University of Nevada, Reno

Alkyne Cyclizations: From α-Carbonyl Bicyclic Furans to Expanded Chiral Hexa-*peri*-hexabenzocoronenes

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Chemistry

by

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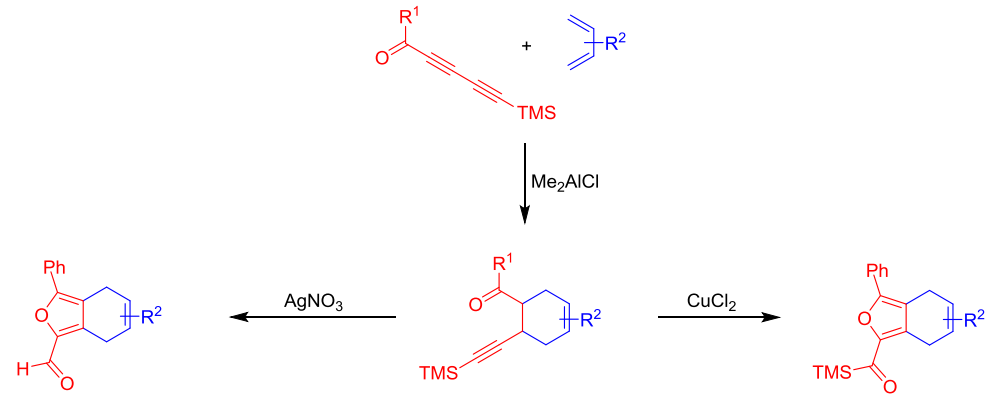
Abstract

The development and utilization of highly functionalized and reactive dienophiles in the Diels–Alder cyclization reaction is of value in producing diversely functionalized, and therefore useful, cyclic products. We have developed a Diels–Alder reaction of conjugated 2,4-diynones, promoted by Lewis acids (Me_2AlCl or $EtAlCl_2$), to produce substituted 2-alkynyl-1,4-cyclohexadiene ('skipped' cyclohexadiene) products in good to excellent yields. The reaction was successful with a variety of cyclic and acyclic dienes as well as with a diversity of 2,4-diynones. The diversely functionalized 1,4-cyclohexadiene products that are obtained from this reaction are of utility as intermediates on the way to synthesizing pharmaceutically relevant cyclic and polycyclic compounds. Those heavily functionalized skipped dienes were cleanly converted into dihydroisobenzofuran (bicyclic furan) derivatives in the presence of π-Lewis acid catalysts. Ketone derivatives were obtained by using $CuCl_2$ as catalyst whereas $AgNO_3$ provides aldehyde analogues. We have also demonstrated a facile one-pot approach to construct bicyclic furan derivatives directly from diynone and diene starting materials.

We also describe the synthesis, characterization, structure and properties of expanded chiral hexa-*peri*-hexabenzocoronenes. The Suzuki cross-coupling between bromo substituted hexa-*peri*-hexabenzocoronene and diynylphenyl borate gives the coupled product. The alkyne benzannulation reaction of coupled product promoted by a mixture of TFA and TfOH afforded the desired final product. The twisted structure of chiral compounds is unambiguously confirmed by X-ray crystallographic analysis and the enantiomers are separated in chiral HPLC.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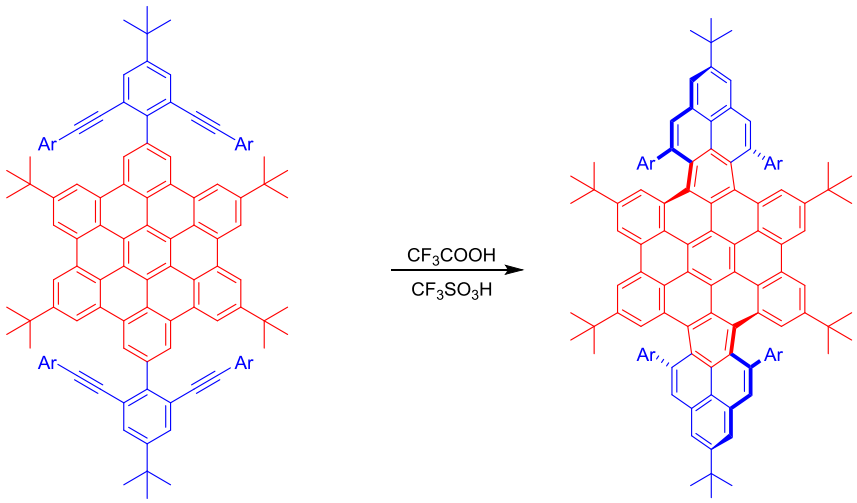
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Dedication

I dedicate this dissertation to my parents (Beni Khanal & Mata Khanal)

for their never-ending love and support.

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I would like to express the deepest appreciation to my advisor, Dr. Wesley A. Chalifoux, for his willingness and enthusiasm in allowing and helping me to grow my chemical knowledge and skillset. I would also like to thank Dr. Chalifoux for always holding the bar high and helping me to become the researcher that I am today. Without his guidance and persistent help this dissertation would not have been possible. I would like to thank my committee members, Dr. Robert S. Sheridan, Dr. Benjamin T. King, Dr. Ravi Subramanian, and Dr. Mark A. Pinsky for their guidance, time, and support. I would also like to thank Dr. Vincent Catalano and Dr. Stephen Spain for instrumentation training and assistance.

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List of Abbreviations/Acronyms

HOMO	=	Highest Occupied Molecular Orbital
LUMO	=	Lowest Unoccupied Molecular Orbital
Exo	=	Exocyclic
Endo	=	Endocyclic
Tet	=	Tetrahedral
Trig	=	Trigonal
Dig	=	Diagonal
NBS	=	*N*-Bromosuccinimide
TFA	=	Trifluoroacetic acid
TfOH	=	Triflic acid
DDQ	=	2,3-dichloro-5,6-dicyanobenzoquinone
*m*CPBA	=	*meta*-Chloroperoxybenzoic acid
DCM	=	Dichloromethane
THF	=	Tetrahydrofuran
PMA	=	Phosphomolybdic acid
CAM	=	Ceric Ammonium Molybdate
NMO	=	N-Methylmorpholine N-oxide
NMR	=	Nuclear Magnetic Resonance
ATR/FTIR	=	Attenuated Total Reflectance–Fourier Transform Infrared
ESI	=	Electrospray Ionization
MALDI	=	Matrix Assisted Laser Desorption/Ionization
HRMS	=	High Resolution Mass Spectrometry
TOF-MS	=	Time-of-flight Mass Spectrometry

1 Introduction

1.1 The Diels-Alder Cycloaddition

The Diels-Alder cycloaddition was discovered in 1928 by Otto Diels and Kurt Alder who received the Nobel Prize in 1950 for the work on the [4+2] cycloaddition.[1] The Diels-Alder cycloaddition is a pericyclic reaction between a dienophile (alkene or alkyne) and a conjugated diene to generate a six-membered cyclic product. The driving force of the reaction is the formation of energetically more stable σ-bonds. Due to the potential applicability of this methodology, various researches in the field of Diels-Alder cycloadditions are still ongoing.[2] In the Diels-Alder reaction, the overlap between the highest occupied molecular orbital (HOMO) of diene and the lowest unoccupied molecular orbital (LUMO) of dienophile occurs in order to form the product (**Figure 1-1**). A pericyclic reaction between a dienophile **1.1** and diene **1.2** forms a six-membered cyclic compound **1.3** bearing an alkene moiety.[3]

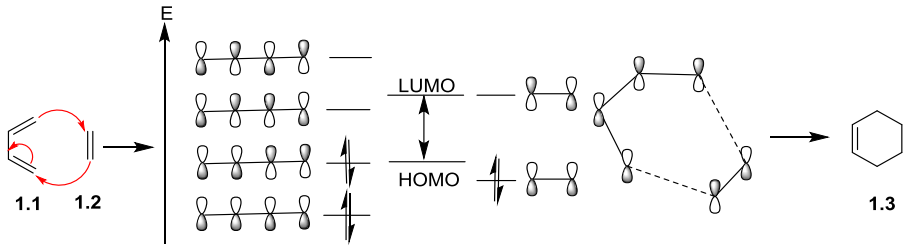
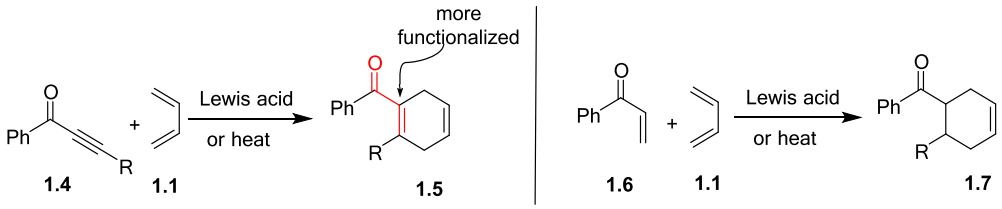


Figure 1-1: Diels-Alder reaction between **1.1** and **1.2** to form six-membered ring **1.3**.

Since its discovery, the Diels-Alder reaction has been modified in a number of ways, particularly by introducing more functionality in the products. A compound bearing a variety of functional groups can participate in different chemical transformations while an analogous non-functionalized derivative tends to be lower in energy and therefore less

useful. For example, ynone **1.4** undergoes Diels-Alder cycloaddition with diene **1.1** and generates a functionalized product **1.5** having enone moiety (in red) whereas the traditional substrate **1.6** undergoes cyclization with **1.1** generating the less functionalized adduct **1.7** (**Scheme 1-1**).[4]



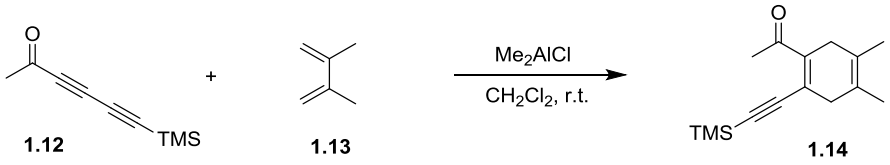
Scheme 1-1: Diels-Alder cyclization of ynone **1.4** vs enone **1.6** as dienophile.

The Diels–Alder reaction has been proven to be one of the most powerful ways to synthesize six-membered cyclic products.[3] These cyclic products commonly serve as key intermediates for the synthesis of important biologically active compounds.[5-9] Alkenes typically serve as the most commonly utilized dienophiles in the Diels–Alder reaction producing cyclohexene products whereas the utilization of alkynes as dienophiles in the Diels–Alder reaction is much less common, but provides highly useful 1,4-cyclohexadiene ('skipped' cyclohexadiene) products.[10-17] The most common method utilized for the production of 'skipped' cyclohexadienes is the dissolved metal reduction of arenes, the Birch reduction.[18,19] The use of dissolved alkali metals in ammonia is not particularly functional group tolerant, including alkyne functional groups, and would be a problem for base-sensitive compounds. Birch reduction of arenes provides the formation of skipped cyclohexadienes without any functionality on it which does not allow a further utility of the products (**Scheme 1-2**). For example, Birch reduction of compound **1.8** affords non-functionalized skipped cyclohexadiene **1.9**. The product **1.9** lacks functional groups other

than an isolated double bond making it less useful in further chemical transformation. Similarly, when electron deficient arene, acetophenone (**1.10**), is reduced under birch conditions, a skipped cyclohexadiene product **1.11** is obtained.[20]

Scheme 1-2: Birch reduction of arenes **1.8** and **1.10**.

On the other hand, skipped cyclohexadienes bearing a variety of functional groups can be generated by utilizing Diels-Alder cycloaddition of conjugated diynones with dienes (**Scheme 1-3**).[21] A conjugated diynone **1.12** is reacted with diene **1.13** in the presence of Lewis acid (Me_2AlCl) in dichloromethane to get the product **1.14** bearing alkyne functionality which otherwise could not be obtained by Birch reduction. Cyclohexadiene product **1.14** also bears α, β-unsaturated ketone functionality which is not possible to get in Birch reduction (product **1.11** from Birch reduction, **Scheme 1-2**). This example shows that Diels-Alder cycloaddition of conjugated diynones provides diversely functionalized skipped cyclohexadienes.



Scheme 1-3: Diels-Alder cyclization of diynone **1.12** with diene **1.13** to get **1.14**.

Therefore, the development of a mild and functional group tolerant method for the cyclization of alkynes to provide substituted 'skipped' cyclohexadienes is of value as these compounds will serve as useful intermediates for the synthesis of many biologically

important cyclic and polycyclic compounds (skipped dienes). Ynones are inherently valuable dienophiles because of their ability to transfer useful functionality to the Diels-Alder product. While a few examples of ynone [4 + 2] cyclizations have been reported in the literature, ynone pericyclic routes remain largely unexplored.[4,22]

1.2 Alkyne Cyclizations

Alkyne cyclization constitutes an important class of chemical transformations in organic synthesis. The triple bond is among the most important functional groups in organic chemistry, lending itself to a number of photochemical as well as chemical cascade transformations. Unique to alkynes is the ability to form up to four new bonds at the expense of the two alkyne π-bonds or even be completely disassembled with the formation of six new bonds. Due to its utility and ubiquity, a detailed understanding and prediction of regioselectivities for alkyne cyclization reactions is needed.

The mode of alkyne cyclizations is also classified by Baldwin rules as seen in alkane and alkene cyclization reactions (**Figure1-2**).[23] Baldwin developed a classification of cyclization processes based on three factors.[24] For example, *5-exo* –dig, the first of which (5) indicates the number of atoms in the forming ring. The second prefix (*exo*) describes the position of the bond that has to be broken in the cyclization relative to the forming ring and can have any value ≥3. The second prefix, *exo*- vs. *endo*-, describes the position of the bond that has to be broken in the cyclization reaction, relative to the forming ring. *Exo* indicates that the breaking bond is outside of (exocyclic to) the formed ring, whereas *endo* indicates that the breaking bond is inside of (endocyclic to) the new ring. The last prefix

(dig) represents the hybridization at the ring closure point (dot in **Figure 1-2**). Tet (tetrahedral) refers to sp^3, trig (trigonal) refers to sp^2, and dig (diagonal) refers to sp-hybridized atom. All three factors involved in the classification of alkyne cyclization reaction (ring size, *exo*- vs. *endo*-attack and hybridization at the site of attack) are critical in determining whether a particular cyclization mode is favorable or not. This dissertation pertains to alkyne cyclization reactions and can proceed either by a 5-*exo*-dig or 6-*endo*-dig cyclization pathway.

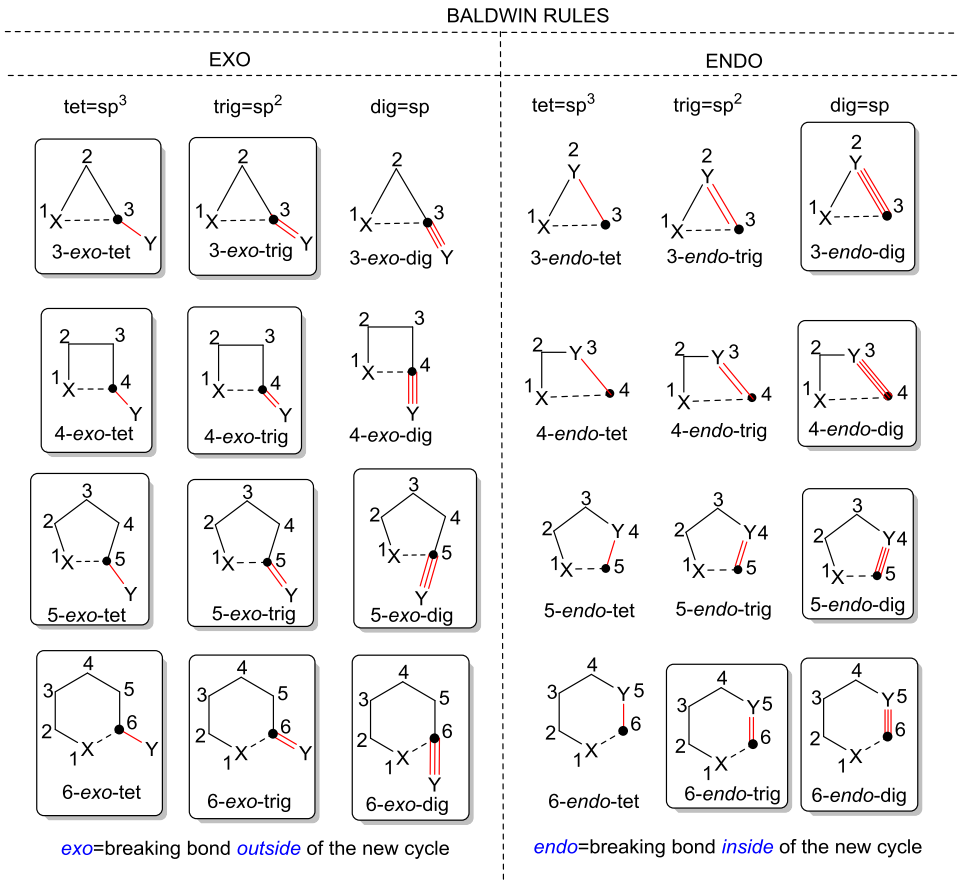
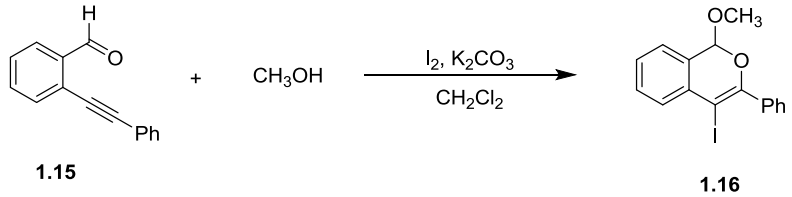


Figure 1-2: Patterns of cyclization for 3-to 6-membered rings. Reactions predicted to be favorable by Baldwin are boxed.

An example of electrophilic cyclization of acetylenic carbonyl compounds was demonstrated to synthesize oxygen heterocycles by Larock and co-workers (**Scheme 1-4**).[25] The cyclization of the o-(1- alkynyl)benzaldehydes **1.15** with iodine in the presence of methanol and potassium carbonate proceeded via a 6-*endo*-dig cyclization to afford isochromene product **1.16**.

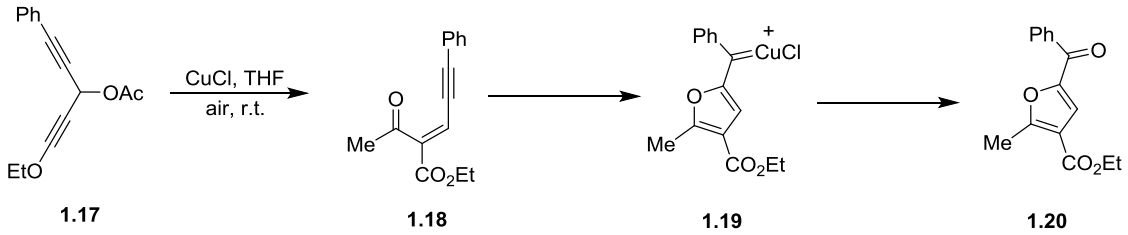


Scheme 1-4: Synthesis of oxygen heterocycle by electrophilic cyclization of acetylenic aldehyde.

1.3 One-Pot Reactions

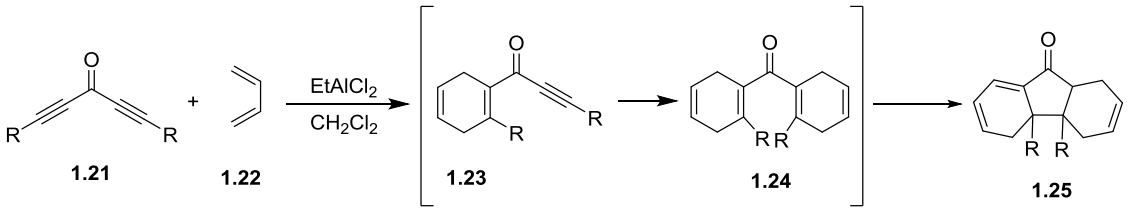
The incorporation of two or more reactions into a cascade process is always a powerful tool for the synthesis of complex products from relatively cheap and simple starting materials. The use of inexpensive, high energy starting materials to accomplish multiple bond formations in a single reaction flask is not only a resourceful approach to solving complex synthesis problems, but can also drastically reduce chemical waste production in our society.

A copper-catalyzed atom-economy cascade reaction via isomerization/carbonyl-alkyne cyclization/oxidation sequence was reported by Barluenga and co-workers (**Scheme 1-5**).[26] The unsymmetrical bis-propargylic ester **1.17** undergoes copper-catalyzed cycloisomerization to generate metallocarbene **1.19** via an enynone intermediate **1.18**. The carbene oxidation then allows the preparation of 2-acyl furan **1.20**.



Scheme 1-5: Cu-catalyzed cascade synthesis of substituted furan derivatives.

The Chalifoux lab recently reported a Lewis acid promoted tandem cyclization sequence that initiates with a multicomponent double Diels–Alder reaction of cross-conjugated diynones, followed by a Nazarov cyclization to efficiently produce [6-5-6] tricyclic products with excellent regio- and diastereoselectivity (**Scheme 1-6**).[27] Diels-Alder reaction between diynone **1.21** and diene **1.22** first generates the monocyclic ketone intermediate **1.23**, followed by a second Diels- Alder reaction to furnish bicyclic intermediate **1.24**. The intermediate **1.24** having necessary functionality, undergoes a Nazarov cyclization to ultimately provide [6-5-6] tricyclic product **1.25**. A single Lewis acid catalyst ($EtAlCl_2$) drives this multicomponent/cascade reaction through both the double Diels-Alder reaction and a Nazarov cyclization.

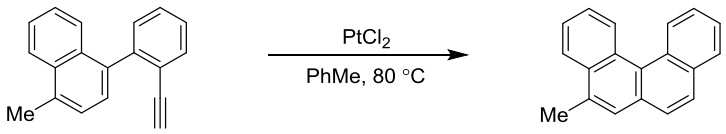


Scheme 1-6: Lewis acid catalyzed synthesis of tricyclic core via a cascade double Diels-Alder/Nazarov reaction.

1.4 Alkyne Benzannulation

The non-oxidative cyclization of alkyne substituents onto aryl moieties to generate new aryl rings is known as an alkyne benzannulation reaction. Alkyne benzannulation, an efficient and mild method, does not involve oxidative aryl-aryl coupling (cyclodehydrogenation) to extend the π-conjugation of readily available aromatics. Alkyne benzannulation reactions have been shown to proceed with a variety of π-Lewis acids,[28-30] Bronsted acids, [31-33] and other electrophiles.[34,35]

An example of a benzannulation reaction promoted by Lewis acids was reported for the synthesis of benzo[c]phenanthrene analogues (**Scheme 1-7**).[36] The Pt-catalyzed cycloisomerization reaction of 1-(2-ethynylphenyl)naphthalene derivatives **1.26** yielded benzo[c]phenanthrene analogues **1.27** that are otherwise not easy to access.

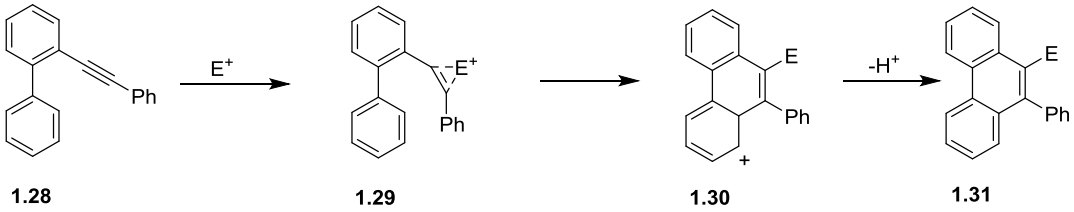


1.26 **1.27**

Scheme 1-7: Lewis acid catalyzed synthesis of benzo[c]phenanthrene derivatives.

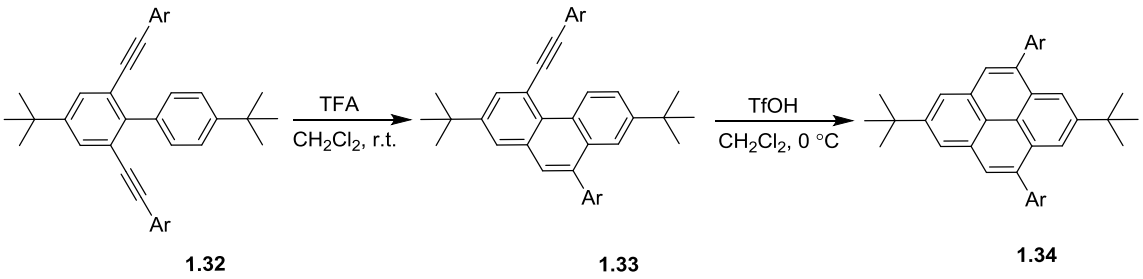
An efficient synthesis of substituted polycyclic aromatic compounds under very mild reaction conditions using eletrophiles such as ICl, I_2 and NBS has been developed by Larock and co-workers (**Scheme 1-8**).[35] The treatment of 2-(1-alkynyl)biphenyl **1.28** with some electrophile generates an electrophile-acetylene complex **1.29**. An electrophilic attack of this intermediate on the neighboring aromatic ring of the biaryl moiety provides

with another intermediate **1.23**. Finally, **1.30** undergoes deprotonation to generate the desired polycyclic aromatic **1.31**. This method provides bromine- or iodine-containing products that can be readily elaborated to more complex compounds by using known organo-palladium chemistry.



Scheme 1-8: Electrophilic benzannulation reaction to generate polycyclic aromatics.

An alkyne benzannulation reaction promoted by a mixture of Bronsted acids (TFA and TfOH) is recently reported to synthesize pyrene, peropyrene and teropyrene derivatives (**Scheme 1-9**).[37] The treatment of 2,6-dialkynylbiphenyls **1.32** with TFA in anhydrous CH_2Cl_2 at room temperature afforded the monocyclized product, phenanthrene derivative **1.33**. The subsequent addition of stronger acid TfOH at 0 °C provided pyrene derivative **1.34** by the cyclization of remaining alkyne.



Scheme 1-9: Bronsted acid catalyzed synthesis of pyrene derivatives.

1.5 Conclusion

The perfect design and modification of efficient synthetic methodologies is of great value in organic research. We can arrive at valuable structural motifs and materials by utilizing structurally robust starting materials in well-known organic reactions such as Diels-Alder cycloaddition, alkyne cyclization/benzannulation, etc. Also, the combination of many organic reactions into a one-pot operation reduces the number of procedural steps making it a more economically viable process.

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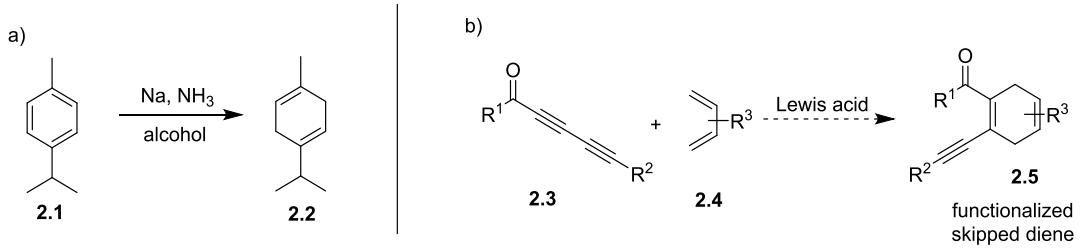
2. Synthesis of 2-Alkynyl-1,4-cyclohexadienes via a Diels–Alder Reaction of Conjugated 2,4-Diynones

2.1 Introduction

The development and utilization of highly functionalized and reactive dienophiles in the Diels- Alder[1] cyclization reaction is of value in producing diversely functionalized, and therefore useful, cyclic products. These cyclic products commonly serve as key intermediates for the synthesis of important biologically active compounds.[2-7] The most common method utilized for the production of "skipped" cyclohexadienes is the dissolved metal reduction of arenes, the Birch reduction[8,9] (**Scheme 2-1a**). When the substituted benzene **2.1** treated with sodium metal in ammonia, skipped diene **2.2** was obtained by reduction. The use of dissolved alkali metals in ammonia is not particularly functional group tolerant, including alkyne functional groups, and would be a problem for base sensitive compounds. Therefore, the development of a mild and functional group tolerant method for the cyclization of alkynes to provide substituted "skipped" cyclohexadienes is of value as these compounds will serve as useful intermediates for the synthesis of many biologically important cyclic and polycyclic compounds.

The Diels-Alder reaction has been proven to be one of the most powerful ways to synthesize 6-membered cyclic products. Alkenes typically serve as the most commonly utilized dienophiles in the Diels-Alder reaction producing cyclohexene products whereas the utilization of alkynes as dienophiles in the Diels-Alder reaction is much less common but provide highly useful 1,4-cyclohexadiene ("skipped" cyclohexadiene) products

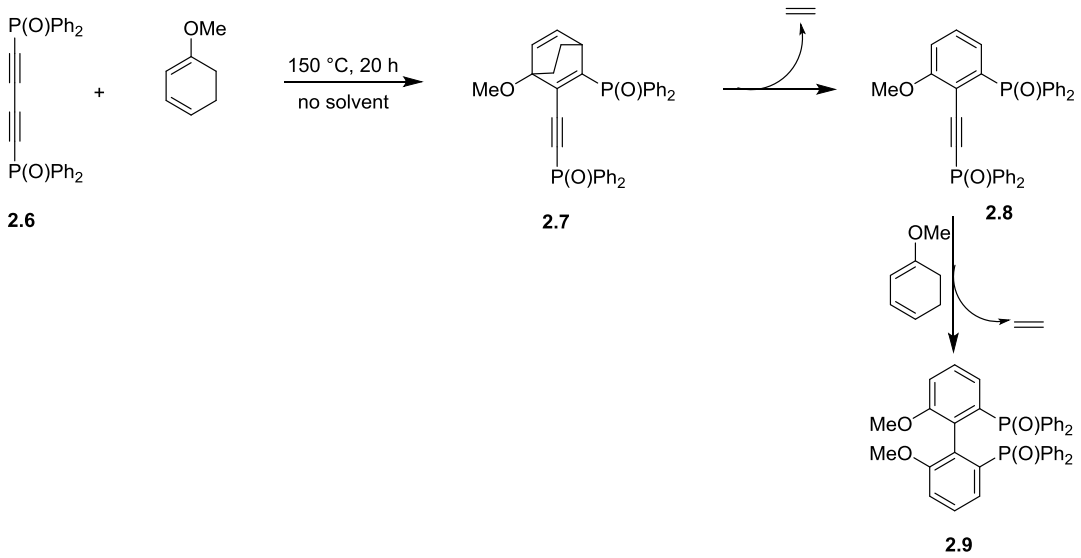
(**Scheme 2-1b**).[10-20] We believed a Diels-Alder reaction between a diynone such as **2.3** and a diene like **2.4** would afford the functionalized skipped diene **2.5**. The generation of those skipped dienes is otherwise not possible via Birch reduction. The Diels-Alder product **2.5** could serve as a potential synthetic intermediate for various organic compounds and biologically important natural products as it bears modifiable functional groups (electron-rich and electron-poor alkenes, ketone and alkyne).



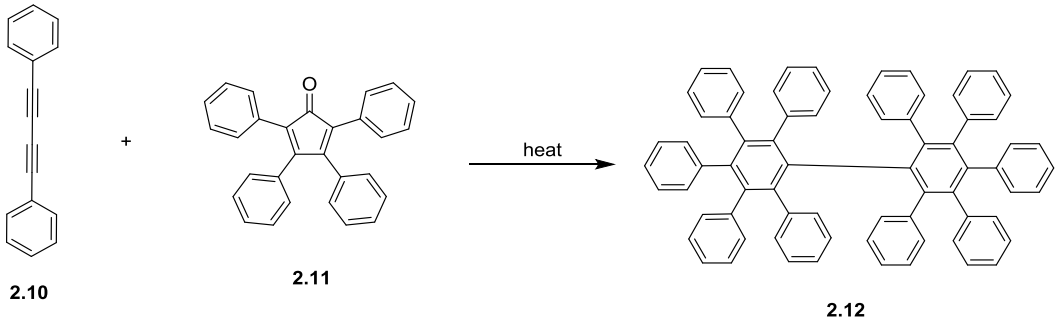
Scheme 2-1: (a) Birch reduction. (b) Proposed synthesis of functionalized skipped diene.

Diynes are useful precursors in cycloaddition reactions for the synthesis of polycyclic organic compounds. The cycloaddition reactions of inactivated diynes are generally carried out in elevated temperature. Clegg and co-workers[21] attempted a thermal bis-cyclization between a diyne and a cyclic diene to afford a biphenyl derivative **(Scheme 2-2)**. An inactivated diyne **2.6** reacts with 1-methoxy-1,3-cyclohexadiene to form Diels-Alder adduct **2.7** which upon elimination of ethylene affords compound **2.8**. The remaining alkyne in compound **2.8** further reacts with another molecule of diene and finally generates product **2.9**. Another thermal cycloaddition reaction was reported in 1963 by Becker and co-workers.[22] Bisphenylbutadiyne **2.10** was heated with tetracyclone **2.11** at 260 ^{o}C to get a polycyclic aromatic hydrocarbon **2.12** (**Scheme 2-3**). We were curious as to whether diynone **2.3** bearing carbonyl group (when activated by Lewis acid) would undergo double

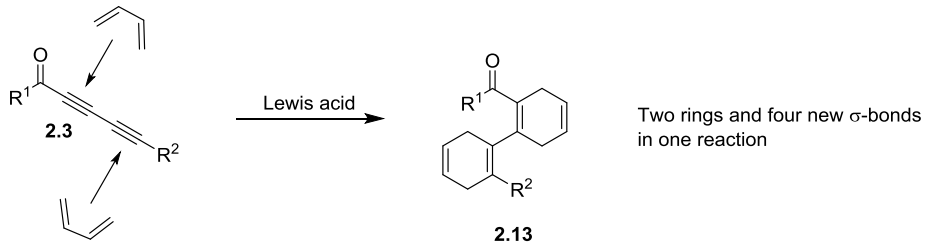
Diels-Alder reaction in order to make two rings and multiple bonds in a single reaction generating compound **2.13** (**Scheme 2-4**).



Scheme 2-2: Thermal cycloaddition reaction of diyne to synthesize biphenyl derivative.



Scheme 2-3: Thermal cycloaddition reaction to synthesize polyaromatic compounds.

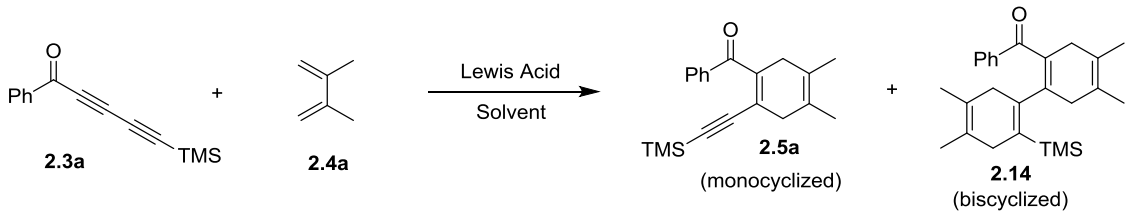


Scheme 2-4: Proposed double Diels-Alder reaction of diynone.

2.2 Double Diels-Alder Reaction of Conjugated 2,4-Diynones

We initiated our study choosing diynone **2.3a** and diene **2.4a** as the model starting materials. Diynone **2.3a** was synthesized in one step from commercially available starting materials,[23] and diene **2.4a** was commercially available. We screened a variety of common Lewis acids that have been shown to work well in activating alkynyl ketones in Diels-Alder cycloadditions (**Table 2-1**). When the reaction was attempted with dimethylaluminum chloride, we observed the formation of only mono-cyclized product **2.5a** (entry 1). The reactions with more Lewis acidic ethylaluminum dichloride and titanium chloride also failed to afford bis-cyclized product **2.14** (entries 2 and 3). The use of $SnCl_4$, $ZnCl_2$, BF_3•OEt_2 and $FeCl_3$ resulted in no conversion of the starting material to desired products (entries 4-7). The use of π-Lewis acids also proved to be unsuccessful in providing mono/bis-cyclized product (entries 8-10). We got similar results with all of these catalysts while changing the solvent from dichloromethane to toluene.

Table 2-1: Preliminary screening of Lewis acids for the double Diels-Alder reaction.



Entry	Lewis acid	Temperature (^{o}C)	Time (h)	**2.5a**	**2.14**
1	Me_2AlCl	r.t.	6	Yes	No
2	$EtAlCl_2$	0	6	Yes	No
3	$TiCl_4$	0	6	Yes	No
4	$SnCl_4$	0	6	No	No
5	$ZnCl_2$	r.t.	6	No	No
6	$BF_3{\cdot}OEt_2$	0	6	No	No
7	$FeCl_3$	r.t.	6	No	No
8	$PtCl_2$	r.t.	6	No	No
9	$AuCl_3$	r.t.	6	No	No
10	Ph_3PAuCl+AgOTf	r.t.	6	No	No

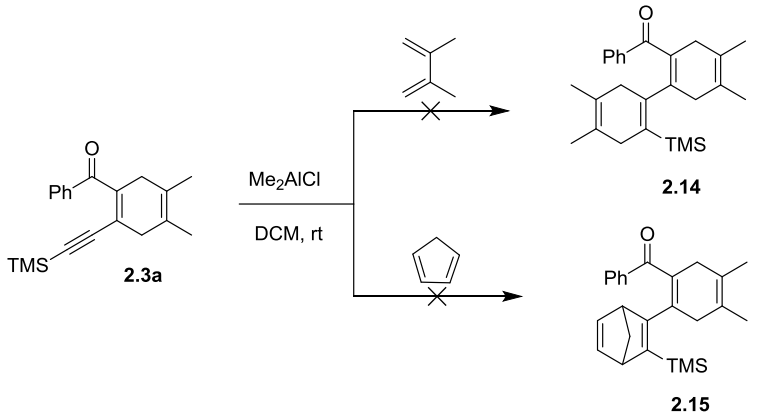
We then moved ahead to observe the effect of temperature on the bis-cyclization (**Table 2-2**). When we attempted the thermal cycloaddition reaction at 100 ^{o}C in sealed tube, only mono-cyclized product **2.5a** was observed on the basis of ^{1}H NMR and GC analysis (entry

1). We did not observe the formation of bis-cyclized product **2.14** even at high temperatures (entries 2 and 3). We also tried the reaction in the absence of solvent, which also proved to be ineffective in generating bis-cyclized product (entry 4).

Table 2-2: Thermal cycloaddition reaction between diynone **2.3a** and diene **2.4a**.

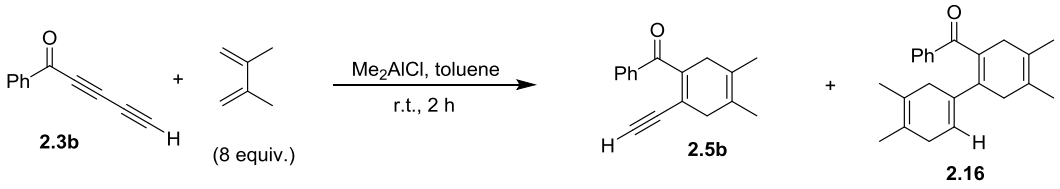
Entry	Temperature (°C)	Solvent	Observation
1	100	xylene	Only mono-cyclized
2	200	biphenyl ether	Only mono-cyclized
3	250	biphenyl ether	Only mono-cyclized
4	200	no solvent	Only mono-cyclized

We then thought to carry out bis-cyclization reaction in step-wise manner (**Scheme 2-5**). First, we synthesized compound **2.5a** via a Diels-Alder cycloaddition of our regular diynone **2.3a** with diene **2.4a.** We treated compound **2.5a** with 10 equivalents of 2,3-dimethyl-1,3-butadiene and cyclopentadiene in two separate reactions. None of these reactions were successful in providing the desired products **2.14** and **2.15** respectively.



Scheme 2-5: Stepwise attempt for bis-cyclization.

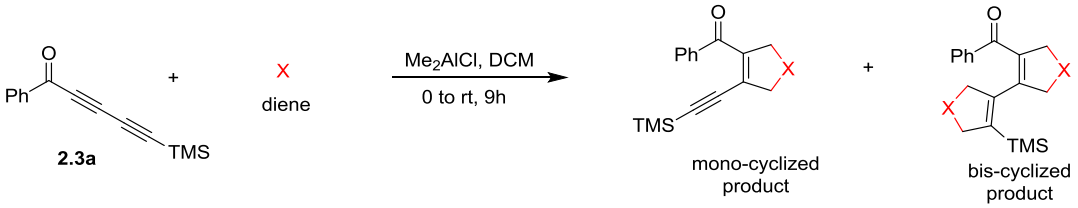
Since a two-fold Diels-Alder cycloaddition to give the desired product was unsuccessful, we suspected that the sterics from the bulkier TMS group might be hindering the second Diels-Alder. We then synthesized relatively less stable diynone **2.3b** by desilylation of **2.3a** under standard conditions and subjected in the reaction immediately expecting the product **2.16** (**Scheme 2-6**). The formation of only mono-cyclized product **2.5b** from the terminal diynone **2.3b** proved that the second Diels-Alder reaction was not influenced by the sterics of bulkier TMS-substituents.

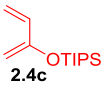


Scheme 2-6: Diels-Alder reaction of terminal diynone.

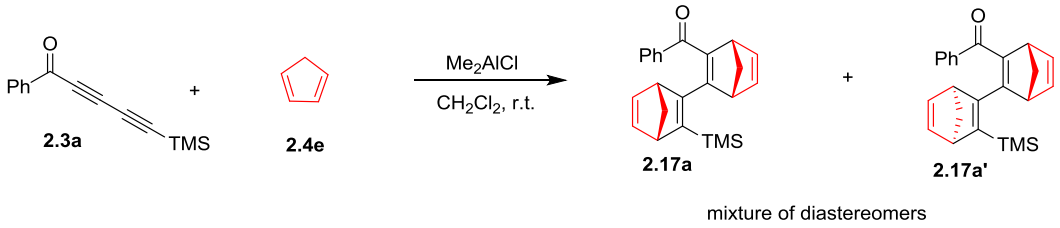
Next, we screened a variety of acyclic and cyclic dienes with diynone **2.3a** in dichloromethane solvent (**Table 2-3**). Acyclic dienes such as isoprene (**2.4b**) and **2.4c** resulted in the generation of only mono-cyclized product. When the reaction was attempted with furan **2.4d** as a diene component, a mess of crude products was obtained which was not characterized. Surprisingly, cyclopentadiene **2.4e** reacted with diynone **2.3a** to afford the desired bis-cyclized product.

Table 2-3: Preliminary screening of dienes with diynone **2.1a**.



Entry	Diene	Equivalents	Product
1	 **2.4b**	8	mono
2	 **2.4c**	5	mono
3	 **2.4d**	8	not characterized
4	 **2.4e**	8	bis

The Diels-Alder reaction of diynone **2.3a** with cyclopentadiene **2.4e** (8 equiv.) in dichloromethane solvent provided an inseparable mixture of diastereomers **2.17a** and **2.17a′** (**Scheme 2-7**). We then attempted this reaction in a variety of solvents in order to improve the diastereoselectivity (**Table 2-4**). However, the change of solvent did not improve the diastereomeric ratio but provided an equimolar mixture of diastereomers.



Scheme 2-7: Double Diels-Alder reaction of diynone **2.1a** with diene **2.2e**.

The reaction using 10 equivalents of cyclopentadiene **2.4e** resulted in the formation of bis-cyclized products **2.17a** and **2.17a′** as a 1.3:1 mixture of diastereomers in good yield with 71% (entry 8). This was confirmed by infrared and NMR spectroscopic analysis, as well as by mass spectrometry. A number of solvents and temperatures were explored but resulted in no improvement of diastereomeric ratio (dr).

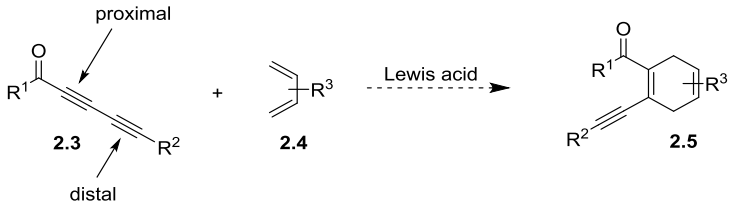
Table 2-4: Screening of solvent in double Diels-Alder reaction to improve diastereoselectivity.

Entry	Solvent	Time (h)	**2.17a + 2.17a′**	Diastereomeric ratio
1	toluene	1	Yes	1:1
2	Et_2O	1	No	-
3	benzene	1	Yes	1:1
4	hexane	1	Yes	1:1
5	CCl_4	1	Yes	1:1
6	DCE	1	Yes	1:1
7	TFT	1	Yes	1:1
8	DCM	1	Yes	1.3:1
9	$CDCl_3$	1	Yes	1:1

This multicomponent double Diels-Alder reaction was of high interest to us as a one-pot formation of polycyclic compounds. Unfortunately, attempts to invoke a double Diels-Alder reaction with any of the other dienes listed in table **2-3** proved unsuccessful even under forcing conditions.

2.3 Regioselective Diels-Alder Reaction of Conjugated 2,4-Diynones

Our group is interested in utilizing 2,4-diynones as high-energy and highly functionalized substrates in cyclization reactions. These substrates have proven to be useful in a number of transformations.[24-27] To the best of our knowledge, Lewis acid catalyzed Diels-Alder reactions of 2,4-diynones have not been reported. We proved that cyclization between 2,4-diynone **2.3** and diene **2.4** occurred regioselectively on the more electron deficient proximal alkyne to produce product **2.5** (**Scheme 2-8**). This would result in the formation of highly functionalized "skipped" cyclohexadiene products that could be utilized in a number of transformations to arrive at other useful compounds.



Scheme 2-8. Proposed regioselective Diels–Alder reaction of diynones.

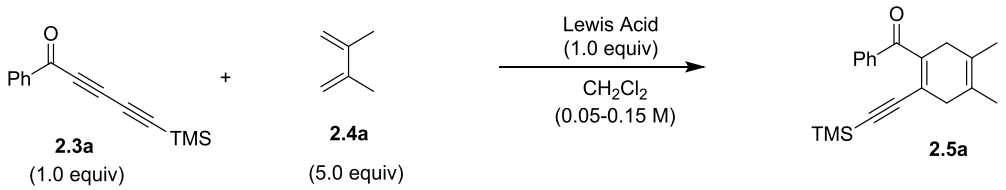
Therefore, we decided to report a study on the Diels-Alder cyclization reaction of conjugated 2,4-diynones promoted by Lewis acids.

We began our study using a TMS-substituted 2,4-diynone **2.3a**, which is synthesized in one step from commercially available starting materials, and commercially available 2,3-dimethyl-1,3-butadiene **2.4a**. We screened a variety of common Lewis acids used for Diels-Alder reactions (**Table 2-5**). When **2.3a** was treated with excess **2.4a** in the presence of Me_2AlCl in dichloromethane solvent we observed clean conversion to cyclic product

2.5a in 88% isolated yield. The more Lewis acidic $EtAlCl_2$ also provided **2.5a** in 82% isolated yield but the reaction was observed to be less clean by thin layer chromatography (TLC) and ^1H NMR (entry 2). The reaction was also promoted by $AlCl_3$ and $TiCl_4$ (entries 3 and 4), but in lower isolated yields. Interestingly, the use of BF_3•OEt_2 in dichloromethane resulted only in the decomposition of diene **2.4a** and leaving **2.3a** unreacted with no detectable desired cyclic product **2.3a** (entries 5). However, when we conducted the same reaction using acetonitrile as the solvent we obtained **2.5a** in 72% yield (entry 6). Other strong Lewis acids such as BCl_3 and BBr_3 were also successful in producing **2.5a** in 77% and 62% yields, respectively (entries 7 and 8). The use of $SnCl_4$, $FeCl_3$ and $ZnCl_2$ resulted in no conversion of the starting material (entries 9-11). We also explored π-Lewis acids that also proved to be ineffective in providing **2.5a** (entries 12-14). The use of Me_2AlCl as the Lewis acid proved to be the most successful so we decided to assess the scope of this reaction with this catalyst.

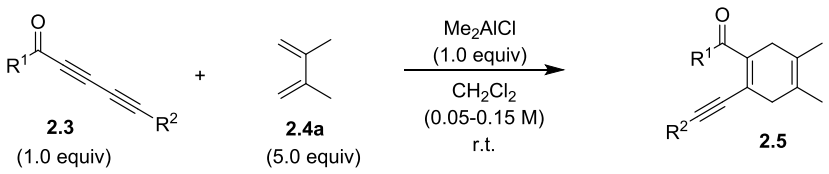
The cyclization reaction between a variety of substituted 2,4-diynones **2.3a**, **2.3c-i** and diene **2.4a** was evaluated (**Table 2-6**). Alkyl substituted 2,4-diynones were tolerated, with **2.5c** being isolated in good yield (entry 2). Electron-rich and electron-poor aryls, substituted in the *ortho* and *para* positions, were also tolerated (entries 3-6).

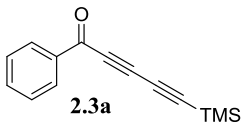
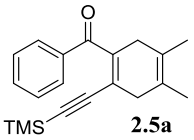
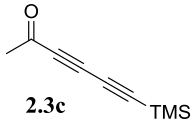
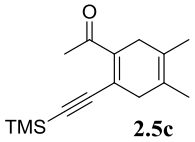
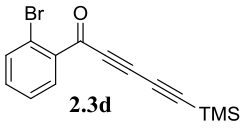
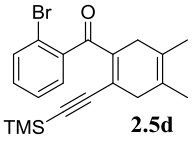
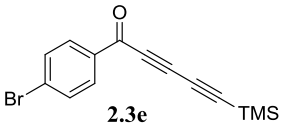
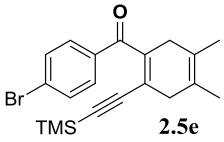
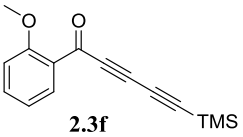
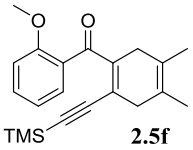
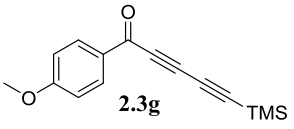
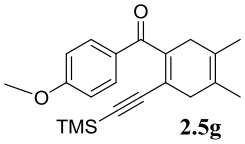
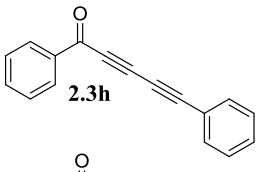
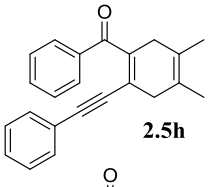
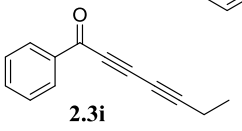
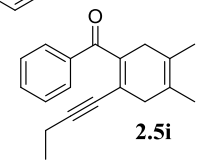
Table 2-5: Lewis acid screening for Diels-Alder reaction between diynone **2.3a** and diene **2.4a**.



Entry	Lewis acid	Temp (°C)	Time (h)	**3a**, Yield (%)
1	Me_2AlCl	r.t.	1	88
2	$EtAlCl_2$	0 to r.t.	1	82
3	$AlCl_3$	r.t.	4	41
4	$TiCl_4$	0 to r.t.	3.5	57
5	$BF_3{\bullet}OEt_2$	0 to r.t.	1	0
6	$BF_3{\bullet}OEt_2$	r.t.	3	72
7	BCl_3	0	1	77
8	BBr_3	-78 to 0	1	62
9	$SnCl_4$	0 to r.t.	1	0
10	$FeCl_3$	r.t.	3	0
11	$ZnCl_2$	r.t.	3	0
12	$PtCl_2$	r.t.	3	0
13	$AuCl_3$	r.t.	3	0
14	Ph_3PAuCl + AgOTf	r.t.	3	0

Table 2-6: Diynone scope for the Diels-Alder reaction with **2.2a**.

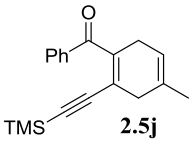
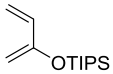
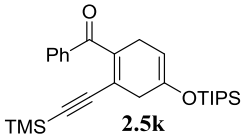
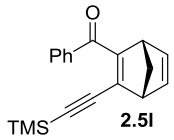
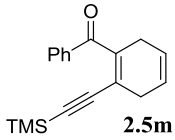
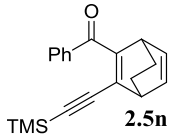
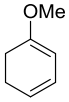
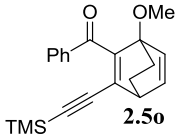
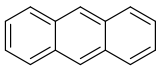
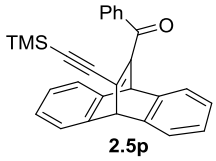


Entry	Diynone	Product	Yield (%)
1	 **2.3a**	 **2.5a**	88
2	 **2.3c**	 **2.5c**	61
3	 **2.3d**	 **2.5d**	57
4	 **2.3e**	 **2.5e**	79
5	 **2.3f**	 **2.5f**	51
6	 **2.3g**	 **2.5g**	59
7	 **2.3h**	 **2.5h**	68
8	 **2.3i**	 **2.5i**	94

Substitution of the distal alkyne with aryl or alkyl groups also successfully provided cyclic products such as **2.5h** and **2.5i** in 68% and 94% yields, respectively.

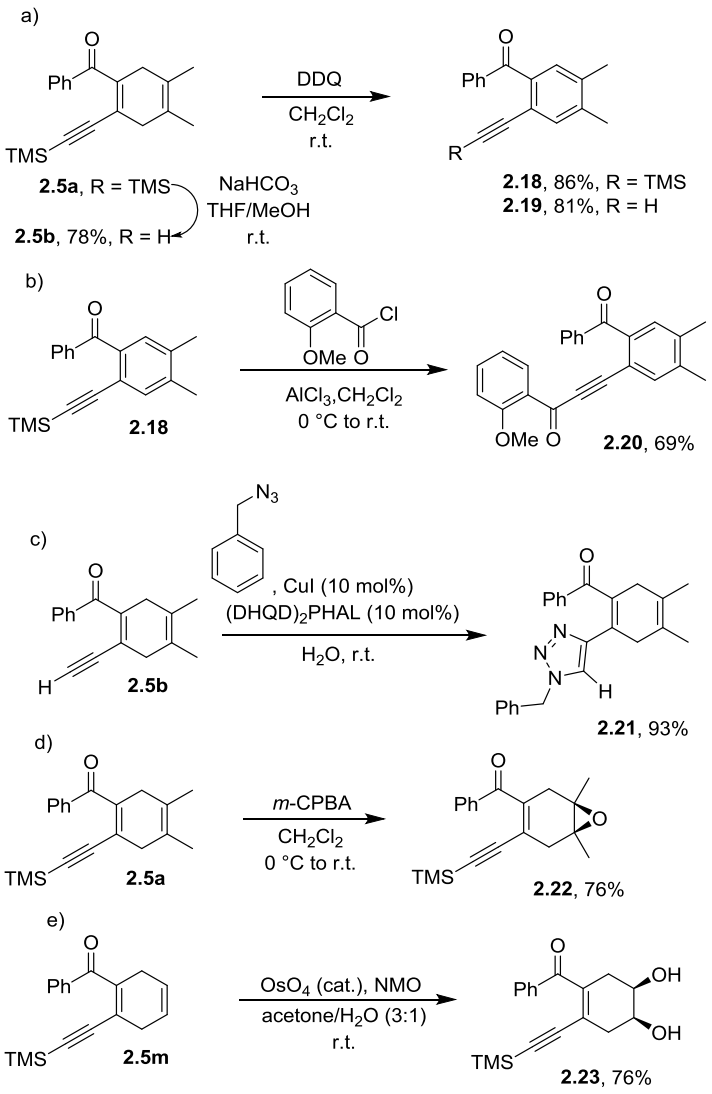
We also investigated different dienes **2.4** with 2,4-diynone **2.3a** under the standard reaction conditions (**Table 2-7**). The acyclic dienes such as **2.4b** and **2.4c** gave cyclized products **2.5j** and **2.5k** in 63% and 57% yields, respectively (entries 1 and 2). When we conducted the reaction of **2.3a** with 1.6 equivalents of cyclopentadiene **2.4e** at room temperature we could exclusively get bridged bicyclic product **2.5l** in 74% yield (entry 3). What was interesting was that conducting the reaction using 10 equivalents of cyclopentadiene **2.4e** resulted in the formation of a mixture of diastereomers **2.17a** and **2.17a′** (already discussed in chapter 2.2). The cyclization with 1,3-butadiene **2.4f** formed the corresponding cyclic product **2.5m** in good yield with 64% (entry 4). We then turned our attention to other cyclic dienes and 1,3-cyclohexadiene **2.4g** formed product **2.5n** in 68% isolated yield (entry 5). Methoxy-substituted cyclic diene **2.4h** provided product **2.5o** in good yield as a single regioisomer (entry 6). The structure of regioisomer **2.5o** was unambiguously confirmed by COSY and HMBC spectra. There was no reaction between **2.3a** and a tricyclic diene anthracene **2.4i** in the presence of Me_2AlCl, even after 6 hours. However, product **2.5p** was cleanly obtained in excellent yield when the reaction was carried out using the more Lewis acidic $EtAlCl_2$ (entry 7).

Table 2-7: Diene scope for the Diels-Alder reaction with **2.3a**.

Entry	Diene	Product	Yield (%)
1	 **2.4b**	 **2.5j**	63
2	 **2.4c**	 **2.5k**	57
3	 **2.4e**	 **2.5l**	74
4	 **2.4f**	 **2.5m**	64
5	 **2.4g**	 **2.5n**	68
6	 **2.4h**	 **2.5o**	83
7	 **2.4i**	 **2.5p**	86

It is well known that an alkyne functional group is an extremely useful handle that can be converted to a number of other functional groups[28] or utilized in cross-coupling

reactions.[29-31] We carried out a few reactions to demonstrate the utility of product **2.5**. We were able to cleanly remove the TMS group on **2.5a** under standard protodesilylation conditions to obtain the skipped diene **2.5b** bearing a terminal alkyne moiety in excellent yield (**Scheme 2-9**, a). Compounds **2.5a** and **2.5b** were easily oxidized using DDQ to *o*-ethynylbenzophenone derivatives **2.18** and **2.19** in 86% and 81%, respectively. This method provides a route to highly substituted *o*-ethynylbenzophenone derivatives, which are valuable intermediates in the formation of desirable carbo- and heterocyclic compounds.[32-37] Silyl-substituted acetylenes have been reported to undergo Friedel-Crafts acylation reactions with acid chloride derivatives.[38] We were concerned that the electron-withdrawing benzoyl group in **2.18** would significantly deactivate the alkyne and retard the reaction. To our surprise, the Friedel-Crafts reaction of **2.18** with *o*-methoxybenzoyl chloride resulted in the formation of **2.20** in good yield (**Scheme 2-9**, b). Terminal alkyne **2.5b** was found to react with phenyl azide and underwent clean conversion to triazene **2.21** under "click" conditions reported by Sarma and coworkers (**Scheme 2-9**, c).[11] To demonstrate chemoselective functionalization of the isolated alkene we subjected substrate **2.5a** to *m*CPBA to produce epoxide **2.22** in very good yield (**Scheme 2-9**, d). Finally, the selective dihydroxylation of **2.5m** under standard conditions provided diol **2.23** in good yield (**Scheme 2-9**, e). This is just a small handful of protecting-group free transformations that compound **2.5** can undergo. One can imagine a host of other useful transformations that these compounds can undergo to generate a variety of useful, and highly functionalized products in relatively few steps.



Scheme 2-9: Conversion of Diels-Alder products into useful organic compounds.

2.4 Conclusion

In conclusion, we have explored the Diels–Alder reaction of conjugated diynones with a variety of cyclic and acyclic dienes promoted by Me_2AlCl or $EtAlCl_2$. This method enables the formation of 2-alkynyl-1,4-cyclohexadienes (cyclic 'skipped' dienes) in good to

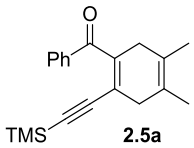
excellent yields. The diversely functionalized 1,4-cyclohexadiene products that are obtained from this reaction are of utility as intermediates on the way to synthesizing pharmaceutically relevant cyclic and polycyclic compounds. However, the attempt of bis-cyclization was not promising, we attempted double Diels-Alder reaction of conjugated diynone with a variety of dienes in different conditions of temperature, solvent and catalysts.

2.5 Experimental

General Methods: All reactions were performed in flame-dried glassware under a N_2 atmosphere. Solvents were degassed and dried by standard methods before use. Purification of the crude products was carried out by column chromatography using silica gel. Analytical TLC was performed on a silica gel GF 254 plate. The TLC plates were visualized under ultraviolet (UV, 254 nm) light or by staining with PMA or CAM. NMR spectra were recorded on a 400 or 500 MHz NMR spectrometer in $CDCl_3$. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26). Data for ^1H NMR are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m= multiplet, br=broad), coupling constant (*J*) in Hertz, and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$, δ 77.16). Infrared (IR) spectra were recorded on an ATR/FTIR spectrometer as a thin film on a composite of zinc selenide and diamond crystal and only

major functional group peaks are reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a high-resolution Q-TOF mass spectrometer (ionization mode: ESI). Commercially available reagents and solvents were used without further purification. Diynones **2.3a-f** [23,39]and **2.3g-h**[40] as well as diene **2.4c**[41] were synthesized according to reported procedures.

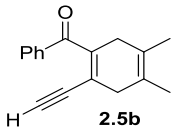
General Procedure for Diels-Alder reaction of diynones: To a solution of diynone **1** (1.0 equiv.) and diene **2** (5.0 equiv.) in dichloromethane (ca. 0.05-0.15 M) was added dimethylaluminum chloride (1.0 M in hexanes, 1.0 equiv.) slowly over 10 minutes. The reaction mixture was stirred at room temperature for 1-5 h, quenched with dilute aq. $NaHCO_3$, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel).



2.5a

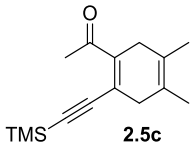
1-benzoyl-2-[2-(trimethylsilyl) ethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5a): This reaction was performed according to the general procedure (305 mg of diynone **2.3a** and 748 μL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5a** (366 mg, 88%) as a pale yellow oil: R_f = 0.52 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93-7.86 (m, 2H), 7.55-7.50 (m, 1H), 7.44-7.39 (m, 2H), 3.02-2.95 (m, 2H), 2.91-2.84 (m, 2H), 1.67 (s, 6H, 2 x CH3), –0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7, 141.9, 137.2, 133.0, 129.8, 128.5, 122.2 (2 coincidental peaks), 120.5, 103.2, 101.7, 38.0, 35.0,

18.3, 18.1, –0.4; IR (cast film) ν 2959, 2858, 2813, 2142, 1656, 1598, 1580, 1448 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{24}NaOSi$ 331.1494; Found 331.1490.



2.5b

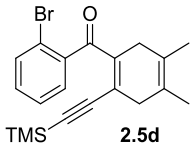
1-benzoyl-2-ethynyl-4,5-dimethyl-1,4-cyclohexadiene (2.5b): To a solution of **2.5a** (300 mg, 0.972 mmol) in 1:1 methanol/tetrahydrofuran (20 mL) was added Na_2CO_3 (206 mg, 1.94 mmol). The reaction mixture was stirred at room temperature for 10 h. The excess Na_2CO_3 was removed by filtration, the solvent removed in vacuo, and the residue purified by column chromatography (toluene) to yield **2.5b** (179 mg, 78%) as yellow liquid: R_f = 0.49 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94-7.90 (m, 2H), 7.59-7.54 (m, 1H), 7.48-7.43 (m, 2H), 2.99-2.88 (m, 4H), 2.83 (s, 1H), 1.69 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 143.0, 136.2, 133.4, 129.7, 128.6, 122.2, 121.9, 118.1, 82.9, 81.6, 37.7, 35.1, 18.2, 18.1; IR (cast film) ν 3292, 3057, 2989, 2915, 2858, 2814, 2249, 1663, 1598, 1448 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}NaO$ 259.1093, Found 259.1096.



2.5c

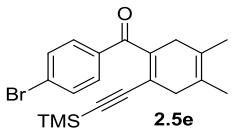
1-ethanoyl-2-[2-(trimethylsilyl)ethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5c): This reaction was performed according to the general procedure (183 mg of diynone **2.3c** and 630 μL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5c**

(168 mg, 61%) as yellow solid: Mp 92-96 °C; R_f = 0.34 (2:1 CH_2Cl_2/hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 2.96-2.90 (m, 2H), 2.90-2.84 (m, 2H), 2.59 (s, 3H), 1.65 (s, 3H), S4 1.63 (s, 3H), 0.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.3, 141.6, 125.9, 122.8, 121.1, 105.3, 104.8, 40.4, 33.5, 30.8, 18.2, 17.7, –0.3; IR (cast film) ν 2958, 2922, 2148, 1679, 1601, 1249 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}NaOSi$, 269.1338; Found: 269.1332.



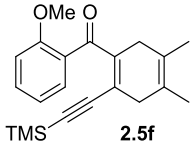
2.5d

1-(2-bromobenzoyl)-2-[2-(trimethylsilyl) ethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5d): This reaction was performed according to the general procedure (300 mg of diynone **2.3d** and 1.10 mL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5d** (217 mg, 57%) as a yellow solid: Mp 73-76 °C; R_f = 0.32 (1:1 CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56-7.51 (m, 1H), 7.40-7.35 (m, 1H), 7.35-7.26 (m, 2H), 3.14-3.06 (m, 2H), 2.96-2.88 (m, 2H), 1.72 (s, 3H), 1.66 (s, 3H), –0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.4, 142.4, 139.7, 133.1, 131.3, 130.0, 128.1, 127.2, 122.5, 121.2, 120.3, 105.7, 102.0, 40.5, 33.6, 18.2, 17.7, –0.1; IR (cast film) ν 2955, 2133, 1644, 1611, 1589, 1303 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}BrNaOSi$ 409.0599; Found 409.0595.



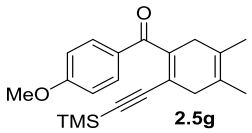
2.5e

1-(4-bromobenzoyl)-2-[2-(trimethylsilyl) ethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5e): This reaction was performed according to the general procedure (150 mg of diynone **2.3e** and 600 μL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5e** (150 mg, 79%) as yellow solid: Mp 77-83 °C; R_f = 0.42 (1:1 CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81-7.72 (m, 2H), 7.61-7.52 (m, 2H), 3.03-2.96 (m, 2H), 2.92-2.85 (m, 2H), 1.69 (s, 6H, 2 x CH3), –0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.4, 141.1, 136.1, 131.7, 131.3, 128.1, 122.1, 122.0, 121.6, 103.0, 102.8, 38.1, 34.8, 18.2, 18.0, –0.5; IR (cast film) ν 2919, 2850, 2137, 1658, 1584 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}BrOSi$ 409.0599, Found 409.0593.



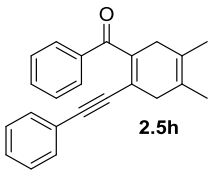
2.5f

1-(2-methoxybenzoyl)-2-[2-(trimethylsilyl) ethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5f): This reaction was performed according to the general procedure (150 mg of diynone **2.3f** and 650 μL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5f** (100 mg, 51%) as a reddish brown solid: Mp 86-91 °C; R_f = 0.26 (2:1 CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47-7.43 (m, 1H), 7.43-7.37 (m, 1H), 6.99-6.93 (m, 1H), 6.91-6.86 (m, 1H), 3.79 (s, 3H), 3.06-2.99 (m, 2H), 2.89-2.82 (m, 2H), 1.69 (s, 3H), 1.65(s, 3H), –0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.4, 158.6, 142.4, 132.7, 130.5, 130.2, 122.6, 122.4, 121.5, 120.7, 111.7, 102.7, 102.5, 56.1, 39.6, 34.0, 18.2, 17.9, –0.1; IR (cast film) ν 2951, 2859, 2817, 2144, 1649, 1595 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{26}NaO_2Si$ 361.1600; Found 361.1602.



2.5g

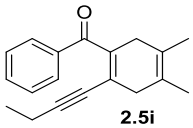
1-(2-methoxybenzoyl)-2-[2-(trimethylsilyl) ethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5g): This reaction was performed according to the general procedure (250 mg of diynone **2.3g** and 1.00 mL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5g** (195 mg, 59%) as yellow solid: Mp 63-67 °C; R_f = 0.25 (2:1 CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91-7.84 (m, 2H), 6.92-6.86 (m, 2H), 3.83 (s, 3H), 2.98-2.92 (m, 2H), 2.88-2.81 (m, 2H), 1.65 (s, 6H, 2 x CH3), –0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.2, 163.8, 142.2, 132.1, 129.8, 122.1, 122.0, 119.2, 113.6, 103.3, 100.8, 55.5, 37.6, 35.0, 18.1, 18.0, –0.4; IR (cast film) ν 2962, 2144, 1644, 1601, 1578, 1244 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{26}NaO_2Si$ 361.1600; Found 361.1595.



2.5h

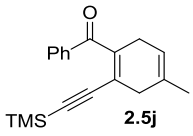
1-benzoyl-2-[2-(phenylethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5h): This reaction was performed according to the general procedure (199 mg of diynone **2.3h** and 1.00 mL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5h** (183 mg, 68%) as pale yellow solid: Mp 134-137 °C; R_f = 0.24 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01-7.96 (m, 2H), 7.58-7.53 (m, 1H), 7.50-7.44 (m, 2H),7.22-7.16 (m, 1H), 7.16-7.11 (m, 2H), 6.87-6.83 (m, 2H), 3.11-3.05 (m, 2H), 3.04-2.98 (m, 2H), 1.73 (s, 6H, 2 x CH3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5, 140.7, 137.2, 133.0, 131.3, 129.8, 128.5,

128.3, 128.0, 122.7, 122.3, 122.0, 120.9, 96.4, 88.1, 38.1, 35.1, 18.2, 18.1; IR (cast film) *v* 2888, 2804, 2205, 1645, 1594 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ for $C_{23}H_{20}NaO$ 335.1412; Found 335.1421.



2.5i

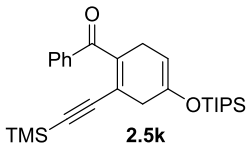
1-benzoyl-2-[2-(ethylethynyl]-4,5-dimethyl-1,4-cyclohexadiene (2.5i): This reaction was performed according to the general procedure (96 mg of diynone **2.3i** and 700 µL of diene **2.4a**). Purification by column chromatography (toluene) afforded **2.5i** (130 mg, 94%) as pale yellow solid: Mp 50-54 °C; R_f = 0.41 (toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91-7.86 (m, 2H), 7.54-7.48 (m, 1H), 7.45-7.39 (m, 2H), 3.01-2.93 (m, 2H), 2.89-2.81 (m, 2H), 1.93 (q, J= 7.5 Hz, 2H), 1.67 (s, 6H, 2 x CH_3), 0.68 (t, J= 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.1, 139.4, 137.4, 132.7, 129.6, 128.3, 122.2, 122.2, 121.3, 99.0, 78.8, 38.5, 34.9, 18.2, 18.0, 13.3, 13.0; IR (cast film) *v* 2980, 2915, 2812, 2220, 1655, 1596, 1580 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{20}NaO$ 287.1412; Found 287.1402.



2.5j

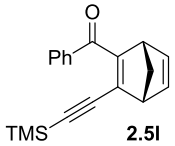
1-benzoyl-2-[2-(trimethylsilyl) ethynyl]-4-methyl-1,4-cyclohexadiene (2.5j): This reaction was performed according to the general procedure (301 mg of diynone **2.3a** and 450 mg of diene **2.4b**). Purification by column chromatography (toluene) afforded **2.5j** (245 mg, 63%) as a pale yellow oil: R_f = 0.54 (toluene); ^1H NMR (CDCl3, 500 MHz) δ

7.93-7.88 (m, 2H), 7.57-7.51 (m, 1H), 7.46-7.39 (m, 2H), 5.49-5.45 (m, 1H), 3.10-3.03 (m, 2H), 2.88-2.82 (m, 2H), 1.73 (s, 3H), –0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.9, 141.7, 137.0, 133.1, 130.2, 129.7, 128.4, 119.8, 117.1, 103.3, 101.6, 35.8, 29.4, 22.8, –0.4; IR (cast film) v 2961, 2858, 2818, 2144, 1655, 1598, 1581, 1448 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{22}NaOSi$ 317.1338; Found 317.1330.



2.5k

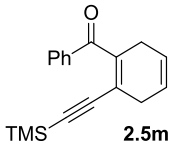
1-benzoyl-2-[2-(trimethylsilyl)ethynyl]-4-[[tris(1-methylethyl)silyl]oxy]-1,4-cyclohexadiene (2.5k): This reaction was performed according to the general procedure (299 mg of diynone **2.3a** and 1.50 g of diene **2.4c**). Purification by column chromatography (toluene) afforded **2.5k** (340 mg, 57%) as a pale yellow oil: R_f = 0.62 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93-7.89 (m, 2H), 7.58-7.52 (m, 1H), 7.47-7.41 (m, 2H), 4.92-4.88 (m, 1H), 3.16 (dt, J = 8.0, 3.6 Hz, 2H), 2.98 (t, J = 7.9 Hz, 2H), 1.24-1.15 (m, 3H), 1.14-1.04 (m, 18H), –0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 146.8, 142.0, 136.8, 133.2, 129.8, 128.5, 119.2, 102.8, 101.6, 98.4, 35.0, 29.5, 18.2, 12.8, –0.4; IR (cast film) v 3059, 2945, 2867, 2148, 1687, 1661, 1598, 1581, 1463 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{40}NaO_2Si_2$ 475.2465; Found 475.2457.



2.5l

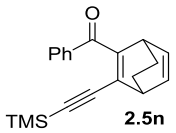
2-benzoyl-3-[2-(trimethylsilyl) ethynyl]bicyclo[2.2.1]hepta-2,5-diene (2.5l): This reaction was performed according to the general procedure using 1.6 equivalents of diene

2.4e (326 mg of diynone **2.3a** and 153 mg of diene **2.4e**). Purification by column chromatography (toluene) afforded **2.5l** (312 mg, 74%) as a pale red oil: R_f = 0.43 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77-7.73 (m, 2H), 7.53-7.48 (m, 1H), 7.42-7.36(m, 2H), 6.99-6.95 (m, 1H), 6.85-6.81 (m, 1H), 4.07 (br s, 1H), 3.78 (br s, 1H),2.26 (d, J= 6.9 Hz, 1H), 2.13 (d, J= 6.9 Hz, 1H), –0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 192.4, 157.5, 146.3, 142.8, 140.9, 138.2, 132.4, 129.5, 128.0, 113.1, 100.1,70.2, 58.8, 52.6, –0.4; IR (cast film) ν 2959, 2135, 1632, 1572, 1551, 1447, 1248 cm^{-1}; HRMS (ESI-TOF) m/z:$[M+H]^+$ Calcd for $C_{19}H_{21}OSi$ 293.1356; Found 293.1358.



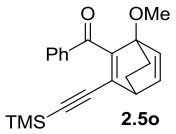
2.5m

1-benzoyl-2-[2-(trimethylsilyl) ethynyl]-1,4cyclohexadiene (2.5m): This reaction was performed according to the general procedure (307 mg of diynone **2.3a** and excess diene **2.4f**, which was condensed into a separate flask then transferred by cannula into the reaction mixture). Purification by column chromatography (toluene) afforded **2.5m** (244 mg, 64%) as a colorless oil: R_f = 0.45 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96-7.88 (m, 2H), 7.57-7.52 (m, 1H), 7.46-7.41 (m, 2H), 5.81-5.72 (m, 2H), 3.10-3.03 (m, 2H), 2.98-2.92 (m,2H),–0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 141.7, 136.9, 133.1, S7129.8, 128.5, 123.0, 122.9, 119.8, 103.3, 101.9, 31.1, 28.3, –0.4; IR (cast film) ν 3036, 2959, 2896, 2820, 2144, 1655, 1597, 1581, 1269 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaOSi$ 303.1181; Found 303.1176.



2.5n

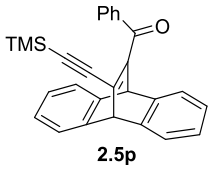
1-benzoyl-2-[2-(trimethylsilyl) ethynyl] bicyclo [2.2.2] octa-1,4-diene (2.5n): This reaction was performed according to the general procedure (300 mg of diynone **2.3a** and 529 mg of diene **2.4g**). Purification by column chromatography (toluene) afforded **2.5n** (278 mg, 68%) as a pale yellow oil: R_f = 0.39 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72-7.66 (m, 2H), 7.52-7.46 (m, 1H), 7.41-7.33 (m, 2H), 6.47-6.40 (m, 2H), 4.22 (s, 1H), 3.79 (s, 1H), 1.65-1.51 (m, 2H), 1.51-1.37 (m, 2H), –0.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.3, 149.3, 138.3, 135.9, 134.2, 133.6, 132.4, 129.7, 128.1, 106.3, 101.5, 45.0, 39.5, 25.6, 24.8, –0.3; IR (cast film) ν 3057, 2957, 2871, 2140, 1640, 1598, 1574, 1274 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}NaOSi$ 329.1338; Found 329.1331.



2.5o

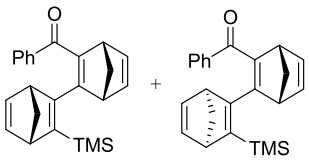
1-benzoyl-2-[2-(trimethylsilyl) ethynyl]-6-methoxybicyclo [2.2.2] octa-1,4-diene (2.5o): This reaction was performed according to the general procedure (301 mg of diynone **2.3a** and 727 mg of diene **2.4h**). Purification by column chromatography (toluene) afforded **2.5o** (372 mg, 83%) as a pale yellow oil: R_f = 0.43 (1:5 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86-7.78 (m, 2H), 7.55-7.49 (m, 1H), 7.44-7.37 (m, 2H), 6.58 (d, J= 8.1 Hz, 1H), 6.46 (dd, J= 8.1, 6.1 Hz, 1H), 3.68-3.64 (m, 1H), 3.36 (s, 3H), 1.92 (dt, J= 10.2,4.0 Hz, 1H), 1.76-1.61 (m, 2H), 1.54-1.45 (m, 1H), –0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz)

δ 194.2, 151.8, 137.3, 134.4, 133.1, 132.9, 130.0, 129.8, 128.4, 104.0, 100.5, 86.4, 54.6, 43.1, 31.4, 25.8, –0.4; IR (cast film) ν 2948, 2830,2143, 1657, 1596, 1580 cm^{-1}; HRMS (ESITOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{24}NaO_2Si$ 359.1443; Found 359.1441.



2.5p

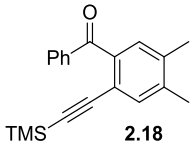
11-benzoyl-12-[2-(trimethylsilyl) ethynyl]-9,10-dihydro-9,10-ethenoanthracene (2.5p): This reaction was performed using a modification to the general procedure [143 mg of diynone **2.3a**, 308 mg of anthracene **2.4i**, and 1 equiv. of $EtAlCl_2$ (630 μL, 0.630 mmol, 1M in hexane)]. Purification by column chromatography (toluene) afforded **2.5p** (220 mg, 86%) as pale yellow oil: R_f = 0.46 (toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.61-7.57 (m, 2H), 7.52-7.47 (m, 1H), 7.47-7.43 (m, 4H), 7.37-7.32 (m, 2H), 7.12-7.04 (m, 4H), 5.73 (s, 1H), 5.27 (s, 1H), –0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.0, 152.3, 144.2, 143.7, 140.5, 138.1, 132.6, 129.6, 128.1, 125.8, 125.2, 123.9, 123.8, 112.0, 100.4, 58.2, 52.7, –0.4; IR (cast film) ν 3066, 2959, 2137,1637, 1597, 1568 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{24}NaOSi$ 427.1494; Found 427.1488.



2.17a **2.17a'**

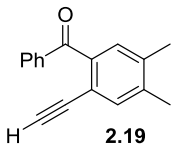
2-benzoyl-2′-trimethylsilyl-3,3′-bibicyclo[2.2.1]hepta-2,5-diene (2.17a & 2.17a′): This reaction was performed according to the general procedure using 10 equivalents of diene **2.4e** (302 mg of diynone **2.3a** and 436 mg of diene **2.4e**) to yield crude **2.17a** and **2.17a′**

as an inseparable mixture of diastereomers in a 1.3:1 ratio. Purification by column chromatography (toluene) afforded **2.17a** and **2.17a′** (340 mg, 71%) as pale yellow oil: R_f = 0.23 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (mixture of diastereomers) 7.68-7.62 (m, 2H), 7.60-7.54 (m, 2H), 7.45-7.23 (m, 6H), 7.06-7.00 (m, 2H), 6.87-6.82 (m, 1H), 6.67-6.63 (m, 1H), 6.57-6.51 (m, 2H), 6.46-6.42 (m, 1H), 6.31-6.26 (m, 1H), 4.09-4.04 (m, 1H), 3.96-3.92 (m, 1H), 3.69-3.65 (m, 1H), 3.54-3.46 (m, 3H), 3.35-3.31 (m, 1H), 3.21-3.16 (m, 1H), 2.30-2.22 (m, 2H), 2.05-1.99 (m, 2H), 1.63-1.58 (m, 1H), 1.49-1.44 (m, 2H), 1.11-1.06 (m, 1H), –0.03 (s, 9H), –0.15 (s, 9H); IR (cast film) ν 2969, 1625, 1447, 1338 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{26}NaOSi$ 381.1651; Found 381.164



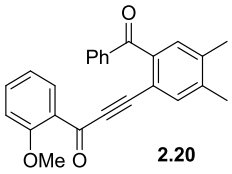
2.18

1-benzoyl-4,5-dimethyl-2-(trimethylsilylethynyl) benzene (2.18): To a solution of **2.5a** (231 mg, 0.749 mmol) in 30 mL dichloromethane was added DDQ (337 mg, 1.48 mmol) and the mixture stirred at room temperature for 5 h. The reaction mixture was washed with water, brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (toluene) to afford **2.18** (197 mg, 86%) as a pale yellow oil: R_f = 0.47 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87-7.82 (m, 2H), 7.60-7.54 (m, 1H), 7.48-7.42 (m, 2H), 7.35 (s, 1H), 7.31 (s, 1H), 2.33 (s, 3H), 2.31 (s, 3H), –0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.2, 139.7, 139.3, 137.9, 137.7, 133.9, 132.8, 130.2, 129.9, 128.2, 119.1, 102.9, 99.6, 19.7, 19.5, –0.4; IR (cast film) ν 2958, 2155, 1597, 1660, 1448 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}NaOSi$ 329.1332; Found 329.1334.



2.19

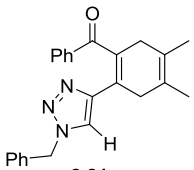
1-benzoyl-4,5-dimethyl-2-ethynylbenzene (2.19): To a solution of **2.5b** (107 mg, 0.453 mmol) in 20 mL dichloromethane was added DDQ (115 mg, 0.507 mmol) and the resulting solution stirred at room temperature for 5 h. The reaction mixture was washed with water, brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (toluene) to afford **2.19** (86 mg, 81%) as a colorless oil: R_f = 0.38 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83-7.79 (m, 2H), 7.59-7.54 (m, 1H), 7.47-7.41 (m, 2H), 7.39 (s, 1H), 7.22 (s, 1H), 2.96 (s, 1H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.7, 139.7, 139.5, 137.7, 137.6, 134.8, 133.1, 130.4, 130.0, 128.4, 118.3, 81.6, 81.2, 19.9, 19.7; IR (cast film) ν 3288, 3056, 2920, 2104, 1656, 1597, 1448 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}O$ 235.1117; Found 235.1116.



2.20

3-(2-benzoylphenyl)-1-(2-methoxyphenyl)-2-propyn-1-one (2.20): To a solution of **2.18** (172 mg, 0.561 mmol) and 2-methoxybenzoyl chloride (105 mg, 0.616 mmol) in 25 mL dichloromethane was added aluminum chloride (88 mg, 0.65 mmol) slowly over 3 minutes at room temperature. The reaction mixture was stirred at room temperature for 1h. The reaction was quenched with dilute aq. $NaHCO_3$, the layers separated, the organic layer dried over anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo and the

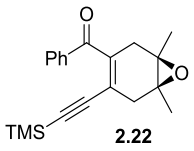
crude product was purified by column chromatography (1:3 EtOAc/hexanes) to yield **2.20** (143 mg, 69%) as pale yellow oil: R_f = 0.41 (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68-7.63 (m, 1H), 7.52-7.46 (m, 2H), 7.43-7.36 (m, 4H), 7.35 (s, 1H), 7.02 (s, 1H), 6.98-6.93 (m, 1H), 6.83-6.77 (m, 1H), 3.69 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.8, 190.6, 160.7, 159.2, 142.5, 142.1, 139.1, 134.2, 132.1, 131.0, 130.0, 128.90, 128.86, 128.5, 128.4, 125.1, 124.9, 120.7, 111.6, 56.0, 20.7, 20.1; IR (cast film) ν 2924, 2251, 1710, 1643, 1597 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{20}NaO$ 3391.1305; Found 391.1309.



2.21

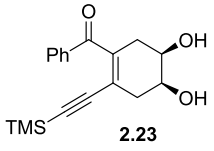
1-benzyl-2-(1-benzyl-1H-1,2,3-triazol-4-yl)-4,5-dimethylcyclohexa-1,4-diene (2.21): To a solution of **2.5b** (113 mg, 0.478 mmol) and benzyl azide (73 mg, 0.55 mmol) in 30 mL deionized water was added copper iodide (11 mg, 0.058 mmol) and $(DHQD)_2PHAL$ (41 mg, 0.053 mmol). The reaction mixture was stirred at room temperature for 1h. The reaction was extracted with EtOAc (100 mL) and the organic layer washed with water, dilute HCl, and brine. The organic layer was dried over $MgSO_4$ then filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (1:3 EtOAc/hexanes) to afford **2.21** (164 mg, 93%) as a light brown sticky gum: R_f = 0.36 (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82-7.79 (m, 2H), 7.47-7.42 (m, 1H), 7.32-7.27 (m, 2H), 7.27-7.24 (m, 1H), 7.24-7.19 (m, 2H), 7.14 (s, 1H), 6.92-6.88 (m, 2H), 5.28 (s, 2H), 3.33-3.26 (m, 2H), 2.99-2.93 (m, 2H), 1.76 (s, 3H), 1.69 (s, 3H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 200.7, 146.0, 135.4, 134.6, 133.6, 133.3, 129.3, 129.0, 128.7, 128.5, 127.5, 124.8, 123.0, 122.1, 121.7, 53.8, 35.9, 35.5, 18.3, 18.1; IR (cast film) ν 2857, 2812, 1657, 1596, 1579, 1448, 1269 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{24}N_3O$ 370.1914; Found 370.1914.



2.22

3-benzoyl-1,6-dimethyl-4-(trimethylsilylethynyl)-7-oxabicyclo[4.1.0]hept-3-ene (2.22): To a solution of **2.5a** (40 mg, 0.13 mmol) in dichloromethane (15 mL) at 0 °C was added *m*-chloroperbenzoic acid (46 mg, 0.26 mmol). The resulting solution was stirred at 0 °C for 10 minutes then warmed to room temperature and stirred for 50 minutes. The reaction was quenched with dilute aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (1:3 EtOAc/hexanes) to afford **2.22** (37 mg, 76%) as a white solid: Mp 86-88 °C; R_f = 0.59 (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90-7.86 (m, 2H), 7.56-7.50 (m, 1H), 7.44-7.38 (m, 2H), 2.88-2.60 (m, 4H), 1.42 (s, 2 x CH_3, 6H), –0.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.1, 140.5, 136.8, 133.2, 129.9, 128.5, 118.8, 102.9, 101.8, 60.7, 60.6, 37.2, 34.2, 19.3, 19.1, –0.5; IR (cast film) ν 2960, 2144, 1659, 1449, 1250 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{24}NaO_2Si$ 347.1438; Found 347.1440.



2.23

1-benzoyl-4,5-dihydroxy-2-(trimethylsilylethynyl)cyclohexene (2.23): Compound **2.5m** (55 mg, 0.20 mmol) was dissolved in 32 mL 3:1 acetone/water, the flask wrapped with aluminum foil and OsO_4 (0.1 mL, 1% in H_2O), 0.004 mmol) was added followed by the addition of NMO (0.1 mL, 50% in H_2O, 0.42 mmol). The resulting solution was stirred in the dark at room temperature for 16 h. The reaction mixture was transferred to a separatory funnel and diluted with EtOAc (100 mL). The mixture was washed with brine, the organic layer dried with $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (EtOAc) to yield compound **2.23** (48 mg, 76%) as a white sticky solid: R_f = 0.47 (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93-7.87 (m, 2H), 7.58-7.51 (m, 1H), 7.46-7.40 (m, 2H), 4.12-4.02 (m, 2H), 2.92-2.80 (m, 2H), 2.80-2.70 (m, 1H), 2.67-2.52 (m, 3H), –0.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.6, 141.2, 136.7, 133.4, 129.9, 128.6, 119.3, 102.8, 102.1, 68.05, 68.04, 35.6, 32.7, –0.5; IR (cast film) ν 3310, 2923, 2253, 1645, 1250; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{22}NaO_3Si$ 337.1230; Found 337.1225.

