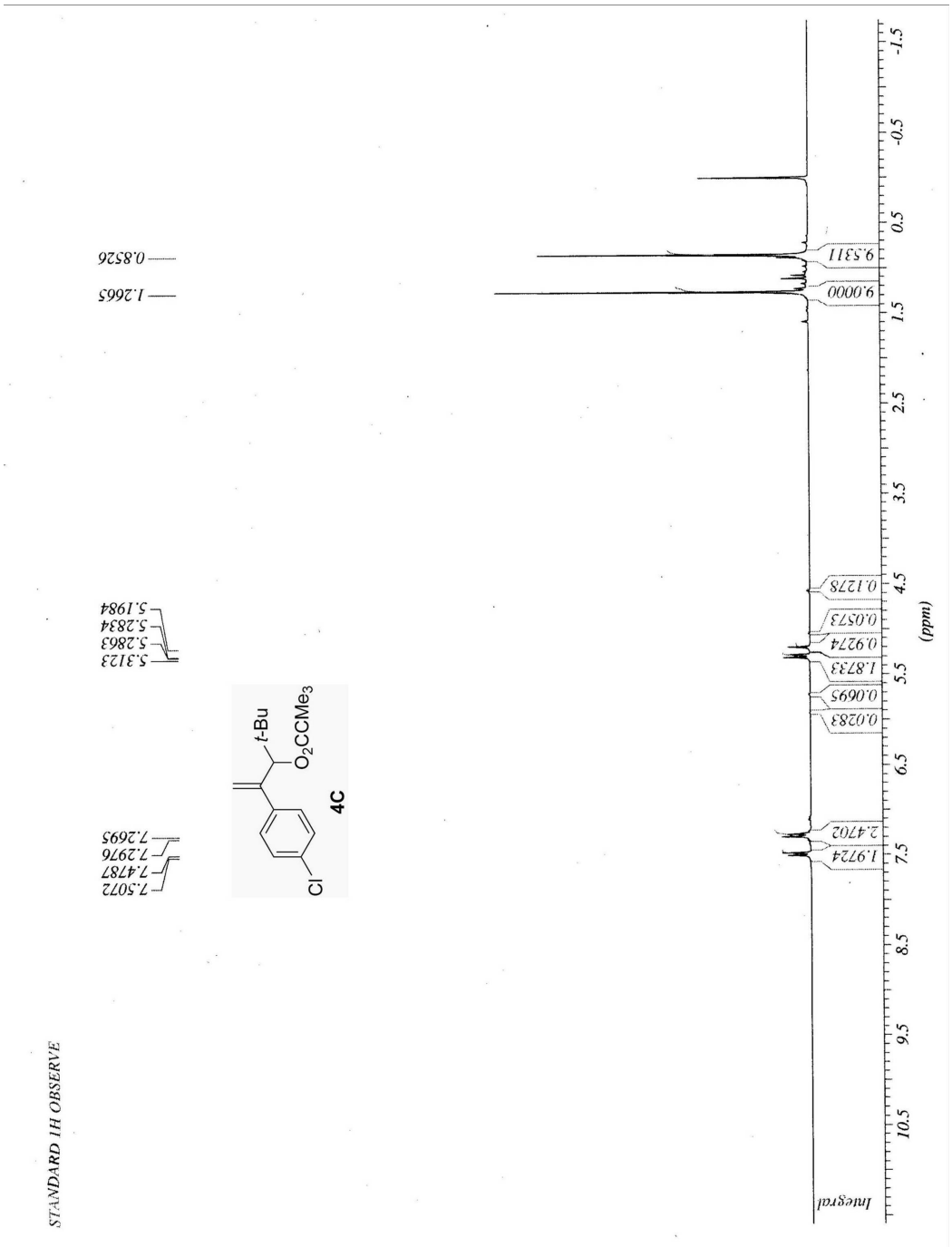


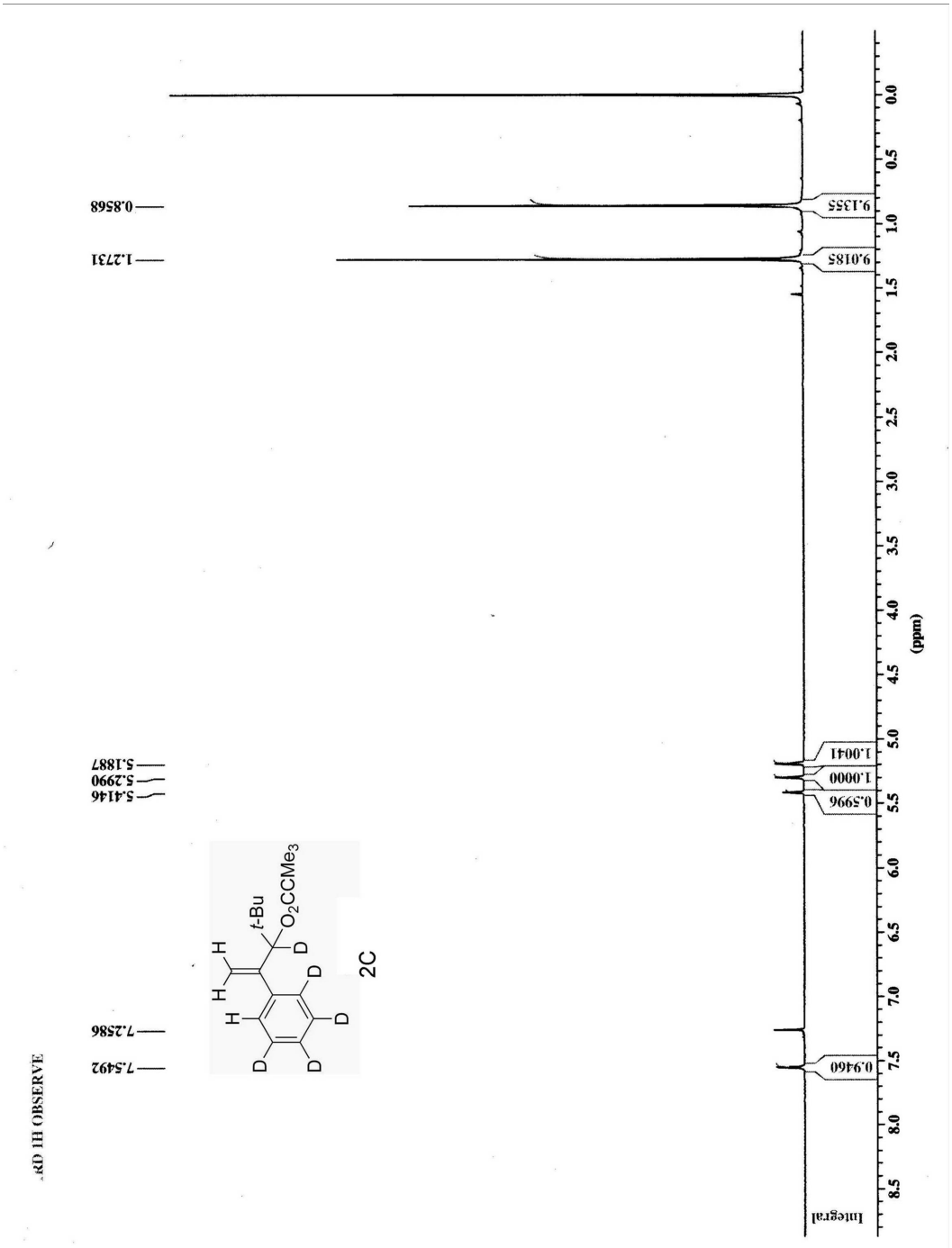


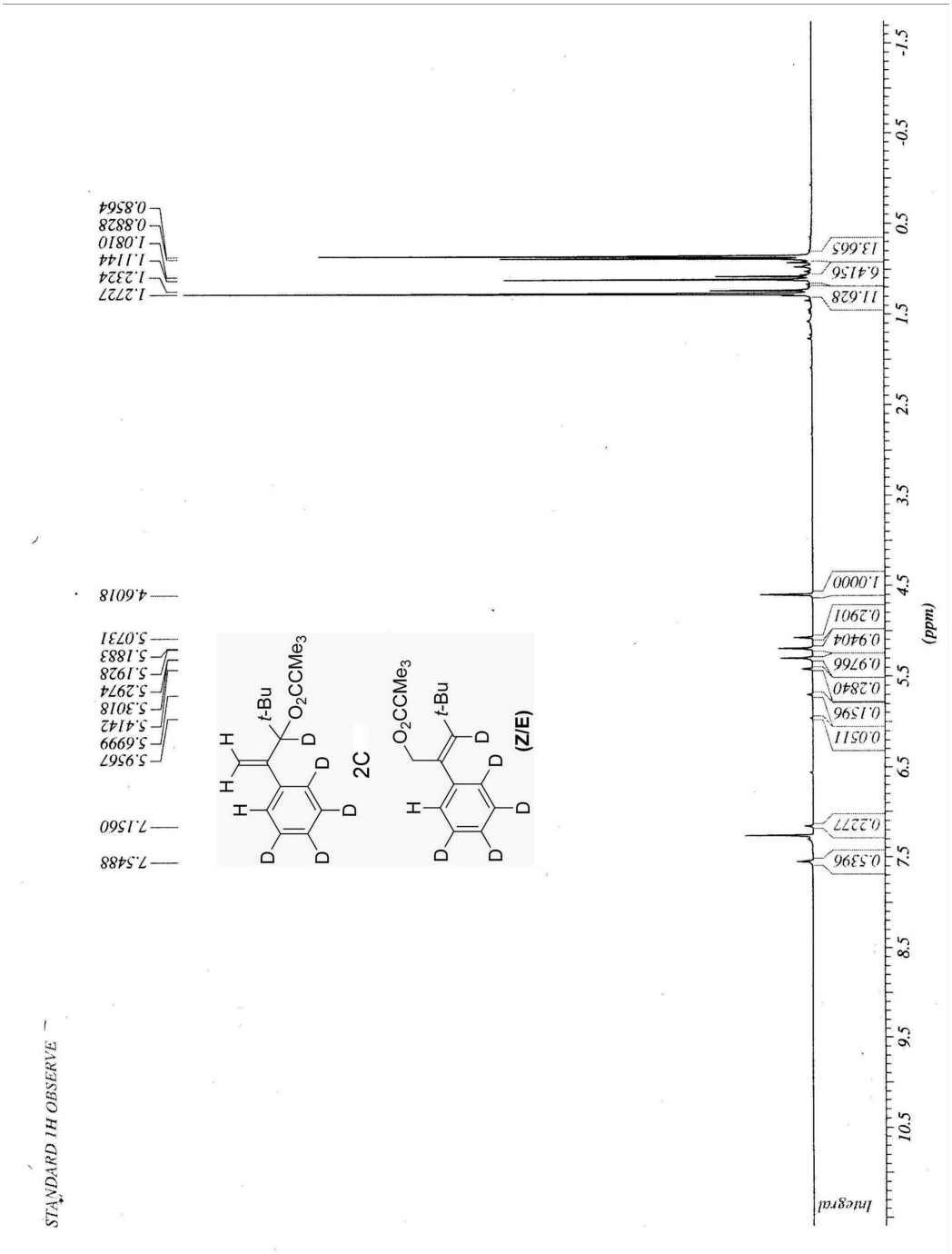


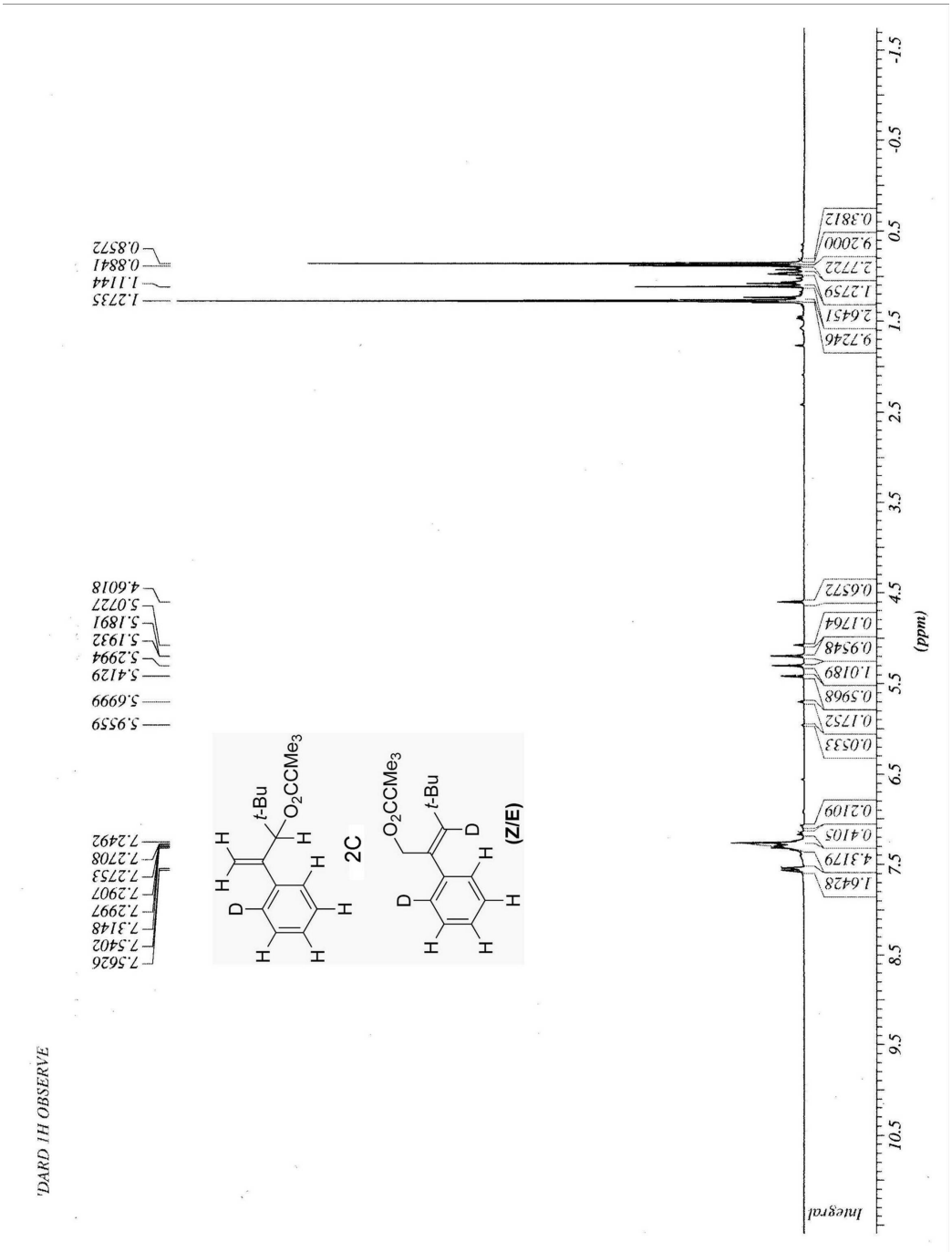


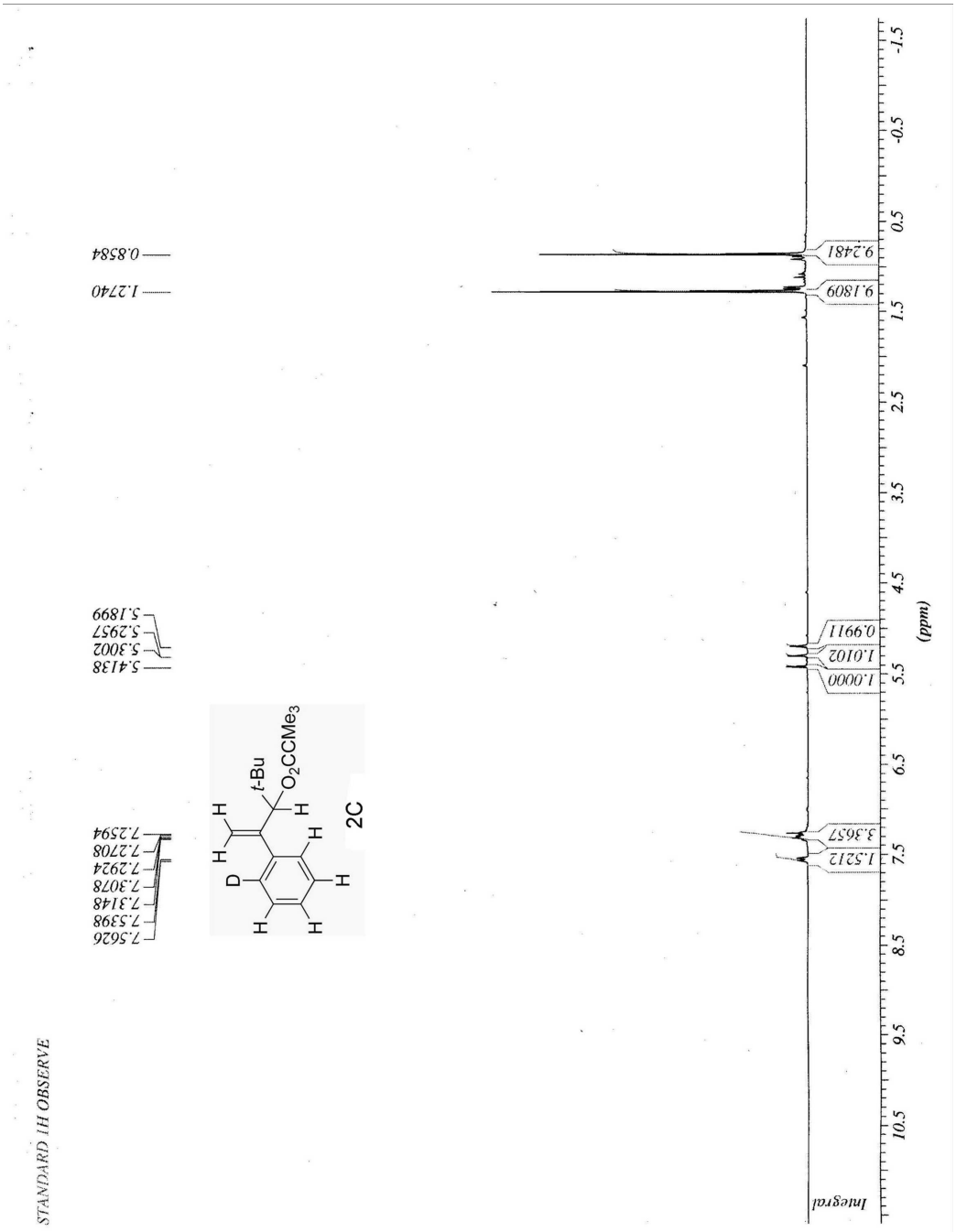


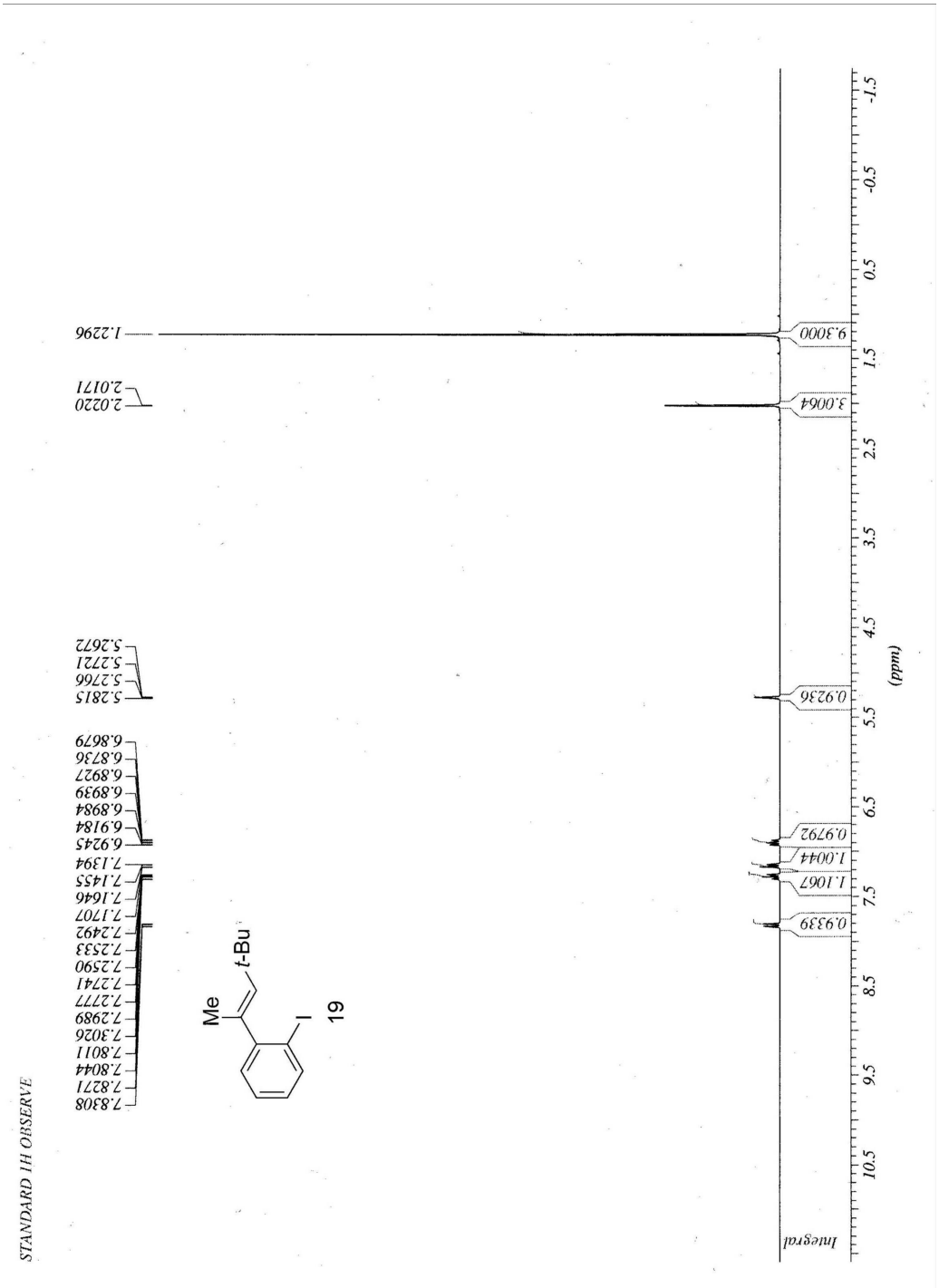


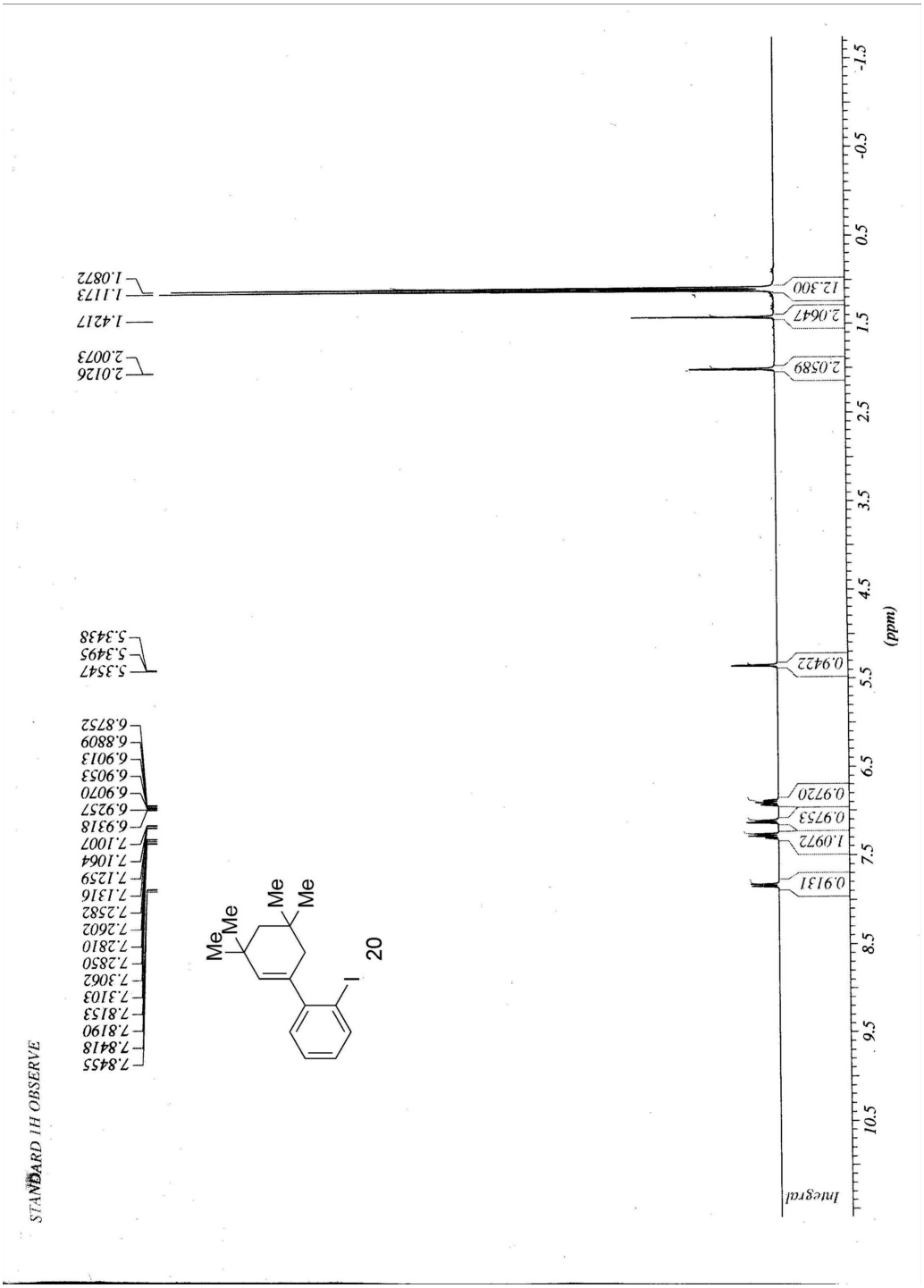


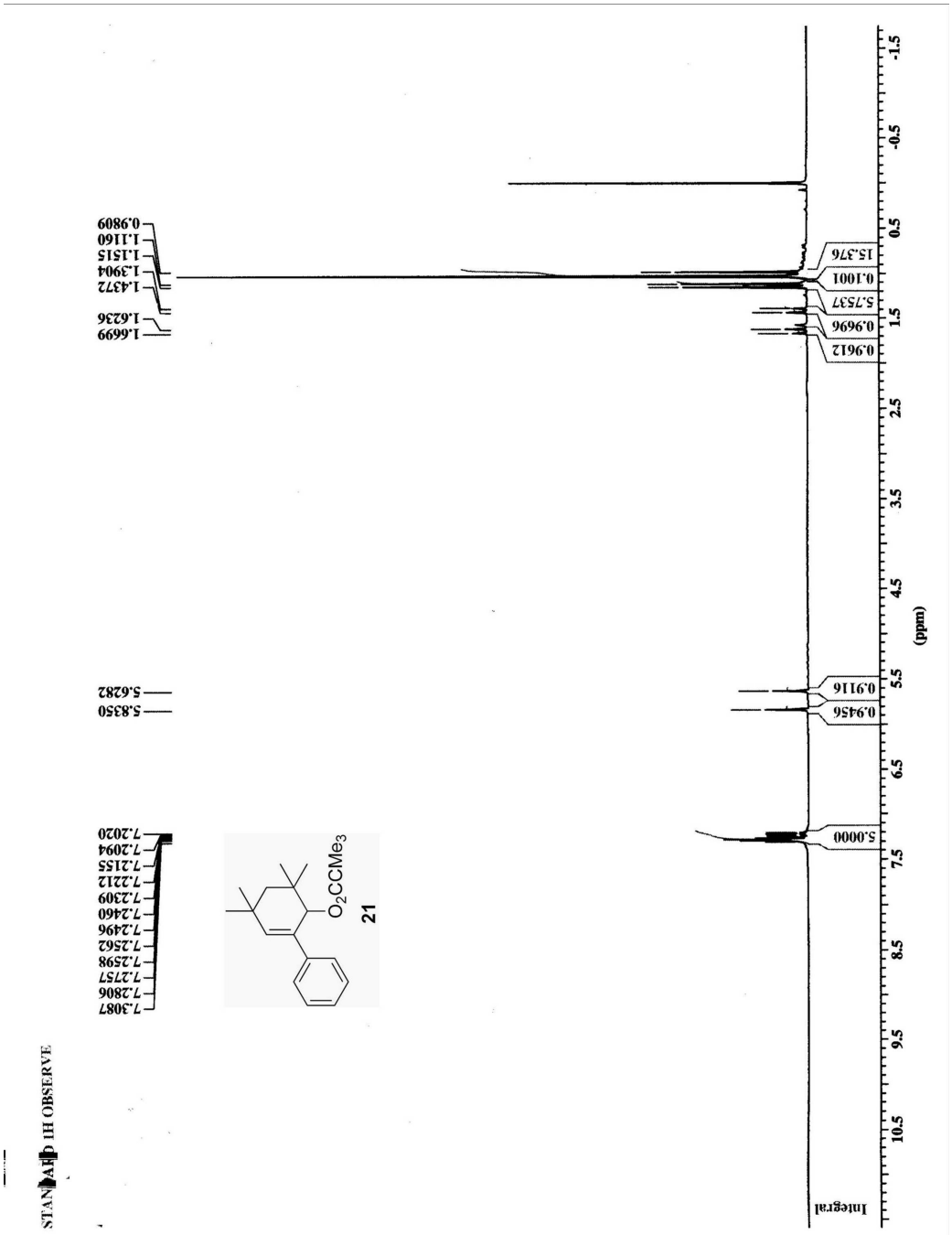


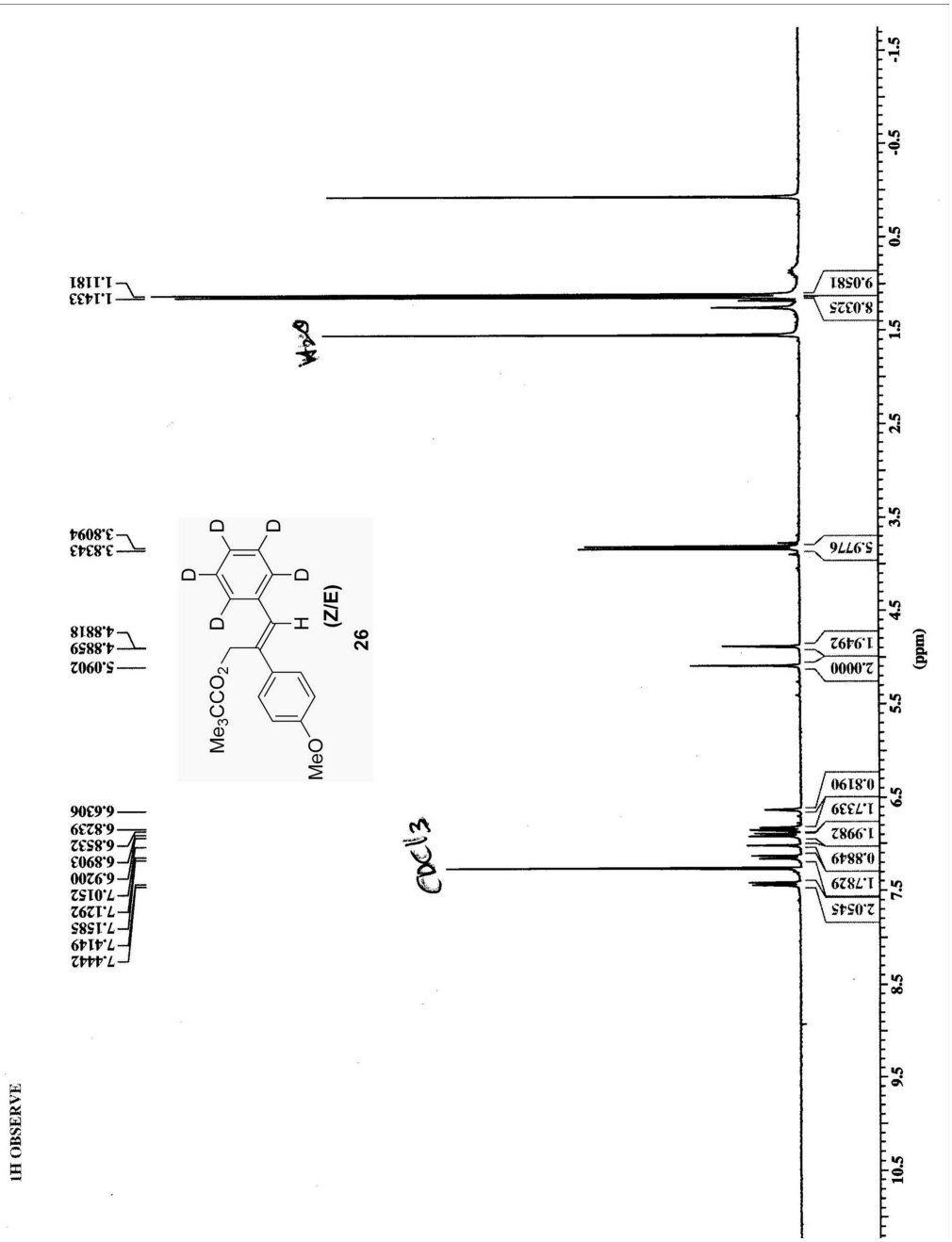


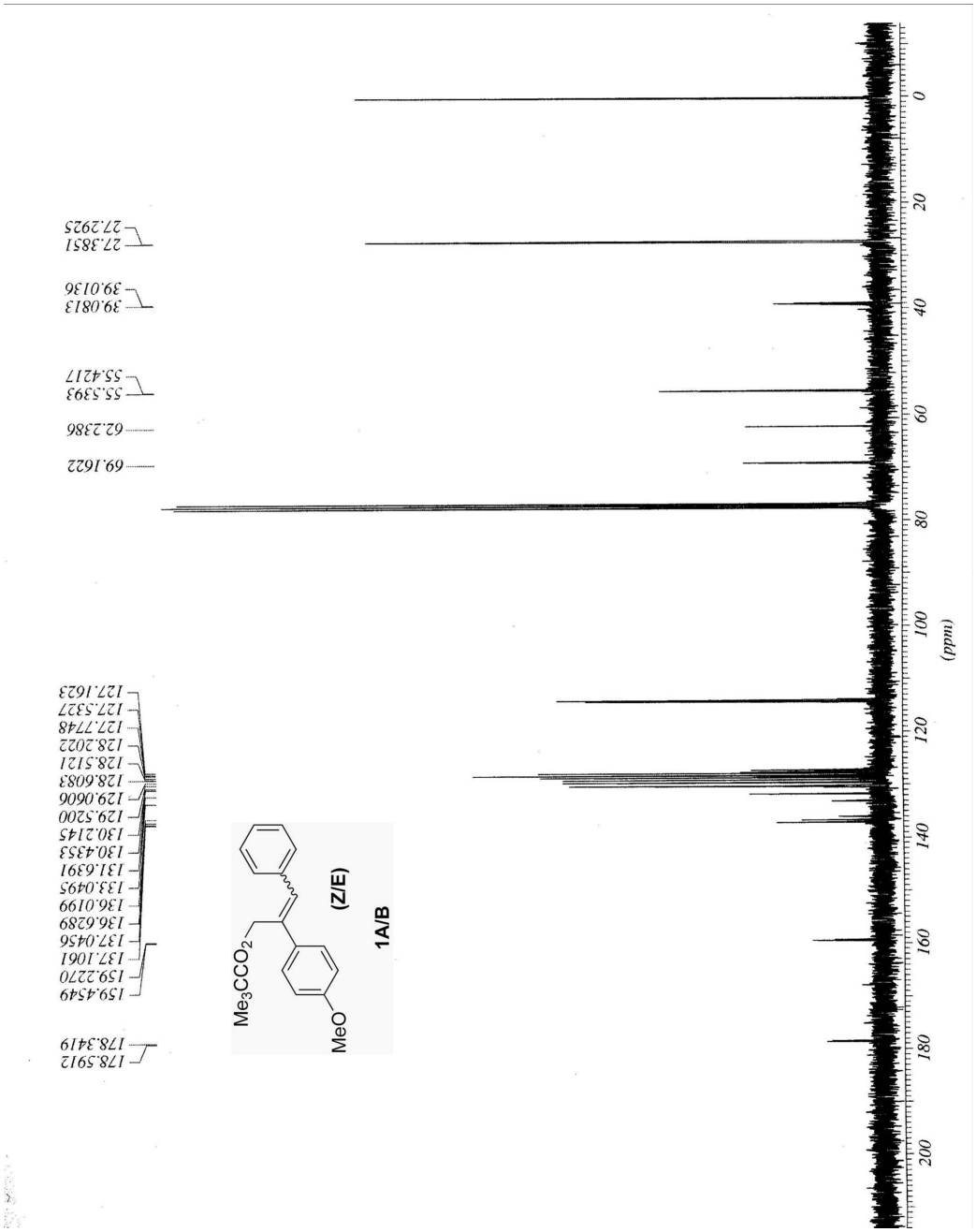


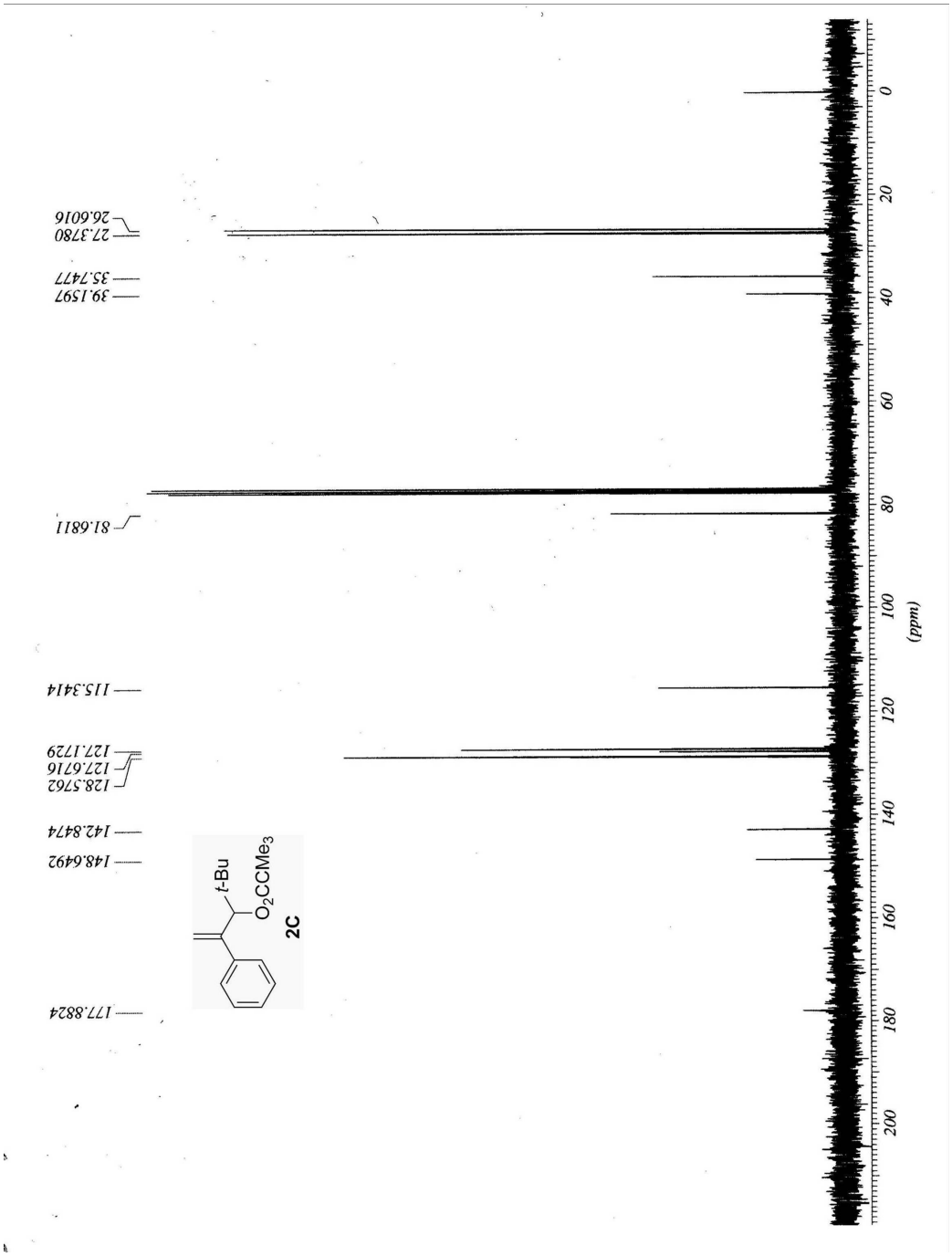


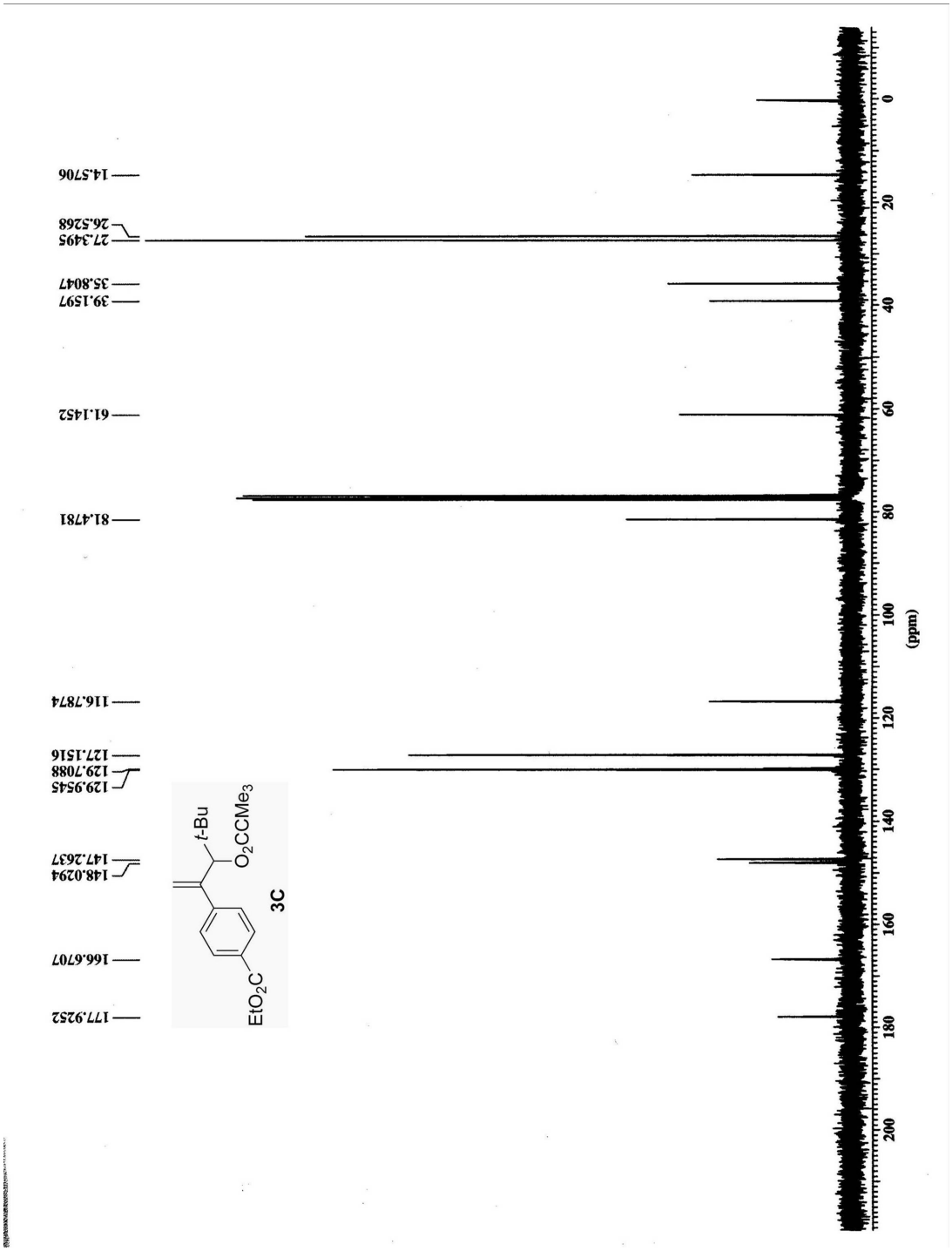


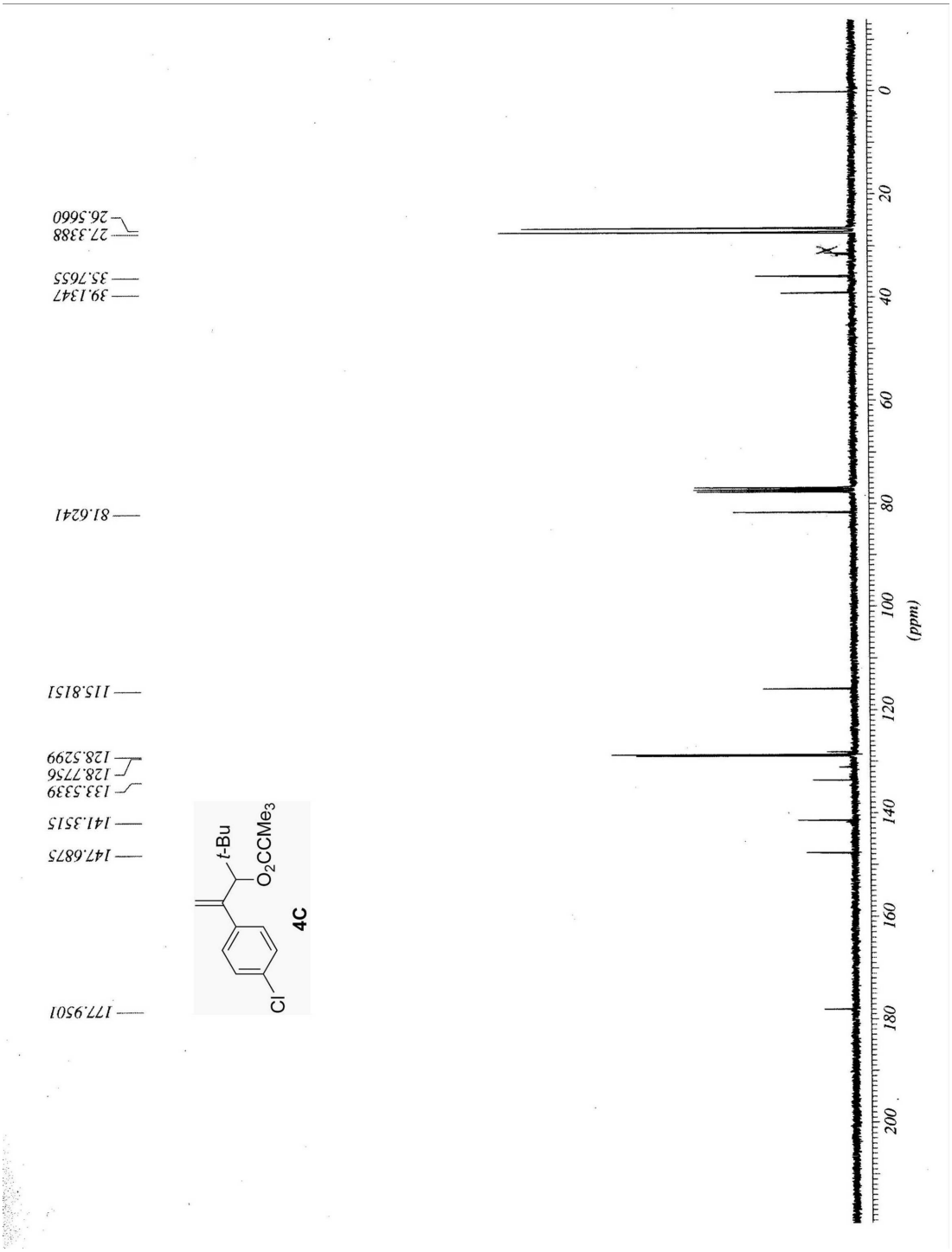


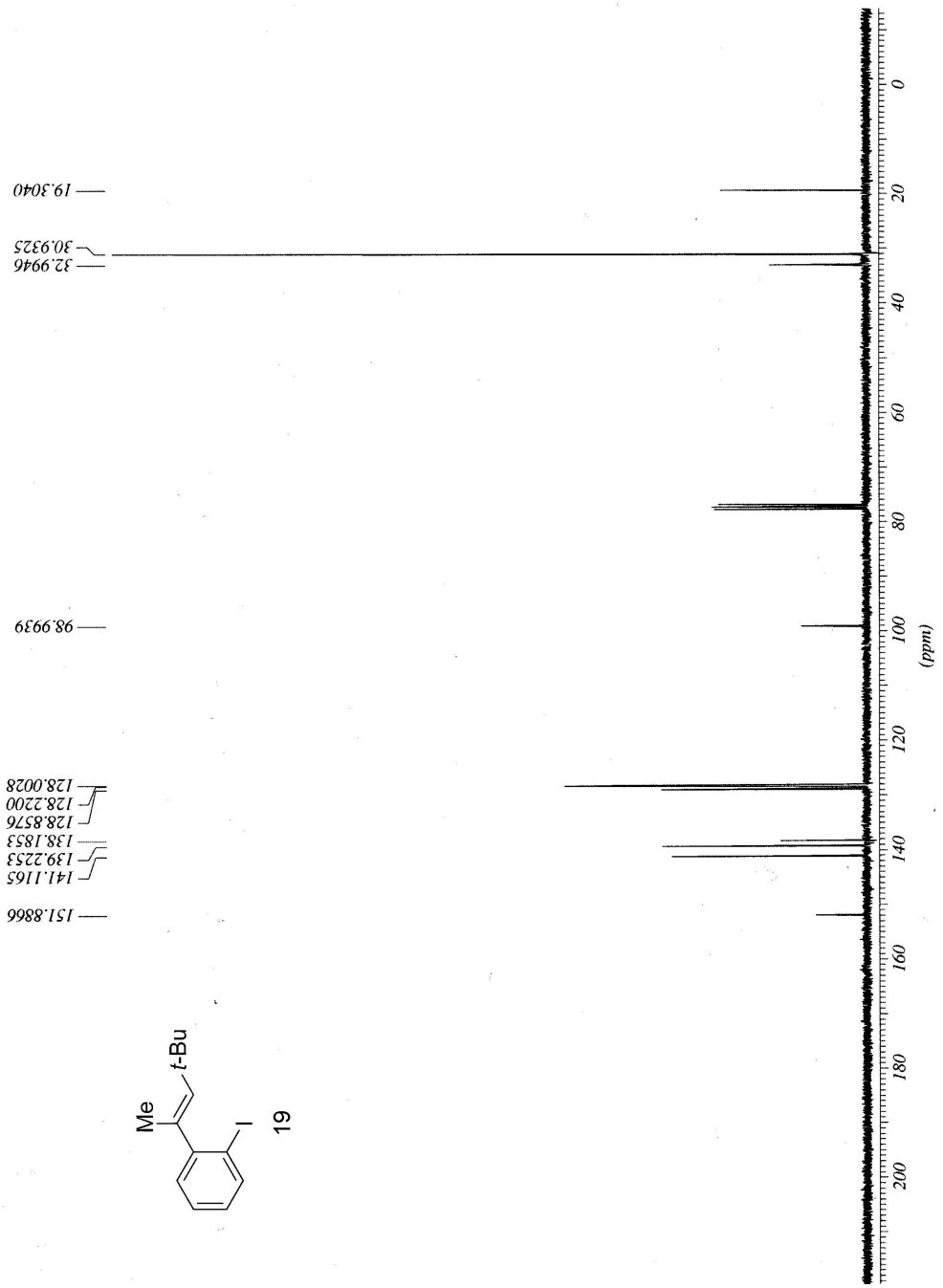


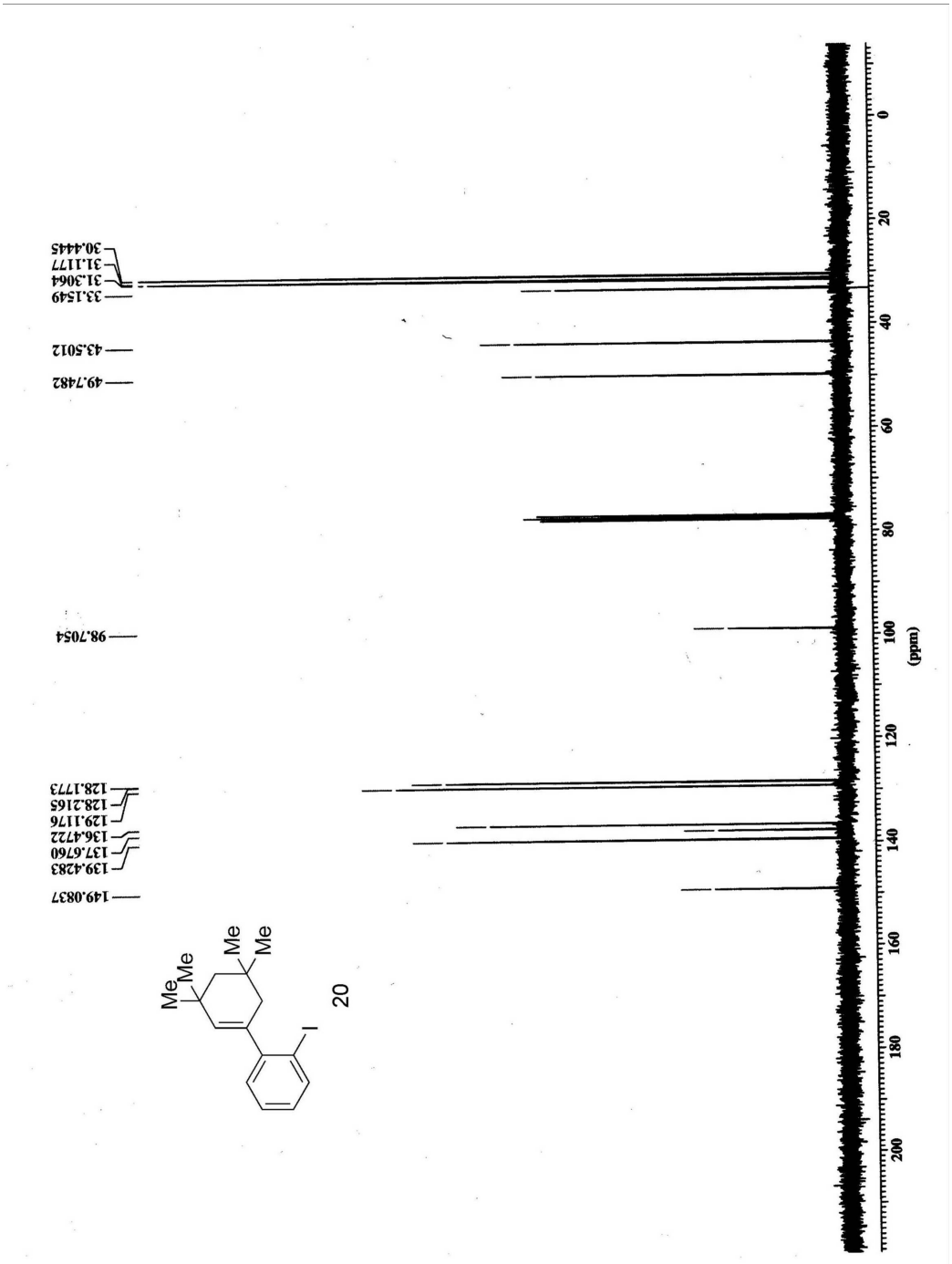


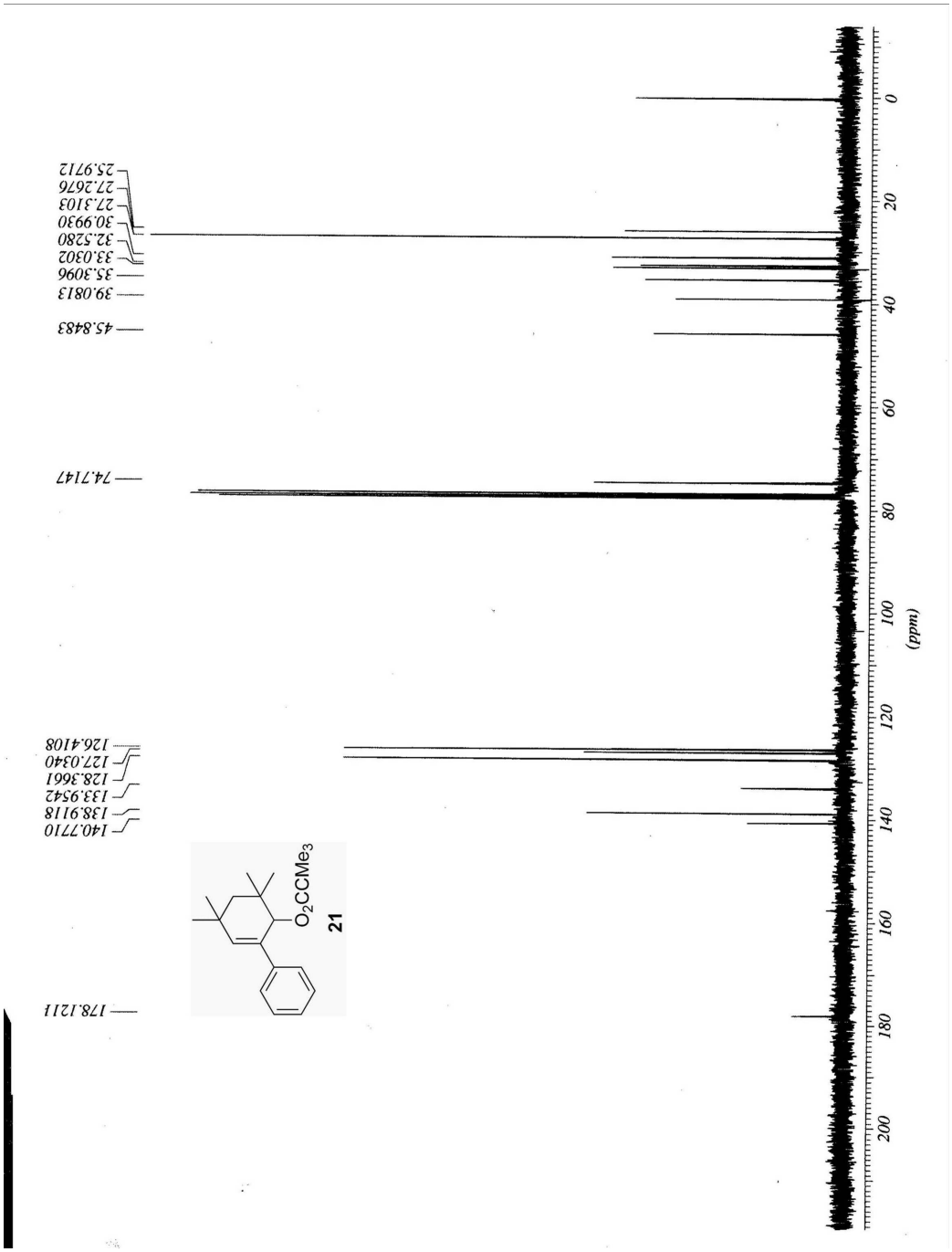




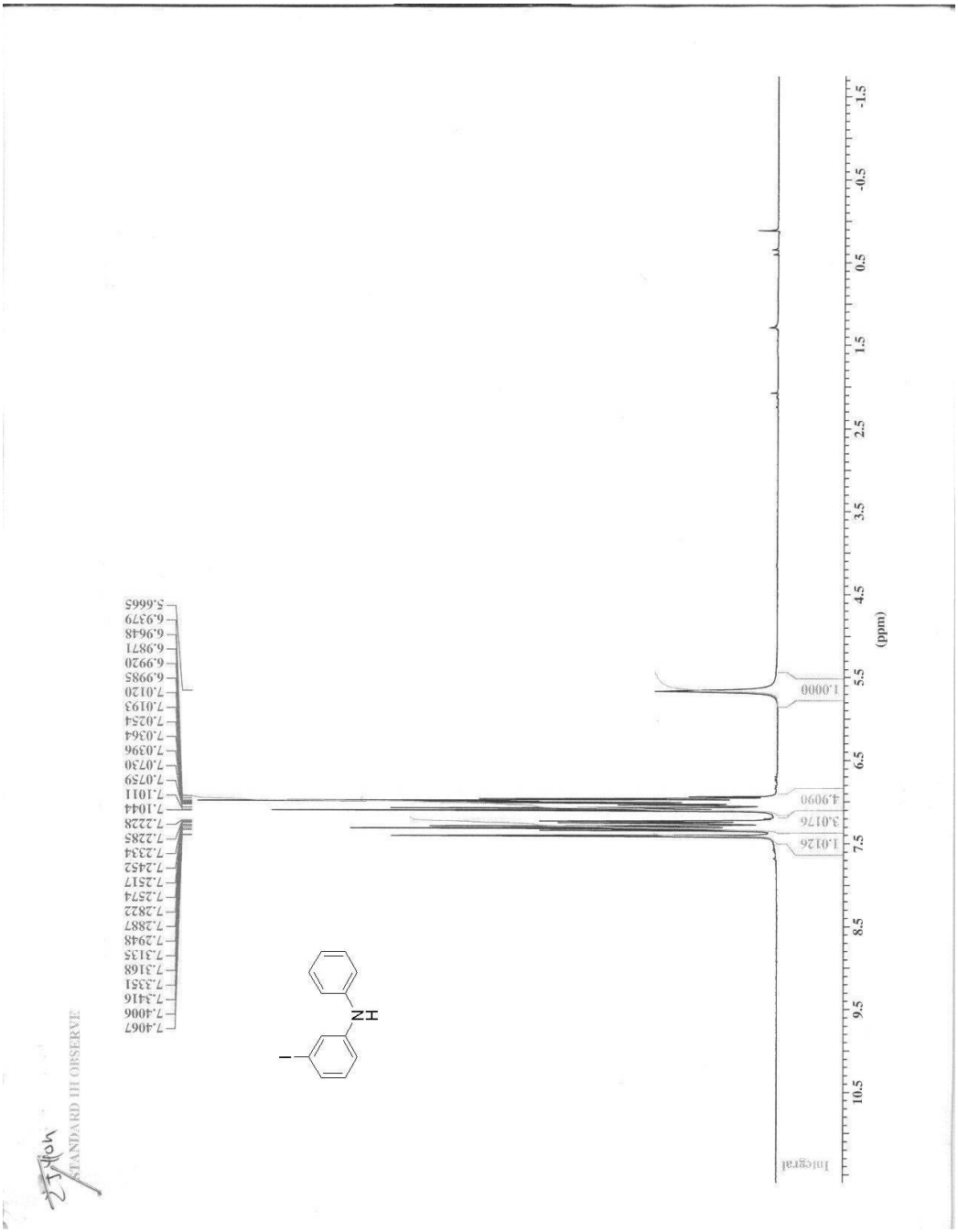


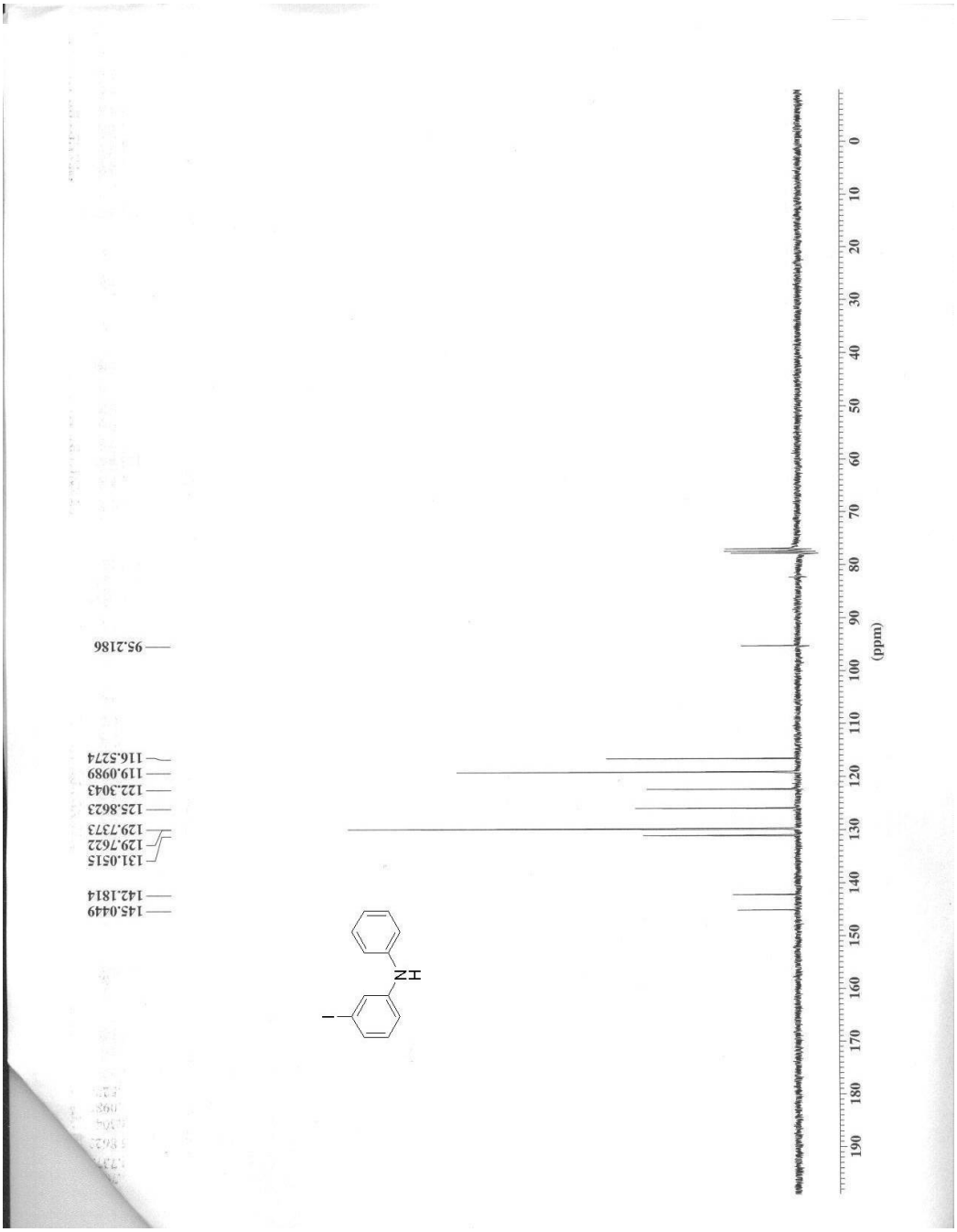


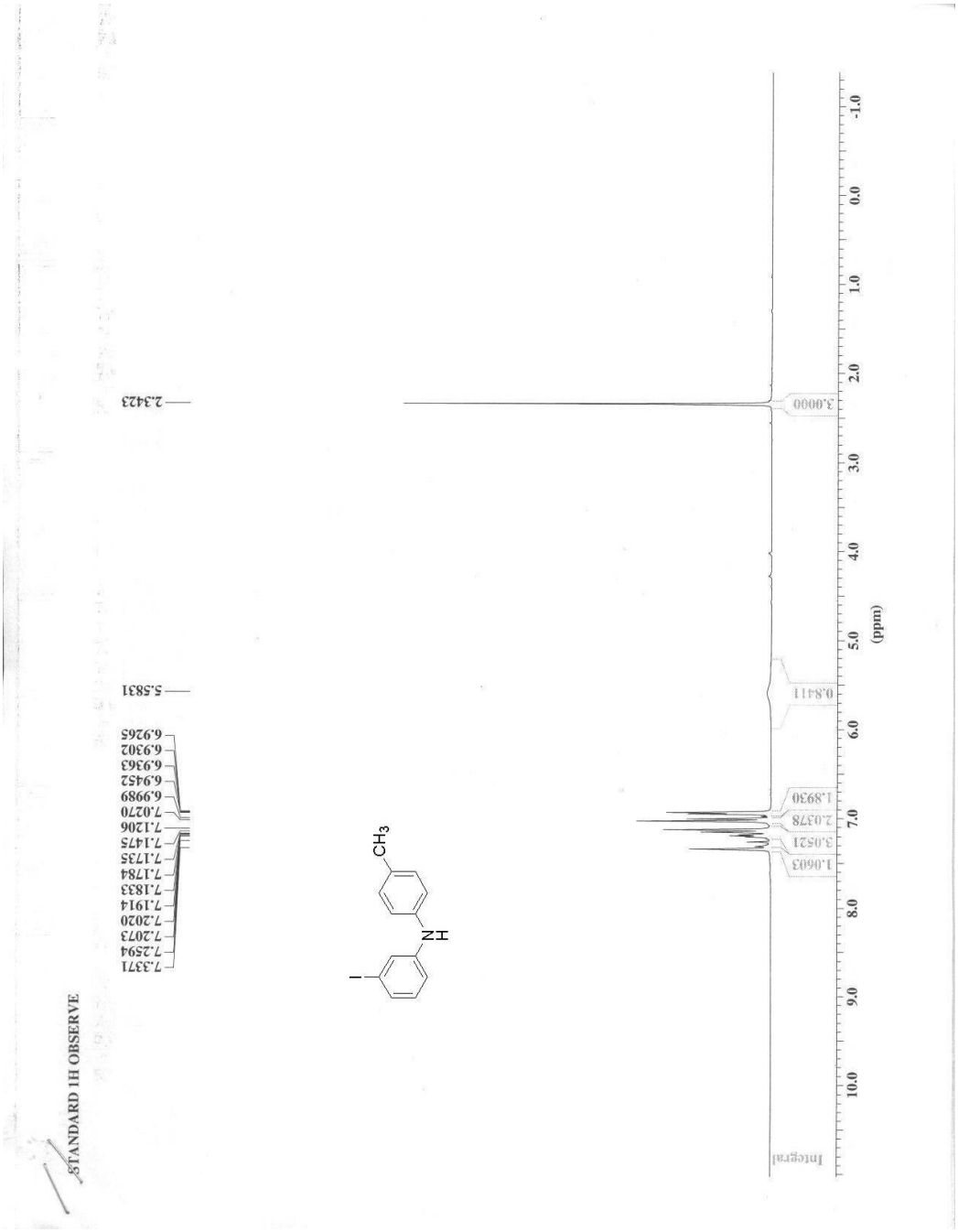


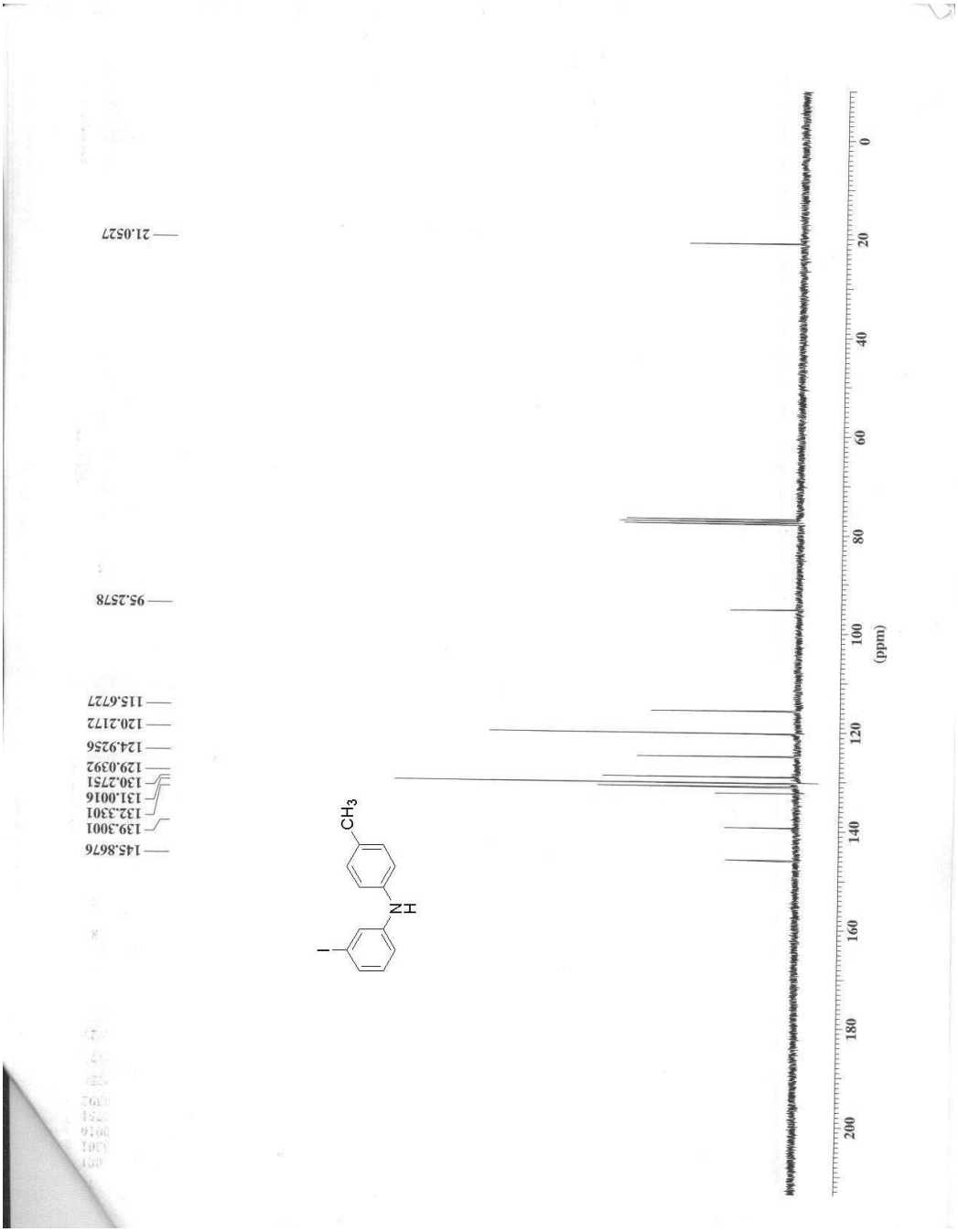


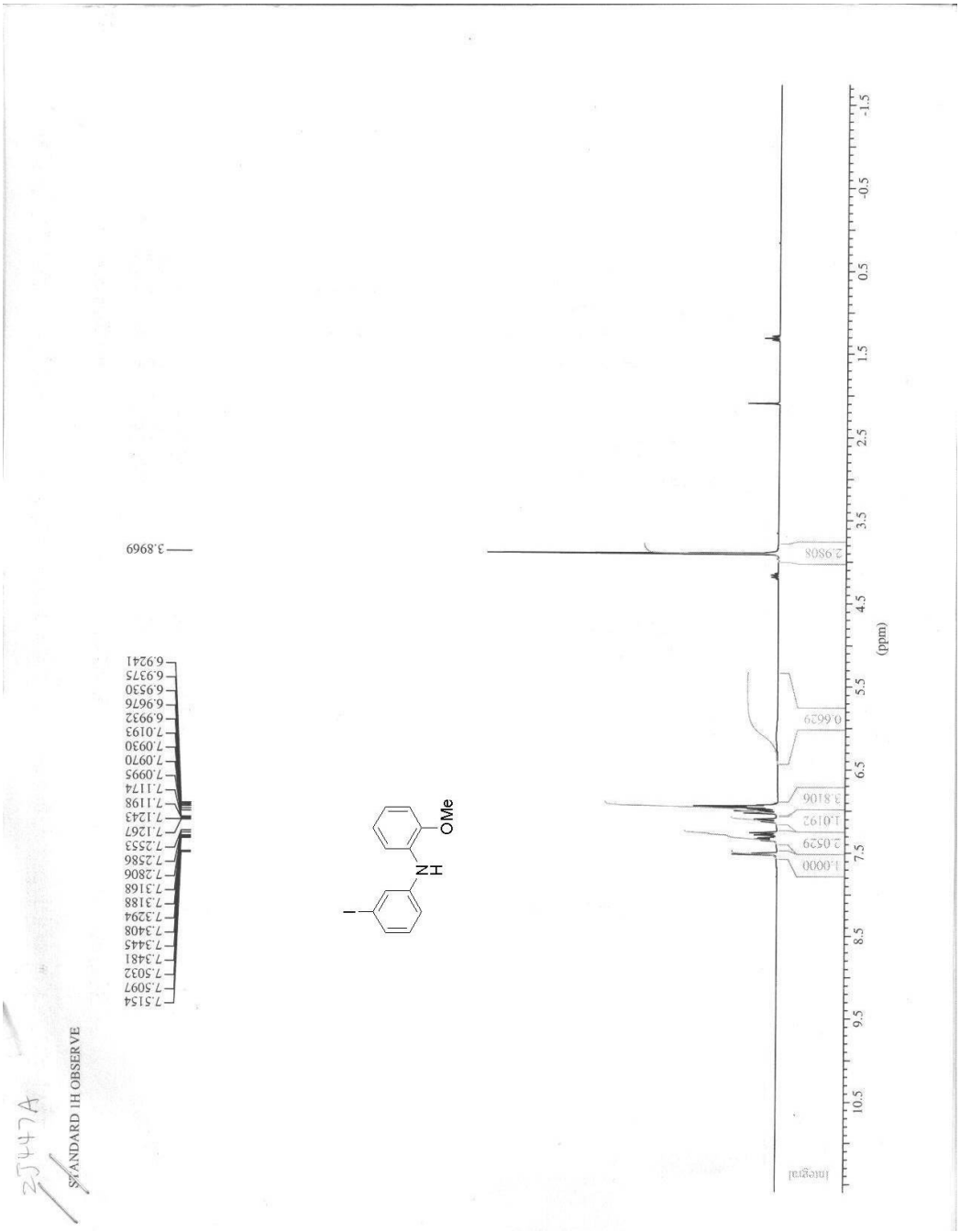
APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

