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Palladium and electrophilic cyclization approaches to carbo- and heterocyclic compounds

by

Dawei Yue

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Richard C. Larock, Major Professor
Daniel Armstrong
William Jenks
George Kraus
Victor Lin

Iowa State University

Ames, Iowa

2004

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Dawei Yue

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Program

To my parents and my wife,

for their love, patience, support and encouragement.

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LIST OF ABBREVIATIONS

aq	aqueous
Bu	butyl
t-Bu	*tert*-butyl
cat.	catalytic
d	doublet
dd	doublet of doublet
eq	equation
equiv	equivalent
Et	ethyl
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infrared
m	multiplet
Me	methyl
mL	milliliter(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho

o-tol	*o*-tolyl
Ph	phenyl
q	quartet
s	singlet
satd	saturated
t	triplet
tert	tertiary
TLC	thin layer chromatography
TMS	trimethylsilyl

GENERAL INTRODUCTION

Palladium-catalyzed organic transformations have become indispensable for many common and state-of-art syntheses. In recent years, a variety of palladium-based methods have been developed which demonstrate palladium's ability to produce a wide range of carbo- and heterocycles. These reactions have proven to be general in scope and exhibit a high degree of regio- and stereospecificity. Palladium catalysts have also been shown to be tolerant of considerable functionality and are not generally moisture or air sensitive.

Electrophilic cyclization has been widely used in organic synthesis. However, this type of cyclization has mainly been limited to the cyclization of carbon-carbon double bonds. The cyclization of compounds with carbon-carbon triple bonds is relatively unexplored. Previous work by Cacchi, Flynn, Barluenga and Larock has shown that iodine and other electrophiles can be used for the synthesis of benzo[*b*]furans, benzo[*b*]thiophenes, indoles and isoquinolines. This type of cyclization is generally viewed as proceeding through an intramolecular, stepwise electrophilic addition and dealkylation mechanism involving a cationic intermediate. The mild reaction conditions and high efficiency encouraged us to further explore the generality of this synthetic approach to biologically interesting benzo[*b*]furans, isochromenes and coumestans.

The Larock group has recently discovered new 1,4-palladium migrations from an aryl to an aryl, a vinyl to an aryl, an aryl to an alkyl and an alkyl to an aryl position. Utilizing these novel migrations in synthesis has also been explored. We have investigated the possibility of other types of Pd migration reactions and their synthetic applications. As a result, an unusual 1,4-palladium migration from an aryl to an imidoyl position has been realized and its synthetic applications have also been explored.

Dissertation Organization

This dissertation is composed of four chapters. The chapters presented herein are written following the guidelines for a full paper in the *Journal of Organic Chemistry* and are composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgements, and references.

Chapter 1 describes the synthesis of 2,3-disubstituted benzo[*b*]furans by palladium catalyzed coupling and electrophilic cyclization of terminal alkynes. This process has proven to be highly efficient. Various electrophiles undergo this process and give high yields of the desired cyclization products.

Chapter 2 presents the synthesis of heterocycles by the electrophilic cyclization reactions of acetylenic aldehydes, ketones and imines. The overall synthetic process involves the coupling of terminal acetylenes with *o*-haloarenecarboxaldehydes and ketones by a palladium/copper-catalyzed coupling reaction, followed by electrophilic cyclization with various electrophiles in the presence of proper nucleophiles.

Chapter 3 examines the synthesis of coumestan and coumestrol by selective electrophilic cyclization, followed by palladium-catalyzed intramolecular carbonylation and lactonization. The biologically interesting coumestan system can be quickly constructed by this very efficient approach.

Chapter 4 serves to expand the scope and synthetic utility of an unusual 1,4-palladium through space migration. The synthesis of various fluoren-9-ones has been accomplished by the palladium-catalyzed intramolecular C-H activation of imines derived from 2-iodoaniline and biarylcarboxaldehydes. This methodology makes use of a novel 1,4-palladium

migration from an aryl position to an imidoyl position to generate the key imidoyl palladium intermediate, which undergoes intramolecular arylation to produce imines of complex polycyclic compounds containing the fluoren-9-one core structure.

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

CHAPTER 1. SYNTHESIS OF 2,3-DISUBSTITUTED BENZO[*b*]FURANS BY THE PALLADIUM-CATALYZED COUPLING OF *o*-IODOANISOLE AND TERMINAL ALKYNES, FOLLOWED BY ELECTROPHILIC CYCLIZATION

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

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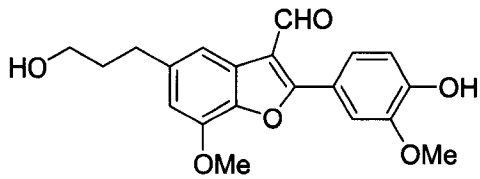
Abstract

2,3-Disubstituted benzo[*b*]furans are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of *o*-iodoanisole and terminal alkynes, followed by electrophilic cyclization using I_2, Br_2, PhSeCl and *p*-$O_2NC_6H_4SCl$. Aryl- and vinylic-substituted alkynes undergo electrophilic cyclization in excellent yields. Biologically important furopyridines can be prepared by this approach in high yields.

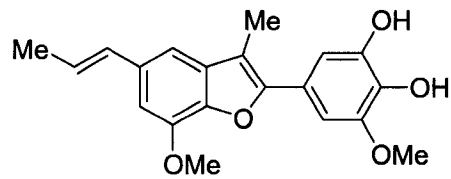
Introduction

The benzo[*b*]furan nucleus is prevalent in a wide variety of biologically active natural and unnatural compounds.[1] Many 2-arylbenzofuran derivatives are well known to exhibit a broad range of biological activities, such as anticancer,[2] antiproliferative,[3] antiviral,[4] antifungal,[5] immunosuppressive,[6] antiplatelet,[7] antioxidative,[8] insecticidal,[9] anti-inflammatory,[10] antifeedant,[11] and cancer preventative activity.[12] These compounds are also important calcium blockers[13] and phytoestrogens.[14] For instance, XH-14[15] was the first

reported nonnucleoside-type potent adenosine A_1 agonist[16] and obovaten is known as an active antitumor agent.[17]



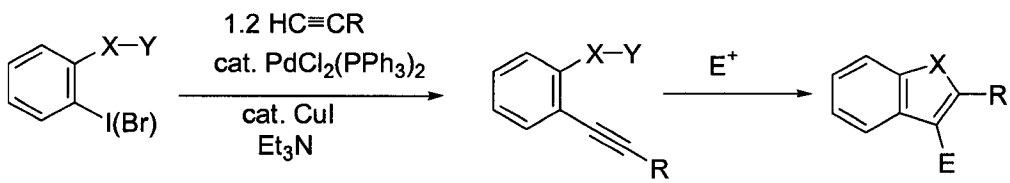
XH-14



obovaten

There has been growing interest in developing a general and versatile synthesis of benzo[*b*]furan derivatives. A number of synthetic approaches to this class of compounds have been introduced in recent years.[18] One common approach to heterocycles that has been utilized for the synthesis of benzo[*b*]furans,[19] benzo[*b*]thiophenes,[20] indoles[21] and isoquinolines[22] has been electrophilic cyclization of the corresponding 2-(1-alkynyl)-phenols, -thioanisoles, -anilines and -imines respectively (Scheme 1).

Scheme 1



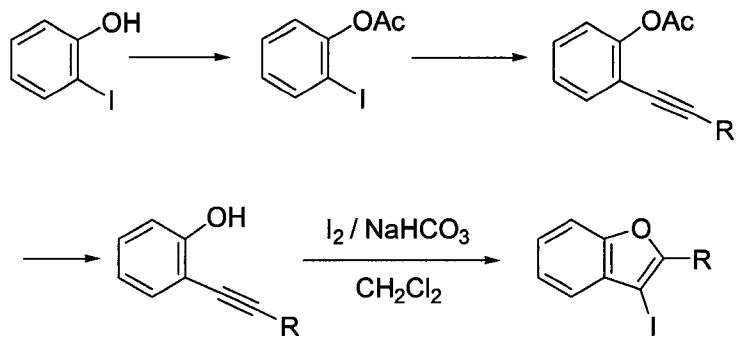
X-Y = O-H, S-Me, NMe_2, CH=N-*t*-Bu

E^+ = Br_2, NBS, I_2, PhSeCl, *p*-$O_2NC_6H_4SCl$

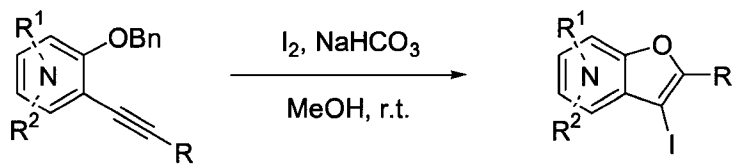
Our and other's recent success in the synthesis of benzo[*b*]thiophenes,[20] indoles[21] and isoquinolines[22] encouraged us to examine the possibility of preparing benzo[*b*]furans by the same strategy involving a palladium/copper-catalyzed alkyne coupling, followed by electrophilic cyclization. Cacchi and co-workers reported an approach to the synthesis of 3-iodobenzo[*b*]furans by a related process involving iodocyclization (Scheme 2).[19]

Unfortunately, the protecting and deprotecting steps required to synthesis the alkynylphenol are not particularly attractive synthetically. Some of the alkynylphenols are also relatively unstable. In another paper, Cacchi has demonstrated an analogous cyclization of benzylic

Scheme 2



ethers to generate furopyridines and reported that the *o*-hydroxyalkynylpyridines are not stable and cyclize spontaneously to give furopyridines (eq 1).[23] We have attempted to make



(1)

this overall approach more attractive synthetically by examining the preparation and cyclization of the corresponding methyl ethers using a variety of commercially available electrophiles. Herein, we wish to report an efficient approach to 2,3-disubstituted benzo[*b*]furans and furopyridines involving the palladium/copper-catalyzed coupling of various iodoanisoles and an iodomethoxypyridine and terminal alkynes, followed by electrophilic cyclization.

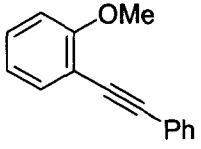
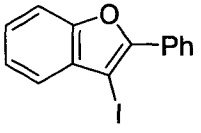
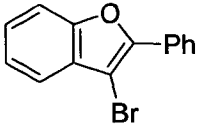
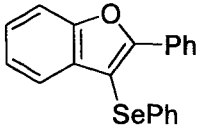
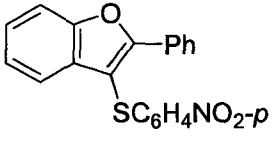
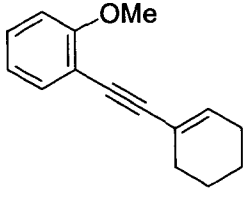
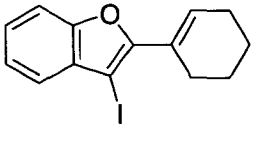
Results and Discussion

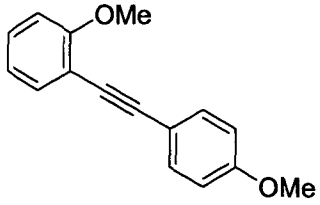
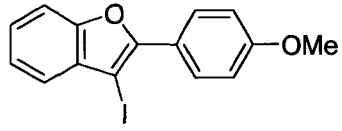
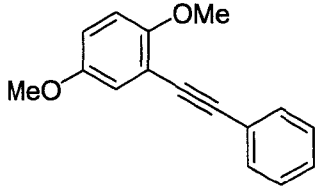
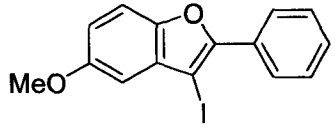
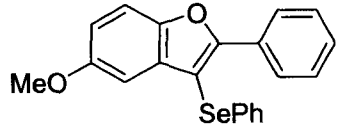
The arylalkynes required for our approach to benzo[*b*]furans are readily prepared by the Sonogashira coupling[24] of commercially available *o*-iodoanisole (5.0 mmol) and terminal alkynes (6.0 mmol) using a catalyst consisting of 2 mol % $PdCl_2(PPh_3)_2$ and 1 mol % CuI in the presence of Et_3N (12.5 mL) as the solvent at room temperature. The yields of this process range from 70 to 94% and this procedure should readily accommodate considerable functionality.

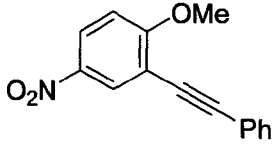
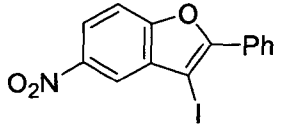
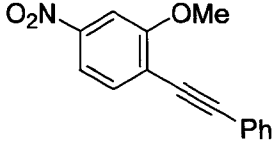
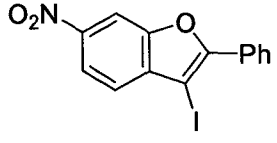
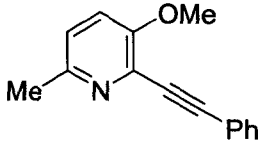
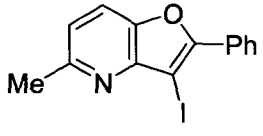
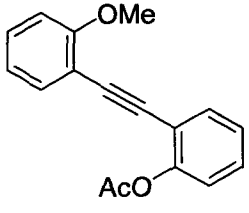
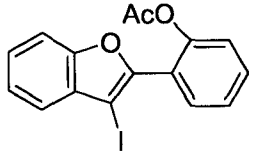
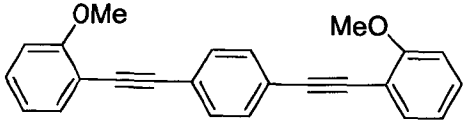
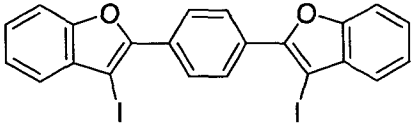
We first examined the reaction of our alkynes (0.25 mmol in 3 mL of CH_2Cl_2) with I_2 (2.0 equiv in 2 mL of CH_2Cl_2) under our well established reaction conditions for the synthesis of benzo[*b*]thiophenes[20] and indoles[21] (Scheme 1). We were pleased to see that 2-(phenylethynyl)anisole reacted in less than 3 h at room temperature to afford 3-iodo-2-phenylbenzo[*b*]furan in an 87% yield (Table 1, entry 1). In order to extend this approach to other benzo[*b*]furans, we have also looked at a range of other readily available electrophiles. So far, Br_2, *p*-$O_2NC_6H_4SCl$ and PhSeCl have been successfully employed in this electrophilic cyclization, providing excellent yields of the desired cyclization products (Table 1, entries 2-4).

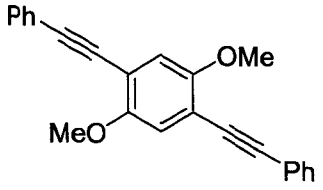
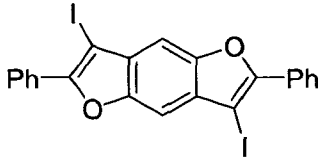
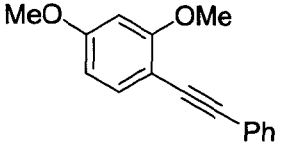
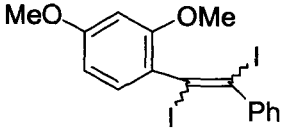
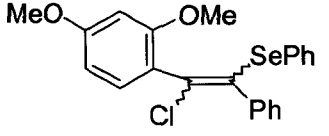
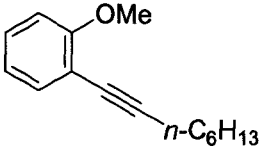
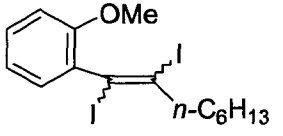
The nature of the substituents attached to the triple bond and the arene have a major impact on the success of the reaction. Virtually no difference in the rates of reaction or the overall yields have been observed using a vinylic alkyne and arylalkynes bearing certain types of functionality on the aromatic ring (entries 1-16). However, alkynes bearing a single alkyl group (entries 19, 20 and 25) fail to undergo electrophilic cyclization. Instead, an almost quantitative yield of the product of simple addition of the electrophile to the alkyne triple bond was obtained (entries 19, 20 and 25). In order to form a furan moiety, the

Table 1. Synthesis of benzo[*b*]furans by electrophilic cyclization.[a]

entry	alkyne	electrophile	product	% yield
1	 **1**	I_2	 **2**	87
2	**1**	Br_2	 **3**	98
3	**1**	PhSeCl	 **4**	100
4	**1**	p-$O_2NC_6H_4SCl$	 **5**	85
5	 **6**	I_2	 **7**	80

6	**6**		PhSeCl		**8**	88
7		**9**	I_2		**10**	100
8	**9**		PhSeCl		**11**	96
9		**12**	I_2		**13**	74
10	**12**		PhSeCl		**14**	90

11		**15**	I_2		**16**	80
12		**17**	I_2		**18**	67
13		**19**	I_2		**20**	67
14		**21**	I_2		**22**	95
15		**23**	I_2		**24**	97

16		**25**	I_2	 **26**	60
17		**27**	I_2		66[b]
18	**27**		PhSeCl		80[b]
19		**28**	I_2		98[b]
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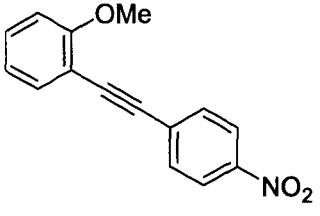
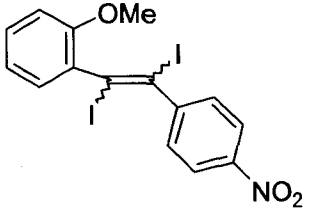
21		**29**	I_2		-[c]

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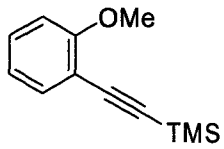
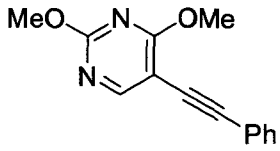
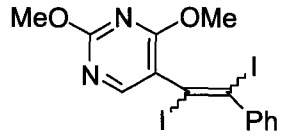
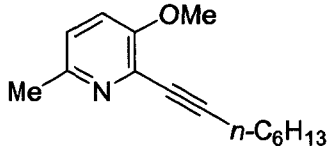
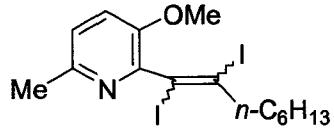
23		**30**	I_2			-[c]
24		**31**	I_2		**32**	68
25		**33**	I_2		**34**	66

[a]All reactions were run with 0.25 mmol of the alkyne, 2 equiv of electrophile in 5 mL of CH_2Cl_2 at 25 °C. [b]None of the desired cyclization product was observed. [c]An inseparable mixture was obtained.

oxygen of the methoxy group has to undergo a five *endo-dig* attack on the carbon-carbon triple bond. However, a methoxy group *para* to the triple bond increases the electron density on the distal end of the triple bond (Figure 1) and promotes addition of the electrophile to the triple bond, rather than cyclization (entries 17, 18 and 24).

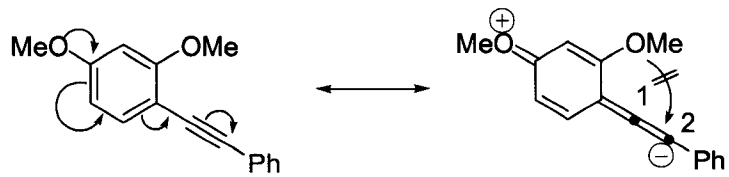


Figure 1. Methoxy electron-donating effect towards the triple bond

The presence of a nitro group in compound **29** decreases the electron density on C_1 (Figure 2), and again favors simple addition of the electrophile to the alkyne triple bond (entries 21 and 22). On the other hand, the presence of an electron-withdrawing group, such

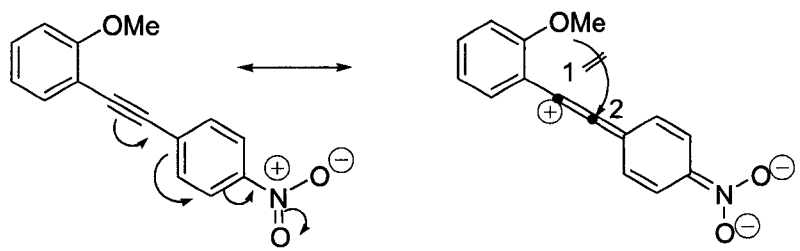


Figure 2. Nitro electron-withdrawing effect towards the triple bond

as a nitro group on the methoxy-substituted arene favors electrophilic cyclization, although a longer reaction time is generally required (entries 11 and 12). The more electron deficient C_2 position is more likely to undergo attack by the nucleophilic oxygen of the methoxy group than the C_1 position, because of either the resonance effect of the nitro group *para* to the carbon-carbon triple bond (Figure 3) or the inductive effect of the electron-poor arene. The trimethylsilyl-substituted alkyne **30** failed to undergo electrophilic cyclization and

provided an inseparable mixture of unidentifiable compounds, which is consistent with Cacchi's earlier results (entry 23).[19]

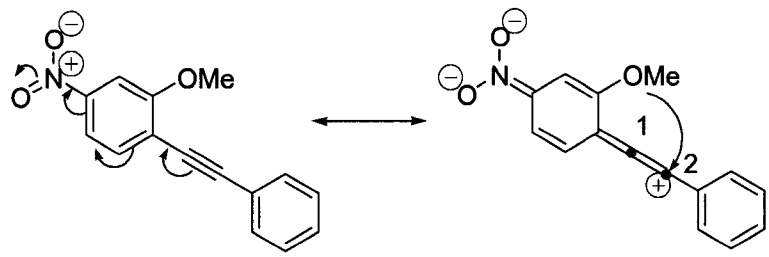


Figure 3. Nitro electron-withdrawing effect towards the triple bond

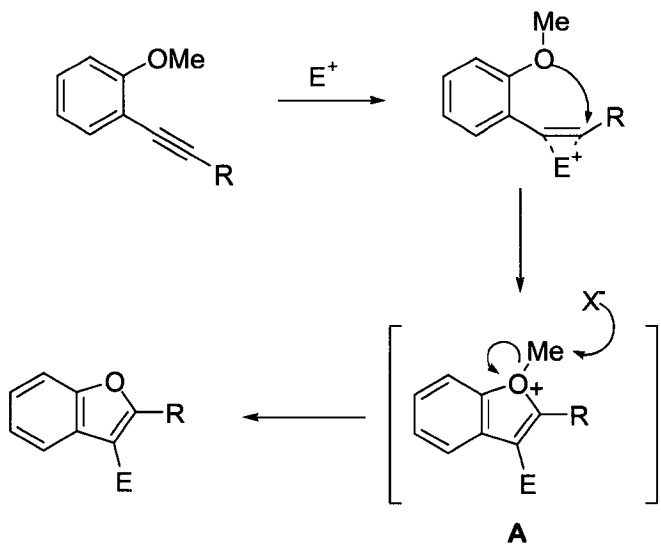
Compound **21** with both a methoxy and an acetoxy group in positions *ortho* to the triple bond undergoes electrophilic cyclization onto the methoxy group to produce compound **22** in a 95% yield (entry 14). This should be quite useful for the regioselective synthesis of benzofurans. Thus, the more nucleophilic methoxy group more readily attacks the triple bond, affording the corresponding cyclization product.

We have also investigated the possibility of carrying out double iodocyclizations, which might be quite useful for the quick assembly of systems with extended conjugation. Compounds **23** and **25** undergo iodocyclization to afford double cyclization products in 97% and 60% yields respectively (entries 15 and 16).

While Cacchi reported the successful synthesis of several furopyridines by electrophilic cyclization of *o*-(benzyloxy)alkynylpyridines, we have examined the cyclization of an *o*-methoxyalkynylpyridine and found that a methyl group can also be a good leaving group in this reaction. Pyridine derivative **19** was treated with I_2 under our standard electrophilic cyclization conditions to afford the desired furopyridine in a 67 % yield. This provides a convenient alternative route to the synthesis of furopyridines, since methoxypyridines are more readily available than (benzyoxy)pyridines in many cases.

Mechanistically, we believe that these cyclizations proceed by *anti* attack of the electrophile and the oxygen of the methoxy group on the alkyne to produce an intermediate **A**, which undergoes methyl group removal via S_N2 displacement by nucleophiles present in the reaction mixture (Scheme 3). In most cases, the nucleophile is presumably the halide remaining in solution.

Scheme 3



Conclusions

We believe that this approach to 3-iodobenzo[*b*]furans and furopyridines should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting iodide functionality into other substituents. For example, the resulting heterocyclic iodides should be particularly useful as intermediates in many palladium-catalyzed processes, like Sonogashira,[24] Suzuki,[25] and Heck[26] cross-coupling processes.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using 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 [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of ethyl ether, hexanes, ethyl acetate, and CH_2Cl_2 were purchased from Fisher Scientific Co. 2-Iodoanisole, 2-bromo-1,4-dimethyoxybenzene, 1-bromo-2,4-dimethoxybenzene, 2-iodo-4-nitroanisole, 2-iodo-5-nitroanisole, resorcinol, 4-iodoanisole, 1-iodo-4-nitrobenzene, phenylacetylene, 1-cyclohexenyl acetylene, 1-octyne, trimethylsilylacetylene, and Et_3N were purchased from Aldrich Chemical Co., Inc. The palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd.

General procedure for the palladium/copper-catalyzed formation of *o*-(1-alkynyl)anisoles. To a solution of Et_3N (12.5 mL), $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mmol of *o*-iodoanisole and 6.0 mol of terminal acetylene (stirring for 5 min beforehand), CuI (1 mol %) was added and stirring was continued for another 2 min before flushing with Ar. The flask was then sealed. The mixture was allowed to stir at room temperature for 3-6 h and the

resulting solution was filtered, washed with satd aq NaCl and extracted with diethyl ether (2 x 15 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

2-(Phenylethynyl)anisole (1). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.89 (d, J = 8.4 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 7.29-7.33 (m, 4H), 7.50 (d, J = 7.2 Hz, 1H), 7.55-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 56.0, 85.9, 93.6, 110.9, 112.6, 120.7, 123.7, 128.2, 128.3, 129.9, 131.8, 133.7, 160.1; IR (neat, cm^{-1}) 3058, 2926, 2855, 2226; HRMS calcd for $C_{15}H_{12}O$ 208.0888, found 208.0894.

2-[(Cyclohex-1-enyl)ethynyl]anisole (6). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.05-7.26 (m, 4H), 6.20 (s, 1H), 3.77 (s, 3H), 2.09-2.35 (m, 4H), 1.20-1.67 (m, 4H); IR (neat, cm^{-1}) 3048, 2944, 2222; HRMS calcd for $C_{15}H_{16}O$ 212.1201, found 212.1206.

1-Methoxy-2-[(4-methoxyphenyl)ethynyl]benzene (9). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 3.87 (s, 3H), 6.83-6.93 (m, 4H), 7.26 (t, J = 8.0 Hz, 1H), 7.46-7.50 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 55.4, 55.9, 84.5, 93.6, 110.8, 112.8, 114.0, 115.8, 120.6, 129.6, 133.2, 133.5, 159.6, 159.9; IR (neat, cm^{-1}) 2227; HRMS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.1000.

1,4-Dimethoxy-2-(phenylethynyl)benzene (12). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 3.86 (s, 3H), 6.80-6.84 (m, 2H), 7.05 (s, 1H), 7.30-7.34 (m, 3H), 7.56 (d, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.7, 85.9, 93.6,

112.3, 113.1, 115.9, 118.3, 123.6, 128.4, 128.4, 131.8, 153.4, 154.7; IR (neat, cm^{-1}) 3058, 2926, 2855, 2227, 1464, 1435, 749; HRMS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0999.

4-Nitro-2-(phenylethynyl)anisole (15). The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 4.01 (s, 3H), 6.96 (d, J = 9.2 Hz, 1H), 7.36-7.38 (m, 3H), 7.56-7.58 (m, 2H), 8.20 (dd, J = 9.2, 2.8 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.8, 83.5, 95.6, 110.5, 113.9, 122.7, 125.7, 128.6, 129.1, 129.2, 132.0, 141.3, 164.6; IR (neat, cm^{-1}) 3058, 2926, 2855, 2225; HRMS calcd for $C_{15}H_{11}NO_3$ 253.0739, found 253.0742.

5-Nitro-2-(phenylethynyl)anisole (17). The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 4.01 (s, 3H), 7.37-7.38 (m, 3H), 7.57-7.62 (m, 3H), 7.75 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 8.4, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6, 84.3, 98.6, 105.8, 115.9, 119.9, 122.7, 128.6, 129.3, 132.1, 133.7, 148.2, 160.3; IR (neat, cm^{-1}) 3047, 2215; HRMS calcd for $C_{15}H_{11}NO_3$ 253.0739, found 253.0741.

2-Ethynyl-1-methoxybenzene. The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 3.32 (s, 1H), 3.89 (s, 3H), 6.87-6.93 (m, 2H), 7.32 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.9, 80.2, 81.3, 110.7, 111.2, 120.6, 130.4, 134.3, 160.7; IR (neat, cm^{-1}) 3058, 2222; HRMS calcd for C_9H_8O 132.0575, found 132.0577.

2-[(Cyclohex-1-enyl)ethynyl]-1,4-dimethoxybenzene. The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.61-1.70 (m, 4H), 2.14-2.16 (m, 2H), 2.25-2.28 (m, 2H), 3.76 (s, 3H), 3.84 (s, 3H), 6.24-6.26 (m, 1H), 6.80-6.81 (m, 2H), 6.95-6.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 22.5, 26.0, 29.4, 55.9, 56.6, 83.0, 95.5, 112.2, 113.6, 115.3, 118.1, 120.9, 135.5, 153.3, 154.4; IR (neat, cm^{-1}) 2226; HRMS calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1312.

3-Methoxy-6-methyl-2-(phenylethynyl)pyridine (19). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.90 (s, 3H), 7.06-7.15 (m, 2H), 7.33-7.36 (m, 3H), 7.61-7.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 55.8, 85.7, 93.7, 118.8, 122.9, 123.5, 128.4, 128.9, 132.3, 150.6, 155.3; IR (neat, cm^{-1}) 2217; HRMS calcd for $C_{15}H_{13}NO$ 233.0997, found 233.1002.

2-Acetoxy-2'-methoxy-diphenylacetylene (21). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.87 (s, 3H), 6.88 (d, J = 8.7 Hz, 1H), 6.92 (td, J = 7.5, 0.9 Hz, 1H), 7.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.20 (td, J = 7.5, 1.5 Hz, 1H), 7.26-7.35 (m, 2H), 7.46 (dd, J = 7.5, 1.8 Hz, 1H), 7.59 (dd, J = 7.5, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 55.8, 88.3, 90.9, 110.9, 112.3, 118.0, 120.6, 122.4, 126.0, 129.4, 130.2, 133.1, 133.7, 151.6, 160.1, 169.1; IR (neat, cm^{-1}) 2213, 1770; HRMS calcd for $C_{17}H_{14}O_3$ 266.0943, found 266.0946.

1,4-*Bis*[(2-methoxyphenyl)ethynyl]benzene (23). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 6H), 6.88-6.96 (m, 4H), 7.30 (t, J = 7.6 Hz, 2H), 7.48-7.53 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 56.0, 87.7, 93.4, 110.8, 112.4, 120.7, 123.4, 130.1, 131.7, 133.7, 160.1; IR (neat, cm^{-1}) 2210; HRMS calcd for $C_{24}H_{18}O_2$ 338.1307, found 338.1315.

2,5-Dimethoxy-1,4-di(phenylethynyl)benzene (25). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 6H), 7.04 (s, 2H), 7.32-7.37 (m, 6H), 7.56-7.59 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 56.7, 85.9, 95.2, 113.6, 115.9, 123.4, 128.5, 128.6, 131.9, 154.1; IR (neat, cm^{-1}) 2227; HRMS calcd for $C_{24}H_{18}O_2$ 338.1307, found 338.1314.

2,4-Dimethoxy-1-(phenylethynyl)benzene (27). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 3.87 (s, 3 H), 6.46 (d, J = 6.0 Hz, 2H), 7.27-7.34 (m, 3H), 7.42 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.5, 56.0, 86.0, 92.1, 98.6, 105.0, 105.1, 124.0, 127.9, 128.4, 131.6, 134.5, 161.3, 161.4; IR (neat, cm^{-1}) 3058, 2926, 2855, 2227, 1464, 1435, 749; HRMS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.1000.

2-(1-Octynyl)anisole (28). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.88-0.93 (m, 3H), 1.30-1.34 (m, 4H), 1.46-1.50 (m, 2H), 1.60-1.65 (m, 2H), 2.47 (t, J = 7.2 Hz, 2H), 3.87 (s, 3H), 6.85 (d, J = 8.4 Hz, 1H), 6.88 (td, J = 7.5, 0.9 Hz, 1H), 7.24 (td, J = 8.1, 1.8 Hz, 1H), 7.37 (dd, J = 7.5, 1.8 Hz, 1H); HRMS calcd for $C_{15}H_{20}O$ 216.1514, found 216.1519.

1-Methoxy-2-[(4-nitrophenyl)ethynyl]benzene (29). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.92-6.99 (m, 2H), 7.37 (t, J = 8.4 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.0, 91.6, 91.4, 110.9, 111.4, 120.8, 123.7, 130.8, 131.1, 132.4, 133.9, 147.0, 160.4; HRMS calcd for $C_{15}H_{11}NO_2$ 253.0739, found 253.0745.

2-(Trimethylsilylethynyl)anisole (30). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 3.68 (s, 3H), 6.64-6.71 (m, 2H), 7.08 (td, J = 8.4, 2.0 Hz, 1H), 7.24 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.3, 56.0, 98.6, 101.5, 110.8, 112.5, 120.5, 130.2, 134.4, 160.5.

2,4-Dimethoxy-5-(phenylethynyl)pyrimidine (31). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H), 4.06 (s, 3H), 7.32-7.35 (m, 3H), 7.51-7.54 (m,

2H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 54.6, 55.2, 80.8, 95.5, 100.2, 122.9, 128.4, 128.6, 131.6, 161.3, 164.2, 170.4; IR (neat, cm^{-1}) 2207 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2O_2$ 240.0899, found 240.0901.

3-Methoxy-6-methyl-2-(1-octynyl)pyridine (33). The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.28-1.33 (m, 8H), 1.43-1.48 (m, 2H), 1.61-1.68 (m, 2H), 2.47 (s, 3H), 2.49 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 7.04 (dd, J = 19.8, 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.9, 22.8, 23.5, 28.6, 29.2, 29.2, 29.3, 31.9, 56.0, 77.1, 95.7, 118.5, 122.7, 133.0, 150.1, 154.8; IR (neat, cm^{-1}) 2217; HRMS calcd for $C_{17}H_{25}NO$ 259.1936, found 259.1941.

General procedure for the iodo- and bromocyclizations. To a solution of 0.25 mmol of the alkyne and 3 mL of CH_2Cl_2, 2 equiv of I_2 or Br_2 dissolved in 2 mL of CH_2Cl_2 was added gradually. The reaction mixture was flushed with Ar and allowed to stir at room temperature for the desired time. The excess I_2 or Br_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by diethyl 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 the eluent.

3-Iodo-2-phenylbenzo[*b*]furan (2). The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.28-7.51 (m, 7H), 8.16-8.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 61.3, 111.4, 122.1, 123.7, 125.9, 127.7, 128.7, 129.4, 130.2, 132.7, 153.2, 154.1; IR (neat, cm^{-1}) 3058, 1450; HRMS calcd for $C_{14}H_9IO$ 319.9698, found 319.9700.

3-Bromo-2-phenylbenzo[*b*]furan (3). The product was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.36-7.52 (m, 7H), 8.24-8.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 105.1, 122.4, 123.9, 125.5, 125.8, 128.8, 129.0, 129.9, 133.3, 137.9, 138.4, 139.4; IR (neat, cm^{-1}) 3026; HRMS calcd for $C_{14}H_9BrO$ 217.9837, found 217.9840.

2-(Cyclohex-1-enyl)-3-iodobenzo[*b*]furan (7). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.66-1.70 (m, 2H), 1.77-1.79 (m, 2H), 2.25-2.29 (m, 2H), 2.59-2.64 (m, 2H), 6.77-6.79 (m, 2H), 7.24-7.28 (m, 2H), 7.35-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.7, 25.9, 26.9, 59.1, 111.0, 121.7, 123.3, 125.2, 128.2, 132.0, 132.2, 153.5, 155.3; HRMS calcd for $C_{14}H_{13}IO$ 324.0011, found 324.0020.

3-Iodo-2-(4-methoxyphenyl)benzo[*b*]furan (10). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.99 (d, J = 8.0 Hz, 2H), 7.28-7.31 (m, 2H), 7.39-7.45 (m, 2H), 8.10 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.5, 59.7, 111.2, 114.1, 121.7, 122.8, 123.6, 125.4, 129.2, 132.8, 153.4, 153.9, 160.5; HRMS calcd for $C_{15}H_{11}IO_2$ 349.98038, found 349.98100.

3-Iodo-5-methoxy-2-phenylbenzo[*b*]furan (13): The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.88 (s, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 8.14 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.2, 61.3, 104.1, 112.1, 114.9, 127.6, 128.7, 129.4, 130.3, 133.3, 149.0, 154.0, 156.9; IR (neat, cm^{-1}) 3058, 2926, 2855, 2227, 1464, 1435, 749; HRMS calcd for $C_{15}H_{11}IO_2$ 349.9804, found 349.9810.

3-Iodo-5-nitro-2-phenylbenzo[*b*]furan (16). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.50-7.58 (m, 4H), 8.15-8.18 (m, 2H), 8.27 (dd, J = 12.0, 3.2 Hz,

1H), 8.37 (d, J = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 60.9, 111.9, 118.7, 121.5, 127.8, 128.9, 129.0, 130.4, 133.6, 144.9, 156.5, 157.0; IR (neat, cm^{-1}) 3058, 2926; HRMS calcd for $C_{14}H_{18}INO_3$ 364.9549, found 364.9551.

3-Iodo-6-nitro-2-phenylbenzo[*b*]furan (18). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.50-7.56 (m, 4H), 8.18-8.21 (m, 2H), 8.23 (dd, J = 8.4, 2.0 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 60.6, 107.8, 119.5, 122.1, 128.0, 129.0, 129.0, 130.7, 138.5, 146.1, 152.6, 158.4; IR (neat, cm^{-1}) 3058, 2926; HRMS calcd for $C_{14}H_{18}INO_3$ 364.9549, found 364.9552.

3-Iodo-5-methyl-2-phenylfuro[3,3-*b*]pyridine (20). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.73 (s, 3H), 7.14 (d, J = 8.4 Hz, 1H), 7.46-7.54 (m, 3H), 7.62 (d, J = 8.4 Hz, 1H), 8.21-8.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.7, 64.4, 118.5, 120.6, 127.8, 128.8, 129.9, 130.0, 145.8, 148.9, 156.0, 156.2; IR (neat, cm^{-1}) 1775; HRMS calcd for $C_{14}H_{10}INO$, 334.9808, found 334.9809.

2-(2-Acetoxyphenyl)-3-iodobenzo[*b*]furan (22). The product was obtained as a yellow oil: mp 218 ^{0}C (dec); ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 7.25 (dd, J = 8.1, 1.2 Hz, 1H), 7.32-7.40 (m, 3H), 7.44-7.53 (m, 3H), 7.82 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 65.4, 111.4, 122.1, 123.3, 123.7, 123.8, 126.0, 126.1, 131.2, 131.7, 131.9, 148.8, 152.3, 154.6, 169.4; IR (neat, cm^{-1}) 1771; HRMS calcd for $C_{16}H_{11}IO_3$, 377.9753, found 377.9758.

2,2'-(1,4-Phenylene)-*bis*[3-iodobenzo[*b*]furan] (24). The product was obtained as a white solid: mp 256-257 °C; ^{1}H NMR ($CDCl_3$) δ 7.34-7.42 (m, 4H), 7.47-7.53 (m, 4H),

8.36 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 62.3, 111.5, 122.2, 123.9, 126.3, 127.5, 130.7, 132.8, 152.5, 154.2; HRMS calcd for $C_{22}H_{12}I_2O_2$ 561.8927. Found 561.8934.

3,7-Diiodo-2,6-diphenylbenzo[1,2-b:4,5-b']difuran(26). The product was obtained as a white solid: mp >300 ^0C (dec); HRMS calcd for $C_{22}H_{12}I_2O_2$ 561.8927. Found 561.8933.

5-(1,2-Diiodo-2-phenylethenyl)-2,4-dimethoxypyrimidine (32). The product was obtained as yellow oil and ready to decompose.

2-(1,2-Diiodo-*n*-1-decenyl)-6-methyl-3-methoxy-pyridine (34): The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.88-0.92 (m, 3H), 1.25-1.44 (m, 10 H), 1.65-1.70 (m, 2H), 2.50 (s, 3H), 2.72-2.77 (m, 1H), 2.84-2.89 (m, 1H), 3.86 (s, 3H), 7.10 (dd, J = 13.5, 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 23.7, 28.5, 28.6, 29.4, 29.7, 32.1, 49.1, 56.1, 91.0, 107.4, 120.1, 124.1, 149.5, 149.7, 151.9; IR (neat, cm^{-1}) 1715; HRMS calcd for $C_{15}H_{21}I_2NO$ 484.9713. Found 484.9720.

General procedure for the *p*-$O_2NC_6H_4SCl$ and PhSeCl cyclizations. To a solution of 0.25 mmol of the alkyne and CH_2Cl_2 (5 mL), 0.375 mmol of *p*-$O_2NC_6H_4SCl$ or PhSeCl was added. The mixture was flushed with Ar and allowed to stir at 25 °C for 2-6 h. The reaction mixture was washed with 20 mL of water and extracted with diethyl ether. The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was further purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-Phenyl-3-(phenylselenyl)benzo[*b*]furan (4). The product was obtained as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.13-7.17 (m, 3H), 7.22 (t, J = 4.0 Hz, 1H), 7.27-7.32 (m, 4H), 7.43

(t, J = 7.6 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 8.19-8.21 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 99.9, 111.4, 121.4, 123.6, 125.4, 126.4, 128.0, 128.7, 129.4, 129.5, 130.3, 131.6, 132.1, 154.3, 157.4; IR (neat, cm^{-1}) 3058, 2926; HRMS calcd for $C_{20}H_{14}OSe$ 350.0211, found 350.0220.

3-*p*-Nitrophenylsulfenyl-2-phenylbenzo[*b*]furan (5). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.22 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.35-7.46 (m, 5H), 7.60 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 102.1, 111.9, 120.1, 124.1, 124.4, 125.9, 126.0, 127.6, 128.9, 129.3, 130.1, 130.1, 145.6, 146.4, 154.2, 158.6; IR (neat, cm^{-1}) 3058, 2926; HRMS calcd for $C_{20}H_{13}NO_3S$ 347.0617, found 347.0622.

2-(Cyclohex-1-enyl)-3-(phenylselenyl)benzofuran (8). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.64-1.66 (m, 2H), 1.72-1.74 (m, 2H), 2.19-2.21 (m, 2H), 2.50-2.51 (m, 2H), 6.09-6.10 (m, 1H), 7.10-7.15 (m, 5H), 7.28-7.31 (m, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.0, 25.9, 30.4, 114.0, 122.2, 124.7, 125.0, 126.0, 129.3, 131.7, 132.0, 133.3, 138.4, 142.0, 152.1; IR (neat, cm^{-1}) 3025; HRMS calcd for $C_{20}H_{18}OSe$ 354.0523, found 354.0533.

2-(4-Methoxyphenyl)-3-(phenylselenyl)benzo[*b*]furan (11). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.95 (d, J = 8.0 Hz, 2H), 7.11-7.23 (m, 4H), 7.26-7.53 (m, 3H), 7.48-7.53 (dd, J = 8.4 Hz, 7.6 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.1, 98.0, 111.2, 114.1, 121.1, 123.0, 123.5, 125.0, 126.3, 129.1, 129.5, 131.8, 132.3, 154.1, 157.7, 160.6; HRMS calcd for $C_{21}H_{16}O_2Se$ 380.0317, found 380.0328.

5-Methoxy-2-phenyl-3-(phenylselenyl)benzo[*b*]furan (14). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 6.90-6.93 (m, 2H), 7.12-7.17 (m, 3H), 7.29 (d, J = 8.0 Hz, 2H), 7.36-7.44 (m, 4H), 7.18 (d, J = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.0, 99.6, 103.3, 112.0, 114.5, 126.4, 127.9, 128.6, 129.3, 129.4, 129.5, 130.4, 131.6, 132.9, 149.2, 156.7, 158.2; IR (neat, cm^{-1}) 3058, 2926, 2855, 2227, 1464, 1435, 749; HRMS calcd for $C_{21}H_{16}SeO_2$ 380.0317, found 380.0328.

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CHAPTER 2. AN EFFICIENT SYNTHESIS OF HETEROCYCLES BY ELECTROPHILIC CYCLIZATION OF ACETYLENIC ALDEHYDES, KETONES AND IMINES

Based on a communication to be submitted to *Organic Letters* and a paper to be published in the *Journal of Organic Chemistry*

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Abstract

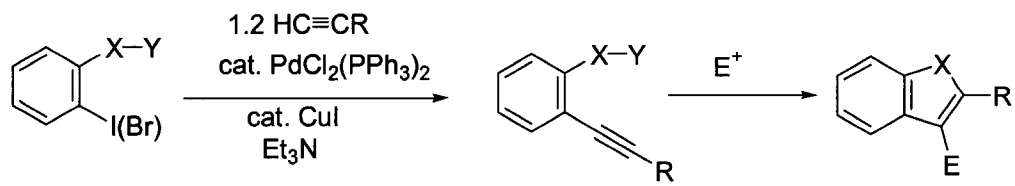
Highly substituted 1*H*-isochromenes and 1,2-dihydroisoquinolines can be prepared in high yields at room temperature by reacting *o*-(1-alkynyl)arenecarboxaldehydes, ketones and the corresponding imines with I_2, *p*-$O_2NC_6H_4SCl$ or PhSeBr and various alcohols or carbon-based nucleophiles.

Introduction

The electrophilic cyclization of functionally-substituted alkenes has provided an extremely useful route for the synthesis of a wide variety of heterocyclic and carbocyclic compounds, which have often proven useful as intermediates in the synthesis of natural products and pharmaceuticals.[1] The analogous chemistry of alkynes has been far less studied, although it would appear to be a very promising route to an extraordinary range of useful, functionally-substituted heterocycles and carbocycles.[2] Our recent work has indicated that benzothiophenes,[3] isoquinolines[4] and isocoumarins[5] can be easily synthesized

by the electrophilic cyclization of appropriate functionally-substituted alkynes using iodine-, sulfur- and selenium-containing electrophiles under exceptionally mild reaction conditions (Scheme 1). Others have recently reported a number of analogous, very useful iodine-promoted cyclizations of functionally-substituted alkynes.[6]

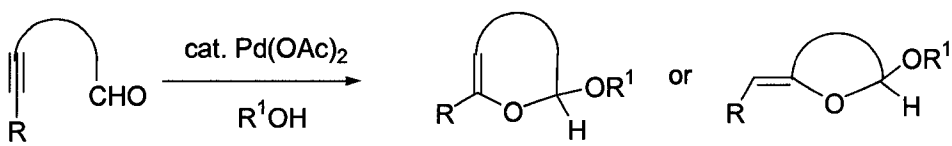
Scheme 1



X-Y = O-H, S-Me, NMe_2, CH=N-*t*-Bu

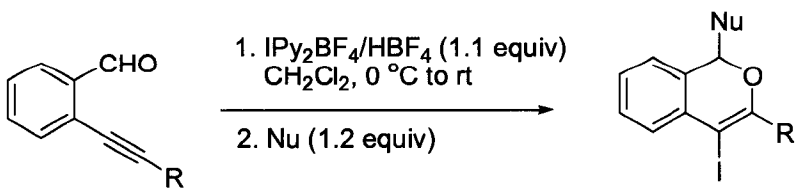
E^+ = Br_2, NBS, I_2, PhSeCl, *p*-$O_2NC_6H_4SCl$

Recently, Yamamoto reported an interesting cyclization of acetylenic aldehydes to 1-alkoxy-1*H*-isochromenes catalyzed by palladium.[7] The Pd(II) salt employed was claimed to exhibit a dual role as both a Lewis acid and a transition-metal catalyst (eq 1).



(1)

In a more recent study, the analogous preparation of 1*H*-isochromenes has been achieved upon reaction of bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) and HBF_4 with the same acetylenic carbonyl precursors in the presence of various nucleophiles (eq 2).[8]



(2)

The use of expensive IPy_2BF_4 together with $B(OMe)_3$ or toxic, strongly acidic HBF_4, and the relatively complicated stepwise procedure employed make this approach a bit unwieldy synthetically. Furthermore, the scope of this cyclization has yet to be reported.

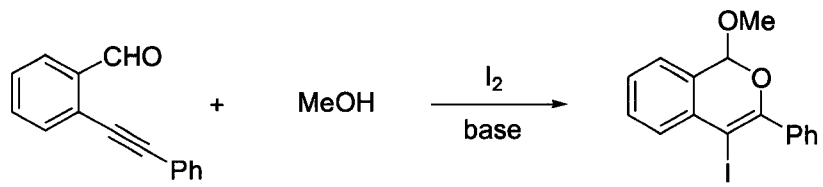
We simultaneously found that this three component reaction[9] proceeds smoothly by using various electrophiles, such as I_2, *p*-$O_2NC_6H_4SCl$ and PhSeBr, to generate the corresponding iodine-, sulfur- and selenium-substituted heterocycles in high yields under very mild reaction conditions. Herein, we wish to report a much more efficient and convenient approach to these types of heterocycles involving electrophilic cyclization using a range of electrophiles and nucleophiles.

Results and Discussion

Our initial studies were aimed at finding optimal reaction conditions for the electrophilic cyclization of the *o*-(1-alkynyl)benzaldehydes. Our investigation began with the reaction of *o*-(phenylethynyl)benzaldehyde (**1**), methanol and I_2 (Table 1).
The reaction was first attempted using 0.25 mmol of *o*-(phenylethynyl)benzaldehyde (**1**), 1.2 equiv of methanol, 1.0 equiv of K_2CO_3 and 1.2 equiv of I_2 in CH_2Cl_2 at room temperature. Iodocyclization proceeded smoothly and provided an 88 % yield of the desired product **2**. Other solvents, such as CH_3CN and DMF, were also investigated and proved to be far less effective. $KHCO_3$ and NEt_3 were also investigated as bases. While $KHCO_3$ provided a slightly lower yield of the desired product than K_2CO_3, NEt_3 proved to be ineffective and none of the desired product was detected. Although CH_2Cl_2 is not a good solvent for K_2CO_3, the presence of K_2CO_3 was crucial for a clean, high yielding reaction. K_2CO_3 is presumed to neutralize the by-product HI of the electrophilic cyclization, which can also react with the

acetylenic aldehyde and generate the corresponding pyrilium salt.[10] Increasing the amount of methanol from 1.2 equiv to using MeOH as the solvent resulted in a lower yield. 1.2 Equiv of I_2 has proven to be enough to achieve a high yield. Further increasing the amount of I_2 did not give better yields.

Table 1. Iodocyclization of 2-(phenylethynyl)benzaldehyde



1 **2**

solvent	MeOH (equiv)	I_2 (equiv)	base (equiv)	% yield
CH_2Cl_2	1.2	1.2	K_2CO_3 (1.0)	88
CH_3CN	1.2	1.2	K_2CO_3 (1.0)	40
DMF	1.2	1.2	K_2CO_3 (1.0)	trace
CH_2Cl_2	1.2	1.2	$KHCO_3$ (1.0)	70
CH_2Cl_2	2.0	2.5	K_2CO_3 (1.0)	80
CH_2Cl_2	2.0	2.5	K_2CO_3 (2.0)	78
MeOH	-	2.5	K_2CO_3 (2.0)	68

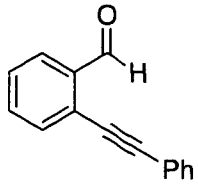
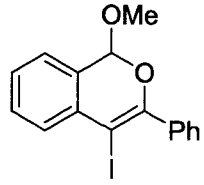
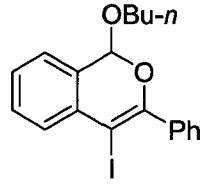
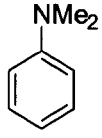
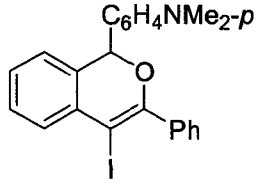
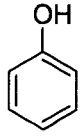
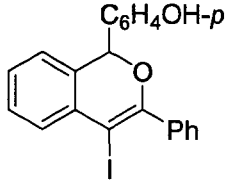
Based on the above optimization efforts, the combination of 1.2 equiv of nucleophile, 1.0 equiv of K_2CO_3, 1.2 equiv of I_2 and using CH_2Cl_2 as the solvent at room temperature gave the best results. This procedure has been used as our standard reaction conditions for subsequent electrophilic cyclizations. To test the generality of this chemistry, acetylenic aldehydes bearing different substituents on the carbon-carbon triple bond were synthesized in high yields by the palladium/copper-catalyzed coupling of *o*-bromobenzaldehyde and the corresponding terminal alkynes.[11] The resulting acetylenic aldehydes were then allowed to react under our standard electrophilic cyclization conditions to afford the corresponding 1*H*-

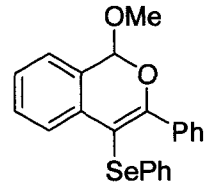
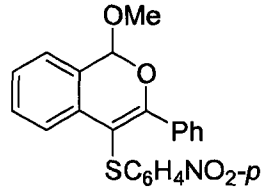
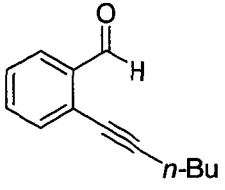
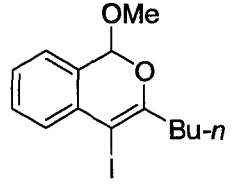
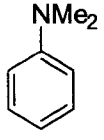
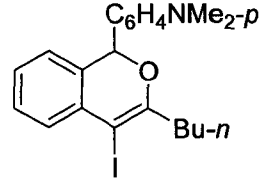
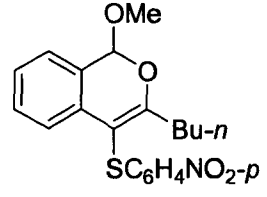
isochromene products in good to excellent yields. The results are summarized in Table 2. Alkynes bearing an aromatic ring, as well as alkyl and vinylic substituents, all react well with methanol and ethanol to provide the desired iodocyclization products in good yields (entries 1, 2, 7 and 10). Interestingly, not only alcohols, but also electron-rich aromatic compounds, such as *N,N*-dimethylaniline and phenol, can be used as nucleophiles, affording iodocyclization products in generally good to excellent yields (entries 3, 4, 8 and 11). On the other hand, anisole and 1,4-dimethoxybenzene did not react as nucleophiles and provided unidentifiable products. In all cases where we have run comparable reactions, the reactions with readily available, inexpensive I_2 have given higher yields than the process using the expensive iodonium salt and HBF_4 used by Barluenga.[8]

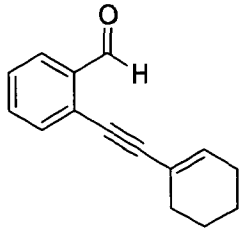
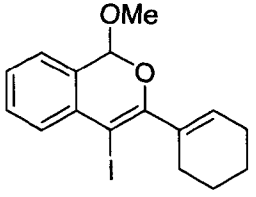
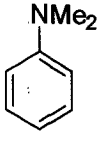
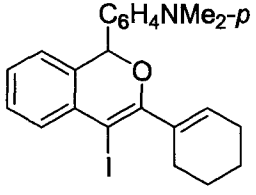
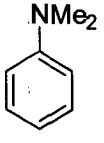
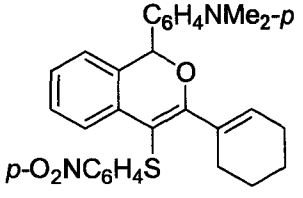
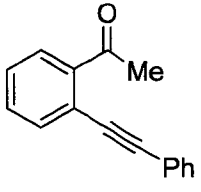
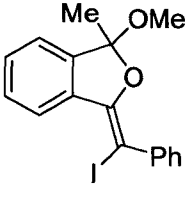
To further explore the scope of this cyclization, commercially available sulfur and selenium electrophiles have also been used in this process and have been found to provide decent yields of the desired cyclization products using both methanol and *N,N*-dimethylaniline as nucleophiles (entries 5, 6, 9 and 12). The reactions with I_2 and *p*-$O_2NC_6H_4SCl$ were completed in a shorter period of time and gave higher yields of products than those with PhSeBr.

