Bispropargyl Sulfones, Ethers, Sulfonamides and N-substituted Enediynes: Synthesis and Reactivity

Thesis submitted to the

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of

Doctor of Philosophy

by

Debaki Ghosh

Under the supervision of

Prof. Amit Basak

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KHARAGPUR

APRIL 2016

Dedicated to

My Family

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List of publications

- Ghosh, D.; Jana, S.; Panja, A.; Anoop, A. A.; Basak, A. Reactivity of conformationally constrained bispropargyl sulfones: complete preference for 6π-electrocyclization process *Tetrahedron* **2013**, *69*, 8724.

- Ghosh, D.; Biswas, S.; Ghosh, K.; Basak, A. Garratt–Braverman cyclization on basic alumina: a greenprotocol with improved selectivity *Tetrahedron Lett.* **2014**, *55*, 3934.

- Ghosh, D.; Pal, P.; Basak, A. Sonogashira Coupling and Garratt-Braverman Cyclization in Tandem: Formation of Four C–C Bonds Leading to the Synthesis of Aryl Dihydro Isofurans and Isoindoles *Tetrahedron Lett.* **2015**, *56*, 1964.

- Panja, A.; Ghosh, D.; Basak, A. A chemo-enzymatic route to differentially protected aryl-naphthalenes. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 893.

- Roy, B.; Hatial, I.; Ghosh, D.; Addy, P.S.; Basak, A. Synthesis of Fused γ-Lactam Derivatives by Intramolecular Carbene Insertion and Aza-Wittig Reaction *Indian J. Chem., Sect B*, **2013**, *90*, 1841.

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- Diamond Jubilee Symposium on Recent Trends in Chemistry (October 21-23, 2011), organized by Department of Chemistry, Indian Institute of Technology Kharagpur, India.

DECLARATION

I certify that

a) The work contained in the thesis is original and has been done by myself under the guidance of my supervisor.

b) The work has not been submitted to any other Institute for any degree or diploma.

c) I have followed the guidelines provided by the Institute in preparing the thesis.

d) I have conformed to the norms and guidelines given in the Ethical Code of Conduct of the Institute.

e) Whenever I have used materials (data, theoretical analysis, and text) from other sources, I have given due credit to them by citing them in the text of the thesis and giving their details in the references. Further, I have taken permission from the copyright owners of the sources, whenever necessary.

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Abbreviations

Ar	Aryl
aq	aqueous
BC	Bergmann Cyclization
Bn	Benzyl
cm	Centimeter
1,4-CHD	1,4-Cyclohexadiene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
DHP	Dihydropyran
DMP	Dess-Martin Periodinane
DNA	Deoxyribonucleic Acid
DFT	Density Functional Theory
DCM	Dichloromethane
DIPEA	N,N-Diisopropyl ethyl amine
DMAP	N, N-Dimethylamino pyridine
DMF	N, N-Dimethylformamide
DMSO	Dimethylsulfoxide
EtOAc	Ethyl acetate
e.g	For example
eq	Equivalent
ESI	Electro Spray Ionization
et al.	And others
Et_3N	Triethylamine
FTIR	Fourier Transform Infrared Spectroscopy
GB	Garratt-Braverman
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
i.e	That is

IR	Infrared Spectroscopy
kcal	Kilo calories
kj	Kilo joules
*m*CPBA	*meta*-Chloroperoxybenzoic acid
min	minute
mL	milliliter
mol	Mole
mmol	millimoles
Ms	Methanesulfonyl
MSC	Myers-Saito Cyclization
m.p	Melting point
NMR	Nuclear Magnetic Resonance
Ns	*p*-nitrobenzenesulfonyl
PE	Petroleum Ether
Ph	Phenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
rt	Room temperature
SC	Schmittel Cyclization
TBAB	Tetrabutylammonium bromide
TEA	Triethylamine
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TS	Transition State
UV	Ultraviolet
vs	Versus

Symbol	
°C	Degree celcius
Δ	Heat
hυ	Light (Irradiation)
Å	Angstrom (10^{-10} m)
α	Alpha
β	Beta
γ	Gamma
g	Gram
h	Hour
K	Kelvin
k	Rate constant
m	Meta
o	Ortho
p	Para
T	Temperature
μL	Microlitre

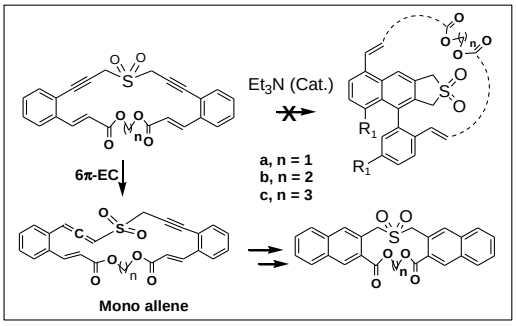
NMR data

s	singlet
bs	broad singlet
d	doublet
t	triplet
q	quartet
m	multiplet
δ	chemical shift in ppm
J	coupling constant in Hz
Hz	Hertz
MHz	Mega Hertz

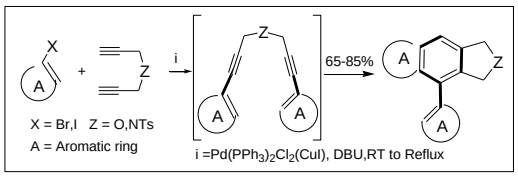
Abstract

Bispropargyl Sulfones, Ethers, Sulfonamides and N-substituted Enediynes: Synthesis and Reactivity

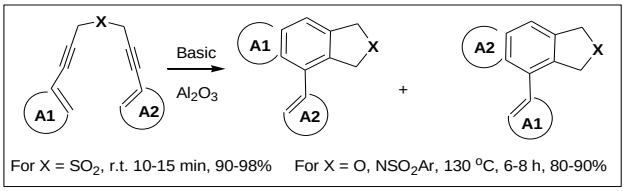
Cycloaromatization reaction involving radicals is an atom economical and elegant pathway for the generation of substituted benzene derivatives where from a closed-shell neutral molecule, unstable reactive centers (*e.g.* diradicals) are created. The Garratt-Braverman cyclization (GBC) is a self-quenching radical cyclization process and is the main topic of interest of the present thesis. In the **first chapter** we have given a brief introduction on various cycloaromatization processes. This is followed by a description of the synthesis and reactivity *bis*-dieneyl propargyl sulfones (**Chapter 2**). These sulfones under basic condition isomerize to the corresponding *bis*-Z-dienylallenic sulfones which are capable of undergoing two parallel processes, namely, GBC and 6π-electrocyclization (6π-EC) with a preference towards GBC. By incorporating conformational constraint in these molecules, we have successfully reversed the preference towards 6π-EC (**Scheme 1**). In **Chapter 3**, we have discussed the results of carrying out GBC on a basic alumina surface. This protocol produced the aryl-naphthalenes in high yields and also showed higher selectivity for GB cyclization of unsymmetrical ethers and sulfonamides as compared to conventional solution phase synthesis (**Scheme 2**). In **Chapter 4** we have described a multistep one-pot synthesis of dihydro isofurans and isoindoles. The usual procedure for the synthesis of aryl dihydro isofuran and isoindole derivatives requires three steps. By carrying out two Sonogashira coupling steps and GB cyclization in a single pot, we have obtained better overall yield in comparison to the synthesis *via* multistep procedure (**Scheme 3**). In **Chapter 5** the synthesis of a 1,8-diamino naphthalene based enediyne has been described. The effect of intramolecular H-bonding present in the system in lowering the onset temperature for Bergman Cyclization has been demonstrating by comparing the reactivity reported for the13-membered cyclic enediyne (**Scheme 4**).



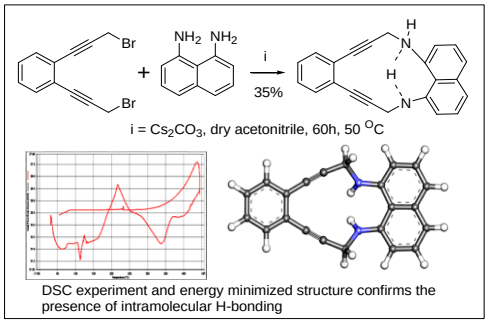
Scheme 1: GBC vs. 6π-EC



Scheme 3: One pot synthesis of aryl naphthalene



Scheme 2: GBC on basic alumina



Scheme 4: Proton sponge based enediyne

Keywords: Garratt-Braverman, 6π-EC, diradical, basic alumina, one pot, enediyne, H-bonding

CONTENTS

Chapter 1

An Overview on Cycloaromatization Reaction

1.1 Introduction

Cycloaromatization is an atom economical and straightforward pathway for the generation of substituted benzene derivatives. Most of the cycloaromatization reactions can be classified as either a cyclization of a reactive species like cation, anion and radical or pericyclic ring closure. Metal mediated or catalyzed cycloaddition of alkynes also plays a crucial role in this field. Radical cyclization, in particular, serves as a most powerful tool for the generation of cyclic system where from a closed-shell neutral molecule, unstable reactive centers (e.g diradicals) are created. In general its mechanistic pathway involves the breaking of two π-bonds and formation of one σ-bond, thus resulting in a net loss of a chemical bond which makes the reaction thermodynamically less favourable. The aromatic stabilization gained in the product partially compensates thermodynamic loss. These unusual reactions allow radical transformations to occur without the need for external radical initiators because simultaneous formation of two radical centers is coupled to the bond-forming step. In addition to the structural diversity outlined above, there is increasing evidence that cycloaromatization reactions extend far beyond radical chemistry to encompass processes where aromatization is coupled to the formation of zwitterions and carbenes. The two radical centers in a diradical are truly independent only if there is no coupling between the two odd electron centers. On the other hand, pericyclic ring closure proceeds *via* breaking and formation of several bonds and cyclic reorganization of electron density without involvement of any unstable reactive intermediate.

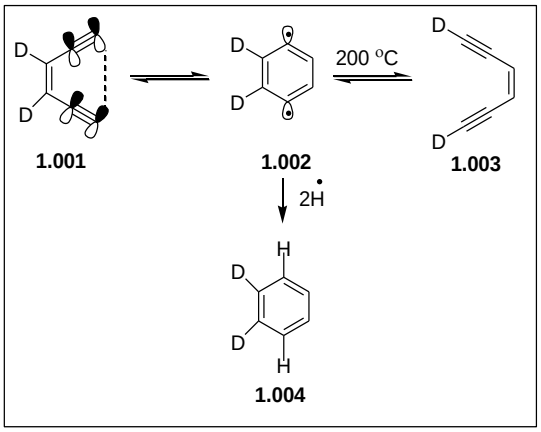
Enediyne and enyne allenes are the two most suitable structural motifs for cycloaromatization as σ bond formation and aromatization of the π system involves two orthogonal π arrays. Radical based cycloaromatization includes the Bergman cyclization, Schreiner-Pascal cyclization, Myers-Saito cyclization, Schmittel cyclization, Moore cyclization, Garratt-Braverman cyclization, Hopf cyclization, Wang cyclization and the Matzger cyclization, whereas the Pericyclic cycloaromatization includes 6π-electro- cyclization, dehydro Diels-Alder reaction, Wulff-Dotz reaction, the Theodor Wagner-Jauregg reaction. Another useful and direct method is thermal and transition metal catalyzed [2+2+2] cycloaddition. Among the above mentioned diradical reactions, Bergman, Myers-Saito, Schmittel and Moore cyclizations which quench *via* abstraction of atom from external source, find

application in cancer chemotherapy[1] as they can abstract H atom from the sugar-phosphate backbone of DNA resulting in its cleavage.[2] However in the Garratt-Braverman cyclization process, the *bis*-propargylic system and in the Hopf cyclization, the resulting diradicals from *bis*-allenes undergo self quenching phenomenon without interacting with any external sources which makes them less important in medicinal chemistry. Diradicals are also very much important in synthesis of various aromatic compounds[3] including conducting polymers.[4]

Here in this introductory chapter, we are going to discuss briefly these cycloaromatization procedures including their discovery, modification and features.

1.2 Bergman Cyclization

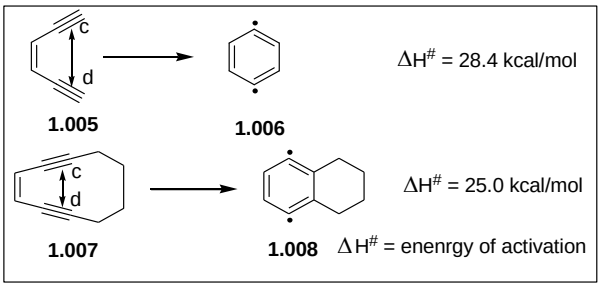
In 1972, Bergman and co-workers[5] found that upon heating above 200 ^{o}C, (*Z*)-3-hexene-1,5-diynes **1.001** generate 1,4-didehydrobenzene σ,σ-diradical **1.002** which in presence of H donor produced corresponding arene through C^1-C^6 diradical cyclization. The reaction is found to be exothermic with an activation energy barrier of 28.5 kcal/mol and first order in enediyne with the formation of diradical in the rate limiting step **(Scheme 1.01).**



Scheme 1.01: Schematic representation of Bergman cyclization

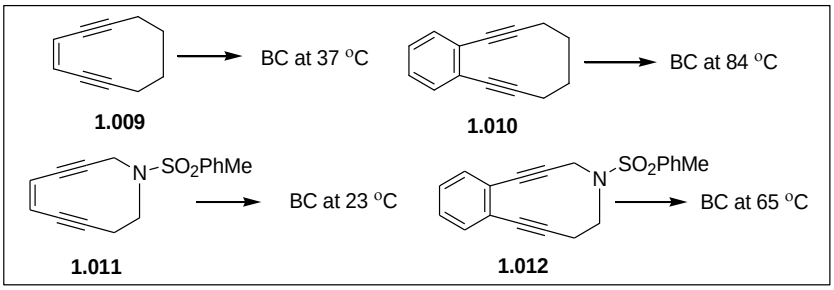
Generally the cyclization is induced thermally or photochemically as the cyclizations have high activation energy barrier. When enediyne natural products, capable of undergoing cycloaromatization at physiological temperature were found,[6] people began to investigate geometric factors that affect the cyclization.

In 1988, Nicolaou *et al.*[7] proposed a hypothesis that for spontaneous cyclization at ambient temperature, the (c,d) distance *i.e.* the distance between the two alkyne termini (**Scheme 1.02**) should be in the range of 3.20-3.31 Å which was later modified to 2.90-3.40 Å by Schreiner[8] using DFT. Cyclic enediynes always have shorter (c,d) distance (~ 3.25 Å) than acyclic enediynes (~ 4.12 Å) which results in cyclic enediynes having lower activation energy barrier compared to the acyclic one (**Scheme 1.02**).



Scheme 1.02: Activation energy for BC of cyclic and acyclic enediynes

When the double bond belongs to an aromatic ring, the cyclization is slower in case of cyclic enediyne (**Scheme 1.03**)**.** Considering retro-Bergman and hydrogen abstraction in kinetic measurement, Hirama *et al.*[9] has explained how change in rate determining step alters the effect of benzannelation process.

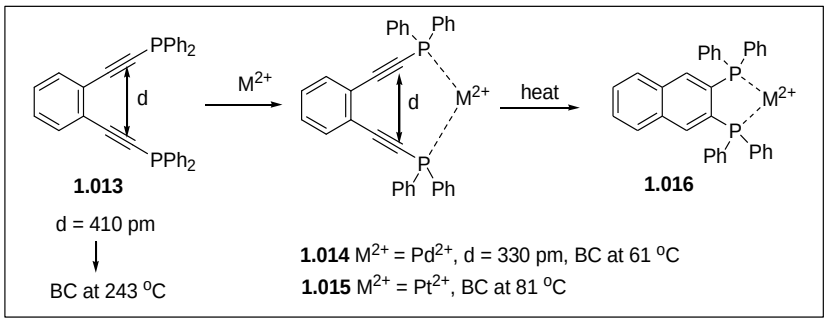


Scheme 1.03: BC of 10 membered cyclic and benzannulated enediynes

Kim and Russell[10] observed that if the ground f of the enediyne is more polar than the transition state then the polar solvents stabilizes the ground state better than the transition state subsequently increasing the activation energy of BC in polar solvent and vice-versa in less polar solvents.

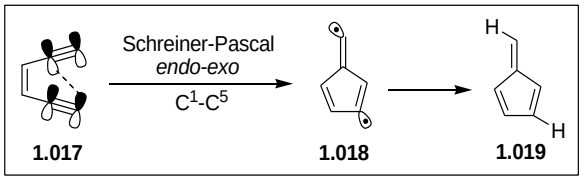
Metals can thermally activate stable enediyne by σ-donor coordination and π-complexation inducing marked reduction in the thermal barrier to the Bergman cyclization (**Scheme 1.04**). In 1995, Buchwald *et al.*[11] showed that after chelation

with $PdCl_2$, the cyclization of **1.013-1.016** was accelerated and activation energy barrier decreased by 6 kcal/mol. Numerous metals such as Cu[12a-c], Ni[12c], Ru[12d], Pd[12e] and Pt[12e] have been used with great success. Mg(II) complexes have also shown exciting results.[13]



Scheme 1.04: Effect of metal complexation on BC

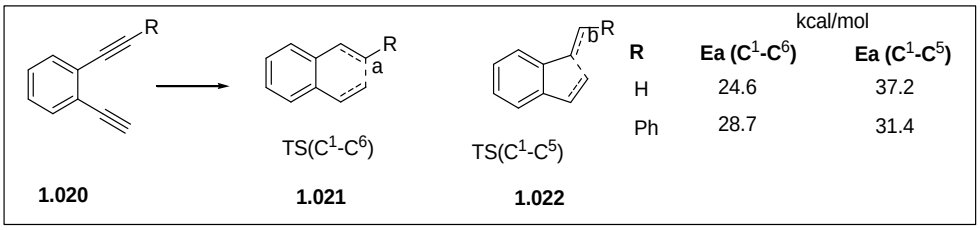
1.3 Schreiner-Pascal Cyclization



Scheme 1.05: Schematic representation of Schreiner- Pascal cyclization

The thermal C^1-C^5 cyclization of enediyne is known as the Schreiner-Pascal cyclization (**Scheme 1.05**). Schreiner *et al.*[14] in 2001, employed computational studies for the parent enediyne, which demonstrated a significantly higher energy barrier for the C^1-C^5 diradical cyclization than for the C^1- C^6 pathway but in sterically challenging systems, theoretical calculations suggest that the difference in energy between five and six-membered ring formations is considerably reduced. Hence this preference can be reversed.

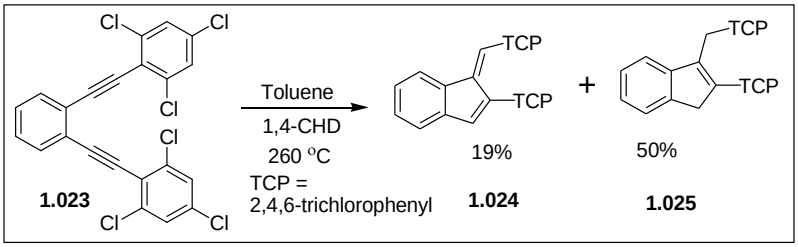
Later in 2008, Pascal *et al.*[15] screened some benzannulated enediynes substituted at the alkyne end. Activation energy for the Bergman cyclization increases by 4 kcal/mol when the hydrogen atom is replaced by a phenyl group (likely a steric effect), but for the C^1-C^5 pathway it decreases by 6 kcal/mol. Incorporation of 2,6-dichlorophenyl group or 2,6-dimethylphenyl group at alkyne termini R, both slows



Scheme 1.06: Activation Energies for the cyclization of monosubstituted 1,2-diethynylbenzene

the Bergman cyclization process. So, it can be concluded that, this is a steric effect and not an electronic effect (**Scheme 1.06**).

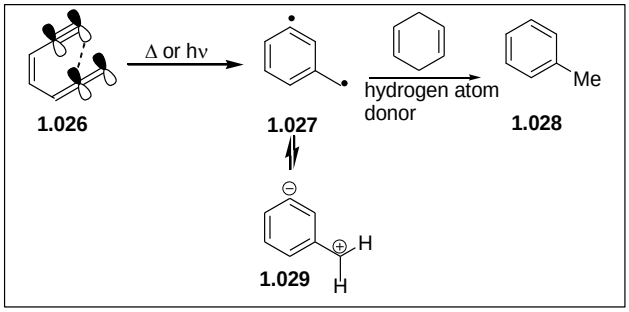
Pascal and co-workers[15] attached 2,4,6-trichlorophenyl (TCP) groups at both the alkyne termini which provided both conjugative effect as well as steric hindrance. The conjugation delocalized the generated diradical with the terminal aryl rings to favour the cyclization. Again, the steric repulsion between the two aryl groups disfavoured reaction by the BC pathway. As a result, the reaction exclusively followed the Schreiner-Pascal cyclization, no trace amount of the Bergman cyclization product was formed (**Scheme 1.07**).



Scheme 1.07: Thermolysis of enediyne 1.023

1.4 Myers-Saito Cyclization

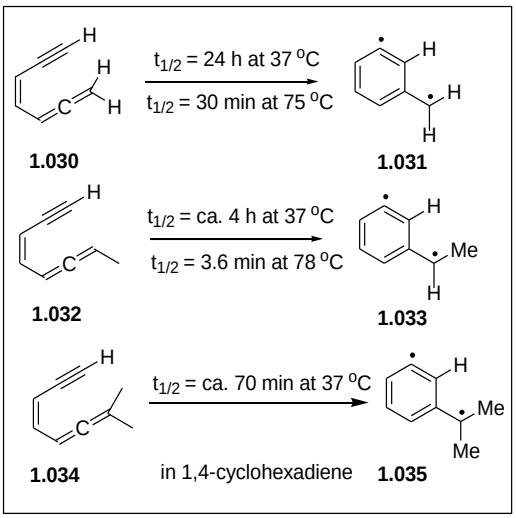
The first order thermal or photochemical cycloaromatization of (*Z*)-1,2,4-heptatriene-6-yne to α,3-didehydrotoluene *via* 1,4-toluene σ, π-diradical intermediate through C^2-C^7 connectivity is known as the Myers-Saito cyclization.[16-17]



Scheme 1.08: Myers-Saito cyclization

Since (c,d) distance of enyne-allenes is shorter than that of enediynes, the Myers-Saito cyclization is more facile and strongly exothermic ($\Delta H \approx -15\pm3$ kcal/mol), whereas the Bergman cyclization is modestly endothermic ($\Delta H \approx 14$ kcal/mol). Both theoretical and experimental evidence support the existence of equilibrium between **1.027** and the zwitterion **1.029** (**Scheme 1.08**)**.** The increase in ionic character is believed to decrease the efficiency of DNA cleavage through the established diradical mechanism.

Presence of methyl group at the allenic end of an enyne-allene[16a] increases the rate of the reaction as it stabilizes the generated benzylic radical (**Scheme 1.09**).



Scheme 1.09: Substitution effect on the rate of Myers-Saito cyclization

In ground state, enyne-allene exists as s-*trans* or twisted s-*trans* conformer, whereas the presence of a substituent at C-3 position, in order to minimize the steric interaction, compels it to attain s-*cis* or twisted s-*cis* conformation which is favoured for the Myers-Saito[17b] cyclization hence lowers the activation energy. The effect has been shown in **Figure 1.1.**

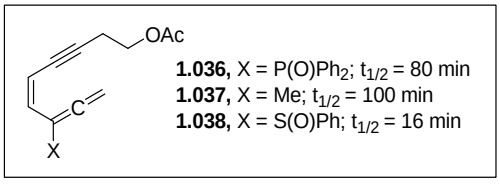
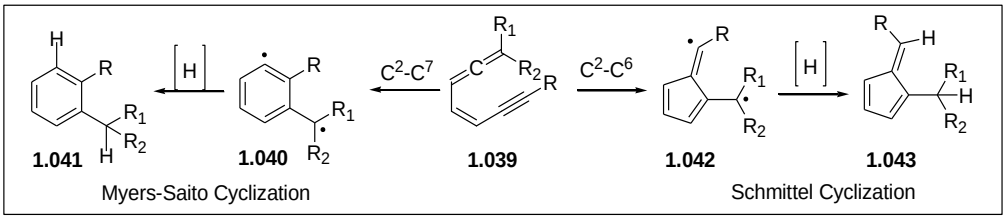


Figure 1.1: C-3 substitution effect on Myers-Saito cyclization

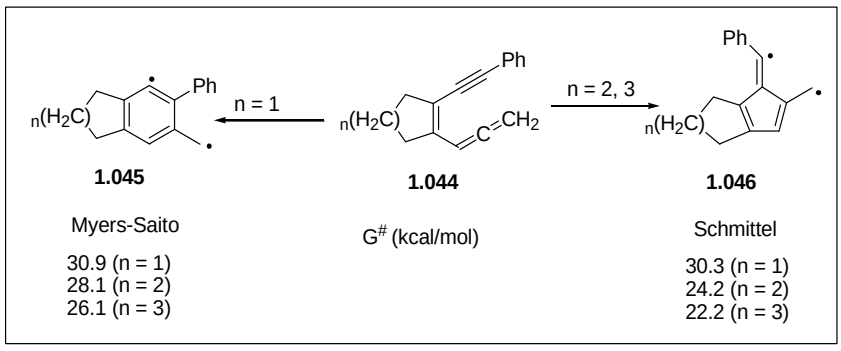
1.5 Schmittel Cyclization

Most of the thermal cyclization of enyne-allenes results in the formation of six-membered rings through the C^2–C^7 pathway. However in 1995, Schmittel *et al.*[18] reported their surprising discovery that some of the masked enyne-allene model system exhibit a novel thermal cyclization model *via* the C^2–C^6 pathway by replacing the hydrogen at the acetylene terminus with an aryl group or a sterically bulky group (R = *t*-Bu or TMS, **Scheme 1.10**).[19]



Scheme 1.10: The Schmittel cyclization

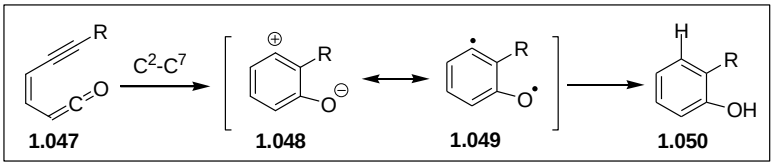
Initially, the switch in the mode of the reaction from the Myers-Saito to the Schmittel cyclization or vice versa, was thought to be a result of the stabilizing effect of the aryl group on the vinyl radical. This novel C^2–C^6 cyclization involves a very short-lived benzofulvene diradical intermediate **1.042** (lifetime < 10^{-8} s). Replacement of the hydrogen at the acetylene unit by a phenyl group[20] stabilizes the vinyl diradical **1.042** over **1.040** subsequently raises the barrier of the MS cyclization by 5 kcal/mol whereas decreases by 3 kcal/mol for the Schmittel cyclization, presumably by steric hindrance and ground state stabilization of the acetylene moiety; therefore the reaction follows the Schmittel cyclization pathway. Thus by introducing strain in the molecule, the preference can be altered (**Scheme 1.11)**.[21]



Scheme 1.11: Switch from the C^2-C^7 cyclization to the C^2-C^6 cyclization

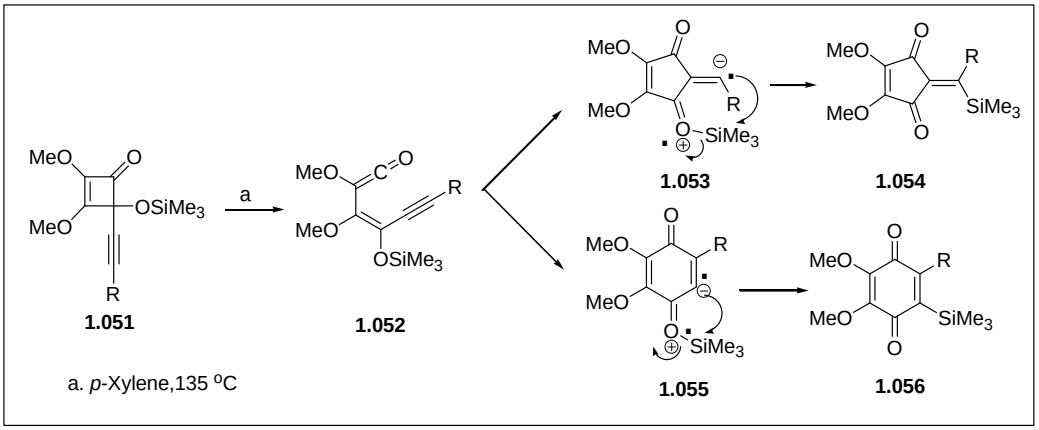
1.6 Moore Cyclization

Enyne-ketene having an oxygen atom at allene termini undergoes a cyclization analogous to Myers-Saito *via* diradical intermediate. This cyclization is known as Moore cyclization.[22] The diradical can also acquire the zwitterionic form **1.048** as exocyclic oxygen atom present facilitates its formation **(Scheme 1.12)**.



Scheme 1.12: Moore cyclization

In 1985, Moore *et al*. synthesized 4-alkynyl-2,3-dimethoxy-4-(trimethyl-siloxy)cyclobutenones **1.051** and its thermolysis was carried out in refluxing *p*-xylene (135 ^{o}C). They found that, when R is an electron withdrawing group, formation of cyclopentenediones **1.054** is favoured and electron releasing groups favour the quinones **1.056**. The proposed mechanism for the conversion of **1.051** to **1.054** and **1.056** is provided in **Scheme 1.13**. Though such migration of a silyl moiety from oxygen to carbon is rare, here it is viewed as being a favourable transformation since such would result in the conversion of zwitterionic intermediates to neutral products.

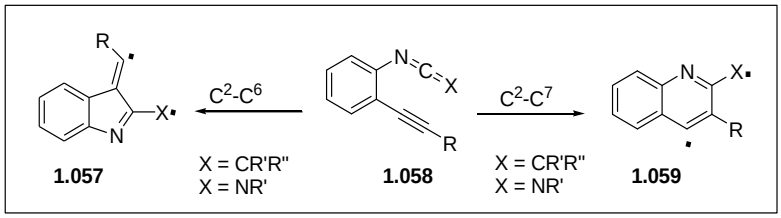


Scheme 1.13: Initial work by Moore *et al*.

Thus different organic products can be prepared by proper trapping of the zwitterionic intermediate, formed during the course of Moore cyclization of substituted eneyne-ketene.[23]

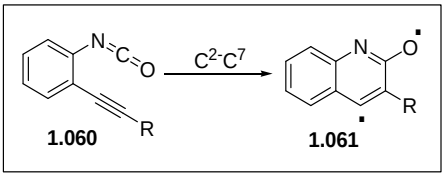
1.7 Wang Cyclization

Wang and co-workers[24] reported that benzannulated enyne-ketenimines and benzannulated enyne carbodiimides also undergo the C^2-C^7 and/or C^2-C^6 cyclization *via* diradical formation depending on the alkynyl substituents (**Scheme 1.14**).



Scheme 1.14: Wang cyclization of enyne-ketenimines and enyne carbodiimides

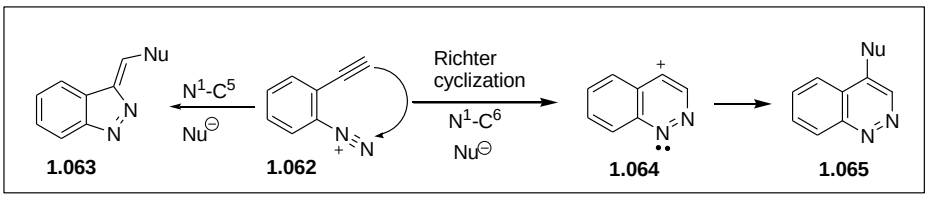
Enyne-isocyanates prepared by Wang and co-workers[25] undergo a cyclization analogous to the Myers-Saito cyclization *via* diradical formation pathway (**Scheme 1.15**). Unlike other hetero-enyne allene systems, such as enyne-allene, enyne-ketene, enyne-ketenimine and enyne-carbodiimide, the cycloaromatization reactions of enyne-isocyanates appear to require higher temperature and are more in favour of the C^2-C^7 cyclization pathway.



Scheme 1.15: Cyclization of enyne-isocyanate

1.8 Richter Cyclization

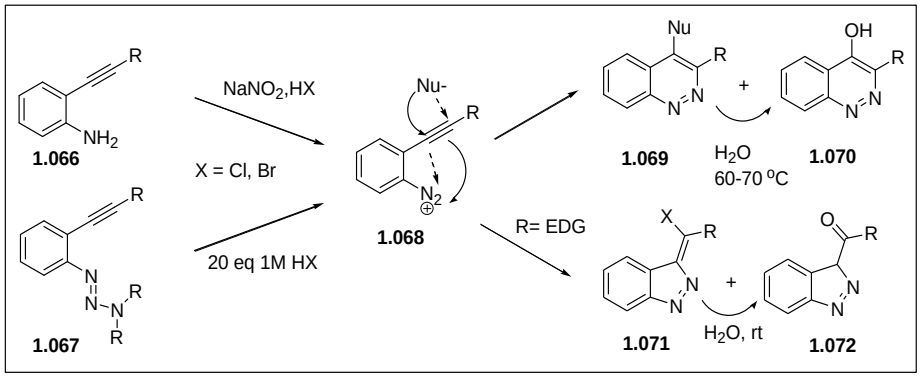
In 1883, Von Richter[26] first reported the ionic cyclization of *vic*-(alkynyl) benzenediazonium. This mechanism is based on direct cycloaromatization *via* the nucleophilic attack of the alkyne at the polarized diazonium moiety, which leads to the formation of an aryl cation as shown in **Scheme 1.16**.



Scheme 1.16: Richter cyclization of ethynyl aryl diazonium salt

Terminal aryl groups have a significant effect on reactivity. Terminal donor groups favour the cyclization and direct it toward the N^1-C^5 (5-*exo*) products. The effect of the terminal aryl substituent on the electronic structure of the reactants is small; but in the transition state, the terminal aryl moiety rotates to provide selective TS stabilization to the developing positive charge at the alkyne β-carbon.

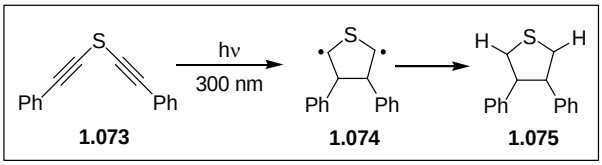
Initially formed diazonium salt **1.068** cyclizes to **1.069** and **1.070** at room temperature upon competitive nucleophilic attack of halide and water. When R is an electron donating group, the alkyne becomes polarized and cyclization produces **1.071** and **1.072.**



Scheme 1.17 Cinnolines and indazoline *via* Richter-type reaction pathways

1.9 Matzger's Work

Matzger and his coworker[27] in 2003, first demonstrated that photo irradiation of *bis*-(phenylethynyl) sulfide **1.073** in hexanes/ 1,4-cyclohexadiene produced 3,4-diphenyl thiophene **1.075** *via* 2,5-didehydrothiophene intermediate **1.074** (**Scheme 1.18**).

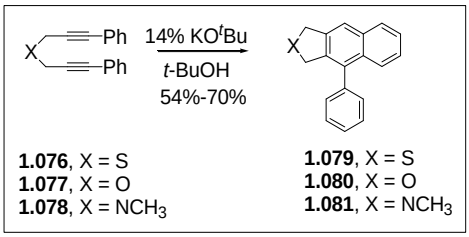


Scheme 1.18: Photochemical activation of *bis*-(phenylethynyl) sulfide

The reaction, [2+2] cycloaddition, thermally being unfavourable does not proceed below 240 ^oC.

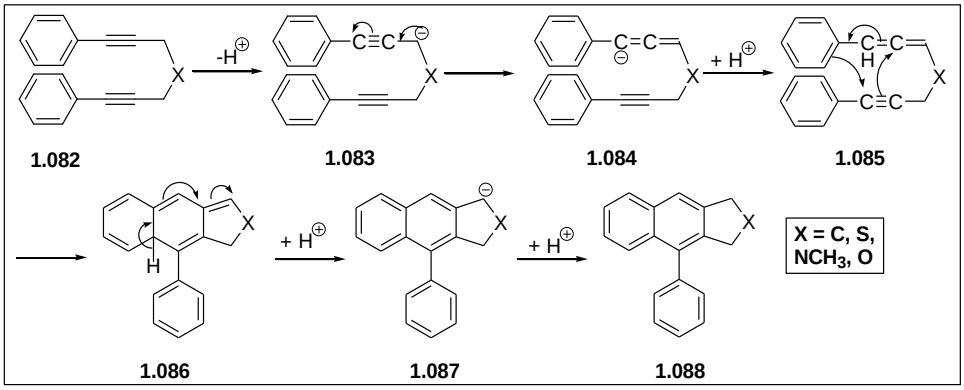
1.10 Garratt-Braverman Cyclization

In 1964, Iwai and Ide[28] showed that 1,7-diphenyl-1,6-heptadiyne and diyne derivative cyclizes with *t*-BuOK in *t*-BuOH to produce naphthalene derivative under mild condition. They carried out the reaction on *bis*-(3-phenyl-2-propargyl) sulfide **1.076** and successfully afforded 4-phenyl-1,3-dihydronaphtho[2,3-c]furan **1.079**. Extension of this process for some other diacetylenic derivatives was found fruitful (**Scheme 1.19**).



Scheme 1.19: Base catalyzed rearrangement of phenyl *bis*-propargyl systems by Iwai and Ide

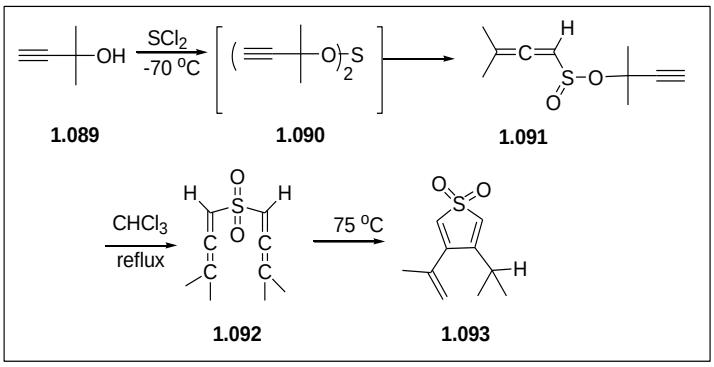
The negative correlation between the reaction time and the electronegativity suggests that proton abstraction from methylene group between triple bond and heteroatom is the preliminary step of the cyclization process. So they concluded that in presence of base, the propargyl system **1.082** undergoes prototropic rearrangement to produce allenic system **1.084** followed by the attack involving π electron of aromatic ring attacking on another triple bond and subsequent attack of the triple bond to the allenic carbon atom (**Scheme 1.20**).



Scheme 1.20: Mechanism proposed by Iwai and Ide

In 1974, Braverman[29] and his co-worker studied the thermal behavior of propargylic sulfoxylates and found that tetramethyldiallenyl sulfone **1.092** upon

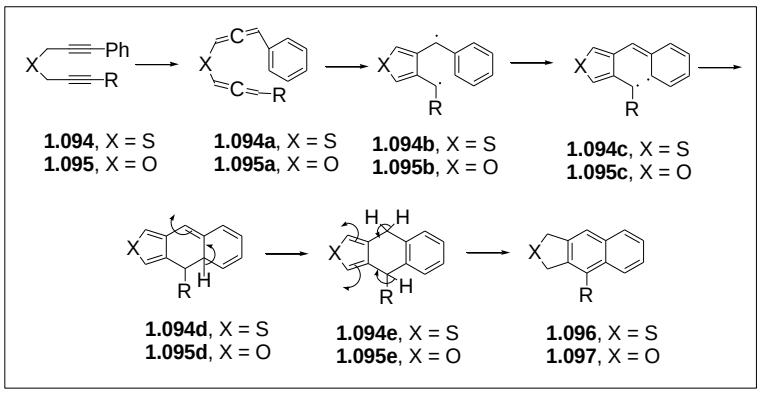
heating at 75 ^{o}C produces thiophene-1,1-dioxo derivative **1.093** in good yield (**Scheme 1.21**).



Scheme 1.21: Braverman's work on *bis*-allenic sulfone rearrangement

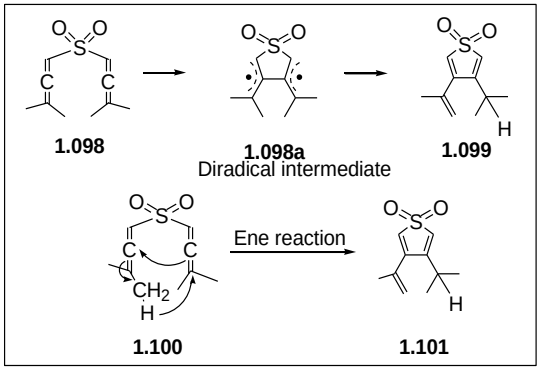
Kinetic study showed that the rate of the rearrangement was insensitive to the polarity of the solvent which eliminates the probability of ionic mechanism operating for the process.

The similar type of reactions of Iwai and Ide was carried out by Garratt *et al.*[30] in 1975. The treatment of **1.094** and **1.095** with K^{t}BuO in THF at 20 ^{o}C for 10 minutes produced **1.094e** and **1.095e** which under more vigorous basic condition or under base treatment for longer time resulted in **1.096** and **1.097**. Looking at the intermediate, Garratt proposed a mechanism contradictory to mechanism proposed by Iwai and Ide. They believed that the *bis*-acetylene rearranges to *bis*-allene which then undergoes intramolecular dimerization to produce heterocyclic *bis*-methylene diradical followed by prototropic rearrangement (**Scheme 1.22**).



Scheme 1.22: Mechanism proposed by Garratt

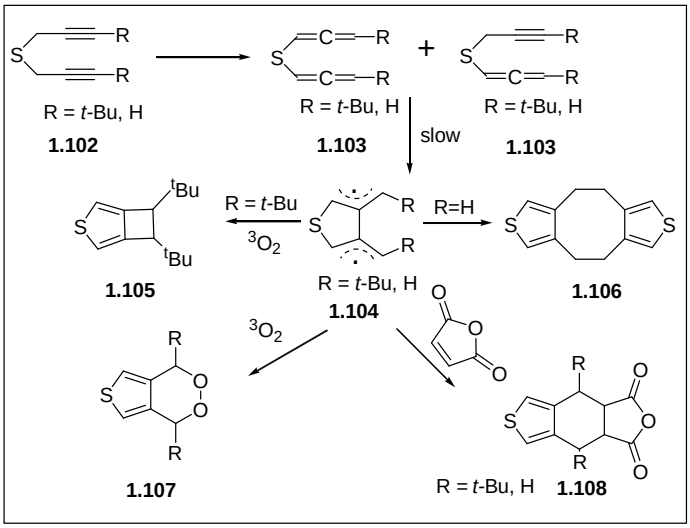
Based on the observation, two possible mechanisms (**Scheme 1.23**) for the reaction can be proposed- i) it is a two step process where in the first as well as rate



Scheme 1.23: Two possible mechanisms for rearrangement

determining step a 2,2'-*bis*-allyl diradical is formed, followed by a rapid proton abstraction and formation of new double bond. In the second step hydrogen transfer of the diradical takes place or ii) the reaction is an intramolecular ene reaction or can also be regarded as a symmetry allowed 1,5-hydrogen shift.

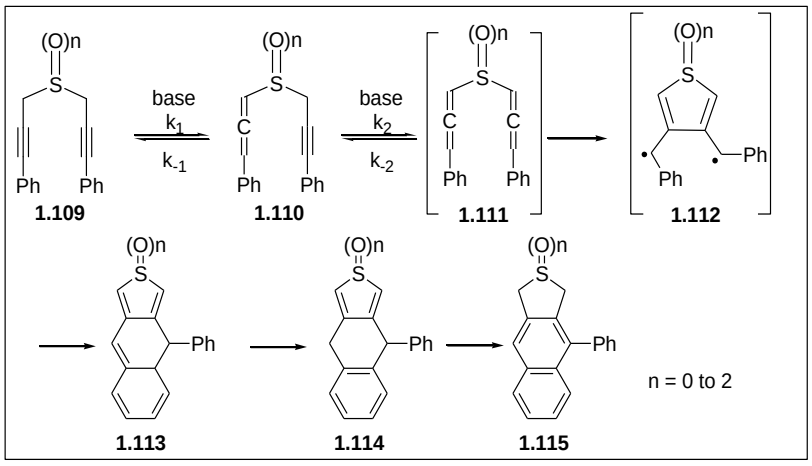
So there was always confusion about the actual mechanism for the process. To confirm the right pathway, in 1990 Braverman[31] performed a kinetic experiment with *bis*-allene which confirmed that the cyclization is a two step process. According to both Garratt and Braverman, the rearrangement is a two-step process involving intramolecular formation of a 2, 2'-*bis*-allyl type diradical intermediate **1.104** in the first, rate determining stage, followed by a fast intramolecular hydrogen abstraction and formation of the new double bond (**Scheme 1.24**). The rearrangement is now known as the Garratt-Braverman rearrangement.



Scheme 1.24: Mechanism involving diradical intermediate proposed by Garratt and Braverman

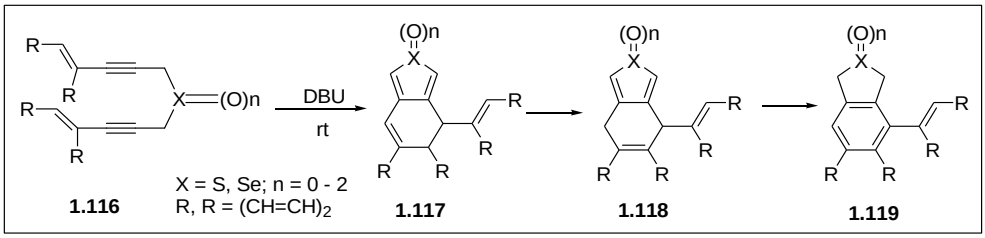
Garratt *et al.*[32] carried out the reaction in presence of $^3O_2$ and successfully isolated peroxy products. They also isolated **1.105** and **1.106** by trapping the diradical intermediate generated from *bis*-allenes **1.104** and **1.108** with maleic anhydride (**Scheme 1.24**), which are in accord with the proposed diradical mechamism. Taking the above evidences into consideration, the possible involvement of any ionic intermediate was ruled out.

Braverman[33] proposed that the isomerization of *bis*-propargyl sulfoxide **1.109** to propargyl allene **1.110** is the rate determining step and it is about three times slower than the second isomerization from **1.110** to diallene **1.111**. Therefore the effect of solvent polarity and the relative acidity of the α-hydrogen are the sole factors on the reaction rate regardless of the nature of the diradical intermediate **1.112** (**Scheme 1.25**).



Scheme 1.25: Tandem isomerization, cyclization and aromatization of bridged propargylic systems

Thus, the rate of conversion for **1.116b** in $CDCl_3$ is slower than the rate in DMSO-d_6. As the acidity of α-hydrogen decreases in the following order sufone > sulfoxide > sulfide, the rate of cyclization also decreases from sulfone to sulfide as shown in **Table 1.1**.



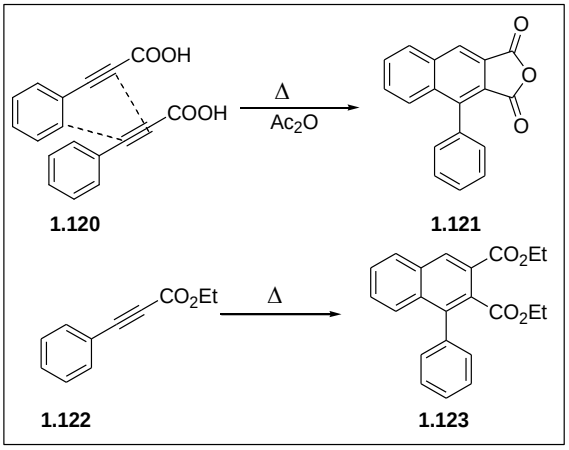
Scheme 1.26: Solvent polarity effect on GB cyclization

Entry	Substrate	n	X	Solvent	Time	Product (yield %)
1	**1.116a**	0	S	$CHCl_3$	72 h	No reaction
2	**1.116b**	1	S	$CHCl_3$	1 h	**1. 119b** (100%)
3	**1.116b**	1	S	DMSO-d_6	5 min	**1. 119b** (100%)
4	**1.116c**	2	S	$CDCl_3$	15 min	**1. 119c** (100%)
5	**1.116d**	0	Se	DMSO	16 h	**1. 119d** (21%)

Table 1.1: Tandem isomerization, cyclization and aromatization of bridged propargylic systems

1.11 Dehydro Diels-Alder (DDA) Reactions

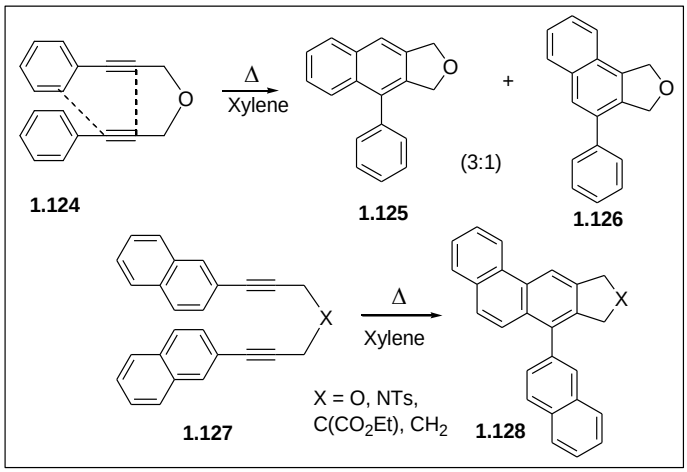
These are dehydrogenated variants of Diels-Alder reaction. Under this topic we will discuss the reaction between an enyne or aryl acetylene and another multiple bond that leads to the formation of an aromatic ring *via* isomerization of the initial [4+2] product.



Scheme 1.27: First DDA reaction

In 1895, Michael and Bucher reported that dimerization of **1.120** in the presence of acetic anhydride in a sealed tube give anhydride **1.121** (**Scheme 1.27**).[34] The same product was later obtained in the presence of phosphoryl chloride[35] and from a mixture of 3-phenylpropiolic acid chloride, pyridine, and acetylacetone.[36] The ethyl ester **1.122** undergoes the DDA reaction upon heating, giving the diester **1.123**.[37]

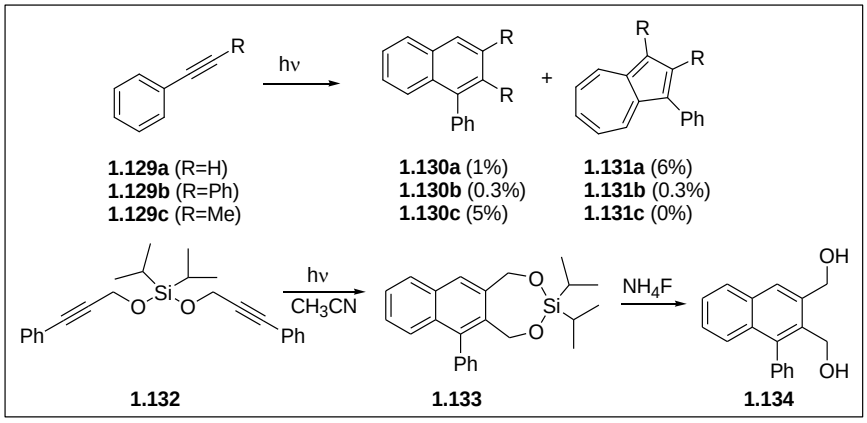
Shibata and co-workers[38] upon heating of di-(3-phenylpropargyl) ether, **1.124**,



Scheme 1.28: Work done by Shibata *et al.*

in xylene, obtained DDA reaction product **1.125** and the rearranged compound **1.126** in a ratio of 3:1 (**Scheme 1.28**). When the phenyl groups were replaced by a naphthyl moiety as in **1.127**, only the DDA reaction product **1.128** was obtained.

Diels-Alder reaction is a thermally allowed but photochemically forbidden process, according to the Woodward-Hoffmann rules that are based on orbital symmetry considerations. If the reaction mechanism is a multistage process and the first step is the formation of only one chemical bond, then the statement is no longer applicable. Hence, it is somewhat surprising that so little was known about the photochemical Dehydro Diels-Alder reaction (PDDA), a representation of which is shown in **Scheme 1.29**.



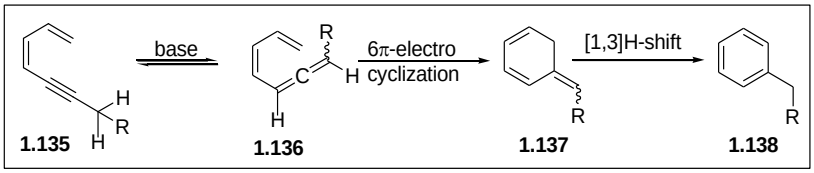
Scheme 1.29: Photochemical Dehydro Diels-Alder reaction (PDDA).

The photochemical dimerization of phenylacetylenes **1.129** has been known for a long time but it has limited preparative value because the yields of the PDDA

products **1.130** were very low and often the azulenes **1.131** were formed as main products.[39] In 1995, Fleming reported on the PDDA cyclization of the silyl *bis*-(phenylpropargyl) ether **1.132** to the naphthalene **1.133** and subsequent deprotection to the diol **1.134**.[40]

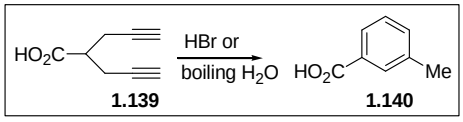
1.12 6π-Electrocyclization

6π-electrocyclisation is a thermally allowed disrotatory pericyclic ring closing process. Under basic conditions, depending on the electronic nature of the dienyne, it may be possible to thermally isomerize the alkyne to an allene. 6π-electrocyclization followed by a formal [1,3]-H shift provides a reasonable pathway for production of aromatic product (**Scheme 1.30**) .



Scheme 1.30: Base catalyzed 6π-electrocyclization

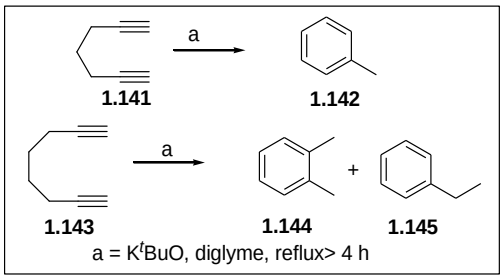
In 1907, Perkin and Simonsen[41] showed that *m*-toluic acid **1.140** can be synthesized from 2-(prop-2-yn-1-yl)pent-4-ynoicacid **1.139** by treating it with hydrobromic acid or boiling water. Their proposed mechanism involved hydration of both alkynes and an intramolecular Aldol reaction as key isomerization events (**Scheme 1.31**).



Scheme 1.31: Work done by Perkin and Simonsen

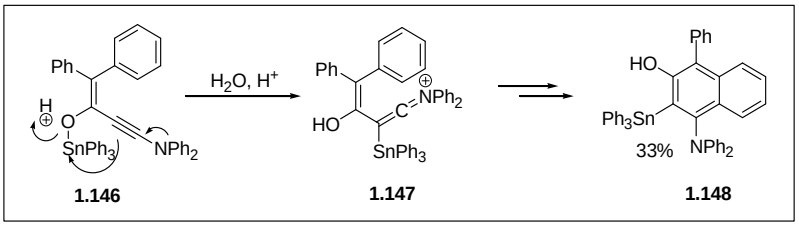
Later, in 1960 Eglinton and co-workers[42] independently synthesized **1.139** from a known route and reinvestigated this transformation. No cyclizaiton was observed under Perkin and Simonsen's conditions. However, quantitative formation of **1.140** was obtained by refluxing **1.139** in presence of aqueous KOH. Treating simple diynes **1.141** and **1.143** with K^{t}BuO in refluxing diglyme resulted in the formation of toluene **1.142** and a mixture of *o*-xylene **1.144** /ethylbenzene **1.145**, respectively (**Scheme 1.32**). Eglinton suggested a 6π-electrocyclization from an allene

structure as the key carbon bond forming step and ruled out the mechanism proposed by Perkin and Simonsen.



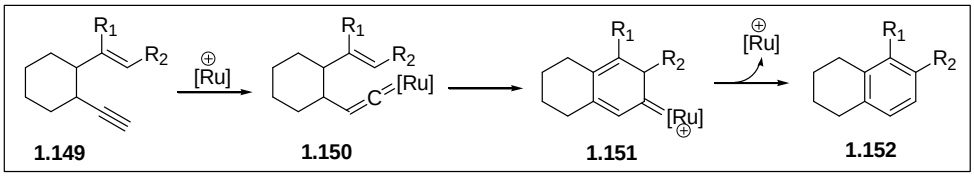
Scheme 1.32: Cycloaromatization resulting from base-catalyzed diyne isomerization

Though base-induced isomerization pathway represents the most common way to bring about a 6π-electrocyclization but it is not the only possible route. Himbert and co-workers[43] have used alkoxystannane dienynes, **1.146**, with a highly nucleophilic amino alkyne substituent to induce a [1,3]-shift of the tin moiety resulting in the formation of the iminiumene **1.147** (**Scheme 1.33**). Compound **1.147** then follows cyclization and tautomerization to give the product **1.148**.



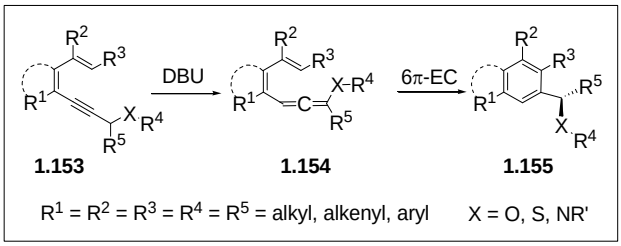
Scheme 1.33: 6π-Electrocyclization from a 1, 3-Stannane shift

In 1996, first metal vinylidene diyne cycloaromatization was reported by Merlic and Pauly[44]. A variety of terminal alkene modified dienynes were shown to cyclize in relatively high yield under Ru (II) catalysis. Diyne having terminal alkyne upon reaction with certain transition metal complexes can form metal vinylidene complex subsequently proceeding through a 6π-electrocyclization and formal [1,2]-H transfer/ demetalation to result in an aromatic product (**Scheme 1.34**).



Scheme 1.34: The first example of metal vinylidene diyne cycloaromatization

Recently, in 2011, H. Zhou and co-workers[45] have reported a comprehensive study of heteroatom (O, N, and S)-promoted propargylallenyl isomerization and electrocyclization, which may offer convenient protocols to various polysubstituted benzenes (**Scheme1.35**).



Scheme 1.35: Heteroatom promoted propargyl-allenyl isomerization and electrocyclization

Introduction of the electron withdrawing group on the nitrogen not only improves the reaction itself but also affords a useful way to get functionalized amine derivatives. In the absence of electron withdrawing group, the propargyl-allenyl isomerization and electrocyclization might still be possible in the presence of DBU with the assistance of heating.

1.13 [2+2+2] Cycloaromatization

The [2+2+2] cycloaddition is an elegant, atom efficient and group tolerant strategy complementary to the Diels-Alder reaction for the synthesis of aromatic carbo- and heterocycles, involving the formation of several C–C bonds in a single step. [2+2+2] cycloaddition can be classified into three types- intermolecular reaction of three alkynes, semi intramolecular reaction of diyne and monoalkyne and intra-molecular cyclization of a triyne (**Figure 1.02**). Bertholet, in 1866,[46] carried out thermal cyclization of three acetylene molecules to produce benzene. This was the first report of [2+2+2] cycloaromatization. Though the above trimerization is a symmetry allowed exothermic process with (ΔH = -594 kJ/mol) but requires high temperature or catalyst because of kinetic factors and entropic consideration.

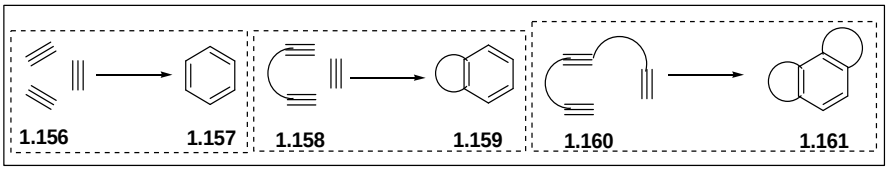
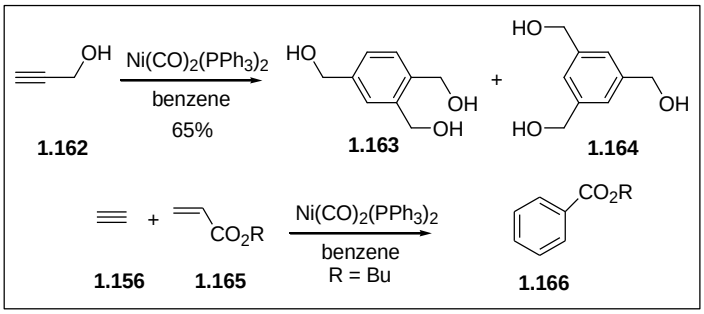


Figure1.02: General representation of intramolecular [2+2+2] cycloadditions

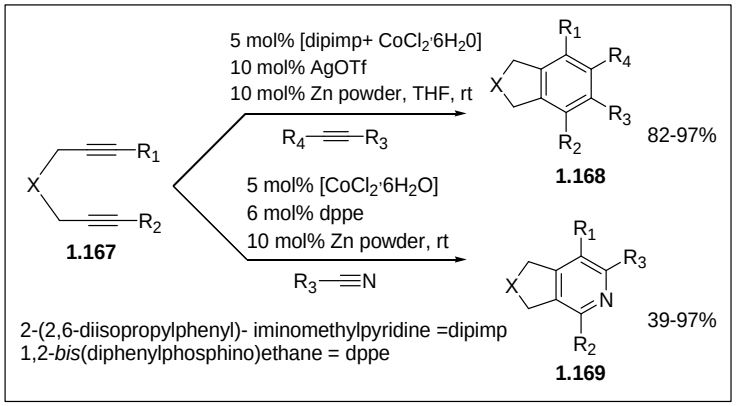
Reppe *et al.*[47] in 1948 accelerated the application of metal catalysts in this area. They first reported transition metal catalyzed cyclotrimerization of acetylenes to benzene derivatives using $[Ni(CO)_2(PPh_3)_2]$ between 25 ^oC and 80 ^oC (**Scheme 1.36**).



Scheme 1.36: Work of Reppe *et al.*

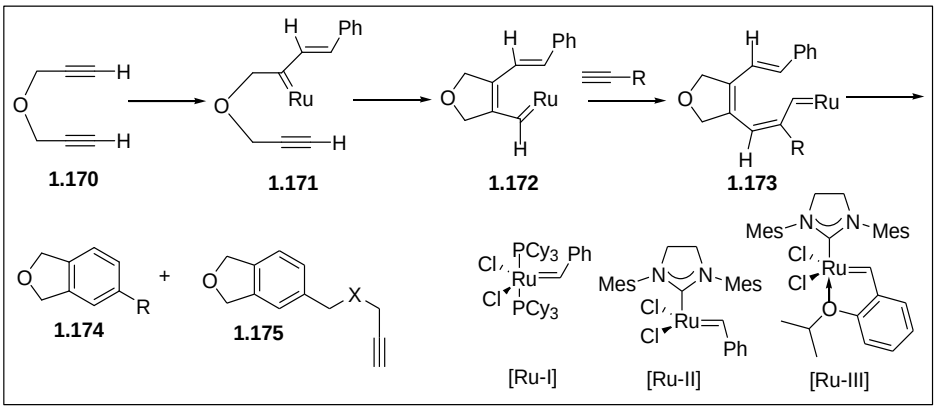
Since then, various transition metal catalysts based on Ni, Co, Pd, Cr, Rh, Ru, Fe, Zr, Nb, Ir, and Ta have been used. Heiz and co-workers[48] have reported that even a single palladium atom supported on MgO (100) films can catalyze the production of benzene from acetylene at low temperature (300 K).

Literature survey reveals that Volhardt *et al*.[49] have extensively used cobalt complexes to mediate efficient [2+2+2] cycloadditions. The ability of cobalt complexes is well known to promote powerful synthetic transformations, and continues to be a non-expensive and efficient option in many cases (**Scheme 1.37**).[49]



Scheme 1.37: Cobalt mediated cycloaromatization of tethered alkyne

Grubbs' catalyst has also been found to mediate cyclotrimerization [2+2+2] reactions. Blechert *et al*. reported for the first time that Ru(I) is an efficient catalyst for the intramolecular cyclotrimerization of alkynes. A cascade metathetic mechanism was postulated where vinyl carbene complexes would be the reactive intermediates.[50]

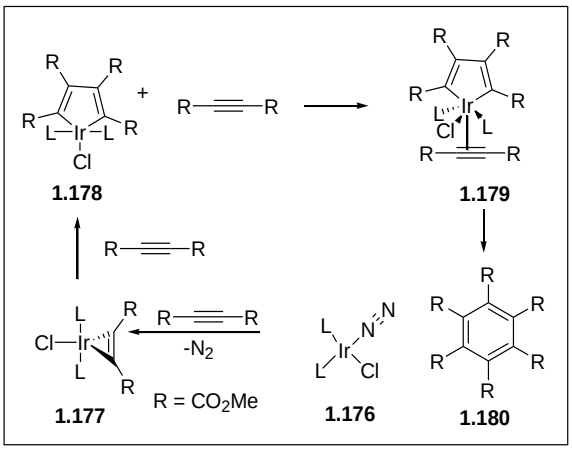


Scheme 1.38: Use of Grubbs' catalyst in cycloaromatization reactions

Castells and coworkers[51] used second-generation Grubbs' catalyst and Hoveyda- Grubbs' catalyst and found that they were also able to catalyze both crossed [2+2+2] cyclotrimerization of diynes with alkynes and di- or trimerizations of diynes (**Scheme 1.38**).

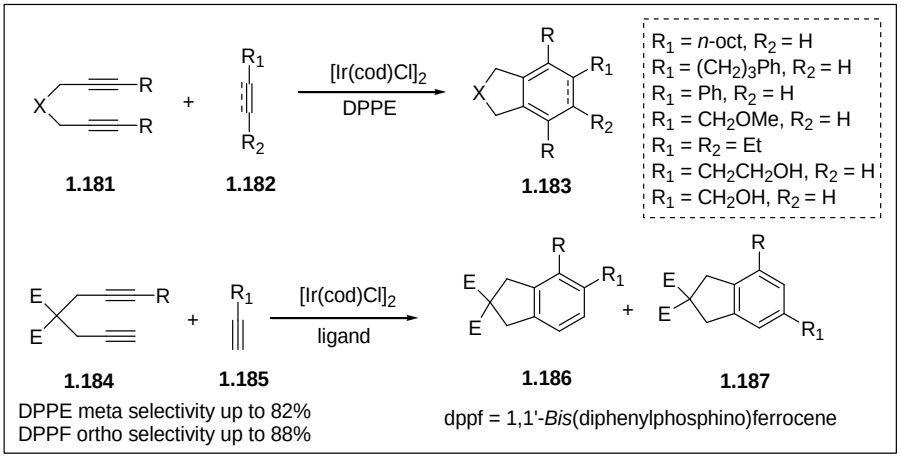
Iridium catalyst has also been found to provide new and efficient protocol cycloaddition of diynes with monoynes and monoenes. The reactions proceeded under benign conditions to give polysubstituted benzene derivatives and cyclohexadiene derivatives in moderate yield.

The first example of Iridium catalyzed cycloaromatization[52] was reported in 1968 where the preparation of a iridacyclopentadiene consisted of the reaction of $[IrCl(N_2)(PPh_3)_2]$ with dimethyl acetylene-dicarboxylate (DMAD) as shown in **Scheme 1.39**.



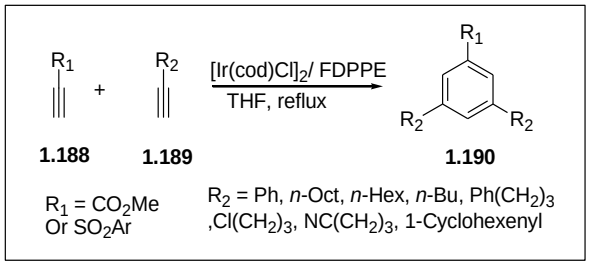
Scheme 1.39: First Iridium catalyzed transformation

After this, several works have been published on iridium catalysts in the [2+2+2] cycloaddition reaction. As a recent example, in 2005, Takeuchi[53] showed that $[Ir(cod)Cl]_2$/DPPE was found to be a new catalyst for the cycloaddition of α,ω-diynes with monoynes to give polysubstituted benzene derivatives in high yields. Internal monoynes as well as terminal monoynes could be used. The reaction tolerates a broad range of functional groups such as alcohol, amine, alkene, ether, halogen, and nitrile. The reaction of 1,6-octadiyne derivatives with 1-alkynes gives *ortho* and *meta* products (**Scheme 1.40**).



Scheme 1.40: Work done by Takeuchi *et al*.

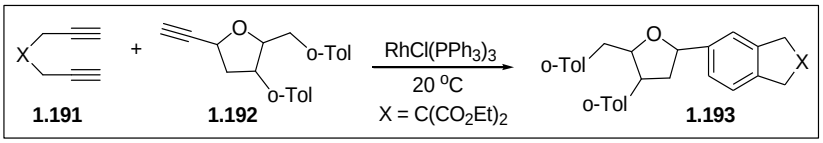
In 2008 they found that[54] $[Ir(cod)Cl]_2$ in combination with 1,2-*bis* (dipenta-fluorophenylphosphino)ethane catalyzes the chemo and regioselective cyclo trimeri-zations of different alkynes giving a single product in high yields (**Scheme 1.41**).



Scheme 1.41: $[Ir(cod)Cl]_2$ catalyzed cyclotrimerization

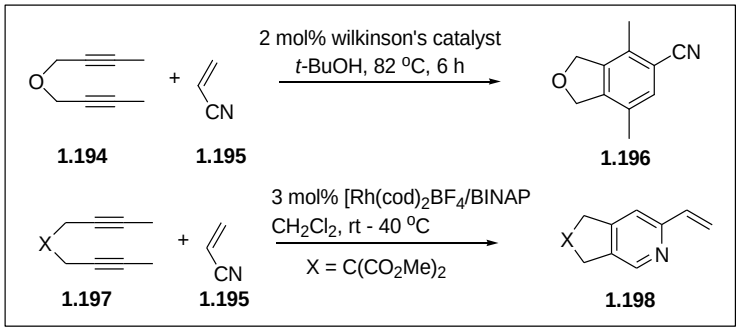
Muller first reported the stoichiometric reaction of rhodacyclopentadienes which were formed by the reaction of Wilkinson's catalyst $[RhCl(PPh_3)_3]$ with α,ω-diynes and monoynes to form substituted benzene derivatives.[55]

Recently, Kotora, Hocek, and co-workers[56] reported the catalytic [2+2+2] cyclotrimerization of α,ω-diynes with C-ethynyldeoxyribo-side under mild reaction conditions to form variously substituted C-aryldeoxyriboside derivatives (**scheme 1.42**).



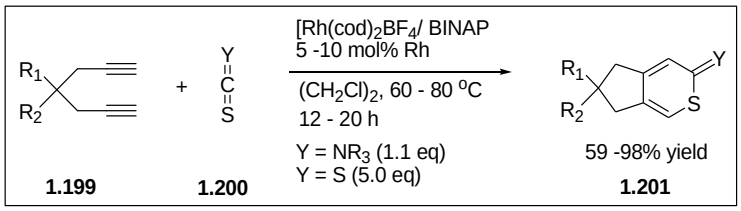
Scheme 1.42: Ru catalyzed [2+2+2] cyclotrimerization

Rhodium catalyst has been applied to the [2+2+2] cyclo addition of alkynes with isocyanates and isothiocyanates leading to substituted heterocycles. Different Rh catalyst was investigated by Grigg *et al.*[57] and Takana *et al.*[58] Grigg reported that when 1,6-diyne is treated with acrylonitrile in the presence of 2% $RhCl(PPh_3)_3$ at 82 °C for 6 h, it afforded a nitrile **1.196** in 59% yield by reacting with the double bond of acrylonitrile. On the other hand, when Takana treated the similar diyne **1.197** with the cyano group of **1.195** in presence of 3% $[Rh(cod)_2]BF_4$/BINAP at room temperature, it reacted with the triple bond of acrylonitrile and afforded the vinylpyridine **1.198** in good yield without the formation of nitrile **1.196** (**Scheme 1.43**).



Scheme 1.43: Heterocycle prepation *via* Rh(I) catalysis

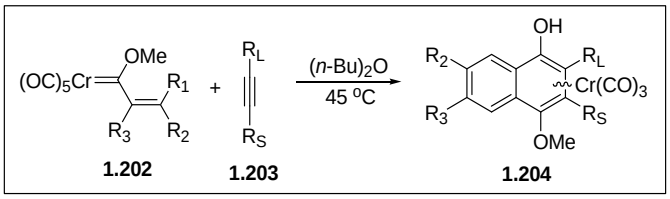
Tanaka has reported[59] that the above rhodium(I)/BINAP complex effectively catalyzes [2+2+2] cycloaddition of 1,6-diynes with isothiocyanates to give bicyclic thiopyranimines in good yield. The reaction with carbon disulfide also proceeded to give bicyclic dithiopyrones **1.201**(**Scheme 1.44**)



Scheme 1.44: Rhodium-catalyzed [2+2+2] cycloaddition of 1,6-diynes

1.14 Dotz-Wulff Reaction

In 1975, by K. H. Dotz,[60] a highly efficient one-pot, thermal [3+2+1]-benzannulation reaction of α,β-unsaturated Fischer carbene complexes with alkynes was discovered. Methoxy (phenyl)carbene chromium complex upon gentle warming produces $Cr(CO)_3$-coordinated substituted phenol **1.204** (**Scheme 1.45**). As the reaction was extensively developed by W. Wulff, they share the name of the reaction.

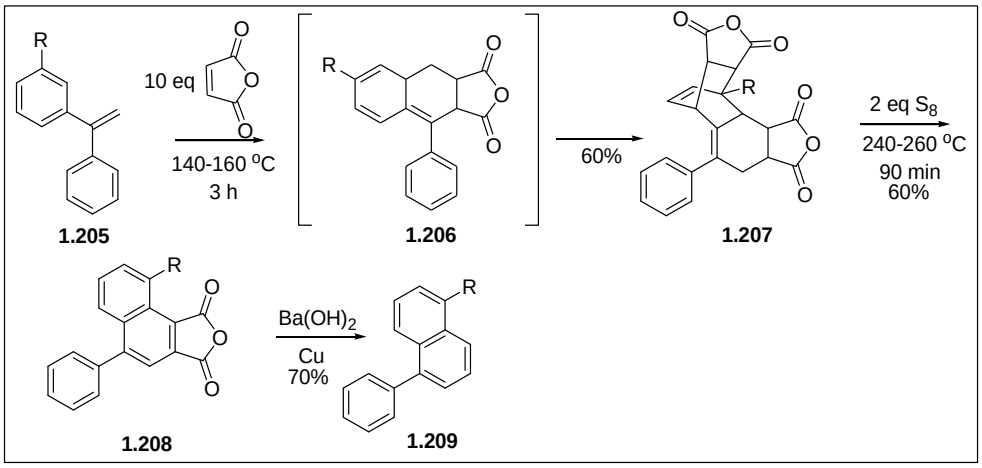


Scheme 1.45: [3+2+1]-Benzannulation reaction of three different ligands

The first as well as the rate limiting step of the reaction involves the loss of carbon monoxide from the Fischer carbene complex. Large alkyne substituent (R_L) occupies the position neighboring the phenol and the smallest alkyne substituent (R_S) neighboring the methoxy group. Hence, this reaction is more useful for terminal alkynes than internal alkynes. The chromium complex upon mild oxidation like aerial oxidation or ceric ammonium nitrate liberates the free phenolic derivative.

1.15 Wagner-Jauregg Reaction

This Wagner-Jauregg[61] reaction describes the unique double Diels-Alder reaction of two equivalents of maleic anhydride to asymmetrical diphenylethylene, It shows that under specific structural conditions conjugation of a benzene ring with an exocyclic double bond gives a reactive dienic system, whereas styrene itself forms only copolymers with maleic anhdride. The enhanced resonance in the styrene system owing to the presence of another α-phenyl group governs the reaction.



Scheme 1.46: Wagner-Jauregg reaction

Steric interaction of the *ortho* hydrogens in the two rings of **1.205** forces one of the rings out of the plane and enhances the co-planarity of the other with the unsaturated side-chain. In the second place, the intermediate **1.206**, instead of reestablishing an aromatic ring by double bond migration, adds another molecule of the dienophile to form *bis*-adduct **1.207**. The Diels–Alder product **1.207** can be re-aromatized using elemental sulfur at high temperature, followed by a second rearomatization by decarboxylation with barium hydroxide and copper (**Scheme 1.46**).

1.16 Reference

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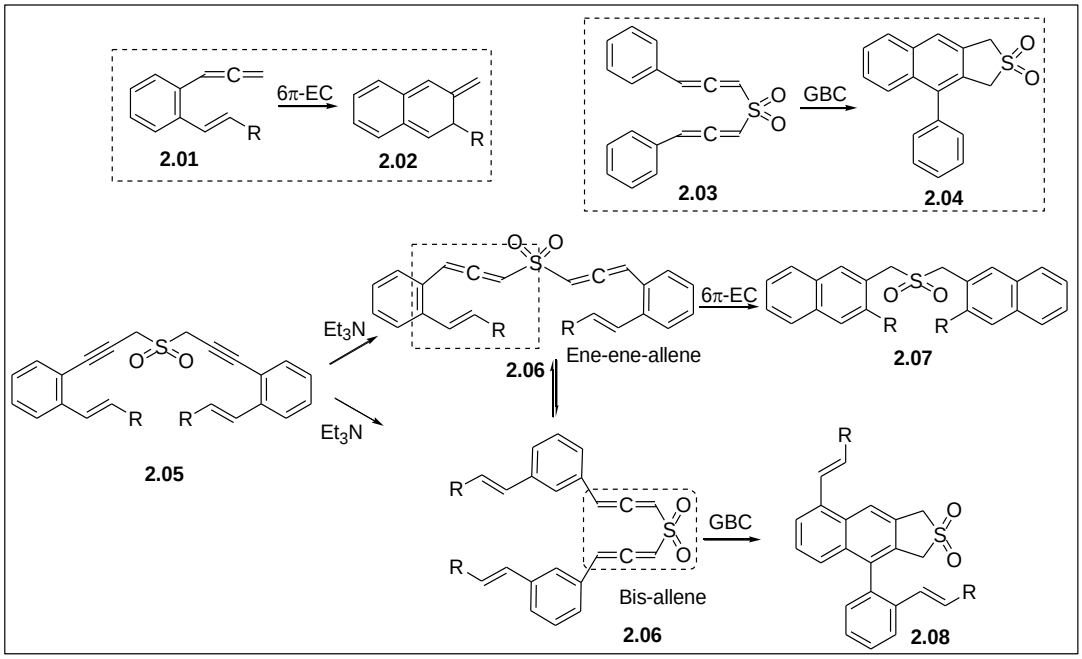
Chapter 2

Conformational Constraint Induced Preference for 6π-Electrocyclization over Garratt-Braverman Process for *Bis*-Propargyl Sulfone

2.1 Introduction

Molecules having functional groups capable of undergoing more than one reaction simultaneously under similar type of reaction condition are of great interest.[1] For such types of reaction, it is important to know the favorable pathway under a particular condition so that their synthetic importance and potential can be fully explored. Acyclic *bis*-propargyl sulfones (**2.05**) with an *ortho* alkenyl moiety- representing such a system can follow more than one reaction pathways. Under basic condition, these can undergo 6π-electrocyclization[2] (**2.07**) and/or Garratt-Braverman cyclization[3] (**2.08**) *via bis*-diene-allene intermediates. These possibilities are represented in **Scheme 2.1**.



Scheme 2.1: 6π-Electrocyclization and Garratt-Braverman cyclization of *bis*-*Z*-dienyl allenic sulfone

In reality, the reaction generally produces a mixture of products arising through GB cyclization and 6π-Electrocyclozation with a bias towards the GBC product.[4] The reaction never showed complete preference for any particular pathway except for the *cis*-alkene system in which case, exclusively GBC product was formed (**Figure 2.1**). However, complete preference for 6π-EC over GBC was never achieved.

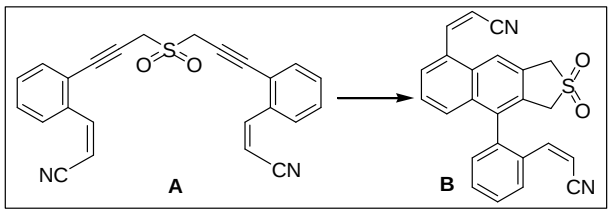


Figure 2.1 Complete preferences for GB cyclization over 6π-electrocyclization

2.2 Previous Work

As mentioned above, the reactivity of various acyclic diene-yne sulfones (**A-H**) have earlier been studied in our laboratory (**Figure 2.2**).[4] Under base catalyzed conditions, these sulfones isomerized to the ene-ene-allenes which were capable of undergoing both 6π-electrocyclization and GB cyclization processes (**Scheme 2.1**). The results reported by Mondal *et al*.[4] are shown in **Table 2.1**.

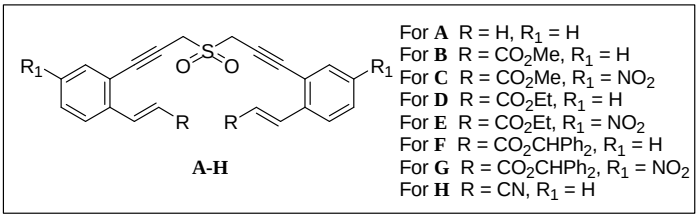


Figure 2.2: Previously synthesized *bis*-dieneyne sulfones A-H

Entry	Sulfone	Temperature (°C)	Time	% of GB Product	% of 6π-EC Product	Combined yield (%)
1	**A**: R = R_1 = H	rt	8 h	66.66	33.34	82
2	**B**: R = CO_2Me R_1 = H	0	15 d	89.20	10.80	80
		rt	72 h	73.64	26.06	80
		60	4 h	29.66	70.34	82
3	**C**: R = CO_2Me R_1 = NO_2	rt	52 h	73.68	26.32	87
4	**D**: R = CO_2Et R_1 = H	0	15 d	88.92	11.08	82
		rt	72 h	72.4	27.6	85
		60	4 h	28.8	71.2	90
5	**E**: R = CO_2Et R_1 = NO_2	rt	56 h	55.64	44.36	93
6	**F**: R = CO_2CHPh_2 R_1 = H	rt	75 h	69.5	30.5	89
7	**G**: R = $COOCHPh_2$ R_1 = NO_2	rt	60 h	44.38	55.62	95
8	**H**: R = CN *(trans)* R_1 = H	rt	72 h	77.78	22.22	84

Table 2.1: Results of triethyl amine treatment of sulfones A-H[4]

This study led to the conclusion that GB cyclization is preferred over 6π-EC at room temperature but at higher temperature 6π-EC process became predominant. The temperature effect indicated that the GB cyclization is kinetically controlled and 6π-EC is a thermodynamically controlled process.

A similar situation is also present in *bis*-propargylic sulfones with *ortho* alkynyl moiety represented by structure **I**. Here base induced isomerization generated a situation in which the intermediate *bis*-allene could undergo GB cyclization and/or Myers-Saito/ Schmittel cyclization. The authors have reported an exclusive preference for these molecules to undergo GB cyclization under basic condition **(Figure 2.3)**.[1,5]

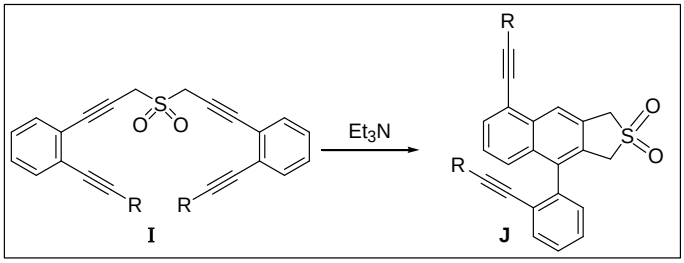


Figure 2.3 Reactivity of acyclic bis-propargyl sulfone

Later on, it has also been demonstrated that incorporation of conformational constraint in these sulfones shifted the preference from GBC towards the Myers-Saito cyclization (MSC) or Schmittel cyclization (SC) upon base treatment.[5] Relieving the strain again brought back the selectivity towards GB cyclization pathway. Since allene can easily be generated from the propargyl sulfone, cyclic systems capable of forming an intermediate with both an ene-yne-allene and *bis*- allenic sulfones were choosen. The previous reported results are summarized in **Figure 2.4**.[5]

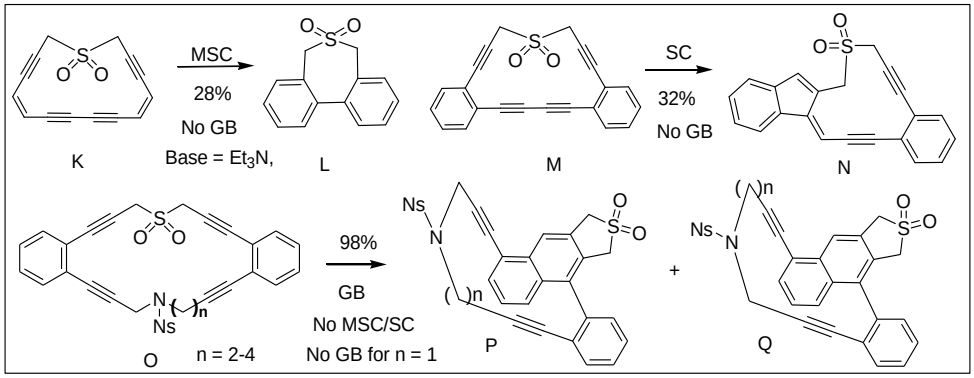


Figure 2.4: Reactivity of cyclic enediynyl sulfones[5]

2.3 Objective

The main objective of this part of work was to study the effect of structural modification on *bis*-propargyl sulfone with *ortho* alkenyl moiety systems so that the reaction will favour the electrocyclization. Encouraged by the reported success mentioned in **Scheme 2.4**, we framed our objectives as outlined below:

- To check whether incorporation of conformational constraint in these systems alters the preference.
- To know what happens to the reaction pathway when the constraint is reduced.
- To investigate the mechanistic detail in case there is substantial effect of conformation constraint on the reaction outcome.

To achieve the above objectives, we have designed three cyclic *bis*-propargyl sulfones **2.20a-c** with *ortho*-alkenyl end tied up through spacer and checked their reactivity under basic condition.