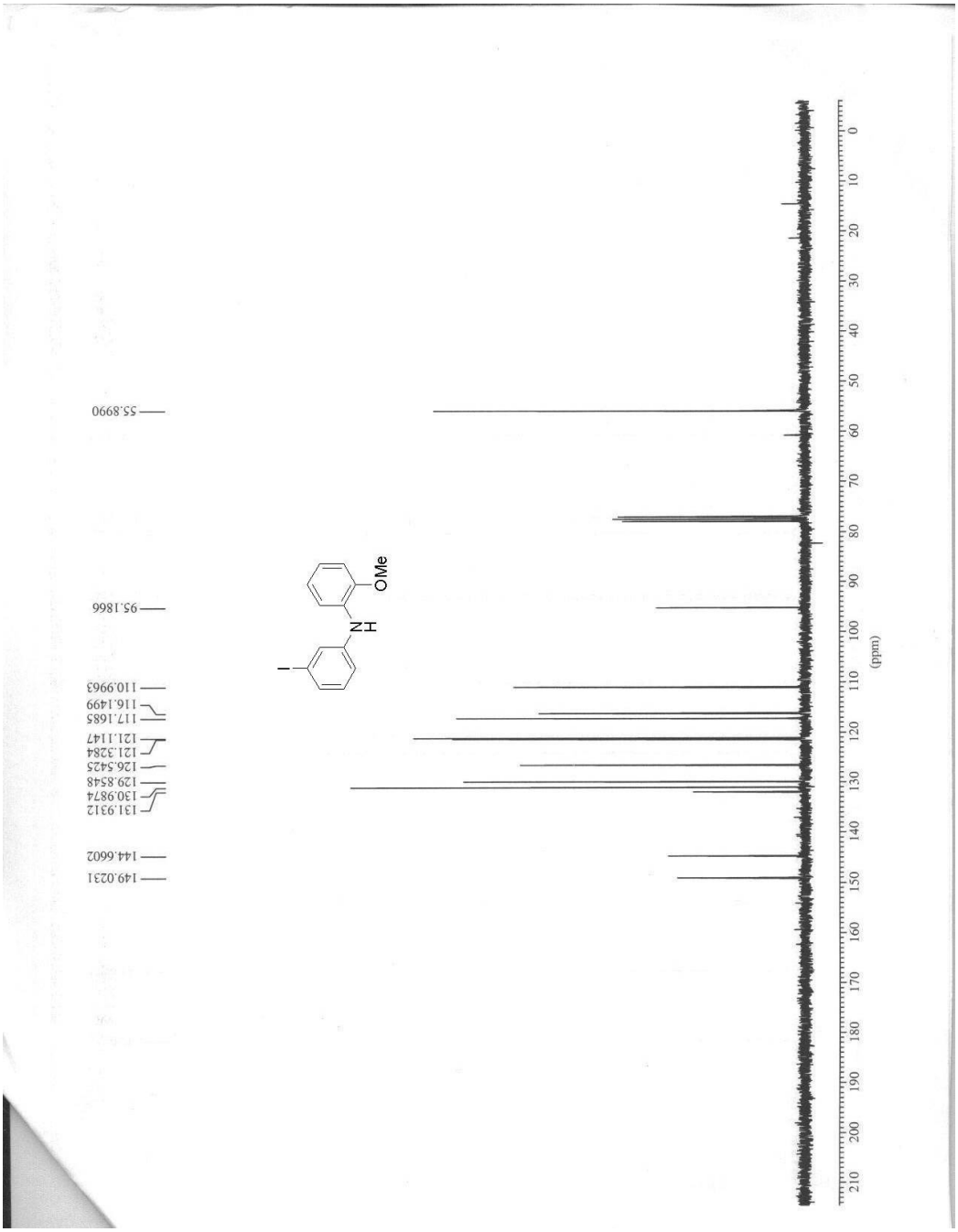


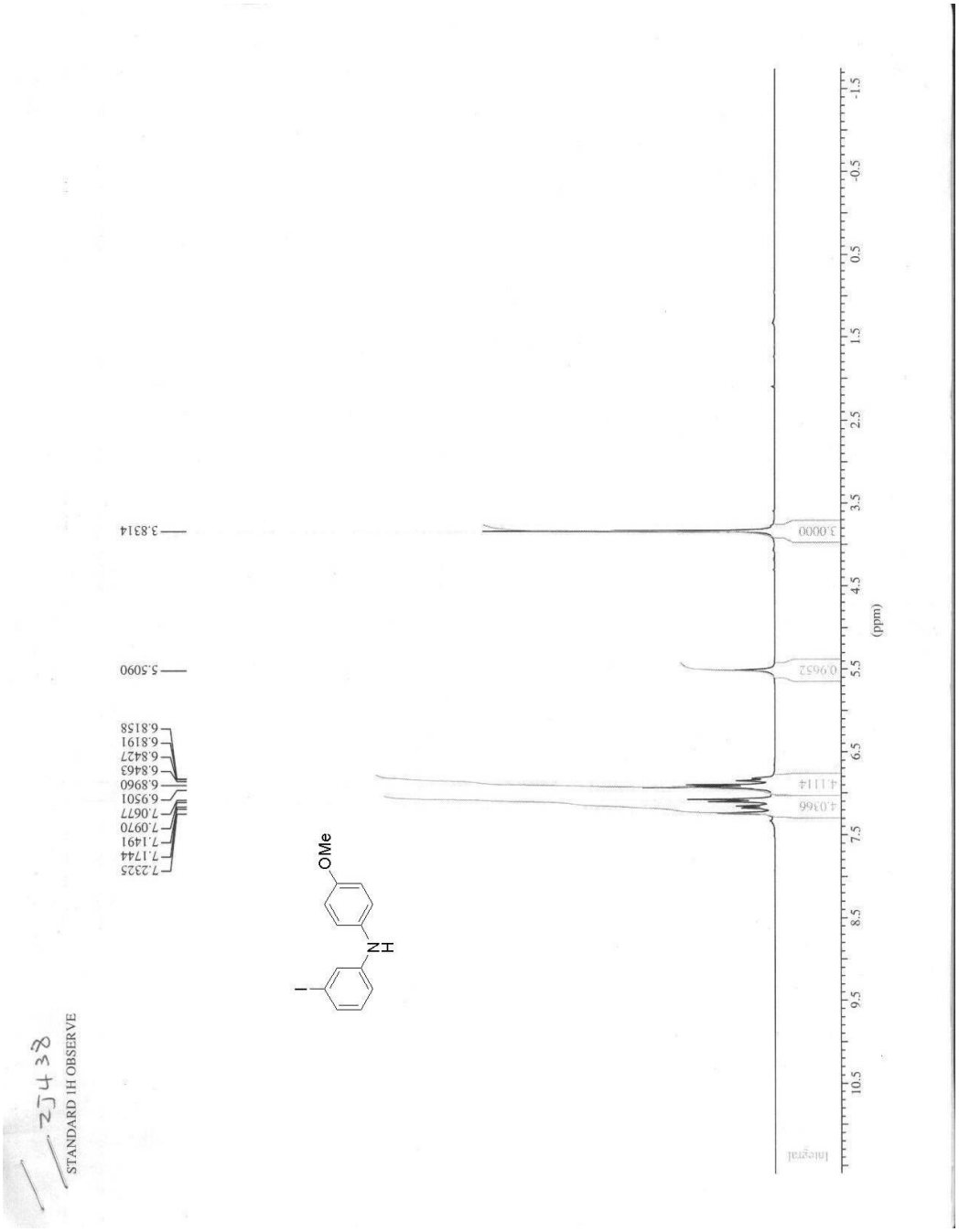


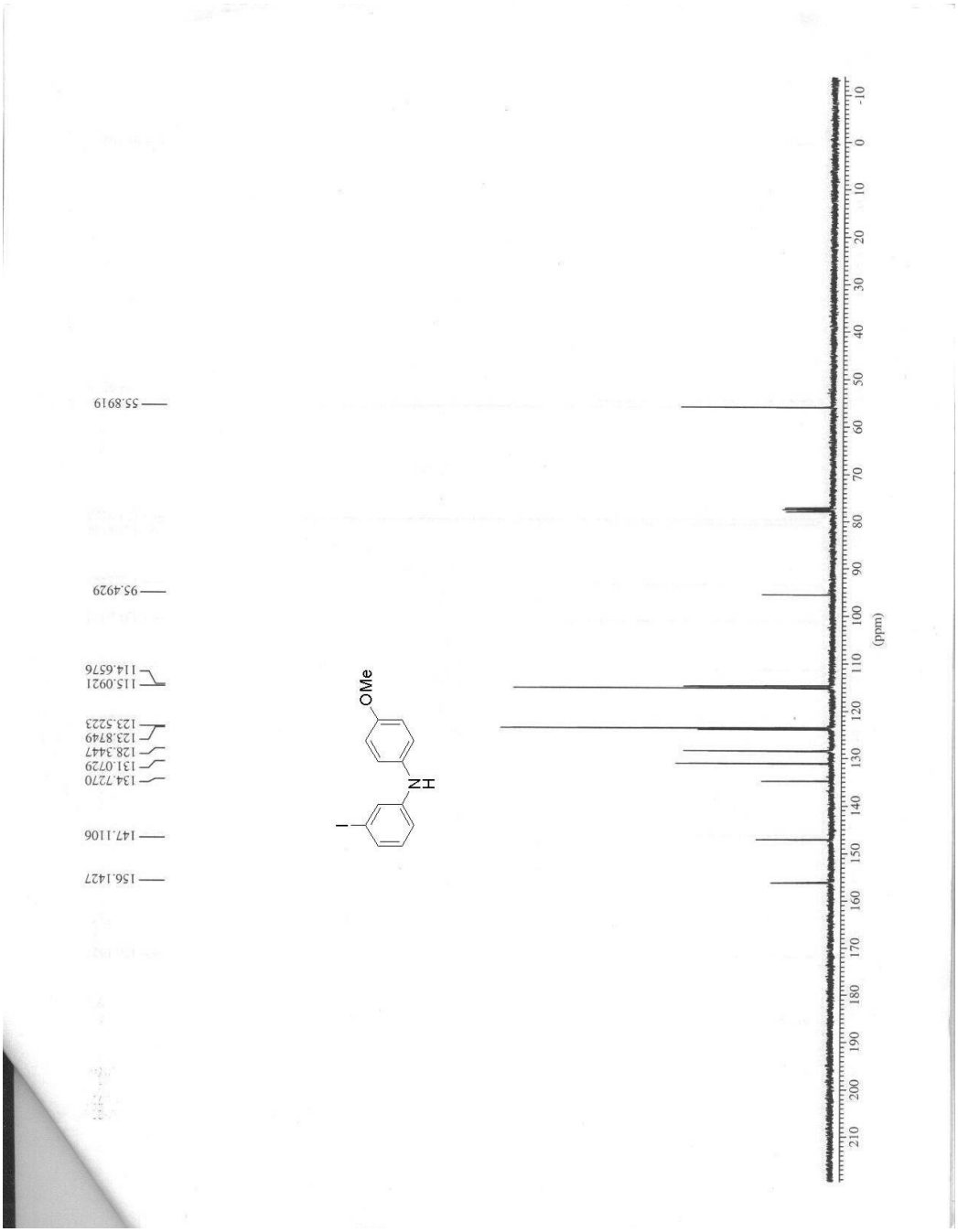


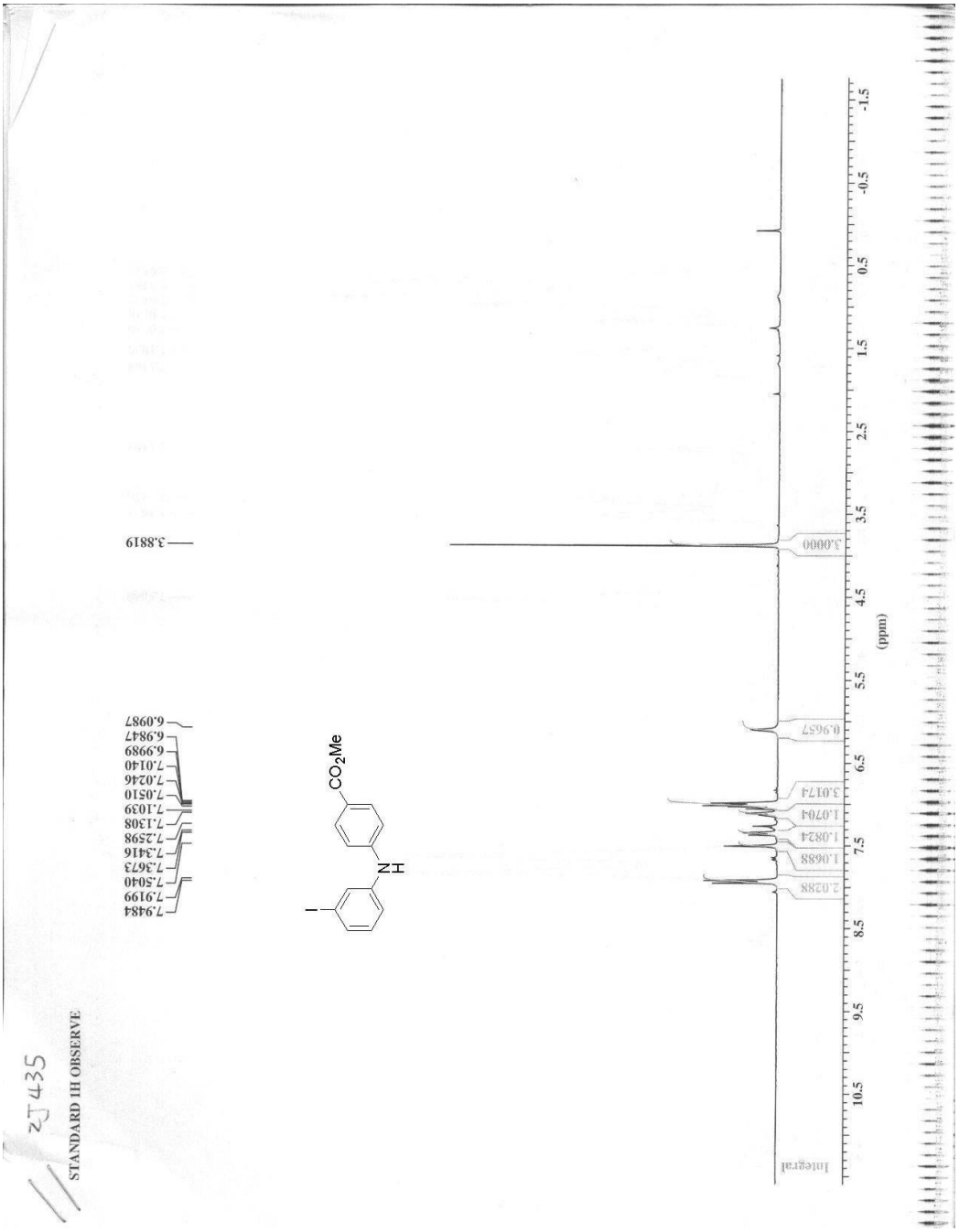


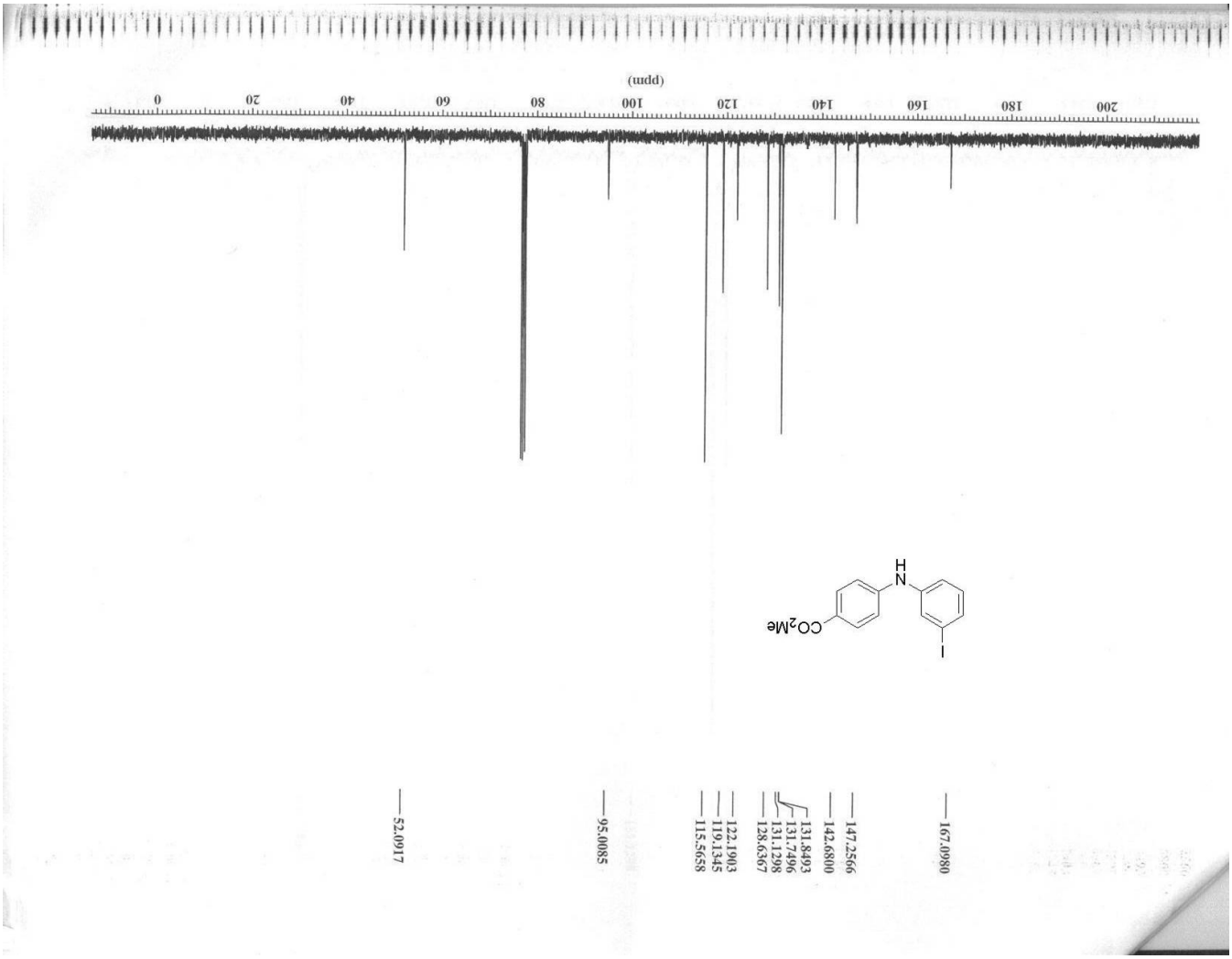


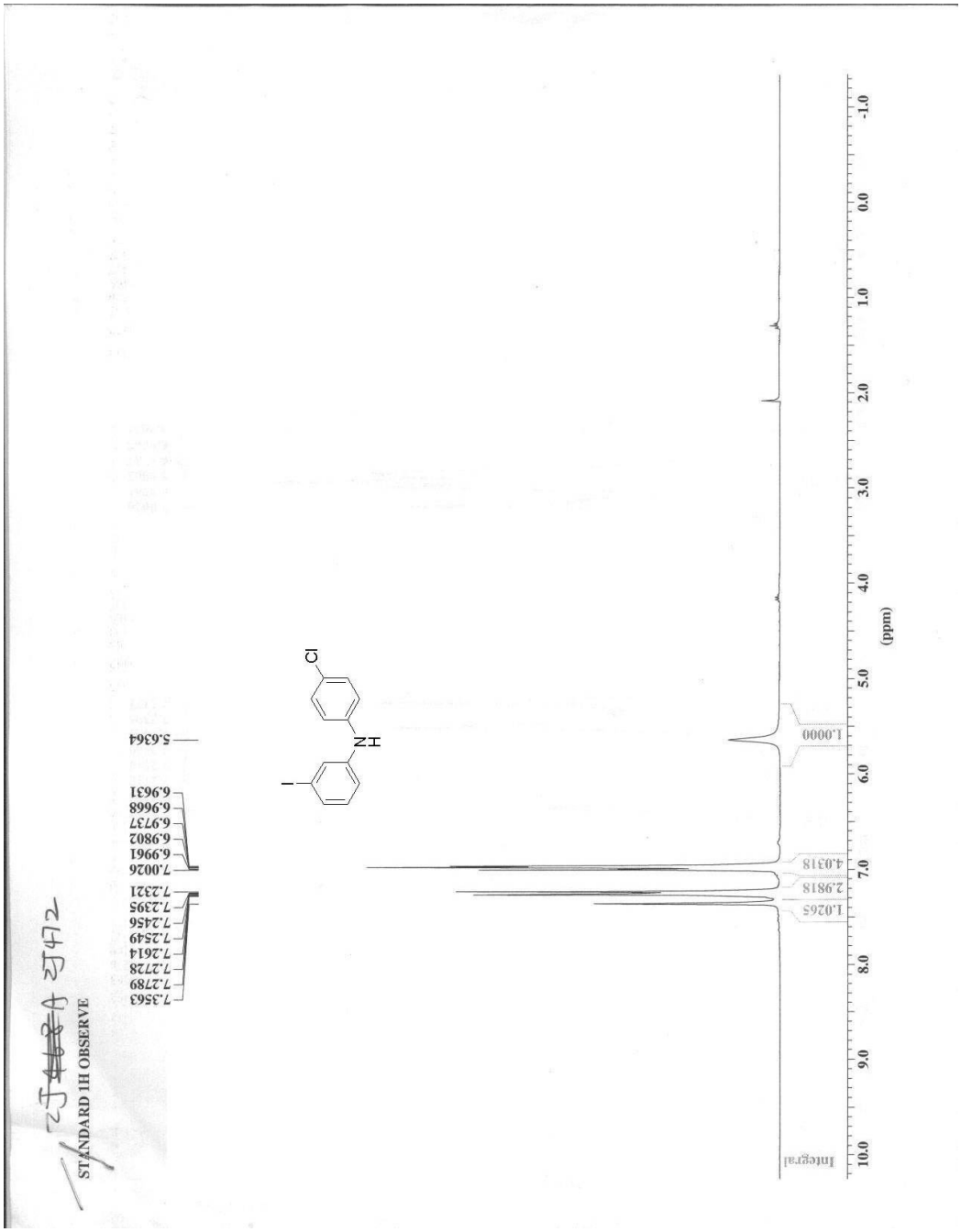


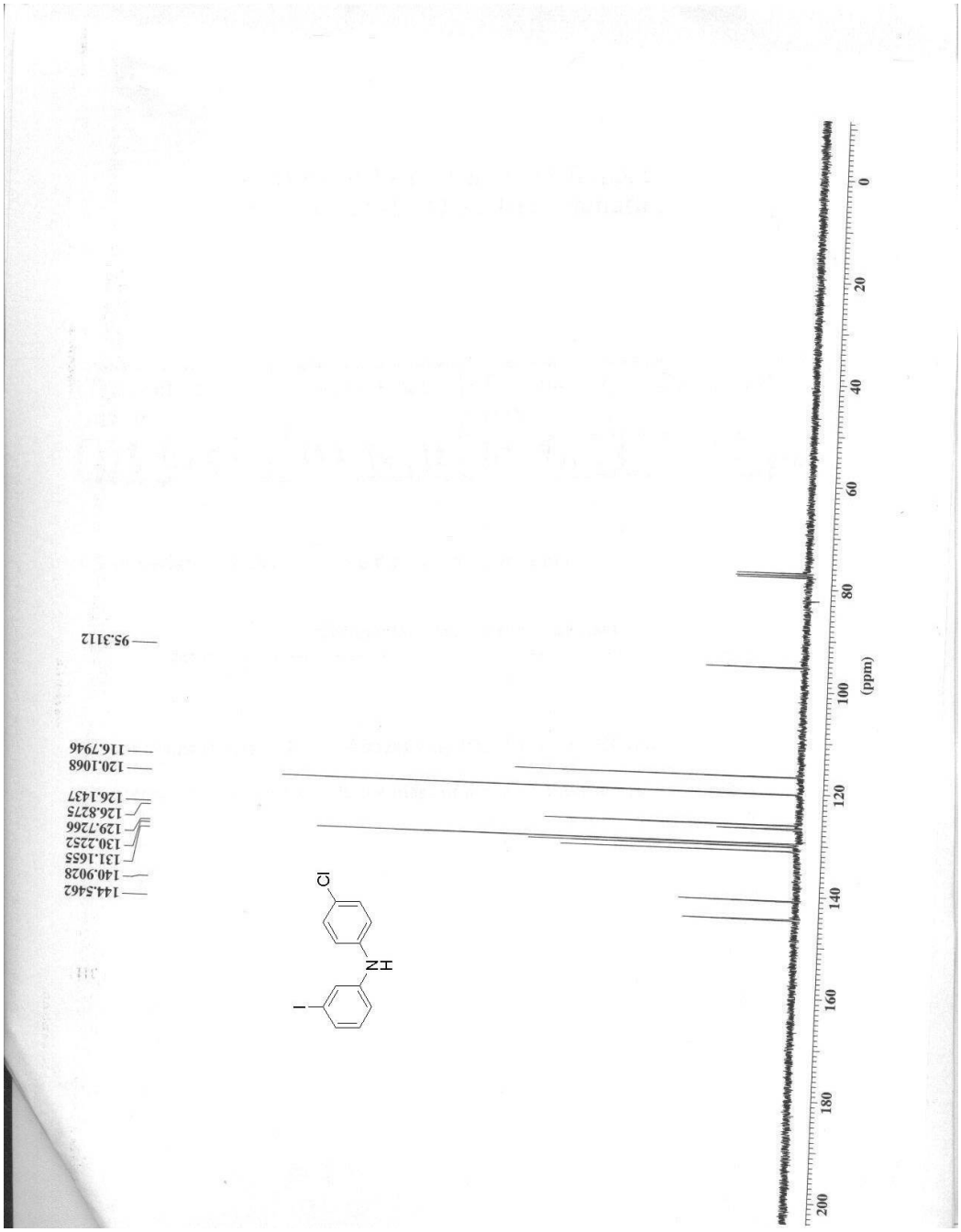


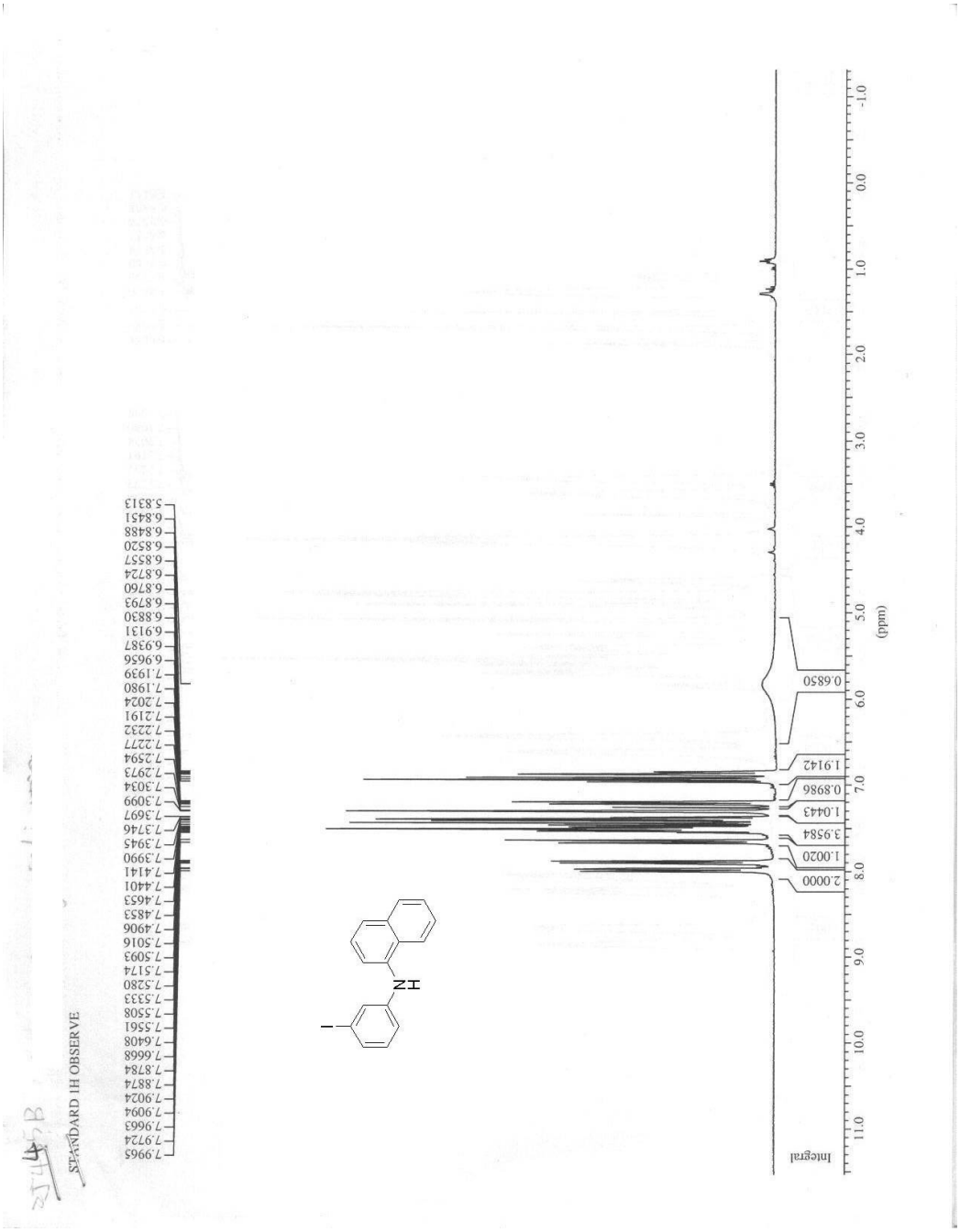


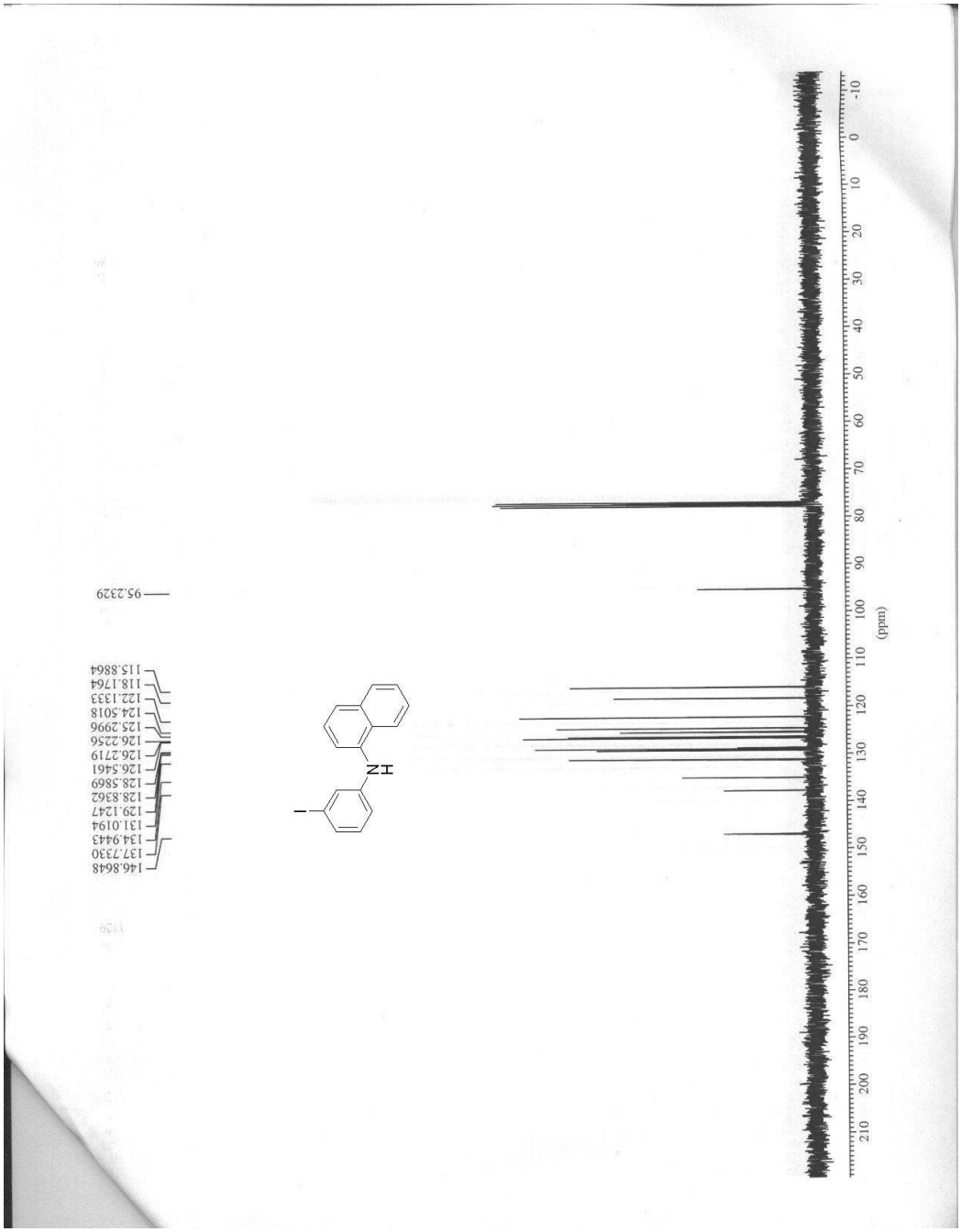


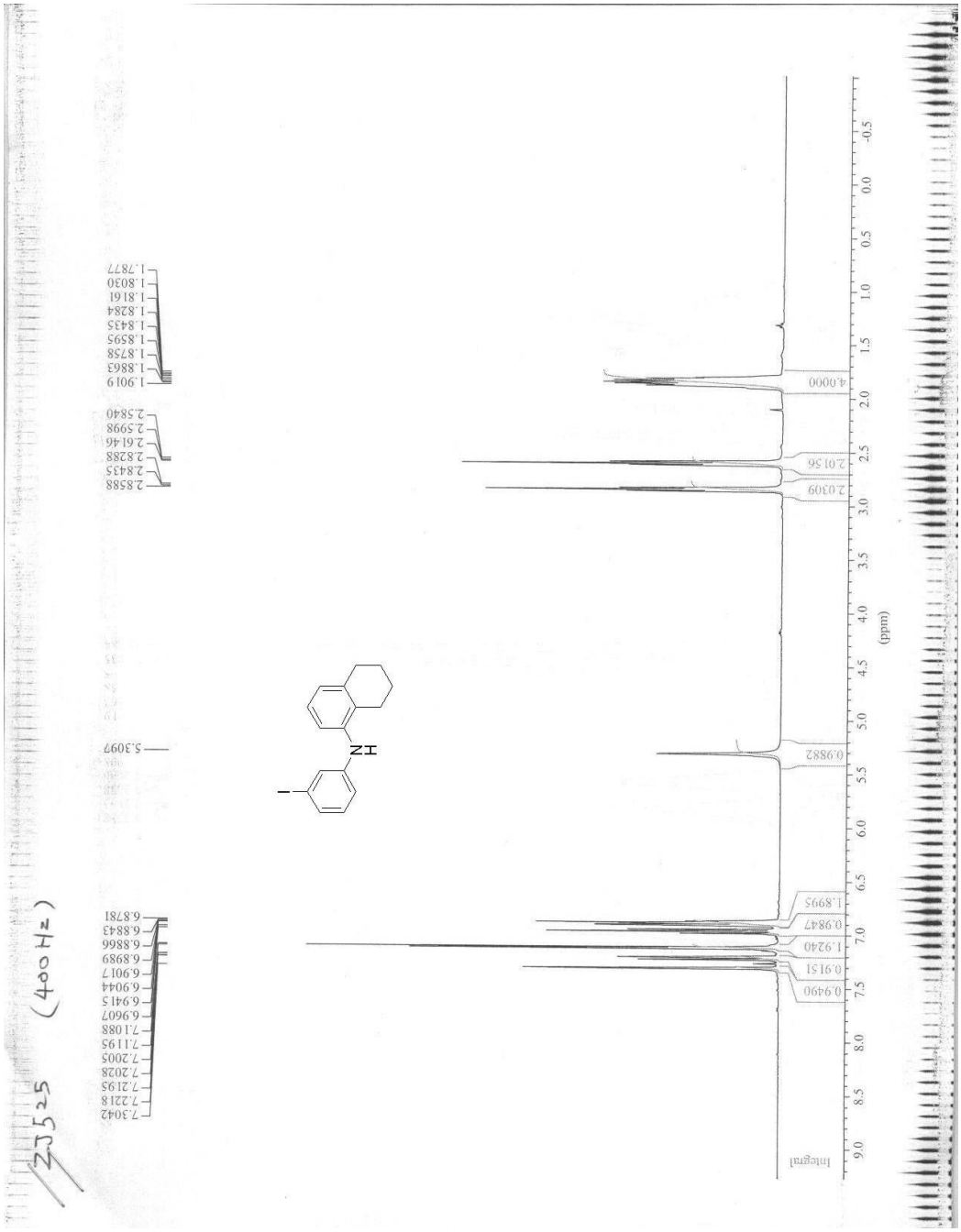


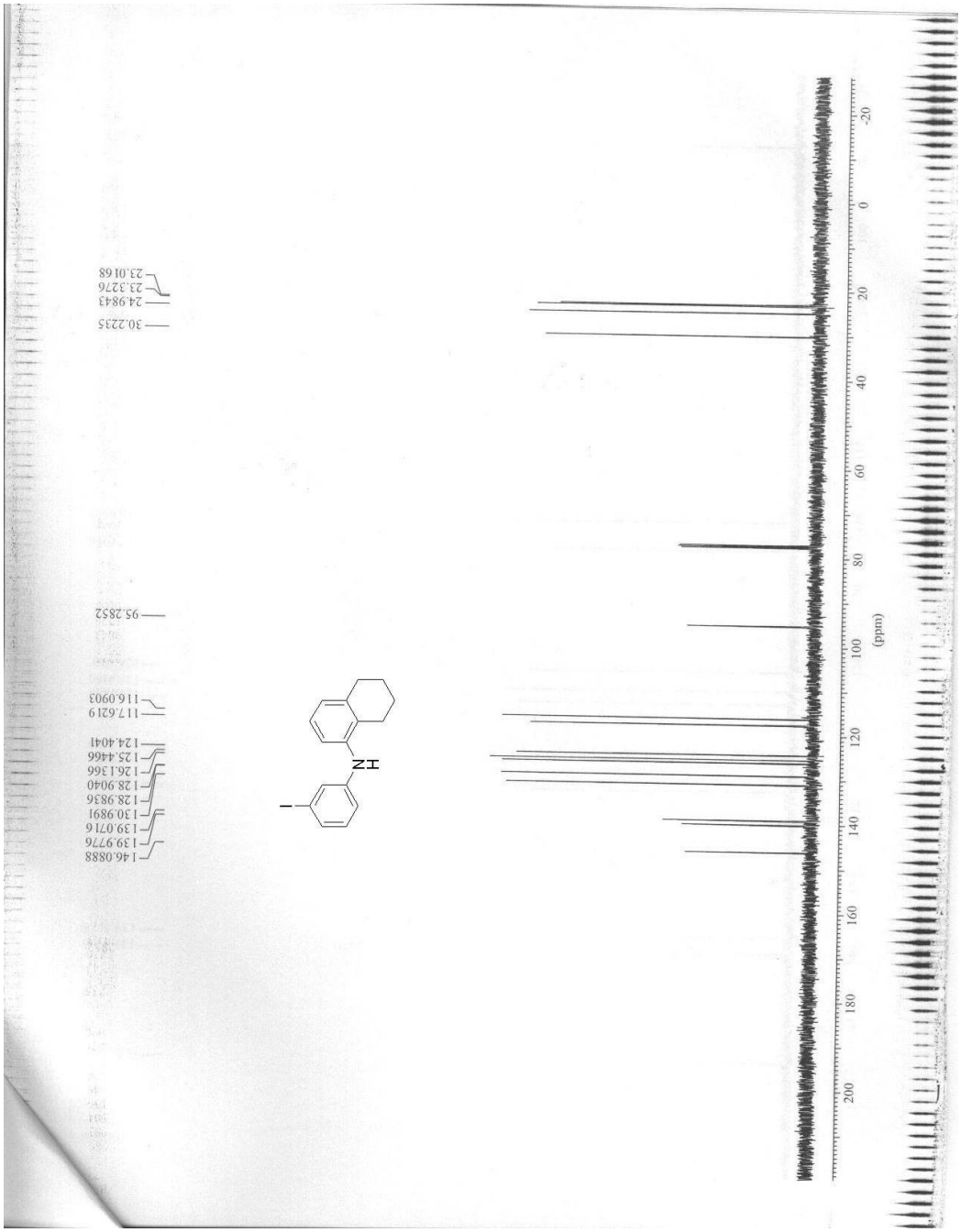


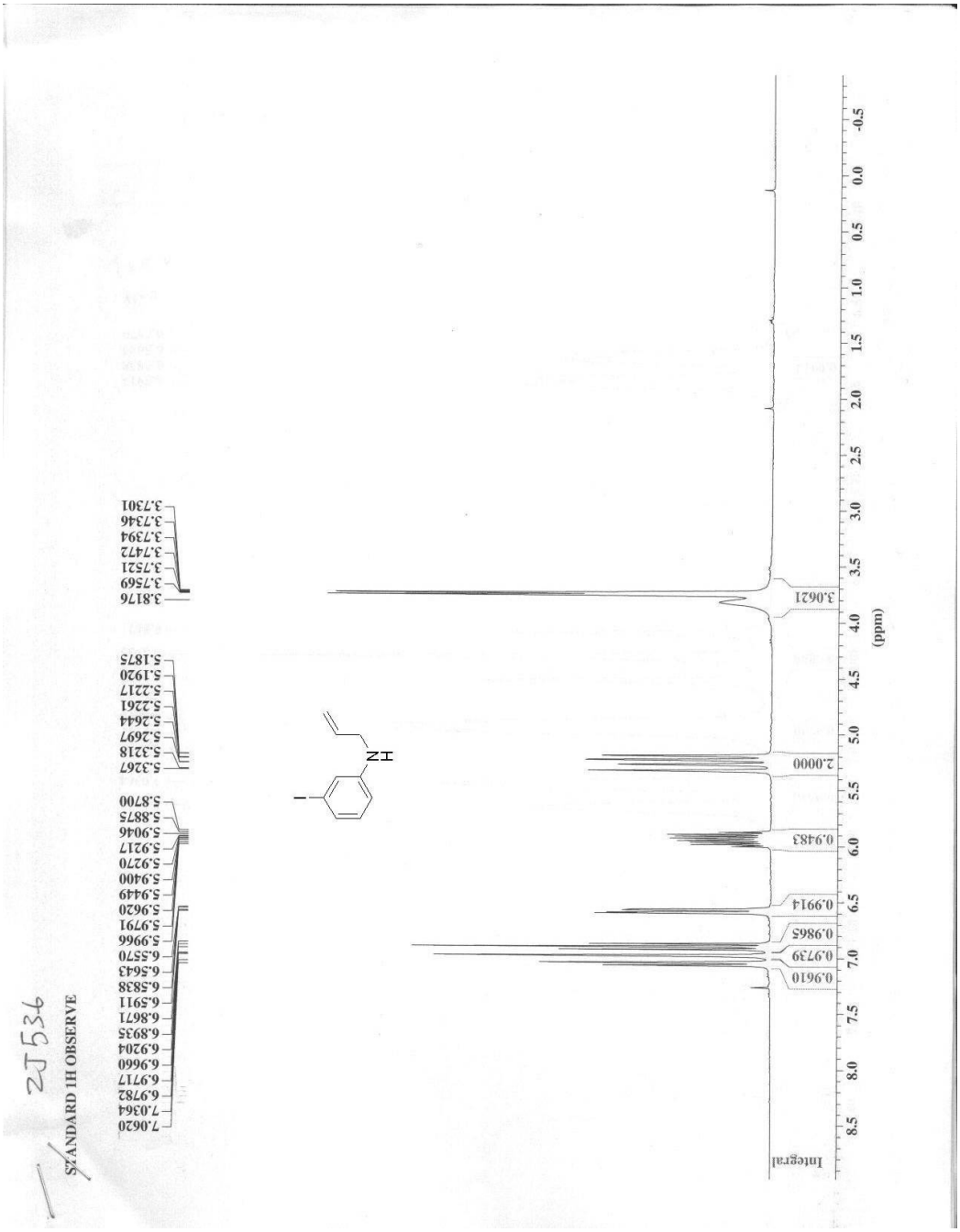


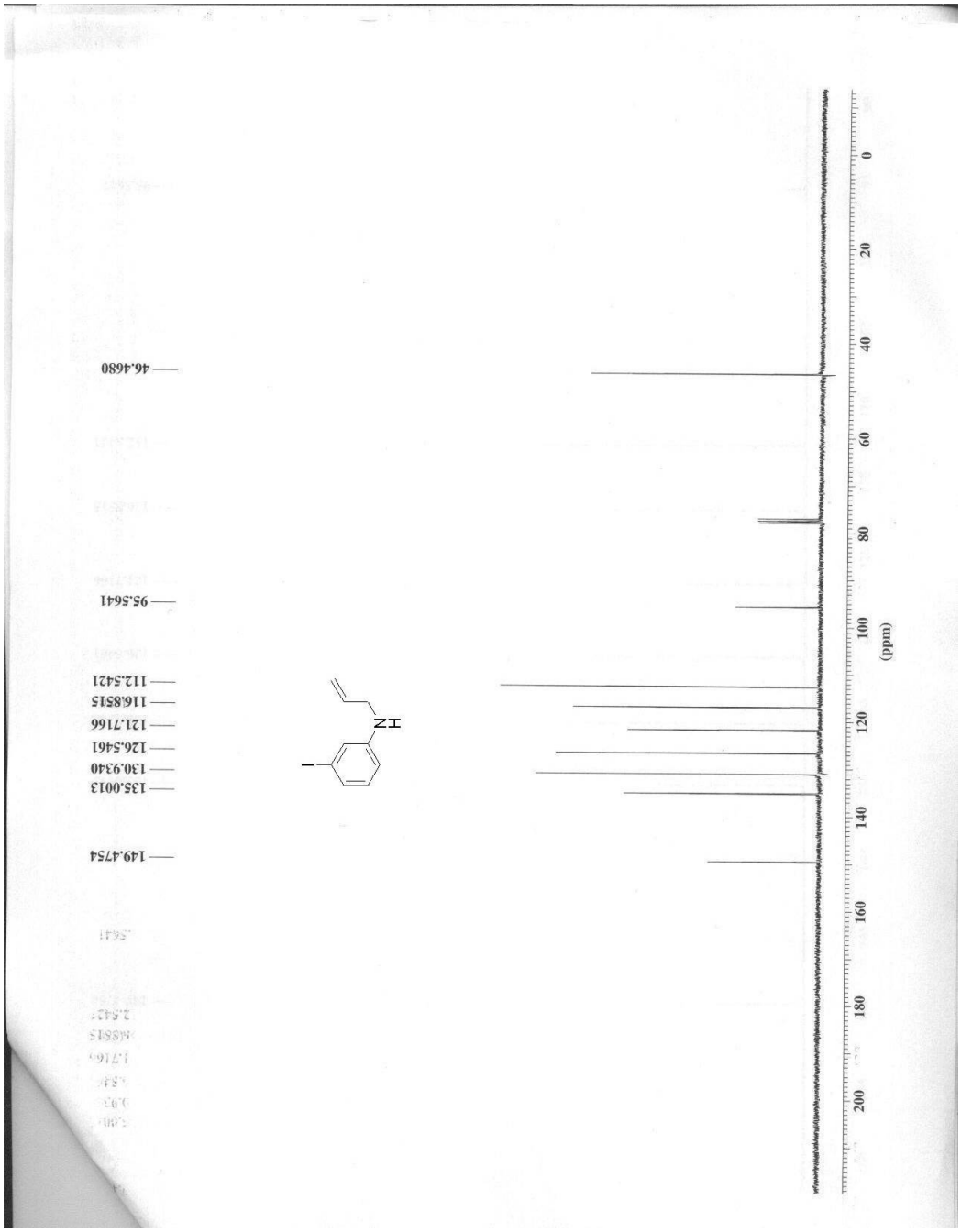


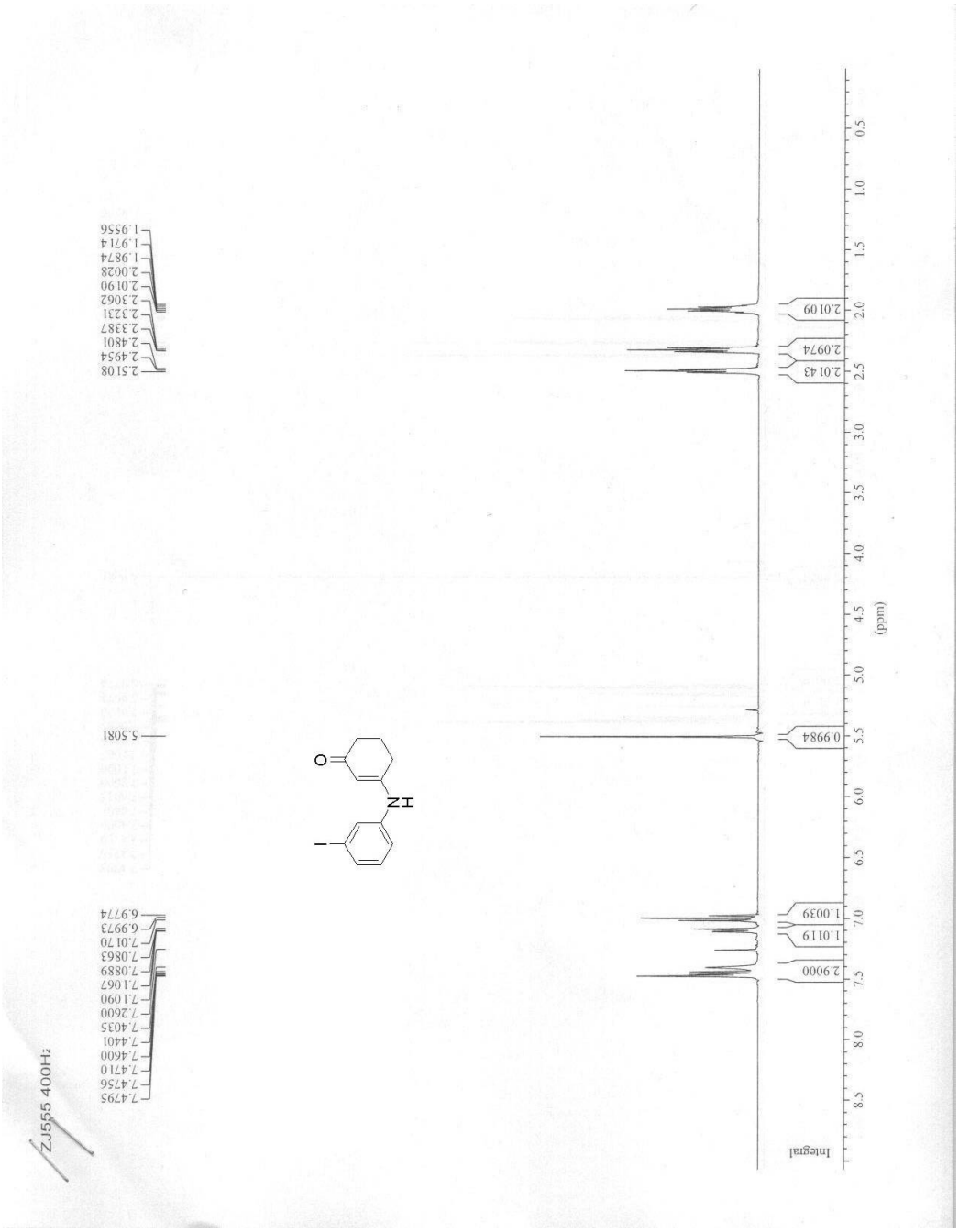


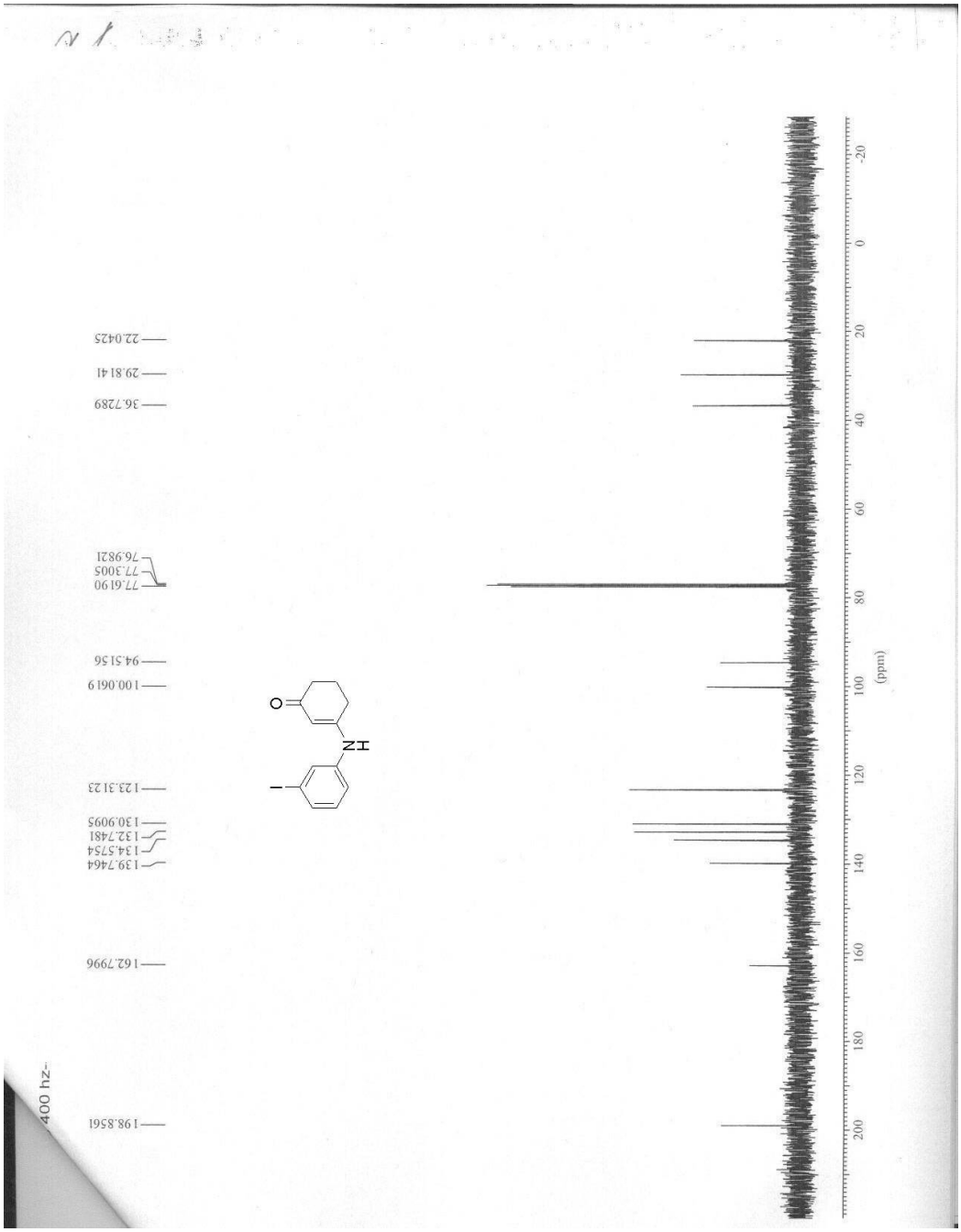


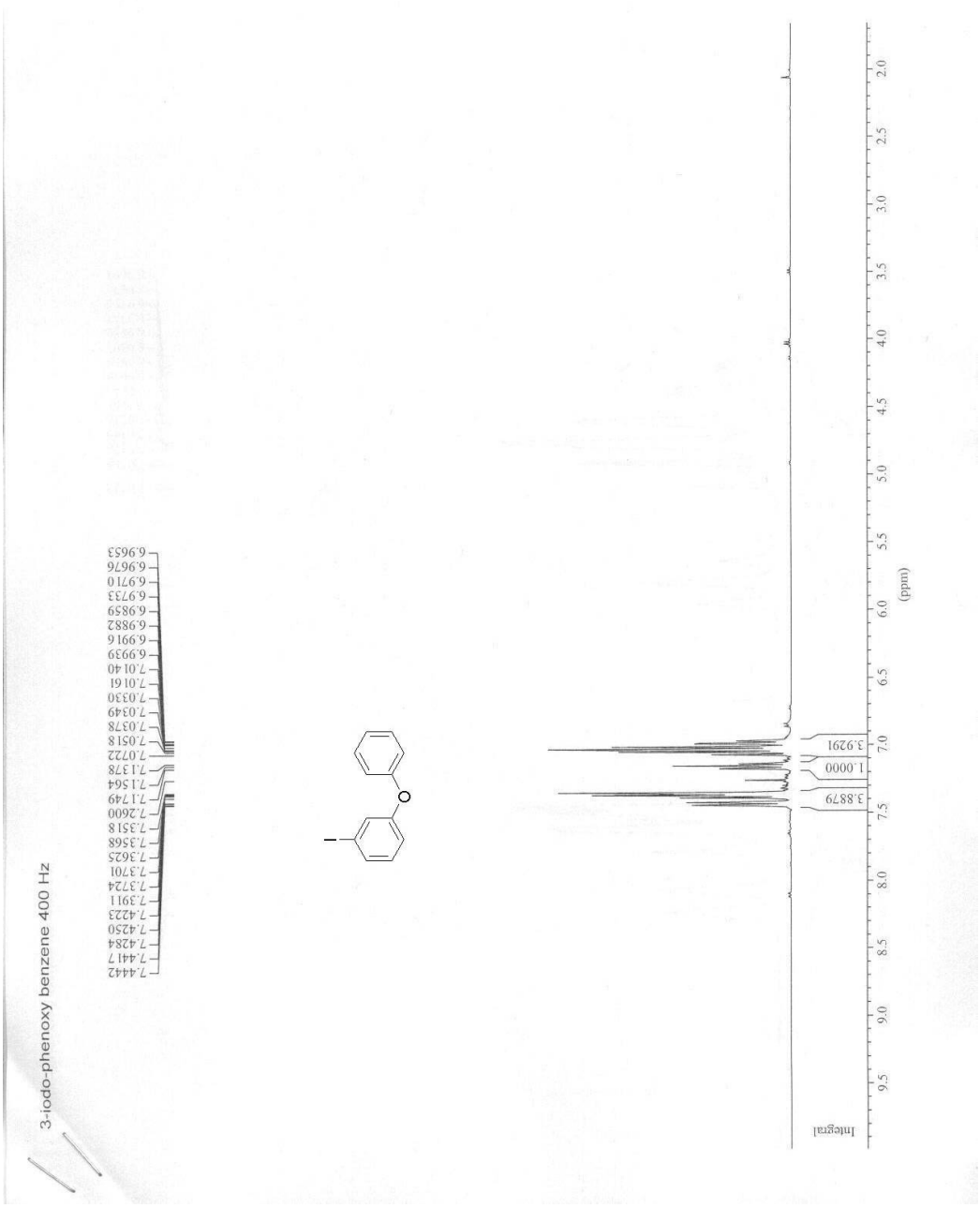


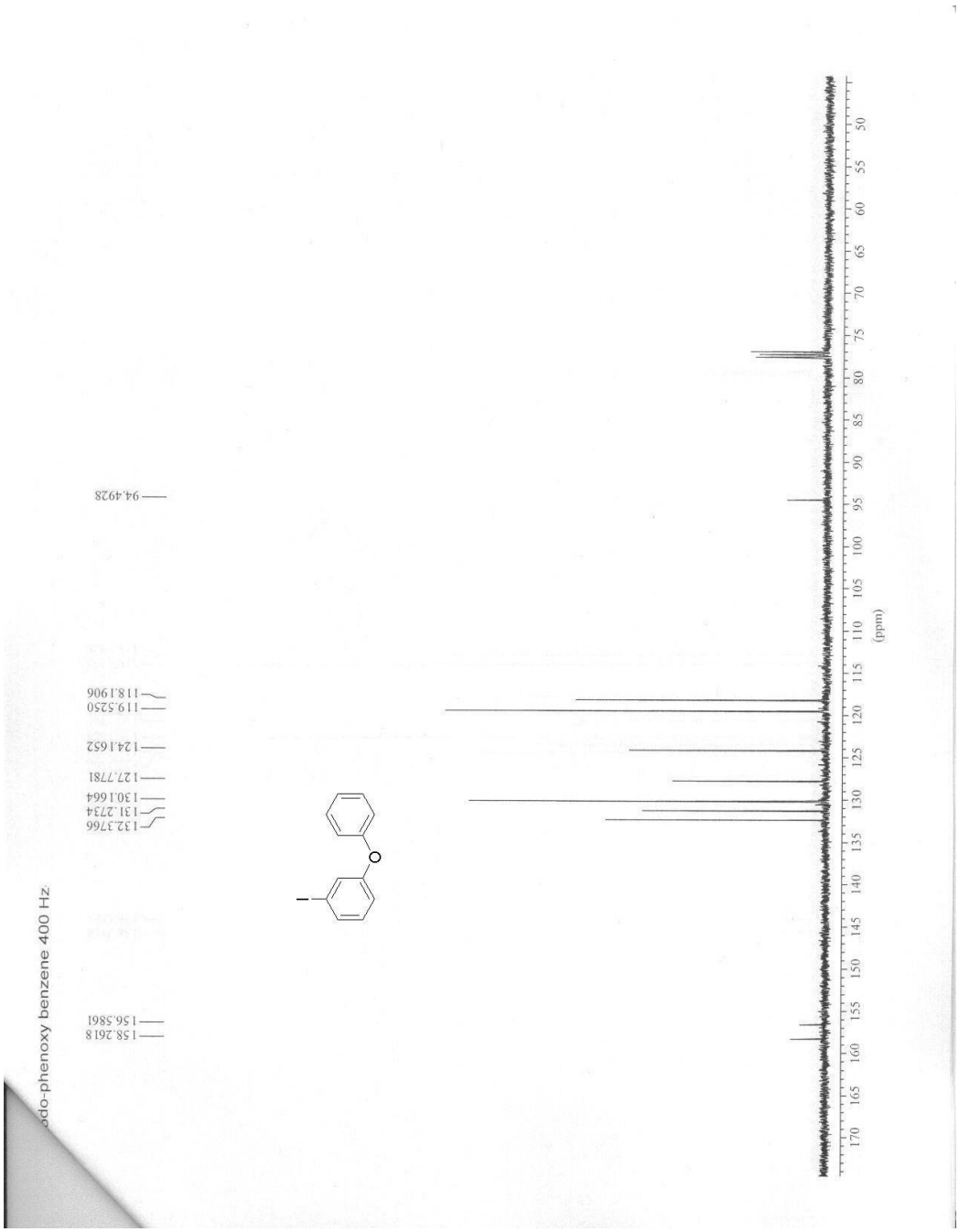


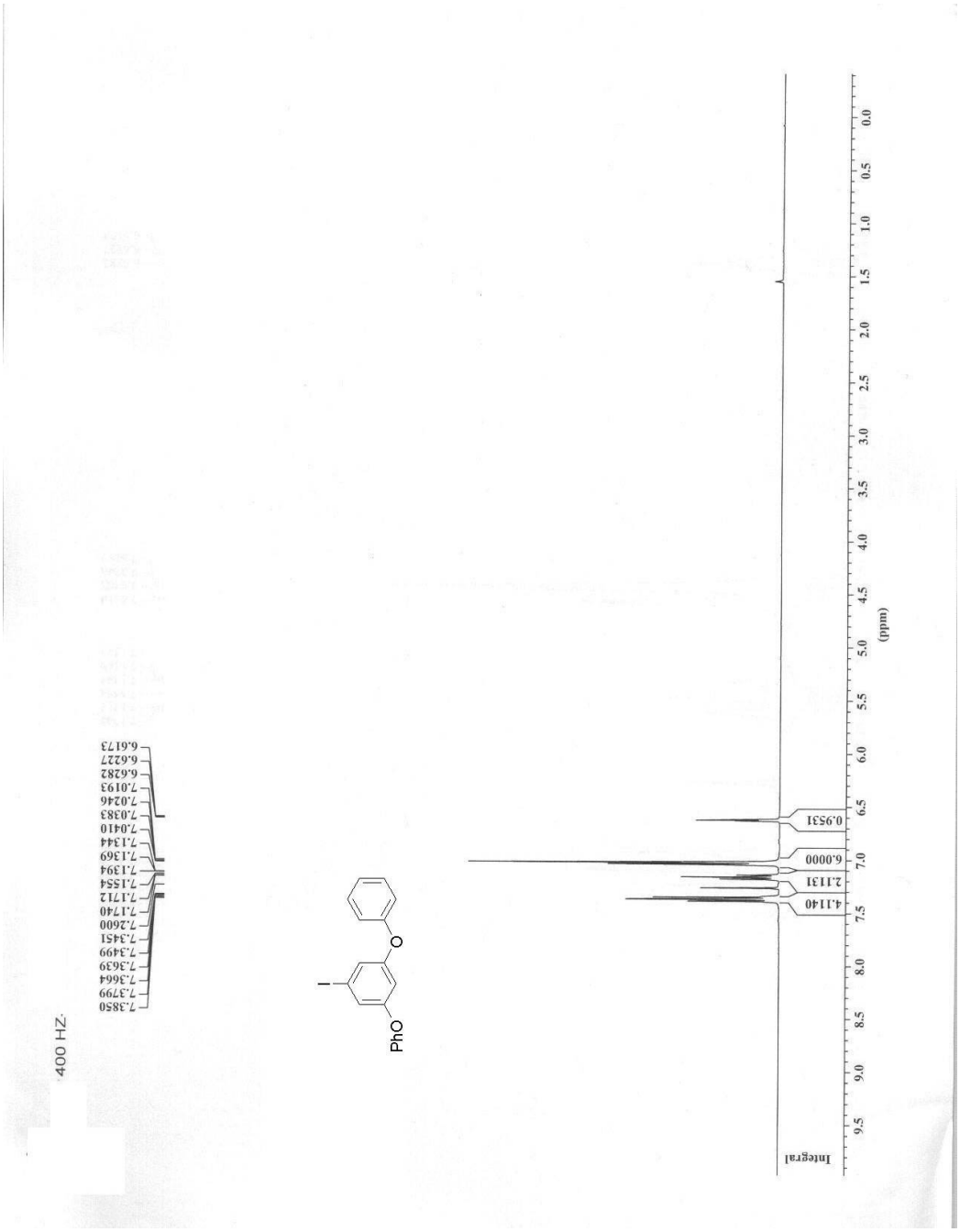


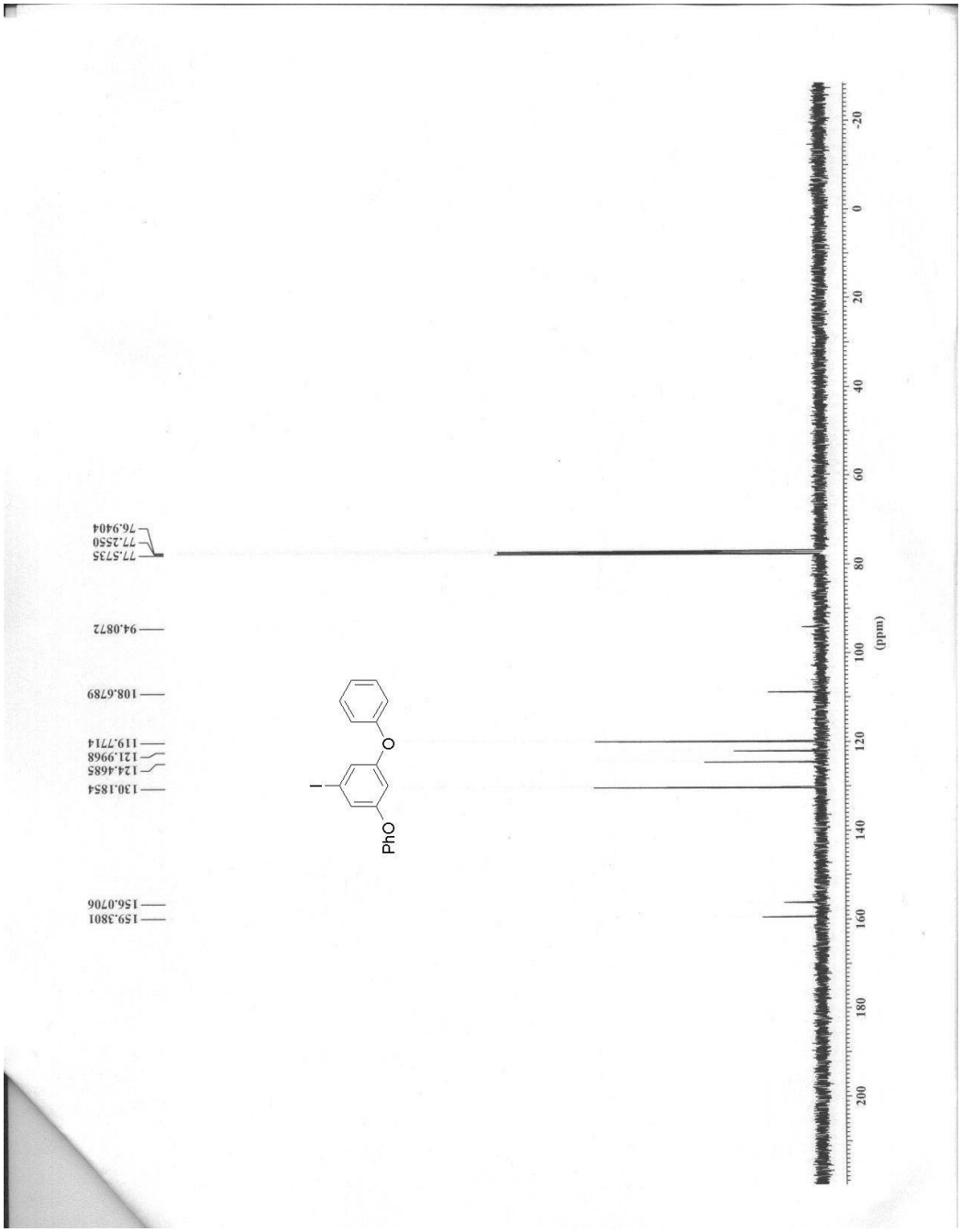


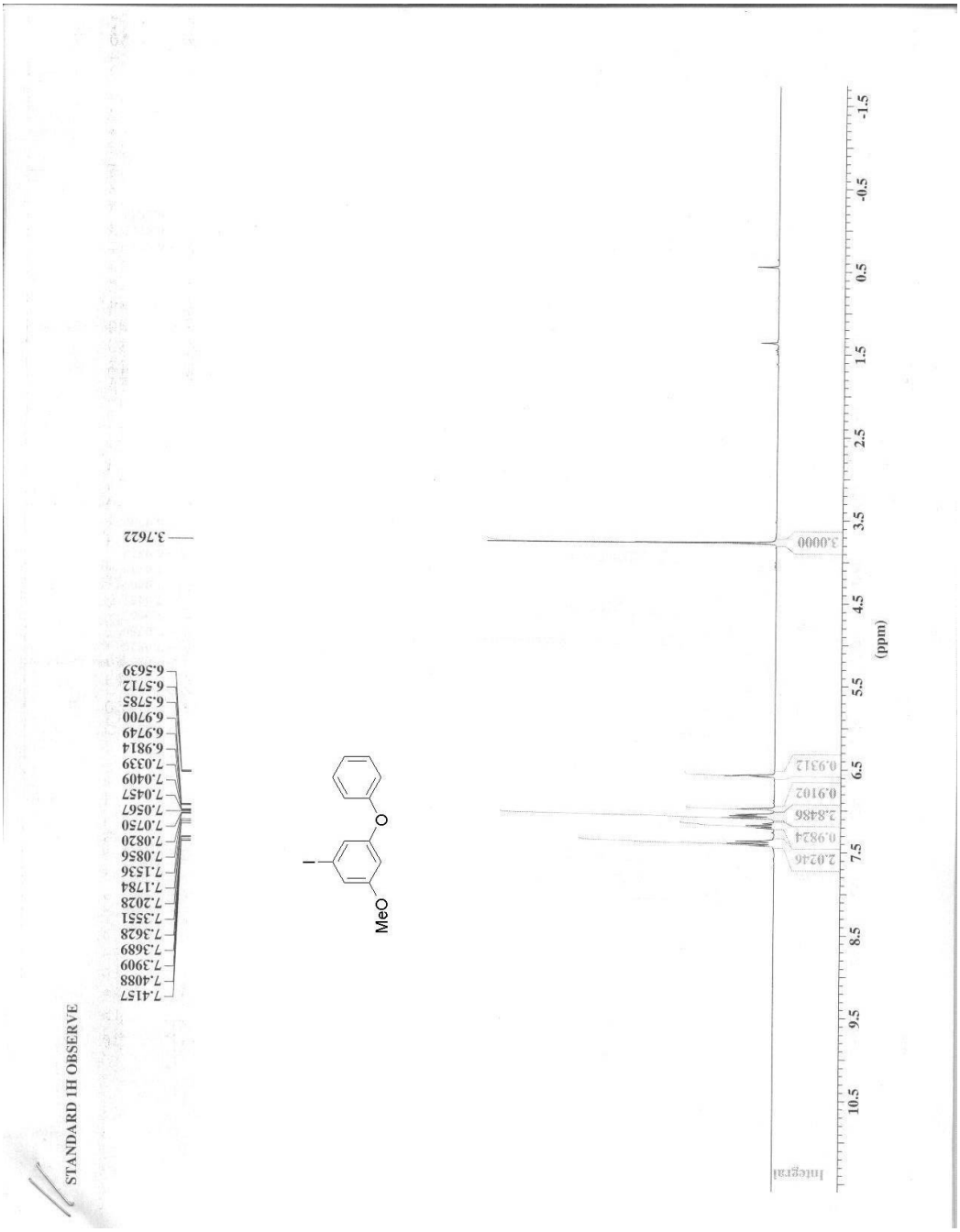


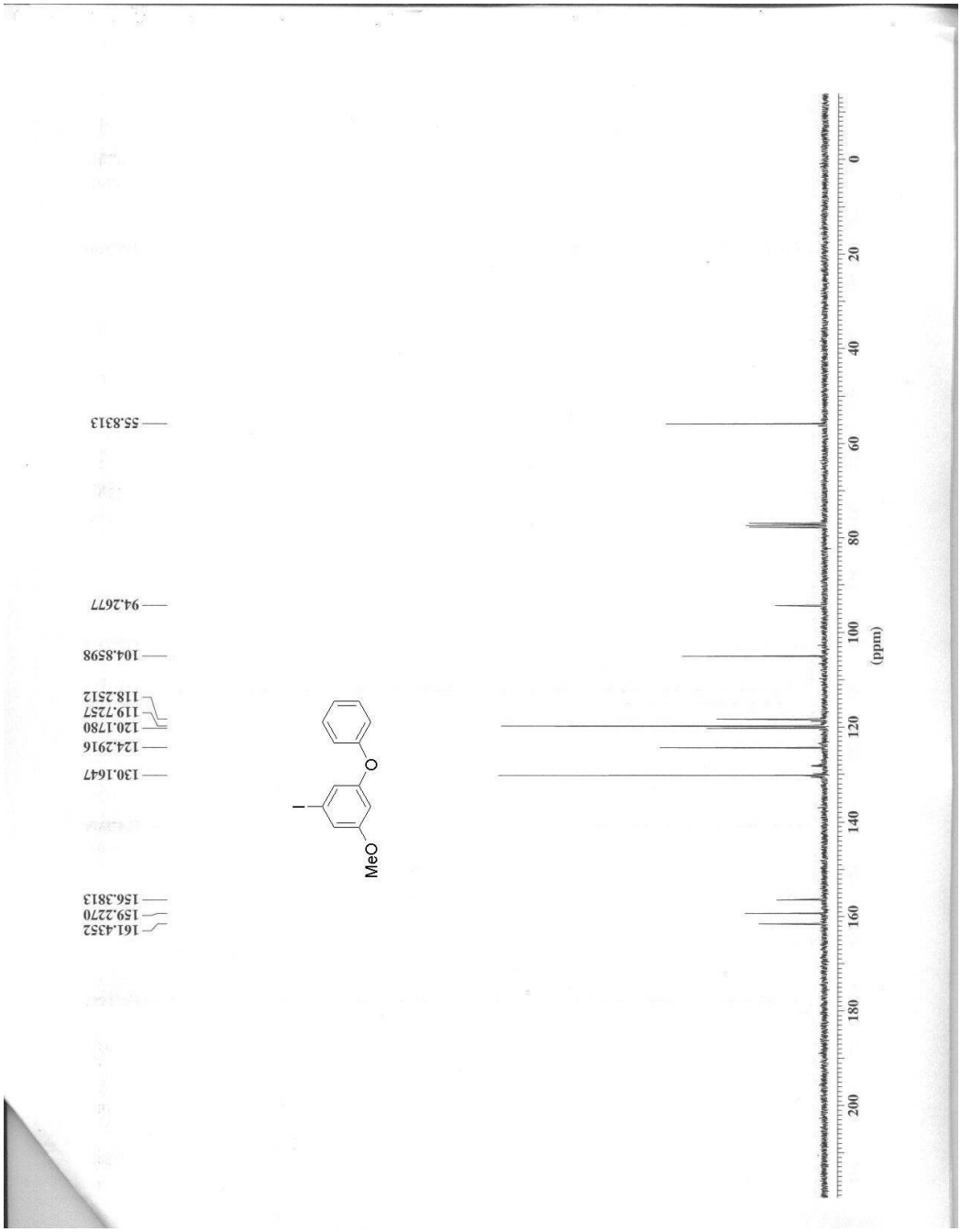


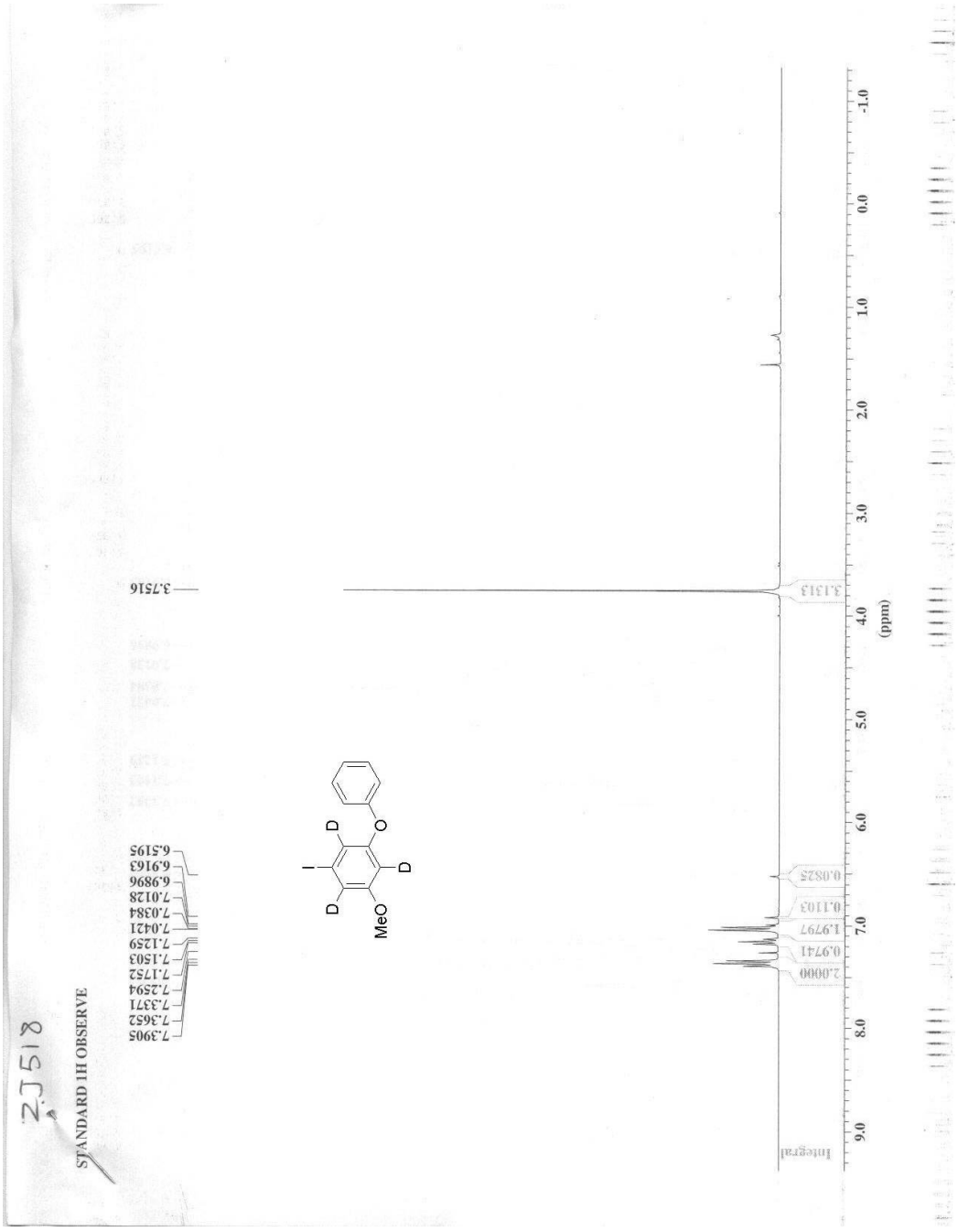


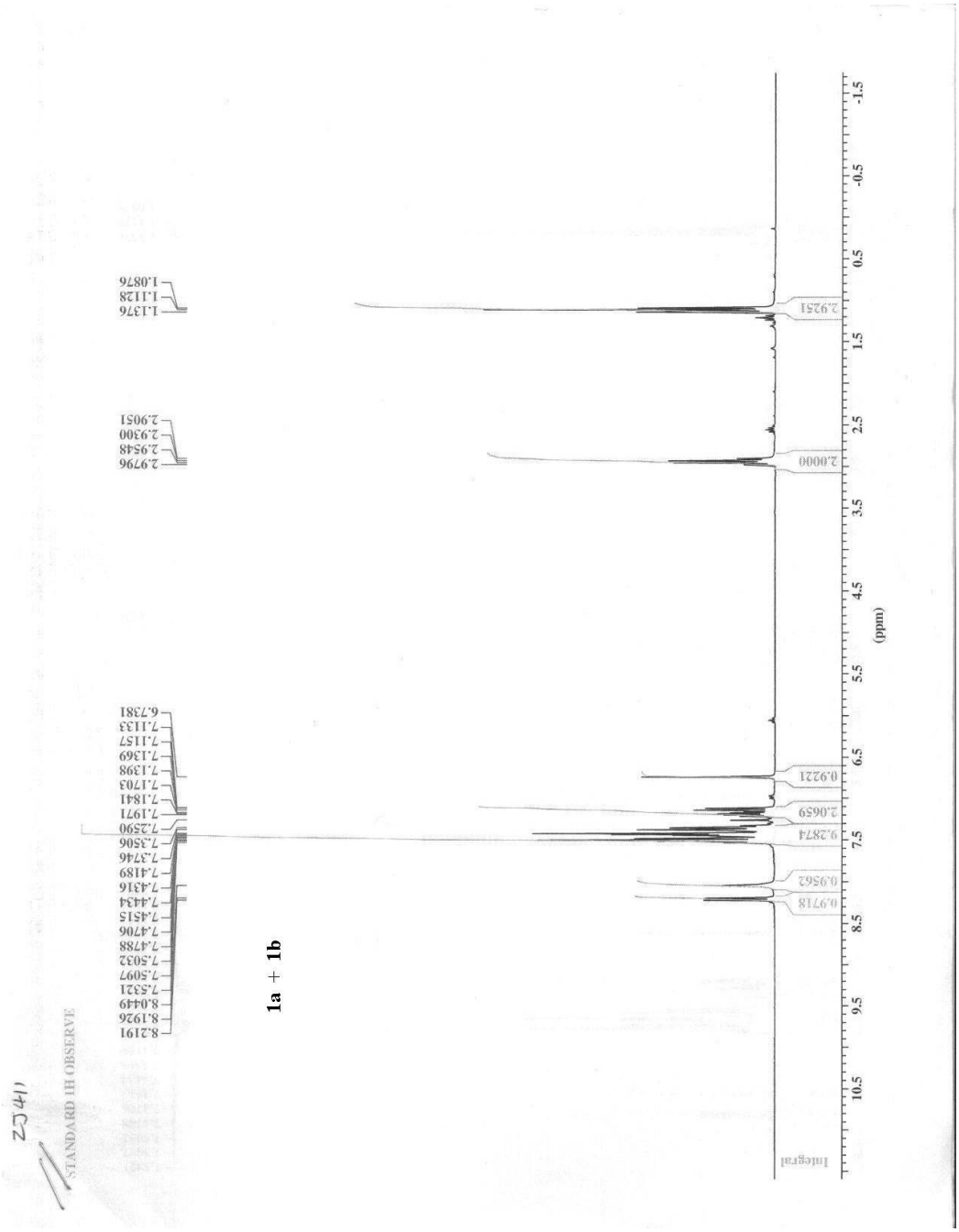


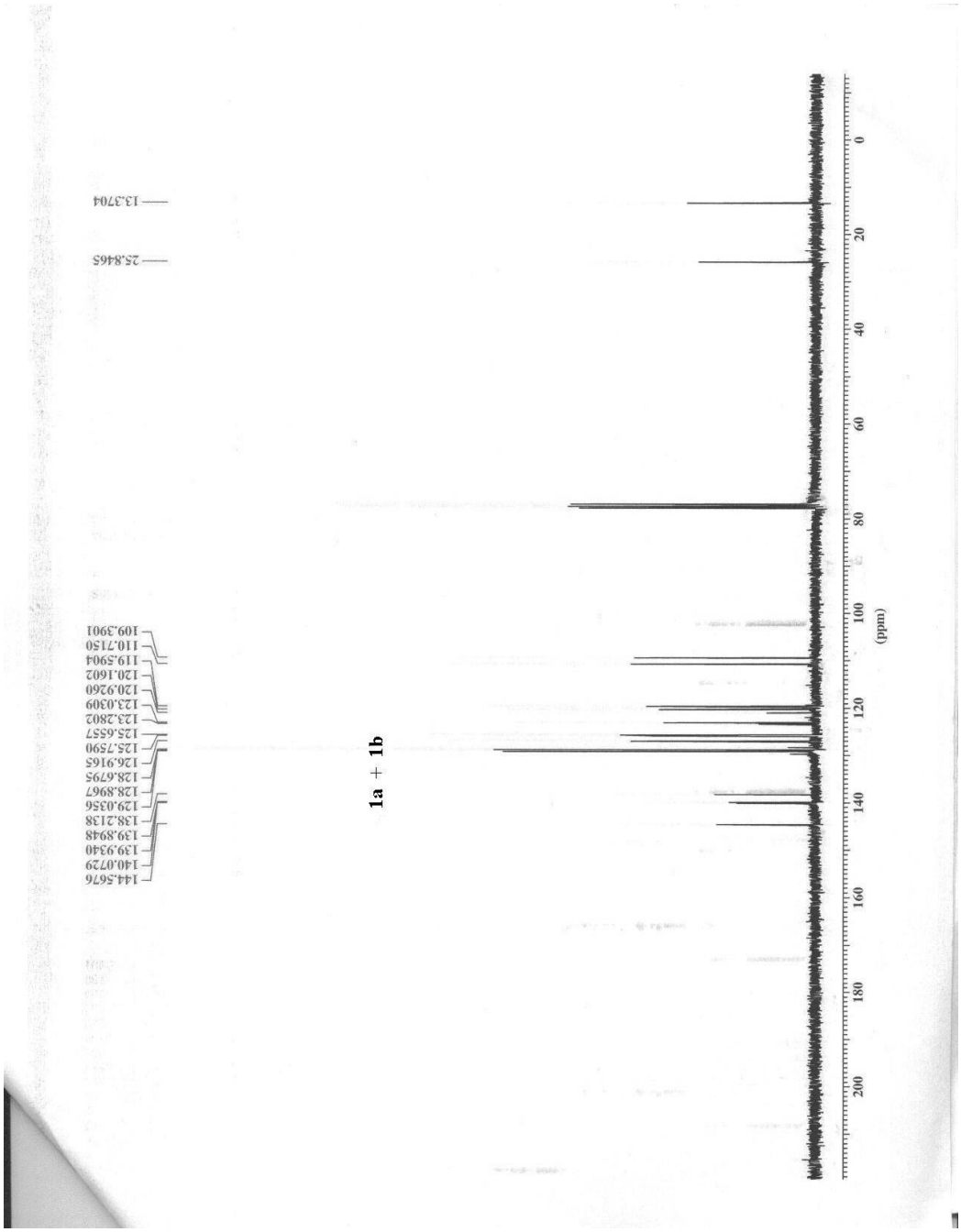


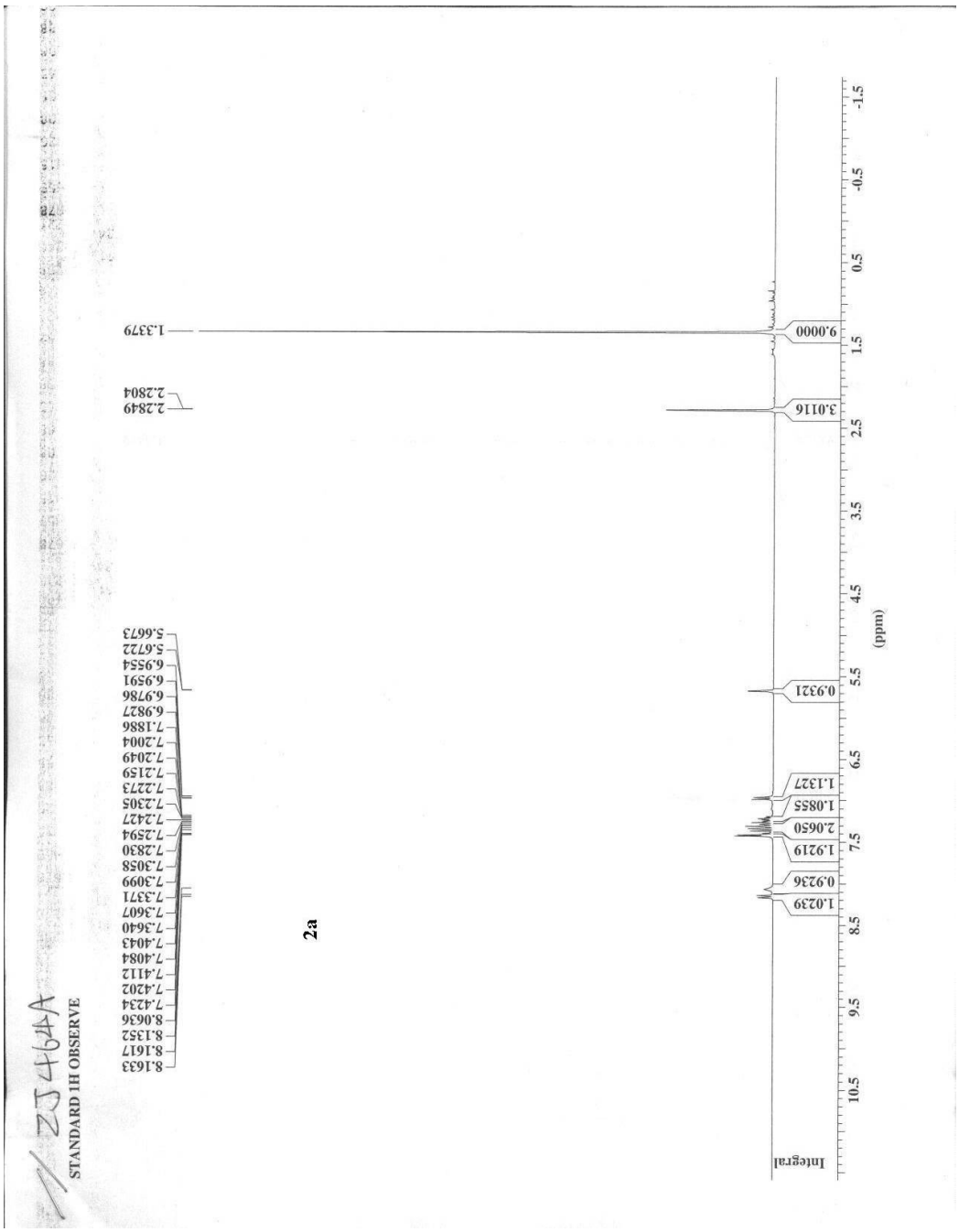


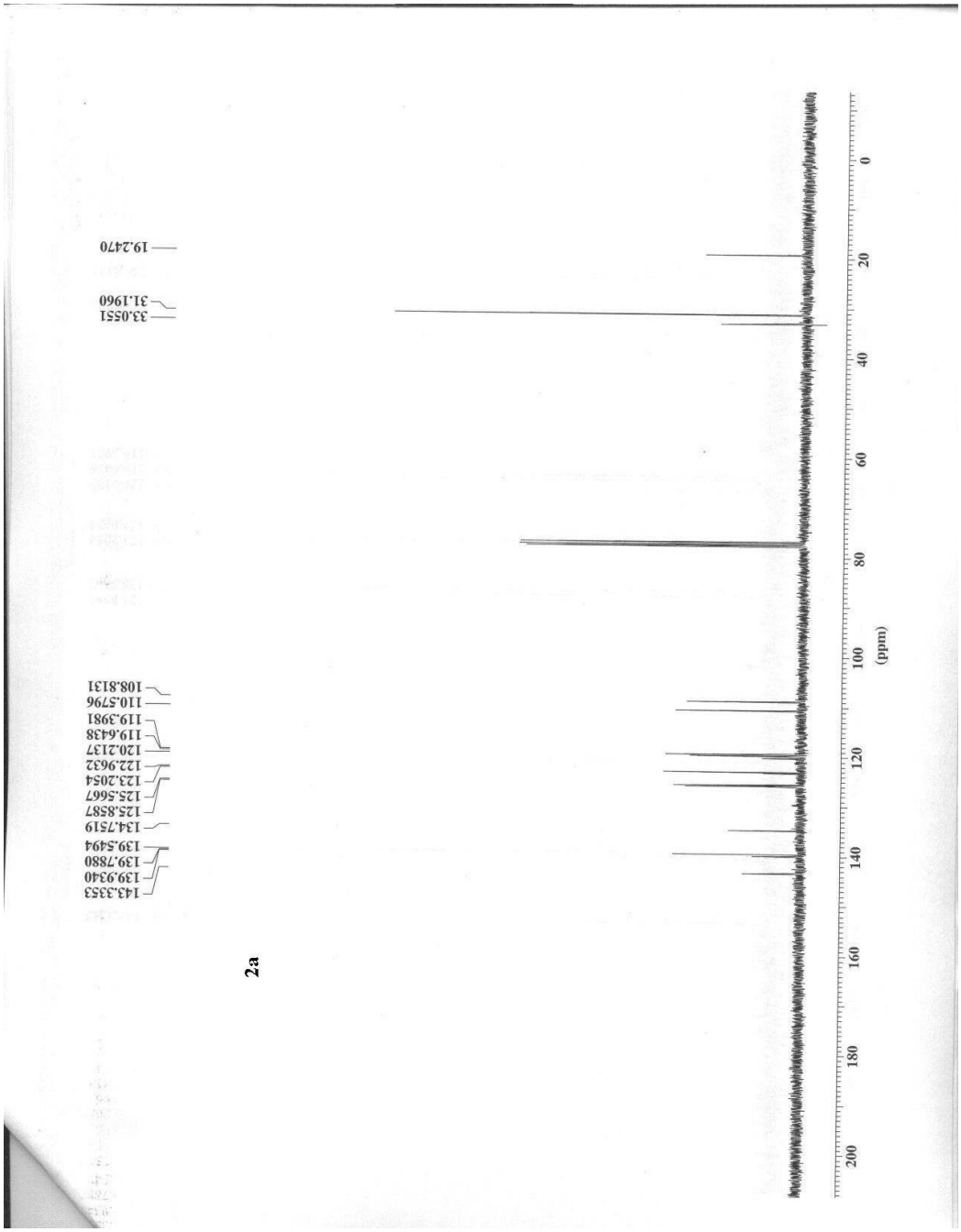


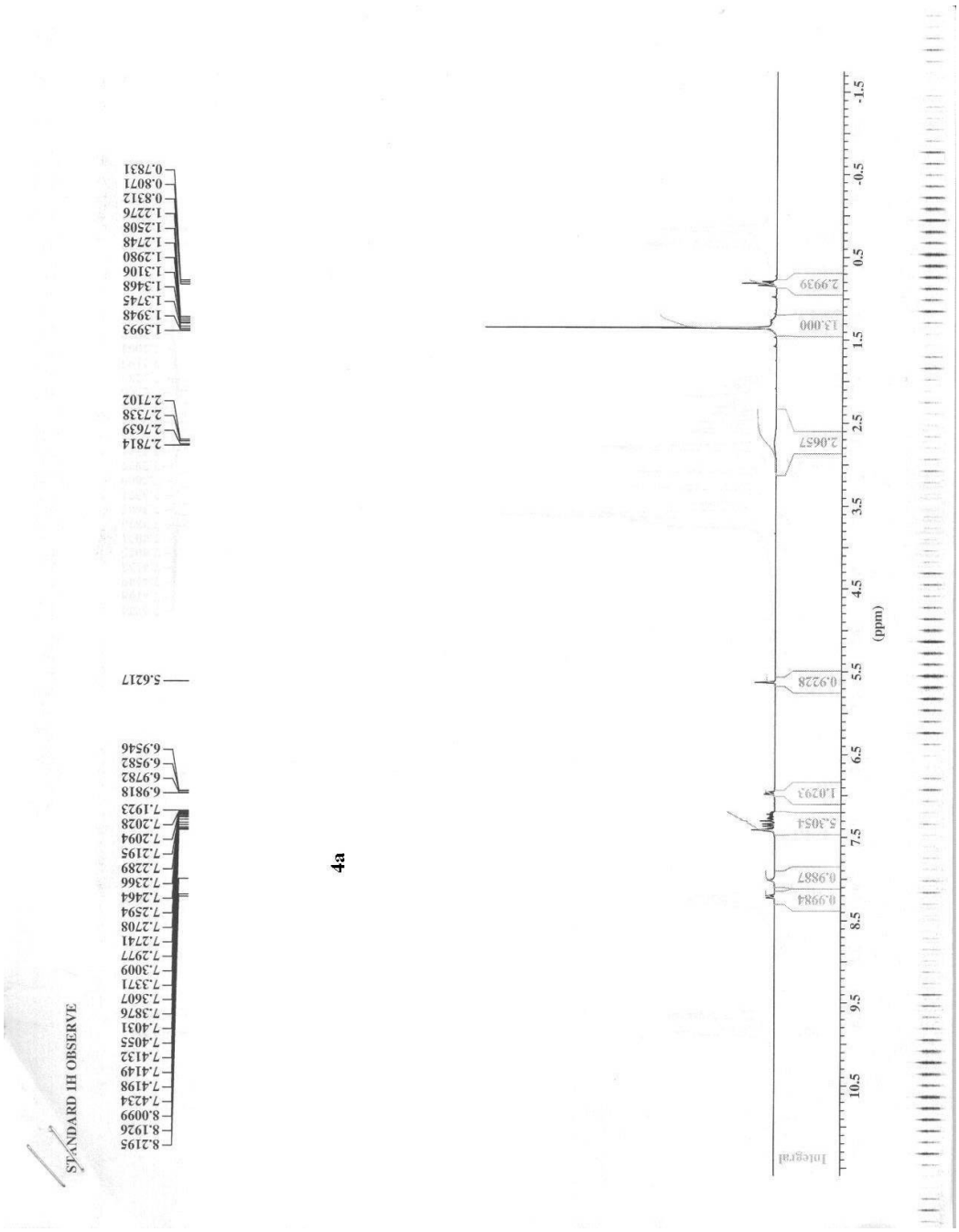








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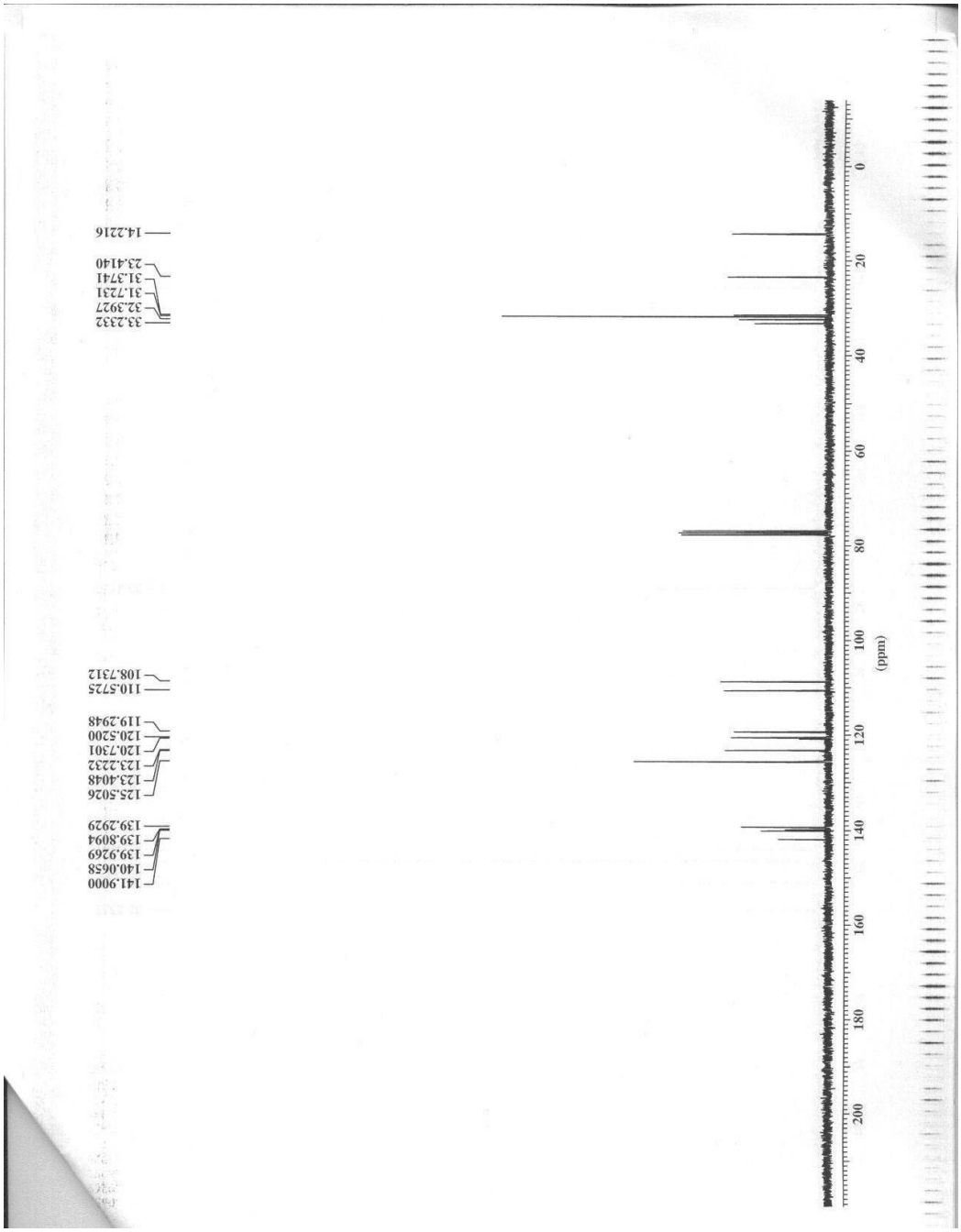