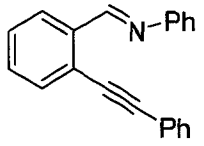
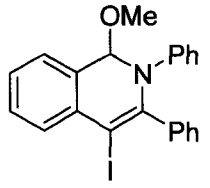
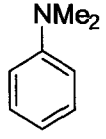
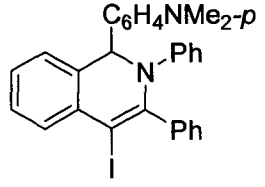
Besides the benzaldehyde derivatives, ketone **16** has also been allowed to react with I_2 under our reaction conditions (entry 13). This reaction proceeded smoothly to provide a 90 % yield of a 5-exo-dig cyclization product, rather than the six-membered ring ether formed by the electrophilic cyclization of analogous benzaldehyde derivatives. The use of K_2CO_3 provides very mild basic conditions and avoids the acid-initiated, partial decomposition of this cyclization product described in Barluenga's paper.[8]

Table 2. Electrophilic cyclization of acetylenic aldehydes, ketones and imines[a]

entry	alkyne		nucleophile	electrophile	product		% isolated yield
1		**1**	MeOH	I_2		**2**	93[b]
2		**1**	EtOH	I_2		**3**	81
3		**1**		I_2		**4**	88
4		**1**		I_2		**5**	35[c]

5		**1**	MeOH	PhSeBr		**6**	65
6		**1**	MeOH	p-$NO_2C_6H_4SCl$		**7**	74
7		**8**	MeOH	I_2		**9**	84
8		**7**		I_2		**10**	70
9		**7**	MeOH	p-$NO_2C_6H_4SCl$		**11**	73

10		**12**	MeOH	I_2		**13**	81
11		**12**		I_2		**14**	83
12		**12**		p-$NO_2C_6H_4SCl$		**15**	70
13		**16**	MeOH	I_2		**17**	90

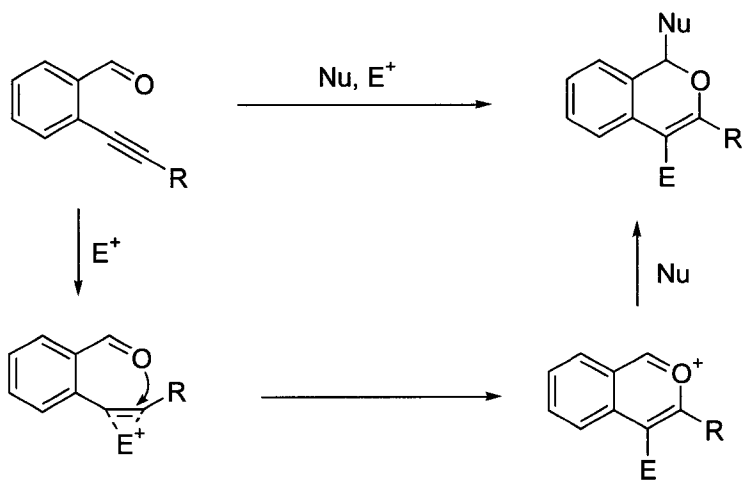
14		**18**	MeOH	I_2		**19**	25[d]
15		**18**		I_2		**20**	60[d]

[a]The reactions were run under the following conditions, unless otherwise specified. While stirring a solution of 2.5 mL of CH_2Cl_2 containing 0.25 mmol of the alkyne, 0.30 mmol of the nucleophile and 0.25 mmol of K_2CO_3, 0.30 mmol of electrophile were added and the resulting mixture was further stirred at room temperature until the total disappearance of the starting material as indicated by TLC analysis. [b]The reaction was run on a 1.0 mmol scale; the 0.25 mmol scale reaction provides an 88 % yield of compound **2**. [c]A 25 % yield of O-nucleophile trapping product was also observed. [d]The yields were determined by ^1H NMR spectroscopic analysis due to the apparent instability of the products.

Iminoalkyne **18** has also been allowed to react under our usual cyclization conditions in the hope that after attack of the nucleophile, the reaction might provide biologically interesting dihydroisoquinoline derivatives. However, for some reason, a large amount of an unidentifiable salt was generated when MeOH was used as the trapping agent. Only about 25 % of the desired cyclization product was observed upon ^{1}H NMR spectroscopic analysis (entry 14). On the other hand, using *N,N*-dimethylaniline as the nucleophile under the same reaction conditions gave a 60 % yield of the desired iodocyclization product (entry 15).

Interestingly, when we followed the stepwise procedure described in Barluenga's paper, we were unable to get high yields of the desired iodocyclization products. Instead, an unreactive solid, presumed to be the pyrilium salt, was generated. Based on this observation, a possible mechanism is proposed in Scheme 2. We believe that these cyclizations proceed

Scheme 2



by *anti* attack of the electrophile and the carbonyl on the alkyne to produce a pyrilium intermediate. Before it forms an insoluble precipitate,[10] the pyrilium intermediate is immediately trapped by the nucleophile present in the reaction mixture.

Conclusions

We believe that this approach to heterocycles should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, sulfur and selenium functionalities into other substituents. For instance, the resulting heterocyclic iodides should be particularly useful intermediates in many palladium-catalyzed processes, such as Sonogashira,[11] Suzuki,[12] Stille,[13] and Heck[14] cross couplings.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using 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 [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of ethyl ether, hexanes, ethyl acetate, and CH_2Cl_2 were purchased from Fisher Scientific Co. 2-Bromobenzaldehyde, 2-iodoacetophenone, phenylacetylene, 1-cyclohexenyl acetylene, 1-hexyne, PhSeCl, PhSeBr, *p*-$O_2NC_6H_4SCl$, $PhNMe_2$, phenol and Et_3N were purchased from Aldrich Chemical Co., Inc. The palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd.

Starting materials. The 2-(1-alkynyl)benzaldehydes were prepared by the Sonogashira coupling of 2-bromobenzaldehyde with various terminal alkynes.[15] The same procedure was used to prepare 2-(phenylethynyl)acetophenone. All commercially available compounds were used as received.

General procedure for the synthesis of 4-iodo-1*H*-isochromenes. Into a solution of the 2-(1-alkynyl)benzaldehyde, K_2CO_3 (1.0 equiv) and the nucleophile (1.2 equiv) in CH_2Cl_2 (0.25 mmol), I_2 (1.2 equiv) was added and the solution was stirred at room temperature until the total disappearance of the starting material as determined by TLC analysis. The reaction mixture was then quenched with satd aq $Na_2S_2O_3$ (5.0 mL) and water (5.0 mL). The resulting solution was extracted by diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford pure compounds.

4-Iodo-1-methoxy-3-phenyl-1*H*-isochromene (2). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H), 6.12 (s, 1H), 7.34 (d, J = 7.0 Hz, 1H), 7.42 (t, J = 7.0 Hz, 1H), 7.54-7.57 (m, 4H), 7.72-7.74 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 55.9, 73.7, 99.8, 125.3, 127.0, 127.7, 127.8, 129.2, 129.6, 129.8, 129.9, 131.2, 137.2, 151.6; IR (neat, cm^{-1}) 3039, 2936, 1052; HRMS calcd for $C_{16}H_{13}IO_2$ 363.9960, found 363.9964.

1-*n*-Butoxy-4-iodo-3-phenyl-1*H*-isochromene (3). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.38-1.50 (m, 2H), 1.62-1.72 (m, 2H), 3.76-3.84 (m, 1H), 4.00-4.04 (m, 1H), 6.13 (s, 1H), 7.21 (dd, J = 7.4, 1.0 Hz, 1H), 7.35

(td, J = 7.4, 1.1 Hz, 1H), 7.43-7.50 (m, 4H), 7.61-7.66 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.6, 31.9, 68.9, 74.0, 99.1, 125.6, 127.8, 128.0, 128.2, 129.5, 129.9, 130.0, 130.2, 131.8, 137.8, 152.2; IR (neat, cm^{-1}) 3063, 3032, 2956, 2931, 2870, 1594, 1483; HRMS calcd for $C_{19}H_{18}IO_2$ 406.0430, found 406.0438.

1-(4-Dimethylaminophenyl)-4-iodo-3-phenyl-1*H*-isochromene (4). The product was obtained as a white solid (mp = 51 °C, dec): ^{1}H NMR ($CDCl_3$) δ 3.02 (s, 6H), 6.21 (s, 1H), 6.74-6.77 (m, 3H), 7.24-7.36 (m, 7H), 7.53-7.58 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 40.4, 72.9, 80.6, 112.1, 124.8, 126.2, 127.5, 128.3, , 128.9, 129.2, 129.4, 130.4, 131.5, 133.4, 136.7, 150.6, 154.6; IR (neat, cm^{-1}) 3046, 1612, 1524; HRMS calcd for $C_{23}H_{20}INO$ 454.0668, found 454.0660.

1-(4-Hydroxyphenyl)-4-iodo-3-phenyl-1*H*-isochromene (5). The product was obtained as an orange syrup: ^{1}H NMR ($CDCl_3$) δ 5.50 (br s, 1H), 6.23 (s, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 7.23-7.25 (m, 3H), 7.34-7.36 (m, 4H), 7.53-7.55 (m, 2H), 7.63 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 73.2, 80.2, 115.3, 124.8, 127.6, 127.7, 128.5, 129.0, 129.3, 129.9, 130.2, 130.9, 131.1, 133.3, 136.6, 154.5, 155.9; IR (neat, cm^{-1}) 3569, 3044, 1174; HRMS calcd for $C_{21}H_{15}IO_2$ 426.0117, found 426.0119.

1-Methoxy-3-phenyl-4-phenyselenyl-1*H*-isochromene (6). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 6.13 (s, 1H), 7.09 (d, J = 4.8 Hz, 1H), 7.15 (t, J = 5.4 Hz, 2H), 7.23-7.40 (m, 9H), 7.56-7.59 (m, 2H), 7.73 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.4, 76.9, 100.4, 125.7, 125.7, 126.6, 127.5, 127.6, 127.9, 128.4, 129.3, 129.4, 129.8, 130.0, 131.4, 133.6, 136.4, 157.1; IR (neat, cm^{-1}) 3063, 2968, 1021, 960; HRMS calcd for $C_{22}H_{18}O_2Se$ 394.0472, found 394.0479.

1-Methoxy-4-*p*-nitrophenylsulfenyl-3-phenyl-1*H*-isochromene (7). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 6.17 (s, 1H), 7.24-7.27 (m, 2H), 7.35-7.43 (m, 6H), 7.58-7.61 (m, 3H), 8.03 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.7, 100.5, 102.6, 123.8, 124.3, 125.6, 126.0, 127.7, 128.1, 128.2, 129.5, 129.9, 130.1, 130.2, 134.7, 145.3, 148.6, 158.8; IR (neat, cm^{-1}) 3093, 3065, 2930, 2833, 1594, 1510, 1337; HRMS calcd for $C_{22}H_{17}NO_4S$ 391.0878, found 391.0883.

3-*n*-Butyl-4-iodo-1-metoxy-1*H*-isochromene (9). The product was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 3H), 1.43-1.64 (m, 2H), 1.64-1.84 (m, 2H), 2.63-2.92 (m, 2H), 3.63 (s, 3H), 5.92 (s, 1H), 7.21 (d, J = 7.1 Hz, 1H), 7.34 (td, J = 7.1, 1.3 Hz, 1H), 7.43 (td, J = 7.9, 1.3 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.1, 29.3, 36.9, 55.4, 73.3, 99.1, 125.2, 126.6, 126.8, 128.4, 129.5, 130.8, 154.5; IR (neat, cm^{-1}) 3029, 2956, 1078; HRMS calcd for $C_{14}H_{17}IO_2$ 344.0273, found 344.0288.

1-(4-Dimethylaminophenyl)-3-*n*-butyl-4-iodo-1*H*-isochromene (10). The product was obtained as a white solid (mp = 51 °C, dec): ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 5.4 Hz, 3H), 1.22-1.38 (m, 2H), 1.44-1.53 (m, 2H), 2.50-2.80 (m, 2H), 2.97 (s, 6H), 5.99 (s, 1H), 6.66 (d, J = 5.6 Hz, 1H), 6.72 (d, J = 6.4 Hz, 2H), 7.11 (t, J = 5.6 Hz, 1H), 7.19 (d, J = 6.5 Hz, 2H), 7.29 (t, J = 5.7 Hz, 1H), 7.40 (d, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.5, 30.1, 32.7, 56.1, 63.9, 99.9, 115.6, 122.9, 124.3, 125.4, 126.0, 127.2, 127.3, 129.7, 130.1, 145.2, 148.6; IR (neat, cm^{-1}) 3062, 2955, 2926, 2858, 2806, 1736, 1612, 1524; HRMS calcd for $C_{21}H_{24}INO$ 433.0903, found 433.0913.

3-*n*-Butyl-1-methoxy-4-*p*-nitrophenylsulfenyl-1*H*-isochromene (11). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.26-1.39 (m,

2H), 1.57-1.67 (m, 2H), 2.57-2.67 (m, 1H), 2.79-2.89 (m, 1H), 3.64 (s, 3H), 6.04 (s, 1H), 7.20-7.28 (m, 6H), 8.05 (d, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.5, 30.1, 32.7, 56.1, 63.9, 99.9, 122.9, 124.3, 125.4, 126.0, 127.2, 127.4, 129.7, 130.1, 145.2, 148.6; IR (neat, cm^{-1}) 3062, 2955, 1736, 1612, 1524; HRMS calcd for $C_{20}H_{21}NO_4S$ 371.1192, found 371.1199.

3-(Cyclohex-1-enyl)-4-iodo-1-methoxy-1*H*-isochromene (13). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.72-1.78 (m, 4H), 2.24-2.38 (m, 4H), 3.64 (s, 3H), 5.92 (s, 1H), 6.14 (m, 1H), 7.14 (dd, J = 7.2, 1.3 Hz, 1H), 7.32 (td, J = 7.2, 1.3 Hz, 1H), 7.42 (td, J = 7.7, 1.5 Hz, 1H), 7.53 (dd, J = 7.7, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.3, 24.9, 26.7, 55.6, 71.9, 99.4, 125.2, 127.0, 127.2, 129.4, 129.6, 131.3, 132.9, 135.2, 153.8; IR (neat, cm^{-1}) 3034, 2926, 1024; HRMS calcd for $C_{16}H_{17}IO_2$ 368.0273, found 368.0273.

1-(4-Dimethylaminophenyl)-3-(cyclohex-1-enyl)-4-iodo-1*H*-isochromene (14). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.56-1.66 (m, 4H), 2.03-2.17 (m, 4H), 2.96 (s, 6H), 5.98-5.99 (m, 1H), 6.02 (s, 1H), 6.68-6.72 (m, 3H), 7.12 (t, J = 6.0 Hz, 1H), 7.17 (d, J = 6.4 Hz, 2H), 7.30 (t, J = 5.7 Hz, 1H), 7.45 (d, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.6, 25.3, 27.0, 31.2, 57.0, 71.9, 80.5, 112.3, 117.6, 125.1, 127.3, 128.4, 128.8, 129.6, 131.9, 133.2, 133.7, 135.3, 157.6; IR (neat, cm^{-1}) 2927, 2855, 1613, 1523; HRMS calcd for $C_{23}H_{24}INO$ 457.0903, found 457.0913.

Synthesis of 1,3-dihydro-3-[(E)-1-iodo-1-phenylmethylene]-1-methoxy-1-methylisobenzofuran (17). To a stirred mixture of 2-(phenylethynyl)acetophenone (0.25 mmol), K_2CO_3 (1.0 equiv) and MeOH (1.2 equiv) in CH_2Cl_2 (5 mL), I_2 (1.2 equiv) was added and the mixture was stirred until no starting material remained as indicated by TLC

analysis. The reaction mixture was quenched with satd aq $Na_2S_2O_3$ (5.0 mL) and water (5.0 mL). The mixture was extracted with diethyl ether and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford a pale yellow solid (*unstable*): ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 3.01 (s, 3H), 7.23-7.71 (m, 4H), 7.25 (d, J = 7.2 Hz, 1H), 7.31-7.45 (m, 3H), 8.82 (d, J = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.6, 50.5, 65.9, 110.1, 122.1, 125.5, 127.3, 127.7, 128.9, 130.0, 130.3, 133.8, 141.7, 142.6, 150.9; HRMS calcd for $C_{17}H_{15}IO_2$ 378.0117, found 378.0121.

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CHAPTER 3. SYNTHESIS OF COUMESTANS BY SELECTIVE ELECTROPHILIC CYCLIZATION, FOLLOWED BY PALLADIUM-CATALYZED INTRAMOLECULAR CARBONYLATION: AN EFFICIENT SYNTHESIS OF COUMESTROL

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

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Abstract

Coumestan and coumestrol are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of appropriately substituted *o*-iodoanisoles and terminal alkynes and selective electrophilic cyclization using I_2, followed by palladium-catalyzed intramolecular carbonylation and subsequent lactonization.

Introduction

Heterocyclic compounds, particularly indole[1] and benzo[*b*]furan[2] derivatives, are of interest because they occur widely in nature and have unique biological activities.[1-3] Many methods for the synthesis of indoles[4] and benzo[*b*]furans[5] have already been reported. Among them, the cyclization of 2-(1-alkynyl)phenol or 2-(1-alkynyl)aniline derivatives is a powerful method for constructing such ring systems, because of the ready availability of the starting materials and the overall efficiency of this approach.[4,5] Recently, we developed a

very efficient method to quickly construct benzo[*b*]thiophenes,[6] indoles[7] and benzo[*b*]furans[8] by a palladium/copper-catalyzed coupling of terminal alkynes and appropriate functionally-substituted aryl halides, followed by electrophilic cyclization. Methyl groups on sulfur, nitrogen and oxygen are easily removed by the nucleophiles present in the solution. This approach should have wide applicability, because of the extremely mild reaction conditions and the versatility of the resulting iodoheterocycles.

Phytoestrogens are plant-derived compounds that structurally or functionally mimic mammalian estrogens and therefore are considered to play an important role in the prevention of cancers, heart disease, menopausal symptoms and osteoporosis.[9] Coumestans are a group of plant phenols that show estrogenic activity.[9] Their presence in forage crops has been associated with the disruption of the reproductive performance of livestock.[10] A few coumestans isolated from plants have shown uterotropic activity.[11]

The main coumestans with phytoestrogenic effects are coumestrol and 4′-methoxycoumestrol (Figure 1).[9] Coumestrol was isolated from alfalfa, and strawberry,

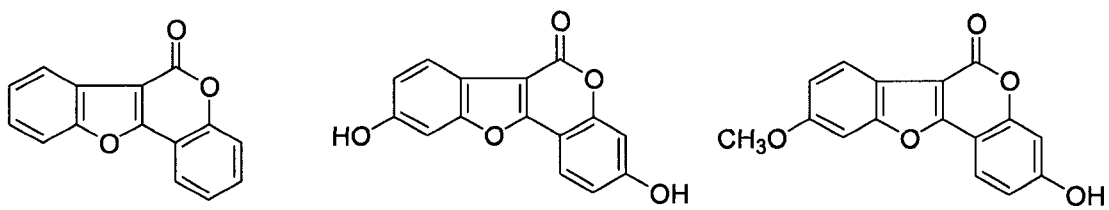


Figure 1

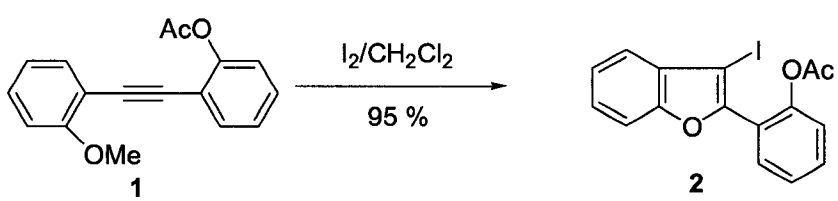
lucerne and ladino clover by Bickoff *et al.* in the 1950's.[12] Since the structure of coumestrol has some resemblance to the well known (*E*)-4,4′-dihydroxystilbene derivatives, which have potent pharmacological activity, it is not surprising that coumestrol shows estrogenic activity.[13] Coumestrol has higher binding affinities to ERβ than the other phytoestrogen

compounds.[14] *In vitro* coumestrol has been reported to inhibit bone resorption and to stimulate bone mineralization.[15] Coumestans are less common in the human diet than isoflavones, yet similar to isoflavones, they are also found in food plants, such as sprouts of alfalfa and mung bean, and they are especially prevalent in clover.[16] Soy sprouts also show high levels of coumestrol.[17]

Total syntheses of coumestrol have been reported by several groups using different approaches.[12d,13,18] However, most of the reported methods required multiple steps and produced only modest yields. Furthermore, a number of naturally occurring coumestan isoflavones have been discovered[19] and their biological effects are currently under investigation.[20] Considering the numerous important physiological effects estrogens have on the human body and the potential of phytoestrogens for human health, it is highly desirable to develop more efficient and direct methods for the synthesis of coumestans and derivatives. Utilizing our highly efficient basic approach to benzothiophenes,[6] indoles,[7] and benzofurans[8] developed earlier, we here present a new approach to the synthesis of the coumestan core structure and the synthesis of coumestrol.

Results and Discussion

During our study of the synthesis of benzo[*b*]furans,[8] we found that compound **1** can be easily cyclized under our iodocyclization conditions to afford compound **2** in a 95% yield with the acetoxy group still intact (eq 1). The high chemoselectivity of this process allows

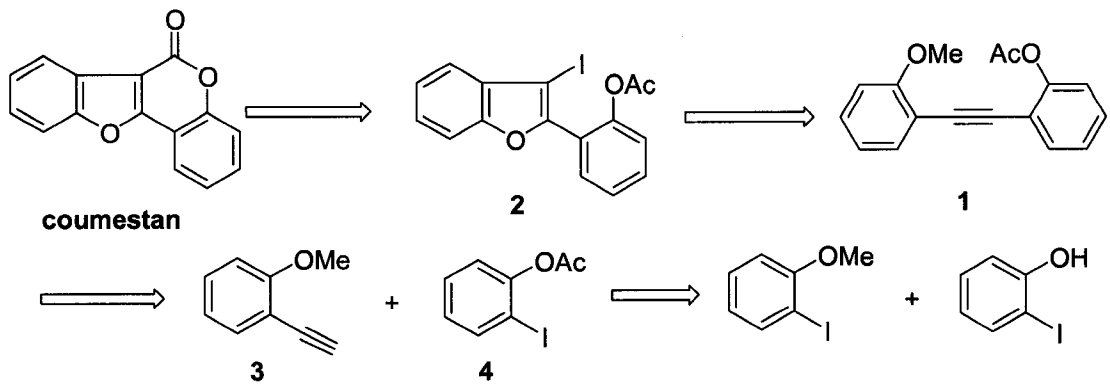


(1)

selective cyclization onto either end of the alkyne by careful choice of the protecting group on the oxygen functionality.

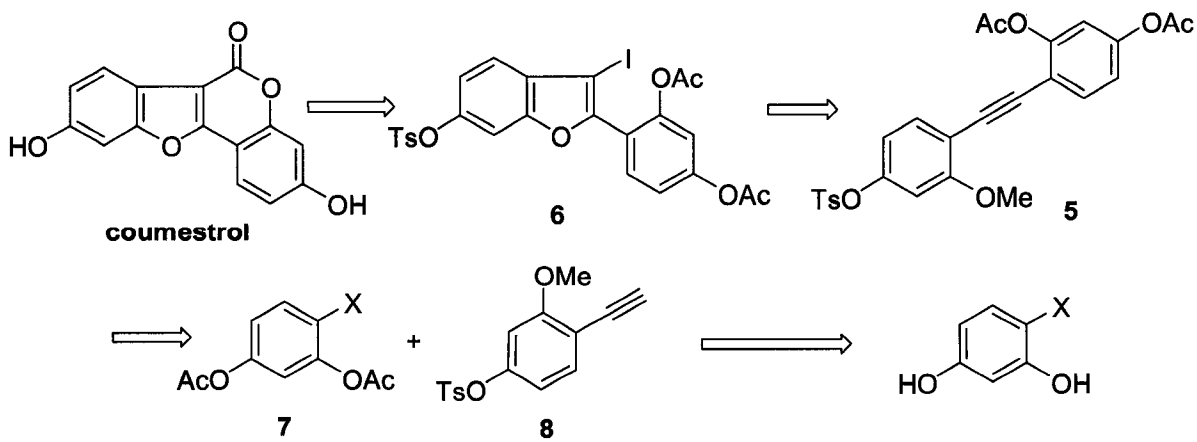
Based on this result, we set out the following strategy for the synthesis of coumestan (Scheme 1). By using our iodocyclization, compound **1** can be easily cyclized to compound

Scheme 1



2, which could produce the coumestan ring system by either a one pot carbonylation and lactonization or a stepwise approach. Compound **1** can be easily synthesized by a Sonogashira reaction between arenes **3** and **4**.[21] Compounds **3** and **4** can in turn be synthesized from 2-iodoanisole and 2-iodophenol respectively. Using the same basic methodology (Scheme 2), coumestrol might be synthesized by carbonylation and

Scheme 2



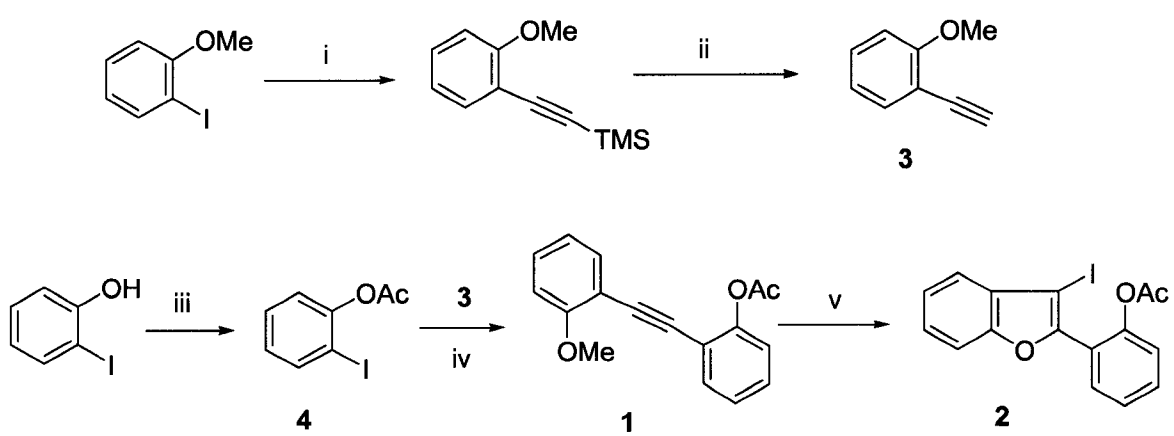
subsequent lactonization of iodobenzofuran **6**, which should be easily synthesized from

diarylacetylene **5** by electrophilic cyclization using iodine. Compound **5** should be easily synthesized from arenes **7** and **8**, which might be prepared from the same resorcinol derivative **9**.

Synthesis of the coumestan ring system

Commercially available 2-iodoanisole and 2-iodophenol were used as the starting materials for the synthesis of coumestan. The Sonogashira coupling of 2-iodoanisole with trimethylsilylacetylene catalyzed by 2 mol % of $PdCl_2(PPh_3)_2$ in the presence of 1 mol % of CuI and 1.5 equiv of Et_3N in DMF, followed by desilylation using *n*-Bu_4NF (TBAF) in THF, gave compound **3** in a 95% overall yield for the two steps. In the meanwhile, 2-iodophenol was acetylated to give compound **4** in essentially a quantitative yield.

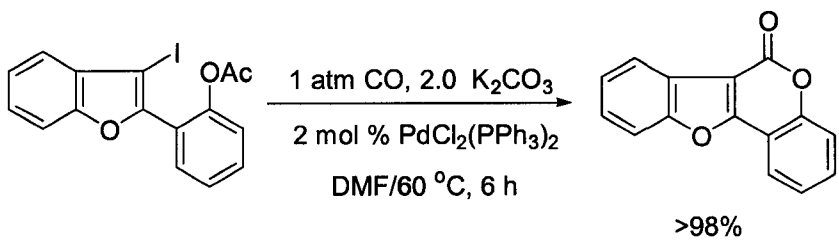
Scheme 3



Reagents, conditions and yields: i, 1.2 equiv of trimethylsilylacetylene, 2 mol % of $PdCl_2(PPh_3)_2$, 1 mol % of CuI, 1.5 equiv of Et_3N, DMF, 60 °C, 2 h, 96%; ii, 1.0 equiv of TBAF, THF, 25 °C, 99%; iii, 1.2 equiv of AcCl, 2 equiv of Et_3N, THF, 0 °C, 1 h, >99%; iv, 1.2 equiv of **3**, 2.0 mol % of $PdCl_2(PPh_3)_2$, 1.0 mol % of CuI, 2.0 equiv of Et_3N, DMF, 60 °C, 2 h, 95%; v, 1.2 equiv of I_2, CH_2Cl_2, 25 °C, 12 h, 95%.

Under the same Sonogashira coupling conditions used above, compound **3** reacted with **4** and afforded a 95% yield of compound **1**. Compound **1** was treated with iodine at 25 °C to produce compound **2** in a 95% yield after 12 h (Scheme 3).

Compound **2** was then treated with a palladium catalyst and 1 atm of CO in the hope that we might affect carbonylation and lactonization in one step. A brief optimization of the reaction conditions showed that when 2 mol % of $PdCl_2(PPh_3)_2$ was used as the catalyst, 2.0 equiv of K_2CO_3 was used as the base and DMF was used as the solvent, both carbonylation and lactonization proceeded smoothly under a balloon of CO at 60 °C, affording almost a quantitative yield of coumestan after 6 h (eq 2). Coumestan was identified based on a comparison with previously reported data.[18e,22]



(2)

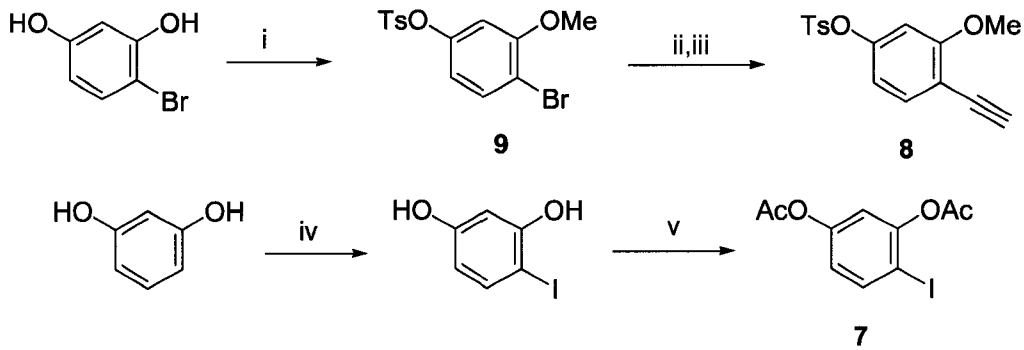
Synthesis of coumestrol

(a) Synthesis of the substituted phenylacetylene derivative (Scheme 4)

Commercially available 4-bromoresorcinol was selectively tosylated and the resulting phenol was converted into the methyl ether in two steps in a 79% overall yield. The Sonogashira coupling[21] of aryl bromide **9** with 1.2 equiv of trimethylsilylacetylene, followed by desilylation with *n*-Bu_4NF, provided compound **8** in an 88% overall yield.

2,4-Diacetoxyiodobenzene (**7**) was prepared in almost a quantitative yield by acetylation of 4-iodoresorcinol, which was synthesized by the iodination of resorcinol using ICl. Our usual Sonogashira coupling reaction conditions were ineffective for the coupling

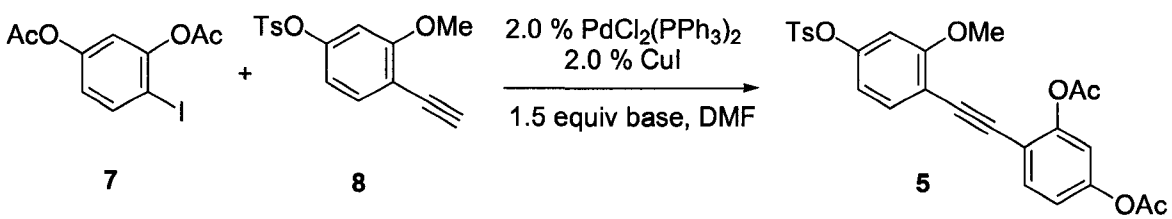
Scheme 4



Reagents, conditions and yields: i, 1.1 equiv of TsCl, 3.0 equiv of K_2CO_3, acetone, reflux, 21 h; then 2.0 equiv of MeI, reflux, 3 h, 79%; ii, 1.2 equiv of trimethylsilylacetylene, 2 mol % of $PdCl_2(PPh_3)_2$, 1 mol % of CuI, 1.5 equiv of Et_3N, DMF, 100 °C, 6h , 89%; iii, 1.0 equiv of TBAF, THF, 25 °C, 10 min, 99%; iv, 1.0 equiv of ICl, Et_2O, 25 °C, 1 h, 70%; v, 2.5 equiv of AcCl, 5.0 equiv of Et_3N, THF, 0 °C, 1 h, >98%.

of arenes **7** and **8**. A large amount of the homocoupling product of acetylene **8** was obtained. A brief optimization of the Sonogashira coupling showed that using *i*-Pr_2NH as the base and DMF as the solvent at 60 °C provided the best yield of acetylene **5** (eq 3, Table 1).[23] The desired coupling product **5** was obtained in a 95% yield in 1 h.

Table 1. Sonogashira coupling of terminal alkyne **8** and halide **7**.

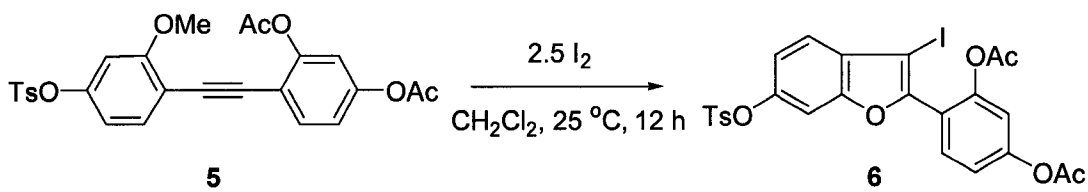


(3)

entry	base	temp (°C)	time (h)	% yield
1	Et_3N	100	1.5	40
2	Et_3N	25	1.5	60
3	*i*-Pr_2NH	80	1.5	50
4	*i*-Pr_2NH	60	1.5	95
5	*i*-Pr_2NH	25	1.0	-

(b) Iodocyclization

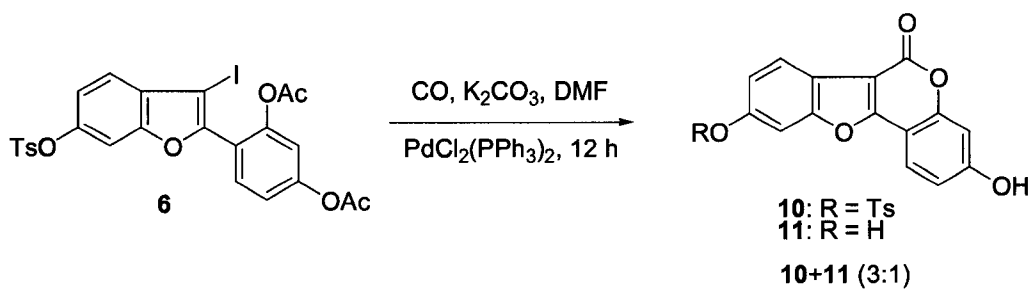
Using our standard iodocyclization conditions, compound **5** was successfully cyclized to benzofuran **6** in a 98% yield in 12 h, although the reaction time is substantially longer than our usual iodocyclization reactions and 2.5 equiv of I_2 were used (eq 4). The reaction was incomplete and a large amount of starting material was recovered when only 1.2 equiv of I_2 were used.



(4)

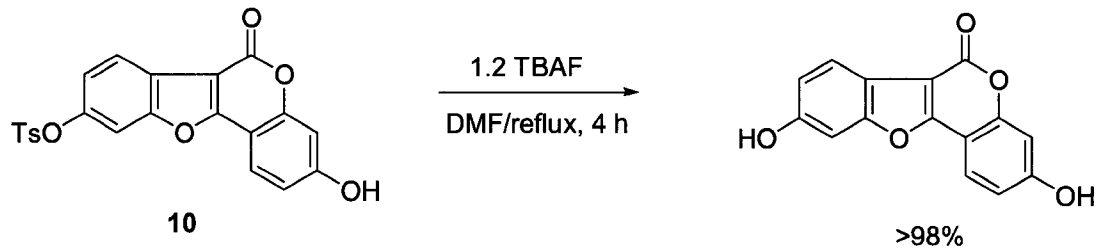
(c) Carbonylation and lactonization

Under the optimal conditions for carbonylation and subsequent lactonization for coumestan, compound **13** was converted to coumestrol **11** in only a 20% yield, together with a 60% yield of the coumestrol tosylate **10** (eq 5). The tosyl derivative was further



(5)

converted to coumestrol in a quantitative yield by using 1.1 equiv of TBAF in DMF under reflux for 2 h (eq 6). A separate experiment showed that without further purification, the mixture of coumestrol (**11**) and tosyl derivative **10** could be converted to coumestrol in a 75% yield using 1.2 equiv of TBAF in DMF under reflux in 4 h.



(6)

Conclusions

A general synthetic method has been developed for the synthesis of coumestan and its derivatives under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of *o*-iodoanisole derivatives and terminal alkynes and their selective electrophilic cyclization using I_2, followed by palladium-catalyzed intramolecular carbonylation and lactonization. Biologically interesting coumestrol has been synthesized in a 75% overall yield in three steps from the corresponding diarylacetylene derivative.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using 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 [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of THF, DMF, diethyl ether, ethyl acetate and hexanes were purchased from Fisher Scientific Co. *n*-Bu_4NF was purchased from Lancaster Synthesis, Inc. 2-Iodophenol, 2-iodoanisole, 4-bromoresorcinol, resorcinol, MeI, TsCl, AcCl, *i*-Pr_2NH and Et_3N were obtained from Aldrich Chemical Co., Inc.

4-Iodoresorcinol. This compound was prepared according to a literature procedure.[18d] A solution of resorcinol (2.75 g, 25.0 mmol) and ICl (4.0 g, 25.0 mmol) in dry Et_2O (25 mL) was stirred at room temperature for 1 h. Water (50 mL) and Na_2SO_3 (1.0 g) were added to the mixture and the aqueous phase was then extracted with Et_2O. The combined organic solution was washed successively with water and satd aq NaCl, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography [AcOH-$CHCl_3$ (1:9)] and alumina chromatography [hexane-AcOEt (2:1)] to afford 4-iodoresorcinol as colorless oil (4.13 g, 70%): ^{1}H NMR ($CDCl_3$) δ 5.21 (br s, 2H), 6.27 (dd, J = 8.2, 2.8 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 7.46 (d, J = 8.6 Hz, 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. The spectral properties were identical to those previously reported.[18d]

2-Acetoxy-2'-methoxy-diphenylacetylene (1). A mixture of 2-ethynylanisole (6.00 mmol), 2-iodophenyl acetate (5.00 mmol), CuI (0.06 mmol) and $PdCl_2(PPh_3)_2$ (0.12 mmol) in a mixture of Et_3N (2.0 equiv) and DMF (50 mL) was heated at 60 °C for 2 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with Et_2O and the combined extracts were washed successively with water and satd aq NaCl. The organic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel with hexane-

AcOEt as eluent to give **1** (96%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.87 (s, 3H), 6.88 (d, J = 8.7 Hz, 1H), 6.92 (td, J = 7.5, 0.9 Hz, 1H), 7.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.20 (td, J = 7.5, 1.5 Hz, 1H), 7.26-7.35 (m, 2H), 7.46 (dd, J = 7.5, 1.8 Hz, 1H), 7.59 (dd, J = 7.5, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 55.8, 88.3, 90.9, 110.9, 112.3, 118.0, 120.6, 122.4, 126.0, 129.4, 130.2, 133.1, 133.7, 151.6, 160.1, 169.1; IR (neat) 1771 cm^{-1}; HRMS calcd for $C_{17}H_{14}O_3$ 266.0946, found 266.0943.

2-(2-Acetoxyphenyl)-3-iodobenzo[*b*]furan (2). A solution of **1** (2.50 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 1 min. 2.5 Equiv of I_2 was added and the resulting mixture was allowed to stir at 25 °C for 12 h. Satd aq $Na_2S_2O_3$ (5 mL) was added to the mixture, which was further stirred for 2 min. The resulting mixture was then extracted with Et_2O. The combined organic solution was washed successively with water and satd aq NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was successively purified by flash chromatography on silica gel using hexane-AcOEt as eluent to afford **2** as a yellow oil (95%): ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 7.25 (dd, J = 8.1, 1.2 Hz, 1H), 7.32-7.40 (m, 3H), 7.44-7.53 (m, 3H), 7.82 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 65.4, 111.4, 122.1, 123.3, 123.7, 123.8, 126.0, 126.1, 131.2, 131.7, 131.9, 148.8, 152.3, 154.6, 169.4; IR (CH_2Cl_2) 1771 cm^{-1}; HRMS calcd for $C_{16}H_{11}IO_3$ 377.9758, found 377.9753.

2-Methoxyphenylacetylene (3). The product was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.32 (s, 1H), 3.89 (s, 3H), 6.87-6.93 (m, 2H), 7.32 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.9, 80.2, 81.3, 110.7, 111.2, 120.6, 130.4, 134.3,

160.7; IR (neat, cm^{-1}) 3058, 2222, 1750; HRMS calcd for C_9H_8O 132.0575. Found 132.0577.

2,4-Diacetoxy-2'-methoxy-4'-tosyloxy-diphenylacetylene (5). A mixture of 2-ethynyl-4-tosyloxy-anisole (5.00 mmol), 2,4-diacetoxy-1-iodobenzene (6.00 mmol), CuI (0.06 mmol) and $PdCl_2(PPh_3)_2$ (0.12 mmol) in a mixture of *i*-Pr_2NH (6.00 mmol) and DMF (25 mL) was heated at 60 °C for 1 h. Water was added to the mixture, which was extracted with Et_2O and the combined extracts were washed with water and satd aq NaCl. The organic solution was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel using hexane-AcOEt as the eluent to give **1** (96%) as a yellow solid: mp 234-236 ^{0}C; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.34 (s, 3H), 2.44 (s, 3H), 3.78 (s, 3H), 6.49 (dd, J = 8.4, 2.4 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 7.01 (dd, J = 8.4, 2.4 Hz, 1H), 7.30-7.33 (m, 3H), 7.54 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.3, 21.9, 56.1, 88.6, 89.6, 106.1, 111.4, 114.4, 115.2, 116.4, 119.4, 128.8, 130.0, 132.2, 133.4, 134.0, 145.8, 150.7, 151.1, 152.0, 160.8, 168.4, 168.8; IR (neat, cm^{-1}) 1770, 1768; HRMS calcd for $C_{26}H_{22}O_8S$ 494.1041, found 494.1036.

2-(2,4-Diacetoxyphenyl)-3-iodo-6-(tosyloxy)benzo[*b*]furan (6). A solution of **5** (2.50 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 1 min. 2.5 Equiv of I_2 was added and the resulting mixture was allowed to stir at 25 °C for 12 h. Satd aq $Na_2S_2O_3$ (5 mL) was added to the mixture, which was further stirred for 2 min. The resulting mixture was then extracted with Et_2O. The combined organic extracts were washed with water and satd aq NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography using hexane-AcOEt as the eluent to afford **2** as a yellow solid (98%): mp 300 ^{0}C, dec; ^{1}H NMR ($CDCl_3$) δ 2.18 (s,

3H), 2.33 (s, 3H), 2.45 (s, 3H), 6.99 (dd, J = 8.4, 2.1 Hz, 1H), 7.10-7.18 (m, 3H), 7.33 (t, J = 7.2 Hz, 3H), 7.73 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.4, 21.9, 64.9, 106.1, 117.4, 118.9, 119.4, 120.2, 122.4, 128.8, 130.1, 130.7, 132.2, 132.3, 145.8, 148.1, 149.2, 152.4, 153.3, 153.7, 168.8; IR (neat, cm^{-1}) 1770; HRMS calcd for $C_{16}H_{11}IO_3$ 605.9851, found 605.9846.

4-Ethynyl-3-methoxyphenyl tosylate (8). A mixture of 1-bromo-2-methoxy-4-(tosyloxy)benzene (2.0 g, 5.6 mmol), trimethylsilylacetylene (0.66 g, 6.72 mmol), CuI (10 mg, 0.06 mmol) and $PdCl_2(PPh_3)_2$ (85 mg, 0.12 mmol) in a mixture of Et_3N (5 mL) and DMF (20 mL) was heated at 100 °C for 6 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with Et_2O and the combined extracts were washed with water and satd aq NaCl. The organic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel using hexane-AcOEt (5:1) as the eluent to give the TMS-acetylene (2.05 g, 98%) as a colorless solid: mp 104-106 °C (lit.[18d] mp 105-107 °C); ^1H NMR ($CDCl_3$) δ 0.24 (s, 9H), 2.44 (s, 3H), 3.75 (s, 3H), 6.45 (dd, J = 8.4, 2.2 Hz, 1H), 6.54 (d, J = 2.2 Hz, 1H), 7.30 (d, J = 8.5 Hz, 3H), 7.69 (d, J = 8.4 Hz, 2H); IR (neat, cm^{-1}) 1380, 1280, 1180. The spectral properties were identical to those previously reported.[18d]

A solution of the TMS-acetylene (1.12 g, 3.00 mmol) and TBAF (1.0 M solution in THF; 3.0 mL, 3.00 mmol) in THF (60 mL) was vigorously stirred at room temperature for 5 min. Water was added to the mixture, which was extracted with Et_2O. The organic solution was washed with water and satd aq NaCl, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel using hexane-AcOEt (3:1) as the eluent to afford **8** (0.90 g, 99%) as yellow viscous oil: ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.30 (s, 1H),

3.79 (s, 3H), 6.48 (dd, J = 8.4, 2.2 Hz, 1H), 6.59 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5, 1H), 7.72 (d, J = 8.4 Hz, 2H); IR (neat, cm^{-1}) 1380, 1280, 1180; HRMS calcd for $C_{16}H_{14}O_4S$ 302.0615, found 302.0611.

4-Bromo-3-methoxyphenyl tosylate (9). A mixture of 4-bromoresorcinol (10.0 g, 53.0 mmol), K_2CO_3 (22.0 g, 159 mmol) and TsCl (11.1 g, 58.0 mmol) in acetone (150 mL) was refluxed for 21 h. MeI (15.0 g, 106 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic extracts were washed with water and satd aq NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was further purified by flash chromatography on silica gel using hexane-AcOEt (3:1) as the eluent to give 1-bromo-2-methoxy-4-(tosyloxy)benzene (15.0 g, 79%) as white powder: mp 69-71 °C (lit.[1] mp 69-72 °C); ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.79 (s, 3H), 6.41 (dd, J = 8.5, 2.5 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H); IR (neat, cm^{-1}) 1380, 1280, 1180. The spectral properties were identical to those previously reported.[18d]

4-Iodo-3-methoxyphenyl tosylate. A mixture of 4-iodoresorcinol (1.60 g, 6.78 mmol), K_2CO_3 (2.82 g, 20.4 mmol) and TsCl (1.40 g, 7.40 mmol) in acetone (30 mL) was refluxed for 15 h. MeI (2.89 g, 20.4 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic extracts were washed with water and satd aq NaCl, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was further purified by flash

chromatography on silica gel using hexane-AcOEt (4:1) as the eluent to give 4-Iodo-3-methoxyphenyl tosylate (1.53 g, 56%) as a yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.77 (s, 3H), 6.30 (dd, J = 8.5, 2.5 Hz, 1H), 6.52 (d, J = 2.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H); IR (neat, cm^{-1}) 1380, 1280, 1180. The spectral properties were identical to those previously reported.[18d]

Synthesis of coumestan. 2-(2-Acetoxyphenyl)-3-iodobenzo[*b*]furan (**2**) was used as the starting material for the synthesis of coumestan.[24] DMF (1.0 mL), $PdCl_2(PPh_3)_2$ (0.005 mmol), K_2CO_3 (0.5 mmol), and 3-iodobenzo[*b*]furan (**2**) (0.25 mmol) were stirred under an Ar atmosphere at room temperature for 5 min. The mixture was flushed with CO and fitted with a balloon of CO. The reaction mixture was heated to 60 °C with vigorous stirring for 12 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (15 mL) and washed with water (30 mL) and brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on a silica gel column to afford coumestan in a 100% yield. The compound was obtained as a white solid: mp 180-181 °C (lit.[25] mp 181-182 °C); ^{1}H NMR ($CDCl_3$) δ 7.39-7.53 (m, 4H), 7.59-7.69 (m, 2H), 8.04 (dd, J = 7.8, 1.5 Hz, 1H), 8.13-8.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 106.1, 112.0, 112.9, 117.7, 122.1, 123.7, 124.9, 125.4, 127.0, 132.1, 153.9, 155.8, 158.3, 160.2; IR (CH_2Cl_2) 1737 cm^{-1}; HRMS calcd for $C_{15}H_8O_3$ 236.0476, found 236.0473. The spectral properties were identical to those previously reported.[25]

Synthesis of coumestrol (11). 2-(2,4-Diacetoxyphenyl)-3-iodo-6-(tosyloxy)benzo[*b*]furan (**6**) was used as the starting material for the synthesis of coumestrol.

DMF (1.0 mL), $PdCl_2(PPh_3)_2$ (0.005 mmol), K_2CO_3 (0.5 mmol), and the 3-iodobenzo[*b*]furan **6** (0.25 mmol) were stirred under an Ar atmosphere at room temperature for 5 min. The mixture was flushed with CO and fitted with a balloon of CO. The reaction mixture was heated to 60 °C with vigorous stirring for 12 h. 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 anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column to afford coumestrol **11** (20%) and coumestrol tosylate **10** (60%).

Coumestrol tosylate **10**. The compound was isolated as white solid: mp >360 ^{0}C; ^{1}H NMR (CD_3OD) δ 2.46 (s, 3H), 6.87-6.88 (m, 1H), 6.91-6.95 (m, 2H), 7.03-7.07 (m, 1H), 7.41-7.44 (m, 3H), 7.72 (d, J = 8.1 Hz, 2H), 7.88 (t, J = 9.0 Hz, 2H).

A mixture of the coumestrol derivative **10** (0.10 mmol) and *n*-Bu_4NF (0.10 mmol) in DMF (5 mL) was stirred at 100 °C for 2 h. The resulting mixture was diluted with water and extracted with diethyl ether (2 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to afford coumestrol as white solid in a 99% yield: mp >360 °C (lit. mp 385 °C); ^{1}H NMR (DMSO-d_6) δ 6.90-6.96 (m, 3H), 7.16-7.17 (d, J = 1.8 Hz, 1H), 7.68-7.71 (d, J = 8.4 Hz, 1H), 7.84-7.87 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 98.7, 102.1, 103.0, 104.2, 113.7, 114.0, 114.6, 120.6, 122.7, 154.6, 155.9, 157.0, 157.6, 159.5, 161.2; IR (CH_2Cl_2) 3500-2850, 1703 cm^{-1}; HRMS calcd for $C_{15}H_8O_5$ 268.0375, found 268.0371. The spectral properties were identical to those previously reported.[18e]

Acknowledgements

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CHAPTER 4. 1,4-PALLADIUM MIGRATION FROM AN ARYL TO AN IMIDOYL POSITION, FOLLOWED BY INTRAMOLECULAR ARYLATION: SYNTHESIS OF FLUOREN-9-ONES

Based on a communication to be submitted to the *Journal of the American Chemical Society*

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Abstract

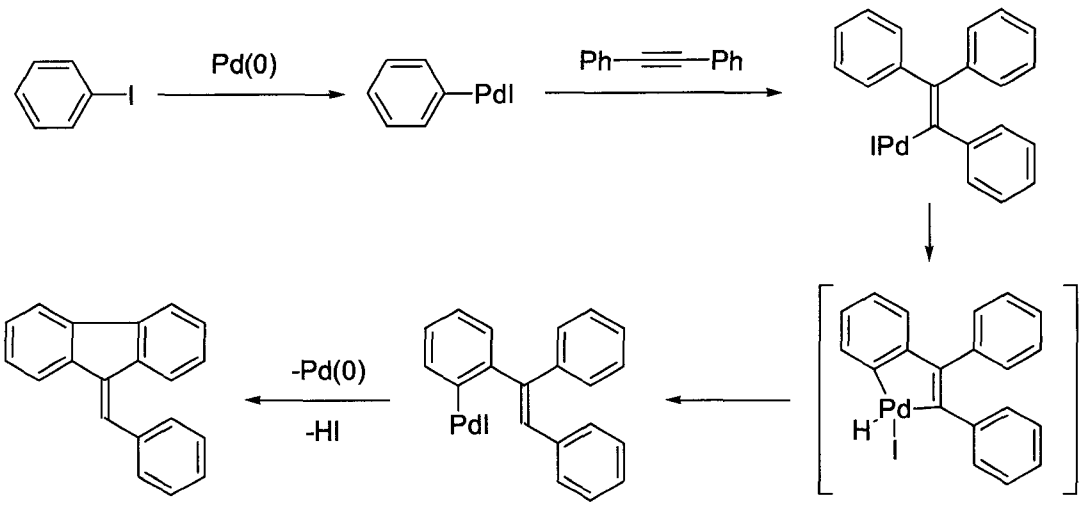
The synthesis of various fluoren-9-ones has been accomplished by the Pd-catalyzed intramolecular C-H activation of imines derived from *o*-iodoaniline and biarylcarboxaldehydes. This methodology makes use of a 1,4-palladium migration to generate the key imidoylpalladium intermediate, which undergoes intramolecular arylation, producing imines of complex polycyclic compounds containing the fluoren-9-one core structure. This methodology offers an efficient approach to the biologically interesting fluoren-9-one ring system.

Introduction

The ability of palladium to activate C-H bonds has been used extensively in organic synthesis.[1] In recent years, palladium-catalyzed C-H activation has received considerable attention due to the wide variety of reactions this metal can catalyze. For instance,

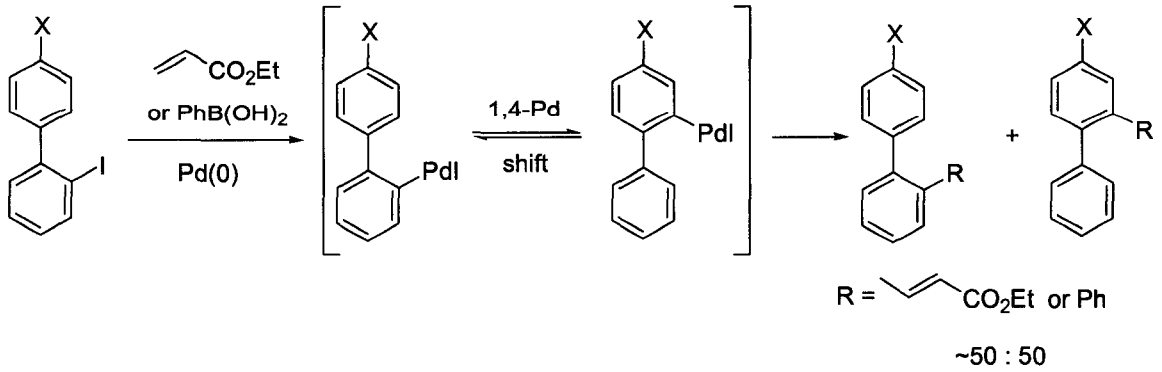
catalytic amounts of palladium salts have been used to activate the addition of C-H bonds of electron-rich arenes to alkenes and alkynes, as well as to undergo other transformations, such as carbonylation.[2] We have reported that the Pd-catalyzed intramolecular C-H activation in the rearrangement of organopalladium intermediates derived from aryl halides and internal alkynes provides a novel route to 9-benzylidene-9H-fluorenes (Scheme 1).[3]

Scheme 1



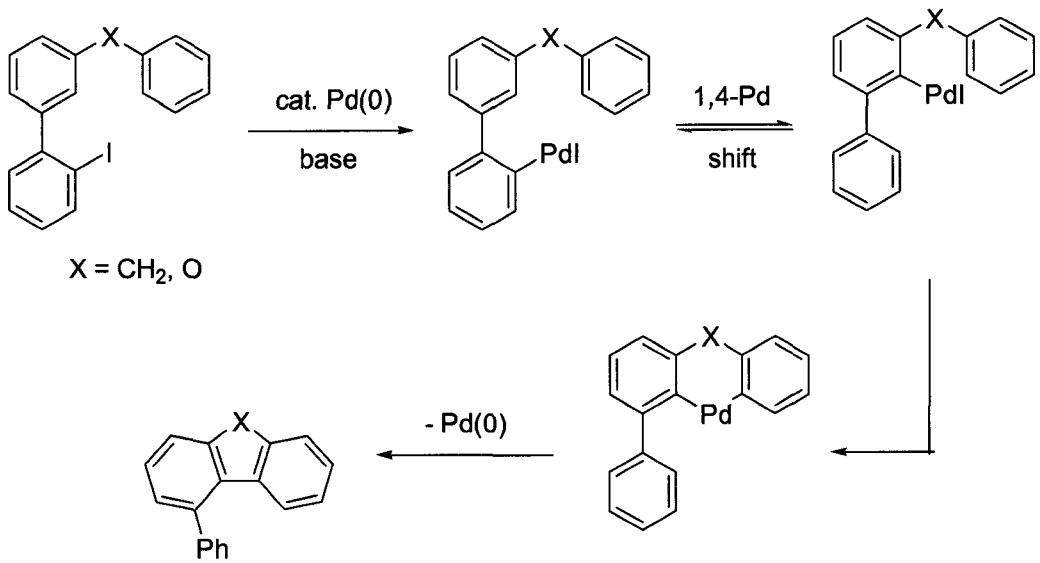
Similarly, intramolecular C-H activation in organopalladium intermediates derived from *o*-halobiaryls leads to a 1,4-palladium migration.[4] We have already shown that such intermediates can be trapped by Heck,[4] Suzuki[5] and alkyne annulation[6] reactions (Scheme 2).

Scheme 2



We recently reported a novel synthesis of fused polycycles using this Pd aryl-aryl migration process.[6] This methodology involves the use of palladium C-H activation to catalyze a 1,4-palladium migration within biaryls, generating key arylpalladium intermediates, which subsequently undergo C-C bond formation by intramolecular arylation to produce fused polycycles (Scheme 3).

