

**The Development of Pi-Extension Strategies for the Conversion of Strained Benzenoid
Macrocycles to Curved, PAH Segments of Carbon Nanotubes**

by

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A dissertation submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Doctor of Philosophy

Auburn, Alabama
December 11, 2021

Keywords: cycloparaphenylenes, *p*-terphenyls, aromatization, macrocycles, strain energy,
Scholl reaction, pi-extension, cross-coupling.

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Abstract

Chapter 1: The synthesis of smallest carbon nanoring, [4]CPP and its potential precursor has been an area of interest for last decade. The challenge associated with synthesis of this highly strained nanoring is macrocyclization as well as aromatization. Two viable macrocyclization protocols have been delineated for the strained macrocycle synthesis and several intermediates as the potential precursor for [4]CPP have been synthesized.

Chapter 2: A series of bent *p*-terphenyl-containing macrocycles have been synthesized, then regioselectively brominated, arylated, and subsequently subjected to a Scholl-based cyclodehydrogenation reaction. Shortening the alkyloxy bridging unit of these macrocycles increases the bend in the *p*-terphenyl unit, as well as the strain energy (SE) of the central *para*-phenylene ring system. For the first time, incremental increases in SE of the macrocyclic structure of this class of benzenoid compounds has been investigated in the context of pi-extension to strained PAH systems using the Scholl reaction. The mechanistic pathway of these Scholl reaction has been investigated on the basis of both experimental and computational results.

Chapter 3: A series of substituted (central arene unit), bent *p*-terphenyl containing macrocycles with different homologs have been synthesized from macrocyclic α -ketol and the alkynylated functionalized *p*-terphenyl containing macrocycle is amenable to ICl-mediated annulation reaction. The formation of chiral, twisted and highly strained phenanthrene unit containing macrocycles incorporate with Iodine as a functional group handle by alkyne benzannulation shows high prospective in terms of pi-extension on benzenoid macrocycles.

Acknowledgments

It is my pleasure to thank those who made this dissertation research possible. First, I would like to express my deepest gratitude to my advisor Dr. Bradley L. Merner. It has been a great fortune to have an advisor who encouraged me continually and convincingly conveyed a spirit of adventure in regard to research and excitement in regard to teaching. His instruction helped me to be an independent thinker and developed the skill as an experimentalist. His altruistic guidance and support have helped me overcome many difficult situations during this journey and complete this dissertation.

I am also grateful to Dr. Stewart Schneller, Dr. Steven Mansoorabadi, Dr. Ming Chen and Dr. Zhihua Jiang for serving as my advisory committee. I would also like to express gratitude to Dr. Rashad Karimov, my lab mates Ana, Nirmal, Kara, Sydney, Hank, Jacob, Mengzhou, Didimos, Taiwo and other members of the Merner group from 2015-2021 for their inspiring discussion, advice and friendship. My regards also go to Dr. Phani Raj Pokkuluri for his expertise in obtaining X-ray crystal structures for my compounds, Drs. Alvaro Herrera and Melissa Boersma for their assistance in obtaining nuclear magnetic resonance (NMR) spectroscopic and mass spectrometric (MS) data. I would also like to thank the Department of Chemistry and Biochemistry and the National Science Foundation for financial support throughout my graduate program.

I am equally thankful to family members, especially my parents and sister, for their love, help, support, and encouragement despite the physical distance between us.

Lastly, I would like to thank my wife, Susmita Hazra, for her unending encouragement, sacrifice, support and patience. I thank my son Nibir Saha and daughter Neethika Saha who are my source of joy and happiness, for sacrificing my company during this period.

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List of Abbreviations

Å	Angstroms
Ac	Acetyl
Ac ₂ O	Acetic anhydride
AIBN	2,2'-Azobis(2-methylpropionitrile)
APEX	Annulative pi-extension
Ar	Aromatic ring
ASE	Aromatic stabilization energy
B3LYP	Becke 3-Parameter (Exchange), Lee, Yang, Parr
Bpin	Boronic acid pinacol ester
B ₂ (pin) ₂	Bis(pinacolato)diborane
bpy	2,2'-Bipyridyl
CDIs	Coronene tetracarboxdiimide
CNB	Carbon nanobelt
CNTs	Carbon nanotubes
cod	1,5-cyclooctadiene
CPP	Cycloparaphenylene
CPPNs	Cycloparaphenylene-2,6-naphthylene
CVD	Chemical vapor disposition
CuOTf	Copper(II) trifluoromethanesulfonate
dba	Dibenzylideneacetone

DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
<i>dr</i>	Diastereomeric ratio
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	Diisopropylethyl amine (Hünig's base)
DIPA	Diisopropyl amine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
FGI	Functional group interconversion
FVP	Flash vacuum pyrolysis
G II	Grubbs second generation
GNR	Graphene nanoribbon
GPC	Gel permeation Chromatography

HBC	Hexa- <i>peri</i> -hexabenzocoronene
H-G II	Hoveyda-Grubbs second generation
HK	Hydroxyketone
HPB	Hexaphenylbenzene
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
<i>i</i> -Pr	Isopropyl
<i>i</i> -Pr ₂ NH	Diisopropylamine
IPA	Isopropyl alcohol
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
MALDI-TOF-MS	Matrix assisted laser desorption ionization-time of flight mass spectrometry
Me	Methyl
MeOH	Methanol
MOM	Chloromethyl methyl ether
M.S.	Molecular sieves
MsOH	Methanesulfonic acid
MTPP	(3,3'') <i>meta</i> -Terphenylophane
<i>n</i> -BuLi	<i>n</i> -Butyllithium
Nap	Napthalenide
NBS	<i>N</i> -bromosuccinimide

NEt ₃	Triethylamine
NMR	Nuclear magnetic resonance
OFET	Organic field-effect transistor
OLED	Organic light emitting diode
PAH	Polycyclic aromatic hydrocarbon
PCC	Pyridinium chlorochromate
PDAPP	Poly(2,6-dialkynyl- <i>para</i> -phenylene)
PhH	Benzene
PhMe	Toluene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
<i>pp</i>	<i>Para</i> -phenylene
PPh ₃	Triphenylphosphine
<i>p</i> -TsOH	<i>para</i> -Toluenesulfonic acid
pyr.	Pyridine
RCM	Ring-closing metathesis
<i>R_f</i>	Retention factor
S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SE	Strain energy
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
TEA	Triethylamine

TES	Triethylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
Tf ₂ O	Trifluoromethanesulfonic anhydride
TIPS	Triisopropylsilane
TLC	Thin layer chromatography
TsCl	Toluenesulfonyl chloride
UV	Ultraviolet
UV/vis	Ultraviolet/visible
VT-NMR	Variable temperature nuclear magnetic resonance

CHAPTER 1: Towards the Synthesis of [4]Cycloparaphenylene.

1. Introduction

1.1 Cycloparaphenylenes: Macrocyclic benzenoid segments of carbon nanotubes

Carbon nanotubes (CNTs) were first discovered by Iijima in 1991.¹ CNTs can be viewed as rolled-up structures of a hypothetical sheet of graphene. Depending on how the graphene sheet is rolled, different *chiralities* of CNTs are afforded. These can be classified as zigzag (**1b**), armchair (**1c**) and chiral CNTs (**1d**, Figure 1). Due to their impressive physical properties, such as electrical, optical, magnetic, as well as thermal properties, CNTs have received much attention from the materials chemistry community. Slicing CNTs perpendicular to the main axis can produce three types of nanoring structures. These are classified as: $[n]$ cyclacenes (**1e**), nanorings that result from linear annulation or zigzag nanostructures; $[n]$ cycloparaphenylene ($[n]$ CPPs, **1f**) which represent the smallest benzenoid segment of armchair CNTs; and cycloparaphenylene-2,6-naphthylene ($[n]$ CPPNs, **1g**) which represent the smallest structural unit of chiral CNTs (Figure 1).²

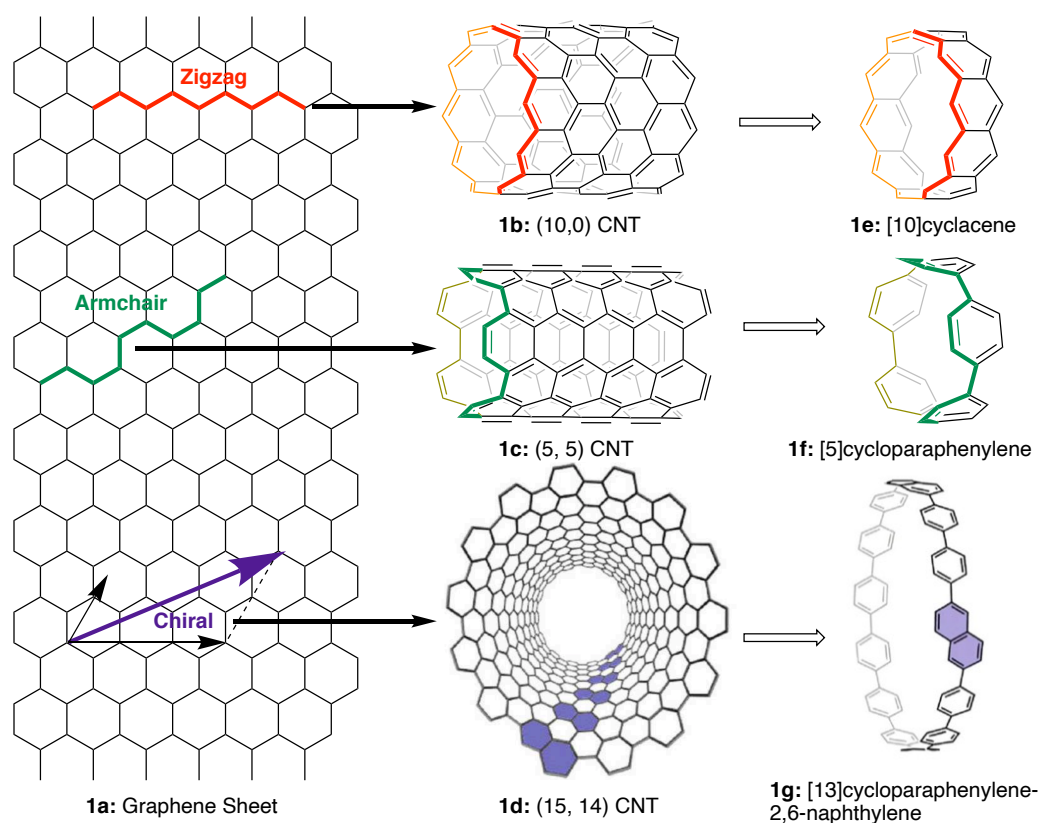


Figure 1. Chiral index of carbon nanotube².

Among the three nanorings ring segments, the $[n]$ CPPs represent a macrocyclic template from which a monodisperse, single chirality, armchair CNT could be synthesized. An $[n]$ CPP is a macrocyclic benzenoid system that is formed by connecting benzene rings at their 1 and 4 (*para*) positions, where n represents the number of benzene rings contained within the macrocyclic framework. In addition to being potential seeds for the bottom-up chemical synthesis of armchair CNTs,³⁻⁶ the $[n]$ CPPs have been attracting a great deal of attention amongst theoretical and synthetic chemists for their size-dependent optoelectronic properties^{7,8} and supramolecular properties⁹ due to the distorted p -orbitals their macrocyclic structures possess.

In the sections below I will describe the evolution of $[n]$ CPP syntheses over the past 13 years, focusing the synthetic strategies employed in assembling increasingly more strained targets. As the value of “ n ” decreases the challenge of synthesizing the CPP increases, as does the strain energy of the individual macrocycles. As is relevant to this dissertation emphasis will be placed on the macrocyclization and aromatization strategies employed.

1.1.1 Early attempts to synthesize $[n]$ CPPs

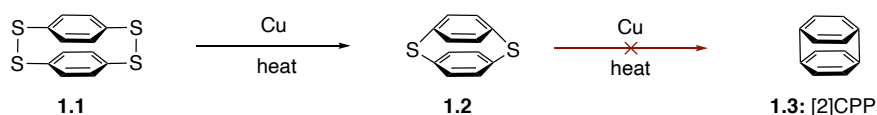
The first attempt of synthesizing an $[n]$ CPPs was reported in 1934 by Parekh and Guha.¹⁰ Their strategy was to synthesize the most straightforward and smallest CPP, [2]CPP (**1.3**) from tetra-thia[2,2]paracyclophane **1.1** by sequential bridge contraction (Scheme 1a). The main drawback of their proposal was to introduce a large amount of strain energy (SE) through a Cu mediated thermal desulfination reaction, which requires extremely harsh reaction conditions. Thus, it was unlikely that such a highly strained molecule like [2]CPP would form using this strategy.

In 1993, Vögtle and coworkers proposed several synthetic approaches to $[n]$ CPPs.¹¹ Although their attempts towards the syntheses of $[n]$ CPPs did not successful, their worked paved the way for many (later) successful synthetic strategies in the field. Their initial approach was planned to utilize 1,4-*syn*-bis(4-halophenyl) cyclohexane derivatives **1.4** and **1.5** as a pre-arene subunit, which, due to its L-shaped structure, should facilitate the macrocyclization step later in the synthesis. According to their synthetic plan, they successfully synthesized the macrocyclization precursors **1.4** and

1.5; however, upon treatment with magnesium metal to form the Grignard reagents, followed by copper(II) chloride, this approach only resulted in the formation of oligomers and polymers instead of desired macrocycle **1.6**.

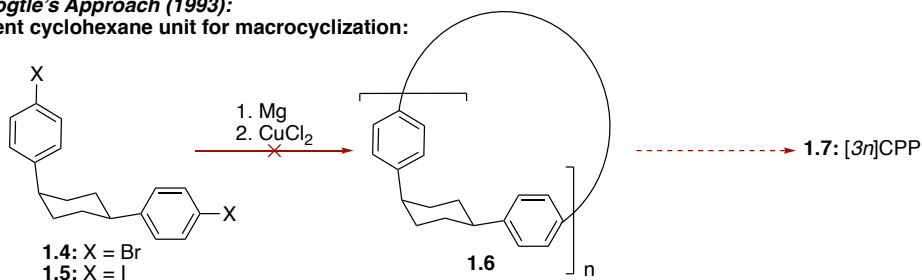
In their second approach, Vögtle and coworkers attempted the synthesis of [8] and [10]CPP by utilizing the Wittig reaction to assemble a macrocyclic enyne, followed by Diels-Alder reaction to convert the enyne units into benzene rings. The syntheses of macrocyclic enynes **1.10** and **1.11** were successful, using a Wittig-based cyclooligomerization reaction, albeit in low yield; however, the cycloaddition/aromatization strategy did not afford the desired CPP targets.

a) Parekh and Guha's Approach (1934):

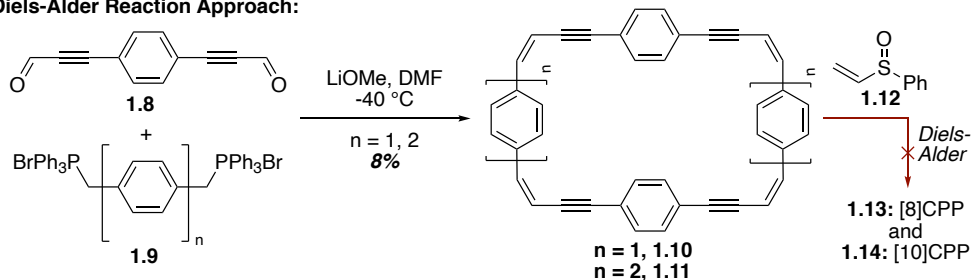


b) Vögtle's Approach (1993):

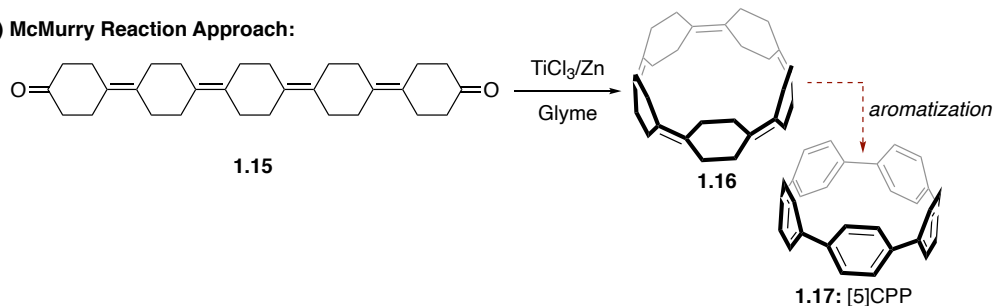
i) Bent cyclohexane unit for macrocyclization:



ii) Diels-Alder Reaction Approach:



iii) McMurry Reaction Approach:



Scheme 1. Early Synthetic Attempts for the Preparation of CPPs.

The third approach investigated by Vögtle and co-workers, was an attempted synthesis of the highly strained target, [5]CPP (SE = 119 kcal/mol). Their synthetic approach was based on the work of McMurry and co-workers,¹² who previously reported the synthesis of macrocycle **1.16**. Under influence of low valent titanium, diketone **1.15** was converted to macrocycle **1.16**, which was only detected by mass spectrometry. The attempted conversion of **1.16** to [5]CPP (**1.17**) was not investigated.

Though Vögtle was not able to synthesize an [n]CPP, his synthetic approaches and strategies were influential towards the future successful syntheses of the [n]CPPs. The first successful synthesis of an [n]CPP was reported in 2008 by Bertozzi and Jasti,¹³ more than 70 years after the earliest attempted synthesis by Parekh and Guha. From 2008 to 2021, cycloparaphenylenes with $n = 18$ to 5 have been reported by several groups, with Jasti, Itami, Yamago and Wang arguably making the biggest contributions to this field of chemical synthesis. The synthetic strategies that have been developed by each of these groups over the past 13 years will be highlighted in the section below.

1.2 Successful strategies for the synthesis of small [n]CPPs ($n = 9-5$)

The strain energy (SE) of the macrocyclic ring containing the *para*-linked benzene units of an [n]CPP, as well as the SE per arene (*para*-phenylene) unit (SE_{pp}) for [n]CPP increases with the decreasing size or diameter of the corresponding nanohoops (Figure 2). Likewise, the optoelectronic behavior and magnetic susceptibility of the [n]CPPs changes, as the HOMO-LUMO gap narrows, as the SE increases. To date, [5]CPP (**1.17**) is the smallest [n]CPP to be synthesized. Its structure possesses 119 kcal/mol of SE, with the individual arene units being strained, relative to that of a planar benzene, by 24 kcal/mol. The next smallest [n]CPP in the series is [4]CPP (**2f**), which contains a total SE of 144 kcal/mol, which corresponds to a SE_{pp} of 36 kcal/mol. Thus, the individual benzene rings of [4]CPP contain a calculated SE value that is identical to the resonance or aromatic stabilization energy (ASE) typically attributed to planer benzene itself. The existence of a (4,4) armchair CNT, which contains a [4]CPP subunit is an indication that this highly strained arene macrocycle does exist. The question is, can it be synthesized in free-standing form? Thus, in the context of synthetic and physical organic chemistry, many research groups are tackling this challenging endeavor, including ours.

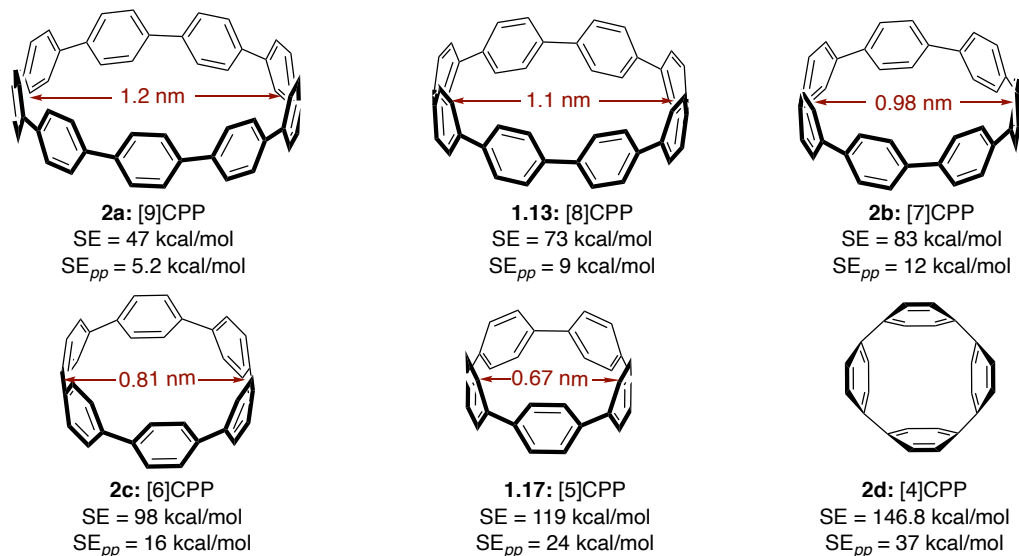
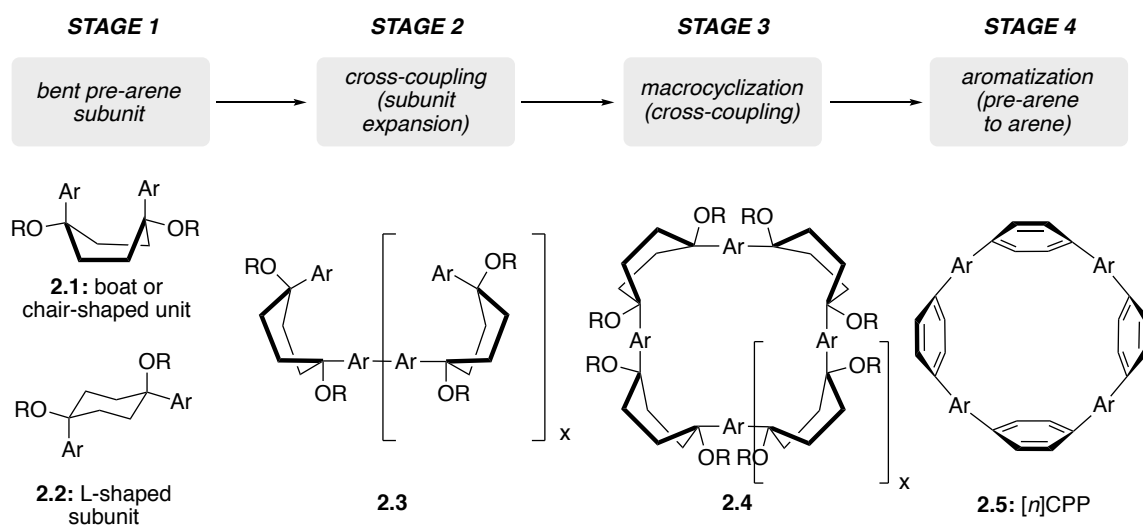


Figure 2: Variation of strain energy with the size of $[n]$ CPPs.

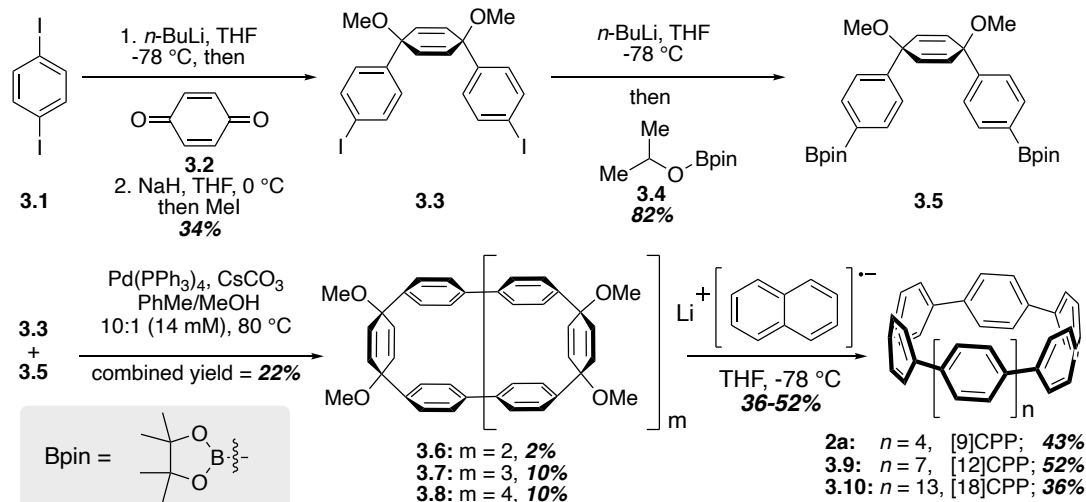
All of the reported syntheses of $[n]$ CPPs can be generalized into four synthetic stages⁷. The first stage involves constructing a bent, pre-arene subunit containing appropriately functionalized aryl groups, which are part of six-membered ring containing a *syn*-1,4-diol (**2.1** and **2.2**, Scheme 2). The *syn*-1,4-diol stereochemistry is critical to the success of stage 3 of the synthesis, as these pre-arene provide the necessary kink or bend for macrocycle assembly. Stage 2 involves elongation of the pre-arene subunits by employing cross-coupling reaction to afford acyclic oligomers that contain two or more of the L-shaped subunits. Stage 3 is arguably the most important stage of the syntheses, which involves macrocycle formation (e.g., **2.4**). Typically, macrocyclization has been accomplished via a transition metal-mediated or metal-catalyzed reactions. Early approaches to $[n]$ CPPs (e.g., **2.5**) involved macrocyclization through cross-coupling reactions.¹³ In later years, more powerful synthetic methods for macrocyclization were developed to afford size-selectivity, as well as more highly strained macrocycles with smaller diameters (of the $[n]$ CPP). The final stage, stage 4, involves aromatization of the pre-arene unit to afford the remaining benzene rings of the desired $[n]$ CPP. Like macrocyclization, several innovative protocols have been developed during the course of these synthetic investigations of the $[n]$ CPPs.



Scheme 2. A generalized four-stage synthetic approach to [n]CPPs.

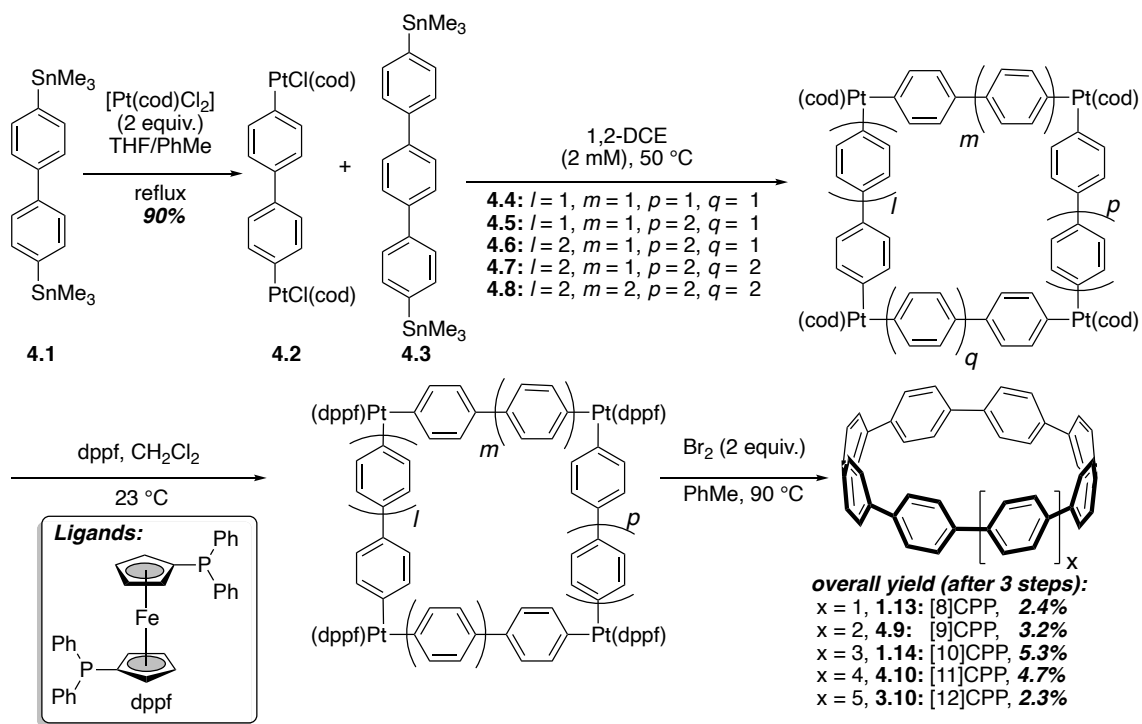
1.2.1 Unselective syntheses of [n]CPPs ($n > 9$)

Early reports of [n]CPP syntheses utilized unselective, shot-gun-based macrocyclization protocols that featured Suzuki coupling, nickel-based (Yamamoto) coupling and platinum square-based strategies. The first of these came about seven decades after the initial reported synthetic endeavor. In 2008, Bertozzi and Jasti reported the first successful synthesis of [9], [12] and [18]CPP¹³. In their approach, they prepared the diiodide of 3,6-*syn*-dimethoxy-cyclohexa-1,4-diene (**3.3**) by diastereoselective addition of (4-iodophenyl) lithium to benzoquinone **3.2** followed by protection of the resulting diol as the methyl ether (Scheme 3). The protected, *syn*-cyclohexadiene-1,4-diol **3.3** moiety provides both the bend and rigidity necessary for macrocyclization, while also acting as a masked aromatic unit. Diiodide **3.3** was converted to bis-boronate **3.5** in 82% yield, and subsequently **3.3** and **3.5** were engaged in a Suzuki cross-coupling reaction under high dilution conditions (14 mM) to afford a mixture of macrocycles ($m = 2$, **3.6**; $m = 3$, **3.7**; $m = 4$, **3.8**) in a combined yield of 22%. The mixture was easily separated by column chromatography, and the (comparatively) lower strain energy associated with the larger macrocycles, **3.7** and **3.8**, contributes majorly to combined yield. Subsequent aromatization of each macrocycle with lithium naphthalenide at low temperature via reduction of the benzylic ether units, two successive single-electron transfer processes, provided [9]- (**2a**), [12]- (**3.10**) and [18]CPP (**3.11**).



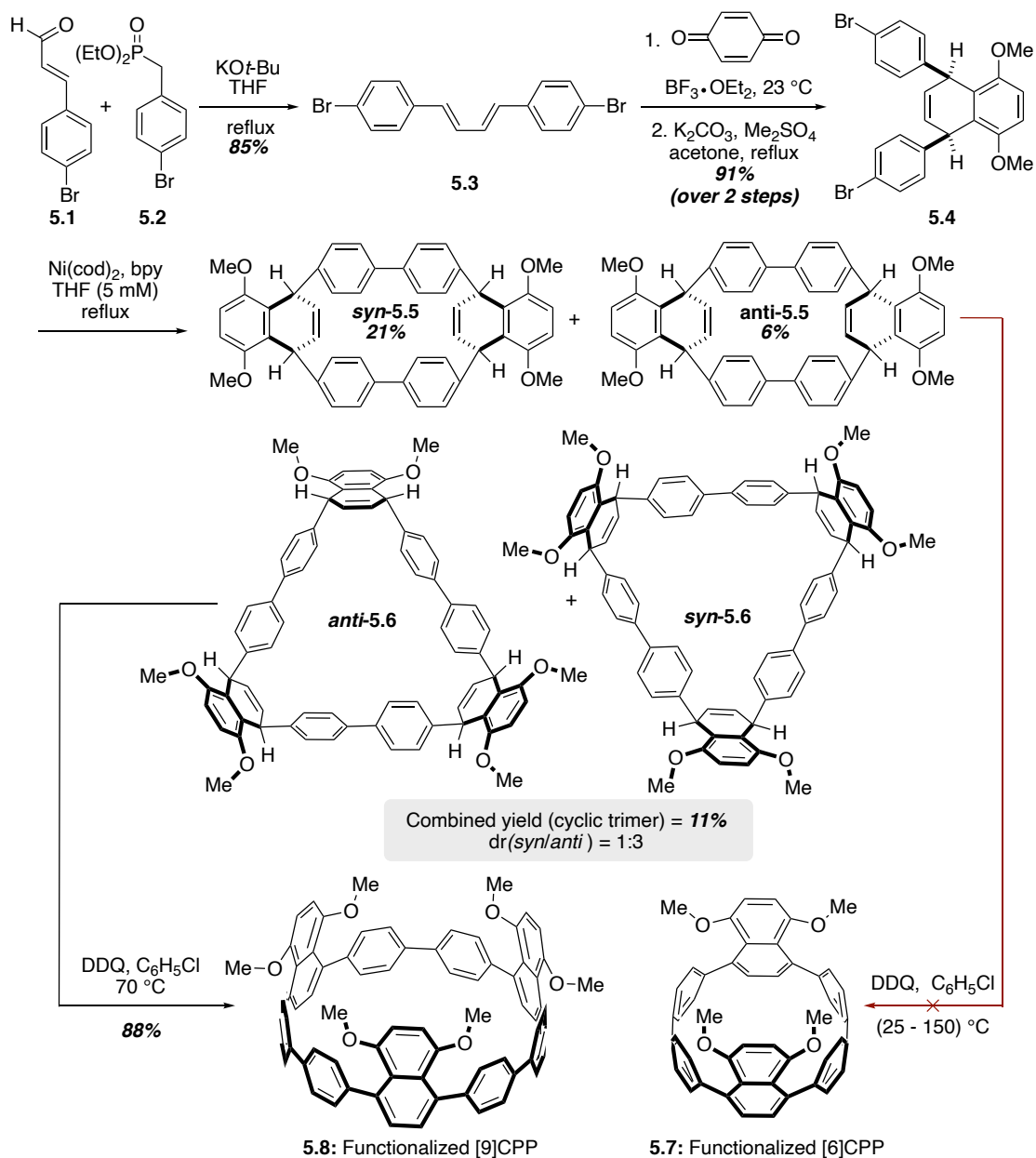
Scheme 3. First-generation, unselective synthesis of [9], [12] and [18]CPP

In 2011, Yamago co-workers reported the random synthesis of larger $[n]$ CPPs, where $n = 8$ to 13. Their strategy relied on the rapid formation of Pt-based metallacycles, discarding a multistep approach that involved elaboration of masked pre-arene units. The so-called “Pt-square-based approach” did not require a kinked *syn*-1,4-diol unit to facilitate macrocyclization, capitalizing on the placing the metal at the four corners of the metallacycle.⁹ In 2010, the Yamago group reported the unselective syntheses of [8]-[12]CPPs.¹⁴ Their synthetic approach started with the formation of bis(platinum)biphenyl **4.2** from bis(stannyl)biphenyl **4.1**, using two equivalents of dichloro(1,5-cyclooctadiene)platinum(II). In the macrocyclization step, treatment of bis(platinum)biphenyl **4.2** with a stoichiometric amount of bis(stannyl) terphenyl **4.3** provided a mixture random metallacycles **4.4** to **4.8** instead of formation of single tetranuclear platinacycle **4.6** (a precursor to [10]CPP). Subsequent ligand exchange with 1,1'-bis(diphenylphosphino)ferrocene, followed by bromine induced reductive elimination, afforded a mixture of larger $[n]$ CPPs (**1.13**, **4.9**, **1.14**, **4.10** and **3.10**) which were easily separated by gel permeation chromatography (GPC). This strategy featured reduced synthetic steps, moderate overall yields, and provided access to larger sized $[n]$ CPPs, enabling an investigation of their opto-electronic properties.



Scheme 4. Unselective synthesis of larger diameter $[n]$ CPPs from platinacycles.

In 2014, Wang and co-workers reported the synthesis of a triply-annulated [9]CPP derivative, specifically with three 5,8-dimethoxynaphth-1,4-diyl units contained within the [9]CPP framework (**5.8**, Scheme 5). Their approach utilized an unselective macrocyclization step, which featured a Ni-mediated reductive coupling reaction.¹⁵ The synthesis commenced with a Horner-Wadsworth-Emmons reaction to afford diene **5.3**, which was subsequently subjected to a diastereoselective Diels-Alder reaction with *p*-benzoquinone, followed by methylation of the resultant *syn*-1,4-diol to give dibromide **5.4** in 77% yield over three steps. Subjecting the dibromide **5.4** to a Yamamoto macrocyclization, at high dilution, afforded a separable mixture of cyclic dimer (**5.5**) and cyclic trimer (**5.6**) products, each as a mixture of *syn* and *anti*-diastereomers. Attempted aromatization of *syn*-**5.5** and *anti*-**5.5** did not afford the desired [6]CPP derivative **5.7**, pointing to a weaker aromatization strategy, which involved oxidation/dehydrogenation. On the contrary, both cyclic trimers *syn*-**5.6** and *anti*-**5.6** successfully underwent aromatization under oxidative conditions to form the [9]CPP derivative **5.8** in a 88% yield.

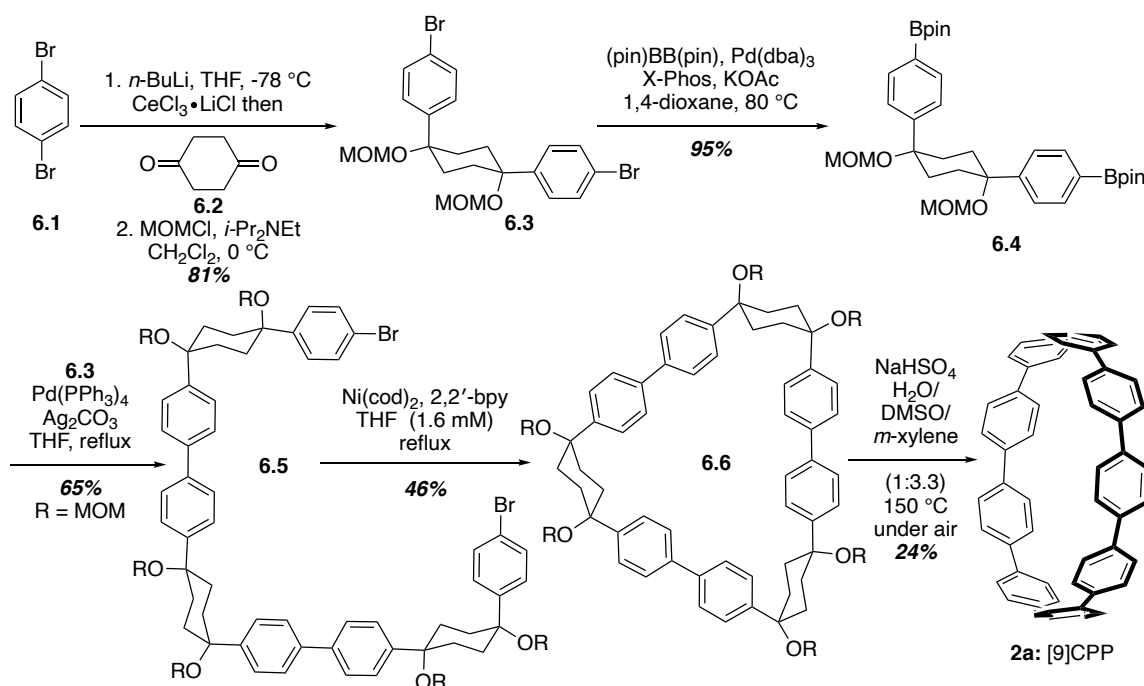


Scheme 5. Unselective synthesis of functionalized [9]CPP.

1.2.1.1 Size-Selective synthesis of [9]CPP

In 2009, Itami and co-workers reported a selective synthesis of [12]CPP, using the L-shaped *syn*-1,4-bisaryl substituted cyclohexane as a bent, masked arene unit.¹⁶ In 2012, the same group introduced the selective synthesis of other, carbon nano hoops, namely, [9], [10], [11] and [13]CPP with an improved strategy for accessing the key *syn*-1,4-bisaryl substituted cyclohexane moiety.¹⁷ Their size-selective synthetic route to [9]

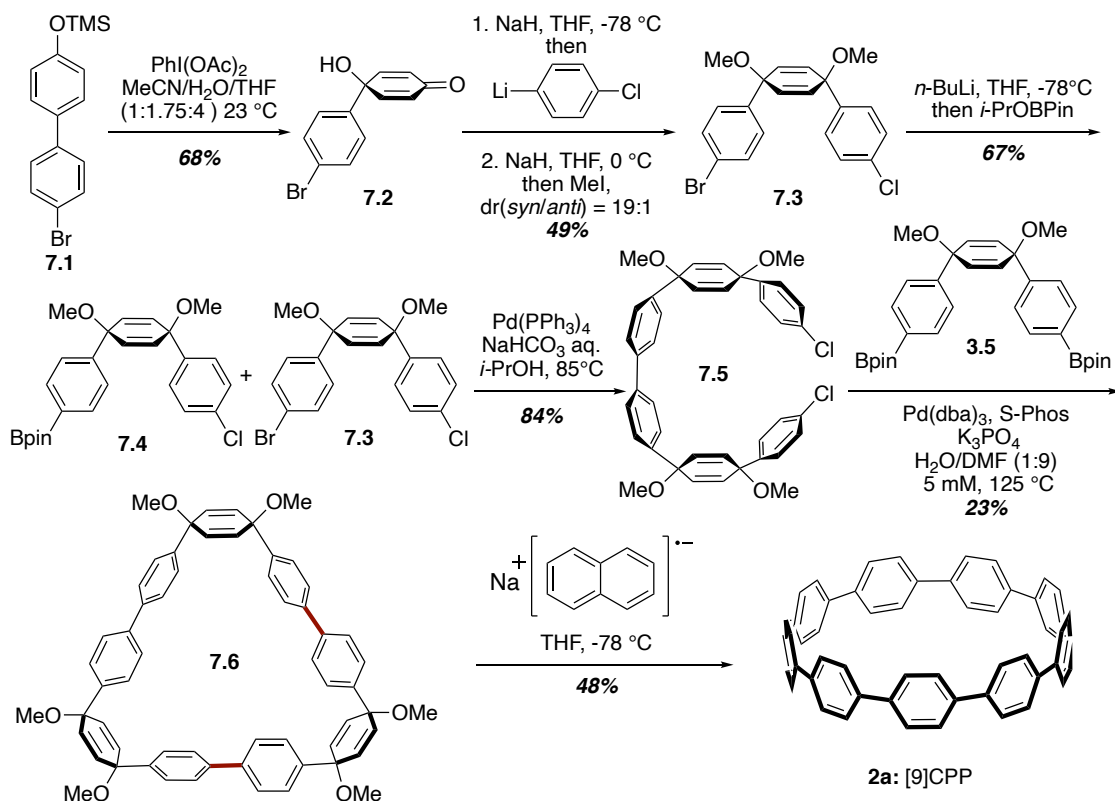
CPP starts with the diastereoselective addition of the organocerium reagent generated from 1,4-dibromobenzene (**6.1**) to cyclohexane-1,4-dione (**6.2**), followed by protection of hydroxyl groups as methoxymethyl (MOM) ethers to afford the *syn*-**6.3** as the major diastereomer (Scheme 6). Miyaura borylation of **6.3** gives the L-shaped diboronate **6.4** in 95% yield. The macrocyclic precursor, acyclic C-shaped dibromide **6.5**, was produced by a cross-coupling reaction between L-shaped dibromide **6.3** and L-shaped diboronate **6.4**. The Yamamoto coupling of C-shaped dibromide **6.5** at high dilution furnished the selective macrocyclic trimer **6.6** while introducing a moderate level of strain energy (SE = 8.0 kcal/mol).¹⁸ Dehydrative aromatization of macrocycle **6.6** with sodium hydrogen sulfate in the presence of air, produced [9]CPP (**2a**) in 24% yield. In this strategy, three L-shaped building blocks containing three rings each, two arene units and one masked arene, were employed in a stepwise manner to facilitate the synthesis of a macrocyclic precursor to [9]CPP.



Scheme 6. Size-selective synthesis of [9]CPP

In 2011, Jasti and co-workers reported the selective synthesis of [7]CPP (**2b**) using dichloride **7.5** as a key macrocyclization precursor (Scheme 7; see also Scheme 12 for [7]CPP synthesis).¹⁹ Later in 2012, following an identical strategy, the synthesis of moderately strained [*n*]CPPs, $n = 7$ to 12, were reported by Jasti co-workers using

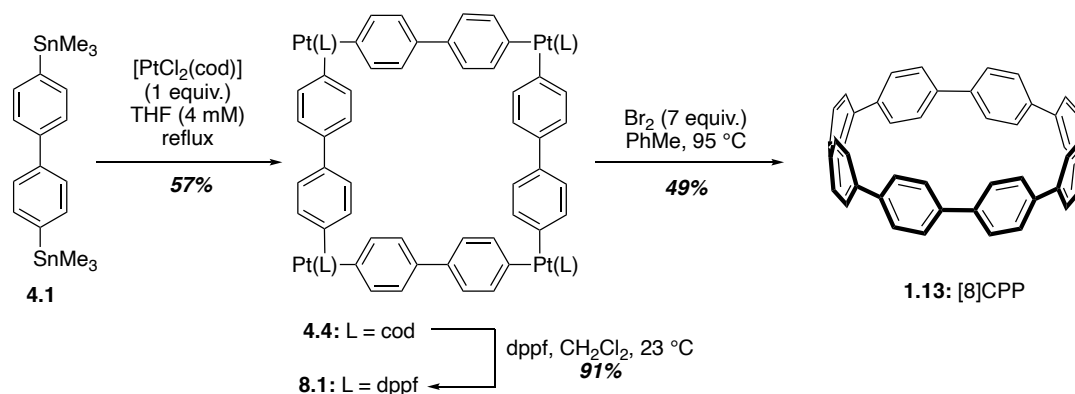
size-selective macrocyclization reactions.²⁰ Their synthesis of [9]CPP started with the assembly of cyclohexadiene **7.3**, which provides the curvature necessary for macrocyclization. This unsymmetrical cyclohexa-1,4-diene unit, was obtained from silyl-protected bromophenol **7.1** which underwent oxidative dearomatization to form enone **7.2**, followed by diastereoselective addition of 4-chlorophenyllithium to the resultant enone (*d.r.* = 19:1) in presence of sodium hydride. Subsequent methylation afforded **7.3** in 49% yield over three steps. The differentiated halide groups present in **7.3** is crucial for subsequent cross coupling reactions. The aryl bromide present in **7.3** was selectively converted to boronate ester **7.4** through lithium-halogen exchange, followed by reactive the resulting anion with (isopropoxy)pinacolborane. The aryl chloride functionality of **7.3** remained unchanged during the course of this reaction and was also a spectator during the Suzuki coupling reaction with **7.5**. In order to engage the aryl chloride units in the Suzuki cross-coupling reaction, more reactive conditions, featuring Buchwald's S-Phos ligand were required. Indeed, cross-coupling between dichloride **7.5** and aryl diboronate **3.5** in the presence of a Pd(II)-catalyst at high dilution (5 mM), gave the desired macrocycle **7.6** in 23% yield. While the macrocyclization step can be viewed as low yielding, selectivity was achieved. Finally, the reductive aromatization of macrocycle **7.6** with sodium naphthalenide at low temperature provided [9]CPP (**2a**) in 48% yield.



Scheme 7. Size-selective synthesis of [9]CPP using reactivity of halide in cross-coupling reaction.

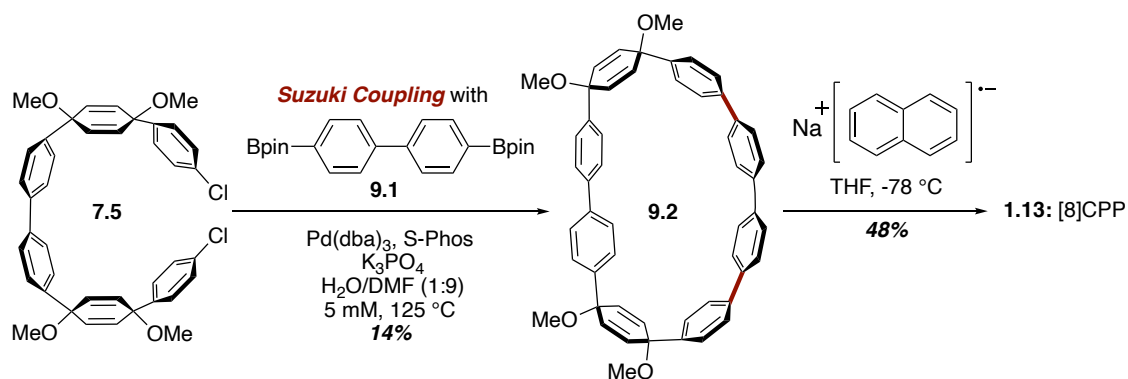
1.2.2 Synthesis of [8]CPP

In 2010, Yamago and co-workers reported a short and high yielding synthetic route to [8]CPP by forming a metallacycle as precursor to the, at the time, smallest [n]CPP.¹⁴ Using this strategy Yamago has also reported a size-selective synthesis of [12]CPP.⁹ Their synthetic approach relies on the formation of a strain free tetranuclear platinacycle **4.4**, which is assembled by transmetalation of a stannylated arene precursor **4.1** with a stoichiometric amount of dichloro(1,5-cyclooctadiene)platinum(II) (Scheme 8). The square planar geometry of Pt(II) as well as *cis* substitution in platinum complex **4.4**, with bond angles of 90°, facilitates the formation of the square metallacycle **4.4**. Subsequent ligand exchange using 1,1'-bis-(diphenylphosphino)ferrocene (dppf) followed by bromine induced reductive elimination, afforded [8]CPP (**1.13**) in 49% yield.



Scheme 8. Size-Selective synthesis of [8]CPP from a square-shaped metallacycle.

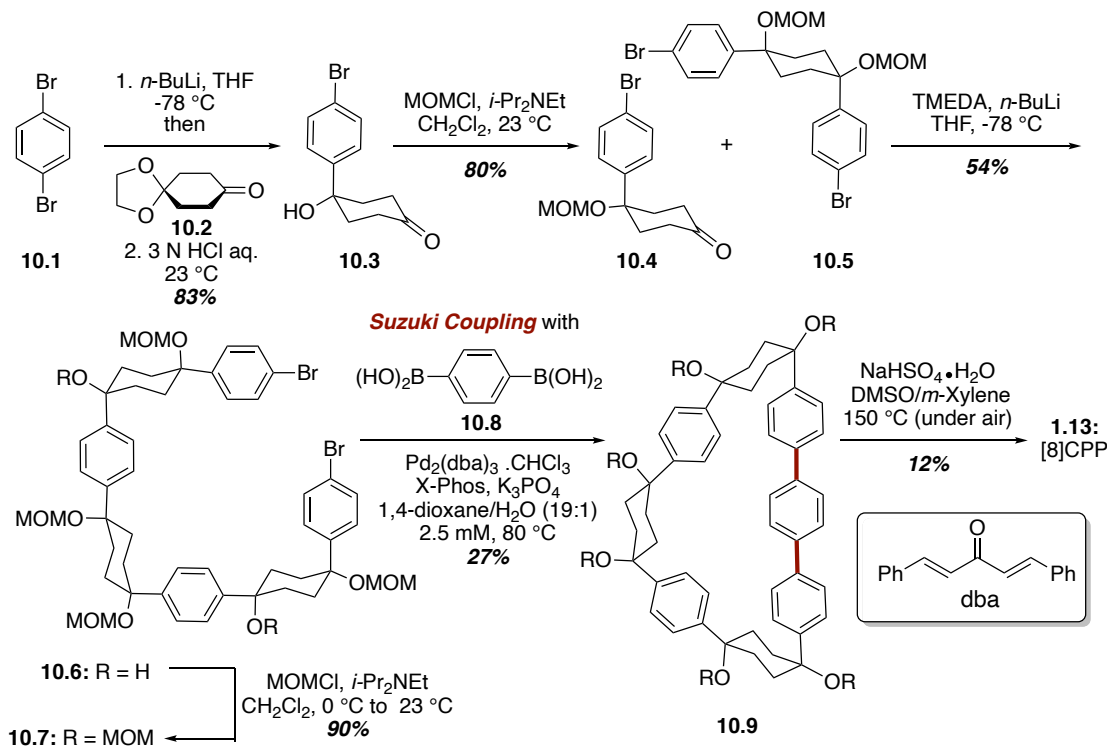
Jasti and co-workers also reported a size-selective synthesis of [8]CPP using a modified approach that was described in Scheme 7, albeit much lower yielding than that reported by Yamago. Simply changing the diboronate cross-coupling partner to **9.1**, and engaging **7.5** in a Suzuki cross-coupling reaction gave macrocycle **9.2** in 14% yield.²⁰ Finally, reductive aromatization of **9.2** afforded [8]CPP (**1.13**) in 48% yield.



Scheme 9. Size-selective synthesis of [8]CPP from reductive aromatization.

In 2012, Itami and co-workers reported a size-selective synthesis of [8]CPP, which utilized one 3-ring L-shaped subunit and two, 2-ring L-shaped subunits (**10.5** and **10.4**, respectively, Scheme 10) to form a key macrocyclization precursor. The 2-ring L-shaped building block **10.4** was accessed from 1,4-dibromobenzene (**10.1**) over three steps. The dual lithiation of 3-ring L-shaped building block **10.5**, followed by subsequent diastereoselective addition to 2 equivalents of MOM protected ketone **10.4** (i.e., a 2-ring L-shaped subunit) **10.4**, afforded the acyclic C-shaped intermediate **10.6** containing seven of the eight rings required for [8]CPP. After MOM protection, the C-shaped macrocyclic precursor **10.7** was subjected to a Suzuki cross-coupling reaction

with 1,4-benzenediboronic acid (**10.8**) to afford macrocycle **10.9**, containing all eight rings of the desired target. Dehydration followed by oxidation of **10.9** gave [8]CPP (**1.13**) in 1% yield over six steps.

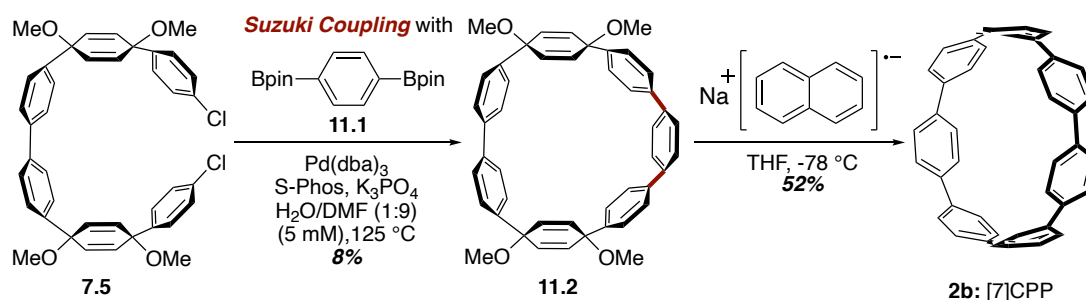


Scheme 10. Size-selective synthesis of [8]CPP from dehydrative aromatization.

1.2.3 Synthesis of [7]CPP

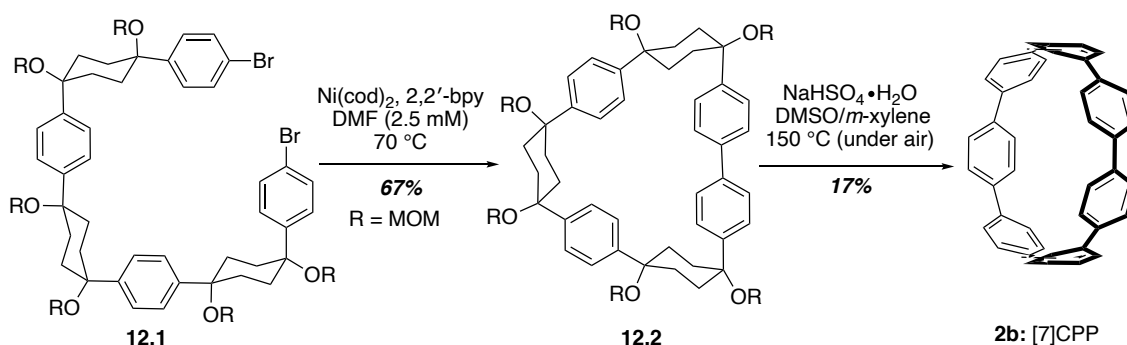
[7]Cycloparaphenylene stood as the smallest and most strained of the carbon nanohoos for nearly one year, after Jasti and co-workers first reported its synthesis in 2011. It was at this stage that the Jasti group first reported the synthesis of the important macrocyclization building block **7.5**, which has featured prominently in the synthesis of larger and less strained homologs ($n = 8$ and 9) mentioned above. When **7.5** was engaged in a Suzuki cross-coupling reaction with diboronate **11.1** macrocycle **11.2** was afforded in 8% yield.²⁰ While the macrocyclization was low yielding, pointing to the weakness of cross-coupling-based approaches to strained macrocycles, it was selective in furnishing only the 7-ring-containing (macrocycle) precursor of [7]CPP. Finally,

reductive aromatization of **11.2** in the presence of sodium naphthalenide at low temperature afforded [7]CPP (**2b**) with an overall yield 1.5%, over eight steps.



Scheme 11. Size-selective synthesis of [7]CPP from reductive aromatization.

A year later, in 2012, Itami and co-workers were able to engage C-shaped subunit **10.7** in a Ni(0)-mediated, direct arylation reaction to furnish **12.2** in an impressive 67% yield.²¹ Using their standard dehydration/oxidation aromatization sequence, [7]CPP (**2b**) was afforded in 17% yield from **12.2**. This synthesis of an increasingly strained carbon anonhoop is important for two reasons: 1) it demonstrates that directed arylation reactions are much better suited for challenging macrocyclization reactions than cross-coupling reactions, and 2) it demonstrates that the Itami pre-arene subunit is not as easily aromatized as the Jasti pre-arene subunit.



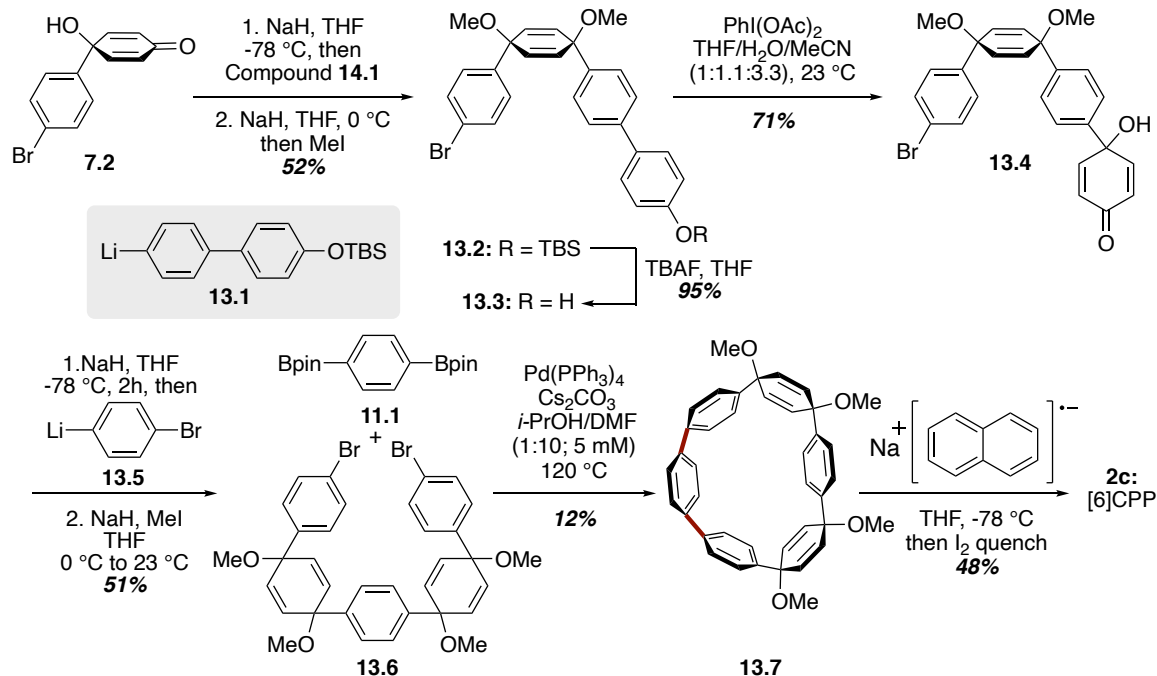
Scheme 12. Size-selective synthesis of [7]CPP.

1.2.4 Synthesis of [6]CPP

In moving from [7] to [6]CPP, the amount of strain energy per backbone carbon atom of the nano hoop structure increases steeply. In order to accommodate this high level of strain energy, powerful aromatization reaction and protocols have to be employed.

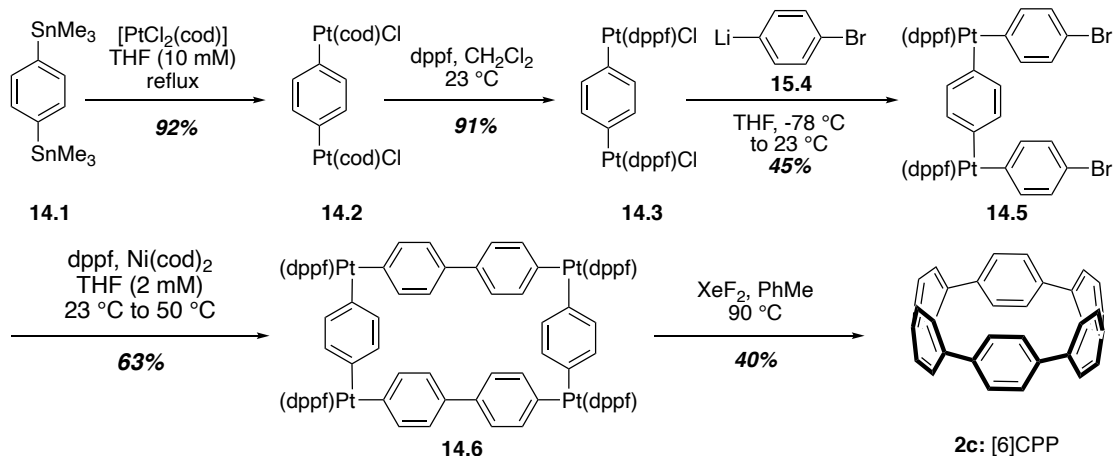
Likewise, assembling the macrocyclic framework of the nanohoop requires strategic placement of pre-arene subunits within macrocyclic precursors to provide the necessary curvature to facilitate C-C bond formation. In general, directed arylation, and [2+2+2] cyclootrimerization reactions are best suited for macrocycle assembly of the smallest [n]CPPs, and reductive aromatization protocols have been employed in successful syntheses.

In 2012, Jasti and co-workers developed the first synthesis of the highly strained [6]CPP by modifying the structure of the macrocyclization precursor, from their previously reported [7]CPP synthesis.²⁴ Their approach started with the diastereoselective addition of TBS-protected aryllithium **13.1** to dienone **7.2** followed by cleavage of silyl ether protecting groups with tetrabutylammonium fluoride to afford phenol **13.3**. Oxidative dearomatization of phenol **13.3** afforded enone **13.4** in 71% yield, which was subsequently converted to the key macrocyclization precursor **13.6** using a standard protocol developed in the Jasti laboratory. Dibromide **13.6** contains three arene units and two bent cyclohexadiene units, which provides a degree of curvature to enable macrocyclization with boronate ester **11.1**. Subjecting **11.1** and **13.6** to a Suzuki cross-coupling reaction affords macrocycle **13.7** in 12% yield. The low yield of this reaction underscores the limitations/weakness of cross-coupling reactions in macrocycle synthesis. Completion of the synthesis of [6]CPP (**2c**) required reductive aromatization of **13.7**, which, at the time gave the most strained carbon nanohoop in 48% yield.



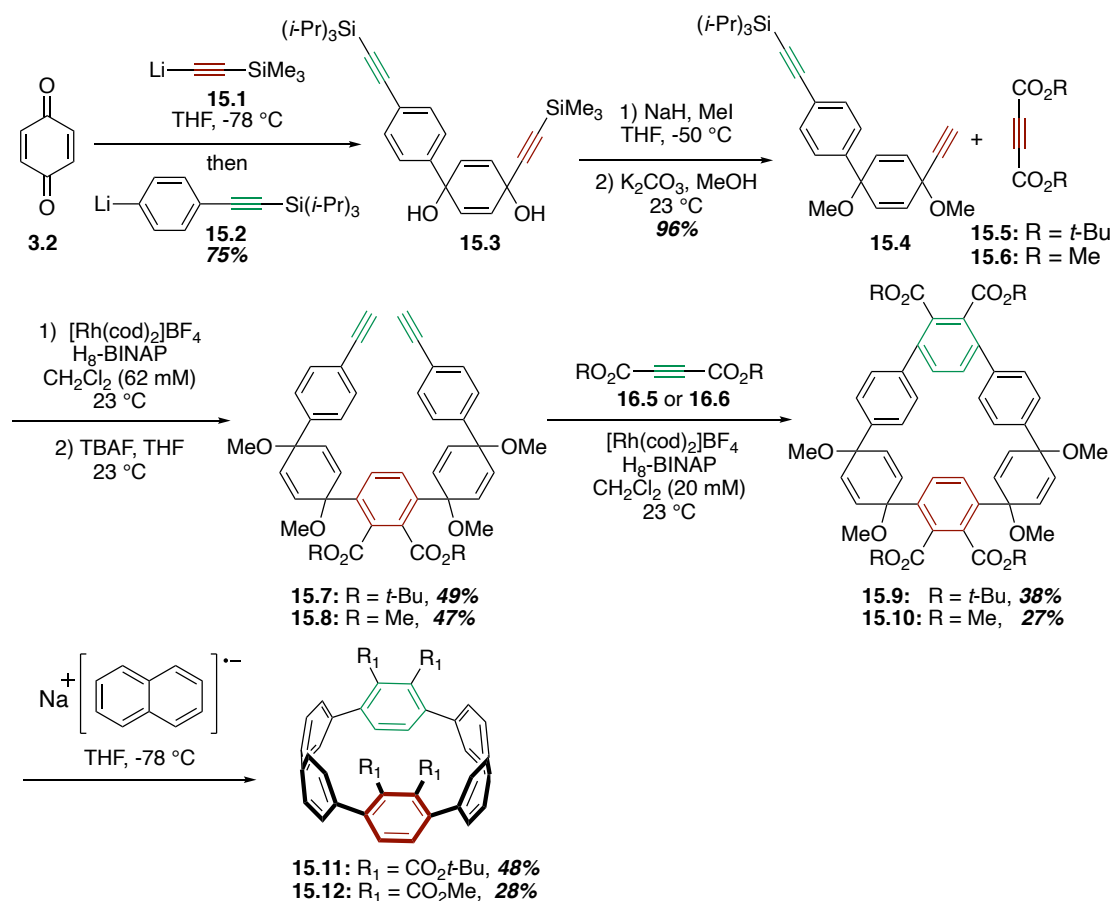
Scheme 13. Size-selective synthesis of [6]CPP by using Suzuki cross-coupling.

A year later, in 2013, Yamago and co-workers reported the synthesis of [6]CPP by using a Ni(0)-mediated homocoupling as the key step in their short synthetic route.²⁵ The synthetic approach starts with the treatment of stannylated arene **14.1** with two equivalents of a Pt(II) reagent to furnish **14.2** in 92% yield. After ligand exchange of **14.2** to afford **14.3**, aryllithium addition to both Pt-centers of **14.3** gave dibromide **14.4** in 45% yield. This bis(*para*-haloaryl)dinuclearplatinum complex, **14.5**, was engaged in a reductive coupling reaction with Ni(cod)₂ at 2 mM concentration to furnish metallacycle **14.6**, in 63% yield. Reductive elimination of the homo-coupled product **14.6** with XeF₂ formed [6]CPP (**2c**) in 40% yield. Once again, the Yamago Pt-square-based approach to carbon nano hoops proved to be efficient and relatively high yielding.



Scheme 14. Size-Selective synthesis [6]CPP from a square-shape metallacycle.

Recently, Tanaka and co-workers reported a new method for the construction of macrocyclic precursors to $[n]$ CPPs. Their strategy draws inspiration from the Jasti approach, where they have cleverly employed a [2+2+2] cyclotrimerization reaction to assemble macrocycles containing functionalized arene units (Scheme 15).²⁶ Furthermore, this strategy can be used to install both functionalized arenes and kinked cyclohexa-1,4-diene units, depending on the alkyne reaction partners employed. This adjoining nature of two identical alkyne units with a different alkyne in the [2+2+2] reaction helps to stitch together a macrocyclic precursor, or a macrocycle, depending on the stage at which it is employed, without assembling L or U-shaped units directly. Their synthesis of a five ring-containing U-shaped diynes **15.7** and **15.8**, started with the stepwise 1,2-addition of silylated organolithium reagents **15.1** and **15.2** to *p*-benzoquinone (**3.2**) to afford bis-silylated diyne **15.3** in 75% yield. Methylation of the 1,4-diol unit, followed by selective desilylation provided monosilylated diyne **15.4** in 96% yield. Diyne **15.4** was then subjected to a cationic rhodium(I) H_8 -BINAP-catalyzed cross-alkyne cyclotrimerization reaction with dialkylated acetylenedicarboxylates **15.5** and **15.6**, followed by subsequent desilylation to furnish U-shaped diynes **15.7** and **15.8**. A second intermolecular cross-alkyne cyclotrimerization of diyne **15.7** and **15.8** with same rhodium catalyst gave macrocycles **15.9** and **15.10**. Reductive aromatization with sodium naphthalenide afforded functionalized [6]CPPs **15.11** and **15.12**.



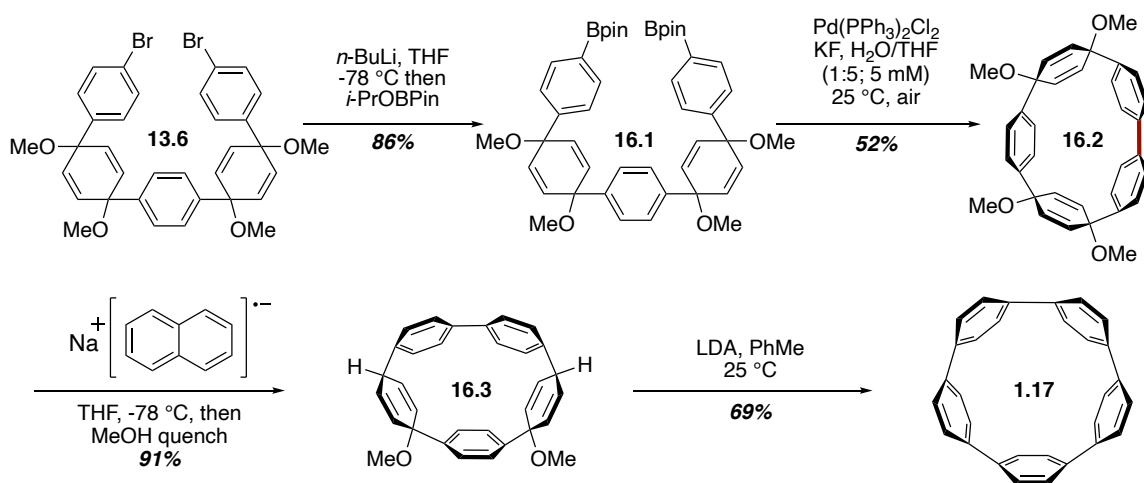
Scheme 15. Size-Selective synthesis functionalized [6]CPP by stepwise cyclotrimerization.

1.2.5 Synthesis of [5]CPP

To date, [5]CPP is the most strained ($SE_{cpp} = 119$ kcal/mol; $SE_{pp} = 24$ kcal/mol) cycloparaphenylene that has been synthesized. Only the Jasti and Yamago groups have successfully achieved the syntheses of [5]CPP using a similar biangular macrocyclic precursor containing all five cyclic units (three arene and 2 pre-arene units) of [5]CPP. The two approaches are quite similar but differ in their macrocyclization and aromatization strategies.

Jasti and coworkers synthesis commenced from the previously reported dibromide **13.6**. Conversion of the aryl bromide units to boronates, to afford **16.1**, was achieved in 86% yield. During one of their syntheses of [10] CPP, where **13.6** and **16.1** were engaged in a Suzuki cross-coupling reaction to form the desired macrocycle precursor, a significant amount of a macrocyclic by-product was afforded. This by-

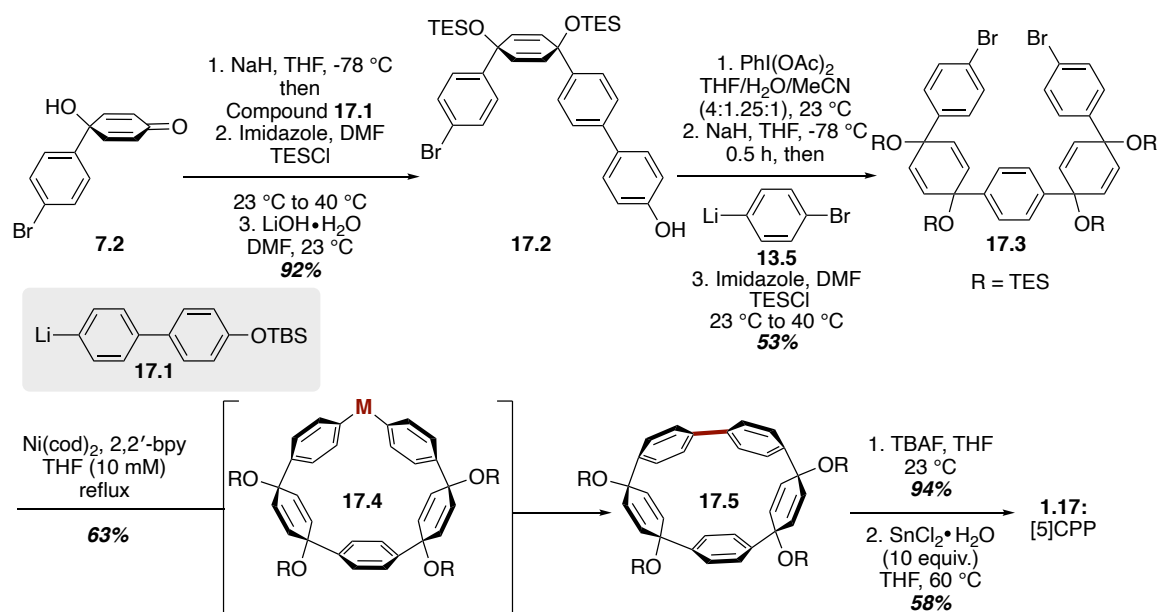
product was later discovered to be the intramolecular cyclization product of **16.1**, which was surprisingly formed. This accidental cyclization, the result of not rigorously removing oxygen from the reaction medium, led to the development of a powerful macrocyclization strategy that has been employed numerous times by Jasti and also in this dissertation (see below). This macrocyclization induced 32 kcal/mol of strain energy with a yield of 52%. In 2017, the yield of this macrocyclization was optimized to give 95% yield, by employing stoichiometric amounts of Pd(II) and excess potassium fluoride.²⁸ Treating **16.2** with sodium naphthalenide afforded a partially reduced product **16.3** and not the intended aromatized product [5]CPP. This was the first time that this reductive aromatization protocol did not furnish the desired [n]CPP directly, which is due to the high strain energy and extreme curvature found in the final product, [5]CPP. To address this, Jasti and co-workers were able to develop a strategy that involved the elimination of two equivalents of methanol from **16.3** upon treatment with LDA to furnish [5]CPP (**1.17**), in 69% yield.



Scheme 16. Size-selective synthesis highly strained [5]CPP by homo-coupling.

In 2014, using a Yamamoto reaction to facilitate macrocyclization, Yamago and co-workers reported an alternative synthesis of [5]CPP.²⁹ The Yamago approach, shares many similarities with the previously discussed synthesis by Jasti and co-workers, with only a light variation in the end-game strategy. Their synthesis starts with the diastereoselective addition of 4-lithio-4'-(*tert*-butyldimethylsiloxy)biphenyl (**17.1**) to the sodium alkoxide of enone **7.2**, followed by selective deprotection of the TBS group to afford phenol **17.2**. The oxidative dearomatization of phenol **17.2** followed by addition of

organolithium **13.5** and TES protection of the resulting 1,4-diol afforded dibromide **17.3** in 53% yield over three steps. In next step, the dibromide **17.3** was subjected to macrocyclization via a Yamamoto reaction at 10 mM concentration to afford **18.5** in 63% yield. The deprotection of the TES groups followed by reductive aromatization by tin(II) chloride monohydrate afforded [5]CPP (**1.17**) in 51% yield over two steps. In 2015, Yamago and co-workers reported an optimized aromatization strategy that featured the ate complex H_2SnCl_4 .³⁰ Application of these aromatization conditions gave [5]CPP in 72% yield.

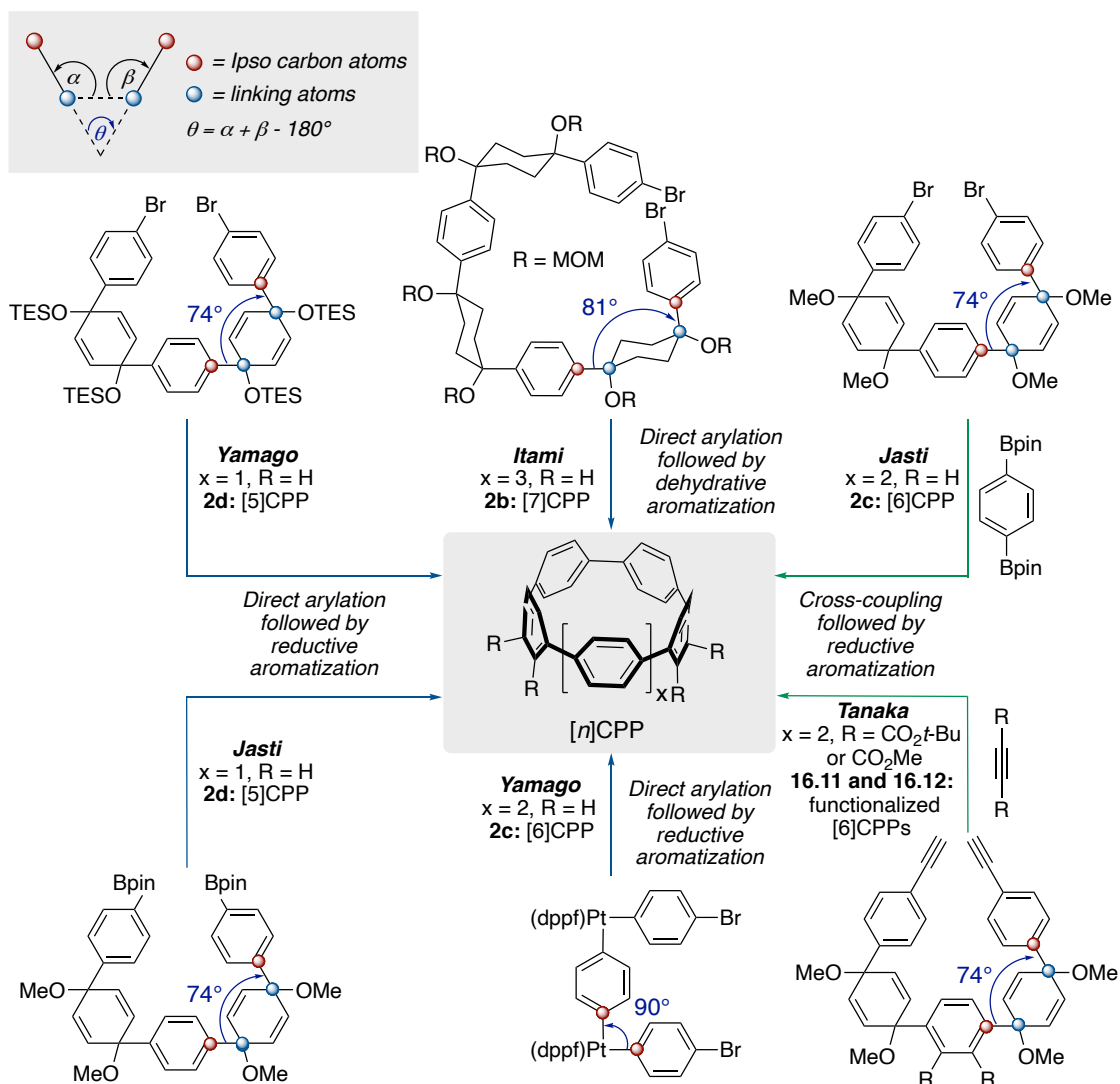


Scheme 17. Size-selective synthesis of [5]CPP through Yamamoto coupling.

1.3 Pre-organization of angular units towards the synthesis of strained [n]CPPs.

The successful synthetic strategies used to access highly strained [n]CPPs are dependent on the pre-organization of macrocyclization precursors. The *syn*-1,4-disubstituted, angular or masked *p*-phenylene unit plays an important role in providing the necessary curvature to orient the reacting vertices within proximity to undergo carbon-carbon bond formation during macrocyclization. The directing angle, θ , which is measured at two linking atoms of the pre-arene unit and two *ipso* carbon atoms of the

arene system in the corner unit (the directing angle is shown Scheme 19).³¹ In their syntheses of [5] and [6]CPP, the Jasti, Yamago and Tanaka groups (**2d**, **2c**, **15.11** and **15.12**, Scheme 18) used either a *syn*-1,4-disubstituted cyclohexadiene unit with a directing angle of 74° or a platinum complex with a directing angle of 90°. It is worth noting that the Itami group has used *syn*-1,4-disubstituted cyclohexane units with directing angles of 81° to synthesize several [*n*]CPPs, the smallest of which being [7]CPP (**2b**).³¹ Presumably, this subunit provides an acceptable directing angle to facilitate smaller macrocycle formation; however, the aromatization strategy employed is weaker than those of Yamago and Jasti. The “corner units” that have been employed in [*n*]CPP syntheses are assembled in a stereoselective fashion, providing an acute directing angle. Moreover, the number and location of bent pre-arene units incorporated in an acyclic precursor are crucial for the success of the macrocyclization, especially in the context of highly strained carbon nanohoops such as [5] (**1.17**) and [6]CPP (**2c**).



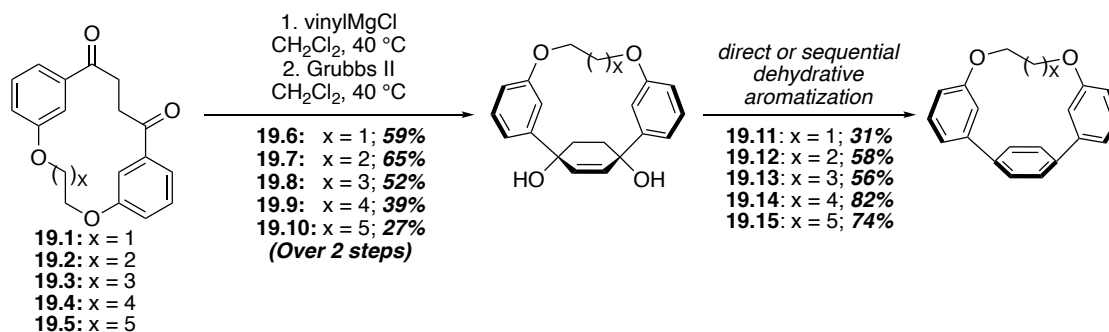
Scheme 18. Directing angles of angular units for the synthesis of highly strained [n]CPPs.

In the case of [5]CPP, only two successful syntheses have been reported with both of these requiring optimized aromatization protocols and one, the Jasti synthesis, a novel macrocyclization reaction. Furthermore, it remains as the smallest and most strained of the [n]CPPs to be synthesized. The seven-year gap that has ensued since the nearly simultaneous reports by Yamago and Jasti suggest that the synthesis of [4]CPP is a much more challenging endeavor, and likely will require both modified aromatization and macrocyclization protocols for assembling this highly strained carbon nano hoop. It is unclear as to whether the directing angles of the *syn*-1,4-diolcyclohexa-2,5-diene units will provide the correct direct angle for macrocyclization, or how many of these masked arene units will need to be incorporated in a macrocyclization precursor to

enable construction of a 4-ring precursor to [4]CPP. However, it is clear that the synthetic challenge is significant and thus worth pursuing, from the standpoint of physical and synthetic organic chemistry. In the remaining sections of this chapter, I will describe the work I have completed towards the synthesis of this highly strained benzenoid macrocycle.

1.4 A non-cross-coupling-based approach to highly distorted *p*-terphenyl-containing macrocycles

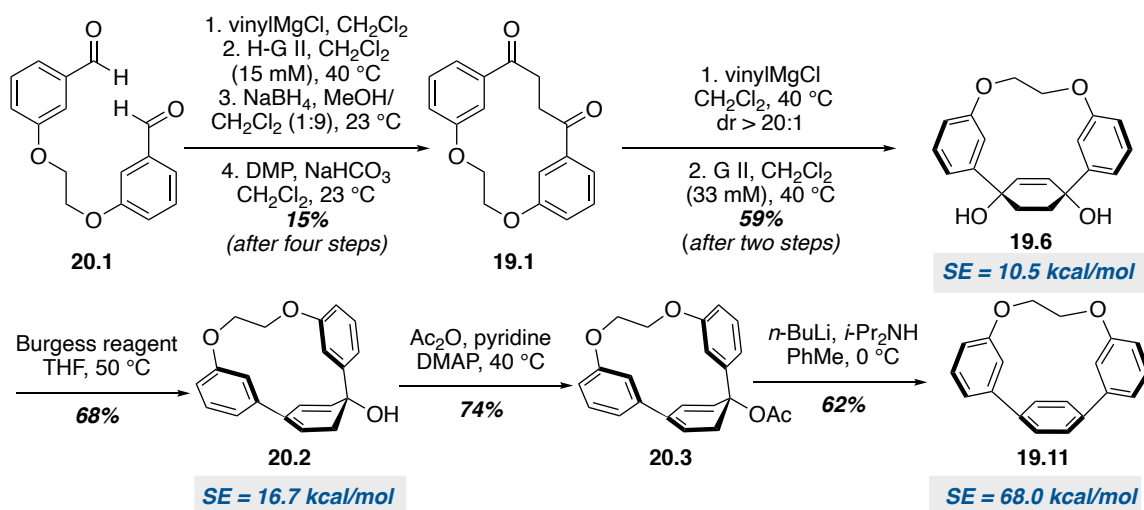
In 2015, the Merner group reported the synthesis of a bent, *p*-terphenyl-containing macrocycle using a non-cross-coupling-based approach to form highly strained biaryl bonds and *para*-phenylene units.³² Their strategy relied on the assembly of a relatively unstrained macrocyclic 1,4-diketone and the subsequent conversion of the 1,4-diketone **19.1-19.5** unit into a bent *para*-phenylene ring (**19.11-19.15**; Scheme 19). In 2016, the same group reported the synthesis of the smallest homologue in the series of these *p*-terphenyl-containing macrocycles, *i.e.*, **19.11**, where the central *para*-phenylene unit of **19.11** was calculated to be more strained than a monomer unit of [4]CPP.



Scheme 19. A general approach of conversion of 1,4-diketone to *para*-terphenyl-containing macrocycles.

The synthesis of **19.11** commenced with dialdehyde **20.1**, which was converted to macrocyclic 1,4-diketone **19.1** using a streamlined synthetic protocol that is amenable to gram-scale synthesis. A diastereoselective Grignard reaction of **19.1** with vinylmagnesium chloride furnished a bis-allylic-1,4-diol, which was directly subjected to ring-closing metathesis to afford macrocycle **19.6** in 59% overall yield. Aromatization of the cyclohex-2-ene-1,4-diol unit of **19.6** was accomplished by first monodehydration with the Burgess reagent, followed by acetylation and an LDA-mediated elimination of acetic

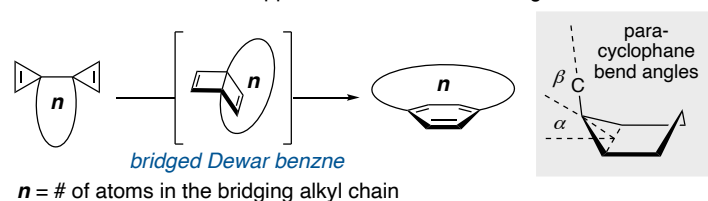
acid to furnish **10.11**. The SE of **19.11**, at 68.0 kcal/mol, is indicative of the highly strained nature of the macrocycle and is notable in that the final aromatization reaction was capable of installing 51 kcal/mol of SE into the macrocyclic backbone of **19.11**. Specifically, the generation of a single, new *p*-phenylene unit enables the introduction of this high SE.



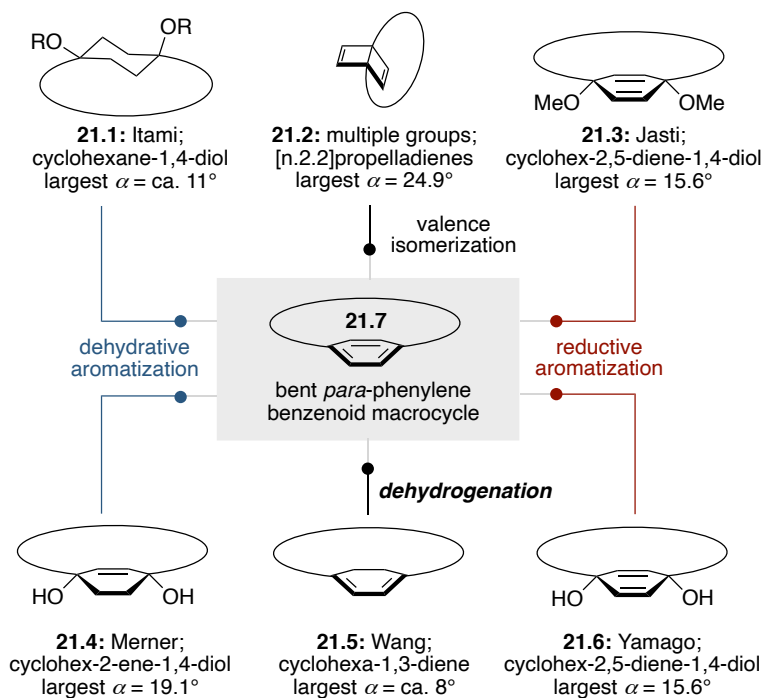
Scheme 20. A non-cross-coupling-based approach to highly strained *p*-terphenyl-containing macrocycle.

The introduction of 51 kcal/mol of SE in the last step of the synthesis of **19.11** is remarkable when one considers that the ASE of benzene is only 36 kcal/mol. Also, it suggests that this aromatization strategy may be capable of introducing the necessary SE into the backbone of [4]CPP at the end of its chemical synthesis. As summary of aromatization strategies that have been employed in strained *p*-phenylene syntheses is summarized in Scheme 21. Among these, the reductive aromatizations reported by Jasti and Yamago and the direct or sequential dehydrative aromatization strategy developed by the Merner group have resulted in the largest SE increases, and boat deformation angles (α) introduced into the *p*-phenylene ring system. In the case of the Merner approach, an α angle of 19.1°, which is nearly identical to that calculated for [4]CPP has been accomplished. Furthermore, the SE of central arene unit of *p*-terphenyl-containing macrocycle (SE = 42.6 kcal/mol) is more strained than a monomer unit of [4]CPP (SE_{*pp*} = 36 kcal/mol).³³

A. Valence isomer-based approach to bent benzene rings



B. Approaches to moderately and highly strained *p*-phenylenes

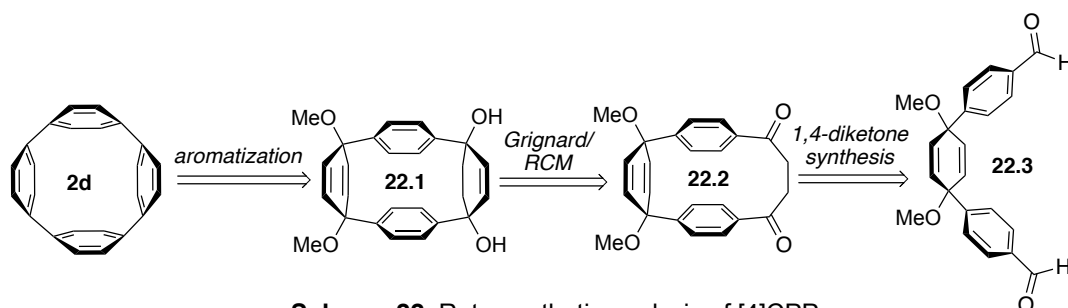


Scheme 21. Summary of aromatization strategies for bent-*para*-phenylene macrocycles.

1.4.1 First-generation retrosynthetic analysis of [4]CPP

When considering a synthetic approach to [4]CPP several important factors must be germane to plan. These include: 1) a macrocyclization strategy to enable the synthesis of potential 4-ring precursor to [4]CPP; 2) an aromatization strategy that is capable of overcoming the SE possessed in the macrocyclic backbone of [4]CPP and bending the *p*-phenylene units to the extent that they are deformed in the carbon nano hoop. With the successful synthesis of **19.11**, coupled with our 1,4-diketo macrocycle-based approach, a retrosynthetic analysis that capitalizes on both of these facets was proposed.

It was envisaged that [4]CPP could be simplified to macrocyclic precursor **22.1**, which contains two pre-arene units and two slightly deformed arene units. One of the pre-arene units is akin to those used by Jasti co-workers, and the other a cyclohex-2-ene-1,4-diol system, which would enable further simplification to 1,4-diketone macrocycle **22.2**. It was anticipated that the addition of vinylmagnesium chloride to **22.2** would be diastereoselective, given the precedent that has been established in the Merner laboratory for 18-membered 1,4-diketones, and that a ring-closing metathesis reaction would afford **22.1** in the forward direction. The macrocyclic 1,4-diketone **22.2** was assumed to be accessible from dialdehyde **22.3** using a RCM-based protocol developed in our group. The remaining discussion in this section will focus on the synthesis of **22.2**, as it represents a key stage in the total synthesis of [4]CPP.

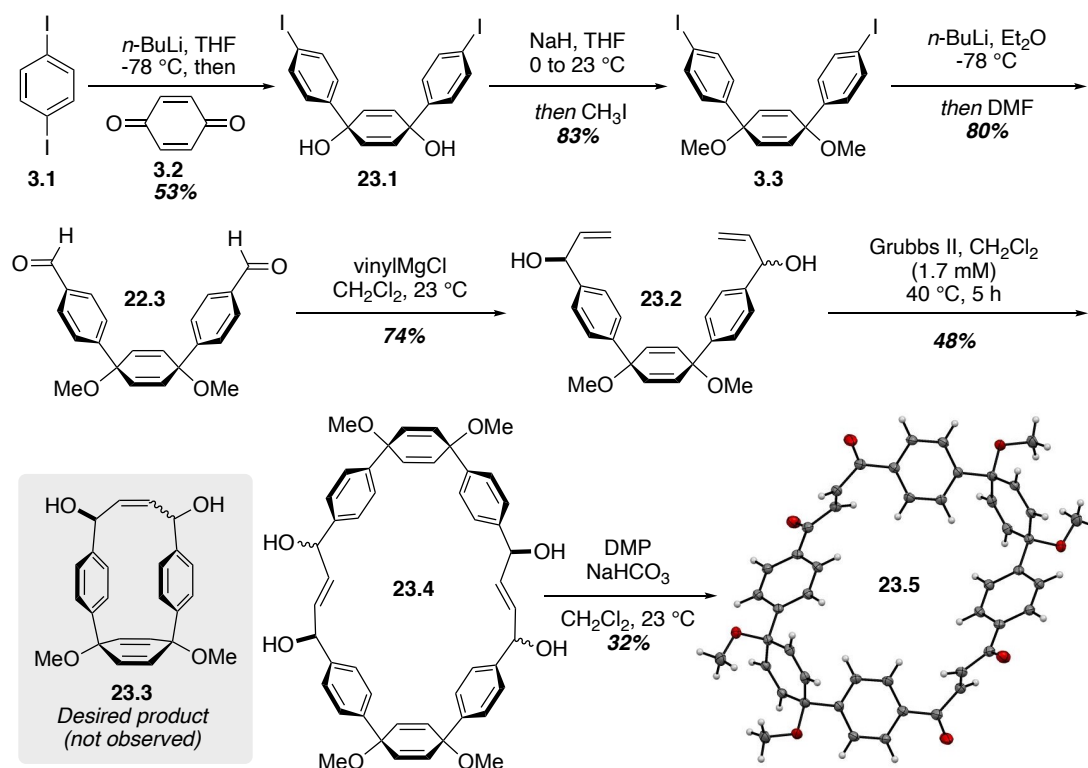


Scheme 22. Retrosynthetic analysis of [4]CPP.

1.4.1.1 A ring-closing metathesis-based approach

Execution of the synthetic plan, in particular the synthesis of **22.2**, commenced with the preparation of diaryliodide **3.3**, which has been utilized by Jasti and co-workers in all their syntheses of $[n]$ CPPs. Following their reported procedure the addition of *p*-benzoquinone **3.2** to *in situ* generated (4-iodophenyl)lithium, followed by methylation of the resulting alcohols gave **3.3** in 41% overall yield. Diiodide **3.3** was then formylated via a halogen-metal exchange with *n*-butyllithium, followed by quenching the resulting dianion with DMF to afford **22.3** in 80%. To implement the streamlined, 1,4-diketone synthesis developed in our laboratory,³³ dialdehyde **22.3** was treated with vinylmagnesium chloride to yield bis-allylic-1,4-diol **23.2** in 73% yield. Subsequent treatment of **23.2** with the Grubbs' second-generation catalyst at high dilution (1.7 mM) did not afford the desired macrocycle **23.3**. Instead of formation of macrocyclic allylic diol **23.3** via a RCM reaction, the only product isolated from this metathesis reaction was a dimerized macrocyclic **23.4** in a 48%. The structure of this by-product was confirmed after oxidation of **23.4** with the Dess-Martin reagent furnished a white solid from which

recrystallization from dichloromethane/hexane produced crystals **23.5** suitable for X-ray crystallographic analysis. Several sets of RCM conditions with different metathesis catalysts, solvents and temperatures were screened for the conversion of **23.2** to **23.3**; however, all of these led to dimerization and decomposition of the starting material. Disappointed by the outcome of the RCM reaction, an alternative strategy to access **22.2** was pursued.

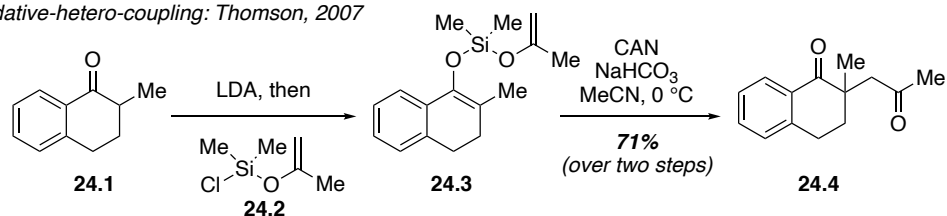


Scheme 23. 1st generation approach for macrocyclization by using ring-closing metathesis.

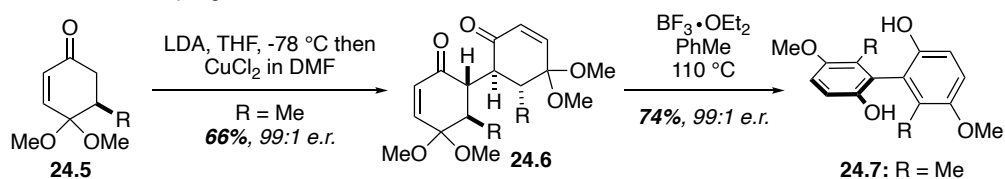
1.4.1.2 An oxidative enolate coupling-based approach

In 2007, Thomson and co-workers reported that bis-silyl enol ethers such as **24.3** undergo intramolecular oxidative enolate coupling to form 1,4-diketones such as **24.4** (Scheme 24).³⁴ In 2011, the same group implemented oxidative enolate coupling of **24.5** towards the syntheses of 1,4-diketone which was previously reported by Saegusa.^{35,36} The homo dimerization of ketone **24.5** via a Cu(II)-mediated enolate coupling provided 1,4-diketone in 66% yield with 99:1 *e.r.* Later, they utilized 1,4-diketone **24.6** in the enantioselective synthesis of biphenols **45.7**.³⁷

A. Oxidative-hetero-coupling: Thomson, 2007

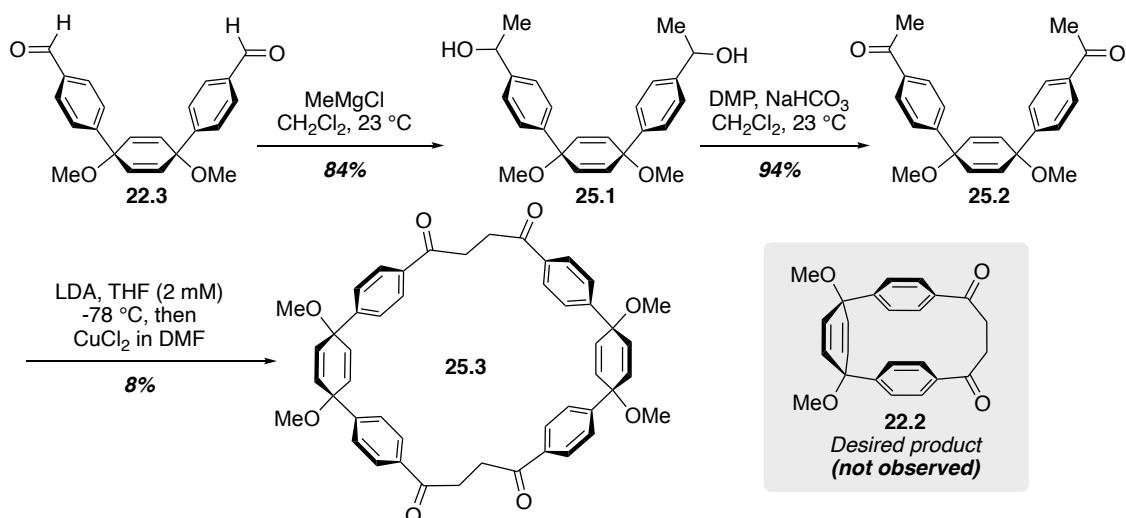


B. Oxidative-enolate-coupling: Thomson, 2011



Scheme 24. 1,4-diketone synthesis via oxidative enolate coupling.

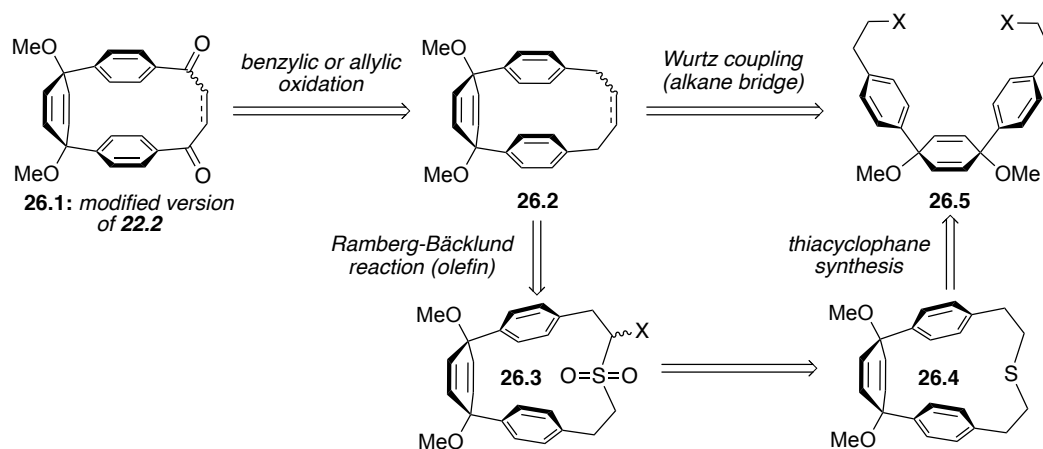
It was proposed that this oxidative enolate coupling could be employed in the synthesis of **22.2**. In order to attempt this reaction, the formyl groups of **22.3** would have to be converted to methyl ketones. Thus, dialdehyde **22.3** was treated with methylmagnesium chloride to afford diol **25.1** in 84% yield. Dess-Martin oxidation of **25.1** in the presence of sodium bicarbonate gave the desired diketone **25.2** in 94% yield. Subjecting **25.2** to the oxidative enolate-coupling conditions reported by Thomson and co-workers, at high dilution (2 mM), afforded a dimerized product **25.3** in 8% yield instead of desired macrocyclic 1,4-diketone **25.2**. The structure of the dimerized product **25.3** was confirmed by mass spectrometry. Like the RCM-based approach, several sets of reaction conditions, which modified the temperature and reagent concentration of the macrocyclization reaction, were attempted; however, the best results obtained are presented in Scheme 25.



Scheme 25. 1st generation approach for macrocyclization by using enolate-coupling.

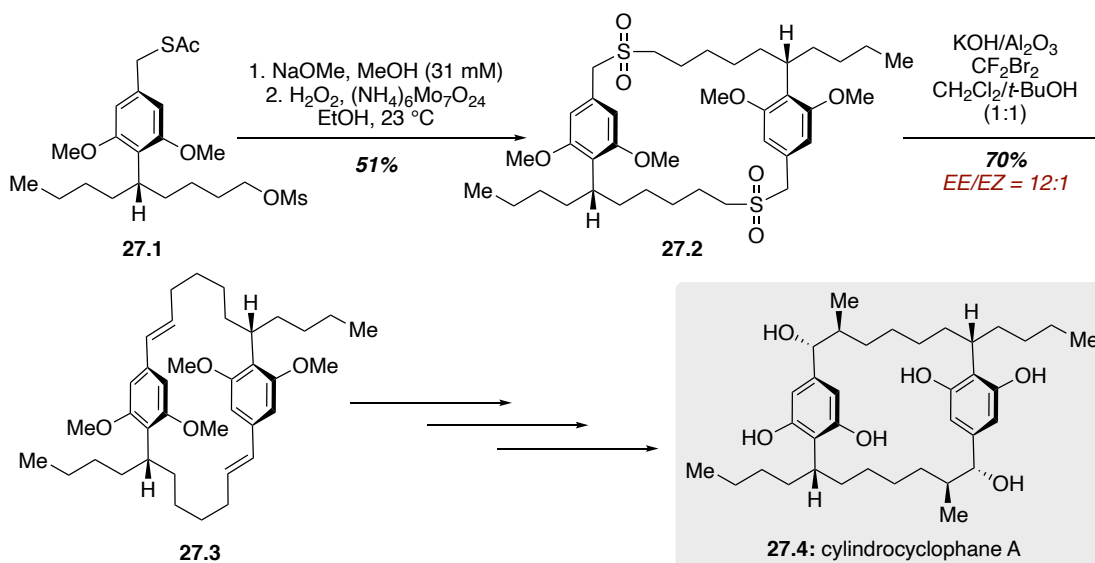
1.4.1.3 Ramberg-Bäcklund and Wurtz-coupling-based approaches to 22.2

A second-generation retrosynthetic analysis was proposed, where it was anticipated that **22.2** or a modified version that contained an olefin unit within the bridge would provide the opportunity for additional disconnections. In this regard, the macrocyclic enone **26.1** could be synthesized via benzylic or allylic oxidation of cyclophane **26.2**, while the saturated version of **26.2** could be afforded from a benzylic oxidation of the alkane-bridging unit (Scheme 26). In the case of the former, a Ramberg-Bäcklund reaction was envisaged from the alpha-halo sulfone **26.3**, which can be brought back to cyclophane thioether **26.4**. The 19-membered macrocyclic thioether **26.4** can be formed from bis-(2-haloethyl) substituted arene **26.5**, which would also be the starting material required for a Wurtz-type macrocyclization reaction. Both of these strategies have been employed in large macrocyclic ring assembly.



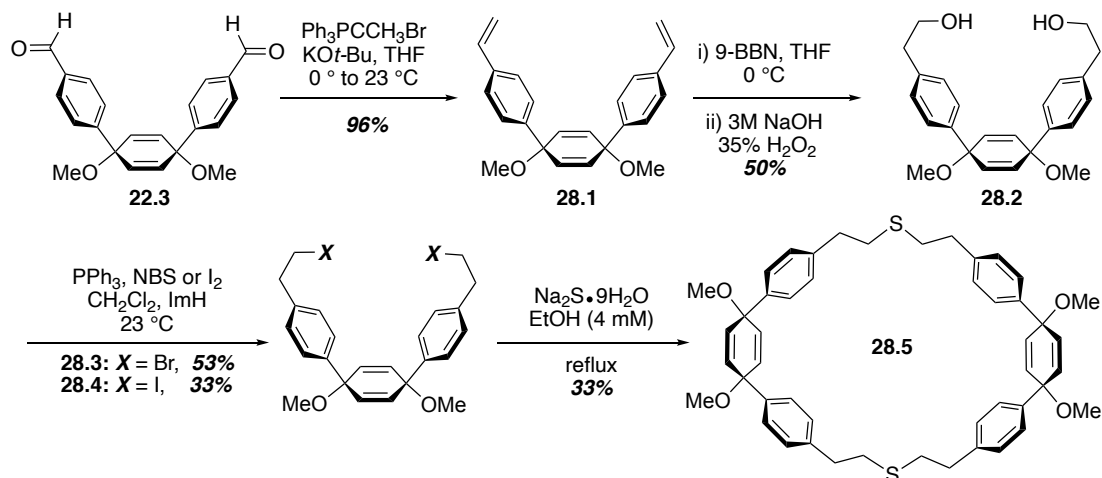
Scheme 26. 2nd Generation approach to diketone **22.2**.

In 2010, K. C. Nicolaou and co-workers reported a short and efficient total synthesis of the [7.7]paracyclophane-containing natural product Cylindrocyclophane A (**27.4**, Scheme 27).³⁸ Their synthetic route relied on dimerization of compound **27.1** via S_N2 -based macrocyclization reaction to afford a bis(thioether), which was subsequently oxidized to the sulfone derivative **27.2** in 51% overall yield. The ring contraction of the macrocyclic bis-sulfone **27.2** was achieved in the presence of alumina-impregnated potassium hydroxide afforded and dibromodifluoromethane to afford macrocyclic diene **27.3** in 70% yield. The bis-olefin unit of the 22-membered macrocyclic diene **27.3** provided the necessary functional group handles to enable the elaboration of this macrocycle to the natural product **27.4**.



