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Development of Synthetic Pathways for Macrocyclic Acetylenes

Chi-Yuan Tseng

Thesis submitted to the
Eberly College of Arts and Sciences
at West Virginia University
In partial fulfillment of the requirements
for the degree of

Master of Science
in
Chemistry

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Morgantown, West Virginia

2013

Keywords: Macrocyclic Acetylenes, Schmittel Cyclization
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ABSTRACT

A synthetic sequence was developed for the preparation of a diindeno-fused 4*H*-cyclopenta[*def*]phenanthrene derivative containing two bromo substituents as a potential building block for the construction of macrocyclic acetylenes. The synthetic sequence required the preparation of a benzannulated enediyne, 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene. The Sonogashira reaction between 1,3-dibromo-2-iodobenzene and (trimethylsilyl)ethyne produced 1,3-dibromo-2-[(trimethylsilyl)ethynyl]benzene. Metal-halogen exchange with *n*-butyllithium followed by iodination with iodine furnished 1-bromo-3-iodo-2-[(trimethylsilyl)ethynyl]benzene. A second Sonogashira reaction with phenylethyne followed by desilylation then furnished 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene.

Treatment of an excess of 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene with lithium diisopropylamide followed by condensation with 2,2-dimethoxy-1,3-indandione furnished the corresponding propargylic diol as the major adduct and the corresponding mono-ol as the minor adduct. On exposure to thionyl chloride, the diol underwent a Schmittel cascade cyclization reaction to produce the diindeno-fused 4*H*-cyclopenta[*def*]phenanthrene derivative containing two bromo substituents. The presence of the two bromo substituents provides handles for additional Sonogashira reactions for the construction of macrocyclic acetylenes.

Dedicated To

My parents

and

My wife, Yi Ching Chen

ACKNOWLEDGMENTS

I sincere appreciate my advisor, Dr. Kung K. Wang, for his guidance, support, patience, and encouragement during my graduate student life. Dr. Wang taught me the skills and abilities in chemistry, and inspired me to be a better person. I am very proud and grateful to be his student.

I would like to express gratitude to my research committee members, Dr. Jeffrey L. Petersen and Dr. Björn C. G. Söderberg for their helpful advice, guidance, and kindness. They helped me to expand my knowledge and think in a logical way.

I would also like to thank to Dr. Novruz Akhmedov for his generous assistance in NMR spectroscopy, and all my laboratory mates, Changfeng Huang, Yiwei Huang, and Yang-Sheng Sun for their assistance, and friendship throughout these years. The valuable discussions with them in the lab will be precious memories for me.

Financial support from C. Eugene Bennett Department of Chemistry at West Virginia University is gratefully acknowledged.

Finally, I would like to express my special appreciation to my family: my grandma, my parents, and my sister for their unconditional love and support; my wife, Yi-Ching Chen, for her unselfish love to me.

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Part I

Development of Synthetic Pathways for Macrocyclic Acetylenes

1. Introduction

Macrocyclic acetylenes are a type of cyclic molecules that contain one or more acetylenic units as part of the cyclic structures. The presence of the acetylenic units and the linking carbon fragments highlight the features of macrocyclic acetylenes. Over the past few decades, macrocyclic acetylenes have been studied extensively for their physicochemical and supramolecular properties.[1-6] Macrocyclic acetylenes contain special structural features, including the π electron resonance of the acetylenic bonds, the molecular shape, the distorted electronic distribution, and the cavity inside the molecule. In addition, the exposed acetylenic chains make the macrocyclic acetylenes highly reactive. Based on these, macrocyclic acetylenes have been considered as potential intermediates for the synthesis of fullerenes.[7]

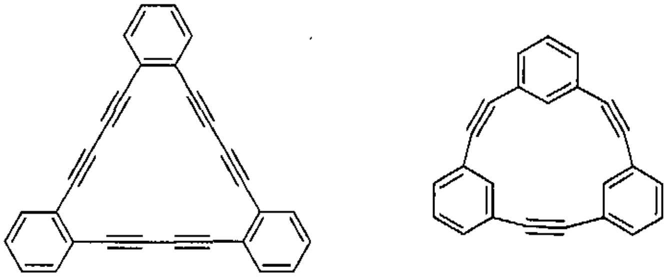
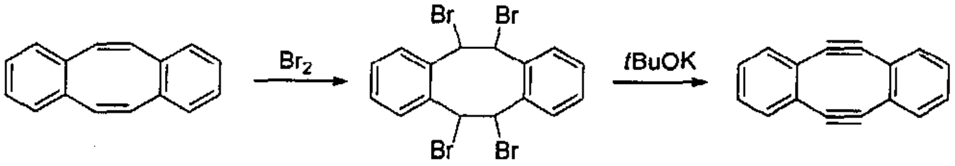


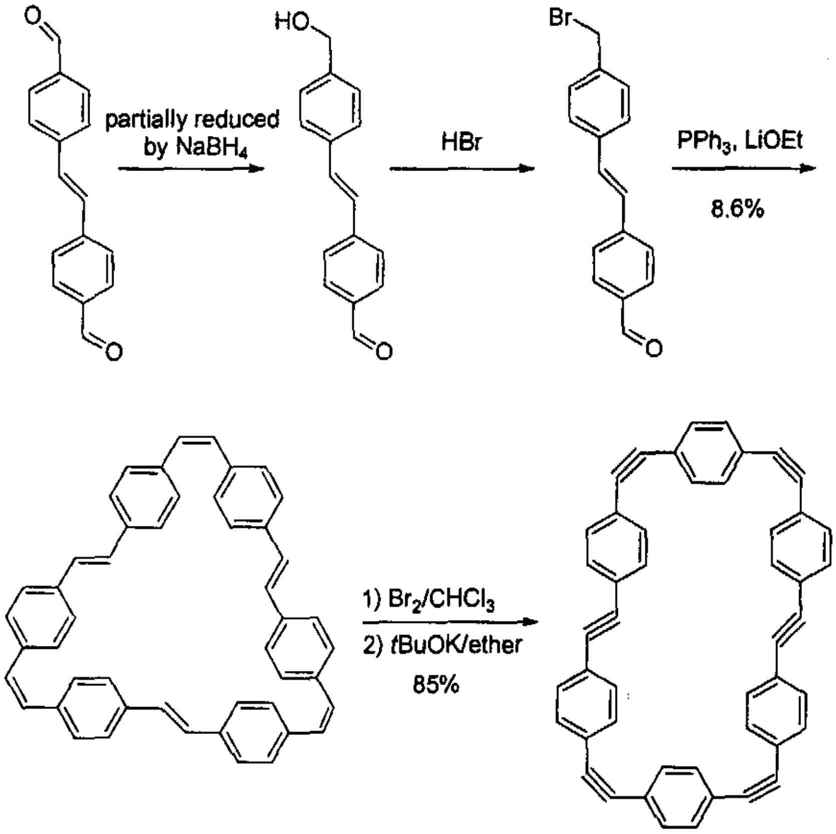
Figure 1 Two examples of macrocyclic acetylenes

Several synthetic methods for the preparation of macrocyclic acetylenes have been reported, including bromination-dehydrobromination of the corresponding cycloalkenes (Scheme 1).[8-10]



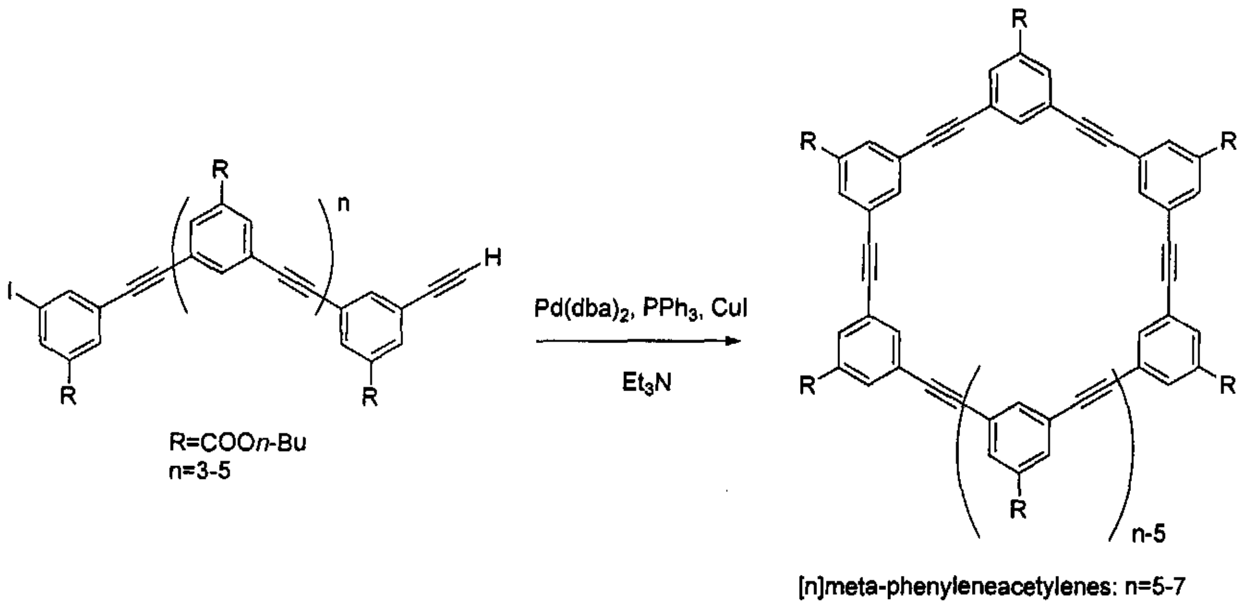
Scheme 1

This method represents a simple and efficient way to prepare macrocyclic acetylenes especially for strained cases. Most of the small macrocyclic acetylenes are prepared by this method. However, one of the limitations of this synthetic route is the difficulty in synthesizing cyclic alkenes as precursors for the corresponding macrocyclic acetylenes. The larger cycloalkene precursor are harder to prepare (Scheme 2).[11,12]


partially reduced by $NaBH_4$
HBr
PPh_3, LiOEt
8.6%
1) $Br_2/CHCl_3$
2) *t*BuOK/ether
85%

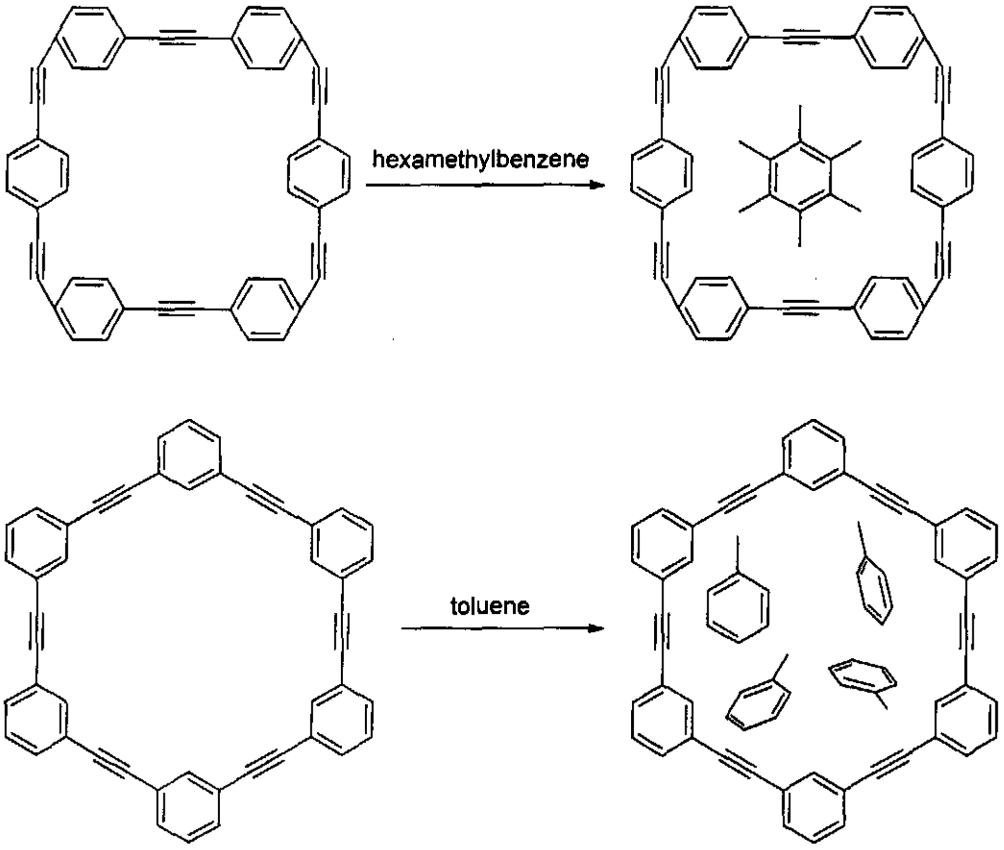
Scheme 2

On the other hand, coupling reactions have also found success in the preparation of macrocyclic acetylenes. In particular, the Sonogashira intra- or intermolecular coupling reaction[13] has been adopted for the synthesis of a wide variety of macrocyclic acetylenes. For example, a series of cyclic [n]meta-phenylacetylenes (n = 5-7) have thus been synthesized (Scheme 3).[14] However, the preparation of strained cases has been found to be very challenging using the coupling method.