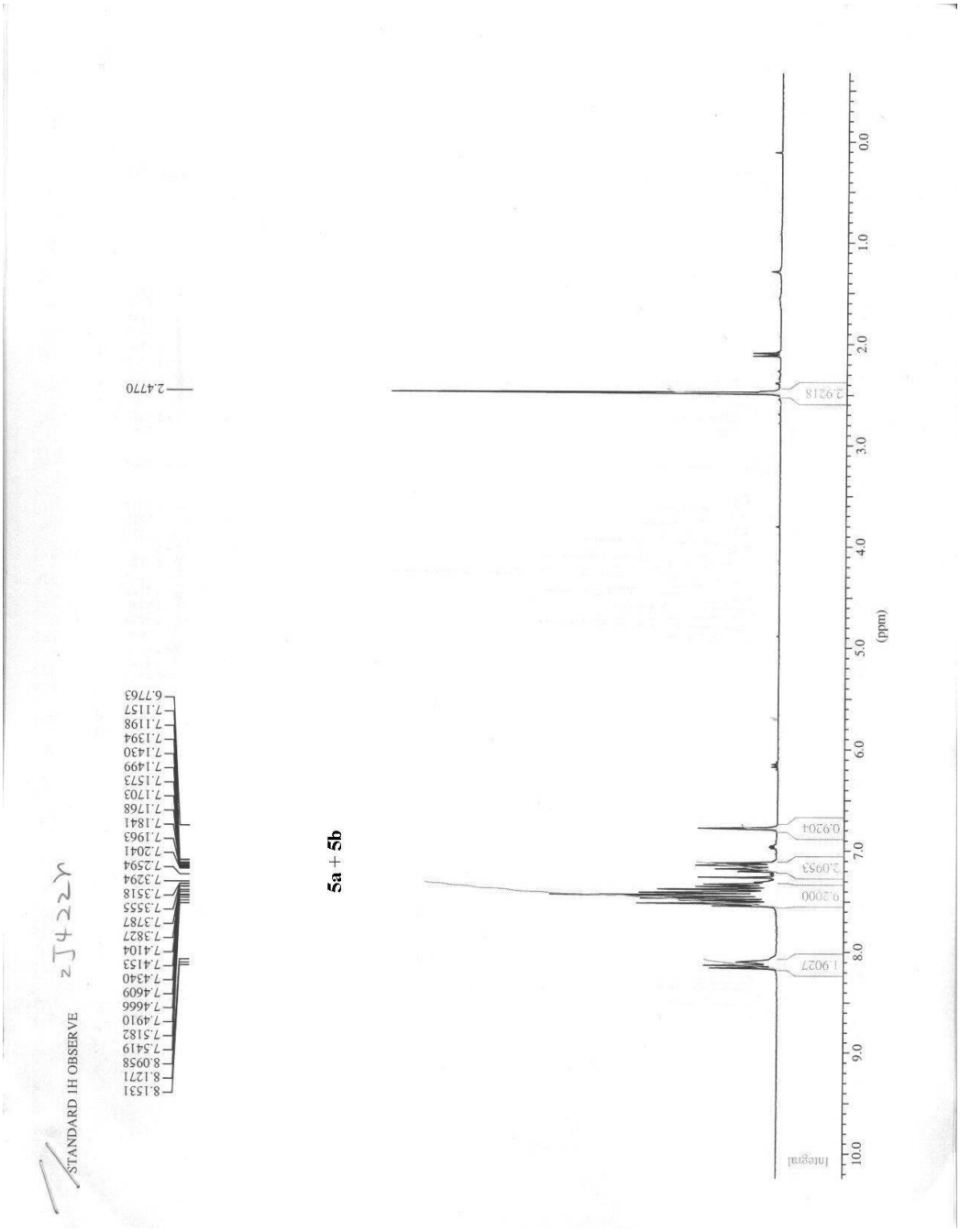

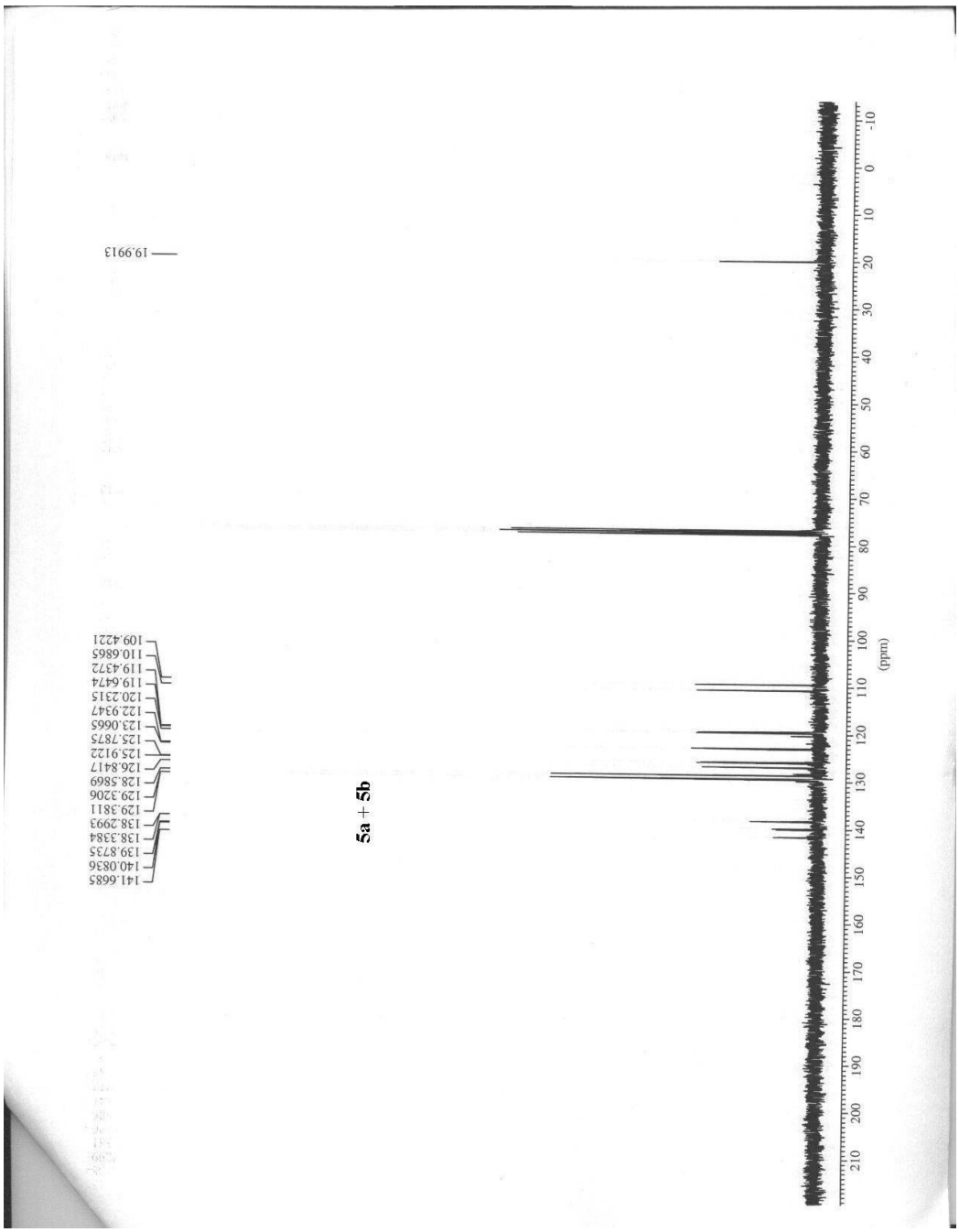

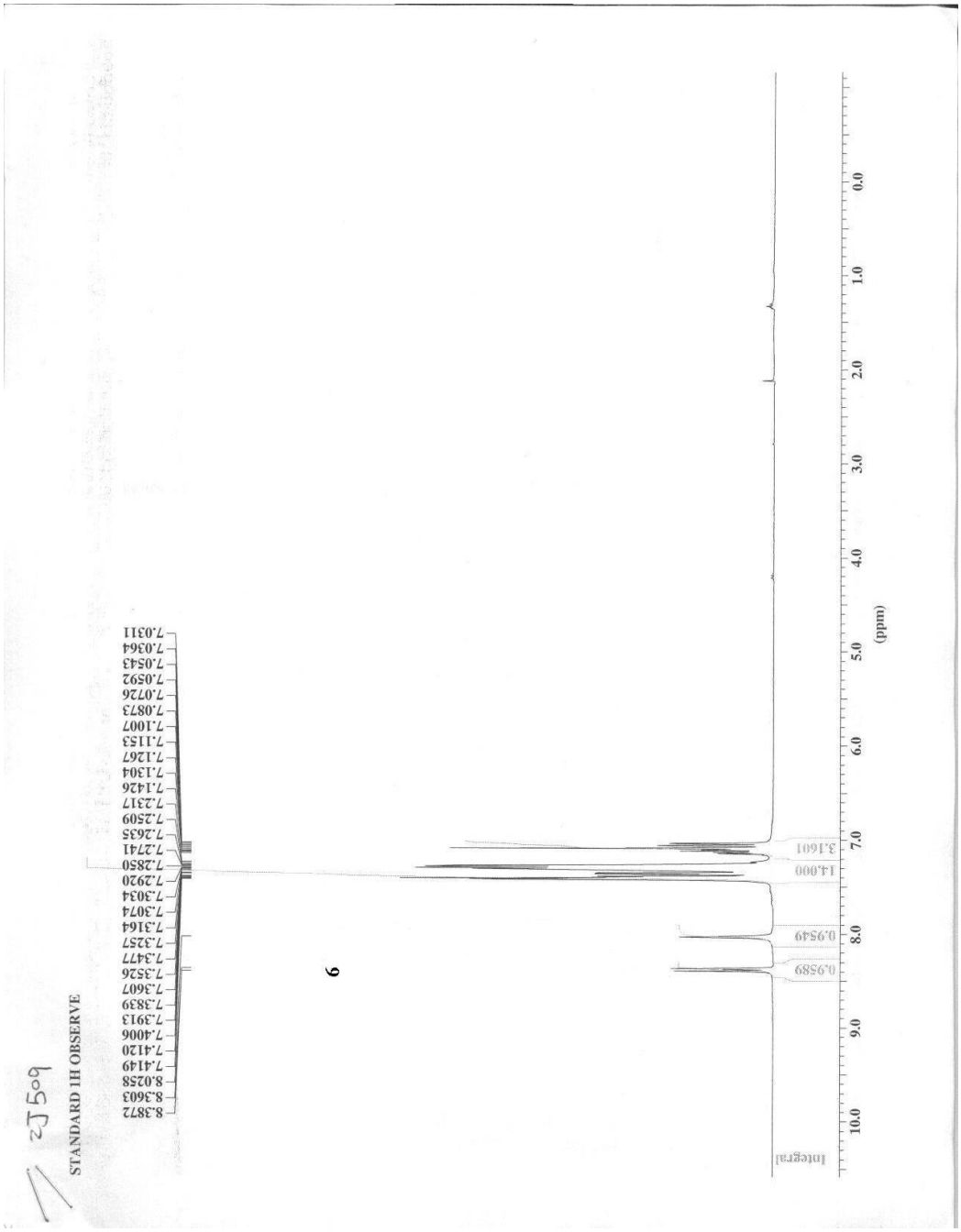

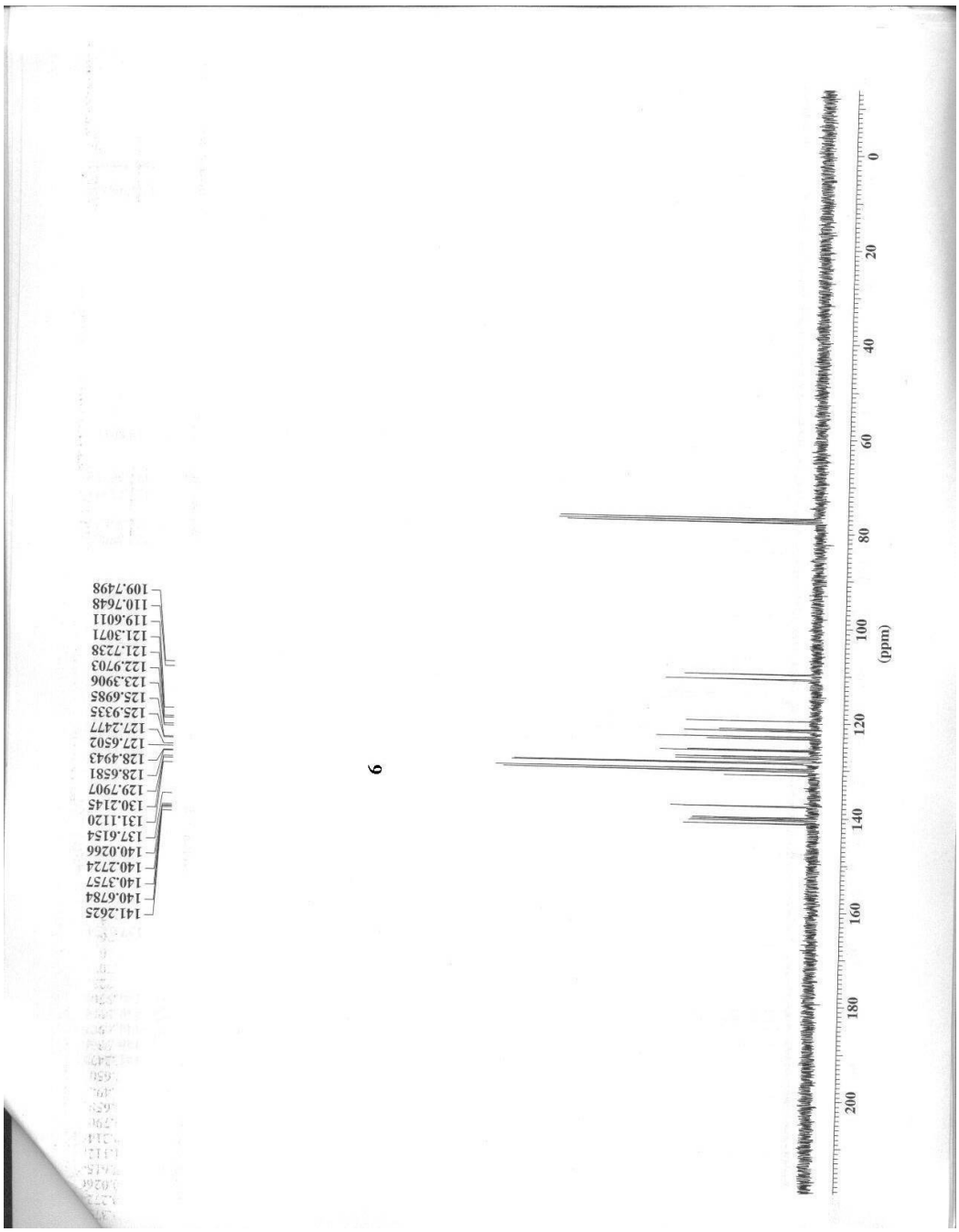

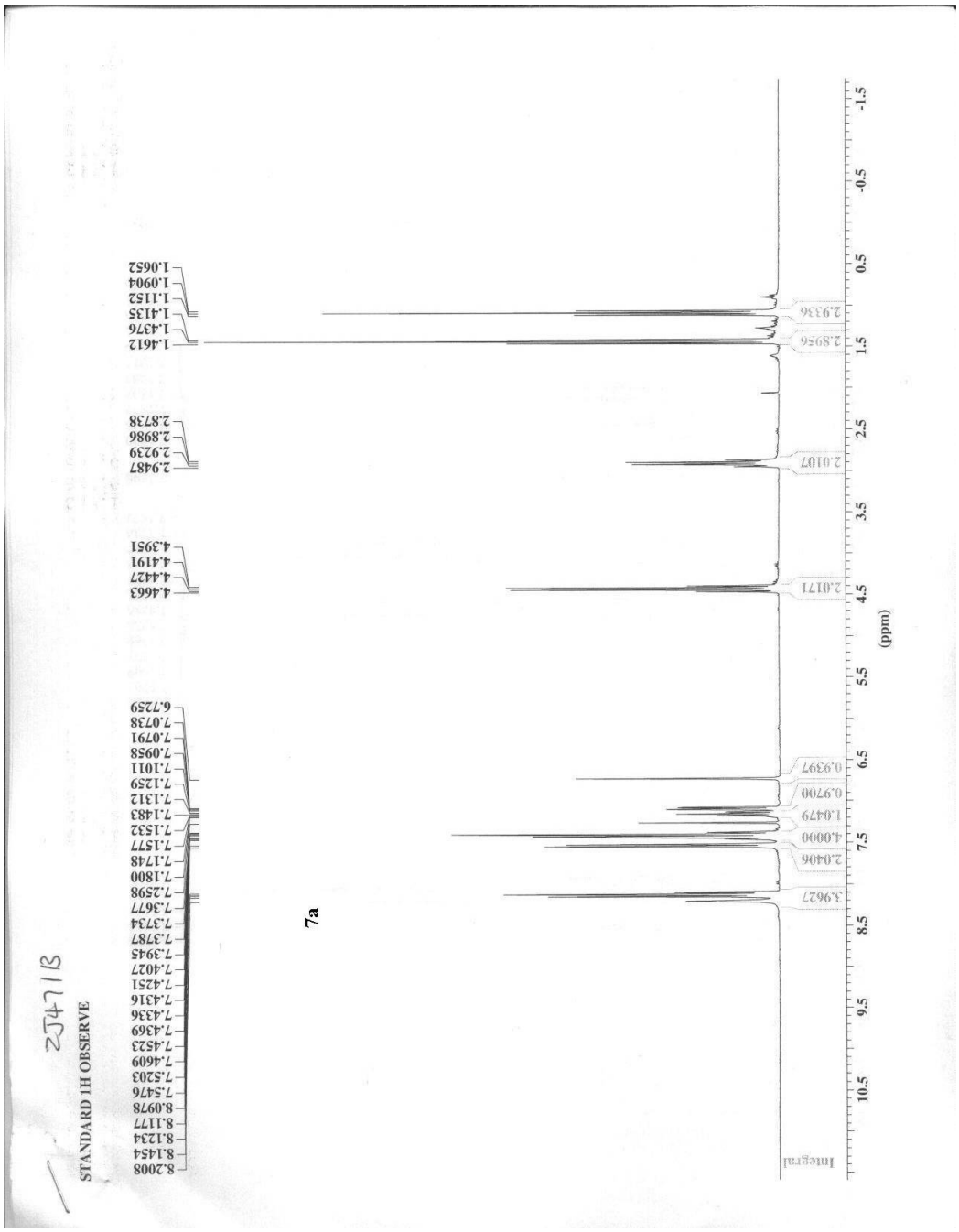

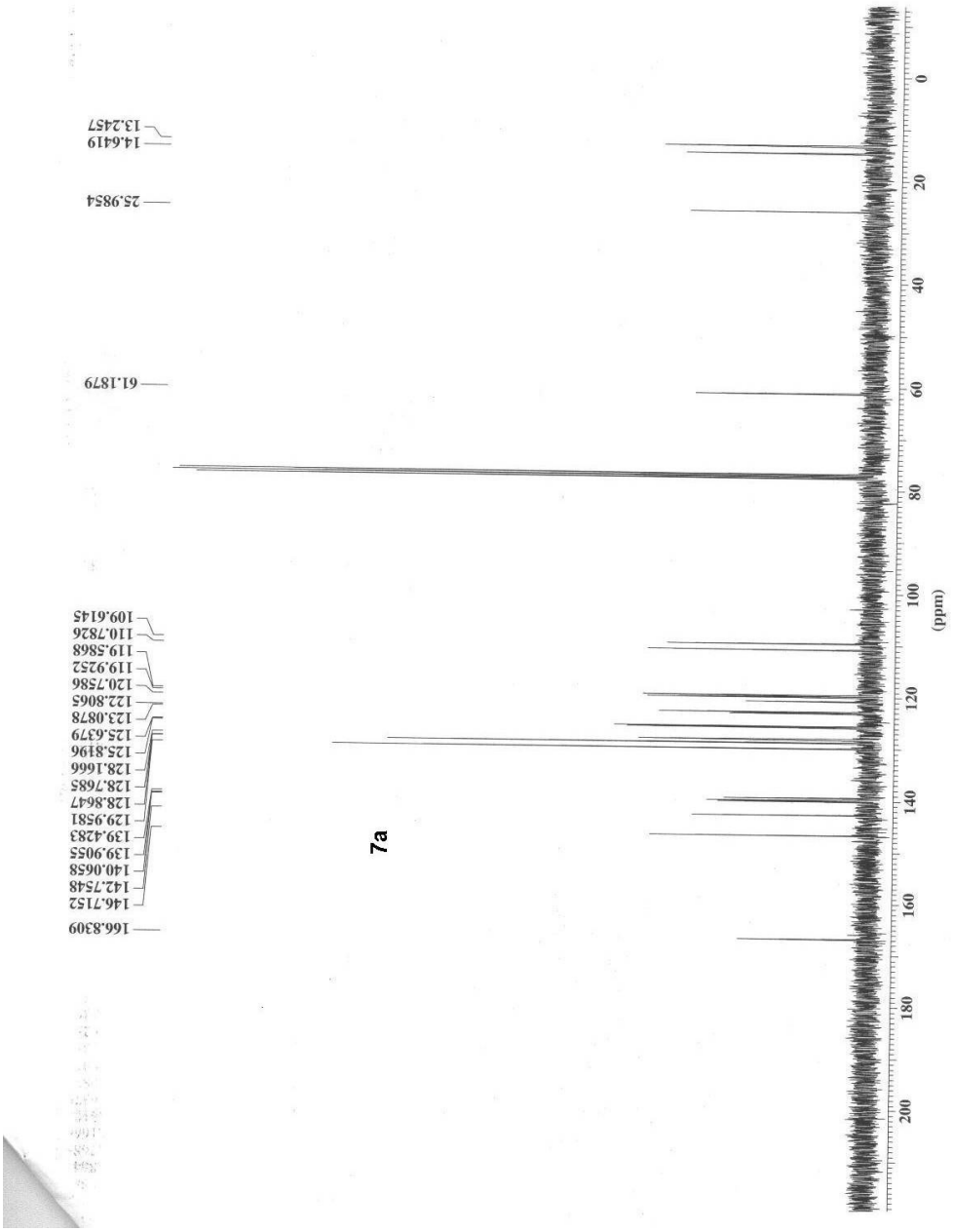

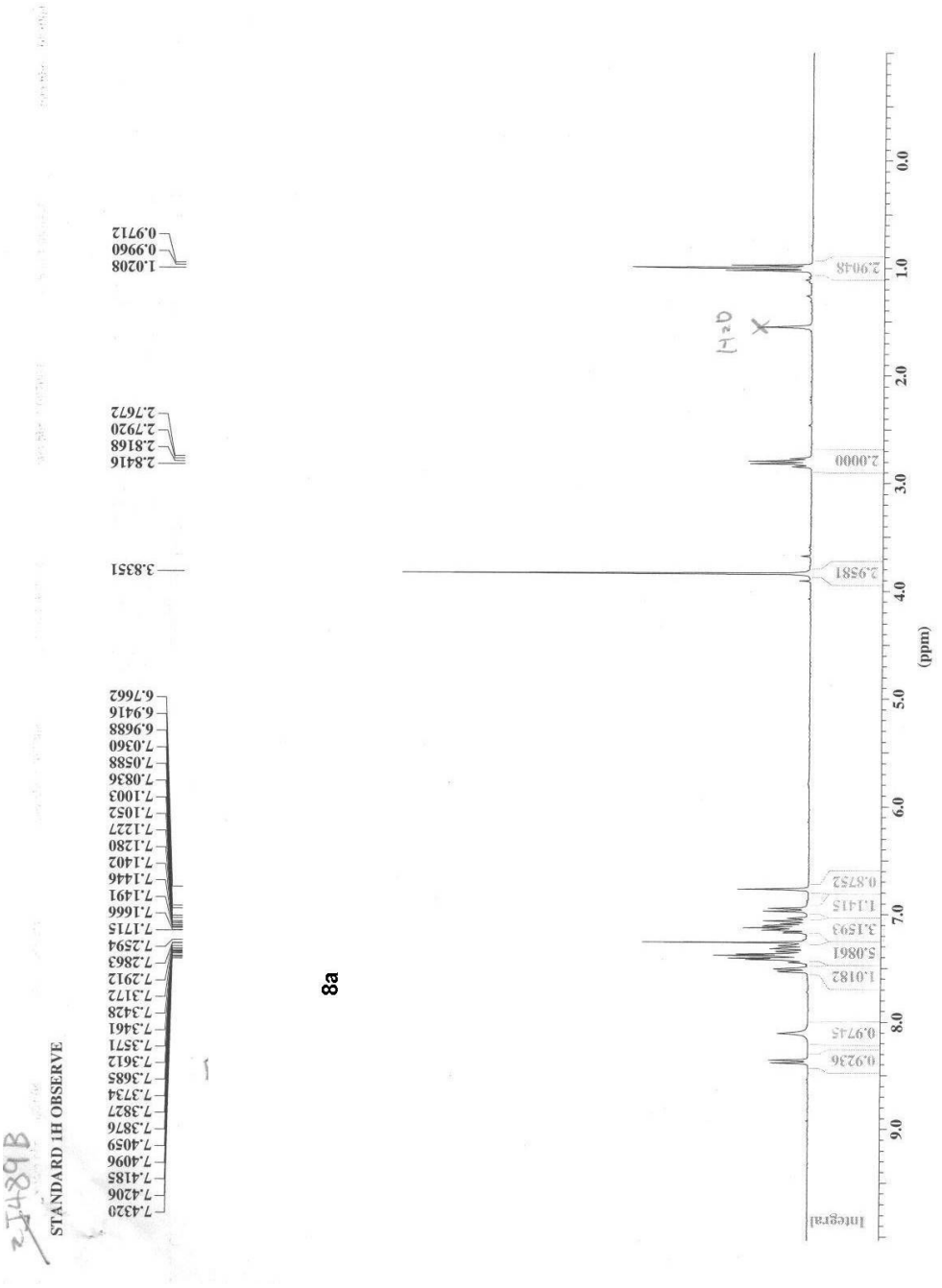

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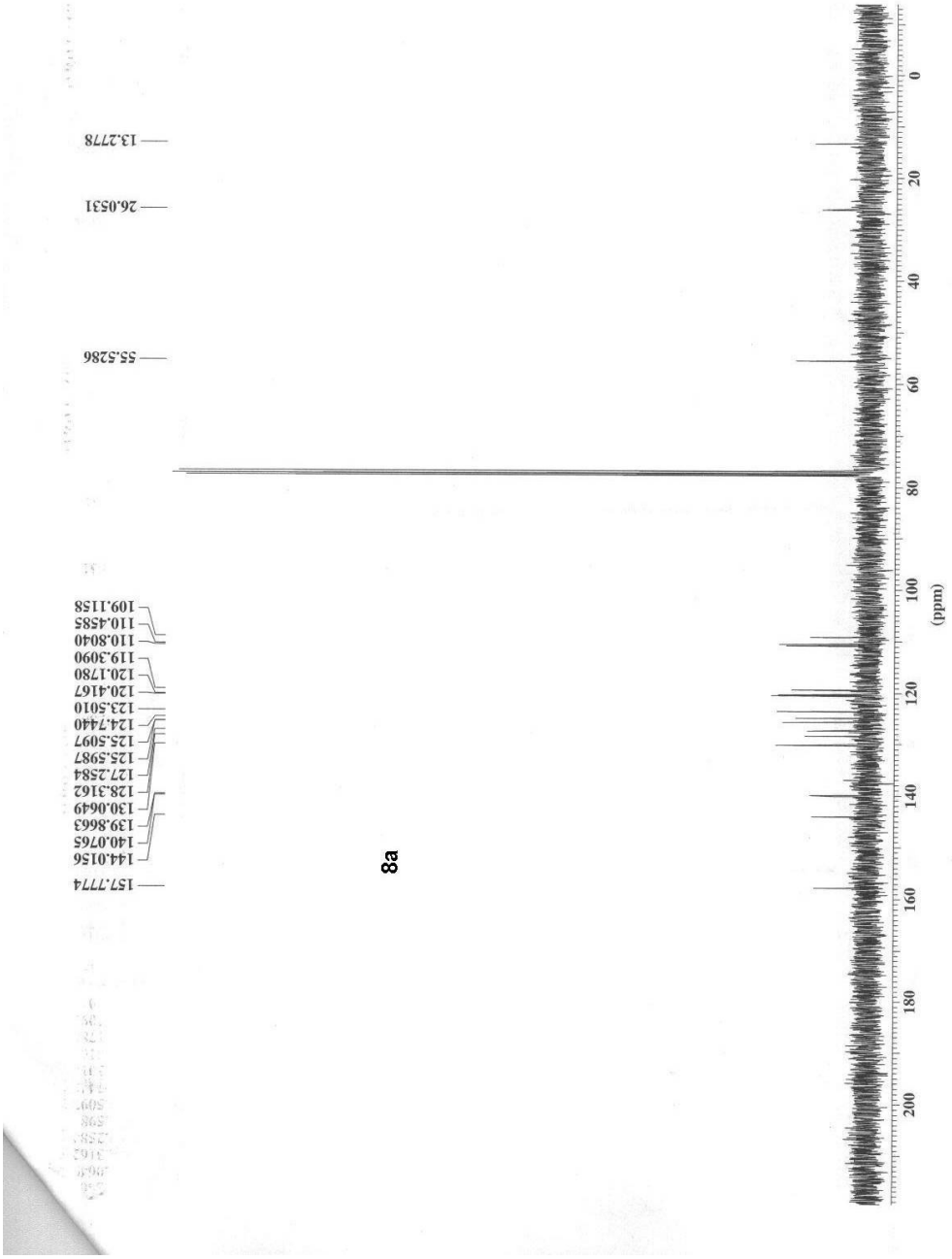

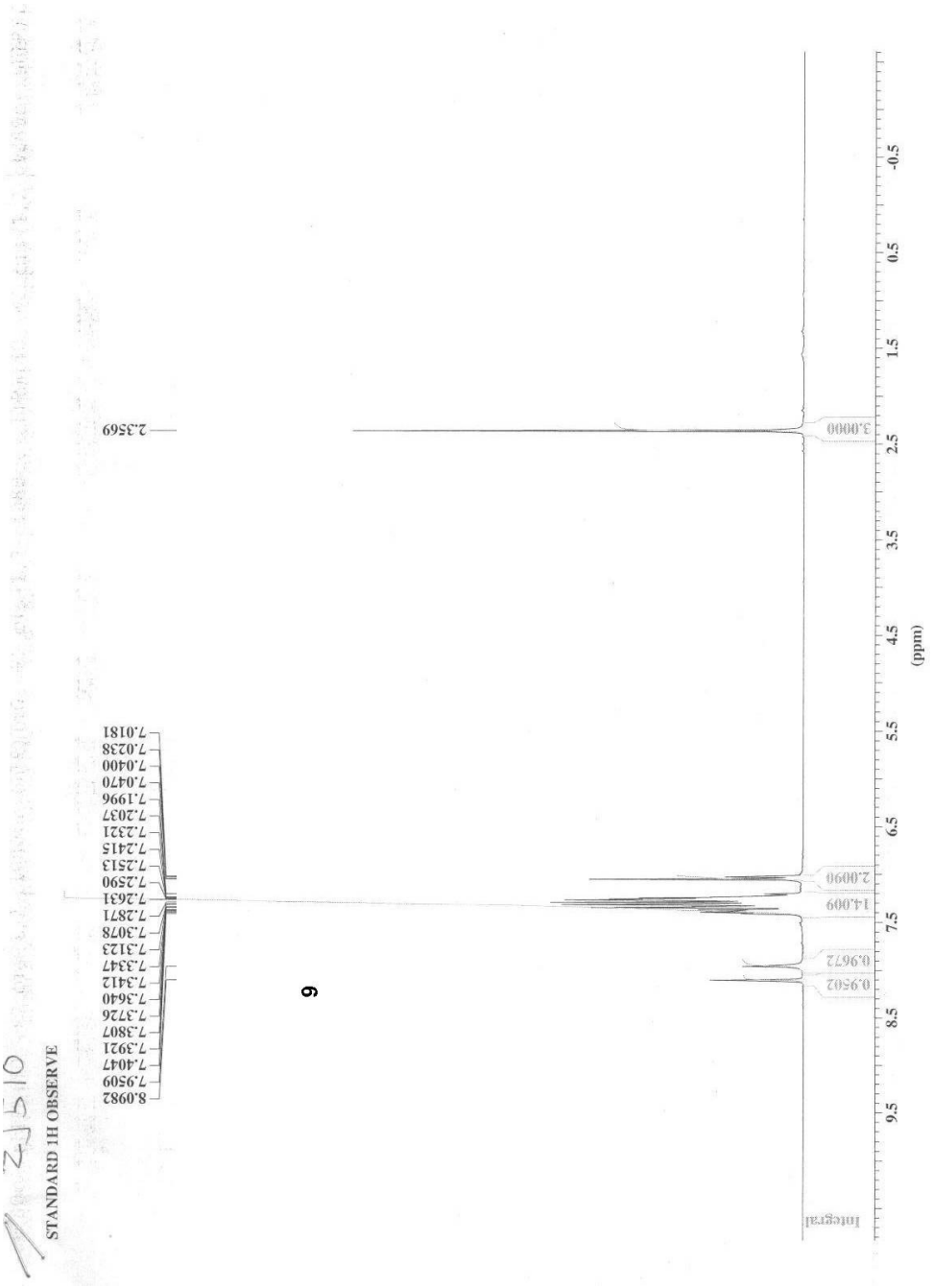

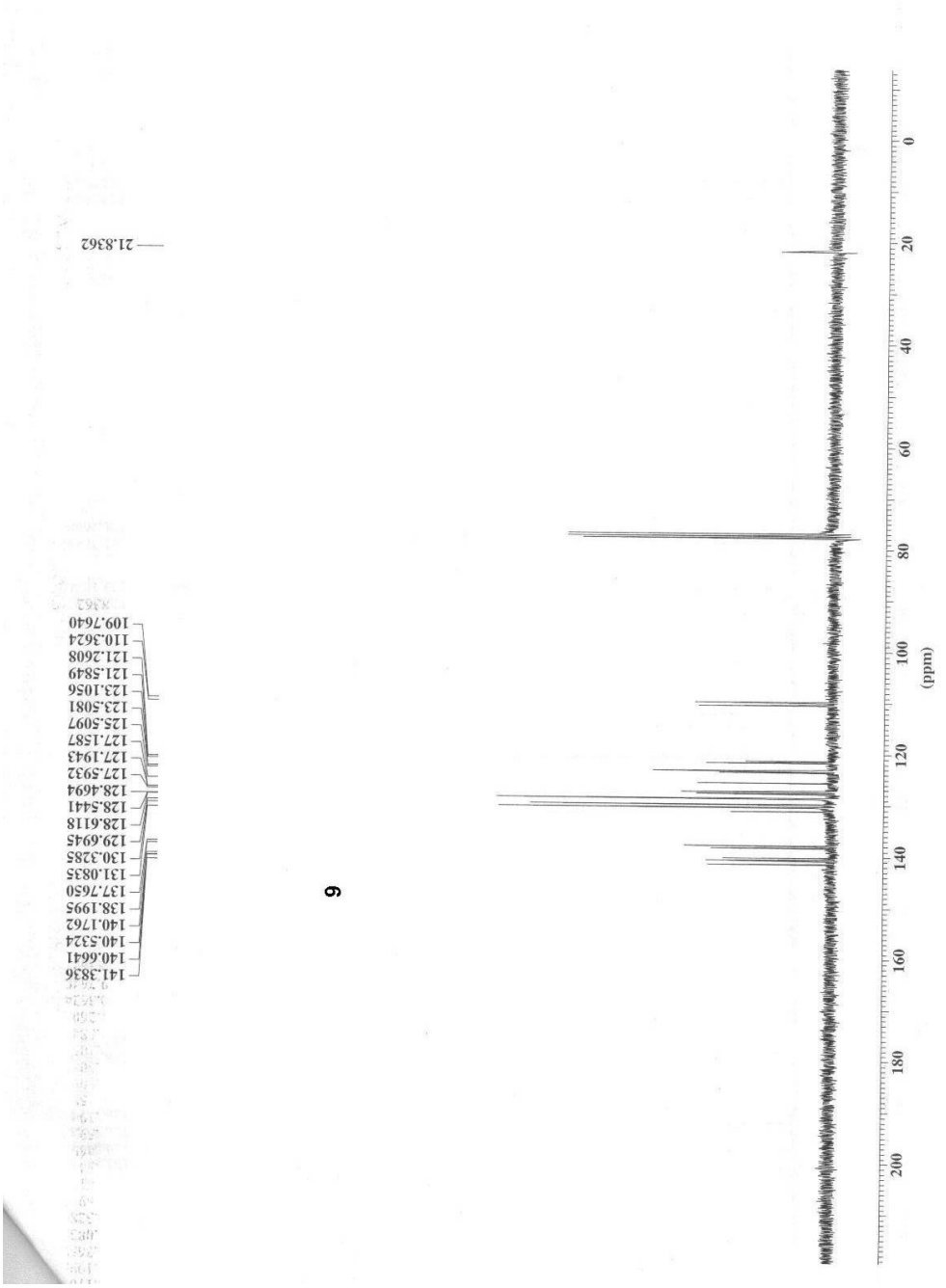

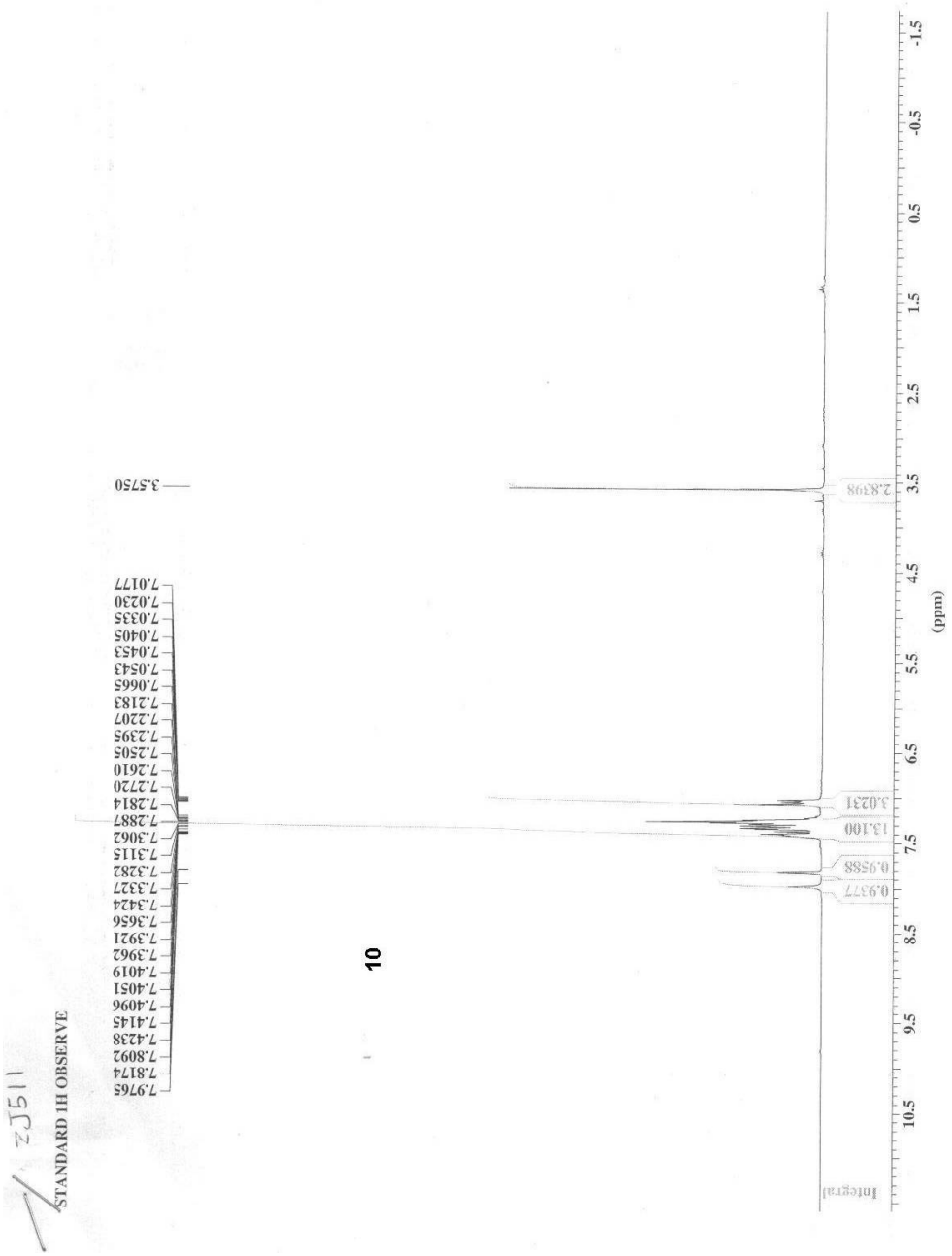

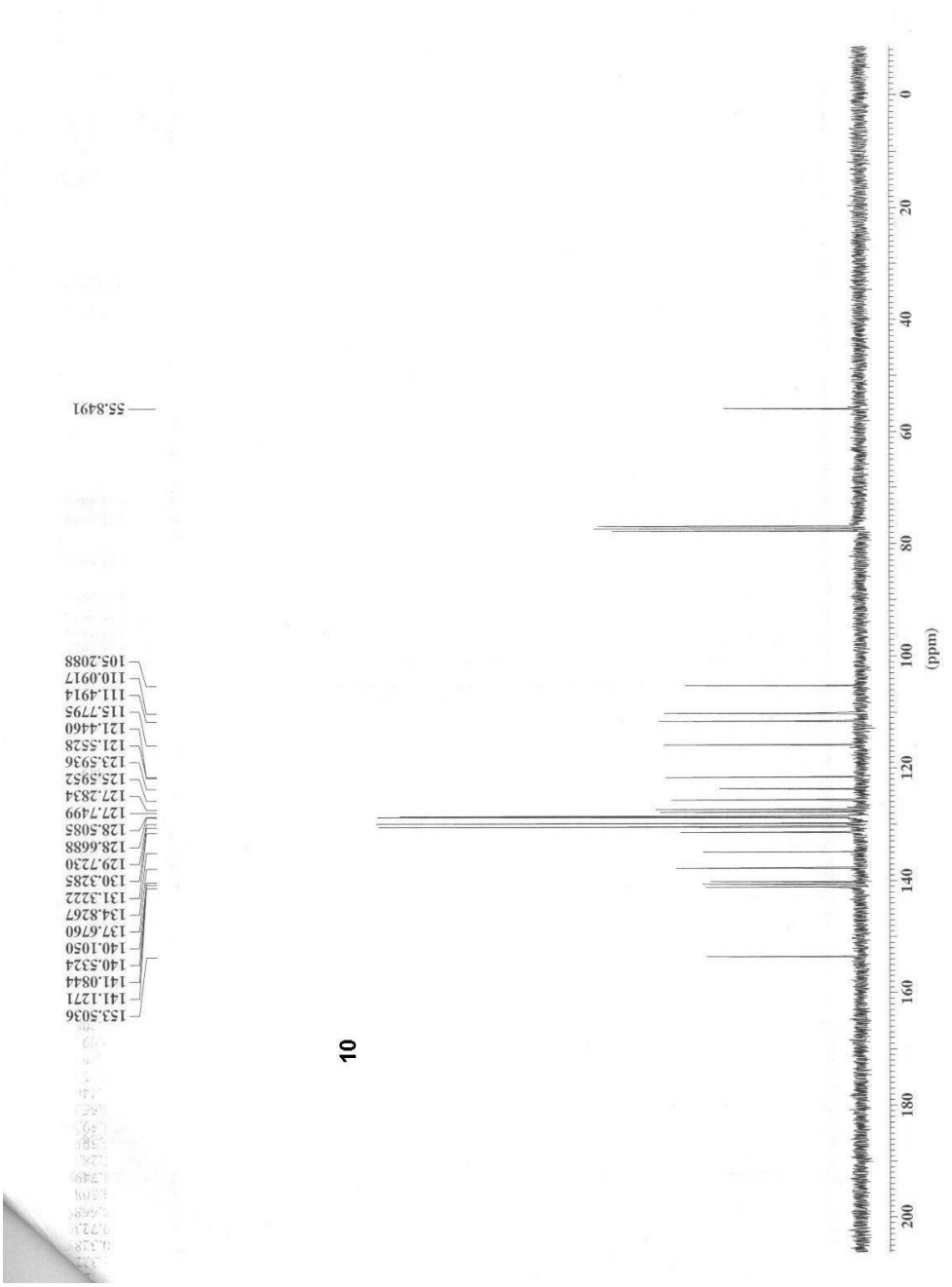

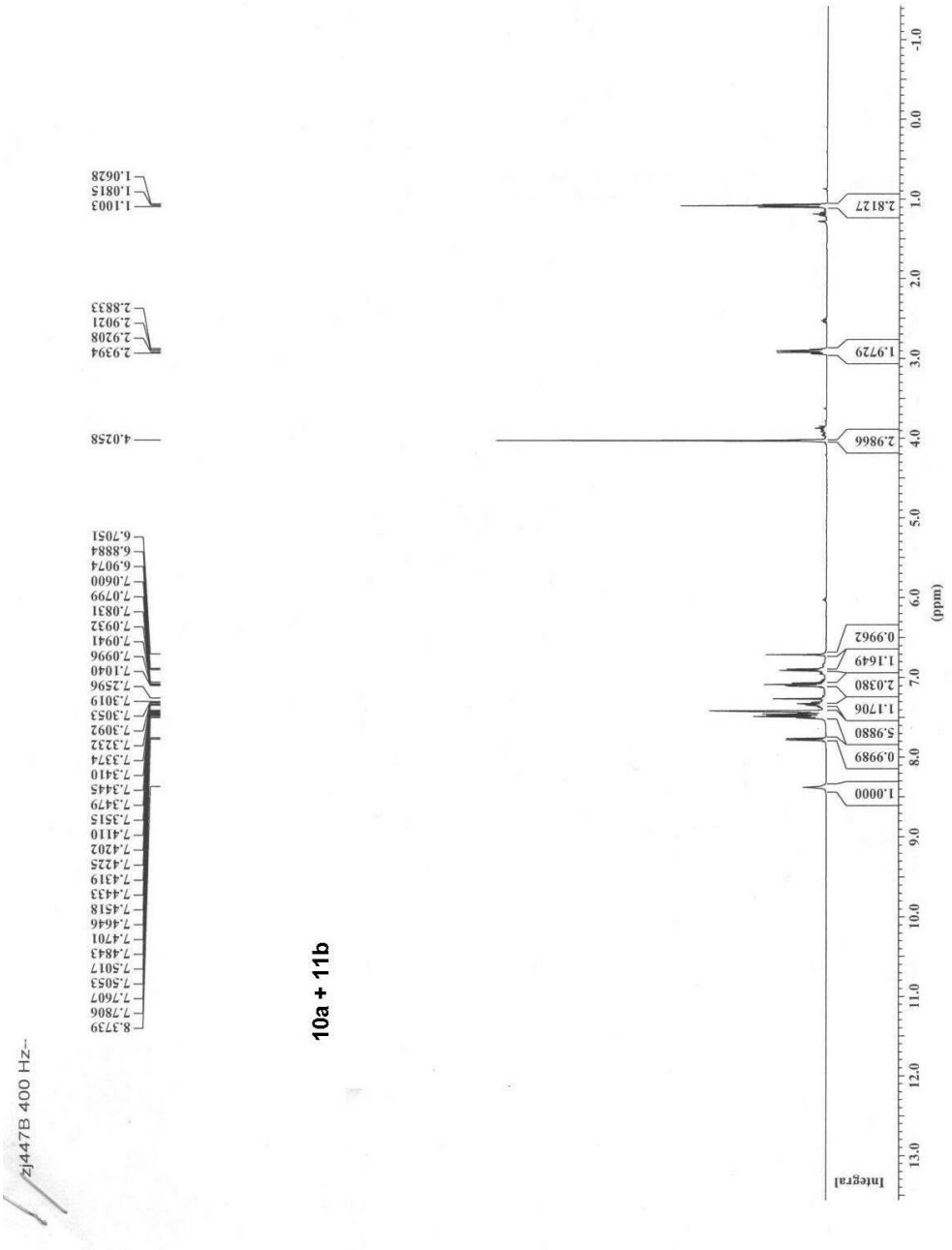

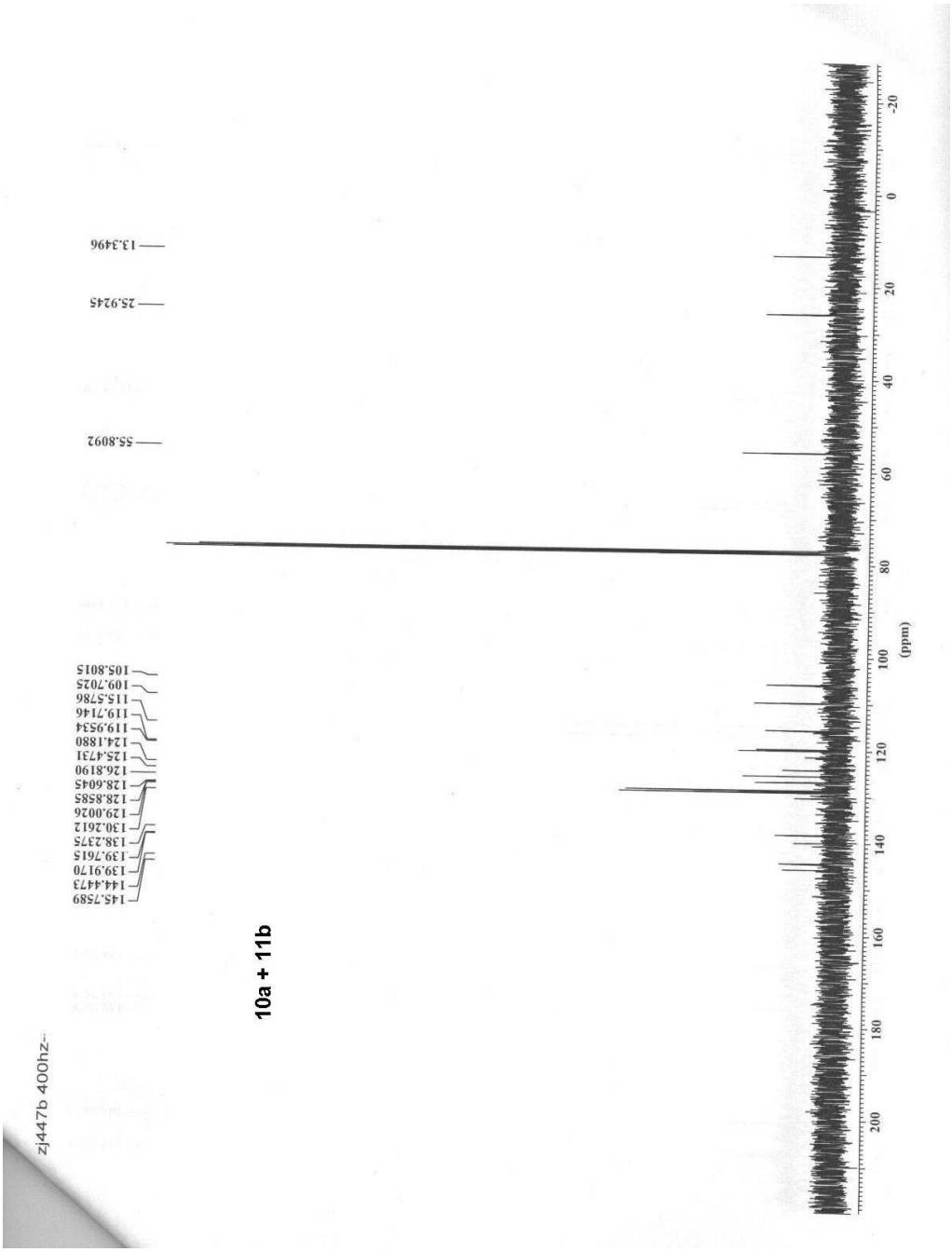

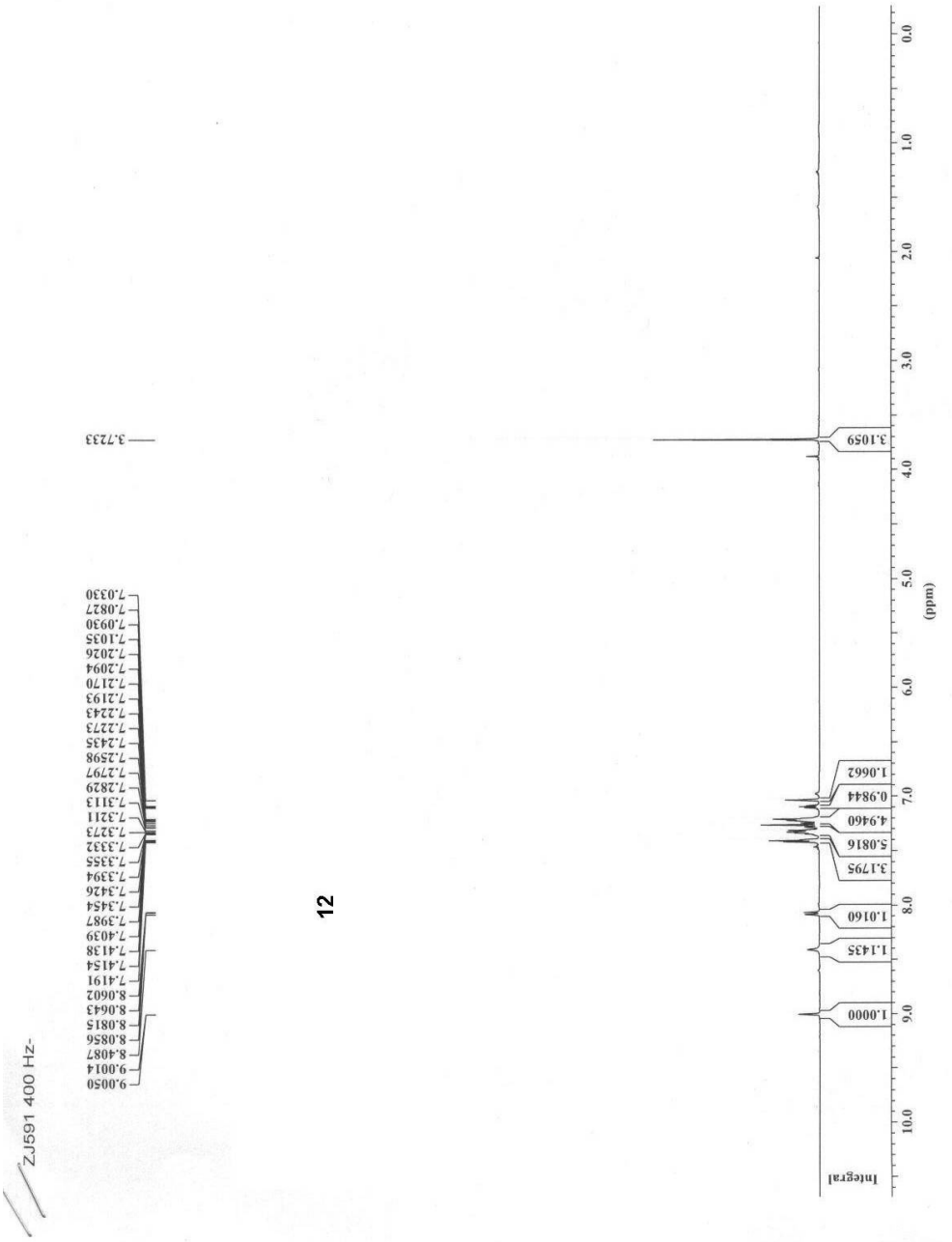

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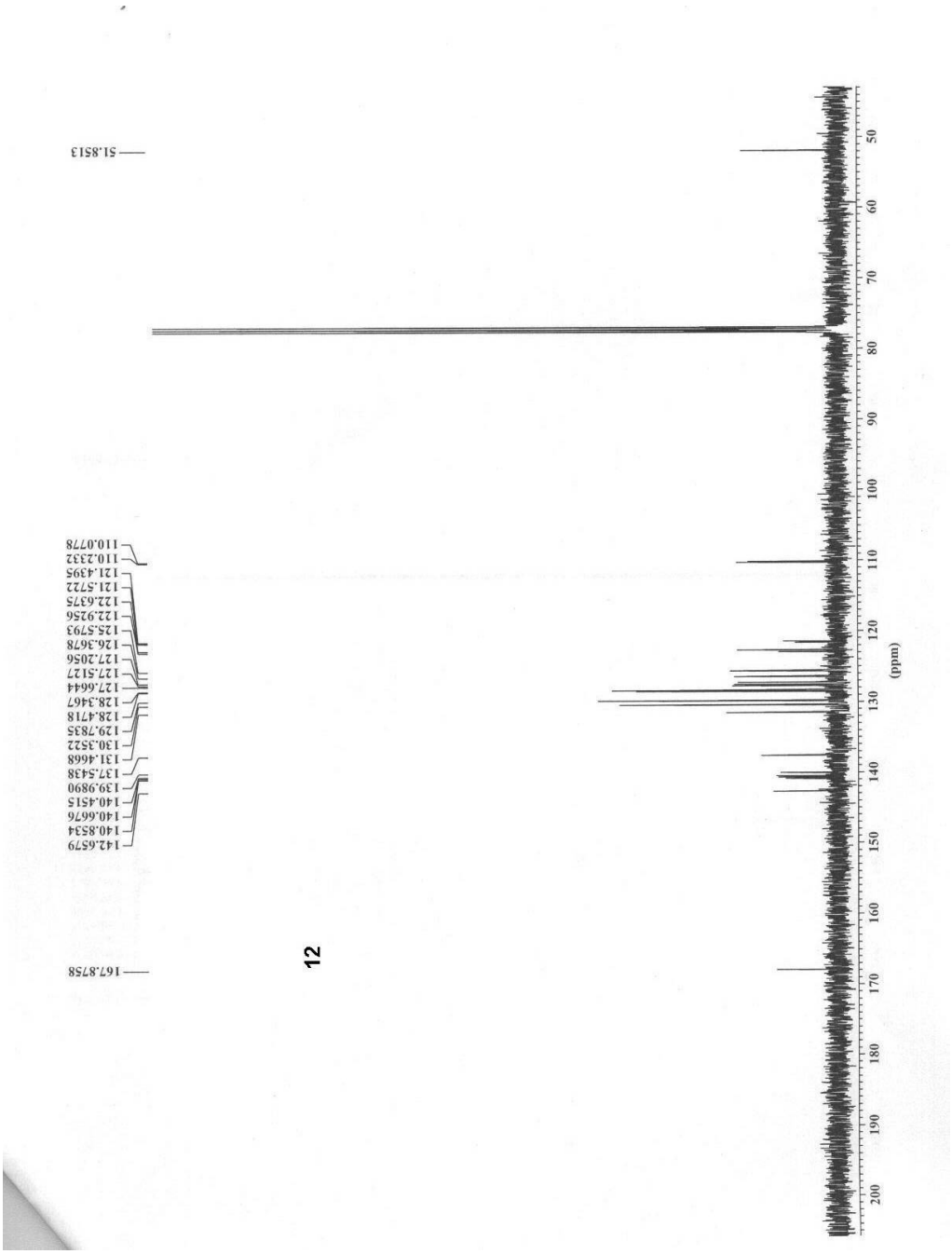