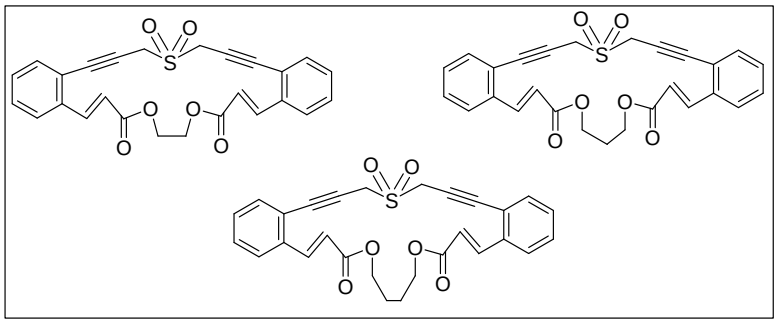


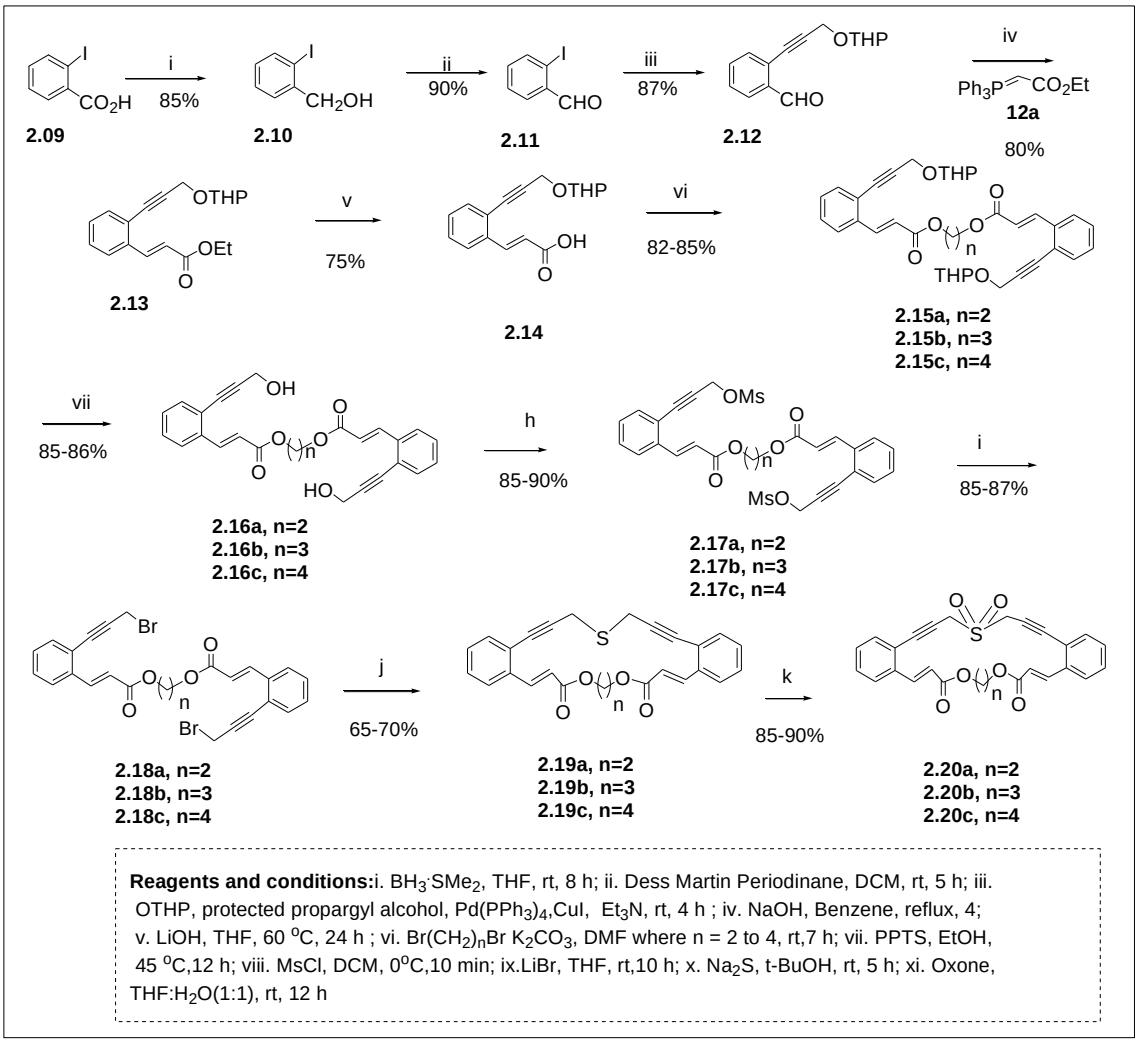
Figure 2.5: Targeted sulfones

2.4 Results and Discussion

2.4.1 Synthesis of the Targeted Sulfones

The synthesis started with 2-iodobenzoic acid **2.09** which was reduced to the corresponding alcohol **2.10** using borane-dimethyl sulfide in THF at room temperature. Oxidation of the alcohol using Dess-Martin periodinane produced the corresponding aldehyde, **2.11**, which served as the starting material for Sonogashira coupling. The reaction[6] was carried out using THP protected propargyl alcohol as the alkyne partner. The product **2.12** was then subjected to Wittig reaction[7] to introduce *ortho*-alkenyl moiety. Thus it was reacted with the ylide **12a** generated from phosphonium salt of

bromo ethylacetate to produce the α,β unsaturated ester **2.13**. LiOH mediated hydrolysis of **2.13** in THF resulted in free carboxylic acid **2.14**. To incorporate the conformational constraint by introducing spacers, the carboxylic acid **2.14** was reacted with various dibromo alkanes to produce the diesters **2.15a-c** with increasing



Scheme 2.2: Synthesis of the sulfones

of THP protection by PPTS in EtOH gave the desired alcohols **2.16a-c**. These were then converted to their corresponding mesylates **2.17a-c** (MsCl, Et_3N) followed by the reaction with LiBr to produce the bromides **2.18a-c**. The bromides were converted to cyclic sulfides **2.19a-c** by reacting with Na_2S in *t*-BuOH. In general methanol is used as solvent during sulfide formation but in our case we used *t*-BuOH to avoid *trans*-esterification. Finally, the sulfides were converted to the sulfones **2.20a-c** *via* oxone[9]

mediated oxidation. We avoided *m*-CPBA because of the possibility of epoxidation of the alkene. The synthesis is shown in **Scheme 2.2**.

2.4.2 Spectral Characterization of a Representative Sulfone 2.20a

Since the synthesized sulfone **2.20a** is C_2 symmetric, its proton NMR spectrum comprised signals of integral values of 10 protons for its 20 protons (taking the smallest integral value corresponding to one proton). ^{1}H NMR of compound **2.20a** showed a singlet for protons H_i and H_j at δ 4.55 ppm. Methylene protons H_a and H_b appeared at δ 4.56 ppm as singlet. Alkene proton H_h appeared as doublet at δ 6.49 ppm whereas H_g, being more deshielded, appeared at δ 8.13 ppm as doublet. The coupling constant of 16.0 Hz between H_g and H_h confirms the *trans*-geometry of the double bond. The aromatic protons appeared as three sets of multiplet between δ 7.67-7.30 ppm. The assignments and the spectrum are shown in **Figures 2.6** and **2.7** respectively.

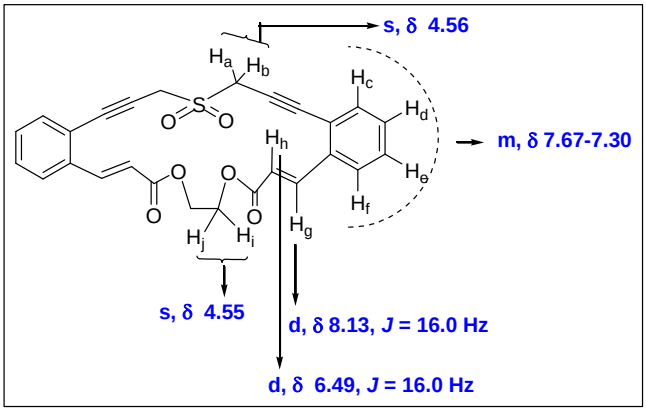


Figure 2.6: ^{1}H NMR assignment of compound 2.20a

The ^{13}C spectrum showed the presence of 13 different carbons as the molecule is C2 symmetric. The propargylic carbon atom C_a appeared at δ 44.9 ppm in the ^{13}C spectrum (**Figure 2.8**). The two acetylenic carbons, C_b and C_c appeared at δ 85.3 and δ 82.0 ppm respectively. Peaks for aromatic carbons (C_d-C_i) and the alkene carbons appeared between δ 119.7 to δ 142.1 ppm. The peak at δ 166.4 ppm corresponds to the carbonyl carbon of the ester functional group. The methylene carbon C_m appeared at δ 62.6 ppm.

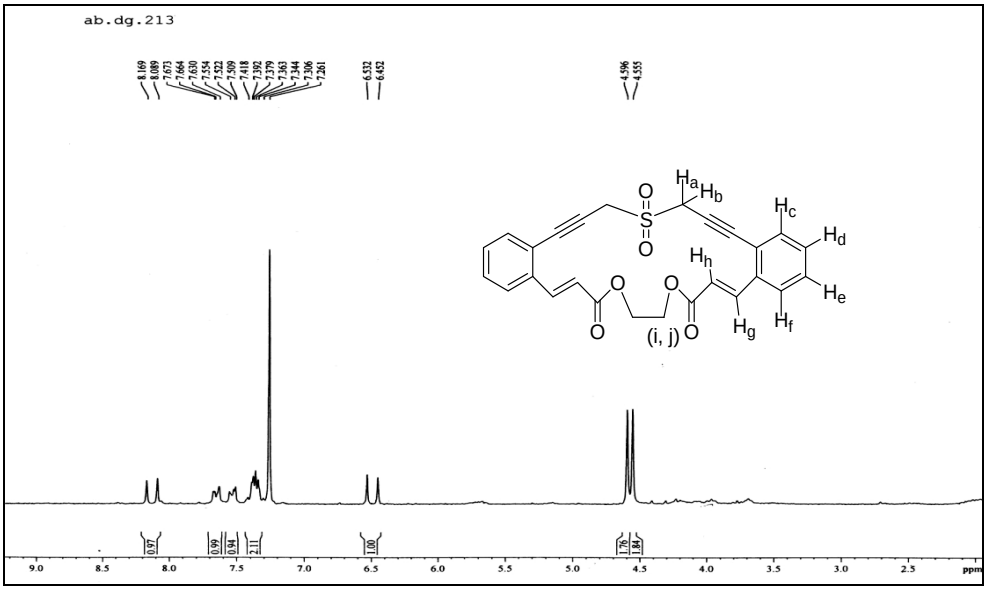


Figure 2.7: ^{1}H NMR spectrum of compound 2.20a (200 MHz)

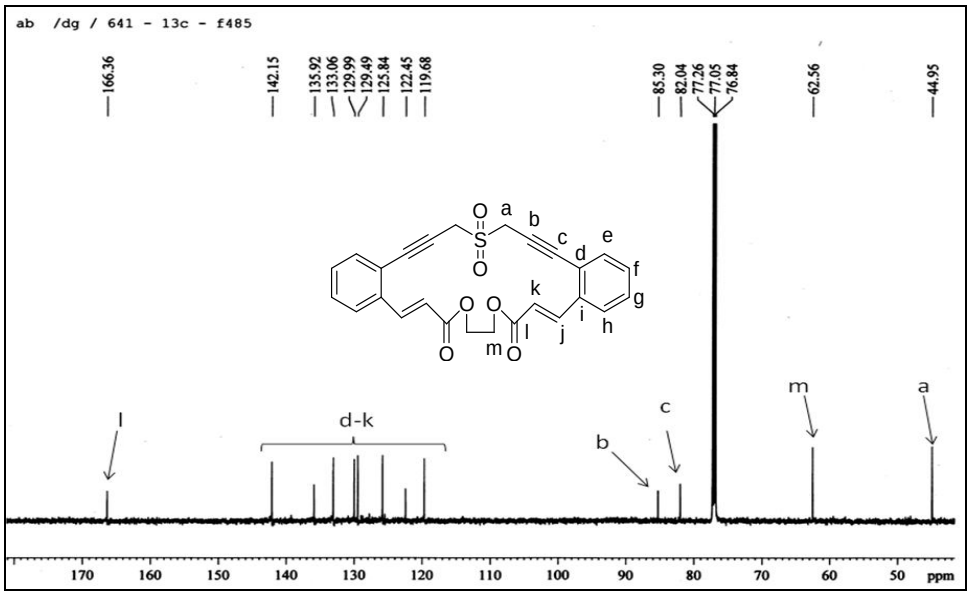


Figure 2.8: ^{13}C NMR spectrum of compound 2.20a (200 MHz)

2.4.3 Reactivity of *Bis*-propargyl Sulfones upon Base Treatment

The reactivity of the sulfones **2.20a-c** under basic condition was studied by NMR. The initial experiment was carried out with the sulfone **2.20a**. For this purpose, the sulfone was dissolved in $CDCl_3$ and then treated with catalytic amount of Et_3N at room temperature. ^{1}H-NMR spectrum at different time points was recorded. The peaks

corresponding to the starting material began to decrease with time while new peaks started to appear in the spectrum (**Figure 2.9**).

We stopped the reaction at 30 h when some solid compound began to precipitate from solution and the TLC mostly showed the formation of predominantly one product.

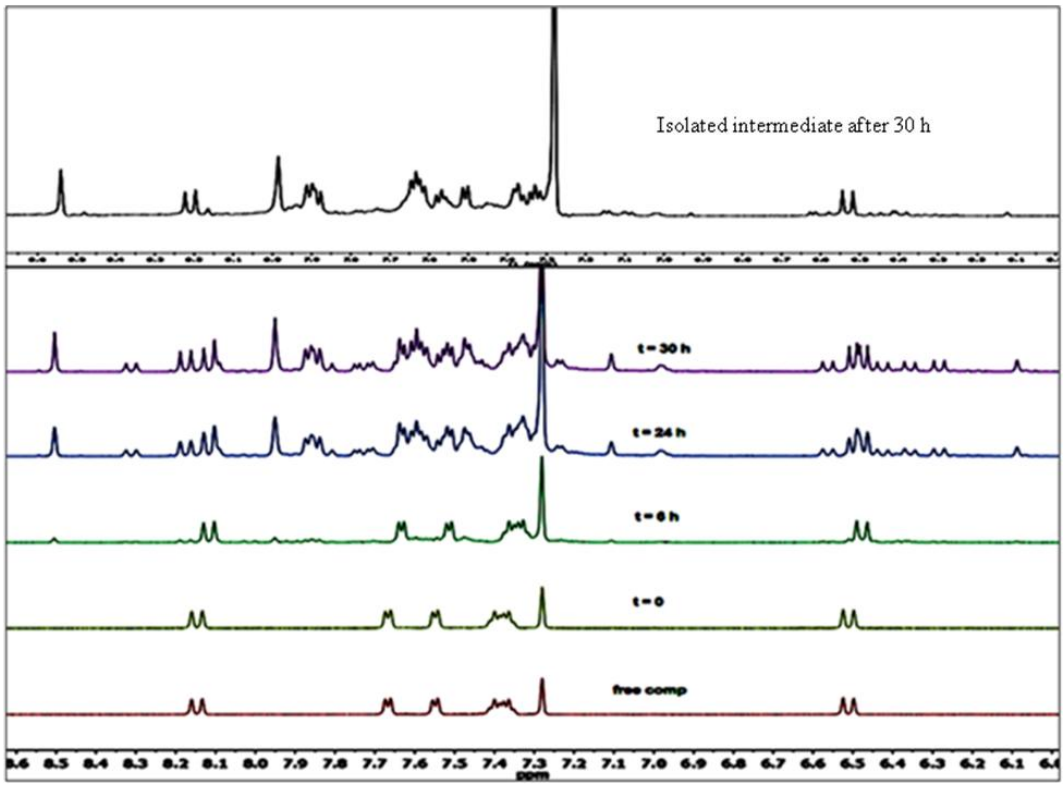


Figure 2.9: ^{1}H NMR of 2.20 in $CDCl_3$ taken at different time points (t = 0, immediately after TEA addition, 600 MHz)

We wanted to isolate and identify the intermediate so that we can establish the mechanistic path. For that purpose we first took out the solvent from the NMR tube and washed the solid precipitate with *n*-hexane and dried. The crude solid was then dissolved in $CDCl_3$ (applying heat) and its ^{1}H NMR was recorded. Interestingly the product still showed a pair of doublets at ~ δ 6.5 ppm and ~ δ 8.2 ppm, each corresponding to one proton, with a coupling constant of 16.0 Hz showing the presence of one cinnamate system in the product. The NMR spectrum also showed two singlets at ~ δ 4.5 and ~ δ 5.2 ppm, each corresponding to two protons (**Figure 2.10)**. These two peaks may correspond to propargylic and benzylic protons. Based on the ^{1}H-NMR profile, we

characterized the solid product as **2.22a** and its mechanism of foration is shown in **Scheme 2.3**.

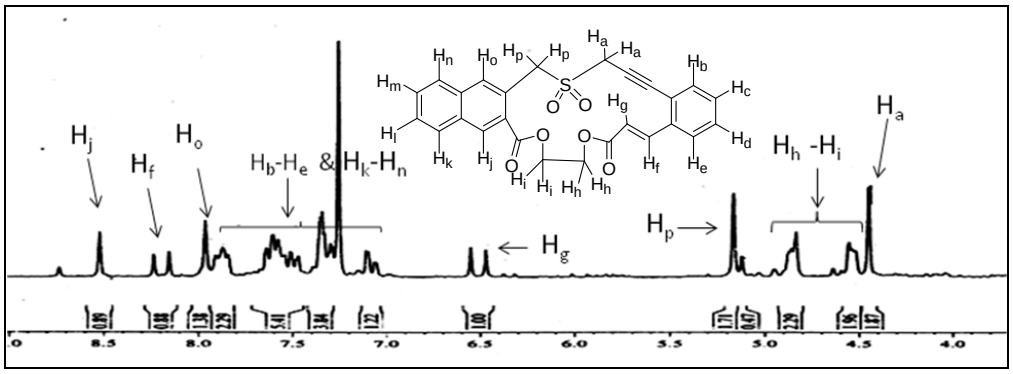
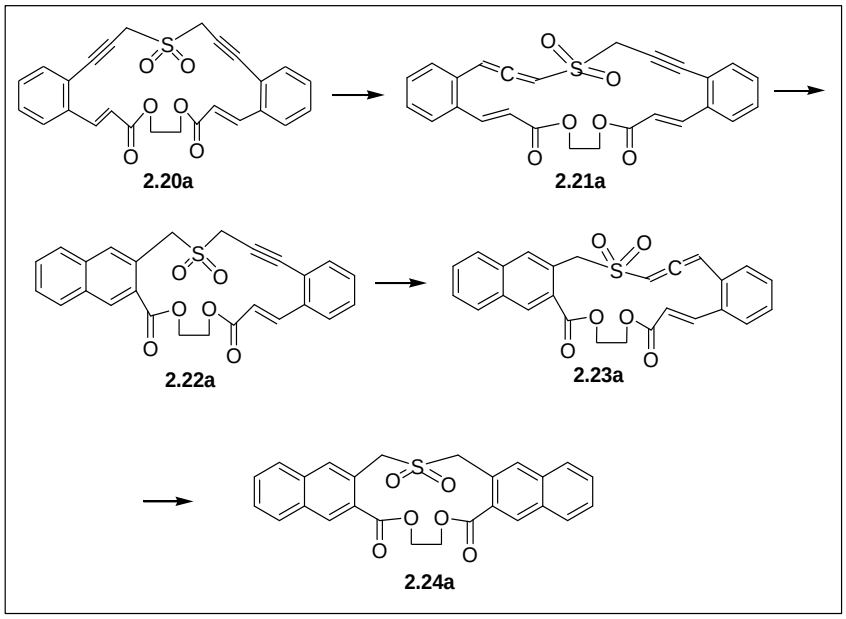


Figure 2.10: ^{1}H NMR isolated monoallene 2.22a

It was quite obvious that, the formation of the product **2.22a** is possible if the reaction proceeds *via* the formation of monoallene **2.21a** and subsequent 6π-electrocyclization (**Scheme 2.3**).



Scheme 2.3: Proposed stepwise mechanism

We thought, it would be interesting to find out whether the reaction could proceed further if allowed to continue. Thus the compound **2.22a** was further treated with Et_3N and interestingly it underwent another round of cyclization *via* further isomerization to allene **2.23a** followed by electrocyclization to result in **2.24a** (**Scheme 2.3**). We did not

observe any trace of GB product, at least to the NMR detection limit. The ^{1}H-NMR of compound **2.24a** has been shown in **Figure 2.11**.

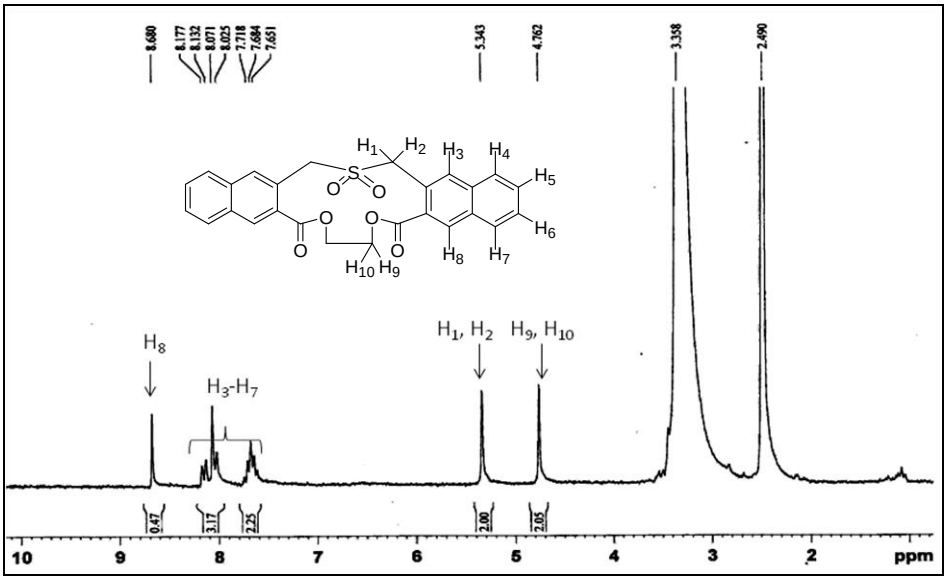
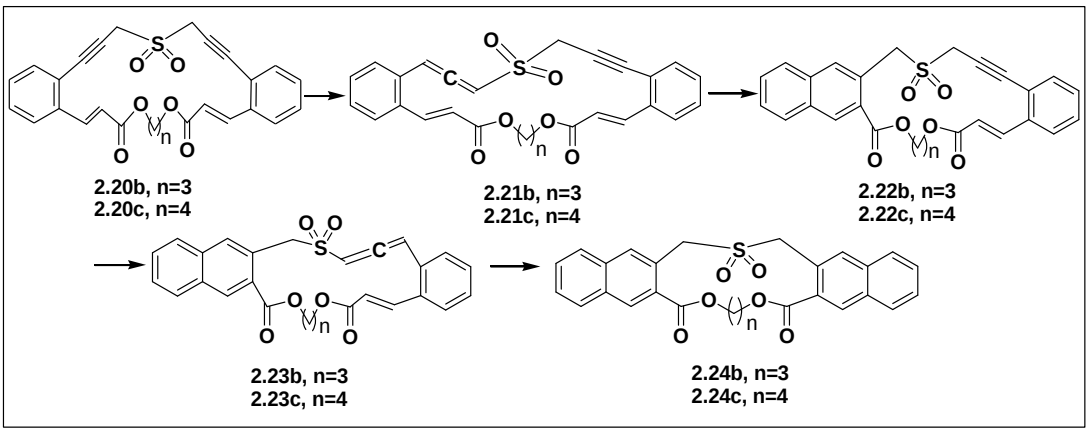


Figure 2.11: ^{1}H NMR 2.24a in d_6-DMSO

The other two sulfones **2.20b** and **2.20c** were treated in the same way. They also behaved in similar fashion producing only the 6π-EC products. Most likely, these sulfones also followed the sequence of isomerization to monoallene and then reacting *via* 6π-EC pathway and repeating the same sequence like **2.20a** (**Scheme 2.4**). This is also supported by ^{1}H-NMR taken at different time points.

We expected that release from conformation constraint might bring back Garratt-Braverman cyclization. Interestingly, no GB product was found even if the constraint was reduced *i.e* spacer length was increased. Upon base treatment, both the compounds, **2.20b** and **2.20c**, showed similar behavior and underwent 6π-electrocyclization only. This fact indicated that perhaps higher spacer length may be required to bring back the GB mode of reactivity in these molecules.



Scheme 2.4: Proposed mechanism for the formation of 2.20b & 2.20c

The results have been summarized in **Table 2.1**.

Substrate	Condition	Product	Yield (%)
2.20a	Et_3N, rt, 48h	**2.24a**	70
2.20b	Et_3N, rt, 54h	**2.24b**	75
2.20c	Et_3N, rt, 50h	**2.24c**	80

Table 2.1: Result of cyclization of sulfones

2.5 Spectral Characterization

Structure elucidation of final 6π-electrocyclization products was carried out from NMR and mass spectral data analysis. A characteristic spectral feature of one of the three final products has been mentioned here, as representative of the whole series.

Since the final cyclized products are symmetrical, we have explained the NMR of one symmetrical half portion. In the ^{1}H NMR of compound **2.24a**, the methylene protons (H_a and H_b) appeared as a two proton singlet at δ 5.34. Another set of methylene protons (H_i, H_j) appeared as singlet at the δ 4.76 ppm. Among the aromatic protons, proton H_h appeared most downfield at δ 8.68 ppm as a singlet. Other aromatic protons appeared as two sets of multiplets between δ 8.17-7.65 ppm. In ^{13}C NMR, disappearance of four acetylenic carbons indicated the formation of 6π-eletrocyclized product. **Figure 2.11**

shows the ^{1}H NMR assignment of **2.24a**. In the mass spectrum, peak at m/z = 483.0883 corresponded to MH^+.

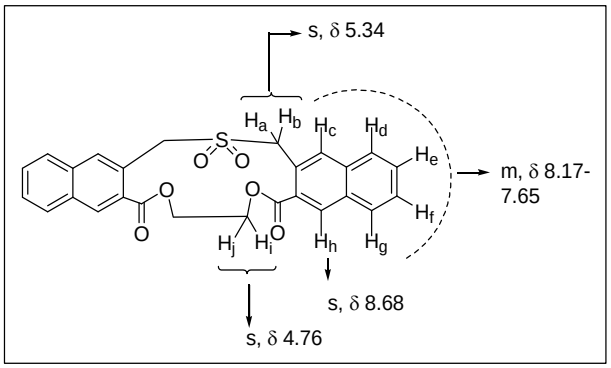
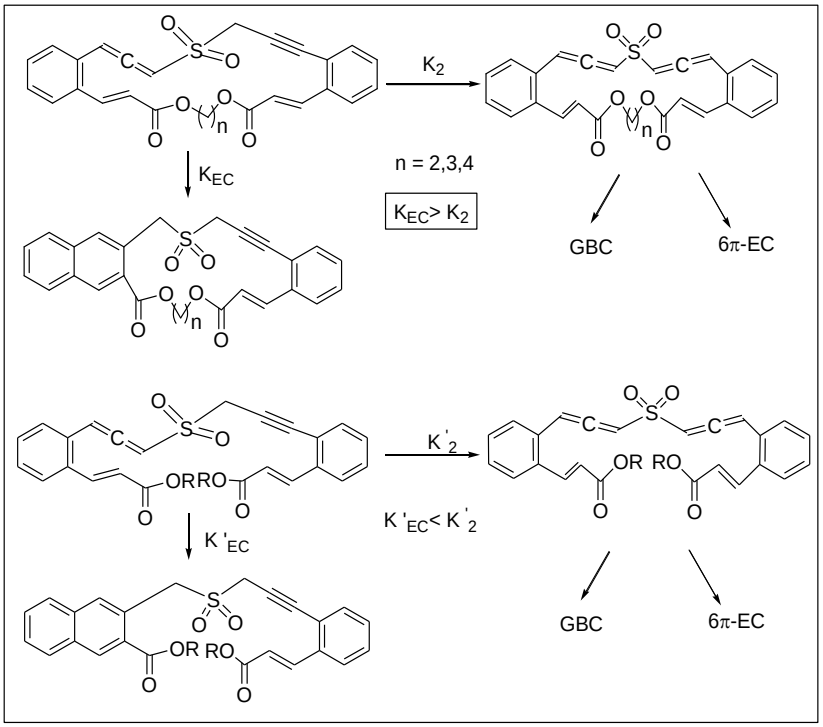


Figure 2.12: ^{1}H NMR assignment of compound 2.24a

2.6 Possible Reason for Changed Product Profiles

As already reported,[4] acyclic *bis*-propargylic sulfones upon base treatment undergo 6π-EC as well as GB cyclization from the *bis*-allenic form. NMR study indicated a different sequence of steps for the reaction of cyclic sulfones **2.20a-c** as compared to their acyclic counterparts.



Scheme 2.5: Isomerization of *bis*-propargyl sulfone

Both the cyclic and acyclic sulfone upon base treatment first isomerizes to the mono allenic sulfone. The subsequent fate of this monoallene will depend upon the ease of 6π-EC with respect to further isomerization to the *bis*-allene. We propose (which is also supported by computations[10]) that isomerization of the monoallene to the bis-allene will be difficult in case of cyclic sulfones because of conformational constraint. On the other hand, the monoallenes in cyclic sulfones are geometrically pre-organized for undergoing the 6π-EC process. This explains why we have observed exclusive 6π-EC in case of cyclic sulfones. For the acyclic system, isomerization to the *bis*-allene from the monoallene can be expected to be much faster because of conformational flexibility; hence both 6π-EC and GB processes occur in these systems.[4] The situation is shown in **Scheme 2.5**.

Commputation analysis of these systems was carried out by Mr. Saibal Jana under the guidance of Prof. A. Anoop. The argument based on differential stability of mono and *bis*-allene in cyclic and acyclic systems was supported by these results.[10]

2.7 Conclusion

In conclusion, we have successfully designed a protocol for shifting the reactivity of *ortho*-alkenyl propargyl sulfones towards 6π-EC completely from the generally observed mixed reactivity of GB and 6π-EC. Our experimental findings of occurrence of exclusive 6π-EC product from these sulfones upon base treatment demonstrated the importance of conformational constraint. The study has also indicated a different mechanism for the reactivity of cyclic vis-à-vis acyclic sulfones involving mono-allene vs bis-allene. The computational study also shows that the reactivity of cyclic systems towards stepwise 6π-EC involving the monoallene intermediate is different from the mechanism for acyclic system. These results portrayed a clear picture to understand both the electronic and conformational constraints administrating the course of reactions involving these types of systems.

2.8 Experimental

2.8.1 General Experimental

Melting points (m.p) were recorded on a Toshniwal hot-coil stage melting point apparatus and were uncorrected. Among the spectra, ^{1}H and ^{13}C–NMR were recorded on a 200 MHz (Bruker, 400 MHz (Bruker) and 600 MHz (Bruker) spectrometer. Deuterated chloroform ($CDCl_3$) was used as solvent unless otherwise mentioned. Proton and carbon spectra were referenced internally to solvent signals, using values of δ = 7.26 ppm for proton and δ = 77.23 ppm for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparently and b = broad signal. All coupling constants (*J*) are given in Hz. Chemical shifts were expressed in δ unit and ^{1}H-^{1}H coupling constants in Hz. Mass spectra were obtained from CRF-IIT, Kharagpur.

All the dry solvents used for reactions were purified according to the standard protocols. Benzene and tetrahydrofuran (THF) were distilled from sodium/ benzophenone under inert atmosphere. Chloroform and dichloromethane (DCM) were dried over phosphorous pentoxide (P_2O_5) or calcium hydride (CaH_2). Ethanol and methanol were dried first over calcium oxide (CaO) and then over magnesium turnings. Acetonitrile, triethylamine (Et_3N) and *n*-butylamine were distilled from calcium hydride. Potassium carbonate (K_2CO_3) was dried by heating followed by vacuum drying. Acetone was distilled from iodine/potassium permanganate under dry argon/nitrogen atmosphere. All the solvents for chromatography (column and preparative layer) were distilled prior to use. In most of the column chromatographic purifications, ethyl acetate (EA/EtOAc) and petroleum ether (PE) of boiling range 60-80 ^{o}C were used as eluents. Columns were prepared with silica gel (Si-gel, 60-120 mesh, SRL).

The phrase “usual work-up” or worked up in “usual manner” refers to the washing of the organic phase with water, brine, drying over anhydrous sodium sulphate, filtration and evaporation under reduced pressure.

Procedure for Reduction of Carboxylic Acid to Alcohol (2.10)

In an oven-dried, round bottom flask, fitted with a side arm capped by a rubber septum was charged with 2-iodobenzoic acid **2.09** (1 g, 4.03 mmol) in THF. The solution was cooled to 0 ^{o}C keeping it in ice bath. A 2.5 M solution of borane dimethyl sulfide (4 mL, 5.64 mmol) was added slowly with stirring. The ice bath was then removed and the mixture was stirred at room temperature. After completion of the reaction (8 h) as indicated by the TLC, the mixture was worked up by EtOAc (25 mL x 3)/water, dried over Sodium Sulfate and then evaporated. The pure compound was isolated by column chromatography (Si-gel, PE:EA = 7:1). The structure of the compound was confirmed by comparison of its ^{1}H NMR data to that of literature report.

Procedure for Oxidation of Alcohol to Aldehyde (2.11)

To a well stirred solution of 2-iodobenzyl alcohol **2.10** (0.695 g, 2.97 mmol) in DCM, 1.2 equivalent of Dess-Martin periodinate was added portion wise. After stirring at ambient temperature for 5 h, the mixture was diluted with saturated sodium bicarbonate solution. The resulting biphasic mixture was stirred vigorously. The layers were separated and the aqueous layer was extracted with DCM (20 mL x 3). The combined organic layers were dried over sodium sulfate. The desired compound was purified by silica gel column chromatography with pet ether-ethyl acetate (10:1) as eluent. The structure of the compound was confirmed by comparison of its ^{1}H NMR data to that of literature report.

Procedure for Sonogashira Coupling (2.12)

2-iodobenzaldehyde **2.11** (1.272 g, 5.48 mmol), 3 mol% $Pd(PPh_3)_2Cl_2$ (0.189 g), 20 mol% CuI (0.3 g) and THP protected propargyl alcohol (1 mL, 6.58 mmol) were added in succession to 20 mL of degassed Et_3N and left at room temperature. After the completion of the reaction, the reaction mixture was then poured into ethyl acetate and the organic layer was washed with saturated NH_4Cl solution and brine, dried over anhydrous sodium sulfate. Evaporation in vacuum gave residue from which the product was isolated by Silica-gel column chromatography using petroleum ether-ethyl acetate (20:1) mixture as eluent. The structure of the compound was confirmed by comparison of its ^{1}H NMR data to that of literature report.[11]

Procedure for (Carbethoxymethylene)triphenylphosphorane Preparation

Ethylbromo acetate (0.414 mL, 3.59 mmol) was added drop wise into a solution of PPh_3 (1 g, 1.1 mmol) in benzene (25 mL) at room temperature. It was stirred for 4-5 hrs. The separated solid was filtered through Buchner funnel and the residue was washed with pet ether. The resulting white solid was taken in mixture benzene (29 mL) and aq. NaOH solution (2.14 g in 18 mL water). The mixture was stirred until both layers became clear. The benzene layer was dried over sodium sulfate and concentrated. The white salt was recrystallized from distilled pet ether.

Procedure for Wittig Reaction

Aldehyde **2.12** was weighed (1.5 g, 6.17 mmol) in a round bottom flask and dissolved in benzene (25 mL). To this solution previously prepared ylide (carbethoxymethylene)triphenylphosphorane (2.15 g, 6.17 mmol) was added. The reaction mixture was refluxed for 4 h. The solution was then evaporated and the crude residue was then subjected to column chromatography (PE:EA = 15:1 as eluent).

Procedure for Hydrolysis of Ethyl Ester to Carboxylic Acid (2.14)

The ethyl ester **2.13** (1.67 g, 5.34 mmol) was dissolved in THF (30 mL) and LiOH (0.64 g, 26.68 mmol) was added to it. The reaction was stirred at 60 ^oC for 24 h. It was then diluted with water and acidified with dilute HCl. The compound was isolated by extracting with EtOAc (25 mL x 3). After evaporation of the organic layer, the crude compound was purified by silica gel column chromatography (petroleum ether-ethyl acetate (1:1) mixture as eluent).

General Procedure for Re-esterifacation with Dibromide

To a stirring solution of **2.14** (1 mmol) in DMF (30 mL), alkyl dibromide (0.5 eq) [$Br(CH_2)_nBr$ where n = 2 to 4] was added. Activated K_2CO_3 (2.5 eq) was added to this solution and stirred for 6-7 h at room temperature. A saturated brine solution was added to the reaction mixture and the solution was stirred for another 1 h. The compound was extracted with EtOAc (30 mL x 4). Silica gel column chromatography furnished the desired product in each case.

General Procedure for THP Deprotection

To a solution of THP protected alcohol *i.e.* **2.15a-c** in EtOH (20 mL), catalytic amount of PPTS (5 mol %) was added and stirred at 45 ^{o}C. EtOH was evaporated after the completion of the reaction (12 h). Usual work up with EtOAc (25 mL x 2) and purification using silica gel column chromatography afforded the desired product (PE:EA = 1:1 as eluent).

General Procedure for Mesylation and Bromide Formation Reaction

The alcohol **2.16a-c** (0.7 mmol) was treated with triethylamine (2 eq) and mesyl chloride (3 eq) in dry DCM (15 mL) at 0 °C under nitrogen atmosphere for 10 min. The reaction was quenched by the addition of brine (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried (anhydrous Na_2SO_4), evaporated and the crude mesylate was vacuum-dried. To the mesylate **2.17a-c** (0.3 mmol) in dry THF (5 mL), LiBr (2 eq) was added and stirred for 10 h. After the completion of the reaction, removal of solvent followed by Silica gel column filtration with petroleum ether-ethyl acetate (PE:EA = 15:1) afforded the pure bromide.

General Procedure for Synthesis of Sulfide

The bromide **2.18a-c** (0.1 mmol) was taken in THF (10 mL) and stirred at 0 °C. Saturated solution of Sodium sulfide (0.5 eq) in water was added to it. Phase transfer catalyst TBAB was added and the reaction mixture was allowed to stir at room temperature for 5 h. After usual work up with water and ethyl acetate (10 mL x 3), the organic layer was evaporated and the crude product was subjected to Silica gel column chromatography for isolation of the pure sulfide (PE:EA = 7:1 as eluent).

General Procedure for Oxidation of Sulfides to Sulfones

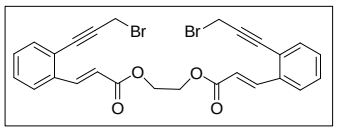
To a solution of compound **2.19a-c** (0.05 mmol) in THF: H_2O (1:1), oxone (0.25 mmol) was added and the mixture was stirred for 12 h at room temperature. The reaction mixture was worked up by EtOAc/water, dried over Sodium Sulfate and then evaporated. The compounds (**2.20a-c)** were isolated by column chromatography (Si-gel, PE:EA = 2:1).

General Procedure for 6π-Electrocyclization Reaction

Sulfone (10-15 mg) was taken in NMR tube and dissolved in $CDCl_3$ (600 μL). Catalytic amount of Et_3N (10 mol %) was added and reaction was monitored by recording proton NMR in different time interval. Reaction mixture was worked up by chloroform/water and the final products were isolated in pure form by column chromatography (Si-gel, DCM/methanol or PE/EA mixture as eluent).

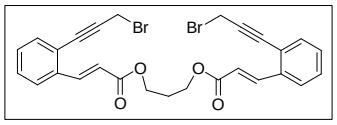
2.8.2 NMR Spectral Data of Some Selected Compounds

(3-[2-(3-Bromo-prop-1-ynyl)-phenyl]-acrylic acid 2-{3-[2-(3-bromo-prop-1-ynyl)-phenyl]-acryloyloxy}-ethyl ester (2.18a)



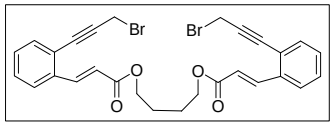
State: gummy liquid; **Yield**: 87%; δ_H **(**200 MHz, $CDCl_3$): 8.15 (d, 2H, *J* = 16.0 Hz), 7.65-7.61 (m, 2H), 7.51-7.46 (m, 2H), 7.35-7.29 (m, 4H), 6.55 (d, 2H, *J* = 16.0 Hz), 4.51 (s, 4H), 4.20 (s, 4H). δ_C (50 MHz, $CDCl_3$): 166.5, 142.7, 136.0, 133.2, 129.9, 129.1, 126.2, 122.9, 119.5, 90.3, 84.17, 62.4, 14.8.

3-[2-(3-Bromo-prop-1-ynyl)-phenyl]-acrylic acid 3-{3-[2-(3-bromo-prop-1-ynyl)-phenyl]-acryloyloxy}-propyl ester (2.18b)



State: gummy liquid; **Yield**: 85%; δ_H (200 MHz, $CDCl_3$): 8.14 (d, 2H, *J* = 16.0 Hz), 7.6-7.32 (m, 8H), 6.54 (d, 2H, *J* = 16.0 Hz), 4.43 (t, 4H, *J* = 6.0 Hz), 4.25 (s, 4H, *J* = 6.0 Hz), 2.17 (t, 2H, *J* = 6.0 Hz). δ_C (50 MHz, $CDCl_3$): 166.4, 142.7, 135.8, 132.8, 129.7, 128.5, 125.6, 123.8, 119.5, 91.49, 80.7, 60.3, 29.3, 14.1.

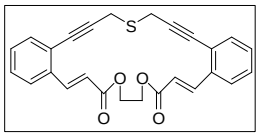
3-[2-(3-Bromo-prop-1-ynyl)-phenyl]-acrylic acid 4-{3-[2-(3-bromo-prop-1-ynyl)-phenyl]-acryloyloxy}-butyl ester (2.18c)



State: gummy liquid; **Yield**: 86%; δ_H (200 MHz, $CDCl_3$): 8.11(d, 2H, *J* = 16.0 Hz), 7.64-7.6 (m, 4H), 7.50-7.46 (m, 4H), 6.51 (d, 2H, *J* = 16.0 Hz), 4.29-4.16 (m, 8H), 1.87 (s,

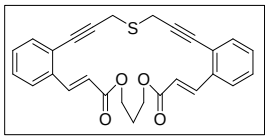
4H). δ_C (50 MHz, $CDCl_3$): 166.5, 142.2, 136.0, 133.1, 129.7, 129.1, 126.1, 122.8, 119.7, 90.2, 84.1, 61.4, 28.1, 14.9.

18,21-Dioxa-5-thia-tricyclo[23.4.0.09,14]nonacosa-1(29),9(14),10,12,15,23,25,27-octaene-2,7-diyne-17,22-dione (2.19a)



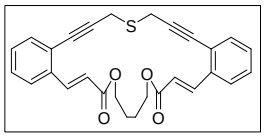
State: gummy liquid; **Yield**: 87%; δ_H (200 MHz, $CDCl_3$): 8.18 (d, 2H, *J* = 16.0 Hz), 7.62-7.58 (m, 2H), 7.50-7.45 (m, 2H), 7.33-7.26 (m, 4H), 6.51 (d, 2H, *J* = 16.0 Hz), 4.55 (s, 4H), 3.92 (s, 4H). δ_C (50 MHz, $CDCl_3$): 166.5, 142.9, 135.7, 132.9, 129.8, 128.5, 126.2, 123.8, 119.3, 91.0, 81.1, 62.6, 20.2.

18,22-Dioxa-5-thia-tricyclo[24.4.0.09,14]triaconta-1(30),9(14),10,12,15,24,26,28-octaene-2,7-diyne-17,23-dione (2.19b)



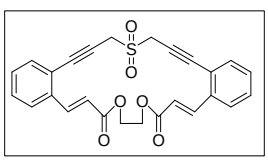
State: gummy liquid; **Yield**: 87%; δ_H (200 MHz, $CDCl_3$): 8.26 (d, 2H, *J* = 16.0 Hz), 7.65-7.30 (m, 8H), 6.47(d, 2H, *J* = 16.0 Hz), 4.44 (t, 4H, *J* = 6.0 Hz), 3.88 (s, 4H), 2.17 (t, 2H, *J* = 6.0 Hz). δ_C (50 MHz, $CDCl_3$): 166.6, 142.4, 135.7, 133.1, 129.6, 128.6, 126.0, 123.4, 11.5, 91.5, 83.0, 64.0, 54.4, 23.2.

18,23-Dioxa-5-thia-tricyclo[25.4.0.09,14]hentriaconta-1(31),9(14),10,12,15,25,27,29-octaene-2,7-diyne-17,24-dione (2.19c)



State: gummy liquid; **Yield**: 70%; δ_H (200 MHz, $CDCl_3$): 8.26 (d, 2H, *J* = 16.0 Hz), 7.65-7.3 (m, 8H), 6.47 (d, 2H, *J* = 16.0 Hz), 4.49-4.41 (m, 4H), 3.81 (s, 4H), 1.81 (s, 4H). δ_C (50 MHz, $CDCl_3$): 162.5, 142.4, 135.7, 133.1, 129.6, 128.6, 126.0, 123.4, 119.6, 91.4, 83.2, 61.9, 30.2, 19.0.

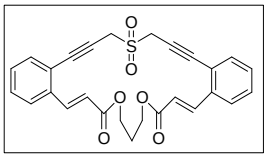
5,5-Dioxo-18,21-dioxa-5l6-thia-tricyclo[23.4.0.09,14]nonacosa-1(29),9(14),10,12,15,23,25,27-octaene-2,7-diyne-17,22-dione (2.20a)



State: gummy liquid; **Yield**: 88%; δ_H (200 MHz, $CDCl_3$): 8.12 (d, 2H, *J* = 16.0 Hz) 7.67-7.63 (m, 2H), 7.55-7.50 (m, 2H), 7.48-7.30

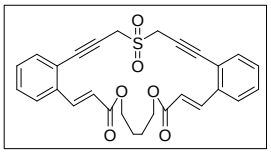
(m, 4H), 6.49 (d, 2H, *J* = 16.0 Hz), 4.60 (s, 4H), 4.55 (s, 4H). δ_C (50 MHz, $CDCl_3$): 166.6, 166.0, 143.4, 142.4, 142.1, 136.2, 133.9, 133.4, 132.0, 130.0, 129.8, 128.9, 128.4, 126.6, 126.1, 122.8, 122.2, 120.4, 120.0, 85.6, 82.4, 62.9, 45.3. HRMS: Calculated for $C_{26}H_{20}O_6SNa$ [MNa^+] 483.0878, found 483.0869.

5,5-Dioxo-18,22-dioxa-5l6-thia-tricyclo[24.4.0.09,14]triaconta-1(30),9(14),10,12,15, 24,26,28-octaene-2,7-diyne-17,23-dione (2.20b)



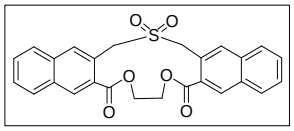
State: gummy liquid; **Yield**: 85%; δ_H (200 MHz, $CDCl_3$): 8.16 (d, 2H, *J* = 16.0 Hz), 7.61-7.50 (m, 4H), 7.34-7.30 (m, 4H), 6.43 (d, 2H, *J* = 16.0 Hz), 4.48 (s, 4H), 4.40 (t, 4H, *J* = 5.8 Hz), 2.12 (t, 2H, *J* = 5.6 Hz). δ_C (50 MHz, $CDCl_3$): 166.4, 142.1, 136.1, 133.2, 129.7, 129.4, 125.6, 122.3, 119.9, 85.6, 81.6, 60.2, 45.7, 27.9. HRMS: Calculated for $C_{27}H_{22}O_6SNa$ [MNa^+] 497.1035, found 497.1017.

5,5-Dioxo-18,23-dioxa-5l6-thia-tricyclo[25.4.0.09,14]hentriaconta-1(31),9(14),10,12, 15,25,27,29-octaene-2,7-diyne-17,24-dione (2.20c)



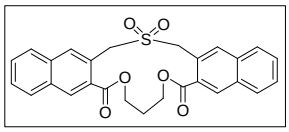
State: gummy liquid; **Yield**: 90%; δ_H (200 MHz, $CDCl_3$): 8.13(d, 2H, *J* = 16.0 Hz), 7.68-7.30 (m, 8H), 6.54 (d, 2H, *J* = 16.0 Hz), 4.55 (s, 4H), 4.36 (s, 4H), 1.93 (s, 4H). δ_C (50 MHz, $CDCl_3$): 166.5, 143.3, 142.3, 142.0, 136.1, 133.8, 133.2, 131.8, 130.1, 129.9, 129.6, 128.8, 128.3, 126.5, 126.0, 122.6, 122.1, 120.3, 119.8, 85.5, 82.2, 62.7, 45.1, 27.8. HRMS: Calculated for $C_{28}H_{24}O_6SNa$ [MNa^+] 511.1191, found 511.1211.

Spectral Data for Compound 2.24a



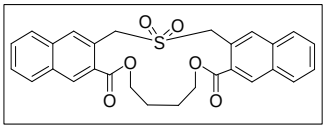
State: white solid; [m.p > 200 °C]; **Yield**: 70%; δ_H (200 MHz, d_6-DMSO): 8.68 (s, 2H), 8.17-8.029 (m, 6H), 7.71-7.65 (m, 4H), 5.34 (s, 4H), 4.76 (s, 4H). δ_C (50 MHz, d_6-DMSO): 167.2, 134.5, 133.8, 132.2, 129.5, 129.3, 128.9, 128.2, 127.9, 123.4, 63.9, 59.5. Calculated for $C_{26}H_{20}O_6SNa$ [MNa^+] 483.0878, found 483.0883.

Spectral Data for Compound 2.24b



State: white solid; [m.p > 200 °C]; **Yield**: 75%; δ_H (200 MHz, d_6-DMSO): 8.62 (s,2H), 8.18-8.01 (m, 6H), 7.75-7.69 (m, 4H), 5.07 (s, 4H), 4.61 (s, 4H). δ_C (50MHz, d_6-DMSO): 166.9, 134.1, 133.47, 131.9, 129.2, 129.0, 128.6, 127.8, 127.5, 123.0, 63.5, 59.1, 25.9. HRMS: Calculated for $C_{27}H_{22}O_6SNa$ [MNa^+] 497.1035, found 497.1023.

Spectral Data for Compound 2.24c



State: white solid; [m.p > 200 °C]; **Yield**: 80%; δ_H (200 MHz, $CDCl_3$): 8.53(s, 2H), 7.96-7.87 (m, 6H), 7.64-7.59 (m, 4H), 5.08 (s, 4H), 4.64 (s, 4H), 2.08 (s, 4H); δ_C (50 MHz, $CDCl_3$): 167.6, 134.2, 133.4, 132.4, 132.4, 129.27, 128.7, 128.5, 127.7, 127.5, 122.2, 64.4, 56.8, 25.5. HRMS: Calculated for $C_{28}H_{24}O_6SNa$ [MNa^+] 511.1191, found 511.1205.