R
n
I
H
R
R
R=COOn-Bu
n=3-5
Pd(dba)2, PPh3, CuI
Et3N
R
R
R
R
R
R
n-5
[n]meta-phenyleneacetylenes: n=5-7

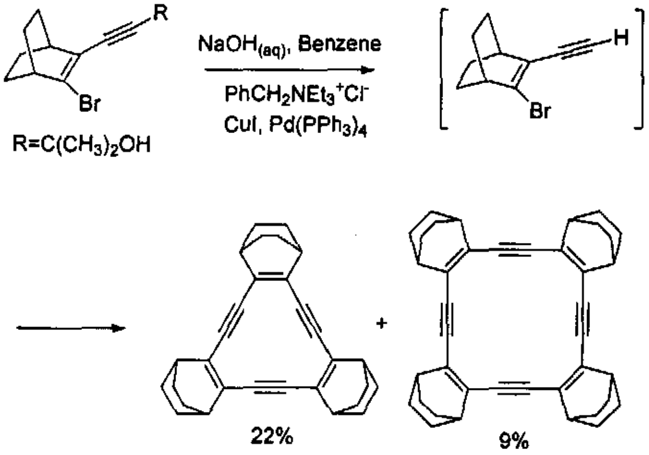
Scheme 3

Another interesting feature of macrocyclic acetylenes is the cavity inside the molecule. The synthesis of macrocyclic acetylenes could allow the construction of a large-sized carbon ring. With a large carbon ring, macrocyclic acetylenes could encapsulate one or more small molecules inside the cavity to form multi-inclusion type complexes (Scheme 4).[15] In addition, the ring size and the shape of the linking carbon fragments could allow macrocyclic acetylenes to encapsulate only certain guest molecules selectively.



Scheme 4

Macrocyclic acetylenes with a planar π electronic conjugate system inside the molecule have also been synthesized. This type of macrocyclic acetylenes has been used for the study of the electron-donating capability of the carbon fragment. A series of macrocyclic acetylenes adopting bicycle[2.2.2]octene (BCO) as the linking carbon fragment has been reported. The reduction potentials of these macrocyclic acetylenes showed that the lager the numbers of the BCO unit present in the molecule the easier it is to oxidize the molecule (Scheme 5).[16]

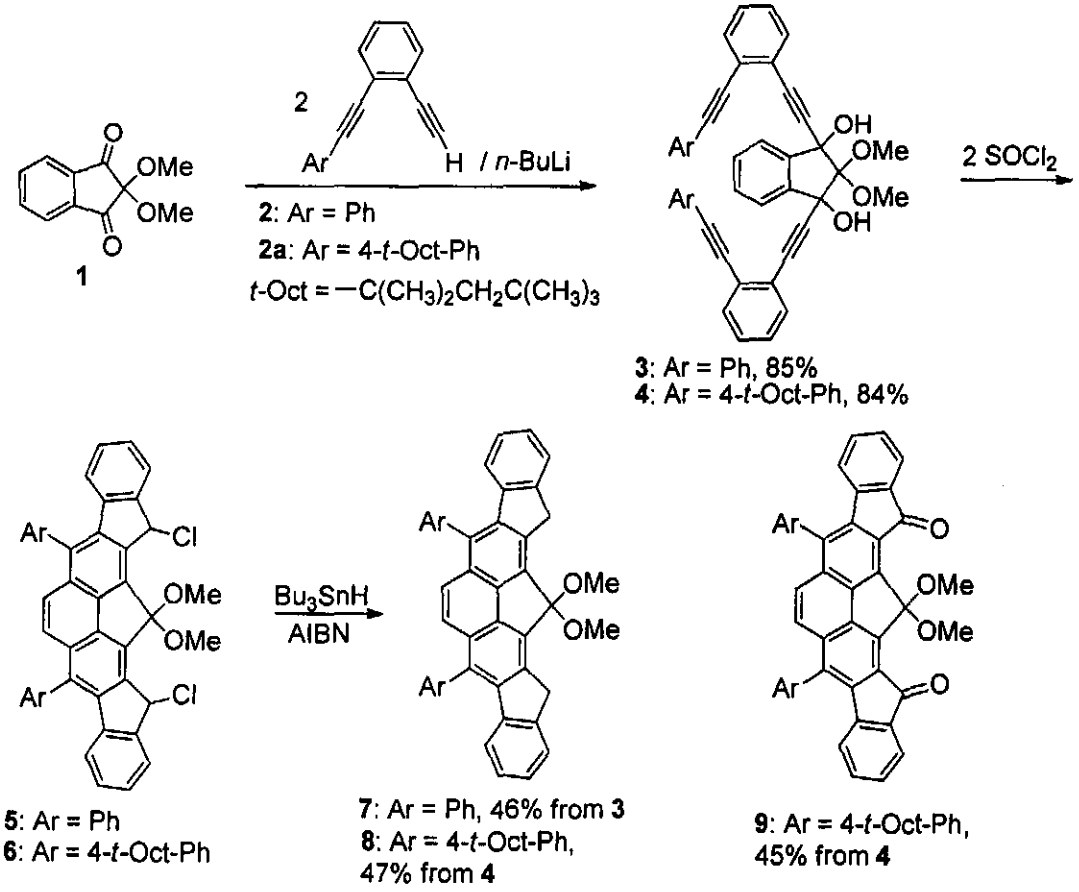


Scheme 5

Because of their interesting structural features and potential applications in a variety of areas, macrocyclic acetylene continue to attract the attention of synthetic organic chemists with new design and synthesis of these molecules containing novel molecular architectures.[17,18] Our goal in this research project is to provide new types of linking carbon fragments in the synthesis of macrocyclic acetylenes.

2. Research Plan

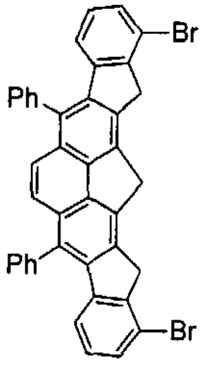
Our group previously reported an efficient route to produce highly unsaturated polycyclic aromatic compounds **7** and **8** from 2,2-dimethoxy-1,3-indandione (**1**) (Scheme 6).[19] The 2,2-dimethoxy-1,3-indandione (**1**) was prepared from commercially available 2,2-dihydroxyindane-1,3-dione in one step.[9] Condensation of diketone **1** with lithium acetylides **2** and **2a** produced benzannulated enediynyl alcohols **3** and **4**, respectively. When the alcohols **3** and **4** were exposed to thionyl chloride, the cyclized dichlorides **5** and **6** were produced, respectively. Reduction of these dichlorides **5** and **6** with tributyltin hydride produced **7** in 46% yield and **8** in 47% yields for the last two steps. Likewise, diketone **9** was obtained by air oxidation of **6** in the presence of a 2 M NaOH solution.



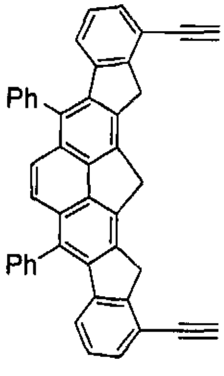
1
2
Ar
H / n-BuLi
2: Ar = Ph
2a: Ar = 4-t-Oct-Ph
t-Oct = —C(CH3)2CH2C(CH3)3
OMe
OH
2 SOCl2
3: Ar = Ph, 85%
4: Ar = 4-t-Oct-Ph, 84%
Cl
Bu3SnH
AIBN
O
5: Ar = Ph
6: Ar = 4-t-Oct-Ph
7: Ar = Ph, 46% from 3
8: Ar = 4-t-Oct-Ph, 47% from 4
9: Ar = 4-t-Oct-Ph, 45% from 4

Scheme 6

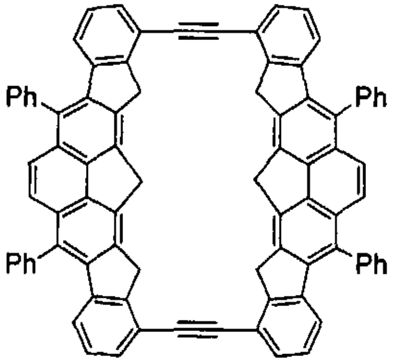
This research project will adopt the same synthetic strategy outlined in Scheme 6 for the preparation of **10** possessing two bromo substituents. The dibromide **10** could be further functionalized by using the Sonogashira reactions with 2 equivalents of (trimethylsilyl)acetylene, leading to diacetylene **11**, with the two acetylenic groups in essentially parallel orientation. By repeating the Sonogashira reactions between **10** and **11**, the macrocyclic acetylene **12** could thus be produced. The MM2-optimized structure of **12** shows that the aromatic carbon framework has a slight twist, but is essentially free of severely distorted bond angles. The two acetylenic groups remain essentially linear.



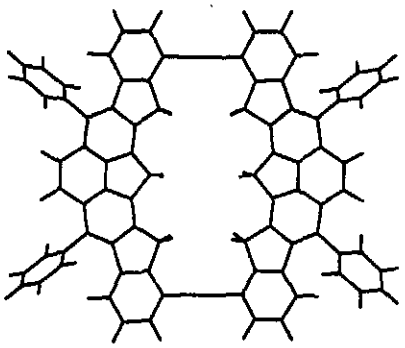
10



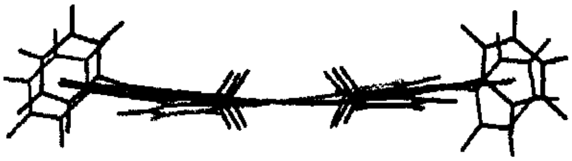
11



12



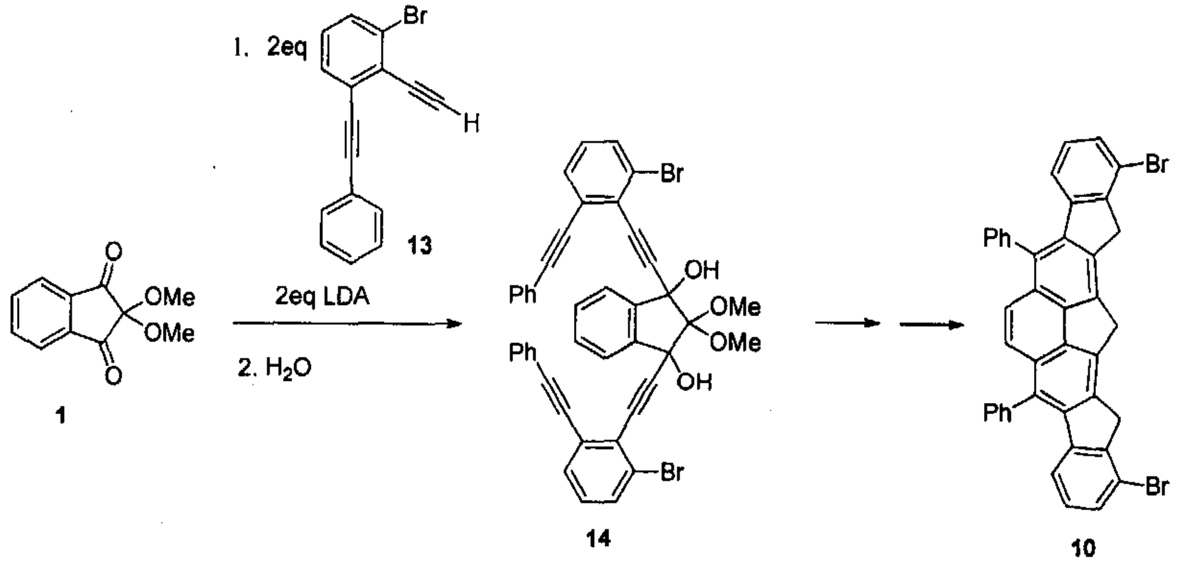
12 MM2-optimized, top view



12 MM2-optimized, side view

Figure 2 Structures of compounds **10**, **11**, and **12**

The positions of the two bromo substituents in **10** play an important role in the design of the synthetic route for the macrocyclic acetylene **12**. The two bromo substituents, both attached on the C-1 position of the two fluorene subunits in **10**, provided handles for the Sonogashira reactions and also insured the parallel orientation of the two acetylenic groups of diacetylene **11**. In the Sonogashira cross-coupling reactions between **10** and **11**, following the first Sonogashira reaction, the remaining acetylene and the second aryl bromide could undergo an intramolecular Sonogashira reaction to form macrocyclic acetylene **12**. Because of the rigid carbon frameworks in **10** and **11** and the optimal positions of the two bromo substituents in **10** and the two acetylenic groups in **11**, it is highly likely that after the first Sonogashira reaction, the remaining acetylenic group and the second aryl bromide would undergo an intramolecular Sonogashira reaction to form macrocyclic acetylene **12**. In order to produce dibromide **10**, it is necessary to prepare diacetylene **13** bearing a bromo substituent for condensations with diketone **1** to obtain the important precursor propargylic diol **14** (Scheme 7).