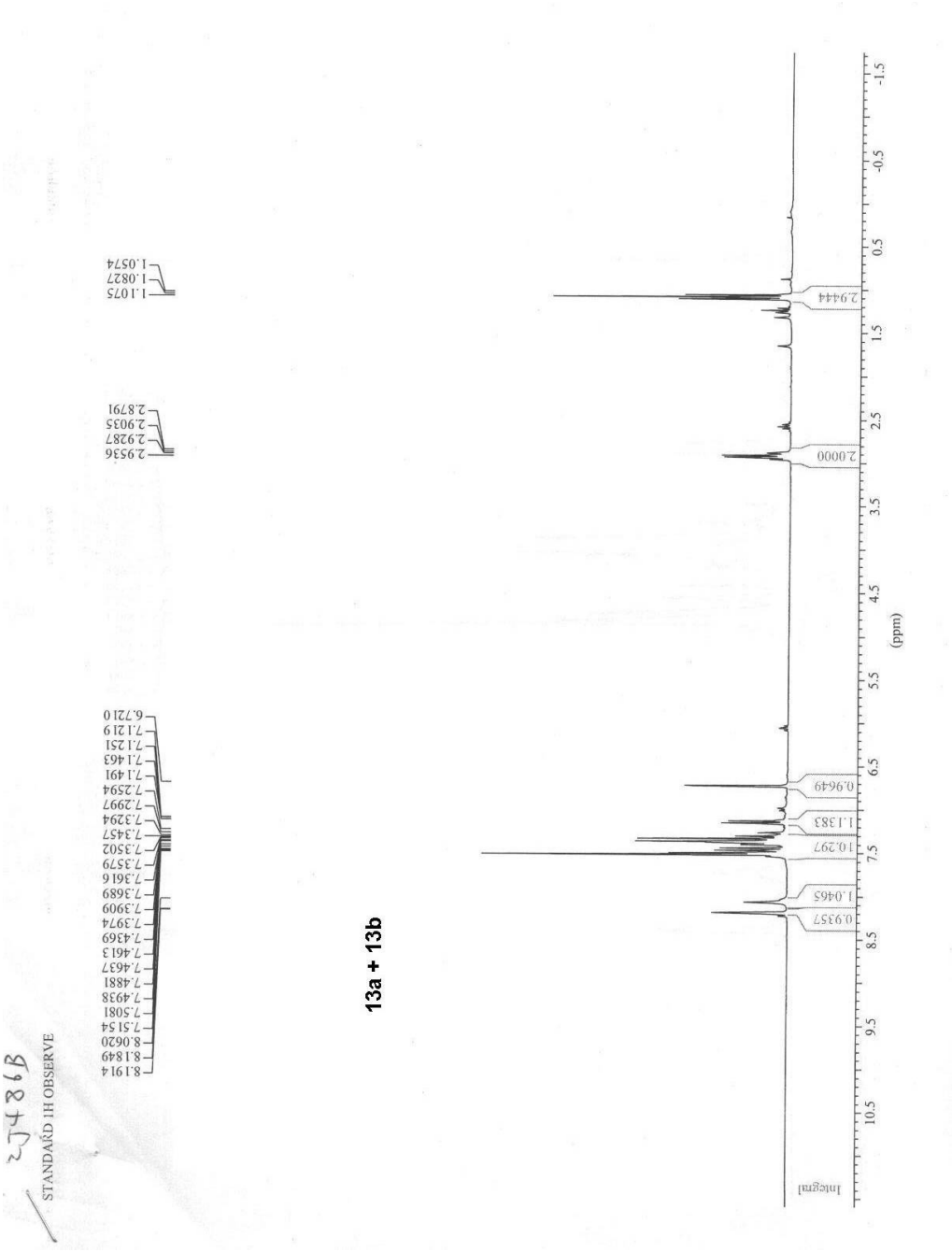

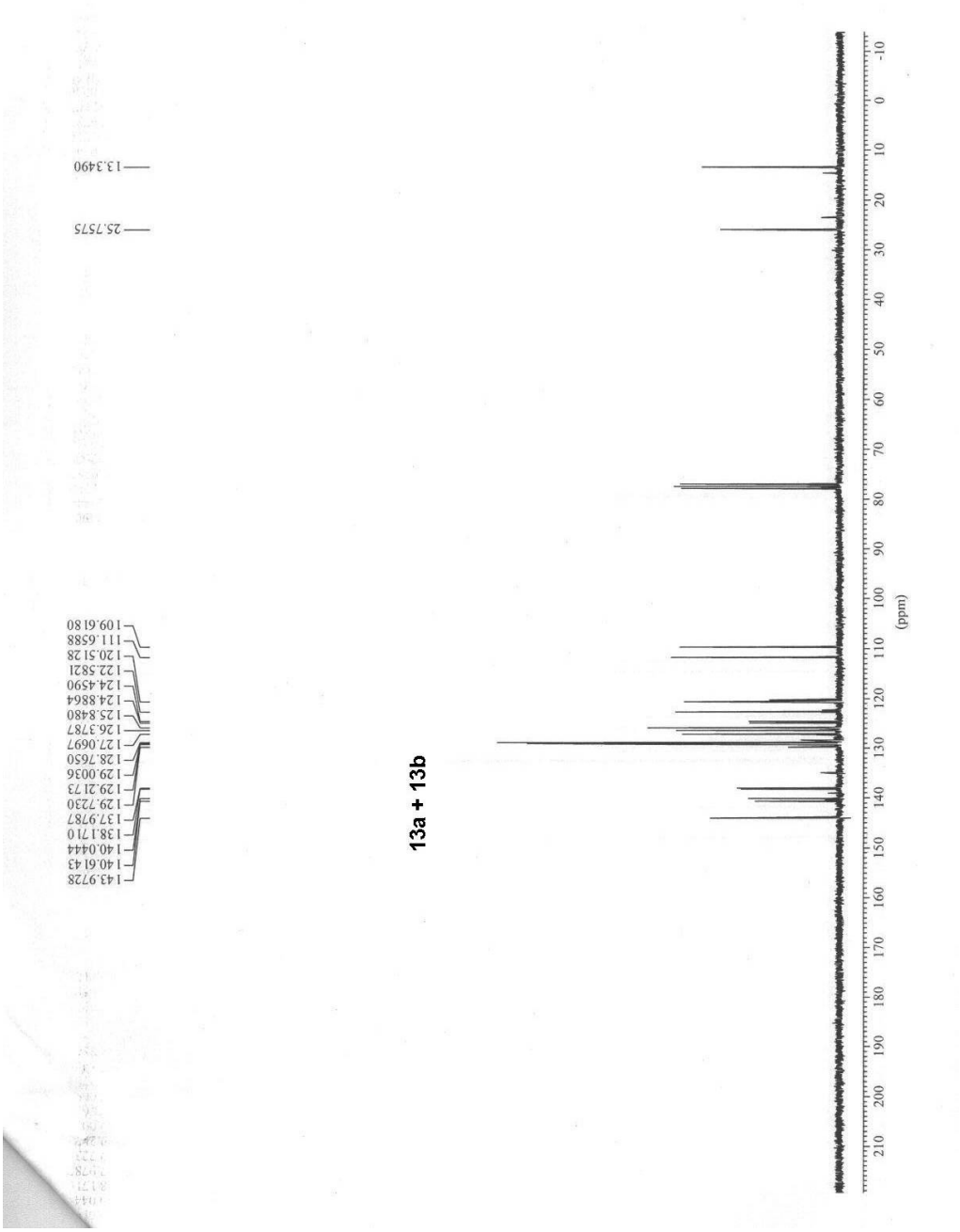

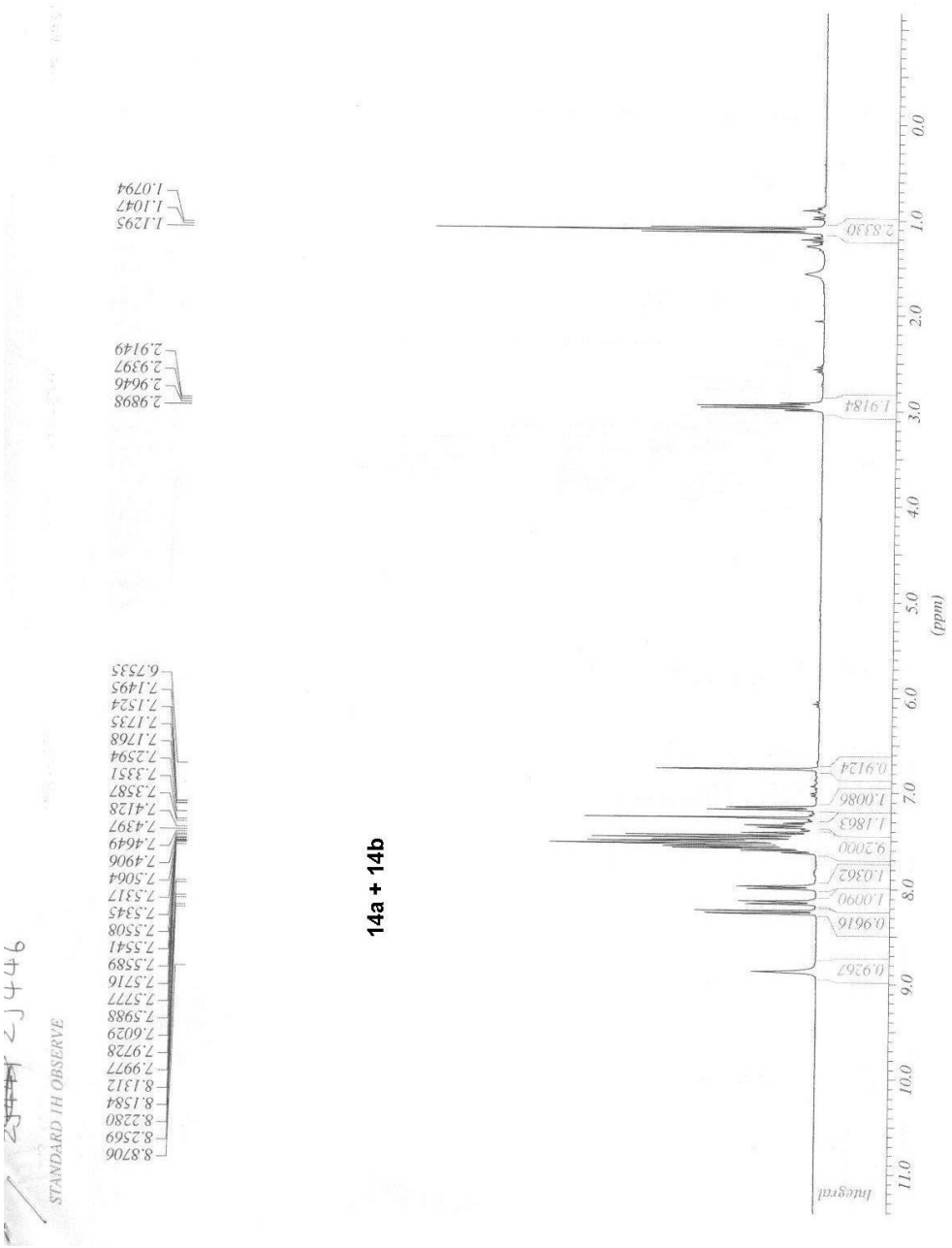

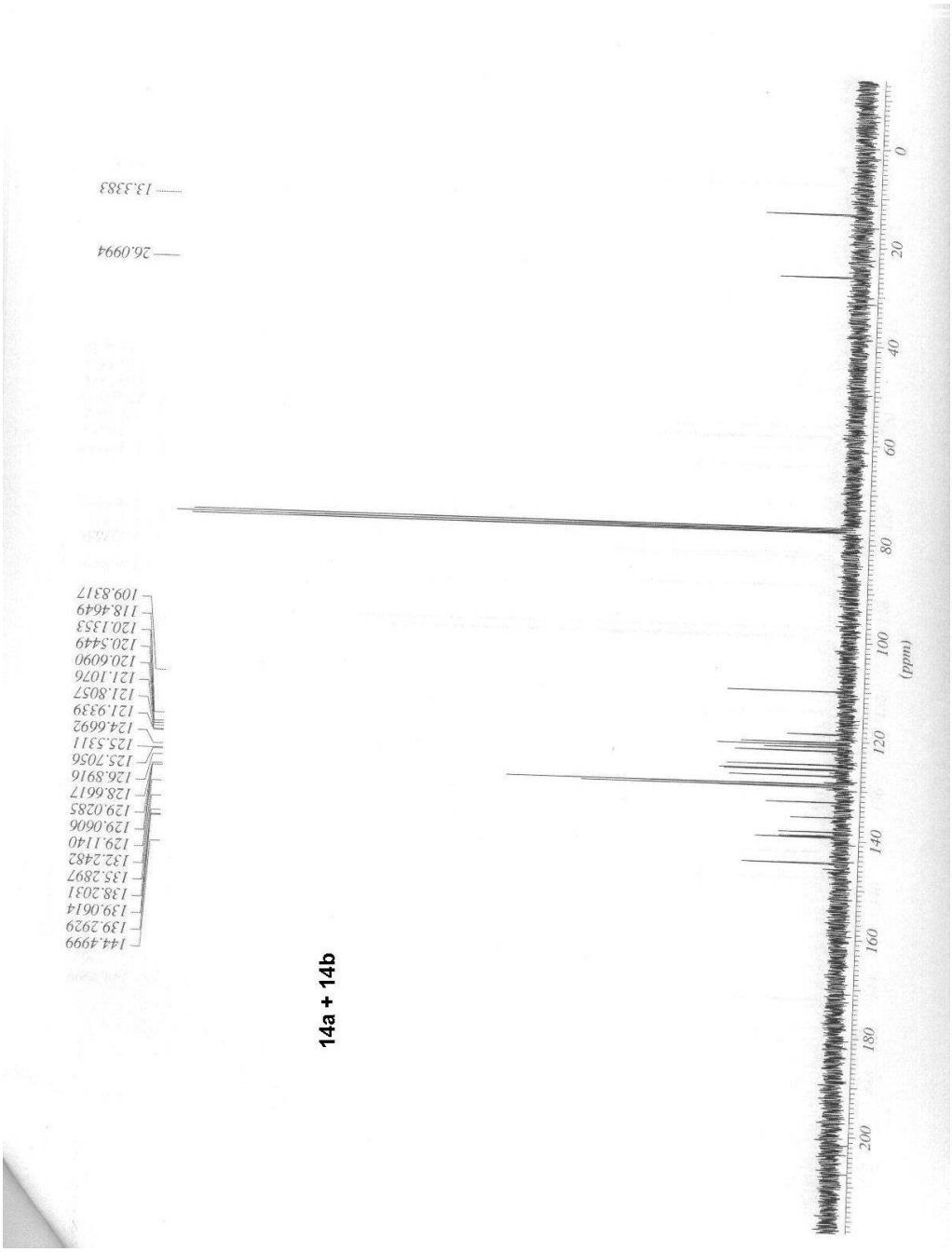

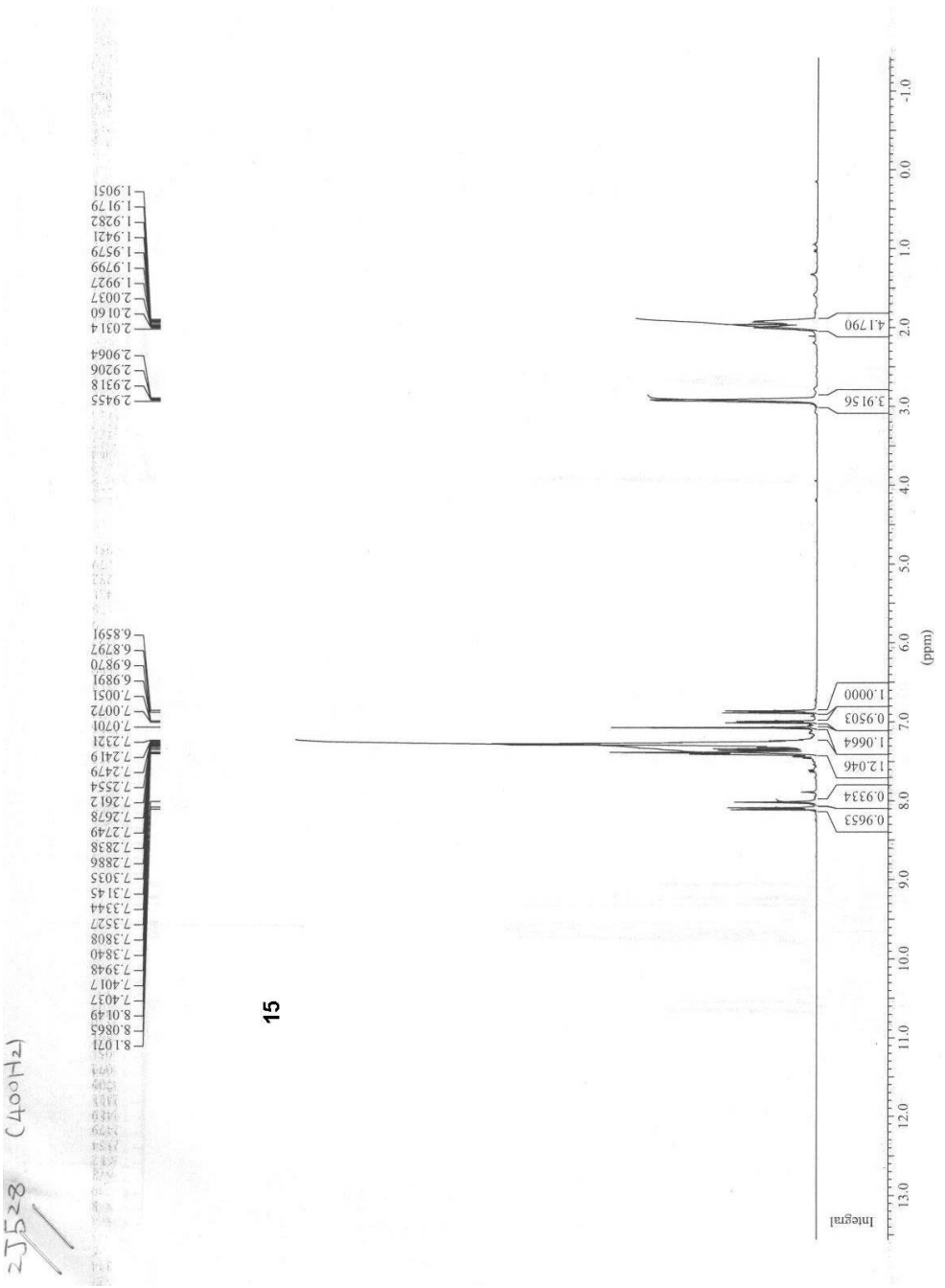

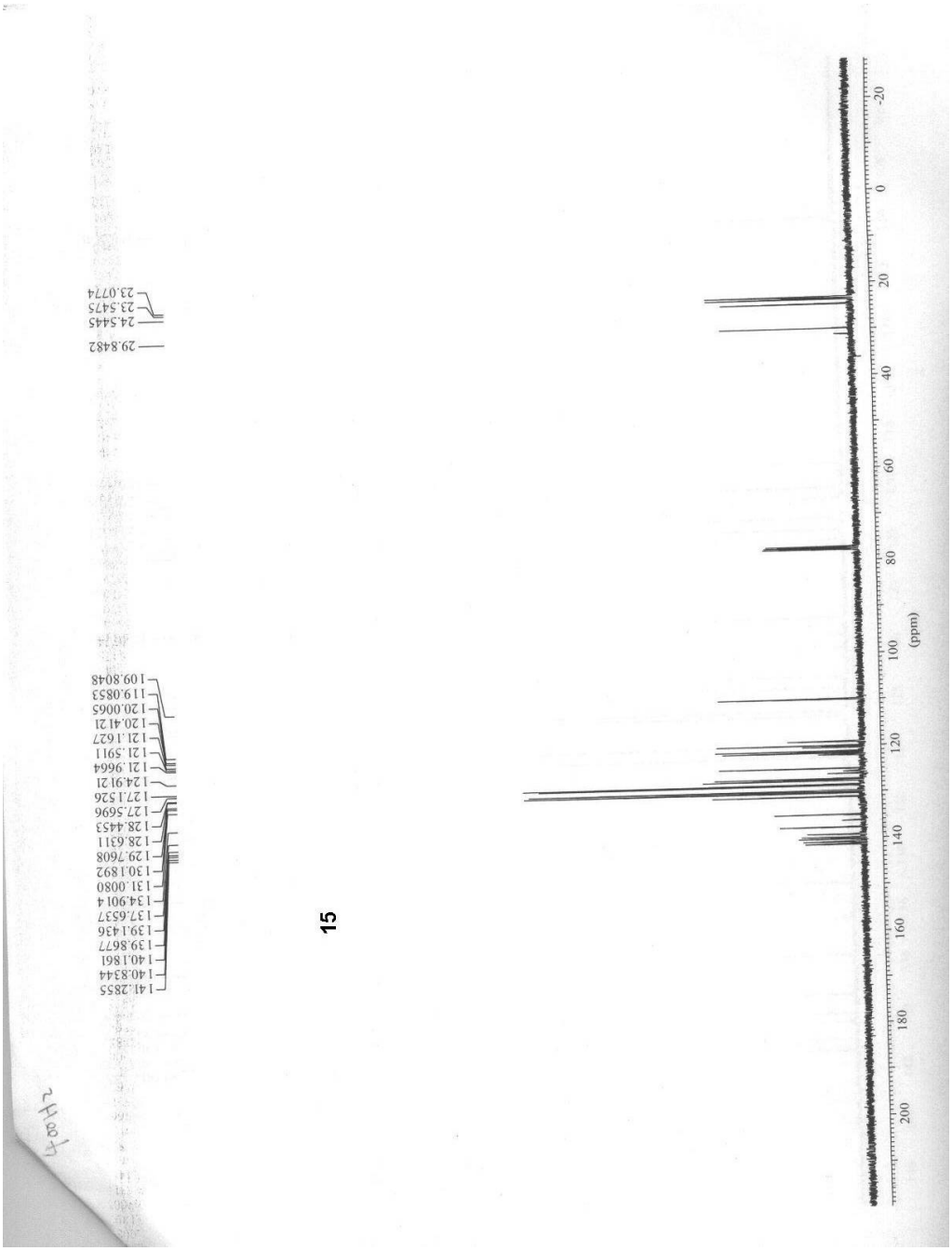

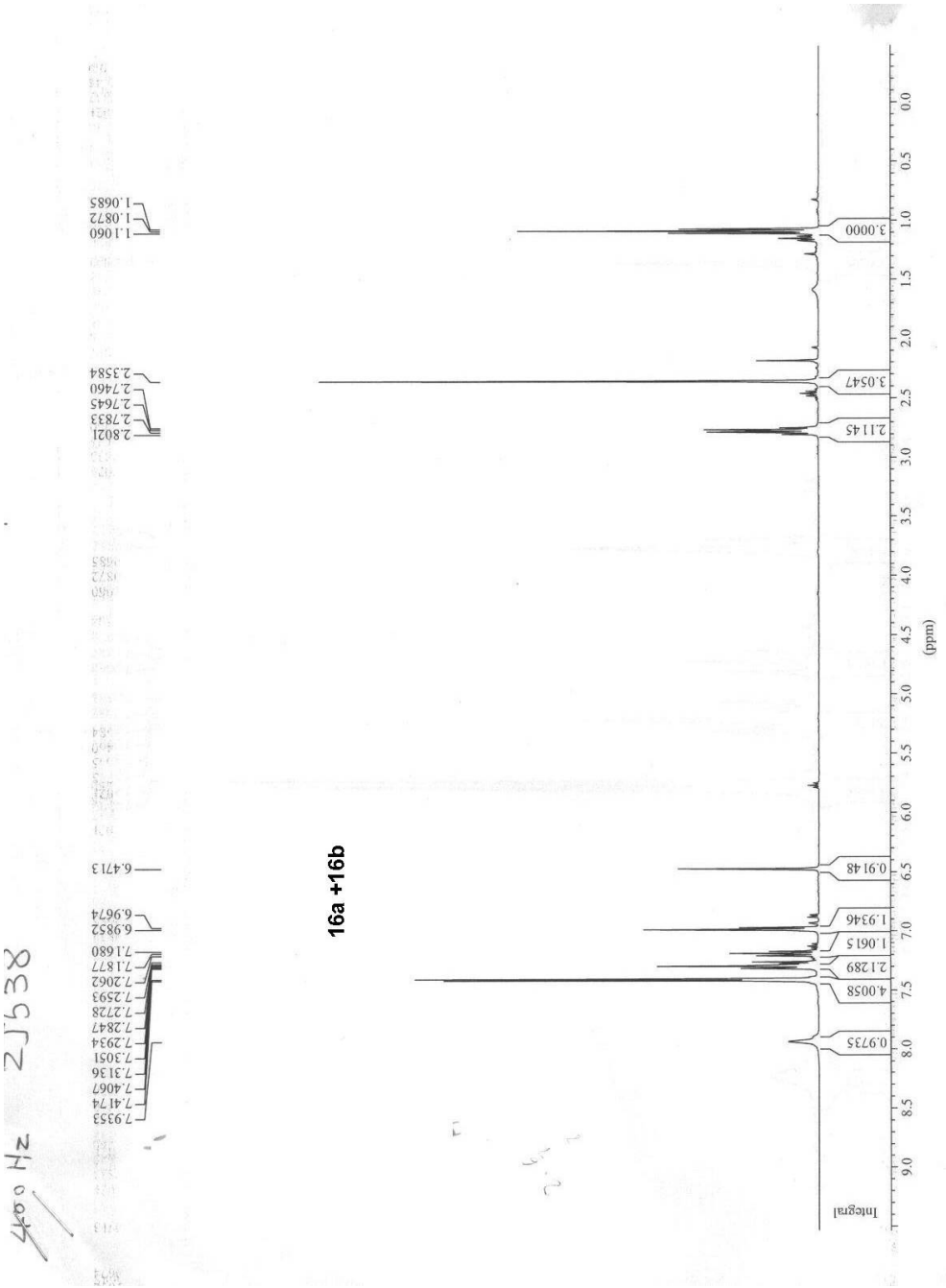

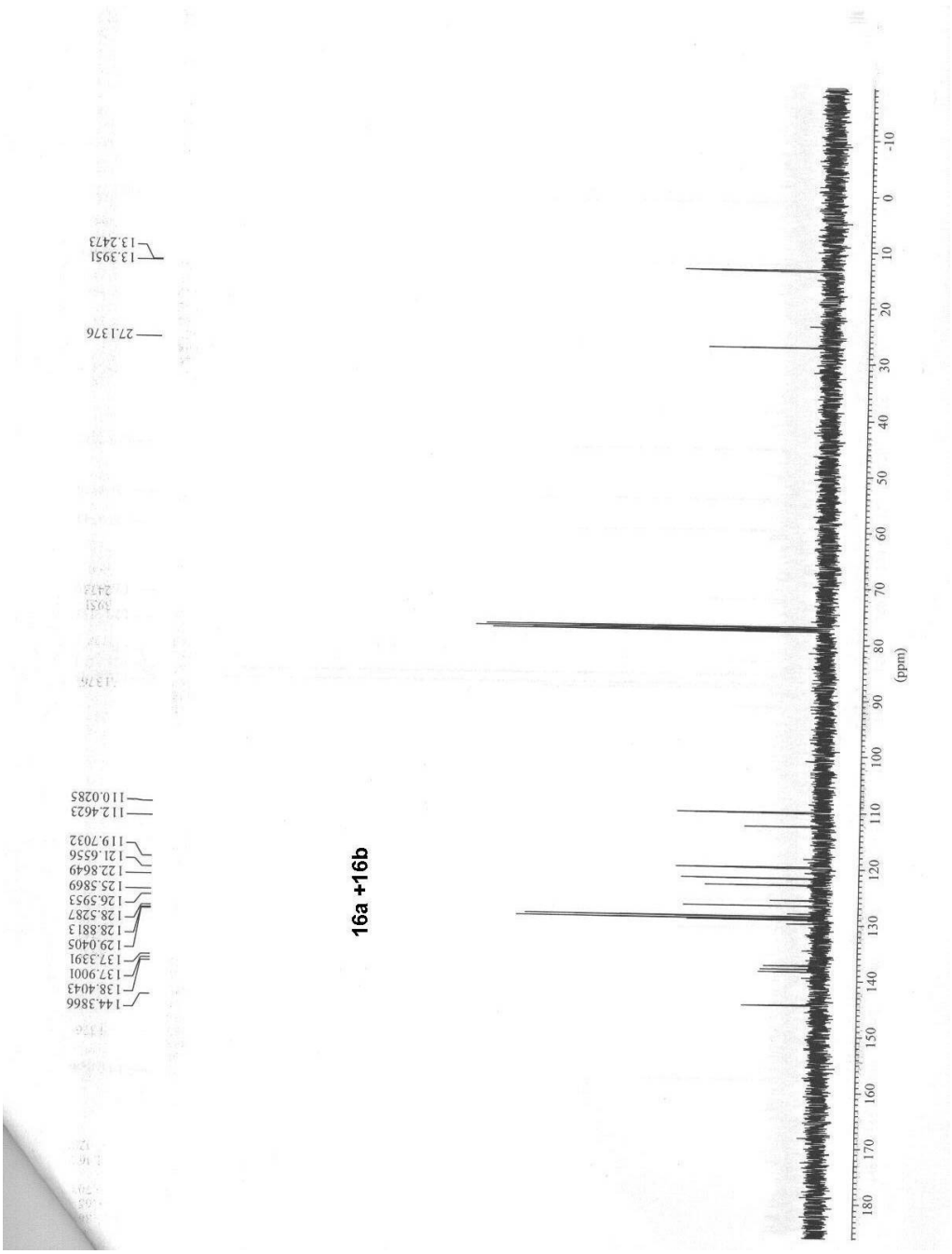

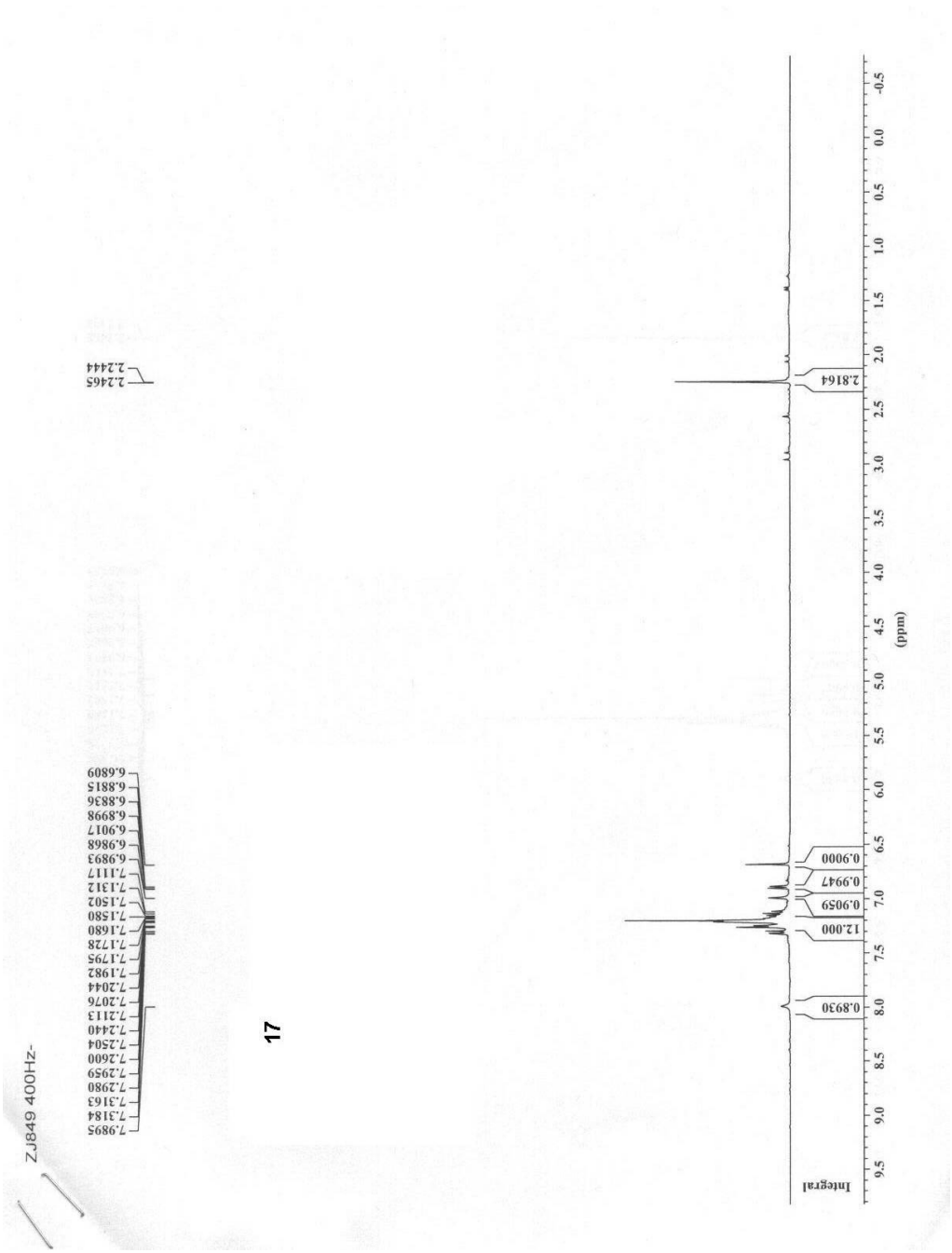

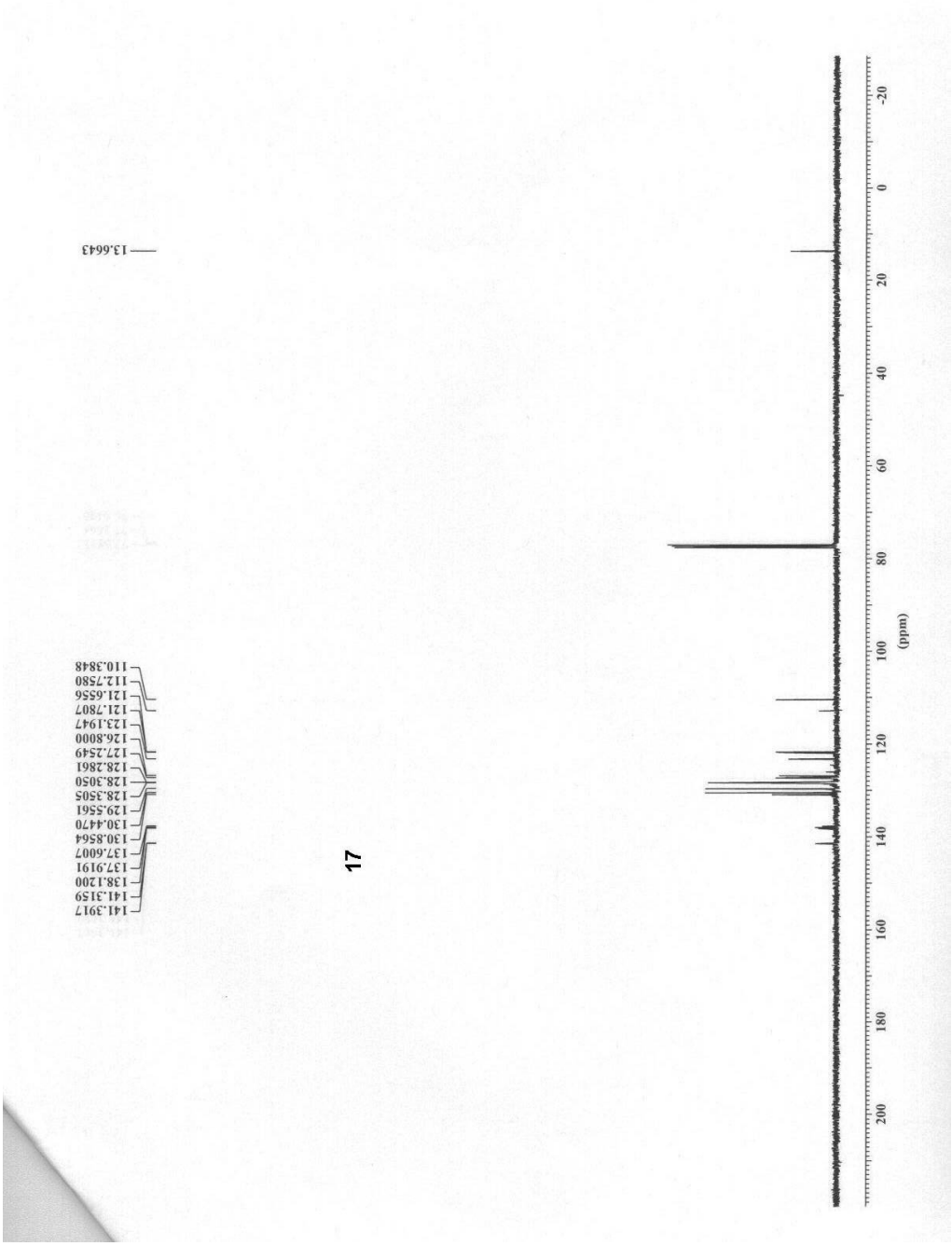

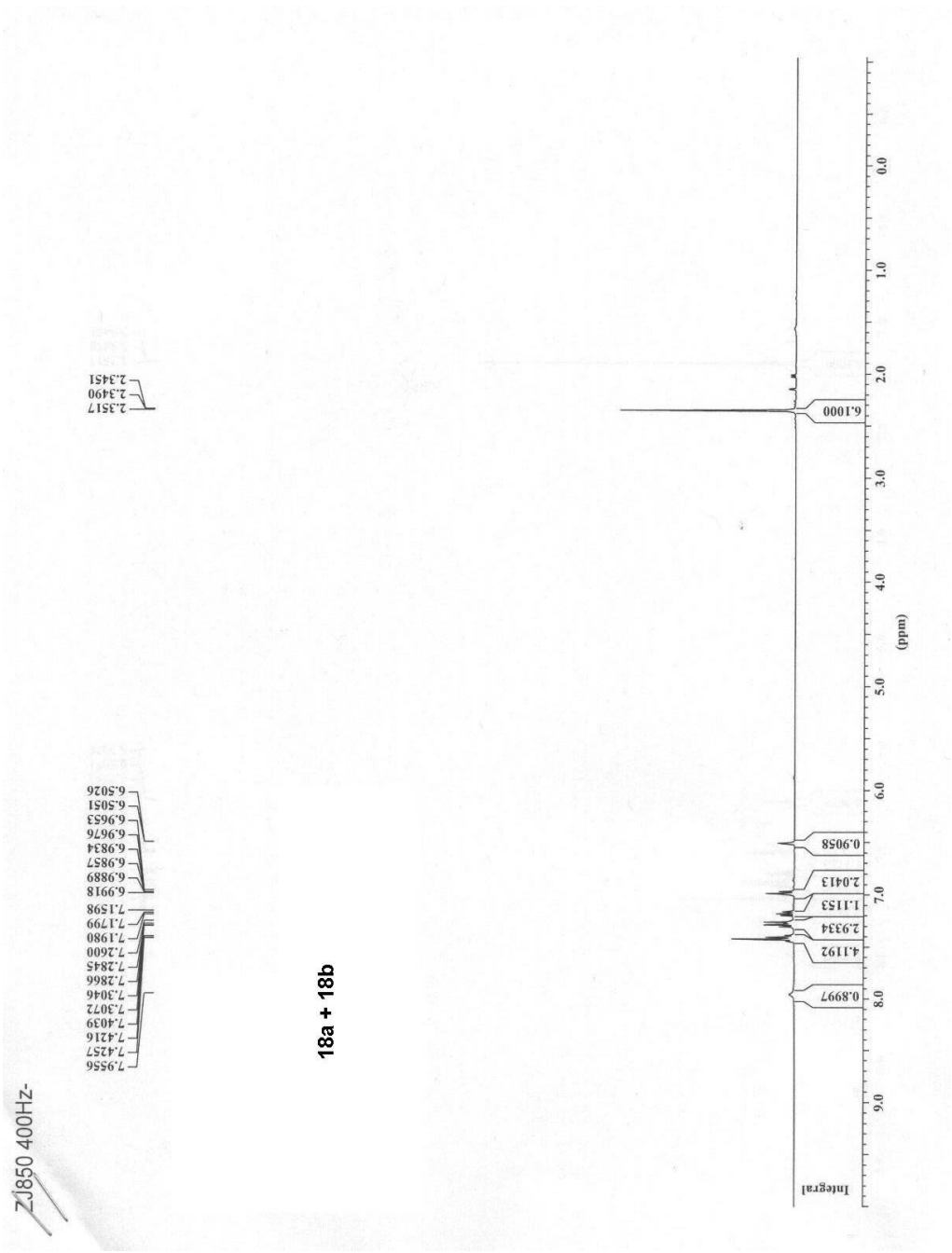

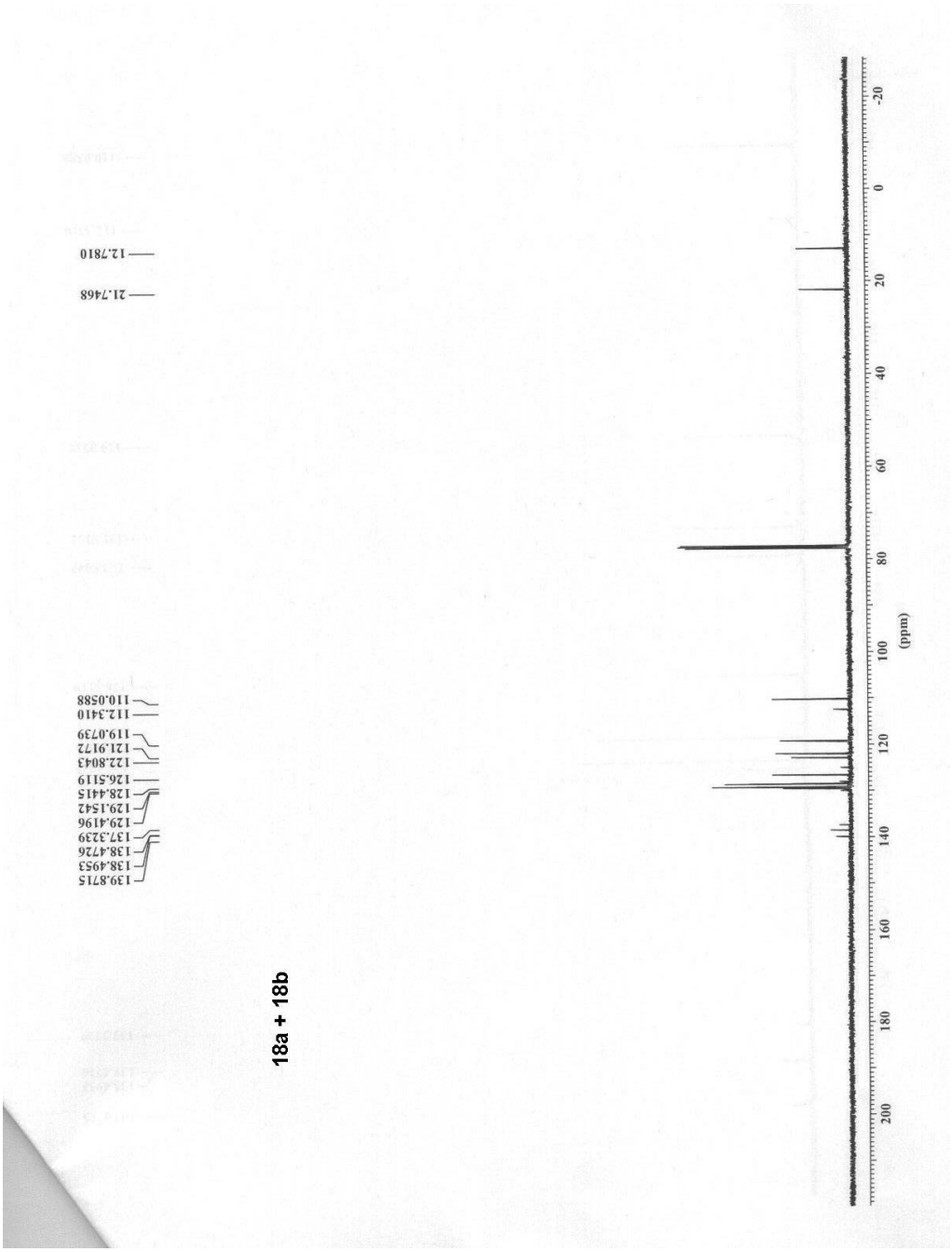

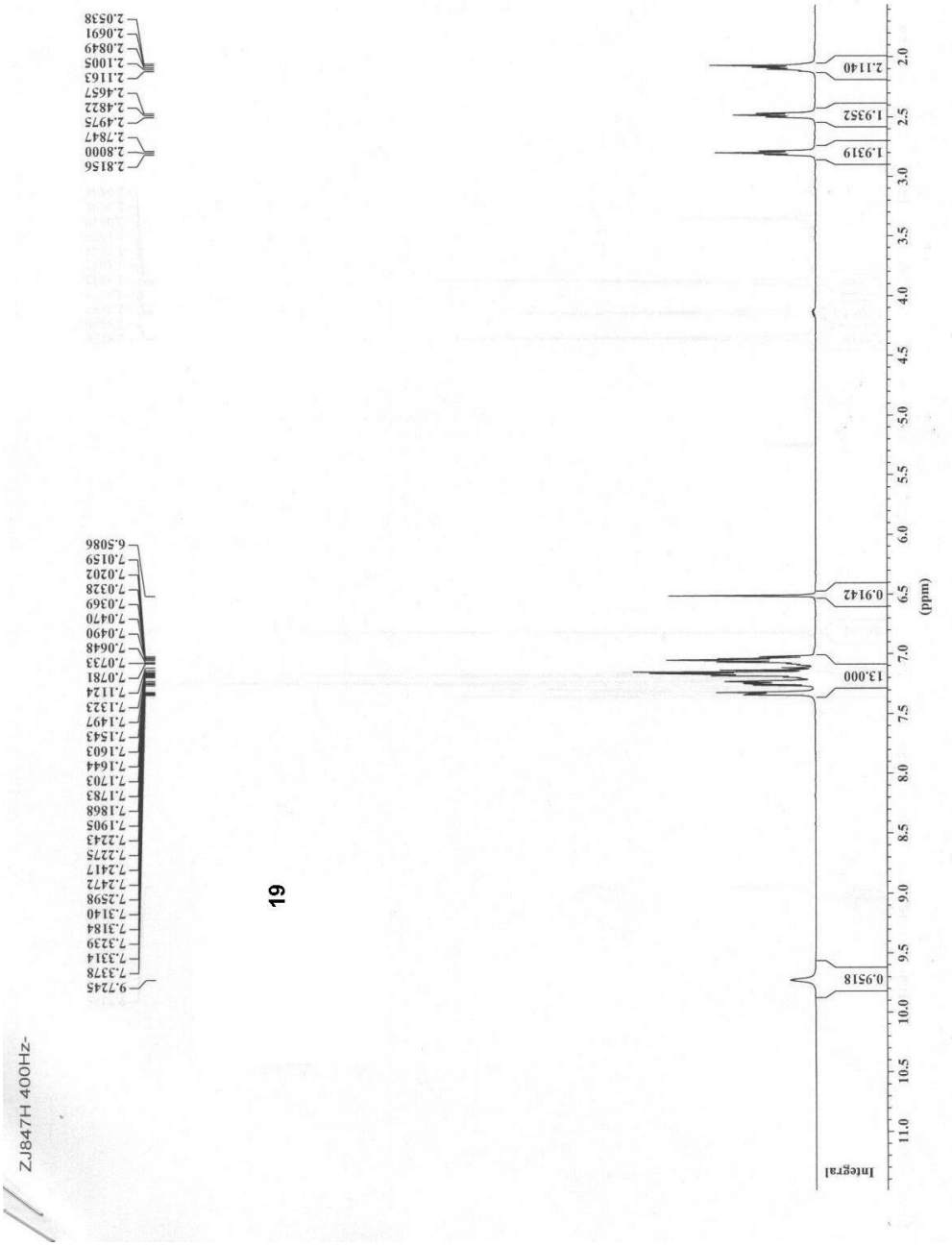

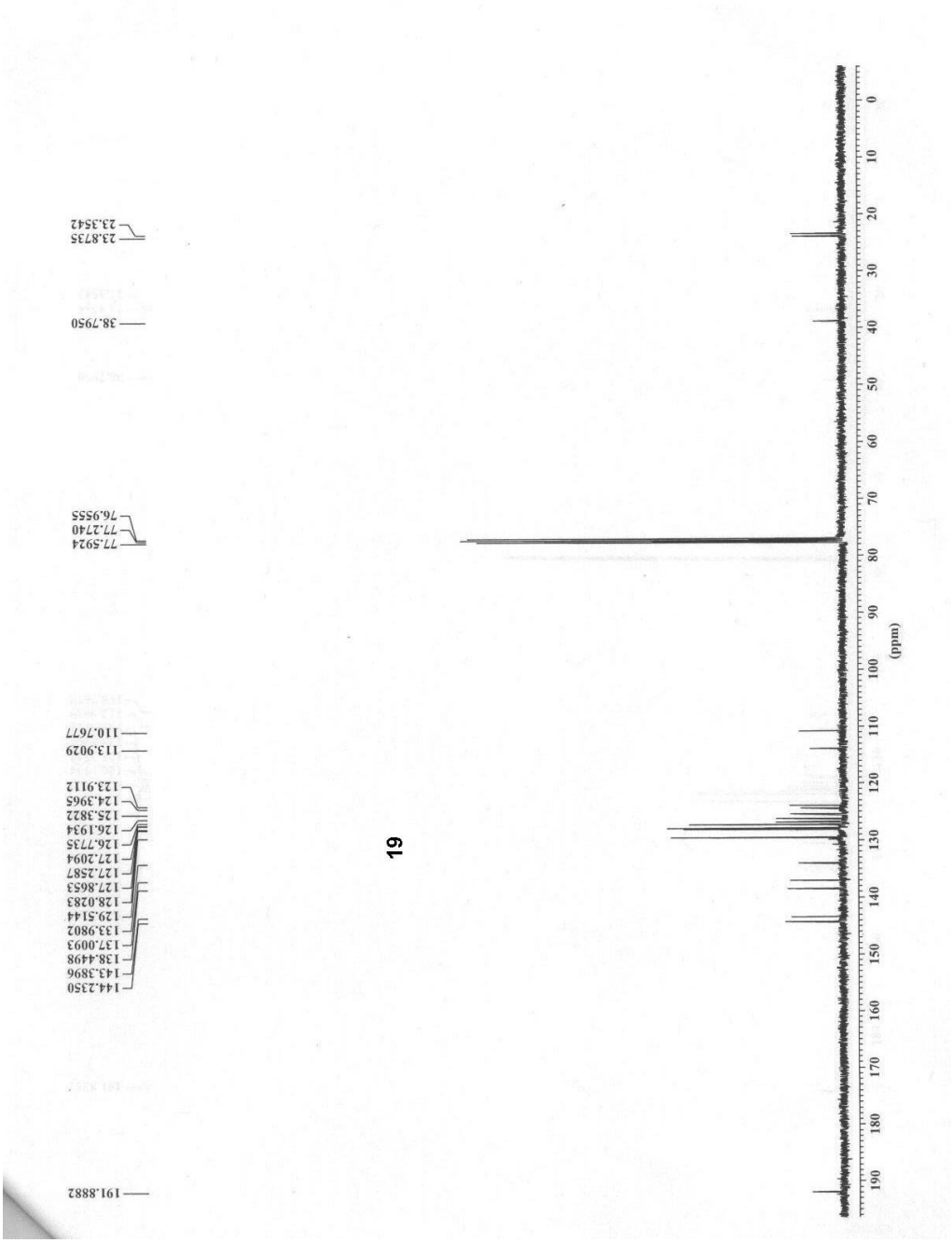

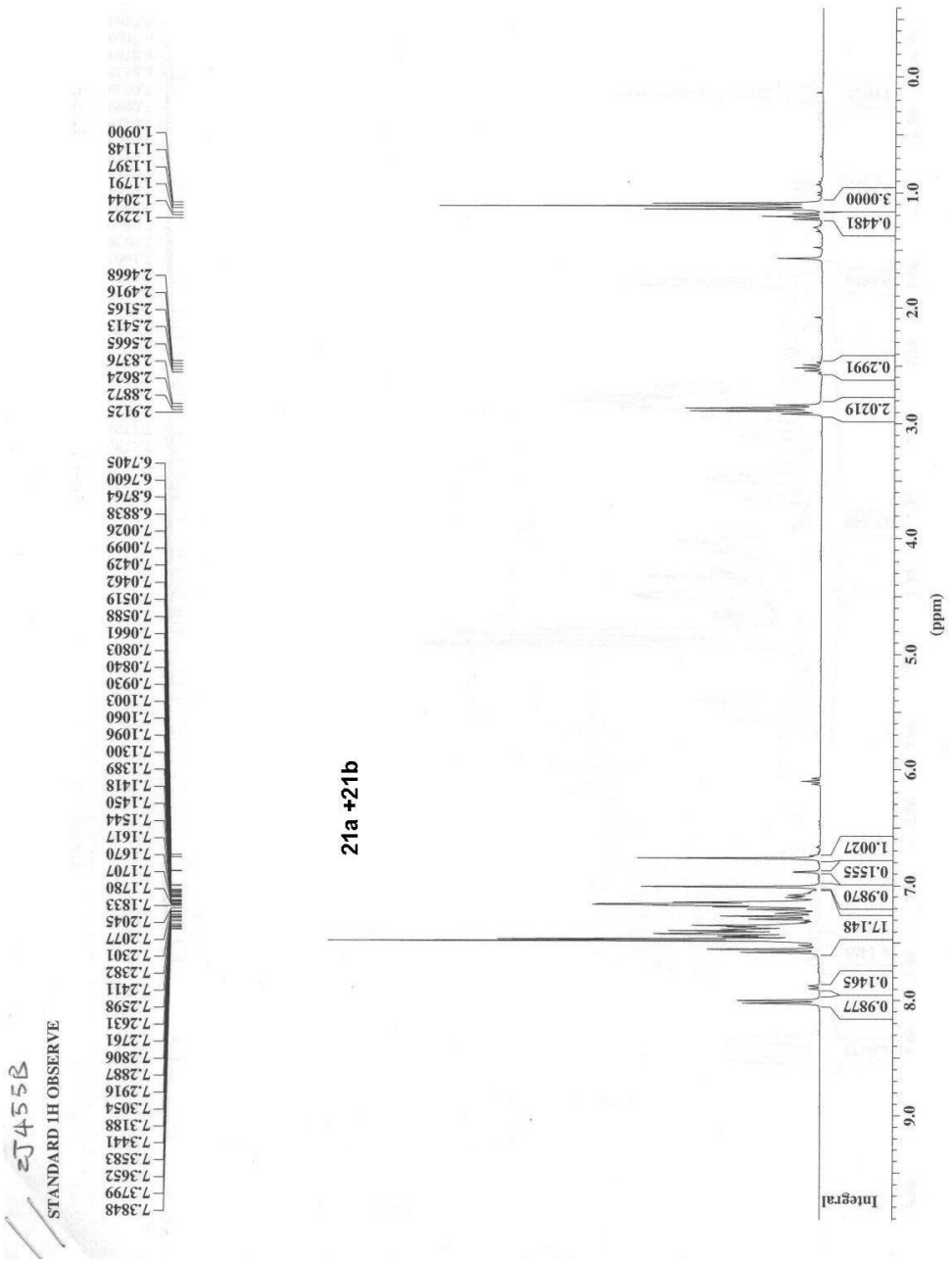

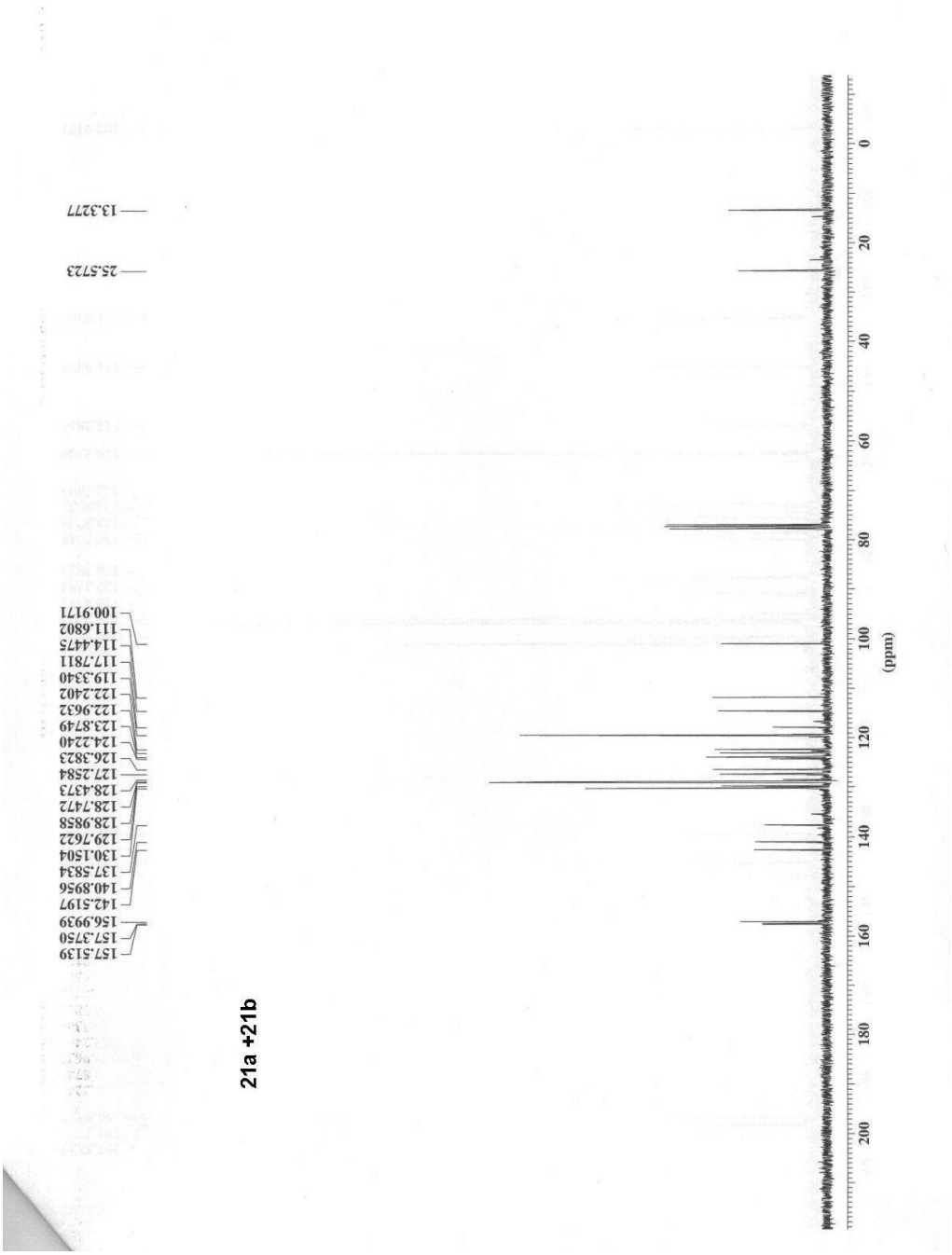

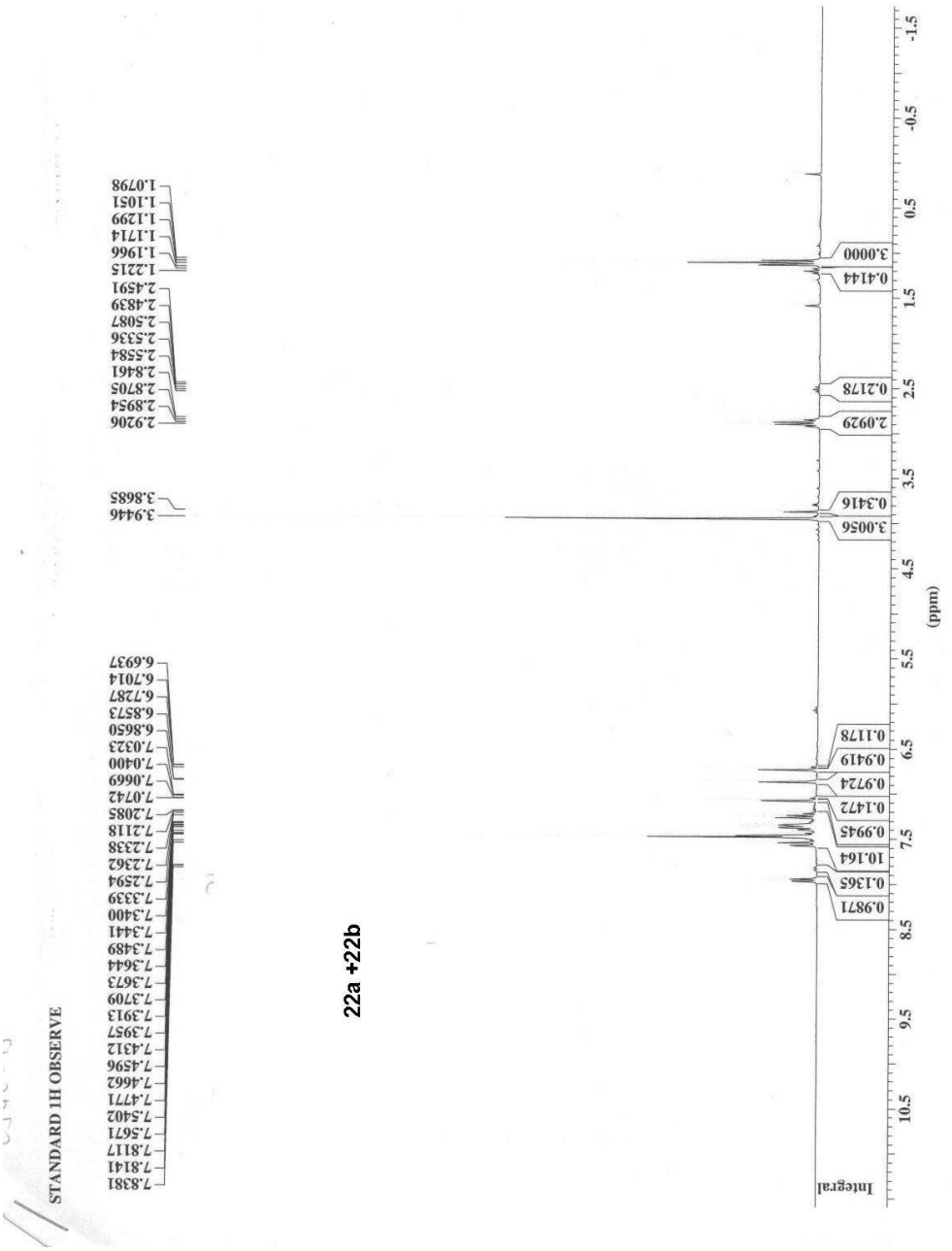

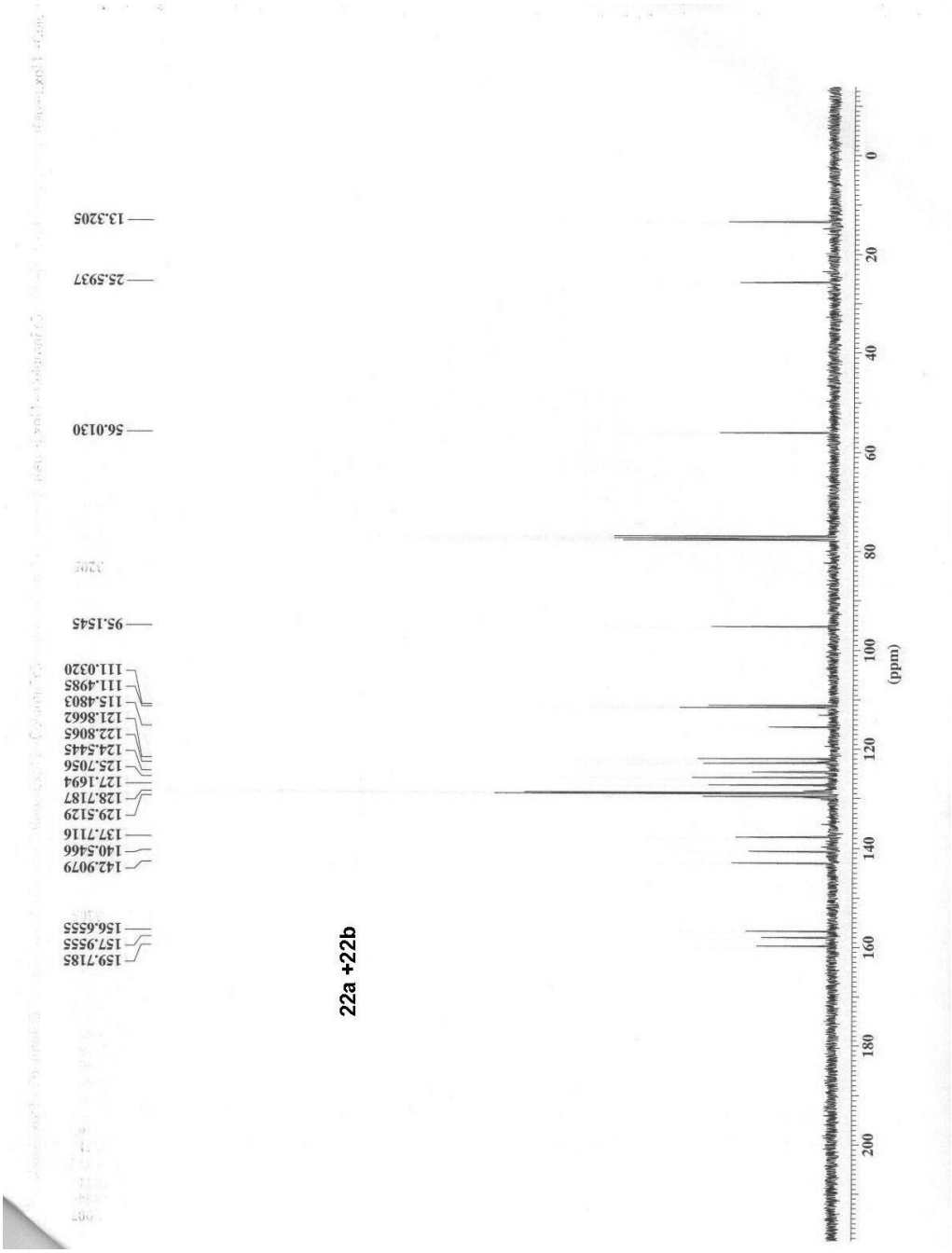

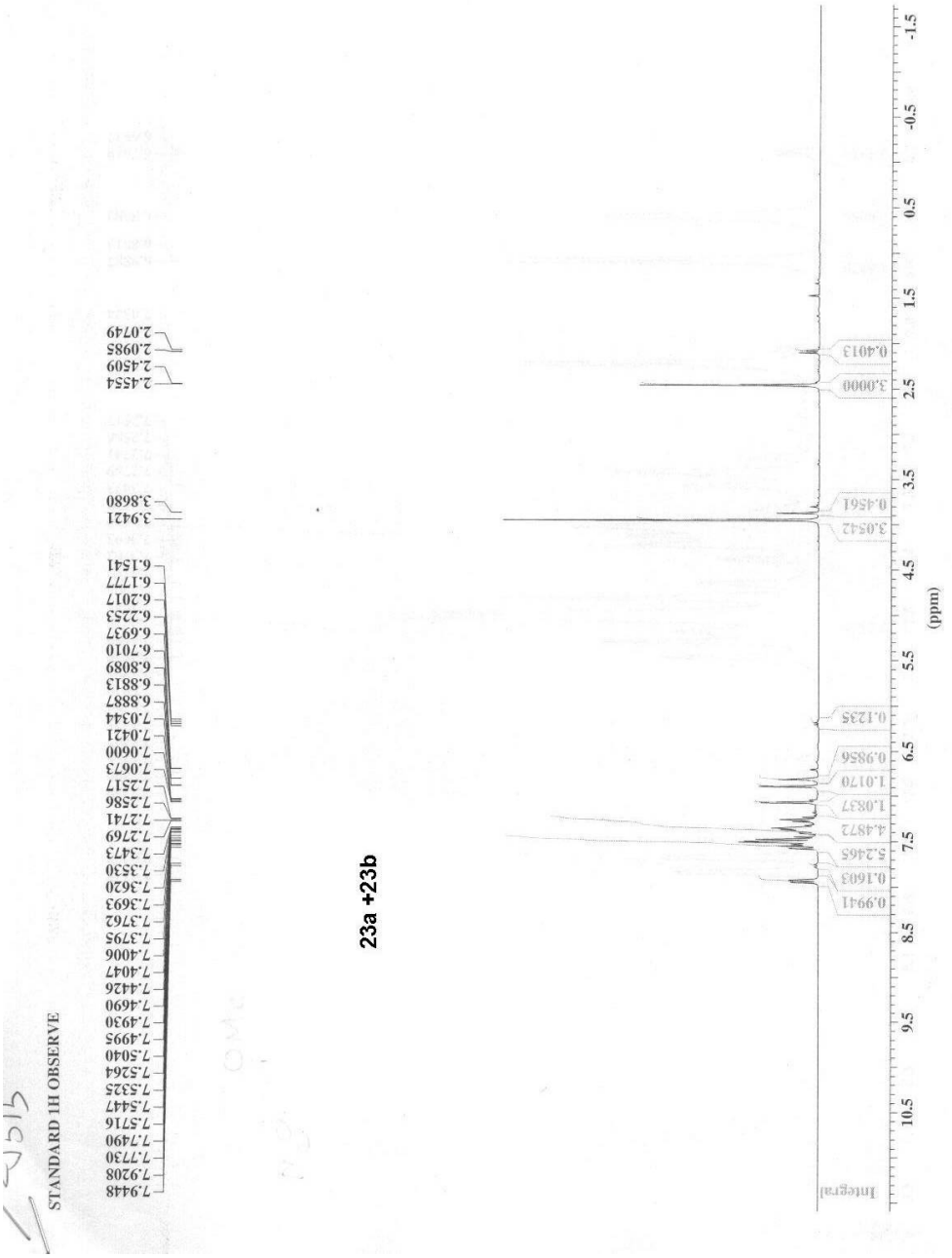

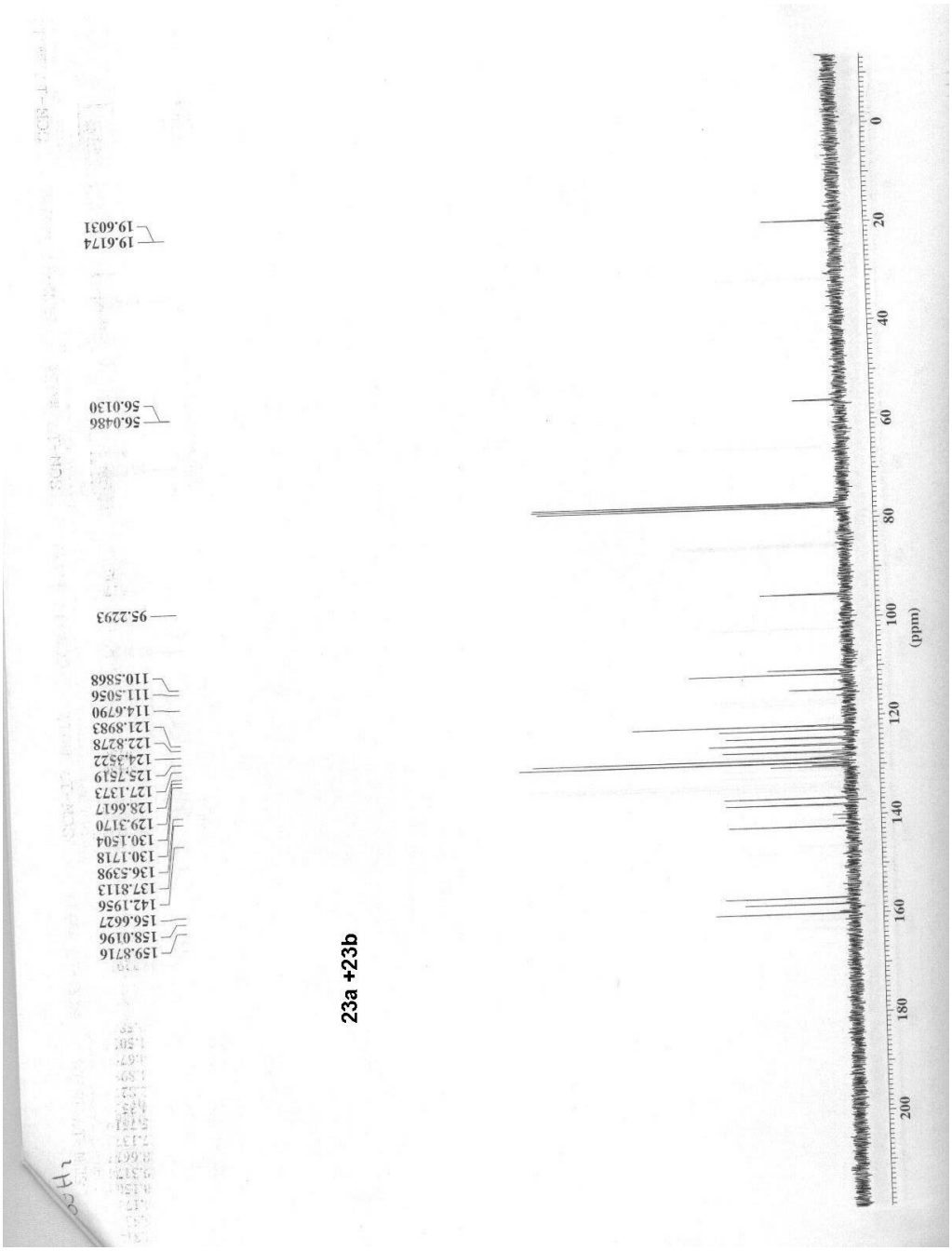

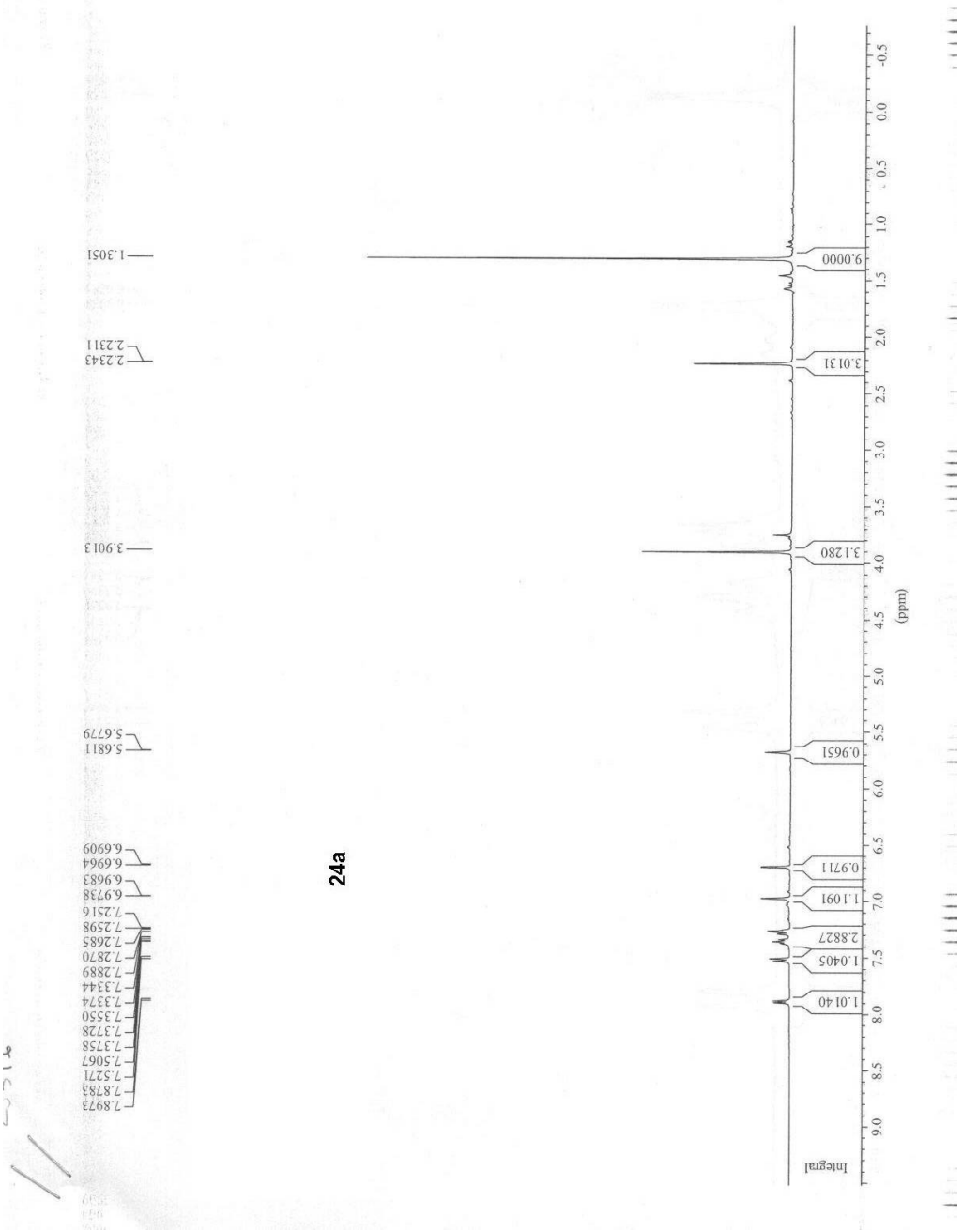

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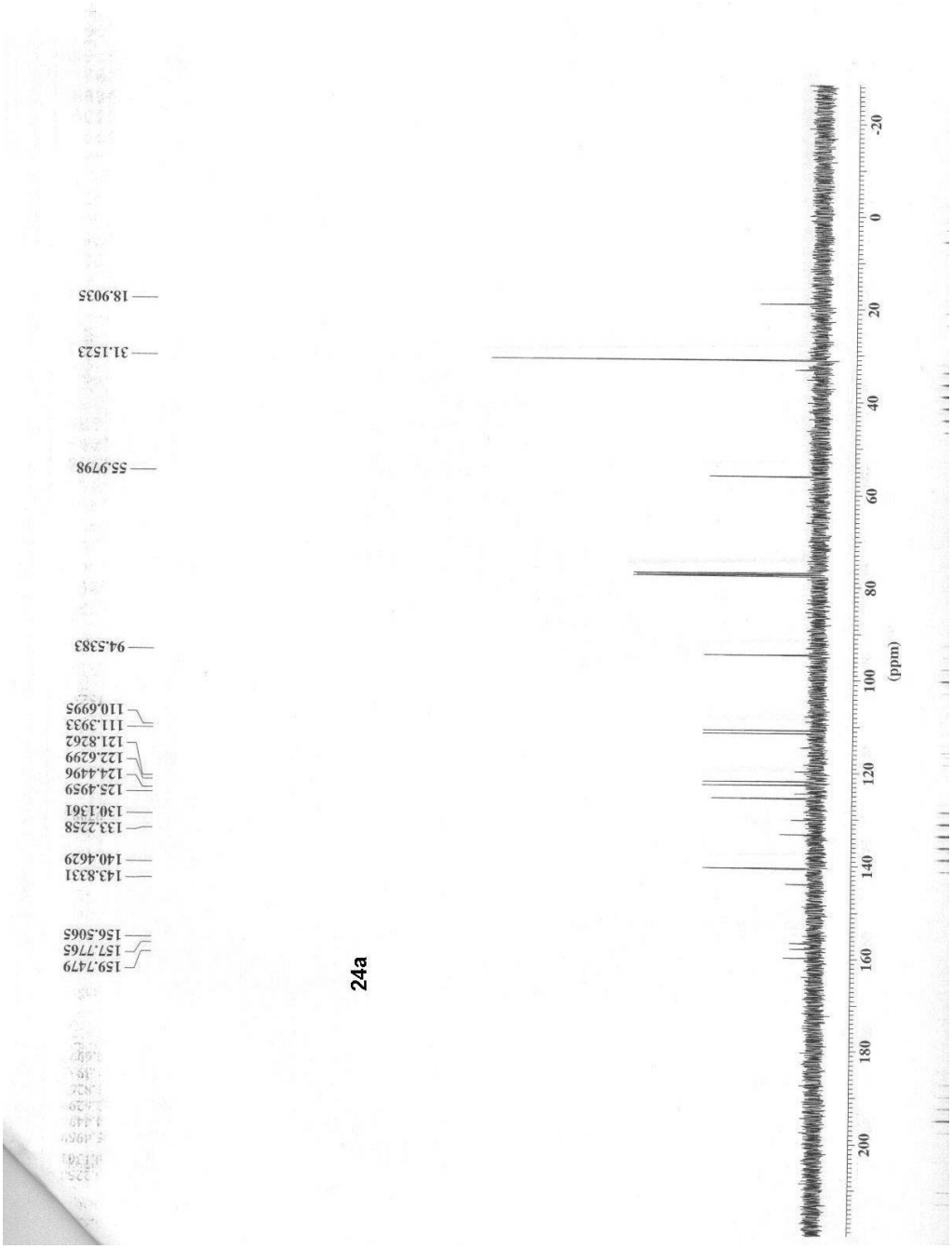
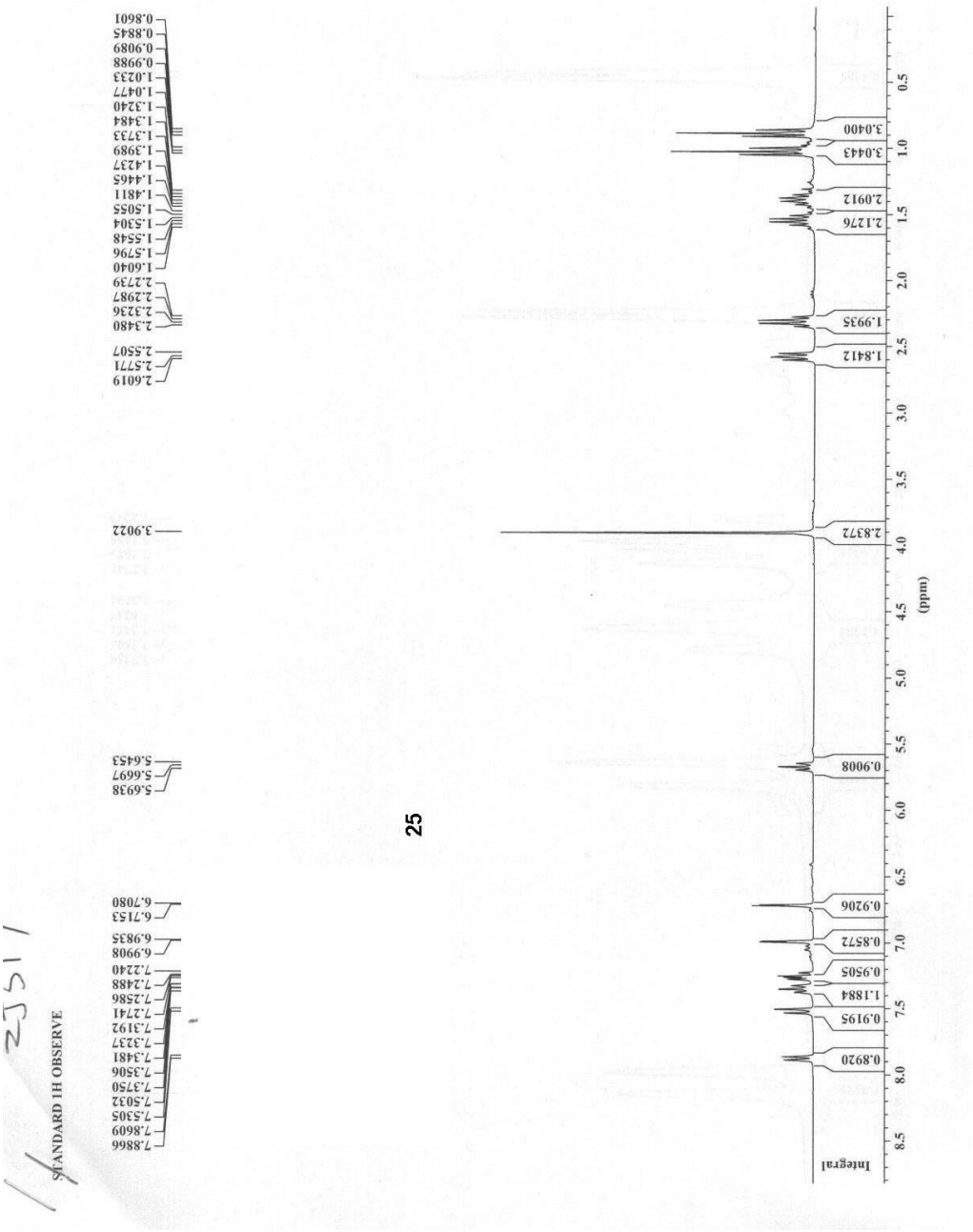
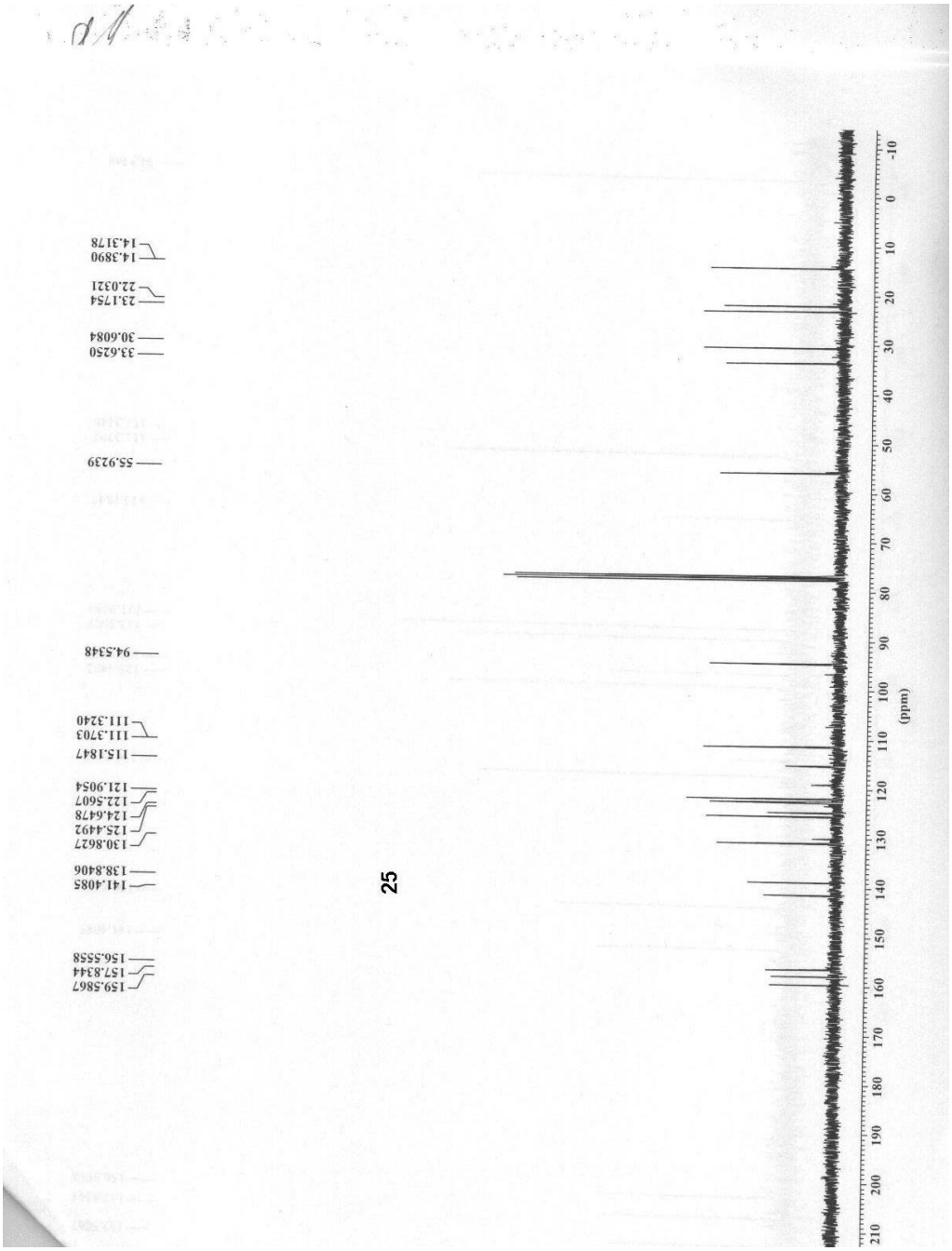
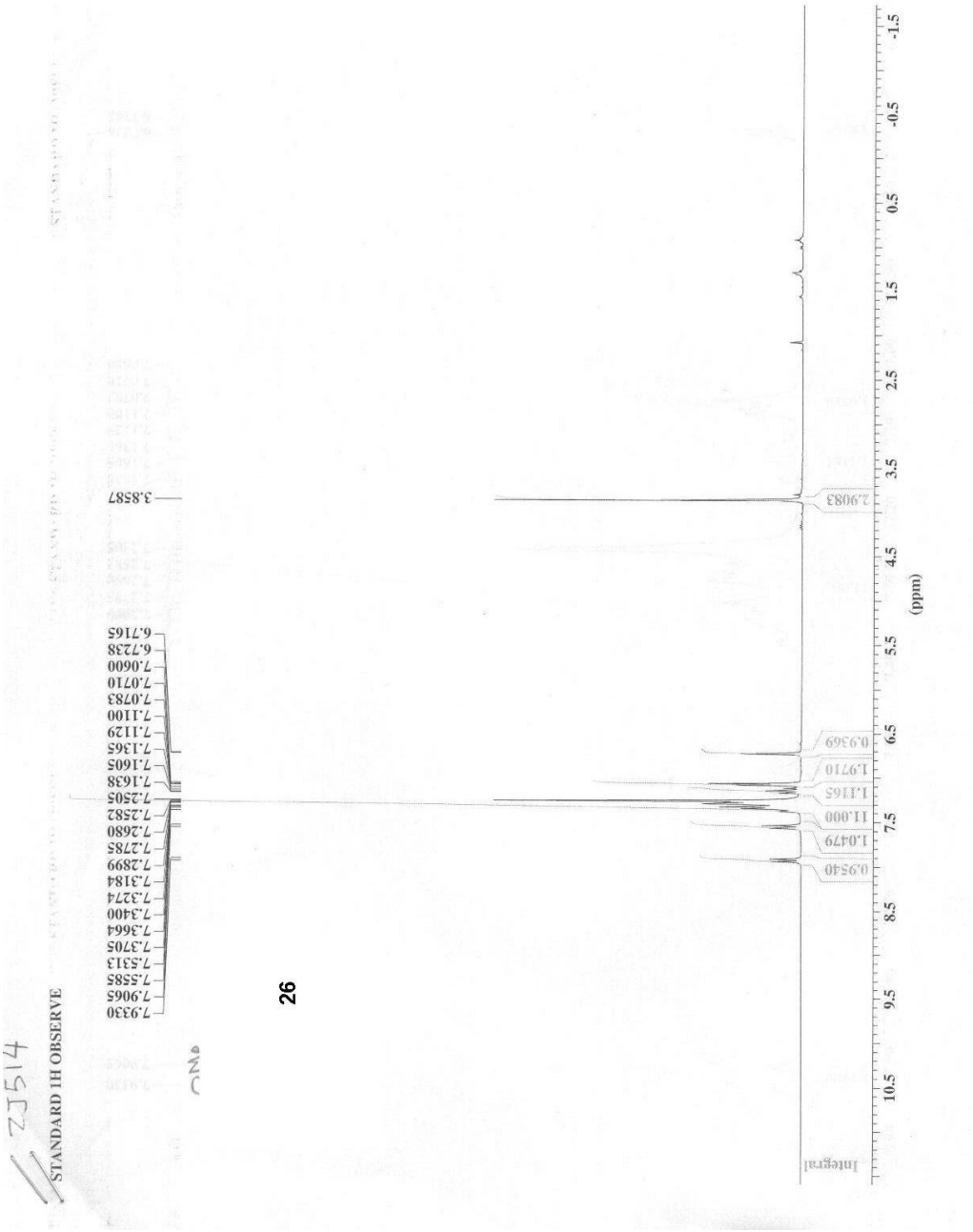
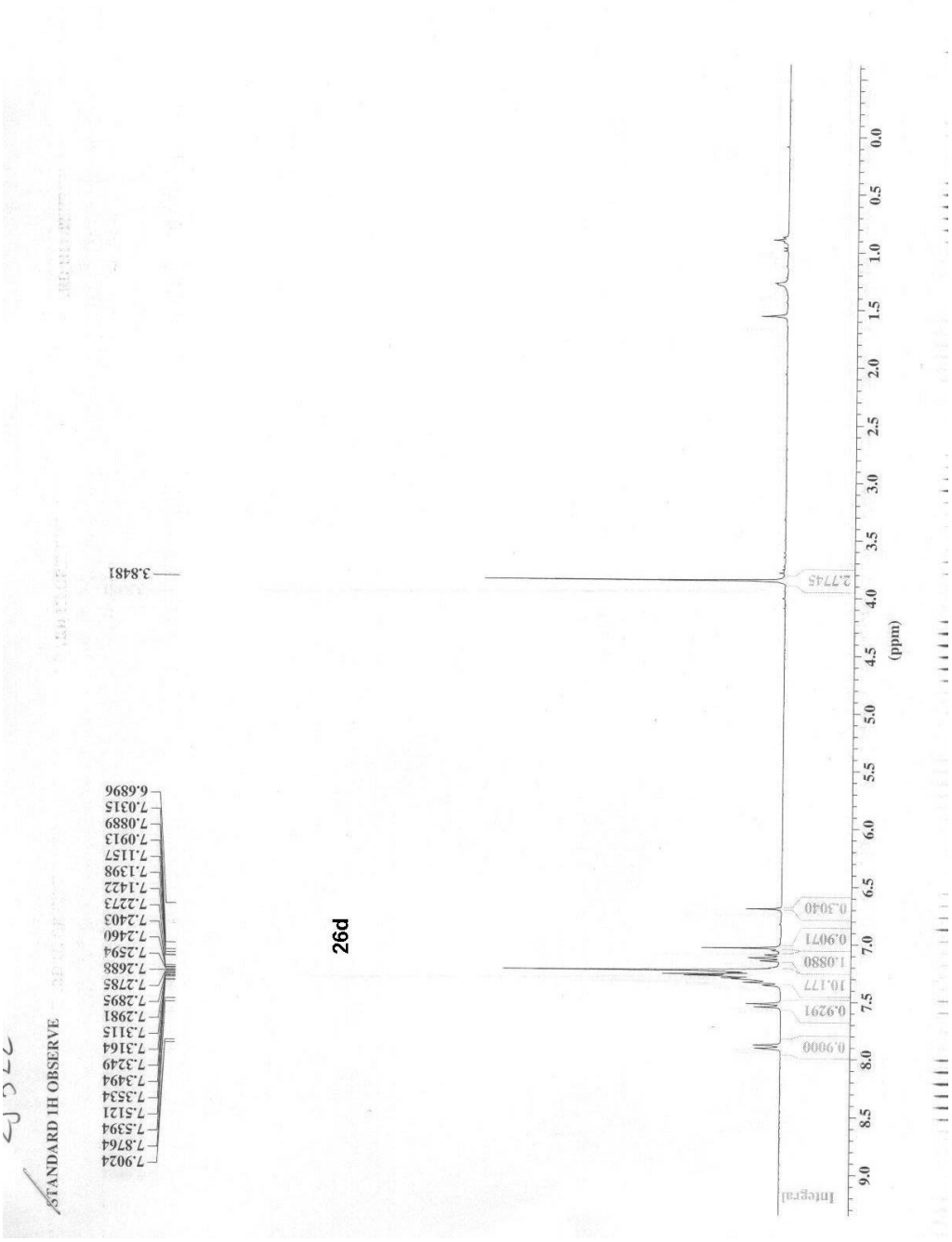
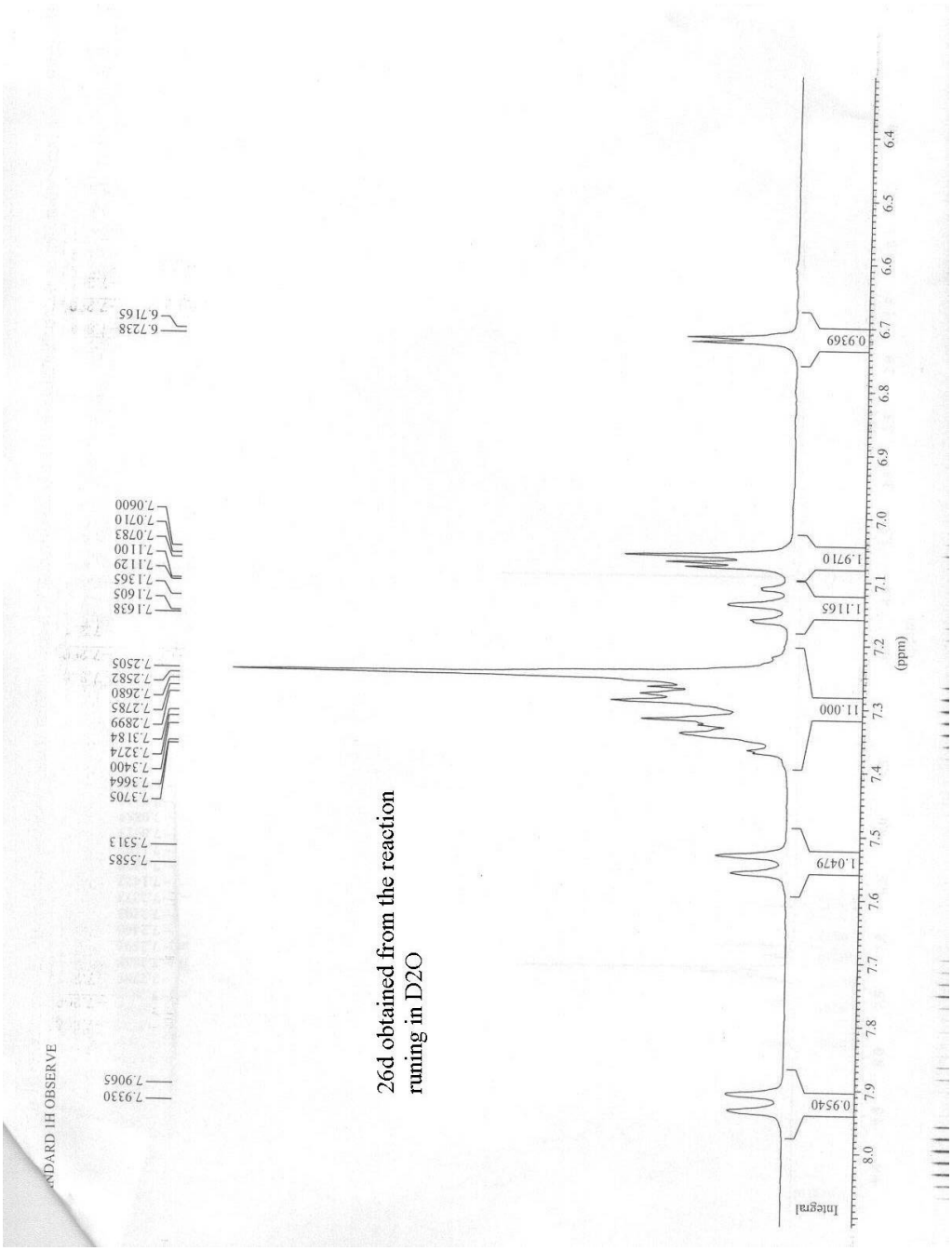