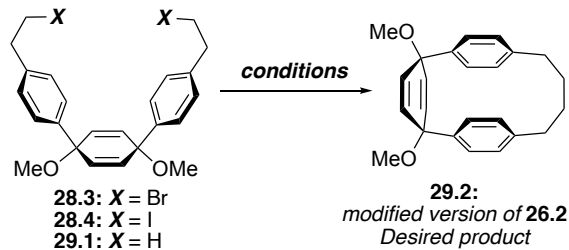
Scheme 27. The Ramberg-Bäcklund reaction in the synthesis of cyclindrocyclophane A.

Following the synthetic plan proposed in Scheme 26 for macrocyclic thioether **26.4**, dialdehyde **22.3** was subjected to a Wittig reaction with methyltriphenyl phosphonium bromide in the presence of potassium *tert*-butoxide to afford bis-styrene derivative **29.1** in 96% yield. Hydroboration-oxidation of **28.1** furnished the diol **28.2** in 50% yield, which was directly subjected to an Appel reaction with either NBS to afford dibromide **28.3** (53%) or iodine to afford diiodide **28.4** (33%). When these macrocyclization precursors were separately subjected to a hot ethanolic solution of sodium sulfide nonahydrate,³⁹ at 4 mM concentration, only the dimerized macrocyclic **28.5** was formed, and not the desired macrocycle **26.4**. Optimized thiacyclophane/macrocyclization conditions reported by Bodwell and co-workers using sodium sulfide adsorbed on alumina⁴⁰ were attempted with dihalide **28.4**. Under the suggested high dilution conditions (3 mM) in dichloromethane/ethanol (10:1) did not result in the formation of the desired thioether **26.4**, but rather led to complete recovery of starting material **28.3**.



Scheme 28. Attempted synthesis of **26.4** via *Ramberg-Bäcklund* reaction.

With **28.3** and **28.4** in hand, focus was directed towards using a Wurtz-type coupling to enable macrocyclization. Several sets of reaction conditions were attempted, including a samarium-mediated and Ni-catalyzed protocol that had been reported by Feng and co-workers (entry 1, Scheme 29).⁴¹ Under these conditions, no starting material was consumed, even at elevated temperatures and after several attempts. A different organometallic-type coupling reaction, which employed both manganese and copper was carried out in aqueous media and applied on dihalide **28.3** (entry 2, Scheme 29).⁴² Again, there was no observable change in the TLC analysis of this reaction, and ^1H NMR spectroscopy confirmed that only starting material was recovered. More standard Wurtz reaction conditions were employed using sodium metal with dihalide **28.3** in presence of tetraphenylethylene (entry 3, Scheme 29).⁴³ Under these conditions the cyclohexadiene unit succumbs to rearrangement. Finally, an *n*-butyllithium-mediated reaction, which had been previously reported by Bodwell and co-workers during their synthesis of pyrene-containing macrocycles, was attempted. Under these conditions, a single halogen metal exchange reaction takes place, followed by an intramolecular $\text{S}_{\text{N}}2$ reaction. When subjecting **28.4** to these conditions, only dehalogenated starting material was obtained (entry 4, Scheme 29).



Entry	Substrate	Conditions	Result
1.	X = Br	NiCl ₂ , Sm HMPA, THF reflux	NR*
2.	X = Br	Mn, CuCl ₂ H ₂ O, 23 °C	NR*
3.	X = Br	Na, TPE THF, -78 °C	unidentified by-products
4.	X = I	<i>n</i> -BuLi, THF -78 °C	29.1; 38%

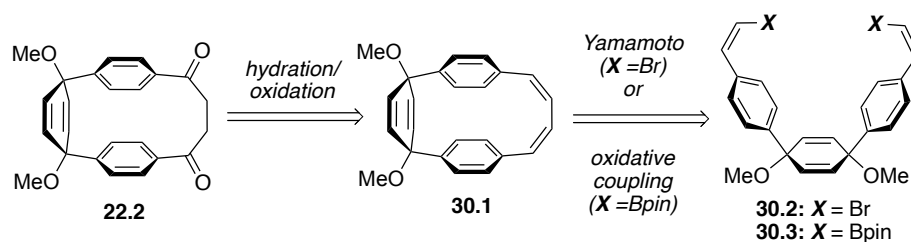
NR* = no reaction; recovered starting material or dehalogenated starting material

Scheme 29. Wurtz coupling-based approach to **29.2**.

1.4.1.3 Oxidative boronate and reductive coupling-based approaches to **30.1**

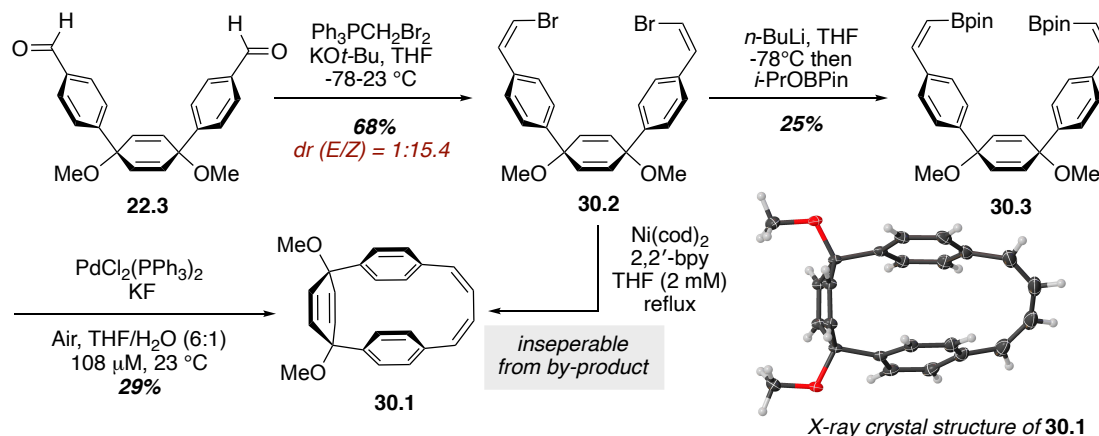
At this juncture, it was clear that the synthesis of **22.2** was more challenging than initially anticipated, and despite the relatively low amount of SE embedded in the macrocyclic backbone of **22.2**, all of the attempted strategies proved to be weak for facilitating the desired macrocyclization. As such, a slight modification to the structure of **22.2** was made, which would enable the application of two powerful macrocyclization reactions – an oxidative boronate coupling or a Ni-mediated reductive coupling. Both of these reactions had proven their worth in the syntheses of [5]CPP, and would not require major changes to the initially proposed route to [4]CPP.

Molecular simplification of **22.2** to the 1,3-diene-containing macrocycle **30.1**, could be accomplished via hydration and oxidation transforms (Scheme 30). Disconnection of the central C_{sp}²-C_{sp}² sigma bond of the four atom-bridging unit, would bring the synthesis of **22.2** back to dienes **30.2** and **30.3**. Finally, both **30.2** and **30.3** could be reduced to dialdehyde **22.3**, which had been successfully employed in a Wittig reaction earlier (see scheme 28).



Scheme 30. Modified retrosynthetic analysis of **22.2** - oxidative boronate or reductive coupling-based macrocyclization reactions.

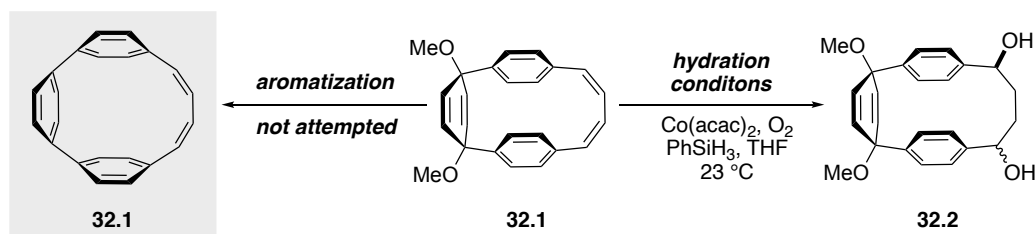
In the forward direction, the Wittig reaction of dialdehyde **22.3** with (bromomethyl) triphenylphosphonium bromide afforded bis-vinyl bromide **30.2** as predominately the *Z,Z*-configured diastereomer. The Ni-mediated macrocyclization of dibromide **30.2** did afford the desired product; however, it was contaminated with an inseparable by-product. Alternatively, dibromide **30.2** could be converted to the bis-boronate **30.3**, which under oxidative coupling condition at high dilution (108 μM) afforded the desired macrocyclic diene **30.1** in 29% yield. Recrystallization of **30.1** from ethyl acetate/hexane produced crystals suitable for X-ray crystallographic analysis, which confirmed the *Z,Z*-configuration of the 1,3-diene unit.



Scheme 31. Synthesis of macrocyclic diene **30.1** via an oxidative boronate coupling reaction.

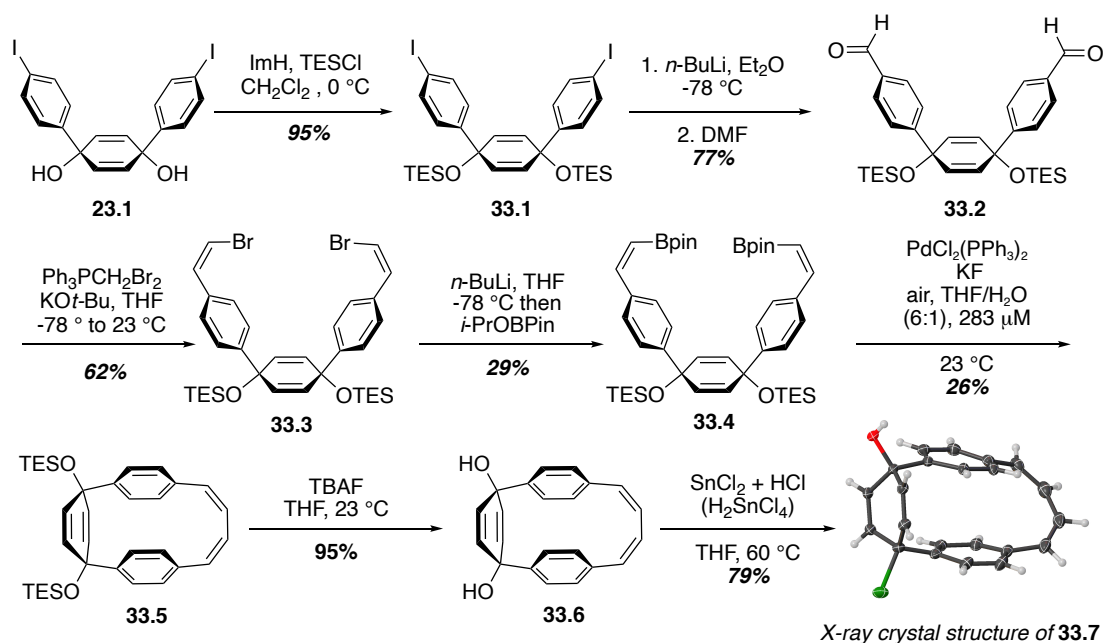
It was hoped that the olefin units within the bridging 1,3-diene group, which are more strained than those of the cyclohexa-1,4-diene, would succumb to a selective hydration reaction; however, this was not to be. Several different hydration protocols, including the powerful Mukaiyama hydration reaction, were employed on this macrocyclic diene. No selectivity was observed, as all of the alkene units appeared to be functionalized in these reactions. To address this, it was proposed that

aromatization of the cyclohexa-1,4-diene unit could precede the hydration of the olefin units, which would be strain-relieving in going from **30.1** to **32.1**. However, **32.1** contains three of the four highly strained *p*-phenylene units of [4]CPP, which could lead to undesired hydration reactions of the strained arene units. Nonetheless, a lot could be gleaned from the aromatization of **30.1**, and thus it was pursued.



Scheme 32. Attempted hydration and aromatization reactions of **30.1**.

The *syn*-1,4-diol **23.1** was protected as triethylsilane ether **33.1** in near quantitative yield. From here, diiodide **33.1** was formylated using the same reaction conditions developed in Scheme 34 to afford the dialdehyde **33.2** in 77% yield. Dialdehyde **33.2** was subjected to a Wittig reaction with the ylide derived from (bromomethyl)triphenylphosphonium bromide to give the bis-vinyl bromide **33.3** in a 62% yield. Conversion of dibromide **33.3** to bis-boronate **33.4** was accomplished in 29% yield. Macrocyclization of **33.4** under conditions provided macrocyclic diene **34.5** in 26% yield. Cleavage of the triethylsilane groups with tetrabutylammonium fluoride furnished 1,4-diol **33.6** in 95% yield and set the stage to attempt a different aromatization protocol. Using the mild conditions reported by Yamaogo and co-workers in 2015, afforded the chlorinated product **33.7** in 79% yield, instead of the desired aromatization product **32.1**.



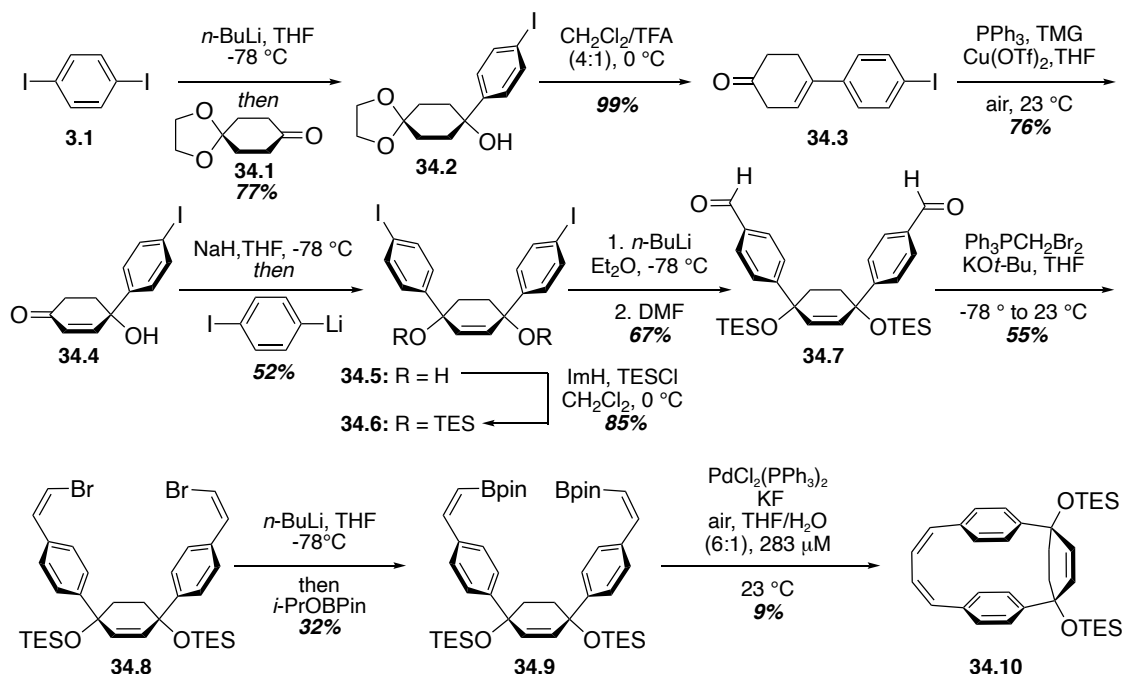
Scheme 33. Aromatization approach of cyclohexadiene unit of macrocyclic diene.

1.4.1.4 Synthesis of a cyclohex-2-ene-1,4-diol containing analog of 30.1

As mentioned in the retrosynthetic analysis, one of the important outcomes of the exploring the total synthesis of [4]CPP would be to compare the Merner dehydrative aromatization strategy to that of the Jasti and Yamago reductive aromatization protocols. Due to the inability to aromatize the pre-arene unit in **30.1** and **33.6** using standard protocols, the opportunity to compare these aromatization strategies in the context of synthesizing **35.10** (Scheme 34) presented itself. However, in order to do so, a novel synthetic approach to cyclohex-2-ene-1,4-diol analog of **30.1** and **33.6** had to be developed.

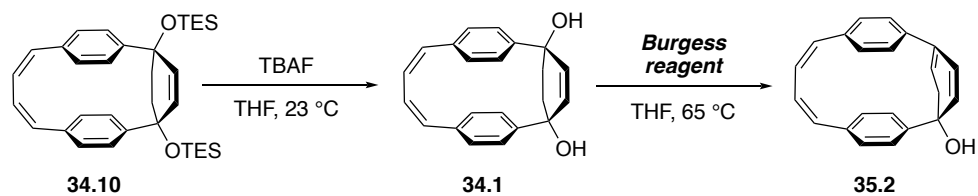
The synthesis of **34.10** commenced with the addition of in situ generated (4-iodophenyl) lithium to the monoacetal of cyclohexane-1,4-dione **34.1** to afford the monoarylated product **34.2** in 77% yield. A one-pot acid-mediated deprotection of the acetal and dehydration reaction afforded cyclohexenone **34.3** in quantitative yield. The oxidation of **34.3**, as reported by Yin and co-workers,⁴⁴ gave 4-hydroxy enone **34.4** in 76% yield. Deprotonation of **34.4** with sodium hydride, followed by addition of the aryllithium reagent, ensures that diol **34.5** is obtained as predominately the *syn*-1,4-diol (52% isolated yield). After triethylsilane protection on *syn*-1,4-diol **34.5**, treatment of **34.6** with *n*-BuLi followed by quenching the resulting dianion with DMF, affords the

dialdehyde **34.7** in 67% yield over two steps. The Wittig reaction of dialdehyde **34.7** with (bromomethyl)triphenylphosphonium bromide gave dibromide **34.8** in 55% yield. Conversion of the dibromide to the bis-boronic ester provided the macrocyclization precursor **34.9** in 32% yield. Oxidative coupling of **34.9** gave the desired macrocycle **34.10** in only 9% yield; however, this sequence was only carried out once and none of the yields presented here are optimized.



Scheme 34. Synthesis of [4]CPP precursor **34.10**.

At this stage of the project, only 1 mg of **34.10** was available, and due to time constraints, only a single set of experiments could be attempted. Cleavage of the silyl ethers with TBAF furnished the diol **35.1**, which was subjected to dehydration with the Burgess reagent. Based on TLC and ^1H NMR analysis, the monodehydration product **35.2** was obtained, which is consistent with what was observed during the synthesis of the highly strained *p*-terphenyl-containing macrocycle **20.2** (Scheme 20). It is unfortunate that time did not permit further manipulation of **35.2** to the **32.1**; however, the work described here will enable another student to pursue the synthesis of **32.1** using the described synthetic approach.

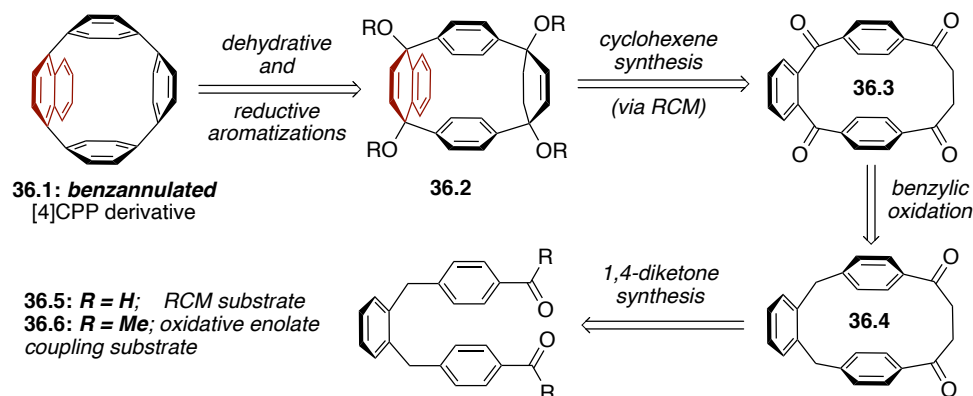


Scheme 35. attempted aromatization of **34.10** - *1 mg scale*.

1.4.5 Towards the synthesis of a macrocyclic precursor for naphthannulated [4]CPP derivative.

During the attempted synthesis of macrocyclic precursors of [4]CPP, containing cyclohexadiene units, it was discovered that RCM, oxidative enolate, Wurtz, and thioether forming reactions to facilitate macrocyclic 1,4-diketone synthesis, were not possible. Presumably, this can be attributed to the rigidity of the pre-arene unit, which makes the energy barrier for macrocyclization prohibitive. To further explore some of these macrocyclization strategies and to synthesize a cyclophane derivative containing a 1,4-diketo-bridging unit, an alternative, more flexible macrocyclization precursor was selected. It was reasoned that incorporation of two methylene carbon atoms at the benzylic positions and the placement of a *Z*-configured olefin unit within one of the tethering groups, should facilitate macrocyclization based on molecular modeling. The simplest, *i.e.*, the easiest compound to synthesize, would be dialdehyde **36.5**, which contains an *ortho*-xylene unit. Incorporation of this tether would require a structural modification to the target, *i.e.*, incorporation of a naphthalene ring or benzannulated ring, but would not change the scope of the work.

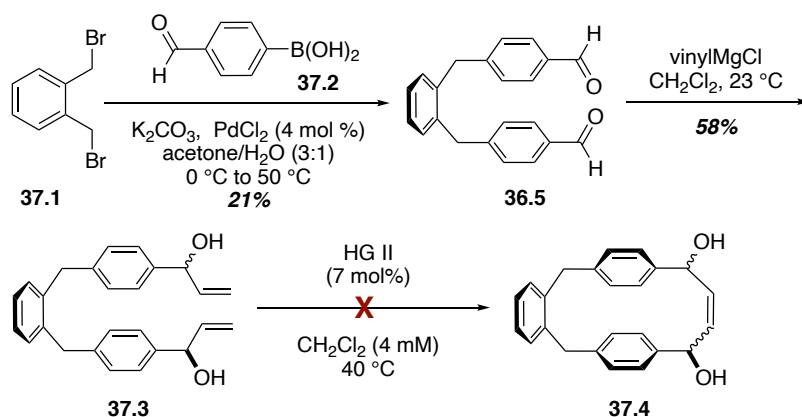
The retrosynthetic analysis of the modified [4]CPP target **36.1** can be simplified to **36.2** via dehydrative and reductive aromatization transforms (Scheme 36). The cyclohexene units of **36.2** can be assembled from ring-closing metathesis in the forward sense, reducing the synthesis of **36.2** to tetraketone **36.3**. Here, it was proposed that benzylic oxidation could be employed, yielding **36.3** from diketone **36.4** as the penultimate retrosynthetic precursor. From this diketone, it was hoped that further investigation of the RCM and oxidative enolate-coupling-based macrocyclization reactions would shed some light on their applicability in [4.4]paracyclophane synthesis.



Scheme 36. Retrosynthetic analysis of naphthannulated [4]CPP derivative.

1.4.5.1 RCM-based approach to 1,4-diketone **36.4**

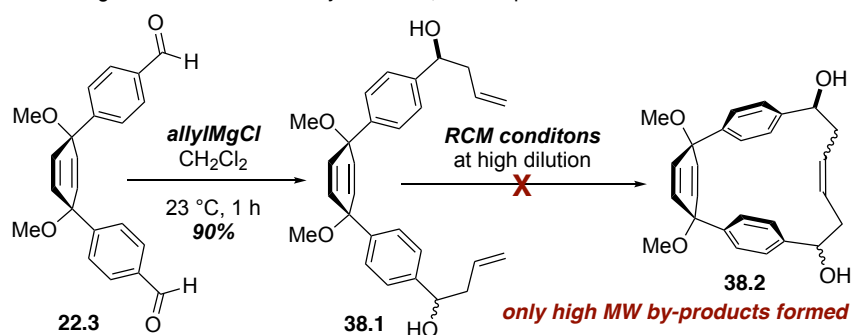
The first approach to diketone **36.4**, started with the Suzuki coupling of *ortho*-xylene dibromide **37.1** and 4-formylphenyl boronic acid **37.2** to give dialdehyde **36.5** in 21% yield. Addition of vinylmagnesium chloride to a dichloromethane solution of dialdehyde **36.5** provided bis-allylic diol **37.3**, which was subjected to RCM with the Hoveyda-Grubbs second-generation catalyst at high dilution (4 mM). Unfortunately, under these and other attempted RCM conditions, no macrocyclization product was afforded. It appears that higher molecular weight products were obtained from this reaction; however, unlike previous metatheses reactions, no material suitable for characterization was isolated.



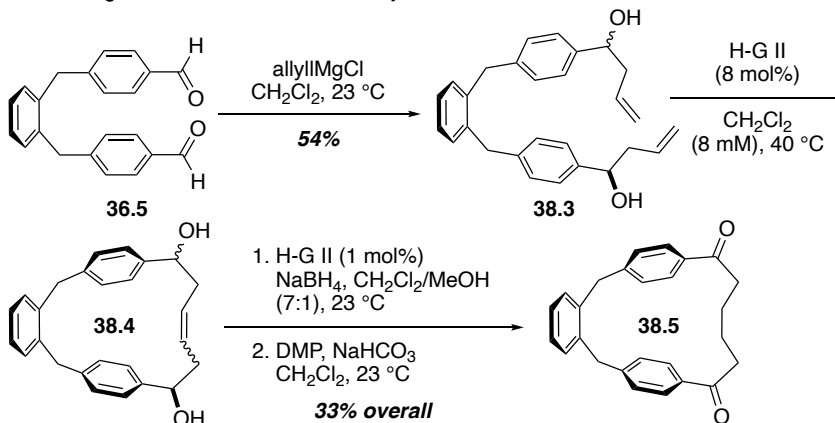
Scheme 37. Attempted synthesis of **36.4** via RCM-based macrocyclization.

To compare the flexibility (or rigidity, depending on one's viewpoint) of substrates like **37.3** to that of **23.2** in metathesis reactions, a homologated bis-olefin macrocyclization precursor was synthesized for both of these substrates. Treatment of dialdehyde **22.3** with allylmagnesium chloride gave the bis-allylic diol **38.1** in 90% yield. Subjecting **38.1** to olefin metathesis conditions, led only to the formation of high molecular weight by-products and presumably a dimeric product that results from metathesis then RCM. In the case of *ortho*-xylene derivative **36.5**, a Grignard reaction with allylmagnesium chloride furnished the macrocyclization precursor **38.3** in 54% yield, and upon treatment with the Hoveyda-Grubbs second-generation catalyst, the desired macrocyclization product was produced as a mixture of 1,6-diol and olefin diastereomers. After transfer hydrogenation of the olefin unit in **38.4** and oxidation of the mixture of *syn* and *anti*-1,6-diols, macrocyclic 1,6-diketone **38.5** was isolated in pure form, in 33% yield over three steps. The success of this reaction was cause for optimism that *ortho*-xylene-based macrocyclization precursors may be more suitable for the synthesis of 1,4-diketone **36.4**.

A. homologated RCM reaction of cyclohexa-1,4-diene precursor **38.1**



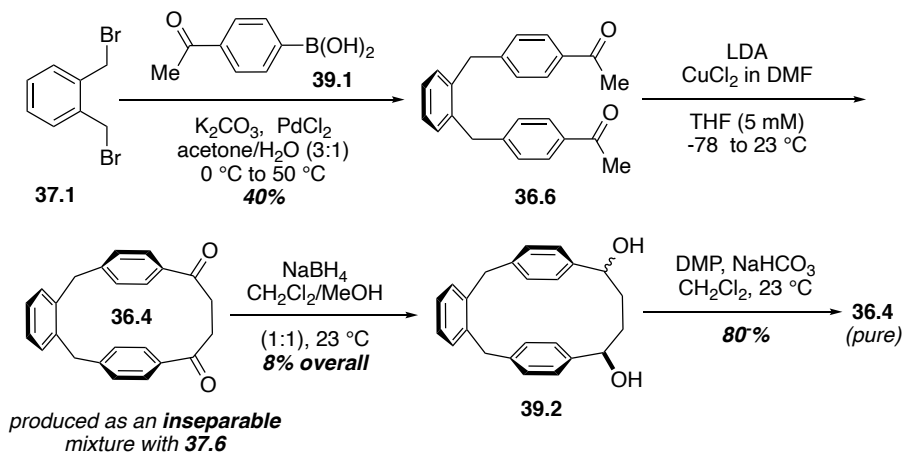
B. homologated RCM reaction of *ortho*-xylene derivative **38.3**



Scheme 38. Homologated RCM reaction of **38.1** and **38.3**.

1.4.5.2 Oxidative enolate coupling-based approach to 1,4-diketone **36.4**

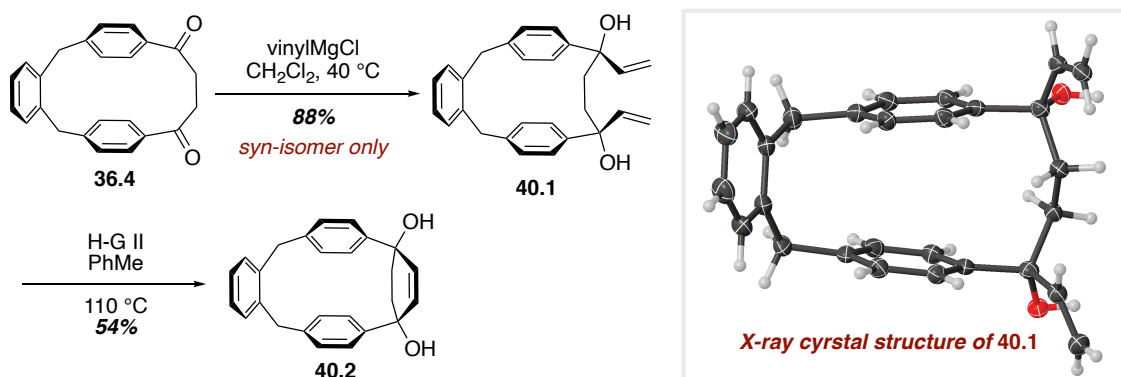
The synthesis of a 16-membered, *ortho*-xylene-containing macrocyclic 1,4-diketone **36.4** was pursued using an oxidative enolate coupling (**36.6**, R = Me, Scheme 39). This required the synthesis of bis methyl ketone **36.6**, which was accomplished via a Suzuki reaction of dibromide **37.1** and boronic acid **39.1** (Scheme 39). The Cu(II)-mediated enolate-coupling of **36.6** did afford the desired macrocyclic 1,4-diketone; however it was not separable from the starting material, which was not (entirely) consumed. In order to access pure **36.4**, it was necessary to reduce the mixture with sodium borohydride, which produced chromatographically separable diols. The macrocyclic 1,4-diol **39.2** was isolated in 8% overall yield from **36.6** and then subjected to a Dess-Martin oxidation to afford **36.4** in pure form (80% yield). The synthesis of the 16-membered macrocyclic 1,4-diketone **67.4** represents a significant milestone for this project, finally capitalizing on one of the main synthetic goals originally proposed in Scheme 36.



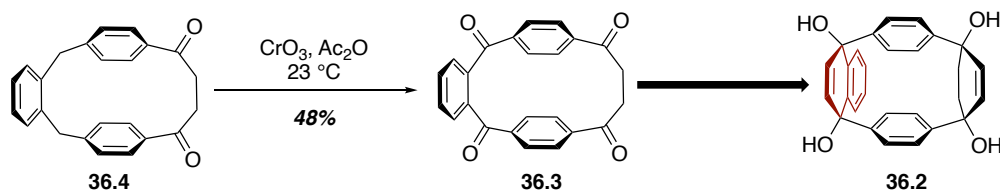
Scheme 39. Synthesis of macrocyclic diketone **36.4** via an oxidative enolate coupling reaction.

Due to time constraints, and a limited quantity of **36.4** available – complicated by the low yielding oxidative enolate-coupling reaction – only a handful of experiments could be attempted on diketone **36.4**. The first of which was a Grignard reaction of **36.4** with vinylmagnesium chloride, which gave *syn*-1,4-diol **40.1** as a single diastereomer. Fortunately, recrystallization of **40.1** from ethyl acetate/hexane produced crystals suitable for X-ray crystallography, corroborating the correct relative stereochemistry.

As can be seen from the solid-state structure of **40.1**, the olefin units are positioned on the perimeter of the macrocycle and vastly separated. In order for the olefin units to come within proximity to undergo a RCM reaction, a significant conformational change must take place within the macrocyclic backbone, which undoubtedly will require bending the central arene units. To this end, it was necessary to heat the reaction to 110 °C in toluene in the presence of the Hoveyda-Grubbs second-generation catalyst to afford cyclohex-2-ene-1,4-diol **40.2** in 54% yield. It should be noted that no conversion takes place below this temperature.



To understand the reactivity of benzylic positions of **36.4**, an oxidation with chromium trioxide was attempted. To our delight, this reaction gave the desired tetraketone **36.3** in 48% yield. Unfortunately, the story ends here. Due to time constraints and other ongoing projects (see Chapters 2 and 3), no further experiments were carried out on this material. However, the synthesis of **40.2** and **36.3** leaves this portion of the project in a great place for a new graduate student to take over.



1.5 Conclusion

Clearly, the synthesis of [4]CPP is a daunting challenge, but one definitely worth pursuing. During the course of three years of synthetic investigations, two viable macrocyclization protocols have been delineated and several advanced intermediates, which can conceivably be converted into the highly strained carbon nanohoop, have been synthesized. The biggest disappointment is that time has run out and I will not get to finish the synthesis of this molecule. Nonetheless, I close this chapter of my doctoral studies knowing that I have left this project in a great position for an incoming graduate student. Three of the four rings contained within the macrocyclic framework of [4]CPP have been incorporated into a macrocyclic, advanced intermediate. Furthermore, bridging groups that contain functional group handles for future synthetic manipulations have been installed in these advanced intermediates.

One of the most gratifying accomplishments of these studies is that the originally proposed, novel cyclophane-based approach to [4]CPP has been demonstrated to be a viable synthetic pathway to macrocyclic precursors of this challenging target. Furthermore, the dehydrative aromatization reaction that has been developed in the Merner laboratory, has not failed! Partial dehydration has taken place for **35.2**, and with access to larger quantities of the requisite precursors, I am confident that a pathway to aromatization will be developed shortly.

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CHAPTER 2 Pi-Extension of Strained Benzenoid Macrocycles Using the Scholl Reaction.

2.1 Introduction

The development of size-selective syntheses of $[n]$ CPPs in last decade, drew considerable attention to this class of molecules and their application to the bottom-up chemical synthesis of armchair segments (or edges) of CNTs and pi-extended PAH units of these curved macrocyclic hydrocarbon systems. To date, the preparation of functionalized $[n]$ CPPs, as well as the attempted pi-extension of these systems towards higher order carbon nanostructures have been reported by several research groups.¹⁻³ Due to the high amounts of strain energy contained within the macrocyclic backbone of smaller $[n]$ CPPs, most attempts of direct pi-extension have failed. The conversion of strained benzenoid macrocycles into strained polycyclic aromatic hydrocarbon-containing macrocycles remains as a significant for chemical synthesis. This is largely due to a poor understanding of the interplay of strain and aromaticity and connecting these important concepts to synthetic method development. This chapter will focus on the development of annulative pi-extension (APEX) reactions of linear and macrocyclic benzenoid systems. In particular, a detailed investigation of the Scholl reaction and its application to the synthesis of sidewall segments of CNTs via pi-extension of a strained *p*-terphenyl-containing macrocycles will be discussed.

2.1.1 Polycyclic Aromatic Hydrocarbons (PAHs)

Aromatic compounds containing two or more fused benzene rings within their structural configuration are considered to be polycyclic aromatic hydrocarbons. A strip of PAHs with a width of less than 100 nm are known as graphene nanoribbons (GNRs). PAHs and GNRs have gained attention in various field of materials chemistry due to their potential applications. PAHs and GNRs have been used in polymer films,⁴ sensors,⁵ electronic devices,⁶ and have shown extraordinary thermal, optical and biological properties because of their microporous nature.^{7,8} PAHs are formed by either anthropogenic sources of pollution or incomplete combustion of carbon-containing fuels such as wood, coal, diesel, fat, tobacco, and incense. PAHs are considered to be high-risk pollutants to the environment and have been found to be toxic in living systems. Some PAHs containing angular frameworks and these are suspected to be highly

carcinogenic⁹ and immunotoxicogenic to various life forms, due to their thermostability, hydrophobicity properties.¹⁰

PAHs are mostly colorless, white or pale yellow solids.¹¹ The molecular arrangement of aromatic rings (*i.e.*, aromatic sextets) within a PAH can be linear, angular or in clustered (Figure 3). Depending on the number of fused aromatic rings, PAHs are classified as small or large (PAHs). Small PAHs have up to six fused aromatic rings and have been widely used in scientific studies due to their availability. Anthracene (**3a**) and phenanthrene (**3b**) are the smallest PAHs, which contain three benzene rings in linear and angular fashion, respectively. Large PAHs contain more than six aromatic rings. Hexa-*peri*-hexabenzocoronene (HBC, **3o**) is a large PAH, which is also known as a “nanographene molecule,” due to its width of greater than 1 nm.⁷ Furthermore, based on the arrangement of aromatic sextets, PAHs are also classified as: 1) *alternant PAHs*, containing only fusion of six-membered rings, whereas 2) *non-alternant PAHs*, like fluoranthene (**3c**) and corannulene (**3m**), contain ring fusion of aromatic sextets that inscribe a non-6-membered ring, *i.e.*, a five-membered ring.¹² Alternant *PAHs* are typically planar, unless they belong to the helicene family of PAHs or they are tethered at to remote positions to form a macrocyclic structure known as a cyclophane.¹³ Macrocycles that contain short tethering units, typically alkyl chains, can cause the PAH to bend or distort from planarity.

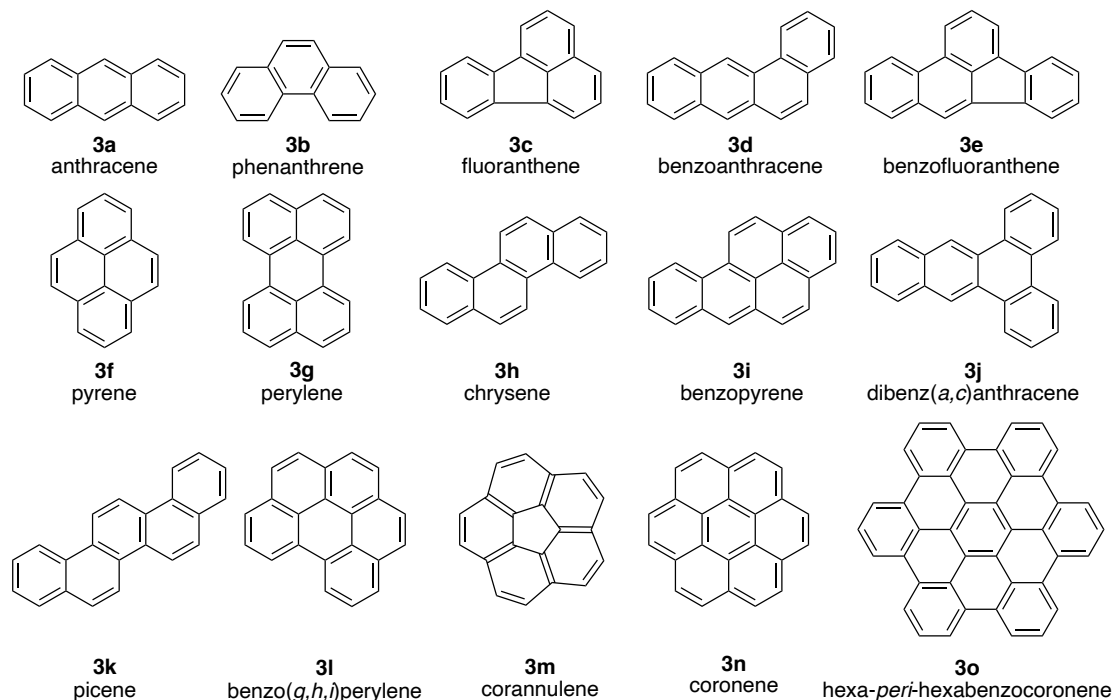


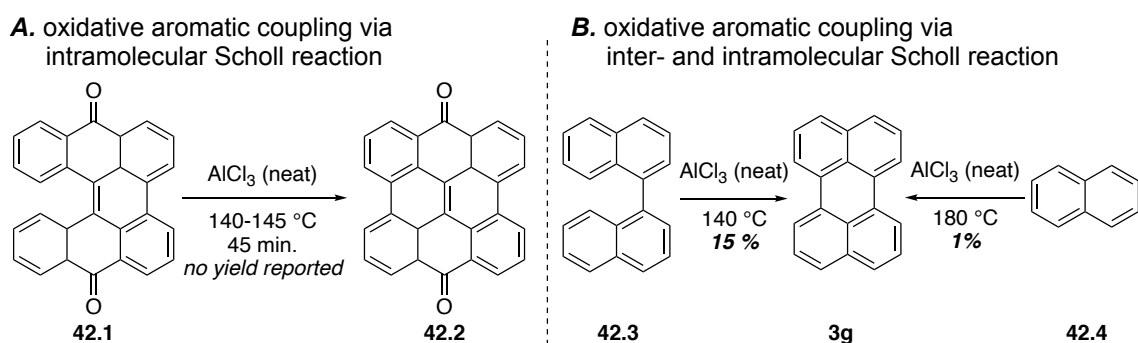
Figure 3: Selected polycyclic aromatic hydrocarbons.

2.1.2 Synthesis of planar PAHs

2.1.2.1 Application of the Scholl reaction to planar PAHs synthesis

The Swiss chemists Scholl, Clar and Zander are pioneers in the field of polycyclic aromatic hydrocarbon synthesis.¹⁴ In 1910, Scholl introduced an expansion of polycyclic arenes by carbon-carbon covalent bond formation in presence of Lewis acid, such as aluminum chloride at elevated temperatures.¹⁵ Later, due to the advancement of analytical and spectroscopic measurement, the isolation and characterization of isomeric PAHs formed under these harsh reactions conditions have been improved, which ultimately led to the development of improved oxidative arylation conditions. Reactions of this type are known as the “Scholl reaction” in the chemical synthesis community. In 1910, Scholl and Mansfield reported the conversion of quinone **42.1** to the pi-extended quinone **42.2** in presence of anhydrous aluminum chloride for 45 minutes at 140-150 °C (Scheme 42A).¹⁵ Though the yield was not reported, this is the first reported oxidative aromatic coupling in presence of Lewis acid. In the same year, to further explore this reaction as a tool for PAH synthesis, the same group proposed the synthesis of perylene (**3g**) from naphthalene (**42.4**) using aluminum chloride as Lewis acid at 180 °C via an inter-, followed by intramolecular C-C bond formation (Scheme 42B). The reported yield

was low at only 1%, which can be attributed to decomposition and polymerization of the starting material at these high reaction temperatures.¹⁶ The isolated yield of **3c** could be improved by modifying the substrate and the reaction conditions. In this case, perylene (**3g**) was synthesized from 1,1'-binaphthalene (**42.3**) upon heating with aluminum chloride at lower temperature, via intramolecular Scholl reaction 15% yield.¹⁶

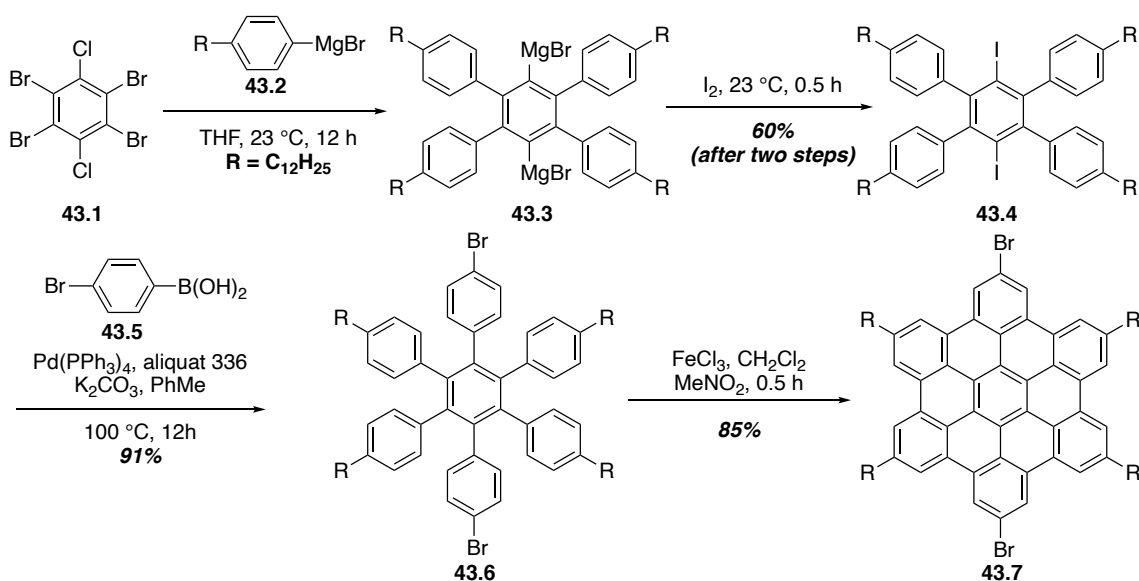


Scheme 42. Early oxidative aromatic coupling reactions by Scholl *et. al.*

Over the last century, numerous modifications of the original Scholl oxidative arylation reaction have been developed. The major change in these reactions has involved modification of the oxidant, which is typically employed in a stoichiometric quantity to accomplish the cyclodehydrogenation. In modern chemistry, the Scholl reaction can be achieved by using a variety of oxidants such as aluminium trichloride, iron(III) chloride, molybdenum(v) chloride, copper(II) chloride, antimony(V) chloride, copper(II) trifluoromethanesulfonate (CuOTf), boron trifluoride diethyl etherate, phenyliodobis(trifluoroacetate) (PIFA), and 2,3-dichloro-5,6-dicyano benzoquinone (DDQ). These oxidants alone, or in combination with each other, allow the oxidative arylation reaction to be conducted under milder conditions, compared to the originally reported, high temperature conditions. This advancement has enabled higher yielding reactions that are tolerable of more functional groups, as well as the formation of multiple C-C bonds in a single synthetic operation. The latter leading to rapid increases in molecular complexity to furnish pi-extended PAHs. As such, cyclodehydrogenation reactions to couple aromatic rings have been recognized as powerful tools to produce large PAHs frameworks from relatively simple precursors.

Müllen and co-workers have applied the Scholl reaction for the pi-extension of hexa-substituted benzene rings, to furnish various nanographene molecules. In 2008,

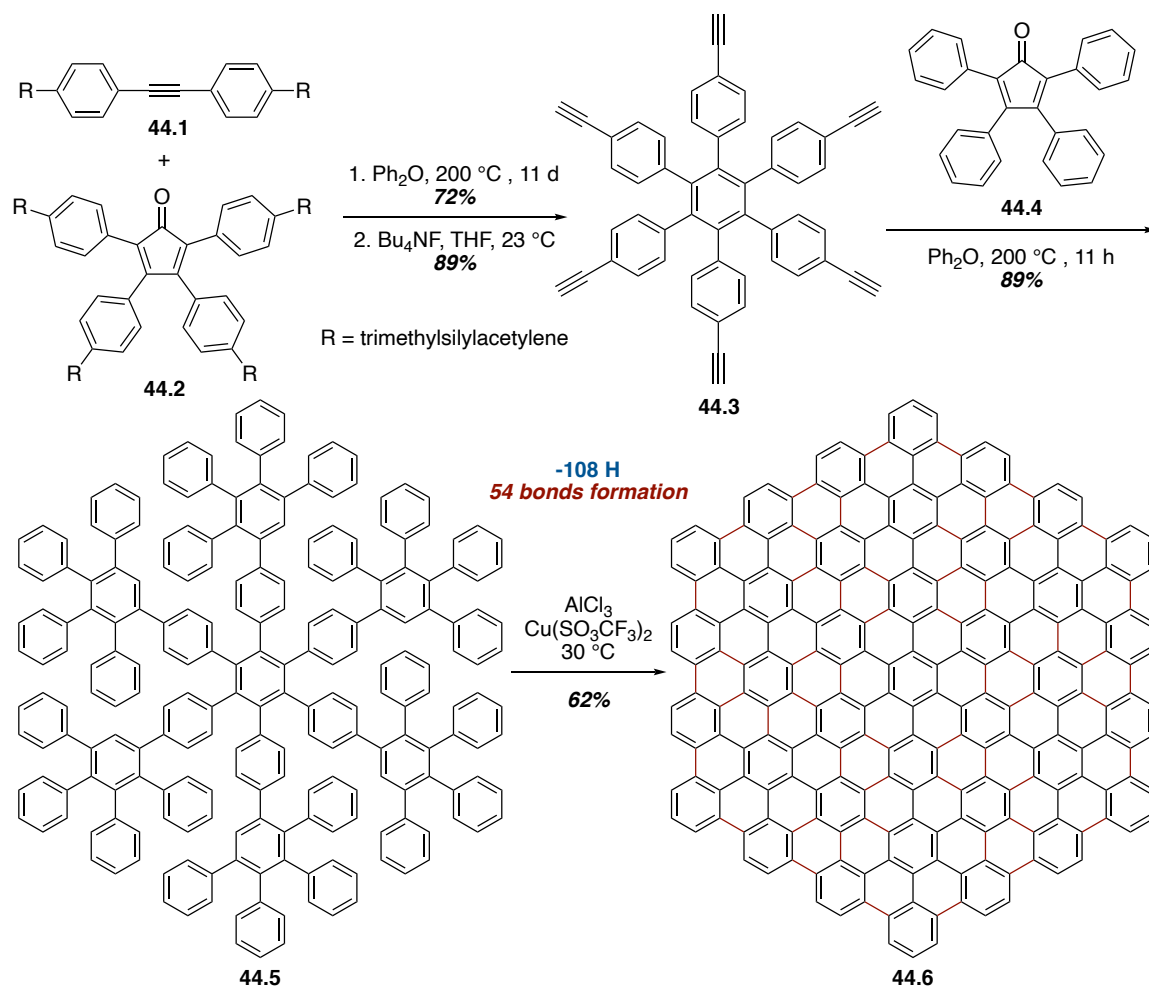
Müllen group reported the synthesis of a hexa-*peri*-hexabenzocoronene (HBC) derivative **43.7** by utilizing a late-stage Scholl reaction in multi-step approach (Scheme 43).¹⁷ They prepared tetra aryl-substituted diiodobenzene **43.4** from 1,2,3,5-tetrabromo-3,6-dichlorobenzene (**43.1**) in 60% yield by first a Grignard exchange reaction, followed by electrophilic substitution reaction with iodine. The sterically hindered diiodide **43.4** afforded hexaphenylbenzene (HPB) **43.6** in 91% yield upon employing optimized conditions of the Suzuki-Miyaura cross-coupling with 4-bromophenylboronic acid **43.5**. Cyclodehydrogenation of dibromide **43.6** in the presence of iron(III) chloride afforded the nanographene HBC derivative **43.7** in a 85% yield.



Scheme 43. Synthesis of HBC **43.7** via the Scholl reaction.

In 2002, the Müllen group developed the synthesis of giant, 222 carbon-containing graphene sheet **44.6** by sequential [4+2] cycloaddition reactions, followed by oxidative arylation.¹⁸ The synthesis of the hexaphenylacetylene derivative **44.3** was accomplished through a [4+2] cycloaddition of alkyne **44.1** and cyclopentadienone **44.2**, followed by cleavage of trimethylsilyl groups in 64% yield over two steps. The less hindered alkyne (central triple bond) of **44.1** was selectively engaged (as the dienophile) in the [4+2] cycloaddition. Subjecting **44.3** to six successive [4+2] cycloaddition reactions with cyclopentadienone **44.4** over an 11 h period, afforded the oligophenylene **44.5** in 89% yield. The powerful oxidative aromatic coupling of oligophenylene **44.5** provided PAH **44.6** (Scheme 44) by forming 54 new C-C bonds in the presence of $AlCl_3$

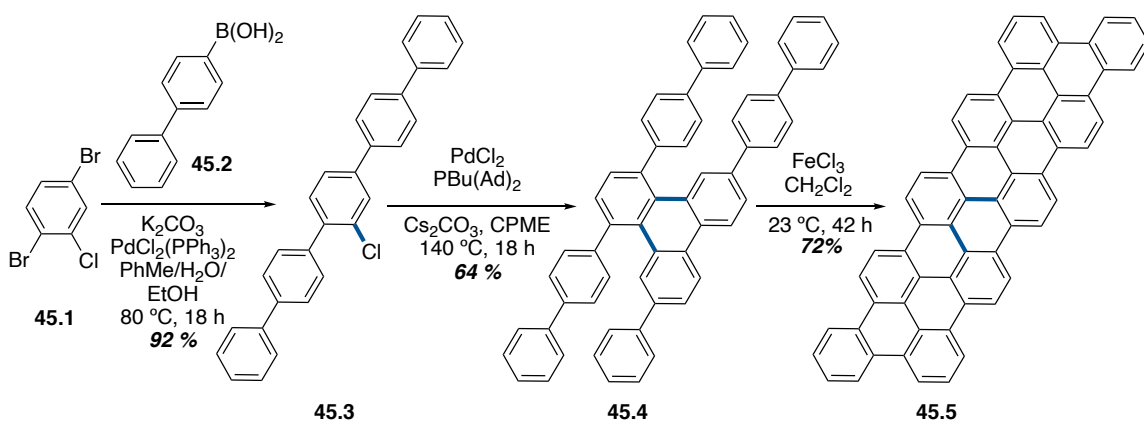
and $\text{Cu}(\text{OTf})_2$. This work from Müllen and co-workers represents a rare example of the synthesis of a giant nanographene without any solubilizing substituents under solution-phase conditions. Moreover, the nanographene was completely characterized by both spectroscopic techniques.



Scheme 44. Synthesis of giant nanographene **44.6** via the Scholl reaction.

In 2019, Itami and co-workers reported the convergent synthesis of an arm-chair-edged graphene nanoribbon (GNR) segment **45.5** by stitching together pre-oriented, polyarylated precursor **45.4** via the Scholl reaction (Scheme 45).¹⁹ The functionalized pentaphenyl unit **45.3** was synthesized via Suzuki cross-coupling of 1,4-dibromo-2-chlorobenzene (**45.1**) with 4-biphenylboronic acid **45.2** in 92% yield. Under palladium-catalyzed conditions, annulative dimerization of **45.3** provided triphenylene derivative **45.4** in 64% yield. The assembly of two linear pentaphenyl units, held together by two

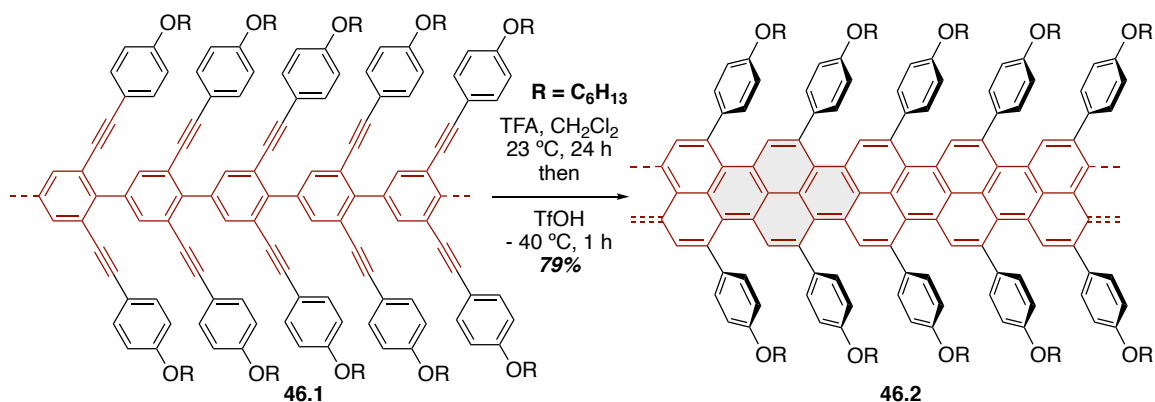
C-C bonds (blue bonds, Scheme 45) facilitated in the late-stage annulation under oxidative arylation conditions to furnish the GNR substructure **45.5** in 72% yield. This work is significant as it showcases the innovative utilization of a simple aryl chloride into partial ring fusion of the GNR precursor and a late-stage Scholl reaction to furnish the synthesis of fully fused planar nanographene unit.



Scheme 45. Itami's synthesis of GNR substructure **45.5** via annulative chlorophenylene dimerization.

2.1.2.2 *Pi-extension via alkyne-based annulation reactions*

Recently, Chalifoux and co-workers have introduced an alkyne cyclization reaction as annulation strategy for the synthesis of pyrenoid PAHs. In 2016, Chalifoux synthesized pyrene-based graphene nanoribbons (GNR) **46.2** from the poly(2,6-dialkynyl-*para*-phenylene) (PDAPP) **46.1** (Scheme 46).²⁰ The synthesis started with the conversion of an aniline derivative to PDAPP by sequential Sonogashira and Suzuki cross-coupling reactions (not shown in Scheme 46). The poly alkynylated material **46.1** was then subjected to a Brønsted acid-promoted alkyne benzannulation reaction to afford GNR **46.2** in 79% yield. These pyrene-based narrow GNR are highly soluble in number of common organic solvents, which enabled the extensive characterization of these materials.

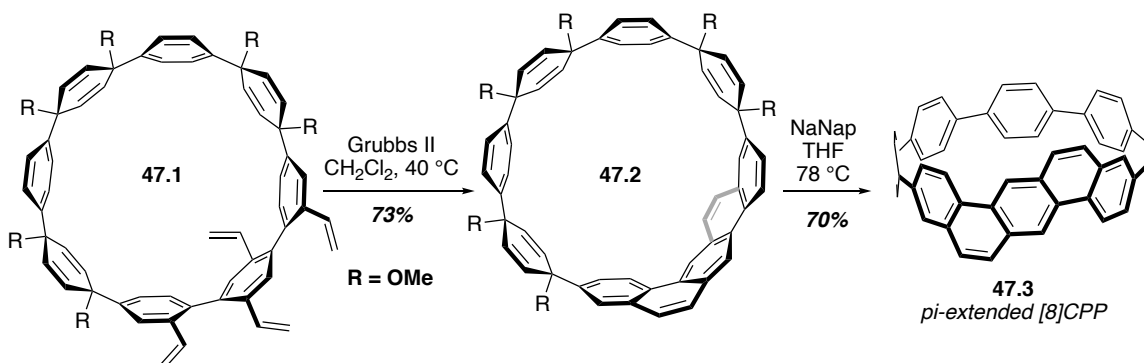


Scheme 46. Alkyne benzannulation reactions in the synthesis graphene nanoribbons (GNRs).

2.1.3 Synthesis of curved PAHs

2.1.3.1 Ring-closing metathesis in curved PAHs synthesis

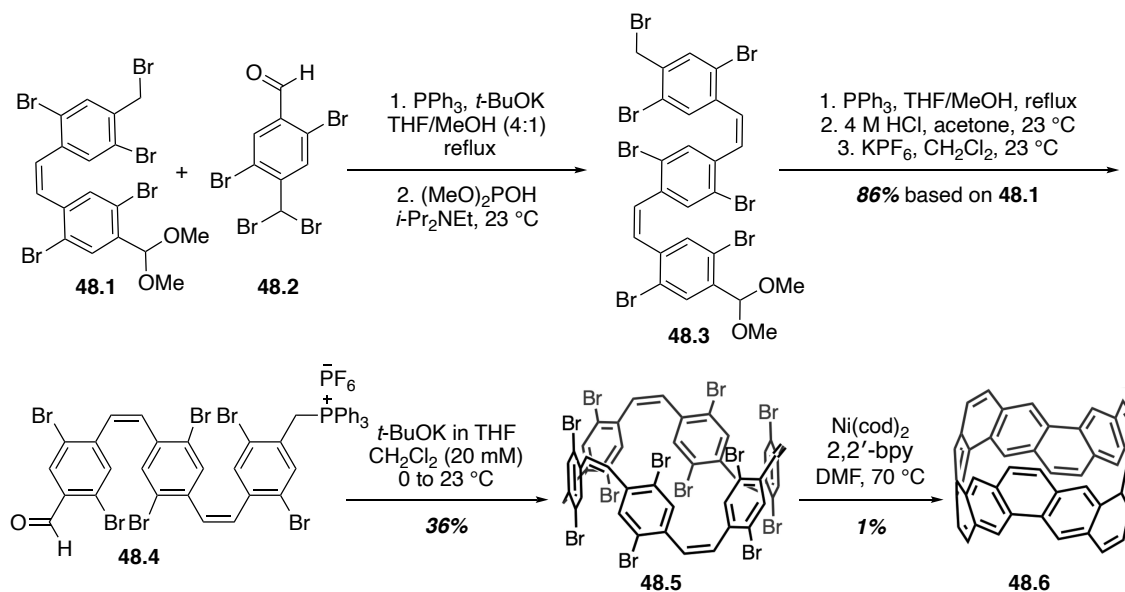
Formation of a cyclic alkene product by an olefin metathesis reaction is known as ring-closing metathesis (RCM). This powerful cyclization reaction has featured in the synthesis of small, medium, and large rings over the past three decades, and has revolutionized the field of chemical synthesis, with respect to ring-forming reactions. In 2016, Jasti and co-workers successfully employed this powerful strategy on curved macrocyclic styrene derivative **47.1** (Scheme 47).²¹ The RCM-based strategy for annulation on the macrocyclic backbone of a series of vinylated $[n]$ CPP precursors, followed by aromatization furnished a pi-extended $[8]$ CPP **47.3**, representing the first successful example of pi-extension about an $[n]$ CPP. During their studies, the Jasti group found that this strategy could be used to introduce up to 24 kcal/mol of SE into the macrocyclic backbone of a curved CPP precursor, to afford new PAH/CNT sidewall segments.



Scheme 47. Pi-extended $[8]$ CPP synthesis by the ring-closing metathesis.

2.1.3.2 The synthesis of a carbon nanobelts using Yamamoto coupling

In 2017, Itami and co-workers reported the first synthesis of a carbon nanobelt (CNB) **48.6**, which is also segment of an armchair (6,6) CNT. Their strategy involved sequential *Z*-selective Wittig reactions to assemble styrenyl intermediates, and later a styrene-based macrocycle derivative that was appropriately substituted with aryl bromide units, which would later be engaged in a nickel-mediated aryl-aryl coupling reaction as the key annulation step for PAH synthesis.²² The Wittig reaction of stilbene-based benzylic bromide **48.1** (which is also a Wittig product) with aldehyde **48.2**, followed by monodebromination to give bis-stilbene **48.3** containing three aryl unit. Formation of the phosphonium salt of **48.3**, followed by deprotection of the acetal unit with hydrochloric acid and counterion ion exchange to afford the PF₆ salt took place in one-pot and provided the bifunctional intermediate **48.4** in 86% yield from **48.1**. Subsequent cyclodimerization of **48.4** afforded macrocycle **48.5** in 36% yield. The *Z*-configured olefin geometry ensured that the Yamamoto coupling of **48.5** would furnish the nanobelt **48.6** in 1% yield. Though the annulation step was very low yielding, this marked the first example of fully conjugated, fully ring-fused, rigid belt structure that was completely characterized by spectroscopic and spectrometry experiments. This carbon nanobelt **48.6** is an isomer of [12]cyclophenacene (**48.7**), and the estimated SE of nanobelt **48.6** (119.5 kcal/mol) is almost the same as that of [12]cyclophenacene (Figure 4; 115.1kcal/mol).



Scheme 48. Synthesis of carbon nanobelt **48.6** via Yamamoto coupling.

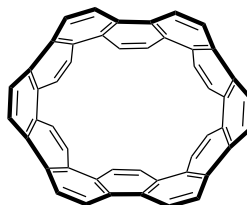
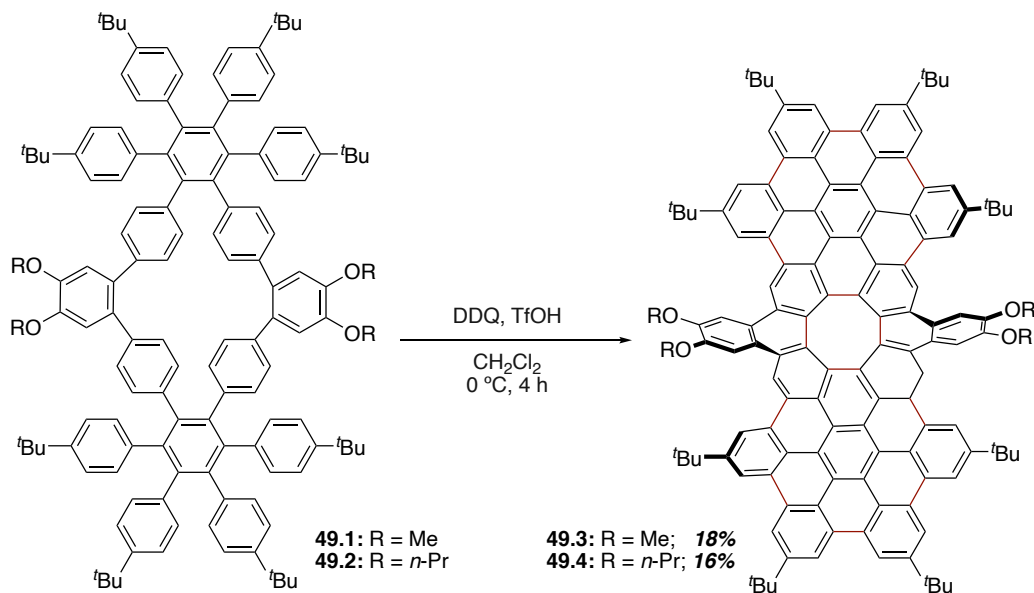


Figure 4: Structure of [12]cyclophenacene.

2.1.3.3 *Synthesis of carbon curved aromatic compounds using the Scholl reaction.*

In 2017, Miao and co-workers employed a late-stage Scholl reaction in their synthesis of twisted nanographenes **49.3** and **49.4** (Scheme 49). These structures contain a central [8]circulene moiety within a the polycyclic framework, consisting of 96 sp^2 hybridized carbon atoms.²³ Hexaphenyl benzene units were installed into the macrocycles **49.1** and **49.2** via [4+2] cycloaddition reactions between alkyne and cyclopentadienone units, as described above (not shown in Scheme 49). A subsequent Scholl reaction under conditions developed by Rathore and co-workers²⁴ on macrocycles **49.1** and **49.2** furnished the pi-extended [8]circulene units of **49.3** and **49.4** in 18% and 16% yield, respectively, resulting in the formation of 14 new carbon-carbon bonds.

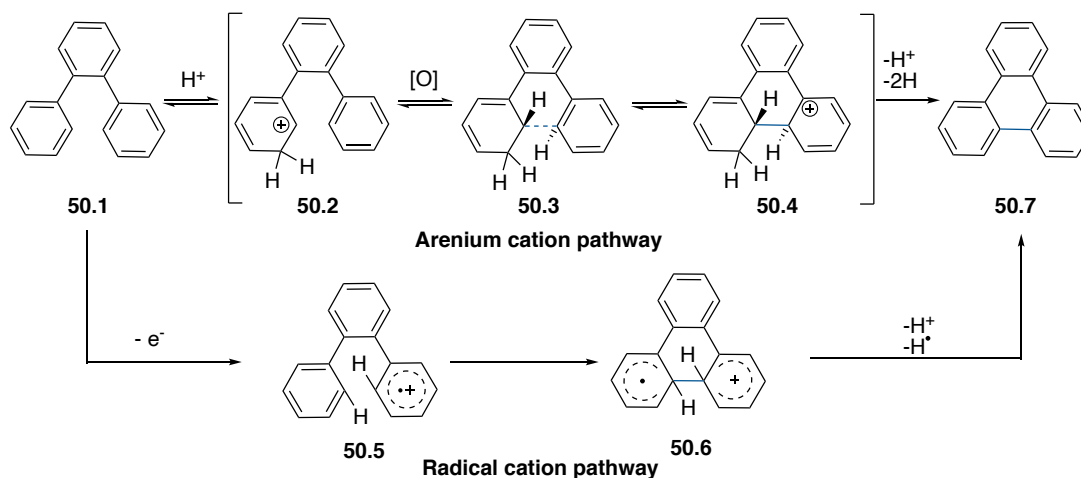


Scheme 49. Synthesis of twisted nanographene using Scholl reaction.

2.2 Mechanism of Scholl reaction

The early literature defined the Scholl reaction as *“a dehydrogenation of aromatic nuclei under the influence of aluminum chloride that results in the formation of a condensed ring system.”*²⁵ Later, Balaban and Nenitzescu offered a modified definition which described the reaction as *“the elimination of two aryl-bound hydrogens accompanied by the formation of an aryl-aryl bond under the influence of a Friedel-Crafts catalysts.”*²⁶ Kerner and Baddeley proposed two possible mechanisms for the Scholl reaction. Kenner, along with Baddeley²⁷ firstly proposed a radical cation mechanism for this cyclodehydrogenative reaction (Scheme 50). Later on, Baddeley suggested that the Scholl reaction may proceed via the formation of a σ -complex between a Lewis acid and aromatic unit,²⁶ followed by the formation of arenium cation as the intermediate which can undergo electrophilic attack and ultimately dehydrogenation (Scheme 50). In Scheme 50, for simplicity, a proton has been used for the formation of arenium cation; however, in principle a Lewis acid can be employed for the same purpose. In both reaction mechanisms, H₂ (or 2H) is eliminated during the course of the cyclodehydrogenation, which is under influence of an oxidant and catalyst.

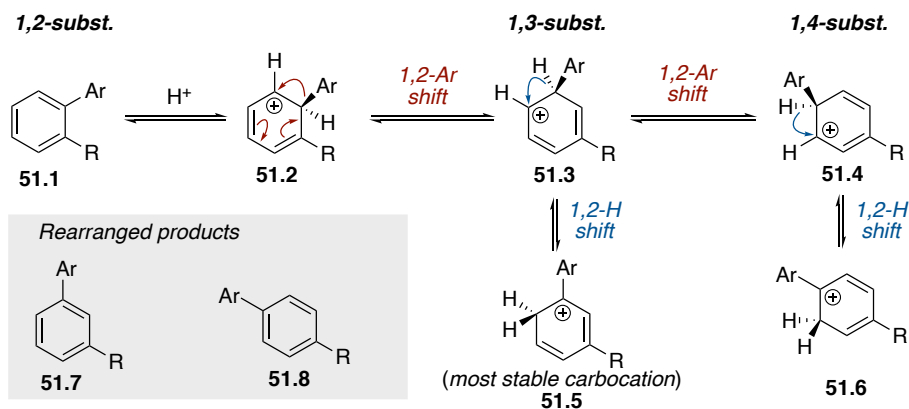
The exact mechanism of Scholl reaction is controversial and still poorly understood. Various factors such as reaction conditions (reagent, temperature etc.), electronic and steric effects, as well as substituent positions influence the mechanistic pathway. Despite our limited knowledge with respect to the exact reaction mechanism, this technique is frequently applied in the field of complex PAH synthesis and has proven to be quite powerful in enhancing the library of hydrocarbon compounds.



Scheme 50. Two alternative possible pathways for Scholl reaction.

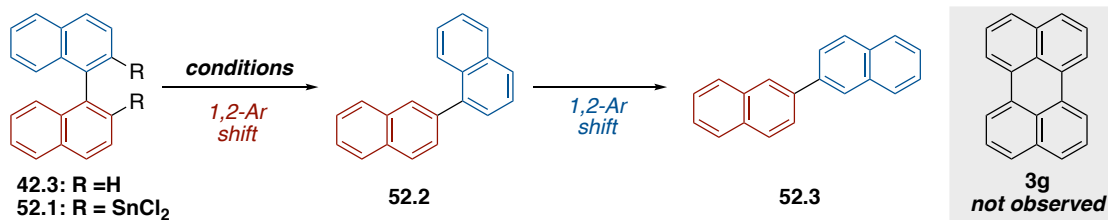
2.2.1 Unpredictable rearrangements from the Scholl reaction

Typically, metal chlorides are employed as oxidants in the Scholl reaction, and this can result in the formation of hydrochloric acid during the course of reaction. The hydrochloric acid produced can lead to undesired reactions of intermediates or products produced, typically resulting in chlorinated by-products. To reduce these effects, the reaction mixture can be purged with a continuous stream of an inert gas, such as argon or nitrogen. Moreover, intramolecular Scholl reactions can undergo rearrangement or isomerization due to the formation of cationic intermediates which succumb to 1,2-aryl or 1,2-hydride shifts (Scheme 51). Observation of the latter supports the arenium cation mechanism. In 2012, Johnson and co-workers described that a 1,2-aryl shift, followed by a 1,2-hydride shift occurs to favor the formation of the *meta*-substituted rearranged product **51.7** via formation of lowest energy cation **51.5**.²⁸



2.2.1.1 Unpredictable rearrangements during Scholl reactions to form planar PAHs.

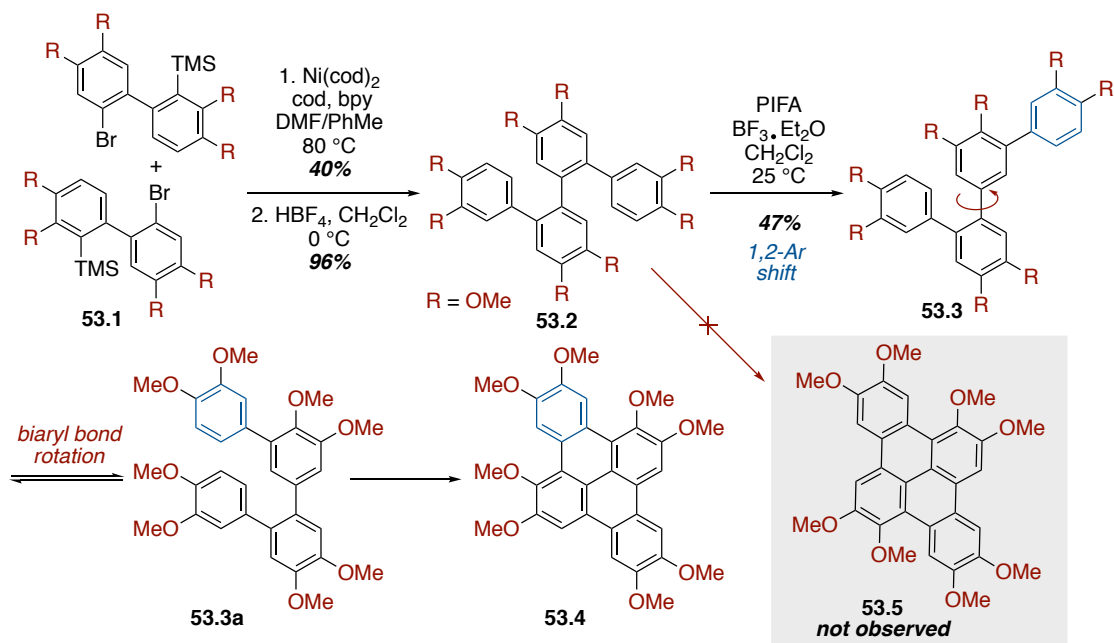
In 1965, Kovacic and Koch investigated the Scholl reaction on 1,1'-binaphthyl (**42.3**) (entry 1 and 2, Scheme 52) in presence of metal halides and oxidants at room temperature.²⁹ Analysis of the crude products revealed that the major product formed was 2,2'-binaphthyl (**52.3**) with the minor product, 1,2'-binaphthyl (**52.2**), resulting from a single aryl migration. This was believed to occur via *ipso* arenium ion formation, with no formation of cyclized product perylene (**3g**). Later on, Zubieta and co-workers also investigated the Scholl reaction with bis-organotin derivatives of 1,1'-binaphthyl **52.1** in presence of trifluoromethanesulfonic acid at room temperature (entry 3, Scheme 52). Here they observed complete conversion of 1,1'-binaphthyl **52.1** into 2,2'-binaphthyl (**52.3**).³⁰ Recently, Johnson and co-workers established the mechanism of this acid catalyzed isomerization of **42.3** to 1,2'-binaphthyl (**52.2**) and 2,2'-binaphthyl (**52.3**) using both experimental evidence and computational studies (entry 4, Scheme 52).³¹ During the course of rearrangement, a 1,2-aryl shift followed by 1,2-hydride shift provided *meta* isomer product **52.3** via formation of the lowest energy cation as shown in Scheme 51 (*i.e.*, intermediate **51.5**). All of these investigations demonstrated that the low yield in *classic Scholl reaction* to cyclize 1,1'-binaphthyl (**42.3**) to perylene (**3g**, Scheme 42B) at elevated temperature, can be attributed to a low equilibrium concentration of 1,1'-binaphthyl (**42.3**), as this reaction results in the conversion of the starting material to less strained 1,2'- and 2,2'-binaphthyl isomers (**52.2** and **52.3**), respectively.



Entry	R	Condition	Product ratio 42.3 or 52.1:52.1:52.3
1.	H	AlCl ₃ , CuCl ₂ , <i>o</i> -Cl ₂ C ₆ H ₄ , (20-25) °C	20:15:65
2.	H	MoCl ₅ , <i>o</i> -Cl ₂ C ₆ H ₄ , (20-25) °C	0:5:95
3.	SnCl ₂	CF ₃ SO ₃ H, CH ₂ Cl ₂ , 23 °C	0:0:100
4.	H	CF ₃ SO ₃ H, C ₂ H ₄ Cl ₂ , 23 °C	0:3:97

Scheme 52. Rearrangement product formation from Scholl reaction.

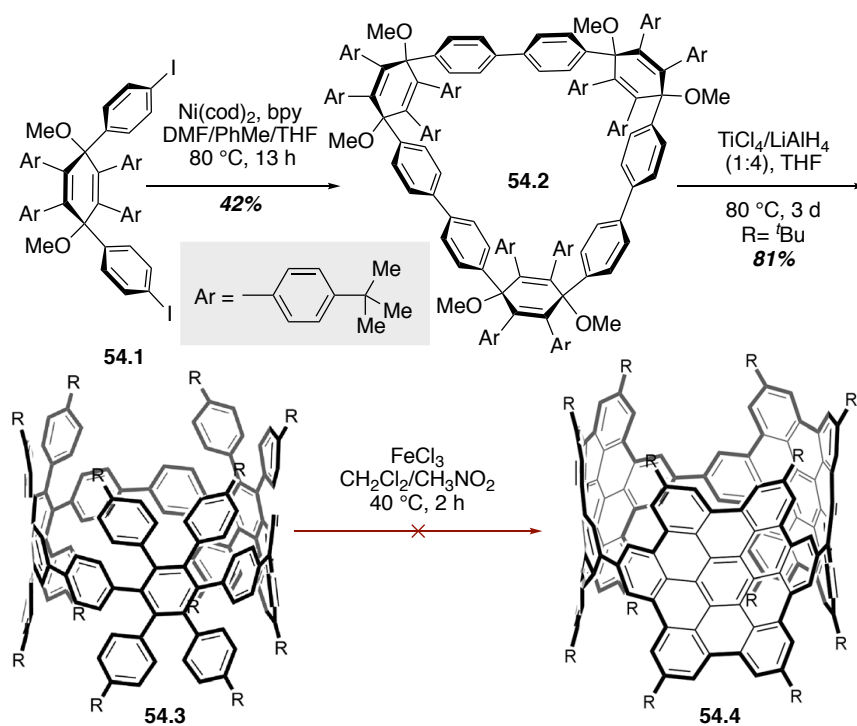
Rearrangements are a common phenomenon in the Scholl oxidation. Identification of rearranged products by mass spectrometry or even simple nuclear magnetic resonance (NMR) experiments can be challenging, due to the formation of isomeric materials that have similar aromatic units. Before the advancement of modern NMR techniques, rearranged products obtained during the course of these reactions were reported incorrectly in literature. For instance, in a series of articles, Musgrave reported that the Scholl oxidation of octamethoxyquaterphenyl **53.2** provided octamethoxynaphthacene **53.5** (Scheme 53). Their assignment was based on basic 1D NMR analysis.^{32–34} In 2008, King and co-workers³⁵ reinvestigated the same Scholl reaction of octamethoxyquaterphenyl **53.2**; however, this time they used modern, 2D-NMR techniques and single-crystal X-ray diffraction analysis to confirm the product as as rearranged PAH **53.4** instead of **53.5**. This proved that the original assignment by Musgrave and co-workers was indeed incorrect. In their stepwise synthesis, the King group employed a nickel-mediated homocoupling on 2-bromo-2'-trimethylsilyl-4,4',5,5'-tetramethoxybiphenyl (**53.1**) followed by removal of the TMS group afforded octamethoxyquaterphenyl **53.2** in 38% yield over two steps. When the methoxy-substituted *ortho*-quaterphenyl **53.2** was subjected to a cocktail mixture of oxidants, the rearranged, annulated product **53.4** was formed via 1,2-aryl shift to afford **53.3**, followed by intramolecular Scholl reaction from conformer **53.3a**.



Scheme 53. Scholl oxidation of octamethoxyquaterphenyl **53.2**.

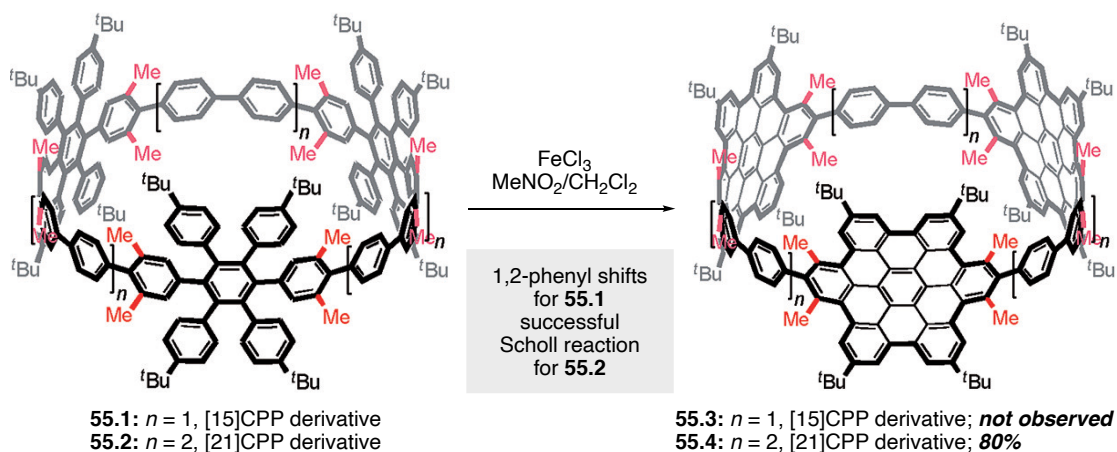
2.2.1.2 Rearrangements during Scholl reactions to synthesize curved PAHs.

In the last decade, several groups have attempted to develop pi-extension strategies to convert benzenoid macrocycles into PAH-containing macrocycles. During these attempts 1,2-aryl shifts that result in the strain relief about the macrocyclic backbone were observed. In 2012, Müllen and co-workers reported the synthesis of dodeca-arylated [9]CPP derivative **54.3** ($SE_{pp} = 10.4$ kcal/mol, $SE_{CPP} = 93.9$ kcal/mol, Scheme 54) which have higher strain energy than that of [9]CPP ($SE_{CPP} = 65.6$ kcal/mol).³⁶ Starting from 2,3,5,6-tetraaryl-*syn*-1,4-diol derivative **54.1**, macrocycle **54.2** was obtained by a Yamamoto coupling reaction in 42% yield. Reductive aromatization of the cyclohexadiene units of macrocycle **54.2** in presence of a low valent titanium reagent, afforded the dodeca-arylated [9]CPP derivative **54.3** in a good yield. Scholl oxidation of **54.3** using Iron(III) chloride afforded a partially dehydrogenated and chlorinated by-products instead of the desired, pi-extended HBC-based nano hoop **54.4**. The by-products produced in this reaction were identified on the basis of matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS).



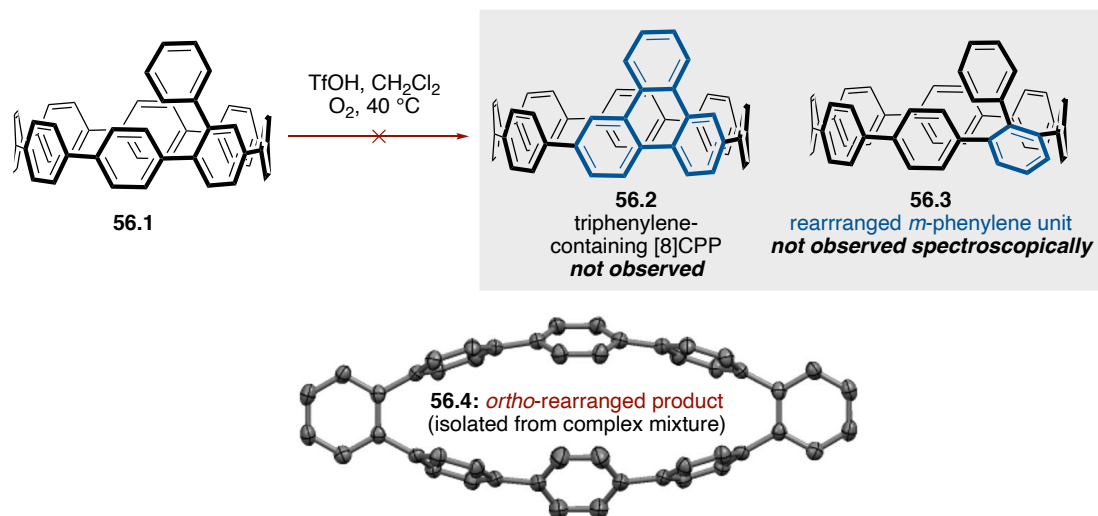
Scheme 54. Müller's attempted synthesis of [3]HBC nano hoop **54.4**.

In 2015, Müller group synthesized polyarylated macrocycles **55.1** and **55.2** containing a [15] or [21]CPP unit, respectively with the introduction of strategically placed methyl groups on *para*-phenylene units within the macrocyclic backbone. The purpose of these methyl groups was to prevent any undesired 1,2-aryl shift reactions.³⁷ Subjecting polyarylated macrocycle **55.1** ($SE_{pp} = 2.7$ kcal/mol, $SE_{CPP} = 40.5$ kcal/mol) to standard cyclodehydrogenation conditions did not result in the formation of the pi-extended product **55.3**, but rather a 1,2-aryl shift product was observed. However, application of this strategy to a homologous, albeit, less strained [21]CPP derivative **55.2** ($SE_{pp} = 1.3$ kcal/mol, $SE_{CPP} = 27.3$ kcal/mol) afforded the HBC-incorporated [21]CPP **55.3** in 80% yield.



Scheme 55. Synthesis of HBC-incorporated [21]CPP derivative **55.4** using the Scholl reaction.

In 2016, Jasti and co-workers investigated a Scholl-based annulation protocol for the pi-extension of a monophenylated [8]CPP derivative **56.1** ($SE_{pp} = 9.2$ kcal/mol, $SE_{CPP} = 73.6$ kcal/mol).³⁸ Monophenylated [8]CPP derivative **56.1** required an eight step synthesis, where the phenyl ring was installed at an early stage in the synthesis, via 2-phenyl-1,4-benzoquinone (not shown in Scheme 60).³⁹ Macrocyclic **56.1** was then subjected to a Scholl reaction using a slight modification of Rathore's conditions.²⁴ Under these conditions, the desired cyclodehydrogenation to afford triphenylene-containing [8]CPP **56.2** did not occur, but rather mixtures of isomeric macrocycles such as **56.3** and dephenylated, rearranged macrocycle **56.4**, as well as other ring-opened products, were obtained. It should be noted that Jasti and co-workers did synthesize an authentic sample of **56.2** using a different synthetic strategy, which incorporated the triphenylene unit into a macrocyclic precursor at an earlier stage in the synthesis. At this point, it is clear that the success of Scholl reaction on curved PAHs are related to the pre-organization as well as SE of the macrocycle.



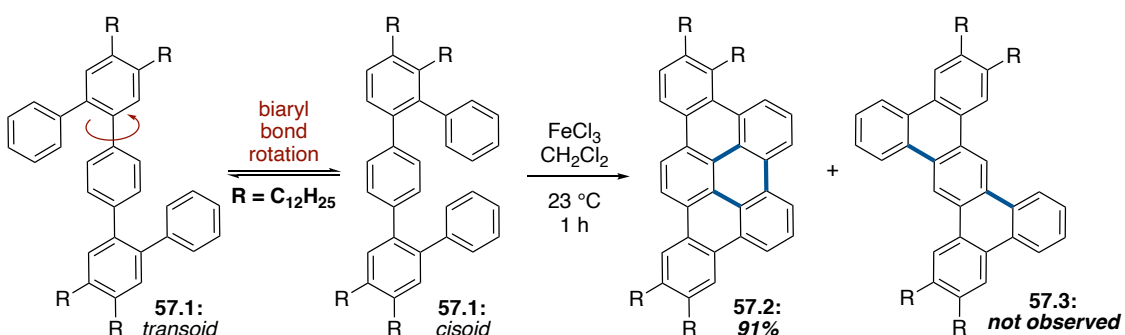
Scheme 56. Jasti and co-workers attempted synthesis of **56.2** using a Scholl reaction.

2.2.2 Predicting regiochemistry in the Scholl reaction

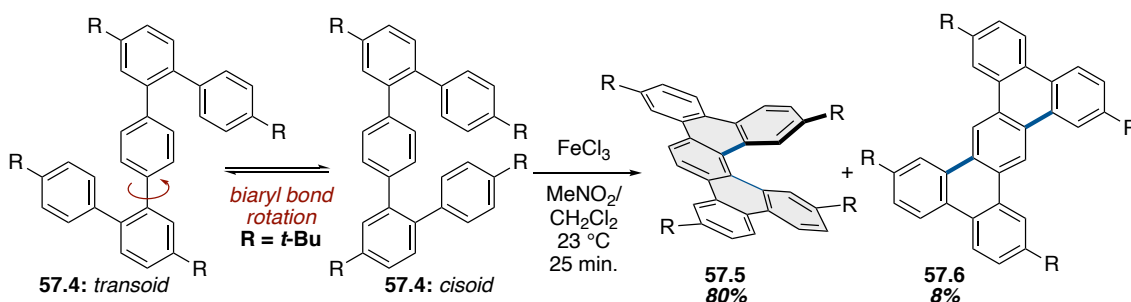
Other than being unpredictable with respect to rearrangement, the Scholl reaction in some cases provided undesired regiochemical outcome via nonobvious mode of cyclization. For instance, in 2011 Müllen and co-workers applied Scholl oxidation on aryl substituted *p*-terphenyl **57.1** towards the intended tetrabenzanthracene product **57.3** (Scheme 57A).⁴⁰ However, when **57.1** was subjected to mild Scholl reaction conditions only the undesired constitutional isomer **57.2** was afforded in 91% yield, proceeding through a more congested (*cisoid*) cyclodehydrogenation pathway, with formation of additional carbon-carbon bond across the fjord region of the intermediate PAH. In same year, Durola and co-workers synthesized 2,2''-bis(4-*tert*-butylphenyl)-*p*-terphenyl (**57.4**) and investigated its Scholl reaction (Scheme 57B).⁴¹ During the oxidative arylation, the more congested *cisoid* mode of cyclization provided the helicene product **57.5** in 80% yield and the less congested, *transoid* cyclization product **57.6** in only 8% yield. Due to the presence of the bulky *tert*-butyl groups, further carbon-carbon bond formation across the fjord region, as was the case in the Müllen did not occur, yielding the highly distorted [5]helicene **57.5** as the major product. This type of unexpected regiochemical outcome of Scholl reaction, with formation of the more strained PAH, was encouraging for our own investigations of annulative pi-extension of bent *p*-terphenyl units into curved sidewall segments of CNTs (see section 2.3).

In 2012, Hilt and co-workers investigated this annulation reaction both experimentally and computationally using *p*-terphenyl **57.7**, which is virtually identical to the system investigated by Müllen group (Scheme 57C).⁴² During the Scholl reaction of **57.7** using Iron(III) chloride as an oxidant, the more congested mode of cyclization, as well as formation of a carbon-carbon bond across the fjord region afforded PAH **57.9** in 95% yield. The observed result the *cisoid* mode of cyclization was attributed to the uneven distribution of orbital coefficients about the central ring (after a single annulation **57.8**), with the site of the second annulation reaction being larger than the other *ortho*-carbon.

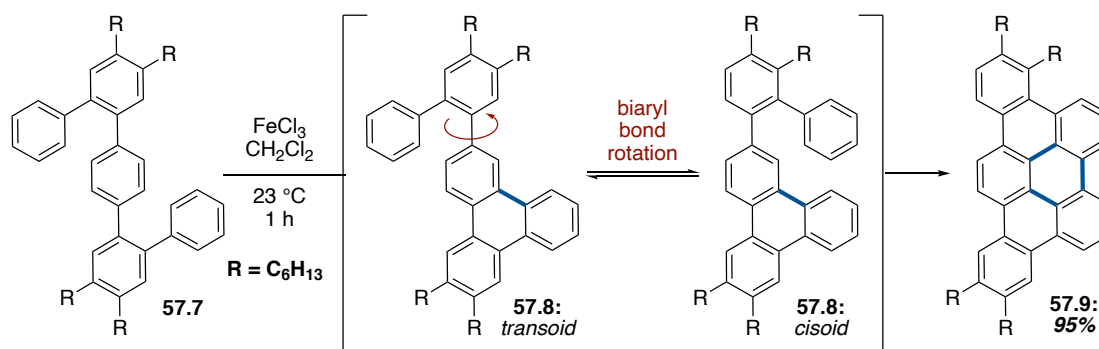
A. Müllen and co-workers synthesis of 57.2



B. Durola and co-workers synthesis of 57.5



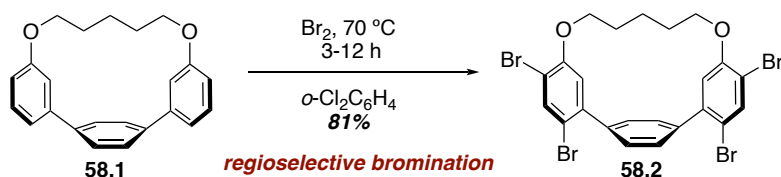
C. Hilt and co-workers synthesis of 57.9 and computational investigation



Scheme 57. Unexpected regiochemical outcomes of the Scholl reaction.

2.3. Annulative pi-extension of a homologous series of strained benzenoid macrocycles using the Scholl reaction

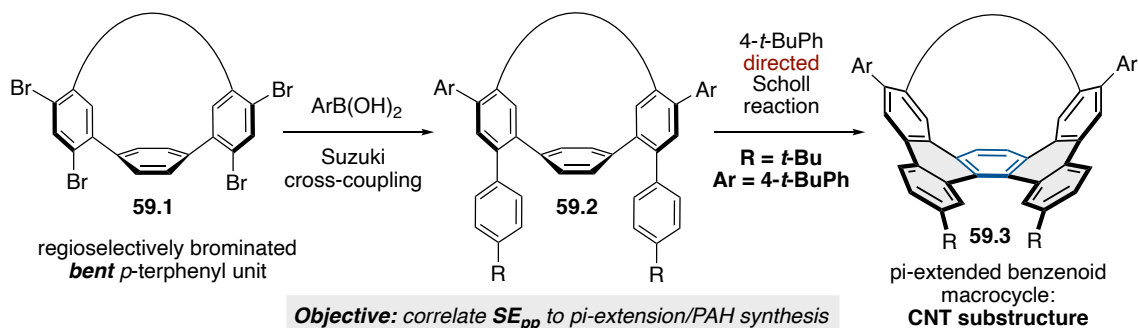
In 2015, Merner and co-workers reported the non-cross-coupling-based approach to *para*-phenylene-bridged benzenoid macrocycles as described in chapter 1 (Scheme 19). In their initial report, regioselective bromination of a 17-membered *p*-terphenyl-containing macrocycle was achieved to afford **58.2** in 81% yield (Scheme 58).⁴³ It is noteworthy to mention that the central, and most strained arene unit of **58.1** does not undergo bromination or any strain-relief driven process. The remaining sections of this chapter are focused on the synthesis of a homologous series of *p*-terphenyl containing macrocycles, late-stage installation of bromide functional group handles in regioselective manner, and the exploration of annulative pi-extension methods that lead to the conversion of bent benzene units to bent PAH units.



Scheme 58. Regioselective bromination of **58.1**.

The main objective of this work was to extensively explore oxidative arylation reactions on a homologous series of strained *p*-terphenyl-containing macrocycles, which can be viewed as model substrates of $[n]$ CPPs. The degree of strain energy imposed on the *p*-terphenyl nuclei of these benzenoid macrocycles would be controlled, or fine-tuned, by manipulating the length of the alkoxy bridging unit of the cyclophanes. This would enable a detailed investigation of pi-extension reactions, and our understanding of the interplay of two competing energetic factors – strain and aromaticity. Ultimately, these studies would allow for the correlation of SE within the macrocycle and *p*-phenylene units with the success or failure of the Scholl reaction and speak more to its synthetic utility in pi-extension reactions of strained benzenoid systems (Scheme 59). At the time of these initial investigations, only a few examples of the Scholl reaction on curved benzenoid systems had been reported (see Schemes 54, 55 and 56). This was due to limited synthetic methods for the late-stage installation of useful functional groups, to enable the elaboration of $[n]$ CPPs into viable arylation precursors. At the time of these studies, the latter required multistep synthesis for each derivative to be

investigated. Inspired by the work of Durola and co-workers (Scheme 57B), we sought to exploit the 4-*tert*-butylphenyl group as the arene unit for pi-extension at the bent *p*-terphenyl system of **59.2** to avoid undesired, unwanted, or uncontrollable rearrangement reactions. These studies will enhance our understanding of reaction mechanisms that lead to possible by-product formation by rearrangement or fragmentation reactions en route to pi-extended macrocycles such as **59.3**.

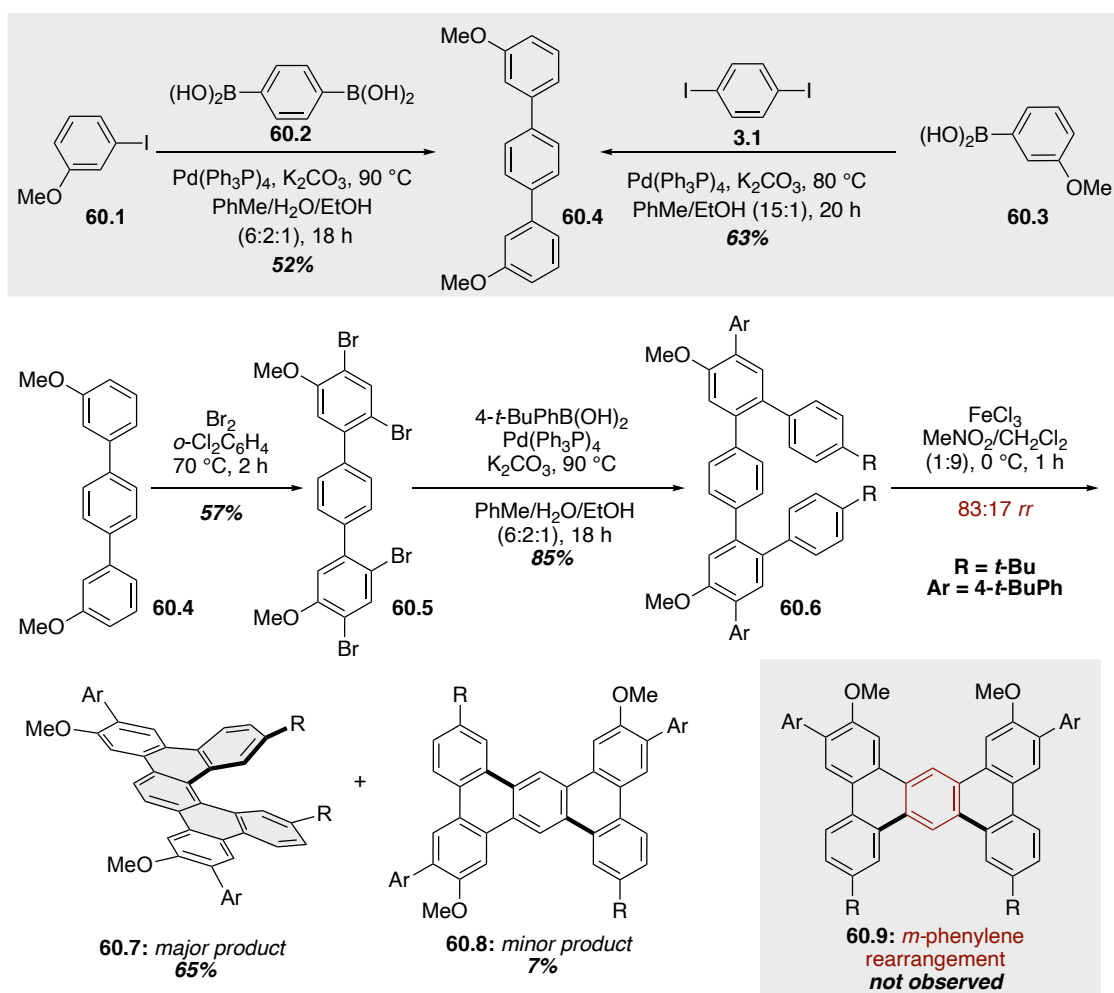


Scheme 59. Overview of APEX investigation on bent *p*-terphenyl-containing macrocycles.

2.3.1 Synthesis of a model *p*-terphenyl and its subsequent pi-extension via Scholl reaction

Both Müllen and Durola had shown that the cyclodehydrogenation reactions of substituted planar *p*-terphenyl derivatives afforded cyclization products that proceed through a more sterically/congested conformation (Scheme 57A and 57B). This was encouraging for the planned APEX study. To understand whether or not electronics (alkoxy substituents on the *p*-terphenyl) has an effect on the mode of cyclization or regiochemical outcome of Scholl reaction, a planar, non-macrocylic *p*-terphenyl derivative **60.6** was synthesized (Scheme 60). 3,3''-Dimethoxy-*p*-terphenyl (**60.4**) was synthesized using two different Suzuki cross-coupling-based protocols. The first involved a reaction of 3-iodoanisole (**60.1**) with 1,4-benzenediboronic acid (**60.2**) to give **60.4** in 52% yield. Simple switching the cross-coupling partners to 3-methoxyphenylboronic acid (**60.3**) and 1,4-diiodobenzene (**3.1**), with slightly modified reaction conditions, afforded **60.4** in an improved 63% yield. Subjecting **60.4** to an excess of bromine in *ortho*-dichlorobenzene at 70 °C for two hours, afforded tetrabromo-*p*-terphenyl **60.5** in 57% yield. The tetrabromide was converted to 4,4'',6,6''-tetrakis(4-*tert*-butylphenyl)-3,3''-dimethoxy-*p*-terphenyl (**60.6**) in 85% yield using a Suzuki cross-

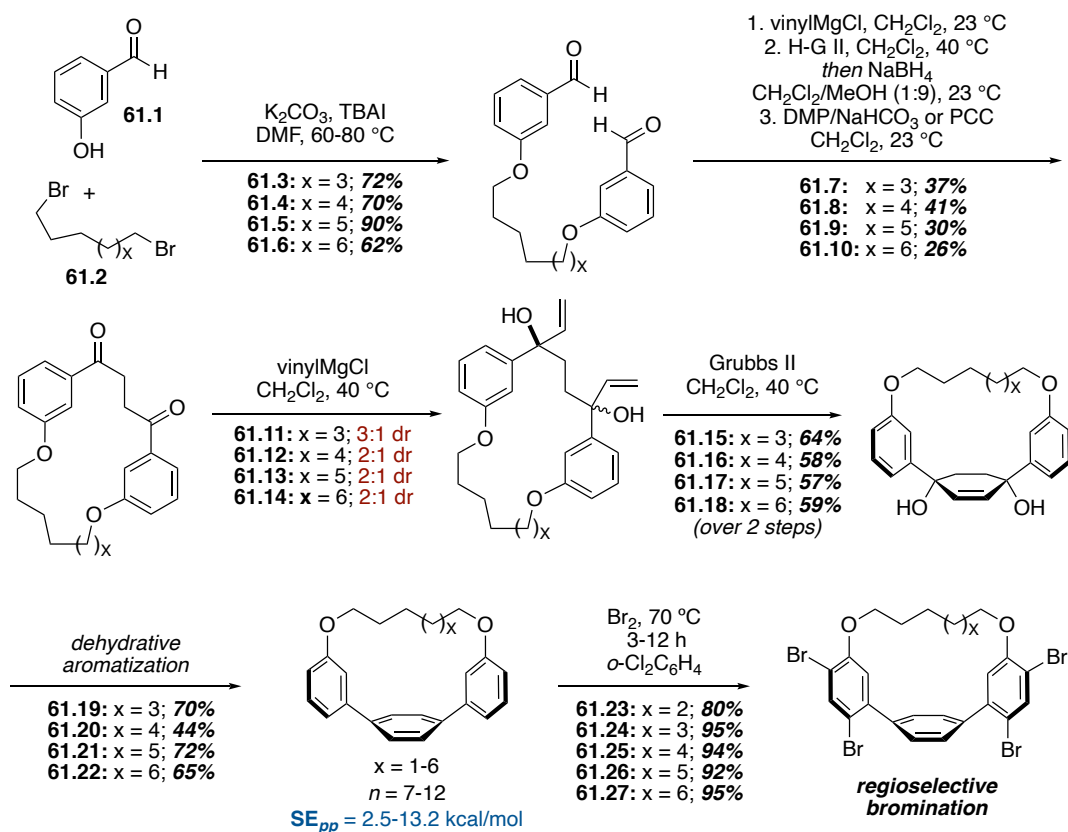
coupling reaction with 4-*tert*-butylphenylboronic acid. Treatment of **60.6** with 8.0 equivalent of iron(III) chloride as a solution in 1:9 nitromethane/dichloromethane led to the formation of [5]helicene **60.7** (*cisoid* cyclization) in 65% yield and tetrabenz-(*a,c,h,j*)anthracene (*transoid* cyclization) derivative **60.8** in 7% yield. Direct analysis of the crude reaction mixture indicated that the regioselectivity of this reaction was 83:17 *r.r.* and that **60.9**, the result of *para*- to *meta*-phenylene rearrangement followed by cyclodehydrogenation, is not formed. The results of this study suggested that the presence of alkoxy substituents in the 3 and 3''-positions of an arylated *p*-terphenyl systems does not affect the regiochemical outcome of this reaction and no 1,2-aryl migrations can be attributed to electronic factors.



Scheme 60. Scholl-based pi-extension of model *p*-terphenyl **60.6**.

2.3.2 Regioselective bromination on *p*-terphenyl containing macrocycles

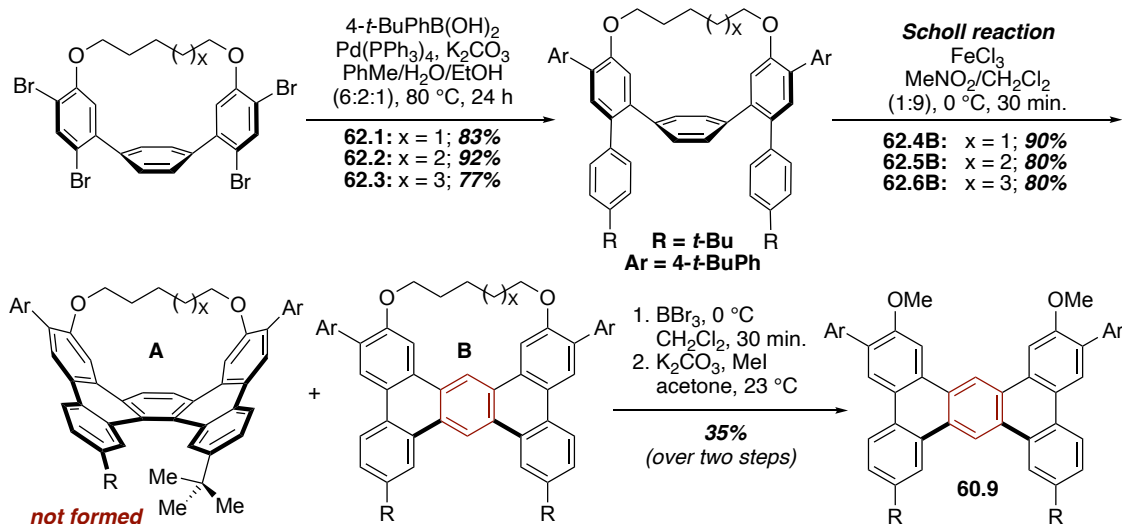
The synthesis of bent *p*-terphenyl-containing macrocycles with alkyloxy bridging units ($n = 4-8$ atoms, 14-18 member macrocycles, respectively) from macrocyclic-1,4-diketones was discussed in the previous chapter (see section 1.4, Scheme 19). A homologous series of larger *p*-terphenyl containing macrocycles (*i.e.*, 19-22 member macrocycles, **61.19-63.22**, Scheme 61) were synthesized starting from 3-hydroxy benzaldehyde (**61.1**) using our four-stage, six-step synthetic protocol. Upon completing the synthesis of a homologous series of *p*-terphenyl-containing macrocycles (19-22 member macrocycles, $n = 9-12$) **61.19-61.22**, which do not succumb to protic acid-mediated rearrangements, these six homolog were subjected to the bromination reaction described in Scheme 58.⁴³ Once again, the reaction proved to be completely regioselective, furnishing only tetrabromides (18-22 member macrocycles, $n = 8-12$) **61.23-60.27** in 80-95% yield with no strain relief bromination of the central *para*-phenylene rings.



Scheme 61: Synthesis of brominated *p*-terphenyl macrocycles **61.23-61.27**.