2.6 References

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3 One-Pot Synthesis of α-Carbonyl Bicyclic Furans via a Sequential Diels-Alder/5-Exo-Dig Cyclization/Oxidation Reaction

3.1 Introduction

α-Carbonyl bicyclic furans and their derivatives are important structures that exist in several natural products and synthetic drug molecules (**Figure 3-1**). Polyketide **3.1**, bearing a dihydroisobenzofuranone skeleton, was isolated from *Phialomycs macrosporus* MCI3226[1] and potentially contains immuno-suppressive and anti-inflammatory activities because it inhibits intercellular adhesion molecule (ICAM-1) expression.[2] Asperfuranone,[3,4] isolated from *Aspergillus nidulans*, exhibits the antiproliferative activity property against human nonsmall cell lung cancer A549 cells.[5] Bhimamycin B is a quinone antibiotic that was isolated from a terrestrial *Streptomyces* sp. and also displays pronounced antibacterial activity.[6,7] Furans also serve as important synthetic building blocks for a number of biologically important heterocyclic compounds.[8-11]

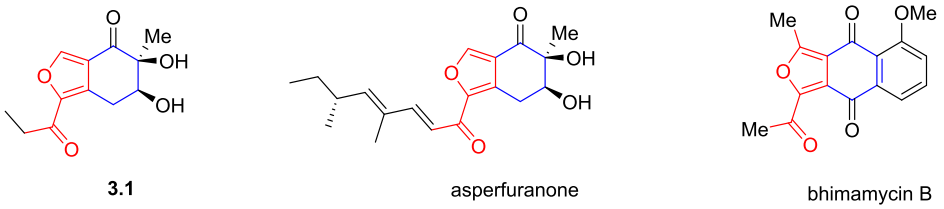
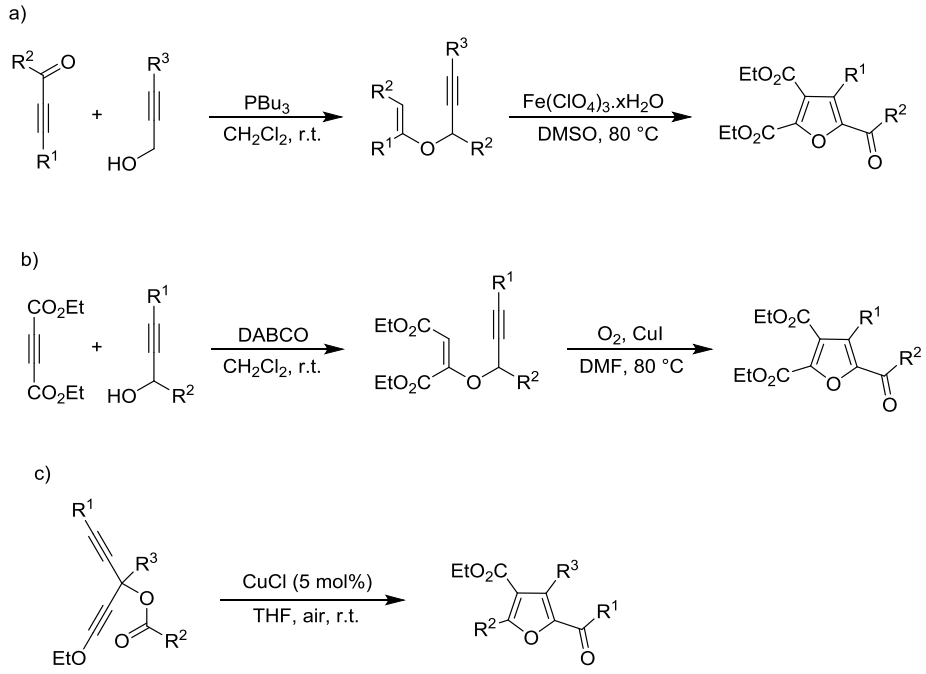


Figure 3.1: Selected biologically active molecules containing an α-carbonyl dihydroisobenzofuran moiety.

There have been several methods reported over the years for the generation of a furan moiety.[12-16] However, there have been very few reports for the direct synthesis of α-

carbonyl furans.[12,17,18] The Jiang group[12] reported the synthesis of polysubstituted α-carbonyl furan derivatives via $Fe(ClO_4)_3$-catalyzed intramolecular rearrangement/cyclization/oxidation reaction sequence (**Scheme 3-1**, a). The same group developed a copper(I)-catalyzed domino process for the regiospecific synthesis of furan aldehydes/ketones which proceeds through a rearrangement/dehydrogenation oxidation/carbene oxidation sequence of 1,5-enynes (**Scheme 3-1**, b).[17] Another regioselective Cu(I)-catalyzed synthesis of 2-acylfurans from readily available bis-propargylic esters was reported by Barluenga and co-workers (**Scheme 3-1**, c).[18] To the best of our knowledge, there have been no reports for the direct synthesis of bicyclic dihydroisobenzofurans. Herein, we report a one-pot sequential Diels−Alder/5-exo-dig cyclization/oxidation reaction for the formation of bicyclic dihydroisobenzofuranones from easily accessible diynone starting materials.



Scheme 3-1: a) Iron-catalyzed synthesis of α-carbonyl furans. b) Cu(I)-catalyzed synthesis of α-carbonyl furans. c) Cu(I)-catalyzed synthesis of α-carbonyl furans from propargylic esters.

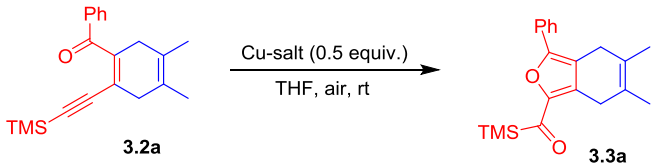
3.2 Copper(II)-Catalyzed Synthesis of α-Carbonyl Bicyclic Furans

Conjugated diynones represent a class of high-energy starting materials that can participate in a number of useful transformations. Recent examples include asymmetric transfer hydrogenation to make diyne-containing natural products,[19] synthesis of polyynes,[20,21] and the "abnormal" hexadehydro Diels−Alder (HDDA) reaction.[22,23] We recently reported a Lewis acid promoted regioselective Diels−Alder reaction of conjugated diynones for the synthesis of 2-alkynyl-1,4-cyclohexadienes **3.2a** (**Table 3-1**).[24] With the carbonyl group and alkyne moiety adjacent to one another, we envisioned that **3.2a** could serve as an

intermediate for an intramolecular carbonyl-alkyne cyclization in the presence of π-Lewis acid catalysts, leading to the generation of furans such as **3.3a**. We have shown that the isolated double bond in **3.3a** efficiently undergoes chemoselective dihydroxylation;[24] thus, one can imagine **3.3a** as an advanced synthetic intermediate for the total synthesis of polyketide natural products such as **3.1** and asperfuranone.

We decided to explore copper salts as catalysts since they are relatively cheap, bench stable, and nontoxic reagents and were shown to catalyze carbonyl-alkyne cyclizations to generate α-acylfurans.[17,18] We explored the cyclization reaction of compound **3.2a** using 50 mol % of copper catalyst in tetrahydrofuran solvent (**Table 3-1**). Only a trace amount of desired product **3.3a** was produced in the presence of $CuSO_4 \cdot 5H_2O$ and $Cu(OAc)_2$ after 18 h (entries 1 and 2). Interestingly, we did not observe any conversion to the desired product using $Cu(OTf)_2$ (entry 3). However, $CuCl_2$ rapidly and cleanly gave desired product **3.3a** in 85% isolated yield (entry 4). Other copper halides also provided **3.3a**, albeit in slightly lower yields and/or longer reaction times (entries 5−8). Other than a nominal increase in reaction time, lowering the catalyst loading to 20 mol % had no effect on the overall yield (entry 9). The silyl ketone functionality obtained in **3.3a** is highly useful

Table 3-1: Screening of various commercial copper catalysts.



Entry	Catalyst	Time (h)	Yield (%)

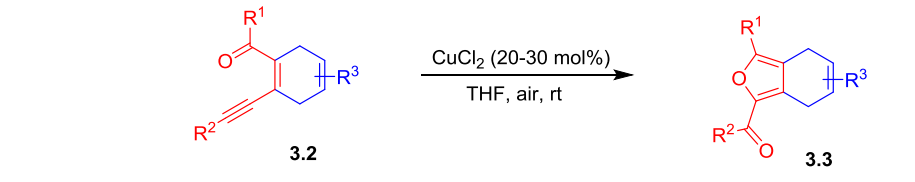
1	$CuSO_4 \cdot 5H_2O$	18	trace
2	$Cu(OAc)_2$	18	trace
3	$Cu(OTf)_2$	18	0
4	$CuCl_2$	1	85
5	$CuBr_2$	3	65
6	CuCl	1	76
7	CuBr	3	62
8	CuI	6	55
9	$CuCl_2$	2.5	85[c]

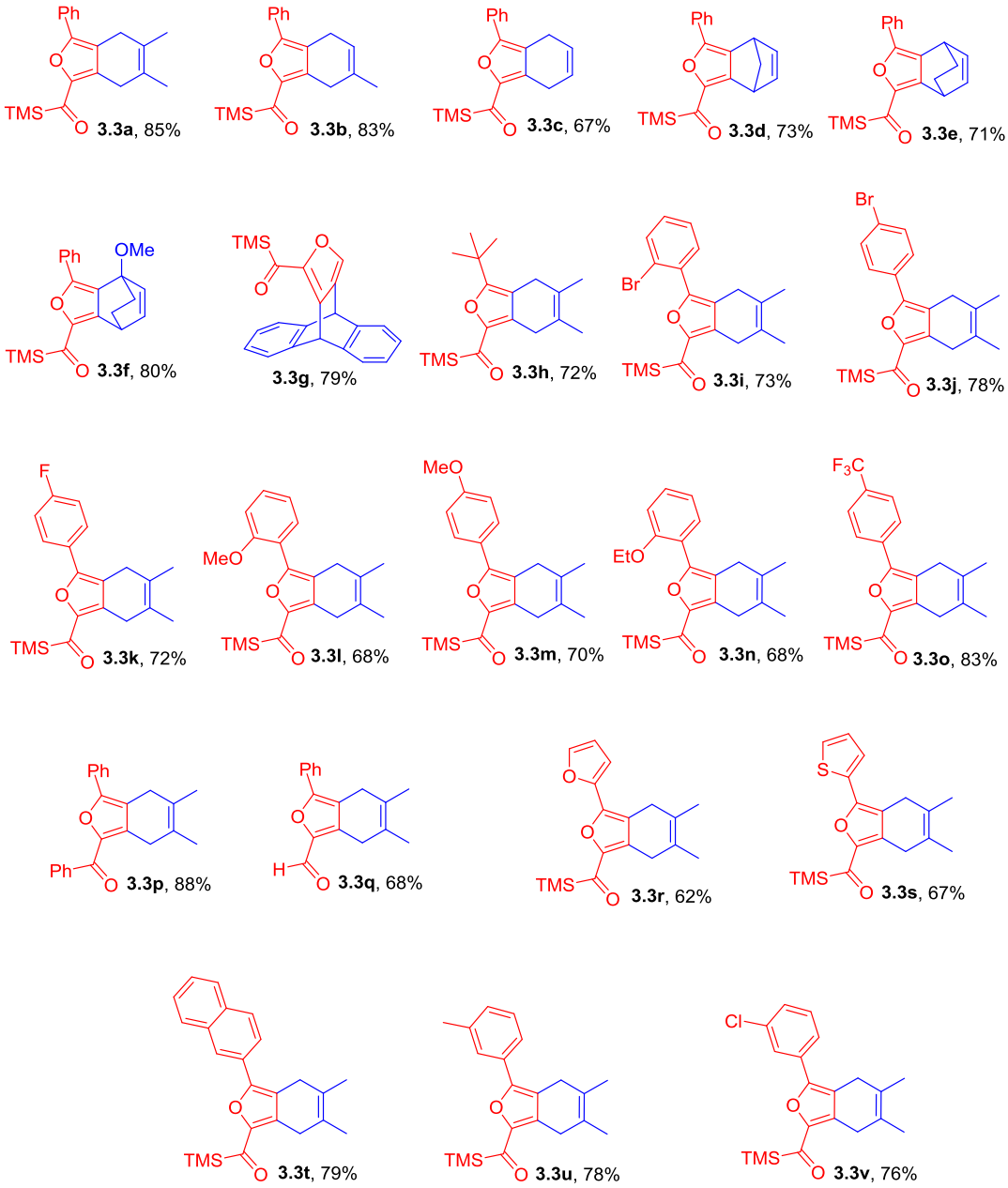
for further chemical elaboration via nucleophilic addition/Brook-rearrangement processes to afford valuable handles such as silyl enol ethers[25,26] and allenes.[27-29]

With reaction conditions in hand, we then proceeded to explore the scope of the reaction. Substituted cyclohexadiene starting materials **3.2** were prepared as previously reported.[24] Various substituents and bridged-bicyclic systems were tolerated (**3.3a**−**3.3f**, **Table 3-2**). Compound **3.2g** cyclized cleanly to **3.3g** demonstrating the utility of this reaction by providing access to useful heterocyclic triptycene analogs.[30] The sterically demanding *tert*-butyl ketone derivative **3.2h** worked well to provide **3.3h** in good yield. Other alkyl groups (i.e., R = CH_3) with an enolizable α hydrogen failed to produce desired product and resulted

in a large amount of baseline (TLC) material along with a small amount of an acetophenone product due to oxidation of the cyclohexadiene ring. Various acyl groups (R^1 = aryl) performed well in the reaction (**3.3i−3.3n**, **Table 3-2**). In fact, even an electron-poor aryl **3.2o** worked well to produce **3.3o** in 83% isolated yield. Compound **3.2p** containing a phenyl-terminated alkyne also cyclized cleanly to provide **3.3p** in excellent yield. Single crystals suitable for X-ray crystallographic analysis were obtained for compound **3.3p** by slow evaporation of solvents from dichloromethane solution (**Figure 3-3**). Terminal alkyne substrate **3.3q** (R^2 = H) also cyclized successfully to provide the aldehyde-substituted furan **3.3q** in good yield. This is an exciting result, as the aldehyde functional handle provides a nice entry point for further chemical elaboration. Reactions with heterocyclic ketones were also successful to afford products **3.3r** and **3.3s** in 62% and 67%, respectively. Larger aryl ketones and meta-substituted aryls also performed well (**3.3t−3.3v**, **Table 3-2**).

Table 3-2: Substrate scope.





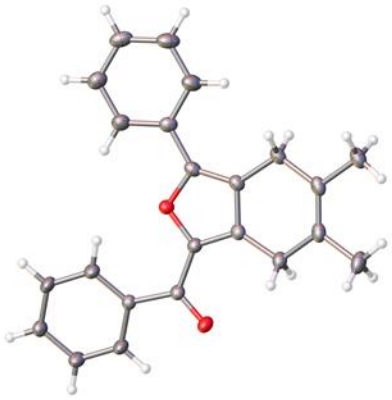


Figure 3-3: Single crystal X-ray structure of compound **3.3p** (50% probability). Crystals suitable for single-crystal X-ray diffraction were obtained by slow evaporation of a solution of **3.3p** in dichloromethane.

Table 3-3: Crystal parameters and refinement metrics of compound **3.3p**.

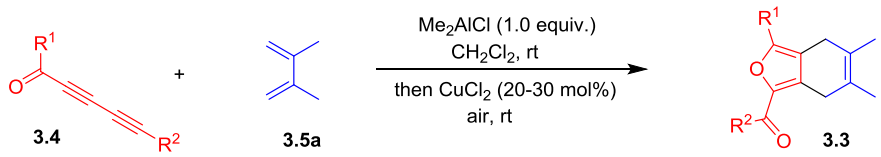
Empirical formula	$C_{23}H_{20}O_2$	Crystal size	0.305 x 0.092 x 0.023 mm^3
Formula weight	328.39	Theta range for data collection	1.316 to 29.575°
Temperature	100(2) K	Index ranges	-6<=h<=6, -42<=k<=41 -14<=l<=15
Wavelength	0.71073 Å	Reflections collected	32590
Crystal system	Monoclinic	Independent reflections	4658 [R(int) = 0.0446]
Space group	$P2_1/n$	Completeness to theta= 25.242°	100.0 %
F(000)	696	Absorption correction	Multi-scan
Unit cell dimensions	a = 4.9054(4) Å	Max. and min. transmission	0.7460 and 0.6335
	b = 30.944(2) Å	Refinement method	Full-matrix least-squares on F^2
	c = 11.0135(8) Å		
	α= 90°		
	β= 94.3203(13)°	Extinction coefficient	n/a
	γ = 90°	Data/restraints/parameters	4658 / 0 / 228
Volume	1667.0(2) $Å^3$	Goodness-of-fit on F^2	0.856
Z	4	Final R indices [I>2sigma(I)]	R1 = 0.0581, wR2 = 0.1505
Density (calculated)	1.308 Mg/m^3	R indices (all data)	R1 = 0.0716, wR2 = 0.1627
Absorption coefficient	0.082 mm^{-1}	Largest diff. peak and hole	0.434 and -0.224 $e.Å^{-3}$

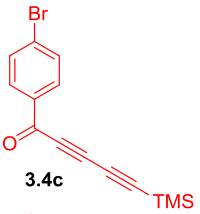
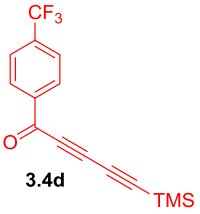
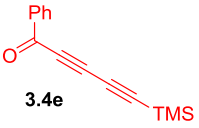
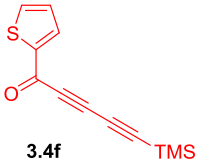
3.3 One-Pot Synthesis of α‑Carbonyl Bicyclic Furans via a Sequential 2 Diels−Alder/5-Exo-Dig Cyclization/Oxidation Reaction

A significant thrust in our group's research efforts involves the utilization of high-energy alkyne-containing substrates in multicomponent, sequential, and tandem reactions to quickly arrive at biologically relevant polycyclic scaffolds.[31-33] Therefore, we wondered if we could streamline this methodology and make it more useful by combining the Diels−Alder cycloaddition (used to synthesize **3.2**), the 5-exo-dig cyclization, and the oxidation reaction steps into a one-pot operation. This would allow direct and rapid access to valuable dihydroisobenzofurans directly from simple diynone starting materials. This would effectively result in the formation of heavily functionalized bicyclic furans in a single reaction step from relatively simple and readily available precursors.

We initiated our study with diynone **3.4a** and diene **3.5a** in the presence of both Me_2AlCl and $CuCl_2$ catalysts. Owing the fact that Diels-Alder reaction performed well in dichloromethane but 5-exo-dig cyclization/oxidation reaction performed in tetrahydrofuran, we screened the one-pot reaction in these two solvents and found that dichloromethane performed the best. The Diels−Alder cycloaddition between diynones **3.4** and **3.5a** was carried out under a nitrogen atmosphere until the reaction was complete (**Table 3-4**). The reaction flask was then opened to the atmosphere followed by the addition of $CuCl_2$, and the reaction was allowed to stir in the open atmosphere until complete. A small scope of diynones **3.4** was explored. Diynone **3.4a** was cleanly

Table 3-4: Diynone scope for one-pot reaction.

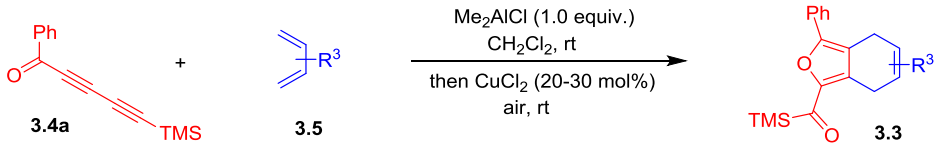


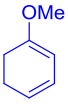
Entry	Diynone	Product	Yield (%)
1	 3.4a	**3.3a**	64
2	 3.4b	**3.3h**	64
3	 3.4c	**3.3j**	67
4	 3.4d	**3.3o**	74
5	 3.4e	**3.3p**	70
6	 3.4f	**3.3s**	56

converted to **3.3a** in 64% isolated yield. The sterically hindered *tert*-butyl substituted diynone **3.4b** easily produced the corresponding product **3.3h** in 64% isolated yield. Aryl-substituted diynones **3.4c** and **3.4d** provided the desired products **3.3j** and **3.3o** in 67% and

74% yields, respectively. The phenyl-terminated diynone **3.4e** performed very well to provide the benzoyl-substituted dihydroisobenzofuran **3.3p** in 70% yield. The heterocyclic diynone **3.4f** also worked to deliver product **3.3s** in 56% yield. Interestingly, diynals (R^1 = H) do not give intermediate **3.3** under these reaction conditions but rather undergo a hetero Diels−Alder to give a diyne-substituted dihydropyran.

Table 3-5: Copper-catalyzed diene scope for one-pot reaction.

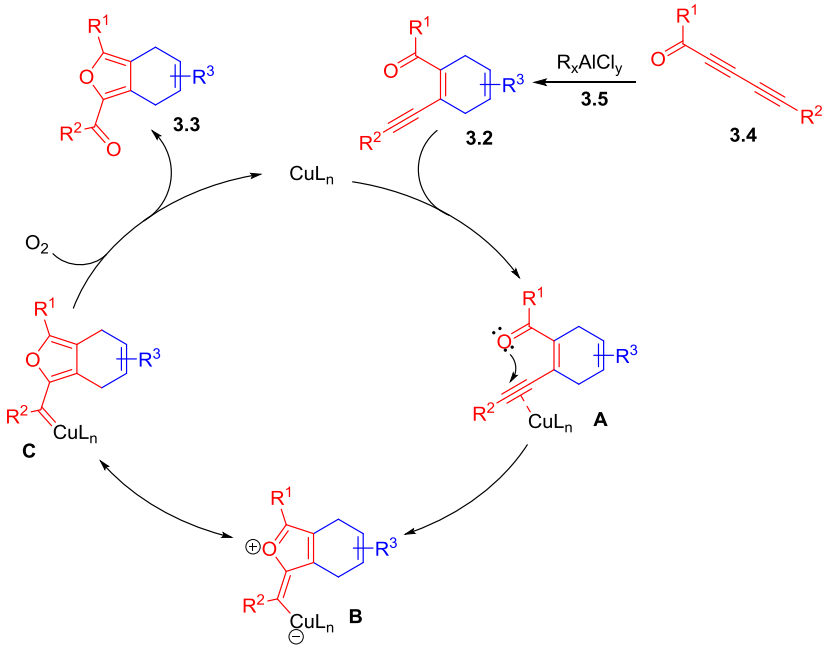


Entry	Diene	Product	Yield (%)
1	 **3.5b**	**3.3b**	60
2	 **3.5c**	**3.3c**	55
3	 **3.5d**	**3.3d**	63
4	 **3.5e**	**3.3e**	69
5	 **3.5f**	**3.3f**	83

We also explored the scope of dienes in this one-pot reaction sequence (**Table 3-5**). The reaction worked well with isoprene **3.5b** to provide **3.3b** in good yield and regioselectivity

(entry 1). The reaction with less reactive 1,3-butadiene **3.5c** also worked to provide **3.3c** in 55% yield (entry 2). Cyclic dienes were also tolerated in the reaction to provide the respective bridged-bicyclic products **3.3d−3.3f** in good yields (entries 3−5). It should be noted that the yields of this one-pot sequence are on par with the overall yield when each reaction is done separately. This procedure is highly beneficial, as it allows one to save time, costs, effort, and purification steps and reduce waste streams.[34]

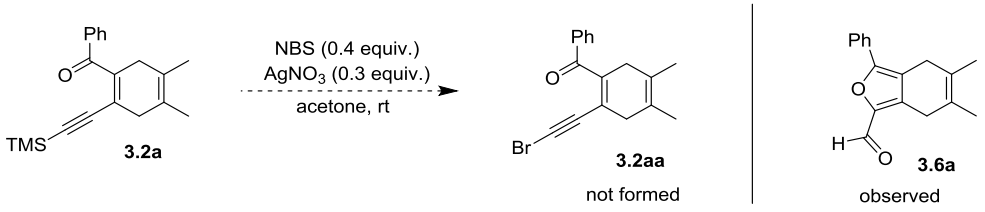
A proposed reaction mechanism for the one-pot synthesis of α-carbonyl furans is depicted below (**Scheme 3.2**). First, the Lewis acid catalyzed Diels−Alder reaction of diynone (**3.4**) with diene (**3.5**) affords 1,4-cyclohexadiene intermediate **3.2**. Complexation/activation of the alkyne by $CuCl_2$ (**A**) followed by a 5-exodig cyclization provides the metallocarbene intermediate **B/C**. Oxygen metathesis of intermediate **B/C** provides dihydroisobenzofuran product **3.3** and regeneration of the copper (II) catalyst.[17,18,35]



Scheme 3-2: Proposed reaction mechanism.

3.4 Silver-catalyzed Synthesis of Dihydroisobenzofuran Carboxaldehyde Derivatives via a One-Pot Protodesilylation/Cyclization/Oxidation Reaction

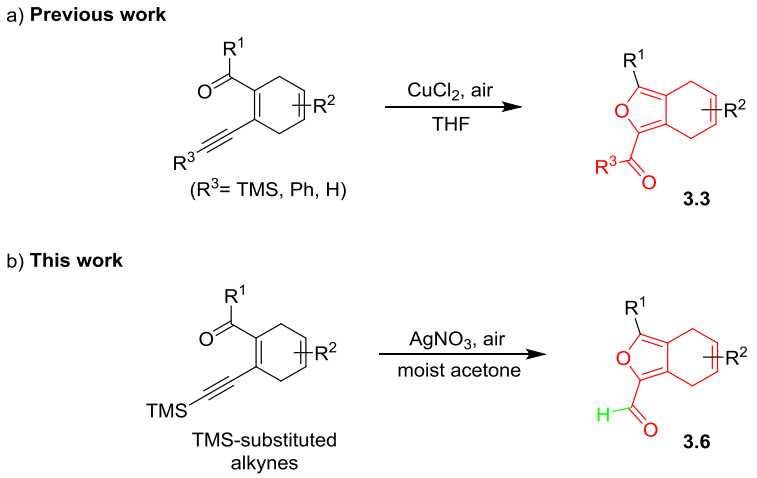
We have reported the synthesis of heavily functionalized skipped dienes such as **3.2a** via a regioselective Diels-Alder reaction of conjugated diynones **3.4a** with diene **3.5a**.[36] Those skipped dienes can be utilized as the potential intermediates for a number of organic transformations as well as useful sequential reactions. While exploring the synthetic utility of **3.2a**, one of the reactions we tried was the synthesis of **3.2aa** by following a reported literature procedure.[37] We were thinking about the use of **3.2aa** as a cross-coupling partner in different reactions. When we stirred the mixture of **3.2a**, $AgNO_3$ and NBS in moist acetone at room temperature, it did not produce **3.2aa** (expected) but instead gave **3.6a** exclusively (**Scheme 3.3**). We excluded NBS from the reaction and the substrate was stirred in moist acetone with $AgNO_3$ at room temperature to reproduce **3.6a**. Here, we describe the scope of this serendipity.



Scheme 3-3. Serendipitous formation of bicyclic furan aldehyde.

In synthetic chemistry, it is of great importance tying related chemical transformations in a one-pot reaction since it helps to quickly arrive at the target molecule using fewer synthetic steps. Previous work in our group represents the copper catalyzed cyclization/oxidation reaction of skipped diene intermediates to generate

dihydroisobenzofuran ketones (**Scheme 3-4**, a).[38] Herein we have studied the silver catalyzed protodesilylation/cyclization/oxidation sequential reaction for the formation of dihydroisobenzofuran aldehydes (**Scheme 3-4**, b). Since this synthetic method affords the compounds bearing aldehyde functional group, it opens new windows for further chemical elaborations.

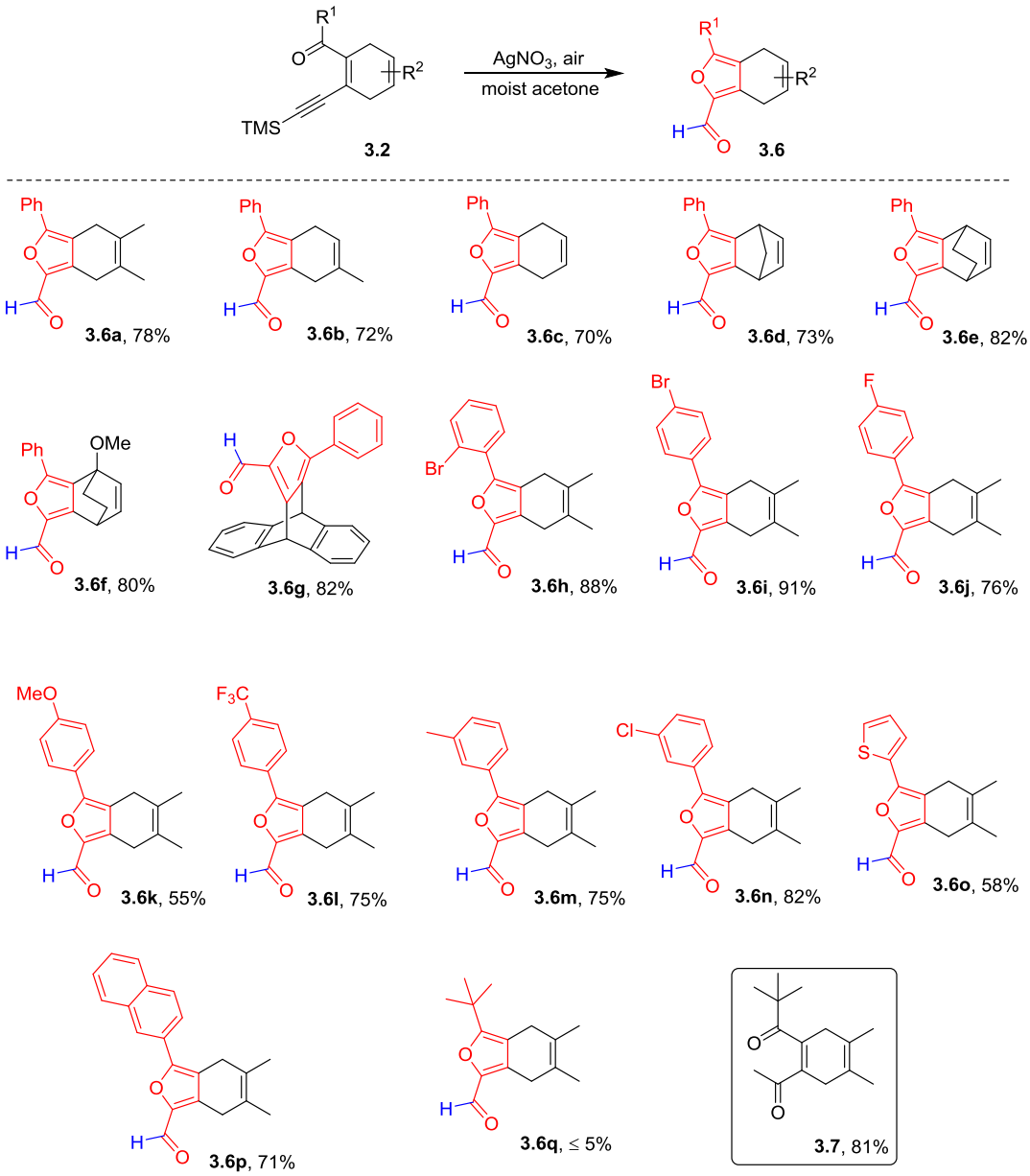


Scheme 3-4. Synthesis of α-carbonyl bicyclic furans.

Silver salts are known to catalyze the cyclization of enynones with molecular oxygen for the synthesis of α-carbonyl furans.[39] Silver nitrate being a relatively cheap, bench stable and nontoxic chemical we did not bother the optimization of reaction with other silver salts and proceeded to assess the scope of this $AgNO_3$ catalyzed reaction. The starting materials **3.2** were prepared as previously reported.[38]

First, a variety of phenyl-substituted enynones were tested as the substrates. Alkyl substituents in cyclohexadiene ring were well tolerated with very good isolated yields (**3.6a-6c**, **Table 3-6**). Bridged-bicyclic and tricyclic systems were also tolerated generating the products in 73-82% yields (**3.6d-6g**, **Table 3-6**). Bromo-substituted aryl ketone **3.2h**

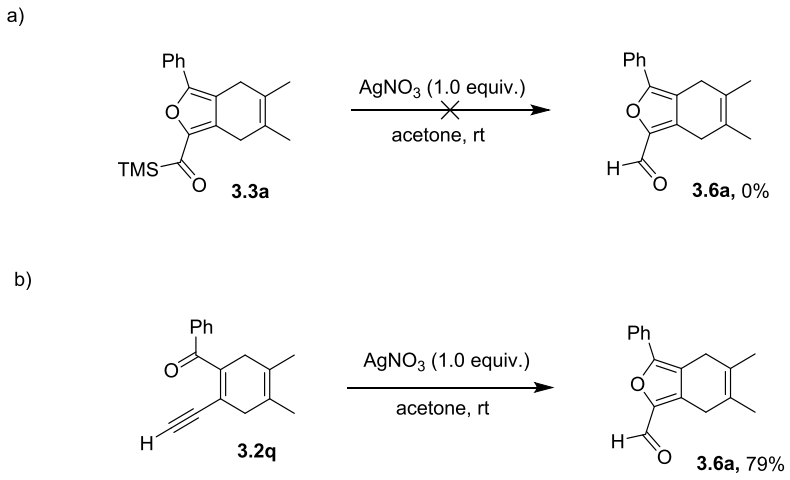
Table 3-6: Silver-catalyzed diene scope for one-pot reaction.



cleanly cyclized to **3.6h** with an excellent yield of 88%. Likewise, substrates bearing substituents in *para* positions **3.2i** and **3.2j** were cyclized to yield **3.6i** and **3.6j** in 91% and 76% respectively. Compound **3.2k** bearing electron-rich aryl ketone provided **3.6k** with

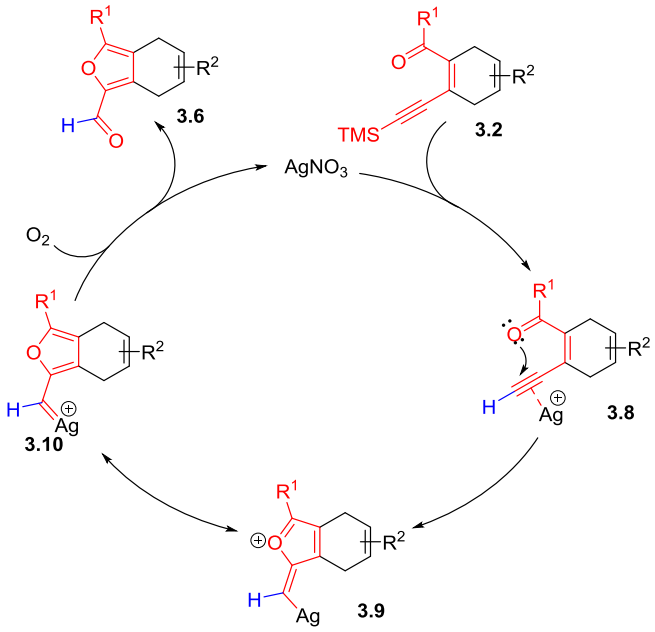
55% yield and compound **3.2l** having electron-poor aryl ketone afforded **3.6l** with 75% yield after chromatographic purification. *Meta* substituted aryls **3.2m** and **3.2n** also worked very well in this reaction providing **3.6m** and **3.6n** in 75% and 82% respectively. The reaction was also successful with heterocyclic ketone (**3.6o**, **Table 3-6**). Naphthyl substituted ketone **3.2p** worked well and the product **3.6p** was isolated in 71%. When *tert*-butyl ketone derivative **3.2q** was used as a substrate, we isolated compound **3.7** in 81% and the expected product **3.6q** was formed in less than 5% as indicated by ^{1}H NMR of the crude product.

The two possible routes for this transformation may be desilylation followed by cyclization/oxidation or cyclization/oxidation followed by desilylation (**Scheme 3-5**). When compound **3.3a** was subjected in our standard reaction condition, we did not observe the formation of product **3.6a** (**Scheme 3-5**, a). On the other hand, compound **3.2q** afforded product **3.6a** in a very good yield, 79% (**Scheme 3-5**, b). Therefore, we realized that the protodesilylation of starting material occurs first and the other route is ruled out.



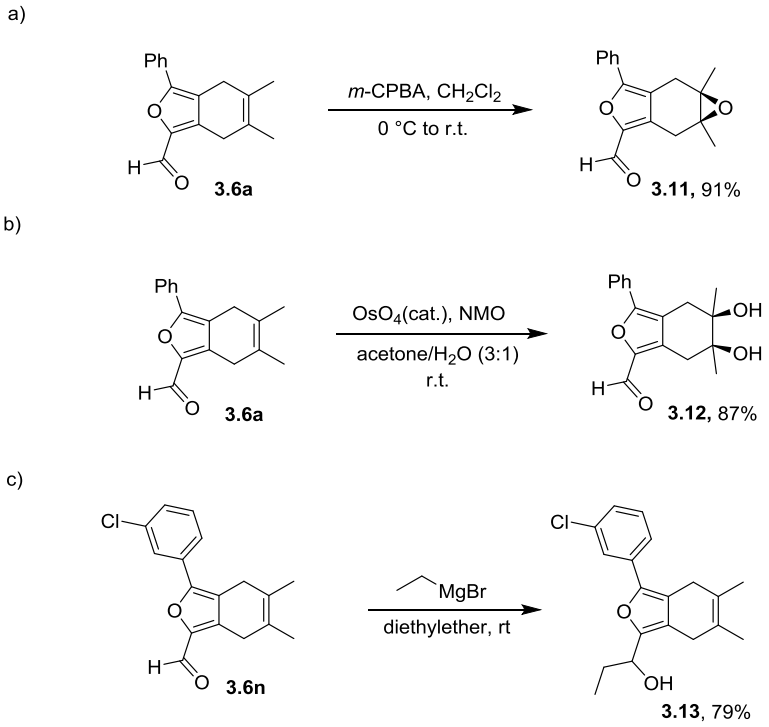
Scheme 3-5. Possible routes for the formation of **3.6a**.

A proposed reaction mechanism is depicted in (**Scheme 3.6**) on the basis of the previous reports[12,17,39,40] and our reaction results. First, the protodesilylation of TMSalkyne **3.2** affords terminal alkyne **3.8**. Then the carbonyl oxygen attacked the silver activated terminal alkyne and metallocarbene intermediate **3.9/3.10** was formed via a 5-exo-dig cyclization. Finally, **3.9/3.10** was oxidized to dihydroisobenzofuran carboxaldehyde **3.6** with molecular oxygen and silver catalyst was regenerated.



Scheme 3-6: Proposed reaction mechanism.

We were able to carry out a few transformation reactions of product **3.6** to show its utility (**Scheme 3-7**). Compound **3.6a** was converted to an epoxide **3.11** in excellent yield, 91%, under standard conditions with *m*CPBA (**Scheme 3-7**, a). A diol **3.12** was synthesized in 87% from **3.6a** under standard conditions (**Scheme 3-7**, b). An addition of freshly prepared ethyl Grignard reagent to **3.6n** afforded compound **3.13** in 79% isolated yield (**Scheme 3-7**, c).



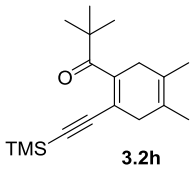
Scheme 2-7: Synthetic utility of product **3.6**.

3.5 Conclusion

In conclusion, we have demonstrated an unprecedented methodology for the synthesis of bicyclic α-carbonyl derivatives via 5-exo-dig/cyclization reaction. We also discussed a facile synthesis of α-carbonyl dihydroisobenzofuranones from easily accessible diynone starting materials in a two-step sequential reaction promoted by a mixture of Me_2AlCl and $CuCl_2$ catalysts. This one-pot procedure reduces the number of procedural steps making it a more economically viable process. The α-carbonyl dihydroisobenzofuranones can serve as highly functionalized advanced intermediates toward the synthesis of biologically active natural and unnatural products. Moreover, silver-catalyzed synthesis of dihydroisobenzofuran carboxaldehyde derivatives was realized in good yields.

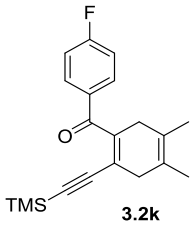
3.6 Experimental

Reagents were purchased reagent grade from commercial suppliers and used without further purification unless otherwise noted. Dichloromethane and tetrahydrofuran were purified using a PureSolv MD 5 solvent purification system. Where appropriate, reactions were performed in standard, dry glassware under an inert atmosphere of N_2. Purification of the crude products was carried out by column chromatography using Silica gel irregular 60 Å (40−60 μm) from VWR International. Thin-layer chromatography (TLC) was performed on glass sheets covered with silica gel 60 F_{254} from Millipore a Corporation and visualization by UV light. NMR spectra were recorded on a 400 or 500 MHz NMR spectrometer in $CDCl_3$ or DMSO. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26; DMSO, δ 2.50). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in hertz, and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$, δ 77.16; DMSO, δ 39.52). Infrared (IR) spectra were recorded on a Thermo Nicolet 6700 FT-IR (diamond ATR), and only major functional group peaks are reported as cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a high-resolution Q-TOF mass spectrometer (ionization mode: ESI). Commercially available chemicals were used without further purification. All diynones were synthesized according to the reported procedures.[41-44] Compounds **3.2a−3.2g**, **3.2i**, **3.2j**, **3.2l**, **3.2m**, **3.2p**, and **3.2q** are known compounds and were prepared according to the reported procedure.[24]



3.2h

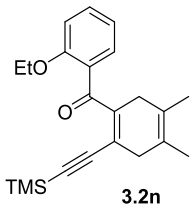
4,5-Dimethyl-1-[2,2-(dimethyl)ethanoyl)-2-[2-(trimethyl-silyl)ethynyl]-1,4-cyclohexadiene (3.2h). This was synthesized following a known procedure[24] (311 mg, 1.51 mmol of diynone and 262 mg, 3.19 mmol of diene). Purification by column chromatography (silica gel, toluene) afforded **3.2h** (275 mg, 64%) as a pale yellow liquid: R_f = 0.51 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.77−2.67 (m, 4H), 1.60 (br s, 6H, 2 × CH_3), 1.22 (s, 9H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 216.1, 145.4, 122.8, 121.0, 113.8, 104.1, 97.4,199 44.3, 36.7, 35.6, 27.6, 18.2, 18.1, −0.1; IR (cast film) ν 2961, 2144, 1690, 1478, 1249 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{29}OSi$ 289.1982; found 289.1985.



3.2k

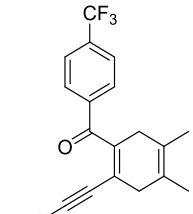
1-(4-Fluorobenzoyl)-4,5-dimethyl-2-[2-(trimethylsilyl)-ethynyl]-1,4-cyclohexadiene (3.2k). This was synthesized following a known procedure[24] (315 mg, 1.29 mmol of diynone and 422 mg, 5.14 mmol of diene). Purification by column chromatography (silica gel, toluene) afforded **3.2k** (350 mg, 83%) as a pale yellow solid: R_f = 0.52 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96−7.89 (m, 2H), 7.14−208 7.04 (m, 2H), 3.01−2.94 (m, 2H), 2.91−2.84 (m, 2H), 1.68 (s, 6H),−0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.1, 166.0 (d, J = 254.4 Hz), 141.5, 133.6 (d, J = 3.0 Hz), 132.4 (d, J = 9.3 Hz), 122.12, 122.09, 120.8,

115.1 (d, J = 21.9 Hz), 103.1, 102.1, 38.0, 34.9, 18.2, 212 18.1, −0.4; IR (cast film) ν 2963, 2140, 1649, 1595, 1503, 1229 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}FOSi$ 327.1575; found 327.1594.



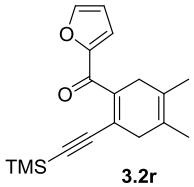
3.2n

1-(2-Ethoxybenzoyl)-4,5-dimethyl-2-[2-(trimethylsilyl)-ethynyl]-1,4-cyclohexadiene (3.2n). This was synthesized following a known procedure[24] (213 mg, 0.787 mmol of diynone and 219 mg, 2.66 mmol of diene). Purification by column chromatography (silica gel, dichloromethane) afforded **3.2n** (238 mg, 87%) as a pale yellow solid: R_f = 0.55 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.48 (m, 1H), 7.43−7.36 (m, 1H), 7.00−6.93 (m, 1H), 6.88−6.83 (m, 1H), 4.02 (q, J = 7.0 Hz, 2H), 3.07−2.98 (m, 2H), 2.88−2.78(m, 2H), 1.69 (s, 3H), 1.66 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), −0.08 (s, 8H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.1, 158.3, 143.5, 133.0,130.6, 130.2, 122.5, 121.5, 120.8, 119.8, 112.4, 102.9, 101.5, 64.4, 39.1,34.1, 18.3, 18.0, 14.6, 0.0; IR (cast film) ν 2960, 2144, 1652, 1595,1452, 1248 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{28}O_2SiNa$ 375.1751; found 375.1762.



3.2o

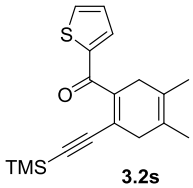
1-[4-(Trifluoromethyl)benzoyl]-4,5-dimethyl-2-[2-(trimethylsilyl)ethynyl]-1,4-cyclohexadiene (3.2o). This was synthesized following a known procedure[24] (252 mg, 0.856 mmol of diynone and 313 mg, 3.81 mmol of diene). Purification by column chromatography (silica gel, toluene) afforded **3.2o** (286 mg, 88%) as a pale yellow solid: R_f = 0.67 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01−7.93 (m, 2H), 7.72−7.64 (m, 2H), 3.05−2.99 (m, 2H), 2.94−2.88 (m, 2H), 1.70 (s, 3H), 1.68 (s, 3H), −0.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.4, 140.7, 140.6, 134.2 (q, J = 32.5 Hz),130.0, 125.4 (q, J = 3.7 Hz), 123.9 (q, J = 272.7 Hz), 122.8, 122.2, 122.0, 103.6, 102.9, 38.4, 34.8, 18.2, 18.0, −0.6; IR (cast film) ν 2962, 2142, 1660, 1410, 1324 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{21}H_{23}F_3OSiNa$ 399.1362; found 399.1356.



3.2r

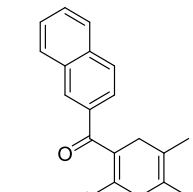
1-(2-Furoyl)-4,5-dimethyl-2-[2-(trimethylsilyl)ethynyl]-1,4- cyclohexadiene (3.2r). This was synthesized following a known procedure[24] (129 mg, 0.596 mmol of diynone and 172 mg, 2.09 mmol of diene). Purification by column chromatography (silica gel, 1:4 EtOAc/hexane) afforded **3.2r** (123 mg, 70%) as a light red solid: R_f = 0.56 (1:4 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60−7.54 (m, 1H), 7.19−7.12 (m, 1H), 6.51−6.44 (m, 1H), 2.95−2.88 (m, 2H),2.85−2.78 (m, 2H), 1.61 (br s, 6H, 2 × CH3), −0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 185.4, 152.3, 146.8, 140.9, 121.9, 121.8, 120.7, 120.1, 112.2, 102.7, 100.5, 37.9, 34.4, 18.0, 17.9, −0.3; IR (cast film) ν 2959, 2143, 1643,

1563, 1463, 1249 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{23}O_2Si$ 299.1462; found 299.1462.



3.2s

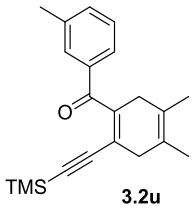
4,5-Dimethyl-2-[2-(trimethylsilyl)ethynyl]-1-(2-thiophene-carbonyl)-1,4-cyclohexadiene (3.2s). This was synthesized following a known procedure[24] (313 mg, 1.35 mmol of diynone and 567 mg, 6.90 mmol of diene). Purification by column chromatography (silica gel, toluene) afforded **3.2s** (284 mg, 67%) as a light red solid: R_f = 0.44 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74−7.70 (m, 1H), 7.68−7.63 (m, 1H), 7.11−7.06 (m, 1H), 3.00−2.93 (m, 2H), 2.90−2.83 (m,2H), 1.66 (br s, 6H, 2 × CH_3), −0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 126MHz) δ 190.7, 143.5, 142.3, 135.1, 134.4, 128.0, 122.1, 121.9, 119.4, 103.1, 100.9, 37.6, 34.8, 18.2, 18.1, −0.4; IR (cast film) ν 2958, 2146, 1631, 1516, 1411, 1249 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{23}OSSi$ 315.1233; found 315.1235.



3.2t

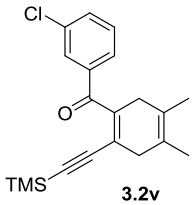
4,5-Dimethyl-2-[2-(trimethylsilyl)ethynyl]-1-(2-naphthoyl)-1,4-cyclohexadiene (3.2t). This was synthesized following a known procedure[24] (330 mg, 1.19 mmol of diynone and 387 mg, 4.71 mmol of diene). Purification by column chromatography (silica gel, 1:1

dichloromethane/hexane) afforded **3.2t** (327 mg, 77%) as a pale yellow solid: R_f = 0.52 (1:1 dichloromethane/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.43−8.39 (m, 1H), 8.02−7.97 (m, 1H), 7.96−7.91 (m, 1H), 7.89−7.82 (m, 2H), 7.59−7.47 (m, 2H), 3.13−3.04 (m, 2H), 2.99−2.89 (m, 2H), 1.71 (br s, 6H, 2 × CH_3), −0.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.4, 141.8, 135.7, 134.4, 132.6, 132.1, 129.7, 128.3, 128.2, 127.7, 126.5, 124.9, 122.2, 122.0, 121.0, 103.2, 101.9, 38.1, 35.0, 18.2, 18.0, −0.8; IR (cast film) ν 2959, 2148, 1649, 1291 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{27}OSi$ 359.1826; found 359.1813.



3.2u

4,5-Dimethyl-1-(3-methylbenzoyl)-2-[2-(trimethylsilyl)ethynyl]-1,4-cyclohexadiene (3.2u). This was synthesized following a known procedure[24] (232 mg, 0.965 mmol of diynone and 243 mg, 2.95 mmol of diene). Purification by column chromatography (silica gel, 1:1 dichloromethane/hexane) afforded **3.2u** (222 mg, 72%) as a pale yellow oil: R_f = 0.50 (1:1 dichloromethane/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68−7.61 (m, 2H), 7.31−7.22 (m, 2H), 2.99− 2862.90 (m, 2H), 2.87−2.78 (m, 2H), 2.33 (s, 3H), 1.62 (br s, 6H, 2 × CH_3), −0.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.5, 141.8, 137.8, 137.0, 133.5, 129.8, 128.1, 126.9, 121.9, 121.8, 120.1, 103.1, 101.3, 37.7, 34.8, 21.2, 18.0, 17.9, −0.6; IR (cast film) ν 2958, 2142, 1651, 1248 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{26}OSiNa$ 345.1645; found 345.1626.

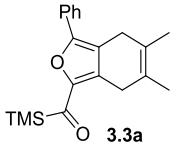


3.2v

1-(3-Chlorobenzoyl)-4,5-dimethyl-2-[2-(trimethylsilyl)ethynyl]-1,4-cyclohexadiene (3.2v). This was synthesized following a known procedure[24] (172 mg, 0.659 mmol of diynone and 189 mg, 2.30 mmol of diene). Purification by column chromatography (silica gel, 2:3 dichloromethane/hexane) afforded **3.2v** (189 mg, 84%) as a pale yellow solid: R_f = 0.41 (2:3 dichloromethane/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82−7.79 (m, 1H), 7.74−7.70 (m, 1H), 7.48− 2997.44 (m, 1H), 7.35−7.30 (m, 1H), 2.98−2.93 (m, 2H), 2.88−2.83 (m, 2H), 1.64 (br s, 6H, 2 × CH_3), −0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 196.9, 140.8, 139.0, 134.5, 132.6, 129.64, 129.55, 127.6, 122.0, 121.9, 121.8, 102.8 (2 coincidental peaks), 38.0, 34.7, 18.1, 17.9, −0.5; IR (cast film) v 2960, 2142, 1657, 1567, 1490, 1249 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{23}ClOSiNa$ 365.1099; found 365.1099.

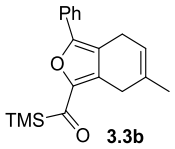
General Procedure 1: Copper-Catalyzed Cyclization of Compound 3.2:

To a solution of **3.2** (1.0 equiv) in tetrahydrofuran (15 mL) was added $CuCl_2$ (20−30 mol %). The reaction mixture was stirred at room temperature (open to air) for 2−4 h, quenched with aq. NH_4Cl, dried over anhydrous $MgSO_4$, and filtered. After the solvent was removed in vacuo, the residue was purified by column chromatography (silica gel) to afford compound **3.3**.



3.3a

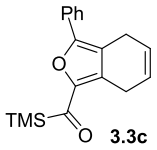
4,7-Dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran(3.3a). Compound **3.3a** was synthesized according to general procedure 1 (87 mg, 0.28 mmol of **3.2a** and 8 316mg, 0.06 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3a** (77 mg, 85%) as a pale yellow solid: R_f = 0.32 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86−7.67 (m, 2H),7.55−7.41 (m, 2H), 7.39−7.29 (m, 1H), 3.48−3.38 (m, 2H), 3.38− 3203.26 (m, 2H), 1.80 (s, 3H), 1.78 (s, 3H), 0.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.7, 151.6, 149.5, 131.1, 129.1, 128.7, 128.3, 125.5, 123.3, 121.8, 119.9, 29.9, 29.7, 19.5, 19.2, −2.3; IR (cast film) v 2914, 1523, 1447, 1246 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{25}O_2Si$ 325.1618; found 325.1615.



3.3b

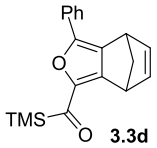
4,7-Dihydro-6-methyl-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3b). Compound **3.3b** was synthesized according to general procedure 1 (97 mg, 0.33 mmol of **3.2b** and 10 mg, 0.074 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3b** (85 mg, 83%) as a yellow solid: R_f = 0.34 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79−7.73 (m, 2H), 7.50−7.44 (m, 2H), 7.39−7.33 (m, 1H), 5.62−5.55 (m, 1H), 3.47−3.38 (m, 4H), 1.84 (s, 3H), 0.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.9, 151.6, 149.9, 131.5, 131.0, 129.1, 128.39, 128.36, 125.5, 118.8, 117.2, 28.1, 23.9,

23.5, −2.3; IR (cast film) ν 2963, 1521, 1445 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{23}O_2Si$ 311.1462; found 311.1460.



3.3c

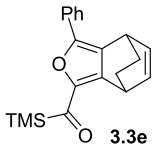
4,7-Dihydro-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3c). Compound **3.3c** was synthesized according to general procedure 1 (109 mg, 0.389 mmol of **3.2c** and 11 mg, 0.082 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3c** (78 mg, 67%) as a pale yellow solid: R_f = 0.27 (toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.80−7.72 (m, 2H), 7.48 (m, 2H), 7.40−7.33 (m, 1H), 5.95−5.85 (m, 2H), 3.52 (s, 2H), 3.47 (s, 2H),0.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 223.0, 151.9, 150.1,131.0, 129.1, 128.4, 127.3, 125.5, 124.1, 122.8, 118.6, 23.5, 23.4, −2.3; IR (cast film) ν 2959, 1520 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{21}O_2Si$ 297.1305; found 297.1300.



3.3d

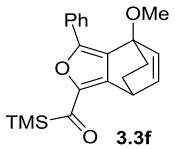
4,7-Dihydro-4,7-methano-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3d). Compound **3.3d** was synthesized according to general procedure 1 (34 mg, 0.12 mmol of **3.2d** and 4mg, 0.03 mmol of $CuCl_2$). Purification by column chromatography (silica gel, 1:9 EtOAc/hexanes) afforded **3.3d** (27 mg, 75%) as a pale yellow solid: R_f = 0.39 (1:9 EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500MHz) δ 7.75−7.70 (m, 2H), 7.47−7.40 (m, 2H), 7.36−7.29 (m, 1H),6.79−6.76 (m, 1H), 6.76−6.72 (m, 1H), 4.19 (br s, 1H), 4.10 (br s, 1H),

2.53−2.49 (m, 1H), 2.46−2.41 (m, 1H), 0.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.4, 148.3, 146.0, 144.9, 141.9, 141.8, 137.2,130.7, 129.5, 129.0, 128.4, 128.1, 125.1, 68.5, 44.9, 44.5, −2.3; IR (cast film) ν 2971, 1534, 1490, 1248 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{21}O_2Si$ 309.1305; found 309.1325.



3.3e

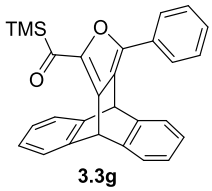
4,7-Dihydro-4,7-ethano-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3e). Compound **3.3e** was synthesized according to general procedure 1 (139 mg, 0.453 mmol of **3.2e** and15 mg, 0.11 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3e** (103 mg, 71%) as a pale yellow solid: R_f = 0.31 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85−7.68 (m, 2H), 7.51−7.40 (m, 2H), 7.37−7.32 (m, 1H), 6.61−6.45 (m, 2H), 4.55−4.50 (m, 1H), 4.31−4.26 (m, 1H), 1.71−1.52 (m, 4H), 0.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 223.1, 148.0, 145.0, 138.5, 135.0, 134.9, 131.1, 130.2, 129.1, 128.4, 125.6, 33.0, 32.7, 25.9, 25.4,−2.2; IR (cast film) ν 2940, 1528 cm^{-1}; HRMS (ESI-TOF) m/z: [M +H]$^+$ calcd for $C_{20}H_{23}O_2Si$ 323.1462; found 323.1456.



3.3f

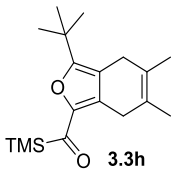
4,7-Ethano-4,7-dihydro-4-methoxy-1-[(trimethylsilyl)-carbonyl]-3-phenylisobenzofuran (3.3f). Compound **3.3f** was synthesized according to general procedure 1 (87 mg, 0.26 mmol of **3.2f** and 7mg, 0.05 mmol of $CuCl_2$). Purification by column chromatography (silica gel, 1:4 EtOAc/hexanes) afforded **3.3f** (74 mg, 80%) as a

pale yellow solid: R_f = 0.46 (1:4 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.98−7.91 (m, 2H), 7.48−7.41 (m, 2H), 7.40−7.34 (m, 1H), 6.65−6.61 (m, 1H), 6.51−6.44 (m, 1H), 4.51−4.44 (m, 1H), 3.36 (s, 3H), 1.92−1.79 (m, 2H), 1.75−1.66 (m, 2H), 0.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 223.5, 148.1, 146.1, 137.0, 135.7, 133.6, 130.6,129.2, 128.8, 128.5, 128.0, 81.6, 53.9, 32.3, 31.6, 26.7, −2.3; IR (cast film) ν 2953, 1527 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{24}O_3SiNa$ 375.1387; found 375.1371.



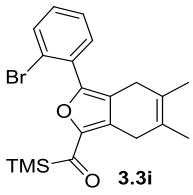
3.3g

9,10[3′,4′]-Furano-9,10-dihydro-12-[(trimethylsilyl)-carbonyl]-14-phenylanthracene (3.3g). Compound **3.3g** was synthesized according to general procedure 1 (109 mg, 0.269 mmol of **3.2g** and 8 mg, 0.06 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3g** (89 mg, 79%) as a pale yellow spongy solid: R_f = 0.43 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84−7.78 (m, 2H), 7.55−7.47 (m, 4H), 7.47−7.36 (m, 4H), 7.11−7.04 (m, 4H), 6.03 (s, 1H), 5.70 (s, 1H), 0.36 (m, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 223.4, 148.6, 145.9, 144.5, 144.3, 138.6, 131.7, 130.7, 129.2, 128.8, 126.1, 125.9, 125.7, 124.9, 124.0, 46.8, 46.3, −2.4; IR (cast film) ν 2959, 1533, 1458 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{24}O_2SiNa$ 443.1438; found 443.1467.



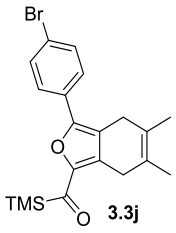
3.3h

3-tert-Butyl-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3h). Compound **3.3h** was synthesized according to general procedure 1 (115 mg, 0.397 mmol of **3.2h** and 13 mg, 0.097 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3h** (88 mg, 72%) as a pale yellow solid: R_f = 0.28 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.38−3.33 (m, 2H), 3.19−3.14 (m, 2H), 1.74 (br s, 6H, 2 × CH_3), 1.38 (s, 9H), 0.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 221.6, 160.0, 151.1, 128.2, 123.0, 122.0, 116.4, 34.6, 29.7, 29.2, 29.0, 19.5, 19.1, −2.5; IR (cast film) ν 2961, 1518 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{29}O_2Si$ 305.1931; found 305.1927.



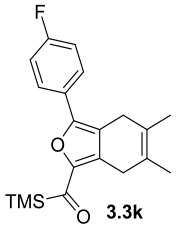
3.3i

3-(2-Bromophenyl)-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3i). Compound **3.3i** was synthesized according to general procedure 1 (53 mg, 0.14 mmol of **3.2i** and 6 mg, 0.04 mmol of $CuCl_2$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.3i** (41 mg, 73%) as a pale yellow solid: R_f = 0.6 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70−7.64 (m, 1H), 7.43−7.34 (m, 2H), 7.29−7.22 (m, 1H), 3.45−3.38 (m, 2H), 3.11−3.03 (m, 2H), 1.75 (s, 3H), 1.70 (s, 3H), 0.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 223.5, 152.4, 149.1, 133.8, 132.0, 131.7, 130.7, 127.6, 127.4, 123.3, 122.9, 122.1, 121.8, 29.9, 28.3, 19.4, 19.2, −2.4; IR (cast film) ν 2900, 1521, 1439 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{23}BrO_2SiNa$ 425.0543; found 425.0536.



3.3j

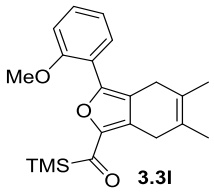
3-(4-Bromophenyl)-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3j). Compound **3.3j** was synthesized according to general procedure 1 (167 mg, 0.431 mmol of **3.2j** and 14 mg, 0.10 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3j** (135 mg, 78%) as a pale yellow solid: R_f = 0.43 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz); δ 7.62−7.55 (m, 4H), 3.46−3.35 (m, 2H), 3.32−3.21 (m, 2H), 1.79 (s, 3H), 1.77 (s, 3H), 0.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.8, 151.5, 148.3, 132.3, 129.9, 128.5, 126.8, 123.3, 122.3, 121.5, 120.3, 29.8, 29.6, 19.4, 19.2, −2.3; IR (cast film) ν 2959, 1519, 1482 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}BrO_2Si$ 403.0723; found 403.0707.



3.3k

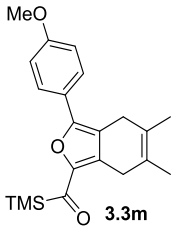
3-(4-Fluorophenyl)-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3k). Compound **3.3k** was synthesized according to general procedure 1 (221 mg, 0.677 mmol of **3.2k** and 21 mg, 0.16 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3k** (164 mg, 72%) as a yellow powdered solid: R_f = 0.38 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78−7.69 (m, 2H), 7.22−7.12 (m, 2H), 3.48−3.37 (m, 2H), 3.35−3.24 (m, 2H), 1.81 (s,

3H), 1.78 (s, 3H), 0.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.6, 162.6 (d, J = 249.5 Hz), 151.5, 148.7, 128.7, 127.4 (d, J = 3.3 Hz), 127.3 (d, J = 8.2 Hz), 123.4, 121.6, 119.4, 116.3 (d, J = 22.0 Hz), 29.73, 29.67, 19.5, 19.2, −2.3; IR (cast film) ν 2960, 1497, 1441 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}FO_2Si$ 343.1524; found 343.1538.



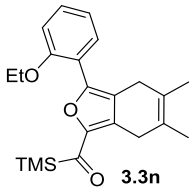
3.3l

4,7-Dihydro-3-(2-methoxyphenyl)-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3l). Compound **3.3l** was synthesized according to general procedure 1 (87 mg, 0.28 mmol of **3.2l** and 9 mg, 0.07 mmol of $CuCl_2$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.3l** (67 mg, 68%) as a pale yellow solid: R_f = 0.44 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57−7.51 (m, 1H), 7.43−7.36 (m, 1H), 7.10−7.04 (m, 1H), 7.03−6.99 (m, 1H), 3.89 (s, 3H), 3.49−3.41 (m, 2H), 3.17−3.06 (m, 2H), 1.78 (s, 3H), 1.75 (s, 3H), 0.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.6, 157.0, 152.4, 148.5, 130.5, 130.1, 128.4, 123.0, 122.5, 121.7, 120.8, 120.1, 111.5, 55.4, 30.0, 29.1, 19.5, 19.2, −2.4; IR (cast film) ν 2915, 1762, 1493 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{27}O_3Si$, 355.1724; found: 355.1730.



3.3m

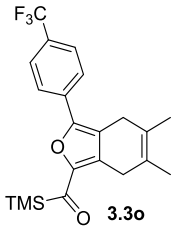
4,7-Dihydro-3-(4-methoxyphenyl)-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3m). Compound **3.3m** was synthesized according to general procedure 1 (109 mg, 0.322 mmol of **3.2m** and 12 mg, 0.089 mmol of $CuCl_2$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.3m** (79 mg, 70%) as a pale yellow solid: R_f = 0.46 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75−7.68 (m, 2H), 7.05−6.97 (m, 2H), 3.87 (s, 3H), 3.43 (s, 2H), 3.31 (s, 2H), 1.81 (s, 3H), 1.78 (s, 3H), 0.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 221.9, 159.8, 151.4, 149.9, 129.0, 127.1, 124.0, 123.3, 121.8, 118.4, 114.6, 55.5, 29.81, 29.79, 19.5, 19.2, −2.2; IR (cast film) ν 2963, 1497, 1436 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{27}O_3Si$, 355.1724; found 355.1724.



3.3n

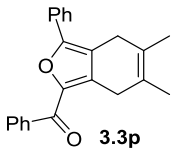
3-(2-Ethoxyphenyl)-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3n). Compound **3.3n** was synthesized according to general procedure 1 (152 mg, 0.431 mmol of **3.2n** and 12 mg, 0.089 mmol of $CuCl_2$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.3n** (107 mg, 68%) as a pale yellow solid: R_f = 0.42 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.53 (m, 1H), 7.40−7.34 (m, 1H), 7.08−7.03 (m, 1H), 7.02−6.98 (m, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.50−3.42 (m, 2H), 3.20−3.11 (m, 2H), 1.78 (s, 3H), 1.75 (s, 3H), 1.45 (t, 3H), 0.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.6, 156.3, 148.7, 130.38, 130.36, 128.5, 122.9, 122.7, 121.8, 120.7, 120.4, 112.4, 110.1, 64.1,30.0, 29.3, 19.5, 19.2,

15.0, −2.3; IR (cast film) *v* 2978, 1763, 1518,1451, 1246, cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for$C_{22}H_{28}O_3SiNa$ 391.1700; found 391.1710.



3.3o

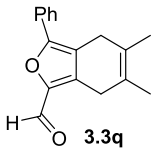
3-(4-Trifluoromethylphenyl)-4,7-dihydro-5,6-dimethyl-1[(trimethylsilyl)carbonyl]isobenzofuran (3.3o). Compound **3.3o** was synthesized according to general procedure 1 (143 mg, 0.380 mmol of **3.2o** and 11 mg, 0.082 mmol of $CuCl_2$). Purification by column chromatography (silica gel, 1:9 EtOAc/hexanes) afforded **3.3o** (123 mg, 83%) as a pale yellow solid. R_f = 0.58 (1:9 EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.90−7.82 (m, 2H), 7.77−7.69 (m, 2H), 3.47−3.41 (m, 2H), 3.39−3.31 (m, 2H), 1.83 (s, 3H), 1.80 (s, 3H), 0.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 223.5, 151.7, 147.7, 134.2, 129.8 (q, *J* = 32.8 Hz), 128.4, 126.1 (q, *J* = 3.9 Hz), 125.5, 124.1 (q, *J* =264.3 Hz), 123.4, 121.7, 121.4, 29.8, 29.5, 19.5, 19.2, −2.3; IR (castfilm) *v* 2939, 1717, 1450 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}F_3O_2Si$ 393.1492; found 393.1488.



3.3p

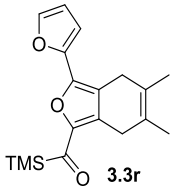
1-Benzoyl-4,7-dihydro-5,6-dimethyl-3-phenylisobenzofuran (3.3p). Compound **3.3p** was synthesized according to general procedure 1 (40 mg, 0.13 mmol of **3.2p** and 3 mg,

0.03 mmol of $CuCl_2$). Purification by column chromatography (silica gel, 1:5 EtOAc/hexanes) afforded **3.3p** (38 mg, 88%) as a pale yellow solid: R_f = 0.56 (1:4 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18−8.14 (m, 2H), 7.79−7.74 (m, 2H), 7.61−7.56 (m, 1H), 7.56−7.51 (m, 2H), 7.49−7.43 (m,2H), 7.38−7.32 (m, 1H), 3.57 (s, 2H), 3.40 (s, 2H), 1.84 (br s, 6H, 2×CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 182.6, 149.7, 145.3, 138.2,135.6, 132.1, 130.8, 129.7, 129.0, 128.43, 128.38, 125.7, 123.3, 121.7,120.1, 30.5, 30.0, 19.5, 19.3; IR (cast film) ν 2914, 1627, 1492, 1449 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{21}O_2$ 329.1536; found 329.1543.



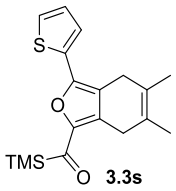
3.3q

4,7-Dihydro-5,6-dimethyl-3-phenyl-1-isobenzofurancarboxaldehyde (3.3q). Compound **3.3q** was synthesized according to general procedure 1 (73 mg, 0.31 mmol of **3.2q** and 9mg, 0.07 mmol of $CuCl_2$). Purification by column chromatography(silica gel, toluene) afforded **3.3q** (53 mg, 68%) as a pale yellow solid: R_f = 0.25 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.78 (s, 1H), 7.85− 7.79 (m, 2H), 7.50−7.44 (m, 2H), 7.41−7.35 (m, 1H), 3.49−3.43 (m, 2H), 3.38−3.33 (m, 2H), 1.83 (br s, 6H, 2×CH_3); ^{13}C NMR (DMSO, 126 MHz) δ 177.3, 150.5, 144.7, 129.5, 129.2, 129.0, 125.5, 122.2, 121.3, 119.5, 28.6, 27.2, 19.0, 18.9; IR (cast film) ν 2860, 1659, 1451 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{16}O_2Na$ 275.1043; found 275.1044.



3.3r

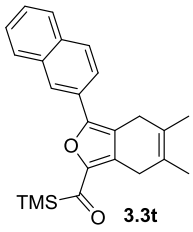
3-(2-Furanyl)-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3r). Compound **3.3r** was synthesized according to general procedure 1 (98 mg, 0.33 mmol of **3.2r** and 9 mg, 0.07 mmol of $CuCl_2$). Purification by column chromatography (silica gel, 1:4 EtOAc/hexane) afforded **3.3r** (68 mg, 65%) as a pale yellow solid: R_f = 0.46 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.50 (m, 1H), 6.73−6.64 (m, 1H), 6.57−6.50 (m, 1H), 3.44− 3.35 (m, 2H), 3.33−3.23 (m, 2H), 1.80 (s, 3H), 1.78 (s, 3H), 0.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.4, 146.8, 143.3, 142.7, 128.2, 123.1, 121.9, 119.4, 111.9, 108.0, 29.6, 28.2, 19.4, 19.2, −2.4; IR (cast film) ν 2958, 1517, 1438, 1247, cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{22}O_3SiNa$ 337.1230; found 337.1237.



3.3s

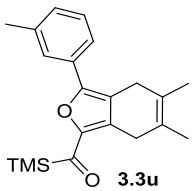
4,7-Dihydro-5,6-dimethyl-3-(2-thienyl)-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3s). Compound **3.3s** was synthesized according to general procedure 1 (112 mg, 0.356 mmol of **3.2s** and11 mg, 0.082 mmol of $CuCl_2$). Purification by column chromatography (silica gel, toluene) afforded **3.3s** (74 mg, 62%) as a pale yellow solid: R_f = 0.28 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.36 (m, 2H), 7.18−7.13 (m, 1H), 3.47−3.38 (m, 2H), 3.27−3.17 (m, 2H), 1.82 (s, 3H), 1.79 (s, 3H), 0.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.3, 151.2, 146.2, 133.5, 128.5, 128.2, 126.1, 124.6, 123.4, 121.5, 119.0, 29.7, 28.9,

19.5, 19.3, −2.3; IR (cast film) *v* 2918, 1688, 1532, 1409, 1252, cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{22}O_2SSiNa$ 353.1002; found 353.0997.



3.3t

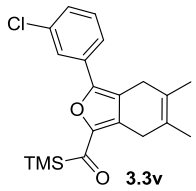
4,7-Dihydro-5,6-dimethyl-3-(2-naphthyl)-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3t). Compound **3.3t** was synthesized according to general procedure 1 (122 mg, 0.340 mmol of **3.2t** and 11 mg, 0.082 mmol of $CuCl_2$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.3t** (100 mg, 79%) as a pale yellow solid: R_f = 0.52 (dichloromethane); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.20−8.16 (m, 1H), 7.96−7.90 (m, 3H), 7.88−7.83 (m, 1H), 7.56−7.48 (m, 2H), 3.50−3.42 (m, 4H), 1.85 (s, 3H), 1.81 (s, 3H), 0.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.6, 151.7, 149.7, 133.5, 133.0, 128.9, 128.8, 128.6, 128.5, 127.9, 126.9, 126.8, 125.0, 123.4, 123.0, 121.7, 120.3, 30.0, 29.7, 19.5, 19.2, −2.2; IR (cast film) *v* 2867, 1672, 1521, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{27}O_2Si$ 375.1775; found 375.1779.



3.3u

4,7-Dihydro-5,6-dimethyl-3-(3-methylphenyl)-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3u). Compound **3.3u** was synthesized according to general procedure 1 (173 mg, 0.536 mmol of **3.2u** and 15 mg, 0.11 mmol of

$CuCl_2$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.3u** (139 mg, 78%) as a pale yellow solid: R_f = 0.55 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61−7.55 (m, 2H), 7.40−7.35 (m, 1H), 7.20−7.15 (m, 1H), 3.46−3.40 (m, 2H), 3.38−3.31 (m, 2H), 2.45 (s, 3H), 1.82 (s, 3H), 1.79 (s, 3H), 0.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 222.6, 151.5, 149.8, 138.7, 131.0, 129.2, 129.0, 128.7, 126.2, 123.3, 122.8, 121.8, 119.8, 29.8, 29.7, 21.9, 19.5, 19.2, −2.3; IR (cast film) ν 2923, 1761, 1691, 1450, 1282 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{26}O_2SiNa$ 361.1594; found 361.1587.



3.3v

3-(3-Chlorophenyl)-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3v). Compound **3.3v** was synthesized according to general procedure 1 (93 mg, 0.27 mmol of **3.2v** and 8 mg, 0.06 mmol of $CuCl_2$). Purification by column chromatography (silica gel, 1:1 dichloromethane/hexane) afforded **3.3v** (74 mg, 76%) as a pale yellow solid: R_f = 0.32 (1:1 dichloromethane/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72−7.68 (m, 1H), 7.66−7.60 (m, 1H), 7.43−7.36 (m, 1H), 7.34−7.28 (m, 1H), 3.44−3.38 (m, 2H), 3.35−3.28 (m, 2H), 1.81 (s, 3H), 1.78 (s, 3H), 0.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 223.1, 151.5, 147.8, 135.1, 132.7, 130.4, 128.4, 128.2, 125.3, 123.4, 123.3, 121.5, 120.8, 29.7, 29.6, 19.5, 19.2, −2.3; IR (cast film) ν 2959, 1768, 1523, 1409, 1241, cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}ClO_2Si$ 359.1229; found 359.1223.

General Procedure 2: One-Pot Reaction. To a solution of diynone **3.4** (1.0 equiv) and diene **3.5** (3.0 equiv) in dichloromethane (20 mL) was added dimethylaluminum chloride (1.0 M in hexanes, 1.0 equiv) dropwise over 10 min. The reaction mixture was stirred at room temperature under a N_2 atmosphere until **3.4** was completely consumed based on TLC analysis (1−3 h). The reaction mixture was then opened to air, and $CuCl_2$ (20−30 mol %) was added. The reaction mixture was stirred open to air until the reaction was complete (1−3 h), quenched with aq. NH_4Cl and dilute aq. $NaHCO_3$, dried over anhydrous $MgSO_4$, and filtered. After the solvent was removed in vacuo, the residue was purified by column chromatography (silica gel).

4,7-Dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3a). General procedure 2 was used with **3.4a** (190 mg, 0.839 mmol) and **3.5a** (224 mg, 2.72 mmol) in the presence of Me_2AlCl (0.83 mL, 0.83 mmol) and $CuCl_2$ (22 mg, 0.16 mmol). After 6 h, purification by column chromatography (silica gel, toluene) yielded **3.3a** (171 mg, 64%). The spectral data for compound **3.3a** were consistent with what was obtained from using general procedure 1.

4,7-dihydro-6-methyl-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3b). General procedure 2 was used with **3.4a** (211 mg, 0.932 mmol) and **3.5b** (195 mg, 2.86 mmol) in the presence of Me_2AlCl (0.93 mL, 0.93 mmol) and $CuCl_2$ (31 mg, 0.23 mmol). After 6 h, purification by column chromatography (silica gel, toluene) yielded **3.3b** (171 mg, 60% yield). The spectral data for compound **3.3b** were consistent with what was obtained from using general procedure 1.

4,7-Dihydro-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3c). General procedure 2 was used with **3.4a** (191 mg, 0.844 mmol) and **3.5c** (excess, 1.0 mL, which was condensed into a separate flask then transferred by cannula into the reaction mixture) in the presence of Me_2AlCl (0.84 mL, 0.84 mmol) and $CuCl_2$ (25 mg, 0.21 mmol). After 5.5 h, purification by column chromatography (silica gel, toluene) yielded **3.3c** (137 mg, 55%). The spectral data for compound **3.3c** were consistent with what was obtained from using general procedure 1.

4,7-Dihydro-4,7-methano-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3d). General procedure 2 was used with **3.4a** (165 mg, 0.729 mmol) and **3.5d** (63 mg, 0.953 mmol) in the presence of Me_2AlCl (0.730 mL, 0.730 mmol) and $CuCl_2$ (27 mg, 0.20 mmol). After 6 h, purification by column chromatography (silica gel, toluene) yielded **3.3d** (141 mg, 63%). The spectral data for compound **3.3d** were consistent with what was obtained from using general procedure 1.

4,7-Dihydro-4,7-ethano-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3e). General procedure 2 was used with **3.4a** (147 mg, 0.650 mmol) and **3.5e** (293 mg, 3.65 mmol) in the presence of Me_2AlCl (0.65 mL, 0.65 mmol) and $CuCl_2$ (21 mg, 0.15 mmol). After 6 h, purification by column chromatography (silica gel, toluene) yielded **3.3e** (145 mg, 69%). The spectral data for compound **3.3e** were consistent with what was obtained from using general procedure 1.

4,7-Ethano-4,7-dihydro-4-methoxy-1-[(trimethylsilyl)carbonyl]-3-phenylisobenzofuran (3.3f). General procedure 2 was used with **3.4a** (221 mg, 0.976 mmol) and **3.5f** (443 mg, 4.02 mmol) in the presence of Me_2AlCl (0.97 mL, 0.97 mmol)

and $CuCl_2$ (31 mg, 0.23 mmol). After 5 h, purification by column chromatography (silica gel, 1:4 EtOAc/hexanes) yielded **3.3f** (284 mg, 83%). The spectral data for compound **3.3f** were consistent with what was obtained from using general procedure 1.

3-*tert*-Butyl-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3h). General procedure 2 was used with **3.4b** (96 mg, 0.46 mmol) and **3.5a** (163 mg, 1.98 mmol) in the presence of Me_2AlCl (0.46 mL, 0.46 mmol) and $CuCl_2$ (17 mg, 0.17 mmol). After 7 h, purification by column chromatography (silica gel, toluene) yielded **3.3h** (89 mg, 64%). The spectral data for compound **3.3h** were consistent with what was obtained from using general procedure 1.

3-(4-bromophenyl)-4,7-dihydro-5,6-dimethyl-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3j). General procedure 2 was used with **3.4c** (99 mg, 0.32 mmol) and **3.5a** (109 mg, 1.32 mmol) in the presence of Me_2AlCl (0.32 mL, 0.32 mmol) and $CuCl_2$ (10 mg, 0.074 mmol). After 4 h, purification by column chromatography (silica gel, toluene) yielded **3.3j** (86 mg, 67%). The spectral data for compound **3.3j** were consistent with what was obtained from using general procedure 1.

3-(4-Trifluoromethylphenyl)-4,7-dihydro-5,6-dimethyl-1[(trimethylsilyl)carbonyl]isobenzofuran (3.3o). General procedure 2 was used with **3.4d** (212 mg, 0.720 mmol) and **3.5a** (237 mg, 2.88 mmol) in the presence of Me_2AlCl (0.72 mL, 0.72 mmol) and $CuCl_2$ (23 mg, 0.17 mmol). After 6.5 h, purification by column chromatography (silica gel, 1:9 EtOAc/hexanes) yielded **3.3o** (209 mg, 74%). The spectral data for compound **3.3o** were consistent with what was obtained from using general procedure 1.

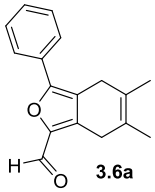
1-Benzoyl-4,7-dihydro-5,6-dimethyl-3-phenylisobenzofuran (3.3p). General procedure 2 was used with **3.4e** (87 mg, 0.37 mmol) and **3.5a** (143 mg, 1.74 mmol) in the presence of Me_2AlCl (0.37 mL, 0.37 mmol) and $CuCl_2$ (12 mg, 0.089 mmol). After 7 h, purification by column chromatography (silica gel, dichloromethane) yielded **3.3p** (85 mg, 70%). The spectral data for compound **3.3p** were consistent with what was obtained from using general procedure 1.

4,7-Dihydro-5,6-dimethyl-3-(2-thienyl)-1-[(trimethylsilyl)carbonyl]isobenzofuran (3.3s). General procedure 2 was used with **3.4f** (109 mg, 0.470 mmol) and **3.5a** (173 mg, 2.11 mmol) in the presence of Me_2AlCl (0.47 mL, 0.47 mmol) and $CuCl_2$ (17 mg, 0.13 mmol). After 6 h, purification by column chromatography (silica gel, toluene) yielded **3.3s** (87 mg, 56%). The spectral data for compound **3.3s** were consistent with what was obtained from using general procedure 1.

General Procedure 3: Silver-Catalyzed Cyclization of Compound 3.2:

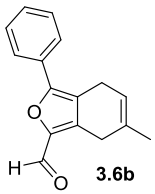
To a solution of **3.2** (1.0 equiv.) in moist* acetone (15 mL) was added $AgNO_3$ (40-70 mol %). The reaction mixture was stirred at room temperature (open to air) for 1-4 h, quenched with brine, dried over anhydrous $MgSO_4$ and filtered. After the solvent was removed in vacuo, the residue was purified by column chromatography (silica gel) to afford compound **3.6**.

*Note: A few drops of water was added to speed up the reaction.



3.6a

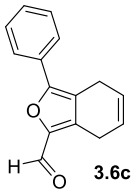
Compound **3.6a** was synthesized according to general procedure (376 mg, 1.22 mmol of **3.2a** and 153 mg, 0.9 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6a** (241 mg, 78%) as a yellow colored solid: R_f = 0.34 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (s, 1H), 7.78 – 7.70 (m, 2H), 7.47 – 7.39 (m, 2H), 7.37 – 7.31 (m, 1H), 3.37 (s, 2H), 3.25 (s, 2H), 1.78 (br s, 6H, 2×CH_3); ^{13}C NMR (DMSO, 126 MHz) δ 176.5, 150.1, 144.4, 133.7, 129.2, 128.5, 128.3, 125.0, 121.7, 120.9, 119.0, 28.3, 26.9, 18.3, 18.2; IR (cast film) ν 2859, 1659, 1450 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}O_2$ 253.1223; found 253.1296.



3.6b

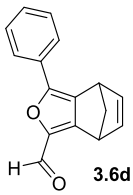
Compound **3.6b** was synthesized according to general procedure (378 mg, 1.28 mmol of **3.2b** and 139 mg, 0.818 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6b** (221 mg, 72%) as a pale yellow solid: R_f = 0.25 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (s, 1H), 7.80 – 7.75 (m, 2H), 7.47 – 7.42 (m, 2H), 7.39 – 7.33 (m, 1H), 5.64 – 5.59 (m, 1H), 3.41 (s, 4H), 1.86 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 176.7, 150.6, 144.7, 133.7, 129.2, 129.1, 128.5, 128.4, 125.1, 118.0, 117.2, 25.4, 22.4, 22.3; IR

(cast film) ν 1666, 1449 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{14}O_2Na$ 261.0886, found 261.0895.



3.6c

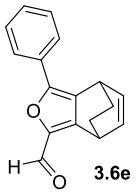
Compound **3.6c** was synthesized according to general procedure (132 mg, 0.471 mmol of **3.2c** and 53 mg, 0.31 mmol of $AgNO_3$). Purification by column chromatography (silica gel, 1:3 EtOAc/hexanes) afforded **3.6c** (73 mg, 70%) as a pale yellow solid: R_f = 0.41 (1:3 EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.79 (s, 1H), 7.83 – 7.75 (m, 2H), 7.50 – 7.42 (m, 2H), 7.41 – 7.34 (m, 1H), 5.97 – 5.90 (m, 2H), 3.59 – 3.52 (m, 2H), 3.50 – 3.43 (m, 2H); ^{13}C NMR (DMSO, 126 MHz) δ 176.8, 150.8, 145.0, 132.7, 129.2, 128.5, 128.4, 125.2, 122.9, 122.0, 118.0, 22.0, 20.7; IR (cast film) ν 1666, 1449 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{12}O_2Na$ 247.0730; found 247.0747.



3.6d

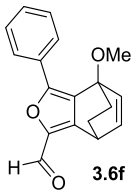
Compound **3.6d** was synthesized according to general procedure (255 mg, 0.872 mmol of **3.2d** and 103 mg, 0.606 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6d** (149 mg, 73%) as a pale yellow solid: R_f = 0.21 (dichloromethane); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.61 (s, 1H), 7.79 – 7.74 (m, 2H), 7.45 – 7.40 (m, 2H), 7.37 – 7.31 (m, 1H), 6.82 (dd, J = 5.4, 3.1 Hz, 1H), 6.73 (dd, J = 5.4, 3.1

Hz, 1H), 4.18 – 4.13 (m, 2H), 2.57 (d, *J* = 7.7, 1H), 2.48 (d, *J* = 7.6, 1H); ^{13}C NMR (DMSO, 126 MHz) δ 176.2, 153.5, 145.4, 142.0, 140.9, 140.6, 136.7, 129.0, 128.6, 128.4, 124.7, 67.3, 43.6, 43.3; IR (cast film) ν 2937, 1666, 1447 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{13}O_2$ 237.0910; found 237.0905.



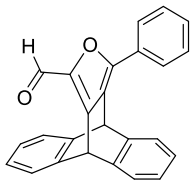
3.6e

Compound **3.6e** was synthesized according to general procedure (243 mg, 0.793 mmol of **3.2e** and 81 mg, 0.47 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6e** (163 mg, 82%) as a pale yellow spongy solid: R_f = 0.21 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.67 (s, 1H), 7.82 – 7.75 (m, 2H), 7.45–7.37 (m, 2H), 7.36 – 7.29 (m, 1H), 6.58 – 6.51 (m, 1H), 6.51 – 6.44 (m, 1H), 4.36 – 4.26 (m, 2H), 1.69 – 1.57 (m, 4H); ^{13}C NMR (DMSO, 126 MHz) δ 175.7, 145.64, 145.55, 140.6, 135.0, 133.3, 129.4, 129.3, 128.6, 128.4, 125.1, 31.8, 31.1, 25.0, 24.7; IR (cast film) ν 2939, 1665, 1447 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_2$ 251.1067; found 251.1085.



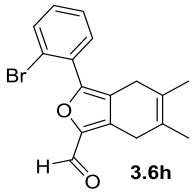
3.6f

Compound **3.6f** was synthesized according to general procedure (416 mg, 1.24 mmol of **3.2f** and 143 mg, 0.842 mmol of $AgNO_3$). Purification by column chromatography (silica gel, 1:4 EtOAc/hexanes) afforded **3.6f** (278 mg, 80%) as a pale yellow solid: R_f = 0.28 (1:4 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.66 (s, 1H), 8.01 – 7.87 (m, 2H), 7.43 – 7.26 (m, 3H), 6.63 (d, J = 8.3 Hz, 1H), 6.48 – 6.35 (m, 1H), 4.29 – 4.21 (m, 1H), 3.30 (s, 3H), 1.86 – 1.79 (m, 2H), 1.77 – 1.64 (m, 2H); ^{13}C NMR (DMSO, 126 MHz) δ 176.5, 146.8, 144.7, 141.0, 135.9, 132.6, 129.2, 129.09, 129.07, 128.3, 127.7, 80.8, 52.9, 30.8, 30.6, 26.1; IR (cast film) ν 2941, 1667, 1447, 1348 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}O_3$ 281.1172; found 281.1185.



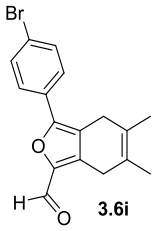
3.6g

Compound **3.6g** was synthesized according to general procedure (212 mg, 0.524 mmol of **3.2g** and 33 mg, 0.19 mmol of $AgNO_3$). Purification by column chromatography (silica gel, toluene) afforded **3.6g** (149 mg, 82%) as a pale yellow spongy solid: R_f = 0.19 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.82 (s, 1H), 7.89 – 7.84 (m, 2H), 7.54 – 7.46 (m, 6H), 7.44 – 7.39 (m, 1H), 7.14 – 7.09 (m, 4H), 5.89 (s, 1H), 5.75 (s, 1H); ^{13}C NMR (DMSO, 126 MHz) δ 176.5, 146.6, 145.9, 144.1, 143.2, 141.4, 131.2, 128.9, 128.8, 128.7, 125.6, 125.4, 125.3, 124.0, 123.8, 44.7, 44.4; IR (cast film) ν 3067, 1668 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{17}O_2$ 349.1223; found 349.1217.



3.6h

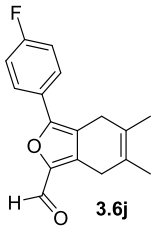
Compound **3.6h** was synthesized according to general procedure (339 mg, 0.875 mmol of **3.2h** and 97 mg, 0.57 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6h** (254 mg, 88%) as a yellow solid: R_f = 0.40 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.75 (s, 1H), 7.68 – 7.61 (m, 1H), 7.43 – 7.39 (m, 1H), 7.38 – 7.33 (m, 1H), 7.29 – 7.23 (m, 1H), 3.44 (s, 2H), 3.09 (s, 2H), 1.78 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 177.0, 150.0, 145.3, 132.9, 132.6, 131.2, 130.9, 130.1, 127.2, 121.8, 121.5, 121.2, 121.0, 27.2, 26.9, 18.3, 18.2; IR (cast film) ν 2859, 1666, 1444 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{15}BrO_2Na$ 353.0148; found 353.0147.



3.6i

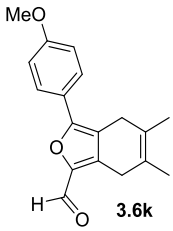
Compound **3.6i** was synthesized according to general procedure (223 mg, 0.576 mmol of **3.2i** and 59 mg, 0.35 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6i** (172 mg, 91%) as a yellow solid: R_f = 0.23 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.73 (s, 1H), 7.63 – 7.59 (m, 2H), 7.57 – 7.54 (m, 2H), 3.41 (br s, 2H), 3.25 (br s, 2H), 1.81 (s, 3H), 1.79 (s, 3H); ^{13}C NMR

(DMSO, 126 MHz) δ 176.8, 148.9, 144.6, 133.6, 131.6, 128.4, 126.9, 121.7, 121.6, 121.0, 119.7, 28.2, 26.9, 18.3, 18.2; IR (cast film) ν 2880, 1655, 1451 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{15}BrO_2Na$ 353.0148; found 353.0145.