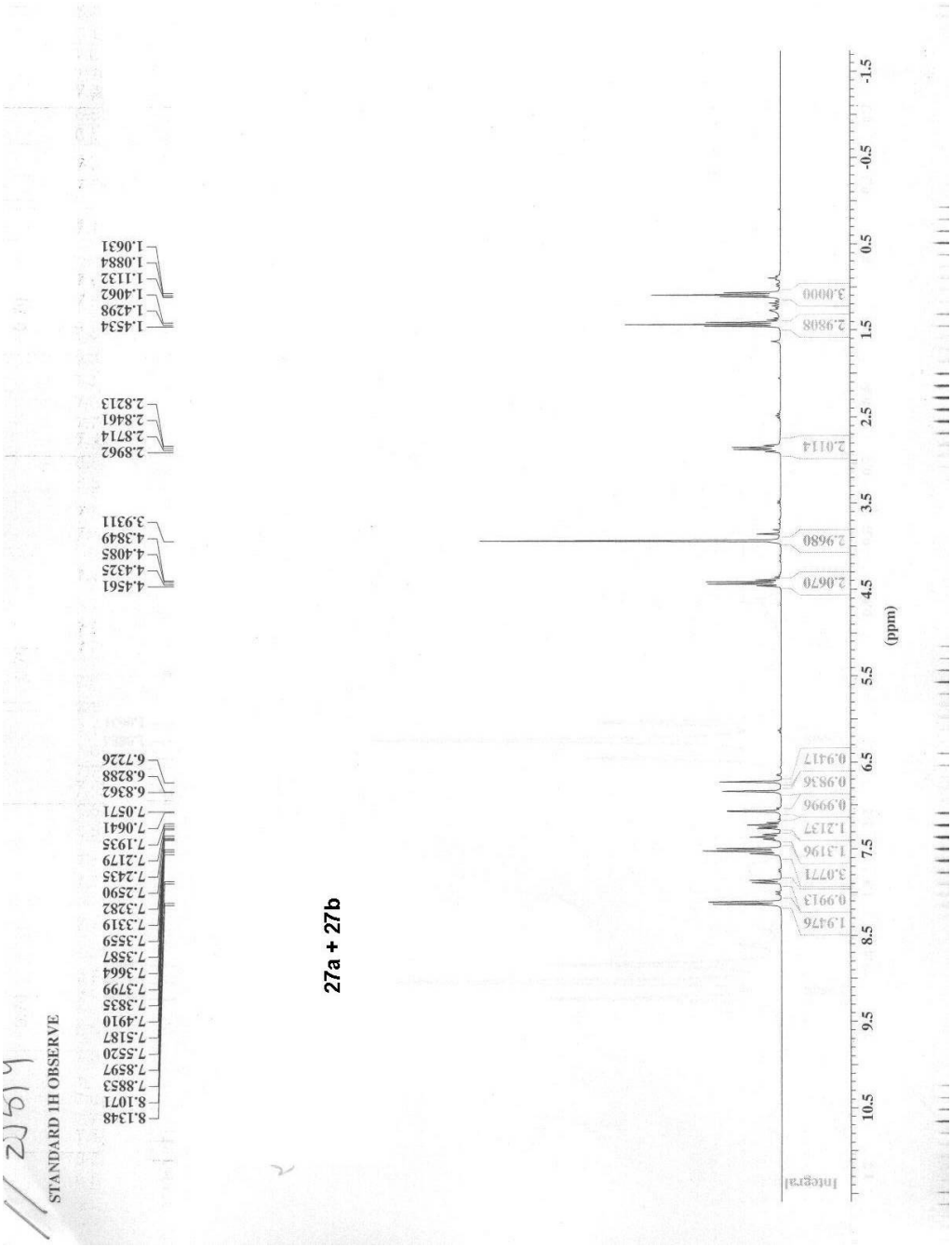


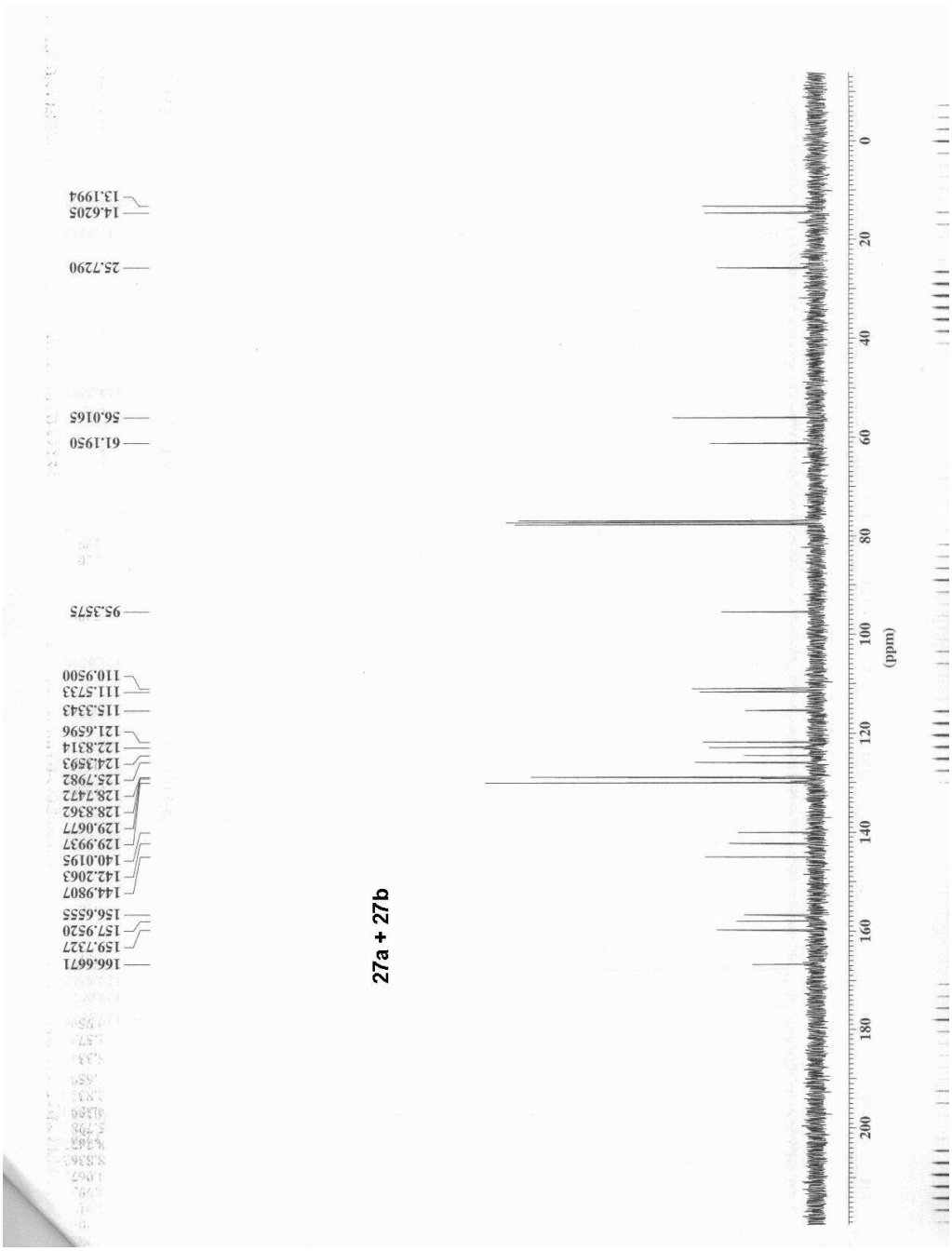


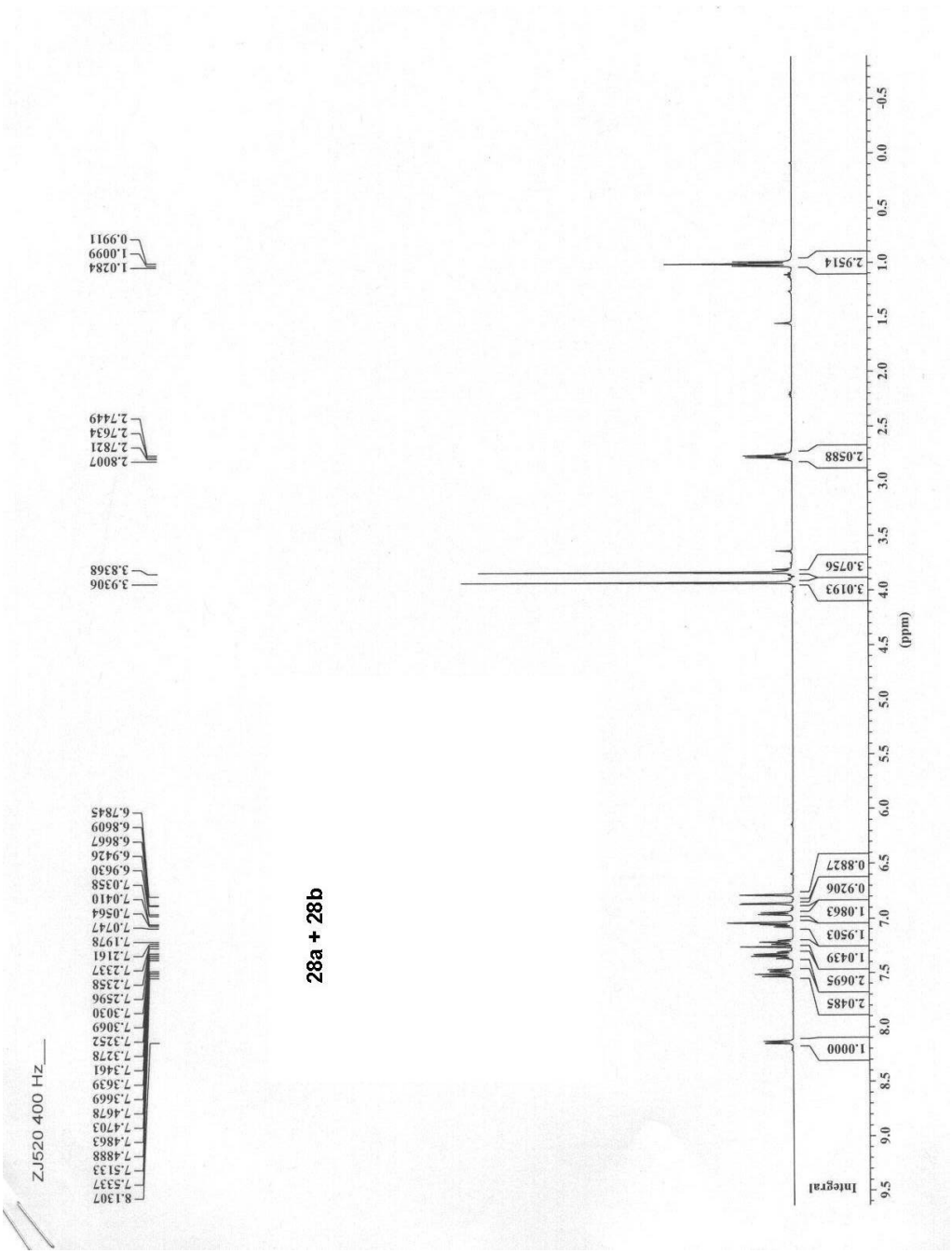


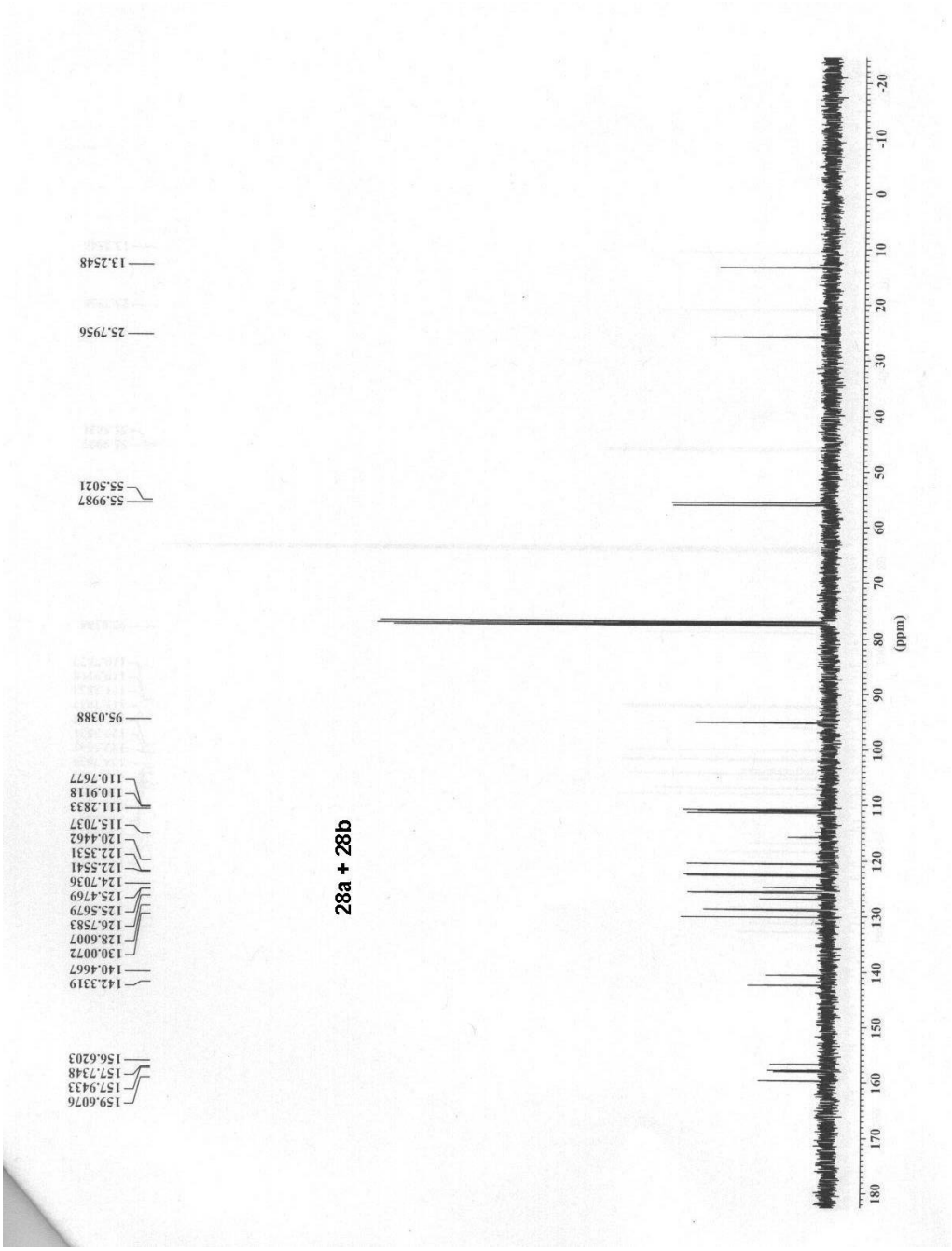




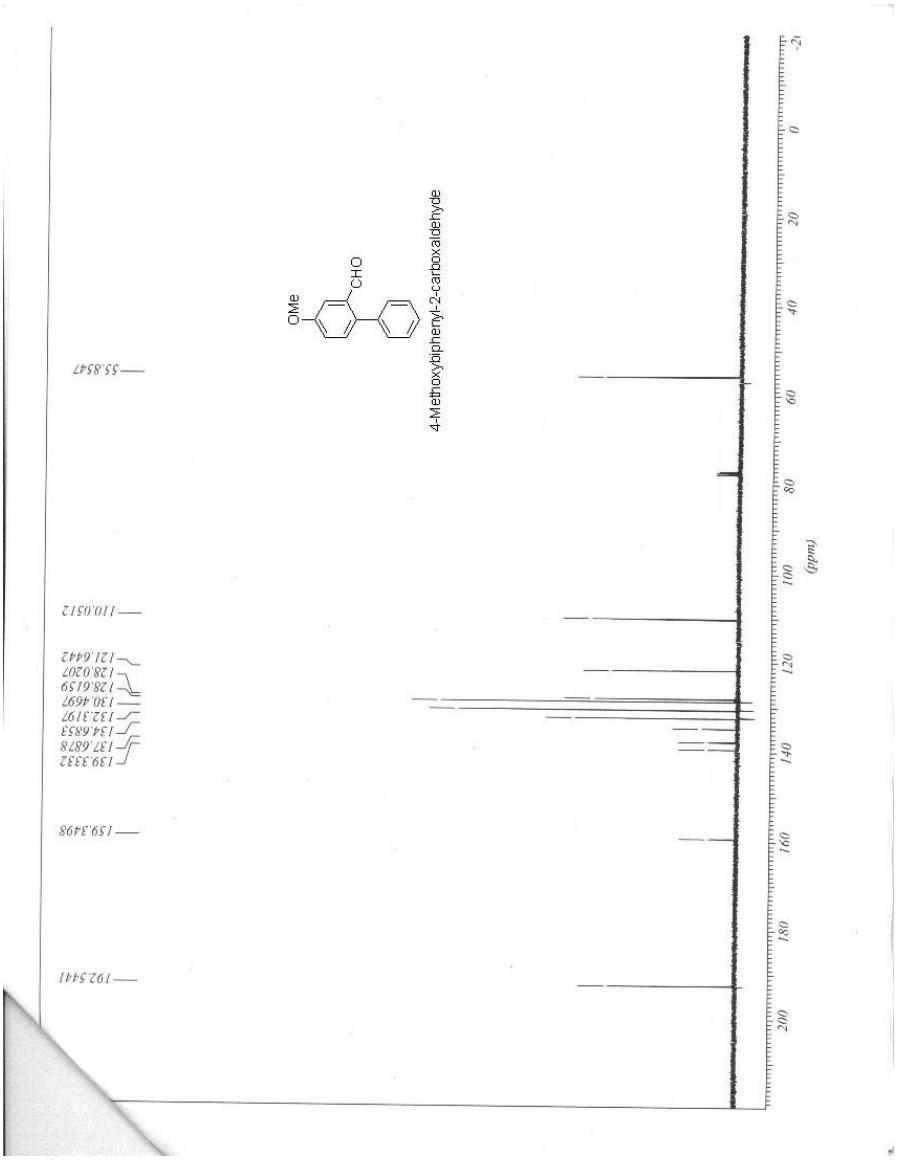


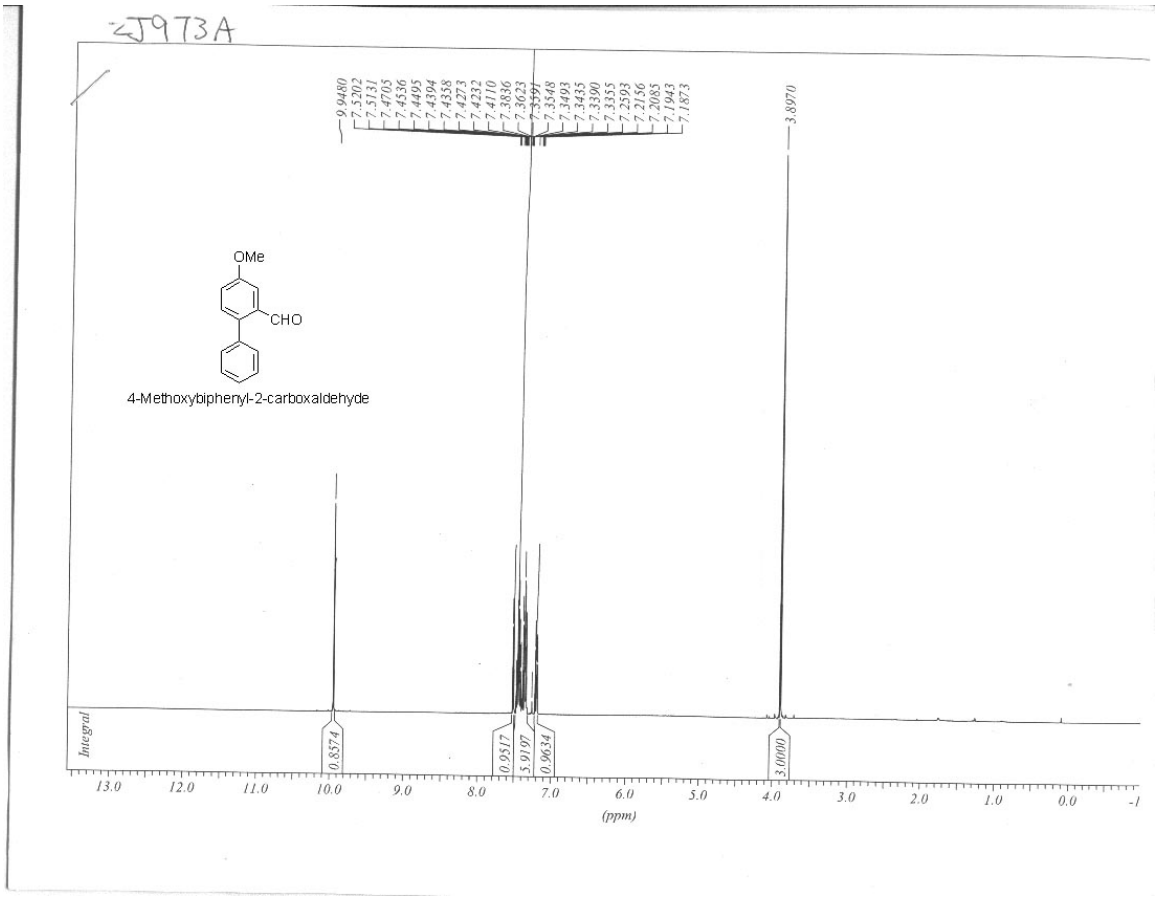


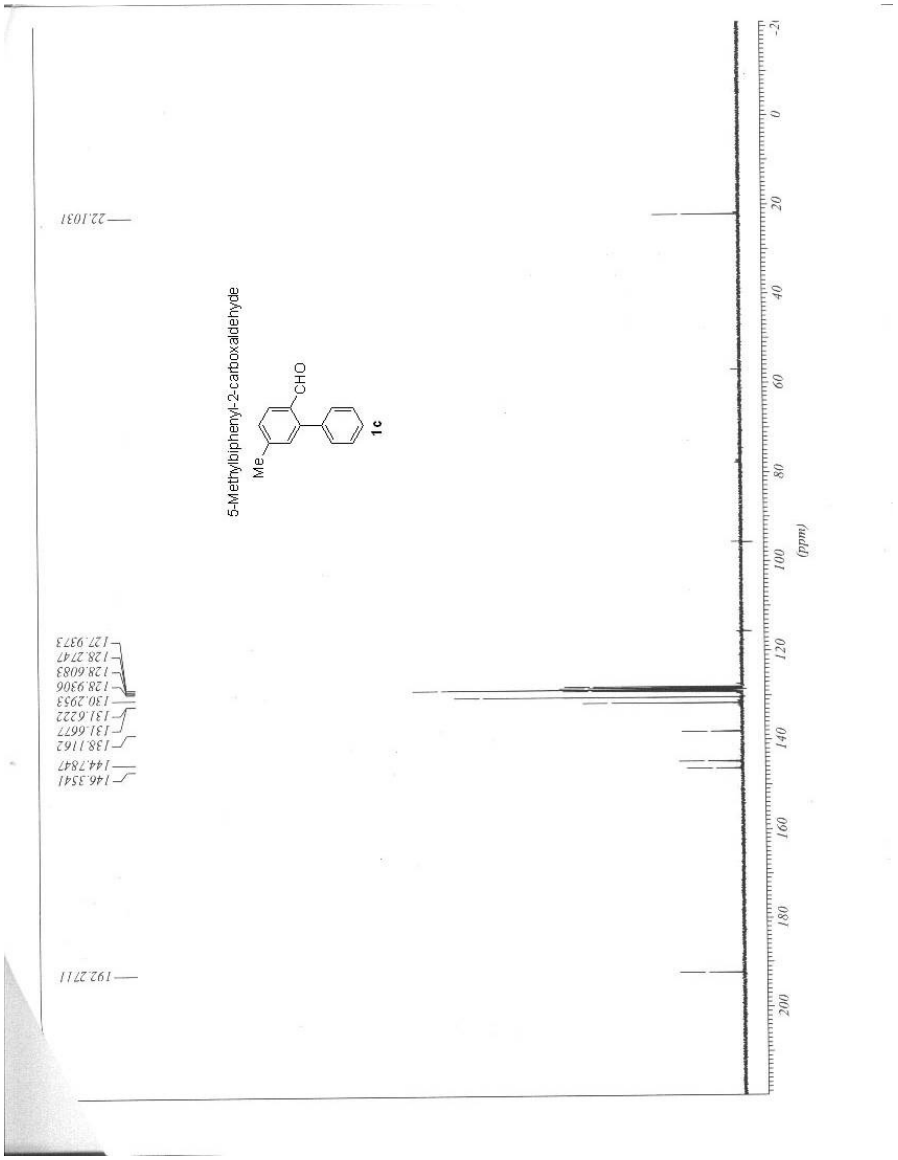


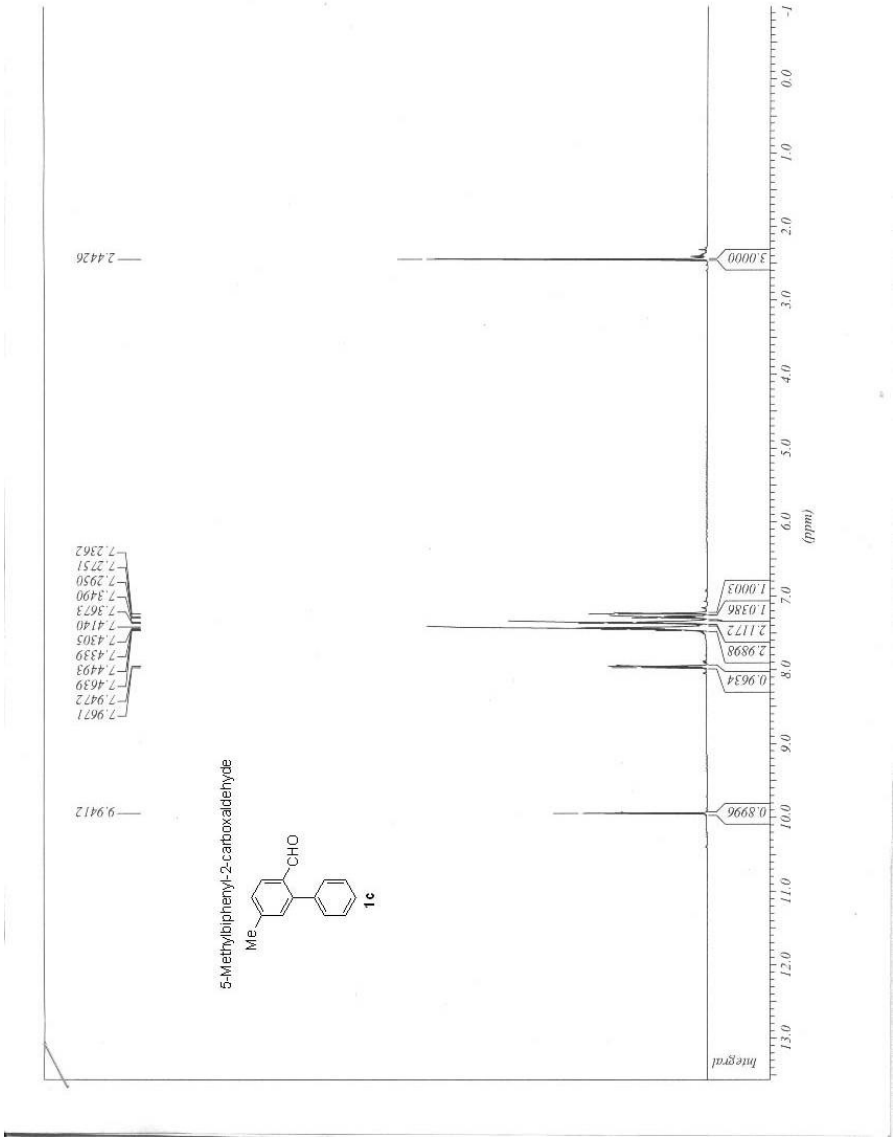


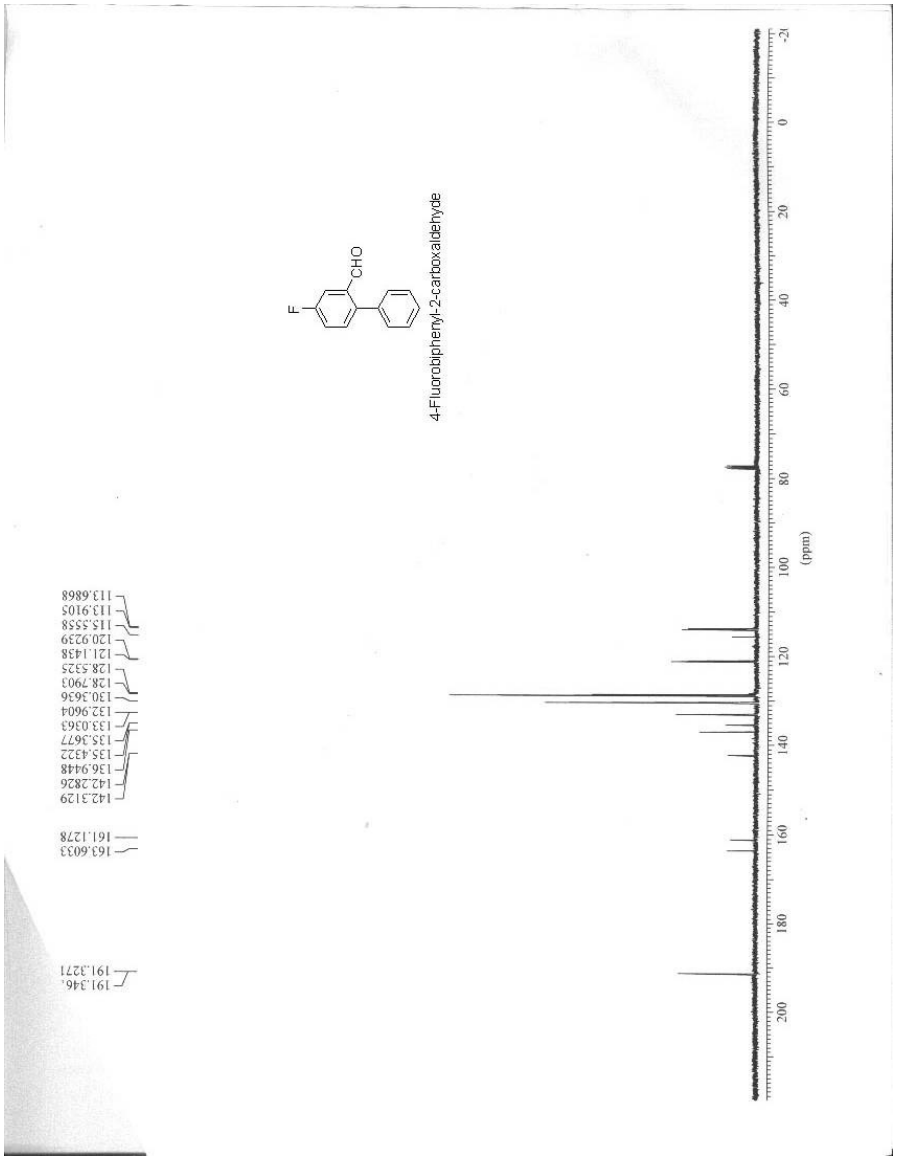
APPENDIX C. CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA

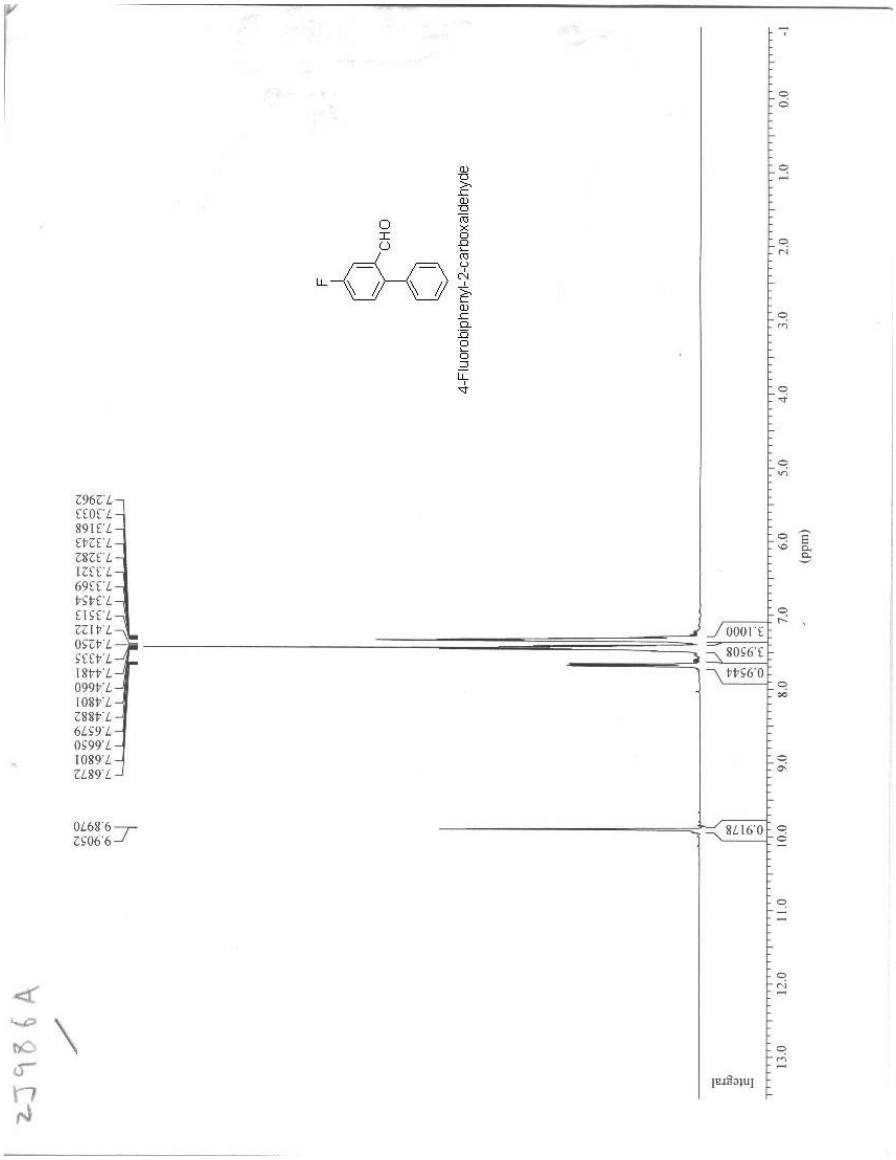


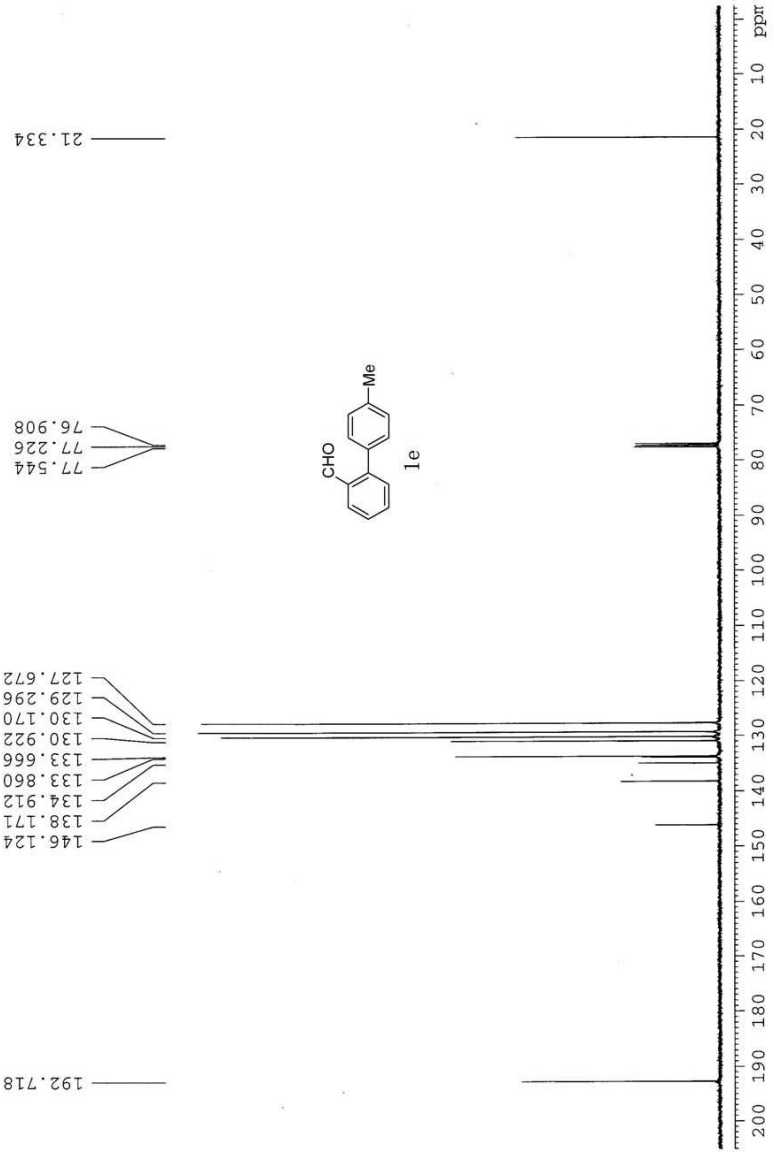


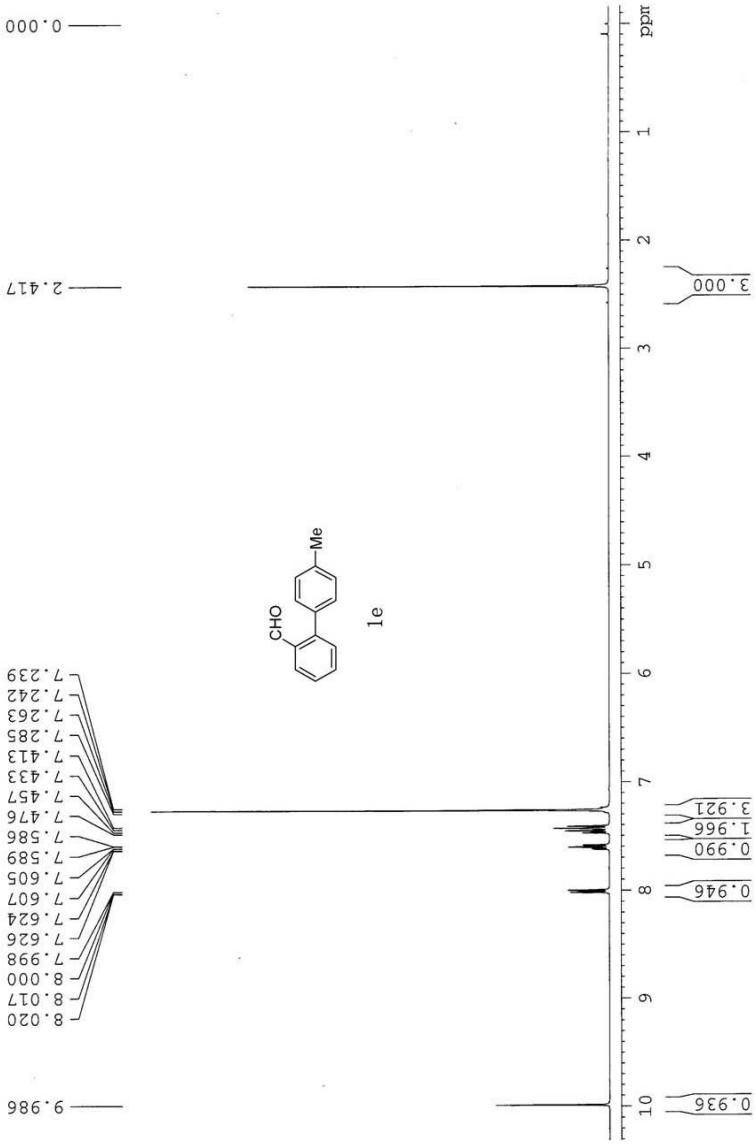


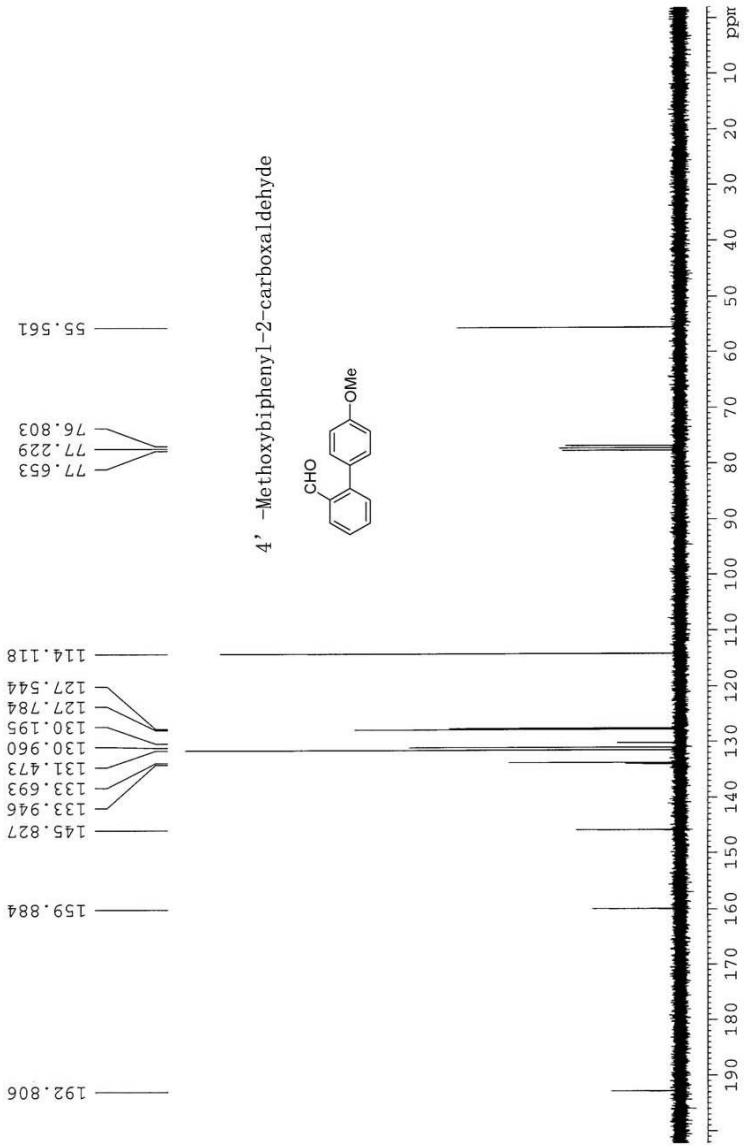


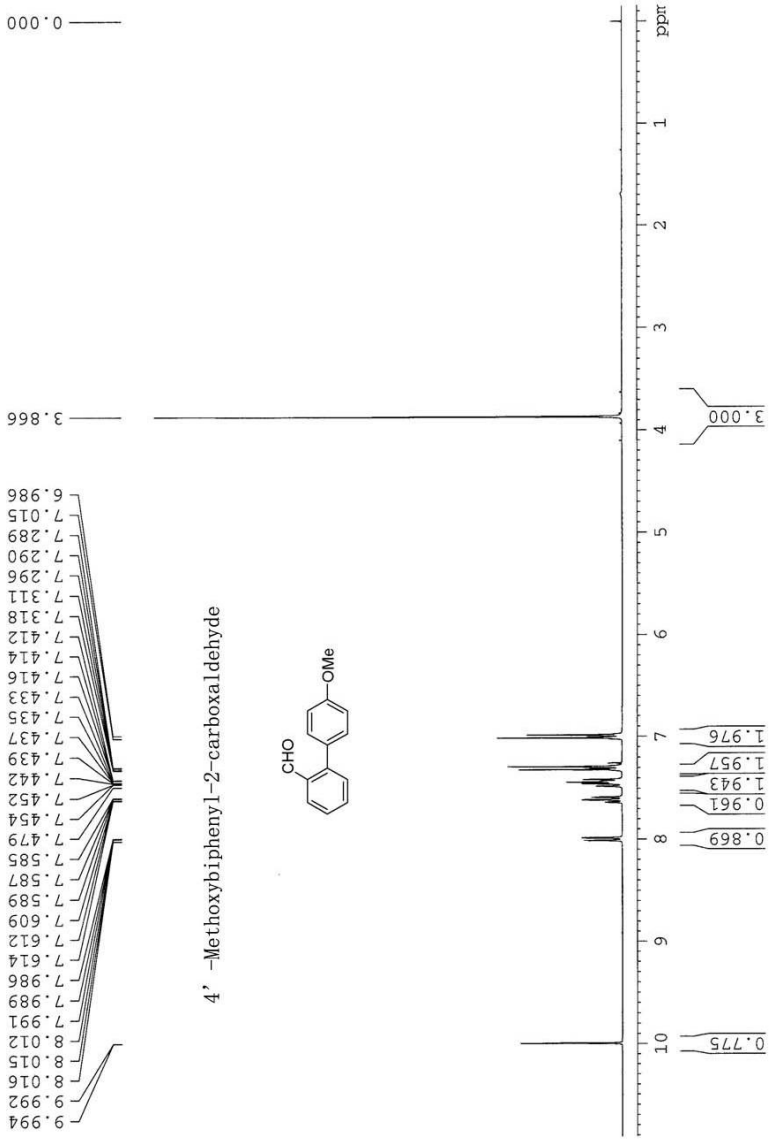


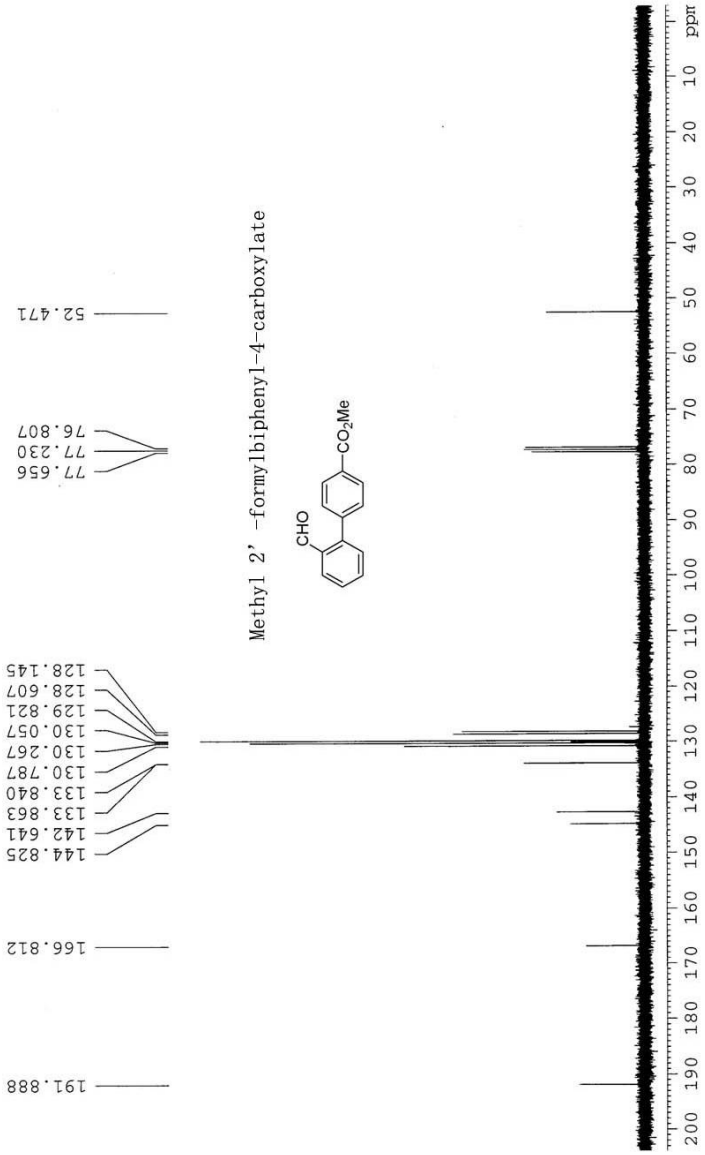


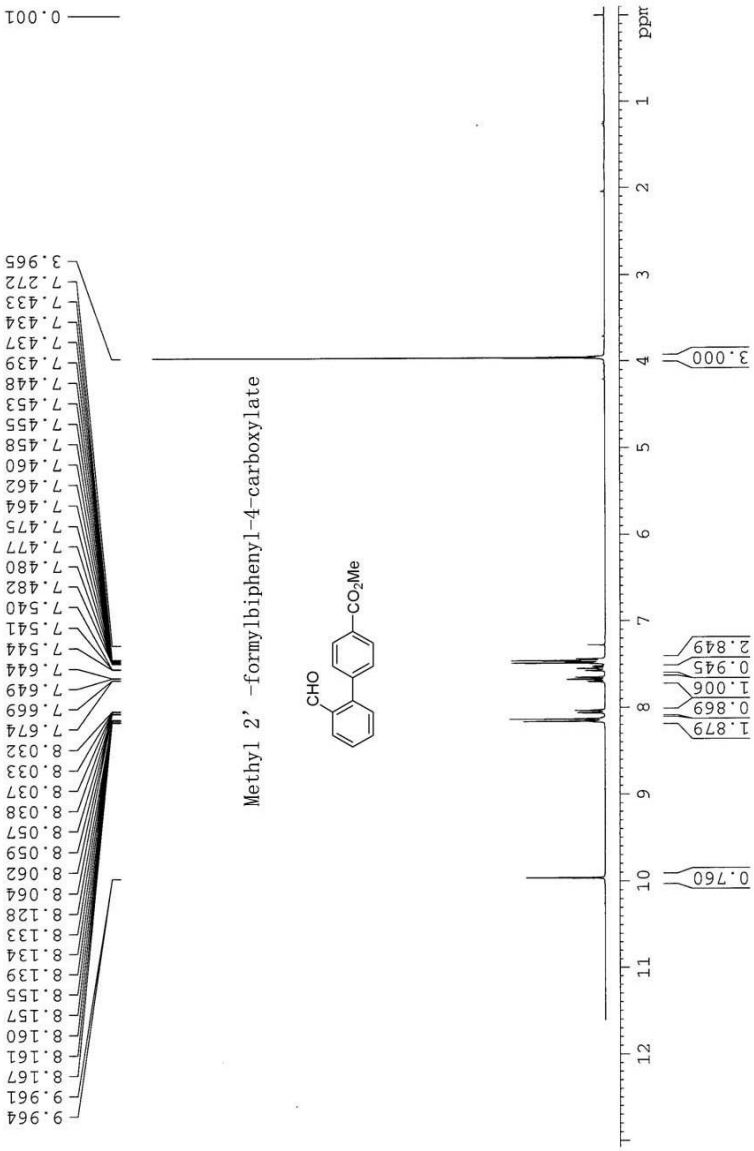


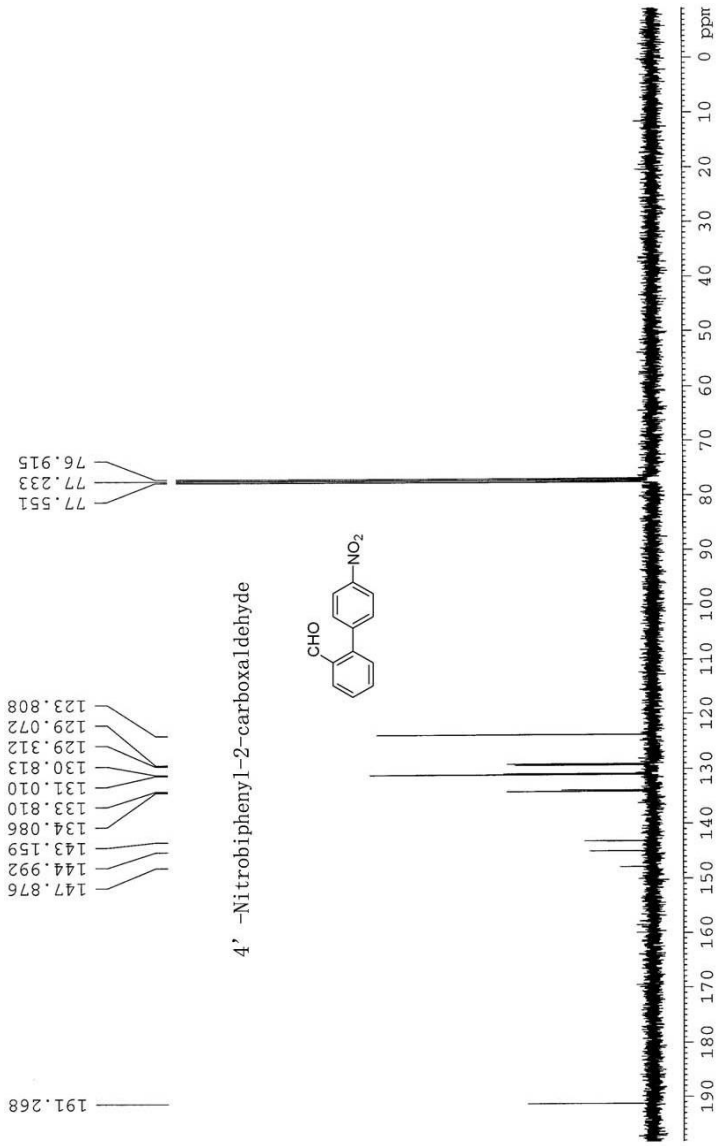


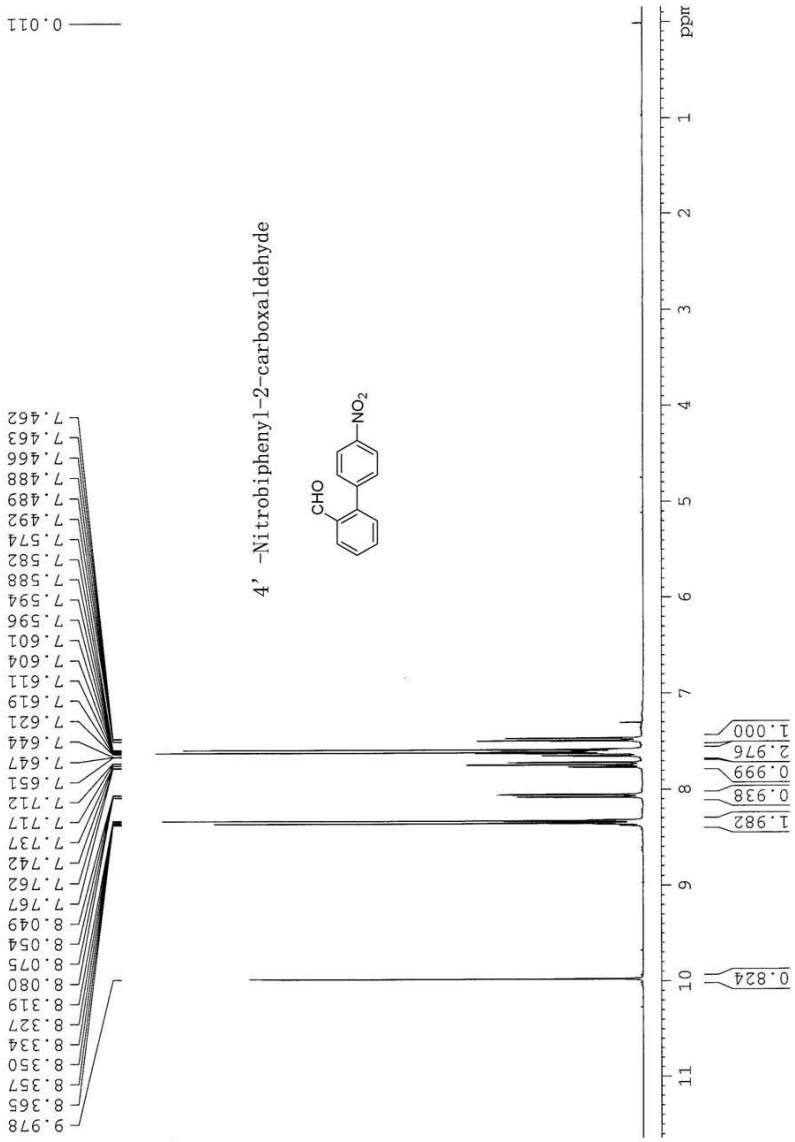


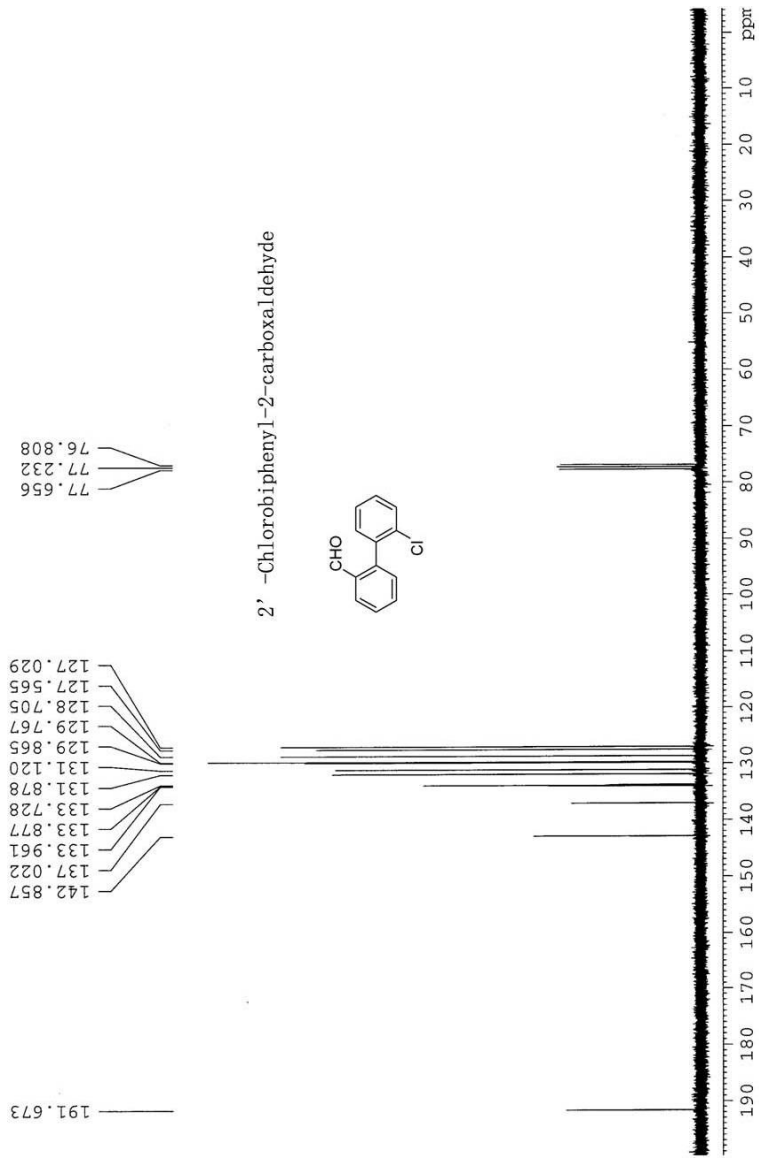


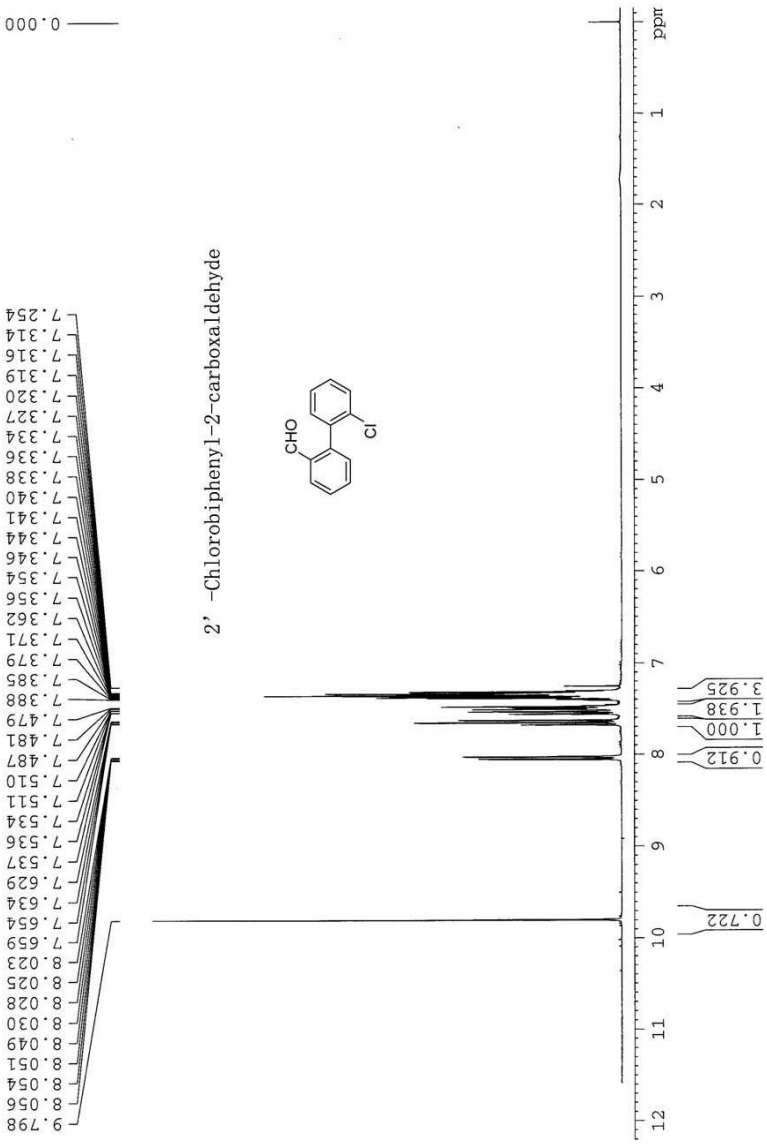


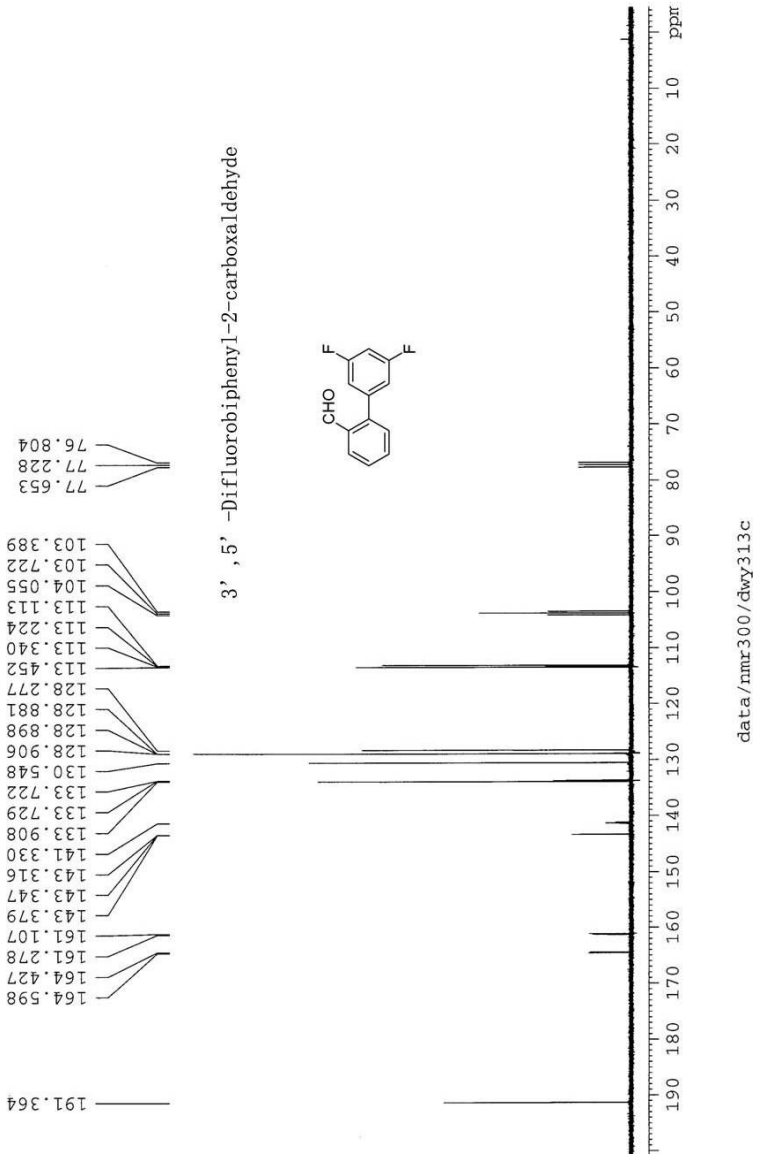


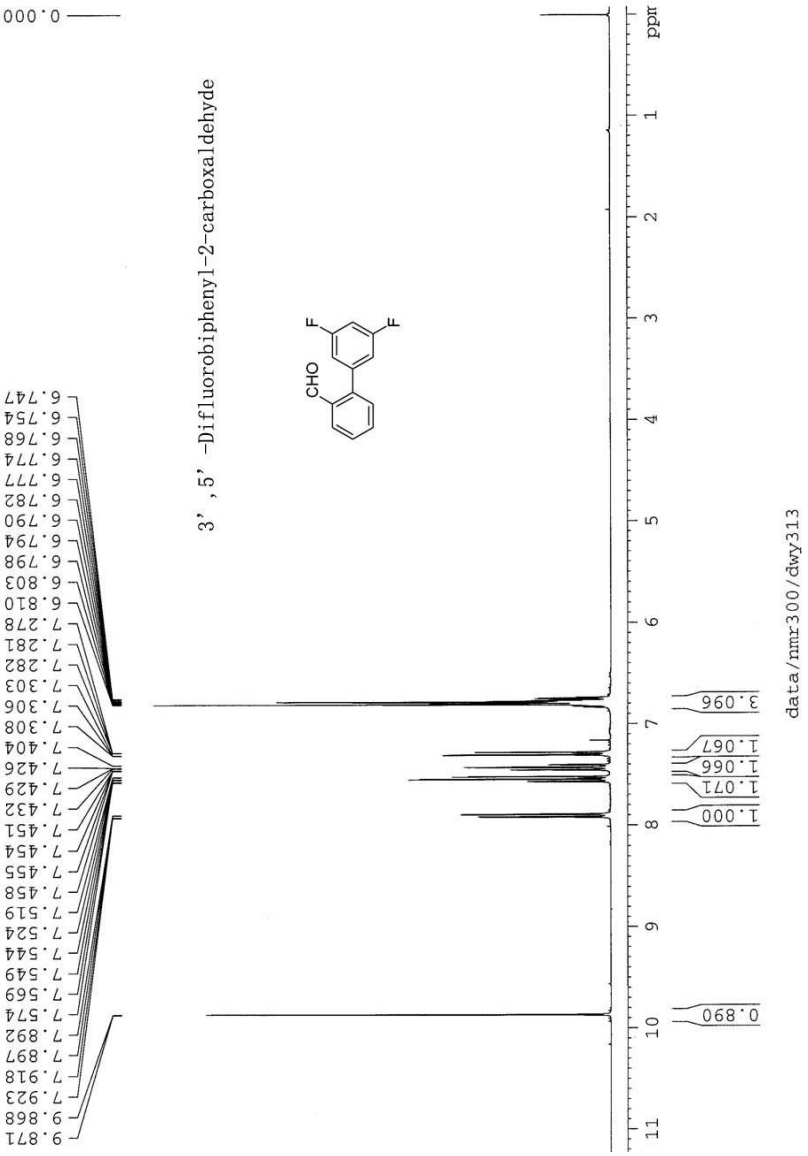


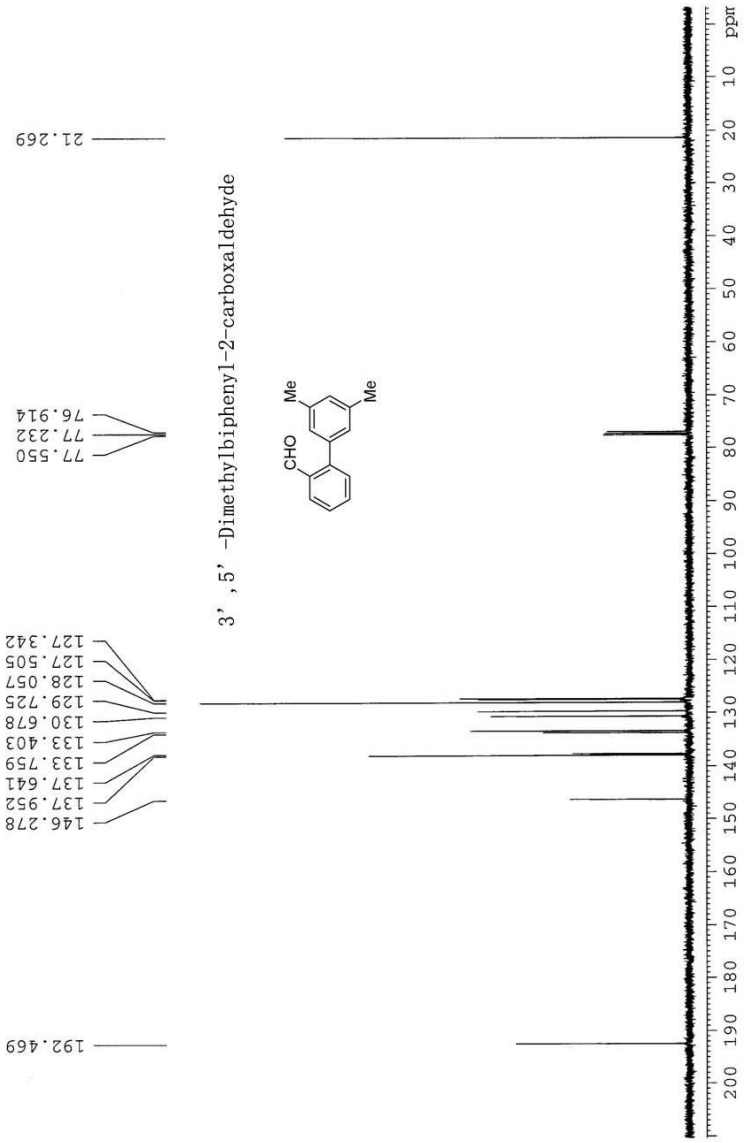


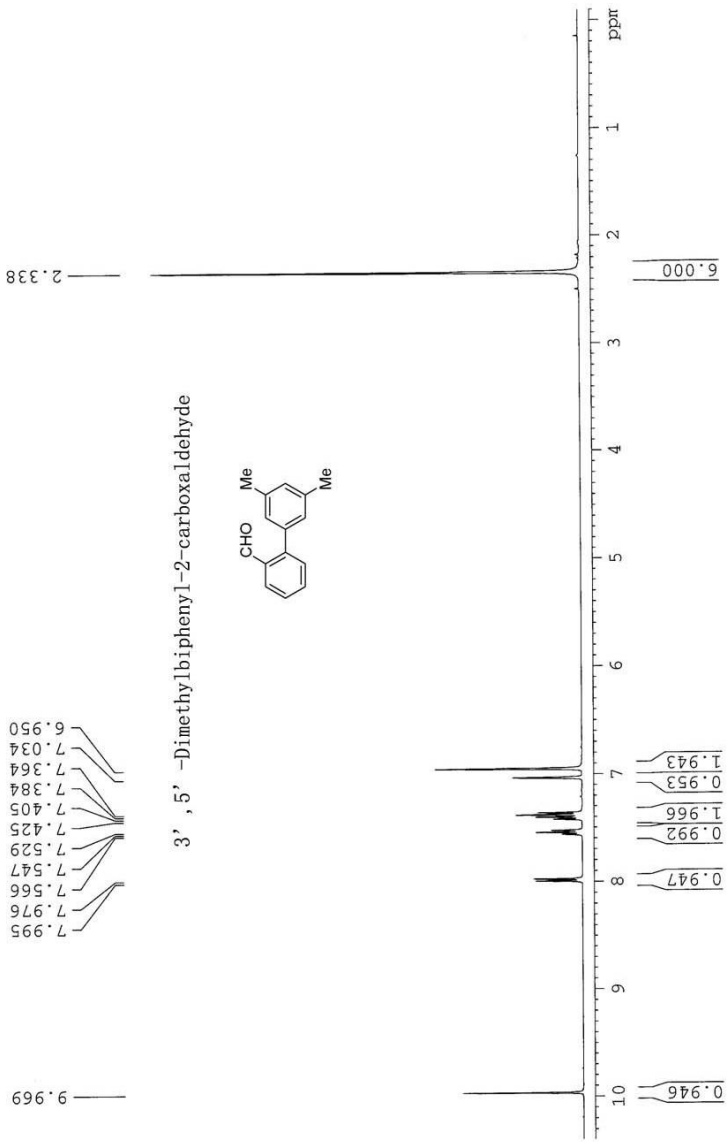


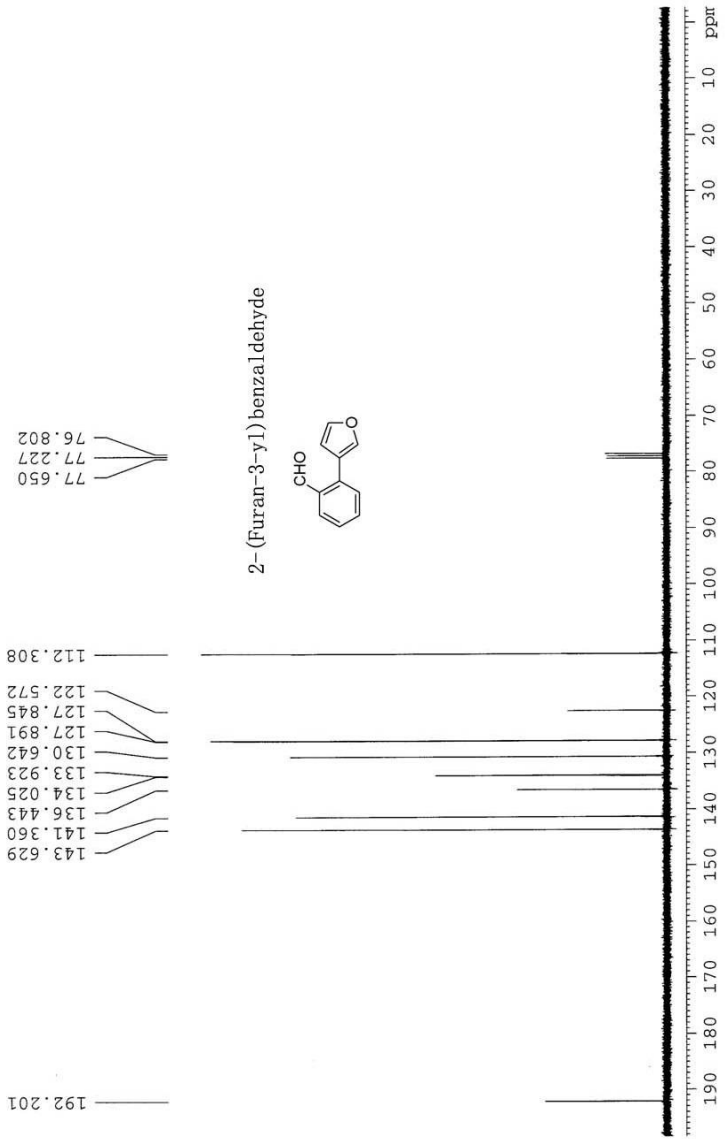


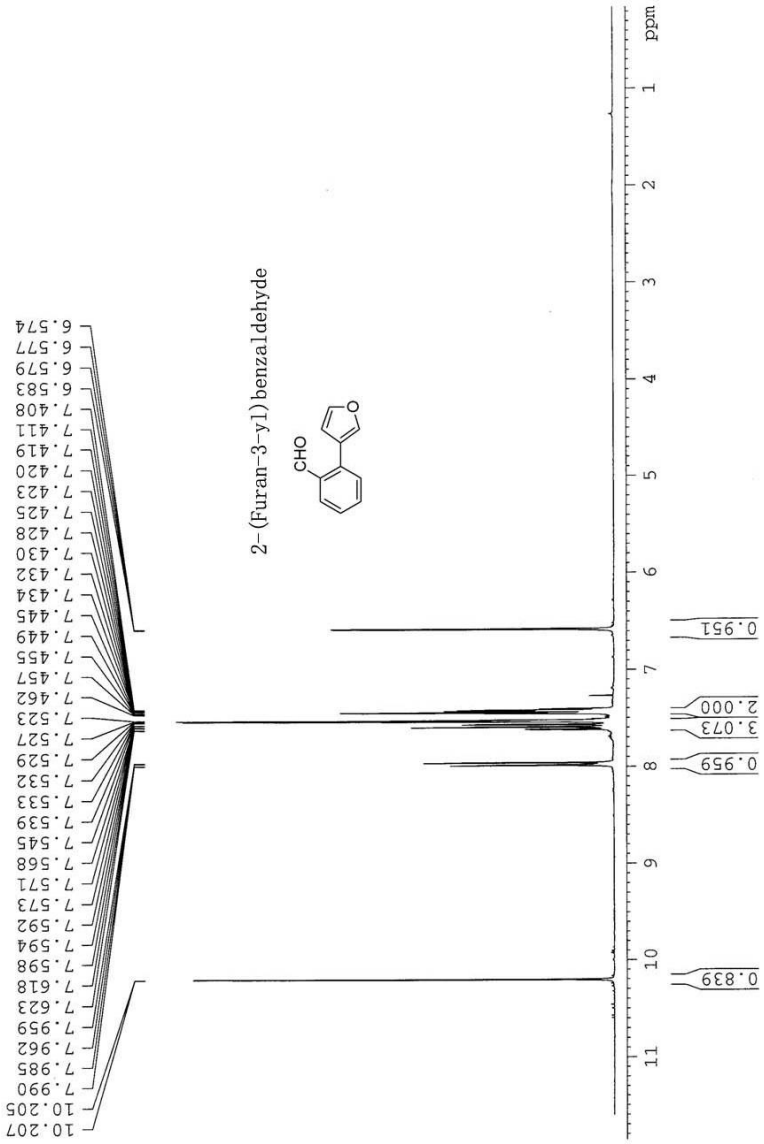


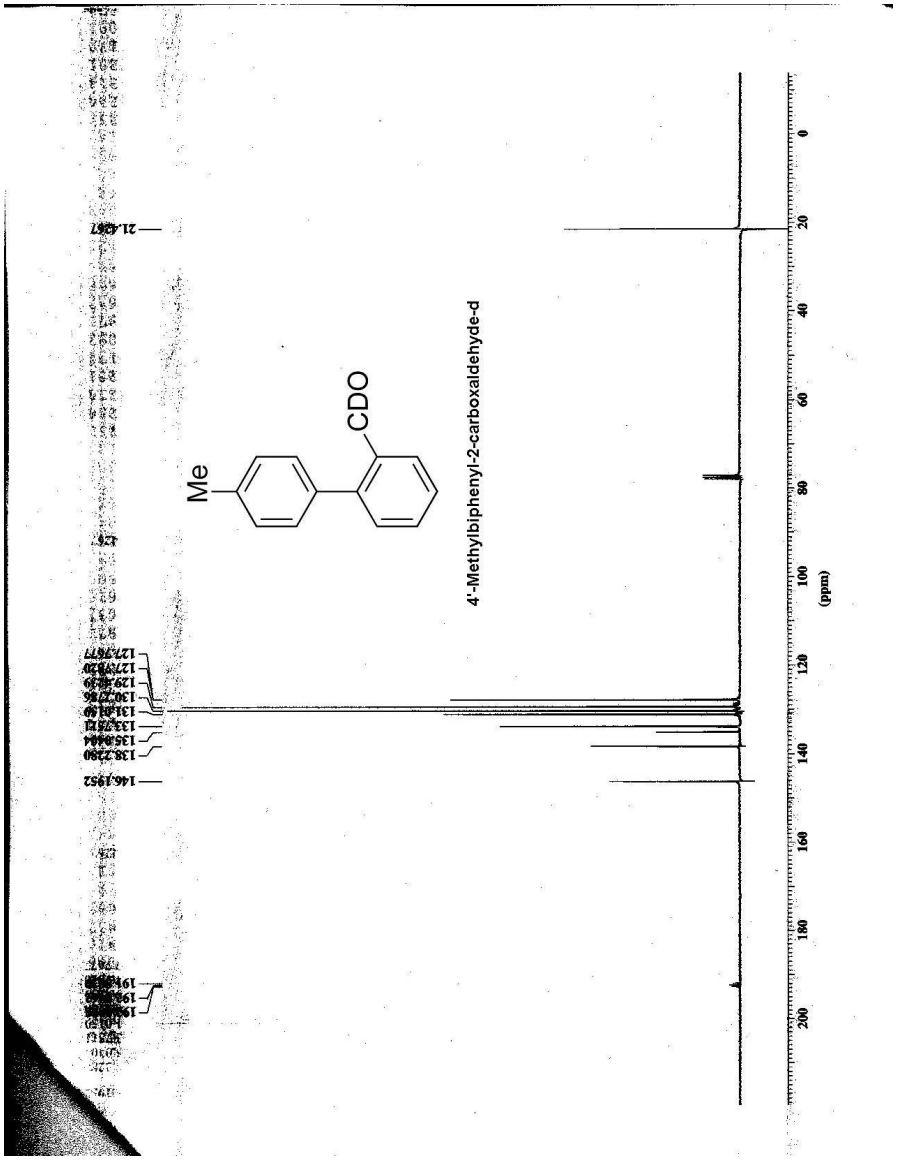


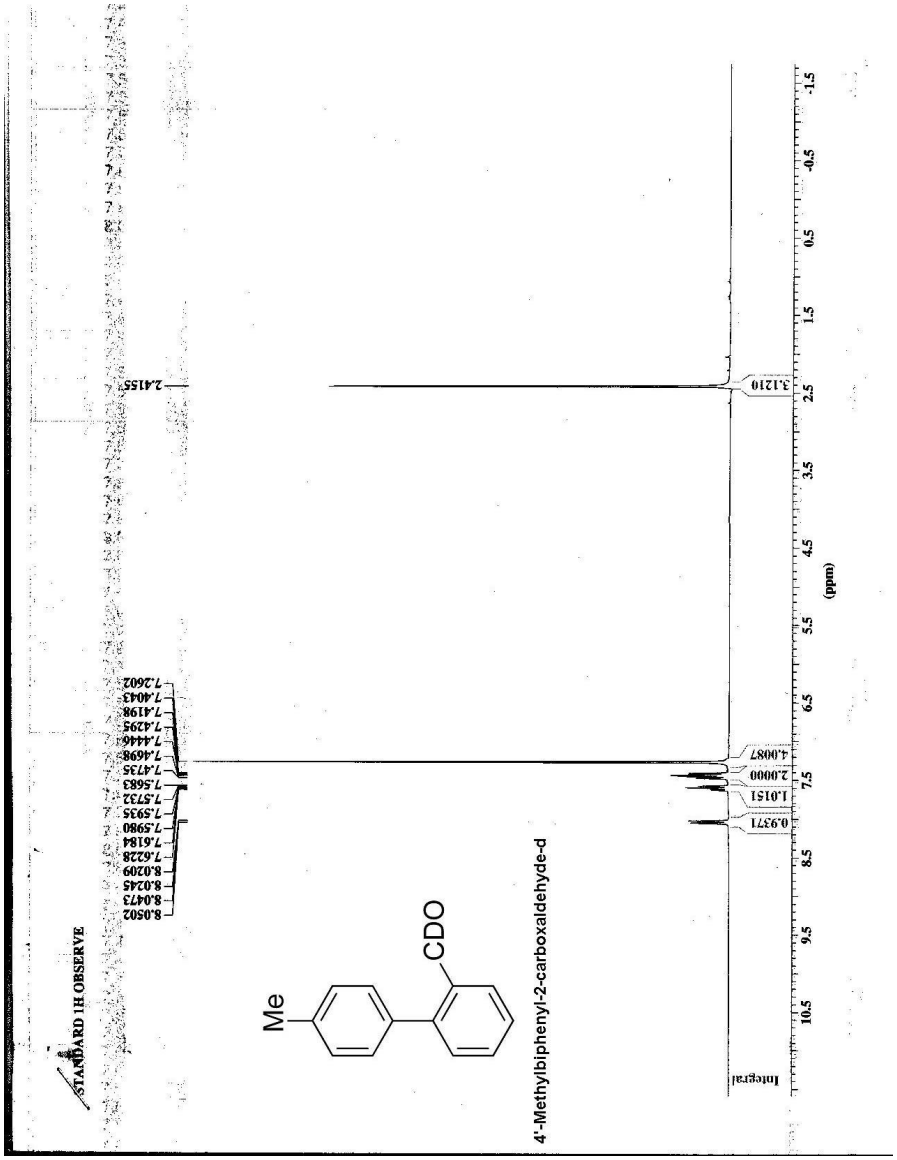


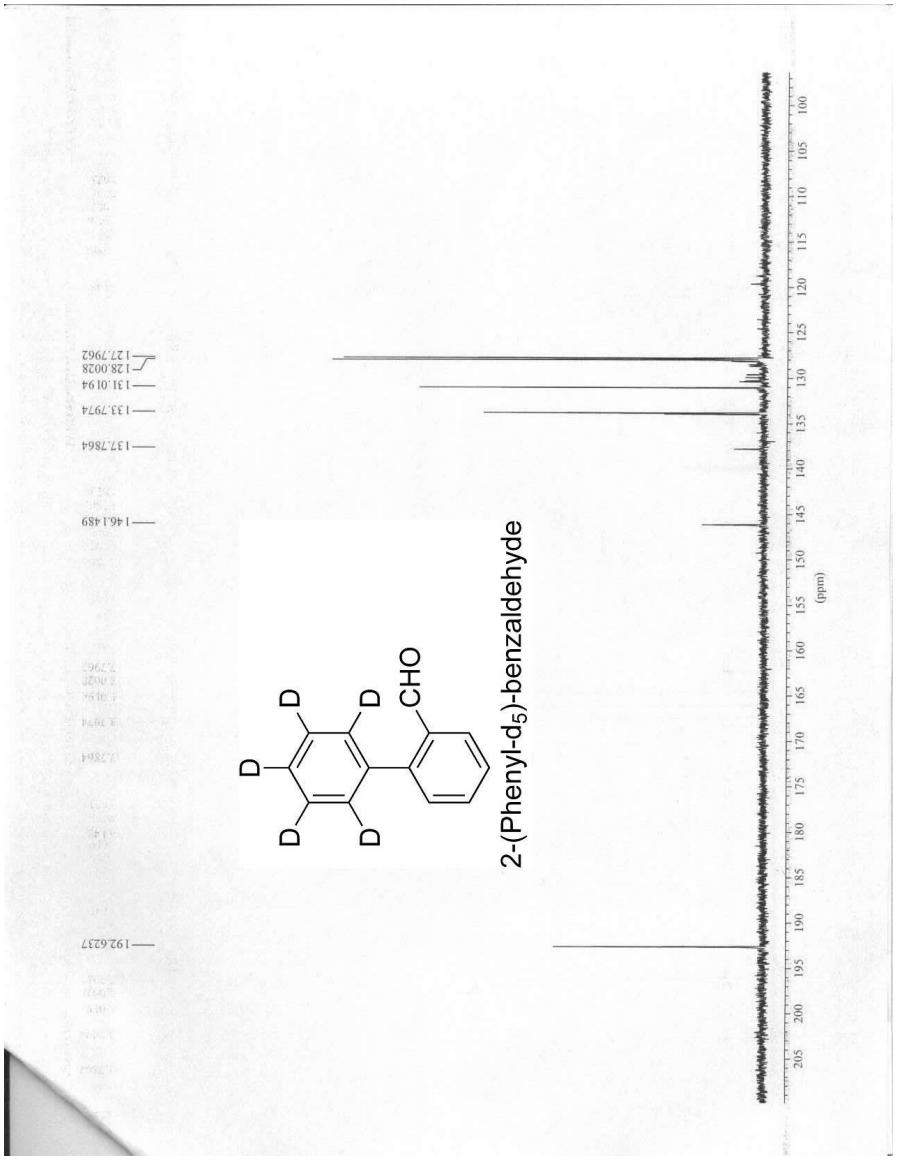


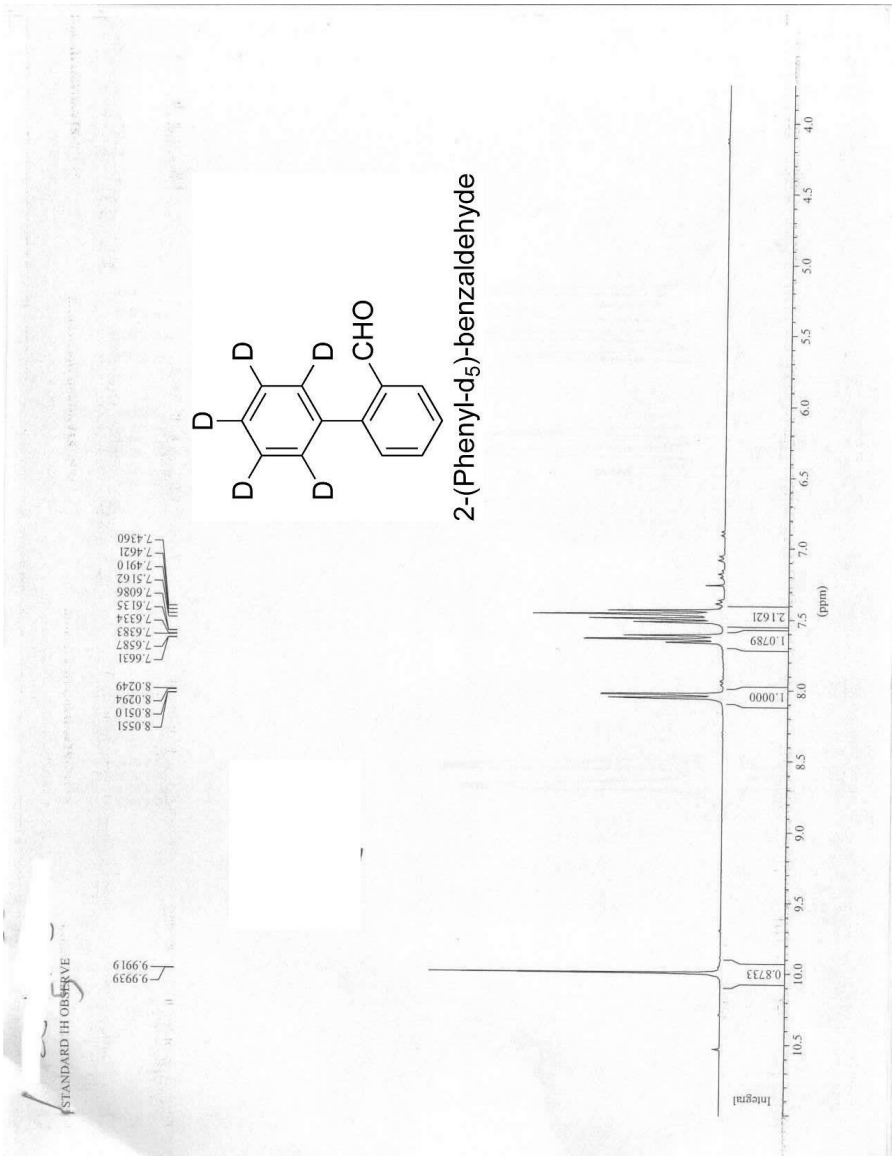


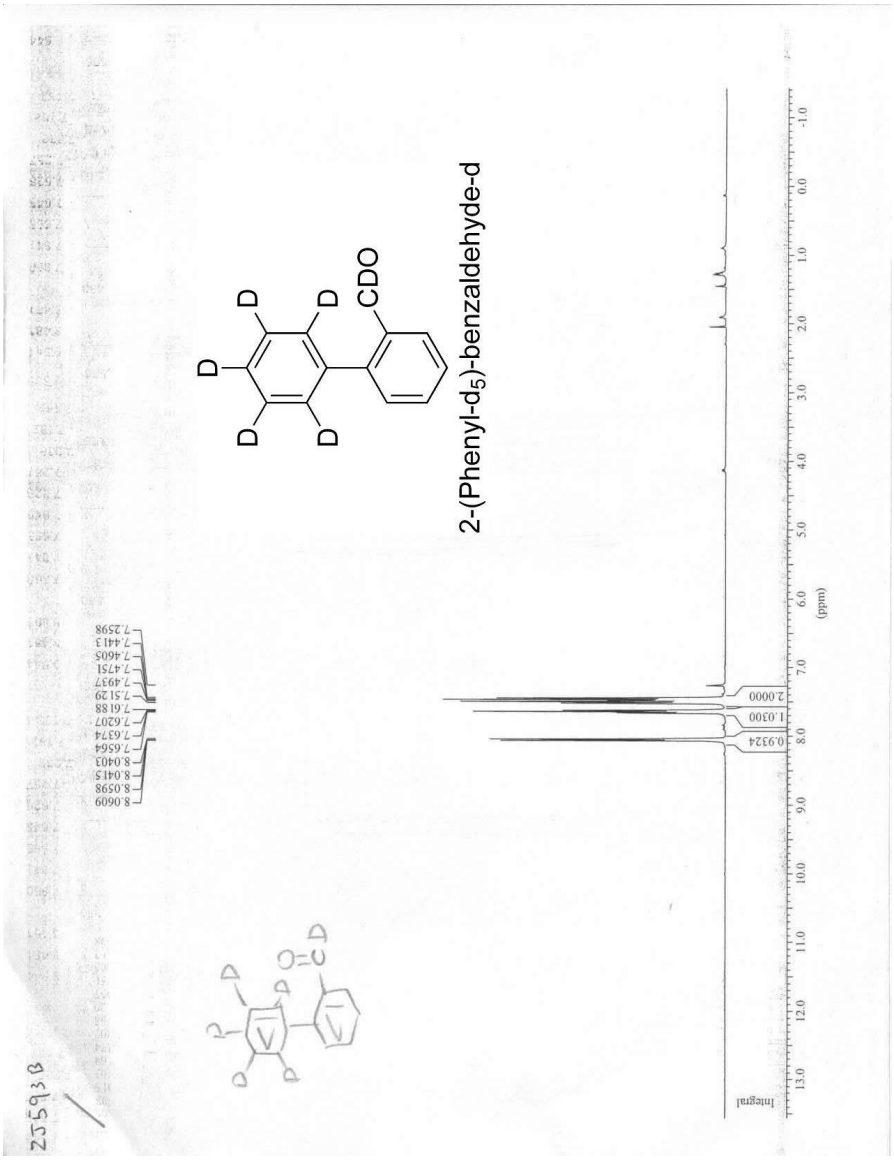


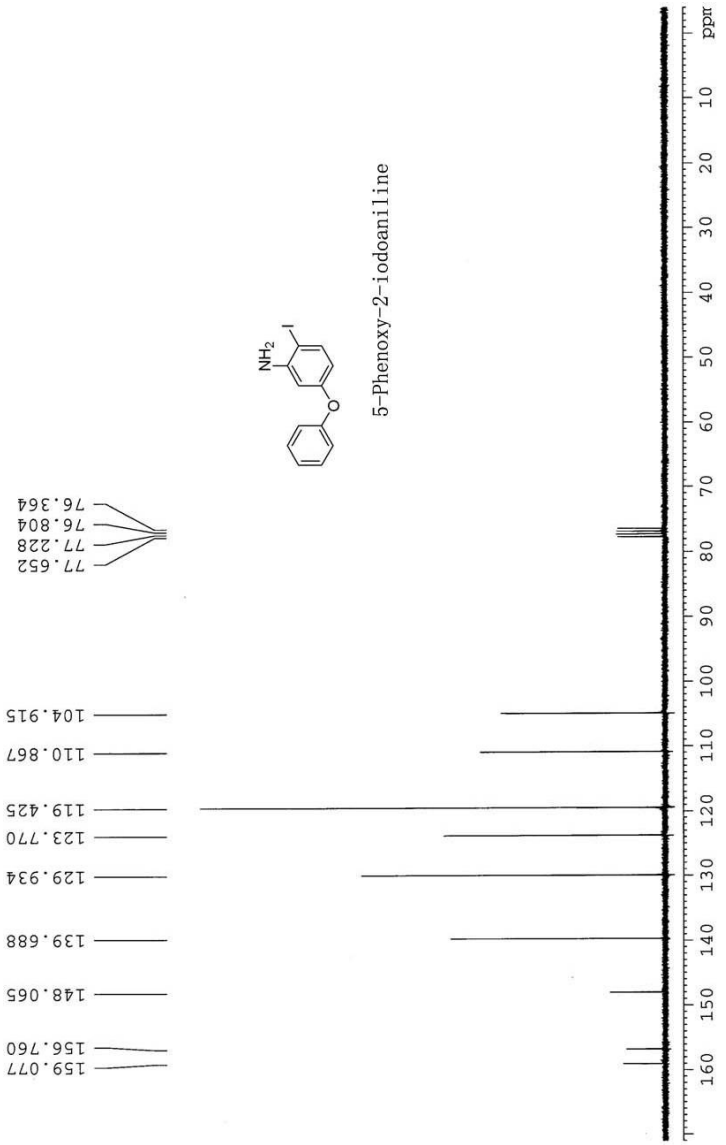


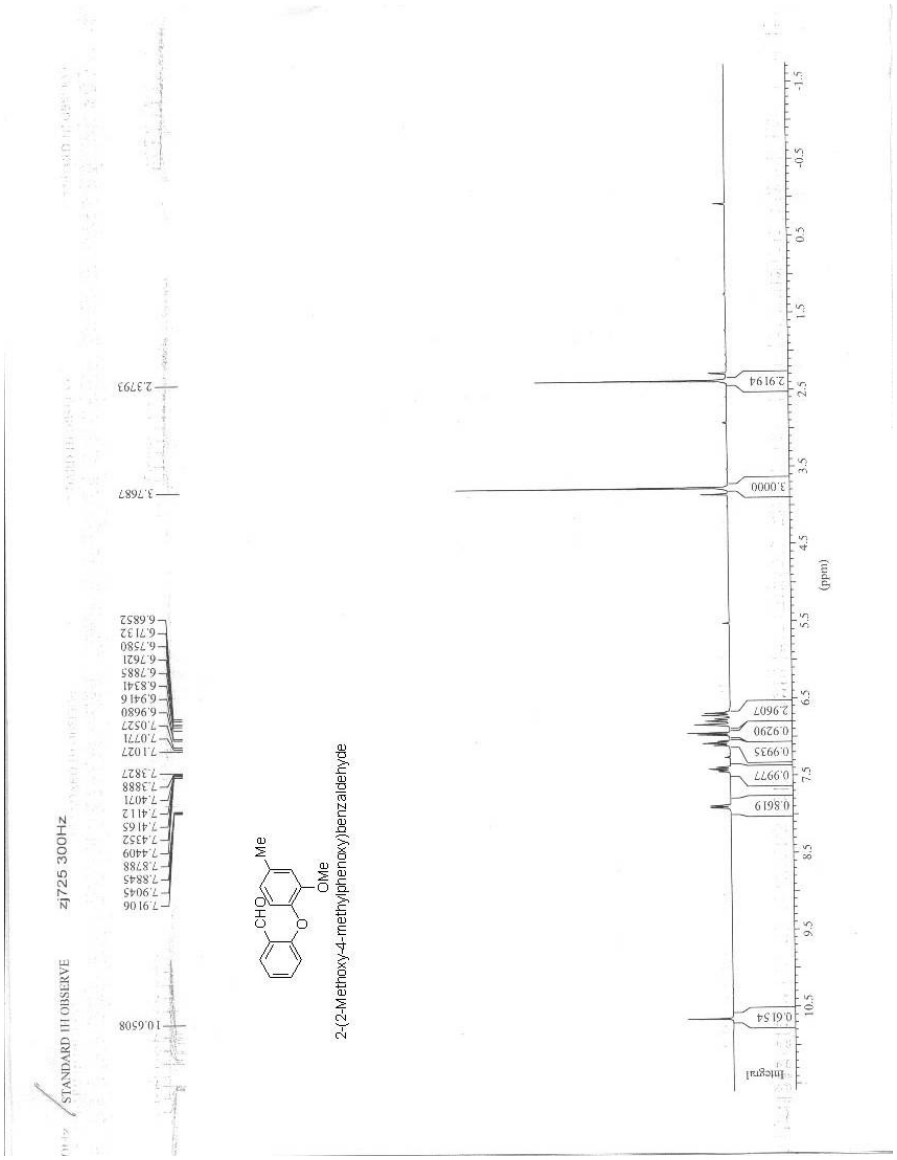


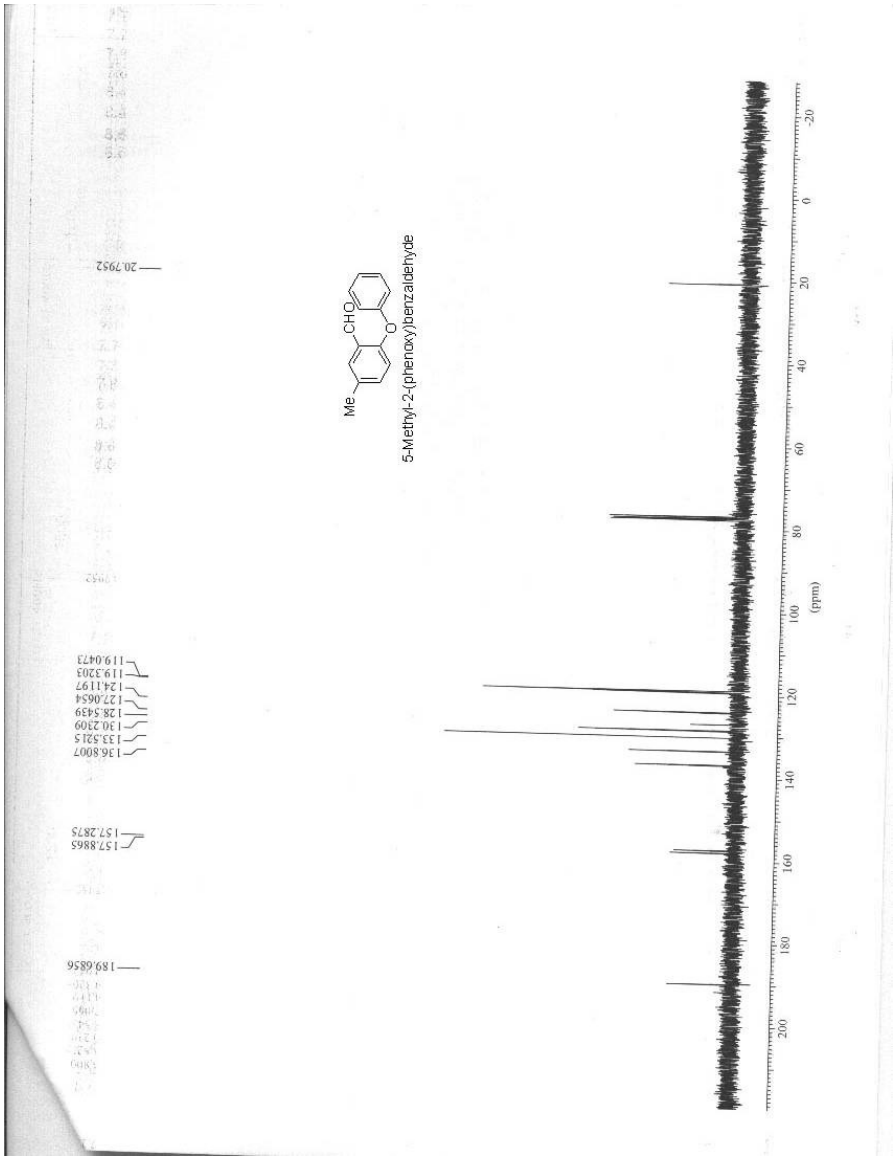


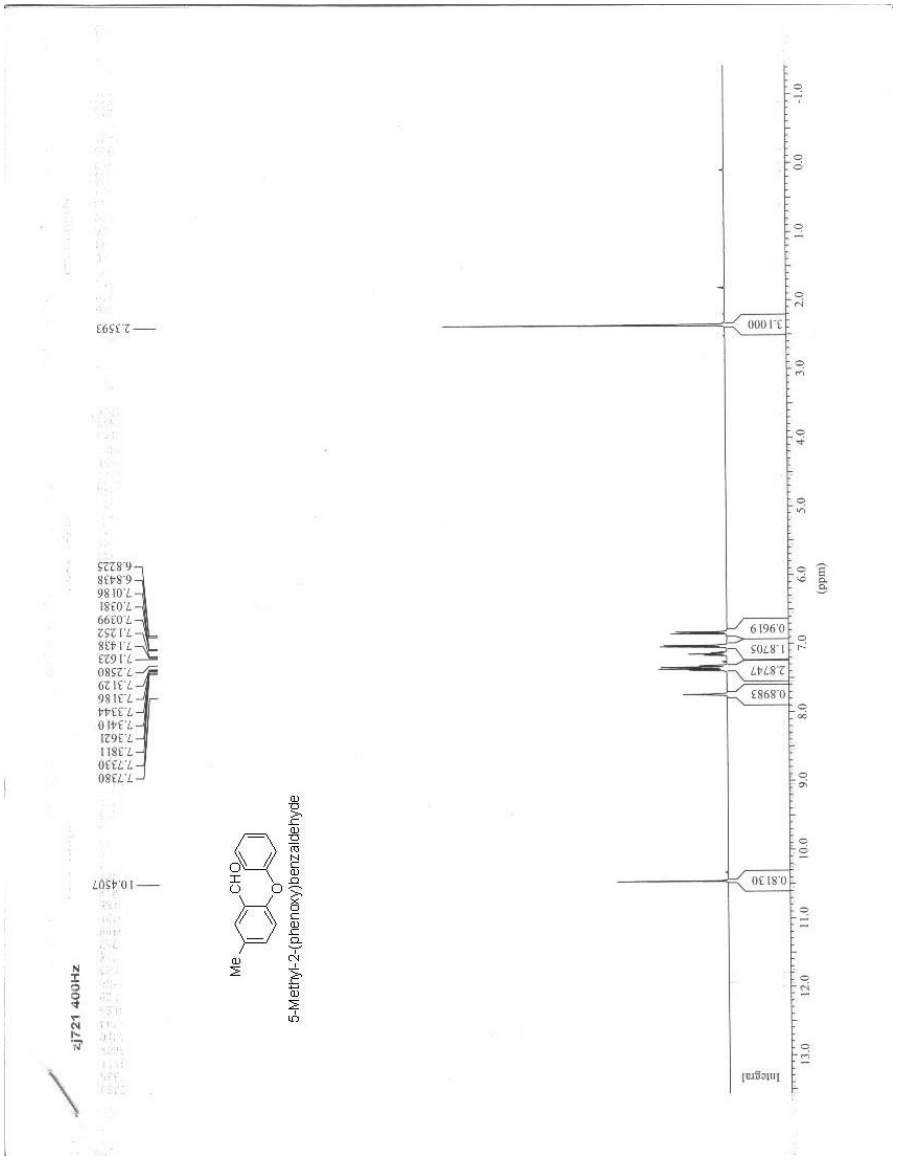


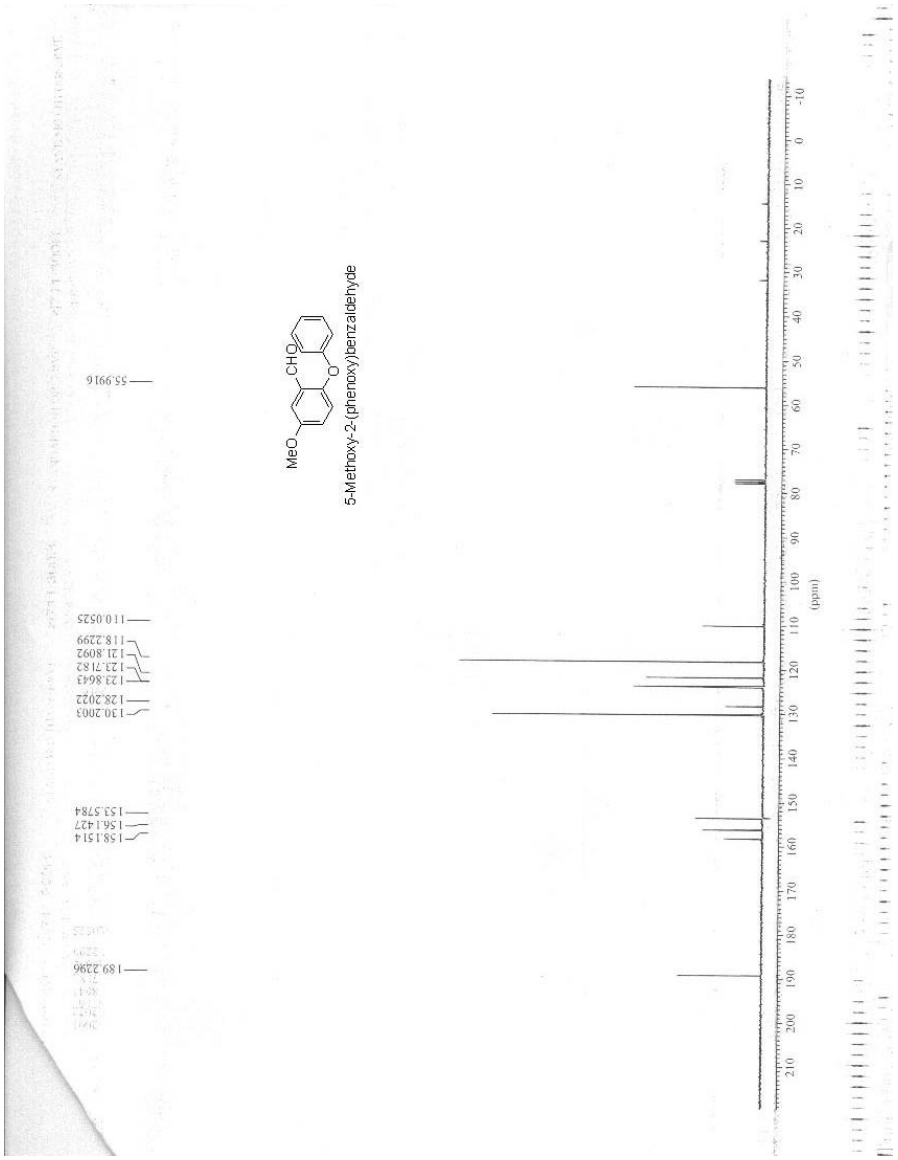


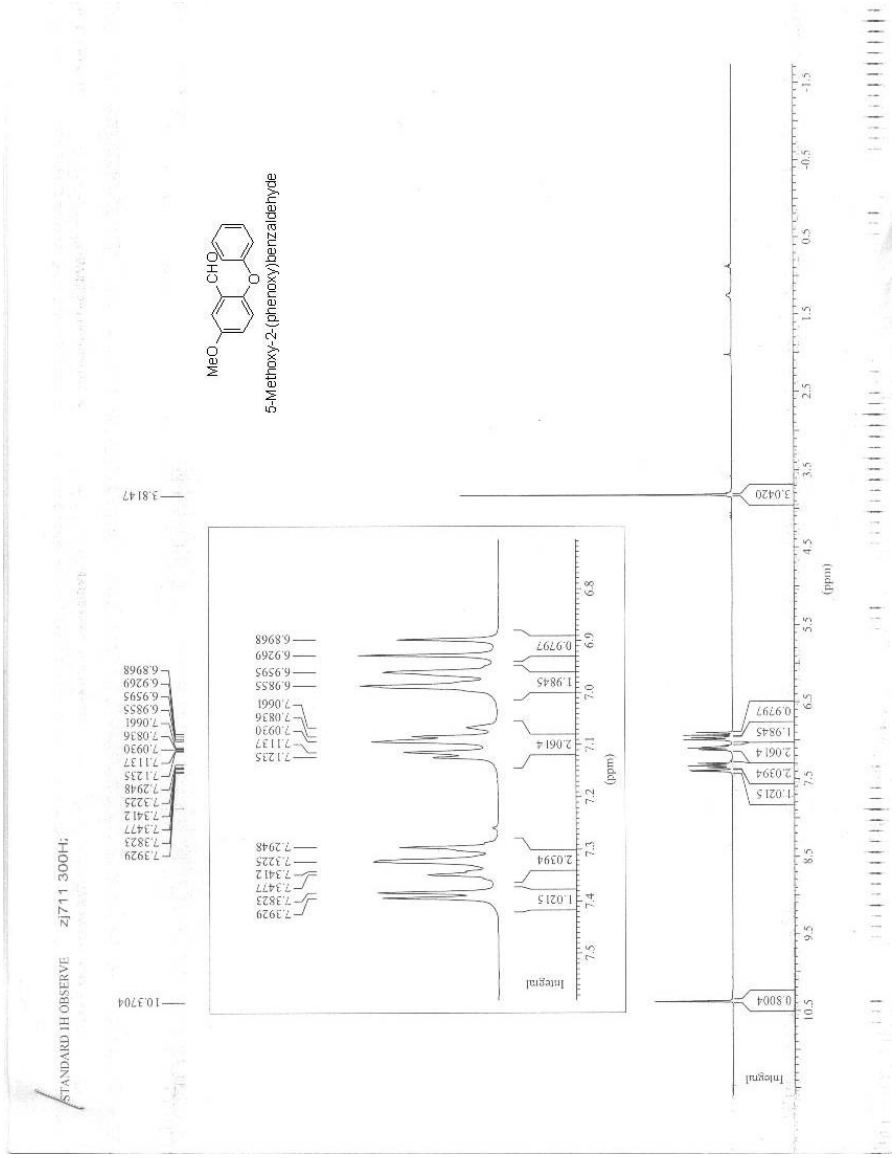


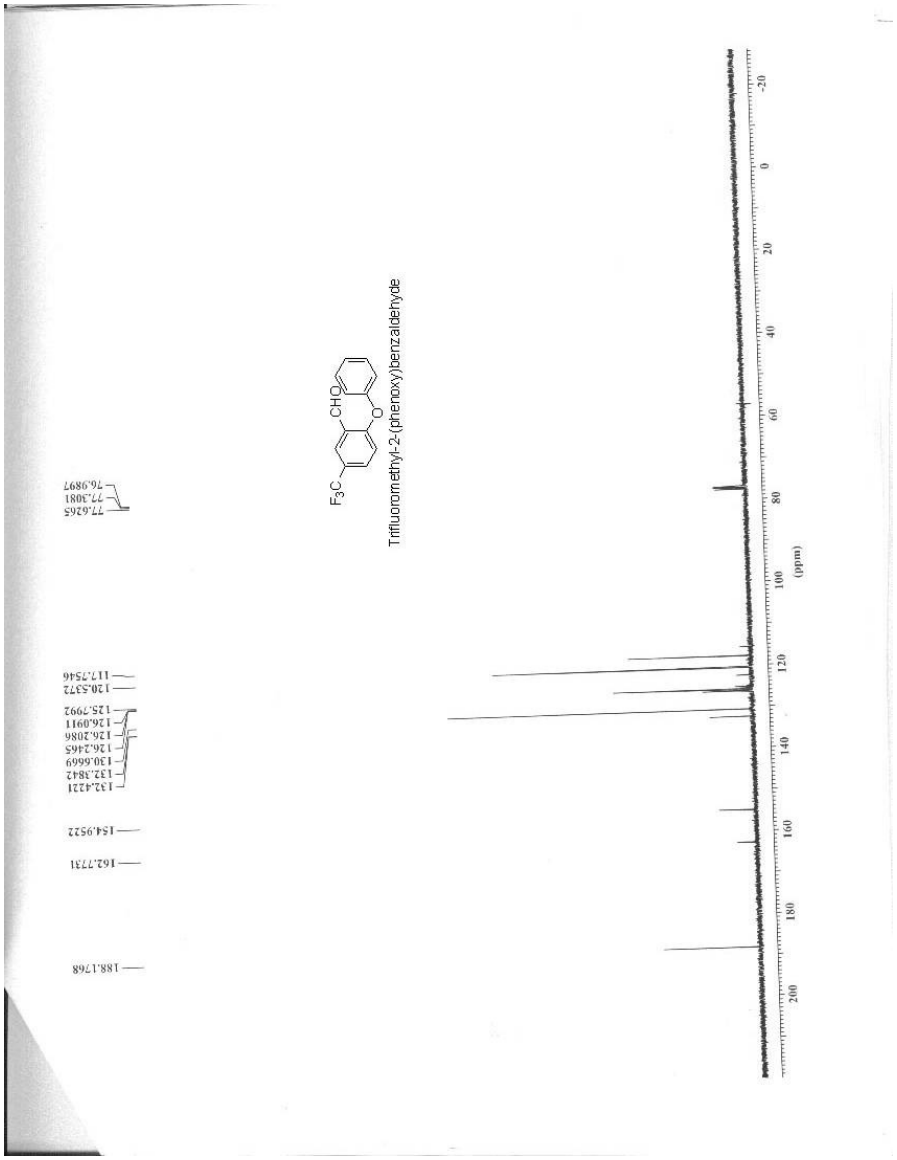


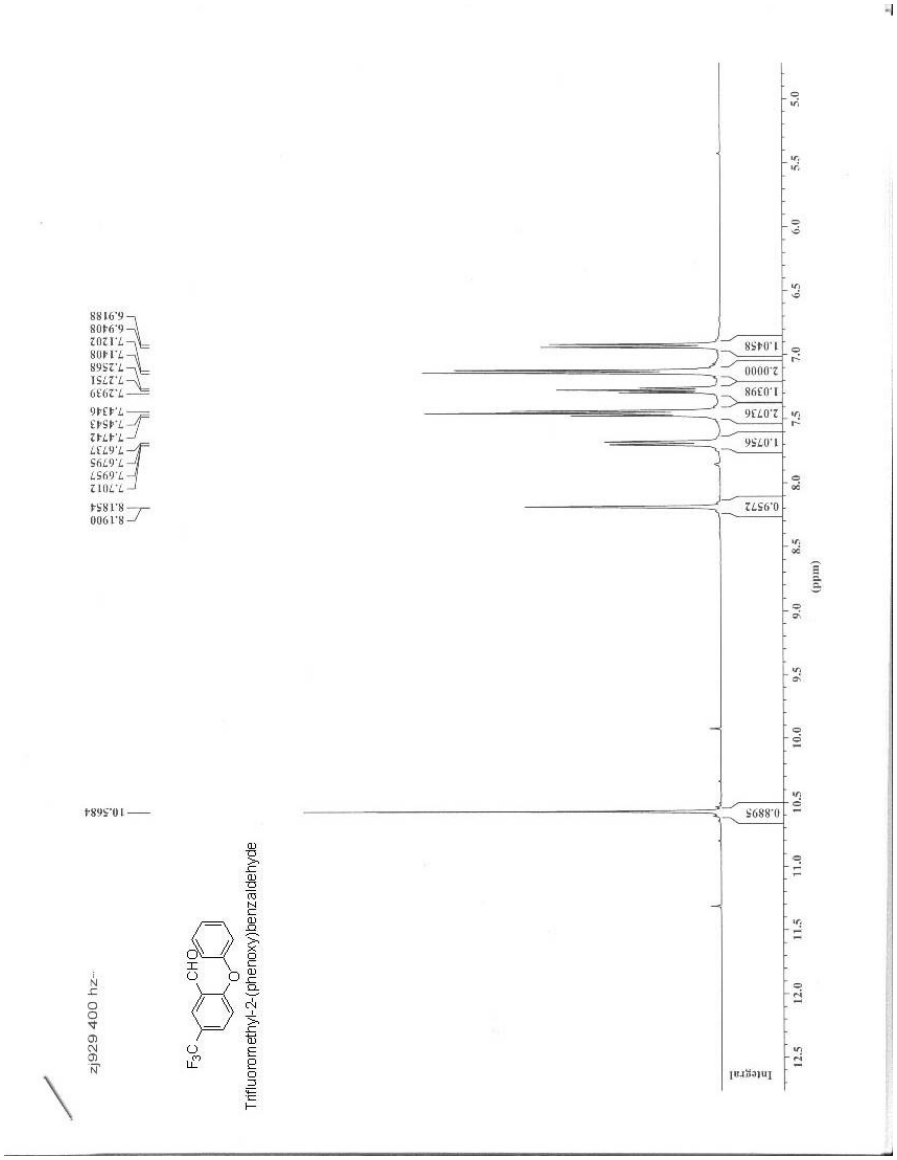


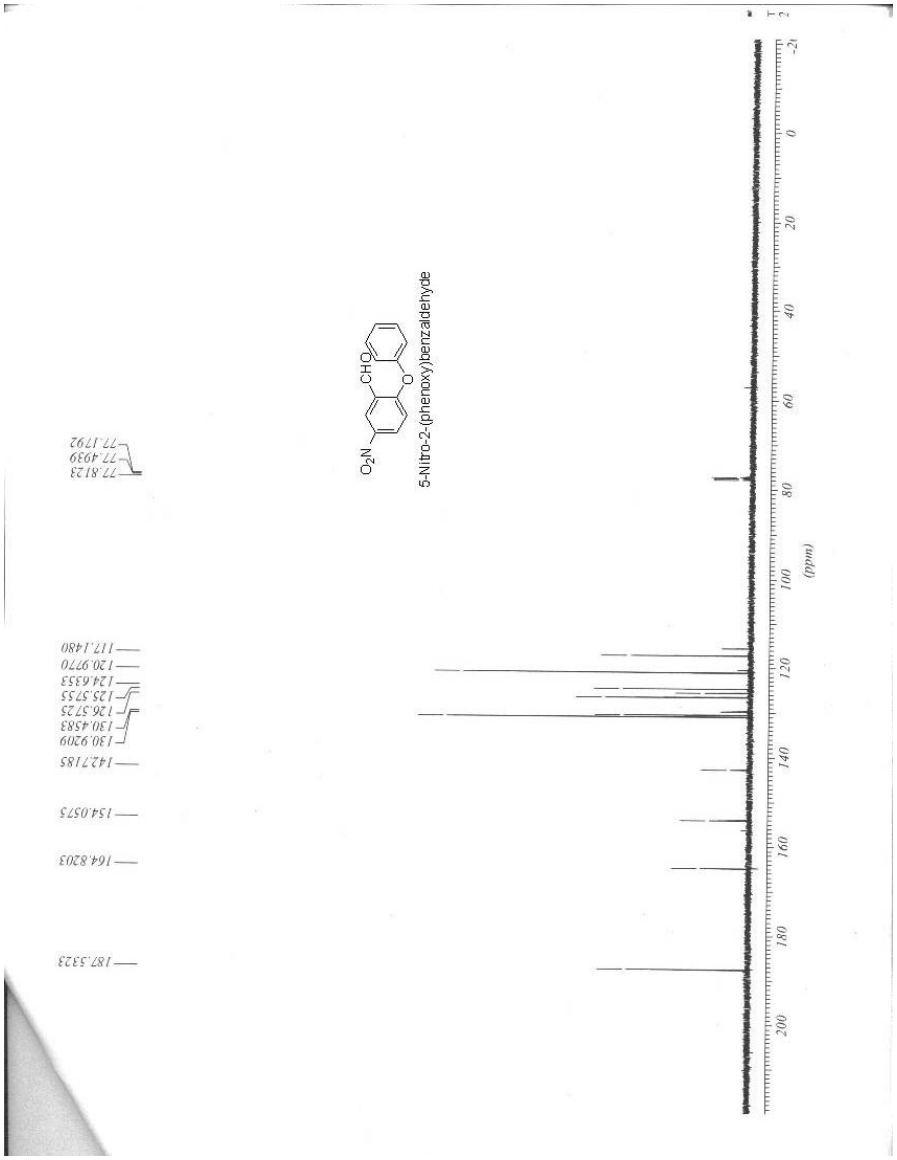


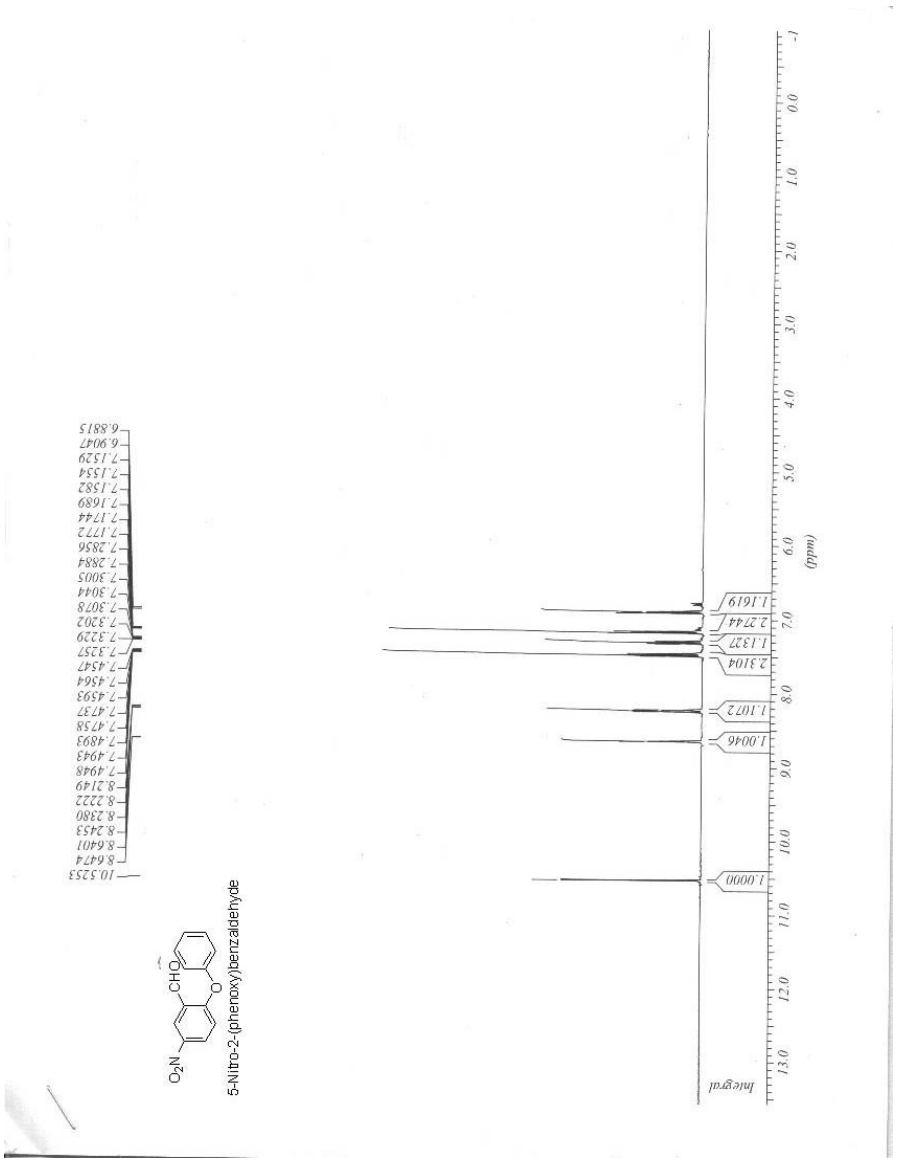


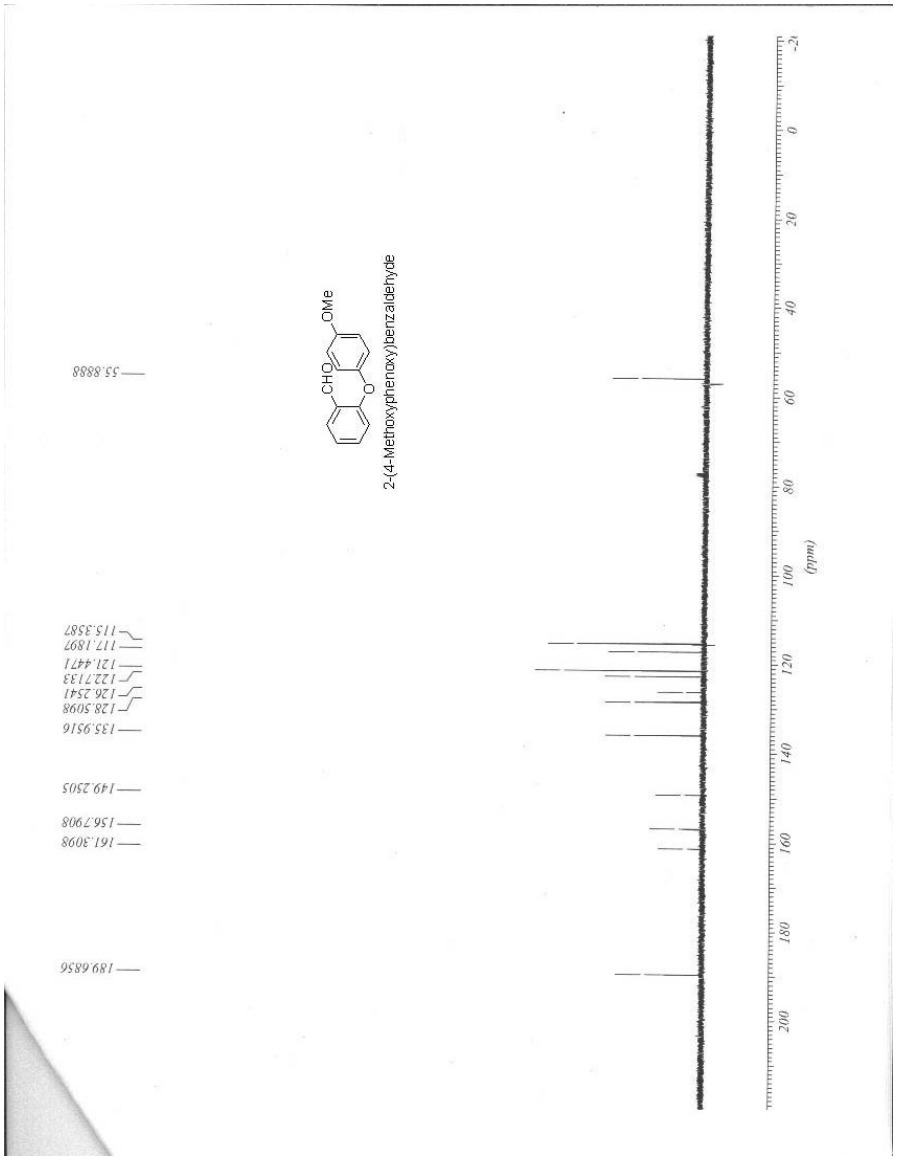


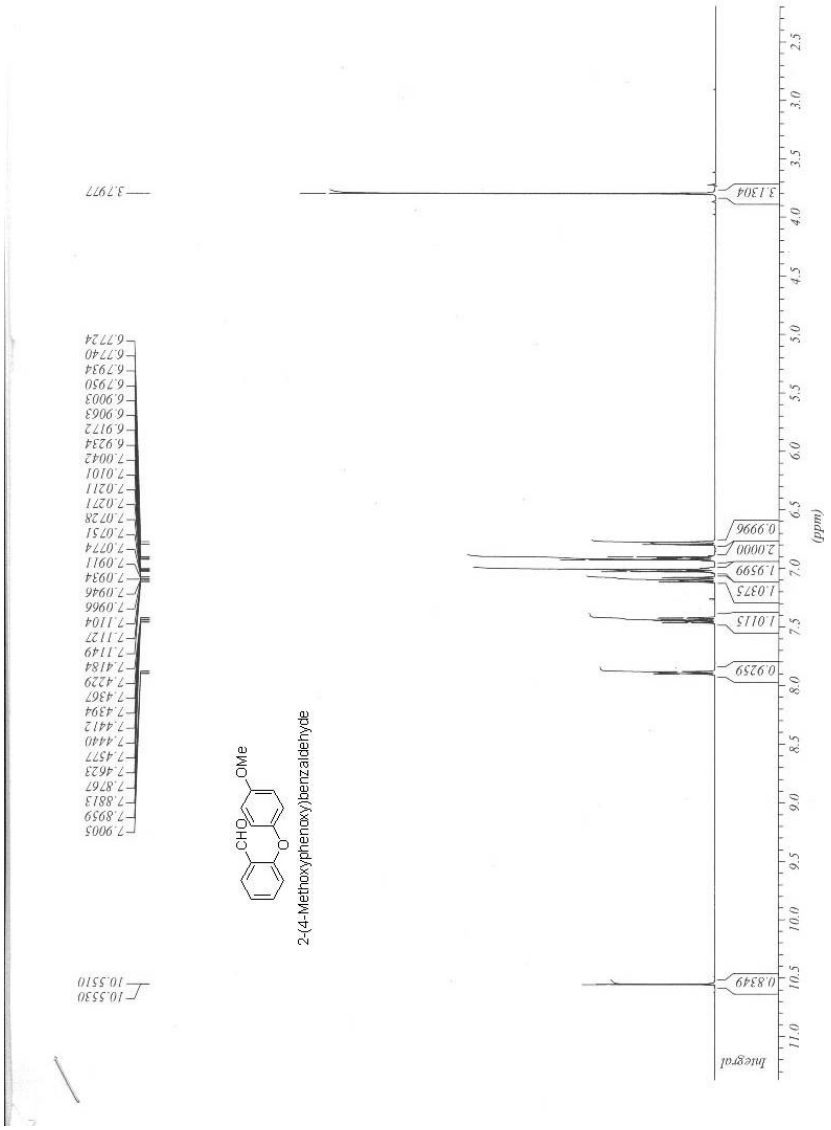


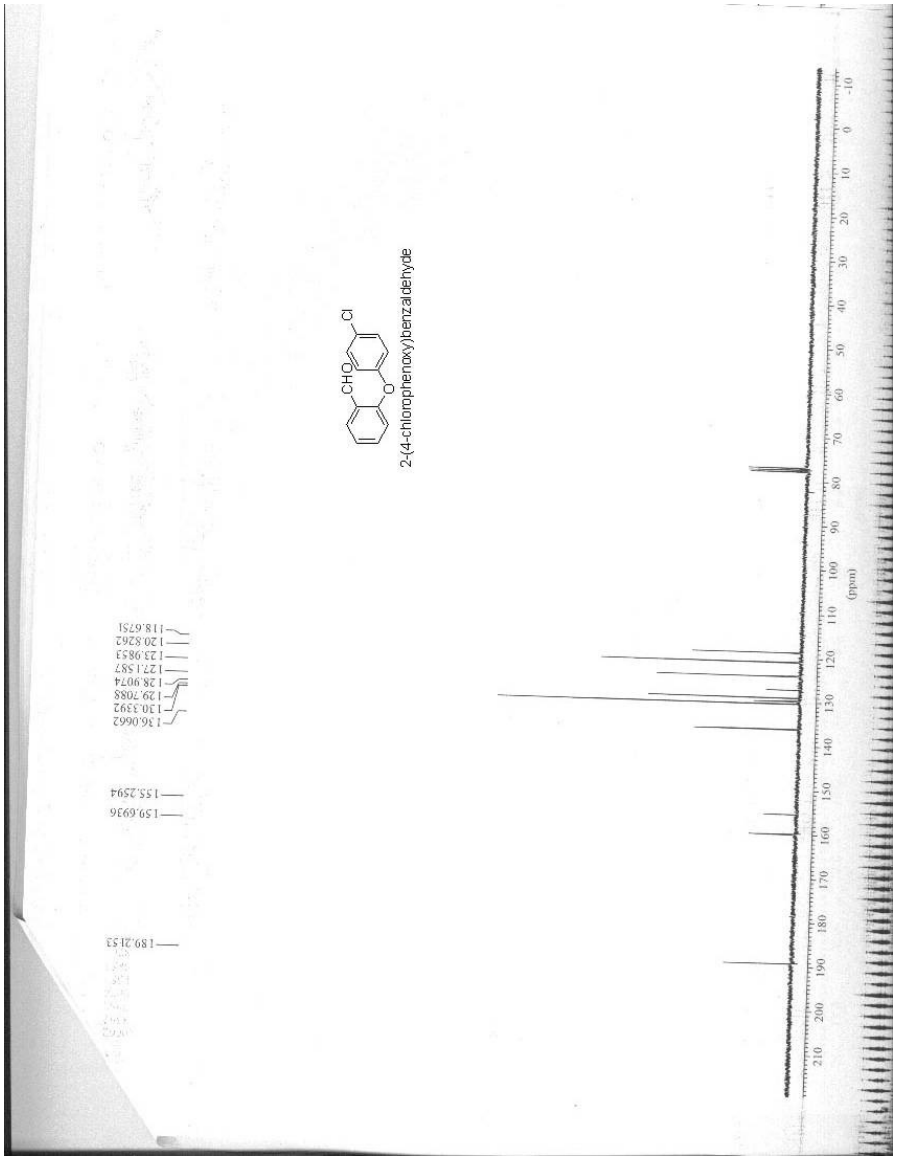


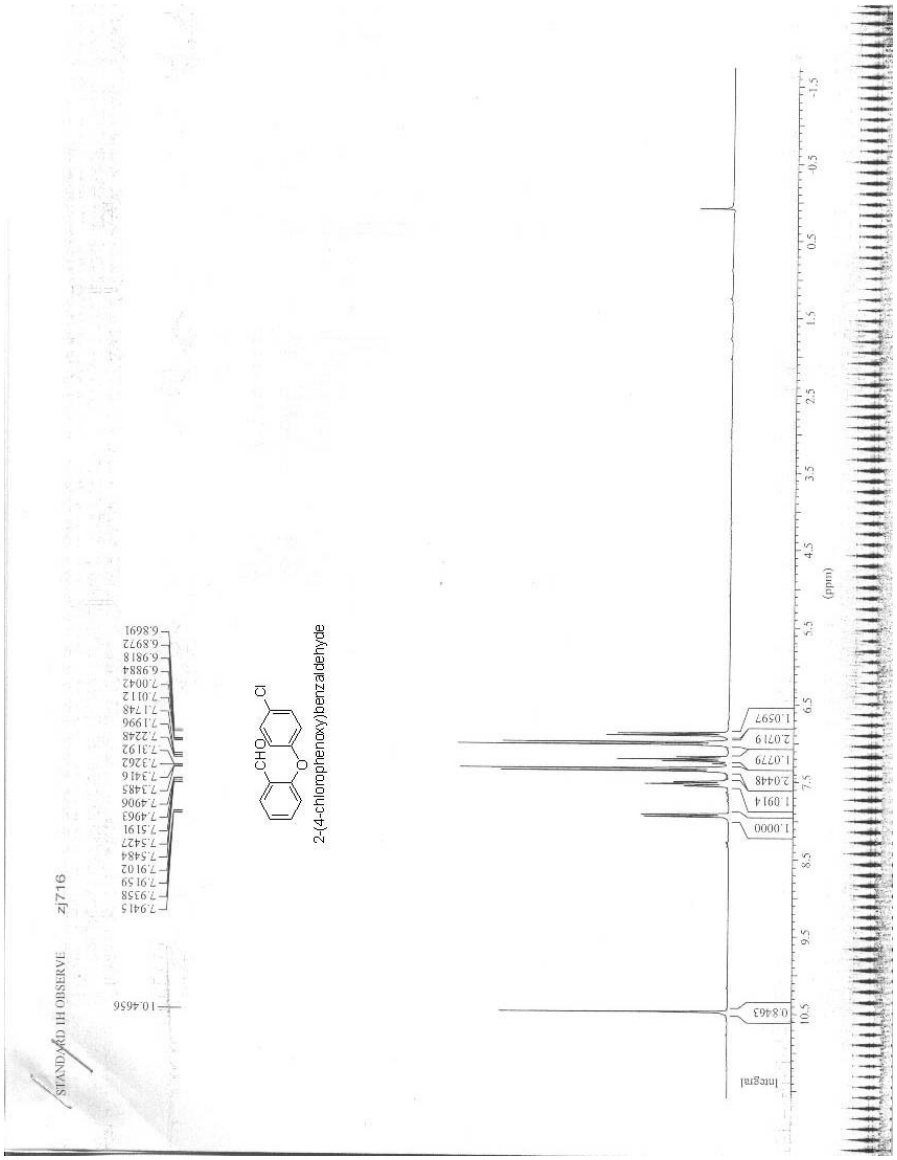


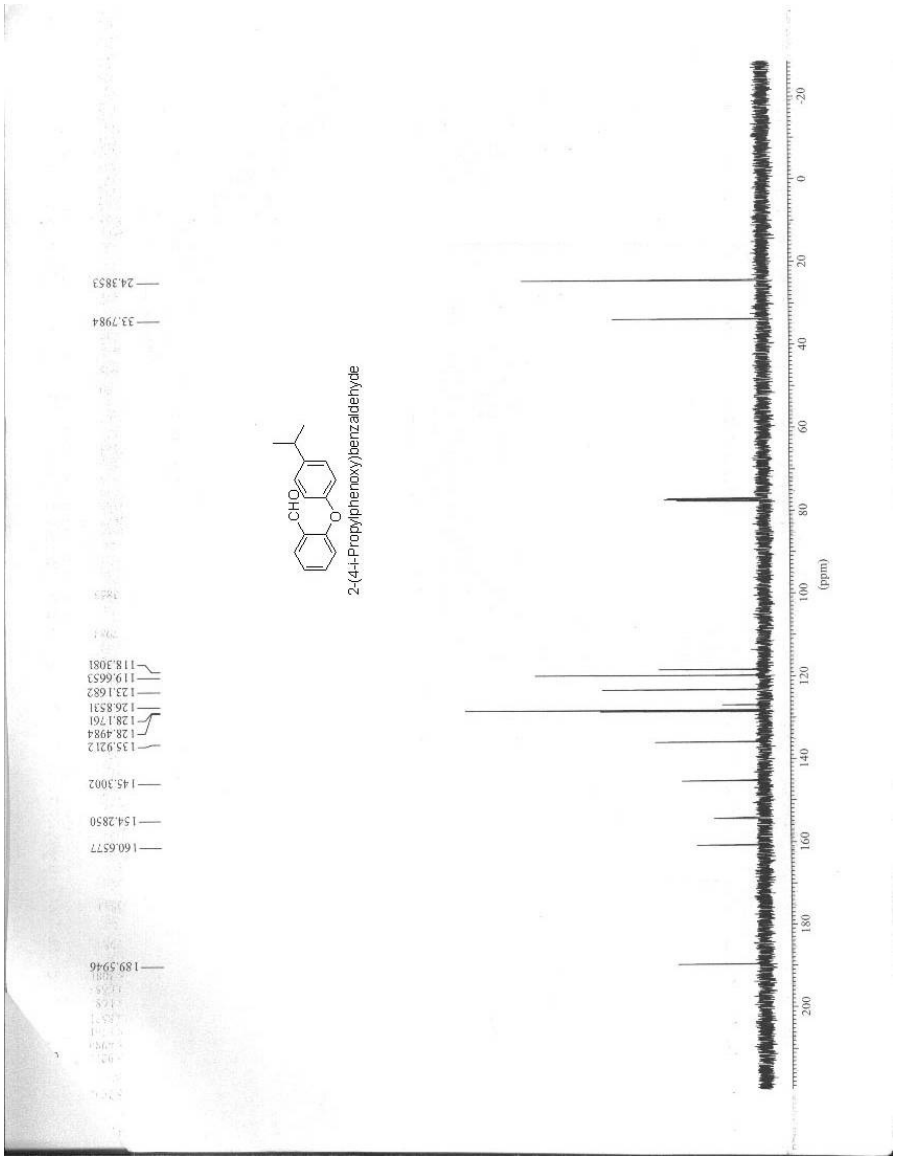


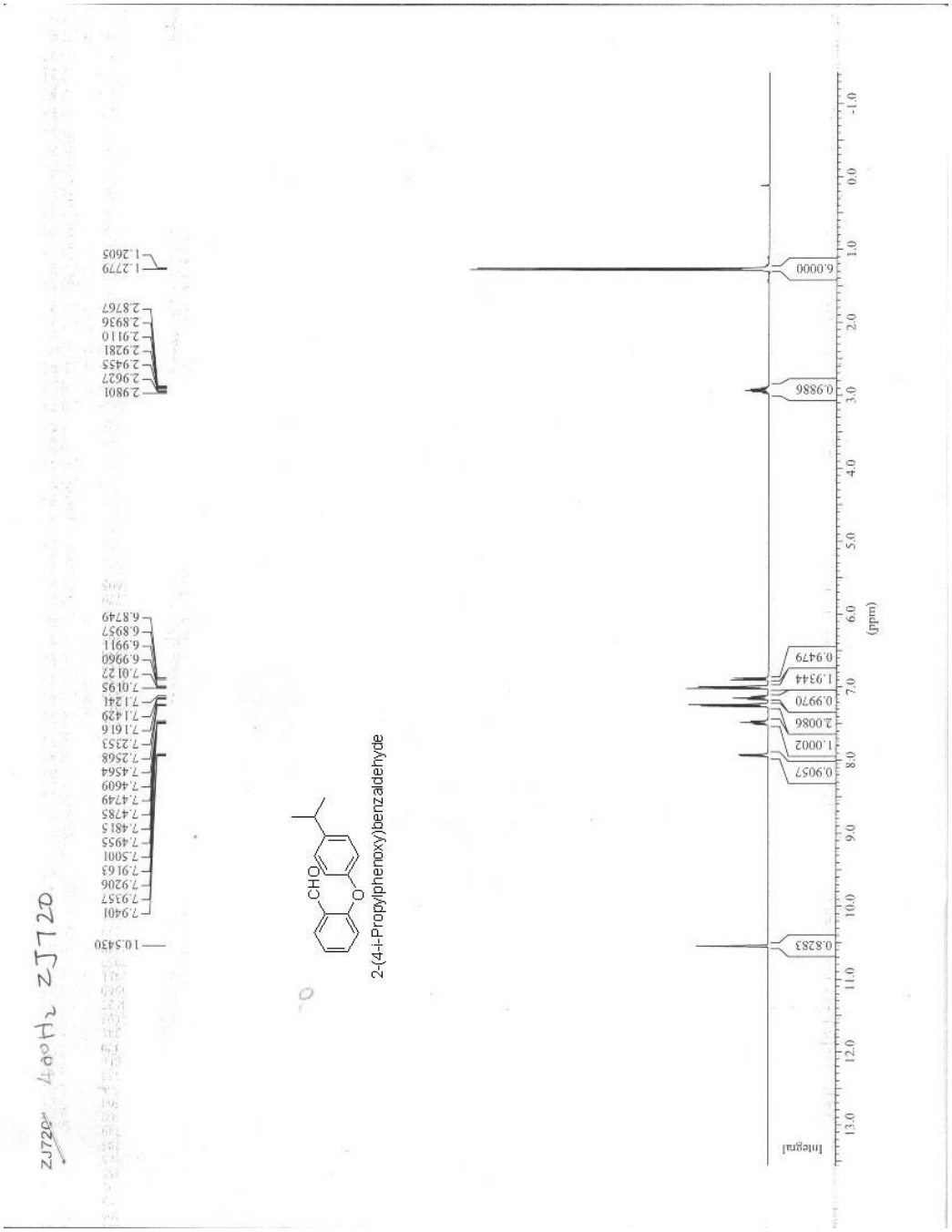