Scheme 3



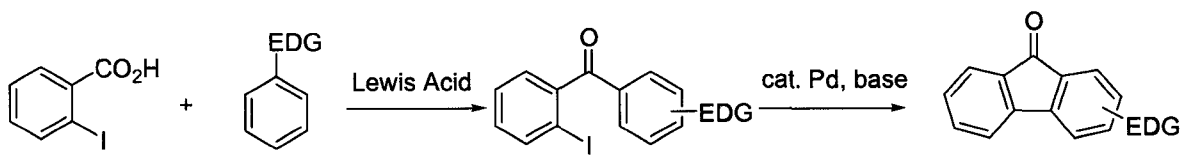
We have also explored other possible Pd migrations and their synthetic applications. Herein, we wish to report an unusual palladium migration from an aryl to an imidoyl position and its application for the synthesis of fluoren-9-ones.

Fluoren-9-ones are a family of natural products displaying a wide range of biological activity,[7] including antibiotic activity[6a] and human telomerase[6b] and protein kinase-C[6c] inhibitory activity. In recent years, fluorenones have attracted much interest because of groundbreaking discoveries in the biomedical field,[6] which include their use as probes for DNA redox chemistry.[6d] Furthermore, fluorenones have been prepared as key synthetic

intermediates for the total synthesis of natural products, such as stealthin and prekinamycin.[8]

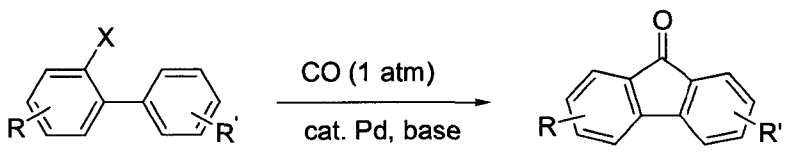
The most useful syntheses of fluorenones include Friedel-Crafts ring closures of biarylcarboxylic acids and derivatives,[9] intramolecular [4 + 2] cycloaddition reactions of conjugated enynes,[10] oxidation of fluorenes,[11] and remote metalation of 2-biphenylcarboxamides or 2-biphenyloxazolines.[12] Unfortunately, these methods suffer some drawbacks, mainly the use of strong Lewis acids,[8] heat,[8,9] or strong nucleophilic bases,[8] which do not tolerate many organic functional groups. Alternatively, the palladium-catalyzed cyclization of *o*-iodobenzophenones[13] (Scheme 4) and the palladium-

Scheme 4



EDG: electron-donating group (OMe, OH)

catalyzed cyclocarbonylation of *o*-halobiaryls[14] (eq 1) provide highly efficient and direct routes to the fluoren-9-one skeleton, as well as other related cyclic aromatic ketones. The

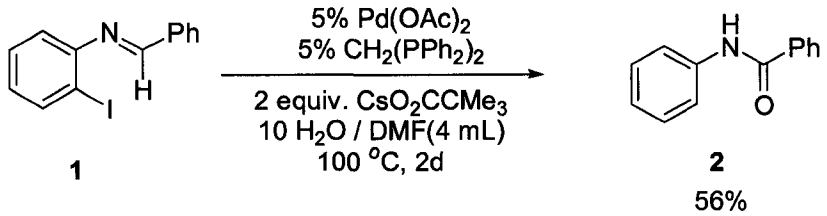


(1)

drawbacks to these palladium approaches are (1) iodobenzophenones and *o*-halobiaryls can be difficult to prepare, (2) the former process is limited by the need for electron-donating groups in the Friedel-Crafts reaction, and (3) the latter process employs toxic CO gas. Thus, new and efficient methods for the preparation of 9-fluorenones are always highly desired.

Results and Discussion

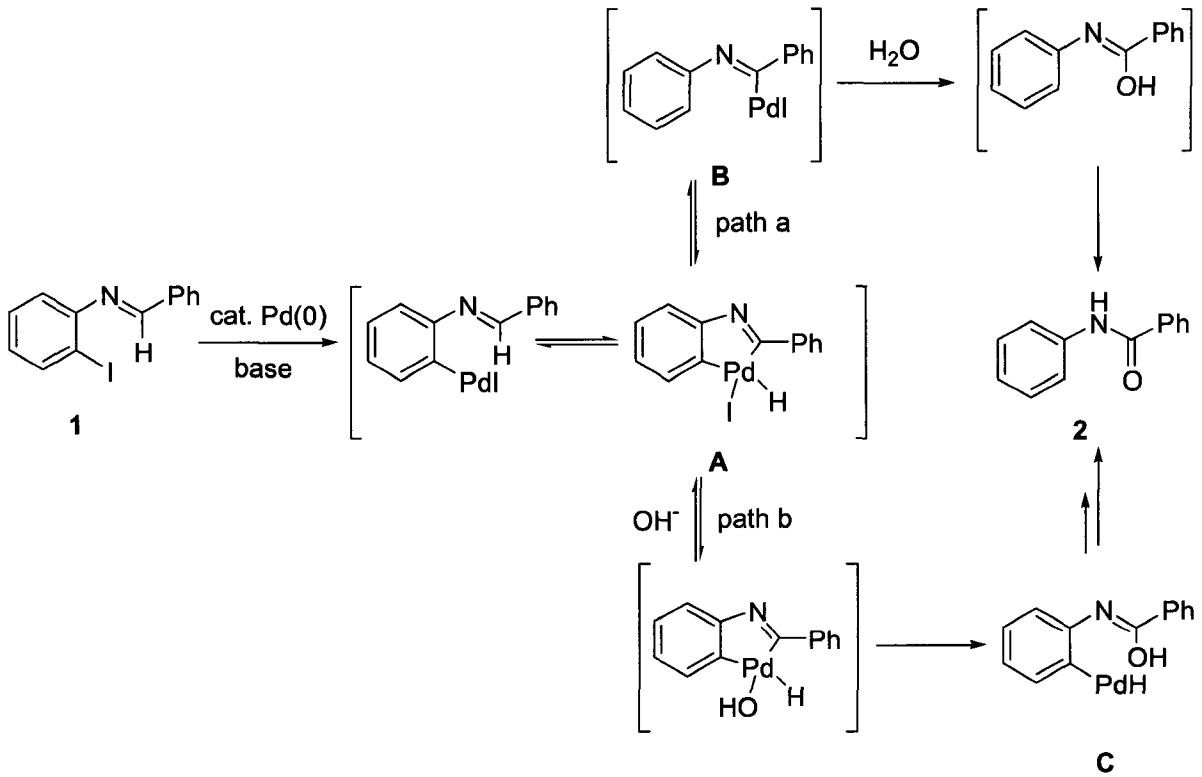
During our studies of other possible palladium migrations, we found that the reaction of imine **1** under our usual palladium migration conditions in the presence of 10 equiv of water produced benzanilide **2** in a 56% yield (eq 2).[15] The formation of this amide



(2)

suggests that a palladium migration from the aryl to the imidoyl[16] position has taken place to generate intermediate **B** via a five-membered ring palladacycle **A** (Scheme 5). This

Scheme 5



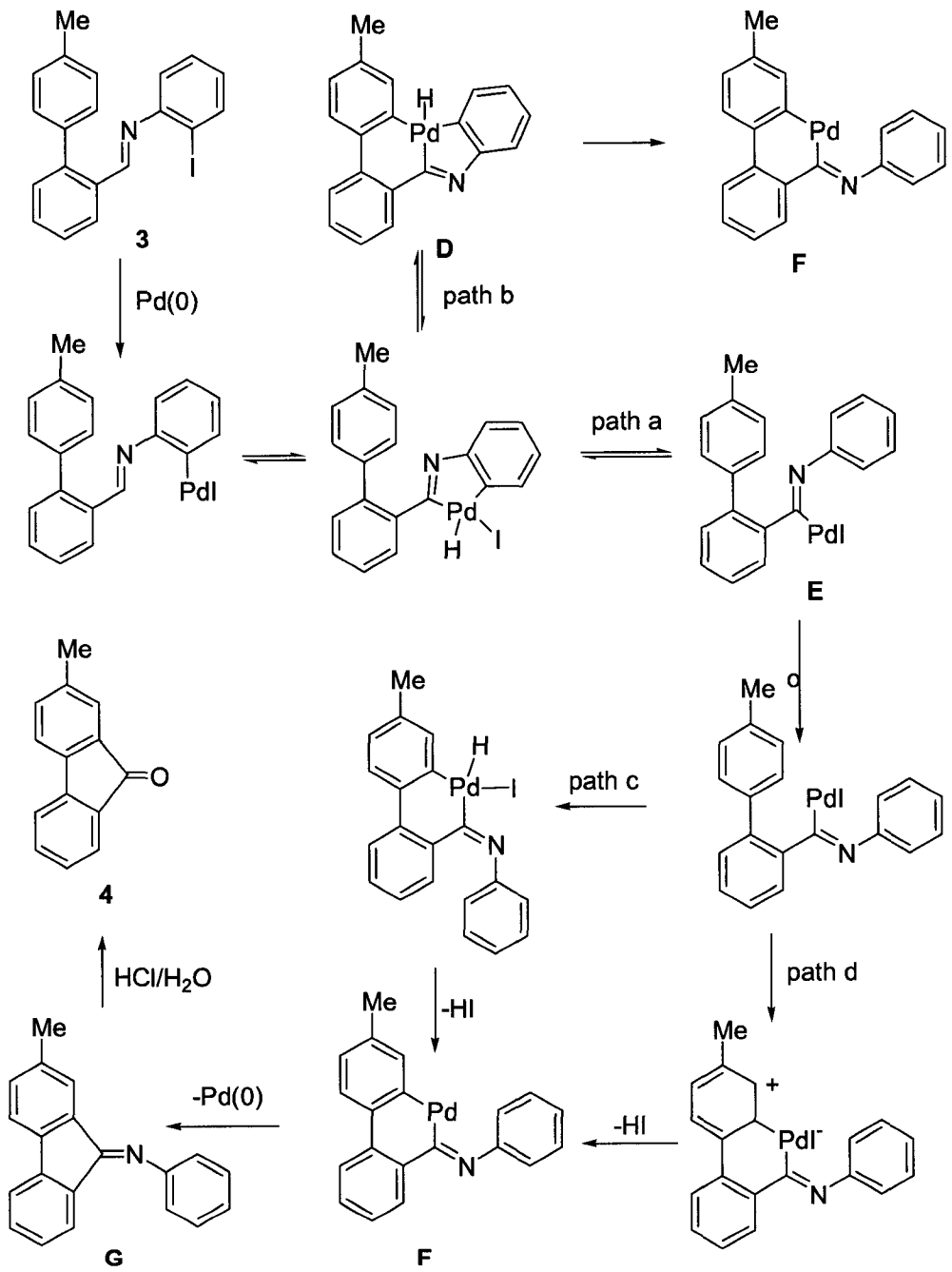
would generate a palladium species which upon hydrolysis and subsequent tautomerization

leads to the benzanilide product (path a). There is, however, another pathway to generate the benzanilide. After the oxidative addition of the Pd(0) to the aryl iodide, the arylpalladium intermediate might insert into the imidoyl-H bond to form a five-membered palladacycle **A**. Without completely migrating to the imidoyl position to form an imidoyl palladium intermediate **B**, the palladium intermediate **A** might undergo ligand exchange and subsequent reductive elimination to produce intermediate **C** (path b). The intermediate **C** then, by further reductive elimination of Pd and tautomerization, might afford benzanilide **2**. The use of a relatively large amount of water and the ease with which imines hydrolyze might account for the fairly low yield of the benzanilide.

To fully understand the mechanism of this unusual palladium migration, we proceeded to investigate a sequential migration/arylation reaction of a more complex imine **3** (Scheme 6). In theory, imine **3** might afford fluoren-9-ylideneaniline if the palladium migrates from an aryl position to an imidoyl position under our Pd migration conditions. Mechanistically, the palladium must first undergo a 1,4-palladium migration from the *ortho* position of the aniline moiety to the imidoyl position (through path a), followed by arylation at the 2' position of the biaryl (Scheme 6; Table 1, entry 1) to generate the desired migration/arylation product. On the other hand, if the palladium intermediate does not undergo a complete through-space 1,4-palladium migration, it would have to undergo a rather unfavorable process (path b) to generate a highly strained complex **D**, which after two reductive eliminations of palladium might afford the final migration product.

Surprisingly, compound **3** readily reacted under our standard reaction conditions at 100 °C and produced a quantitative yield of the desired migration product **G** within 4 h.

Scheme 6

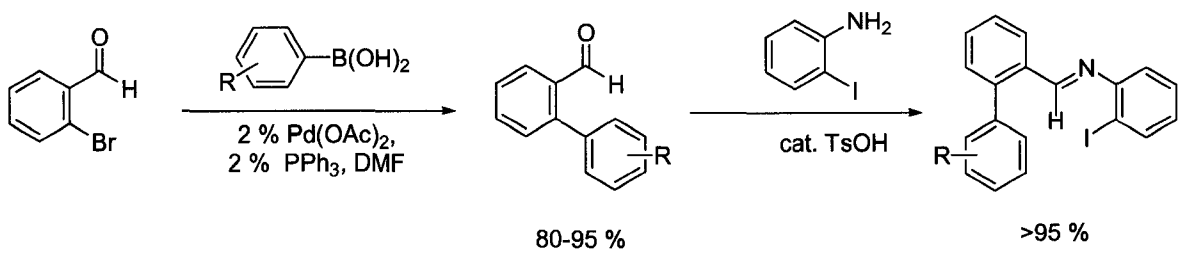


The fairly unstable fluoren-9-ylideneaniline product underwent hydrolysis very easily, affording the corresponding methyl substituted fluoren-9-one **4** in a quantitative yield. The high yield suggests that the palladium intermediate did in fact migrate from the aryl

position to the imidoyl position by a complete through-space 1,4-shift to generate the imidoyl palladium intermediate **E**. The imidoyl palladium intermediate **E** then undergoes either an insertion into the C-H bond of the neighboring arene (path c) or electrophilic aromatic substitution (path d). After elimination of HI, both pathways give a six-membered ring palladacycle **F**. Subsequent reductive elimination and hydrolysis then gives the observed arylation product **4**.

To further explore the generality of this reaction, several biarylcarboxaldehydes were synthesized by simple Suzuki couplings using 2-bromobenzaldehyde and various arylboronic acids. The resulting 2-arylbenzaldehydes were then allowed to react with commercially available *o*-iodoaniline to afford almost quantitative yields of the corresponding imines (Scheme 7). The mild reaction conditions used to prepare these imines should readily accommodate considerable functionality.

Scheme 7



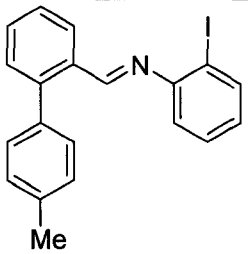
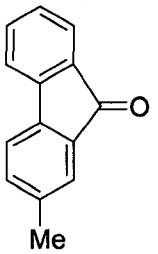
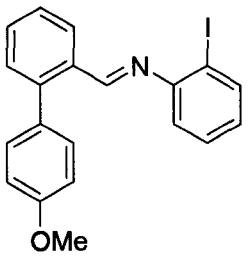
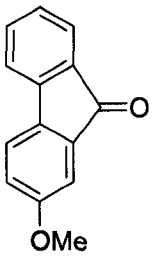
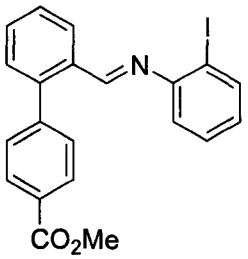
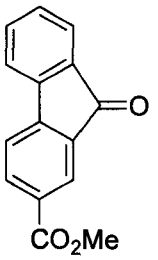
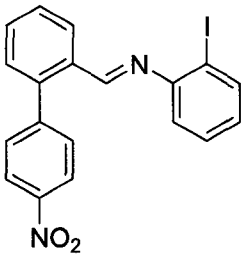
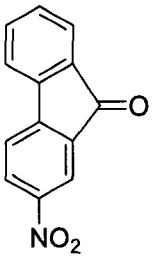
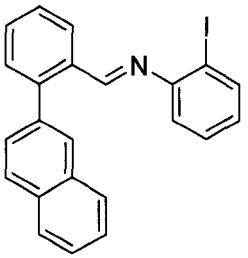
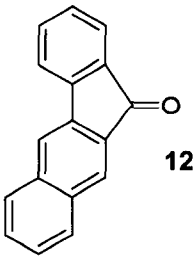
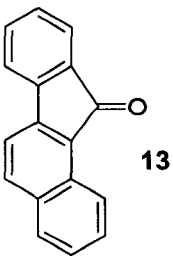
The palladium-catalyzed rearrangement of these imines bearing various functional groups has been investigated under our standard Pd migration reaction conditions. Electron-donating groups, such as methyl and methoxy groups on the biaryl substrates facilitate the arylation step and therefore shorten the reaction time to around 2 to 6 h (Table 1; entries 1, 2, and 6). Although the electron-withdrawing groups, such as a nitro and an

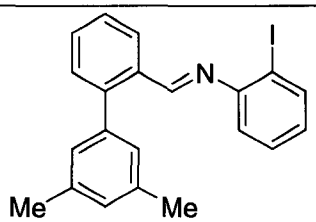
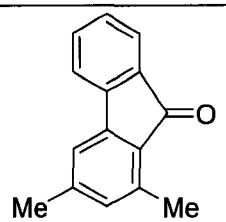
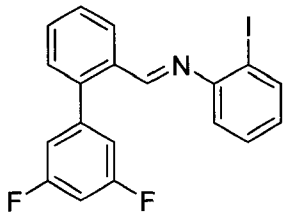
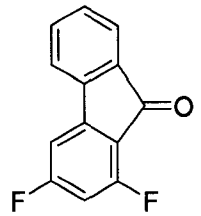
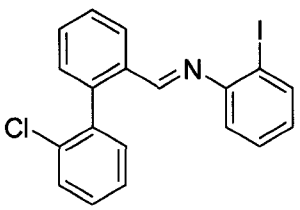
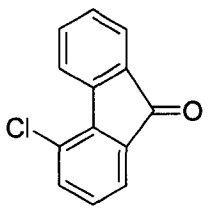
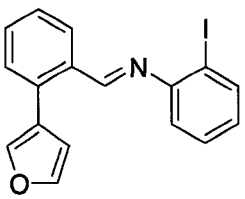
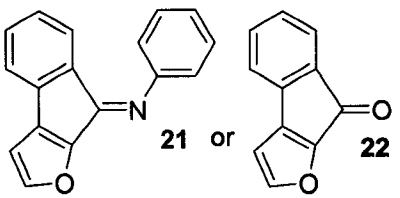
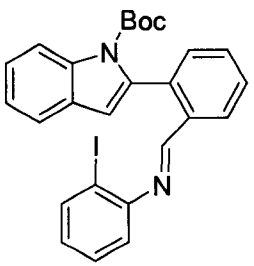
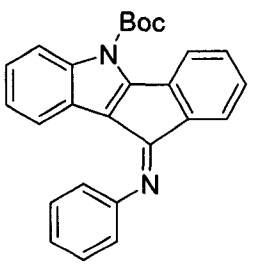
ester group, make the aromatic ring electron deficient, and therefore make the electrophilic aromatic substitution more difficult, they did not affect the overall yields and we were still able to obtain high yields of the desired arylation products (entries 3, 4 and 7). The electron-withdrawing group did, however, affect the reaction time. Substantially longer reaction times were generally required to get complete conversion of these starting materials. In most cases, the yields of the fluoren-9-ones are above 90 %.

Biaryl systems bearing two methyl or two fluoro groups were also investigated. The methyl and fluoro group were presumed to introduce steric hindrance in the final arylation step. A longer reaction time was observed and a slightly lower yield was obtained when the dimethyl substrate was employed (entry 6). The compound with two fluoro groups *meta* to the other aryl group reacted very slowly under our standard reaction conditions and the reaction time was four times as long as that of the dimethyl substrate (entry 7). Both steric and electronic effects appear to account for the difference. Nevertheless, the difluoro product was still obtained in a 95 % isolated yield.

Cyclization of the biphenyl **18** with a chloro group *ortho* to the phenyl was also studied. Theoretically, the interaction of the chloro group in the 2 position and the H in the 2' position favors an arrangement of the two benzene rings perpendicular to each other and therefore disfavors the arylation step, which requires the two benzene rings to lie in the same plane (Figure 1). Statistically, the chloro group also occupies one of the two *ortho* positions that might normally undergo intramolecular arylation. It was not surprising, therefore, that the reaction was not clean and only a 65 % yield of the desired fluoren-9-one product was obtained after 48 h of reaction.

Table 2. Synthesis of fluorenones via 1,4-palladium migration and consequent arylation.[a]

entry	imine		reaction time (h)	product		% yield
1		**3**	4		**4**	100
2		**5**	2		**6**	100
3		**7**	12		**8**	100
4		**9**	12		**10**	100
5		**11**	4	 **12** + 	**13**	91[b] (9:1)

6		**14**	6		**15**	92
7		**16**	24		**17**	95
8		**18**	48		**19**	65[c]
9		**20**	2		**21** or **22**	82 or 50[d]
10		**23**	48		**24**	-

[a]The reaction was carried out under the previously described standard reaction conditions employing 0.25 mmol of the imine, 5 mol % $Pd(OAc)_2$, 5 mol % $(Ph_2P)_2CH_2$ and 2 equivs of CsO_2CCMe_3 in DMF (4 mL) at 100 °C unless otherwise noted. [b]The ratio in parentheses corresponds to the GC yield of products in which the sterically less hindered product was formed predominantly. [c]The reaction temperature was increased to 110 °C. [d]Compound **22** is not stable under our usual hydrolysis conditions; only a 50 % yield of the corresponding ketone product was obtained. In a different run, without the hydrolysis step, the imine intermediate **21** was isolated in an 82% yield.

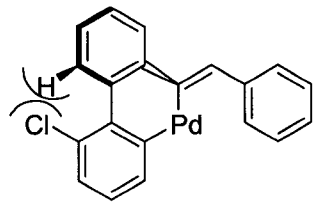


Figure 1. The interaction of H and Cl disfavors the planar transition state

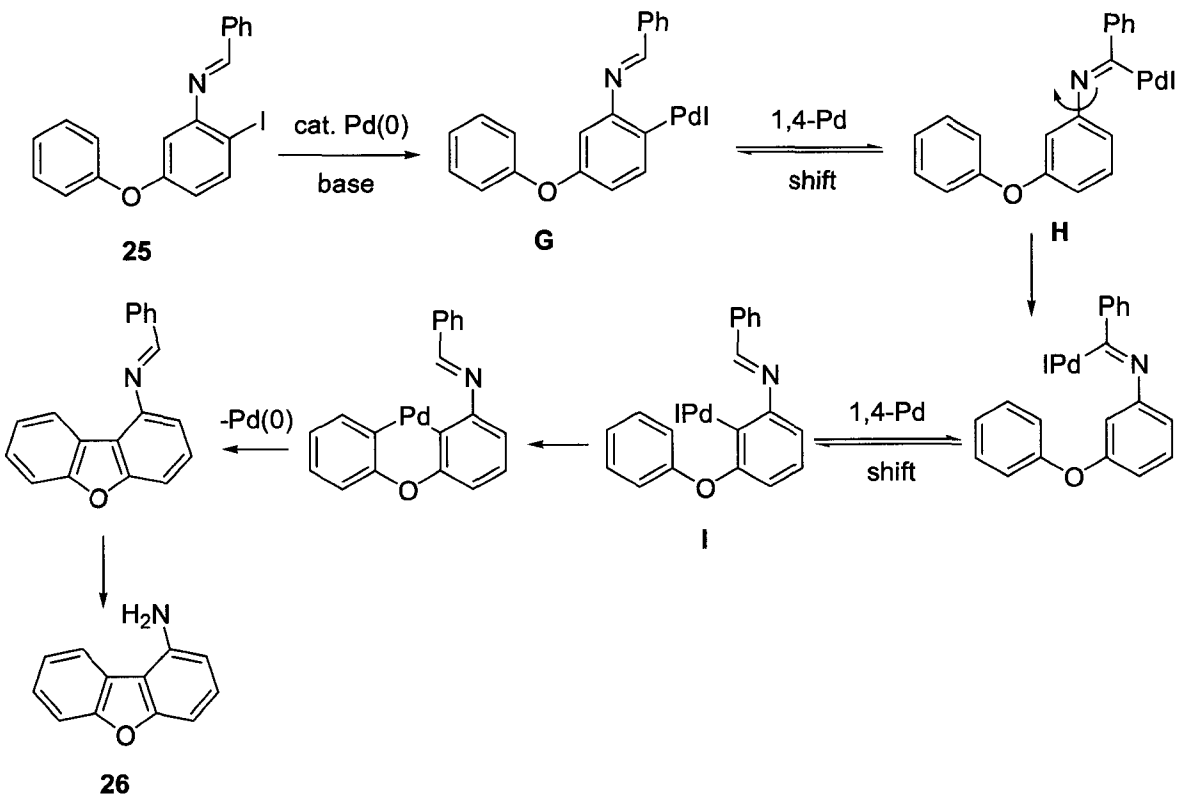
Biaryl substrates bearing a naphthalene, a furan and an indole moiety have also been studied. When the naphthalene substrate was allowed to react under our usual reaction conditions, arylation took place in both the 3 and 1 positions, with the arylation product in the less hindered 3 position predominant (9:1) (entry 5). This is consistent with Campo's result using the palladium-catalyzed cyclocarbonylation of halobiaryls.[14] A 91 % overall yield was obtained.

The furan-containing substrate facilitates electrophilic aromatic substitution and within 2 h the reaction was complete. However, because the resulting 8*H*-indeno[2,1*b*]furan-6-one was not stable under our hydrolysis conditions, we were able to isolate only a 50% yield of the 8*H*-indeno[2,1*b*]furan-6-one (entry 9). Without hydrolysis, the corresponding 8*H*-indeno[2,1*b*]furan-8-ylidene-*N*-phenylamine was obtained in an 82% yield. An indole-containing substrate was also allowed to react under our standard reaction conditions, but none of the desired product was obtained (entry 10). The strain resulting from the fused ring system bearing two adjoining five-membered rings may account for this unfavorable result.

A mechanistically interesting question is whether the imidoyl palladium intermediate can migrate to a second aryl position. In order to explore this possibility, 2-iodo-5-phenoxy-*N*-phenylmethyleneaniline (**25**) was prepared and allowed to react under our

standard Pd migration conditions at 100 °C. After 24 h, this substrate failed to react. By simply increasing the reaction temperature to 120 °C, we were able to obtain the desired 1-aminodibenzo[*b,d*]furan (**26**) in a 35 % yield, although it took 7 d for the reaction to reach completion. The relatively sterically hindered position *ortho* to the phenoxy group apparently hinders Pd migration from the imidoyl position to the more hindered aryl position, thus lengthening the reaction time and lowering the overall yield of this double migration reaction.

Scheme 8



Mechanistically, the palladium apparently first inserts into the aryl iodide bond to form intermediate **G**, which migrates Pd to the imidoyl position by through-space C-H activation. The metal moiety in this first migration intermediate **H** can return to the

original aromatic ring in either the position where it was first generated or the position *ortho* to the phenoxy group to produce intermediate **I**, where it can be trapped by arylation of the other aromatic ring. Simple hydrolysis of the imine affords the corresponding benzaldehyde and the aminodibenzo[*b,d*]furan (**26**) (Scheme 8).

Conclusions

In conclusion, we have been able to establish a novel 1,4-palladium shift from an aryl position to an imidoyl position. This migration of palladium has been established by trapping the imidoylpalladium intermediates by intramolecular arylation. This migration process can be very general and synthetically useful. The biologically interesting fluoren-9-one ring system can be readily synthesized in excellent yields utilizing this novel migration process.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using 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 [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of DME, THF, DMF, diethyl ether, ethyl acetate and hexanes were purchased from Fisher Scientific Co. The arylboronic acids were obtained from Frontier Scientific Co. 2-Iodoaniline, 2-bromobenzaldehyde, Cs_2CO_3, pivalic acid and Et_3N were obtained from Aldrich Chemical Co., Inc.

General procedure for synthesis of the biarylcarboxaldehydes. Into 10 mL of a 2:1 DMF/H_2O solution containing 5.0 mmol of 2-bromobenzaldehyde, 5.0 mmol of Na_2CO_3 and 5.0 mmol of arylboronic acid were added 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 °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'-Methylbiphenyl-2-carboxaldehyde.[17] The compound was obtained as a colorless oil: ^{1}H 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. The compound was obtained as a colorless oil: ^{1}H 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. The compound was obtained as a colorless oil: ^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. The compound was obtained as a colorless oil: ^1H 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).

3',5'-Dimethylbiphenyl-2-carboxaldehyde. The compound was obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.34 (s, 6H), 6.95 (s, 2H), 7.03 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3,127.3, 127.5, 128.1, 129.7, 130.7, 133.4, 133.8, 137.6, 138.0, 146.3, 192.5; HRMS *m/z* 210.1047 (calcd for $C_{15}H_{14}O$, 210.1045).

3',5'-Difluorobiphenyl-2-carboxaldehyde. The compound was obtained as a colorless oil: ^1H 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).

2'-Chlorobiphenyl-2-carboxaldehyde. The compound was obtained as a colorless oil: ^{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).

2-(Furan-3-yl)benzaldehyde. The compound was obtained as a colorless oil: ^{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).

***N-tert*-Butoxycarbonyl-2-(2'-formylphenyl)indole**. The compound was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9H), 6.58 (s, 1H), 7.27 (t, J = 7.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.52-7.61 (m, 3H), 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 8.30 (dd, J = 8.4, 0.8 Hz, 1H), 10.00 (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* 321.1369 (calcd for $C_{20}H_{19}NO_3$, 321.1365).

General procedure for the synthesis of 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 °C until TLC analysis indicates the disappearance of the starting material. 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.

2-Iodo-*N*-(4'-methoxybiphenyl-2-ylmethylene)aniline. The compound was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 6.78 (d, J = 6.8 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.17-7.33 (m, 4H), 7.42 (t, J = 7.2 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 8.28 (s, 1H), 8.42 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.3, 95.0, 113.8, 118.4, 126.9, 127.5, 128.0, 129.3, 130.3, 131.1, 131.2, 131.4, 133.2, 138.9, 143.7, 153.2, 159.3, 160.5; HRMS *m/z* 413.0281 (calcd for $C_{20}H_{16}INO$, 413.0277).

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 °C 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 fluoren-9-one 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. 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-ones, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-Methylfluoren-9-one (4). The reaction mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 47.1 mg (97 %) of the indicated compound as a yellow solid: mp 90-91 °C (lit.[18] mp 92 °C); ^{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 spectral properties were identical to those previously reported.[1]

2-Methoxyfluoren-9-one (6). The reaction mixture was chromatographed using 6:1 hexanes/ethyl acetate to afford 52.6 mg (100 %) of the indicated compound as a yellow solid: mp 78-79 °C (lit.[1] mp 78 °C); ^{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}. The spectral properties were identical to those previously reported.[19]

Methyl fluorenone-2-carboxylate (8).[20] The compound was obtained as a yellow oil: ^{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; HRMS *m/z* 238.0634 (calcd for $C_{15}H_{10}O_3$, 238.0630).

2-Nitrofluoren-9-one (10).[21] The compound was obtained as a yellow solid: mp 221-223 ^{0}C, lit mp 222-224 ^{0}C; ^{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; HRMS *m/z* 225.0429 (calcd for $C_{13}H_7NO_3$, 225.0426).

Benzo[*b*]fluoren-11-one (12). The compound was obtained as a yellow oil: ^{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; HRMS *m/z* 230.0734 (calcd for $C_{17}H_{10}O$, 230.0732).

Benzo[*a*]fluoren-11-one (13). The compound was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) 7.24-7.27 (m, 1H), 7.40-7.44 (m, 3H), 7.56-7.60 (m, 3H), 7.75 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 8.93 (dd, J = 8.4, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) 118.2, 120.1, 124.0, 124.5, 126.6, 127.0, 128.7, 129.4, 129.6, 130.3, 134.3, 134.6, 134.8, 136.0, 144.0, 146.3, 195.5; HRMS *m/z* 230.0736 (calcd for $C_{17}H_{10}O$, 230.0732).

1,3-Dimethylfluoren-9-one (15). The compound was obtained as a yellow oil. The spectral properties were identical to those previously reported.[22]

***N*-(1,3-Dimethyl-9*H*-fluoren-9-ylidene)aniline.** The compound was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.69 (s, 3H), 6.46 (d, J = 7.6 Hz, 1H), 6.86

(td, J = 7.6, 1.2 Hz, 1H), 6.93-6.95 (m, 3H), 7.15 (t, J = 7.2 Hz, 1H), 7.23-7.28 (m, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.53 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.8, 21.9, 118.1, 118.3, 119.9, 123.6, 127.1, 127.5, 129.4, 131.3, 131.4, 131.9, 132.5, 138.3, 141.5, 142.8, 143.5, 152.5, 164.2; HRMS *m/z* 283.1365 (calcd for $C_{21}H_{17}N$, 283.1361).

1,3-Difluorofluoren-9-one (17).[23] The compound was obtained as a yellow oil: ^{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).

***N*-(1,3-Difluoro-9*H*-fluoren-9-ylidene)aniline**. The compound was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.51 (d, J = 8.0 Hz, 1H), 6.77 (dd, J = 7.6, 2.0 Hz, 1H), 6.97-7.05 (m, 3H), 7.13 (dd, J = 7.6, 2.0 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.33 (td, J = 7.6, 0.8 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 103.9 (d), 104.7 (t), 118.2, 119.5 (m), 120.9, 124.4, 127.5, 128.5, 129.2, 129.5, 131.7, 131.9, 141.8, 146.1 (m), 151.7, 158.8 (d), 160.5 (d), 161.4 (d), 164.6 (d), 167.1 (d); HRMS *m/z* 291.0864 (calcd for $C_{19}H_{11}F_2N$, 291.0860).

4-Chlorofluoren-9-one (19).[24] The compound was obtained as a yellow oil: ^{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 (21)**. The compound was obtained as a yellow oil: ^{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).

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).

2-Iodo-5-phenoxy-*N*-phenylmethyleneaniline (25). This compound was prepared following the procedure for the preparation of biaryl-2-ylmethyleneanilines. The resulting imine was used for the next step without further characterization.

1-Aminodibenzo[*b,d*]furanamine (26). The compound was obtained as a yellow oil. The spectral properties were identical to those previously reported.[25]

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GENERAL CONCLUSIONS

In this dissertation the scope and limitations of several electrophilic cyclization processes have been presented. In particular, electrophilic cyclization has been used for the synthesis of a variety of heterocycles, including benzo[*b*]furans, isochromenes, dihydroisoquinolines, isobenzofurans and coumestans. An unusual palladium migration has also been explored and applied to the synthesis of fluoren-9-ones.

Chapter 1 describes the synthesis of 2,3-disubstituted benzo[*b*]furans by the palladium-catalyzed coupling and electrophilic cyclization of terminal alkynes. A highly chemoselective electrophilic cyclization has been achieved by carefully choosing the protecting group on the oxygen functionality. Various electrophiles, such as I_2, Br_2, PhSeCl and *p*-$O_2NC_6H_4SCl$, can be used to introduce different functionalities into the desired cyclization products. The success of this process is dependent upon the substituents on the arenes and the carbon-carbon triple bond. While vinylic- and aryl-substituted acetylenes undergo electrophilic cyclization smoothly, alkyl and trimethylsilyl acetylenes don't react under our standard electrophilic cyclization conditions. Furopyridines can also be synthesized in good yields by our electrophilic cyclization using *o*-methoxyalkynylpyridines.

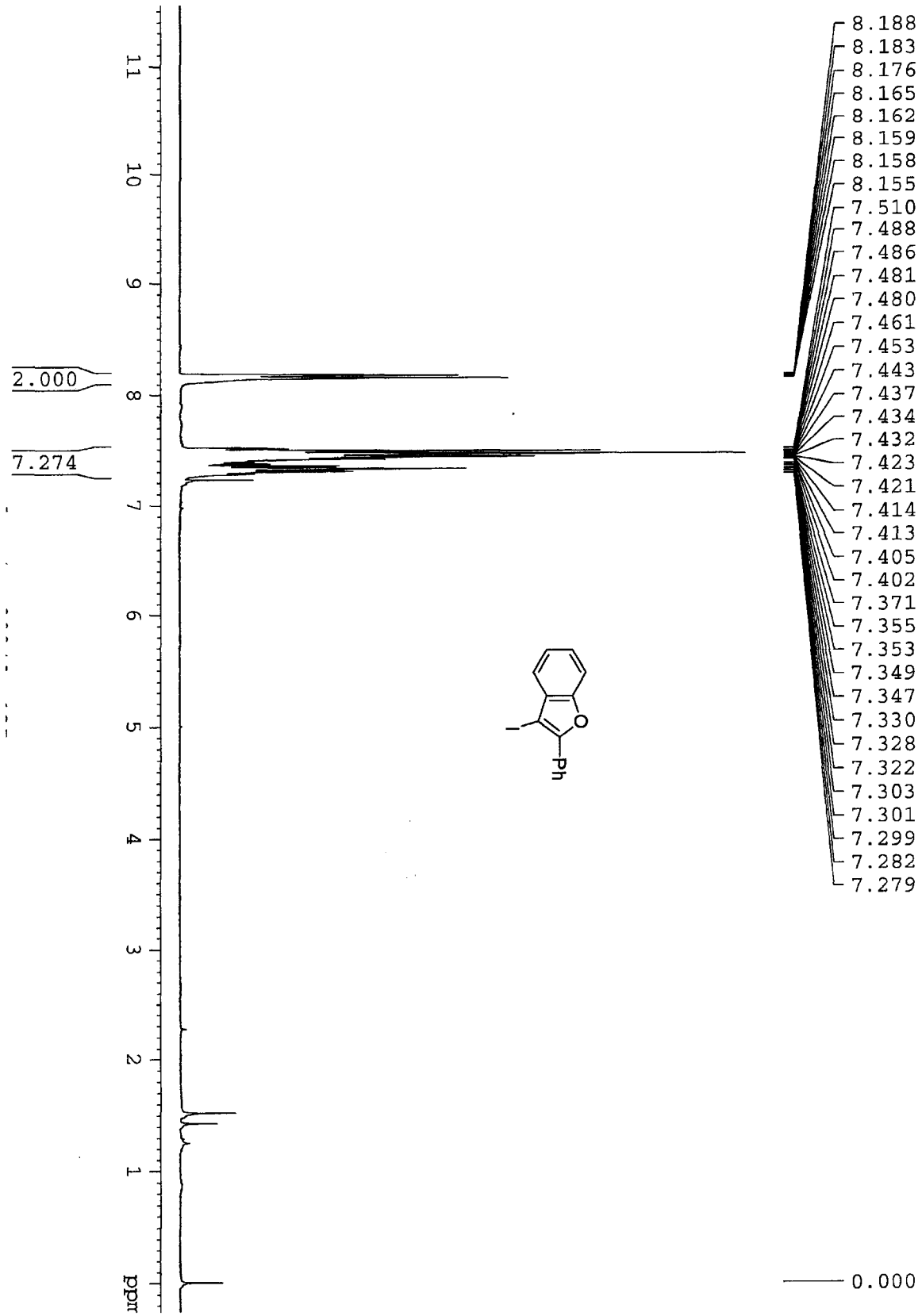
Chapter 2 presents the synthesis of heterocycles by electrophilic cyclization reactions of acetylenic aldehydes, ketones and imines. The overall synthetic process involves the coupling of a terminal acetylene with *o*-iodoarenecarboxaldehydes or ketones by a palladium-catalyzed coupling reaction, followed by electrophilic cyclization with various electrophiles in the presence of proper nucleophiles. Oxygen- and nitrogen-containing

heterocycles can be quickly assembled by this three component process in good to excellent yields. The resulting heterocyclic compounds, however, are generally unstable and hard to purify.

Chapter 3 describes the synthesis of coumestan and coumestrol by selective electrophilic cyclization, followed by palladium-catalyzed intramolecular carbonylation and lactonization. The biologically interesting coumestan system can be quickly constructed by this very efficient approach from common starting materials. The palladium-catalyzed reaction effects as both carbonylation and lactonization in one step. The success of this overall approach relies on the selectivity of our electrophilic cyclization approach to the corresponding benzo[*b*]furans.

Chapter 4 examines the scope and synthetic utility of a 1,4-Pd through space migration. The synthesis of various fluoren-9-ones has been accomplished by the Pd-catalyzed intramolecular C-H activation of imines derived from 2-iodoaniline and biarylcarboxaldehydes. This methodology makes use of a novel 1,4-palladium migration from an aryl position to an imidoyl position to generate the key imidoyl palladium intermediate, which undergoes intramolecular arylation to produce imines of complex polycyclic compounds containing the fluoren-9-one core structure. Both electronic effects and steric effects have been investigated. While steric effects play an important role and longer reaction times and lower yields are observed in more hindered systems, the electronic effects do not lower the overall yields. The imine products can be easily converted to the corresponding fluoren-9-ones upon hydrolysis under very mild reaction conditions.

APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA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8.162
8.159
8.158
8.155
7.510
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7.486
7.481
7.480
7.461
7.453
7.443
7.437
7.434
7.432
7.423
7.421
7.414
7.413
7.405
7.402
7.371
7.355
7.353
7.349
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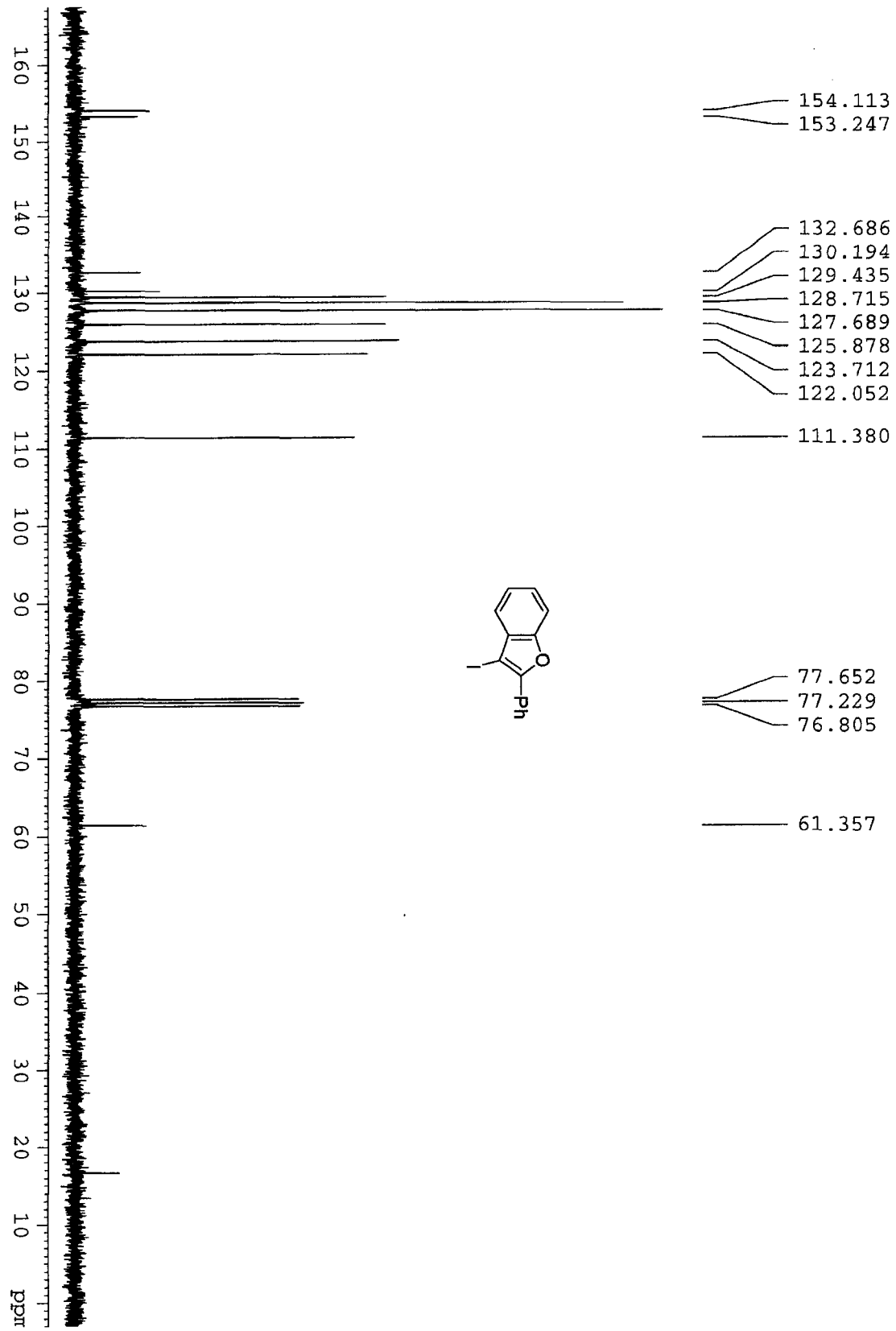
O
Ph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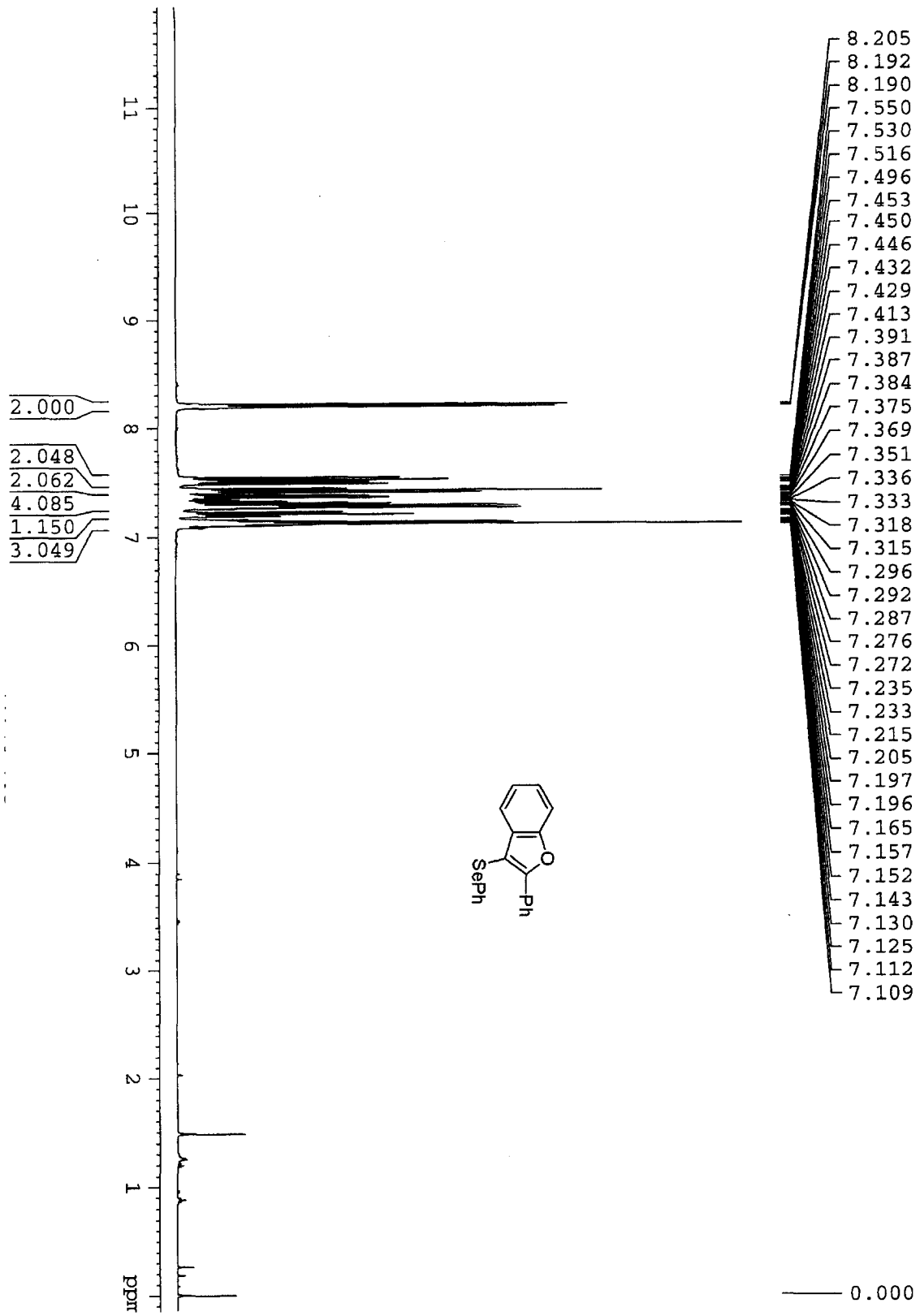
76.805
61.357
Ph
ppm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4
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2
1
0
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Ph
O
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8.190
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7.530
7.516
7.496
7.453
7.450
7.446
7.432
7.429
7.413
7.391
7.387
7.384
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7.351
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7.287
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7.272
7.235
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7.215
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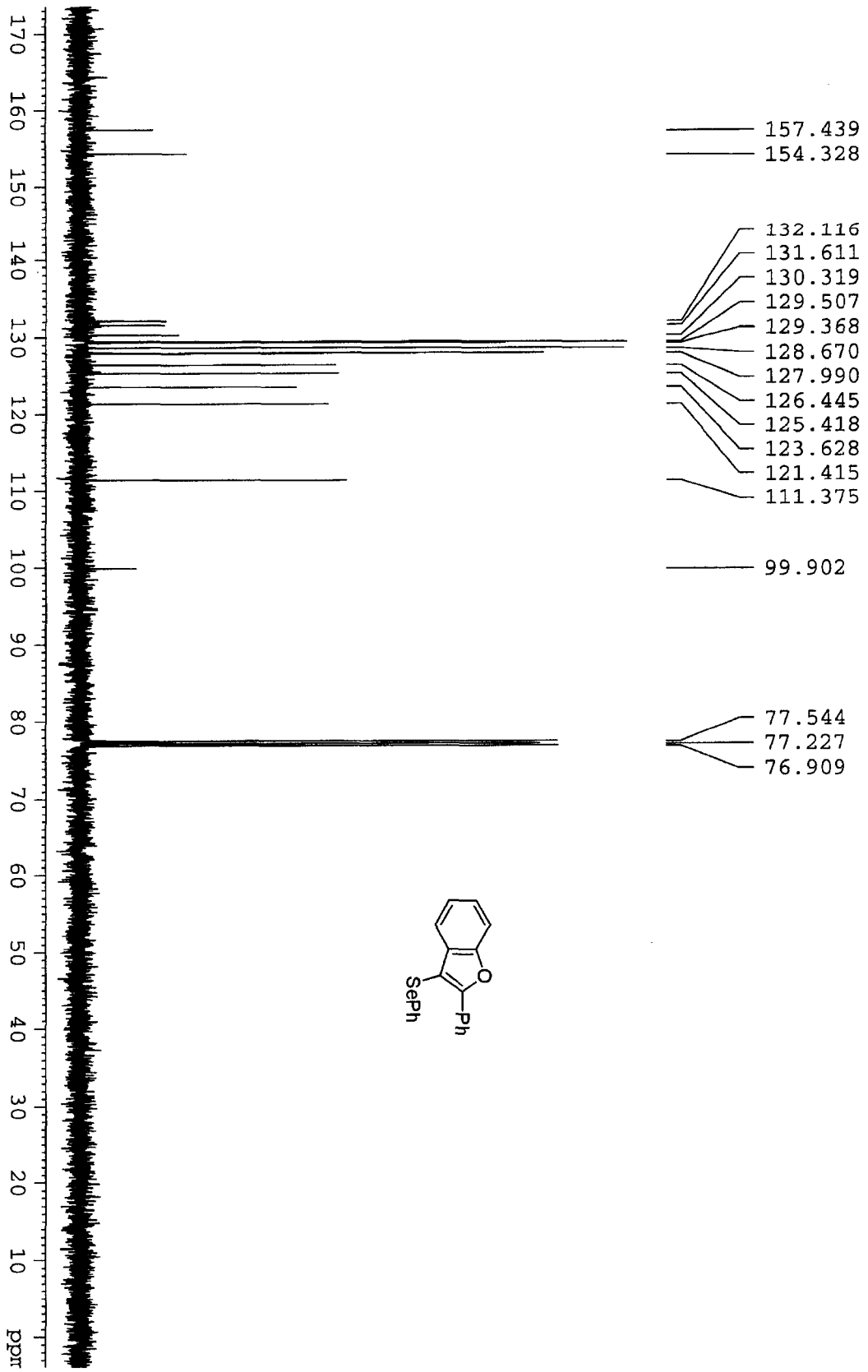
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O
Ph
ppm

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8.012
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7.586
7.457
7.441
7.421
7.415
7.411
7.399
7.391
7.373
7.353
7.270
7.251
7.230
7.208
2.000
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1.017
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3.136
-0.009
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8.5
8.0
7.5
7.0
6.5
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4.0
3.5
3.0
2.5
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1.0
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ppm
O
Ph
SC6H4NO2-p