3.6j

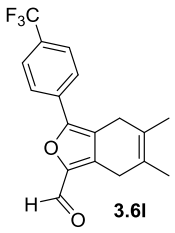
Compound **3.6j** was synthesized according to general procedure (178 mg, 0.545 mmol of **3.2j** and 68 mg, 0.40 mmol of $AgNO_3$). Purification by column chromatography (silica gel, 1:4 EtOAc/hexanes) afforded **3.6j** (113 mg, 76%) as a yellow solid: R_f = 0.47 (1:4 EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.73 (s, 1H), 7.79 – 7.73 (m, 2H), 7.17 – 7.12 (m, 2H), 3.42 (br s, 2H), 3.27 (br s, 2H), 1.82 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 176.6, 161.8 (d, *J* = 248.0 Hz), 149.3, 144.5, 133.8, 127.4 (d, *J* = 8.6 Hz), 125.9 (d, *J* = 3.3 Hz) , 121.7, 121.0, 118.8, 115.6 (d, *J* = 22.0 Hz), 28.1, 26.9, 18.4, 18.2; IR (cast film) ν 2920, 1657, 1449 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{15}FO_2Na$ 293.0948; found 293.0757.



3.6k

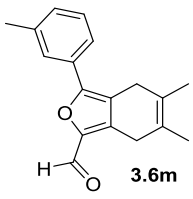
Compound **3.6k** was synthesized according to general procedure (143 mg, 0.422 mmol of **3.2k** and 51 mg, 0.30 mmol of $AgNO_3$). Purification by column chromatography (silica

gel, 1:3 EtOAc/hexanes) afforded **3.6k** (65 mg, 55%) as a yellow solid: R_f = 0.48 (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.71 (br s, 1H), 7.78 – 7.71 (m, 2H), 7.01 – 6.95 (m, 2H), 3.86 (s, 3H), 3.43 (br s, 2H), 3.28 (br s, 2H), 1.81 (br s, 6H, 2× CH_3); ^{13}C NMR (DMSO, 126 MHz) δ 176.1, 159.6, 150.7, 144.1, 134.3, 126.8, 122.0, 121.9, 121.0, 117.5, 114.4, 55.0, 28.3, 27.0, 18.5, 18.3; IR (cast film) ν 2914, 1655, 1449 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}O_3$ 283.1329; found 283.1348.



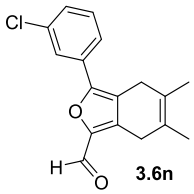
3.6l

Compound **3.6l** was synthesized according to general procedure (113 mg, 0.300 mmol of **3.2l** and 24 mg, 0.14 mmol of $AgNO_3$). Purification by column chromatography (silica gel, toluene) afforded **3.6l** (72 mg, 75%) as a pale yellow solid: R_f = 0.21 (toluene); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 7.88 – 7.77 (m, 2H), 7.69 – 7.60 (m, 2H), 3.38 (s, 2H), 3.27 (s, 2H), 1.80 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 177.1, 148.1, 145.0, 133.2, 132.7, 128.3 (q, J = 32.1 Hz), 125.5, 125.3, 123.5 (q, J = 272.2 Hz), 121.5, 120.98, 120.96, 28.2, 26.8, 18.3, 18.1; IR (cast film) ν 2935, 1679, 1324 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{15}F_3O_2Na$ 343.0916; found 343.0937.



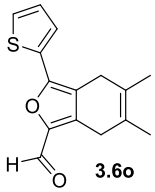
3.6m

Compound **3.6m** was synthesized according to general procedure (347 mg, 1.07 mmol of **3.2m** and 112 mg, 0.660 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6m** (213 mg, 75%) as a yellow solid: R_f = 0.27 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.75 (s, 1H), 7.64 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.35 (dd, J = 7.7 Hz, 1H), 7.19 (d, J =7.6 Hz, 1H), 3.44 (s, 2H), 3.33 (s, 2H), 2.43 (s, 3H), 1.84 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 176.5, 150.3, 144.4, 137.9, 133.8, 129.2, 129.1, 128.4, 125.4, 122.4, 121.8, 121.0, 118.9, 28.3, 26.9, 20.4, 18.4, 18.2; IR (cast film) v 2859, 1659, 1449 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{18}H_{18}O_2Na$ 289.1199; found 289.1196.



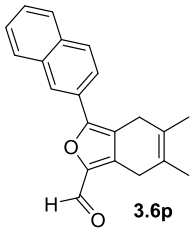
3.6n

Compound **3.6n** was synthesized according to general procedure (789 mg, 2.30 mmol of **3.2n** and 263 mg, 1.55 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6n** (544 mg, 82%) as a yellow solid: R_f = 0.3 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.78 (s, 1H), 7.78 (s, 1H), 7.70 – 7.65 (m, 1H), 7.42 – 7.36 (m, 1H), 7.36 – 7.31 (m, 1H), 3.45 (s, 2H), 3.33 (s, 2H), 1.84 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 177.1, 148.3, 144.8, 133.6, 133.5, 131.1, 130.5, 128.1, 124.4, 123.7, 121.7, 121.0, 120.2, 28.1, 26.9, 18.4, 18.3; IR (cast film) v 2859, 1663, 1446 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{15}ClO_2Na$ 309.0653; found 309.0651.



3.6o

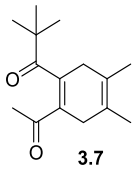
Compound **3.6o** was synthesized according to general procedure (154 mg, 0.490 mmol of **3.2o** and 61 mg, 0.36 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6o** (74 mg, 58%) as a pale yellow solid: R_f = 0.25 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.68 (s, 1H), 7.46 – 7.42 (m, 1H), 7.42 – 7.39 (m, 1H), 7.15 – 7.10 (m, 1H), 3.39 (s, 2H), 3.17 (s, 2H), 1.81(s, 3H), 1.79 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 176.1, 146.9, 144.1, 134.0, 131.1, 128.0, 127.5, 125.6, 121.5, 121.2, 118.1, 27.6, 27.0, 18.5, 18.3; IR (cast film) ν 2860, 1657, 1453 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}O_2S$ 259.0787; found 259.0789.



3.6p

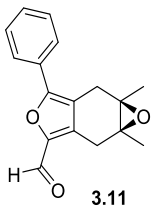
Compound **3.6p** was synthesized according to general procedure (319 mg, 0.890 mmol of **3.2p** and 76 mg, 0.45 mmol of $AgNO_3$). Purification by column chromatography (silica gel, dichloromethane) afforded **3.6p** (192 mg, 71%) as a yellow solid: R_f = 0.26 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.79 (s, 1H), 8.26 – 8.20 (m, 1H), 7.94 – 7.88 (m, 3H), 7.86 – 7.80 (m, 1H), 7.55 – 7.49 (m, 2H), 3.48 – 3.38 (m, 4H), 1.86 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 176.7, 150.3, 144.7, 134.1, 132.6, 132.4, 128.3, 128.1, 127.2, 126.7, 126.6, 126.4, 124.7, 122.4, 121.9, 121.0, 119.6, 28.4, 27.0, 18.5,

18.4; IR (cast film) ν 2858, 1659, 1444 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{18}O_2Na$ 325.1199; found 325.1171.



3.7

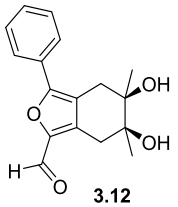
To a solution of **3.2q** (593 mg, 2.05 mmol) in moist acetone (40 mL) was added $AgNO_3$ (216 mg, 1.27 mmol). The resulting solution was stirred at room temperature for 1 h. The reaction was quenched with brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, 1:4 EtOAc/hexanes) to afford **3.7** (61 mg, 81%) as a pale yellow solid: R_f = 0.24 (1:4 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.93 – 2.86 (m, 2H), 2.81 – 2.73 (m, 2H), 2.13 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.5, 198.0, 149.1, 128.8, 122.4, 121.0, 43.3, 37.2, 33.5, 27.6, 27.4, 18.3, 17.9; IR (cast film) ν 2963, 1675, 1615, 1457, 1356 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{19}O_2$ 255.1380; found 255.1376.



3.11

To a solution of **3.6a** (63 mg, 0.25 mmol) in dichloromethane (20 mL) at 0 °C was added *m*-chloroperbenzoic acid (88 mg, 0.51 mmol). The resulting solution was stirred at 0 °C for 10 minutes then warmed to room temperature and stirred for 1 h. The reaction was

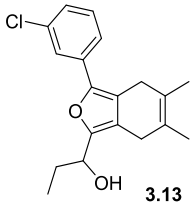
quenched with 1M NaOH, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, 1:1 EtOAc/hexanes) to afford **3.11** (61 mg, 91%) as a pale yellow solid: R_f = 0.45 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 7.74 – 7.69 (m, 2H), 7.49 – 7.435 (m, 2H), 7.41 – 7.35 (m, 1H), 3.63 (d, J = 18.9 Hz, 1H), 3.35 (d, J = 17.5 Hz, 1H), 3.09 (d, J = 7.1 Hz, 1H), 3.04 (d, J = 8.3 Hz, 1H), 1.54 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 176.7, 151.2, 145.3, 132.7, 128.9, 128.51, 128.48, 125.3, 117.6, 59.7, 59.4, 28.0, 27.0, 18.9, 18.7; IR (cast film) ν 2928, 1665, 1495 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{17}O_3$ 291.0992; found 291.1050.



3.12

Compound **3.6a** (47 mg, 0.18 mmol) was dissolved in 20 mL 3:1 acetone/water, the flask wrapped with aluminum foil and OsO_4 (0.2 mL, 1% in H_2O, 0.008 mmol) was added followed by the addition of NMO (0.1 mL, 50% in H_2O, 0.42 mmol). The resulting solution was stirred in the dark at room temperature for 14 h. The reaction mixture was transferred to a separatory funnel and diluted with EtOAc (100 mL). The mixture was washed with brine, the organic layer dried with $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, EtOAc) to yield compound **3.12** (45 mg, 87%) as a white solid: R_f = 0.46 (EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.66 (s, 1H), 7.76 – 7.70 (m, 2H), 7.46 – 7.40 (m, 2H), 7.39 – 7.33 (m, 1H), 3.21

(d, *J* = 17.8 Hz, 1H), 3.12 (d, *J* = 16.2 Hz, 1H), 2.98 (d, *J* = 17.8 Hz, 1H), 2.88 (d, *J* = 16.1 Hz, 1H), 2.65 (br s, 1H), 2.63 (br s, 1H), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 176.6, 150.9, 145.2, 135.8, 129.4, 128.6, 128.4, 125.2, 120.3, 72.5, 72.0, 34.7, 33.1, 23.0, 22.8; IR (cast film) *v* 3421, 2976, 1652, 1448 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{18}O_4Na$ 309.1097; found 309.1081.



3.13

To a solution of **3.6n** (125 mg, 0.436 mmol) in dry diethyl ether (15 mL) was added freshly prepared ethyl magnesium bromide (2 mL, 1.11 M in ether, 2.22 mmol). The resulting solution was stirred at room temperature for 10 minutes under N_2. It was then quenched by distilled water and extracted with dichloromethane. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, 2:3 EtOAc/hexanes) to afford **3.13** (107 mg, 79%) as a white solid: R_f = 0.46 (2:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.26 (dd, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 4.60 (t, *J* = 7.1 Hz, 1H), 3.25 – 3.19 (m, 2H), 3.10 – 3.04 (m, 2H), 2.20 (br s, 1H), 1.97 – 1.89 (m, 2H), 1.78 (s, 3H), 1.74 (s, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.3, 143.5, 134.7, 133.7, 129.9, 126.1, 123.9, 122.7, 122.4, 122.1, 118.9, 118.8, 68.8, 30.1, 28.8, 27.4, 19.5, 19.4, 10.2; IR (cast film) *v* 3378, 2926, 1594, 1475 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{19}H_{21}ClO_2Na$ 339.1122; found 339.1127.

3.7 References

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4 Synthesis of Expanded Hexa-*peri*-hexabenzocoronenes by Two and Four-fold Alkyne Benzannulation Reaction

4.1 Introduction

Hexa-peri-hexabenzocoronenes (HBCs), with 13 fused benzene rings, is a class of polycyclic aromatic hydrocarbons that have attracted considerable attention due to their ability to self-organize into discotic liquid crystals and because of their interesting electrochemical

properties.[1-5] The substituents on the periphery of the HBCs solely determine the liquid phase formation (**Figure 4-1**).

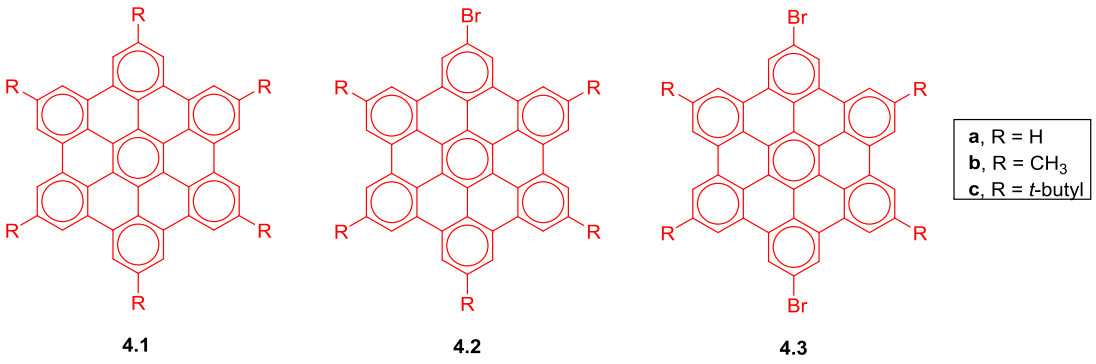


Figure 4-1: Hexa-*peri*-hexabenzocoronenes (HBCs) with/without bromo substituents.

Linear alkyl substituents favor the liquid crystalline phase (such as **b**) whereas bulky groups such as *t*-butyl (**c**) inhibit such phase formation.[4] Bulkier alkyl groups on the periphery also help to solubilize the HBCs in common organic solvents. However, the electronic properties depend on the HBC core and are resilient to the substituents. Large disc-like HBC derivatives exhibit interesting electronic and optical properties due to their extensive electron delocalization and intrinsic chemical stability.[6] HBC compounds are

expected to be useful components in the area of molecular electronics and optoelectronics. In addition, such molecules can form columnar stacks by aggregation.[7,8]

Extension of the π-electron system (aromatic sextets) by condensing aromatic rings is a current emerging area in the field of organic materials. Most impressive examples of graphene nanoribbons have been reported by Mullen and co-workers.[9-11] On the other hand, recent impressive developments of carbon nanobelts have been reported by Itami and co-workers.[12,13] By expanding conjugation, we can enhance the desired properties of the functional materials, such as π-π stacking causing a high carrier transportation,[14,15] photophysical response in the visible and near-infrared regions,[16,17] and the band gap control for semiconducting materials with low redox potentials.[18,19]

4.2 Target HBC Molecules and Retrosynthesis

We planned for the synthesis of chiral π-molecules **4.4** and **4.5** which have more aromatic sextets compared to parent HBCs (**Figure 4-2**).

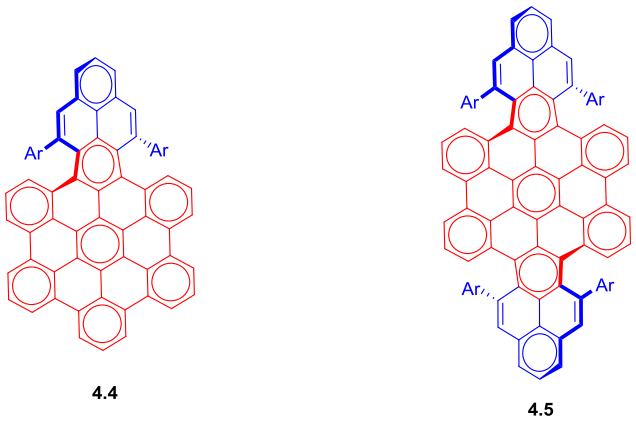


Figure 4-2: Expanded hexa-*peri*-hexabenzocoronenes (our target compounds).

The synthesis of organic materials via multiple steps is always challenging. We should consider the starting materials which are easy to prepare or commercially available. The number and selection of reaction steps should also be taken in consideration.

To simplify the synthetic route for above molecules, we did a careful retrosynthetic analysis by considering compound **4.4** (**Figure 4-3**). If we cleave the indicated two bonds in compound **4.4**, we can arrive at a diyne compound **4.6**. Compound **4.6** can be turned into **4.4** by employing two-fold alkyne benzannulation reaction. In our group, we have shown the synthesis of polycyclic aromatic hydrocarbons via alkyne benzannulation reaction promoted by a mixture of trifluoroacetic acid (TFA) and triflic acid (TfOH).[20,21]

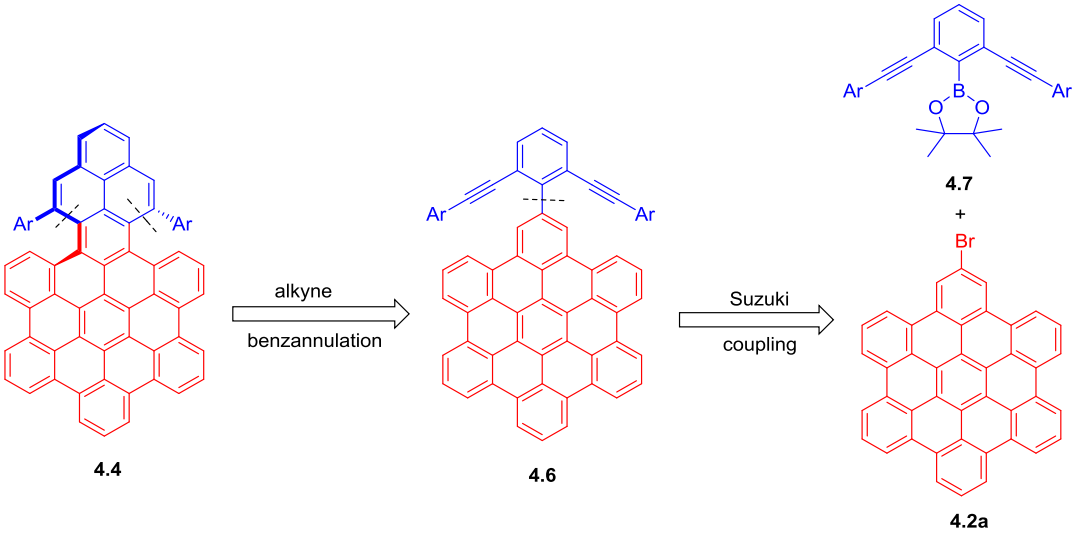


Figure 4-3: Retrosynthetic analysis of compound **4.4** leading to the precursors **4.2a** and **4.7**.

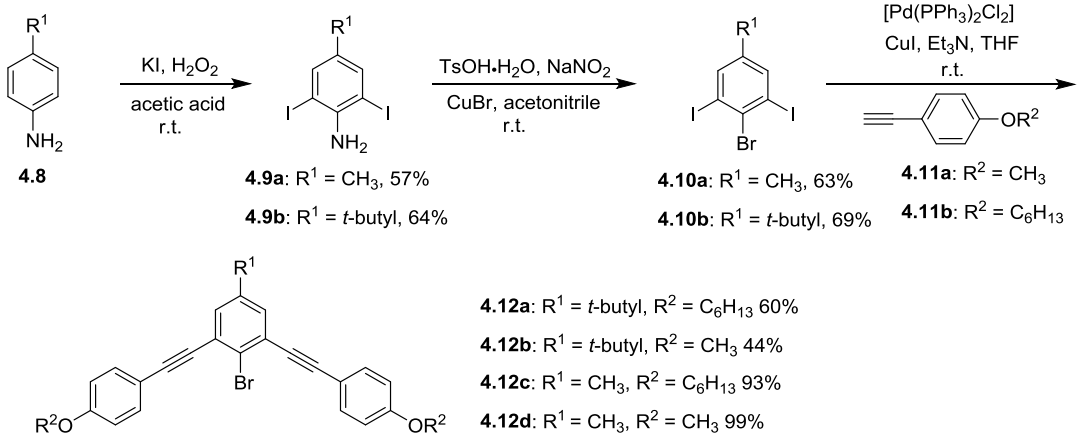
We can try the same conditions for a benzannulation reaction to arrive at our final product. Further, the cleavage of the indicated bond in diyne **4.6** leads us to the two possible coupling partners; diynylphenyl borate **4.7** and HBC **4.2a**, bearing one bromo substituent.

The two coupling partners **4.7** and **4.2a** can cross-couple under Suzuki conditions to afford the intermediate compound **4.6**.

The structurally similar but more π-extended compound **4.5** can also be obtained in an analogous manner as compound **4.4**. To start this project, we first considered a quick and easy preparation of the corresponding synthetic precursors.

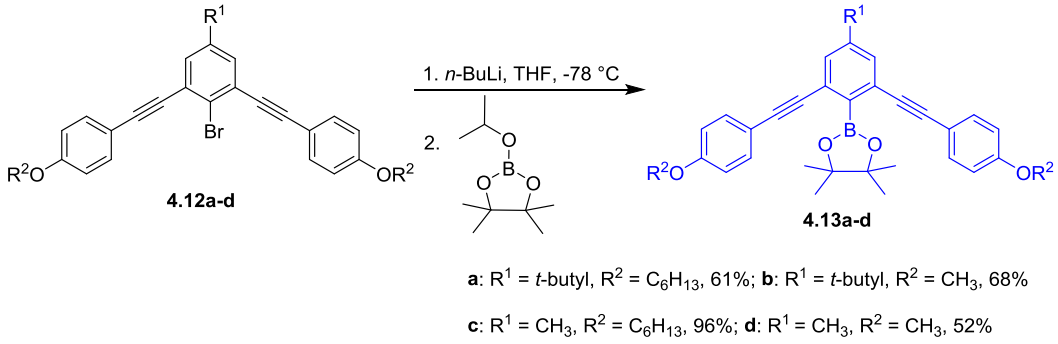
4.2.1 Synthesis of Diynylphenyl Borate

The Chalifoux group developed a new method to prepare diynylphenyl borate **4.12** (**Scheme 4-1**).[20] We initiated from commercially available amine **4.8** which was diiodinated to yield compound **4.9** in moderate yields. After Sandmeyer's reaction of compound **4.9**, substituted diiodobromobenzene **4.10** was formed with good yields. Compound **4.10** under double selective Sonogashira cross-coupling reaction with terminal alkyne **4.11** yielded bromodiyne compound **4.12**.



Scheme 4-1: Synthesis of diynylbromophenyl derivatives **4.12**.

Lithium halogen exchange reaction of **4.12** with *n*-BuLi followed by the treatment with isopropoxy boronic acid pinacol ester resulted in the formation of one of our coupling partners **4.13** (**Scheme 4-2**). To tune the solubility and crystallinity of final product, we prepared four derivatives of diynylphenyl borate.



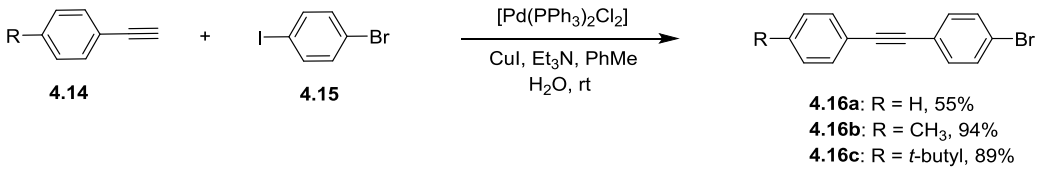
Scheme 4-2: Synthesis of diynylphenyl borate derivatives **4.13**.

4.2.2 Synthesis of Hexa-peri-hexabenzocoronenes

A variety of synthetic methods have been used to prepare hexa-peri-hexabenzocoronenes.[22-25] All those synthetic methods involve complicated experimental workup and gave the desired product in very low yield. Mullen and co-workers have developed a method for the synthesis of parent HBC as well as six-fold symmetric alkyl- and alkylphenyl-substituted HBCs.[26-28] The Mullen group has also reported an alternate and efficient way to prepare HBC derivatives carrying different substituents in periphery.[29] In addition, this method allows us to synthesize HBCs bearing one or two bromo

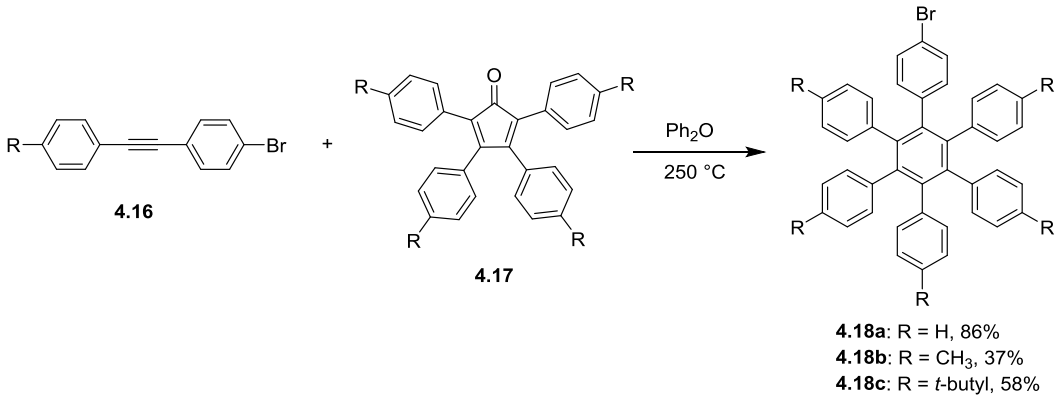
substituents. On the basis of Mullen's synthetic approach, various HBCs carrying one or two bromo substituents were synthesized.

Substituted diphenylacetylenes **4.16a**,[30] **4.16b**[30] and **4.16c**[31] were first prepared according to reported procedures by cross-coupling reaction between terminal alkyne **4.14** and 4-bromoiodobenzene **4.15** (**Scheme 4-3**). Compound **4.16a** was isolated in modest yield of 55% but compounds **4.16b** and **4.16c** were obtained in excellent yields of 94% and 89% respectively.



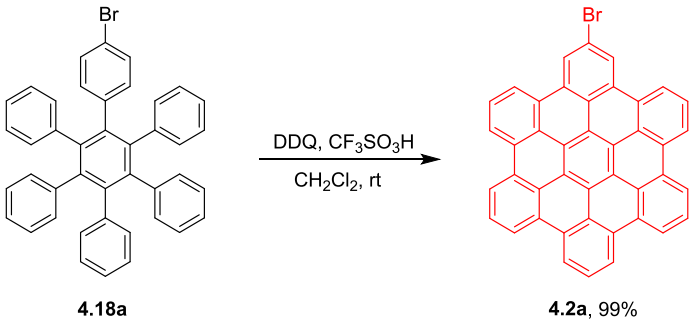
Scheme 4-3: Synthesis of substituted diphenylacetyles **4.16** by cross-coupling reaction between **4.14** and **4.15**.

Hexaphenylbenzene (HPB) derivatives were prepared by a Diels-Alder cycloaddition between appropriate tetraphenylcyclopentadienone derivatives and substituted diphenylacetylenes followed by cheletropic extrusion of CO. Compound **4.16** was reacted with appropriate tetraarylcyclopentadienone **4.17** in refluxing diphenyl ether to afford HPB derivatives **4.18** (**Scheme 4-4**). After the reaction, the HPB product was dissolved in dichloromethane and then precipitated by adding either methanol or hexane. No column chromatography was needed to purify the HPB derivatives.



Scheme 4-4: Cycloaddition reaction between **4.16** and **4.17** to give hexaphenylbenzenes carrying one bromine atom.

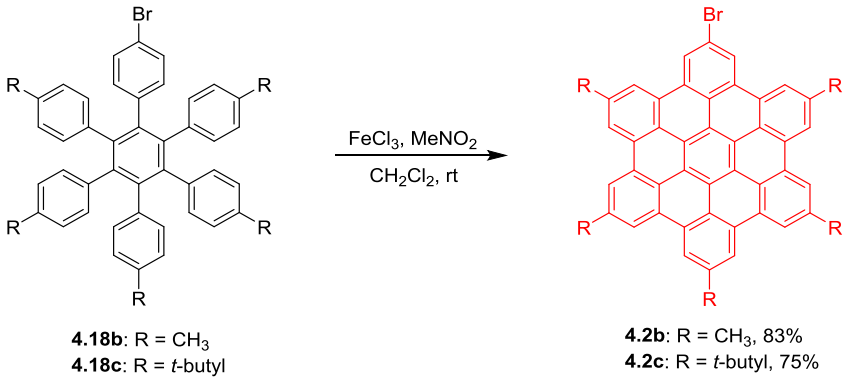
We then prepared substituted HBCs carrying one bromine atom from hexaphenylbenzene derivatives by utilizing the Scholl reaction.[32,33] Depending upon the yield and mixture of fully-cyclized and partially cyclized products, HPB derivatives behave differently with $FeCl_3/MeNO_2$ conditions and DDQ/CF_3SO_3H conditions. HBC **4.2a** was obtained by a Scholl-type oxidative cyclodehydrogenation (aryl-aryl coupling) of HPB **4.18a** with the recently developed DDQ/CF_3SO_3H[34] in quantitative yield (**Scheme 4-5**). The main obstacle with HBC **4.2a** is it's insolubility in common organic solvents.



Scheme 4-5: Cyclodehydrogenation reaction of compound **4.18a** to form HBC **4.2a**.

We then focused on the preparation of HBC molecules bearing alkyl substituents in their periphery to enhance the solubility.

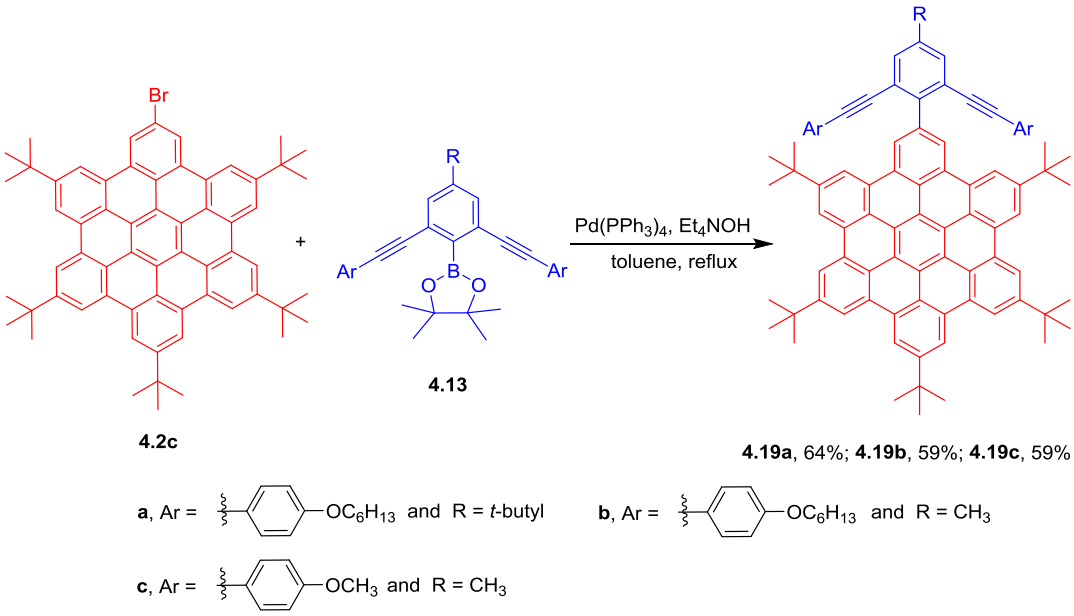
Compounds **4.2b** and **4.2c** were prepared from corresponding HPB derivatives **4.18b** and **4.18c** by utilizing Scholl reaction with $FeCl_3/MeNO_2$ in 83% and 75% respectively (**Scheme 4-6**). After finishing the synthesis and testing the solubility, it was found that HBC **4.2b** is also not soluble enough in common organic solvents. The poor solubility of HBCs **4.2a** and **4.2b** could be related to strong π-stacking that leads to the quick precipitation. HBC **4.2c** has bulkier *tert*-butyl substituents and hence is fairly soluble in common organic solvents. We did not encounter any difficulties in purification and characterization of **4.2c**. Gordon and co-workers[31] have shown the synthetic utility of soluble HBC **4.2c** by synthesizing two bipyridine hexa-*peri*-hexabenzocoronene ligands functionalized with bulky *tert*-butyl groups. Thus, we considered compound **4.2c** as the model HBC substrate in our synthetic strategy.



Scheme 4-6: Scholl reaction of compound **4.18** to form HBC **4.2**.

4.2.3 Synthesis of Final Product

The synthesis of final product was accomplished after two steps. Having two coupling partners **4.2c** and **4.13** on hand, we first attempted Suzuki cross-coupling reaction to afford coupled diyne product **4.19** (**Scheme 4-7**). We synthesized three different derivatives **4.19a**, **4.19b** and **4.19c** in 64%, 59% and 59% respectively.

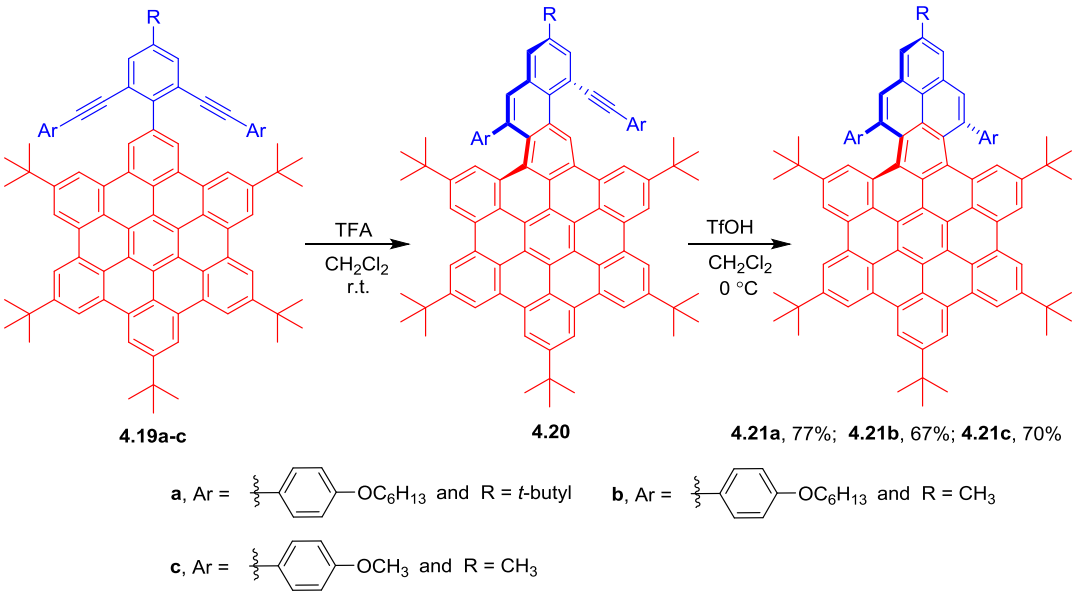


Scheme 4-7: Suzuki cross-coupling reaction between **4.13** and **4.2c** to form compound **4.19**.

All the coupled derivatives **4.19a**, **4.19b** and **4.19c** are soluble in $CDCl_3$ for spectroscopic characterization. The soluble nature of coupled products allows for easy purification by column chromatography.

The Suzuki product **4.19** was then subjected to double alkyne benzannulation reaction with the mixture of trifluoroacetic acid and triflic acid to get final desired product **4.21** (**Scheme 4-8**). Upon treatment of TFA with **4.19** in anhydrous CH_2Cl_2 at room temperature, monocyclized product **4.20** was formed (not isolated, checked by TLC). After complete monocyclization was observed, TfOH was added at 0 °C to cyclize the remaining alkyne.

If monocyclization occurs from top, it forces the cyclization of remaining alkyne from bottom giving the formation of chiral product. Three derivatives **4.20a**, **4.20b** and **4.20c** were synthesized in 77%, 67% and 70% respectively. All the derivatives were fully characterized by NMR and MALDI analysis.



Scheme 4-8: Alkyne benzannulation reaction of compound **4.19** to get compound **4.21**.

Excellent separation of the enantiomers of chiral **4.20c** was achieved by HPLC using a column packed with a chiral stationary phase based on amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica gel (**Figure 4-4**). Elution with hexane/THF (96/4 v/v) gave two nicely resolved peaks with retention times of 3.7 and 5.2 min.

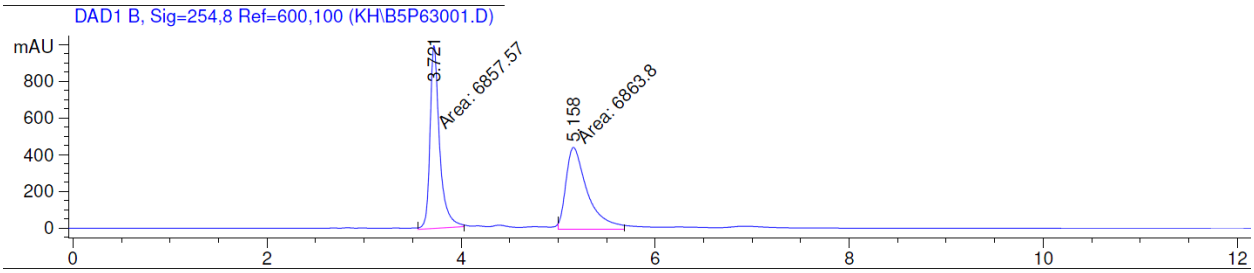


Figure 3

Figure 4-4: Chiral HPLC traces of compound **4.21c**.

4.2.4 X-ray Crystallography

Expanded chiral HBCs **4.21a-c** are soluble in common organic solvents resulting in a red coloration.

The structure of chiral **4.21c** was unambiguously confirmed by X-ray crystallographic analysis. Single crystals of **4.21c** were grown by slowly evaporating solvents from solutions in benzene/MeOH. The X-ray crystal structure clearly shows a twisted π-system which forces two aryl substituents out of the plane. Also, chiral **4.21c** can possibly exists as (*P*,*P*)- and (*M*,*M*)-enantiomers.

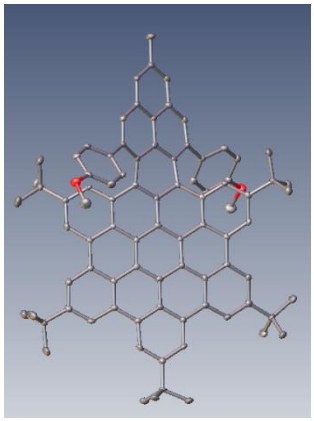


Figure 4-5: Single crystal X-ray structure of compound **4.21c**.

Table 4-1: Crystal parameters and refinement metrics of compound **4.21c**.

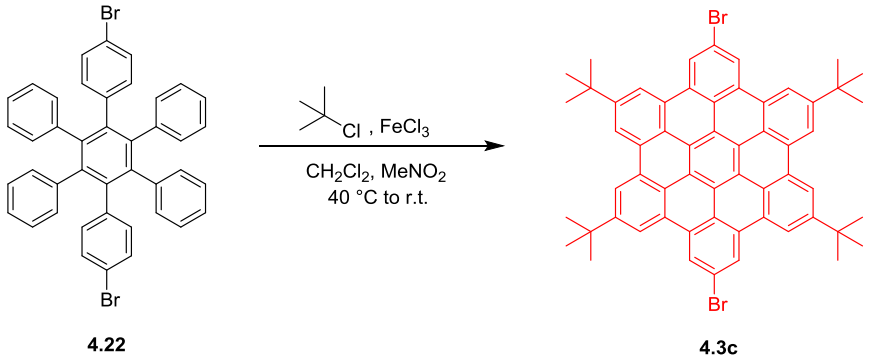
Empirical formula	$C_{205}H_{182}O_5$	Crystal size	0.132 x 0.120 x 0.012 mm^3
Formula weight	2725.50	Theta range for data collection	1.289 to 24.999°
Temperature	100(2) K	Index ranges	-18<=h<=18, -19<=k<=19, -36<=l<=36
Wavelength	0.71073 Å	Reflections collected	131976
Crystal system	Triclinic	Independent reflections	26655 [R(int) = 0.1503]
Space group	P-1	Completeness to theta= 24.999°	100.0 %
F(000)	2904	Absorption correction	Multi-scan
Unit cell dimensions	a=15.2784(5) Å	Max. and min. transmission	0.7460 and 0.6597
	b=16.7836(6) Å c=30.4030(11) Å α=102.1260(10)° β=92.5540(10)° γ=95.5890(10)°	Refinement method	Full-matrix least-squares on F^2
		Extinction coefficient	n/a
		Data/restraints/parameters	26655 / 585 / 2078
Volume	7569.0(5) $Å^3$	Goodness-of-fit on F^2	1.029
Z	4	Final R indices [I>2sigma(I)]	R1 = 0.0657, wR2 = 0.1156
Density (calculated)	1.196 Mg/m^3	R indices (all data)	R1 = 0.1540, wR2 = 0.1318
Absorption coefficient	0.070 mm^{-1}	Largest diff. peak and hole	0.755 and -0.481 $e.Å^{-3}$

4.3 Four-fold Alkyne Benzannulation

After the successful synthesis of chiral compound **4.21** by double alkyne benzannulation, we turned our attention towards the synthesis of further extended HBC compound **4.5** in an analogous manner as **4.21a-c**.

We first prepared HBC **4.3a** having no alkyl substituents and **4.3b** carrying methyl substituents on periphery by known procedure.[35] Due to poor solubility of **4.3a** and **4.3b** in common organic solvents, we decided to prepare soluble HBC **4.3c** bearing four *t*-butyl and two bromo substituents.

Smaldone and co-workers[36] have reported the preparation of **4.3c** from HPB **4.22** in a one-pot reaction using $FeCl_3$ both as a Lewis acid catalyst and as an oxidant, a modification of previously reported procedure.[37] When we repeated this method (**Scheme 4-9**), we isolated compound **4.3c** in very low yield (19%). Also, the major problem in this reaction was the difficulty in purification of crude that contained a mixture of partially cyclized compounds and the desired product.

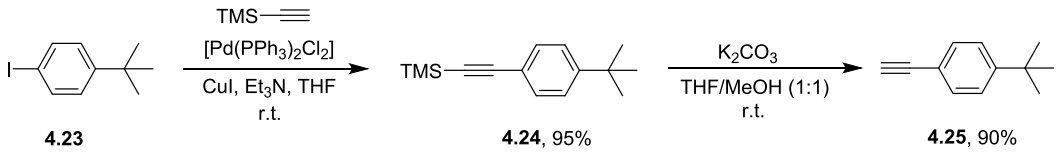


4.22 **4.3c**

Scheme 4-9: One-pot reaction of compound **4.22** to directly form HBC **4.3c**.

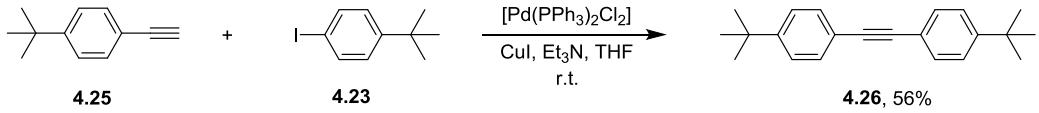
We then attempted an alternative route to synthesize HBC **4.3c** which was adapted from Mullen's well-known procedure.

Synthesis of 4-bromo-4′-*tert*-butyldiphenylacetylene **4.26** was accomplished by a sequence of Sonogashira coupling reactions. First, 4-*tert*-butyliodobenzene **4.23** was coupled with trimethysilylacetylene to give compound **4.24** with excellent yield (**Scheme 4-10**).



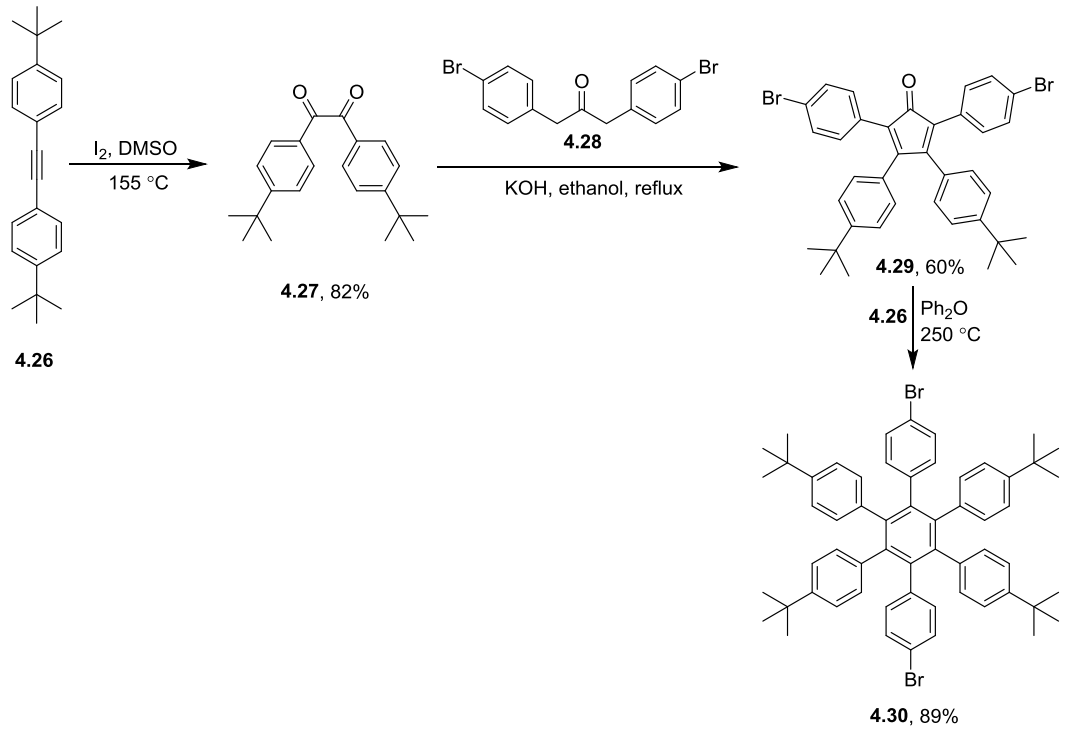
Scheme 4-10: Preparation of compound **4.25**.

After deprotection of the triple bond with potassium carbonate in THF/MeOH, terminal alkyne **4.25** was coupled with 4-*tert*-butyliodobenzene **4.23** yielding symmetrical alkyne **4.26** in moderate yield (**Scheme 4-11**).



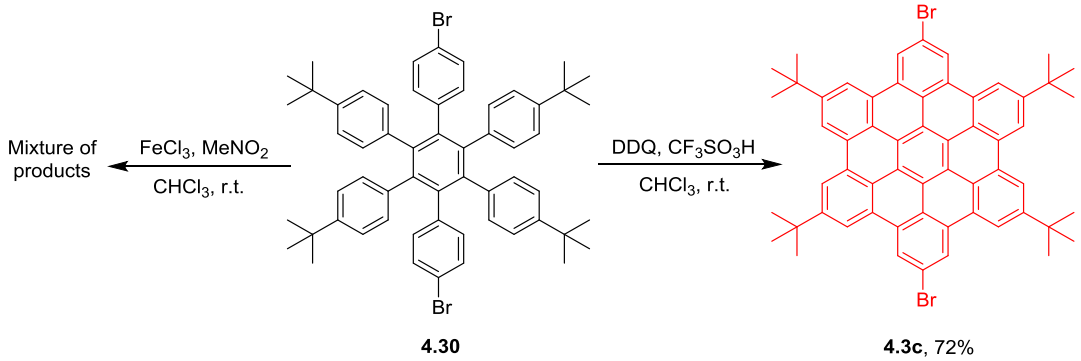
Scheme 4-11: Cross-coupling reaction between **4.23** and **4.25** to get symmetrical alkyne **4.26**.

Oxidation of the above synthesized 4,4′-*tert*-butyldiphenylacetylene **4.26** with I_2 in DMSO at 155 °C resulted in the 1,2-diketone **4.27**with 82% isolated yield after chromatographic purification (**Scheme 4-12**). Two-fold Knoevenagel condensation between **4.27** and 1,3-diarylacetone **4.28** in refluxing ethanol yielded the substituted tetraarylcyclopentadienone **4.29** (60%). The mixture of diphenylacetylene **4.26** and tetraarylcyclopentadienone **4.29** was then reacted in a [4+2] cycloaddition in refluxing diphenylether to give substituted HPB **4.30** in excellent yield (89%). This compound was found to have poor solubility in dichloromethane but it was fairly soluble in chloroform.



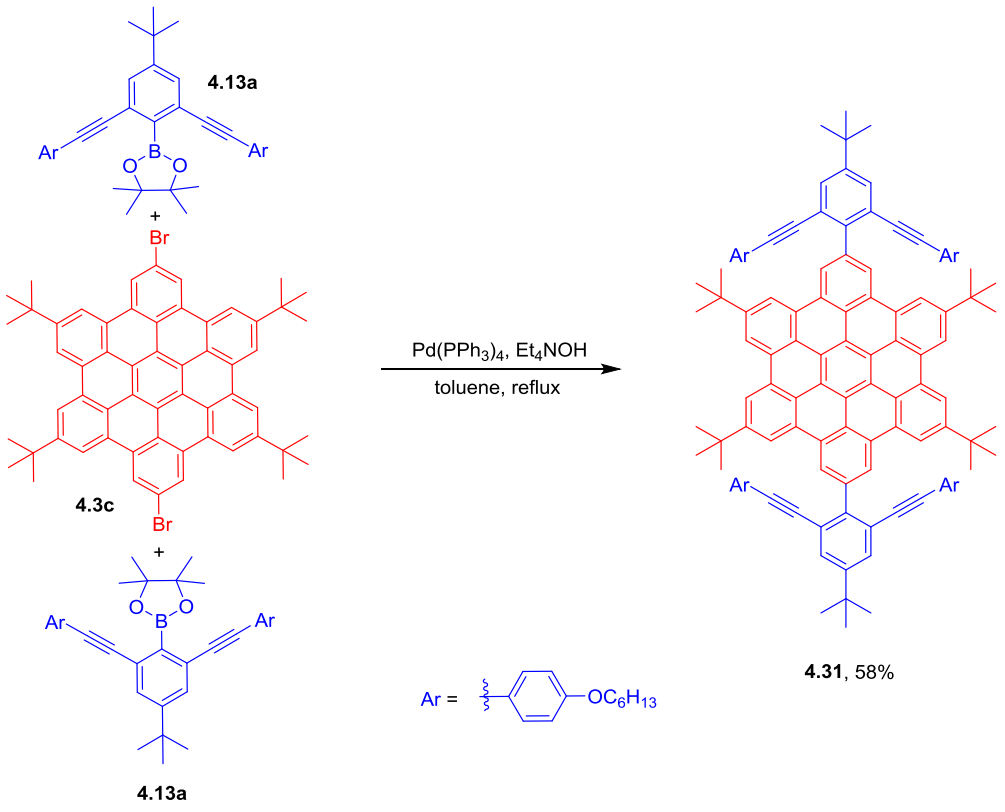
Scheme 4-12: Synthesis of substituted hexaphenylbenzene **4.30**.

We attempted to transform the appropriately substituted hexaphenylbenzene into the corresponding HBC by applying the Scholl conditions ($FeCl_3/MeNO_2$) in chloroform solvent suitable for synthesizing alkyl-substituted derivatives.[31] However, reaction of the HPB **4.30** bearing two bromo substituents under these oxidative conditions resulted in an inseparable mixture of products (**Scheme 4-13**). According to NMR spectrometric analysis of crude product, the mixture was found to contain fully cyclized and partially cyclized products. Using the cyclodehydrogenation conditions with DDQ/CF_3SO_3H in chloroform, we were able to synthesize HBC **4.3c** in good yield (72%).



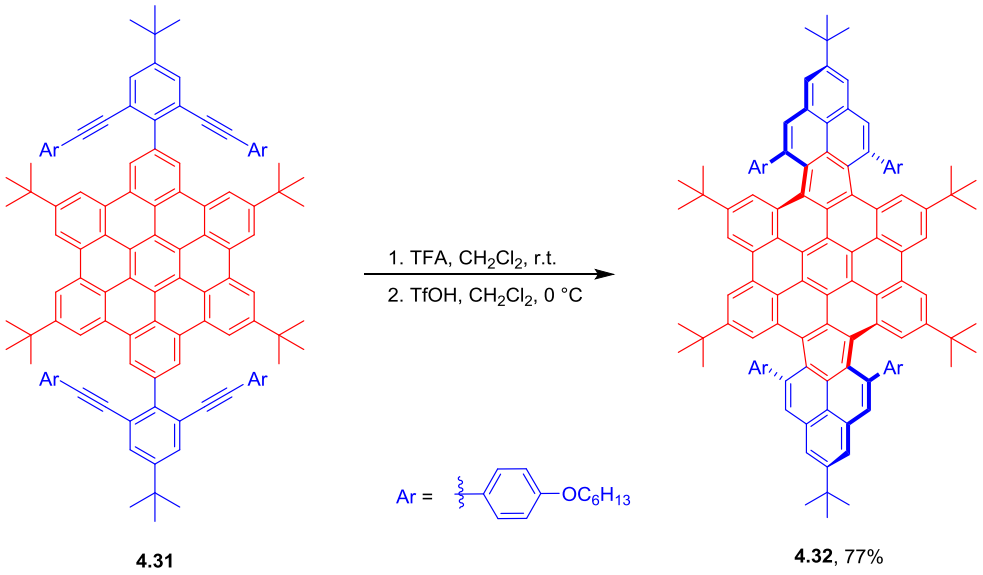
Scheme 4-13: Synthesis of substituted HBC **4.3c** from **4.30** carrying two bromines.

We then proceeded to do a double Suzuki cross-coupling reaction between **4.3c** and **4.13a** (**Scheme 4-14**). The tetrayne product **4.31** was isolated in 58% yield after purification by column chromatography.



Scheme 4-14: Double Suzuki cross-coupling reaction between **4.3c** and **4.13a** to form tetrayne **4.31**.

The synthesis of final product **4.32** was accomplished under our standard alkyne benzannulation condition that involves the treatment of compound **4.31** in anhydrous dichloromethane with TFA at room temperature followed by the addition of TfOH at 0 °C (**Scheme 4-15**). Compound **4.32**, a red colored solid was obtained in 77%.



4.31 **4.32**, 77%

Scheme 4-15: Four-fold alkyne benzannulation reaction of compound **4.31** to get compound **4.32**.

4.3.1 Possible isomers of compound 4.32

Depending upon the modes of four-fold alkyne cyclization, compound **4.31** can possibly exist as five isomers: **A**, **B**, **C**, **D** and **E** (**Figure 4-4**). Isomers **B** and **E** are chiral (no plane of symmetry) whereas **A**, **C** and **D** have plane of symmetry and hence are achiral (meso compounds). Any molecule that lacks both inversion center (*i*) and mirror plane (σ) is chiral. Isomers **B** and **E** belong to point groups C_1 and D_2 respectively. Similarly, achiral isomers **A**, **C** and **D** belong to point groups C_{2v}, C_{2h} and C_{2h} respectively.

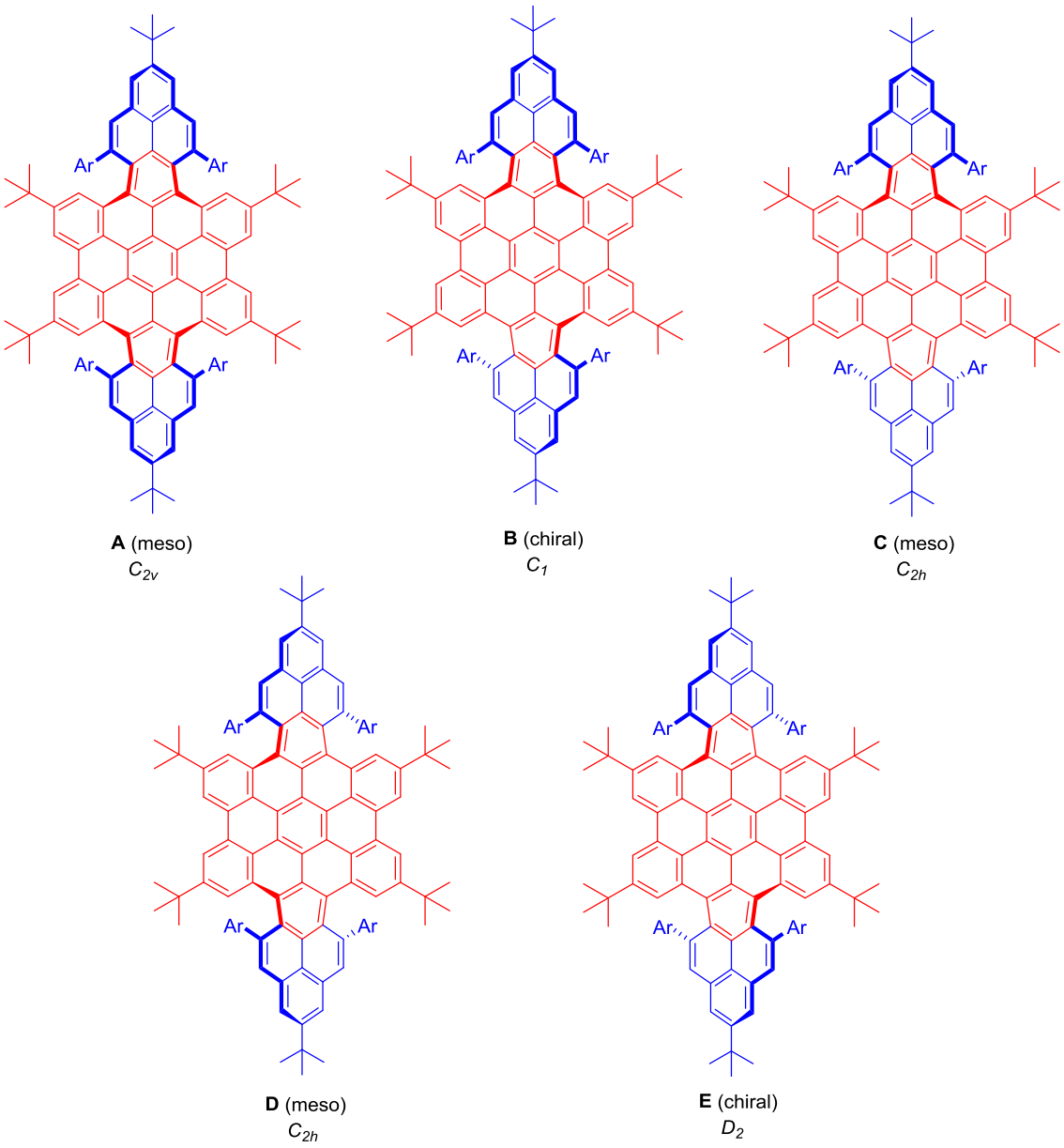


Figure 4-6: All the possible isomers of compound **4.32**.

4.3.2 Reason for the Formation of Isomers D and E

If we consider the step-wise cyclization of 4 alkyne moieties in compound **4.30**, it would be easier in understanding the formation of only isomers **D** and **E** (**Figure 4-4**). After the first alkyne cyclization, an intermediate bearing three alkyne moieties **F** is formed. If first alkyne cyclization happens from the top face as in **F**, the alkyne **2** is pushed down and is forced to react only from the bottom face (opposite of first alkyne). However, alkyne **3** has two choices: top or bottom. If alkyne **3** cyclizes from top, compound **G** is formed. If alkyne **3** cyclizes from the bottom face, compound **H** is generated. Once alkyne **3** reacts, it fixes the position of alkyne **4**. In compound **G**, alkynes **2** and **4** are forced to cyclize from bottom resulting the formation of meso isomer **D**. On the other hand, compound **H** generates chiral isomer **E**. Isomers **A**, **B** and **C** are not likely to get formed because having the two alkynes on the same phenyl group cyclize on the same face imparts a very high strain penalty.

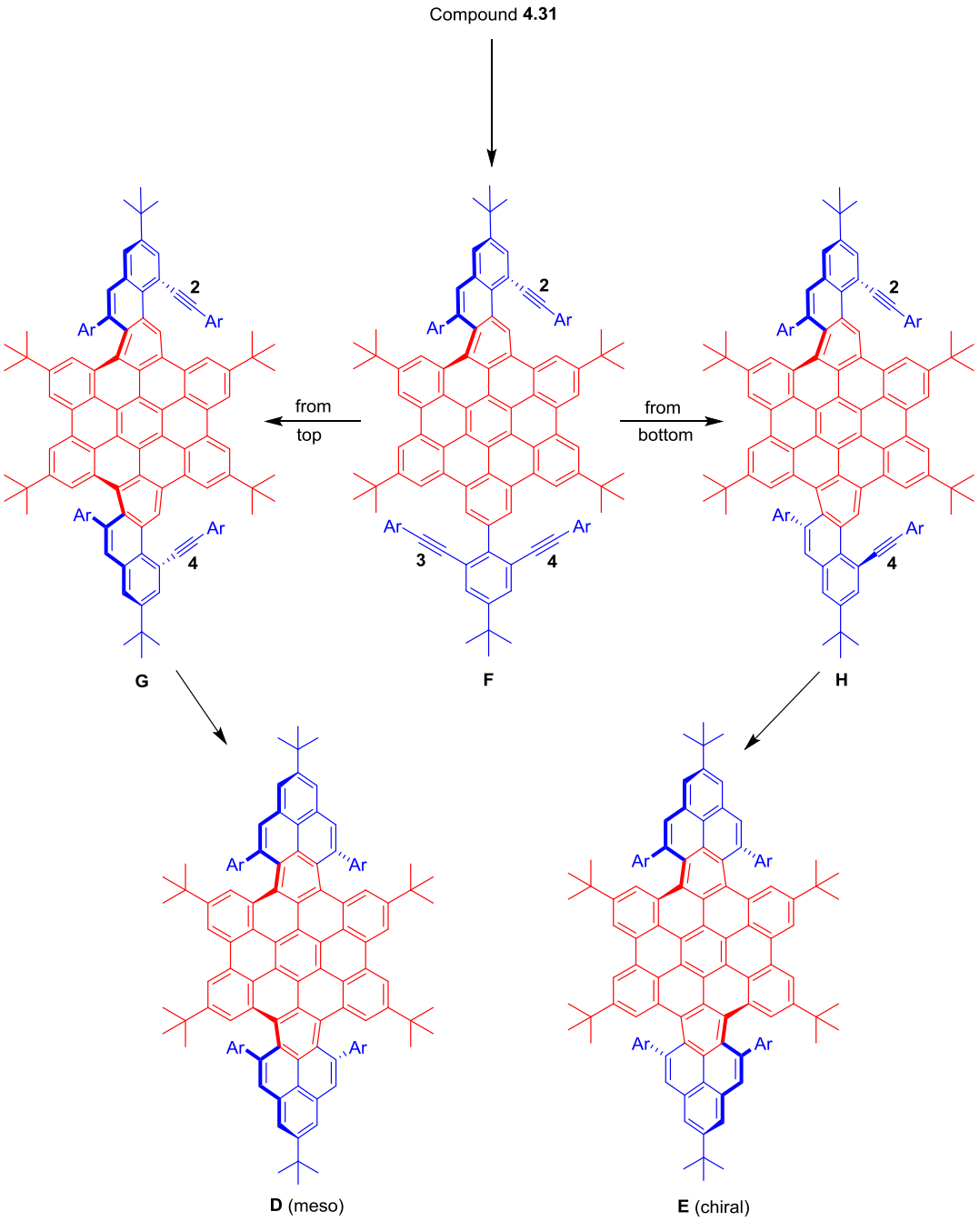


Figure 4-7: Explanation for the formation of isomers **D** and **E**.

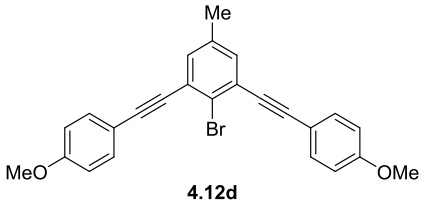
4.4 Conclusion

In summary, this study has explored the synthesis and characterization of two types of expanded HBC molecules that are chiral and have greater number of aromatic sextets than parent HBCs. The successful synthesis of these compounds was accomplished by employing Suzuki cross-coupling reaction between two coupling partners followed by alkyne benzannulation reaction of the coupled product. Due to high solubility in common organic solvents, the synthesized compounds were fully characterized, the enantiomers were separated in chiral HPLC, and the structure was unambiguously confirmed by X-ray crystallographic analysis. The study of chiroptical properties such as CD spectra and the potential application of those compounds as organic materials are under way.

4.5 Experimental

General Methods: Reagents were purchased reagent grade from commercial suppliers and used without further purification unless otherwise noted. CH_2Cl_2 was purified using a PureSolv MD 5 solvent purification system. Where appropriate, reactions were performed in standard, flame-dried glassware under an inert atmosphere of N_2. Purification of the crude products was carried out by column chromatography using silica gel irregular 60 Å (40-60 micron) from VWR International. Analytical TLC was performed on glass sheets covered with silica gel 60 F_{254} from Millipore a Corporation. The TLC plates were visualized under ultraviolet light (UV, 254 nm) light. NMR spectra were recorded on a 400

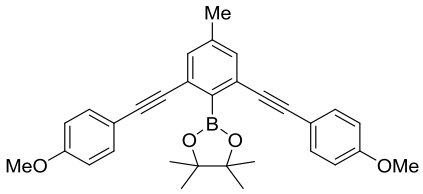
or 500 MHz NMR spectrometer in $CDCl_3$. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26). Data for ^1H NMR are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m= multiplet, br=broad), coupling constant (J) in Hertz, and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$, δ 77.16). Infrared (IR) spectra were recorded on an ATR/FTIR spectrometer as a thin film on a composite of zinc selenide and diamond crystal and only major functional group peaks are reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a high-resolution Q-TOF mass spectrometer (ionization mode: ESI). Compounds **4.2a-c**, **4.5a**, **4.5b**, **4.12a-d**, **4.25** and **4.27** were synthesized according to reported procedures.



4.12d

To a solution of 2-bromo-5-methyl-1,3-diiodobenzene **4.9a** (1.09 g, 2.57 mmol) and the terminal alkyne **4.11a** (1.3 g, 9.8 mmol) in THF (70 mL) and Et_3N (40 mL), were added CuI ( ) and $Pd(PPh_3)_2Cl_2$ ( ). The resulting mixture was stirred under a N_2 atmosphere at room temperature for 13 h. The ammonium salt was then removed by filtration. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, hexane:dichloromethane = 1:1, v/v) to yield pure **4.12d** as a colorless solid (1.09 g, yield 99%): R_f = 0.28 (hexane/dichloromethane 1:1); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.54 – 7.51 (m, 4H), 7.30 (s, 2H), 6.91 – 6.88 (m, 4H), 3.84 (s, 6H),

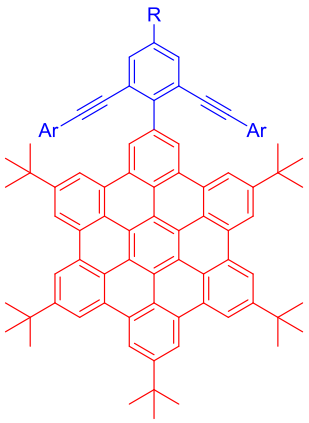
2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.1, 136.8, 133.4, 133.1, 126.4, 125.0, 115.2, 114.2, 93.9, 87.3, 55.5, 20.7.

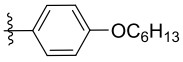


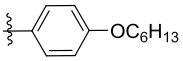
4.13d

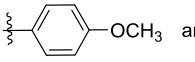
To a solution of **4.12d** (770 mg, 1.78 mmol) in THF (60 mL) at -78 °C was added a solution of n-butyllithium in hexanes (3.5 mL, 1.6 M, 5.6 mmol). After stirring for 1.5 h at -78 °C, isopropoxyboronic acid pinacol ester (522 mg, 2.8 mmol) was added, the reaction removed from the cooling bath and allowed to warm. Upon reaching room temperature the reaction was quenched by the addition of H_2O, and then extracted with dichloromethane. The extract was washed with water, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane:dichloromethane = 1:3, v/v) to yield pure **4.13d** as a colorless solid (426 mg, yield 52%): R_f = 0.41 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 – 7.43 (m, 4H), 7.29 (s, 2H), 6.89 – 6.85 (m, 4H), 3.83 (s, 6H), 2.31 (s, 3H), 1.37 (s, 12H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.7, 139.0, 133.1, 132.2, 127.1, 115.8, 114.1, 90.2, 88.6, 84.3, 55.4, 25.2, 21.2.

Compound 4.19



4.19a: Ar =  and R = *t*-butyl

4.19b: Ar =  and R = CH_3

4.19c: Ar =  and R = CH_3

Bromo-HBC **4.2c** (1.0 equiv.) and 2,6-diynylphenyl borate **4.13** (1.0 equiv.) were dissolved in toluene. A solution of Et_4NOH (10 mL, 1M) was also added and the resulting solution was thoroughly degassed by bubbling with N_2 gas. $Pd(PPh_3)_4$ (0.1 equiv.) was then added to the solution and the reaction was stirred under a N_2 atmosphere for 24 h. The reaction was cooled, diluted with water, extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography.

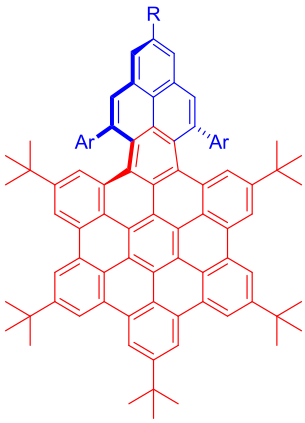
4.19a: This compound was synthesized by using **4.2c** (68 mg, 0.08 mmol), **4.13a** (87 mg, 0.13 mmol), Et_4NOH (10 mL) and $Pd(PPh_3)_4$ (21 mg, mmol). Purification by column

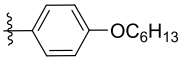
chromatography (silica gel, hexane:DCM = 4:1, v/v) afforded **4.19a** (68 mg, 64%) as a yellow solid.

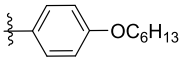
4.19b: This compound was synthesized by using **4.2c** (373 mg, 0.423 mmol), **4.13b** (387 mg, 0.625 mmol), Et_4NOH (15 mL) and $Pd(PPh_3)_4$ (38 mg, mmol). Purification by column chromatography (silica gel, hexane:EtOAc = 9:1, v/v) afforded **4.19b** (320 mg, 59%) as a yellow solid.

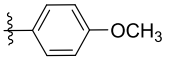
4.19c: This compound was synthesized by using **4.2c** (329 mg, 0.373 mmol), **4.13c** (257 mg, 0.537 mmol), Et_4NOH (20 mL) and $Pd(PPh_3)_4$ (56 mg, mmol). Purification by column chromatography (silica gel, hexane:DCM = 2:3, v/v) afforded **4.19c** (253 mg, 59%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.09 (s, 2H), 9.63 (s, 2.0 Hz, 8H), 9.58 (s, 2H), 7.91 (s, 2H), 7.29 – 7.20 (m, 4H), 6.59 – 6.48 (m, 4H), 3.61 (s, 6H), 2.75 (s, 3H), 2.10 (s, 27H), 1.85 (s, 18H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.5, 149.5, 149.3, 149.3, 142.5, 137.4, 136.6, 133.4, 133.1, 130.9, 130.8, 130.6, 130.1, 125.5, 125.0, 124.3, 124.3, 124.2, 124.1, 121.3, 121.04, 120.97, 120.8, 119.8, 119.2, 119.1, 119.0, 115.1, 113.8, 93.4, 88.5, 55.1, 36.0, 35.8, 32.3, 32.0, 21.1; MS (MALDI-TOF): calcd for $[C_{87}H_{76}O_2]^+$ 1152.58, found 1152.65.

Compound 4.20



4.21a: Ar =  and R = *t*-butyl

4.21b: Ar =  and R = CH_3

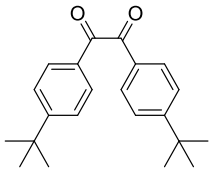
4.21c: Ar =  and R = CH_3

In a 100 mL flame-dried flask, compound **4.19** (0.1 mmol) was dissolved in 40 mL of anhydrous CH_2Cl_2. Trifluoroacetic acid (570 mg, 5 mmol) was added and the reaction stirred under nitrogen. After stirring for 1 h at room temperature (TLC showed no residual **4.19**), the reaction was cool down to 0 °C. A CH_2Cl_2 solution (1 mL) of triflic acid (15 mg, 0.1 mmol) was added slowly. After stirring for 20 min at 0 °C, the reaction was quenched with saturated $NaHCO_3$ solution (5 mL). The solution was then washed with H_2O (2 x 30 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by column chromatography.

4.21a: This compound was synthesized from **4.19a** (57 mg, 0.04 mmol). Purification by column chromatography (silica gel, hexane:DCM = 7:3, v/v) afforded **4.21a** (44 mg, 77%) as a red solid.

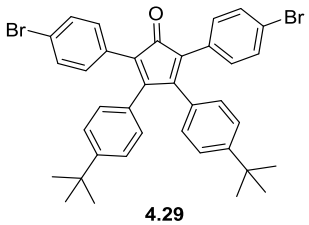
4.21b: This compound was synthesized from **4.19b** (243 mg, 0.188 mmol). Purification by column chromatography (silica gel, hexane:DCM = 3:2, v/v) afforded **4.21b** (163 mg, 67%) as a red solid.

4.21c: This compound was synthesized from **4.19c** (84 mg, 0.07 mmol). Purification by column chromatography (silica gel, hexane:DCM = 3:2, v/v) afforded **4.21c** (59 mg, 70%) as an orange solid. MS (MALDI-TOF): calcd for $[C_{87}H_{76}O_2]^+$ 1152.58, found 1152.43.



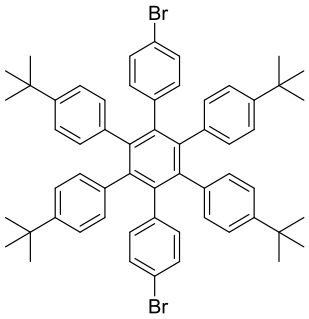
4.27

A mixture of 4,4'-*tert*-butyldiphenylacetylene **4.25** (2.0 g, 6.9 mmol) and iodine (1.06 g, 4.18 mmol) in dimethyl sulfoxide (35 mL) was stirred at 155 °C overnight. After cooling to room temperature, the reaction mixture was poured into an aqueous sodium thiosulfate solution (100 mL) and extracted with dichloromethane. The organic phase was washed with water and dried ($MgSO_4$). After evaporation of the solvent the residue was purified by column chromatography with hexane/dichloromethane 1:1 to yield **4.26** (1.8 g, 82%) as a grey solid: R_f = 0.26 (1:1 dichloromethane/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, J = 8.5 Hz, 4H), 7.52 (d, J = 8.6 Hz, 4H), 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 194.7, 159.0, 130.7, 130.0, 126.1, 35.5, 31.1; IR (cast film) ν 2962, 1669, 1602, 1221, 1181 cm^{-1}.



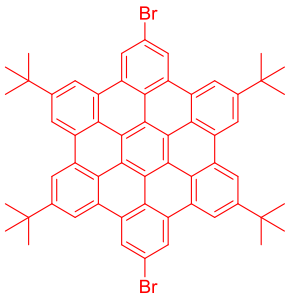
4.29

A solution of potassium hydroxide (261 mg, 4.65 mmol) in ethanol (7 mL) was added to a refluxing solution of **4.26** (632 mg, 1.96 mmol) and 1,3-bis(4-bromophenyl)propan-2-one **4.27** (705 mg, 1.92 mmol) in ethanol (20 mL). After the addition of KOH, the yellow solution changed to blue. The reaction was kept stirring for 30 minutes at reflux. It was cooled and the solvent was removed under reduced pressure. The crude was purified by column chromatography (silica gel, hexane:DCM = 1:1, v/v) to afford compound **4.28** (759 mg, 60%) as a purple solid: R_f = 0.18 (1:4 dichloromethane/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (d, J = 8.4 Hz, 4H), 7.20 (d, J = 8.1 Hz, 4H), 7.14 (d, J = 8.3 Hz, 4H), 6.82 (d, J = 8.0 Hz, 4H), 1.30 (s, 18H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.8, 155.4, 152.3, 131.8, 131.3, 130.0, 129.7, 129.1, 125.0, 124.0, 121.8, 34.9, 31.3.



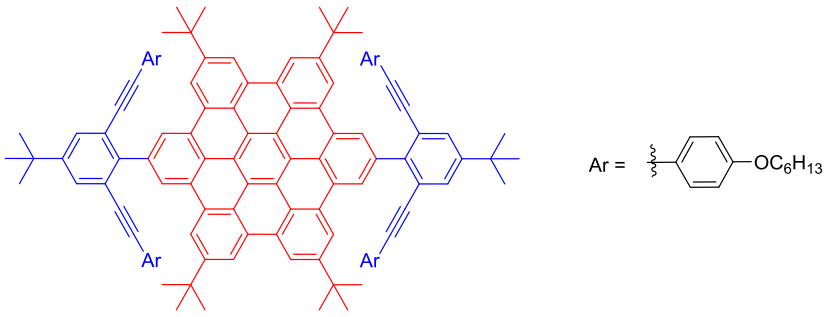
4.30

A purple solution of **4.25** (781 mg, 2.69 mmol) and **4.28** (730 mg, 1.12 mmol) in diphenyl ether (15 mL) was bubbled with N_2 for 10 minutes. The solution was then refluxed at 250 °C for 20 h. After cooling to room temperature, the solid was precipitated with cold hexane and filtered to get **4.29** (913 mg, 89%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 – 6.93 (m, 4H), 6.87 – 6.81 (m, 8H), 6.73 – 6.68 (m, 4H), 6.67 – 6.60 (m, 8H), 1.13 (s, 36H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.1, 140.7, 140.1, 139.2, 137.4, 133.3, 131.1, 129.7, 123.6, 119.4, 34.3, 31.4.



4.3c

A solution of **4.29** (107 mg, 0.117 mmol) in anhydrous chloroform (30 mL) was cooled to 0 °C. Then, DDQ (237 mg, 1.04 mmol) was added followed by the addition of CF_3SO_3H (0.5 mL). The resulting solution was stirred at 0 °C for 20 min. and at room temperature for 3 h. The reaction was quenched by saturated aq. K_2CO_3 solution, extracted in DCM and dried over $MgSO_4$. The solvent was removed under reduced pressure to get fairly pure **4.3c** (76 mg, 72%) as a pale yellow solid.



4.31

Dibromo-HBC **4.3c** (58 mg, 0.06 mmol) and 2,6-diynylphenyl borate **4.13a** (123 mg, 0.186 mmol) were dissolved in toluene. A solution of Et_4NOH (10 mL, 1M) was also added and the resulting solution was thoroughly degassed by bubbling with N_2 gas for 20 minutes. $Pd(PPh_3)_4$ (38 mg, mmol) was then added to the solution and the reaction was stirred under a N_2 atmosphere for 14 h. The reaction was cooled, diluted with water, extracted with

CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane:DCM = 4:1, v/v) to afford compound **4.30** (63 mg, 58%) as a yellow solid: R_f = 0.18 (1:4 dichloromethane/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.86 (s, 4H), 9.40 (d, J = 1.7 Hz, 4H), 9.35 (d, J = 1.7 Hz, 4H), 7.93 (s, 4H), 7.15 – 7.06 (m, 8H), 6.48 – 6.40 (m, 8H), 3.70 (t, J = 6.6 Hz, 8H), 1.65 (s, 36H), 1.62 – 1.58 (m, 26H), 1.34 – 1.27 (m, 10H), 1.26 – 1.21 (m, 14H), 0.83 (t, J = 6.9 Hz, 12H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.1, 150.6, 149.4, 142.3, 136.6, 133.2, 130.8, 130.6, 130.1, 130.0, 125.5, 125.0, 124.1, 123.8, 121.2, 121.2, 119.7, 118.9, 114.8, 114.4, 93.1, 88.8, 68.0, 35.8, 34.9, 32.0, 31.6, 31.5, 29.1, 25.7, 22.6, 14.1.

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4.6 References

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Appendix

^{1}H and ^{13}C spectra for new compounds

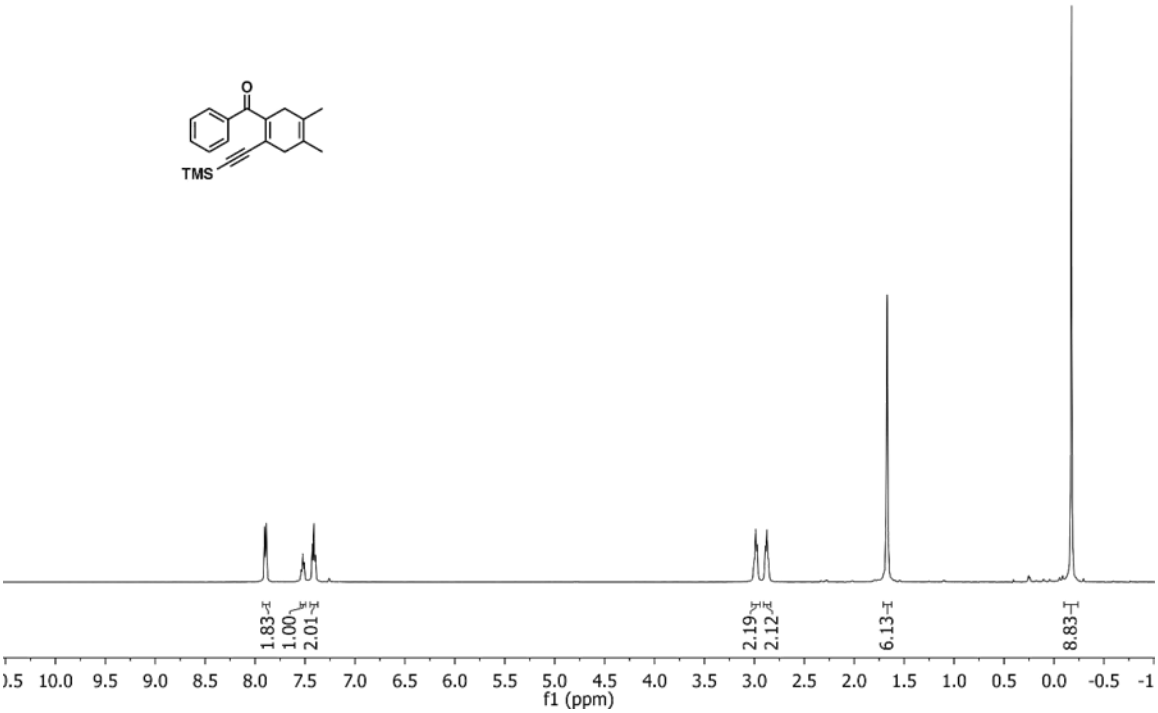


Figure S1. ^{1}H NMR spectrum of compound **2.5a**.

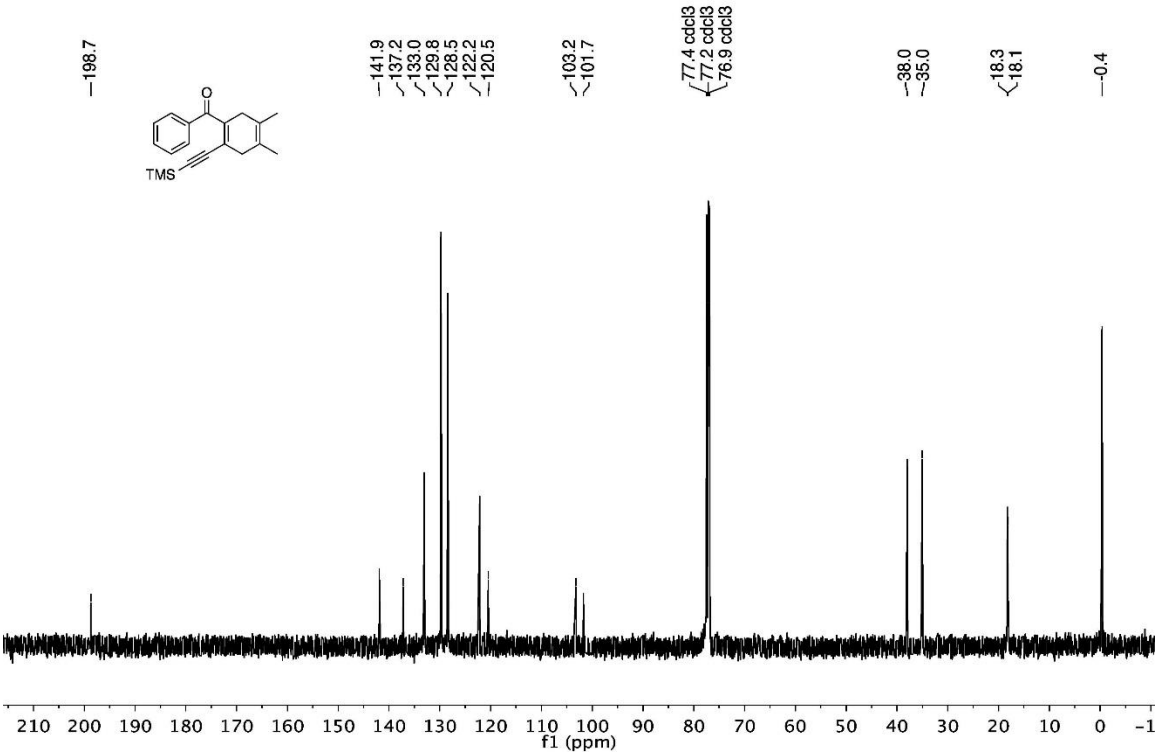


Figure S2. ^{13}C NMR spectrum of compound **2.5a**.

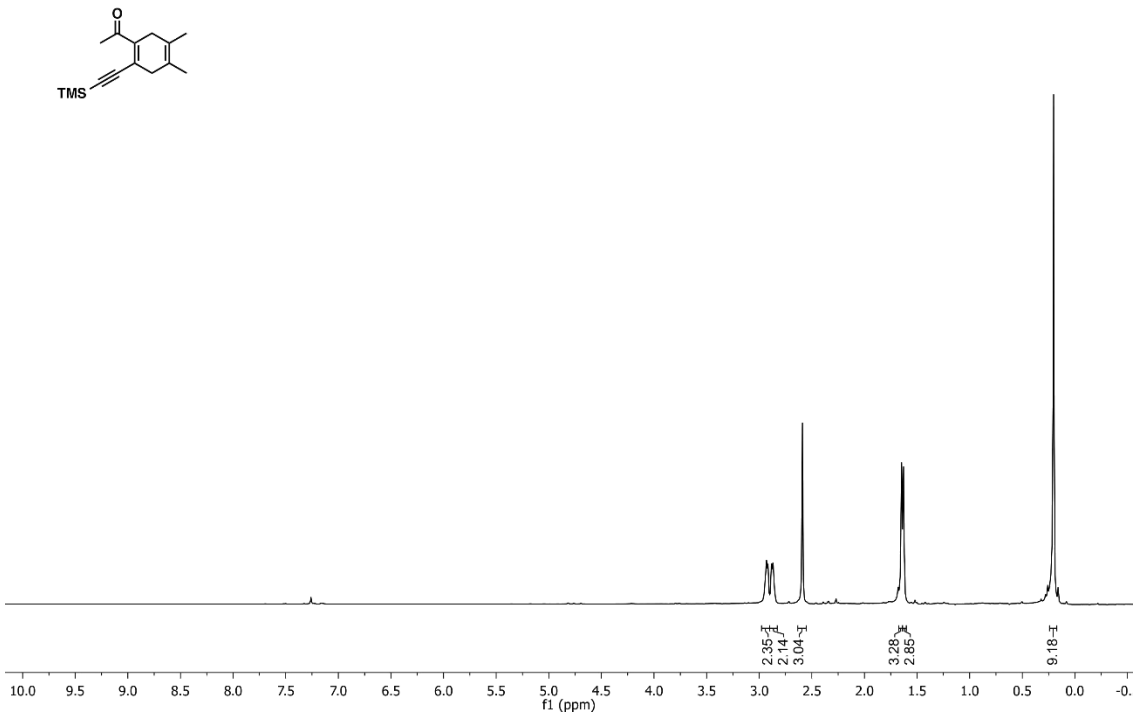


Figure S3. ^{1}H NMR spectrum of compound **2.5c**.

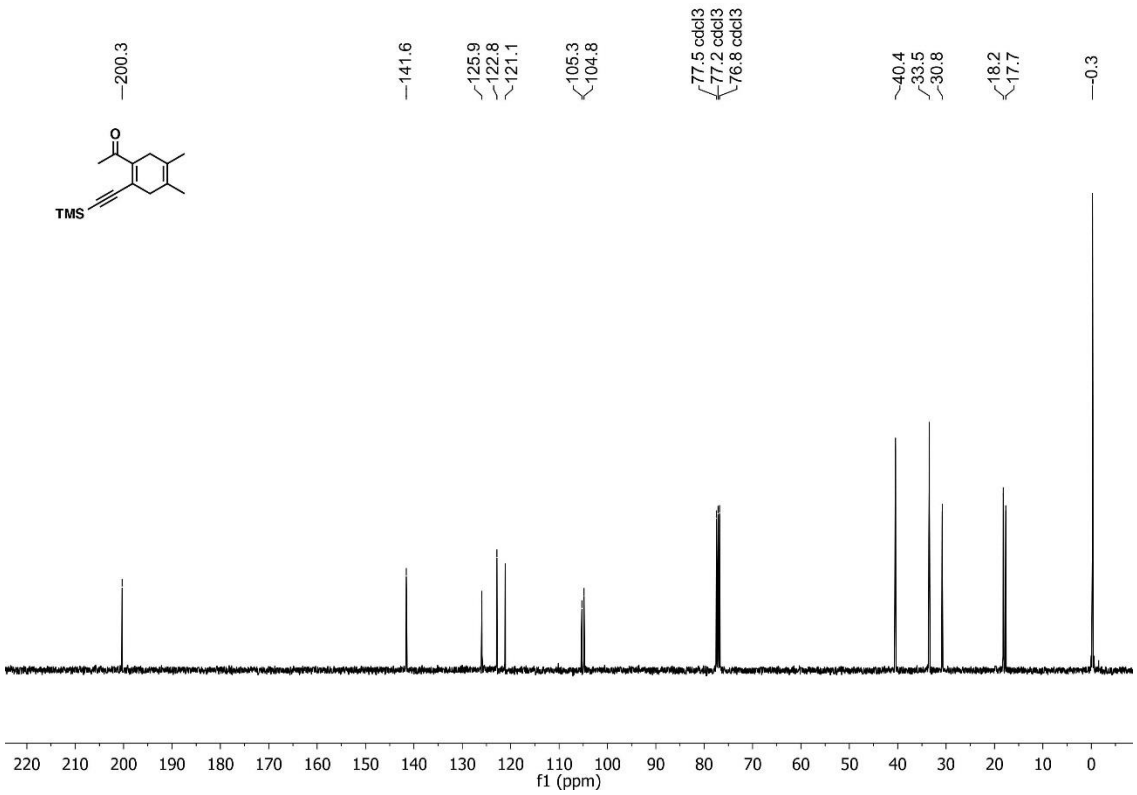


Figure S4. ^{13}C NMR spectrum of compound **2.5c**.