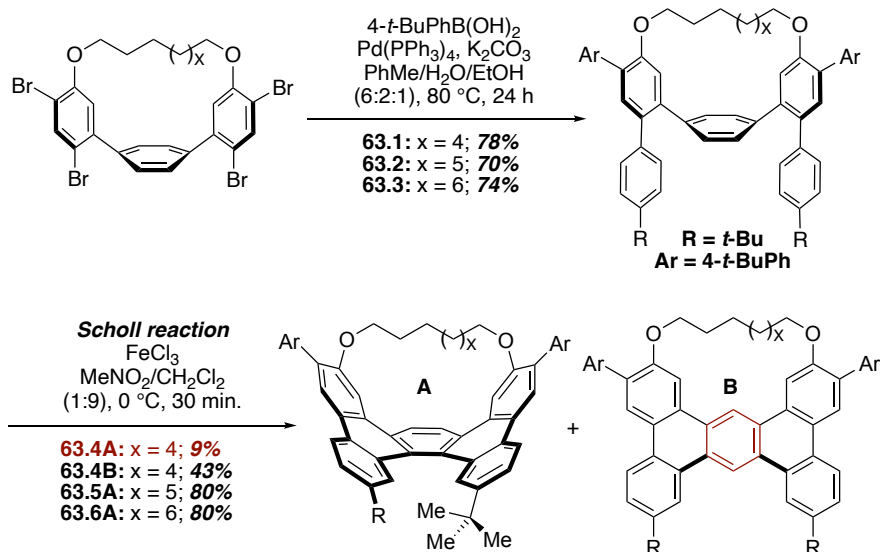
2.3.3 Synthesis of arylated macrocycles **62.1-62.3** and **63.1-63.3**, and an investigation of their Scholl reaction

With a series of brominated homologs in hand, focus was placed on the conversion these products to tetraarylated derivatives via a Suzuki cross-coupling reaction, and to subsequently investigate their Scholl reactions. Under standard Suzuki cross-coupling conditions ($\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , $\text{PhMe}/\text{H}_2\text{O}/\text{C}_2\text{H}_5\text{OH}$ (6:2:1) at 80 °C), previously reported by Müllen and Durola, the four-fold arylation reactions of bromides **58.2** and **61.23-61.27** proceeded in high yield (70-92%; Scheme 62 and Scheme 63) to furnish six arylated homologs **62.1-62.3** and **63.1-63.3** for the Scholl reaction study. Tetraarylated *p*-terphenyl macrocycles **62.1-62.3** and **63.1-63.3** were subjected to the identical Scholl reaction conditions that led to the successful synthesis of helicene derivative **60.7** to the most strained homologs, **62.1-62.3**, gave a single PAH-containing macrocycle in 80-90% yield. The ^1H NMR spectra of the macrocycles produced from the Scholl reactions of **62.1-62.3** showed nine aromatic signals, with a pair of low-field singlets at ~9.5 and 9.2 ppm. This pointed to the structure of tetrabenz(*a,c,h,j*)anthracene-containing macrocycles **62.4B**, **62.5B** and **62.6B**, which could result from 1,2-aryl shift reaction at some point along the reaction pathway; however, there are several possibilities for this rearrangement (see below). The desired *cisoid* pi-extension product would produce only eight aromatic signals in the ^1H NMR spectra of **62.1A-62.3A**, as well as a shielded singlet for the *tert*-butyl protons of the desired helicene (see Supporting Information, Appendix 2). The PAH structure contained within these macrocyclic systems was ultimately confirmed to be that of tetrabenz(*a,c,h,j*)anthracene **60.9** when a BBr_3 -mediated cleavage of alkyloxy bridging unit of **62.4B**, followed by methylation of the resulting diol, produced a PAH that was virtually identical to that of **60.8** (Scheme 60) with the exception of two low-field, bay-region singlets at 10.10 and 9.73 ppm.



Scheme 62. Synthesis of arylated macrocycles **62.1-62.3** and investigation of their Scholl reactions.

At this juncture, homologs containing a central *para*-phenylene unit with greater than 4.9 kcal/mol of SE led only to the formation of tetrabenz(*a,c,h,j*)anthracene-containing macrocycles. The remaining three homologues, **63.1-63.3**, contain longer alkoxy bridging units and thus, less strained *para*-phenylene rings ($\text{SE}_{pp} = 2.5\text{-}4.3$ kcal/mol). Subjecting macrocycles **63.2** ($\text{SE}_{pp} = 3.0$ kcal/mol) and **63.3** ($\text{SE}_{pp} = 2.5$ kcal/mol) to the Scholl reaction conditions described above resulted in the formation of desired annulation products **63.5A** and **63.6A** respectively as single regioisomers in 80% yield (Scheme 63). No rearrangement cyclization was observed for these homologues. In the case of arylated macrocycle **63.1** ($\text{SE}_{pp} = 4.3$ kcal/mol), pi-extension to afford the desired PAH-containing macrocycle **63.4A** does take place; however, it is accompanied by the formation of **63.4B**. The ratio of annulation products was determined to be 83:17 (^1H NMR analysis) in favor of the rearranged isomer. Nonetheless, regioisomeric macrocycles **63.4A** (9%) and **63.4B** (43%) could be separated and characterized. To test the stability of **63.4A**, it was resubjected to identical reaction conditions under which it was formed. No decomposition or subsequent rearrangement was observed, and **63.4A** was quantitatively recovered.



Scheme 63. Synthesis of arylated macrocycles **63.1-63.3** and investigation of their Scholl reactions.

All attempts to grow crystals suitable for X-Ray crystallographic analysis of **63.4A** were unsuccessful. However, an optimized geometry was obtained using density functional theory calculations with B3LYP functional and 6-31G* basis set (Figure 4). The structure of **63.4A** is both twisted and bent due to the presence of the [5]helicene moiety and the octyloxy group bridging the PAH structure, respectively. The end-to-end bend of the dibenzo[*f,j*]picene unit of **63.4A** is 31.8°, and the SE of this pi-system is 46.9 kcal/mol. The former was calculated by measuring the angle between the two most distant carbon atoms of the PAH and the centroid of the central aromatic ring of **63.4A**. The latter was obtained using a method previously reported by Höger, Grimme, and co-workers.⁴⁴ Upon annulation about the bent *p*-terphenyl backbone of **63.4**, 27.7 kcal/mol of SE is introduced into the macrocyclic structure of **63.4A** (SE_{61.4} = 19.2 kcal/mol). The torsional twist angle (θ) of the dibenzo[5]helicene unit of **63.4A** is 23.3°, which is smaller than θ of 25.1° measured for the unperturbed dibenzo[5]helicene **60.7**.⁴⁵ Bending the dibenzo[5]helicene unit of **63.4A** compresses the angle θ and brings the *tert*-butyl groups closer together, which could raise the activation barrier for the annulation reaction of **63.1** and related homologues, relative to that of **60.7**. The distance between the fjord region carbon atoms for **63.4A** is only slightly smaller than that of **60.7** (*cf.* 3.03-3.04 Å).

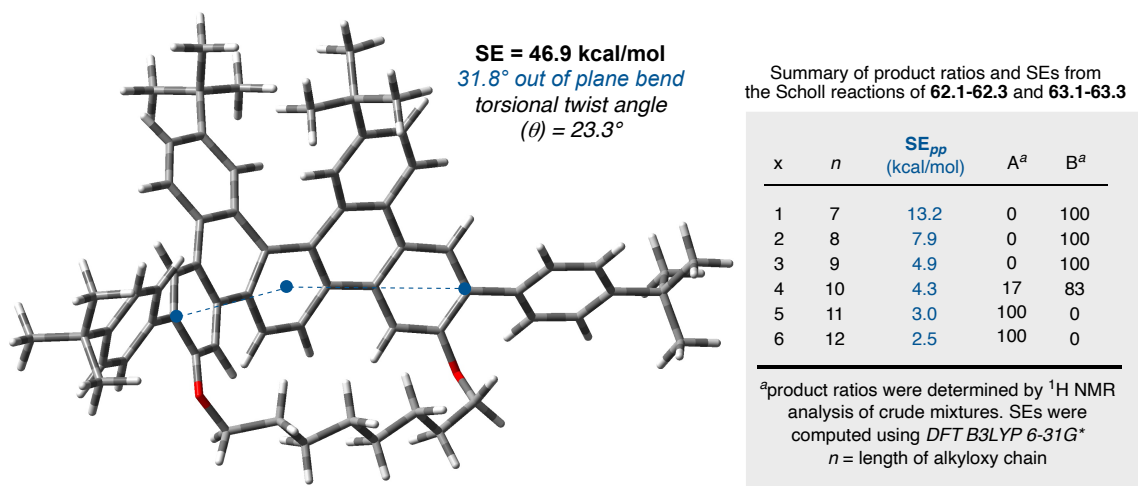


Figure 5: Optimized geometry of **63.4A** (DFT-B3LYP 6-31G*) and SE summary of Scholl reactions.

2.3.3.1 Photophysical properties of **60.7** and **63.4A**

The absorption spectra for **60.7** and **63.4A** show four absorption bands with λ_{\max} of 365 and 368 nm, respectively (Figure 5). Unlike other bent PAHs, which are typically blue-shifted relative to the unperturbed, planar compound, the dibenzo[*f,j*]picene, or dibenzo[5]helicene, unit of **63.4A** is only slightly blue shifted. Time-dependent DFT calculations (B3LYP/6-31G* level of theory) predict a red shift in the electronic absorption spectra of **63.4A** relative to that of **60.7**, with λ_{\max} of 351 and 345 nm, respectively. The fluorescence spectra of **63.4A** and **60.7** shows two emission bands with λ_{\max} of 438 nm for both compounds. The fluorescence quantum yields (emission efficiencies) of **63.4A** and **60.7** were measured to be 0.25 and 0.12, respectively. The increased emission efficiency of **63.4A** is likely due to constraints imposed by alkyloxy bridging unit, which makes for a more ridged dibenzo[5]helicene fluorophore. To the best of our knowledge, **63.4A** is the first example of a bent analogue of this PAH, and it appears that bending an already twisted PAH unit does not have a pronounced effect on the photochemical properties of dibenzo[*f,j*]picene.

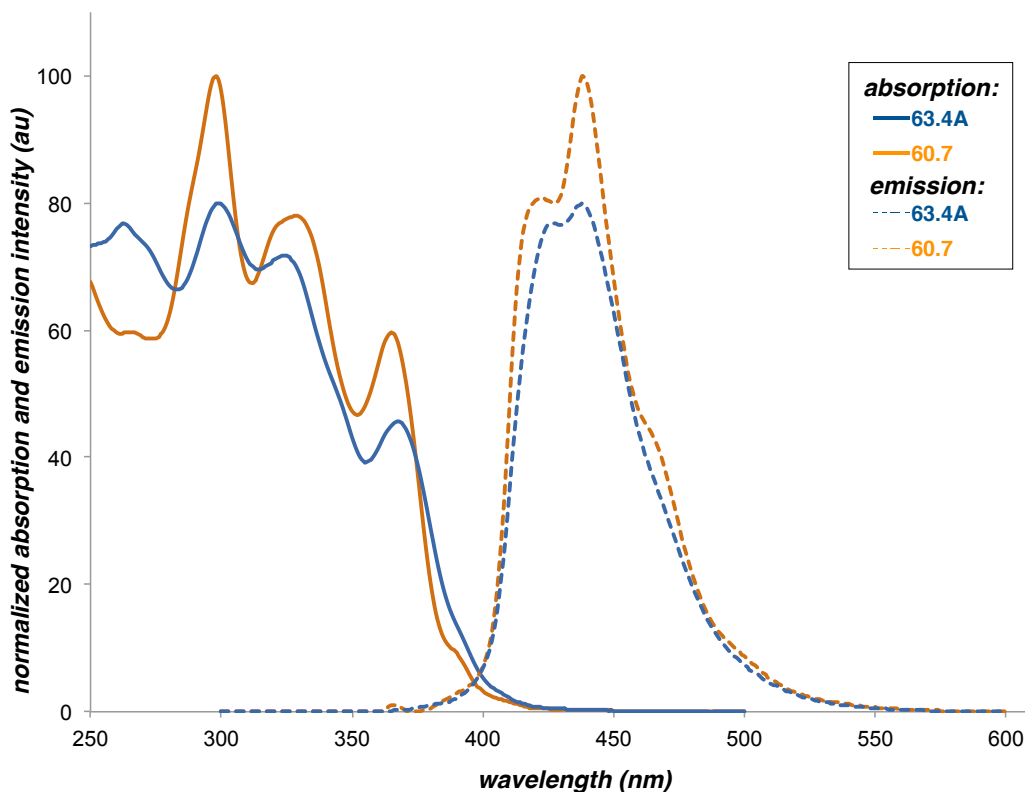


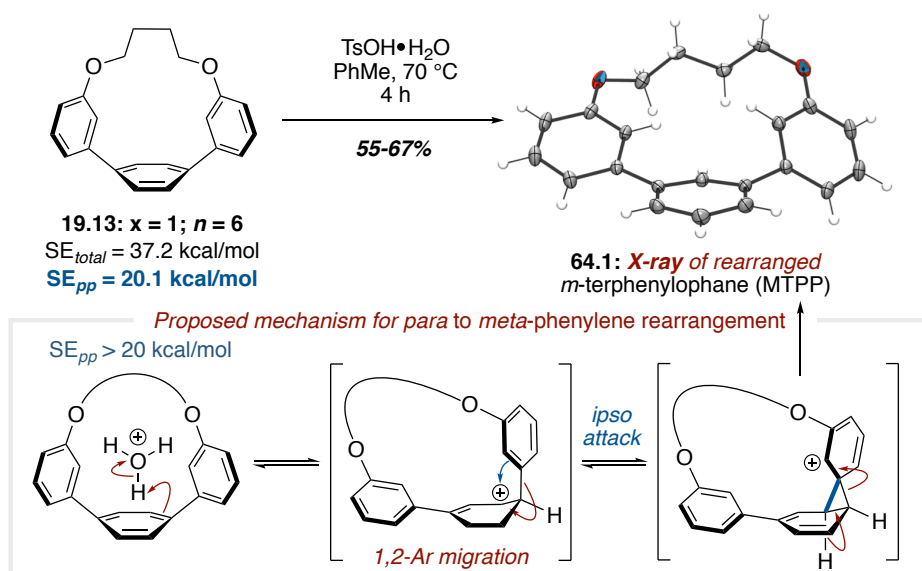
Figure 6: UV-vis and fluorescence spectra of **63.4A** (blue, 2.0×10^{-5} M) and **60.7** (orange, 5.0×10^{-5} M). Fluorescence spectra were measured with 365 nm excitation.

2.4 Time course NMR experiments and mechanistic investigation of the Scholl reaction of strained *p*-terphenyl-containing macrocycles

The synthetic investigations presented above, indicated that the Scholl reaction should be applicable to the pi-extension of strained benzenoid systems that contain a strain energy less than 4 kcal/mol when focusing solely on the *p*-phenylene ring system to be annulated. While this is a useful guiding principle, there are other factors that come into play when considering such pi-extension reactions. These include, the newly formed PAH and its associated aromatic stabilization energy (ASE), the total amount of strain that is introduced into the macrocyclic backbone of the structure under investigation, as well as the molecular orbital preference for such cyclizations to occur. In the case of the first two points, we sought to investigate the stage at which the rearrangement reactions take place in the strained *p*-terphenyl-containing macrocycles studied above. To do this, we subjected the four most strained homologs **62.1-62.3** and **63.1** as well as their unsubstituted derivatives to a ^1H NMR time course study. The objective of this study was to pinpoint where the rearrangement takes place.

2.4.1 Time course NMR experiment design and results

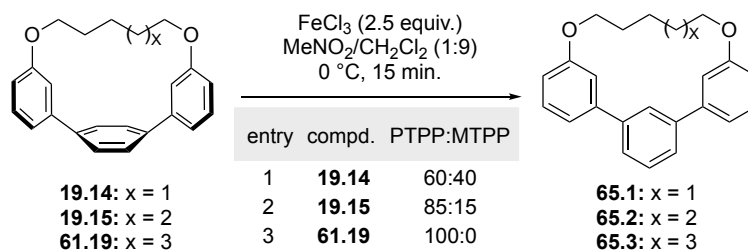
The oxidative arylation reaction conditions that were successfully employed above required the use of FeCl_3 . All other Lewis or protic acid-mediated conditions led to the recovery of starting materials, *i.e.*, no pi-extension, or partial decomposition of the starting material. Moreover, in order to facilitate the desired cyclodehydrogenation process, the reaction temperature had to be kept at 0 °C, and a 1:9 ratio of nitromethane and dichloromethane was found to be the optimal solvent combination, where nitromethane is essential for dissolving FeCl_3 . During these studies, it was found that up to 28 kcal/mol of strain energy could be introduced into the macrocyclic backbone of a 20-membered, *p*-terphenyl-containing macrocyclic ring system, while affording a pi-extended, dibenzo[*f,j*]picene unit that was both curved and twisted. In smaller macrocyclic systems, only a rearranged PAH product was afforded; however, it was unclear as to when the rearrangement reaction occurred. The desired Scholl reaction involves the formation of two new carbon-carbon bonds onto a strained *p*-terphenyl ring system, and in particular, onto a strained, central *p*-phenylene ring. The latter bears most of the strain within the macrocyclic framework of the homologs investigated. Since each carbon-carbon bond formation en route to the desired dibenzo[*f,j*]picene results in an increase of strain energy within the macrocycle, both experimental and computational investigations of these Scholl reactions was pursued.



Scheme 64. *para* to *meta*-phenylene rearrangement in strained *p*-terphenyl-containing macrocycles

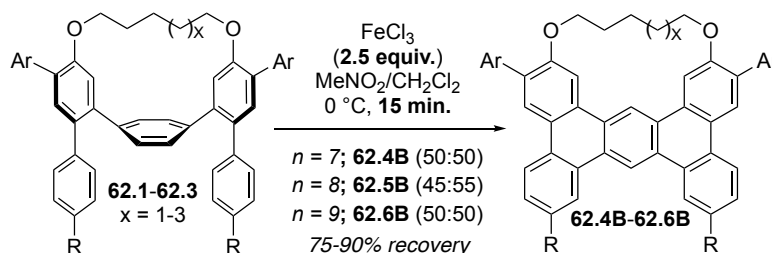
During the development of a dehydrative aromatization protocol for synthesizing highly strained *p*-terphenyl-containing macrocycles from 2015-2017, Merner and co-workers reported that the central *p*-phenylene ring of the 16-membered macrocyclic homolog of **19.13** was susceptible to protic acid-mediated rearrangement (Scheme 64). This only occurred in systems where the central *p*-phenylene ring had greater than 20 kcal/mol of SE. Specifically, the rearrangement was from a *p*-phenylene unit to a less strained *m*-phenylene unit (Scheme 65). It is conceivable that such a reaction takes place when macrocycles **19.14**, **19.15** and **61.19** are subjected to the Lewis acid-mediated conditions of the Scholl reaction, which would account for the observed rearrangements in the more strained homologs. To better understand the stability of the central *p*-phenylene rings under these reaction conditions, both arylated and non-arylated *p*-terphenyl-containing macrocycles were subjected to Scholl reaction conditions where the progress of these reactions were monitored at specific time intervals with a controlled amount of FeCl₃ oxidant. In the initial screening of the Scholl reaction conditions presented in Scheme 62, it was determined that 8.0-10.0 equivalents, *i.e.*, 4.0-5.0 equivalents per C-C bond formed, were required to convert 100% of the starting material to product(s). Thus, it was reasoned that 2.5 equivalents of FeCl₃ would result in incomplete conversion of the starting material and enable the observation of rearranged or partially cyclized intermediates, which would help us better understand the mechanism of this reaction on strained *p*-terphenyl-containing macrocycles.

Subjecting three of the most strained, non-arylated, *p*-terphenyl-containing macrocycles to the designed experimental conditions gave interesting results (Scheme 65). In the case of the most strained homolog **19.14**, a 17-membered macrocyclic ring system, a 60:40 ratio of unchanged starting material (PTPP) and rearranged (MTPP) product was observed by ¹H NMR analysis. It should be noted that no significant starting material decomposition was observed under these conditions. In the case of the less strained, larger macrocyclic system **19.15**, an 85:15 ratio of PTPP to MTPP was obtained, while the 19-membered macrocyclic homolog **61.19** did not succumb to PTPP to MTPP rearrangement, as only starting material was recovered after 15 minutes of reaction time.



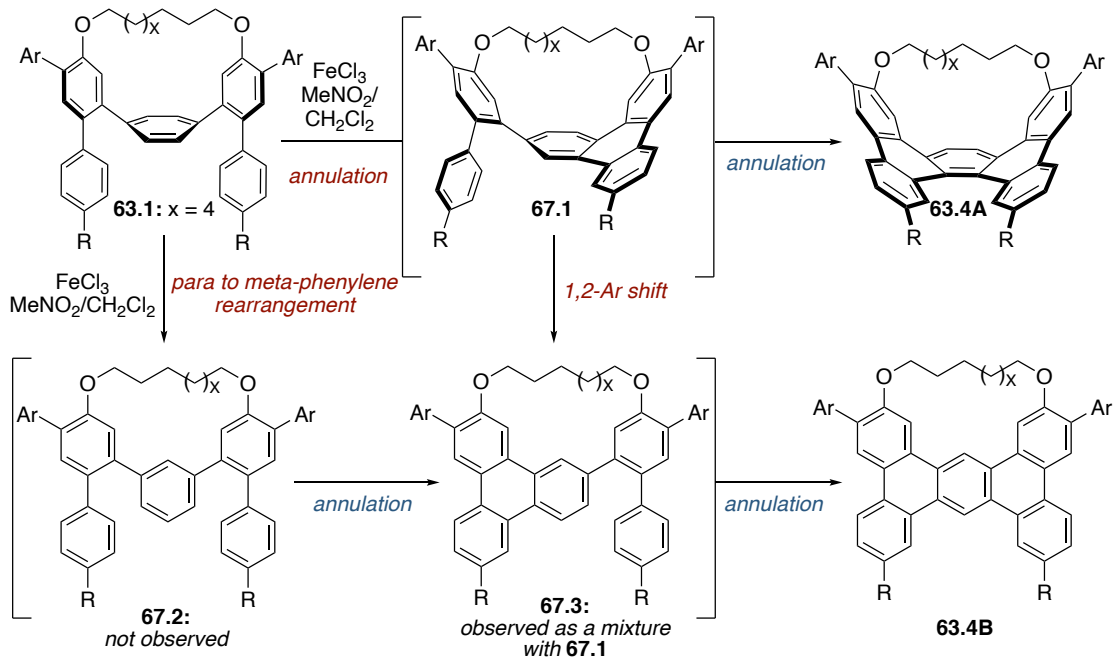
Scheme 65. Extent of *para* to *meta*-phenylene rearrangement.

The results of the ^1H NMR time course experiments presented in Scheme 65 indicate that the central *p*-phenylene ring is not susceptible to *m*-phenylene rearrangement in the case of **61.19** and only partially undergoes rearrangement in the case of **19.15**. Thus, it was interesting to find that when the arylated derivatives of these homologs, **62.1** and **62.3**, were subjected to the same Scholl reaction conditions that essentially a 50:50 ratio of starting material and rearranged products was afforded (Scheme 66). The same result was obtained for the more strained arylated homolog **62.1**; however, the extent of rearrangement, followed by cyclodehydrogenation was in line with the rearrangement observed for the non-arylated homolog **19.14**. The results obtained for **62.2** and **62.3** seems to indicate that the rearrangement reaction, which results in the formation of **62.5B** and **62.6B**, is occurring at a different stage than that of **61.19**. It should be noted that adding aryl substituents to the macrocyclic backbone of **62.1-62.3** does not significantly change the SE of the macrocyclic backbone of these compounds, when compared to their non-arylated analogs. In fact, the *ortho*-aryl substituents about the *p*-terphenyl nucleus of these macrocycles should confer improved kinetic stabilization of the strained, central *p*-phenylene ring system, by partially blocking an approaching electrophile from interacting with the *ipso*-carbon atoms. Electrophilic addition or protonation of these positions leads to strain-relief driven rearrangements, as presented in Scheme 64.



Scheme 66. Extent of rearrangement/annulation in arylated derivatives.

The most strained homolog that afforded the desired dibenzo[*f,j*]picene-based macrocyclic product when subjected to the Scholl reaction was **63.1**. A more detailed analysis of this reaction, via NMR time course experiments, enabled the identification of a partially annulated product **67.1** and a partially annulated-rearranged product, **67.3** (Scheme 67). It should be noted that these intermediate products were never observed in the case of the former examples – **62.1-62.3**. Again, no direct PTPP to MTPP (**63.1** to **67.2**) rearrangement was observed when 2.5 equivalents of FeCl₃ was employed; however, the ratio of starting material to products, **63.1:63.4A:63.4B** was found to be 74:7:19. TLC analysis of this reaction indicated that three new products had formed, with one of these being quite difficult to see at lower reaction concentrations. The major components of the crude reaction mixture were **63.1**, **63.4A**, and **63.4B**, with the latter two compounds corresponding to two of the three new components produced. Upon scaling this reaction up, and subjecting it to the originally designed ¹H NMR time course conditions, enough of the faint product band could be isolated from a preparative TLC purification of the reaction mixture. ¹H NMR analysis of this band indicated that both **67.1** and **67.3** were produced in a 2:1 ratio. This seems to indicate that the initial (desired) cyclodehydrogenation reaction to afford **67.1** is preferred, and that the rearrangement to afford **67.3** takes place occurs after the first annulation reaction. The complete absence of **67.2** in this and all other reactions investigated above supports this 1,2-aryl shift pathway and not an initial PTPP to MTPP rearrangement, *i.e.*, **63.1** to **67.1**.

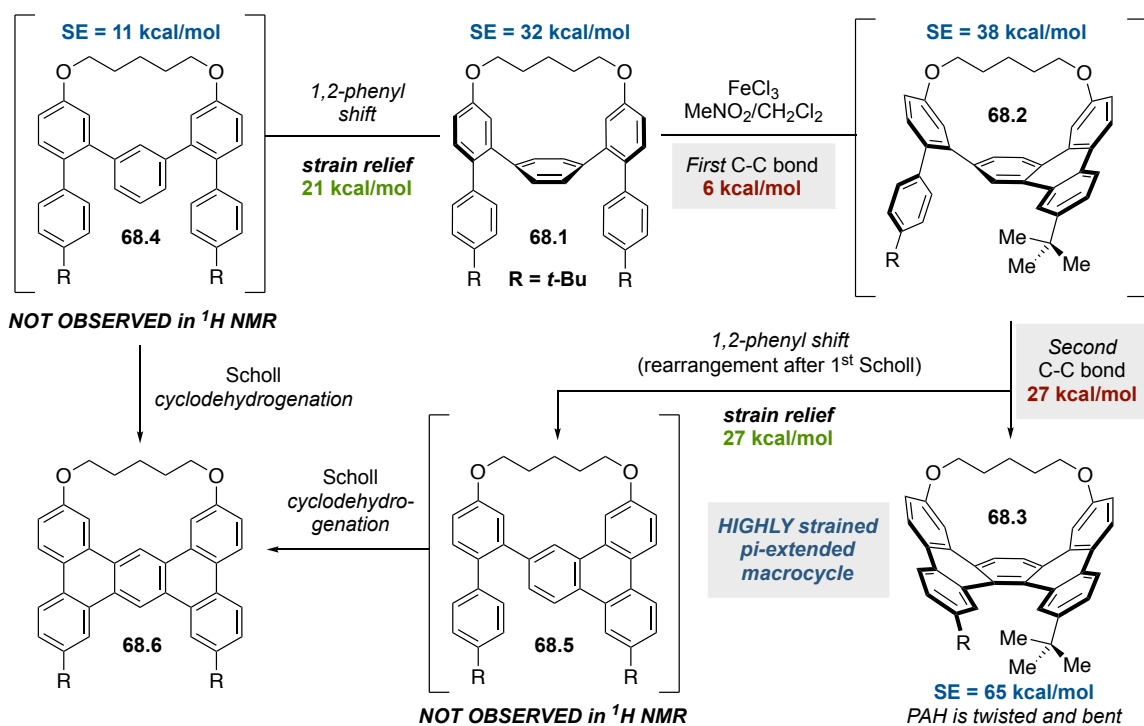


Scheme 67. Time course NMR results for **63.1**, $x = 4$.

2.4.2 Preliminary computational results of the Scholl reactions of **62.1-62.3**

Optimized geometries of the proposed intermediates that could lead to the formation of the rearranged PAH **62.1** ($x = 1$; $n = 7$) were computed using DFT calculations at the B3LYP level of theory. To simplify these calculations, the 4-*tert*-butylphenyl groups at the 6 and 6"-positions were removed. Macrocycle **68.1**, an analog of **62.1**, was found to have a SE of 32 kcal/mol. The initial cyclization/C-C bond forming reaction of **68.1** to afford **68.2** is predicted to introduce an additional 6 kcal/mol of SE into the macrocyclic structure (Scheme 68). Based on the application of the Scholl reaction in the synthesis of warped nanographenes by Itami and co-workers, and the synthesis of severely twisted helicenes by Durola and co-workers, and the studies presented above, the introduction of this amount of SE is within reach of the Scholl reaction. A second annulation reaction to furnish the desired PAH **68.3** is predicted to add an additional 27 kcal/mol of SE, which appears to be prohibitive for this homolog, based on experimental results. A 1,2-phenyl shift from **68.1** to the **68.4**, *i.e.*, *para* to *m*-phenylene rearrangement would relieve 21 kcal/mol of SE, while a 1,2-phenyl shift from **68.2** to **68.5** would relieve approximately 27 kcal/mol of SE. The formation of **68.4** was not observed in any of the ^1H NMR time course experiments conducted. As such, we propose that a 1,2-phenyl shift from **68.2** is likely the preferred pathway for this reaction

in homologs **62.1-62.3** and **63.1**. Furthermore, the fact that *para* to *m*-phenylene rearrangement does not proceed to the same extent as the in non-arylated macrocycles with similar SEs, such as **19.14** and **19.15** (Scheme 65), and not at all for **61.19**, is suggestive that rearrangement takes place at the stage of the **68.2**. Finally, the characterization of an intermediate akin to **67.3** in the case of the Scholl reaction of **63.1** further supports this mechanistic assertion.

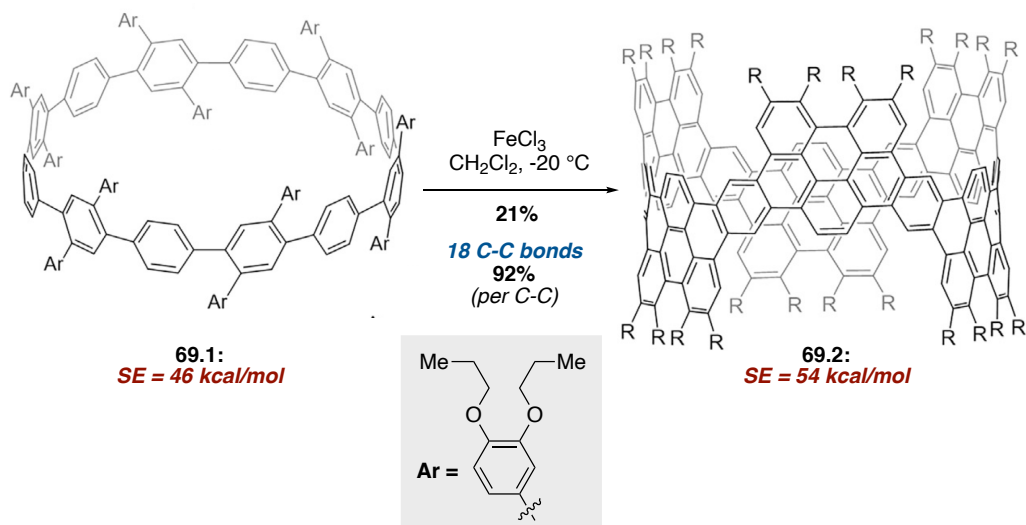


Scheme 68. Computationally derived SEs for C-C bond formations during the Scholl reaction of **68.1**.

2.5 Concluding remarks

Nearly three years of developing synthetic approaches to a homologous series of strained, *p*-terphenyl-containing macrocycles, which can be viewed as model substrates of [*n*]CPP, and experimental investigation of their Scholl reactions has culminated in the following observation: Oxidative arylation reactions can be used for pi-extension of benzenoid macrocycles as long as the SE of the central *p*-phenylene ring to be annulated upon is less than 4 kcal/mol. Of course, this is a general synthetic guideline, and there are many other factors that need to be considered, including the total amount of SE that is introduced into the newly formed PAH, and subsequent annulation reactions that lead to further pi-extension. Nonetheless, the studies presented in this chapter have enriched our understanding of the Scholl reaction as it applies to

annulation of curved aromatic systems. Thus, it was most gratifying to see the application of this strategy by Miao and co-workers in 2019, six months after the publication of our initial communication, to the synthesis of CNB **69.1** using the Scholl reaction of arylated [12]CPP derivative, which our investigations indicated should be possible.⁴⁶



Scheme 69. Synthesis of a (12,12)CNB using a polyarylated [12]CPP derivative.

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Chapter 3 Pi-extension of Benzenoid Macrocycles via Alkyne Annulation: Synthesis of Chiral, Twisted, and Highly Strained Phenanthrene Units

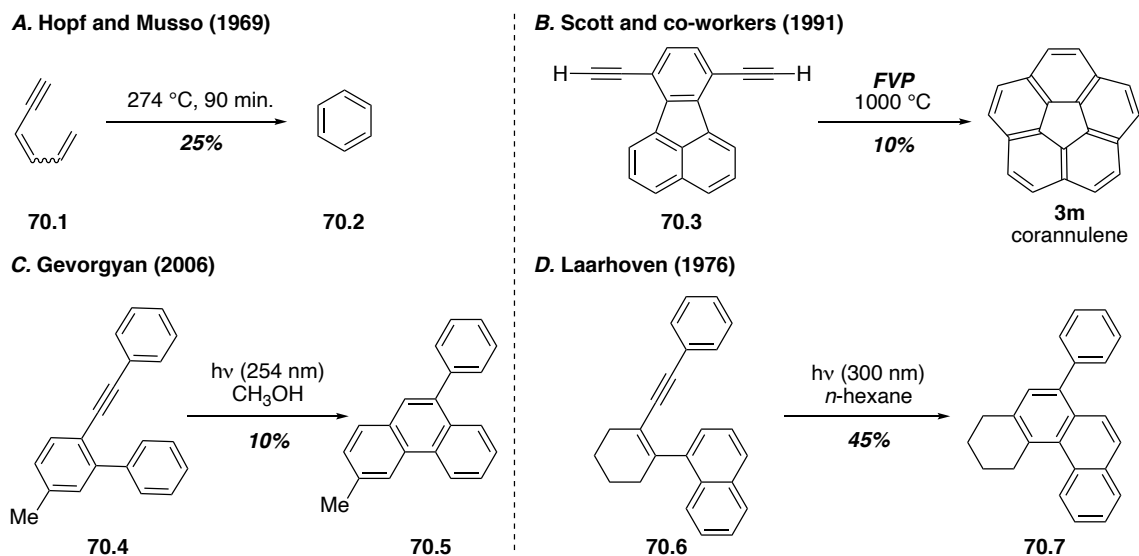
3.1 Introduction

The pi-extension on curved aromatic molecules is a challenging endeavor as was seen in the previous chapter. The success of these reactions depends on the installation of functional groups at selective positions within the molecules that are to undergo pi-extension. In pi-extension reactions that require the induction of strain within the macrocyclic or PAH framework, the gain in aromatic stabilization energy afforded to the new aromatic system must be able to offset the strain energy induced. For these reasons, the synthesis of selectively functionalized, curved benzenoid macrocycles has captivated the synthetic community over the past decade, with an eye on the development of new annulation strategies that can lead to the bottom-up chemical synthesis of carbon nanobelts from carbon nanohoops.

To date, examples describing the successful pi-extension of nanohoops are limited, and only a few synthetic approaches have been reported. These include pi-extension via ring-closing metathesis, Scholl oxidation and Ni-mediated reductive coupling. The synthetic tools available for accomplishing these desired transformations is limited, due to the limited number of functionalized benzenoid macrocycles available to the synthetic community. In last two decades, alkyne benzannulation reactions have become popular for the pi-extension of planar polyaryl derivatives and have even been employed in the synthesis of curved PAHs. The success of these reactions can be attributed to the relatively mild reaction conditions, as well as the rapid construction of large PAHs via cascade reactions. This chapter will focus on the synthesis of benzenoid macrocycles containing strained, functionalized arene units that are amenable to annulation reactions. In particular, pi-extension of *p*-terphenyl-containing macrocycles via alkyne annulation will be featured as the key synthetic tool developed in these investigations.

3.1.1 Catalyst- and reagent-free alkyne benzannulation

In the early literature, alkyne benzannulation of small pi-systems were reported under reagent and catalyst-free techniques. In 1969, Hopf and Musso reported that heating a diastereomeric mixture of 1,3-hexadiene-5-yne **70.1** at 274 °C for 90 minutes leads to the formation of benzene (**70.2**) in 25% yield (Scheme 70A).¹ In 1991, Scott and co-workers reported the synthesis of corannulene (**3m**), a bowl-shaped PAH from **70.3** using flash vacuum pyrolysis (FVP) at 1000 °C (Scheme 70B).² During this transformation a two-fold alkyne benzannulation takes place at elevated temperature. Alkyne benzannulation can also take place via photocyclization (Scheme 70C and 70D), and Gevorgyan and co-workers reported the unexpected formation of phenanthrene **70.5** from 2-ethynylbiphenyl **70.4** during UV measurements of the starting material at 254 nm.³ Laarhoven and co-workers reported the synthesis of **70.7** upon irradiation (350 nm) of enyne substrate **70.6**.⁴ There are only few reported examples of larger nanographene synthesis using photocyclization as a means of alkyne benzannulation. Due to the radical character of these mechanisms, numerous by-products are formed and often products that result in solvent incorporation are isolated.

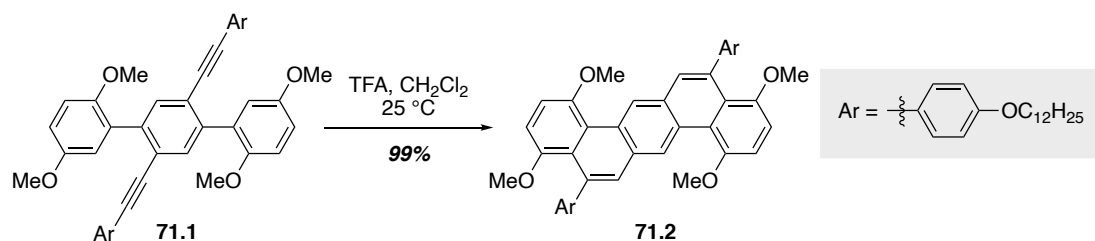


Scheme 70. Catalyst- and reagent-free alkyne benzannulation.

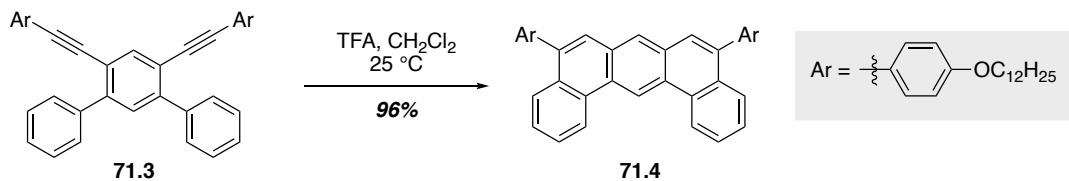
3.1.2 Acid-mediated alkyne benzannulation

Acid-mediated alkyne benzannulation on a substrates having electron-rich aryl groups have been successfully employed in the synthesis of large nanographene materials. One such reaction, the acid-mediated alkyne benzannulation used by Chalifoux and co-workers in the synthesis of pyrene-based GNRs, has already been presented in chapter 2 (section 2.1.2.2, Scheme 46). In 1997, Swager and co-workers reported the two-fold benzannulation reaction on various substitution patterns of a diethynylterphenyl system (Scheme 71).⁵ The TFA-mediated alkyne benzannulation where the aryl group participating in the alkyne benzannulation reaction is oriented in *para* position, such as **71.1**, provided **71.2** in quantitative yield (Scheme 71). Applying the identical conditions to a *meta*-orientated derivative **71.3** gave the desired product **71.4** in 96% yield. However, attempting to cyclize the *ortho*-oriented substrate **71.5** using a Brønsted acid-mediated reaction gave only trace amount of desired [5]helicene product **71.6**, which is sterically strained. The yield of this reaction could be improved by conducting the reaction in presence of silver triflate and iodine. These examples demonstrate that acid-mediated alkyne benzannulation reactions are very effective for planar, unstrained PAH construction, but in case of strained systems, rearrangement reactions can occur in parallel with the desired transformation.

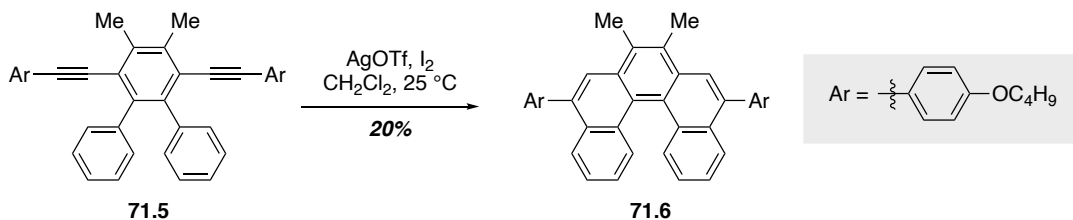
A. Benzannulation for *para*-oriented aryl groups



B. Benzannulation for *meta*-oriented aryl groups



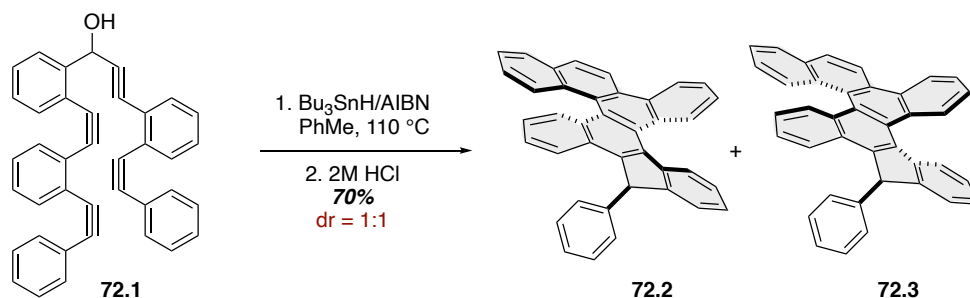
C. Benzannulation for *ortho*-oriented aryl groups



Scheme 71. Brønsted acid-induced alkyne benzannulation of **A.** *para*-, **B.** *meta*-, **C.** *ortho*-substituted terpenyl system.

3.1.3 Radical-mediated alkyne benzannulation

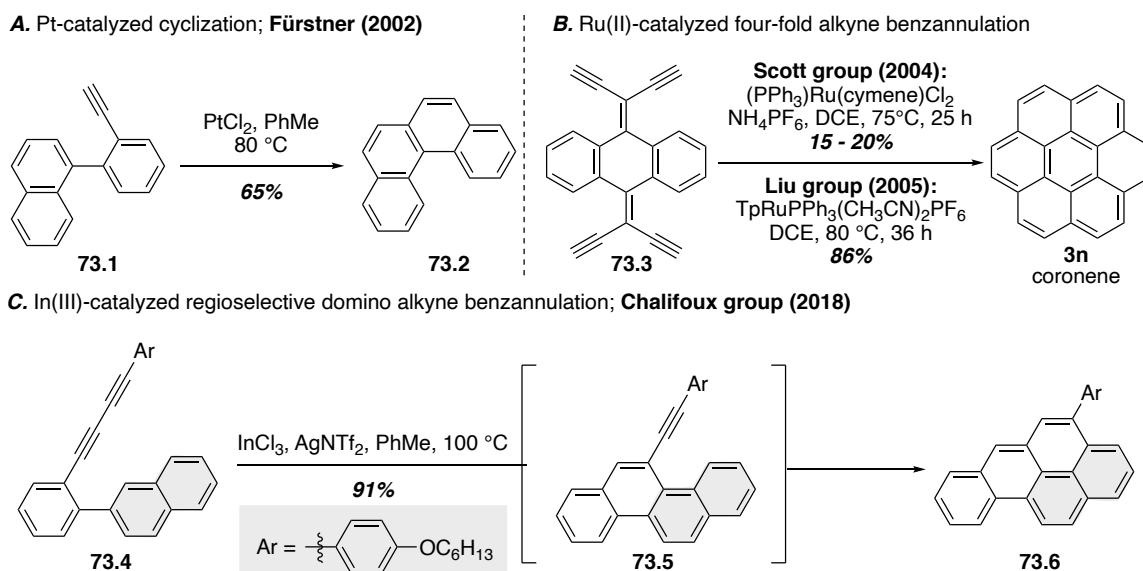
The control of radical-mediated alkyne benzannulation depends on chemo- and regioselectivity of oligoalkynes. Recently, the Alabugin group discovered a tin-mediated radical cascade cyclization of oligoalkynes **71.1** to afford a diastereomeric mixture of helicene products **71.2** and **71.3** by upon formation of four new rings within the polycyclic framework (Scheme 71).⁶ For this example, formation of all-exo cyclization product was regioselectively orchestrated by the propargyl alcohol moiety which directs the initial attack.



Scheme 72. Radical mediated cascade alkyne benzannulation to the formation of diastereomeric helicenes.

3.1.4 Transition metal-catalyzed alkyne benzannulation

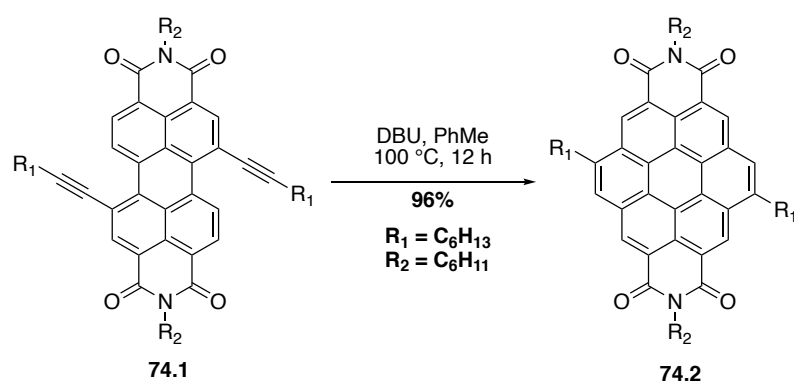
Transition metal activated alkynes can undergo cyclization upon nucleophilic attack from adjacent aromatic rings. In 2002 Fürstner and co-workers reported Pt(II)-catalyzed alkyne benzannulation of *o*-ethynylbiphenyl **73.1** to afford the cyclized product **73.2** in 65% yield (Scheme 73A).⁷ In 2004, Scott and co-workers demonstrated that a four-fold alkyne annulation of bis-endiyne **73.3** could take place to give coronene (**3n**) in 15-20% yield (Scheme 73B).⁸ One year later, the Liu group improved on this transformation by using a more reactive Ru(II) catalyst.⁹ Recently, the Chalifoux group has reported In(III)-catalyzed, domino alkyne benzannulation reactions of diynes such as **73.4** in a high yielding and regioselective manner (Scheme 73C).¹⁰



Scheme 73. Transition metal-catalyzed alkyne benzannulation.

3.1.5 Base-mediated alkyne benzannulation

Coronene tetracarboxdiimides (CDIs) have an aesthetic appeal as solar collectors¹¹ and in lasers.¹² Most recently, these derivatives received attention due to their biological applications,¹³ as well as their promise in the fields of organic light emitting diode (OLED) and organic field-effect transistor (OFET) based materials.¹⁴ Previously, syntheses of these types of materials were lengthy and poor yielding. In 2001, Müllen and co-workers reported the syntheses of CDI derivatives **74.2** using a base-mediated alkyne benzannulation reaction (Scheme 74).¹⁵

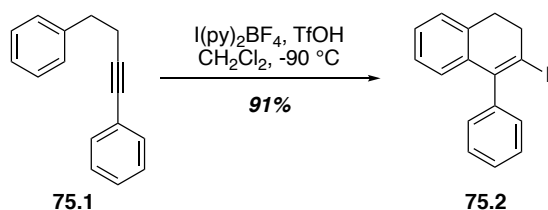


Scheme 74. Base-mediated alkyne benzannulation towards CDIs.

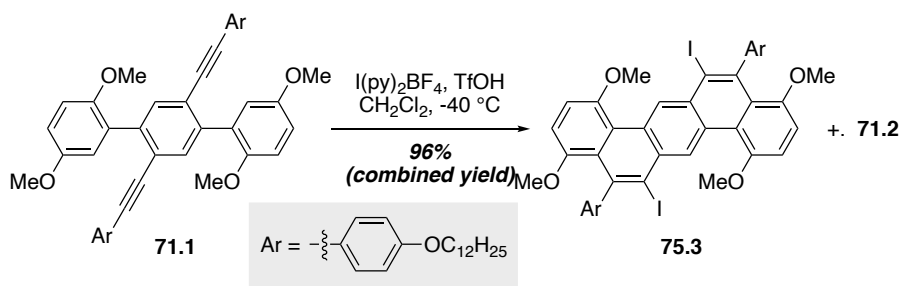
3.1.6 Alkyne benzannulation by iodonium salts or iodine monochloride

Electrophilic iodine reagents are prominent in the way of cyclization reactions of alkynes with neighboring aryl groups that lead to pi-extension. Barluenga is a pioneer in this field, and in 1988, he employed an I(py)₂BF₄ salt as an electrophilic iodine source under relatively mild acidic conditions (TfOH) to produce iodocyclohexene **75.2** from 1,4-diphenyl-1-butyne (**75.1**) in 91% yield (Scheme 75A).¹⁶ In 1997, Swager and co-workers utilized the same protocol to cyclize terphenyl derivative **71.1** to afford a mixture of halogenated (**75.3**) and non-halogenated (**71.2**) products in 96% combined yield (Scheme 76B).¹⁷ The formation of non-halogenated product **71.2** results due to the presence of a protic acid source. Using equal amounts of TfOH and I(py)₂BF₄ helped to enhance the yield of halogenated product **71.1**. This methodology has the added advantage by providing a functional handle, *i.e.*, a vinyl iodide, in the annulation product, which could be used for further chemical transformations.

A. Barluenga (1988)

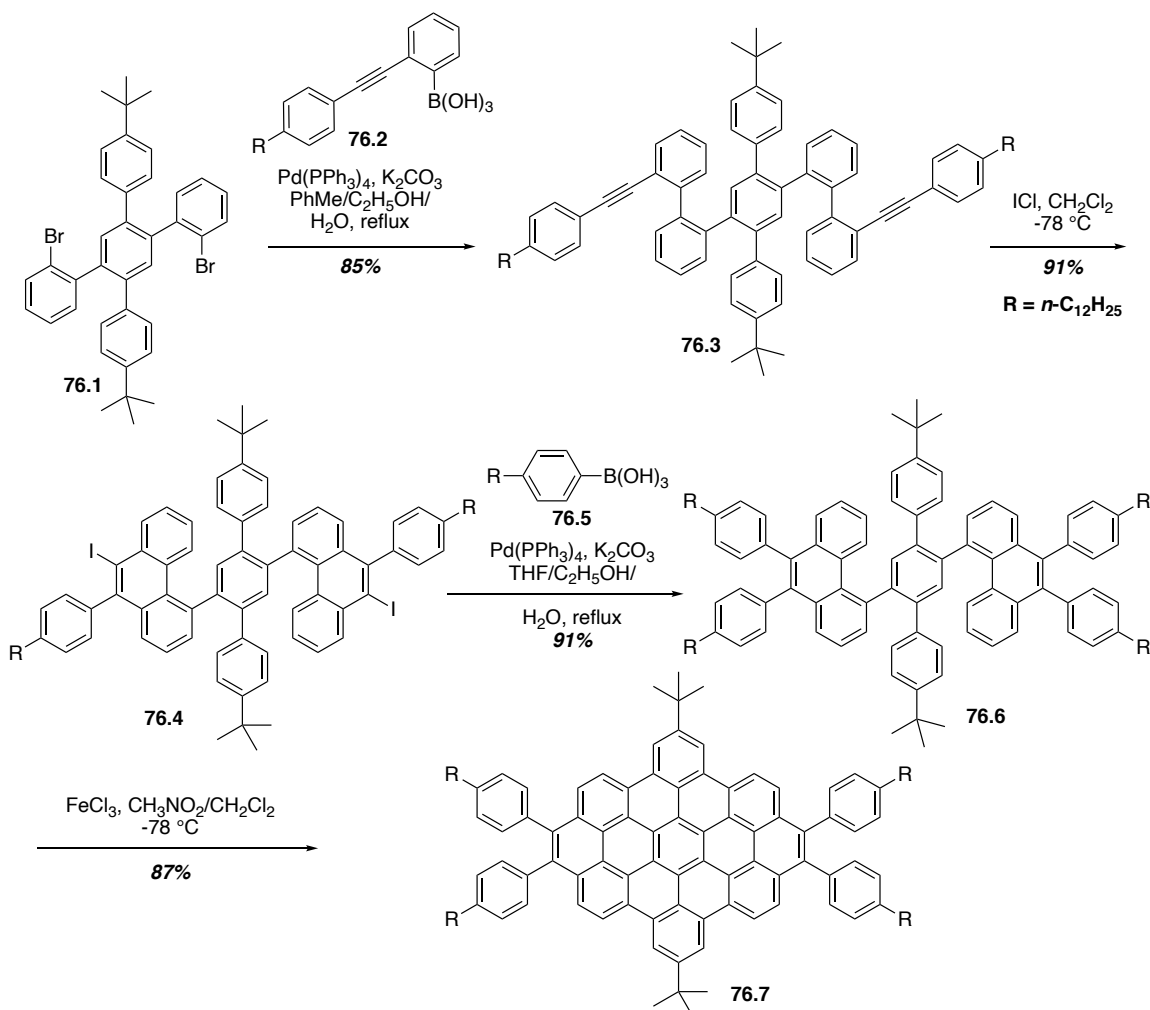


B. Swager (1997)



Scheme 75. Iodonium salt-mediated alkyne benzannulation.

The development of iodine-based reagents for alkyne benzannulation makes this strategy attractive to synthetic community focused on the synthesis of extend, pi-conjugated materials. Mild reagents, such as iodine monochloride (ICl), serves as an electrophilic iodine source in alkyne benzannulation without combination of any Brønsted acid. The reagent draws an attention to the synthesis of PAHs because of its availability, solubility in most of the organic solvent and reactivity as electrophilic source of iodine without any auxiliary chemical sources. Müllen and co-workers recently used a two-fold ICl-mediated alkyne benzannulation in the synthesis of compound **76.3**, which was prepared by Suzuki cross-coupling reaction (Scheme 76).¹⁸ Two new iodinated phenanthrene units in **76.4** serves as further cross-coupling partners en route to synthesize **76.6** via Suzuki cross-coupling with boronic acid **76.5** in 91% yield. The cyclodehydrogenation of **76.6** afforded nanographene **76.7** in 87% yield.

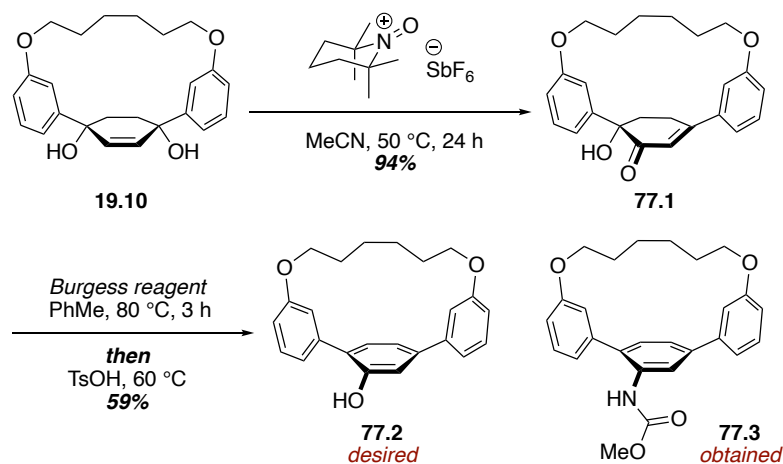


Scheme 76. Synthesis of zig-zag nanographene **76.7** using ICl-induced ring cyclization followed by Scholl oxidation.

3.2 Pi-extension of strained *p*-terphenyl-containing macrocycles via an Iodine monochloride-mediated alkyne annulation reaction

In 2020, during their investigations of oxidative transformations of macrocyclic cyclohex-2-ene-1,4-diols, Merner and co-workers reported the synthesis of a series of macrocyclic alpha-ketols.¹⁹ In the case of 18-membered macrocycle **19.10**, subjecting this substrate to an oxoammonium salt, *i.e.*, TEMPO-SbF₆, in MeCN at 50 °C furnished alpha-ketol **77.1** in 94% yield (Scheme 77). In this report, the authors attempted to dehydrate **77.1**, in hopes to afford the hydroxylated, bent *p*-phenylene ring of **77.2**. To their surprise, dehydration of **77.1** did not occur as planned, but rather gave the carbamolyated *p*-phenylene **77.3**. It should be noted that a non-macrocyclic analog of **85.1** was

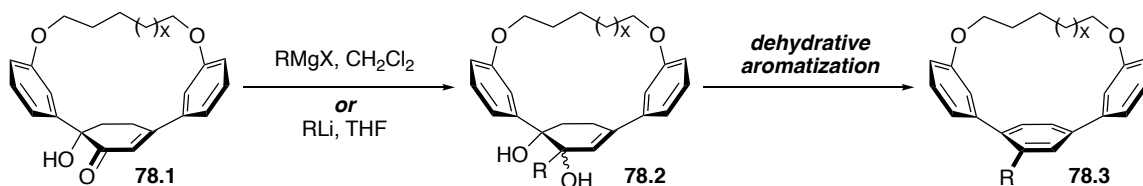
dehydrated to afford the desired, hydroxylated arene unit and that this unexpected reaction with the Burgess reagent is specific to macrocyclic alpha-ketols studied.



Scheme 77. Merner and co-workers unexpected reaction with the Burgess reagent.

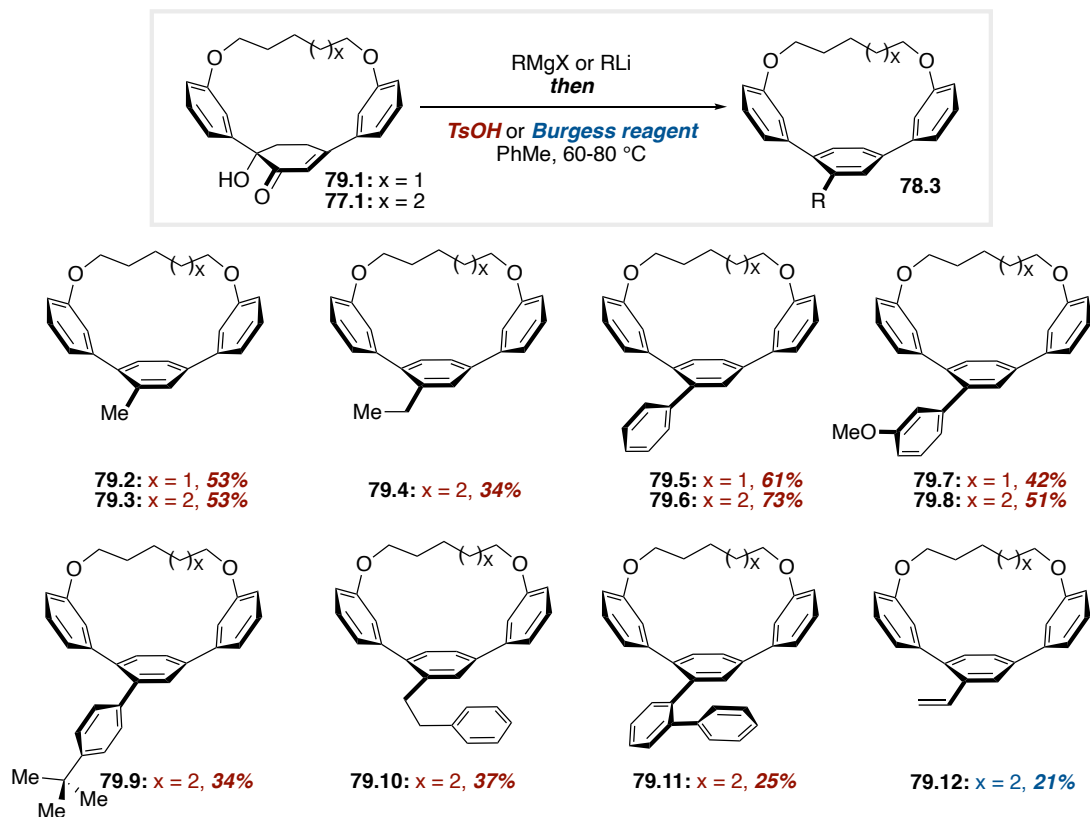
3.2.1 *Synthesis of a library of substituted, bent *p*-terphenyl-containing macrocycles*

The alpha-ketols reported in the aforementioned study were viewed as valuable synthetic precursors to alkyl, alkenyl, alkynyl, or aryl substituted bent *p*-phenylene rings. Thus, it was proposed that **78.1** could be subjected to Grignard or organolithium addition to afford 1,2-diols **78.2**, which could be subsequently dehydrated to furnish **78.3**. The introduction of a substituent at the central *p*-phenylene ring of the strained *p*-terphenyl system of **78.3** would allow for the investigation of pi-extension reactions that involved annulation about the one of electron rich, and less strained arene, units of **78.3**. This study would be complimentary to the pi-extension reactions investigated in Chapter 2, where annulation onto the central *p*-phenylene was attempted. As such, a small library of substituted derivatives of **78.3**, including potential annulation substrates were synthesized (Scheme 78).



Scheme 78. Proposed strategy for substitution of the central *p*-phenylene rings of **78.3**.

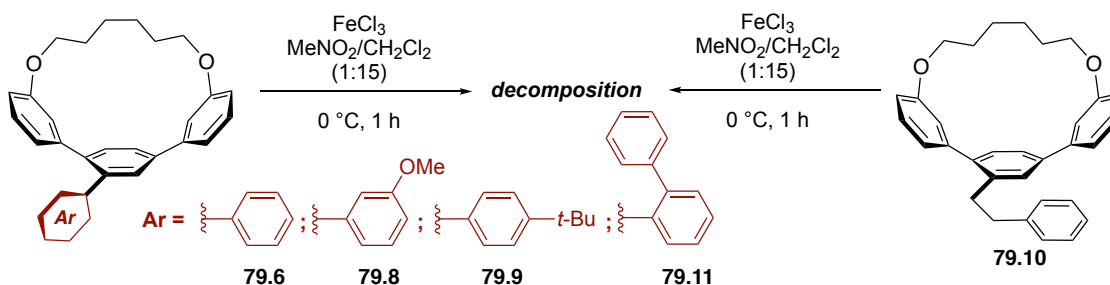
Grignard or organolithium additions to the 18 and 17-membered alpha-ketol homologs **77.1** and **79.1** gave a mixture of diols that could be directly subjected to dehydrative aromatization with TsOH or the Burgess reagent to furnish the desired aromatized products. For the most part, when alkyl (R = Me or Et, e.g., **79.2**, (53%), **79.3** (53%), **79.4** (34%), and R = CH₂CH₂Ph **79.10** (37%)) or alkenyl (R = vinyl, **79.12** (21%)) Grignard reagents were employed, low to moderate yields were obtained over the two-step process. Slightly higher yields of the desired arylated macrocycles **79.5** (R = Ph, 61%), **79.6** (R = Ph, 73%), **79.7** (R = 3-OMePh, 42%) and **79.8** (R = 3-OMePh, 51%) were obtained when this sequence was employed, with the exception of **79.9** (R = 4-*t*-BuPh, 34%) and **79.11** (R = *o*-biphenyl, 25%), which gave comparable yields to the alkylated and alkenylated derivatives. To the best of my knowledge, the strategy presented in Scheme 79 represents the first example where substituted, bent *p*-phenylene containing macrocycles have been synthesized directly from a pre-arene unit. Moreover, this approach allows for the rapid installation of different arylation handles that can be investigated in the context of pi-extension reactions of strained benzenoid macrocycles, which can (potentially) enrich our knowledge of this class of challenging reactions.



Scheme 79. Synthesis of substituted *p*-terphenyl-containing macrocycles.

The most interesting examples, in the context of annulative pi-extension of the *p*-terphenyl nuclei of the macrocycles presented in Scheme 79, include **79.6**, **79.8**, **79.9** and **79.11**. Applying the same Scholl reaction conditions that were delineated in Chapter 2, to these arylated macrocycles resulted in rapid decomposition of the starting material (Scheme 80). This result was incredibly surprising, considering that the non-arylated version of these macrocycles, *i.e.*, **19.15**, Chapter 2, proved to be relatively stable to the Scholl reaction conditions, and only partially succumbed to PTPP to MTPP rearrangement. Moreover, substitution of the bent *p*-phenylene rings of **79.6**, **79.8**, **79.9**, and **79.11** should be more stable than that of the unsubstituted analog **19.15**. This puzzling result simply adds to the ever-growing list of unusual reaction outcomes under Scholl oxidation conditions.

Similarly, when homobenzylic substituted macrocycle **79.10** was subjected to oxidative arylation conditions, a complex mixture of products and significant baseline material was obtained. In the case of the latter substrate, it was envisioned that pi-extension of the central *p*-phenylene ring would be less challenging than the arylated precursors, as it would not be accompanied by an increase in SE about the macrocyclic backbone. In fact, the desired C-C bond formation, followed by dehydrogenation would furnish a phenanthrene unit, which should better accommodate the SE present in the original *p*-phenylene ring of **79.10**. However, it is clear that the desired cyclization under Scholl reaction conditions is not as straightforward as had been originally hoped for.



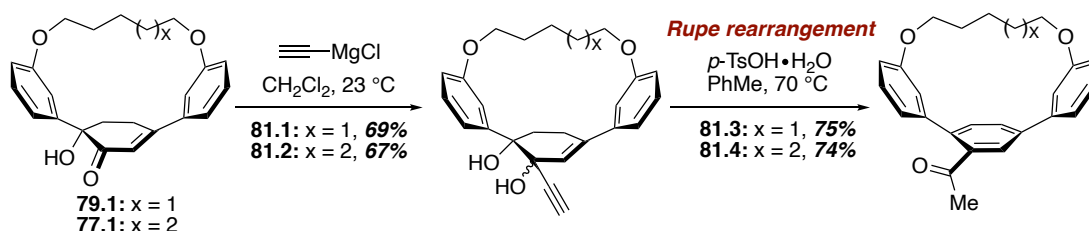
Scheme 80. Attempted Scholl reactions of **79.6**, **79.8**, **79.9**, **79.10** and **79.11**.

3.2.2 Synthesis of alkylnated, bent *p*-terphenyl-containing macrocycles

The application of alkyne-based annulation methods for pi-extension of benzenoid systems into PAHs was covered in the introductory sections of this chapter. While these

reactions have been employed in the synthesis of warped/twisted nanographenes, from planar polyarylated substrates by Chalifoux and co-workers, they have not featured in the synthesis of strained PAH-containing macrocyclic systems. The latter can be attributed to limited synthetic methods available for late-stage functionalization of strained benzenoid macrocycles, and presumably the incompatibility of the alkyne functional group with reactions along the synthetic pathway for preparing such macrocycles. Thus, the Grignard/dehydrative aromatization protocol developed above positions us to explore alkyne-based annulations as a means of pi-extension for strained benzenoid systems.

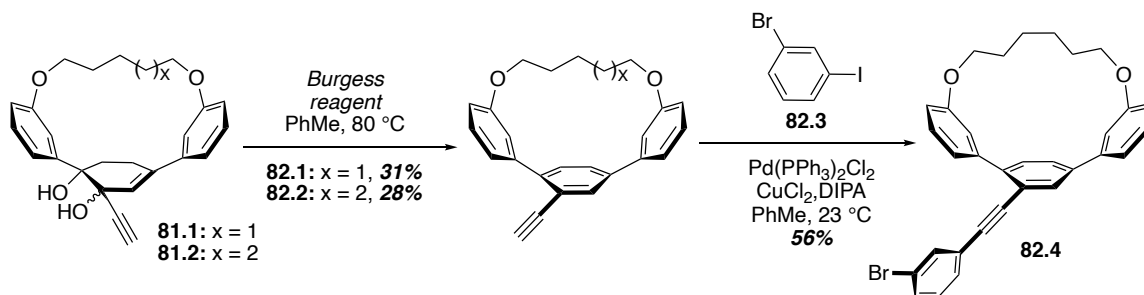
The Grignard reaction of alpha-ketols **79.1** and **77.1** with ethynylmagnesium chloride in dichloromethane furnished diols **81.1** and **81.2** in 69% and 67% yield, respectively. Initially, aromatization of the diols with TsOH in toluene was attempted; however, this reaction did not afford the desired alkynylated *p*-terphenyl-containing macrocycles **82.1** and **82.2**. In this instance the desired dehydrative aromatization is intercepted by a propargylic alcohol reaction, known as the Rupe rearrangement, which results in the formation of methyl ketones **81.3** and **81.4** in 75% and 74% yield, respectively.



Scheme 81. Acid-mediated aromatization of propargylic alcohols **81.1** and **81.2**.

To circumvent the Rupe rearrangements of these propargylic alcohols, dehydrative aromatization of **81.1** and **81.2** with the Burgess reagent was attempted (Scheme 82). Indeed, the alkynylated macrocycles were afforded from this modified procedure; however, the isolated yields of **82.1** and **82.2** were somewhat low at 31% and 28%, respectively. Formation of the desired macrocycles **82.1** and **82.2** was accompanied by the production of an unidentified by-product at this juncture. Nonetheless, the alkyne **82.2** could be engaged in a Sonogashira cross-coupling reaction with 1-bromo-3-iodobenzene (**82.3**) to give bromide **82.4** in 56% yield. Such

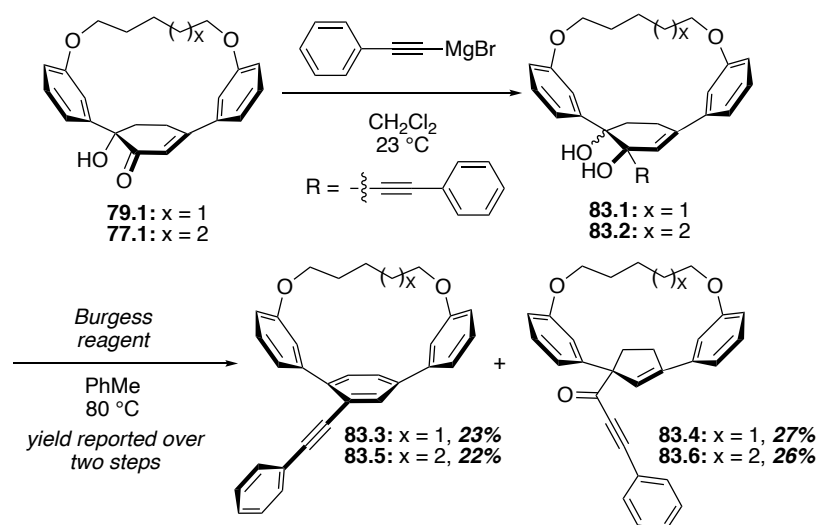
aryl alkynes are necessary to probe the alkyne-based annulation reactions onto the strained *p*-terphenyl ring system of **82.4**.



Scheme 82. Burgess reagent-mediated aromatization of propargylic alcohols **81.1** and **81.2**.

3.2.2.1 An unexpected pinacol-type reaction with the Burgess reagent

While alkynylated macrocycles **82.1** and **82.2** are arguably more versatile as synthetic intermediates, *i.e.*, they can serve as precursors to multiple aryl-alkyne derivatives, a higher yielding synthesis of a phenylethynyl derivative of **82.4** was sought. Treatment of **79.1** and **77.1** with phenylethynylmagnesium bromide in dichloromethane afforded a mixture of 1,2-diols, which were purified and subjected to dehydrative aromatization reactions with the Burgess reagent. The overall yield of the aryl-alkynylated products was marginally improved, when compared to **82.4**; however, aromatization of **83.1** and **83.2** under the Burgess reagent-mediated conditions furnished yet another by-product, which was isolated in comparable yield. Fortunately, crystals suitable for X-ray crystallographic analysis were obtained upon recrystallization of **83.6** from ethyl acetate and hexanes, allowing for the unambiguous determination of the structure of these by-products to be that of **83.4** and **83.6**. During the course of the dehydration reactions of **83.1** and **83.2** with the Burgess reagent a competitive ring-contraction takes place to furnish a cyclopentenyl ketone. The obtained product seems to have resulted from a pinacol-type rearrangement, which is common for tertiary-1,2-diols when subjected to protic or Lewis acids. The fact that this reaction does not occur under TsOH-mediated conditions, where only the Rupe rearrangement product was obtained, is quite surprising, as the Burgess reagent is a neutral, non-acidic reagent. To the best of my knowledge this is the first example of such a reaction occurring on a 1,2-diol in the presence of the Burgess reagent.



Scheme 83. Synthesis of alkynylated *p*-terphenyl-containing macrocycles **83.3** and **83.5**.

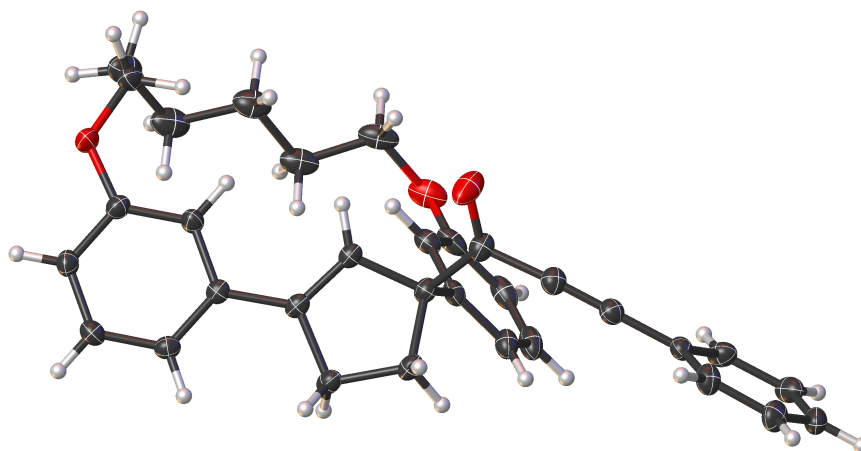
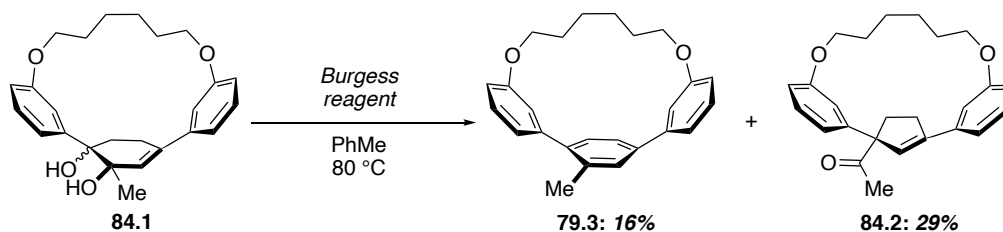


Figure 7: X-ray crystal structure of **43.6**.

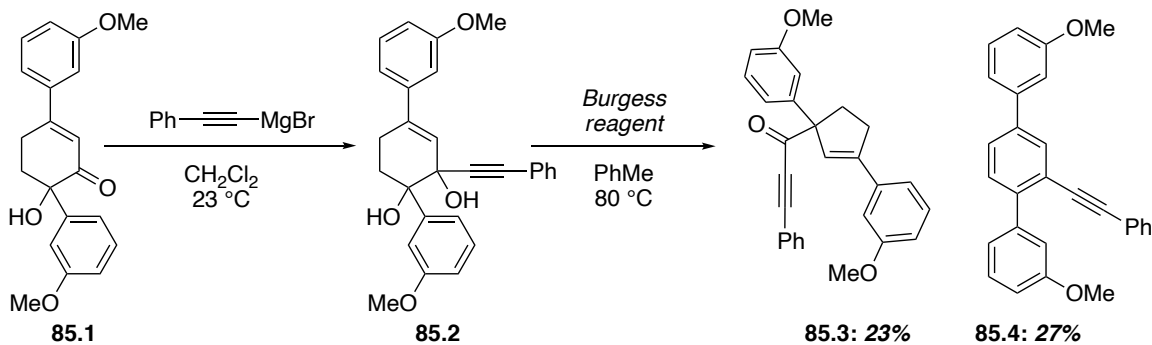
To see if this result was specific to propargylic alcohols, the dehydration of methyl substituted 1,2-diol **84.1** was subjected to the identical reaction conditions. Previously, TsOH was used to aromatize **84.1** (see Scheme 79 and Supporting Information for details); however, when it was subjected to the Burgess reagent under standard dehydrative aromatization conditions, the desired aromatized product **79.3** was produced in only 16% yield, while the cyclopentenyl ketone **84.2** was isolated in 29% yield as the major product of this reaction. This result confirms that the pinacol-type rearrangement with ring contraction that was observed for **83.2** is not specific to propargylic alcohols. As mentioned above, unexpected reactions with the Burgess

reagent have been previously observed in attempted dehydration reactions of alpha-ketols, and these reactions proved to be specific to macrocyclic alpha-ketols. Thus, to better understand this unexpected transformation, and to determine whether or not these rearrangements were specific to macrocyclic systems, an acyclic model compound was synthesized.



Scheme 84. Aromatization of diol **84.1** with the Burgess reagent and unexpected outcome.

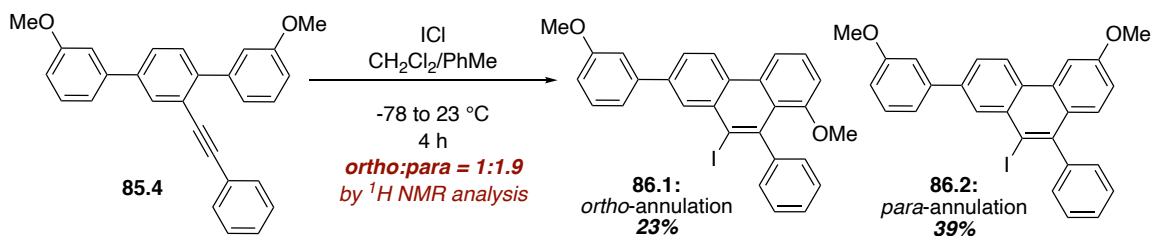
Alpha-ketol **85.1** had been previously synthesized in our laboratory for a different model study with the Burgess reagent. Subjecting **85.1** to a Grignard reaction with phenylethynylmagnesium bromide gave diol **85.2** which was then subjected to the Burgess reagent in toluene at 80 °C. Like its macrocyclic analog **83.1**, diol **83.2** furnished both aromatized and rearranged products in 27% and 23%, respectively (Scheme 85), proving that the observed pinacol-type rearrangement is not specific to macrocyclic alpha-ketols that are necessarily more strained than their acyclic counterparts. It appears that both aromatization and rearrangement pathways have similar energetic profiles, as nearly equal amounts of both products are formed, which is surprising since the aromatization pathway should be more exothermic than the pinacol-type rearrangement pathway. Thus, the energetic barriers associated with the first dehydration reaction, en route the aromatized product, and 1,2-alkyl migration must be comparable.



Scheme 85: Synthesis of non-macrocyclic alkynylated *p*-terphenyl **85.4**.

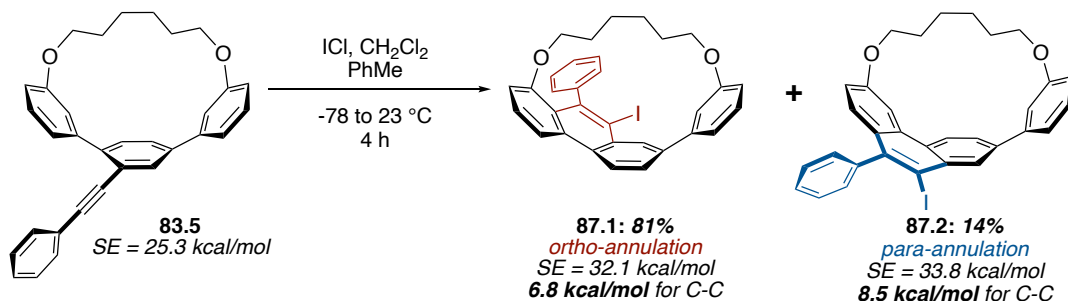
3.2.2.2 Iodine monochloride-mediated *pi*-extension of strained *p*-terphenyl-containing macrocycles

With a synthetic route to alkynylated, bent *p*-terphenyl-containing macrocycles established, focus was placed on employing these substrates in alkyne-mediated annulation reactions and related 6- π electrocyclizations. Before embarking on these investigations with macrocyclic derivatives, the desired annulation protocol was applied to a model *p*-terphenyl **85.4**. Treatment of **85.4** with iodine monochloride in a mixture of dichloromethane and toluene at -78 °C, while slowly warming the reaction mixture to room temperature, resulted in the formation of two regioisomeric products **86.1** and **86.2** in 23% and 39% yield, respectively (Scheme 86). These annulation isomers have been dubbed *ortho* and *para*-annulation products, referring to relationship of the methoxy group and the carbon atom of the aromatic ring that undergoes C-C bond formation. Not surprisingly, the *para*-annulation product, which proceeds through a less congested, and therefore lower energy reaction conformation, is the major constitutional isomer produced in this reaction. Analysis of the crude ^1H NMR spectrum of this reaction indicates that a 1:2 ratio of products is produced.



Scheme 86. ICl-mediated annulation on a non-macrocyclic model system **85.4**.

Application of the same reaction conditions presented in Scheme 87 to the least strained macrocyclic homolog of **85.4.**, *i.e.*, **83.5**, furnished two annulation products, which were tentatively assigned as **87.1** (*ortho*-annulation, 81% yield) and **87.2** (*para*-annulation, 14% yield). This assignment was made on the basis of DFT calculations, which predicted that the *ortho*-annulation product would result in an increase of 6.8 kcal/mol of SE upon C-C bond formation/annulation and that the formation of the *para*-annulation product would require a 8.5 kcal/mol increase in SE to afford the strained phenanthrene unit of **87.2**. Unlike the model cyclization, which preferred the less sterically congested mode of cyclization, annulation in the macrocyclic systems also comes with an increase in SE for the new formed PAH, which is miniscule in the constitutional isomers of the model *p*-terphenyl.



Scheme 87. Iodine monochloride-induced pi-extension of bent *p*-terphenyl **83.5**.

While both compounds could be separated by column chromatography, analysis of their ¹H NMR spectra at room temperature were complicated by conformational flux within the macrocyclic structures or the restricted bond rotation of the phenyl ring due to the proximal iodo group. Both compounds did not display the correct number of aromatic proton signals at room temperature, despite HRMS analysis confirming their molecular formula. Thus, dynamic NMR studies were undertaken to see if the missing aromatic resonances could be ascertained.

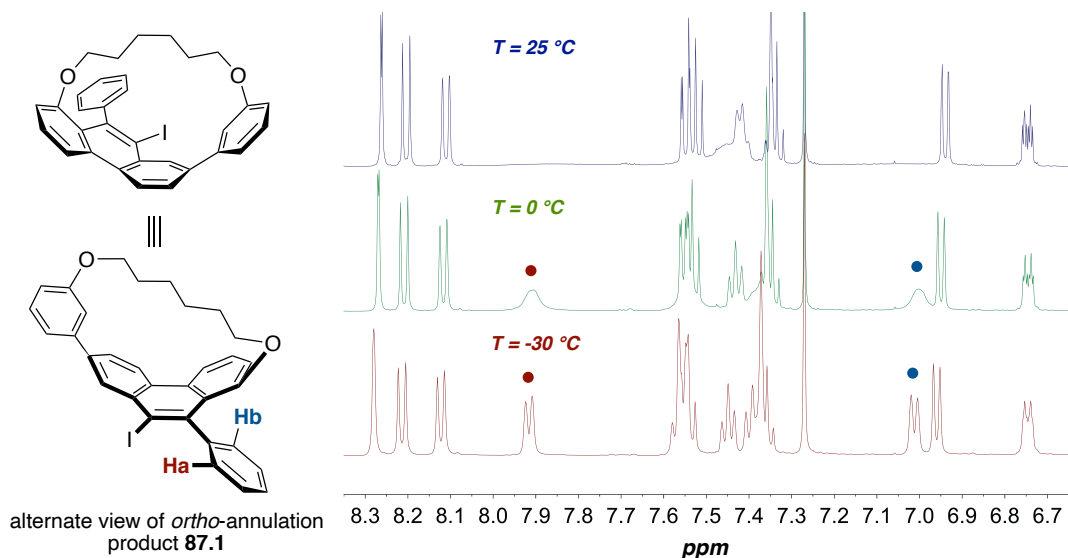
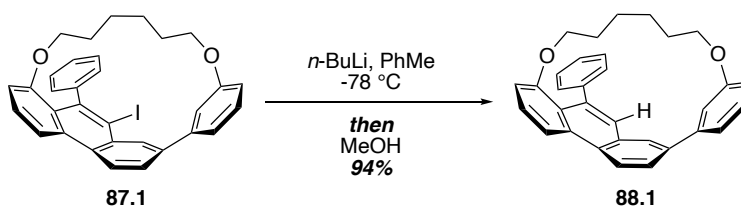


Figure 8. VT-NMR of *ortho*-annulation product **87.1** from -30 to 25 °C

At 25 °C, the protons Ha and Hb (see Figure 8) appear to be near their coalescence temperature, with a broadened signal appearing between 7.4-7.5 ppm. However, as the temperature inside the NMR spectrometer is lowered to 0 °C, resolution of these two nuclei is achieved. Further cooling to -30 °C results in better resolution of these signals, as they now appear as doublets, which allowed for the assignment of all 15 ¹H aromatic signals of **87.1**. It should be noted that dehalogenation of with *n*-BuLi followed by quenching the resulting anion with methanol afforded macrocycle in 94% yield (Scheme 88), which has a well-resolved ¹H NMR spectrum at 25 °C.



Scheme 88. Dehalogenation of **87.1**.

Recrystallization of **87.1** from ethyl acetate and hexanes produced crystals suitable for X-ray crystallography, which allowed for the unambiguous assignment of its structure. As can be seen from the solid-state structure of **88.1**, the newly formed phenanthrene unit, via ICl-mediated pi-extension, is both bent and twisted, making the molecule chiral. Indeed, both enantiomers are produced in during the alkyne annulation

reaction, and these were separated by chiral HPLC and their optical rotations were individually measured (see Supporting Information for details).

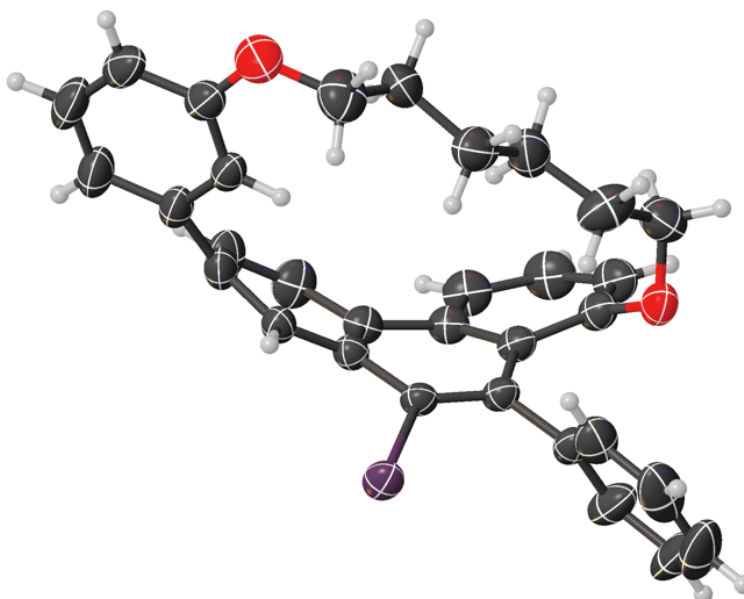
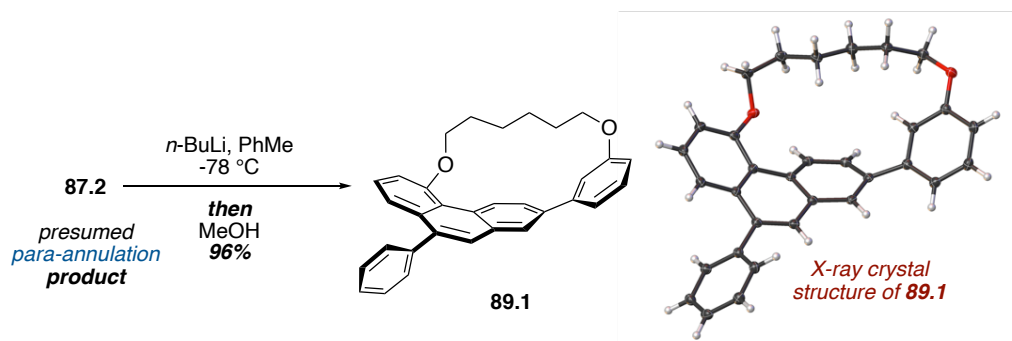


Figure 9: X-ray crystal structure of **87.1** (thermal ellipsoids shown at 50% probability)

While the major product of the ICl-mediated annulation of **83.5** could be assigned as *ortho*-annulation product **87.1**, on the basis of detailed NMR analysis and X-ray crystallography, the structure of the minor product isolated during this reaction was yet to be ascertained. Initially, we believed the structure of the minor product to be the result of *para*-annulation (*i.e.*, **87.2**) due to its similar ^1H NMR spectra when compared to **87.1**. Numerous attempts to grow crystals of **87.2** that would be suitable for X-ray crystallographic analysis did not come to fruition. During the synthesis of **88.1**, it was noted that the dehalogenated product was indeed crystalline. As such, the presumed *para*-annulation product **87.2** was subjected to the same dehalogenation conditions to afford a white solid in 96% yield (Scheme 89). Like **87.1**, the ^1H NMR spectrum of the dehalogenated product was simplified upon removal of the iodine atom, and there appeared to be no significant changes in the aromatic region of the spectrum. At this juncture, crystals suitable for X-ray analysis were afforded upon recrystallization with a mixture of ethyl acetate and hexanes and the structure of the minor annulation product was determined to be that of **89.1**. The connectivity of the phenanthrene unit of **89.1**, indicates that it is the product of *para*-annulation; however, the alkyloxy bridging group

has migrated to form a less strained macrocyclic system. The precise mechanism of this strain-relief bridge migration is still under investigation and unknown at this point. However, it clearly has to occur via a transannular, or intramolecular process as the fidelity of the macrocycle is maintained.



Scheme 89. Identification of minor ICI-mediated annulation byproduct **87.2**.

3.3 Concluding Remarks

The synthesis of substituted, strained *p*-phenylene units from alpha-ketols has enabled the preparation of annulation substrates using a Grignard-dehydration reaction protocol. The most interesting of which proved to be alkynylated derivatives, which can be engaged in an ICI-mediated pi-extension reaction to afford bent and twisted, chiral phenanthrene-containing macrocycles. In developing this pi-extension strategy for strained *p*-terphenyl-containing macrocycles, some interesting reactions of tertiary 1,2-diols were discovered, particularly, a quasi-pinacol rearrangement. This reaction which takes place under neutral reaction conditions, may be applicable to complex molecule synthesis, *eg.*, total synthesis, when acid-sensitive functional groups are present. The full scope of this reaction has not been explored here, but will hopefully continue in the coming years.

The ICI-mediated alkyne annulation that has been developed here holds great promise for future projects in the Merner laboratory. Upon annulation an aryl substituent and a vinyl iodide reaction handle have been installed. Both of these can be used in subsequent pi-extension reactions. The reaction conditions are mild and the products generated appear to be stable. Future work aimed at the synthesis of macrocyclic precursors of [*n*]CPPs, containing alpha-ketol units, should be explored to investigate the synthetic utility of this pi-extension in carbon nanobelt synthesis.

3.4 References

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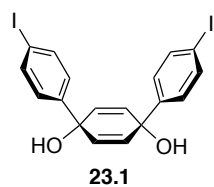
APPENDIX 1:

Supporting Information for

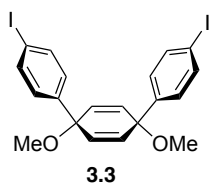
CHAPTER 1 Towards the Synthesis of [4]Cycloparaphenylene.

General Experimental Conditions

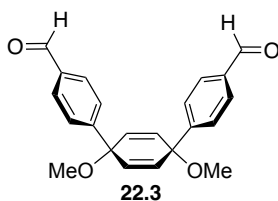
All reactions were run in flame or oven-dried (120 °C) glassware and under a positive pressure of ultra-high pure nitrogen or argon gas. All chemicals were used as received from commercial sources, unless otherwise stated. Anhydrous reaction solvents were purified and dried by passing HPLC grade solvents through activated columns of alumina (Glass Contour SDS). All solvents used for chromatographic separations were HPLC grade (hexanes, ethyl acetate, dichloromethane, chloroform, methanol, and acetone). Chromatographic separations were performed using flash chromatography, as originally reported by Still and co-workers, on silica gel 60 (particle size 43-60 μm), and all chromatography conditions have been reported as height \times diameter in centimeters. Reaction progress was monitored by thin layer chromatography (TLC), on glass-backed silica gel plates (pH = 7.0). TLC plates were visualized using a handheld UV lamp (254 nm) and stained using an aqueous ceric ammonium molybdate (CAM) solution. Plates were dipped, wiped clean, and heated from the back of the plate. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 or 600 MHz, calibrated using residual undeuterated solvent as an internal reference (CHCl_3 , δ 7.27 and 77.2 ppm), reported in parts per million relative to trimethylsilane (TMS, δ 0.00 ppm), and presented as follows: chemical shift (δ , ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, m = multiplet, p = pentet), coupling constants (J , Hz). High-resolution mass spectrometric (HRMS) data were obtained using a quadrupole time-of-flight (Q-TOF) spectrometer and electrospray ionization (ESI).



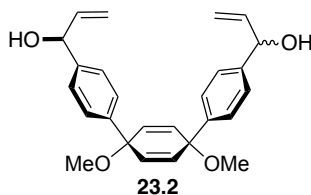
Syn-1,4-diol 23.1: 1,4-diiodobenzene (8.60 g, 26.6 mmol) was dissolved in 50 mL of tetrahydrofuran and cooled to -78 °C. To this solution was added a 1.5 M solution of *n*-butyllithium in hexanes (16.4 mL, 24.4 mmol) over 30 min. The reaction mixture was allowed to stir for 30 min. Benzoquinone (1.32 g, 12.1 mmol) was then added to the reaction as a solid in three equal portions with 15 min interval. The solution was stirred for 2 h and then added water (200 mL) with stirring. The mixture was further diluted by the addition of diethyl ether (100 mL). The layers were separated, and the aqueous layer extracted with diethyl ether (3 \times 50 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (3.5 cm \times 16 cm; 30% ethyl acetate/hexane to 40% ethyl acetate/hexane) to yield **23.1** as white solid (3.30 g, 53%); R_f = 0.23 (40% ethyl acetate/hexane). ^1H NMR (600 MHz, Chloroform-*d*) δ 7.69 (d, J = 8.5 Hz, 4H), 7.17 (d, J = 8.5 Hz, 4H), 6.04 (s, 4H), 2.25 (s, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 143.53, 137.93, 132.18, 127.76, 93.80, 69.38.



Diiodide 3.3: To a dry 100 mL round bottom flask was added 20 mL tetrahydrofuran and sodium hydride (440 mg, 11.0 mmol). The mixture was then cooled to 0 °C and then diol **23.1** (1.47 g, 2.84 mmol) as a solution in 10 mL tetrahydrofuran was added. After 1 h, methyl iodide (2 mL, 5.00 g, 35.2 mmol) was added to the reaction. The reaction mixture was allowed to warm to rt and stirred for additional 18 h. The excess sodium hydride was then quenched by addition of 100 mL water and this mixture was further diluted by addition of 50 mL diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 8% ethyl acetate/hexane to 10% ethyl acetate/hexane) to yield **3.3** as white solid (1.27 g, 83%): R_f = 0.38 (10% ethyl acetate/hexane). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.65 (d, J = 8.4 Hz, 4H), 7.12 (d, J = 8.5 Hz, 4H), 6.07 (s, 4H), 3.41 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 143.27, 137.74, 133.55, 128.24, 93.70, 74.75, 52.28.

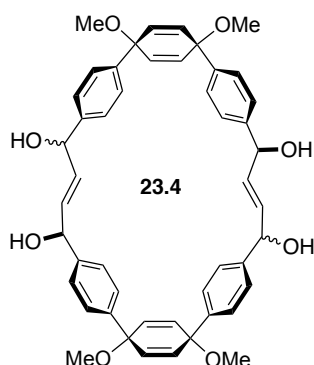


Dialdehyde 22.3: To a dry 100 mL round bottom flask was added 40 mL diethyl ether and methyl protected diiodide **3.1** (1.25 g, 2.29 mmol). The mixture was then cooled to -78 °C and then a 2.47 M solution of *n*-butyllithium in hexanes (3.6 mL, 8.90 mmol) was added over 10 min. After 10 min, *N,N*-dimethyl formamide (1 mL, 4.90 g, 67.0 mmol) was added to the reaction. The reaction mixture was allowed to warm to rt and stirred for additional 1 h then added 100 mL water with stirring. The mixture was further diluted by addition of 50 mL ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 20% ethyl acetate/hexane to 40% ethyl acetate/hexane) to yield **22.3** as white solid (638 mg, 80%): R_f = 0.27 (30% ethyl acetate/hexane). ¹H NMR (600 MHz, Chloroform-*d*) δ 10.02 (s, 2H), 7.85 (d, J = 8.1 Hz, 4H), 7.57 (d, J = 8.0 Hz, 4H), 6.17 (s, 4H), 3.47 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 192.05, 149.87, 136.04, 133.70, 130.17, 126.91, 75.01, 52.41. HRMS (ESI-TOF) calc'd for C₂₂H₂₀O₄Na ([M+Na]⁺) m/z = 371.1259 found 371.1261.



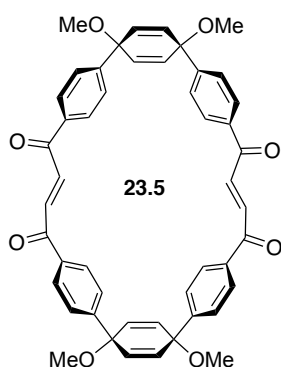
Bis-allylic diol 23.2: Vinylmagnesium chloride (0.80 mL, 1.7 M, 1.36 mmol) was added to a stirred solution of dialdehyde **22.3** (180 mg, 0.52 mmol) in dichloromethane (15 mL) at 23 °C. After 30 min, the reaction was poured into water (15 mL) and further diluted with 1 M HCl (3 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 40% ethyl acetate/hexane to 45% ethyl acetate/hexane) to yield **23.2** as white solid (154 mg, 74%): R_f = 0.24 (40% ethyl acetate/hexane). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, J = 8.6 Hz, 4H), 7.31 (d, J = 7.9 Hz, 4H), 6.09 (s, 4H), 6.01 (ddd, J = 16.7, 10.2, 6.3 Hz, 2H), 5.34 (d, J = 17.1 Hz, 2H), 5.21 - 5.14 (m, 4H), 3.43 (s, 6H), 2.16 (s, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 143.05, 142.03, 140.20, 133.54, 126.62,

126.36, 115.47, 75.25, 74.83, 52.25. HRMS (ESI-TOF) calc'd for $C_{26}H_{28}O_4Na$ ($[M+Na]^+$) $m/z = 427.1885$ found 427.1905.



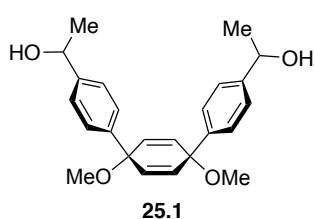
Macrocycle 23.4: Grubbs' second-generation catalyst (7 mg, 0.01 mmol) was added to a stirred solution of allylic diol **23.2** (70 mg, 0.17 mmol) in dichloromethane (100 mL) and the reaction was heated to 40 °C. After 4 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (1.3 cm × 16 cm; 75% ethyl acetate/hexane to 100% ethyl acetate) to yield **23.4** as white solid (31 mg, 48%): $R_f = 0.20$ (80% ethyl acetate/hexane). 1H NMR (600 MHz, Chloroform-*d*) δ 7.35 - 7.27 (m, 8H), 7.26 - 7.15 (m, 8H), 6.14 - 5.72 (m, 12H), 5.24 - 4.98 (m, 4H), 3.66 - 3.18 (m, 12H), 1.72 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.07, 142.04, 133.52, 133.25, 127.00, 126.96, 126.86,

126.81, 126.48, 126.42, 126.38, 74.96, 74.90, 74.87, 74.84, 74.60, 74.52, 52.20, 52.19. HRMS (ESI-TOF) calc'd for $C_{48}H_{48}O_4Na$ ($[M+Na]^+$) $m/z = 775.3247$ found 775.3240.



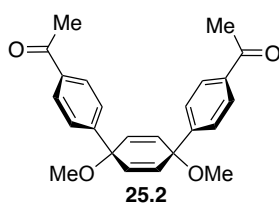
Tetraketone 23.5: The compound **23.4** (13 mg, 0.02 mmol) was dissolved in dichloromethane (4 mL), followed by sequential addition of $NaHCO_3$ (15 mg, 0.18 mmol) and Dess-Martin periodinane (33 mg, 0.07 mmol) at rt. After 10 h, 1:1 saturated solution of $NaHCO_3/20\% Na_2S_2O_3$ solution (10 mL) was added to the reaction and stirred for 1 h. The layers were separated, and the aqueous layer extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 40% ethyl acetate/hexane to 50% ethyl acetate/hexane) to yield **23.5** as white solid (4 mg,

32%): $R_f = 0.24$ (40% ethyl acetate/hexane). 1H NMR (600 MHz, Chloroform-*d*) δ 7.83 (d, $J = 8.5$ Hz, 4H), 7.50 - 7.43 (m, 6H), 6.21 (s, 4H), 3.46 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.78, 148.90, 137.11, 136.33, 133.79, 129.40, 126.75, 75.01, 52.44.

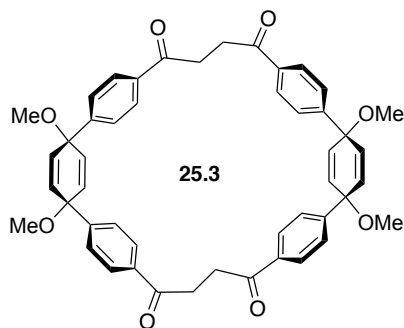


Diol 25.1: Methylmagnesium chloride (0.4 mL, 3.0 M, 1.2 mmol) was added to a stirred solution of dialdehyde **22.3** (178 mg, 0.51 mmol) in dichloromethane (10 mL) at 23 °C. After 20 min, the reaction was poured into water (15 mL) and further diluted with 1 M HCl (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 40% ethyl acetate/hexane to 60% ethyl acetate/hexane) to yield **25.1** as white solid (163 mg, 84%): $R_f = 0.37$ (60% ethyl acetate/hexane). 1H NMR (600 MHz, Chloroform-*d*) δ 7.39 (d, $J = 8.1$ Hz, 4H), 7.32 (d, $J = 8.1$ Hz, 4H), 6.11 (s, 4H), 4.91 - 4.86 (m, 2H), 3.44 (s, 6H), 1.86 - 1.82 (m, 2H), 1.50 - 1.47 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.35, 142.93,

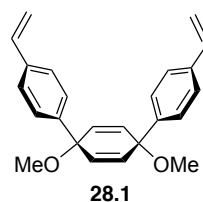
133.62, 133.60, 133.57, 126.39, 125.70, 74.91, 70.39, 52.23, 25.37. HRMS (ESI-TOF) calc'd for $C_{24}H_{28}O_4Na$ ($[M+Na]^+$) $m/z = 403.1885$ found 403.1890.



Diketone 25.2: The compound **25.1** (149 mg, 0.39 mmol) was dissolved in dichloromethane (20 mL), followed by sequential addition of $NaHCO_3$ (124 mg, 1.47 mmol) and Dess-Martin periodinane (386 mg, 0.86 mmol) at 23 °C. After 12 h, 1:1 saturated solution of $NaHCO_3/20\% Na_2S_2O_3$ solution (20 mL) was added to the reaction and stirred for 1 h. The layers were separated, and the aqueous layer extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm \times 16 cm; 40% ethyl acetate/hexane) to yield **25.2** as white solid (138 mg, 94%): $R_f = 0.34$ (40% ethyl acetate/hexane). 1H NMR (600 MHz, Chloroform- d) δ 7.92 (d, $J = 8.7$ Hz, 4H), 7.49 (d, $J = 8.7$ Hz, 4H), 6.14 (s, 4H), 3.46 (s, 6H), 2.61 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.14, 148.44, 136.52, 133.63, 128.81, 126.39, 74.90, 52.40, 27.03. HRMS (ESI-TOF) calc'd for $C_{24}H_{24}O_4Na$ ($[M+Na]^+$) $m/z = 399.1572$ found 399.1566.

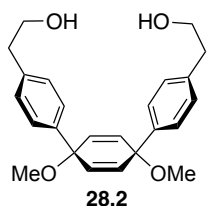


Macrocycle 25.3: Diisopropylamine (0.2 mL, 1.26 mmol) was dissolved in tetrahydrofuran (10 mL) at room temperature and cooled to 0 °C. To this solution was added a 2.4 M solution of *n*-butyllithium in hexanes (0.46 mL, 1.04 mmol) slowly and stirred at 0 °C for 30 min. After 30 min, the mixture was cooled to -78 °C and methyl diketone **25.2** (124 mg, 0.329 mmol) dissolved in tetrahydrofuran (8 mL) was added dropwise to the mixture at -78 °C over 20 min, the reaction became yellow. After 1h, (3.6 mL, 0.302 M, 1.08 mmol) copper (II) chloride in *N,N*-dimethylformamide was added to the reaction at -78 °C and the reaction became green color. After 21 h, saturated ammonium chloride solution (15 mL) was added to the reaction and was further diluted by diethyl ether (15 mL). The layers were separated, and the aqueous layer extracted with diethyl ether (3×15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm \times 16 cm; 40% ethyl acetate/hexane to 60% ethyl acetate/hexane) to yield **25.3** as white solid (10 mg, 8%): $R_f = 0.46$ (50% ethyl acetate/hexane). 1H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, $J = 8.3$ Hz, 4H), 7.93 (d, $J = 8.3$ Hz, 4H), 7.51 (dd, $J = 8.2, 8.2$ Hz, 8H), 6.15 (s, 8H), 3.47 (s, 12H), 2.61 (s, 8H). HRMS (ESI-TOF) calc'd for $C_{48}H_{48}O_8Na$ ($[M+Na]^+$) $m/z = 771.2934$ found 771.2931.

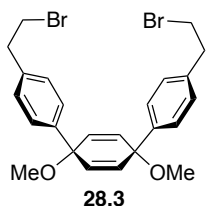


Diene 28.1: To a dry 10 mL round bottom flask was added 3 mL tetrahydrofuran and methyltriphenylphosphonium bromide (626 mg, 1.75 mmol). The mixture was then cooled to 0 °C and then potassium *tert*-butoxide (260 mg, 2.31 mmol) was added and stirred for 20 min. Then dialdehyde **22.3** (67 mg, 0.19 mmol) as a solution in 1 mL tetrahydrofuran was added to the reaction at 0 °C. The reaction mixture was allowed to warm slowly and stirred for additional 18 h.

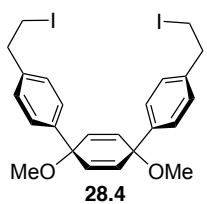
The solvent was removed under reduced pressure and the residue was purified by flash chromatography (1.3 cm × 16 cm; 10% ethyl acetate/hexane to 20% ethyl acetate/hexane) to yield **28.1** as white solid (73 mg, 96%): $R_f = 0.61$ (30% ethyl acetate/hexane). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.25 – 7.19 (m, 8H), 6.61 (dd, $J = 17.6$, 10.9 Hz, 2H), 6.01 (s, 4H), 5.65 (d, $J = 17.6$ Hz, 2H), 5.15 (d, $J = 10.9$ Hz, 2H), 3.34 (s, 6H). $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 143.28, 137.24, 136.77, 134.08, 133.95, 133.51, 128.94, 128.76, 128.71, 126.50, 114.17, 75.03, 52.16.



Diol 28.2: To a dry 10 mL round bottom flask was added 9-BBN (1.2 mL, 0.5 M, 0.6 mmol) and cooled to 0 °C and then bis styrene **28.1** (46 mg, 0.13 mmol) as a solution in tetrahydrofuran (2 mL) was added to the reaction at 0 °C. After 14 h, 3 M NaOH (0.28 mL, 0.08 mmol) and 35% H_2O_2 (0.08 mL, 0.87 mmol) was added to the reaction at 23 °C and refluxed the reaction for another 10 h. After 10 h, the reaction was cooled to 23 °C and water (10 mL) was added to the reaction and further diluted by dichloromethane (10 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 50% ethyl acetate/hexane to 60% ethyl acetate/hexane) to yield **28.2** as white solid (25 mg, 50%): $R_f = 0.28$ (80% ethyl acetate/hexane). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36 (d, $J = 8.3$ Hz, 4H), 7.18 (d, $J = 8.2$ Hz, 4H), 6.11 (s, 4H), 3.88 – 3.81 (m, 4H), 3.44 (s, 6H), 2.86 (t, $J = 6.6$ Hz, 4H), 1.46 (s, 2H).

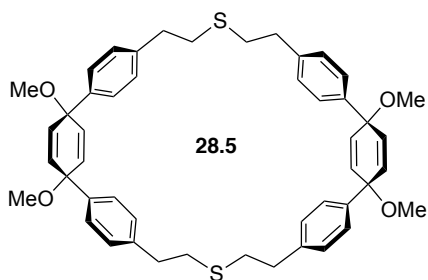


Dibromide 28.3: To a dry 2 mL vial was added dichloromethane (0.5 mL) and triphenyl phosphine (14 mg, 0.05 mmol) and *N*-bromosuccinimide (9 mg, 0.05 mmol) at 23 °C. The color of mixture became pink. After 10 min, imidazole (9 mg, 0.13 mmol) was added to the mixture at 23 °C. After 5 min, ethane diol **28.2** (6 mg, 0.015 mmol) as a solution in dichloromethane (0.5 mL) was added to the reaction at 23 °C. After 3h, water (3 mL) was added to the reaction and the reaction was further diluted by dichloromethane (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 10% ethyl acetate/hexane to 15% ethyl acetate/hexane) to yield **28.3** as white solid (4 mg, 53%): $R_f = 0.25$ (10% ethyl acetate/hexane). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.36 (d, $J = 7.9$ Hz, 4H), 7.16 (d, $J = 7.9$ Hz, 4H), 6.11 (s, 4H), 3.55 (t, $J = 7.5$ Hz, 4H), 3.16 (t, $J = 7.5$ Hz, 4H).