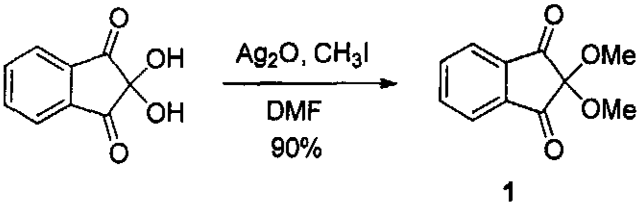


Scheme 7

3. Results and Discussion

3.1 Synthesis of 2,2-dimethoxy-1,3-indandione (1)

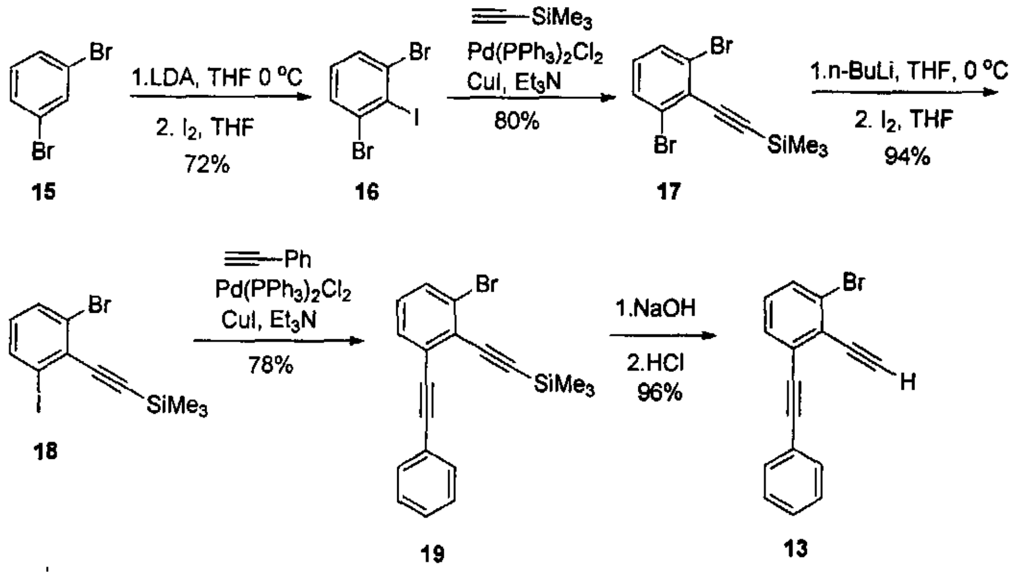
The preparation of the 2,2-dimethoxy-1,3-indandione (**1**) was conducted according to a reported procedure.[20] Treatment of ninhydrin (2,2-dihydroxyindane-1,3-dione) with silver(I) oxide, and iodomethane provided diketone **1** in 90% isolated yield (Scheme 8).



Scheme 8

3.2 Synthesis of 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene (13)

The synthetic procedure for **13** was initially developed by Changfeng Huang of our research group (Scheme 9). Treatment of the commercially available 1,3-dibromobenzene (**15**) with lithium diisopropylamide (LDA) and iodine produced 1,3-dibromo-2-iodobenzene (**16**) in 72% yield.[21] Then a Pd-catalyzed cross-coupling reaction between **16** and (trimethylsilyl)acetylene furnished 1,3-dibromo-2-[2-(trimethylsilyl)ethynyl]benzene (**17**) in 80% yield. Reaction of **17** with *n*-butyllithium and iodine produced 1-bromo-3-iodio-2-[2-(trimethylsilyl)ethynyl]benzene (**18**) in 94% yield. A subsequent Pd-catalyzed cross-coupling reaction between **18** and phenylacetylene provided 1-bromo-2-[2-(trimethylsilyl)ethynyl]-3-(2-phenylethynyl)benzene (**19**) in 78% yield. Desilylation of **19** then produced diacetylene **13** in 96% yield.

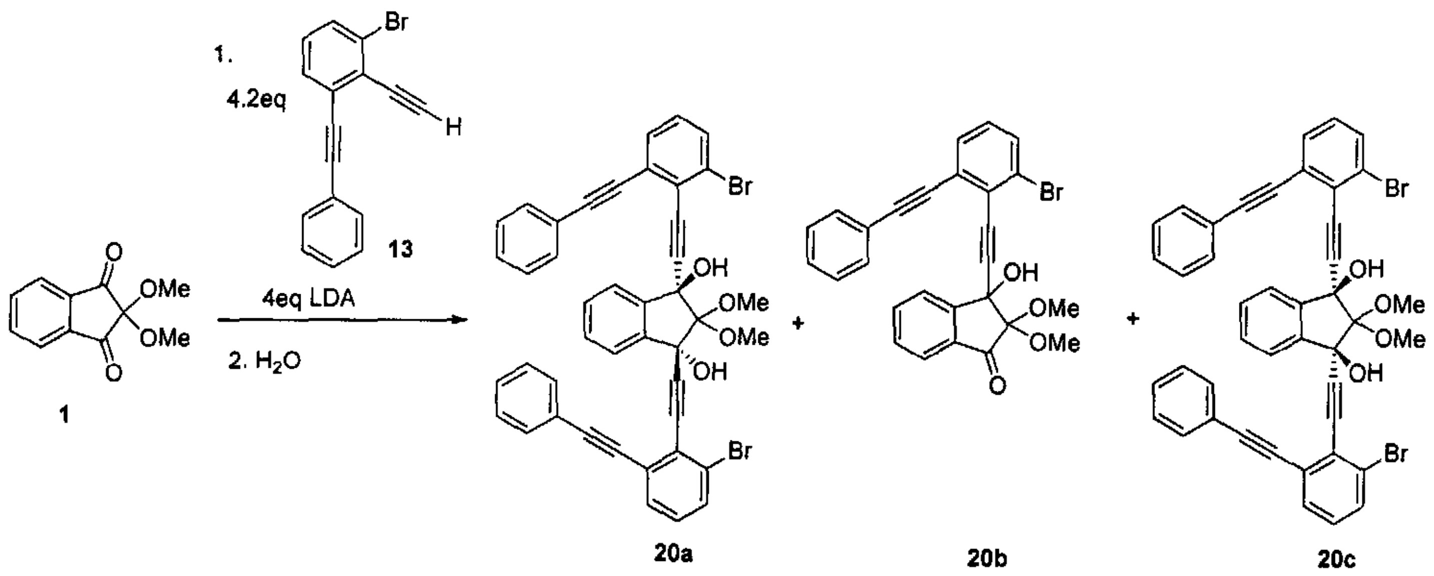


Br
Br
15
1.LDA, THF 0 °C
2. I_2, THF
72%
Br
I
Br
16
$\equiv$—$SiMe_3$
$Pd(PPh_3)_2Cl_2$
CuI, Et_3N
80%
Br
Br
$SiMe_3$
17
1.n-BuLi, THF, 0 °C
2. I_2, THF
94%
Br
I
$SiMe_3$
18
$\equiv$—Ph
$Pd(PPh_3)_2Cl_2$
CuI, Et_3N
78%
Br
$SiMe_3$
19
1.NaOH
2.HCl
96%
Br
H
13

Scheme 9

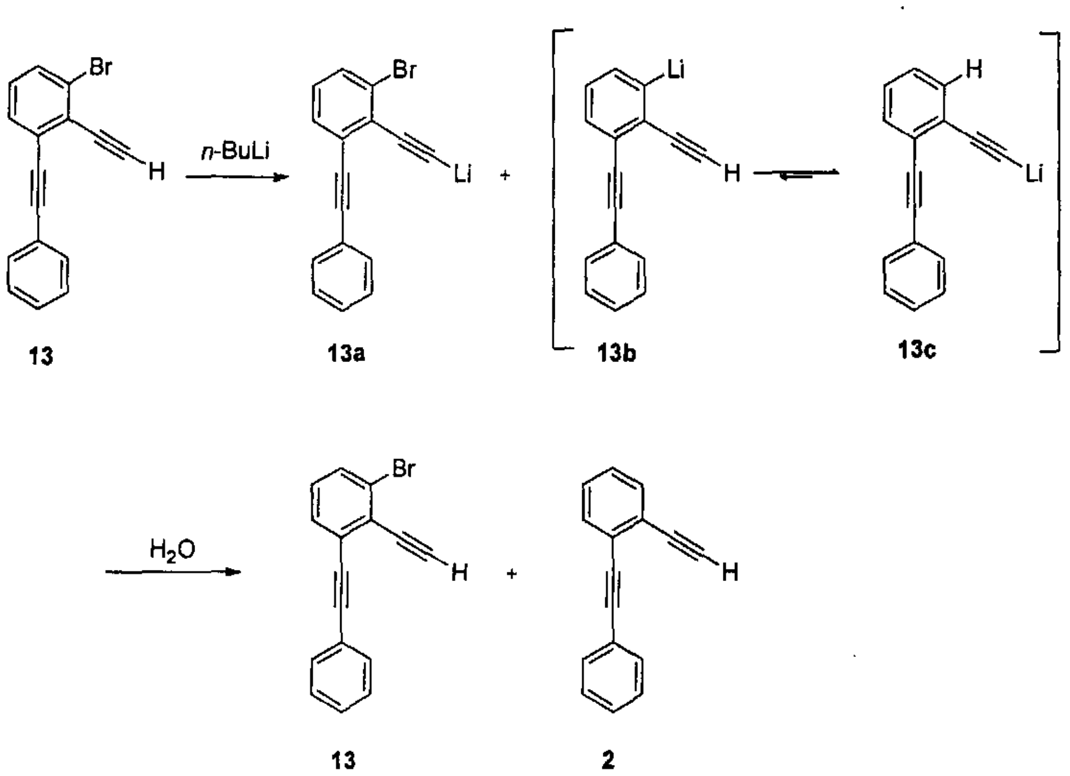
3.3 Schmittel cyclization reaction [22]

Condensation of diketone **1** with the lithium acetylide of **13a**, obtained by lithiation of 1-bromo-2-ethynyl-3-[2-phenylethynyl]benzene (**13**) with LDA, followed by hydrolytic workup produced the *trans* propargylic diol **20a** in 50% yield, mono-propargylic alcohol **20b** in 47% yield, and a small amount of the *cis* propargylic diol **20c** (Scheme 10).



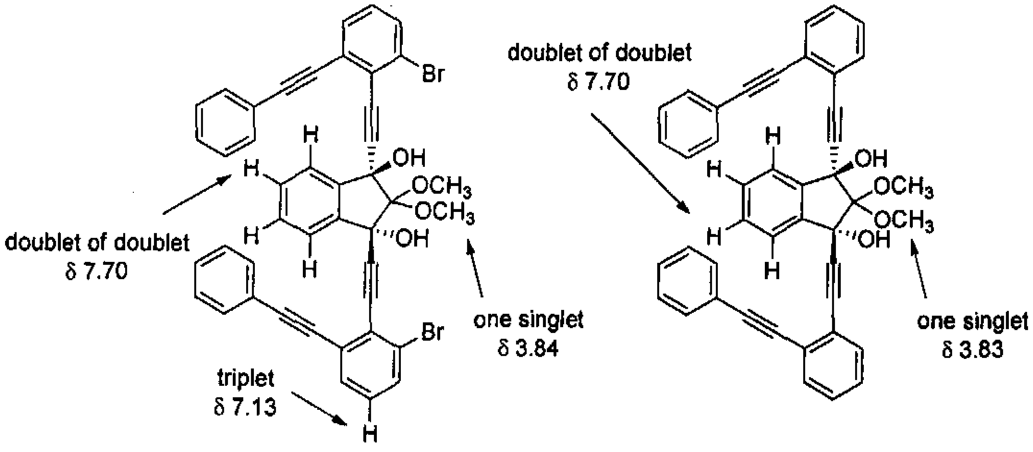
Scheme 10

In the reported synthetic route the lithium acetylide used in the condensation with diketone **1** was prepared by the lithiation of 1-(2-ethynylphenyl)-2-phenylethyne (**2**) with *n*-butyllithium (Scheme 6).[19] However, using *n*-butyllithium for the lithiation of 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene (**13**) was not successful because the undesired metal-bromine exchange reaction competes with lithiation. The ^{1}H NMR spectra of the products after hydrolytic workup indicated the formation of recovered 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene (**13**) and debrominated 1-(2-ethynylphenyl)-2-phenylethyne (**2**) (Scheme 11). In order to prevent the formation of the debrominated adduct, lithium diisopropylamide was used in the condensation reaction and reaction time was carefully monitored and controlled. Using such reaction condition, the formation of the debrominated adduct was avoided.



Scheme 11

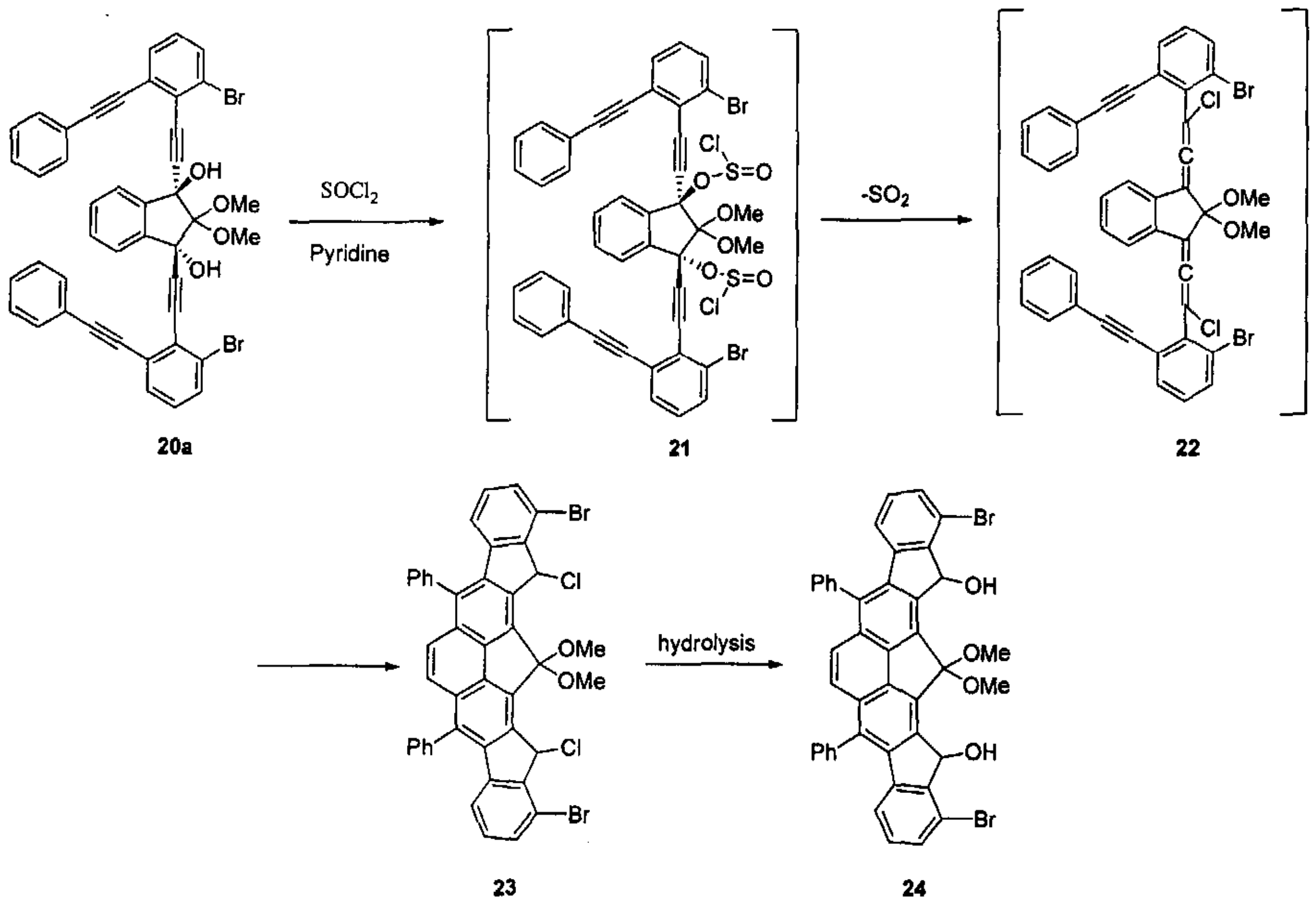
The characteristic ^{1}H NMR signals of the reported *trans*-propargylic diol **3a** was used to identify the corresponding *trans* propargylic diol **20a** possessing two bromo substituents. Both *trans* propargylic diols **3a** and **20a** exhibit ^{1}H NMR signals at δ 7.70 as doublet of doublet arising from the aromatic portion of indane moieties. A singlet at δ 3.84 arising from the two methoxy groups of **20a**, and a singlet at δ 3.83 also arising from the two methoxy groups of **3a** were observed. In addition a triplet signal at δ 7.13 can be attributed to the aromatic hydrogens meta to the bromo substituents in **20a**. The HRMS of **20a** is also consistent with the assigned structure (Figure 3).