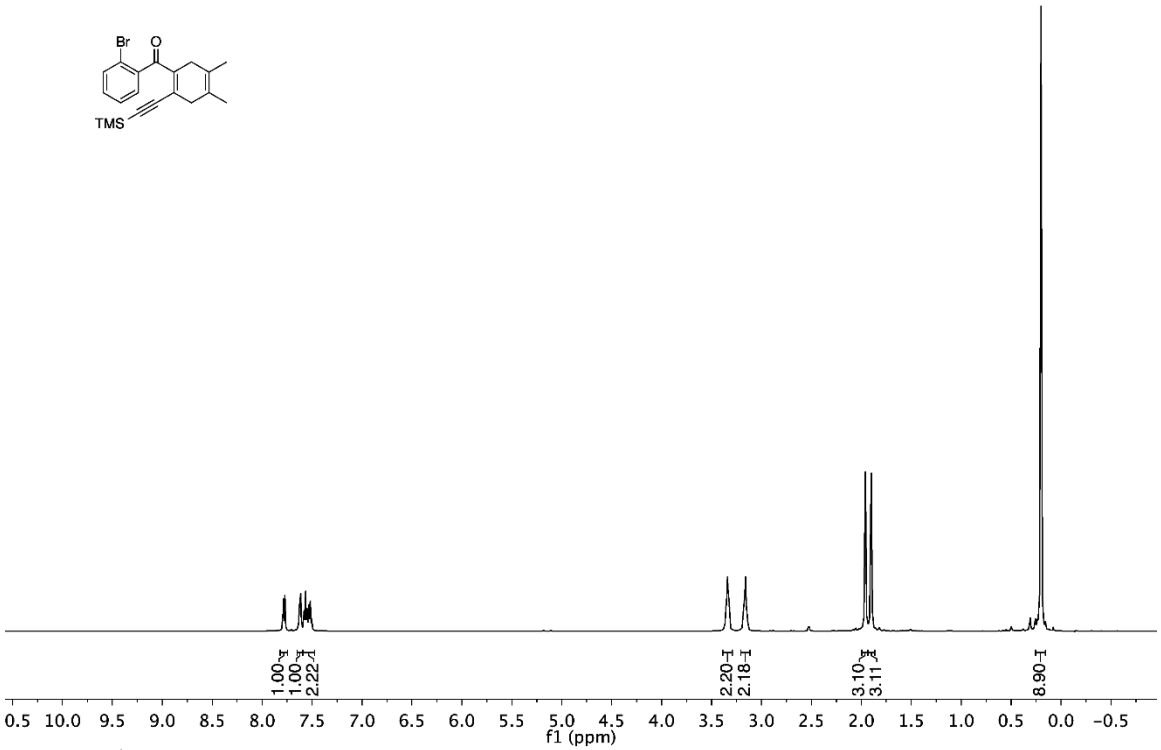


Figure S5. ^{1}H NMR spectrum of compound **2.5d**.

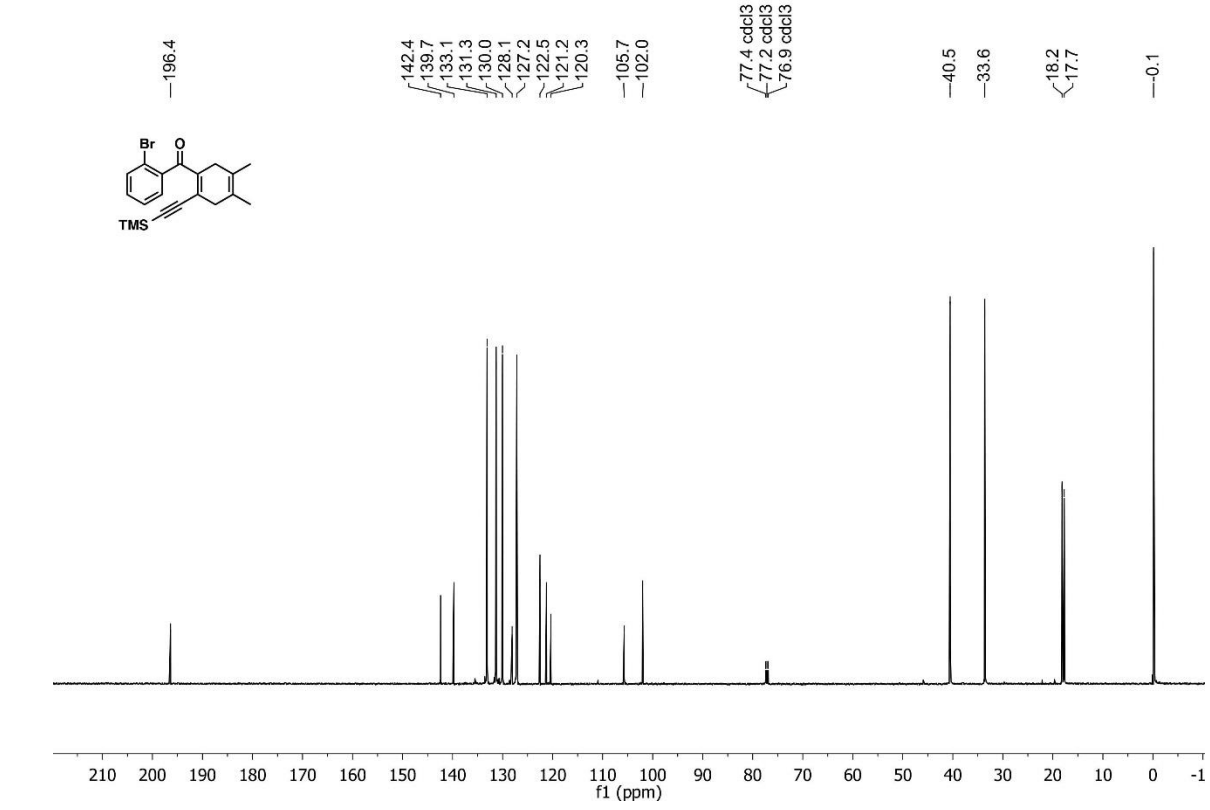


Figure S6. ^{13}C NMR spectrum of compound **2.5d**.

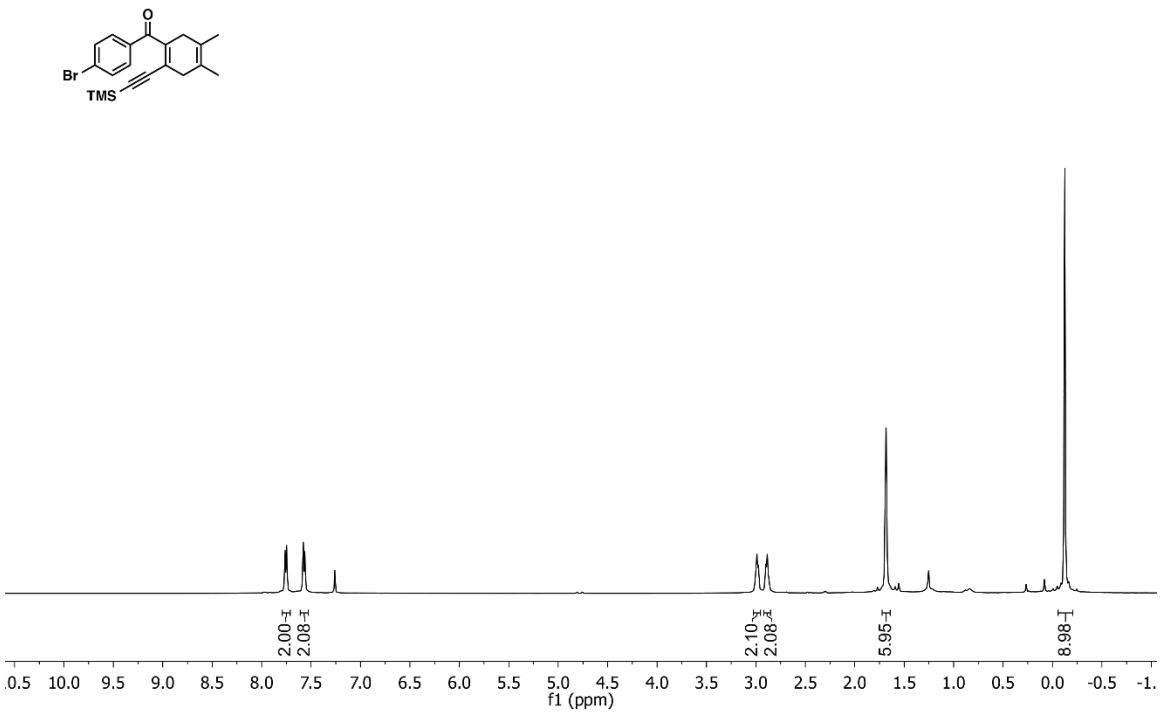


Figure S7. [1]H NMR spectrum of compound **2.5e**.

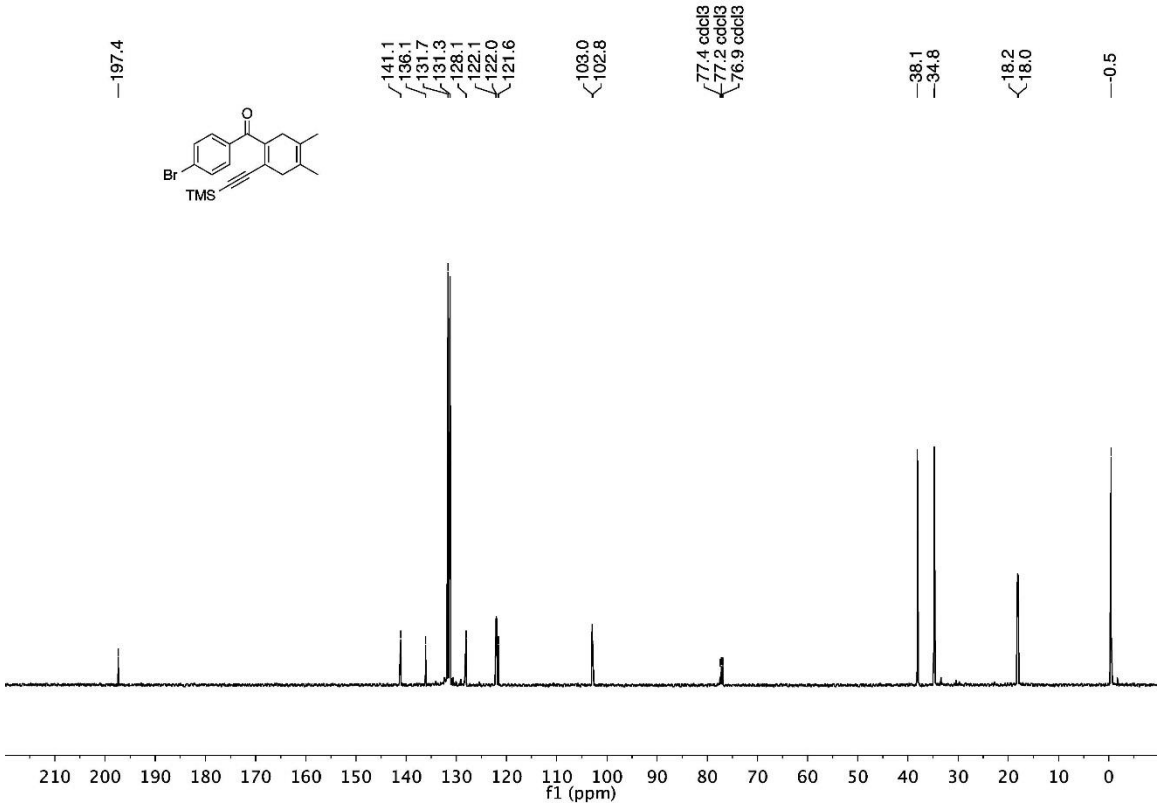


Figure S8. [13]C NMR spectrum of compound **2.5e**.

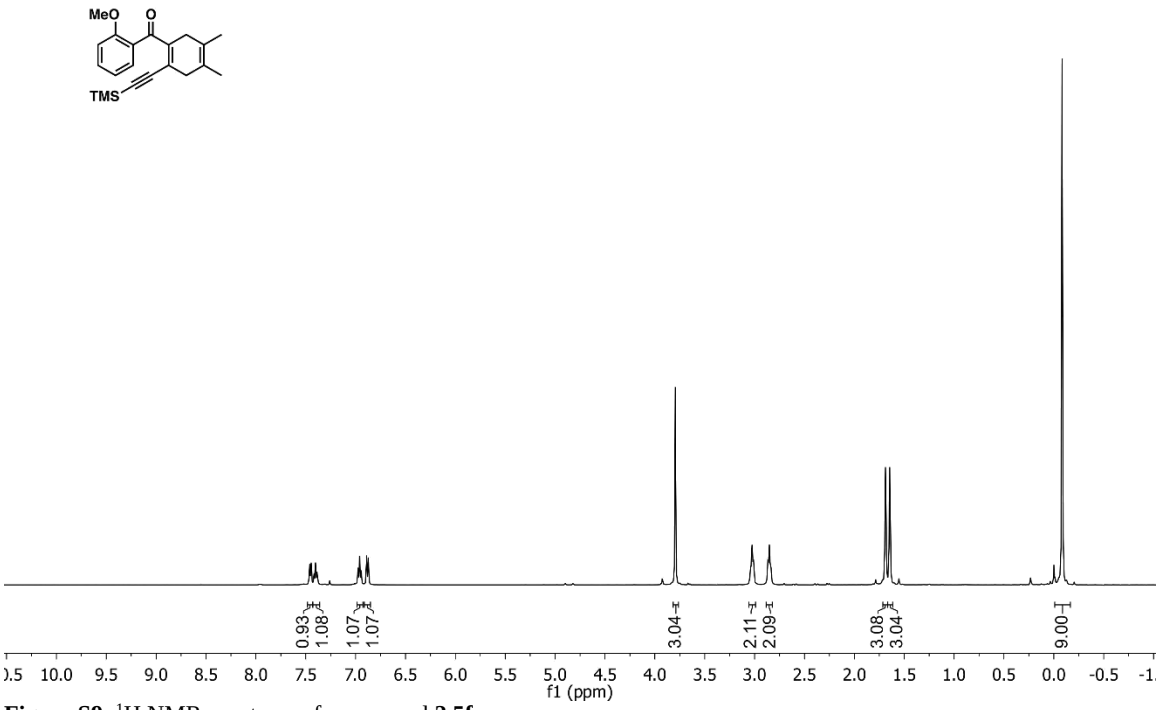


Figure S9. ^{1}H NMR spectrum of compound **2.5f**.

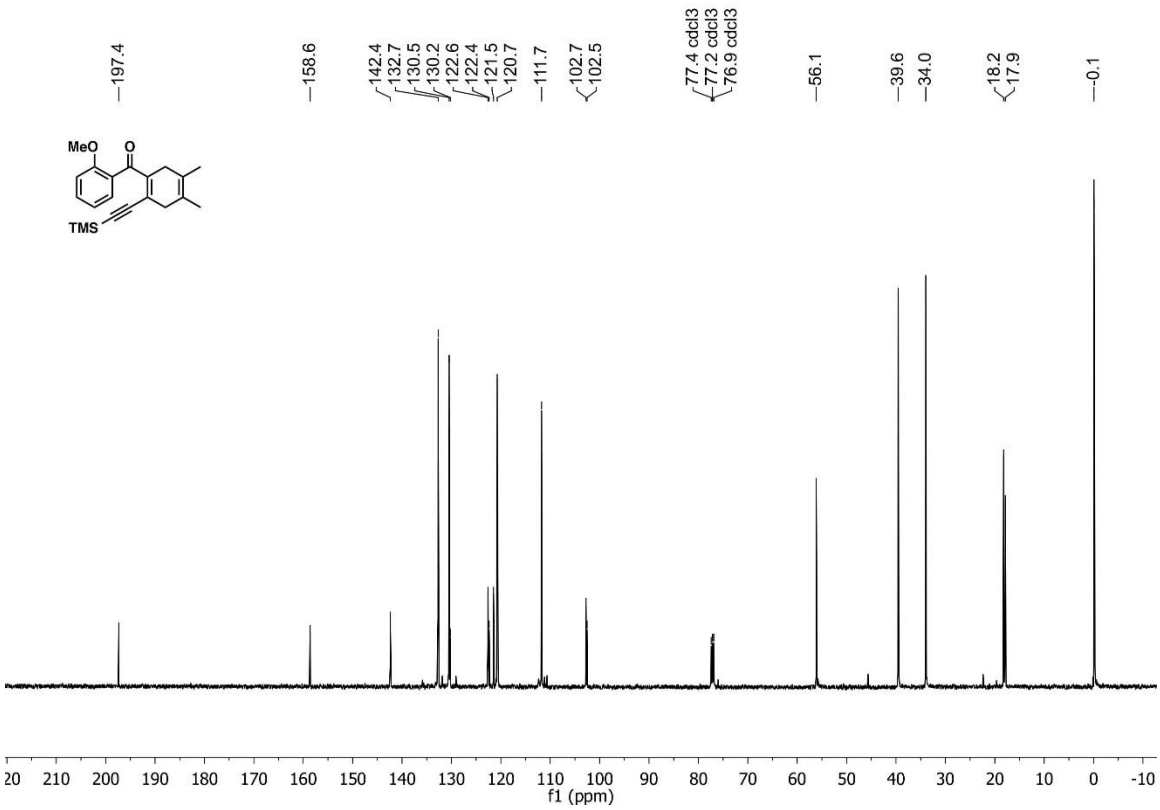


Figure S10. ^{13}C NMR spectrum of compound **2.5f**.

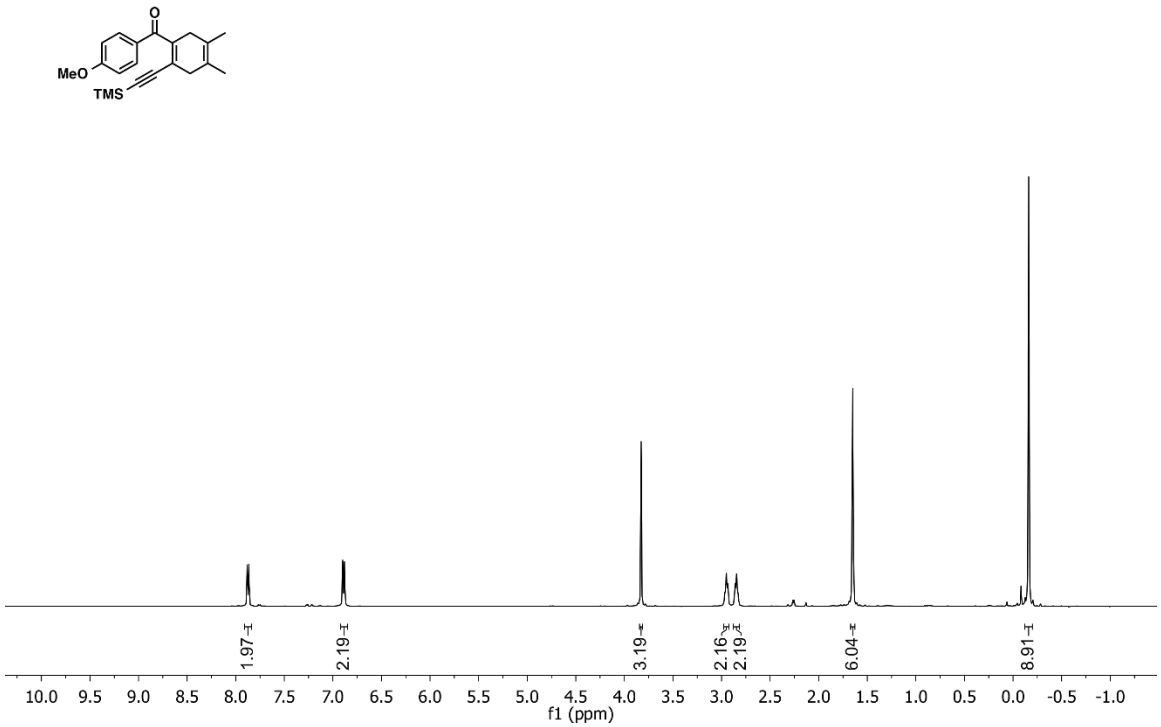


Figure S11. [1]H NMR spectrum of compound **2.5g**.

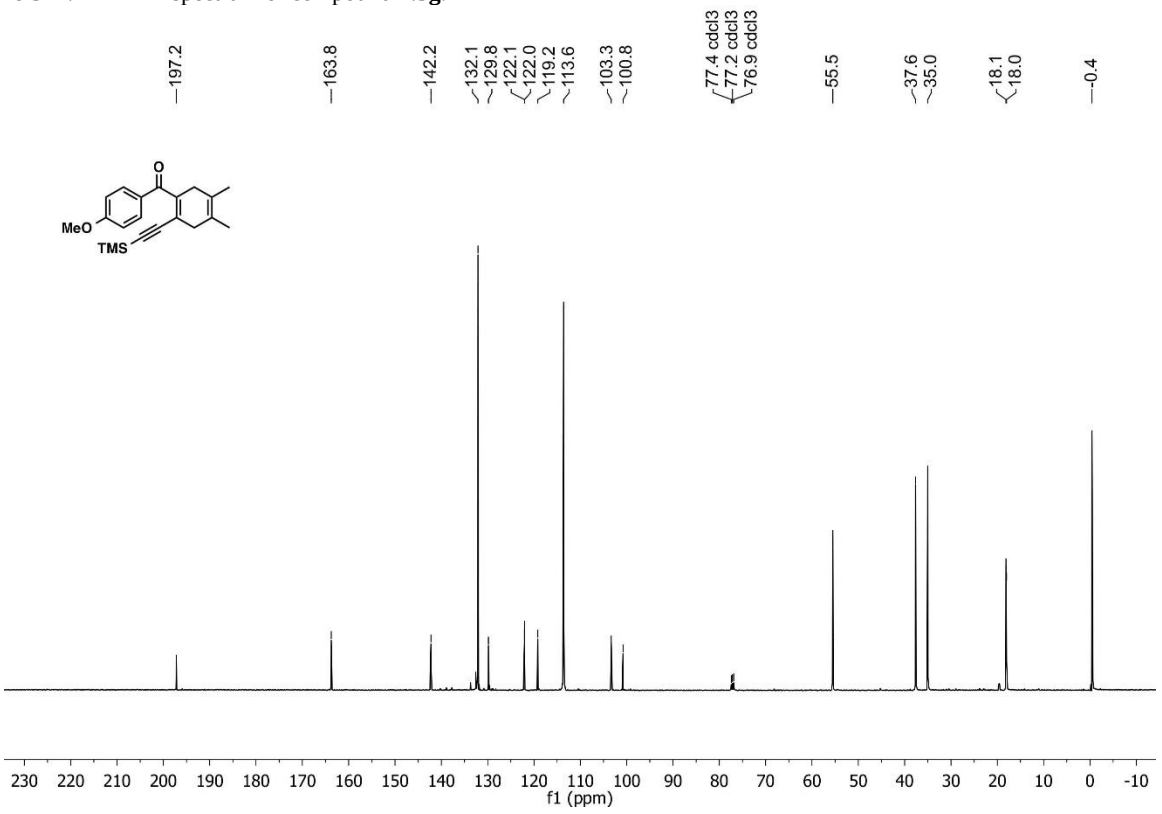


Figure S12. [13]C NMR spectrum of compound **2.5g**.

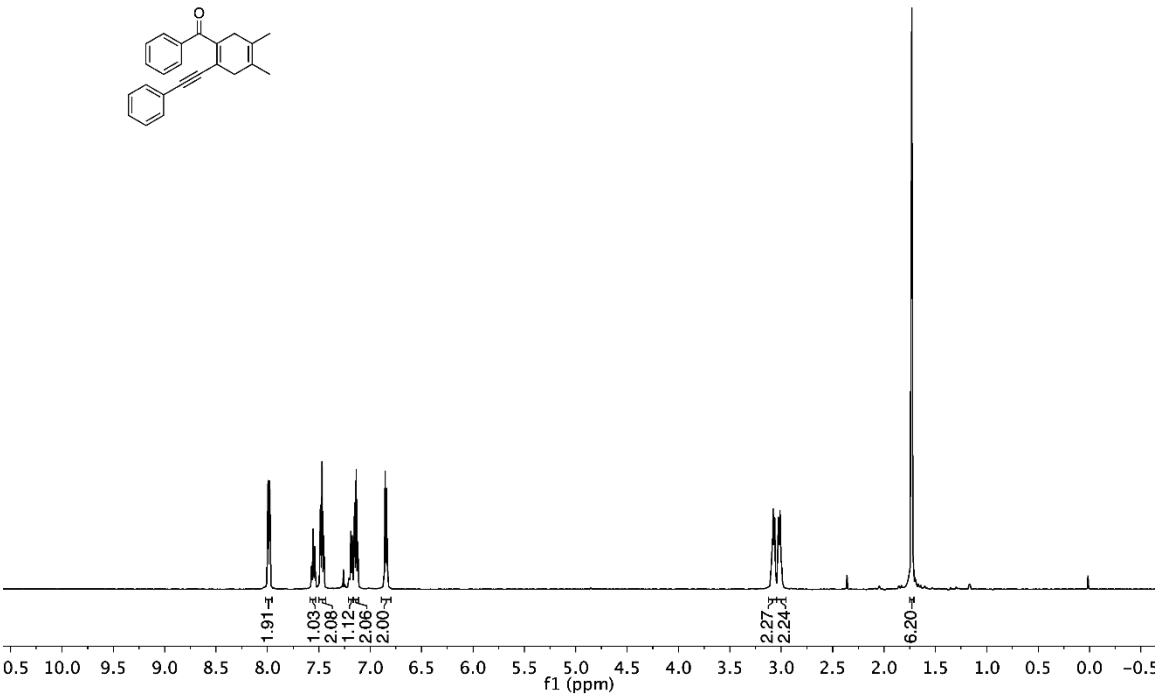


Figure S13. [1]H NMR spectrum of compound **2.5h**.

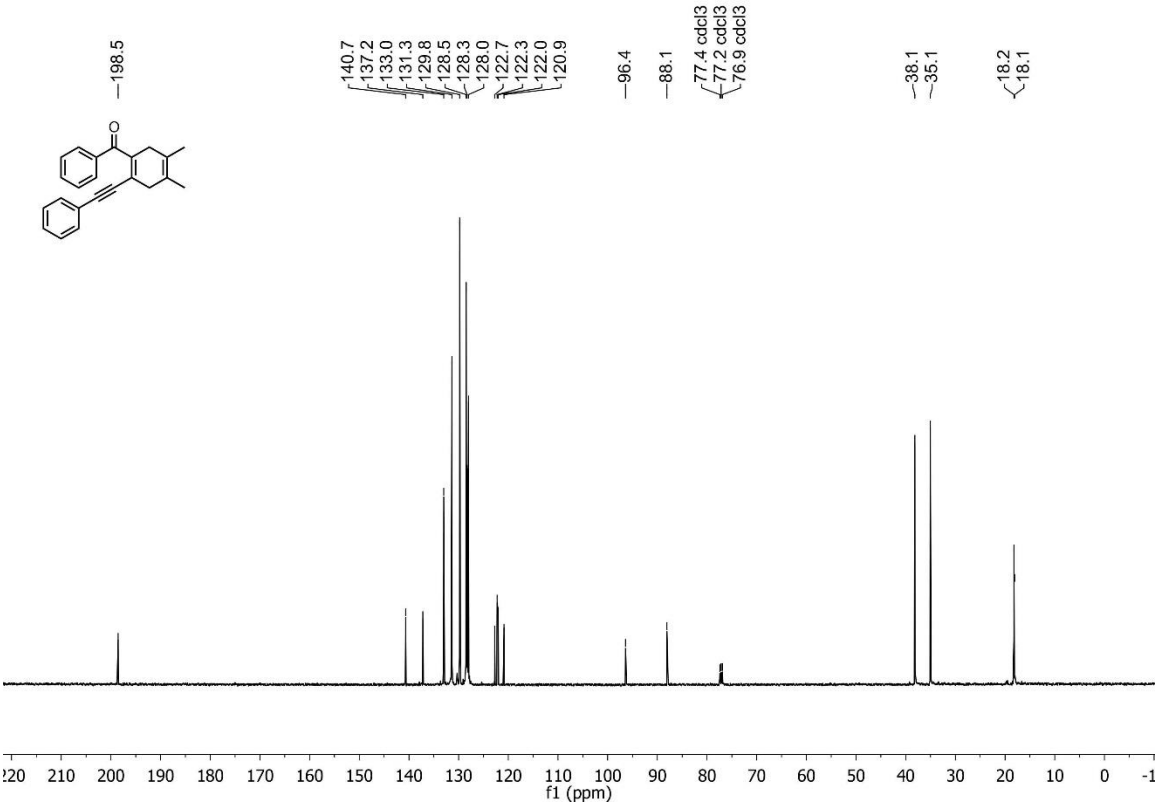


Figure S14. [13]C NMR spectrum of compound **2.5h**.

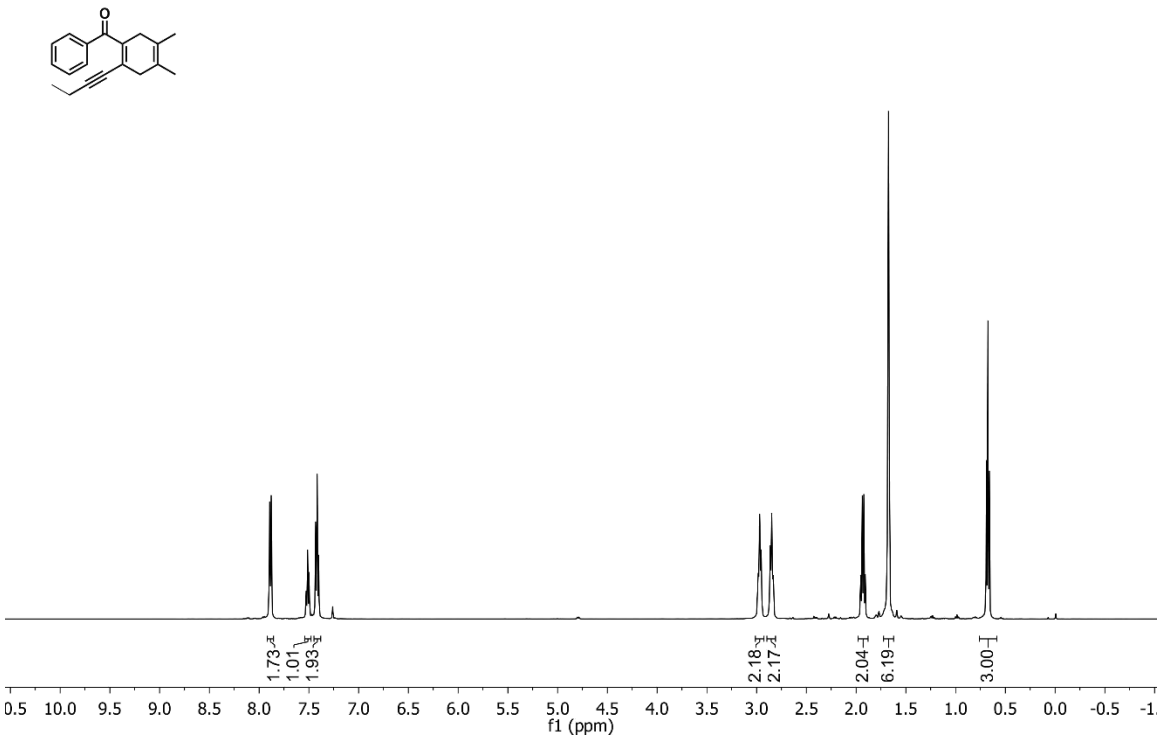


Figure S15. ^{1}H NMR spectrum of compound **2.5i**.

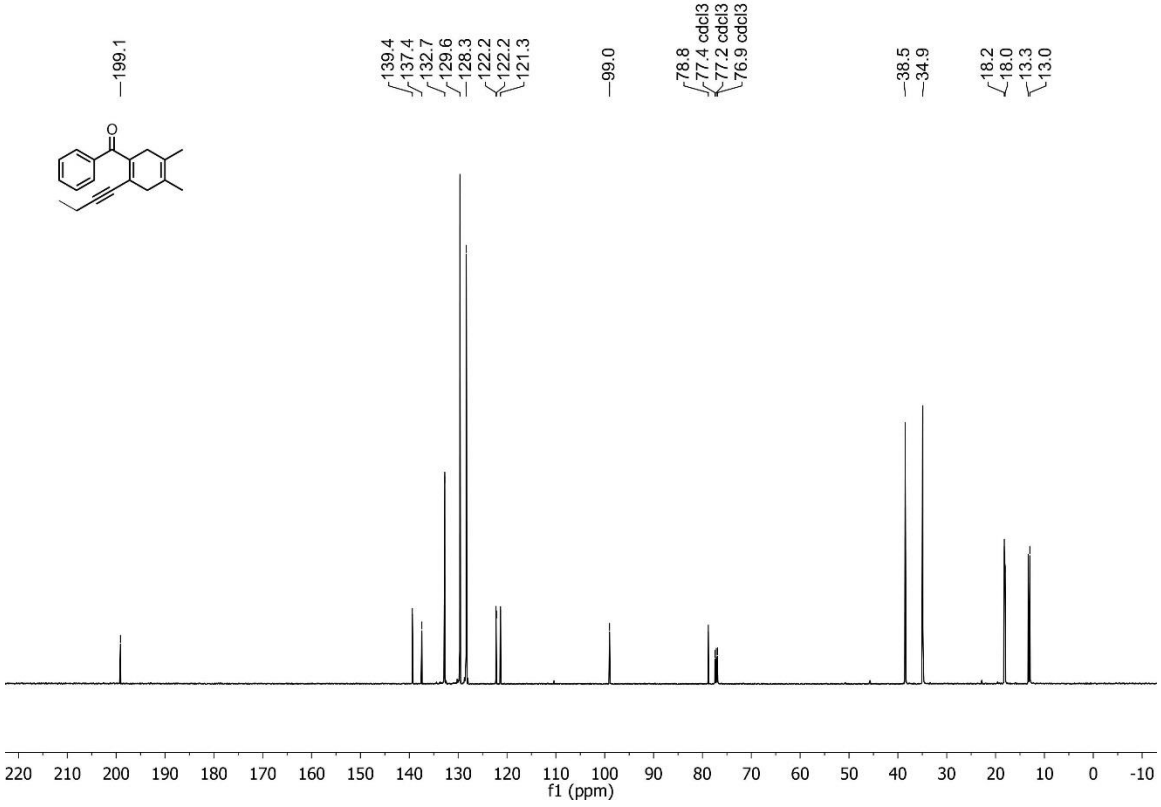


Figure S16. ^{13}C NMR spectrum of compound **2.5i**.

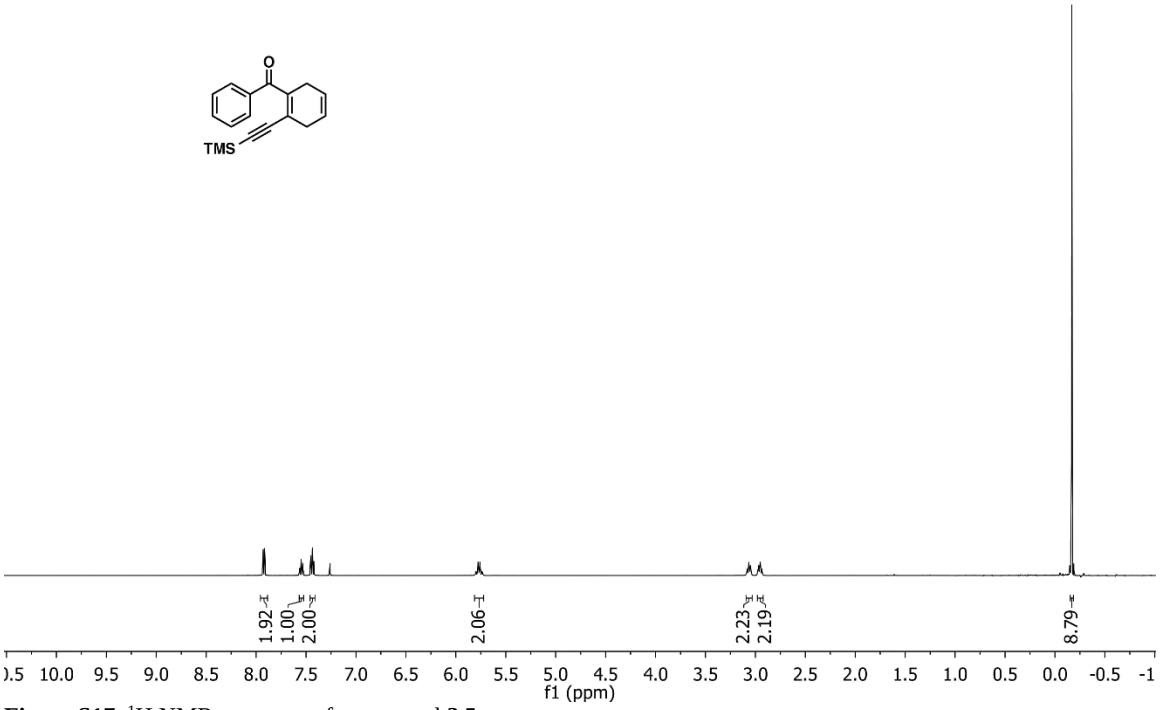


Figure S17. [1]H NMR spectrum of compound **2.5m**.

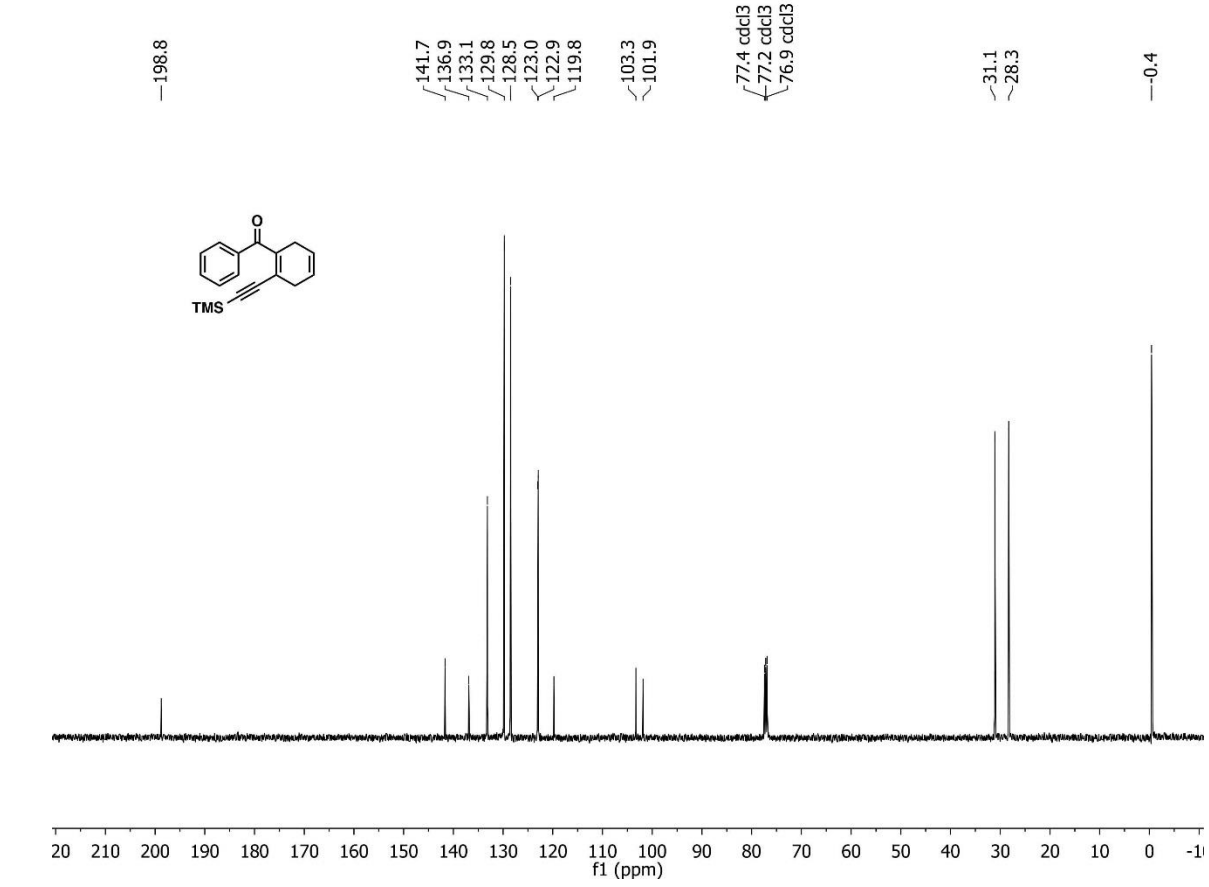


Figure S18. [13]C NMR spectrum of compound **2.5m**.

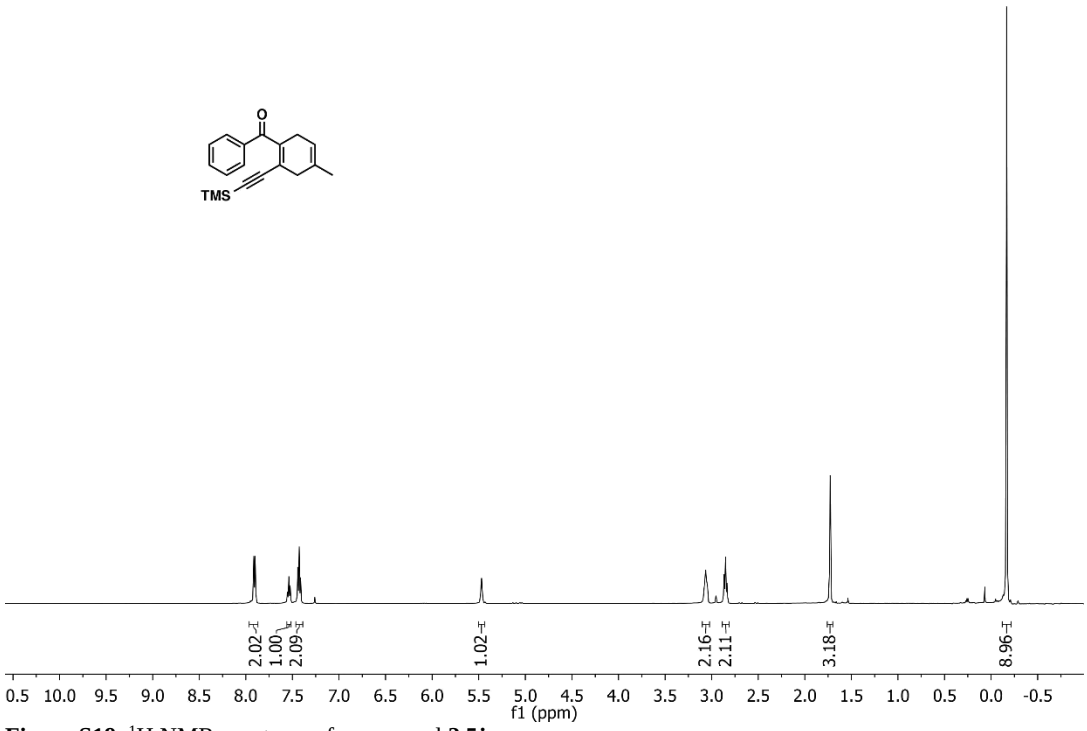


Figure S19. [1]H NMR spectrum of compound **2.5j**.

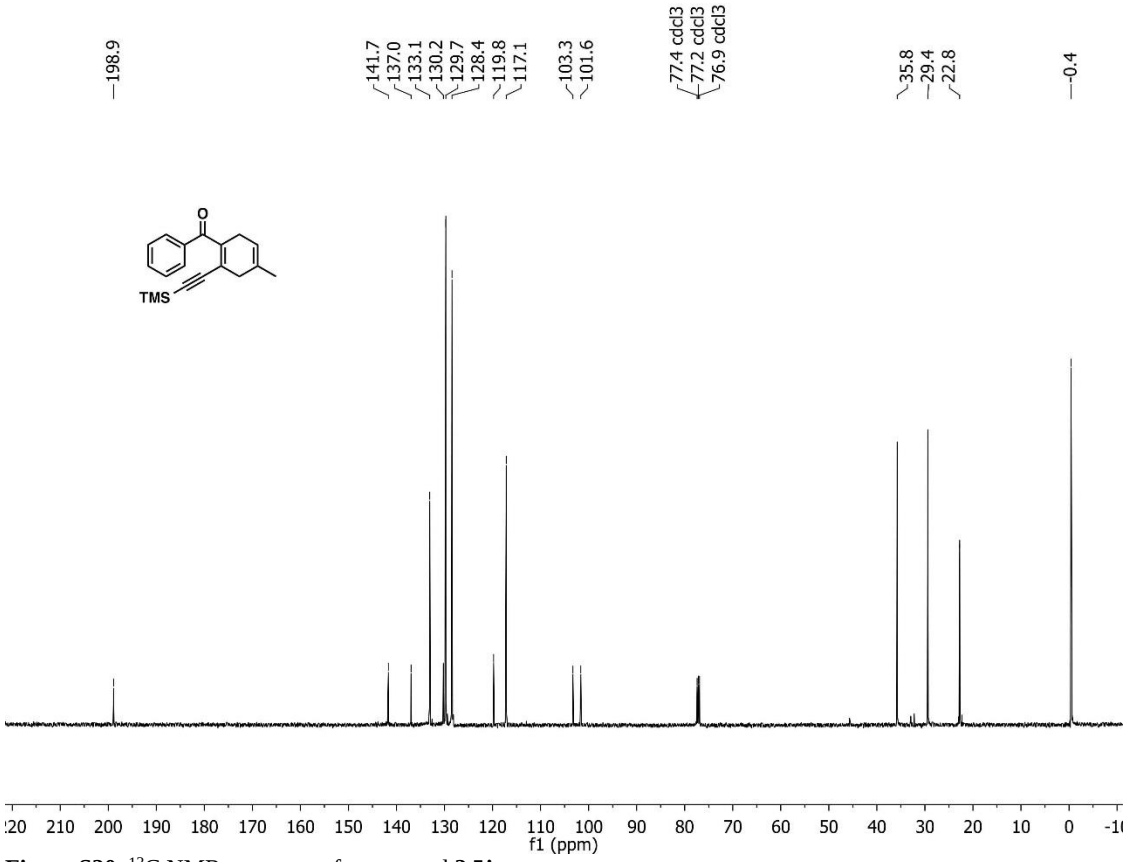


Figure S20. [13]C NMR spectrum of compound **2.5j**.

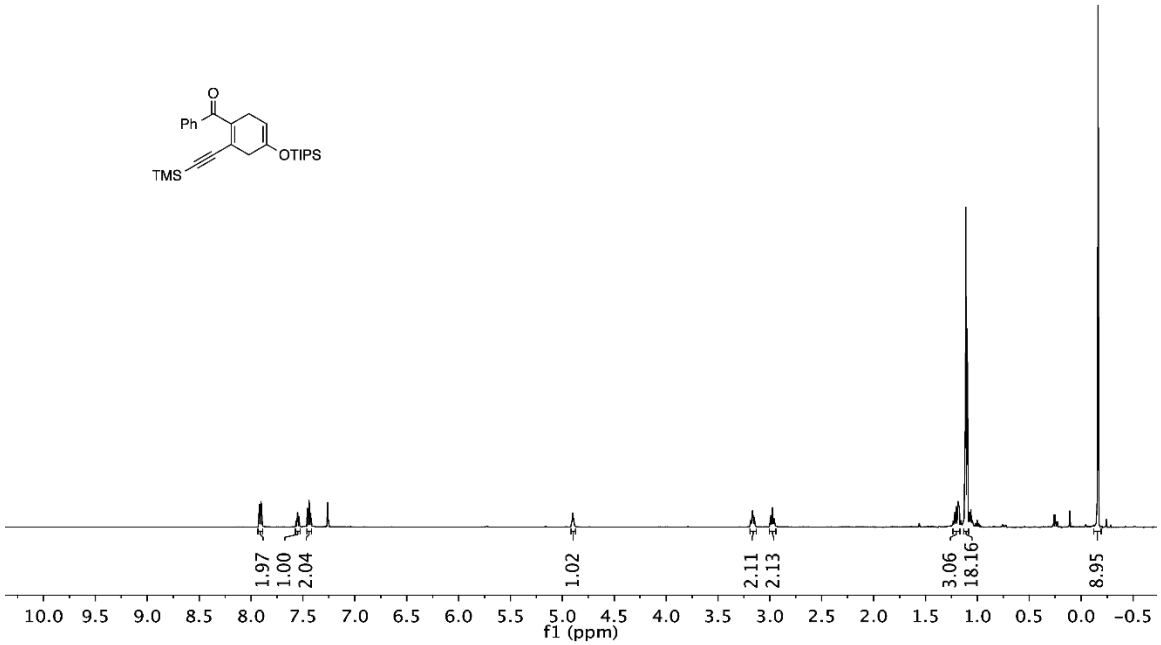


Figure S21. [1]H NMR spectrum of compound **2.5k**.

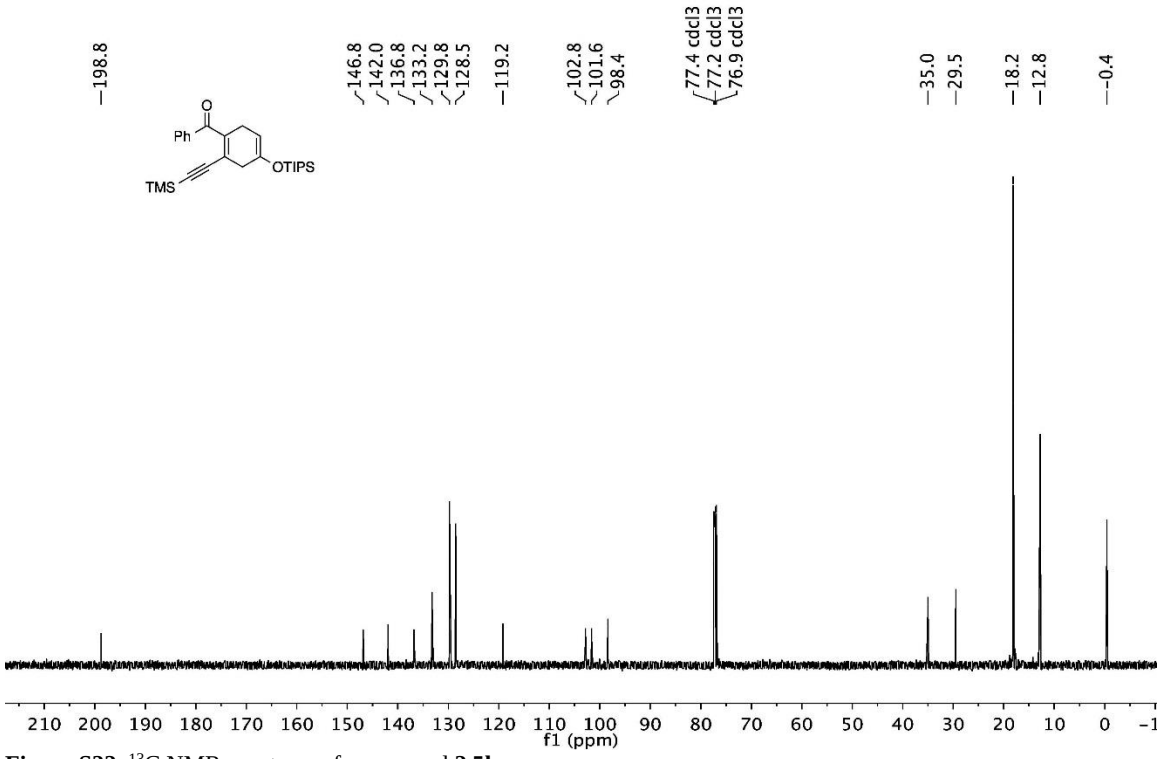


Figure S22. [13]C NMR spectrum of compound **2.5k**.

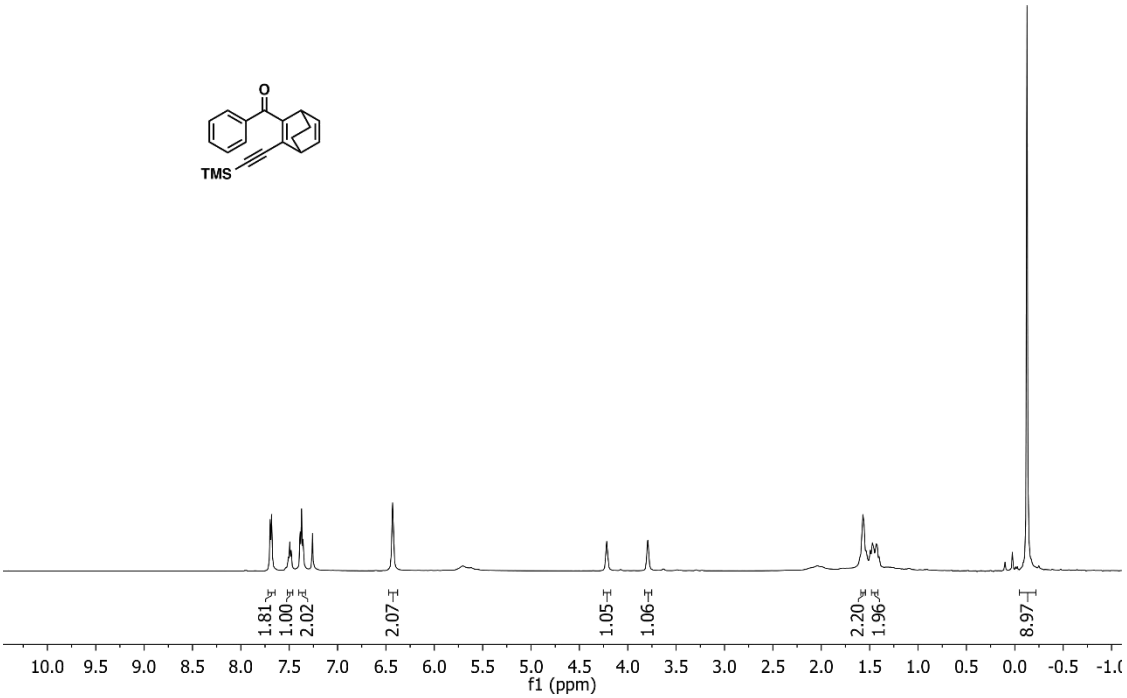


Figure S23. ^{1}H NMR spectrum of compound **2.5n**.

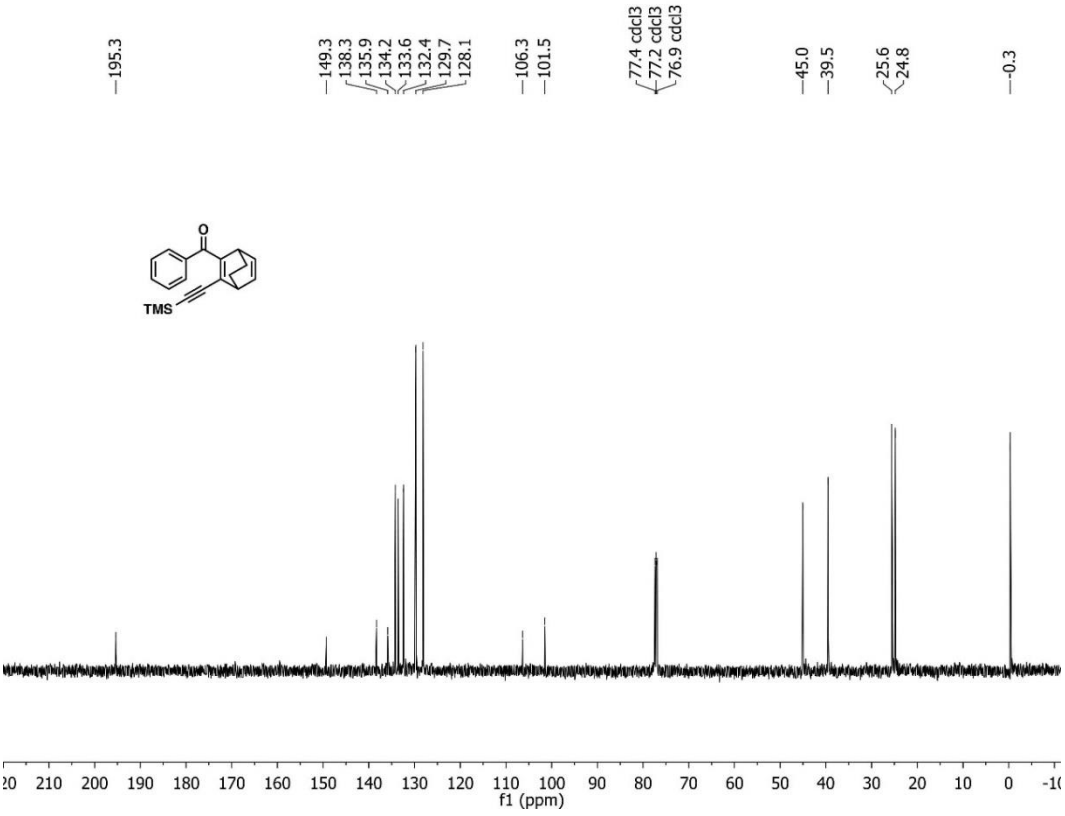


Figure S24. ^{13}C NMR spectrum of compound **2.5n**.

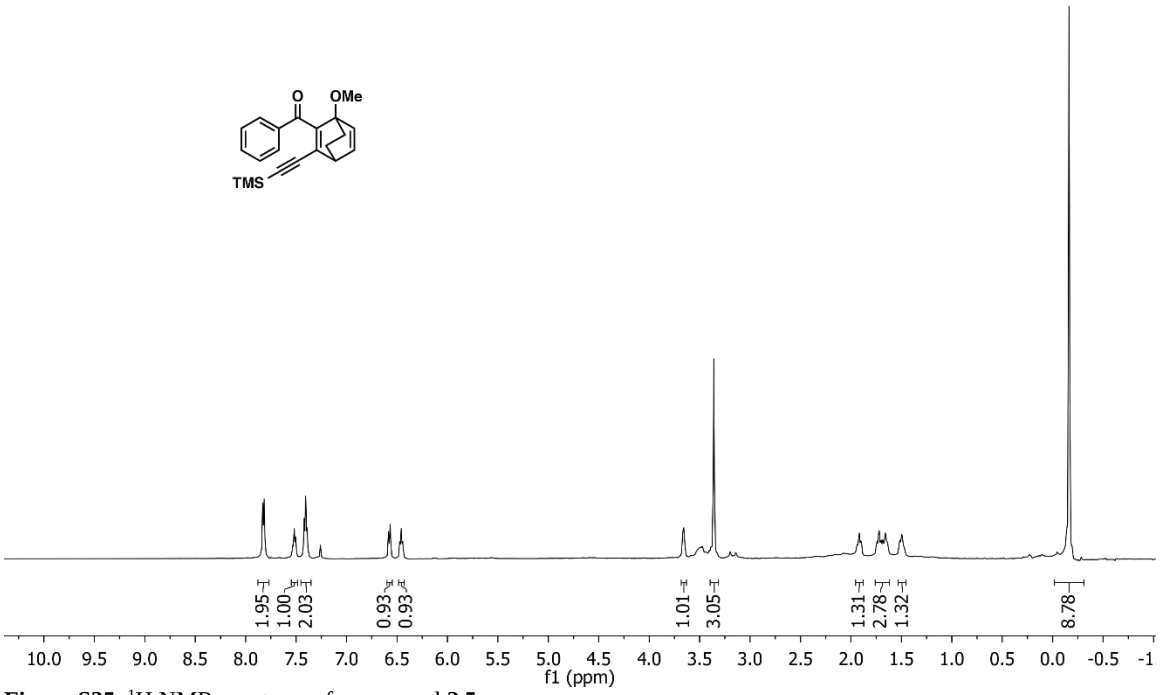


Figure S25. [1]H NMR spectrum of compound **2.5o**.

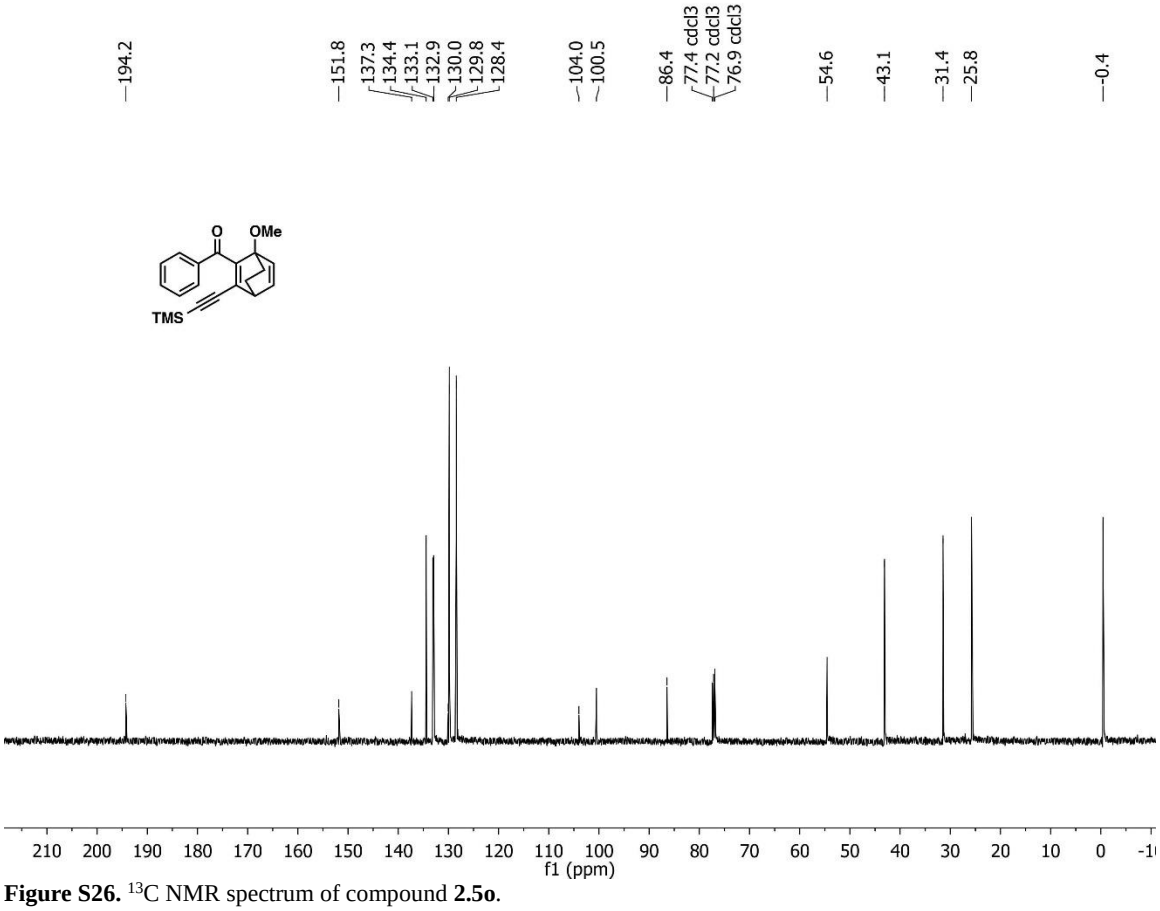


Figure S26. [13]C NMR spectrum of compound **2.5o**.

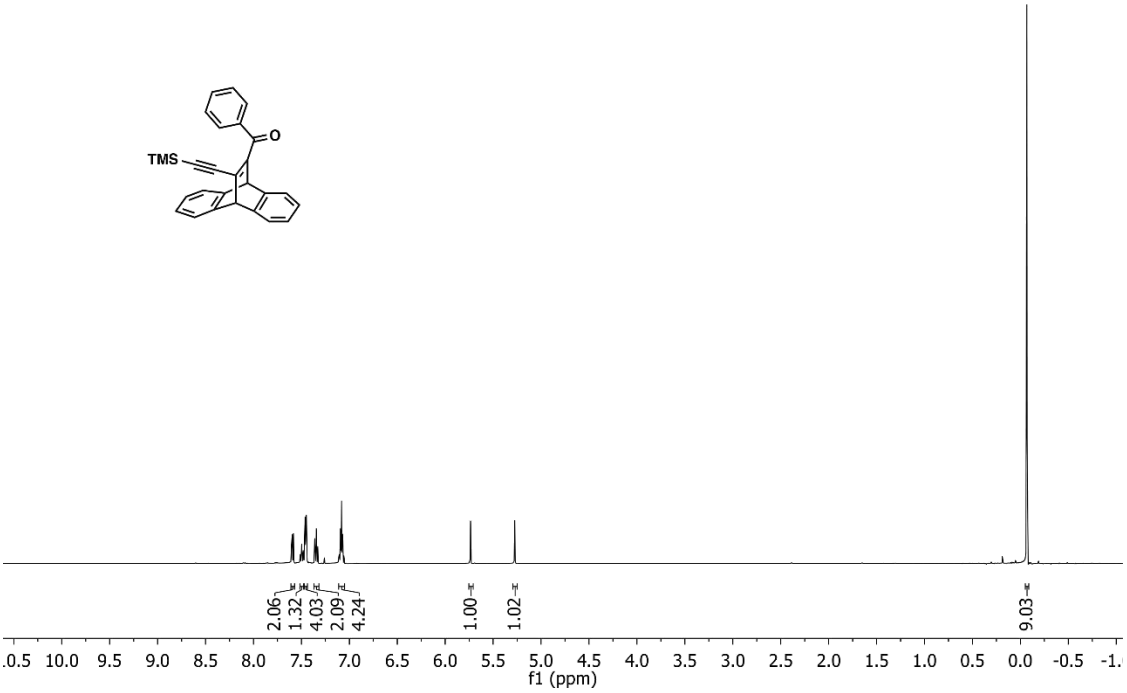


Figure S27. [1]H NMR spectrum of compound **2.5p**.

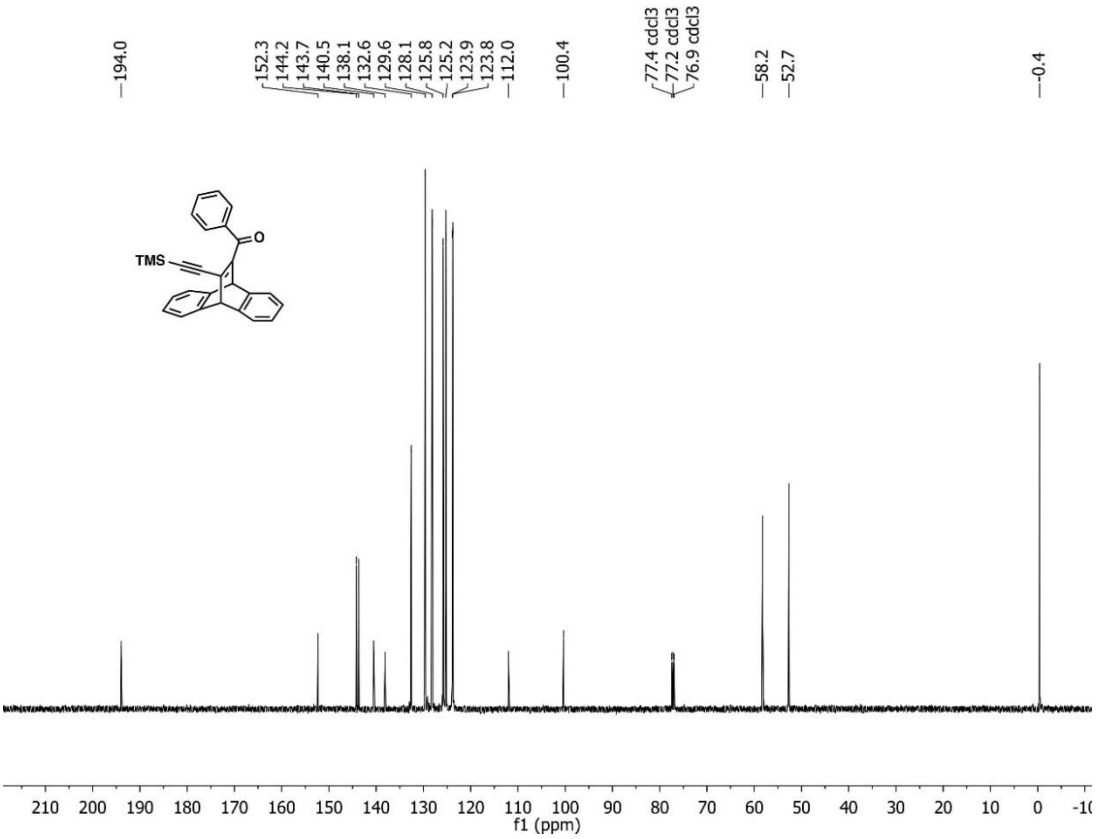


Figure S28. [13]C NMR spectrum of compound **2.5p**.

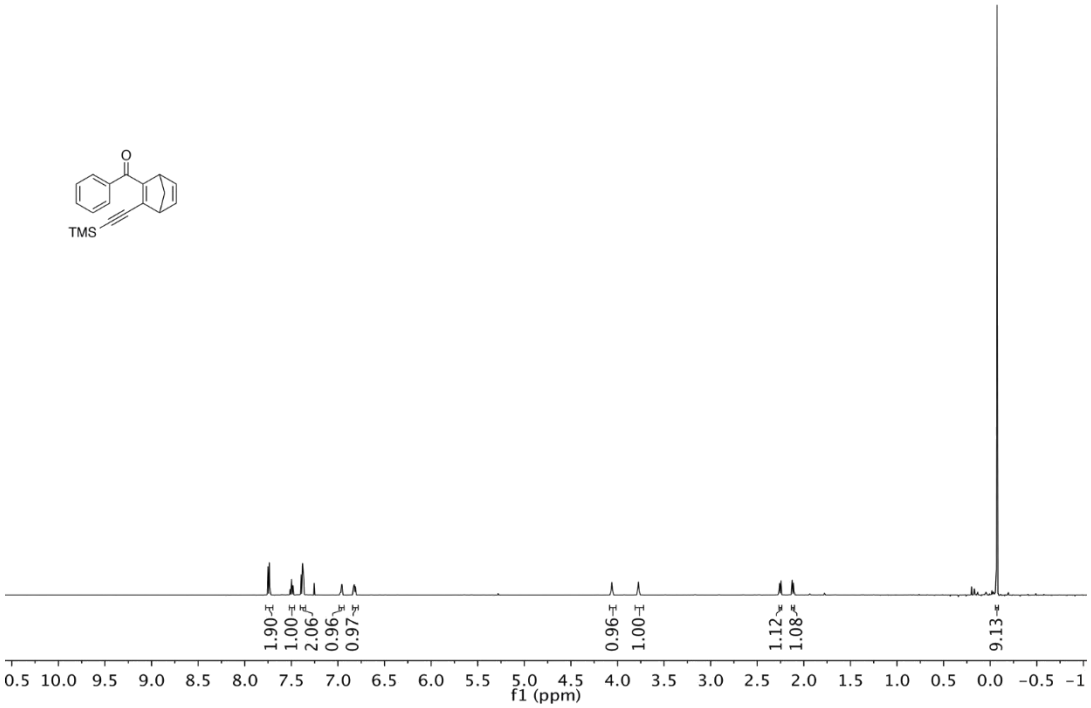


Figure S29. ^{1}H NMR spectrum of compound **2.5l**.

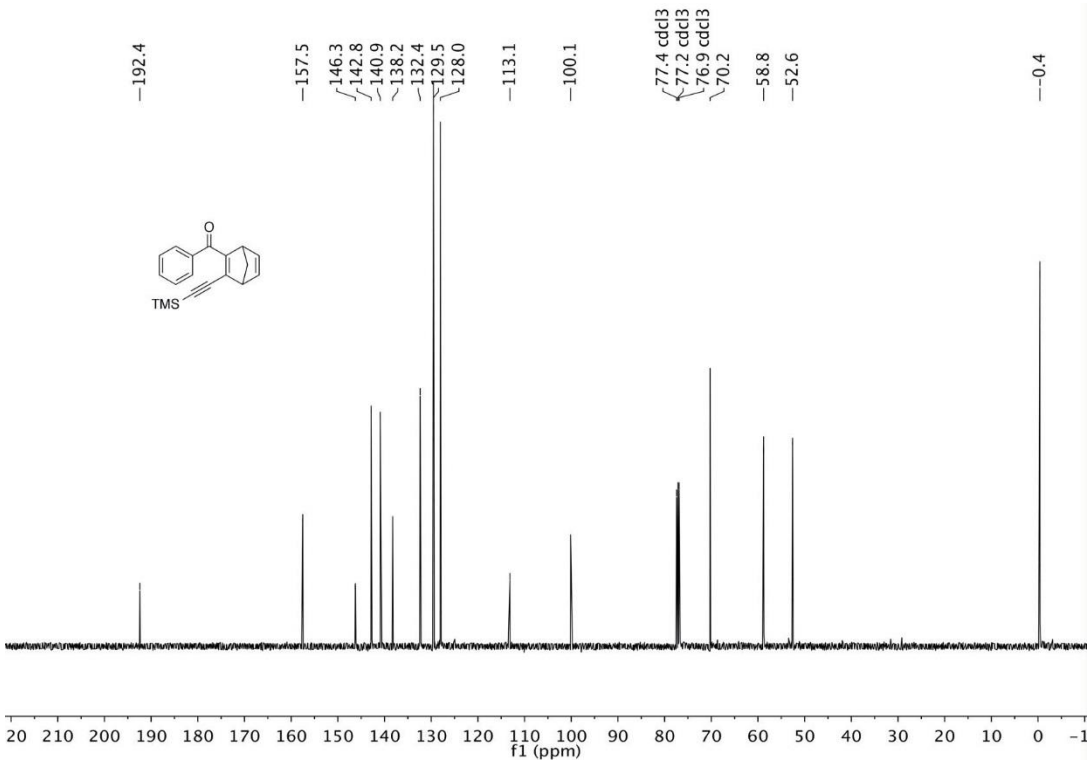


Figure S30. ^{13}C NMR spectrum of compound **2.5l**.

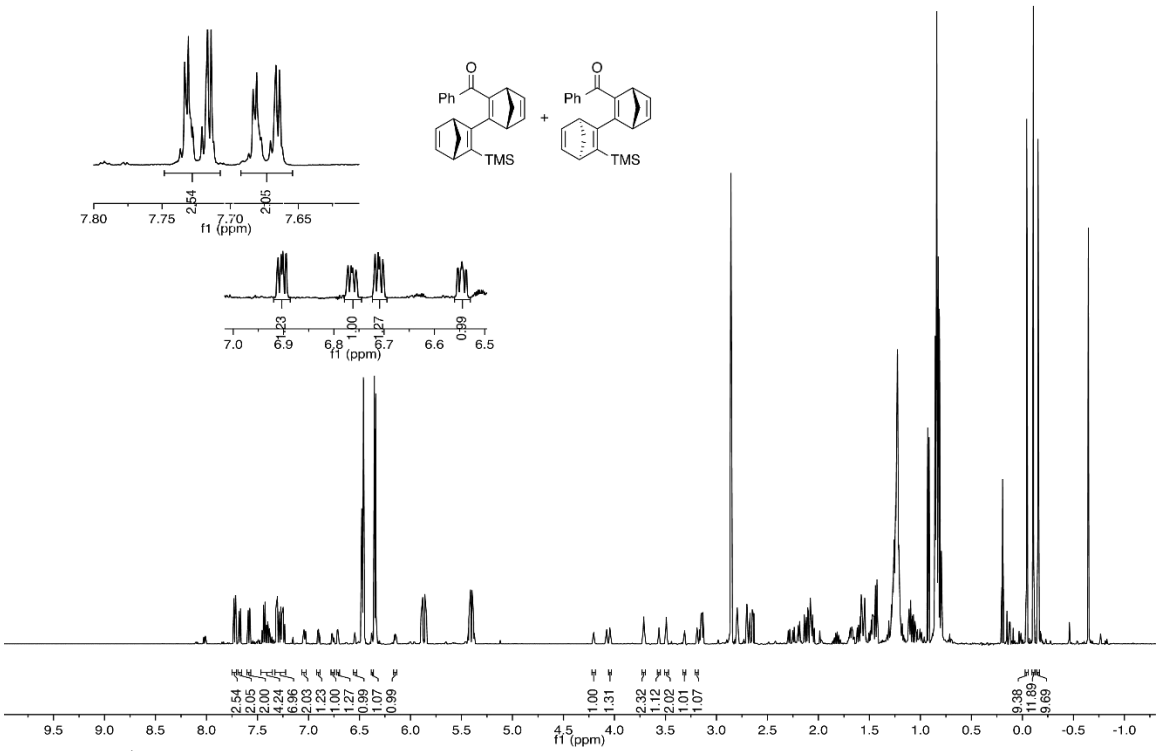


Figure S31. ^{1}H NMR spectrum of crude **2.17a** and **2.17a′** in a 1.3:1 ratio.

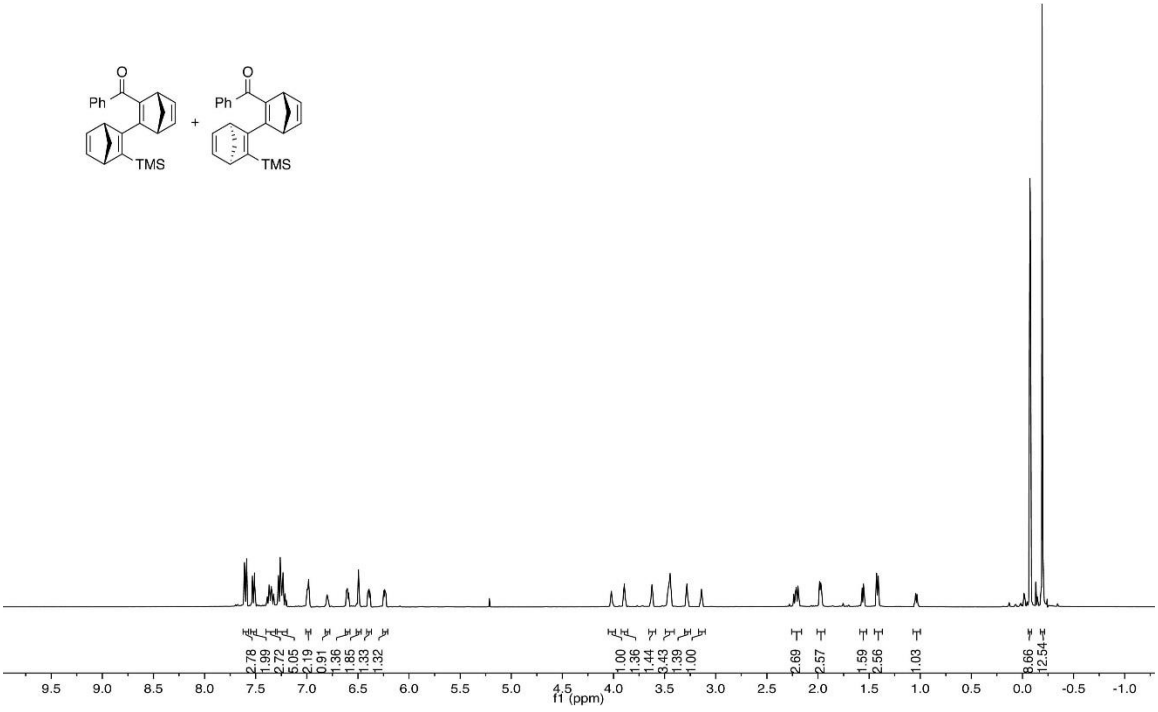


Figure S32. ^{1}H NMR spectrum of **2.17a** and **2.17a′** after purification.

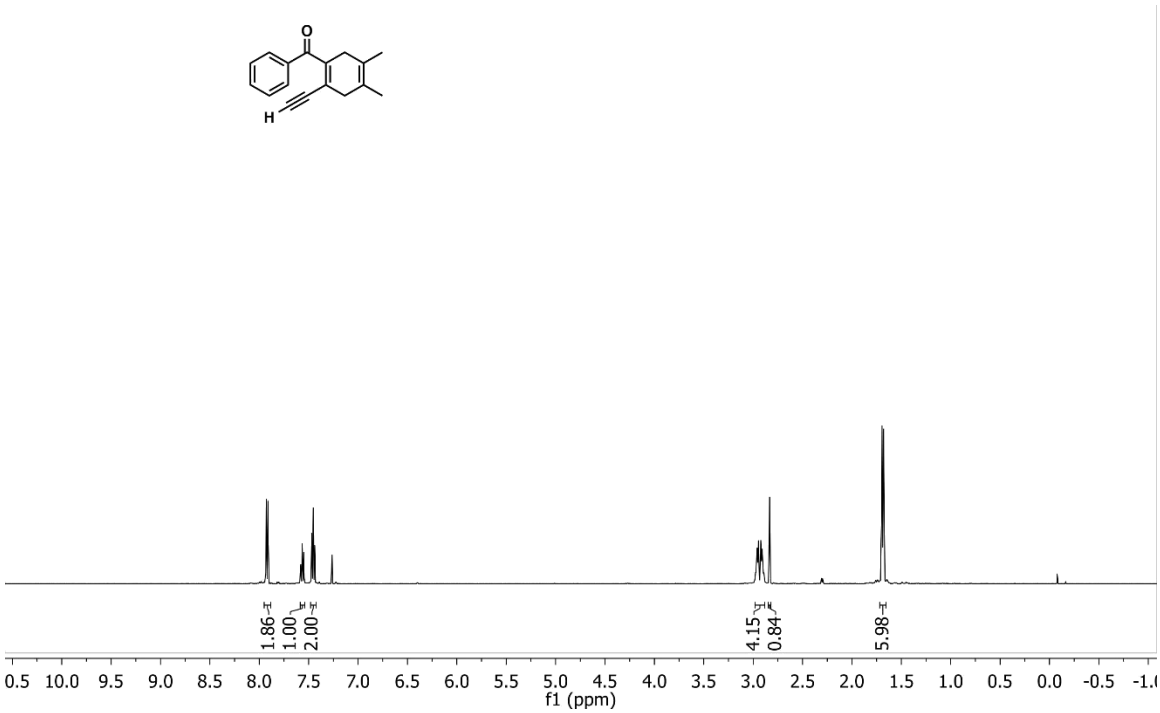


Figure S33. ^{1}H NMR spectrum of compound **2.5b**.

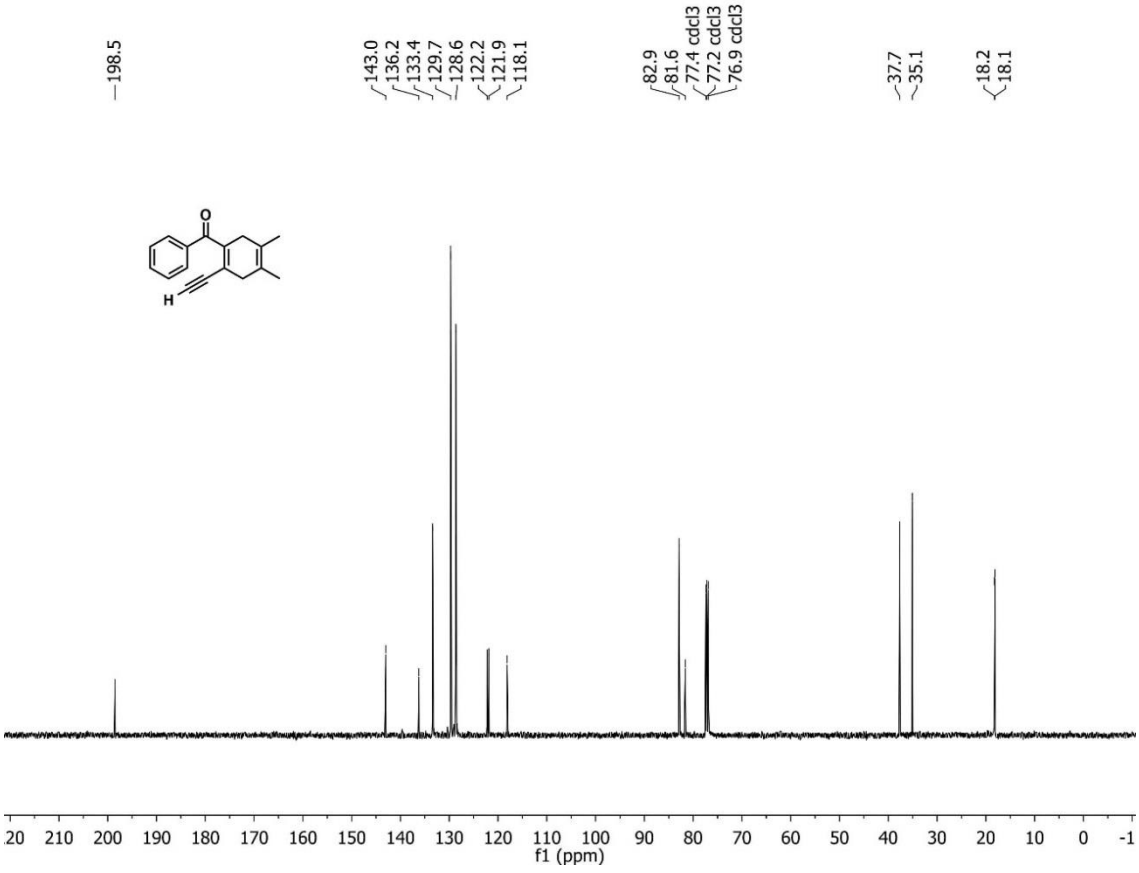


Figure S34. ^{13}C NMR spectrum of compound **2.5b**.

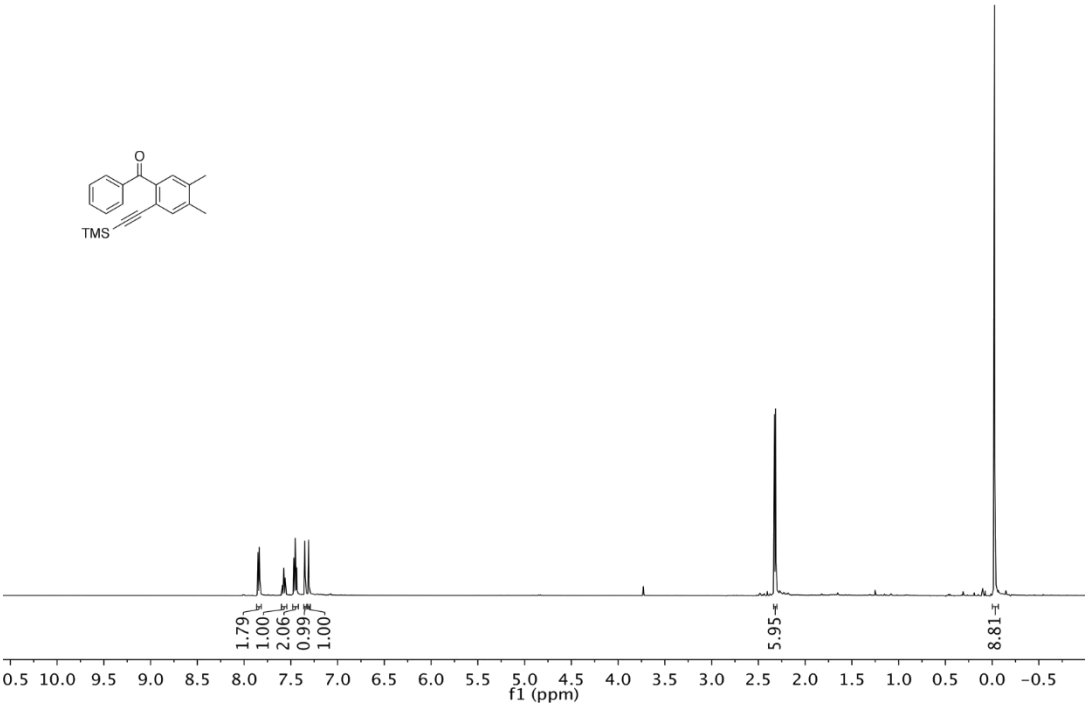


Figure S35. [1]H NMR spectrum of compound **2.18**.

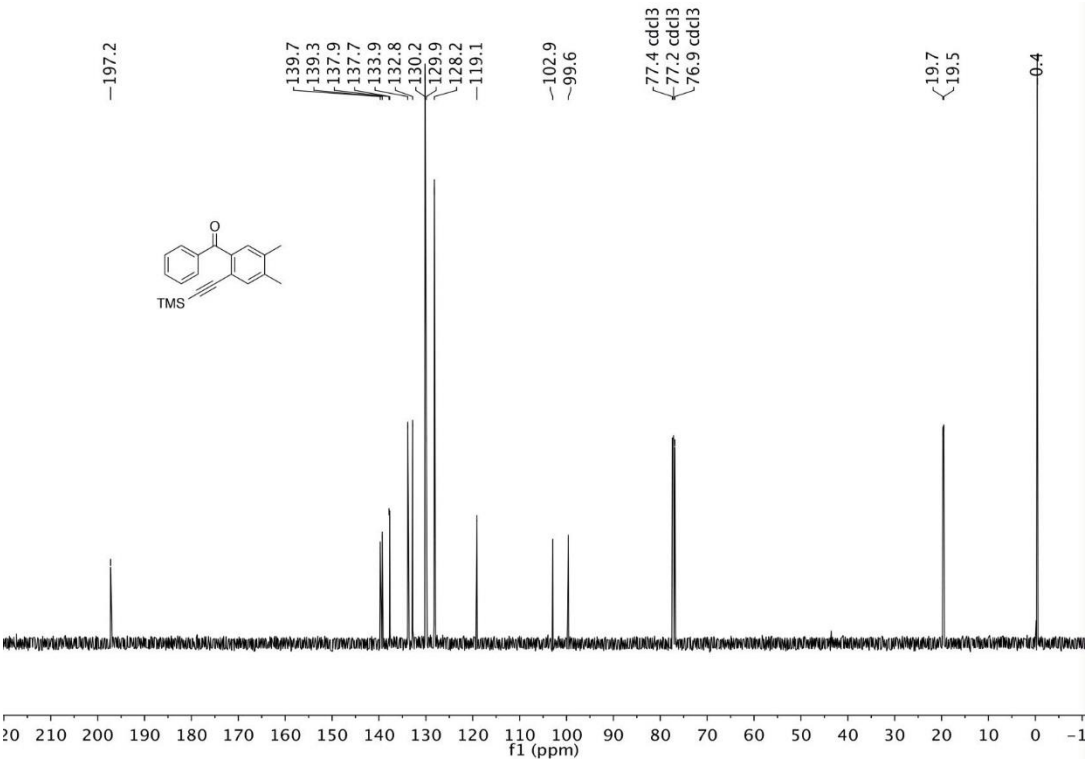


Figure S36. [13]C NMR spectrum of compound **2.18**.