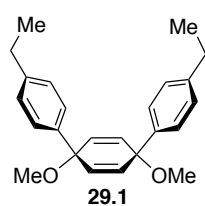
Diiodide 28.4: To a dry 2 mL vial was added dichloromethane (0.5 mL) and triphenyl phosphine (14 mg, 0.05 mmol) and iodine (13 mg, 0.05 mmol) and imidazole (6 mg, 0.09 mmol) at 23 °C. The color of mixture became yellow. After 10 min, ethane diol **28.2** (6 mg, 0.015 mmol) as a solution in dichloromethane (0.5 mL) was added to the reaction at 23 °C. After 3h, water (3 mL) was added to the reaction and the reaction was further diluted by dichloromethane (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL). The

combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 10% ethyl acetate/hexane to 15% ethyl acetate/hexane) to yield **28.4** as white solid (3 mg, 33%): *R_f* = 0.20 (10% ethyl acetate/hexane). ¹H NMR (600 MHz, CDCl₃) δ 7.35 (d, *J* = 8.2 Hz, 4H), 7.14 (d, *J* = 8.2 Hz, 4H), 6.11 (s, 4H), 3.44 (s, 6H), 3.32 (t, *J* = 8.0 Hz, 4H), 3.18 (t, *J* = 8.0 Hz, 4H).



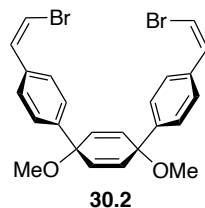
Thiocyclophane 28.5: To a dry 10 mL round bottom flask was added ethanol (2 mL) and warmed at 78 °C. To this hot ethanol, sodium sulfide nonahydrate (0.2 mL, 2.2 mg, 0.009 mmol) as a solution in ethanol/water (7:3) and dibromide **28.3** (4 mg, 0.008 mmol) as a solution in tetrahydrofuran (1 mL) was added simultaneously. After 5 h, water (3 mL) was added to the reaction and the reaction was further diluted by dichloromethane (3 mL). The layers were

separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 10% ethyl acetate/hexane to 20% ethyl acetate/hexane) to yield **28.5** as white solid (1 mg, 33%): *R_f* = 0.19 (20% ethyl acetate/hexane). ¹H NMR (600 MHz, CDCl₃) δ 7.34 (d, *J* = 8.2 Hz, 8H), 7.15 (d, *J* = 8.2 Hz, 8H), 6.08 (s, 8H), 3.43 (s, 12H), 2.88 – 2.85 (m, 8H), 2.79 – 2.75 (m, 8H). HRMS (ESI-TOF) calc'd for C₄₈H₅₂O₄Na ([M+Na]⁺) *m/z* = 779.3205 found 779.3185.



Compound 29.1: The diiodide **28.4** (9 mg, 0.015 mmol) was dissolved in tetrahydrofuran (4 mL) and cooled to -78 °C. To this solution was added a 2.3 M solution of *n*-butyllithium in hexanes (0.01 mL, 0.023 mmol) over 1 min. The reaction was slowly warmed to room temperature and water (3 mL) was added to the reaction which was further diluted by dichloromethane (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL). The

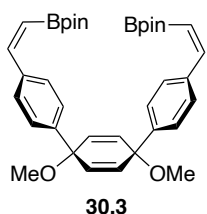
combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 10% ethyl acetate/hexane to 40% ethyl acetate/hexane) to yield **29.1** as white solid (2 mg, 38%): *R_f* = 0.23 (30% ethyl acetate/hexane). ¹H NMR (500 MHz, CDCl₃) δ 7.32 (d, *J* = 6.7 Hz, 4H), 7.15 (d, *J* = 6.7 Hz, 4H), 6.10 (s, 4H), 3.43 (s, 6H), 2.63 (q, *J* = 7.6 Hz, 4H), 1.22 (d, *J* = 7.6 Hz, 6H).



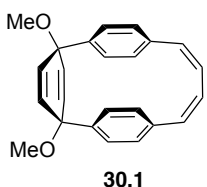
Dibromide 30.2: To a dry 25 mL round bottom flask was added tetrahydrofuran (8 mL) and (bromomethyl) triphenylphosphonium bromide (352 mg, 0.81 mmol). The mixture was then cooled to -78 °C and then potassium *tert*-butoxide (62 mg, 0.55 mmol) was added and stirred for 1 h. Then dialdehyde **3.1** (62 mg, 0.18 mmol) as a solution in 5 mL tetrahydrofuran was added to the reaction at -78 °C. The reaction mixture was allowed to warm slowly and stirred for additional

4 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (1.3 cm × 16 cm; 5% ethyl acetate/hexane to 10% ethyl

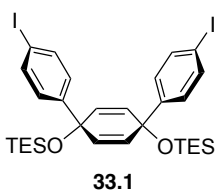
acetate/hexane) to yield **30.2** as white solid (61 mg, 68%): $R_f = 0.39$ (15% ethyl acetate/hexane). $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 7.66 (d, $J = 8.2$ Hz, 4H), 7.42 (d, $J = 8.3$ Hz, 4H), 7.06 (d, $J = 8.1$ Hz, 2H), 6.43 (d, $J = 8.1$ Hz, 2H), 6.13 (s, 4H), 3.45 (s, 6H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 143.64, 134.46, 133.54, 132.19, 129.34, 126.15, 106.72, 75.02, 52.27. HRMS (ESI-TOF) calc'd for $\text{C}_{24}\text{H}_{22}\text{O}_2\text{NaBr}_2$ ($[\text{M}+\text{Na}]^+$) $m/z = 522.9884$ found 522.9886.



Bis-boronate 30.3: Methyl protected bis bromo styrene **30.2** (151 mg, 0.30 mmol) was dissolved in 10 mL of tetrahydrofuran and cooled to -78 °C. To this solution was added a 2.3 M solution of *n*-butyllithium in hexanes (0.3 mL, 0.69 mmol) over 2 min. Immediately after addition of the alkyl lithium reagent, neat isopropyl pinacol borate (530 mg, 2.84 mmol) was added rapidly and the solution was stirred for 2h. Water (20 mL) was then added to the solution and the mixture was further diluted by dichloromethane (10 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm \times 16 cm; 5% ethyl acetate/hexane to 15% ethyl acetate/hexane) to yield **30.3** as white solid (45 mg, 25%): $R_f = 0.38$ (20% ethyl acetate/hexane). $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 7.52 (d, $J = 8.1$ Hz, 4H), 7.35 (d, $J = 8.2$ Hz, 4H), 7.16 (d, $J = 15.0$ Hz, 2H), 6.11 (s, 4H), 5.57 (d, $J = 15.0$ Hz, 2H), 3.44 (d, $J = 3.2$ Hz, 6H), 1.29 (s, 24H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 147.87, 143.38, 137.89, 133.49, 129.01, 125.92, 83.78, 75.05, 52.21, 25.07. HRMS (ESI-TOF) calc'd for $\text{C}_{36}\text{H}_{46}\text{B}_2\text{O}_6\text{Na}$ ($[\text{M}+\text{Na}]^+$) $m/z = 619.3378$ found 619.3354.

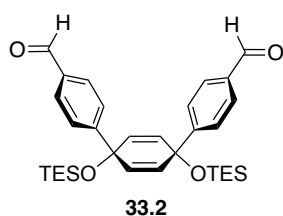


Macrocyclic 1,3-diene 30.1: Methyl protected bis styrene diboronic ester **30.3** (23 mg, 0.038 mmol) was added to a 500 mL round bottom flask with bis(triphenylphosphine)palladium (II) dichloride (2mg, 0.0028 mmol) and boric acid (20 mg, 0.32 mmol). The solid were dissolved in tetrahydrofuran (300 mL) and the mixture was stirred vigorously for 10min. Potassium fluoride (22 mg, 0.378 mmol) was added to the mixture followed by the addition of water (50 mL). The reaction was stirred at room temperature open to the atmosphere for 14 h. The tetrahydrofuran was removed under reduced pressure and the resulting solution was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.8 cm \times 8 cm; 5% ethyl acetate/hexane to 10% ethyl acetate/hexane) to yield **30.1** as white solid (7 mg, 50%): $R_f = 0.40$ (20% ethyl acetate/hexane). $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 6.61 (s, 4H), 6.53 (d, $J = 7.8$ Hz, 4H), 6.44 (d, $J = 7.9$ Hz, 4H), 6.39 (d, $J = 12.3$ Hz, 2H), 6.10 (d, $J = 12.2$ Hz, 2H), 3.35 (s, 6H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 142.56, 138.27, 134.86, 129.58, 126.60, 126.45, 124.99, 77.17, 52.47. HRMS (ESI-TOF) calc'd for $\text{C}_{24}\text{H}_{22}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$) $m/z = 365.1517$ found 365.1517.

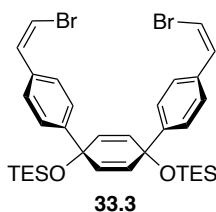


Diiodide 33.1: Syn-1,4-diol **23.1** (1.82 g, 3.54 mmol) was dissolved in 40 mL of dichloromethane and cooled to 0 °C. To this solution was added imidazole (970 mg, 14.2 mmol) at 0 °C. After 30 min, chloro(triethyl)silane (2.10 g, 13.9 mmol) was added to the reaction at

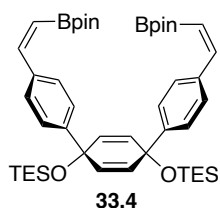
0 °C. The reaction mixture was allowed to warm to rt and stirred for additional 17 h. Water (30 mL) was then added to the solution and the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 5% dichloromethane/hexane to 10% dichloromethane/hexane) to yield **33.1** as white solid (2.50 g, 95%): *R_f* = 0.39 (10% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.5 Hz, 4H), 7.05 (d, *J* = 8.5 Hz, 4H), 5.95 (s, 4H), 0.93 (t, *J* = 7.9 Hz, 18H), 0.60 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 145.94, 137.49, 131.62, 128.13, 93.25, 71.40, 7.26, 6.65.



Dialdehyde 33.2: To a dry 100 mL round bottom flask was added 30 mL diethyl ether and TES protected diiodide **33.1** (2.50 g, 3.36 mmol). The mixture was then cooled to -78 °C and then a 1.48 M solution of *n*-butyllithium in hexanes (5.3 mL, 7.84 mmol) was added over 10 min. After 10 min, *N,N*-dimethyl formamide (1.2 mL, 5.60 g, 76.6 mmol) was added to the reaction. The reaction mixture was allowed to warm to rt and stirred for additional 6 h then added 100 mL water with stirring. The mixture was further diluted by addition of 50 mL ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 5% ethyl acetate/hexane to 10% ethyl acetate/hexane) to yield **33.2** as white solid (1.41 g, 77%): *R_f* = 0.50 (20% ethyl acetate/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.01 (s, 2H), 7.80 (d, *J* = 8.4 Hz, 4H), 7.49 (d, *J* = 8.4 Hz, 4H), 6.05 (s, 4H), 0.95 (t, *J* = 7.9 Hz, 18H), 0.62 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 192.09, 152.61, 131.74, 130.04, 126.71, 71.67, 7.24, 6.66.

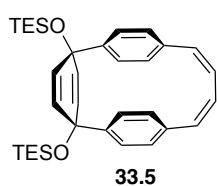


Dibromide 33.3: To a dry 25 mL round bottom flask was added 12 mL tetrahydrofuran and (bromomethyl)triphenylphosphonium bromide (1472 mg, 3.37 mmol). The mixture was then cooled to -78 °C and then potassium *tert*-butoxide (374 mg, 3.33 mmol) was added and stirred for 1 h. Then dialdehyde **33.2** (576 mg, 1.03 mmol) as a solution in 10 mL tetrahydrofuran was added to the reaction at -78 °C. The reaction mixture was allowed to warm slowly and stirred for additional 10 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (1.3 cm × 16 cm; 10% dichloromethane/hexane to 20% dichloromethane/hexane) to yield **33.3** as white solid (448 mg, 62%): *R_f* = 0.47 (20% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.3 Hz, 4H), 7.35 (d, *J* = 8.5 Hz, 4H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 8.1 Hz, 2H), 6.01 (s, 4H), 0.95 (t, *J* = 7.9 Hz, 18H), 0.63 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 146.33, 134.05, 132.27, 131.68, 129.12, 126.01, 106.40, 71.67, 7.30, 6.70.

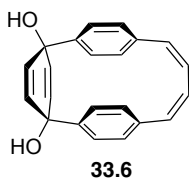


Bis-boronate 33.4: TES protected bis bromo styrene **33.3** (370 mg, 0.53 mmol) was dissolved in 12 mL of tetrahydrofuran and cooled to -78 °C. To this solution was added a 1.4 M solution of *n*-butyllithium in

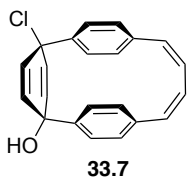
hexanes (0.8 mL, 1.12 mmol) over 2 min. Immediately after addition of the alkyl lithium reagent, neat isopropyl pinacol borate (1 g, 5.80 mmol) was added rapidly and the solution was stirred for 12h. Water (20 mL) was then added to the solution and the mixture was further diluted by dichloromethane (10 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 5% ethyl acetate/hexane to 15% ethyl acetate/hexane) to yield **33.4** as white solid (124 mg, 29%); *R_f* = 0.33 (10% ethyl acetate/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 8.4 Hz, 4H), 7.18 (d, *J* = 14.9 Hz, 2H), 6.00 (s, 4H), 5.58 (d, *J* = 14.9 Hz, 2H), 1.30 (s, 24H), 0.96 (t, *J* = 7.9 Hz, 18H), 0.63 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 148.03, 146.11, 137.57, 131.63, 128.72, 125.72, 83.70, 71.61, 25.02, 7.29, 6.68.



Macrocyclic 1,3-diene 33.5: TES protected bis styrene diboronic ester **33.4** (124mg, 0.15 mmol) was added to a 1 L round bottom flask with bis(triphenylphosphine)palladium (II) dichloride (11 mg, 0.016 mmol) and boric acid (96 mg, 1.55 mmol). The solid were dissolved in tetrahydrofuran (450 mL) and the mixture was stirred vigorously for 10min. Potassium fluoride (190 mg, 3.27 mmol) was added to the mixture followed by the addition of water (80 mL). The reaction was stirred at room temperature open to the atmosphere for 12 h. The tetrahydrofuran was removed under reduced pressure and the resulting solution was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 10% dichloromethane/hexane to 20% dichloromethane/hexane) to yield **33.5** as white solid (22 mg, 26%); *R_f* = 0.32 (20% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.52 (d, *J* = 7.8 Hz, 4H), 6.41 - 6.35 (m, 10H), 6.10 - 6.06 (m, 2H), 0.93 (t, *J* = 7.9 Hz, 18H), 0.58 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 145.86, 137.76, 135.43, 129.66, 126.29, 125.93, 124.77, 73.34, 7.23, 6.59.

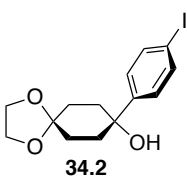


Macrocyclic 1,4-diol 33.6: Tetra-*n*-butylammonium fluoride (100 mg, 0.38 mmol) was added to a stirred solution of TES protected macrocyclic diene **33.5** (22 mg, 0.40 mmol) in tetrahydrofuran (4 mL) at room temperature. After 2 h, water (10 mL) was added to the mixture and further diluted by ethyl acetate (10 mL). The layers were separated, and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 40% ethyl acetate/hexane to 60% ethyl acetate/hexane) to yield **33.6** as white solid (12 mg, 95%); *R_f* = 0.26 (40% ethyl acetate/hexane). ¹H NMR (500 MHz, THF-*d*₈) δ 6.57 (d, *J* = 7.8 Hz, 4H), 6.43 - 6.35 (m, 10H), 6.12 - 6.06 (m, 2H), 2.53 (s, 2H). ¹³C NMR (126 MHz, THF) δ 147.96, 138.91, 137.43, 137.40, 130.93, 127.33, 127.18, 125.62, 72.37.

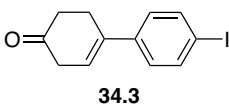


Chloroalcohol 33.7: Tindichloride dihydrate (162 mg, 0.72 mmol) was dissolved in tetrahydrofuran (25 mL) at 23 °C. To this solution 12.1 M hydrochloric acid (0.12 mL, 1.45 mmol) was added and stirred for 30 min.

To a dry 10 mL round bottom flask was added macrocyclic diol **33.6** (6 mg, 0.02 mmol) and dissolved in tetrahydrofuran (2 mL) and warmed at 60 °C. The 29 mM ate complex (0.23 mL, 6.6 mmol) was added to the reaction at 60 °C. After 5 h, the reaction was cooled to room temperature and water (5 mL) was added to the reaction and further diluted by dichloromethane (3 mL). The layers were separated, and the aqueous layer extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 20% ethyl acetate/hexane to 40% ethyl acetate/hexane) to yield **33.7** as white solid (5 mg, 79%): *R_f* = 0.27 (30% ethyl acetate/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.63 - 6.55 (m, 6H), 6.51 (d, *J* = 9.4 Hz, 2H), 6.46 (d, *J* = 7.9 Hz, 4H), 6.40 (d, *J* = 12.0 Hz, 2H), 6.12 (d, *J* = 12.3 Hz, 2H), 2.39 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 143.75, 143.40, 138.87, 138.57, 135.85, 134.83, 129.52, 129.39, 126.71, 125.87, 125.82, 125.39, 125.17, 71.19, 64.01.

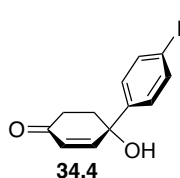


Mono-ketal 34.2: 1,4-diiodobenzene **3.1** (4.37 g, 13.2 mmol) was dissolved in 50 mL of tetrahydrofuran and cooled to -78 °C. To this solution was added a 1.4 M solution of *n*-butyllithium in hexanes (8.5 mL, 24.4 mmol) over 20 min. The reaction mixture was allowed to stir for 20 min. 1,4-Dioxaspiro[4,5]decan-8-one **34.1** (1.7 g, 10.9 mmol) as a solution in 15 mL tetrahydrofuran was added dropwise to the reaction at -78 °C. The solution was stirred for 4 h and then added water (200 mL) with stirring. The mixture was further diluted by the addition of dichloromethane (50 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (2.5 cm × 16 cm; 3% acetone/dichloromethane to 8% acetone/dichloromethane) to yield **34.2** as white solid (3.00 g, 77%): *R_f* = 0.32 (4% acetone/dichloromethane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.30 - 7.27 (m, 2H), 4.06 - 3.94 (m, 4H), 2.19 - 2.03 (m, 4H), 1.82 - 1.75 (m, 2H), 1.73 - 1.67 (m, 2H), 1.51 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 148.58, 137.56, 127.00, 108.47, 92.65, 72.63, 64.65, 64.52, 36.79, 30.90.

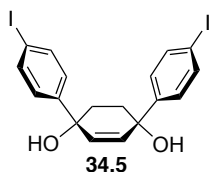


Cyclohexenone 34.3: Compound **34.2** (3.00 g, 8.33 mmol) was dissolved in 50 mL of dichloromethane and cooled to 0 °C. To this solution was added trifluoroacetic acid (12 mL) over 5 min. The solution was stirred for 3 h and then added water (200 mL) with stirring. The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (2.5 cm × 16 cm; 15% ethyl acetate/hexane to 25% ethyl acetate/hexane) to yield **34.3** as white solid (2.45 g, 99%): *R_f* = 0.53 (30% ethyl acetate/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.12 - 6.09 (m, 1H), 3.08 - 3.05 (m, 2H), 2.89 - 2.85 (m, 2H), 2.65 (t, *J* =

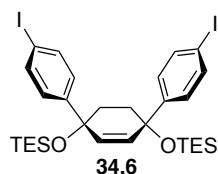
6.9 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 209.74, 140.46, 137.77, 137.12, 127.36, 121.99, 93.01, 40.13, 38.79, 27.94.



Hydroxy enone 34.4: Compound **34.3** (2.45 g, 8.22 mmol) was dissolved in 40 mL of tetrahydrofuran. To this solution was added triphenylphosphine (2.92 g, 11.1 mmol), 1,1,3,3-tetramethylguanidine (410 mg, 3.56 mmol) and copper (II) trifluoromethanesulfonate (155 mg, 0.428 mmol) under air at room temperature. The solution was stirred for 14 h and then added water (200 mL) with stirring. The layers were separated, and the aqueous layer extracted with dichloromethane (3×50 mL). The mixture was further diluted by the addition of dichloromethane (50 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3×50 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (2.5 cm \times 16 cm; 5% acetone/dichloromethane to 10% acetone/dichloromethane) to yield **34.4** as white solid (1.96 g, 76%): $R_f = 0.37$ (8% acetone/dichloromethane). ^1H NMR (500 MHz, Chloroform- d) δ 7.74 (d, $J = 8.5$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 10.1$ Hz, 1H), 6.18 (d, $J = 10.1$ Hz, 1H), 2.67 - 2.60 (m, 1H), 2.42 - 2.26 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3) δ 198.87, 151.45, 143.64, 138.08, 138.05, 130.27, 127.62, 94.17, 72.65, 39.12, 34.58.

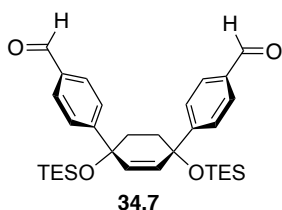


Syn-cyclohex-2-ene-1,4-diol 34.5: Compound **34.4** (304 mg, 0.97 mmol) was dissolved in 15 mL of tetrahydrofuran. To this solution was added sodium hydride (44 mg, 1.10 mmol, 60% in mineral oil) at room temperature and cooled to -78 $^\circ\text{C}$. The solution was stirred for 40 min. In a separate 50 mL flask, 1,4-diodobenzene (980 mg, 2.97 mmol) was dissolved in 20 mL dry tetrahydrofuran. This solution was cooled down to -78 $^\circ\text{C}$. To this solution was added a 1.58 M solution of *n*-butyllithium in hexanes (1.7 mL, 2.70 mmol) was added slowly over 10 min, then the reaction mixture was allowed to stir for 30 min at -78 $^\circ\text{C}$ to give 4-iodophenyllithium reagent. This aryl lithium reagent was transferred to the slurry containing deprotonated ketone via cannula. The resulting mixture was allowed to stir for another 3 h at -78 $^\circ\text{C}$ before it warmed up to room temperature. Water (30 mL) was then added to the reaction with stirring. The mixture was further diluted by the addition of 15 mL dichloromethane. The layers were separated, and the aqueous layer extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm \times 16 cm; 35% ethyl acetate/hexane to 45% ethyl acetate/hexane) to yield *syn* diol **34.5** as white solid (260 g, 52%): $R_f = 0.18$ (40% ethyl acetate/hexane). ^1H NMR (500 MHz, Chloroform- d) δ 7.70 (d, $J = 8.5$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 6.03 (s, 2H), 2.24 (s, 2H), 2.18 - 2.11 (m, 2H), 1.89 - 1.82 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 145.84, 137.76, 134.65, 127.75, 93.47, 72.37, 36.38.

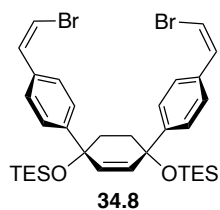


Diiodide 34.6: Diol **34.5** (259 mg, 0.50 mmol) was dissolved in 20 mL of dichloromethane and cooled to 0 $^\circ\text{C}$. To this solution was added imidazole (136 mg, 2.00 mmol) at 0 $^\circ\text{C}$. After 30 min, chloro(triethyl)silane (770 mg, 5.10 mmol) was added to the reaction at 0 $^\circ\text{C}$. The reaction mixture was allowed to warm to rt and stirred for

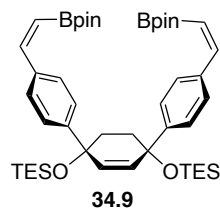
additional 20 h. Water (20 mL) was then added to the solution and the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 5% dichloromethane/hexane to 10% dichloromethane/hexane) to yield **34.6** as white solid (317 mg, 85%): *R_f* = 0.34 (10% dichloromethane/hexane). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.5 Hz, 4H), 7.16 (d, *J* = 8.4 Hz, 4H), 2.16 (dd, *J* = 13.7, 9.4 Hz, 2H), 1.63 (dd, *J* = 13.7, 9.4 Hz, 2H), 0.90 (t, *J* = 7.9 Hz, 18H), 0.52 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (151 MHz, CDCl₃) δ 147.57, 137.33, 134.55, 128.07, 92.87, 74.47, 38.11, 7.29, 6.89.



Dialdehyde 34.7: To a dry 50 mL round bottom flask was added 15 mL diethyl ether and TES protected diiodide **34.6** (317 mg, 0.42 mmol). The mixture was then cooled to -78 °C and then a 1.58 M solution of *n*-butyllithium in hexanes (0.64 mL, 1.01 mmol) was added over 10 min. After 10 min, *N,N*-dimethyl formamide (1.0 mL, 4.00 g, 51.2 mmol) was added to the reaction. The reaction mixture was allowed to warm to rt and stirred for additional 6 h then added 100 mL water with stirring. The mixture was further diluted by addition of 20 mL ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 5% ethyl acetate/hexane to 10% ethyl acetate/hexane) to yield **34.7** as white solid (157 mg, 67%): *R_f* = 0.18 (10% ethyl acetate/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.00 (s, 2H), 7.84 (d, *J* = 8.3 Hz, 4H), 7.62 (d, *J* = 8.4 Hz, 4H), 6.24 (s, 2H), 2.28 - 2.20 (m, 2H), 1.73 - 1.65 (m, 2H), 0.90 (t, *J* = 8.0 Hz, 18H), 0.54 (q, *J* = 8.0 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 192.12, 154.57, 135.65, 134.61, 129.88, 126.61, 74.63, 38.02, 7.27, 6.85.

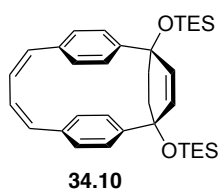


Dibromide 34.8: To a dry 25 mL round bottom flask was added 8 mL tetrahydrofuran and (bromomethyl)triphenylphosphonium bromide (444 mg, 1.01 mmol). The mixture was then cooled to -78 °C and then potassium *tert*-butoxide (111 mg, 0.98 mmol) was added and stirred for 1 h. Then dialdehyde **34.7** (157 mg, 0.28 mmol) as a solution in 5 mL tetrahydrofuran was added to the reaction at -78 °C. The reaction mixture was allowed to warm slowly and stirred for additional 4 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (1.3 cm × 16 cm; 10% dichloromethane/hexane to 15% dichloromethane/hexane) to yield **34.8** as white solid (110 mg, 55%): *R_f* = 0.49 (20% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.40 (d, *J* = 8.1 Hz, 2H), 6.17 (s, 2H), 2.24 - 2.17 (m, 2H), 1.77 - 1.70 (m, 2H), 0.91 (t, *J* = 7.9 Hz, 18H), 0.55 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 148.02, 134.61, 133.81, 132.27, 128.94, 125.91, 106.22, 74.69, 38.07, 7.35, 6.89.

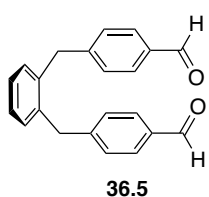


Bis-boronate 34.9: Compound **34.8** (110 mg, 0.16 mmol) was dissolved in 10 mL of tetrahydrofuran and cooled to -78 °C. To this

solution was added a 1.58 M solution of *n*-butyllithium in hexanes (0.24 mL, 0.38 mmol) over 2 min. Immediately after addition of the alkyl lithium reagent, neat isopropyl pinacol borate (433 mg, 2.32 mmol) was added rapidly and the solution was stirred for 6 h. Water (20 mL) was then added to the solution and the mixture was further diluted by dichloromethane (10 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 40% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **34.9** as white solid (40 mg, 32%): *R_f* = 0.22 (60% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.3 Hz, 4H), 7.37 (d, *J* = 8.4 Hz, 4H), 7.19 (d, *J* = 14.9 Hz, 2H), 6.16 (s, 2H), 5.56 (d, *J* = 14.8 Hz, 2H), 2.22 - 2.15 (m, 2H), 1.74 - 1.66 (m, 2H), 1.27 (d, *J* = 3.6 Hz, 24H), 0.91 (t, *J* = 7.9 Hz, 18H), 0.53 (q, *J* = 7.9 Hz, 12H). ¹³C NMR (126 MHz, CDCl₃) δ 148.17, 147.65, 137.48, 134.64, 128.48, 125.60, 83.69, 74.74, 38.15, 25.04, 25.01, 7.36, 6.89.

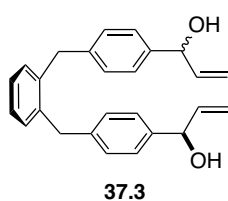


Macrocyclic 1,3-diene 34.10: Bis-boronate **34.9** (20mg, 0.02 mmol) was added to a 100 mL round bottom flask with bis(triphenylphosphine)palladium (II) dichloride (4.00 mg, 0.006 mmol) and boric acid (14 mg, 0.23 mmol). The solid were dissolved in tetrahydrofuran (70 mL) and the mixture was stirred vigorously for 10min. Potassium fluoride (24 mg, 0.41 mmol) was added to the mixture followed by the addition of water (10 mL). The reaction was stirred at room temperature open to the atmosphere for 12 h. The tetrahydrofuran was removed under reduced pressure and the resulting solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 10% dichloromethane/hexane to 20% dichloromethane/hexane) to yield **34.10** as white solid (1.00 mg, 9%): *R_f* = 0.29 (20% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.57 (dd, *J* = 8.1, 2.1 Hz, 2H), 6.47 - 6.41 (m, 4H), 6.33 (dd, *J* = 8.2, 1.9 Hz, 2H), 6.30 - 6.27 (m, 4H), 6.18 - 6.13 (m, 2H), 2.64 (d, *J* = 8.3 Hz, 2H), 2.12 (d, *J* = 8.5 Hz, 2H), 0.82 (t, *J* = 7.9 Hz, 18H), 0.39 (q, *J* = 8.2 Hz, 12H).

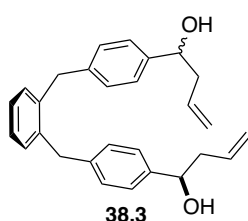


Dialdehyde 36.5: Potassium carbonate (3.62 g, 26.2 mmol), 4-formylphenyl boronic acid (2.27 g, 15.2 mmol) and palladium chloride (38 mg, 0.21 mmol) was added sequentially to a stirred solution of α, α'-dibromo-*o*-xylene **37.1** (1.13 g, 4.29 mmol) in acetone (15 mL) and water (5 mL) at 0 °C under argon and the reaction temperature was raised to 50 °C. After 17 h, water (20 mL) was added to the reaction, and it was further diluted by dichloromethane (20 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (2.5 cm × 16 cm; 80% dichloromethane/hexane to 100% dichloromethane) to yield **36.5** as white solid (290 mg, 21%): *R_f* = 0.46 (100% dichloromethane). ¹H NMR (600 MHz, Chloroform-*d*) δ 9.97 (s, 2H), 7.77 (d, *J* = 7.8 Hz, 4H), 7.29 (dd, *J* = 5.7, 3.3 Hz, 2H),

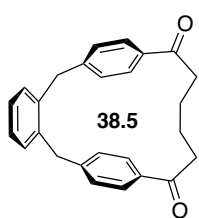
7.20 (d, $J = 7.8$ Hz, 4H), 7.17 (dd, $J = 5.7, 3.4$ Hz, 2H), 3.99 (s, 4H). ^{13}C NMR (151 MHz, CDCl_3) δ 192.24, 147.79, 138.00, 134.84, 131.23, 130.24, 129.47, 127.58, 39.56.



Bis-allylic diol 37.3: Vinylmagnesium chloride (0.4 mL, 1.7 M, 0.68 mmol) was added to a stirred solution of dialdehyde **36.5** (82 mg, 0.26 mmol) in dichloromethane (10 mL) at 23 °C. After 45 min, the reaction was poured into water (15 mL) and further diluted with 1 M HCl (4 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm \times 16 cm; 30% ethyl acetate/hexane to 40% ethyl acetate/hexane) to yield **37.3** as white solid (56 mg, 58%): $R_f = 0.42$ (50% ethyl acetate/hexane). ^1H NMR (600 MHz, Chloroform- d) δ 7.25 - 7.15 (m, 8H), 6.99 (d, $J = 7.7$ Hz, 4H), 6.03 (ddd, $J = 16.7, 10.2, 6.0$ Hz, 2H), 5.34 (d, $J = 17.1$ Hz, 2H), 5.19 (d, $J = 10.4$ Hz, 2H), 5.15 (d, $J = 5.8$ Hz, 2H), 3.95 (s, 4H), 2.33 (s, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 140.37, 140.36, 140.23, 140.12, 139.02, 131.04, 128.99, 126.92, 126.55, 126.52, 115.18, 75.33, 75.31, 39.02. HRMS (ESI-TOF) calc'd for $\text{C}_{26}\text{H}_{26}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$) $m/z = 393.1831$ found 393.1845.

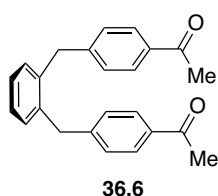


Bis-homoallylic diol 38.3: Allylmagnesium chloride (0.2 mL, 2.0 M, 0.40 mmol) was added to a stirred solution of dialdehyde **37.3** (53 mg, 0.17 mmol) in dichloromethane (8 mL) at 23 °C. After 30 min, the reaction was poured into water (15 mL) and further diluted with 1 M HCl (3 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1 cm \times 16 cm; 2% acetone/dichloromethane to 3% acetone/dichloromethane) to yield **38.3** as white solid (36 mg, 54%): $R_f = 0.41$ (5% acetone/dichloromethane). ^1H NMR (600 MHz, Chloroform- d) δ 7.28 - 7.21 (m, 2H), 7.21 - 7.15 (m, 6H), 6.99 (dd, $J = 7.6$ Hz, 7.6 Hz, 4H), 5.81 (ddt, $J = 17.5, 10.7, 7.3$ Hz, 2H), 5.20 - 5.12 (m, 4H), 4.67 (dt, $J = 9.2, 4.6$ Hz, 2H), 3.95 (s, 4H), 2.52 - 2.42 (m, 2H), 2.38 - 2.31 (m, 2H).



Macrocyclic 1,6-diketone 38.5: Bis-homoallylic diol **38.3** (36 mg, 0.09 mmol) was dissolved in dichloromethane (11 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (5 mg, 0.008 mmol). After 2h, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (9 mL), and sodium borohydride (30 mg, 0.789 mmol) was added. After 4 h, the reaction was poured into water (15 mL) and further diluted with 1M HCl (5 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with water (15 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (8 mL), followed by the sequential addition of NaHCO_3 (50 mg, 0.59 mmol), and Dess-

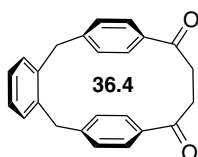
Martin periodinane (85 mg, 0.19 mmol). After 4 h, 1:1 saturated solution of NaHCO₃/20% Na₂S₂O₃ solution (20 mL) was added to the reaction and stirred for 1 h. The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1 cm × 16 cm; 20% ethyl acetate/hexane to 30% ethyl acetate/hexane) to yield **38.5** as white solid (11 mg, 33% from **38.3**): *R_f* = 0.16 (25% ethyl acetate/hexane). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 - 7.37 (m, 4H), 7.33 - 7.28 (m, 4H), 6.74 (d, *J* = 7.8 Hz, 4H), 4.08 (s, 4H), 2.78 - 2.72 (m, 4H), 1.51 (p, *J* = 3.2 Hz, 4H). ¹³C NMR (151 MHz, CDCl₃) δ 202.01, 145.71, 137.75, 133.81, 132.62, 128.28, 127.87, 127.63, 40.07, 39.91, 24.29.



Dimethyl ketone 36.6: Methylmagnesium chloride (0.5 mL, 3.0 M, 1.5 mmol) was added to a stirred solution of dialdehyde **36.5** (180 mg, 0.57 mmol) in dichloromethane (10 mL) at 23 °C. After 20 min, the reaction was poured into water (15 mL) and further diluted with 1 M HCl (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄,

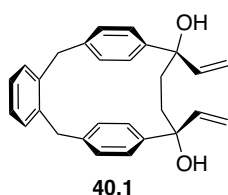
filtered, and concentrated under reduced pressure. The white residue was dissolved in dichloromethane (12 mL), followed by the sequential addition of NaHCO₃ (256 mg, 3.04 mmol), and Dess-Martin periodinane (586 mg, 1.30 mmol). After 18 h, 1:1 saturated solution of NaHCO₃/20% Na₂S₂O₃ solution (20 mL) was added to the reaction and stirred for 1 h. The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 20% ethyl acetate/hexane to 25% ethyl acetate/hexane) to yield **36.6** as white solid (156 mg, 80% from **36.5**): *R_f* = 0.30 (30% ethyl acetate/hexane). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 7.8 Hz, 4H), 7.38 (dd, *J* = 6.2, 3.1 Hz, 2H), 7.26 (dd, *J* = 14.5, 6.2 Hz, 6H), 4.08 (s, 4H), 2.70 (s, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 198.15, 146.20, 138.20, 135.31, 131.09, 129.01, 128.79, 127.38, 39.32, 26.89. HRMS (ESI-TOF) calc'd for C₂₄H₂₃O₂ ([M+H]⁺) *m/z* = 343.1698 found 343.1689.

Alternative procedure: Potassium carbonate (4.60 g, 33.2 mmol), 4-acetylphenyl boronic acid (2.19 g, 13.4 mmol) and palladium chloride (9 mg, 0.05 mmol) was added sequentially to a stirred solution of α, α'-dibromo-*o*-xylene **37.1** (1.36 g, 5.15 mmol) in acetone (15 mL) and water (5 mL) at room temperature under argon and the reaction temperature was raised to 50 °C. After 23 h, water (30 mL) was added to the reaction, and it was further diluted by dichloromethane (20 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (2.5 cm × 18 cm; 20% ethyl acetate/hexane to 25% ethyl acetate/hexane) to yield **36.6** as white solid (742 mg, 42%).



Macrocyclic 1,4-diketone 36.4: Diisopropylamine (0.9 mL, 636 mg, 6.28 mmol) was dissolved in tetrahydrofuran (24 mL) at room temperature and cooled to 0 °C. To this solution was added a 2.45 M

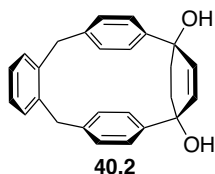
solution of *n*-butyllithium in hexanes (2.2 mL, 5.39 mmol) slowly and stirred at 0 °C for 30 min. After 30 min, the mixture was cooled to -78 °C and dimethyl diketone **36.6** (490 mg, 1.44 mmol) dissolved in tetrahydrofuran (6 mL) was added dropwise to the mixture at -78 °C over 20 min, the reaction became yellow. After 1h, (17 mL, 0.308 M, 5.24 mmol) copper (II) chloride in *N,N*-dimethylformamide was added to the reaction at -78 °C and the reaction became green color. After 21 h, saturated ammonium chloride solution (50 mL) was added to the reaction and was further diluted by diethyl ether (20 mL). The layers were separated, and the aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The white residue was dissolved in 2:1 methanol/dichloromethane (6 mL), followed by addition of sodium borohydride (130 mg, 3.63 mmol). After 40 min, water (10 mL) was added to the reaction and was further diluted by 1M HCl (2 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 50% ethyl acetate/hexane to 70% ethyl acetate/hexane) to yield **39.2** as white solid (39 mg, 8% from **36.6**): *R_f* = 0.34 (70% ethyl acetate/hexane). The white solid **39.2** was dissolved in dichloromethane (10 mL) followed by the sequential addition of NaHCO₃ (48 mg, 0.57 mmol), and Dess-Martin periodinane (111 mg, 0.25 mmol). After 3 h, 1:1 saturated solution of NaHCO₃/20% Na₂S₂O₃ solution (12 mL) was added to the reaction and stirred for 1 h. The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1 cm × 16 cm; 25% ethyl acetate/hexane to 30% ethyl acetate/hexane) to yield **36.4** as white solid (30 mg, 80% from **39.2** and 6% from **36.6**): *R_f* = 0.35 (30% ethyl acetate/hexane). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.39 (s, 4H), 7.25 (dd, *J* = 7.8, 2.1 Hz, 2H), 7.01 (dd, *J* = 8.1, 2.2 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.32 (d, *J* = 8.0 Hz, 2H), 4.05 (d, *J* = 16.1 Hz, 2H), 3.97 (d, *J* = 16.0 Hz, 2H), 3.04 (s, 4H). ¹³C NMR (151 MHz, CDCl₃) δ 202.27, 145.46, 137.86, 134.61, 132.81, 129.12, 128.62, 128.60, 127.99, 127.68, 40.33, 35.78. HRMS (ESI-TOF) calc'd for C₂₄H₂₀O₂Na ([M+Na]⁺) *m/z* = 363.1361 found 363.1395.



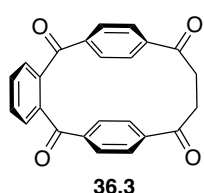
Syn-bis-allylic-1,4-diol 40.1: Vinylmagnesium chloride (0.03 mL, 1.7 M, 0.05 mmol) was added to a stirred solution of macrocyclic diketone **36.4** (7 mg, 0.02 mmol) in dichloromethane (3 mL) at 40 °C. After 20 min, the reaction was poured into water (5 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 5 mL).

The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 6% acetone/dichloromethane to 10% acetone/dichloromethane) to yield **40.1** as white solid (7 mg, 88%): *R_f* = 0.29 (10% acetone/dichloromethane). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 9.7 Hz, 4H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.04 - 6.91 (m, 2H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 6.45 (d, *J* = 9.0 Hz, 1H), 6.29 (p, *J* = 13.1, 10.6 Hz, 3H), 6.15 (d, *J* = 8.2 Hz, 1H), 5.32 (dd, *J* = 17.5, 6.5 Hz, 2H), 5.24 - 5.14 (m, 2H), 4.07 (dd, *J* = 15.6, 8.7 Hz, 2H), 3.96 (d, *J* = 15.7 Hz, 2H), 2.18 - 2.00 (m, 2H), 1.80 - 1.61 (m, 4H). ¹³C NMR (151 MHz, CDCl₃) δ 141.50, 139.02, 138.99, 138.81, 132.43, 132.39, 129.47, 128.72, 128.29,

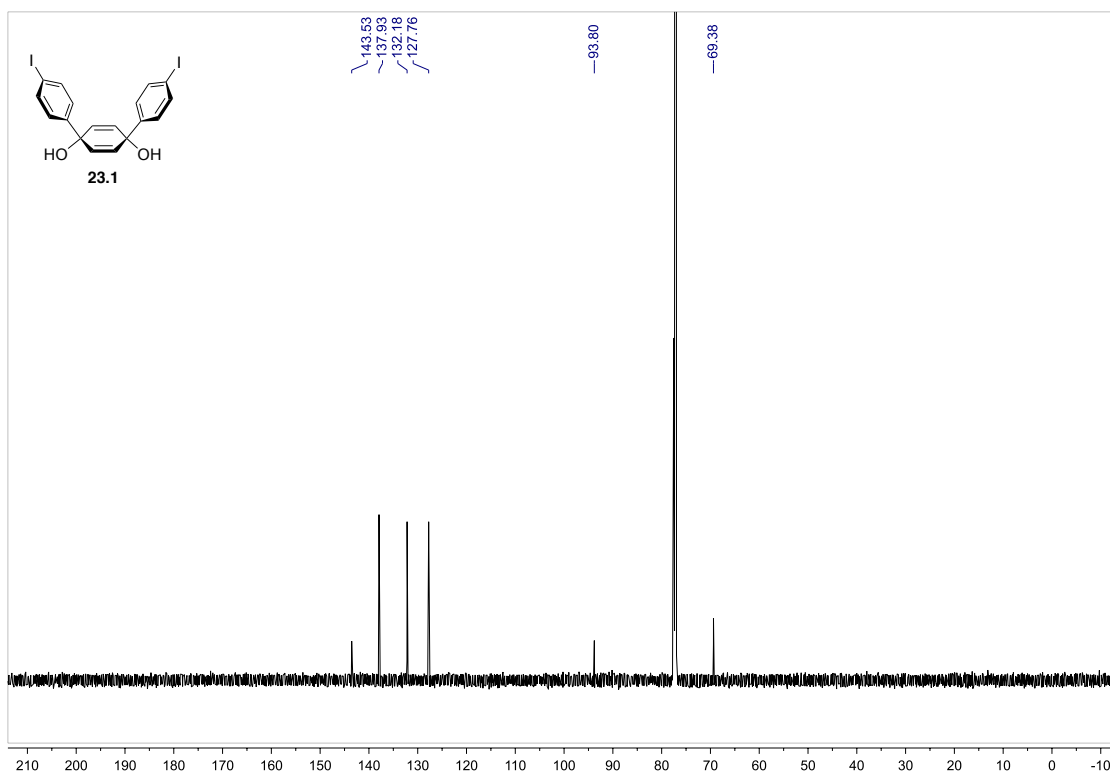
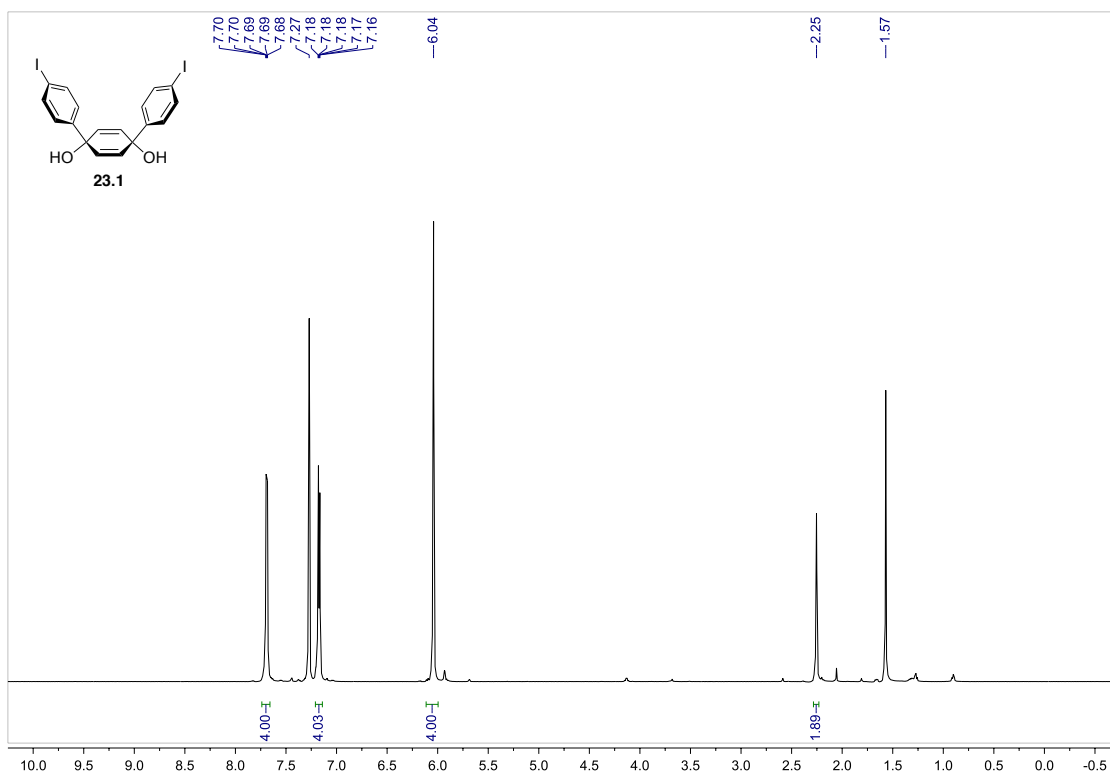
127.44, 127.21, 127.16, 125.71, 125.01, 113.88, 76.60, 76.53, 40.03, 36.95, 36.77, 31.30. HRMS (ESI-TOF) calc'd for $C_{28}H_{28}O_2Na$ ($[M+Na]^+$) $m/z = 419.1987$ found 419.1964.

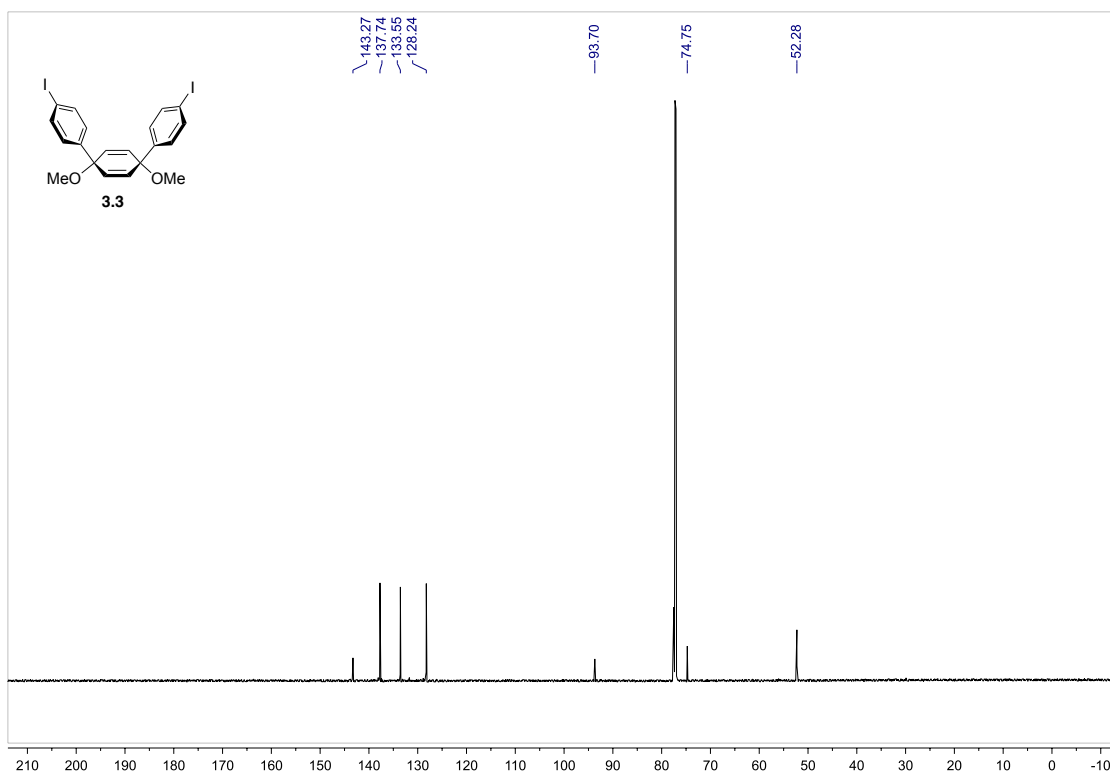
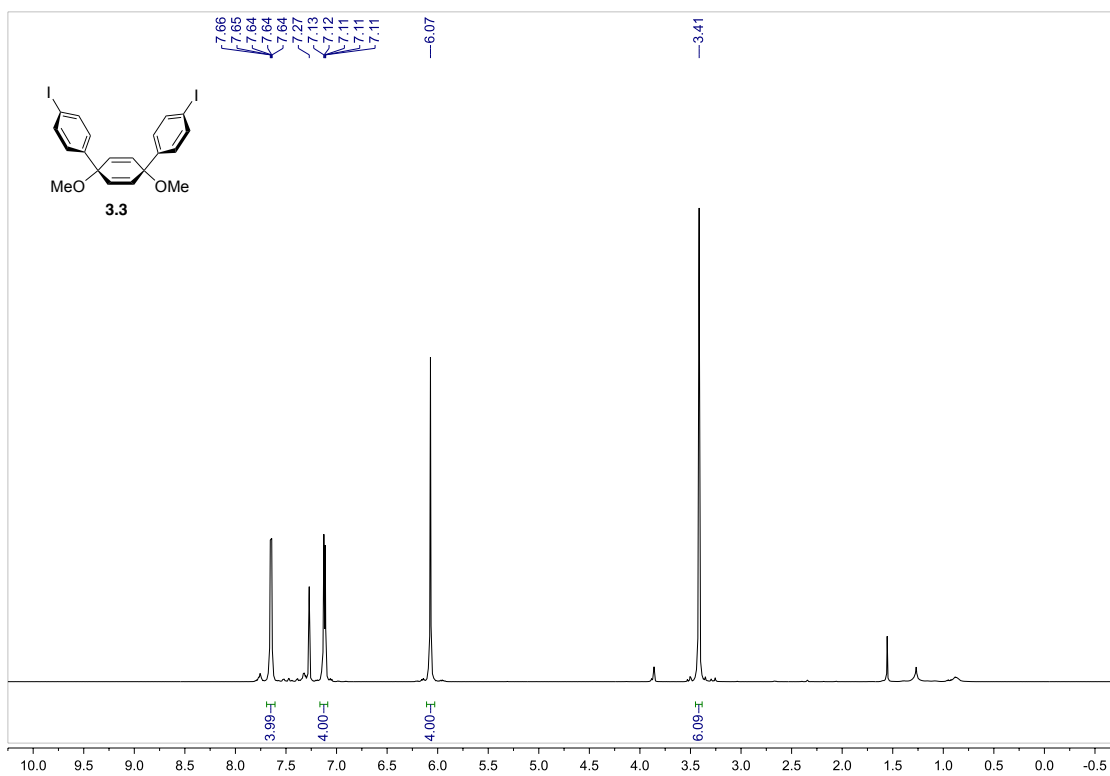


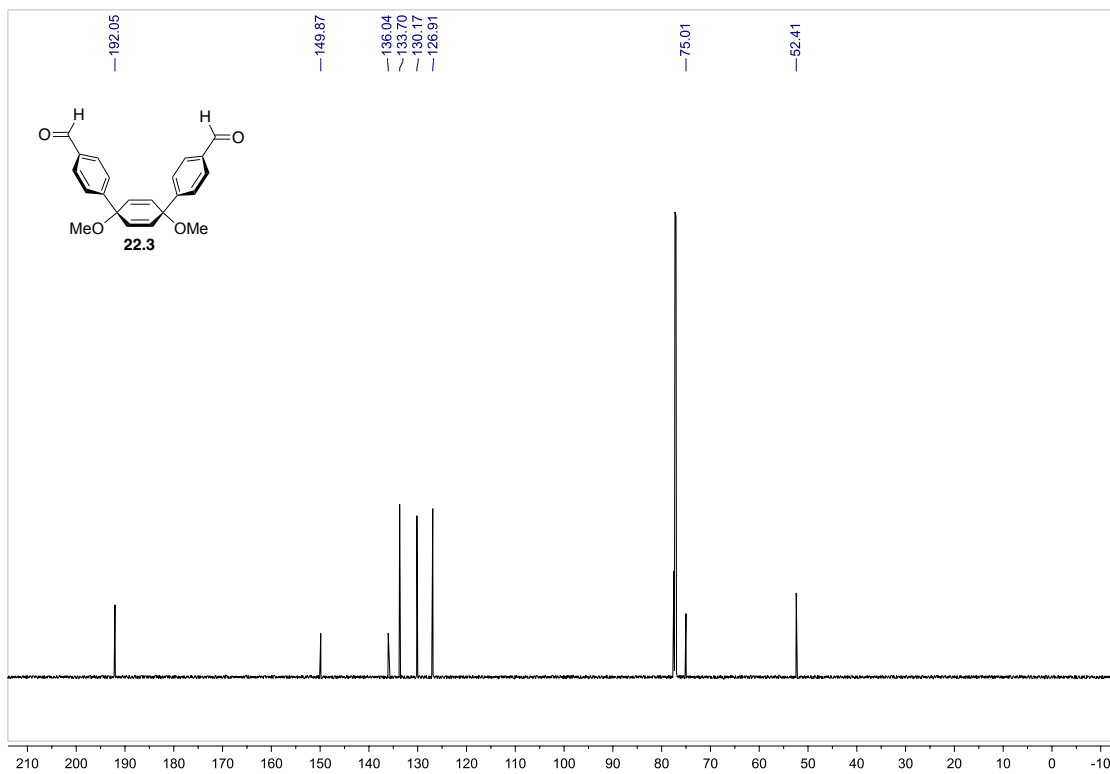
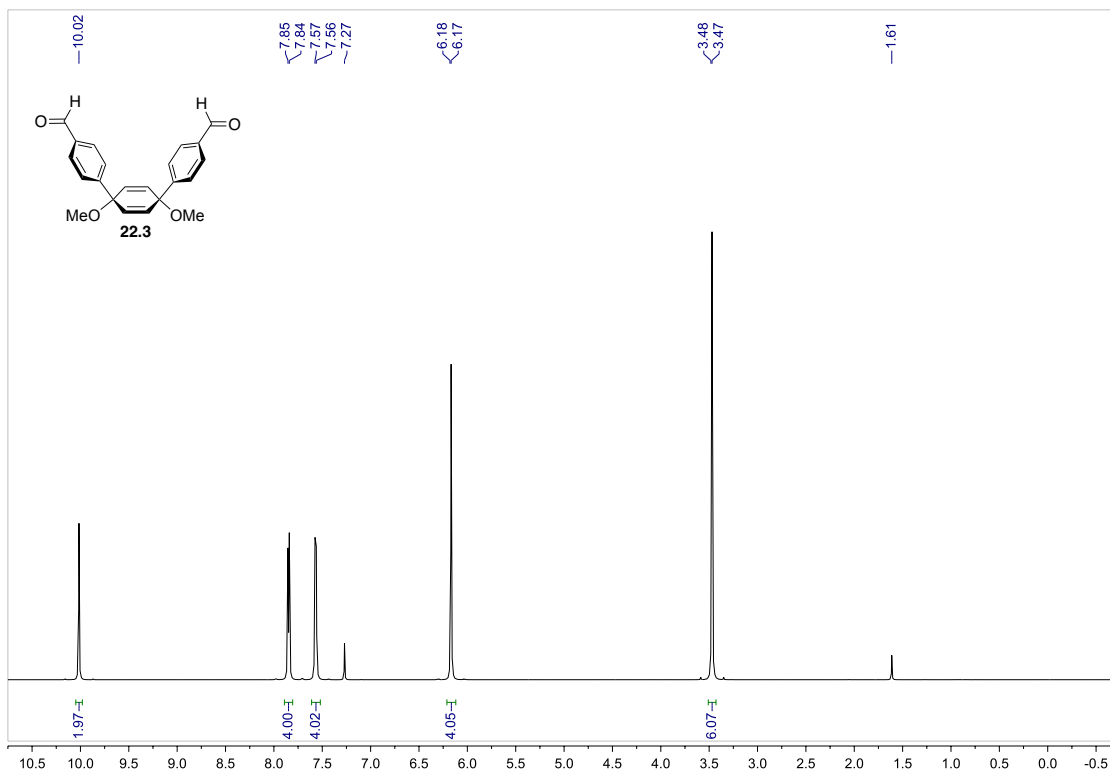
Cyclohex-2-ene-1,4-diol 40.2: Bis-allylic-1,4-diol **40.1** (6 mg, 0.015 mmol) was dissolved in toluene (1.5 mL), heated to 110 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (1 mg, 0.0016 mmol). After 8h, the reaction mixture was concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 50% ethyl acetate/hexane to 70% ethyl acetate/hexane) to yield **40.2** as white solid (3 mg, 54%): $R_f = 0.40$ (60% ethyl acetate/hexane). 1H NMR (500 MHz, Chloroform-*d*) δ 7.33 (dd, $J = 7.7, 1.4$ Hz, 4H), 6.89 - 6.85 (m, 1H), 6.78 - 6.70 (m, 4H), 6.65 - 6.61 (m, 1H), 6.30 (dd, $J = 13.0, 1.4$ Hz, 2H), 6.14 - 6.07 (m, 2H), 3.97 (s, 4H), 2.66 (d, $J = 8.5$ Hz, 1H), 2.56 (d, $J = 8.5$ Hz, 1H), 2.18 - 2.10 (m, 2H), 1.94 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.96, 140.87, 139.44, 139.40, 139.21, 139.09, 137.13, 137.10, 132.59, 132.38, 129.15, 129.01, 128.01, 127.83, 127.70, 127.43, 127.36, 127.33, 125.14, 125.03, 72.04, 71.99, 40.18, 40.07, 33.85, 33.41. HRMS (ESI-TOF) calc'd for $C_{26}H_{24}O_2Na$ ($[M+Na]^+$) $m/z = 391.1674$ found 391.1665.

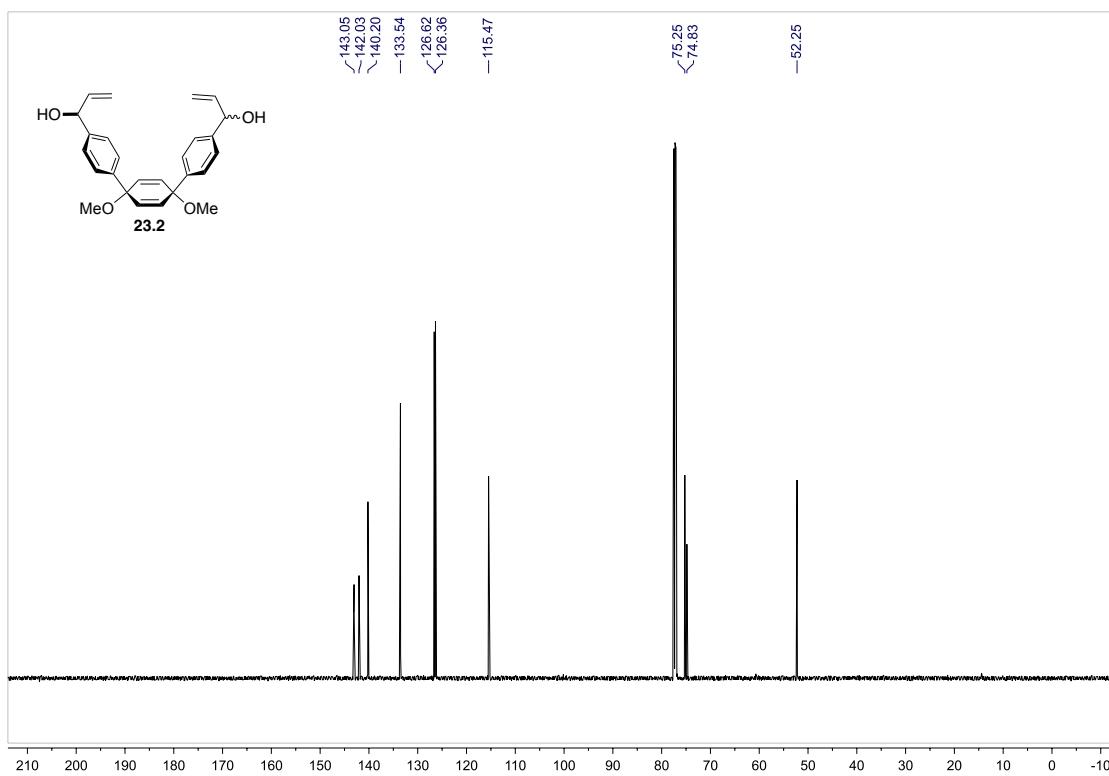
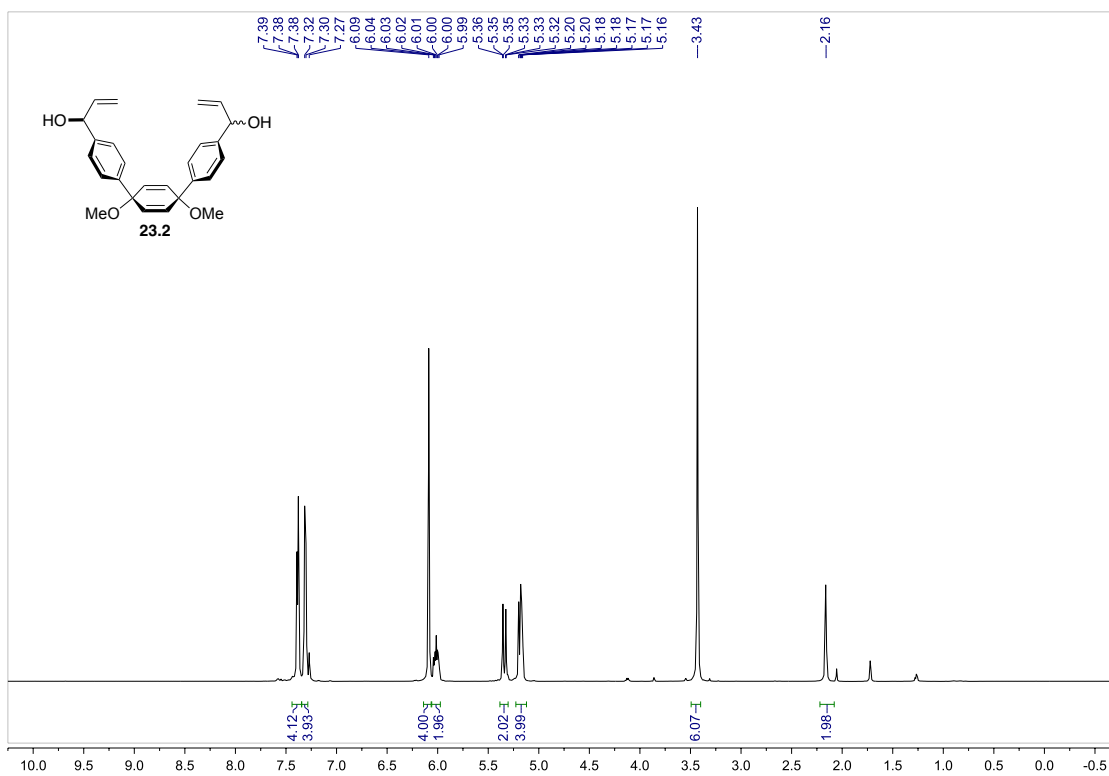


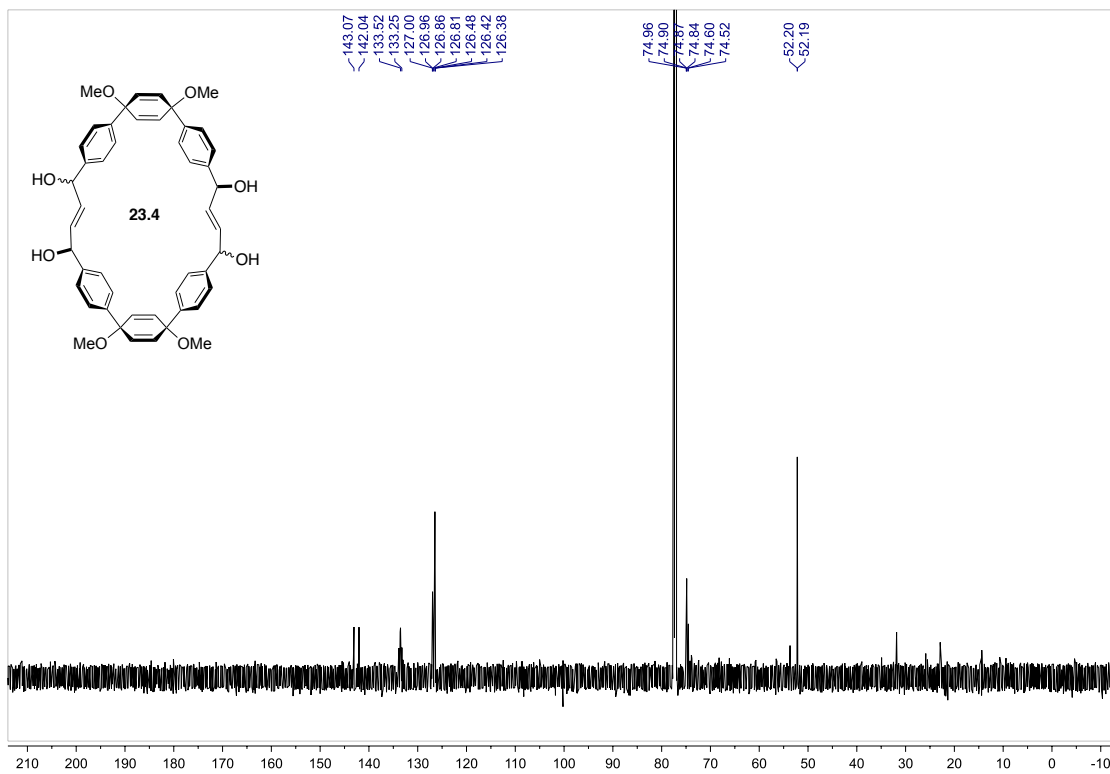
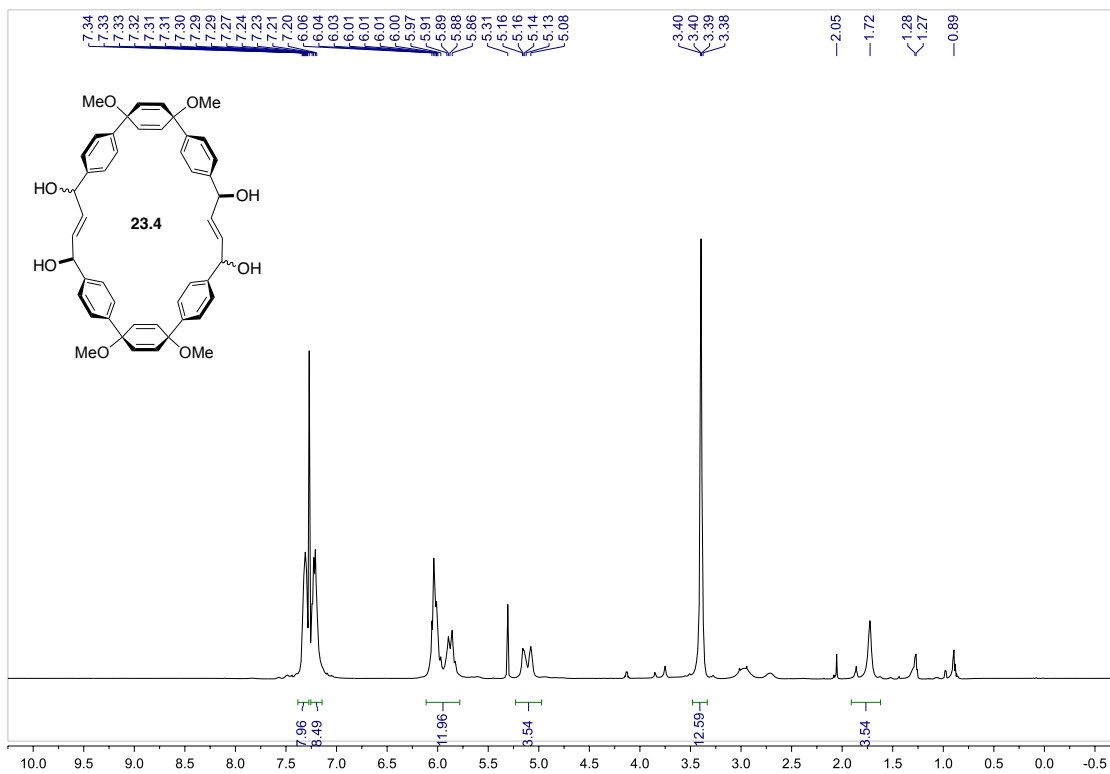
Tetraketone 36.3: Chromium trioxide (26 mg, 0.26 mmol) was added to a stirred solution of macrocyclic 1,4-diketone **36.4** (6 mg, 0.017 mmol) dissolved in acetic anhydride (1mL) at room temperature. After 18 h, the reaction was cooled to 0 °C and 1 M HCl (2 mL) was added to the reaction, and it was further diluted by dichloromethane (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 50% ethyl acetate/hexane to 60% ethyl acetate/hexane) to yield **36.3** as white solid (3 mg, 48%): $R_f = 0.43$ (60% ethyl acetate/hexane). 1H NMR (600 MHz, Chloroform-*d*) δ 7.72 (s, 4H), 7.39 - 7.33 (m, 8H), 3.13 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.64, 196.67, 140.19, 140.04, 139.64, 130.79, 130.36, 128.00, 127.35, 36.09.

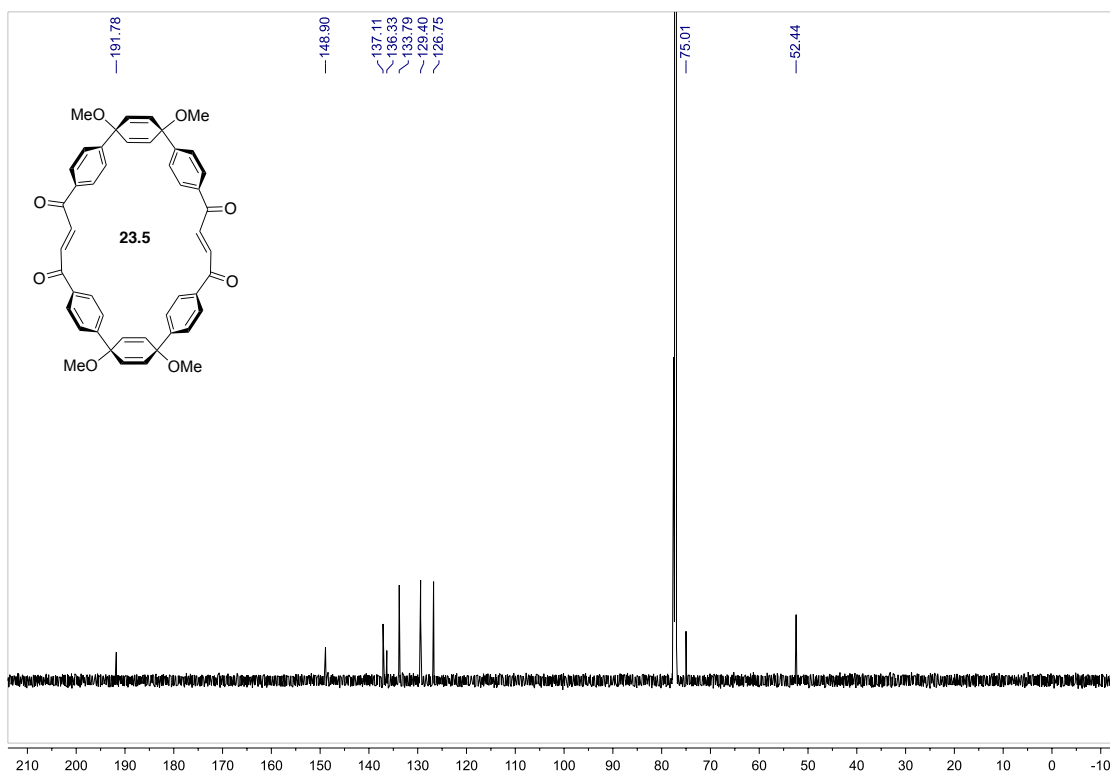
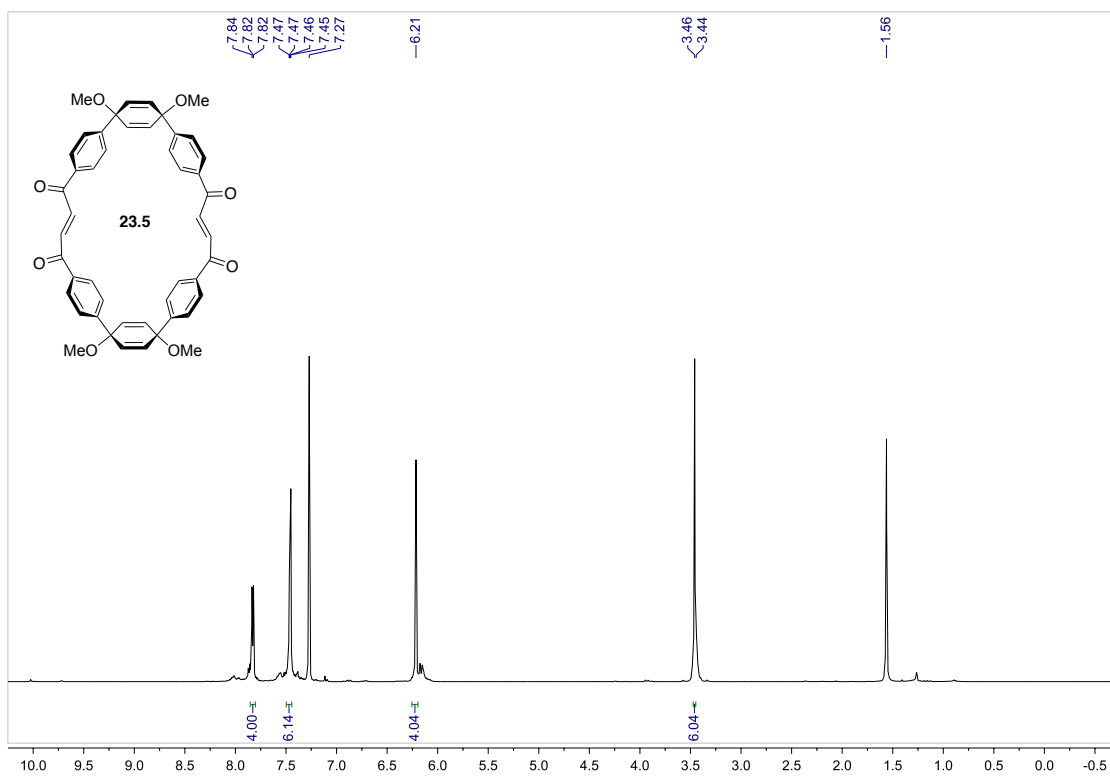


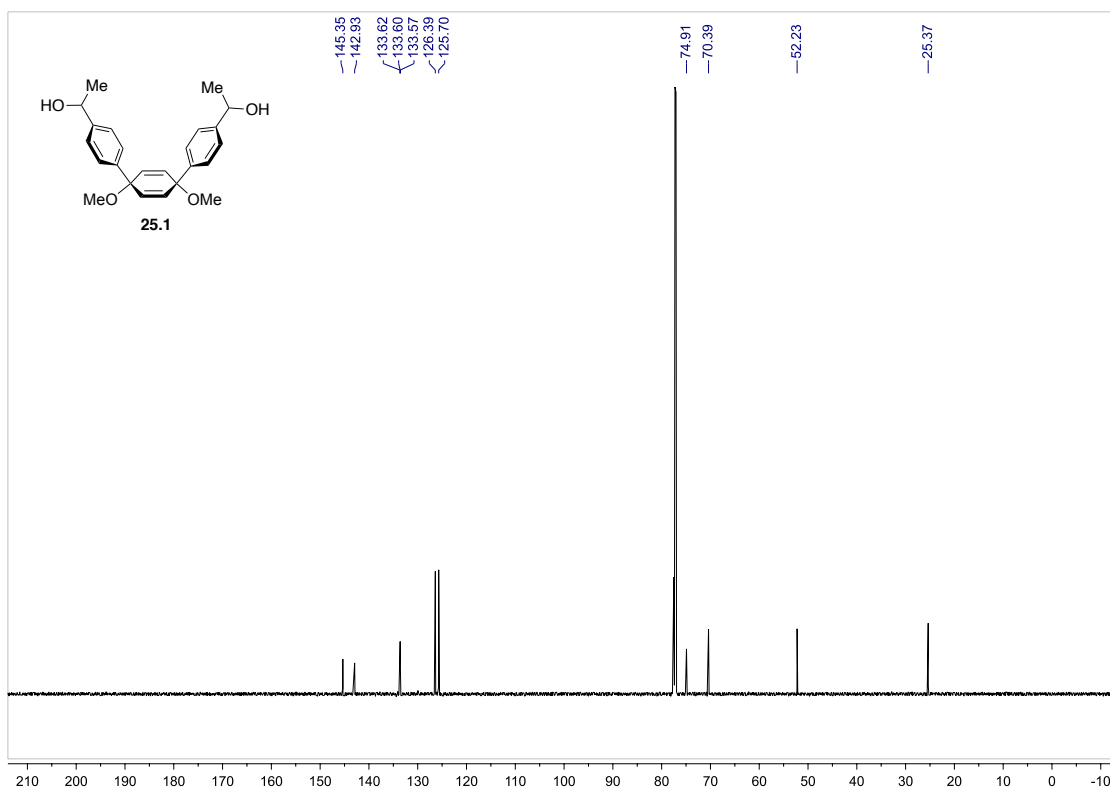
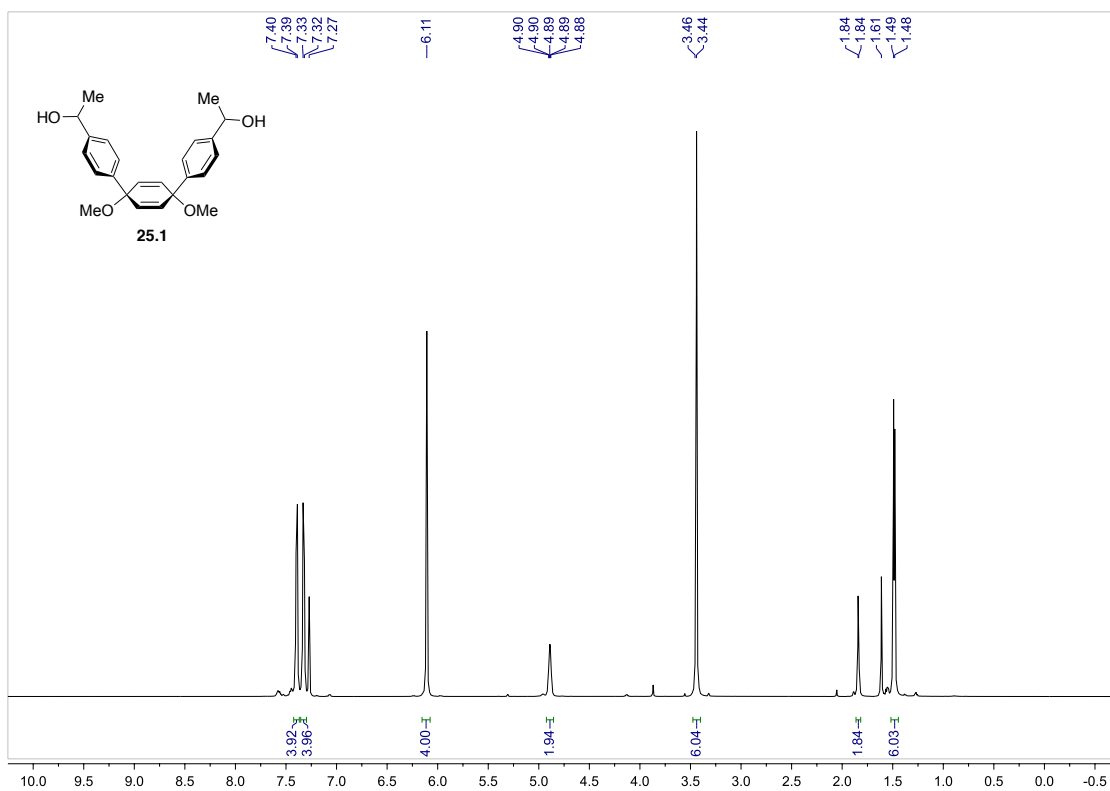


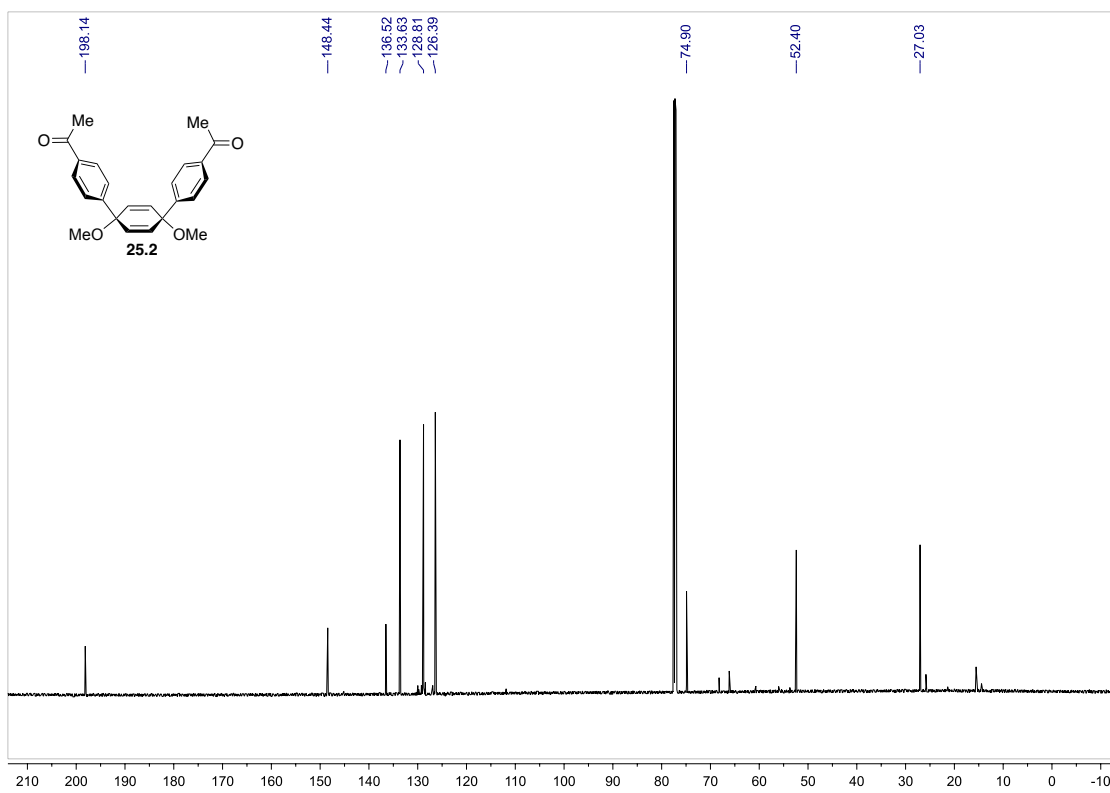
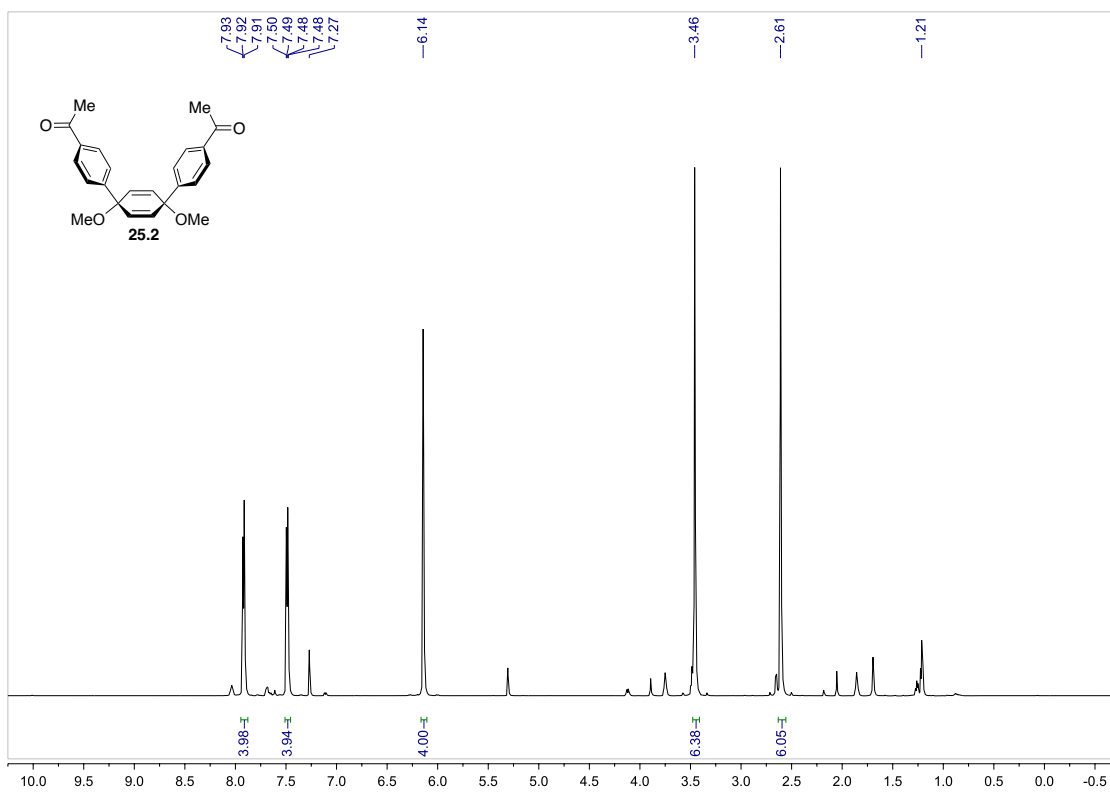


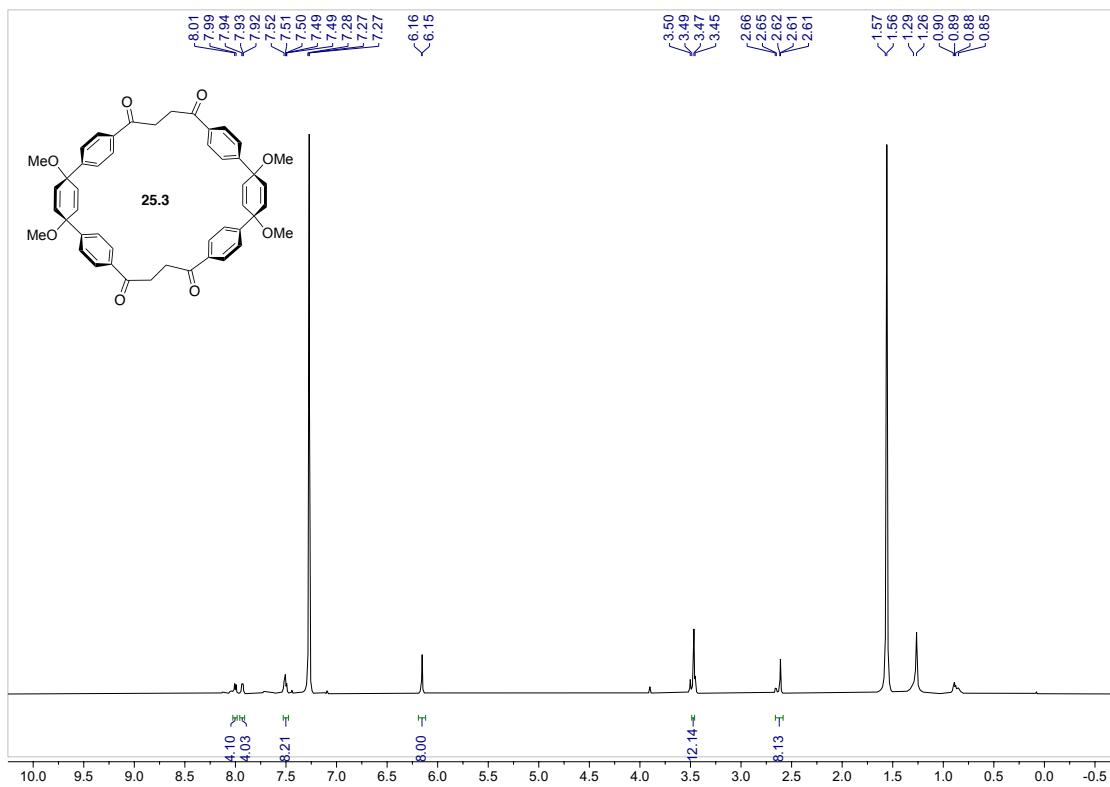


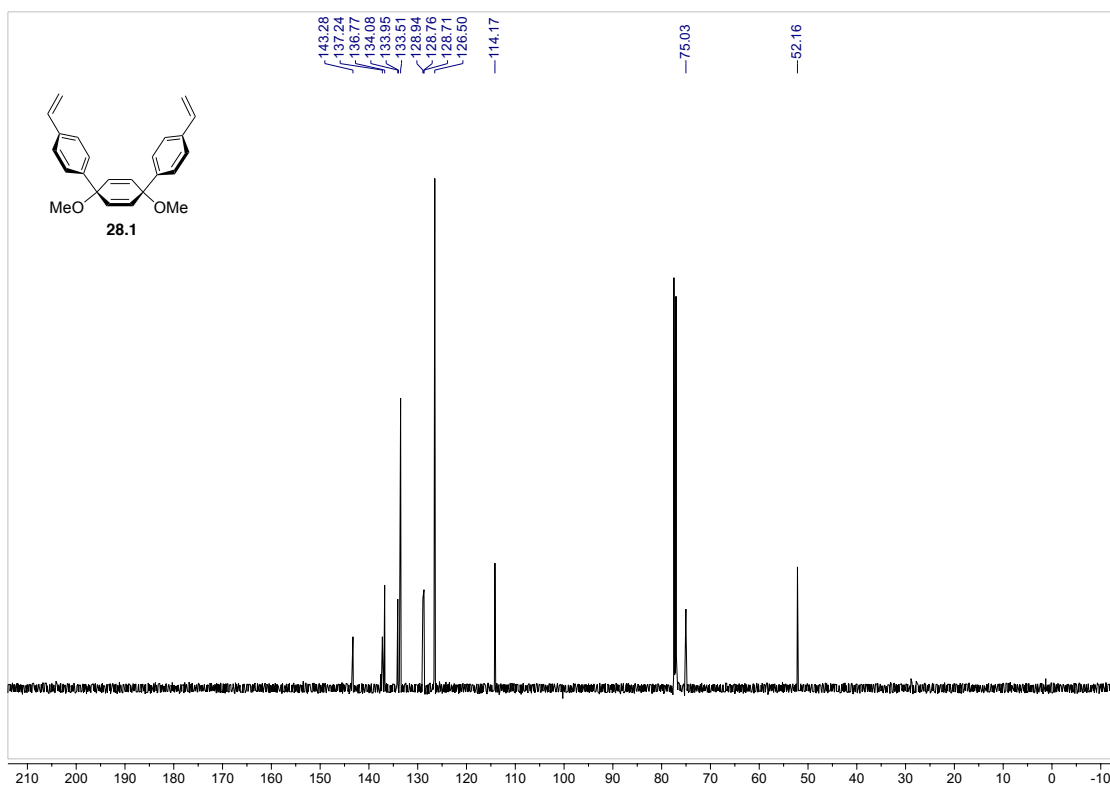
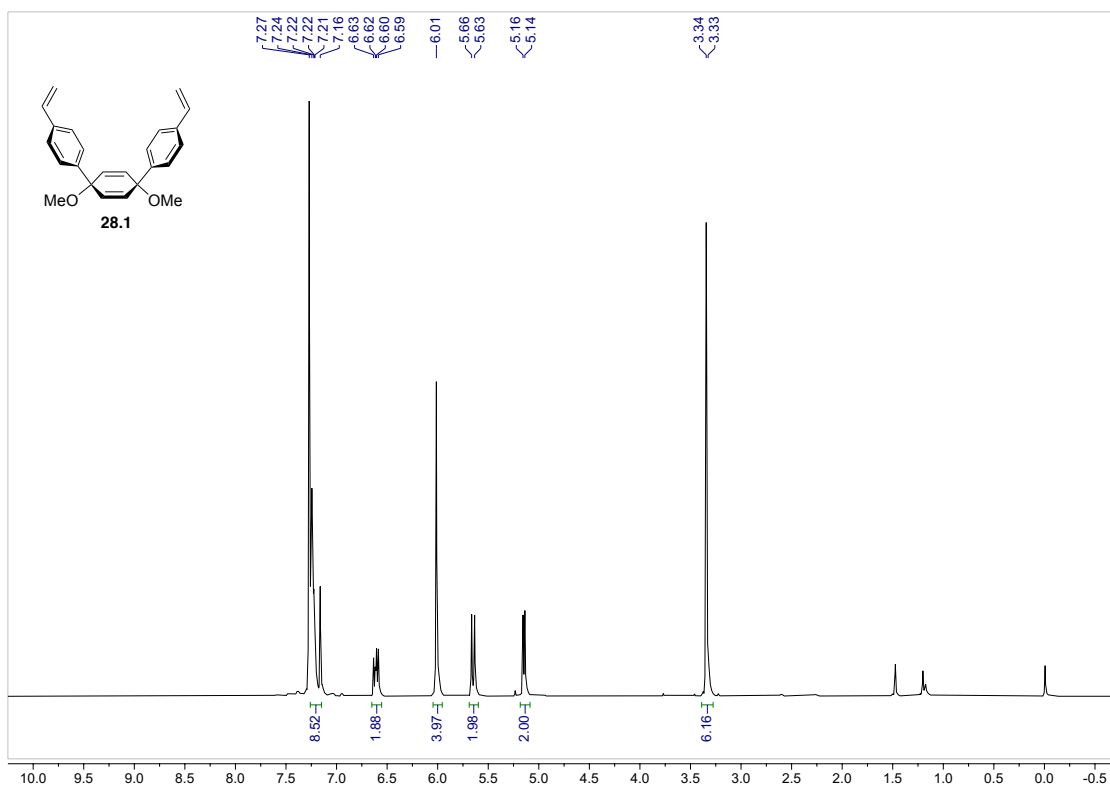


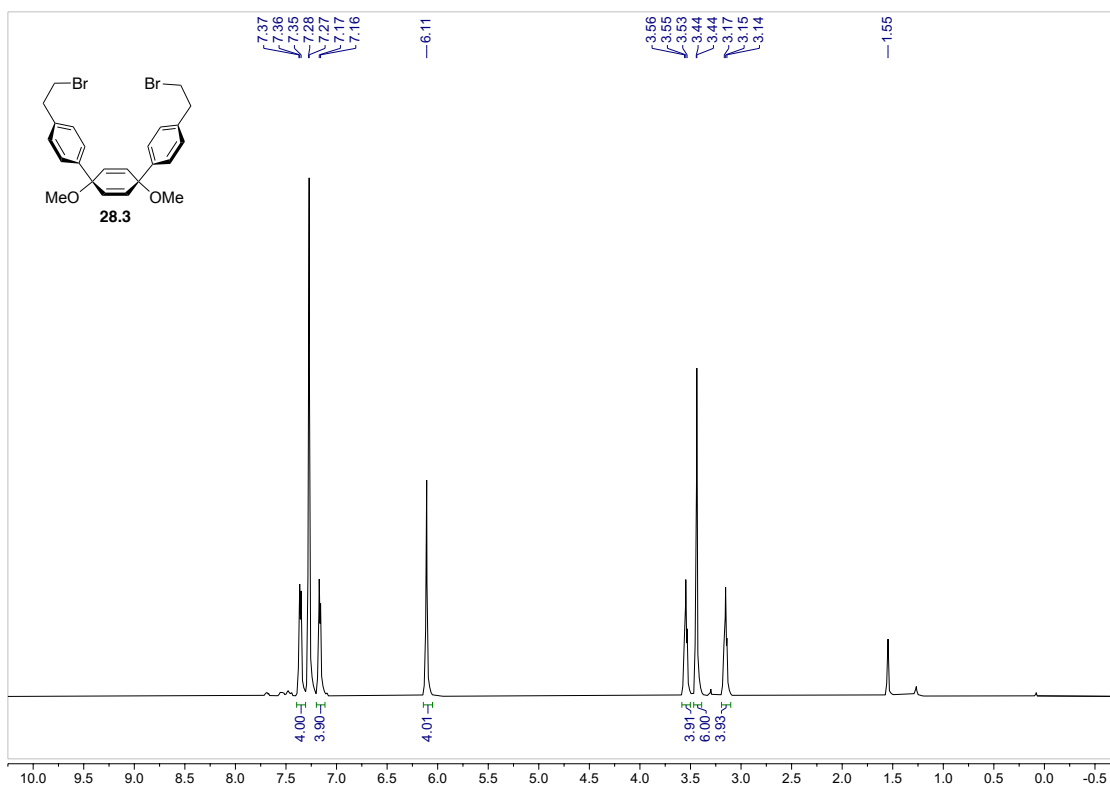
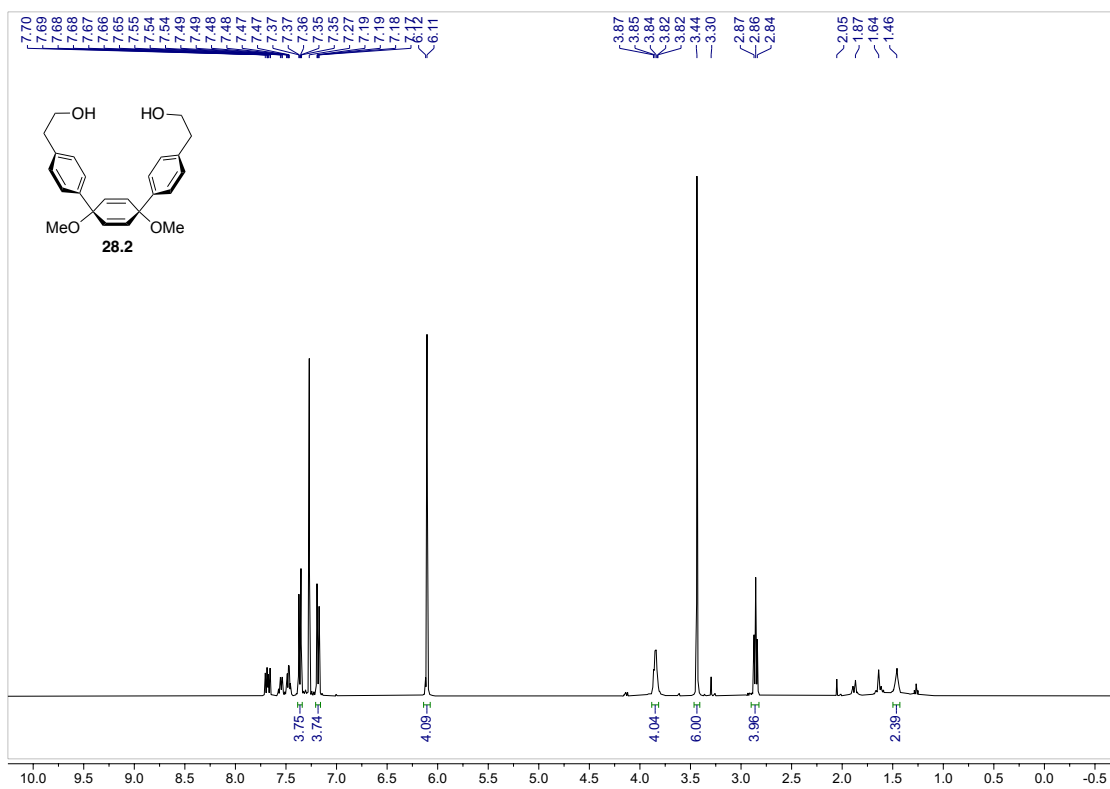


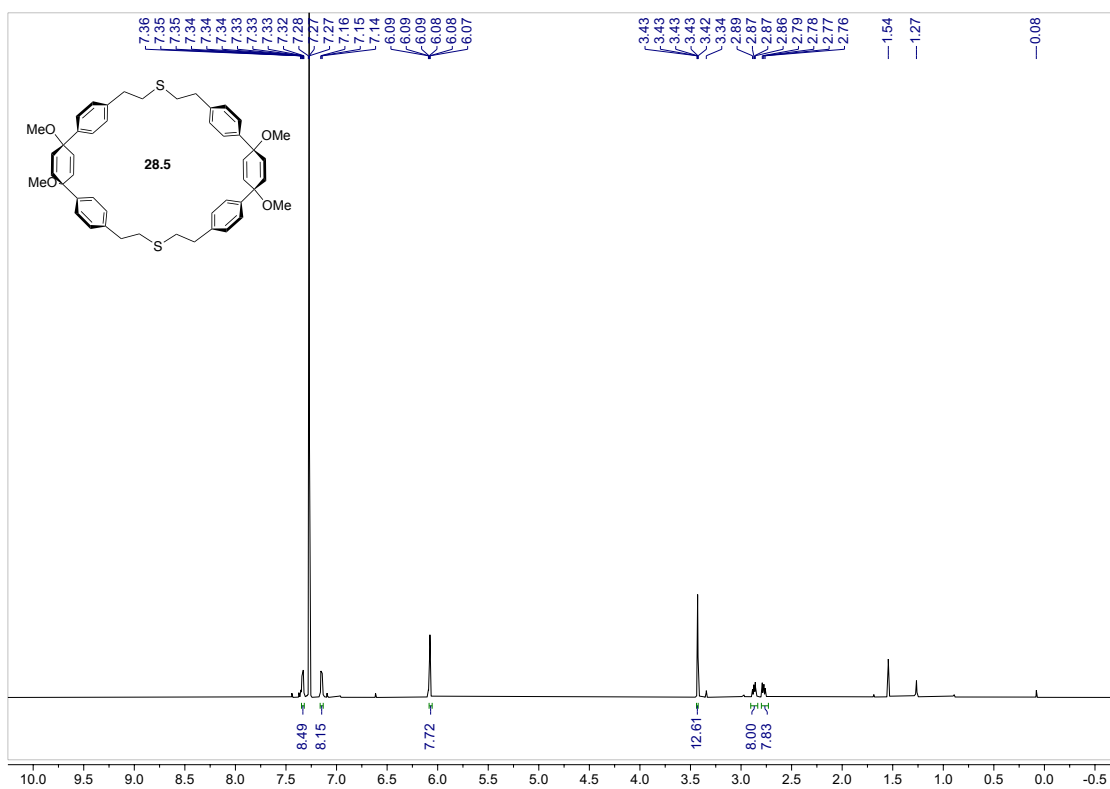
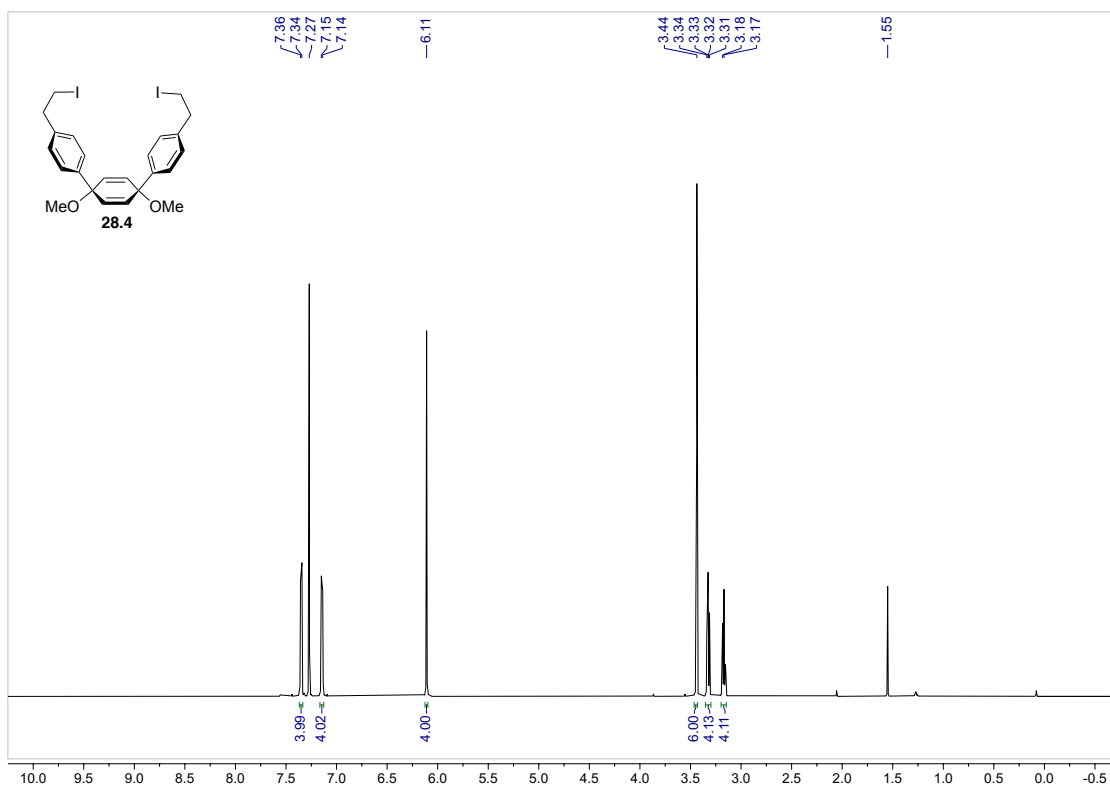