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127.561
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SC6H4NO2-p
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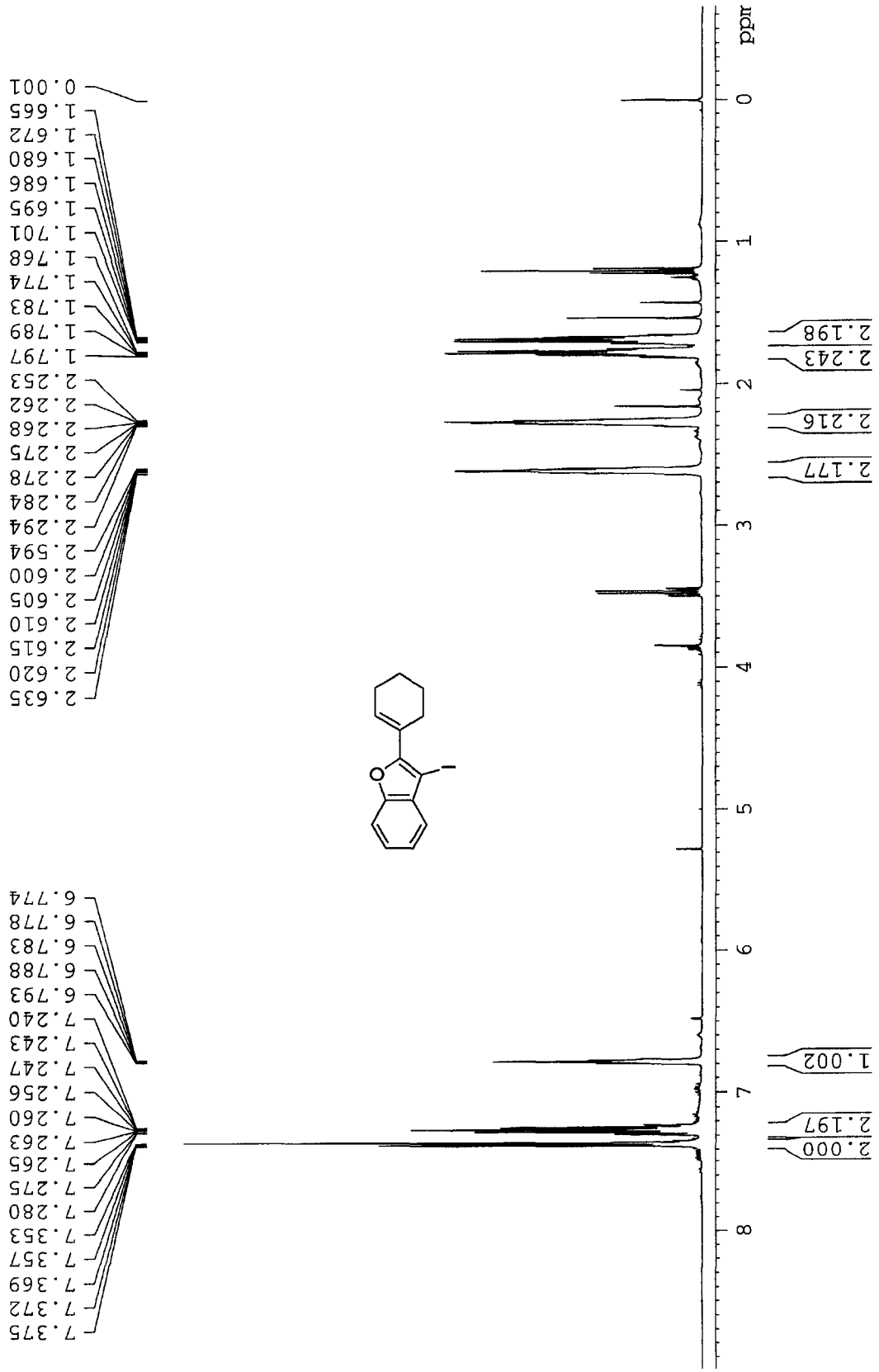
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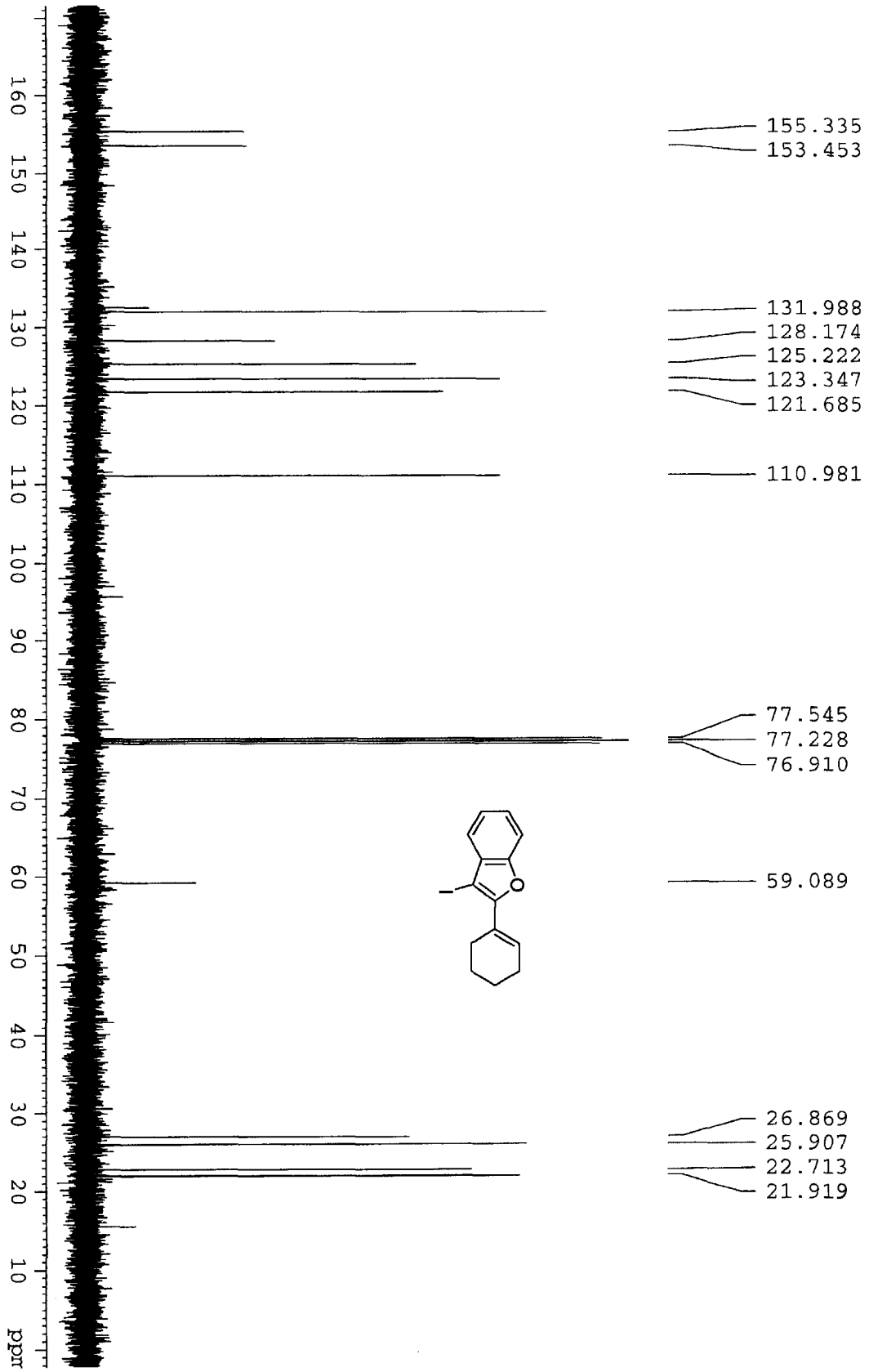
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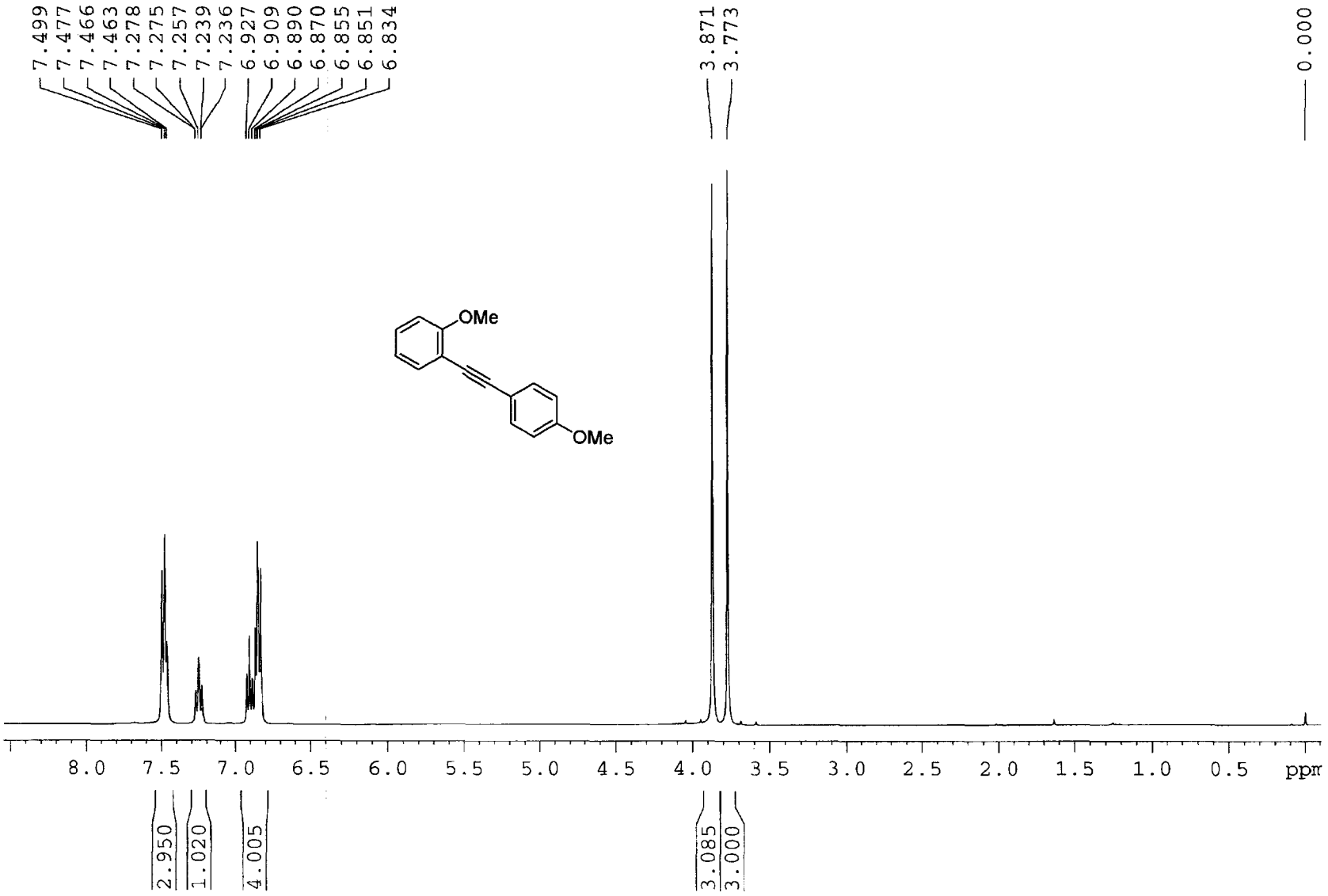
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OMe
OMe
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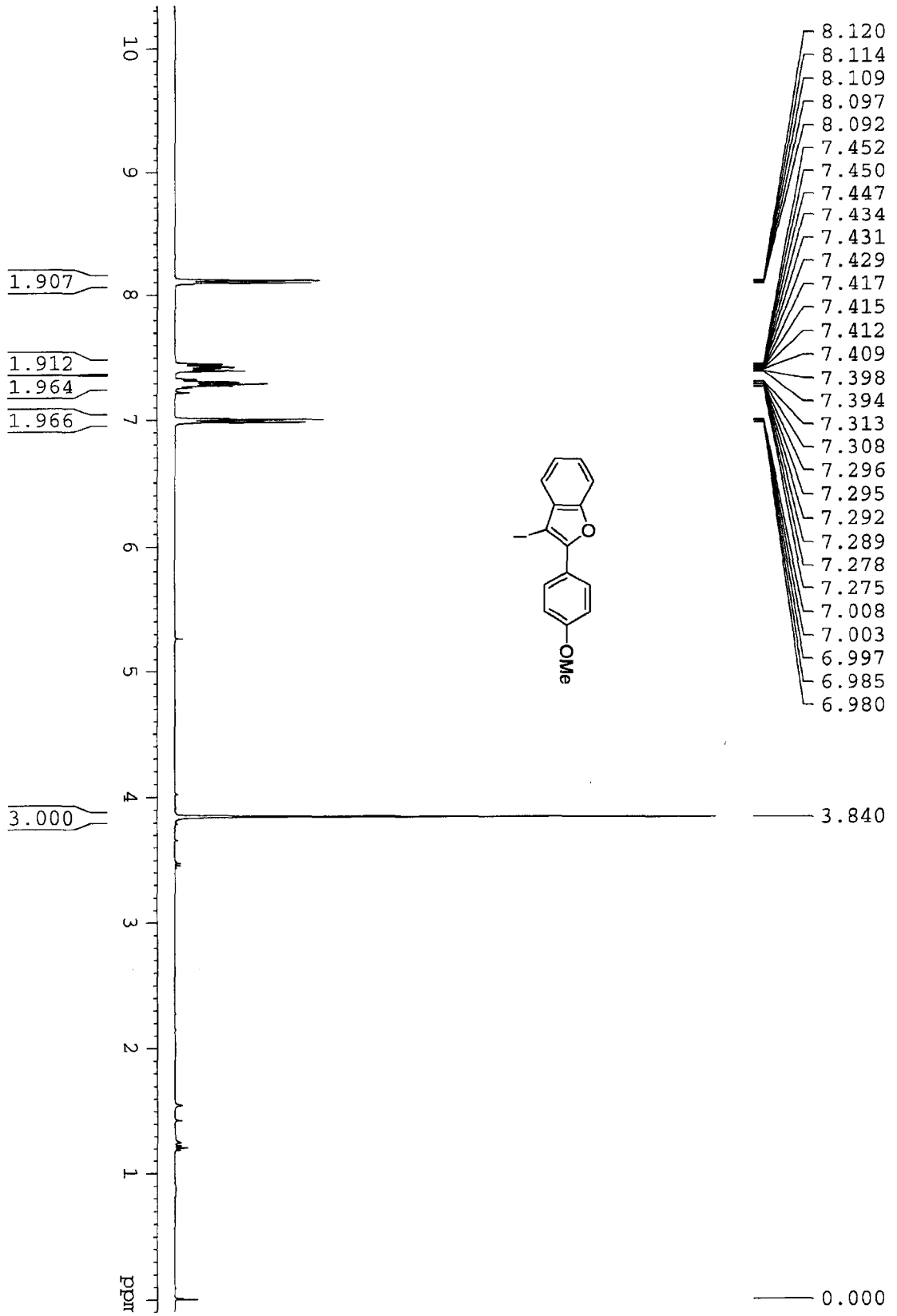
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OMe
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7
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5
4
3
2
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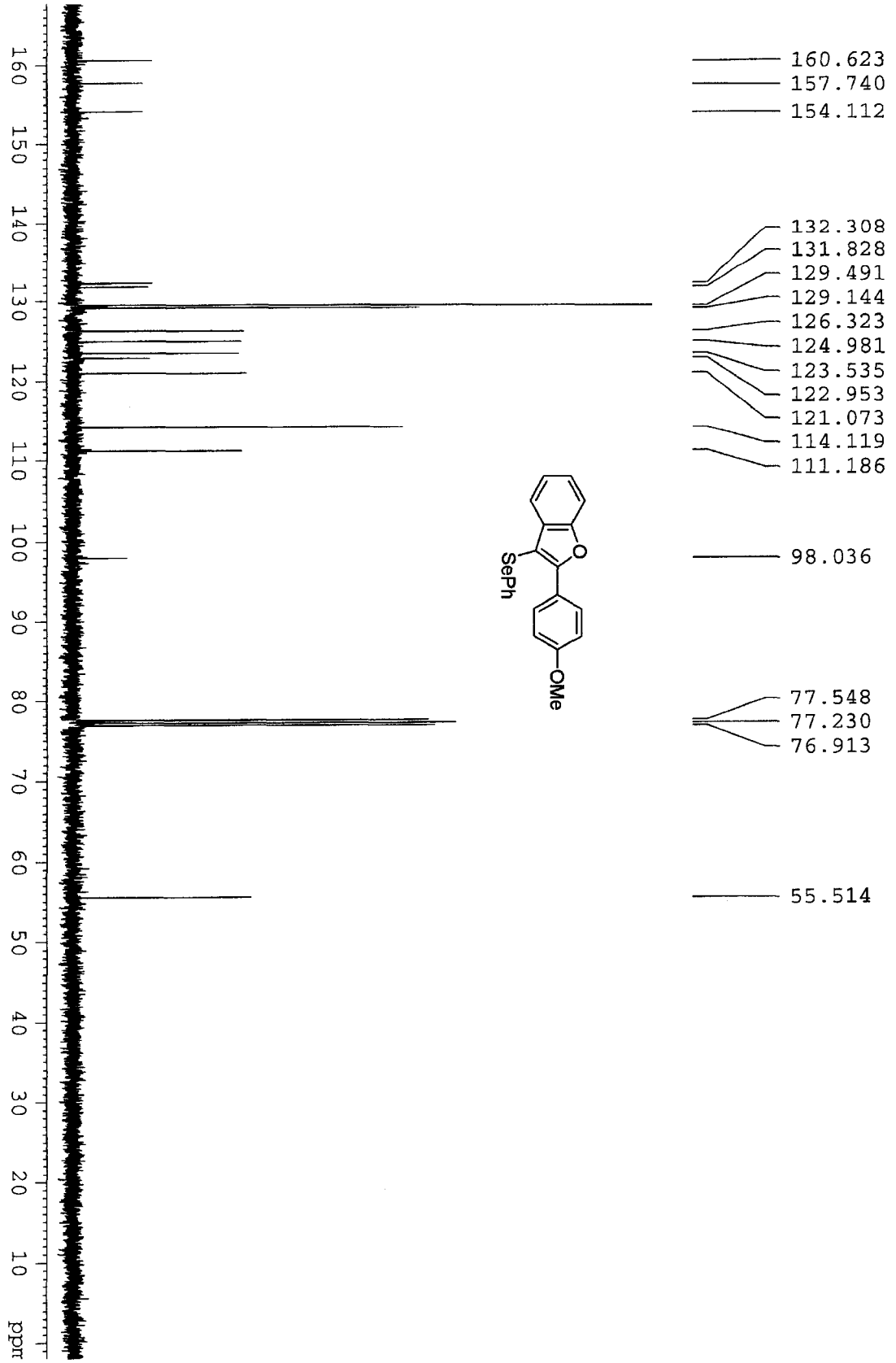
OMe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SePh
OMe
ppm

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0.953
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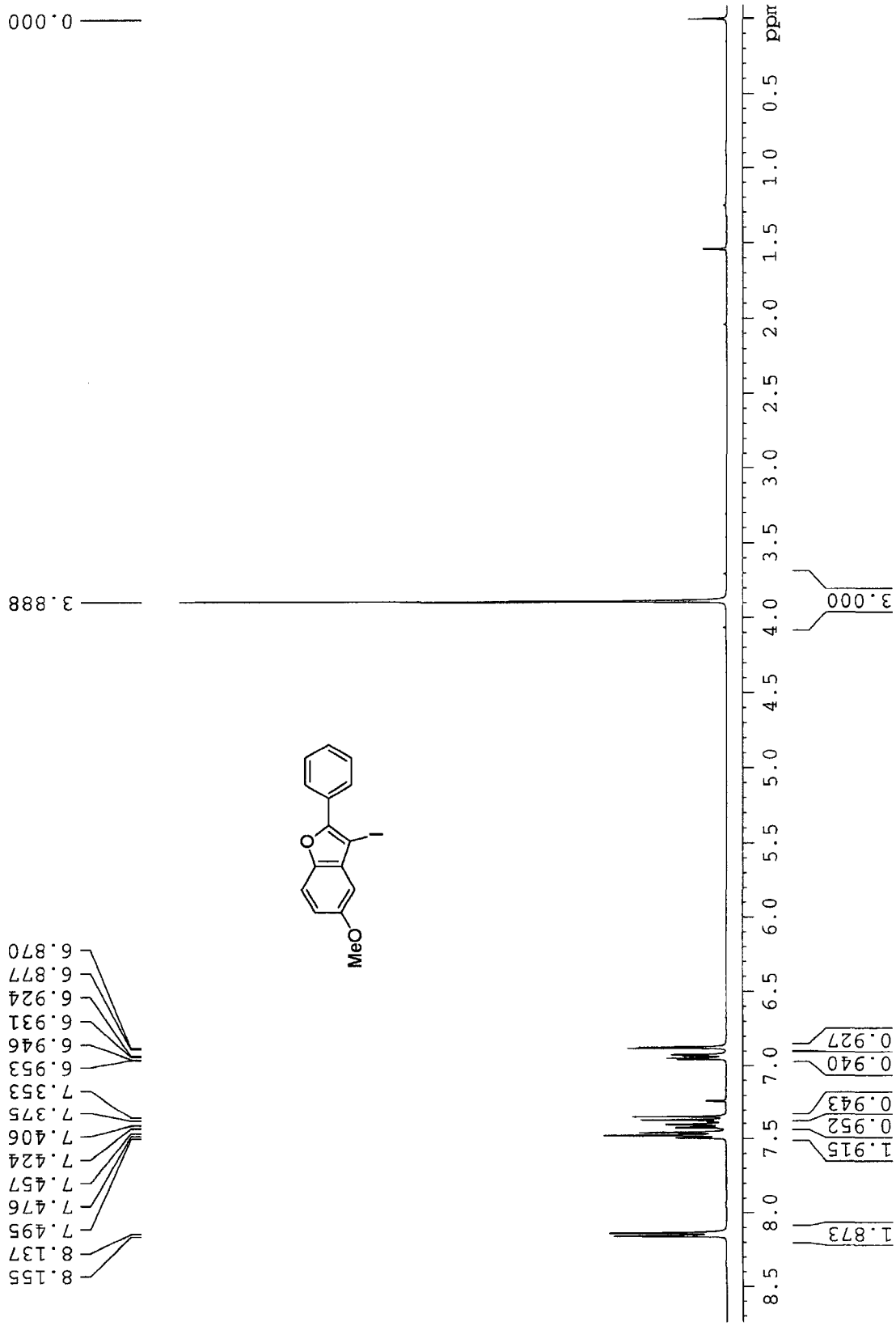
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6.870
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O
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4.0
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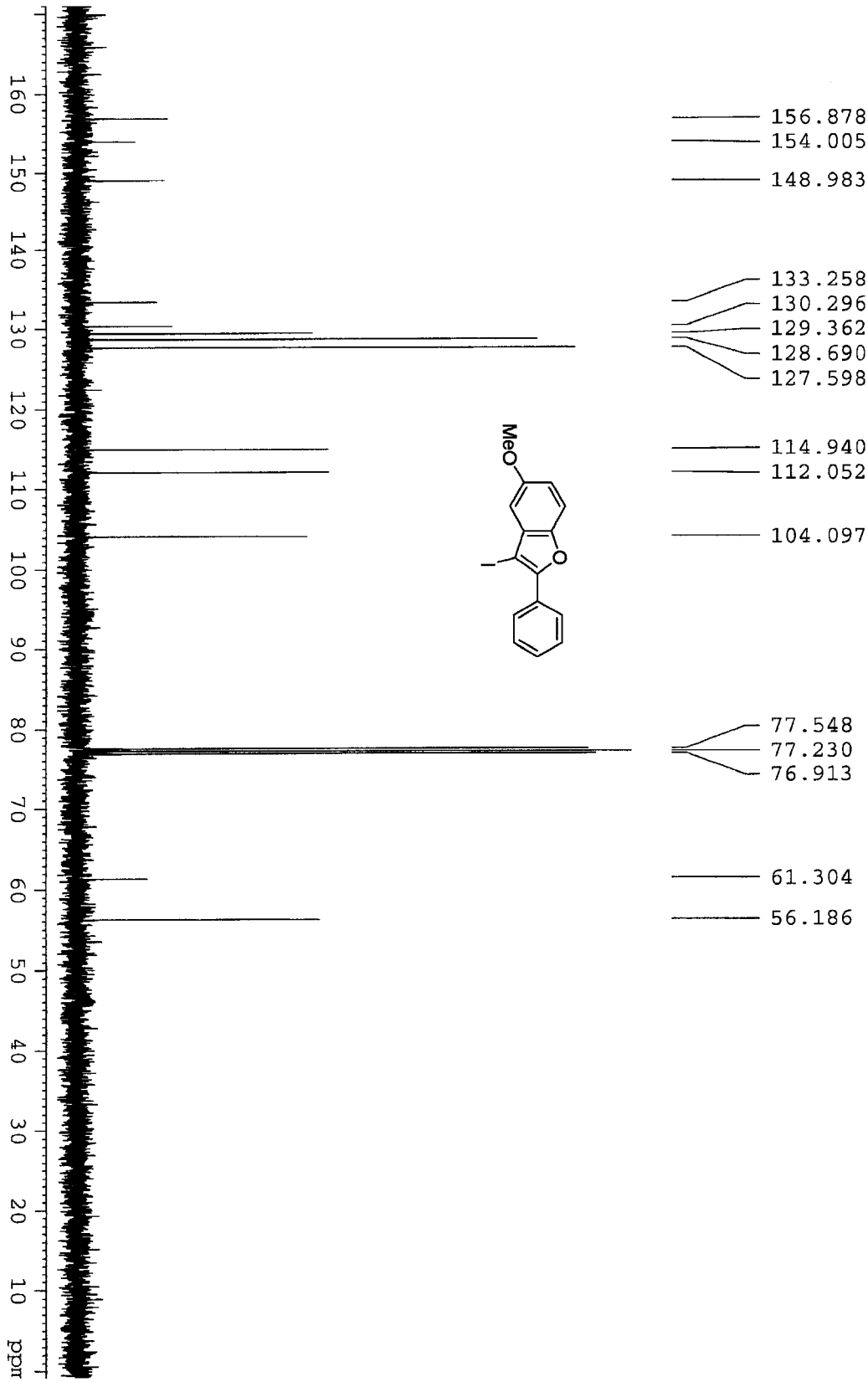
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140
130
120
110
100
90
80
70
60
50
40
30
20
10

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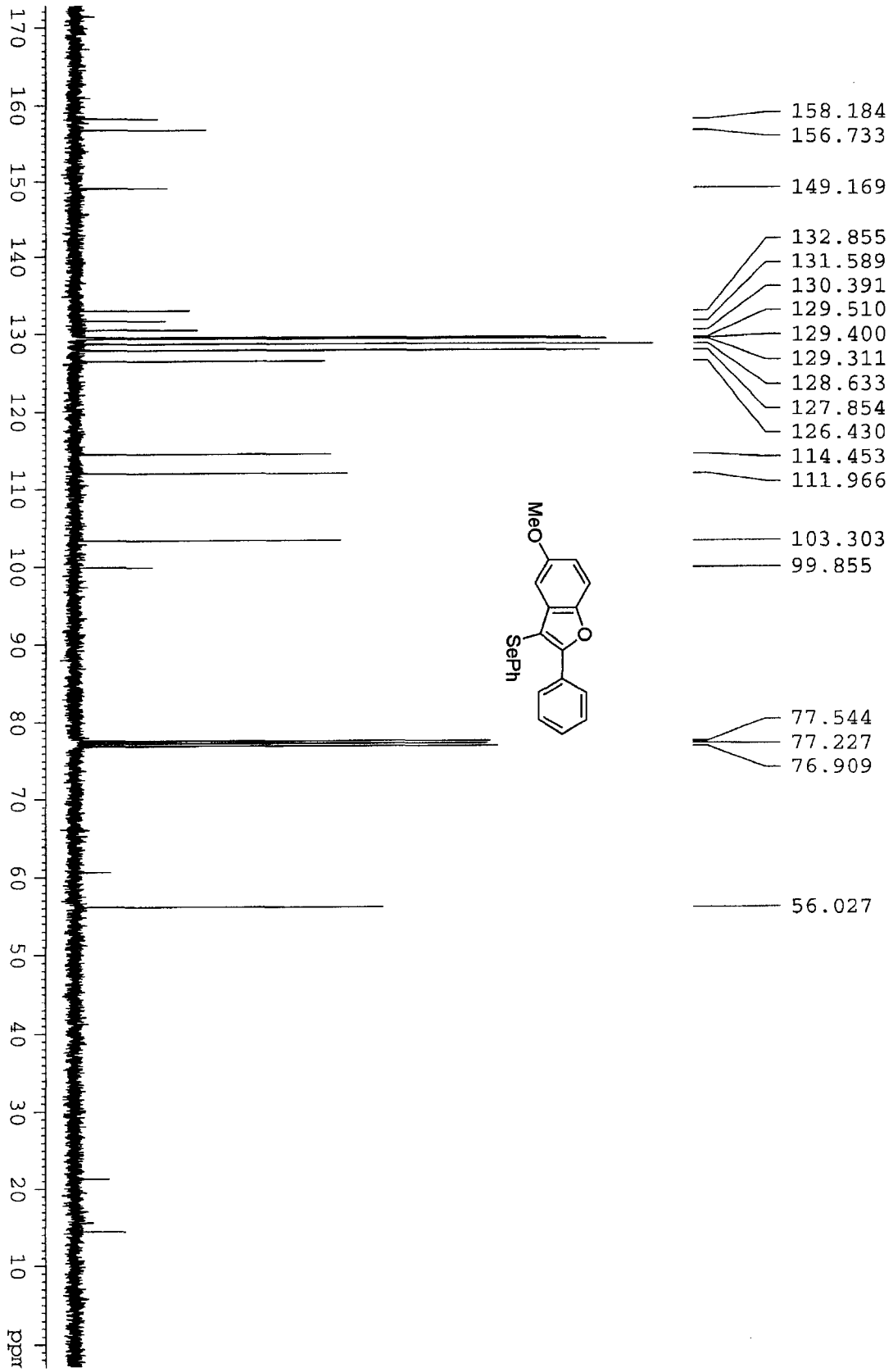
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111.966
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99.855
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76.909
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MeO
SePh
O
ppm

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0.903
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
O2N
OMe
Ph

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129.056
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110.454
95.589
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77.548
77.230
76.912
56.849
O2N
OMe
Ph
ppm

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8.183
8.177
8.161
8.156
8.151
7.582
7.552
7.530
7.528
7.523
7.511
7.504
7.498
0.000
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
O2N
I
O
Ph

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156.486
144.923
133.580
130.427
129.012
128.935
127.822
121.549
118.676
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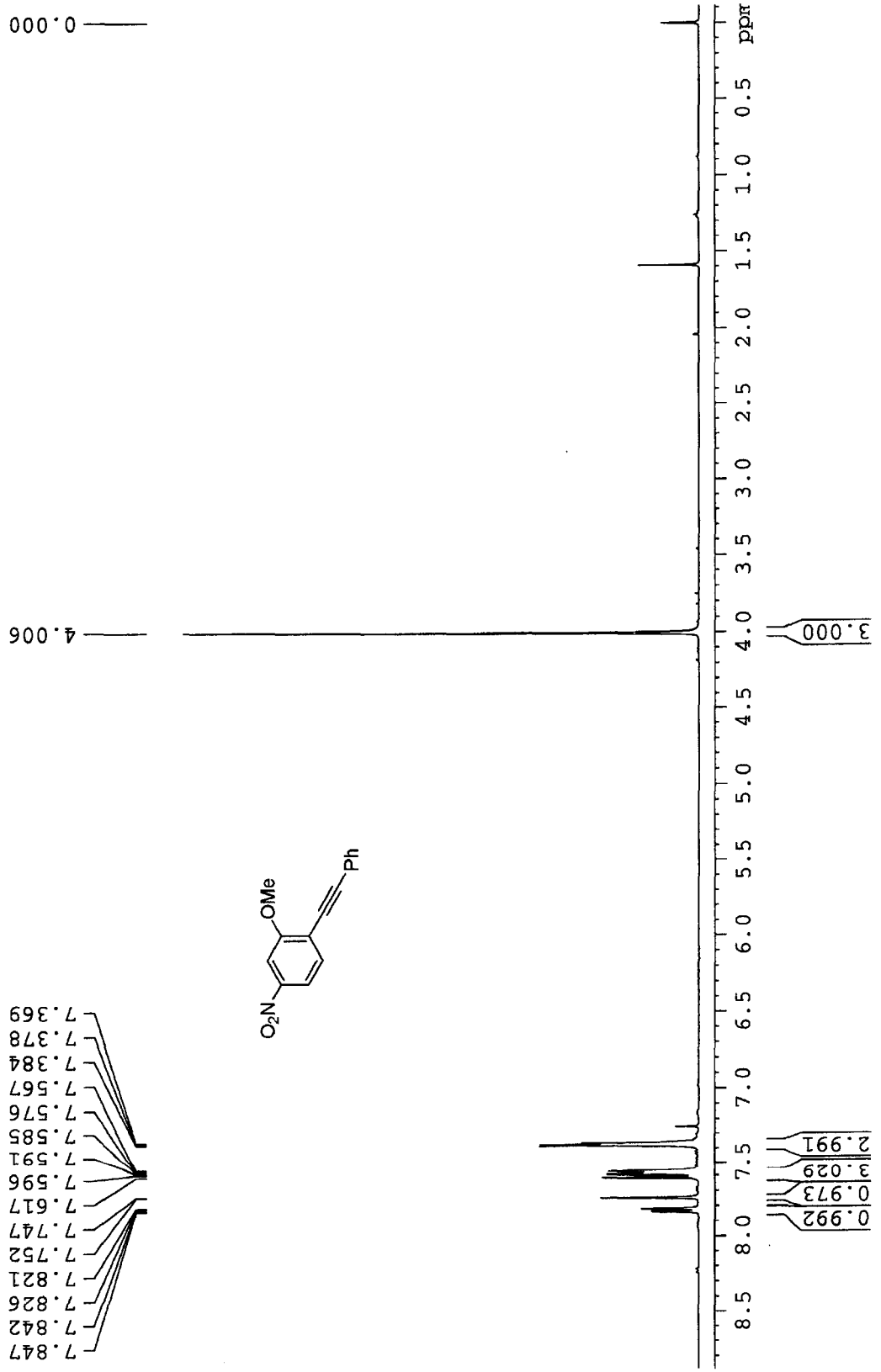
76.804
60.904
O2N
I
O
Ph
ppm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7.826
7.821
7.752
7.747
7.617
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7.591
7.585
7.576
7.567
7.384
7.378
7.369
4.006
0.000
3.000
2.991
3.029
0.973
0.992
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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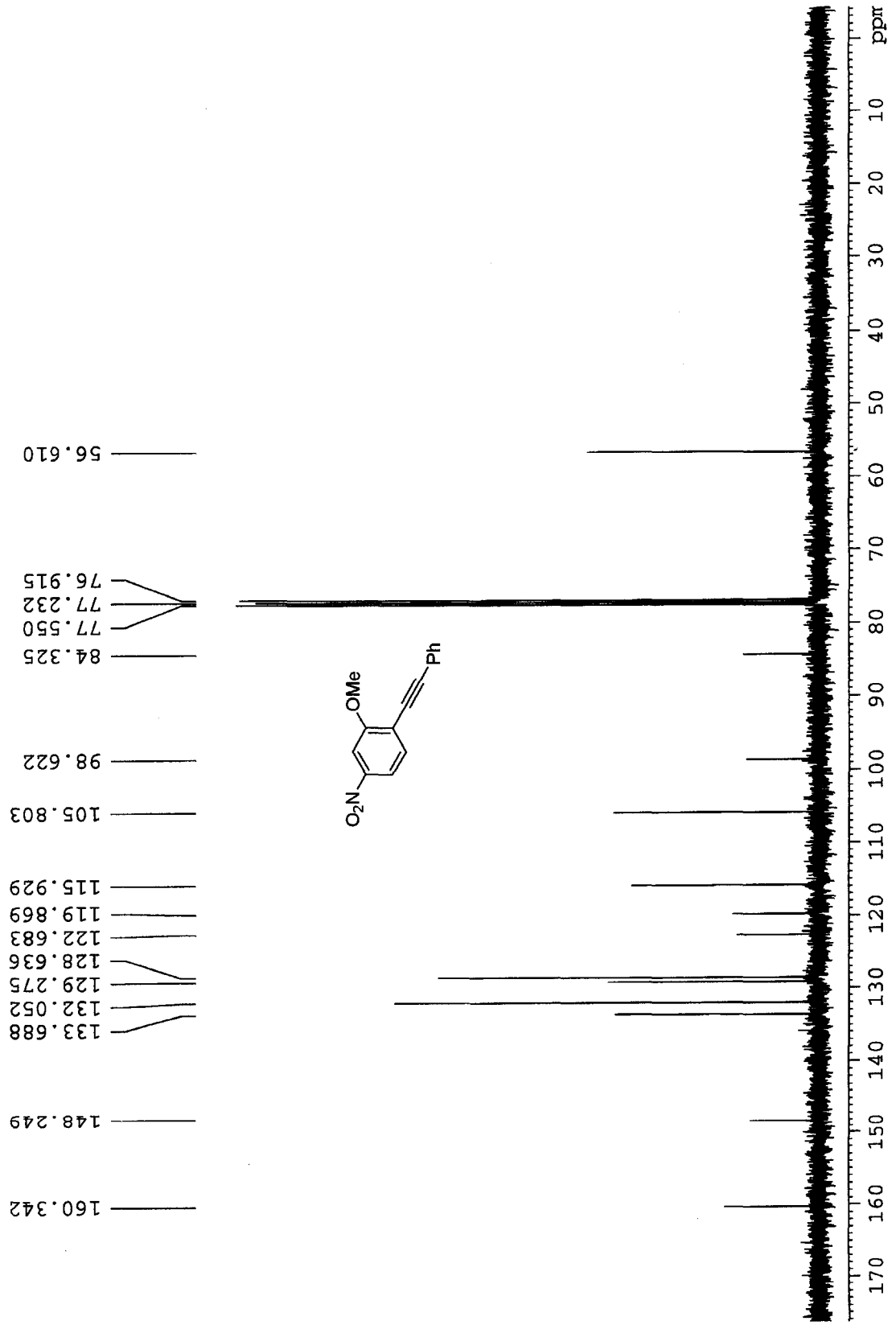
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
OMe
Ph
O_2N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133.688
132.052
129.275
128.636
122.683
119.869
115.929
105.803
98.622
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77.550
77.232
76.915
56.610
OMe
Ph
O_2N
ppm
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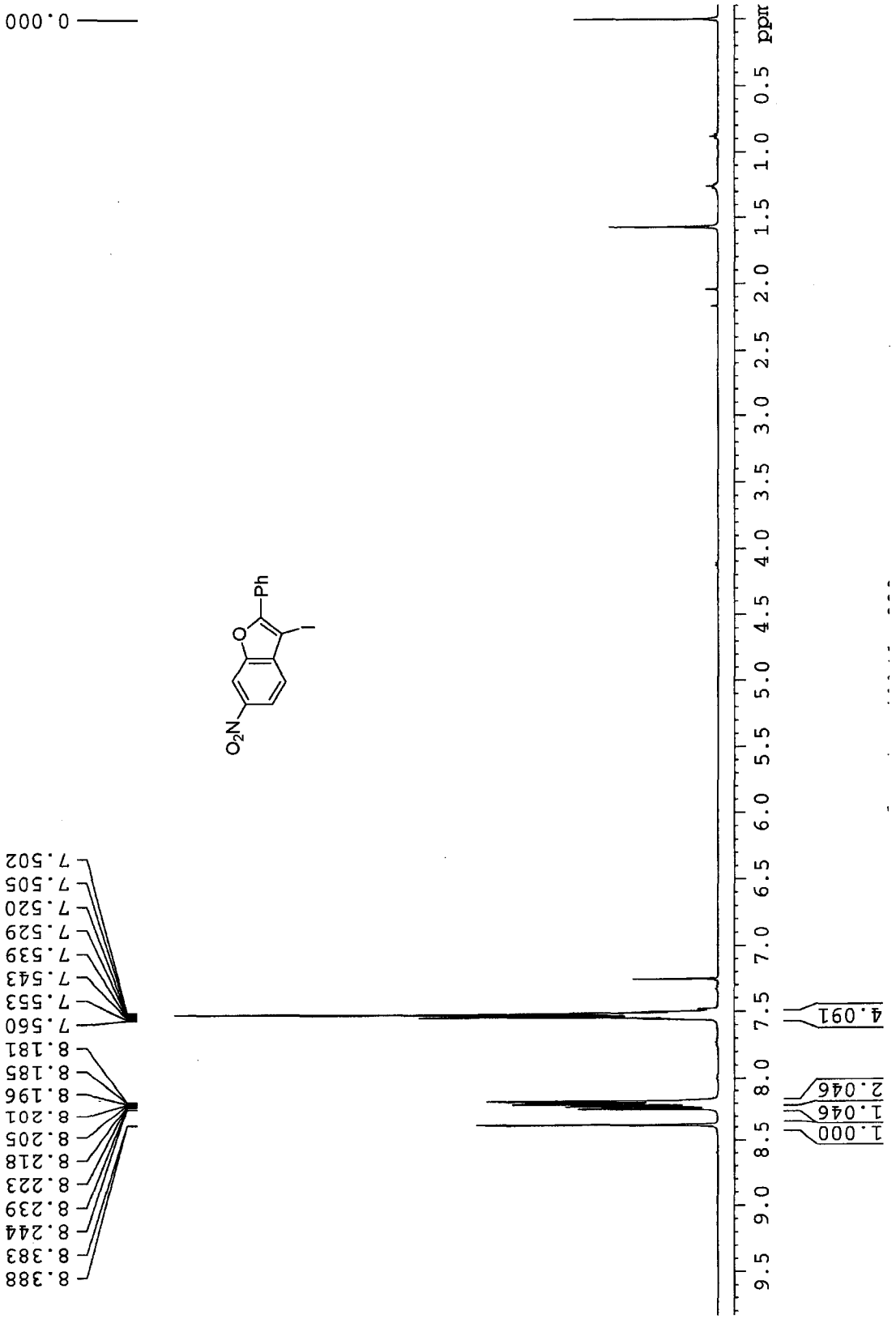
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10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8.383
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8.196
8.185
8.181
7.560
7.553
7.543
7.539
7.529
7.520
7.505
7.502
Ph
I
O_2N
O
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.0
2.5
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1.0
0.5
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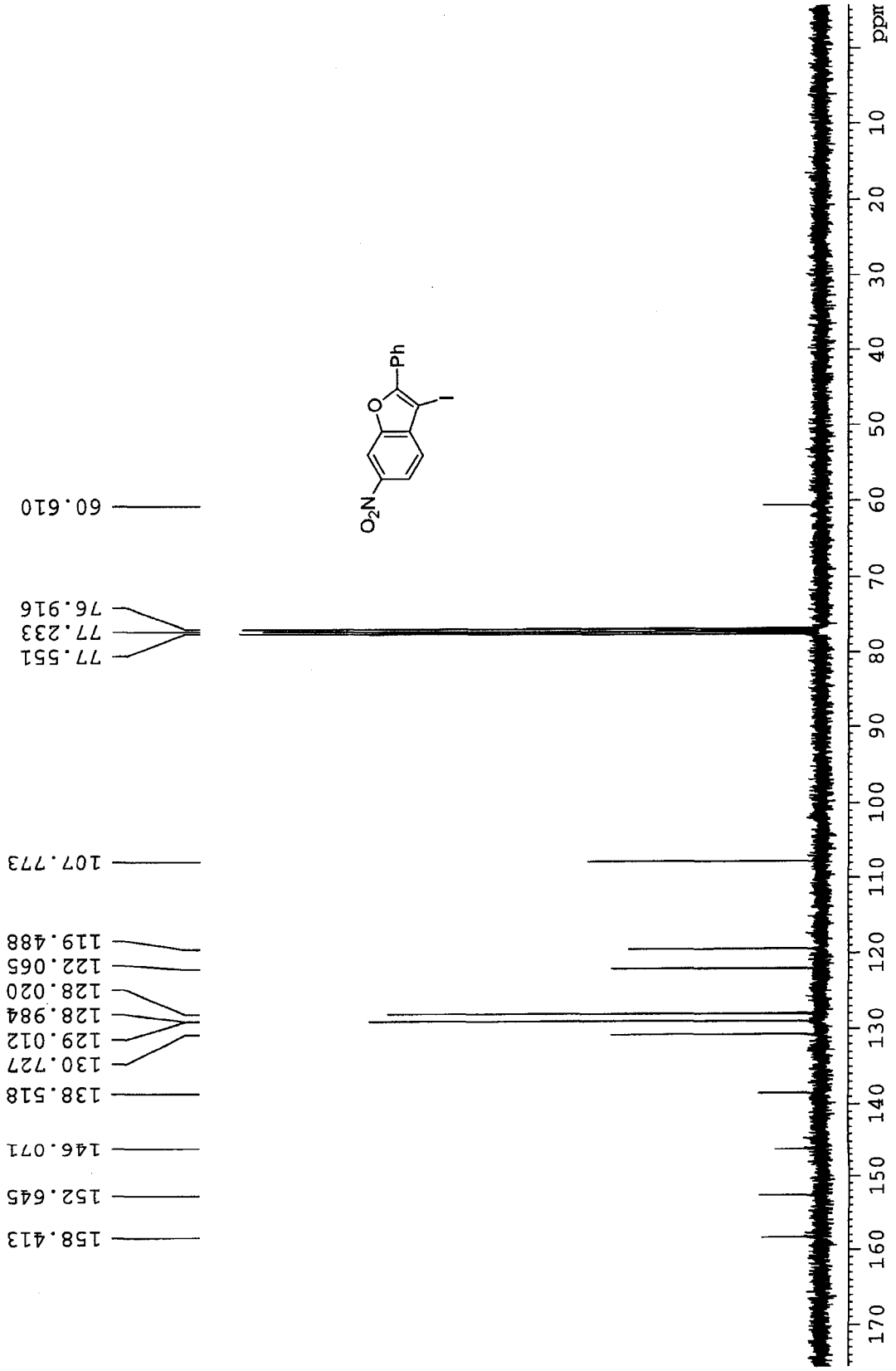
2.046
4.091


ppm
10
20
30
40
50
60
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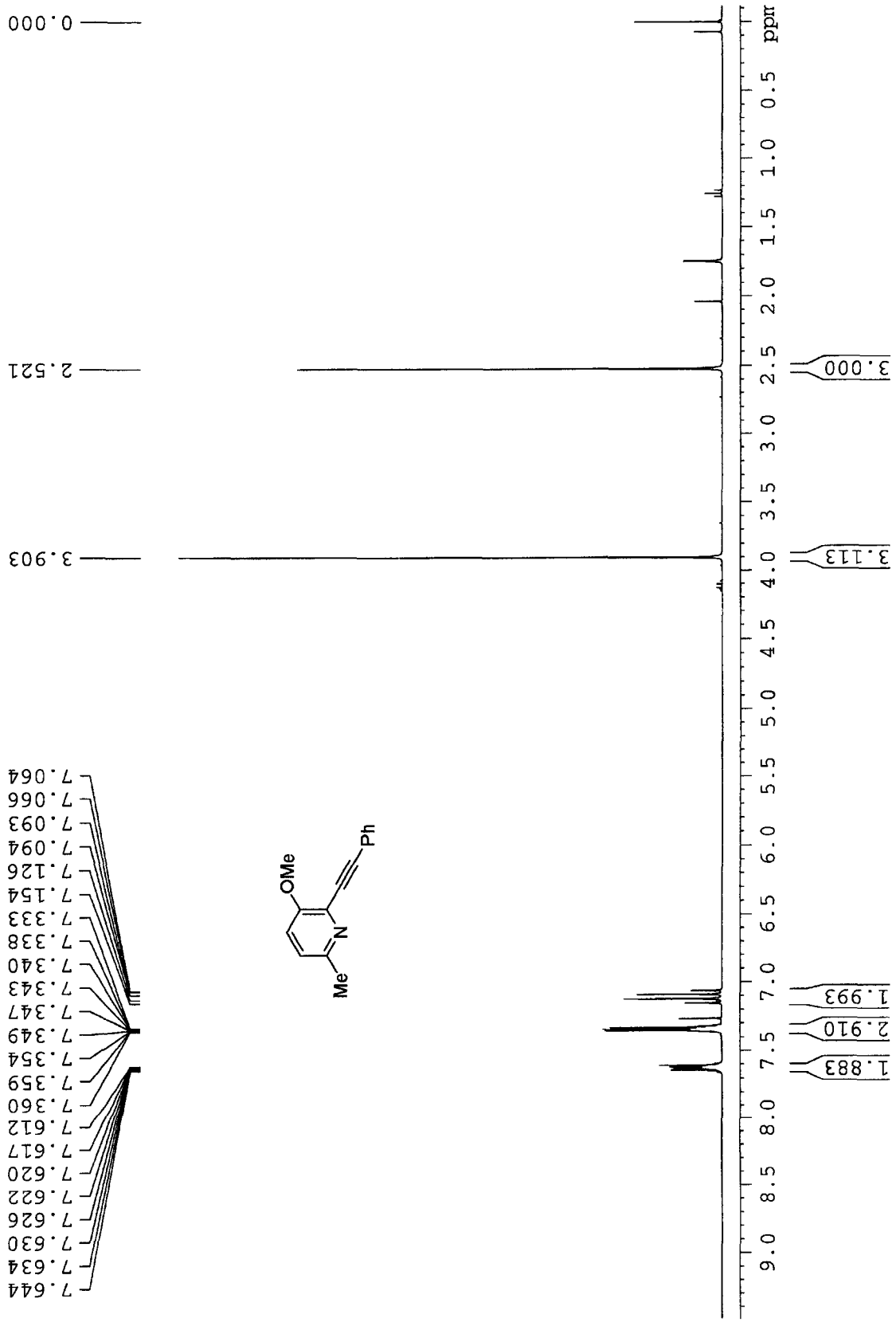
80
90
100
110
120
130
140
150
160
170
60.610
76.916
77.233
77.551
107.773
119.488
122.065
128.020
128.984
129.012
130.727
138.518
146.071
152.645
158.413
Ph
I
O
O_2N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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.000
2.521
3.903
7.644
7.634
7.630
7.626
7.622
7.620
7.617
7.612
7.360
7.359
7.354
7.349
7.347
7.343
7.340
7.338
7.333
7.154
7.126
7.094
7.093
7.066
7.064
Me
N
OMe
Ph
1.883
2.910
1.993
3.113
3.000

155.279
150.567
132.276
128.868
128.410
123.505
122.947
118.790
93.720
85.709
Me
N
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Ph
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155
150
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140
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120
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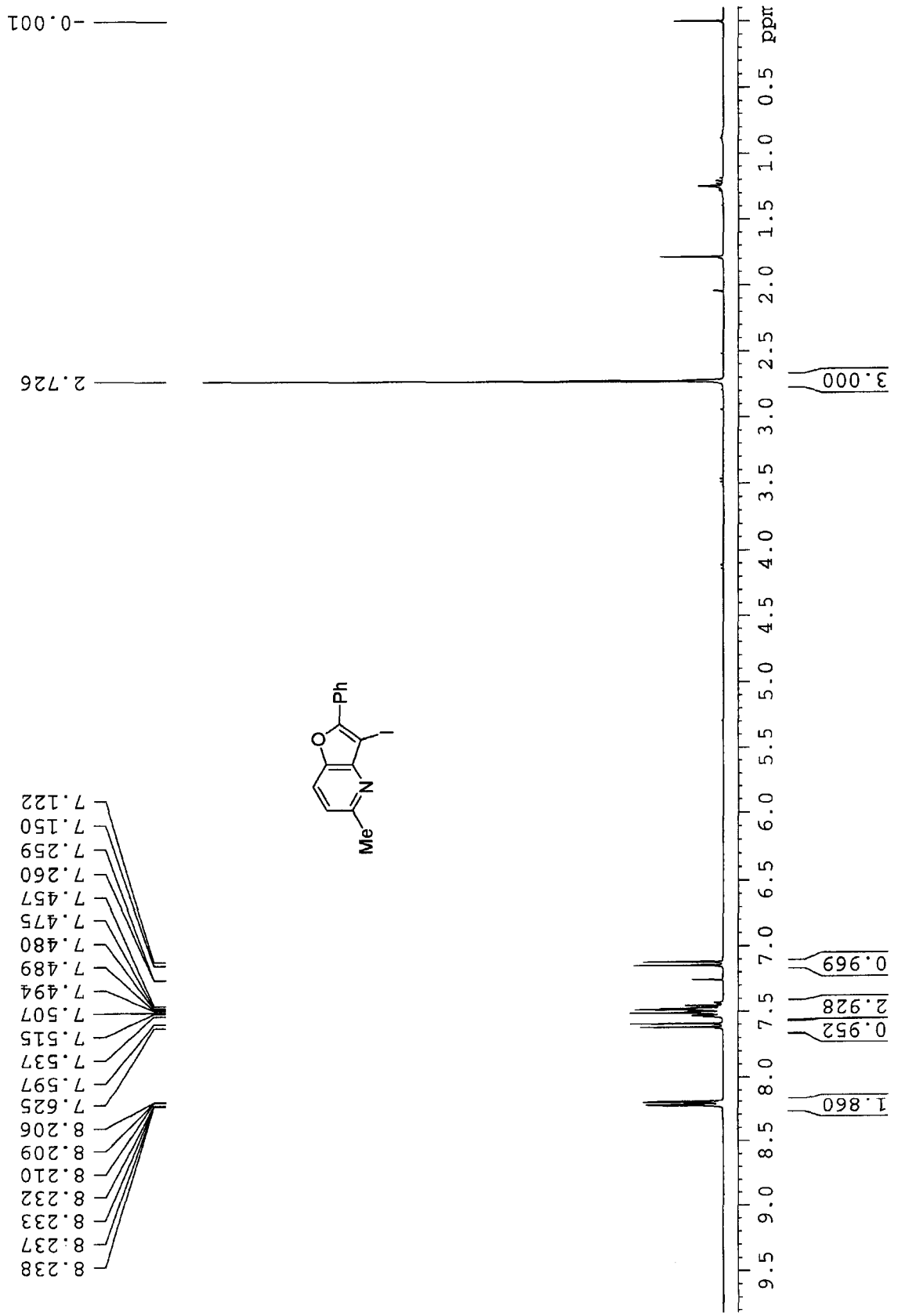
100
95
90
ppm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6.0
5.5
5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
-0.001
2.726
8.238
8.237
8.233
8.232
8.210
8.209
8.206
7.625
7.597
7.537
7.515
7.507
7.494
7.489
7.480
7.475
7.457
7.260
7.259
7.150
7.122
O
N
Me
Ph
I
3.000
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2.928
0.952
1.860

156.183
156.024
148.910
145.811
130.015
129.926
128.783
127.811
120.582
118.510
77.652
77.228
76.805
64.355
24.733
Me
N
I
O
Ph
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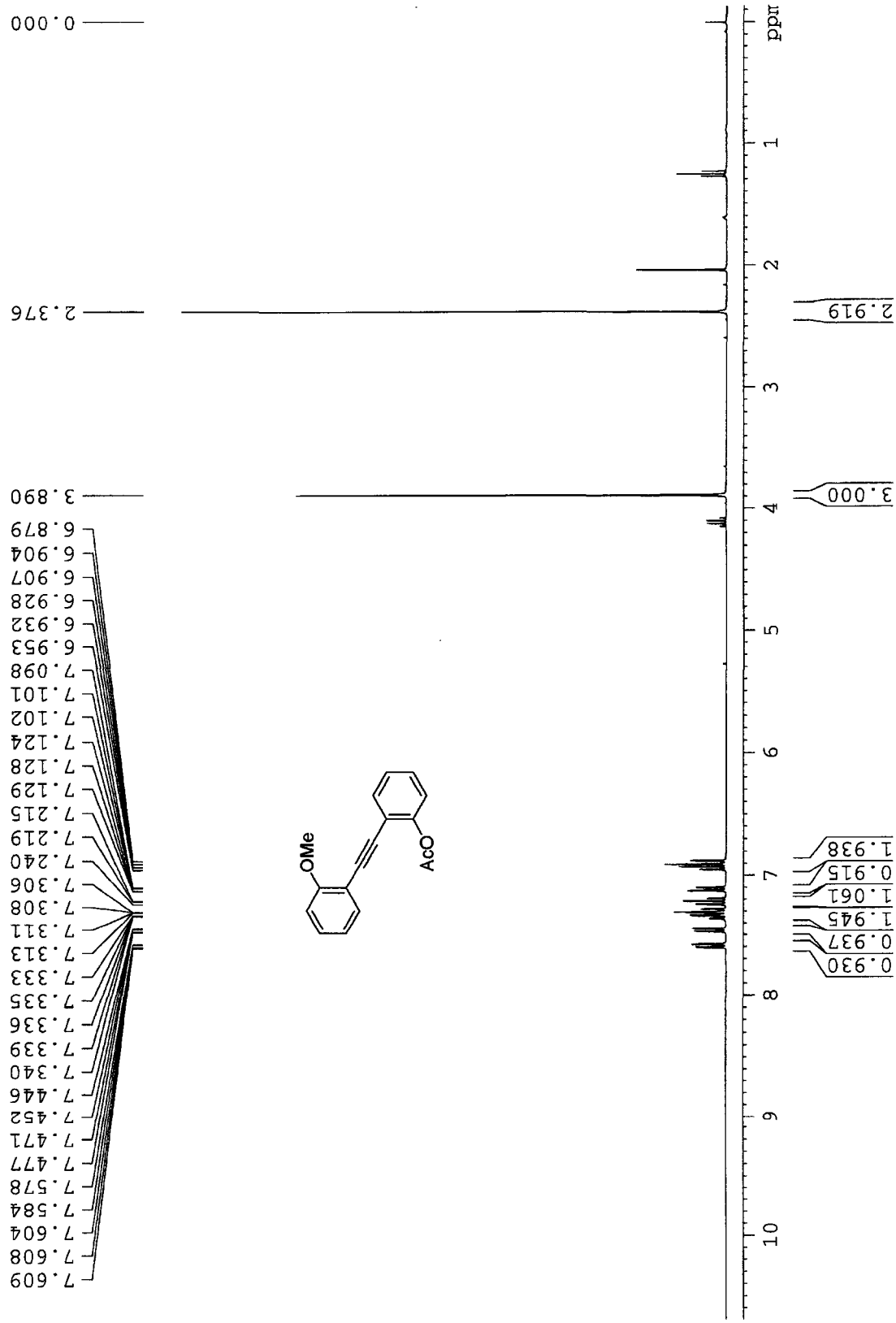
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10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AcO
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0.000
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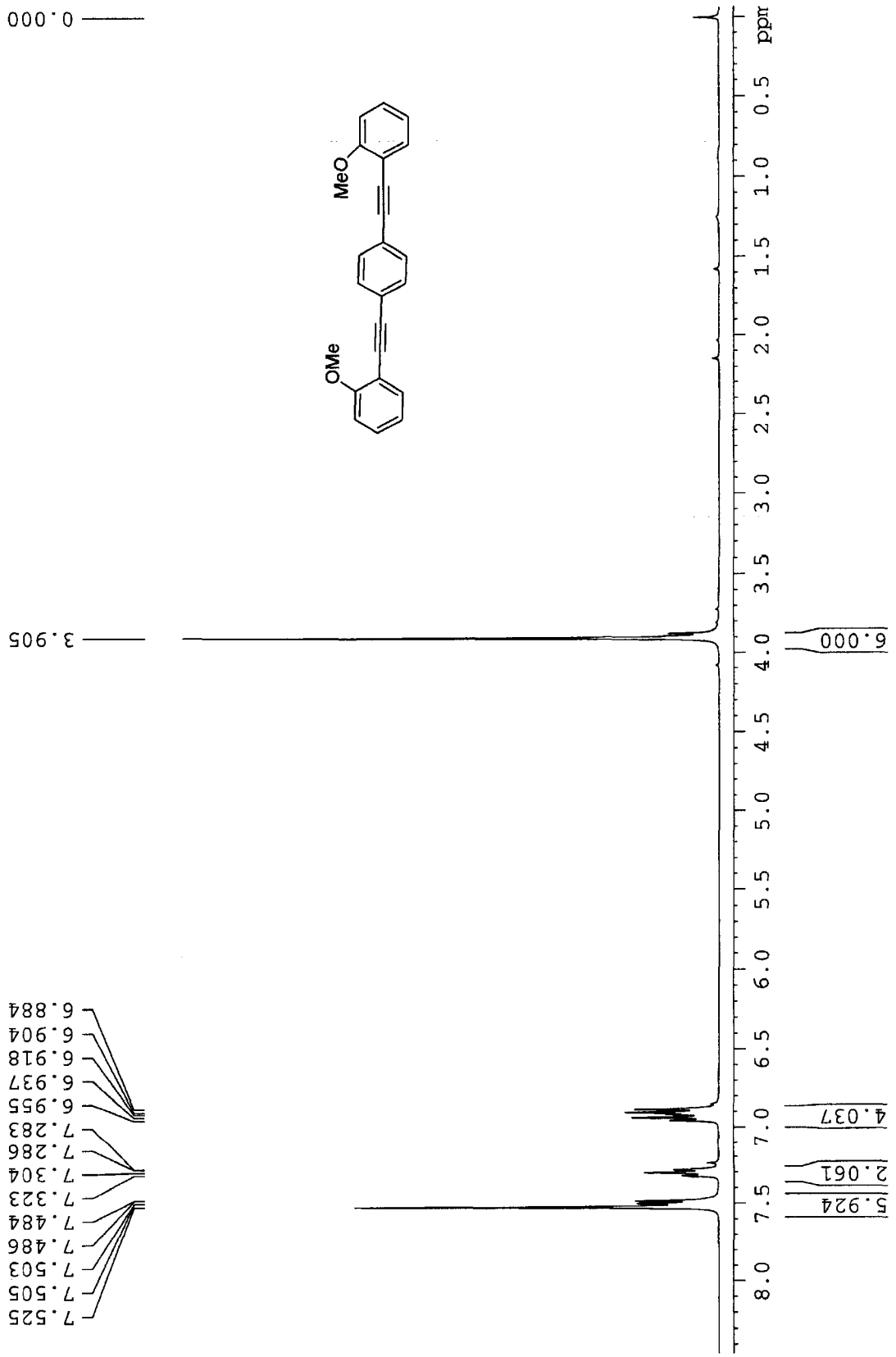
3.890
7.609
7.608
7.604
7.584
7.578
7.477
7.471
7.452
7.446
7.340
7.339
7.336
7.335
7.333
7.313
7.311
7.308
7.306
7.240
7.219
7.215
7.129
7.128
7.124
7.102
7.101
7.098
6.953
6.932
6.928
6.907
6.904
6.879