2.9 ^{1}H and ^{13}C NMR Spectra of Some Selected Compounds

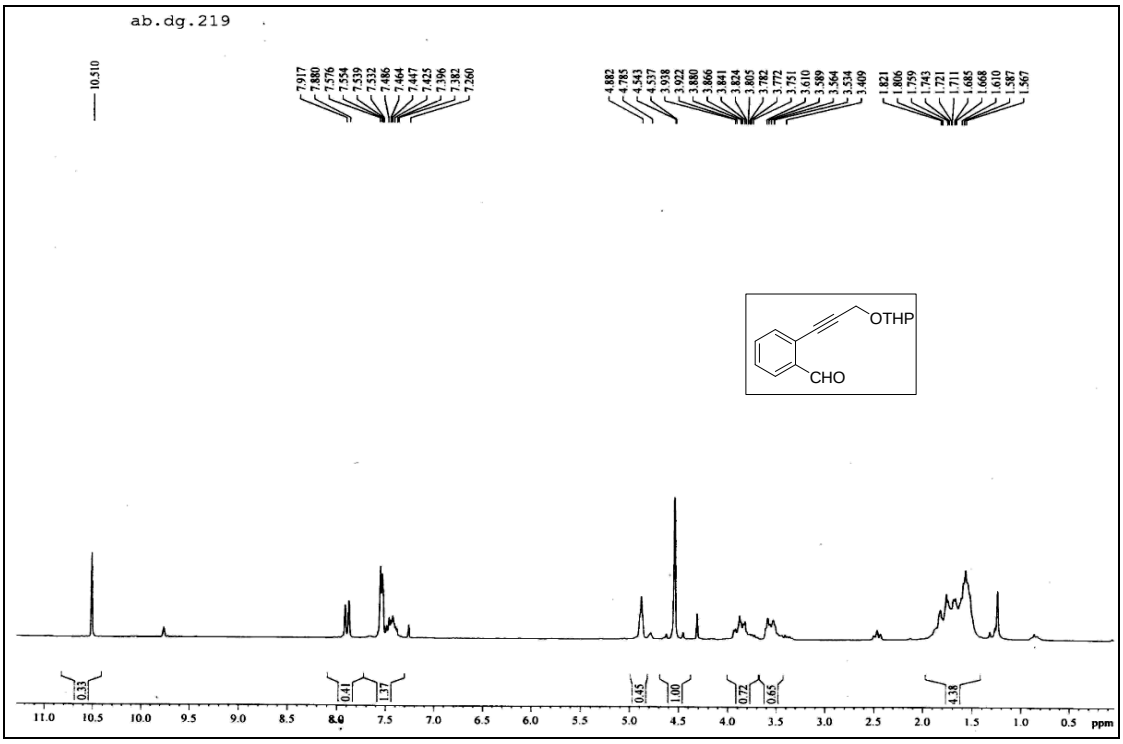


Figure 2.13: ^{1}H NMR of compound 2.12

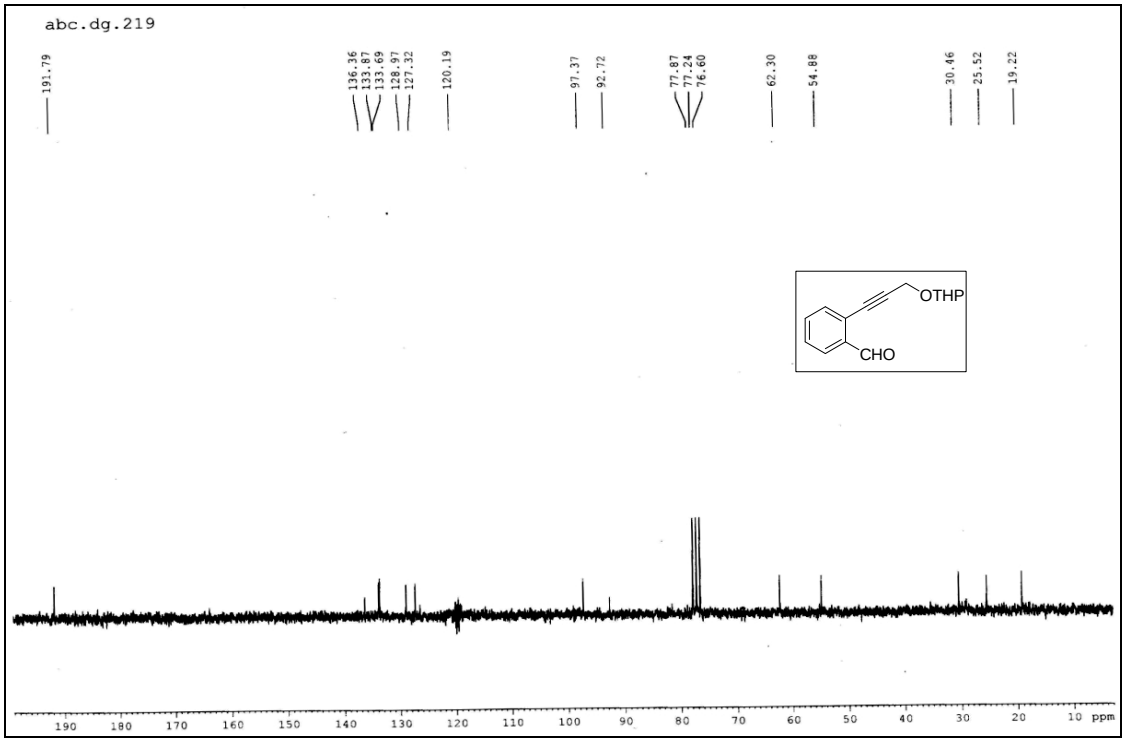


Figure 2.14: ^{13}C NMR spectrum of compound 2.12

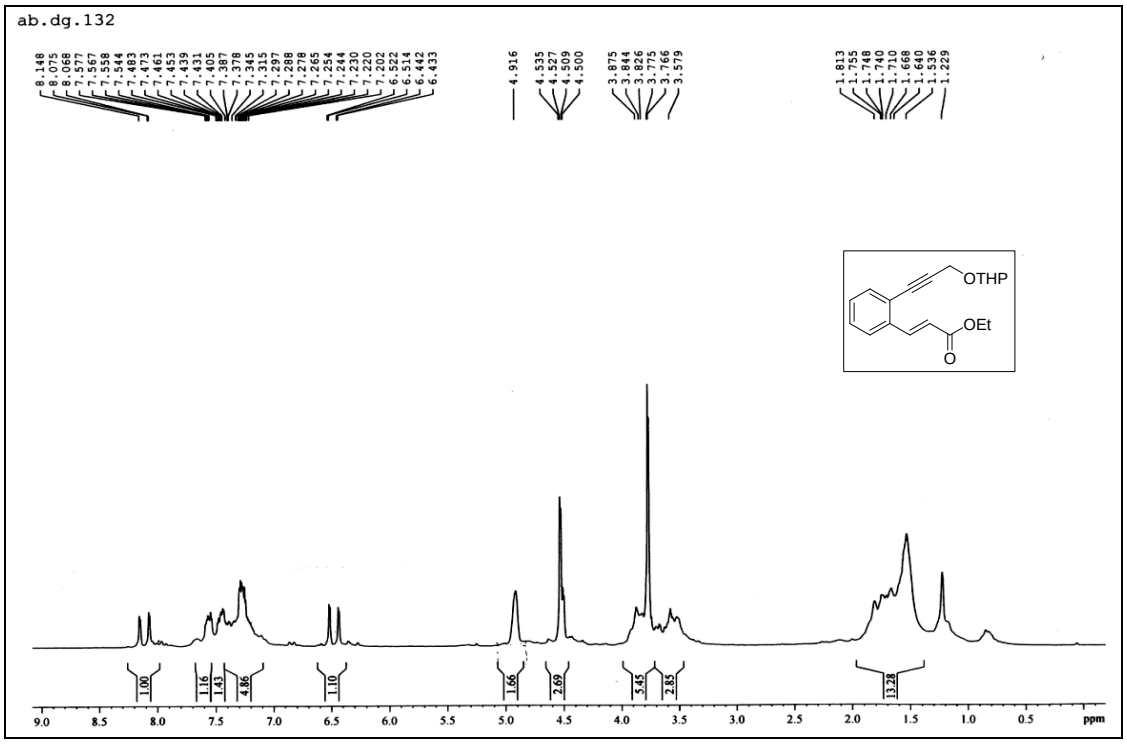


Figure 2.15: ^{1}H NMR of compound 2.13

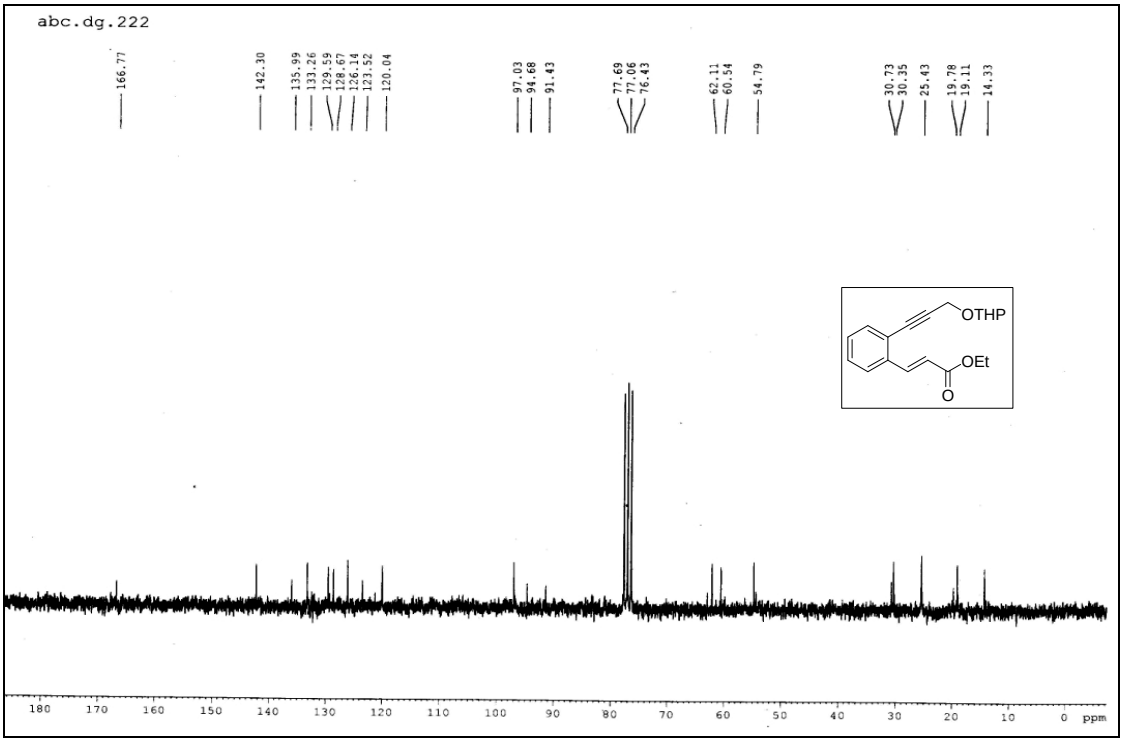


Figure 2.16: ^{13}C NMR spectrum of compound 2.13

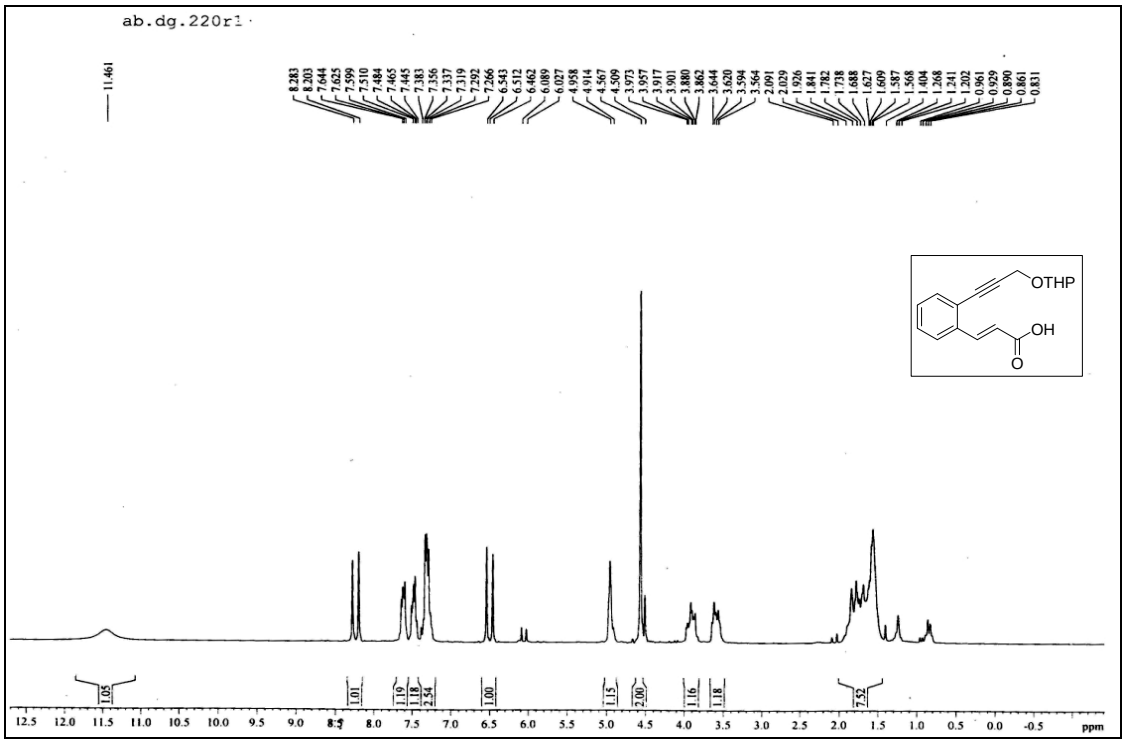


Figure 2.17: ^{1}H NMR of compound 2.14

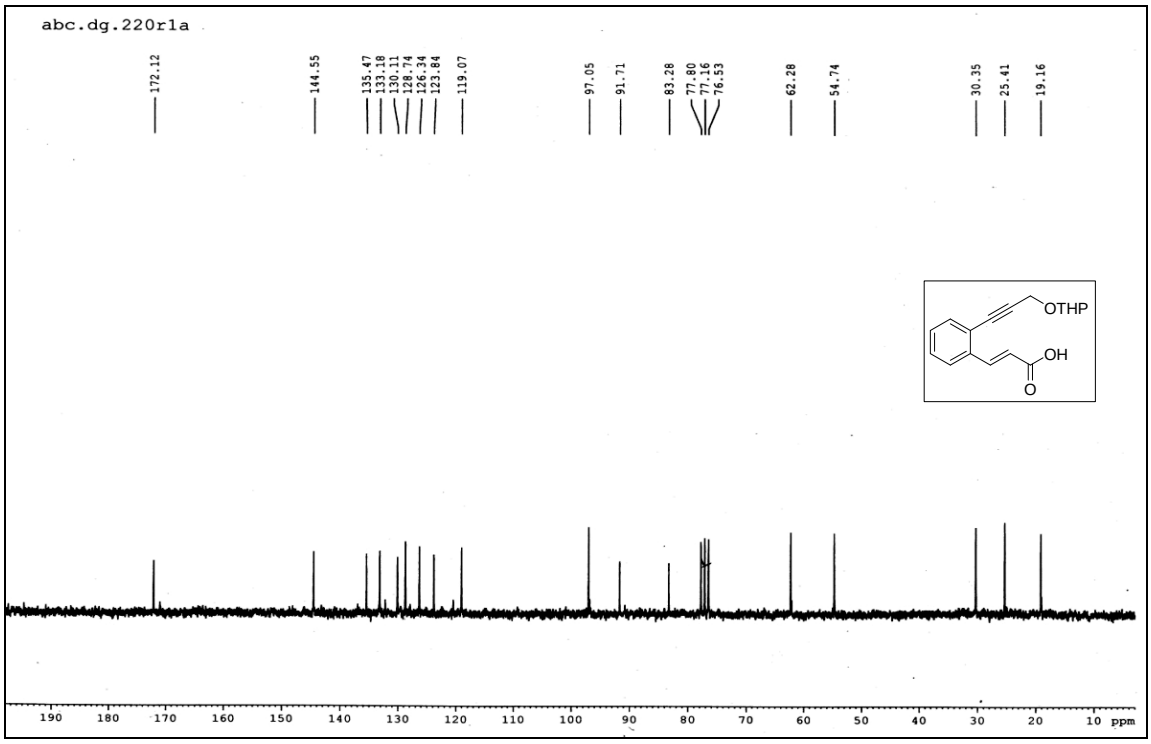


Figure 2.18: ^{13}C NMR spectrum of compound 2.14

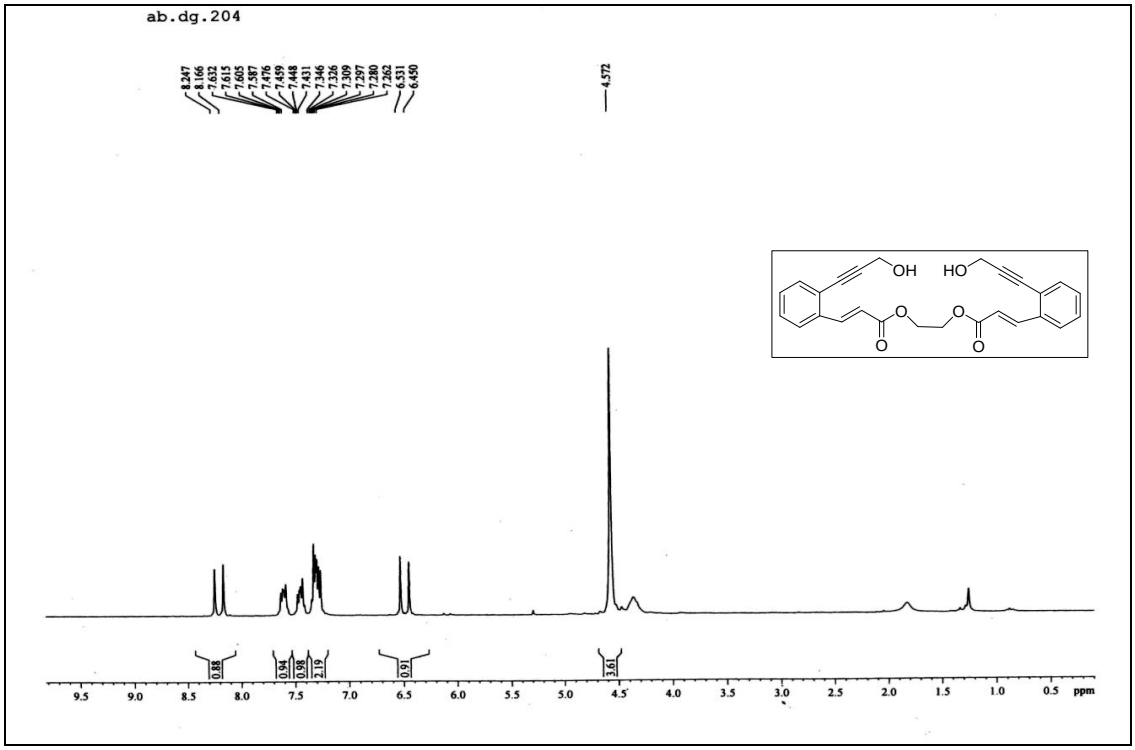


Figure 2.19: ^{1}H NMR of compound 2.16a

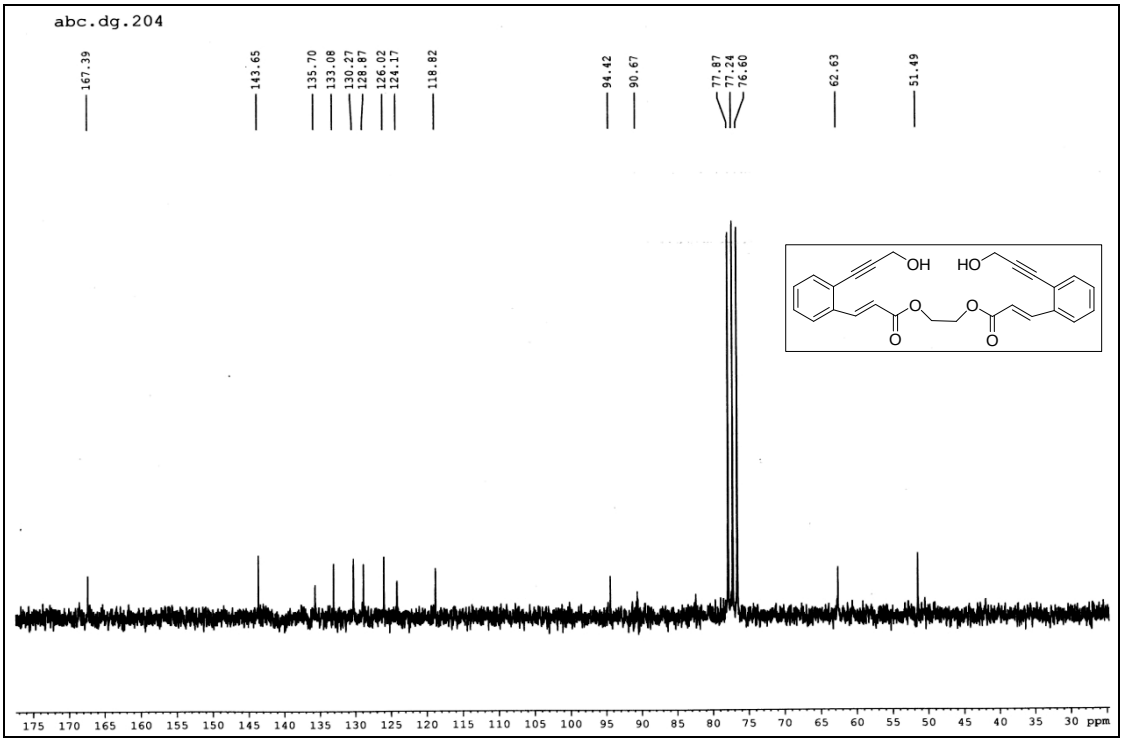


Figure 2.20: ^{13}C NMR spectrum of compound 2.16a

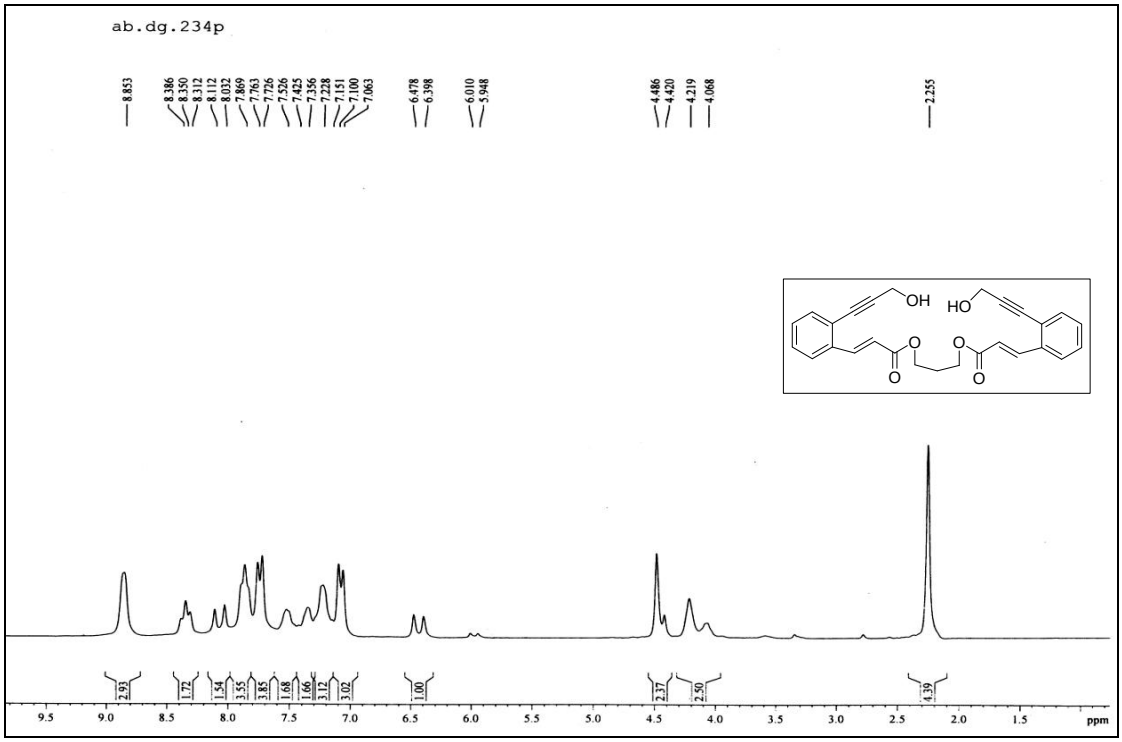


Figure 2.21: ^{1}H NMR of compound 2.16b

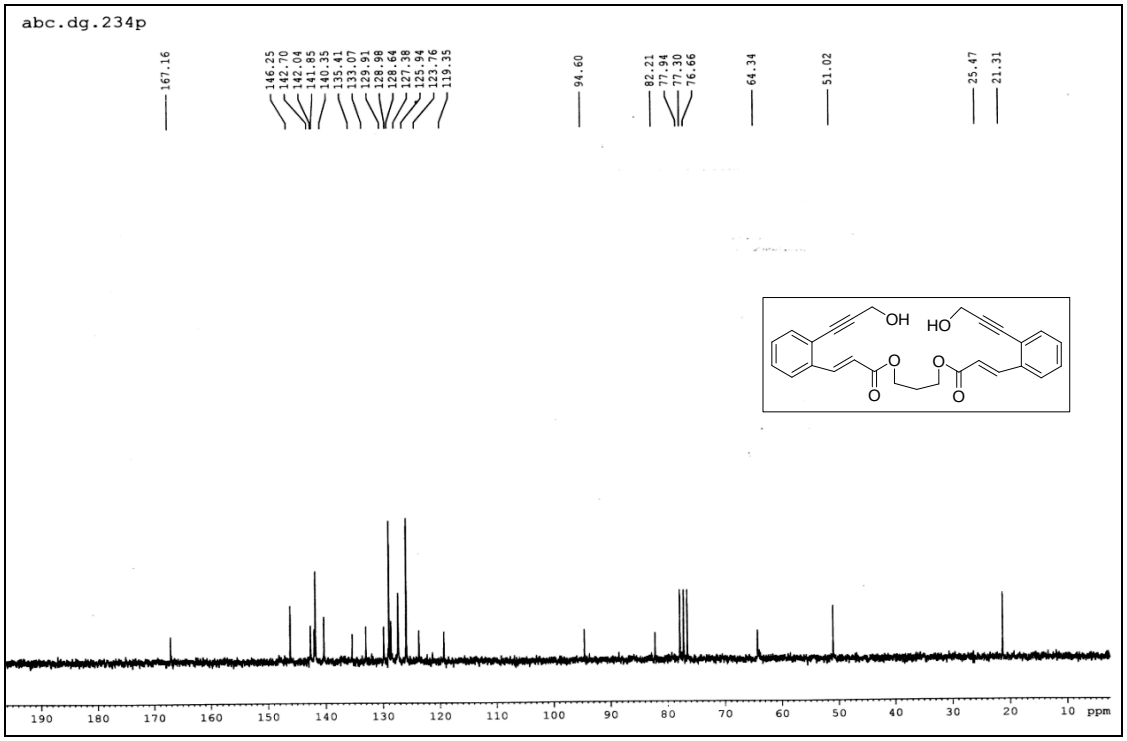


Figure 2.22: ^{13}C NMR spectrum of compound 2.16b

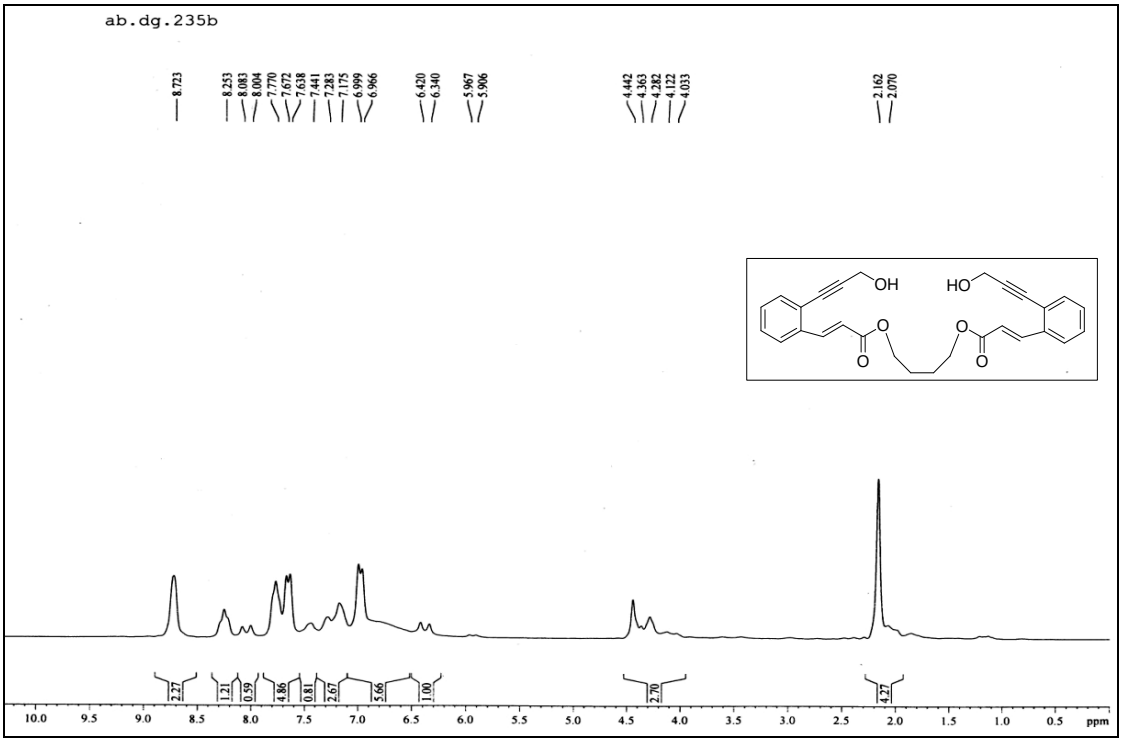


Figure 2.23: ^{1}H NMR of compound 2.16c

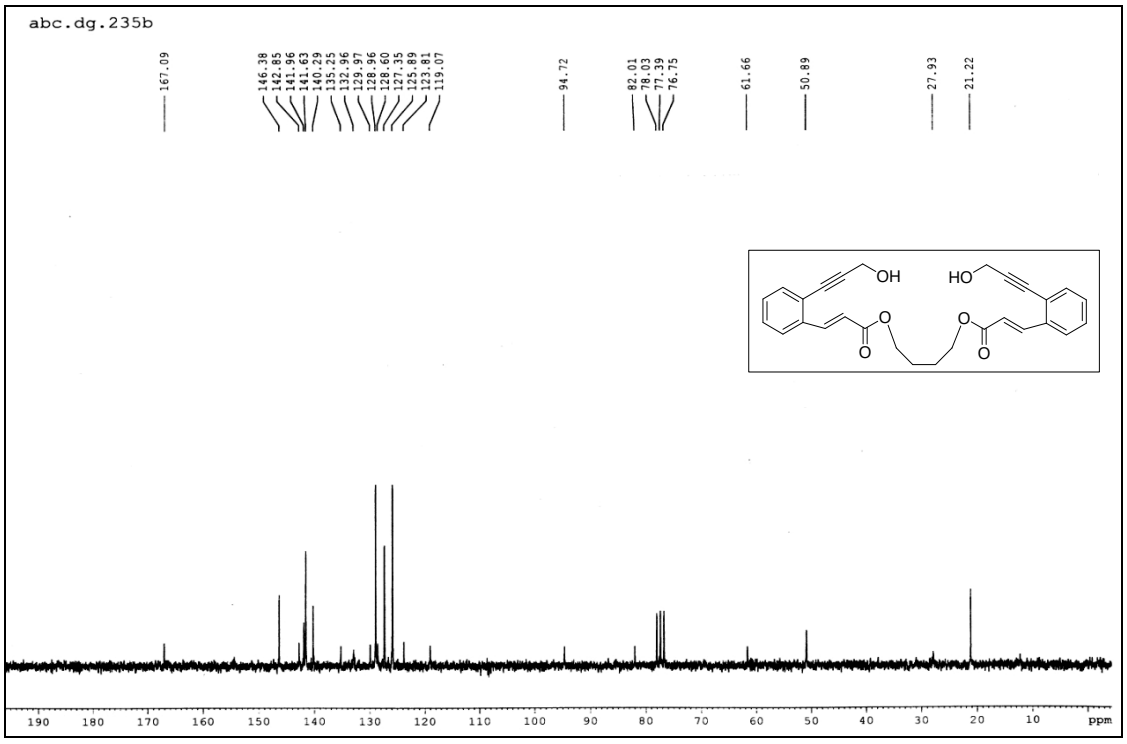


Figure 2.24: ^{13}C NMR spectrum of compound 2.16c

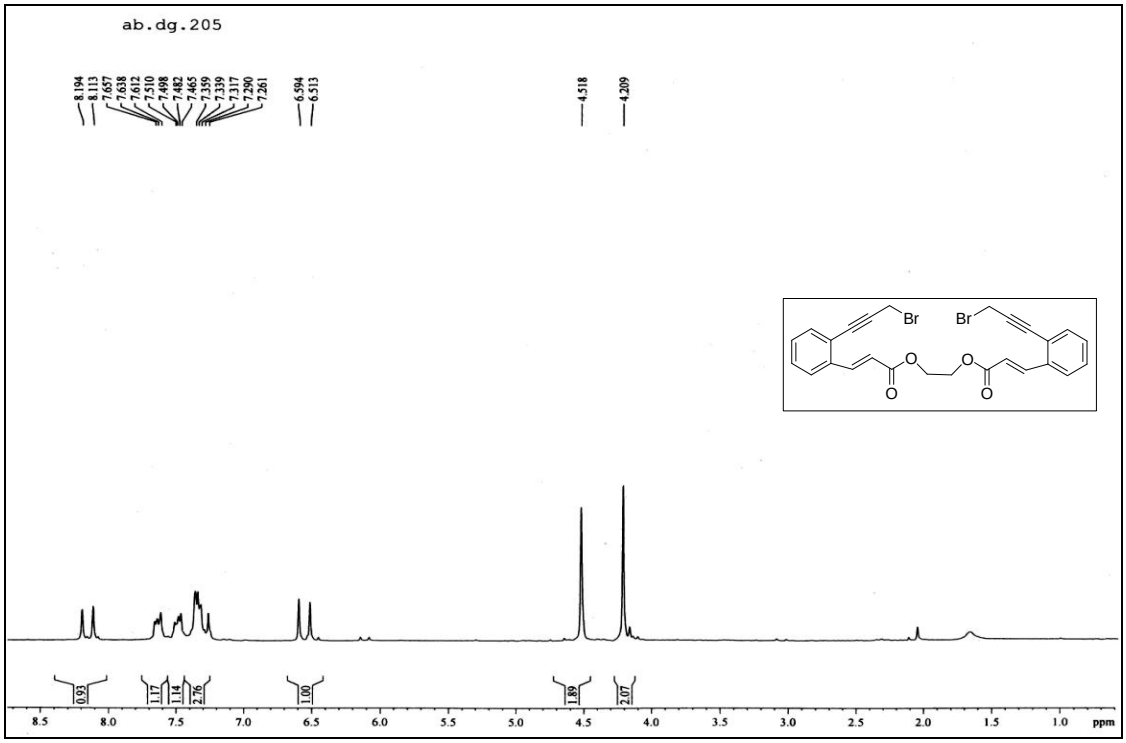


Figure 2.25: ^{1}H NMR of compound 2.18a

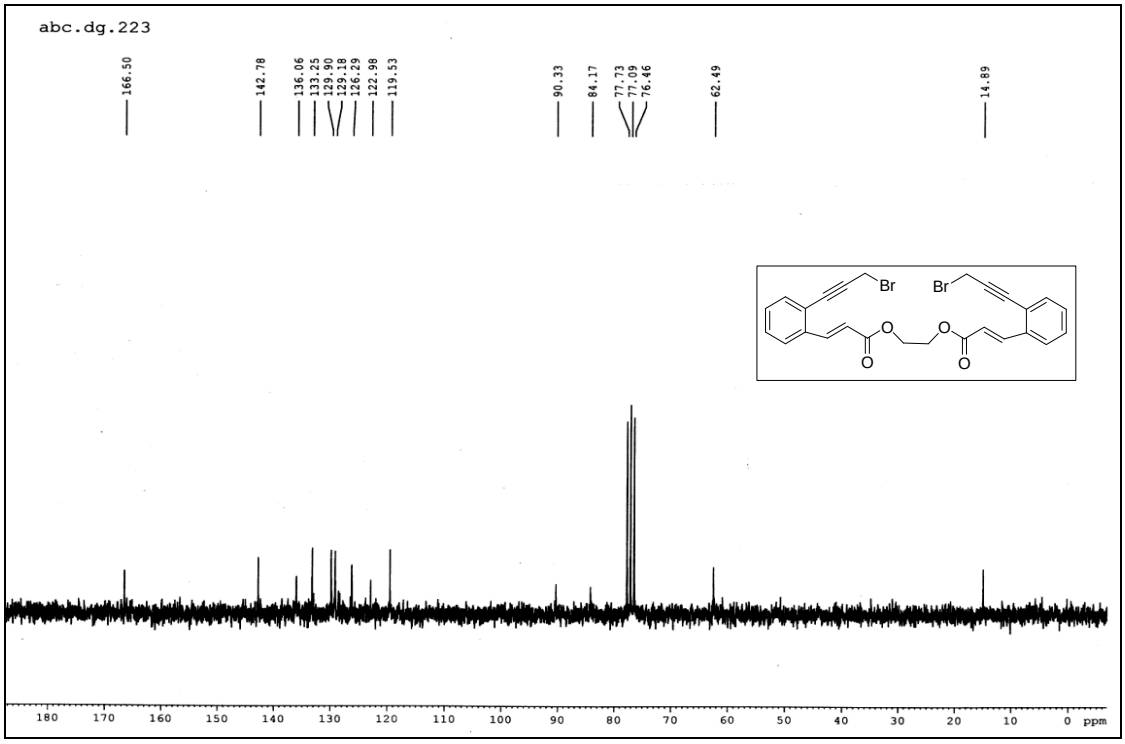


Figure 2.26: ^{13}C NMR spectrum of compound 2.18a

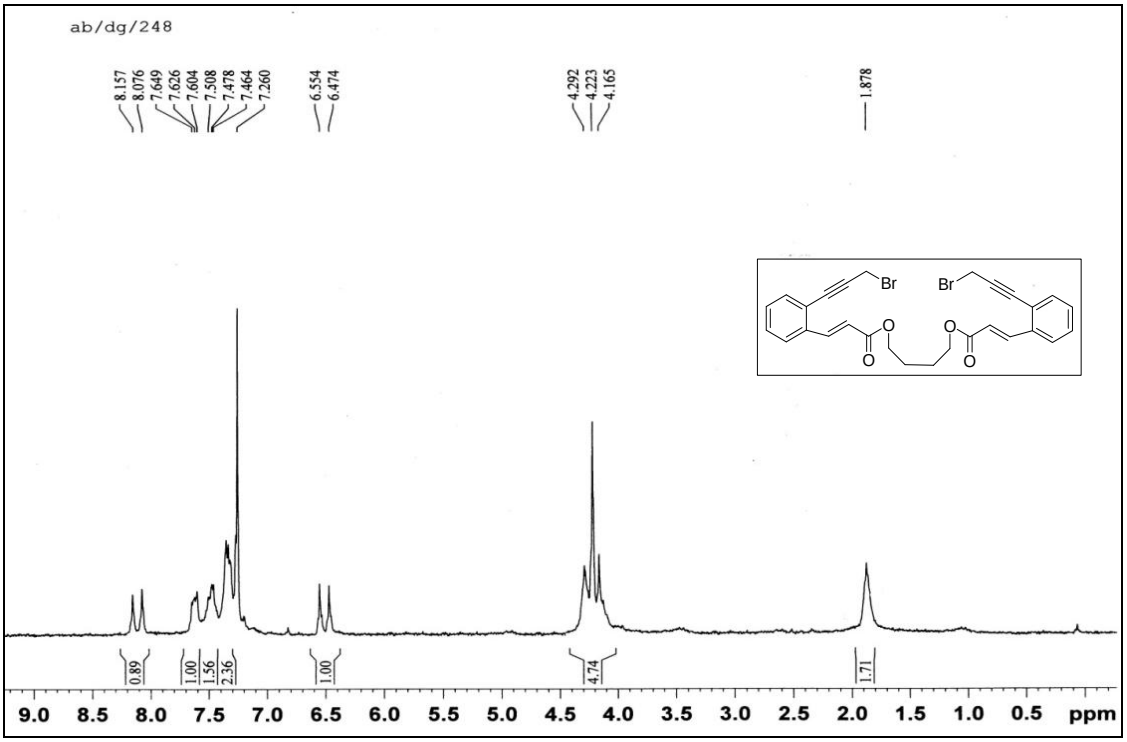


Figure 2.27: ^{1}H NMR of compound 2.18c

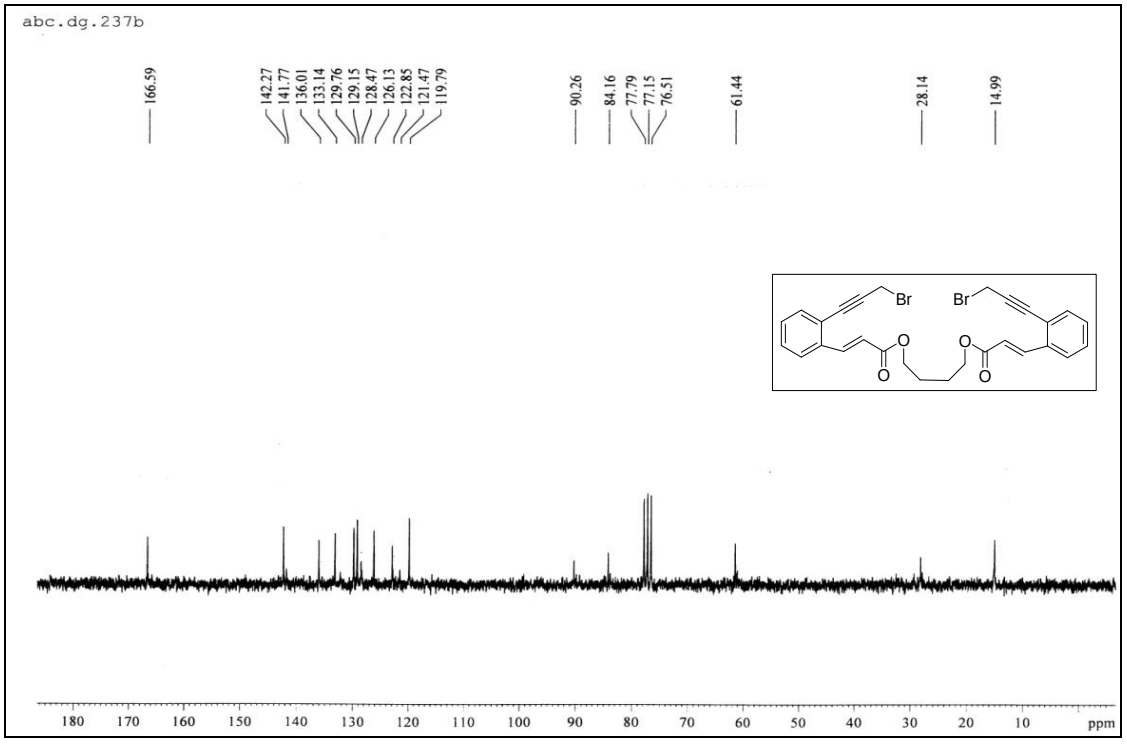


Figure 2.28: ^{13}C NMR spectrum of compound 2.18c

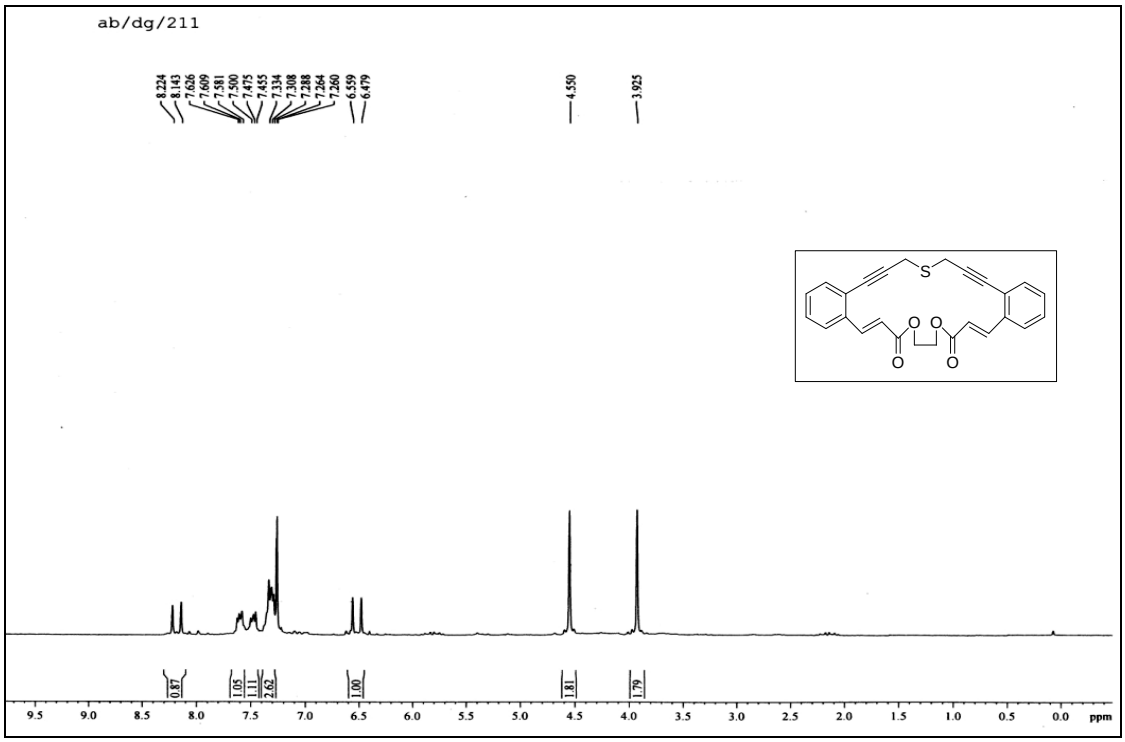


Figure 2.29: ^{1}H NMR of compound 2.19a

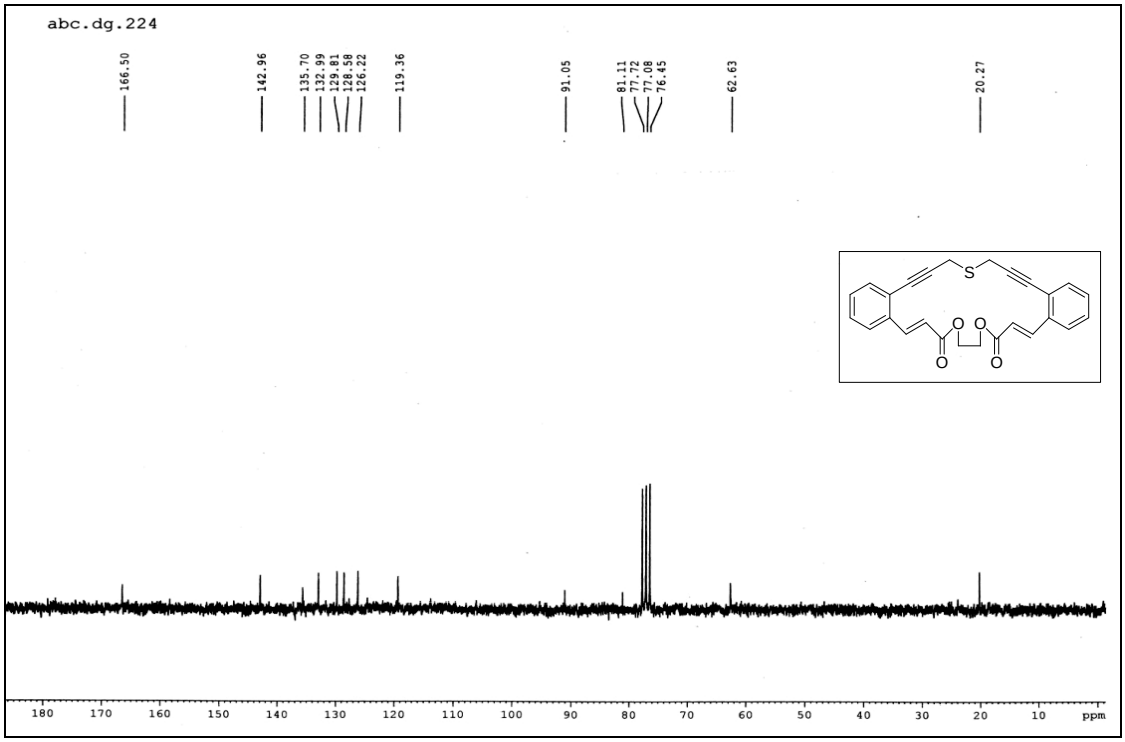
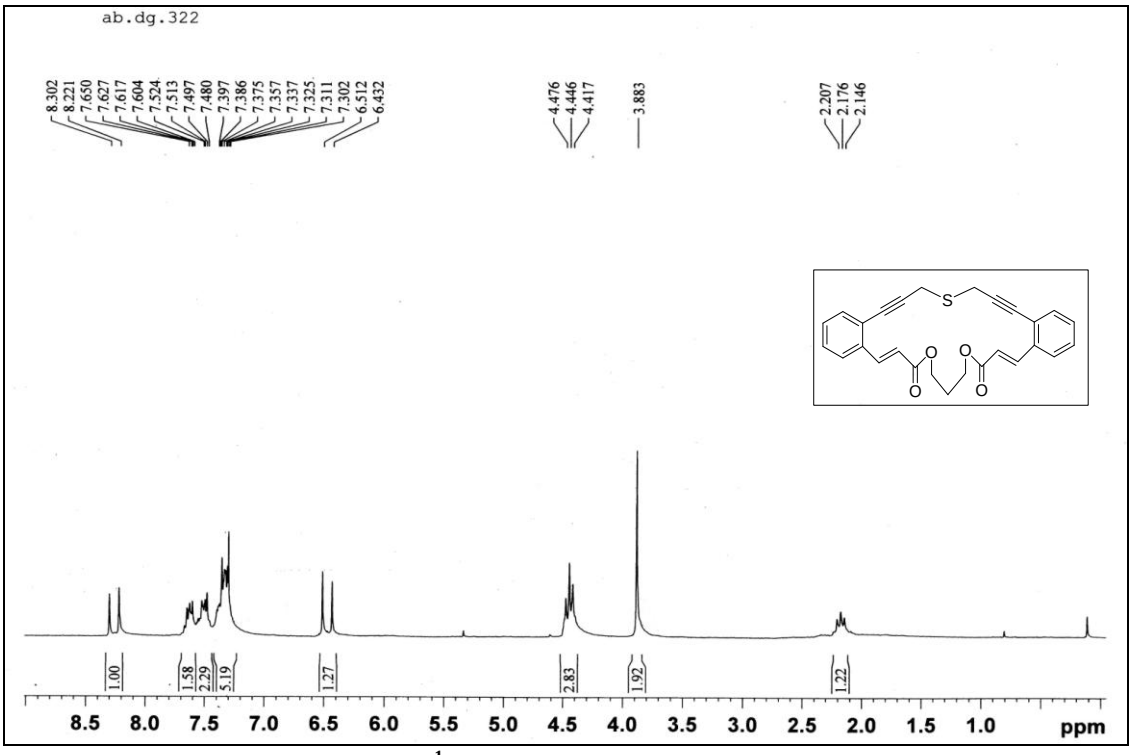


Figure 2.30: ^{13}C NMR spectrum of compound 2.19a



2.31: ^{1}H NMR of compound 2.19b

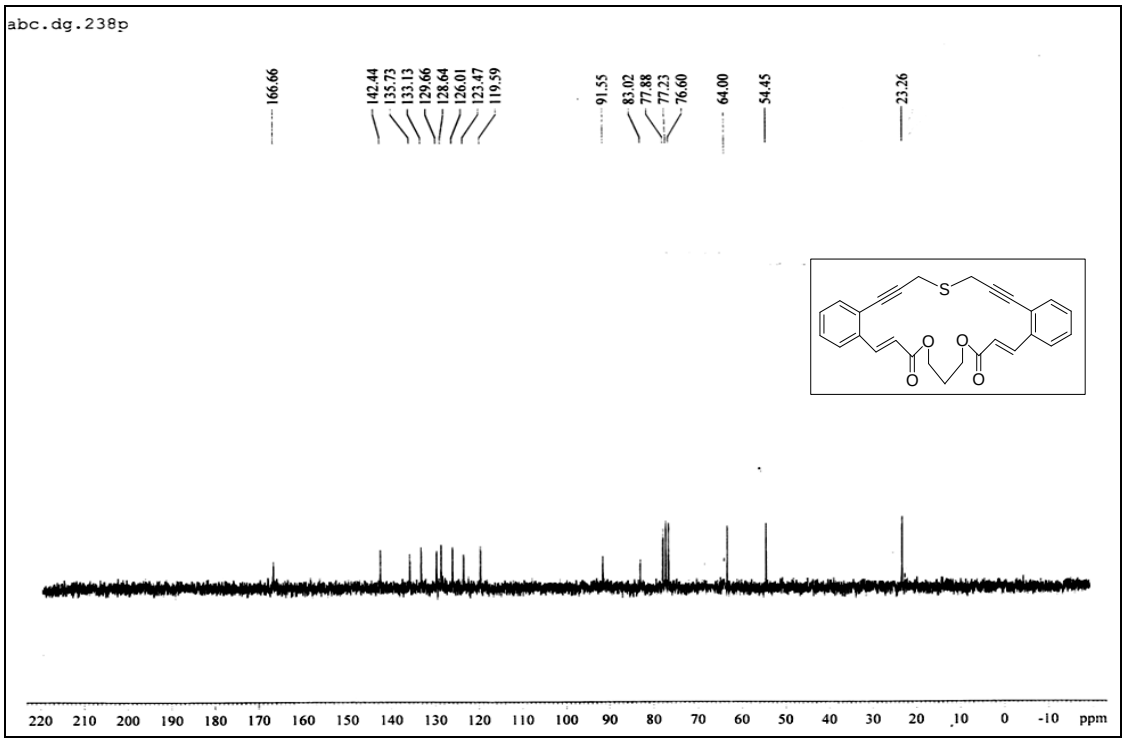


Figure 2.32: ^{13}C NMR spectrum of compound 2.19b

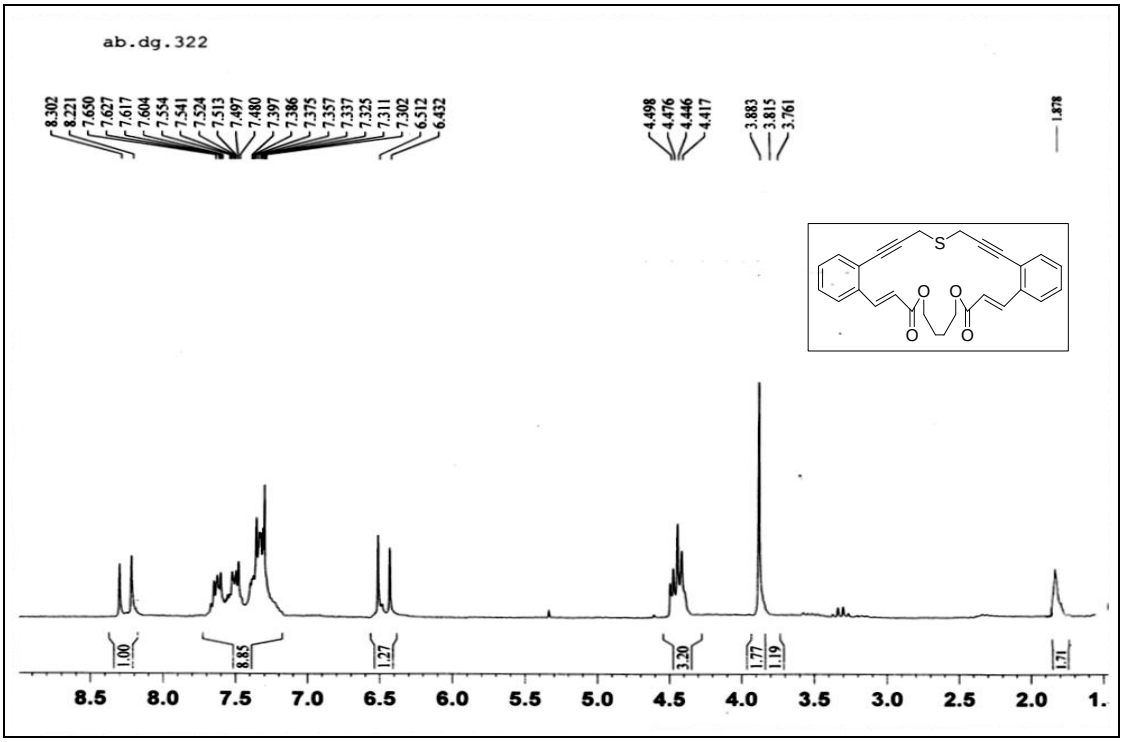


Figure 2.33: ^{1}H NMR of compound 2.19c

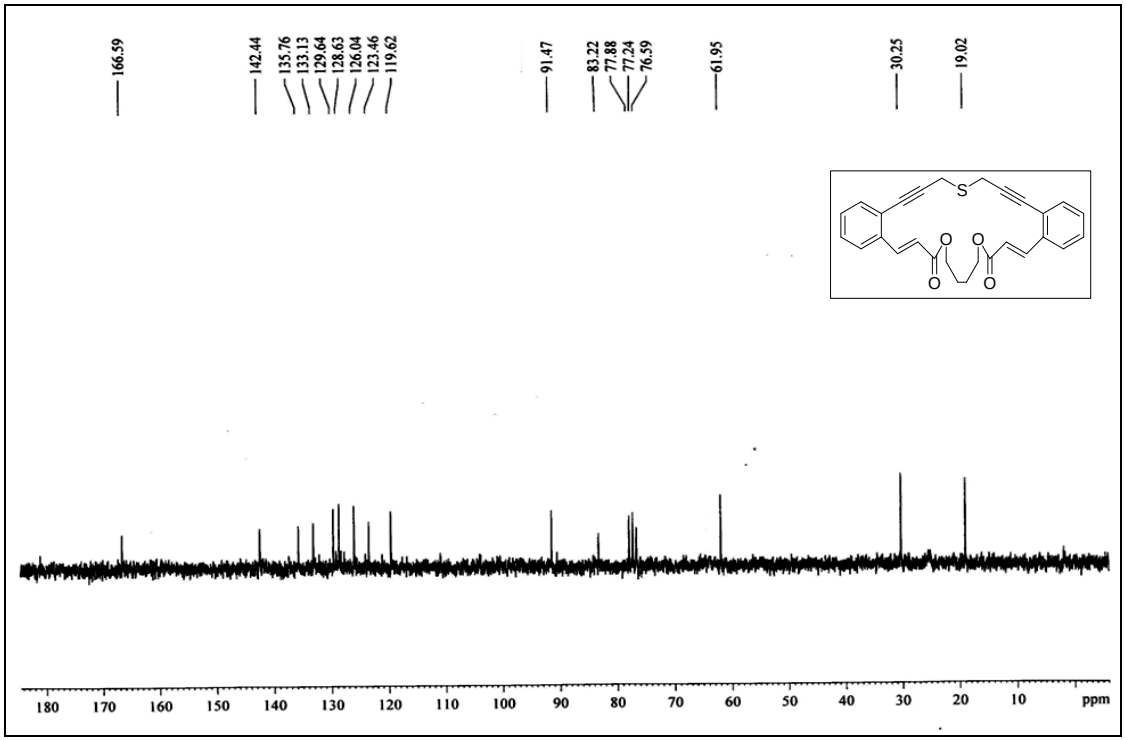


Figure 2.34: ^{13}C NMR spectrum of compound 2.19c

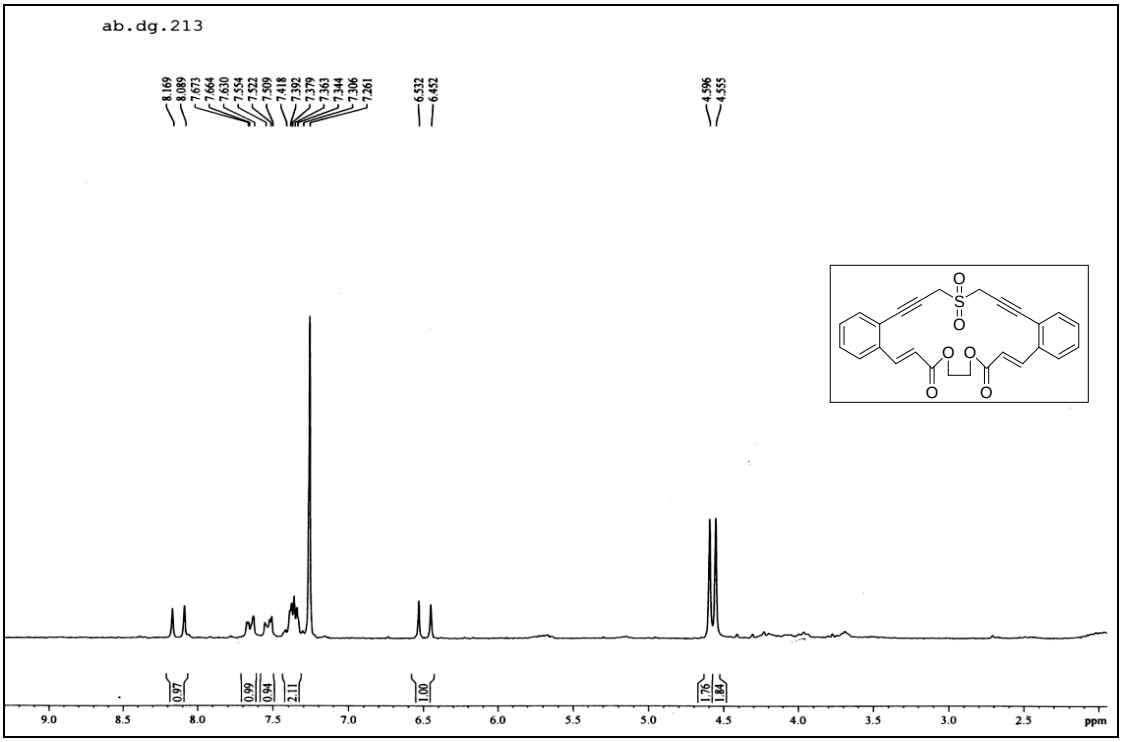


Figure 2.35: ^{1}H NMR of compound 2.20a

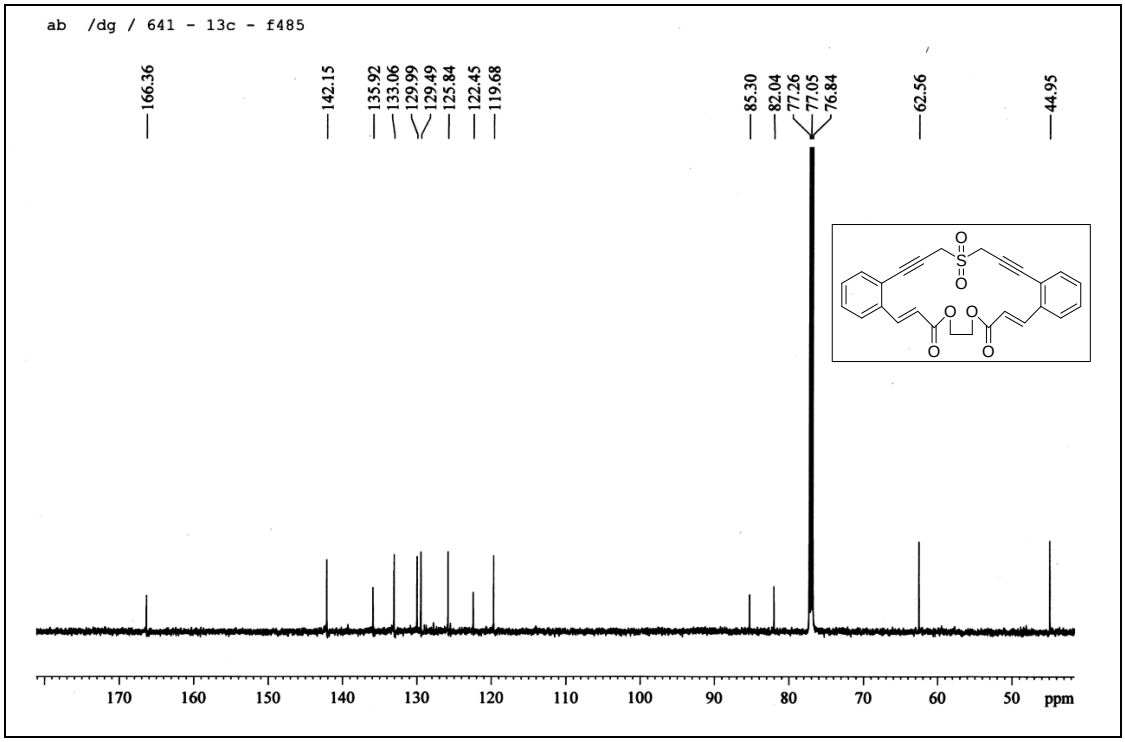


Figure 2.36: ^{13}C NMR spectrum of compound 2.20a

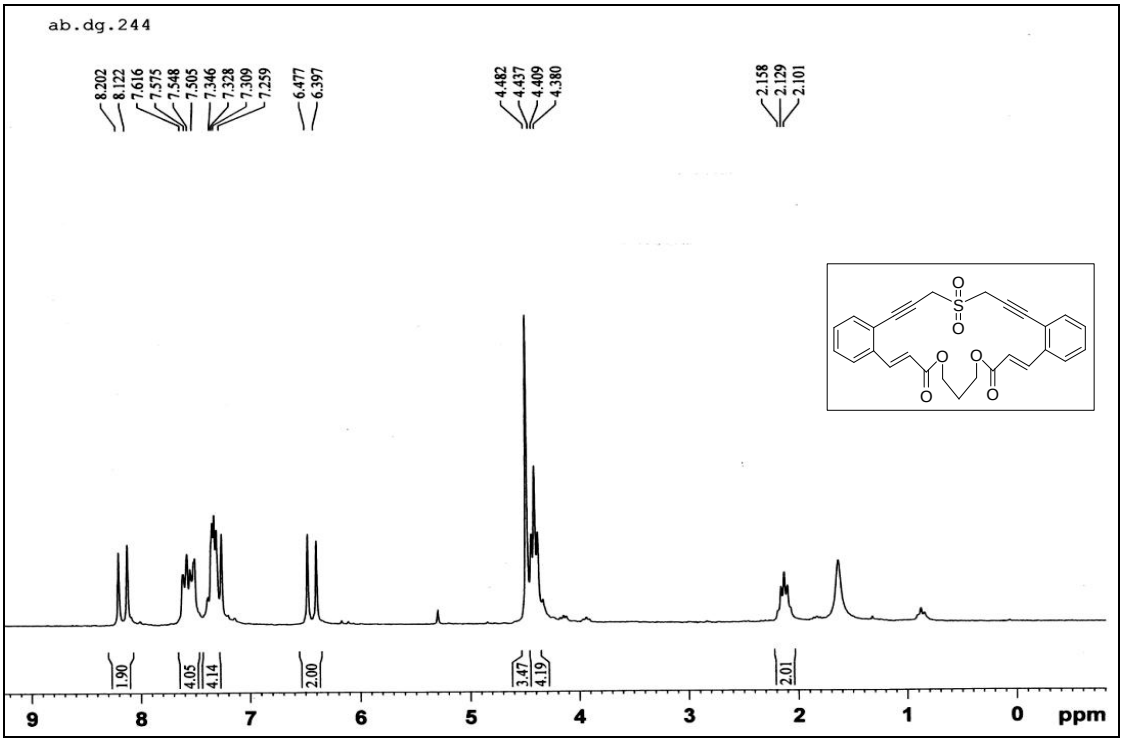


Figure 2.37: ^{1}H NMR of compound 2.20b

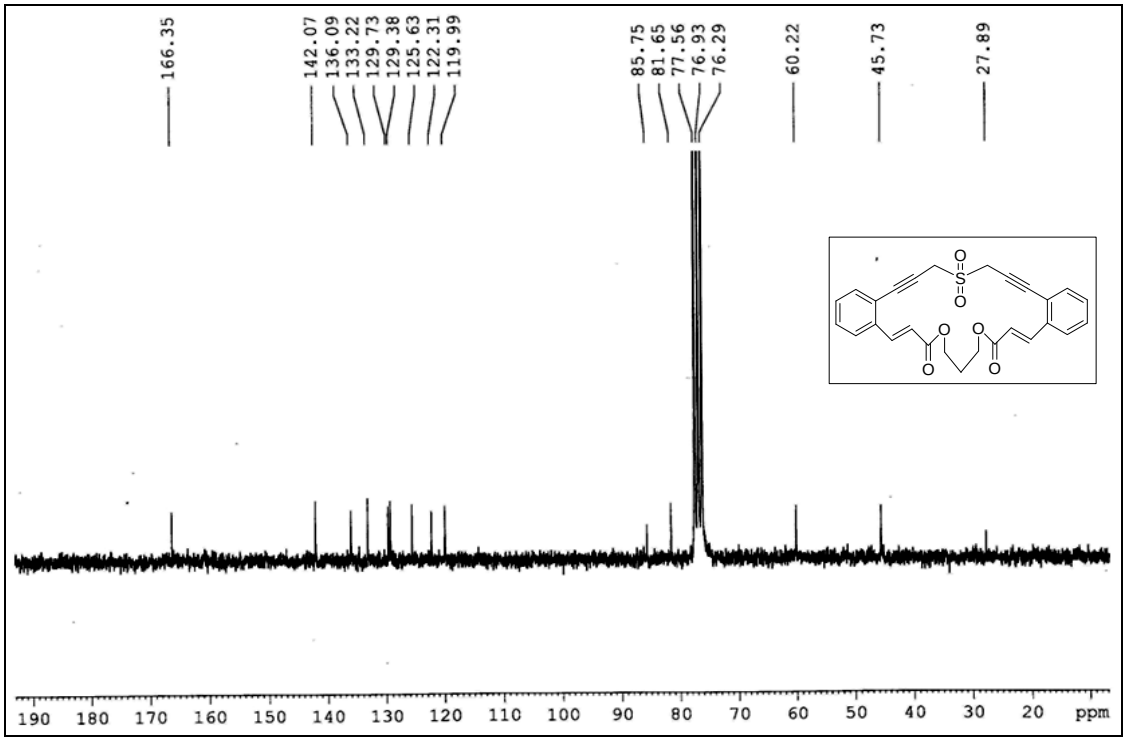


Figure 2.38: ^{13}C NMR spectrum of compound 2.20b

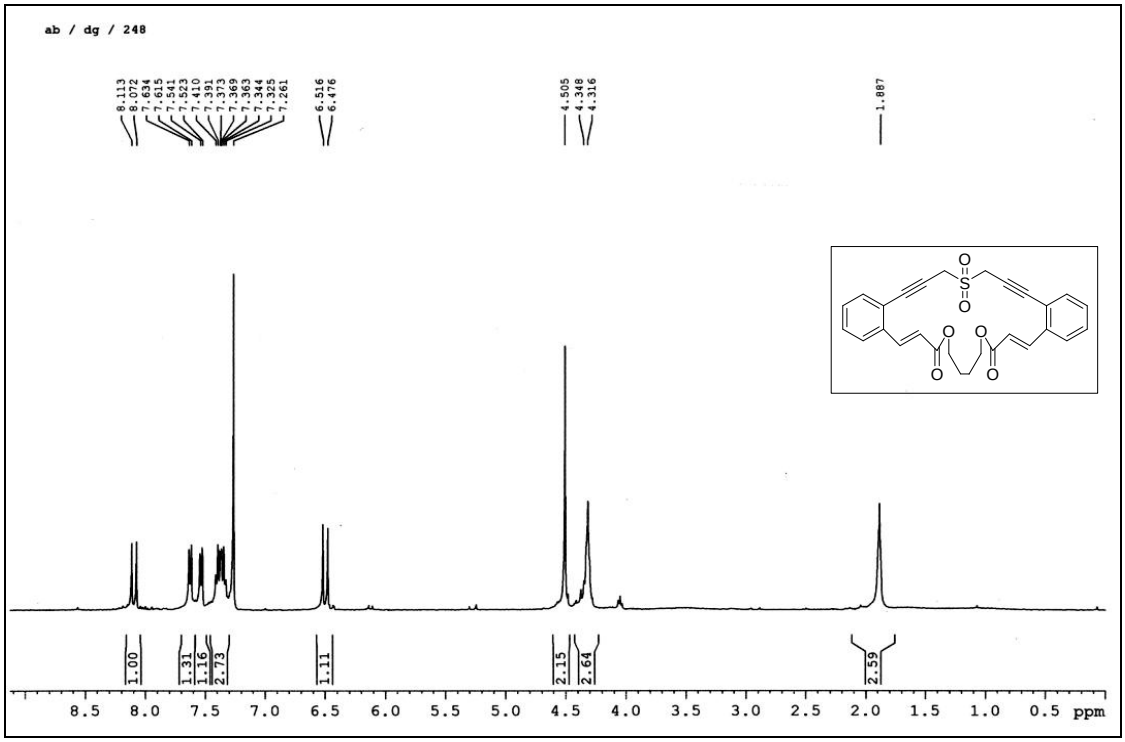


Figure 2.39: ^{1}H NMR of compound 2.20c

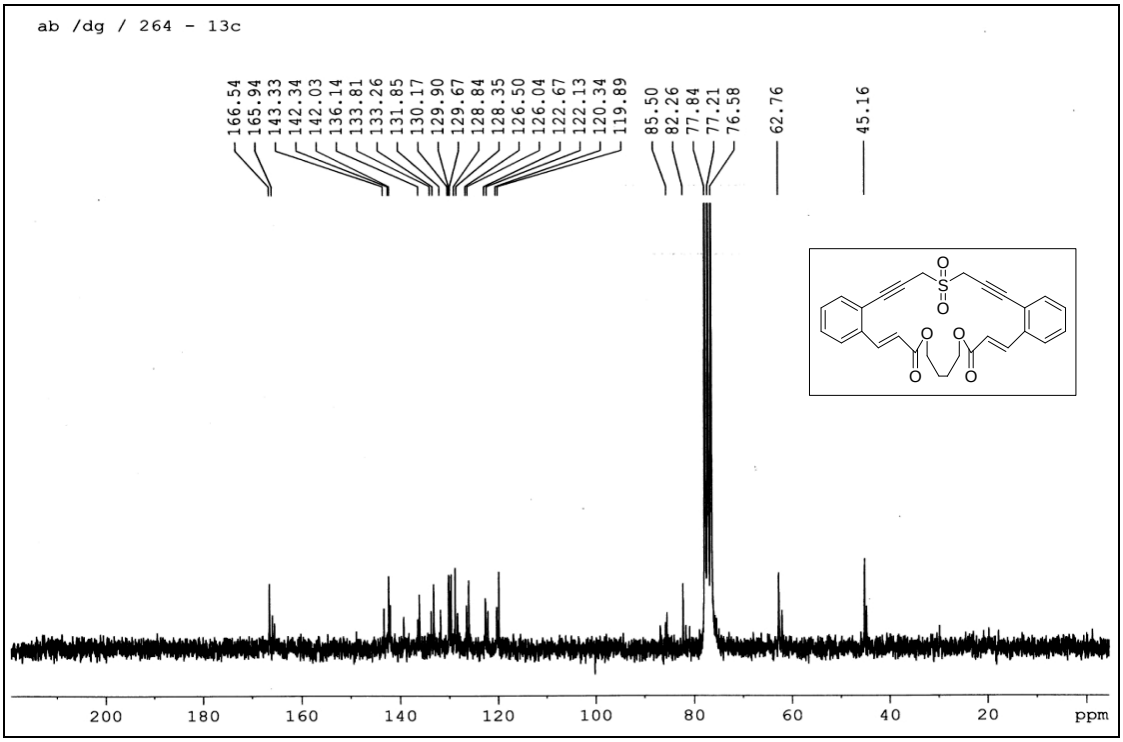


Figure 2.40: ^{13}C NMR spectrum of compound 2.20c

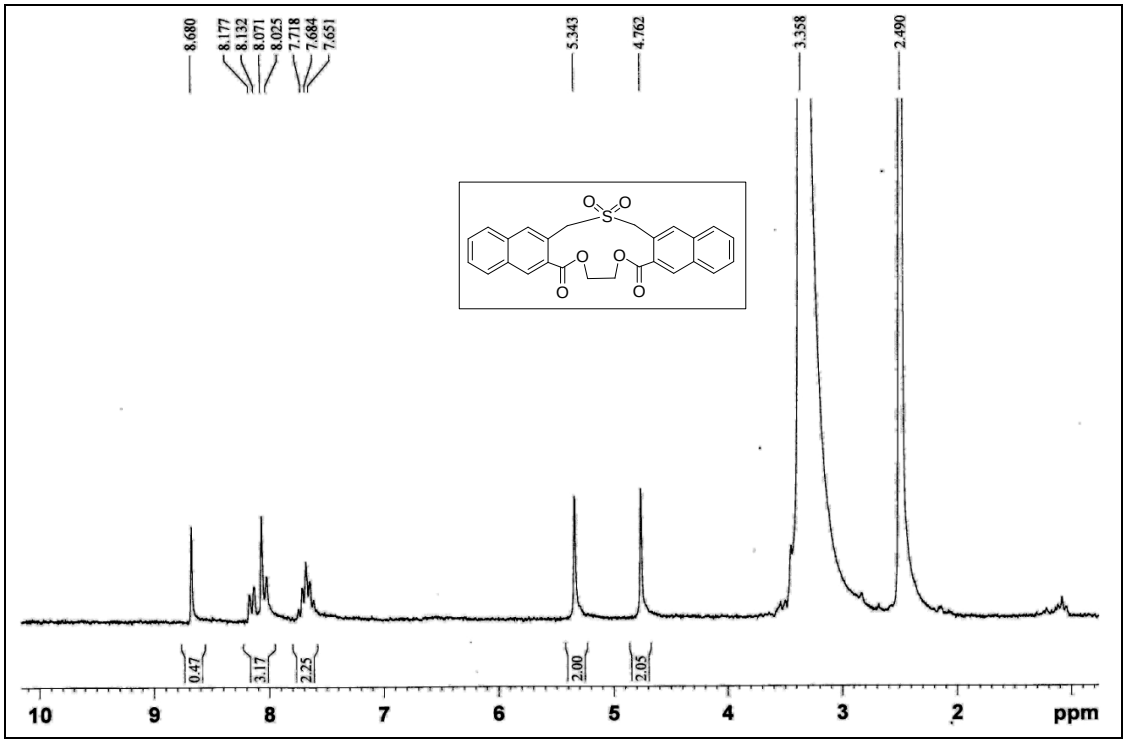


Figure 2.41: ^{1}H NMR of compound 2.24a

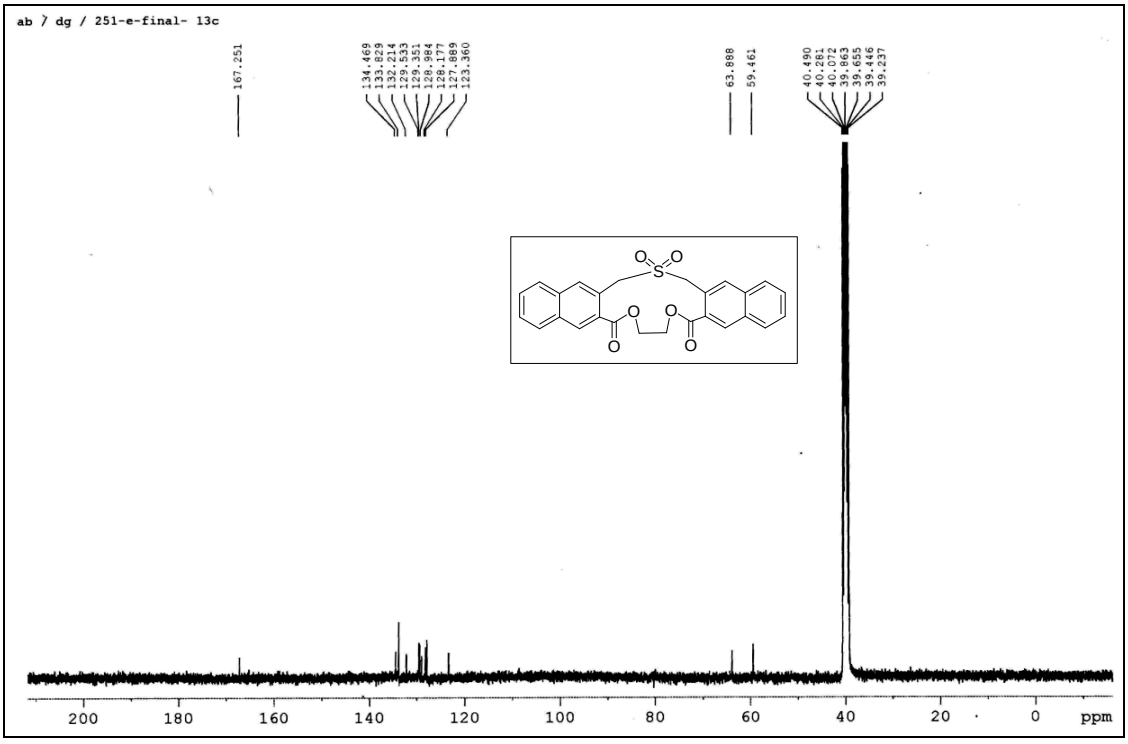


Figure 2.42: ^{13}C NMR spectrum of compound 2.24a

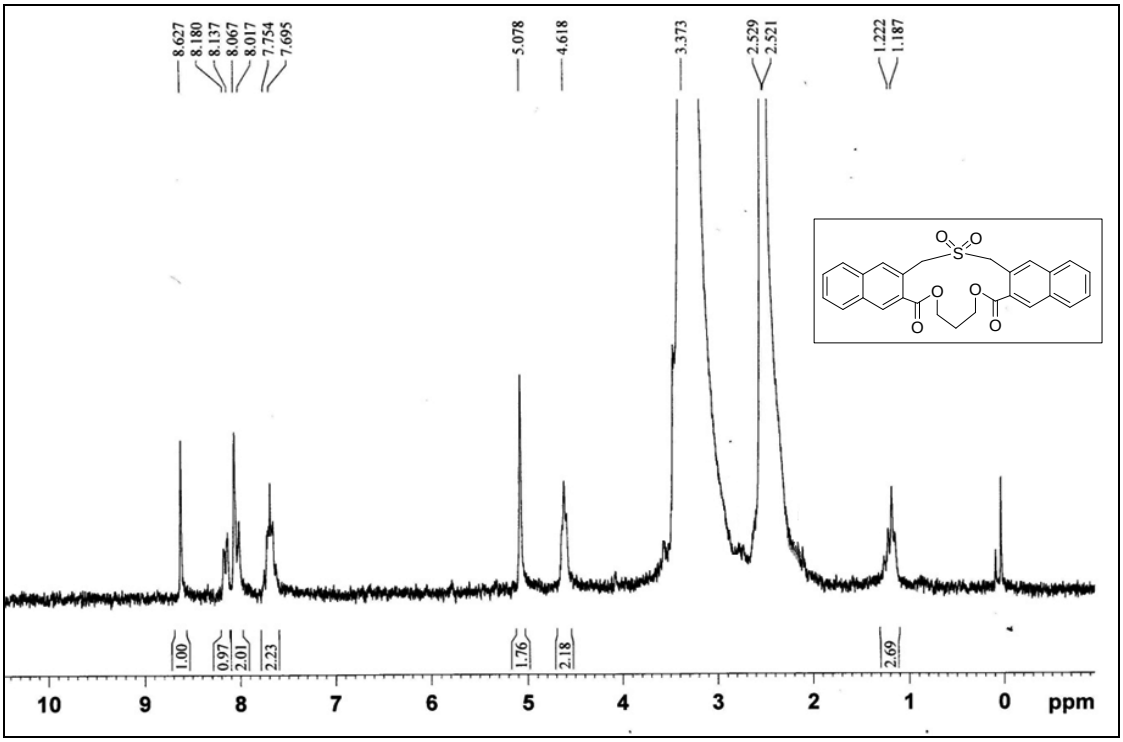


Figure 2.43: ^{1}H NMR of compound 2.24b

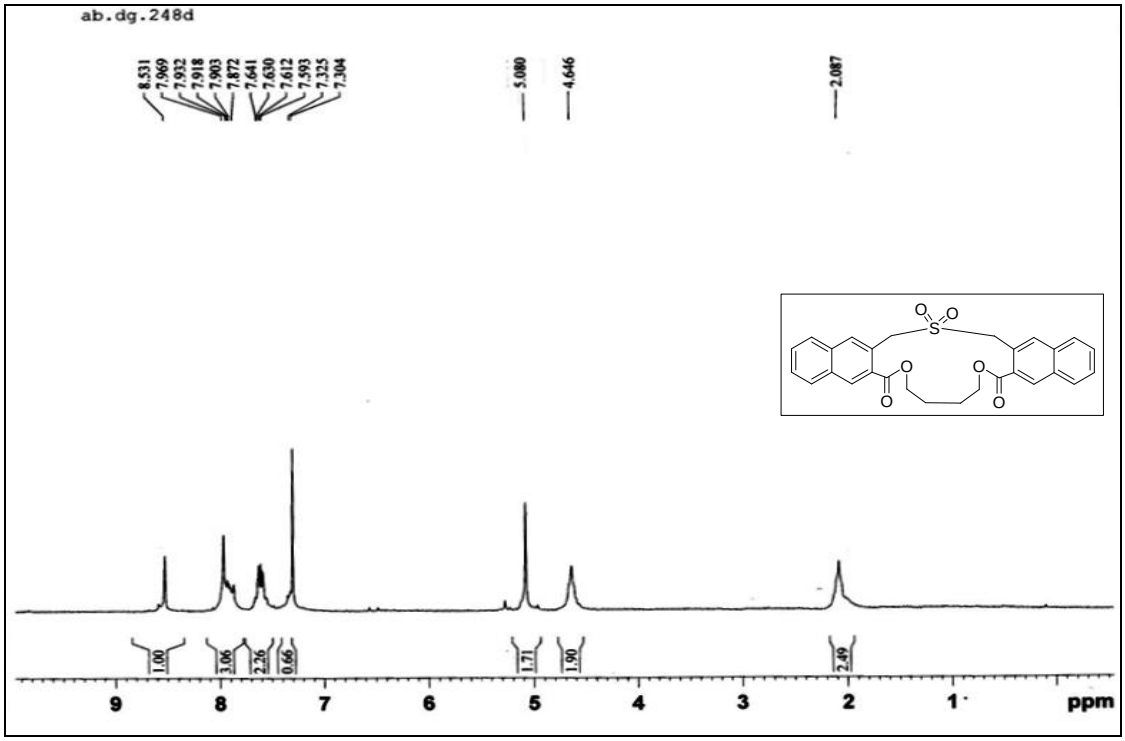


Figure 2.44: ^{1}H NMR of compound 2.24c

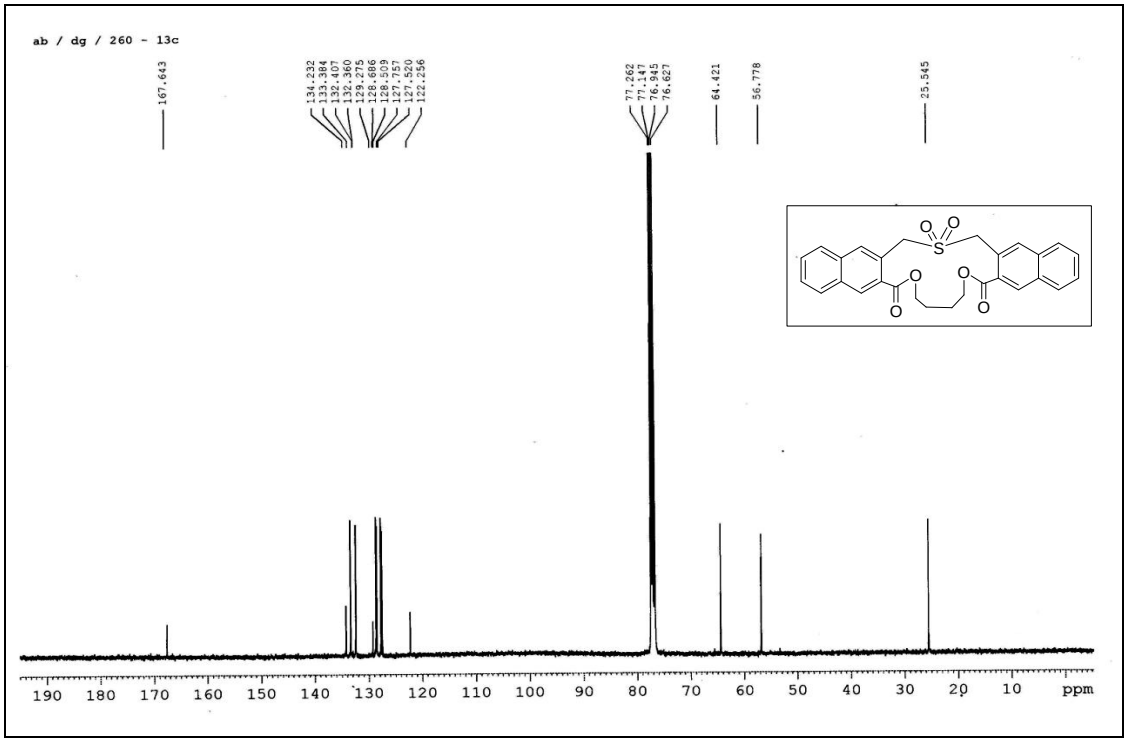


Figure 2.45: ^{13}C NMR spectrum of compound 2.24c

2.10 References

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Chapter 3

A Green Approach Towards Garratt-Braverman Cyclization Using Basic Alumina

3.1 Introduction

In recent years, organic chemists have given much attention towards developing methodologies with inexpensive, eco-friendly, recyclable support mainly due to the growing environmental concerns. Use of solid support under solvent free condition provides many advantages over the conventional solution phase synthesis[1] in terms of product yield, reaction time, benign condition, ease of purification, recyclability of the support[2] and disposal of the solvent.

Organic reactions, carried out on solid surfaces like zeolites[3], clays[4], silica gel,[5,6] alumina,[5,7] and polymers[5a,8] are used classically and all of these posses 'stand-out' surface characteristics. Both naturally occurring and synthetic zeolites are alumino-silicates are three-dimensional structures with interconnecting channels and cavities. If the substrate is small, the reactions take place in the channels or cavities or on the exterior of the surface. Silica gel and alumina do not contain accessible channels or cavities. Instead, these materials have large surface areas and highly porous exteriors which are available to substrates.

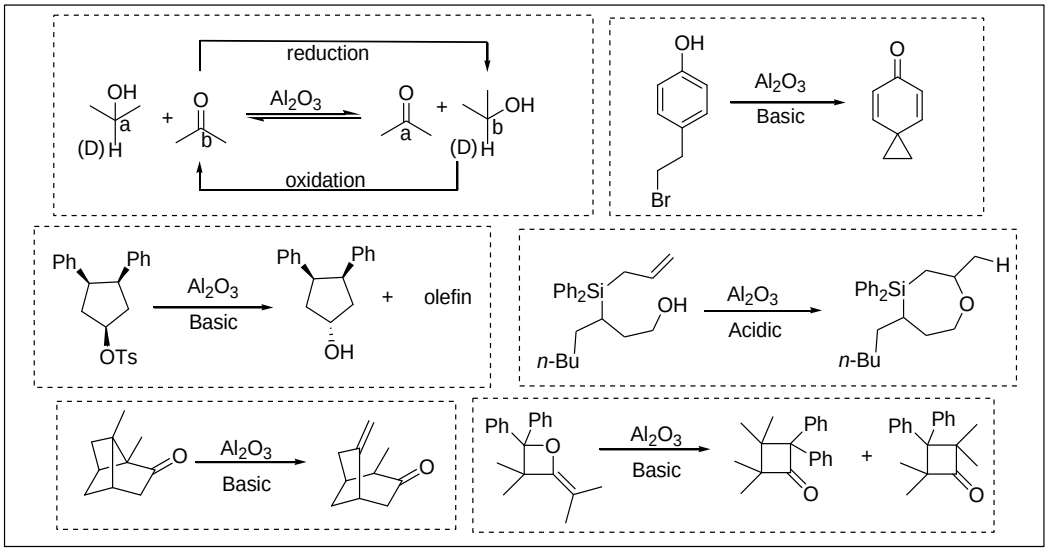
Among all the metal oxides mentioned above, alumina is most useful and interesting. It has a general formula of $Al_2O_3 \cdot (H_2O)_n$ where n can vary from 0 to 3, although they do not contain molecular water.[9] Alumina has been used extensively as adsorbent, filler, catalyst and catalytic support.[9] It has drawn the attention of organic chemists because of its ability to act as catalyst, support and reagent.

Recently we were looking for a suitable alternative protocol for Garratt-Braverman (GB) cyclization,[10] a reaction of importance as it involves the formation of two C–C bonds starting from the susbstrates like *bis*-propargyl sulfones, ethers, and sulfonamides. Triethylamine is basic enough to bring about the rearrangement of the sulfones. For ethers and sulfonamides stronger bases like $KOBu^t$, NaH, DBU or DBN[11] are required. The mechanism of the rearrangement is well established; it proceeds *via* the formation of a *bis*-allene, for which a base is required. Literature survey revealed that, thermolysis of boehmite AlO(OH)(orthorhombic) between 400 ^oC-500 ^oC yields the γ-series of aluminas whose formula is $Al_2O_3 \cdot (H_2O)_n$ where $n<0.6$. Unactivated γ-alumina

is basic having a pH of 9-10 which should be capable of causing the isomerization of propargyl to allene followed by GB reaction. Alumina's ability to carry out other transformations like oxidation, alkylation, heterocycle synthesis and addition reaction[12] under mild conditions is already reported. These properties prompted us to apply basic alumina as a solid support as well as a base for GB reaction under solvent free reaction conditions.

3.2 Organic Reactions on Alumina Surfaces

Alumina has also been found to cause different and sometimes unexpected reaction (**Scheme 3.01**). Carbonyl reduction involving hydride transfer using neutral alumina as support is established by deuterium labeling.[13] Basic alumina promoted intramolecular substitution and sulfonate ester hydrolysis has been carried out successfully.[14,15]Acidic alumina catalyzed intramolecular addition has also been observed.[16]



Scheme 3.01: Applications of alumina in organic synthesis

Alumina can also act as a polar medium to cause molecular rearrangement in organic compounds. Thus alumina has shown its remarkable ability in various roles in heterogeneous reactions.[17,18]

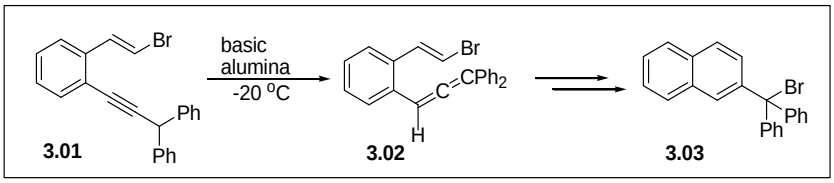
3.3 Objective

Prior to the present work, it has been shown in work from our laboratory that unsymmetrical *bis*-propargyl ethers and sulfonamides with different aryl or heteroaryl substituent at the acetylene termini, upon base treatment undergo GB cyclization with moderate chemoselectivity.[19] It would be better if it is possible to increase the selectivity in favor of a particular product. With these targets in mind, we set our objective as follows:

1. To check whether GB cyclizations of *bis*-propargyl sulfone as well as *bis*-propargyl ether and sulfonamide are feasible on basic alumina support
2. To arrive at a mechanistic model if the reaction occurs on alumina surface
3. To study the selectivity pattern for GB cyclization (if successful)

3.4 Previous Work

Porter and co-workers, in 1990 provided key mechanistic insight into the allene isomerization induced cycloaromatization[20] and provided the evidence for allene generation from propargyl system on alumina surface. The reactive allene was prepared at low temperature by treatment of aryl enyne with activated basic alumina (**Scheme 3.02**).



Scheme 3.02: Allene isomerization in presence of basic alumina

Until the present work our effort on GB cyclization including kinetic, asymmetry induced selectivity and mechanistic studies have been done in solution. The present report is the first one on solid support.

3.5 Present Work

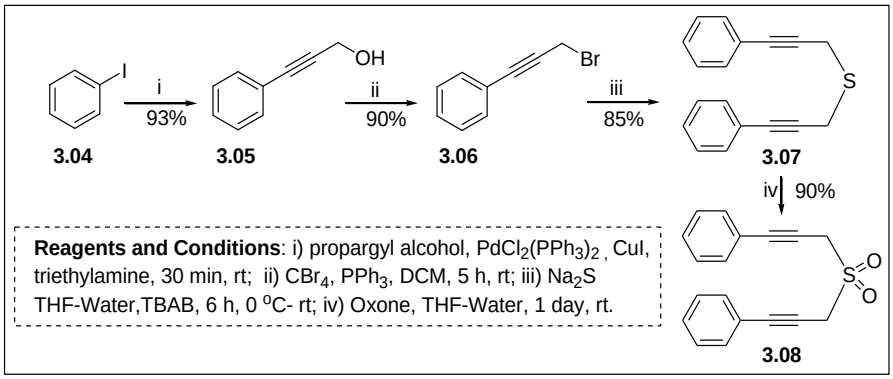
To check the feasibility of our objective, we needed a system equipped with *bis*-propargylic group. For this purpose we designed *bis*-propargyl sulfone, ether and

sulfonamide as allenes can easily be generated from these moieties either at room temperature or at elevated temperature. Thus the compounds were synthesized and characterized and their reactivity is described on solid alumina support in this chapter.

3.6 Results and Discussion

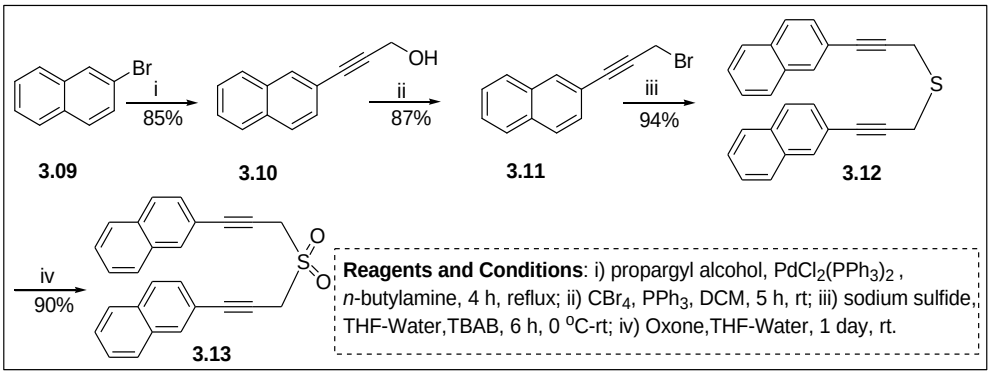
3.6.1 Synthesis of the Sulfones

For our study, we first synthesized *bis*-propargyl sulfones. The synthesis of *bis*-propargyl sulfones started with the Sonogashira coupling of respective iodo or bromoaryl system with propargyl alcohol.



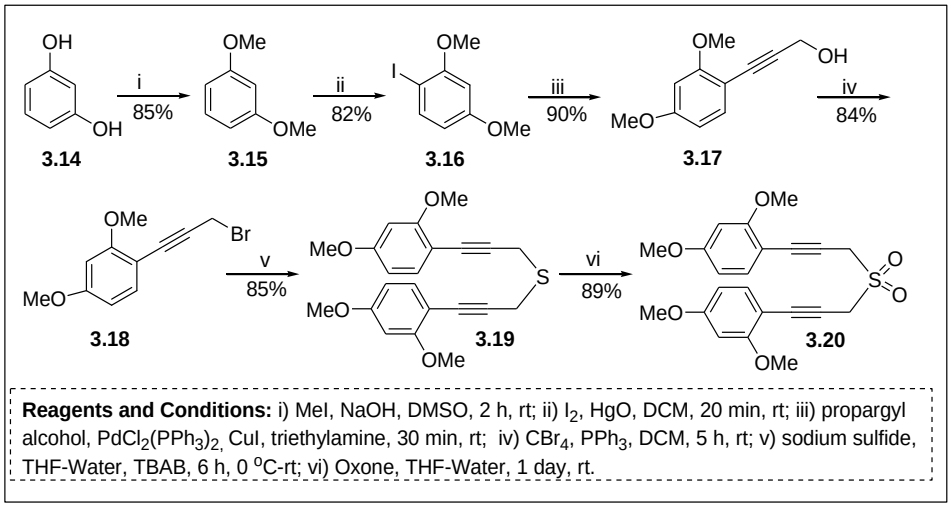
Scheme 3.03: Synthesis of sulfone 3.08

The coupling of iodoaryl systems were carried out at room temperature using triethylamine as base as well as solvent whereas that of bromoaryl compounds were done under refluxing condition using *n*-butylamine. Bromination *via* Appel's method using CBr_4 and PPh_3 produced the corresponding bromo derivatives. The bromides were then allowed to react with Na_2S in a mixture of THF-H_2O medium to give the sulfide. Finally



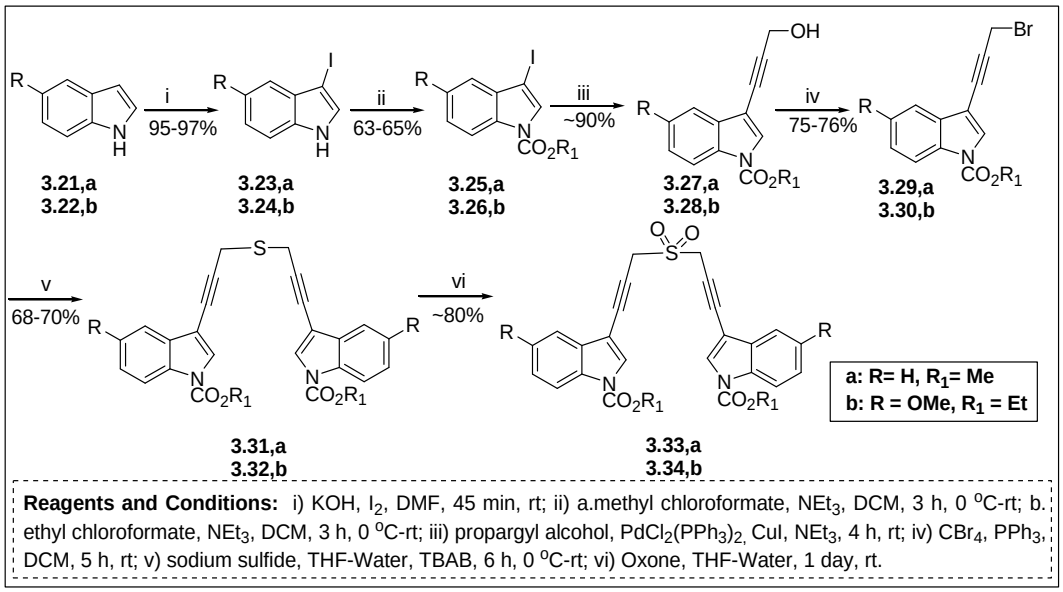
Scheme 3.04: Synthesis of sulfone 3.13

the oxone mediated oxidation of sulfide compounds in THF-H_2O afforded *bis*-propargyl sulfone systems in 90% yiel. The synthesis of the targeted sulfones has been shown in the schemes (**Scheme 3.03** and **Scheme 3.04**).



Scheme 3.05: Synthesis of sulfone 3.20

For the synthesis of sulfone **3.20**, free phenolic –OH groups of resorcinol were protected with methyl iodide in DMSO using NaOH as a base. Compound **3.15** being treated with iodine in presence of red HgO, produced compound **3.16**, the starting material for Sonogashira coupling. The standard protocol was then followed for the synthesis of desired sulfone in 89% yield (**Scheme 3.05**).

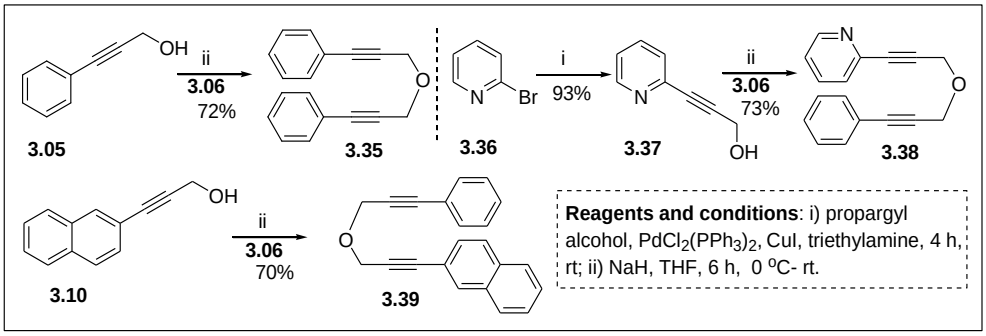


Scheme 3.06: Synthesis of sulfone 3.33 and 3.34

Some heterocyclic sulfones were also synthesized to check whether basic alumina can generate *bis*-allene from those compounds (**Scheme 3.06**). For this purpose we started with simple indole and 5-methoxy indole and iodinated at C3-position followed by the protection of the amine group with methyl or ethyl chloroformate. These iodinated compounds were then subjected to the synthesis of final heterocyclic sulfones in around 80% yield, by a series of reactions like the previous cases.

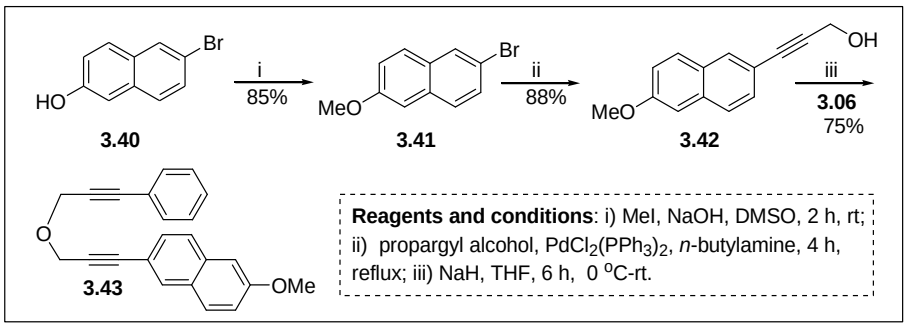
3.6.2 Synthesis of the Ethers

For the synthesis of the targeted *bis*-propargyl ethers, *O*-alkylation was sequentially carried out using common aryl propargyl bromides, **3.06** and **3.11** synthesized earlier from their corresponding alcohol (**Scheme 3.07**).



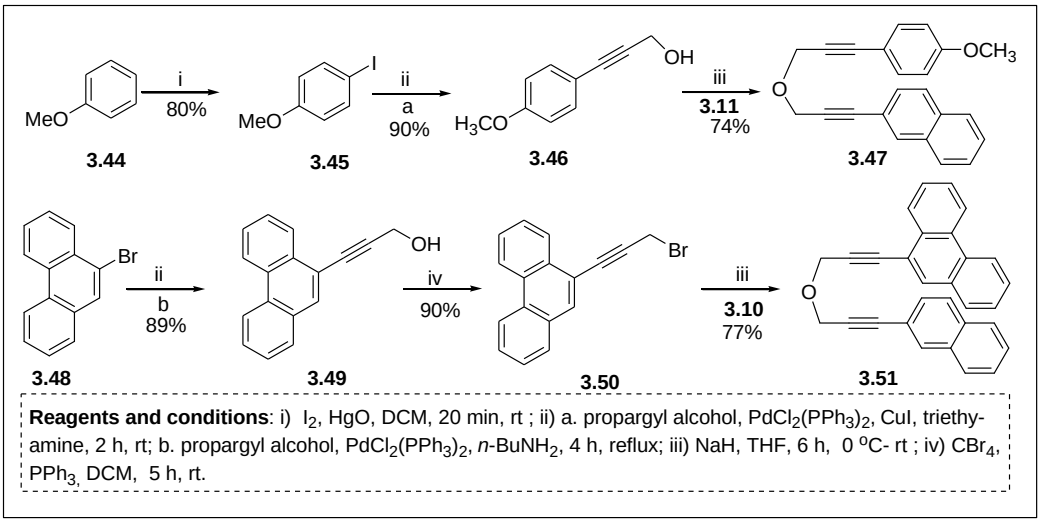
Scheme 3.07: Synthesis of ethers 3.35 and 3.36

For the synthesis of compound **3.43**, we started from 6-hydroxy-2-bromo naphthalene and protected the free phenolic –OH using methyl iodide following standard protocol. Sequential Sonogashira coupling and base mediated *O*-alkylation produced our desired product (**Scheme 3.08**).



Scheme 3.08: Synthesis of ether 3.43

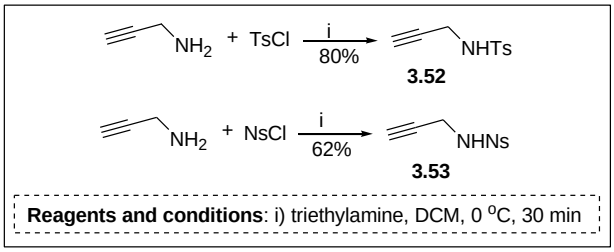
A similar kind of strategy was followed for the synthesis of other ethers **3.47** and **3.51** (**Scheme 3.09**).



Scheme 3.09: Synthesis of ether 3.47 and 3.51

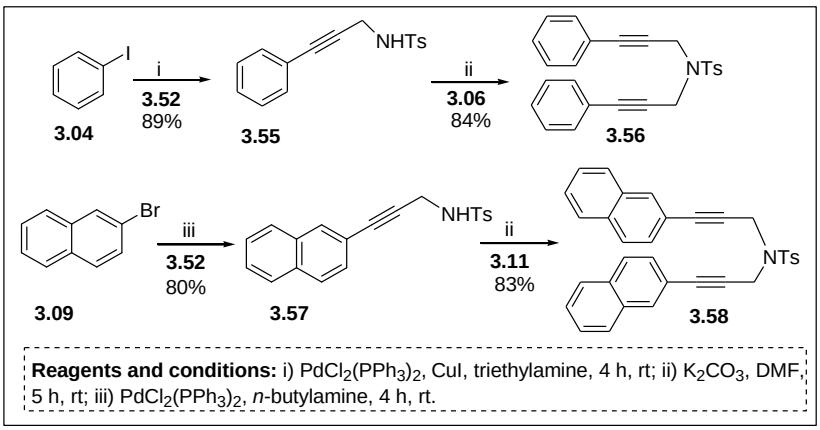
3.6.3 Synthesis of the Sulfonamides

After successfully synthesizing the sulfone and ether derivatives, we then moved to synthesize the sulfonamide derivatives. Similar methodology was followed for the synthesis of sulfonamide compounds. For the ease of our synthesis, we synthesized some common intermediates **3.52** and **3.53** from propargyl amine (**Scheme 3.10**).



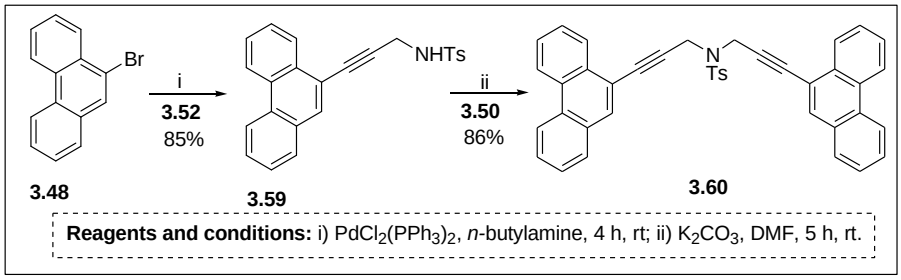
Scheme 3.10: Synthesis of the intermediates

For the synthesis of symmetrical sulfonamides, first **3.52** was reacted with corresponding aryl halide under Sonogashira reaction condition followed by a K_2CO_3 mediated N-alkylation with similar kind of aryl propargyl bromide derivative (**Scheme 3.11**).



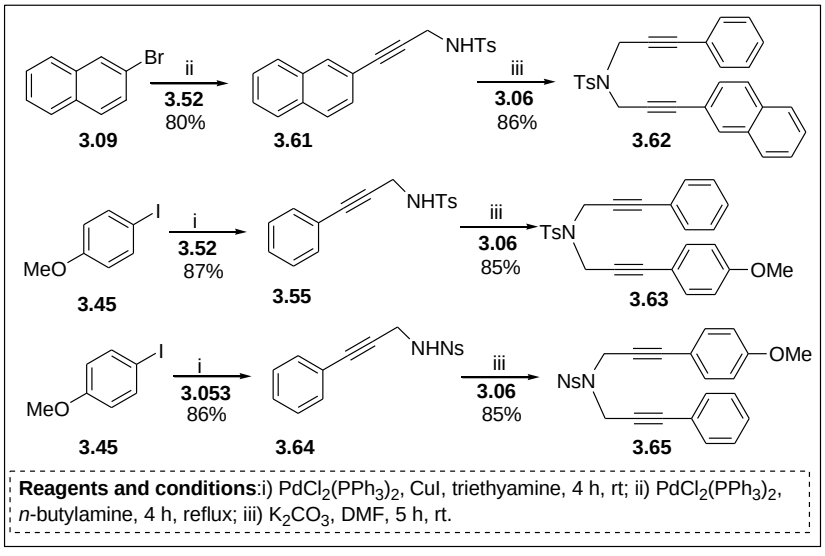
Scheme 3.11: Synthesis of the symmetrical sulfonamides

For our purpose we synthesized three symmetrical sulfonamide systems, shown in **Scheme 3.11** and **Scheme 3.12**.



Scheme 3.12: Synthesis of the symmetrical sulfonamide

We also prepared some unsymmetrical sulfonamides to check selectivity. Using

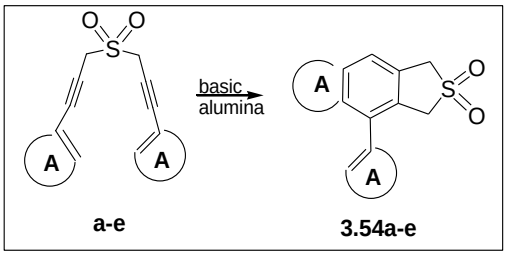


Scheme 3.13: Synthesis of the unsymmetrical sulfonamides

intermediate **3.52** and **3.53** and following similar kind of methodology adapted for the synthesis of symmetrical sulfonamides, we synthesized our desired products (**Scheme 3.13**). After successfully synthesizing our targeted compounds, we checked their reactivity on basic alumina surface

3.6.4 Reactivity of *Bis*-propargyl Systems on Basic Alumina Surface

The basic alumina was first kept at 100 ^{o}C for an hour to remove the physically absorbed water and then cooled down to room temperature under nitrogen atmosphere. The synthesized sulfones were pre absorbed on basic alumina (0.5 mmol substrate; 500 mg basic alumina) and then stirred for 10-15 minutes at room temperature. We monitored the reaction *via* TLC. After the complete consumption of the starting material for every sulfone, the product was isolated simply by extraction with DCM, filtration through celite followed by evaporation. The NMR and mass spectral analysis confirmed our synthesized final product as GB cyclization product. Most importantly, the cyclized products were isolated in high yield and there was no need for column chromatography for purification. The results for the sulfones have been listed below (**Table 3.1**).

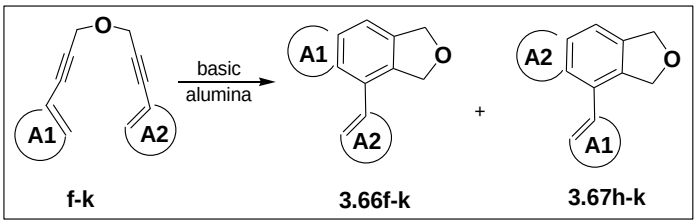


SM	A	Product	% yield
a = 3.08	Phenyl	**3.54a**	95
b = 3.13	2-naphthyl	**3.54b**	93
c = 3.20	2,4-dimethoxyphenyl	**3.54c**	95
d = 3.33	5-methoxy-N-ethoxycarbonyl-3-indolyl	**3.54d**	90
e = 3.34	N-methoxycarbonyl-3-indolyl	**3.54e**	90

Table 3.1: Results of GB reaction of *bis*-propargyl sulfones over basic alumina

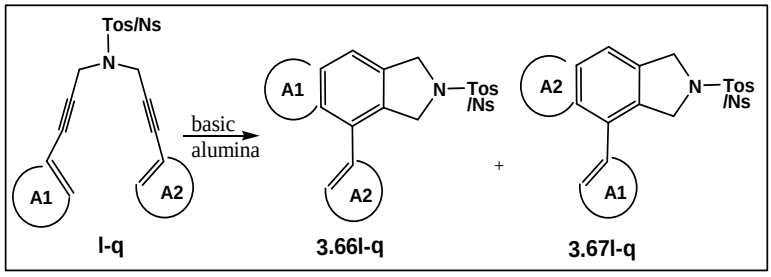
Encouraged by our success with sulfones, we then focused our attention to apply this protocol for propargyl ethers and propargyl sulfonamides to make the

methodology more general. Propargylic hydrogen of ether or sulfonamide has lower acidity compared to that in sulfone systems. As a result to generate the allene in the later cases, it may be necessary to increase the temperature and we found that our hypothesis was right. When the ether and the sulfonamide were pre-absorbed on the surface of the basic alumina and stirred at room temperature for up to 2 days we did not get any new product; only the starting material was recovered. However, when the compounds were absorbed on basic alumina surface and were stirred at 100-130 ^{o}C(depending on the substrate) for ~ 6-8 h, high yields of the dihydro isobenzofuran /dihydro isoindole derivatives were obtained. The results have been summarized in **Table 3.2** and **Table 3.3**. The products were isolated following the same procedure as adapted for the sulfones.



SM	A1	A2	Product	Yield (%)
f = 3.35	phenyl	phenyl	**3.66f**	80
g = 3.38	phenyl	2-pyridyl	**3.67g**	85
h = 3.39	phenyl	2-naphthyl	**3.66h & 3.67h**	88
i = 3.43	phenyl	6-methoxy-2-naphthyl	**3.66i & 3.67i**	85
j = 3.47	4-anisyl	2-naphthyl	**3.66j & 3.67j**	86
k = 3.51	2-naphthyl	9-phenanthryl	**3.66k & 3.67k**	85

Table 3.2: Results of GB reaction of *bis*-propargyl ethers over basic alumina



SM	A1	A2	Product	% yield
l = 3.56 (Tos)	phenyl	phenyl	**3.68l**	87
m = 3.58 (Tos)	2-naphthyl	2-naphthyl	**3.68m**	85
n = 3.60 (Tos)	9-phenanthryl	9-phenanthryl	**3.68n**	89
o = 3.62 (Tos)	phenyl	2-naphthyl	**3.68o & 3.69o**	90
p = 3.63 (Tos)	phenyl	4-anisyl	**3.68p & 3.69p**	85
q = 3.65 (Ns)	Phenyl	4-anisyl	**3.68q & 3.69q**	85

Table 3.3: Results of GB reaction of *bis*-propargyl sulfones over basic alumina

We have mentioned earlier that one of our objectives was to check whether any selectivity for Garratt-Braverman cyclization over basic alumina surface exists or not. Fortunately, our protocol showed an interesting high selectivity in case of unsymmetrical *bis*-propargyl ethers. The selectivity of formation of one product over the other is much higher compared to that obtained during solution phase reaction (**Table 3.4**).

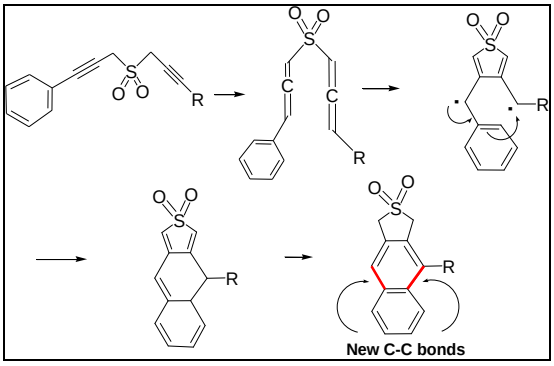
Entry	Substrate	Products	Ratio in the existing protocol under solid phase	Product ratio in solution phase
1	**3.39**	**3.66h & 3.67h**	1:11	1.25:1
2	**3.43**	**3.66i & 3.67i**	1:10	1:1.6
3	**3.47**	**3.66j & 3.67j**	1:11	1:6
4	**3.51**	**3.66k & 3.67k**	1:1.2	1:1.3
5	**3.62**	**3.68o & 3.69o**	1:3	1:1
6	**3.63**	**3.68p & 3.69p**	1:5	3.3:1
7	**3.65**	**3.68q & 3.69q**	1:1.75	4.5:1

Table 3.4: Comparison of selectivity in solid and solution phase

Similar type of selectivity was also observed in case of *bis*-propargyl sulfonamide. Another notable observation for both ether and sulfonamide system was the reversal of selectivity as compared to solvent phase, except for **3.51**, for which the

selectivity remained nearly the same. For sulfonamides **3.63** and **3.65**, reversal of selectivity was observed (**Table 3.4**).

The wide difference in the selectivity suggests that the reaction possibly follows different mechanisms on solid support and in solution. The generally accepted mechanism of GB reaction in solution (**Scheme 3.14**) involves the formation of an intermediate diradical the support for which comes from trapping with $^3O_2$ (Chapter 1). Until now nothing is known about the mechanism when the reaction is carried out on solid phase.



Scheme 3.14: Accepted mechanism for GB cyclization

To explain the probable mechanism of GB reaction on solid phase, it is necessary to know about the structural detail and nature of basic alumina.

3.6.5 Probable Reason Behind the Selectivity

The term alumina refers to a series of ionic solids which have the formula $A1_2O_3 \cdot (H_2O)_n$, where n = 0 to 3, although none of them actually contains H_2O. During the course of thermolysis, hydroxyl groups combine to generate H_2O which is driven from the solids. γ-Alumina, typically formed by heating boehmite between 400 ^oC and 500 ^oC, have the formula $Al_2O_3 \cdot (H_2O)_n$ with n<0.6. The surface of hydrated γ-alumina, as proposed by Peri,[21] is terminated by hydroxyl groups, each of which is directly above an aluminium ion in the next layer of the crystallite (**Figure 3.1**). Water may also be hydrogen bonded to the surface hydroxyl groups. When the solid is heated, physically absorbed H_2O is lost initially and then adjacent hydroxyl groups react with one another by proton transfer to generate oxide ion and water. As a result, we get partially exposed

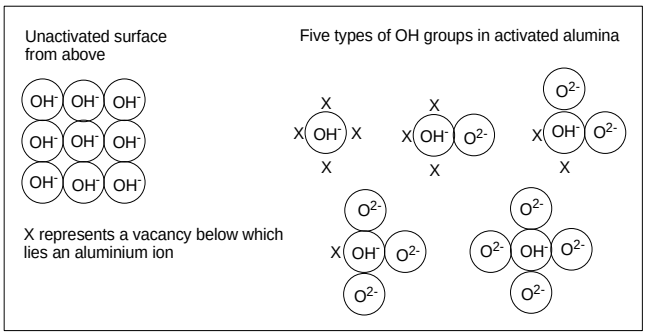


Figure 3.1: Surface of γ-alumina

aluminium cations, which may function as Lewis acid and hydroxyl groups of varying Brønsted activity. Thus γ-alumina has both acidic and basic sites on the surface. It is clear

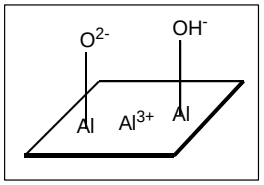
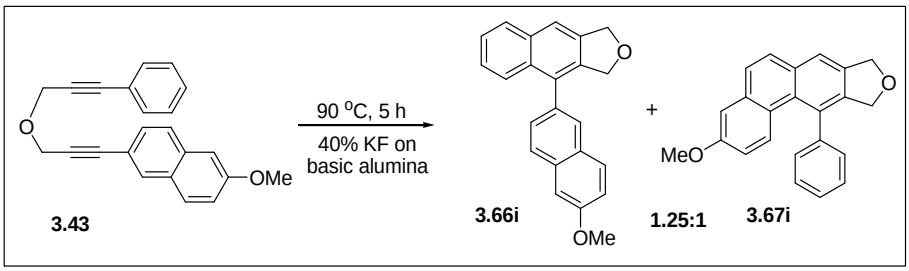


Figure 3.2: Surface of basic alumina

that the surface of alumina provides a polar environment, favorable to many ionic and heterolytic reactions (**Figure 3.2**). Organic substrates have a variety of mechanisms by which they can interact with the surface including hydrogen bond formation and acid-base reactions. In some chemistry, these differences in surface characteristics do have an impact. The surface can play a role in many organic reactions and substrates may interact with the surface anisotropically, not possible in most solutions. The simultaneous effect of these properties gives alumina its mildness and results in unusual selectivity of many organic reactions on alumina surface. Simply we can represent the surface of alumina as shown in **Figure 3.2**.