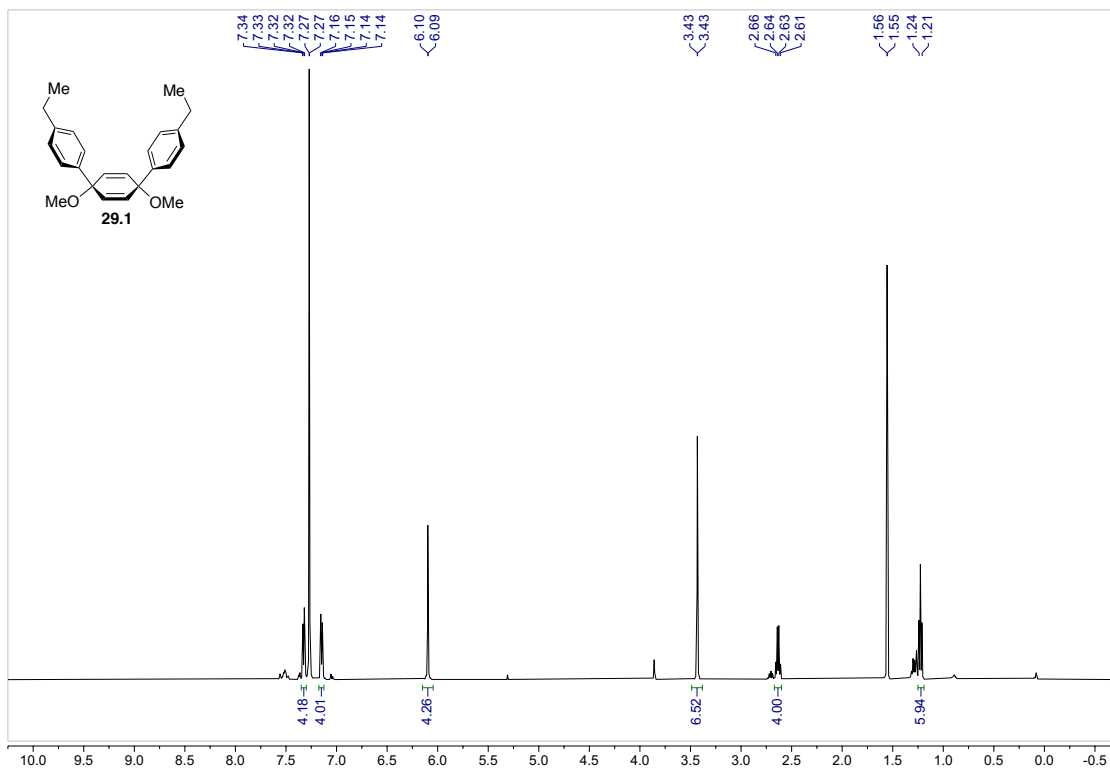


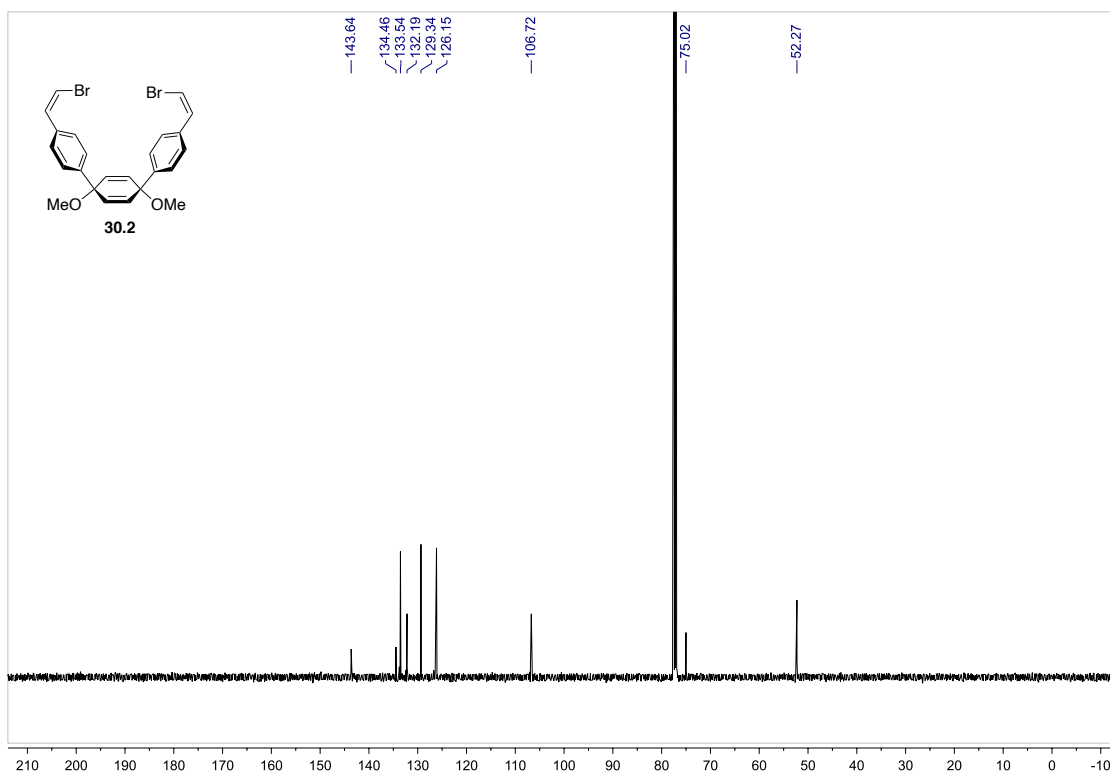
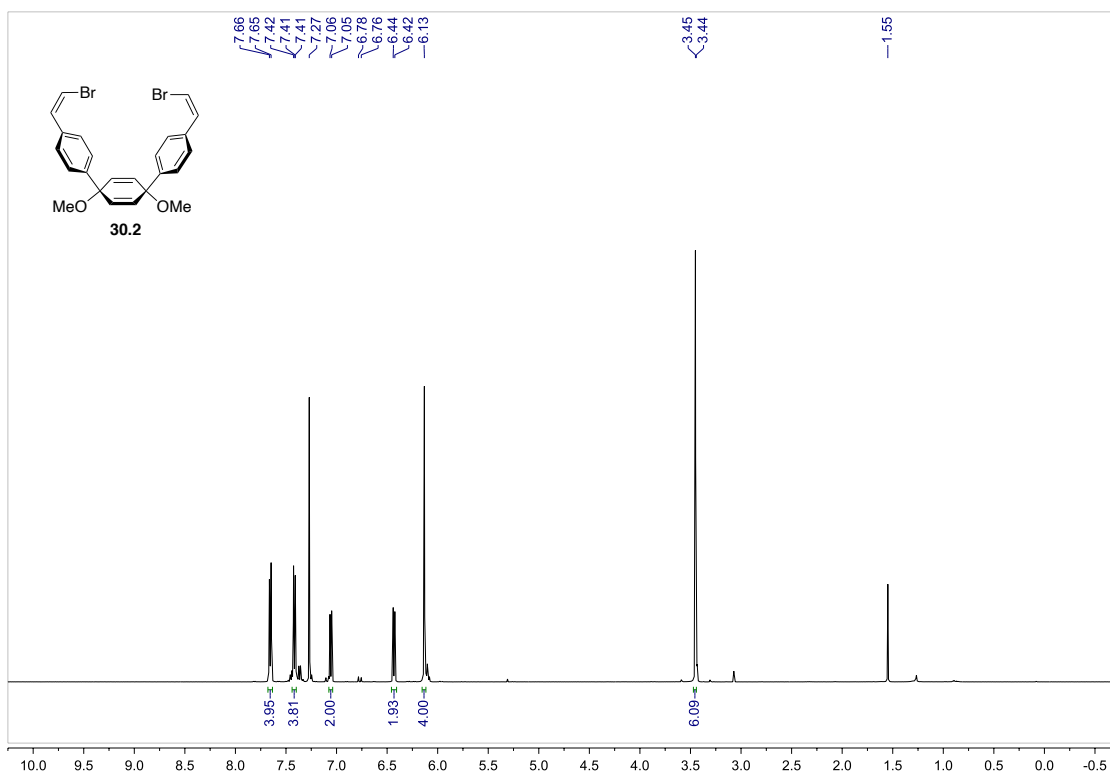


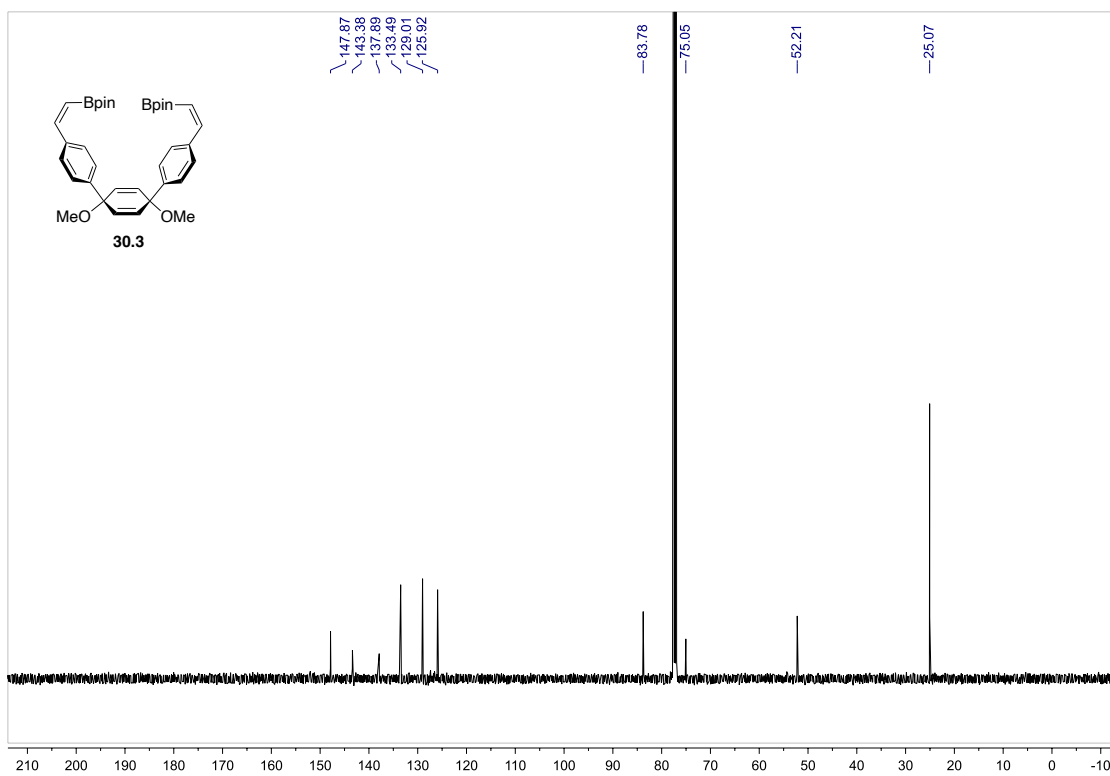
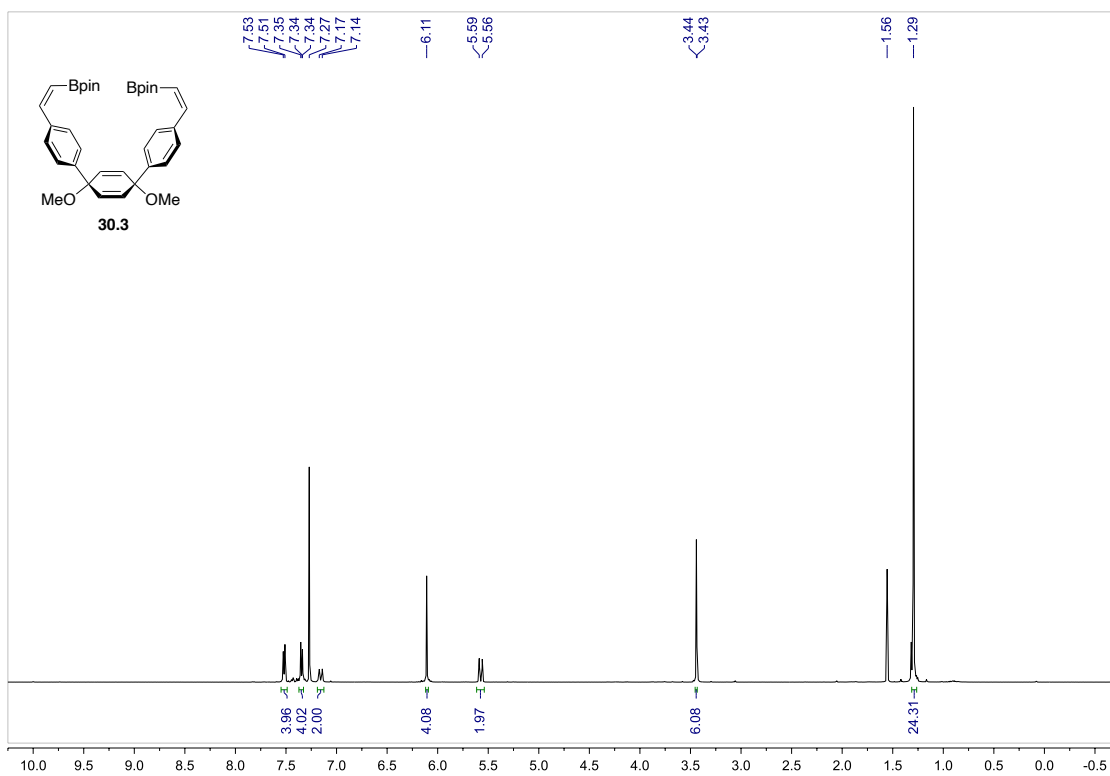


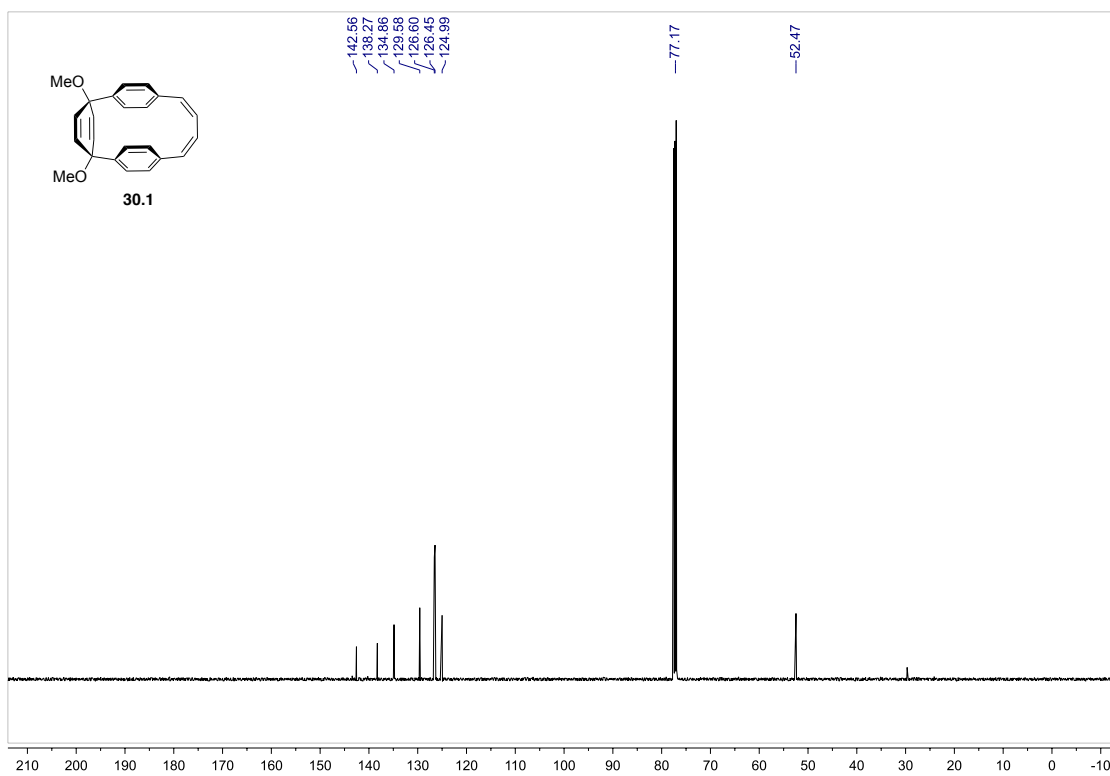
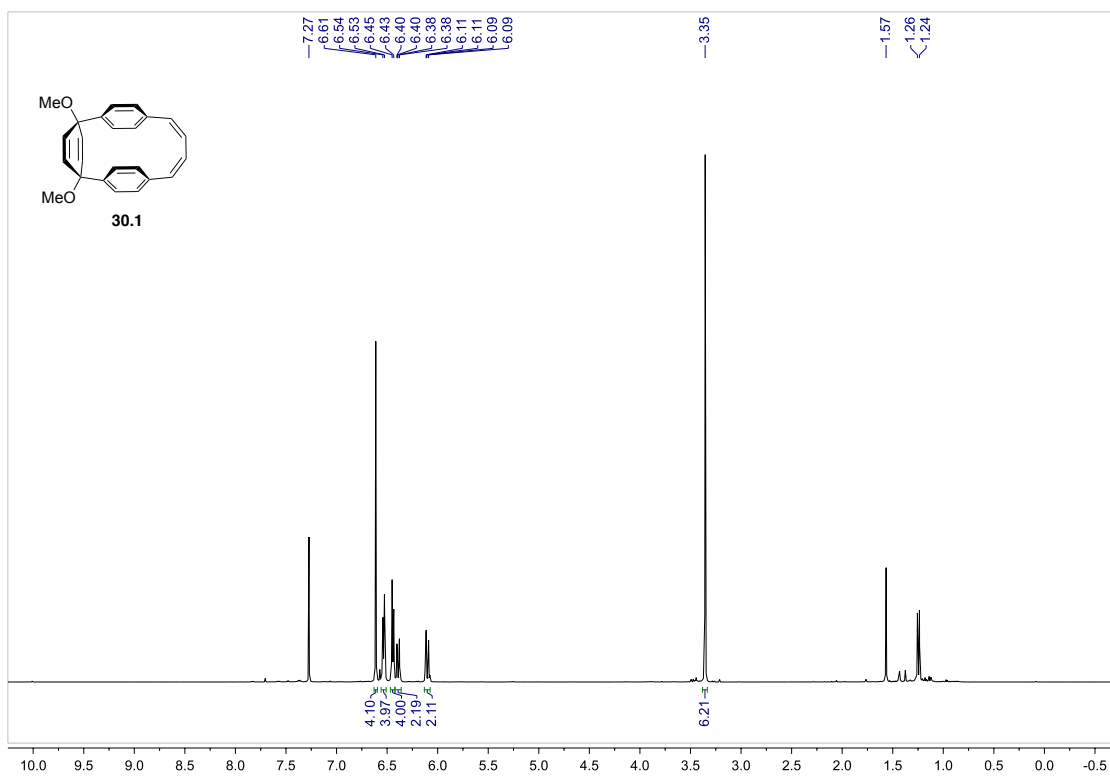


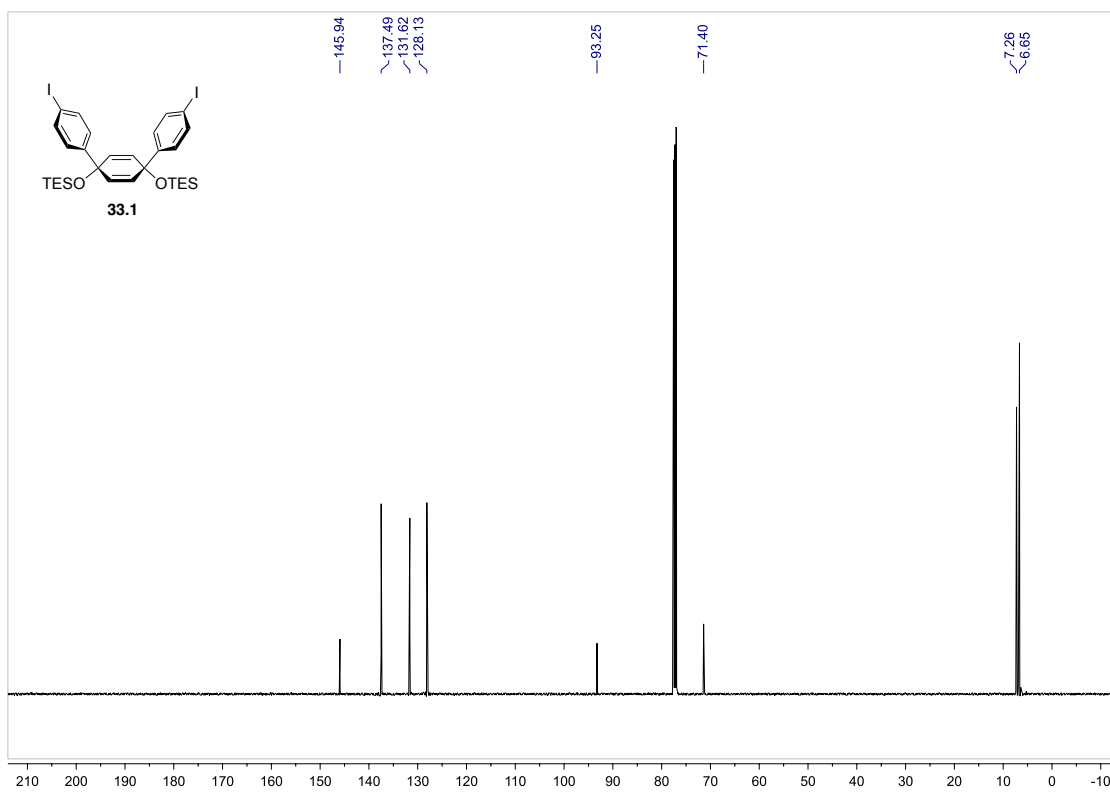
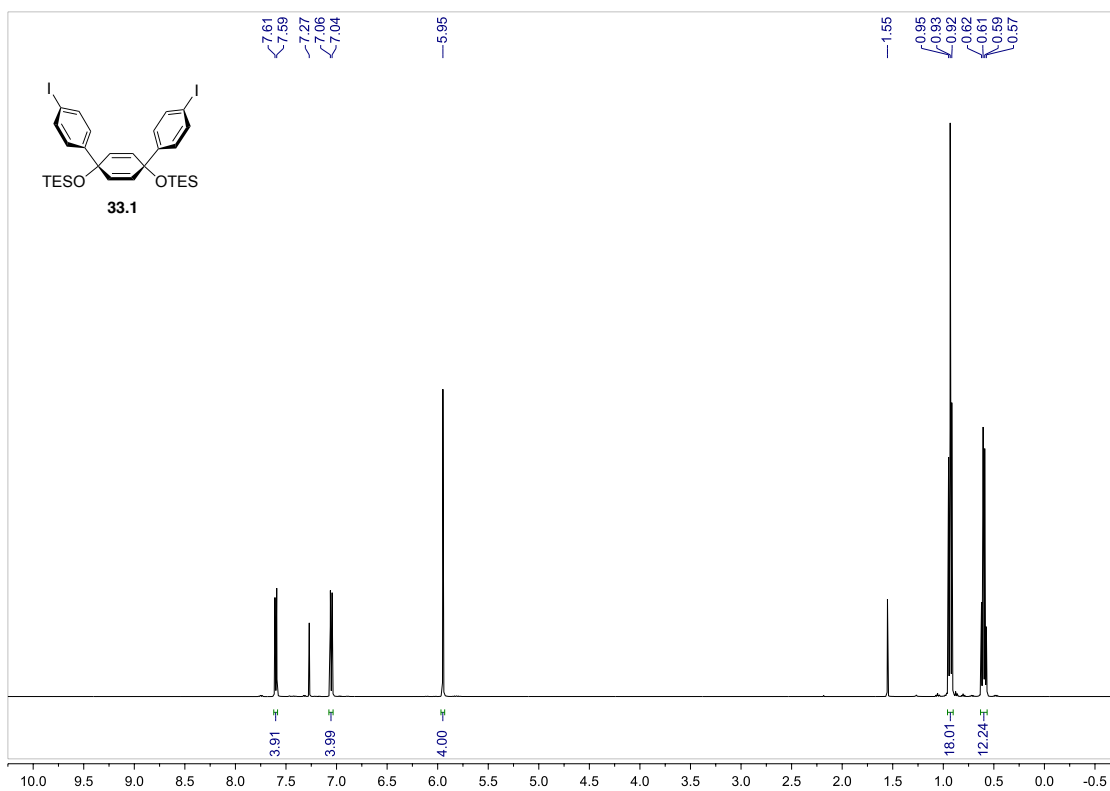


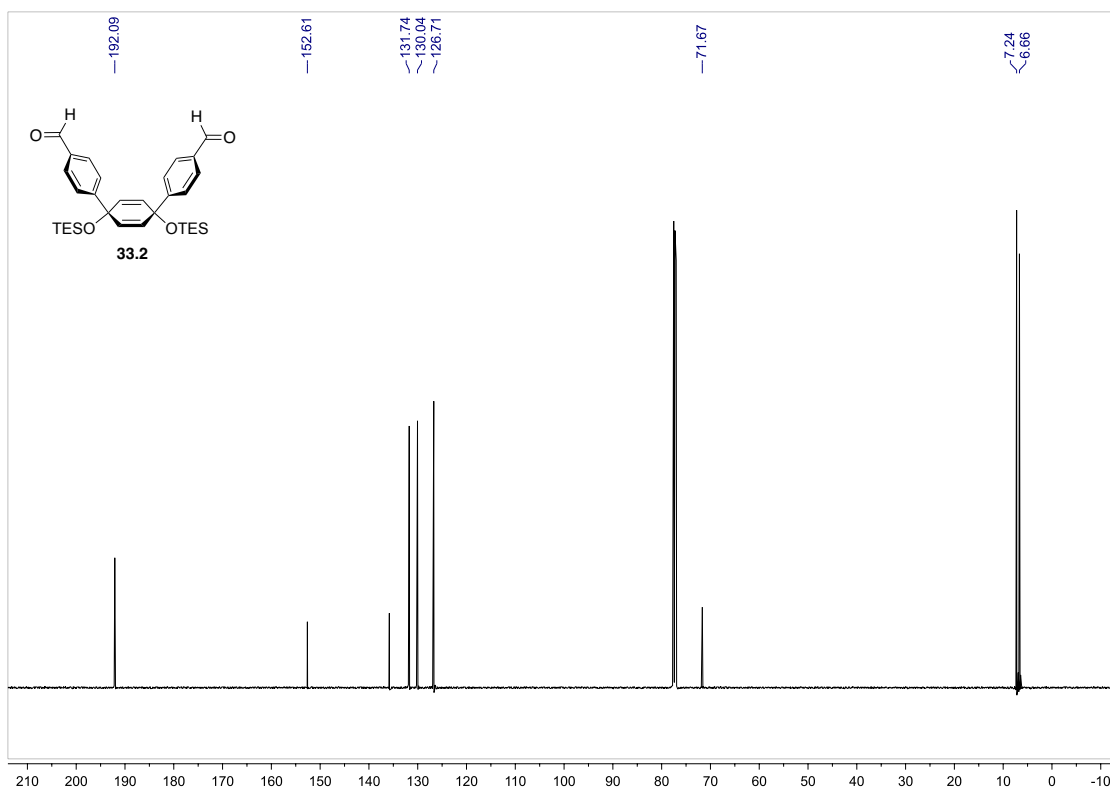
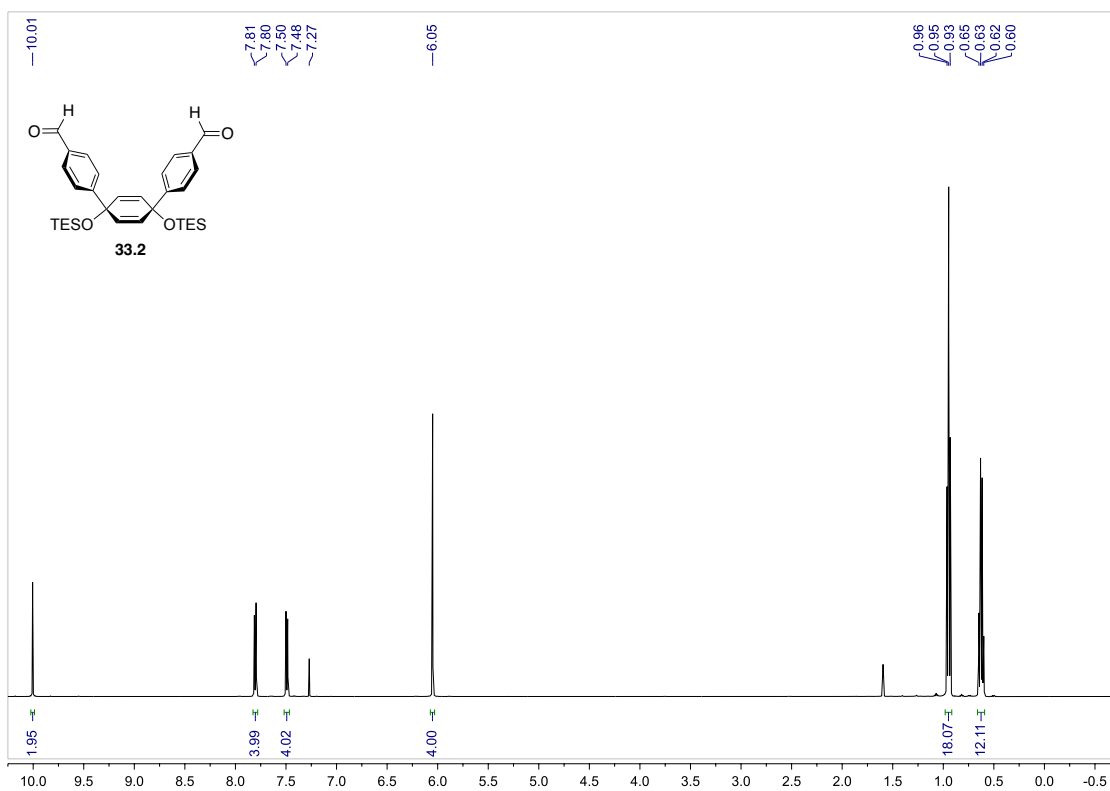


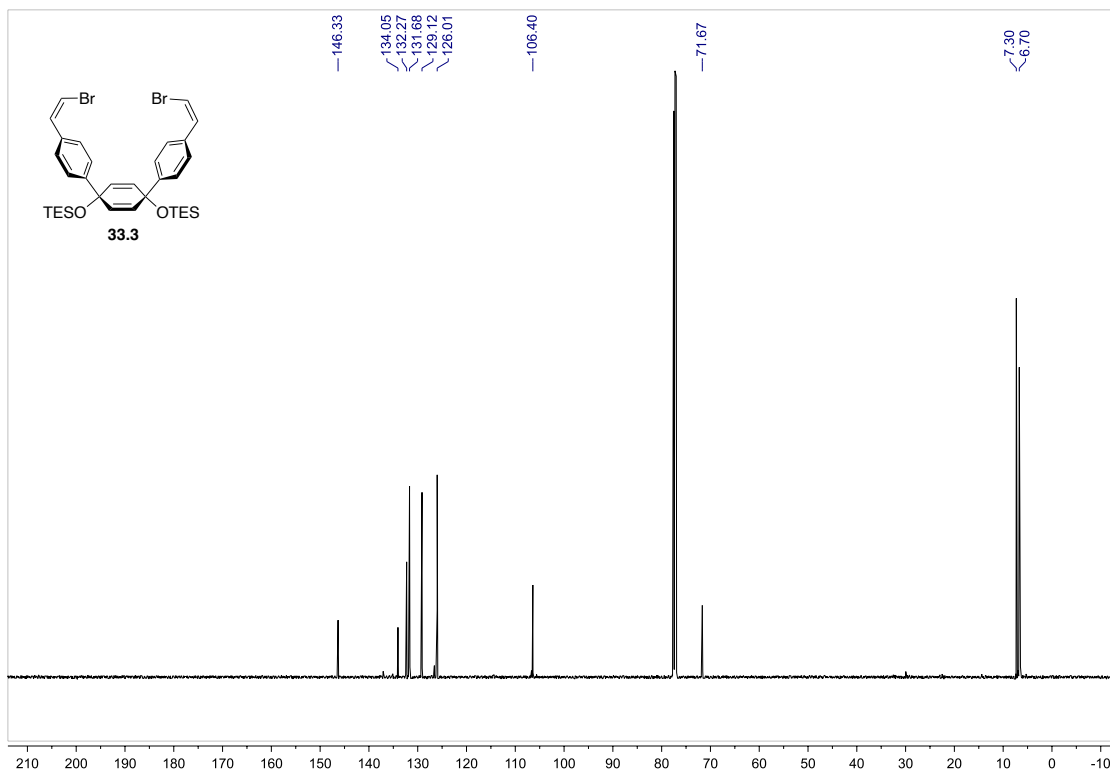
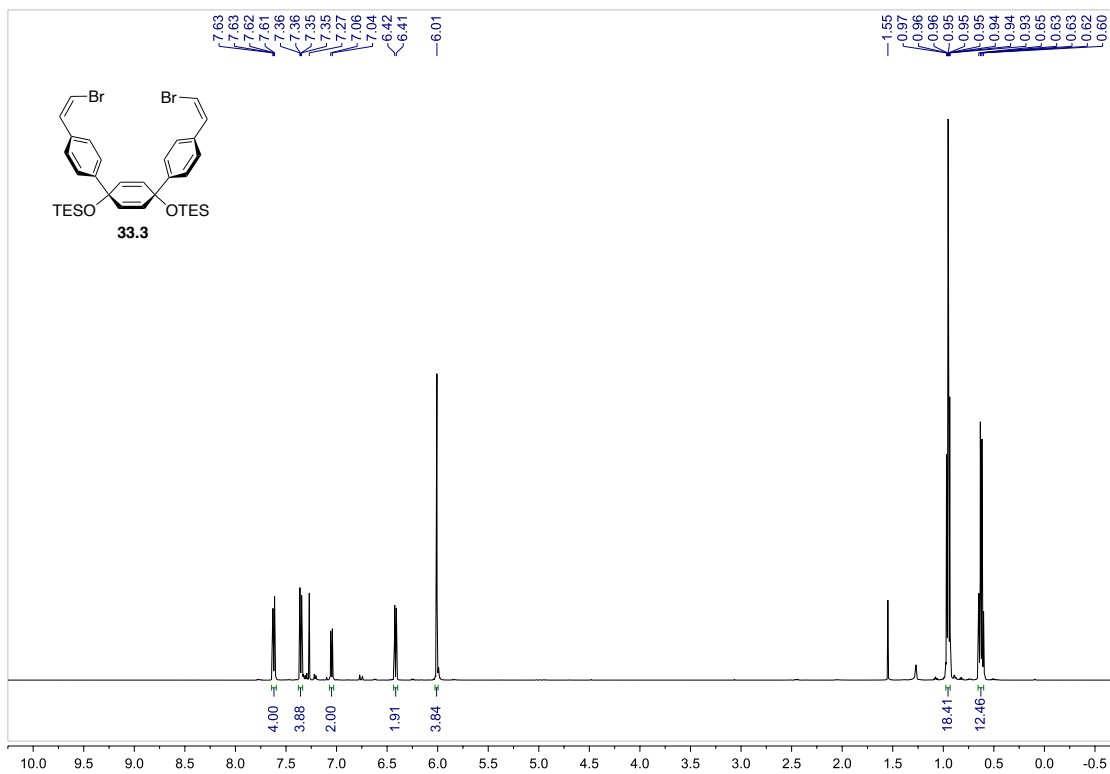


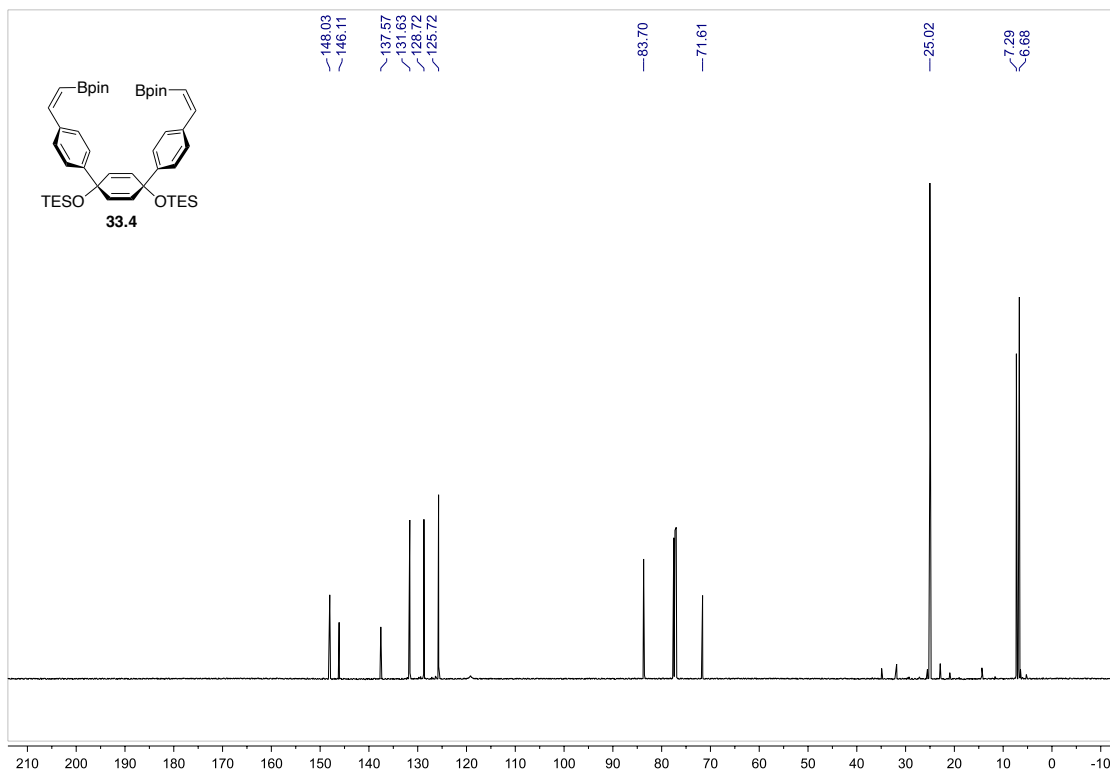
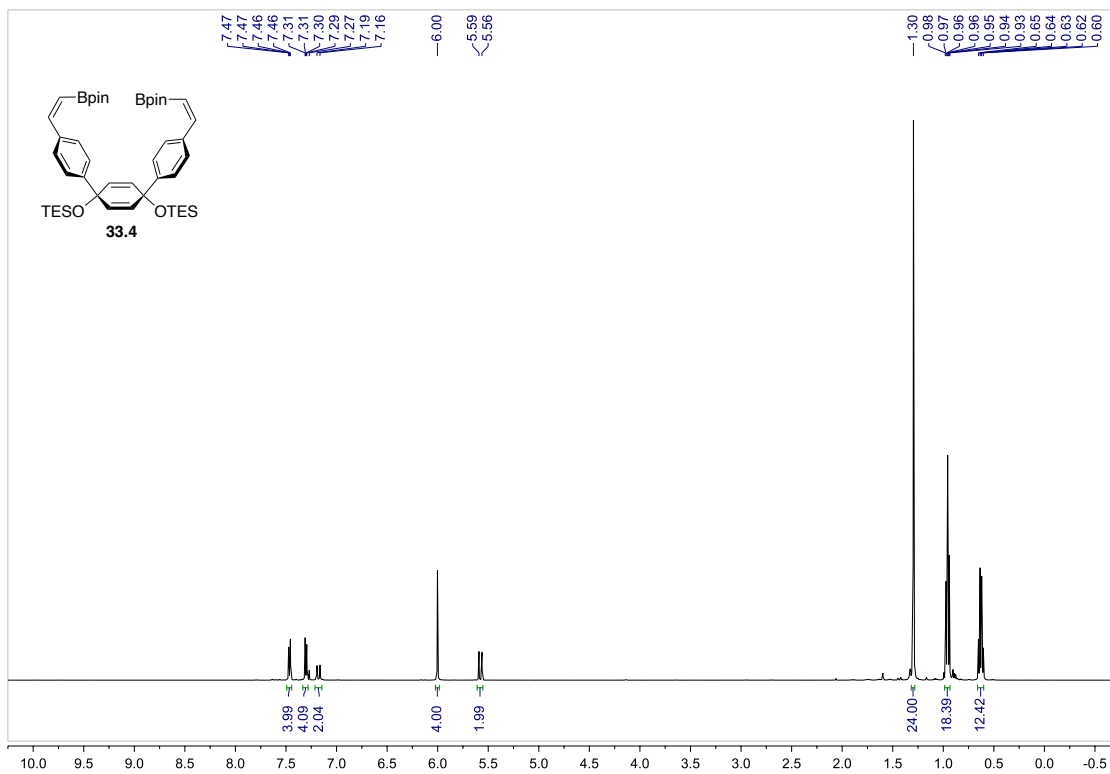


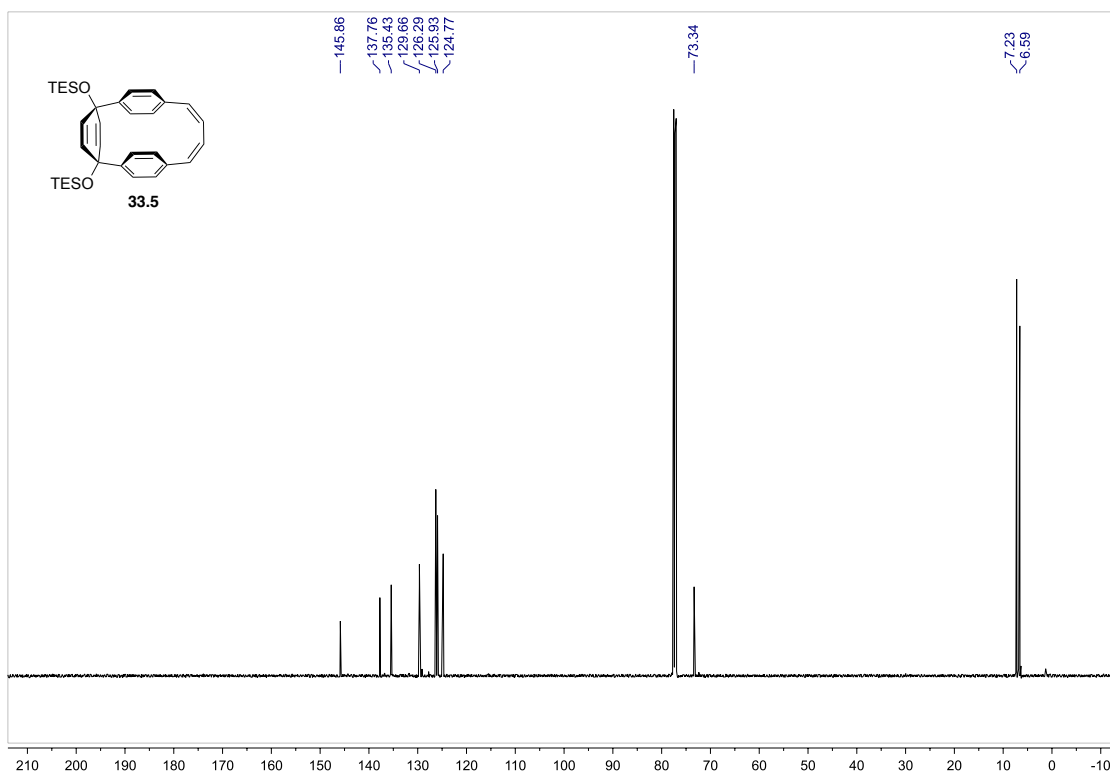
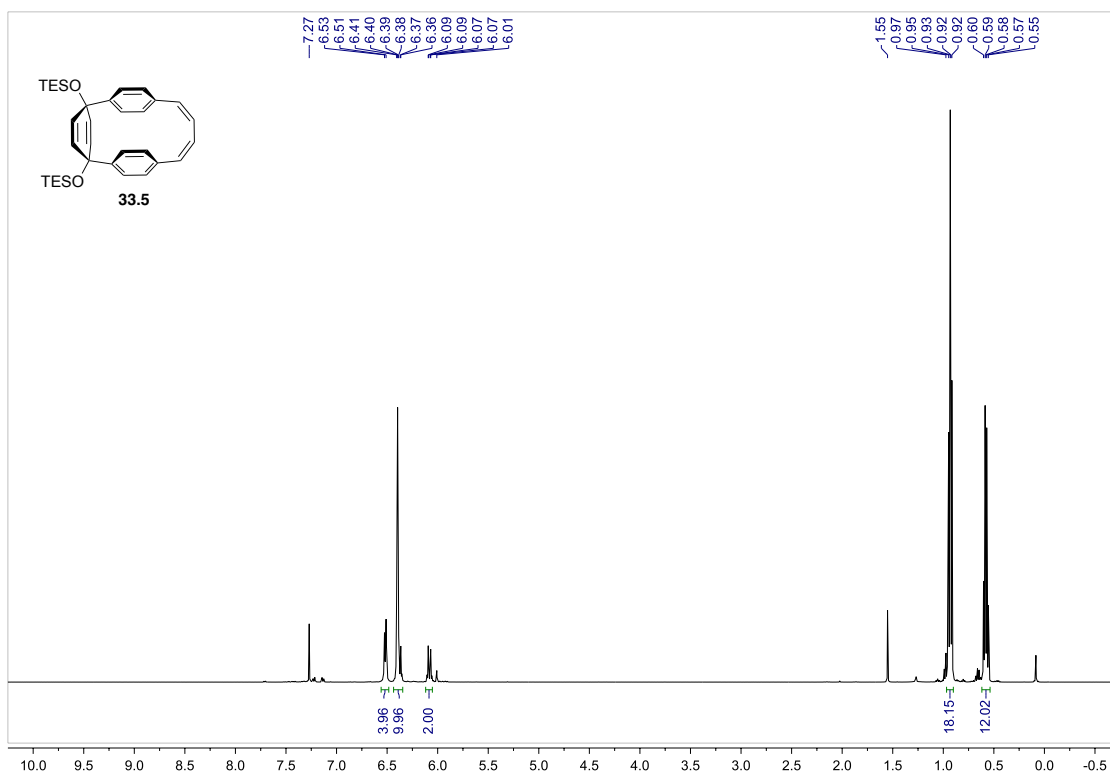


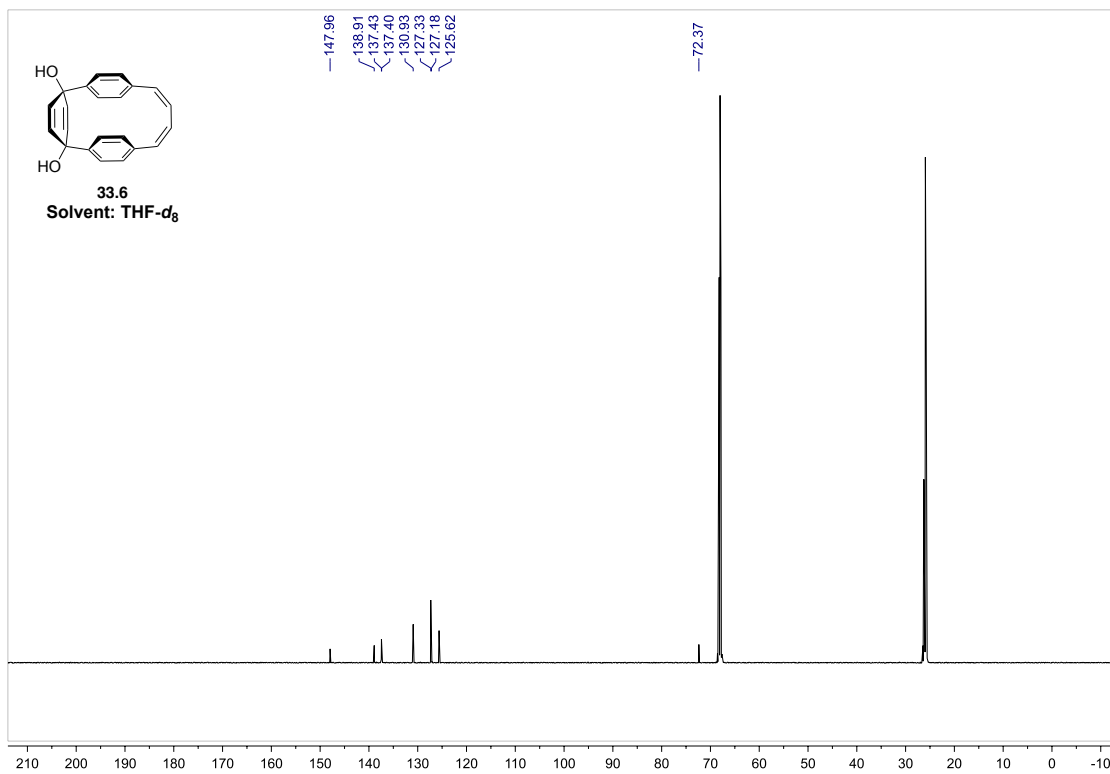
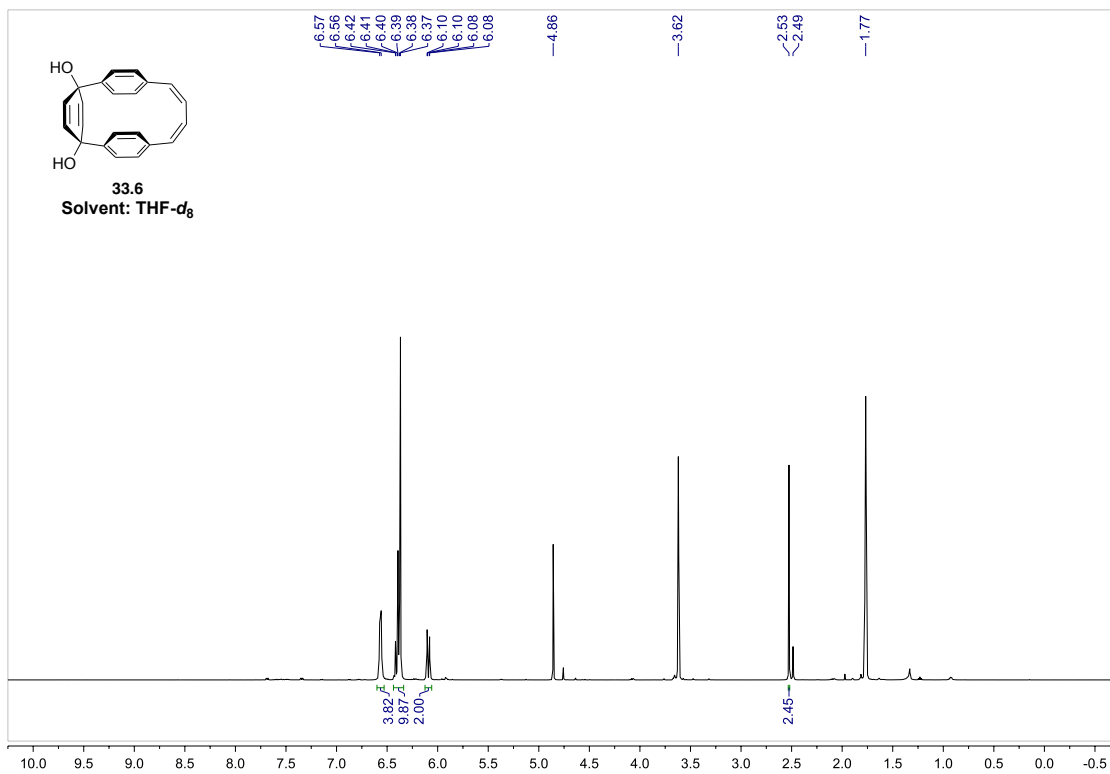


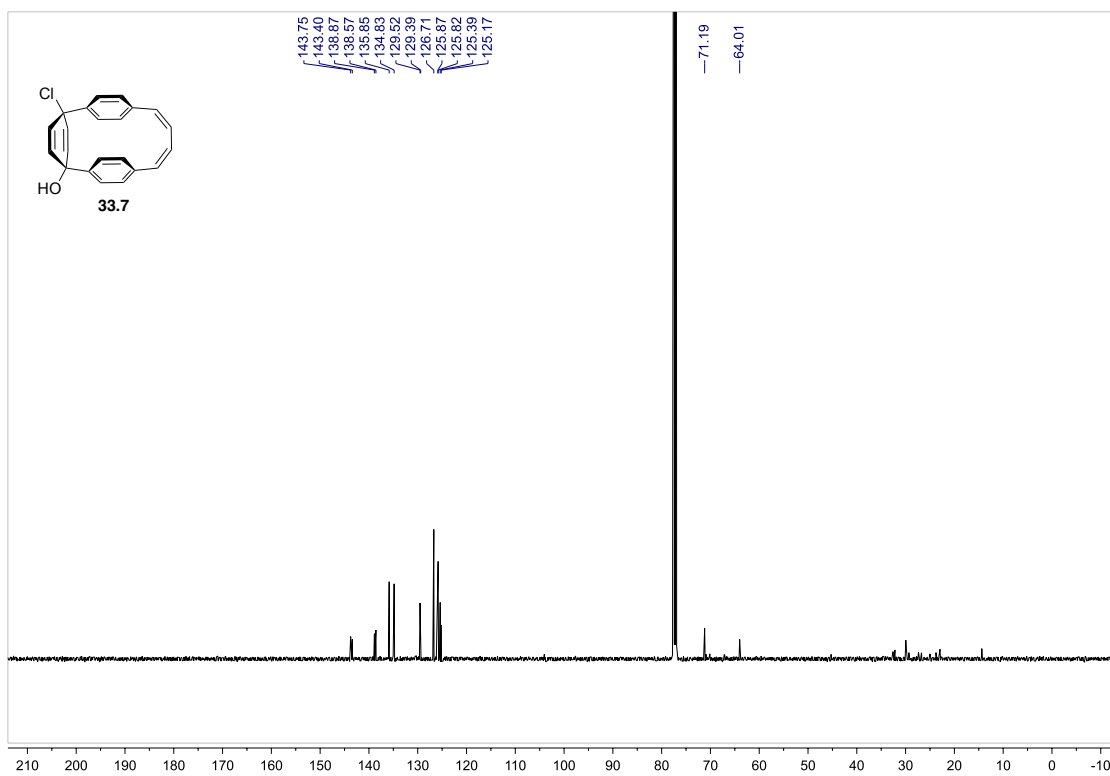
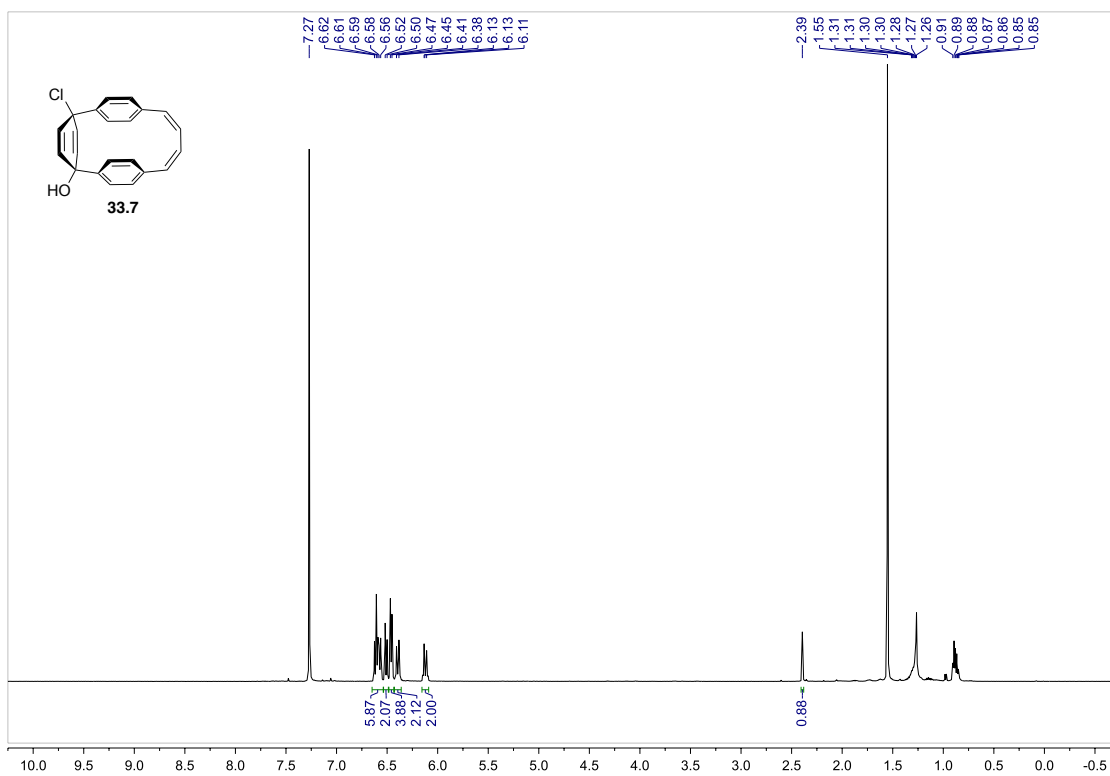


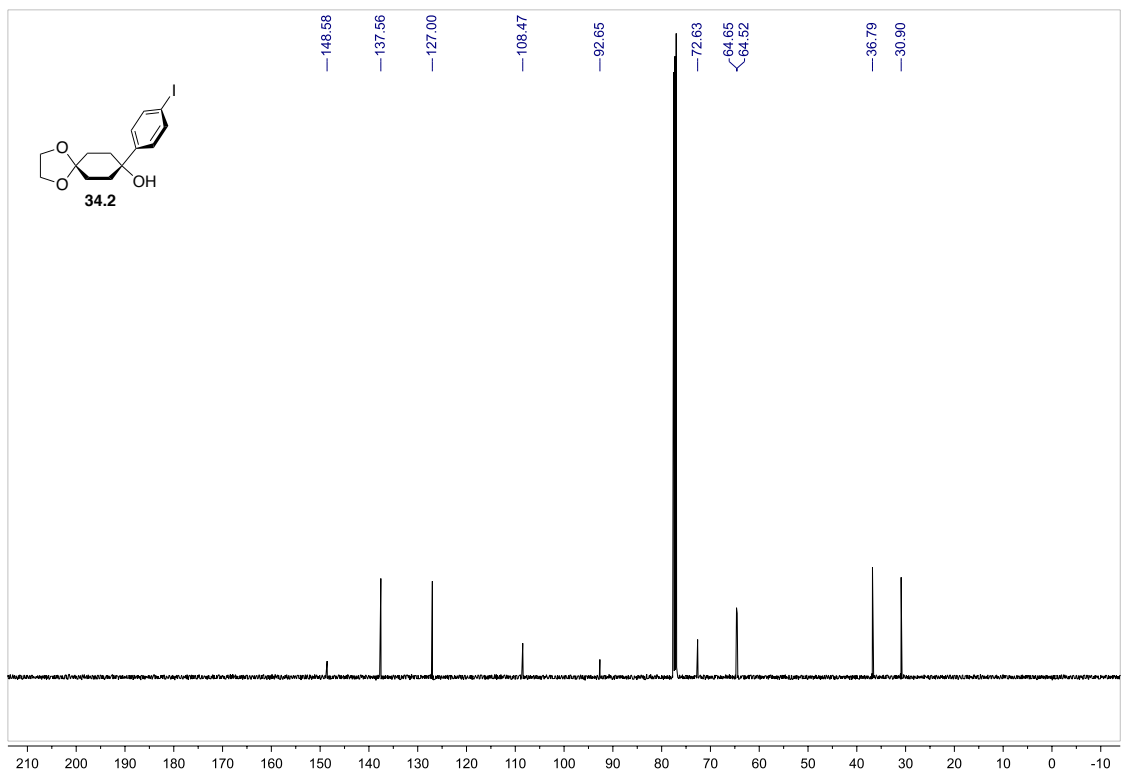
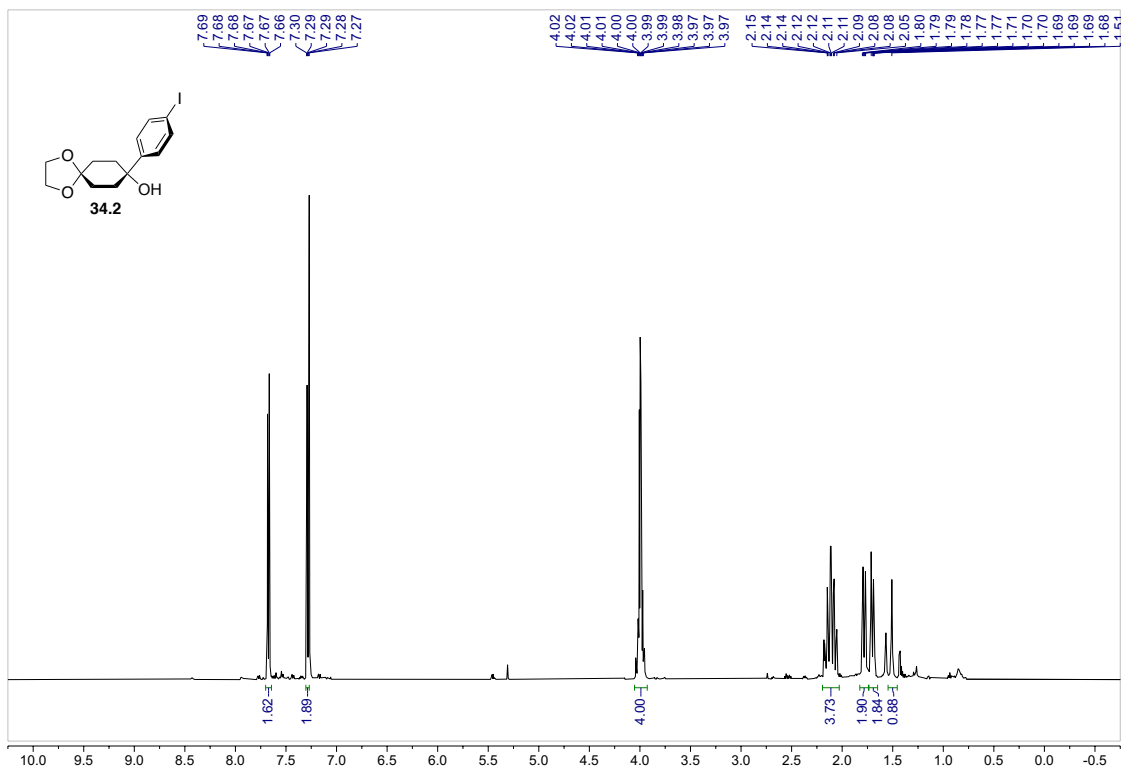


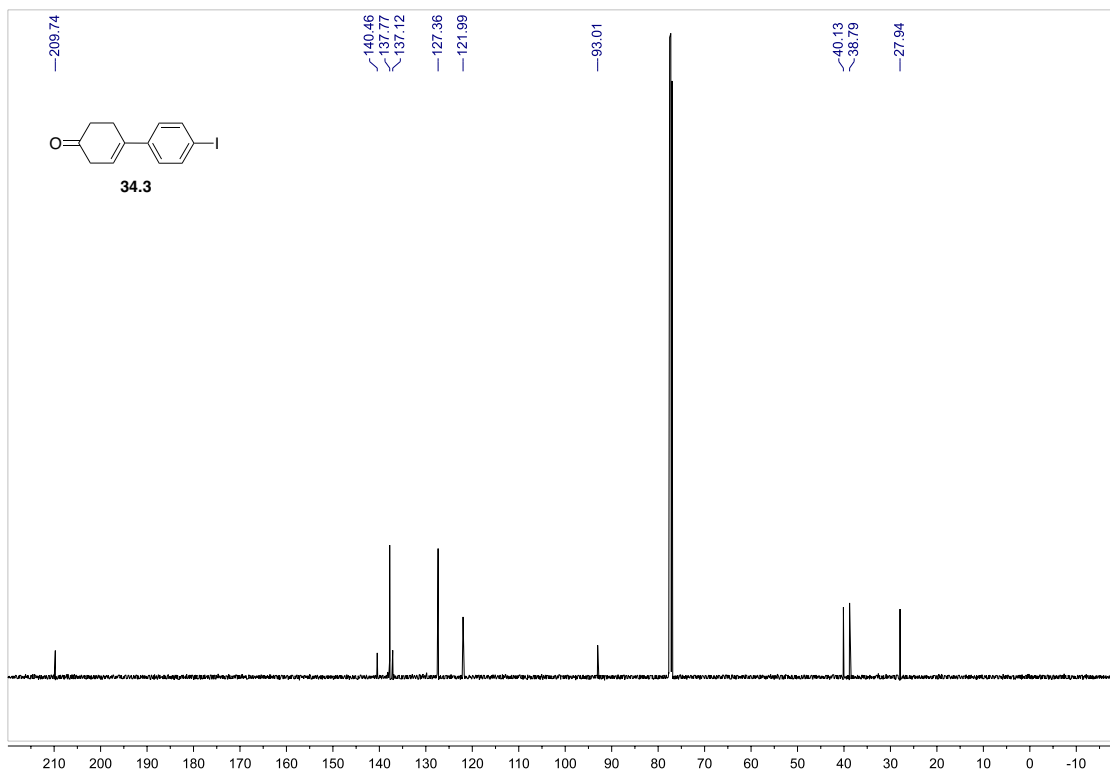
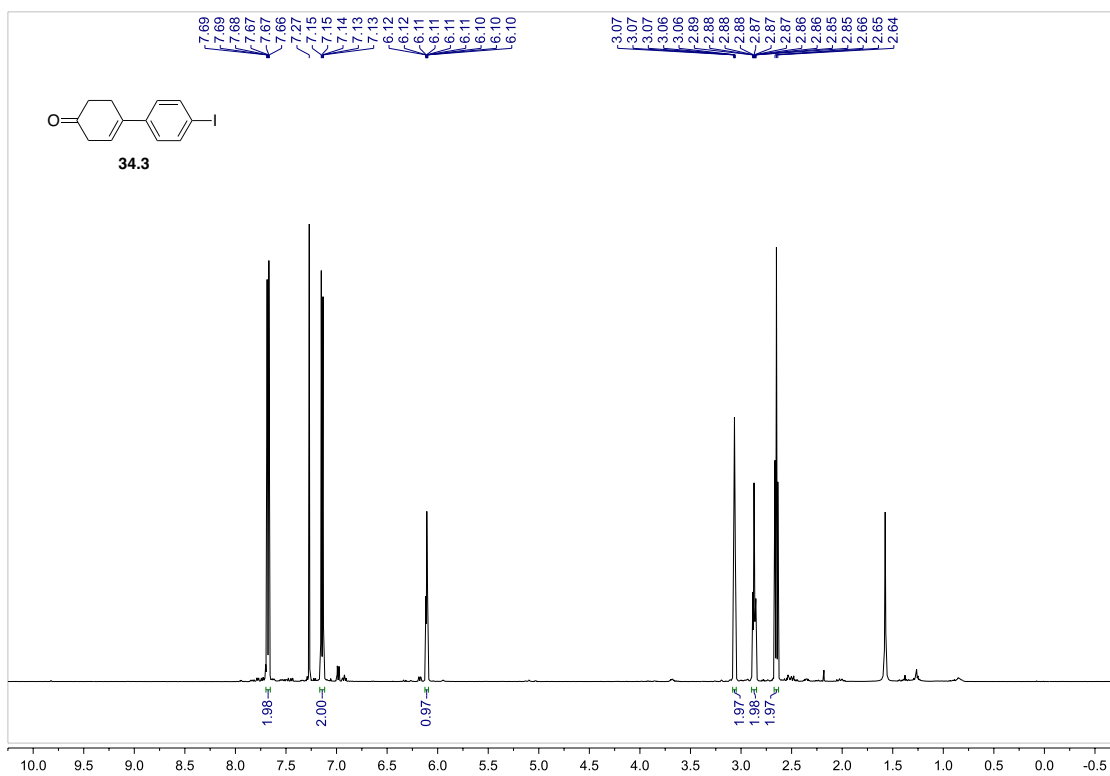


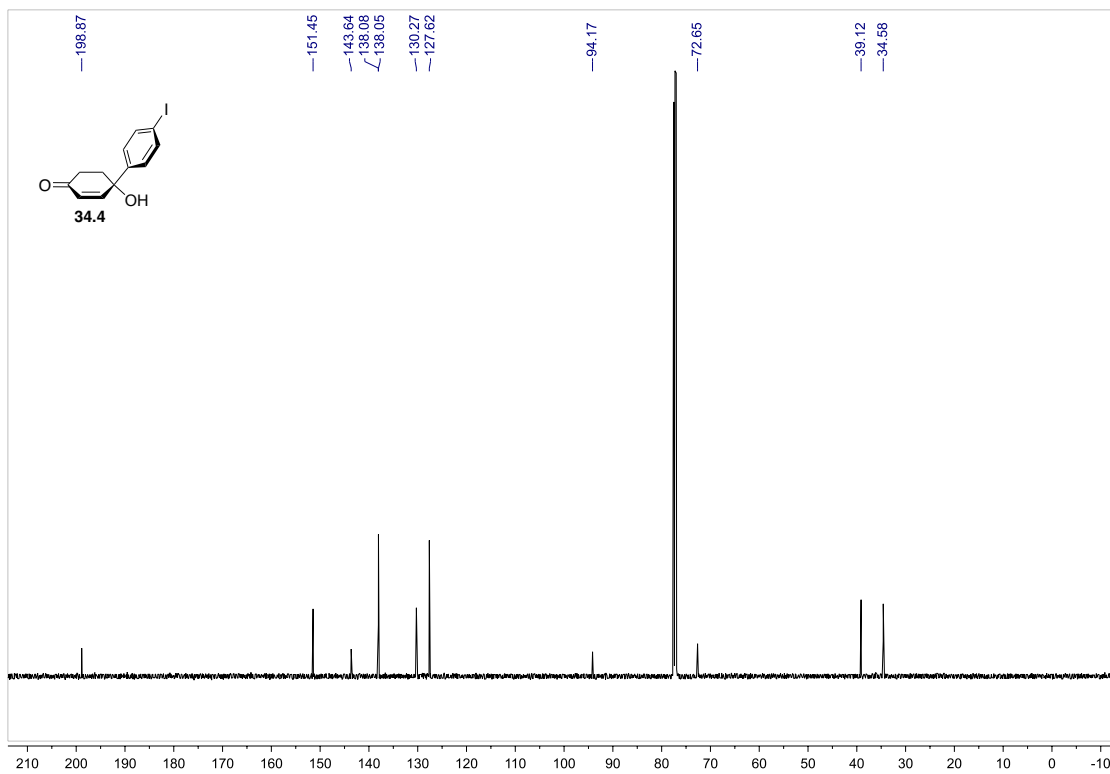
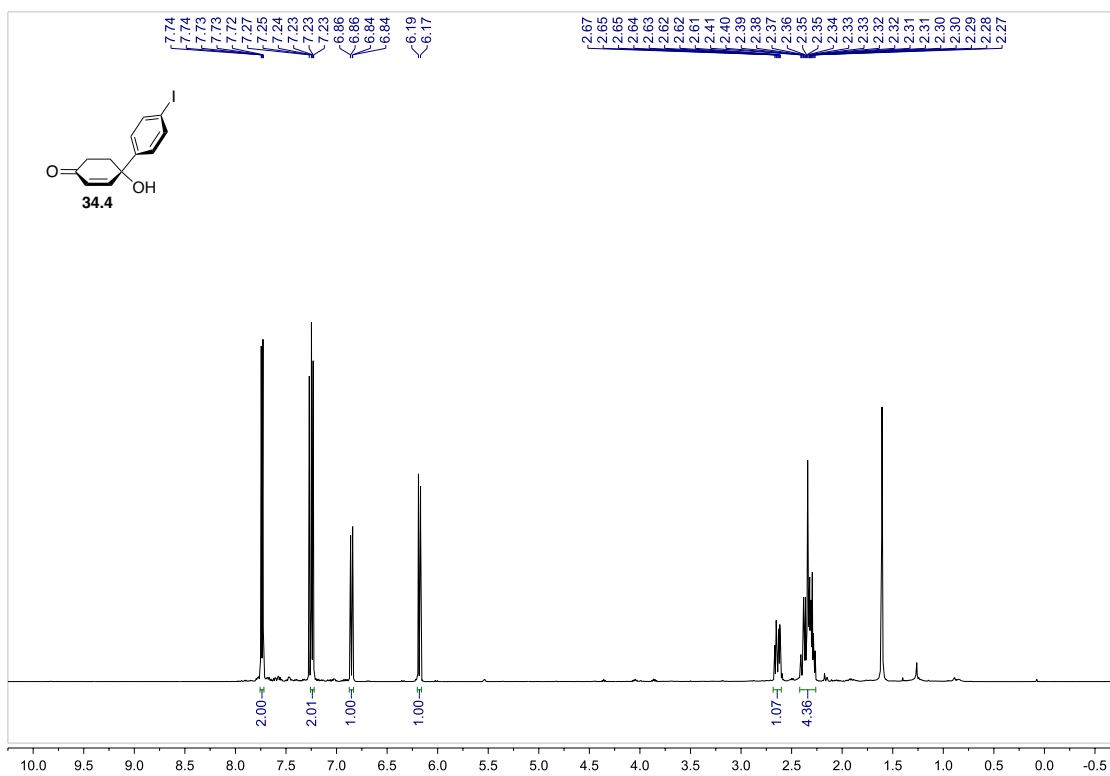


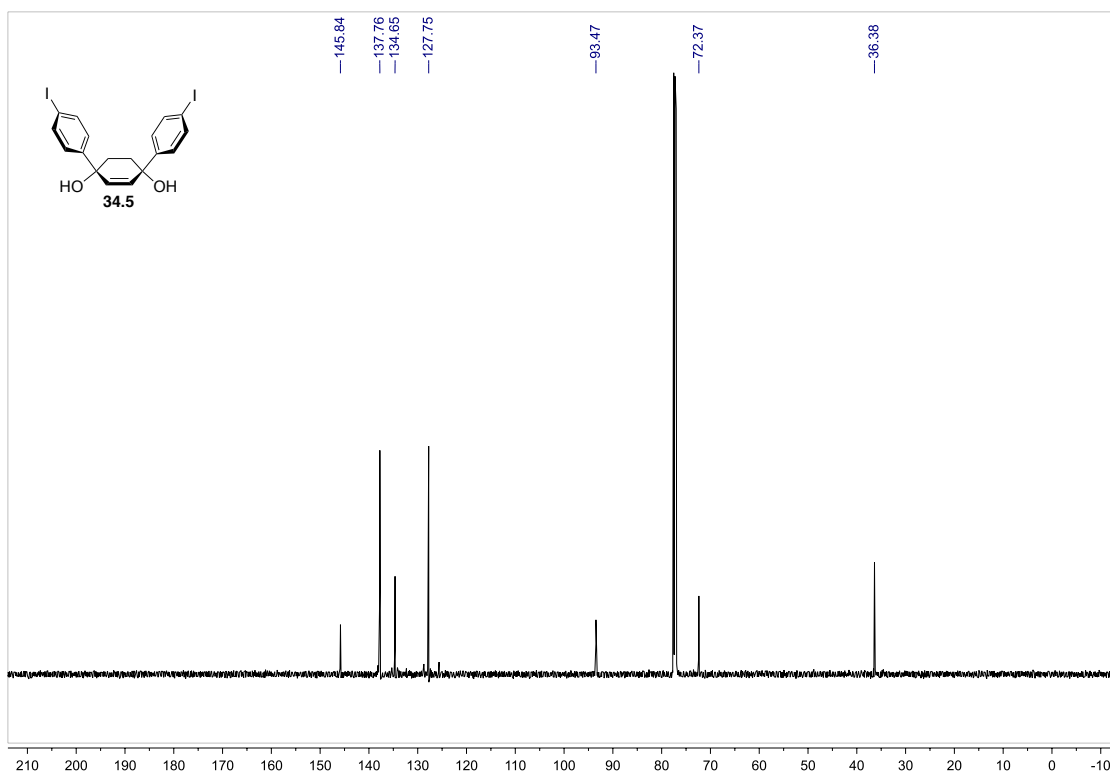
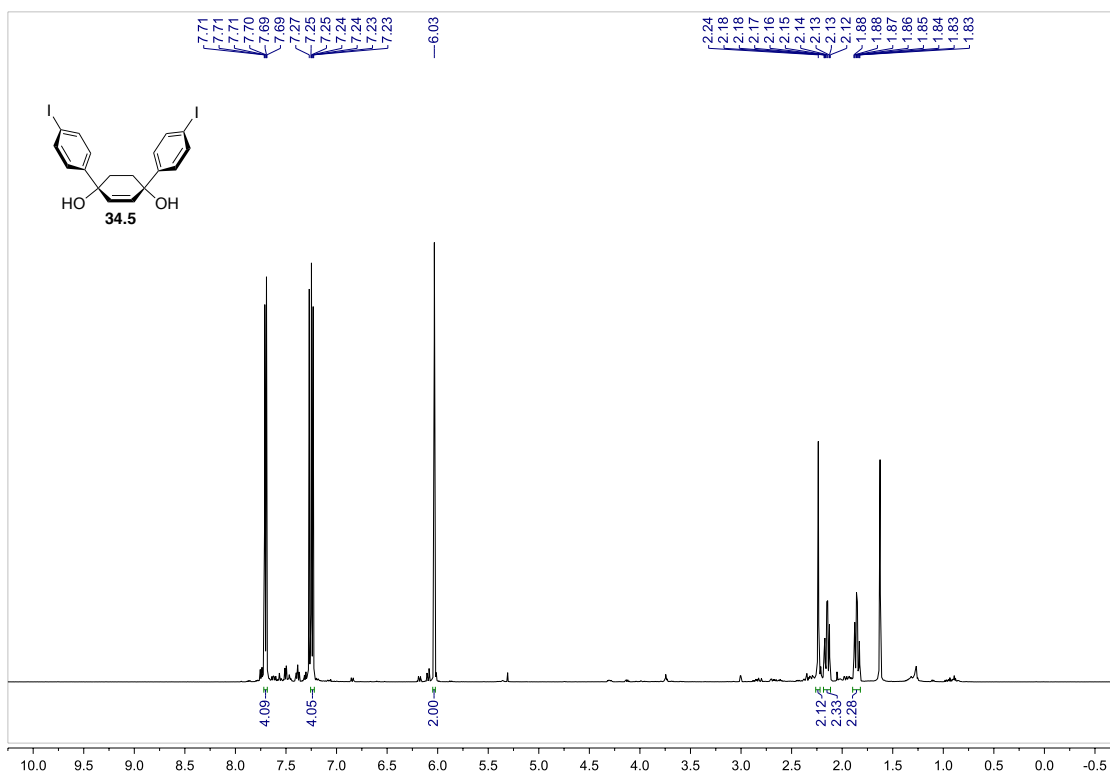


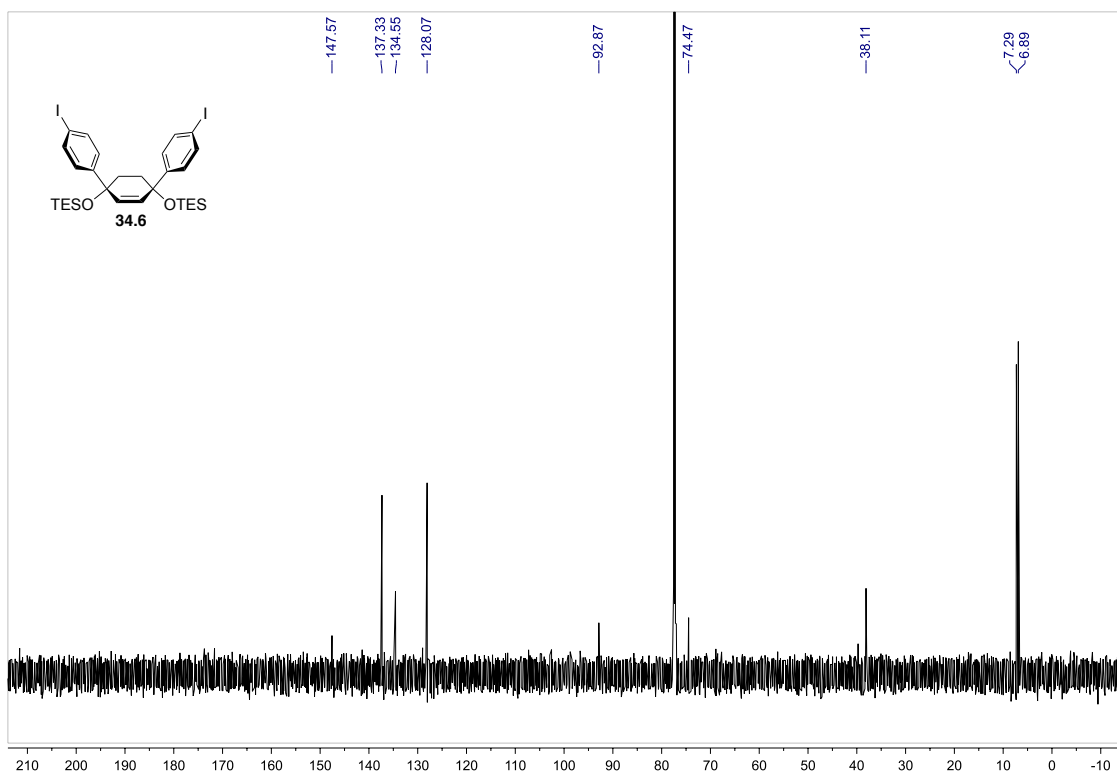
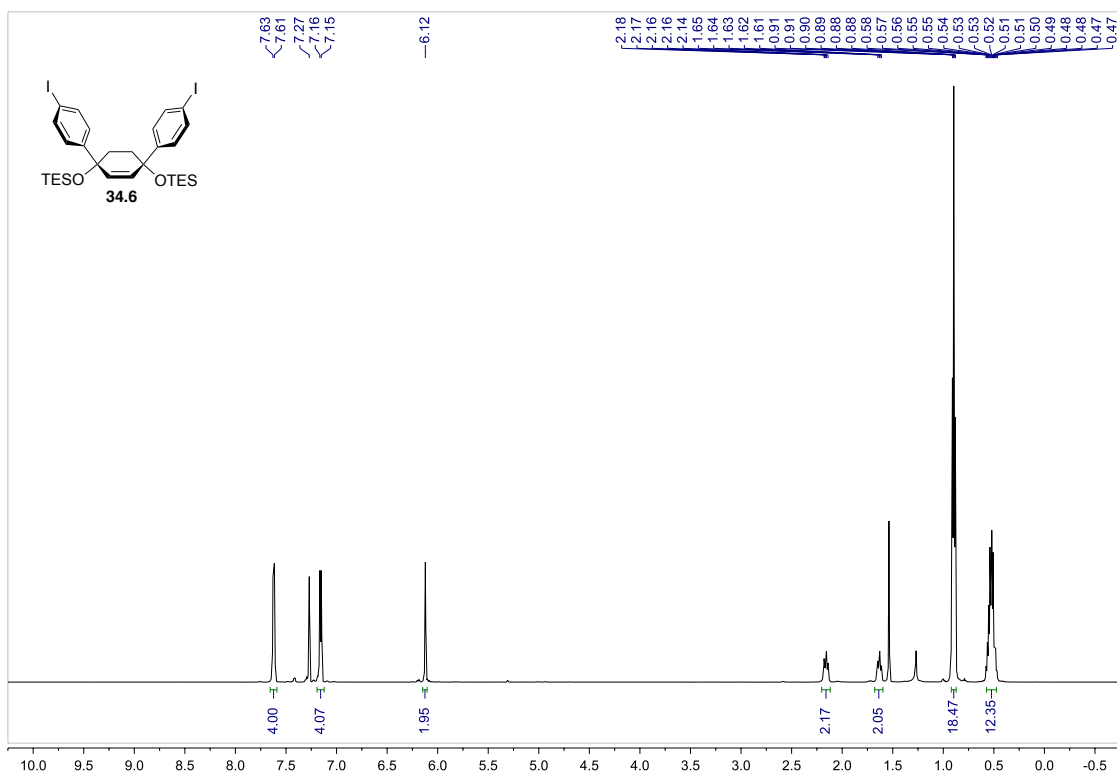


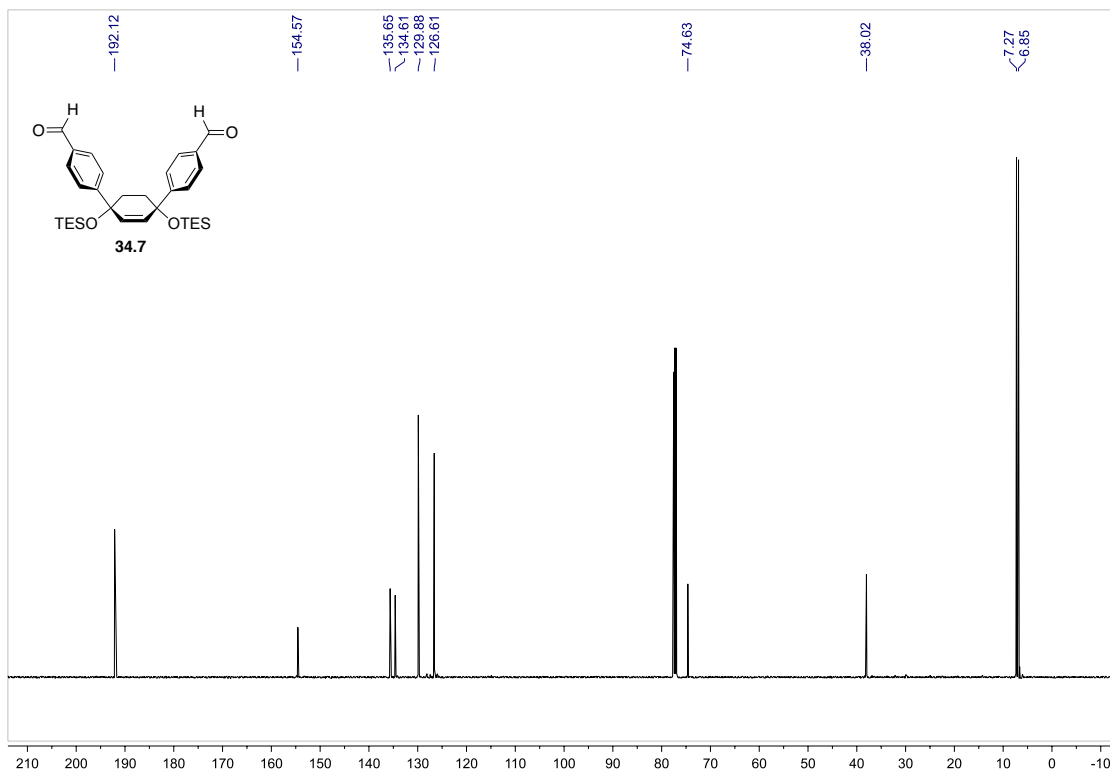
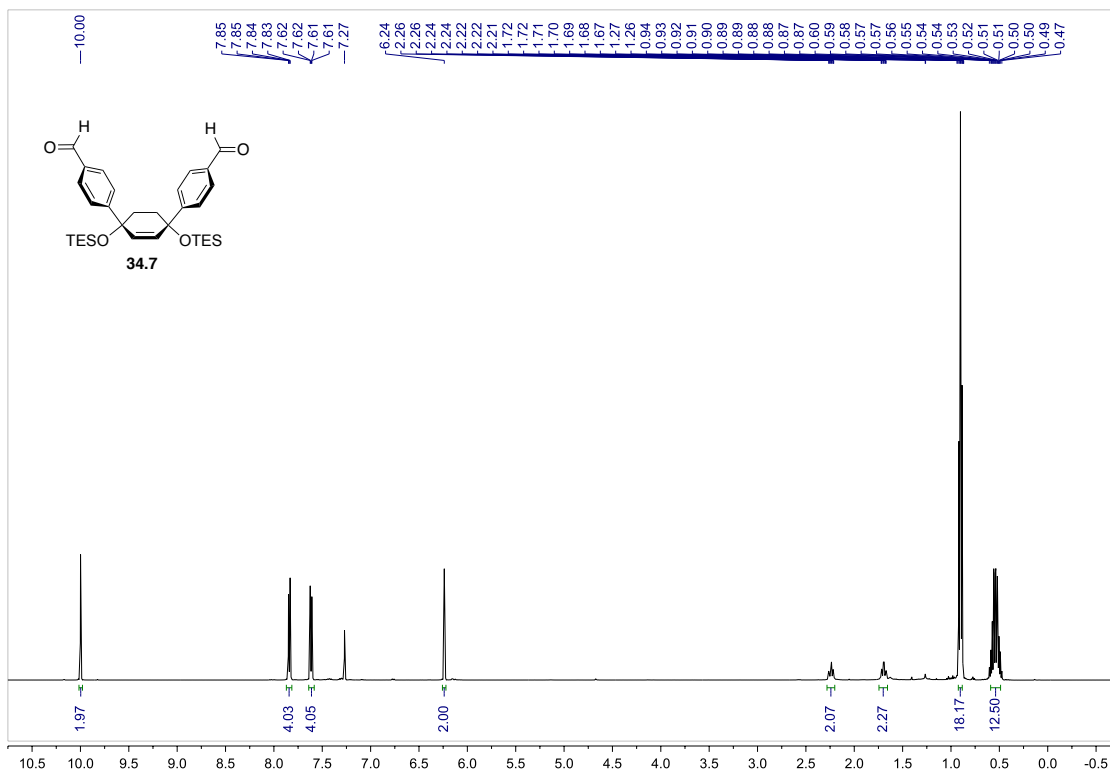


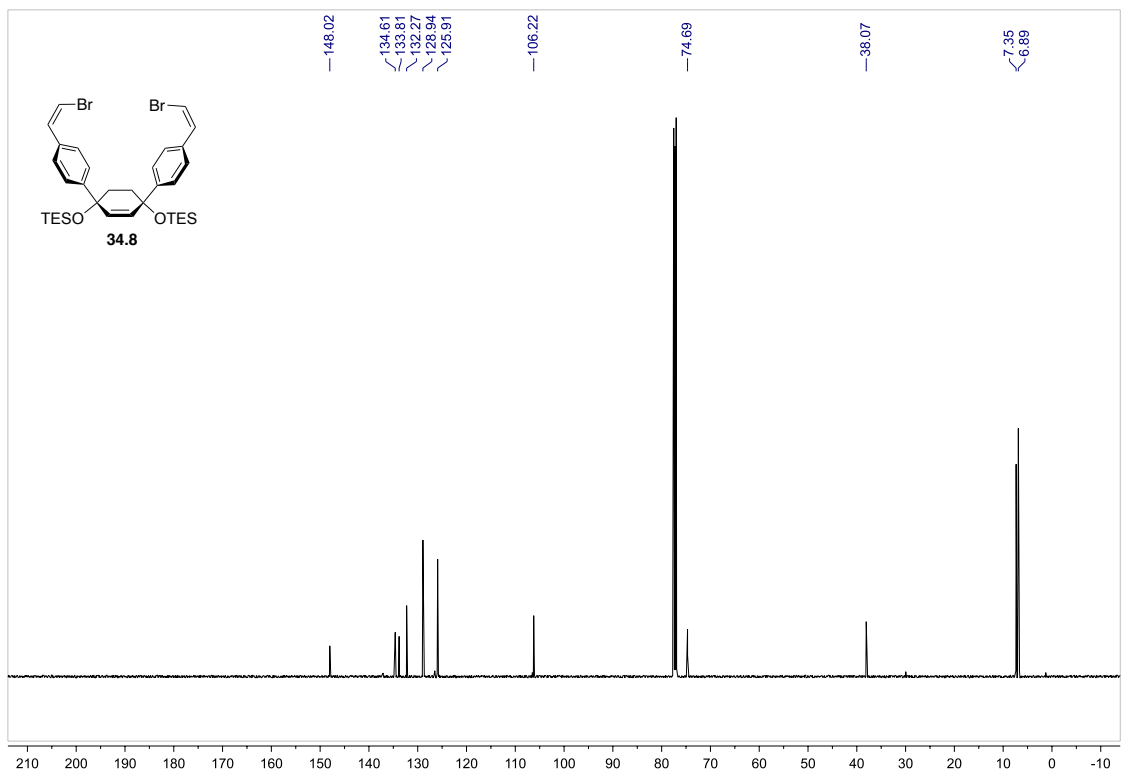
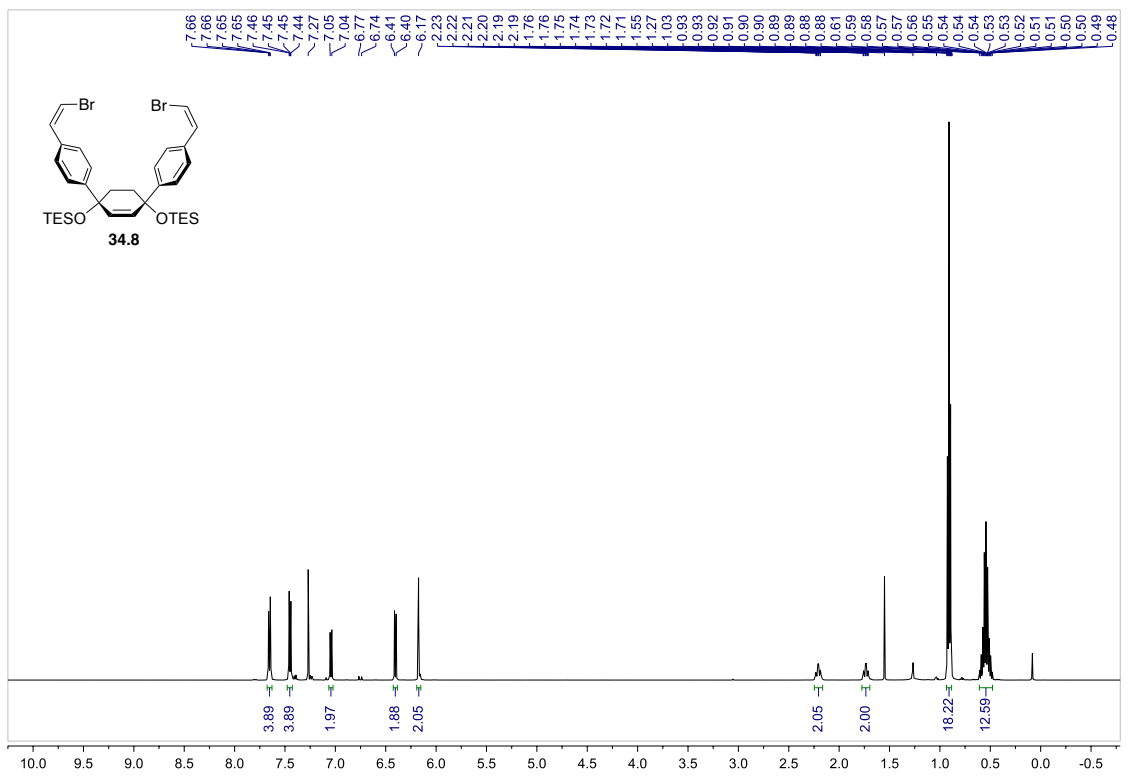


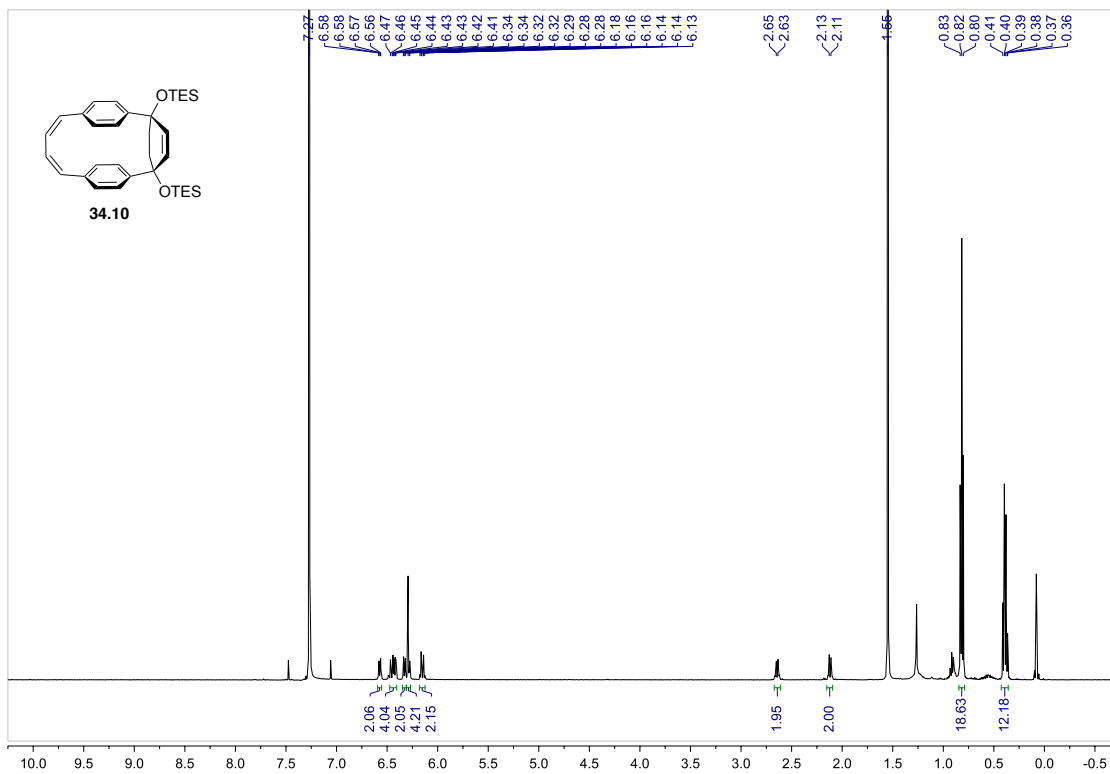


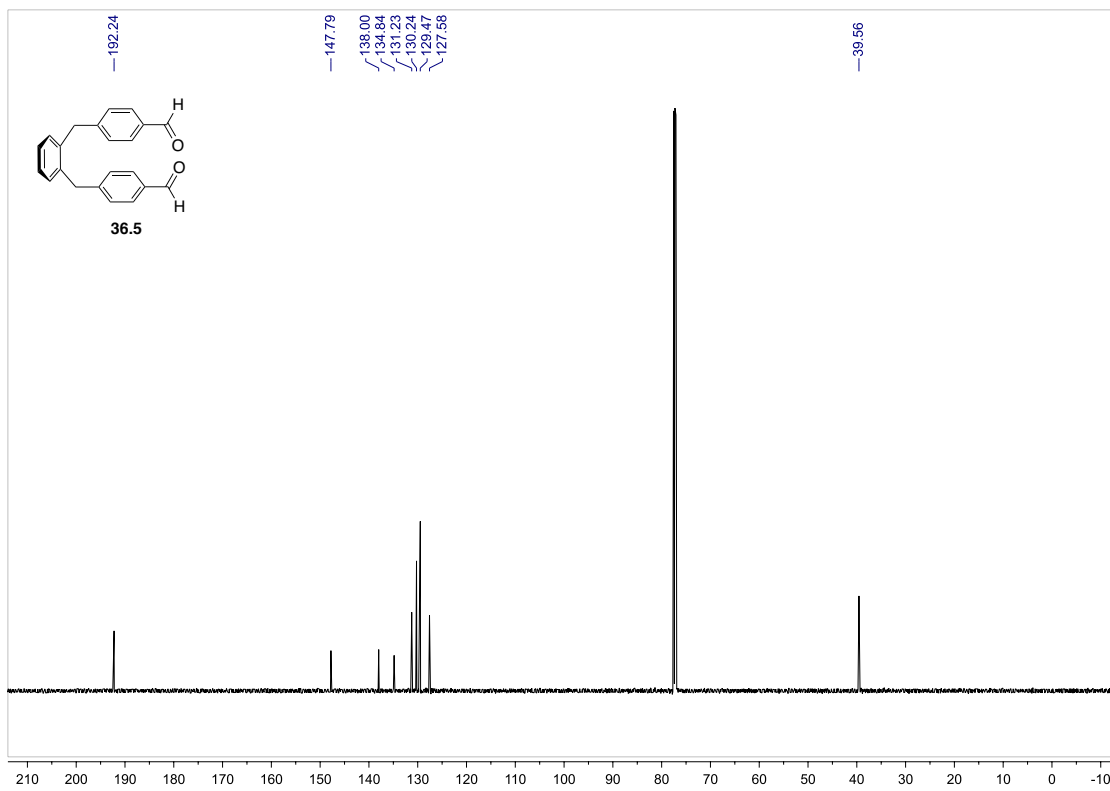
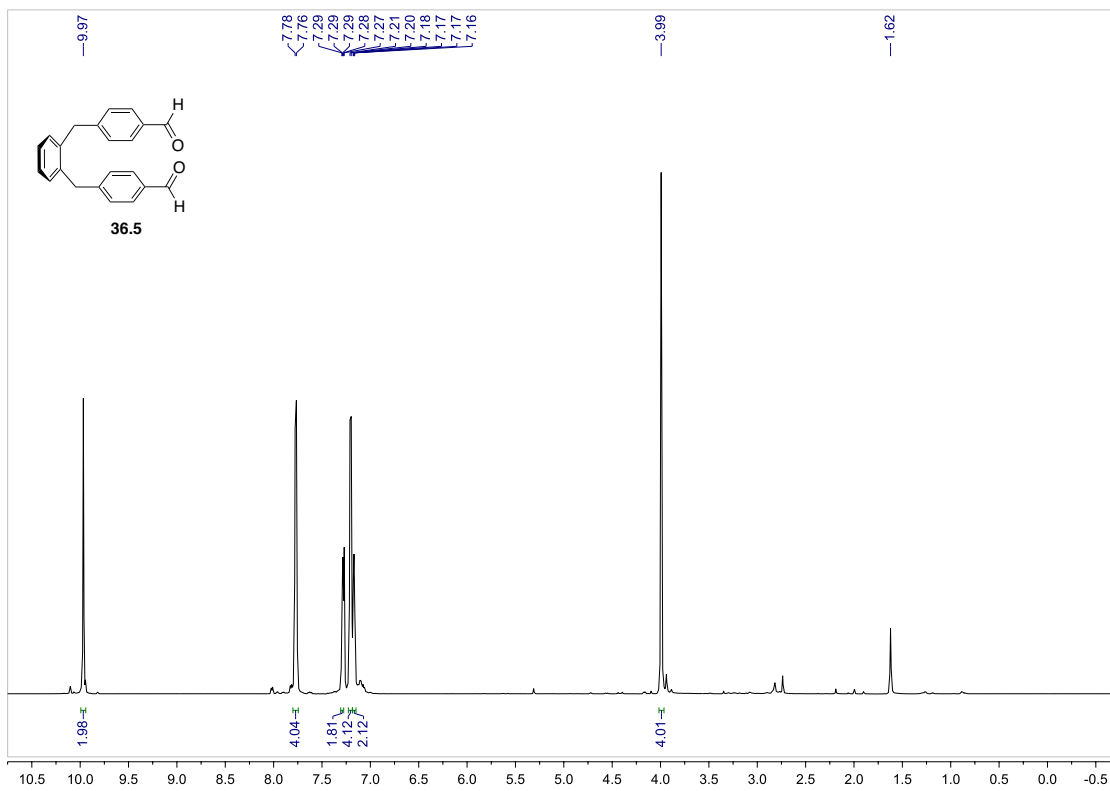


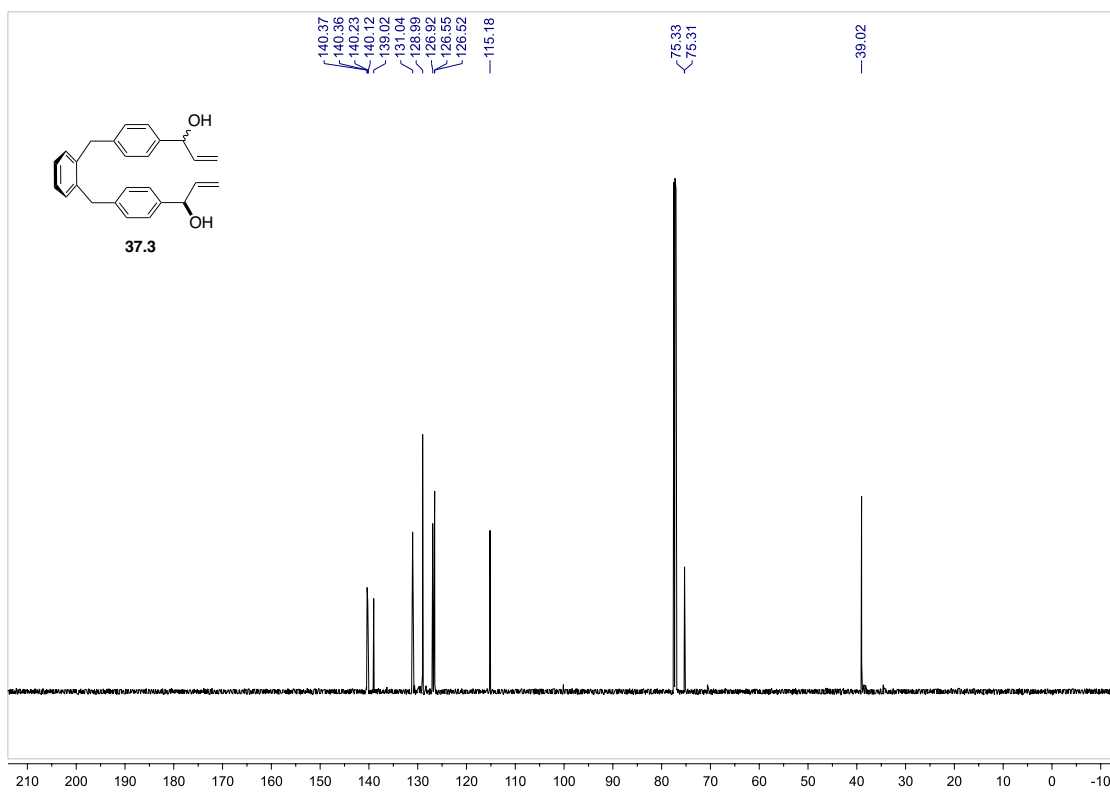
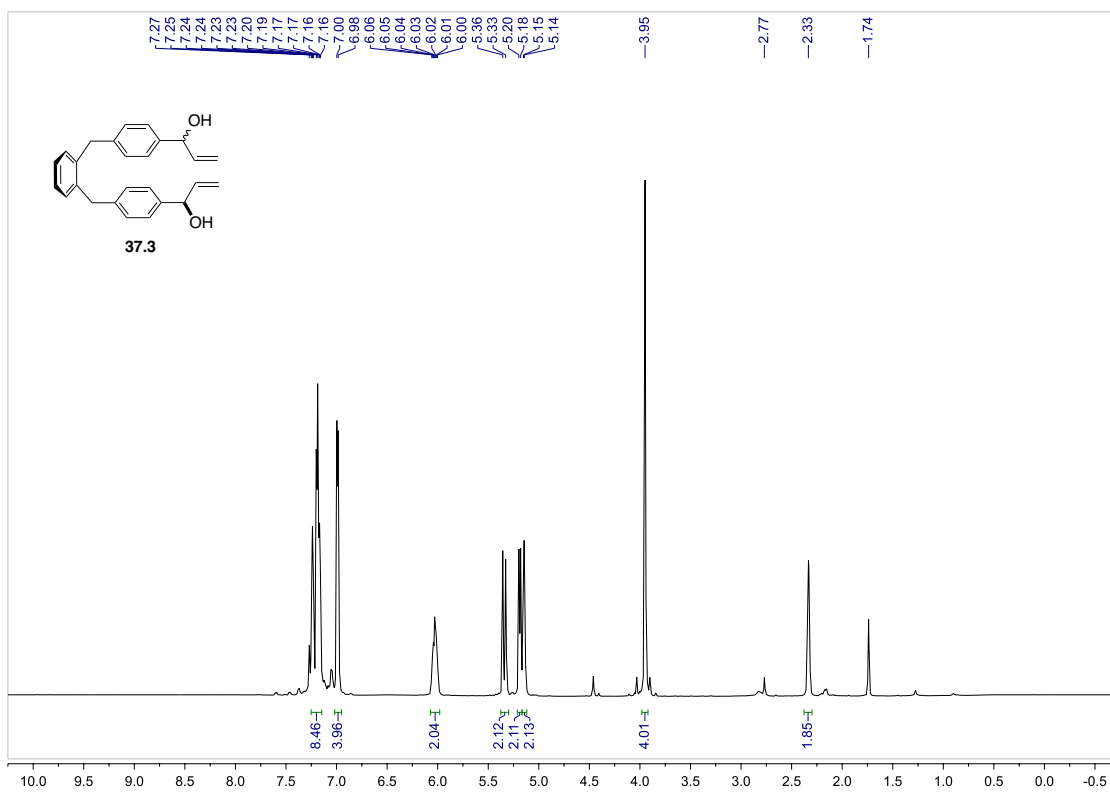