169.108
160.080
151.604
133.685
133.081
130.203
129.396
125.998
122.353
120.627
117.956
112.339
110.895
90.897
88.334
77.652
77.228
76.803
55.835
20.973
AcO
OMe
ppm

7.835
7.829
7.809
7.803
7.530
7.525
7.505
7.504
7.500
7.498
7.482
7.478
7.473
7.465
7.459
7.453
7.452
7.448
7.443
7.441
7.393
7.389
7.374
7.368
7.364
7.352
7.349
7.346
7.342
7.339
7.327
7.323
7.261
7.257
7.234
7.230
2.206
0.000
0.919
2.890
3.101
1.075
2.979
11
10
9
8
7
6
5
4
3
2
1
ppm
AcO

169.373
154.618
152.299
148.769
131.945
131.717
131.158
126.061
126.018
123.758
123.692
123.274
122.099
111.355
77.653
77.229
76.805
65.368
21.264
AcO
ppm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MeO
ppm
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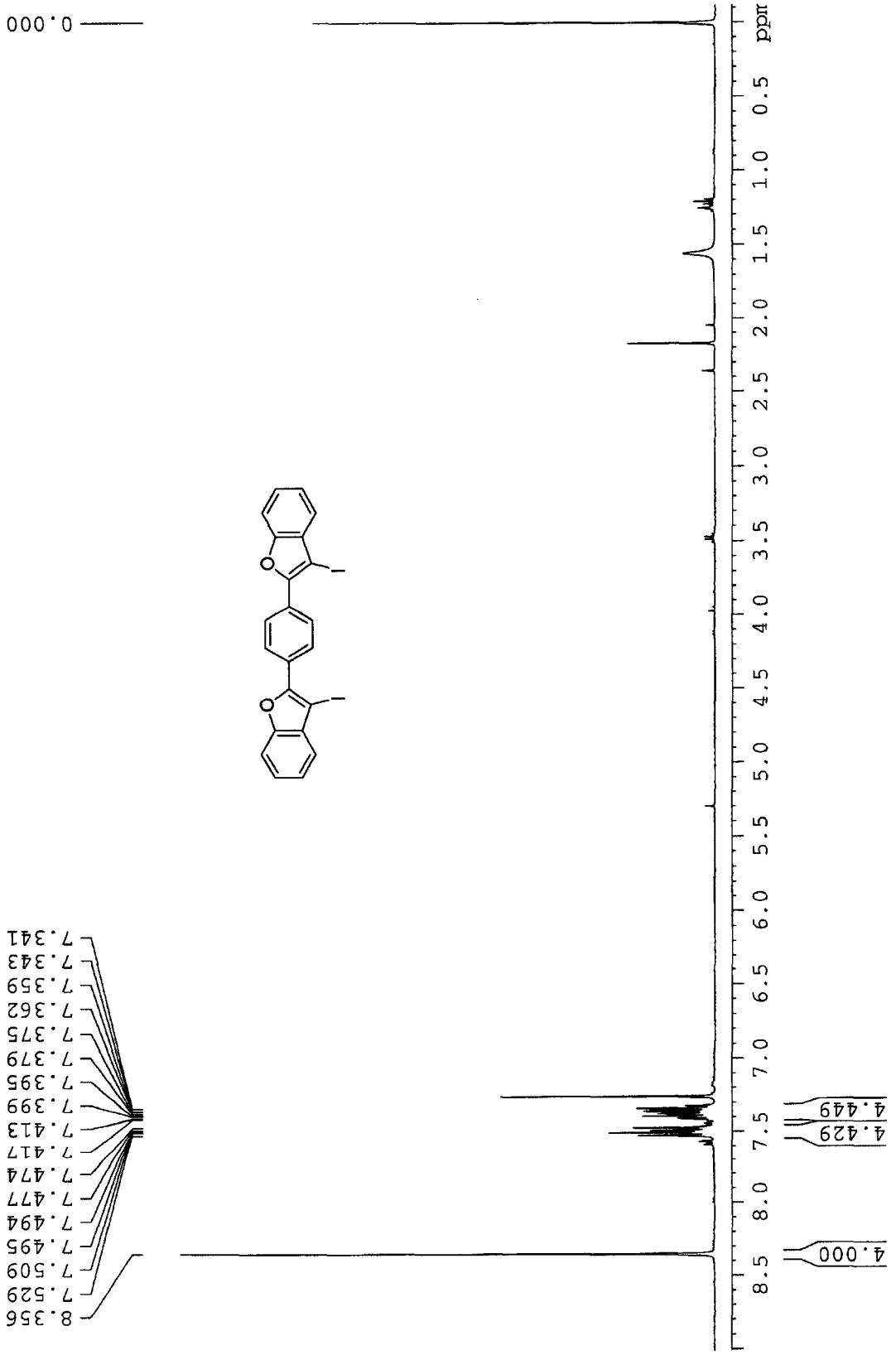
7.505
7.503
7.486
7.484
7.323
7.304
7.286
7.283
6.955
6.937
6.918
6.904
6.884

160.110
133.745
131.674
130.144
123.389
120.681
112.396
110.844
93.417
87.725
77.547
77.229
76.911
55.999
OMe
MeO
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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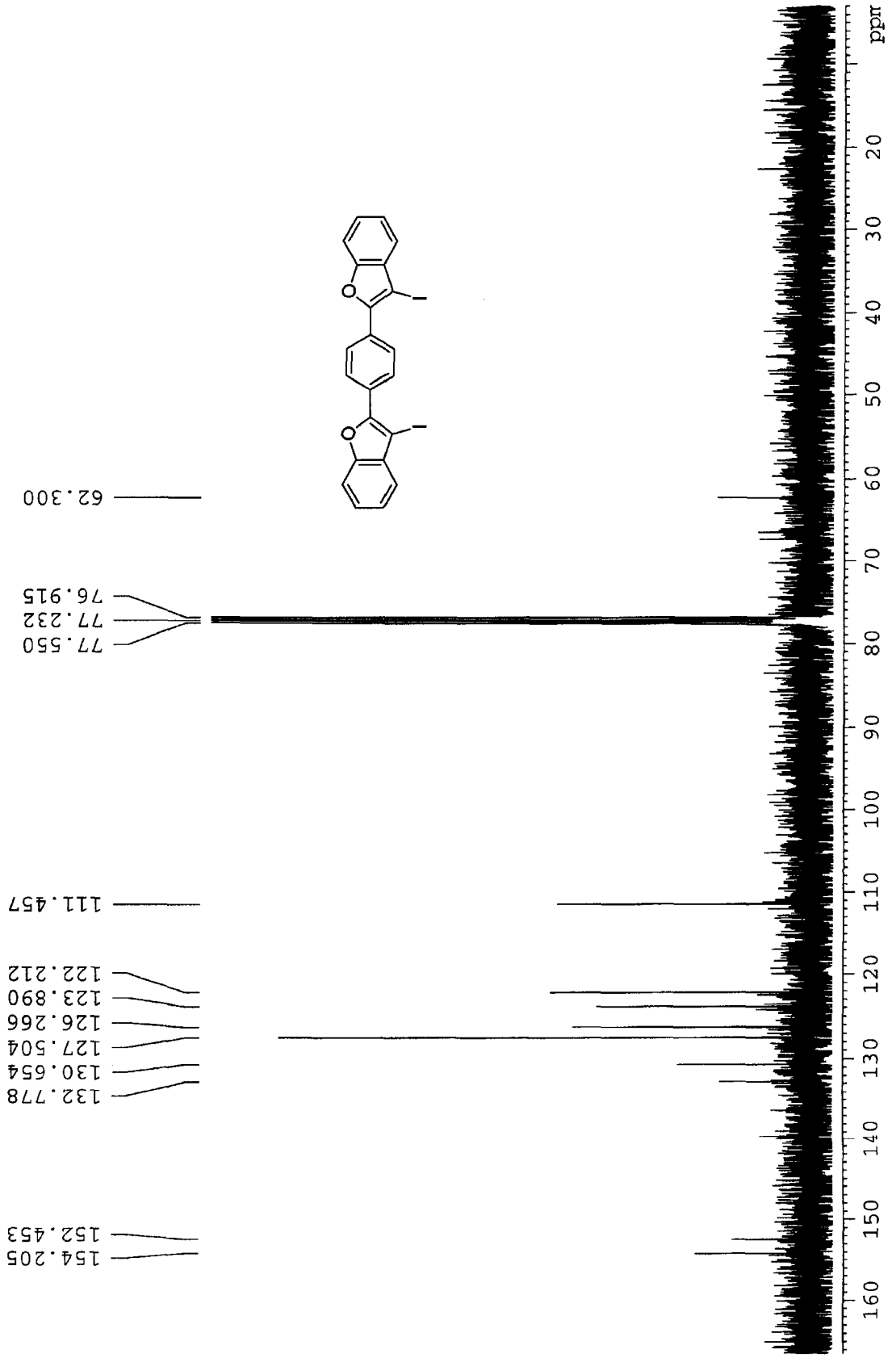
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
4.000
4.429
4.449
0.000
8.356
7.529
7.509
7.495
7.494
7.477
7.474
7.417
7.413
7.399
7.395
7.379
7.375
7.362
7.359
7.343
7.341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76.915
77.232
77.550
111.457
122.212
123.890
126.266
127.504
130.654
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ppm
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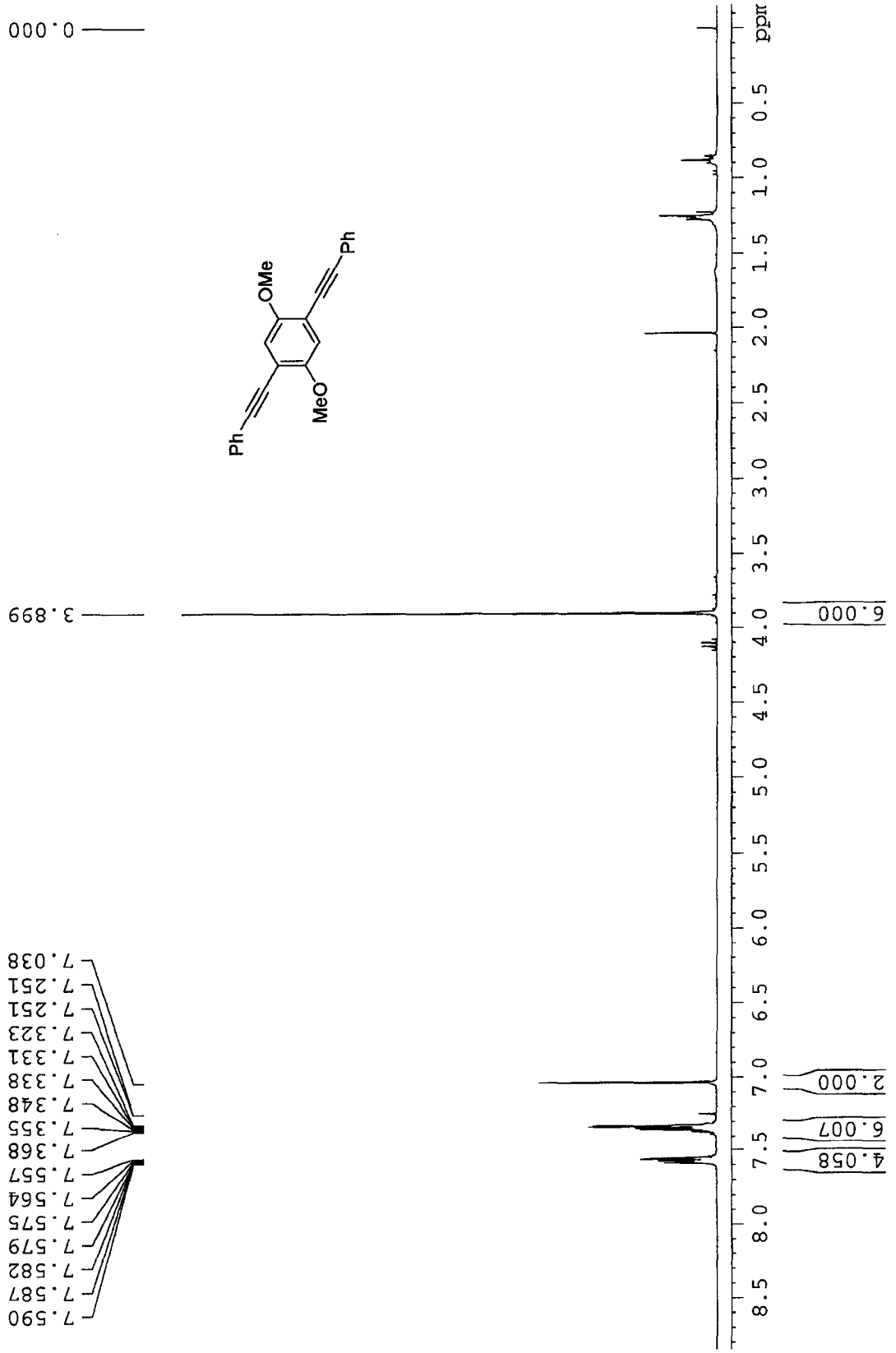
130
120
110
100
90
80
70
60
50
40
30
20


ppm
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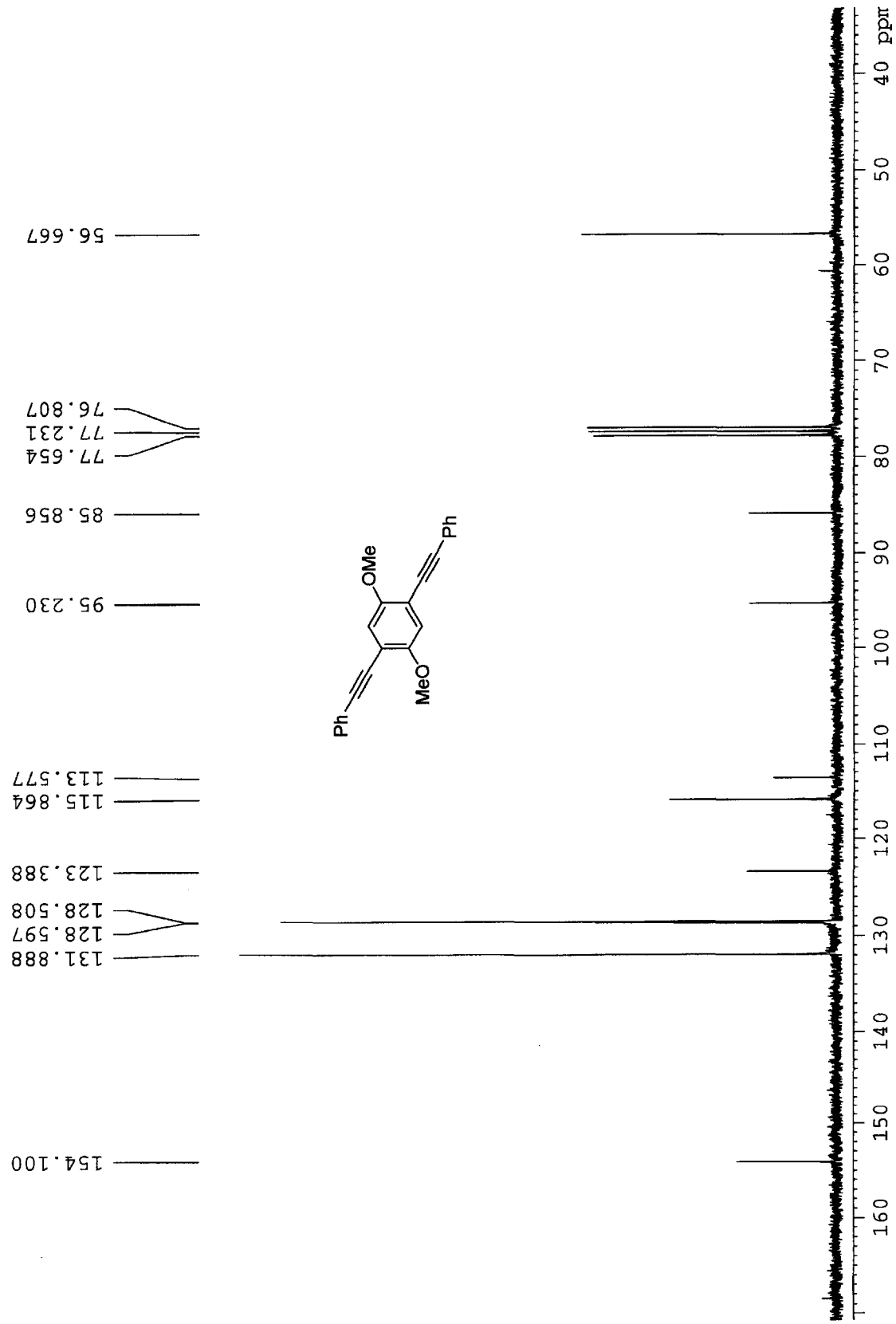
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.000
3.899
7.590
7.587
7.582
7.579
7.575
7.564
7.557
7.368
7.355
7.348
7.338
7.331
7.323
7.251
7.251
7.038
4.058
6.007
2.000
6.000
Ph
MeO
OMe
Ph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95.230
85.856
77.654
77.231
76.807
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Ph
MeO
OMe
Ph
ppm
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50
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70
80
90
100
110
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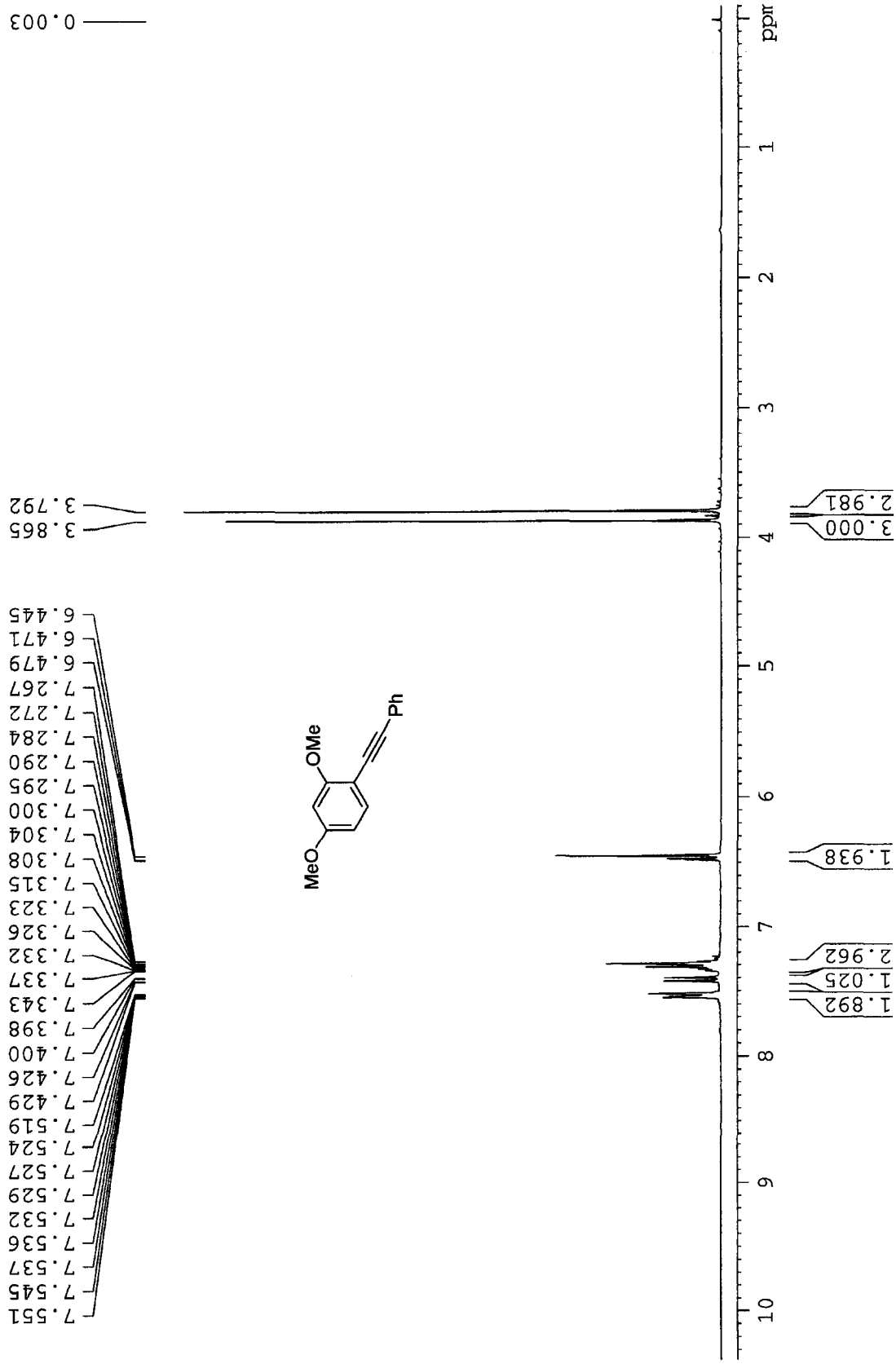
130
140
150
160


ppm
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9
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7
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3
2
1
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6.445
6.471
6.479
7.267
7.272
7.284
7.290
7.295
7.300
7.304
7.308
7.315
7.323
7.326
7.332
7.337
7.343
7.398
7.400
7.426
7.429
7.519
7.524
7.527
7.529
7.532
7.536
7.537
7.545
7.551
MeO
OMe
Ph
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1.025
2.962
1.938
3.000
2.981

7.403
7.391
7.369
7.345
7.342
7.334
7.330
7.327
7.323
7.320
7.316
7.313
7.176
7.173
7.155
7.152
6.568
6.564
6.562
6.559
6.546
6.543
6.541
6.538
6.481
6.476
3.922
3.919
3.848
3.845
0.000
4.995
0.993
0.997
0.992
3.094
3.091
MeO
OMe
I
I
Ph
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.5
4.0
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2.0
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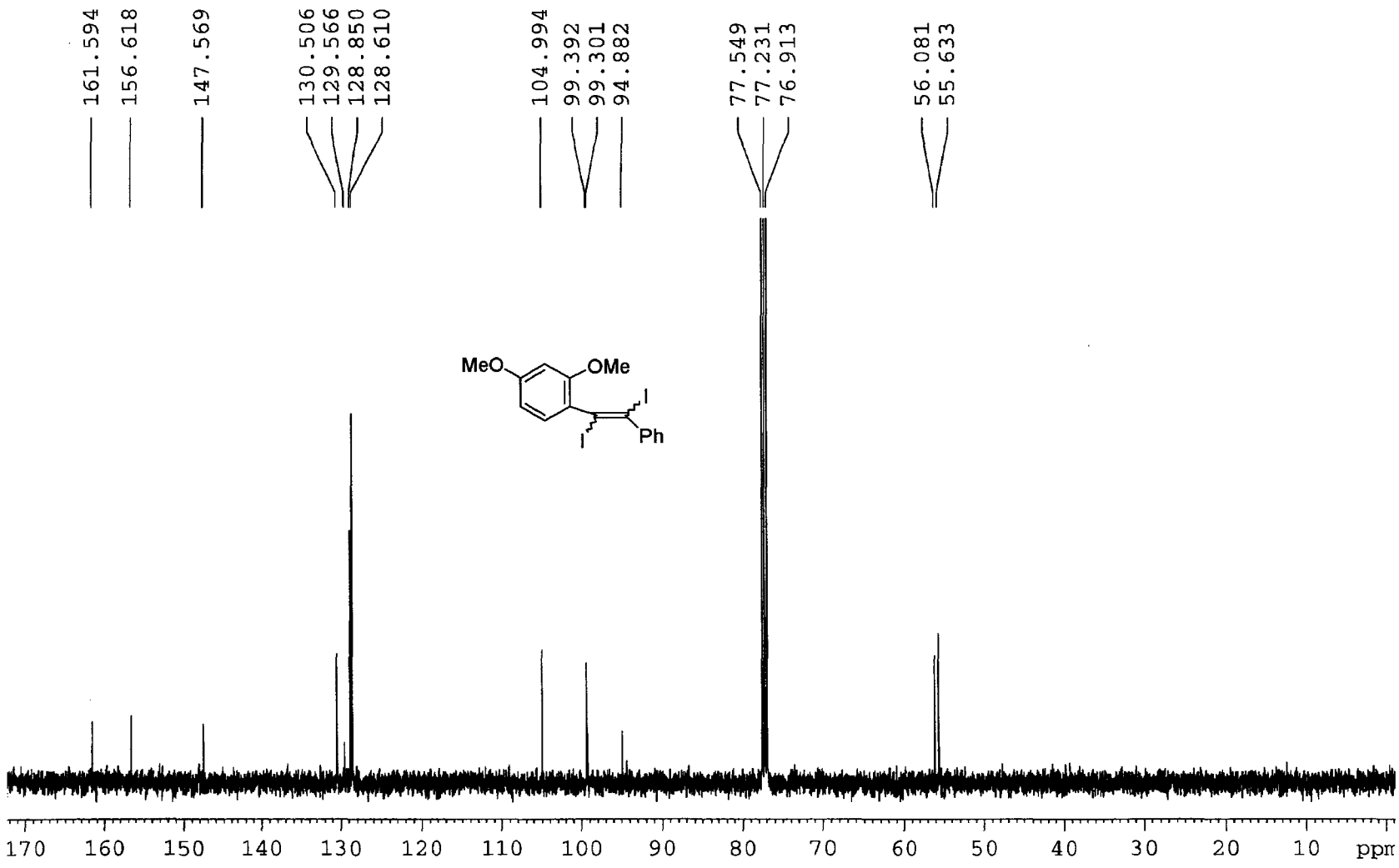
1.0
0.5
ppm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99.392
99.301
94.882
77.549
77.231
76.913
56.081
55.633
MeO
OMe
I
I
Ph
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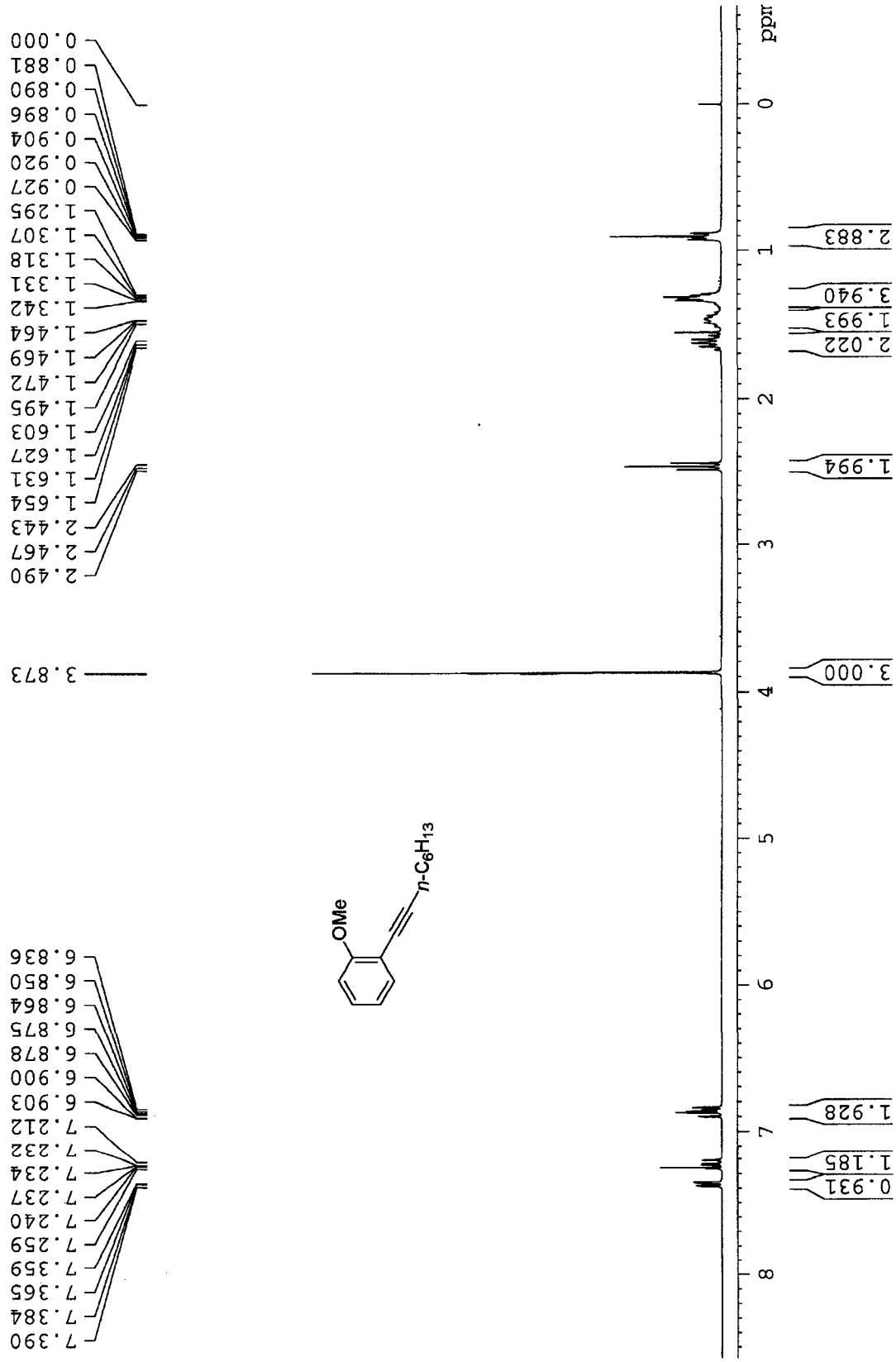
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OMe
n-C6H13
ppm
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2
3
4
5
6
7
8
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2.022
1.994
3.000
1.928
1.185
0.931
3.873
7.390
7.384
7.365
7.359
7.259
7.240
7.237
7.234
7.232
7.212
6.903
6.900
6.878
6.875
6.864
6.850
6.836
2.490
2.467
2.443
1.654
1.631
1.627
1.603
1.495
1.472
1.469
1.464
1.342
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1.295
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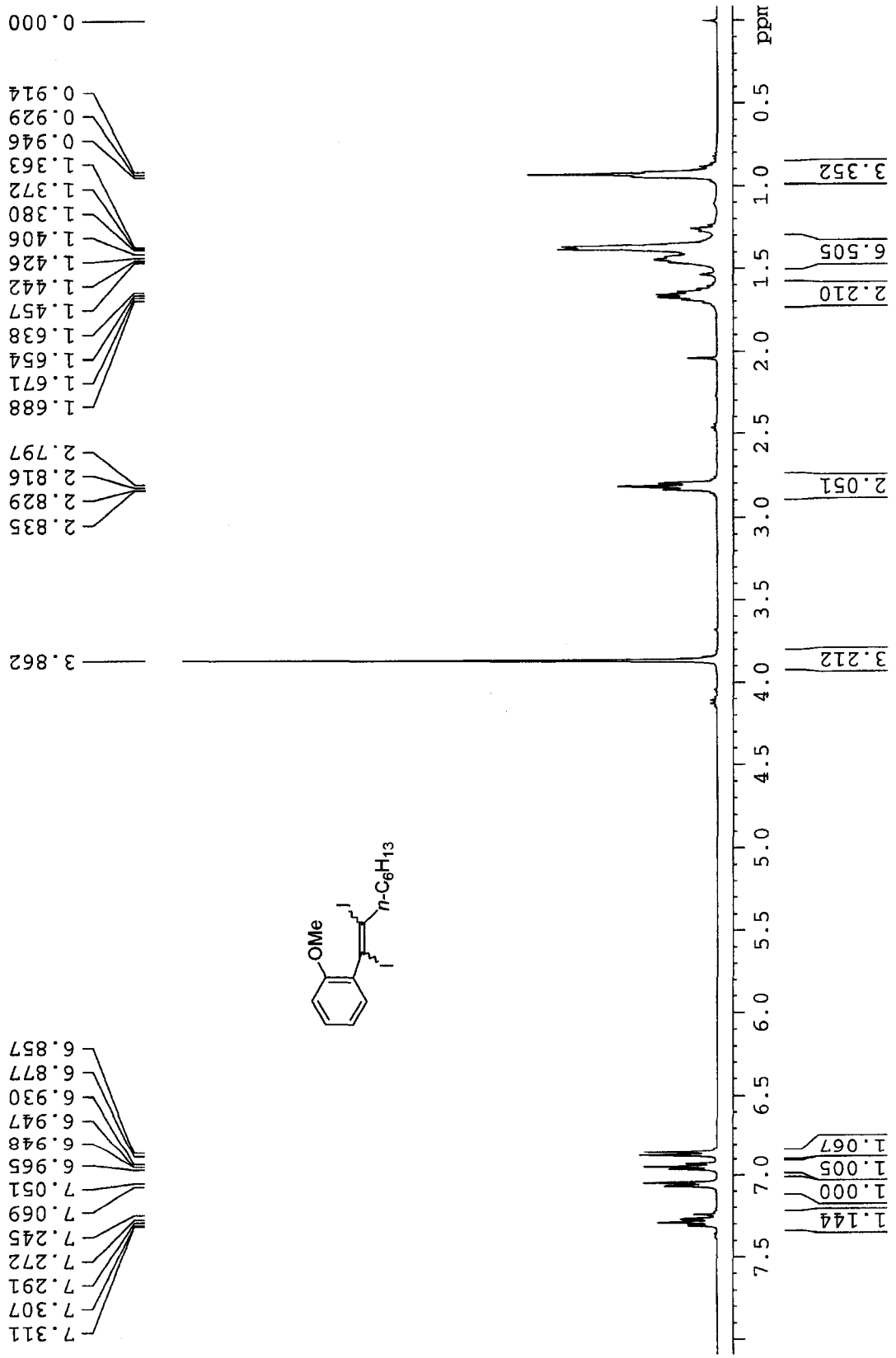
OMe
I
I
n-C6H13
ppm
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0.929
0.946
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1.372
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1.406
1.426
1.442
1.457
1.638
1.654
1.671
1.688
2.797
2.816
2.829
2.835
3.862
6.857
6.877
6.930
6.947
6.948
6.965
7.051
7.069
7.245
7.272
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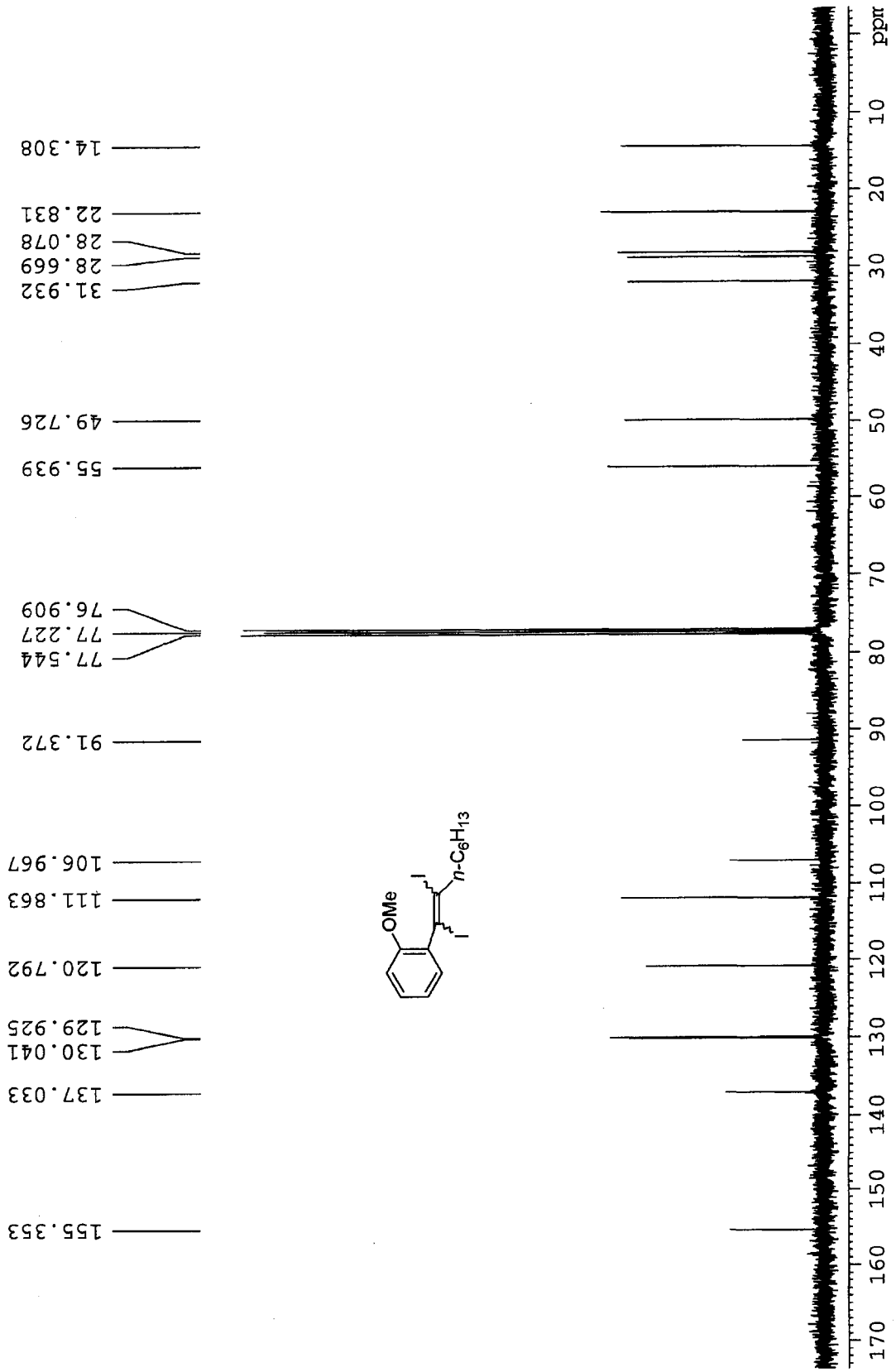
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I
I
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77.227
76.909
55.939
49.726
31.932
28.669
28.078
22.831
14.308
ppm
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150
140
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120
110
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80
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40
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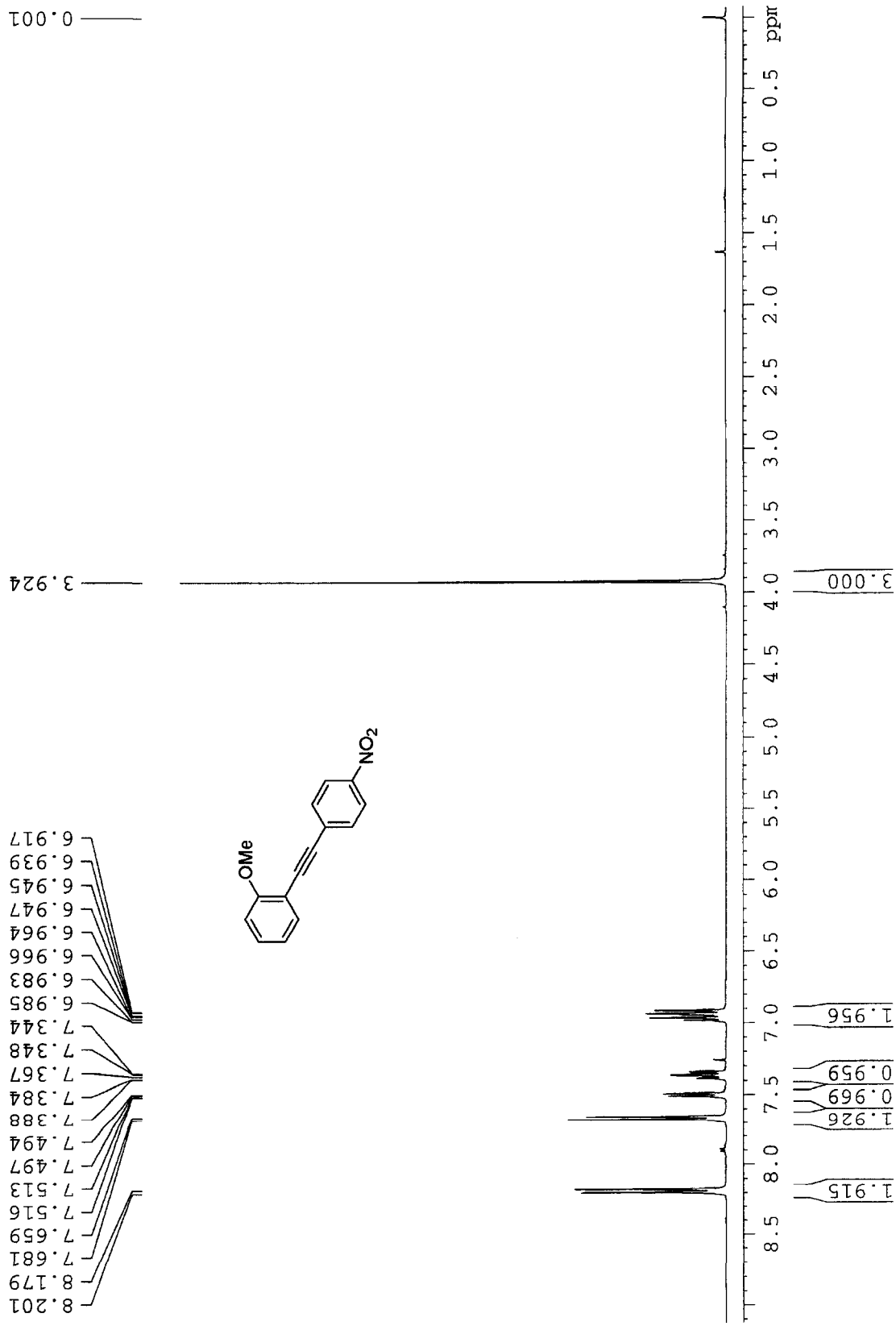
20
10


OMe
NO2
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7.513
7.497
7.494
7.388
7.384
7.367
7.348
7.344
6.985
6.983
6.966
6.964
6.947
6.945
6.939
6.917
3.924
0.001
1.915
1.926
0.969
0.959
1.956
3.000
ppm

160.380
146.952
133.906
132.412
131.070
130.782
123.706
120.759
111.419
110.925
91.740
91.622
77.550
77.233
76.915
55.990
OMe
NO2
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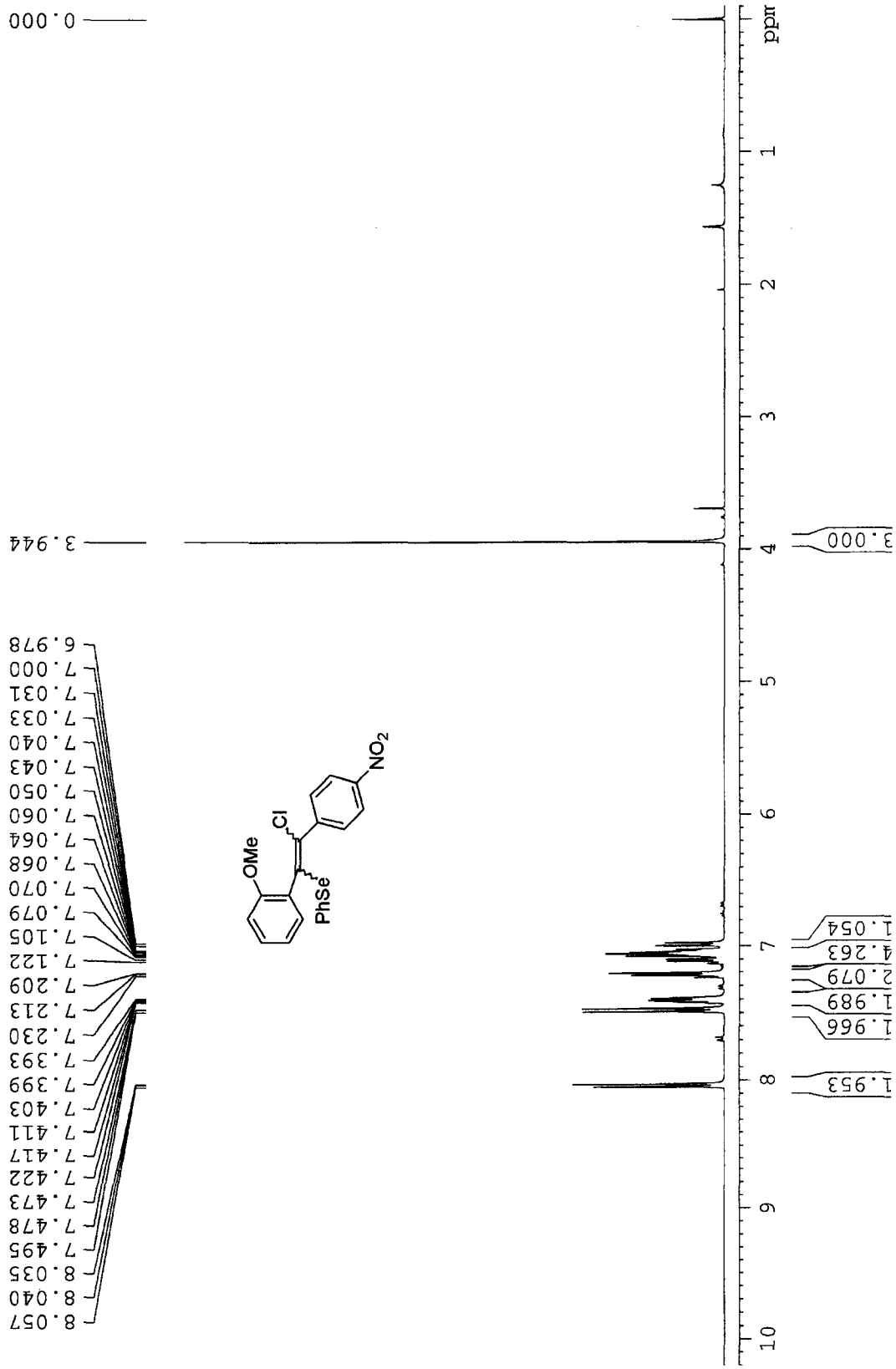
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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Cl
PhSe
NO2
ppm
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8.035
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7.478
7.473
7.422
7.417
7.411
7.403
7.399
7.393
7.230
7.213
7.209
7.122
7.105
7.079
7.070
7.068
7.064
7.060
7.050
7.043
7.040
7.033
7.031
7.000
6.978
3.000
1.054
4.263
2.079
1.989
1.966
1.953

OMe
Cl
PhSe
NO2
ppm
10
9
8
7
6
5
4
3
2
1
0
3.000
1.054
4.263
2.079
1.989
1.966
1.953
3.944
0.000
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8.040
8.035
7.495
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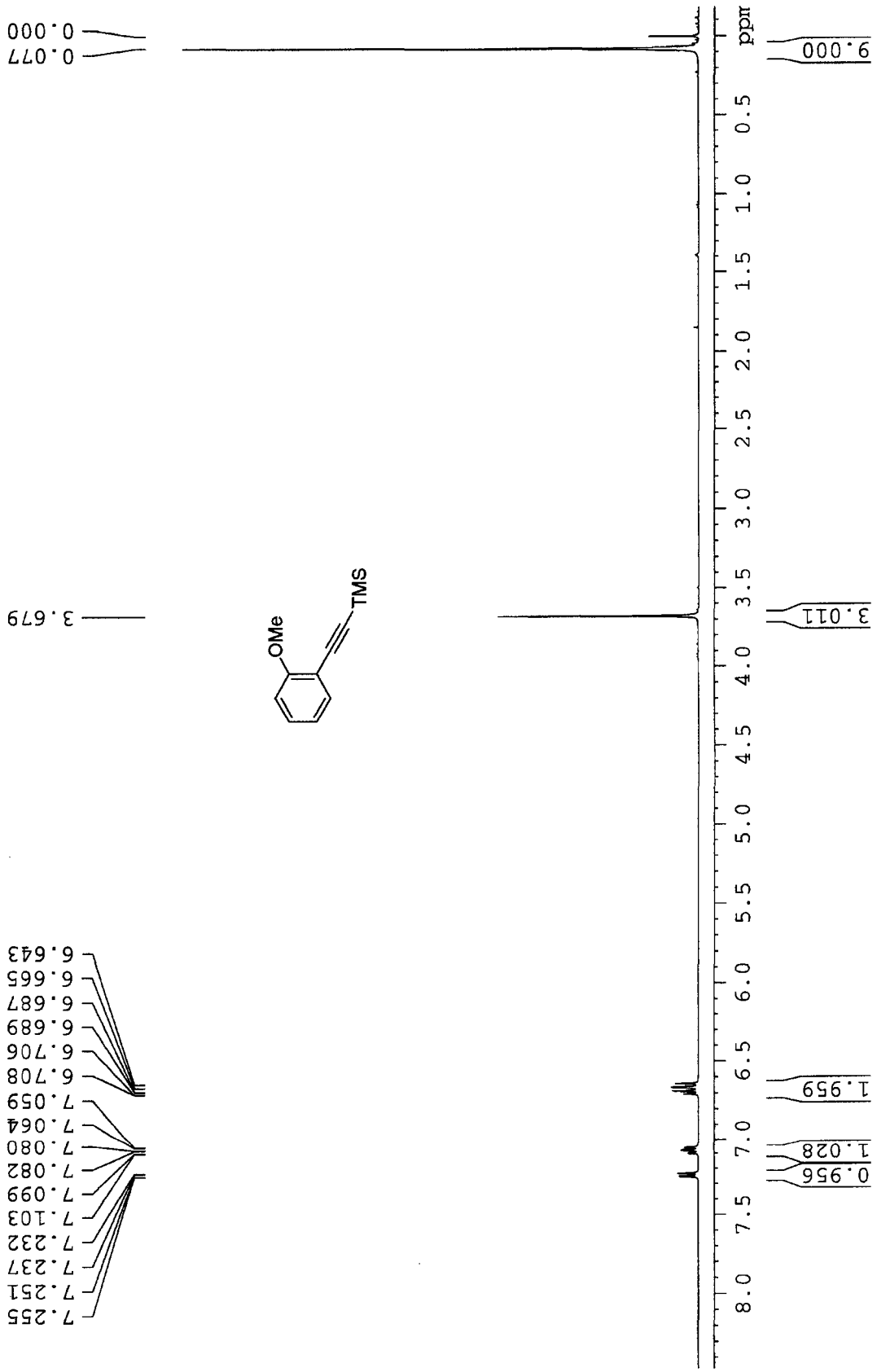
7.393
7.230
7.213
7.209
7.122
7.105
7.079
7.070
7.068
7.064
7.060
7.050
7.043
7.040
7.033
7.031
7.000
6.978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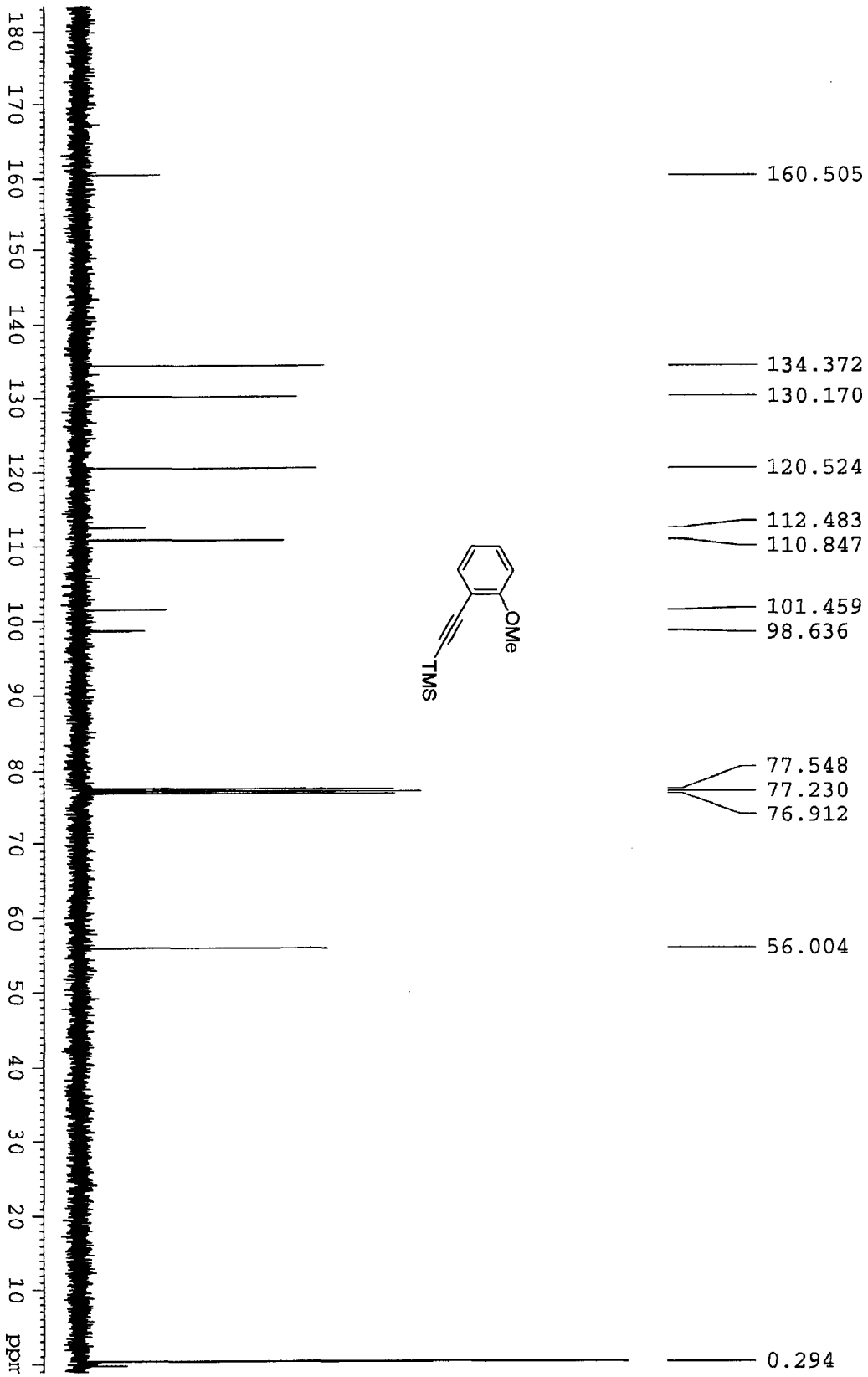
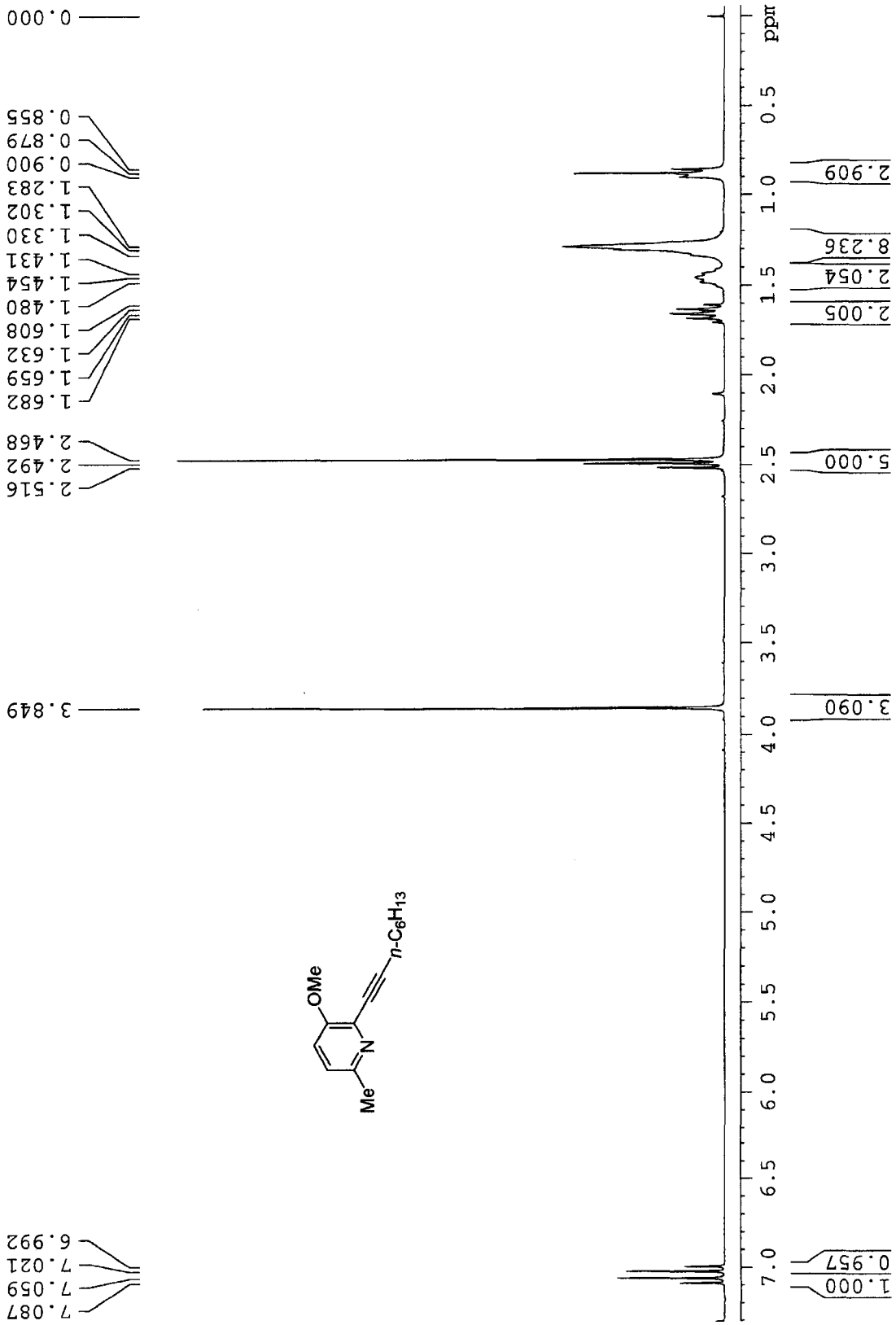
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
9.000
3.011
1.959
1.028
0.956
0.077
0.000
3.679
7.255
7.251
7.237
7.232
7.103
7.099
7.082
7.080
7.064
7.059
6.708
6.706
6.689
6.687
6.665
6.643