Br
doublet of doublet
δ 7.70
H
OH
OCH3
OCH3
OH
one singlet
δ 3.84
Br
triplet
δ 7.13
H
doublet of doublet
δ 7.70
one singlet
δ 3.83

20a **3a**

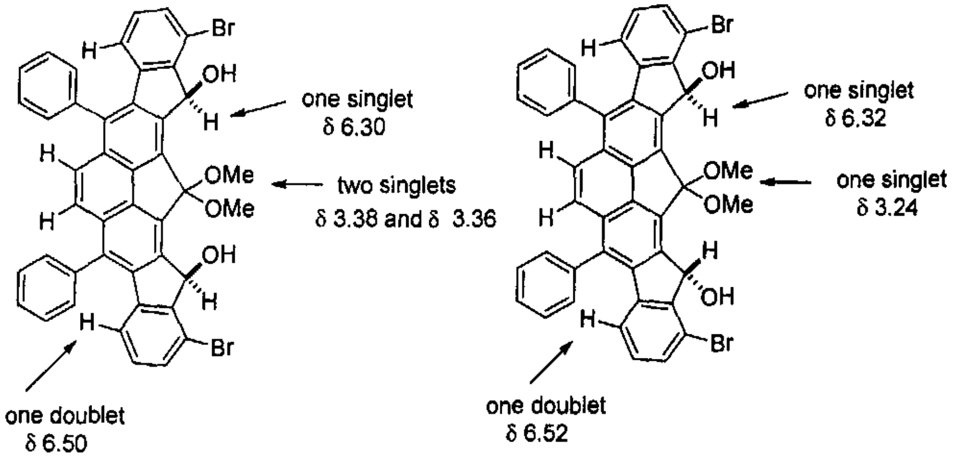
Figure 3 Structures of compounds **20a** and **3a** and the characteristic ^1H NMR signals

Treament of propargylic diol **20a** with thionyl chloride promoted a sequence of reactions with the initial formation of the chlorosulfite **21** followed with two S_Ni' reactions[23] to generate in situ the chlorinated benzoenyne-allene **22** (Scheme 12). Then the following Schmittel cyclization reactions produced the Diels-Alder adduct **23**. Dichloride **23** is prone to hydrolysis, and produced, after column chromatography over silica gel, a small amount of diol **24** as a mixture of the *cis*-isomer **24a** and *trans*-isomer **24b**.



Scheme 12

Due to the orientation of the phenyl substituents in **24a** and **24b,** the neighboring aromatic hydrogens on the benzene rings bearing a bromo substituent are shielded magnetically. As a result, the proton NMR signals of these hydrogen atoms are shifted upfield to δ 6.50 (doublet, **24a**) and δ 6.52 (doublet, **24b**), respectively. In addition, the hydrogens on the five-membered rings of the two fluorenyl subunits exhibit ^{1}H NMR signals at δ 6.30 (singlet, **24a**) and δ 6.32 (singlet, **24b**), respectively. Furthermore, two singlets at δ 3.38 and δ 3.36 arising from the two methoxy groups of **24a**, and a singlet at δ 3.24 arising from the two methoxy groups of **24b** were observed (Figure 4). The HRMS of the mixture is also consistent with the elemental composition of assigned structures.


Br
H
OH
H
one singlet
δ 6.30
H
OMe
OMe
two singlets
δ 3.38 and δ 3.36
H
OH
H
H
Br
one doublet
δ 6.50
Br
H
OH
H
one singlet
δ 6.32
H
OMe
OMe
one singlet
δ 3.24
H
H
OH
H
Br
one doublet
δ 6.52

24a **24b**

Figure 4 Structures of compounds **24a** and **24b** and the characteristic ^{1}H NMR signals

4. Conclusions

Two diindeno-fused 4*H*-cyclopenta[*def*]phenanthrene derivatives containing two bromo substituents (**24a** and **24b**) were synthesized. The synthetic route used an excess of 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene (**13**) for condensation with 2,2-dimethoxy-1,3-indandione (**1**) to prepare the corresponding diols for the Schmittel cyclization reaction, leading to a novel molecular carbon framework of diindeno-fused 4*H*-cyclopenta[*def*]phenanthrene bearing two bromo substituents as handles for further Sonogashira coupling reactions. Such a synthetic sequence could provide a new synthetic pathway for the construction of macrocyclic acetylenes.

Part II

EXPERIMENTAL SECTION

Glassware used for all reactions were dried in an oven (110 °C) for at least 8 hours. All reactions were carried under a nitrogen atmosphere. Dichloromethane, diethyl ether, ethyl acetate, hexanes, and methanol were reagent grade and used as received. All other liquid reagent and solid chemicals were purchased from chemical suppliers and were used as received. Anhydrous tetrahydrofuran ($\geq$ 99.9%), anhydrous diethyl ether ($\geq$ 99. 7%), *N,N*-dimethylformamide (DMF) (anhydrous, 99.8%), Copper(I) iodide, iodomethane, lithium diisopropylamide solution (2.0 M) in THF/*n*-heptane/ethylbenzene, *n*-butyllithium (1.6 M) in hexanes, pyridine (anhydrous), and thionyl chloride were purchased from Sigma-Aldrich. Ninhydrin, triethylamine (99.7%), triphenylphosphine, phenylacetylene, and iodine were purchased from Acros Organics. Silver (I) oxide was purchased from Strem Chemicals, Inc. Bis(triphenylphosphine)palladium(II) dichloride, and trimethylsilylacetylene were purchased from Oakwood Products, Inc. Silica gel for flash column chromatography was purchased from Dynamic Adsorbents. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded in $CDCl_3$ using $CHCl_3$ (^{1}H δ 7.26) and $CDCl_3$ (^{13}C δ 77.0) as internal standards.

1,3-dibromo-2-iodobenzene (16)[21]

A solution of 2.0 mL of 1,3-dibromobenzene (**15**) (3.9 g, 16.5 mmol) in 50 mL of anhydrous THF under a nitrogen atmosphere was cooled to –78 °C. After 15 min of stirring, 25 mL of a 2.0 M solution of LDA (50 mmol) was added dropwise at –78 °C. After 2 hours of stirring at –78 °C, a solution of 6.3 g of iodine (24.8 mmol) in 20 mL of anhydrous THF was introduced dropwise via cannula, and the reaction mixture was allowed to warm to room temperature. After overnight, 30 mL of water was introduced, and the reaction mixture was then extracted with 50 mL of diethyl ether. The organic layer was washed with brine and water, dried with sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/ hexanes) to produce 4.16 g of **16** (11.5 mmol, 72%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.55 (2 H, d, $J = 7.8$ Hz), 7.07 (1 H, t, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 131.3, 131.1, 130.3, 109.3.

1,3-dibromo-2-[2-(trimethylsilyl)ethynyl]benzene (17)

A mixture of 1,3-dibromo-2-iodobenzene (**16**) (3.39 g, 9.36 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.329 g, 0.468 mmol), copper(I) iodide (0.178 g, 0.936 mmol), and triphenylphosphine (49 mg, 0.187 mmol) was dissolved in 30 mL of triethylamine and flushed with nitrogen. After 15 min of stirring, 2.45 mL of (trimethylsilyl)acetylene (1.84 g, 18.7 mmol) was introduced dropwise. Then the reaction mixture was heated to reflux at 69 °C. After 3 hours of reflux, an additional 2.45 mL of (trimethylsilyl)acetylene (1.84 g, 18.7 mmol) was added dropwise. After an additional 3 hours of reflux at 69 °C, 50 mL of water was added, and the reaction mixture was extracted with 50 mL of diethyl ether. The organic layer was filtered to remove precipitates, and the filtrate was dried with sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/30% ethyl acetate in hexanes) to produce 2.49 g of **17** (7.5 mmol, 80 %) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.52 (2 H, d, *J* = 7.8 Hz), 6.99 (1 H, t, *J* = 8.4 Hz), 0.30 (9 H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 131.2, 129.7, 127.0, 126.6, 105.4, 101.7, –0.27.

1-bromo-3-iodio-2-[2-(trimethylsilyl)ethynyl]benzene (18)

A solution of 1.44 g of 1,3-dibromo-2-[2-(trimethylsilyl)ethynyl]benzene (**17**) (4.3 mmol) in 30 mL of anhydrous diethyl ether under a nitrogen atmosphere was cooled to –78 °C. After 15 min of stirring, 4.1 mL of a 1.6 M solution of *n*-butyllithium (6.5 mmol) was introduced dropwise at –78 °C. After 2 hours of stirring at –78 °C, a solution of 1.65 g of iodine (6.5 mmol) in 20 mL of anhydrous diethyl ether was introduced dropwise via cannula, and the reaction mixture was allowed to warm to room temperature. After overnight, 50 mL of water was introduced, and the reaction mixture was extracted with 50mL of diethyl ether. The organic layer was washed with brine and water, dried with sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/30% ethyl acetate in hexanes) to produce 1.54 g of **18** (4.0 mmol, 94 %) as a light-yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.76 (1 H, dd, *J* = 7.8, 1.2 Hz), 7.54 (1 H, dd, *J* = 7.8, 1.2 Hz), 6.81 (1 H, t, *J* = 8.4 Hz), 0.31 (9 H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 137.6, 132.0, 130.9, 130.0, 125.1, 105.3, 104.3, 101.6, -0.29.

1-bromo-2-[2-(trimethylsilyl)ethynyl]-3-(2-phenylethynyl)benzene (19)

A mixture of 1-bromo-3-iodio-2-[2-(trimethylsilyl)ethynyl]benzene (**18**) (1.35 g, 3.6 mmol) , bis(triphenylphosphine)palladium(II) dichloride (0.075 g, 0.10 mmol), and copper(I) iodide (0.034 g, 0.18 mmol) was dissolved in 30 mL of triethylamine and flushed with nitrogen. After 15 min of stirring, 0.46 mL of phenylacetylene was added at room temperature. After overnight, 50 mL of water was introduced, and the reaction mixture was extracted with 50 mL of diethyl ether. The organic layer was filtered to remove precipitates, and the filtrate was dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/30% ethyl acetate in hexanes) to produce 0.99 g of **19** (2.8 mmol, 78 %) as a yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.58–7.56 (2 H, m),7.53 (1 H, dd, J = 7.8, 1.2 Hz), 7.46 (1 H, dd, J = 7.8, 1.2 Hz), 7.385–7.34 (3 H, m), 7.12 (1 H, t, J = 8.4 Hz), 0.29 (9 H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 132.0, 131.7, 130.4, 128.7, 128.6,128.4, 127.9, 127.4, 125.9, 122.9, 104.3, 101.7, 94.2, 87.7, -0.11.