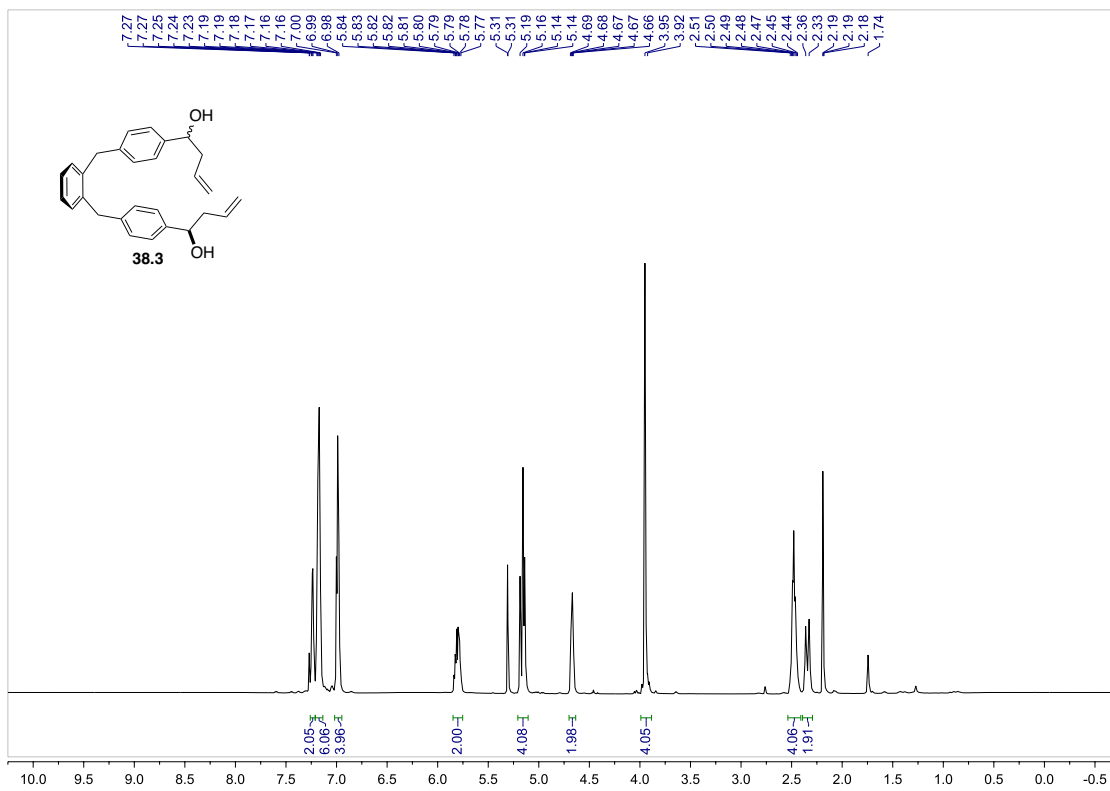


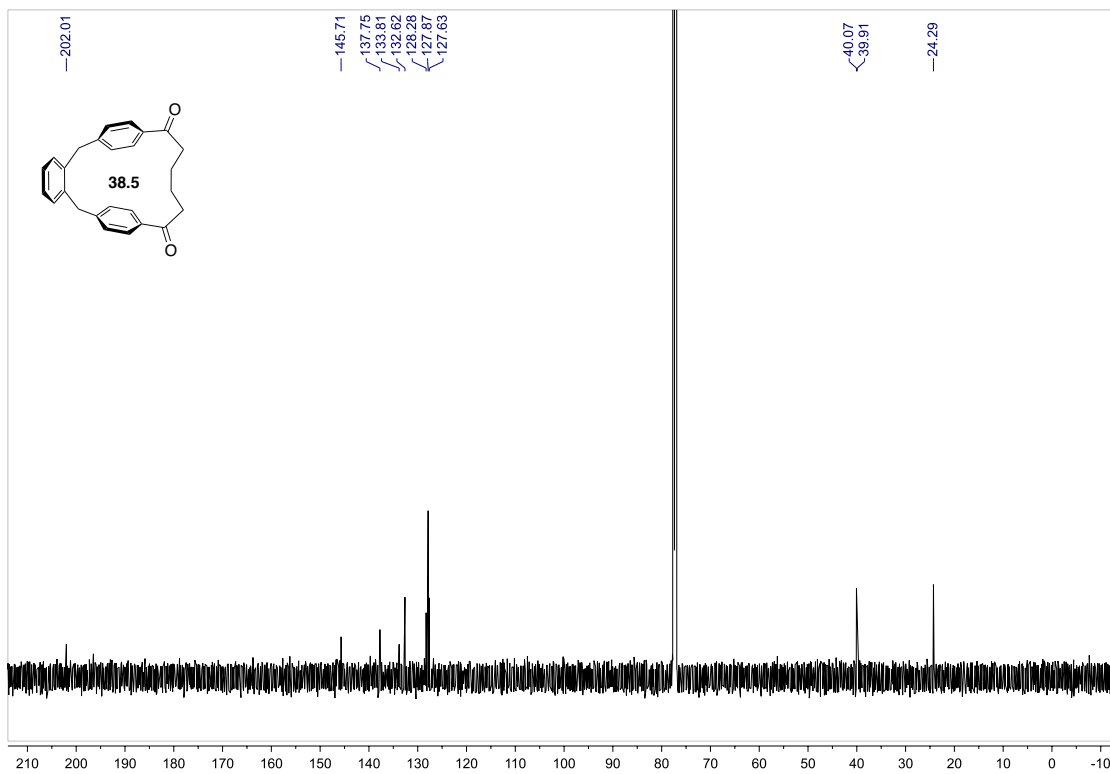
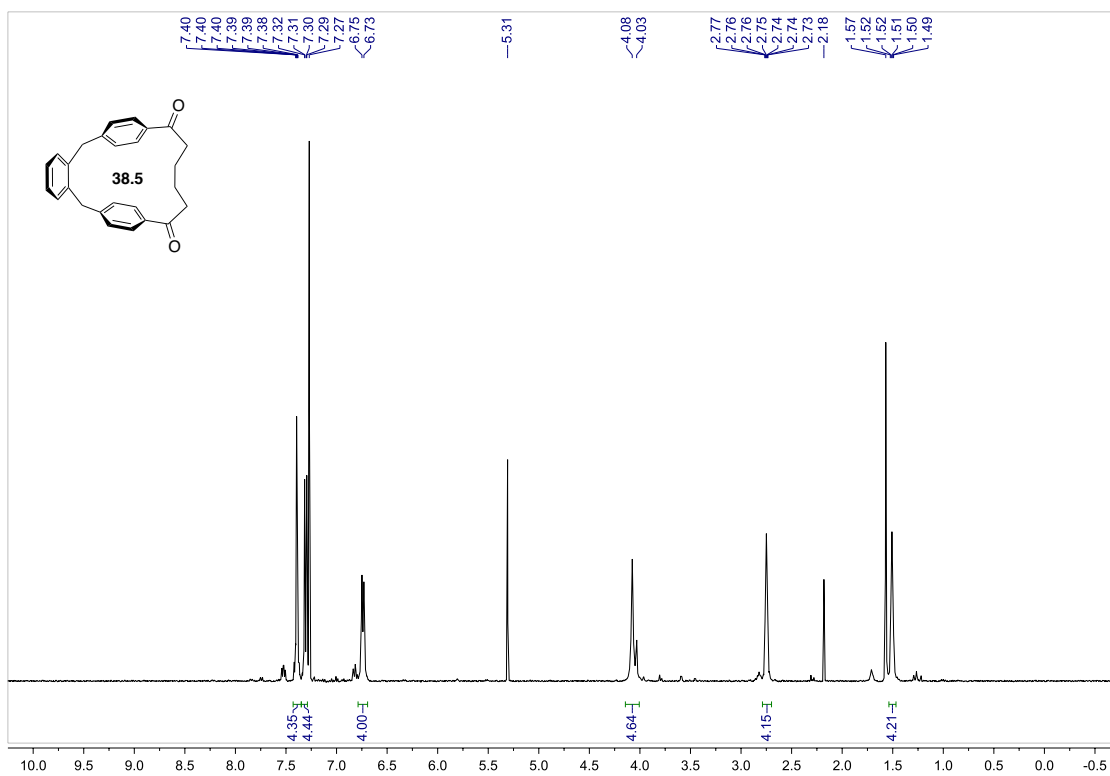


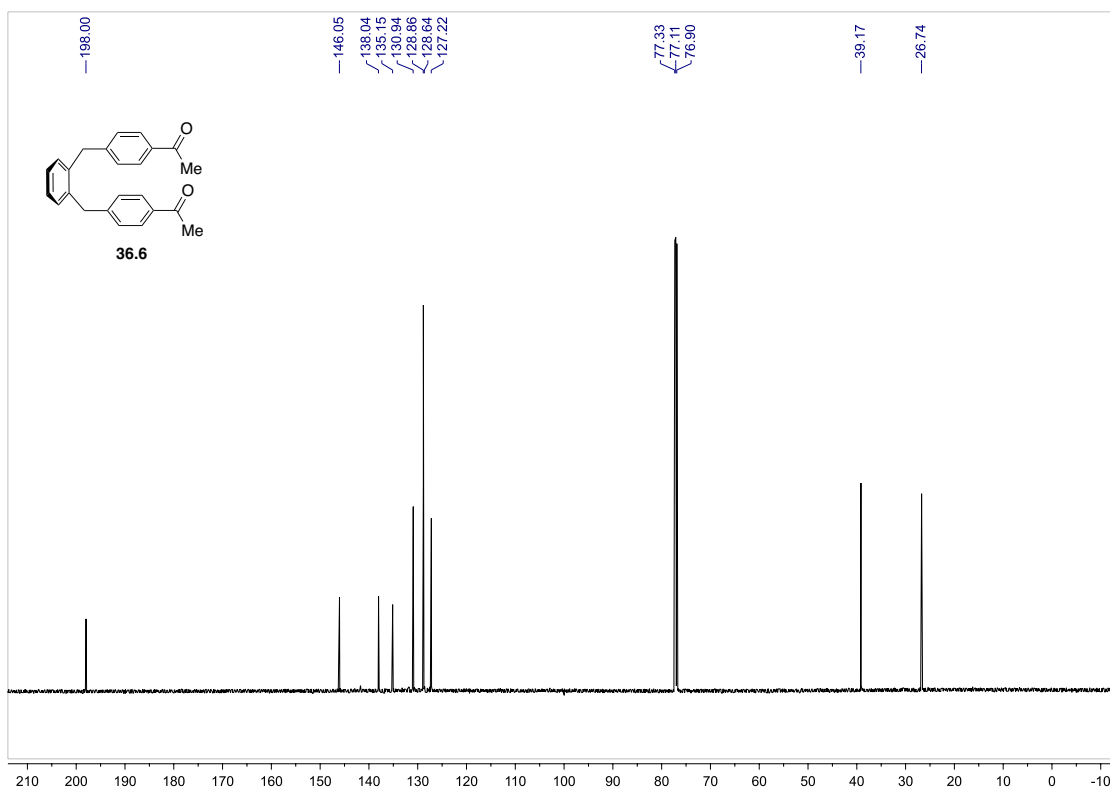
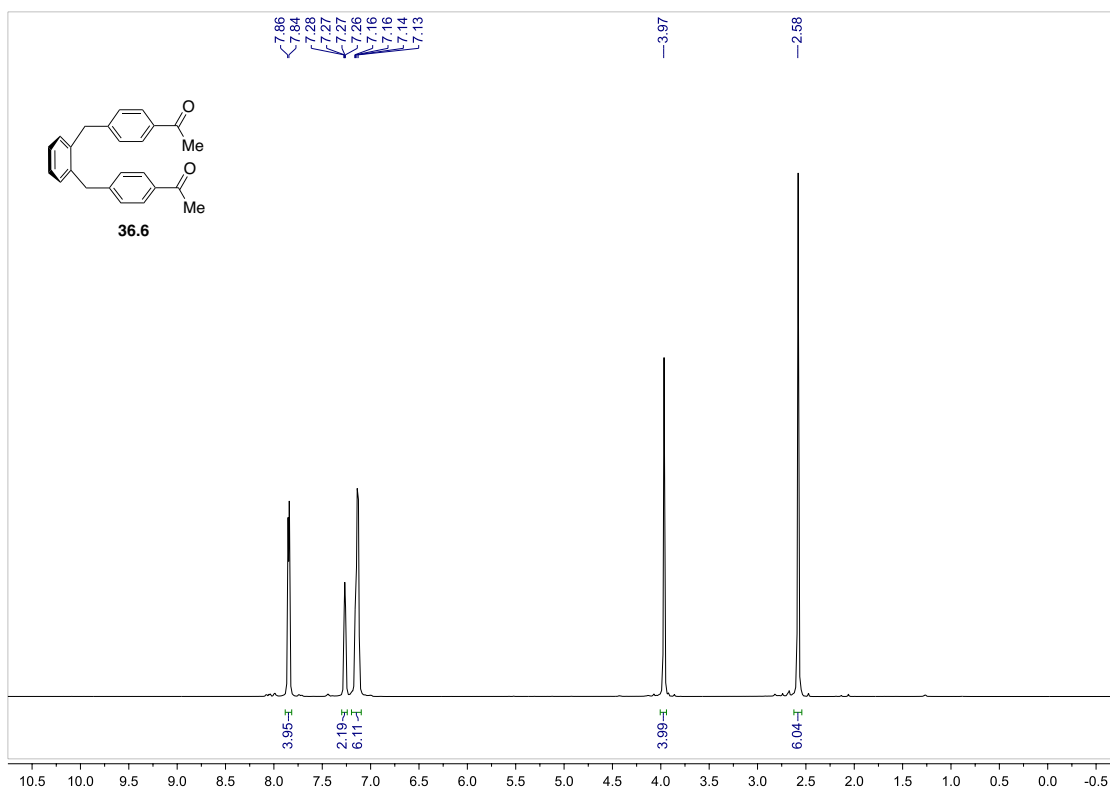


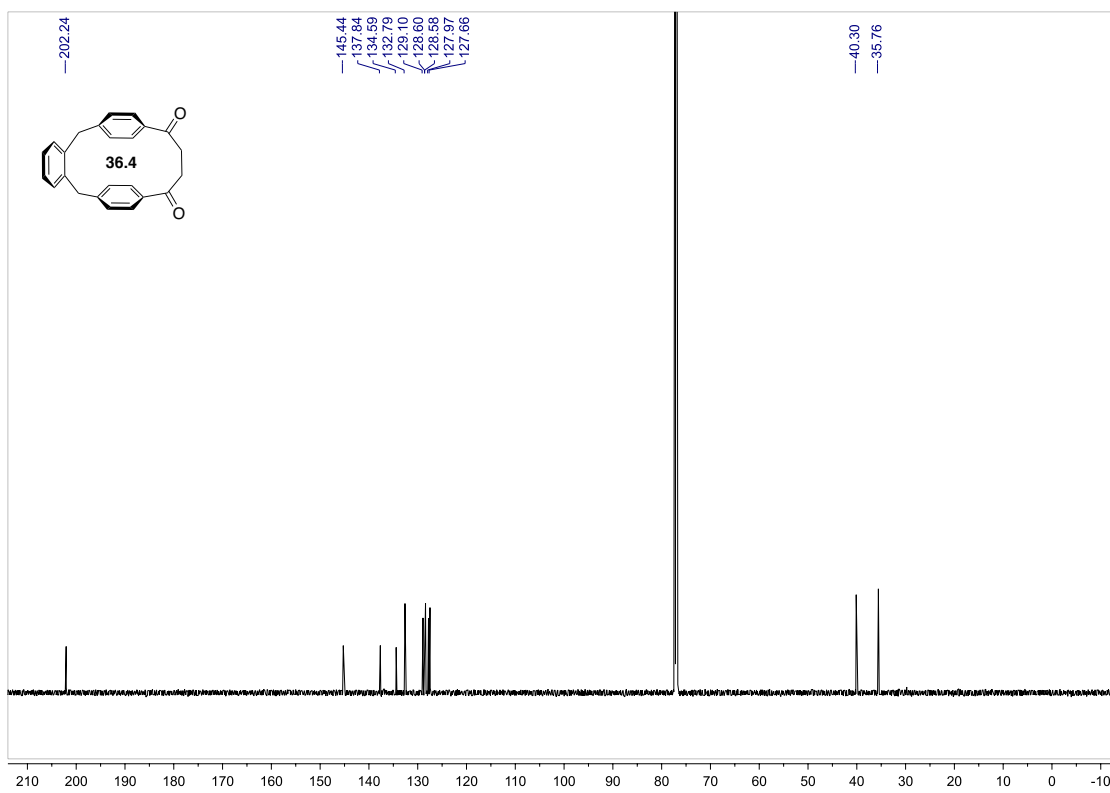
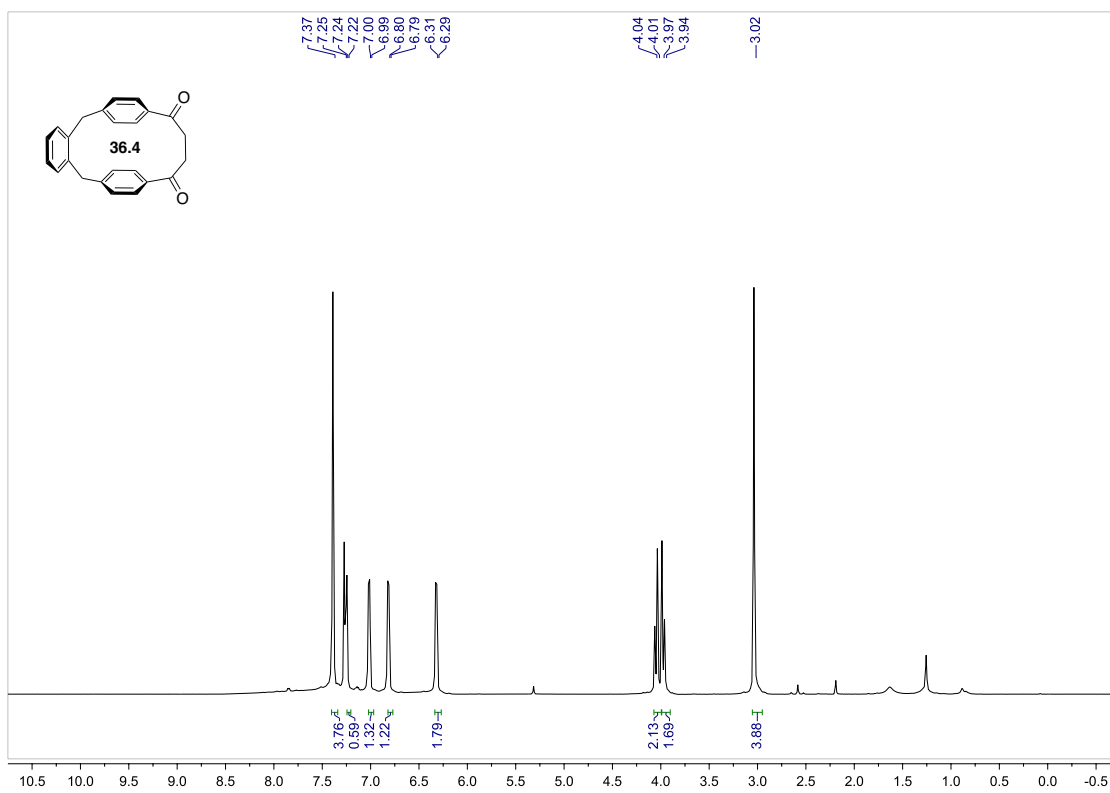


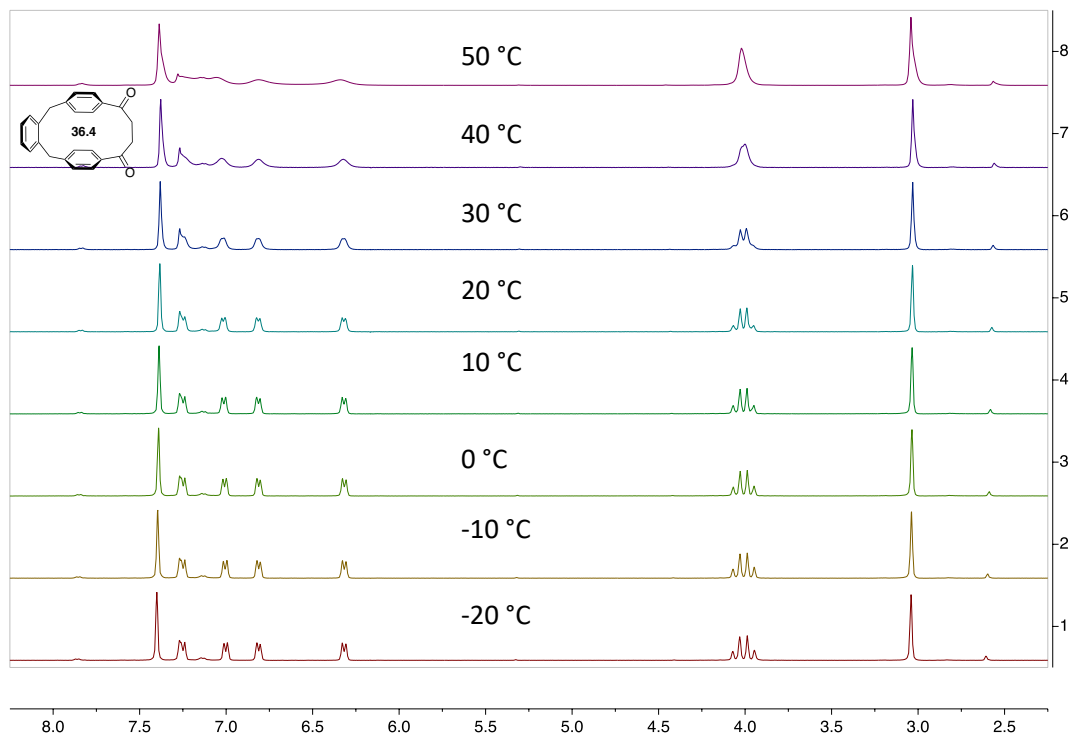




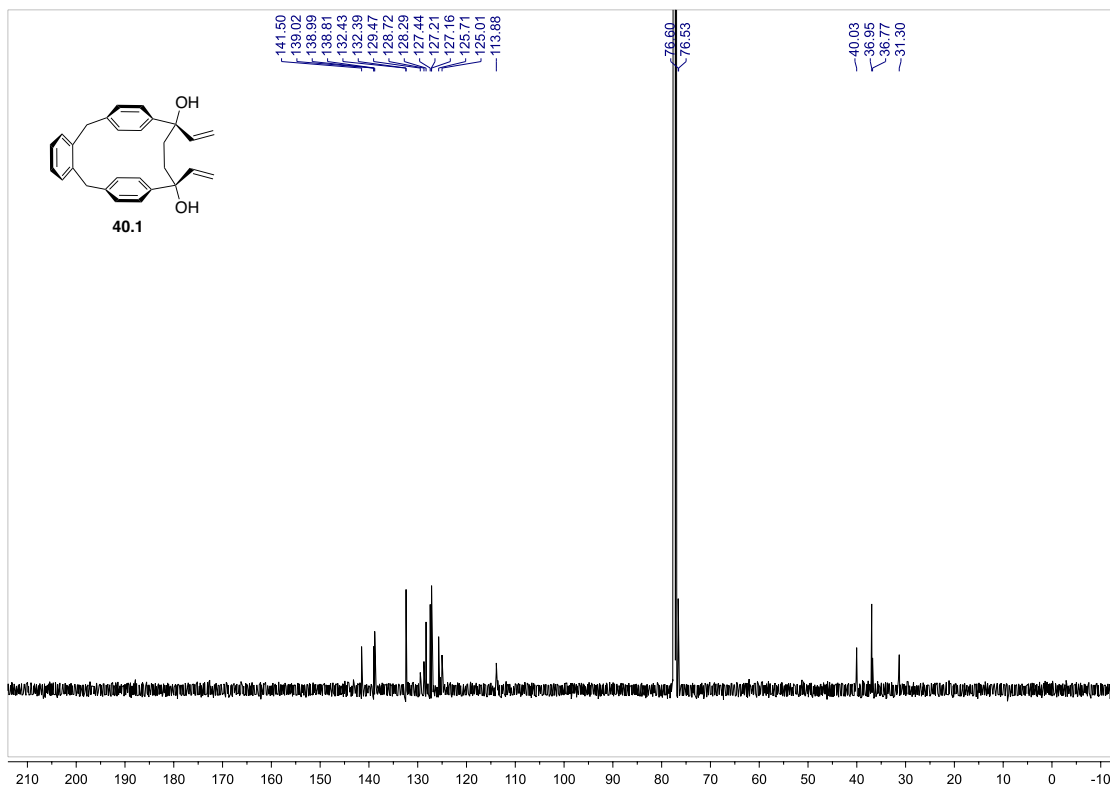
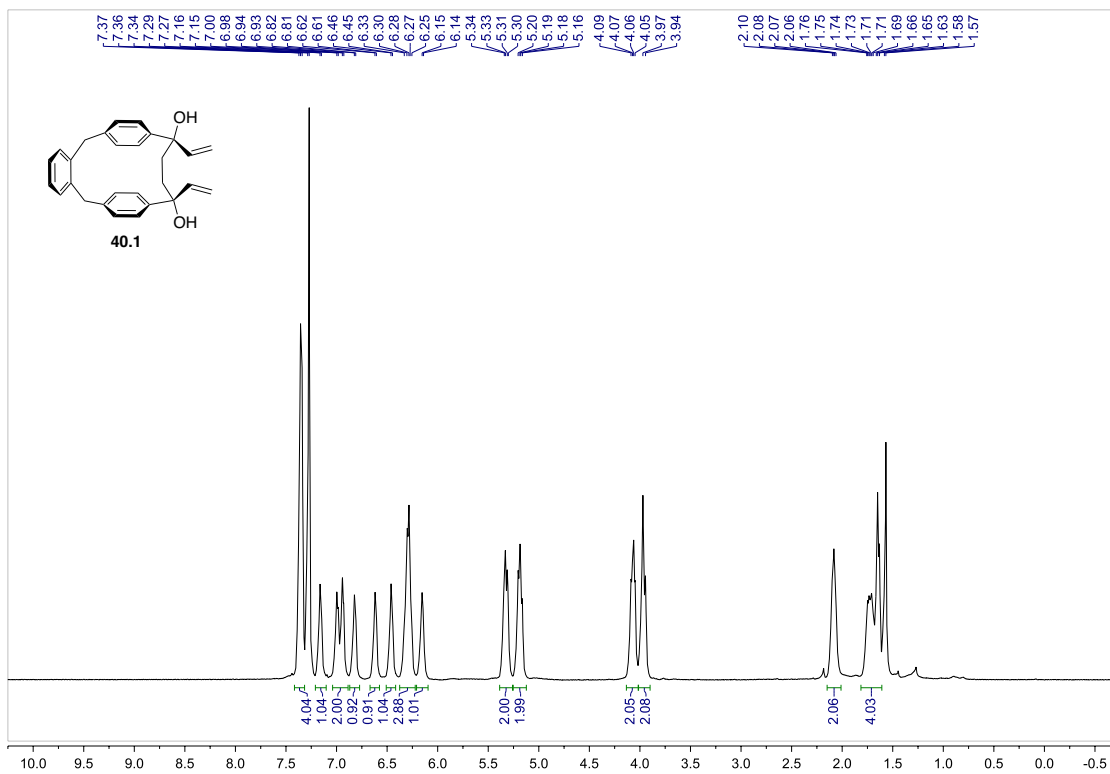


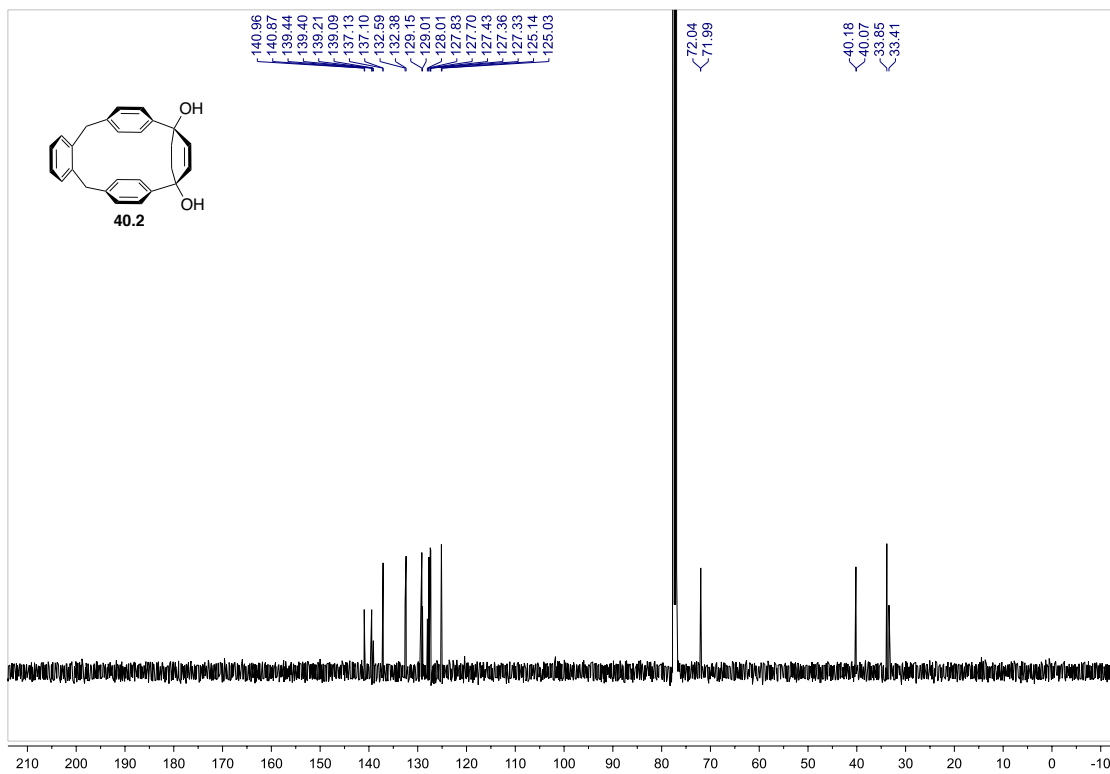
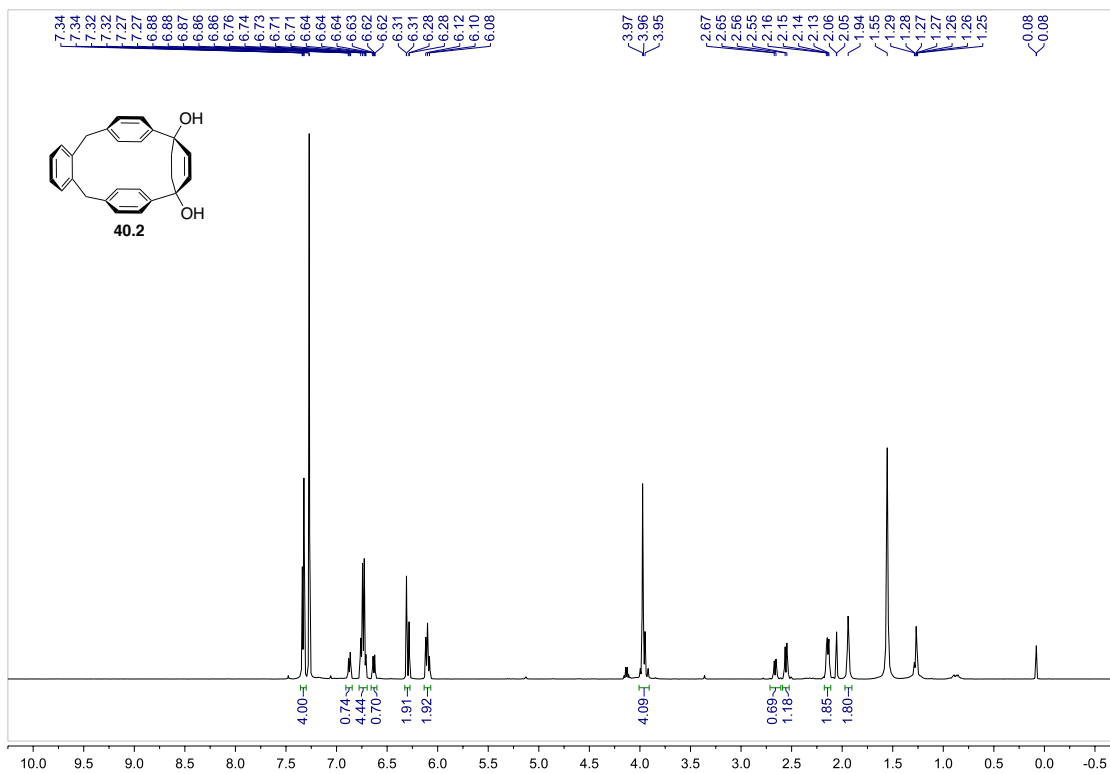


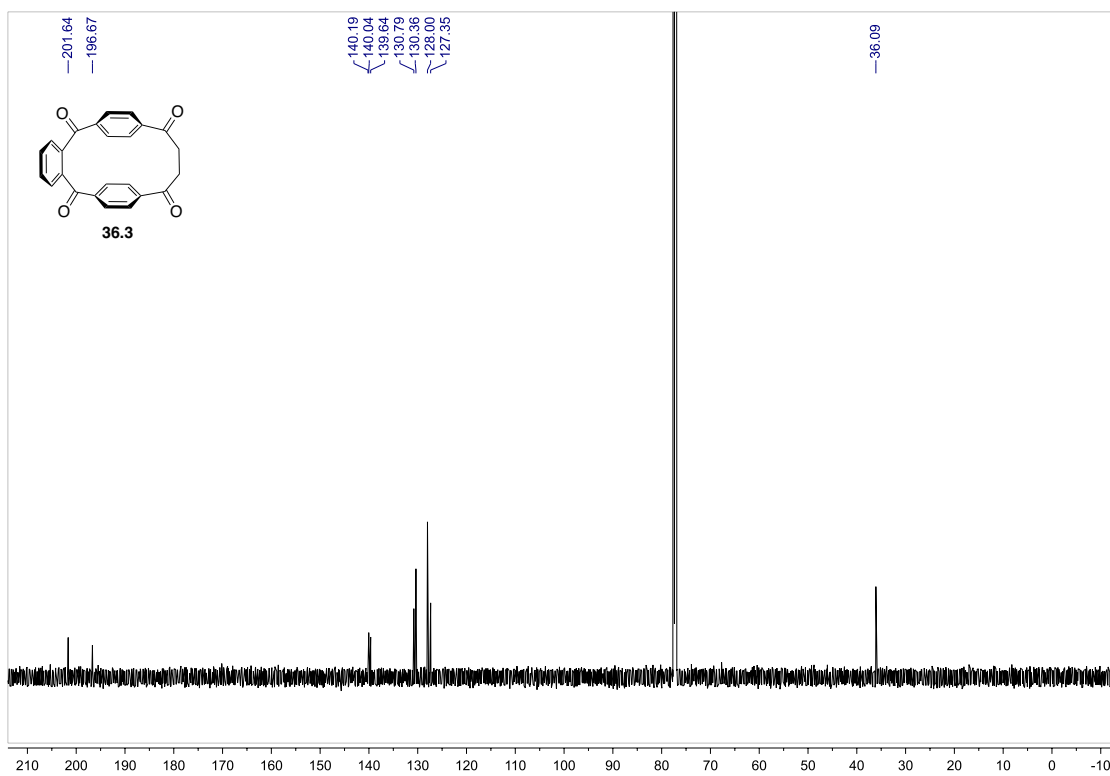
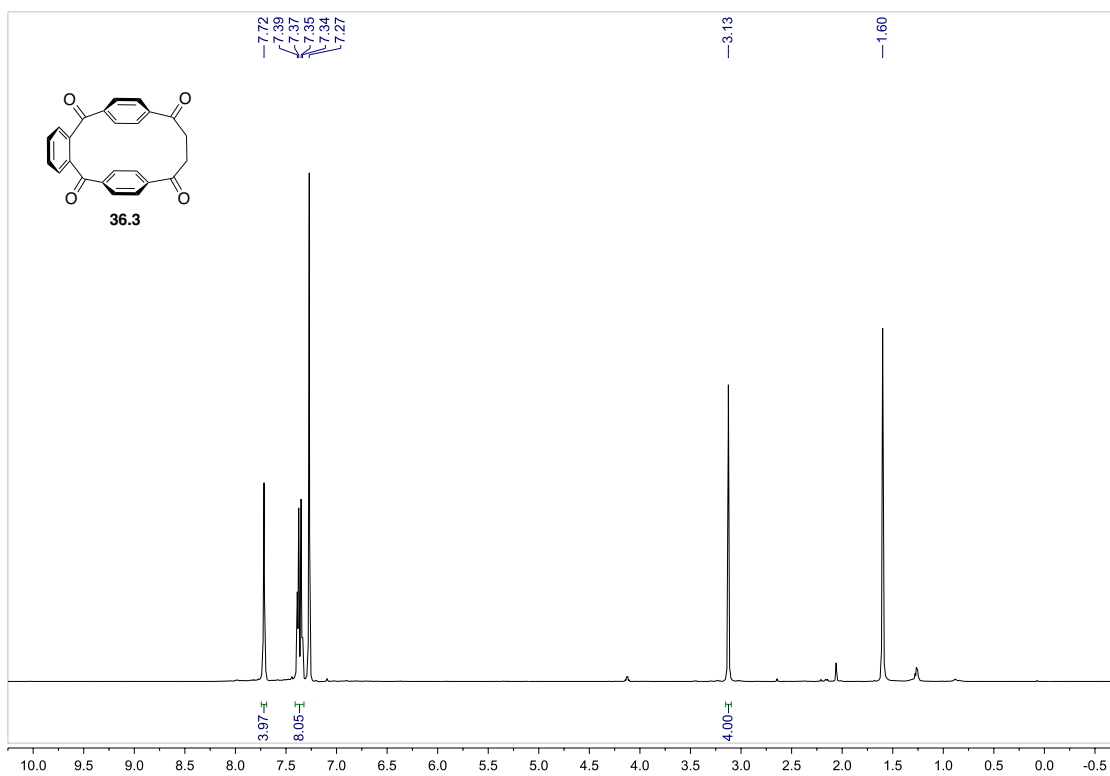




Variable temperature nmr of macrocyclic diketone **38.4**







APPENDIX 2:

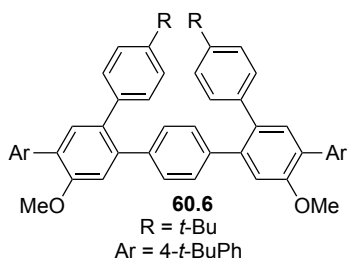
Supporting Information for

CHAPTER 2 π -Extension of Strained Benzenoid Macrocycles Using the Scholl Reaction.

General Experimental Conditions

All reactions were run in flame or oven-dried (120 °C) glassware and cooled under a positive pressure of ultra-high pure nitrogen or argon gas. All chemicals were used as received from commercial sources, unless otherwise stated. Anhydrous reaction solvents were purified and dried by passing HPLC grade solvents through activated columns of alumina (Glass Contour SDS). All solvents, dichloromethane, nitromethane, toluene, ethanol, and water, that were used in Scholl or Suzuki reactions were purged with nitrogen or argon gas for 30 min prior to use. All solvents used for chromatographic separations were HPLC grade (hexanes, ethyl acetate, dichloromethane, chloroform, methanol, and acetone). Chromatographic separations were performed using flash chromatography, as originally reported by Still and co-workers, on silica gel 60 (particle size 43-60 μm), and all chromatography conditions have been reported as height \times diameter in centimeters. Reaction progress was monitored by thin layer chromatography (TLC), on glass-backed silica gel plates (pH = 7.0). TLC plates were visualized using a handheld UV lamp (254 nm) and stained using an aqueous ceric ammonium molybdate (CAM) solution. Plates were dipped, wiped clean, and heated from the back of the plate. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 or 600 MHz, calibrated using residual undeuterated solvent as an internal reference (CHCl_3 , δ 7.27 and 77.2 ppm), reported in parts per million relative to trimethylsilane (TMS, δ 0.00 ppm), and presented as follows: chemical shift (δ , ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constants (J , Hz). High-resolution mass spectrometric (HRMS) data were obtained using a quadrupole time-of-flight (Q-TOF) spectrometer and electrospray ionization (ESI).

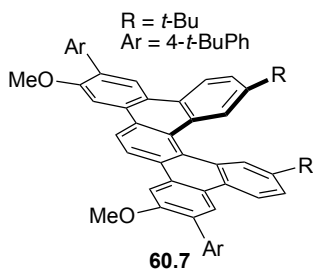
New compounds: procedures and characterization data (listed in chronological order)



4,4",6,6"-tetrakis(4-*t*-butylphenyl)-3,3"-dimethoxy-*p*-terphenyl (60.6): Sodium carbonate (0.731 g, 6.89 mmol, as an aqueous solution, 3 mL H_2O) and 4-*tert*-butylphenylboronic acid (0.332 g, 1.85 mmol) were added sequentially to a stirred solution of **60.5** (0.140 g, 0.231 mmol) in toluene (9 mL), and ethanol (1.5 mL) at room temperature. After the addition was complete, a stream of nitrogen gas was passed over the reaction mixture for 3 min.

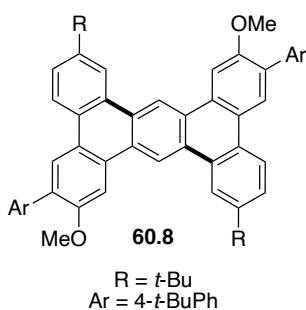
Tetrakis(triphenylphosphine)palladium(0) (0.027 g, 0.023 mmol) was added, and nitrogen gas was once again passed over the reaction mixture for 2 min. The reaction was heated to 90 °C for 16 h and then cooled to room temperature. Once cooled, water (40 mL) and 1 M HCl (10 mL) were added to the reaction mixture and the layers were separated. The aqueous phase was extracted with dichloromethane (3 \times 10 mL), and the combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered,

and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 3-8% ethyl acetate/hexanes) to yield **60.6** as a white solid (0.160 g, 85%); $R_f = 0.42$ (1:19 ethyl acetate/hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.60 – 7.58 (m, 4H), 7.49 – 7.47 (m, 6H), 7.28 – 7.27 (m, 4H), 7.13 (s, 4H), 7.11 – 7.10 (m, 4H), 7.07 (s, 2H), 3.92 (s, 6H), 1.40 (s, 18H), 1.33 (s, 18H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 155.74, 150.05, 149.25, 140.32, 140.02, 138.13, 135.15, 133.42, 133.24, 129.79, 129.73, 129.64, 129.33, 125.26, 124.81, 113.31, 55.98, 34.77, 34.59, 31.60, 31.58; HRMS (EI) calc'd for $\text{C}_{60}\text{H}_{66}\text{O}_2$ ($[\text{M}]^+$) $m/z = 818.5063$, found 818.5024.



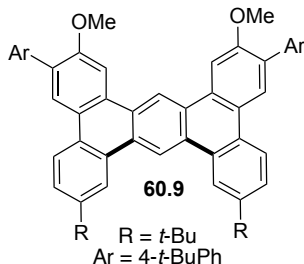
[5]helicene (60.7): A solution of iron(III) chloride (0.16 g, 0.96 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **60.6** (0.040 g, 0.048 mmol) in dichloromethane (8 mL). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon-filled balloon was placed over the reaction. After 1 h, methanol (10 mL) and water (10 mL) were added to the reaction. The layers were separated, and the aqueous phase extracted with dichloromethane (2 × 10 mL). The

combined organic extracts were washed with brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 5% to 8% ethyl acetate/hexanes) to yield tetrabenz(*a,c,h,j*)anthracene **60.8** as a white solid (0.003 g, 7%) and **60.7** as a yellow solid (0.026 g, 65%).



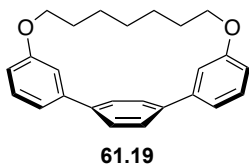
tetrabenz(*a,c,h,j*)anthracene 60.8: $R_f = 0.30$ (1:19 ethyl acetate/hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.89 (s, 2H), 8.93 (d, $J = 2.0$ Hz, 2H), 8.60 (s, 2H), 8.56 (d, $J = 8.6$ Hz, 2H), 8.39 (s, 2H), 7.76 (dd, $J = 8.5, 1.9$ Hz, 2H), 7.74 – 7.72 (m, 4H), 7.59 – 7.57 (m, 4H), 4.20 (s, 6H), 1.59 (s, 18H), 1.44 (s, 18H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 156.26, 150.40, 149.28, 135.58, 131.50, 130.20, 129.57, 129.24, 128.68, 128.63, 128.06, 126.30, 125.81, 125.38, 124.26, 123.16, 119.18, 117.66, 104.15, 55.63, 35.24, 34.83, 31.74, 31.61; HRMS (EI) calc'd for $\text{C}_{60}\text{H}_{62}\text{O}_2$ ($[\text{M}]^+$) $m/z = 814.4750$, found 814.4788.

[5]helicene 60.7: $R_f = 0.17$ (1:19 ethyl acetate/hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.64 (d, $J = 2.1$ Hz, 4H), 8.46 (d, $J = 8.7$ Hz, 2H), 8.26 (d, $J = 2.0$ Hz, 2H), 8.12 (s, 2H), 7.75 (d, $J = 8.1$ Hz, 4H), 7.59 – 7.54 (m, 6H), 4.13 (s, 6H), 1.45 (s, 18H), 1.11 (s, 18H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 156.36, 150.36, 146.88, 135.72, 131.41, 130.20, 130.03, 129.97, 129.65, 129.00, 127.77, 127.51, 126.00, 125.39, 125.20, 124.66, 123.06, 121.50, 104.41, 56.05, 34.86, 34.65, 31.66, 31.16; HRMS (EI⁺) calc'd for $\text{C}_{60}\text{H}_{62}\text{O}_2$ ($[\text{M}]^+$) $m/z = 814.4750$, found 814.4772.



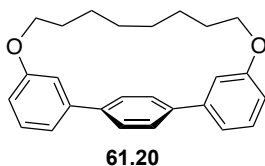
Tetrabenzanthracene 60.9: A solution of boron tribromide (0.014 g, 0.056 mmol, 0.28 M) in dichloromethane was added dropwise to a stirred 0 °C solution of **62.4B** (0.006 g, 0.007 mmol) in dichloromethane (2 mL). After the addition, the reaction was warmed to room temperature. After 1 h the reaction was poured into ice water (10 mL) and stirred for 5 min. The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 5 mL). The combined organic

extracts were washed with brine (10 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The white solid residue was dissolved in acetone (4 mL) and methyl iodide (0.004 g, 0.028 mmol) was added at room temperature. The reaction was heated to 56 °C for 14 h and then cooled to room temperature. Once cooled, water (10 mL) was added, and the layers separated. The aqueous phase was extracted with dichloromethane (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5 × 0.7 cm, 3:7 dichloromethane/hexanes) to yield **60.9** as a white solid (0.002 g, 35%), *R*_f = 0.56 (2:3 dichloromethane/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 10.00 (s, 1H), 9.73 (s, 1H), 8.95 (d, *J* = 2.0 Hz, 2H), 8.58 (s, 2H), 8.54 (d, *J* = 8.6 Hz, 2H), 8.32 (s, 2H), 7.78 – 7.70 (m, 6H), 7.61 – 7.54 (m, 4H), 4.12 (s, 6H), 1.60 (s, 19H), 1.44 (s, 19H); ¹³C NMR (151 MHz, CDCl₃) δ 156.24, 150.43, 149.39, 135.61, 131.52, 130.16, 129.61, 129.43, 128.75, 128.47, 128.02, 126.34, 125.89, 125.43, 124.35, 123.14, 119.34, 117.83, 117.53, 104.18, 55.76, 35.28, 34.87, 31.66, 31.57, 29.92. HRMS (EI) calc'd for C₆₀H₆₂O₂ ([M]⁺) *m/z* = 814.4750, found 814.4788.



1,9-dioxa[9](3,3'')p-Terphenylenophane (61.19): *p*-Toluene sulfonic acid monohydrate (0.174 g, 0.913 mmol) was added to a stirred solution of **61.15** (0.060 g, 0.15 mmol) in toluene (6 mL), and the reaction was heated at 65 °C. After 1 h, the reaction was poured into water (50 mL) and further diluted with a saturated solution of

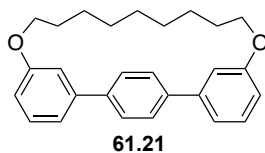
NaHCO₃ (15 mL). The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 50% dichloromethane/hexanes) to afford **61.19** as a white solid (0.038 g, 70%); *R*_f = 0.50 (1:1 dichloromethane/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.52 (s, 4H), 7.38 – 7.34 (m, 2H), 7.28 (d, *J* = 5.9 Hz, 2H), 6.85 (dd, *J* = 8.3, 2.7 Hz, 2H), 6.37 – 6.36 (m, 2H), 4.13 – 4.11 (m, 4H), 1.67 – 1.61 (m, 4H), 1.36 – 1.31 (m, 4H), 1.09 – 1.04 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 157.78, 143.82, 142.70, 130.47, 128.50, 116.82, 116.75, 115.91, 68.87, 30.84, 28.08, 27.27; HRMS (EI) calc'd for C₂₅H₂₆O₂ ([M]⁺) *m/z* = 358.1933, found 358.1925.



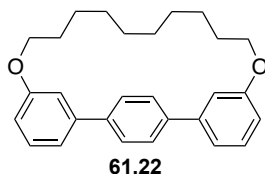
1,10-dioxa[10](3,3'')p-Terphenylenophane (61.20): *p*-Toluene sulfonic acid monohydrate (0.180 g, 0.944 mmol) was added to a stirred solution of **61.16** (0.077 g, 0.19 mmol) in toluene (5.0 mL), and the reaction was heated at 60 °C. After 30 min, the reaction was cooled and poured into water (50 mL) and then further diluted

with a saturated solution of NaHCO₃ (15 mL). The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic

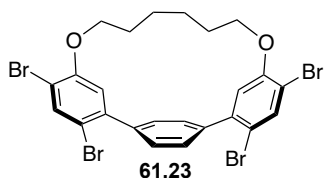
extracts were washed with brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 50% dichloromethane/hexanes) to afford **61.20** as a white solid (0.031 g, 44%); *R_f* = 0.48 (1:1 dichloromethane/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.56 (s, 4H), 7.36 (dd, *J* = 8.2, 7.4 Hz, 2H), 7.29 – 7.25 (m, 2H), 6.86 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 2H), 6.63 (dd, *J* = 2.7, 1.5 Hz, 2H), 4.20 – 4.16 (m, 4H), 1.72 – 1.65 (m, 4H), 1.35 – 1.30 (m, 4H), 1.27 – 1.20 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 158.32, 143.42, 142.21, 130.38, 128.26, 116.94, 115.99, 115.70, 68.26, 30.05, 27.67, 26.47. HRMS (EI) calc'd for C₂₆H₂₈O₂ ([M]⁺) *m/z* = 372.2089, found 372.2099.



1,11-dioxa [11] (3,3'')*p*-Terphenylenophane (61.21): *p*-Toluene sulfonic acid monohydrate (0.126 g, 0.660 mmol) was added to a stirred solution of compound **61.17** (mixture of diastereomers) (0.069 g, 0.17 mmol) in toluene (15 mL), and the reaction was heated at 80 °C. After 2 h, the reaction was cooled to room temperature and poured into water (10 mL) and then further diluted with a saturated solution of NaHCO₃ (10 mL). The layers were separated, and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 5% ethyl acetate/hexanes) to afford **61.21** as a white solid (0.047 g, 72%); *R_f* = 0.39 (1:19 ethyl acetate/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.60 (s, 4H), 7.41 – 7.33 (m, 2H), 7.24 (d, *J* = 7.5 Hz, 2H), 6.97 (s, 2H), 6.89 (dd, *J* = 8.2, 2.5 Hz, 2H), 4.19 (t, *J* = 8.3 Hz, 4H), 1.98 – 1.83 (m, 4H), 1.60 – 1.52 (m, 4H), 1.42 – 1.28 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 158.69, 143.08, 141.65, 130.30, 128.21, 117.63, 116.32, 113.54, 67.16, 32.25, 31.91, 27.77, 25.41; HRMS (EI) calc'd for C₂₇H₃₀O₂ ([M]⁺) *m/z* = 386.2246, found 386.2057.

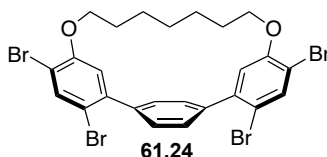


1,12-dioxa[12](3,3'')*p*-Terphenylenophane (61.22): *p*-Toluene sulfonic acid monohydrate (0.164 g, 0.595 mmol) was added to a stirred solution of compound **61.18** (mixture of diastereomers) (0.052 g, 0.12 mmol) in toluene (4.0 mL), and the reaction was heated at 65 °C. After 2.5 h, the reaction was cooled to room temperature and poured into water (40 mL) and then further diluted with a saturated solution of NaHCO₃ (10 mL). The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 50% dichloromethane/hexanes) to afford **61.22** as a white solid (0.031 g, 65%); *R_f* = 0.55 (1:1 dichloromethane/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.66 (s, 4H), 7.41 – 7.32 (m, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.07 – 7.01 (m, 2H), 6.90 (dd, *J* = 8.1, 2.5 Hz, 2H), 4.25 – 4.16 (m, 4H), 1.97 – 1.85 (m, 4H), 1.51 – 1.44 (m, 8H), 1.42 – 1.35 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 158.87, 142.38, 141.02, 130.29, 127.86, 118.04, 116.77, 112.99, 68.28, 31.05, 29.75, 26.96, 25.78; HRMS (ESI) calculated for C₂₈H₃₃O₂ ([M+H]⁺) *m/z* = 401.2475, found 401.2481.



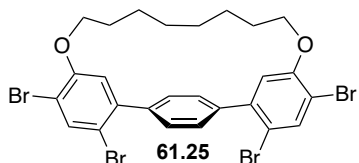
4,4'',6,6''-tetrabromo-1,8-dioxa[8](3,3'')p-terphenylophane (61.23): Bromine (0.368 g, 2.32 mmol) was added to a stirred solution of **19.15** (0.100 g, 0.291 mmol) in 1,2-dichlorobenzene (5.0 mL) at room temperature. The resulting mixture was heated to 80 °C for 2 hours and then cooled to room temperature under a stream of nitrogen gas. After

complete evaporation of the solvent, the residue was dissolved in dichloromethane (20 mL), an aqueous solution of 5% NaHSO₃ (10 mL) was added, and the resulting mixture was stirred for 5 min. The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃ (15 mL) and brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford **61.23** as a white solid (0.180 g, 95%); *R_f* = 0.31 (3:7 dichloromethane/hexanes). ¹H NMR (600 MHz, CDCl₃) δ 7.81 (s, 2H), 7.42 (s, 4H), 5.87 (s, 2H), 4.09 (t, *J* = 7.4 Hz, 4H), 1.58 – 1.56 (m, 4H), 1.08 – 1.05 (m, 4H); ¹³C NMR (151 MHz, CDCl₃) δ 153.02, 143.01, 142.19, 136.41, 129.07, 119.30, 110.93, 110.18, 69.74, 27.55, 27.44; HRMS (EI) calc'd for C₂₄H₂₀O₂Br₄ ([M]⁺) *m/z* = 655.8197, found 655.8224.



4,4'',6,6''-tetrabromo-1,9-dioxa[9](3,3'')p-terphenylophane (61.24): Bromine (0.71 g, 4.4 mmol) was added to a stirred solution of **61.19** (0.020 g, 0.056 mmol) in 1,2-dichlorobenzene (2.0 mL). The resulting mixture was heated to 70 °C for 6 h and then cooled to room temperature

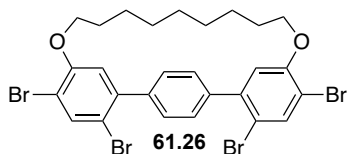
under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL), an aqueous solution of 5% NaHSO₃ (10 mL) was added, and the resulting mixture was stirred for 10 min. The layers were separated, and the aqueous phase extracted with dichloromethane (2 × 15 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃ (20 mL) and brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to yield **61.24** as a white solid (0.038 g, 95%); *R_f* = 0.34 (3:7 dichloromethane/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.80 (s, 2H), 7.45 (s, 4H), 6.23 (s, 2H), 4.13 – 4.10 (m, 3H), 1.72 – 1.67 (m, 4H), 1.29 – 1.24 (m, 4H), 1.16 – 1.09 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 153.50, 142.55, 141.59, 136.20, 128.86, 118.34, 110.79, 110.27, 69.03, 29.71, 26.45, 25.74; HRMS (APCI) calc'd for C₂₅H₂₂O₂Br₅ ([M+Br]⁺) *m/z* = 748.7537, found 748.7537.



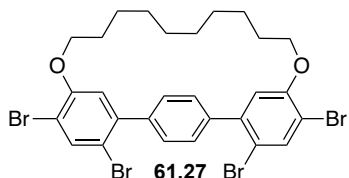
4,4'',6,6''-tetrabromo-1,10-dioxa[10](3,3'')p-terphenylophane (61.25): Bromine (0.178 g, 1.12 mmol) was added to a stirred solution of **61.20** (0.052 g, 0.14 mmol) in 1,2-dichlorobenzene (6 mL). The resulting mixture was heated to 80 °C for 12 h and then cooled to room

temperature under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (15 mL), an aqueous solution of 5% NaHSO₃ (20 mL) was added, and the resulting mixture was stirred for 10 min. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃ (20 mL) and brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to yield **61.25** as a white solid (0.090 g, 93%); *R_f* = 0.37 (3:7 dichloromethane/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.82 (s, 2H), 7.51 (s, 4H), 6.48 (s, 2H), 4.18 (t, *J* = 8.0 Hz, 4H), 1.74 – 1.69 (m, 4H), 1.31 – 1.29 (m, 4H), 1.23 – 1.20 (m,

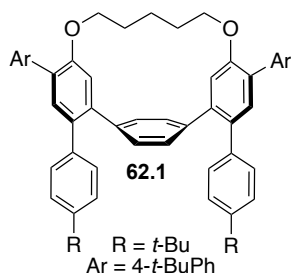
4H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.22, 142.26, 141.19, 136.63, 128.99, 118.33, 111.12, 110.87, 69.93, 29.42, 27.29, 25.92; HRMS (APCI) calc'd for $\text{C}_{26}\text{H}_{24}\text{O}_2\text{Br}_5$ ($[\text{M}+\text{Br}]^-$) $m/z = 762.7693$, found 762.7702.



4,4'', 6,6''-tetrabromo-1,11-dioxa [11] (3,3'')p-terphenylophane (61.26): Bromine (0.150 g, 0.939 mmol) was added to a stirred solution of [11]PTPP (**61.21**) (0.025 g, 0.065 mmol) in 1,2-dichlorobenzene (5 mL). The resulting mixture was heated to 80 °C for 2.5 h and then cooled to room temperature under a stream of nitrogen gas. After evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL), an aqueous solution of 5% NaHSO_3 (10 mL) was added, and the resulting mixture was stirred for 10 min. The layers were separated, and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (20 mL) and brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to yield **61.26** as a white solid (0.042 g, 92%): $R_f = 0.37$ (3:7 dichloromethane/hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.84 (s, 2H), 7.53 (s, 4H), 6.76 (s, 2H), 4.23 – 4.20 (m, 4H), 1.87 – 1.82 (m, 4H), 1.41 – 1.26 (m, 10H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.09, 141.94, 140.58, 136.99, 129.19, 116.37, 111.49, 111.38, 68.05, 31.73, 31.28, 27.41, 25.00; HRMS (EI) calc'd for $\text{C}_{27}\text{H}_{26}\text{Br}_4\text{O}_2$ ($[\text{M}]^+$) $m/z = 697.8666$, found 697.8684.

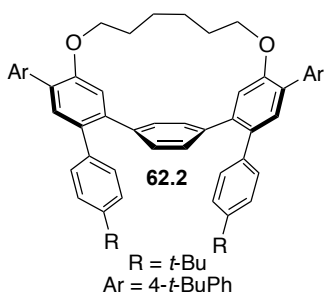


4,4'', 6,6''-tetrabromo-1,12-dioxa [12] (3,3'')p-terphenylophane (61.27): Bromine (0.052 g, 0.32 mmol) was added to a stirred solution of [12]PTPP (**61.22**) (0.016 g, 0.040 mmol) in 1,2-dichlorobenzene (2 mL). The resulting mixture was heated to 80 °C for 3 h and then cooled to room temperature under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL), an aqueous solution of 5% NaHSO_3 (10 mL) was added, and the resulting mixture was stirred for 10 min. The layers were separated, and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (15 mL) and brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to yield **61.27** as a white solid (0.029 g, >95%): $R_f = 0.40$ (3:7 dichloromethane/hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.84 (s, 2H), 7.53 (s, 4H), 6.78 (s, 2H), 4.22 – 4.19 (m, 4H), 1.88 – 1.83 (m, 4H), 1.42 – 1.39 (m, 4H), 1.37 – 1.33 (m, 4H), 1.30 – 1.26 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 154.28, 141.81, 140.43, 137.04, 129.17, 117.02, 112.09, 111.95, 69.27, 30.35, 29.19, 26.75, 25.38; HRMS (APCI) calc'd for $\text{C}_{28}\text{H}_{28}\text{O}_2\text{Br}_5$ ($[\text{M}+\text{Br}]^-$) $m/z = 794.7965$, found 794.7942.



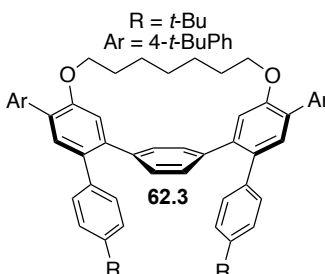
4,4'', 6,6''-tetrakis(4-*t*-butylphenyl)-1,7-dioxa[7](3,3'')p-terphenylenophane (62.1): Sodium carbonate (0.590 g, 5.55 mmol) and 4-*tert*-butylphenylboronic acid (0.272 g, 1.51 mmol) were added sequentially to a stirred solution of **58.2** (0.121 g, 0.185 mmol) in toluene (9 mL), water (3 mL), and ethanol (1.5 mL) at room temperature. After the addition was complete, a stream of nitrogen gas was passed over the reaction mixture for 3 min. Tetrakis(triphenylphosphine)palladium(0) (0.032 g, 0.028

mmol) was added, and nitrogen gas was once again passed over the reaction mixture for 3 min. The reaction was heated to 90 °C for 14 h and then cooled to room temperature. Once cooled, water (20 mL) and 1 M HCl (10 mL) were added, and the layers separated. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5-20% ethyl acetate/hexanes) to yield **62.1** as a white solid (0.132 g, 83%): *R_f* = 0.27 (1:19 ethyl acetate/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.58 – 7.53 (m, 8H), 7.51 (s, 2H), 7.45 – 7.43 (m, 4H), 7.38 – 7.36 (m, 4H), 7.27 (d, *J* = 4.5 Hz, 4H), 6.02 (s, 2H), 4.13 (t, *J* = 7.4 Hz, 4H), 1.59 – 1.53 (m, 4H), 1.37 (s, 18H), 1.32 (s, 18H), 1.27 – 1.21 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 153.36, 150.02, 149.57, 143.98, 140.97, 137.12, 134.98, 132.65, 130.27, 129.97, 129.47, 129.24, 129.03, 125.44, 125.27, 120.40, 68.84, 34.77, 34.69, 31.59, 27.15, 23.37; HRMS (EI) calc'd for C₆₃H₇₀O₂ (M⁺) *m/z* = 858.5376, found 858.5389.



4,4'',6,6''-tetrakis(4-*tert*-butylphenyl)-1,8-dioxa[8](3,3'')p-terphenylenophane (62.2): Sodium carbonate (0.480 g, 4.50 mmol) and 4-*tert*-butylphenylboronic acid (0.215 g, 1.20 mmol) were added sequentially to a stirred solution of **61.23** (0.101 g, 0.150 mmol) in toluene (6 mL), water (2 mL), and ethanol (1 mL) at room temperature. After the addition was complete, a stream of nitrogen gas was passed over the reaction mixture for 3 min. Tetrakis(triphenylphosphine)palladium(0) (0.021 g, 0.015 mmol) was added, and nitrogen gas was once again

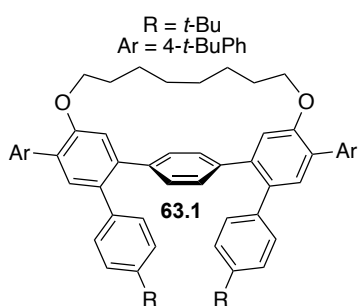
passed over the reaction mixture for 3 min. The reaction was heated to 90 °C for 7 h and then cooled to room temperature. Once cooled, water (20 mL) and 1 M HCl (10 mL) were added, and the layers separated. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5-20% ethyl acetate/hexanes) to yield **62.2** as a white solid (0.120 g, 92%): *R_f* = 0.39 (1:19 ethyl acetate/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.59 – 7.52 (m, 10H), 7.46 (d, *J* = 7.3 Hz, 4H), 7.39 – 7.37 (m, 4H), 7.28 (d, *J* = 4.6 Hz, 4H), 6.15 (s, 2H), 4.10 (t, *J* = 7.3 Hz, 4H), 1.71 – 1.67 (m, 4H), 1.39 – 1.36 (m, 36H), 1.19 – 1.16 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 153.07, 149.97, 149.43, 143.08, 140.86, 137.42, 135.16, 132.78, 130.78, 129.55, 129.47, 129.27, 125.34, 125.25, 119.27, 68.68, 34.76, 34.69, 31.61, 28.20, 27.43; HRMS (ESI) calc'd for C₆₄H₇₃O₂ ([M+H]⁺) *m/z* = 873.5611, found 873.5646.



4,4'',6,6''-tetrakis(4-*tert*-butylphenyl)-1,9-dioxa[9](3,3'')p-terphenylenophane (62.3): Sodium carbonate (0.283 g, 2.67 mmol as an aqueous solution, 2 mL of H₂O) and 4-*tert*-butylphenylboronic acid (0.125 g, 0.712 mmol) were added sequentially to a stirred solution of **61.24** (0.061 g, 0.089 mmol) in toluene (6 mL) and ethanol (1.5 mL) at room temperature. After the addition was complete, a stream of nitrogen gas was passed over the reaction mixture for 3 min. Tetrakis(triphenylphosphine)palladium(0) (0.016 g, 0.014

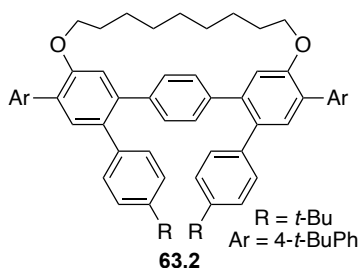
mmol) was added, and nitrogen gas was once again passed over the reaction mixture for 3 min. The reaction was heated to 90 °C for 6 h and then cooled to room temperature.

Once cooled, water (10 mL) and 1 M HCl (10 mL) were added, and the layers separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 1:19 ethyl acetate/hexanes) to yield **62.3** as a white solid (0.061 g, 77%): *R_f* = 0.38 (1:19 ethyl acetate/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.58 (d, *J* = 8.2 Hz, 4H), 7.50 (s, 2H), 7.47 – 7.43 (m, 8H), 7.32 (d, *J* = 8.3 Hz, 4H), 7.27 (s, 2H), 6.53 (s, 2H), 4.17 – 4.14 (m, 4H), 1.79 (t, *J* = 7.9 Hz, 4H), 1.38 (s, 18H), 1.36 – 1.32 (m, 4H), 1.31 (s, 18H), 1.29 – 1.28 (m, 2H), 1.22 – 1.16 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 153.96, 149.94, 149.42, 142.15, 140.54, 137.34, 135.13, 132.82, 131.15, 129.63, 129.39, 129.30, 129.26, 125.24, 125.09, 118.67, 68.92, 34.74, 34.60, 31.59, 31.53, 30.44, 27.53, 27.16; HRMS (APCI) calc'd for C₆₅H₇₅O₂ ([M+H]⁺) *m/z* = 887.5767, found 887.5747.



4,4'',6,6''-tetrakis(4-*t*-butylphenyl)-1,10-dioxa[10](3,3'')*p*-terphenylenophane (63.1): Sodium carbonate (0.390 g, 3.69 mmol, as an aqueous solution, 2 mL of H₂O) and 4-*tert*-butylphenylboronic acid (0.165 g, 0.917 mmol) were added sequentially to a stirred solution of **61.25** (0.084 g, 0.12 mmol) in toluene (6 mL) and ethanol (1.5 mL) at room temperature. After the addition was complete, a stream of nitrogen gas was passed over the reaction mixture for 2 min. Tetrakis(triphenylphosphine)palladium(0) (0.020 g, 0.017 mmol) was added, and nitrogen gas was once again passed

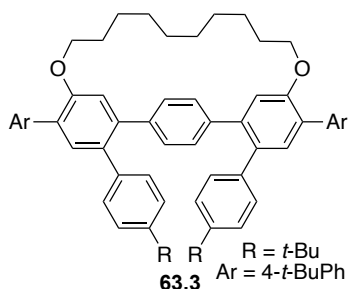
over the reaction mixture for 2 min. The reaction was heated to 90 °C for 3 h and then cooled to room temperature. Once cooled, water (20 mL) and 1 M HCl (10 mL) were added to the reaction mixture, and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 25% to 40% dichloromethane/hexanes) to yield **63.1** as a white solid (0.085 g, 78%): *R_f* = 0.39 (3:7 dichloromethane/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.58 (d, *J* = 8.1 Hz, 4H), 7.49 (s, 2H), 7.46 (d, *J* = 7.9 Hz, 4H), 7.38 (d, *J* = 8.0 Hz, 4H), 7.29 (d, *J* = 7.9 Hz, 4H), 7.23 (s, 4H), 6.73 (s, 2H), 4.22 (t, *J* = 8.0 Hz, 4H), 1.82 – 1.77 (m, 4H), 1.39 – 1.34 (m, 22H), 1.31 – 1.29 (m, 22H); ¹³C NMR (151 MHz, CDCl₃) δ 154.32, 149.90, 149.36, 141.59, 140.19, 137.42, 135.20, 133.16, 131.29, 129.63, 129.36, 129.29, 125.21, 124.98, 117.84, 68.70, 34.74, 34.57, 31.58, 29.48, 27.73, 25.86; HRMS (APCI) calc'd for C₆₆H₇₇O₂ ([M+H]⁺) *m/z* = 901.5924, found 901.5881.



4,4'',6,6''-tetrakis(4-*t*-butylphenyl)-1,11-dioxa[11](3,3'')*p*-terphenylenophane (63.2): Sodium carbonate (0.111 g, 1.05 mmol, as an aqueous solution, 1 mL of H₂O) and 4-*tert*-butylphenylboronic acid (0.052 g, 0.29 mmol) were added sequentially to a stirred solution of **61.26** (0.025 g, 0.036 mmol) in toluene (3 mL) and ethanol (1 mL) at room temperature. After the addition was complete, a stream of nitrogen gas was passed over the reaction mixture for 2 min.

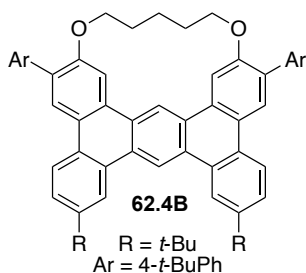
Tetrakis(triphenylphosphine)palladium(0) (0.007 g, 0.005 mmol) was added, and nitrogen

gas was once again passed over the reaction mixture for 2 min. The reaction was heated to 80 °C for 14 h and then cooled to room temperature. Once cooled, water (10 mL) and 1 M HCl (5 mL) were added to the reaction mixture, and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (14 × 1.0 cm, 10% to 30% dichloromethane/hexanes) to yield **63.2** as a white solid (0.022 g, 70%): *R_f* = 0.40 (3:7 dichloromethane/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.59 (d, *J* = 8.0 Hz, 4H), 7.47 – 7.45 (m, 6H), 7.31 – 7.27 (m, 12H), 6.92 (s, 2H), 4.24 (t, *J* = 8.3 Hz, 4H), 1.97 – 1.92 (m, 4H), 1.55 – 1.51 (m, 4H), 1.44 – 1.41 (m, 2H), 1.39 (s, 18H), 1.38 – 1.36 (m, 2H), 1.34 (s, 18H), 1.31 – 1.29 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ 154.17, 149.87, 149.20, 140.96, 139.81, 137.75, 135.30, 134.03, 131.63, 129.58, 129.56, 129.53, 129.31, 125.19, 124.85, 115.93, 67.22, 34.74, 34.58, 31.70, 31.60, 31.36, 31.18, 27.90, 25.32; HRMS (APCI) calc'd for C₆₇H₇₉O₂ ([M+H]⁺) *m/z* = 915.6080, found 915.6055.



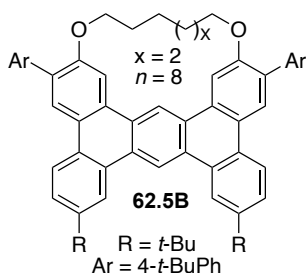
4,4'',6,6''-tetrakis(4-*t*-butylphenyl) 1,12-dioxap[12](3,3'')p-terphenylenophane (63.3**):** Sodium carbonate (0.110 g, 1.05 mol), as an aqueous solution, 1 mL of H₂O and 4-*tert*-butylphenyl boronic acid (0.061 g, 0.34 mmol) were added sequentially to a stirred solution of **61.27** (0.030 g, 0.042 mmol) in toluene (3 mL) and ethanol (1 mL) at room temperature. After the addition was complete, a stream of nitrogen gas was passed over the reaction mixture for 3 min. Tetrakis(triphenylphosphine)palladium(0) (0.005 g, 0.004

mmol) was added, and nitrogen gas was once again passed over the reaction mixture for 2 min. The reaction was heated to 90 °C for 7 h and then cooled to room temperature. Once cooled, water (20 mL) was added to the reaction, and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (14 × 1.0 cm, 100% hexanes to 40% dichloromethane/hexanes) to yield **63.3** as a white solid (0.028 g, 74%): *R_f* = 0.41 (3:7 dichloromethane/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.60 – 7.57 (m, 4H), 7.47 – 7.46 (m, 2H), 7.46 – 7.45 (m, 2H), 7.43 (s, 2H), 7.27 – 7.26 (m, 12H), 6.93 (s, 2H), 4.22 – 4.18 (m, 4H), 1.95 – 1.91 (m, 4H), 1.46 – 1.40 (m, 7H), 1.39 – 1.37 (m, 21H), 1.36 – 1.32 (m, 20H); ¹³C NMR (101 MHz, CDCl₃) δ 154.39, 149.87, 149.20, 140.82, 139.76, 137.89, 135.34, 134.07, 132.07, 129.95, 129.58, 129.49, 129.29, 125.17, 124.83, 116.70, 68.42, 34.74, 34.59, 31.71, 31.60, 30.06, 29.03, 27.57, 25.54; HRMS (ESI) calc'd for C₆₈H₈₁O₂ ([M+H]⁺) *m/z* = 929.6237, found 929.6283.



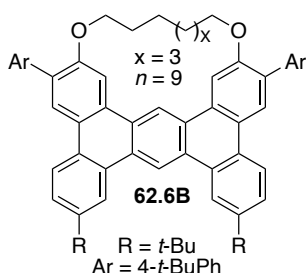
Macrocycle 62.4B: A solution of Iron (III) chloride (0.088g, 0.054 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **62.1** (0.024 g, 0.028 mmol) in dichloromethane (5 mL). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon-filled balloon was placed over the reaction. After 20 min, methanol (5 mL) and water (5 mL) were added. The layers were separated, and the aqueous phase extracted with dichloromethane (2 × 10 mL). The combined organic extracts

were washed with brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (6×1.0 cm, 30% dichloromethane/hexanes) to yield **62.4B** as a white solid (0.021 g, 90%): $R_f = 0.37$ (3:7 dichloromethane/hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.52 (s, 1H), 9.19 (s, 1H), 8.68 (d, $J = 2.0$ Hz, 2H), 8.26 – 8.24 (m, 4H), 7.70 – 7.68 (m, 4H), 7.66 – 7.63 (m, 4H), 7.57 – 7.55 (m, 4H), 3.78 (t, $J = 7.2$ Hz, 4H), 1.84 – 1.76 (m, 4H), 1.53 (s, 18H), 1.46 (s, 18H), 1.29 – 1.26 (m, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 155.25, 150.16, 148.96, 135.74, 130.94, 129.88, 129.52, 129.17, 128.83, 127.87, 127.86, 125.79, 125.50, 125.34, 123.55, 122.96, 119.10, 118.42, 117.18, 105.75, 70.47, 35.09, 34.82, 31.66, 31.51, 29.89, 27.25, 24.32; HRMS (ESI) calc'd for $\text{C}_{63}\text{H}_{66}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 855.5141$, found 855.5167.



Macrocycle 62.5B: A solution of Iron (III) chloride (0.092 g, 0.056 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0°C solution of **62.2** (0.025 g, 0.027 mmol) in dichloromethane (5 mL). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon-filled balloon was placed over the reaction. After 20 min, methanol (5 mL) and water (5 mL) were added. The layers were separated, and the aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic

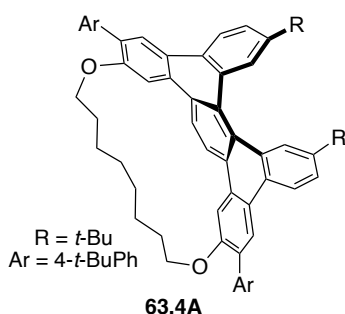
extracts were washed with brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (14×1.0 cm, 20%-35% dichloromethane/hexanes) to yield **62.5B** as a white solid (0.020 g, 80%): $R_f = 0.49$ (2:3 dichloromethane/hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.68 (s, 1H), 9.22 (s, 1H), 8.74 (s, 2H), 8.25 (d, $J = 8.4$ Hz, 2H), 8.20 (s, 2H), 7.78 (s, 2H), 7.70 – 7.67 (m, 6H), 7.57 (d, $J = 8.0$ Hz, 4H), 3.76 – 3.73 (m, 4H), 1.68 – 1.65 (m, 4H), 1.54 (s, 18H), 1.49 (s, 18H), 1.18 – 1.16 (m, 4H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 155.60, 150.05, 148.87, 135.89, 131.14, 129.72, 129.54, 129.01, 128.62, 127.85, 127.81, 125.77, 125.54, 125.33, 123.60, 123.05, 118.93, 117.11, 105.37, 69.90, 35.10, 34.83, 31.69, 31.57, 31.47, 27.49, 24.98; HRMS (ESI) calc'd for $\text{C}_{64}\text{H}_{68}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 869.5298$, found 869.5266.



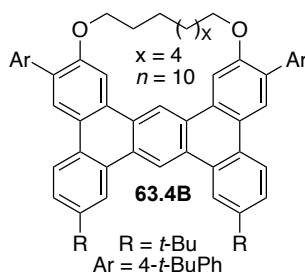
Macrocycle 62.6B: A solution of Iron (III) chloride (0.030 g, 0.18 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0°C solution of **62.3** (0.015 g, 0.017 mmol) in dichloromethane (3 mL). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon-filled balloon was placed over the reaction. After 30 min, additional Iron (III) chloride solution (0.030 g, 0.18 mmol) was added. After 1 h, methanol (5 mL) and water (5 mL) were added. The layers were separated, and the aqueous phase

extracted with dichloromethane (2×10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15×1.0 cm, 30% dichloromethane/hexanes) to yield **62.6B** as a white solid (0.012 g, 80%): $R_f = 0.42$ (2:3 dichloromethane/hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.98 (s, 1H), 9.61 (s, 1H), 8.93 (d, $J = 2.1$ Hz, 2H), 8.54 – 8.49 (m, 4H), 8.30 (s, 2H), 7.75 – 7.71 (m, 6H), 7.57 – 7.55 (m, 4H), 4.38 – 4.33 (m, 4H), 2.08 – 2.00 (m, 4H), 1.59 (s, 18H), 1.45 (s, 18H), 1.31 – 1.26 (m, 6H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 155.41, 150.17, 149.16, 135.90, 131.87, 130.03, 129.63, 129.31, 128.73, 128.41, 127.97, 126.22, 125.72, 125.33, 124.14, 123.11, 119.21,

117.18, 105.74, 100.18, 68.71, 35.21, 34.85, 31.69, 31.53, 28.14, 27.85, 25.54; HRMS (APCI) calc'd for $C_{65}H_{71}O_2$ ($[M+H]^+$) $m/z = 883.5454$, found 883.5446.

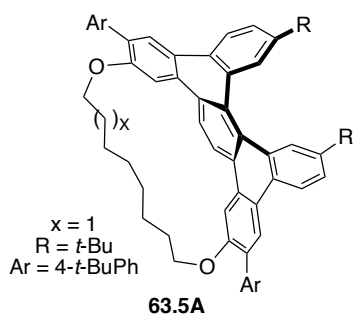


Macrocycles 63.4A and 63.4B: A solution of Iron (III) chloride (0.329 g, 2.03 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred solution of **63.1** (180 mg, 0.20 mmol) in dichloromethane (50 mL) under argon. After 15 min, methanol (10 mL) and water (20 mL) were added. The organic layers were separated, and the aqueous phase was extracted with dichloromethane (3×15) mL. The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20 x 2.5 cm, 1:19 EtOAC/Hexanes) to yield **63.4B** (0.078 g, 43%) as a white solid and **63.4A** (0.016 g, 9%) as a yellow solid.



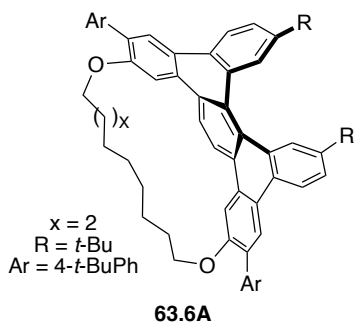
Macrocycle 63.4B: $R_f = 0.44$ (1:19 EtOAC/Hexanes); 1H NMR; (600 MHz, $CDCl_3$) δ 9.91 (s, 1H), 9.56 (s, 1H), 8.8 (s, 2H), 8.44 – 8.42 (m, 4H), 8.07 (s, 2H), 7.78 (d, $J = 7.9$ Hz, 4H), 7.73 (dd, $J = 8.5, 1.8$ Hz, 2H), 7.56 (d, $J = 7.9$ Hz, 4H), 4.00 – 3.99 (m, 4H), 1.85 – 1.83 (m, 4H), 1.57 (s, 18H), 1.46 (s, 18H), 1.37 – 1.33 (m, 4H), 1.28 – 1.25 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.64, 150.16, 149.09, 135.70, 131.06, 129.86, 129.62, 129.18, 128.66, 128.25, 127.94, 125.98, 125.71, 125.29, 123.99, 123.14, 119.14, 117.59, 117.15, 104.91, 69.24, 35.19, 34.83, 31.67, 31.50, 30.10, 29.51, 25.55; HRMS (APCI) calc'd for $C_{66}H_{73}O_2$ ($[M+H]^+$) $m/z = 897.5611$, found 897.5622.

Macrocycle 63.4A: $R_f = 0.23$ (1:19 EtOAC/Hexanes); 1H NMR (400 MHz, $CDCl_3$) 8.62 (s, 2H), 8.49 (d, $J = 2.0$ Hz, 2H), 8.45 (d, $J = 8.9$ Hz, 4H), 7.91 (s, 2H), 7.71-7.69 (m, 4H), 7.62-7.60 (m, 2H), 7.54-7.52 (m, 4H), 4.55-4.40 (m, 4H), 1.64 (q, $J = 7.0, 5.7$ Hz, 4H), 1.51-1.43 (m, 4H), 1.42 (s, 18H), 1.37-1.35 (m, 2H), 1.27-1.22 (m, 2H), 1.20 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.11, 150.05, 146.45, 135.41, 131.63, 131.21, 130.53, 129.44, 129.27, 128.73, 128.26, 125.96, 125.52, 125.41, 125.16, 123.89, 123.04, 121.83, 110.20, 67.92, 34.66, 34.63, 31.44, 31.06, 31.01, 27.86, 27.76; HRMS (EI) calc'd for $C_{66}H_{72}O_2$ ($[M]^+$) $m/z = 896.5532$, found 896.5496.



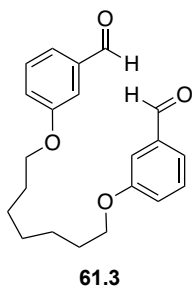
Macrocycle 63.5A: A solution of Iron (III) chloride (0.012 g, 0.070 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **63.2** (0.006 g, 0.007 mmol) in dichloromethane (3 mL). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon-filled balloon was placed over the reaction. After 30 min, methanol (5 mL) and water (5 mL) were added to the reaction. The layers were separated, and the aqueous phase extracted with dichloromethane (3×5 mL). The combined organic extracts

were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5×1.0 cm, 30% dichloromethane/hexanes) to yield **63.5A** as a white solid (0.005 g, 80%): $R_f = 0.32$ (3:7 dichloromethane/hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.64 (s, 2H), 8.55 (s, 2H), 8.47 (d, $J = 8.6$ Hz, 2H), 8.39 (d, $J = 2.0$ Hz, 2H), 7.97 (s, 2H), 7.73 (d, $J = 7.9$ Hz, 4H), 7.59 – 7.54 (m, 6H), 4.50 – 4.39 (m, 4H), 1.89 – 1.78 (m, 4H), 1.67 – 1.62 (m, 4H), 1.57 – 1.53 (m, 4H), 1.43 (s, 18H), 1.32 – 1.29 (m, 2H), 1.14 (s, 18H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 153.76, 150.26, 146.52, 135.68, 131.62, 130.70, 129.99, 129.82, 129.51, 128.65, 128.42, 126.69, 125.99, 125.43, 125.39, 124.13, 123.17, 121.80, 108.11, 69.52, 34.83, 34.70, 33.33, 32.19, 31.63, 31.15, 28.65, 27.45; HRMS (APCI) calc'd for $\text{C}_{67}\text{H}_{75}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 911.5767$, found 911.5812.

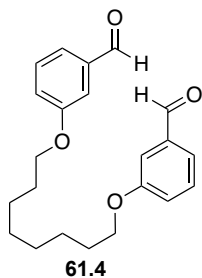


Macrocycle 63.6A: A solution of Iron (III) chloride (0.035 g, 0.21 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **63.3** (0.010 g, 0.011 mmol) in dichloromethane (4 mL). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon-filled balloon was placed over the reaction. After 30 min, methanol (5 mL) and water (5 mL) were added to the reaction. The layers were separated, and the aqueous phase extracted with dichloromethane (3×5 mL). The combined organic extracts

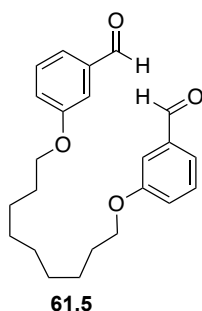
were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5×1.0 cm, 5% ethyl acetate/hexanes) to yield **63.6A** as a white solid (0.008 g, 80%): $R_f = 0.35$ (1:19 ethyl acetate/hexanes) $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.66 (s, 2H), 8.58 (s, 2H), 8.47 (d, $J = 8.6$ Hz, 2H), 8.38 (d, $J = 1.9$ Hz, 2H), 8.11 (s, 2H), 7.74 (d, $J = 7.9$ Hz, 4H), 7.57 – 7.55 (m, 6H), 4.50 – 4.42 (m, 4H), 2.10 – 2.07 (m, 4H), 1.89 – 1.86 (m, 4H), 1.71 – 1.69 (m, 4H), 1.65 – 1.63 (m, 4H), 1.44 (s, 18H), 1.35 – 1.30 (m, 4H), 1.13 (s, 18H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 154.20, 150.23, 146.57, 135.74, 131.44, 130.20, 129.95, 129.69, 129.55, 128.75, 128.12, 126.94, 126.00, 125.35, 124.05, 123.07, 121.80, 106.59, 68.40, 34.82, 34.66, 31.87, 31.63, 31.13, 30.84, 29.89, 26.57, 26.40; HRMS (APCI) calc'd for $\text{C}_{65}\text{H}_{75}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 925.5924$, found 925.59.



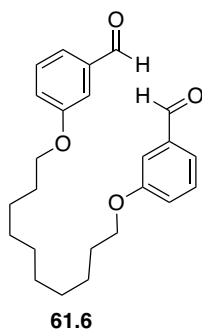
Dialdehyde 61.3: 1,7-Dibromoheptane (6.12 g, 23.7 mmol) was added to a stirred solution of 3-hydroxybenzaldehyde (5.20 g, 42.6 mmol), K_2CO_3 (11.4 g, 82.8 mmol) and tetrabutylammonium iodide (0.875 g, 2.37 mmol) in DMF (50 mL) at room temperature. The reaction was heated at 80 °C for 24 h, at which point water (50 mL) and 1 M HCl (50 mL) were added sequentially. The resulting solution was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (50 mL) and brine (50 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (16×3.8 cm; 60% dichloromethane/hexanes to dichloromethane) to afford **61.3** as a white solid (5.19 g, 72%): $R_f = 0.30$ (7:3 dichloromethane/hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.98 (s, 2H), 7.46 – 7.41 (m, 4H), 7.40 – 7.38 (m, 2H), 7.21 – 7.15 (m, 2H), 4.03 (t, $J = 6.5$ Hz, 4H), 1.83 (dt, $J = 8.3, 6.3$ Hz, 4H), 1.57 – 1.44 (m, 6H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 192.45, 159.88, 137.98, 130.23, 123.63, 122.20, 112.87, 68.40, 29.29, 29.28, 26.18; HRMS (ESI) calc'd for $\text{C}_{21}\text{H}_{25}\text{O}_4$ ($[\text{M}+\text{H}]^+$) $m/z = 341.1747$, found 341.1747.



Dialdehyde 60.4: 1,8-Dibromooctane (5.98 g, 22.0 mmol) was added to a stirred solution of 3-hydroxy benzaldehyde (5.10 g, 41.8 mmol), K_2CO_3 (7.58 g, 54.9 mmol) and tetrabutylammonium iodide (0.811 g, 2.20 mmol) in DMF (70 mL). The reaction was heated at 80 °C for 26 h, at which point the reaction was cooled to room temperature and water (50 mL) and 1 M HCl (50 mL) were added sequentially. The aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 \times 5 cm; 70% dichloromethane/hexanes to dichloromethane) to afford **60.4** as white solid (5.20 g, 70%); $R_f = 0.21$ (7:3 dichloromethane/hexanes); 1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 2H), 7.45 – 7.41 (m, 4H), 7.39 (d, $J = 2.5$ Hz, 2H), 7.19 – 7.16 (m, 2H), 4.04 – 4.00 (m, 4H), 1.85 – 1.78 (m, 4H), 1.51 – 1.39 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.42, 159.87, 137.95, 130.20, 123.56, 122.17, 112.87, 68.42, 29.46, 29.30, 26.14; HRMS (APCI) calc'd for $C_{22}H_{26}O_4Na$ ($[M+Na]^+$) $m/z = 377.1723$, found 377.1725.

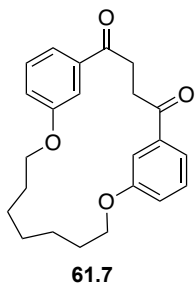


Dialdehyde 61.5: 1,9-Dibromononane (2.28 g, 7.96 mmol) was added to a stirred solution of 3-hydroxy benzaldehyde (1.90 g, 15.6 mmol), K_2CO_3 (2.82 g, 20.4 mmol) and tetrabutylammonium iodide (0.303 g, 0.821 mmol) in DMF (37 mL). The reaction was heated at 80 °C for 24 h, at which point water (20 mL) and 1 M HCl (10 mL) were added sequentially. The aqueous phase was extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 \times 5 cm; 60% dichloromethane/hexanes to dichloromethane) to afford **60.7** as a white solid (2.71 g, 90%); $R_f = 0.39$ (3:2 dichloromethane/hexanes); 1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 2H), 7.46 – 7.41 (m, 4H), 7.39 – 7.38 (m, 2H), 7.20 – 7.15 (m, 2H), 4.02 (t, $J = 6.5$ Hz, 4H), 1.85 – 1.78 (m, 4H), 1.50 – 1.46 (m, 4H), 1.41 – 1.36 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.47, 159.93, 137.99, 130.23, 123.60, 122.22, 112.91, 68.49, 29.69, 29.50, 29.35, 26.22; HRMS (APCI) calc'd for $C_{23}H_{29}O_4$ ($[M+H]^+$) $m/z = 369.2060$, found 369.2063.

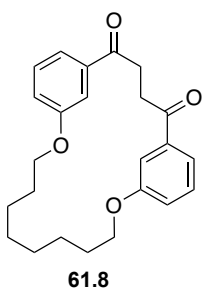


Dialdehyde 61.6: 1,10-Dibromodecane (1.15 g, 3.84 mmol) was added to a stirred solution of 3-hydroxy benzaldehyde (0.890 g, 7.29 mmol), K_2CO_3 (1.32 g, 9.59 mmol) and tetrabutylammonium iodide (0.141 g, 0.383 mmol) in DMF (15 mL). The reaction was heated at 80 °C for 24 h, at which point water (20 mL) and 1 M HCl (10 mL) were added sequentially. The aqueous phase was extracted with dichloromethane (3×15 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 \times 2.5 cm; 60% to 90% dichloromethane/hexanes) to afford **60.6** as a white solid (0.857 g, 62 %); $R_f = 0.26$ (3:2 dichloromethane/hexanes); 1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 2H), 7.47 – 7.41 (m, 4H), 7.40 – 7.37 (m, 2H), 7.21 – 7.14 (m, 2H), 4.02 (t, $J = 6.6$ Hz, 4H), 1.87 – 1.76 (m,

4H), 1.53 – 1.42 (m, 4H), 1.40 – 1.34 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 192.46, 159.91, 137.97, 130.21, 123.57, 122.20, 112.90, 68.49, 29.69, 29.55, 29.33, 26.21; HRMS (ESI) calc'd for $\text{C}_{24}\text{H}_{31}\text{O}_4$ ($[\text{M}+\text{H}]^+$) m/z = 383.2217, found 383.2218.

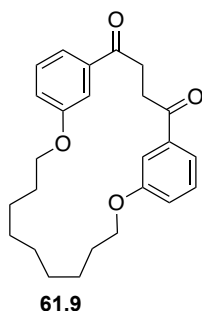


1,4-Diketone 61.7: Vinylmagnesium chloride (1.6 M in THF, 6.2 mL, 7.5 mmol) was added to a stirred 0 °C solution of dialdehyde **61.3** (1.52 g, 4.48 mmol) in dichloromethane (50 mL). After 1 h, the reaction mixture was poured into water (100 mL) and further diluted with 1 M HCl (50 mL). The aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (300 mL) and Hoveyda-Grubbs second-generation catalyst (0.085 g, 0.13 mmol) was added. The reaction was heated at 40 °C for 3 h, after which the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (50 mL), and sodium borohydride (0.851 g, 22.4 mmol) was added. After 11 h, the reaction mixture was poured into water (200 mL) and further diluted with 1 M HCl (20 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (45 mL) followed by the addition of pyridinium chlorochromate (2.90 g, 13.4 mmol). The reaction was stirred for 4 h, at which point silica gel was added to the reaction, and the slurry was passed through a pad of Celite (2.5 cm) and washed with diethyl ether (3 × 20 mL). The filtrate was concentrated under reduced pressure to give a brown residue, which was purified by flash chromatography (20 × 2.5 cm, dichloromethane) to afford 1,4-diketone **61.7** as a white solid (0.61 g, 37% from **61.3**): R_f = 0.37 (dichloromethane); ^1H NMR (600 MHz, CDCl_3) δ 7.48 (d, J = 7.6 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.37 – 7.31 (m, 2H), 7.07 (dd, J = 8.2, 2.6 Hz, 2H), 4.09 (t, J = 6.6 Hz, 4H), 3.31 (s, 4H), 1.80 – 1.76 (m, 4H), 1.49 – 1.43 (m, 6H); ^{13}C NMR (151 MHz, CDCl_3) δ 200.30, 159.13, 138.16, 130.11, 120.99, 120.59, 114.07, 68.07, 35.25, 28.08, 27.92, 25.43; HRMS (ESI) calc'd for $\text{C}_{23}\text{H}_{27}\text{O}_4$ ($[\text{M}+\text{H}]^+$) m/z = 367.1904, found 367.1892.



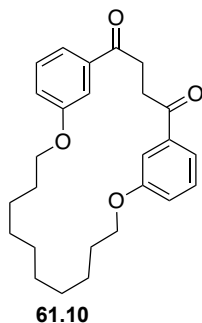
1,4-Diketone 61.8: Vinylmagnesium chloride (1.6 M in THF, 16 mL, 26 mmol) was added to a stirred 0 °C solution of dialdehyde **61.4** (4.15 g, 11.6 mmol) in dichloromethane (80 mL). After 30 min, the reaction mixture was poured into water (30 mL) and further diluted with 1 M HCl (20 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (20 mL) and brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The white residue was dissolved in dichloromethane (800 mL), and Hoveyda-Grubbs second-generation catalyst (0.217 g, 0.347 mmol) was added. The reaction was heated at 40 °C for 5 h, after which the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (120 mL), and sodium borohydride (2.20 g, 58.0 mmol) was added. After 14 h, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (20 mL). The layers were separated, and the aqueous phase extracted with

dichloromethane (3 × 20 mL). The combined organic extracts were washed with a saturated NaHCO₃ solution (30 mL) and brine (30 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (120 mL), followed by addition of pyridinium chlorochromate (7.50 g, 34.8 mmol). The reaction was stirred for 6 h, at which point silica gel was added to the reaction, and the slurry was passed through a pad of Celite (2.5 cm) and washed with diethyl ether (3 × 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (17 × 3.8 cm, 20% ethyl acetate/hexanes) to afford 1,4-diketone **61.8** as a white solid (1.80 g, 41% from **61.4**); *R_f* = 0.38 (1:4 ethyl acetate/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.49 (m, 4H), 7.38 – 7.34 (m, 2H), 7.09 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 2H), 4.11 (t, *J* = 6.8 Hz, 4H), 3.34 (s, 4H), 1.82 – 1.75 (m, 4H), 1.51 – 1.39 (m, 8H); ¹³C NMR (101 MHz, CDCl₃) δ 200.12, 159.11, 138.19, 130.08, 120.81, 120.49, 114.15, 68.24, 34.99, 28.46, 28.06, 25.28; HRMS (ESI) calc'd for C₂₄H₂₉O₄ ([M+H]⁺) *m/z* = 381.2060, found 381.2066.



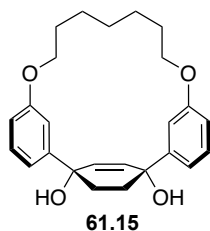
1,4-Diketone 61.9: Vinylmagnesium chloride (1.6 M in THF, 10 mL, 17 mmol) was added to a stirred 0 °C solution of dialdehyde **61.5** (2.56 g, 6.96 mmol) in dichloromethane (50 mL). After 30 min, the reaction mixture was poured into water (130 mL) and further diluted with 1 M HCl (30 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃ (30 mL) and brine (30 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The white residue was dissolved in dichloromethane (470 mL), and Hoveyda-Grubbs second-generation catalyst (0.131 g, 0.209 mmol) was added.

The reaction was heated at 40 °C for 3 h, after which the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (70 mL) and sodium borohydride (1.59 g, 41.8 mmol) was added. After 5 h, the reaction mixture was poured into water (100 mL) and further diluted with 1 M HCl (25 mL). The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated NaHCO₃ solution (30 mL) and brine (30 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (70 mL), followed by addition of pyridinium chlorochromate (4.50 g, 20.8 mmol). The reaction was stirred for 4 h, at which point silica gel was added to the reaction, and the slurry was passed through a pad of Celite (2.5 cm) and washed with diethyl ether (3 × 20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3.8 cm, 20% ethyl acetate/hexanes) to afford 1,4-diketone **61.9** as a white solid (0.83 g, 30% from **61.5**); *R_f* = 0.45 (1:4 ethyl acetate/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.49 (m, 4H), 7.38 – 7.34 (m, 2H), 7.10 – 7.07 (m, 2H), 4.10 (t, *J* = 6.8 Hz, 4H), 3.37 (s, 4H), 1.81 – 1.74 (m, 4H), 1.45 – 1.35 (m, 10H); ¹³C NMR (101 MHz, CDCl₃) δ 200.19, 159.12, 138.48, 129.95, 121.29, 120.53, 113.37, 68.27, 34.58, 28.80, 28.58, 28.22, 25.43; HRMS (ESI) calc'd for C₂₅H₃₁O₄ ([M+H]⁺) *m/z* = 395.2217, found 395.2229.

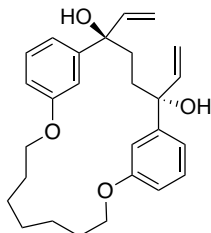


1,4-Diketone 60.10: Vinylmagnesium chloride (1.6 M in THF, 3.1 mL, 4.8 mmol) was added to a stirred 0 °C solution of dialdehyde **61.6** (0.740 g, 1.94 mmol) in dichloromethane (20 mL). After 30 min, the reaction mixture was poured into water (20 mL) and further diluted with 1 M HCl (10 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃ (20 mL) and brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The white residue was dissolved in dichloromethane (130 mL), and Hoveyda-Grubbs second-generation catalyst (0.062 g, 0.099 mmol) was added.

The reaction was heated at 40 °C for 5 h, after which the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (20 mL) and sodium borohydride (0.442 g, 11.6 mmol) was added. After 9 h, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (15 mL). The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated NaHCO₃ solution (20 mL) and brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (20 mL), followed by addition of pyridinium chlorochromate (1.25 g, 5.81 mmol). The reaction was stirred for 30 h, at which point silica gel was added, and the slurry was passed through a pad of Celite (2.5 cm) and washed with diethyl ether (3 × 15 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3.8 cm, 20% ethyl acetate/hexanes) to afford 1,4-diketone **61.10** as a white solid (0.20 g, 26% from **61.6**), *R_f* = 0.45 (1:4 ethyl acetate/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.48 (m, 4H), 7.39 – 7.32 (m, 2H), 7.10 (ddd, *J* = 8.2, 2.4, 1.3 Hz, 2H), 4.10 (t, *J* = 7.0 Hz, 4H), 3.37 (s, 4H), 1.83 – 1.74 (m, 4H), 1.48 – 1.41 (m, 4H), 1.35 – 1.29 (m, 8H); ¹³C NMR (101 MHz, CDCl₃) δ 200.23, 159.25, 138.62, 129.89, 121.40, 120.53, 113.15, 68.22, 34.56, 29.28, 28.63, 28.41, 25.70; HRMS (ESI) calc'd for C₂₆H₃₃O₄ ([M+H]⁺) *m/z* = 409.2373, found 409.2375.



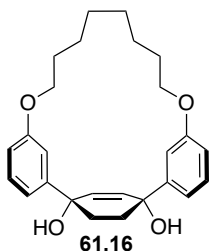
Cyclohex-2-ene-1,4-diol 61.15: Vinylmagnesium chloride (1.6 M in THF, 1.2 mL, 1.9 mmol) was added to a stirred solution of 1,4-diketone **61.7** (0.270 g, 0.738 mmol) in dichloromethane (8 mL) at 40 °C. After 30 min, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). The aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃ (20 mL) and brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 2.5 cm, 20% ethyl acetate/hexanes) to afford allylic alcohol **61.11** (0.145 g, 47%) as an inseparable mixture of diastereomers (73:27 *d.r.*); *R_f* = 0.23 (1:4 ethyl acetate/hexane). The mixture of diastereomers was carried forward without purification. Grubbs second-generation catalyst (0.011 g, 0.013 mmol) was added to a stirred solution of **61.11** (0.110 g, 0.260 mmol) in dichloromethane (7 mL), and the reaction was heated to 40 °C. After 2 h, the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 1.3 cm, 30% to 40% ethyl acetate/hexanes) to afford compound *anti*-**61.11** as a colorless oil (0.027 g, 26%) and **61.15** as an off-white solid (0.066 g, 64%).



anti-61.11

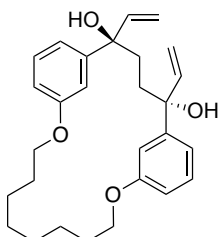
Anti-allylic-1,4-diol 61.11 (*anti-61.11*): $R_f = 0.23$ (1:4 ethyl acetate/hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) 7.27-7.22 (m, 2H), 7.08 (ddd, $J = 7.7, 1.8, 1.0$ Hz, 2H), 6.78 (ddd, $J = 8.2, 2.5, 1.0$ Hz, 2H), 6.72 (t, $J = 2.1$ Hz, 2H), 6.11 (dd, $J = 17.2, 10.6$ Hz, 2H), 5.22 (dd, $J = 17.2, 1.0$ Hz, 2H), 5.08 (dd, $J = 10.6, 1.0$ Hz, 2H), 4.01-3.91 (m, 4H), 1.98 (br s, 2H) 1.95-1.80 (m, 6H), 1.78-1.68 (m, 2H), 1.60-1.51 (m, 4H), 1.50-1.43 (m, 2H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) 159.21, 146.51, 145.09, 129.54, 117.67, 113.36, 112.70, 111.33, 76.72, 67.27, 35.70, 28.04, 26.95, 25.66; HRMS (ESI) calc'd for $\text{C}_{27}\text{H}_{34}\text{O}_4\text{Na}$ ($[\text{M}+\text{Na}^+]$) $m/z = 445.2349$, found 445.2366.

Cyclohex-2-ene-1,4-diol 61.15: $R_f = 0.13$ (3:7 ethyl acetate/hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35 – 7.31 (m, 4H), 6.90 – 6.88 (m, 2H), 6.84 – 6.79 (m, 2H), 6.08 (s, 2H), 4.07 – 3.93 (m, 4H), 2.22 – 2.13 (m, 2H), 1.95 – 1.86 (m, 7H), 1.64 – 1.55 (m, 7H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 158.60, 147.80, 134.57, 129.90, 117.24, 112.90, 112.38, 72.62, 68.04, 36.35, 27.76, 27.39, 26.14; HRMS (ESI) calc'd for $\text{C}_{25}\text{H}_{29}\text{O}_3$ ($[\text{M}-\text{H}_2\text{O}+\text{H}]^+$) $m/z = 377.2111$, found 377.2102.



61.16

Cyclohex-2-ene-1,4-diol 61.16: Vinylmagnesium chloride (1.6 M in THF, 0.50 mL, 0.81 mmol) was added to a stirred solution of 1,4-diketone **61.8** (0.122 g, 0.322 mmol) in dichloromethane (3.0 mL) at 40 °C. After 30 min, the reaction mixture was poured into water (10 mL) and further diluted with 1 M HCl (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (10 mL) and brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to afford allylic alcohol **61.12** as an inseparable mixture of diastereomers (68:32 *d.r.*); $R_f = 0.41$ (1:19 acetone/dichloromethane). The mixture of diastereomers with hydroxy ketone was carried forward and separated after the next synthetic step. The residue was dissolved in dichloromethane (8.0 mL), and Grubbs' second-generation catalyst (0.008 g, 0.01 mmol) was added. The reaction was heated at 40 °C. After 2.5 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 5% to 10% acetone/dichloromethane) to afford *anti-61.12* as colorless oil (0.019 g, 13%) and compound **61.16** as an off-white solid (0.076 g, 58%).



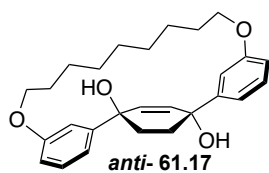
anti-61.12

Anti-allylic-1,4-diol 61.12 (*anti-61.12*): $R_f = 0.41$ (1:19 acetone/dichloromethane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.28-7.24 (m, 2H), 7.04 (ddd, $J = 7.8, 1.8, 0.9$ Hz, 2H), 6.83-6.82 (m, 2H), 6.75 (ddd, $J = 8.2, 2.5, 0.9$ Hz, 2H), 6.12 (dd, $J = 17.3, 10.7$ Hz, 2H), 5.24 (dd, $J = 17.2, 1.0$ Hz, 2H), 5.09 (dd, $J = 10.6, 1.0$ Hz, 2H), 3.98 (t, $J = 5.7$ Hz, 4H), 1.96-1.90 (m, 3H), 1.85-1.74 (m, 6H) 1.60-1.38 (m, 9H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) 159.25, 146.89, 144.89, 129.53, 117.73, 113.05, 112.70, 111.79, 76.75, 67.61, 35.68, 28.65, 27.98, 25.11; HRMS (ESI) calc'd for $\text{C}_{28}\text{H}_{33}\text{O}_2$ ($[\text{M}-2\text{H}_2\text{O}+\text{H}]^+$) $m/z = 401.2474$, found 401.2484.

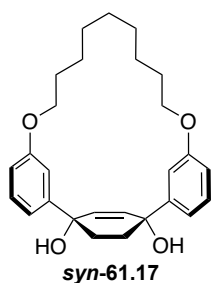
Cyclohex-2-ene-1,4-diol 61.16: $R_f = 0.12$ (1:19 acetone/dichloromethane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39 – 7.31 (m, 4H), 6.95 – 6.93 (m, 2H), 6.82 – 6.75 (m, 2H), 6.01 (s,

2H), 4.03 – 3.91 (m, 4H), 2.20 – 2.12 (m, 4H), 2.00 – 1.93 (m, 2H), 1.85 – 1.67 (m, 6H), 1.54 – 1.48 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.77, 147.85, 134.49, 129.87, 116.97, 114.53, 110.45, 72.60, 67.55, 36.15, 28.57, 26.96, 24.28; HRMS (EI) calc'd for $\text{C}_{26}\text{H}_{28}\text{O}_2$ ($[\text{M}-2\text{H}_2\text{O}]^+$) m/z = 372.2089, found 372.2121.

Cyclohex-2-ene-1,4-diols 61.17: Vinylmagnesium chloride (1.6 M in THF, 0.44 mL, 0.71 mmol) was added to a stirred solution of 1,4-diketone **61.9** (0.127 g, 0.322 mmol) in dichloromethane (3.0 mL) at 40 °C. After 30 min, the reaction mixture was poured into water (10 mL) and further diluted with 1 M HCl (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (10 mL) and brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The white residue was dissolved in dichloromethane (7.0 mL), and Grubbs' second-generation catalyst (0.014 g, 0.016 mmol) was added. The reaction was heated at 40 °C. The reaction was monitored by TLC, and it was observed that both syn and anti-isomers cyclized. After 19 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 10% to 25% acetone/chloroform) to afford *anti*-**61.17** (0.026 g, 19%) and *syn*-**61.17** (0.050 g, 38%) as off-white solids (*d.r.* *syn/anti* = 71:29).



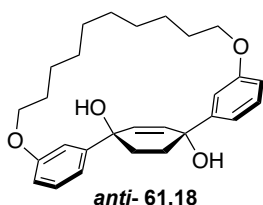
anti-**61.17**: R_f = 0.47 (1:9 acetone/chloroform); ^1H NMR (600 MHz, CDCl_3) 7.31 - 7.27 (m, 2H), 7.23 (t, J = 2.0 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 6.85 (dd, J = 8.2, 2.5 Hz, 2H), 6.00 (s, 2H), 4.21 - 4.14 (m, 4H), 2.44 (d, J = 10.0 Hz, 2H), 2.07 (d, J = 10.0 Hz, 2H), 1.90 - 1.77 (m, 6H), 1.53 - 1.39 (m, 10H). ^{13}C NMR (151 MHz, CDCl_3) δ 158.60, 149.11, 134.59, 129.68, 116.96, 116.24, 109.85, 71.85, 67.85, 35.51, 29.86, 29.84, 27.58, 25.37; HRMS (EI) calc'd for $\text{C}_{27}\text{H}_{30}\text{O}_2$ ($[\text{M}-2\text{H}_2\text{O}]^+$) m/z = 386.2245, found 386.2254.



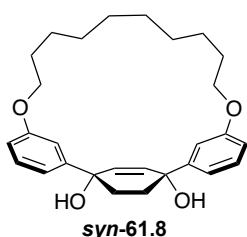
syn-**61.17**: R_f = 0.18 (1:9 acetone/chloroform); ^1H NMR (600 MHz, CDCl_3) 7.34 - 7.27 (m, 4H), 6.87 (t, J = 2.0 Hz, 2H), 6.79 (dt, J = 7.7, 1.9 Hz, 2H), 6.11 (s, 2H), 4.02 - 3.92 (m, 4H), 2.25 (d, J = 3.2 Hz, 2H), 2.21 - 2.14 (m, 2H), 1.95 - 1.91 (m, 2H), 1.79 (qt, J = 10.9, 5.3 Hz, 4H), 1.60 (dt, J = 13.5, 6.8 Hz, 2H), 1.55 - 1.37 (m, 8H). ^{13}C NMR (151 MHz, CDCl_3) δ 158.93, 148.09, 134.78, 130.07, 117.51, 113.56, 111.63, 72.64, 67.71, 36.47, 29.28, 27.95, 27.75, 25.67; HRMS (EI) calc'd for $\text{C}_{27}\text{H}_{30}\text{O}_2$ ($[\text{M}-2\text{H}_2\text{O}]^+$) m/z = 386.2245, found 386.2245.