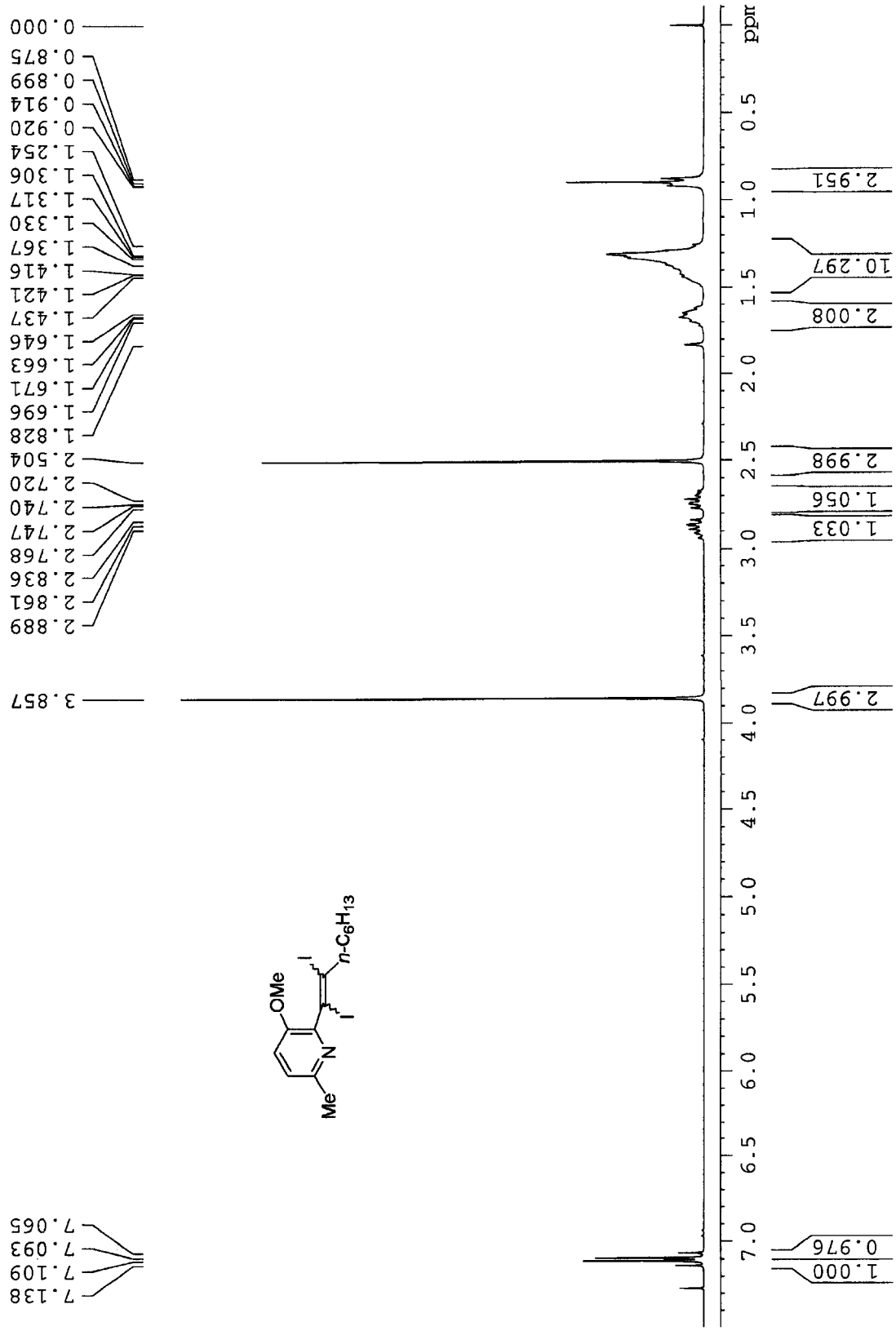

160.505
134.372
130.170
120.524
112.483
110.847
101.459
98.636
77.548
77.230
76.912
56.004
0.294
OMe
TMS
ppm

0.950
2.036
3.133
3.000
3.066
8.400
7.544
7.541
7.533
7.525
7.519
7.511
7.348
7.340
7.336
7.328
7.322
7.290
4.061
4.012
0.000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
MeO
N
N
OMe
Ph

170.440
164.180
161.272
131.622
128.583
128.416
122.914
100.234
95.509
80.802
77.550
77.232
76.915
55.194
54.620
MeO
N
N
OMe
Ph
ppm


ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
1.000
0.957
3.090
5.000
2.005
2.054
8.236
2.909
7.087
7.059
7.021
6.992
3.849
2.516
2.492
2.468
1.682
1.659
1.632
1.608
1.480
1.454
1.431
1.330
1.302
1.283
0.900
0.879
0.855
0.000
Me
N
OMe
n-C6H13

154.808
150.144
133.043
122.656
118.475
95.660
77.655
77.230
77.058
76.806
55.993
31.944
29.301
29.244
29.160
28.611
23.528
22.772
19.908
14.206
Me
N
OMe
n-C6H13
ppm


ppm
0.000
0.875
0.899
0.914
0.920
1.254
1.306
1.317
1.330
1.367
1.416
1.421
1.437
1.446
1.663
1.671
1.696
1.828
2.504
2.720
2.740
2.747
2.768
2.836
2.861
2.889
3.857
7.065
7.093
7.109
7.138
OMe
Me
N
I
I
n-C6H13
2.951
10.297
2.008
2.998
1.056
1.033
2.997
0.976
1.000

151.878
149.653
149.534
124.082
120.062
107.356
91.004
77.654
77.230
76.806
56.069
49.144
32.052
29.660
29.441
28.551
28.503
23.671
22.882
14.335
Me
N
I
OMe
I
n-C6H13
ppm

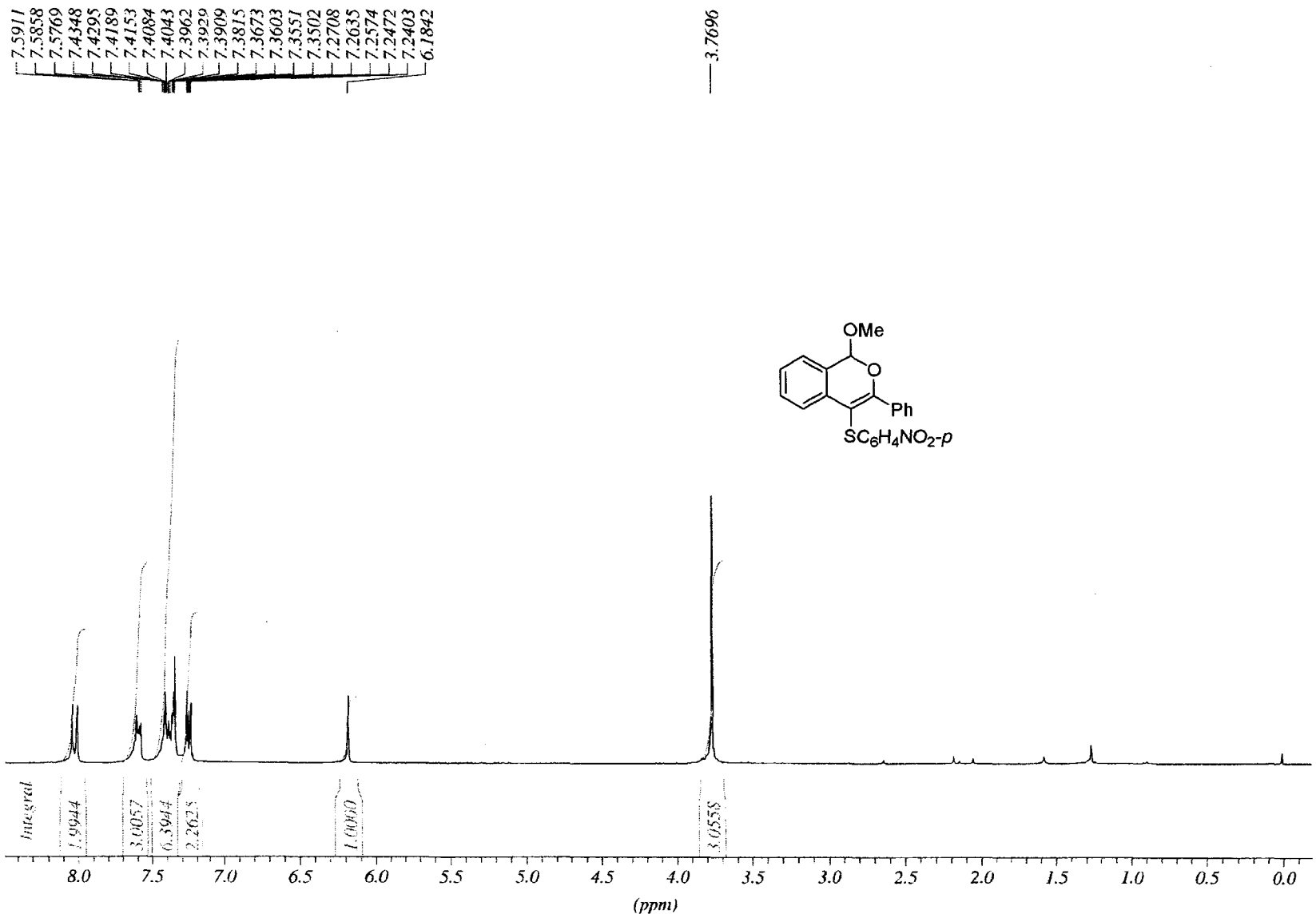
APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

Integral
2.8917
4.0083
1.0640
1.0228
0.9835
1.0000
1.0245
2.0028
2.0518
3.0039
(ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
OBu-n
Ph
7.3245
7.2594
7.2256
7.2240
7.2224
7.2008
7.1975
6.1329
4.0723
4.0504
4.0402
4.0284
4.0182
3.9962
3.8379
3.8160
3.8058
3.7944
3.7838
3.7618
1.7176
1.6948
1.6858
1.6724
1.6642
1.6455
1.6236
1.5027
1.4779
1.4595
1.4530
1.4347
1.4266
1.4107
1.4030
1.3790
0.9789
0.9545
0.9297

152.2072
137.8434
131.7674
130.2394
129.9616
129.8940
129.5058
128.1666
128.0206
127.8318
125.6272
99.1185
77.7385
77.3147
76.8908
73.9775
68.8666
31.9261
19.6103
14.1611
(ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
I
O
OBu-n
Ph

Integral
1.0000
1.8315
8.1179
1.8998
0.9423
0.8820
2.7971
(ppm)
7.3747
7.3708
7.3575
7.3419
7.3355
7.3239
7.3188
7.3165
7.3051
7.3017
7.2939
7.2889
7.2859
7.2591
7.2554
7.2520
7.2371
7.2344
7.2314
7.1740
7.1712
7.1536
7.1497
7.1381
7.1346
7.1030
7.0850
6.1335
5.2986
3.7430
3.6700
1.5500
0.8903
0.0071
OMe
SePh
Ph
O

157.0591
136.4286
133.6271
131.3601
129.9916
129.9423
129.8740
129.7944
129.5935
129.4419
129.3433
128.4221
127.8610
127.7928
127.6260
127.5274
126.6479
125.7002
125.6812
100.3500
77.5738
77.4601
77.2554
76.9370
56.3634
SePh
Ph
O
OMe
(ppm)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7.5858
7.5769
7.4348
7.4295
7.4189
7.4153
7.4084
7.4043
7.3962
7.3929
7.3909
7.3815
7.3673
7.3603
7.3551
7.3502
7.2708
7.2635
7.2574
7.2472
7.2403
6.1842
3.7696
OMe
O
Ph
SC6H4NO2-p
Integral
1.9944
3.0057
6.3944
2.2625
1.0000
3.0558
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

158.7640
148.5922
145.2621
134.7199
130.2252
130.1290
129.9474
129.5307
128.1702
128.1203
127.7250
126.0190
125.6344
124.3273
123.7788
102.6374
100.4969
77.7029
77.2790
76.8552
56.6540
OMe
Ph
SC6H4NO2-p
(ppm)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

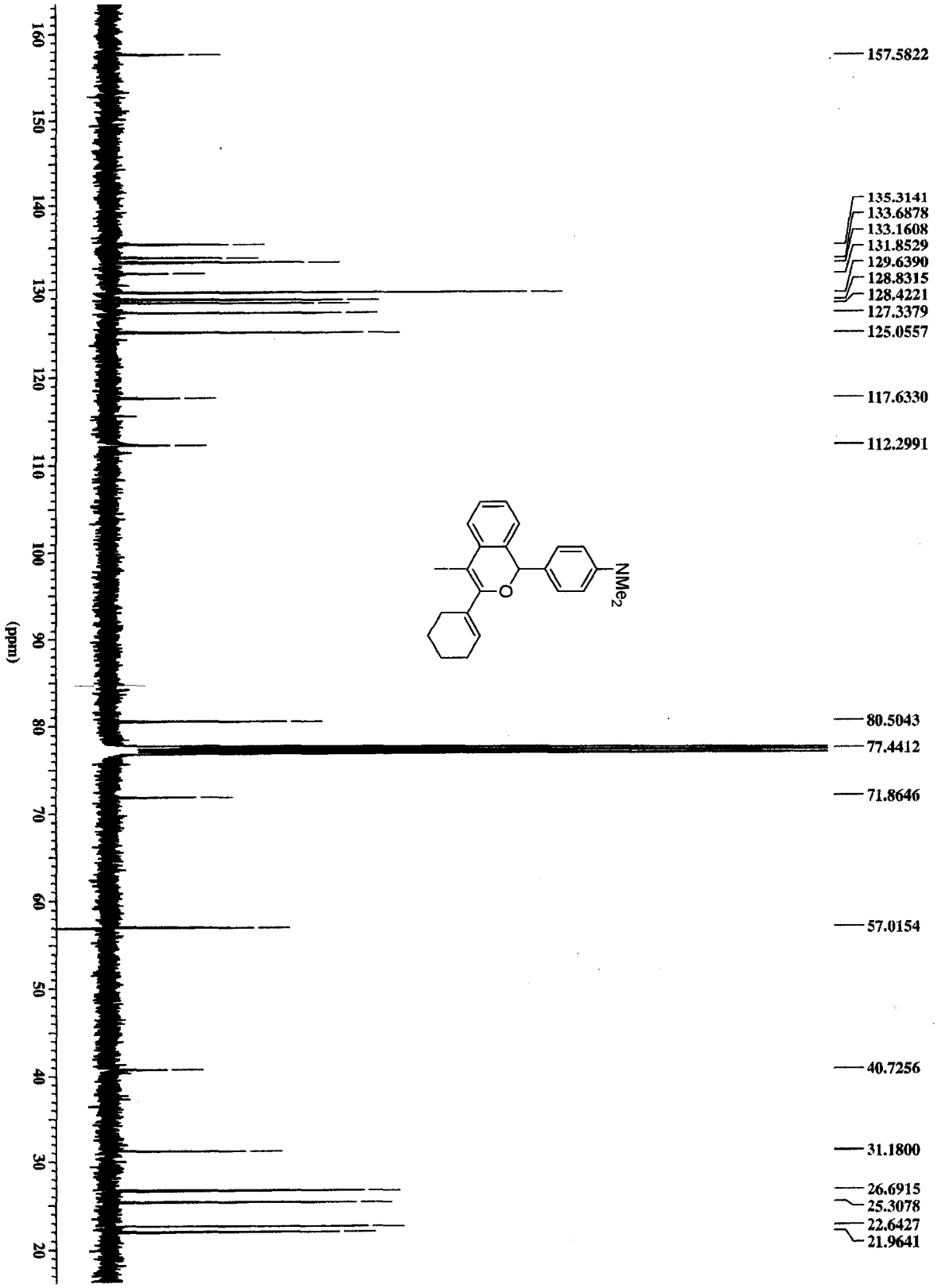
Integral
1.0000
1.0305
1.9528
0.9831
3.0268
0.9599
6.1120
2.1265
2.1251
2.1453
2.9219
(ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
NMe2
Bu-n
O
7.4131
7.3937
7.3136
7.2946
7.2756
7.2580
7.1985
7.1770
7.1246
7.1060
7.0873
6.7342
6.7129
6.6731
6.6546
5.9926
2.9721
2.8037
2.6216
2.6060
2.5866
2.5765
2.5692
2.5577
2.5390
2.5232
1.5054
1.4960
1.4887
1.4805
1.4741
1.4674
1.4631
1.4509
1.3491
1.3331
1.3153
1.2972
1.2793
1.2617
1.2413
0.8816
0.8636
0.8453

148.6393
145.1858
130.0636
129.6997
127.3455
127.2204
126.0452
125.3552
124.2748
122.8532
115.5518
99.9178
77.6838
77.3805
77.0583
63.9074
56.1397
32.6736
30.0654
22.4569
14.0865
(ppm)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
O
Bu-n
NMe2

Integral
1.0000
2.1588
1.1702
1.1680
2.2851
2.2622
3.4106
(ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OMe
O
n-Bu
SC6H4NO2-p
7.2830
7.2785
7.2659
7.2590
7.2549
7.2435
7.2370
7.2248
7.2203
7.2134
7.2049
6.0377
3.6438
2.8913
2.8652
2.8457
2.8396
2.8189
2.7936
2.6654
2.6418
2.6166
2.5954
2.5706
2.1730
1.7334
1.7180
1.6728
1.6671
1.6435
1.6191
1.6052
1.5955
1.5824
1.5694
1.3928
1.3842
1.3692
1.3594
1.3448
1.3334
1.3199
1.3085
1.2963
1.2727
1.2593
0.9520
0.9101
0.8857
0.8613
0.3566
0.0042

148.6313
145.2372
130.0934
129.7123
127.3653
127.1979
126.0297
125.3601
124.2988
122.8884
99.9413
77.6957
77.2719
76.8481
56.1412
32.6812
30.0563
22.4524
14.0613
OMe
n-Bu
SC6H4NO2-p
(ppm)
150
140
130
120
110
100
90
80
70
60
50
40
30
20

7.1790
7.1577
7.1429
7.1239
7.1220
7.1053
6.7157
6.7022
6.6845
6.0157
5.9855
5.9811
5.9772
2.9630
2.1740
2.1228
2.1099
2.0363
2.0310
1.6589
1.6466
1.6303
1.6242
1.6141
1.6065
1.6008
1.5898
1.5747
1.5564
1.2553
0.0009
1.0194
1.0993
3.1595
3.1285
1.0000
1.0147
6.2995
3.0626
1.2192
4.3281
NMe2
O
(ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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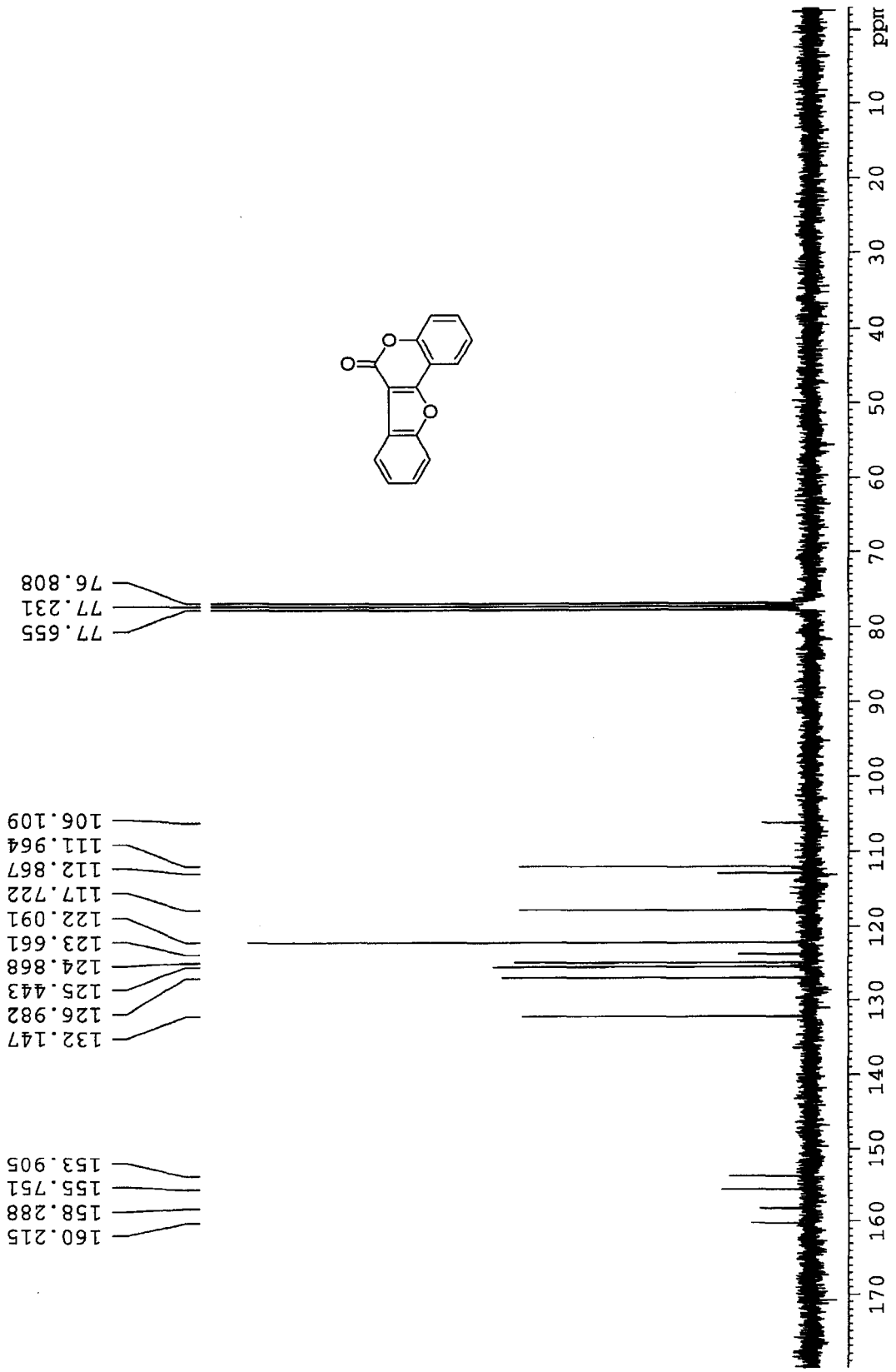
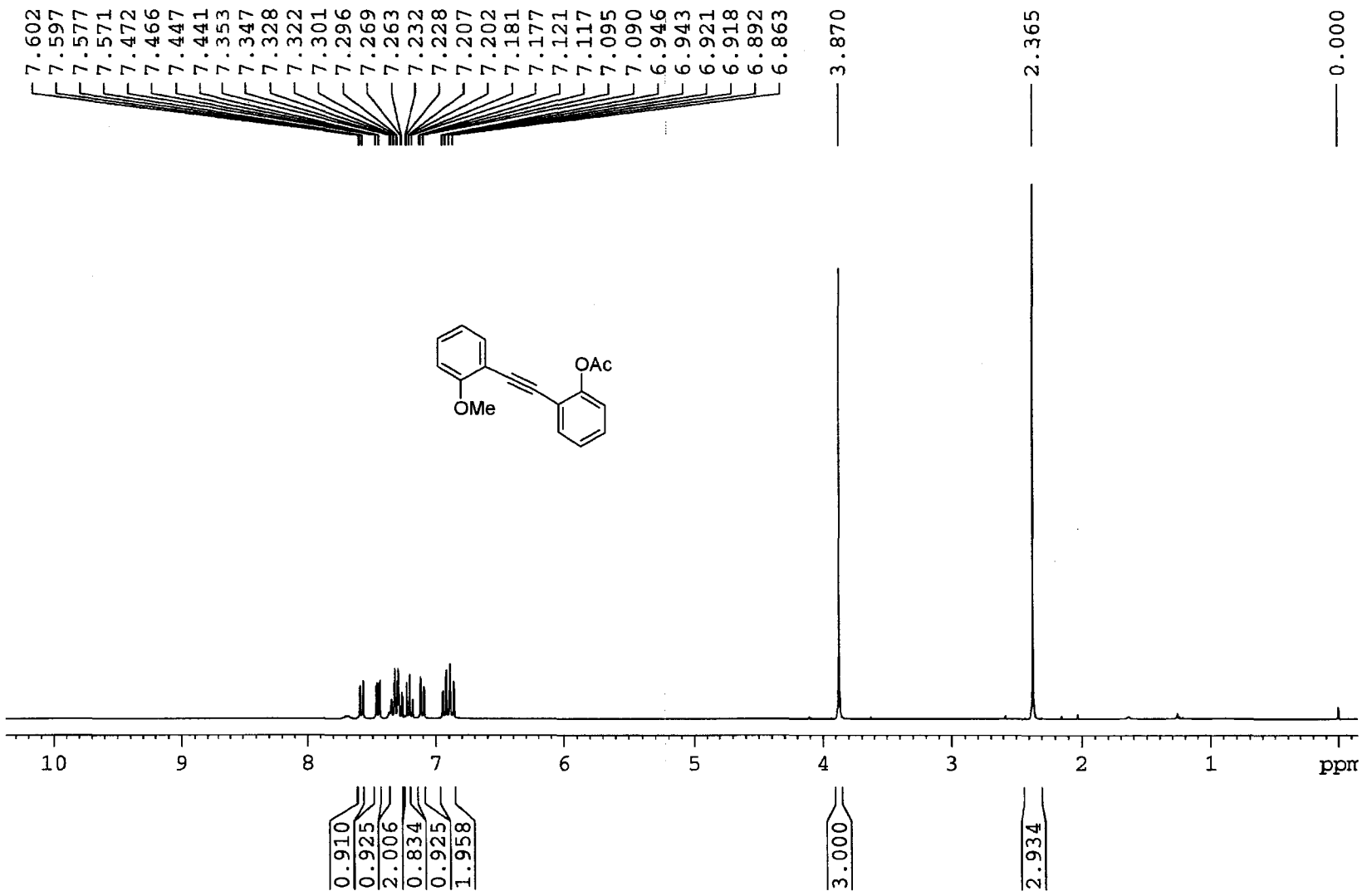
133.6878
133.1608
131.8529
129.6390
128.8315
128.4221
127.3379
125.0557
117.6330
112.2991
80.5043
77.4412
71.8646
57.0154
40.7256
31.1800
26.6915
25.3078
22.6427
21.9641
NMe2
O
(ppm)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

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


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
160.215
158.288
155.751
153.905
132.147
126.982
125.443
124.868
123.661
122.091
117.722
112.867
111.964
106.109
77.655
77.231
76.808
O
O
O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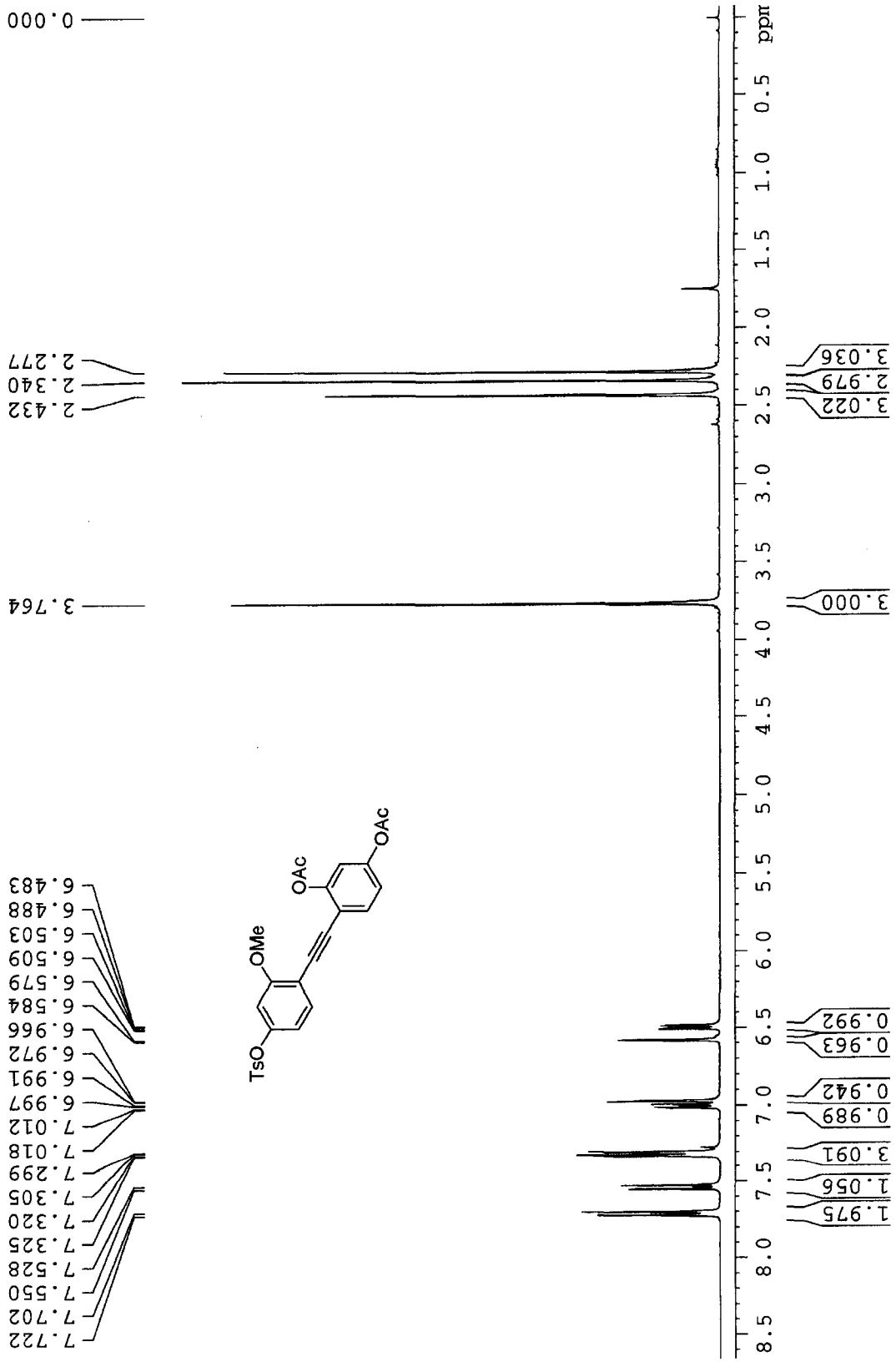
7.597
7.577
7.571
7.472
7.466
7.447
7.441
7.353
7.347
7.328
7.322
7.301
7.296
7.269
7.263
7.232
7.228
7.207
7.202
7.181
7.177
7.121
7.117
7.095
7.090
6.946
6.943
6.921
6.918
6.892
6.863
3.870
2.365
0.000
OAc
OMe
10
9
8
7
6
5
4
3
2
1
ppm
0.910
0.925
2.006
0.834
0.925
1.958
3.000
2.934

169.108
160.080
151.604
133.685
133.081
130.203
129.396
125.998
122.353
120.627
117.956
112.339
110.895
90.897
88.334
77.652
77.228
76.803
55.835
20.973
OMe
OAc
ppm

7.835
7.829
7.809
7.803
7.530
7.525
7.505
7.504
7.500
7.498
7.482
7.478
7.473
7.465
7.459
7.453
7.452
7.448
7.443
7.441
7.393
7.389
7.374
7.368
7.364
7.352
7.349
7.346
7.342
7.339
7.327
7.323
7.261
7.257
7.234
7.230
2.206
0.000
0.919
2.890
3.101
1.075
2.979
OAc
O
ppm
11
10
9
8
7
6
5
4
3
2
1

169.373
154.618
152.299
148.769
131.945
131.717
131.158
126.061
126.018
123.758
123.692
123.274
122.099
111.355
77.653
77.229
76.805
65.368
21.264
OAc
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
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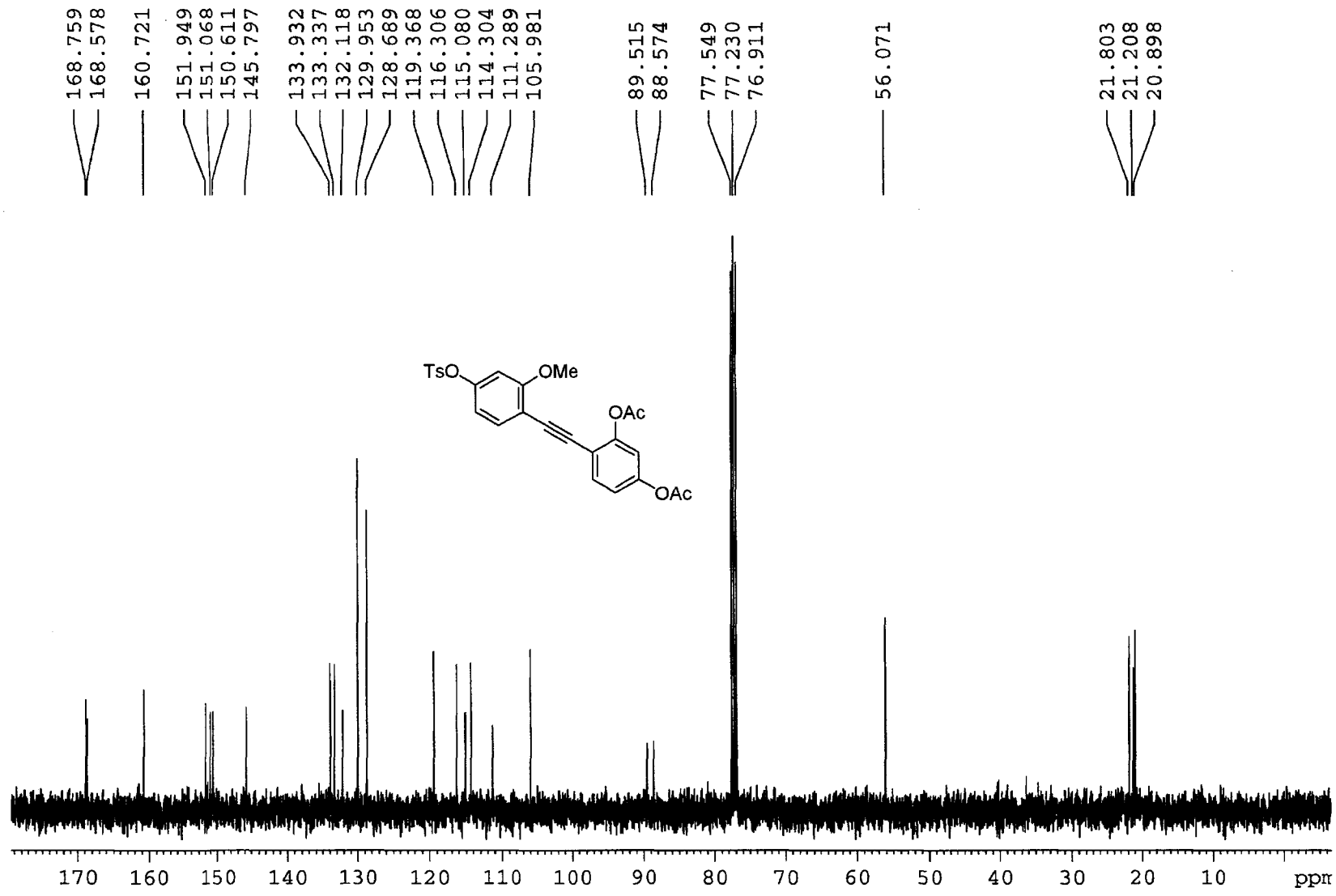
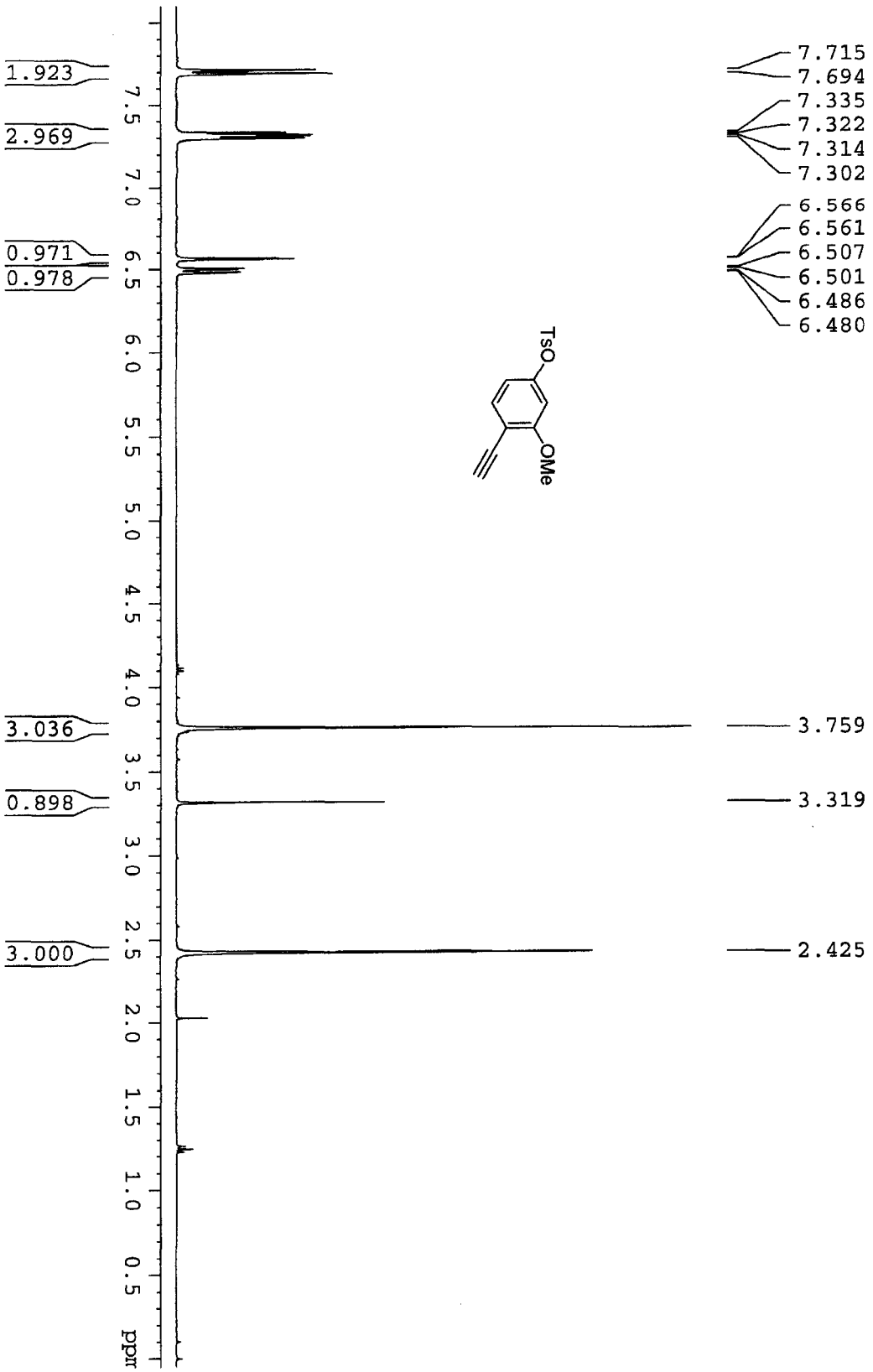
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.000
2.277
2.340
2.432
3.764
7.722
7.702
7.550
7.528
7.325
7.320
7.305
7.299
7.018
7.012
6.997
6.991
6.972
6.966
6.584
6.579
6.509
6.503
6.488
6.483
TsO
OMe
OAc
OAc
1.975
1.056
3.091
0.989
0.942
0.963
0.992
3.000
3.022
2.979
3.036


168.759
168.578
160.721
151.949
151.068
150.611
145.797
133.932
133.337
132.118
129.953
128.689
119.368
116.306
115.080
114.304
111.289
105.981
89.515
88.574
77.549
77.230
76.911
56.071
21.803
21.208
20.898
TsO
OMe
OAc
OAc
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

7.790
7.762
7.739
7.711
7.361
7.333
7.309
7.264
7.176
7.168
7.147
7.140
7.122
7.115
7.109
7.102
7.007
7.000
6.979
6.972
2.451
2.329
2.180
0.000
1.022
1.995
3.124
2.832
0.998
3.114
3.107
3.000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
TsO
O
I
OAc
OAc

168.826
153.729
153.335
152.447
149.165
148.071
145.798
132.270
132.231
130.677
130.077
128.780
122.404
120.237
119.413
118.888
117.419
106.141
77.548
77.230
76.913
64.916
21.941
21.358
21.212
TsO
O
I
OAc
OAc
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10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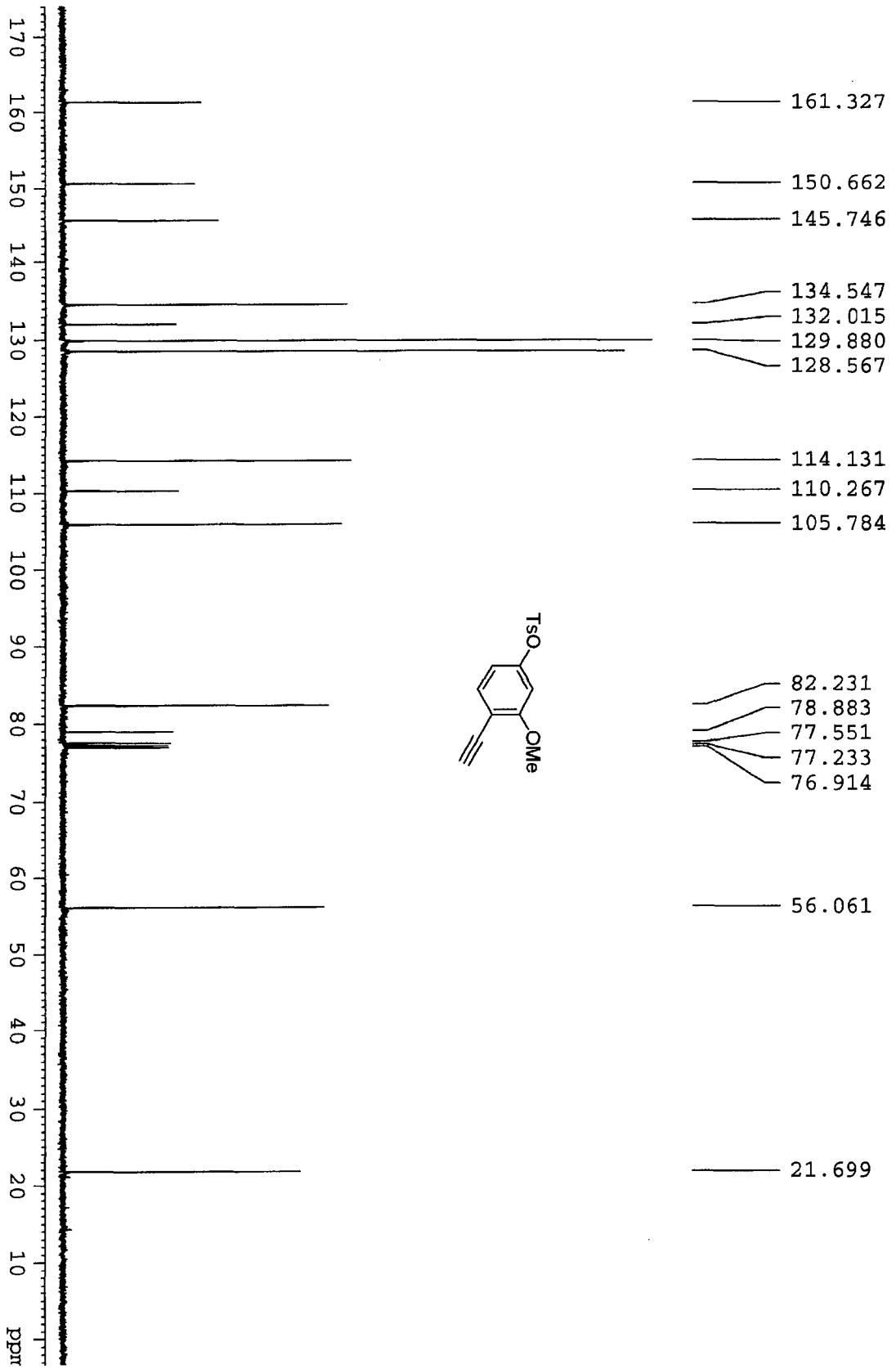
2.969
0.971
0.978
3.036
0.898
3.000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
TsO
OMe
7.715
7.694
7.335
7.322
7.314
7.302
6.566
6.561
6.507
6.501
6.486
6.480
3.759
3.319
2.425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150.662
145.746
134.547
132.015
129.880
128.567
114.131
110.267
105.784
82.231
78.883
77.551
77.233
76.914
56.061
21.699
TsO
OMe
ppm
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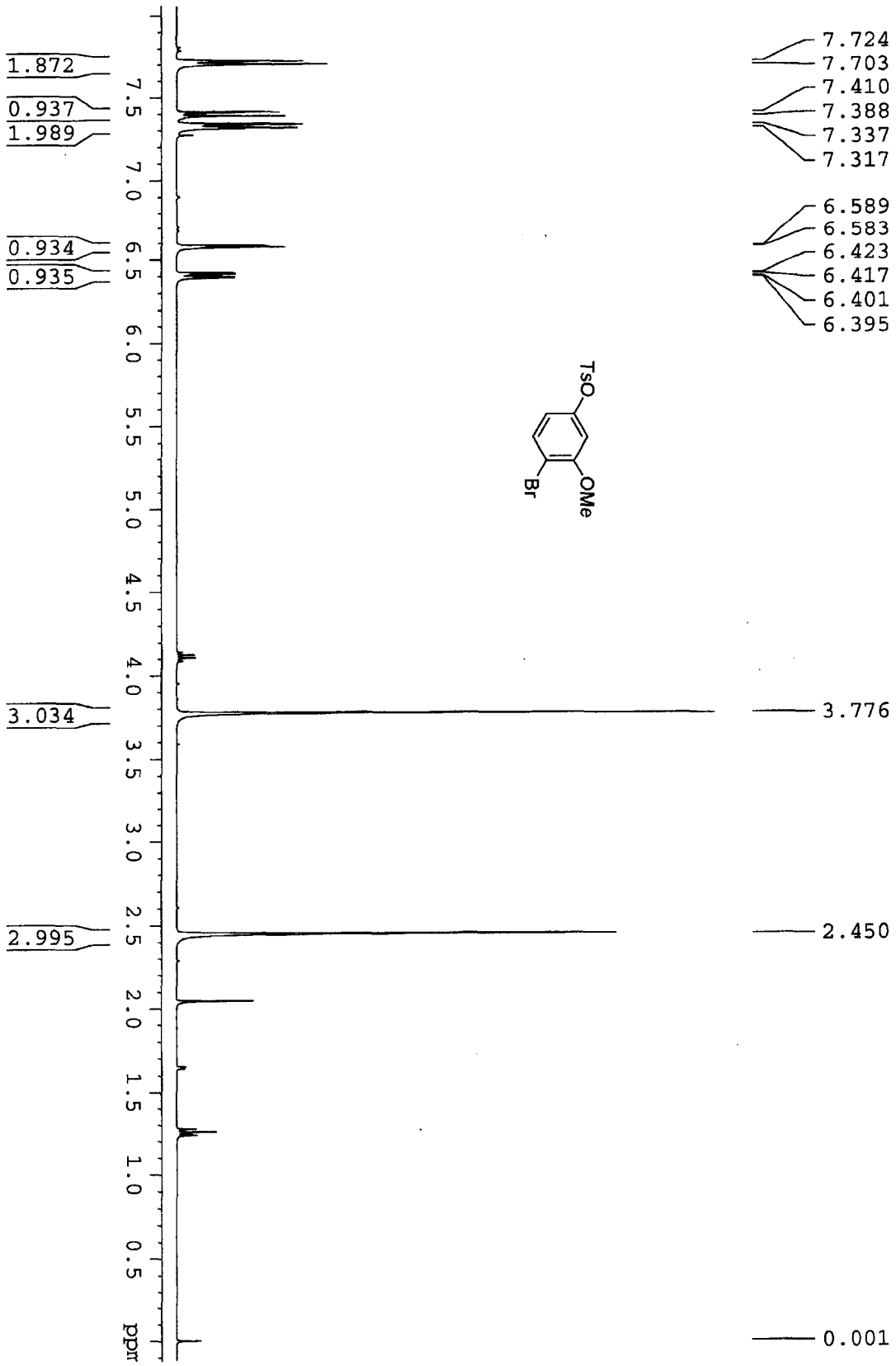
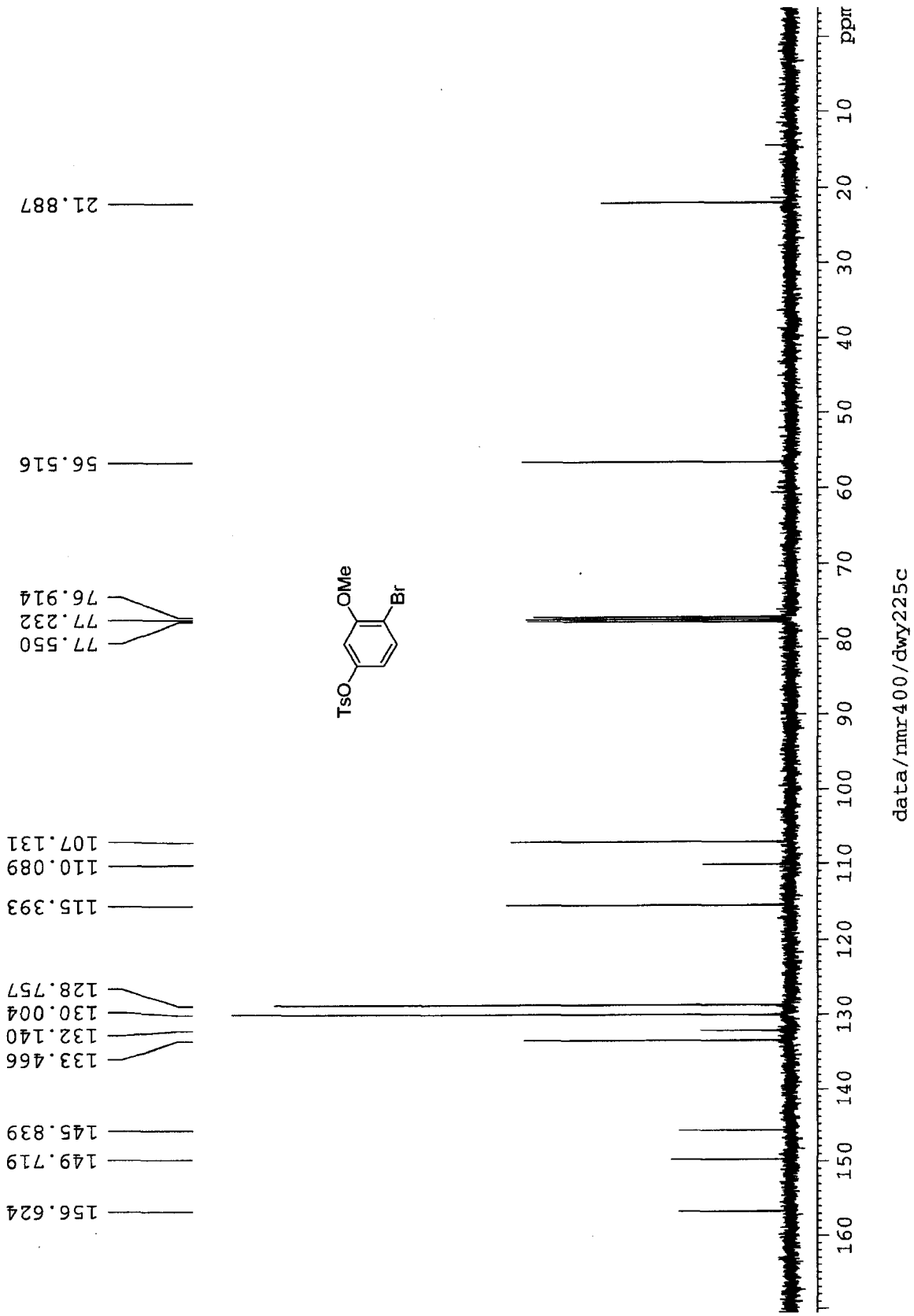
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


1.872
0.937
1.989
0.934
0.935
3.034
2.995
7.724
7.703
7.410
7.388
7.337
7.317
6.589
6.583
6.423
6.417
6.401
6.395
3.776
2.450
0.001
TsO
OMe
Br
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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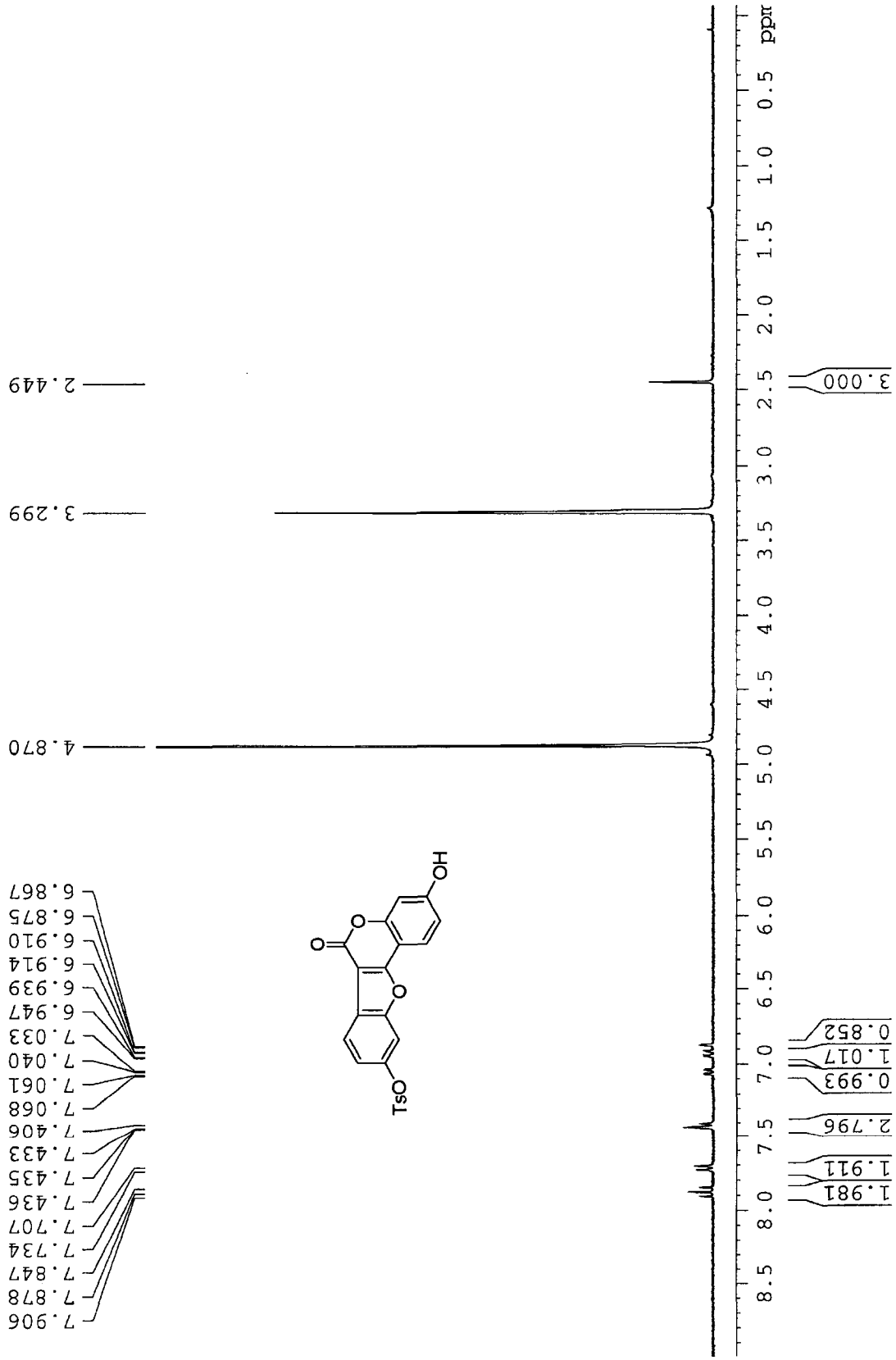
149.719
145.839
133.466
132.140
130.004
128.757
115.393
110.089
107.131
77.550
77.232
76.914
56.516
21.887
TsO
OMe
Br
ppm
data/nmr400/dwy225c

ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
7.877
7.876
7.848
7.847
7.764
7.763
7.736
7.734
7.098
7.097
7.091
7.090
6.945
6.939
6.938
6.932
6.917
6.910
6.903
6.878
6.877
6.870
6.869
4.870
3.298
1.052
1.074
0.934
0.859
1.029
0.982
O
O
O
HO
OH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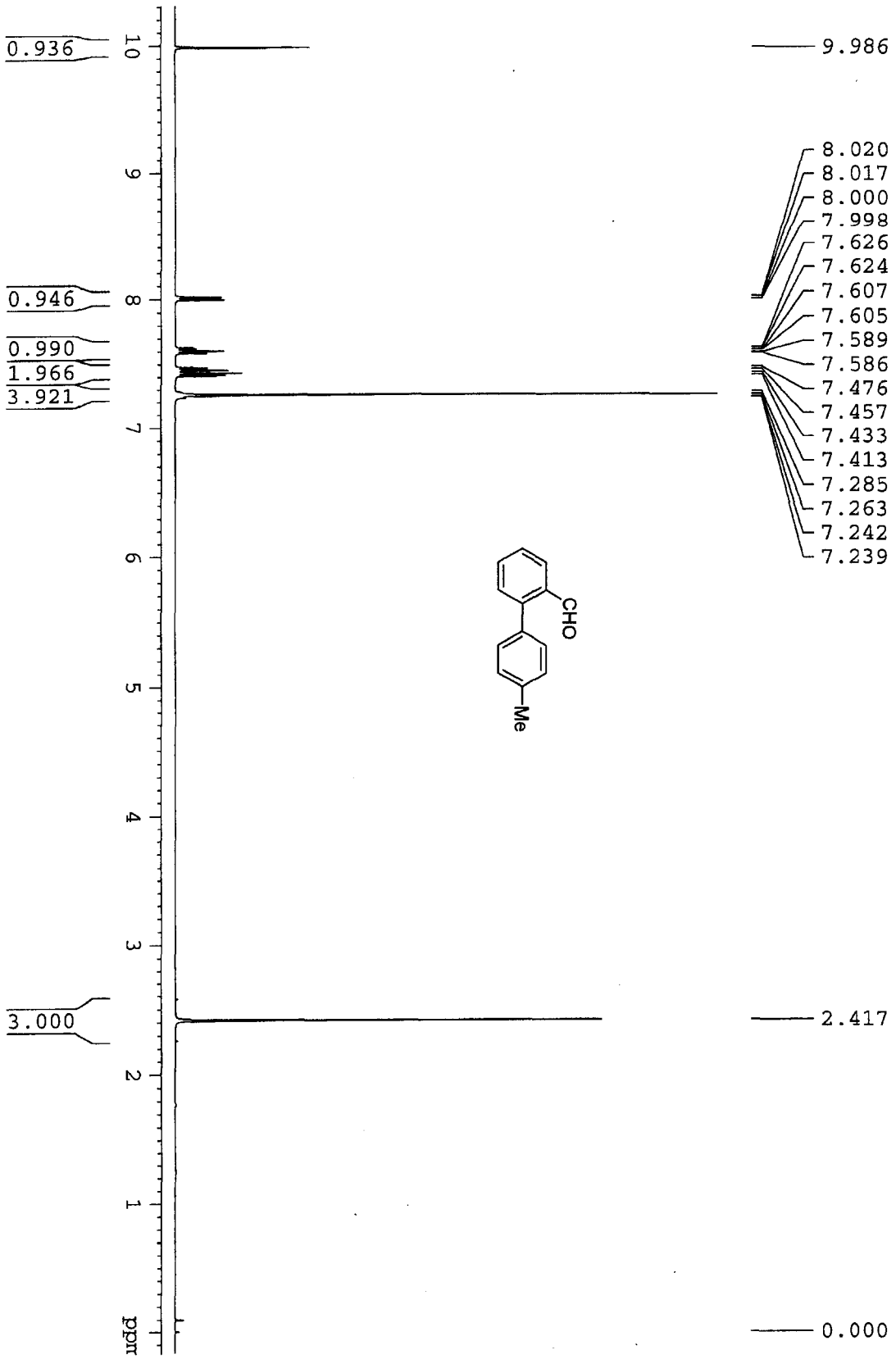
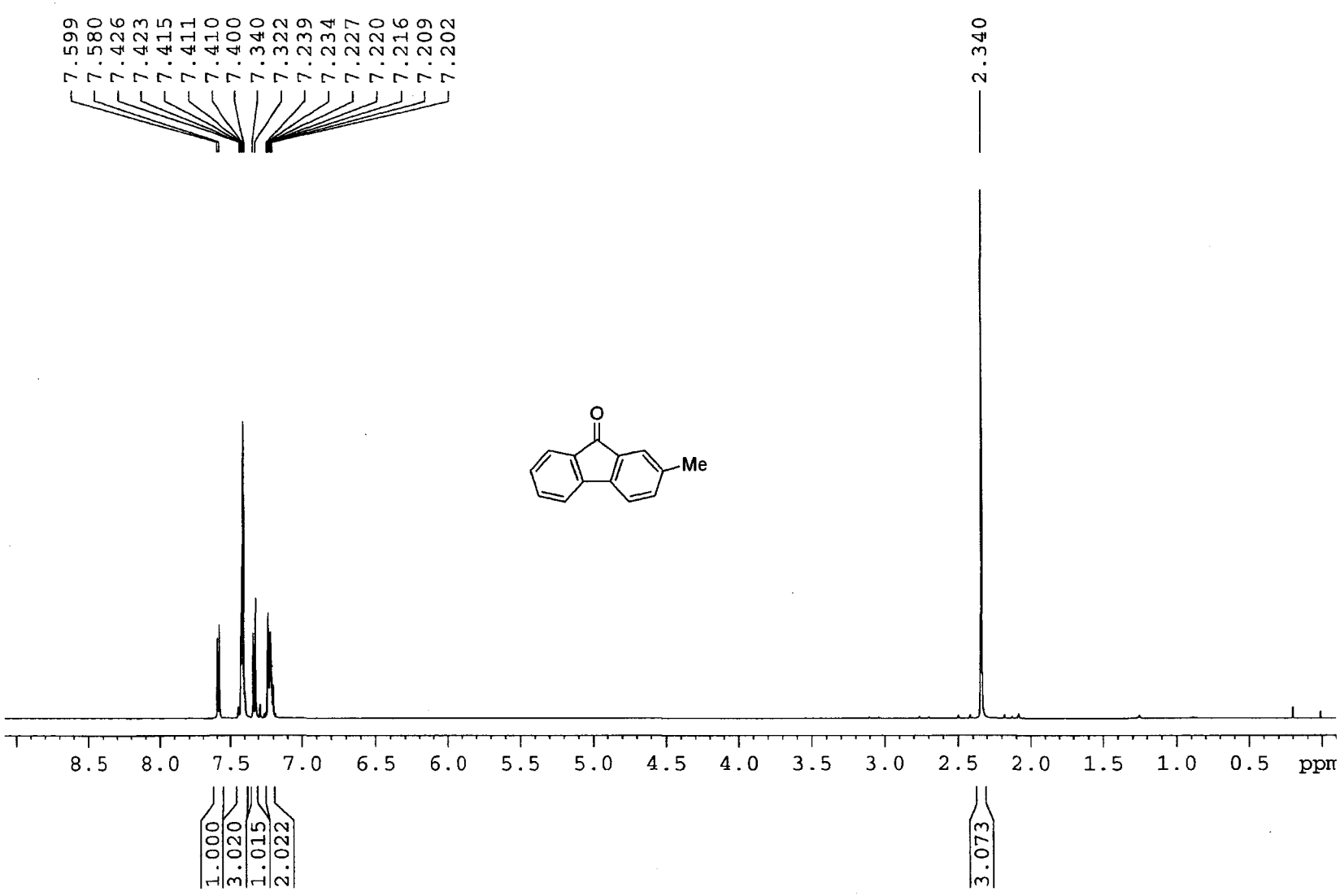
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
3.000
0.852
1.017
0.993
2.796
1.911
1.981
6.867
6.875
6.910
6.914
6.939
6.947
7.033
7.040
7.061
7.068
7.406
7.433
7.435
7.436
7.707
7.734
7.847
7.878
7.906
4.870
3.299
2.449
TsO
O
O
O
HO

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


0.936
0.946
0.990
1.966
3.921
3.000
10
9
8
7
6
5
4
3
2
1
ppm
9.986
8.020
8.017
8.000
7.998
7.626
7.624
7.607
7.605
7.589
7.586
7.476
7.457
7.433
7.413
7.285
7.263
7.242
7.239
2.417
0.000
CHO
Me

192.718
146.124
138.171
134.912
133.860
133.666
130.922
130.170
129.296
127.672
77.544
77.226
76.908
21.334
CHO
Me
ppm



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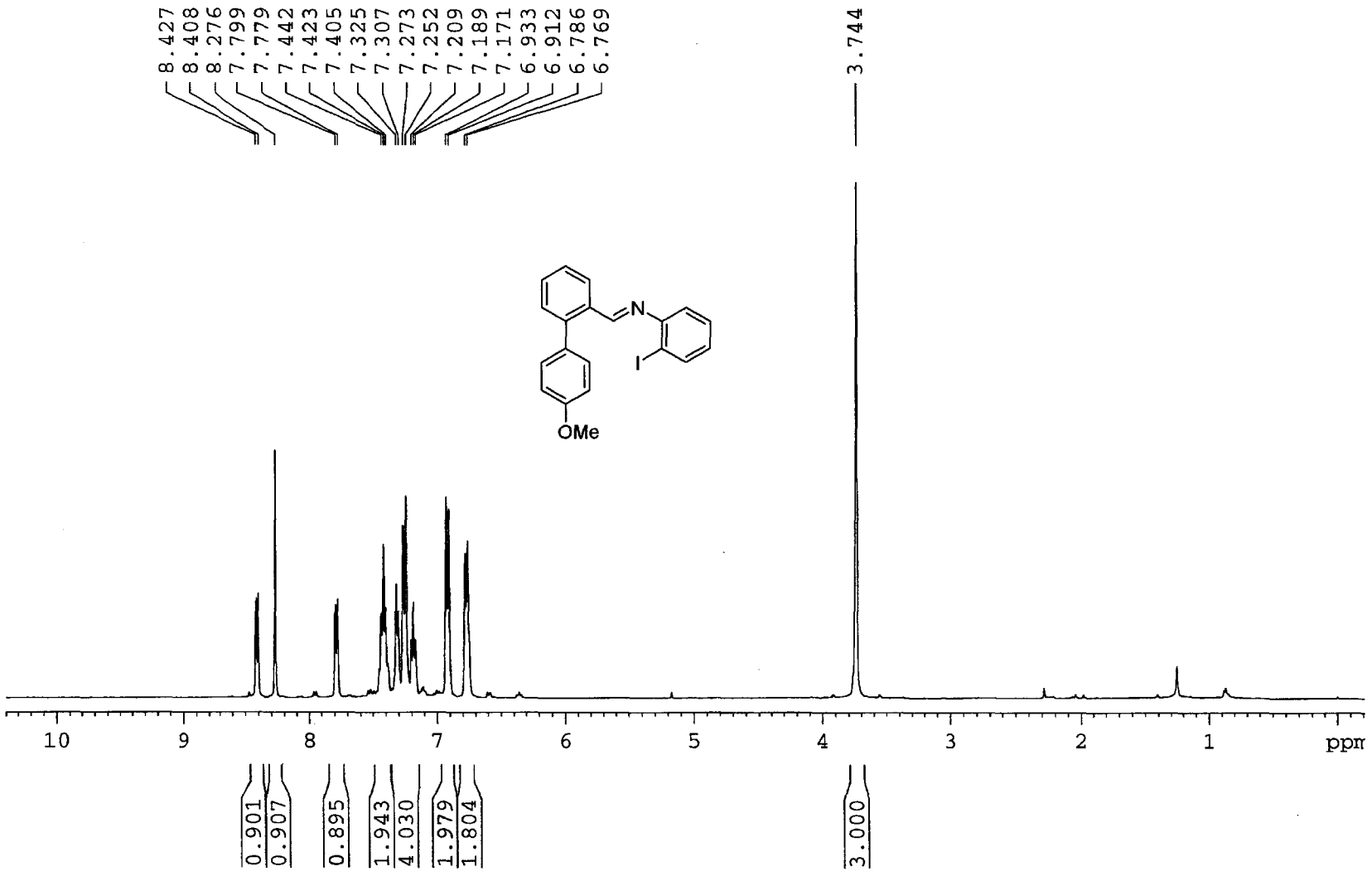
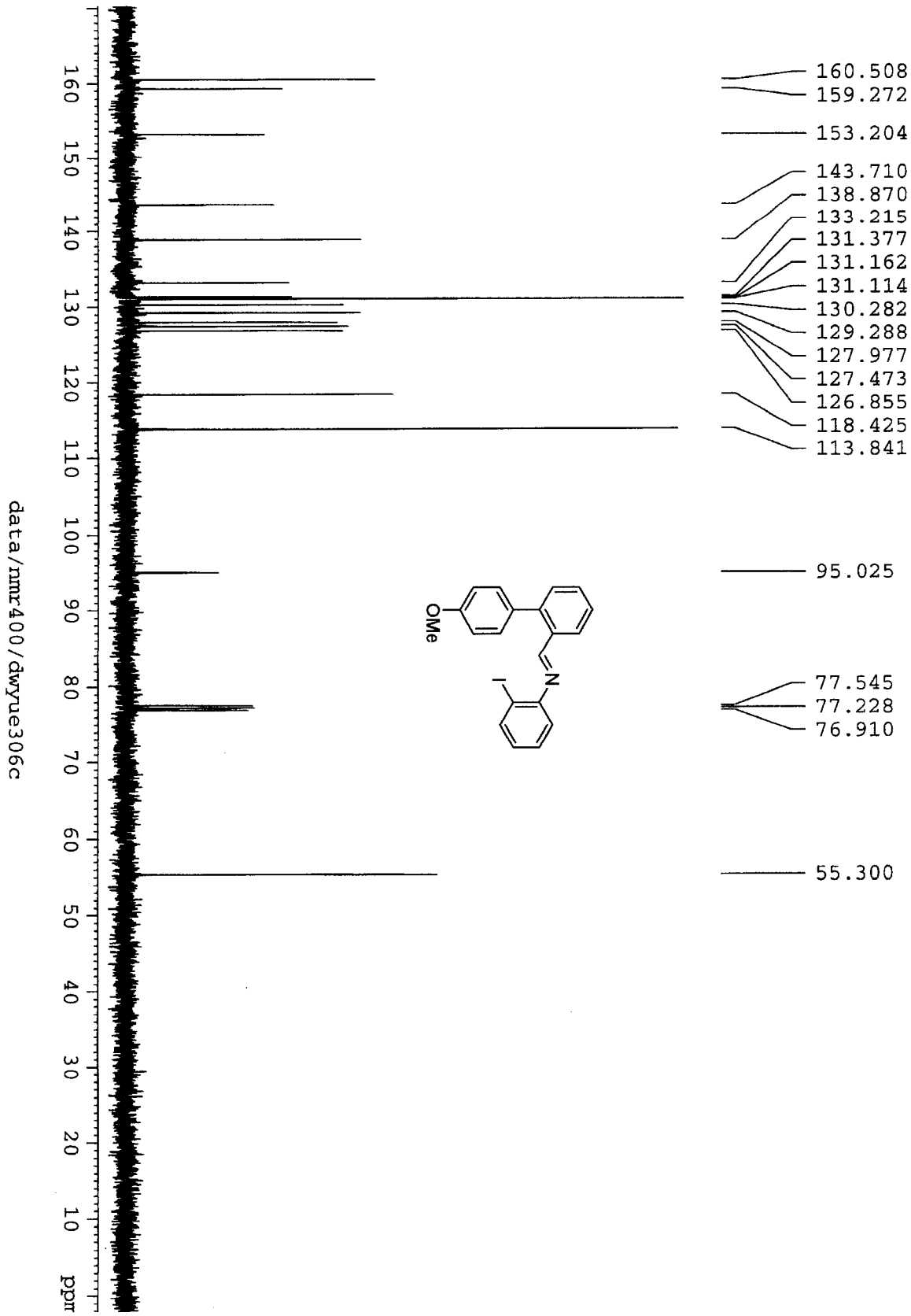


data/nmr400/dwyue306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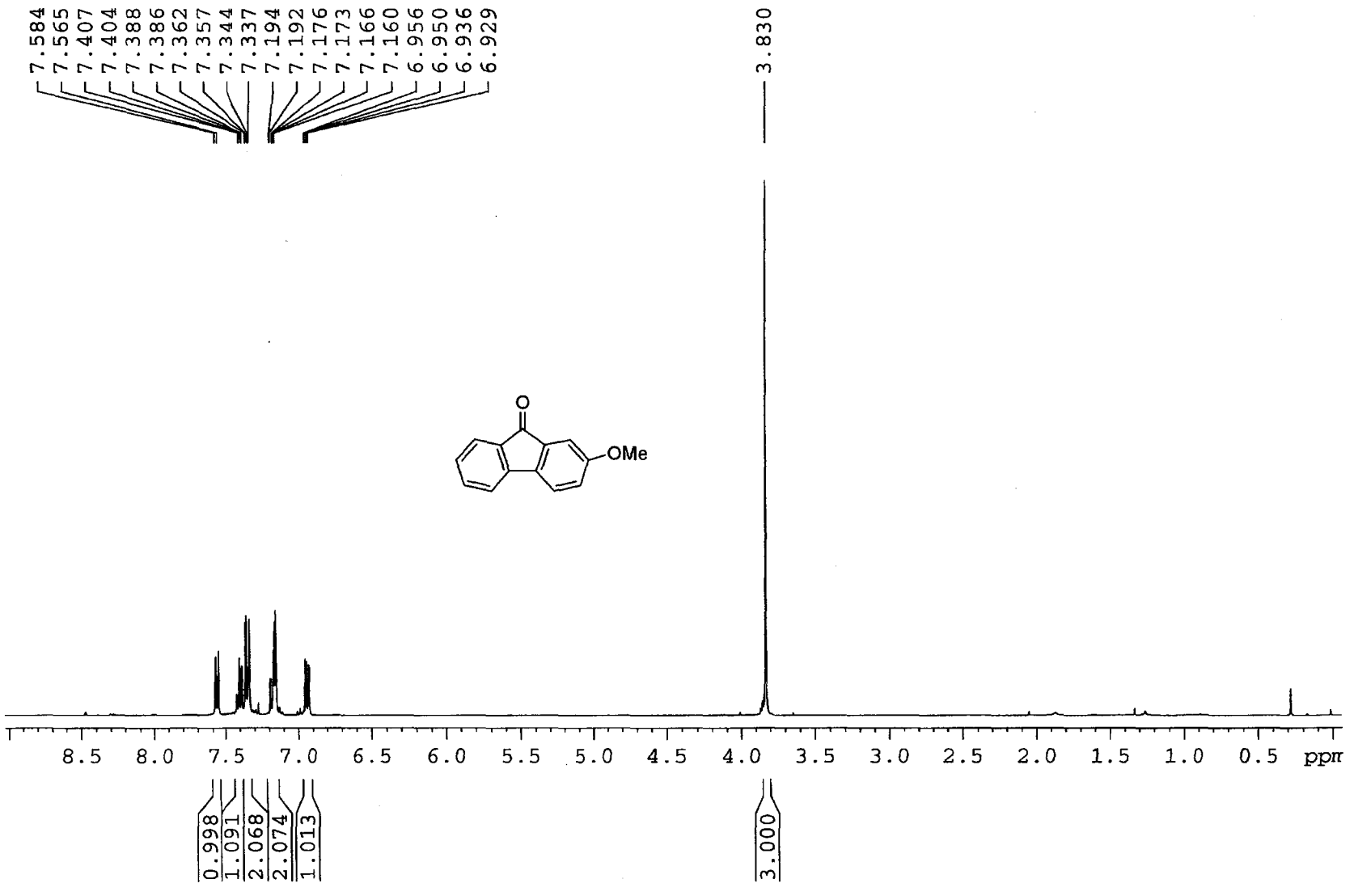
159.272
153.204
143.710
138.870
133.215
131.377
131.162
131.114
130.282
129.288
127.977
127.473
126.855
118.425
113.841
95.025
77.545
77.228
76.910
55.300
OMe
N
ppm
data/nmr400/dwyue306c

0.775
0.869
0.961
1.943
1.957
1.976
3.000
10
9
8
7
6
5
4
3
2
1
ppm
CHO
OMe
9.994
9.992
8.016
8.015
8.012
7.991
7.989
7.986
7.614
7.612
7.609
7.589
7.587
7.585
7.479
7.454
7.452
7.442
7.439
7.437
7.435
7.433
7.416
7.414
7.412
7.318
7.311
7.296
7.290
7.289
7.015
6.986
3.866
0.000

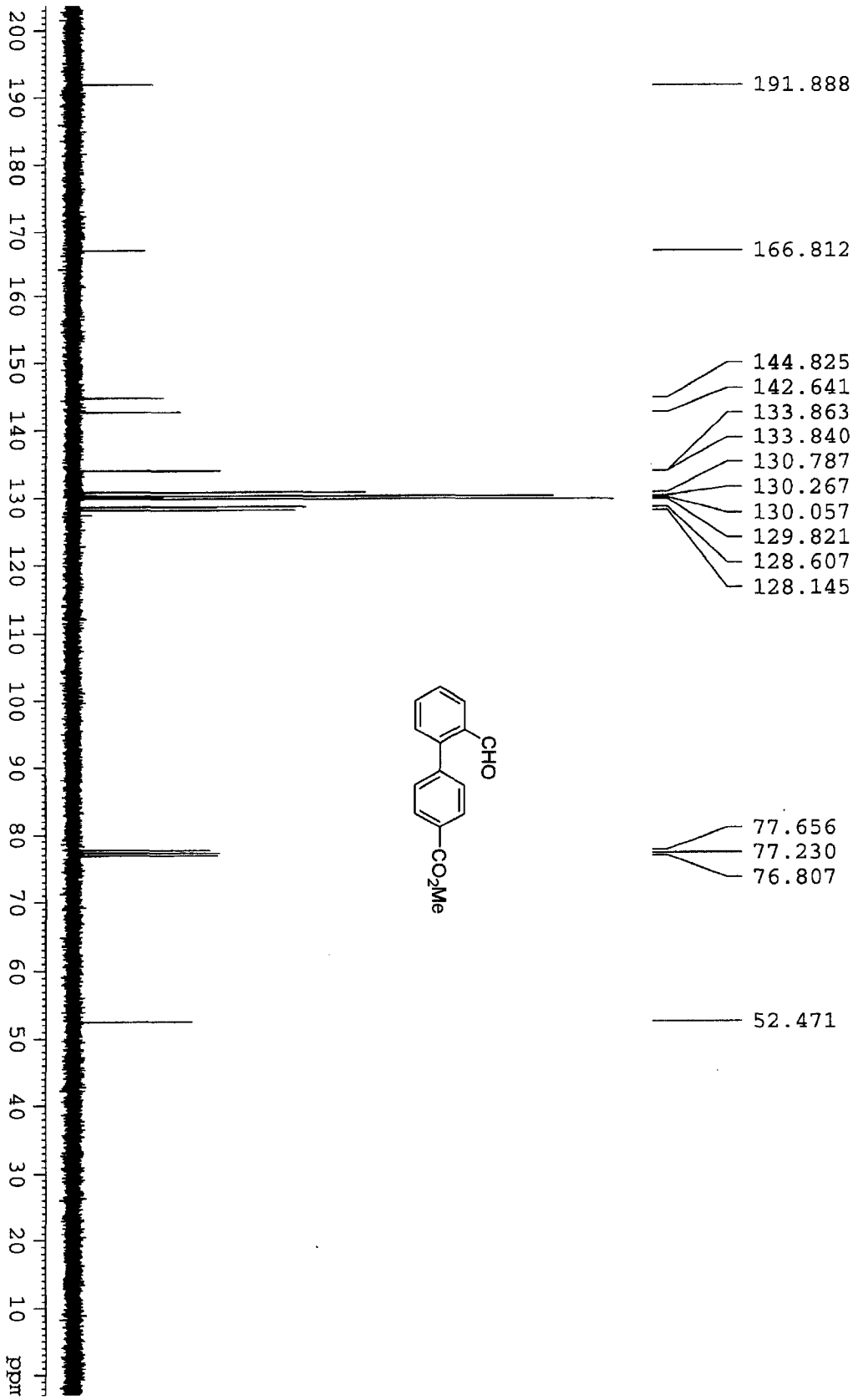
192.806
159.884
145.827
133.946
133.693
131.473
130.960
130.195
127.784
127.544
114.118
77.653
77.229
76.803
55.561
CHO
OMe
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



data/nmr400/dwyue307

194.038
160.922
144.990
137.076
135.970
134.998
134.381
127.984
124.419
121.466
120.332
119.706
109.501
77.547
77.229
76.911
55.818
O
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
data/nmr400/dwyue307c

9.964
9.961
8.167
8.161
8.160
8.157
8.155
8.139
8.134
8.133
8.128
8.064
8.062
8.059
8.057
8.038
8.037
8.033
8.032
7.674
7.669
7.649
7.644
7.544
7.541
7.540
7.482
7.480
7.477
7.475
7.464
7.462
7.460
7.458
7.455
7.453
7.448
7.439
7.437
7.434
7.433
7.272
3.965
0.001
0.760
1.879
0.869
1.006
0.945
2.849
3.000
CHO
CO2Me
ppm
12
11
10
9
8
7
6
5
4
3
2
1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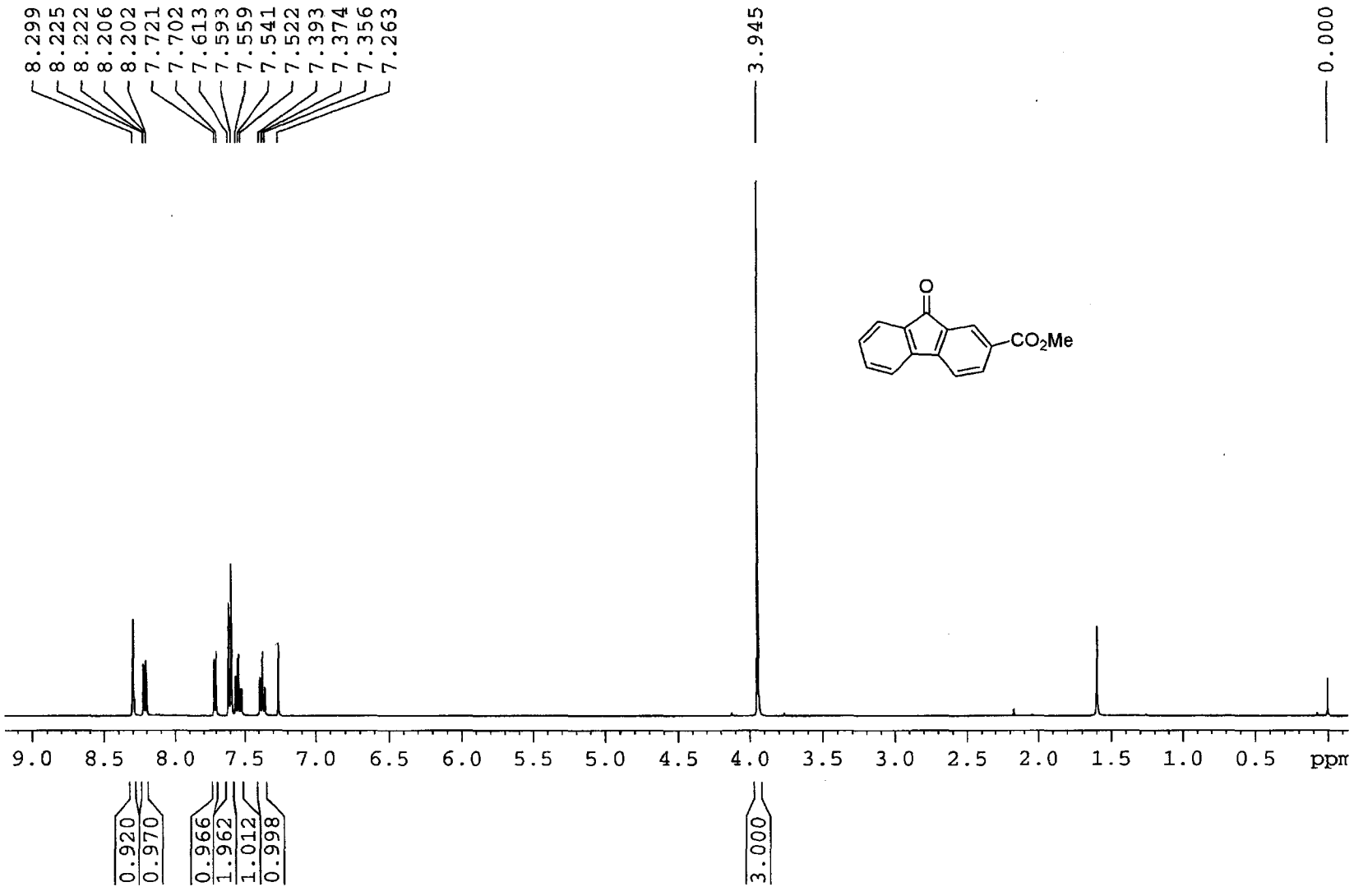
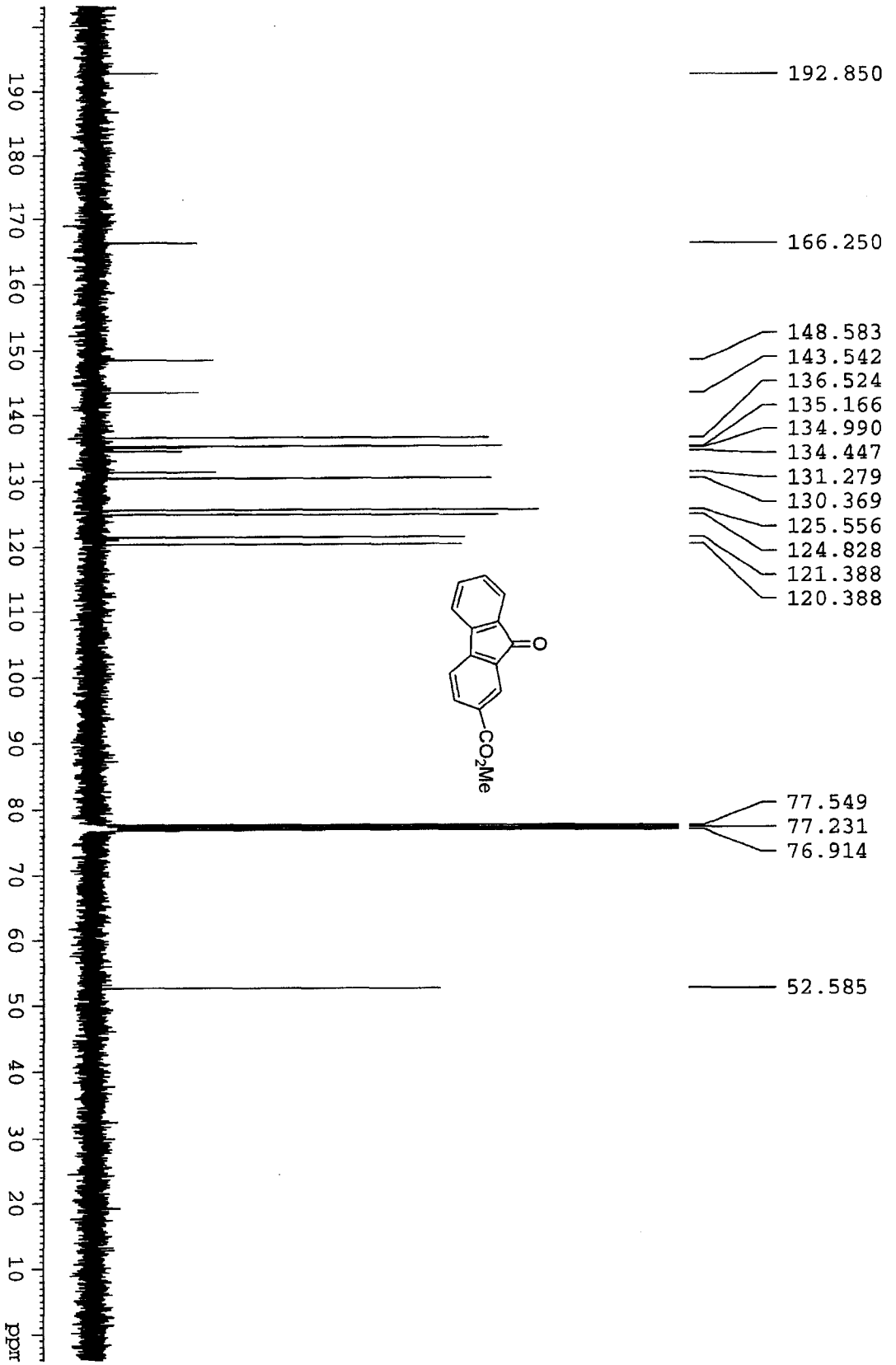
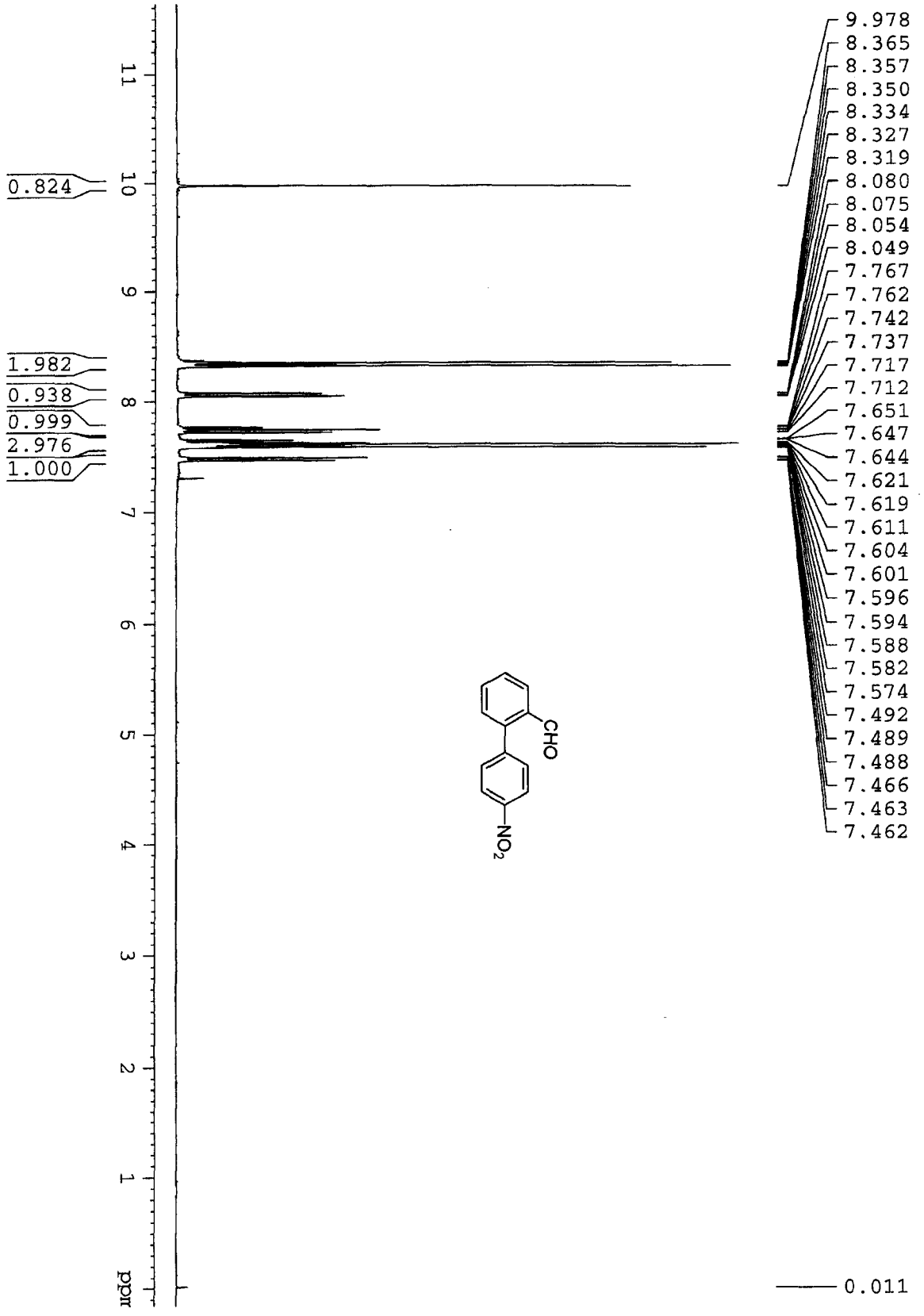
144.825
142.641
133.863
133.840
130.787
130.267
130.057
129.821
128.607
128.145
77.656
77.230
76.807
52.471
CHO
CO2Me
ppm


8.299
8.225
8.222
8.206
8.202
7.721
7.702
7.613
7.593
7.559
7.541
7.522
7.393
7.374
7.356
7.263
3.945
0.000
O
CO2Me
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.920
0.970
0.966
1.962
1.012
0.998
3.000


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
192.850
166.250
148.583
143.542
136.524
135.166
134.990
134.447
131.279
130.369
125.556
124.828
121.388
120.388
O
CO2Me
77.549
77.231
76.914
52.585


9.978
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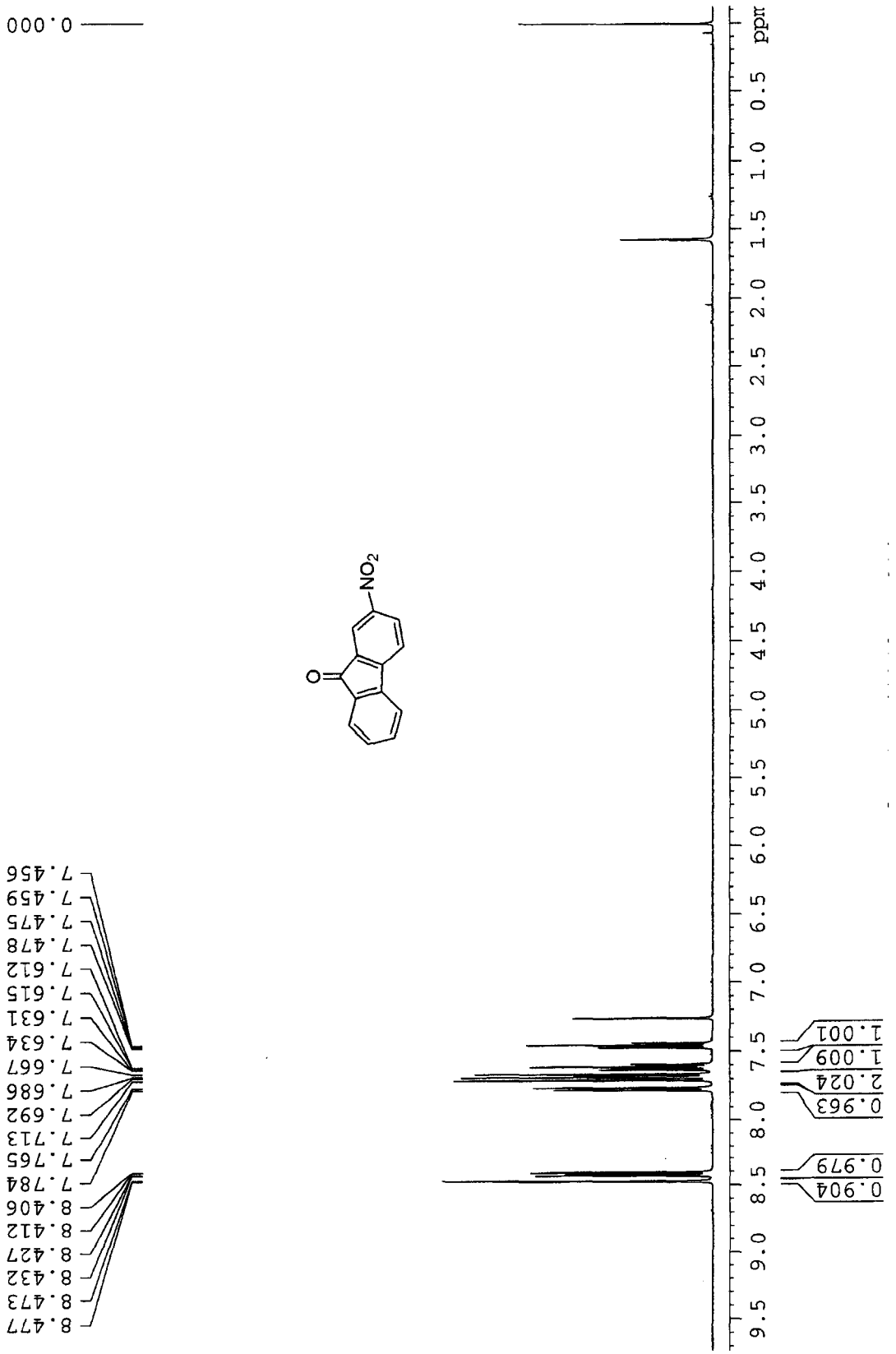
8.357
8.350
8.334
8.327
8.319
8.080
8.075
8.054
8.049
7.767
7.762
7.742
7.737
7.717
7.712
7.651
7.647
7.644
7.621
7.619
7.611
7.604
7.601
7.596
7.594
7.588
7.582
7.574
7.492
7.489
7.488
7.466
7.463
7.462
0.011
0.824
1.982
0.938
0.999
2.976
1.000
CHO
NO2
ppm
11
10
9
8
7
6
5
4
3
2
1

191.268
147.876
144.992
143.159
134.086
133.810
131.010
130.813
129.312
129.072
123.808
77.551
77.233
76.915
CHO
NO2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.000
O
NO2
8.477
8.473
8.432
8.427
8.412
8.406
7.784
7.765
7.713
7.692
7.686
7.667
7.634
7.631
7.615
7.612
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7.475
7.459
7.456
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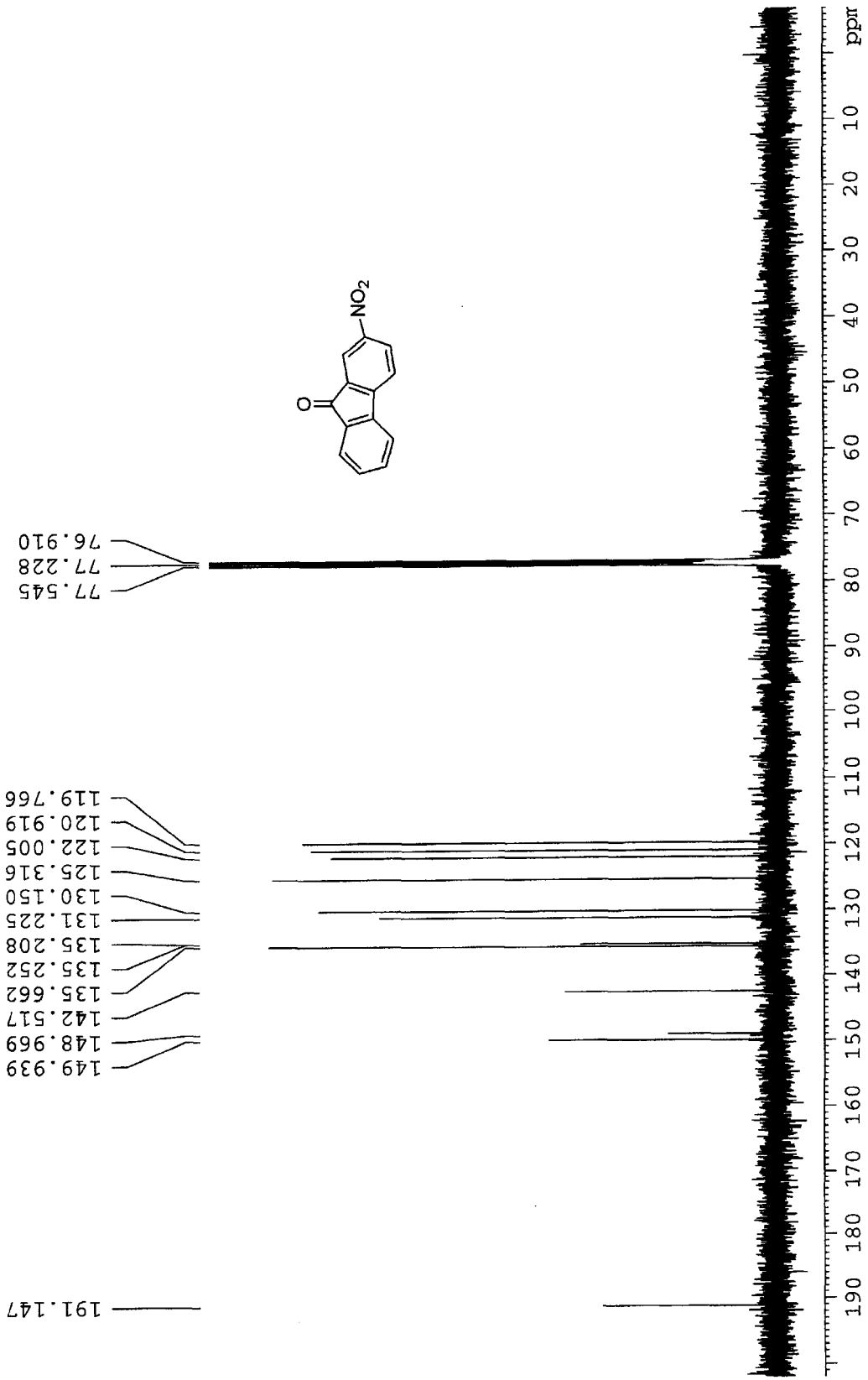
0.979
0.963
2.024
1.009
1.001


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
O
NO2
191.147
149.939
148.969
142.517
135.662
135.252
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131.225
130.150
125.316
122.005
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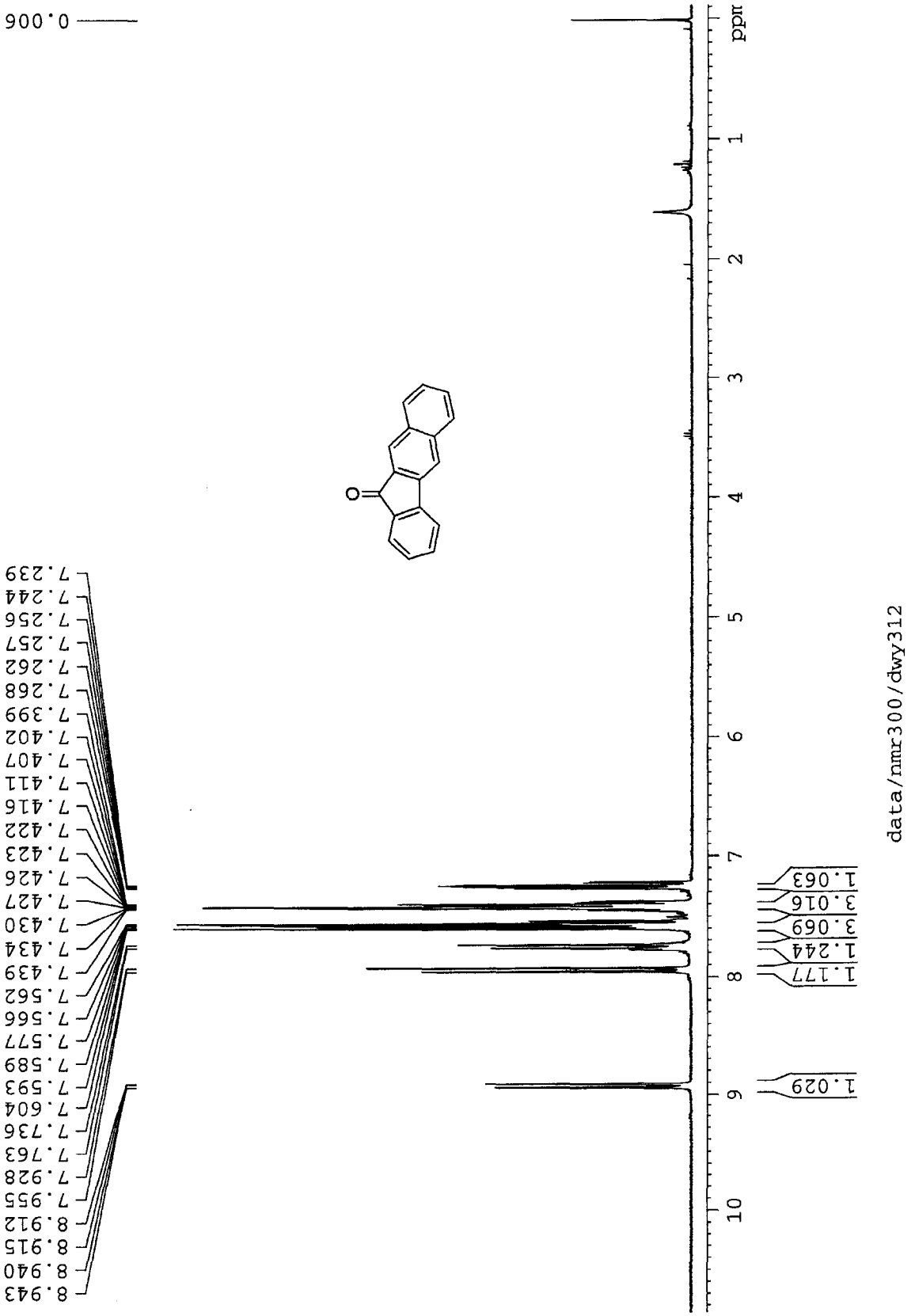
77.228
76.910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8.940
8.915
8.912
7.955
7.928
7.763
7.736
7.604
7.593
7.589
7.577
7.566
7.562
7.439
7.434
7.430
7.427
7.426
7.423
7.422
7.416
7.411
7.407
7.402
7.399
7.268
7.262
7.257
7.256
7.244
7.239
O
ppm
10
9
8
7
6
5
4
3
2
1
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1.244
3.069
3.016
1.063
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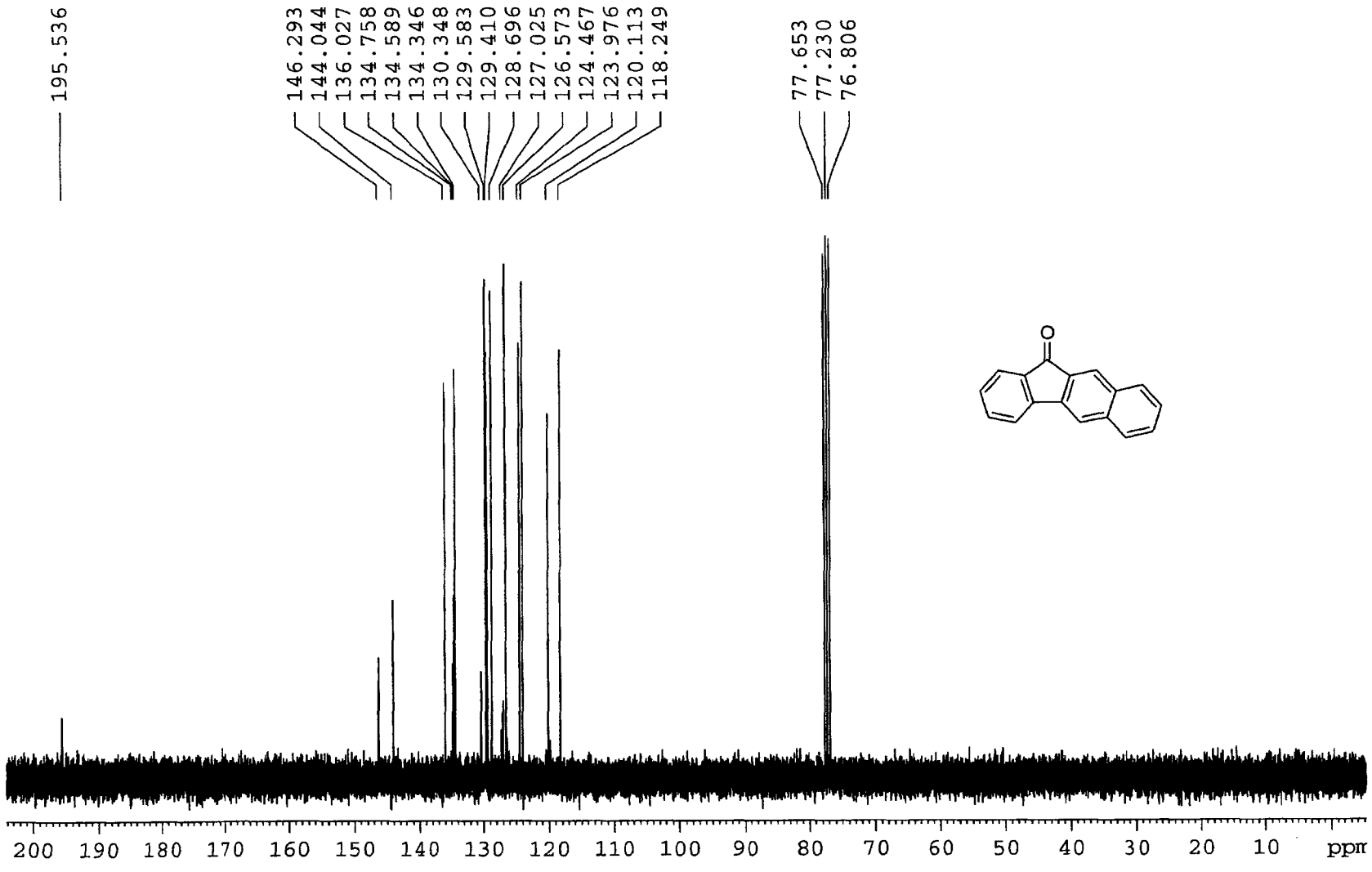
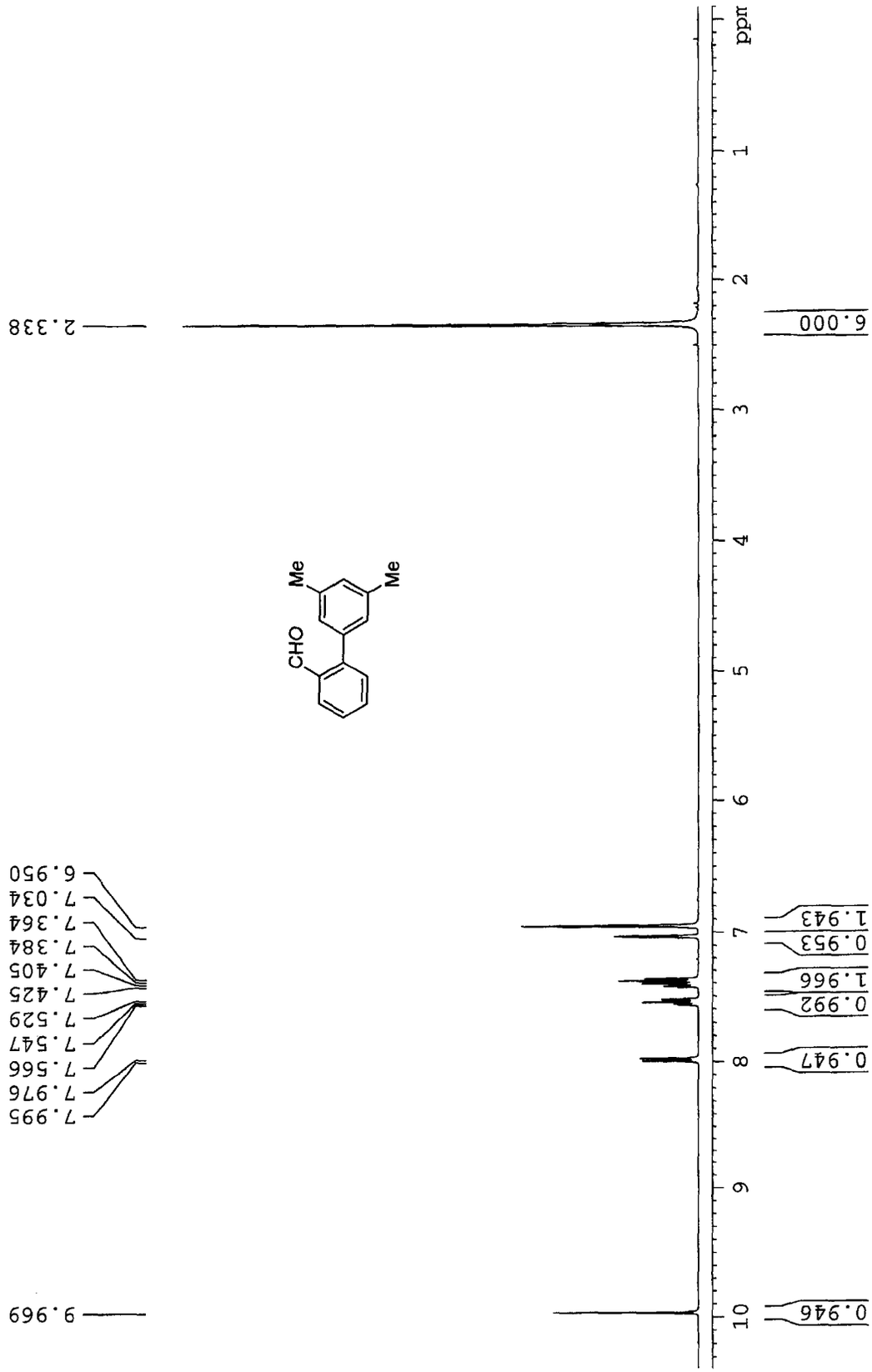
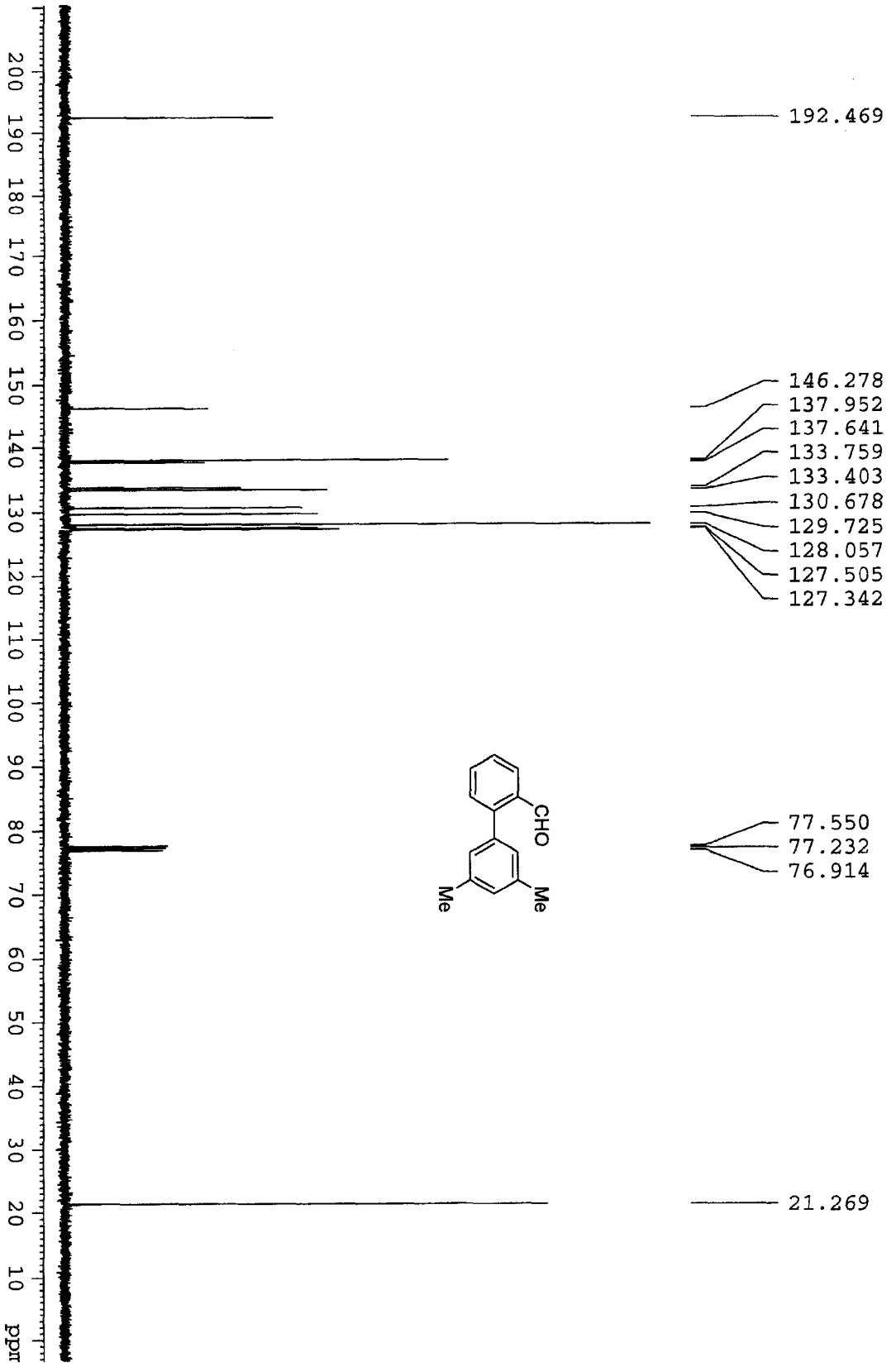


data/nmr300/dwy312c


ppm
10
9
8
7
6
5
4
3
2
1
0.946
0.947
0.992
1.966
0.953
1.943
6.000
9.969
7.995
7.976
7.566
7.547
7.529
7.425
7.405
7.384
7.364
7.034
6.950
2.338
CHO
Me
Me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146.278
137.952
137.641
133.759
133.403
130.678
129.725
128.057
127.505
127.342
77.550
77.232
76.914
21.269
CHO
Me
Me
ppm
200
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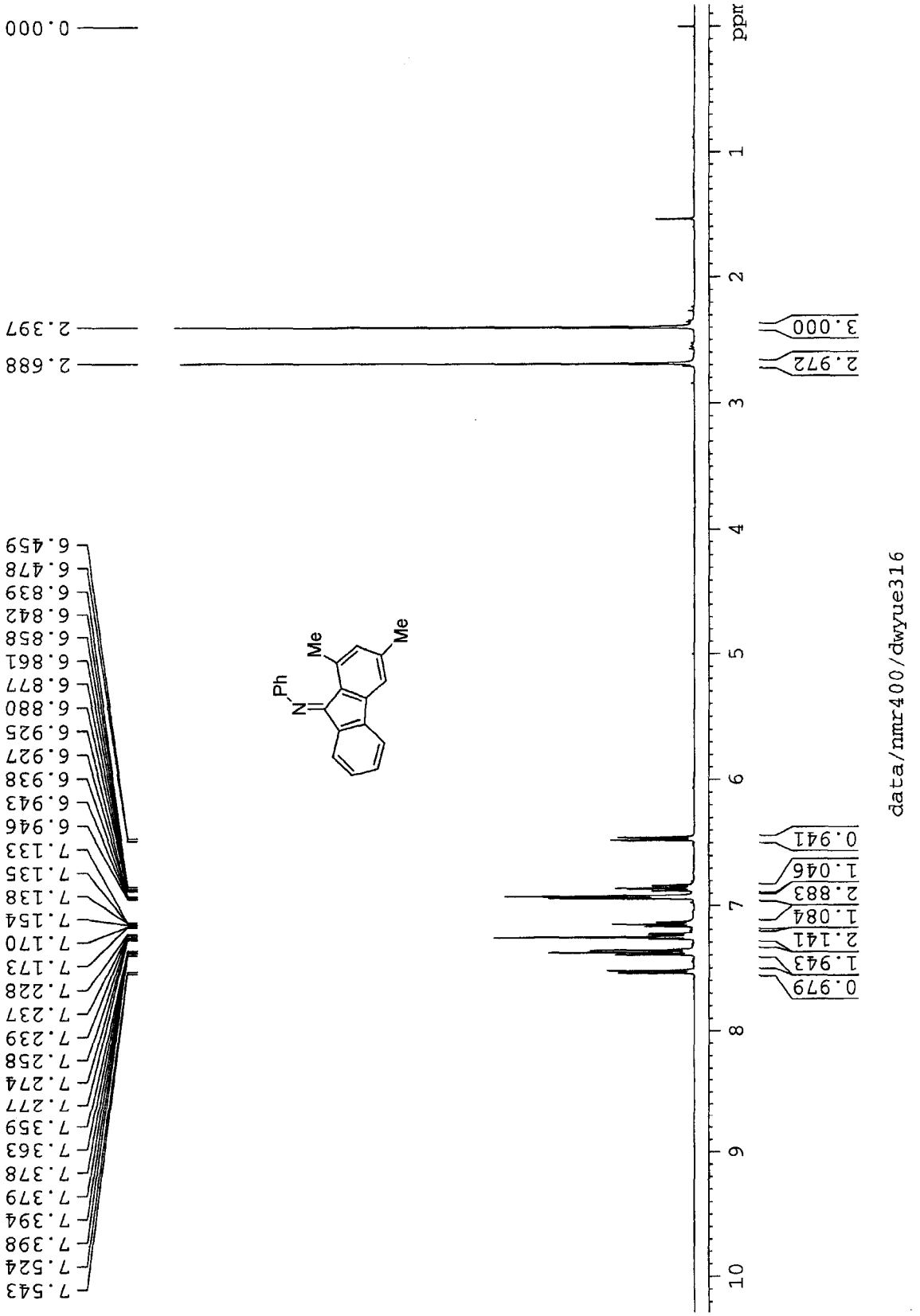
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