1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene (13)

To a solution of 0.41 g of 1-bromo-2-[2-(trimethylsilyl)ethynyl]-3-(2-phenylethynyl)benzene (**19**) (1.15 mmol) dissolved in 30 mL of diethyl ether and 30 mL of methanol was added 20 mL of a 10% sodium hydroxide solution. The reaction mixture was stirred for 3 hours at room temperature, and then extracted with 50 mL of diethyl ether. The organic layer was washed with 25 mL of a 2.0 M solution of hydrochloric acid and 50 mL of water, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/ pure hexanes) to produce 0.31 g of **13** (1.10 mmol, 96%) as a dark-yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.58–7.55 (3 H, m), δ 7.49 (1 H, dd, *J* = 7.8, 1.2 Hz), 7.37–3.36 (3H, m), 7.17 (1 H, t, *J* = 8.4 Hz), 3.68 (1 H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 132.0, 131.8, 130.5, 129.1, 128.8, 128.5, 128.4, 126.3, 125.9, 122.7, 94.4, 87.3, 86.0, 80.8.

propargylic diols 20a, 20c, and propargylic mono-ol 20b

A solution of 0.67 g of 1-bromo-2-ethynyl-3-(2-phenylethynyl)benzene **(13)** (2.4 mmol) in 20 mL of anhydrous THF under a nitrogen atmosphere was cooled to 0 °C. After 15 min of stirring, 1.14 mL of a 2.0 M solution of lithium diisopropylamide (LDA) (2.28 mmol) was added dropwise at 0 °C. After 30 min of stirring at 0 °C, a solution of 0.67 g of diketone **1** (0.57 mmol) in 20 mL of anhydrous THF was introduced dropwise via cannula, and the reaction mixture was allowed to warm to room temperature. After 1 hour of stirring, 20 mL of water was added and the reaction mixture was extracted with 40 mL of diethyl ether. The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/20% ethyl acetate in hexanes) to produce 0.92 g of **20a** (1.2 mmol, 50 %) as a yellow solid and 0.55 g of **20b** (1.13 mmol, 47 %) as yellow solid. **20a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.70 (2 H, dd, *J* = 5.4, 3.0 Hz), 7.53 (2 H, dd, *J* = 7.8, 1.2 Hz), 7.50–7.46 (6 H, m), 7.35–7.29 (6 H, m), 7.21(2H, dd, *J* = 6.0, 3.0 Hz), 7.13 (2 H, t, *J* = 7.8 Hz), 3.84 (6H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 142.0, 132.0, 131.9, 130.7, 129.8, 129.0, 128.6, 128.3, 128.2, 126.5, 126.0, 124.5, 122.7, 109.8, 96.4, 94.2, 87.4, 85.4, 77.3, 53.4; HRMS calcd for $C_{43}H_{28}Br_2O_4Na$ (MNa^+) 791.0226, found 791.0236;

20b: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.89 (1 H, d, *J* = 8.4 Hz), 7.73 (1 H, d, *J* = 7.2 Hz), 7.57–7.34(9 H, m), 7.14 (1H, t, *J* = 8.4 Hz),3.62 (3H, s) 3.59 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.6, 136.2, 131.9, 131.8, 131.7, 131.6, 131.4, 130.6, 129.9, 129.1, 128.6, 128.2, 128.2, 128.2, 128.1, 127.9, 126.0, 125.1, 124.0, 122.5, 102.0, 94.0, 87.1, 86.9, 74.2, 51.9, 51.7; HRMS calcd for $C_{27}H_{19}BrO_4Na$ (MNa^+) 509.0359, found 509.0367.

diols 24a and 24b

A solution of 0.568 g of propargylic diol (**20a**) (0.074 mmol) in 50 mL of anhydrous THF under a nitrogen atmosphere was cooled to 0 °C. After 15 min of stirring, a mixture of 0.03 mL of thionyl chloride (0.44 mmol) and 0.08 mL of anhydrous pyridine (1.0 mmol) in 20 mL of anhydrous THF was added via cannula. Then the reaction mixture was allowed to warm to room temperature. After 1 hour, 20 mL of water and 30 mL methylene chloride were added. The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/20% ethyl acetate in hexanes) to produce little amounts of **24a** and **24b** as dark red solid. Nonaromatic protons were assigned to **24a** and **24b** as indicated earlier in the section of Results and Discussion. **24a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.50 (2H, d), 6.30 (2H, s), 3.38 (3H, s), 3.36 (3H, s); **24b**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.52 (2H, d), 6.32 (2H, s), 3.34 (6H, s); HRMS calcd for $C_{43}H_{29}Br_2O_4$ (MH^+) 767.0427, found 767.0440.

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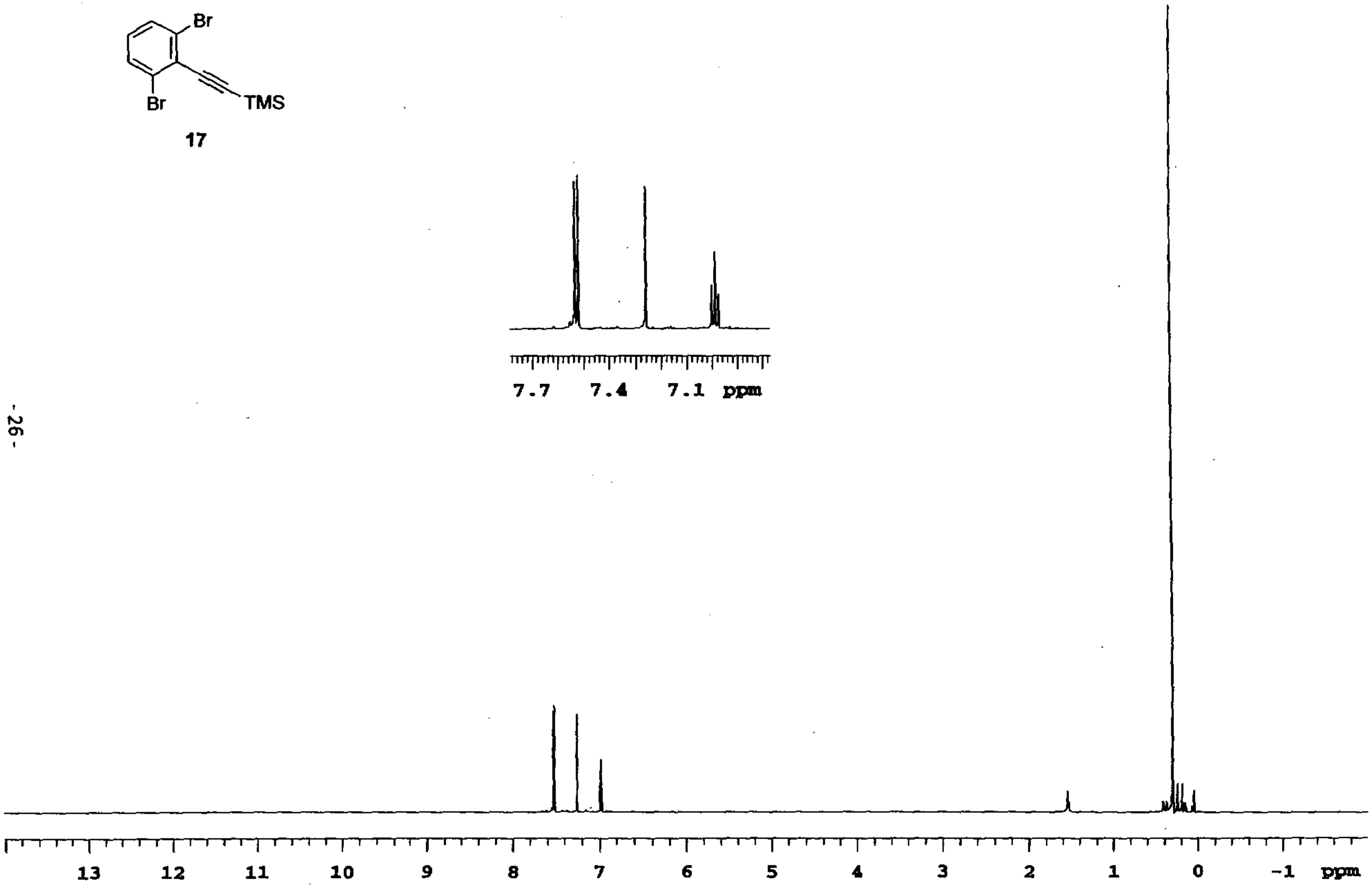
APPENDIX



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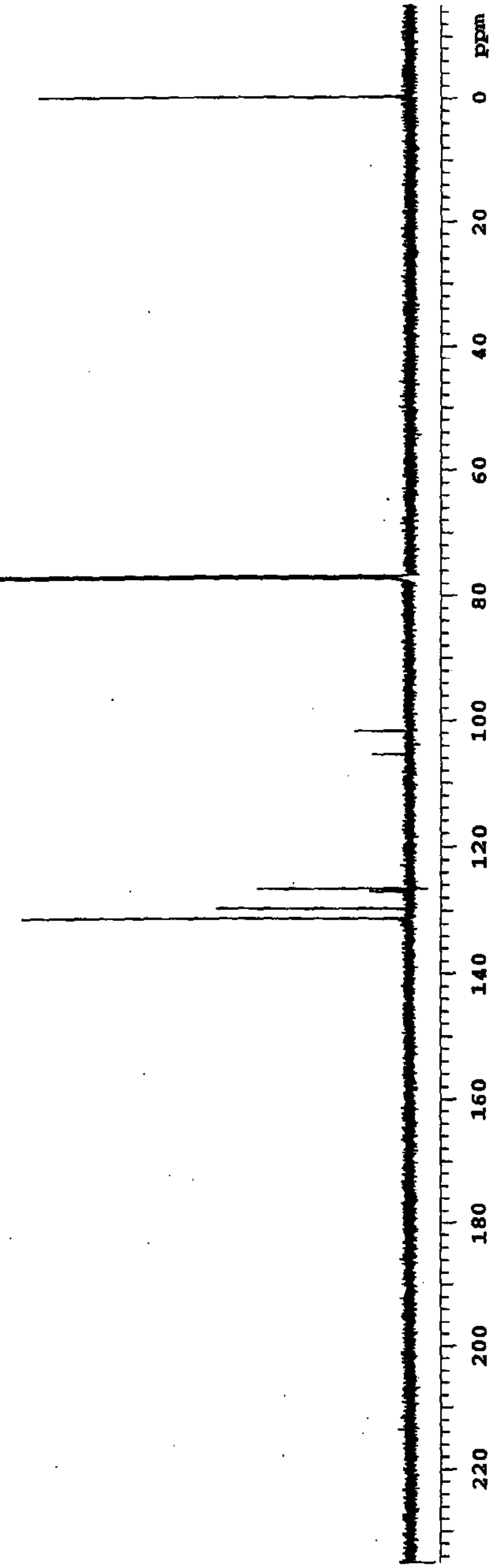

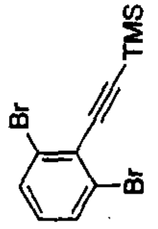

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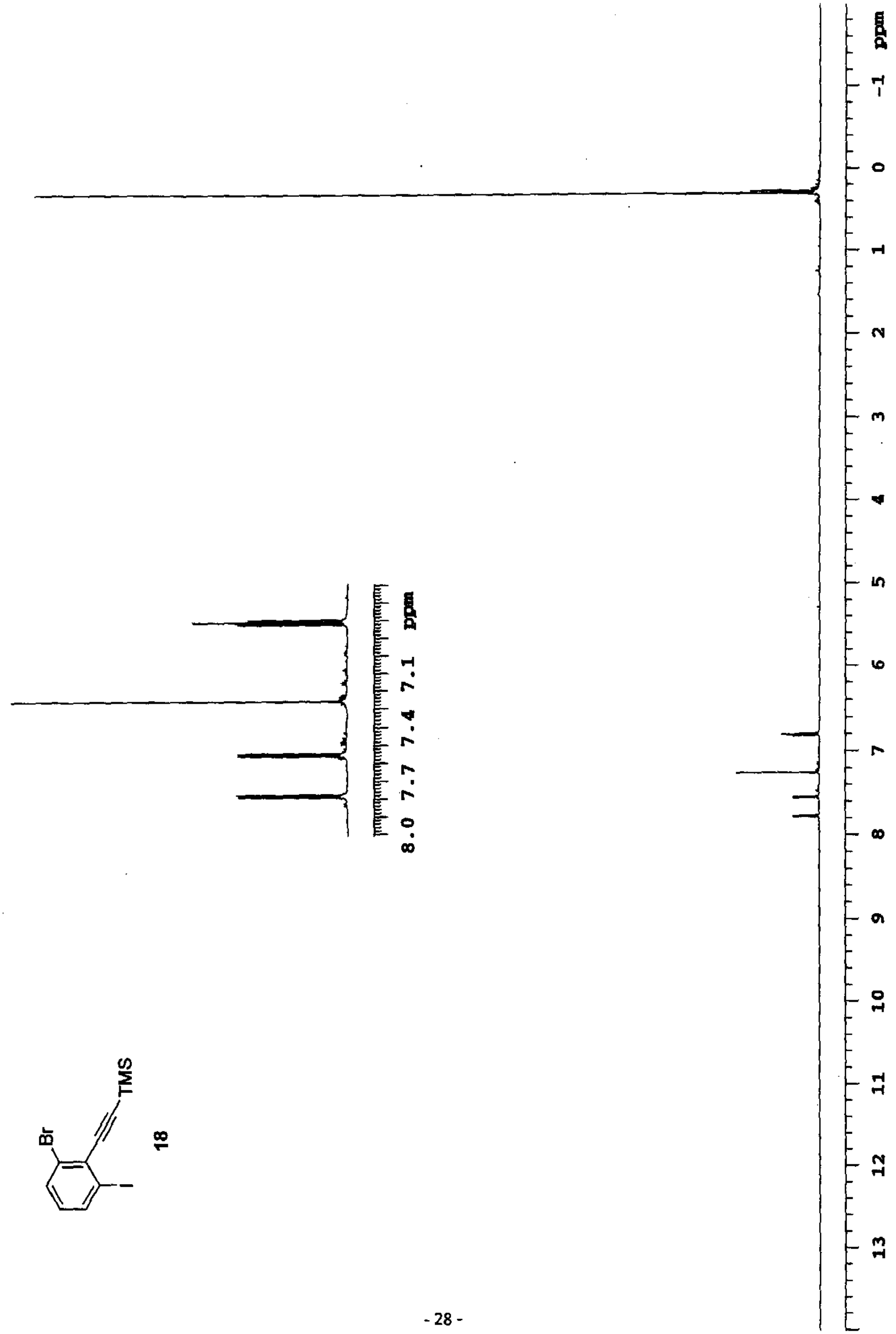