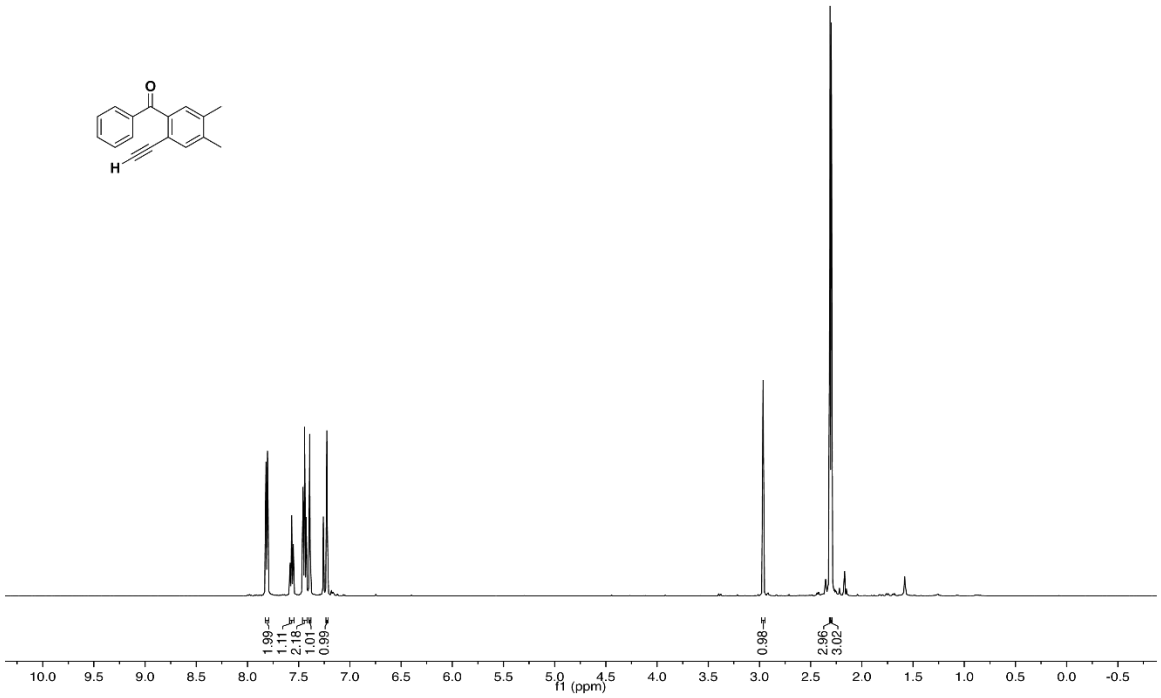


Figure S37. [1]H NMR spectrum of compound **2.19**.

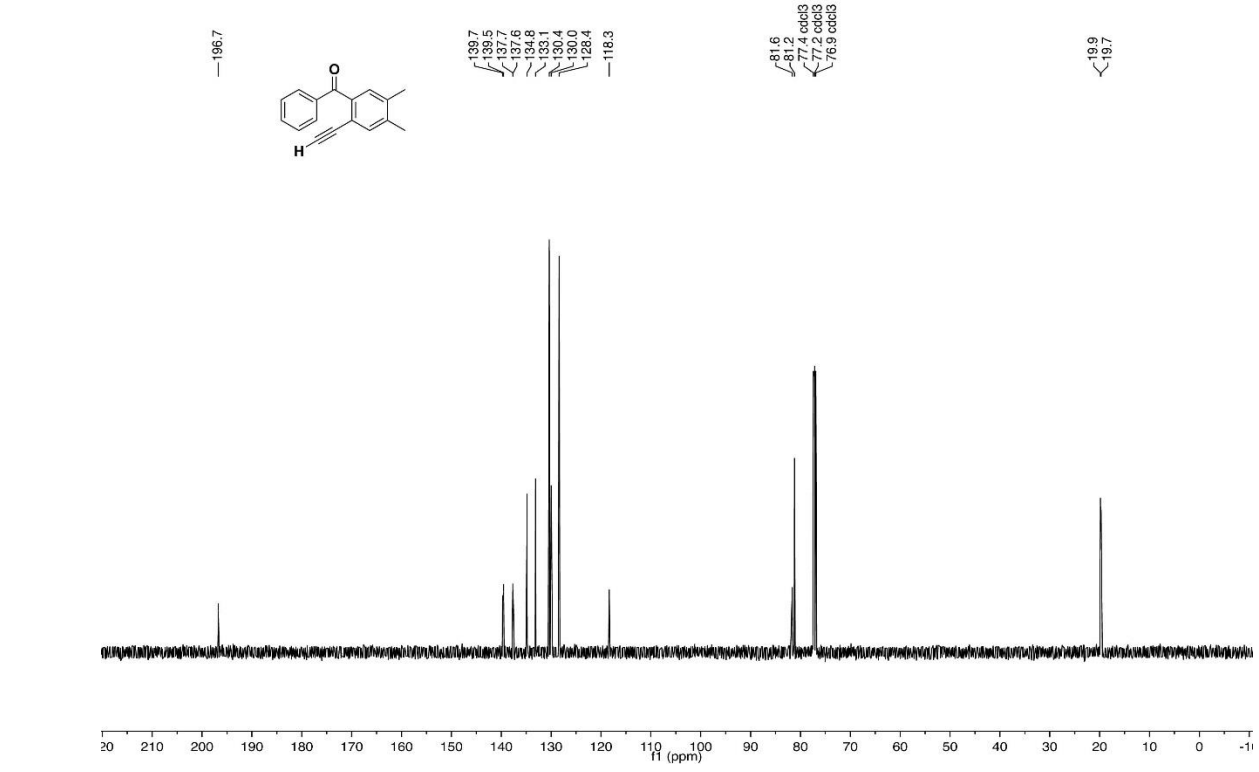


Figure S38. [13]C NMR spectrum of compound **2.19**.

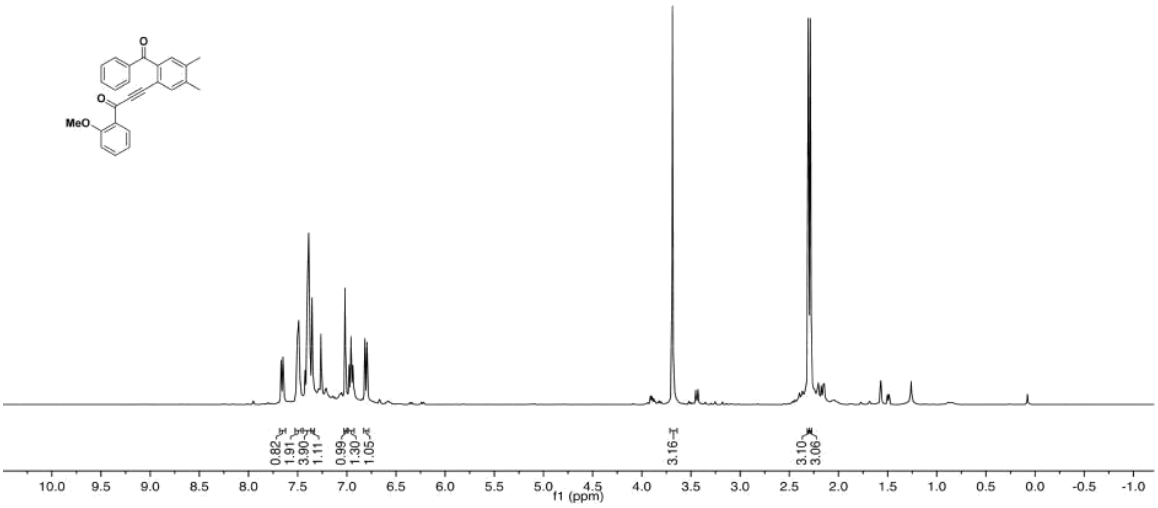


Figure S39. [1]H NMR spectrum of compound **2.20**.

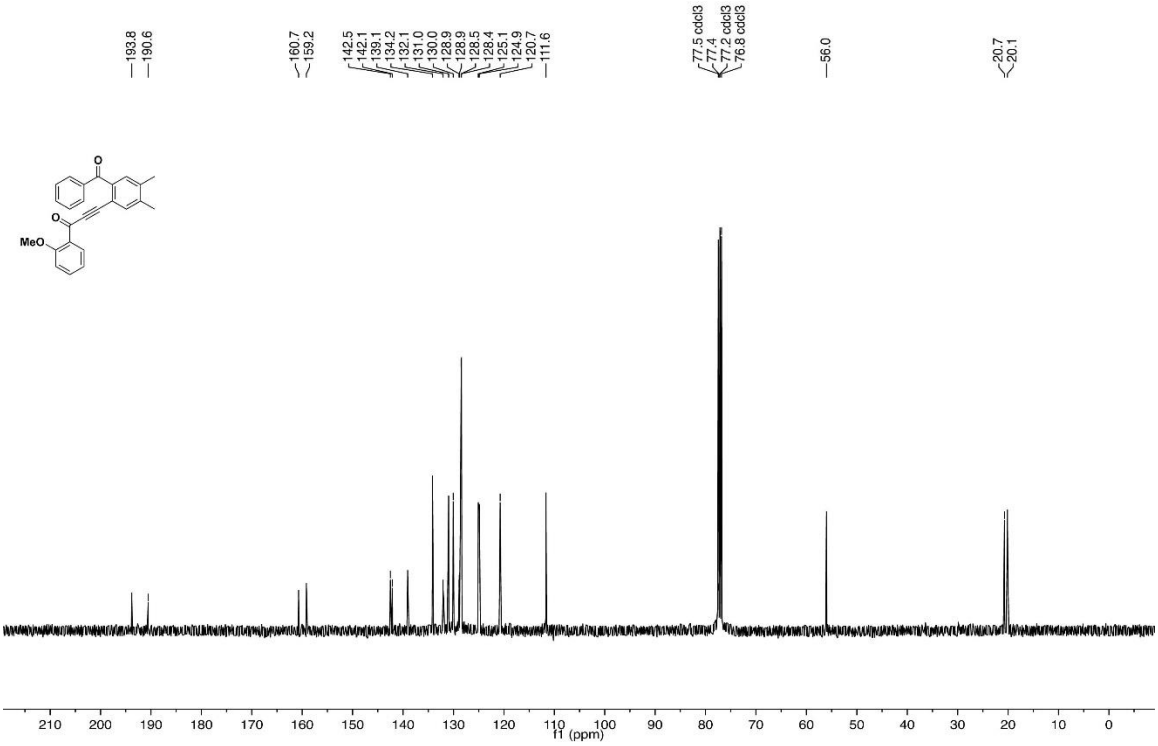


Figure S40. [13]C NMR spectrum of compound **2.20.**

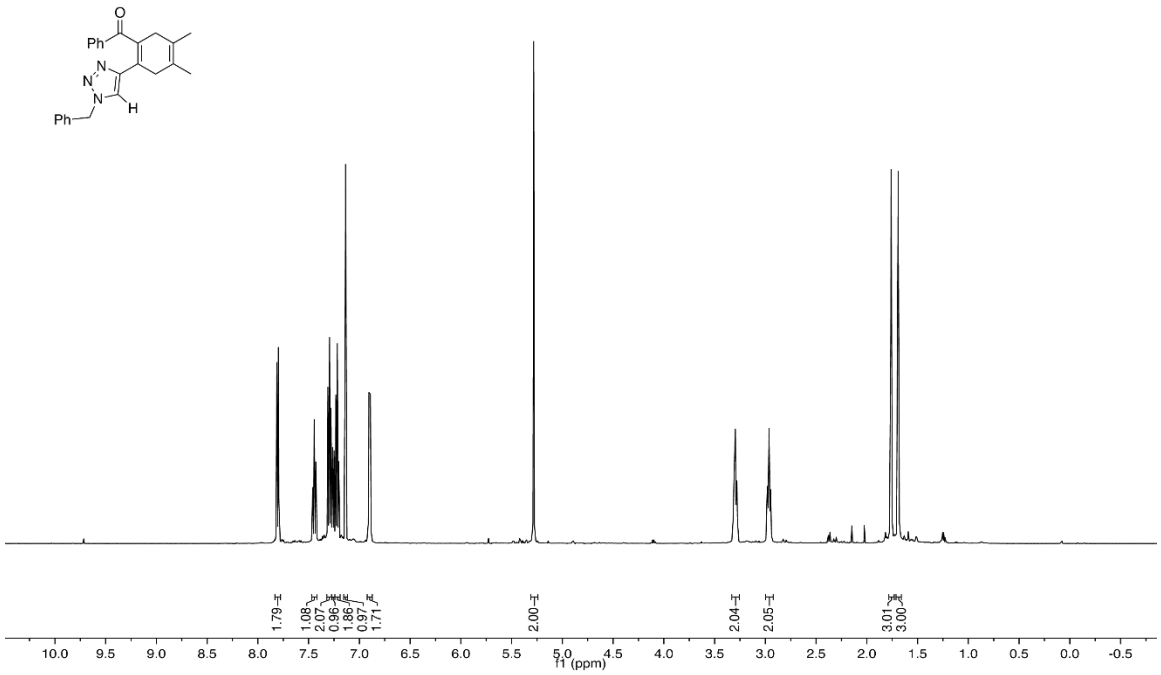


Figure S41. [1]H NMR spectrum of compound **2.21**.

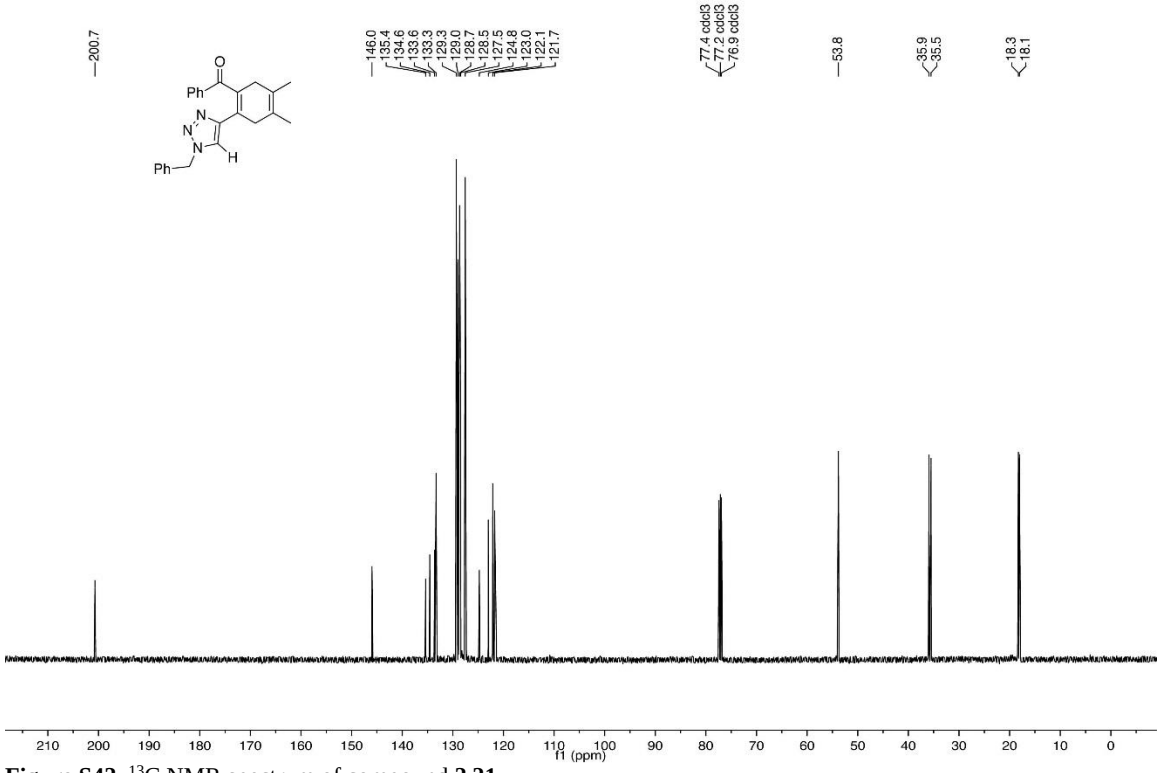


Figure S42. [13]C NMR spectrum of compound **2.21**.

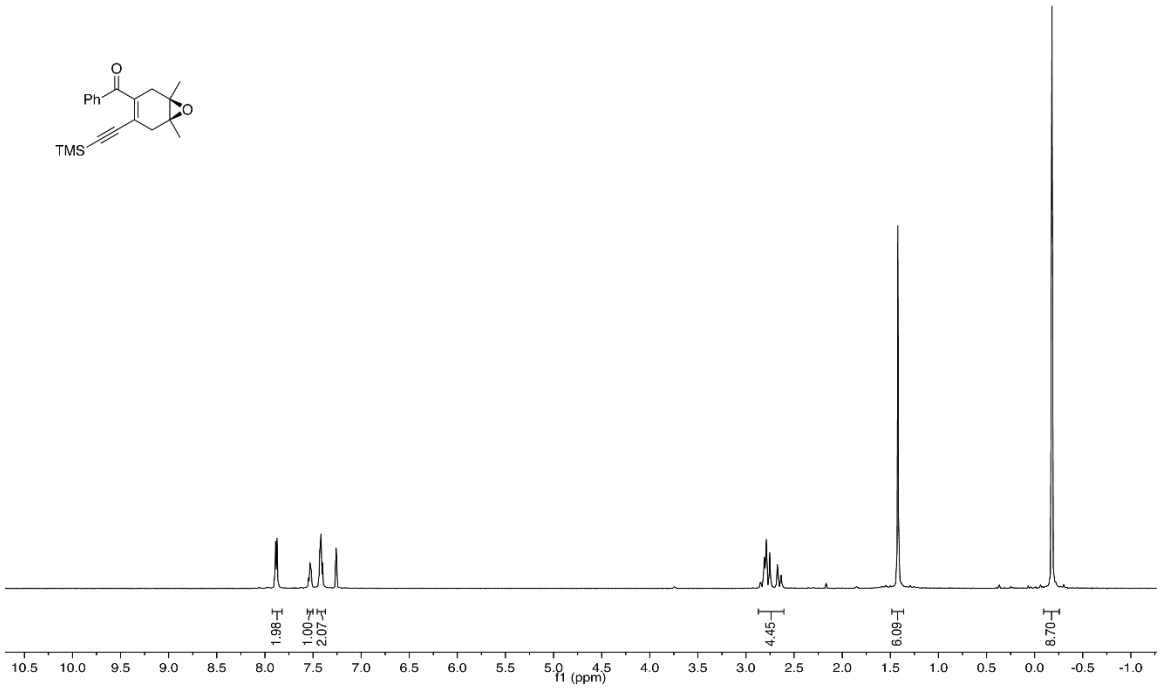


Figure S43. ^{1}H NMR spectrum of compound **2.22**.

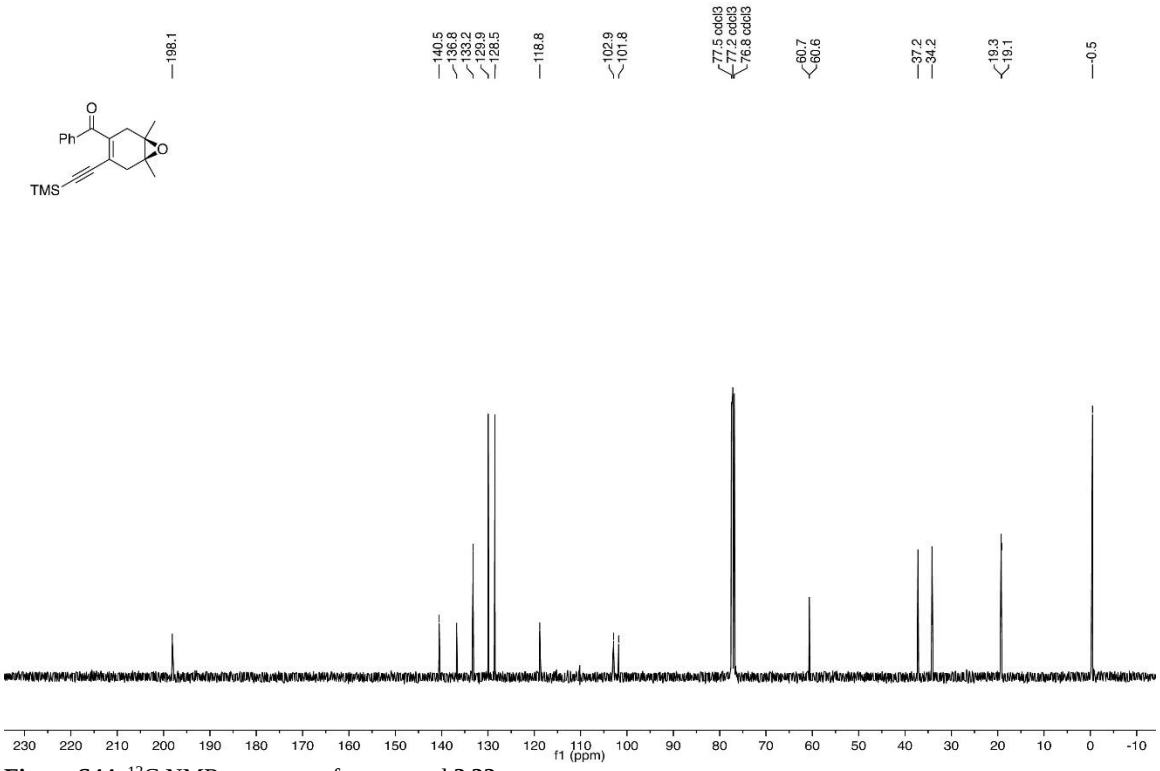


Figure S44. ^{13}C NMR spectrum of compound **2.22**.

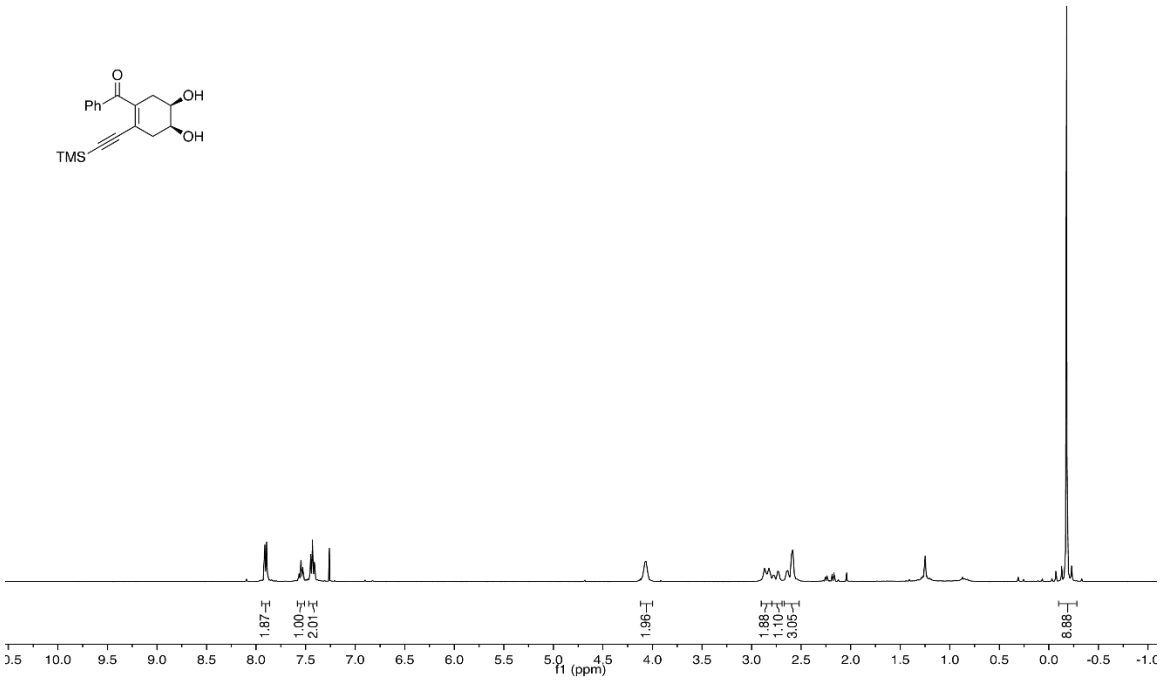


Figure S45. ^{1}H NMR spectrum of compound **2.23**

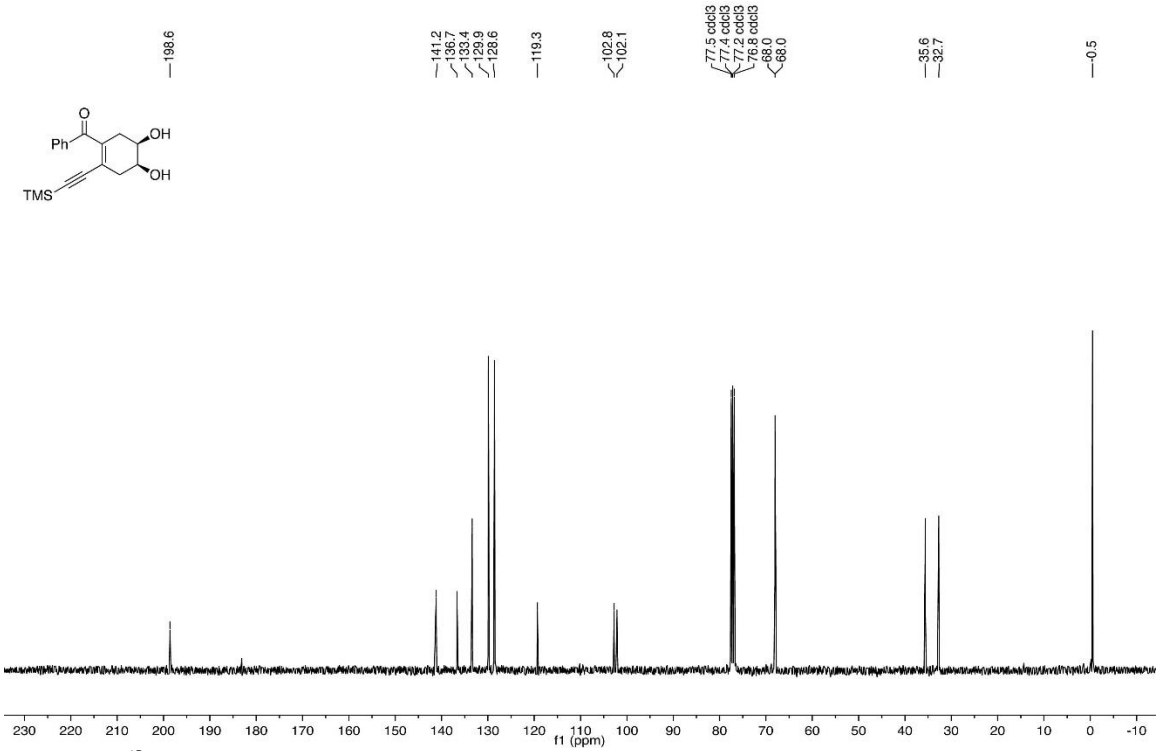


Figure S46. ^{13}C NMR spectrum of compound **2.23**.

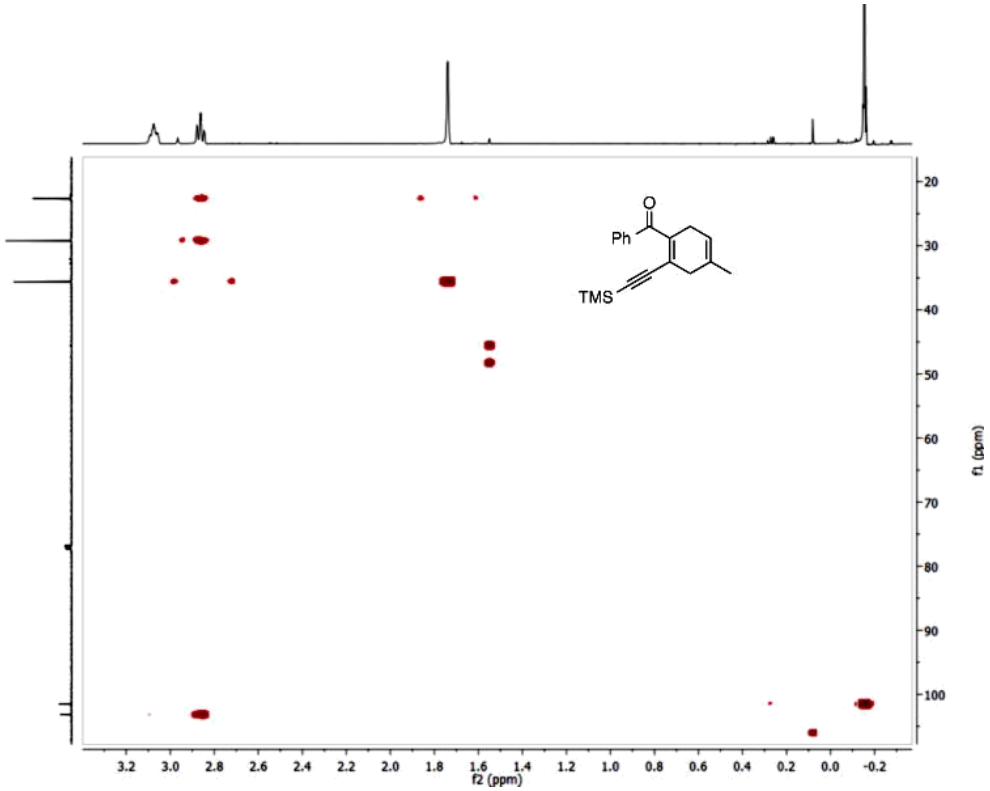


Figure S47. HMBC spectrum of compound **2.5j**.

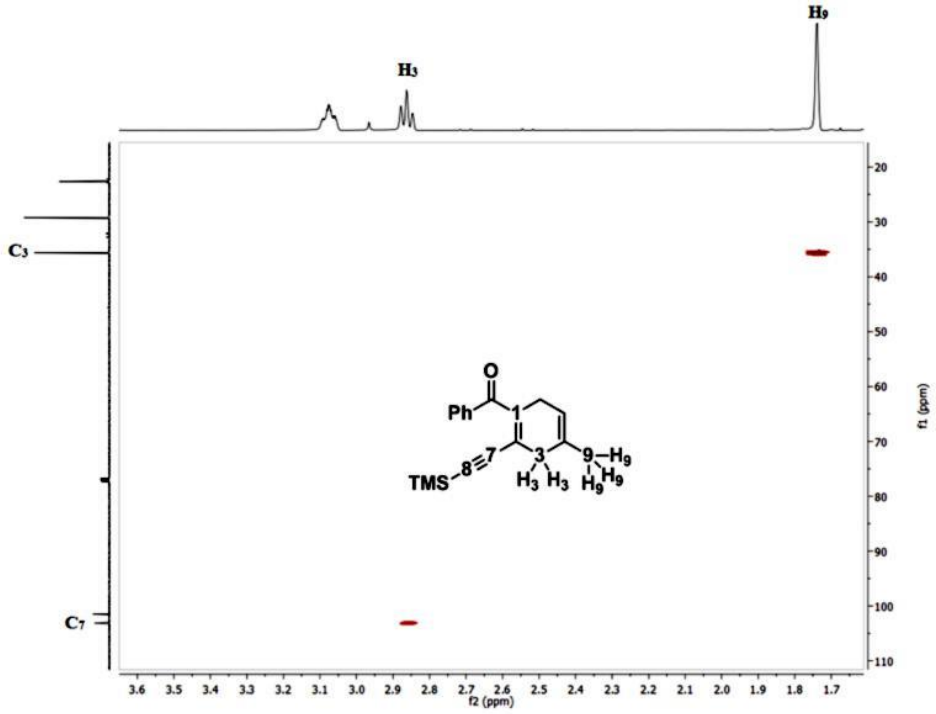


Figure S48. Expanded HMBC spectrum for compound **2.5j** showing the H_3↔C_7 and H_9↔C_3 correlations.

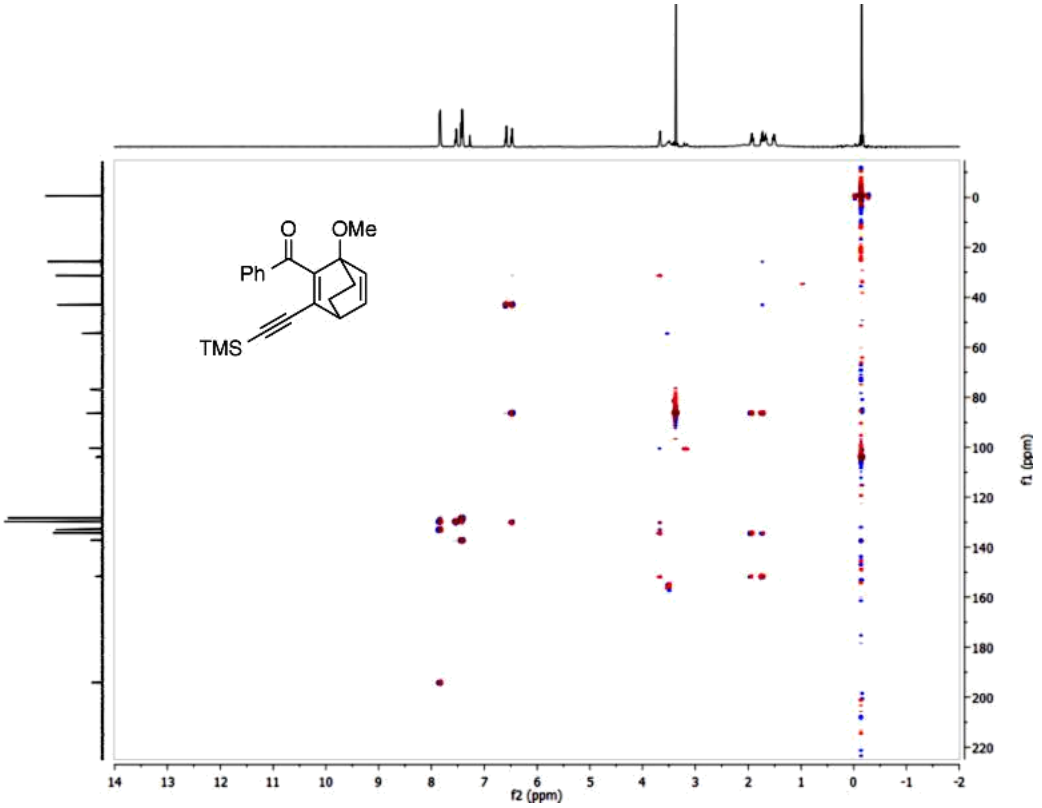


Figure S49. HMBC spectrum of compound **2.5o**.

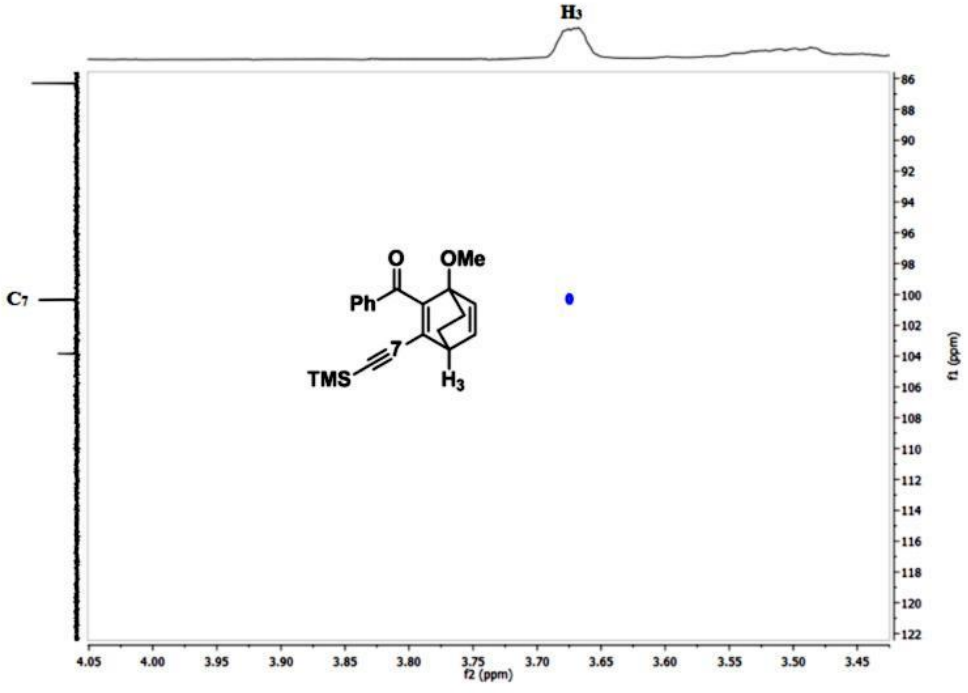


Figure S50. Expanded HMBC spectrum for compound **2.5o** showing the $H_3 \leftrightarrow C_7$ and $H_9 \leftrightarrow C_3$ correlations.

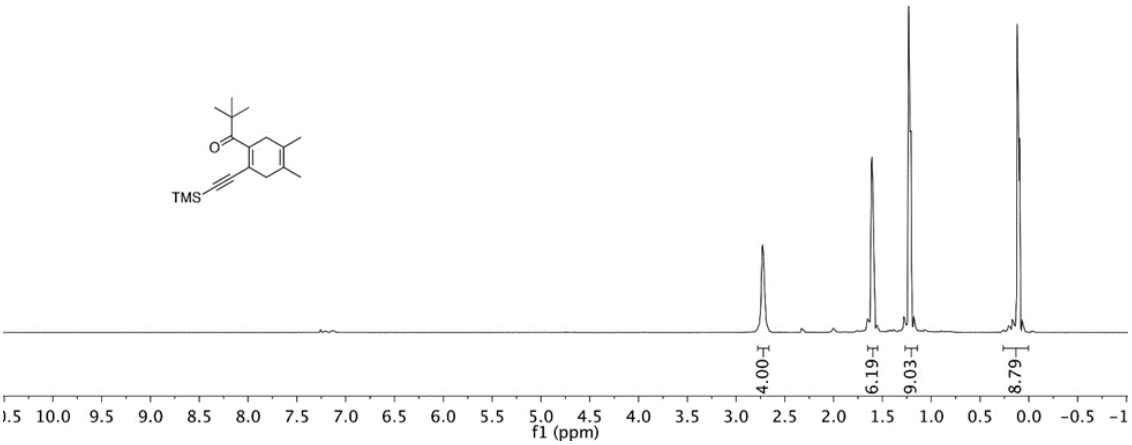


Figure S51. ^{1}H NMR spectrum of compound **3.2h**.

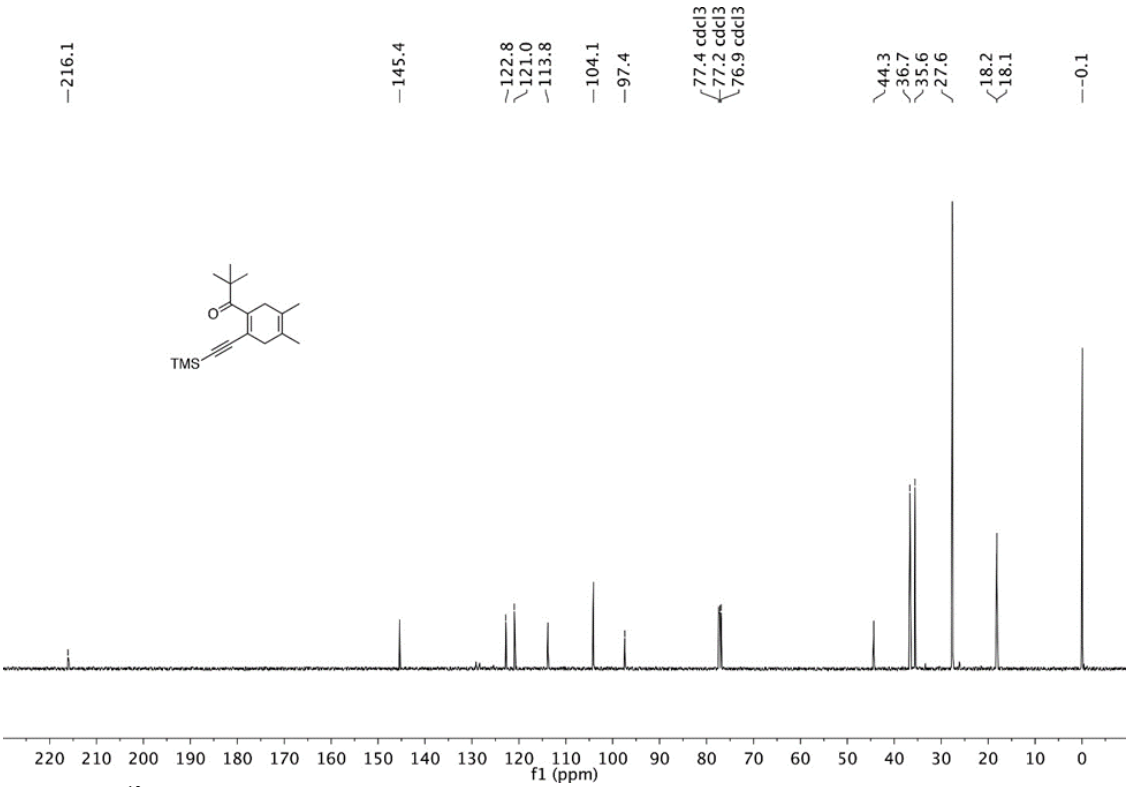


Figure S52. ^{13}C NMR spectrum of compound **3.2h**.

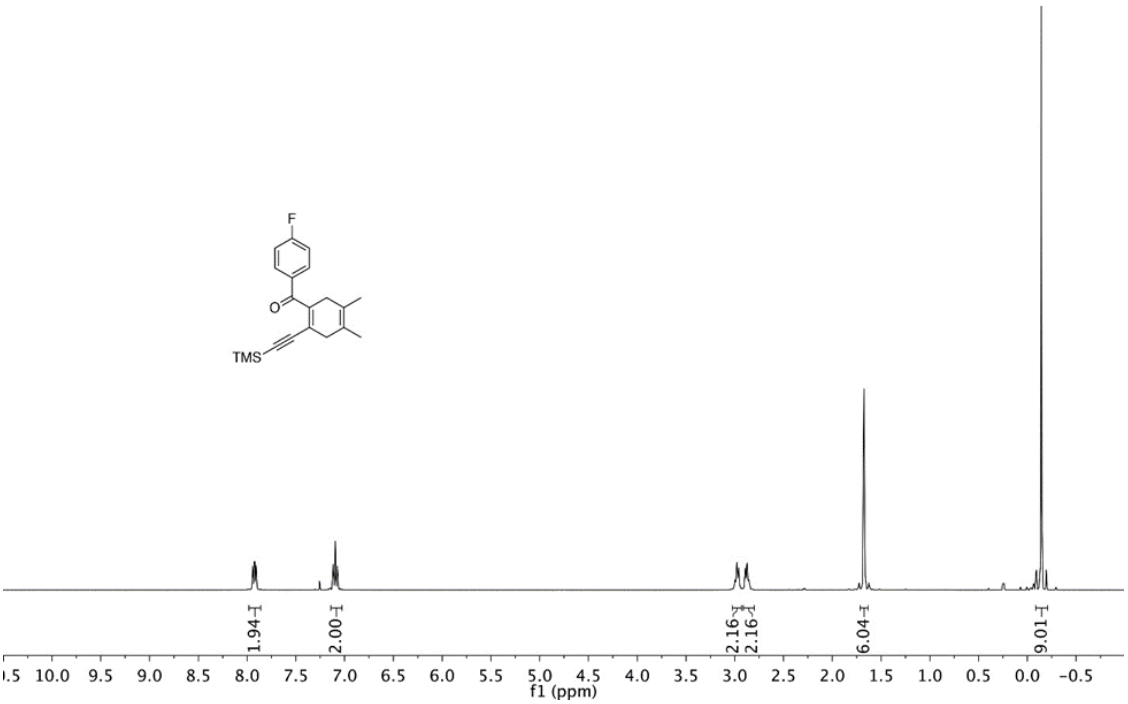


Figure S53. ^{1}H NMR spectrum of compound **3.2k**.

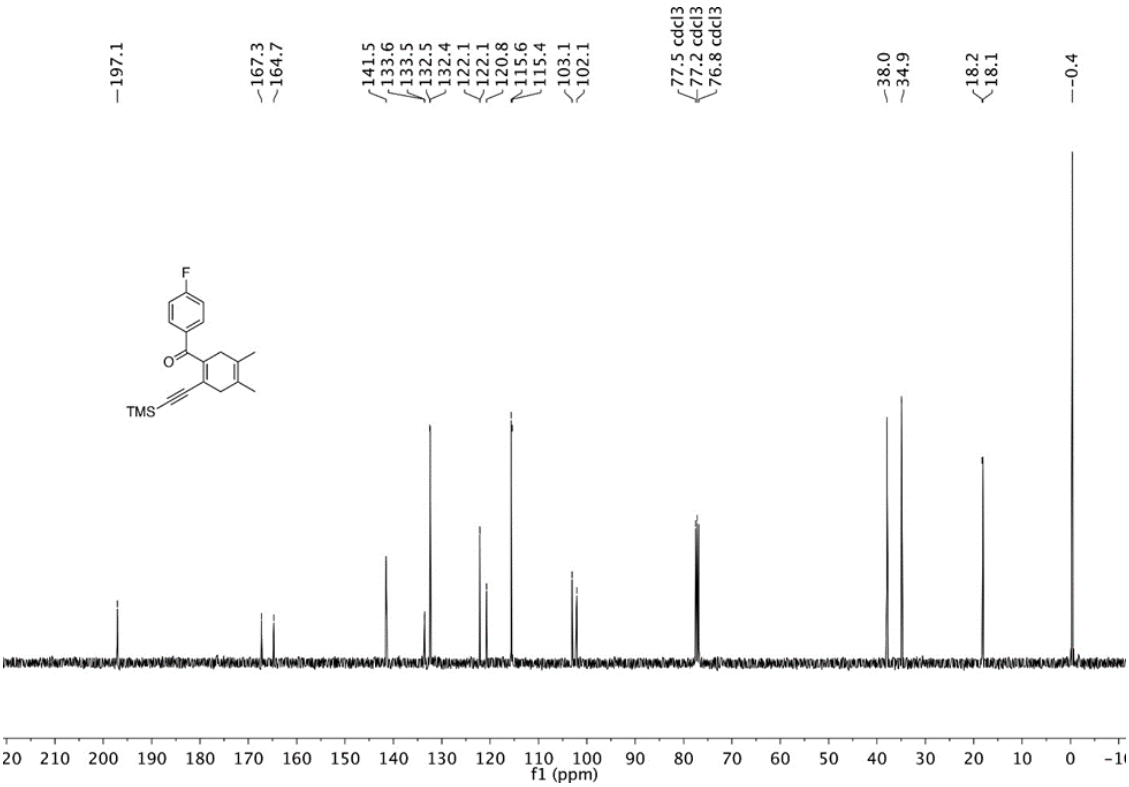


Figure S54. ^{13}C NMR spectrum of compound **3.2k**.

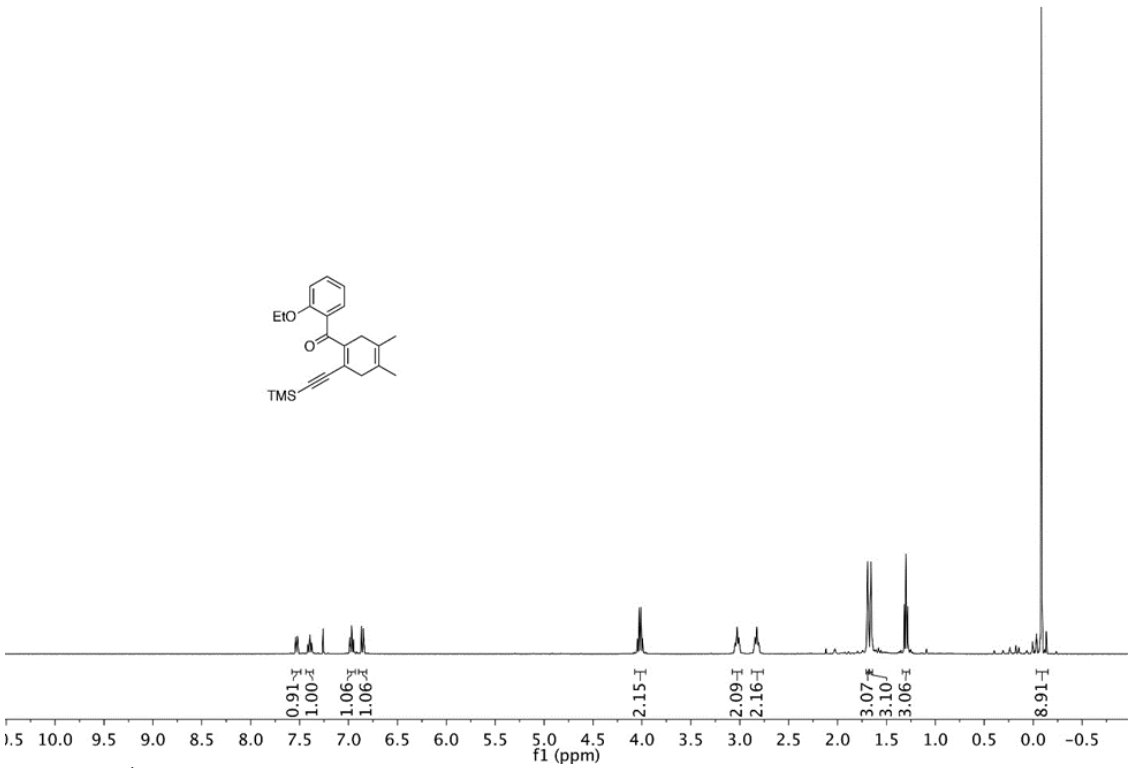


Figure S55. ^{1}H NMR spectrum of compound **3.2n**.

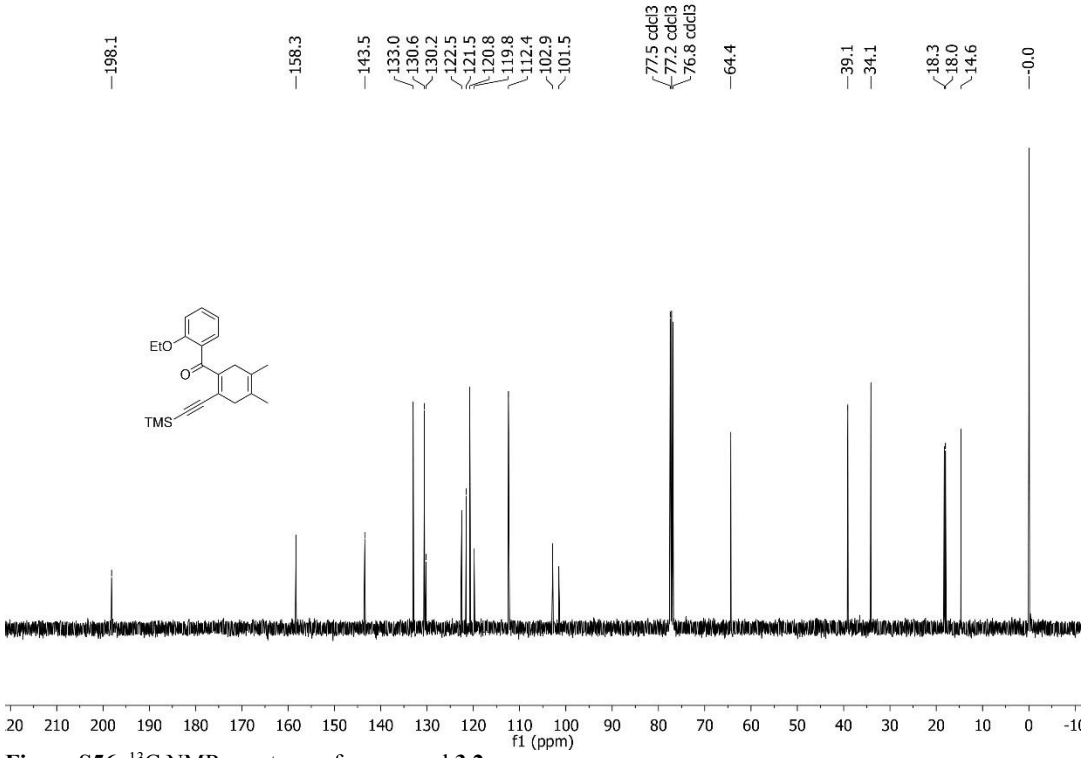


Figure S56. ^{13}C NMR spectrum of compound **3.2n**.

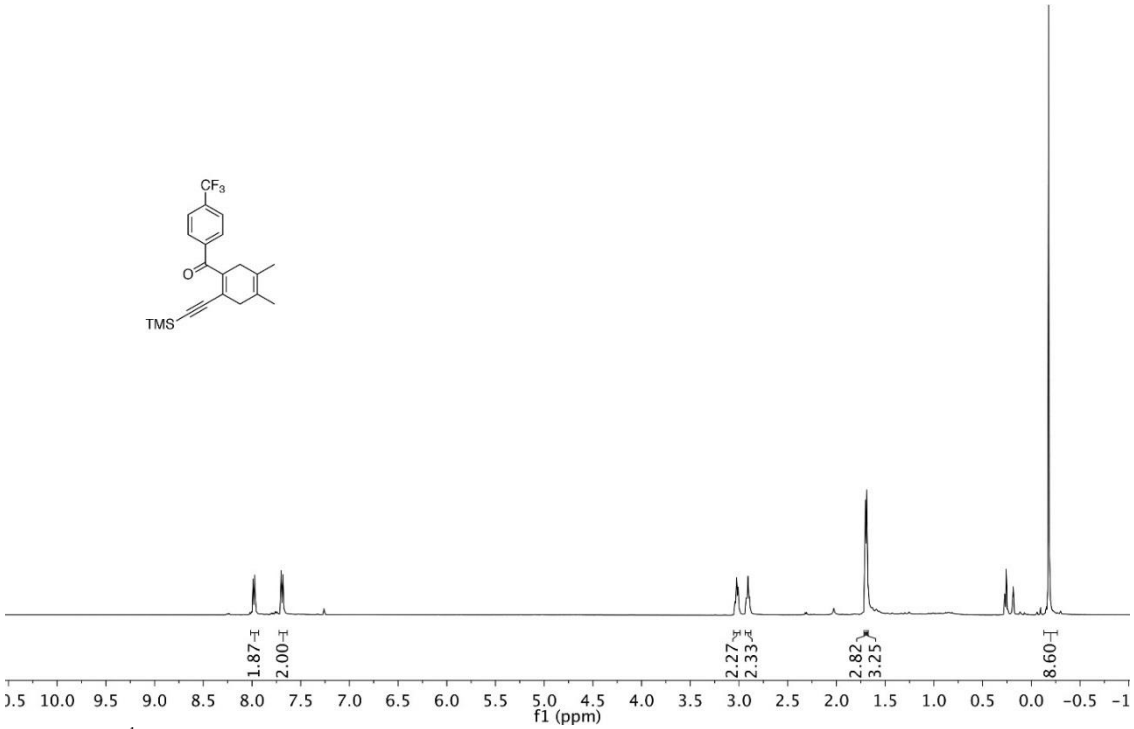


Figure S57. ^{1}H NMR spectrum of compound **3.2o**.

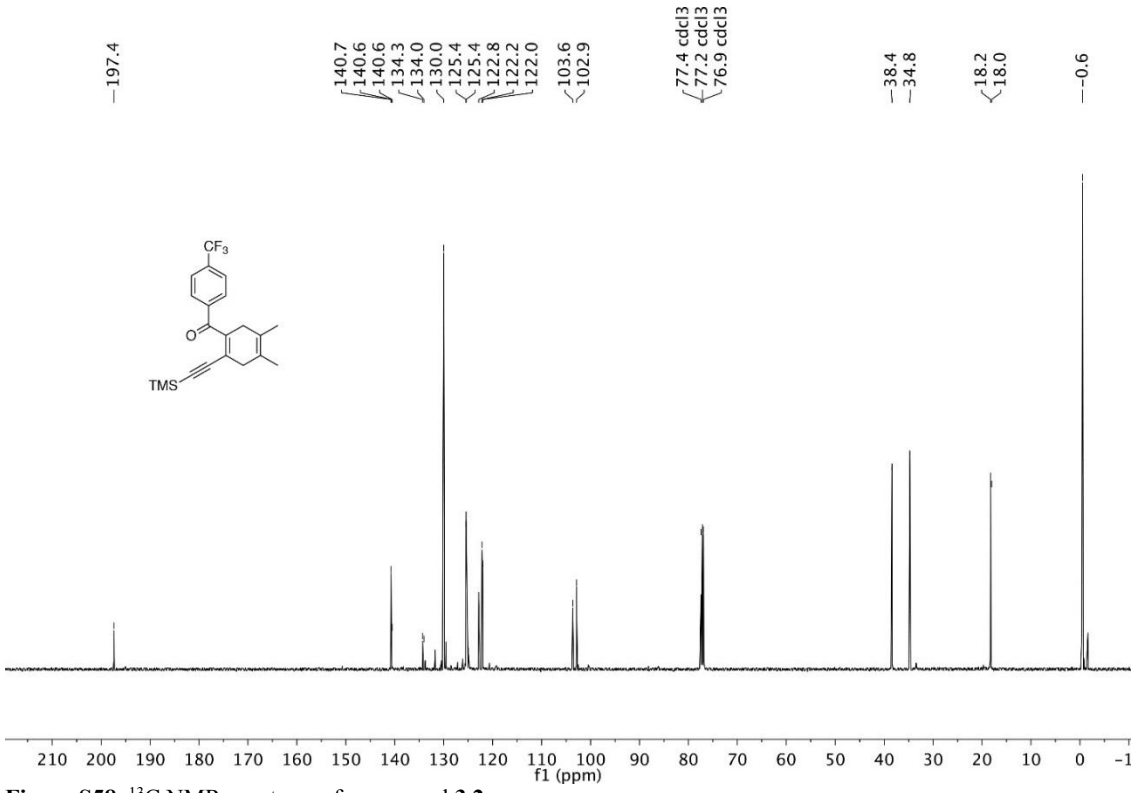


Figure S58. ^{13}C NMR spectrum of compound **3.2o**.

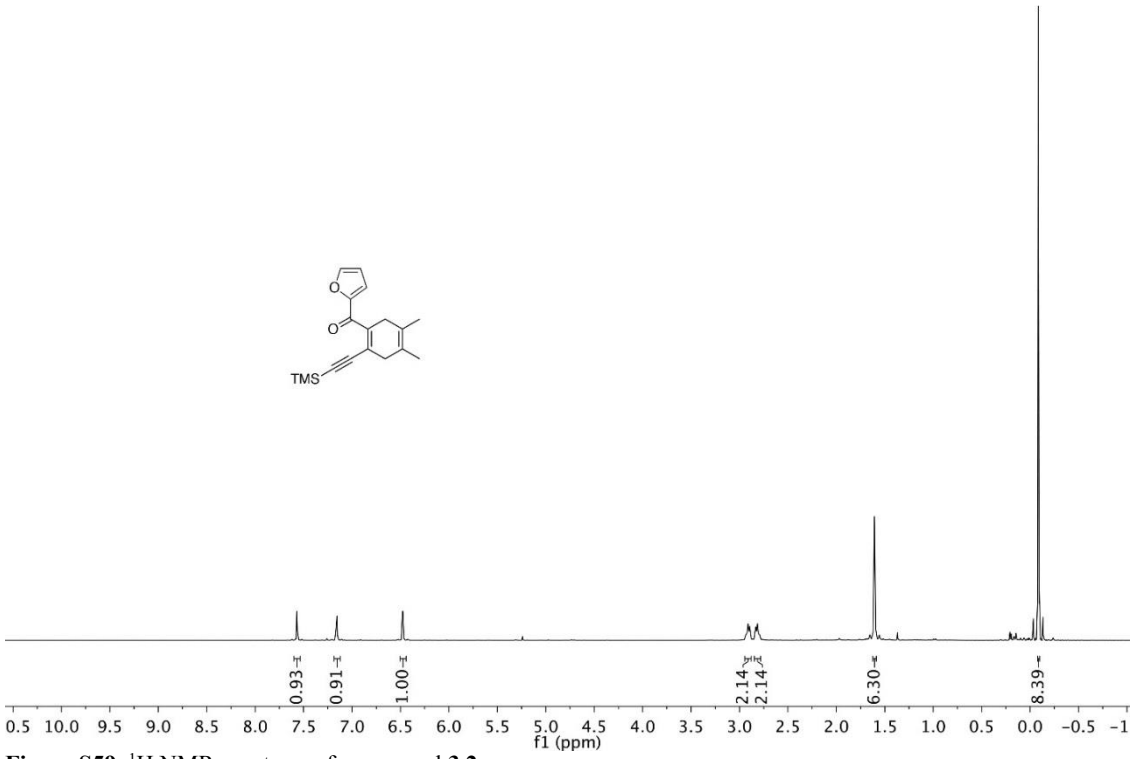


Figure S59. ^{1}H NMR spectrum of compound **3.2r**.

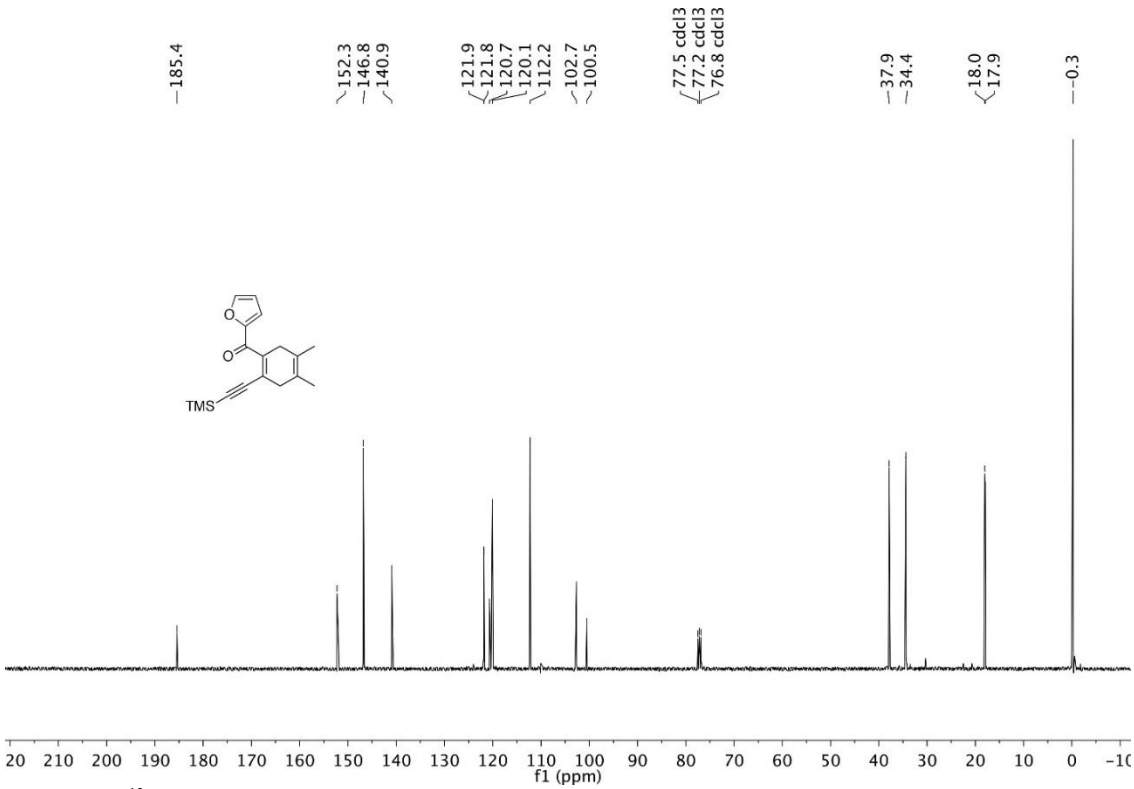


Figure S60. ^{13}C NMR spectrum of compound **3.2r**.

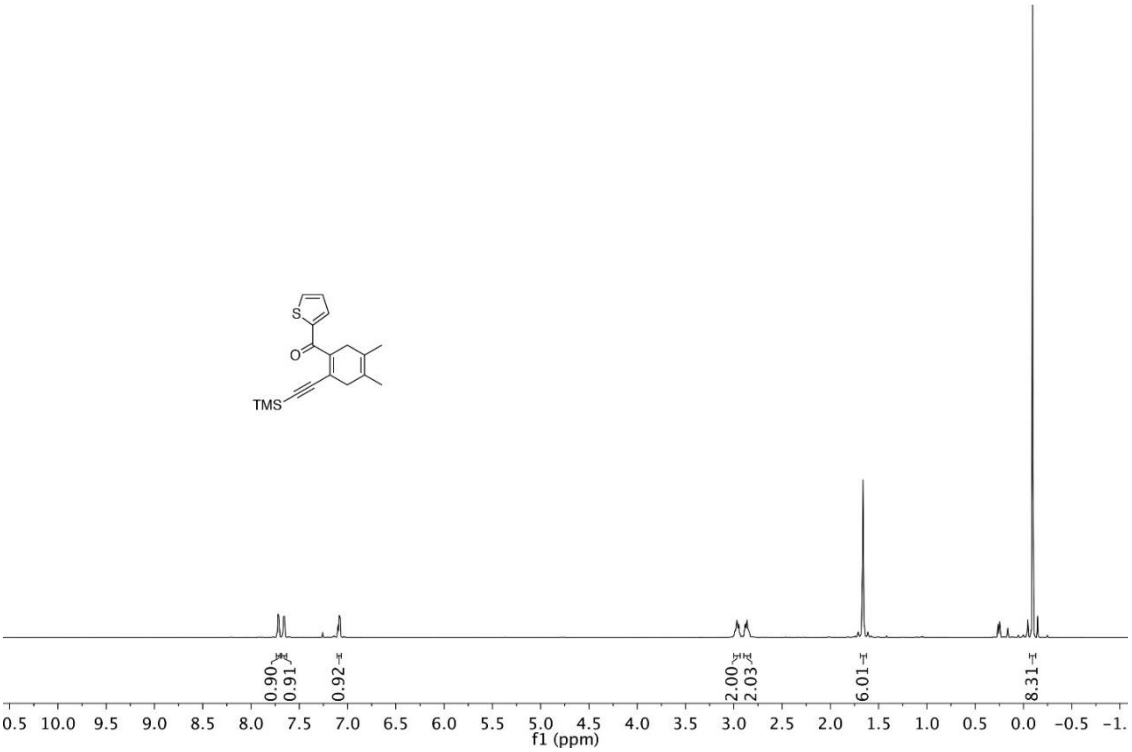


Figure S61. [1]H NMR spectrum of compound **3.2s**.

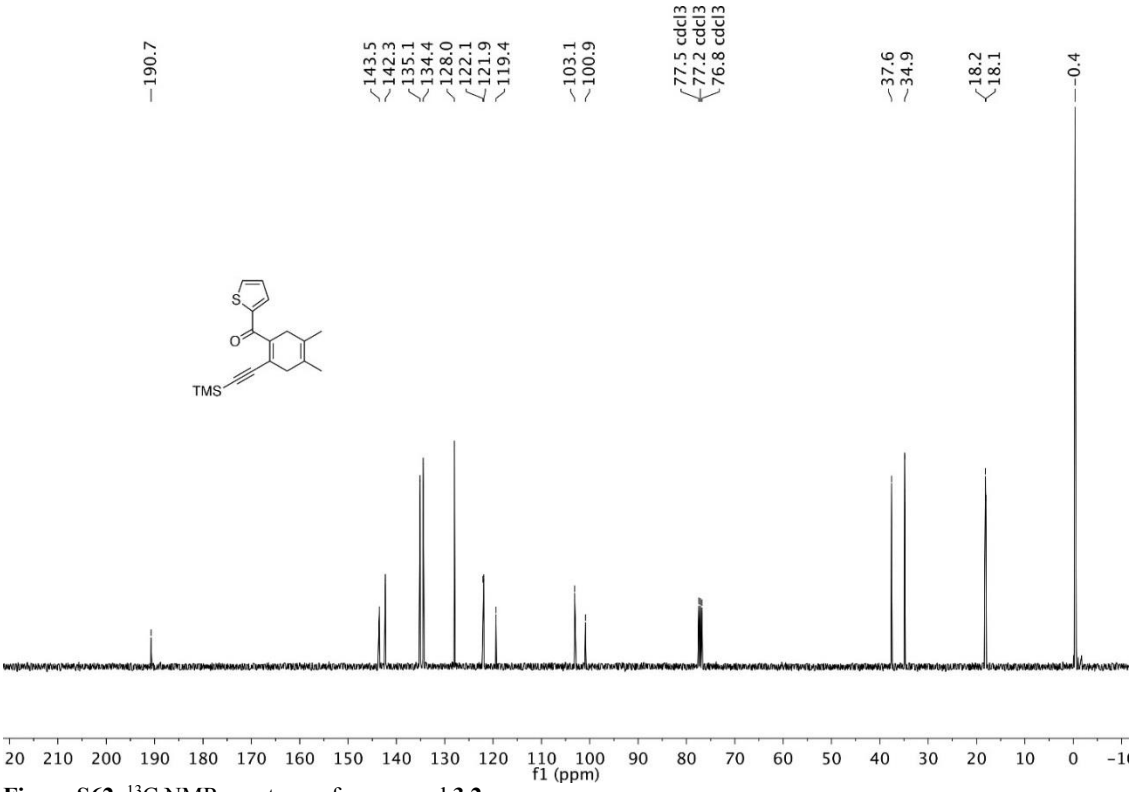


Figure S62. [13]C NMR spectrum of compound **3.2s**.

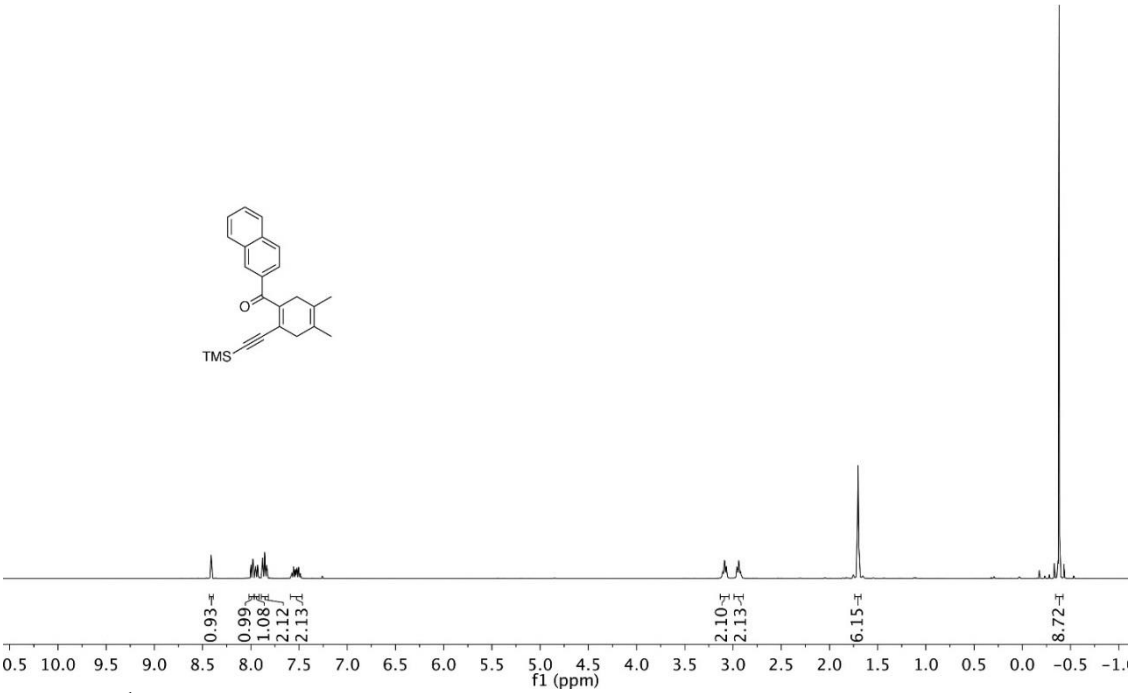


Figure S63. ^{1}H NMR spectrum of compound **3.2t**.

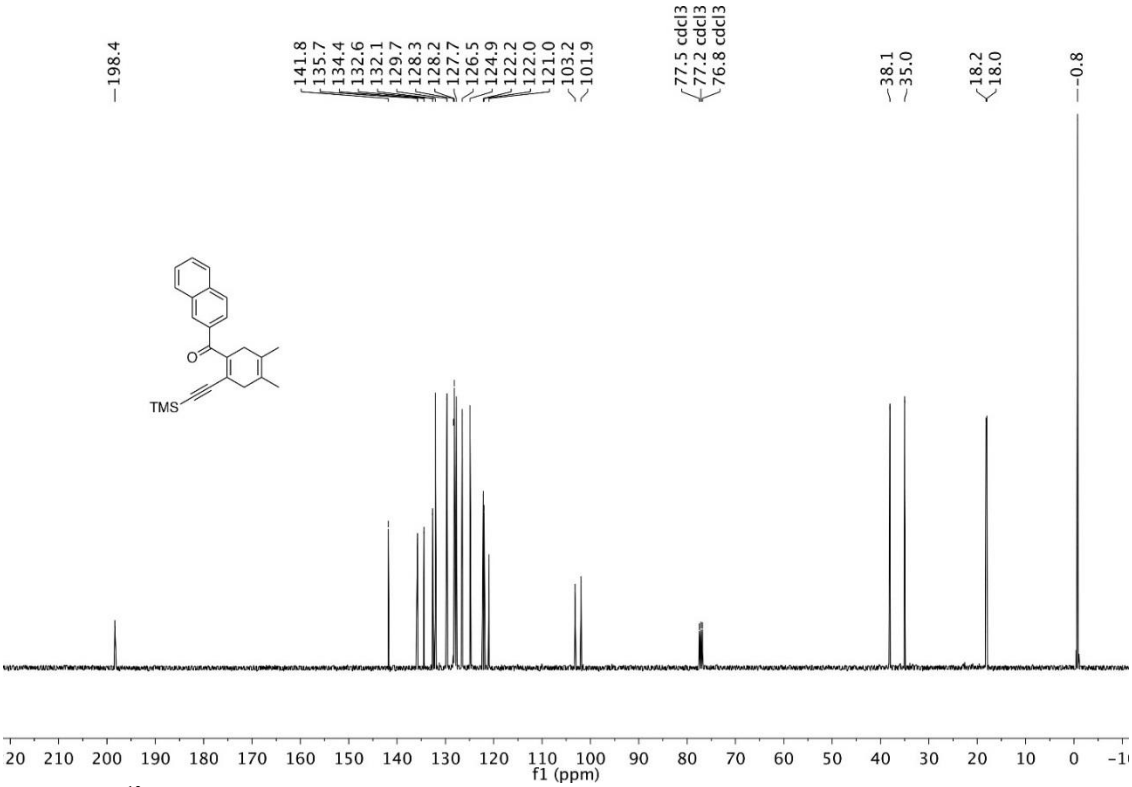


Figure S64. ^{13}C NMR spectrum of compound **3.2t**.

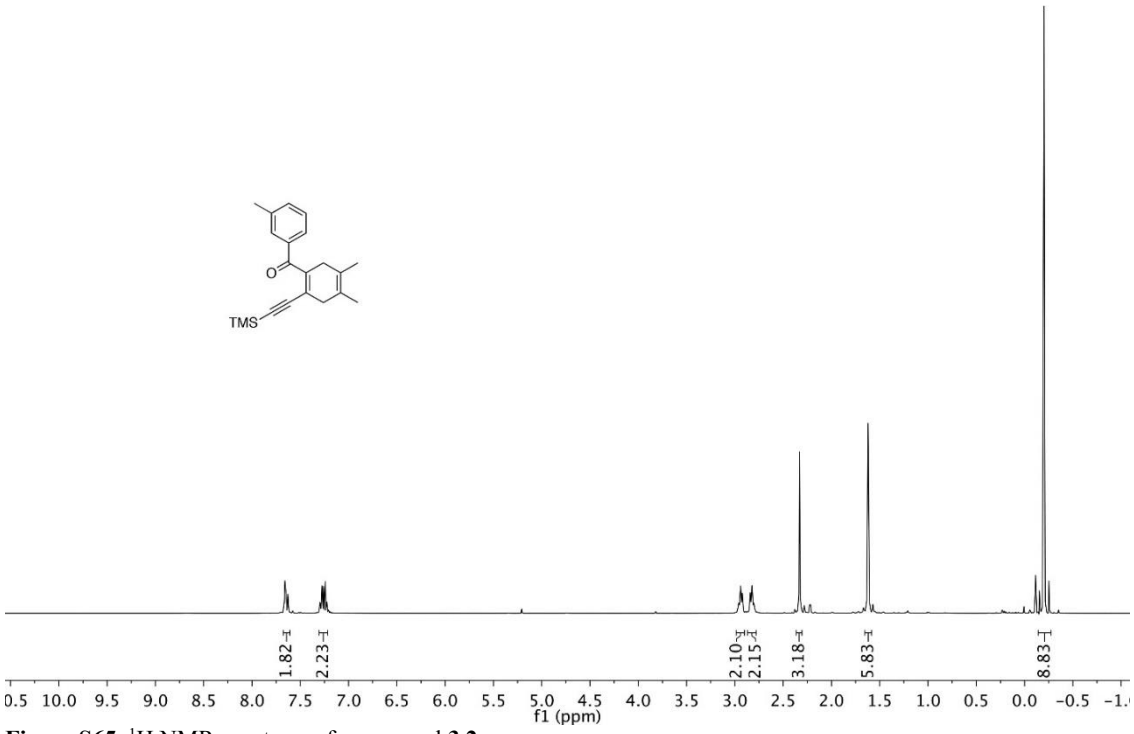


Figure S65. ^{1}H NMR spectrum of compound **3.2u**.

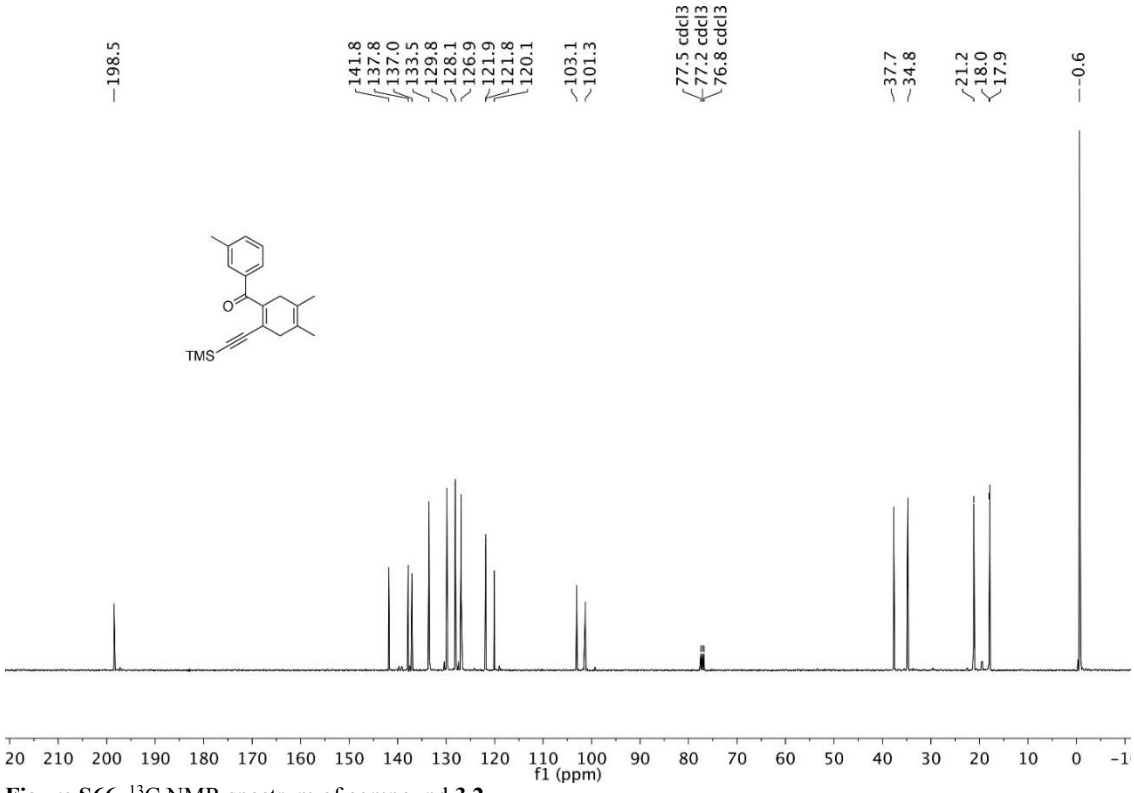


Figure S66. ^{13}C NMR spectrum of compound **3.2u**.

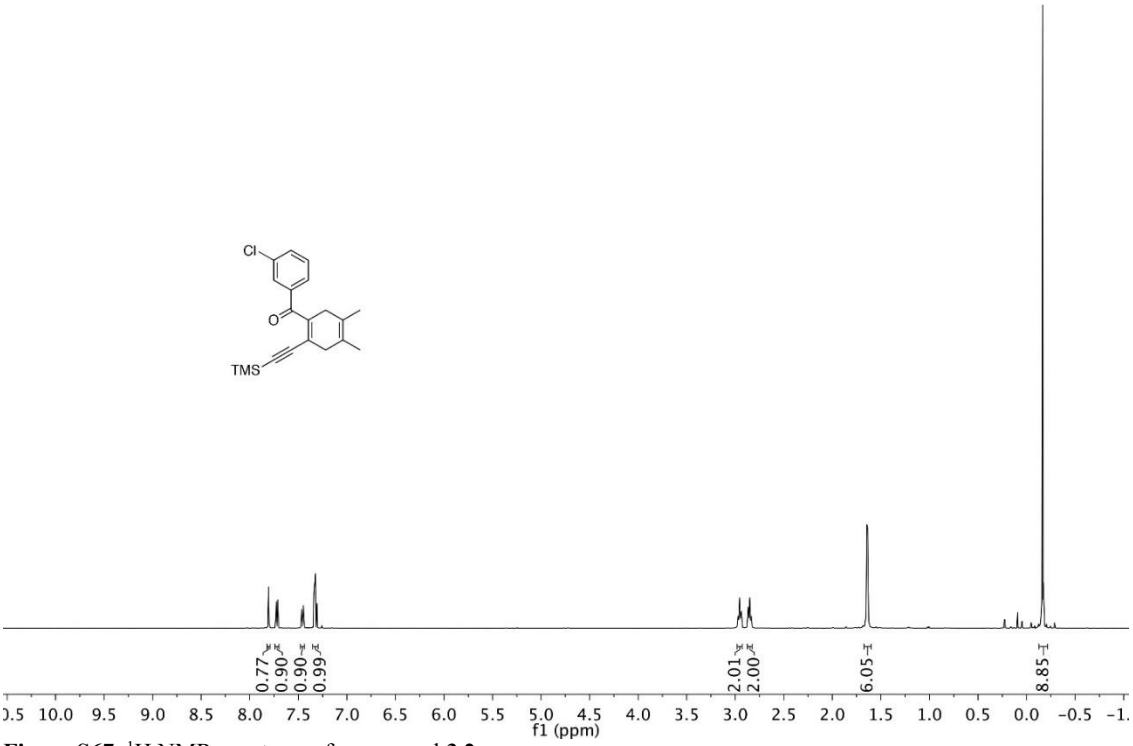


Figure S67. ^{1}H NMR spectrum of compound **3.2v**.

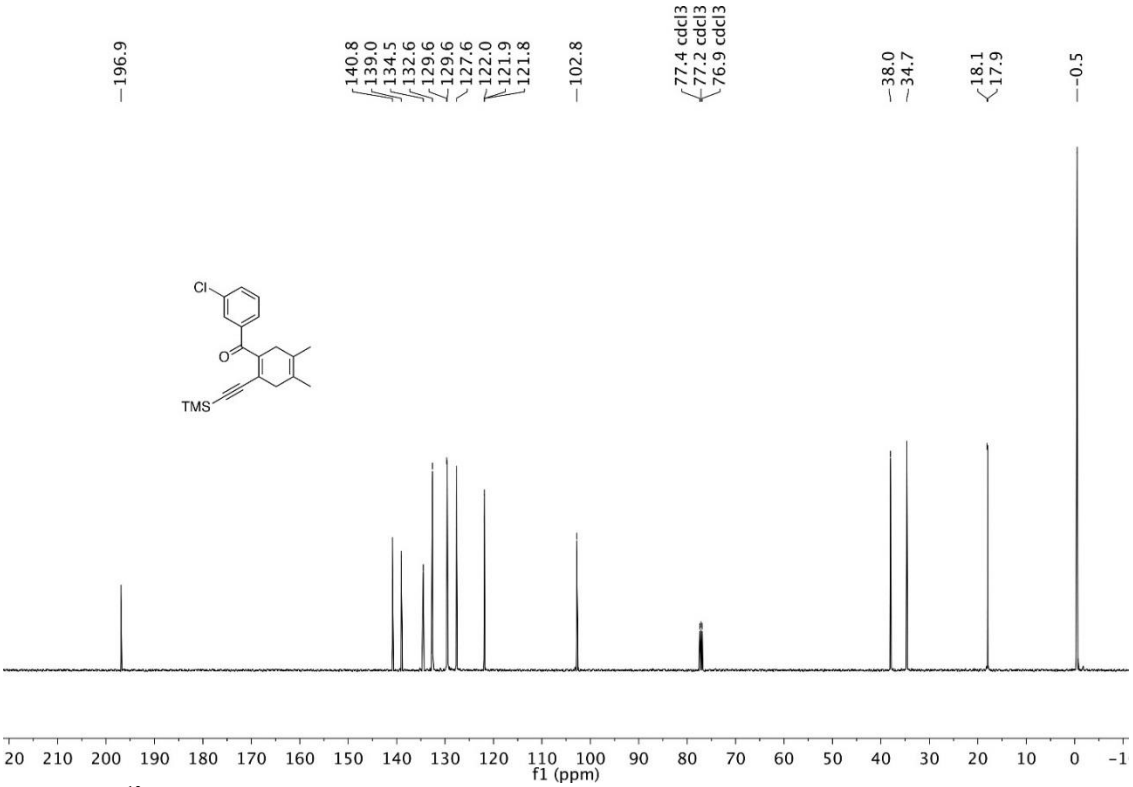


Figure S68. ^{13}C NMR spectrum of compound **3.2v**.

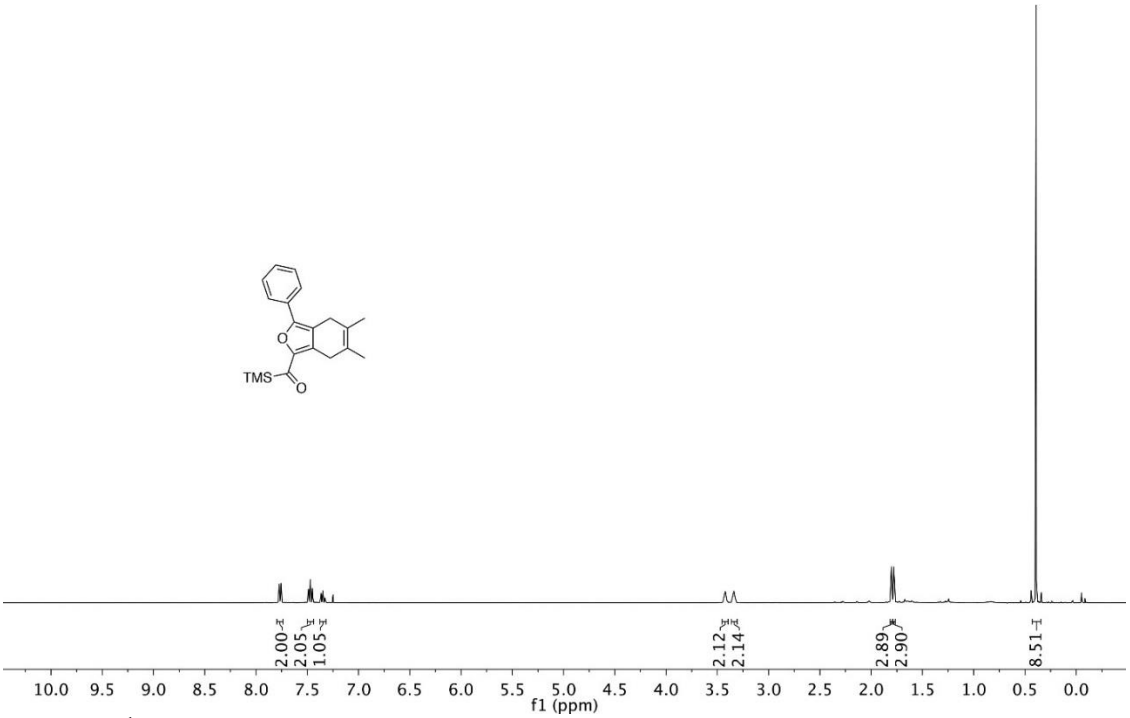


Figure S69. ^{1}H NMR spectrum of compound **3.3a**.