One point that goes against the present protocol is regarding the high temperature used to carry out the GBC of *bis*-propargyl ether and sulfonamide. This prompted us to think for an alternative route to lower the cyclization temperature. In literature we found that a mixture of 40% KF in basic alumina is a good alternative for basic alumina. Thus we carried out the GB reaction of **3.43** on KF-alumina surface. Expectedly, the use of KF-alumina instead of only alumina successfully reduced the reaction temperature and

time but the result was similar to that obtained in solution phase; thus lowering the enhanced selectivity (**Scheme 3.15**).



Scheme 3.15: GBC on KF-basic alumina surface

Although the exact reason for this lowering of selectivity is not known and needs deeper investigation, it seems that the presence of polar environment on the surface plays a key role here. For example, in the presence of KF, there is a loss of polar environment on the aluminium surface. As a result the solid support gives similar result as that of solution phase (**Figure 3.3** and **Figure 3.4**).

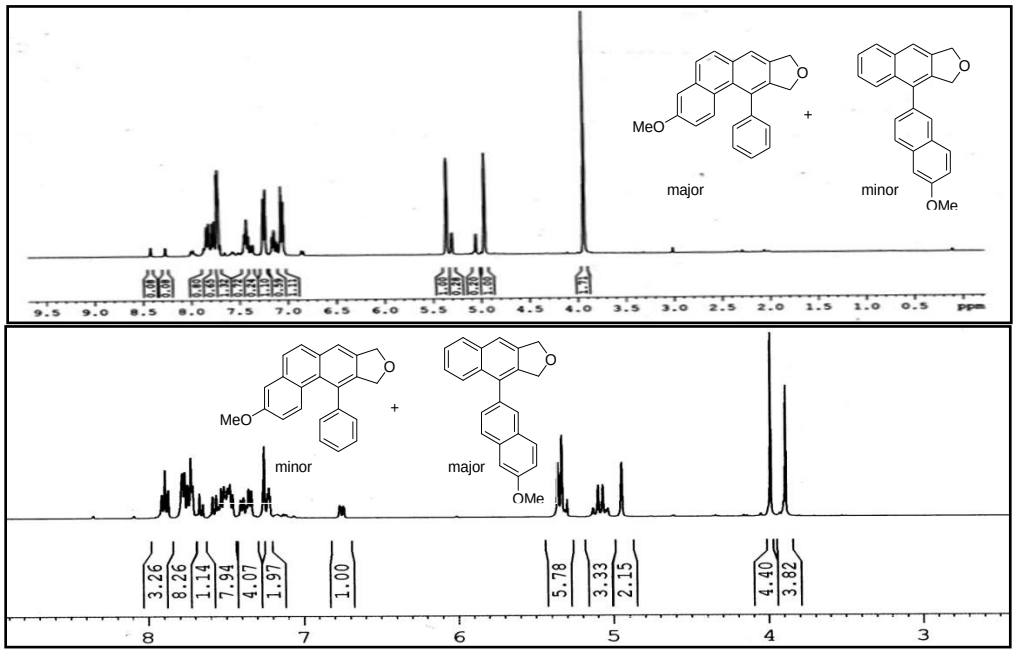


Figure 3.3: ^{1}H NMR of GBC product of 3.43 in basic alumina and KF-basic alumina

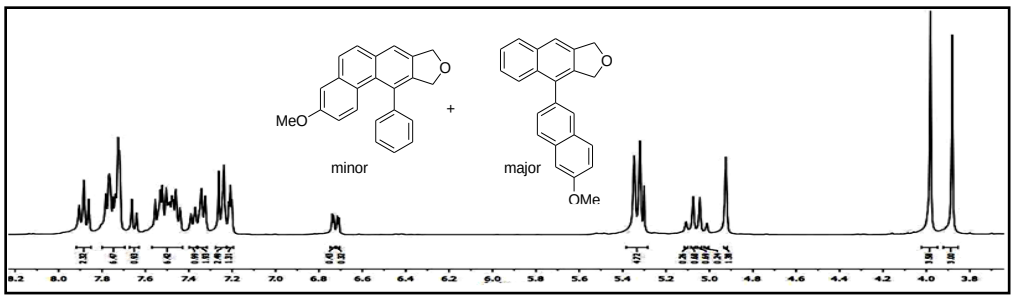
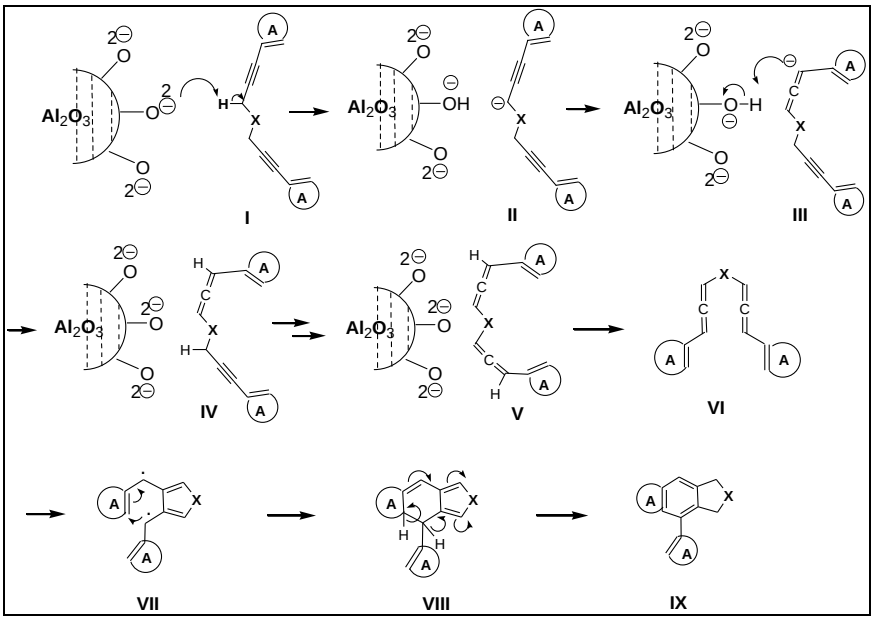


Figure 3.4: ^{1}H NMR of GBC product of 3.43 in solution

Remarkable ability of basic alumina can be ascribed to the presence of Al-O^{-} groups on the alumina surface that acts as a base to assist the isomerization of propargyl to allene system. Possibly, once the *bis*-allene is formed, it undergoes spontaneous cyclization *via* the diradical or any other reactive intermediate to lead to the products. The basic centers also play an important role in facilitating the H^{+} shifts required in order to gain the aromaticity back (**Scheme 3.15**). The solid support after the use for GB cyclization of sulfone was washed with methanol and dried. This recovered basic alumina support was further used and it was used five times without significant loss of activity. However, in case of ether or sulfonamide, the recovered alumina could not be reused because of prolonged heating at high temperature.



Scheme 3.15: Proposed mechanism for alumina mediated GB cyclization

3.7 Conclusion

In conclusion we can say that, we have developed a green and high yielding method for carrying out the GB reaction of various *bis*-propargyl sulfones, ethers and sulfonamides using basic alumina support. Unsymmetrical ethers have shown quite high selectivity. Selectivity in case of sulfonamide is also noticeable. In future, our target is to bring down the temperature required for GB cyclization in case of ether and sulfonamide, to make the process energy efficient. We also want to investigate whether any modification of basic alumina support can lead to complete preference for a particular isomer in case of unsymmetrical systems.

3.8 Experimental

3.8.1 General Experimental

General experimental procedures are same as described in chapter 2.

General Procedure for Iodination of Indole

Indole (1 g, 8.5 mmol) was dissolved in 15 mL rack DMF and KOH (1.2 g, 21.3 mmol) was added to that, followed by addition of 1 eq of iodine (2.2 g, 8.5 mmol) in 10 mL DMF *via* a dropping funnel and stirred for around 45 minutes. The reaction was completed when the violet color solution become colorless. Then the reaction mixture was partitioned between ethyl acetate (30 mL) and water. The organic layer was separated and evaporated over sodium sulfate. The solid residue was directly used for next reaction.

General Procedure for Carbamate Protection

3-iodoindole (2.08 g, 8.5 mmol) was dissolved in 10 mL DCM and cooled to 0 °C. Triethylamine (3.6 mL, 26 mmol) followed by methyl chloroformate (1.3 mL, 1.2 eq) was added drop wise *via* a syringe to that solution. The mixture was stirred until starting material was fully consumed as shown in TLC. DCM was then evaporated in rotor and the crude mass was subjected to silica gel column chromatography (PE:EA = 20:1) to obtain the product in 98% yield. The structure of the product was confirmed by

comparison of its ^{1}H NMR data to that of literature report.[19] Similar method was followed for 5-methoxy indole derivative.

General Procedure for the Sonogashira Coupling

Iodoaryl compound (0.359 g, 1.25 mmol), 3 mol% $Pd(PPh_3)_2Cl_2$ (0.026 g), 20 mol% CuI (0.05 g) and propargyl alcohol (0.07 mL, 1.2 eq) were added in succession to 20 mL of degassed Et_3N and left at room temperature. After the completion of the reaction, the reaction mixture was then poured into ethyl acetate and the organic layer was washed with saturated NH_4Cl solution (20 mL x 3) and brine (15 mL), dried over anhydrous sodium sulfate. Evaporation in vacuum gave oily residue from which the product was isolated by column chromatography (Silica-gel, petroleum ether-ethyl acetate mixture as eluent).

General Procedure for Bromination

To an ice cold solution of the alcohol (0.1 mmol) in dry DCM (10 mL), 1 eq of each triphenylphosphine and carbontetrabromide was added in one portion and stirred. After completion of the reaction, the reaction mixture was diluted with DCM, washed with water (15 mL x 2). The DCM solution was evaporated under vacuum. The crude bromide was purified by column filtration through a short bed of silica gel with ethyl acetate-pet ether as eluent.

General Procedure for Sulfide Formation

The bromide (0.1 mmol) was taken in methanol (5 mL) and stirred at 0 °C. Sodium sulfide (0.05 mmol) dissolved in minimum volume of water was added to the reaction mixture followed by the addition of catalytic amount of TBAB. The reaction mixture was allowed to stir at room temperature until TLC showed disappearance of the bromide. Methanol was evaporated off. The crude was diluted with ethyl acetate (25 mL) and washed with water (20 mL). The organic layer was evaporated and the crude sulfide was subjected to Silica gel column chromatography for isolation.

General Procedure for Sulfonation

To an ice cold solution of the sulfide (0.1 mmol) in 5 mL THF-H_2O, 5 eq of oxone was added. The reaction mixture was allowed to stir at room temperature. After the completion of the reaction, the reaction was diluted with EtOAc and washed with saturated solution of sodium bicarbonate (25 mL x 3). After washing the organic layer with brine, it was evaporated under vacuum and the crude mass was column filtered to get the pure sulfone using ethyl acetate- petroleum ether mixture as eluent.

General Procedure for the *o*-Propargylation

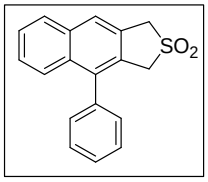
To an ice cold solution of the alcohol 3.035 (1.3 g, 5 mmol) in dry THF, 3 eq of NaH (15 mmol, 60% suspension in mineral oil) was added and mechanically stirred until the evolution of hydrogen ceases. Maintaining the temperature in ice, 1.1 eq of propargyl bromide (5.5 mmol, 80 wt% in toluene) was added drop wise and the reaction mixture was allowed to stir at room temperature for completion. After quenching the reaction by addition of drop wise addition of NH_4Cl, the reaction mixture was partitioned between water (30 mL) and ethyl acetate (40 mL). After usual work up silica gel column chromatography furnished the desired product in good yield.

Procedure for the Preparation of KF/Alumina(40 %)

To a well stirred solution of $KF.2H_2O$ (32g) in water (100 mL), basic alumina was added (30 g, 200-300 mesh). The mixture was stirred for 1 h at 65-75 °C. The water was removed under reduced pressure. The resulting free flowing powder was dried at 120 °C for 4 h and stored under nitrogen atmosphere.

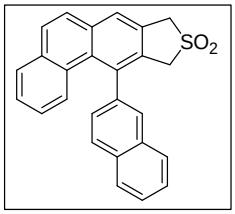
3.8.2 Spectral Data of Some Selected Compounds

4-Phenyl-1,3-dihydro-naphtho[2,3-c]thiophene2,2-dioxide (3.54a)



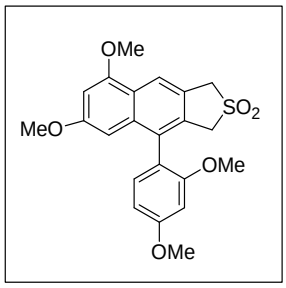
State: brown solid; [m.p = 115 °C]; **Yield**: 95%; δ_H (400 MHz, $CDCl_3$): 7.86 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H), 7.59-7.41 (m, 6H), 7.30-7.26 (m, 2H), 4.57 (s, 2H), 4.23(s, 2H); δ_C (100 MHz, $CDCl_3$): 137.9, 137.5, 133.2, 132.1, 129.5, 128.9, 128.6, 128.3, 128.0, 127.9, 126.9, 126.8, 126.3, 124.9, 57.1, 56.5. HRMS: calculated for $C_{18}H_{15}SO_2$ [MH^+] 295.0787, found 295.0797.

11-Naphthalen-2-yl-8,10-dihydro-9-thia-cyclopenta[*b*]phenanthrene-9,9-dioxide (3.54b)



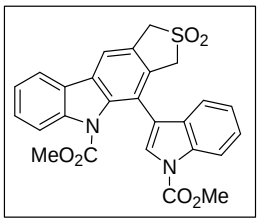
State: brown solid; [m.p = decomposes at 190 °C]; **Yield**: 93%; δ_H (400 MHz, $CDCl_3$): 8.02 (dd, *J* = 16.0 Hz, 8.0 Hz, 2H), 7.89-7.74 (m, 6H), 7.64-7.53 (m, 3H), 7.42-7.36 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.66 (s, 2H), 4.25 (d, *J* = 16.0 Hz, 1H), 4.10 (d, *J* = 16.0 Hz, 1 H); δ_C (100 MHz, $CDCl_3$): 139.7, 139.6, 134.2, 133.9, 133.8, 133.0, 131.2, 131.1, 130.4, 130.2, 129.1, 129.0, 128.9, 128.3, 128.2, 127.8, 127.4, 127.1, 127.0, 126.9, 126.8, 126.7, 126.1, 126.0, 124.6, 124.2, 57.9, 57.8. HRMS: calculated for $C_{26}H_{19}SO_2$ [MH^+] 395.1100, found 395.1110.

4-(2,4-Dimethoxy-phenyl)-6,8-dimethoxy-1,3-dihydro-naphtho[2,3-c]thiophene-2,2-dioxide (3.54c)



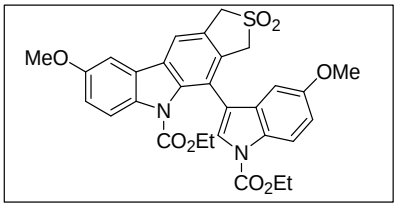
State: viscous liquid; **Yield**: 95%; δ_H (400 MHz, $CDCl_3$): 8.12 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.63-6.61 (m, 2H), 6.54 (s, 1H), 6.51 (s, 1H), 4.58-4.54 (m, 2H), 4.25 (d, *J* = 16.0 Hz, 1H), 4.07 (d , *J* = 16.0 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H); δ_C (100 MHz, $CDCl_3$): 161.4, 158.9, 158.1, 156.7, 134.7, 132.1, 130.6, 125.3, 122.2, 119.1, 118.9, 105.2, 99.3, 98.3, 96.9, 57.8, 56.9, 56.0, 55.8, 55.7, 55.4. HRMS: calculated for $C_{22}H_{23}SO_6$ [MH^+] 415.1210, found 415.1218.

10-(1-Methoxycarbonyl-1H-indol-3-yl)-2,2-dioxo-2,3-dihydro-1H-2λ^6-thia-9-aza-cyclopenta[b]fluorene-9-carboxylic acid methyl ester (3.54d)



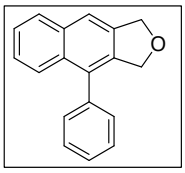
State: brown solid; [m.p > 210 °C]; **Yield**: 90%; δ_H (400 MHz, $CDCl_3$): 8.32 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 5.2 Hz, 2H), 7.59 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.48-7.43 (m, 3H), 7.41-7.31 (m, 1H), 4.62 (s, 2H), 4.44-4.41 (m, 1H), 4.25-4.21 (m, 1H), 4.06 (s, 3H), 2.89(s, 3H); δ_C (100 MHz, $CDCl_3$): 152.0, 140.3, 138.0, 135.6, 131.1, 128.9, 128.6, 128.4, 126.9, 125.9, 124.6, 124.1, 123.9, 122.8, 120.1, 119.9, 119.5, 117.4, 115.9, 115.2, 57.9, 57.6, 54.4, 53.3. HRMS: calculated for $C_{26}H_{21}SN_2O_6$ [MH^+] 489.1115, found 489.1125.

10-(1-Ethoxycarbonyl-5-methoxy-1H-indol-3-yl)-6-methoxy-2,2-dioxo-2,3-dihydro-1H-2λ^6-thia-9-aza-cyclopenta[b]fluorene-9-carboxylic acid ethyl ester (3.54e)



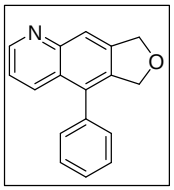
State: brown solid; [m.p > 210 °C]; **Yield**: 90%; **δ_H** (400 MHz, $CDCl_3$): 8.17 (d, *J* = 8.0 Hz, 1H), 8.08-7.95 (m, 2H), 7.60 (s, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.12 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H), 7.03 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H), 6.69 (d, *J* = 1.6 Hz, 1H), 4.65 (s, 2H), 4.62- 4.50 (m, 2H), 4.49 (s, 1H), 4.44 (s, 1H), 3.95 (s, 3H), 3.78-3.66 (m, 4H), 3.39-3.35 (m, 1H), 1.52 (t, *J* = 7.2 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H); **δ_C** (100 MHz, $CDCl_3$): 156.8, 156.7, 151.5, 150.9, 138.2, 134.6, 130.9, 130.0, 129.7, 128.4, 126.7, 125.5, 123.5, 120.1, 119.1, 117.1, 116.6, 116.4, 116.2, 114.7, 103.2, 102.4, 63.8, 63.4, 57.7, 57.6, 56.1, 55.9, 14.6, 13.8. HRMS: calculated for $C_{30}H_{29}SN_2O_8$ [MH^+] 577.1639, found 577.1645.

4-Phenyl-1,3-dihydro-naphtho[2,3-c]furan (3.66f)



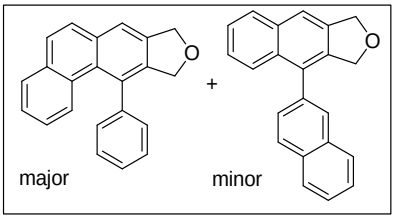
State: viscous liquid; **Yield**: 80%; **δ_H** (400 MHz, $CDCl_3$): 7.88 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 5.2 Hz, 2H), 7.53-7.43 (m, 4H), 7.41-7.36 (m, 3H), 5.29 (s, 2H), 5.04 (s, 2H); **δ_C** (100 MHz, $CDCl_3$): 138.4, 137.9, 137.1, 133.9, 132.8, 132.0, 129.7, 129.6, 129.3, 128.8, 128.3, 127.8, 125.9, 125.8, 119.0, 73.6, 73.1. HRMS: Calculated for $C_{18}H_{15}O$ [MH^+], 247.1117 found 247.1124.

5-Phenyl-6,8-dihydrofuro[3,4-g]quinoline (3.66g)



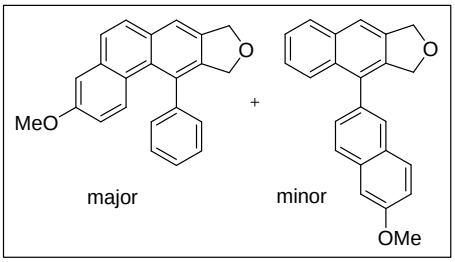
State: brown solid; [m.p = 89 °C]; **Yield**: 85%; **δ_H** (400 MHz, $CDCl_3$): 8.89 (br s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.98(s, 1H), 7.54-7.46 (m, 3H), 7.35-7.26 (m, 3H), 5.33 (s, 2H), 5.05 (s, 2H); **δ_C** (100 MHz, $CDCl_3$): 149.4, 148.1, 141.5, 137.2, 136.6, 134.0, 132.4, 131.4, 129.1, 128.6, 128.0, 127.8, 124.1, 120.5, 119.9, 73.1, 72.4. HRMS: calculated for $C_{17}H_{14}NO$ [MH^+] 248.1070, found 248.1077.

11-Phenyl-8,10-dihydro-9-oxa-cyclopenta[b]phenanthrene (major) , 4-Naphtahalen-2-yl-1,3-dihydro-naptho[2,3-c]furan (minor) (3.66h & 3.67h)



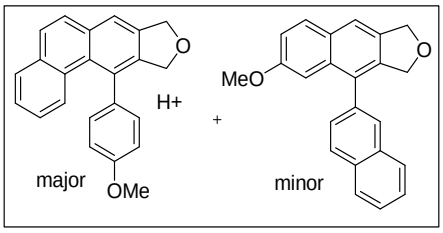
State: yellow solid; **Yield**: 88%; δ_H (400 MHz, $CDCl_3$): 7.99-7.84 (m, 4H, minor), 7.78 (d, *J* = 8.0 Hz , 1H, major), 7.75-7.71 (m, 3H, major), 7.66 (d, *J* = 8.0 Hz, 1H, major), 7.65-7.44 (m, 3H, major and 4H minor), 7.41 (t, *J* = 6.8 Hz, 1H, major), 7.38 (d, *J* = 4.0 Hz, 2H ,major), 7.36-7.31 (m, 4H, minor), 7.10 (t, *J* = 1.6 Hz, 1H, major), 5.32-5.29 (m, 2H, major and 2H, minor), 5.12-5.08 (m, 2H, minor), 5.04 (s, 2H, major); δ_C (100 MHz, $CDCl_3$) (major + minor): 142.8, 139.9, 137.6, 133.9, 133.8, 133.7, 131.0, 130.3, 129.8, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 126.1, 125.4, 120.5, 74.2, 74.1; **DEPT-135** (100 MHz, $CDCl_3$) (major): 130.1, 129.6, 128.8, 128.5, 128.3, 128.1, 127.7, 127.6, 127.5, 125.8, 125.2, 120.3 (all CH), 74.0, 73.9 (all CH_2). HRMS: calculated for $C_{22}H_{16}ONa$ [MNa^+] 319.1099, found 319.1099.

3-Methoxy-11-phenyl-8,10-dihydro-9-oxa-cyclopenta[b]phenanthrene (major), 4-(6-Methoxy-naphthalen-2-yl)-1,3-dihydro-naphtho[2,3-c]furan (minor) (3.66i & 3.67i)



State: beige solid; **Yield**: 85%; δ_H (400 MHz, $CDCl_3$): 7.88 (t, *J* = 8.0 Hz , 2H, minor), 7.74-7.70 (m, 2H, major and 3H, minor), 7.65 (d , *J* = 8.0 Hz, 1H, major), 7.57-7.47 (m, 4H, major and 3H, minor), 7.34-7.32 (m, 2H, major and 2H, minor), 7.21-7.20 (m, 1H, major and 1H, minor), 6.74 (dd, *J* = 6.4 Hz, 3.2 Hz, 1H, major), 5.35-5.29 (m, 2 H, major and 2H, minor), 5.11-5.02 (m, 2H, minor), 4.93 (s, 2H, major) , 3.98 (s, 3H, minor), 3.88 (s, 3H, major); δ_C (100 MHz, $CDCl_3$) (major + minor): 157.4, 142.6, 139.7, 136.4, 135.2, 132.8, 132.7, 129.6, 129.3, 128.5, 128.3, 128.1, 127.6, 127.0, 125.1, 120.3, 115.2, 108.9, 74.0, 73.9, 55.3; **DEPT-135** (100 MHz, $CDCl_3$) (major): 129.6, 129.2, 128.4, 128.1, 127.6, 127.0, 120.3, 115.2, 108.9 (all CH), 74.0, 73.9 (all CH_2), 55.3 (CH_3). HRMS: calculated for $C_{23}H_{18}O_2Na$ [MNa^+] 349.1204, found 349.1205.

6-Methoxy-4-phenyl-1,3-dihydro-naphtho[2,3-c]furan (major), 4-(4-Methoxyphenyl) -1,3-dihydro-naphtho[2,3-c]furan (minor) (3.66j & 3.67j)

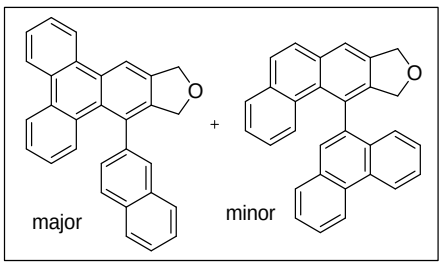


State: brown solid; **Yield**: 85%; δ_H (400 MHz, $CDCl_3$): 7.99-7.96 (m, 2H , minor), 7.94-7.78 (m, 1H, major and 1H, minor), 7.76 (d, *J* = 8.0 Hz , 1H, major), 7.74-7.58 (m, 3H, major), 7.56-7.49 (m, 4H, minor), 7.42 (t, *J* = 8.0 Hz, 1H, major), 7.24 (d, *J* = 8.0 Hz, 1H, major), 7.17-7.11 (m, 2H, major and 2H, minor), 7.04 (t, *J* = 8.0 Hz, 1H, major), 6.94 (d, *J* = 8.0 Hz , 1H, major and 2H, minor), 5.36 (s, 2H, major), 5.30 (s, 2H, minor), 5.11 (d, *J* = 12.0 Hz, 2H, minor), 4.96 (s, 2H, major), 3.93 (s, 3H, major), 3.87(s, 3H, minor); δ_C (100 MHz, $CDCl_3$) (major + minor): 159.3, 140.3, 137.6, 134.9, 133.9, 133.7, 133.6, 131.1, 129.6, 128.7, 128.6, 128.5, 128.1, 127.9, 127.7, 127.6, 126.1, 125.5, 120.4, 119.0, 115.2, 74.3, 74.2, 55.6; **DEPT-135** (100 MHz, $CDCl_3$) (major): 129.4, 128.5, 127.6, 127.5, 127.4, 125.8, 125.2, 120.1, 115.0, (all CH), 74.0, 73.9 (all CH_2), 55.4 (CH_3). HRMS: calculated for $C_{23}H_{19}O_2$ [MH^+] 327.1380, found 327.1385.

Spectrum in the Solvent Phase

δ_H (400 MHz, $CDCl_3$): 7.98-7.87 (m, 1H, major and 2H, minor), 7.83 (d, *J* = 8.0 Hz, 1H, major and 1H, minor), 7.81-7.61 (m, 2H, major and 2H, minor), 7.43 (t, *J* = 7.6 Hz, 1H, major and 3H, minor), 7.37 (d, *J* = 8.0 Hz, 2H, minor), 7.26-7.23 (m, 2H, major), 7.16-7.08 (m, 1H, major and 1H, minor), 7.06 (d, *J* = 8.4 Hz, 3H, major), 5.35 (s, 2H, major), 5.30 (s, 2H, minor), 5.05 (s, 2H, minor), 4.96 (s, 2H, major), 3.94-3.93 (m, 3H, major and 3H, minor); δ_C (100 MHz, $CDCl_3$) (major + minor): 159.2, 140.3, 137.5, 134.9, 133.9, 133.7, 133. 6, 130.9, 129.6, 128.7, 127.9, 127.7, 127.6, 126.0, 125.4, 120.4, 115.2, 114.4, 74.3, 74.2, 55.5; **DEPT-135** (100 MHz, $CDCl_3$) (major): 129.4, 128.5, 127.6, 127.5, 127.4, 125.8, 125.2, 120.2, 115.0, (all CH), 74.0, 73.9 (all CH_2), 55.3 (CH_3).

9-Naphthalen-2-yl-10,12-dihydro-11-oxa-cyclopenta[b]triphenylene, 11-Phenanthre-9-yl-8,10-dihydro-9-oxa-cyclopenta[b]phenanthrene (3.66k & 3.67k)



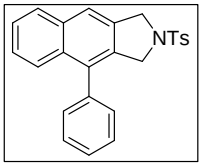
State: brown solid; **Yield**: 85%; δ_H (400 MHz, $CDCl_3$): 8.86-8.83 (m, 1H, minor and 1H, major), 8.66-8.62 (m, 3H, minor), 8.56-8.55 (m, 2H, major), 7.94-7.26 (m, 12H, major and 11H, minor), 6.92 (dt, *J* = 7.2 Hz, 1.2 Hz, 1H, major), 6.82 (t, *J* = 8.0 Hz,

1H, minor), 5.42 (m, 2H, minor and 2H, major), 5.17 (d, *J* = 12.0 Hz, 1H, major), 4.93 (td, *J* = 13.2 Hz,1.2 Hz, 1H, major and 1H, minor), 4.62 (d, *J* = 13.2 Hz, 1 H, minor); δ_C (100 MHz, $CDCl_3$) (major + minor): 141.0, 140.6, 140.5, 138.9, 138.5, 137.9, 134.2, 134.1, 134.0, 133.5 , 132.8, 132.4, 131.9, 131.7, 131.3, 131.2, 130.8, 130.6, 130.5, 130.4, 130.3, 130.2, 129.9, 129.4, 129.3, 129.1, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 126.7, 126.6, 126.5, 125.6, 124.6, 123.7, 123.5, 123.4, 123.3, 123.0, 121.1, 115.1, 74.6, 74.5, 74.2, 74.1; **DEPT-135** (100 MHz, $CDCl_3$): 129.6, 129.1, 128.8, 128.1, 127.9, 127.7, 127.6, 127.4, 127.3, 127.2, 126.9, 126.8, 126.6, 126.5, 126.4, 126.2, 125.8, 125.4, 123.5, 123.2, 123.1, 122.8, 114.8 (all CH), 74.3, 74.2, 73.9, 73.8 (all CH_2). HRMS: Calculated for $C_{30}H_{21}O$ [MH^+] 397.1587, found 397.1594.

Spectrum in the Solvent Phase:

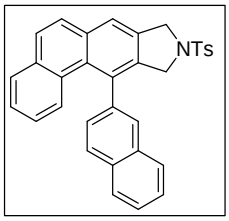
δ_H (400 MHz, $CDCl_3$): 8.86-8.83 (m, 1H, major and 1H, minor), 8.66-8.62 (m, 1H, major and 1H, minor), 8.56-8.55 (m, 1H, major and 1H, minor), 7.94-7.64 (m, 6H, major and 6H, minor), 7.58-7.39 (m, 5H, minor), 7.37-7.26 (m, 5H, major), 6.93 (t, *J* = 8.0 Hz, 1H, major), 6.82 (t, *J* = 7.6 Hz, 1H, minor), 5.40 (t, *J* = 6.8 Hz, 2H, major and 2H, minor), 5.17 (d, *J* = 13.2 Hz, 1H, major), 4.91 (t, *J* = 13.2 Hz, 1H, major and 1H, minor), 4.61 (d, *J* = 13.2Hz, 1H, minor); δ_C (100 MHz, $CDCl_3$) (major + minor): 140.9, 140.6, 140.4, 138.9, 138.4, 137.8, 134.2, 133.9, 133.5, 132.7, 132.3, 131.8, 131.7, 131.2, 131.1, 130.8, 130.5, 130.4, 130.3, 130.2, 130.1, 129.8, 129.3, 129.2, 129.0, 128.7, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 127.3, 127.2, 127.1, 127.0, 126.7, 126.6, 126.4, 126.1, 126.0, 125.6, 123.6, 123.4, 123.3, 122.9, 121.0, 115.0, 74.5, 74.4, 74.1, 74.0.

4-Phenyl-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-benzo[f]isoindole (3.68l)



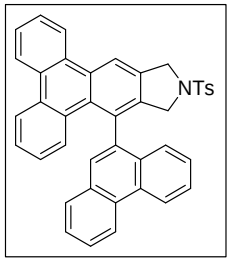
State: brown solid; [m.p = decomposes at 210 °C]; **Yield**: 87%; δ_H (400 MHz, $CDCl_3$): 7.80 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.64 (s, 1H), 7.57-7.43 (m, 5H), 7.37-7.25 (m, 5H), 4.80 (s, 2H), 4.49 (s, 2H), 2.40 (s, 3H); δ_C (100 MHz, $CDCl_3$): 144.3, 138.1, 134.9, 134.8, 134.2, 134.1, 134.0, 132.4, 130.4, 129.9, 129.3, 128.5, 128.3, 126.6, 126.5, 126.4, 121.3, 54.2, 53.7, 22.1. HRMS: Calculated for $C_{25}H_{22}NO_2S$ [MH^+] 400.1366, found 400.1360.

11-Naphthalen-2-yl-9-(toluene-4-sulfonyl)-9,10-dihydro-8H-9-aza-cyclopenta[b] phenanthrene (3.68m)



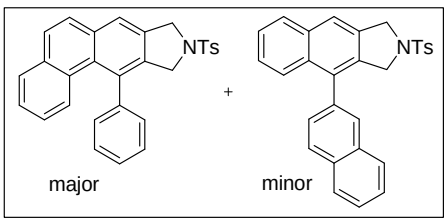
State: brown solid; [m.p = decomposes at 216 °C]; **Yield**: 85%; δ_H (400 MHz, $CDCl_3$): 8.02-8.00 (m, 2H), 7.99-7.45 (m, 11H), 7.38-7.26 (m, 4H), 6.95 (t, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H) , 2.39 (s, 3H); δ_C (100 MHz, $CDCl_3$): 143.9, 139.6, 136.7, 135.2, 134.5, 134.2, 133.9, 133.7, 132.9, 130.7, 130.0, 129.9, 128.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.4, 126.9, 126.8, 126.7, 126.3, 125.7, 122.3, 54.3, 54.2, 21.7. HRMS: Calculated for $C_{33}H_{26}O_2NS$ [MH^+], 500.1679, found 500.1672.

9-Phenanthren-9-yl-11-(toluene-4-sulfonyl)-11,12-dihydro-10H-phenanthro[9,10-f]isoindole (3.68n)



State: brown solid; [m.p > 220 °C]; **Yield**: 89%; δ_H (400 MHz, $CDCl_3$): 8.88-8.85 (m, 2H) , 8.83-8.59 (m, 3H), 8.52 (d, *J* = 8.0 Hz, 1H), 7.82-7.45 (m, 12H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 6.73 (t, *J* = 8.0 Hz, 1H) , 4.94 (s, 2H), 4.30 (d, *J* = 16.0 Hz , 1H), 4.18 (d, *J* = 16.0 Hz, 1H), 2.38 (s, 3H); δ_C (100 MHz, $CDCl_3$): 143.7, 138.5, 137.9, 135.1, 133.8, 133.6, 132.0, 131.8 , 131.3, 130.8, 130.4, 130.3, 129.8, 129.7, 129.6, 128.9, 128.4, 127.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.9, 126.8, 126.0, 123.6, 123.5, 123.3, 123.1, 122.9, 117.0, 54.6, 54.3, 21.5. HRMS: Calculated for $C_{41}H_{30}NO_2S$ [MH^+] 600.1992, found 600.2000.

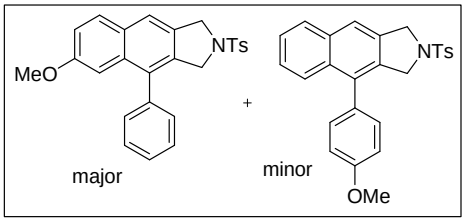
11-Phenyl-9-(toluene-4-sulfonyl)-9,10-dihydro-8H-9-aza-cyclopenta[b]phenanthrene (major); 4-Naphthalen-2-yl-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-benzo[f]isoindole (minor) (3.68o & 3.69o)



State: brown solid; **Yield**: 90%; δ_H (400 MHz, $CDCl_3$): 7.85-7.79 (m, 2H), 7.76-7.67 (m, 4H), 7.61-7.41 (m, 4H), 7.39-7.25 (m, 3H), 7.23-7.05 (m, 3H), 4.86-4.83 (m, 2H, major and 2H, minor), 4.53-4.50 (m, 2H, minor), 4.43 (s, 2H, major), 2.39 (s, 3H, major and 3H, minor); δ_C (100 MHz, $CDCl_3$) (major + minor): 143.9, 142.1, 136.4,

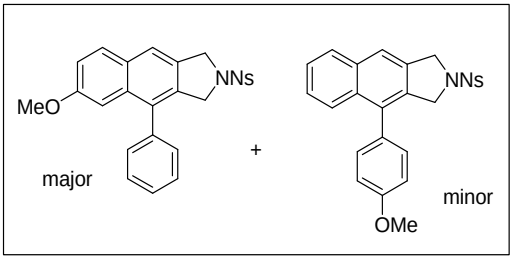
135.4, 134.4, 133.9, 133.6, 131.9, 130.7, 130.0, 129.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.3, 126.3, 125.6, 122.2, 54.3, 54.2, 21.7; **DEPT-135** (100 MHz, $CDCl_3$) (major): 129.9, 129.8, 128.6, 128.2, 128.0, 127.8, 127.6, 127.2, 126.1, 125.4, 122.0 (all CH), 54.1, 54.0 (all CH_2), 21.5(CH_3). HRMS: Calculated for $C_{29}H_{23}NO_2SNa$ [MNa^+] 472.1347, found 472.1348.

6-Methoxy-4-phenyl-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-benzo[f]isoindole; 4-(4-Methoxy-phenyl)-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-benzo[f]isoindole (3.68p & 3.69p)



State: brown solid; **Yield**: 85%; δ_H (400 MHz, $CDCl_3$): 7.75-7.72 (m, 3H, major), 7.51 (s, 1H, major), 7.49-7.44 (m, 3H, major), 7.31-7.18 (m, 4H, major), 7.13-7.03 (m, 1H, major), 6.85 (s, 1H, major), 4.79 (s, 2H, minor), 4.77 (s, 2H, major), 4.50 (s, 2H, minor), 4.46 (s, 2H, major), 3.91 (s, 3H, minor), 3.68 (s, 3H, major), 2.39 (s, 3H, major and 3H, minor); δ_C: (100 MHz, $CDCl_3$) (major + minor): 158.0, 143.9, 137.9, 134.1, 133.8, 133.3, 133.2, 132.1, 130.7, 130.0, 129.5, 129.4, 129.2, 129.1, 128.1, 127.8, 126.1, 120.6, 118.5, 114.4, 104.6, 55.3, 53.7, 53.6, 53.4, 21.7. HRMS: calculated for $C_{26}H_{23}NO_3SNa$ [MNa^+] 452.1296, found 452.1297.

6-Methoxy-2-(4-nitro-benzenesulfonyl)-4-phenyl-2,3-dihydro-1H-benzo[f]isoindole (major), 4-(4-Methoxy-phenyl)-2-(4-nitro-benzenesulfonyl)-2,3-dihydro-1H-benzo[f]isoindole(minor) (3.68q & 3.69q)



State: yellow solid; **Yield**: 85%; δ_H (400 MHz, $CDCl_3$): 8.35 (d, *J* = 8.0 Hz, 3H, major), 8.05-8.02 (m, 3H, major), 7.81(d, *J* = 8.0 Hz, 1H, minor), 7.72 (d, *J* = 8.0 Hz, 3H, minor), 7.63 (d, *J* = 8.0 Hz, 2H, minor), 7.59 (d, *J* = 8.0 Hz, 2H, minor), 7.55-7.08 (m, 5H, major and 2H, minor), 7.05 (d, *J* = 8.0 Hz, 2H, major), 6.85 (d, *J* = 2.0 Hz, 2H, minor), 6.60 (t, *J* = 8.0 Hz, 1H, minor), 4.87 (s, 2H, minor), 4.84 (s, 2H, major), 4.55 (s, 2H, minor), 4.51 (s, 2H, major), 3.92 (s, 3H, minor), 3.68 (s, 3H,

major); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) (major + minor): 158.2, 150.4, 147.3, 143.0, 137.8, 133.5, 133.3, 133.2, 132.9, 131.1,130.6, 129.6, 129.4, 129.3, 129.2, 128.8, 128.2, 128.1, 126.4, 126.3, 126.1, 125.0, 124.6, 124.3, 124.2, 124.1, 120.8, 120.1, 119.3, 118.9, 116.1, 114.5, 104.6, 55.3, 53.9, 53.6, 53.5. HRMS: calculated for $C_{25}H_{21}N_2O_5S$ [MH^+] 461.1171, found 461.1165.

Spectrum in the Solvent Phase

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 8.36 (d, *J* = 8.0 Hz, 2H, major and 2H, minor), 8.04 (d, *J* = 8.0 Hz, 2H, major and 2H, minor), 7.81 (d, *J* = 8.4 Hz, 1 H, major), 7.64 (s, 1H, minor), 7.61 (d, *J* = 8.0 Hz, 2H, major), 7.46-7.37 (m, 2H, major and 5H, minor), 7.19 (d, *J* = 8.4 Hz, 2H, major and 3H, minor), 7.05 (d, *J* = 8.4 Hz, 2H, major), 4.87 (s, 2H major and 2H, minor), 4.55 (s, 2H major and 2H, minor), 3.95 (s, 3H, minor), 3,92 (s, 3H, major); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) (major + minor): 159.6, 143.3, 134.7, 133.8, 133.5, 133.0, 130.7, 129.6, 128.8, 128.4, 128.2, 126.5, 126.4, 126.1, 124.7, 120.9, 114.5, 55.6, 54.0, 53.6.

3.9 ^{1}H and ^{13}C NMR Spectra of Some Selected Compounds (in $CDCl_3$)