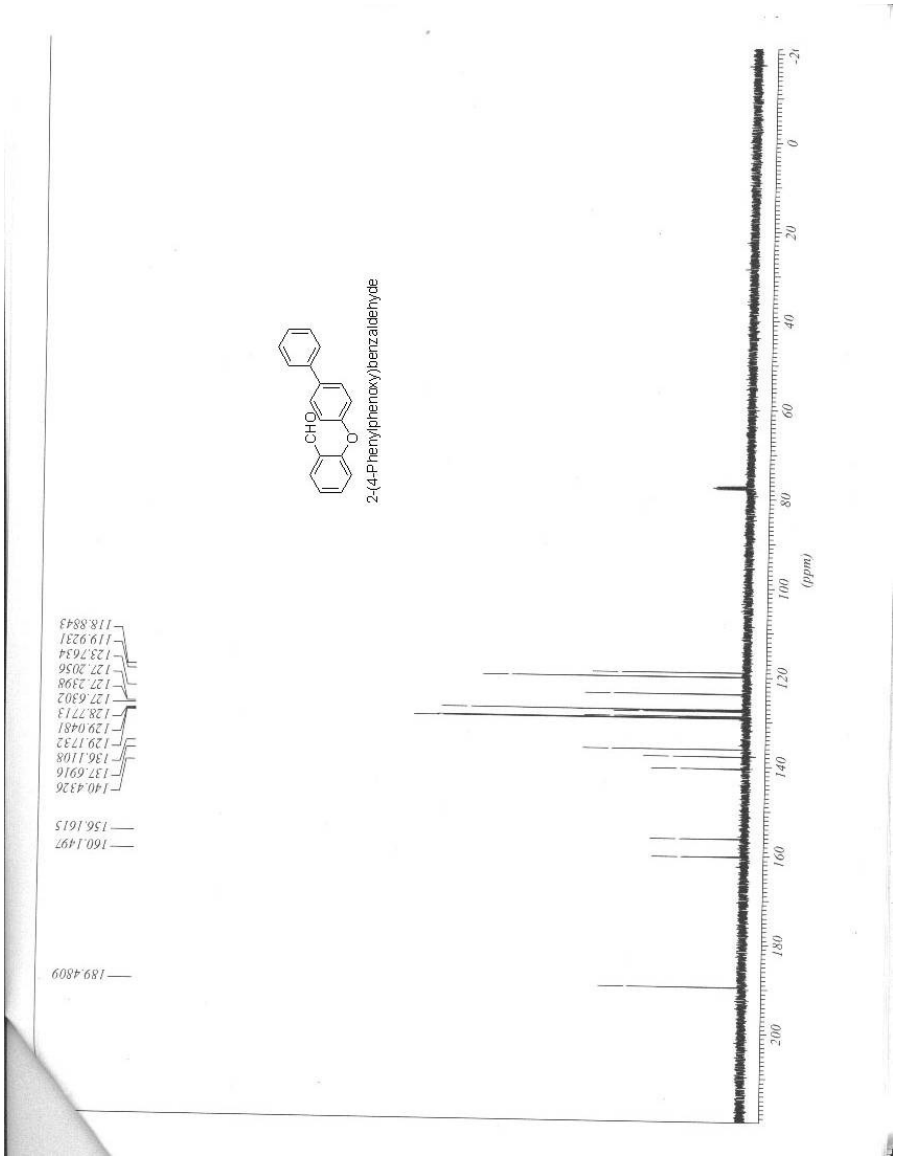


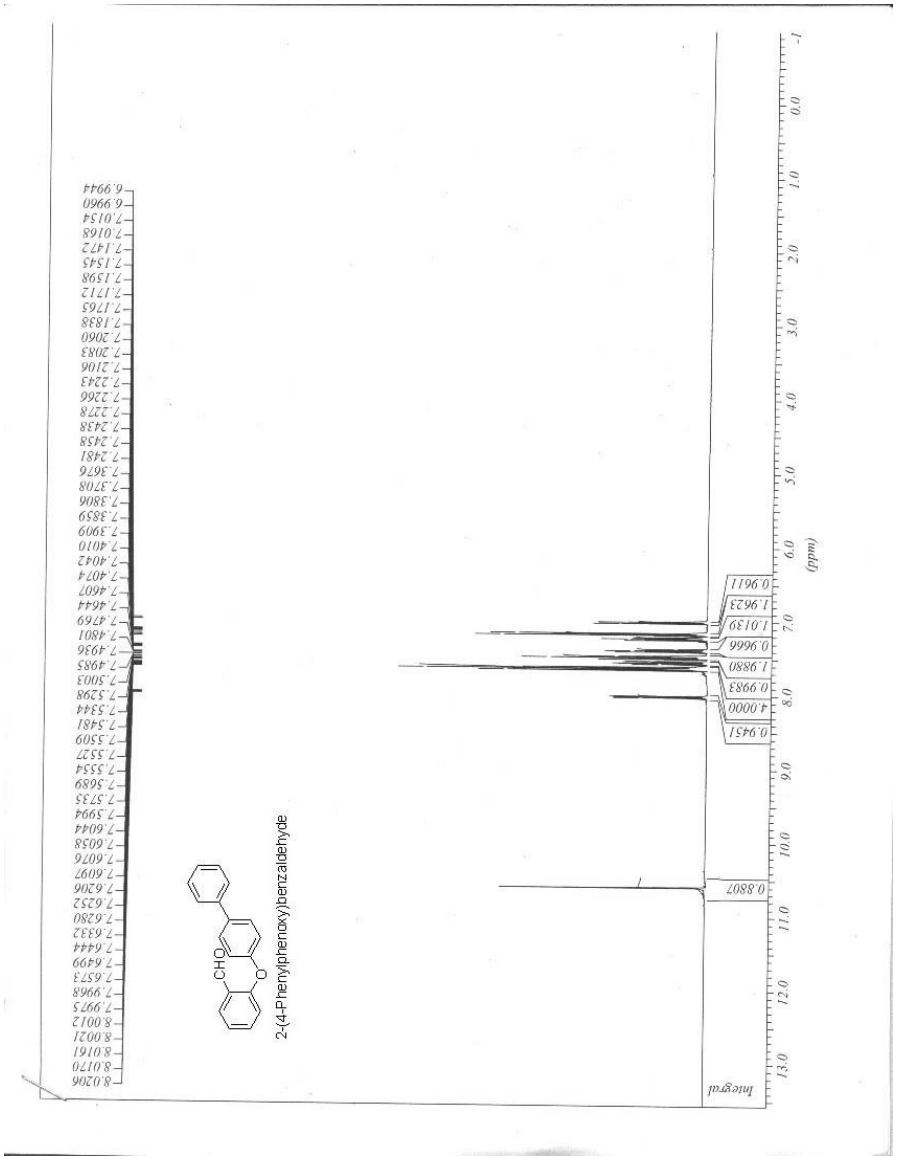


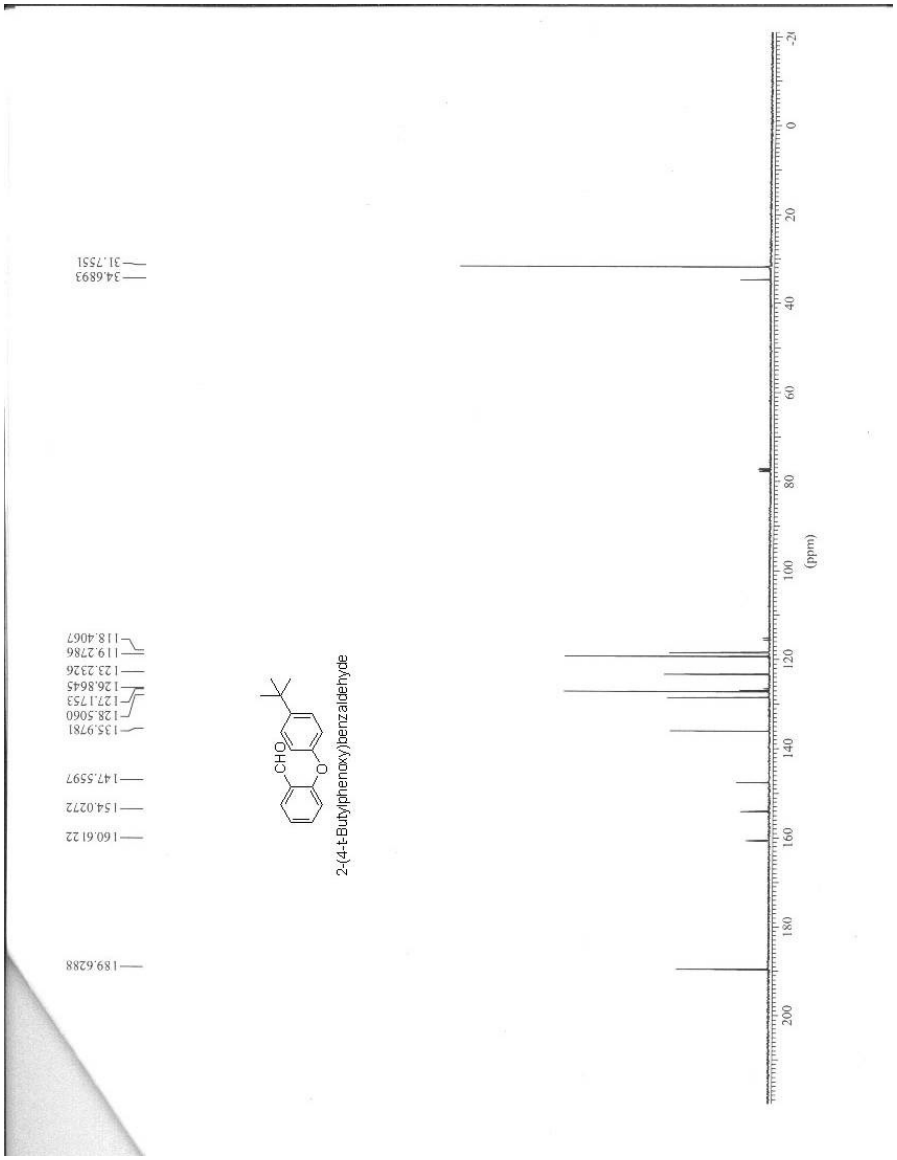


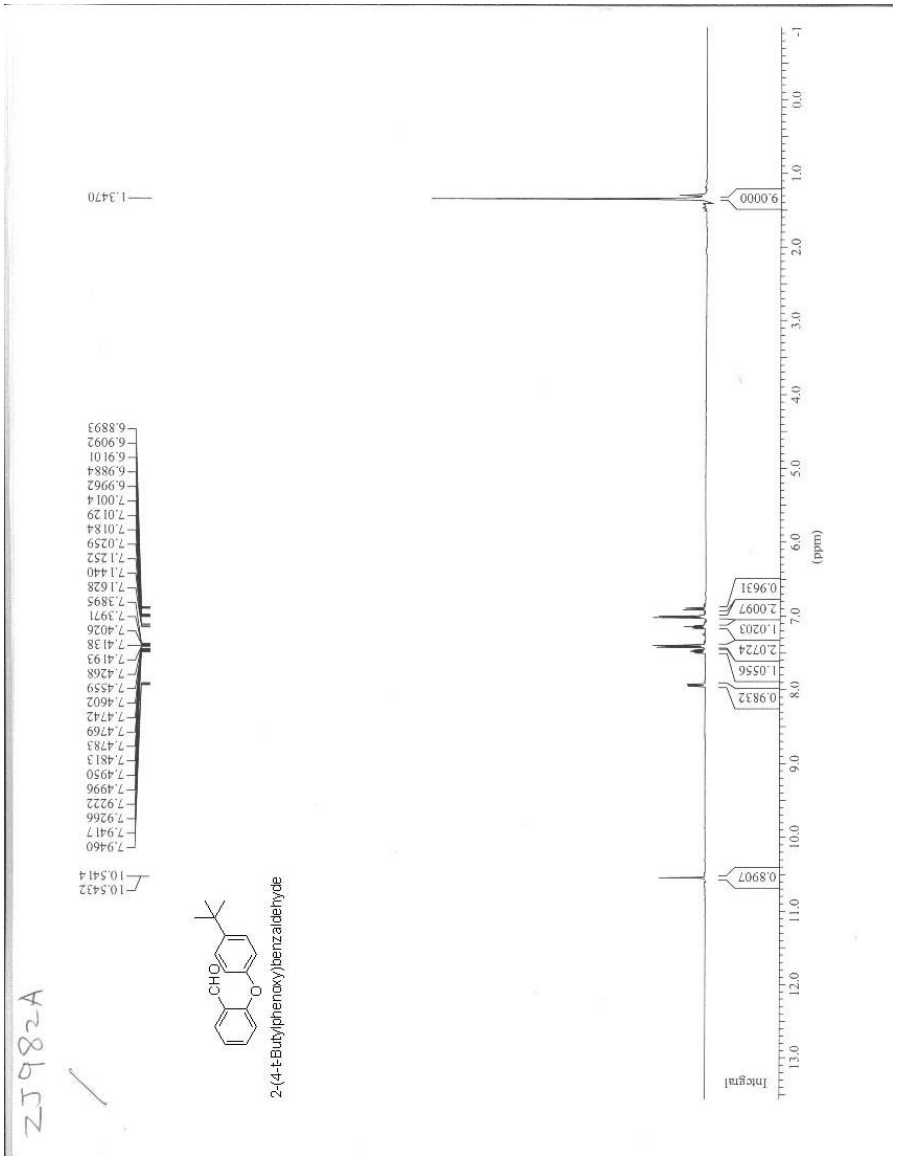


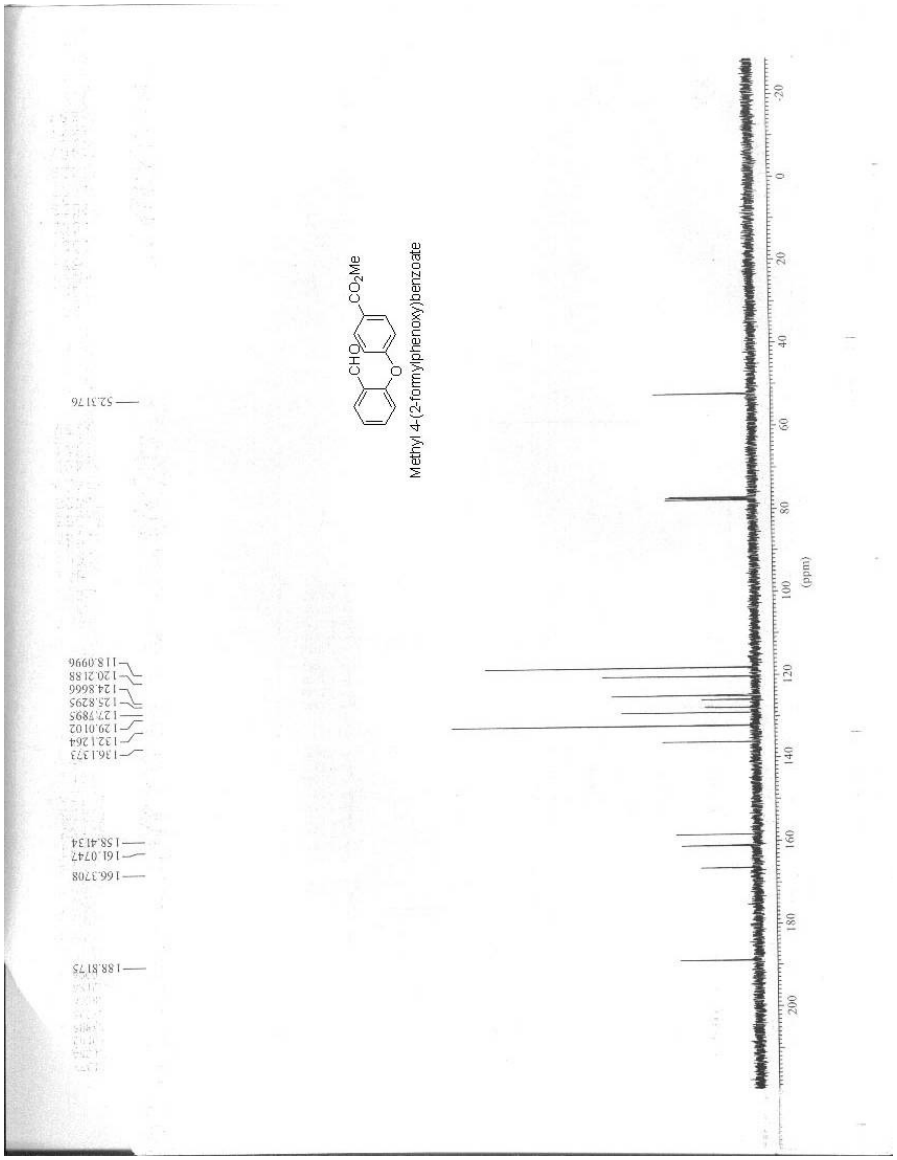


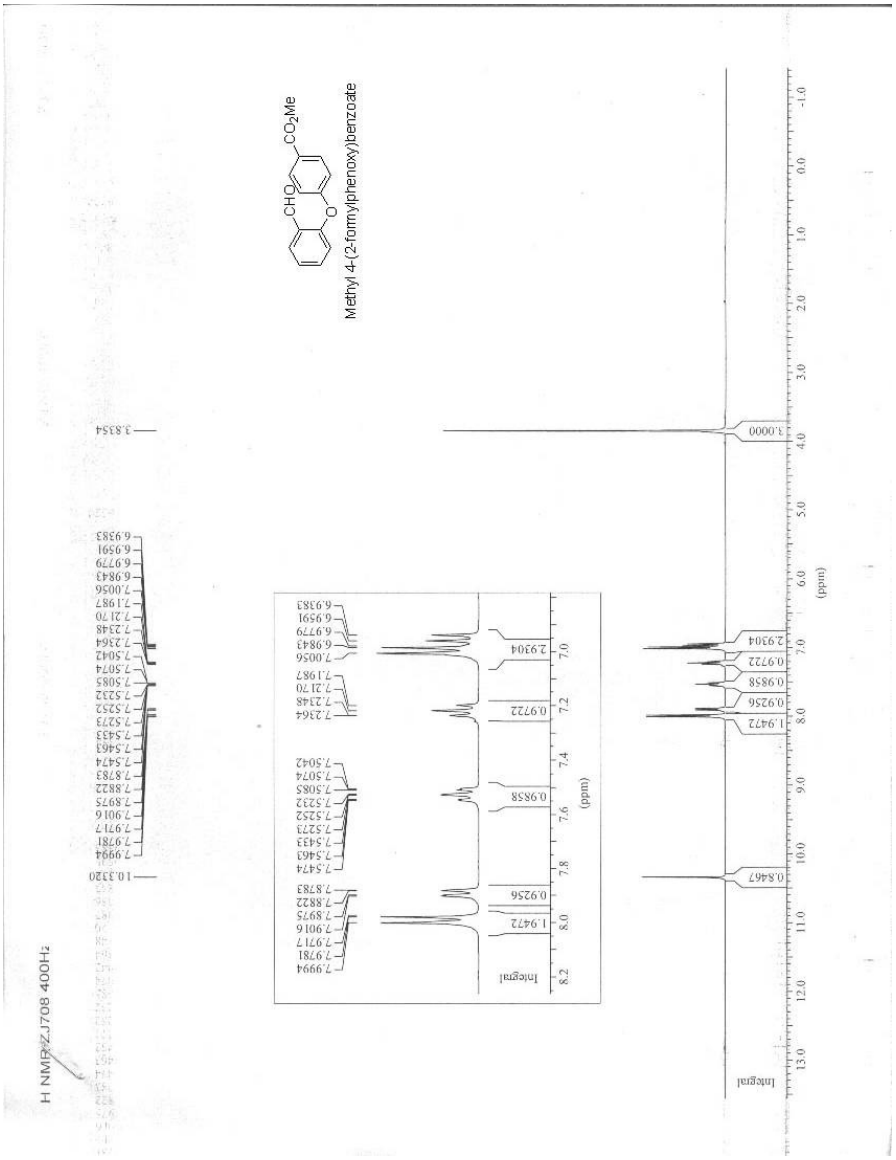


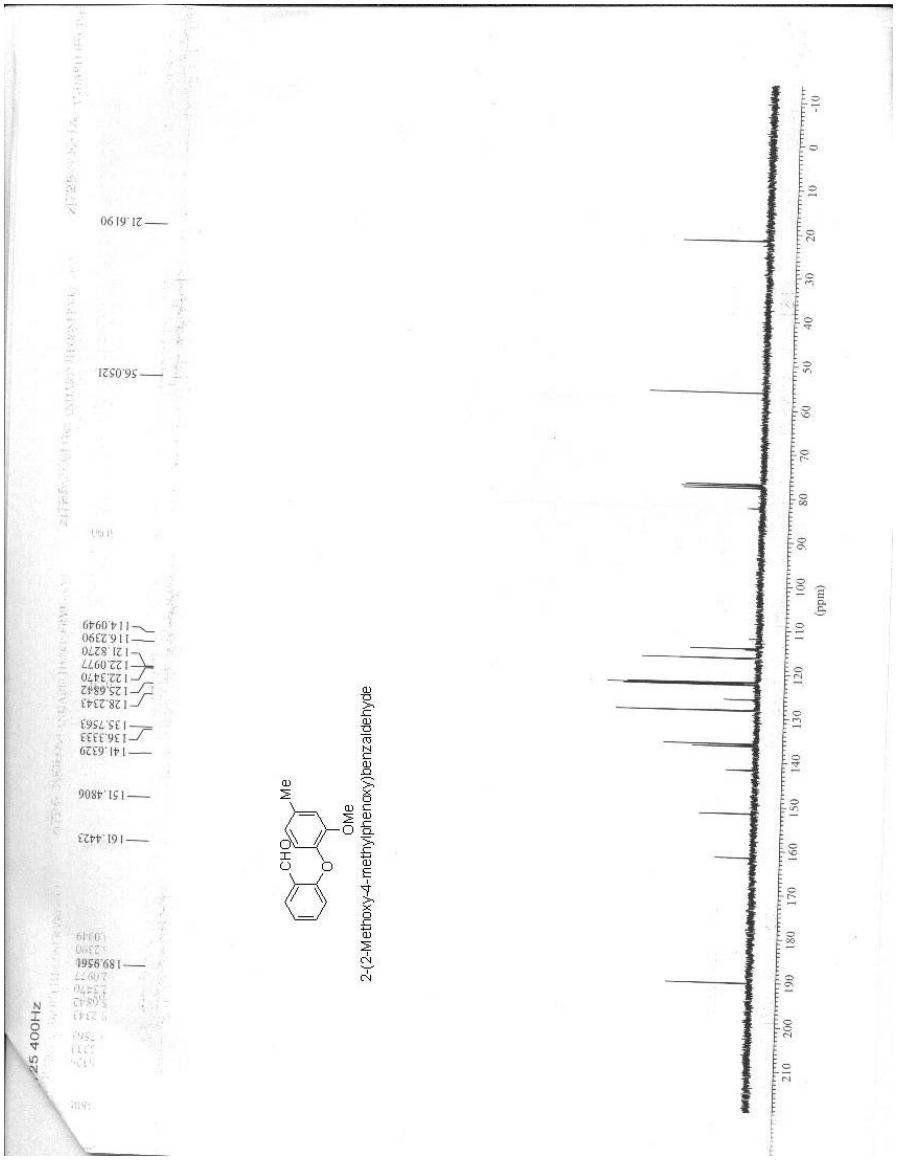


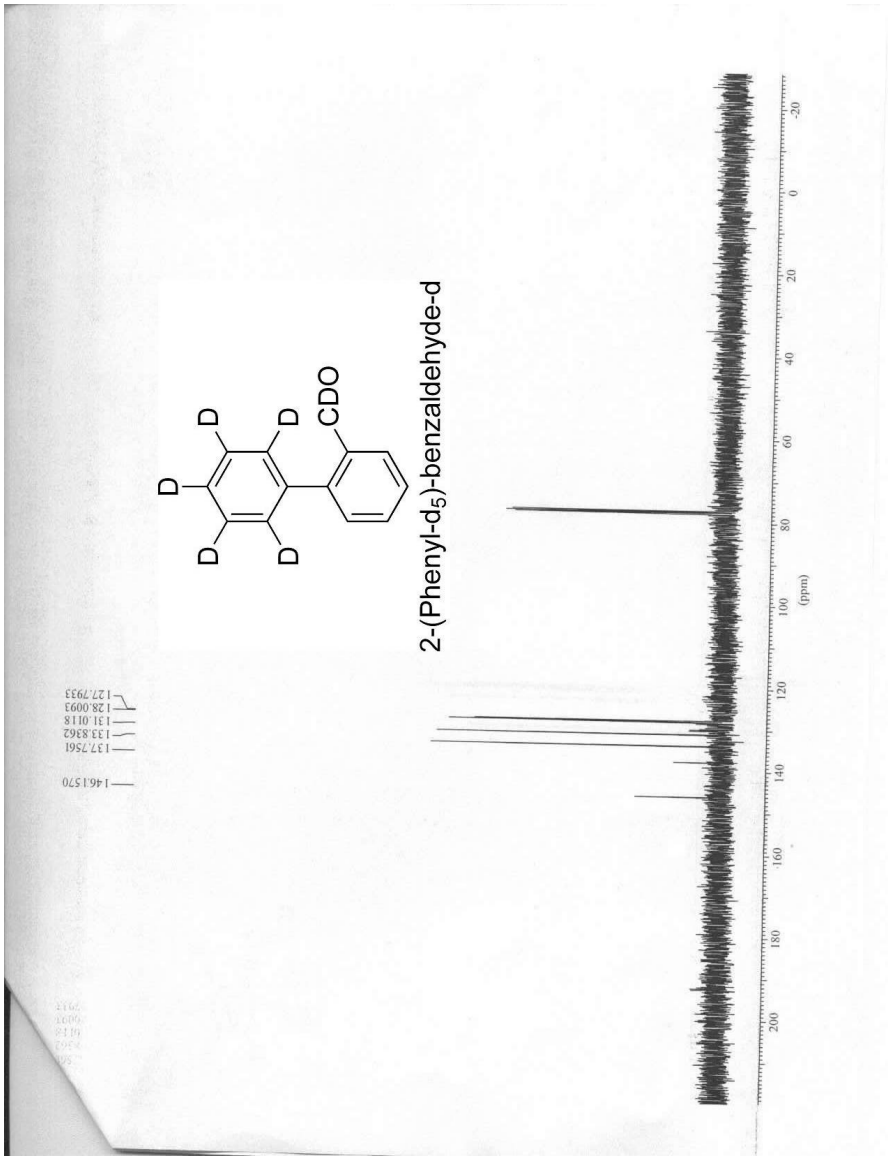


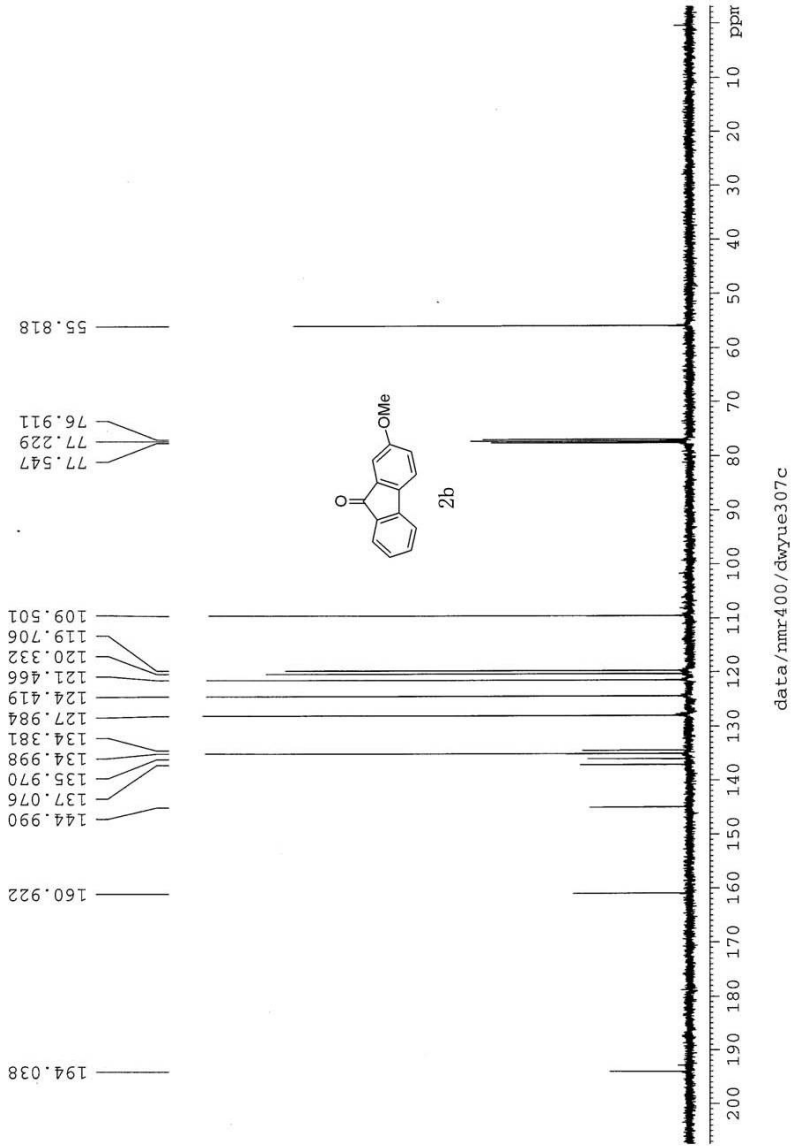


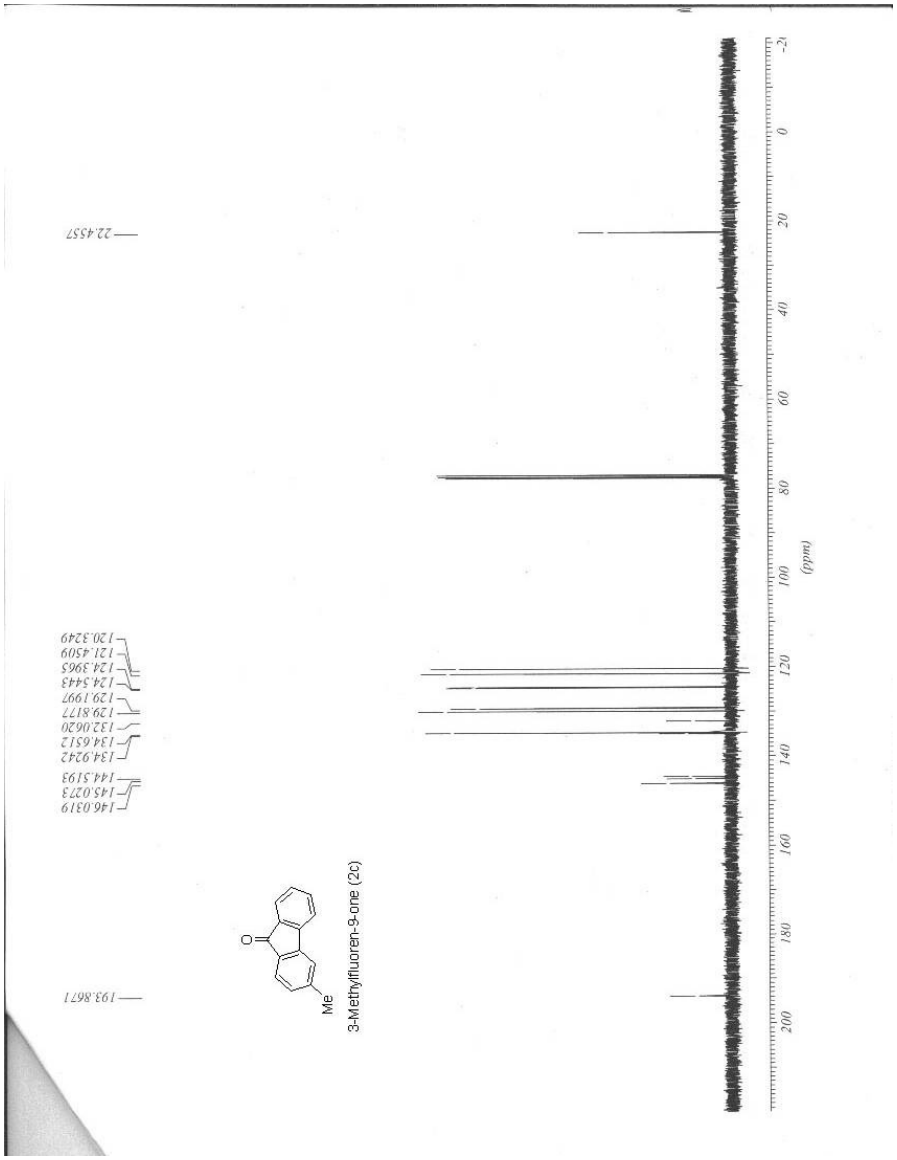


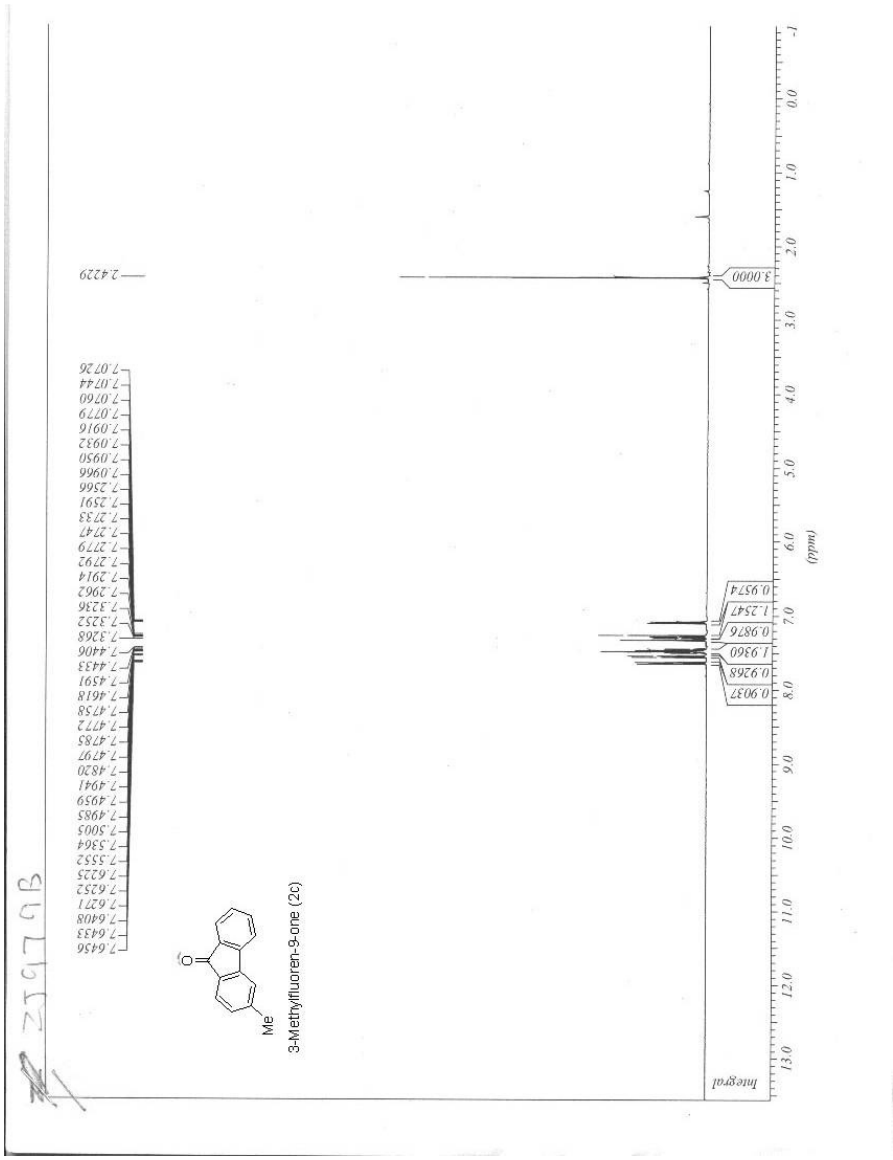


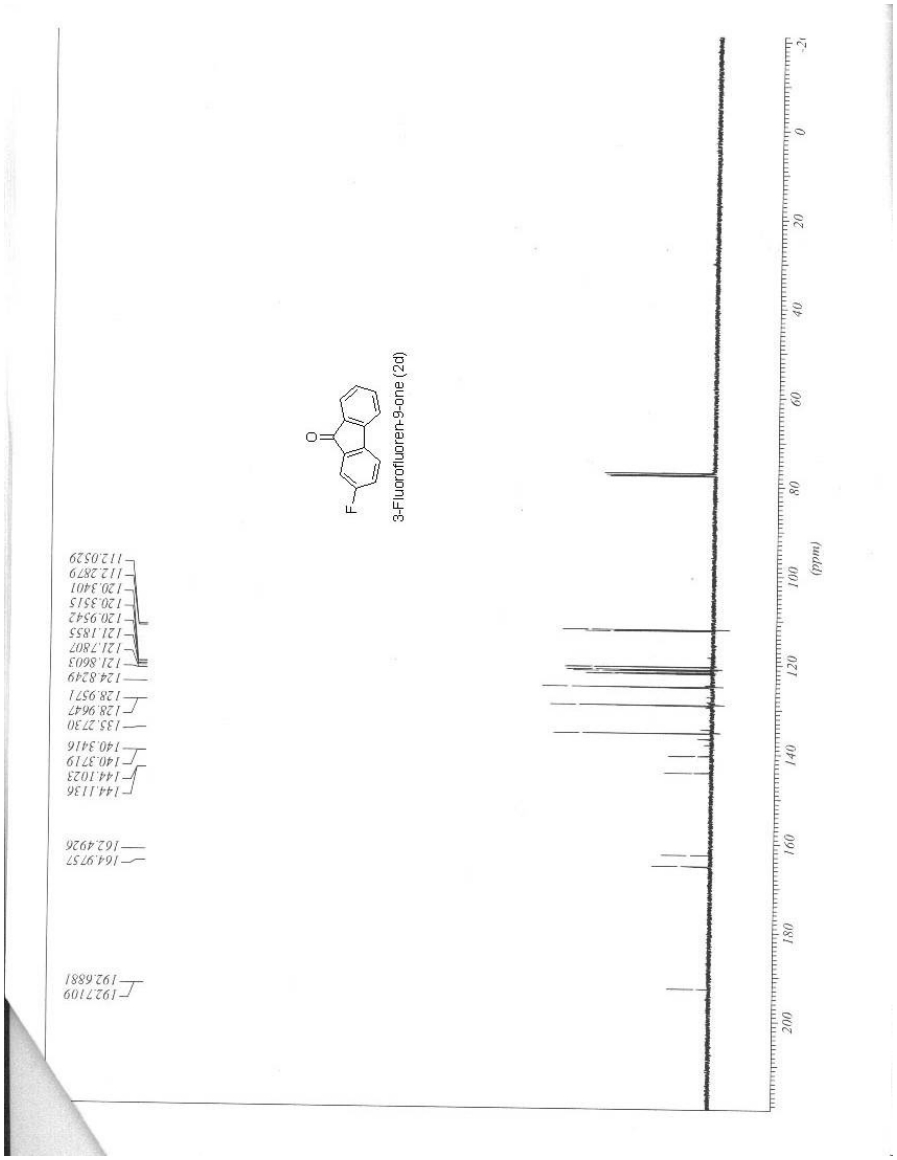


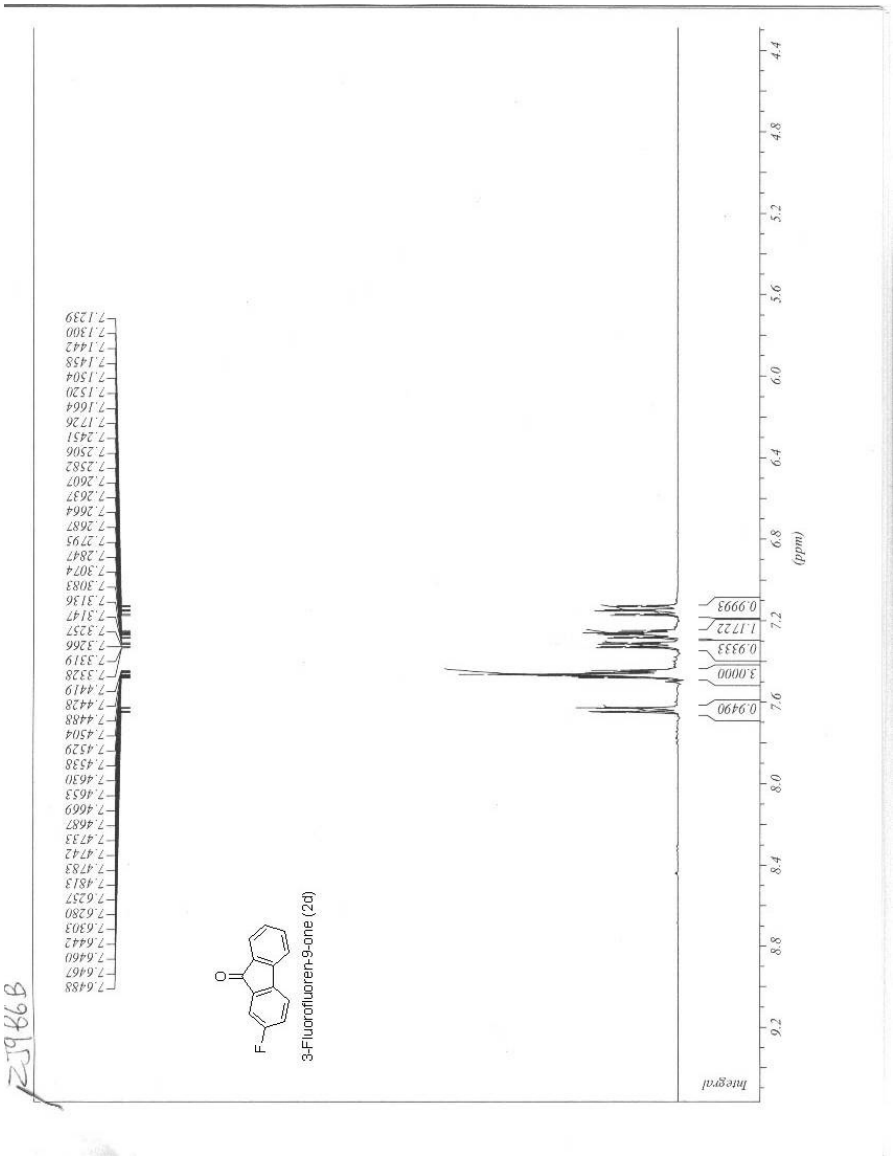


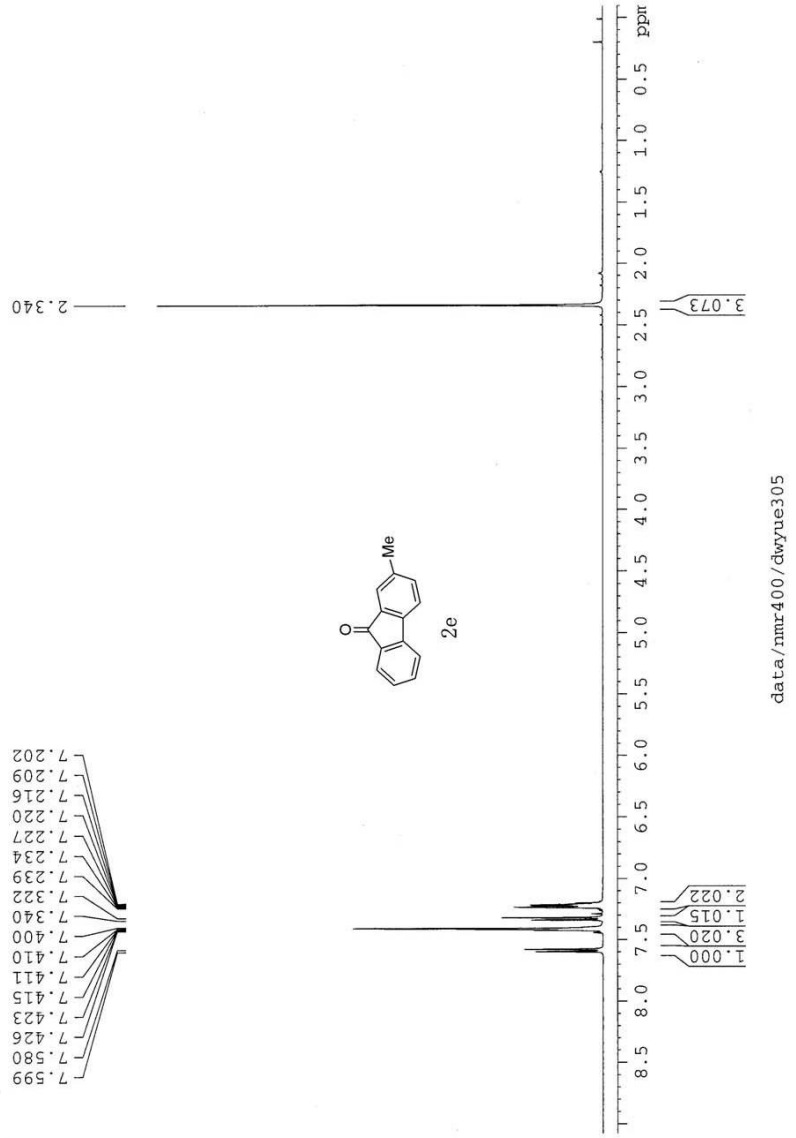


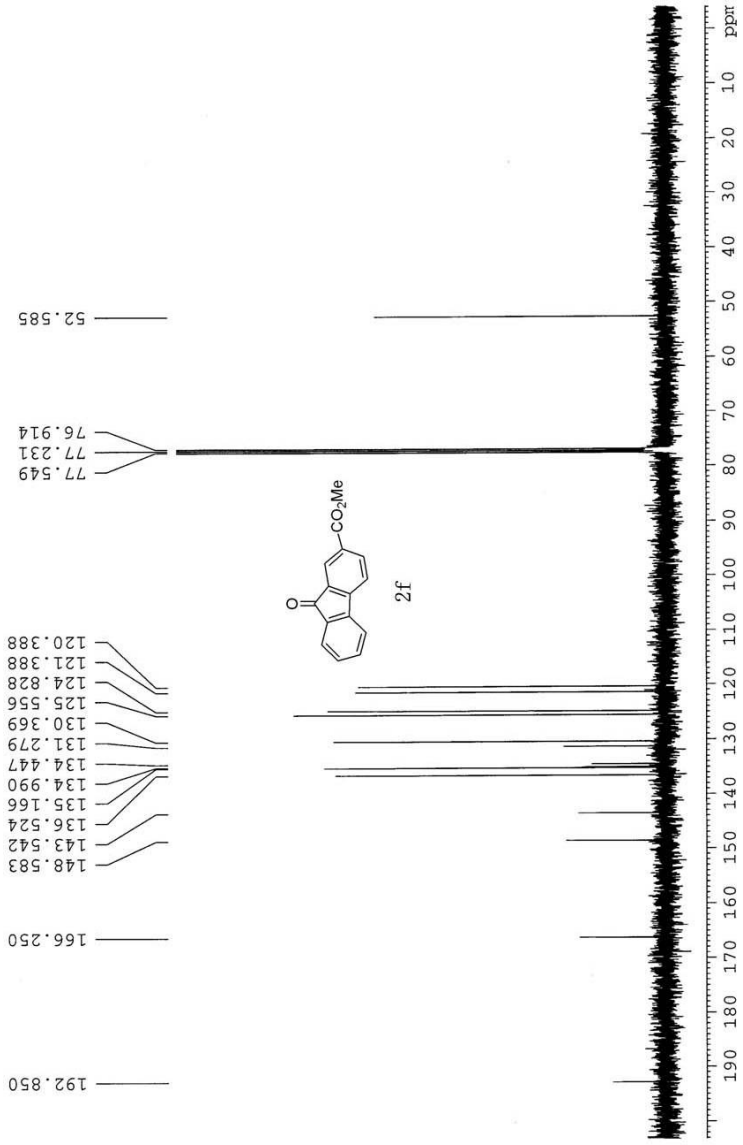


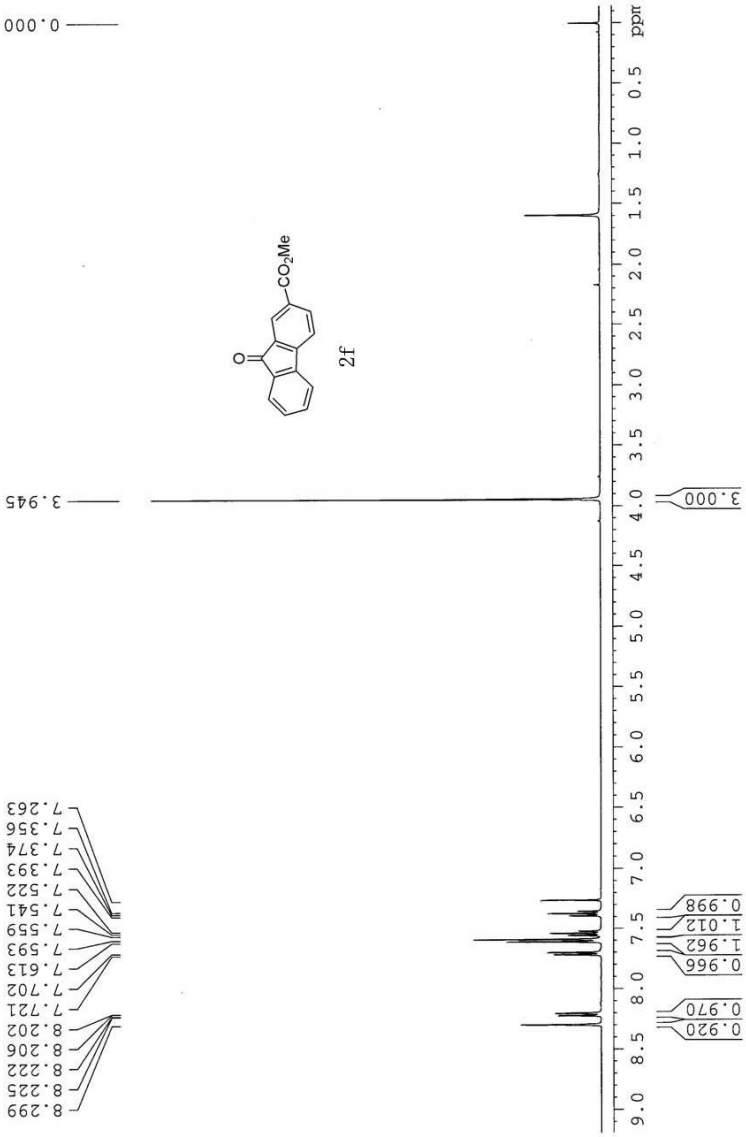


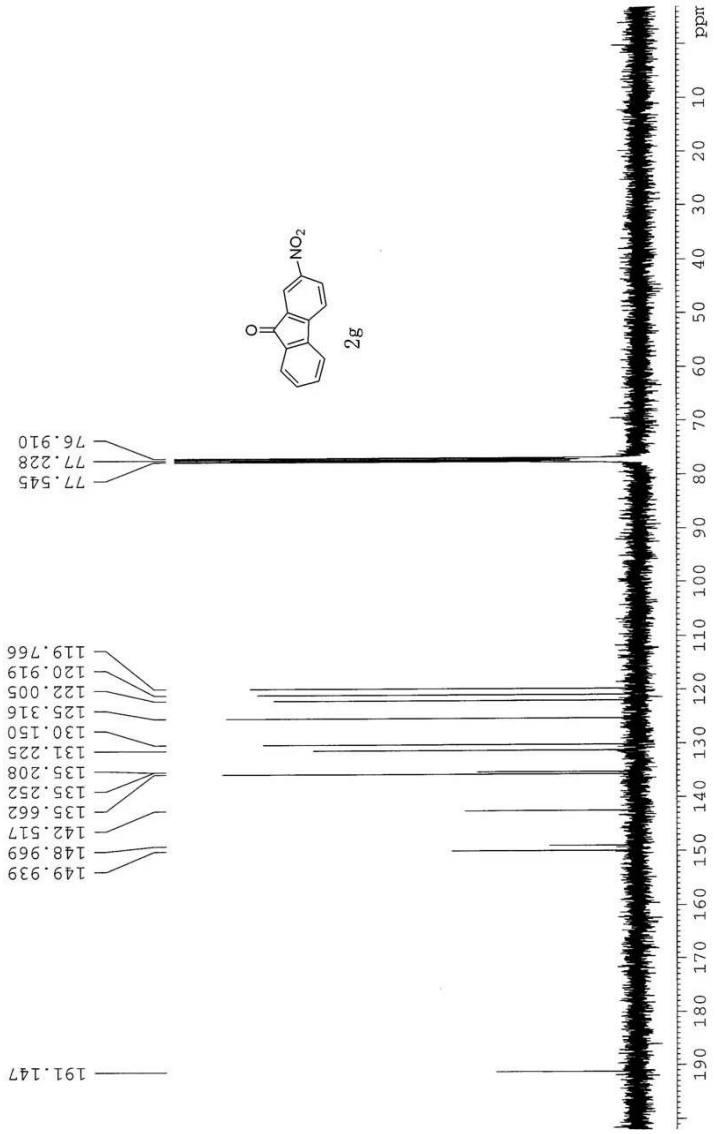


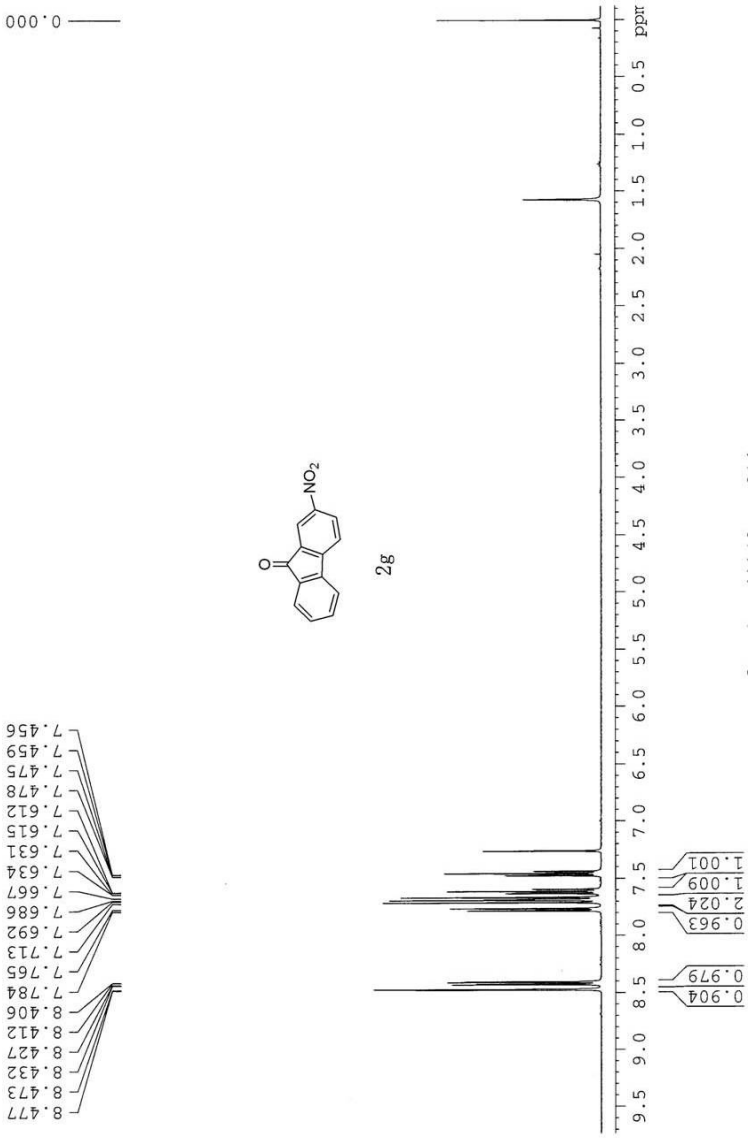


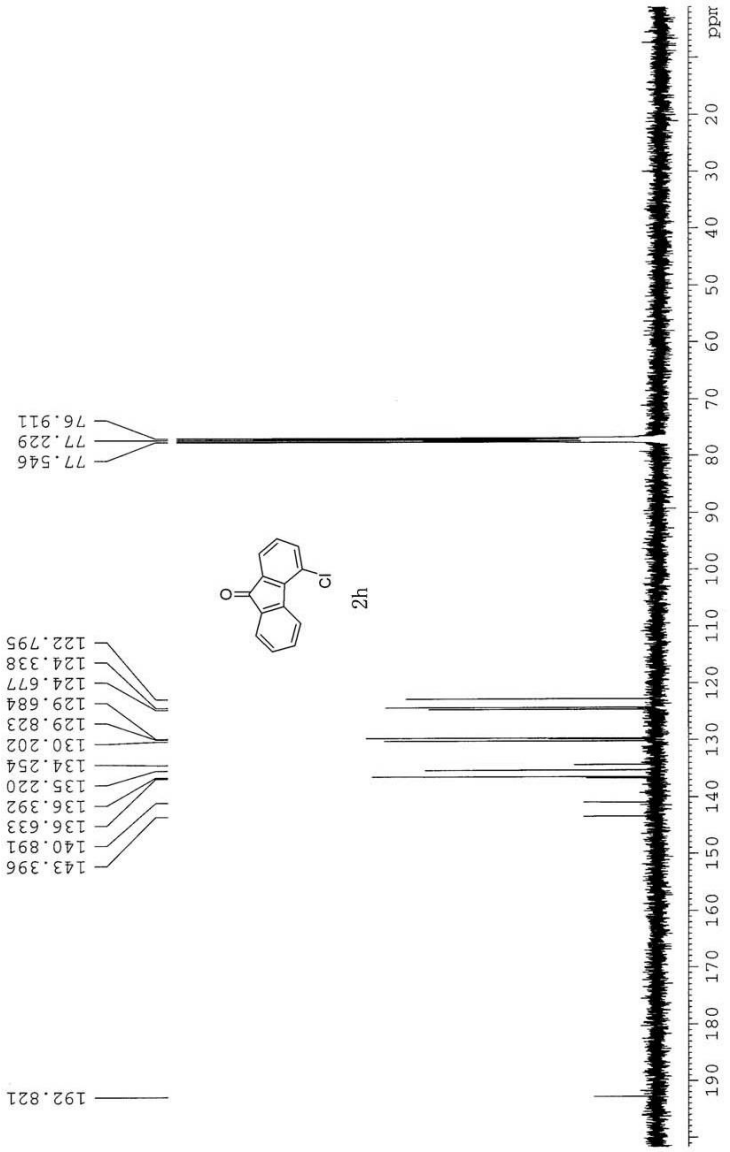


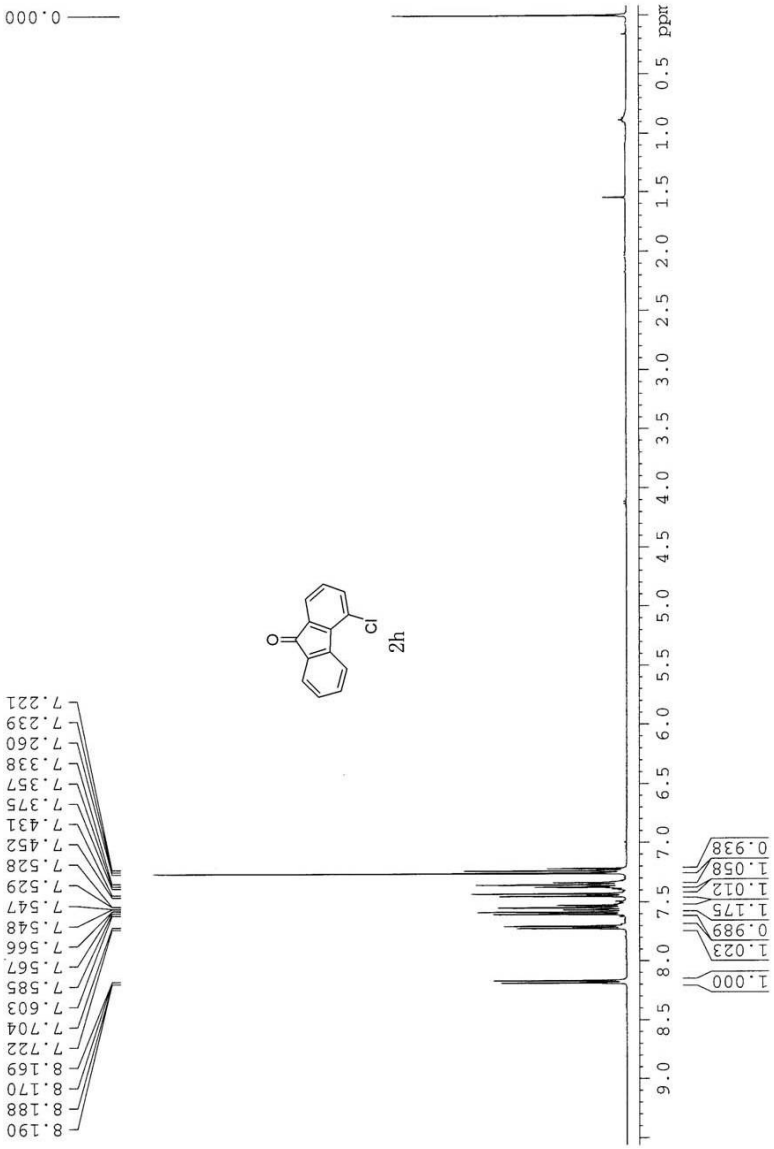


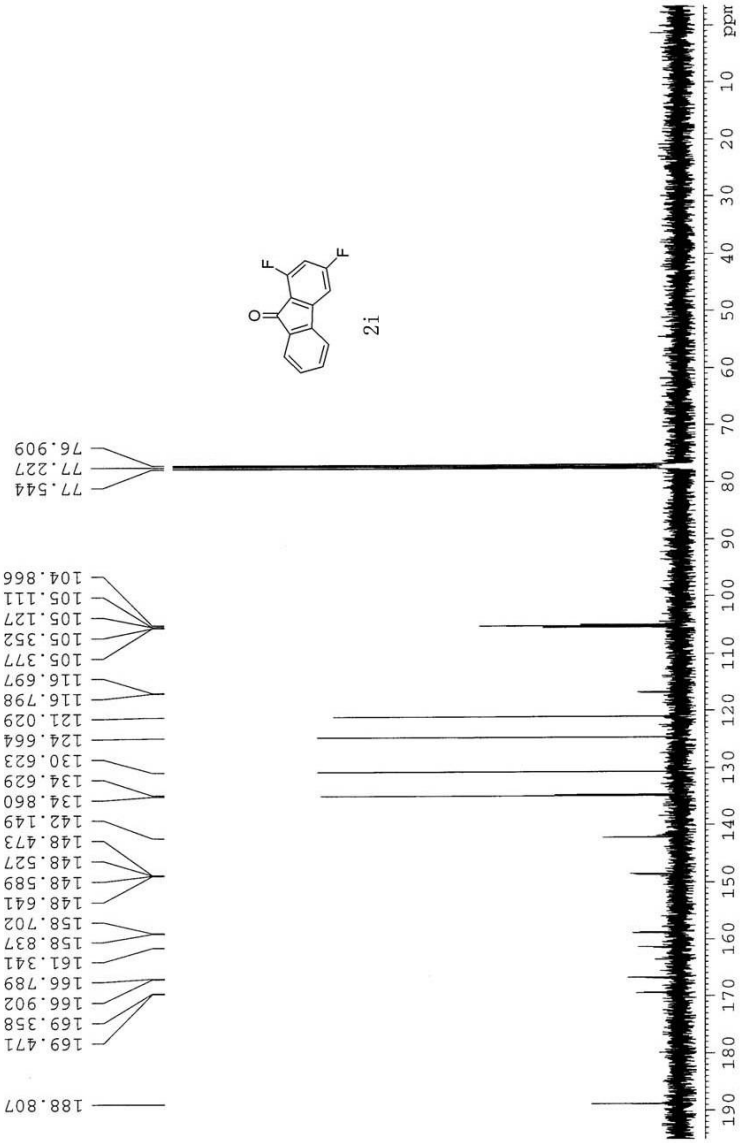


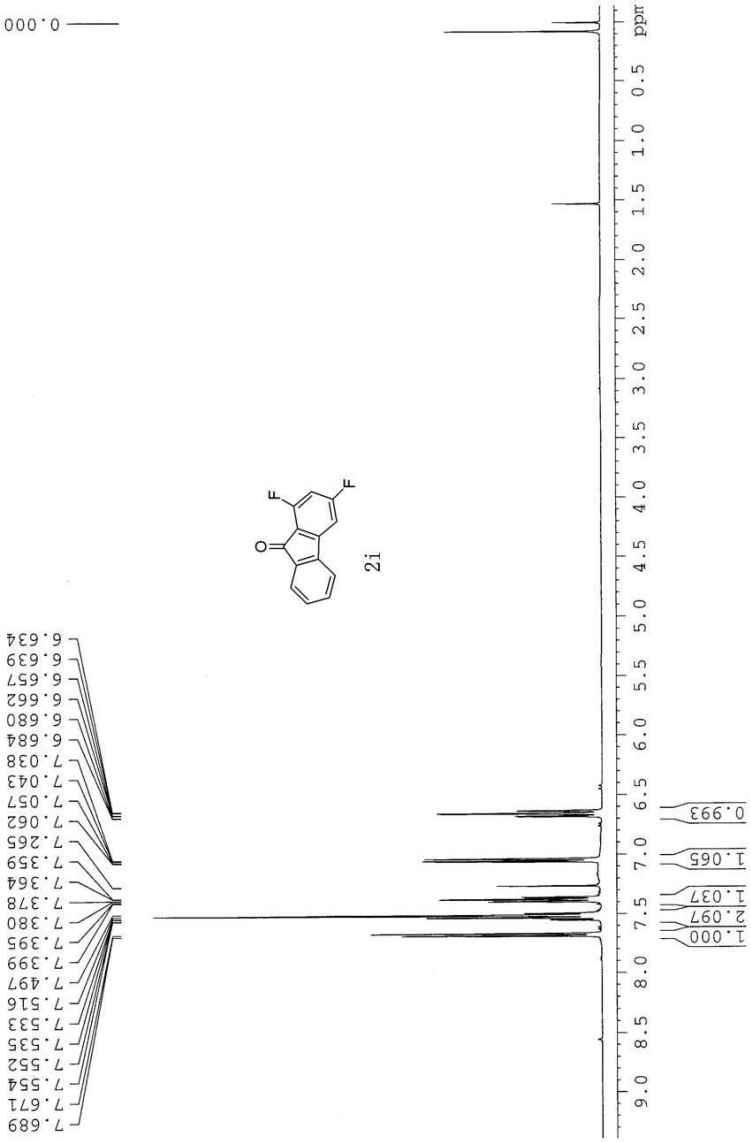


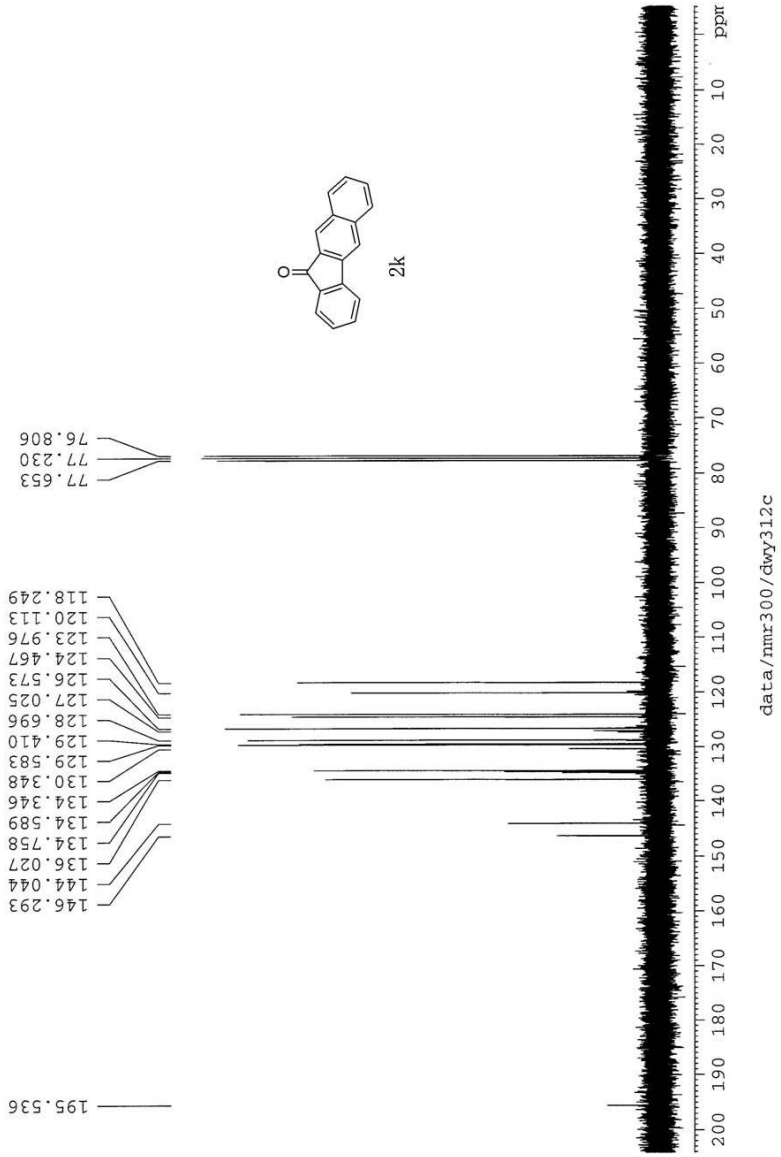


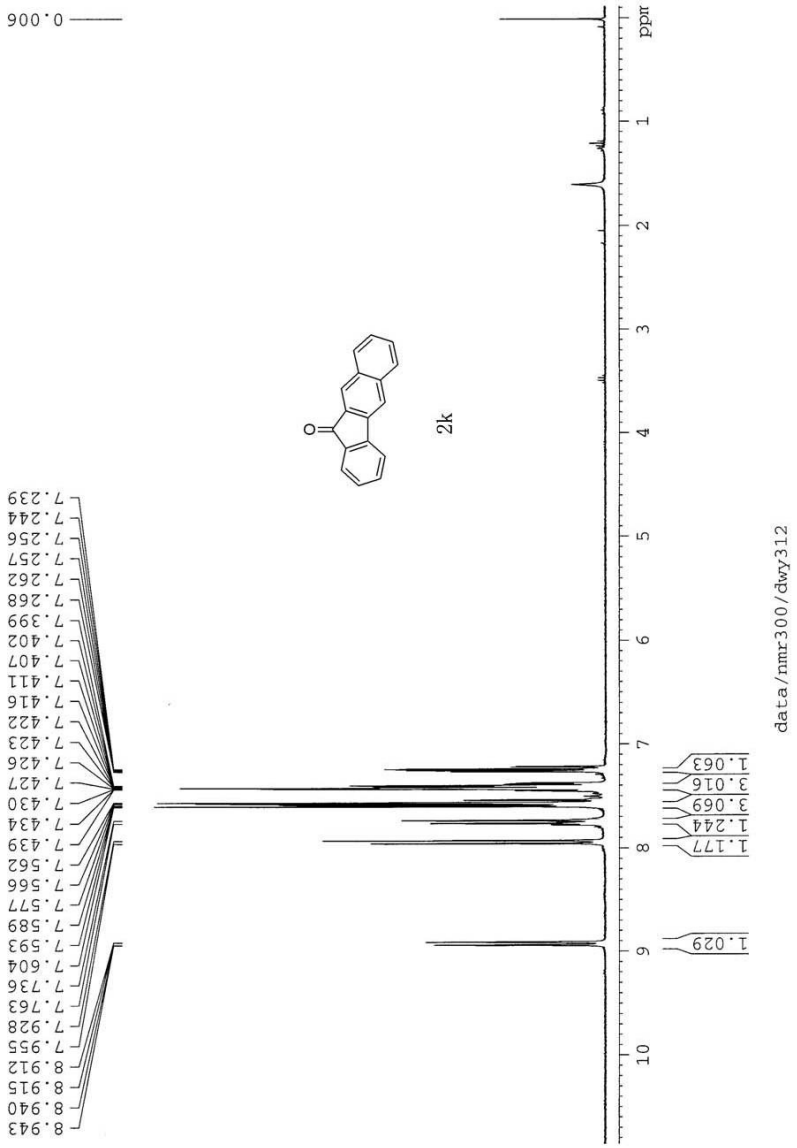


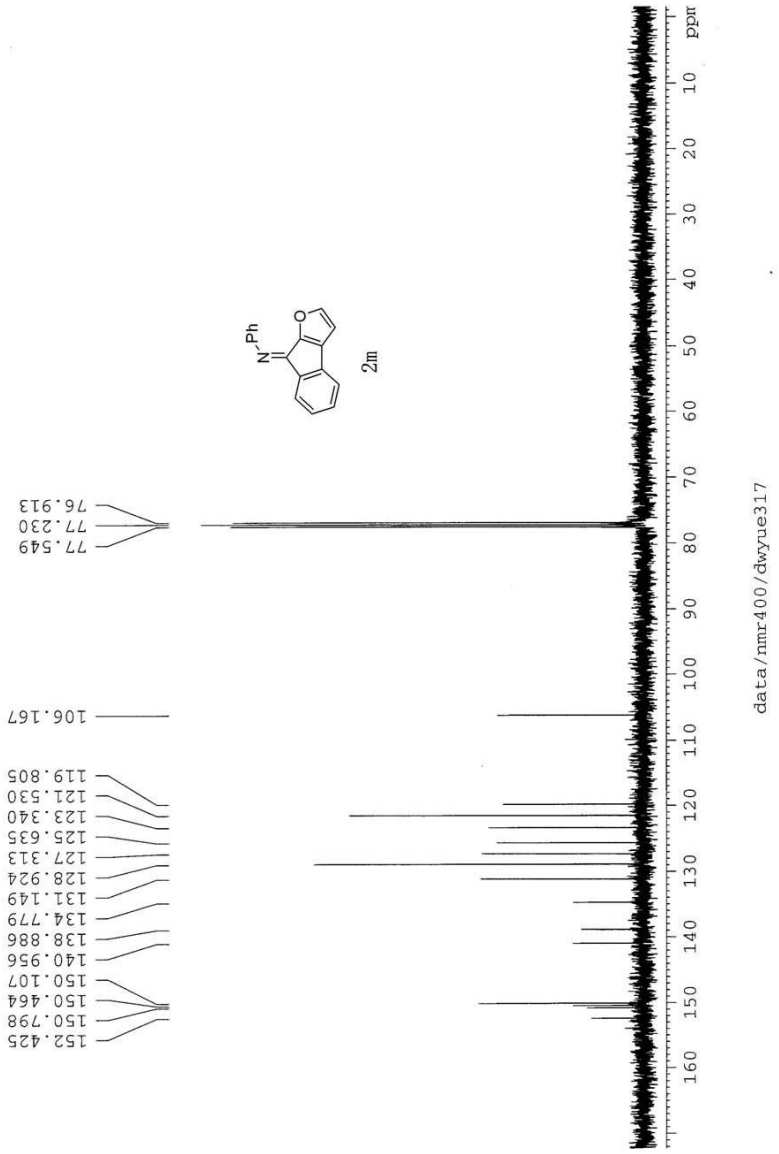


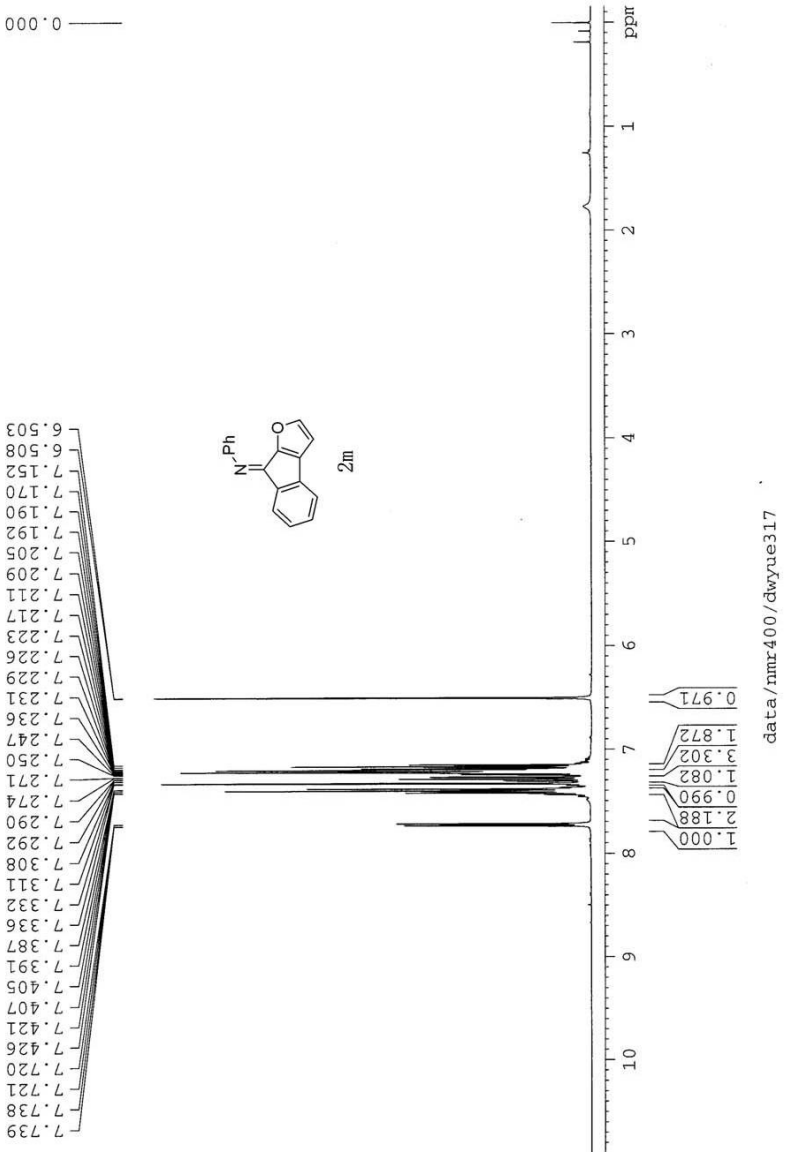


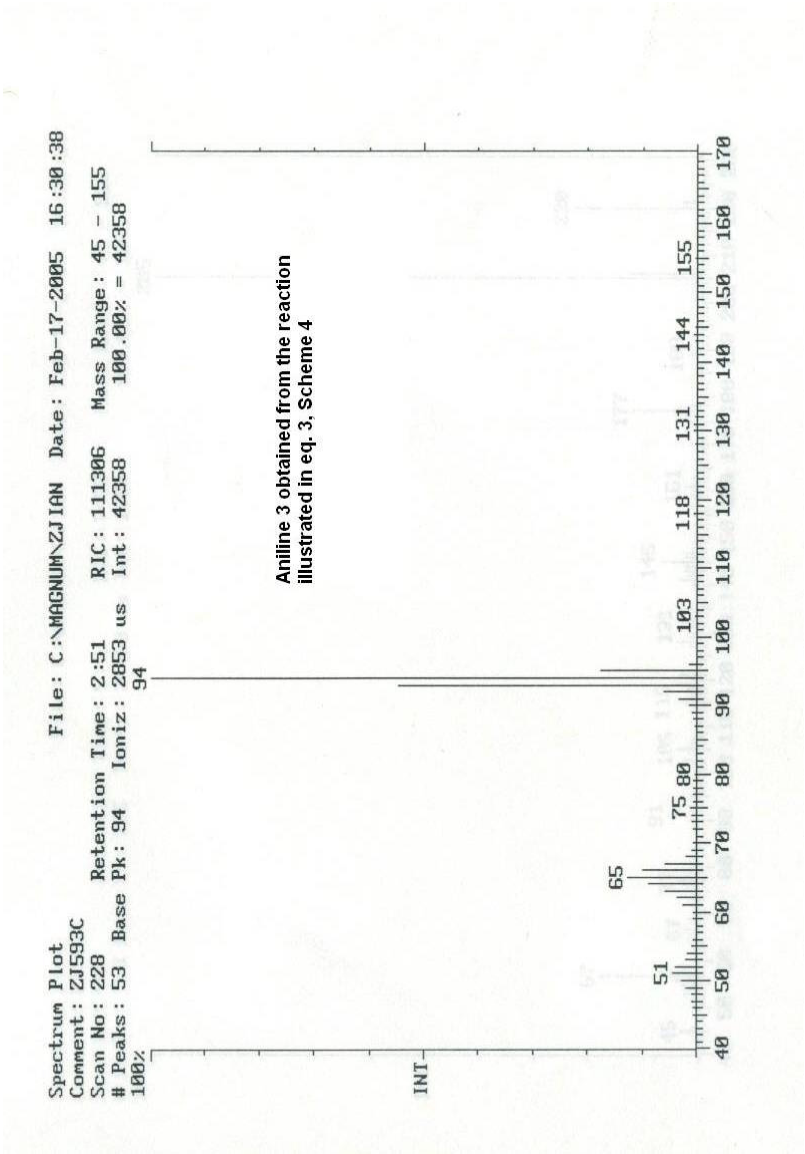


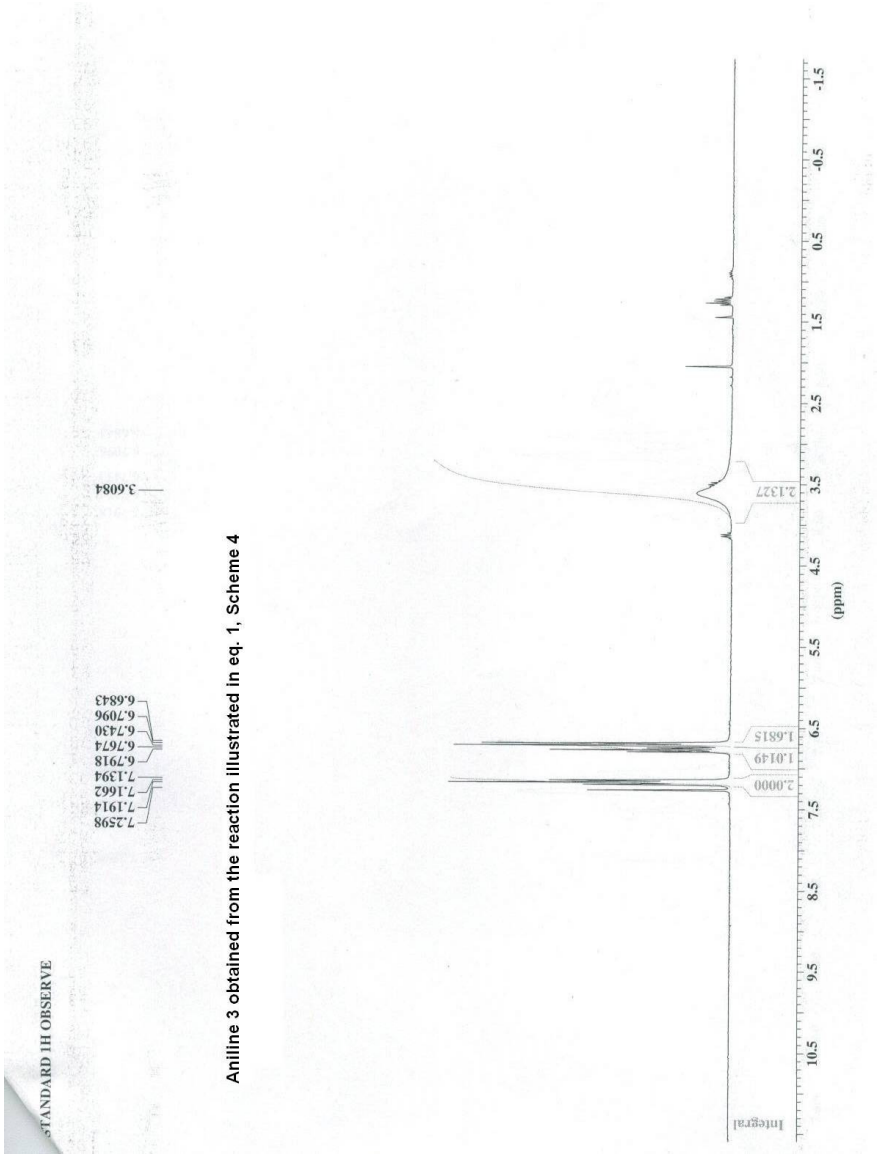




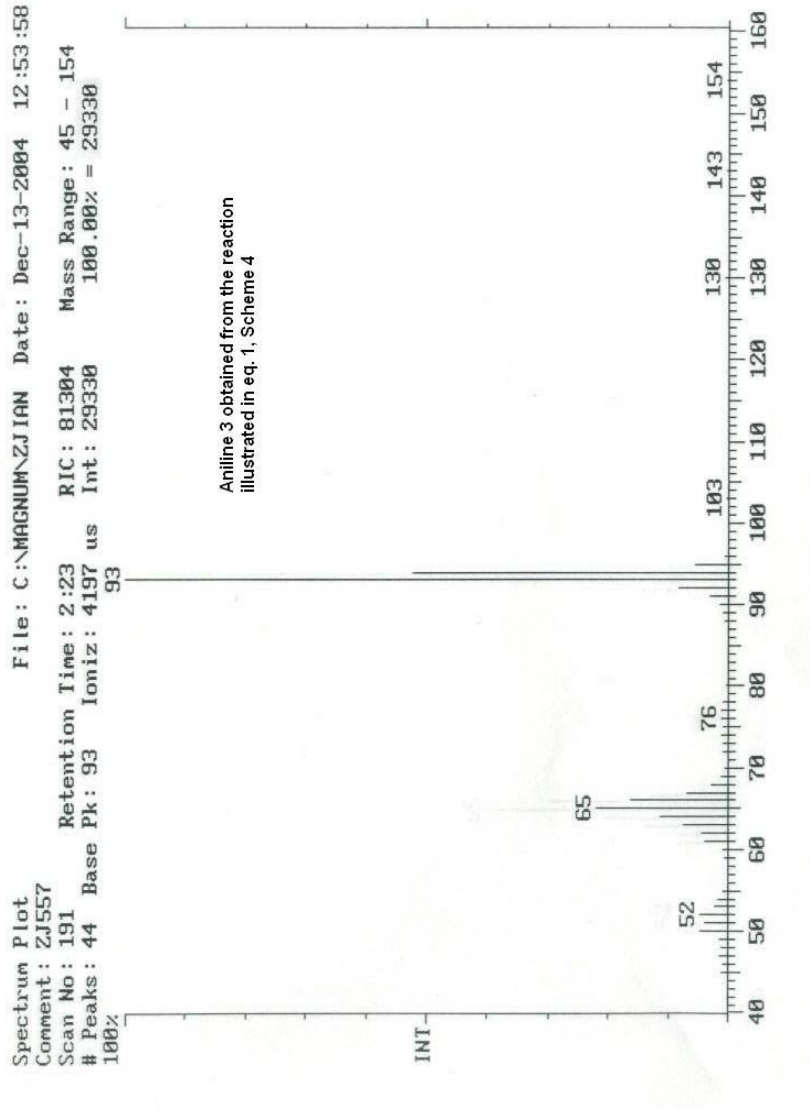


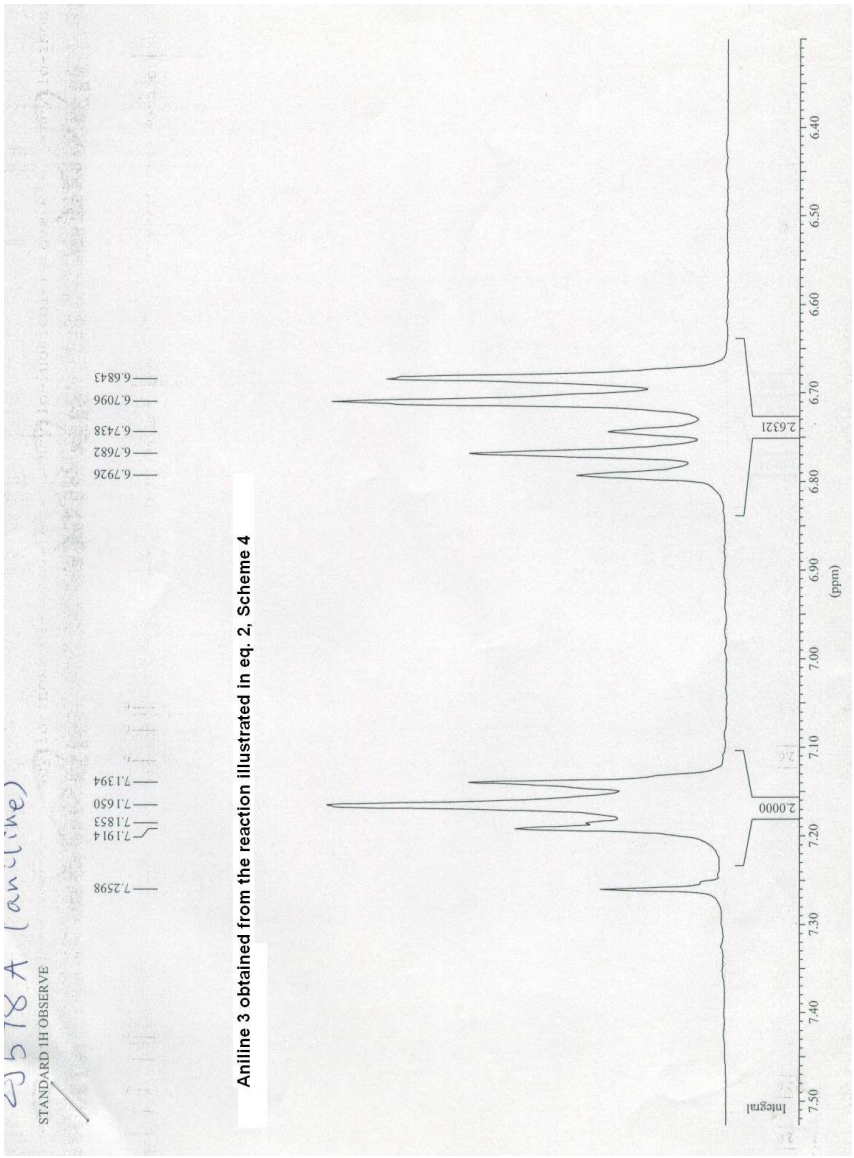




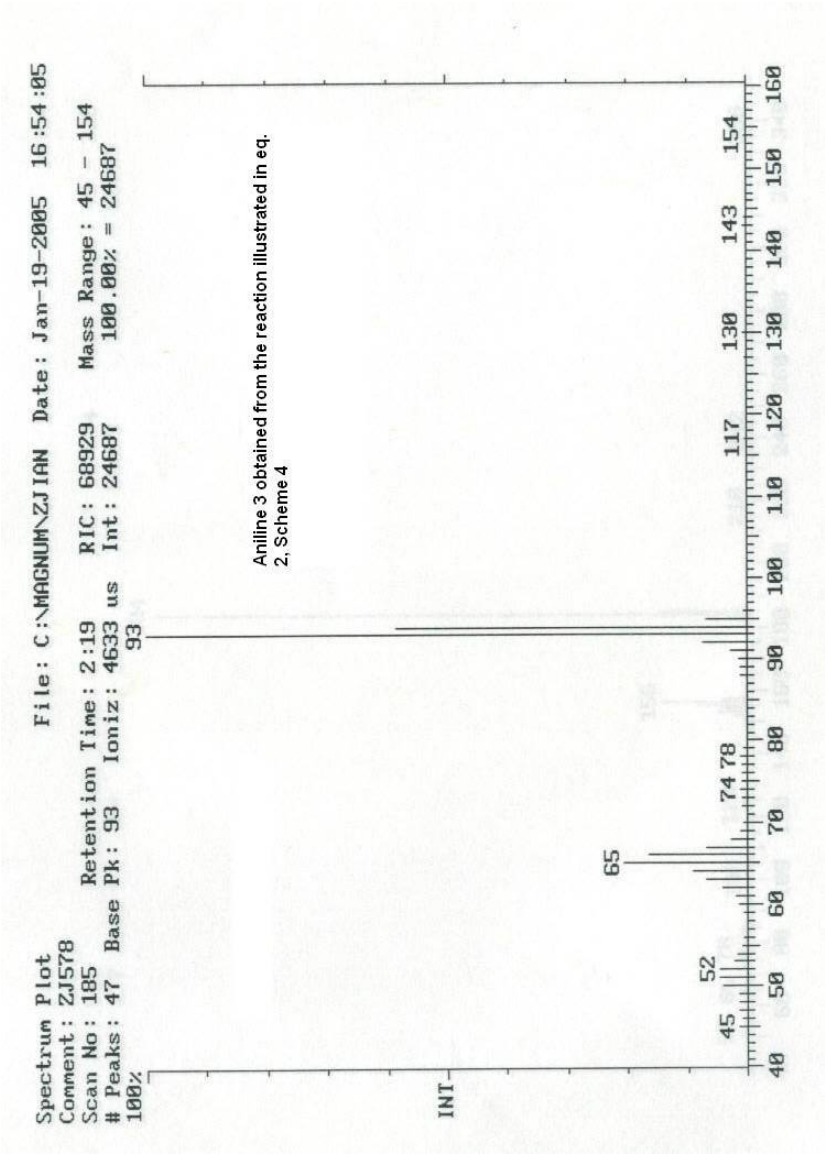


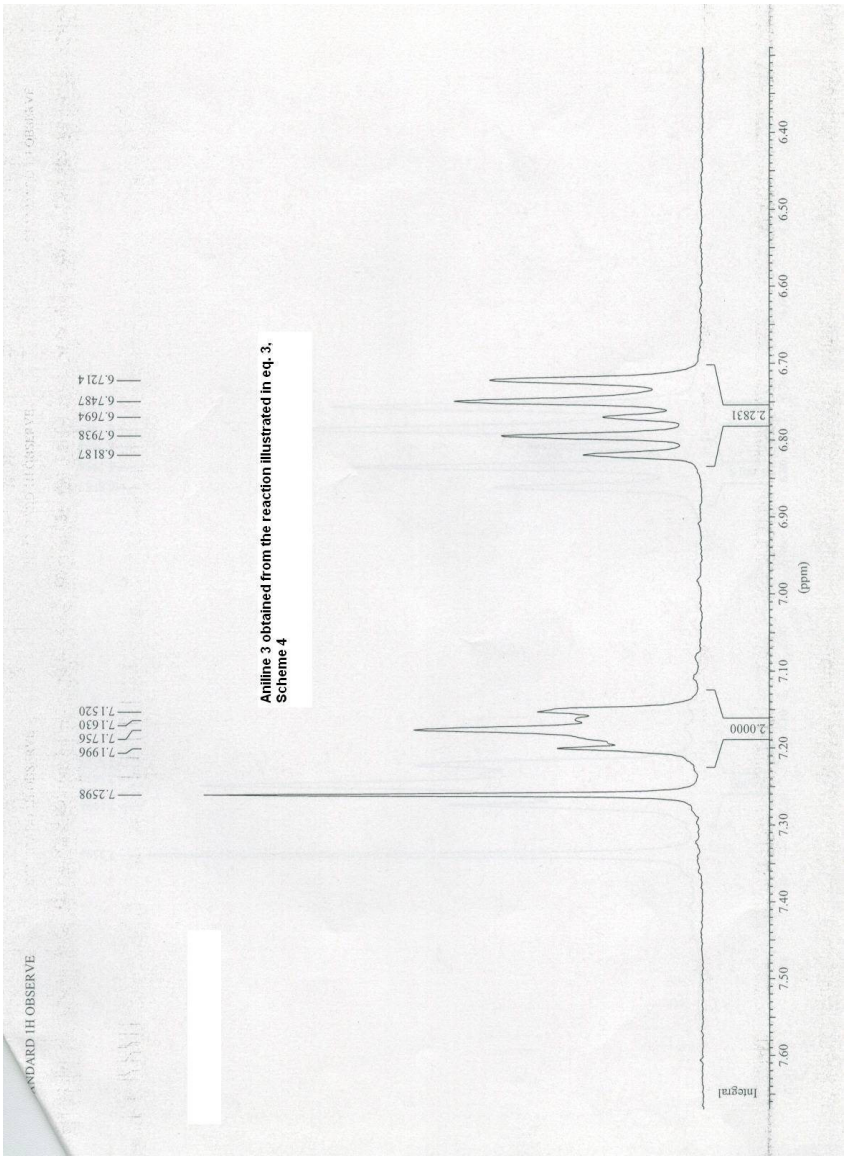
Aniline 3 obtained from the reaction illustrated in eq. 1, Scheme 4

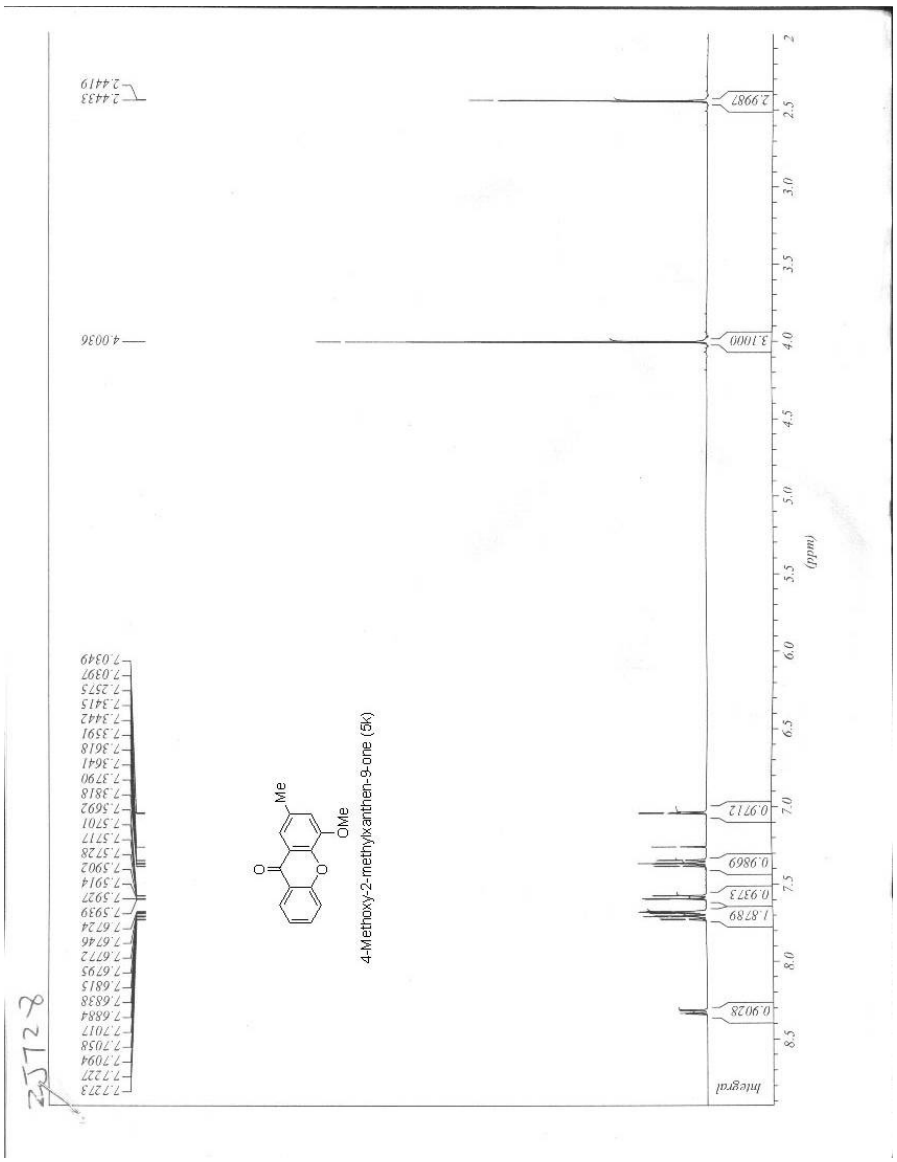


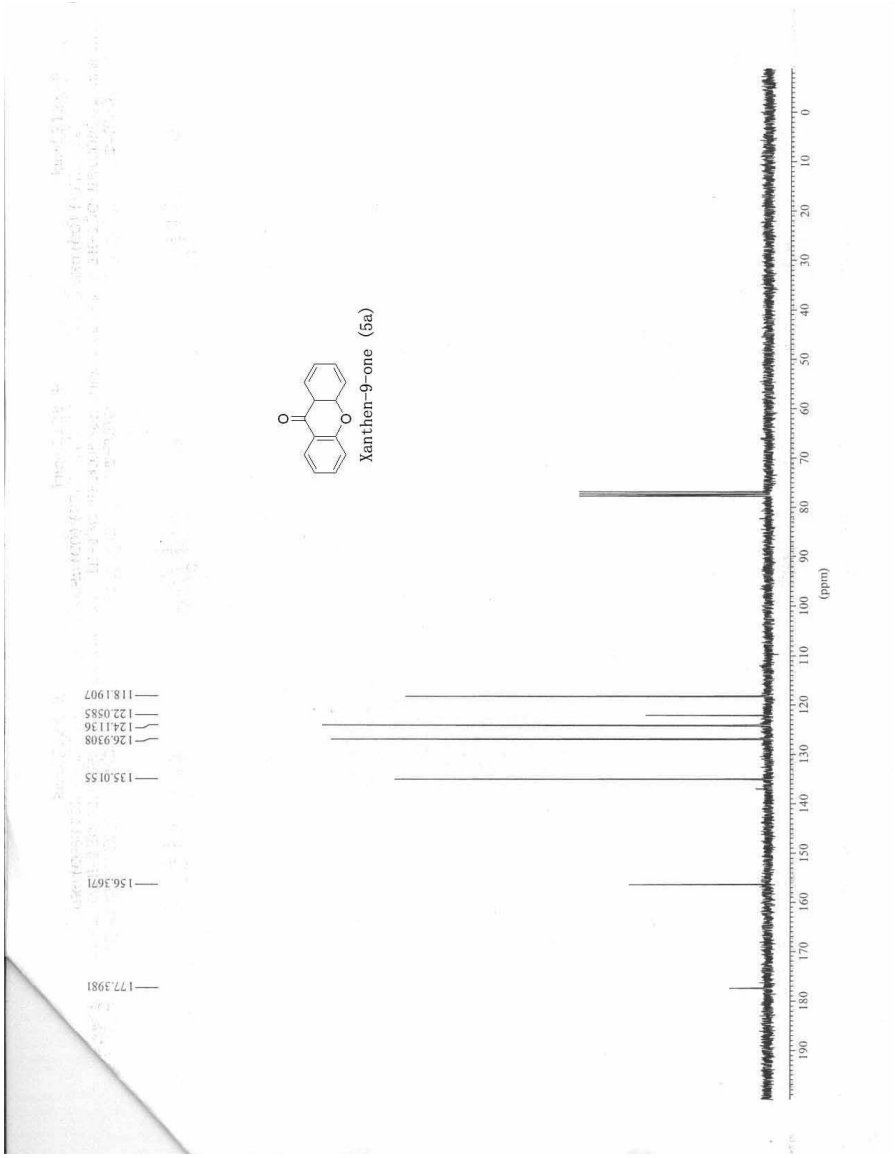


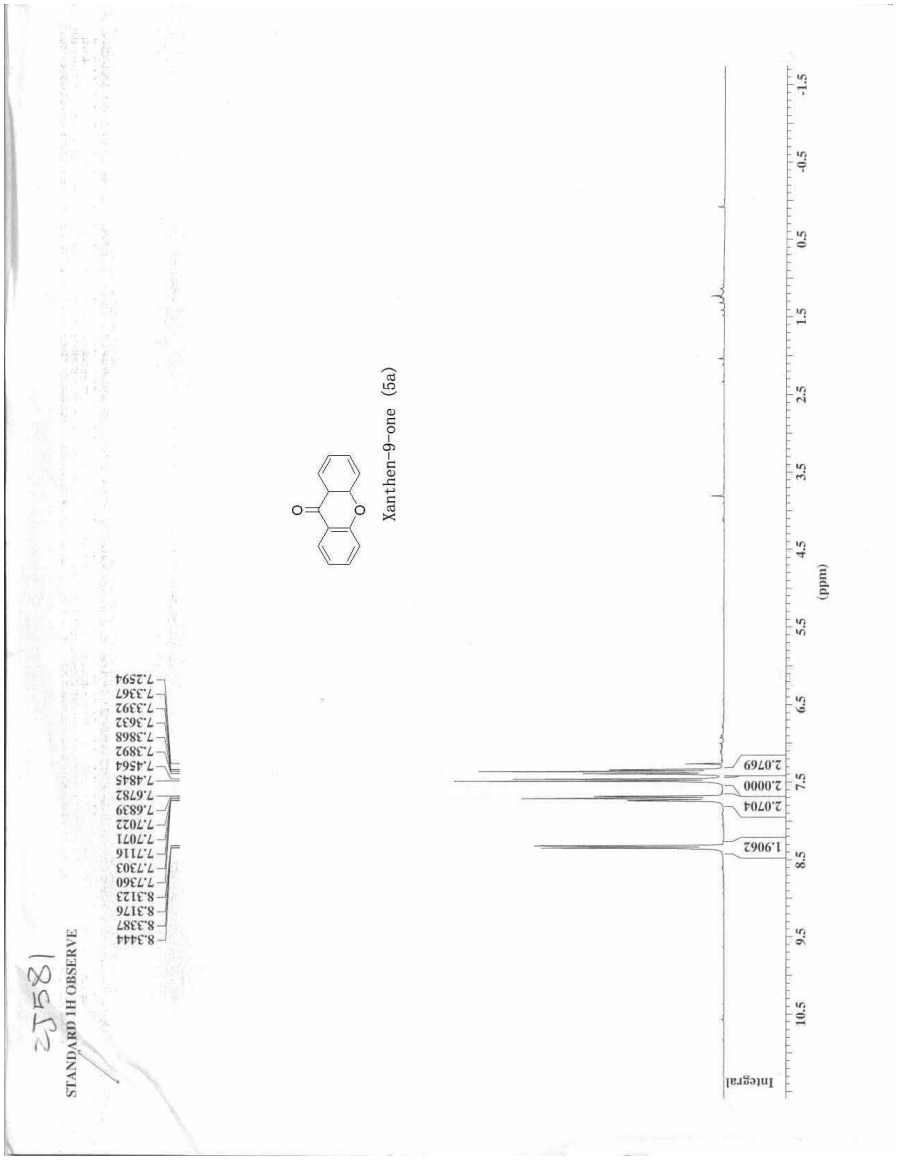
Anilline 3 obtained from the reaction illustrated in eq. 2, Scheme 4