Cyclohex-2-ene-1,4-diols 61.18: Vinylmagnesium chloride (1.6 M in THF, 0.75 mL, 1.2 mmol) was added to a stirred solution of 1,4-diketone **61.10** (0.165 g, 0.415 mmol) in dichloromethane (5.0 mL) at 40 °C. After 30 min, the reaction mixture was poured into water (10 mL) and further diluted with 1 M HCl (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of NaHCO_3 (10 mL) and brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The white residue was dissolved in dichloromethane (5.0 mL), and Grubbs' second-generation catalyst (0.009 g, 0.01 mmol) was added. The reaction was heated at 40 °C. The reaction was monitored by TLC and it was observed that both syn and anti-diastereomers cyclized. After 2.5 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The

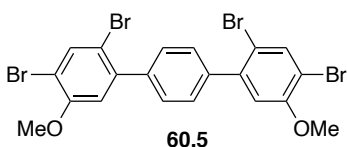
residue was purified by flash chromatography (16 × 1.3 cm, 10% to 25% acetone/dichloromethane) to give *anti*-**61.18** (0.016 g, 18%) and *syn*-**61.18** (0.037 g, 41%) as off-white solids (*d.r.* *syn/anti* = 70:30)



anti-**61.18**: R_f = 0.55 (1:19 acetone/dichloromethane); ^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.24 (m, 2H), 7.23 – 7.20 (m, 2H), 7.14 – 7.09 (m, 2H), 6.84 (ddd, J = 8.2, 2.6, 1.0 Hz, 2H), 5.93 (s, 2H), 4.123 – 4.09 (m, 4H), 2.38 – 2.29 (m, 2H), 2.07 – 2.00 (m, 2H), 1.91 (s, 2H), 1.89 – 1.73 (m, 4H), 1.49 – 1.37 (m, 12H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.70, 148.63, 134.43, 129.75, 117.17, 116.89, 110.42, 72.31, 68.28, 35.80, 30.25, 29.41, 27.57, 25.57; HRMS (ESI) calc'd for *anti*-**60.22** $\text{C}_{28}\text{H}_{35}\text{O}_3$ ($[\text{M}-\text{H}_2\text{O}]+\text{H}]^+$) m/z = 419.2580, found 419.2586.



syn-**61.18**: R_f = 0.11 (1:19 acetone/dichloromethane); ^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.29 (m, 4H), 6.91 – 6.85 (m, 2H), 6.83 – 6.76 (m, 2H), 6.08 (s, 2H), 4.01 – 3.90 (m, 4H), 2.27 – 2.13 (m, 4H), 2.05 – 1.93 (m, 2H), 1.76 (tt, J = 6.8, 3.7 Hz, 4H), 1.56 – 1.47 (m, 2H), 1.43 – 1.34 (m, 10H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.98, 148.09, 134.74, 130.06, 117.50, 113.95, 111.58, 72.52, 67.82, 36.23, 29.03, 27.51, 27.23, 25.41; HRMS (ESI) calc'd for *syn*-**60.22** $\text{C}_{28}\text{H}_{35}\text{O}_3$ ($[\text{M}-\text{H}_2\text{O}]+\text{H}]^+$) m/z = 419.2580, found 419.2583.



4,4'',6,6''-tetrabromo-3,3''-dimethoxy-*p*-terphenyl (60.5): Bromine (0.480 g, 3.00 mmol) was added to a stirred solution of 3,3''-dimethoxy-*p*-terphenyl (**60.4**) (0.080 g, 0.28 mmol) in 1,2-dichlorobenzene (5 mL). The resulting mixture was heated to 70 °C for 2 h and then cooled to room temperature under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (15 mL), a solution of 5% NaHSO_3 (15 mL) was added, and the resulting mixture was stirred for 10 min. The layers were separated, and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 10% to 40% dichloromethane/hexanes) to yield **60.5** as a pale yellow solid (0.096 g, 57%): R_f = 0.51 (2:3 dichloromethane/hexane); ^1H NMR (600 MHz, CDCl_3) δ 7.86 (s, 2H), 7.49 (s, 4H), 6.92 (s, 2H), 3.92 (s, 6H); ^{13}C NMR (151 MHz, CDCl_3) δ 155.43, 142.20, 140.19, 136.83, 129.16, 114.49, 113.19, 111.62, 56.73; HRMS (EI) calc'd for $\text{C}_{20}\text{H}_{14}\text{O}_2\text{Br}_4$ ($[\text{M}]^+$) m/z = 605.7686, found 605.7662.

Time course experiment for 63.1

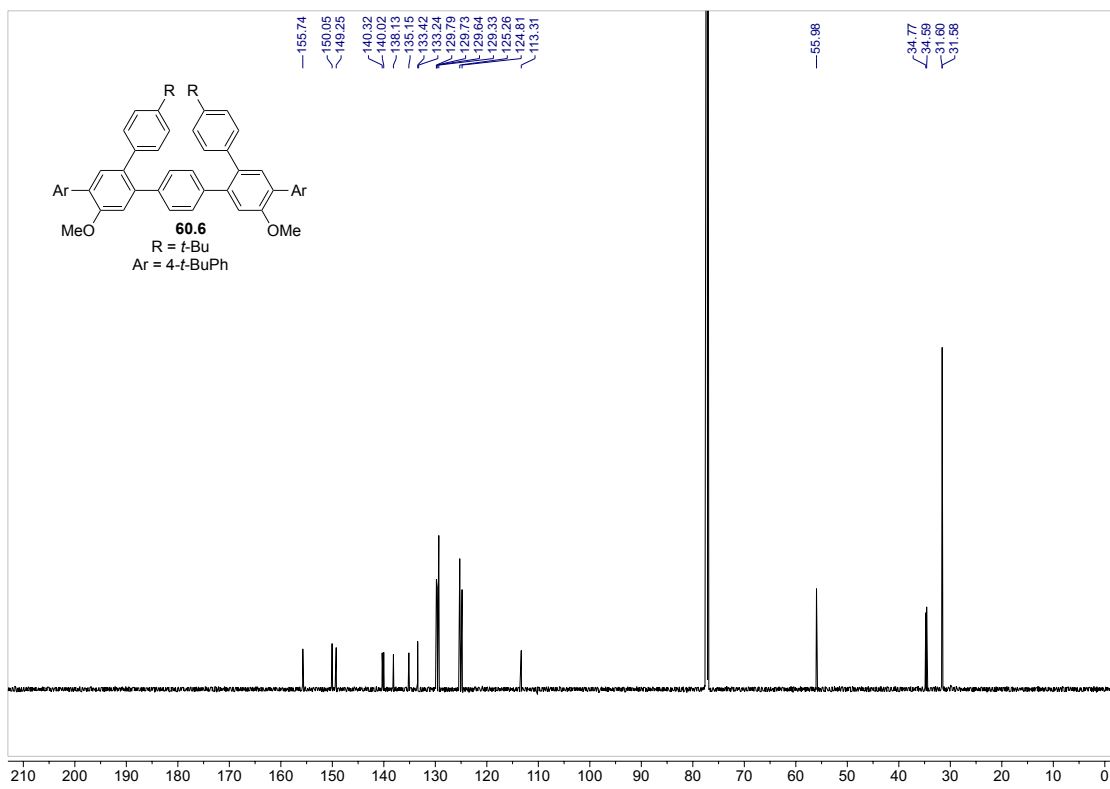
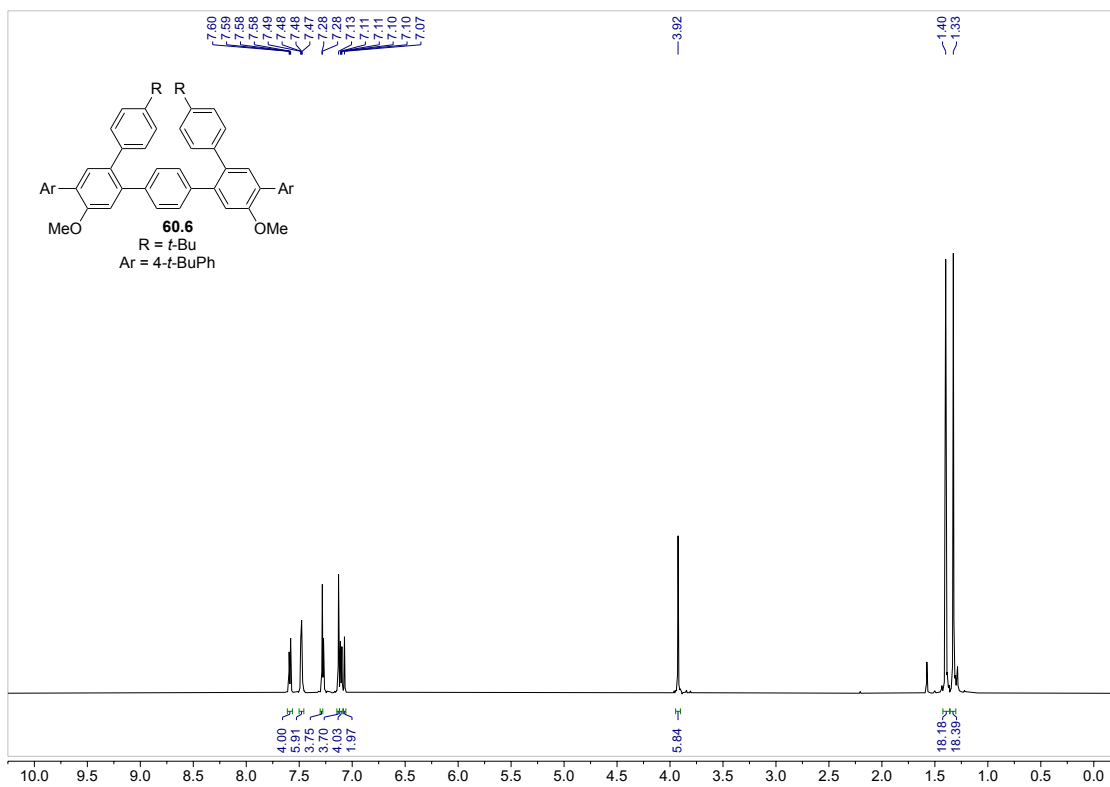
2.5 equivalent FeCl_3 : A solution of Iron (III) chloride (7.00 mg, 0.043 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred solution of **63.1** (16.0 mg, 0.018 mmol) in dichloromethane (4 mL) under argon. After 15 min, methanol (3 mL) and water (5 mL) were added. The organic layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 5) mL. The combined organic extracts were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered and concentrated under

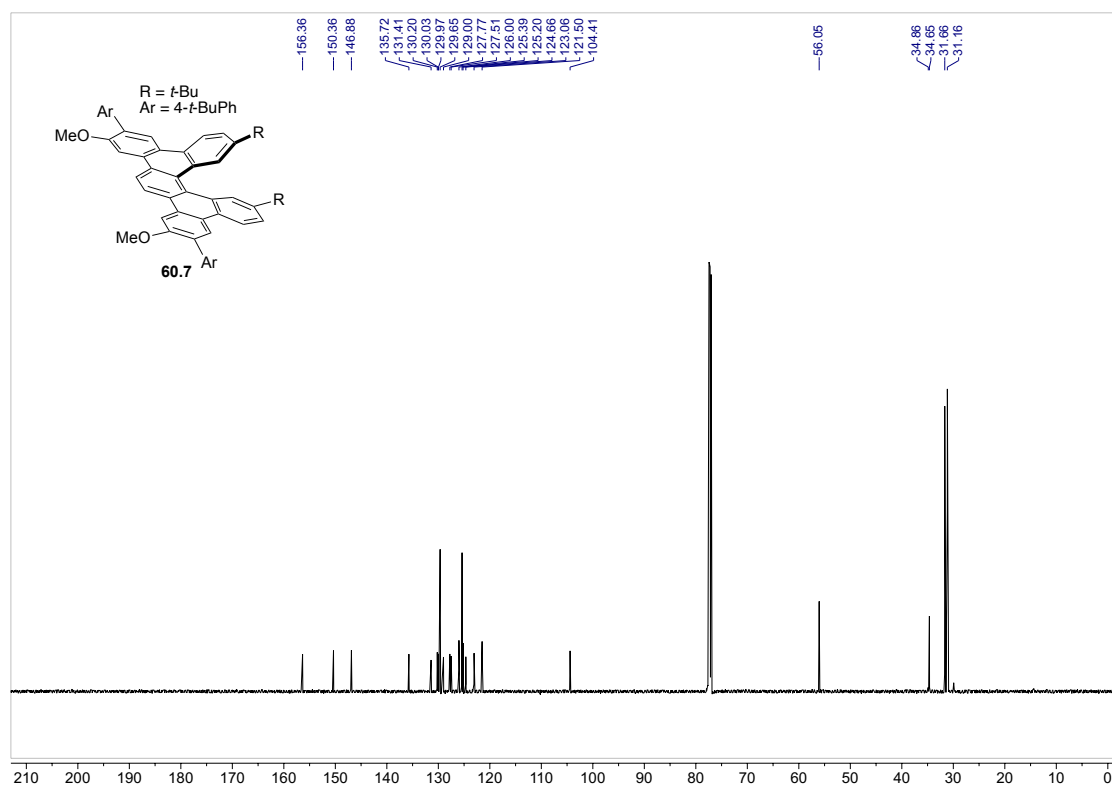
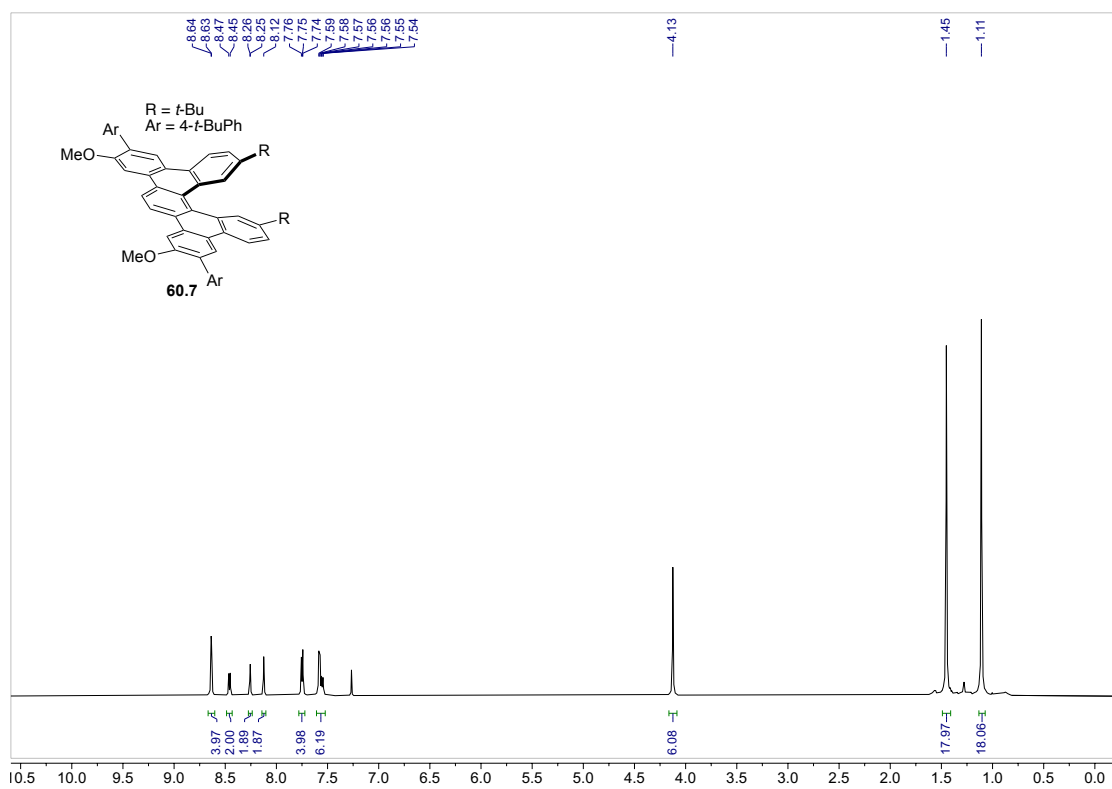
reduced pressure. The crude ^1H nmr was taken in CDCl_3 , the ratio of starting material to products, **63.1:63.4A:63.4B** was found to be 74:7:19. After running ^1H NMR the mixture of compounds was isolated using preparative thin layer chromatography using 5% ethyl acetate/hexane. The intermediate 67.1 and 67.3 as a combined was isolated as band B. ^1H NMR analysis of this band B indicated that both **67.1** and **67.3** were produced in a 2:1 ratio.

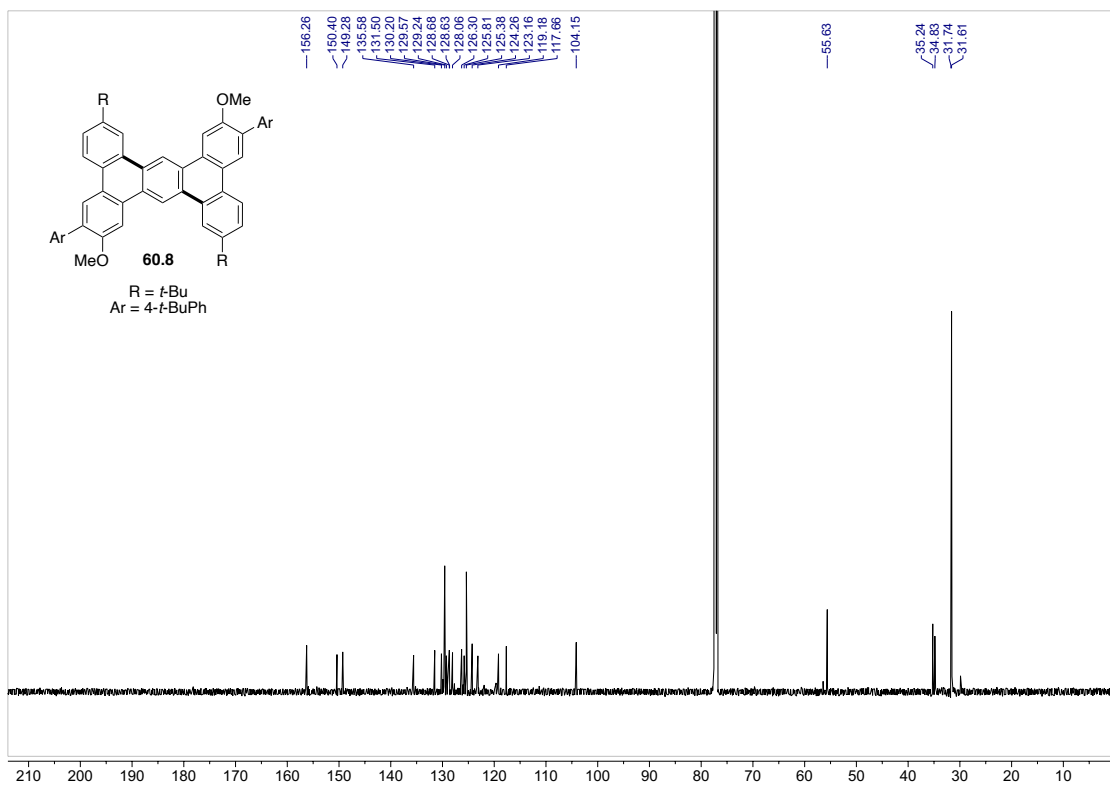
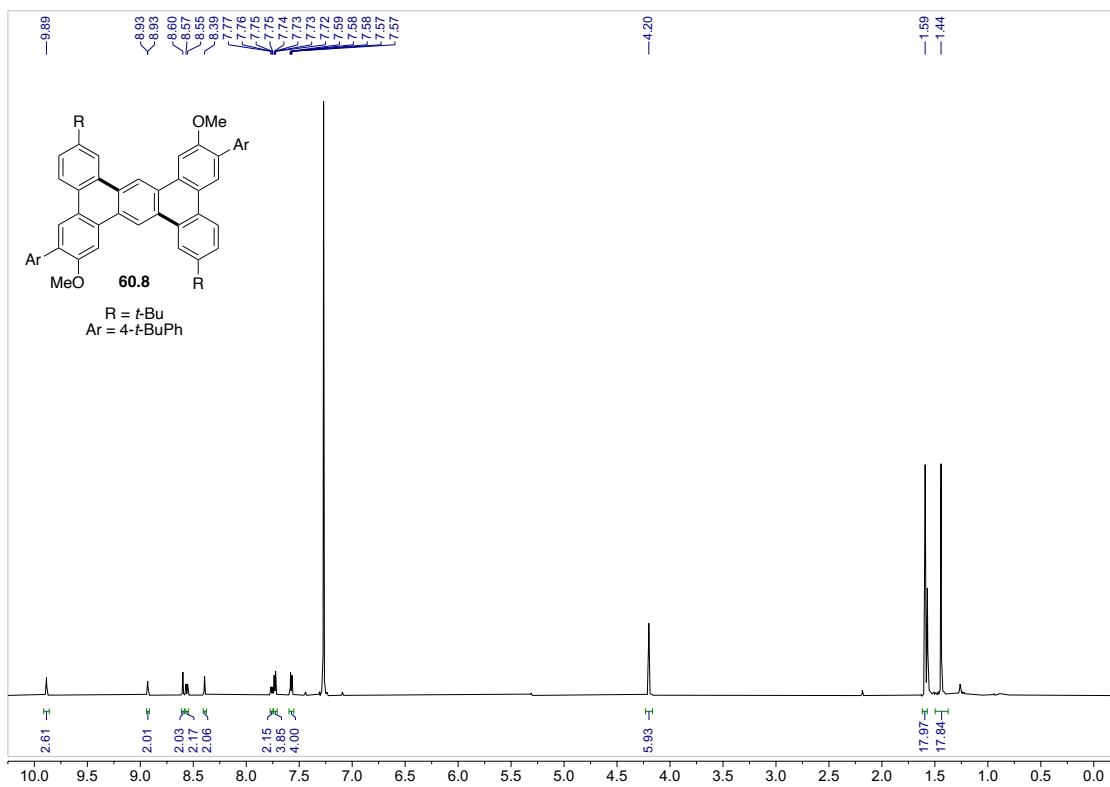
5 equivalent FeCl_3 : A solution of Iron (III) chloride (14.00 mg, 0.086 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred solution of **63.1** (16.0 mg, 0.018 mmol) in dichloromethane (4 mL) under argon. After 15 min, methanol (3 mL) and water (5 mL) were added. The organic layers were separated, and the aqueous phase was extracted with dichloromethane (3×5) mL. The combined organic extracts were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The crude ^1H nmr was taken in CDCl_3 , the ratio of starting material to products, **63.1:63.4A:63.4B** was found to be 43.5:13:43.5.

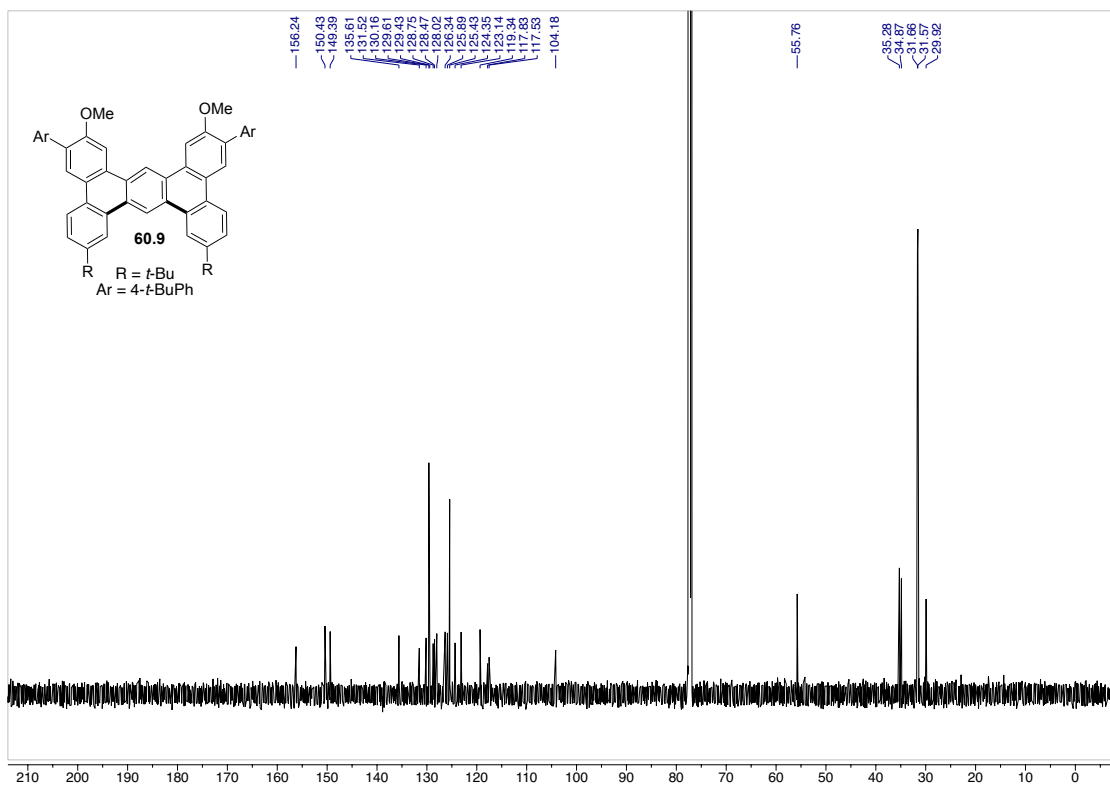
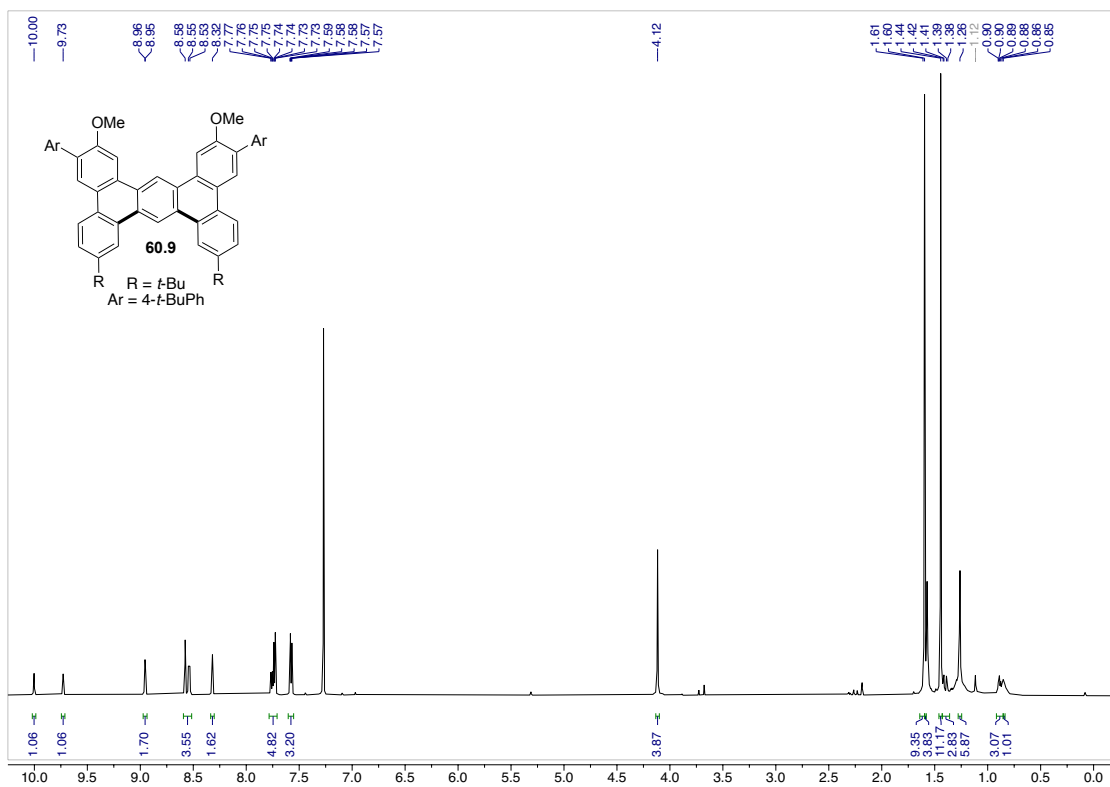
10 equivalent FeCl_3 : A solution of Iron (III) chloride (14.00 mg, 0.086 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred solution of **63.1** (16.0 mg, 0.018 mmol) in dichloromethane (4 mL) under argon. After 15 min, methanol (3 mL) and water (5 mL) were added. The organic layers were separated, and the aqueous phase was extracted with dichloromethane (3×5) mL. The combined organic extracts were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The crude ^1H nmr was taken in CDCl_3 , the ratio of products, **63.4A:63.4B** was found to be 14:86.

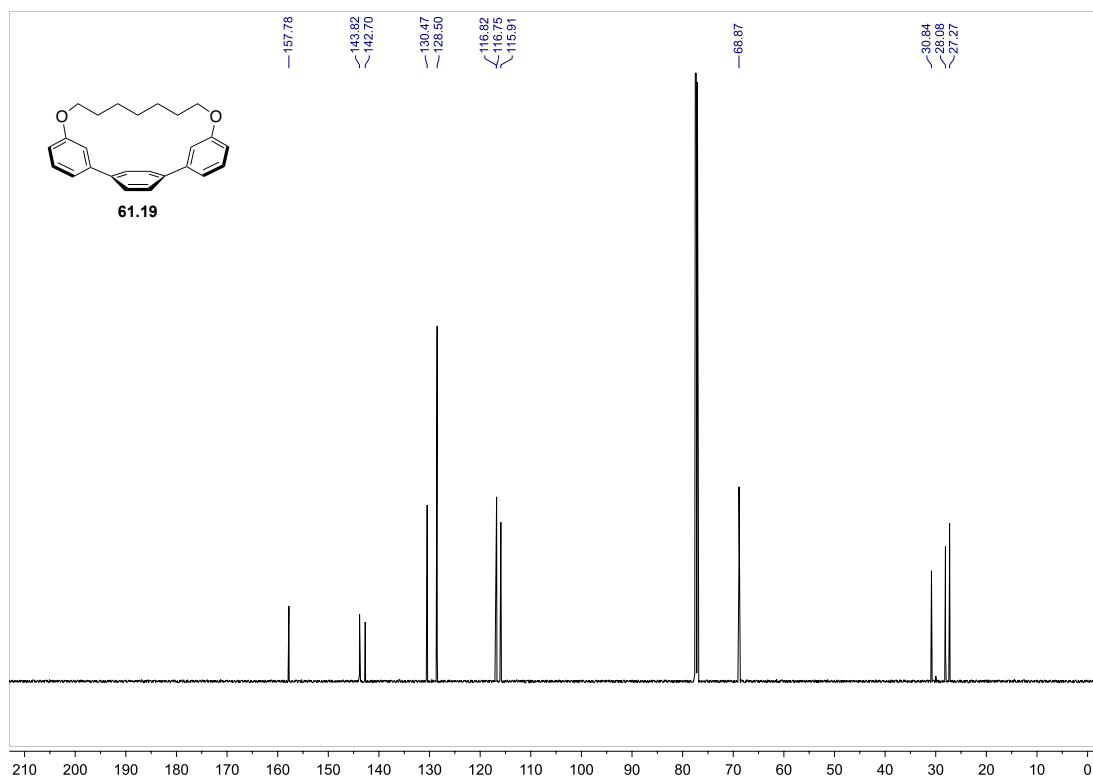
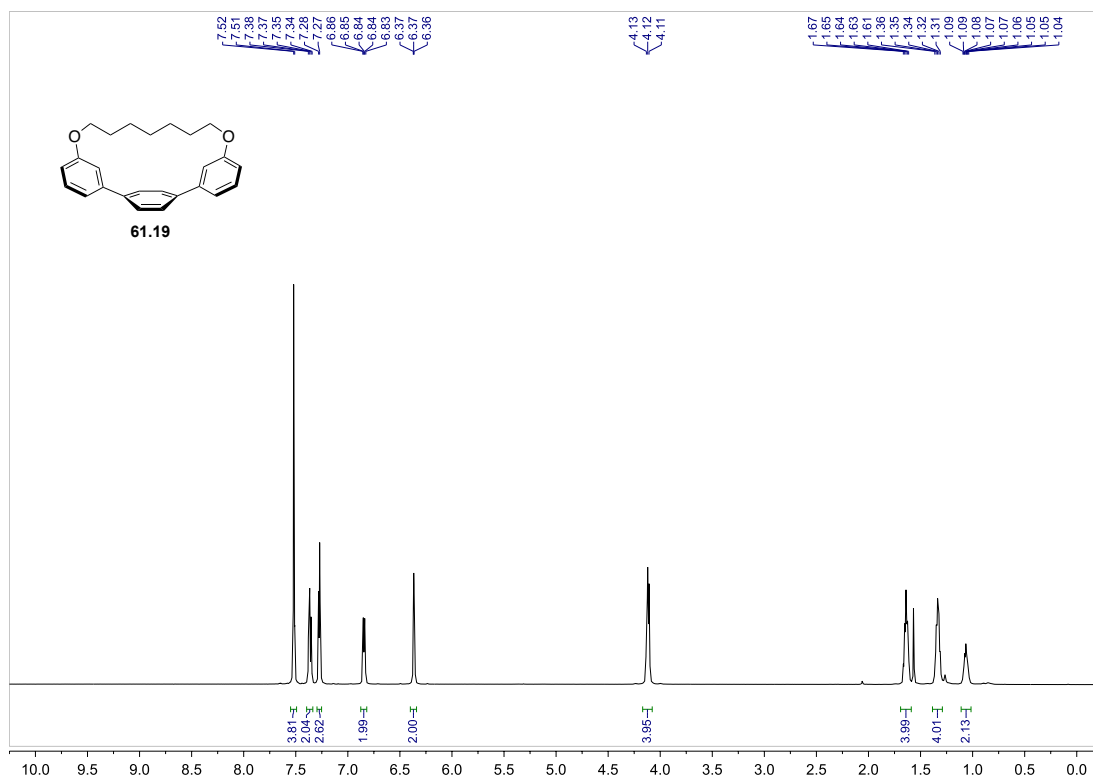
Data analysis of time course experiments: When 2.5 equivalent FeCl_3 was used, the product conversion was 26% as combined of **63.4A** and **63.4B** and the ratio of products **63.4A:63.4B** was 1:2.6. When 5 equivalent FeCl_3 was used, the starting material was 56.5% converted into products **63.4A** and **63.4B** and the ratio of products **63.4A:63.4B** was 1:3.4. When 10 equivalent FeCl_3 was used, the starting material was 100% converted into products **63.4A** and **63.4B** and the ratio of products **63.4A:63.4B** was 1:6.1. The product ratio of **63.4A** to **63.4B** changes with the increase of amount of FeCl_3 .

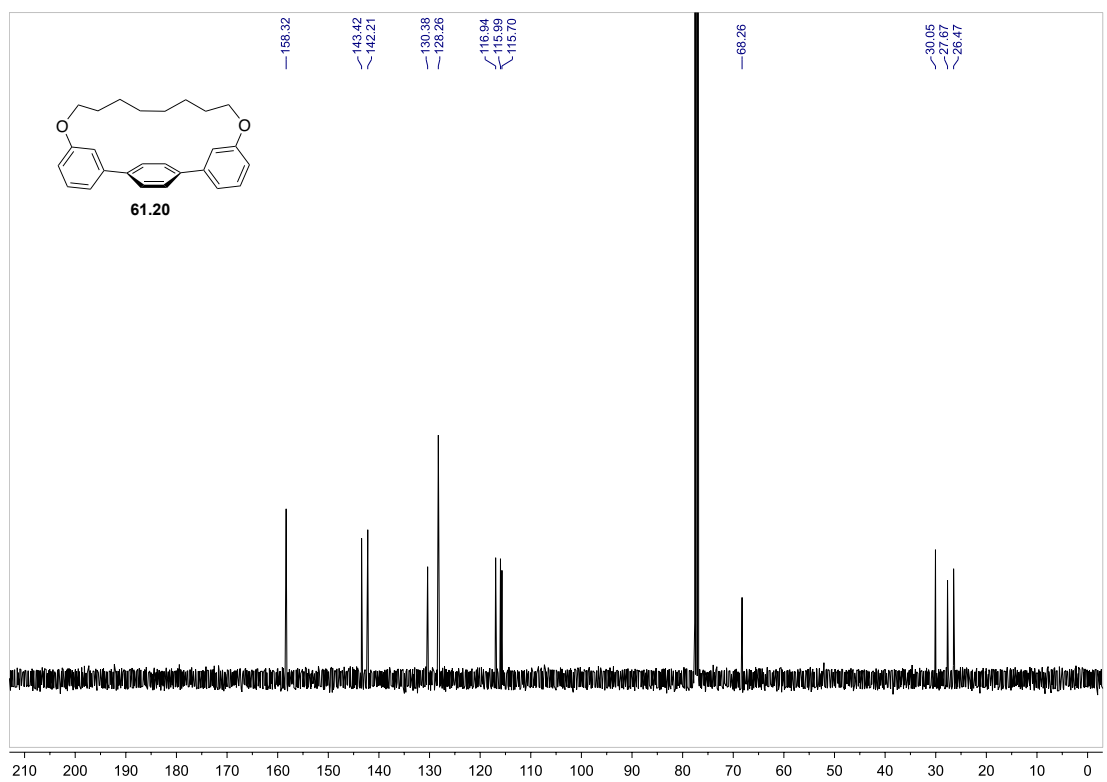
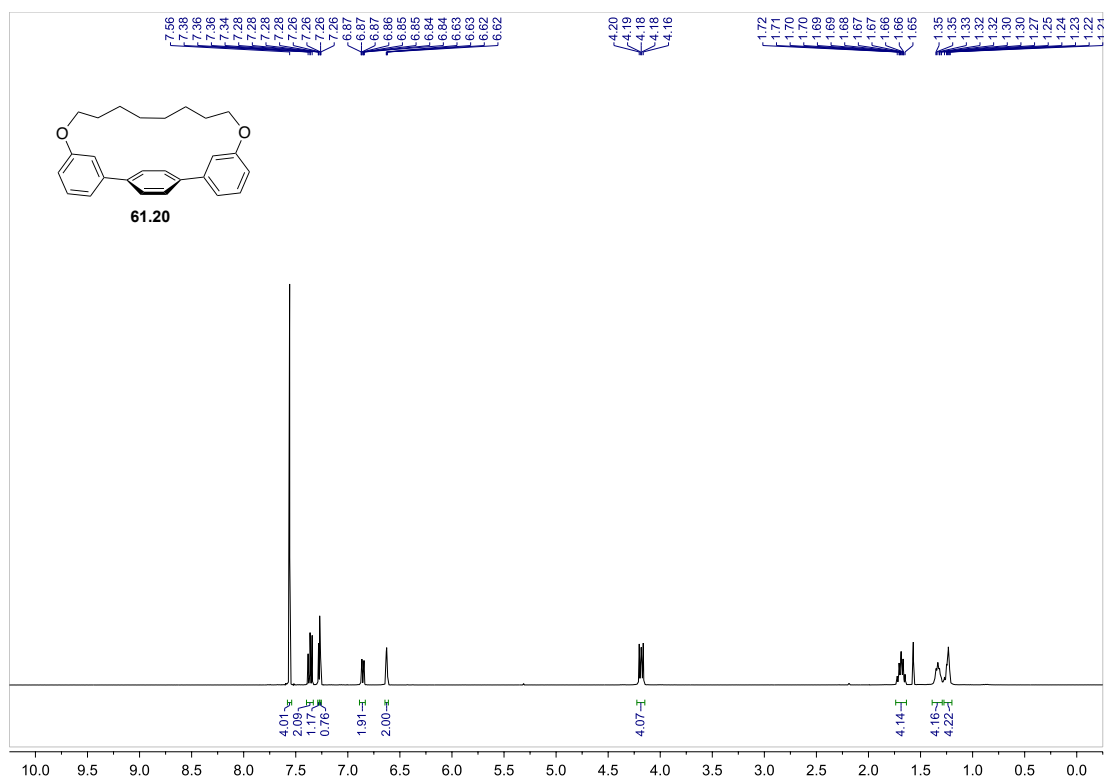


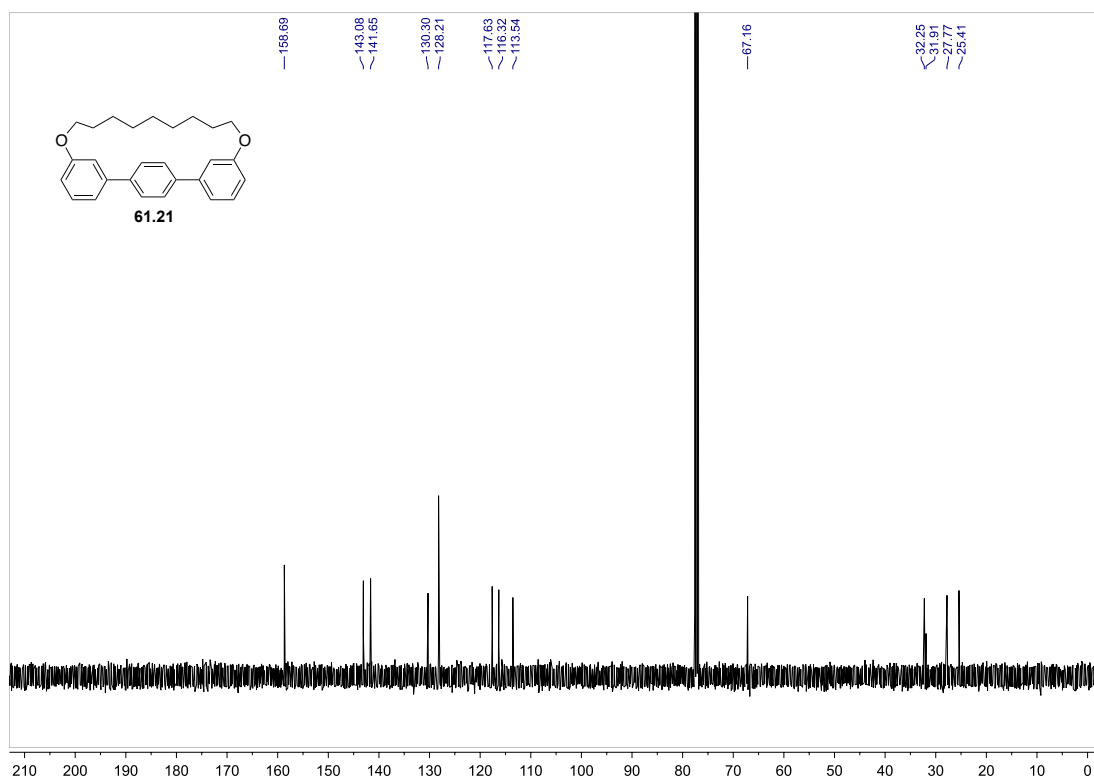
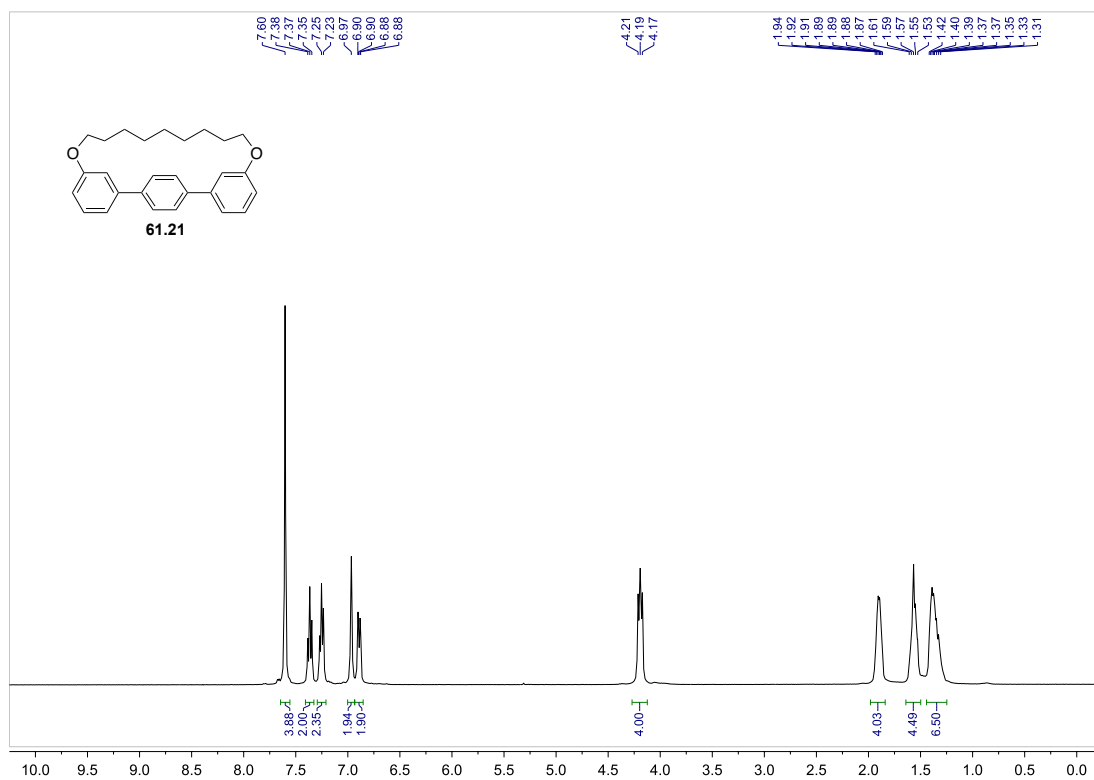


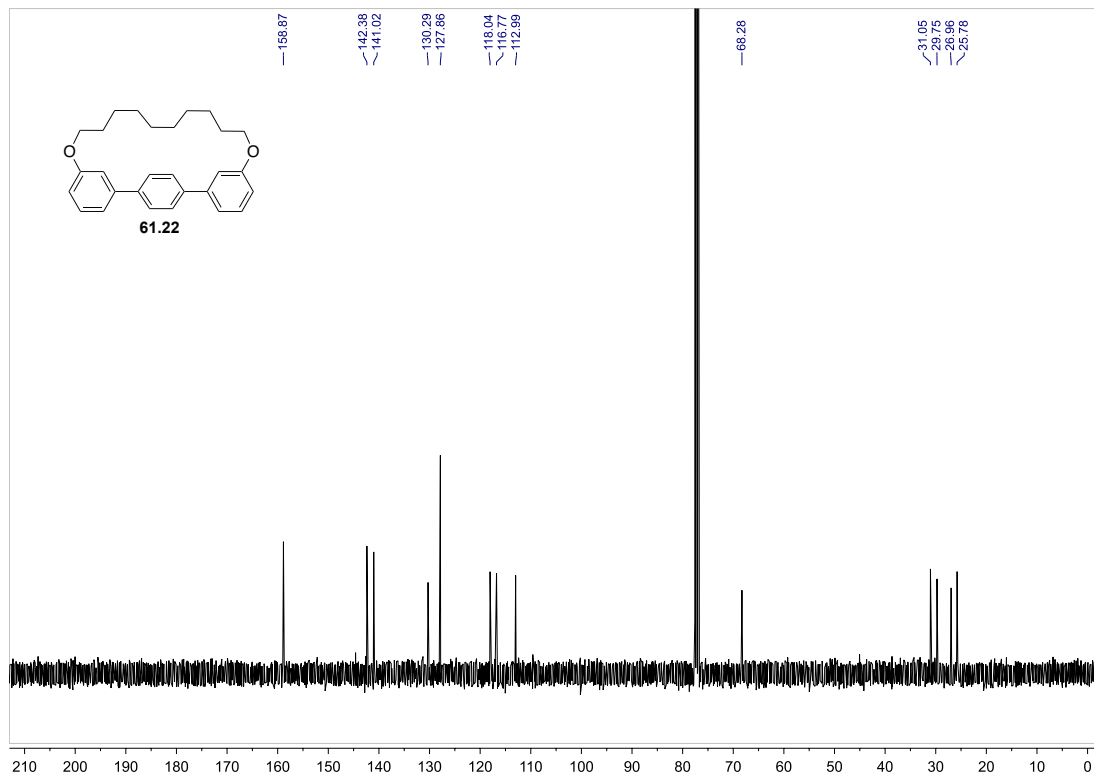
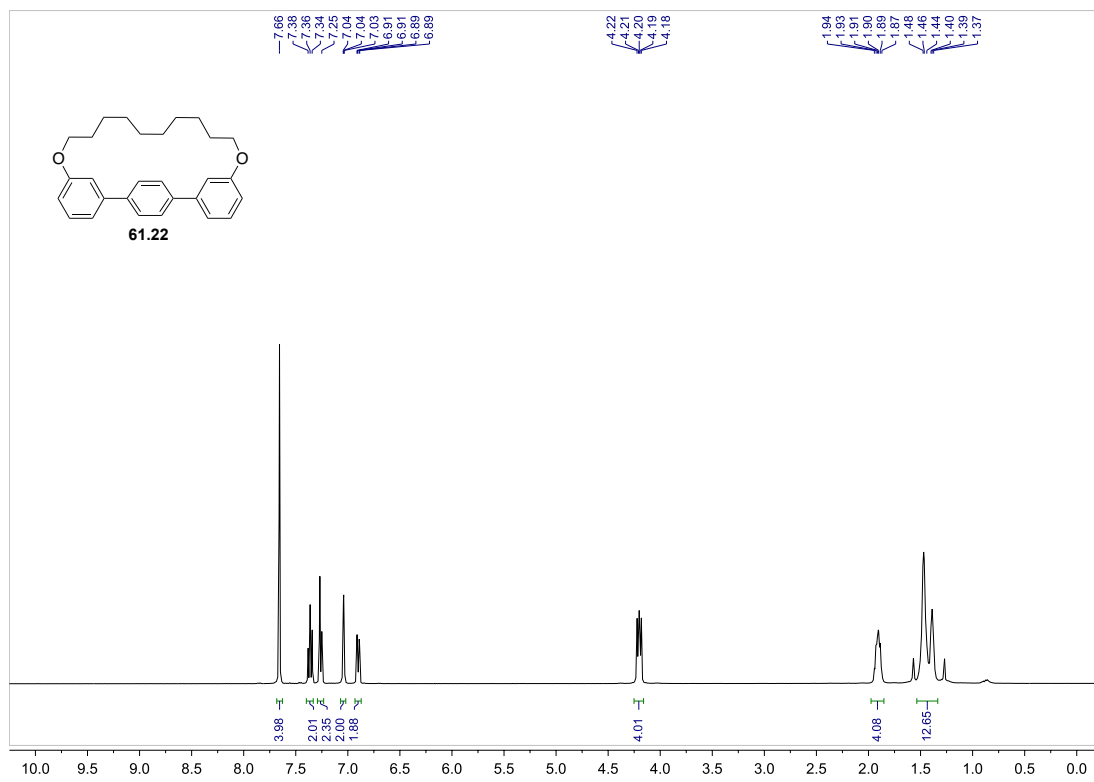


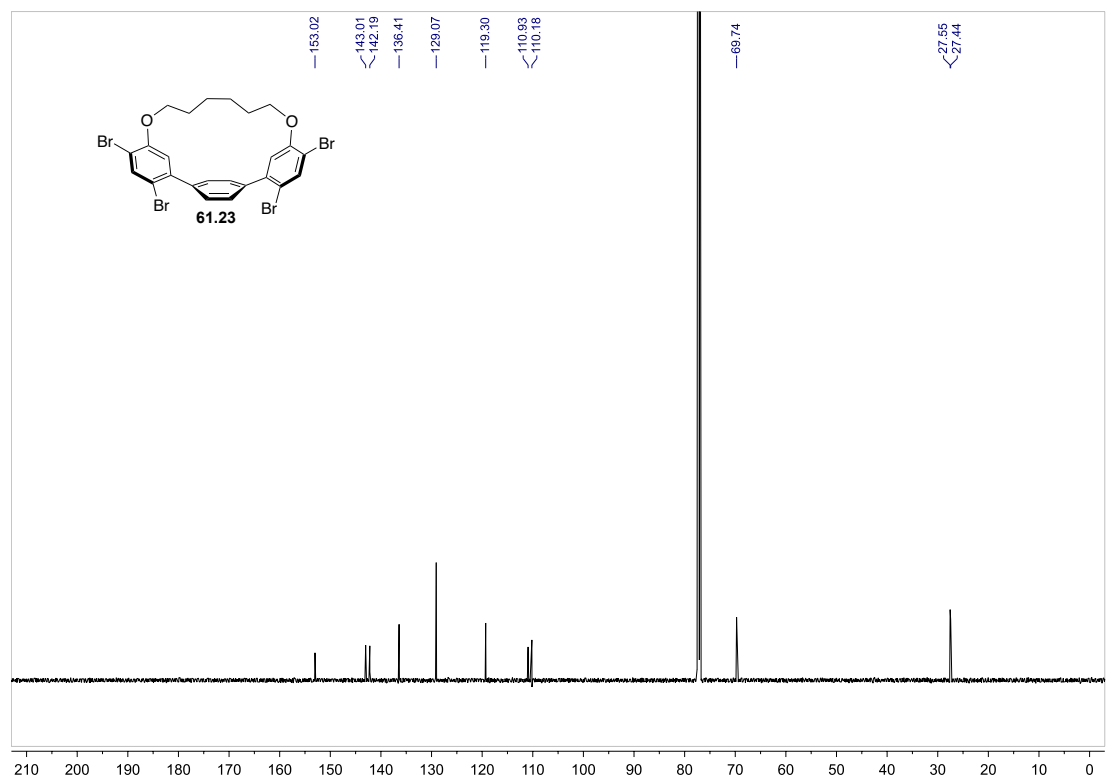
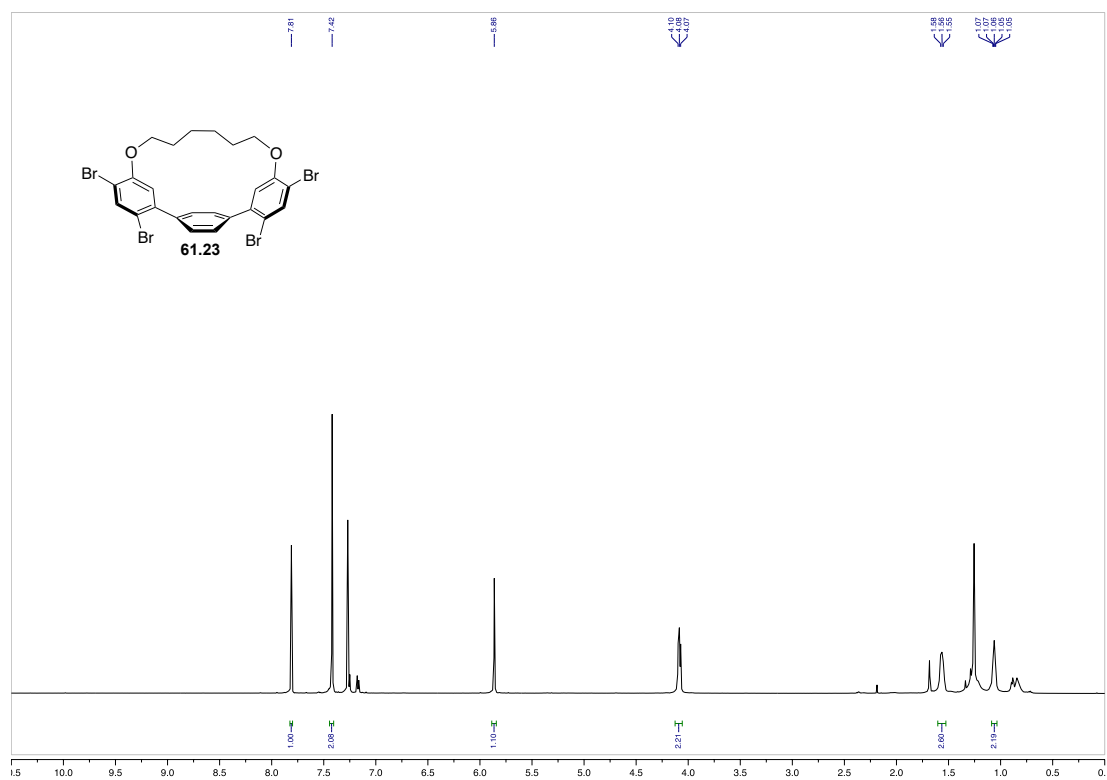


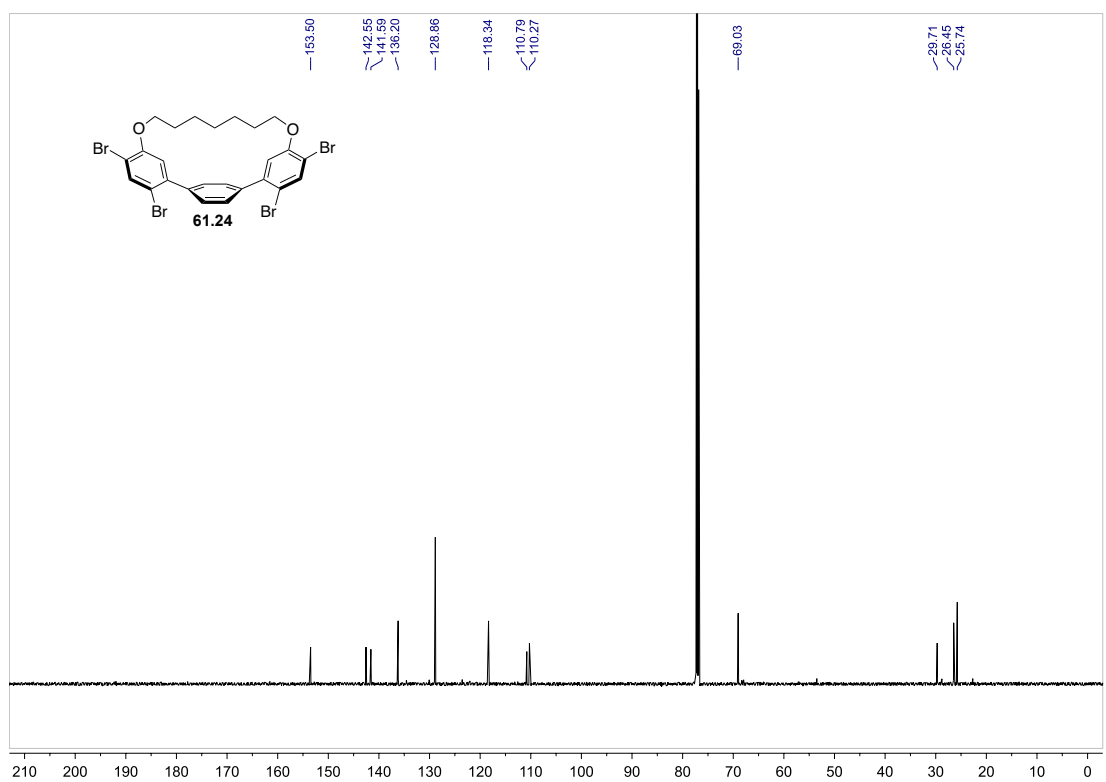
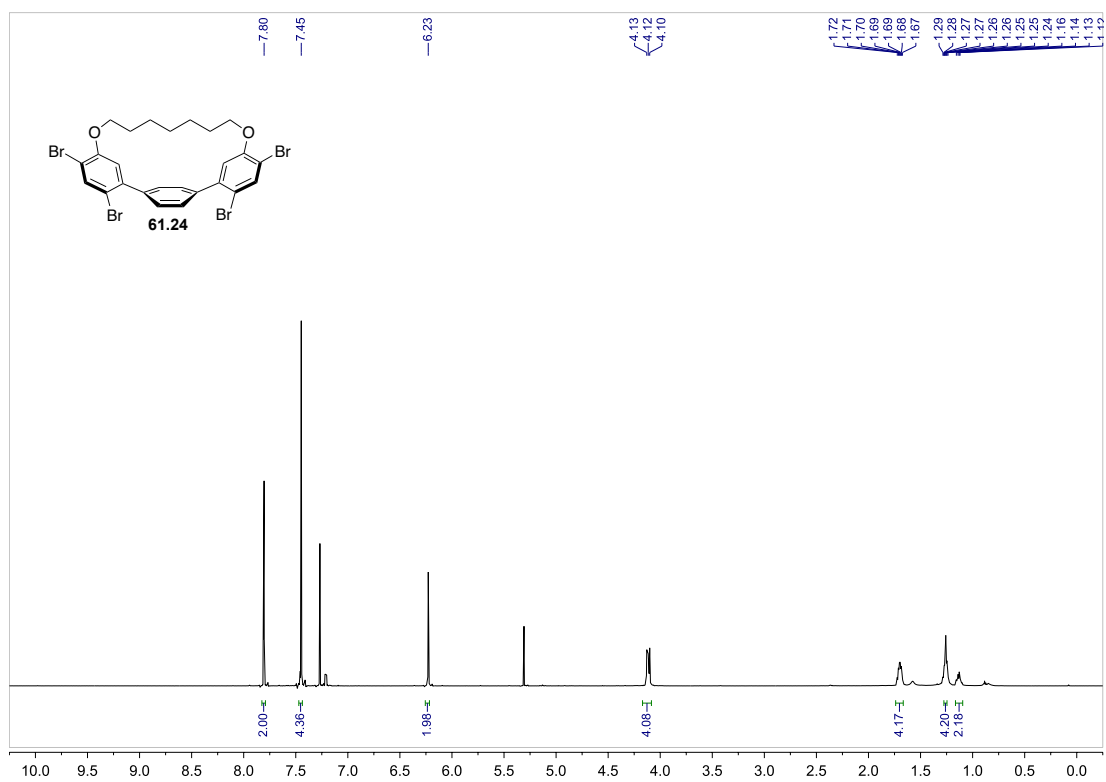


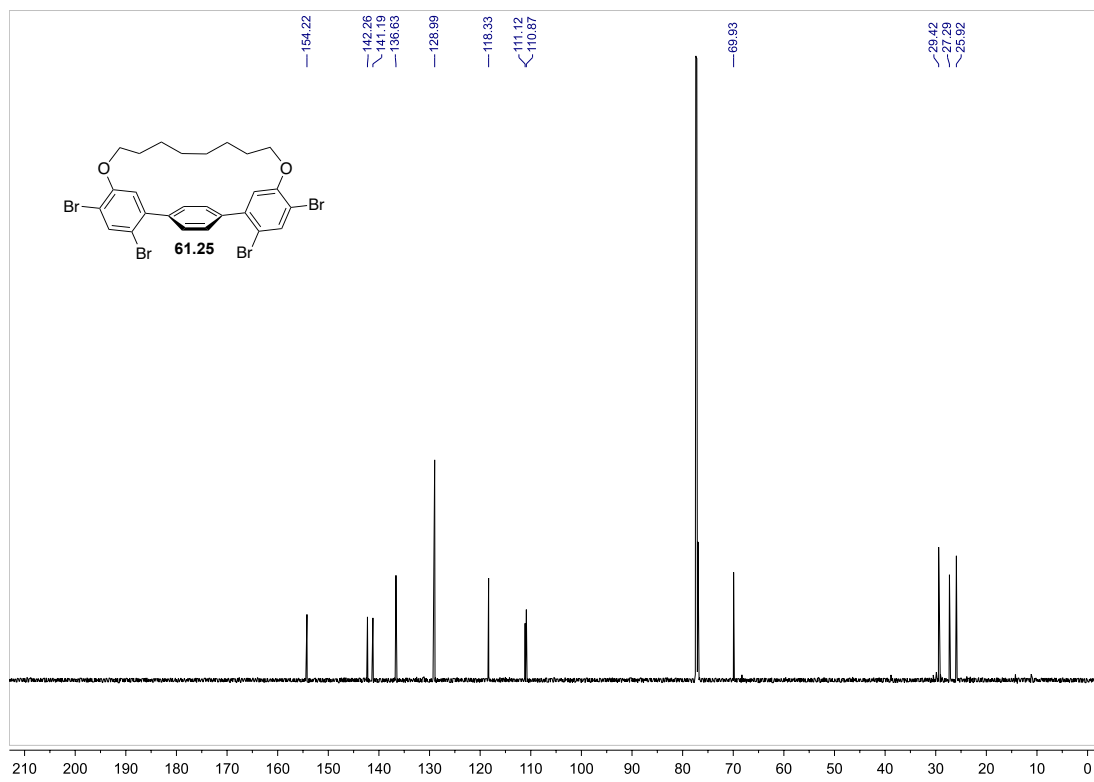
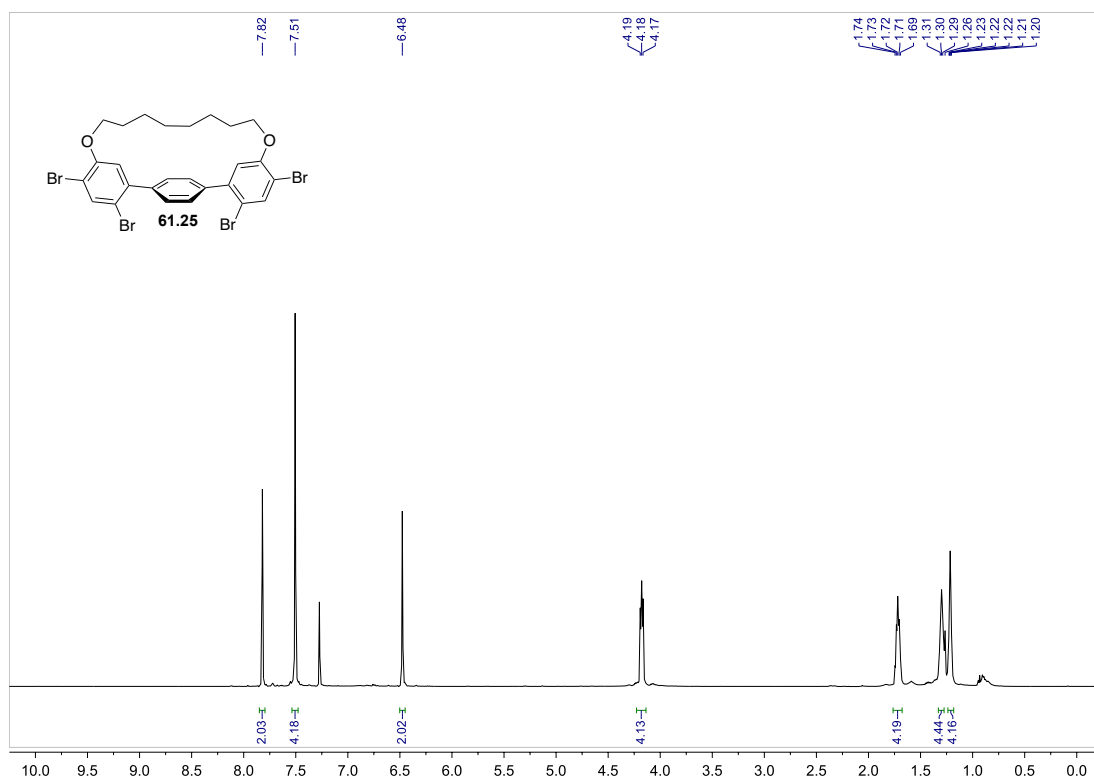


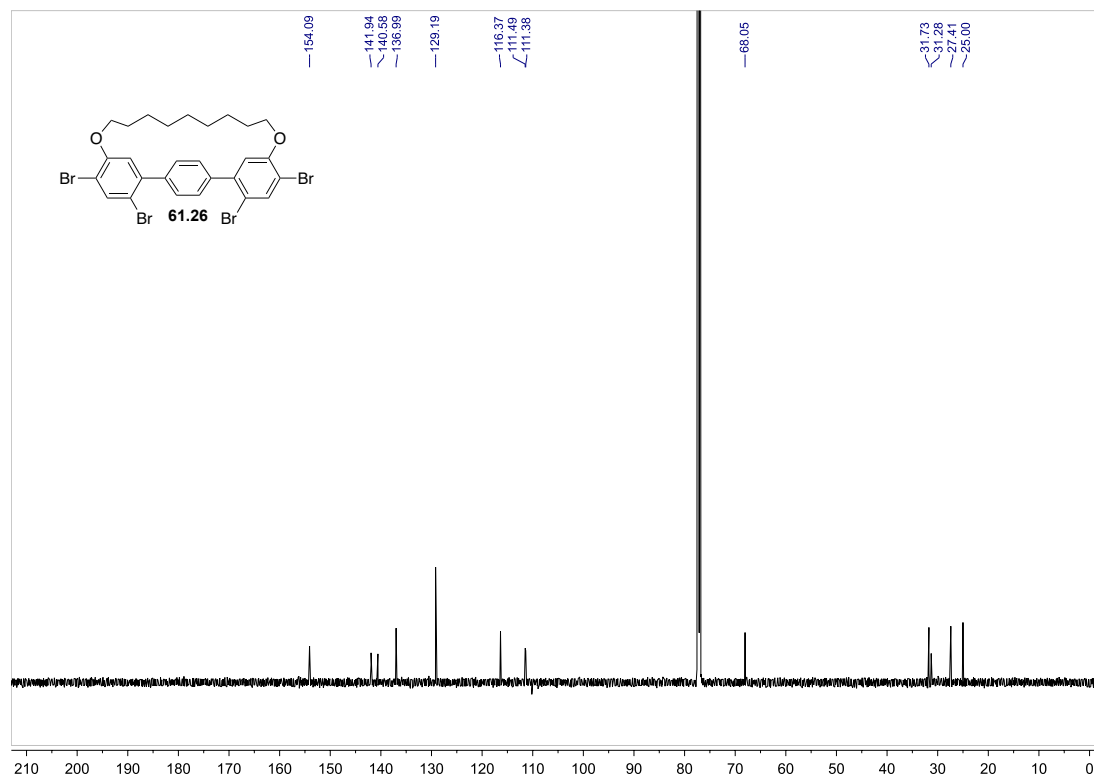
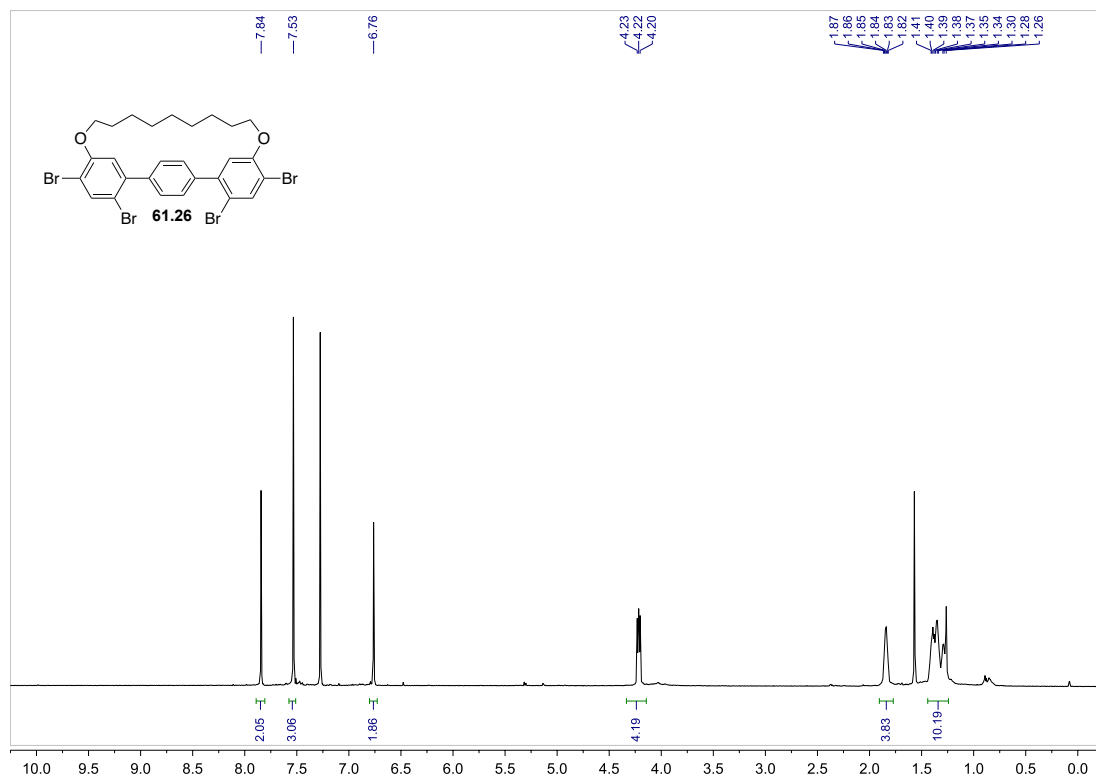


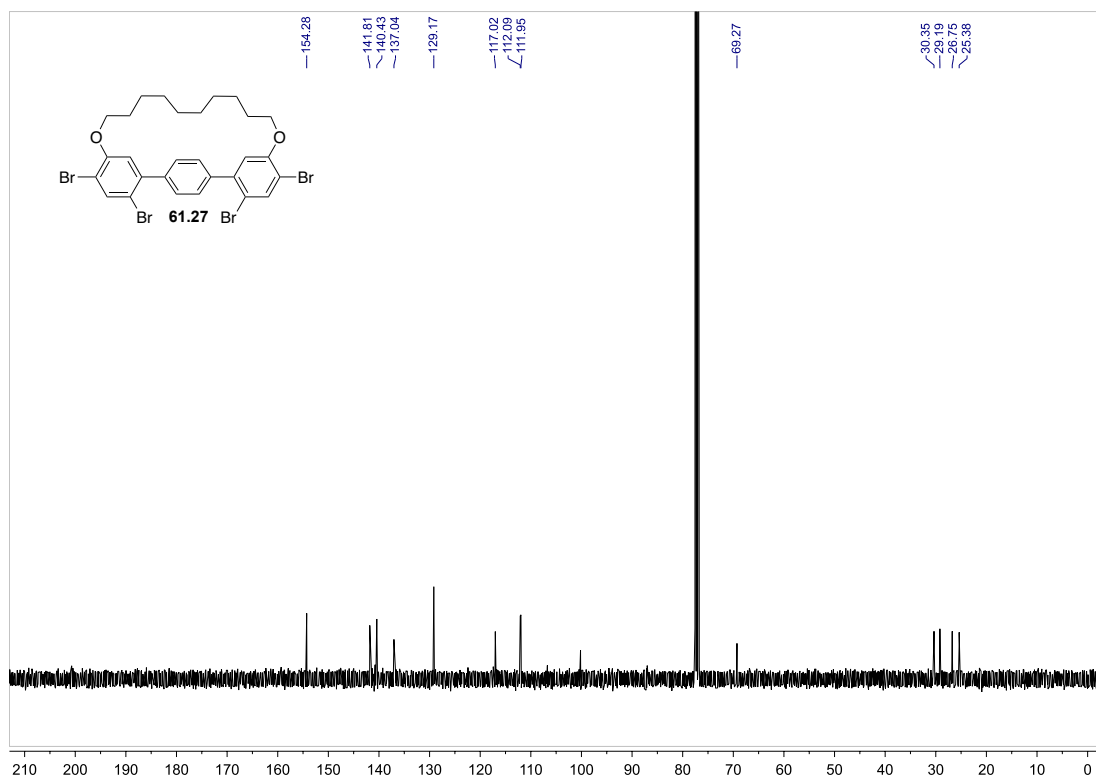
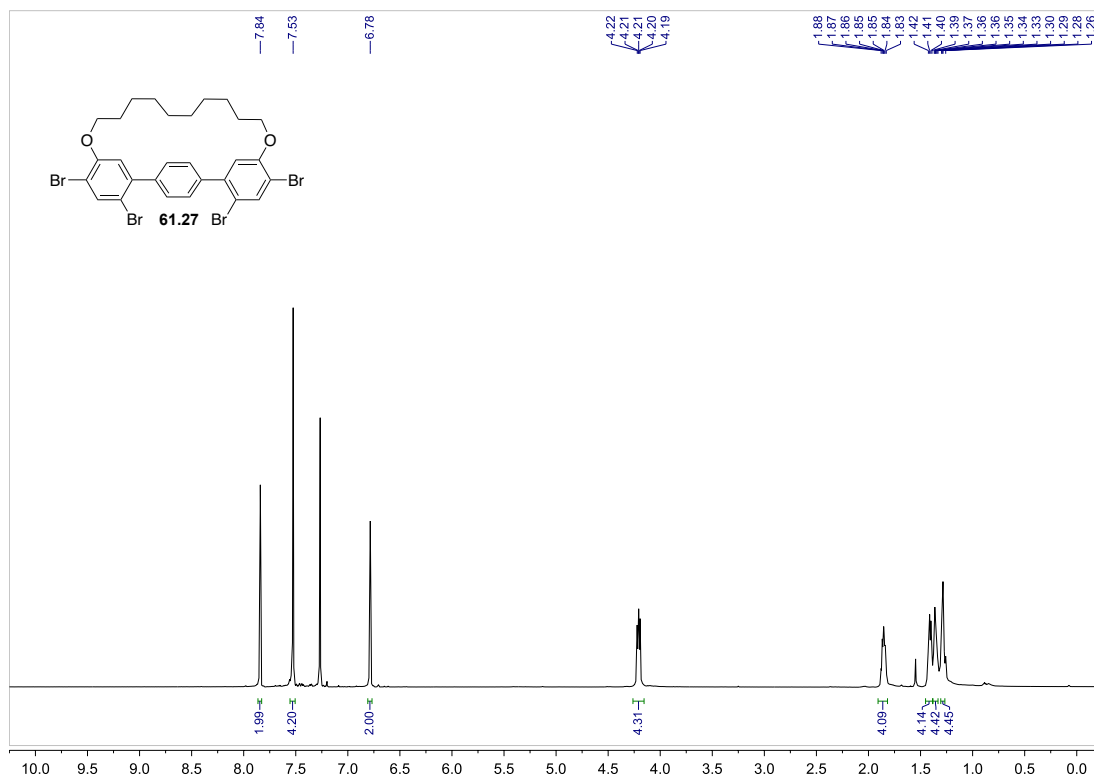


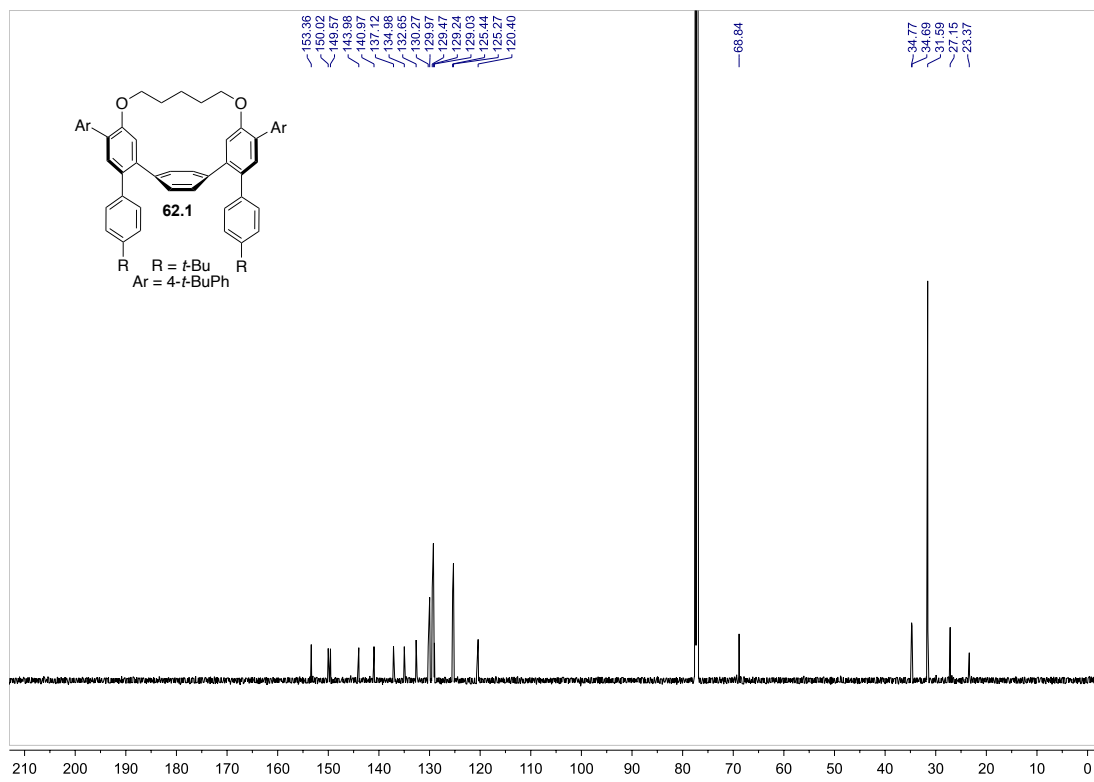
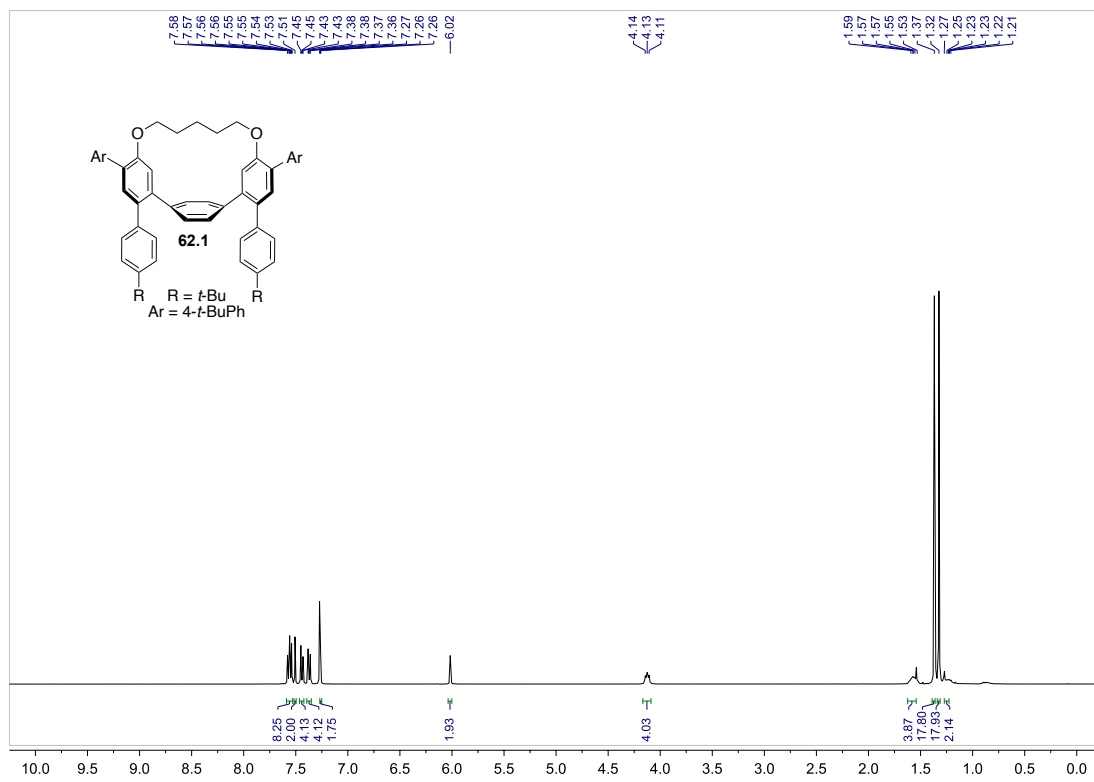


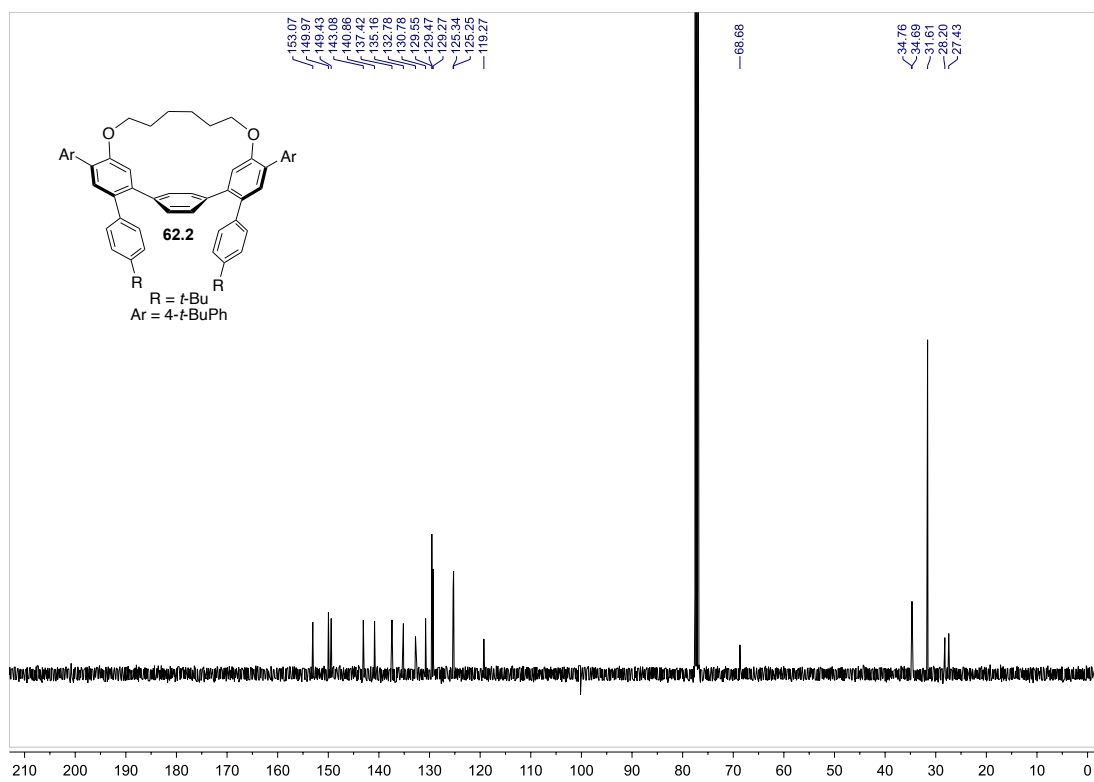
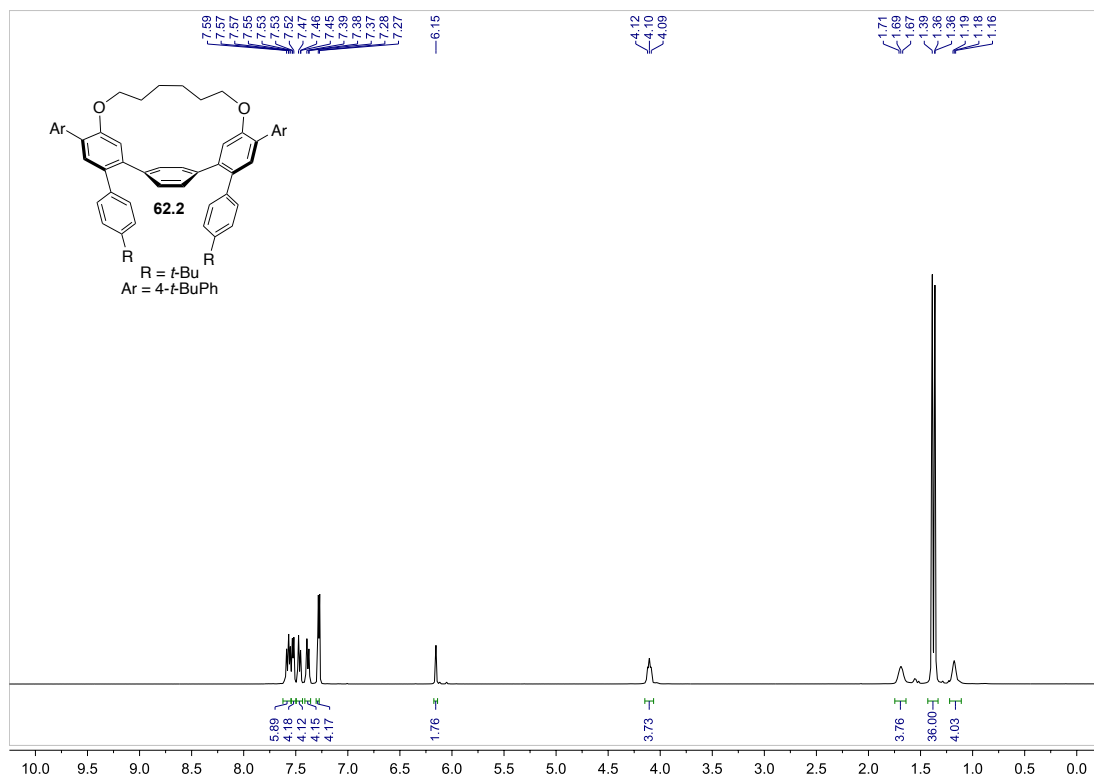


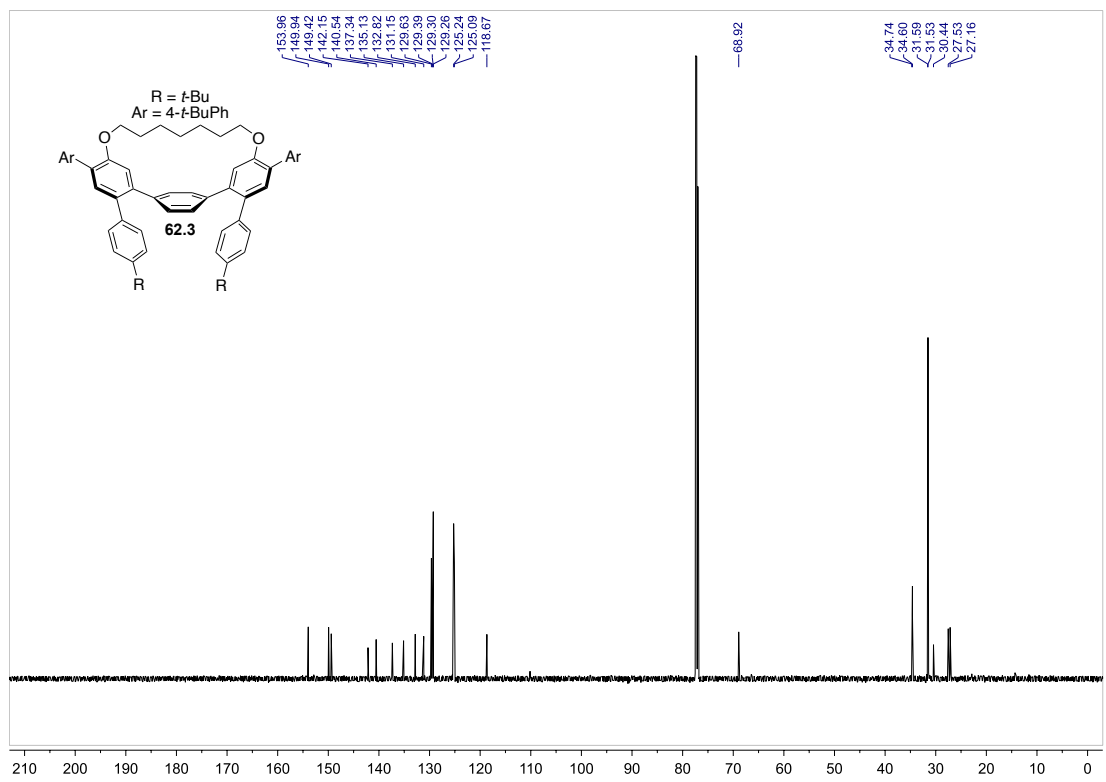
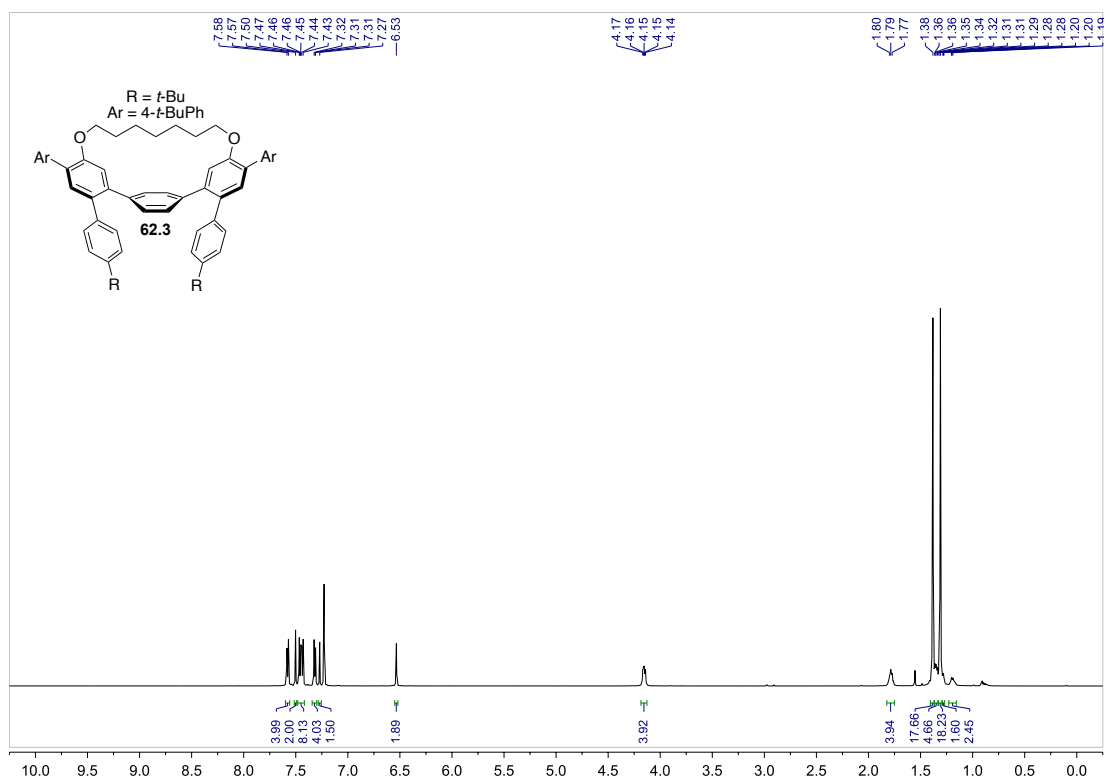


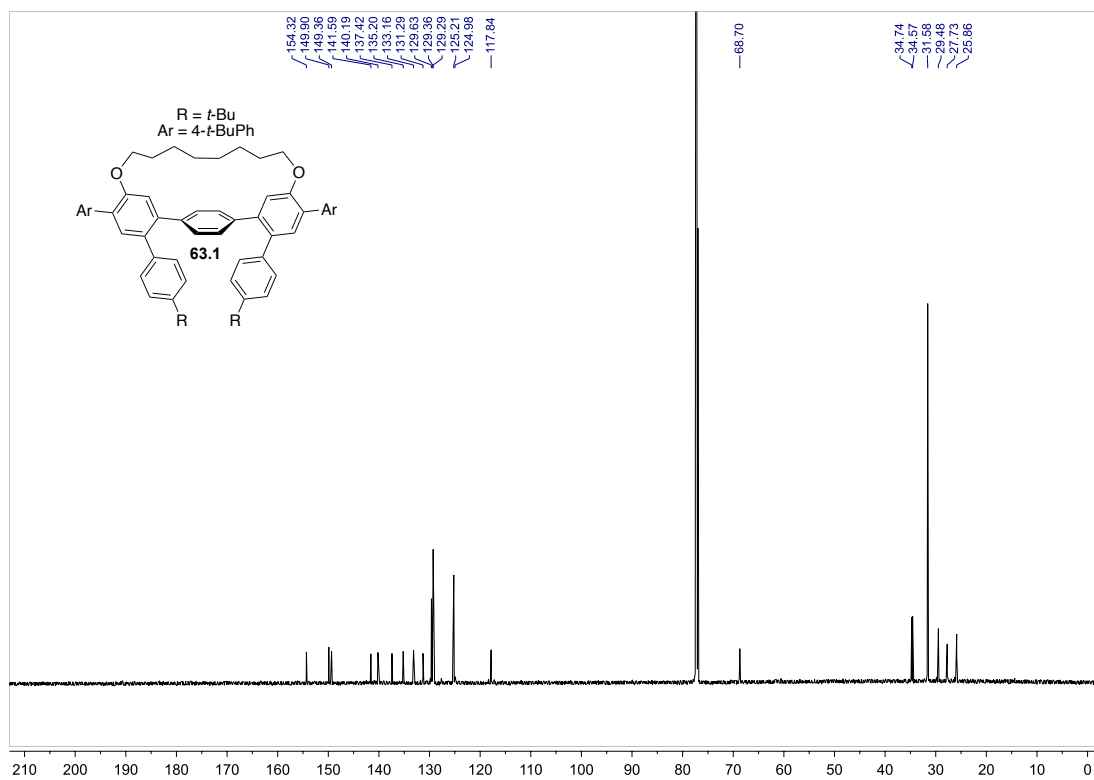
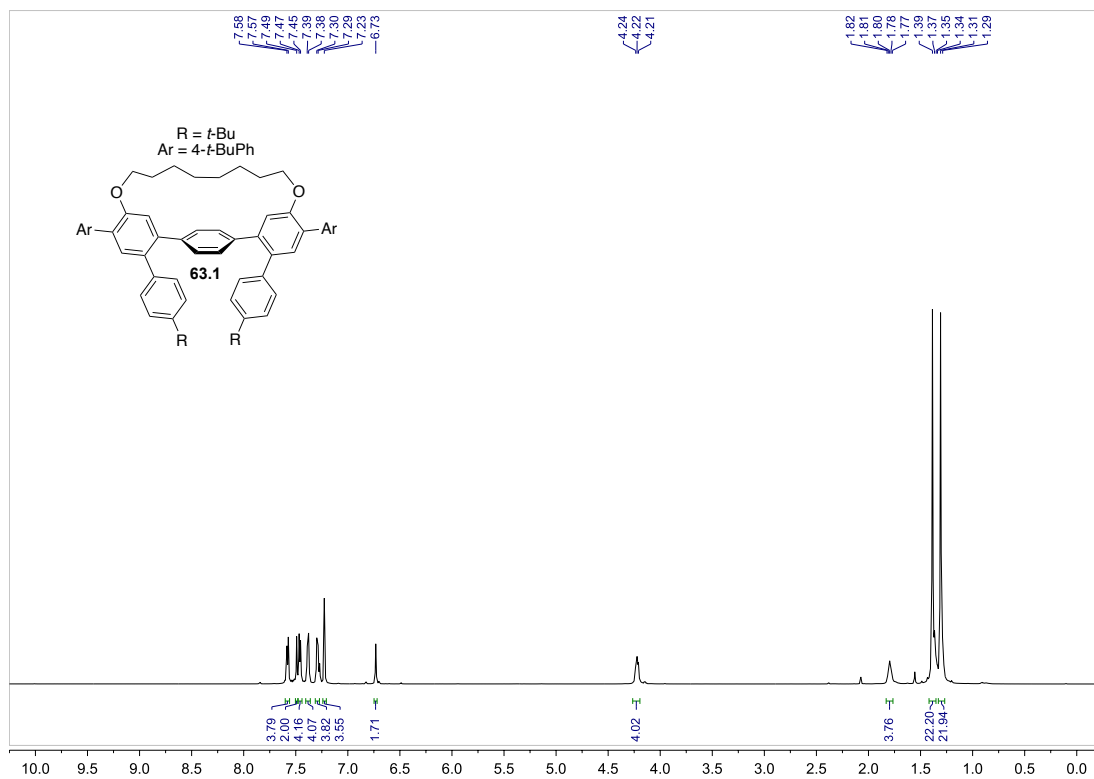


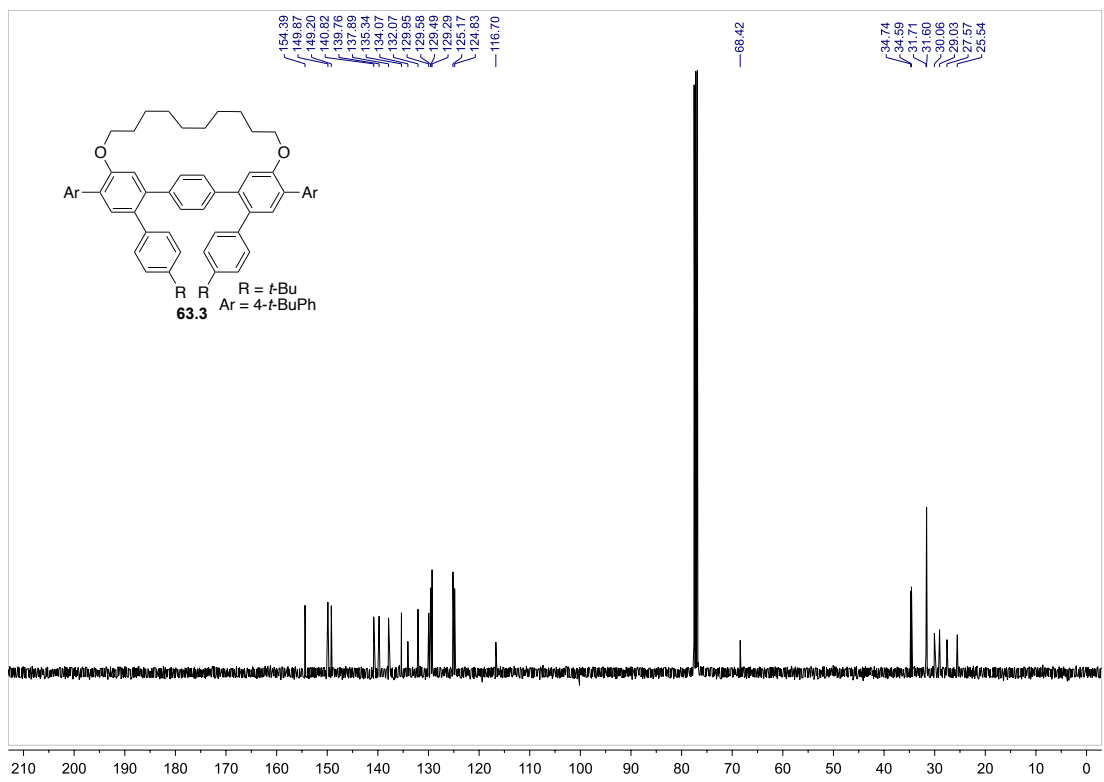
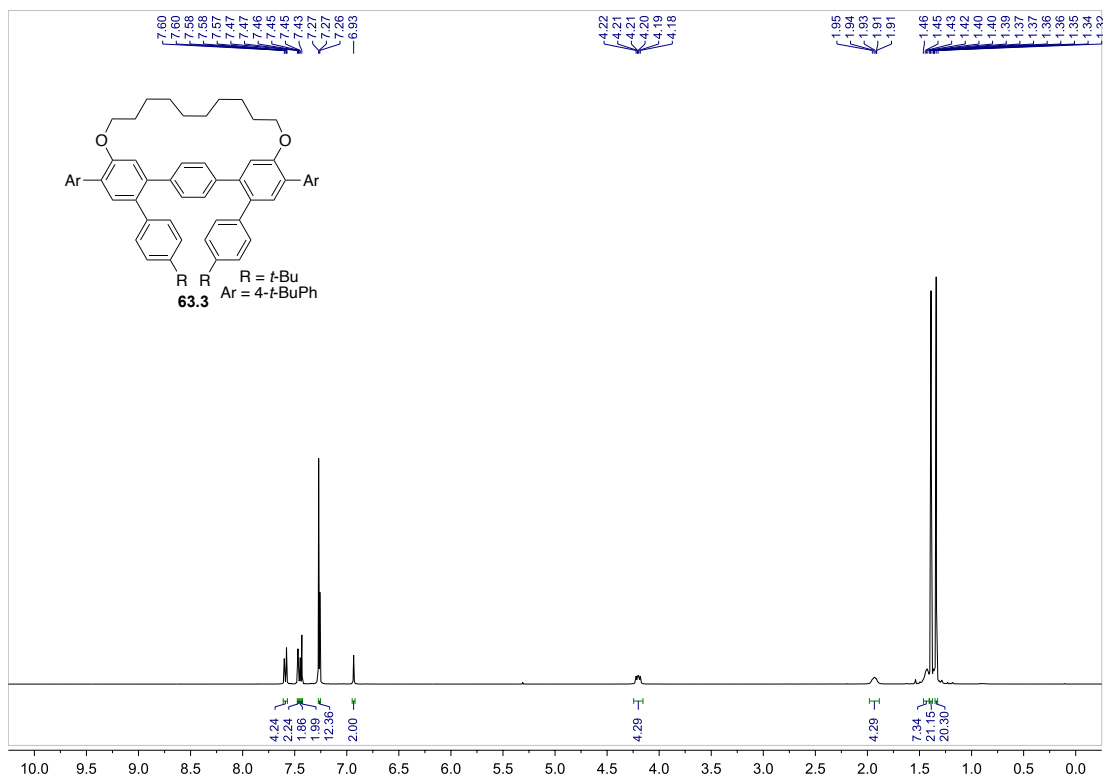


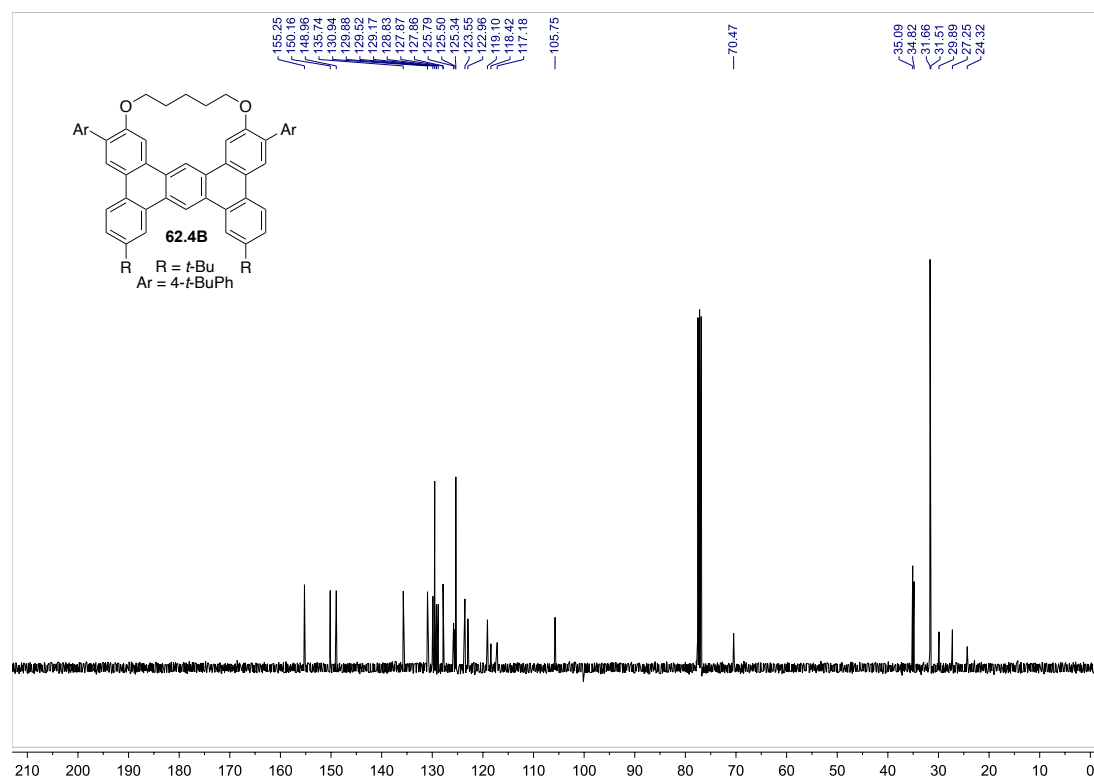
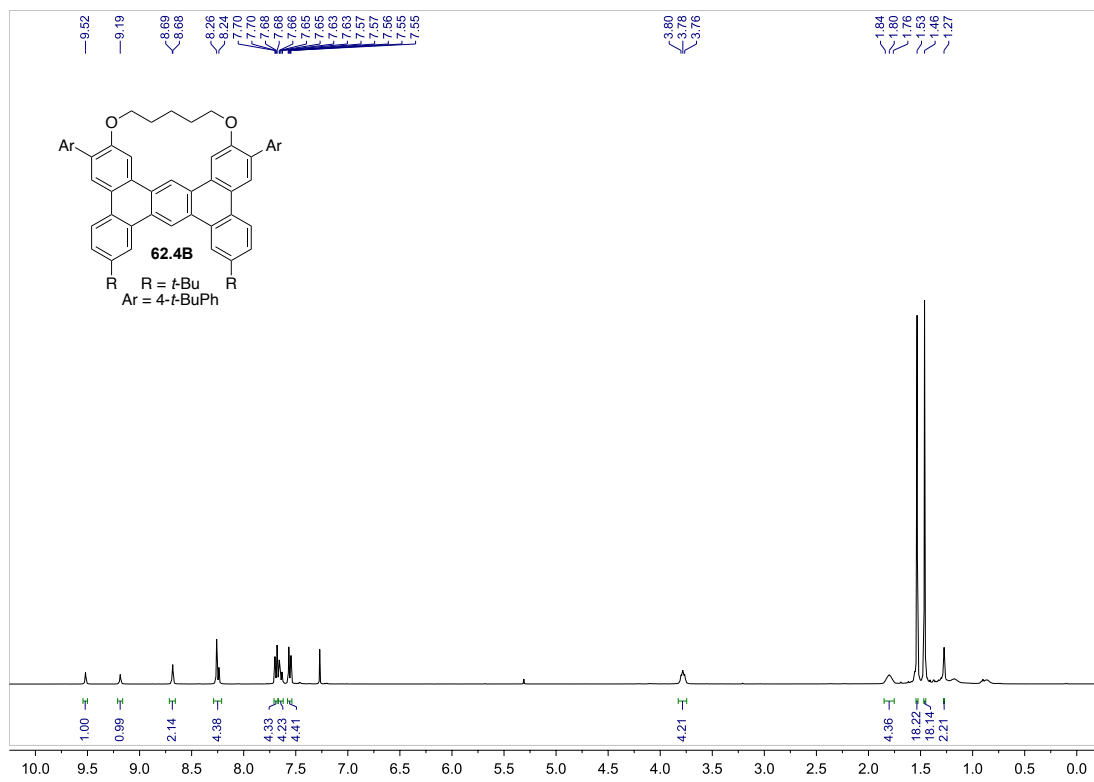