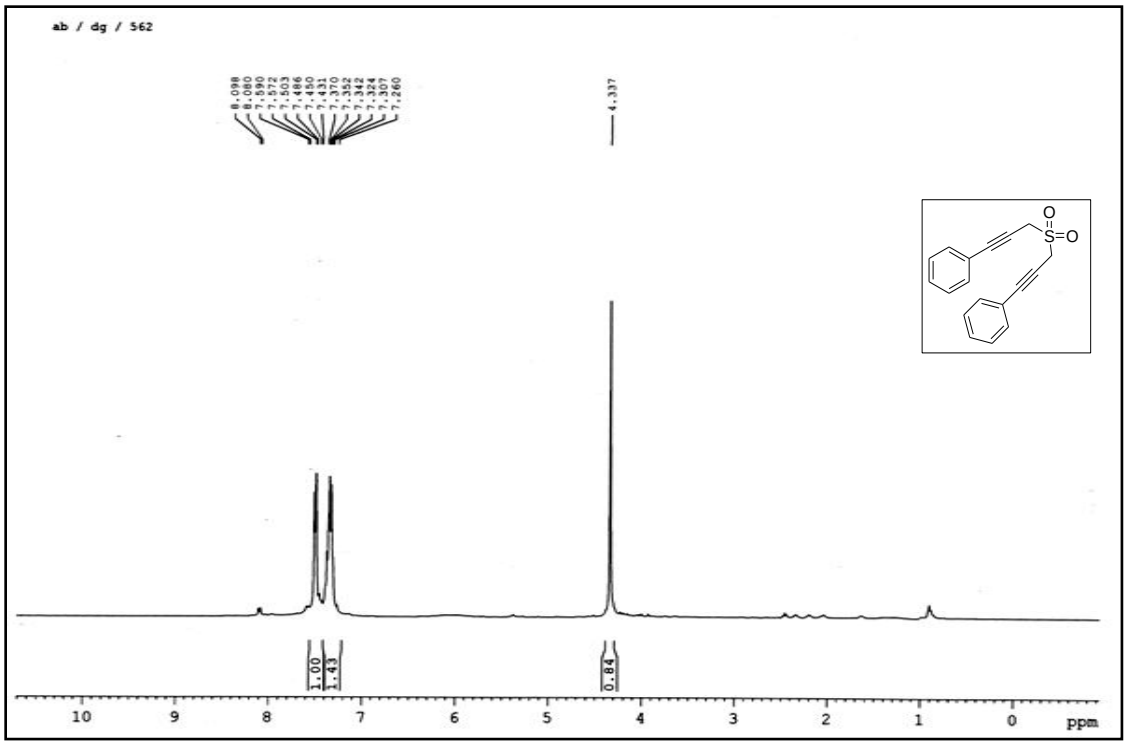


Figure 3.5: ^{1}H-NMR spectrum of compound 3.08

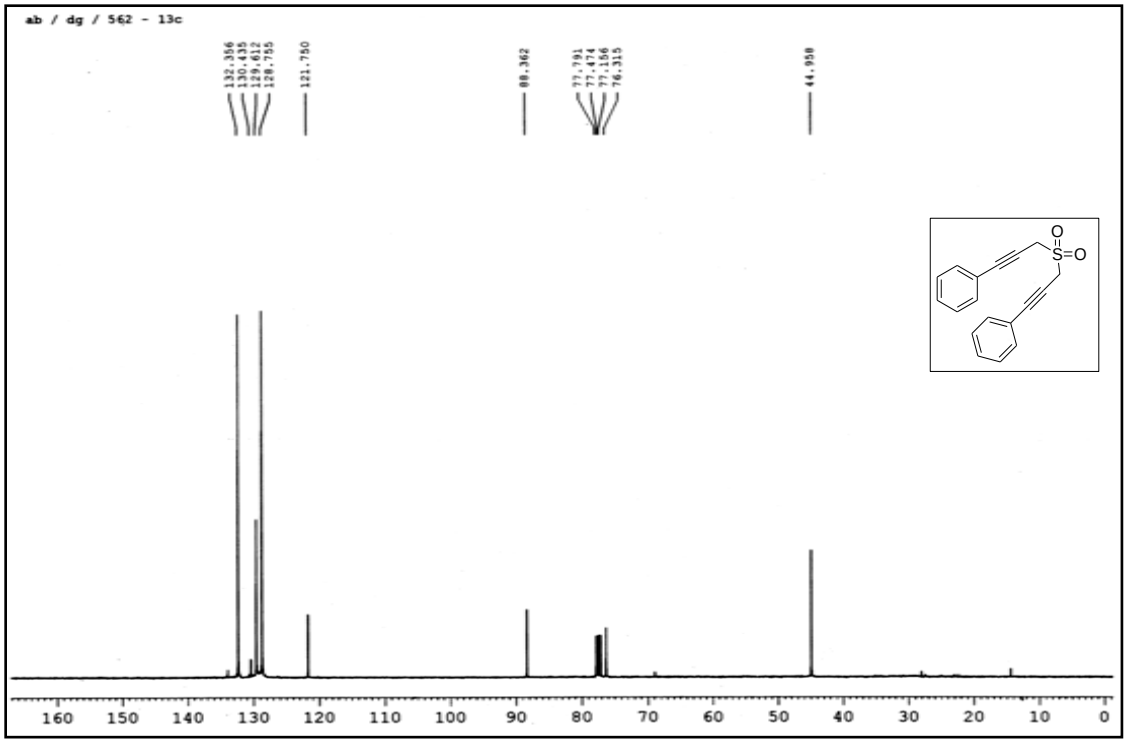


Figure 3.6: ^{13}C-NMR spectrum of compound 3.08

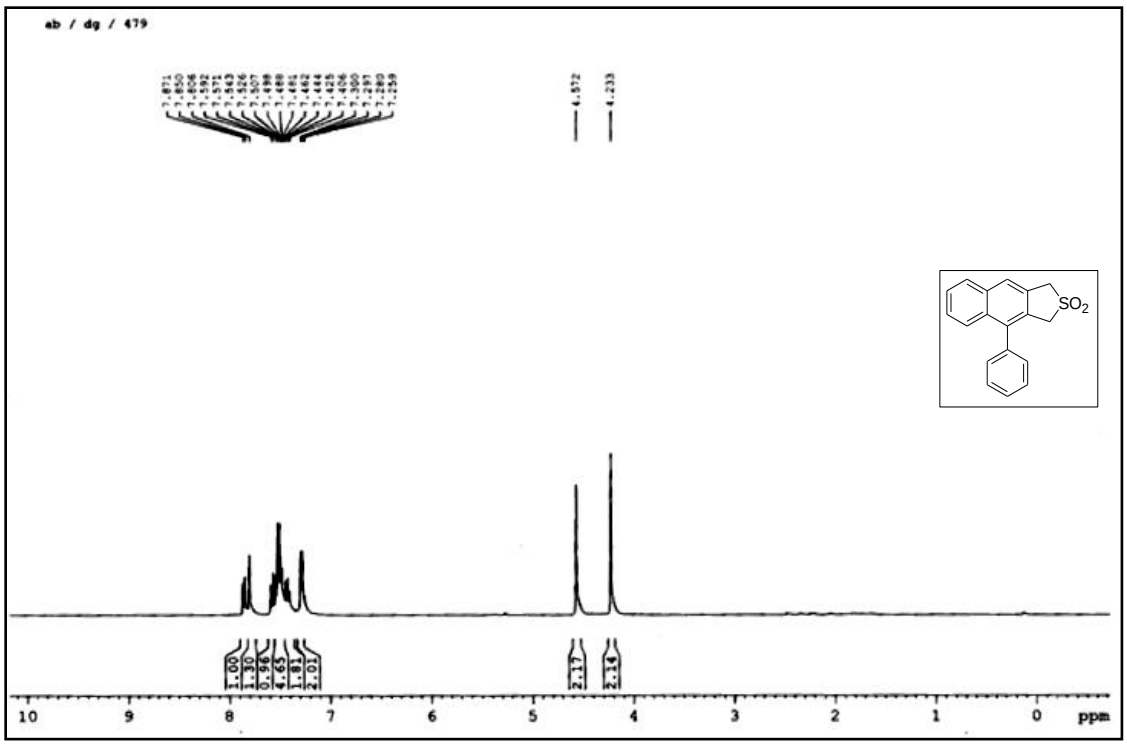


Figure 3.7: ^{1}H-NMR spectrum of compound 3.54a

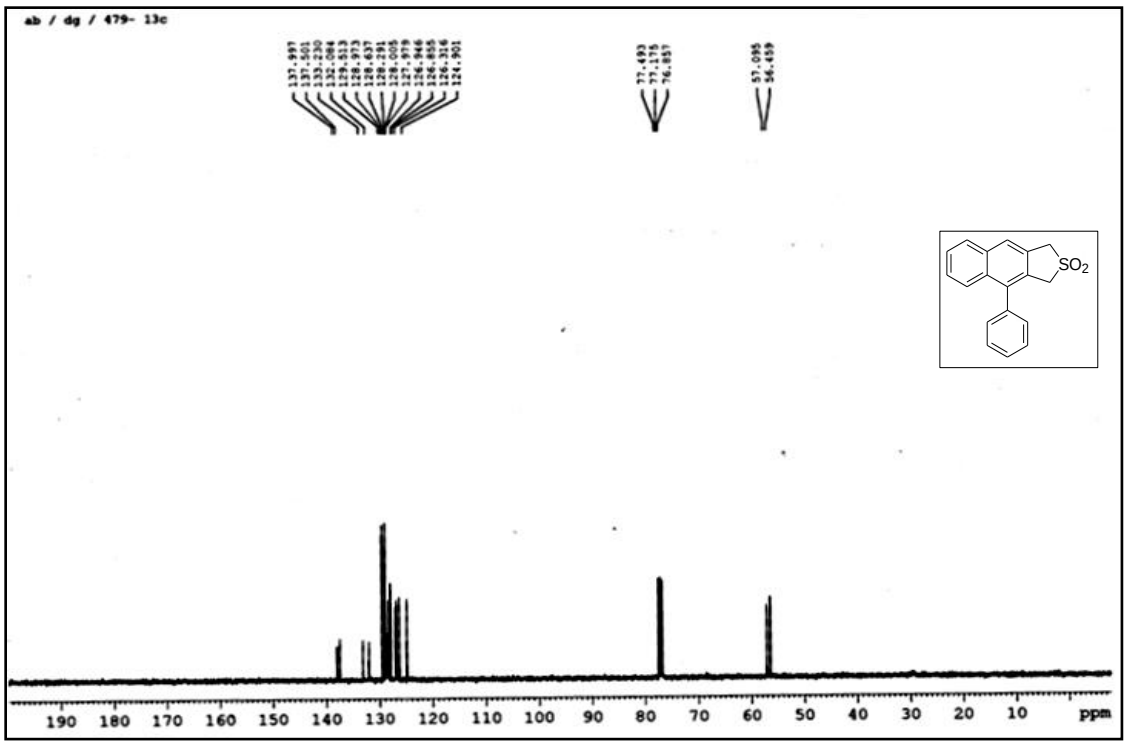


Figure 3.8: ^{13}C-NMR spectrum of compound 3.54a

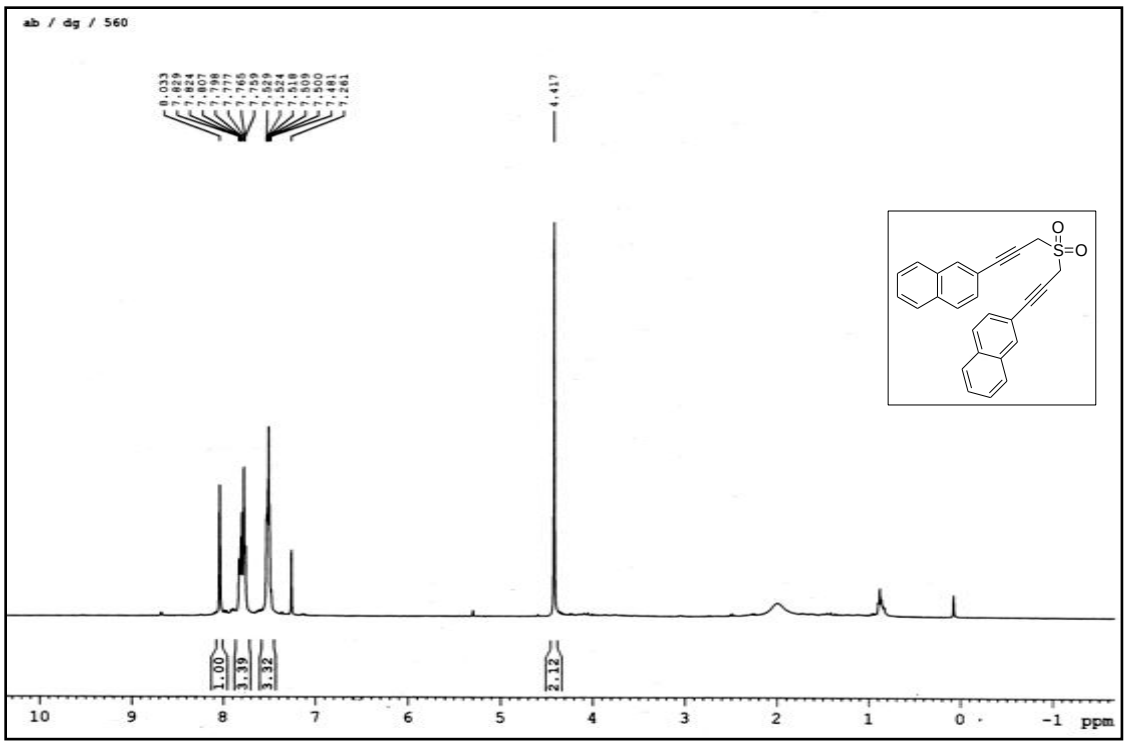


Figure 3.9: ^{1}H-NMR spectrum of compound 3.13

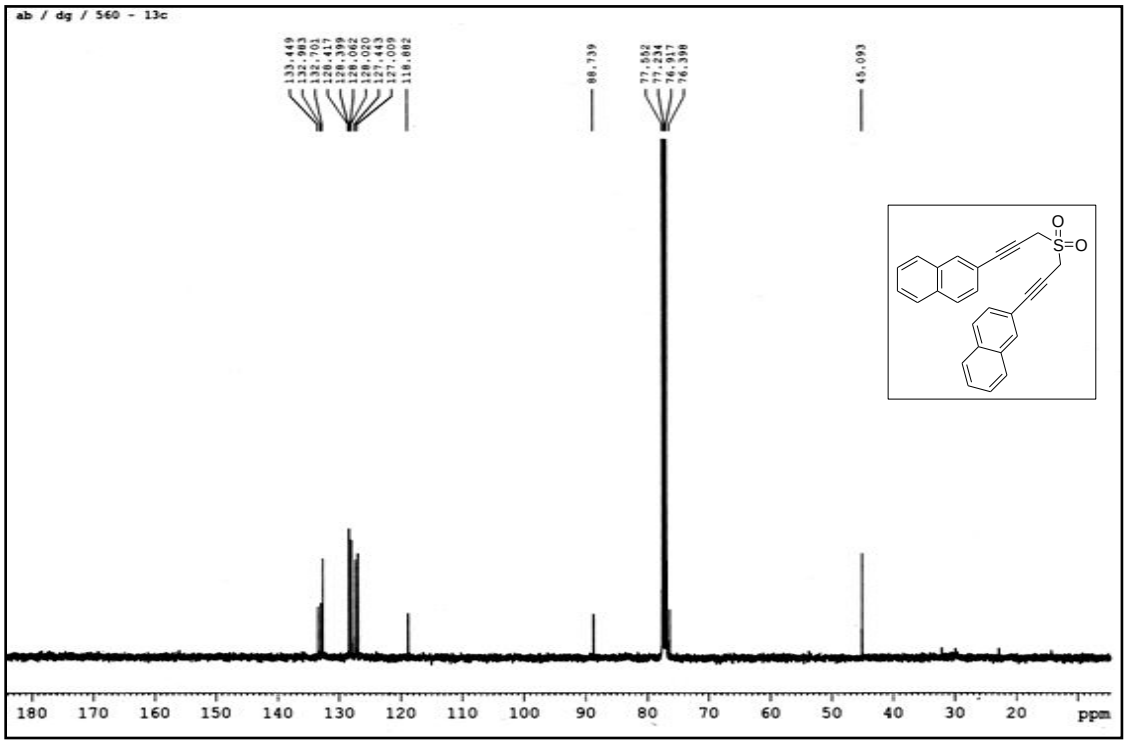


Figure 3.10: ^{13}C-NMR spectrum of compound 3.13

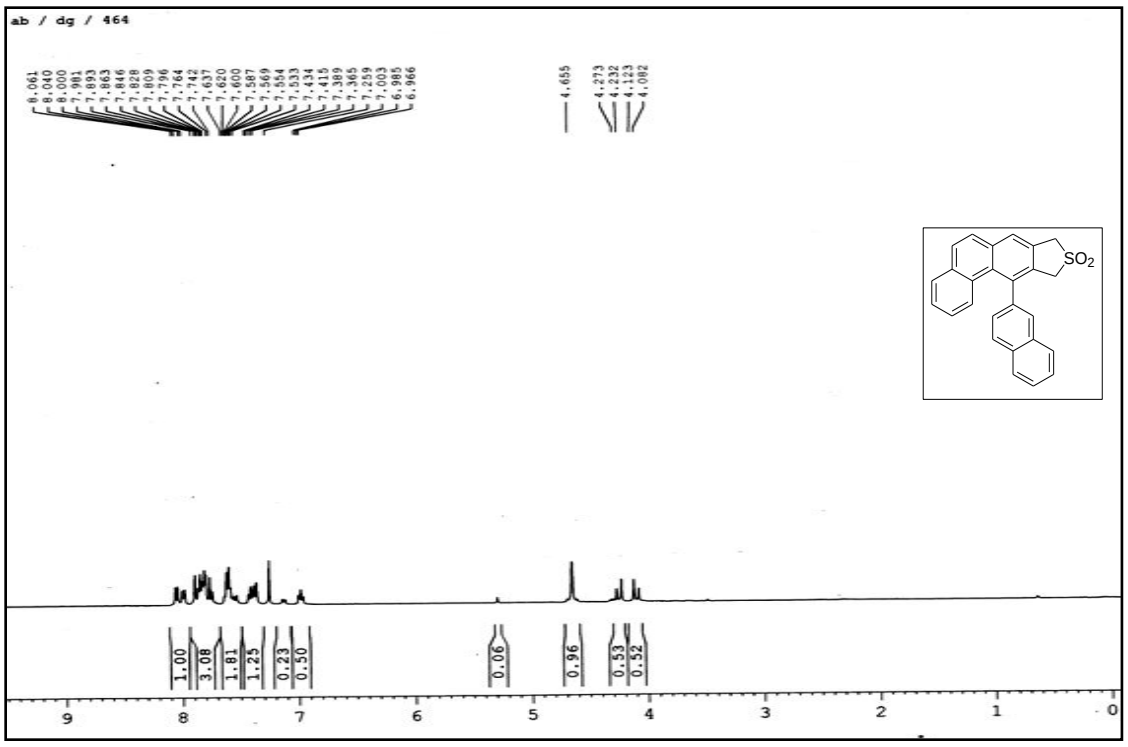


Figure 3.11: ^{1}H-NMR spectrum of compound 3.54b

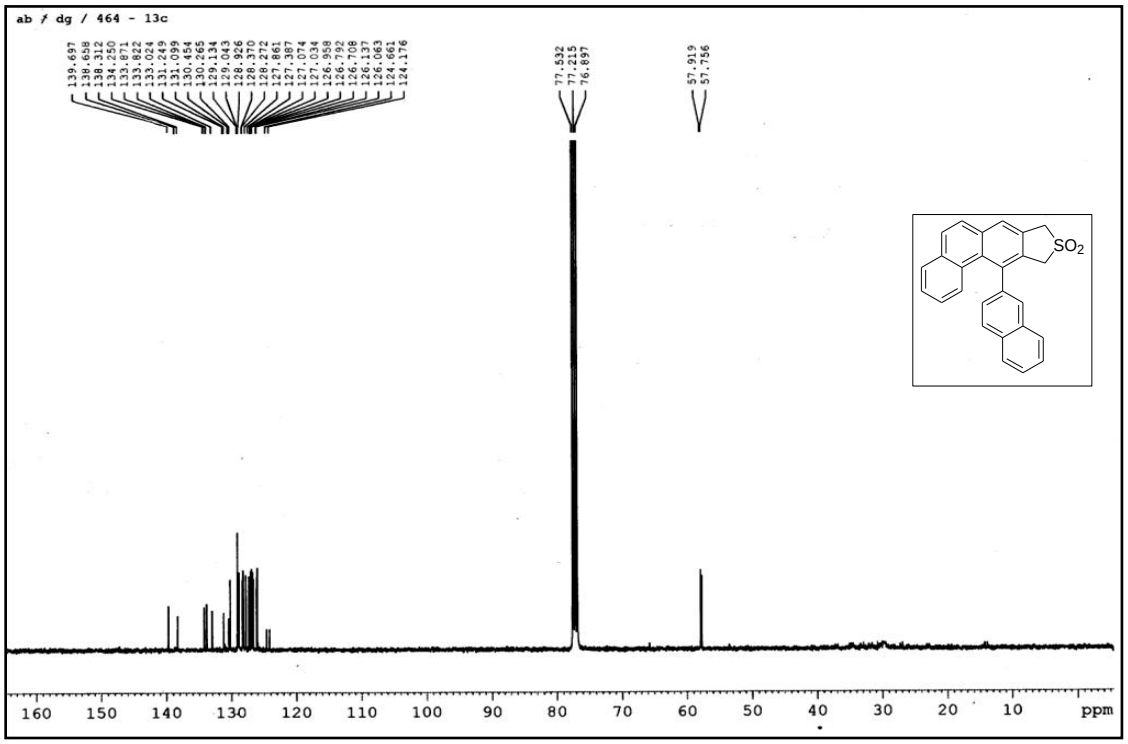


Figure 3.12: ^{13}C-NMR spectrum of compound 3.54b

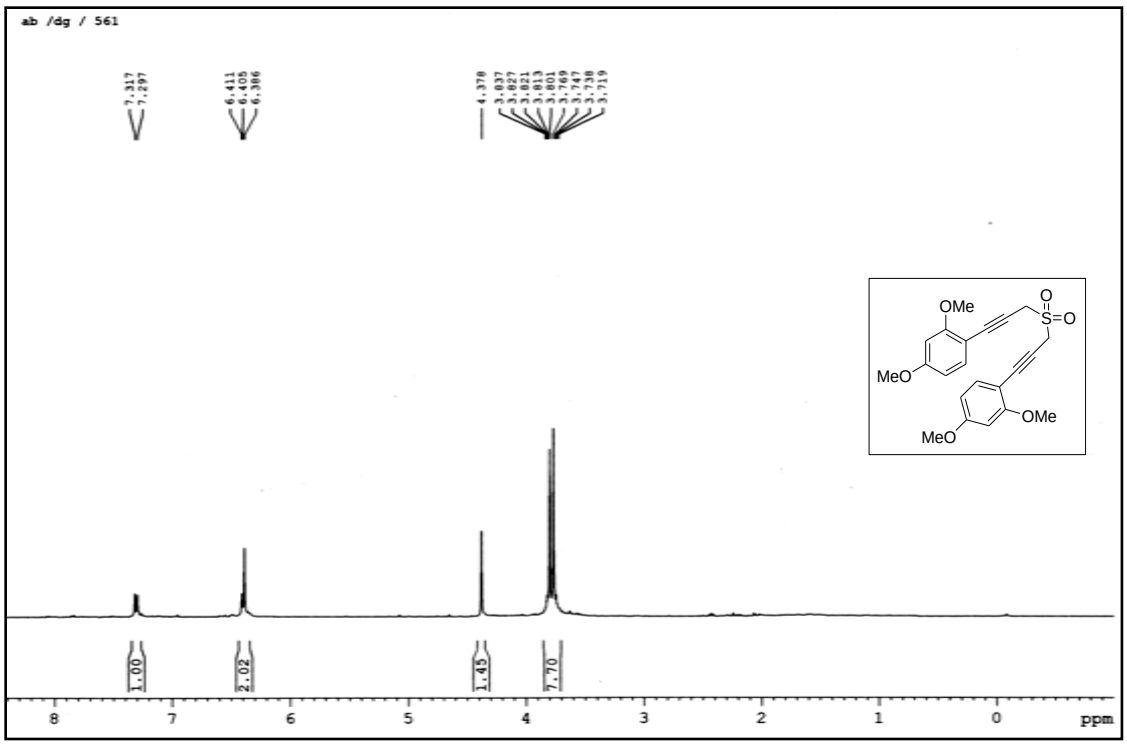


Figure 3.13: ^{1}H-NMR spectrum of compound 3.20

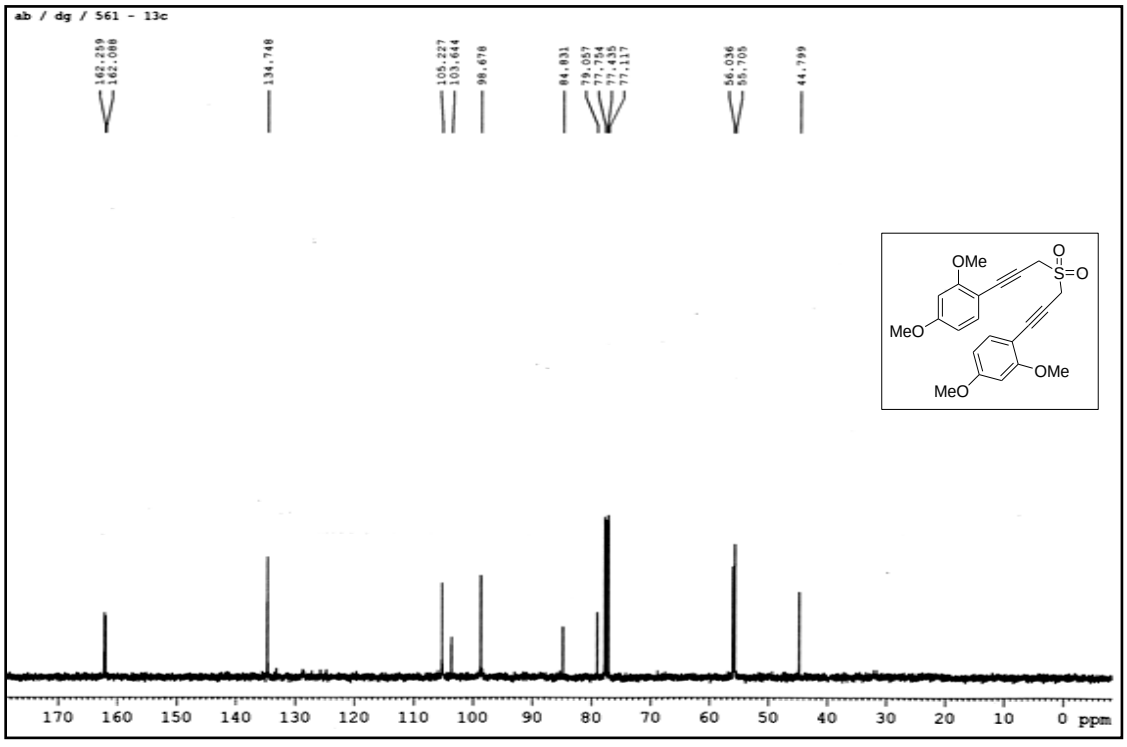


Figure 3.14: ^{13}C-NMR spectrum of compound 3.20

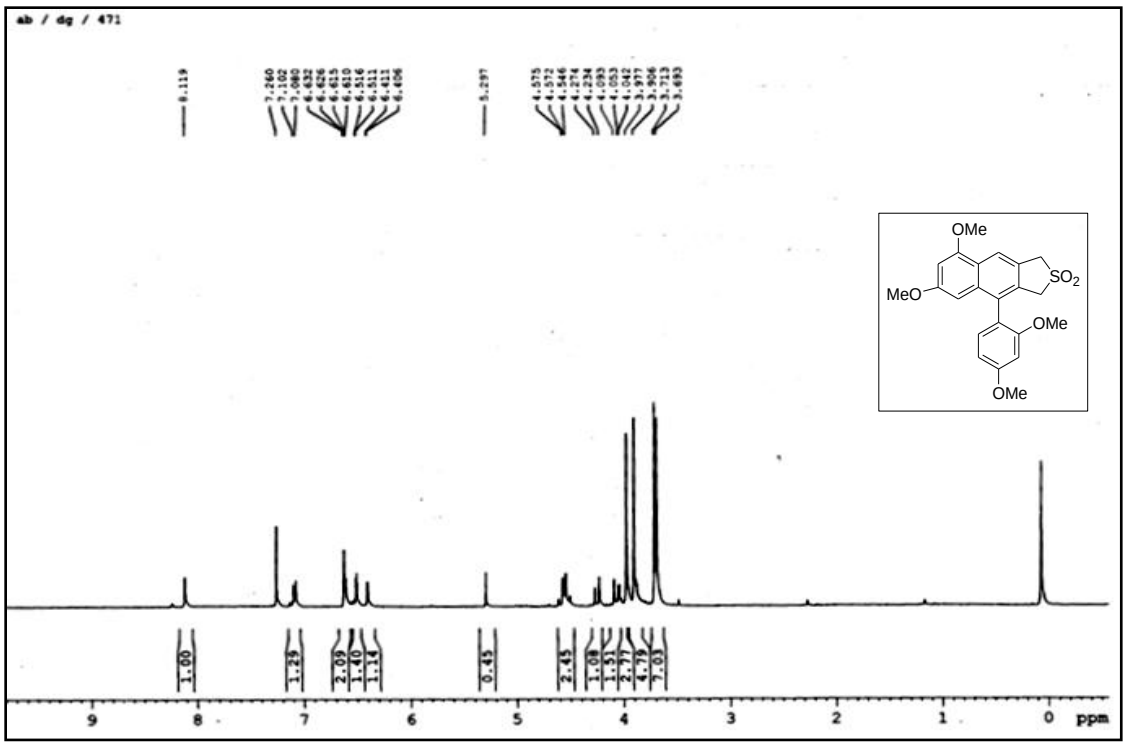


Figure 3.15: ^{1}H-NMR spectrum of compound 3.54c

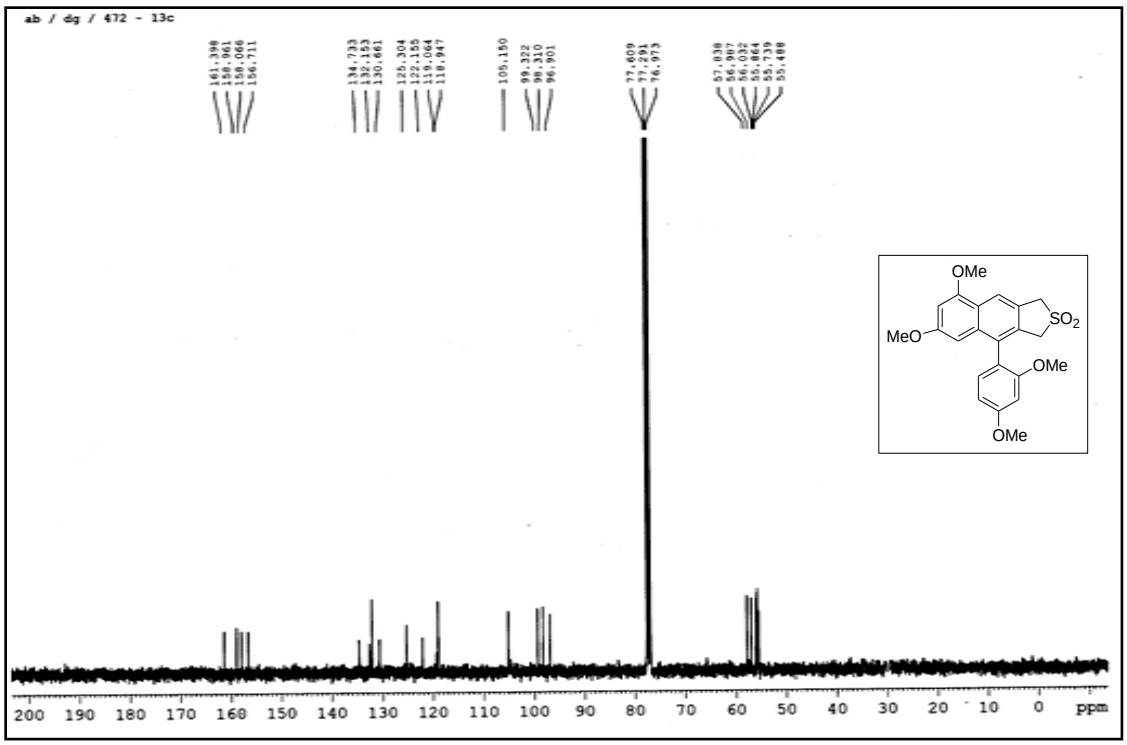


Figure 3.16: ^{13}C-NMR spectrum of compound 3.54c

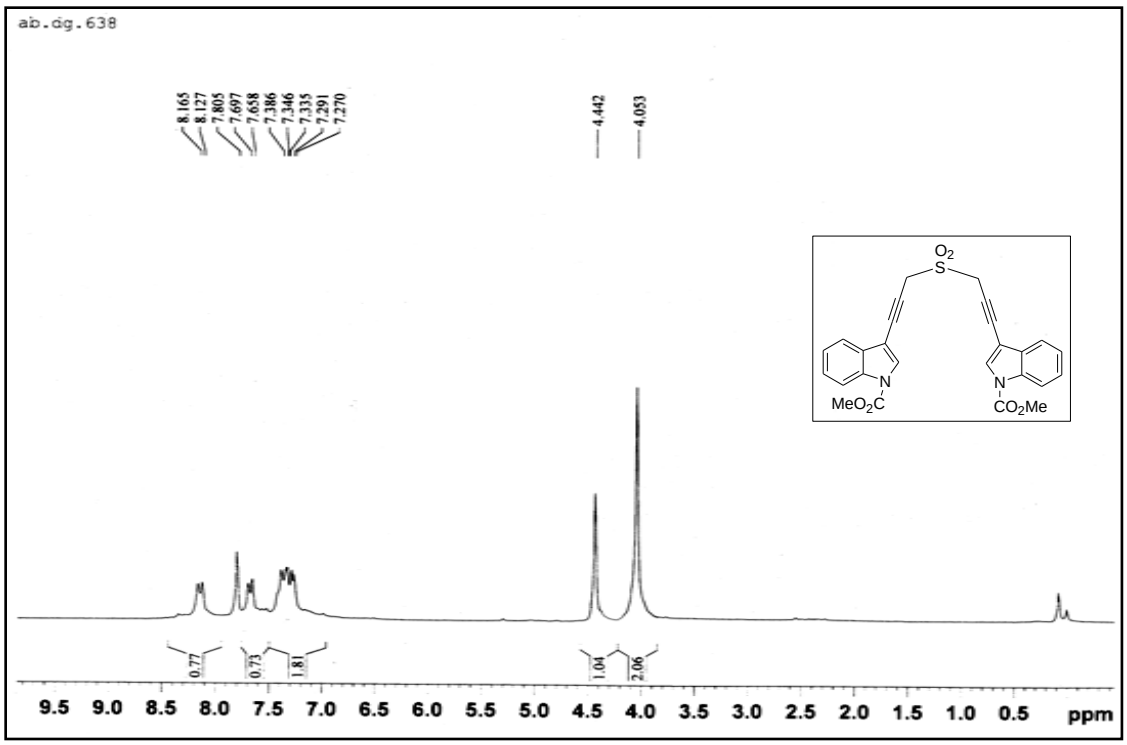


Figure 3.17: ^{1}H-NMR spectrum of compound 3.33

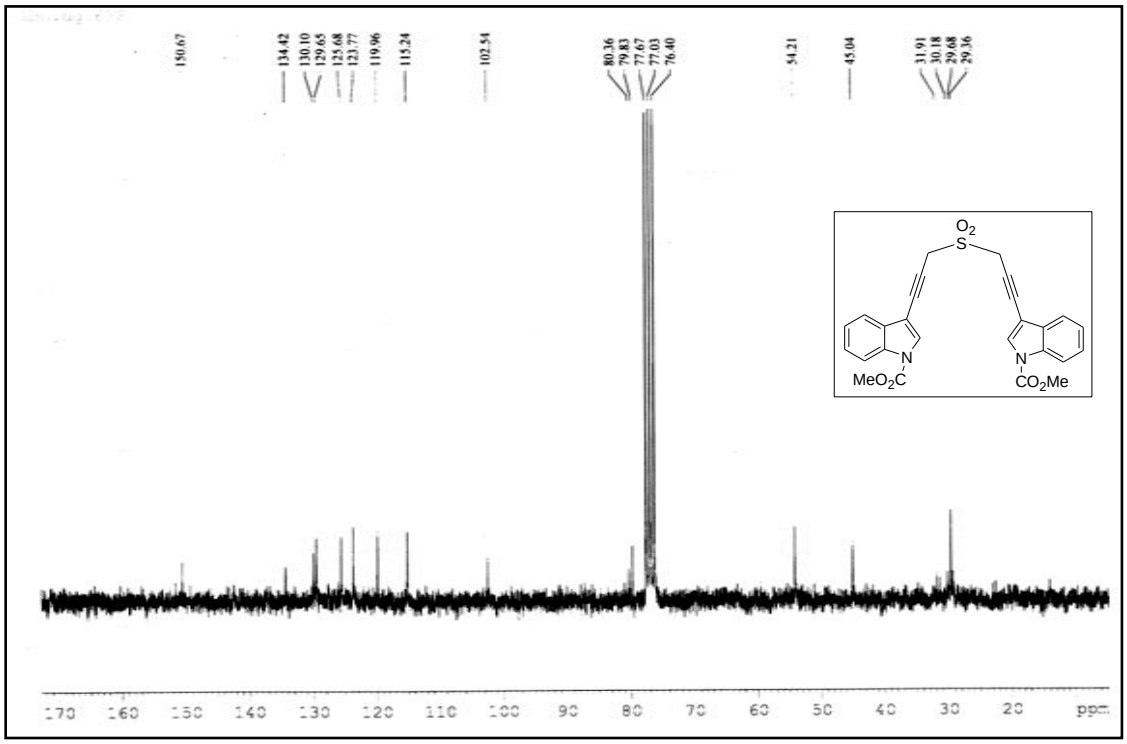


Figure 3.18: ^{13}C-NMR spectrum of compound 3.33

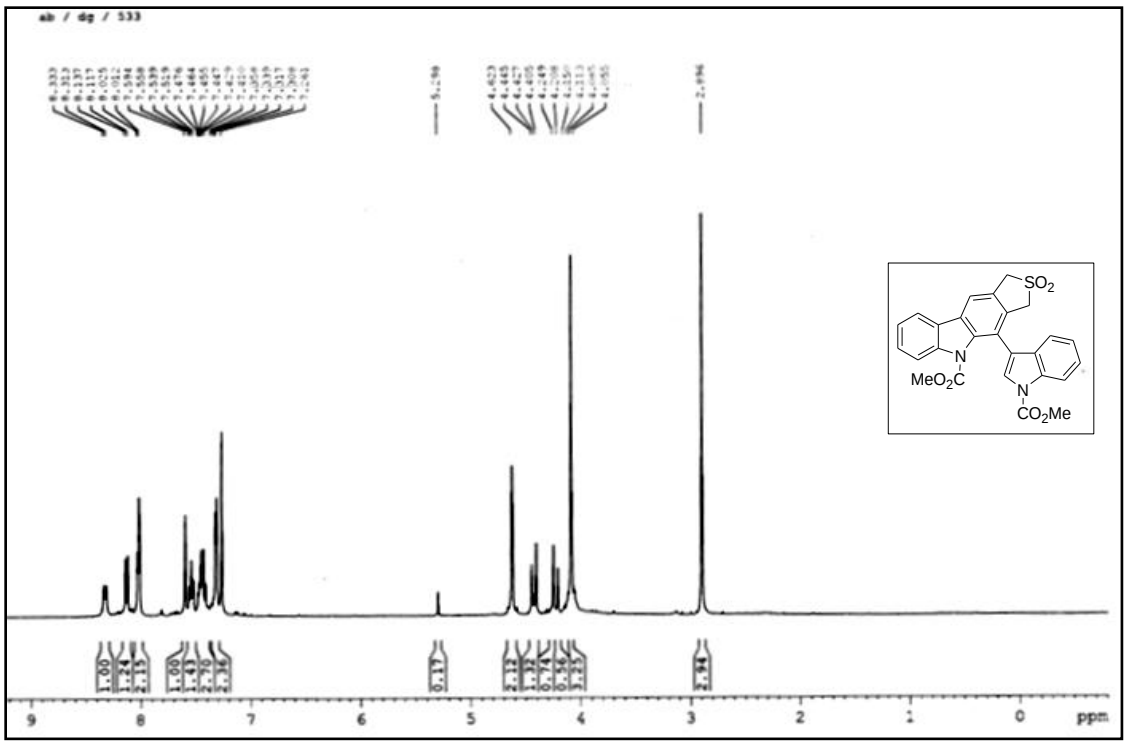


Figure 3.19: ^{1}H-NMR spectrum of compound 3.54d

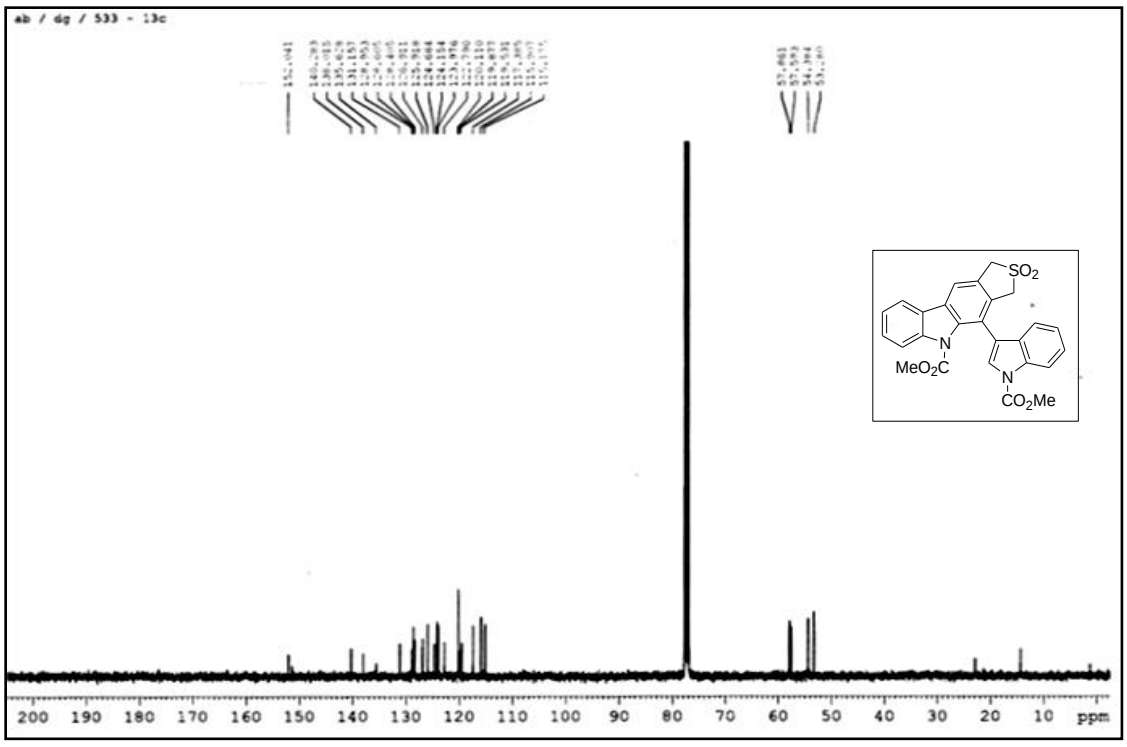


Figure 3.20: ^{13}C-NMR spectrum of compound 3.54d

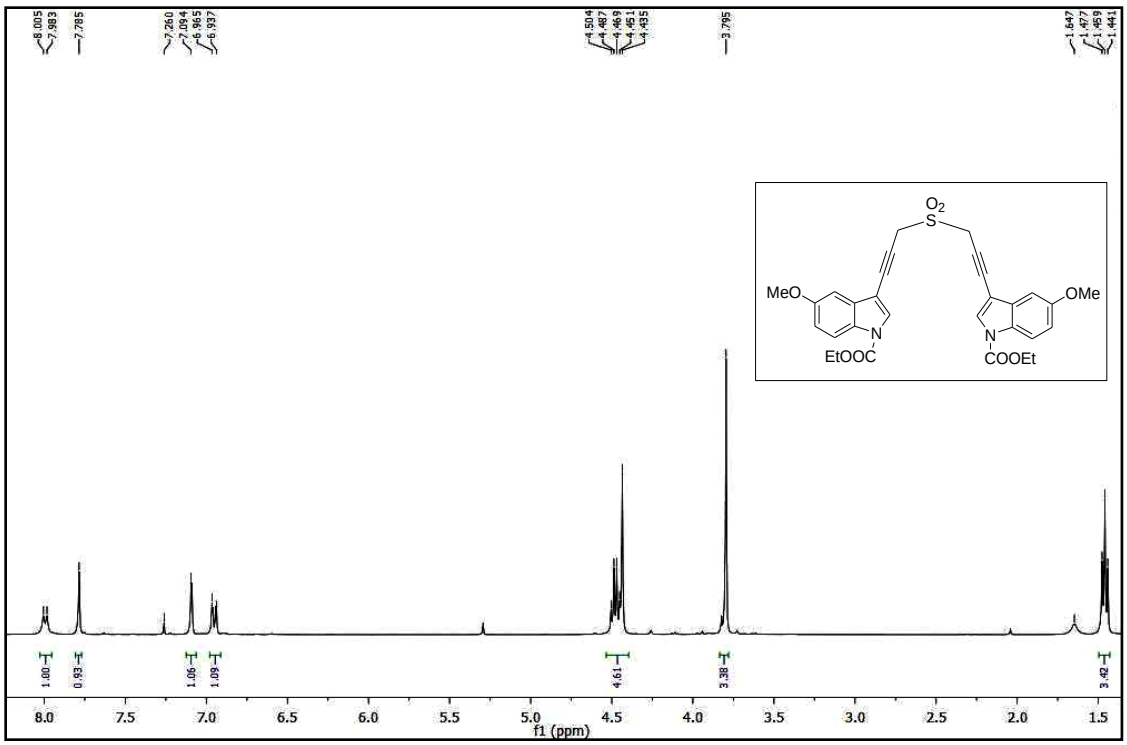


Figure 3.21: ^{1}H-NMR spectrum of compound 3.34

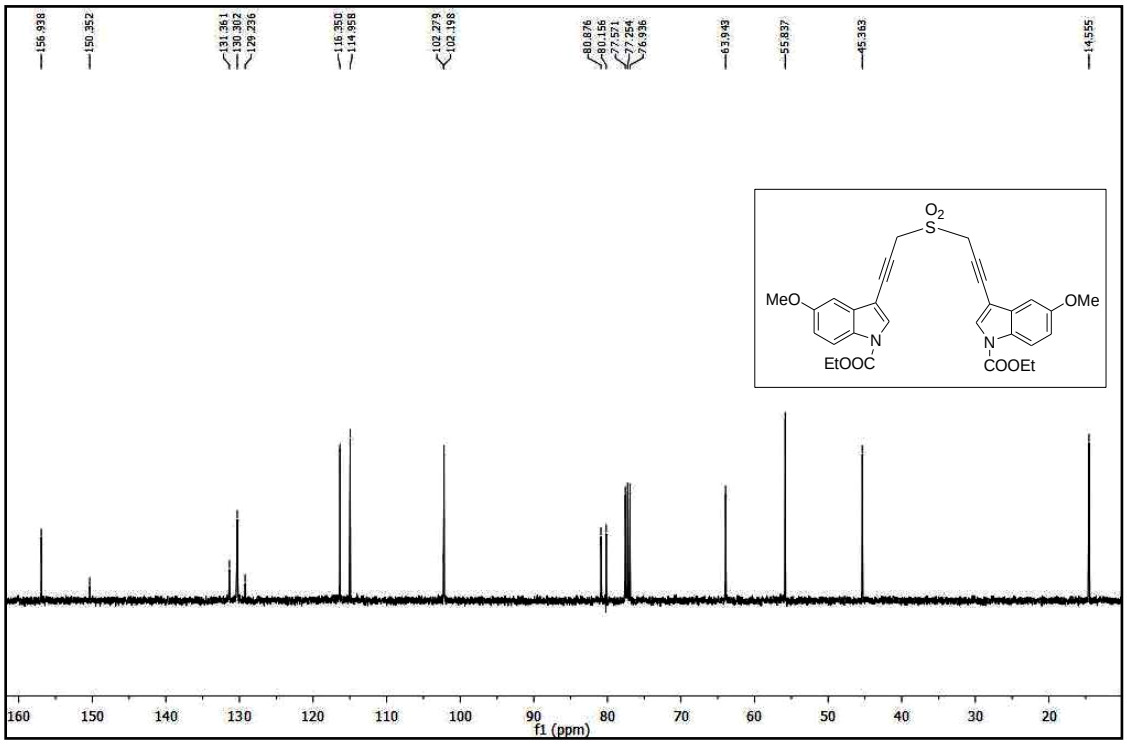


Figure 3.22: ^{13}C-NMR spectrum of compound 3.34

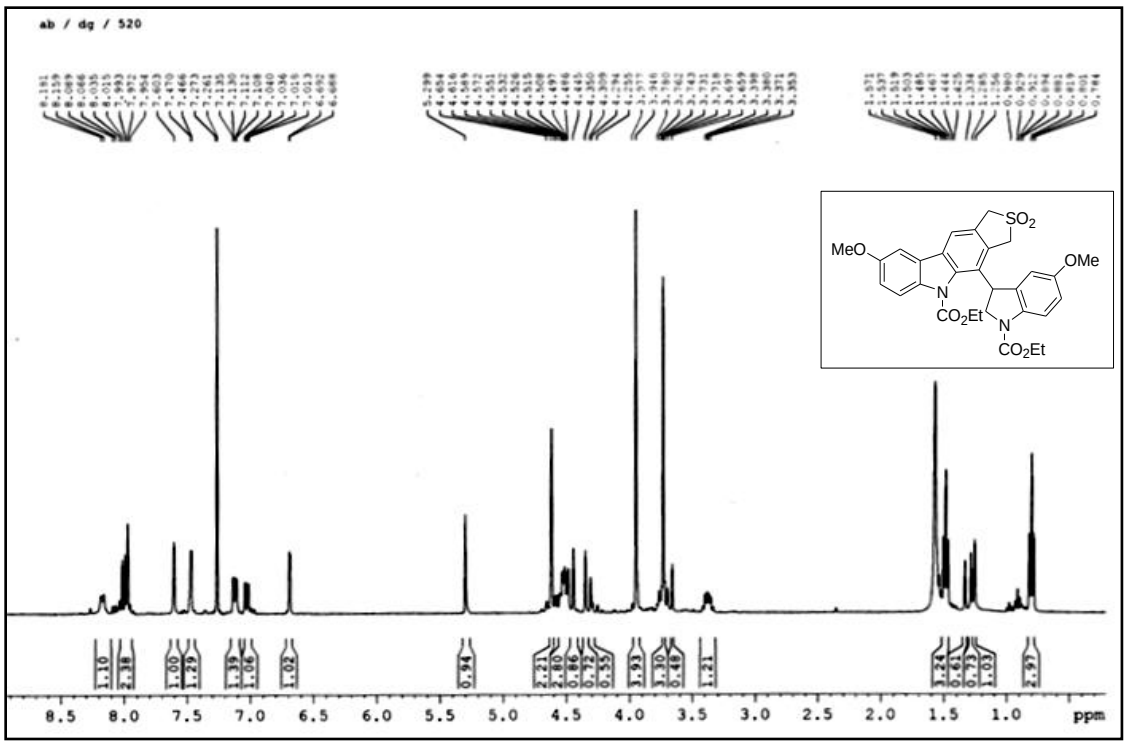


Figure 3.23: ^{1}H-NMR spectrum of compound 3.54e

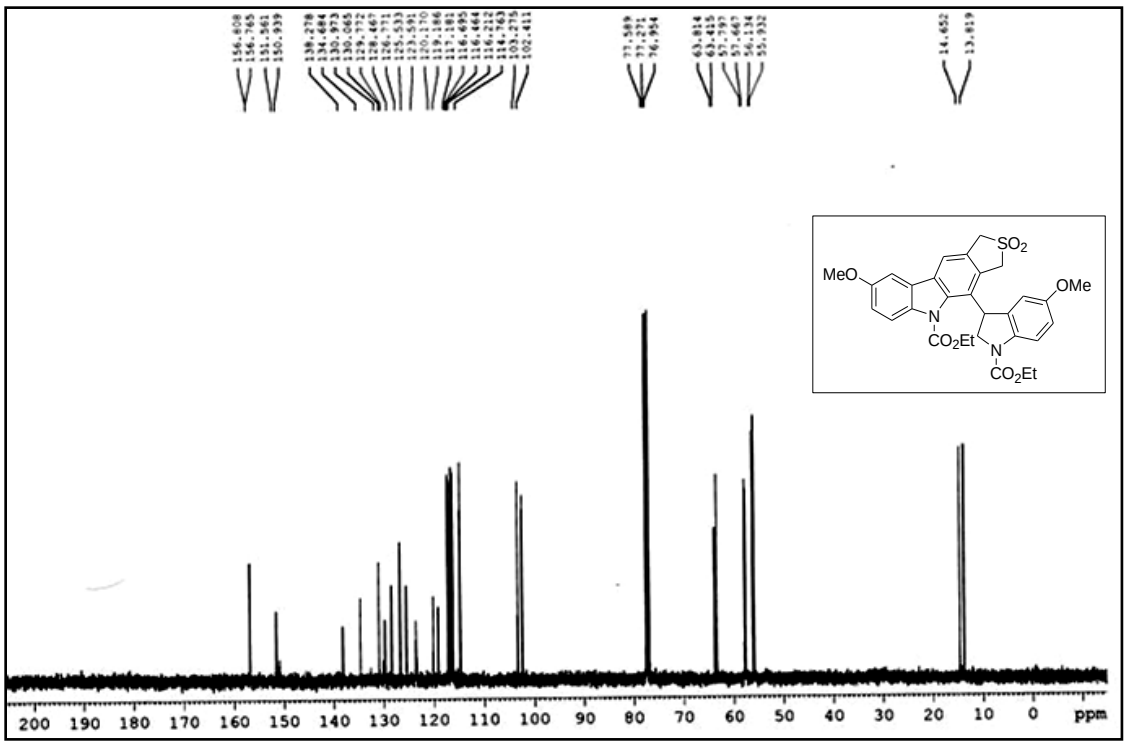


Figure 3.24: ^{13}C-NMR spectrum of compound 3.54e

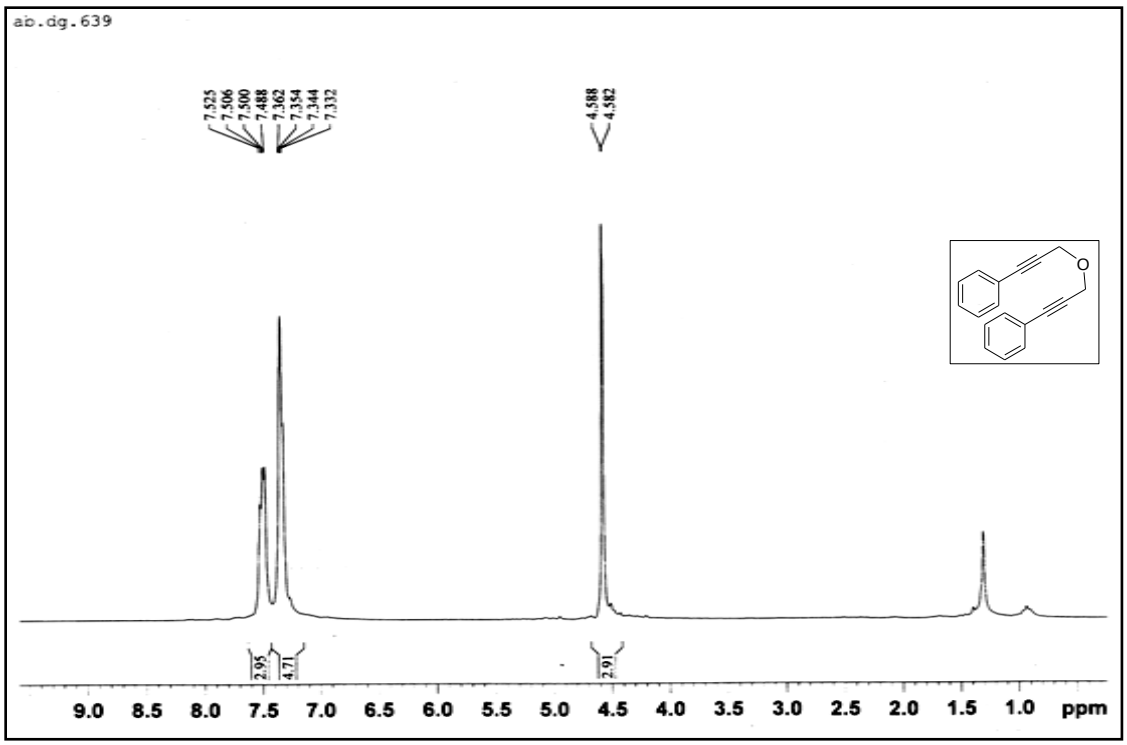


Figure 3.25: ^{1}H-NMR spectrum of compound 3.35

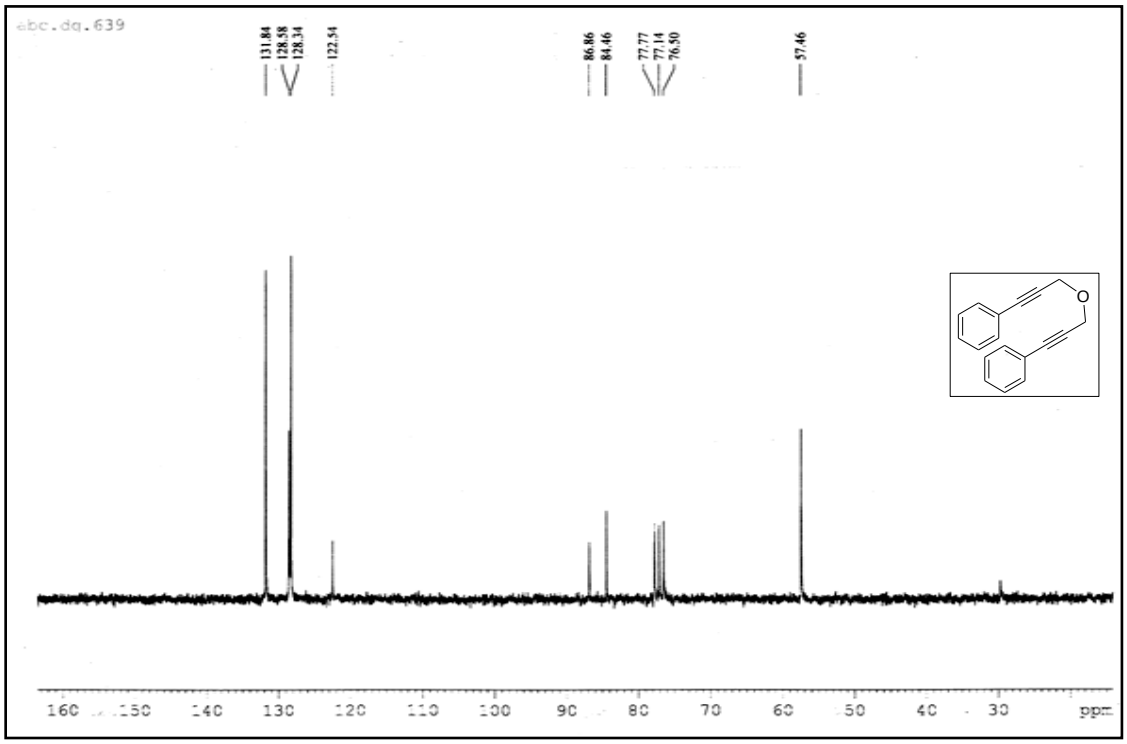


Figure 3.26: ^{13}C-NMR spectrum of compound 3.35

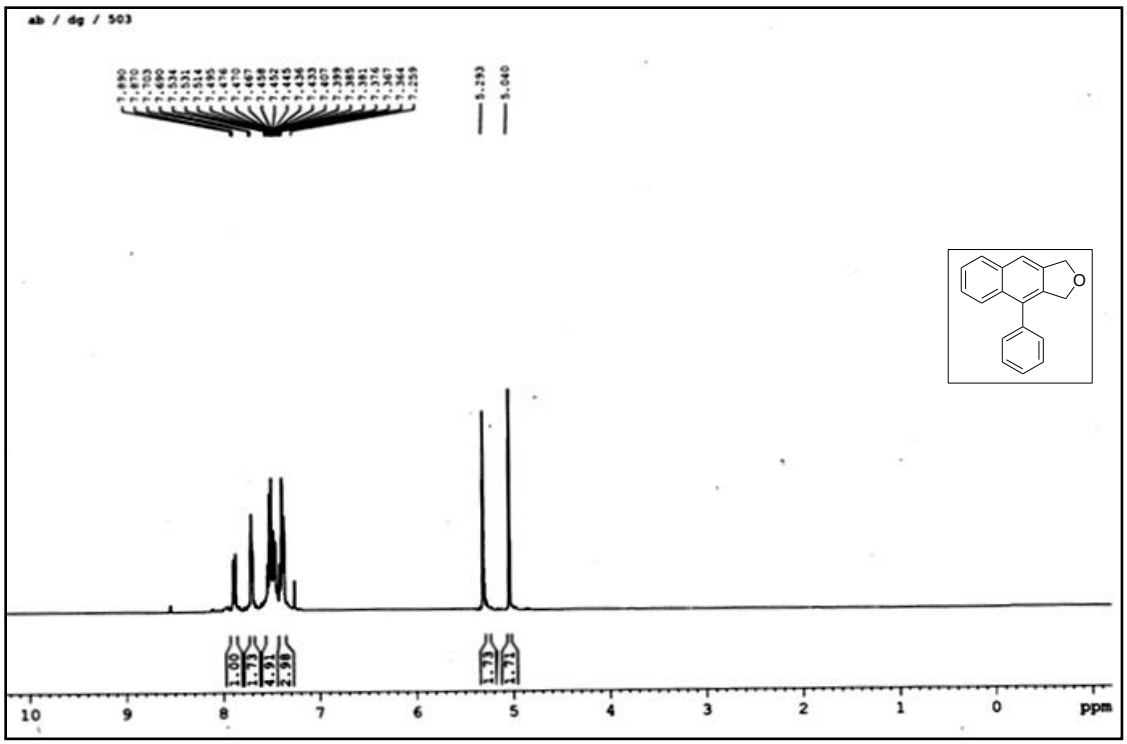


Figure 3.27: ^{1}H-NMR spectrum of compound 3.66f

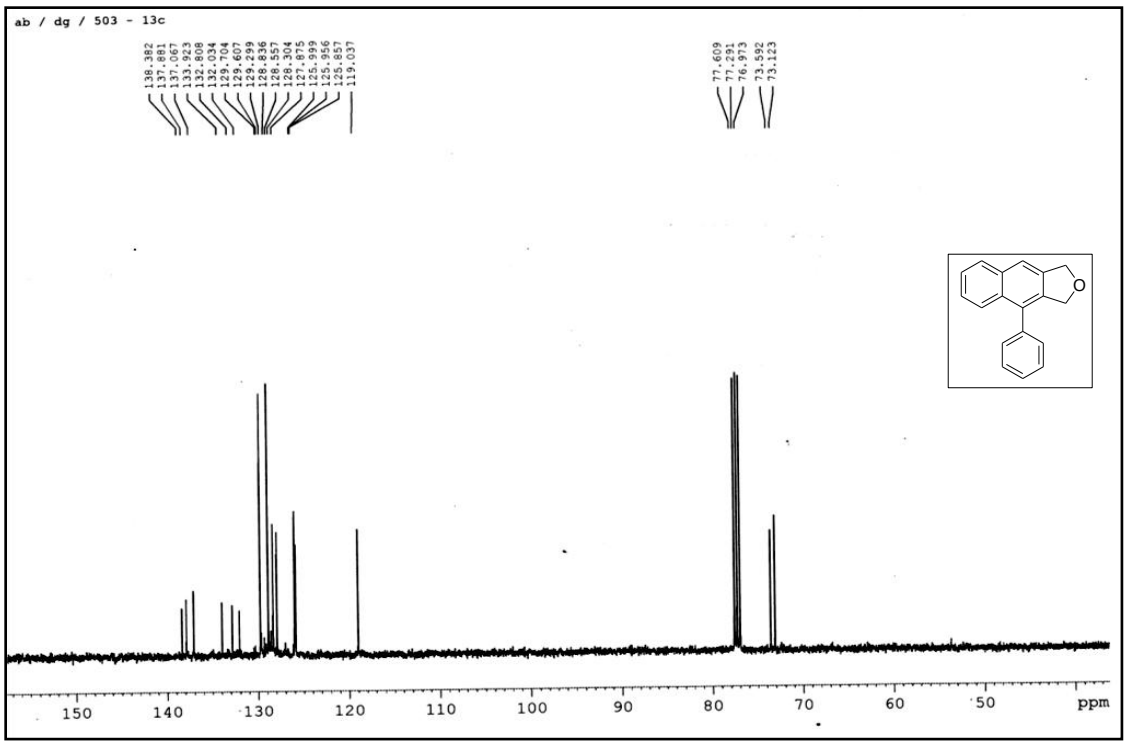


Figure 3.28: ^{13}C-NMR spectrum of compound 3.66f

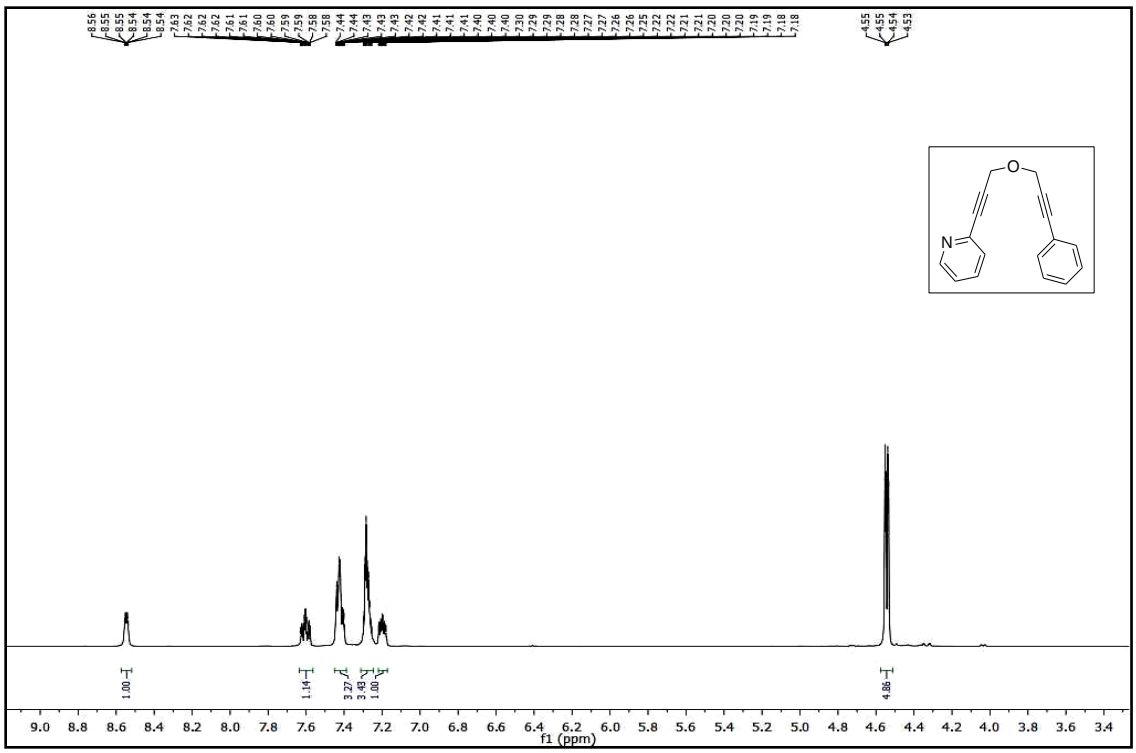


Figure 3.29: ^{1}H-NMR spectrum of compound 3.38

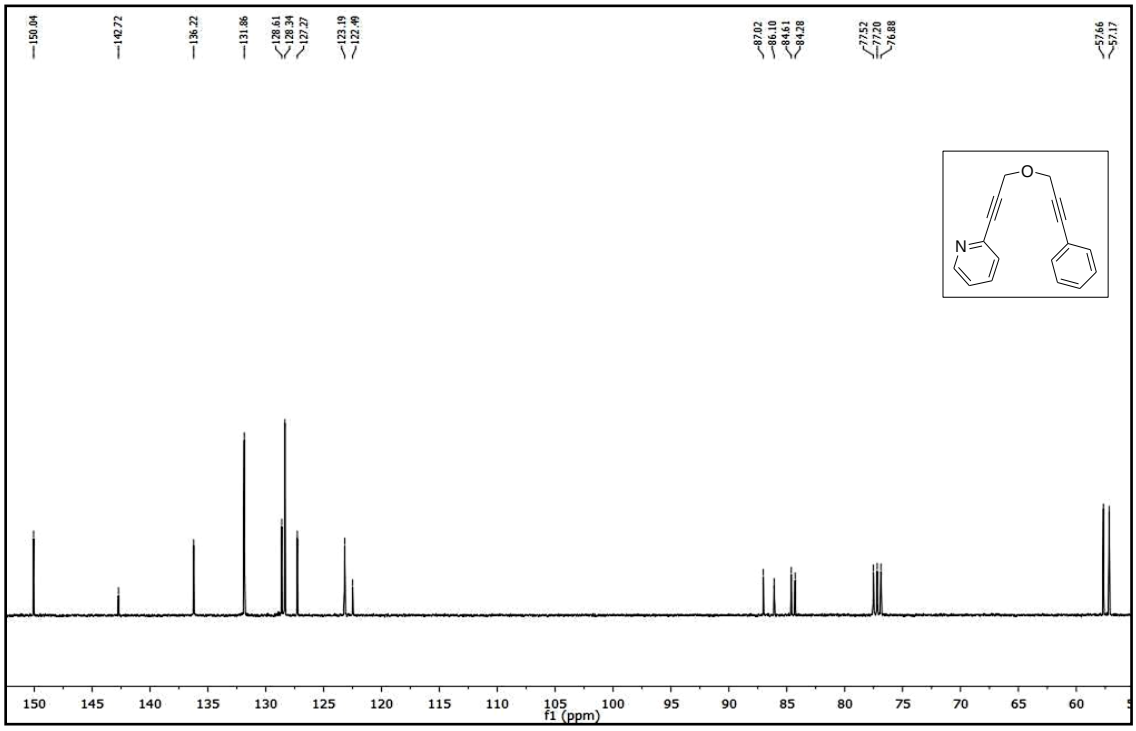


Figure 3.30: ^{13}C-NMR spectrum of compound 3.38

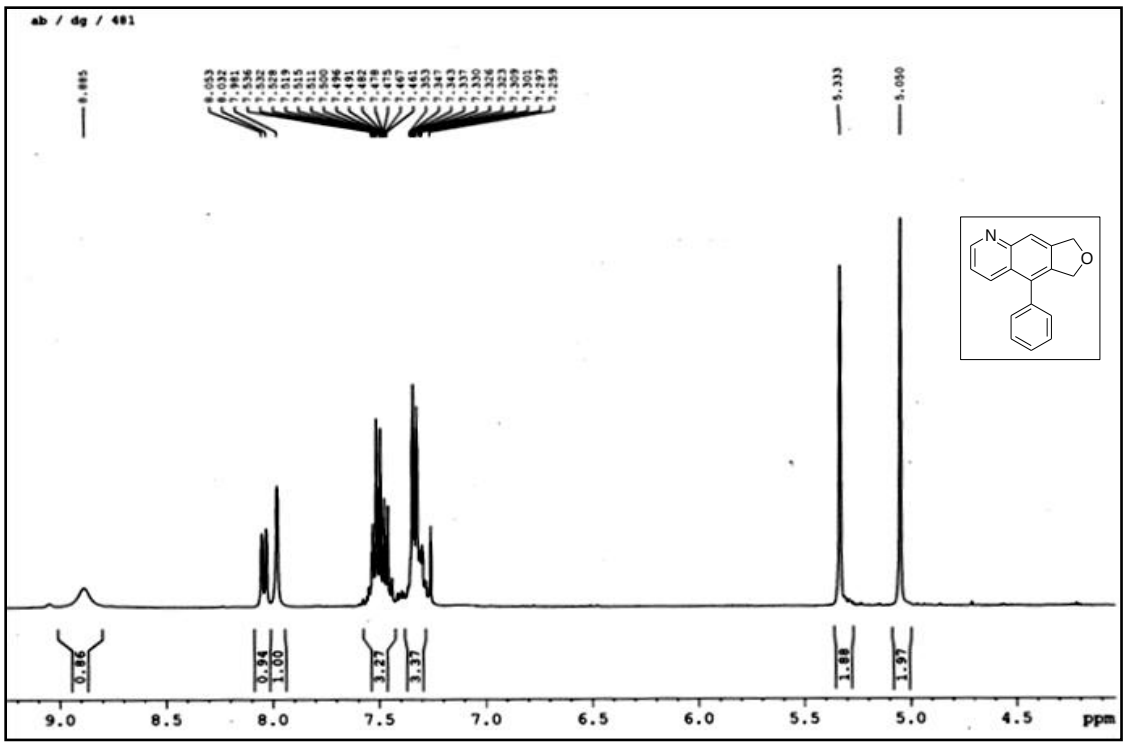


Figure 3.31: ^{1}H-NMR spectrum of compound 3.67g

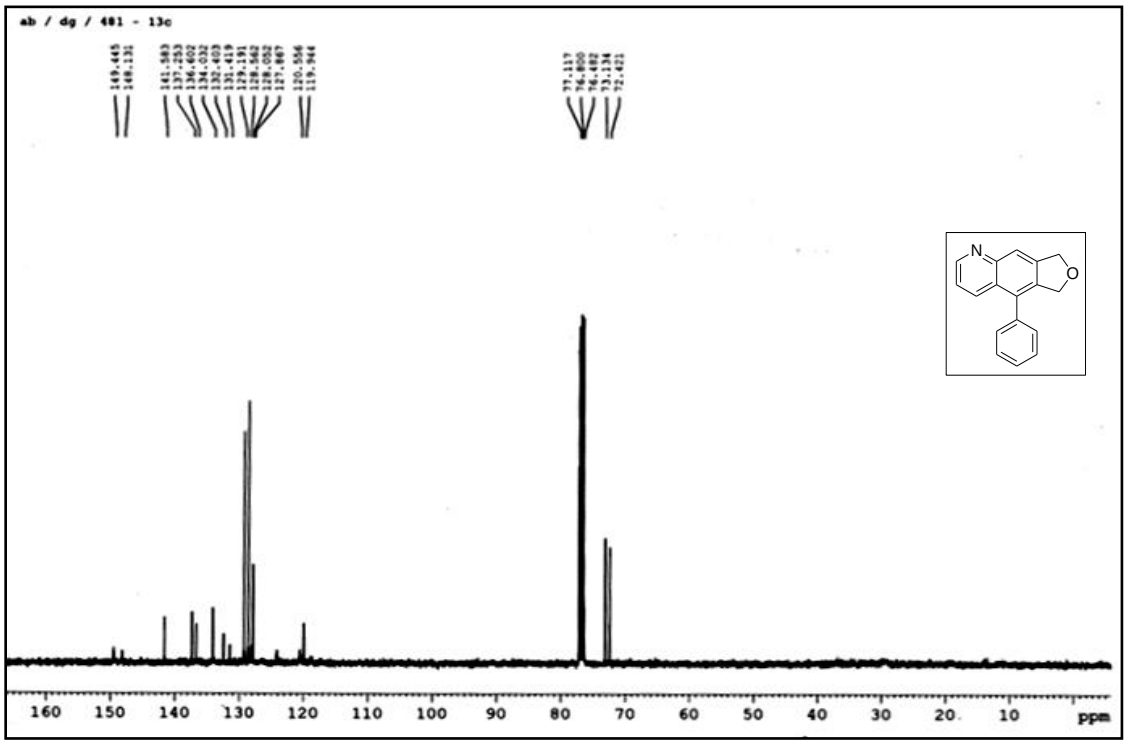


Figure 3.32: ^{13}C-NMR spectrum of compound 3.67g

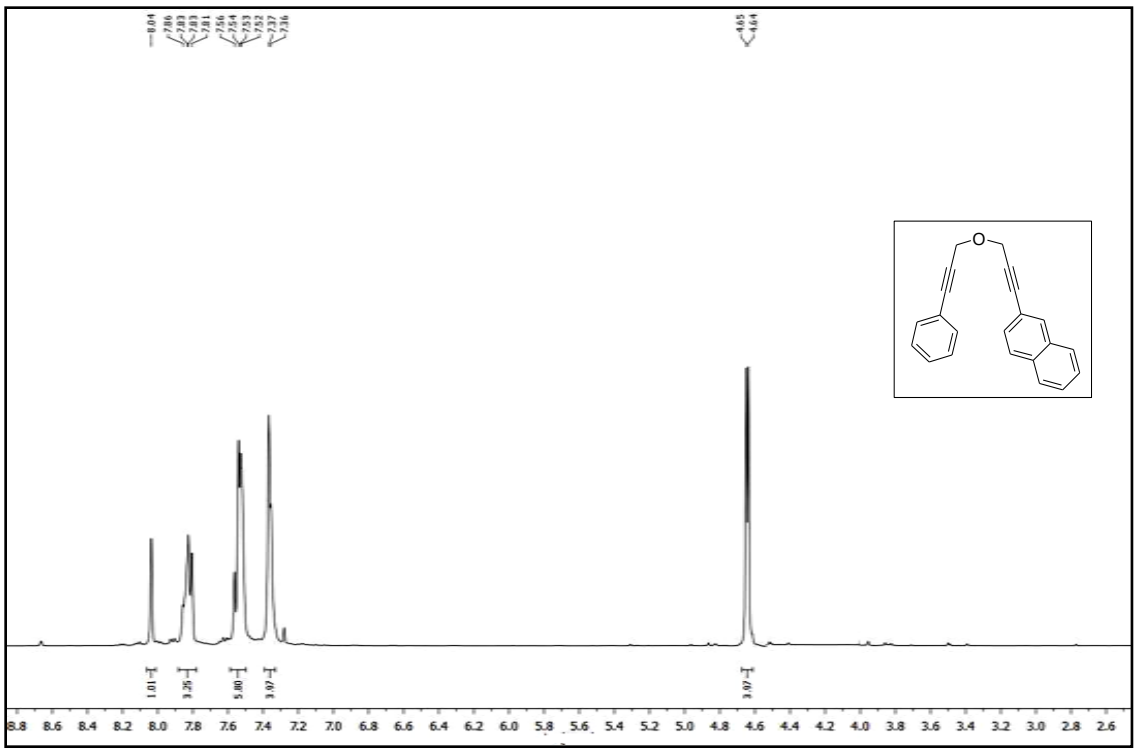


Figure 3.33: ^{1}H-NMR spectrum of compound 3.39

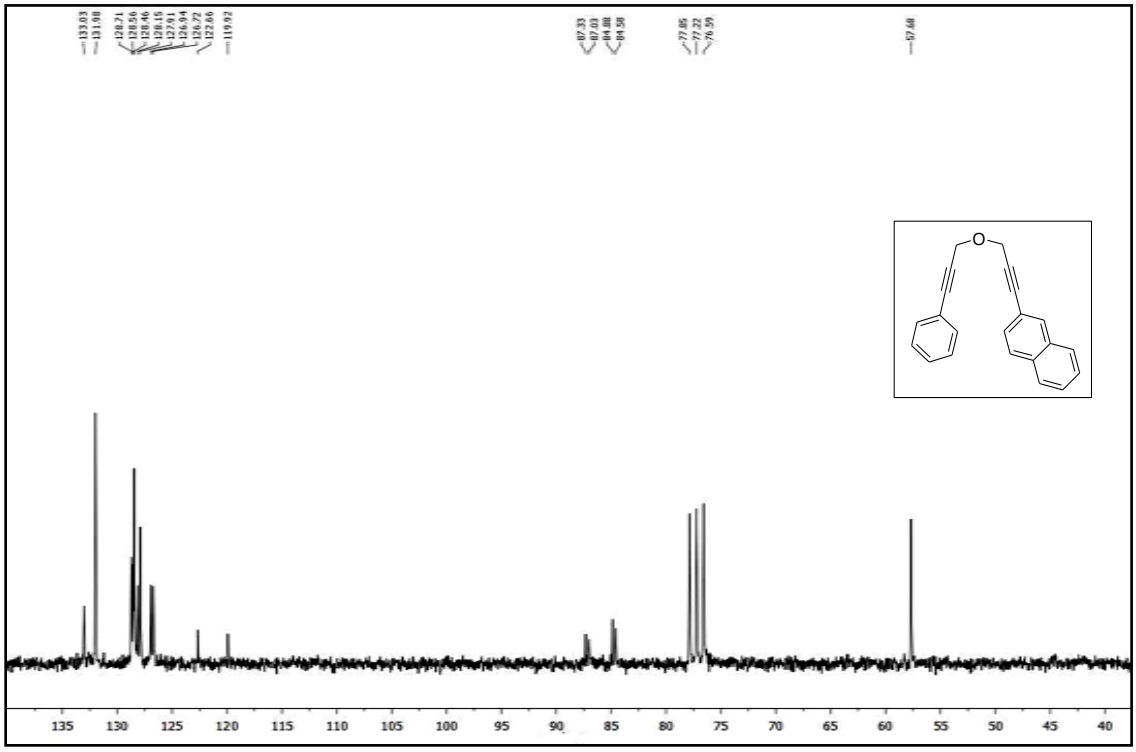


Figure 3.34: ^{13}C-NMR spectrum of compound 3.39

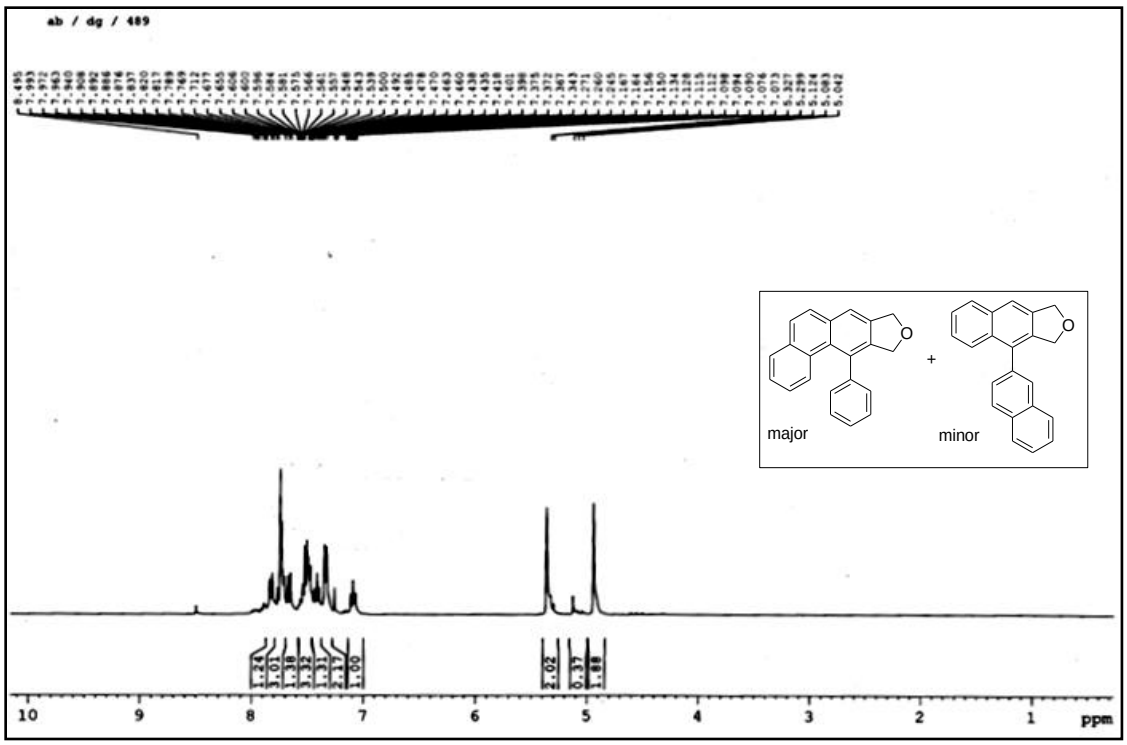


Figure 3.35: ^{1}H-NMR spectrum of compound 3.66h & 3.67h

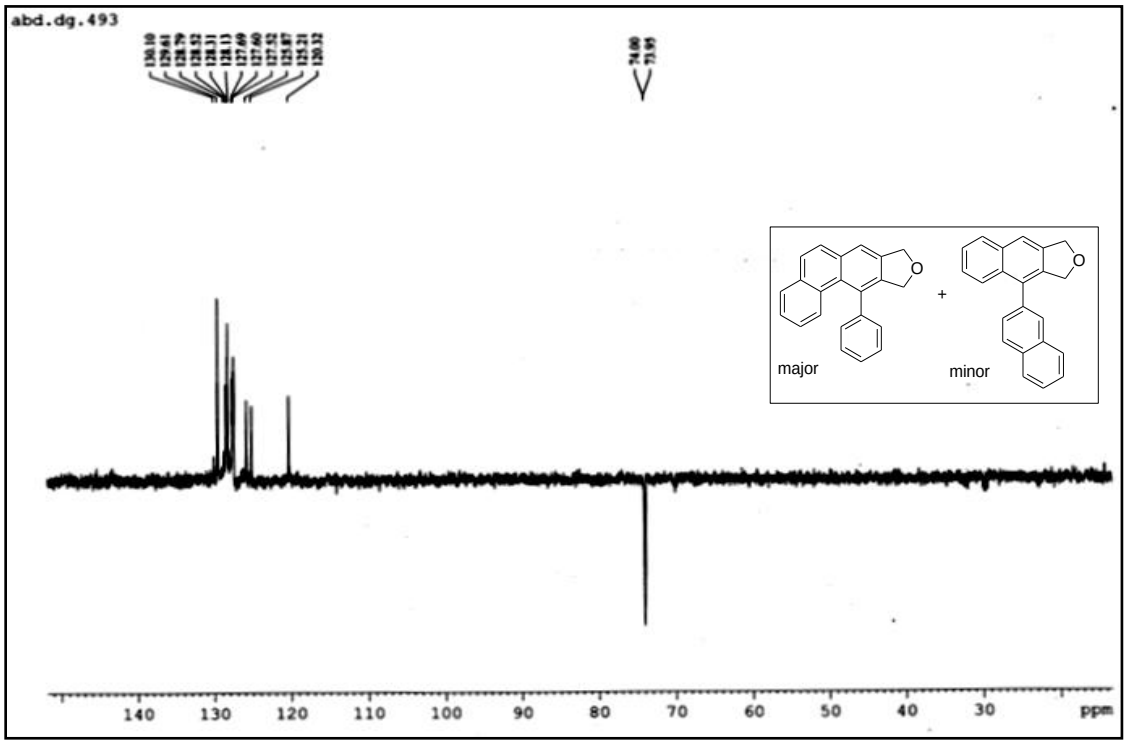


Figure 3.36: DEPT-135 spectrum of compound 3.66h & 3.67h

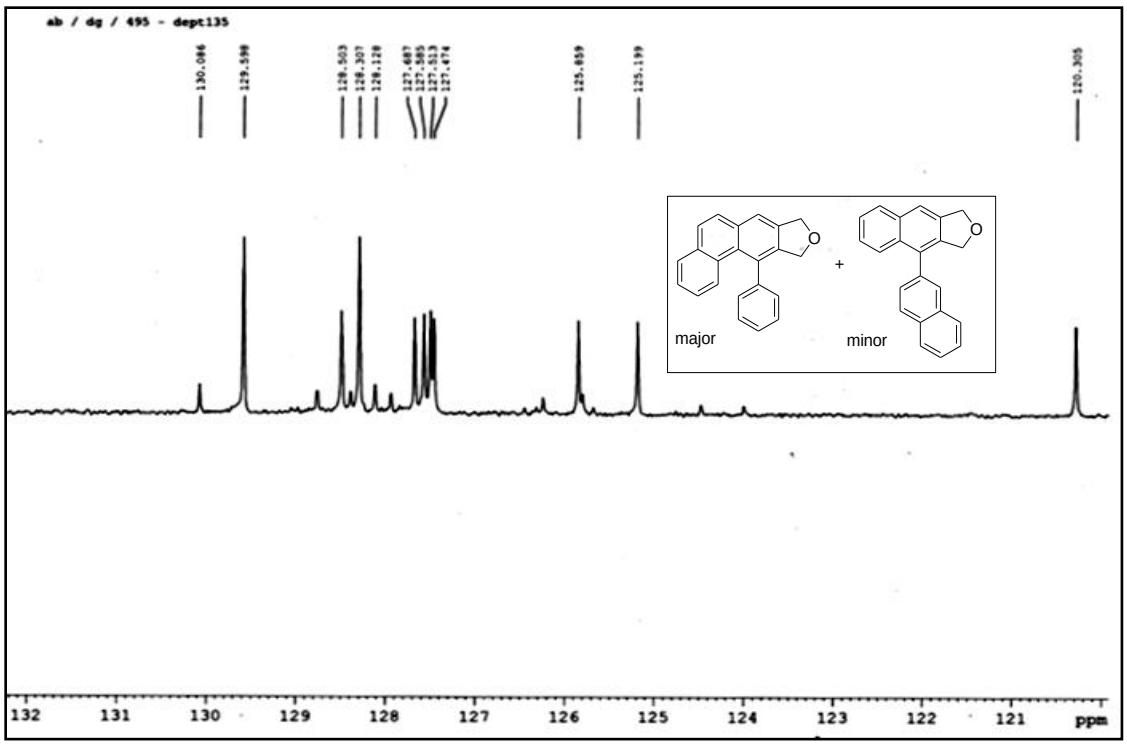


Figure 3.37: DEPT-135 spectrum of compound 3.66h & 3.67h (expanded)

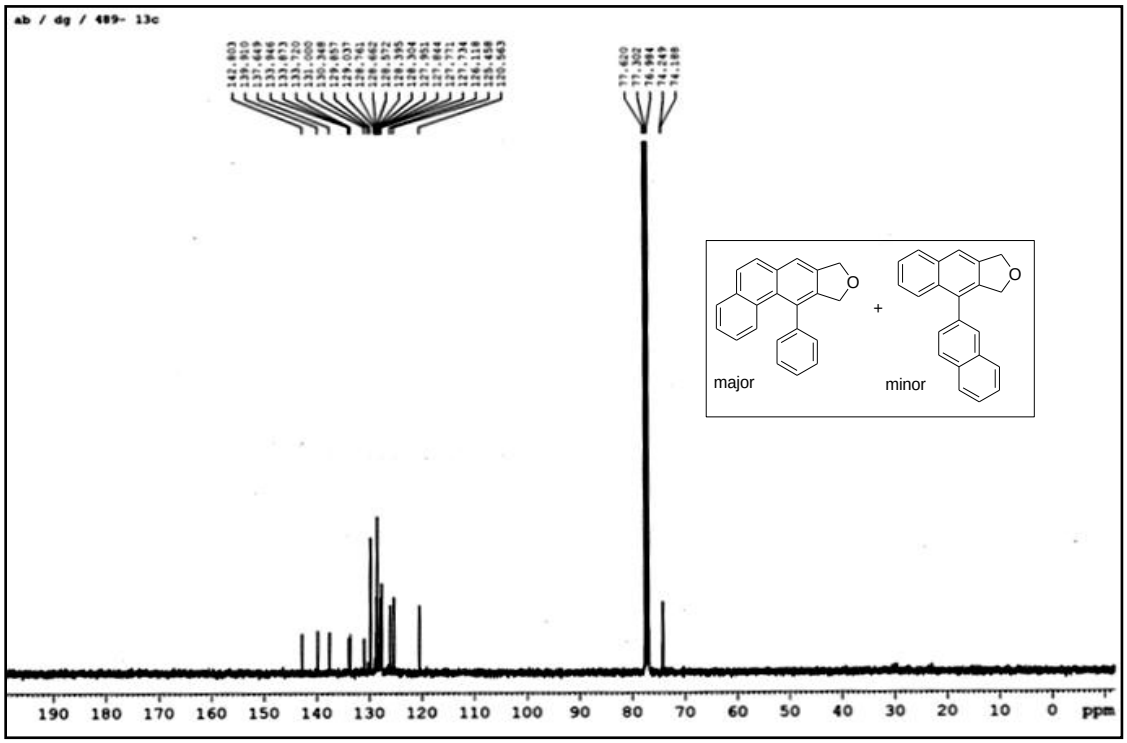


Figure 3.38: ^{13}C-NMR spectrum of compound 3.66h & 3.67h

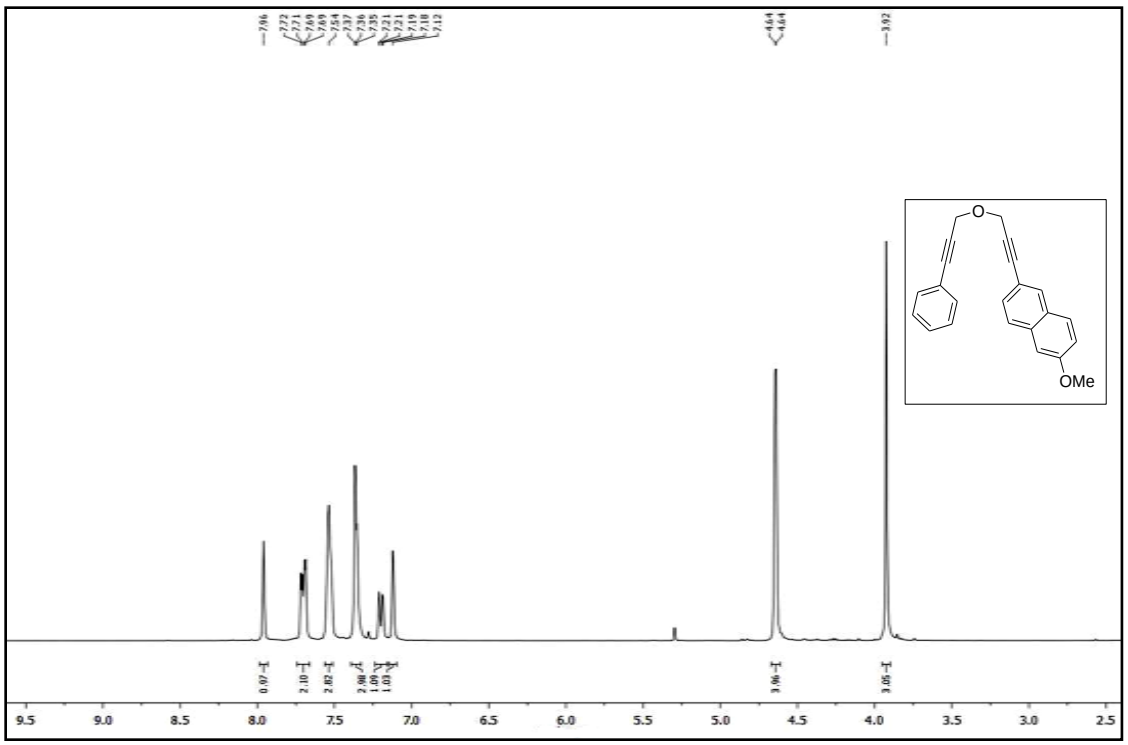


Figure 3.39: ^{1}H-NMR spectrum of compound 3.43

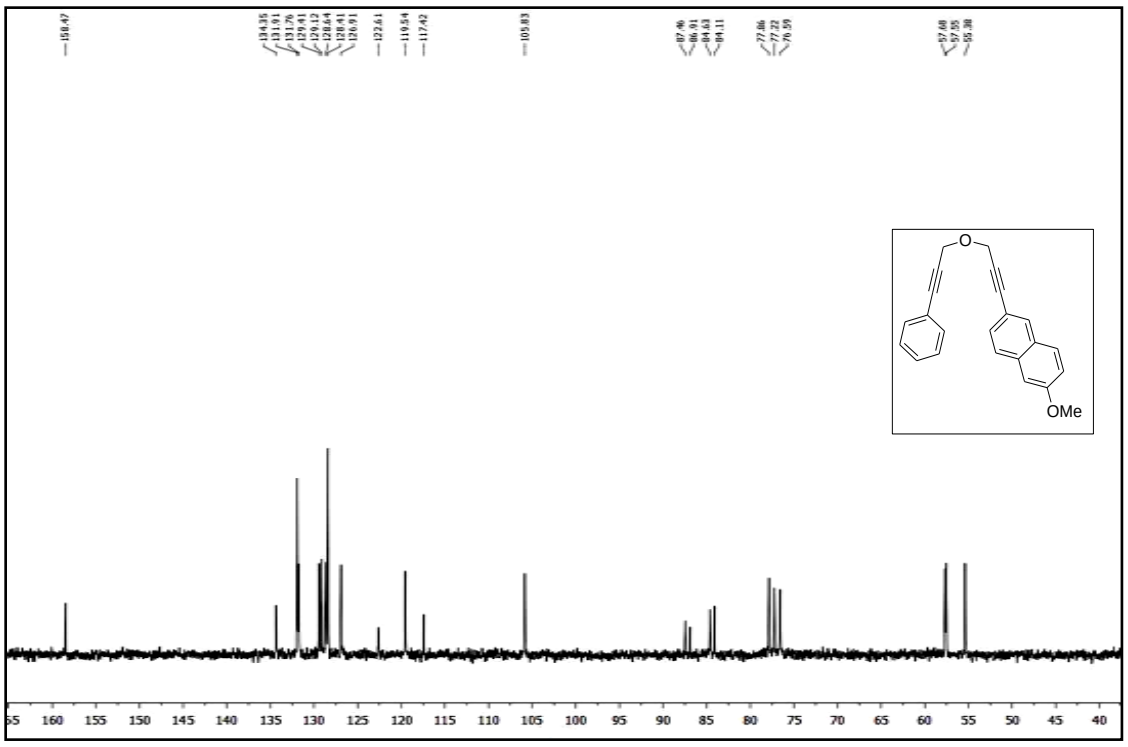


Figure 3.40: ^{13}C-NMR spectrum of compound 3.43

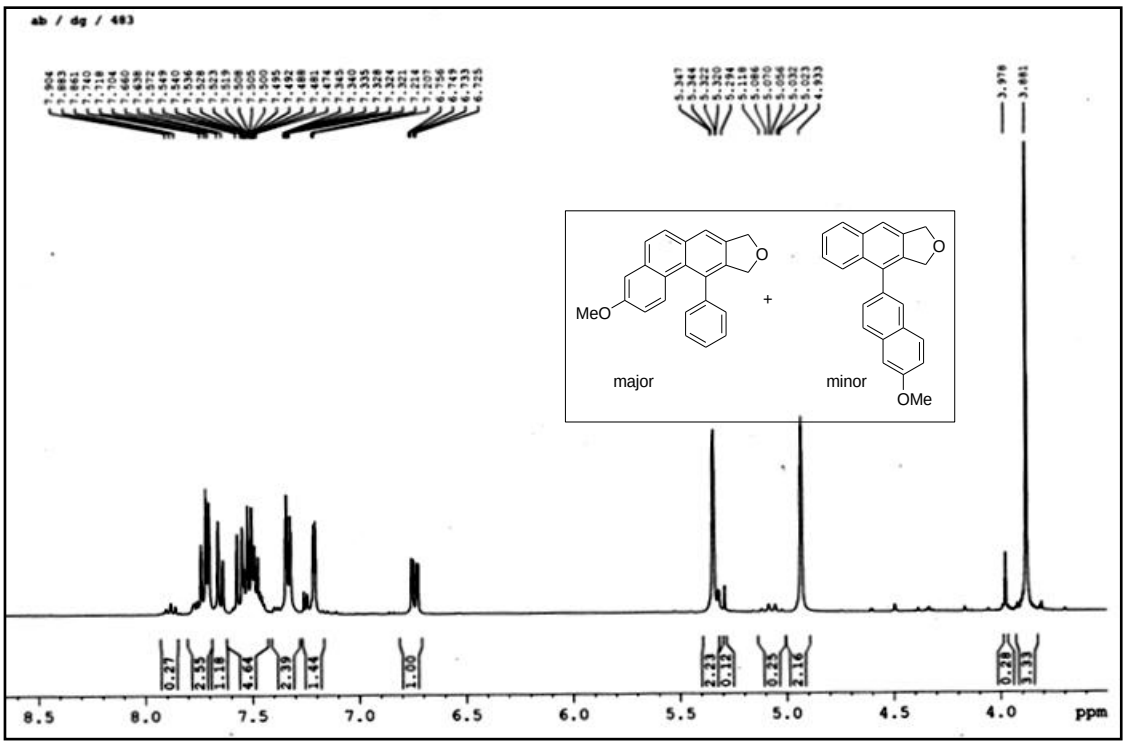


Figure 3.41: ^{1}H-NMR spectrum of compound 3.66i & 3.67i

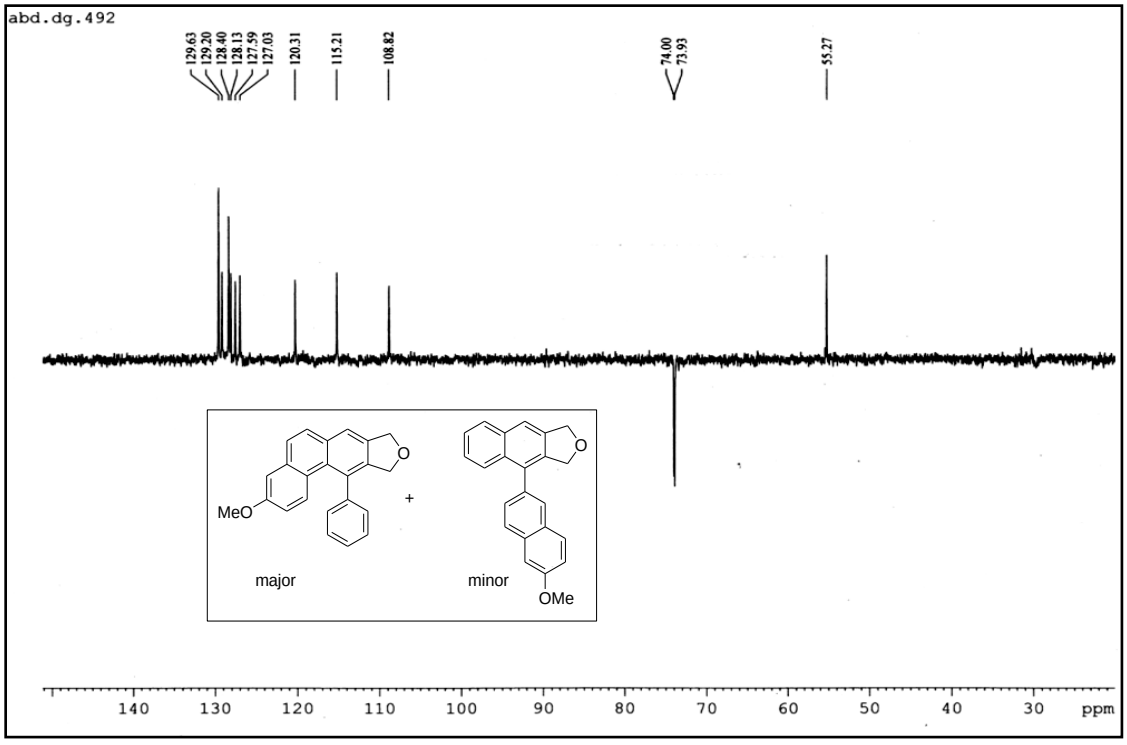


Figure 3.42: DEPT- 135 NMR spectrum of compound 3.66i & 3.67i

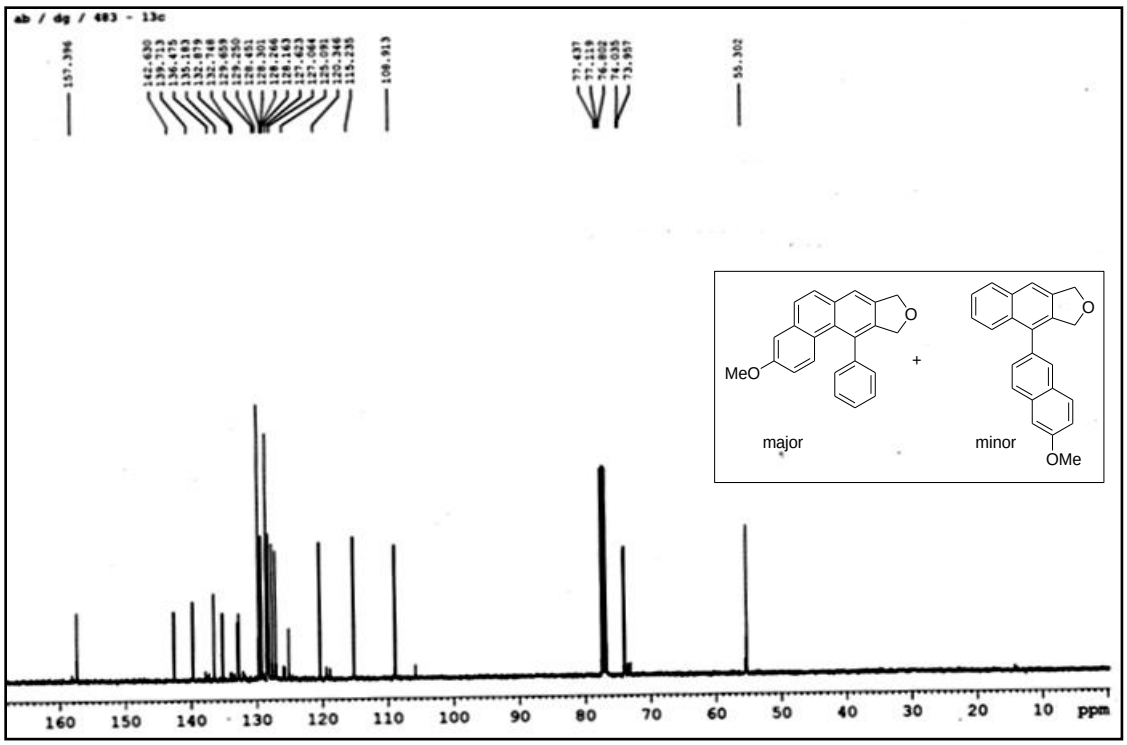


Figure 3.43: ^{13}C-NMR spectrum of compound 3.66i & 3.67i

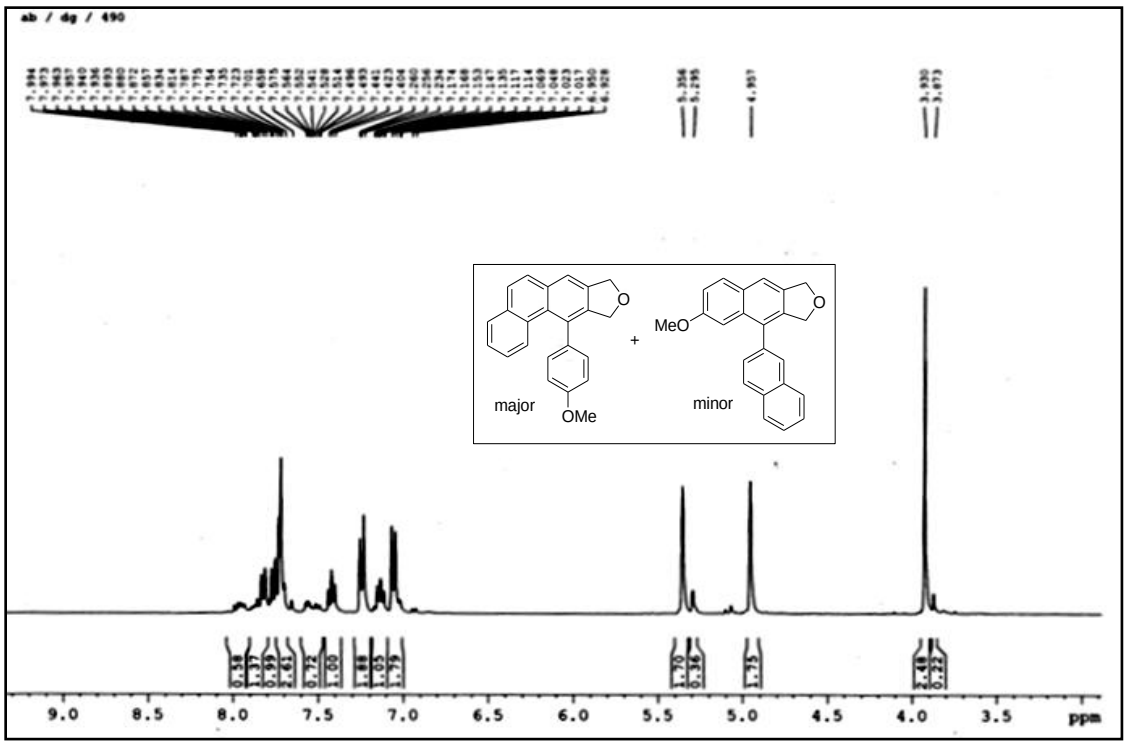


Figure 3.44: ^{1}H-NMR spectrum of compound 3.66j & 3.67j

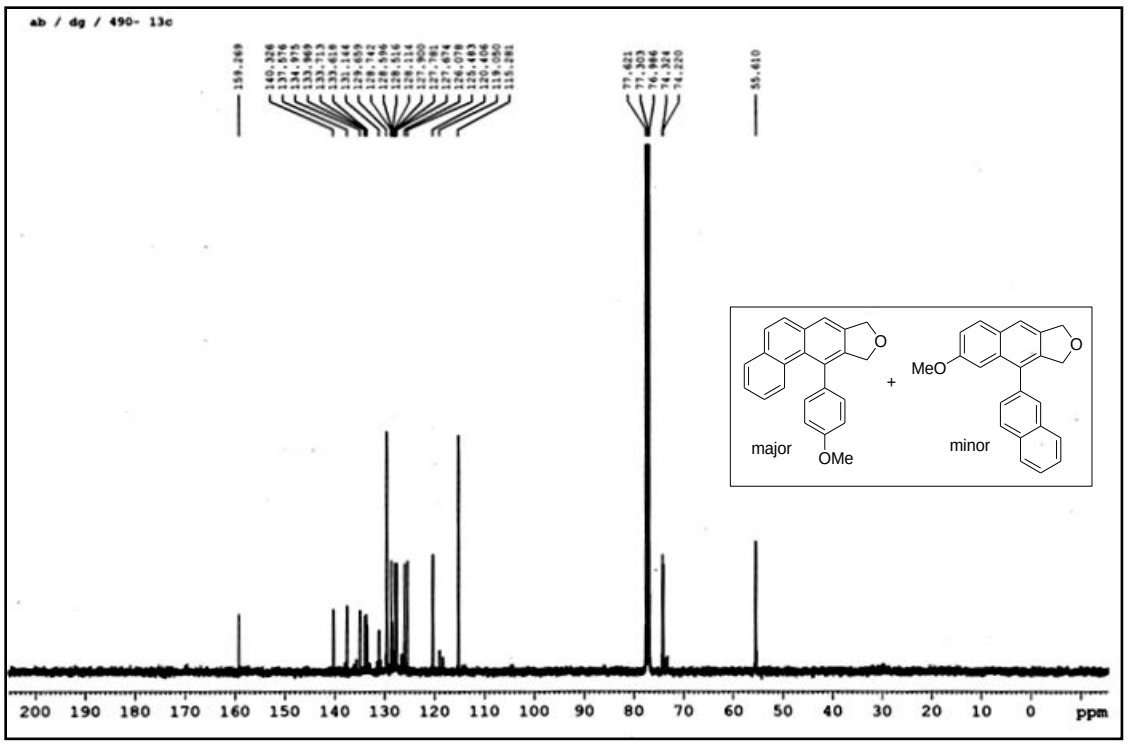


Figure 3.45: ^{13}C-NMR spectrum of compound 3.66j & 3.67j

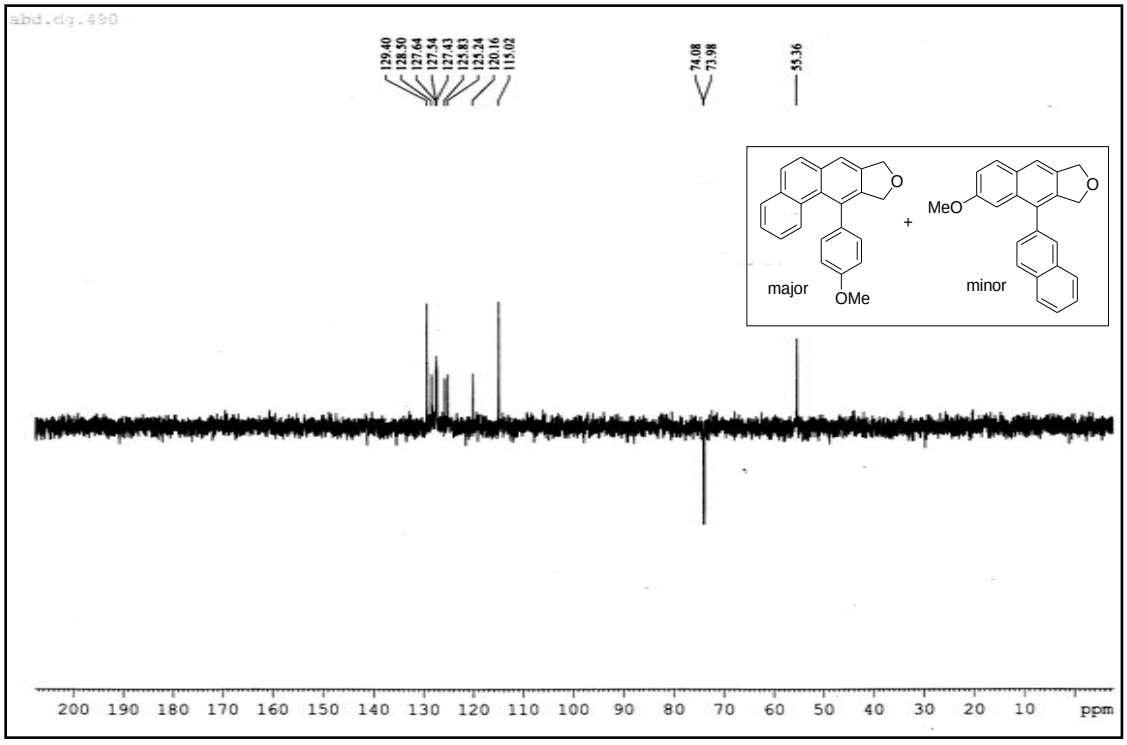


Figure 3.46: DEPT-135 NMR spectrum of compound 3.66j & 3.67j

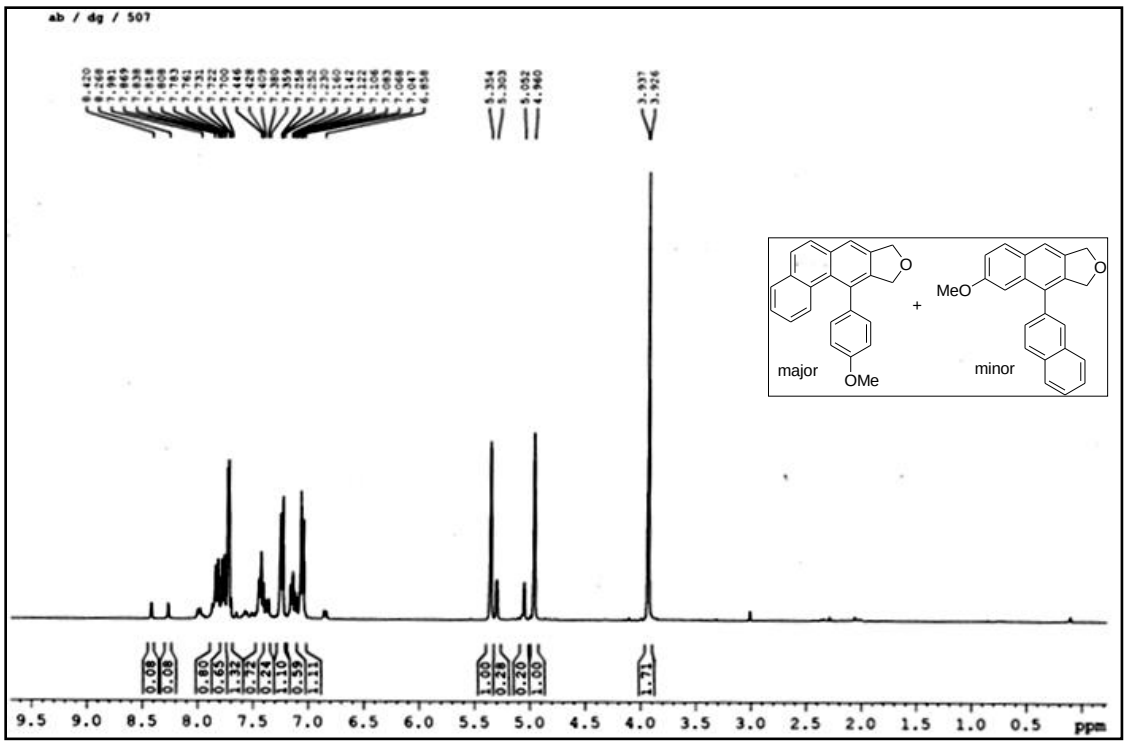


Figure 3.47: ^{1}H-NMR spectrum of compound 3.66j & 3.67j (solvent phase)

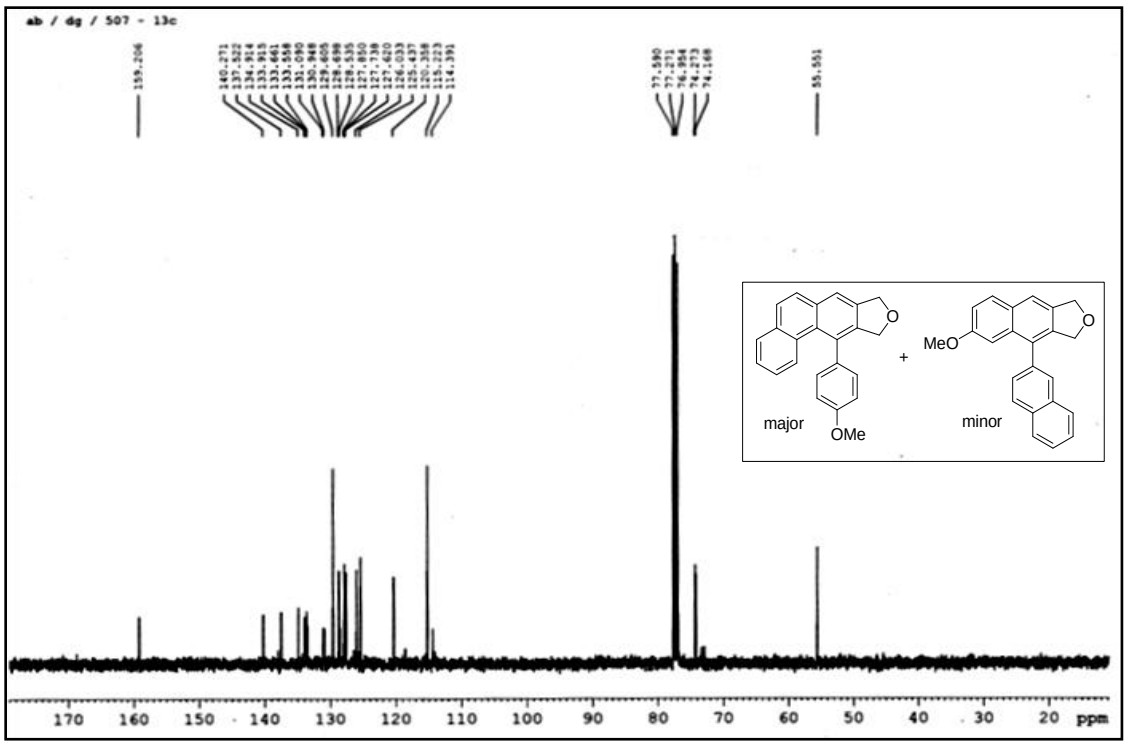


Figure 3.48: ^{13}C-NMR spectrum of compound 3.66j & 3.67j (solvent phase)

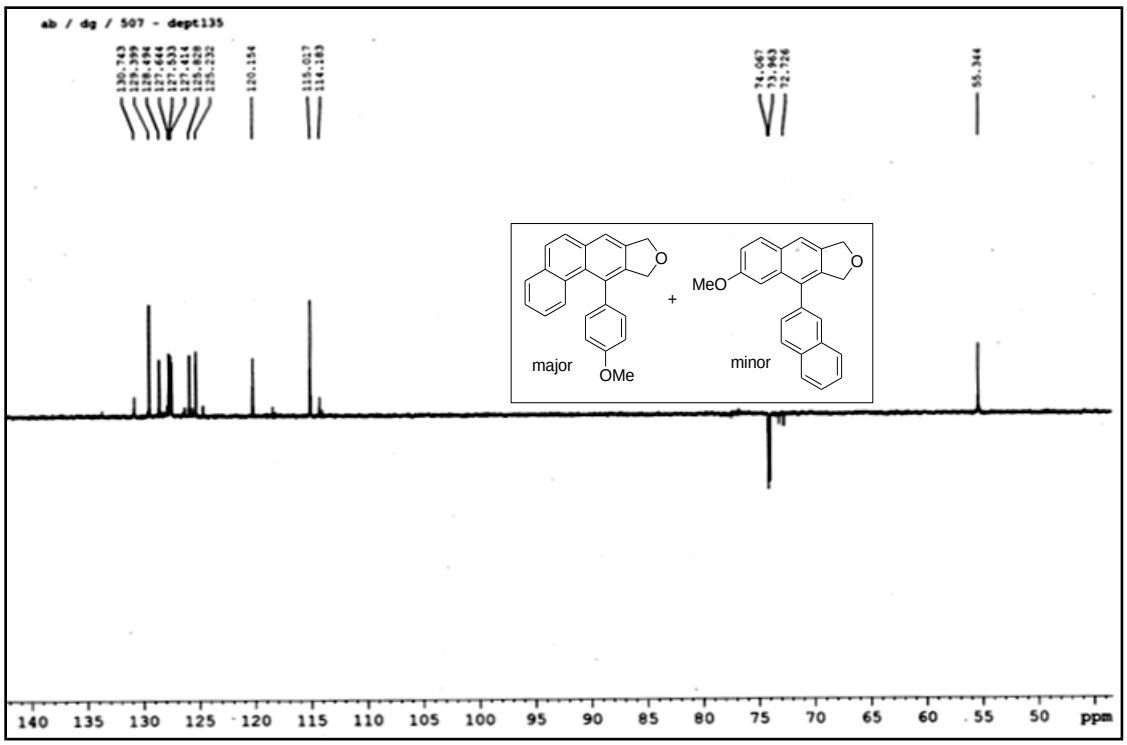


Figure 3.49: DEPT-135 NMR spectrum of compound 3.66j & 3.67j (solvent phase)