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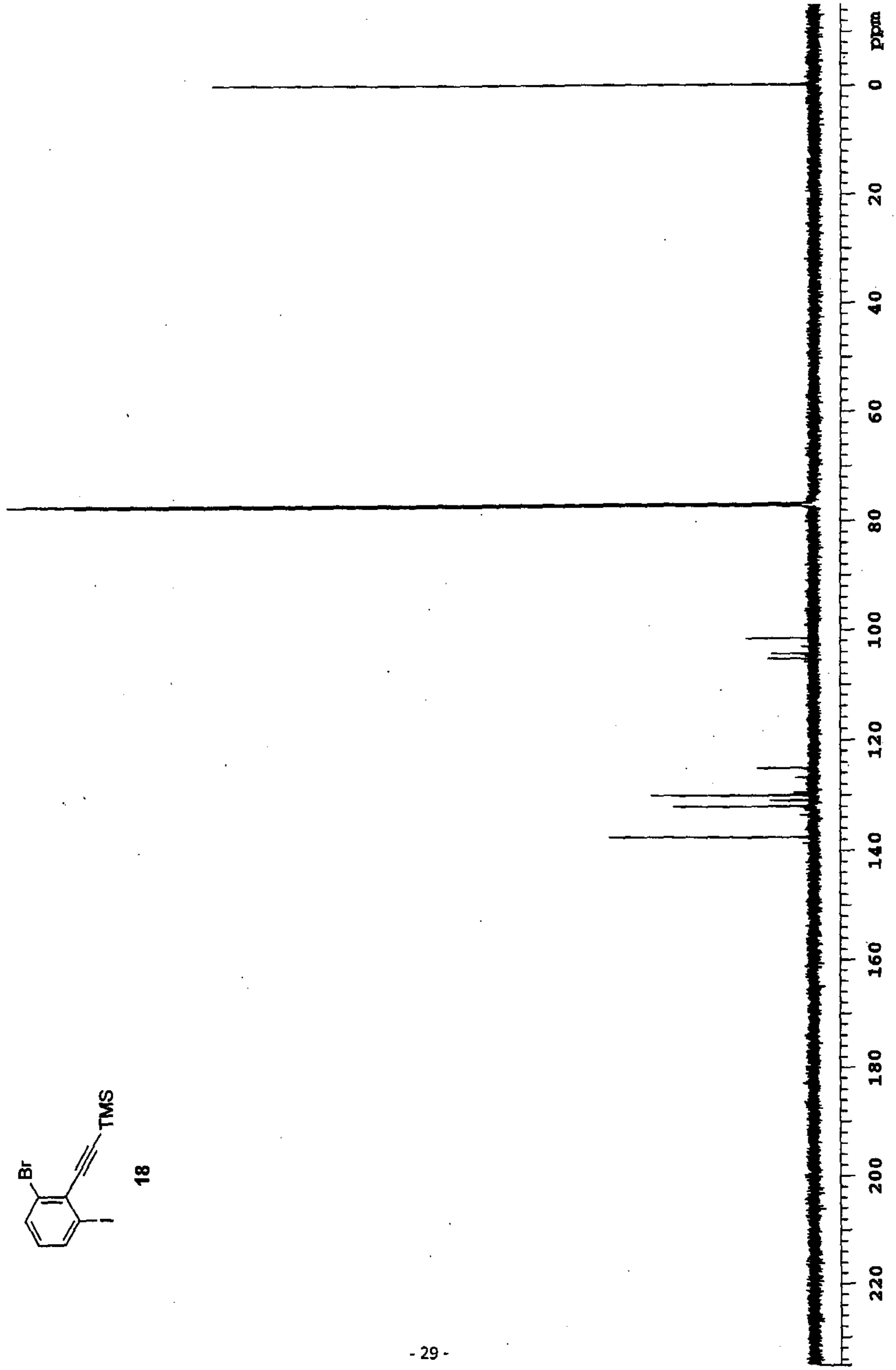

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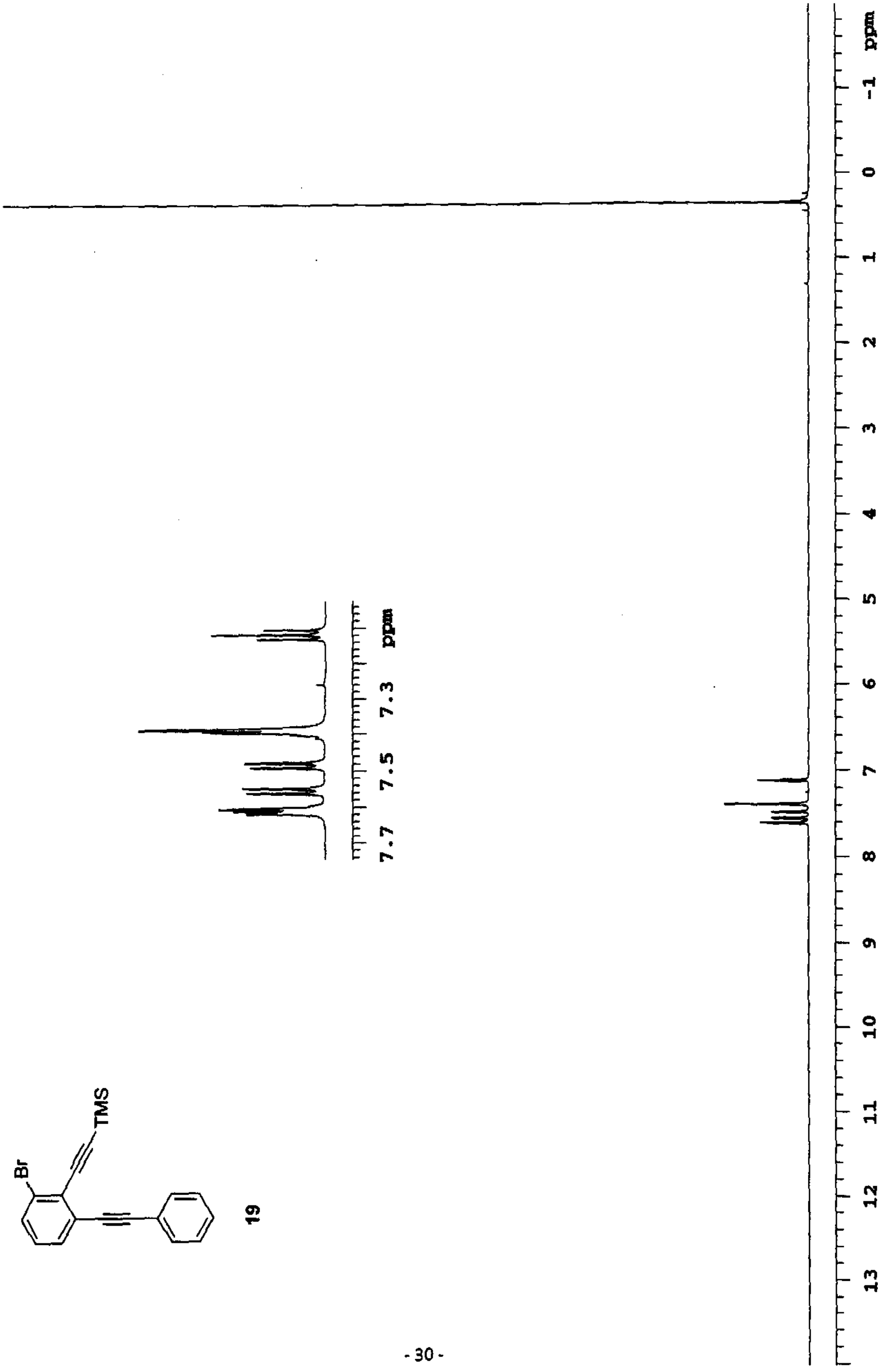

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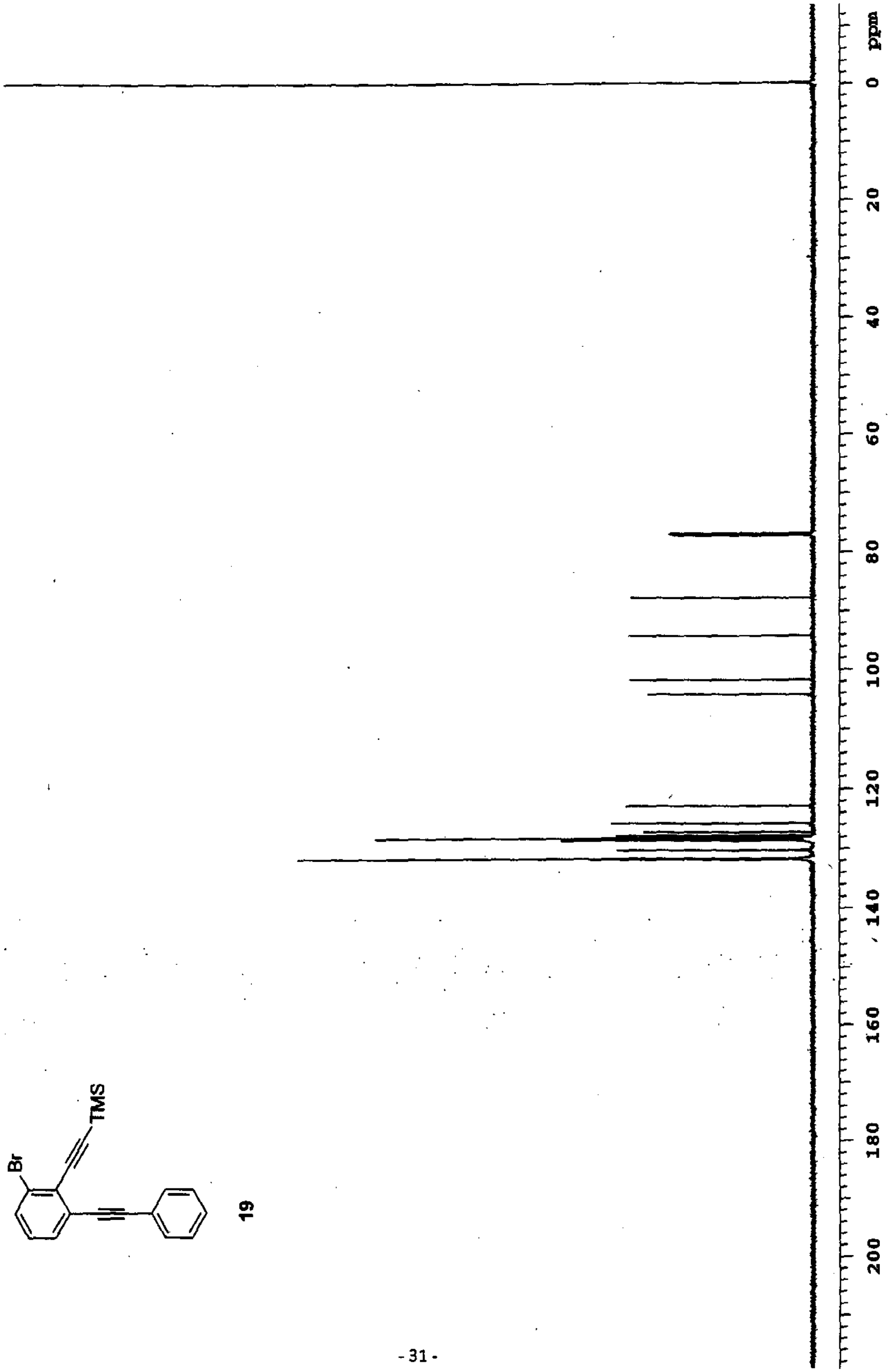

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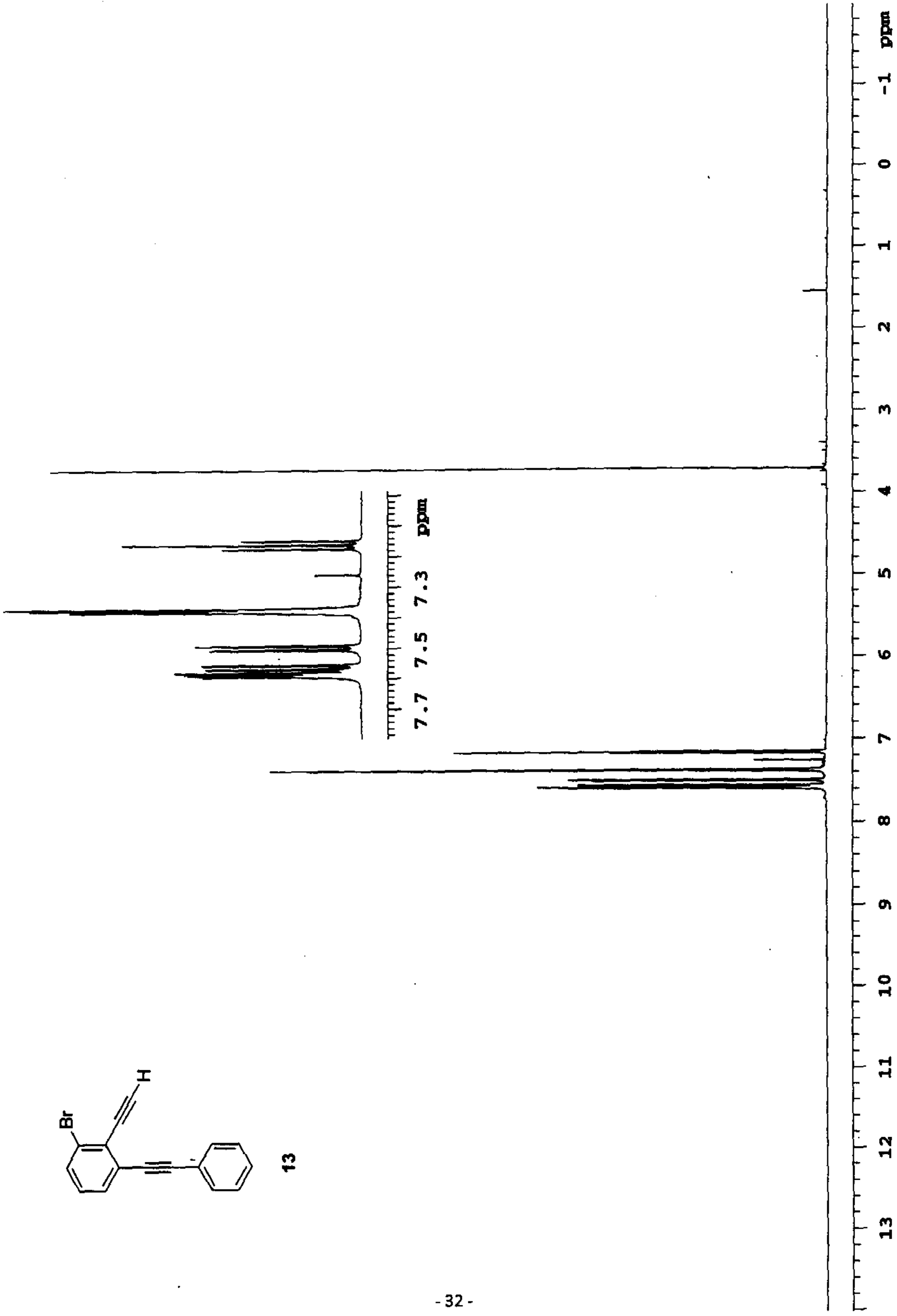