Ph
N
Me
Me
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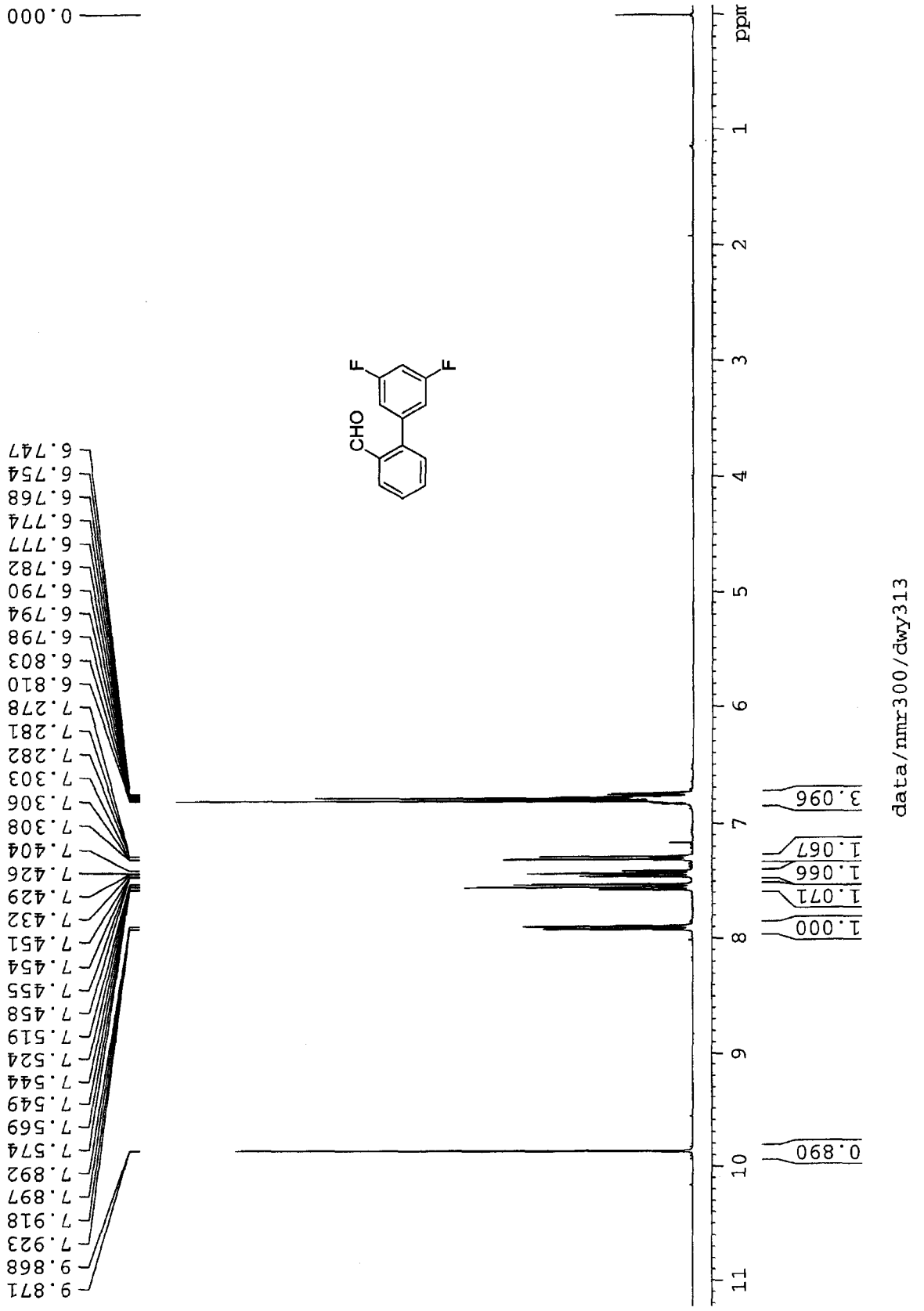
7.524
7.398
7.394
7.379
7.378
7.363
7.359
7.277
7.274
7.258
7.239
7.237
7.228
7.173
7.170
7.154
7.138
7.135
7.133
6.946
6.943
6.938
6.927
6.925
6.880
6.877
6.861
6.858
6.842
6.839
6.478
6.459
2.688
2.397
0.000
0.941
1.046
2.883
1.084
2.141
1.943
0.979
2.972
3.000
ppm
data/nmr400/dwyue316

164.212
152.520
143.537
142.776
141.510
138.343
132.456
131.928
131.434
131.344
129.420
127.508
127.077
123.566
119.933
118.269
118.135
77.546
77.229
76.911
21.920
19.777
N
Ph
Me
Me
ppm
data/nmr400/dwyue316


CHO
F
F
ppm
0.000
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6.754
6.768
6.774
6.777
6.782
6.790
6.794
6.798
6.803
6.810
7.278
7.281
7.282
7.303
7.306
7.308
7.404
7.426
7.429
7.432
7.451
7.454
7.455
7.458
7.519
7.524
7.544
7.549
7.569
7.574
7.892
7.897
7.918
7.923
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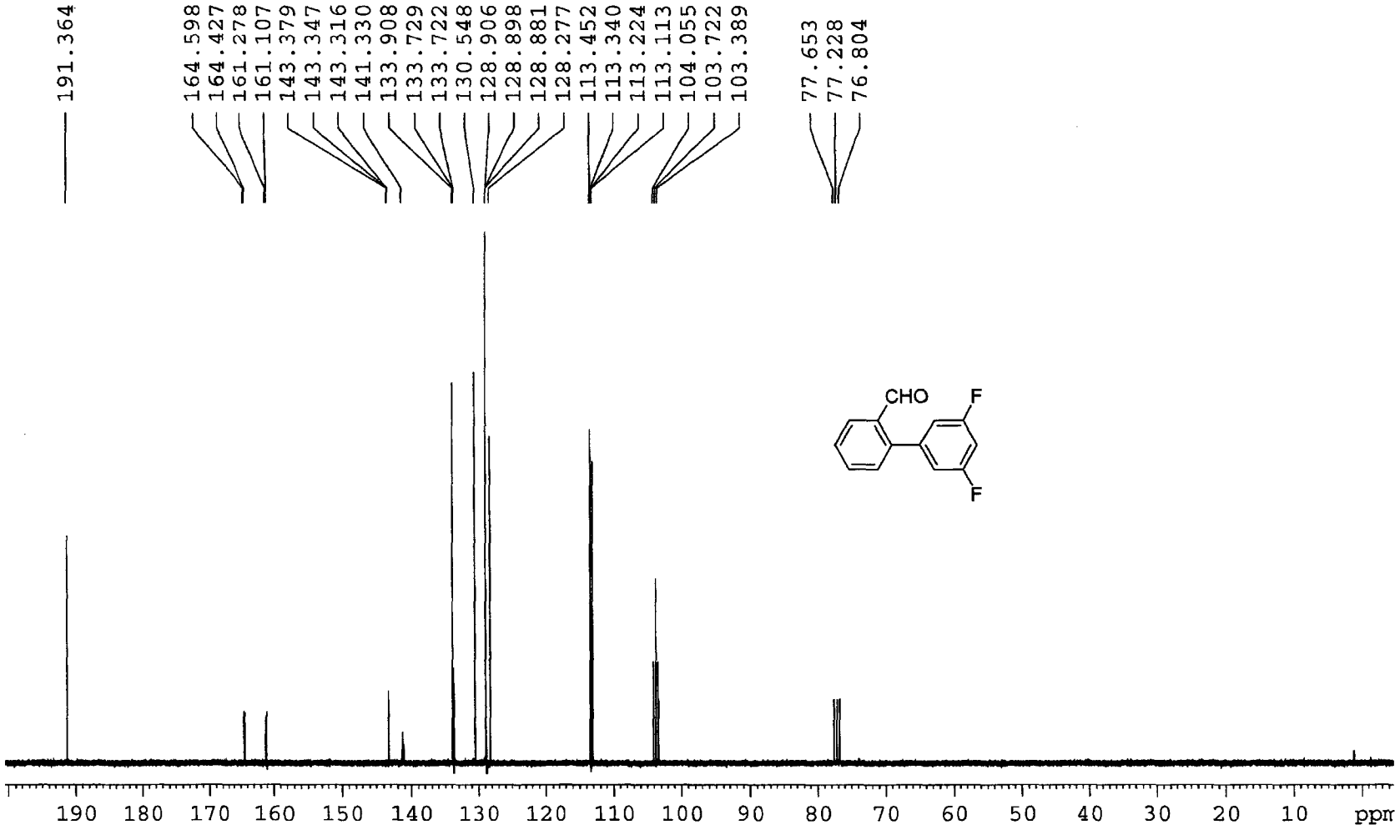
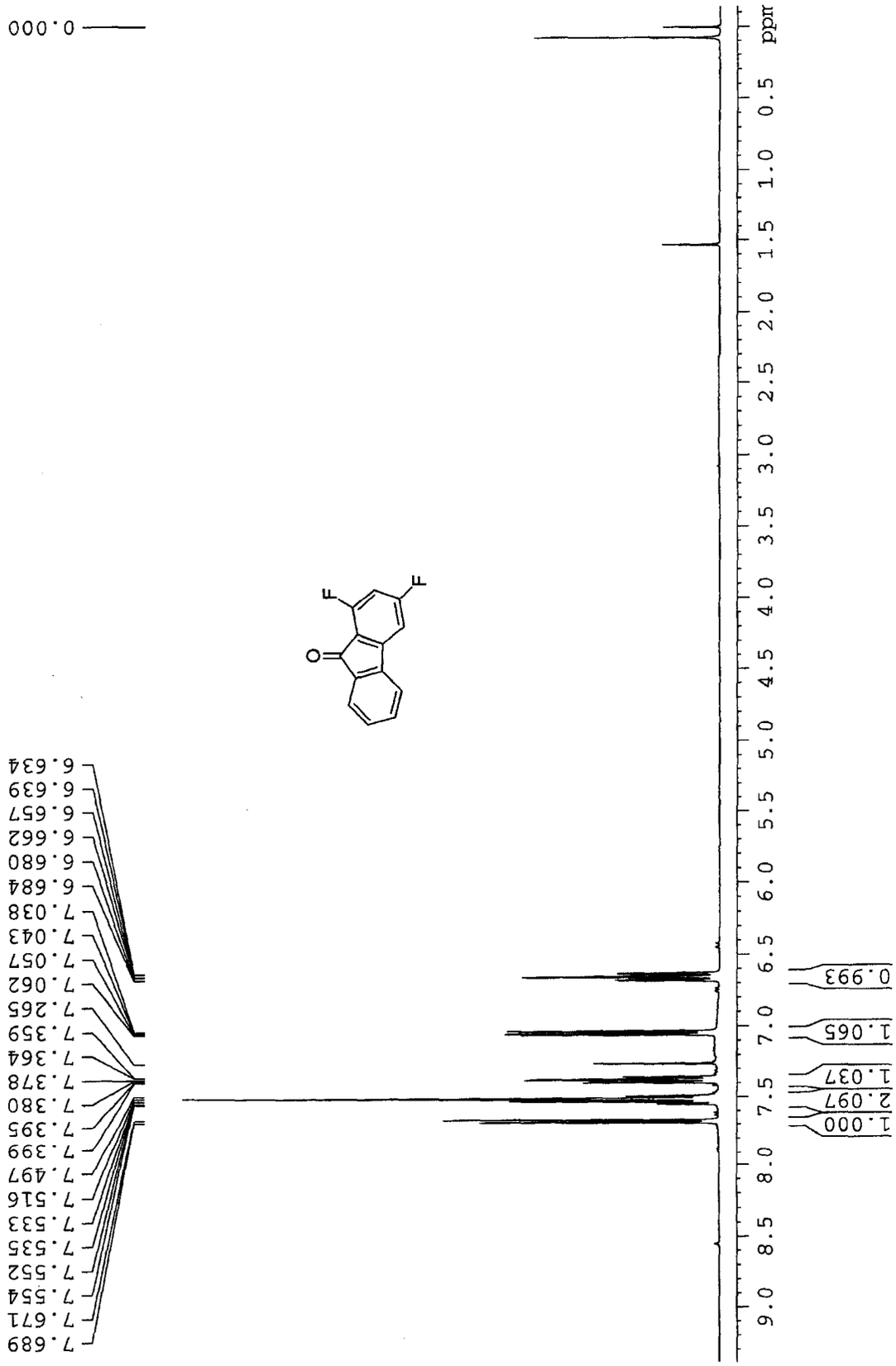
9.871
0.890
1.000
1.071
1.066
1.067
3.096
data/nmr300/dwy313



data/nmr300/dwy313c


F
F
O
7.689
7.671
7.554
7.552
7.535
7.533
7.516
7.497
7.399
7.395
7.380
7.378
7.364
7.359
7.265
7.062
7.057
7.043
7.038
6.684
6.680
6.662
6.657
6.639
6.634
0.000
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
2.097
1.037
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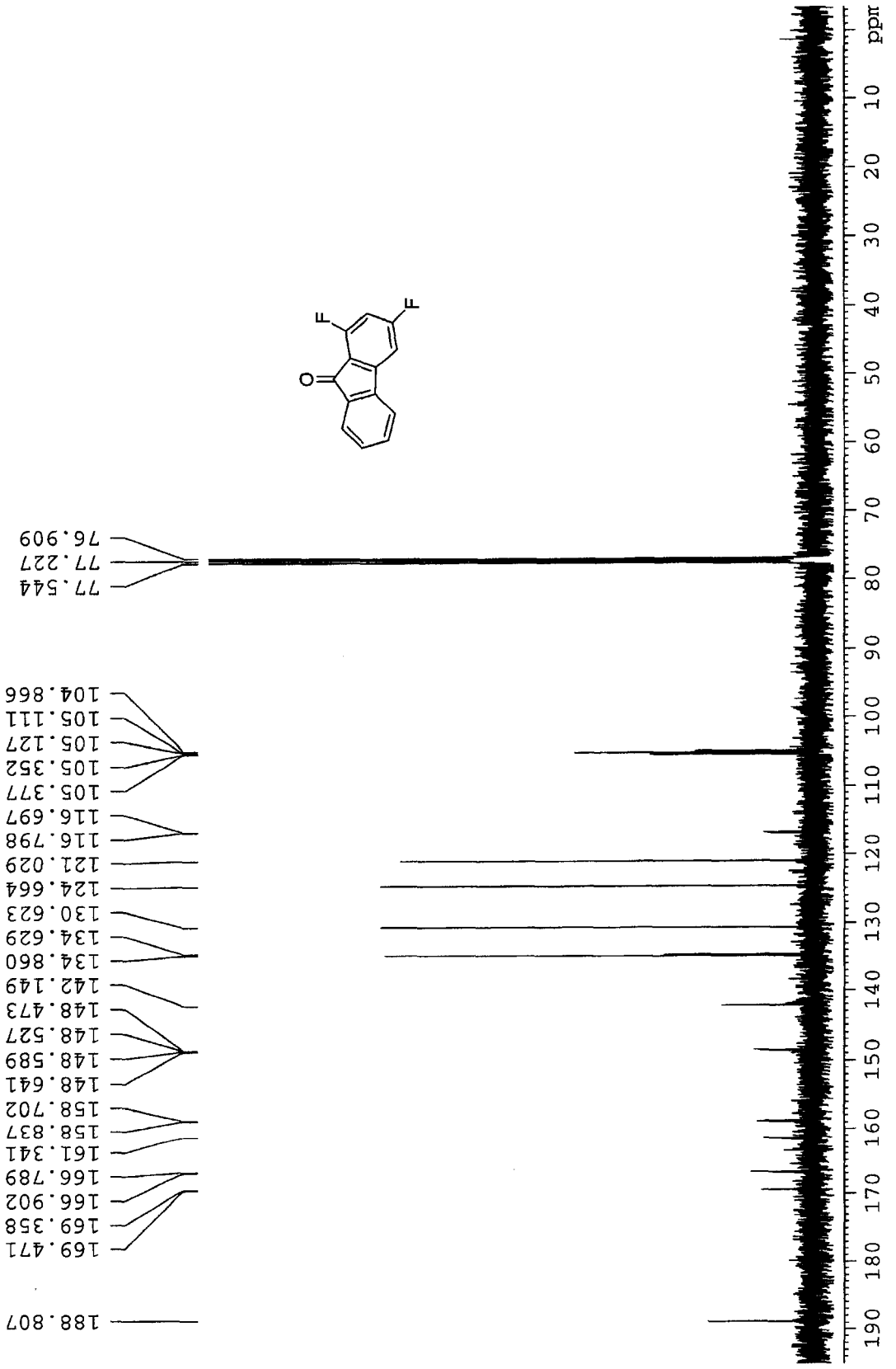
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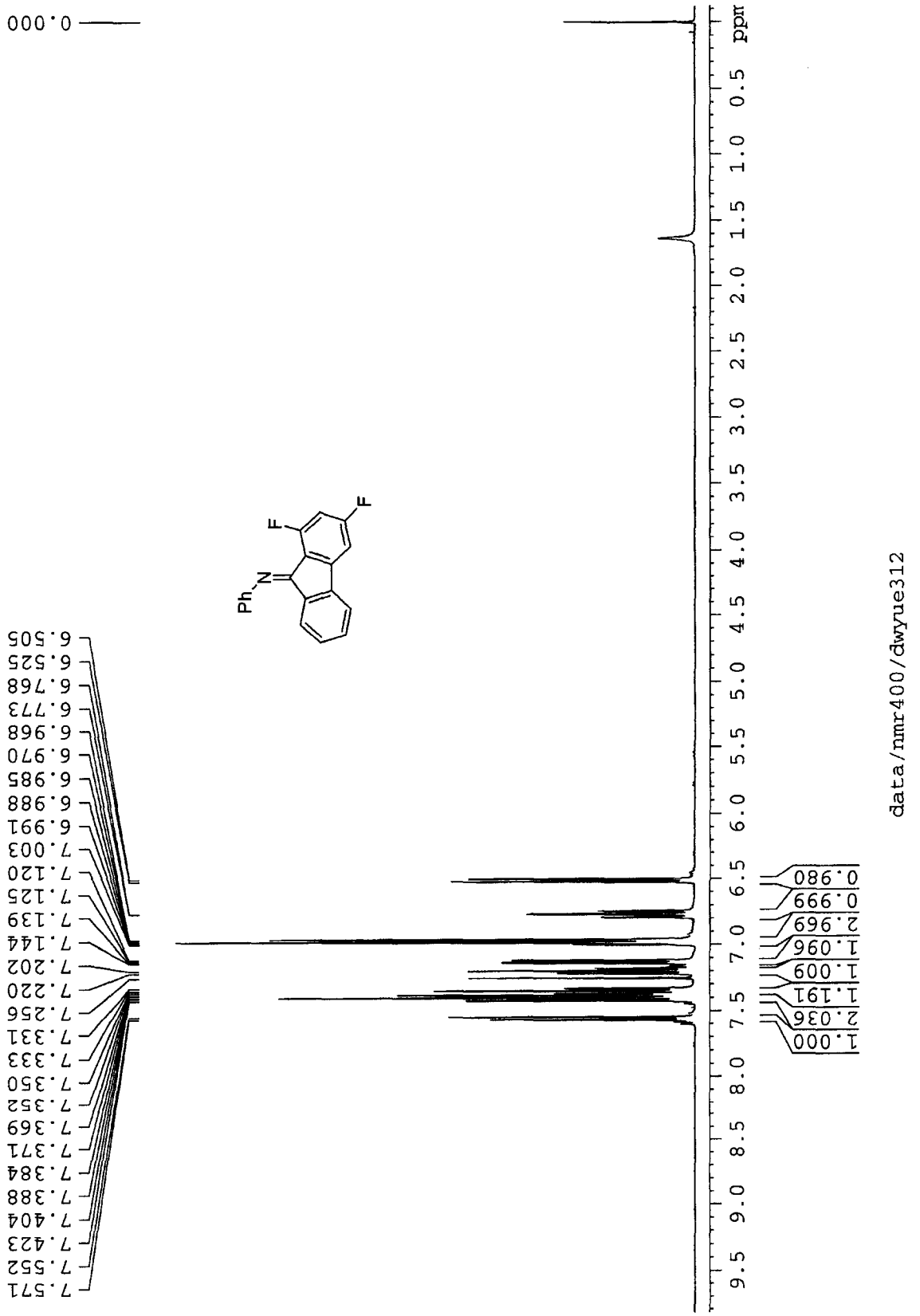
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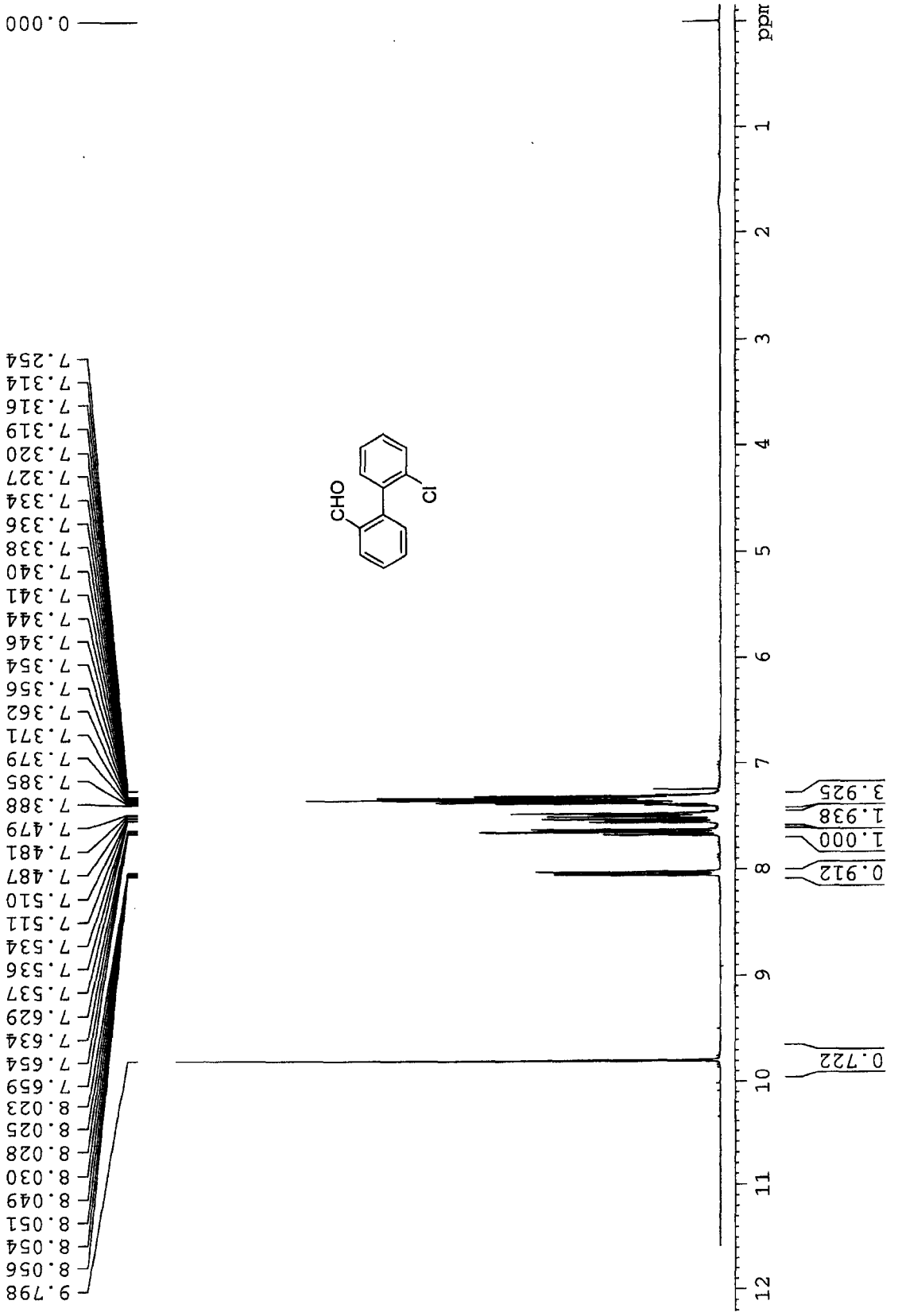
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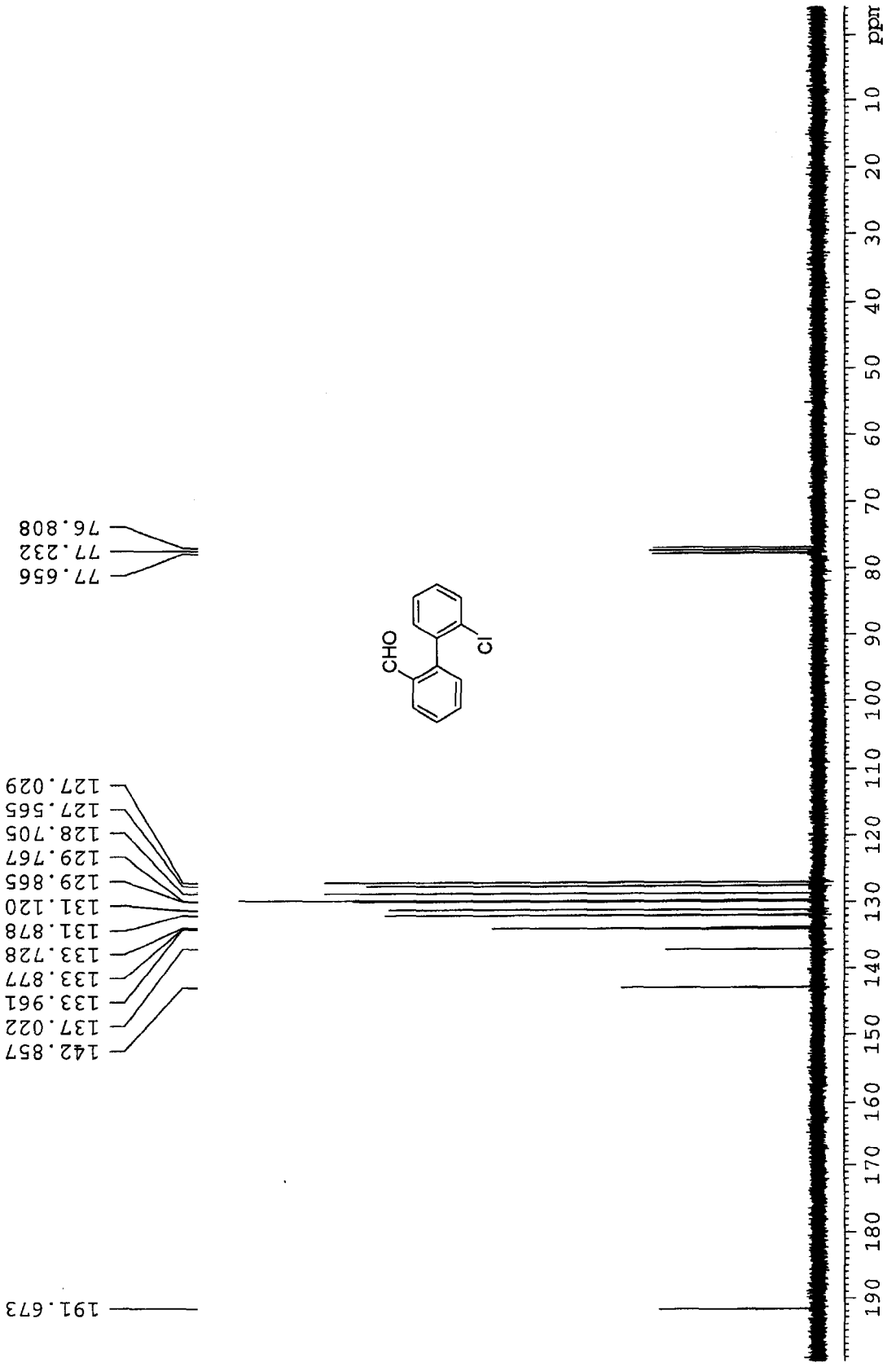
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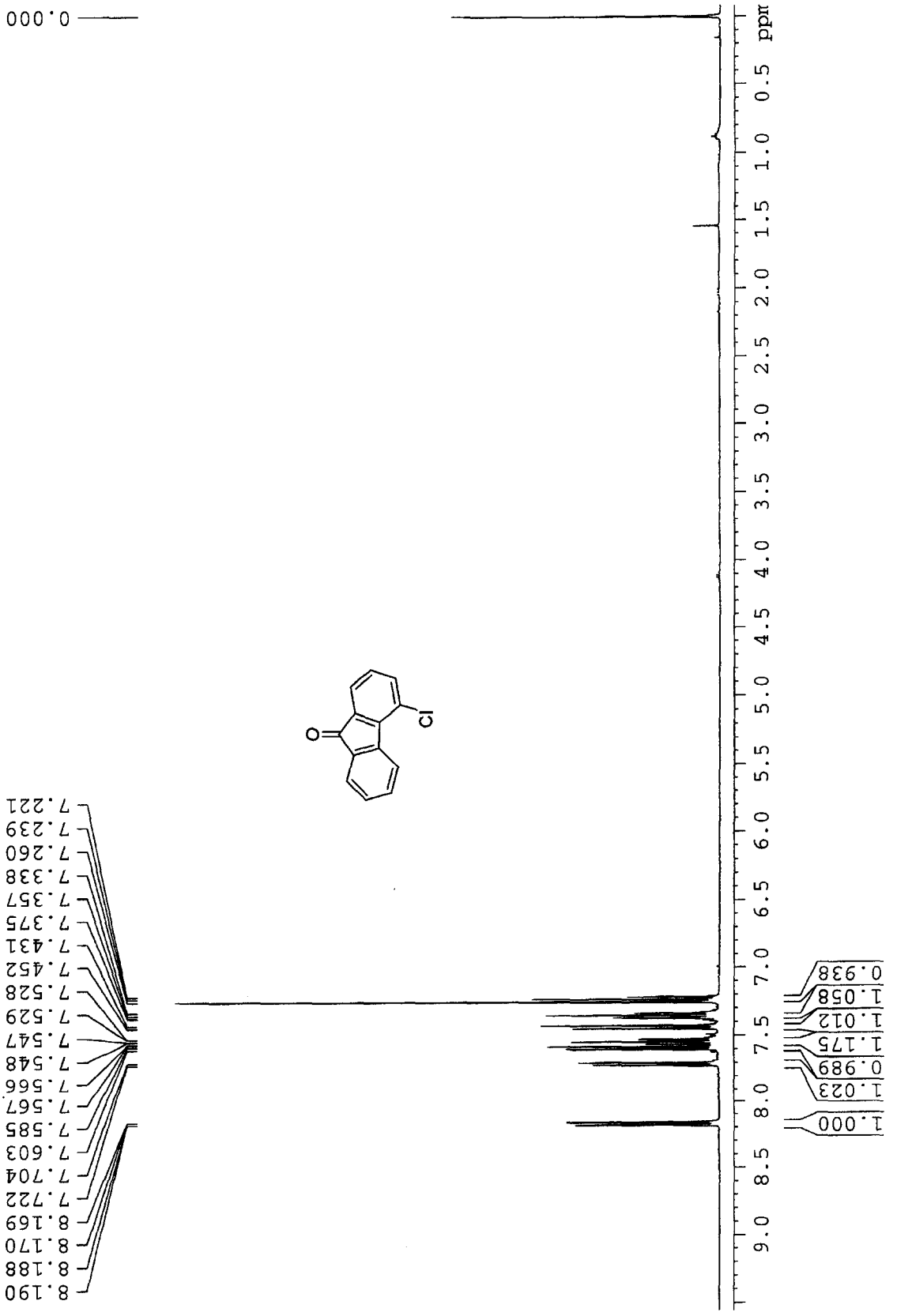
CHO
Cl
ppm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2.5
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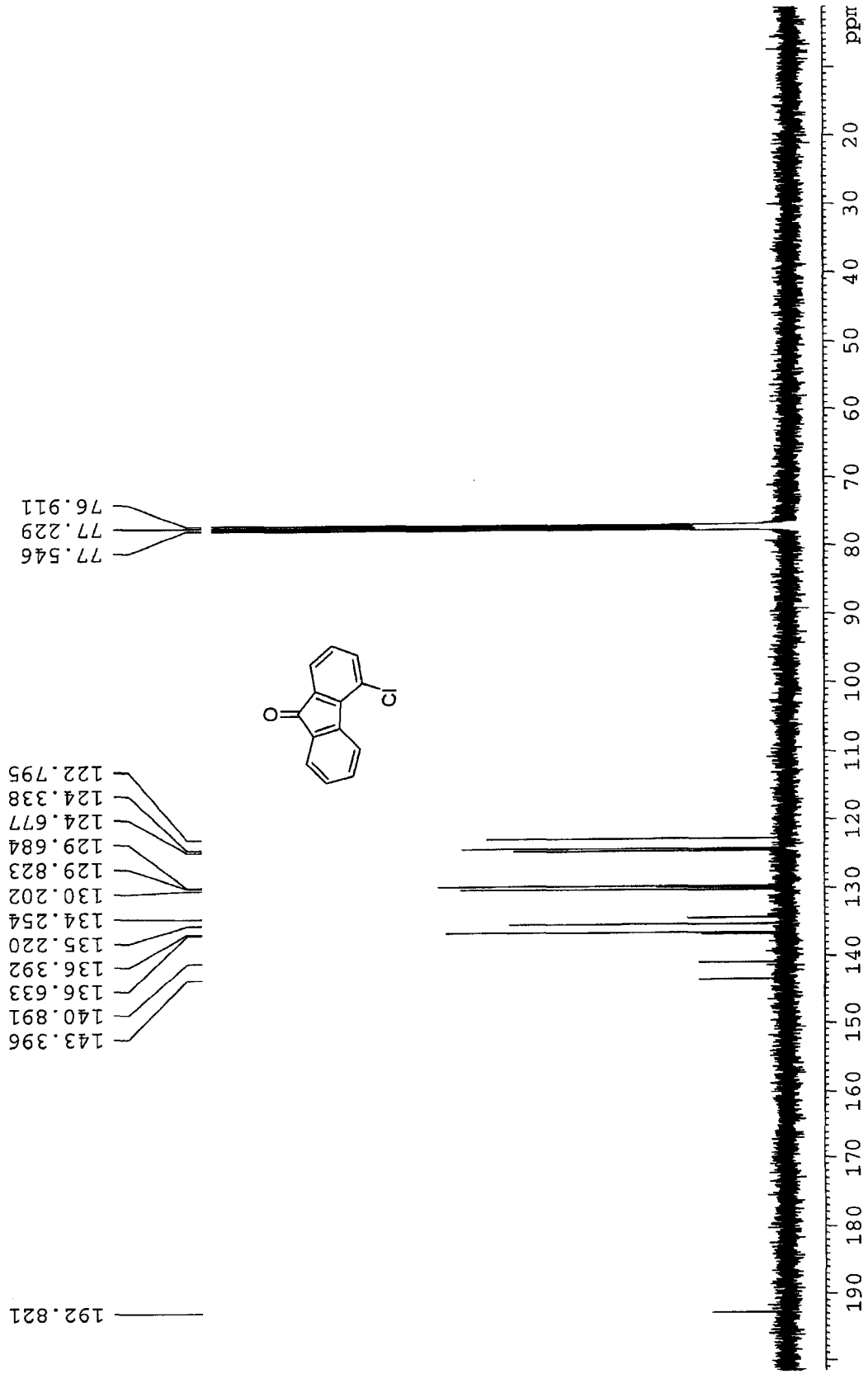
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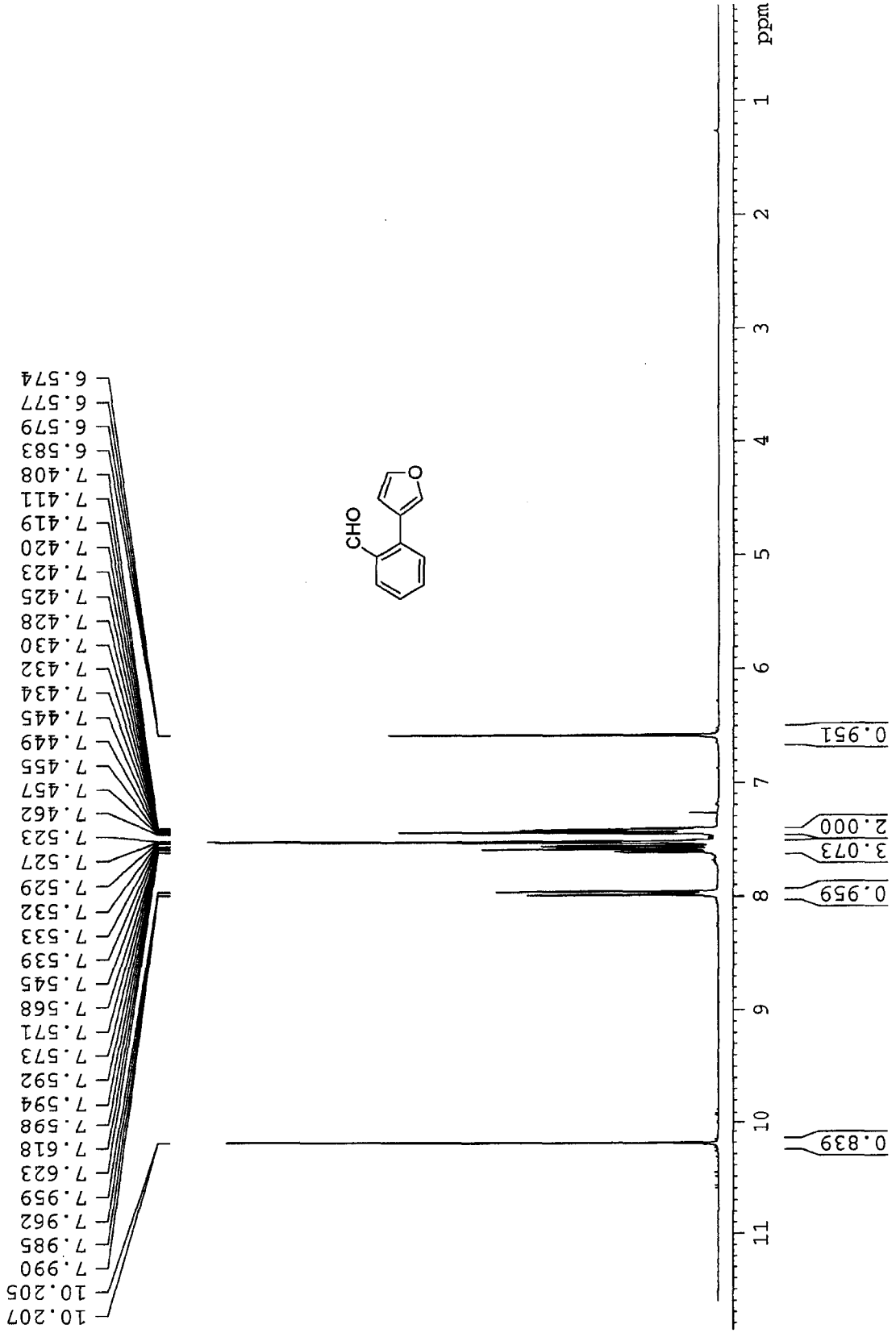
O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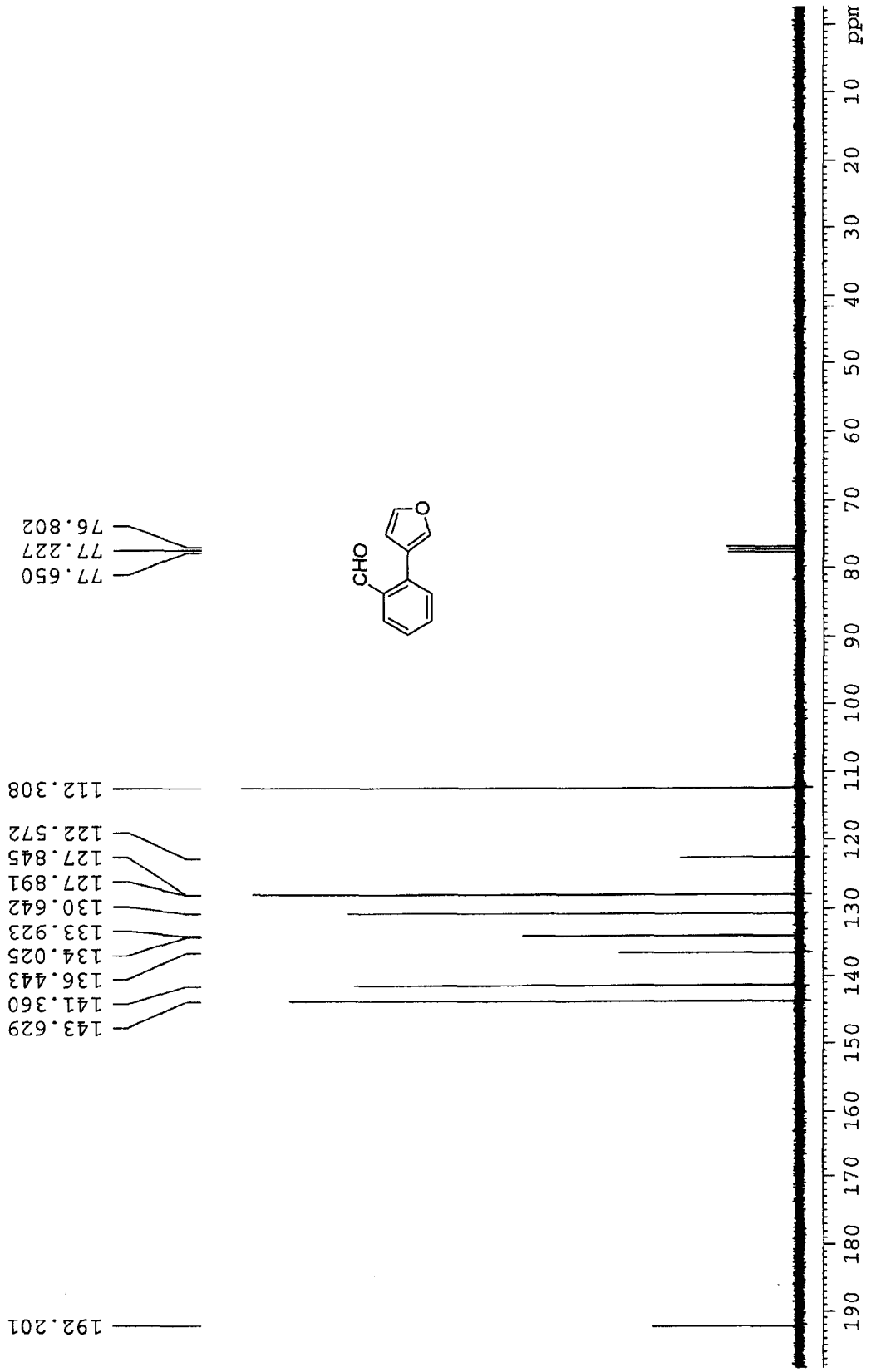
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CHO
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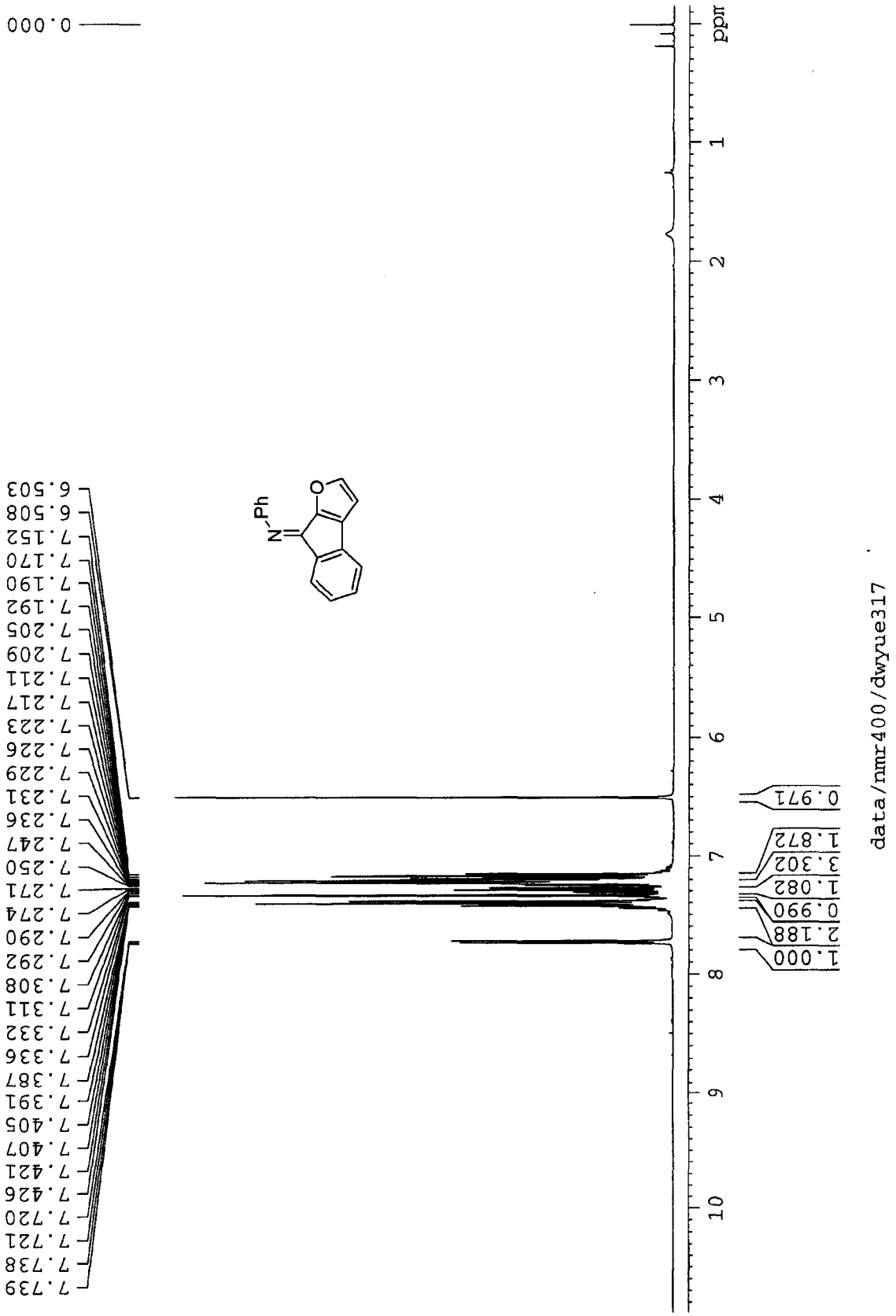
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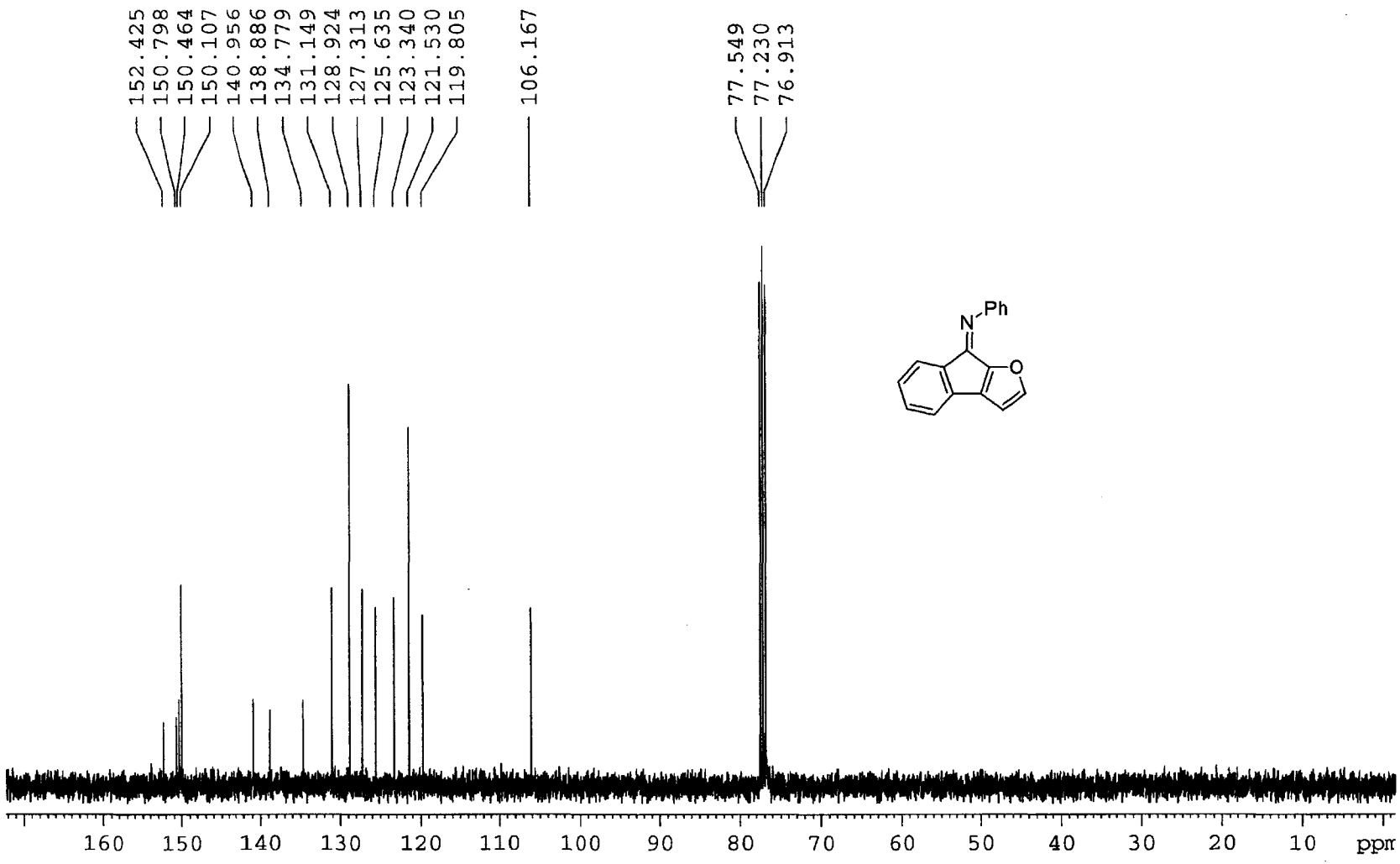

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Boc
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OHC
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7.608
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6.582
1.229
0.000

ppm
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7
6
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NH2
I
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150
140
130
120
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100
90
80
70
60
50
40
30
20
10
NH2
I
O

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