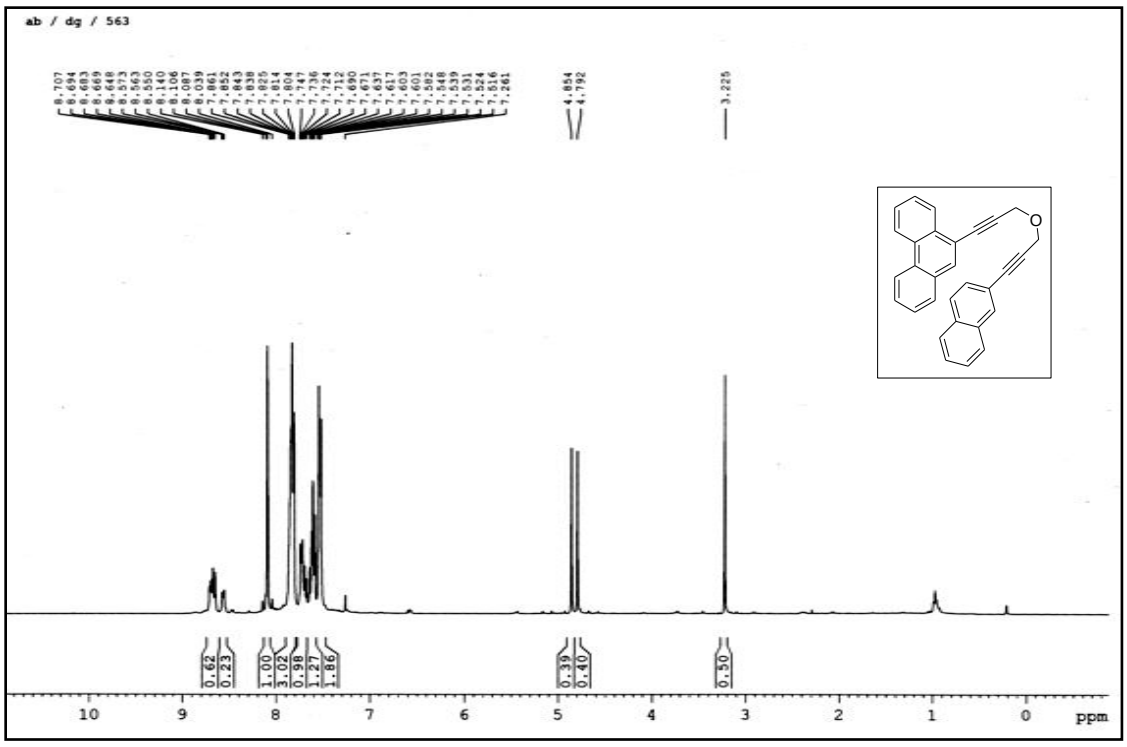


Figure 3.50: ^{1}H-NMR spectrum of compound 3.51

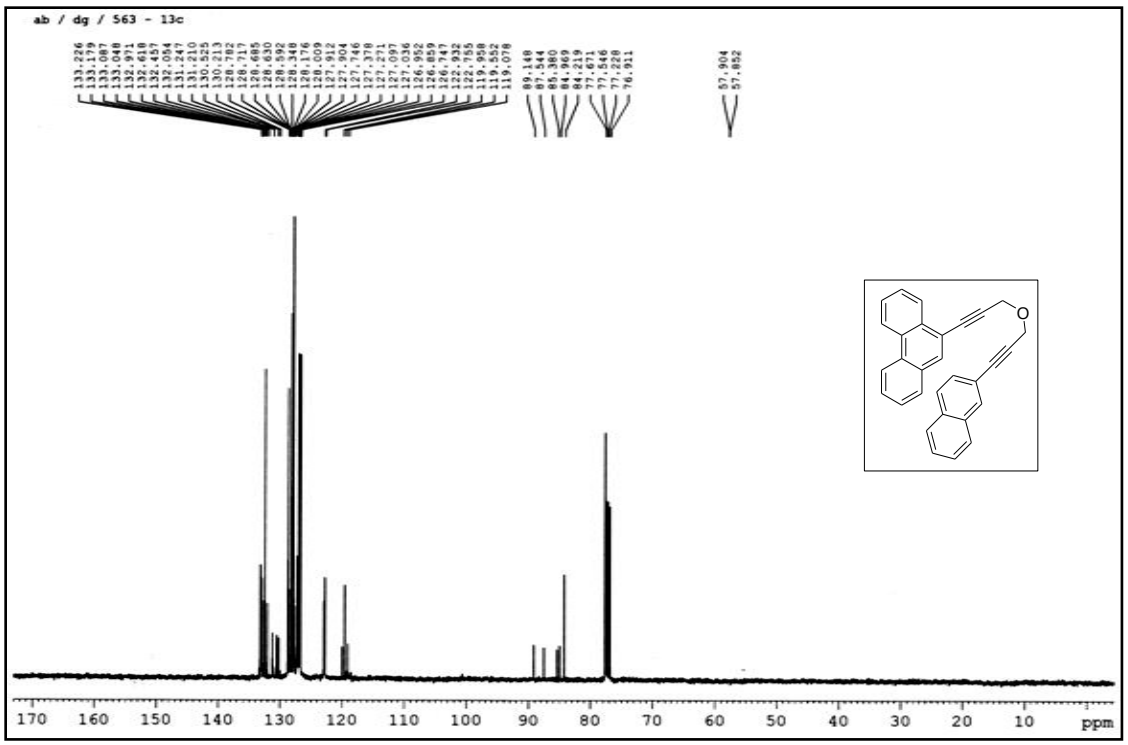


Figure 3.51: ^{13}C-NMR spectrum of compound 3.51

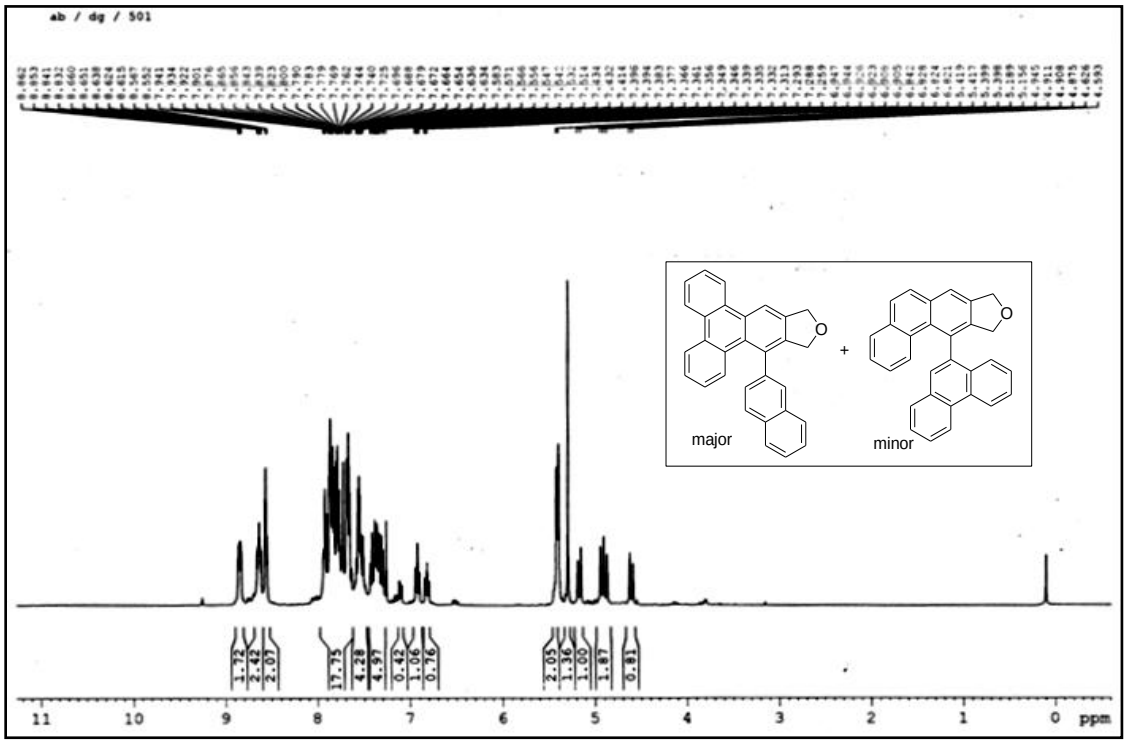


Figure 3.52: ^{1}H-NMR spectrum of compound 3.66k & 3.67k

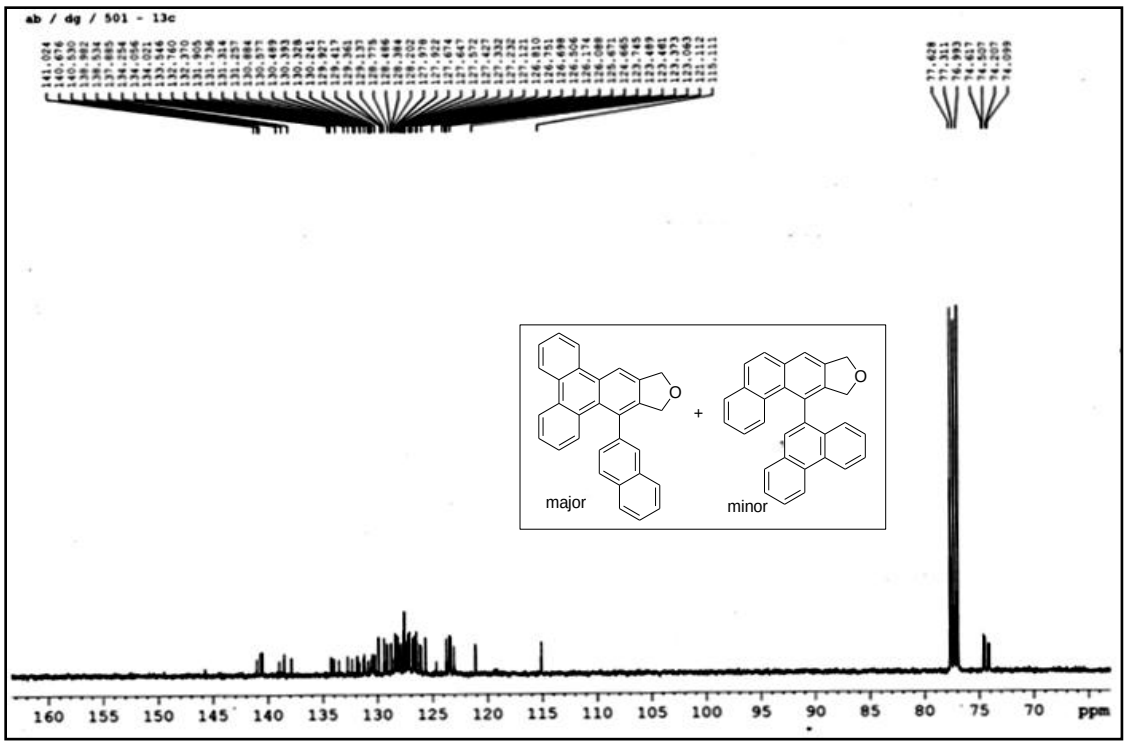


Figure 3.53: ^{13}C-NMR spectrum of compound 3.66k & 3.67k

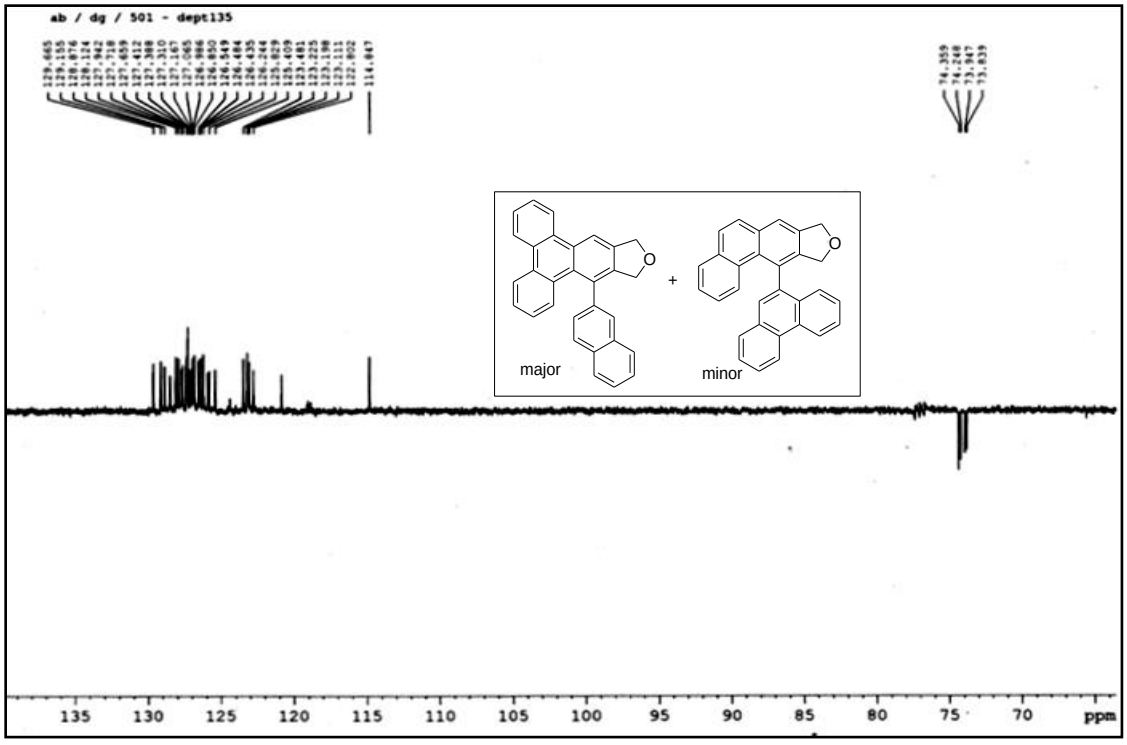


Figure 3.54: DEPT-135 NMR spectrum of compound 3.66k & 3.67k

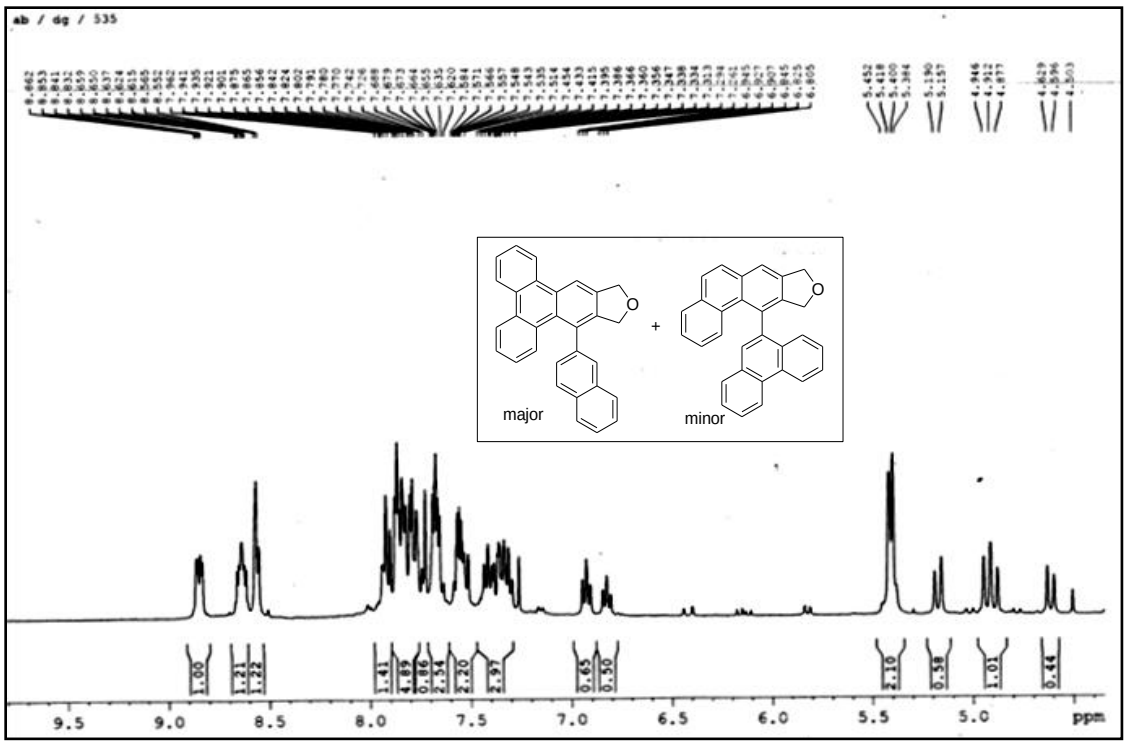


Figure 3.55: ^{1}H-NMR spectrum of compound 3.66k & 3.67k (solvent phase)

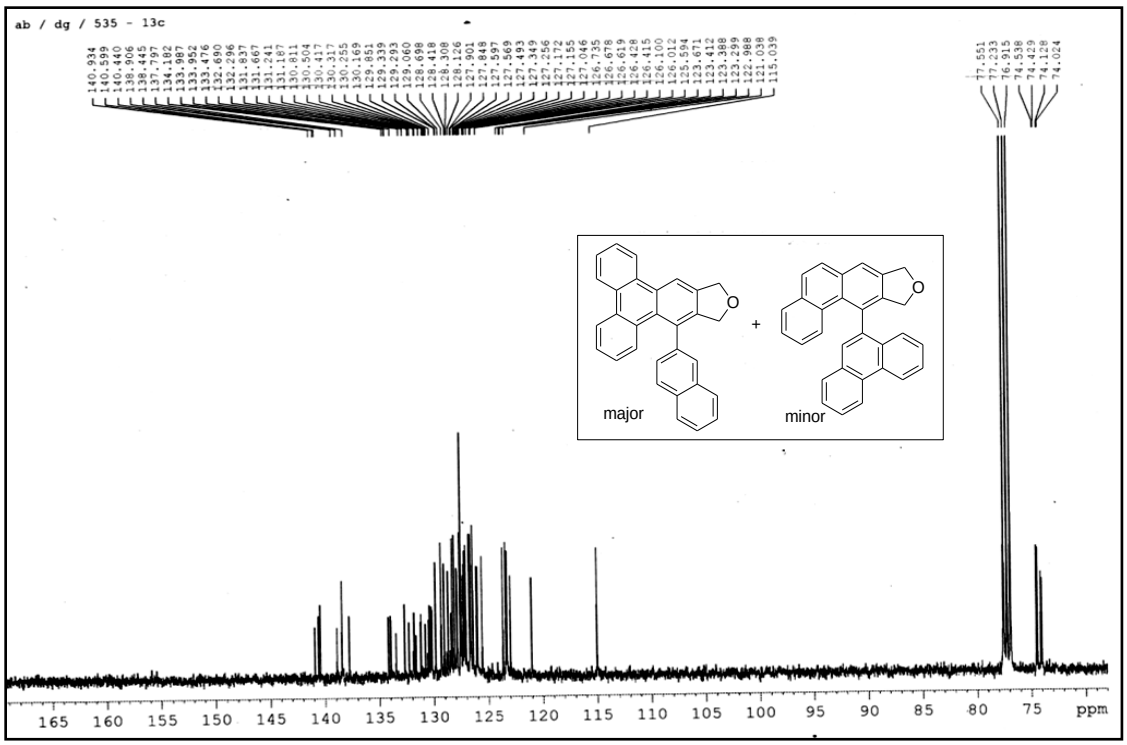


Figure 3.56: ^{13}C-NMR spectrum of compound 3.66k & 3.67k (solvent phase)

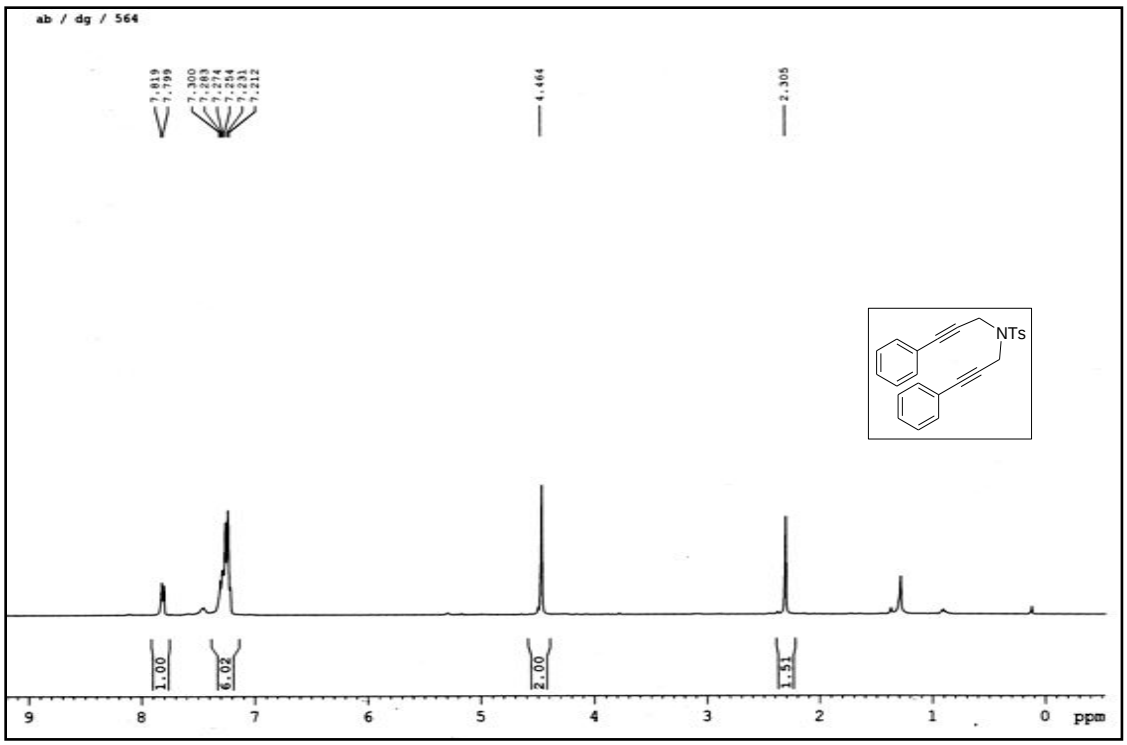


Figure 3.57: ^{1}H-NMR spectrum of compound 3.56

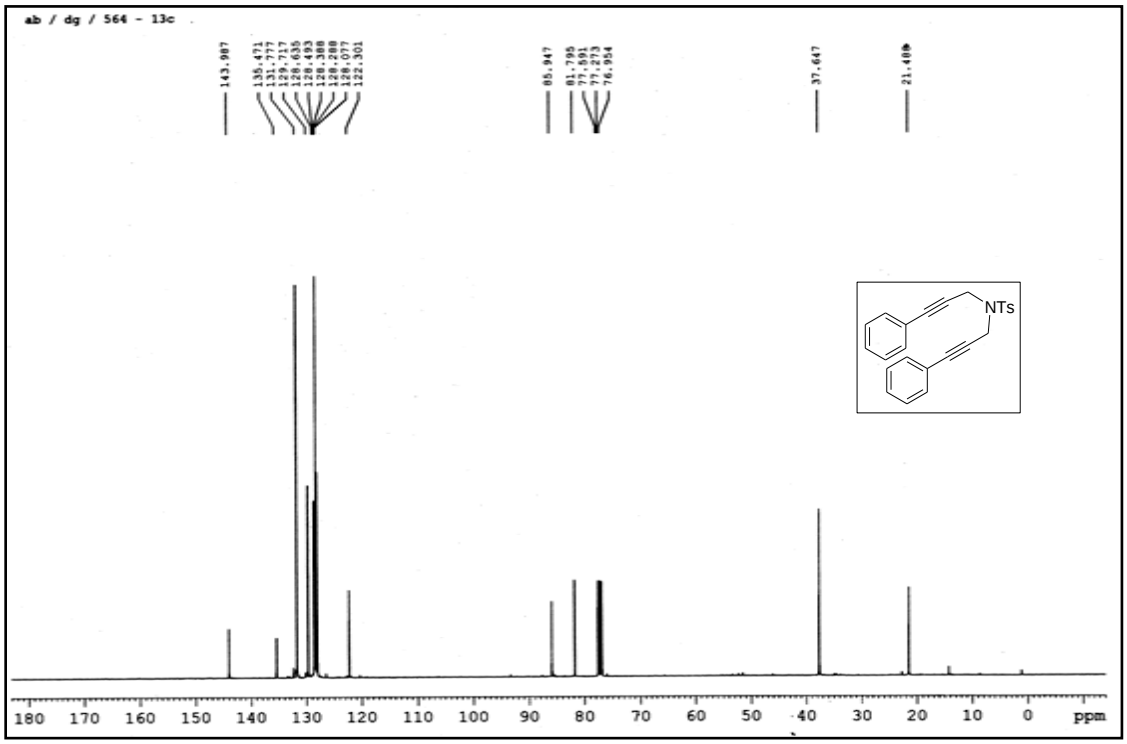


Figure 3.58: ^{13}C-NMR spectrum of compound 3.56

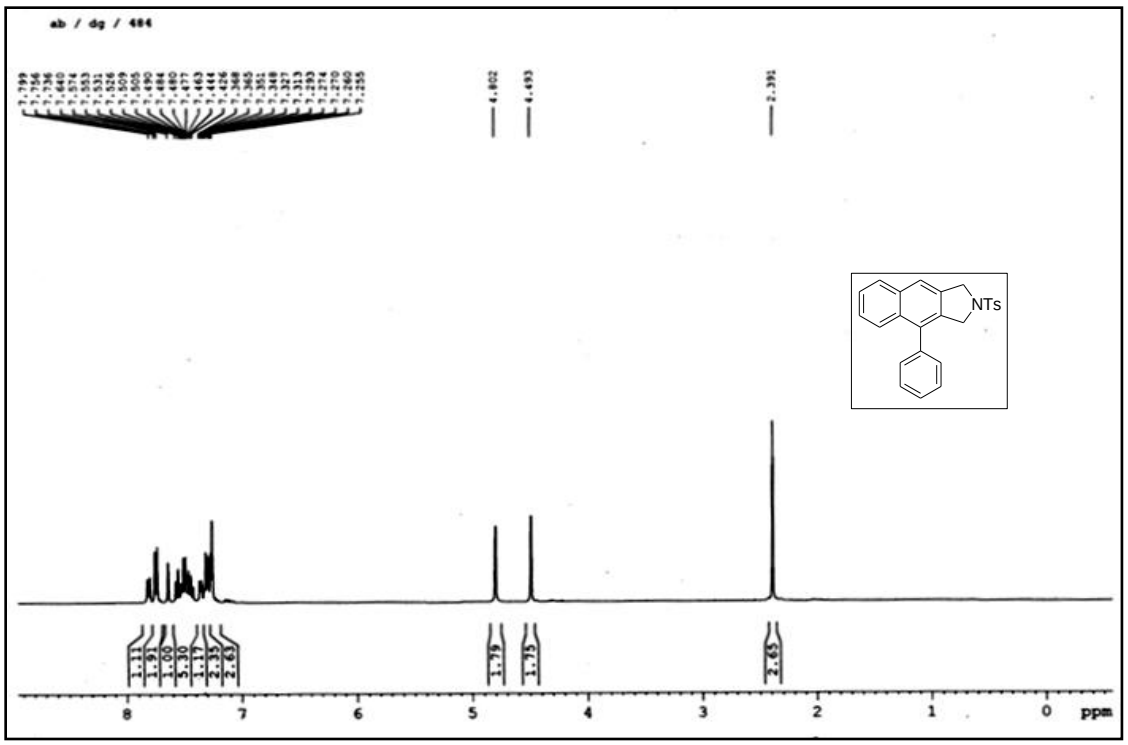


Figure 3.59: ^{1}H-NMR spectrum of compound 3.68l

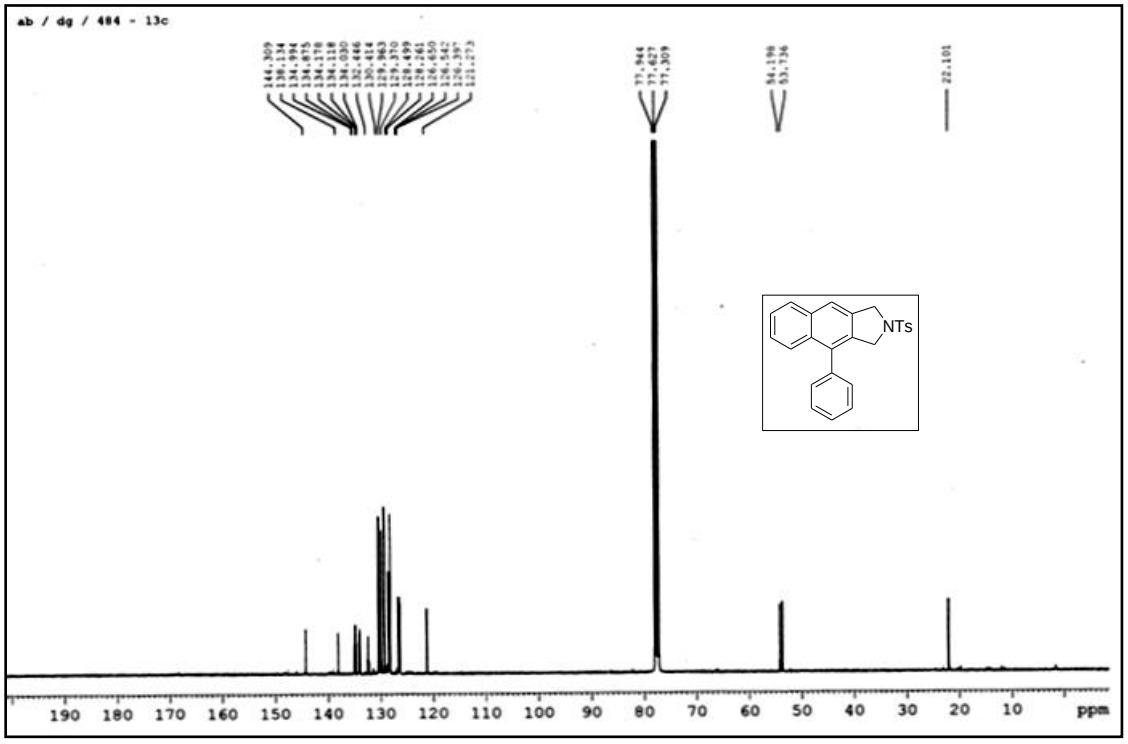


Figure 3.60: ^{13}C-NMR spectrum of compound 3.68l

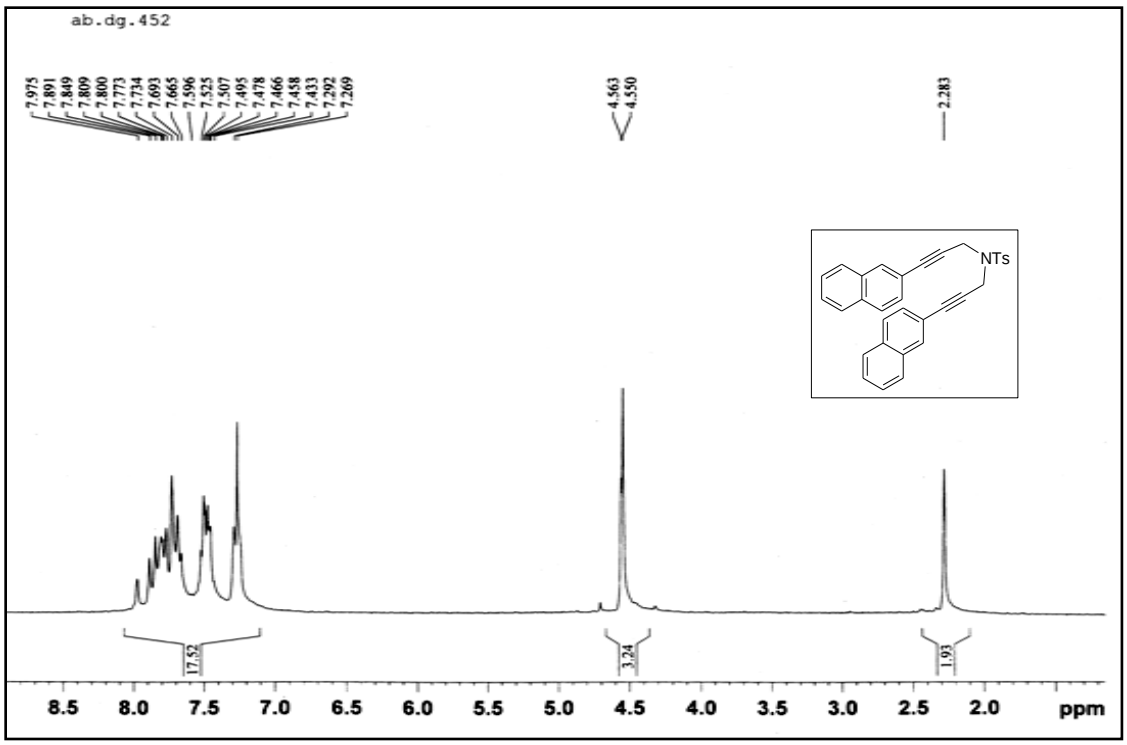


Figure 3.61: ^{1}H-NMR spectrum of compound 3.58

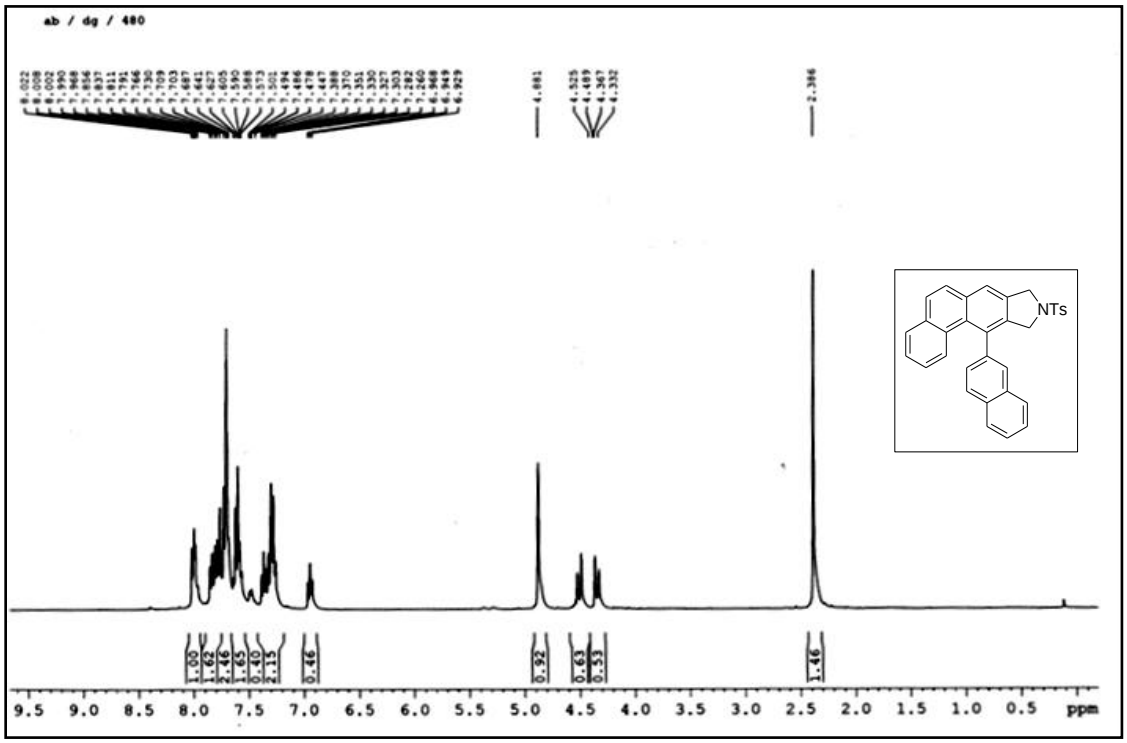


Figure 3.62: ^{1}H-NMR spectrum of compound 3.68m

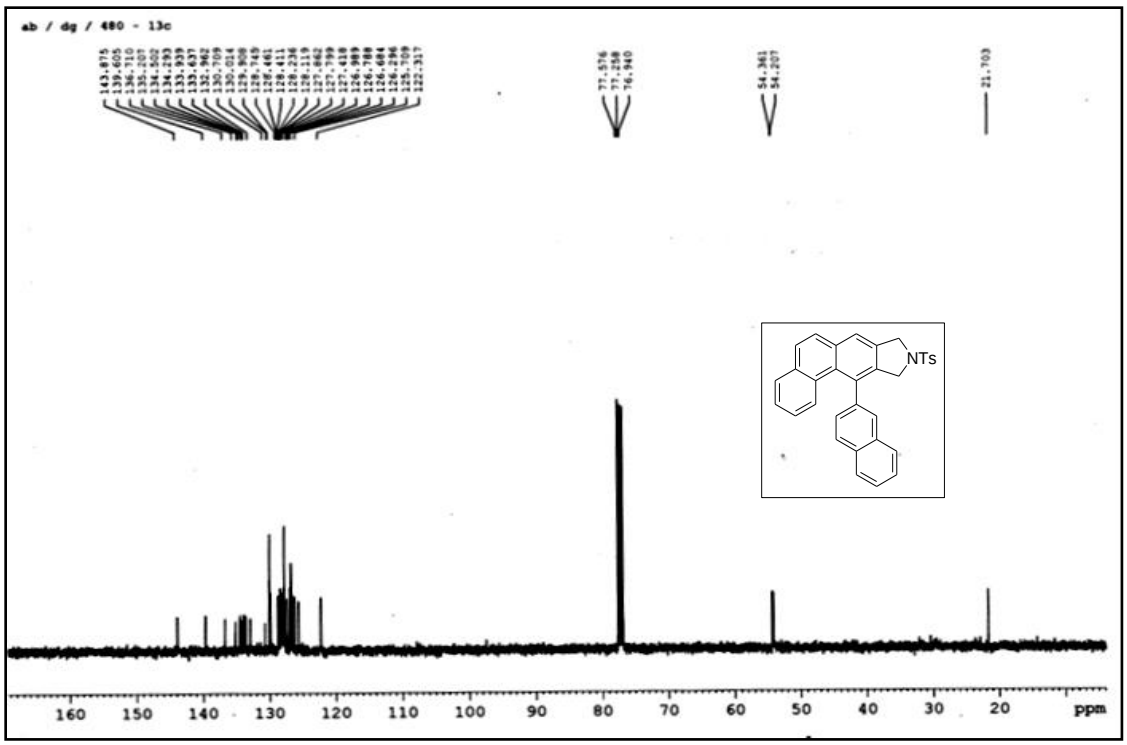


Figure 3.63: ^{13}C-NMR spectrum of compound 3.68m

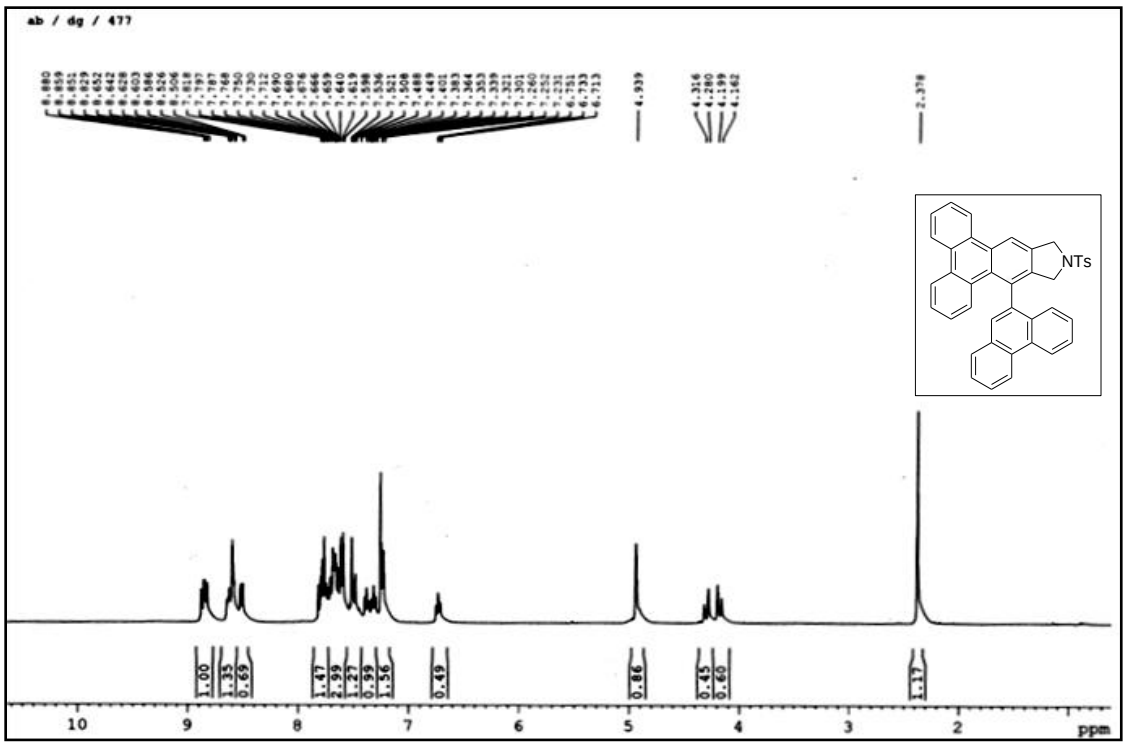


Figure 3.64: ^{1}H-NMR spectrum of compound 3.68n

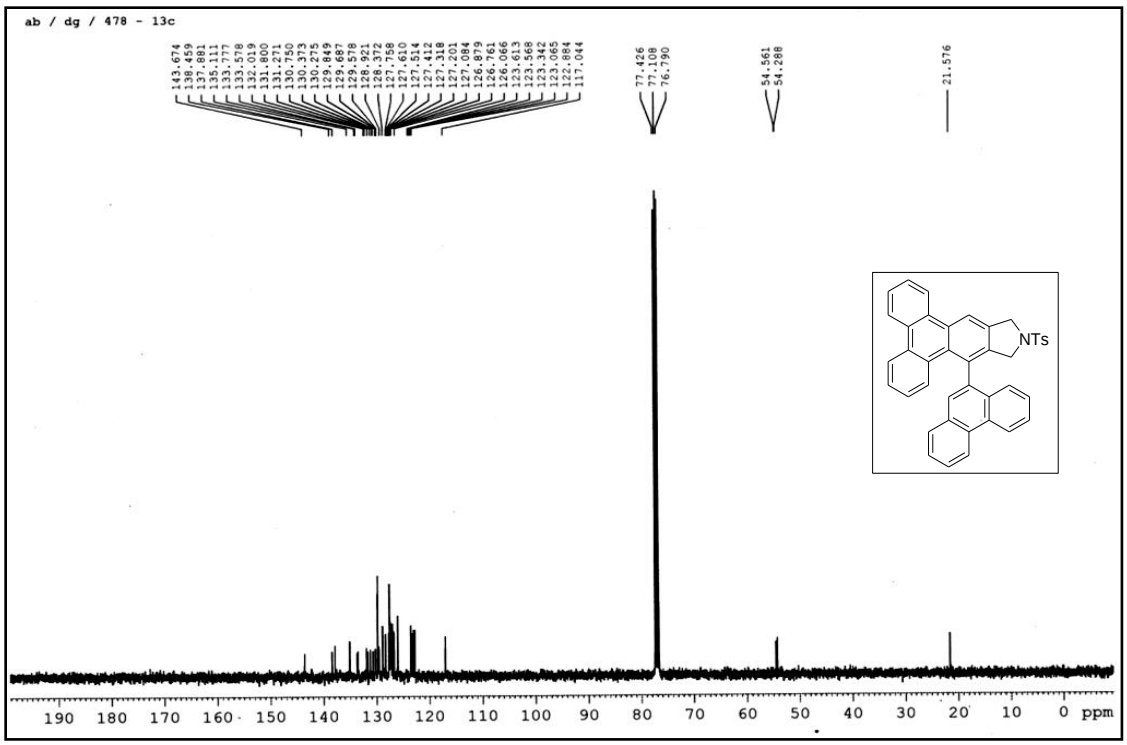


Figure 3.65: ^{13}C-NMR spectrum of compound 3.68n

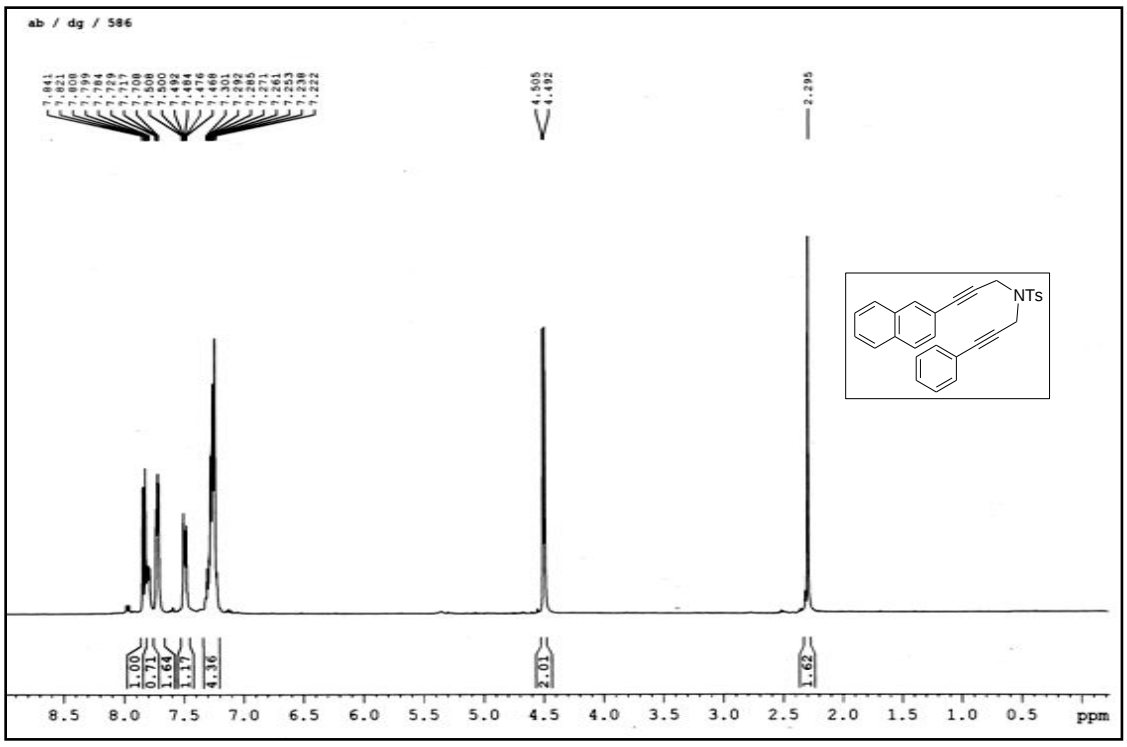


Figure 3.66: ^{1}H-NMR spectrum of compound 3.62

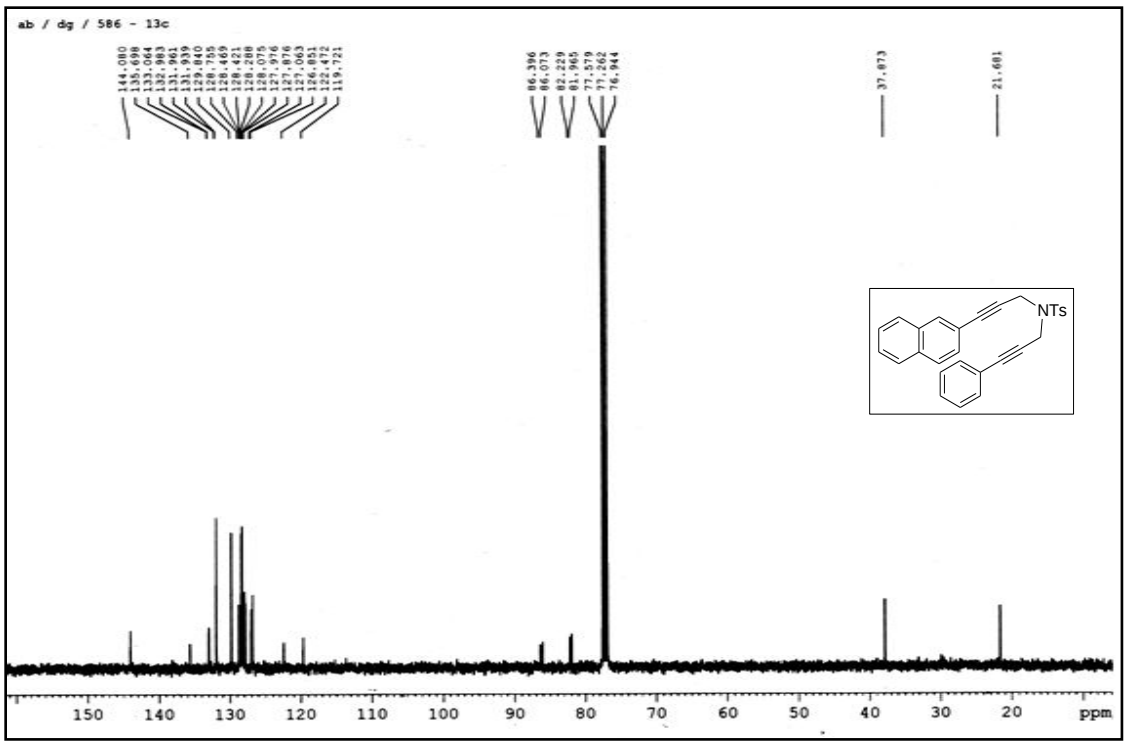


Figure 3.67: ^{13}C-NMR spectrum of compound 3.62

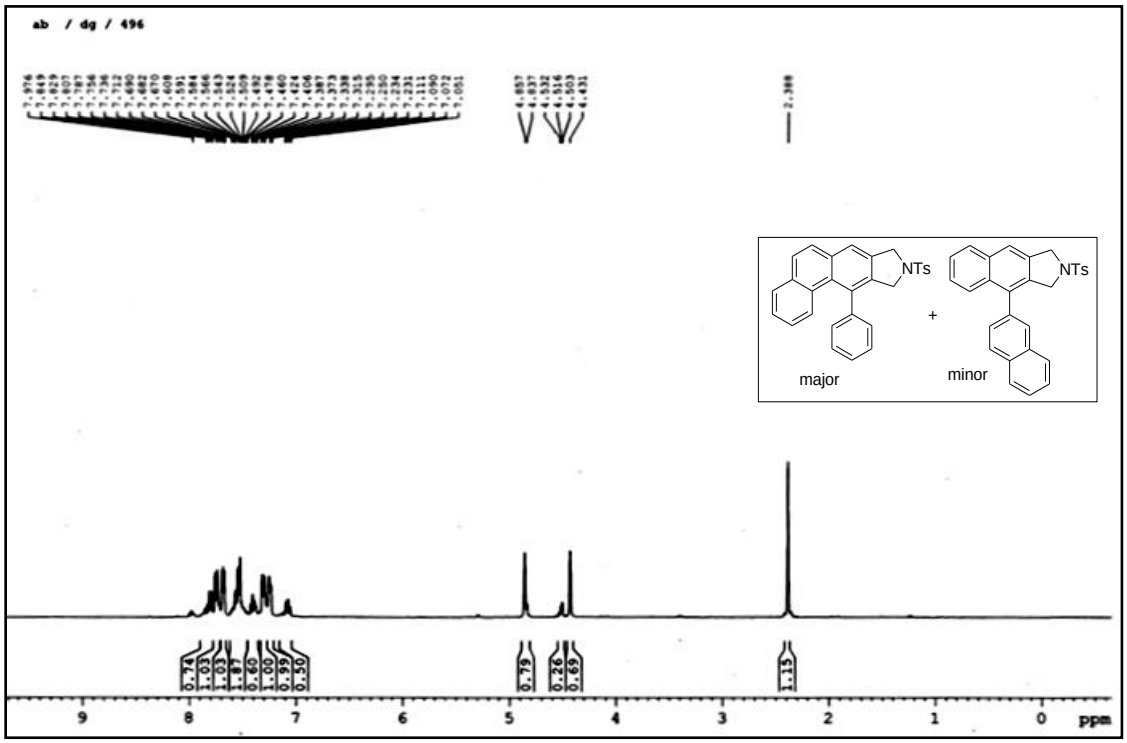


Figure 3.68: ^{1}H-NMR spectrum of compound 3.68o & 3.69o

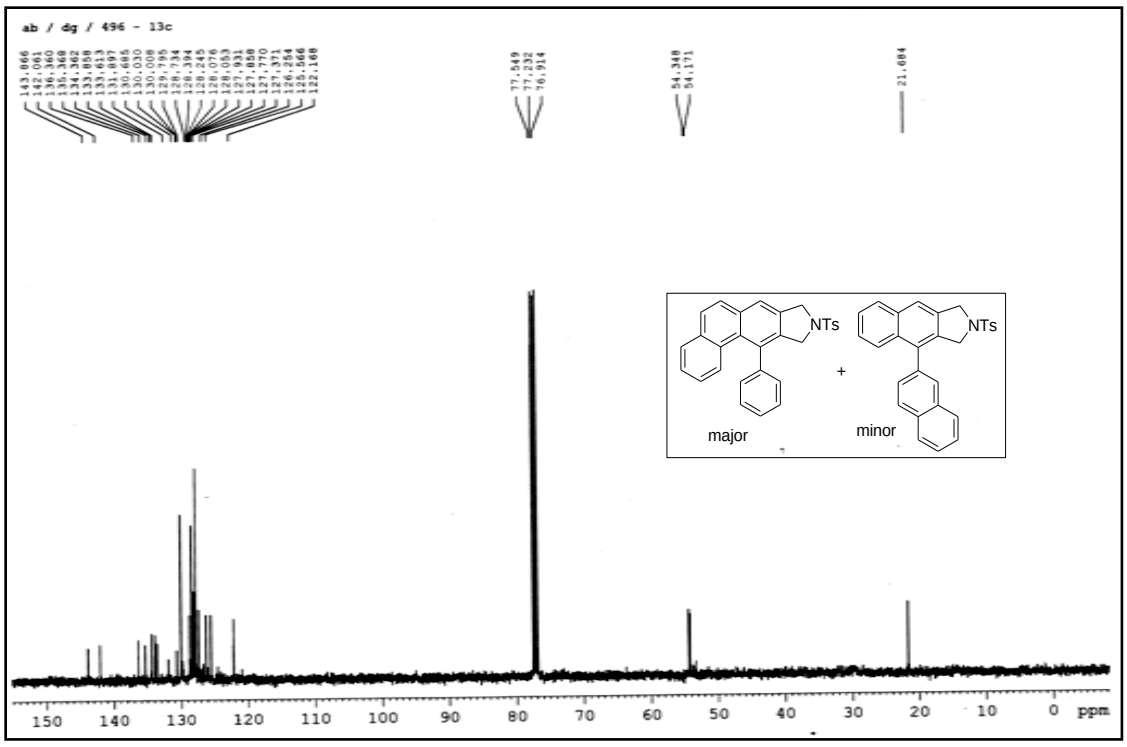


Figure 3.69: ^{13}C-NMR spectrum of compound 3.68o & 3.69o

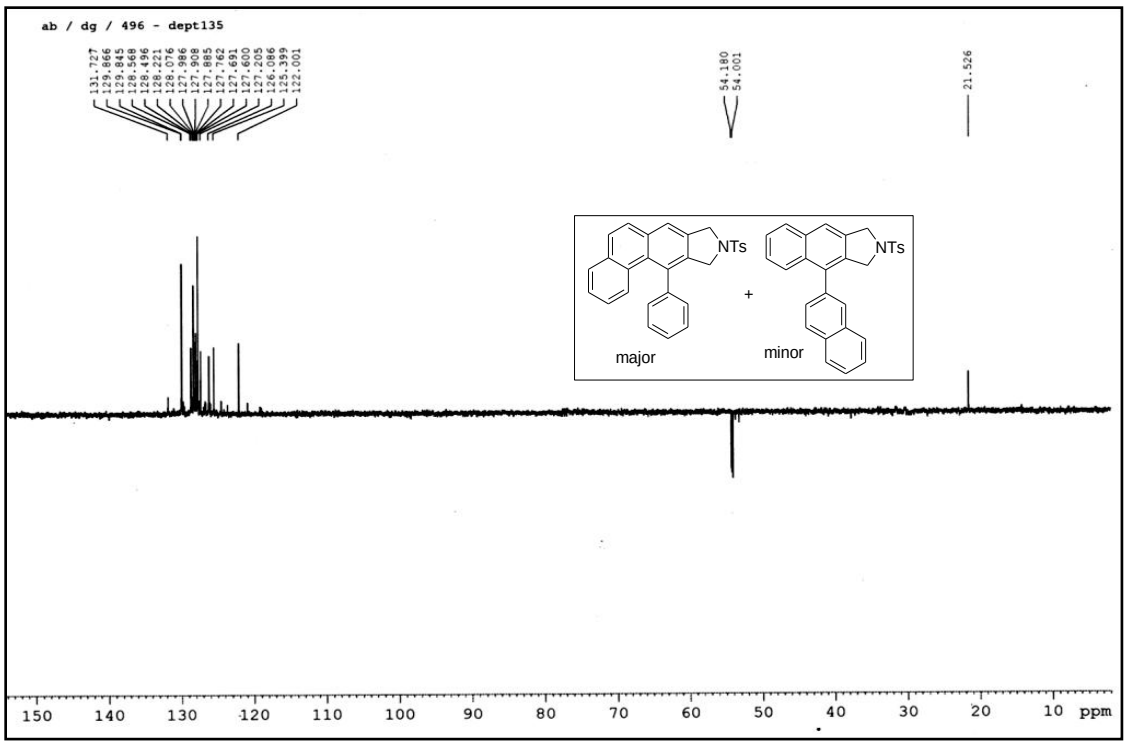


Figure 3.70: DEPT-135 NMR spectrum of compound 3.68o & 3.69o

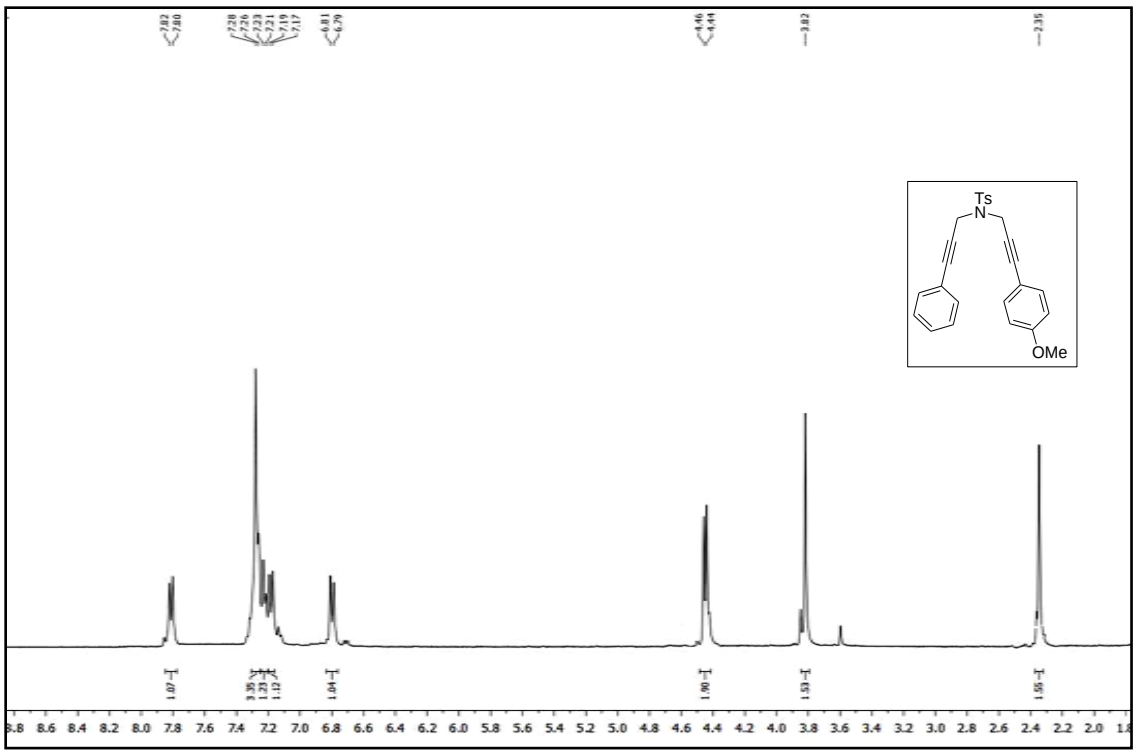


Figure 3.71: ^{1}H-NMR spectrum of compound 3.63

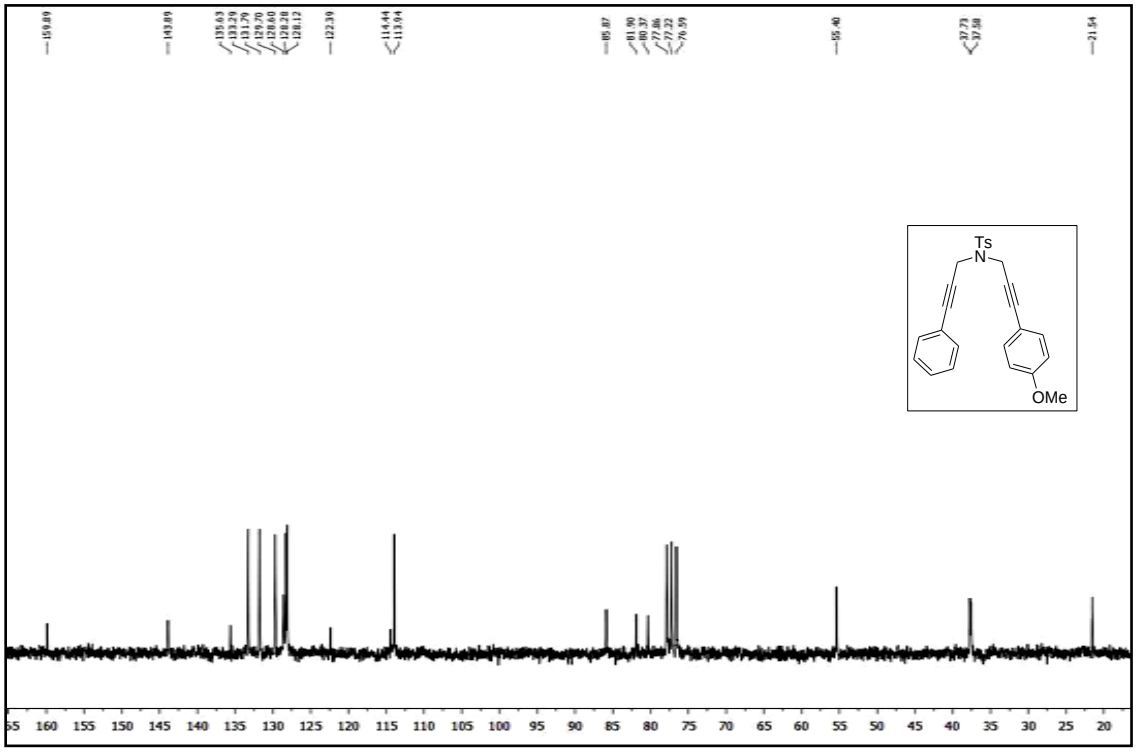


Figure 3.72: ^{13}C-NMR spectrum of compound 3.63

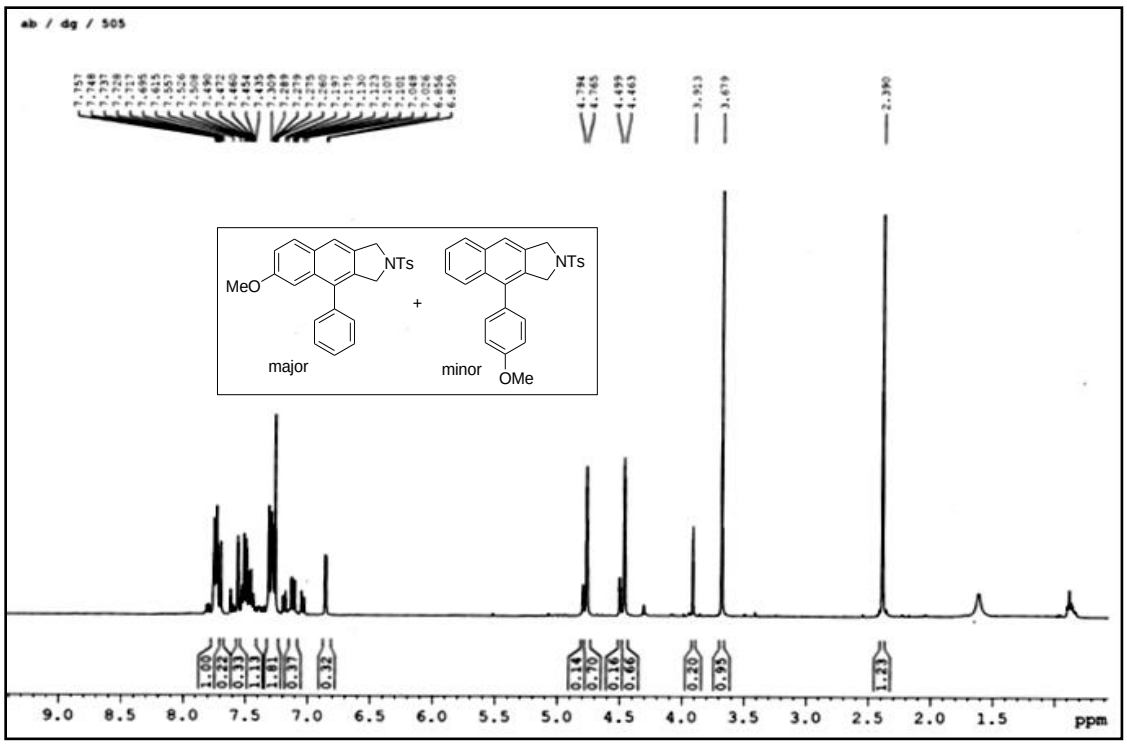


Figure 3.73: ^{1}H-NMR spectrum of compound 3.68p & 3.69p

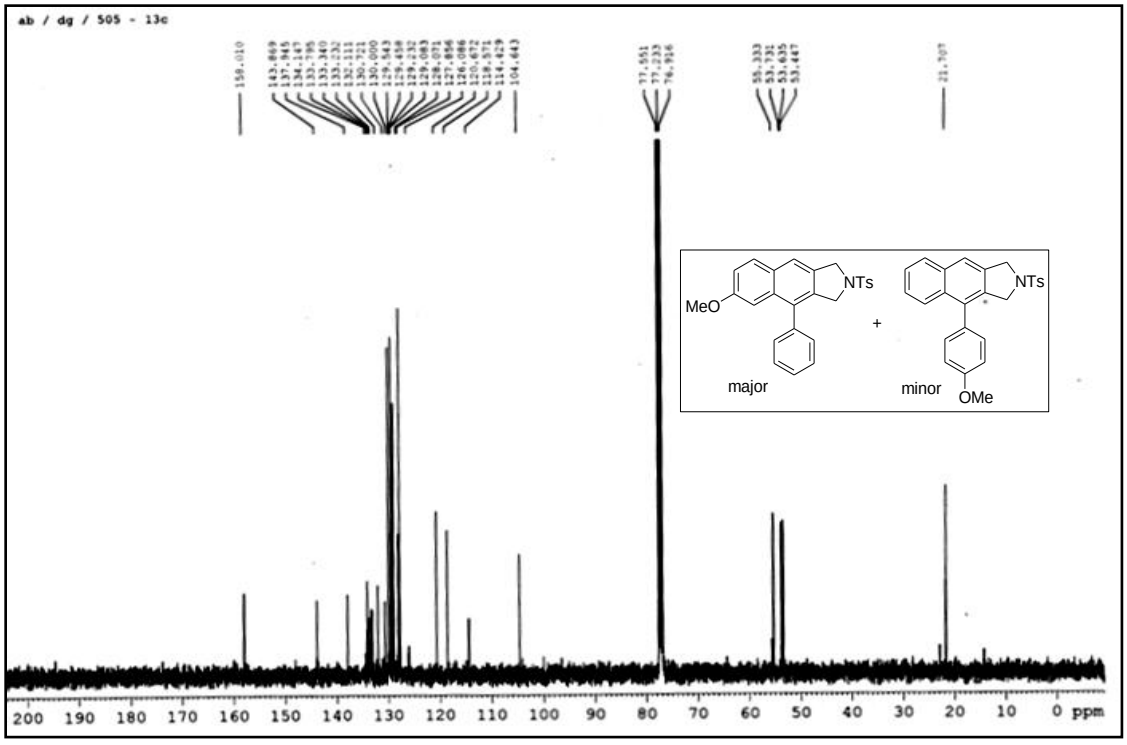


Figure 3.74: ^{13}C-NMR spectrum of compound 3.68p & 3.69p

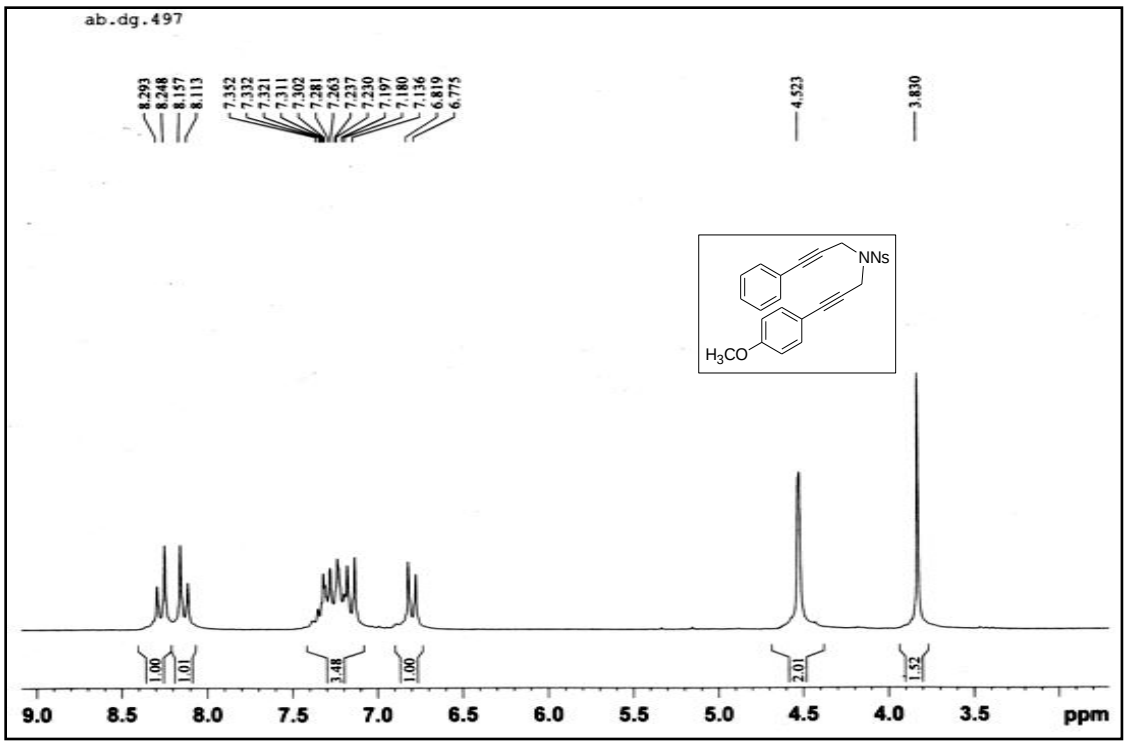


Figure 3.75: ^{1}H-NMR spectrum of compound 3.65

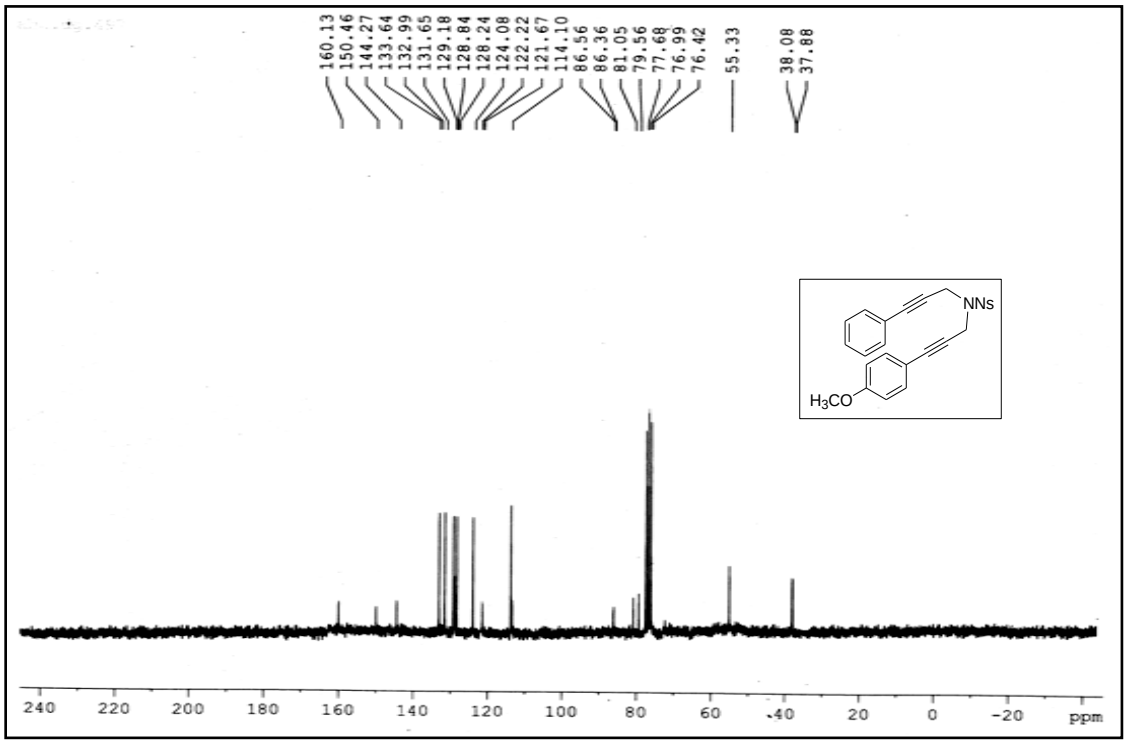


Figure 3.76: ^{13}C-NMR spectrum of compound 3.65

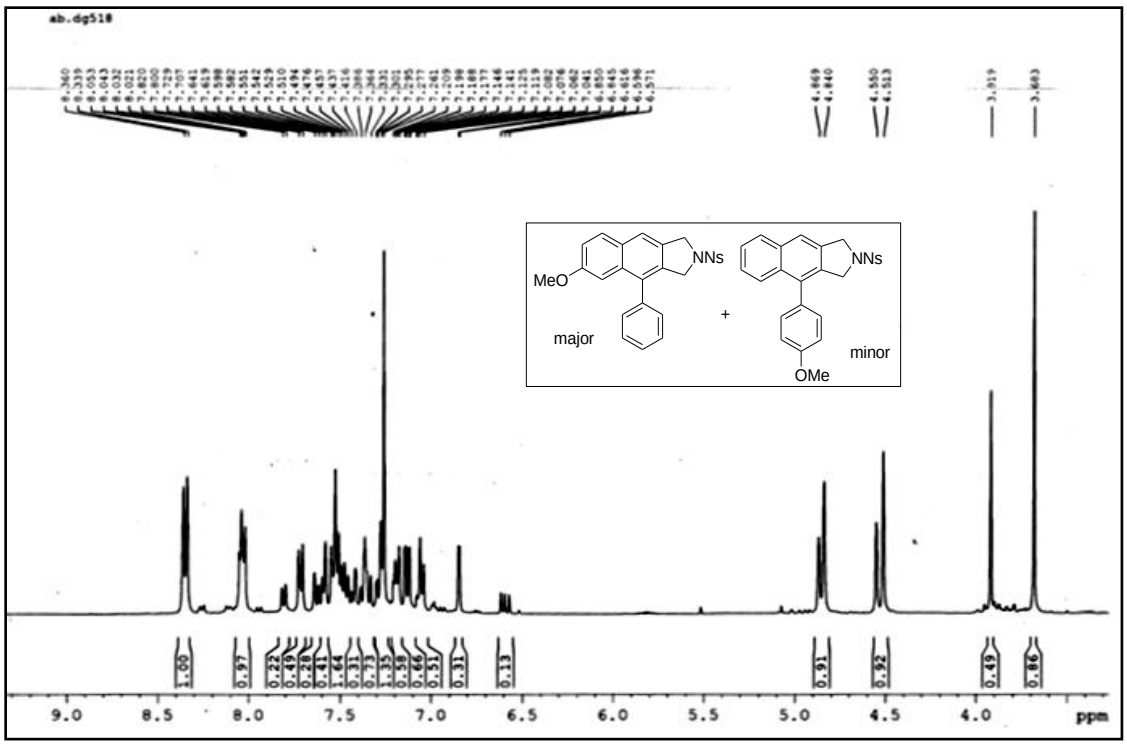


Figure 3.77: ^{1}H-NMR spectrum of compound 3.68q & 3.69q

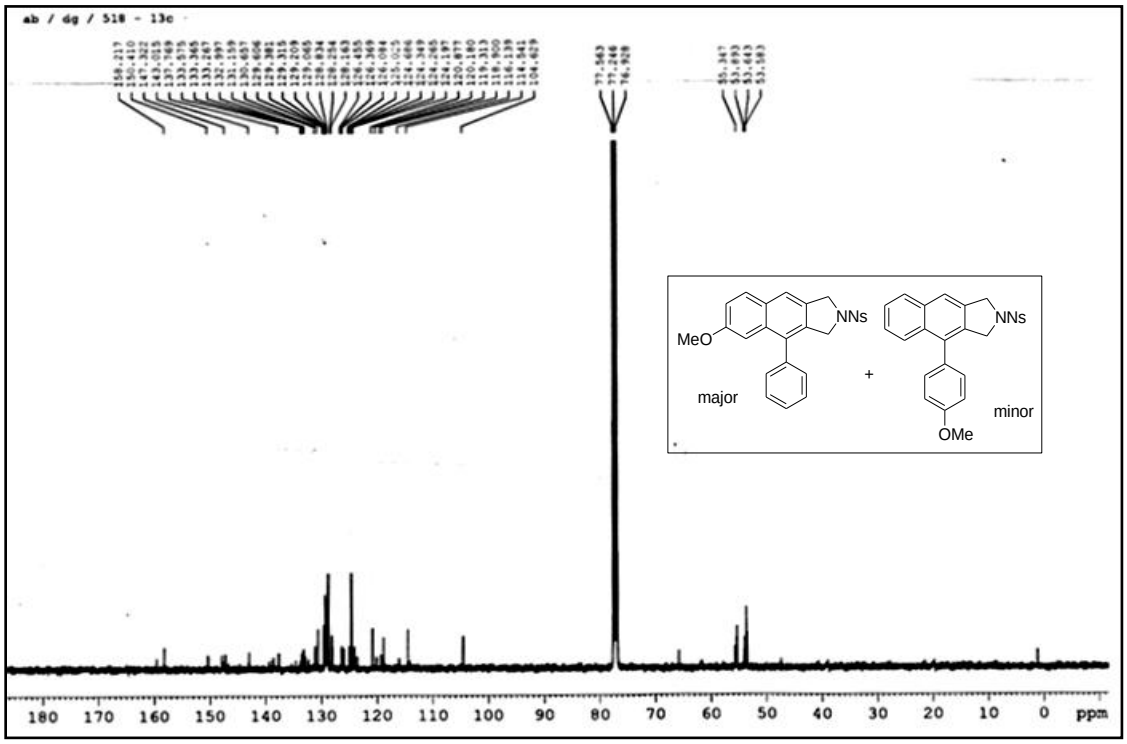


Figure 3.78: ^{13}C-NMR spectrum of compound 3.68q & 3.69q

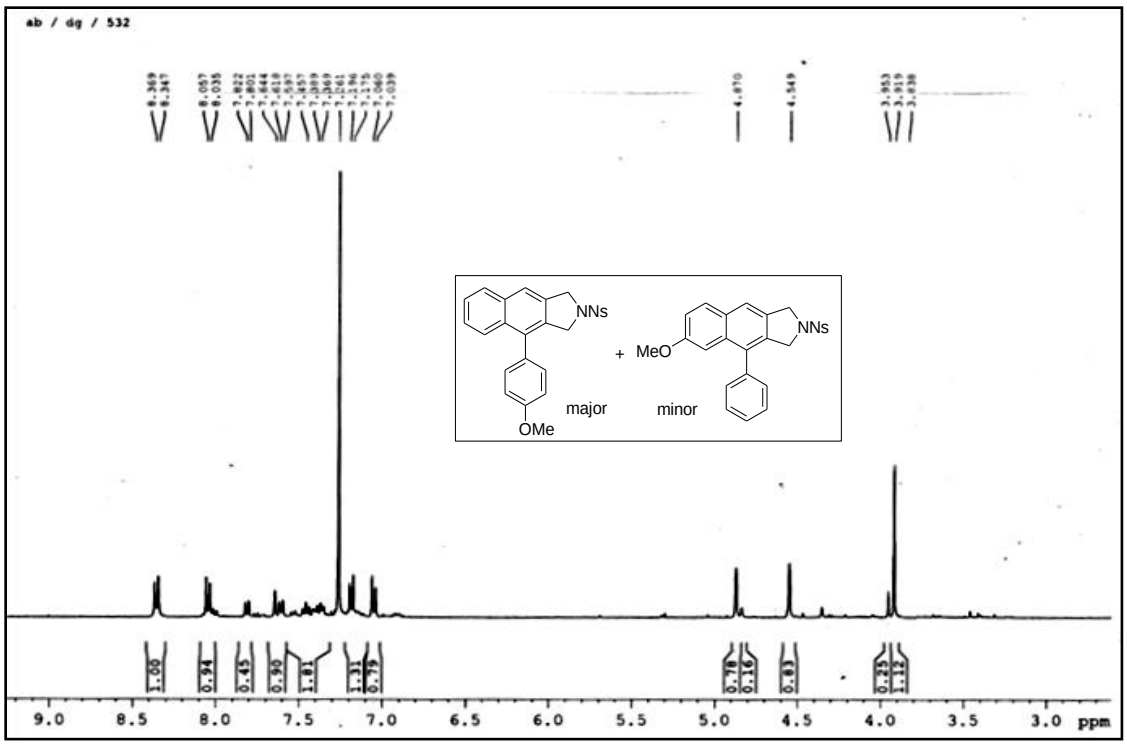


Figure 3.79: ^{1}H-NMR spectrum of compound 3.68q & 3.69q (solvent phase)

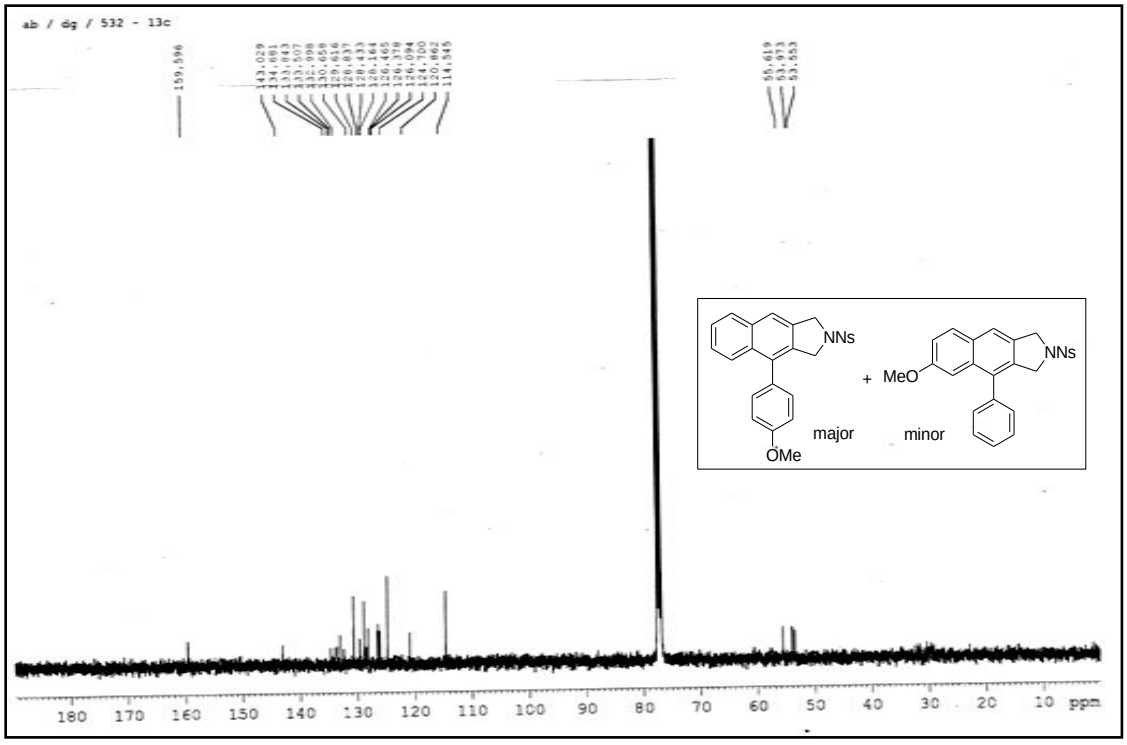


Figure 3.80: ^{13}C-NMR spectrum of compound 3.68q & 3.69q (solvent phase)

3.10 Referenes

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Chapter 4

Sonogashira Coupling and Garratt-Braverman Cyclization in Tandem: Formation of Four C-C Bonds Leading to the Synthesis of Aryl Naphthalenes

4.1 Introduction

Multi-component reactions (MCRs) play an important role in combinatorial chemistry by the virtue of their ability to rapidly foregather three or more reactants and convert them into a product, where most, if not all of the atoms are incorporated in the final product in one-pot (**Figure 4.1**).[1] The strategy has become very popular as it offers a straightforward route to generate molecular complexity and diversity in a single operation in addition to their experimental simplicity, ease of purification, atom economy and high product yields.

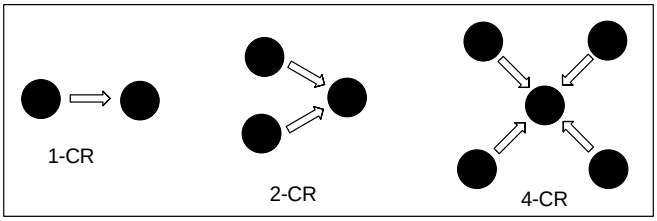


Figure 4.1: Multicomponent reaction

Multi-component reactions can be classified into two classes- In 'True' multi-component mode, all the substrates and reagents are mixed together initially and then

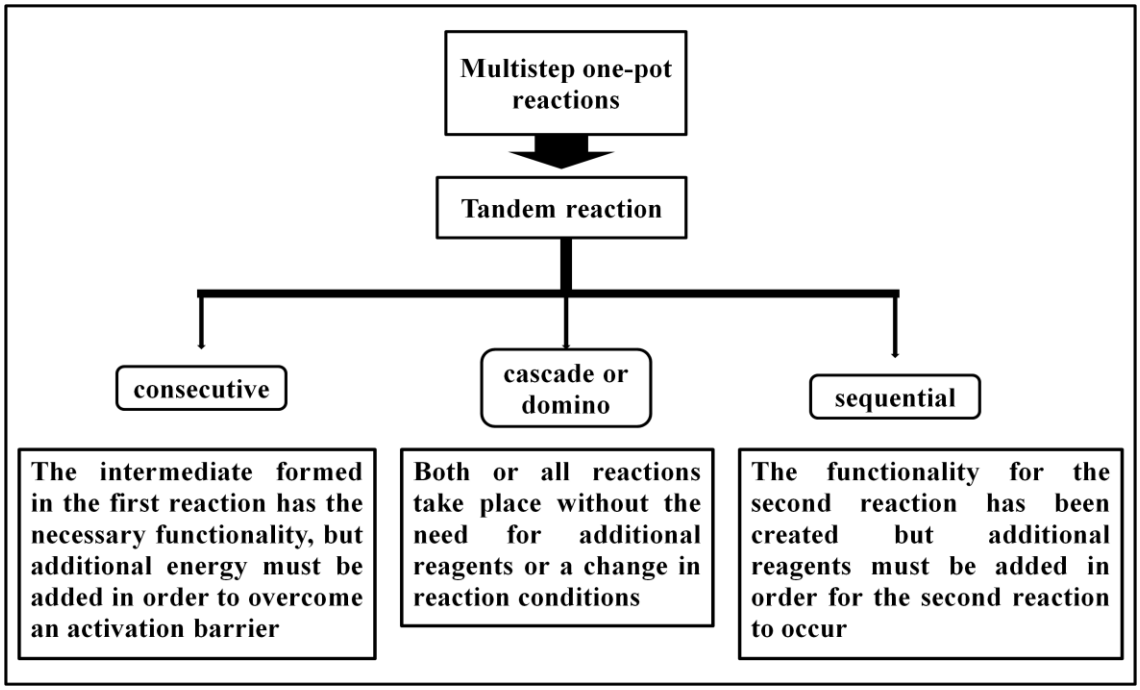
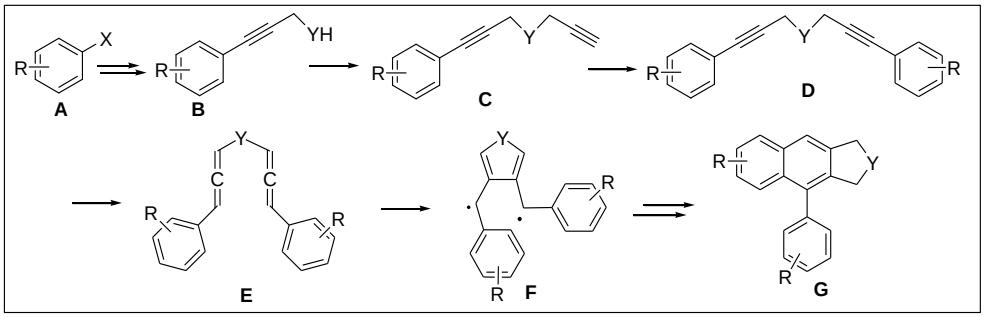


Figure 4.2: Various types of tandem reaction

subsequently processed while in 'One-pot' multi-step mode, several of the reaction components are added to the reaction at a later stage. Tandem reactions are sometimes referred under the nebulous phrase "multistep one-pot reactions". Chemists have categorized tandem reactions into three sets. The first is "cascade or domino" reactions in which both or all reactions take place without the need for additional reagents or a change in reaction conditions. Everything that is necessary for both reactions is incorporated into the starting materials. The second class, "consecutive" reactions, is where the intermediate formed in the first reaction has the necessary functionality, but additional energy must be added in order to overcome an activation energy barrier. The last class is "sequential," where the functionality for the second reaction has been created but additional reagents must be added in order for the second reaction to occur (**Figure 4.2**).

In recent years, we have focused on addressing the mechanistic issues of and exploring the synthetic potential of the Garratt-Braverman reaction.[2-4] The starting materials or precursor for GB cyclization are the *bis*-propargyl systems, like *bis*-propargyl sulfones, ethers and sulfonamides. Upon base treatment these undergo isomerization to a *bis*-allene, followed by the cyclization to the hetero-fused aryl naphthalene *via* the involvement of diradical and subsequent H-shifts.[5] GB cyclization efficiently leads to the formation of two C–C bonds in a single reaction. We have discussed earlier, that, the precursor for GB cyclization are obtained by Sonogashira coupling[6] of bromo/iodo arenes with propargyl alcohol or sulfonamide followed by propargylation and another round of Sonogashira coupling. The complete synthesis of aryl dihydro isofuran (also called phthalan) and isoindole (also known as isoindoline) derivatives are shown in **Scheme 4.1**.



Scheme 4.1: Usual route to accomplish the synthesis of dihydro isofuran/isoindole

We thought that if we can combine all the three reactions and execute with the same set of reagents, then the synthesis of aryl naphthalene moiety will be straightforward, economical and less time consuming process. Since both alkyne-allene isomerization and subsequent GB cyclization take place under basic condition,[7] the thought congregating all the reactions using the same set of reagents seemed quite reasonable. Moreover the ene-yne coupling *i.e* Sonogashira coupling requires basic condition along with Pd(0) as catalyst and CuI as co-catalyst depending on the starting material. We expected that, the catalyst and co-catalyst were not going to impede the subsequent processes of isomerization or cyclization.

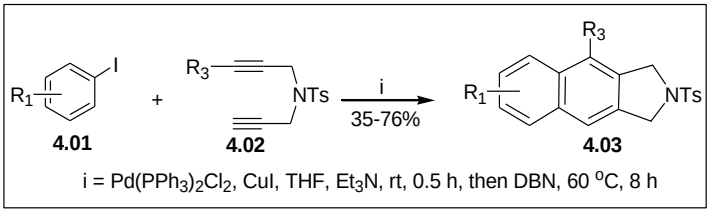
4.2 Objective

Keeping all the above facts in mind, we set our objective as follows

- To carry out the synthesis of aryl dihydro isofurans and isoindoles starting from haloarene in one pot.
- Use of a single base to execute all the base mediated reactions.

4.3 Previous Work

In 2012, Zhu *et al*.[8] reported that, dihydro isoindoles can be synthesized starting from *N-bis*-propargyl sulfonamide in a single pot. Their starting material already had an *N*-aryl propargyl moiety in one chain so that differently substituted aryl *bis*-propargyl system and subsequent cyclization reaction is possible.

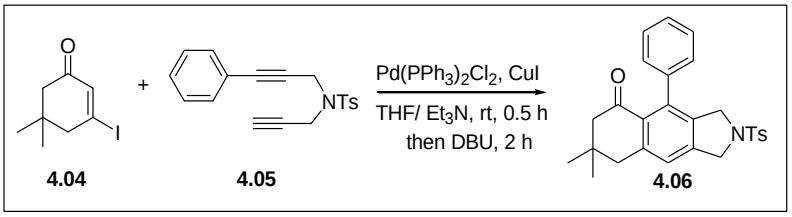


Scheme 4.2: Work done by Zhu *et al.*

They carried out their Pd(0)-mediated ene-yne coupling with iodoarene followed by an intramolecular [4+2] cycloaddition/cycloaromatization for the formation of dihydro isoindoles in tandem fashion. Their method successfully incorporated iodoalkenes and

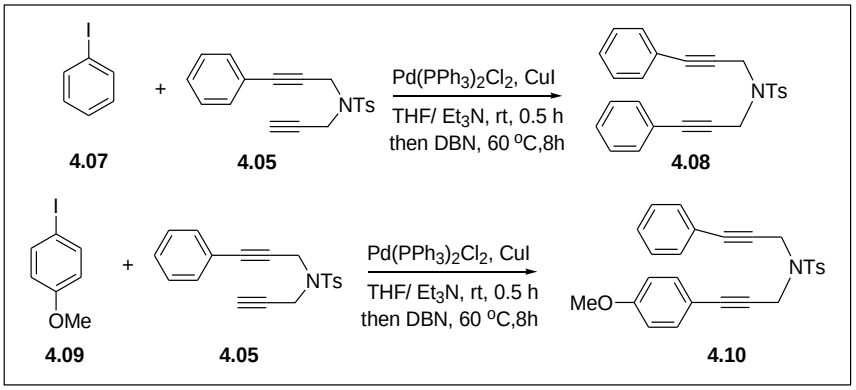
aryl iodides with electron withdrawing groups to result in the target isoindoles as shown in **Scheme 4.2**.