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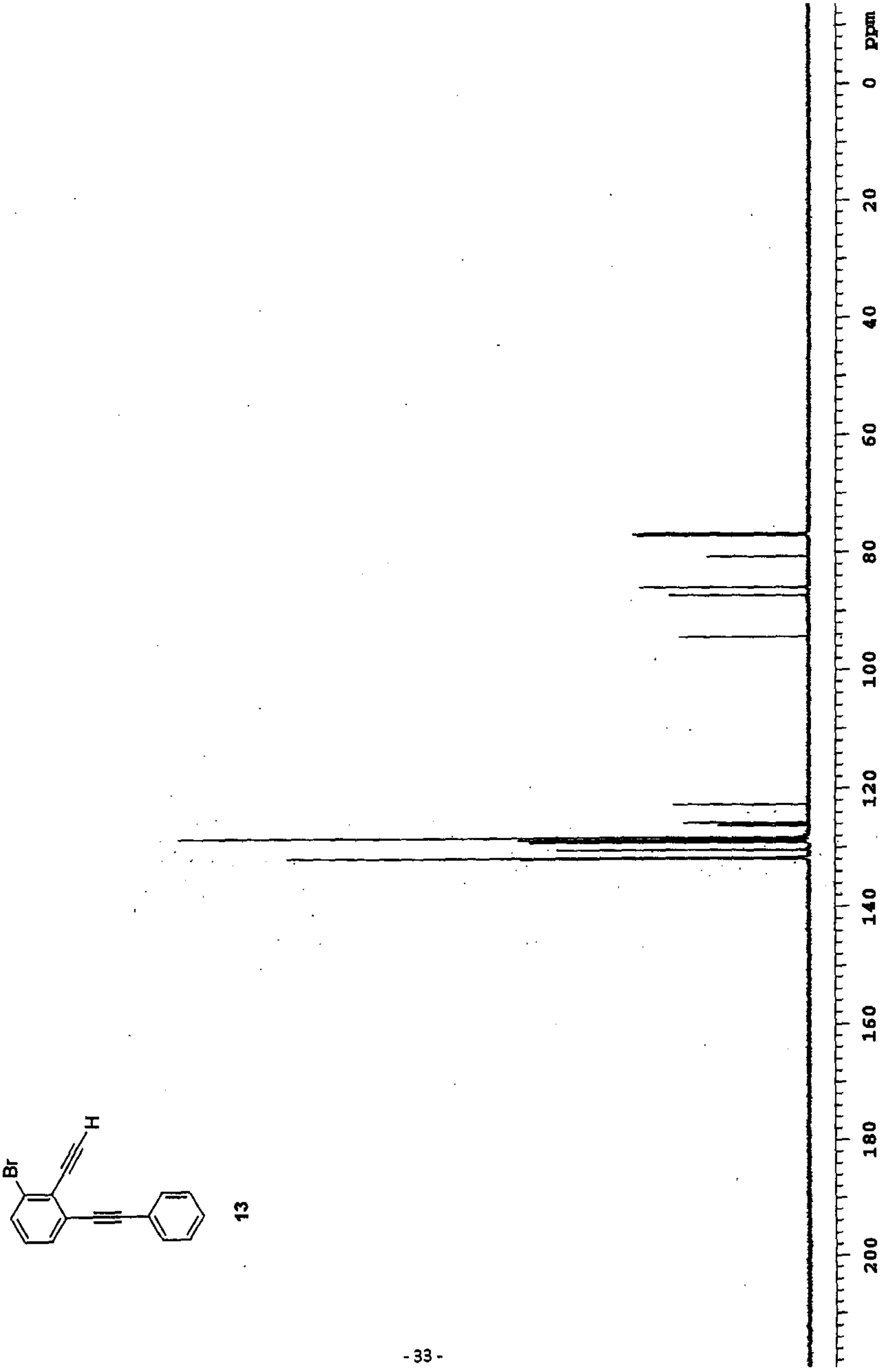

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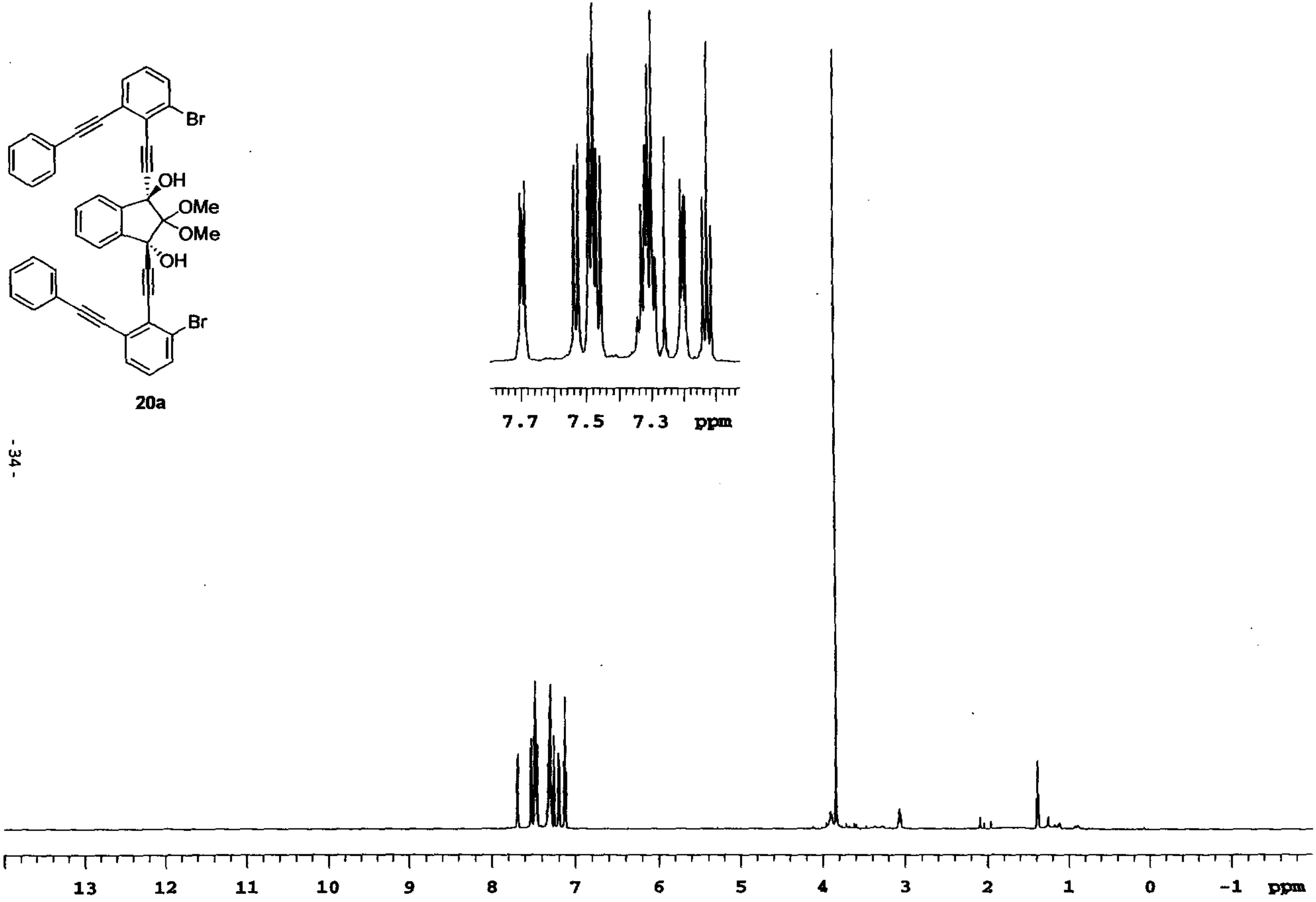

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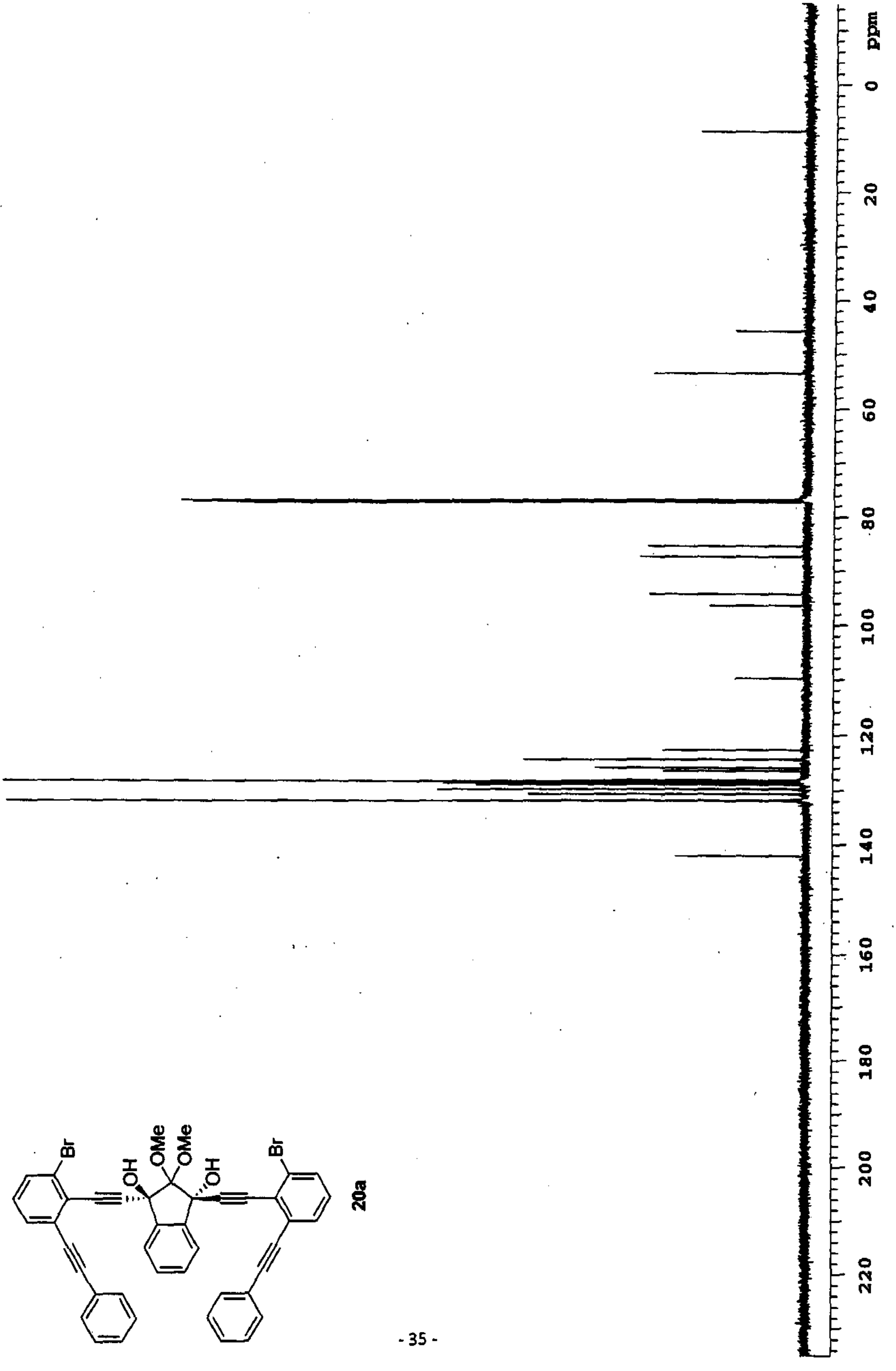