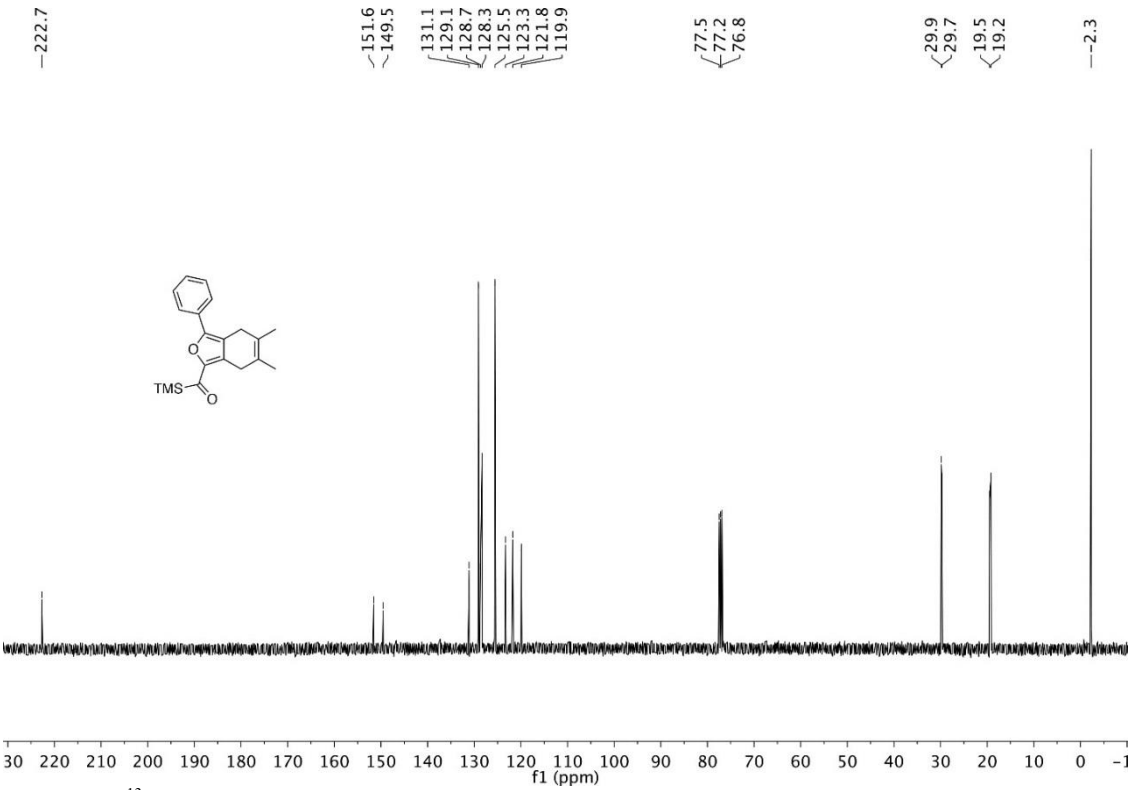


Figure S70. ^{13}C NMR spectrum of compound **3.3a**.

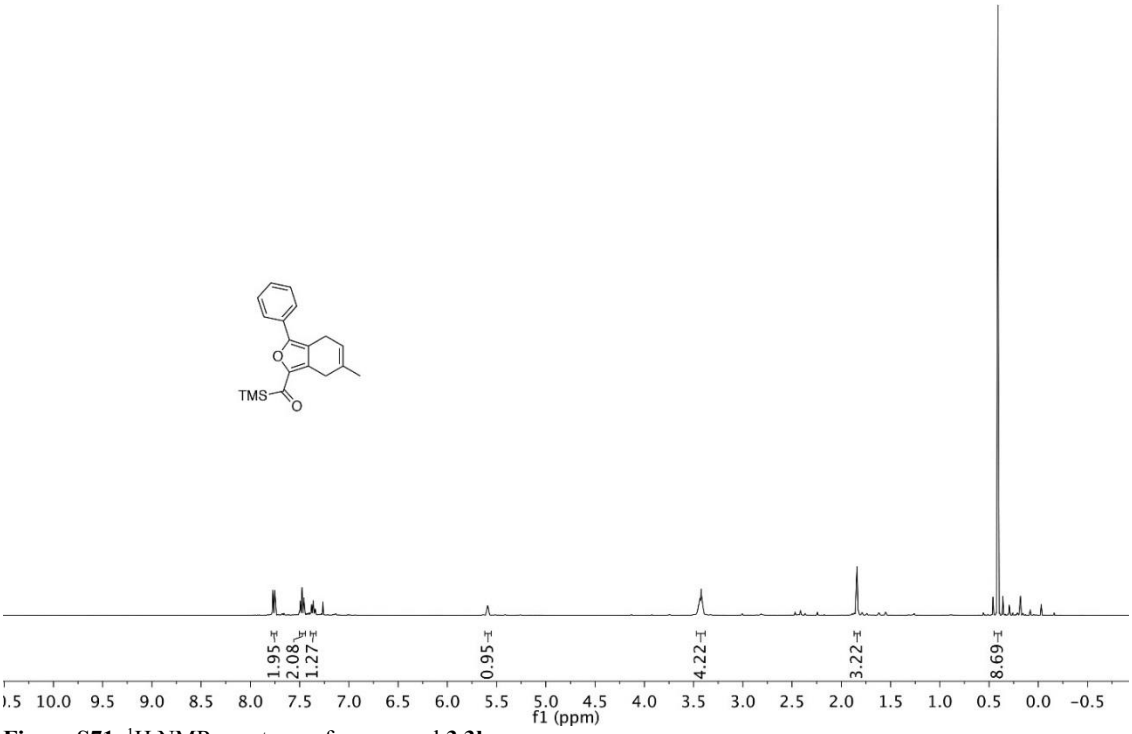


Figure S71. ^{1}H NMR spectrum of compound **3.3b**.

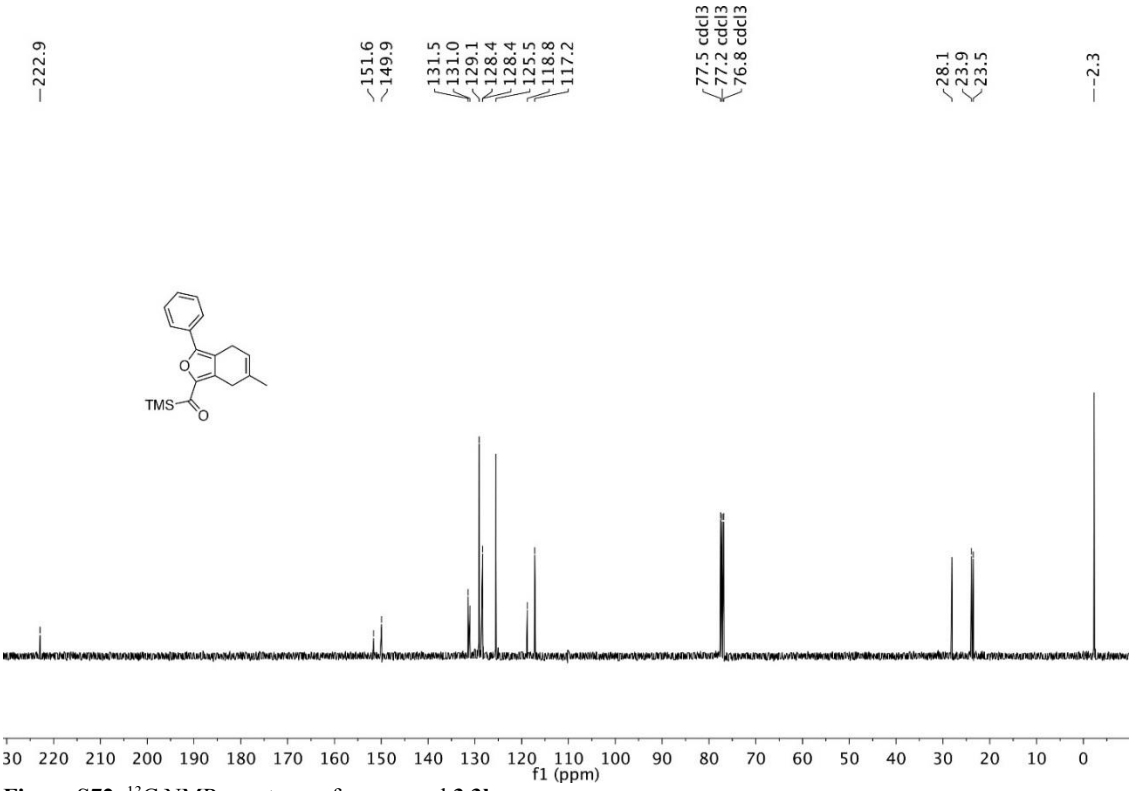


Figure S72. ^{13}C NMR spectrum of compound **3.3b**.

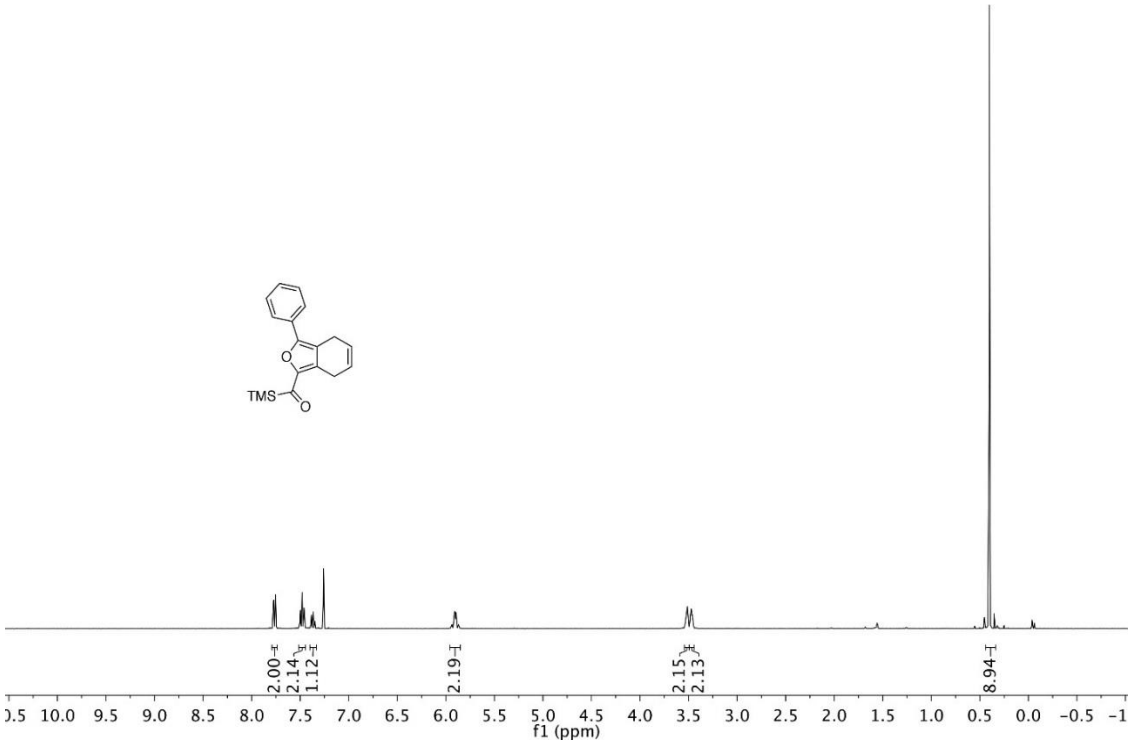


Figure S73. ^{1}H NMR spectrum of compound **3.3c**.

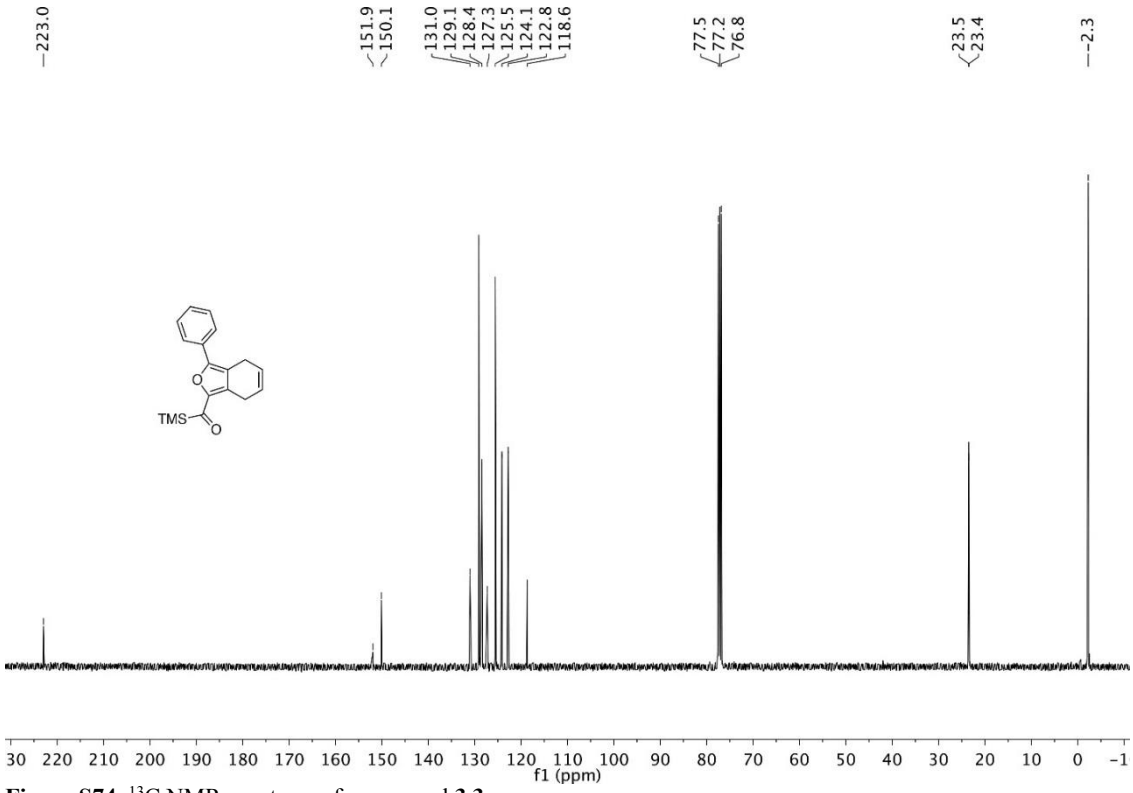


Figure S74. ^{13}C NMR spectrum of compound **3.3c**.

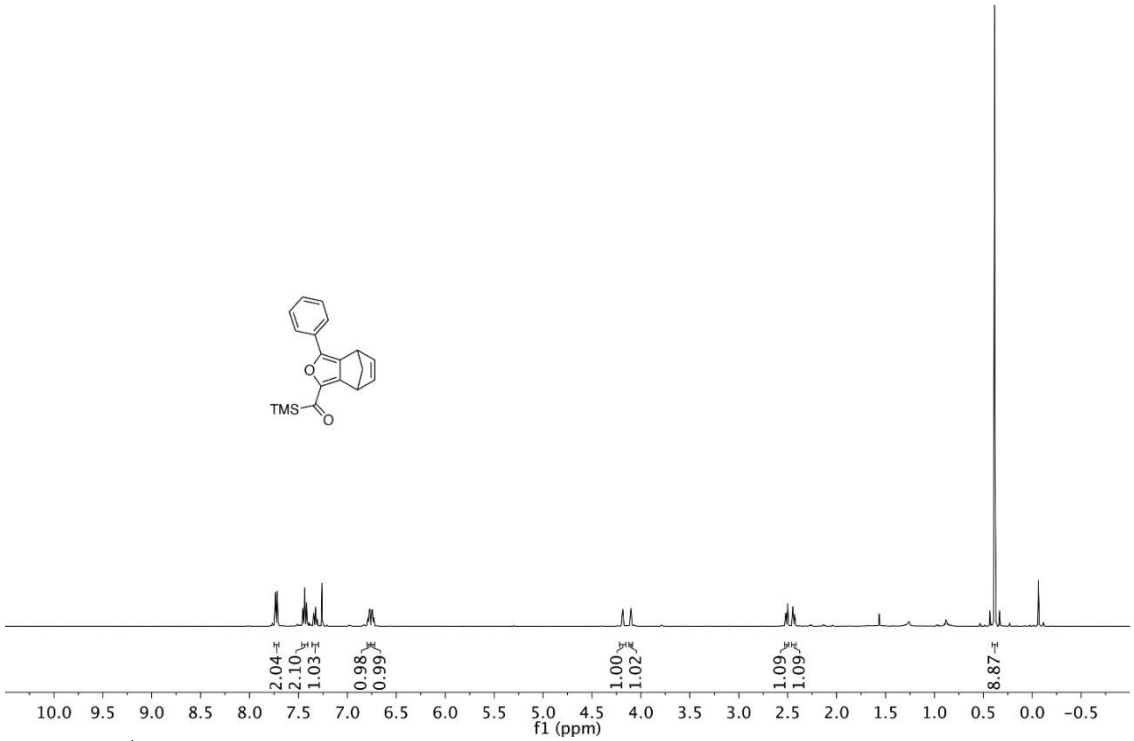


Figure S75. ^{1}H NMR spectrum of compound **3.3d**.

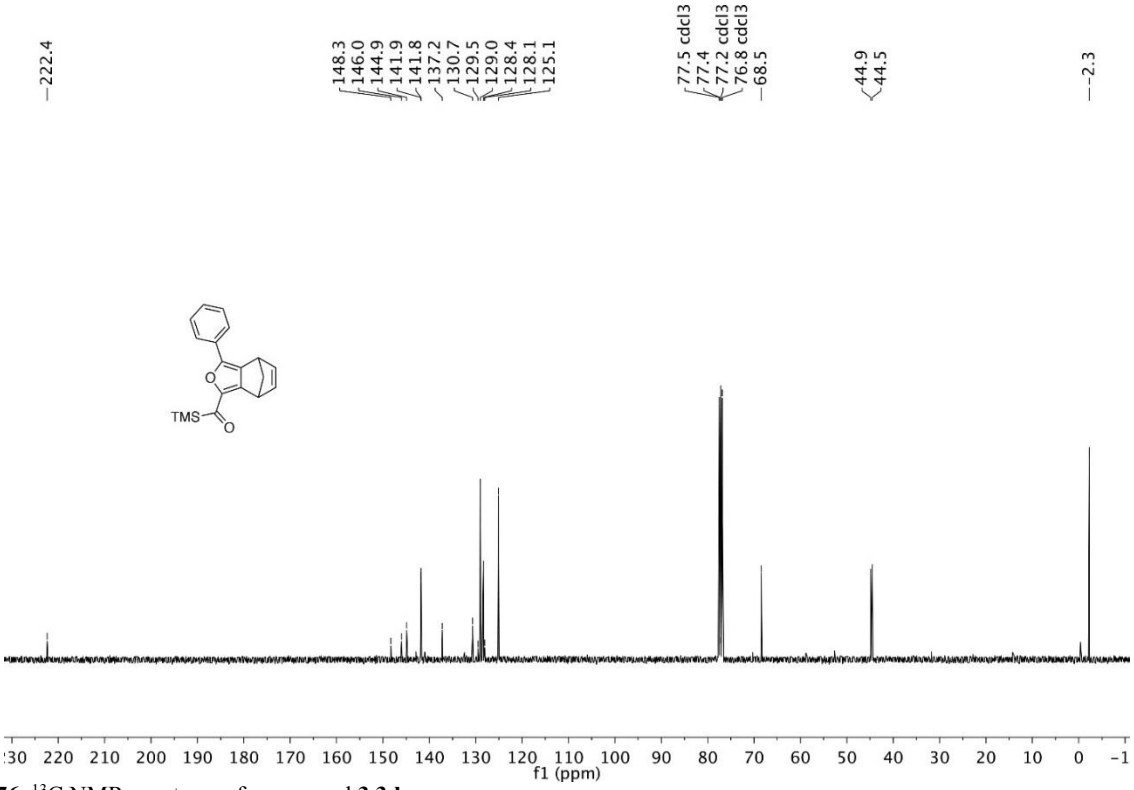


Figure S76. ^{13}C NMR spectrum of compound **3.3d**.

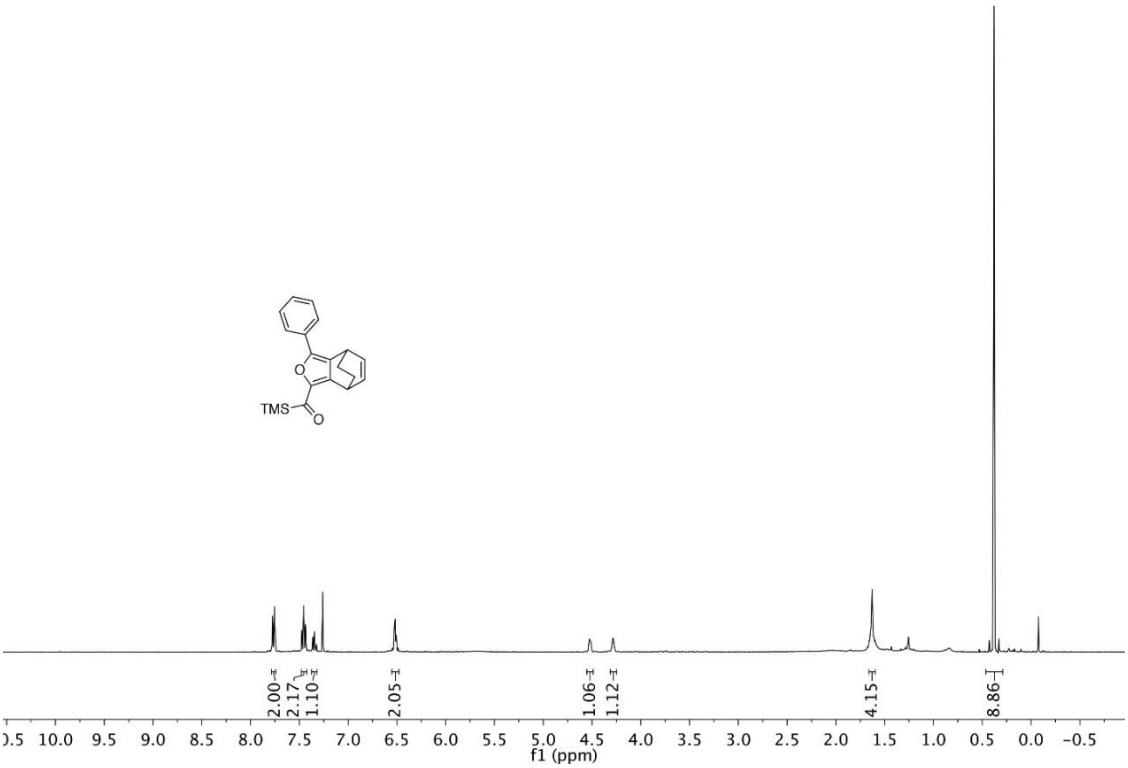


Figure S77. [1]H NMR spectrum of compound **3.3e**.

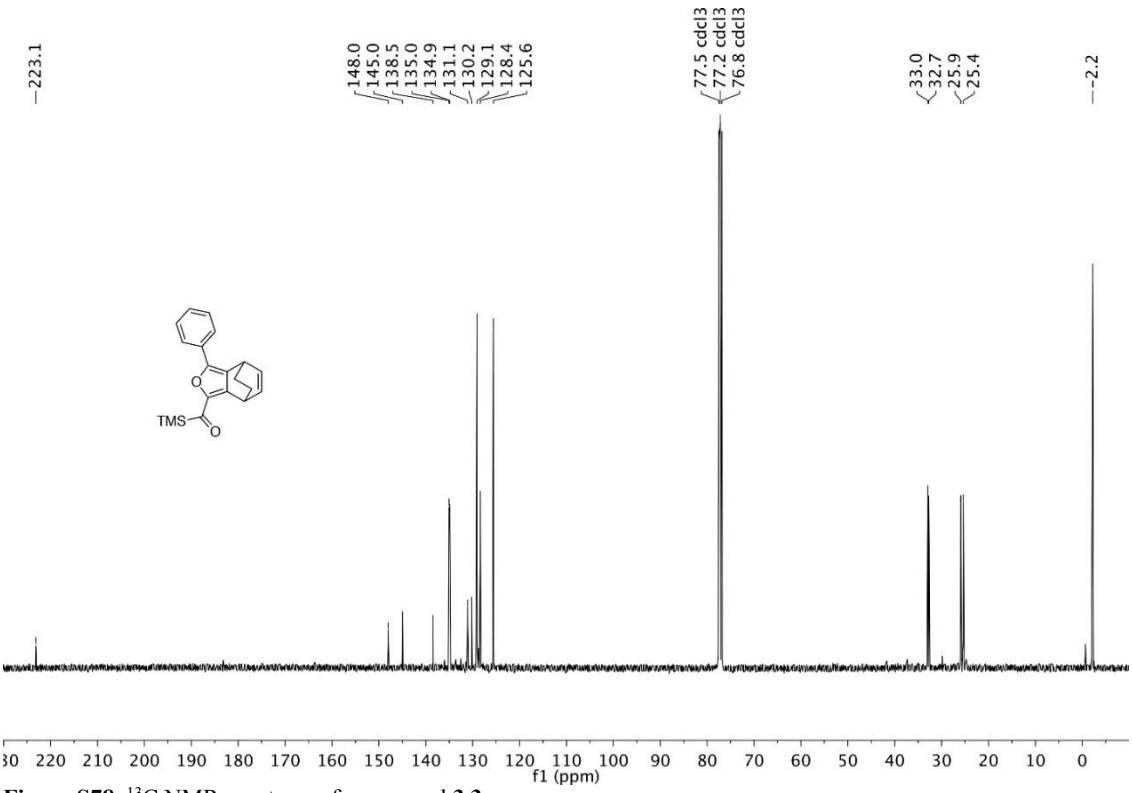


Figure S78. [13]C NMR spectrum of compound **3.3e**.

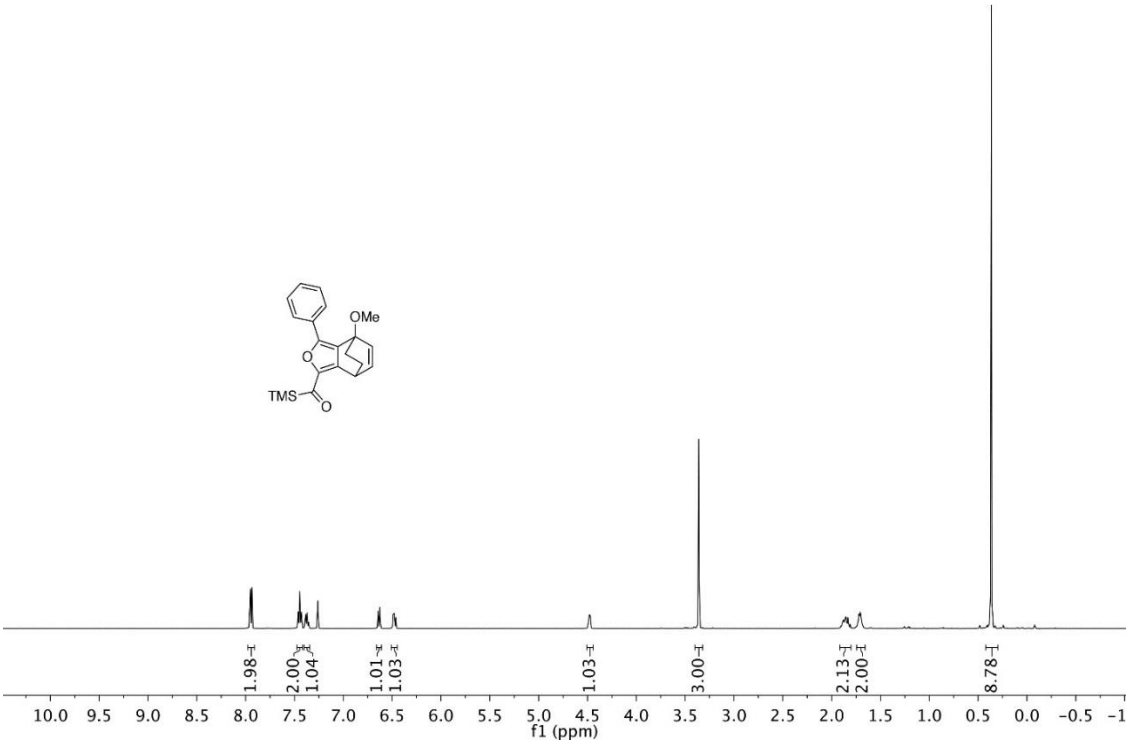


Figure S79. ^{1}H NMR spectrum of compound **3.3f**.

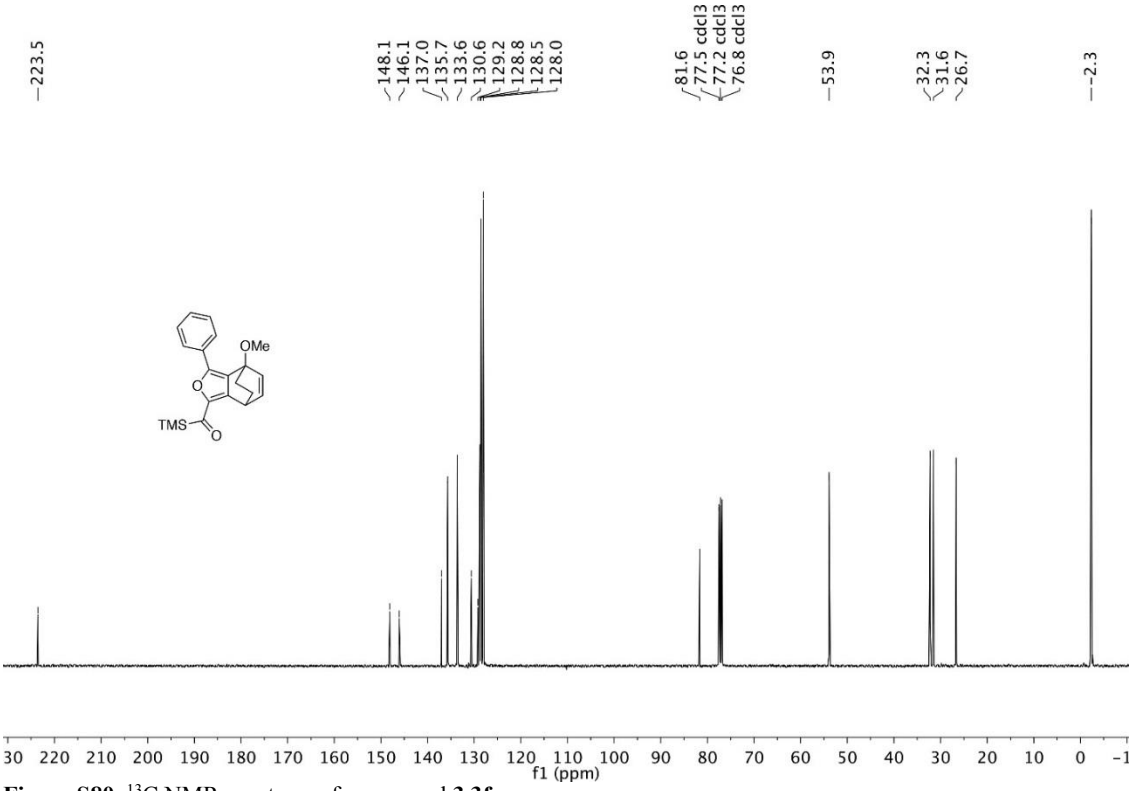


Figure S80. ^{13}C NMR spectrum of compound **3.3f**.

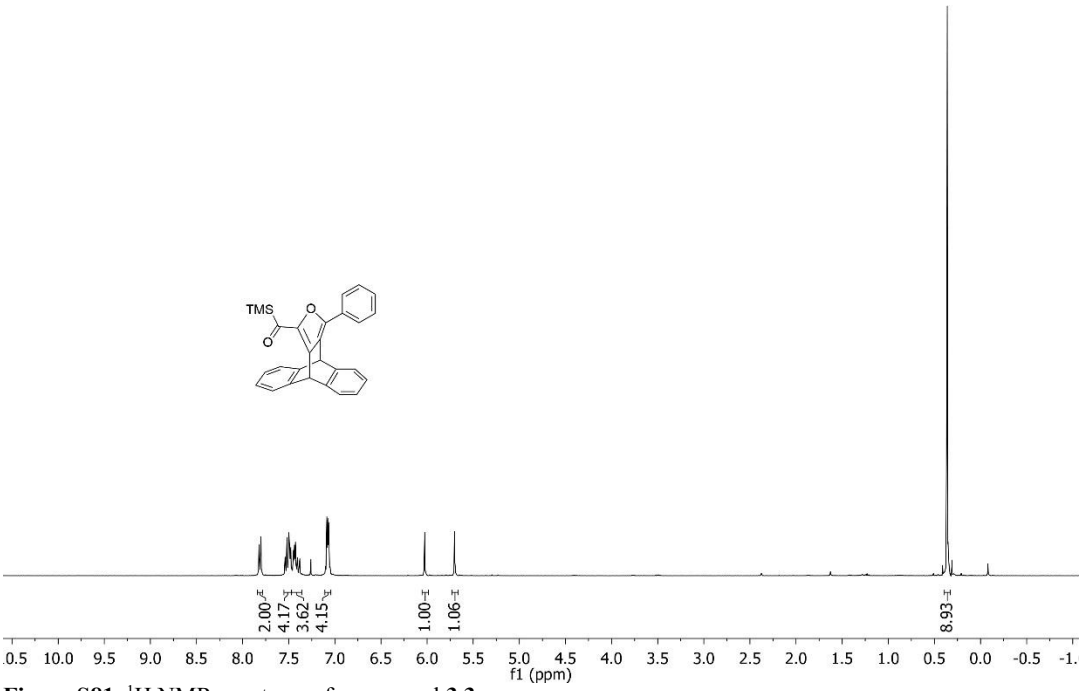


Figure S81. ^{1}H NMR spectrum of compound **3.3g**.

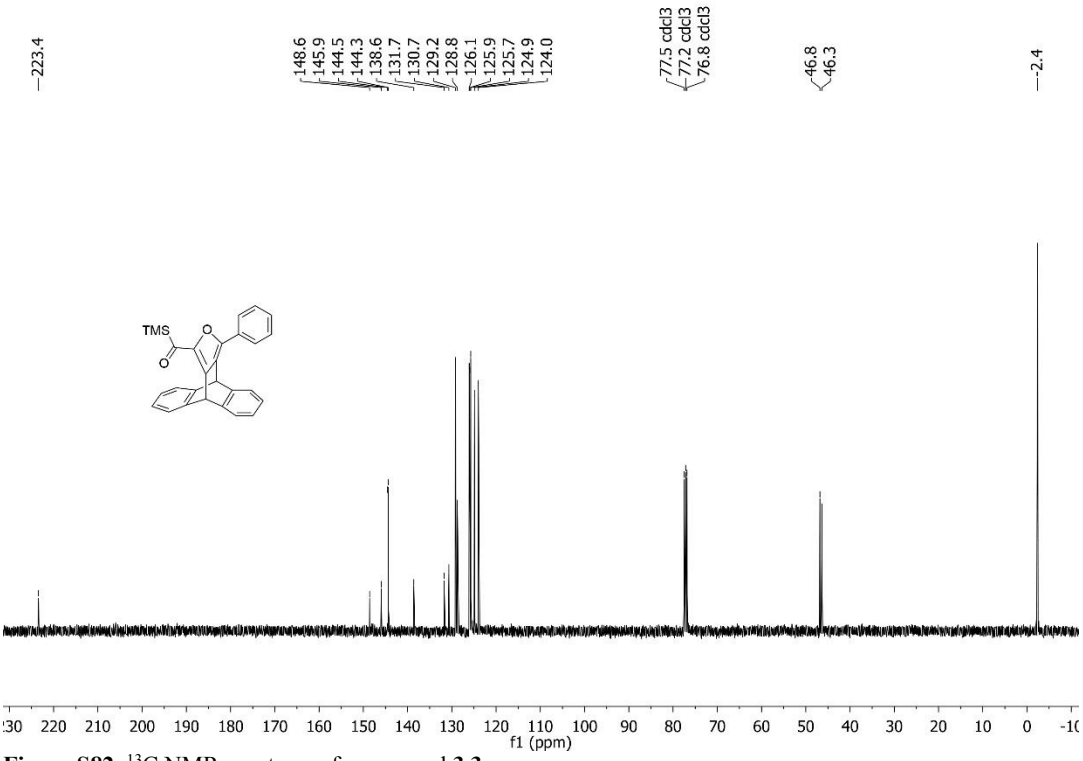


Figure S82. ^{13}C NMR spectrum of compound **3.3g**.

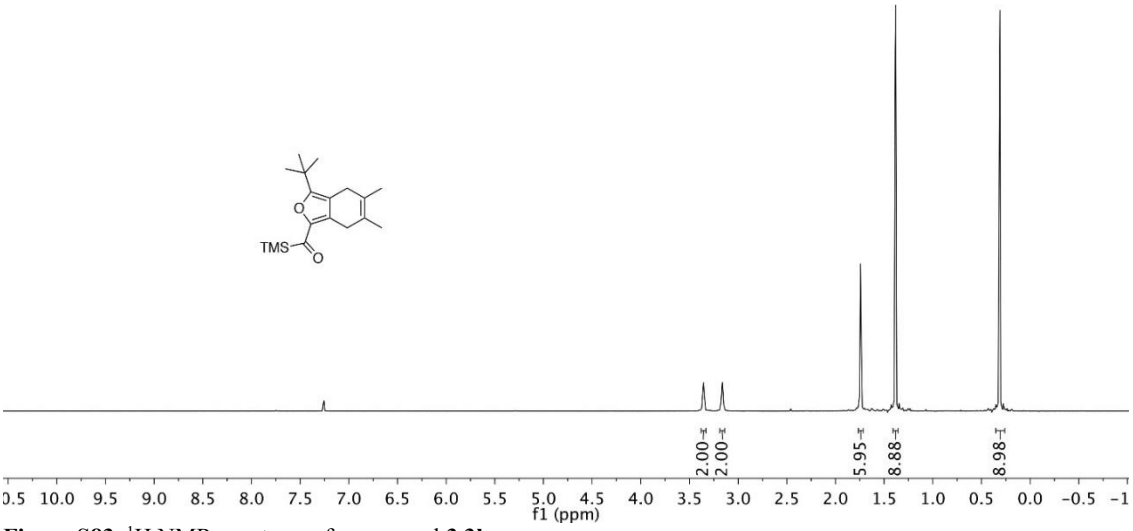


Figure S83. ^{1}H NMR spectrum of compound **3.3h**.

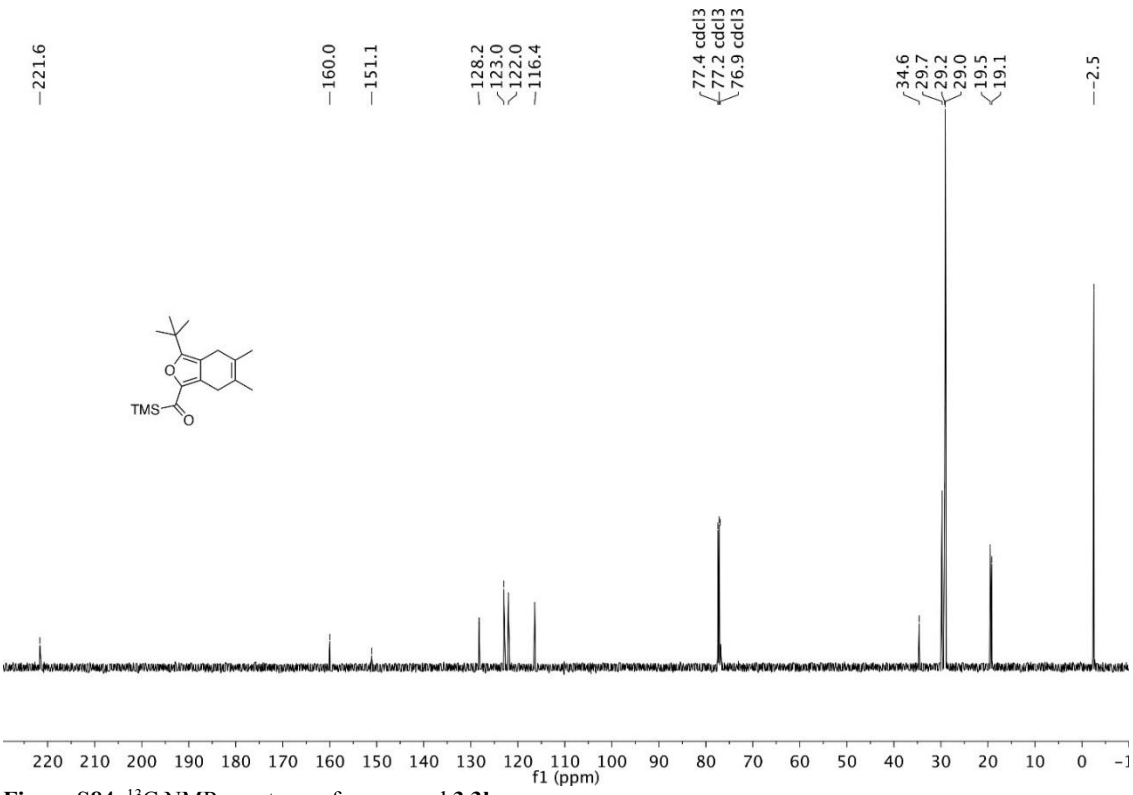


Figure S84. ^{13}C NMR spectrum of compound **3.3h**.

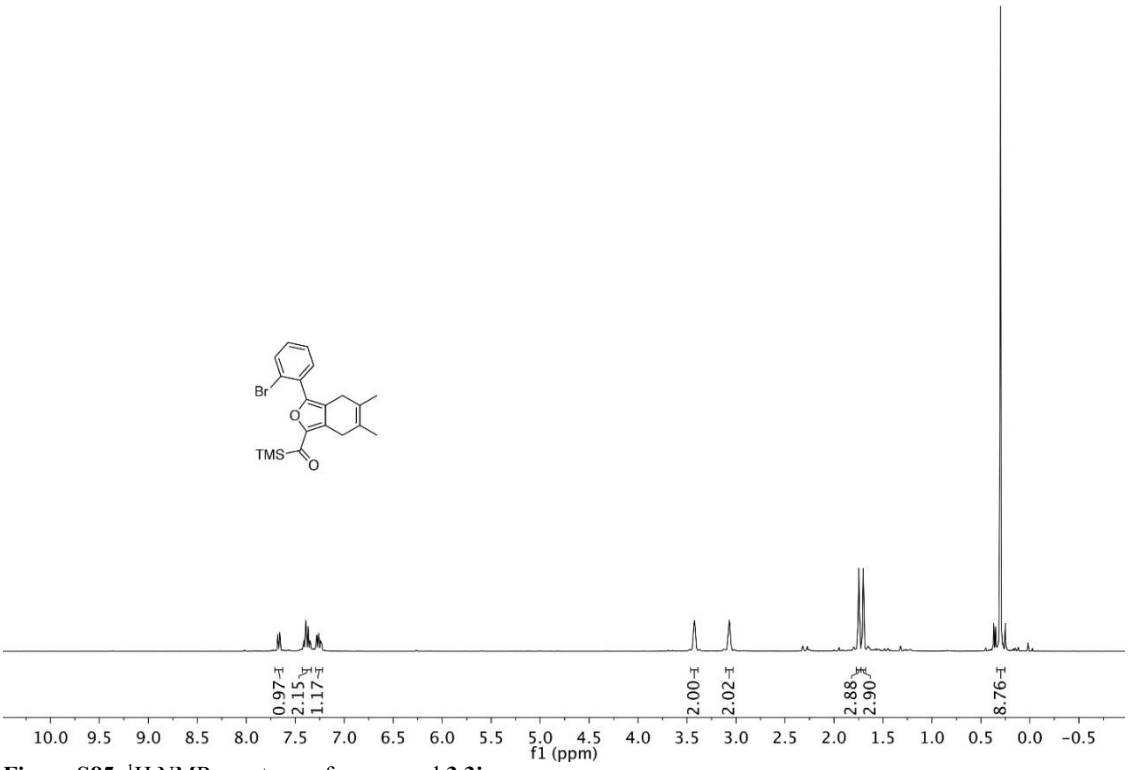


Figure S85. [1]H NMR spectrum of compound **3.3i**.

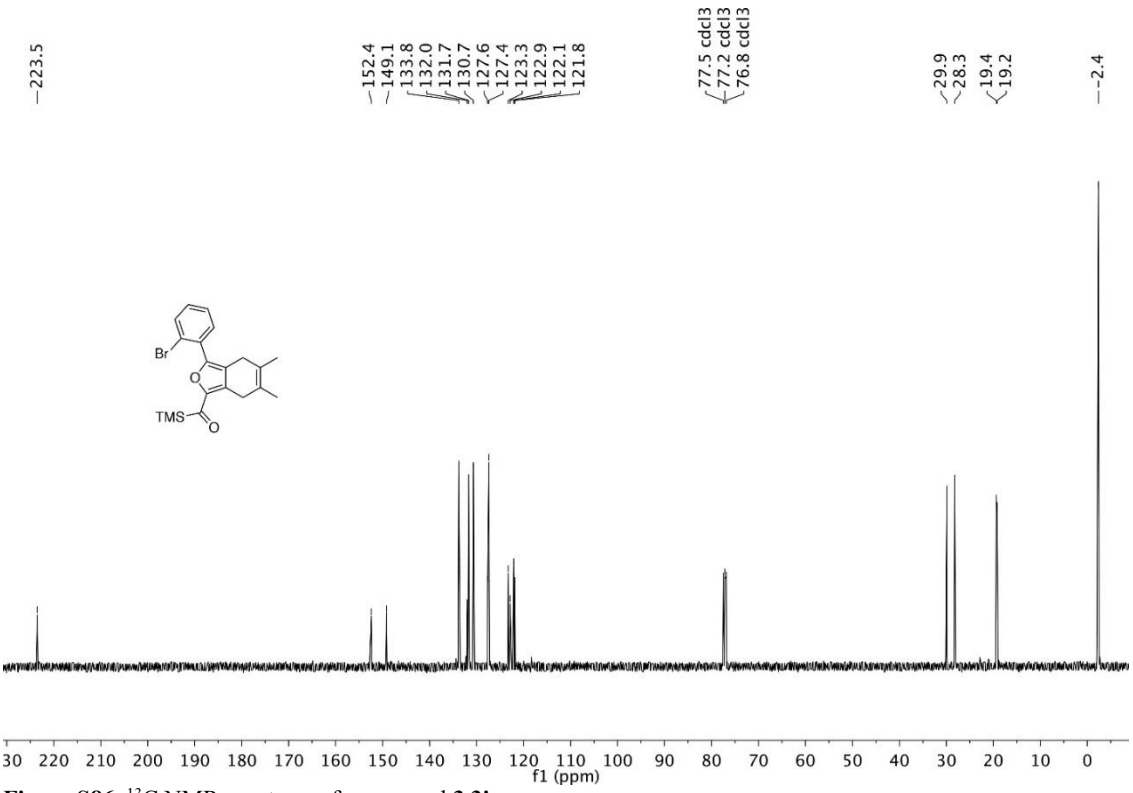


Figure S86. [13]C NMR spectrum of compound **3.3i**.

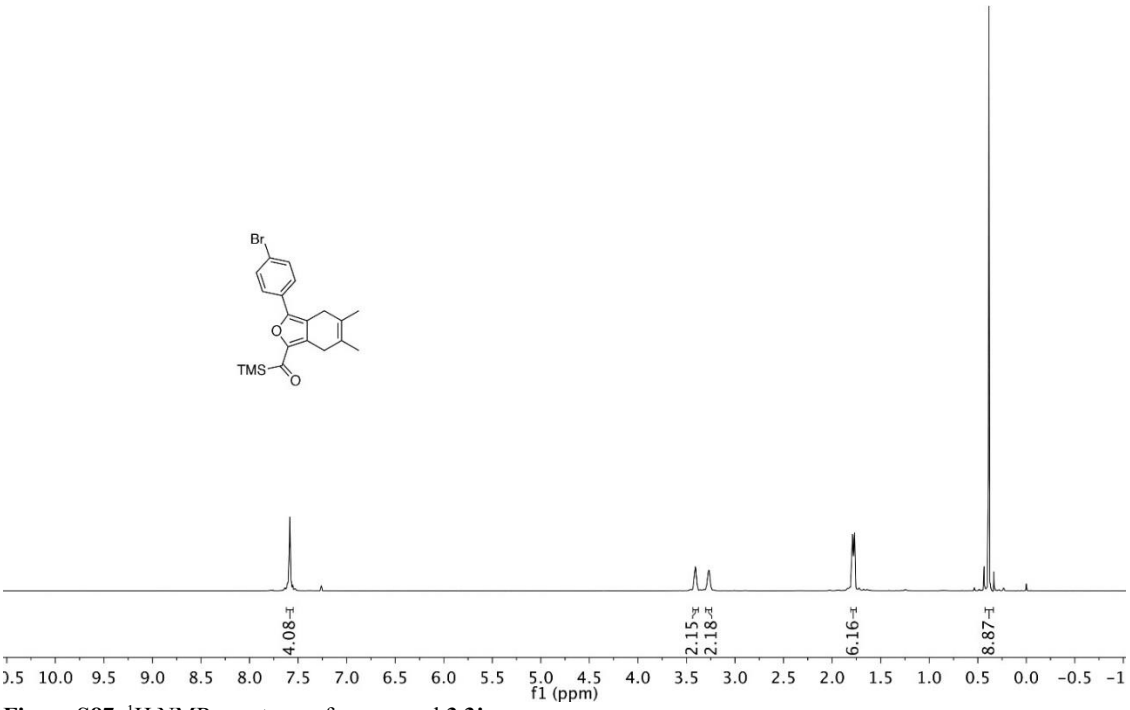


Figure S87. [1]H NMR spectrum of compound **3.3j**.

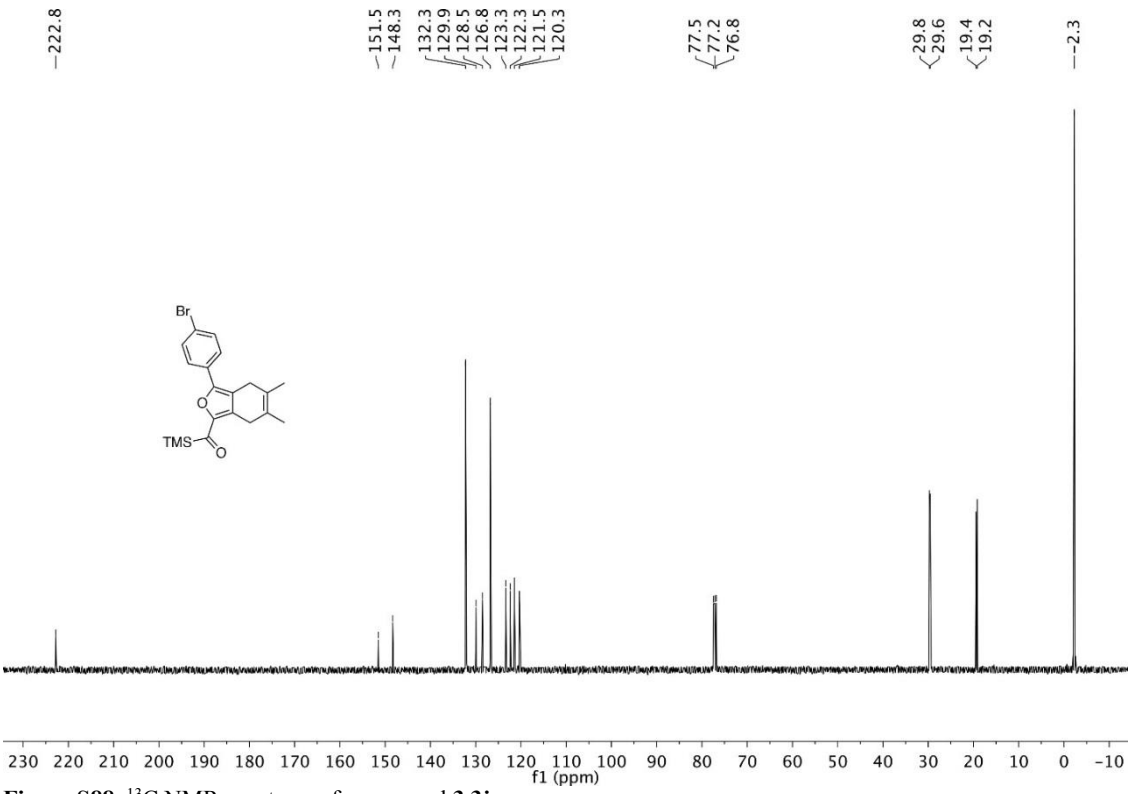


Figure S88. [13]C NMR spectrum of compound **3.3j**.

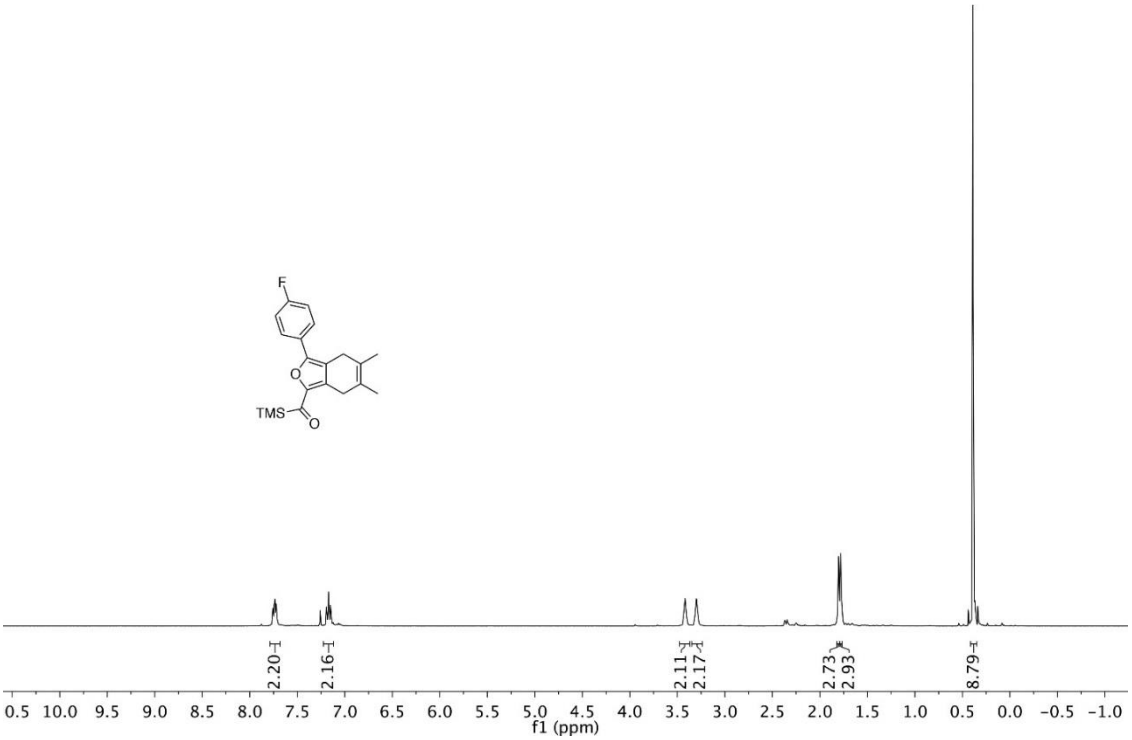


Figure S89. ^{1}H NMR spectrum of compound **3.3k**.

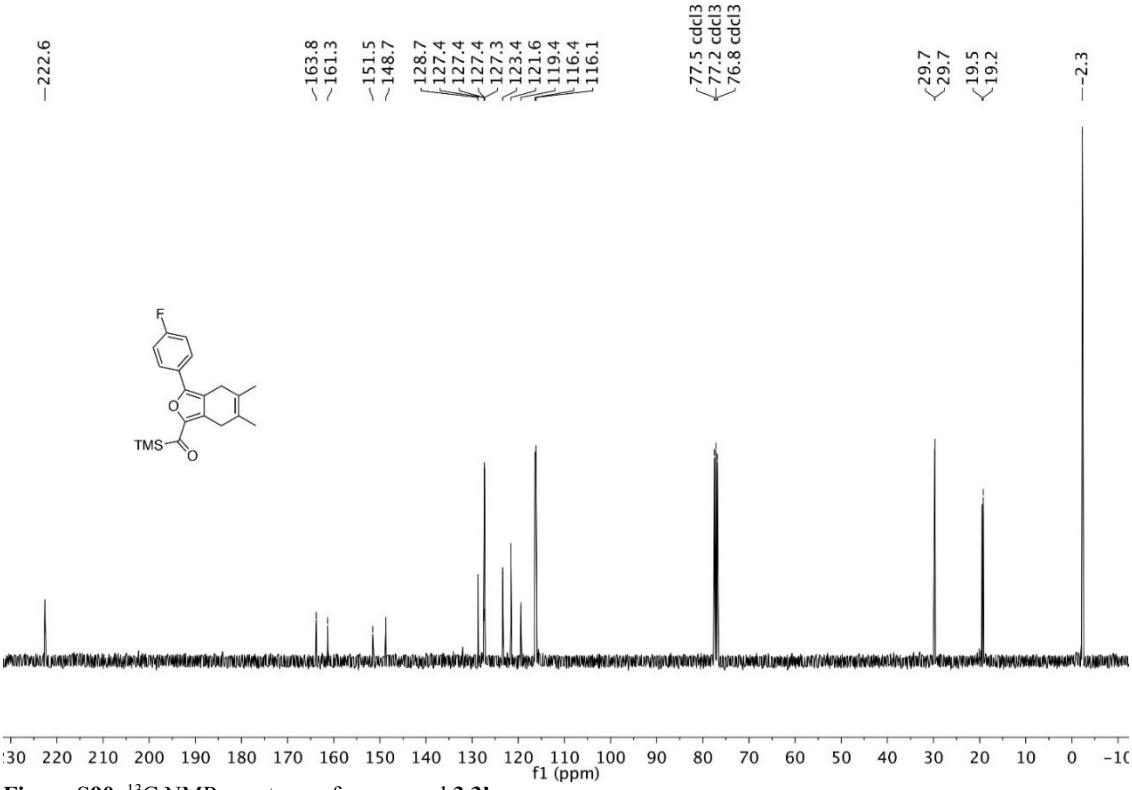


Figure S90. ^{13}C NMR spectrum of compound **3.3k**.

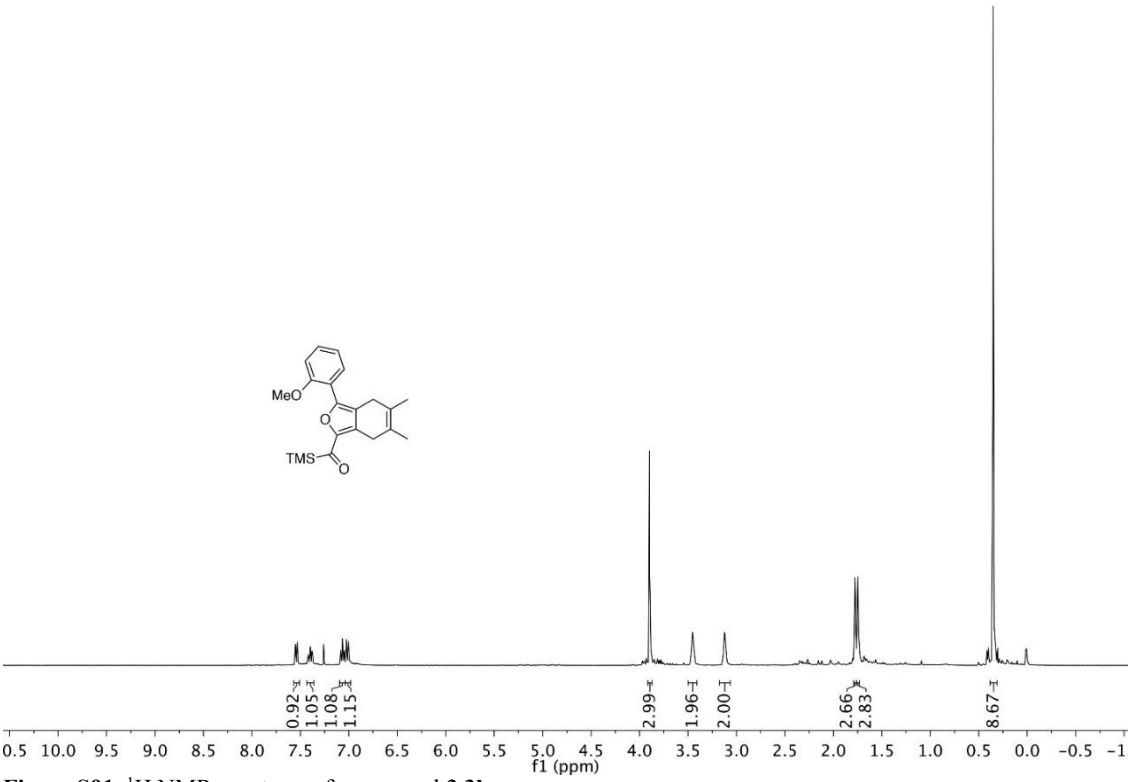


Figure S91. [1]H NMR spectrum of compound **3.3l**.

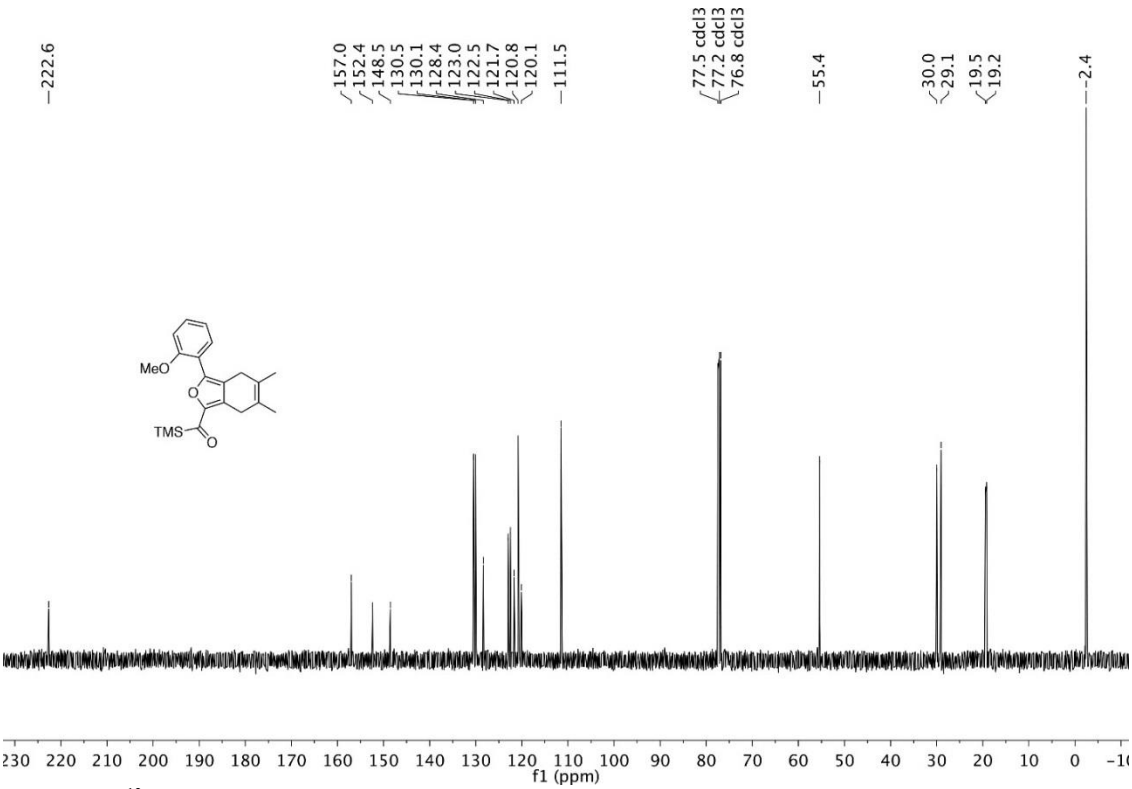


Figure S92. [13]C NMR spectrum of compound **3.3l**.

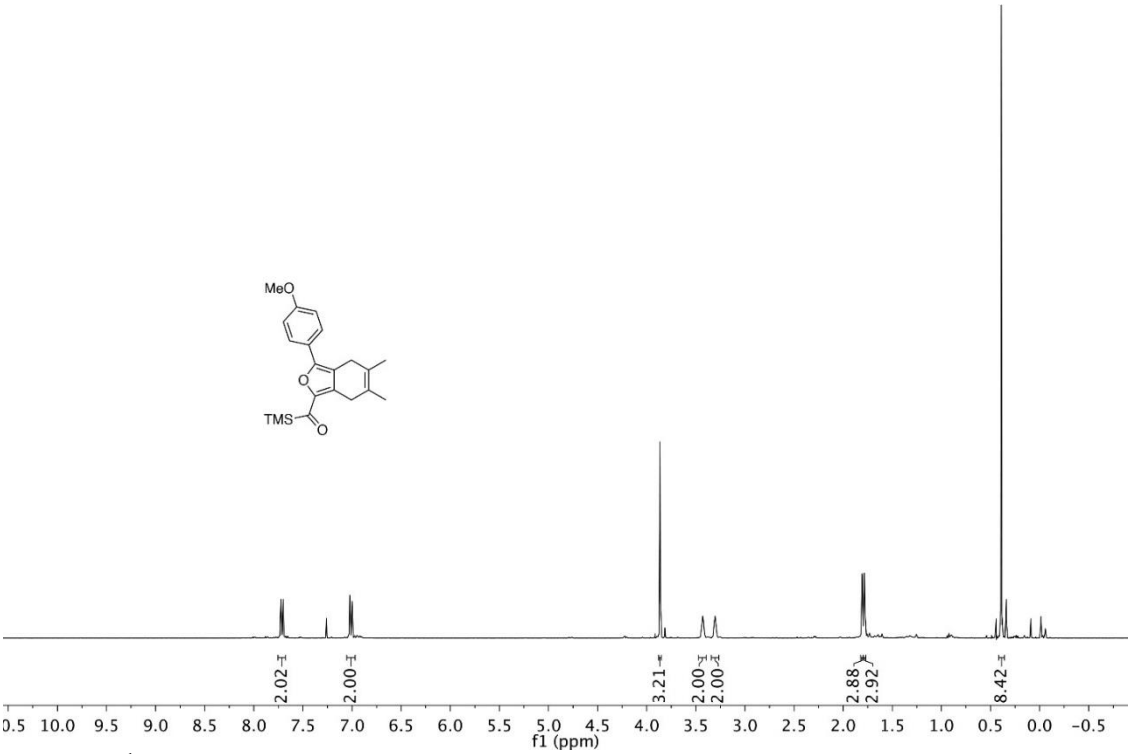


Figure S93. ^{1}H NMR spectrum of compound **3.3m**.

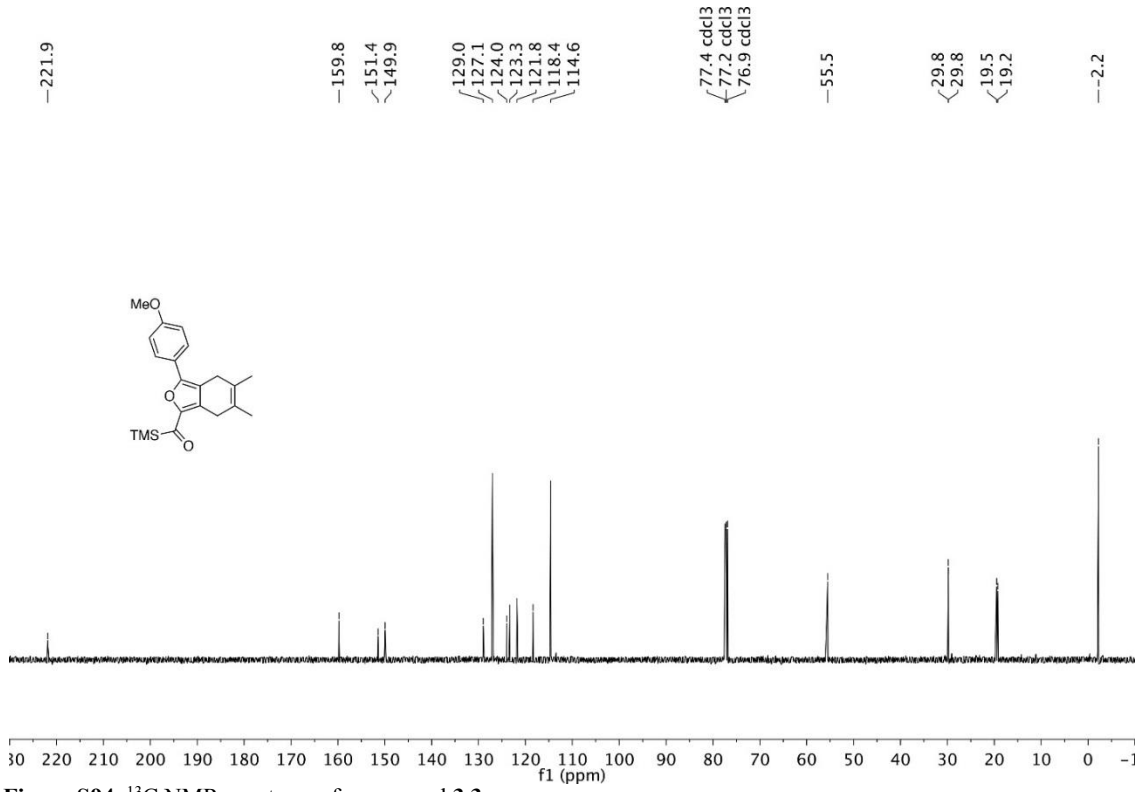


Figure S94. ^{13}C NMR spectrum of compound **3.3m**.

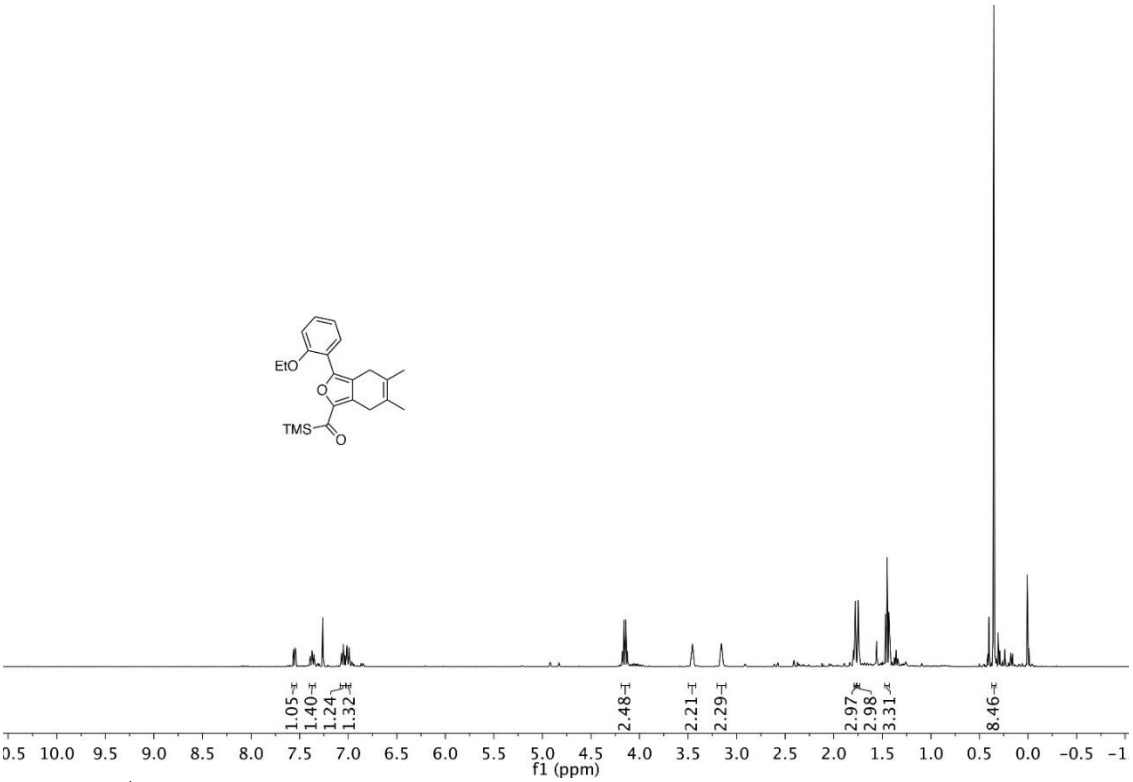


Figure S95. ^{1}H NMR spectrum of compound **3.3n**.

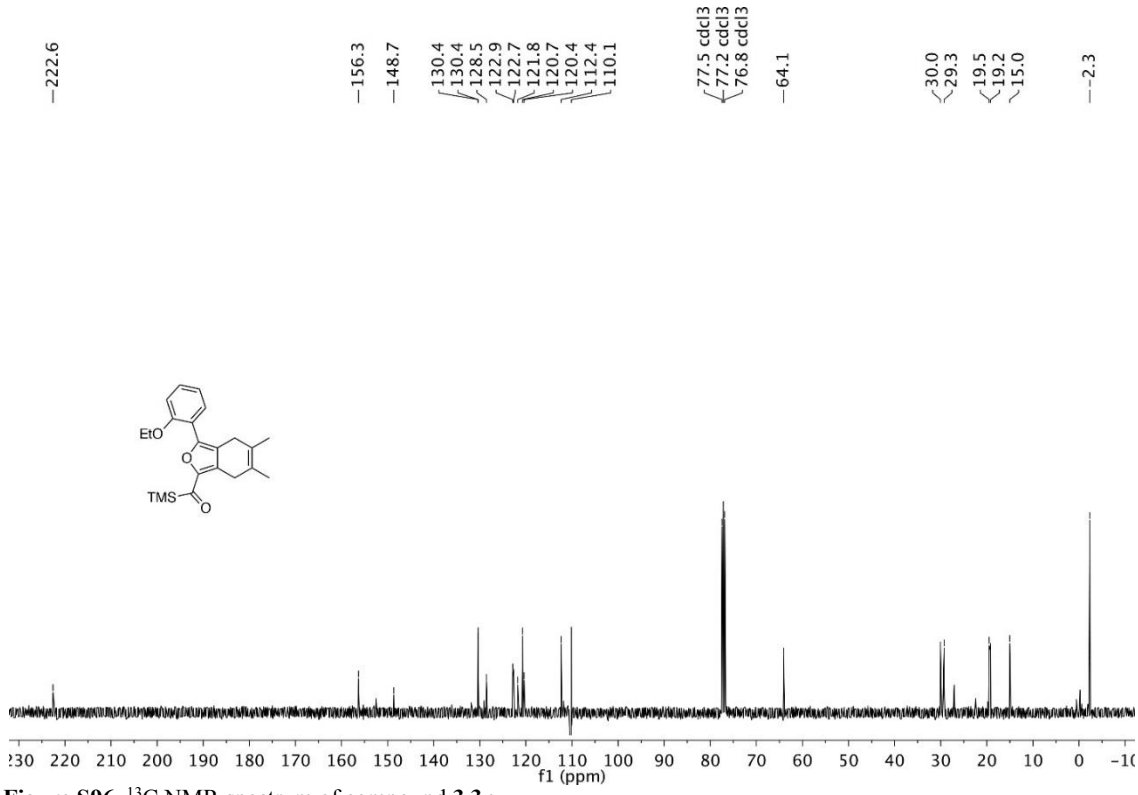


Figure S96. ^{13}C NMR spectrum of compound **3.3n**.

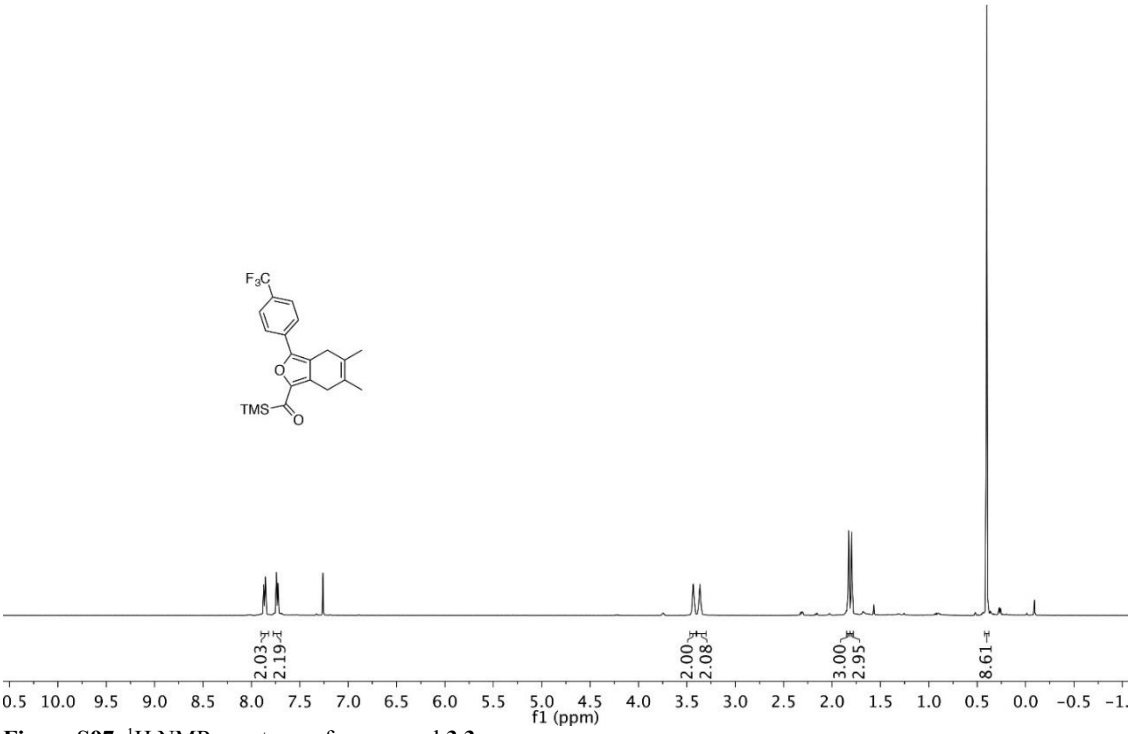


Figure S97. ^{1}H NMR spectrum of compound **3.3o**.

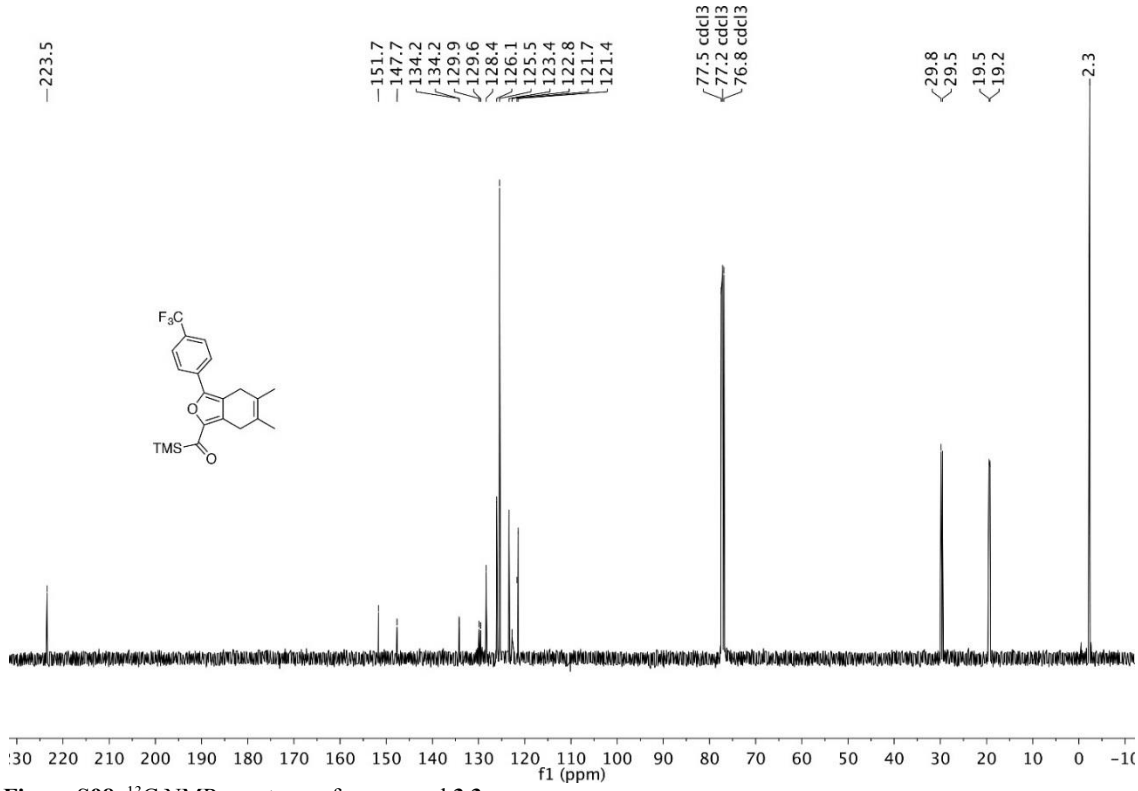


Figure S98. ^{13}C NMR spectrum of compound **3.3o**.

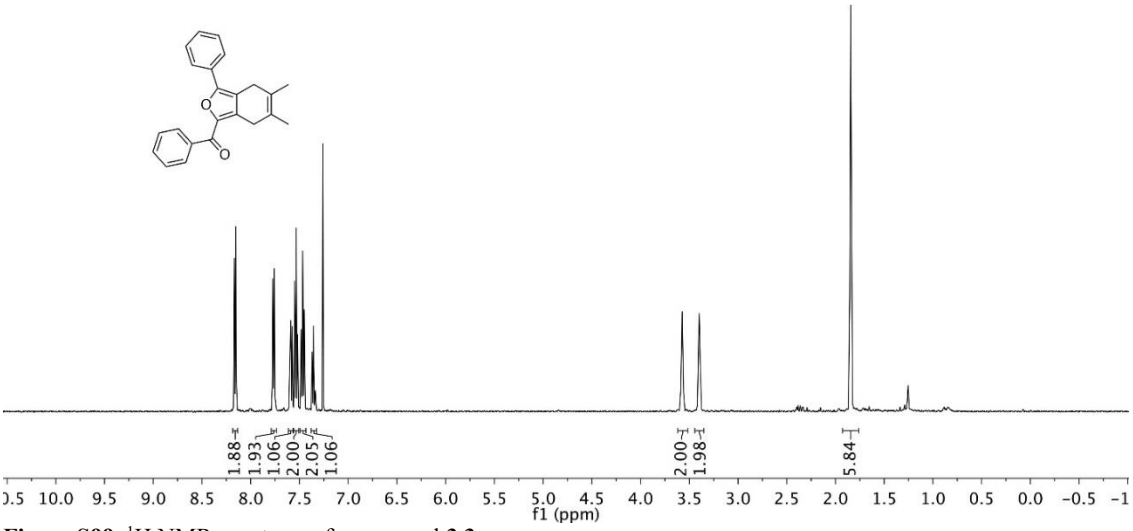


Figure S99. ^{1}H NMR spectrum of compound **3.3p**.

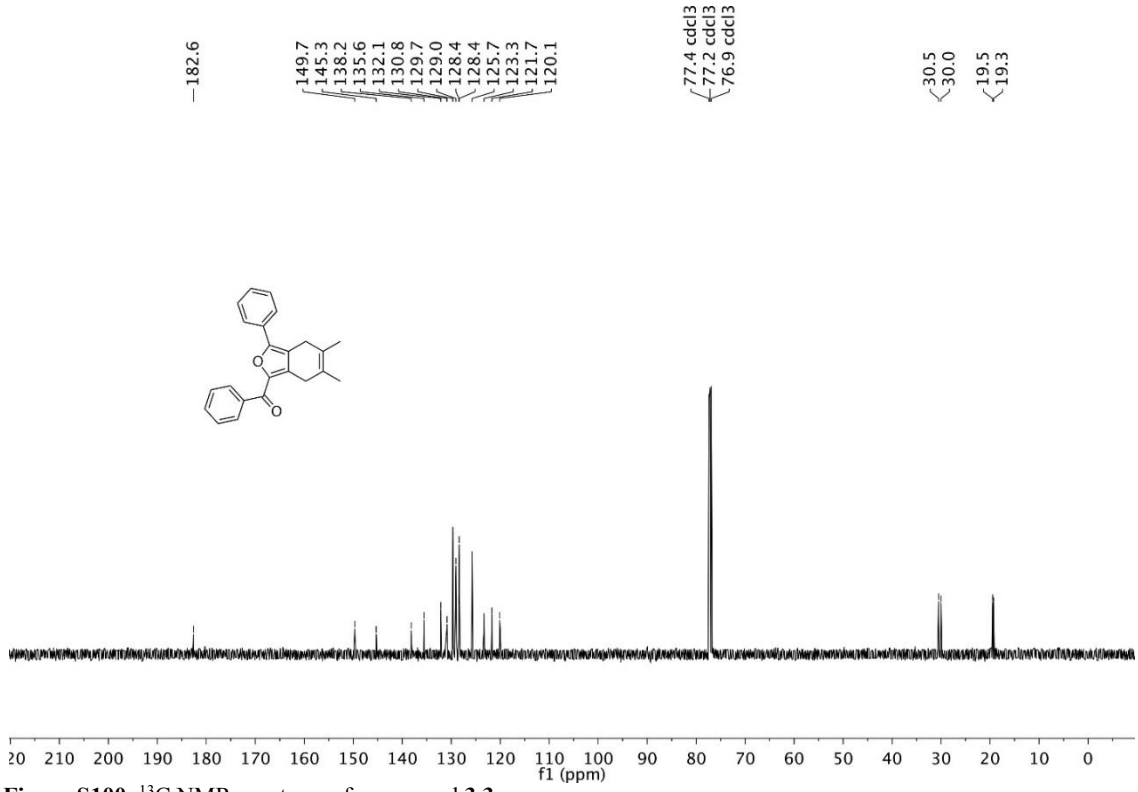


Figure S100. ^{13}C NMR spectrum of compound **3.3p**.

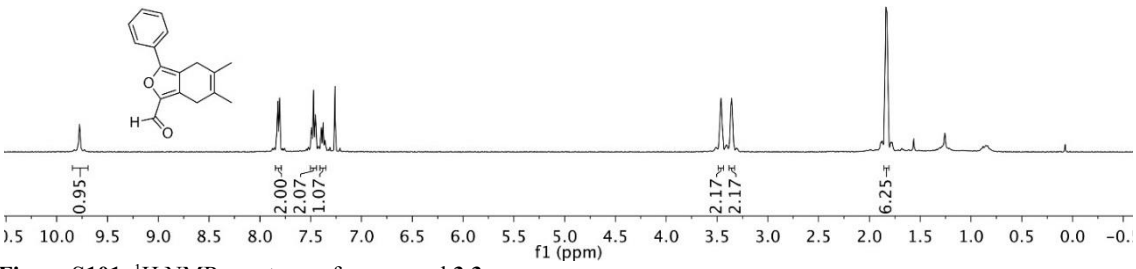


Figure S101. ^{1}H NMR spectrum of compound **3.3q**.

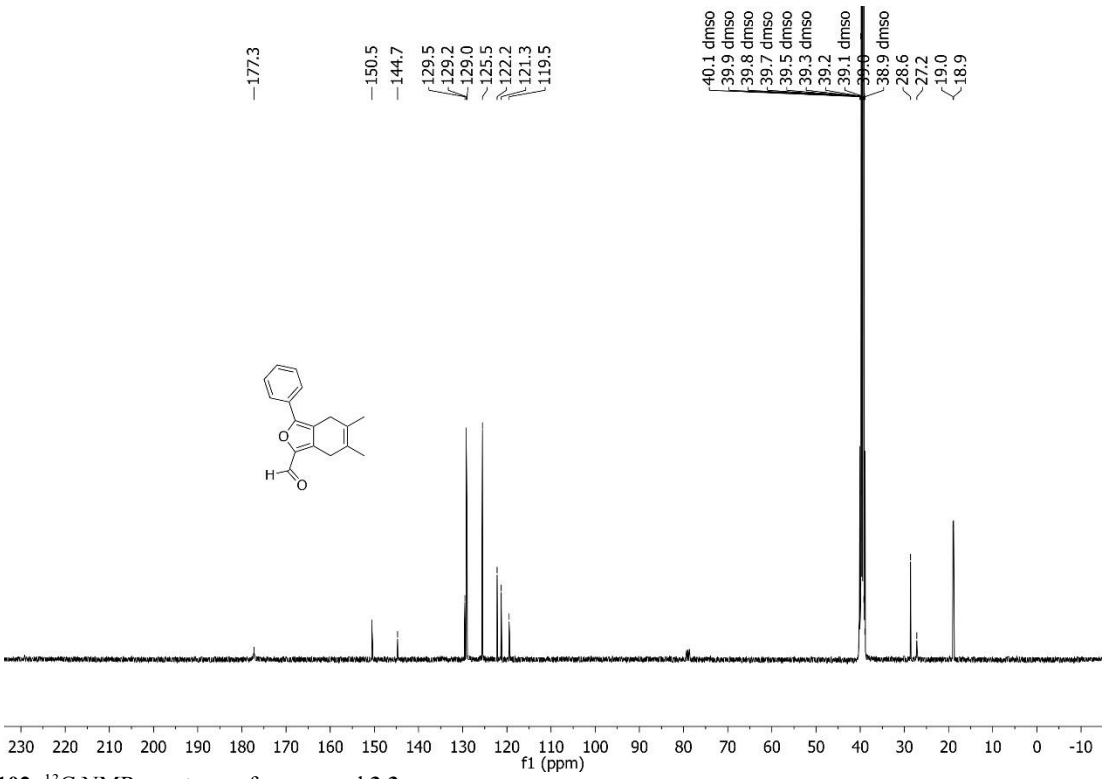


Figure S102. ^{13}C NMR spectrum of compound **3.3q**.

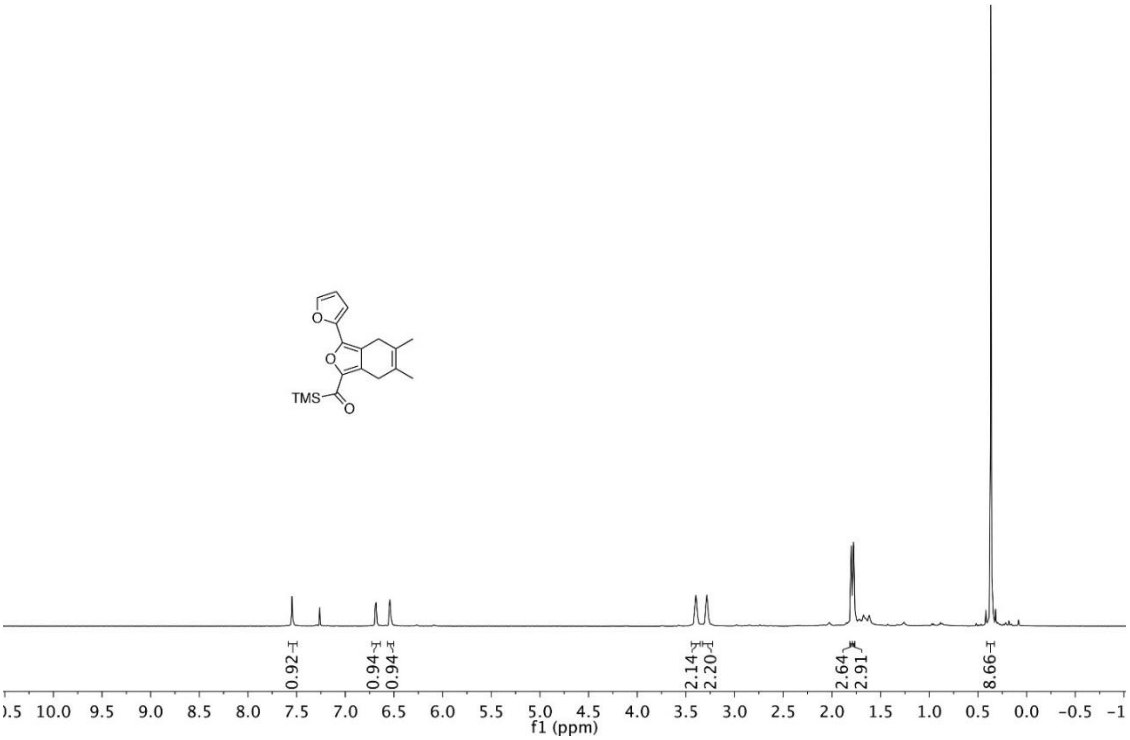


Figure S103. ^{1}H NMR spectrum of compound **3.3r**.