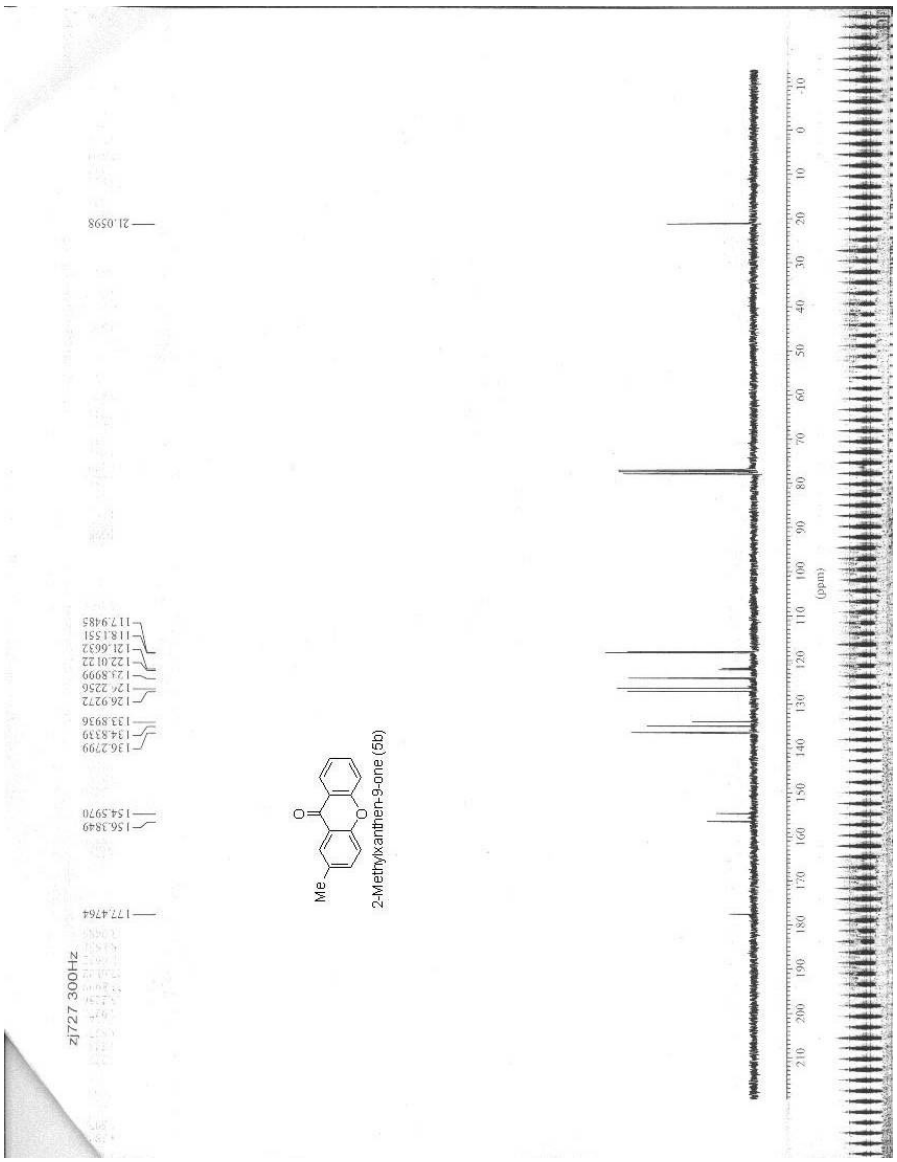


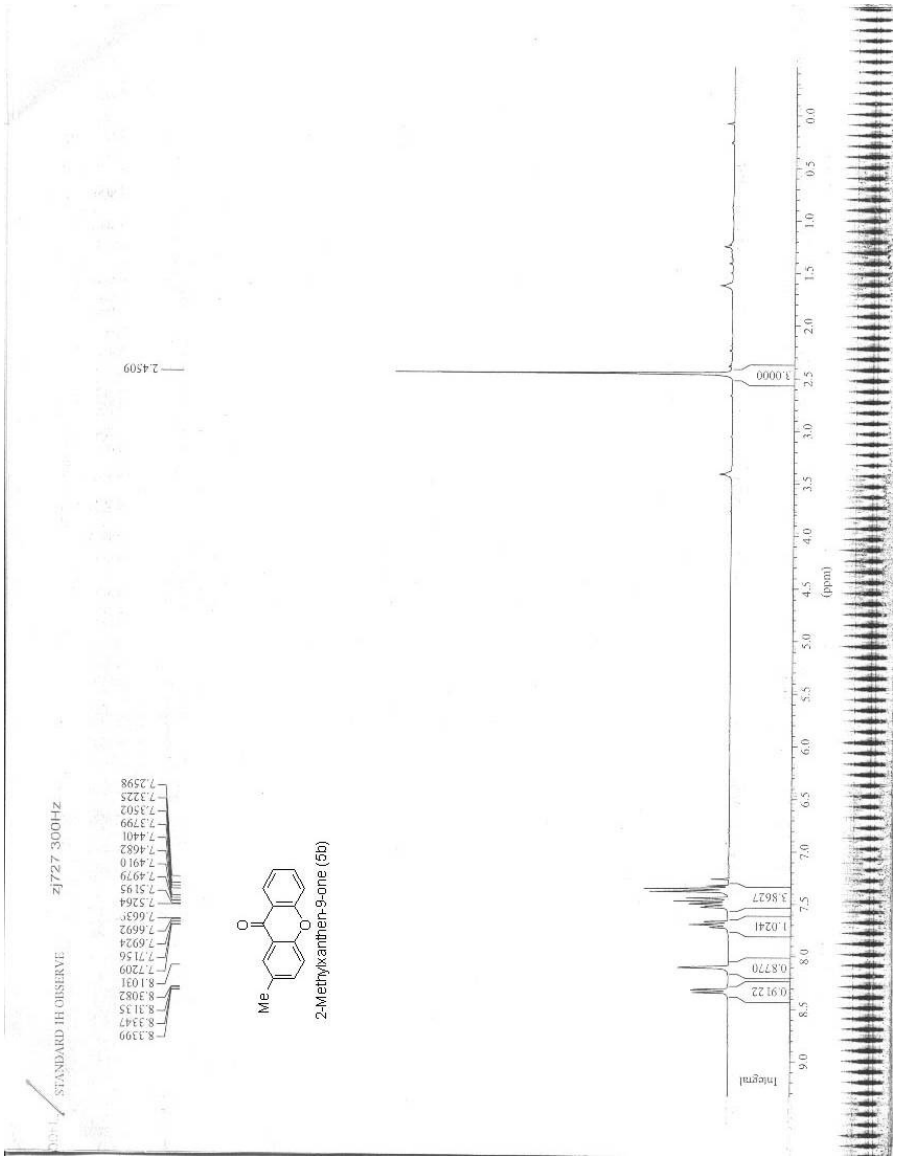


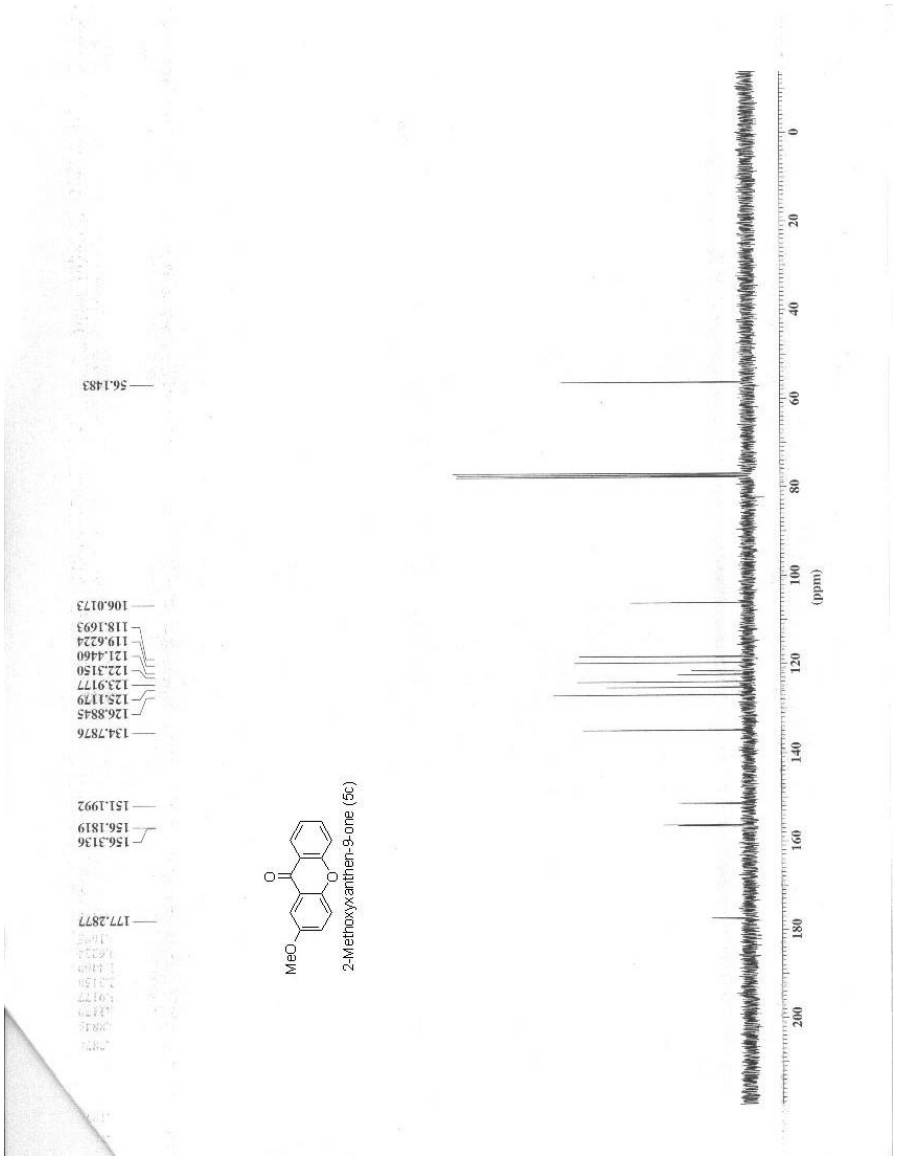


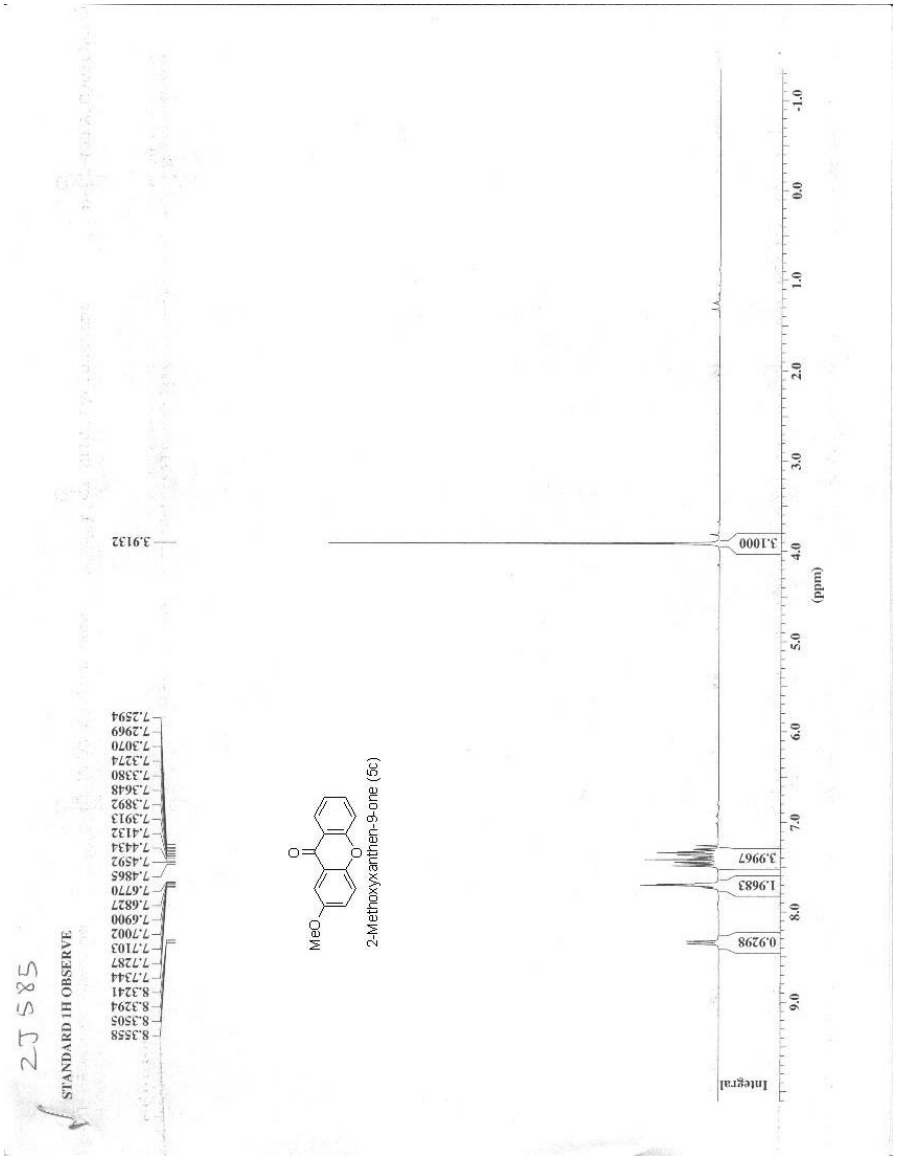


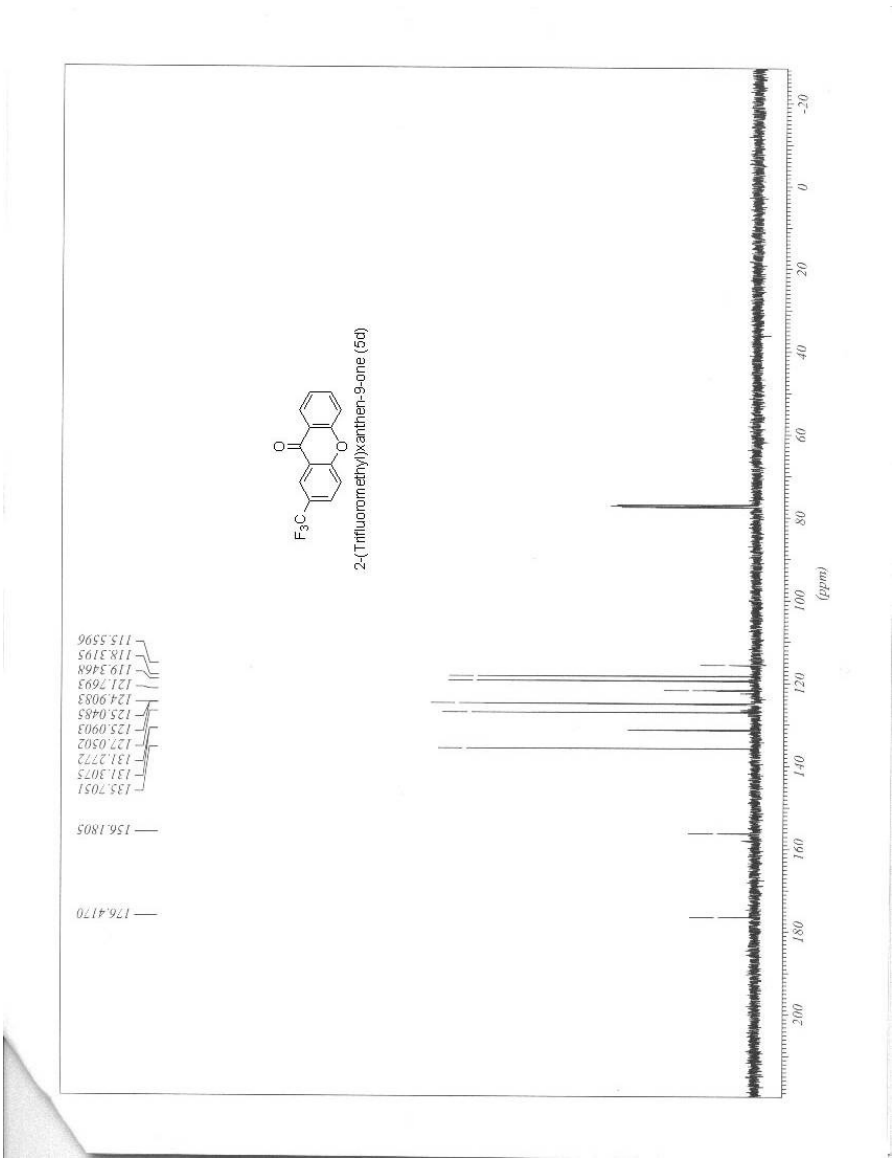


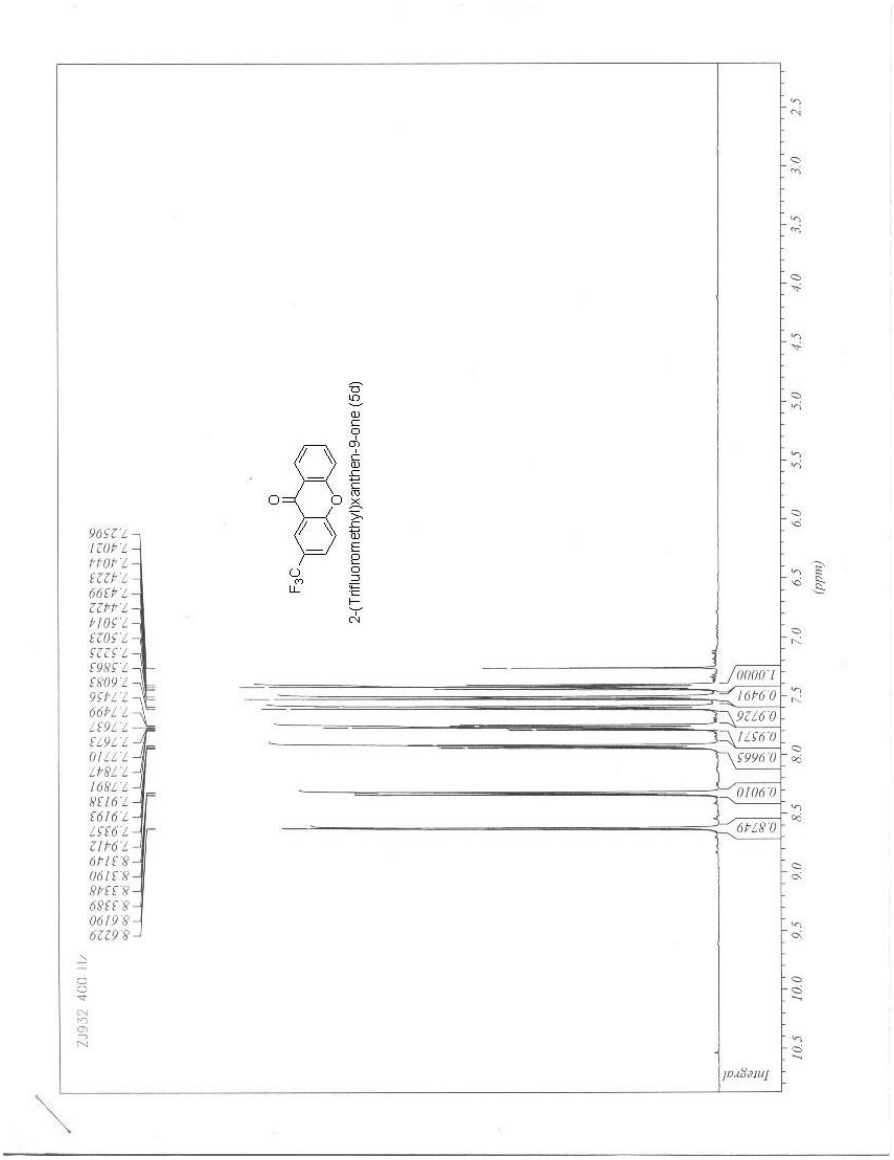


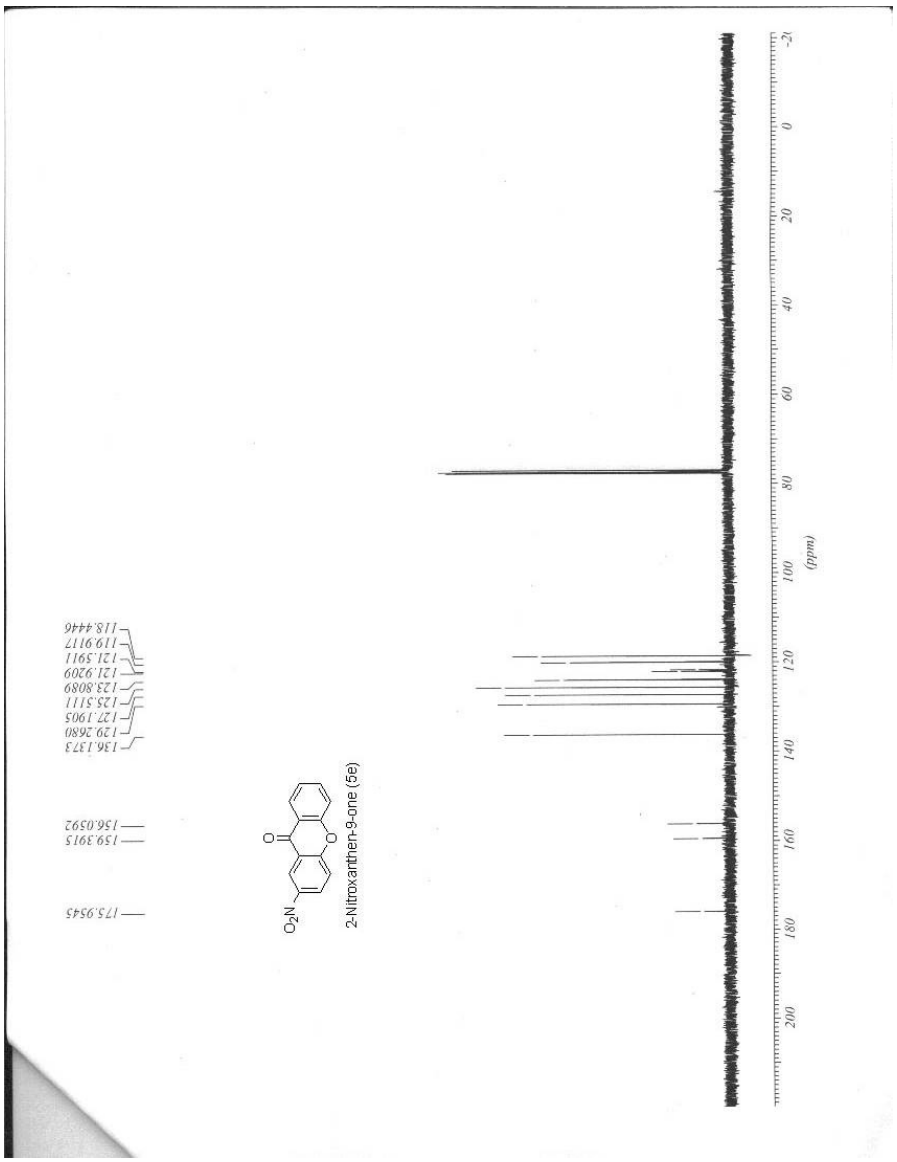


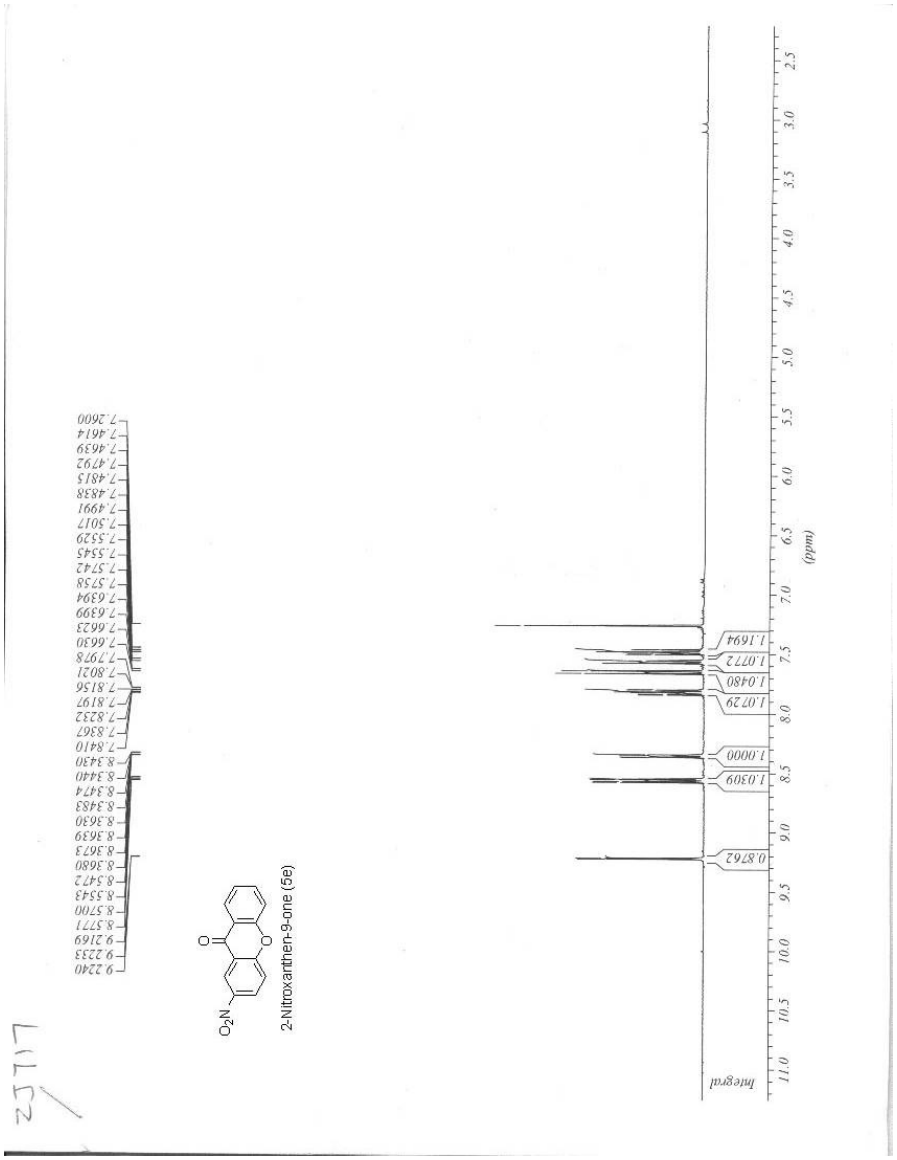


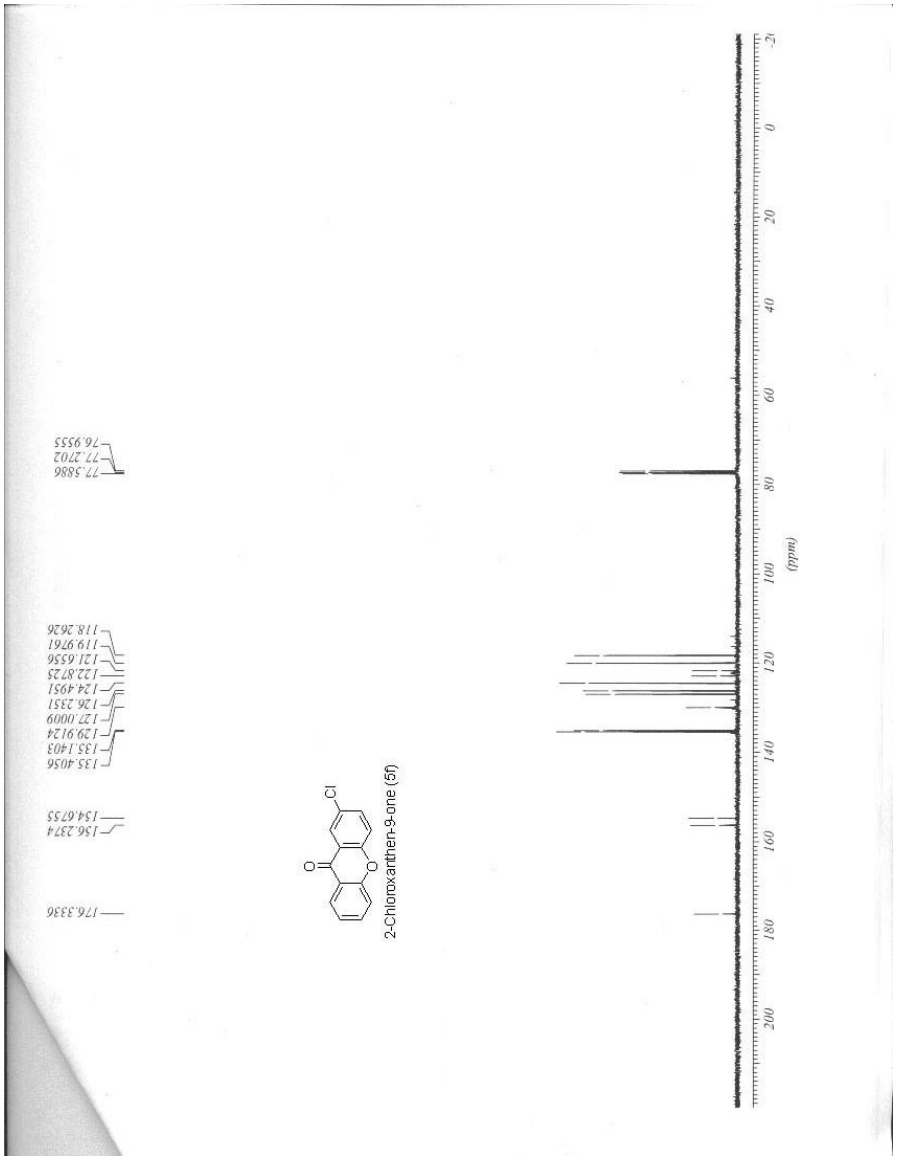


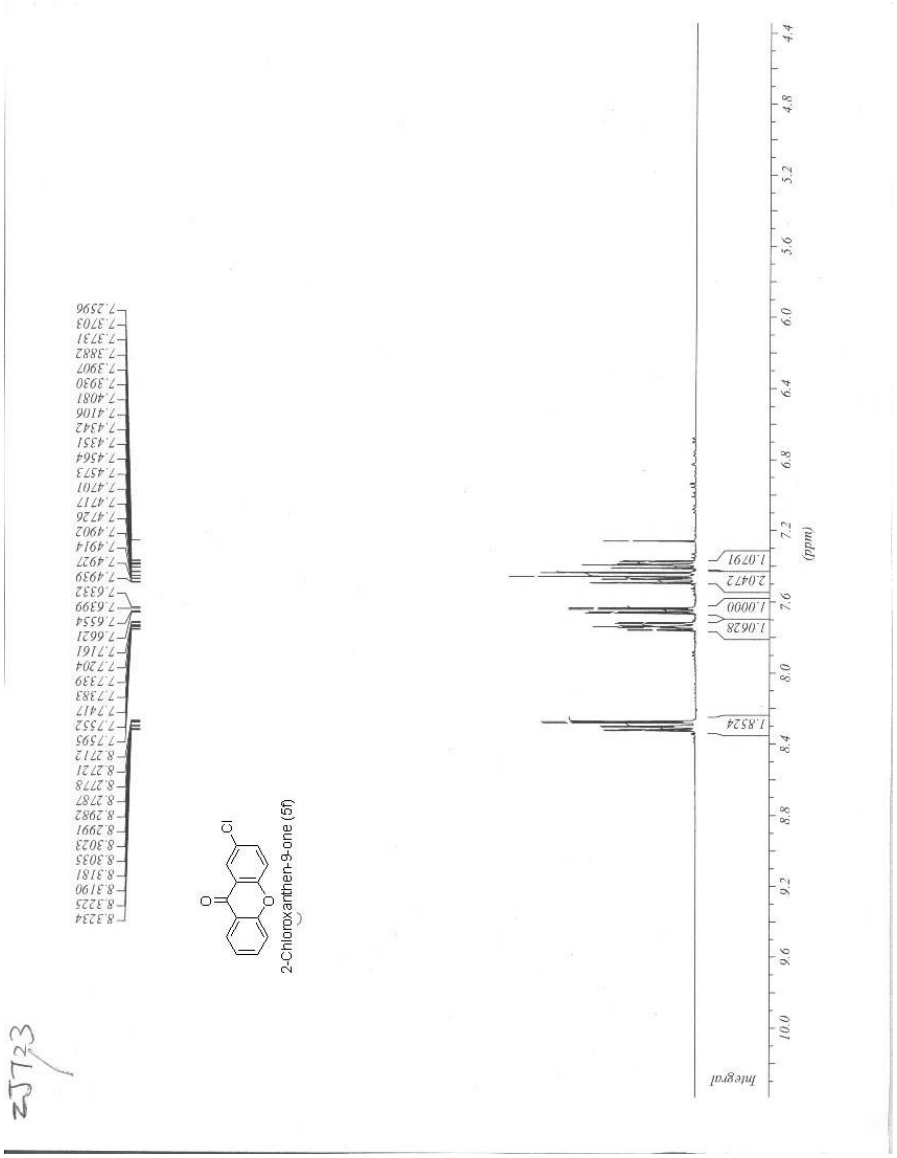


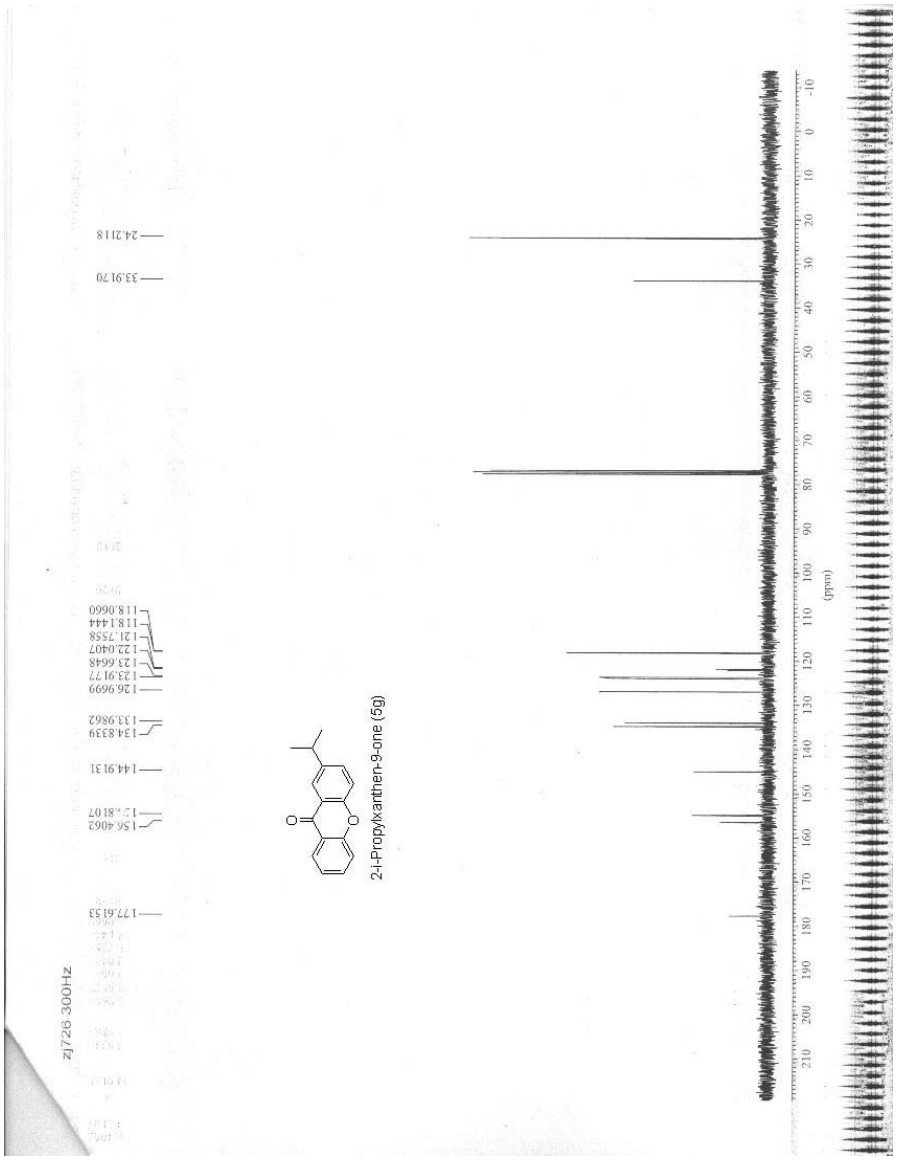


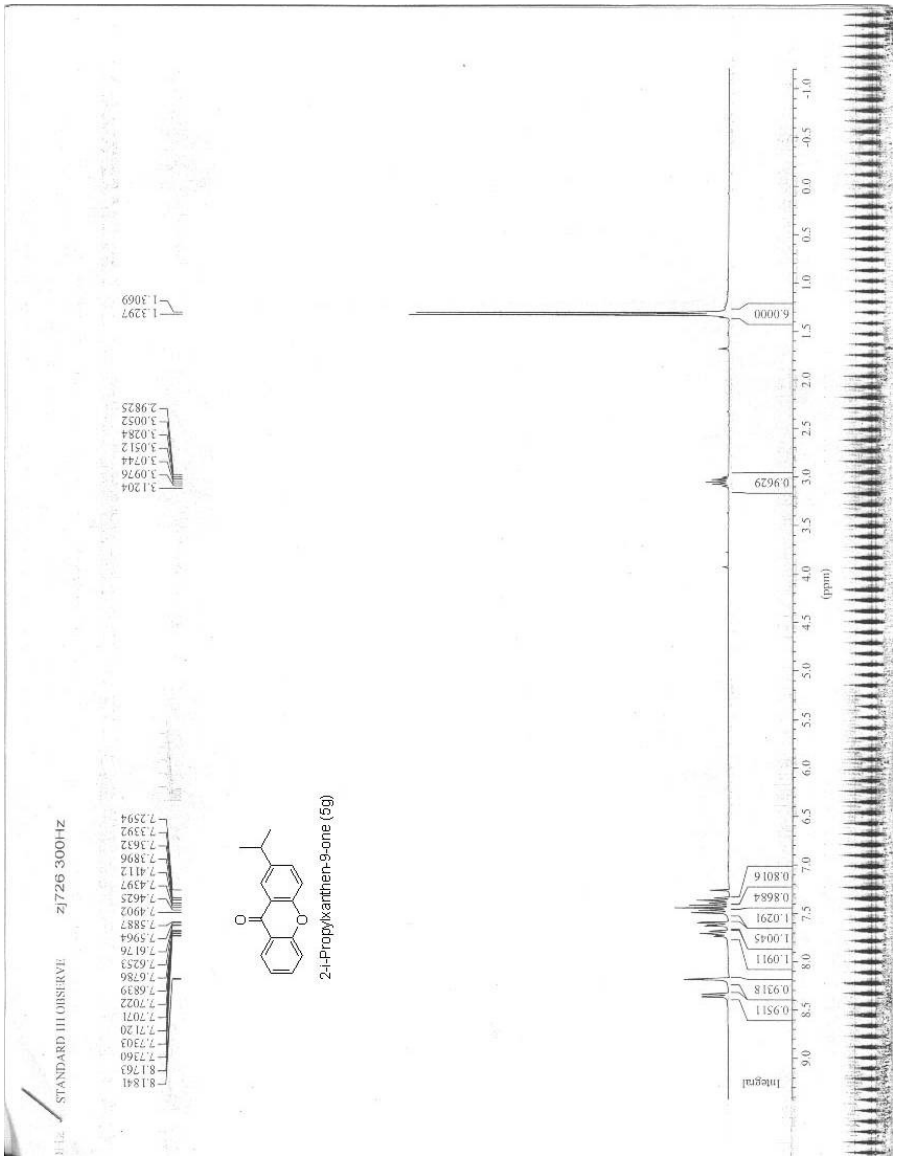


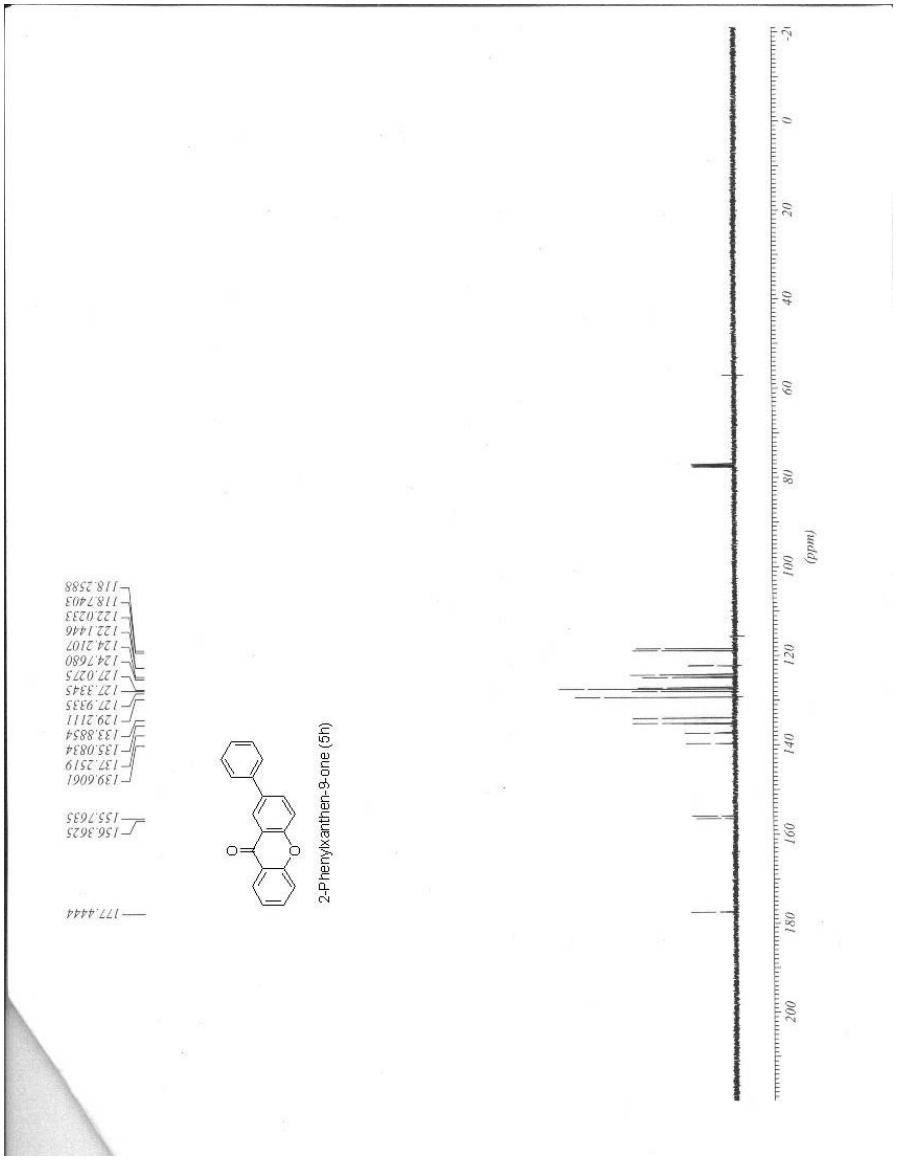


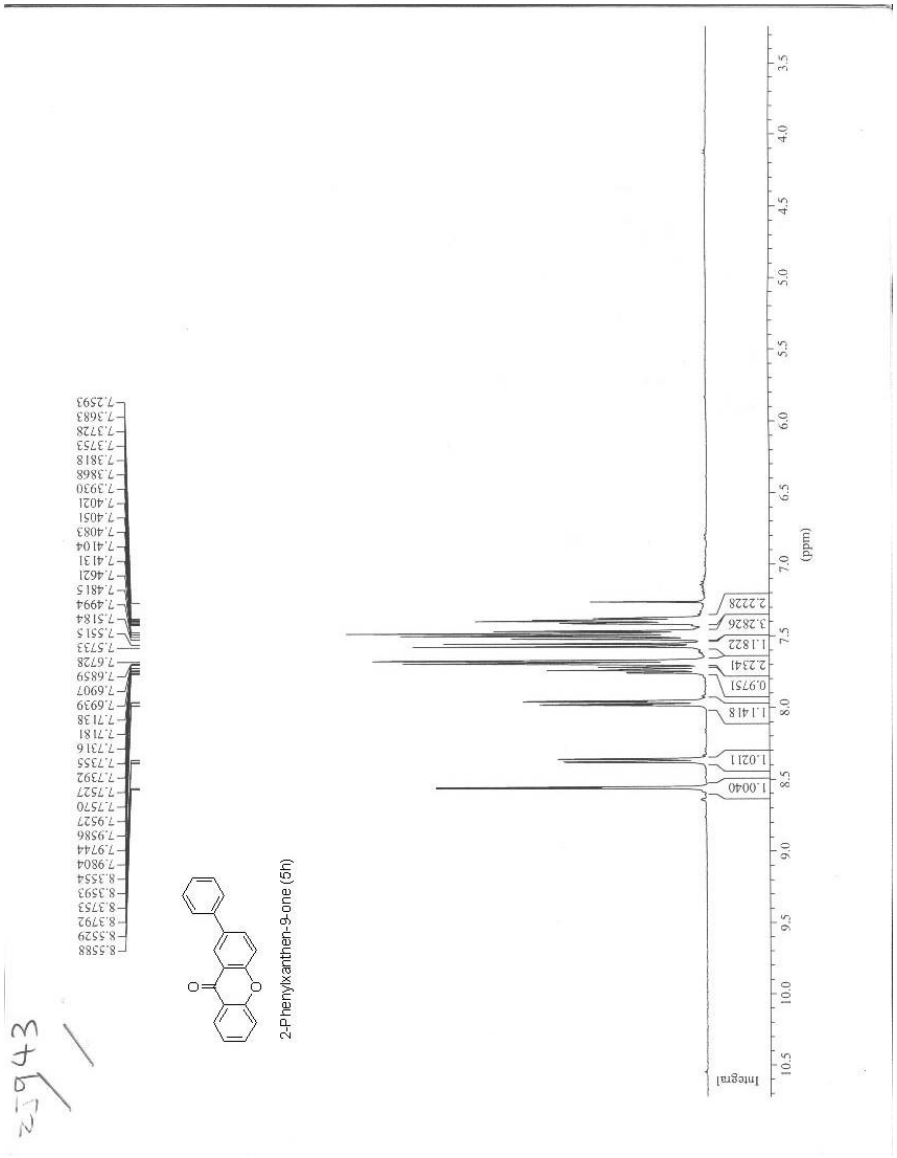


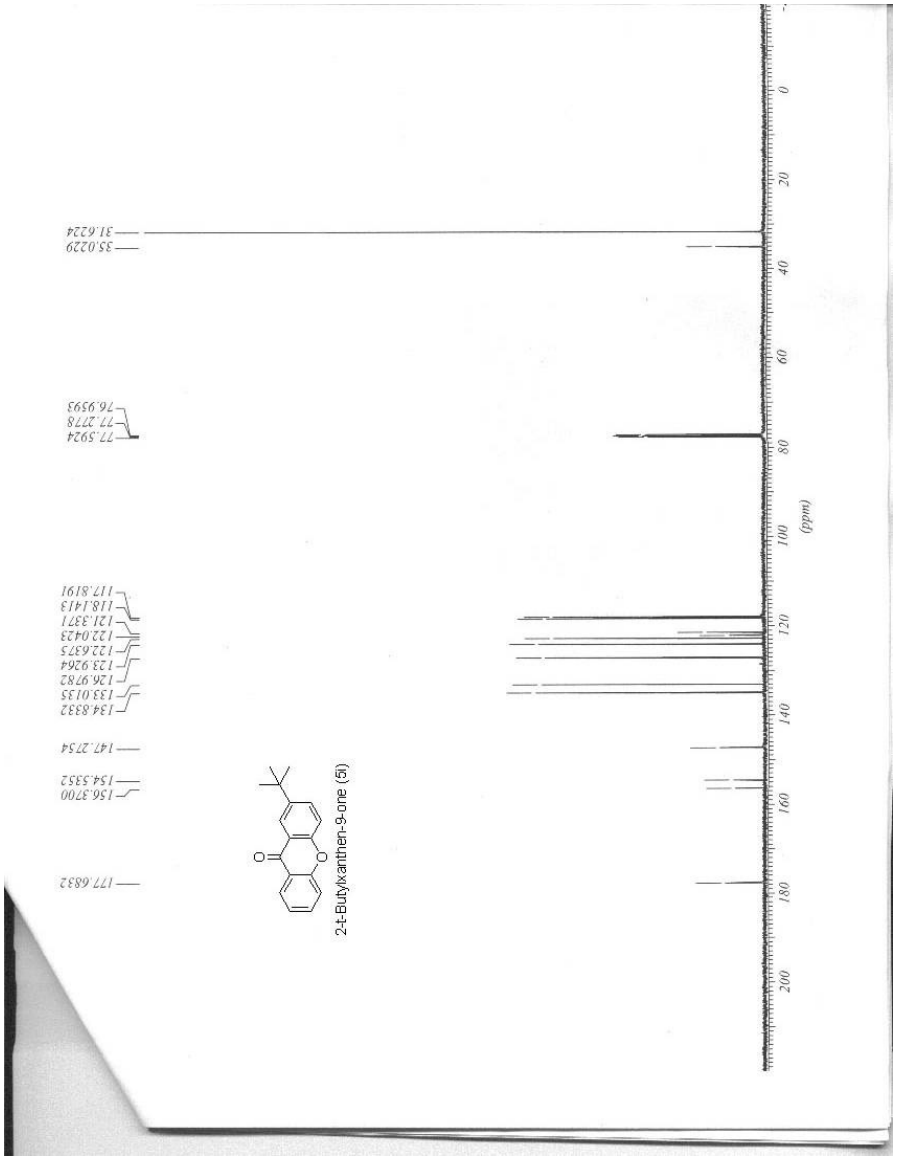


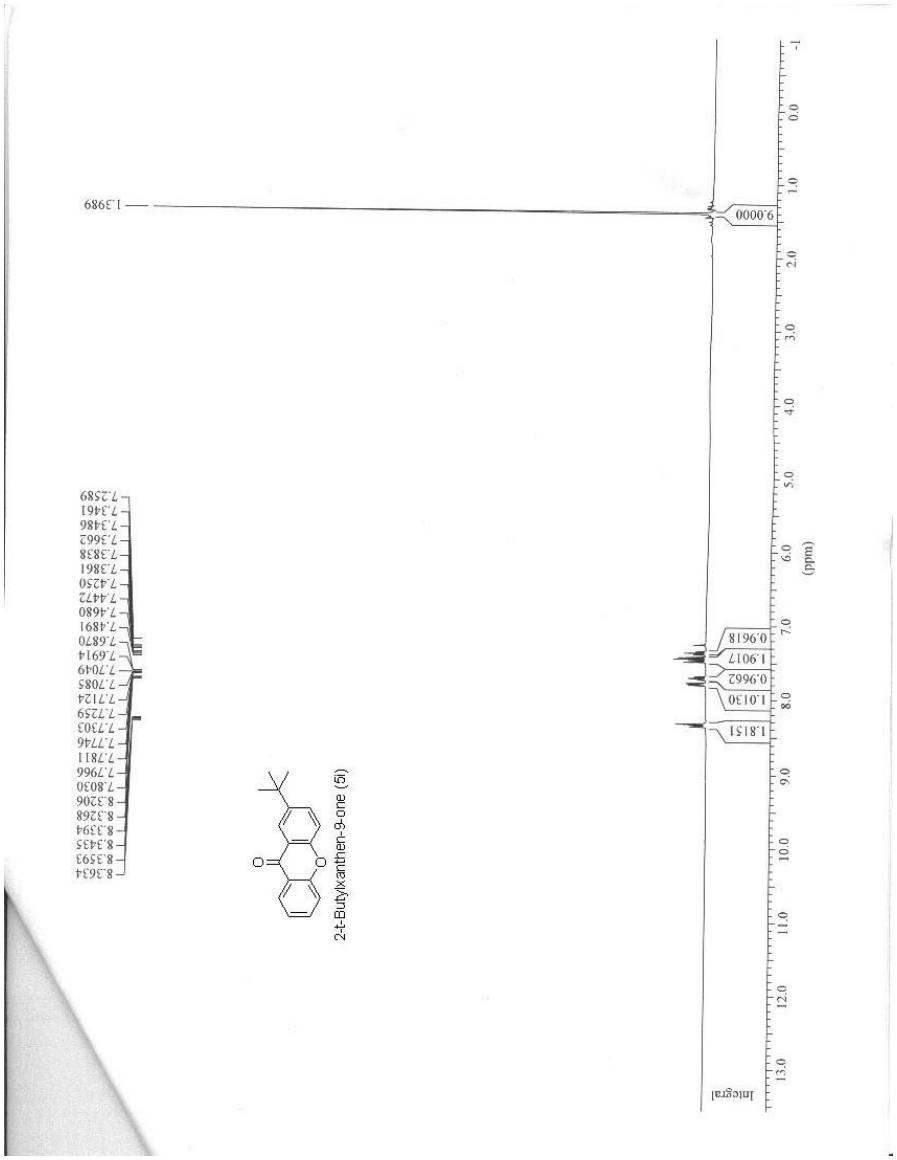


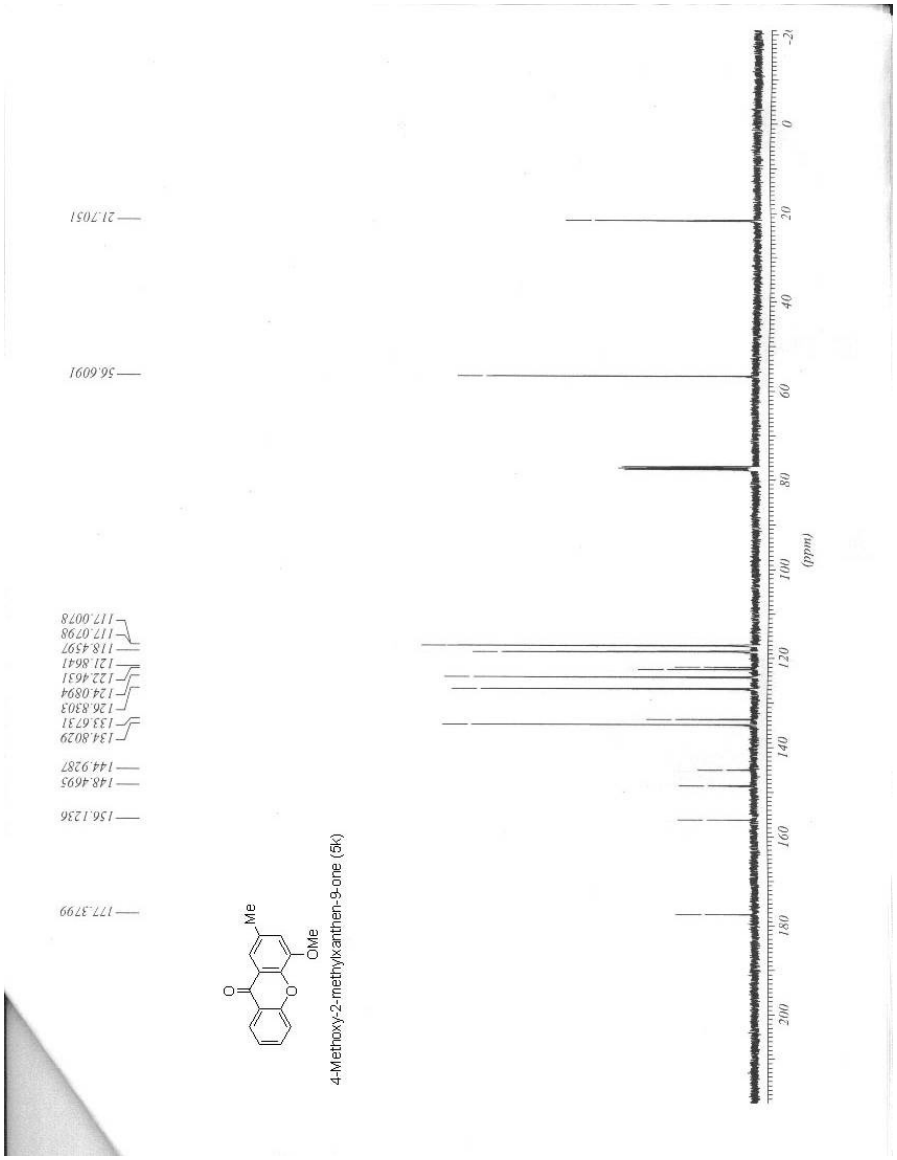




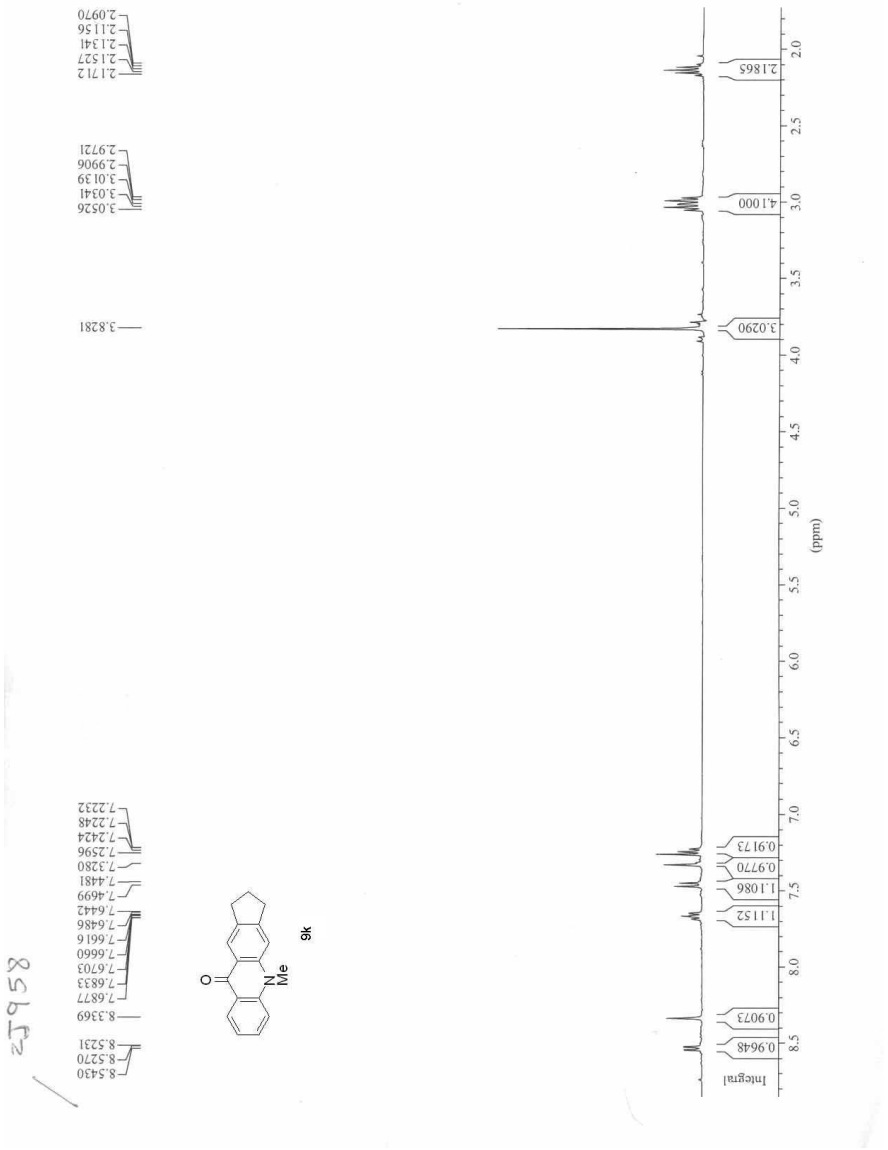


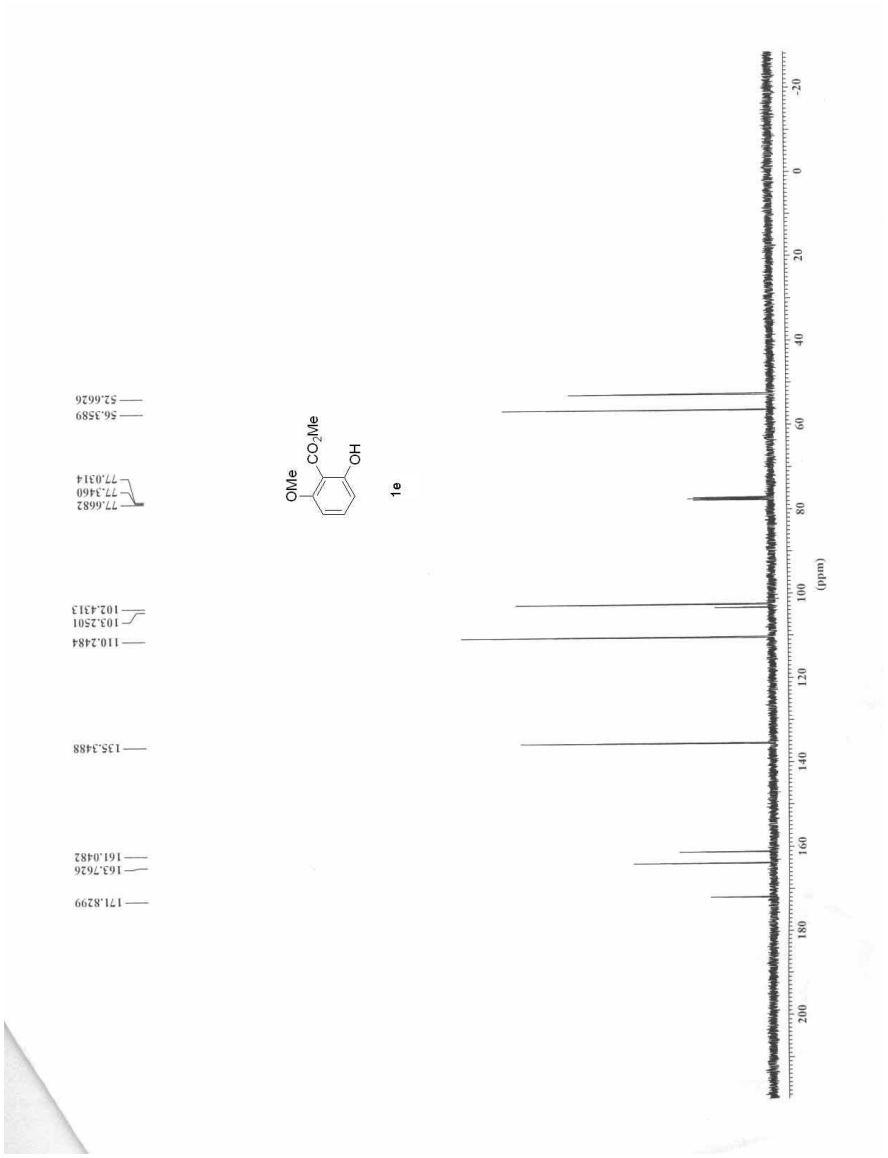


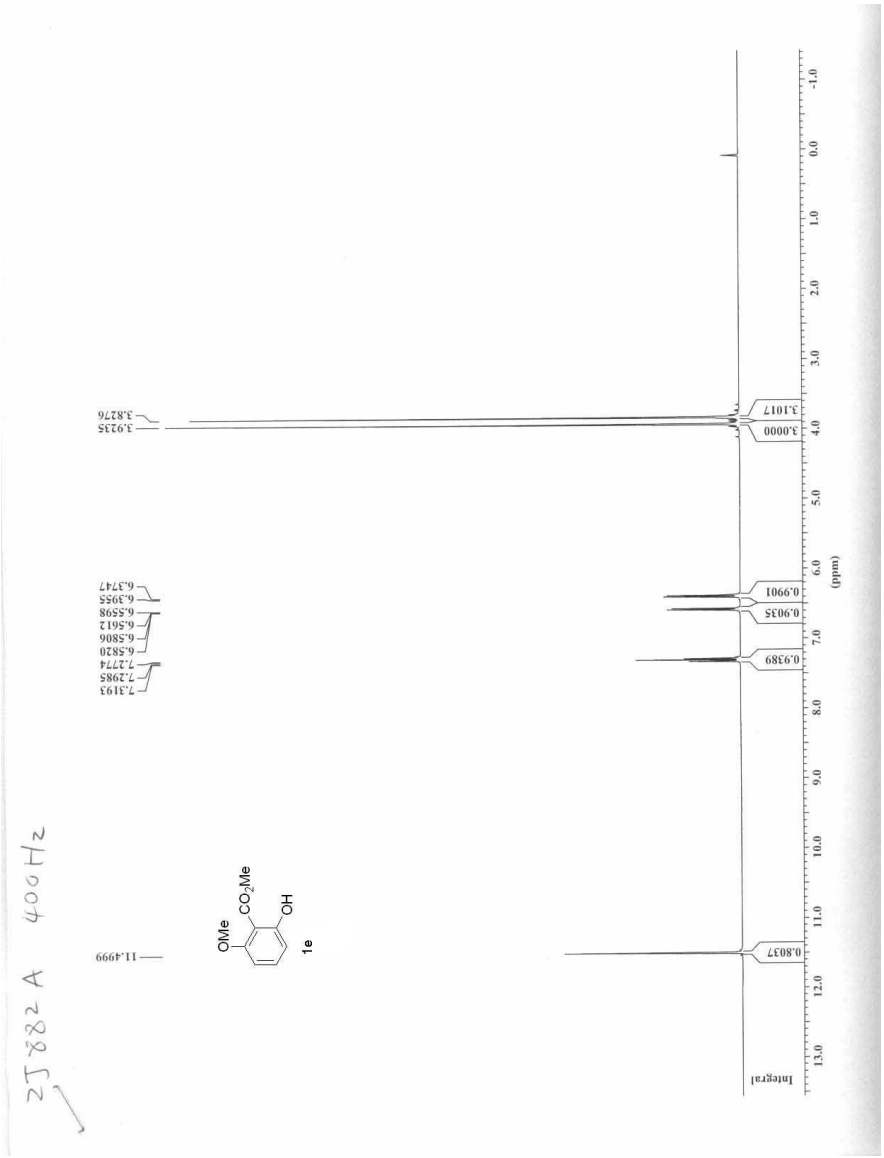


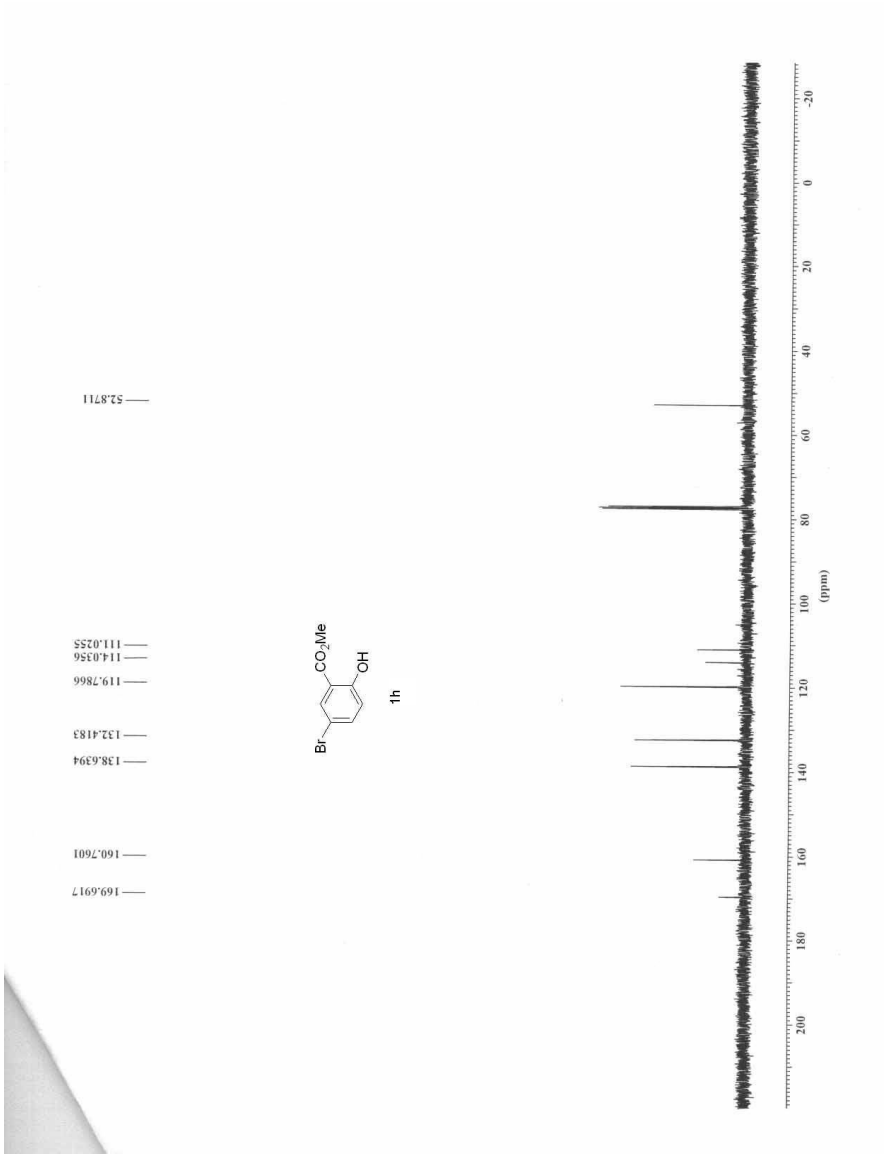


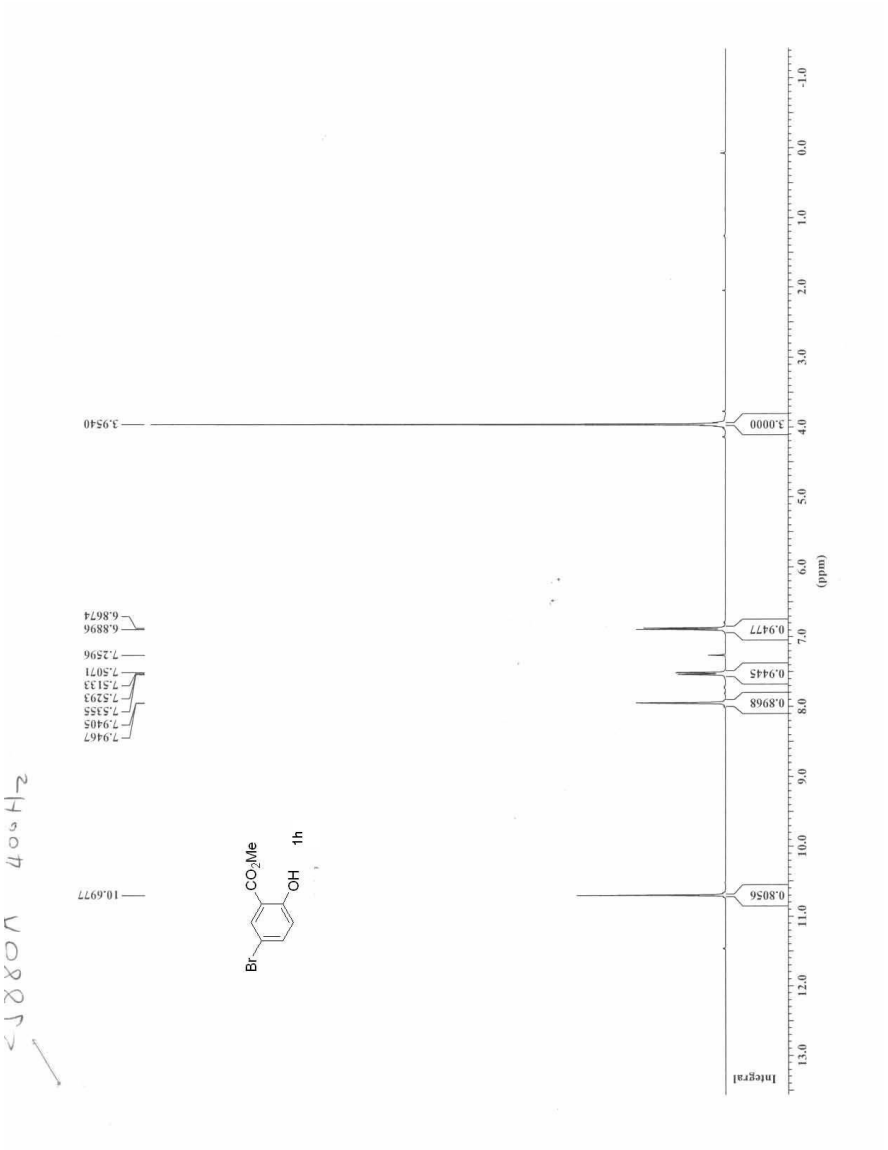
APPENDIX D. CHAPTER 4 ^{1}H AND ^{13}C NMR SPECTRA

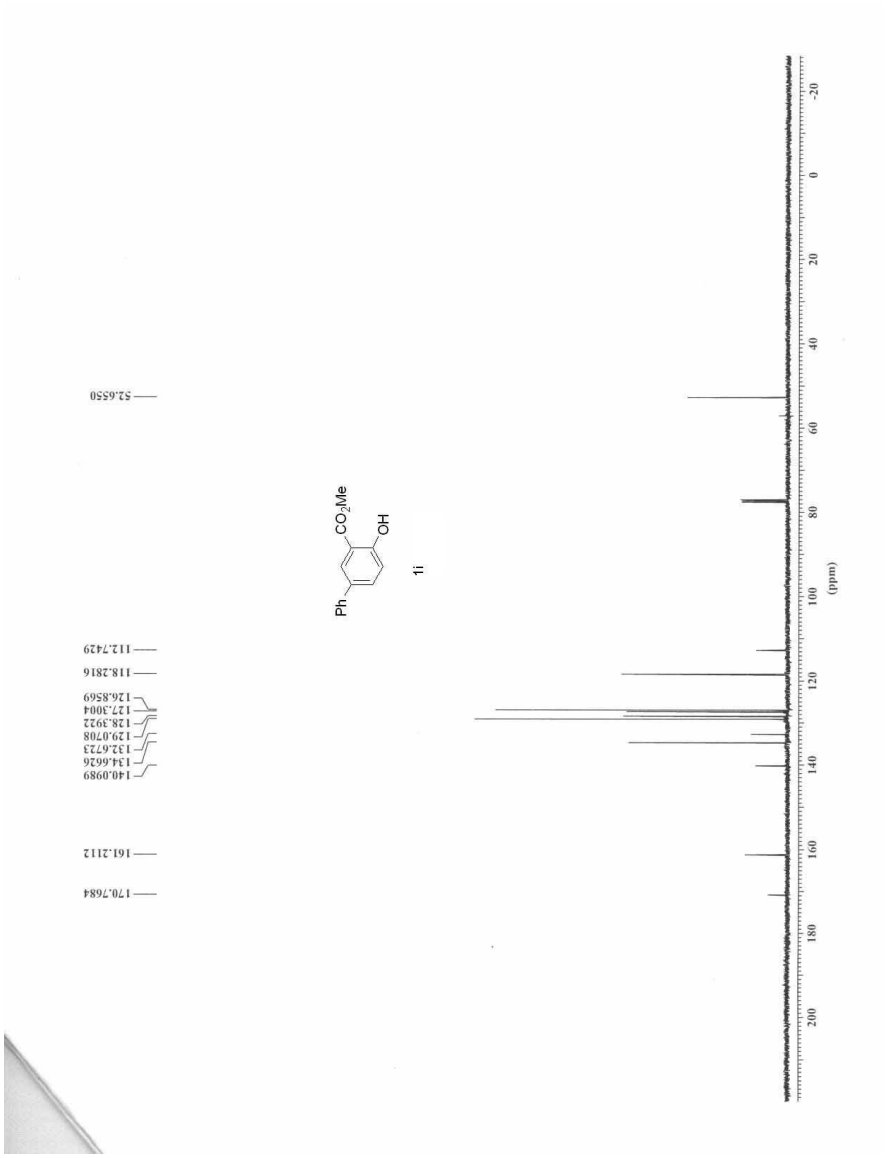


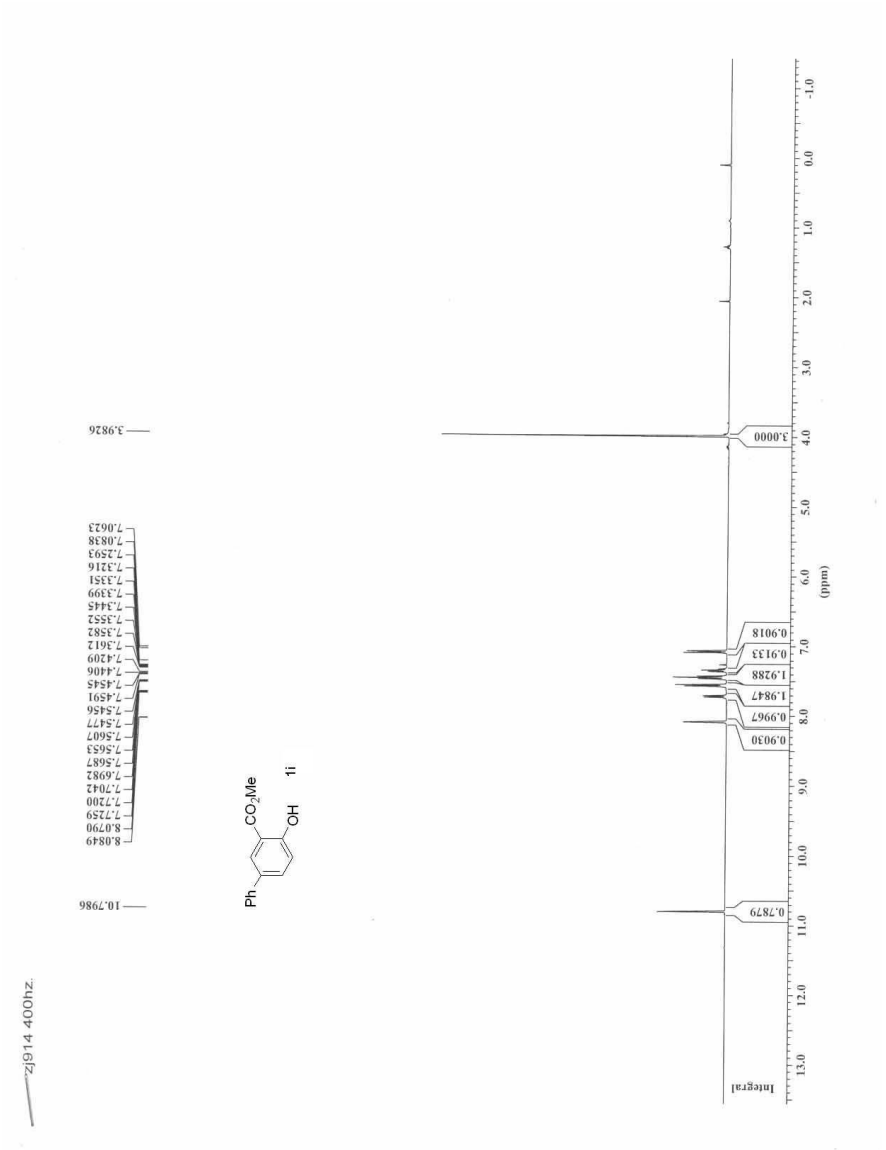


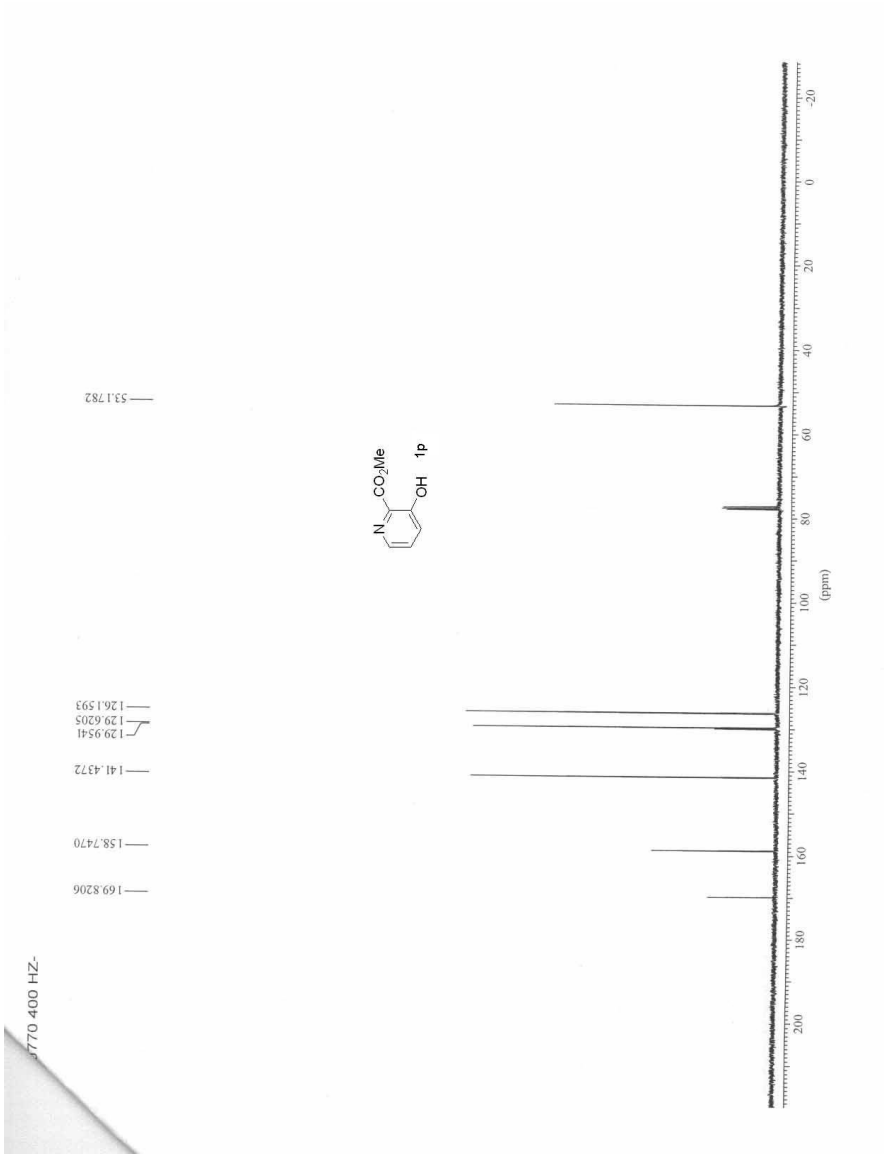


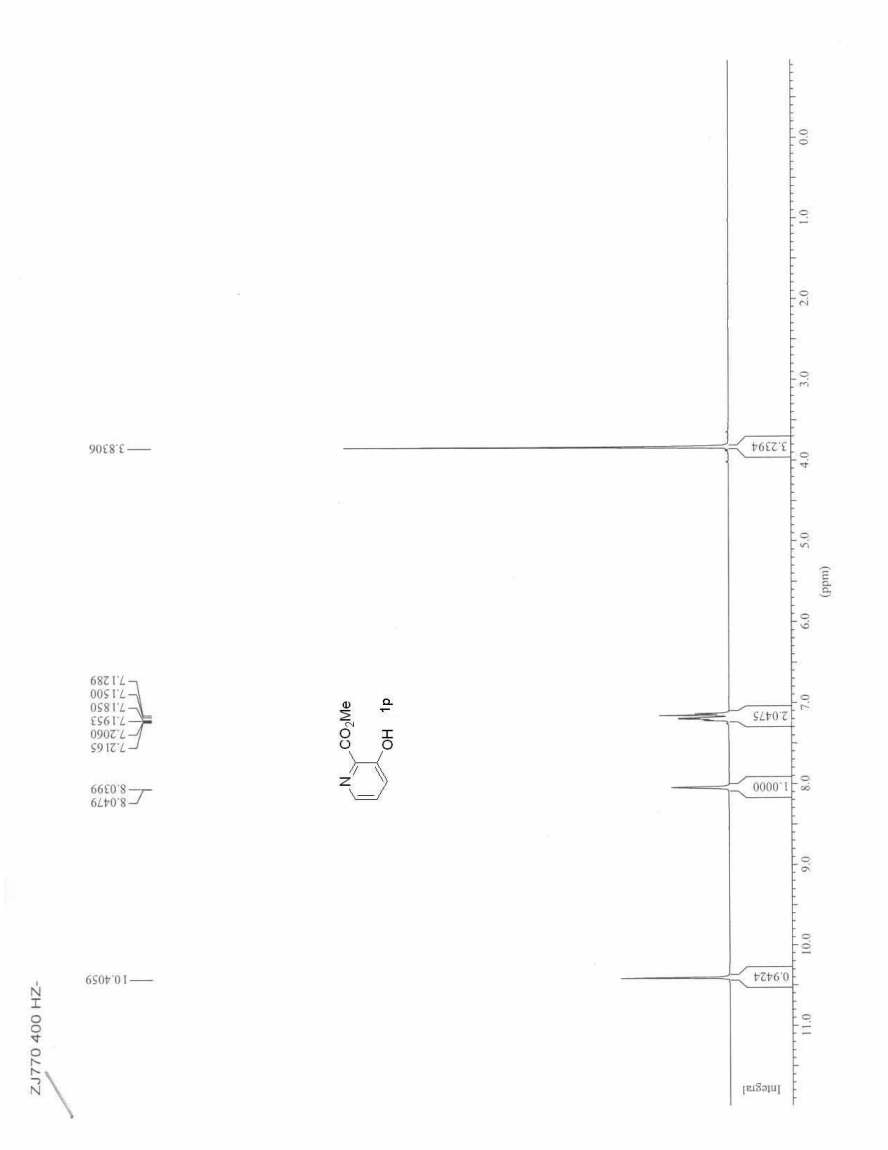


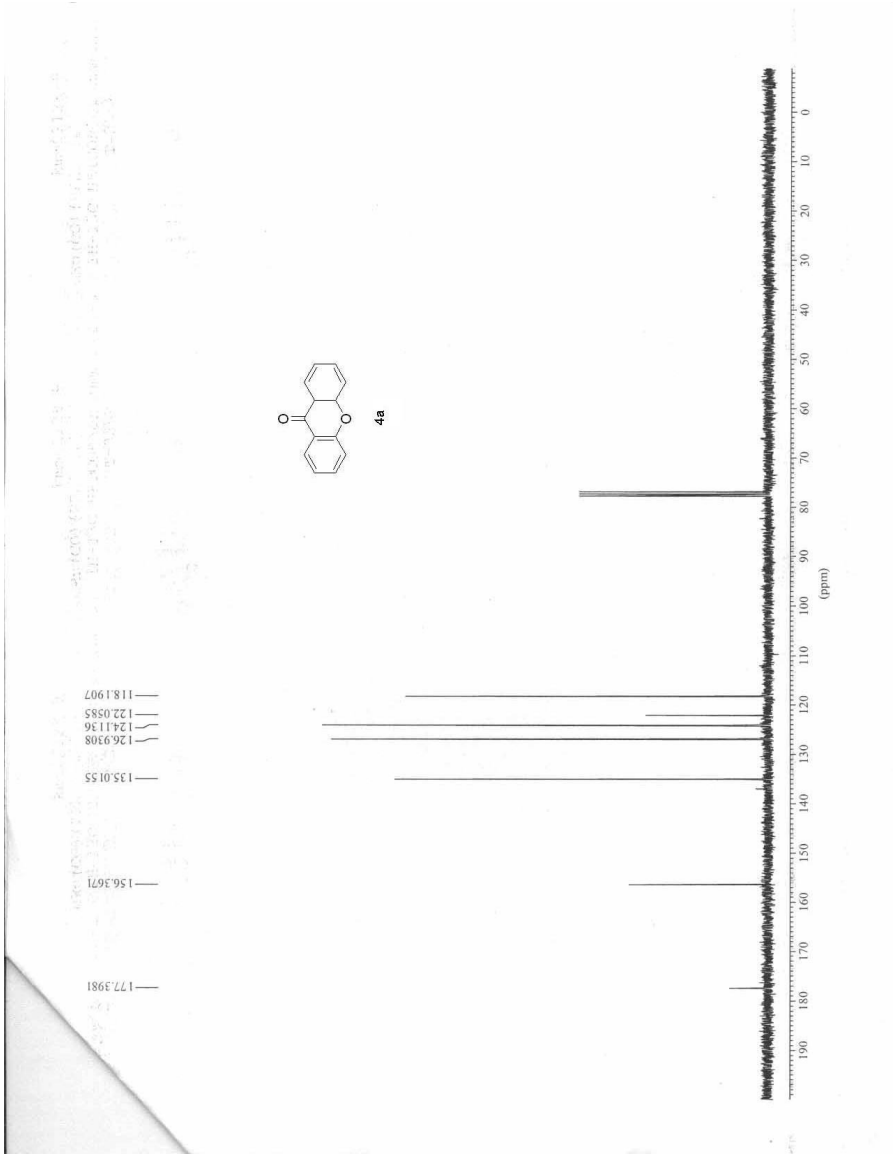


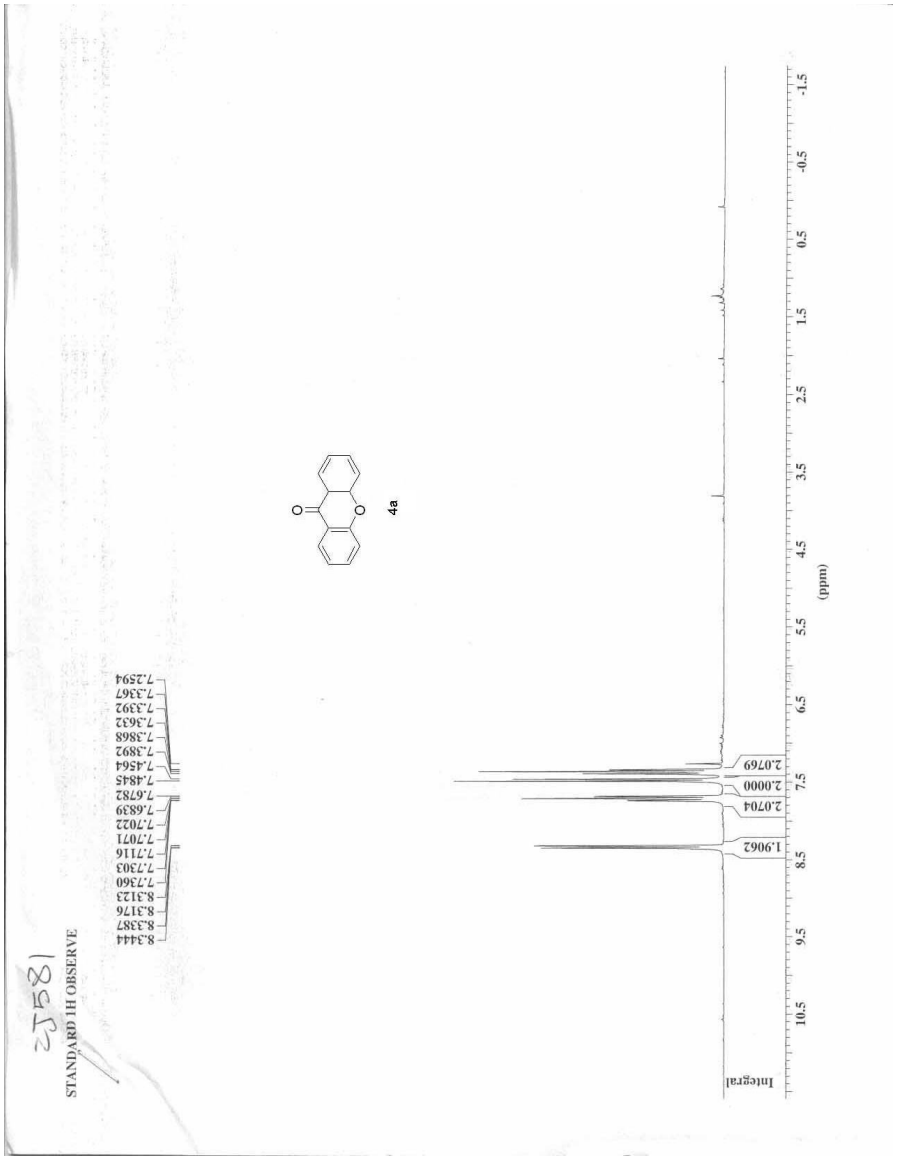


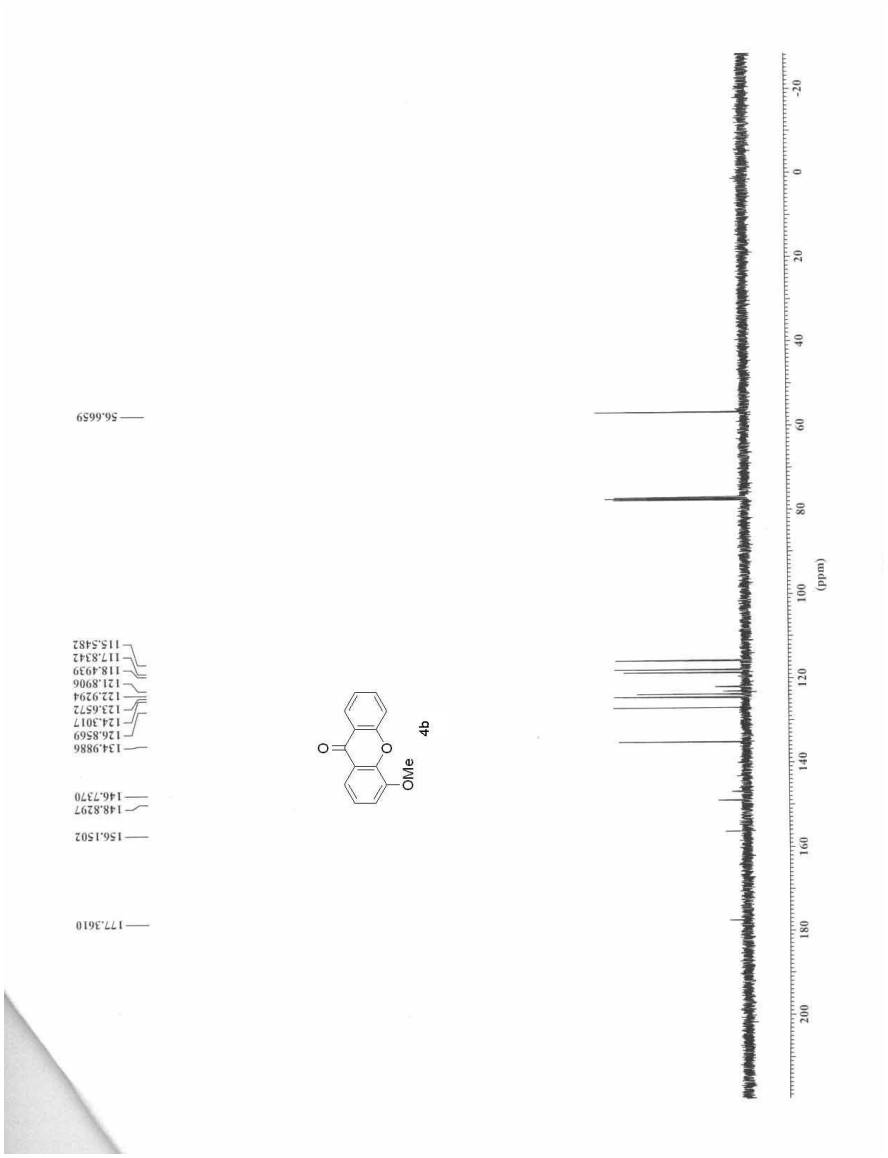


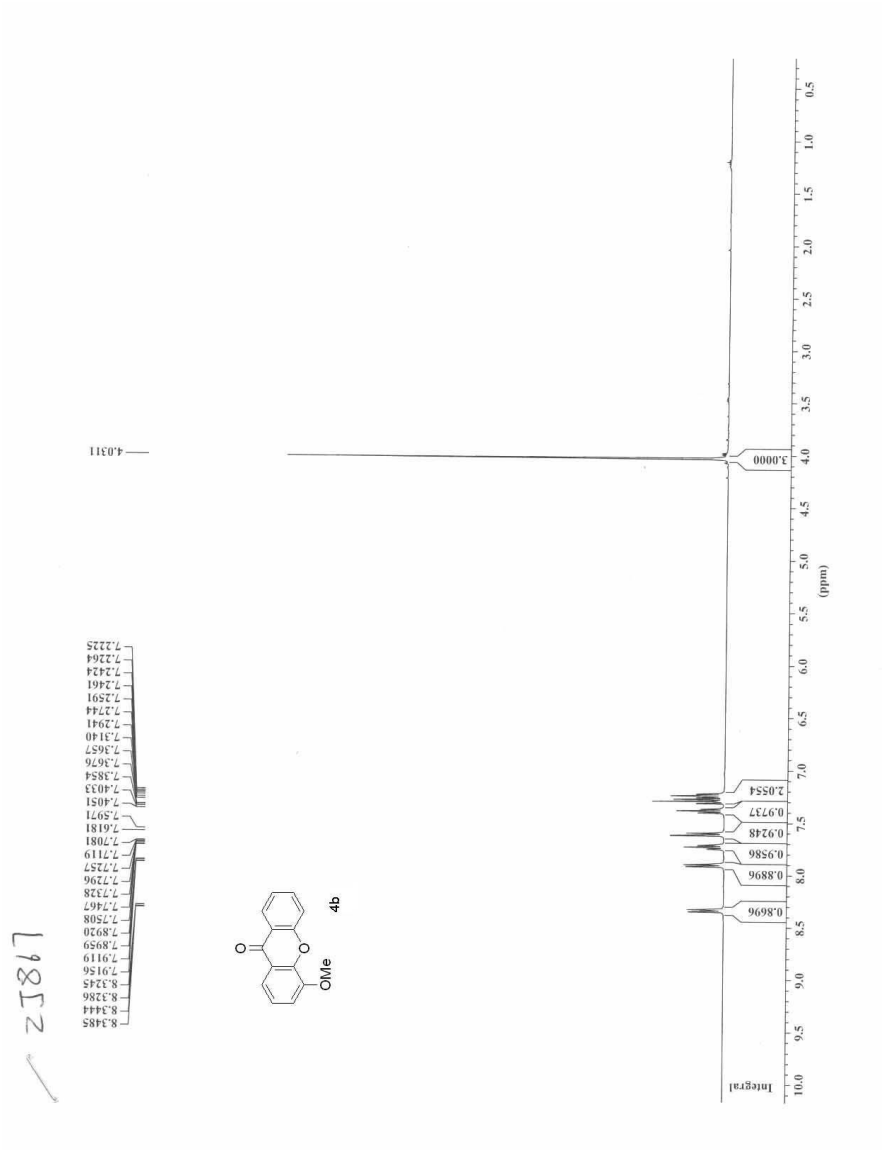











4b
OMe
O
O
Integral
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0.8896
0.8696
4.0311
(ppm)