After fruitfully carrying out the one pot synthesis of compound **4.03**, they also synthesized compound **4.06** from vinyl iodide derivative following the similar protocol **(Scheme 4.3)**.



Scheme 4.3: Reaction conditions for the synthesis of 4.06

However, the above method faced a problem while dealing with simple iodobenzene and iodobenzene with electron donor group like methoxy. In these cases the reaction stopped after the Sonogashira coupling step and only *bis*-propargyl derivatives were isolated. Another disadvantage of this method was the involvement of two different bases, first Et_3N for Sonogashira coupling and then DBU or DBN for the subsequent cyclization **(Scheme 4.4)**.



Scheme 4.4: Limitations of Zhu's method

Considering all the above facts, we designed our protocol and chose the starting material and base.

4.4 Present Work

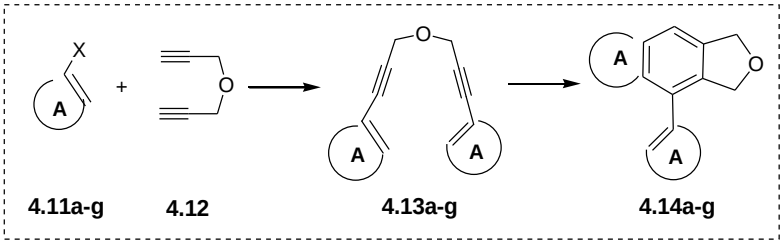
In this present dissertation, our target was to introduce bromoarene as starting material for Sonogashira coupling as well as make the protocol general for both aromatic rings containing electron donating and withdrawing group and accordingly the starting materials were chosen. We also thought to use a single base for the whole process *i.e* Sonogashira coupling and subsequent GB cyclization.

4.5 Results and Discussion

4.5.1 Synthesis of Aryl Dihydro Naphthoisofurans

At first, we conducted the Sonogashira coupling reaction of iodobenzene with propargyl ether in toluene using $Pd(PPh_3)_2Cl_2$ as catalyst and CuI as co-catalyst in presence of DBU as base. Since in general, high temperature is required to bring about the alkyne-allene isomerization or the GB cyclization, toluene was used as solvent. The first reaction of the sequential synthesis was carried out at room temperature because of high reactivity of iodoarenes[9] towards the coupling reaction. The reaction was monitored by ^{1}H NMR. Small aliquots were drawn out at different time intervals and after local work up, the crude reaction mixture was subjected to spectroscopic analysis. Upon completion of the two ene-yne coupling reactions as indicated by ^{1}H NMR, the reaction mixture was refluxed for 8 h. However, unexpectedly, the final aryl naphthalene was isolated in low yield. We then thought to use less reactive bromoaryl replacing iodoaryl and the reaction was carried out under refluxing condition maintaining the temperature at 110 ^oC throughout. After the completion of the reaction (after 8 h), as indicated by TLC, the usual work up and chromatographic purification led to the isolation of the final GBC product in 80% yield. The total multistep procedure includes two Sonogashira couplings and a GB cyclization. If we consider the fact that we have formed four new C–C bonds in a single pot during the course of the synthesis, then the yield can be regarded as excellent.

After successfully synthesizing the compound **4.14a**, we moved forward to apply this protocol to other aromatic compounds to extend the reaction scope (**Table 4.1**). With



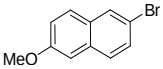
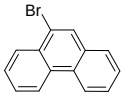
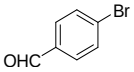
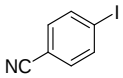
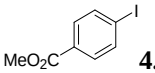
Substrate	Base	Solvent and Condition	Product/Yield (%)	Overall yield (%) *via* route as depicted in Scheme 4.1
 **4.11a**	DBU	Toluene, reflux, 8 h	**4.14a**/80	60
 **4.11b**	DBU	Toluene, reflux, 10 h	**4.14b**/84	61
 **4.11c**	DBU	Toluene, reflux, 10 h	**4.14c**/85	62
 **4.11d**	DBU	Toluene, reflux, 9 h	**4.14d**/80	55
 **4.11e**	DBU	$PdCl_2(PPh_3)_2$ (cat), CuI (cat) Toluene, rt, 6 h, then reflux, 8 h	**4.14e**/70	55
 **4.11f**	DBU	$PdCl_2(PPh_3)_2$ (cat), CuI (cat) Toluene, rt, 8 h, then reflux, 10 h	**4.14f**/70	52
 **4.11g**	DBU	Toluene, reflux, 20 h	**4.14g**/65	51

Table 4.1: Results of one pot synthesis of naphthoisofurans

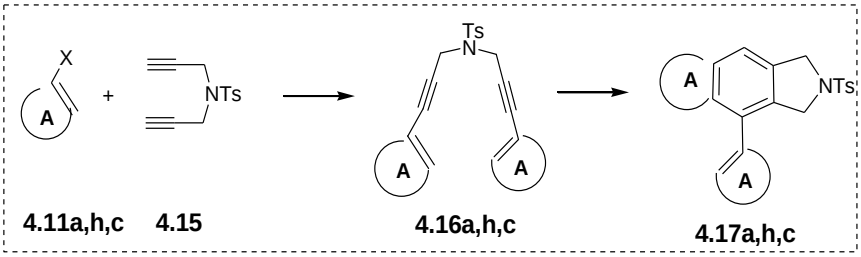
the previous success, we had the optimum condition for bromoarene in hand. Several other bromoarenes were similarly treated with $Pd(PPh_3)_2Cl_2$, propargyl ether and DBU in toluene medium under refluxing condition. In all cases, we isolated the GB products, the dihydro isofurans, in good to excellent yields (considering three reactions in tandem). The results have been shown in **Table 4.1**.

We then employed iodoarenes with an electron withdrawing group (substrates **4.11e** and **4.11f**). At first, the compound was dissolved in toluene and treated with $Pd(PPh_3)_2Cl_2$ as catalyst, CuI as co-catalyst and DBU and stirred at room temperature until the completion of the two Sonogashira couplings. The reaction mixture was then

refluxed for GB cyclization and this time the procedure worked well for them. After usual workup and chromatography, we isolated the dihydro isoindole derivatives in excellent yields. The results have been depicted in **Table 4.1**.

4.5.2 Synthesis of Aryl Dihydro Naphthoisoindoles

Inspired by the success with the ether system, we then explored whether the same protocol works for the sulfonamides. To carry out the one-pot reaction, a solution of bromobenzene and sulfonamido *bis*-propargyl amine in toluene was refluxed in presence of $Pd(PPh_3)_2Cl_2$ and DBU. CuI is not required for the coupling of bromoaryl compounds.



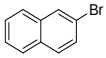
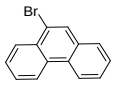
Substrate	Base	Solvent and Condition	Product/Yield (%)	Overall yield (%) *via* Scheme 4.1
 **4.11a**	DBU	Toluene, reflux, 6 h	**4.17a**/82	60
 **4.11h**	DBU	Toluene, reflux, 8 h	**4.17h**/84	62
 **4.11c**	DBU	Toluene, reflux, 8 h	**4.17c**/85	62

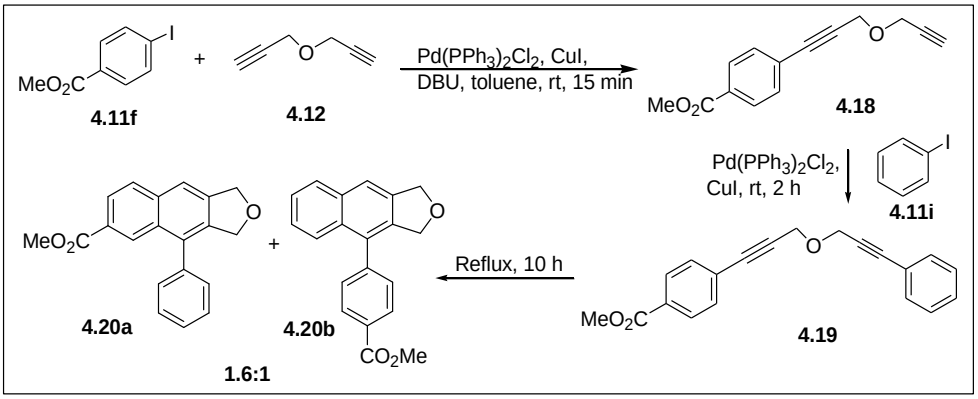
Table 4.2: Result of one-pot synthesis of isoindole derivatives

Gratifyingly, after usual purification procedure, we isolated the dihydro isoindoles in quite good yields. (**Table 4.2**)

Though Zhu's method has some limitations, they provided a unique way to the synthesis of differently substituted dihydro isoindoles starting from an *N-bis*-propargyl sulfonamide. Their method reported 3 new C–C bond formations involving different iodoalkenes; aryl iodides with electron withdrawing groups also gave the target isoindoles.

Inspired by Zhu's success, we also wanted to apply our protocol for the synthesis of dihydro isobenzofuran/isoindole from unsymmetrical propargyl systems. So we attempted the reactions of several haloarenes with propargyl ether **4.12** or sulfonamide **4.15**. According to our strategy, the reaction was carried out by performing the first ene-yne coupling with 1.0 eq of the haloarene. After the completion of first Sonogashira coupling, the second haloarene (1.0 eq) was added for second Sonogashira coupling and the reaction was continued until the completion of the Garratt-Braverman cyclization. Unfortunately, in spite of our all efforts, we were unable to stop the *bis*-eneyne coupling even with 1.0 eq of haloarene and the reaction became complicated as it resulted in a mixture of several products.

Fortunately, in case where the first and the second haloarenes were methyl 4-iodobenzoate **4.11f** and iodobenzene **4.11i**, we could obtain the final dihydro isobenzofuran as a mixture of **4.20a** and **4.20b**. The reaction protocol involved the following: to a well stirred solution of **4.11f** in toluene, catalysts, base and propargyl ether was added. After 15 minutes of the addition, the TLC showed the complete consumption of the starting material and generation of a new product predominantly. The second haloarene **4.11i** and the catalysts were then added. Additional stirring for two hour resulted in the formation of the *bis*-alkyne **4.19**. The reaction mixture was then refluxed for another 10 hours and we obtained a mixture of GB cyclization products **4.20a** and **4.20b** in the ratio of 1.6:1 in good overall yield (**Scheme 4.5**).



Scheme 4.5: Synthesis of aryl dihydroisobenzofuran from mixed haloarenes

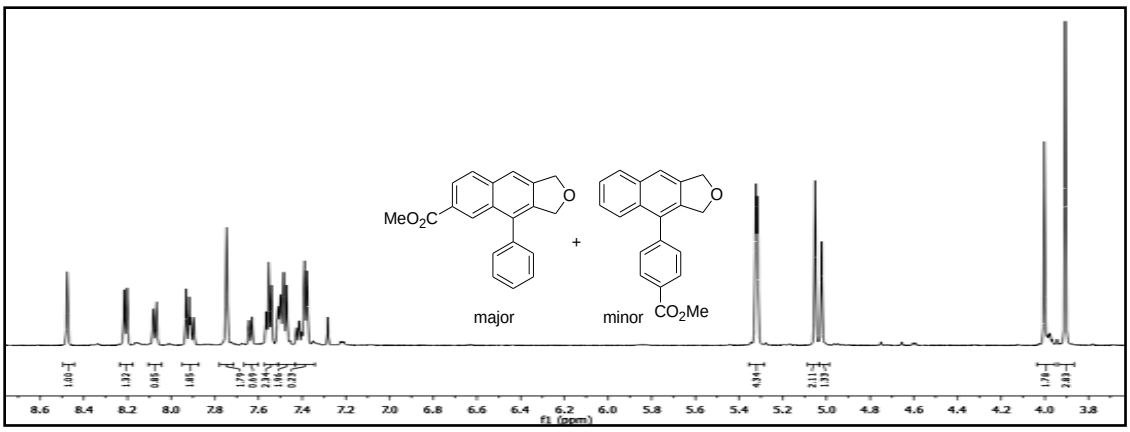


Figure 4.2: ^{1}H NMR of 4.20a and 4.20b

4.6 Conclusion

In conclusion, we have succeeded in synthesizing heterocycle-fused aryl naphthalene *via* successive Sonogashira coupling and Garratt-Braverman cyclization in a single pot. Our method is simple, high yielding and useful as it works well for the synthesis of both dihydro isobenzofuran and isoindole systems. We have only limited success in synthesizing unsymmetrical *bis*-propargyl system in one pot. In future, attempts will be made to explore other reaction conditions to accomplish the synthesis of GB products from unsymmetrical systems.

4.7 Experimental

4.7.1 General Experimental

General experimental procedures are same as described in chapter 2.

General Procedure for the Synthesis of Symmetrical Aryl Dihydro-Isofurans and Isoindoles:

From Iodoaryl Derivative

To a well stirred solution of aryl iodide (2.0 mmol) and the alkyne **4.12/4.15** (2.0 mmol) in toluene (20 mL), DBU (10.0 mmol) was added followed by $PdCl_2(PPh_3)_2$ (6 mol %) and CuI (10 mol%). The reaction mixture was stirred at room temperature till the *bis*-propargyl derivative was formed (6-8 h). The formation of *bis*-propargyl derivative was confirmed by ^{1}H-NMR analysis of the crude mixture. The mixture was then refluxed

at 110 ^{o}C for accomplishing the GB cyclization. After the completion of the reaction (8-10 h), the reaction mixture was evaporated under vacuum and then diluted with water and the aqueous phase was extracted with EtOAc (3× 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated using a rotavapor. The crude product was purified by column chromatography on silica gel.

From Bromoaryl Derivative

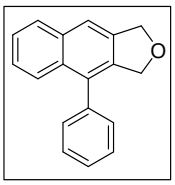
To a well stirred solution of aryl bromide (2.0 mmol) and alkyne **4.12/4.15** (2.0 mmol) in toluene (20 mL), DBU (10.0 mmol) was added followed by $PdCl_2(PPh_3)_2$ (6 mol %) and the mixture was refluxed at 110 ^{o}C. After completion of the reaction (8-20 h), it was evaporated under vacuum and then diluted with water and the aqueous phase was extracted with EtOAc (3× 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel.

Procedure using Mixture of Iodoarenes

To a well stirred solution of methyl 4-iodobenzoate **4.11f** (1.0 mmol) in toluene (25 mL), DBU (5.0 mmol) was added. This was followed by addition of propargyl ether **3** (1.0 mmol), $PdCl_2(PPh_3)_2$ (3 mol %) and CuI (5 mol%) were subsequently added. The mixture was stirred at room temperature for 15 min till 4-(3-Prop-2-ynyloxyprop-1-ynyl)benzoic acid methyl ester (1st coupling product) was formed (checked by ^{1}H NMR of the aliquot). Now iodobenzene (1.0 mmol) and other catalysts (amounts same as used for 1st coupling) were added and stirred for 2 h to complete the second Sonogashira coupling. It was then refluxed at 110 ^{o}C for 10 h to induce the GB cyclization. The mixture was diluted with water and the aqueous phase was extracted with EtOAc (3× 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel using petroleum ether and ethyl acetate as eluent (PE:EA = 3:1).

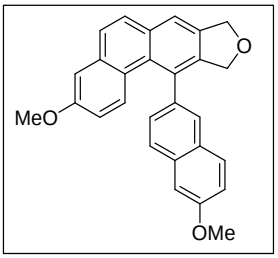
4.7.2 Spectral Data of Some Selected Compounds

4-Phenyl-1,3-dihydronaphtho[2,3-c]furan (4.14a); State: viscous liquid; **Yield**: 80%;



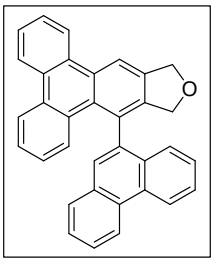
δ_H (600 MHz, $CDCl_3$): 7.90 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 2H), 7.55-7.47 (m, 4H), 7.42-7.39 (m, 3H), 5.33 (s, 2H), 5.06(s, 2H); **δ_C** (150 MHz, $CDCl_3$): 138.2, 137.7, 136.9, 133.7, 132.6, 131.8, 129.5, 128.6, 128.1, 127.7, 125.8, 125.7, 125.6, 118.8, 73.4, 72.9. HRMS: Calculated for $C_{18}H_{15}O$ [MH^+] 247.1117, found 247.1124.

3-methoxy-11-(6-methoxynaphthalen-2-yl)-8,10-dihydrophenanthro[3,2-c]furan (4.14b) State: viscous liquid; **Yield**: 84%; **δ_H** (400 MHz, $CDCl_3$): 7.88 (d, *J* = 8.4 Hz,



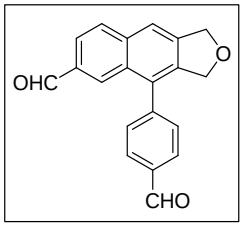
1H), 7.77-7.64 (m, 6H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.26-77.19 (m, 3H), 6.64 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 5.36 (s, 2H), 5.04 (d, *J* = 13.2 Hz, 1H), 4.85 (d, *J* = 12.8 Hz, 1H), 3.99 (s, 3H), 3.85 (s, 3H); **δ_C** (100 MHz, $CDCl_3$): 158.2, 157.5, 140.3, 137.9, 136.4, 135.3, 134.0, 132.9, 129.8, 129.7, 129.4, 128.5, 128.34, 128.3, 127.6, 127.2, 126.8, 125.3, 120.5, 119.5, 115.3, 109.0, 106.1, 74.2, 74.1, 55.6, 55.4. HRMS: Calculated for $C_{28}H_{23}O_3$ [MH^+] 407.1642, found 407.1640.

9-(phenanthren-9-yl)-10,12-dihydrotriphenyleno[2,3-c]furan (4.14c) State: brown solid; [m.p. = decomposes at 214 °C]; **Yield**: 85%; **δ_H** (400 MHz, $CDCl_3$): 8.32 (t, *J* = 10

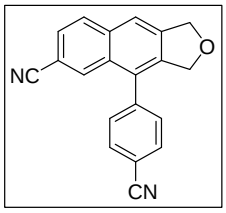


Hz, 2H), 8.74-8.70 (m, 2H), 8.65-8.63 (m, 1H), 8.56 (d, *J* = 8 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.76-7.61 (m, 7H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.78 (t, *J* = 8 Hz, 1H), 5.44 (s, 1H), 4.84 (d, *J* = 13.2 Hz, 1H), 4.67 (d, *J* = 13.2 Hz, 1H); **δ_C** (100 MHz, $CDCl_3$): 141.3, 139.3, 138.3, 132.2, 132.1, 131.7, 131.2, 130.8, 130.4, 130.2, 130.1, 129.4, 129.0, 128.5, 127.6, 127.6, 127.5, 127.3, 127.1, 126.8, 126.5, 126.2, 123.8, 123.5, 123.4, 123.2, 123.0, 115.5, 74.5, 74.3. HRMS: Calculated for $C_{34}H_{23}O$ [MH^+] 447.1743, found 447.1729.

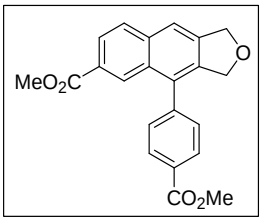
4-(4-formylphenyl)-1,3-dihydronaphtho[2,3-c]furan-6-carbaldehyde (4.14d) State: white solid; [m.p. = 160 °C]; **Yield**: 80%; δ_H (400 MHz, $CDCl_3$): 10.15 (s, 1H), 9.98 (s, 1H), 8.09-8.07 (m, 3H), 8.00-8.95 (m, 2H), 7.81 (s, 1H), 7.57 (d, *J* = 8 Hz, 2H), 5.30 (d, *J* = 11.6 Hz, 2Hz), 5.03 (s, 2H); δ_C (100 MHz, $CDCl_3$): 192.3, 191.8, 143.7, 141.7, 138.6, 137.0, 136.3, 134.5, 133.1, 131.9, 130.9, 130.5, 130.4, 129.7, 123.2, 120.0, 73.5, 72.7. HRMS: Calculated for $C_{20}H_{15}O_3$ [MH^+] 303.1016, found 303.1010.



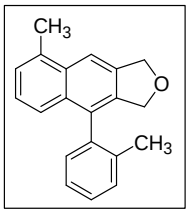
4-(4-cyanophenyl)-1,3-dihydronaphtho[2,3-c]furan-6-carbonitrile (4.14e) State: white solid; [m.p. = decomposes at 130 °C]; **Yield**: 70%; δ_H (400 MHz, $CDCl_3$) 7.98 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 7.88 (d, *J* = 8 Hz, 2H), 7.81 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 2H), 5.31 (s, 2H), 4.99 (s,2H); δ_C (100 MHz, $CDCl_3$): 141.7, 139.3, 135.2, 133.0, 131.4, 131.3, 130.5, 130.4, 129.8, 126.8, 120.2, 119.2, 118.4, 112.8, 110.0, 73.4, 72.6. HRMS: Calculated for $C_{20}H_{13}ON_2$ [MH^+] 297.1022, found 297.1027.



Methyl-4-(4-(methoxycarbonyl)phenyl)-1,3-dihydronaphtho[2,3-c]furan-6-carboxylate (4.14f) State: yellow solid; [m.p. = 135 °C]; **Yield**: 70%; δ_H (600 MHz, $CDCl_3$): 8.38 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 5.32 (s, 2H), 5.03 (s, 2H), 4.01 (s, 3H), 3.90 (s, 3H); δ_C (150 MHz, $CDCl_3$): 167.1, 166.8, 142.2, 140.4, 137.9, 135.8, 133.0, 130.6, 130.1, 129.9, 129.6, 128.5, 128.2, 127.7, 125.4, 119.3, 73.3, 72.6, 52.3, 52.2. HRMS: Calculated for $C_{22}H_{19}O_5$ [MH^+] 363.1227, found 363.1232.



8-methyl-4-o-tolyl-1,3-dihydronaphtho[2,3-c]furan (4.14g) State: brown solid; [m.p. = 120 °C]; **Yield**: 65%; δ_H (600 MHz, $CDCl_3$): 7.96 (s, 1H), 7.42 (d, *J* = 1.8 Hz, 2H), 7.41-7.28 (m, 4H), 7.23 (d, *J* = 7.2 Hz, 1H), 5.41 (s, 2H), 5.05 (d, *J* = 13.2 Hz, 1H), 4.90 (d, *J* = 12.6 Hz, 1H), 2.80 (s, 3H), 2.05 (s, 3H); δ_C (150 MHz, $CDCl_3$): 137.9, 137.5, 136.4, 136.4, 134.3, 132.8, 132.6, 131.9, 130.2, 129.5, 128.0, 126.6, 126.1, 125.5, 124.0, 115.0, 73.8, 73.0, 20.0, 19.7. HRMS: Calculated for $C_{20}H_{19}O$ [MH^+] 275.1430, found 275.1422.

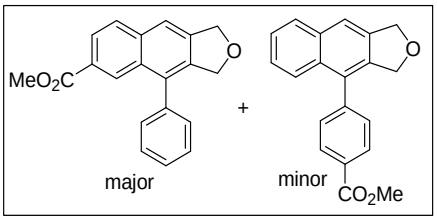


4-Phenyl-2-(toluene-4-sulfonyl)-2,3-dihydro-1H-benzo[f]isoindole (4.17a) State: brown solid; [m.p. = decomposes at 210 °C]; **Yield**: 82%; δ_H (600 MHz, $CDCl_3$): 7.83 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 2H), 7.66 (s, 1H), 7.59 (d, *J* = 5.6 Hz, 1H), 7.55-7.46 (m, 4H), 7.37 (t, *J*= 7.5 Hz, 1H), 7.33 (d, *J* = 9 Hz, 2H) 7.29 (d, *J* = 7.2, 2H), 4.83 (s, 2H), 4.52 (s, 2H), 2.42 (s, 3H); δ_C (150 MHz, $CDCl_3$): 143.7, 137.5, 134.4, 134.3, 133.5 133.4, 131.8, 129.8, 129.4, 128.8, 127.9, 127.9, 127.7, 126.0, 125.9, 125.8, 120.7, 53.6, 53.1, 21.5. HRMS: Calculated for $C_{25}H_{22}NO_2S$ [MH^+] 400.1371, found 400.1360.

11-Naphthalen-2-yl-9-(toluene-4-sulfonyl)-9,10-dihydro-8H-9-azacyclopenta-[b]phenanthrene (4.17h) State: brown solid; [m.p. = decomposes at 216 °C]; **Yield**: 84%; δ_H (600 MHz, $CDCl_3$): 8.03 (t, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.79 (s, 1H), 7.75-7.72 (m, 5H), 7.65-7.56 (m, 3H), 7.40-7.28 (m, 4H), 6.97 (t, *J* = 7.8 Hz, 1H), 4.90 (s, 2H), 4.52 (d, *J* = 14.1 Hz, 1H), 4.36 (d, *J* = 14.1 Hz, 1H), 2.40 (s, 3H); δ_C (150 MHz, $CDCl_3$): 143.7, 139.4, 136.5, 135.0, 134.3, 134.1, 133.7, 133.7, 133.4, 132.8, 130.5 , 129.8, 129.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.2, 126.8, 126.6, 126.5, 126.1, 125.5, 122.1, 54.2, 54.0, 21.5. HRMS: Calculated for $C_{33}H_{26}O_2NS$ [MH^+] 500.1679, found 500.1672.

9-Phenanthren-9-yl-11-(toluene-4-sulfonyl)-11,12-dihydro-10H-phenanthro- [9,10-f]isoindole (4.17c) State: brown solid; [m.p. > 220 °C]; **Yield**: 85%; δ_H (600 MHz, $CDCl_3$): 8.89-8.86 (m, 2H), 8.66 (d, *J* = 5.4Hz, 1H), 8.62 (s, 2H), 8.54 (d, *J* = 7.8 Hz, 1H), 7.84-7.63 (m, 9H), 7.56-7.52(m, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.34(t, *J* = 7.2 Hz, 2H), 7.28-7.26 (m, 2H), 6.75 (t, *J* = 7.5 Hz, 1H), 4.96 (t, *J* = 15 Hz, 2H), 4.32 (d, *J* = 14.1 Hz, 1H), 4.21 (d, *J* = 14.1 Hz, 1H), 2.40 (s, 3H); δ_C (150 MHz, $CDCl_3$): 143.6, 138.4, 137.8, 135.0, 133.7, 133.5, 132.0, 131.7, 131.2, 130.7, 130.3, 130.2, 129.8, 129.79, 129.7, 129.6, 129.5, 128.9, 128.5, 128.3, 127.7, 127.55, 127.46, 127.4, 127.3, 127.1, 127.0, 123.55, 123.51, 123.3, 123.0, 122.8, 116.9, 54.5, 54.2, 21.5. HRMS: Calculated for $C_{41}H_{30}NO_2S$ [MH^+] 600.1997, found 600.2000.

Methyl 4-phenyl-1,3-dihydronaphtho[2,3-c]furan-6-carboxylate (major), Methyl 4-(1,3-dihydronaphtho[2,3-c]furan-4-yl)benzoate (minor) (4.20a and 4.20b) State:



yellow solid; **Yield**: 75%; δ_H (600 MHz, $CDCl_3$): 8.47 (s, 1H, major), 8.21 (d, *J* = 7.8 Hz, 1H, major), 8.07 (d, *J* = 9.6 Hz, 1H, major), 7.92 (d, *J* = 8.4 Hz, 1H, major), 7.90 (d, *J* = 8.4 Hz, 1H, minor), 7.75 (s, 1H major and 1H minor), 7.64 (d, *J* = 8.4 Hz, 1H, minor), 7.56-7.54 (m, 1H, major and 2H, minor), 7.51-7.47 (m, 2H, major and 2H, minor),7.43-7.38 (m, 1H, major and 2H minor), 5.32 (s, 2H, major and 2H minor), 5.05 (s, 2H, major), 5.02 (s, 2H, minor), 4.00 (s, 3H, minor), 3.91 (s, 3H, major); δ_C (150 MHz, $CDCl_3$): (major + minor) 167.3, 166.9, 143.1, 140.4, 137.9, 137.7, 137.3, 136.8, 135.9, 134.2, 133.7, 131.5, 131.4, 131.0, 130.5, 129.9, 129.6, 129.5, 129.4, 128.8, 128.8, 128.3, 128.2, 128.0, 127.4, 126.0, 125.8, 125.3, 125.1, 119.4, 118.7, 73.4, 73.3, 72.8, 72.7, 52.2, 52.1; **DEPT-135** (100 MHz, $CDCl_3$, major + minor) : 129.9, 129.6, 129.4, 128.8, 128.8, 128.0, 126.1, 125.8, 125.3, 125.1, 119.4, 118.7 (all CH), 73.4, 72.8 (all CH_2), 52.2, 52.1 (all CH_3). HRMS: Calculated for $C_{20}H_{14}O_3$ [MH^+] 305.1172, found 305.1174.

4.8 ^{1}H and ^{13}C NMR Spectra of Final Compounds (in $CDCl_3$)

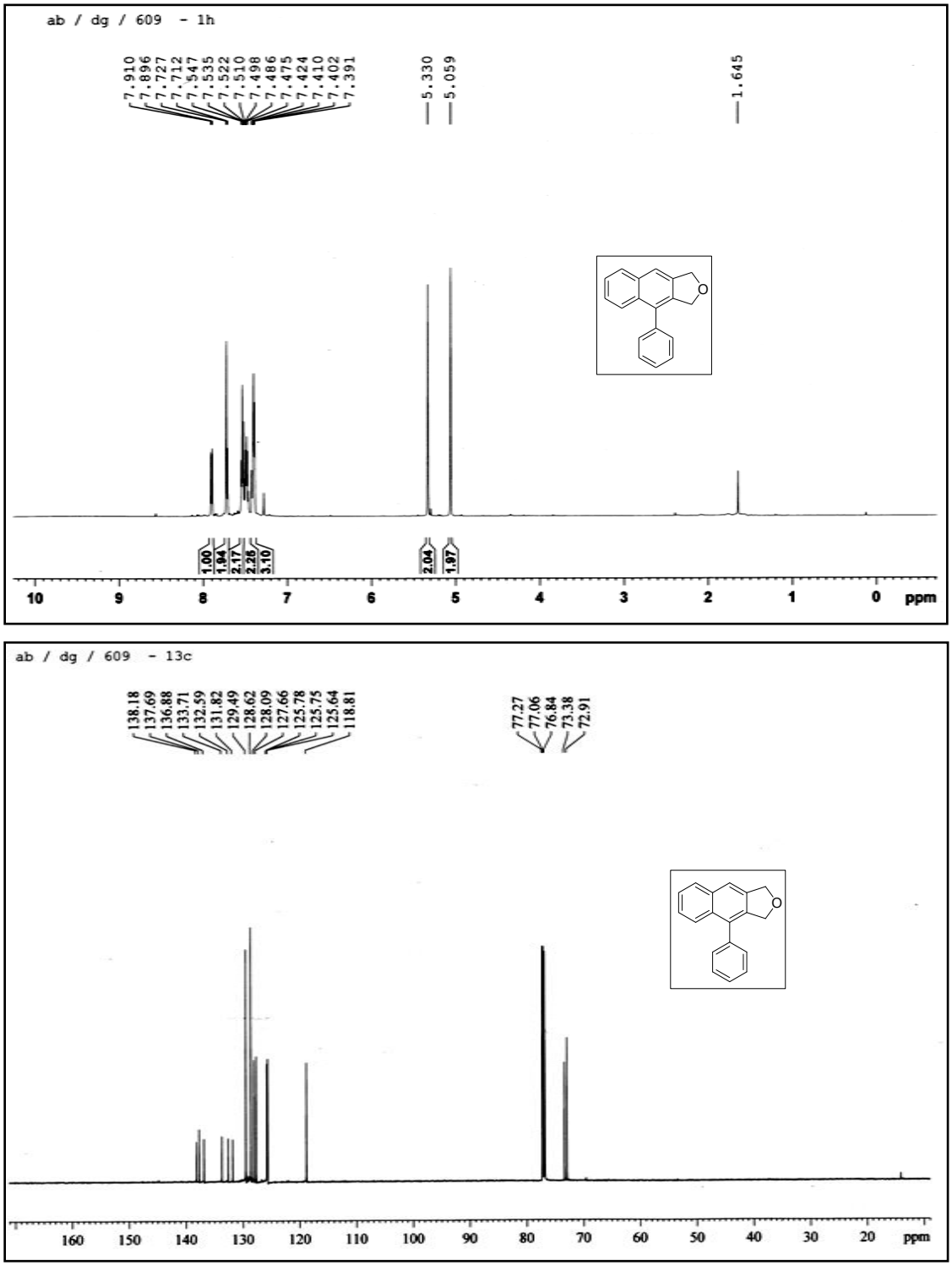


Figure 4.3: ^{1}H and ^{13}C NMR spectra of 4.14a (600 MHz, $CDCl_3$)

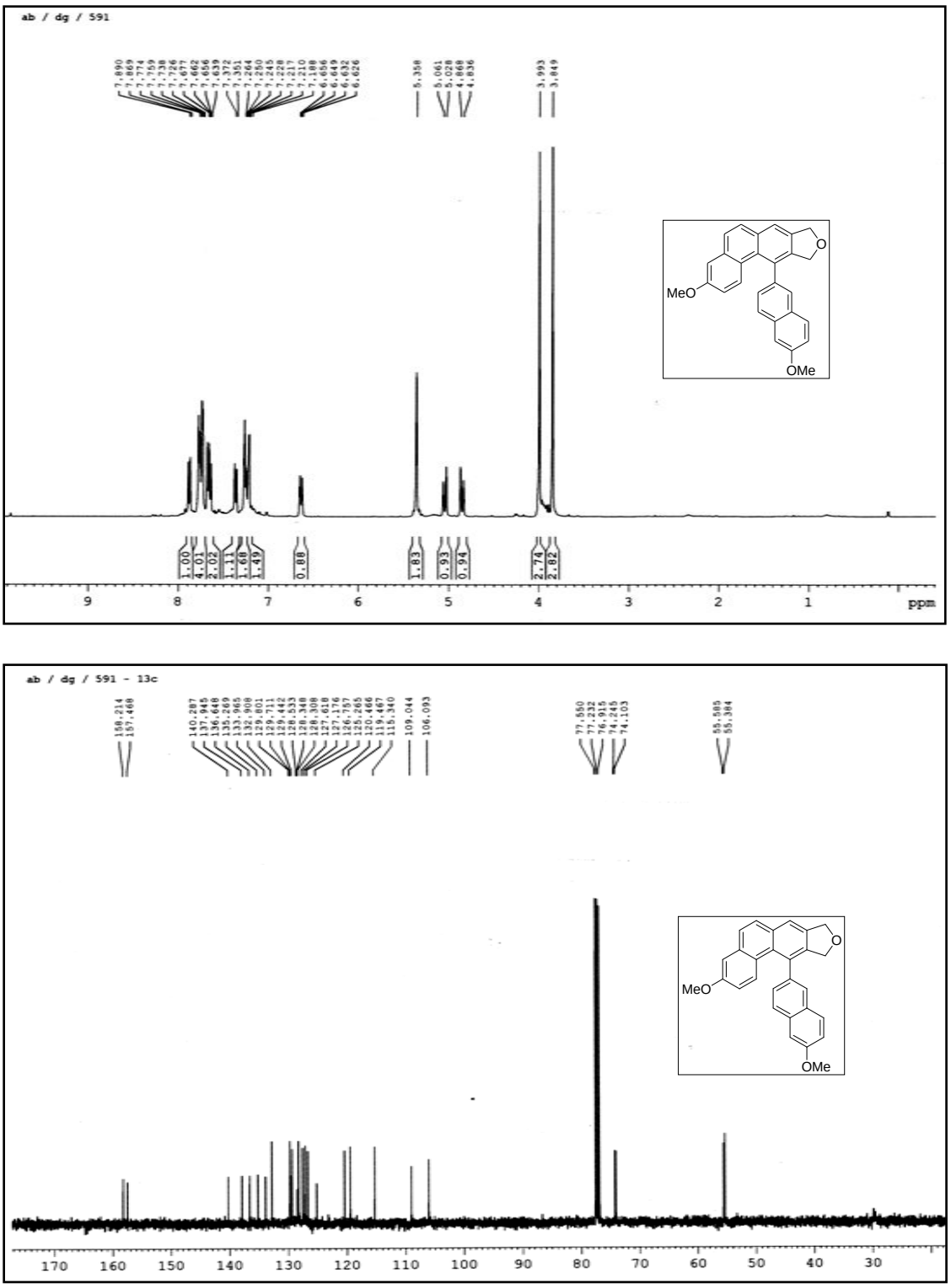


Figure 4.4: ^{1}H and ^{13}C NMR spectra of 4.14b (600 MHz, $CDCl_3$)

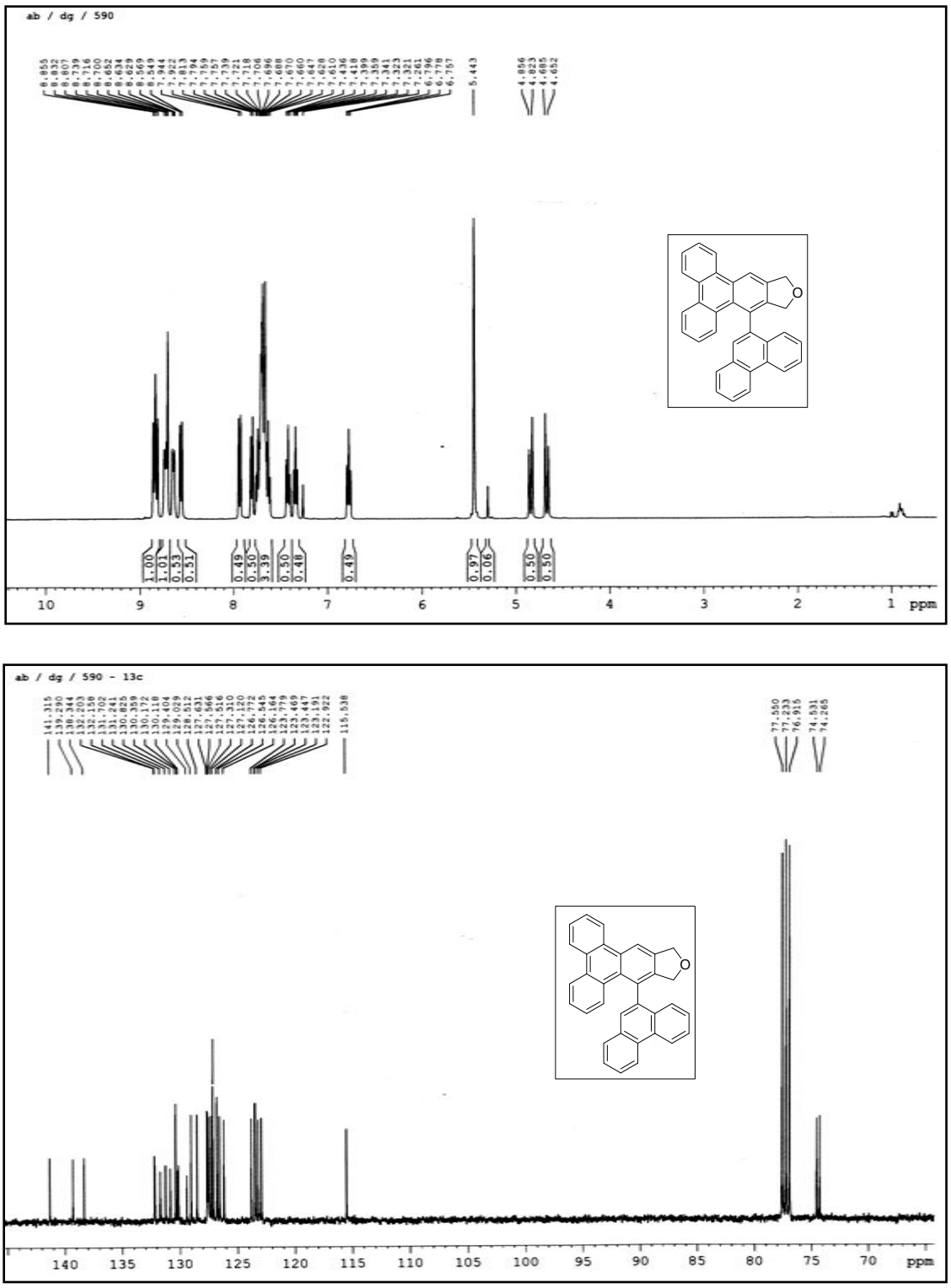


Figure 4.5: ^{1}H and ^{13}C NMR spectra of 4.14c (600 MHz, $CDCl_3$)

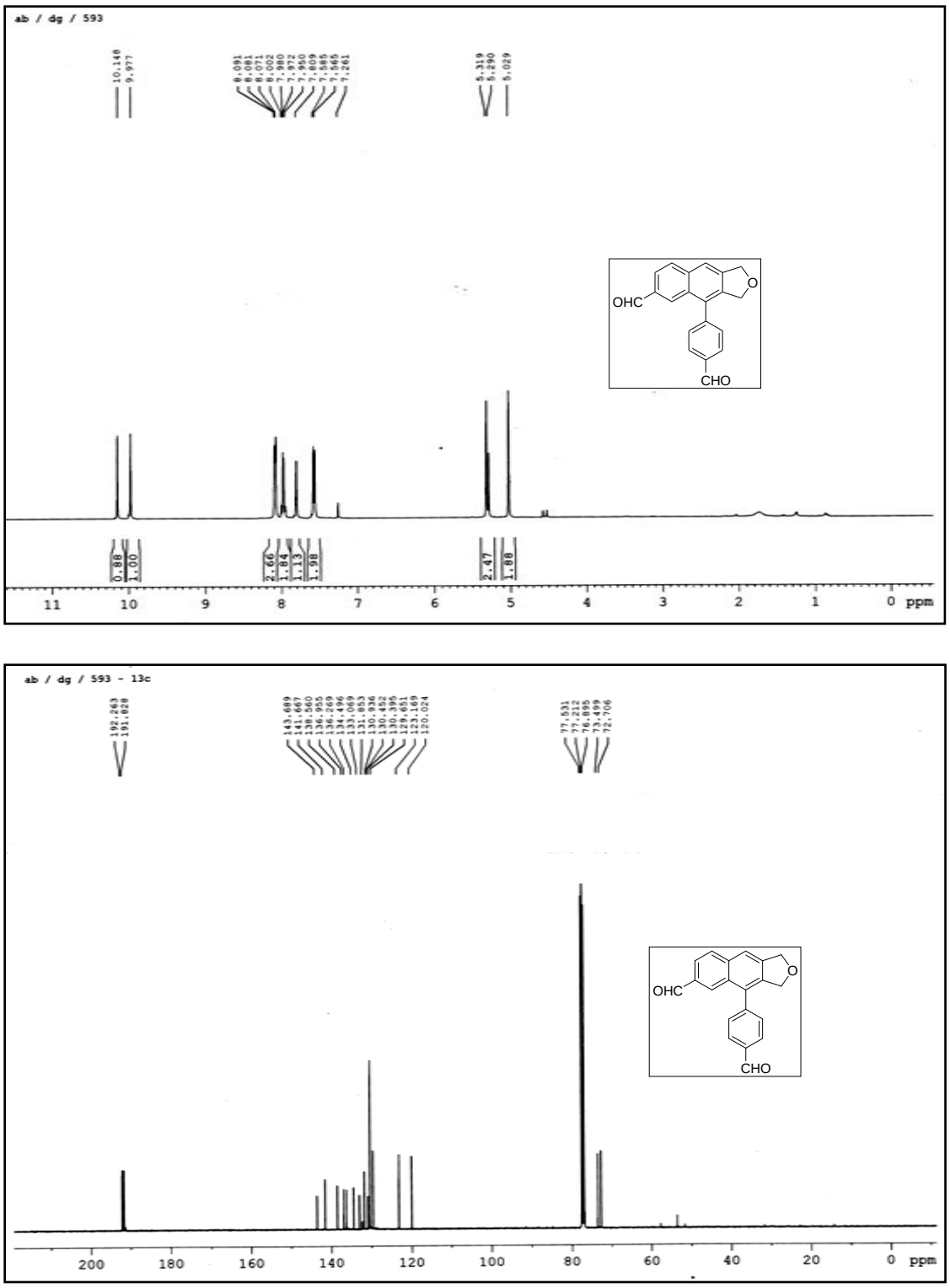


Figure 4.6: ^{1}H and ^{13}C NMR spectra of 4.14d (600 MHz, $CDCl_3$)

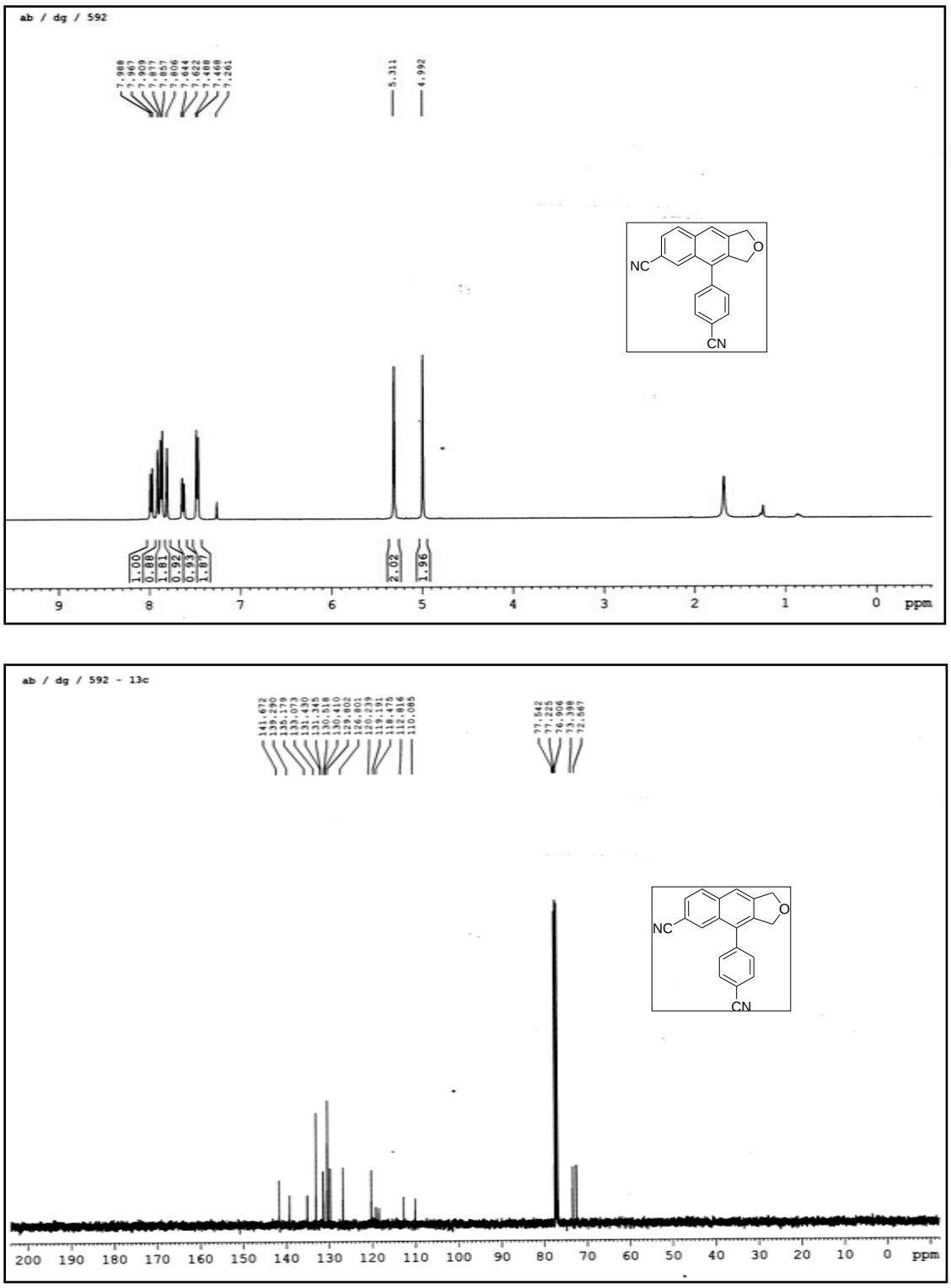


Figure 4.7: ^{1}H and ^{13}C NMR spectra of 4.14e (600 MHz, $CDCl_3$)

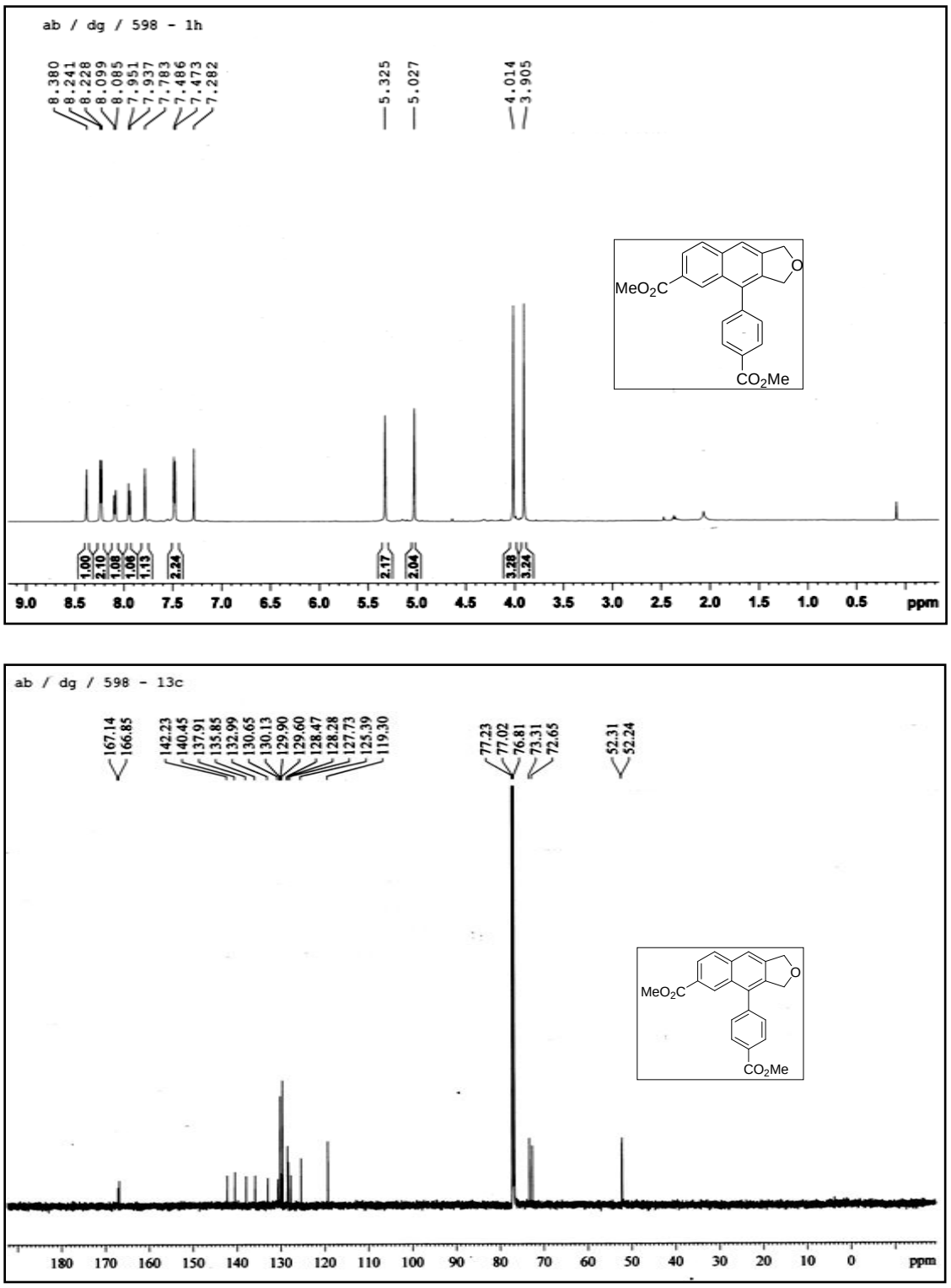


Figure 4.8: ^{1}H and ^{13}C NMR spectra of 4.14f (600 MHz, $CDCl_3$)

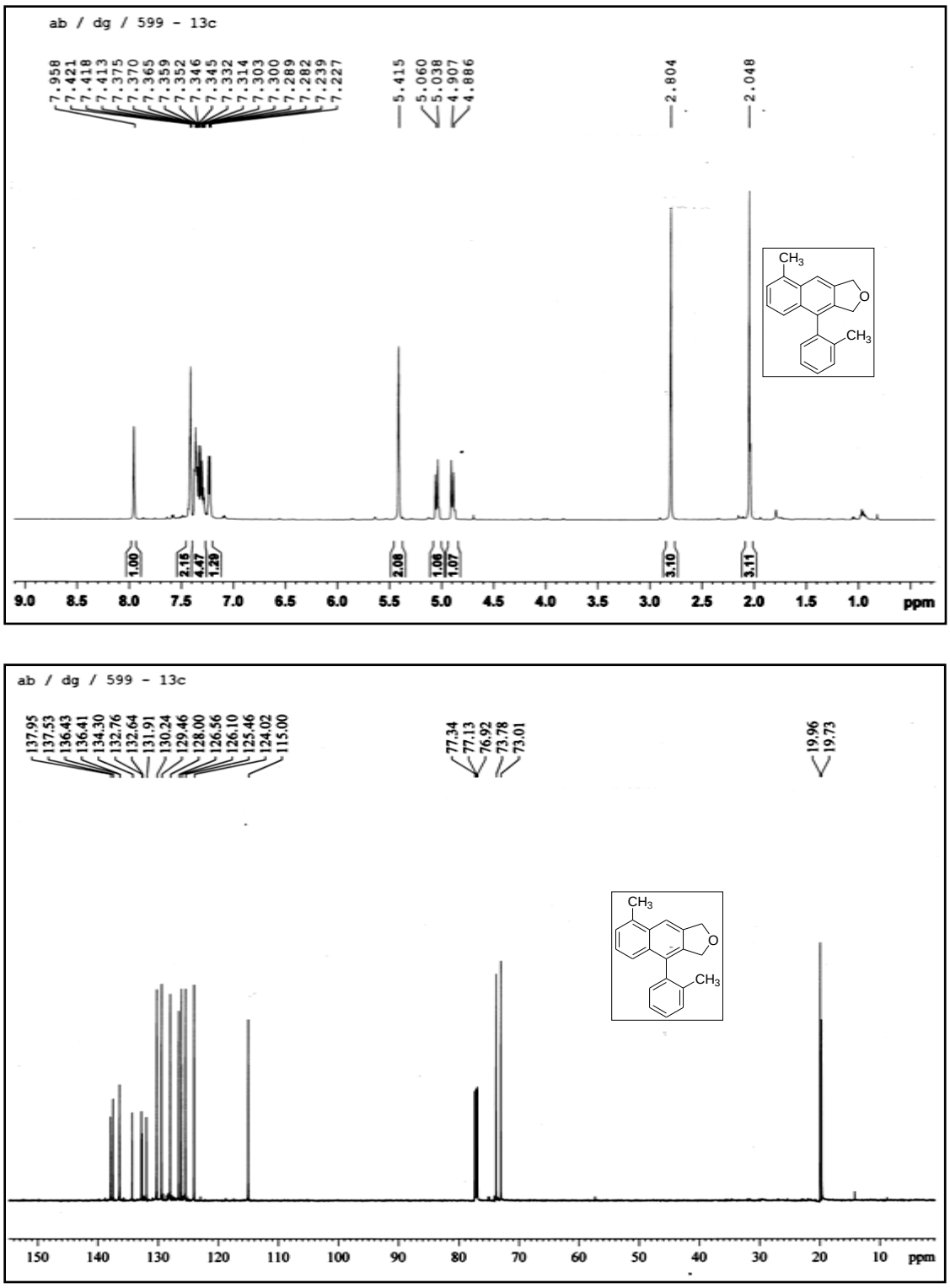


Figure 4.9: ^{1}H and ^{13}C NMR spectra of 4.14g (600 MHz, $CDCl_3$)

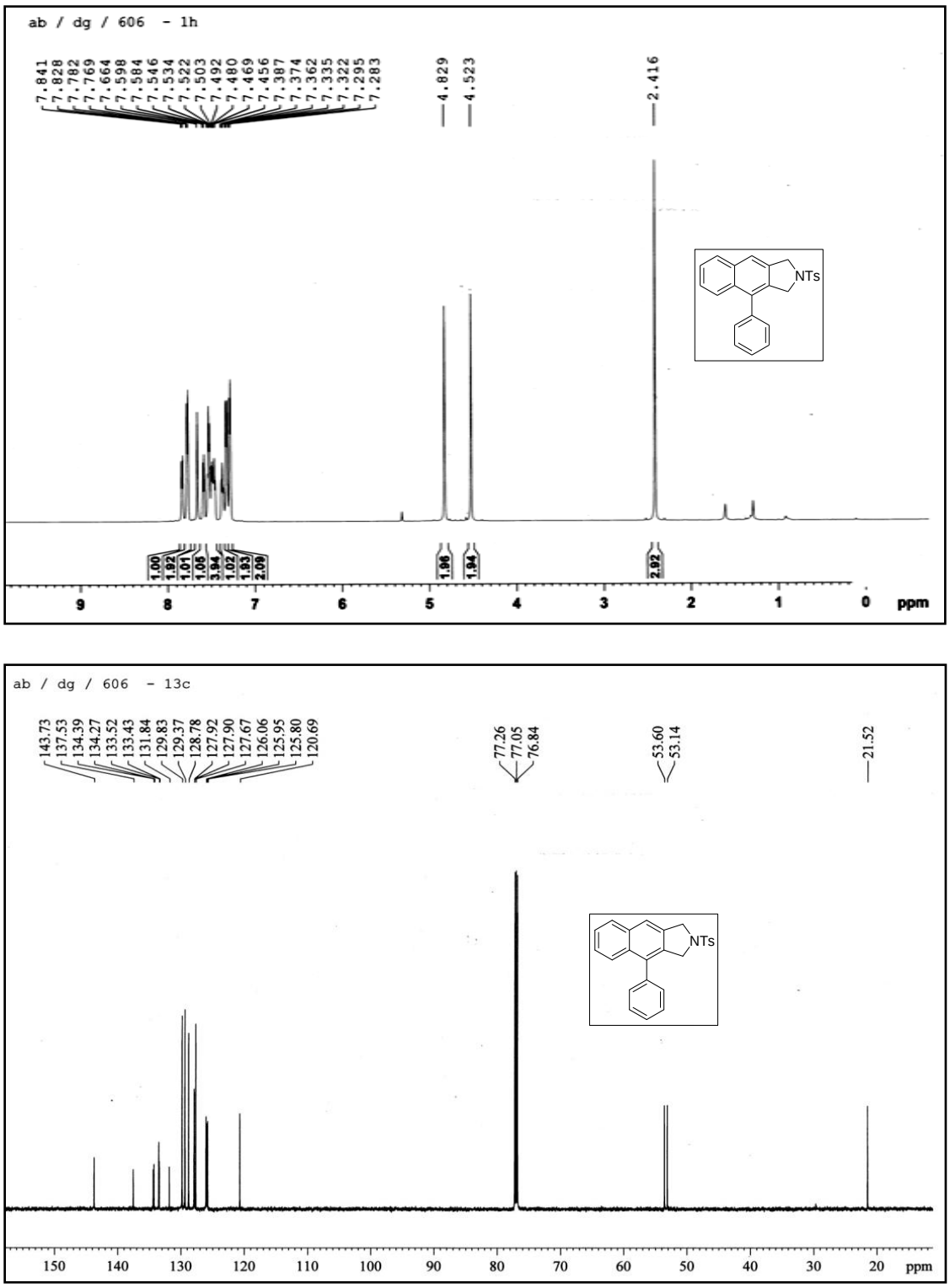


Figure 4.10: ^{1}H and ^{13}C NMR spectra of 4.17a (600 MHz, $CDCl_3$)

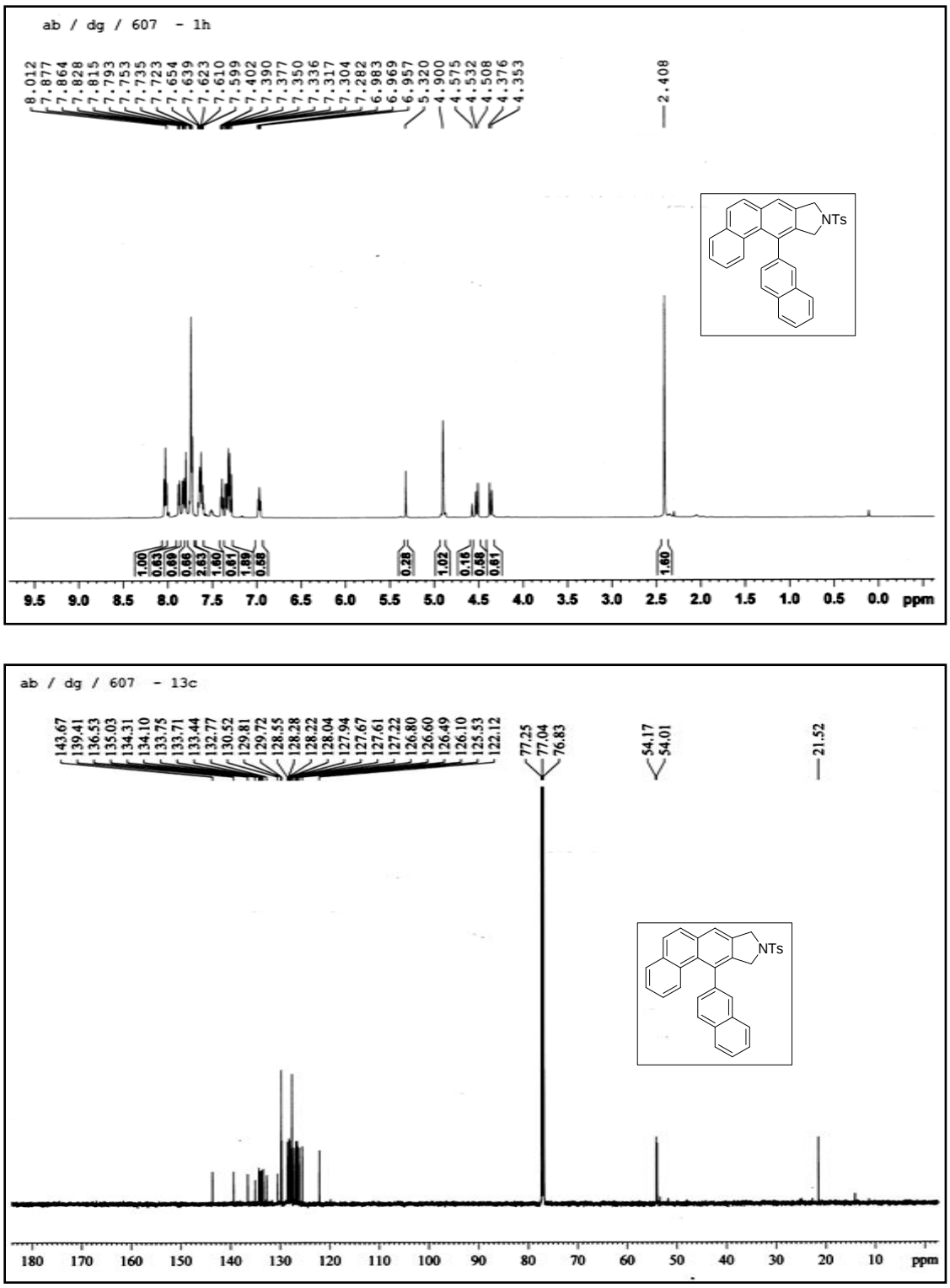


Figure 4.11: ^{1}H and ^{13}C NMR spectra of 4.17h (600 MHz, $CDCl_3$)

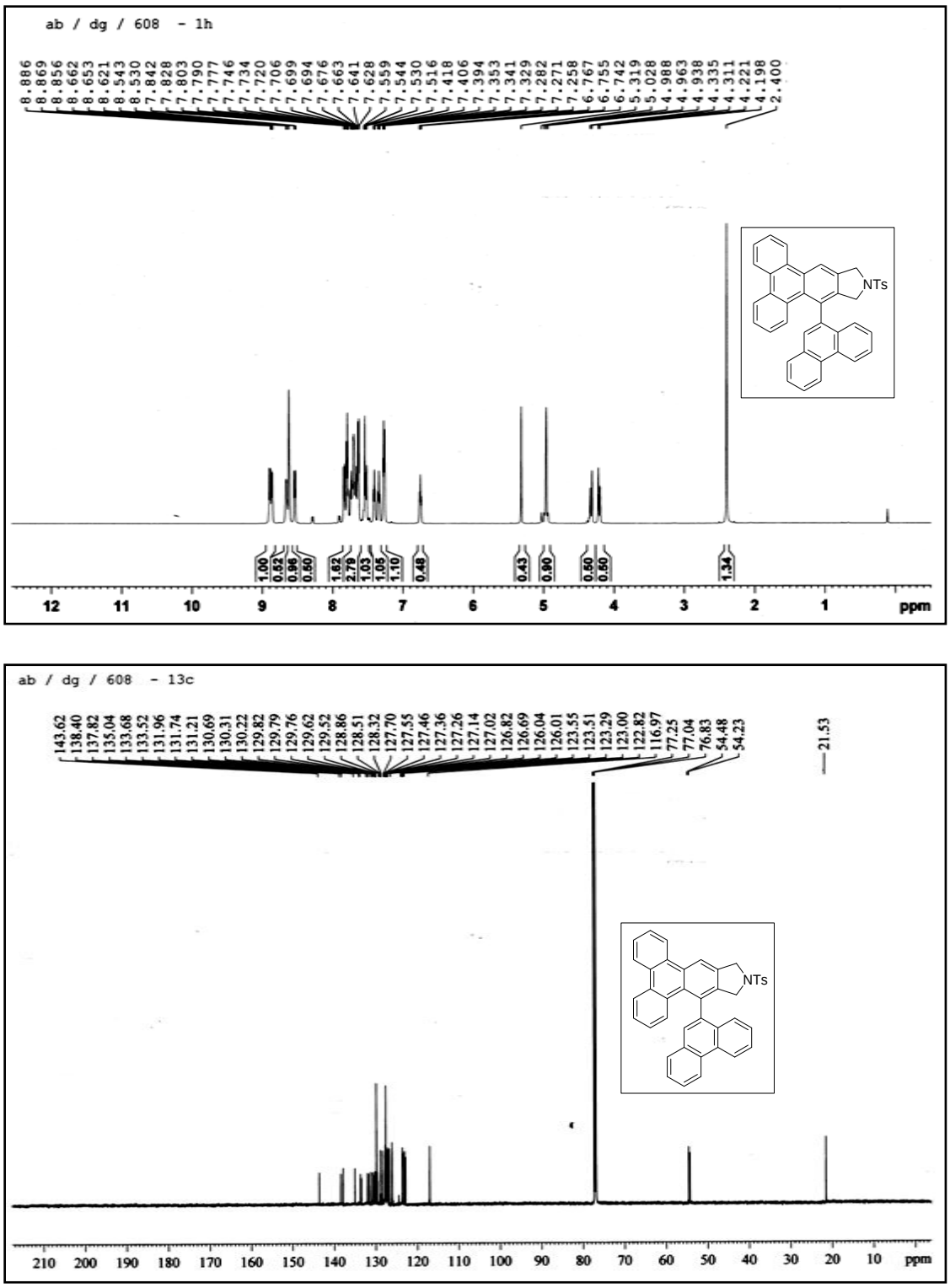


Figure 4.12: ^{1}H and ^{13}C NMR spectra of 4.17c (600 MHz, $CDCl_3$)

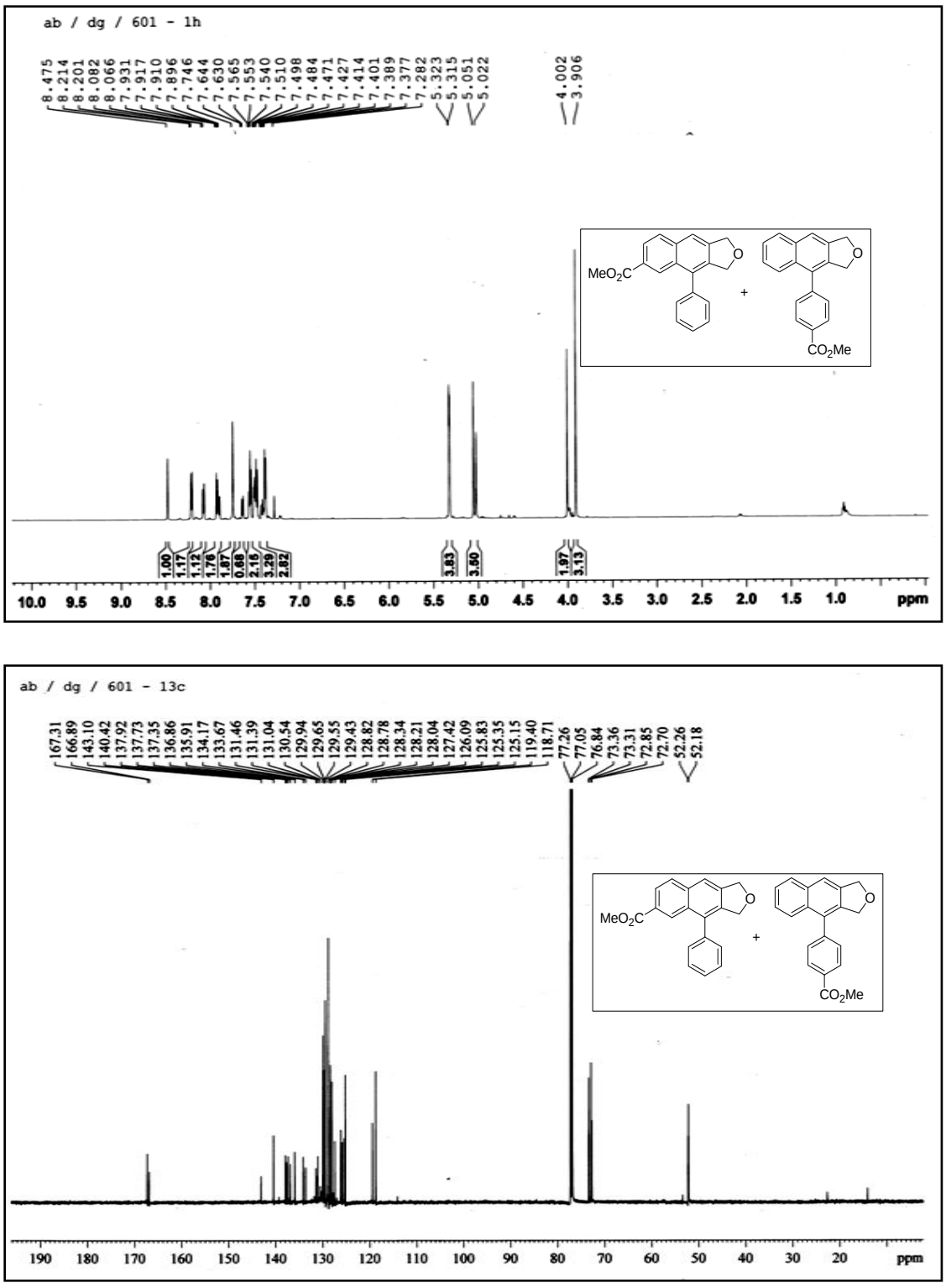


Figure 4.13: ^{1}H and ^{13}C NMR spectra of mixture of 4.20a and 4.20b (600 MHz, $CDCl_3$)

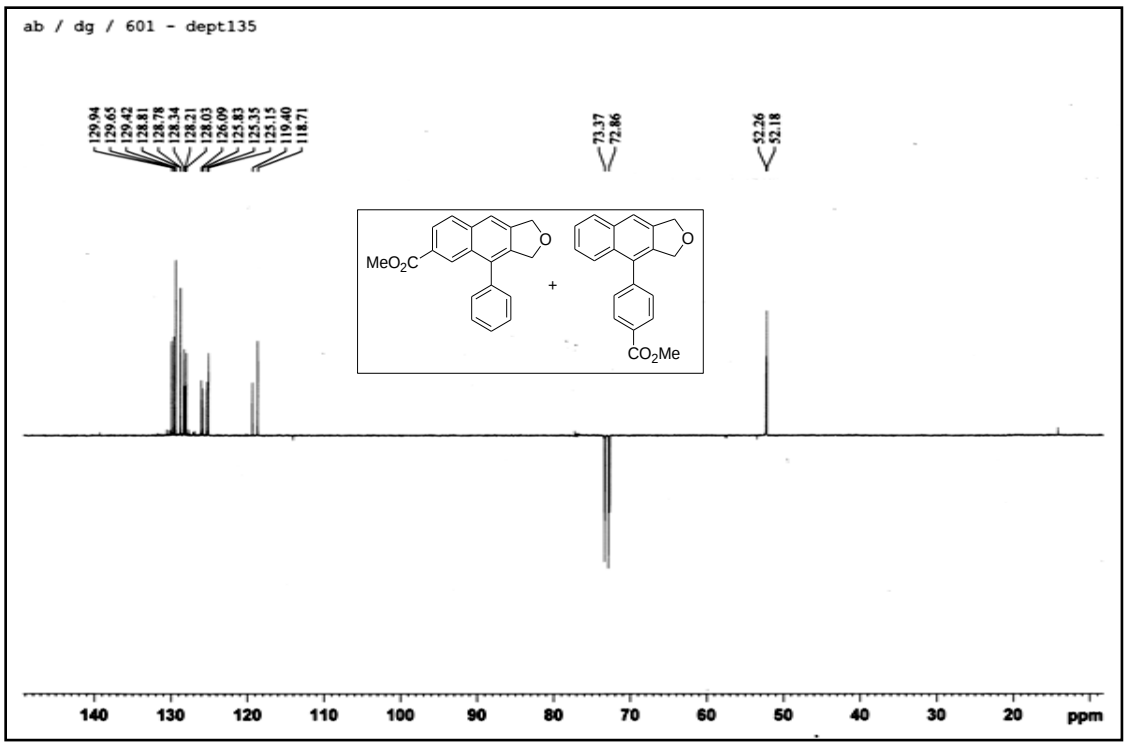


Figure 4.14: DEPT-135 spectrum of mixture of 4.20a and 4.20b (600 MHz, $CDCl_3$)

4.9 References

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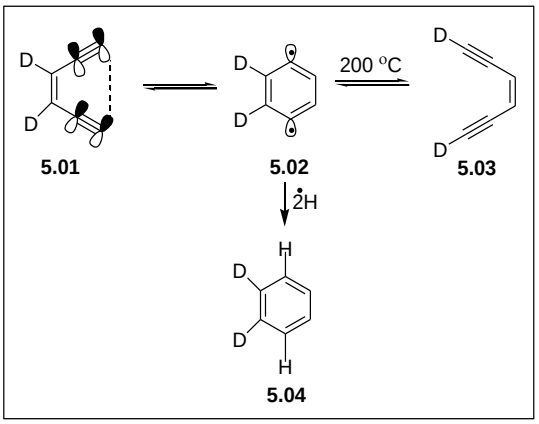
Chapter 5

1,8-Diamino Naphthalene Based Enediynes: H-bond Induced Activation of Bergman Cyclization

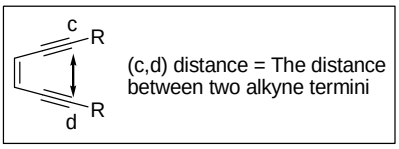
5.1 Introduction

In the early 1970's, Bergman and his coworkers[1] showed that *cis*-hex-3-ene-1,5-diyne **5.01** upon thermolysis, generated a reactive intermediate 1,4-dehydrobenzene diradical which underwent a rearrangement to give product like **5.03**. In presence of suitable proton donor, benzenoid product was also obtained. This cycloaromatization process is known as Bergman cyclization (**Scheme 5.1**).



Scheme 5.1: Schematic representation of Bergman cyclization

In the late 1980's, the discovery[2] of natural enediyne and its DNA damaging activity made scientists interested in designing novel mimic of natural enediyne. However, since the natural enediynes undergo cyclization at 37 °C (the physiological temperature), studies were undertaken to know what prompted them to undergo cyclization readily. In



Scheme 5.2: (c,d)-distance

1988, Nicolaou *et al.*[3] proposed a hypothesis stating that for an enediyne to undergo cyclization spontaneously at ambient temperature, it must possess a (c,d)- distance ranging between 3.20-3.31 Å. Cyclic enediynes of appropriate size have shorter (c,d)-

distance (~ 3.25 Å) than acyclic enediynes (~ 4.12 Å) which results in cyclic enediynes having lower activation energy barrier as compared to the acyclic one.

5.2 Previous Work

Numerous efforts have been given to lower the activation energy barrier for the Bergman cyclization in enediyne by reducing the (c,d)-distance. Previously, our group, as well as a number of other groups, have studied many skeletons. Approaches like metal chelation,[4] π-stacking[5] and *ortho*-effect[6] or pH triggering[7] have been reported to lower the Bergman cyclization activation energy (**Figure 5.1**). Keeping all the previous work in mind, we set our objective as outlined below.

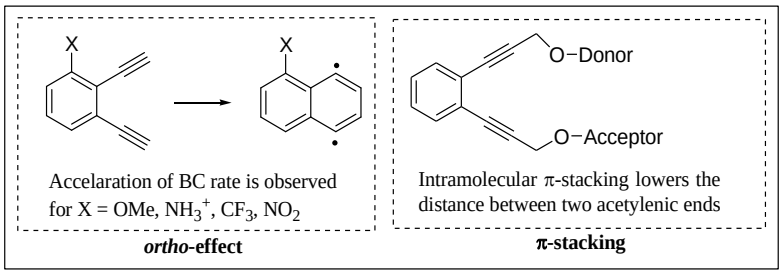


Figure 5.1: Attempts to lower the BC temperature

5.3 Objective

Our intention was not to use any external agent to reduce the (c,d)-distance. Rather we wanted to design a 'proton sponge' type molecule to lower the activation potential of the Bergman reaction where the intramolecular hydrogen bonding will reduce the apparent ring size (**Figure 5.2**).

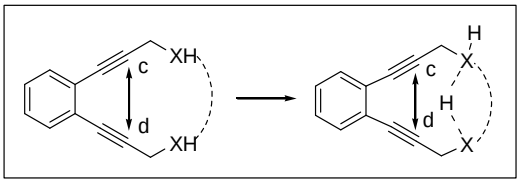


Figure 5.2: Our designed molecule

Strong intramolecular hydrogen bonding potential of 1,8-diamino naphthalene has roused the interest of researchers for a long time.[8] It is mainly used as catalyst or pH sensing material.[9] We tried to make a short route to design a cyclic enediyne skeleton

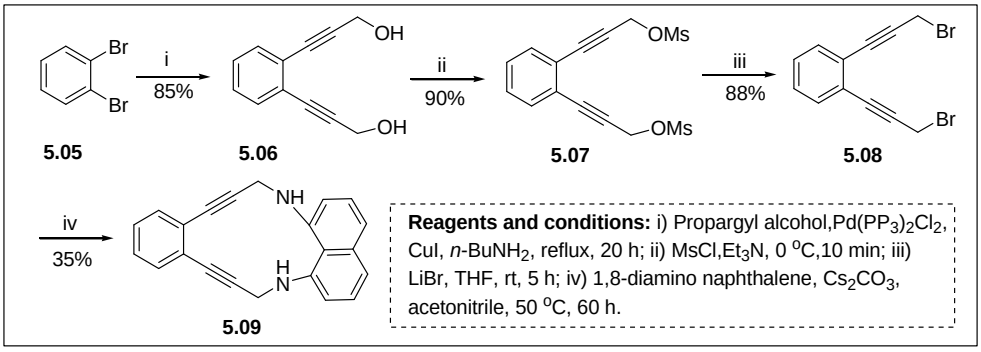
where the intramolecular hydrogen bonding will allow it to behave as diaza enediyne of smaller ring size.

5.4 Results and Discussion

In our present report we tried to make a very simple 13-membered enediyne skeleton where the intramolecular hydrogen bonding will allow it to behave as an 11-membered diaza enediyne.

5.4.1 Synthesis

Our synthesis stared with 1,2-dibromobenzene **5.05**. It was reacted with propargyl alcohol under Sonogashira reaction condition. After refluxing for 20 hours in *n*-butylamine, we obtained the diol **5.06**. Compound **5.06** was then mesylated with MsCl in presence of triethylamine at 0 ^{o}C. The mesylate **5.07** was converted to its corresponding bromide derivative **5.08** by reaction with LiBr in THF. Bis N- propargylation of 1,8-diamino naphthalene was done by reacting it with bromide **5.08** in presence of Cs_2CO_3 in dry acetonitrile. However the yield was poor in spite of continuing the reaction for 60 h at 50 °C. The product **5.09** was isolated as pink solid (**Scheme 5.3**).



Scheme 5.3: Synthesis of our target molecule

5.4.2 Spectral Characterization

Structure elucidation of the final enediyne product was done based on NMR and mass spectral data. Characteristic spectral features of the final compound are mentioned below.

Since the synthesized sulfone **5.09** is C_2 symmetric, its proton NMR spectrum comprised signals of integral values of 7 protons for its 14 protons. In the ^{1}H NMR spectrum of the enediyne **5.09**, the propargylic methylene protons (H_c and H_d) appeared as singlet at δ 4.16 ppm. Most of the aromatic protons (H_a, H_b and H_f, H_g) appeared in the range δ 7.28-7.43 ppm. The aromatic proton, H_e appears at δ 6.63 ppm as douplet with a coupling constant of 6.6 Hz (**Figure 5.3**). Peak at m/z = 309.1399 in the mass spectrum of **5.09** corresponds to the [MH^+] (calculated mass 309.1392[MH^+]).

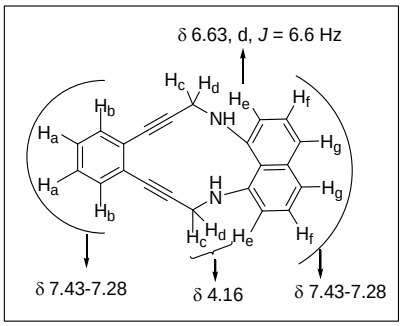


Figure 5.3 ^{1}H NMR assignment of compound 5.09

After successfully synthesizing the target compound, our next target was to confirm the presence of H-bonding. To know whether H-bonding exists or not, we performed several experiments as depicted below.

5.4.3 Energy Minimized Conformation

We wanted to have an energy minimized structure of our synthesized compound so that we can have a appropriate idea about the (c,d)-distance between two acetylene ends and NH···N distance of two amine groups, which will indicate the feasibility of intramolecular hydrogen bonding. We used TURBUMOLE V6.5 software for this purpose using def 2-SVP basis set. Energy minimized structure of compound **5.09** showed a favorable orientation for hydrogen bonding (**Figure 5.4**) with N-H···N bond distance of 2.384 Å and an angle of 104° between NH···N.

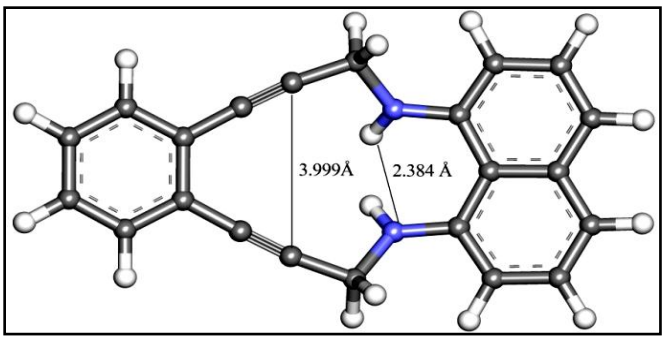


Figure 5.4 Energy minimized structure of enediyne 5.09

It also showed a (c,d)-distance of 3.999 Å. We took another thirteen membered cyclic enediyne **5.10** (**Figure 5.5**), previously synthesized in our laboratory[12] as reference and calculated its (c,d)-distance.

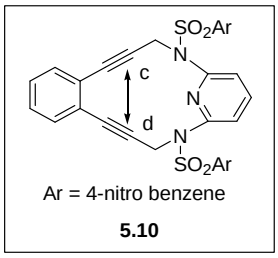


Figure 5.5 Energy minimized structure of enediyne 5.10

The energy minimized configuration of compound **5.10** predicts a (c,d)-distance of 4.342 Å (**Figure 5.6**), whereas for **5.09**, the (c,d)-distance is 3.999Å. From the above observations, we can conclude that the hydrogen bonding induced lowering in the (c,d)-distance should result in a decrease in cyclization temperature.

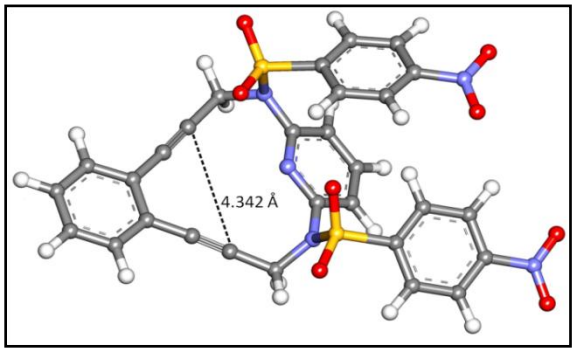


Figure 5.6 Energy minimized structure of enediyne 5.10

5.4.4 Solid State Thermal Reactivity

For further confirmation of the existence of intramolecular hydrogen bonding within the system, we wanted to check the Bergman cyclization temperature. A DSC experiment was performed with 20 mg sample of compound 5.09 in a PerkinElmer DSC instrument. Compound **5.09** showed a strong exothermic peak in thermogram (**Figure 5.7**). The compound had an onset temperature of 150 ^{o}C which is much lower compared to the thirteen membered sulfonamide cyclic enediyne (5.10),[10] where the onset temperature is around 275 ^{o}C.