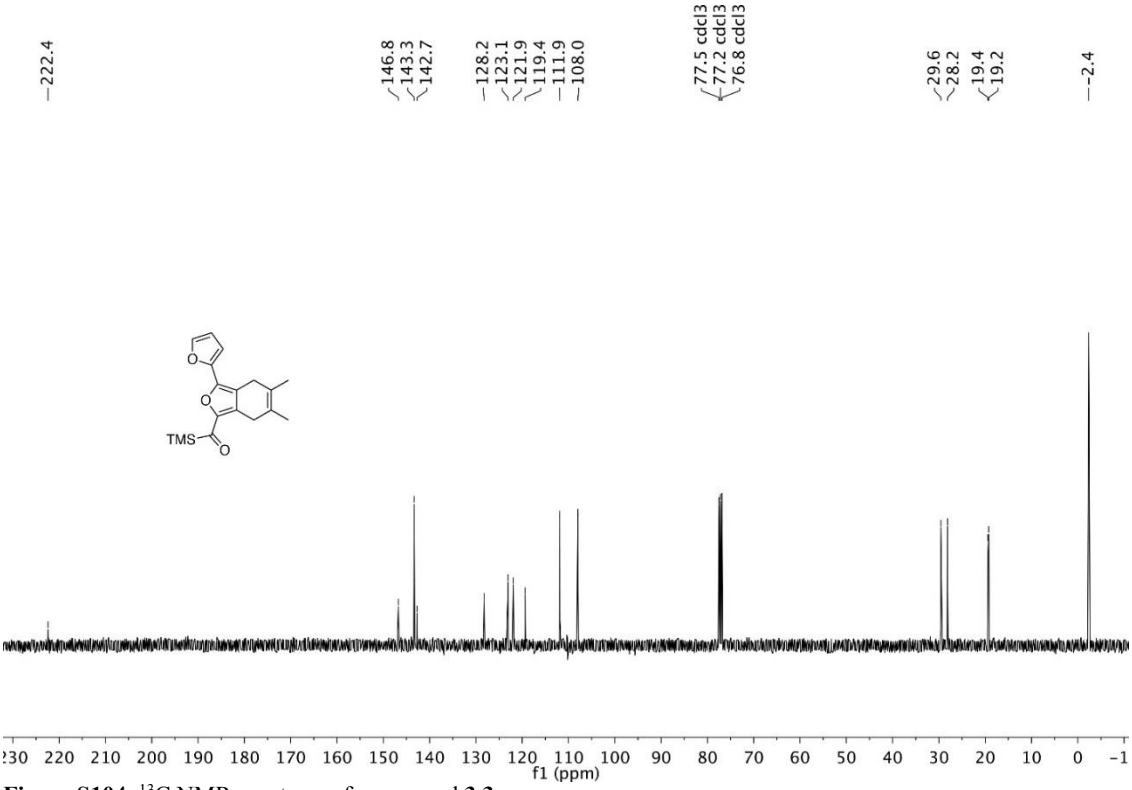


Figure S104. ^{13}C NMR spectrum of compound **3.3r**.

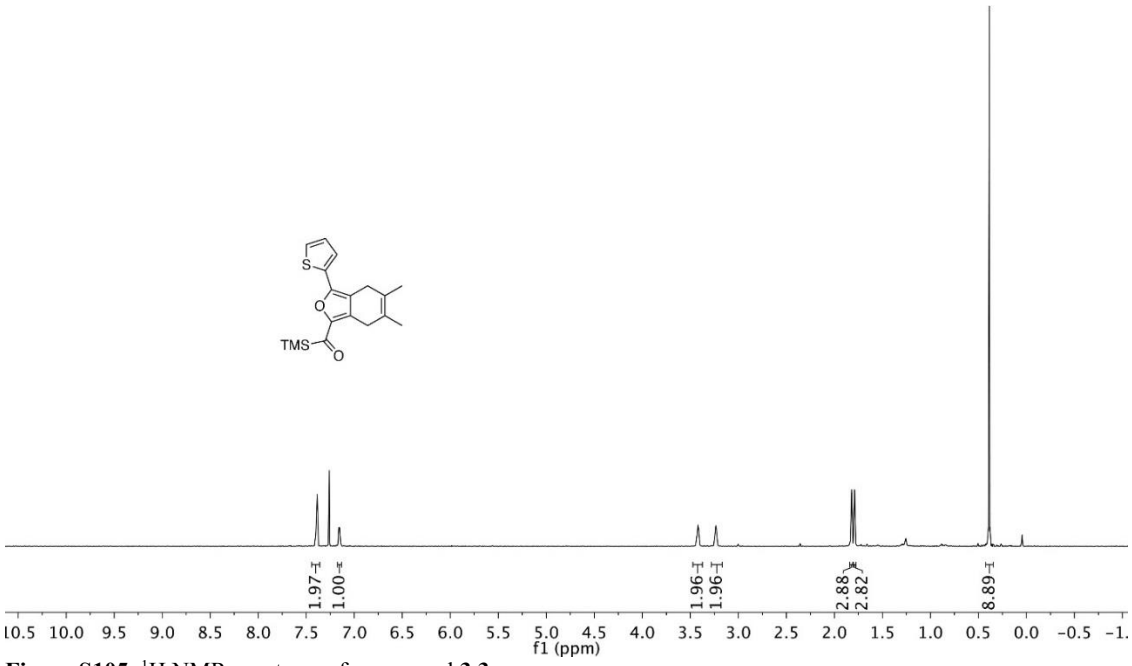


Figure S105. ^{1}H NMR spectrum of compound **3.3s**.

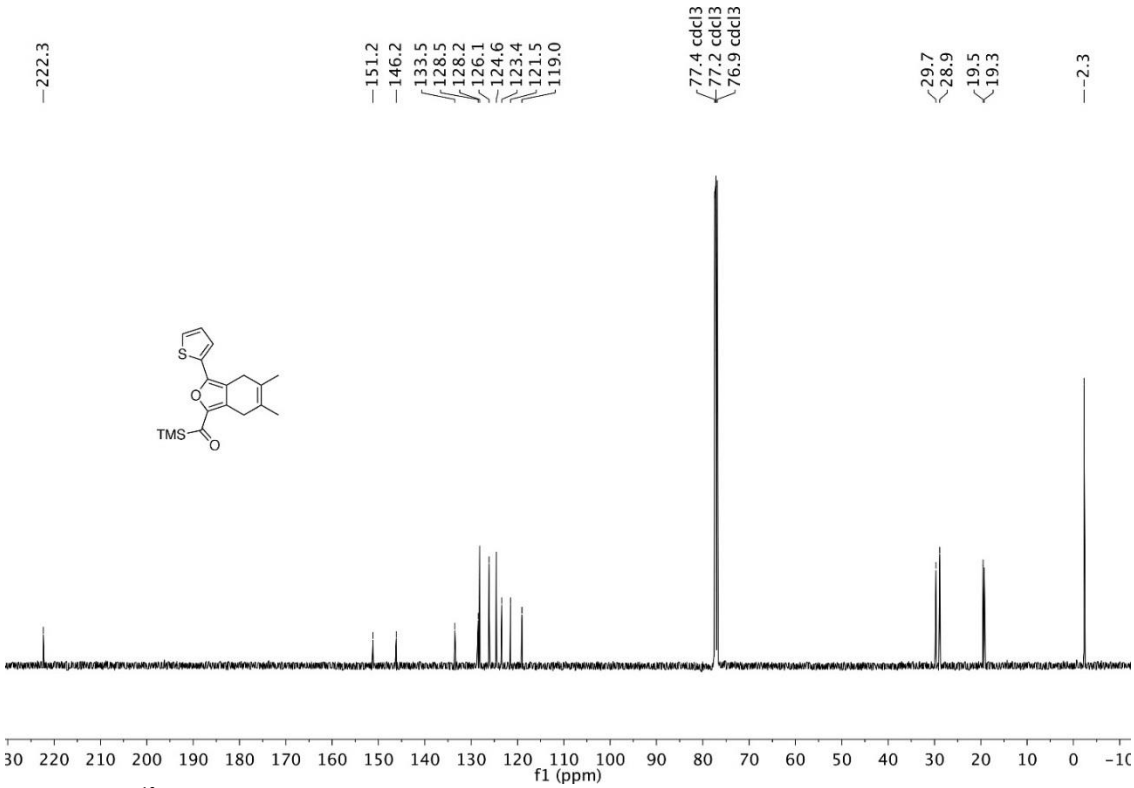


Figure S106. ^{13}C NMR spectrum of compound **3.3s**.

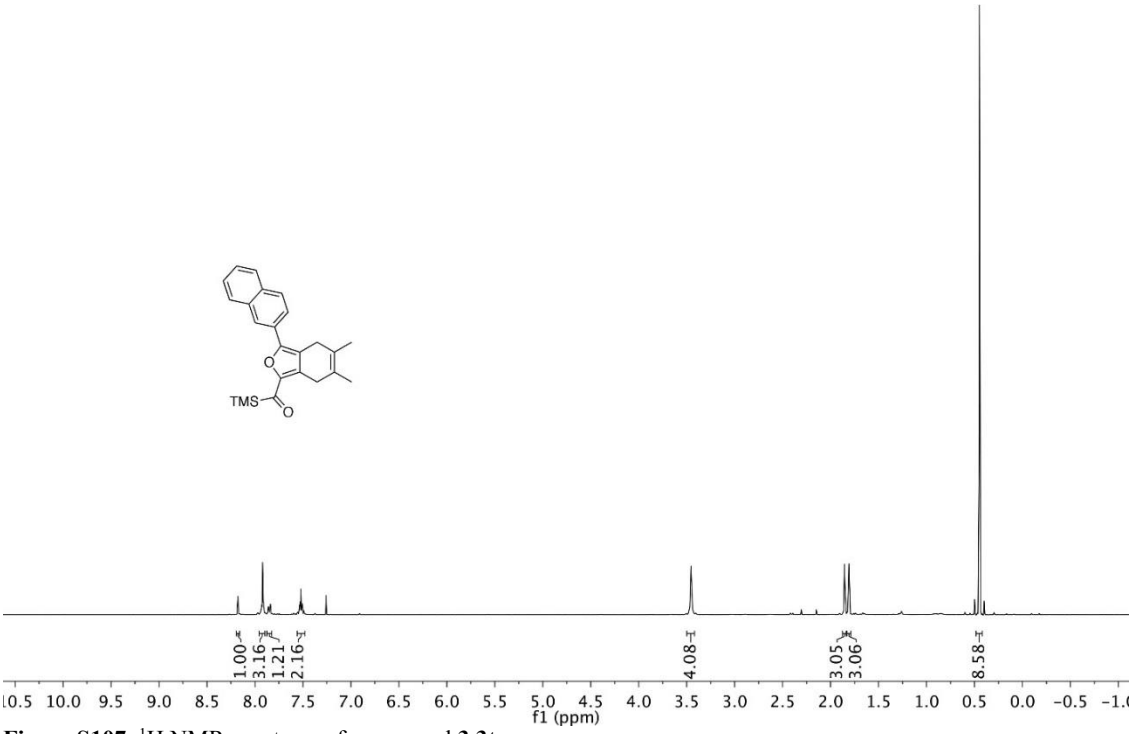


Figure S107. ^{1}H NMR spectrum of compound **3.3t**.

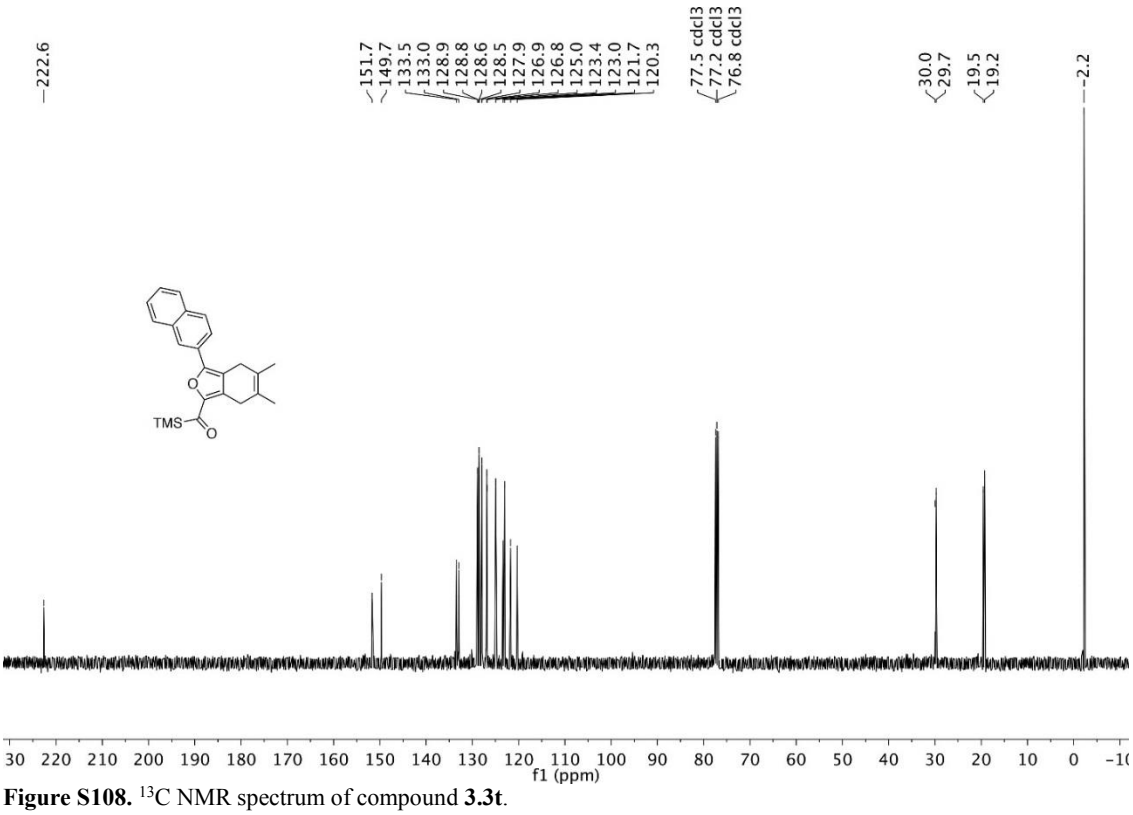


Figure S108. ^{13}C NMR spectrum of compound **3.3t**.

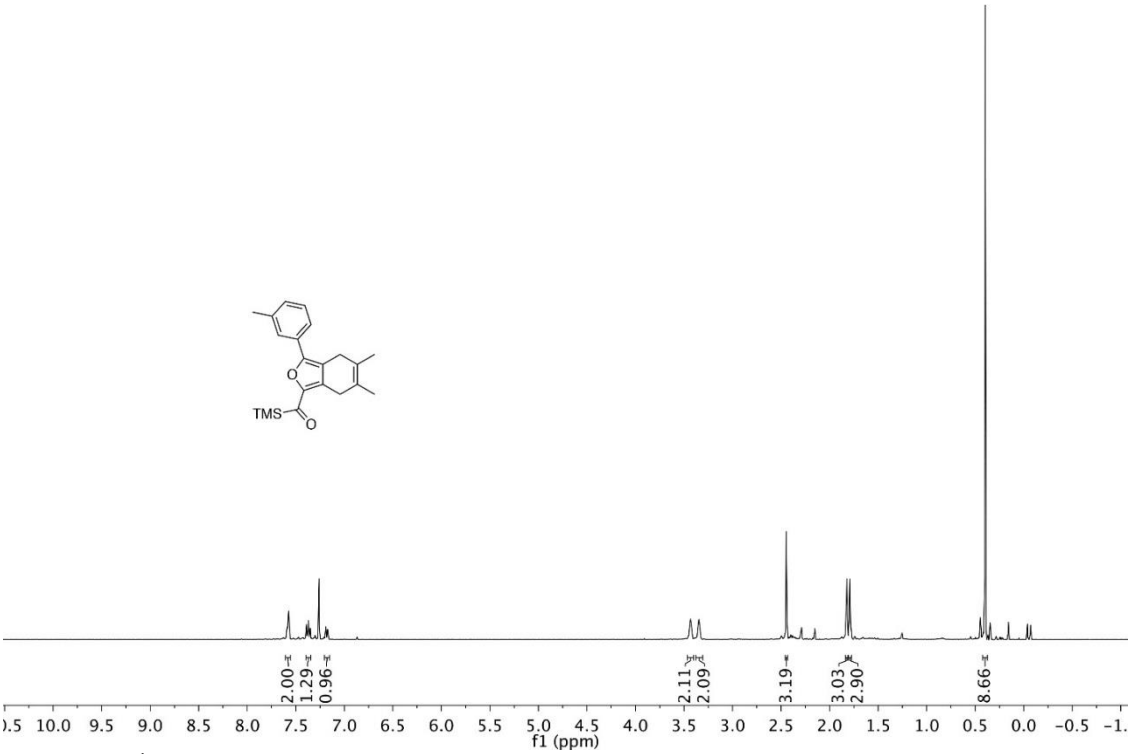


Figure S109. ^{1}H NMR spectrum of compound **3.3u**.

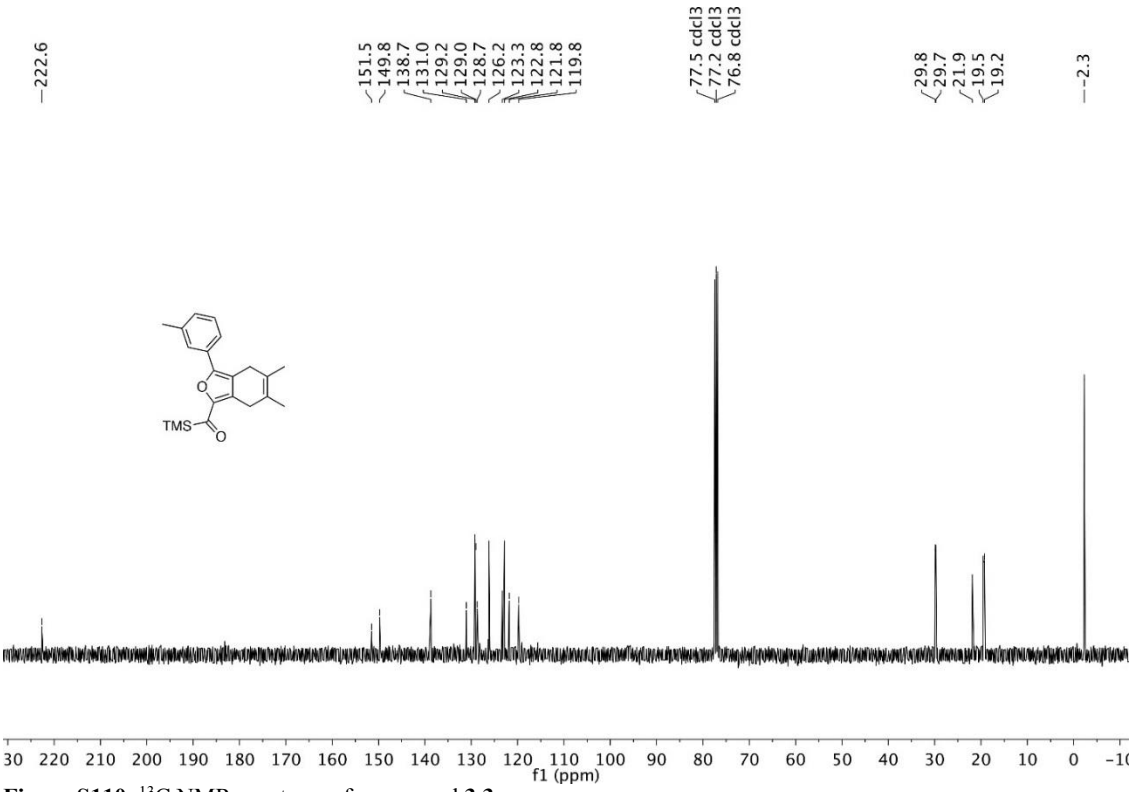


Figure S110. ^{13}C NMR spectrum of compound **3.3u**.

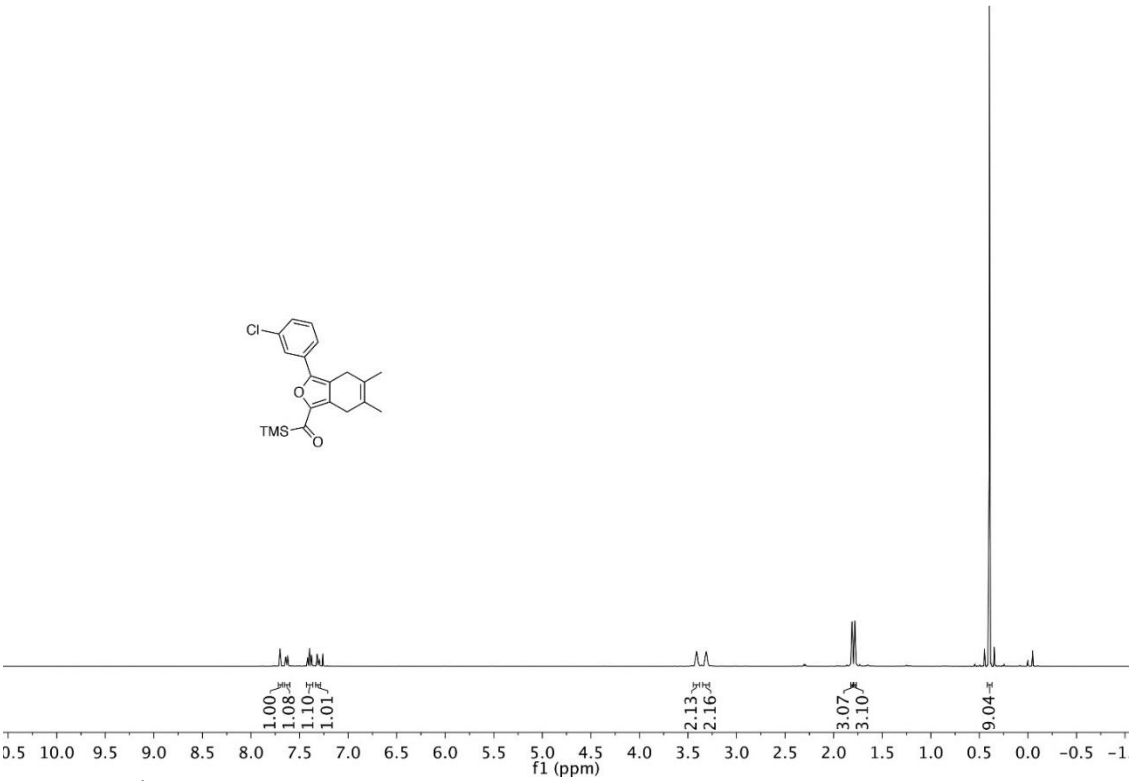


Figure S111. [1]H NMR spectrum of compound **3.3v**.

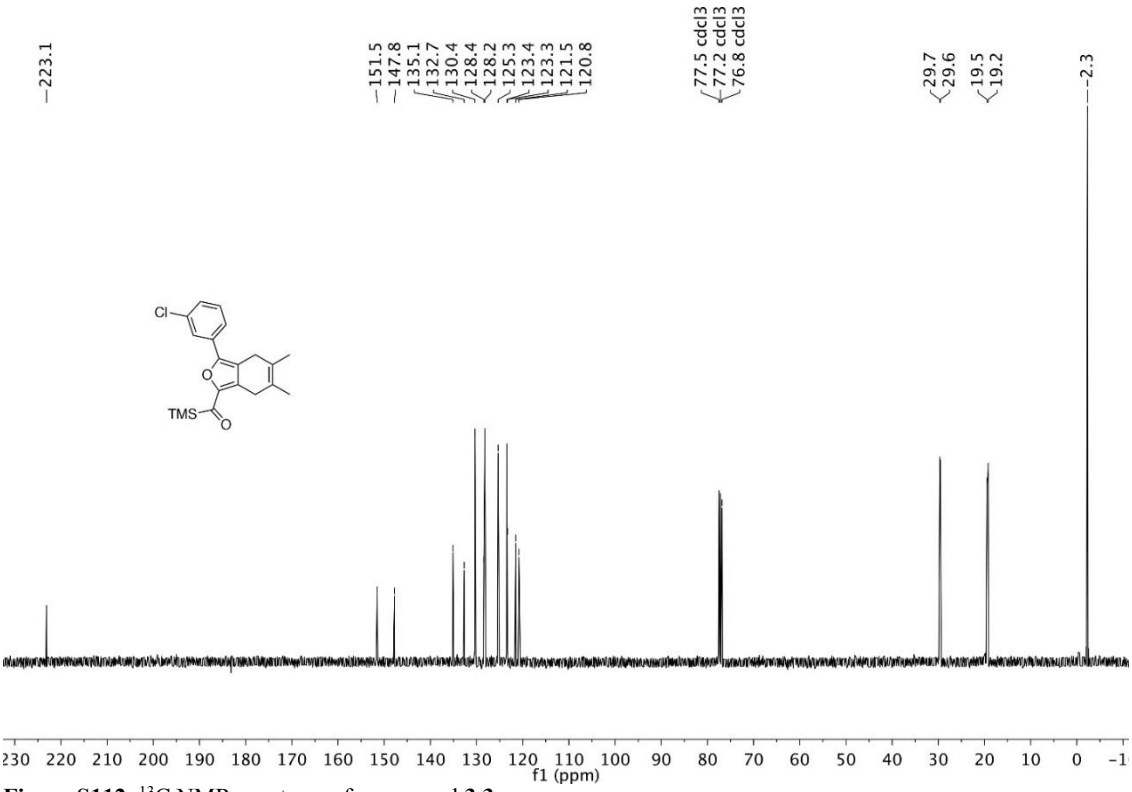


Figure S112. [13]C NMR spectrum of compound **3.3v.**

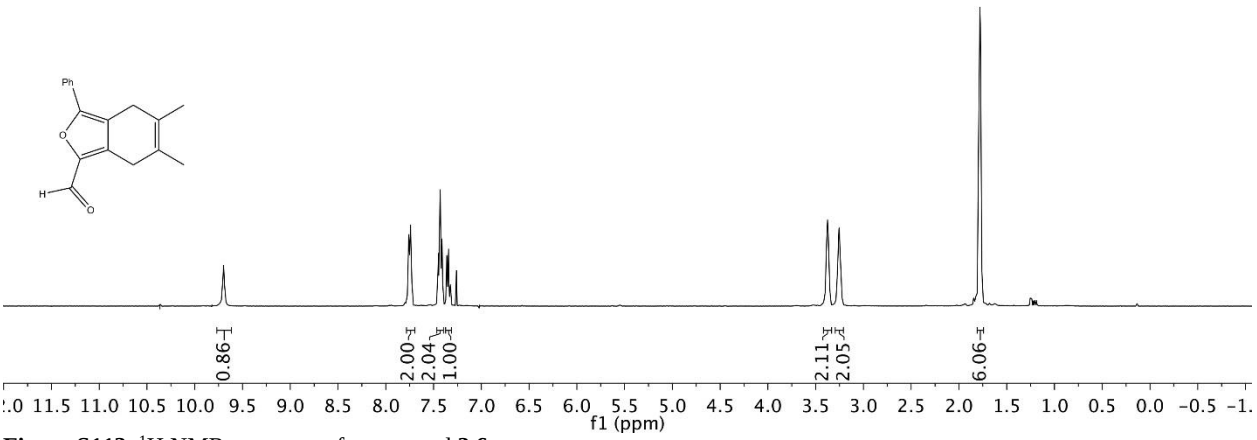


Figure S113. ^{1}H NMR spectrum of compound **3.6a**.

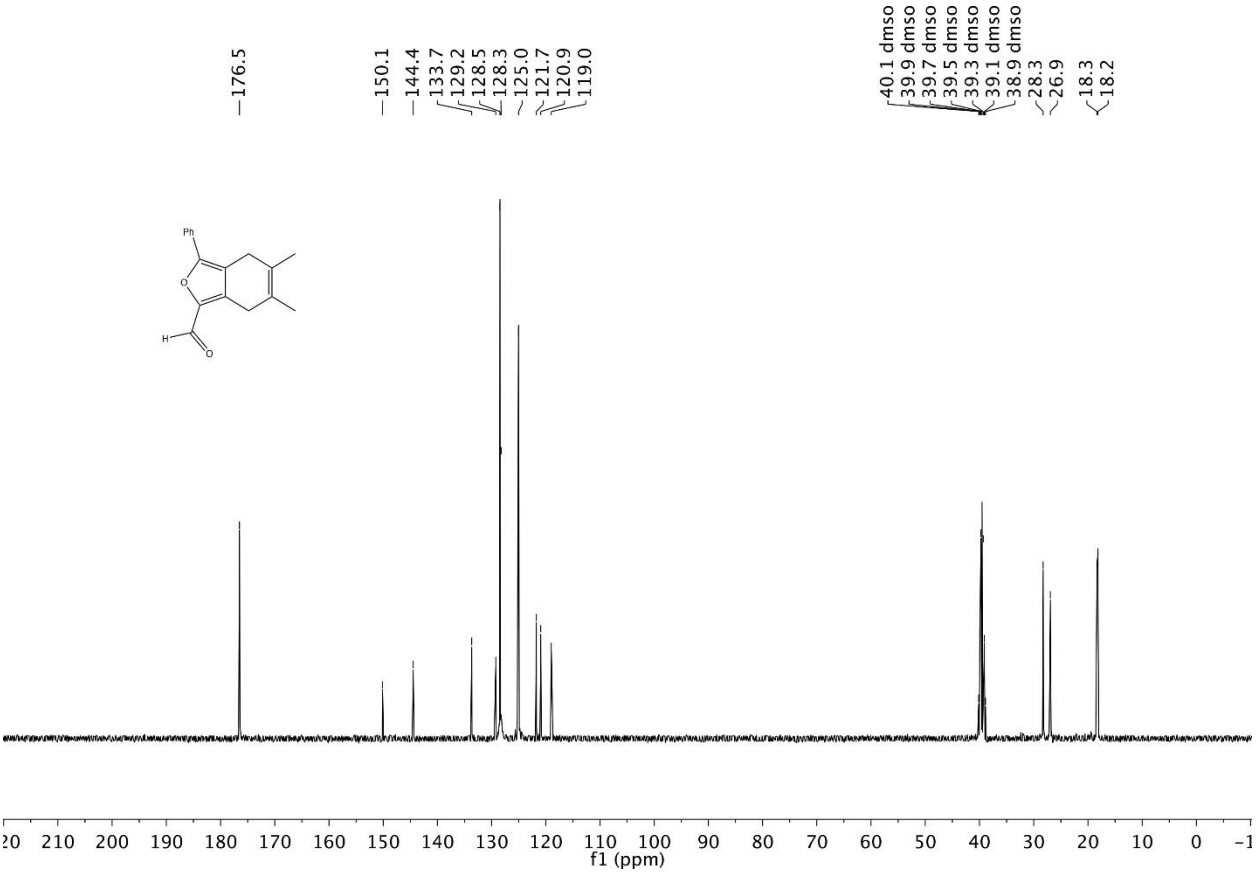


Figure S114. ^{13}C NMR spectrum of compound **3.6a**.

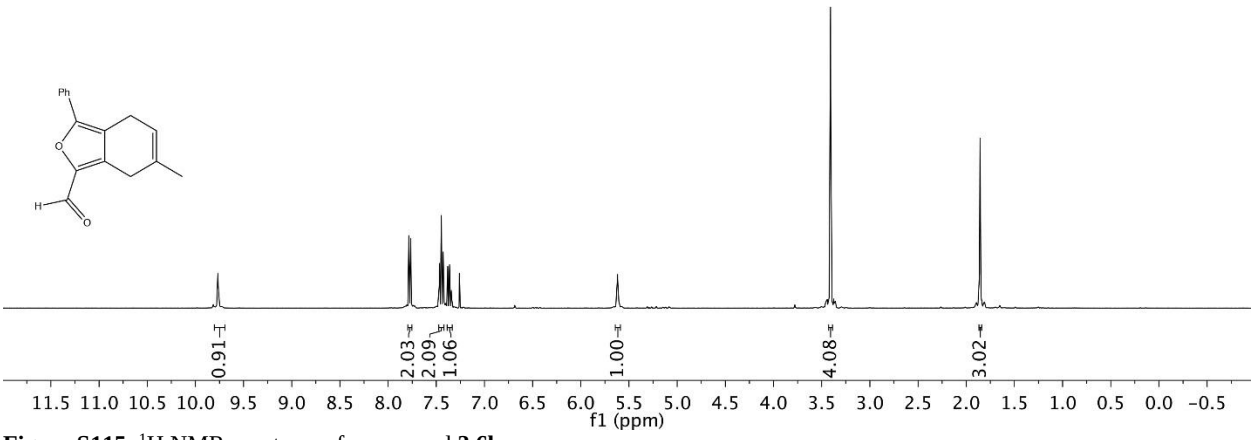


Figure S115. ^{1}H NMR spectrum of compound **3.6b**.

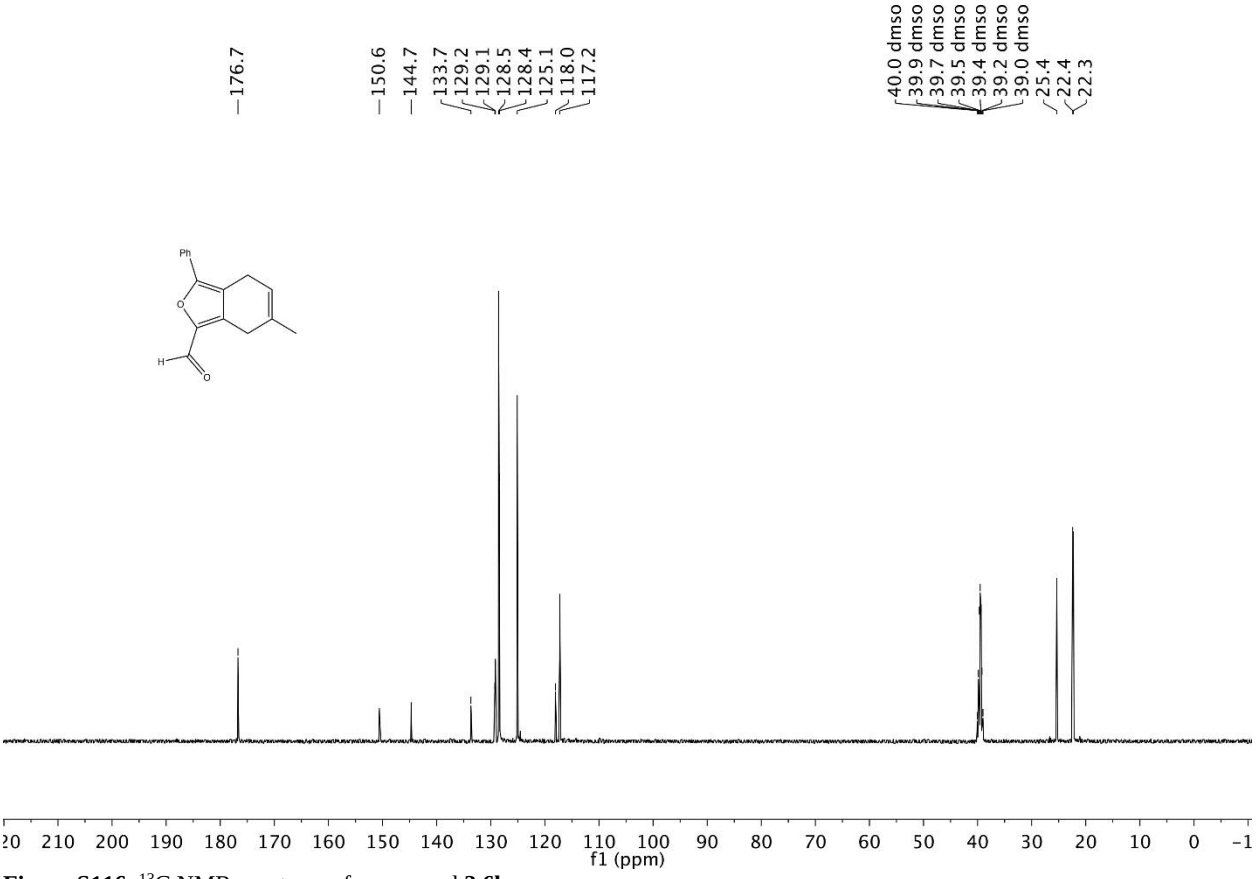


Figure S116. ^{13}C NMR spectrum of compound **3.6b**.

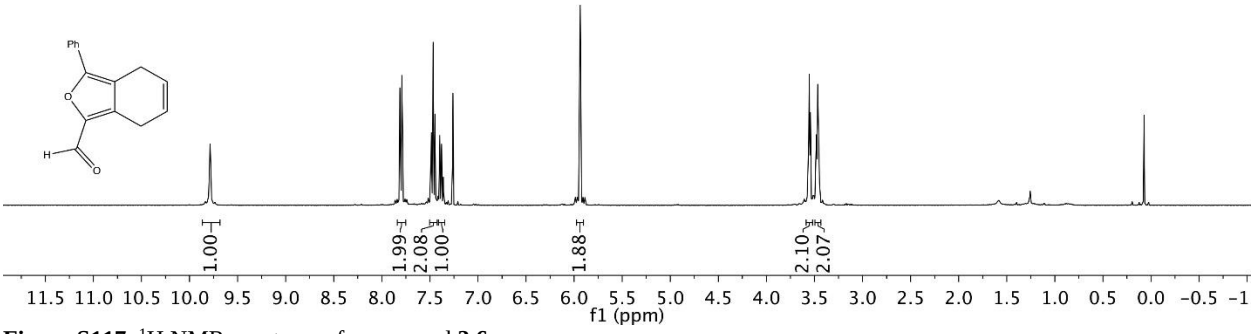


Figure S117. ^{1}H NMR spectrum of compound **3.6c**.

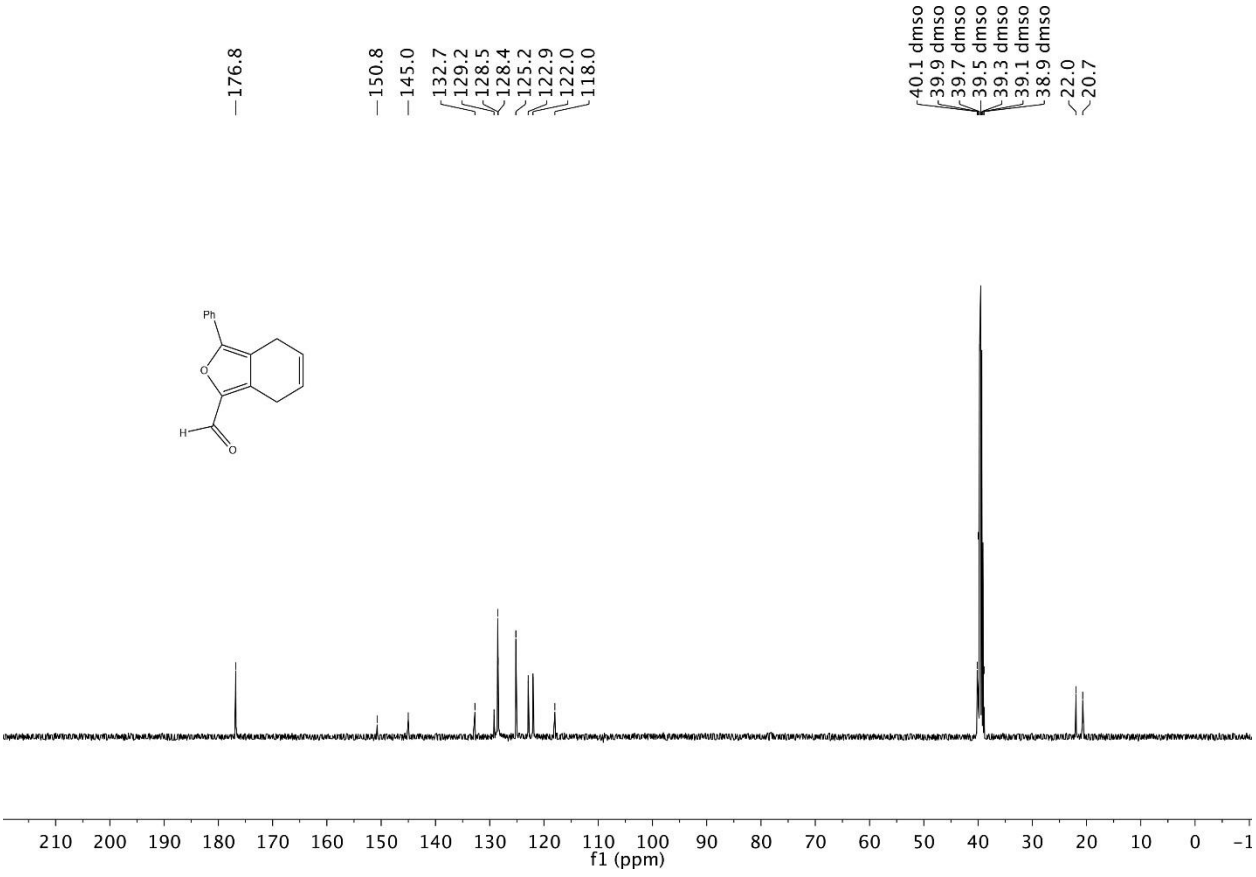


Figure S118. ^{13}C NMR spectrum of compound **3.6c**.

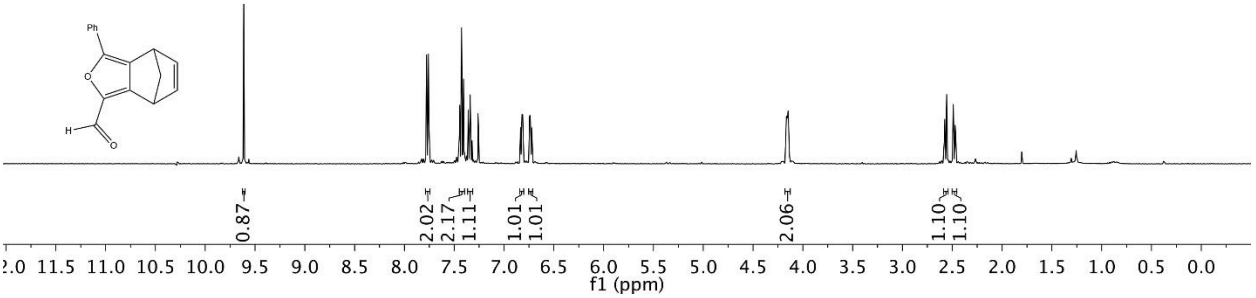


Figure S119. ^{1}H NMR spectrum of compound **3.6d**.

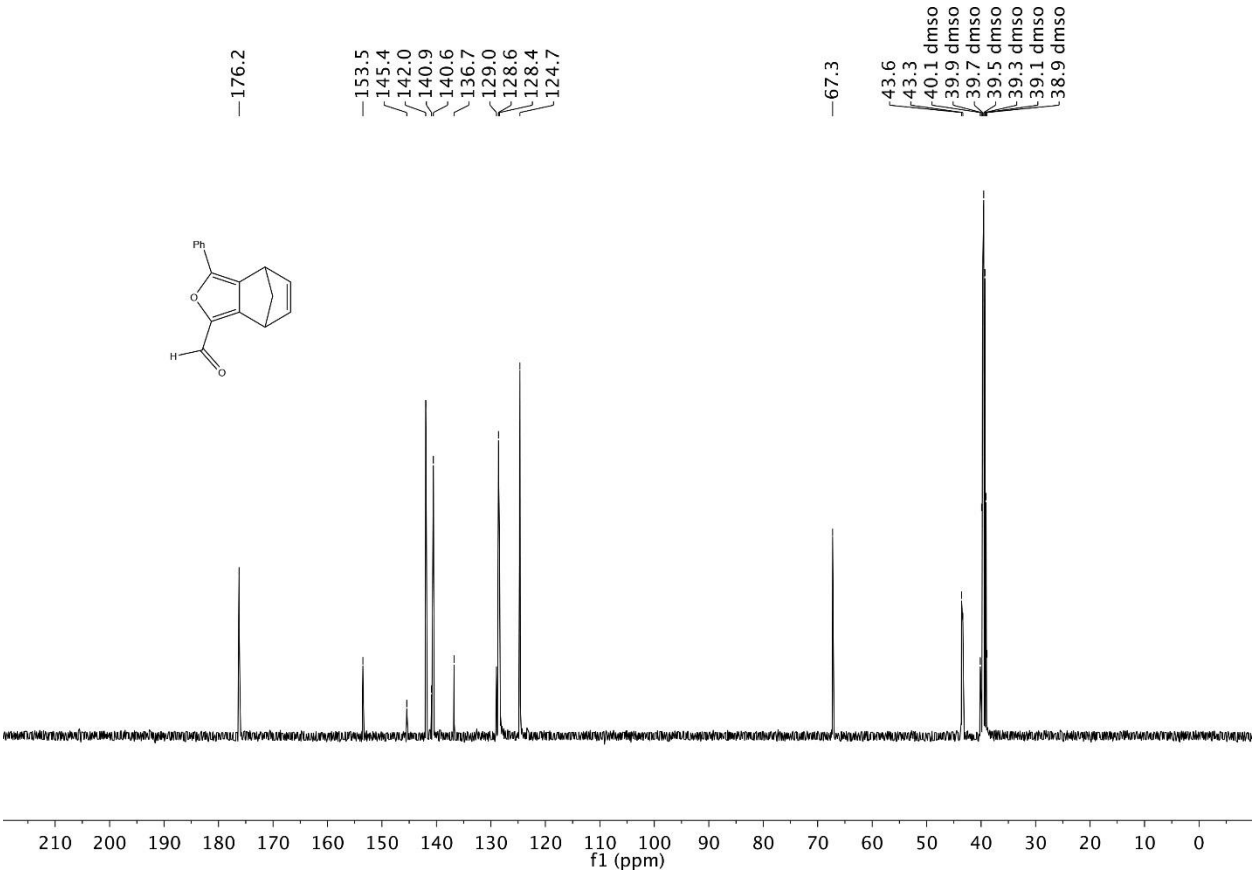


Figure S120. ^{13}C NMR spectrum of compound **3.6d**.

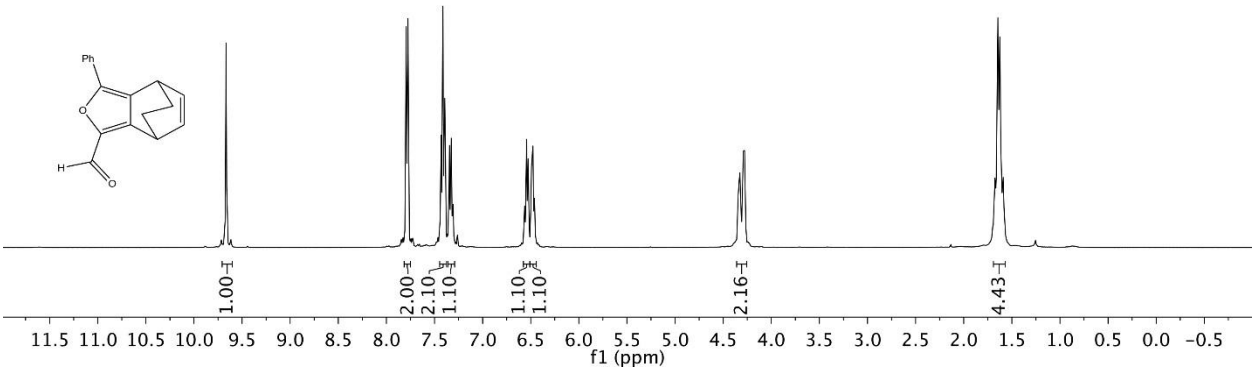


Figure S121. ^{1}H NMR spectrum of compound **3.6e**.

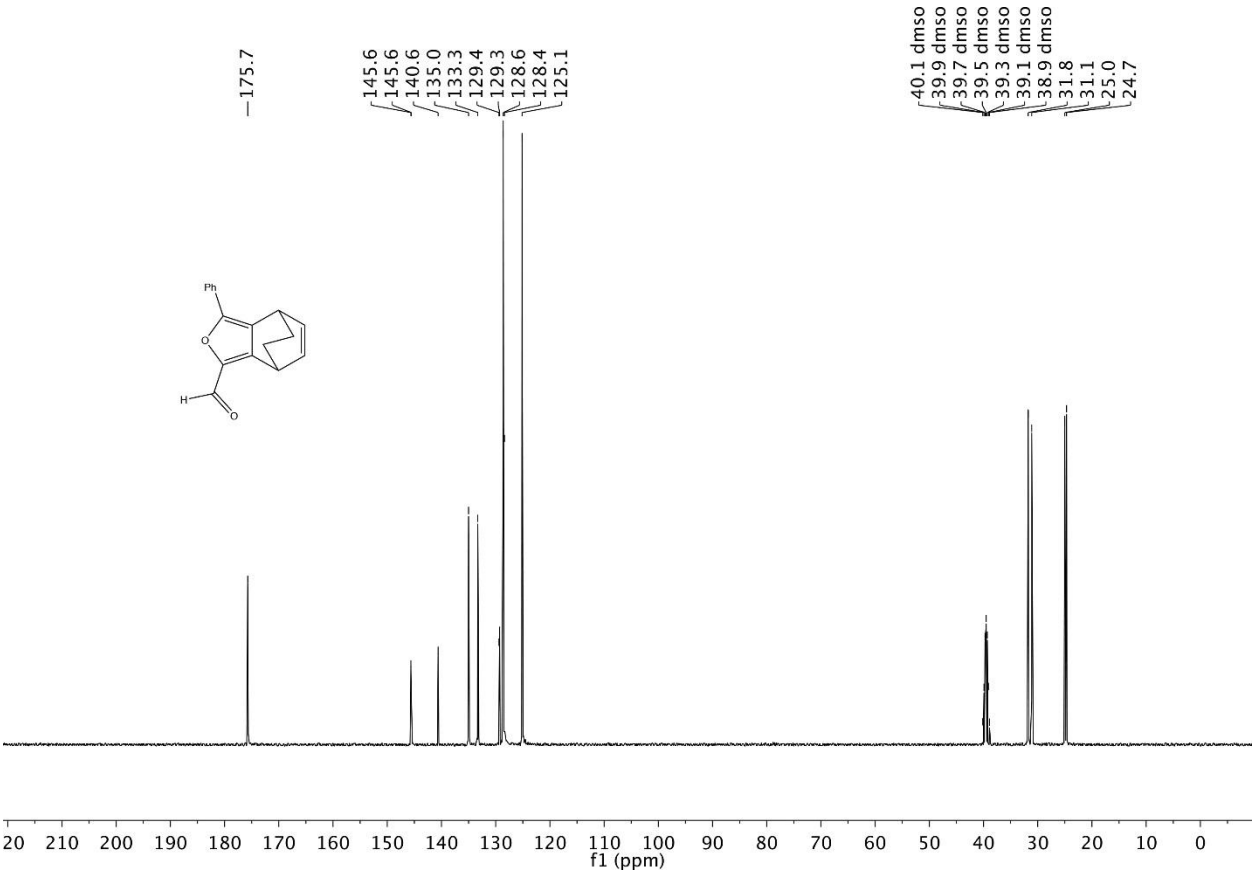


Figure S122. ^{13}C NMR spectrum of compound **3.6e**.

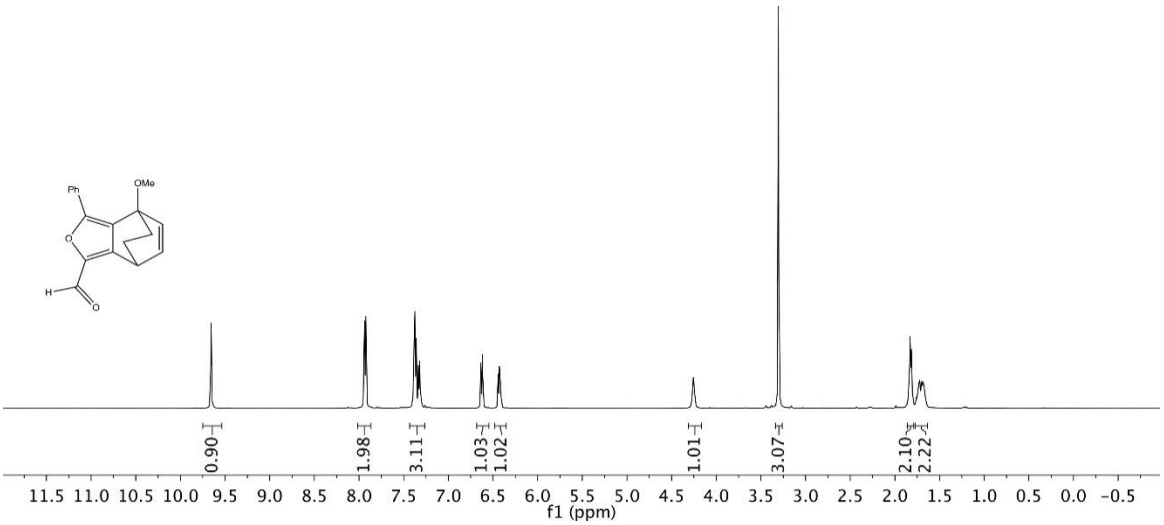


Figure S123. [1]H NMR spectrum of compound **3.6f**.

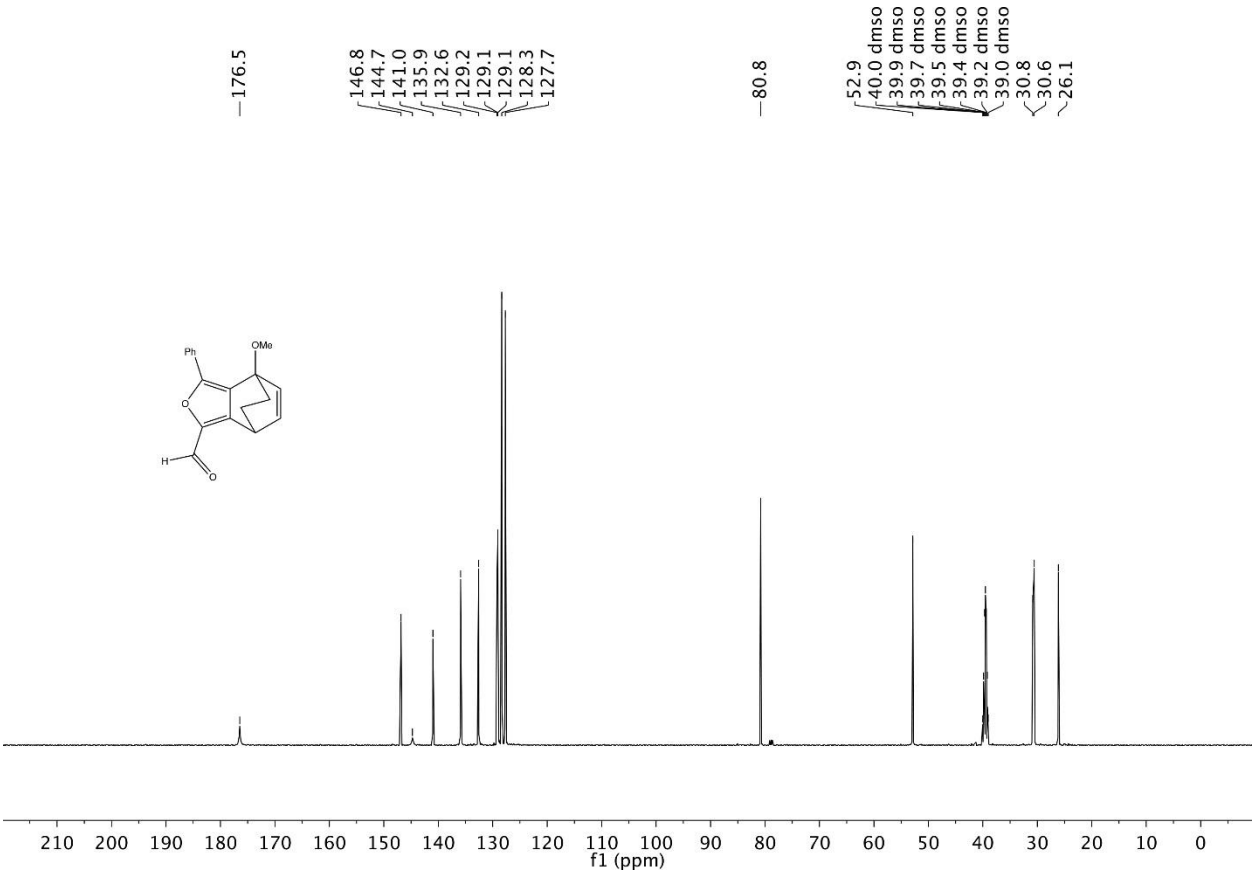


Figure S124. [13]C NMR spectrum of compound **3.6f**.

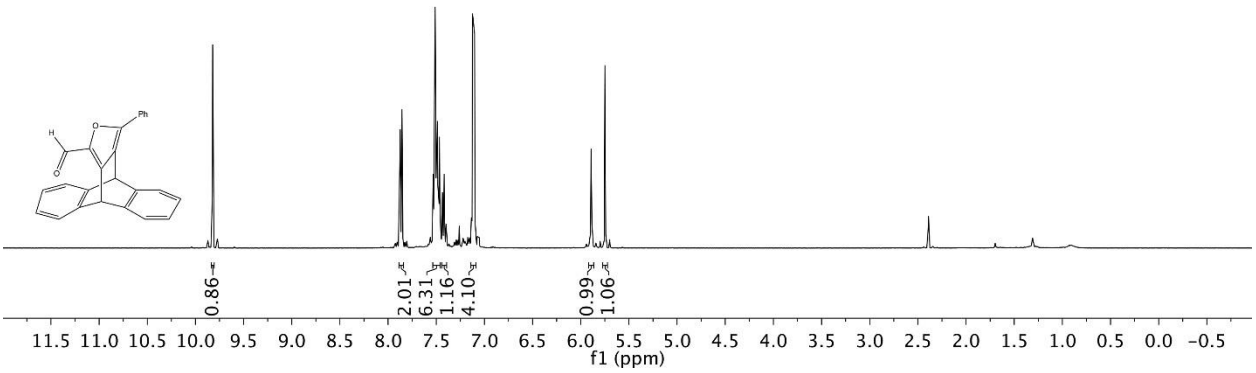


Figure S125. ^{1}H NMR spectrum of compound **3.6g**.

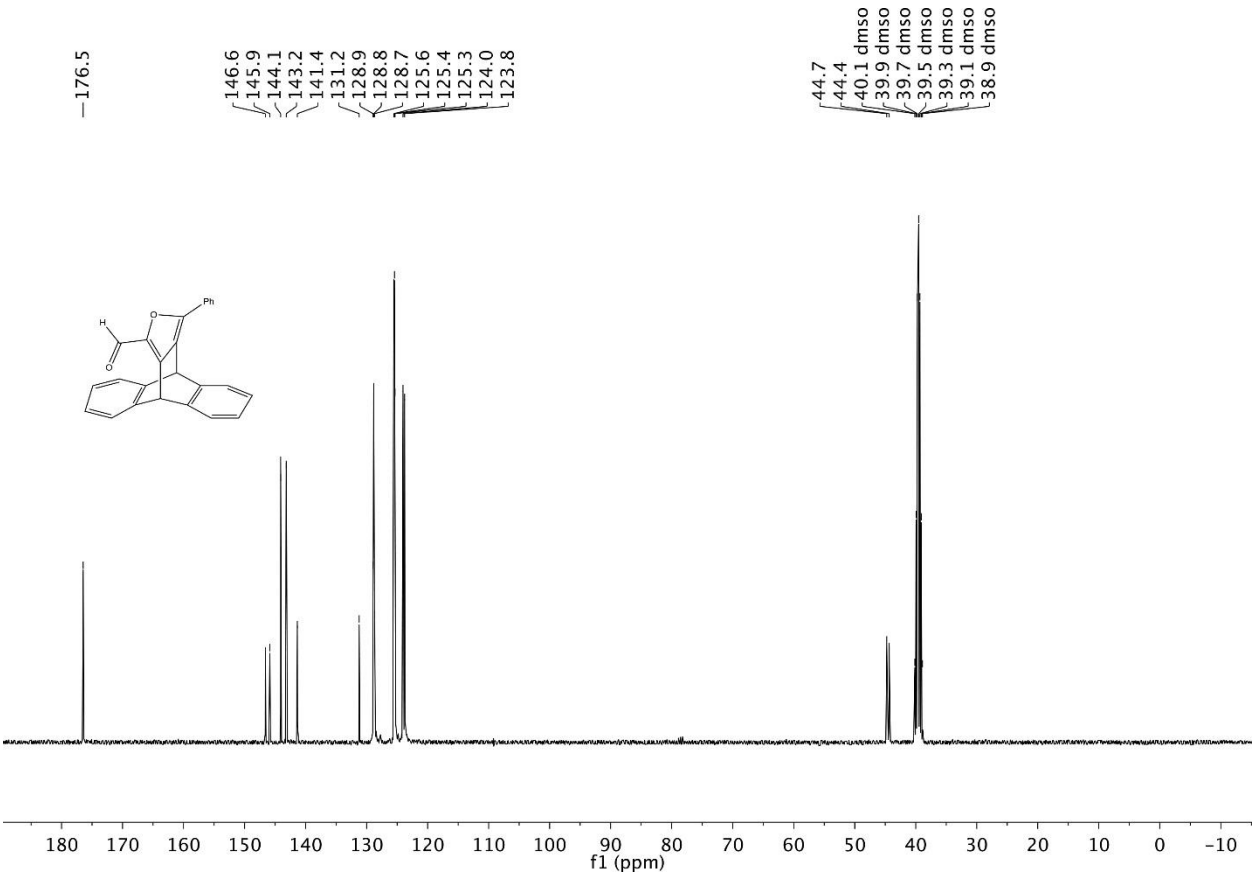


Figure S126. ^{13}C NMR spectrum of compound **3.6g**.

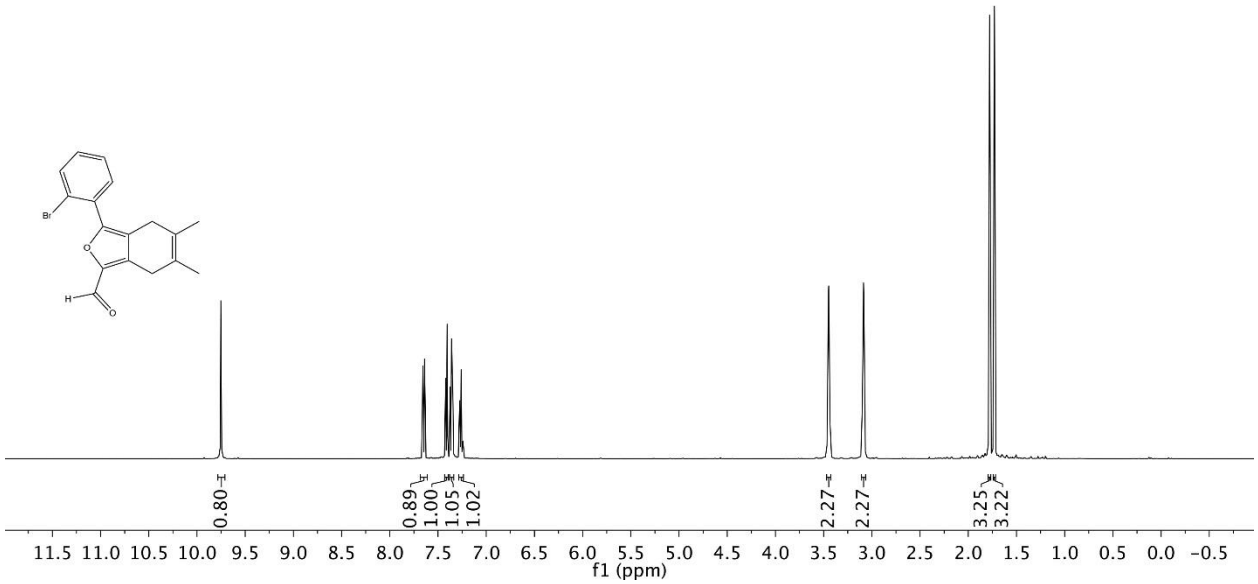


Figure S127. ^{1}H NMR spectrum of compound **3.6h**.

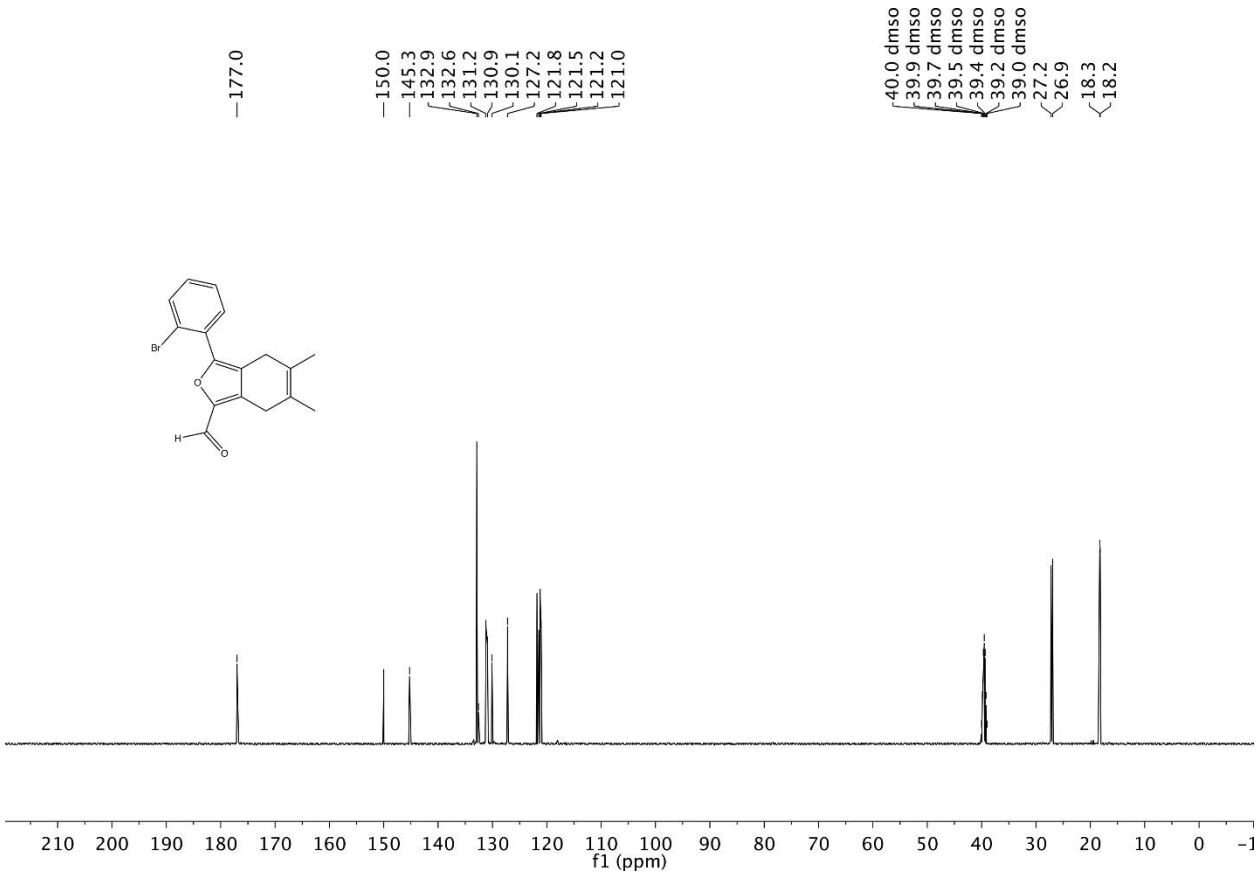


Figure S128. ^{13}C NMR spectrum of compound **3.6h**.

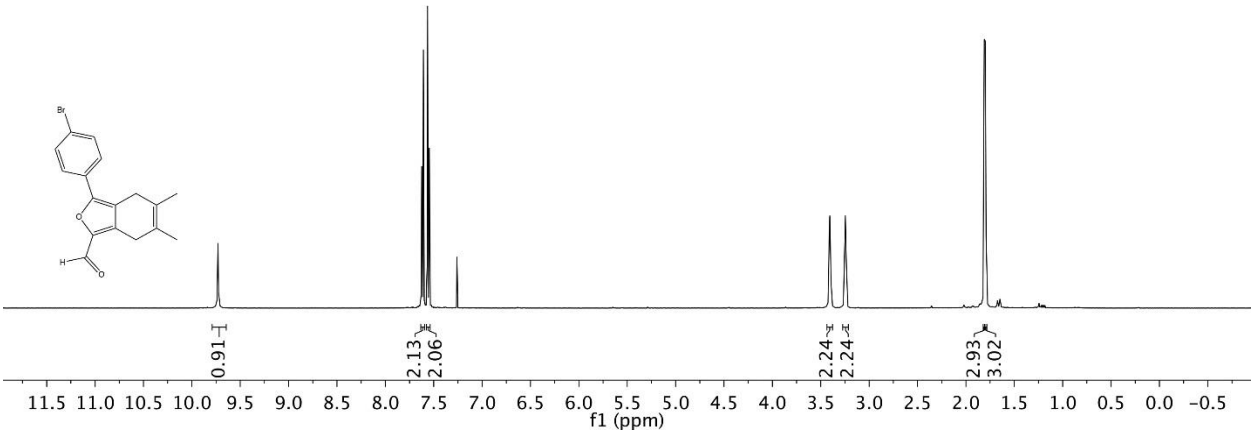


Figure S129. ^{1}H NMR spectrum of compound **3.6i**.

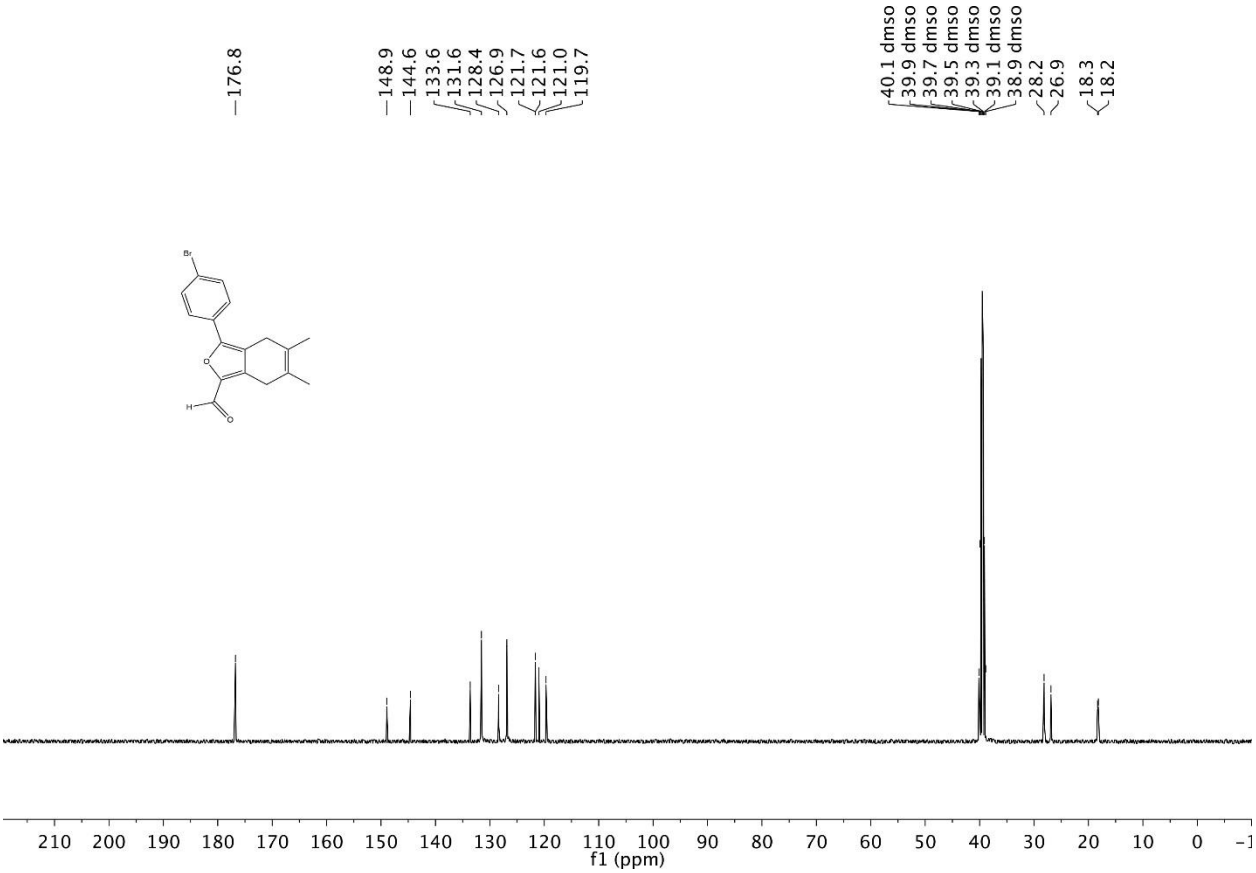


Figure S130. ^{13}C NMR spectrum of compound **3.6i**.

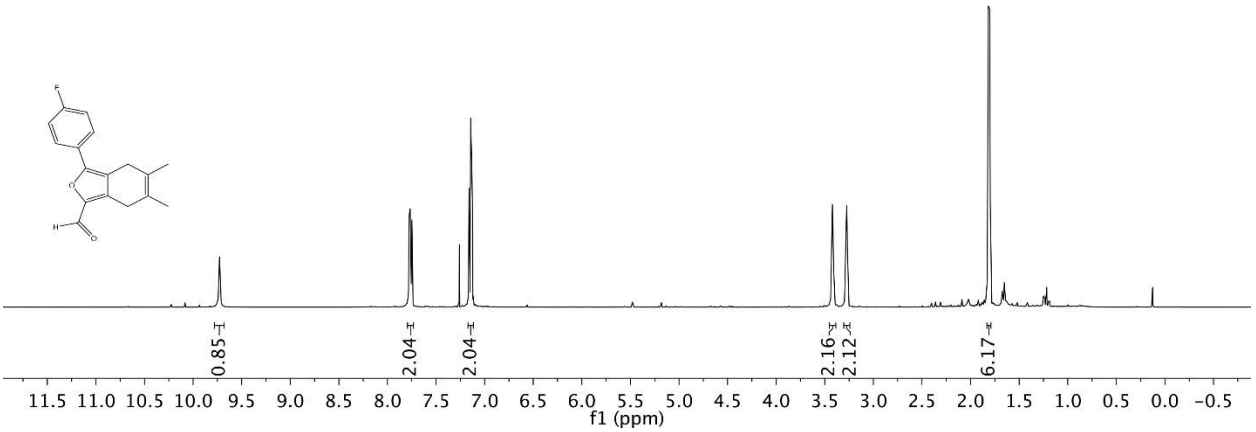


Figure S131. ^{1}H NMR spectrum of compound **3.6j**.

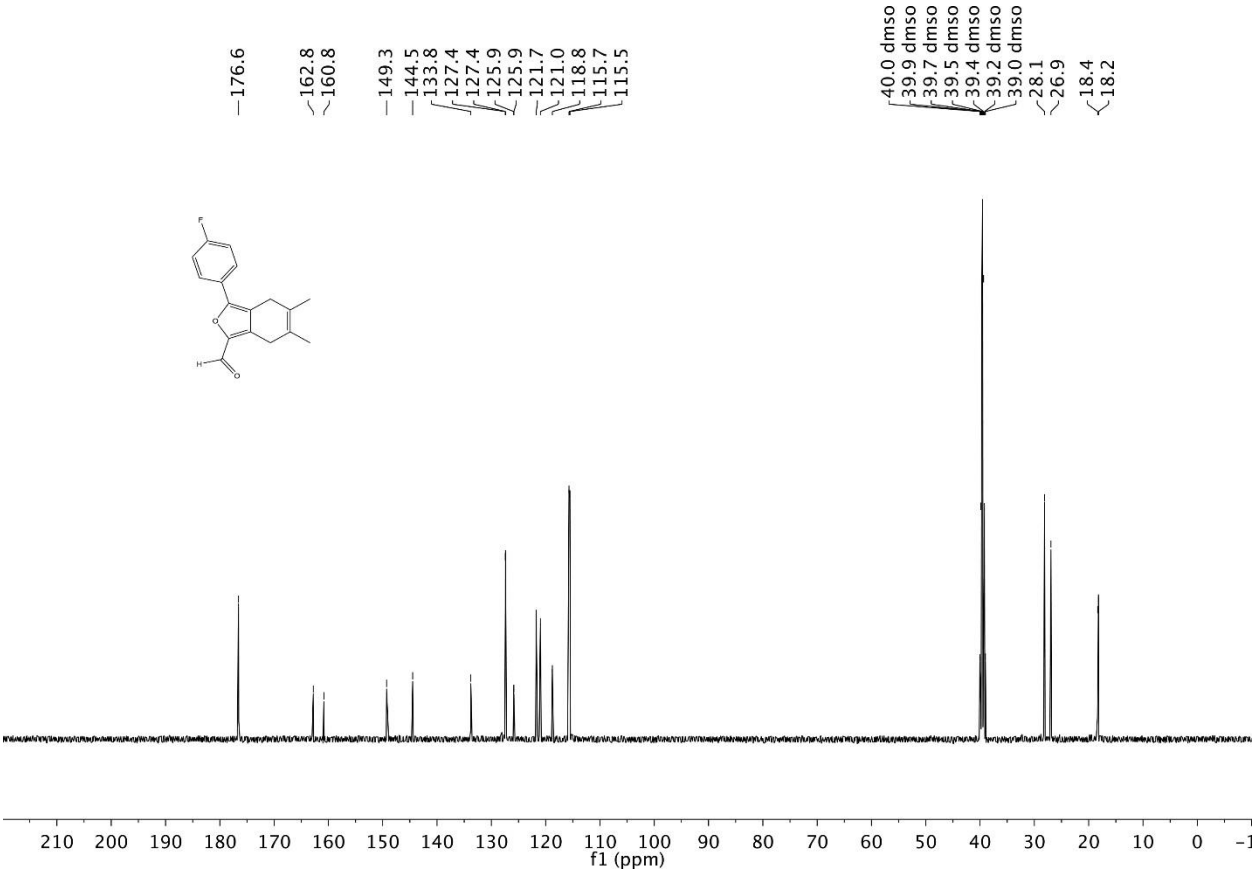


Figure S132. ^{13}C NMR spectrum of compound **3.6j**.

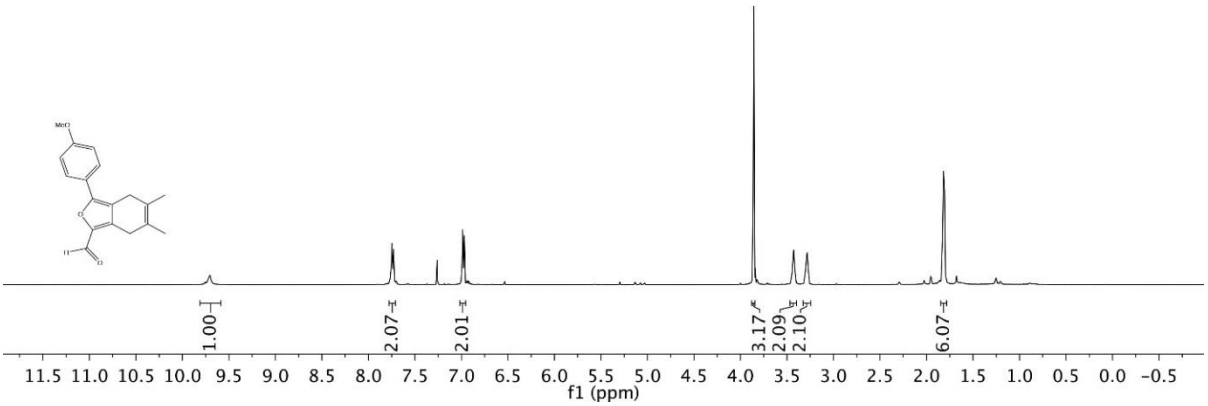


Figure S133. [1]H NMR spectrum of compound **3.6k**.

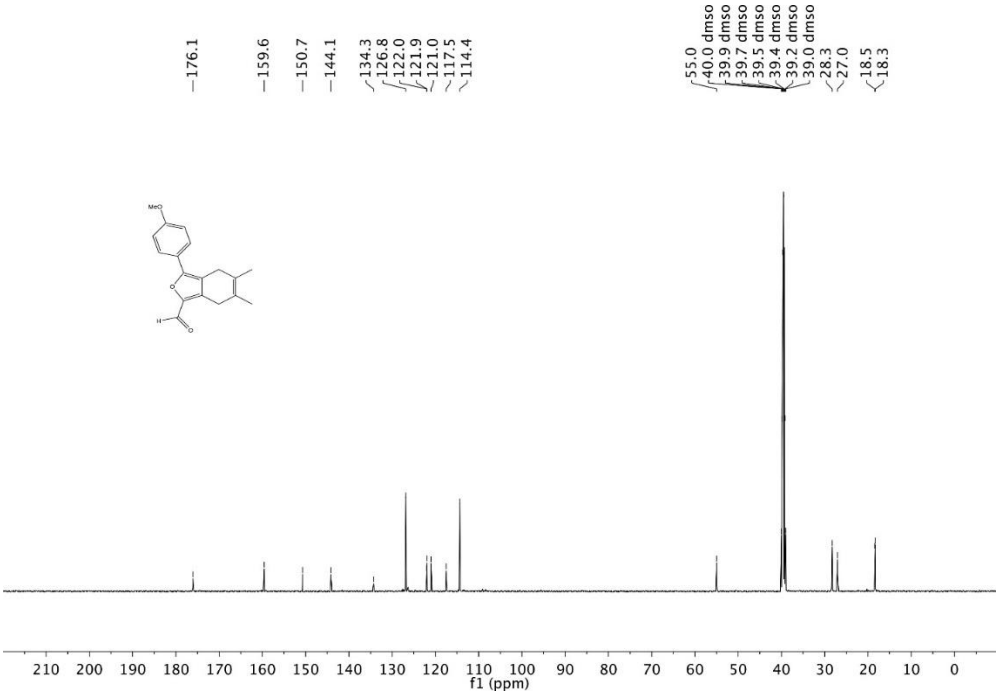


Figure S134. [13]C NMR spectrum of compound **3.6k**.

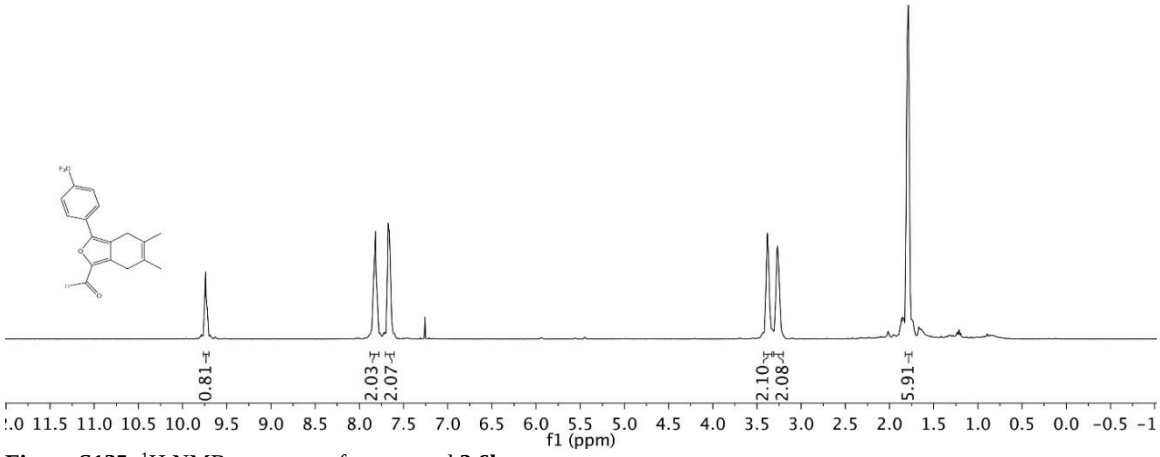


Figure S135. ^{1}H NMR spectrum of compound **3.6l**.

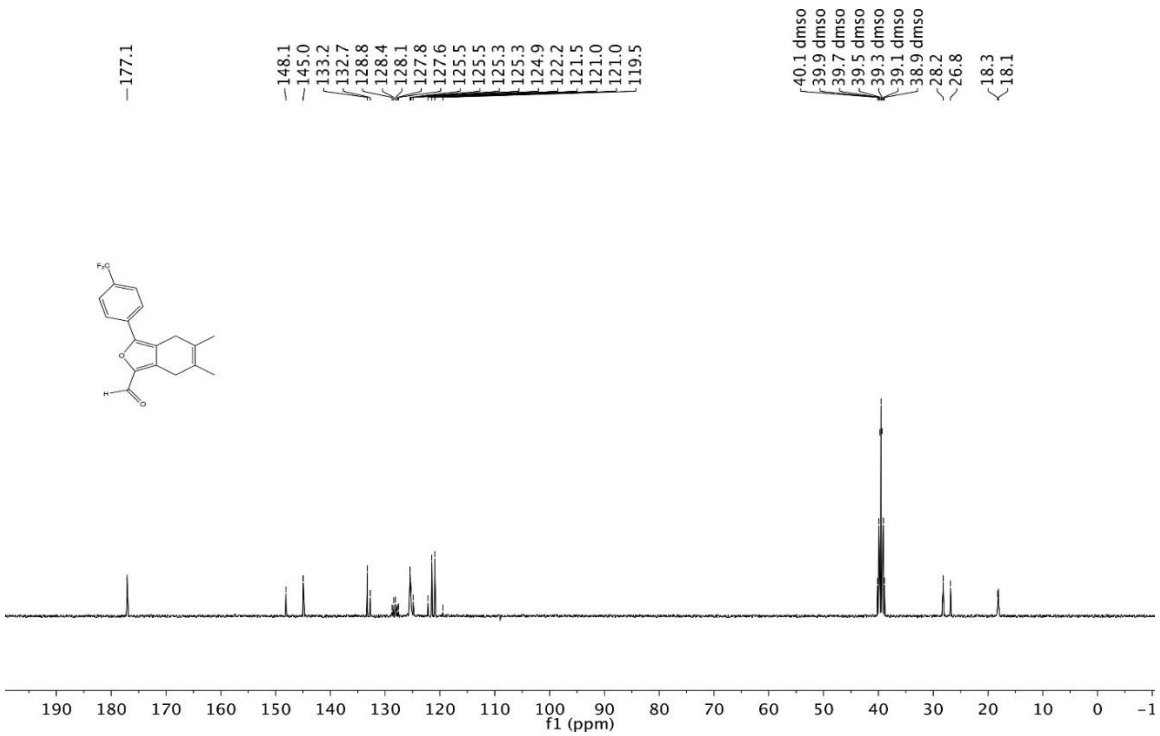


Figure S136. ^{13}C NMR spectrum of compound **3.6l**.

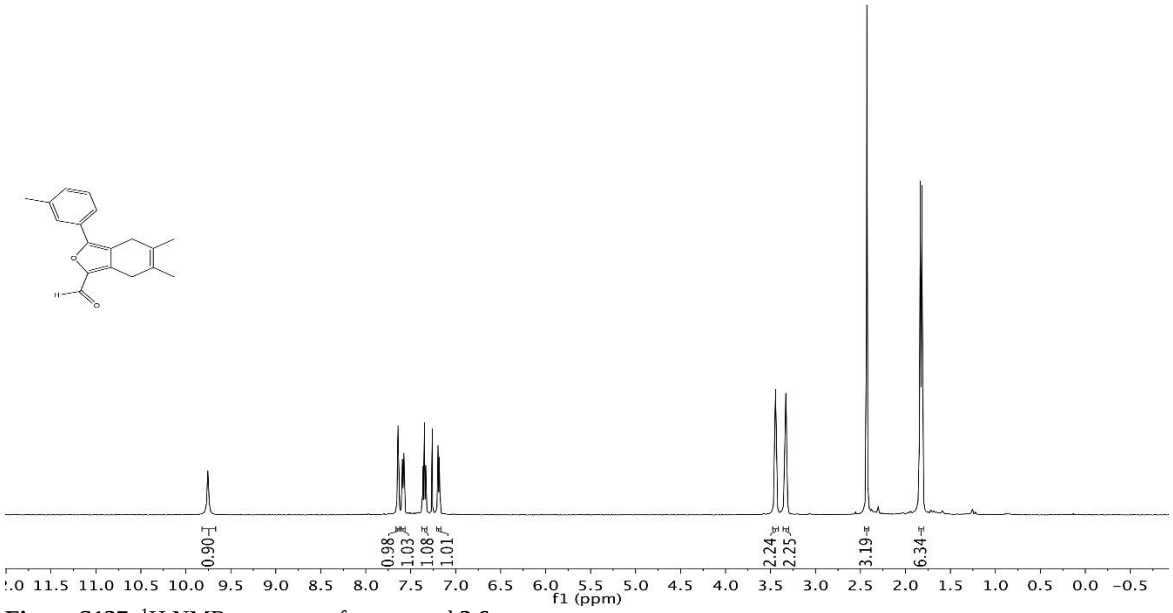


Figure S137. ^{1}H NMR spectrum of compound **3.6m**.