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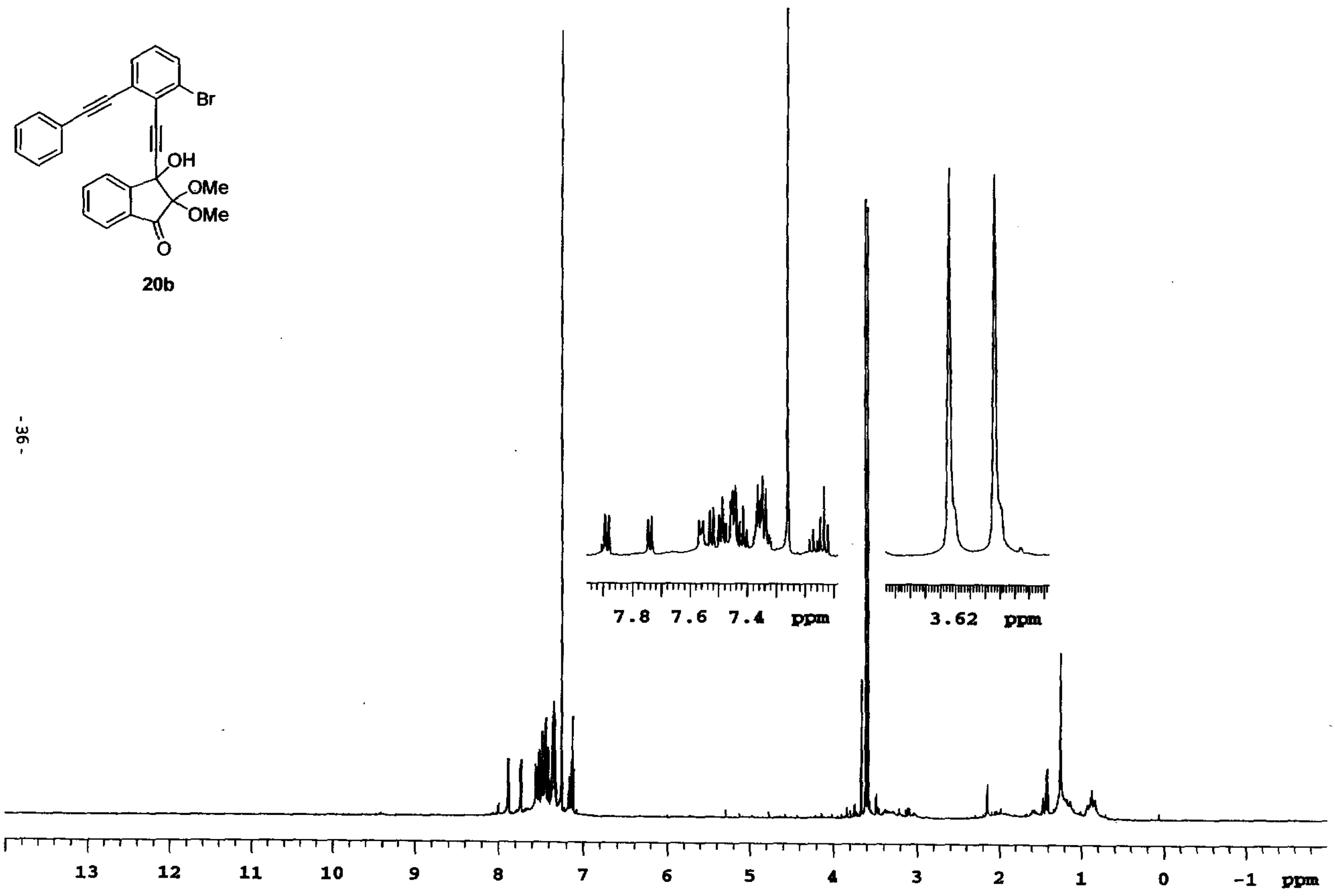

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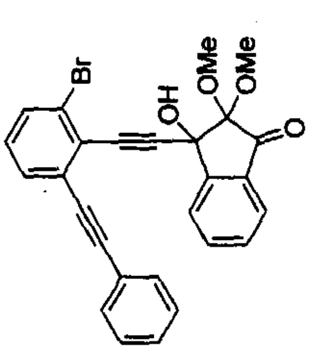
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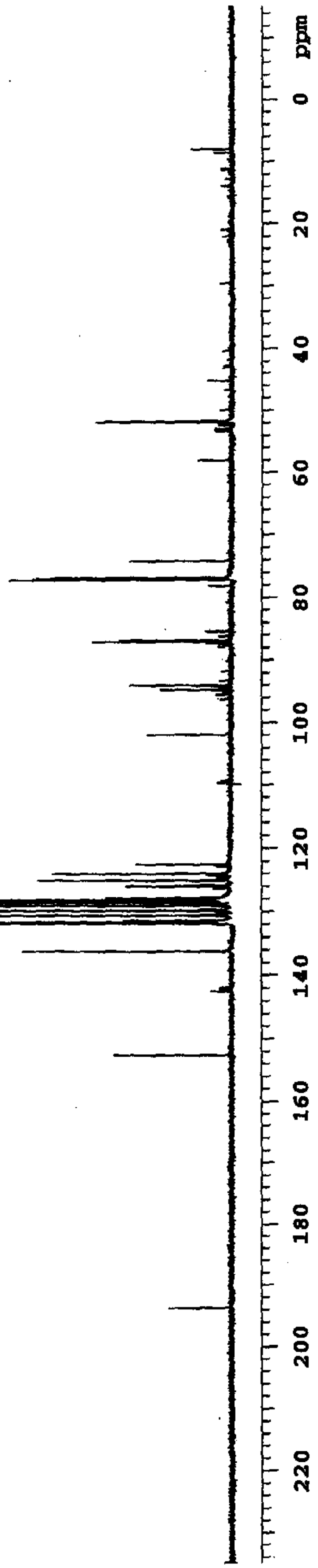
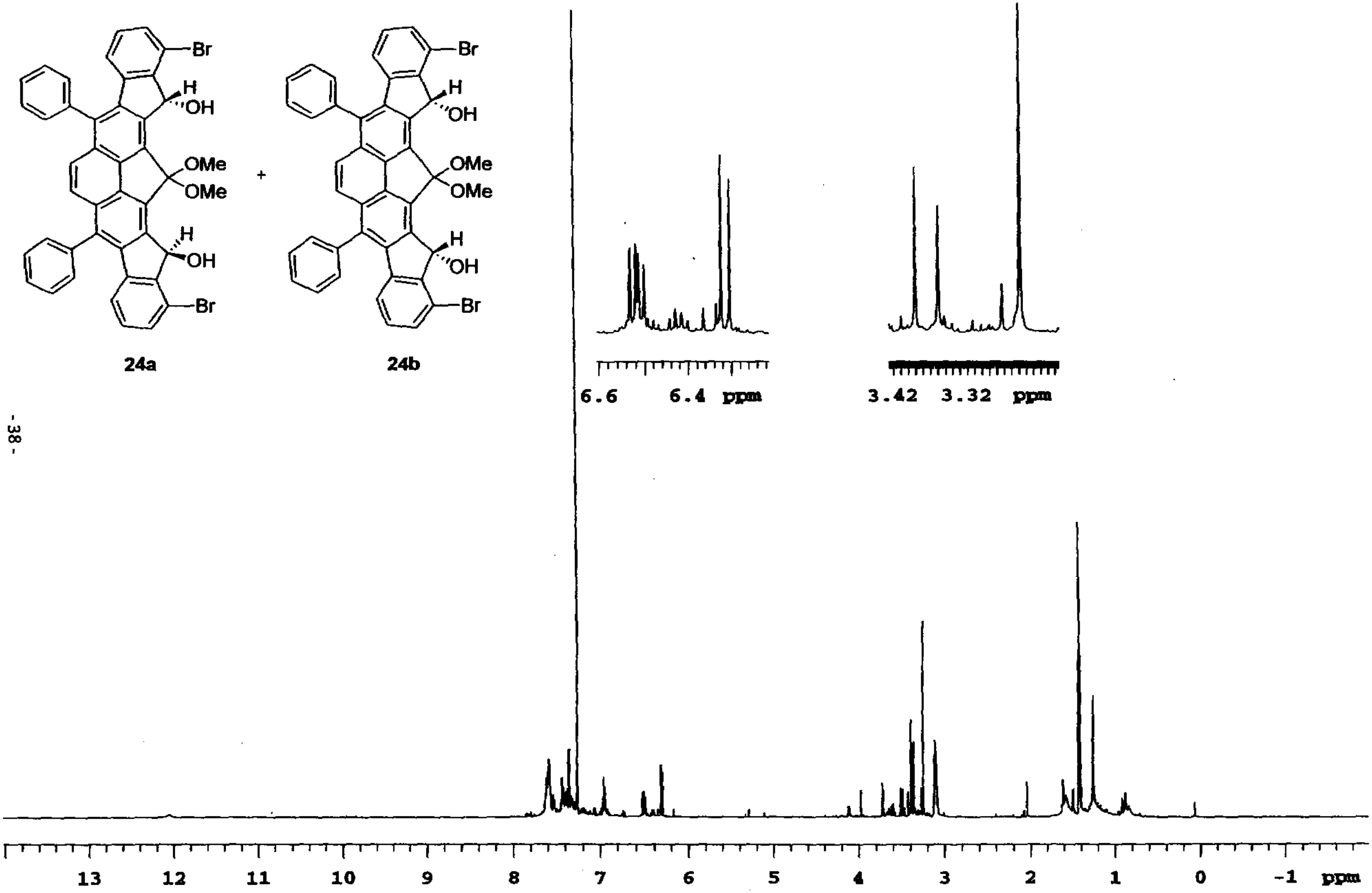
OH
OMe
OMe
O

20b




Br
H
OH
OMe
OMe
H
OH
Br
24a
+
Br
H
OH
OMe
OMe
H
OH
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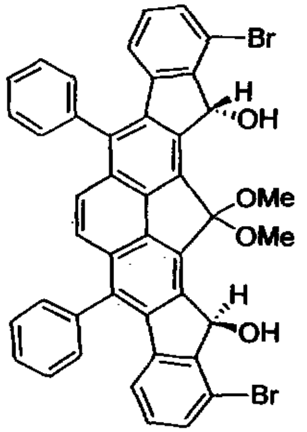
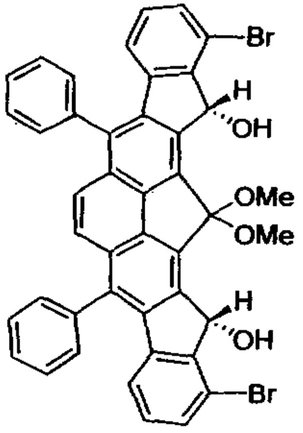
24b
6.6
6.4 ppm
3.42 3.32 ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm


24a

+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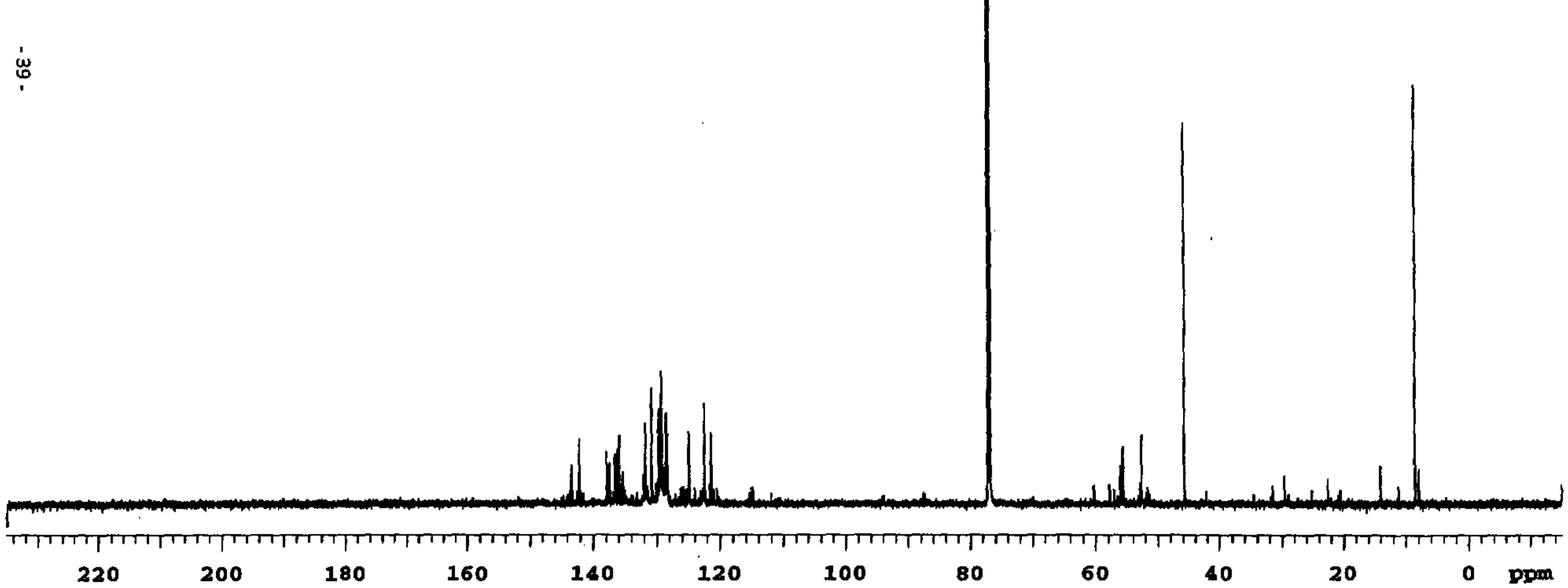

Development of Synthetic Pathways for Macrocyclic Acetylenes

Chi Yuan Tseng

Thesis submitted to the
Eberly College of Arts and Sciences
at West Virginia University
in partial fulfillment of the requirements
for the degree of

Master of Science
in
Chemistry

C. Eugene Bennett Department of Chemistry

APPROVAL OF THE EXAMINING COMMITTEE

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7/10/2013

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