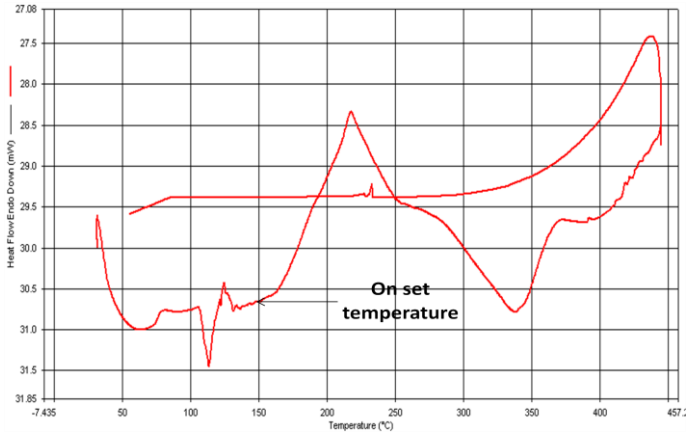


Figure 5.7: DSC plot of compound 5.09

5.4.5 Variable Temperature (VT) NMR Study

In the past, variable temperature NMR experiments have been used to detect if exchangeable protons are involved in intramolecular hydrogen bonds or are not solvent exposed. Their uses and limitations have been detailed for proteins by Williamson and Baxter.[11] We followed the NMR assignment of CsA performed by Kessler,[12] and measured the temperature coefficient (TC) of the NH protons. In support of our initial prediction about the intramolecular hydrogen bonding between the two parallel chains of compound **5.09**, the VT-NMR in d_6-DMSO was recorded **(Figure 5.8)**. With the

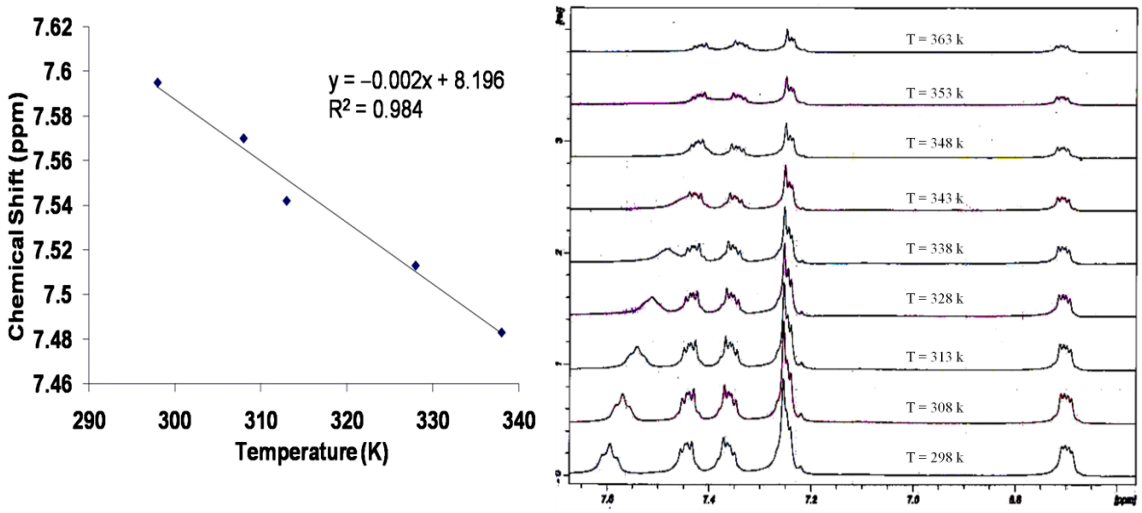


Figure 5.8: VT-NMR (400MHz, d_6-DMSO) of compound 5.09 in between 298-363K

increasing temperature from 25 ^{o}C to 90 ^{o}C, NH protons of compound **5.09** shifted towards more upfield region. We found a negative slope for $\Delta\delta_{NH}/\Delta T$ with a value of 2 x 10^{-3} which is much lower compared to the Kessler limit i.e. 3.4 x 10^{-3}; This clearly indicates the existence of strong intramolecular hydrogen bonding in enediyne **5.09**.

5.5 Conclusion

In conclusion

i) we have successfully accomplished the synthesis of targeted enediyne molecule **5.09**

ii) Presence of intramolecular H-bonding has been demonstrated by theoretical energy minimization as well temperature dependent ^{1}H-NMR shift measurement.

iii) The effect of intramolecular H-bonding in lowering the Bergman Cyclization temperature has been demonstrated.

5.6 Experimental

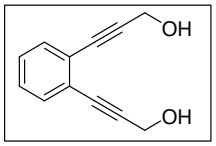
5.6.1 General Experimental and Spectral Data of Some Selected Compounds

General experimental procedures are same as described in chapter 2.

Synthesis of Diol 5.06

1,2-Dibromobenzene (1.0 g, 4.25 mmol), $Pd(PPh_3)_2Cl_2$ (178 mg, 0.25 mmol) and propargyl alcohol (0.56 mL, 9.35 mmol) were added in succession to 30 mL of degassed n-butylamine and left for 20 h at refluxing condition. The reaction mixture was then poured into ethyl acetate and the organic layer was washed with saturated NH_4Cl solution and brine, dried over anhydrous sodium sulfate. Evaporation in vacuum gave an oily residue from which the product was isolated by column chromatography [Si-gel, petroleum ether-ethyl acetate (PE:EA = 1:1) mixture as eluent].

3-[2-(3-Hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (5.06)



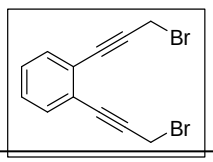
State: viscous liquid; **Yield**: 85%; δ_H (200 MHz, $CDCl_3$): 7.45-7.41(m, 2H), 7.27-7.21(m, 2H), 4.52 (s, 4H); δ_C (50 MHz, $CDCl_3$): 131.4, 128.2, 125.4, 91.8, 84.4, 51.6. HRMS: Calculated for $C_{12}H_{11}O_2$ $[MH^+]$ 187.0759 found 1867.076.

Synthesis of Dibromide 5.08

To an ice-cold solution of alcohol **5.06** (0.5 g, 2.68 mmol) and triethylamine (0.747 mL, 5.37 mmol) in 7 mL dry DCM, mesyl chloride (0.415 mL, 5.37 mmol, 5 times diluted with DCM) was added drop wise. The reaction was complete within 10 minutes. The reaction mixture was partitioned between EtOAc (30 mL x 2) and water (50 mL). The organic layer was dried over Na_2SO_4. The concentrated reaction mixture was used for the next reaction directly.

The mesylated compound **5.07** (0.744 g, 2.17 mmol) was dissolved in 10 mL of dry THF. LiBr (0.471, 2.5 eq) was added to it and stirred for 5 h at room-temperature. The solvent was evaporated and diluted with ethyl acetate. The organic layer was washed with water and brine (20 mL x 2), dried over sodium sulfate and concentrated and subjected to silica gel column chromatography using petroleum ether and ethyl acetate mixture as eluent (PE:EA = 30:1).

1,2-Bis-(3-bromoprop-1-ynyl)benzene (5.08)



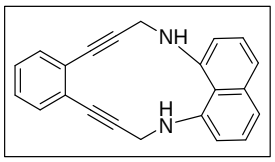
State: viscous liquid; **Yield**: 88%; δ_H (200 MHz, $CDCl_3$): 7.42-7.38(m, 2H), 7.27-7.23 (m, 2H), 4.19 (s, 4H); δ_C (50 MHz, $CDCl_3$): 132.0,

128.6, 125.0, 88.5, 85.0, 15.3. HRMS: Calculated for $C_{12}H_9Br_2$ [MH^+] 310.9071 found 310.9070.

Procedure for the Synthesis of Targeted Enediyne 5.09

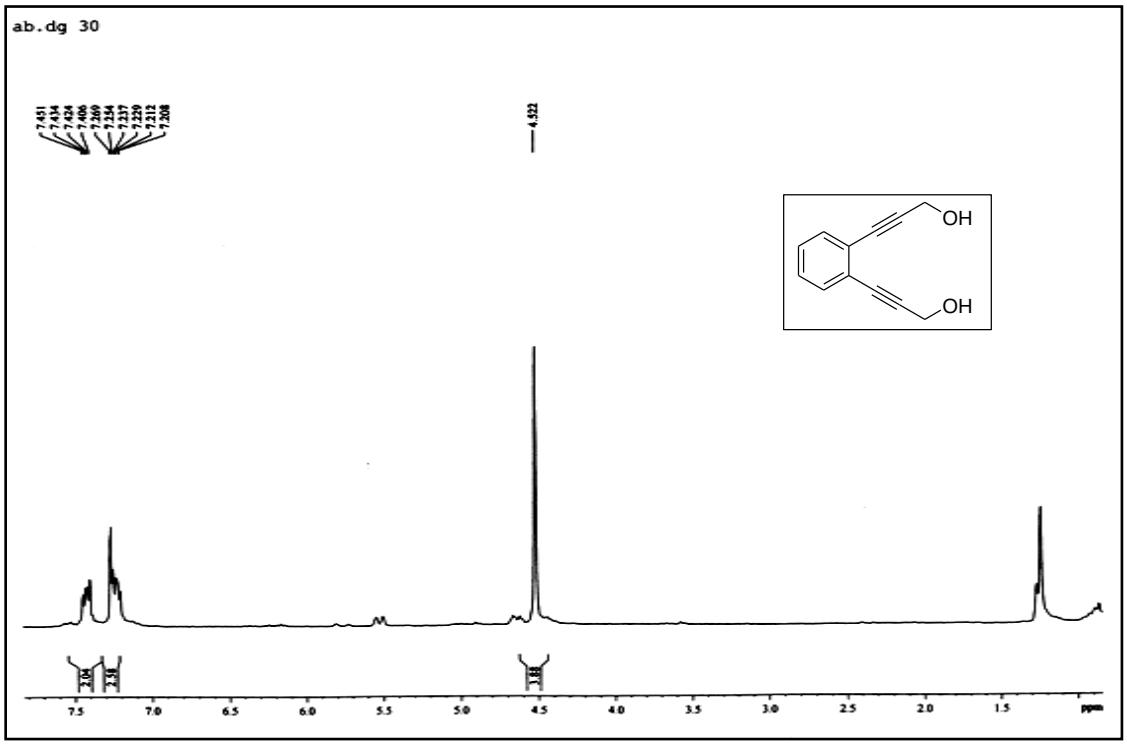
The synthesized bromide (0.156 g, 0.5 mmol) was dissolved in 10 mL of dry acetonitrile. To it Cs_2CO_3 (0.488 g, 1.5 mmol) and 1,8-diaminonaphthalene (0.04 g) were added and the mixture was stirred for 60 h at 50 ^oC. It was then partitioned between ethyl acetate and water (50 mL each). The organic layer was washed with brine, and dried over sodium sulfate and evaporated. The concentrated oily residue was subjected to silica gel ccolumn chromatography using petroleum ether-ethyl acetate mixture as eluent (PE:EA = 2:1)

Spectral Data of Compound (5.09)



State: pink solid; [m.p = 140 °C]: **Yield**: 35%; δ_H (600 MHz, $CDCl_3$): 7.43 (s, 2H), 7.34-7.28 (m, 6H), 6.626 (d, 2H, *J* = 6.6 Hz), 4.16(s, 4H); δ_C (150 MHz, $CDCl_3$): 144.9, 137.0, 129.9, 128.0, 126.9, 126.2, 120.9, 118.5, 111.0, 92.3, 84.1, 53.4. HRMS: Calculated for $C_{22}H_{17}N_2$[MH^+] 309.1392 found 309.1399.

5.7 ^{1}H and ^{13}C NMR Spectra of Some Selected Compounds



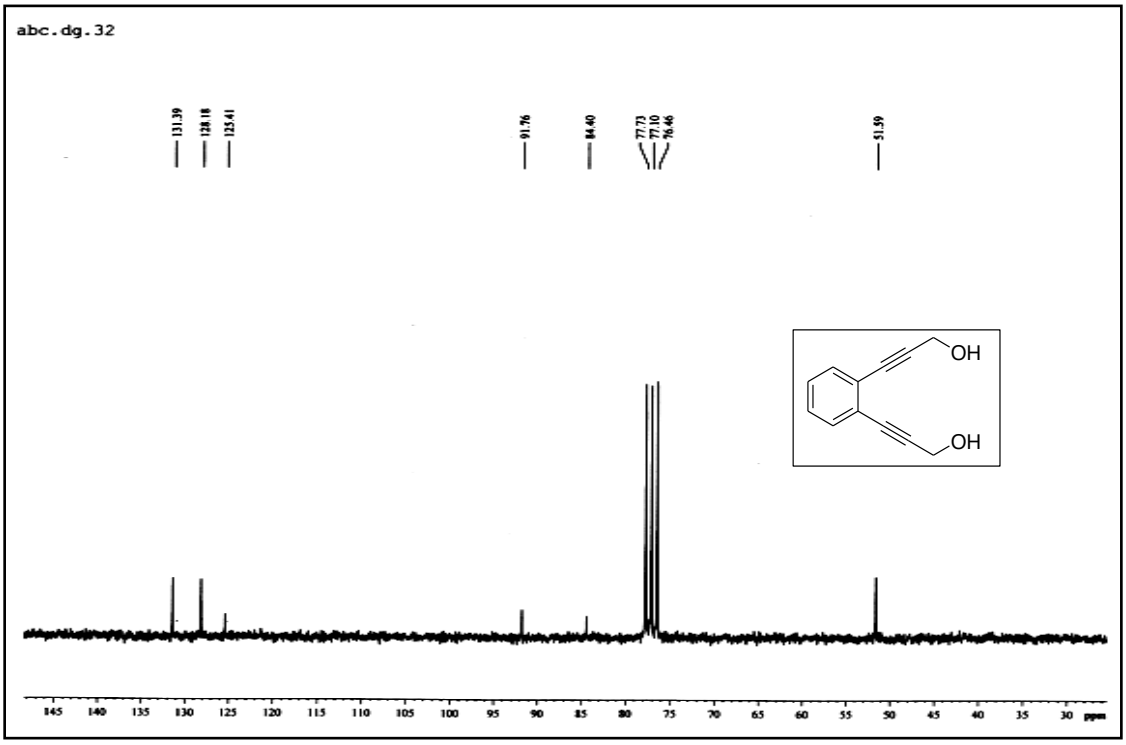


Figure 5.9: ^{1}H and ^{13}C NMR spectra of 5.06 (200 MHz, $CDCl_3$)

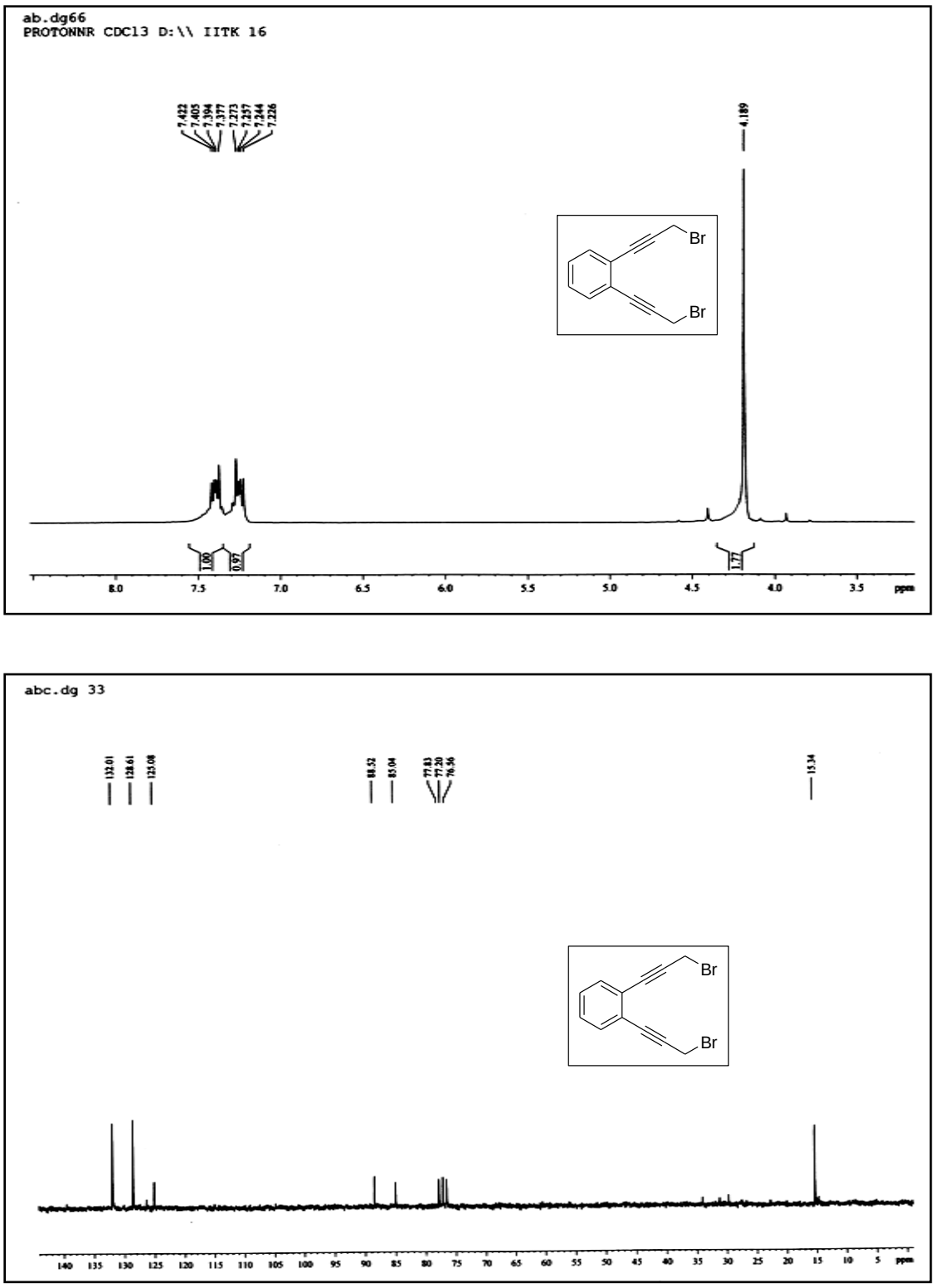


Figure 5.10: ^{1}H and ^{13}C NMR spectra of 5.08 (200 MHz, $CDCl_3$)

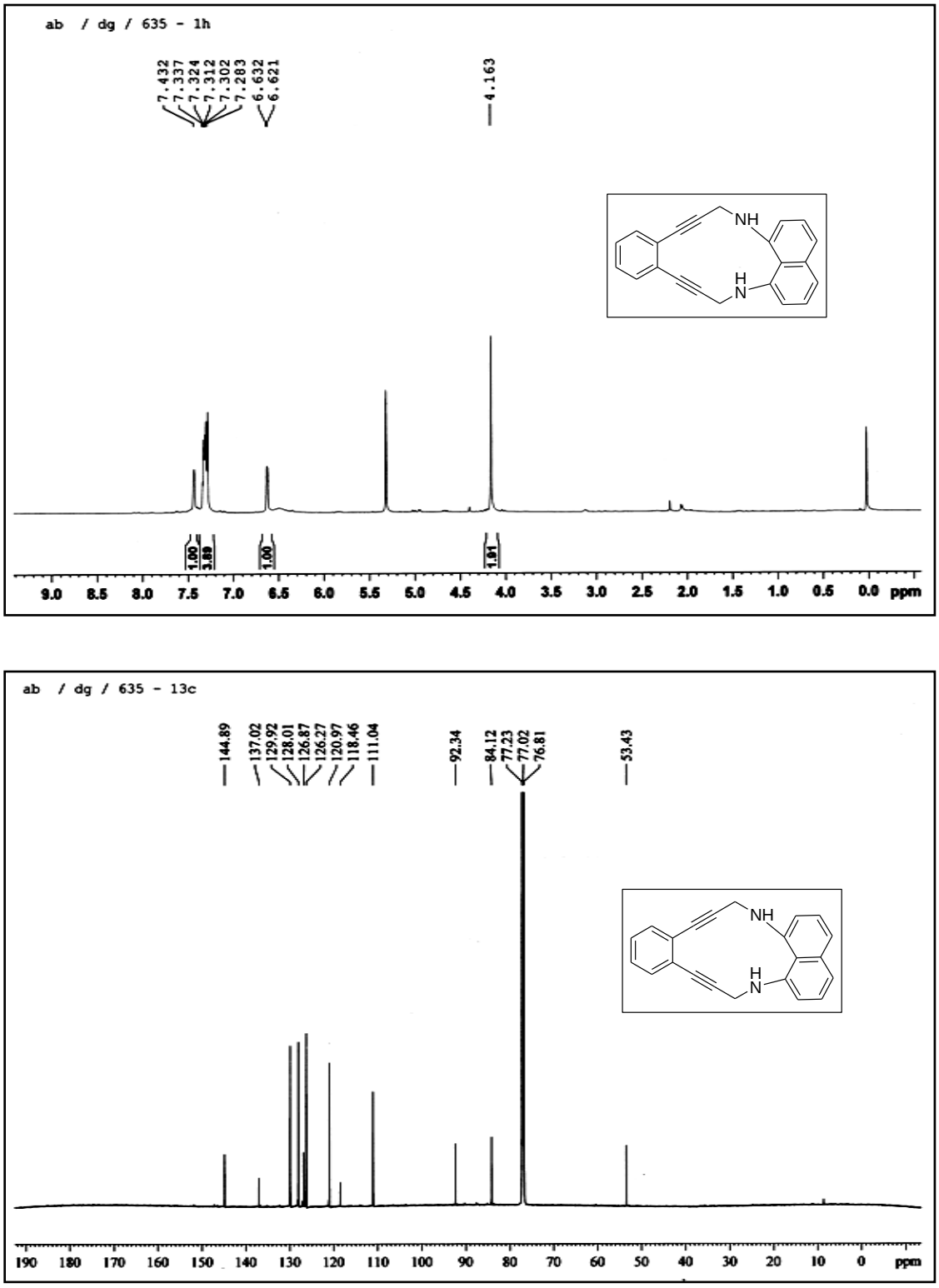


Figure 5.11: ^{1}H and ^{13}C NMR spectra of 5.09 (600 MHz, $CDCl_3$)

5.8 References

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Chapter 6: Summary and Future Scope

6.1 Summary and Contribution Made

In this section of the dissertation, the major findings of the present investigations have been summarized as follows:

1. We have successfully synthesized several cyclic *bis*-dienyl propargyl sulfones which under basic condition, formed 6π-electrocyclization product *via* isomerization to allenic system. Unlike the acyclic *bis*-dienyl propargyl sulfones, where the systems underwent two parallel reactions, namely, GBC and 6π-EC, cyclic systems gave electrocyclization product exclusively. Thus the general preference towards the GBC was successfully switched over to 6π-electrocyclization by incorporation of conformational constraint. The presence of conformational constraint disfavors the formation of *bis*-allene for cyclic sulfones. Hence these cyclic sulfones first isomerized to the mono-allenic sulfone, followed by 6π-EC. The same sequence of reactions is repeated to give final 6π-EC product. The interplay of reactivity and selectivity has thus been developed. The results have the support of computations.
2. A series of aryl naphthalene compounds were prepared in very good yields *via* GB cyclization of various substituted *bis*-propargyl systems, *bis*-propargyl sulfones, ethers and sulfonamides, using basic alumina support. The basic alumina acted as solid support as well as a base to carry out the GB cyclization. The chemoselectivity, shown in this protocol was considerably higher for *bis*-propargyl ether and moderately higher for *bis*-propargyl sulfonamide as compared to that observed in solution phase. The observed selectivity was also reversed in some cases. Reason may be attributed to the differential interaction of the organic substrate with the polar and amphoteric surface of basic alumina leading to unusual selectivity which is not possible in solution.
3. We have successfully synthesized heterocycle-fused aryl naphthalene moiety *via* consecutive Sonogashira coupling and Garratt-Braverman cyclization in a single pot. This method is simple, high yielding and works well for the synthesis of both dihydro isobenzofuran and isoindole systems. The use of a single base for the

whole process *i.e* from Sonogashira coupling to GBC is the highlight of the whole process. However the method worked well for symmetrical substrates. For unsymmetrical systems we have limited success. In future, attempts will be made to explore other reaction conditions to accomplish the one pot synthesis of GB products from unsymmetrical systems.

4. We have developed a new intramolecular H-bonding based strategy to lower the (c,d)-distance in a enediyne molecule. We synthesized our targeted cyclic diaza enediyne molecule and the presence of intramolecular H-bonding has been established by theoretical energy minimization, solid state thermal reactivity analysis as well temperature dependent ^{1}H-NMR shift measurement. The effect of intramolecular H-bonding in lowering the Bergman Cyclization temperature has also been demonstrated.

6.2 Future Scope

The study of various competitive reactions in *bis*-propargyl systems has provided synthetic access to entirely new classes of aromatic compounds with attractive structural motif. These are of immense importance not only to the synthetic community but may hold great significance in terms of biological and material application.

Some eco-friendly, green approaches towards the synthesis of aryl naphthalene derivatives *via* Garratt-Braverman cyclization were made. Use of solid support like basic alumina and one pot synthesis strategy have been applied for these purposes In future, attempts can be made to bring down the temperature required for GB cyclization in case of ether and sulfonamide, to make the method more energy efficient. Investigation can also be made to know whether any modification of basic alumina support can lead to complete preference for a particular isomer in case of unsymmetrical systems.

The one-pot methodology can be investigated to explore other reaction conditions to accomplish the synthesis of GB cyclization products from unsymmetrical *bis*-propargyl systems.

In future, the ability of proton sponge based enediyne molecules to decrease the Bergman cyclization temperature can be well explored by using various diamine molecules with different chain lengths.

Appendices

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Reactivity of conformationally constrained bispropargyl sulfones: complete preference for 6π-electrocyclization process

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ABSTRACT

The reactivity of a series of conformationally constrained bispropargyl sulfones with an ortho alkenyl moiety was studied. Under basic condition, these molecules underwent isomerization, first to monoallene followed by 6π-electrocyclization (6π-EC). Another cycle of isomerization and 6π-EC gave the bis naphthyl sulfones. No Garratt–Braverman (GB) Cyclization product could be isolated even on easing up the strain. Computations with DFT (at BP86-D3/def2-SVP level) indicated that, it is energetically more favorable for the initially formed monoallenic intermediate to undergo electrocyclization rather than isomerize to bisallene. This is in contrast to the acyclic unconstrained counterpart, where isomerization to bisallene is preferred and competing GBC/6π-EC of bisallenes results in mixture of products.

1. Introduction

The reactivity of a series of acyclic bispropargyl sulfones with an ortho alkenyl moiety was recently reported from our laboratory.[1] In basic condition, these molecules underwent 6π-electrocyclization (EC)[2] as well as Garratt–Braverman (GB) cyclization[3] via the bis diene-allene system (Scheme 1). The reaction generally produced a mixture of isomers arising through GB and 6π-EC processes with a bias towards the GB product under ambient conditions. However, the balance could be tilted in favor of the 6π-EC pathway by suitable perturbation of structure and temperature. The reaction never showed complete preference for any particular pathway except for the cis alkene system **D**, which showed exclusive selectivity for GB pathway. It is interesting to note that although step-wise barrier for 6π-EC is lower than that for GBC in these systems, the natural selection of stable substrate conformation that suits GBC plays an important role. To gain further insight on the role of conformation in deciding the partition between the two pathways, we became curious to know the effect of incorporation of conformational constraint in these systems on the course of reaction. Specifically, can we tilt the reaction towards the EC pathway and what happens when the extent of constraint is reduced? Herein we report our results of such a study on the reactivity of sulfones **1a**–**c** with varying spacers linking the alkenyl moieties. The study revealed complete preference for the 6π-EC even when the constraint was relaxed by increasing the spacer length. The results could be nicely explained by computations based on Density Functional Theory (BP86-D3/def2-SVP). It may be noted that these results are in contrast with those obtained in case of *ortho*-alkynyl bispropargyl sulfones, which showed preference for MSC/SC or GB pathway depending upon the spacer length[4] (Scheme 2).

Our strategy to incorporate conformational constraint involved tying up the two ends of the alkene carboxylic acid by coupling with diols. If the compound has to follow GB cyclization pathway, it has to undergo initial isomerization to bisallene and adapt the conformation **M** (Fig. 1). As a first approximation, **N** may represent one of the probable conformations of the biradical where the two radicals are not in a position to self-quench. The conformation **O** through which self-quenching can occur is not structurally distorted; however, because of lack *ortho*-hydrogen, subsequent aromatization cannot occur. The conformation **P** through which self quenching can occur will be structurally distorted. The extent of distortion should depend upon the length of the spacer linking the alkene carboxylates. We expected higher amount of EC product for shorter spacer, which may also occur from the monoallene. The GB product should start to appear as the spacer length increases, due to greater conformational flexibility. Computations also showed that the energy minimized conformation through which quenching can occur is not distorted but is not suitable for quenching because of lack of *ortho*-hydrogens as already mentioned. The rotation of

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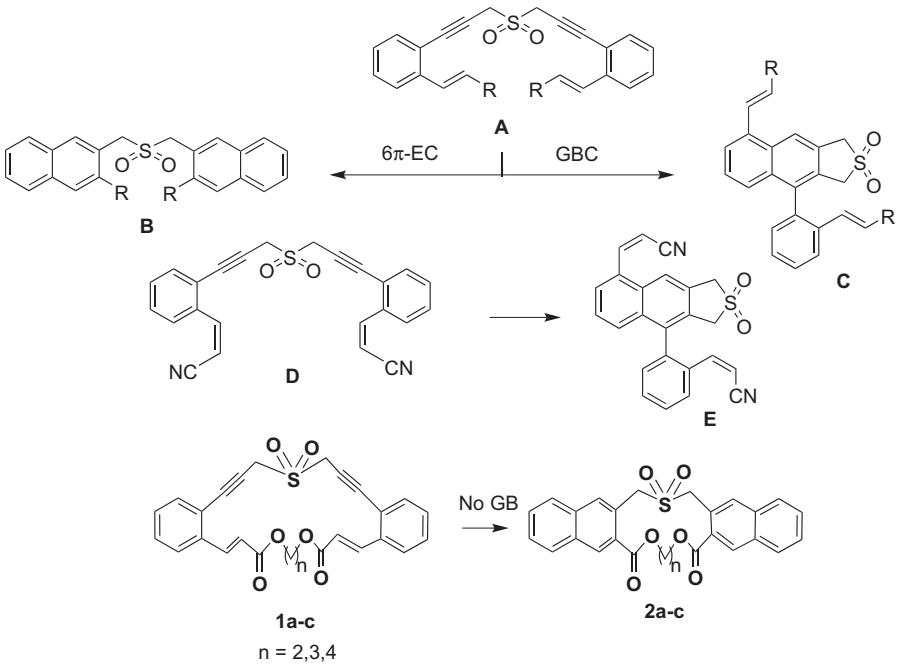
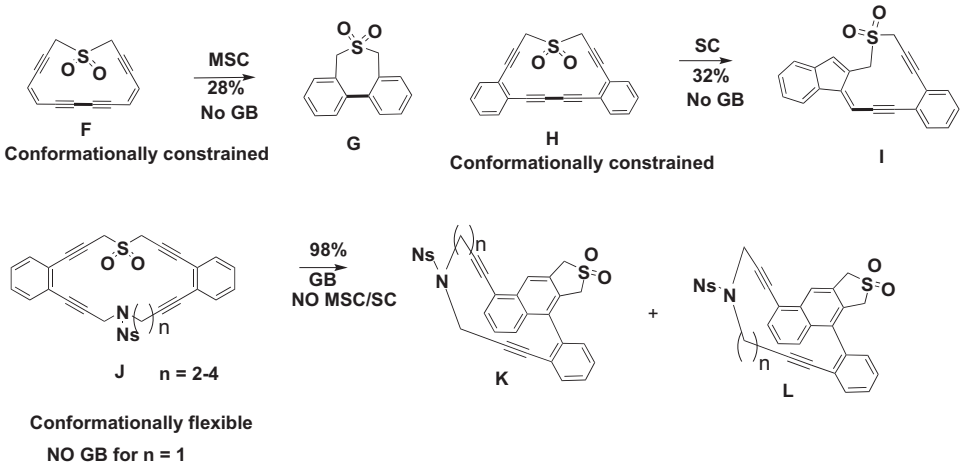


Scheme 1. Reactivity of acyclic and cyclic dieneyne sulfones.



Scheme 2. Reactivity of cyclic enediynyl sulfones.

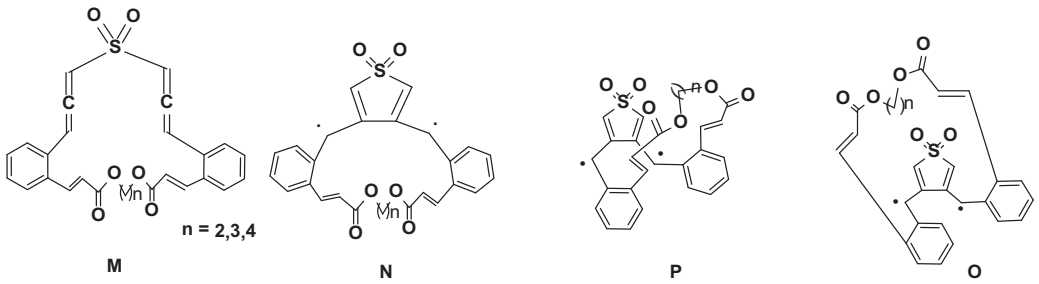


Fig. 1. Possible conformations of GB cyclization pathway of cyclic dieneyne sulfones.

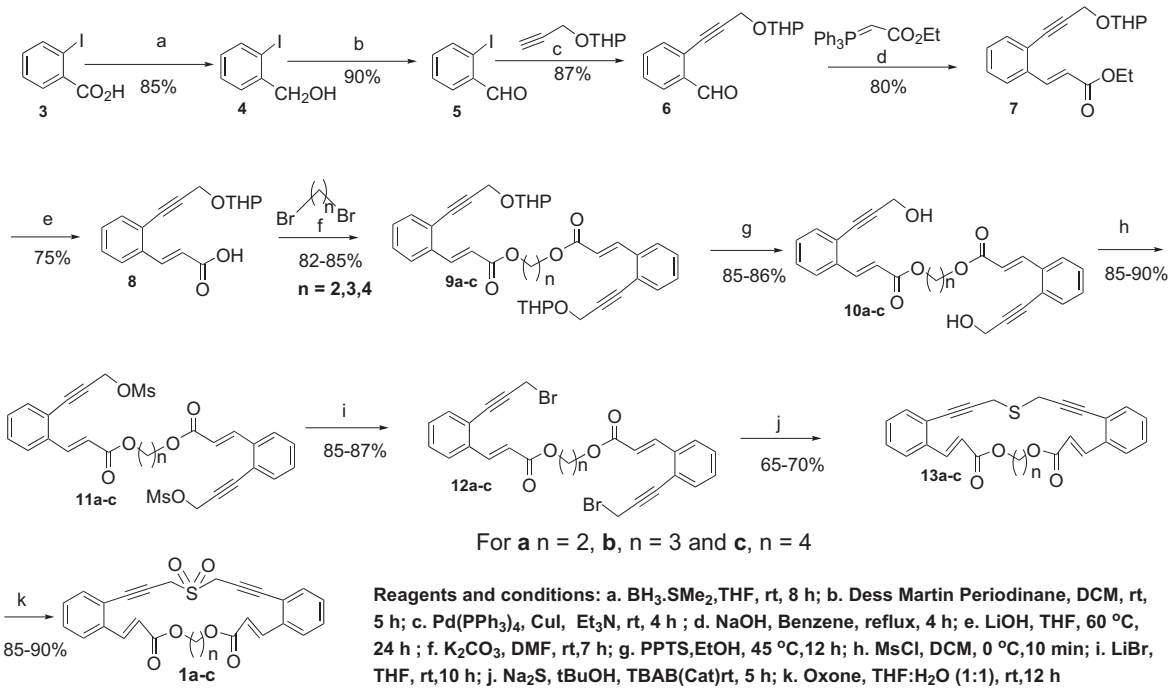
phenyl group is restricted because of the alkenyl linker tying them up.

2. Results and discussions

With this background, we proceeded with the synthesis of the target sulfones **1a**–**c**. The key steps involved are Sonogashira coupling[5] of *O*-iodo benzaldehyde with THP protected propargyl alcohol followed by a Wittig reaction to provide the dieneyne system **7**. Sequential ester hydrolysis and re-esterification with various dibromides produced the bis-esters **9a**–**c**. THP deprotection followed by simple functional group transformation gave the dibromide **12a**–**c**. Intramolecular cyclic sulfide **13a**–**c** formation and followed by oxidation with oxone finally led to the starting sulfones **1a**–**c** (Scheme 3).[1,6]

compared to that of the acyclic ones. Sulfones **1a**–**c** undergo 6π-EC predominantly from the monoallenic form, while acyclic sulfones underwent the same cyclization from the bisallenic form, as dynamic NMR failed show the formation of any product from one cycle of 6π-cyclization, nor any such product could be isolated. To understand this difference in the reactivity of cyclic and acyclic sulfones, we have conducted computational study to estimate the energetic of each of the following pathways: (a) 6π-EC of monoallenic sulfone (MAS, **13a**–**c**), (b) 6π-EC of bisallenic sulfone (BAS), and GBC of BAS. Two most stable conformations selected from the conformational analysis were considered in the analysis (see Computational methods for the details).

Thermodynamic stability of the precursor intermediate that undergo the cyclization step may play an important role. Relative



Scheme 3. Synthesis of target cyclic sulfones.

The experiment was first carried out with the aromatic sulfone **1a**. Thus the compound, dissolved in $CHCl_3$, was treated with TEA (1 equiv) at room temperature. With time, peaks corresponding to the substrate started to decrease while new peaks began to show up (Fig. 2). The reaction was stopped at 30 h when it mostly showed the formation of predominantly one product. Interestingly the product still showed a pair of doublets at δ 6.5 and 8.2, each integrating for one proton, with a coupling constant of 16 Hz showing the presence of one cinnamate system in the product. It was isolated and characterized as **15a**. It was likely to be formed via the monoallene **14a** and subsequent EC. When this molecule was further treated with Et_3N at slightly higher temperature of 45 °C, it got transformed into the double cyclization presumably via another round of isomerization to allene **16a** followed by EC. The other sulfones **1b** and **1c** behaved in a similar fashion thus following the same sequence of isomerization to monoallene and reacting via 6π-EC pathway and repeating the sequence (for mechanism see Scheme 4). The results are shown in Table 1.[7] This is apparent from the ^1H NMR taken at different time points (SD).

From the above NMR study, it is clear that the reaction of these cyclic sulfones **1a**–**c** involves different sequences of steps as stabilities of monoallenic sulfone (MAS), and bisallenic sulfone (BAS), and their precursor bispropargyl sulfone (BPS), show that, in all the cases, **a** (n=2), **b** (n=3), and **c** (n=4), lowest energy conformation of MAS are more stable than the lowest energy conformation of BPS and BAS (Table 2). This is in contrast to the acyclic sulfones where BAS is most stable among the three species. Confinement in the cyclic sulfones makes the bisallenic forms less stable than the bisallenyl forms. Thus, from the thermodynamic point, MAS can be an active intermediate that can undergo cyclization.

To get the complete picture, relative activation free energies for each of these cyclization pathways is more important for the selectivity of the reaction. Hence we have analyzed the cyclization processes by locating the transitions states and cyclized products. 6π-EC from MAS often occurs through an intermediate (shown as RMAS) in which bond-forming carbon atoms come closer by the rotation of the *ortho*-alkenyl group. The respective stepwise barriers from the penultimate intermediate ($\Delta G^{\ddagger}$) are, 11.17, 9.95, 11.79 kcal/mol for n=2, 3, and 4, respectively. Optimized geometries of MAS, RMAS, cyclized product, and the transition state are shown in Fig 3.

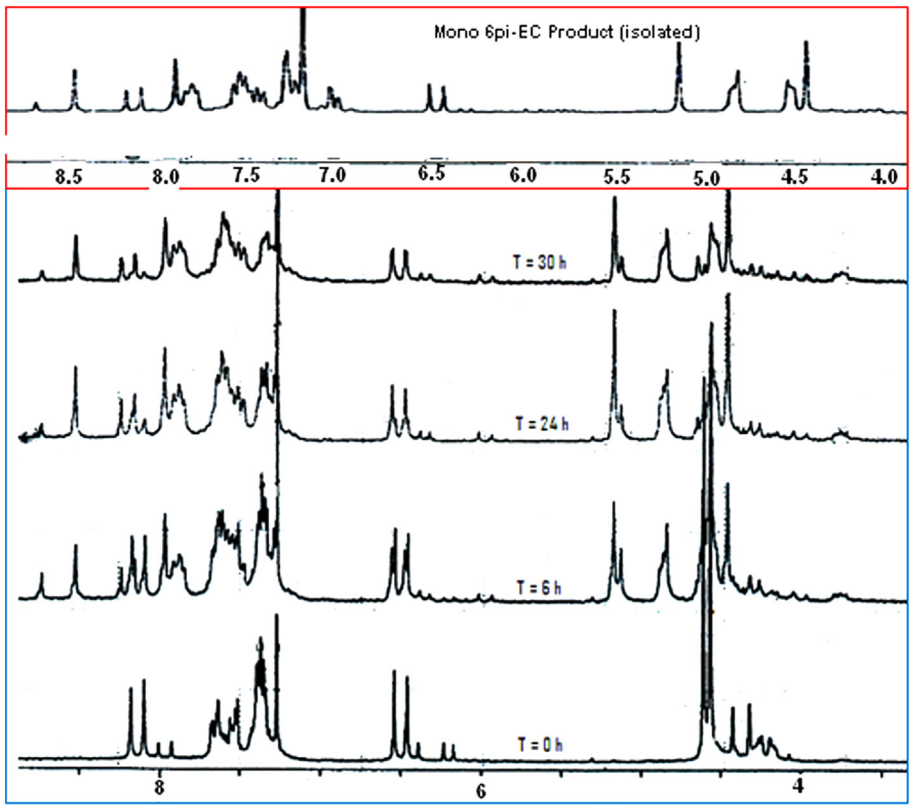
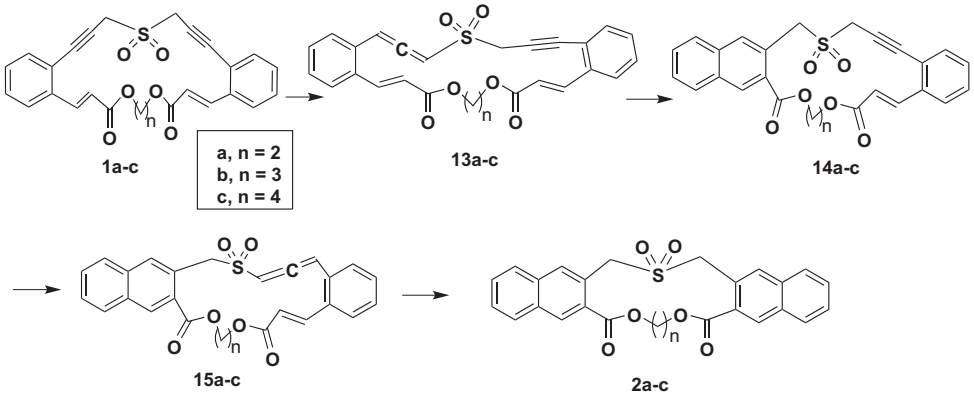


Fig. 2. ^{1}H NMR of **1a** in $CDCl_3$ taken at different time points; top spectrum: ^{1}H NMR of 6π-EC product in $CDCl_3$.



Scheme 4. Proposed stepwise mechanism.

Table 1
Results of cyclization of **1a**–**c**

Substrate	Condition	Product	Yield (%)
1a	Et_3N, RT, 48 h	**2a**	70
1b	Et_3N, RT, 54 h	**2b**	75
1c	Et_3N, RT, 50 h	**2c**	80

Cyclization steps of BAS are relevant when high energy BAS geometries are accessible; for example, at higher temperature, or in presence of stronger bases. BAS can undergo 6π-EC and GBC: two consecutive EC steps to form the final product, or GBC through the formation of biradical intermediate, which further undergoes quenching to form the final product. Between the two conformations of BAS in each case (n=2, 3, and 4), comparison of the TS free energies shows that, one conformation favors GBC while the other favors 6π-EC. Some of the BAS conformations require the rotation of *ortho*-alkenyl groups before it can undergo 6π-EC cyclization. Least energy TS belong to the GBC pathway for each case. GBC has least energy TS for acyclic systems also.

Overall picture from energy profile as depicted in Fig 4, minimum energy pathways lead to the 6π-EC product through MAS intermediate for cyclic sulfones, and favorable pathway for acyclic system is the GBC from BAS. This result is in good agreement with the isolation of the intermediate (**13a**–**c**) and the formation of 6π-EC products (**2a**–**c**).

However, are these energy differences large enough to completely exclude the GBC in all the applied reaction conditions, especially in some conformations when the GBC from BAS has lower barrier than 6π-EC? Inspection of the intermediate biradical

Table 2
Relative free energies (at BP86-D3/def2-SVP level; in kcal/mol) of BPS, MAS, BAS, and TS's for the product formation. The energy of the most stable BPS conformation is taken as the reference (0.0 kcal/mol)

Spacer (*n*)	Conformer	BPS	MAS	Rotated MAS	TS (6π-EC)	BAS	Rotated BAS	TS (6π-EC)	TS (GBC)
2	1	0.00	4.53	—	14.33	9.32	—	18.67	27.57
	2	0.86	−0.32	2.39	13.56	2.87	7.20	23.81	15.80
3	1	0.86	3.94	—	12.63	9.16	—	17.01	26.01
	2	0.00	−0.25	2.77	12.72	2.09	7.69	17.18	15.3
4	1	3.41	8.39	—	17.52	5.37	—	27.18	18.07
	2	0.00	−0.55	4.49	16.28	6.64	9.40	22.18	33.62
0 (acyclic)	1	0.00	2.61		17.18	−0.83		18.81	14.36

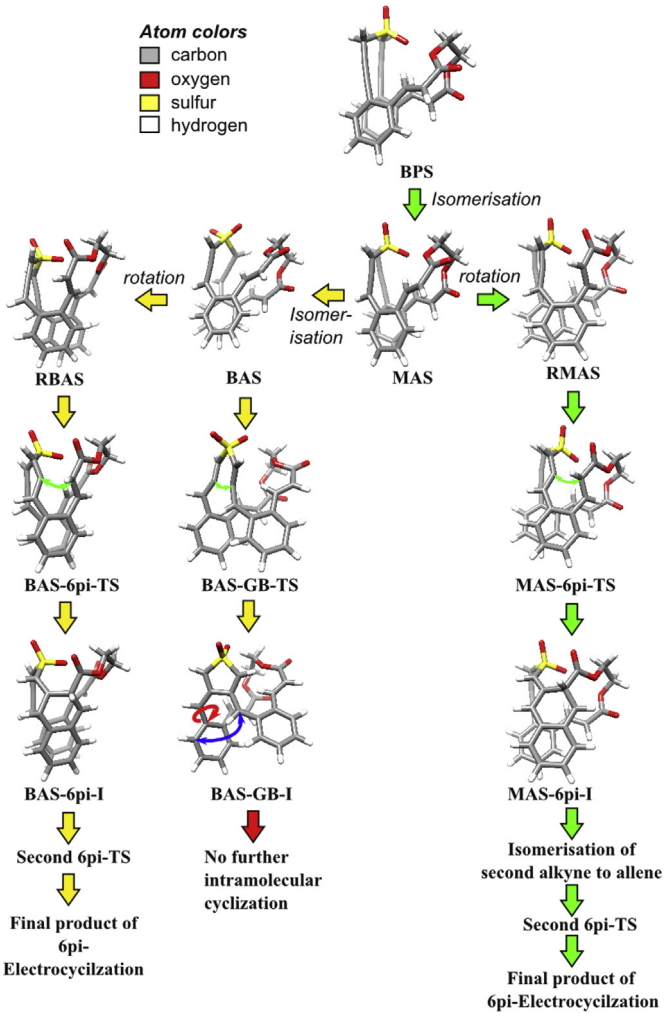


Fig. 3. Three cyclization pathways and the optimized geometries of the relevant structures (*n*=2, conformation **2**).

BAS–GB–I, (Fig. 3) shows that further quenching reaction may not be easy. The rotation of the phenyl group to bring *ortho*-carbon containing H, require an estimated barrier of 19 kcal/mol, too high for a radical reaction.[7] Thus, a reactive biradical will be generated that has no easy internal quenching mechanism and hence, might undergo any of the other processes, namely, H-abstraction, polymerization or decomposition.

In conclusion, our experimental findings of occurrence of exclusive 6π-EC from dieneyne sulfones upon base treatment have been nicely supported by computation. A distinct difference in the mechanism of reactivity of such cyclic systems towards stepwise 6π-EC involving the monoallene intermediate as compared to the acyclic system was observed. These results along with previously observed ones, has helped us to understand the electronic and conformational constraints controlling the course of reactions involving such systems.

2.1. Computational methods

Even though the cyclic bispropargyl sulfones (BPS) in our study are relatively confined compared to the open (acyclic) structure, they have sufficient flexibility to warrant a conformational study. Two phase QM||MM approach was used for choosing the substrate conformation for further study of the mechanism. Ten conformations were generated from short molecular dynamics (MD) simulations using Molecular Mechanics (MM, Amber force field[8]) implemented in Gabedit V.2.3.8.[9] These geometries were further optimized using Density Functional Theory (DFT). BP86 functional[10] with def2-SVP[11] basis set in combination with the third version of the empirical dispersion correction (DFT-D3)[12] was used for all calculations. Resolution of the identity approximation was employed with corresponding auxiliary basis sets[13] for speed-up. All calculations were carried out with Orca 2.9.1 software package.[14] The benchmark studies[15] showed that with the use of DFT-D3 correction, BP86 gives acceptable accuracy. Comparison of BP86 with B3LYP in our previous studies[1] showed that both the functionals are in excellent agreement. Therefore in the current report we only include the results from BP86 functional. Restricted formalism was used for all calculation except for the biradical intermediates in GBC pathways where unrestricted formalism was used.

3. Experimental

3.1. General procedure for oxidation of sulfides to sulfones

To a solution of compound **13a**–**c** (0.05 mmol) in THF/H_2O (1:1), oxone (0.25 mmol) was added and the mixture was stirred for 12 h at room temperature. The compound reaction mixture was worked up by EtOAc/water, dried over Sodium Sulfate and then evaporated. The compounds (**1a**–**c)** were isolated by column chromatography (Si-gel, PE/EA=2:1).

3.2. General procedure for 6π-electrocyclization reaction and spectral data of the final compounds

Sulfone (10–15 mg) was taken in NMR tube and dissolved in $CDCl_3$ (600 μL). Catalytic amount of Et_3N (10 mol %) was added and reaction was monitored by recording proton NMR in different time interval. Reaction mixture was worked up by chloroform/water and the final products were isolated in pure form by column chromatography (Si-gel, petroleum ether/ethyl acetate mixture as eluent).

3.2.1. Spectral data sulfides. For **13a**: δ_H (200 MHz, $CDCl_3$) 8.18 (d, 2H, *J*=16 Hz), 7.62–7.58 (m, 2H), 7.50–7.45 (m, 2H), 7.33–7.26 (m, 4H), 6.51 (d, 2H, *J*=16 Hz), 4.55 (s, 4H), 3.92 (s, 4H**)**; δ_C (50 MHz,

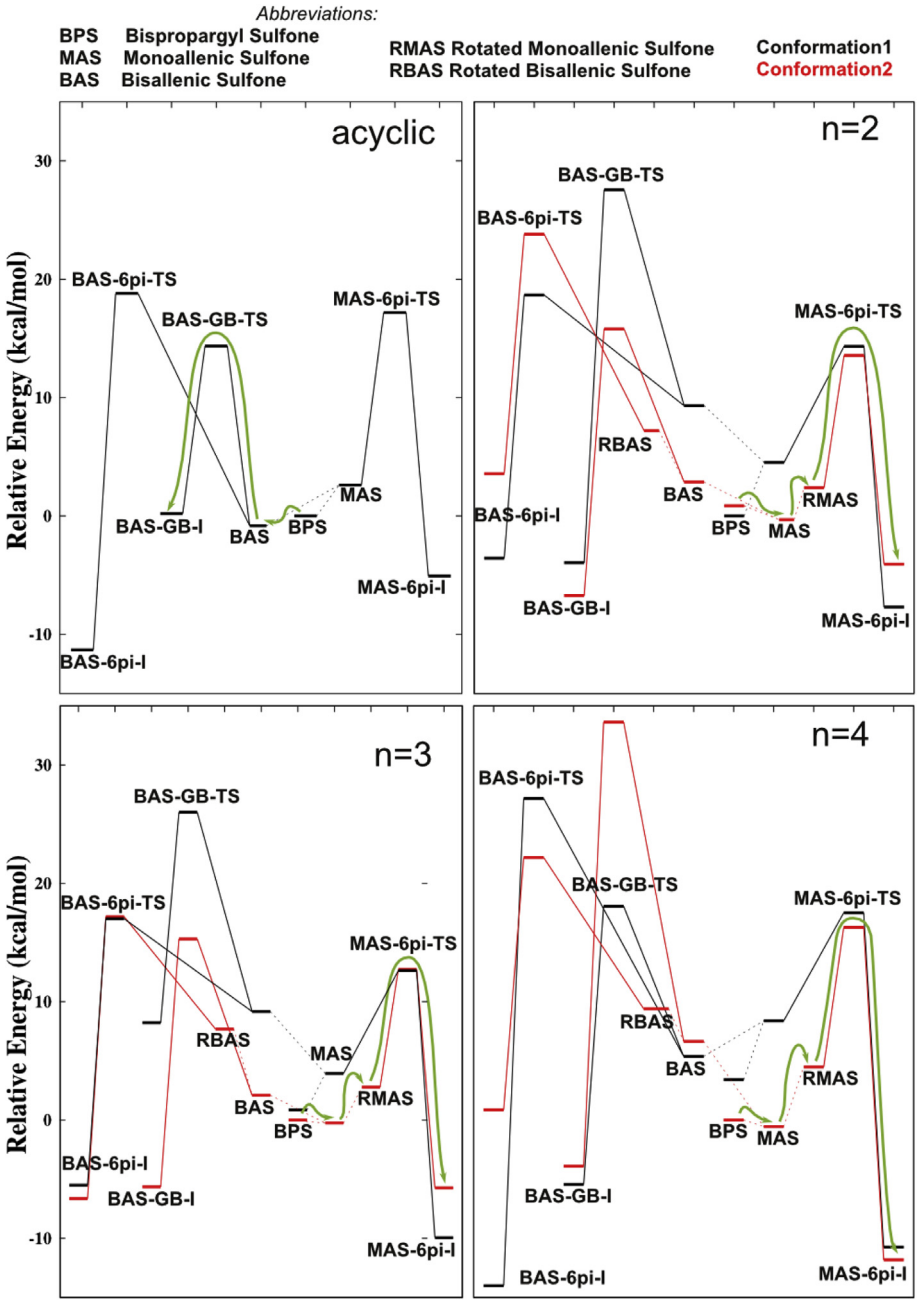


Fig. 4. Reaction profile (Δ*G* in kcal/mol; BP86/def2-SVP) for the cyclization pathways of **1a**–**c**. Two conformations are shown (in black and red). Energy of BPS (center) is considered as the reference. Cyclization pathways through MAS are shown at the right, and pathways through BAS are shown at the left. Green curved arrows indicate the most probable pathway. Optimized geometries of the BPS conformations are given in Supplementary data.

$CDCl_3$) 166.5, 142.9, 135.7, 132.9, 129.8, 128.5, 126.2, 123.8, 119.3, 91.0, 81.1, 62.6, 20.2; Mass *m*/*z* 429 (MH^+).

For **13b**: δ_H (200 MHz, $CDCl_3$) 8.26 (d, 2H, *J*=16 Hz), 7.65–7.30 (m, 8H), 6.47 (d, 2H, *J*=16 Hz), 4.44 (t, 4H, *J*=6 Hz), 3.88 (s, 4H), 2.17 (t, 2H, *J*=6 Hz); δ_C (50 MHz, $CDCl_3$) 166.6, 142.4, 135.7, 133.1, 129.6, 128.6, 126.0, 123.4, 119.5, 91.5, 83.0, 64.0, 54.4, 23.2; Mass *m*/*z* 443 (MH^+).

For **13c**: δ_H (200 MHz, $CDCl_3$) 8.26 (d, 2H, *J*=16 Hz), 7.65–7.3 (m, 8H), 6.47 (d, 2H, *J*=16 Hz), 4.49–4.41 (m, 4H), 3.81 (s, 4H), 1.81 (s, 4H); δ_C (50 MHz, $CDCl_3$) 166.5, 142.4, 135.7, 133.1, 129.6, 128.6, 126.0, 123.4, 119.6, 91.4, 83.2, 61.9, 30.2, 19.0; Mass *m*/*z* 457 (MH^+).

3.2.2. Spectral data sulfones and 6π-EC product. For **1a**: δ_H (200 MHz, $CDCl_3$) 8.12 (d, 2H, *J*=16 Hz), 7.67–7.63 (m, 2H), 7.55–7.50 (m, 2H), 7.48–7.30 (m, 4H), 6.85 (d, 2H, *J*=16 Hz), 4.60 (s, 4H), 4.55 (s, 4H); δ_C (50 MHz, $CDCl_3$) 166.7, 166.1, 143.5, 142.5, 142.2, 136.3, 134.0, 133.4, 132.0, 130.1, 129.8, 129.0, 128.5, 126.6, 126.2, 122.8, 122.3, 120.5, 120.0, 85.7, 82.4, 62.9, 45.3; Calculated for $C_{26}H_{20}O_6S+Na^+$ 483.0878 found 483.0869.

For **2a**: δ_H (200 MHz, DMSO-d_6) 8.68 (s, 2H), 8.17–8.029 (m, 6H), 7.71–7.65 (m, 4H), 5.34 (s, 4H), 4.76 (s, 4H); δ_C (50 MHz, DMSO-d_6): 167.3, 134.5, 133.8, 132.2, 129.5, 129.4, 129.0, 128.2, 127.9, 123.4, 63.9, 59.5; Calculated for $C_{26}H_{20}O_6S+Na^+$ 483.0878 found 483.0883.

For **1b**: δ_H (200 MHz, $CDCl_3$) 8.16 (d, 2H, *J*=16 Hz), 7.61–7.50 (m, 4H), 7.34–7.30 (m, 4H), 6.43 (d, 2H, *J*=16 Hz), 4.48 (s, 4H), 4.40 (t, 4H, *J*=5.8 Hz), 2.12 (t, 2H, *J*=5.6 Hz); δ_C (50 MHz, $CDCl_3$) 166.4, 142.1, 136.1, 133.2, 129.7, 129.4, 125.6, 122.3, 120.0, 85.8, 81.7, 60.2, 45.7, 28.0; Calculated for $C_{27}H_{22}O_6S+Na^+$ 497.1035 found 497.1017.

For **2b**: δ_H (200 MHz, DMSO-d_6) 8.62 (s, 2H), 8.18–8.01 (m, 6H), 7.75–7.69 (m, 4H), 5.07 (s, 4H), 4.61 (s, 4H); δ_C (200 MHz, DMSO-d_6) 166.9, 134.1, 133.5, 131.9, 129.2, 129.0,128.6, 127.8, 127.5,123.0, 63.5, 59.1, 27.7; Calculated for $C_{27}H_{22}O_6S+Na^+$ 497.1035 found 497.1023.

For **1c**: δ_H (200 MHz, $CDCl_3$) 8.13 (d, 2H, J=16 Hz), 7.68–7.30 (m, 8H), 6.54 (d, 2H, J=16 Hz), 4.55 (s, 4H), 4.36 (s, 4H), 1.93 (s, 4H); δ_C (50 MHz, $CDCl_3$) 166.5, 143.3, 142.3, 142.0, 136.1, 133.8, 133.3, 131.9, 130.2, 129.9, 129.7, 128.9, 128.4, 126.5, 126.0, 122.7, 122.1, 120.3, 119.9, 85.5, 82.3, 62.8, 45.2, 27.9; Calculated for $C_{28}H_{24}O_6S+Na^+$ 511.1191 found 511.1211.

For **2c**: δ_H (200 MHz, $CDCl_3$) 8.53 (s, 2H), 7.96–7.87 (m, 6H), 7.64–7.59 (m, 4H), 5.08 (s, 4H), 4.64 (s, 4H), 2.08 (s, 4H); δ_C (50 MHz, $CDCl_3$) 167.6, 134.2, 133.4, 132.4, 132.4, 129.3, 128.7, 128.5, 127.8, 127.5, 122.3, 64.4, 56.8, 25.5; Calculated for $C_{28}H_{24}O_6S+Na^+$ 511.1191 found 511.1205.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.07.099.

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7. Interestingly, in one ^1H NMR experiment, in presence of a stronger base like DBU, the sulfone **1b** immediately isomerized to the bisallene, which was followed by decomposition thus supporting the difficult energy barrier for self-quenching after biradical formation through GB pathway.
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Garratt–Braverman cyclization on basic alumina: a green protocol with improved selectivity

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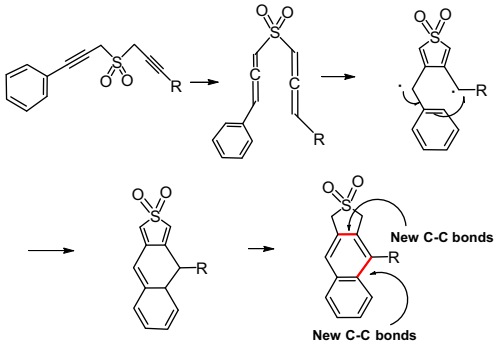
ABSTRACT

A green protocol (compared to the existing methodology) for carrying out Garratt–Braverman cyclization has been developed. The method involves stirring a pre-absorbed bispropargyl sulfone/ether/sulfonamide over basic alumina. The reaction with sulfones was over within 10–15 min at room temperature whereas for the ether/sulfonamide the reaction took 6–8 h at 130 °C. The products, aryl naphthalene derivatives, are obtained by simple filtration through Celite, in excellent yields.

Organic reactions on porous solid support under solvent-free conditions offer many advantages over traditional solution phase synthesis.[1] These include product yields, reaction time, benign conditions, ease of purification and recyclability of the support[2] which are essential attributes of green chemistry. In addition, the solid supports have cavities/channels or large surface area with highly porous exteriors available to substrates.[3] These pores can act as micro reactors where the reactant can bind and undergo the transformation. This can lead to higher selectivity[4] and less side reactions as compared to the same reaction under solution phase. Amongst the many solid supports that have been used, alumina is an important member due to its surface property and well defined porosity.[5] It is also available in basic, neutral and acidic forms and the choice of selection depends upon the nature of the reaction. Some of the examples of reactions on alumina include oxidation, alkylation, addition, heterocycle synthesis etc.[6] Recently, we have developed an interest in expanding the synthetic scope of Garratt–Braverman (GB) cyclization,[7] a reaction of importance as it involves the formation of two C—C bonds (Scheme 1). The usual substrates for GB reaction are bis-propargyl sulfones/ethers/sulfonamides. While triethyl amine can bring about the rearrangement of the sulfones, stronger bases like KOBu^t, NaH or DBN,[8] are required for ethers and sulfonamides. We were interested in finding a suitable alternative but simple protocol for GB cyclization. Since it is widely believed that the rearrangement proceeds via the formation of a bis-allene, for which one needs the base, it occurred to us that basic alumina could be a possible alternative. The latter has a pH of 9–10 which should be enough to cause the required isomerization of propargyl to allene that subsequently undergoes the GB reaction. This is indeed found to be true and herein we report successful GB reaction on basic alumina, the latter performing the dual role as a solid support as well as a basic catalyst. The reaction proceeds in solvent-free conditions



Scheme 1. GB cyclization of bis-propargyl systems.

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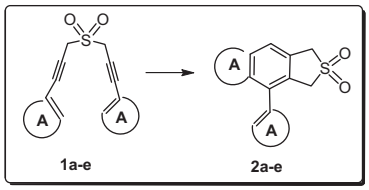
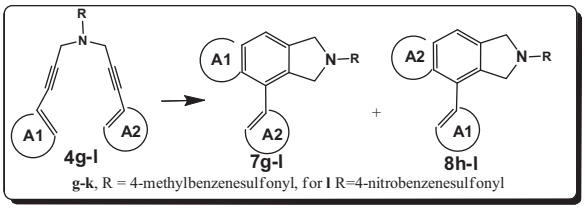
0040-4039/

Table 1
Results of GB reaction of bis-propargyl sulfones over basic alumina



SM	A	Product	% yield
1a	Phenyl	**2a**	95
1b	2-Naphthyl	**2b**	93
1c	2,4-Dimethoxy phenyl	**2c**	95
1d	5-Methoxy N-ethoxy carbonyl 3-indolyl	**2d**	90
1e	N-methoxy carbonyl 3-indolyl	**2e**	90

Table 3
Results of GB reaction of bis-propargyl sulfonamides on basic alumina



SM	A1	A2	Product	% yield
4g	Phenyl	Phenyl	**7g**	87
4h	2-Naphthyl	2-Naphthyl	**7h**	85
4i	9-Phenanthryl	9-Phenanthryl	**7i**	89
4j	Phenyl	2-Naphthyl	**7j** & **8j**	90
4k	Phenyl	4-Anisyl	**7k** & **8k**	85
4l	Phenyl	4-Anisyl	**7l** & **8l**	85

leading to the synthesis of easily isolable aryl naphthalenes in high yields. To the best of our knowledge, this is the first example of GB reaction on a solid support under solvent-free condition.

Initially a series of bis-propargyl sulfones **1a–e** were prepared following the literature procedure.[9] These were pre-absorbed on basic alumina (0.5 mmol substrate: 500 mg alumina) and then stirred at room temperature for 10–15 min. The product aryl naphthalene sulfones were isolated pure in high yields simply by extraction with DCM filtration and evaporation followed by crystallization. The results are compiled in Table 1.

Encouraged by the success with sulfones, we focused on the possible extension of this protocol to GB reaction of propargyl ethers and sulfonamides. We realized that because of lower acidity of the propargylic hydrogens in ethers/sulfonamides as compared to that in sulfones, it may be necessary to raise the temperature which was found to be true. Thus when the ether or the sulfonamide (0.5 mmol) was pre-absorbed on the solid surface of basic alumina (500 mg) and stirred at room temperature for up to 48 h, no product was obtained; only the starting material was recovered. However, high yields of the dihydro isobenzofuran/dihydro isoindole derivatives were obtained when the alumina with pre-absorbed substrates was stirred at 130 °C for 6–8 h (Tables 2 and 3). The products were isolated following the same procedure as adapted for the sulfones.

The known GB products were characterized by comparing with those reported in the lit.[9] while the structures of the unknown products were determined by extensive NMR and mass spectral analysis. Thus for the major product **6n** from the GB reaction of **3n**, the ^{13}C NMR showed 9 aryl C—H signals (Fig. 1). For the other isomer **5n**, 11 aryl C—H signals were expected.

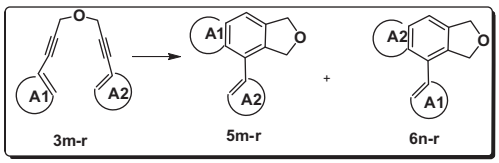
Apart from the operational simplicity, one other interesting feature of this alumina-based protocol is the significantly higher selectivity in case of unsymmetrical ethers and sulfonamides as compared to solution phase (Table 4, entries 1–3, 5) except for **3r** (entry 4), for which the selectivity remained nearly the same. For sulfonamides **4k** and **4l**, reversal of selectivity was observed (entries 6–7).

Thus it appears that the reaction possibly follows different mechanisms on alumina and in solution. The generally accepted mechanism of GB reaction in solution involves the formation of an intermediate diradical; so far, nothing is known about the mechanism when carried out on solid phase. Although knowledge of the latter needs deeper investigation, at this stage, it appears that the loss of resonance energy during formation of product (see mechanism shown in Scheme 1) plays a key role. As the resonance energy per benzene ring is less in naphthalene compared to benzene, the former preferentially participates. Although it is difficult to explain the reversal of selectivity as observed in the reaction of **4k** and **4l** under solid phase conditions, it may be that the bis-allene conformation leading to the major product has a better adaptation in the micro pores.

The remarkable ability of basic alumina can be ascribed to the presence of Al—O^- groups on the alumina surface that acts as a base to assist the isomerization of propargyl to allene system. Once the bis-allene is formed, it undergoes spontaneous cyclization via the diradical[10] or any other reactive intermediate (to be investigated) to lead to the products[11,12] (Scheme 2). The basic centres also played an important role in facilitating the H^+ shifts required in order to regain aromaticity. Regarding recyclability, the solid support after the reaction of sulfones could be reused at least 5 times without significant loss of activity. However, in case of ether or sulfonamide, the recovered alumina could not be reused because of use of prolonged heating at high temperature.

In conclusion we have developed a green and high yielding method for carrying out the GB reaction of various bis-propargyl sulfones, ethers and sulfonamides using basic alumina. The selectivity shown by the unsymmetrical ethers is also very high. Our current efforts' aim is directed towards bringing down the temperature for GB reaction of ethers or sulfonamides.

Table 2
Results of GB reaction of bis-propargyl ethers over basic alumina



SM	A1	A2	Product	Yield (%)
3m	Phenyl	Phenyl	**5m**	80
3n	Phenyl	6-Methoxy-2-naphthyl	**5n** & **6n**	85
3o	Phenyl	2-Naphthyl	**5o** & **6o**	88
3p	Phenyl	2-Pyridyl	**6p** only	85
3q	4-Anisyl	2-Naphthyl	**5q** & **6q**	86
3r	2-Naphthyl	9-Phenanthryl	**5r** & **6r**	85

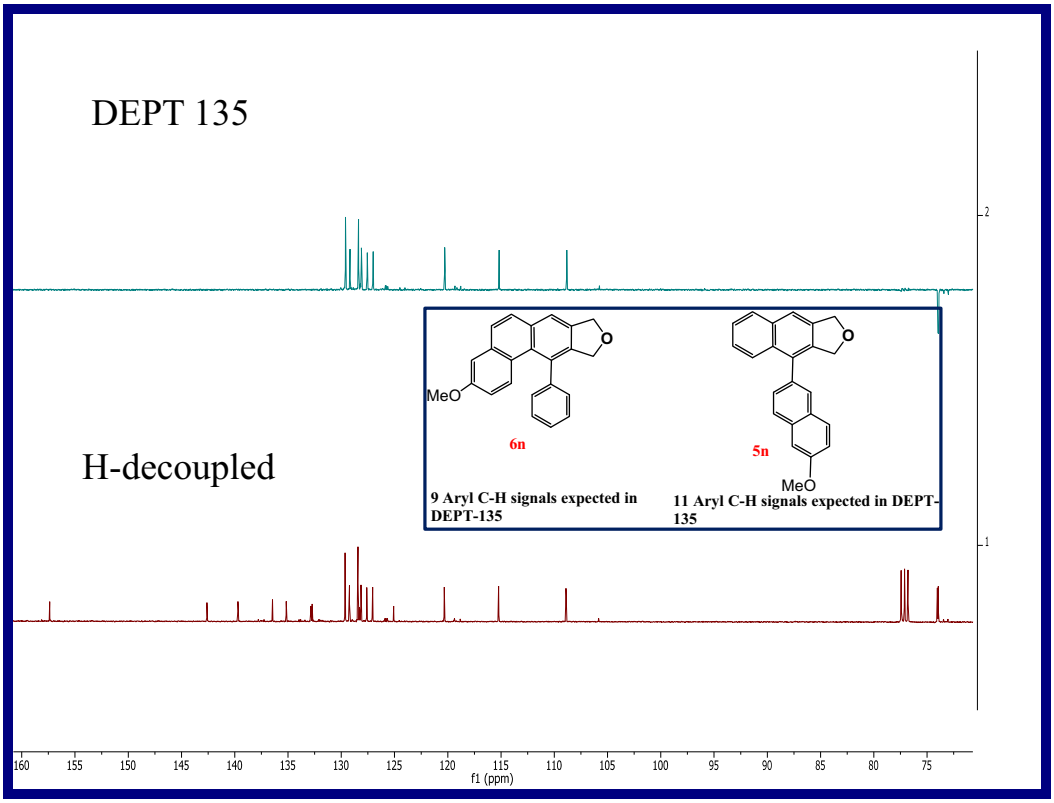
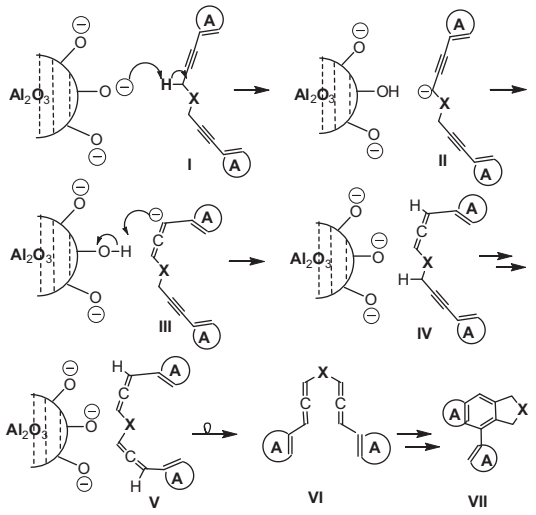


Figure 1. ^{13}C NMR DEPT 135 and H-decoupled of **6n**.

Table 4
Selectivity comparisons for solid and solution phases

Entry	Substrate	Products	Ratio in the existing protocol	Product ratio in solution phase
1	**3n**	**5n** & **6n**	1:11	1.25:1
2	**3o**	**5o** & **6o**	1:10	1:1.6
3	**3q**	**5q** & **6q**	1:11	1:6
4	**3r**	**5r** & **6r**	1:1.2	1:1.3
5	**4j**	**7j** & **8j**	1:3	1:1
6	**4k**	**7k** & **8k**	1:5	3.3:1
7	**4l**	**7l** & **8l**	1:1.75	4.5:1



Scheme 2. Proposed mechanism for alumina mediated GB.[13]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.033.

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11. *Experimental procedure:* A solution of compounds **1a–e** (0.50 mmol) in dichloromethane (5 mL) was added to basic alumina (500 mg) and the contents thoroughly mixed and dried under vacuum. For sulfones: the mixture was stirred at rt for 10–15 min after which it was extracted with ethyl acetate. Filtration followed by evaporation afforded the product which was crystallized from hexane and ethyl acetate mixture. For ethers or sulfonamides, the contents was stirred at 130 °C for 6–8 h, then cooled and proceeded like sulfones.
12. *Spectral data:* Compound **2c**: δ_H (400 MHz, $CDCl_3$): 8.12 (s, 1 H), 7.09 (d, J = 8.0 Hz, 1H), 6.63–6.61 (m, 2H), 6.54 (s, 1H), 6.51 (s, 1H) , 4.58–4.54 (m, 2H), 4.25 (d, J = 16.0 Hz, 1H) , 4.07 (d, J = 16.0 Hz, 1H), 3.97 (s, 3H) , 3.91 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H); δ_C (100 MHz, $CDCl_3$) 161.4, 158.9, 158.1, 156.7, 134.7, 132.1, 130.6, 125.3, 122.2, 119.1, 118.9, 105.2, 99.3, 98.3, 96.9, 57.8, 56.9, 56.0, 55.8, 55.7, 55.4. Mass: m/z 415 (MH^+); Compounds **5r** and **6r**: δ_H (400 MHz, $CDCl_3$): 8.86–8.83 (m, 1H, minor and 1H, major), 8.66–8.62 (m, 3H, minor), 8.56–8.55 (m, 2H, major), 7.94–7.26 (m, 12H, major and 11H, minor), 6.92 (dt, J = 7.2, 1.2 Hz, 1H, major), 6.82 (t, J = 8.0 Hz, 1H, minor), 5.42 (m, 2H, minor and 2H, major), 5.17 (d, J = 12.0 Hz, 1H, major), 4.93 (td, J = 13.2, 1.2 Hz, 1H, major and 1H, minor) ,4.62 (d, J = 13.2 Hz, 1H, minor); δ_C (100 MHz, $CDCl_3$) (major + minor) 141.0, 140.6 , 140.5 , 138.9, 138.5, 137.9, 134.2, 134.1, 134.0, 133.5, 132.8, 132.4, 131.9, 131.7, 131.3, 131.2, 130.8, 130.6, 130.5, 130.4, 130.3, 130.2, 129.9, 129.4, 129.3, 129.1, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 126.7, 126.6, 126.5, 125.6, 124.6, 123.7, 123.5, 123.4, 123.3, 123.0, 121.1, 115.1, 74.6, 74.5, 74.2, 74.1; Mass (ESI): m/z 397 (MH^+).
13. We have repeated the reaction with DBN pre-absorbed on basic Al_2O_3 with one of the bis-propargyl ether **3n** at three temperature conditions, namely, rt (35 °C), 50 °C and 90 °C. There was no reaction at rt or at 50 °C. Prolonged heating at 90 °C led to decomposition. We have also tried KF on basic Al_2O_3. In this case, the reaction of ethers could be accomplished at 80 °C (with basic Al_2O_3 only, the reaction temperature was 130 °C) but at the cost of selectivity. For example, the reaction of unsymmetrical ether **3n** gave the products **5n** and **6n** in the ratio of ~1.15:1 as against 1:11 in basic Al_2O_3 only.

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Sonogashira coupling and Garratt–Braverman cyclization in tandem: formation of four C–C bonds leading to the synthesis of aryl dihydro isofurans and isoindoles

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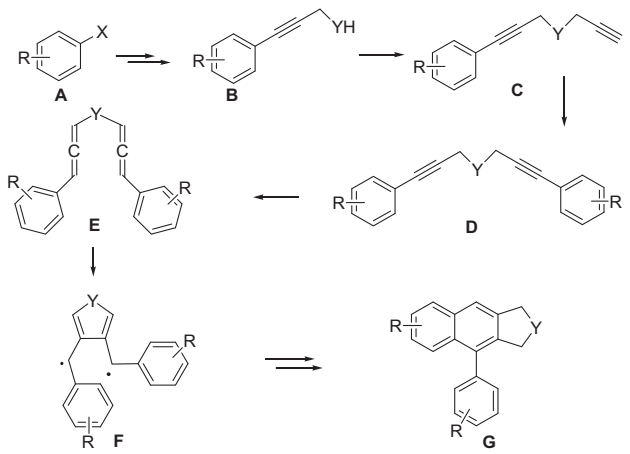
ABSTRACT

In this Letter we report an interesting one pot synthesis of aryl dihydro isofurans and isoindoles, naturally occurring privileged skeletons, in excellent yields from easily accessible starting materials. The process involved carrying out three reactions in a tandem manner leading to 4 C–C bond formations, namely two Sonogashira couplings (2 × 1 C–C bond) followed by Garratt–Braverman Cyclization (2 C–C bond).

The Garratt–Braverman cyclization,[1] discovered nearly 40 years ago, has drawn active interest in the past few years. The recent initiatives have been aimed toward addressing the mechanistic issues[2] and also to explore the synthetic potential[3] of the reaction. The substrates for GB cyclization are the bis-propargyl systems, namely, sulfones, ethers, and sulfonamides. These, under basic conditions, are thought to undergo isomerization to bis-allenes, which then cyclize to the hetero-fused arylnaphthalenes via the involvement of diradical and subsequent H-shifts (Scheme 1).[4] The final outcome of GB cyclization is the efficient formation of two C–C bonds in a single reaction. The precursor bis-propargyl systems (for ethers and sulfonamides) are usually obtained by Sonogashira coupling[5] of bromo/iodo arenes with propargyl alcohol or sulfonamide followed by O/N-propargylation and another round of Sonogashira coupling. Thus the complete synthesis of aryl dihydro isofuran (also called phthalan) and isoindole (also known as isoindoline) derivatives requires three steps. It would be nice if all the three reactions can be clubbed together and executed with the same set of reagents. In this Letter we report the one pot conversion of bromo/iodo arene and bis-propargyl ether/sulfonamide to aryl dihydro isofurans or isoindoles in excellent yields, significantly better in comparison with the overall yield by the usual route. The reaction sequence involved two consecutive Pd (0)-mediated Sonogashira couplings followed by GB cyclization to lead to the products (Scheme 2).

The idea of combining all the reactions using the same set of reagents occurred to us considering the fact that both alkyne–allene isomerization and subsequent cyclization take place under basic condition[6] whereas ene-yne coupling also requires an



Scheme 1. Usual route to accomplish the synthesis of aryl dihydro furan/isoindole.

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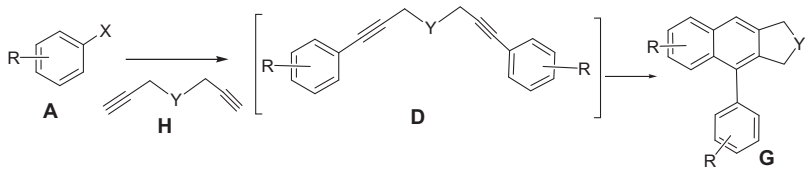
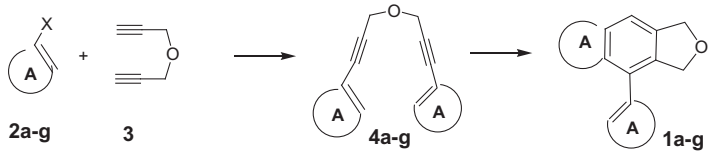
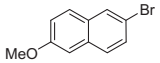
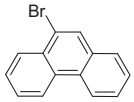
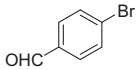
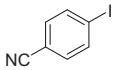
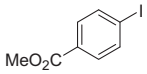
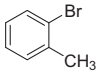
0040-4039/



Scheme 2. The route proposed and followed in the present work.

Table 1
Results of one pot synthesis of naphthoisofurans



Substrate	Base	Solvent and condition	Product/yield (%)	Overall yield (%) via usual route as depicted in Scheme 1
 **2a**	DBU	Toluene, reflux, 8 h	**1a**/80	60
 **2b**	DBU	Toluene, reflux, 10 h	**1b**/84	61
 **2c**	DBU	Toluene, reflux, 10 h	**1c**/85	62
 **2d**	DBU	Toluene, reflux, 9 h	**1d**/80	55
 **2e**	DBU	Toluene, rt, 6 h, then reflux, 8 h	**1e**/70	55
 **2f**	DBU	Toluene, rt, 8 h, then reflux, 10 h	**1f**/70	52
 **2g**	DBU	Toluene, reflux, 20 h	**1g**/65	51

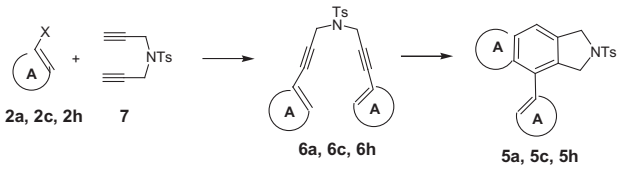
equivalent of base along with Pd (0) and CuI. The latter reagents are expected not to interfere with the subsequent isomerization cum cyclization.

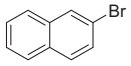
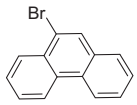
We initiated the study by carrying out the reaction of iodobenzene with $Pd(PPh_3)_2Cl_2$ in the presence of DBU. Toluene was selected as the solvent in view of the high temperature required in effecting the alkyne-allene isomerization. The temperature was initially maintained at 30 °C because of high reactivity of iodoarenes[7] toward the coupling reaction. Upon completion of the two ene-yne coupling reactions as monitored by ^1H NMR, the reaction mixture was refluxed for 8 h. However, to our dismay, the final arylnaphthalene was isolated in low yields. We then replaced the iodo with less reactive bromo benzene and the reaction temperature was maintained at 110 °C throughout. Usual work up and chromatography led to the isolation of the GB product in 82% yield. Considering that 4 new C–C bond formations have taken place in a single pot, the yield can be regarded as excellent.

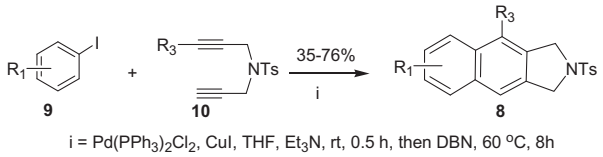
With the optimum conditions in hand, we next examined the reaction scope. Thus several bromoarenes were similarly treated [$Pd(PPh_3)_2Cl_2$, propargyl ether, toluene, reflux]. In all cases, the dihydro isofurans were isolated in good to excellent yields. Interestingly, the reaction also worked well in case of iodoarenes with an electron withdrawing group (substrates **2e** and **2f**). Iodoarenes with electron donor groups, however, failed to work. The results are shown in Table 1.

Following the success with the ether system, we then explored whether the same protocol works for the sulfonamides. Thus a

Table 2
Result of one pot synthesis of isoindole derivatives



Substrate	Base	Solvent and condition	Product/yield (%)	Overall yield (%) via usual route as depicted in Scheme 1
 2a	DBU	Toluene, reflux, 6 h	**5a**/82	60
 2h	DBU	Toluene, reflux, 8 h	**5h**/84	62
 2c	DBU	Toluene, reflux, 8 h	**5c**/85	62

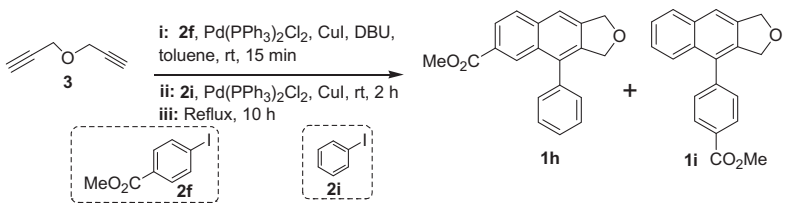


Scheme 3. Reported work by Zhu et al.[8]

solution of bromobenzene and sulfonamido bis-propargyl amine in toluene was refluxed in the presence of $Pd(PPh_3)_2Cl_2$ and DBU. Gratifyingly, after usual workup (vide experimental) and chromatography, we could isolate the dihydro isoindoles in excellent yields (Table 2). It may be mentioned here that recently, Zhu et al.[8] have reported the synthesis of dihydro isoindoles starting from an N-bis-propargyl sulfonamide in which one arm already has an N-aryl propargyl moiety. The method involved one Pd(0)-mediated ene-yne coupling followed by the formation of dihydro isoindoles via, according to the authors, an intramolecular [4+2] cycloaddition cum aromatization. The method reported 3 new C–C bond formations (Scheme 3) involving iodoalkenes; aryl iodides with electron withdrawing groups also gave the target isoindoles. With simple iodobenzene and iodobenzene with electron donor groups like methoxy, the reaction stopped after the Sonogashira step. Also, the method involved the use of two different bases, first Et_3N for Sonogashira coupling and then DBU for the cyclization. On the other hand, our method leads to the formation of **4 C–C** bonds in a single pot requiring the use of DBU as a single base. Moreover, the reaction leads to both isobenzofuran and isoindole derivatives and the yields are also better than the reported ones.[7]

Regarding the possibility of synthesizing dihydro isobenzofuran/isoindole from unsymmetrical propargyl systems, we attempted the reactions of several haloarenes with bis-propargyl ether **3** or sulfonamide **7**. The reaction was carried out by performing the first ene-yne coupling with 1.0 equiv of the haloarene. Then the second haloarene (1.0 equiv) was added and the reaction was continued till the completion of GB cyclization. However, in spite of our best efforts, we failed to stop the bis eneyne coupling even with 1.0 equiv of haloarene and the reaction became complicated. Except in case where the first and the second haloarenes were methyl 4-iodo benzoate (**2f**) and iodobenzene, (**2i**), we could obtain the final dihydroisobenzofuran as a mixture (**1h** and **1i**) from bispropargyl ether **3** (Scheme 4).

In conclusion, we have successfully brought down the synthesis of aryl naphthalenes via successive Sonogashira coupling and Garratt–Braverman Cyclization to a single pot protocol.[9] The method is simple, high yielding and works well for the synthesis of dihydro isobenzofurn and isoindole systems. Future research activity will aim toward solving the problem of synthesis involving unsymmetrical systems.



Scheme 4. Synthesis of aryl dihydroisobenzofuran from mixed haloarenes.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.093.

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9. General experimental procedure:
   To a solution of aryl bromide/iodide (2.0 mmol) and the alkyne **3/7** (1.0 equiv) in toluene, DBU (5 equiv) was added followed by $PdCl_2(PPh_3)_2$ (6 mol %) and CuI (10 mol %). For aryl bromide, the mixture was refluxed at 110 °C for 8–20 h. For aryl iodide, the reaction mixture was stirred at room temperature for 6–8 h and then at 110 °C for 8–10 h. The reaction mixture was evaporated under vacuo and then diluted with water and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated using a rotavap. The crude product was purified by column chromatography on silica gel.