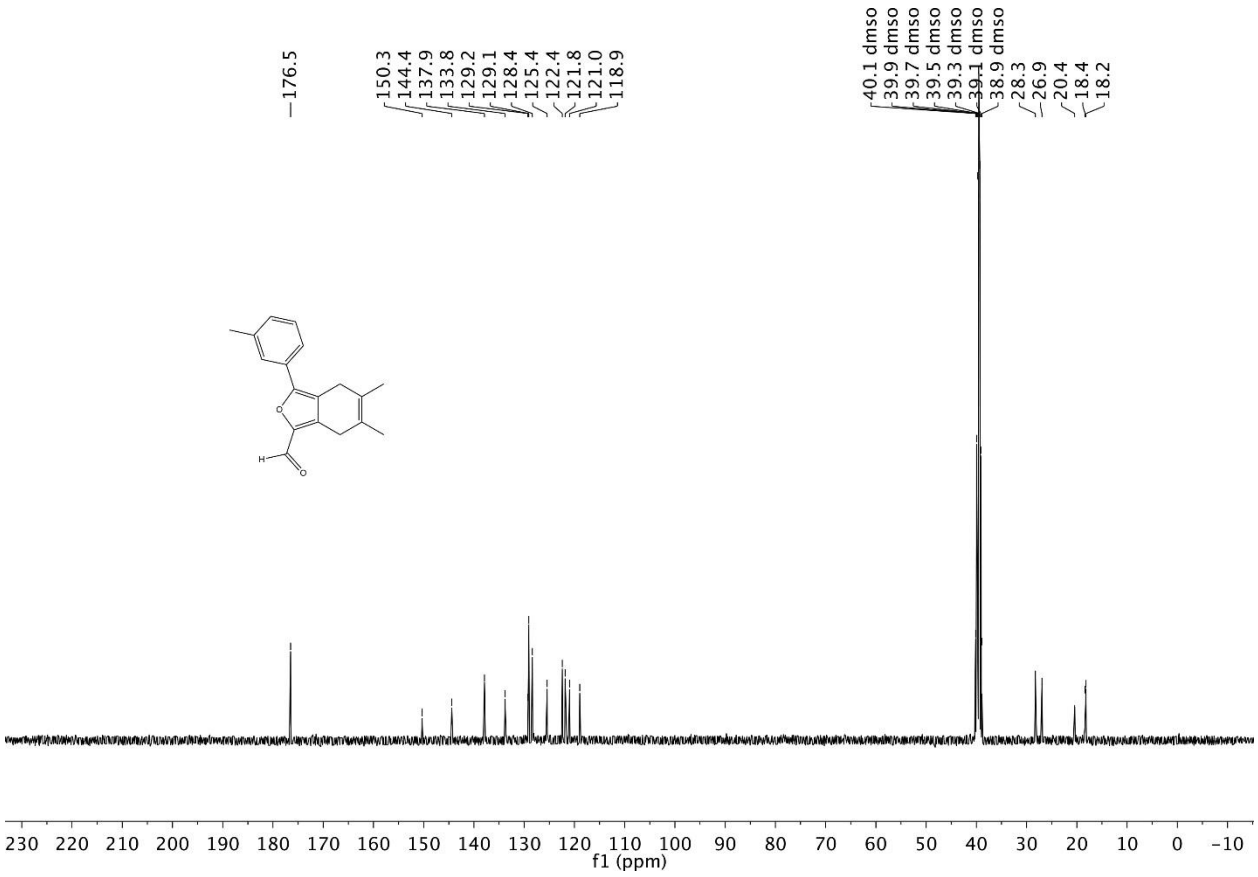


Figure S138. ^{13}C NMR spectrum of compound **3.6m**.

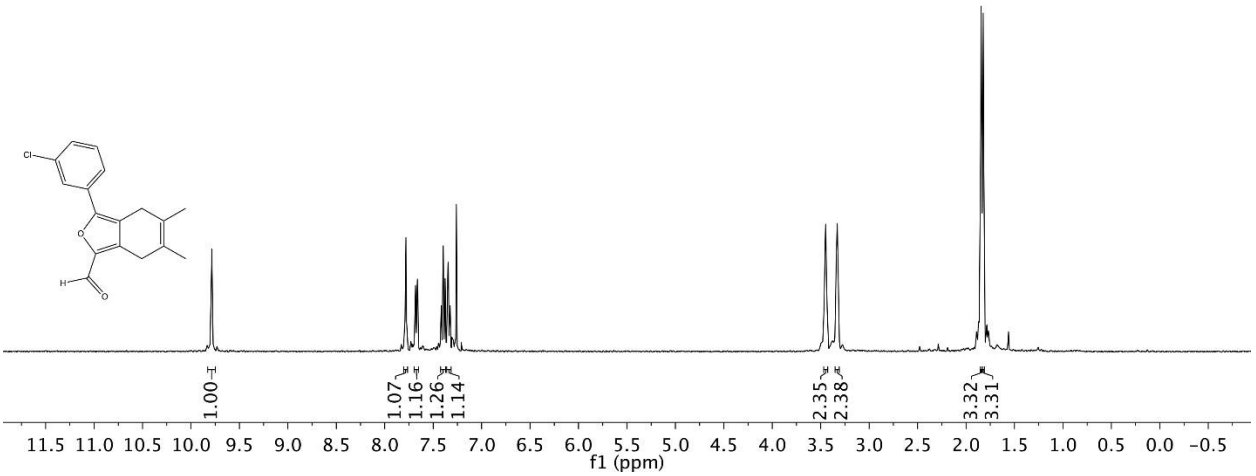


Figure S139. ^{1}H NMR spectrum of compound **3.6n**.

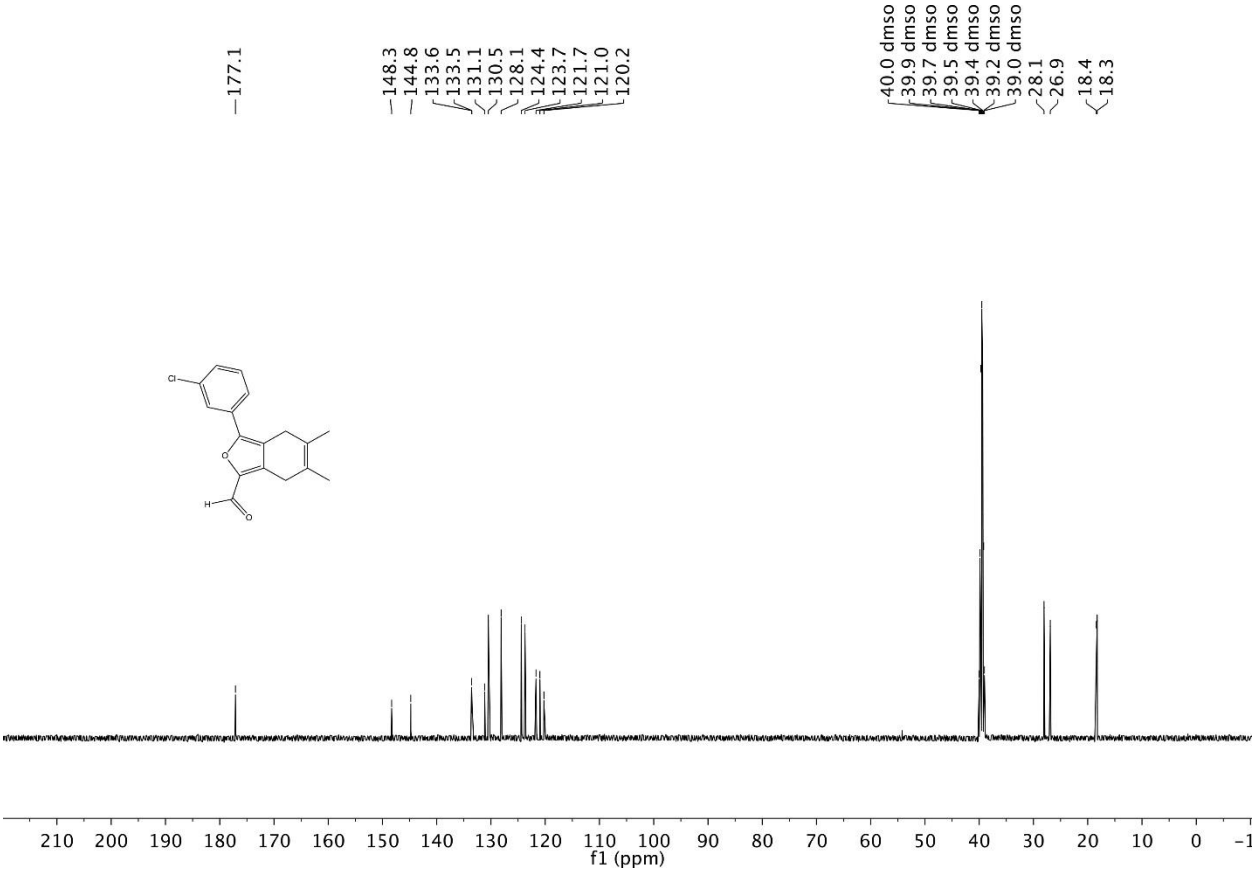


Figure S140. ^{13}C NMR spectrum of compound **3.6n**.

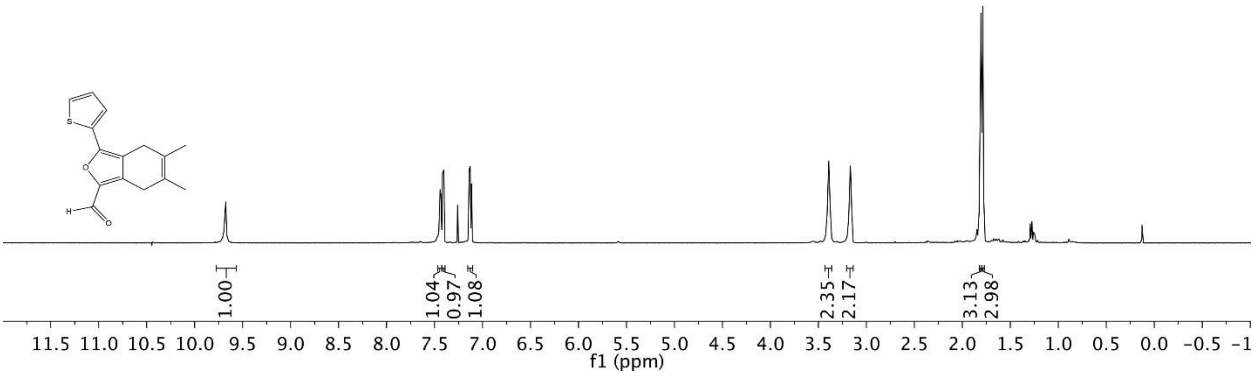


Figure S141. [1]H NMR spectrum of compound **3.6o**.

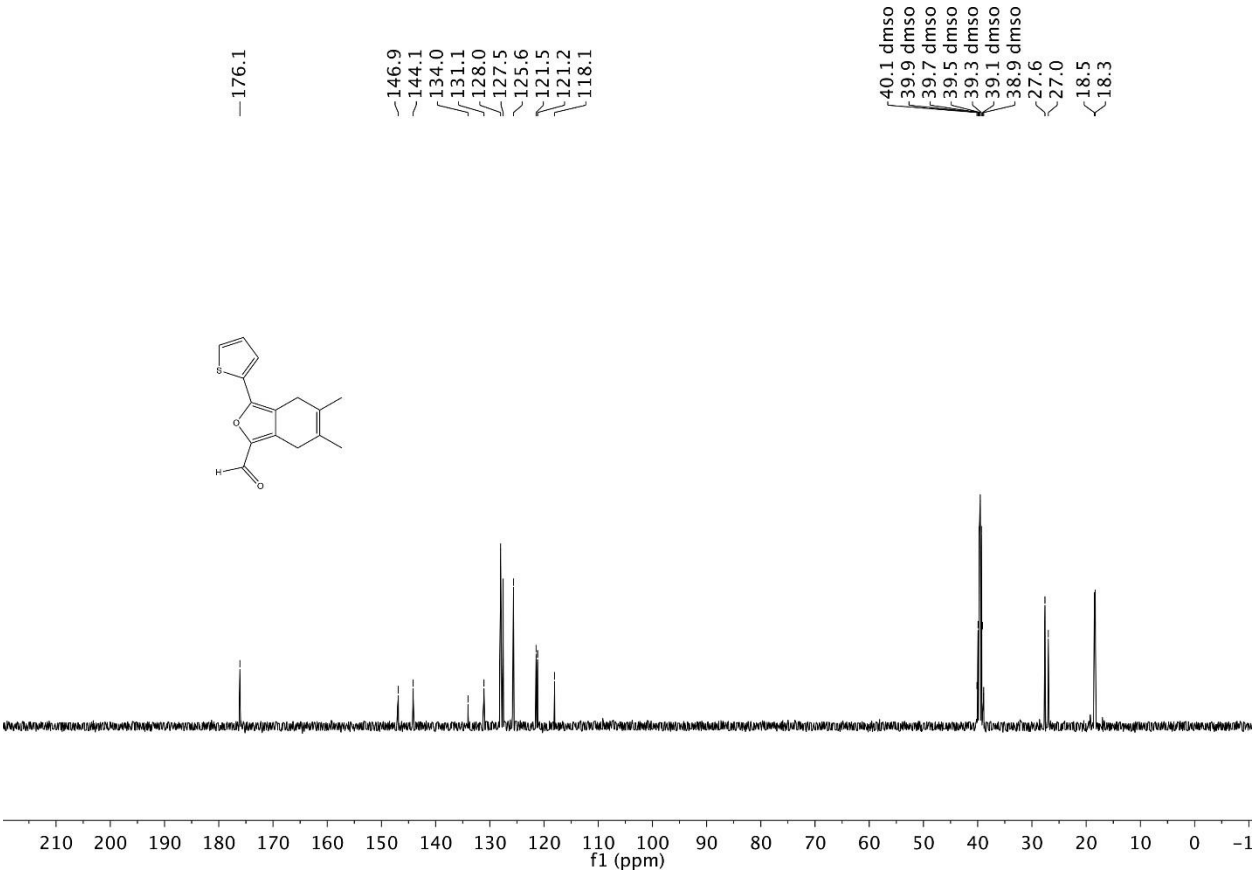


Figure S142. [13]C NMR spectrum of compound **3.6o**.

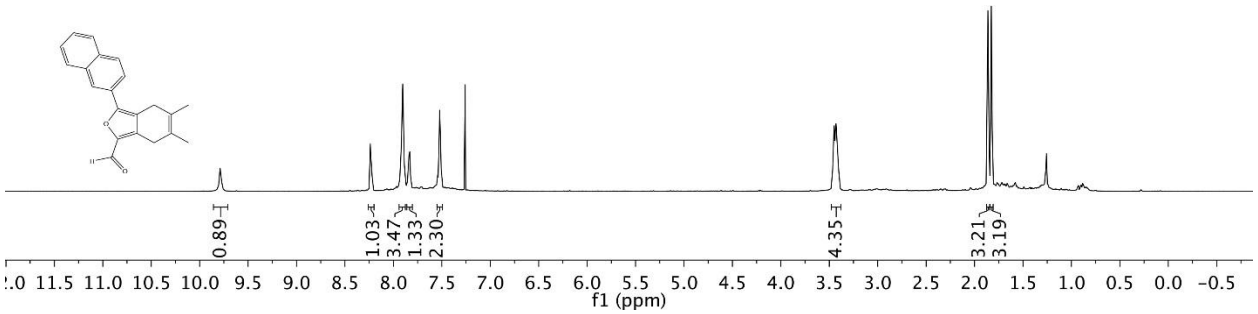


Figure S143. ^{1}H NMR spectrum of compound **3.6p**.

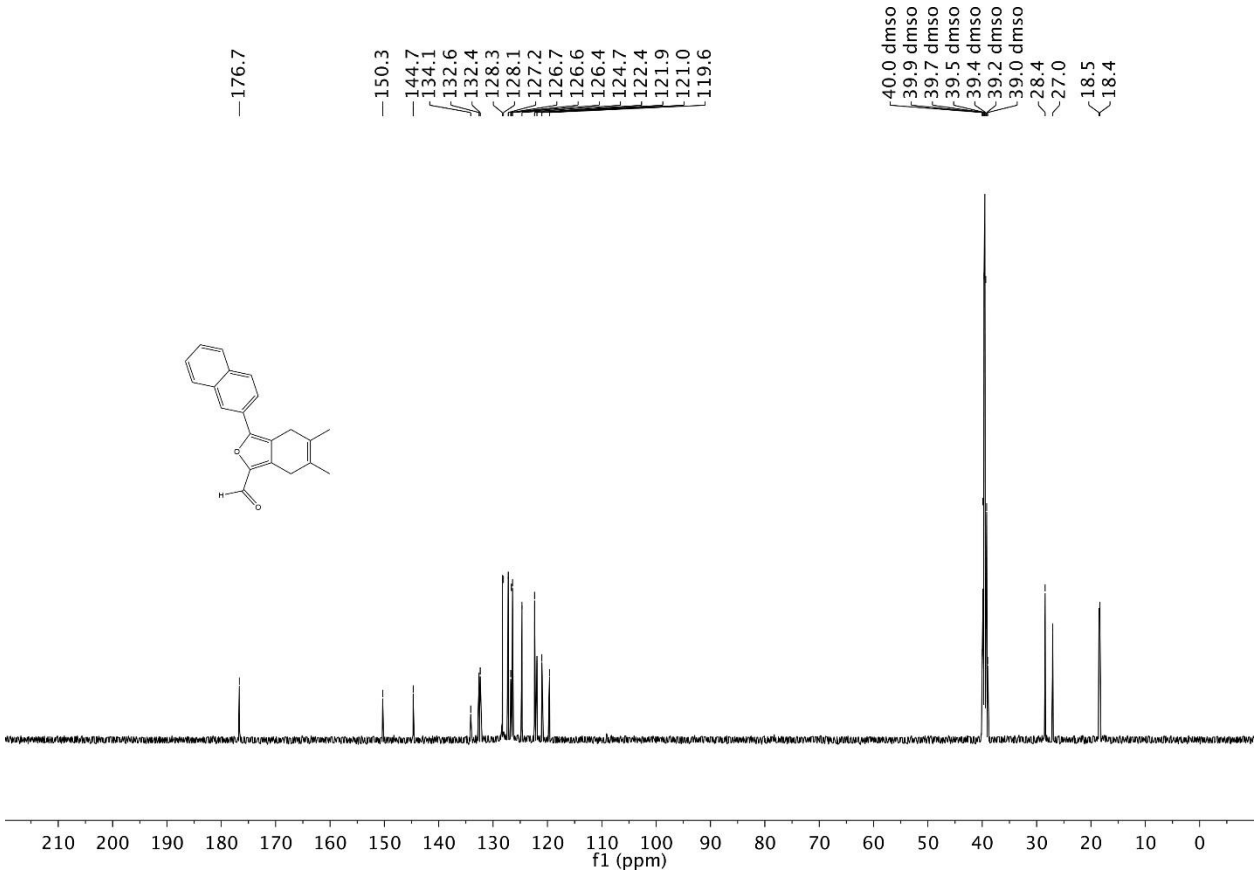


Figure S144. ^{13}C NMR spectrum of compound **3.6p**.

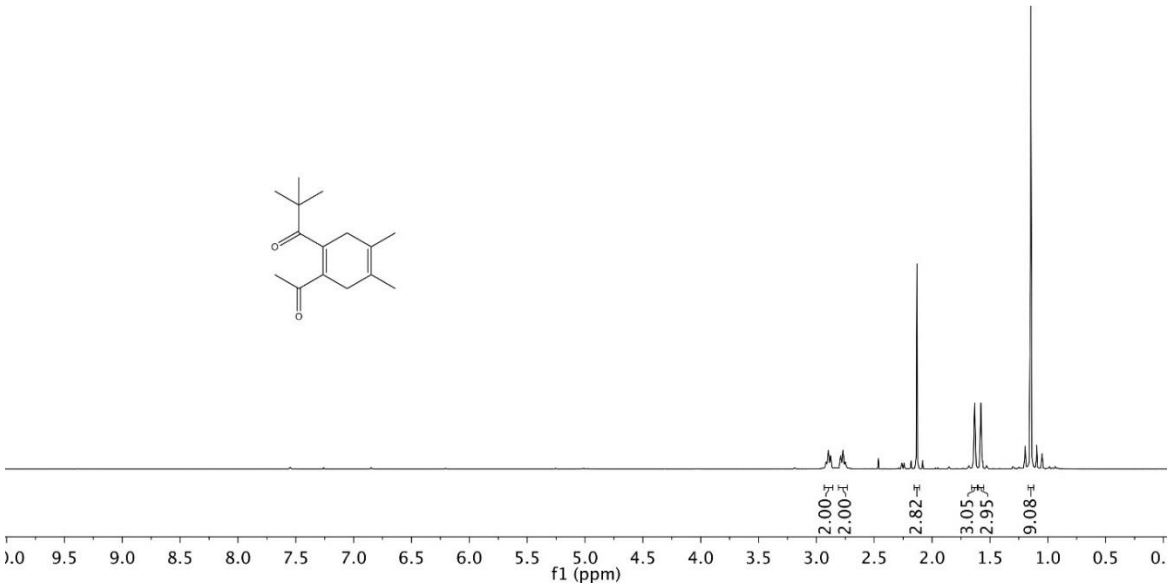


Figure S145. ^{1}H NMR spectrum of compound **3.7**.

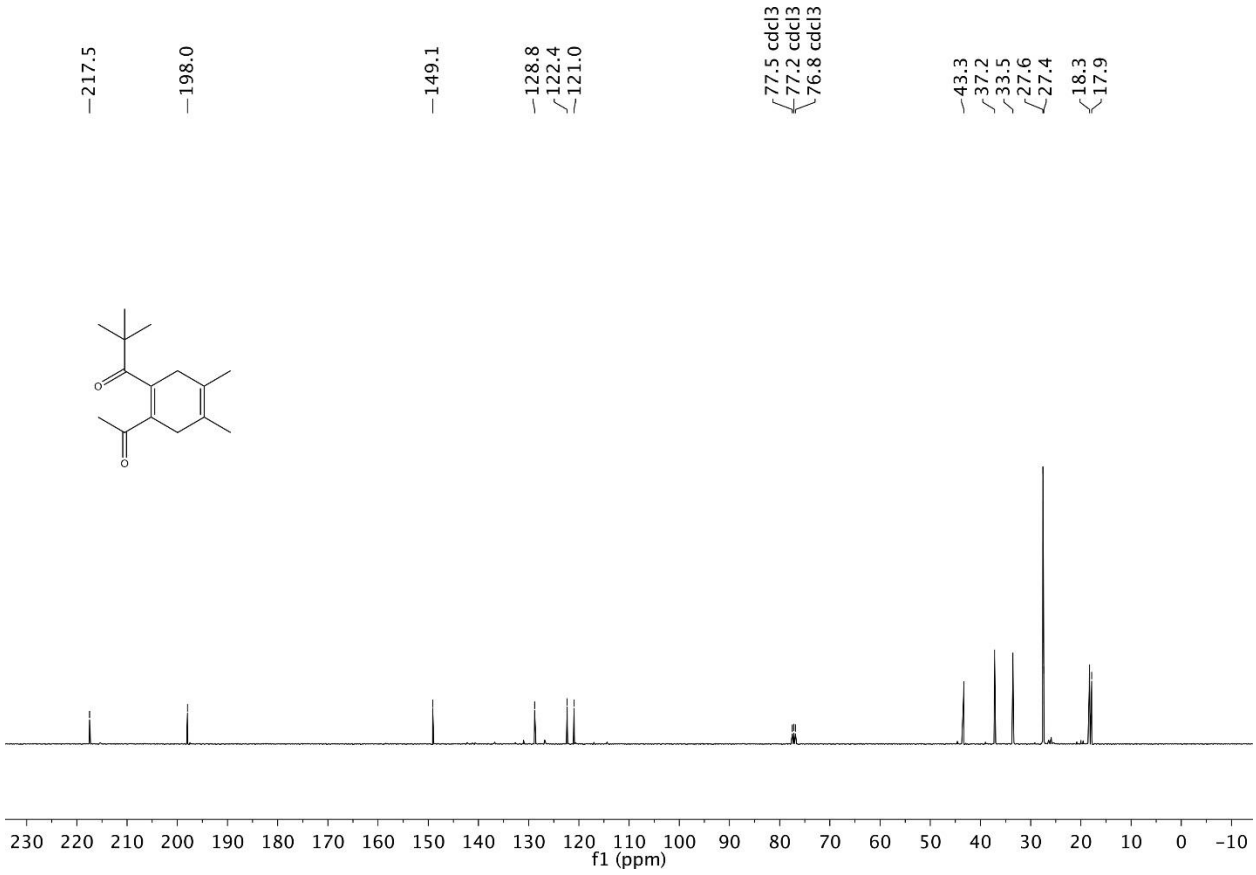


Figure S146. ^{13}C NMR spectrum of compound **3.7**.

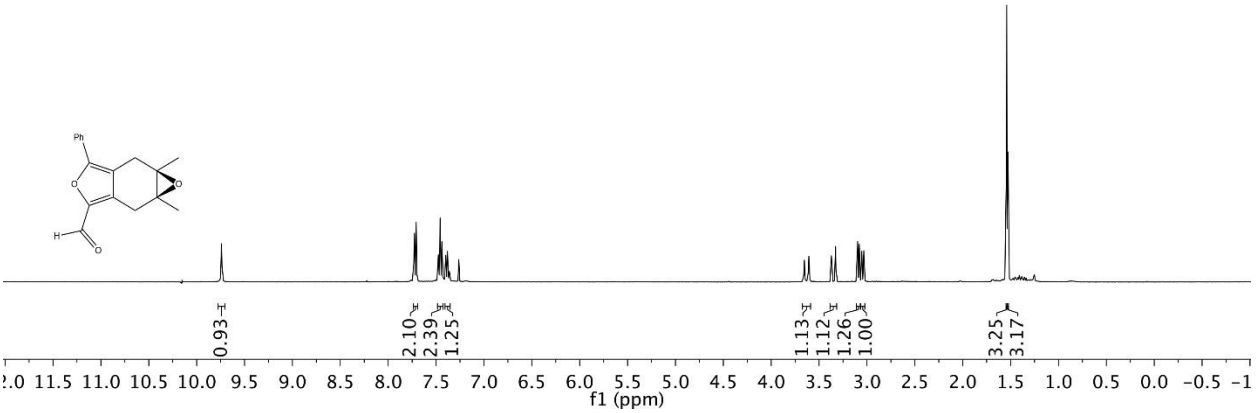


Figure S147. ^{1}H NMR spectrum of compound **3.11**.

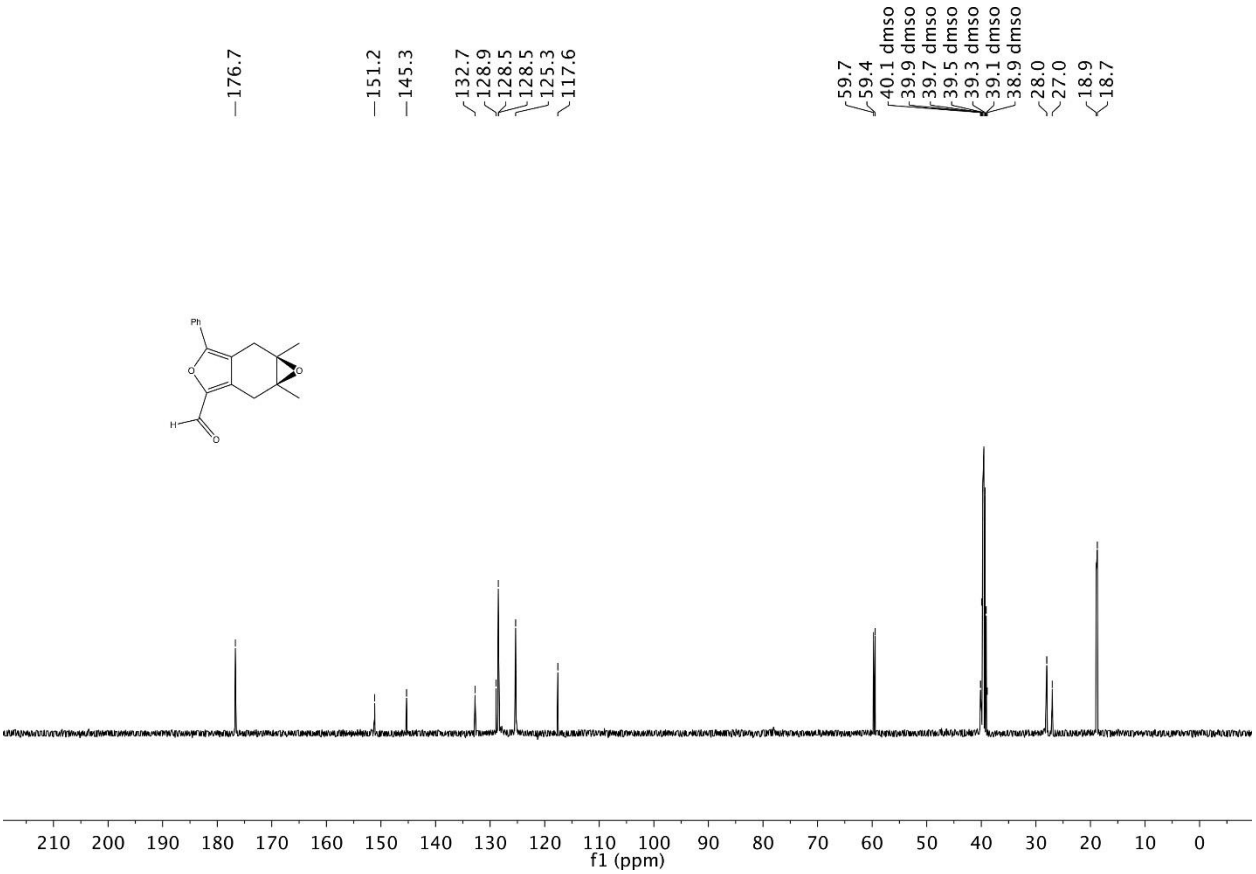


Figure S148. ^{13}C NMR spectrum of compound **3.11**.

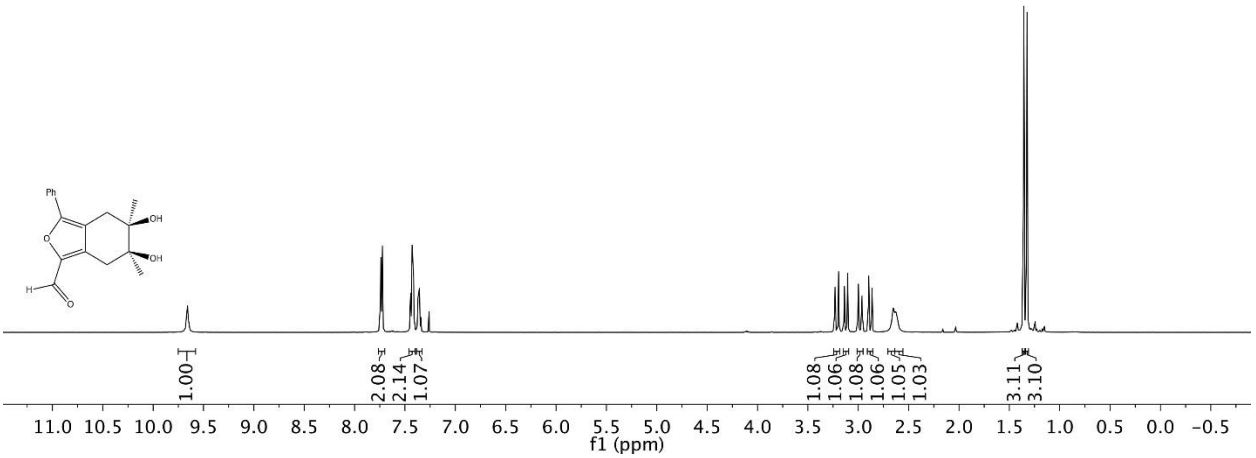


Figure S149. ^{1}H NMR spectrum of compound **3.12**.

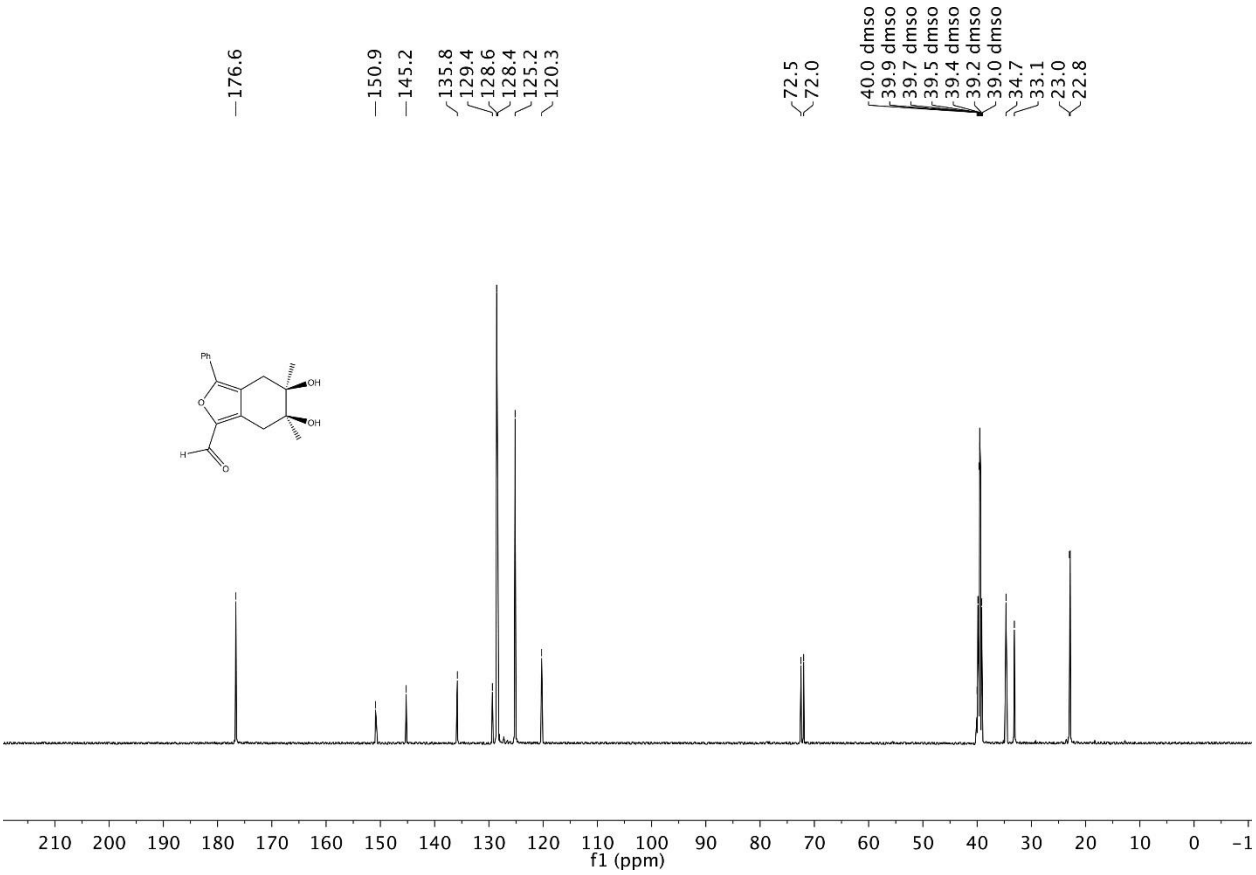


Figure S150. ^{13}C NMR spectrum of compound **3.12**.

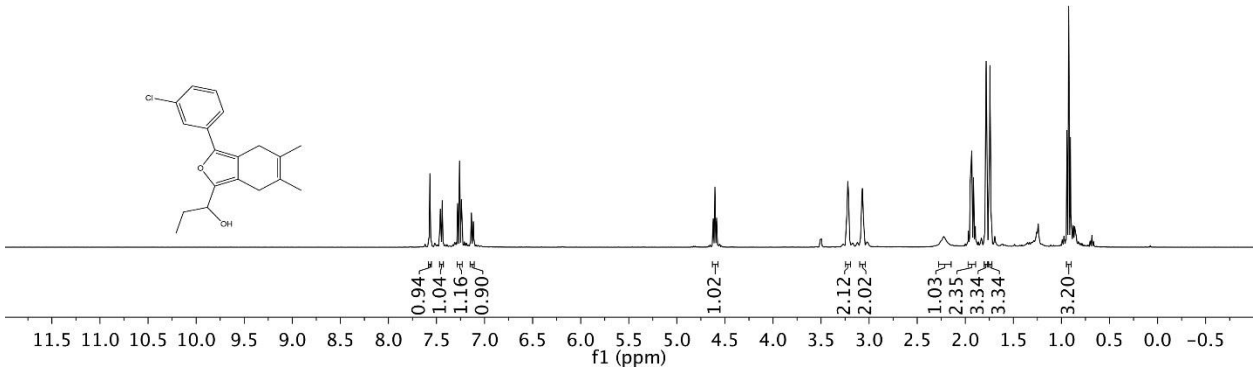


Figure S151. [1]H NMR spectrum of compound **3.13**.

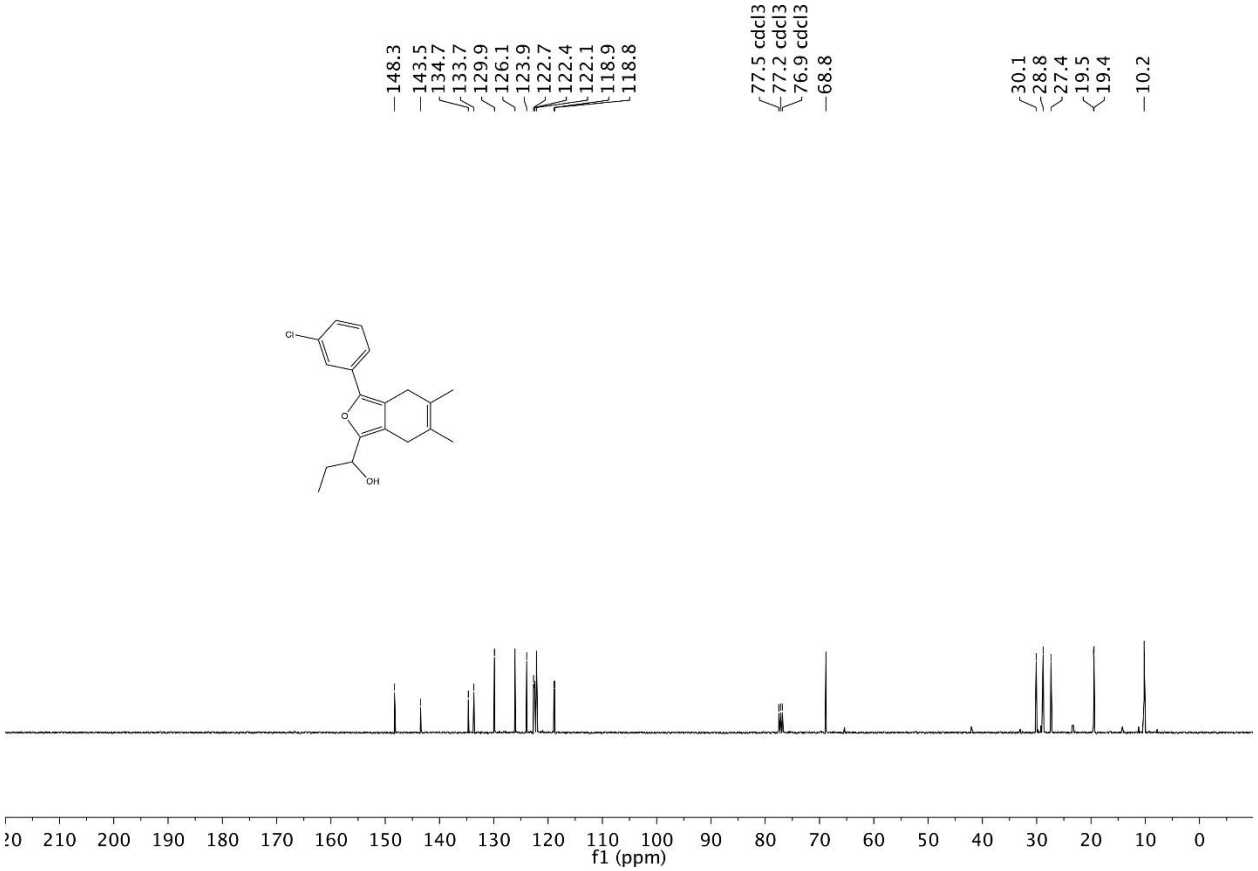


Figure S152. [13]C NMR spectrum of compound **3.13**.

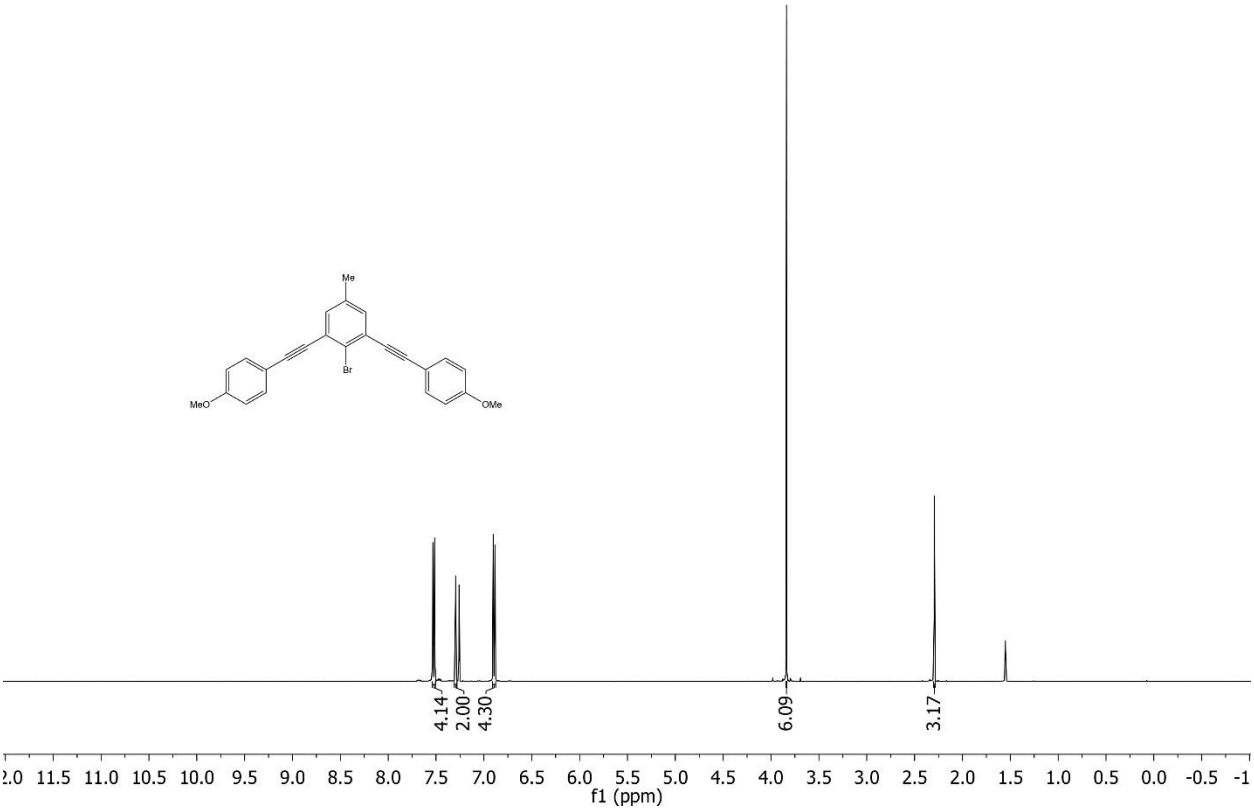


Figure S153. ^{1}H NMR spectrum of compound **4.12d**.

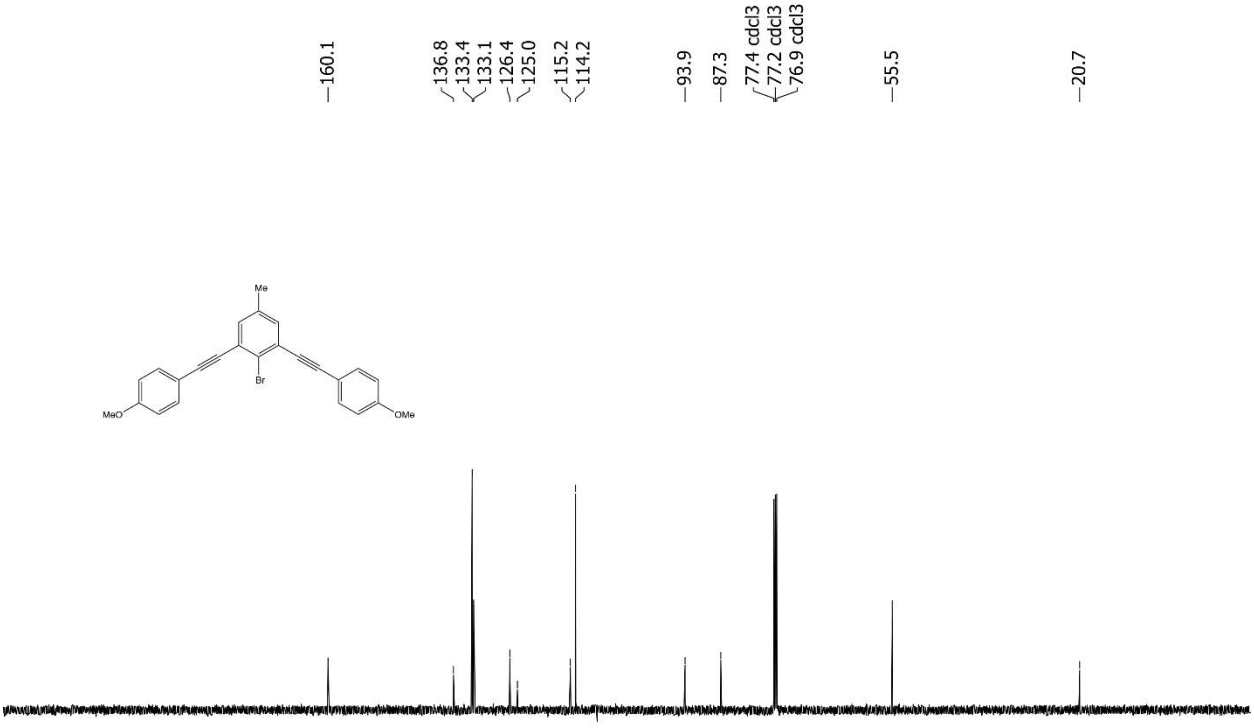
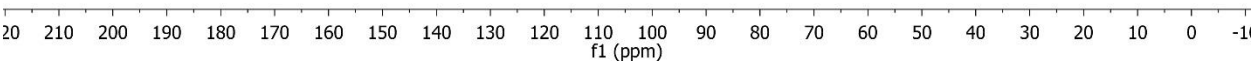


Figure S154. ^{13}C NMR spectrum of compound **4.12d**.



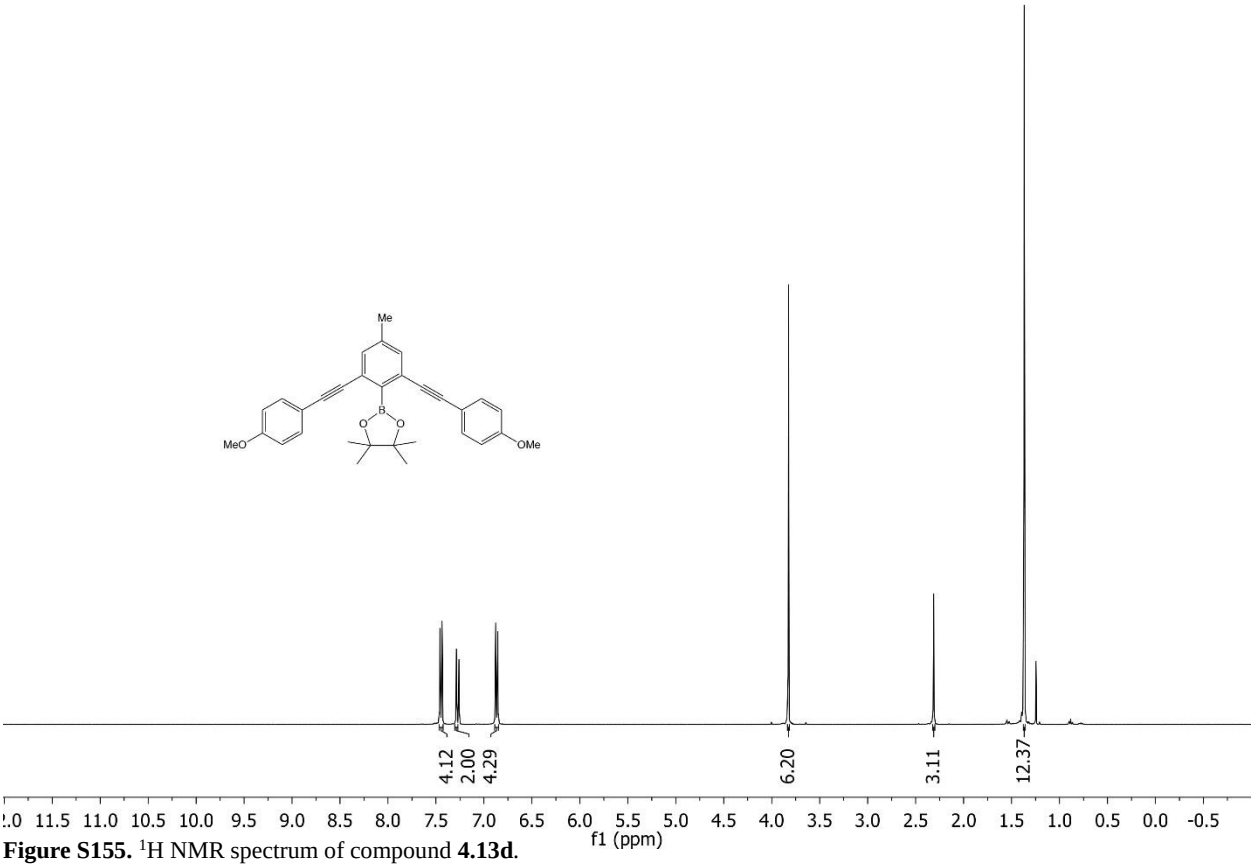


Figure S155. ^{1}H NMR spectrum of compound **4.13d**.

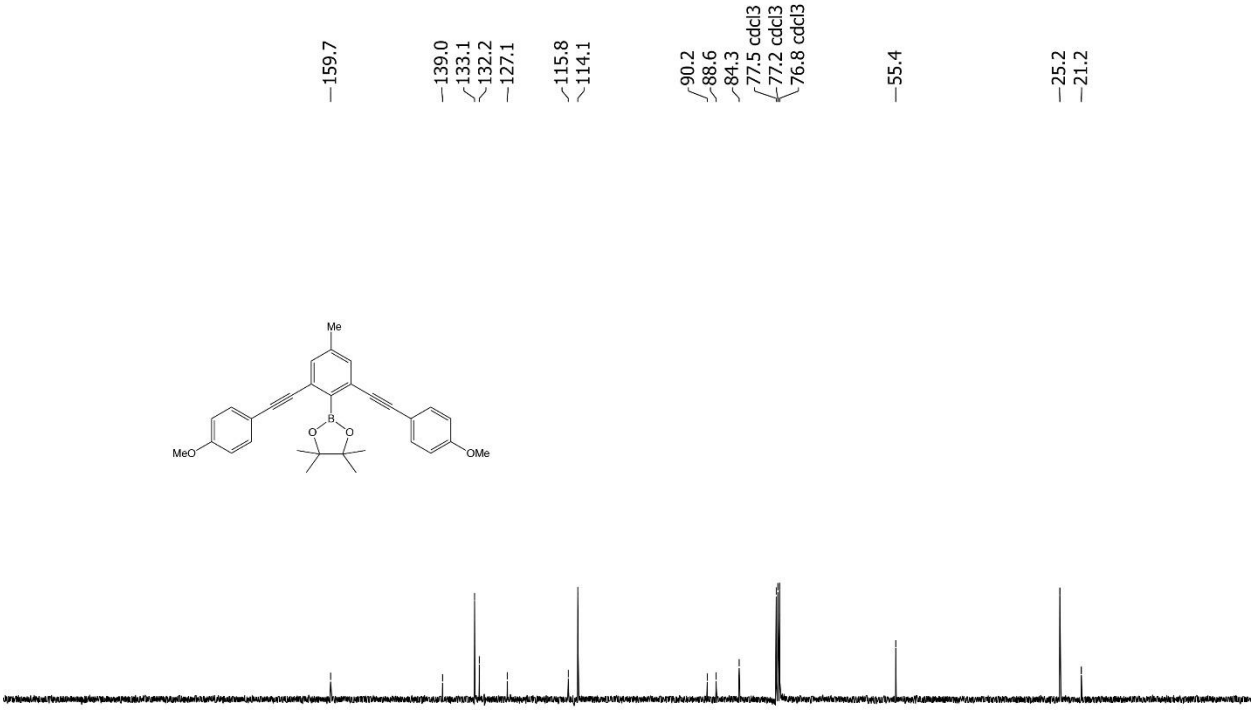


Figure S156. ^{13}C NMR spectrum of compound **4.13d**.

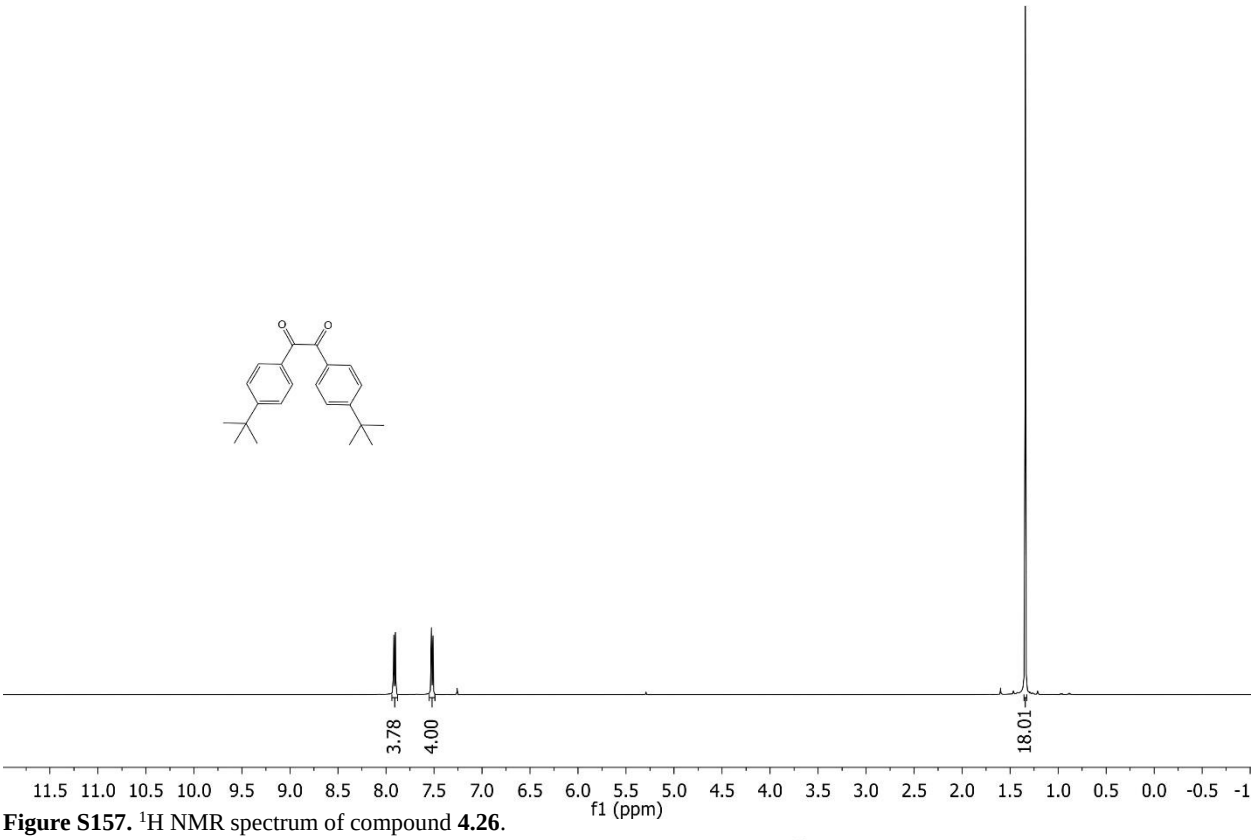


Figure S157. ^{1}H NMR spectrum of compound **4.26**.

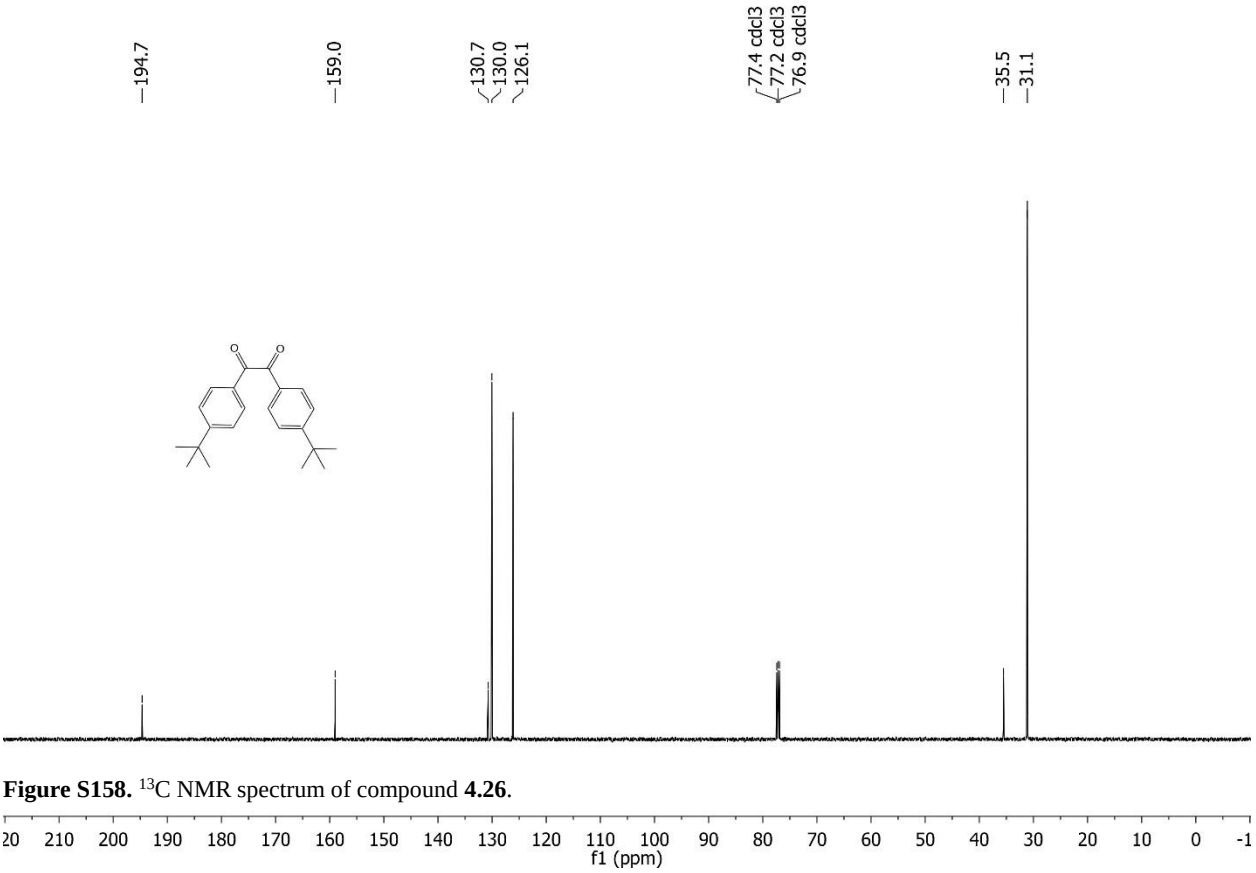


Figure S158. ^{13}C NMR spectrum of compound **4.26**.

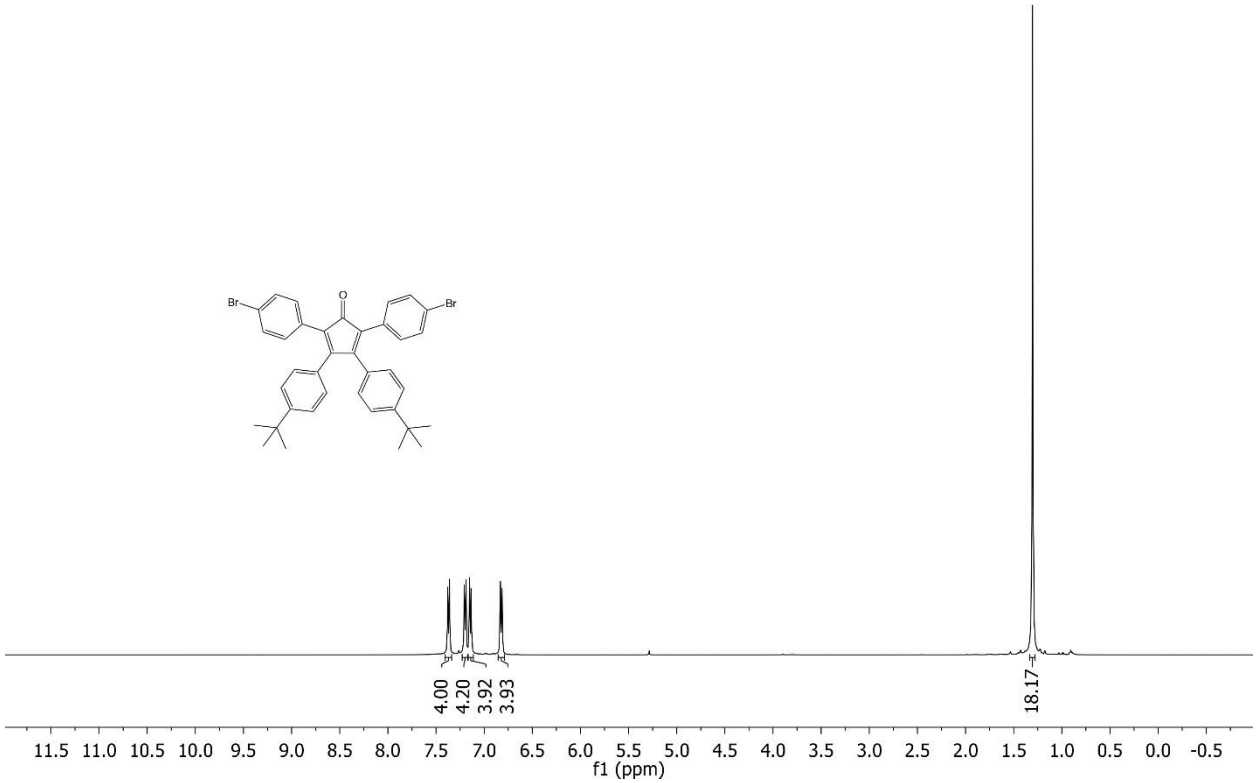


Figure S159. ^{1}H NMR spectrum of compound **4.28**.

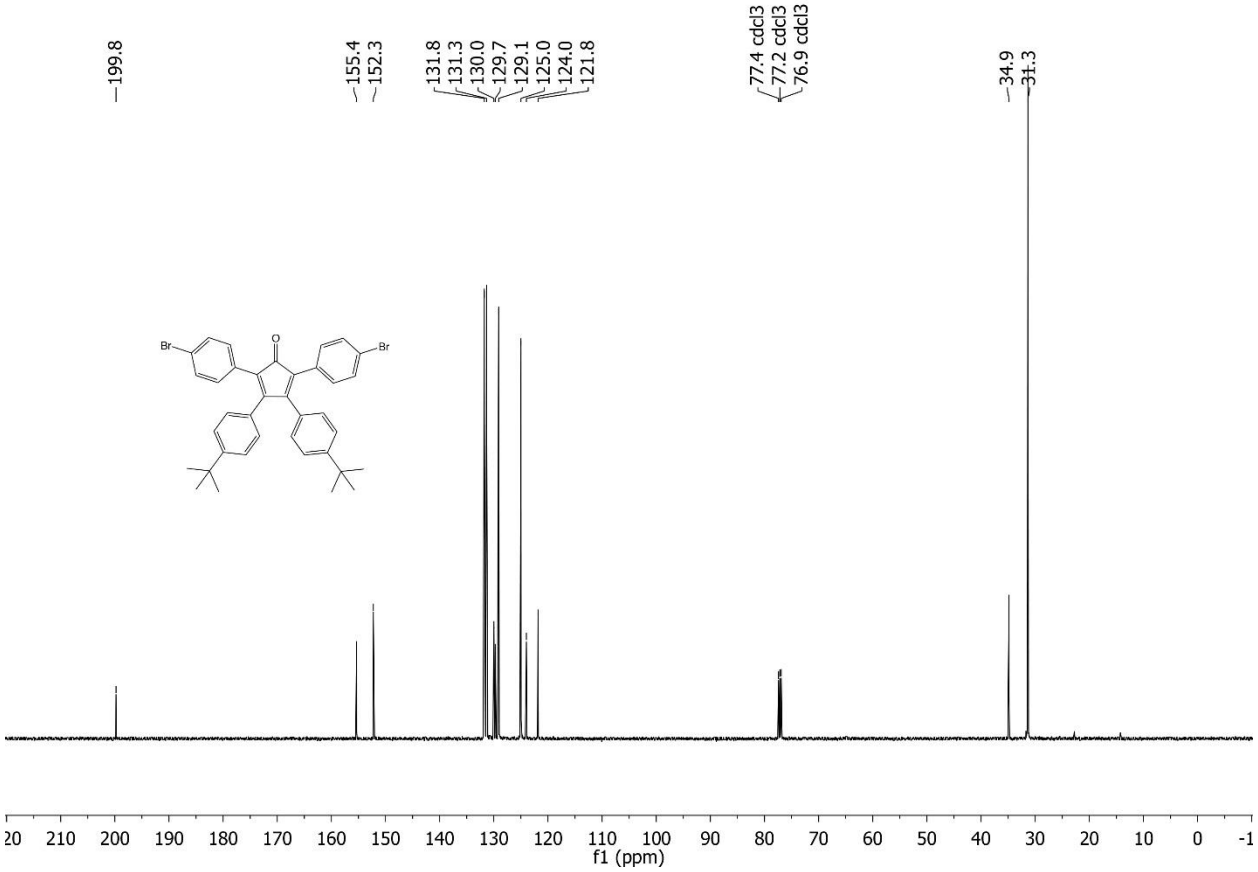


Figure S160. ^{13}C NMR spectrum of compound **4.28**.

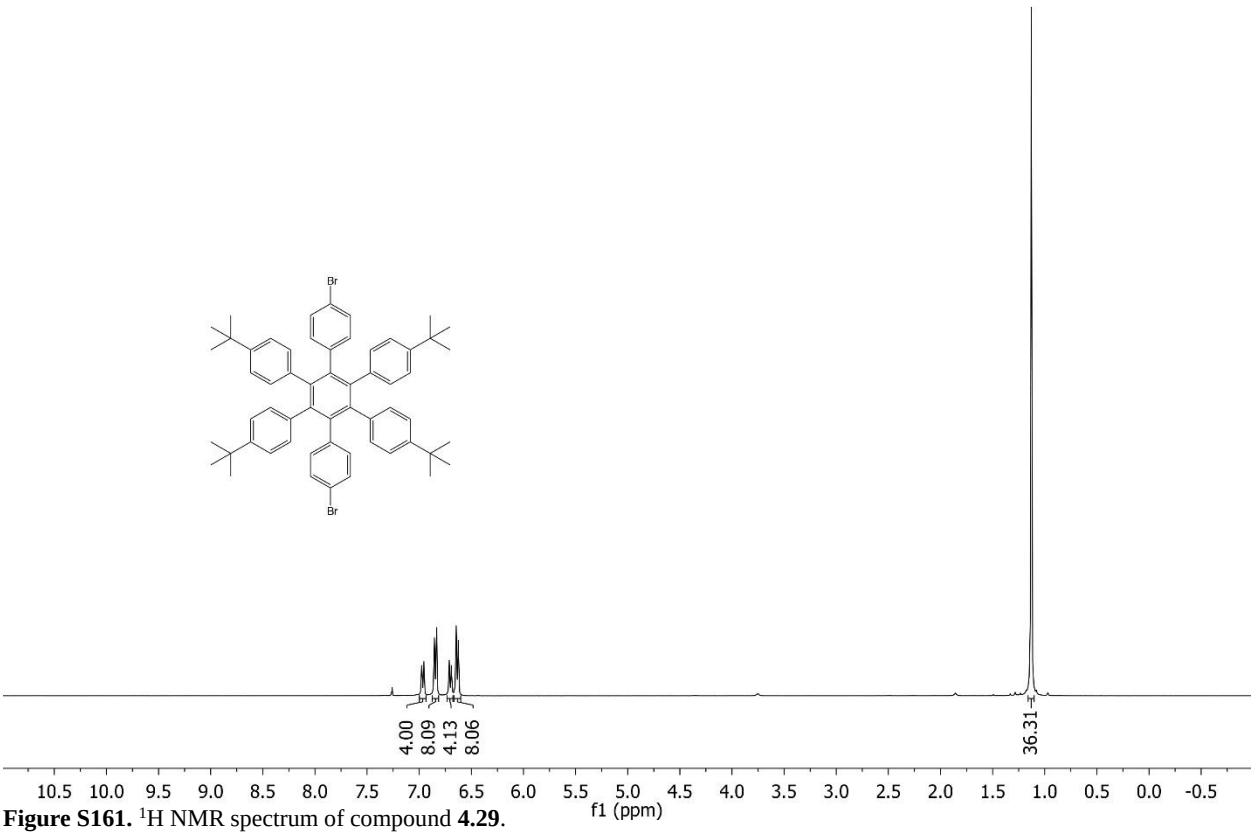


Figure S161. ^{1}H NMR spectrum of compound **4.29**.

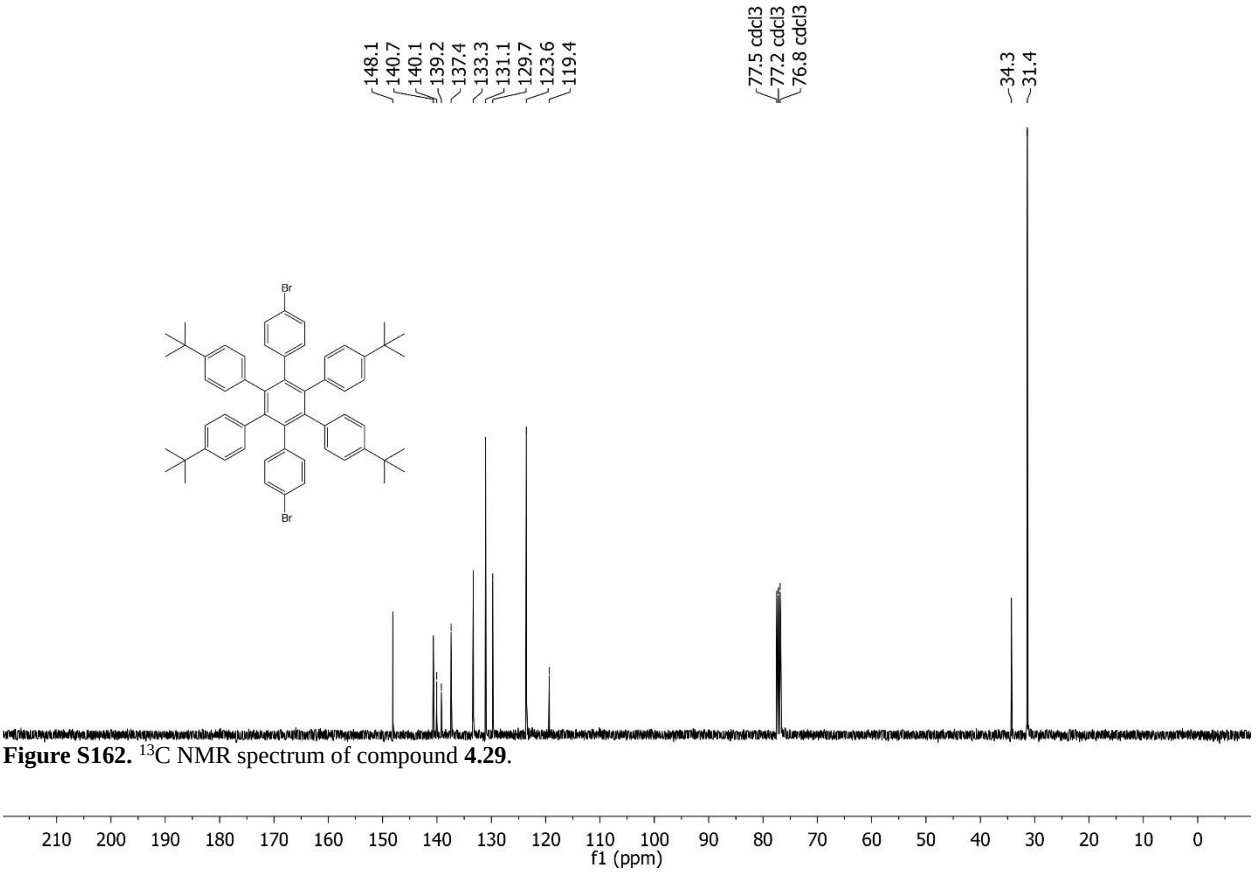


Figure S162. ^{13}C NMR spectrum of compound **4.29**.

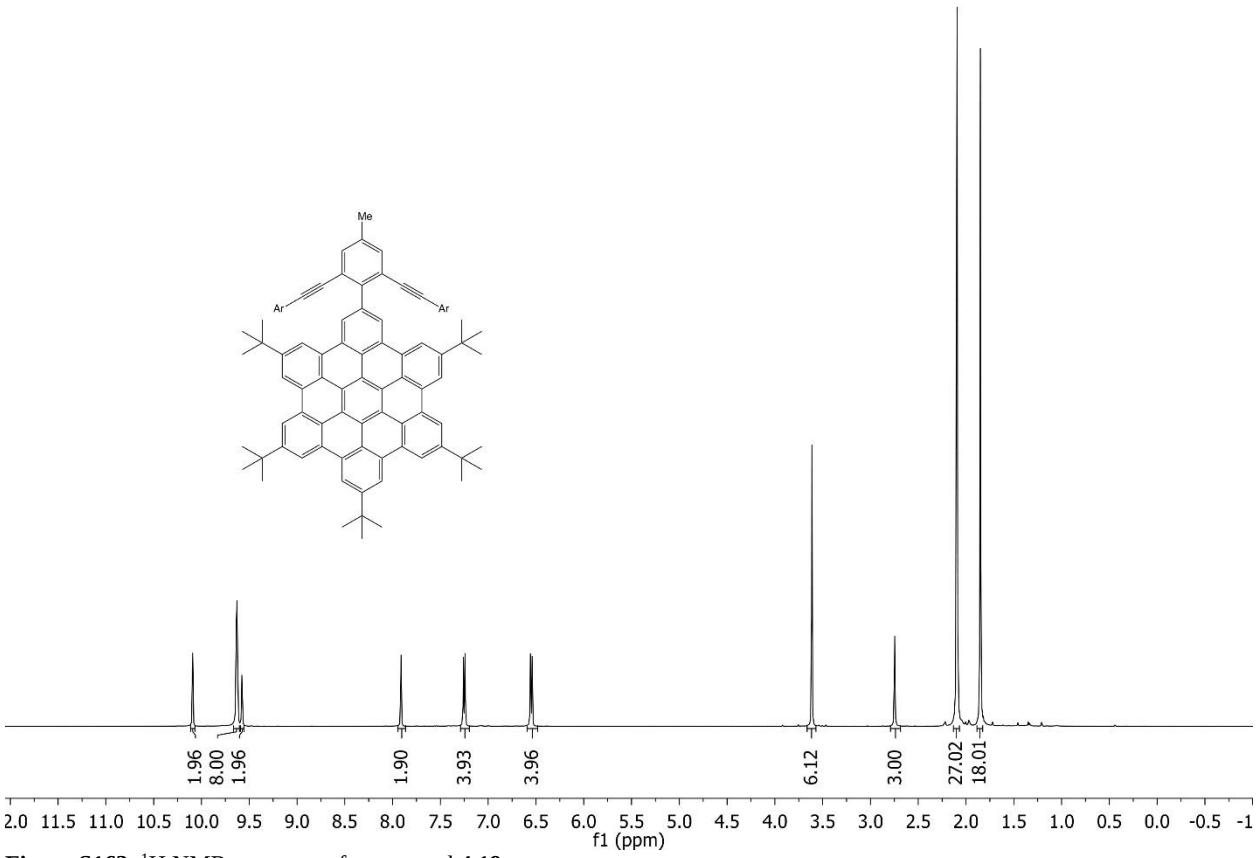


Figure S163. ^{1}H NMR spectrum of compound **4.19c**.

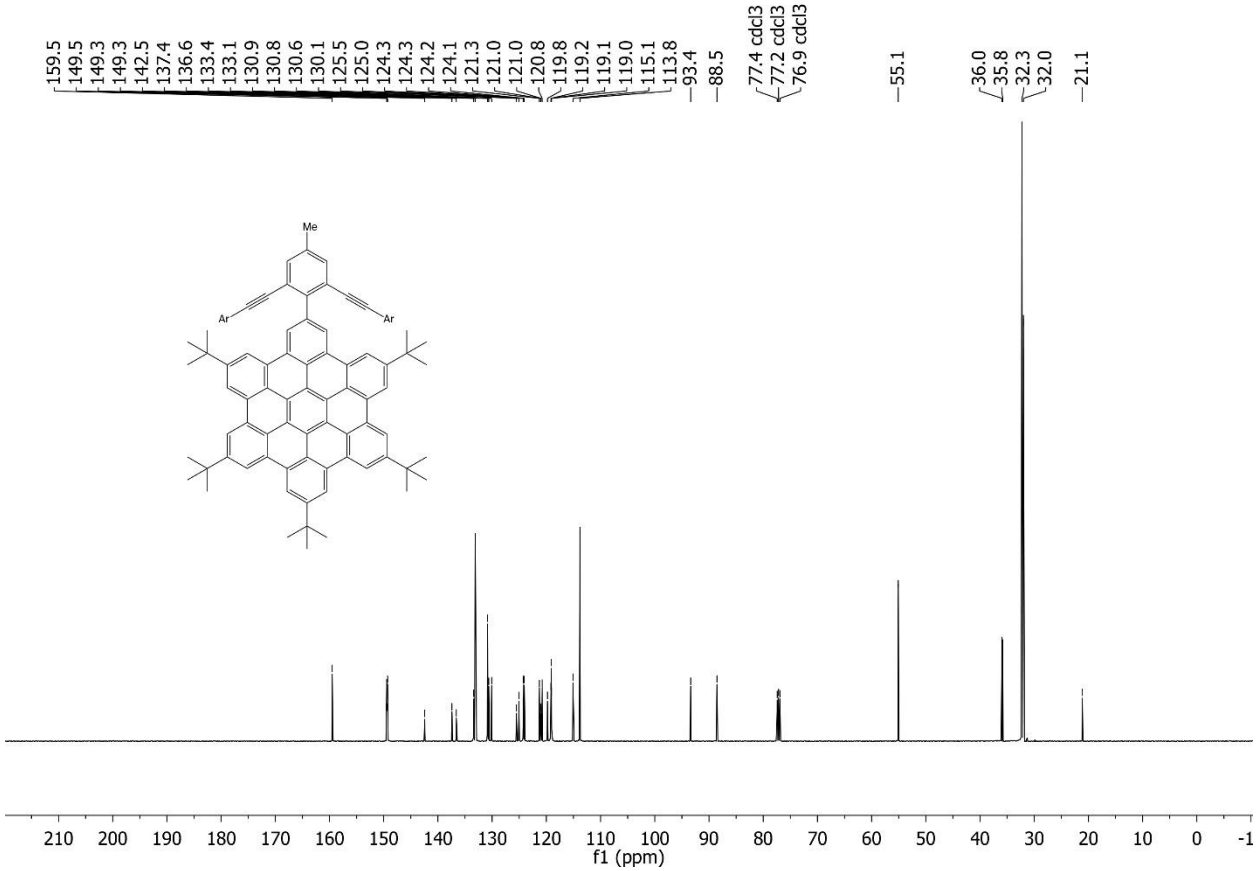


Figure S164. ^{13}C NMR spectrum of compound **4.19c**.

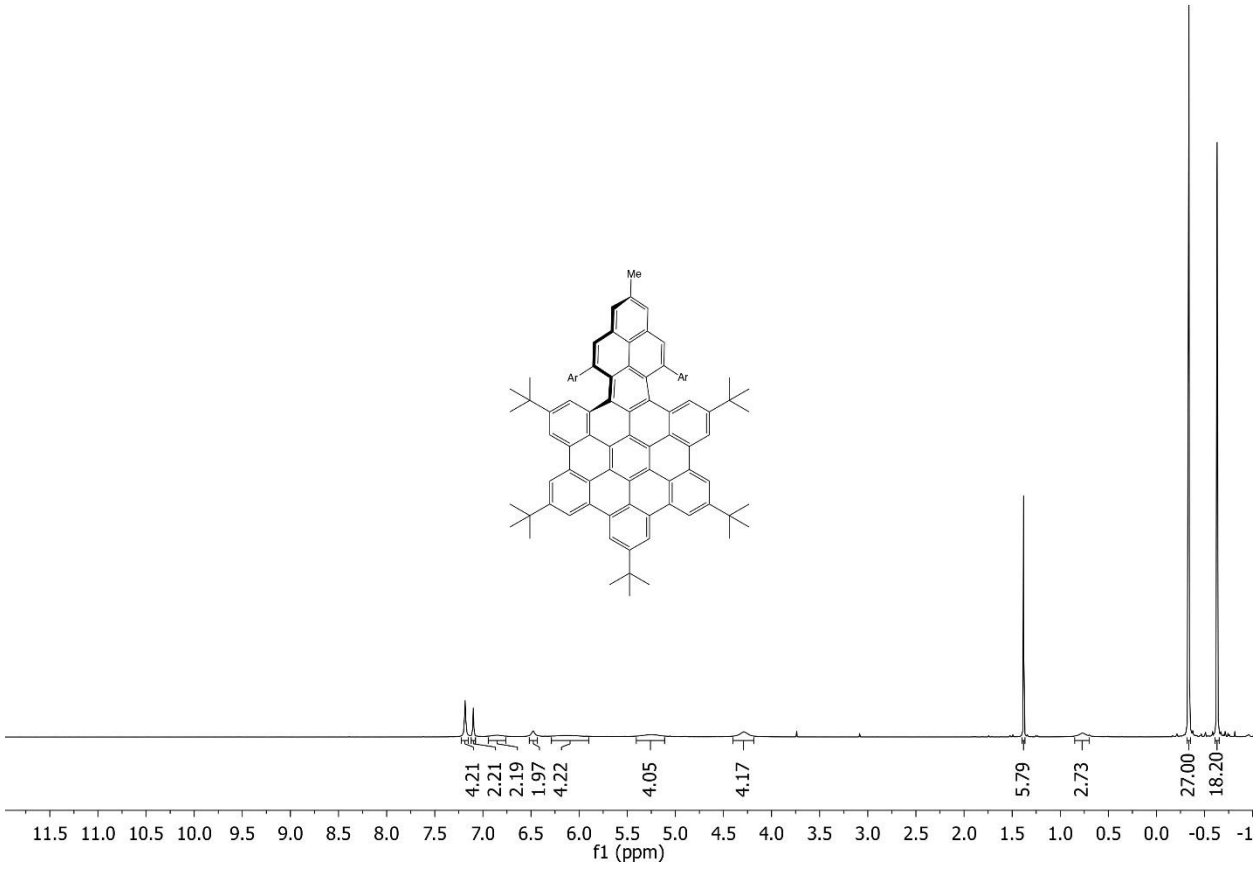


Figure S165. ^{1}H NMR spectrum of compound **4.20c**.

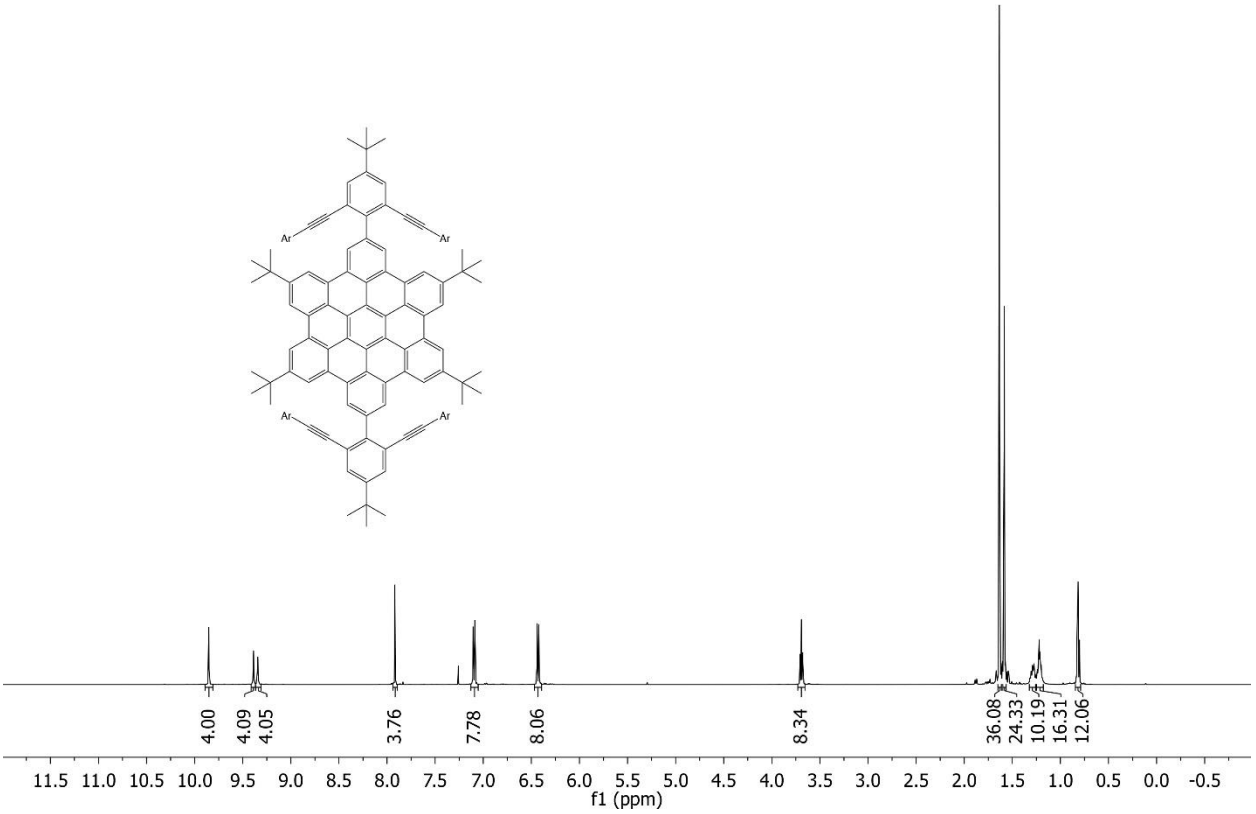


Figure S166. ^{1}H NMR spectrum of compound **4.30**.

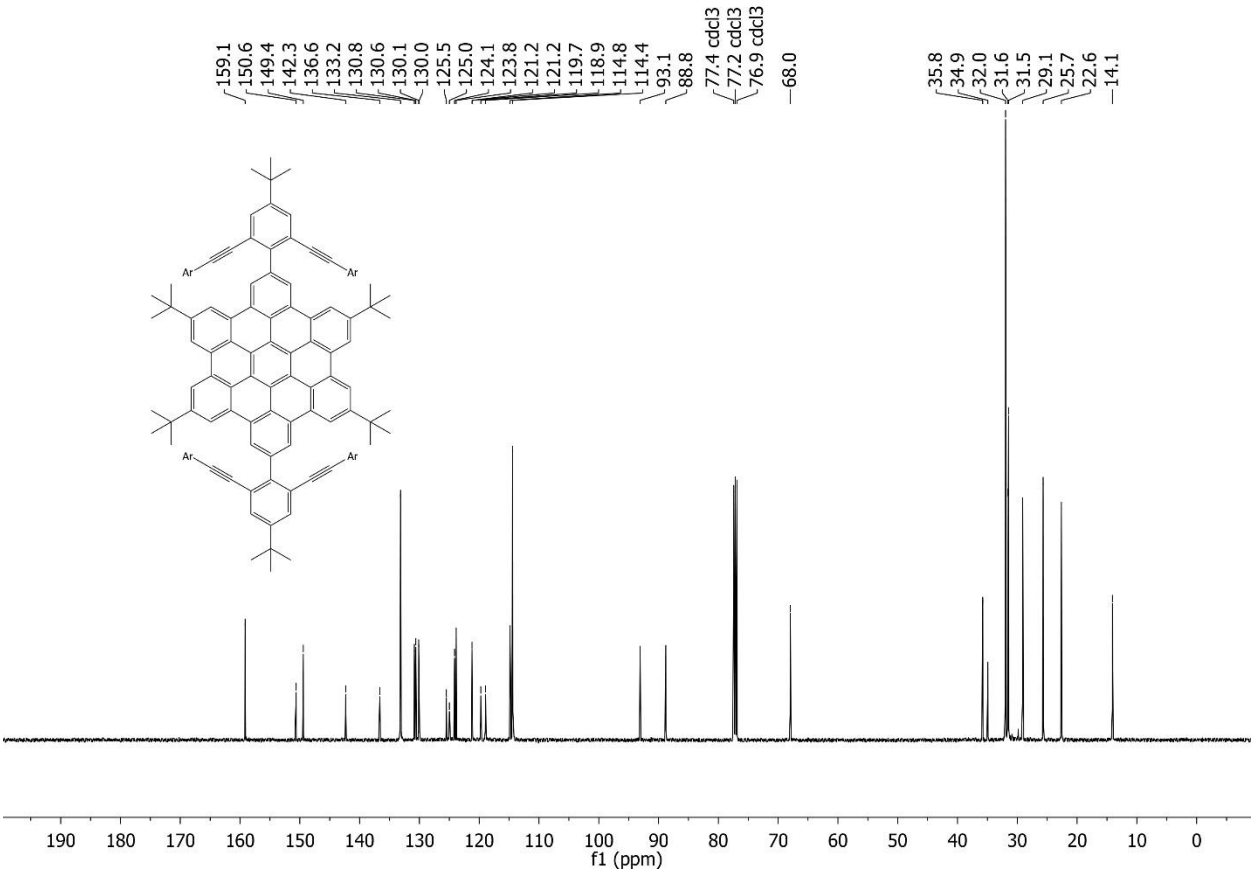


Figure S167. ^{13}C NMR spectrum of compound **4.30**.