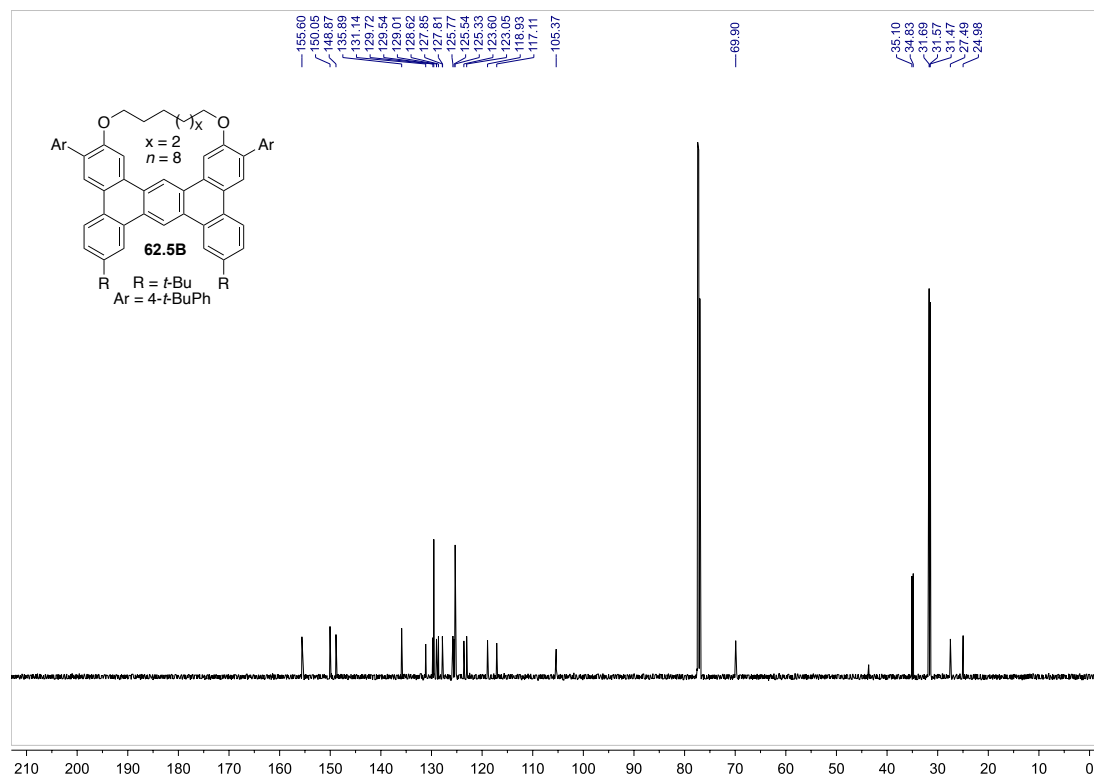
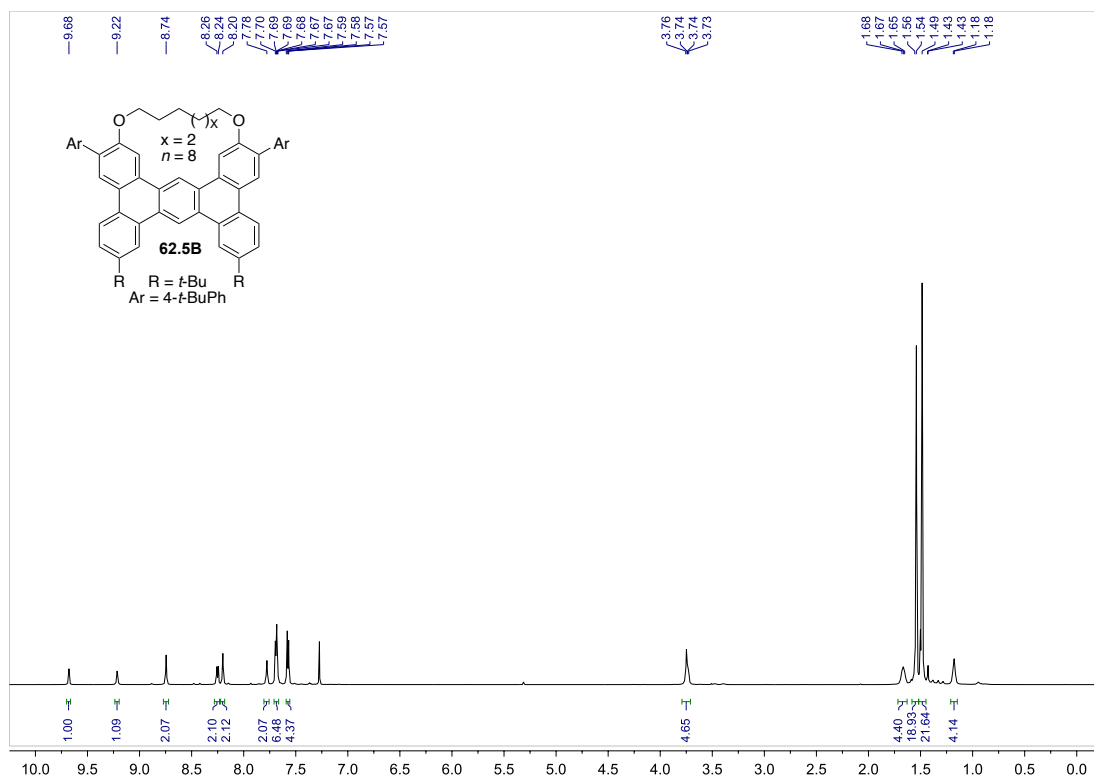


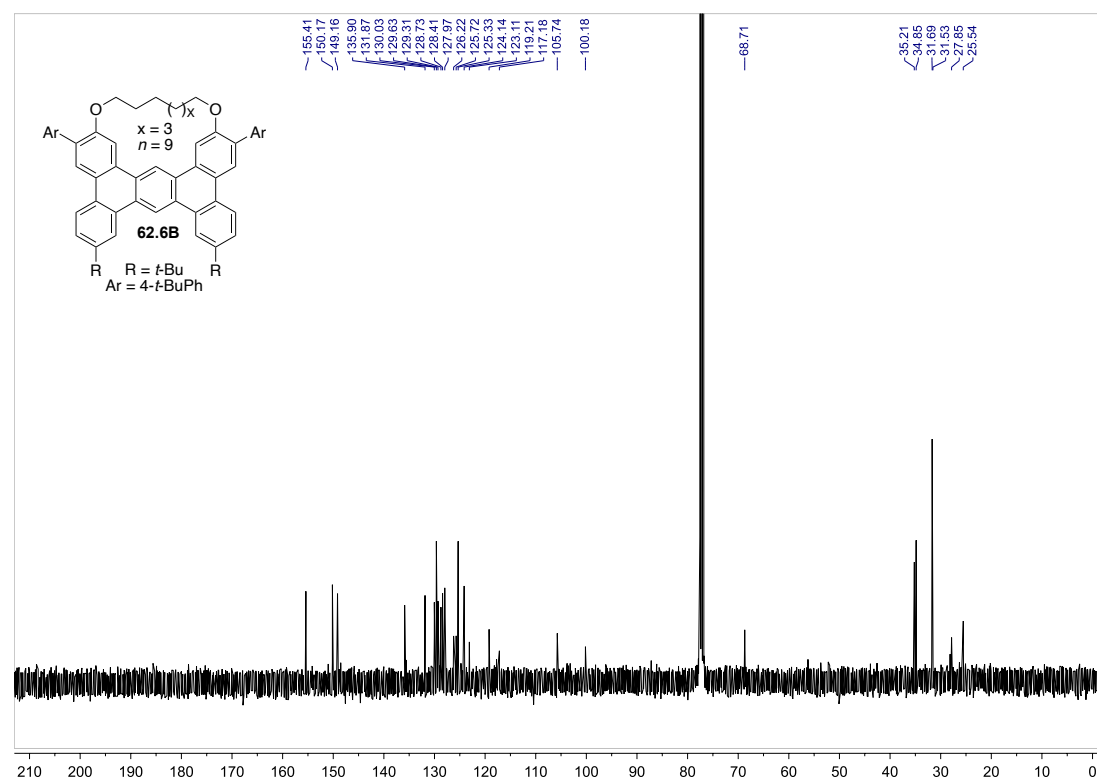
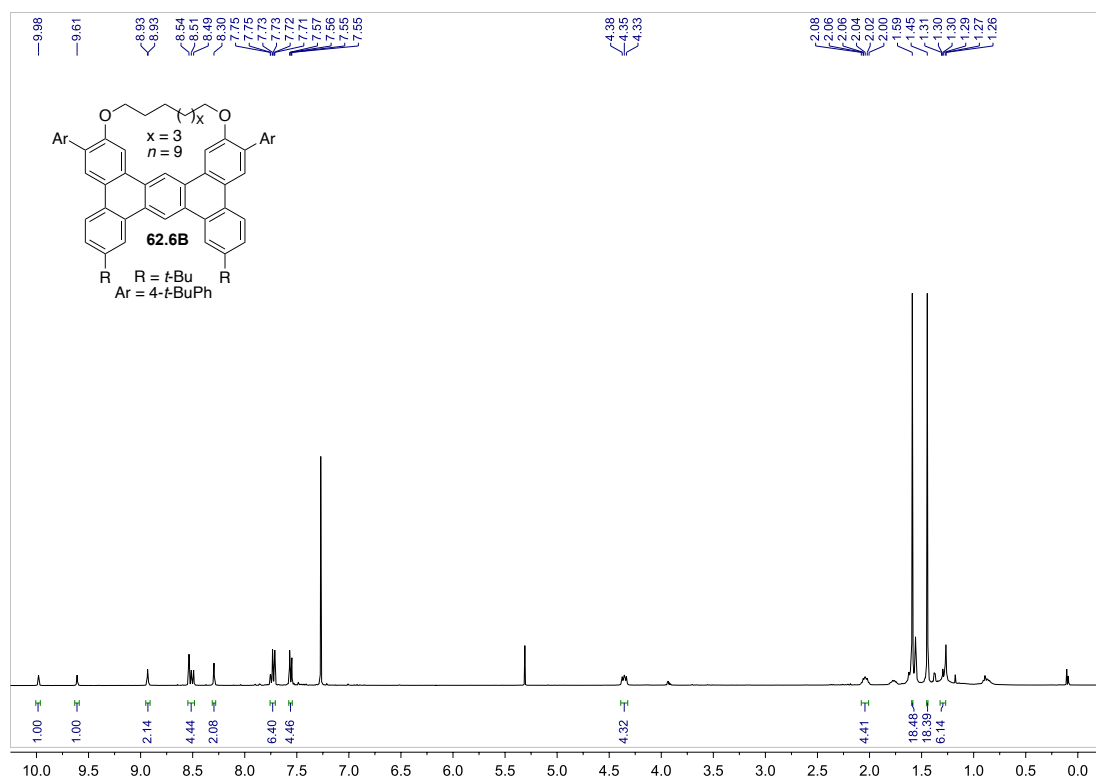


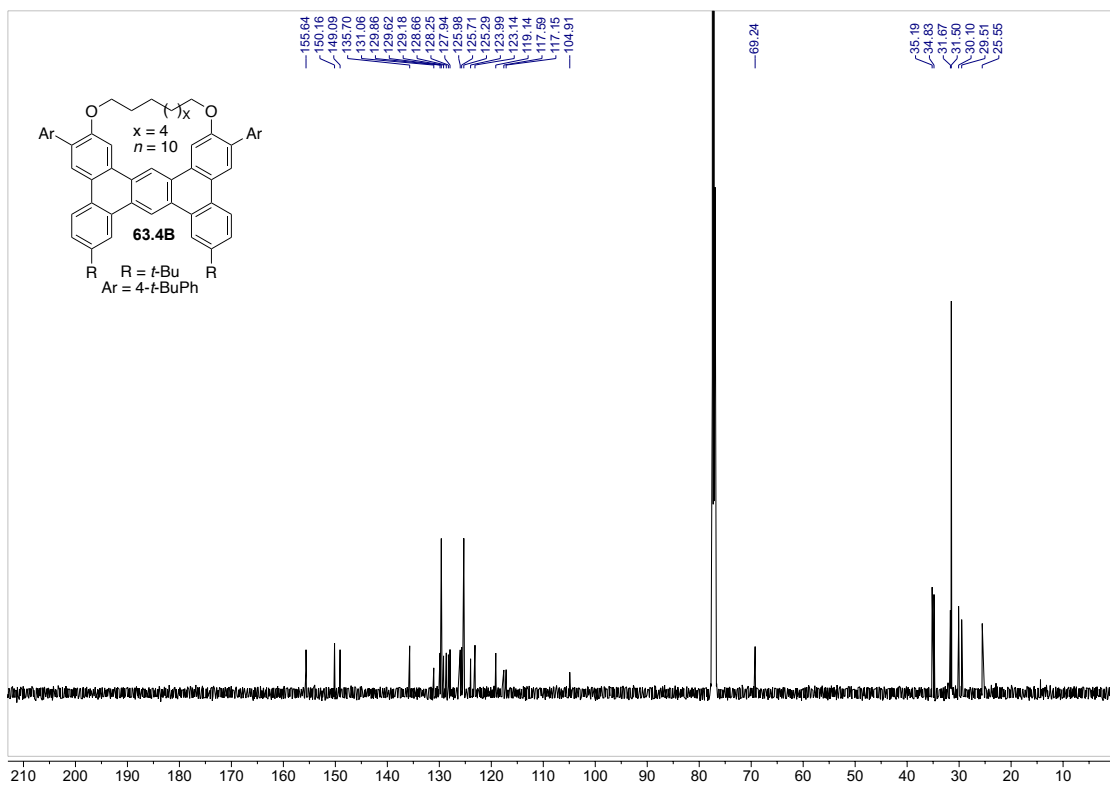
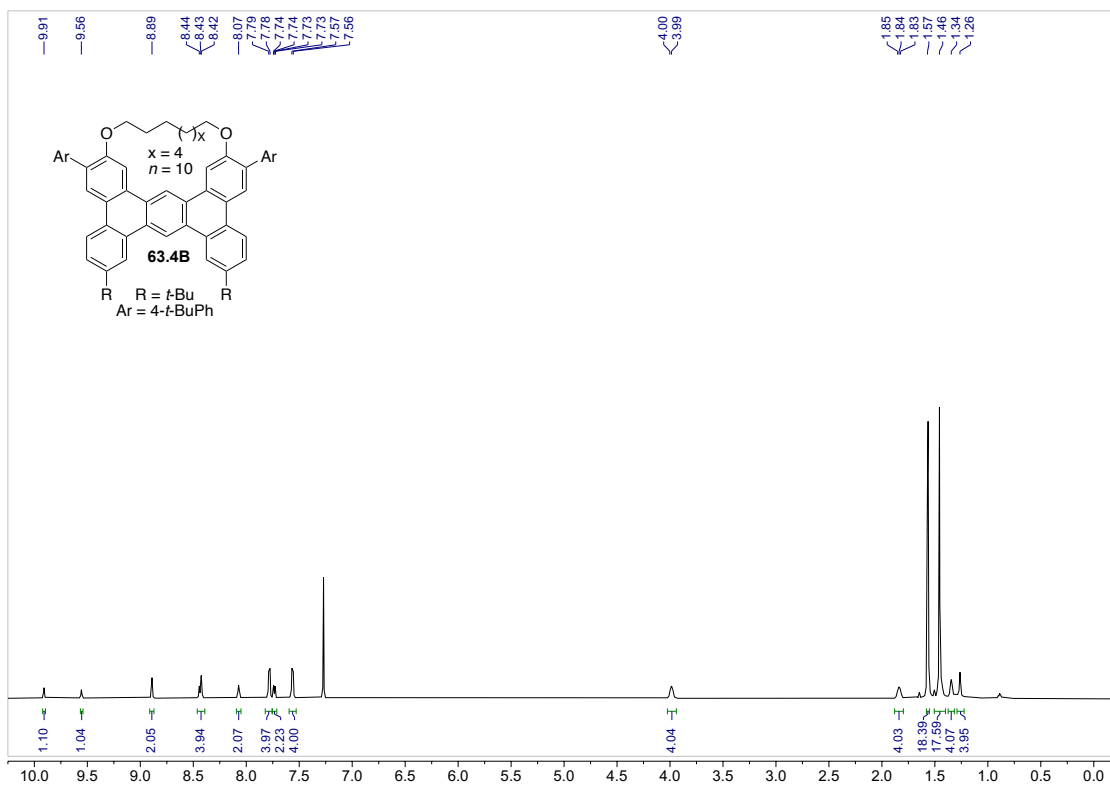


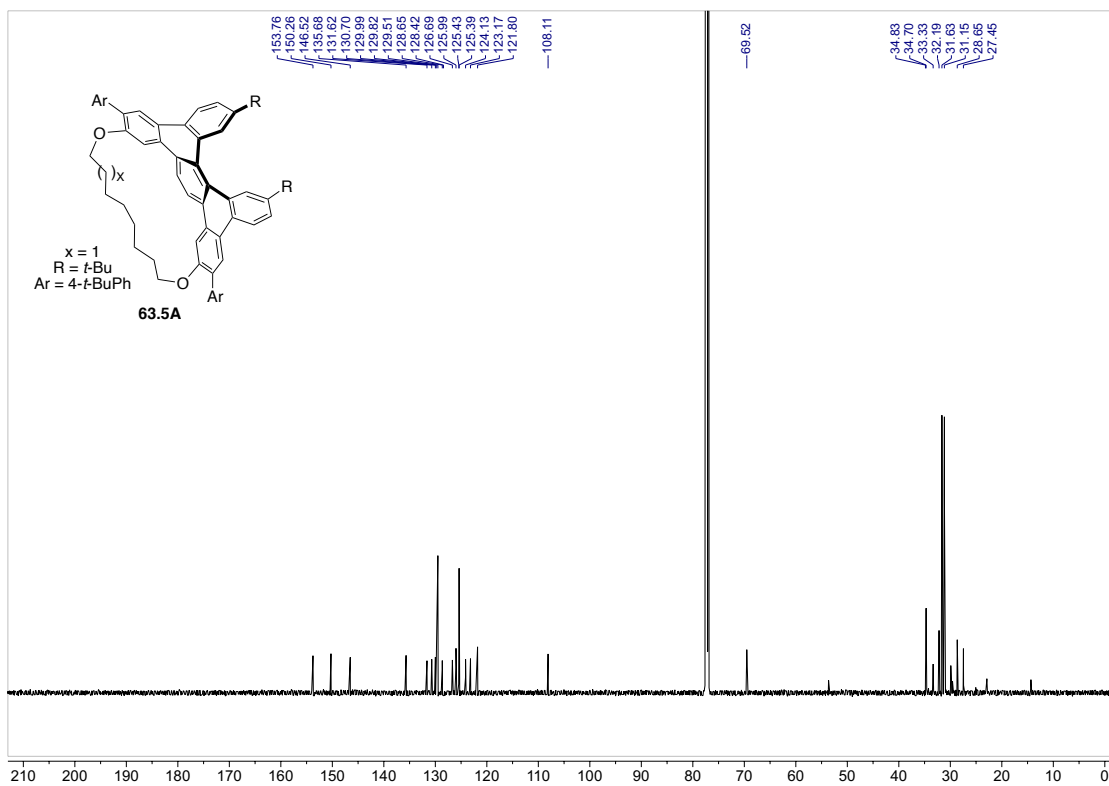
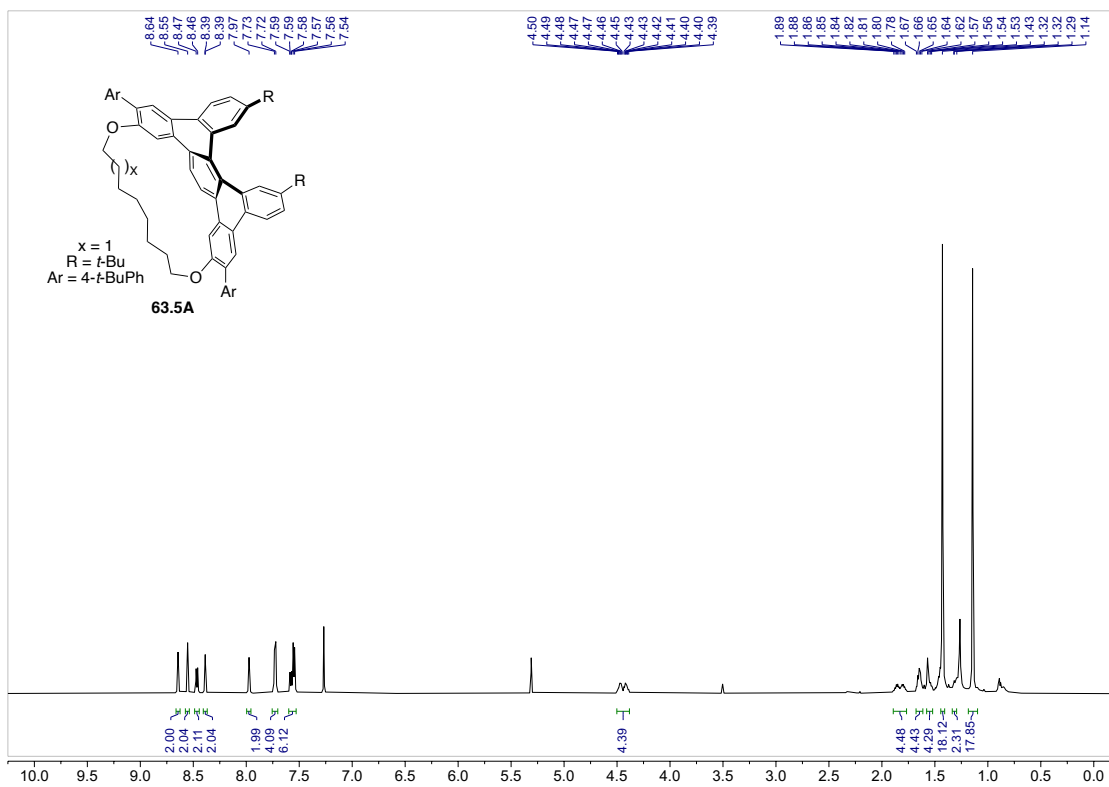


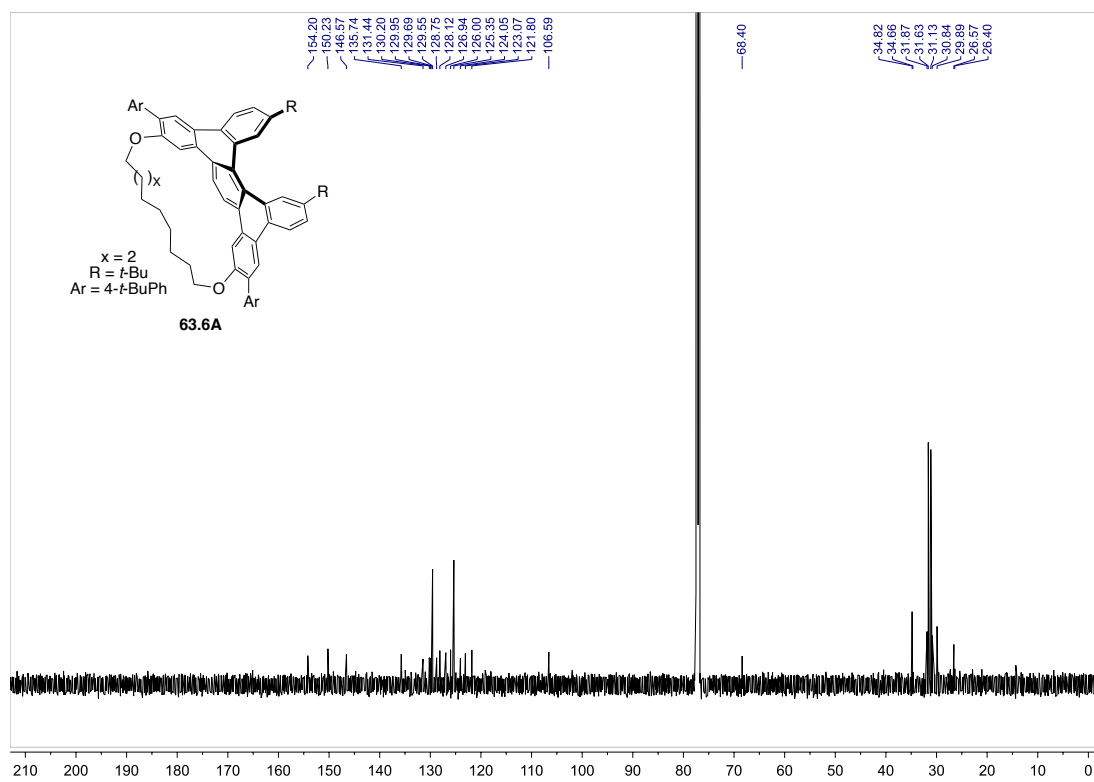
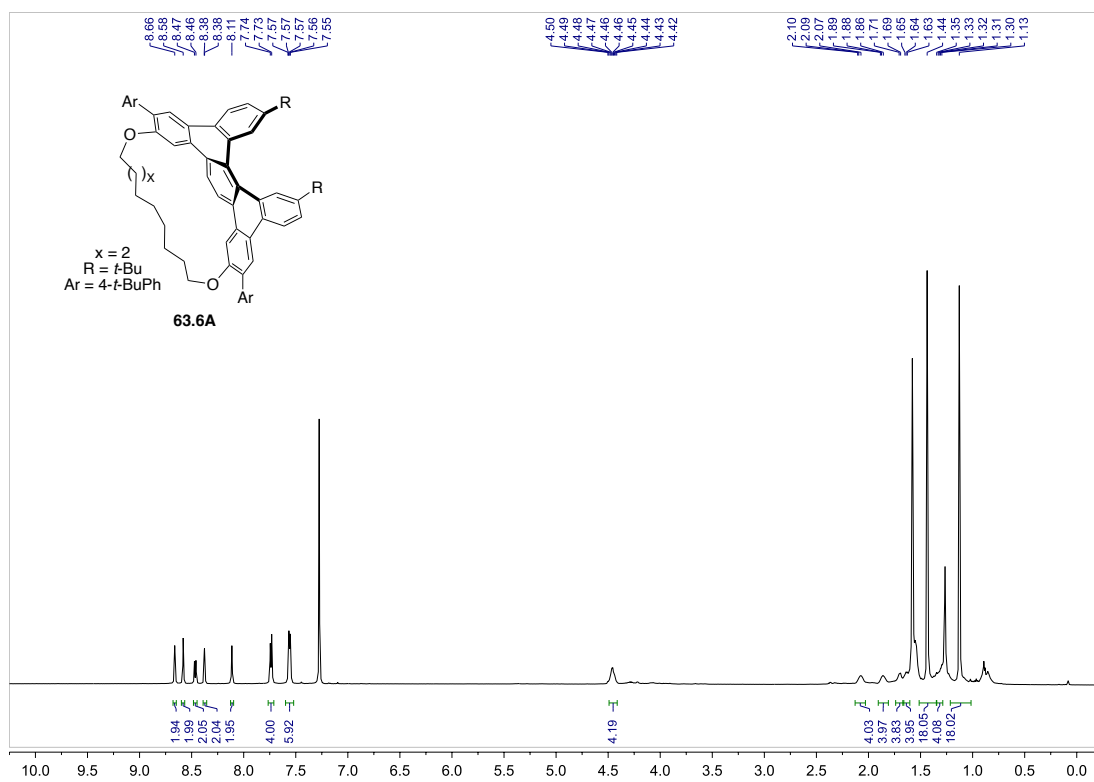


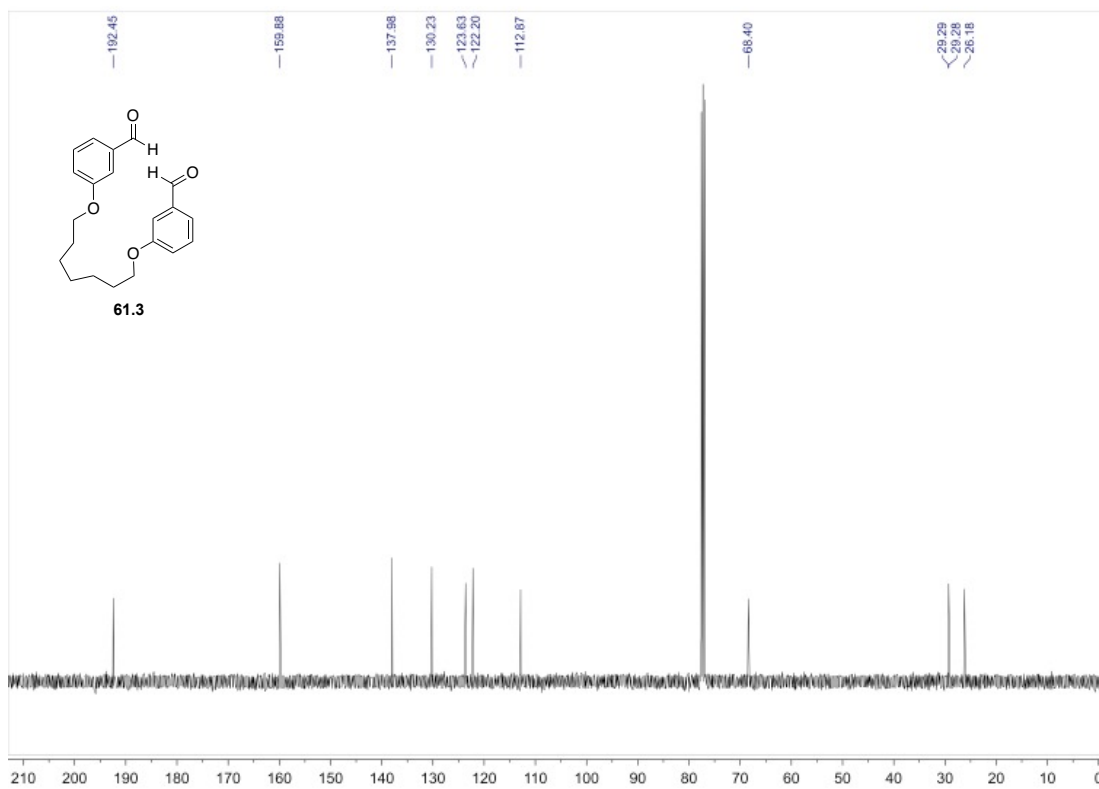
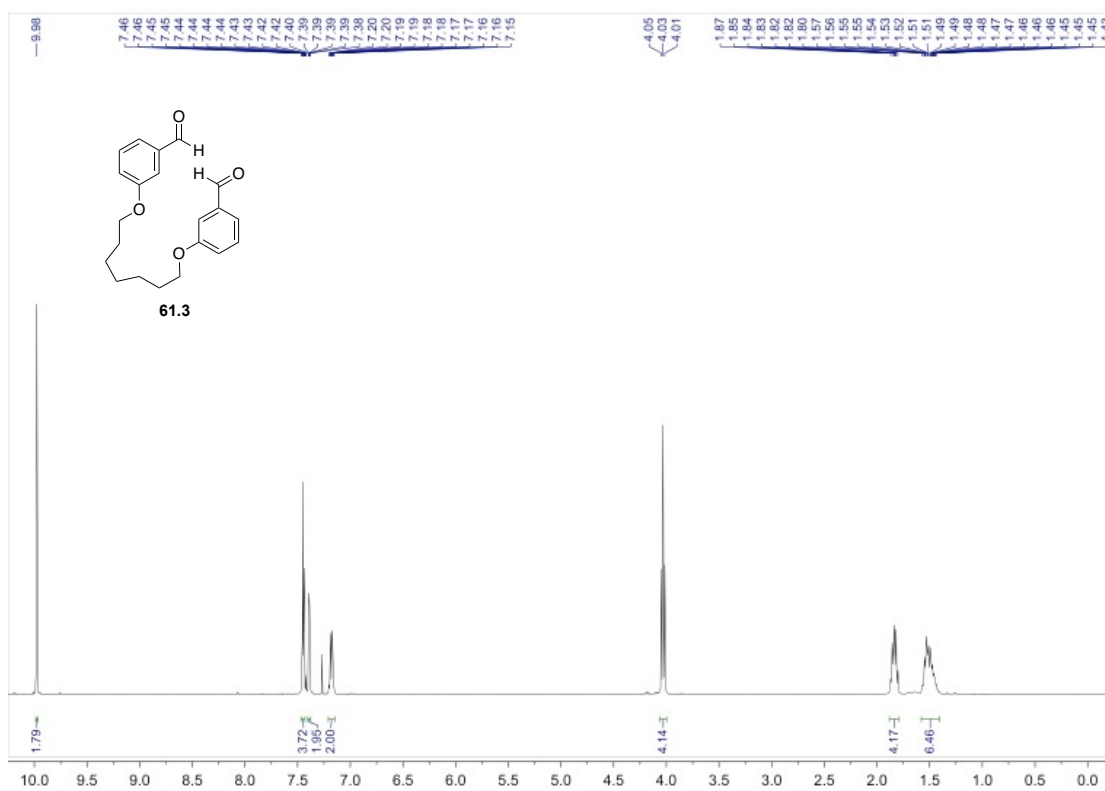


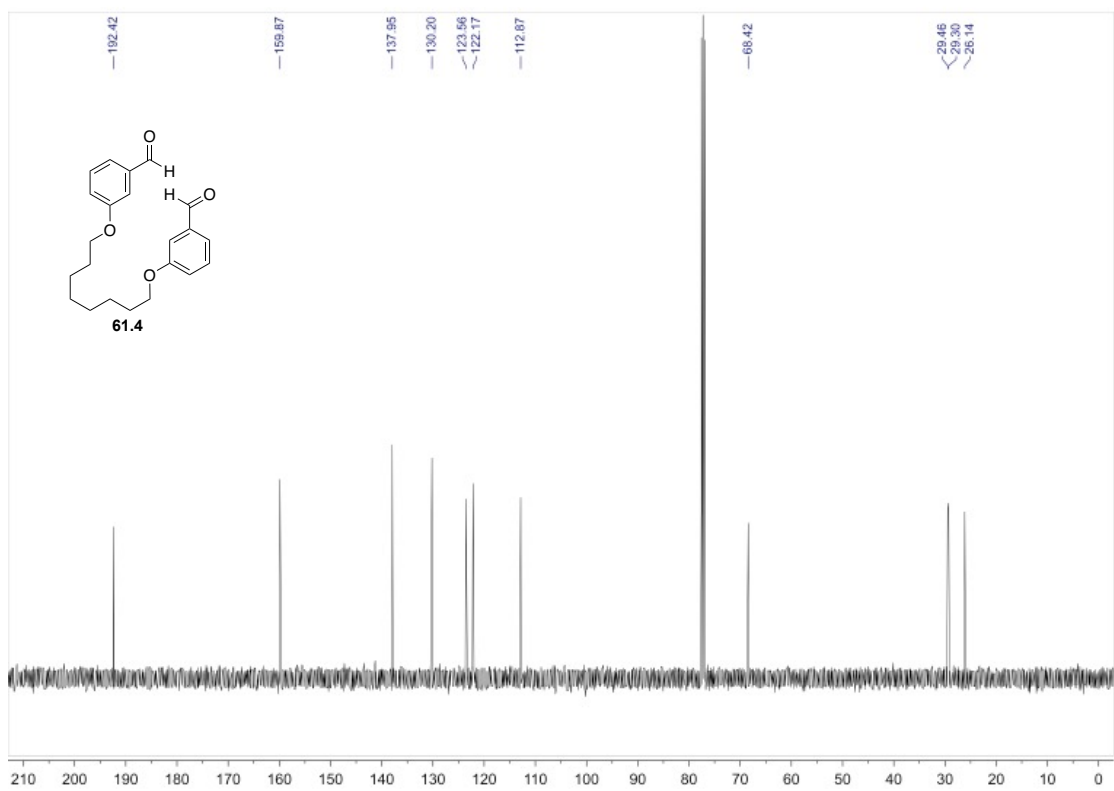
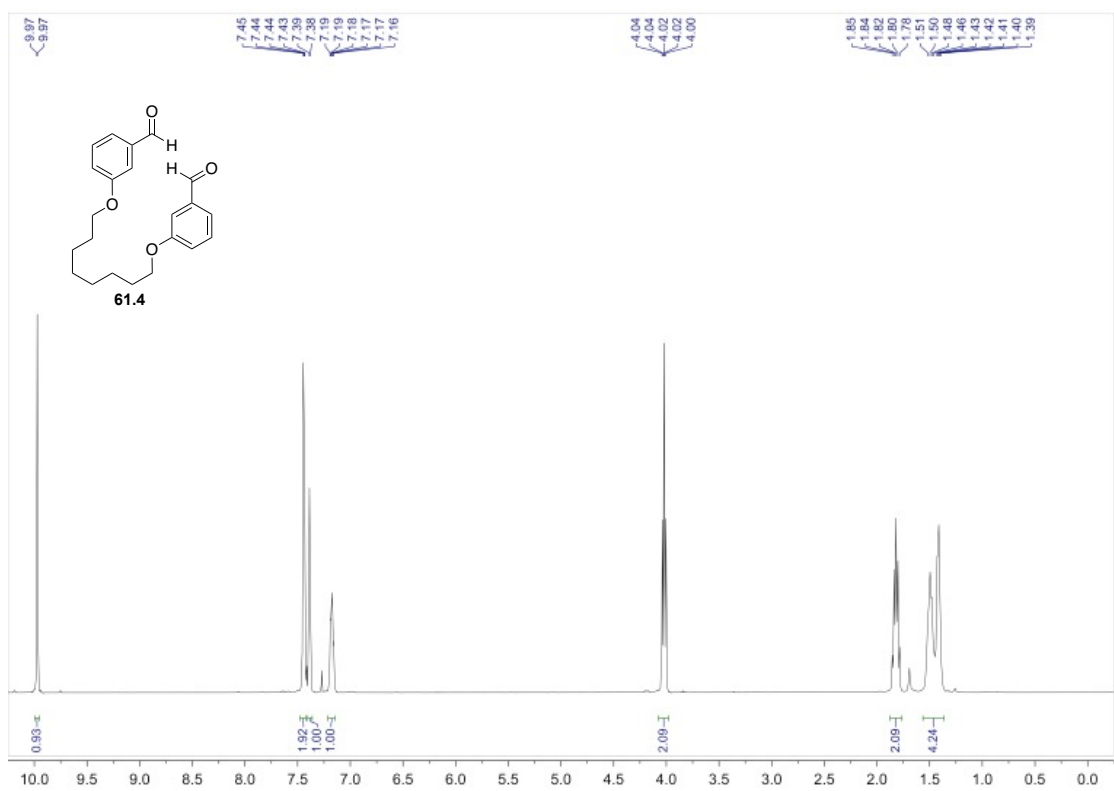


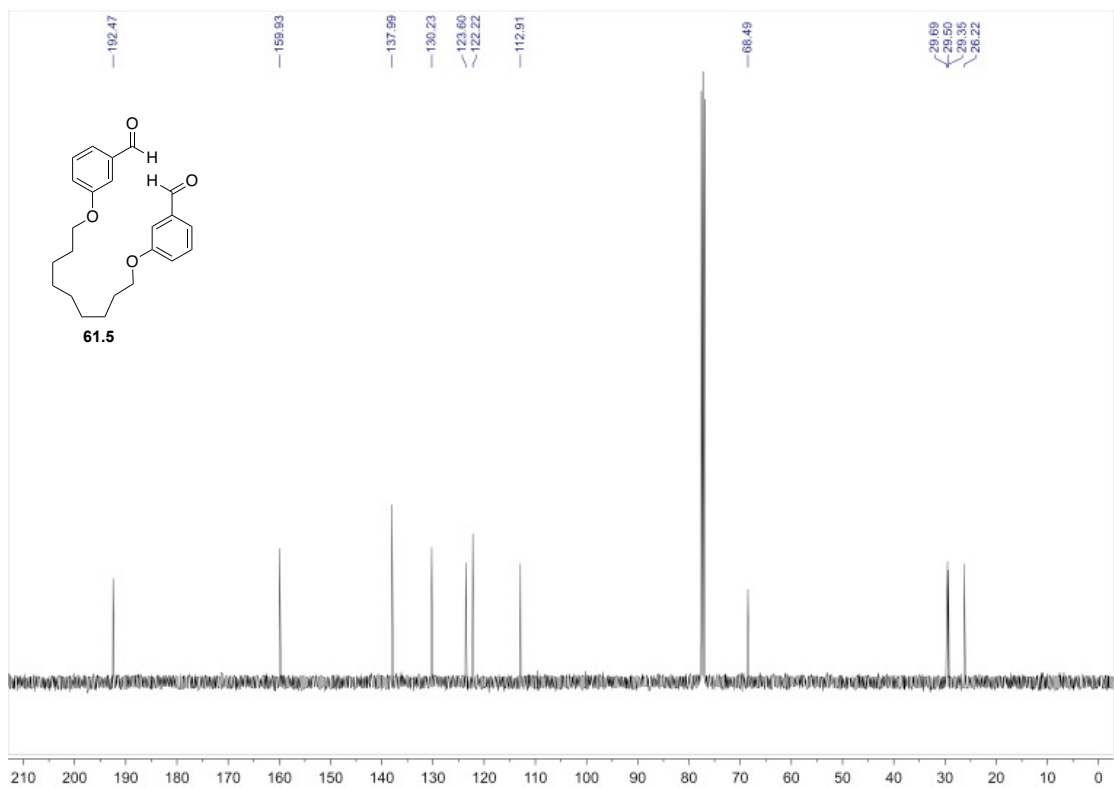
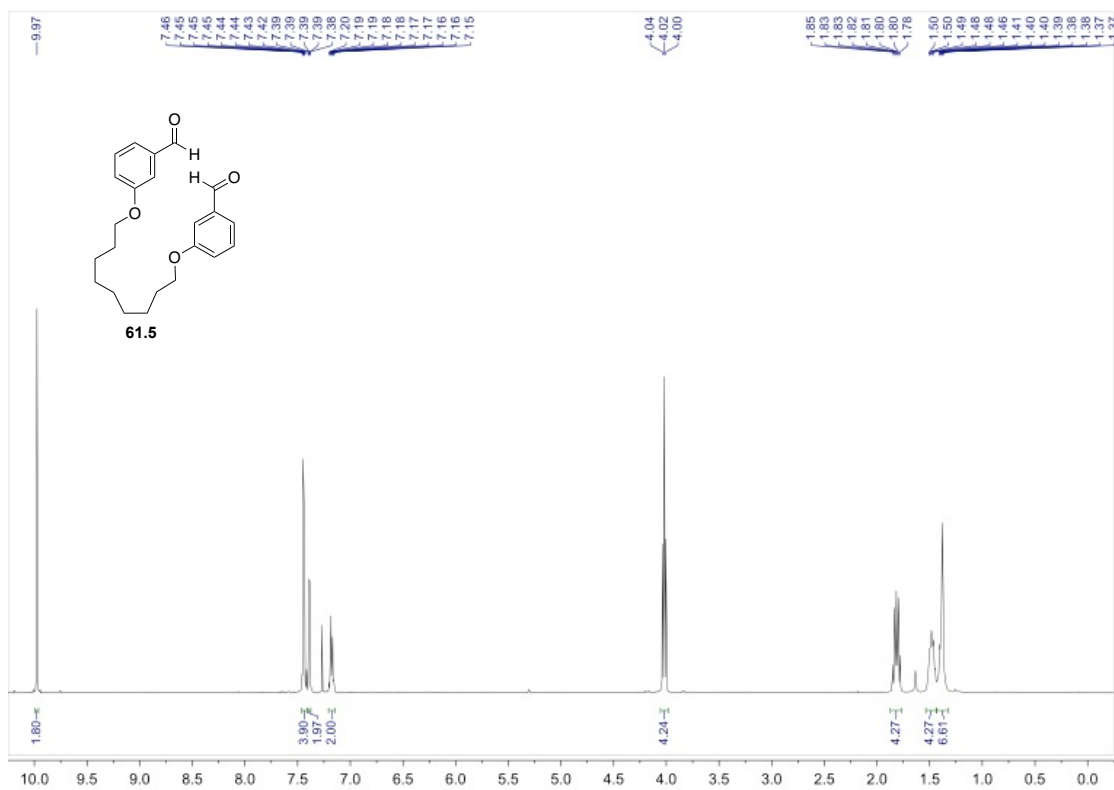


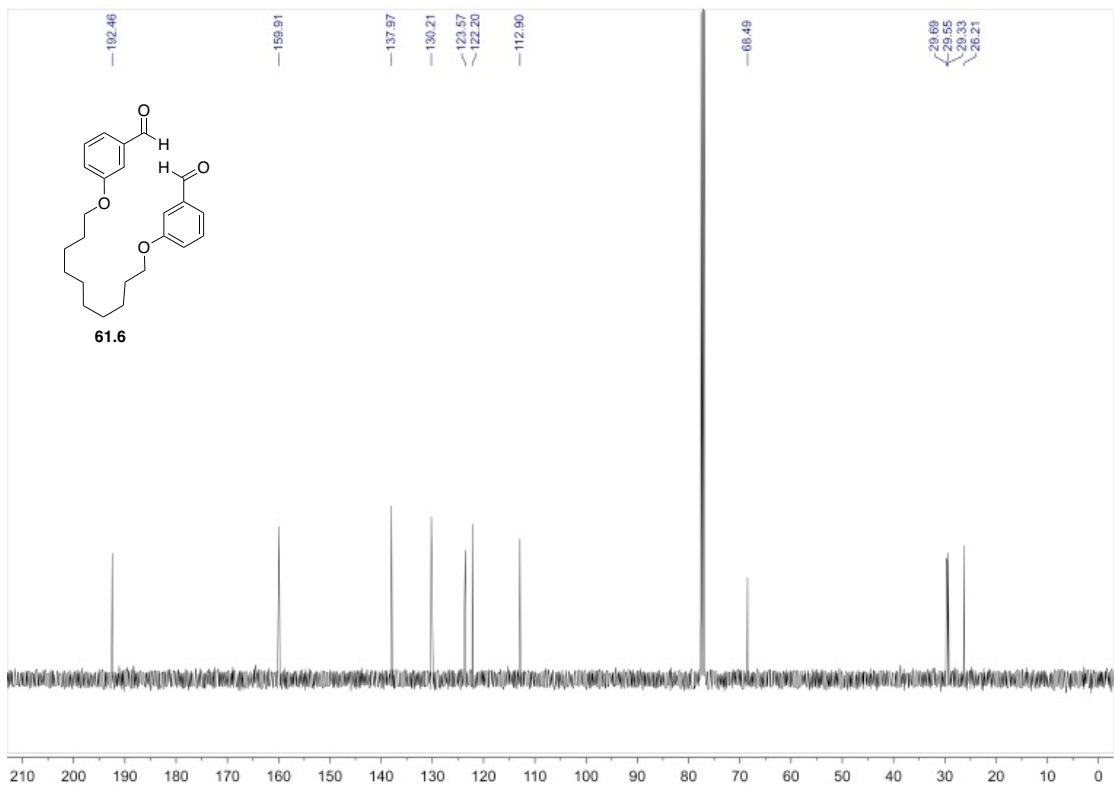
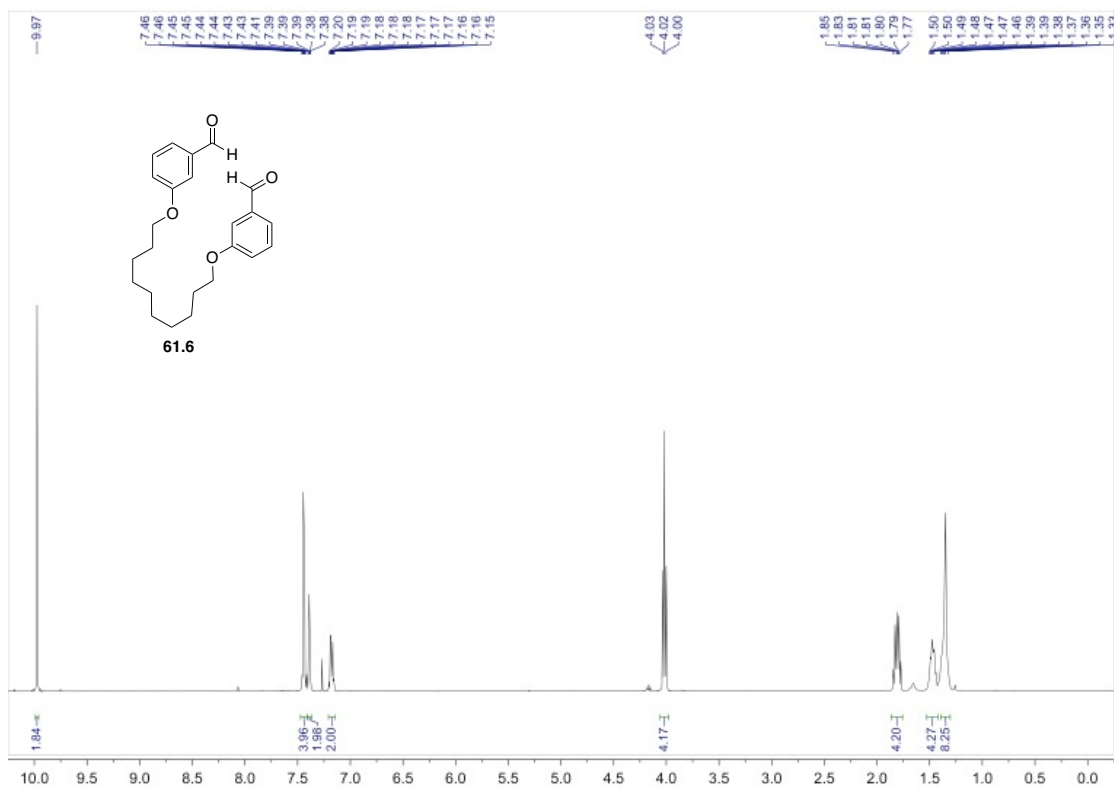


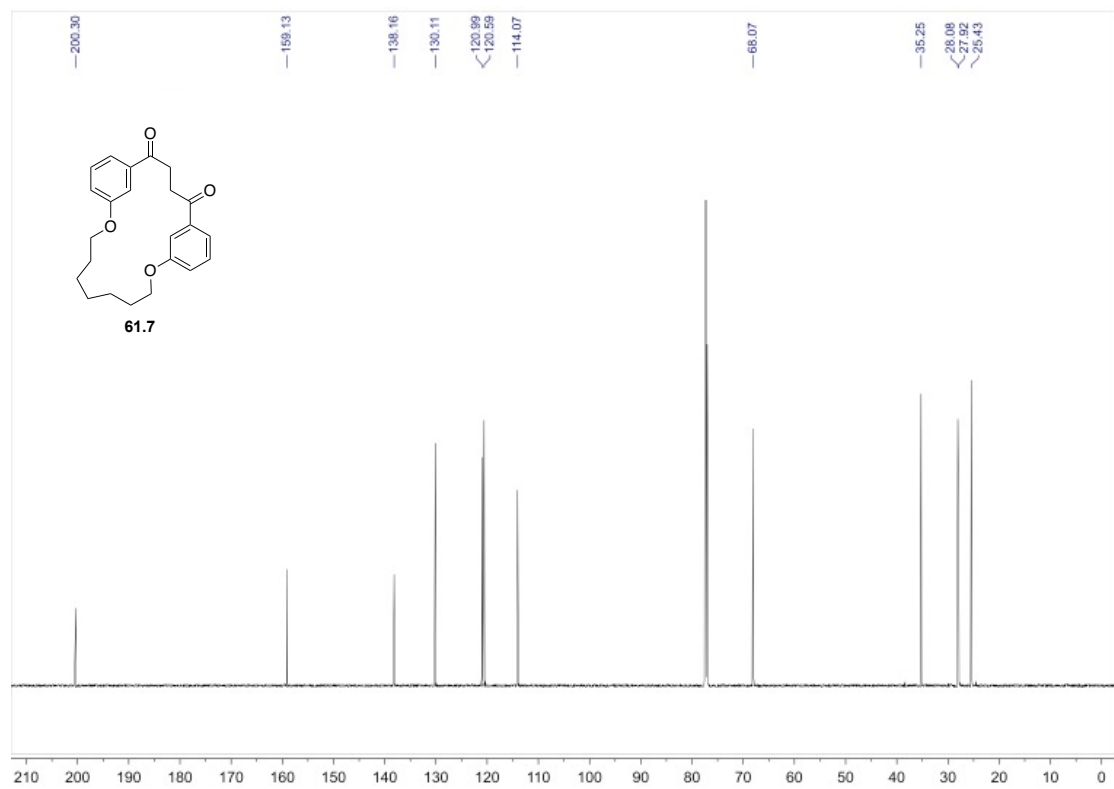
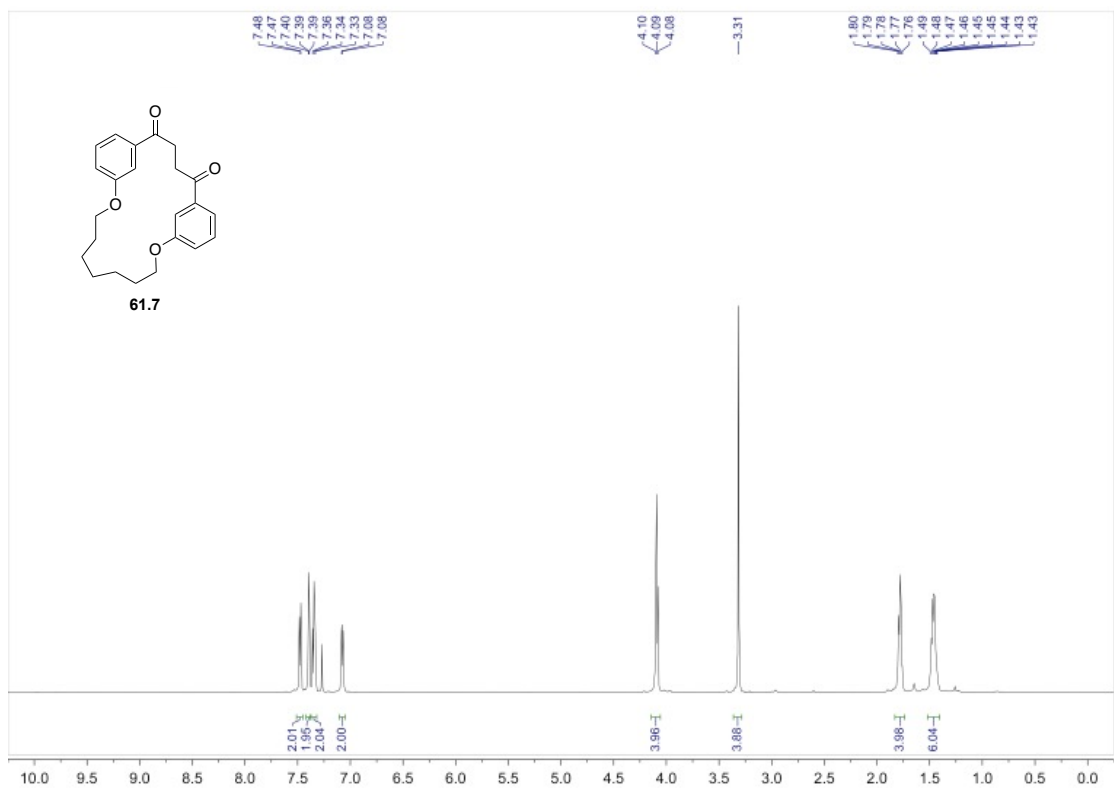


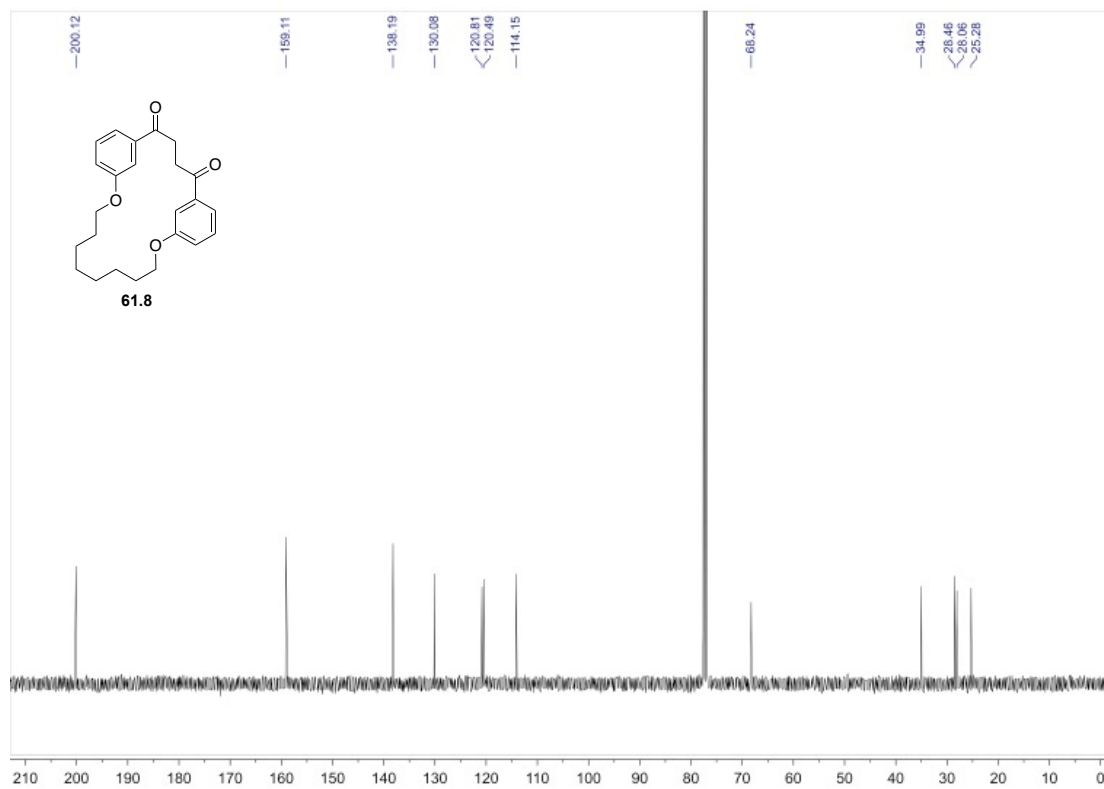
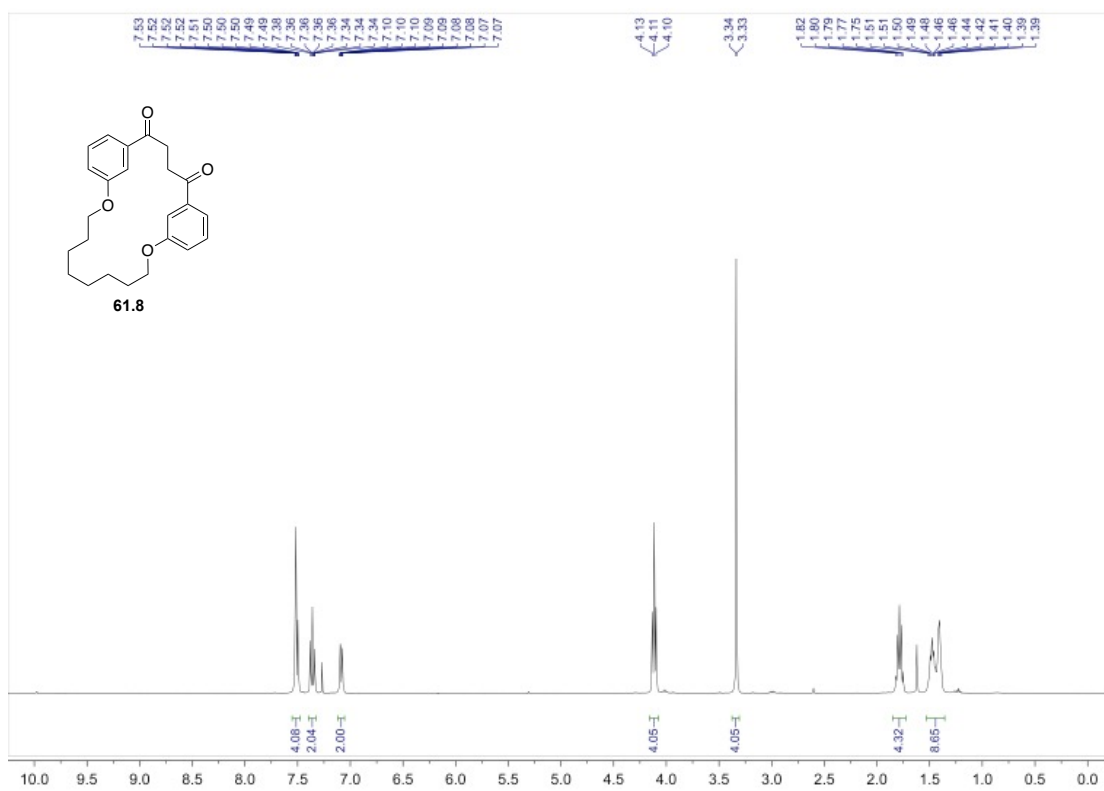


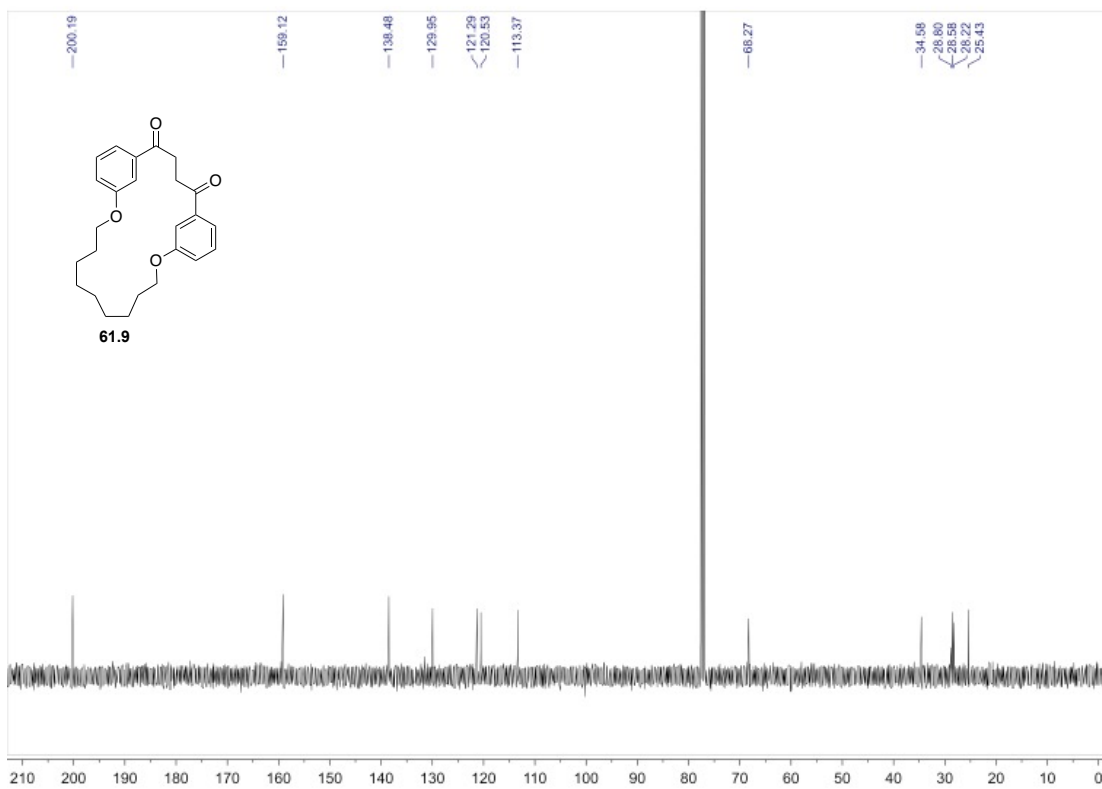
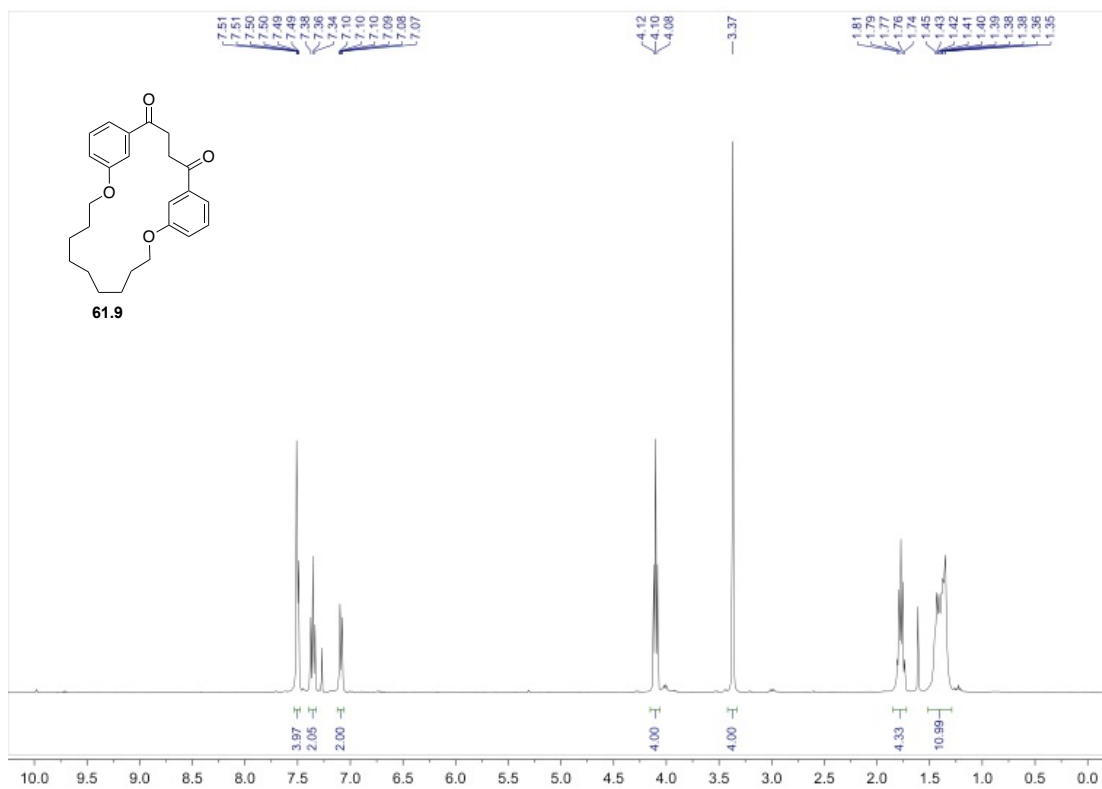


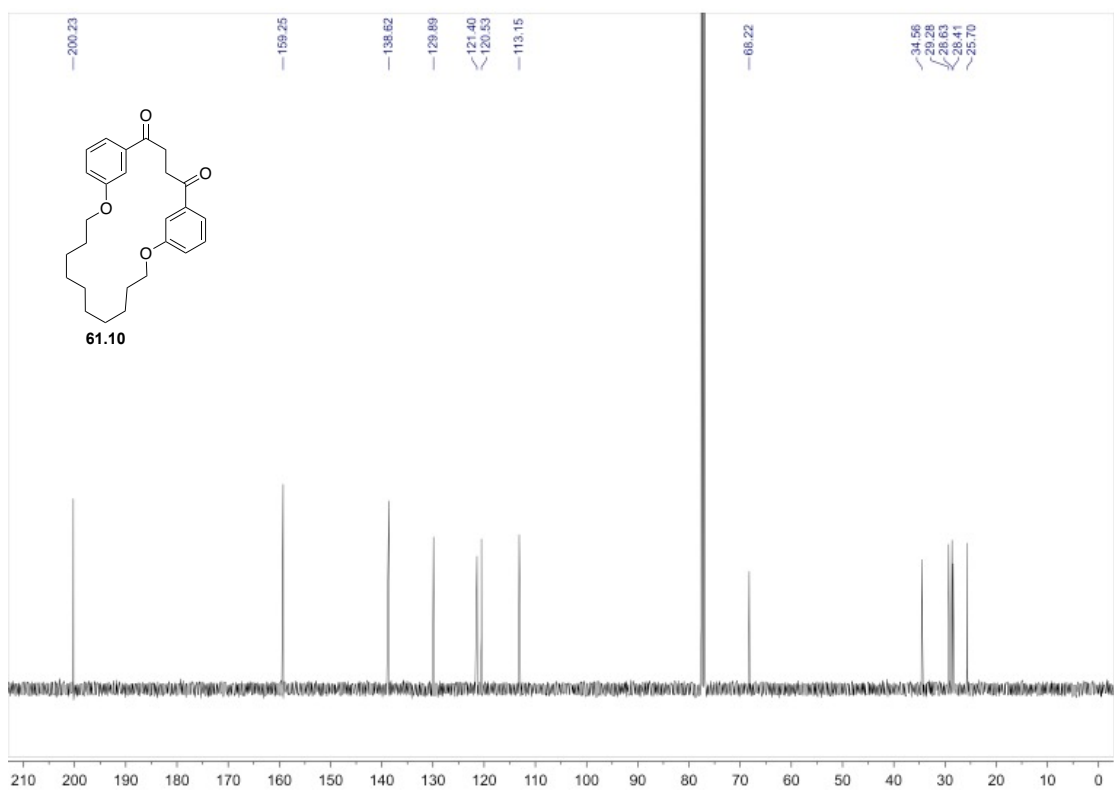
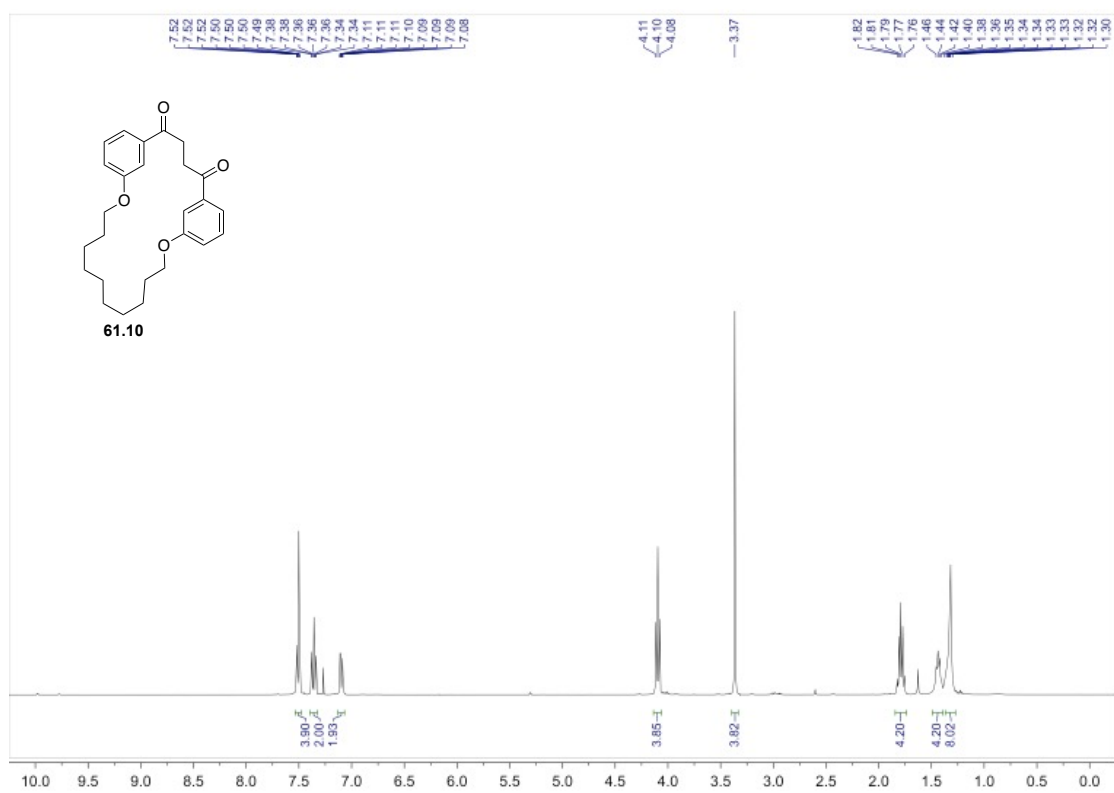


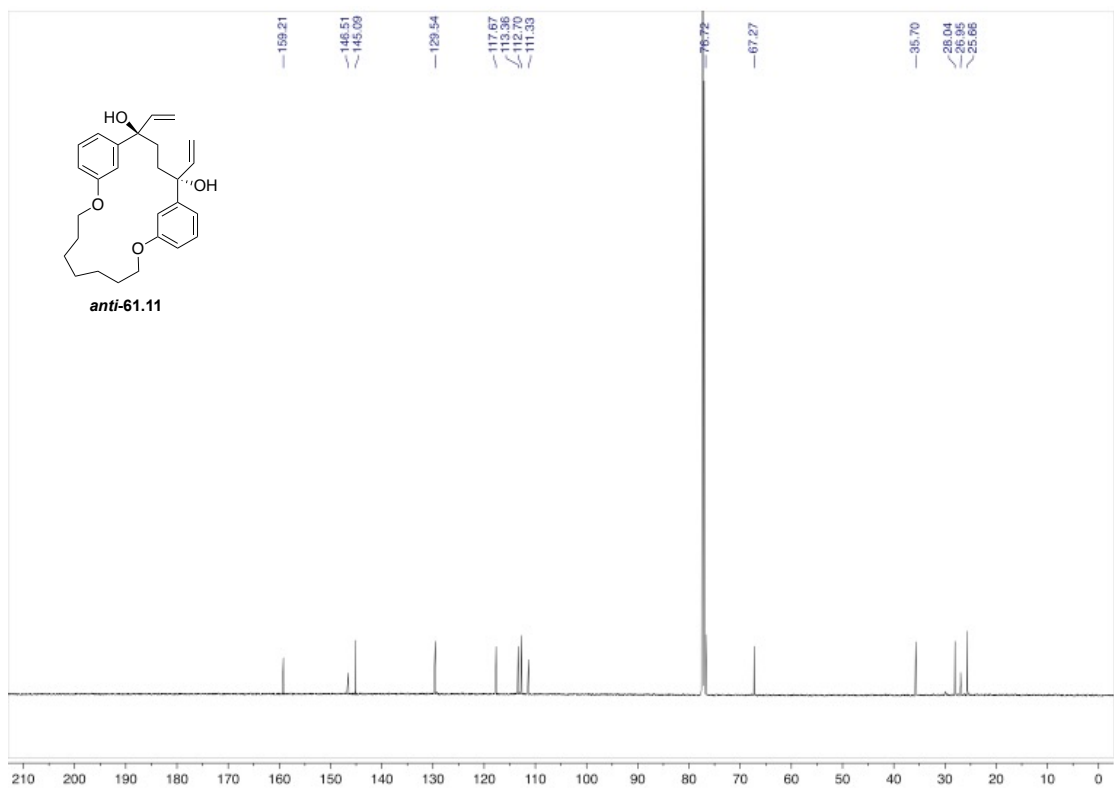
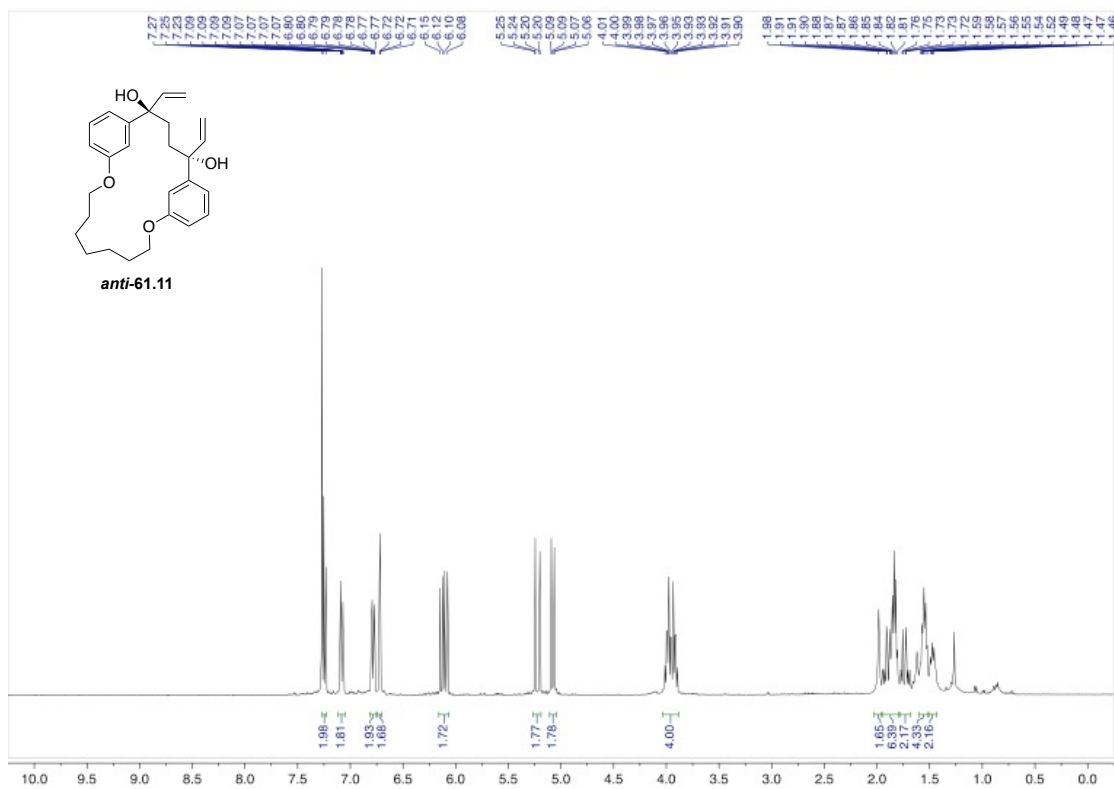


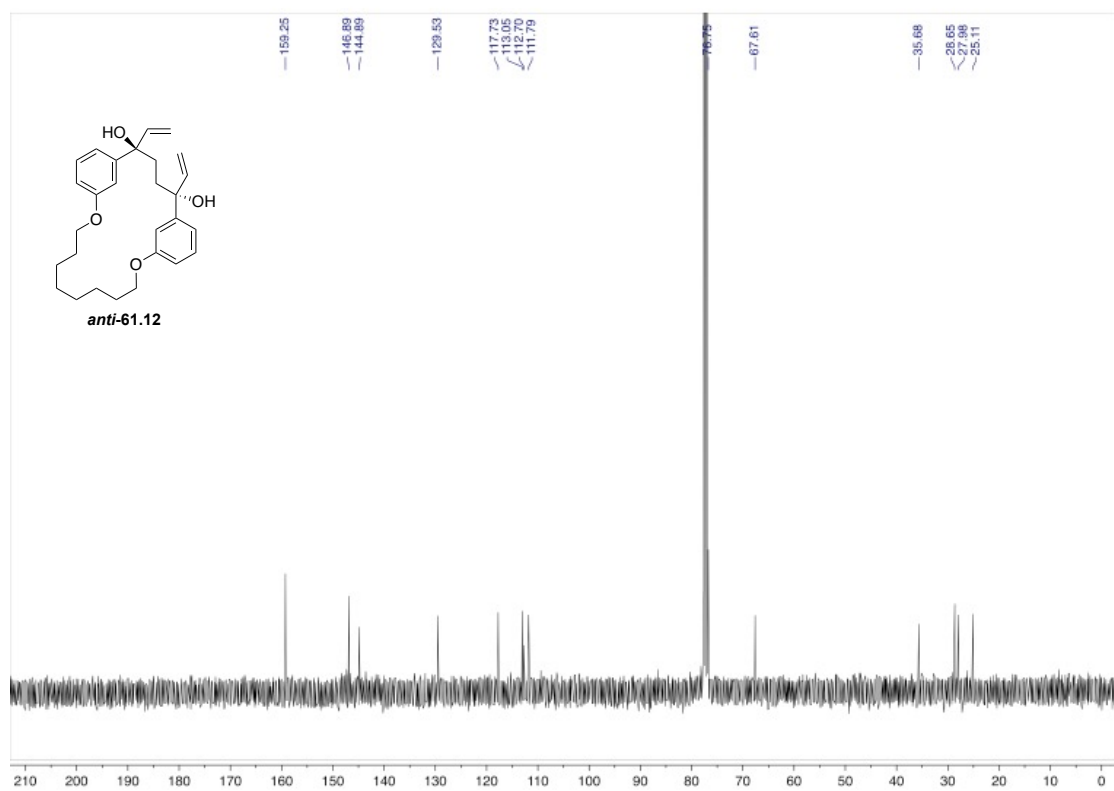
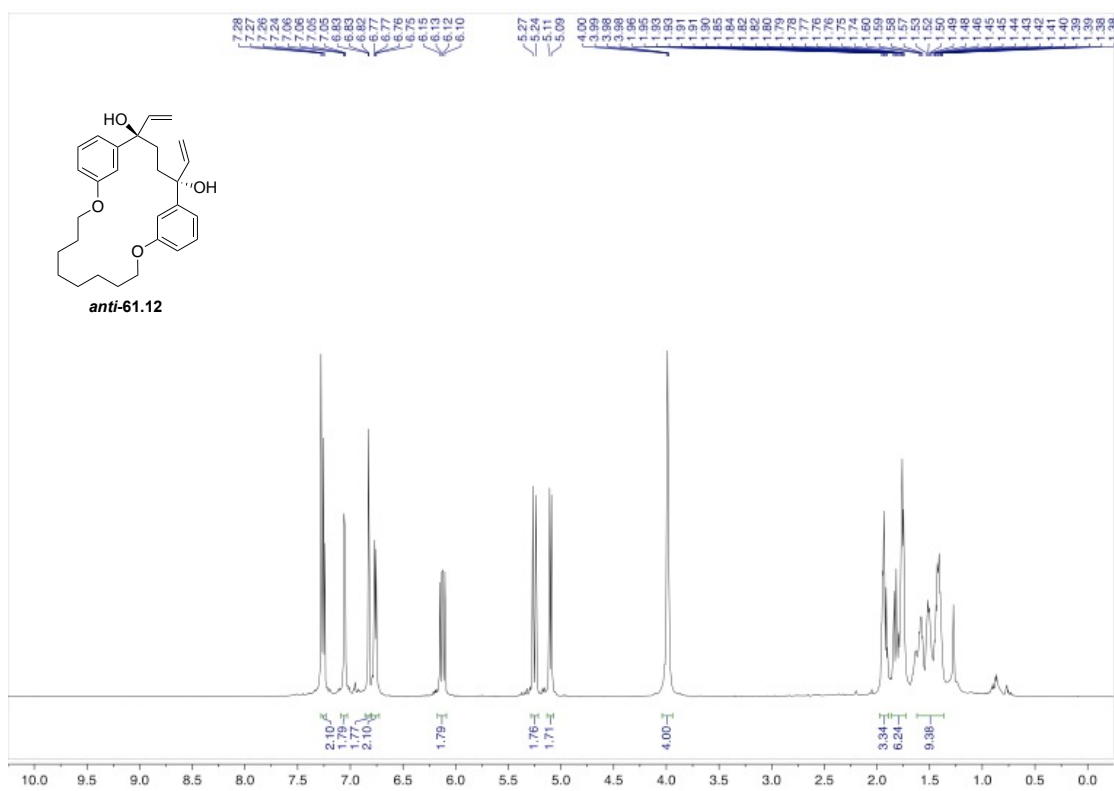


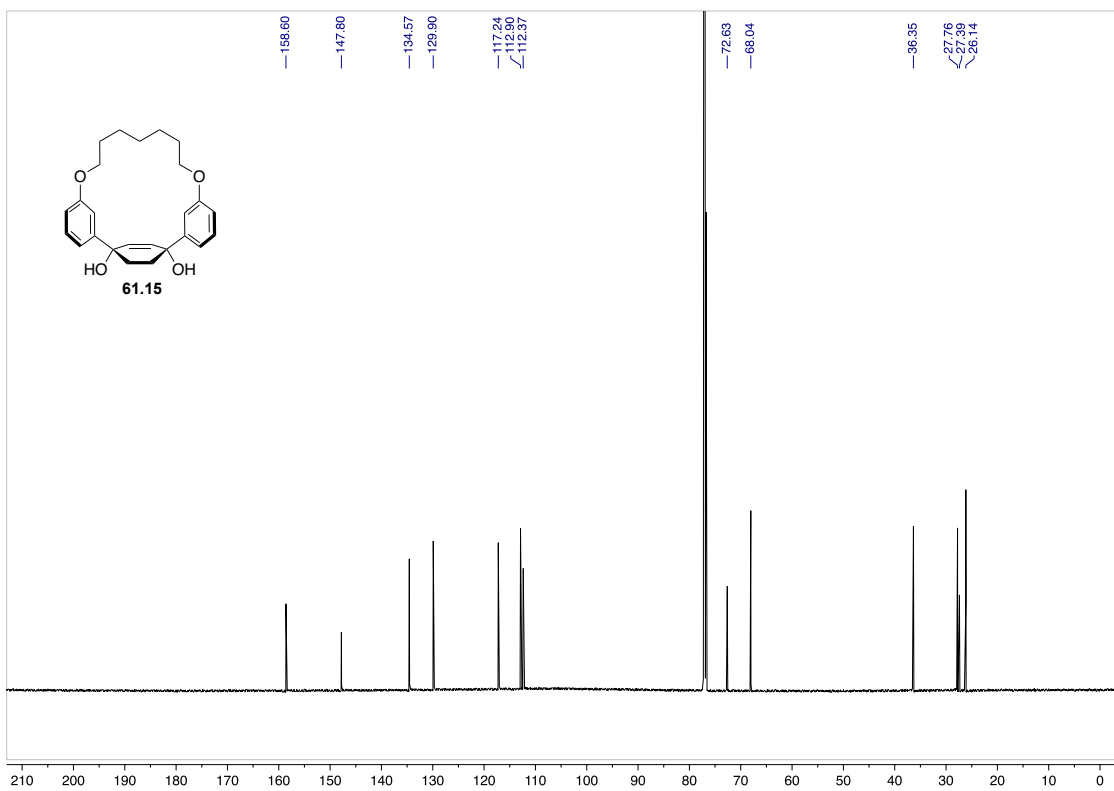
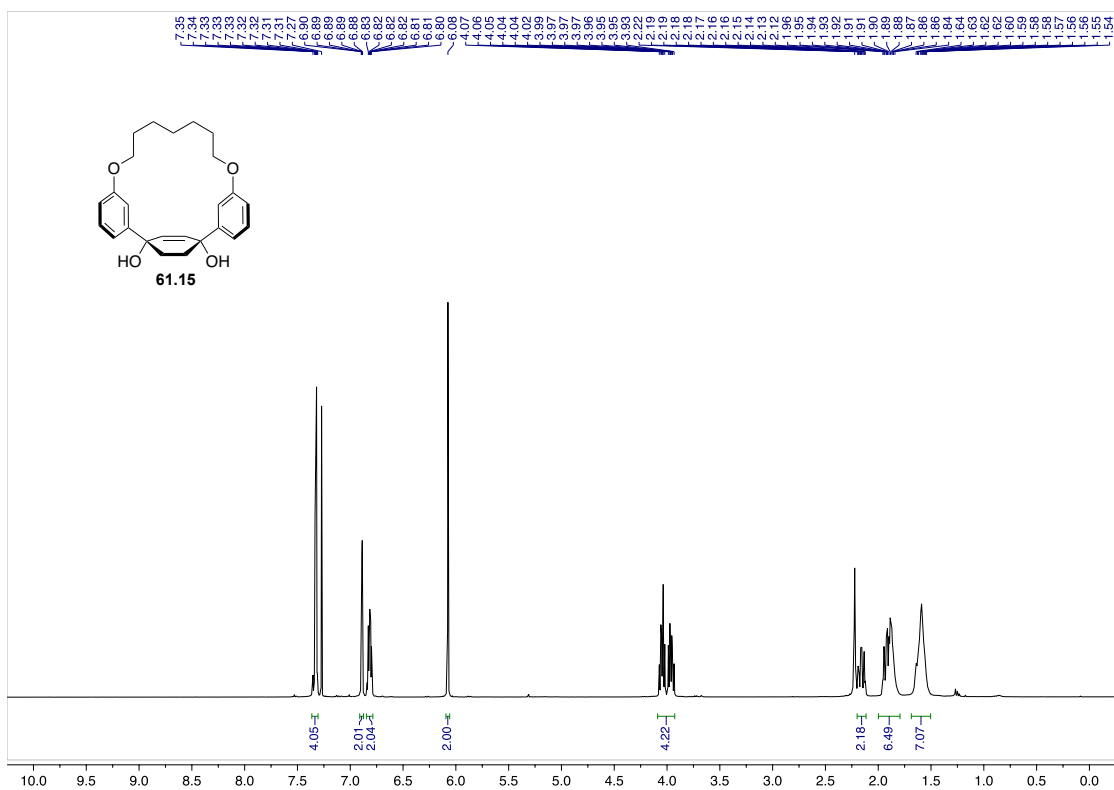


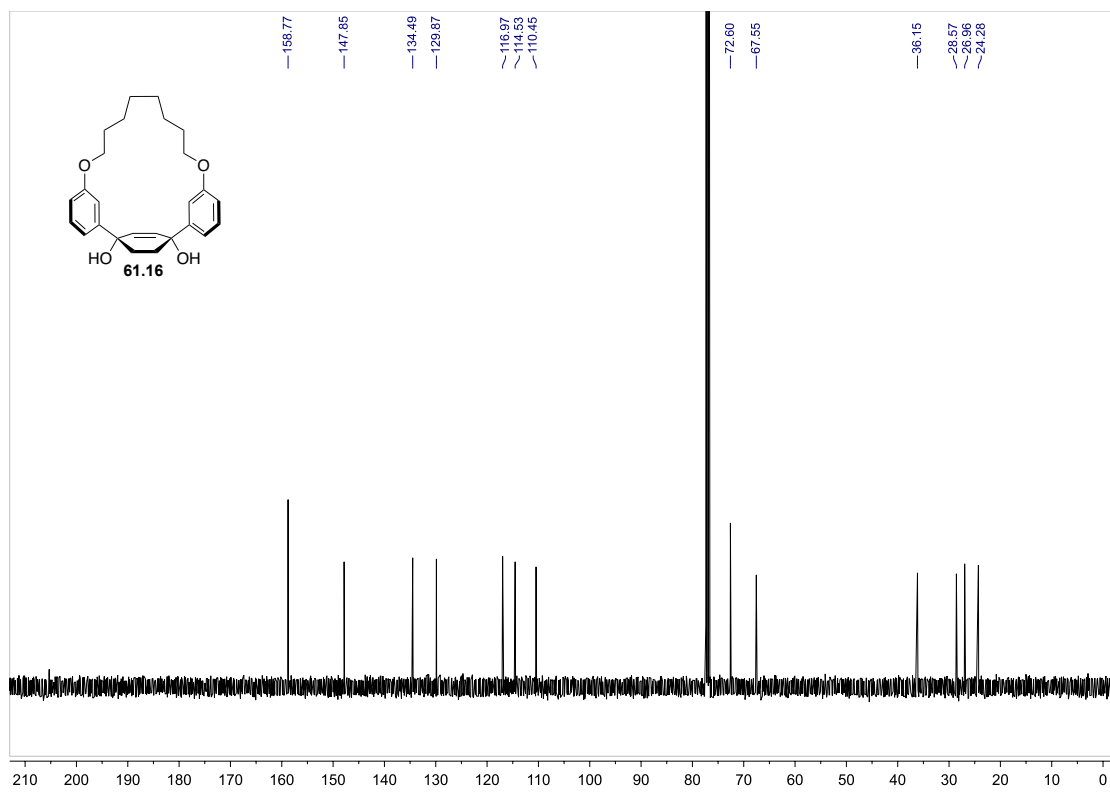
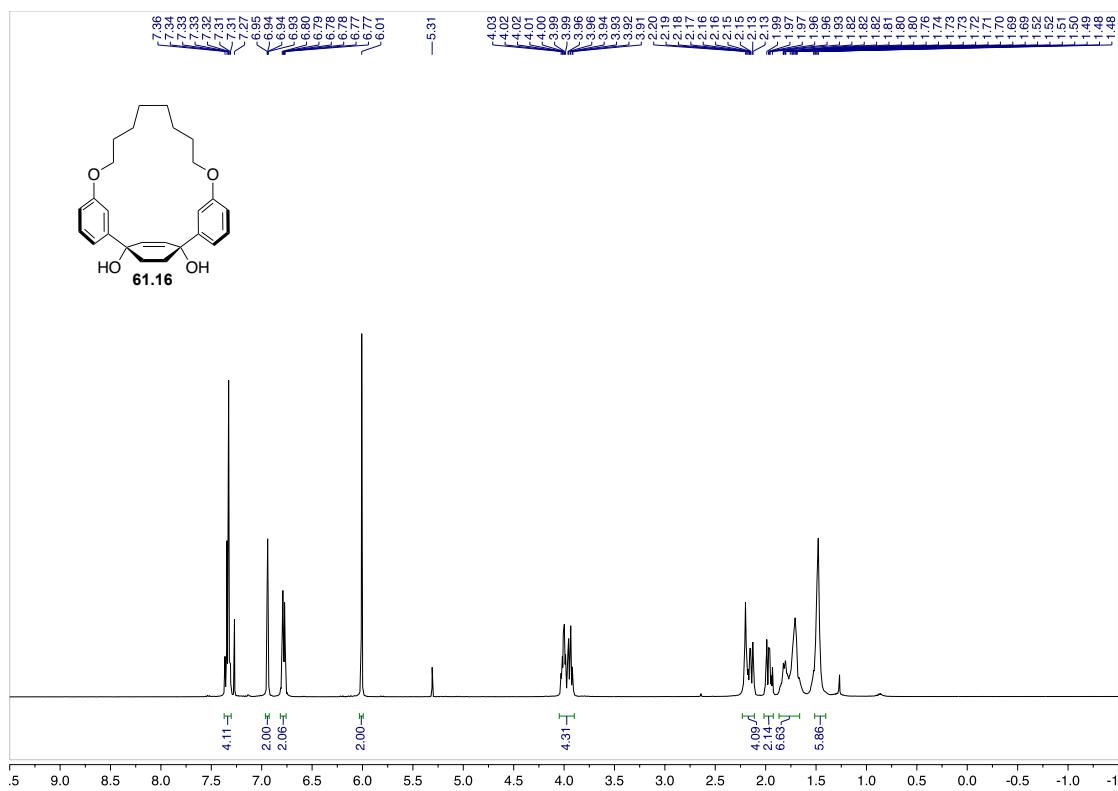


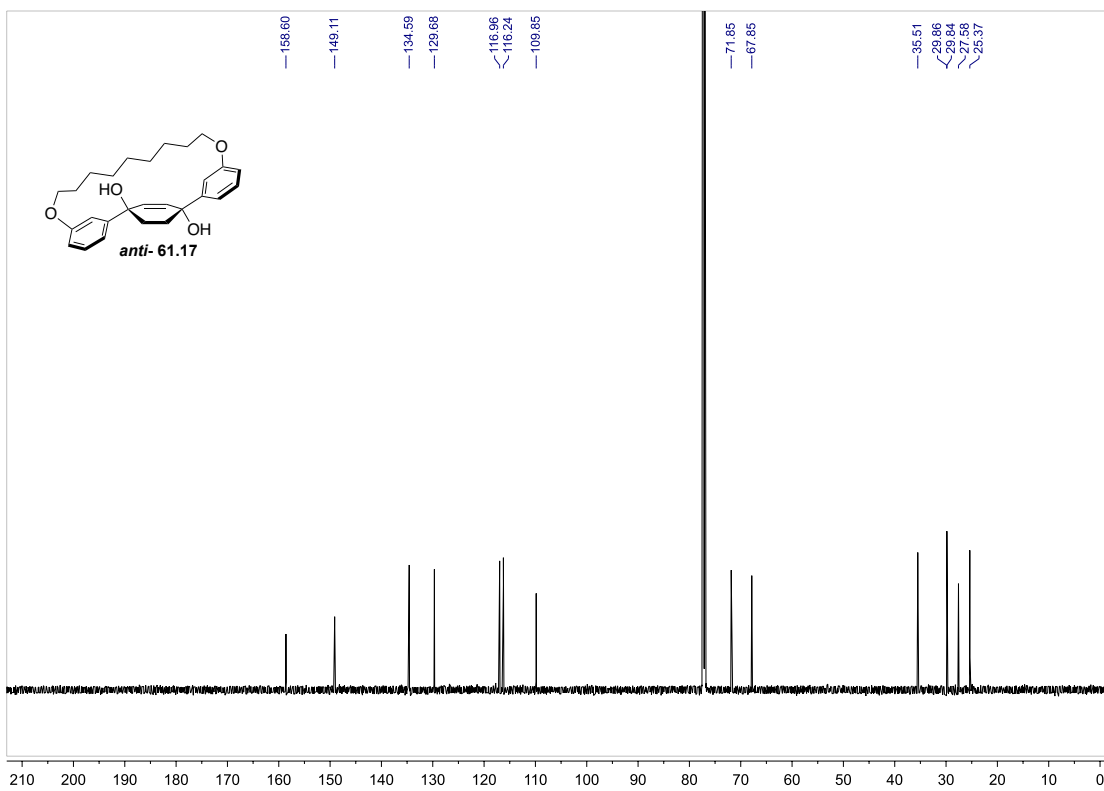
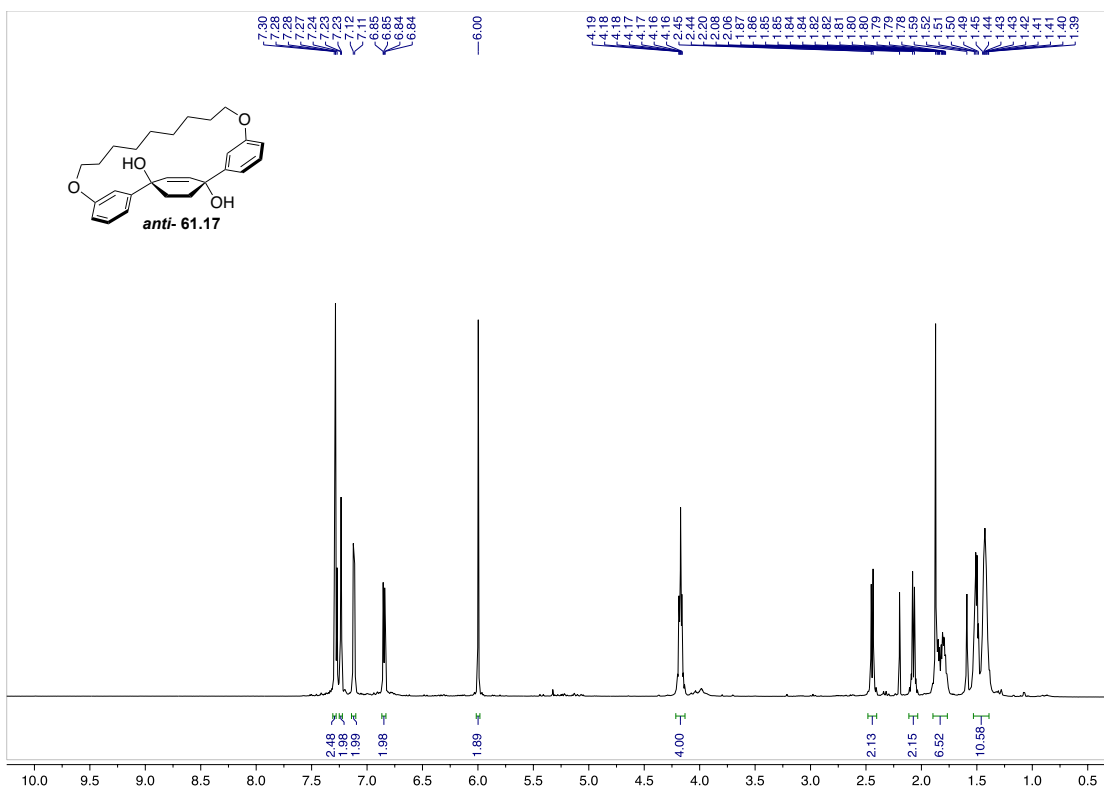


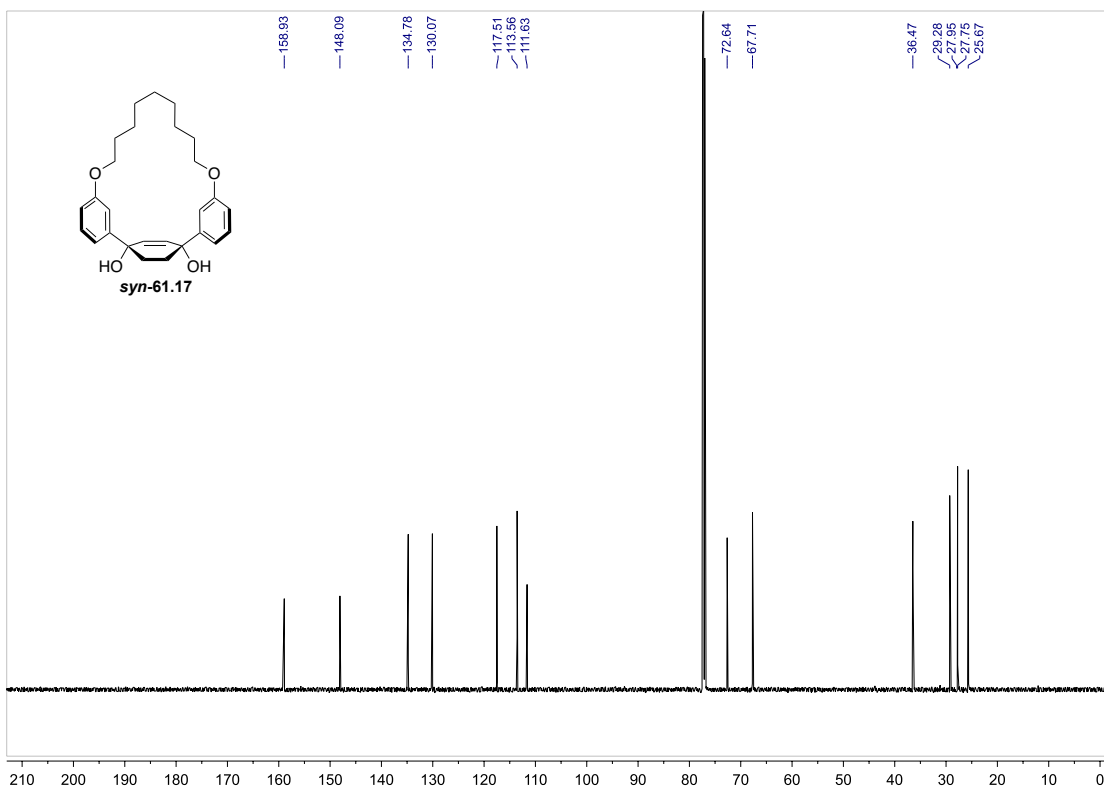
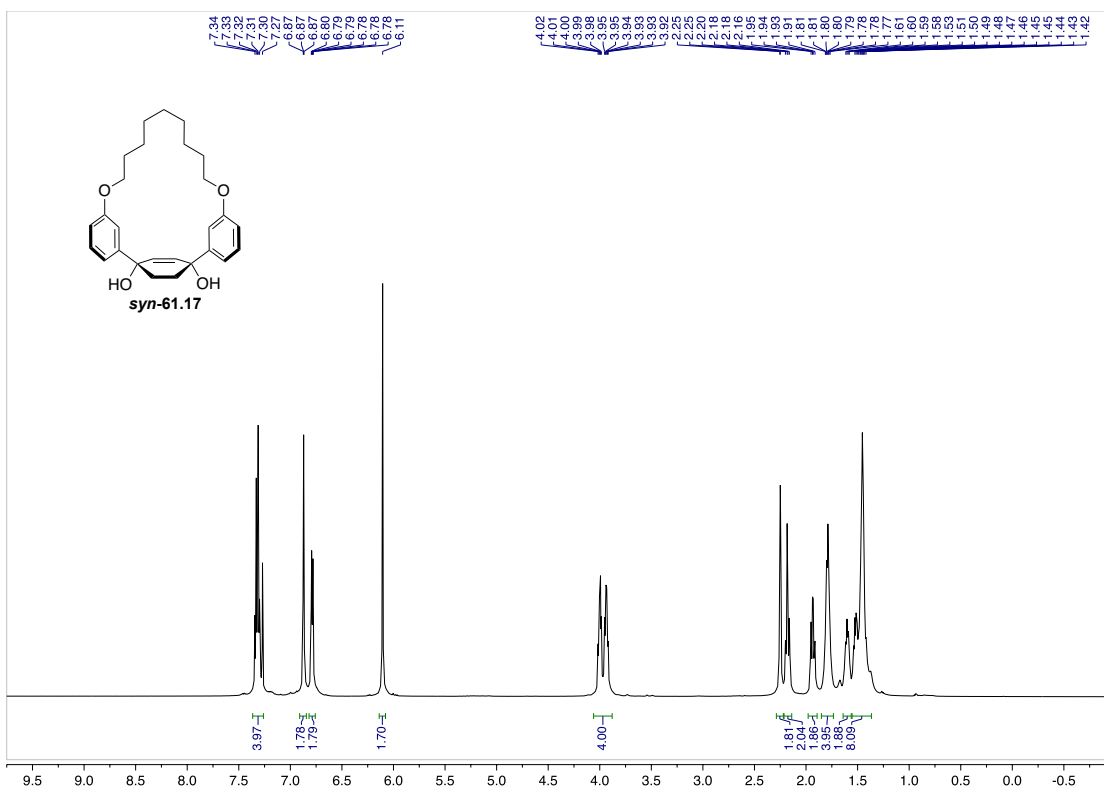


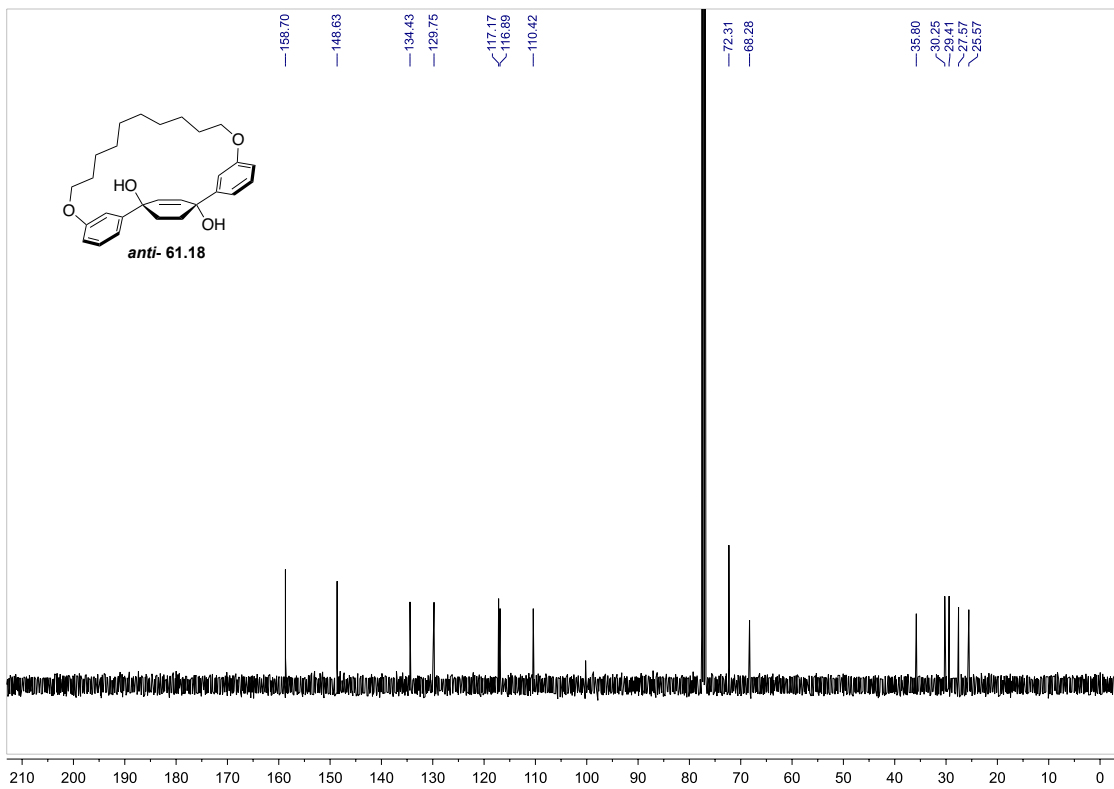
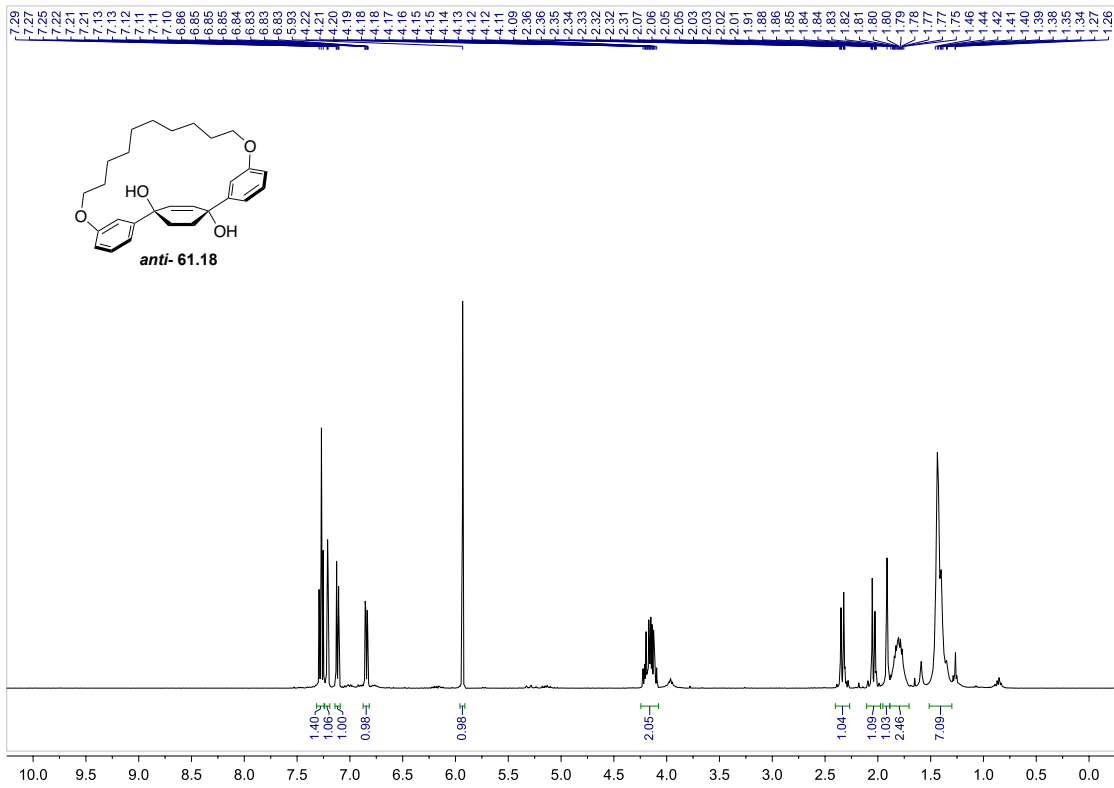


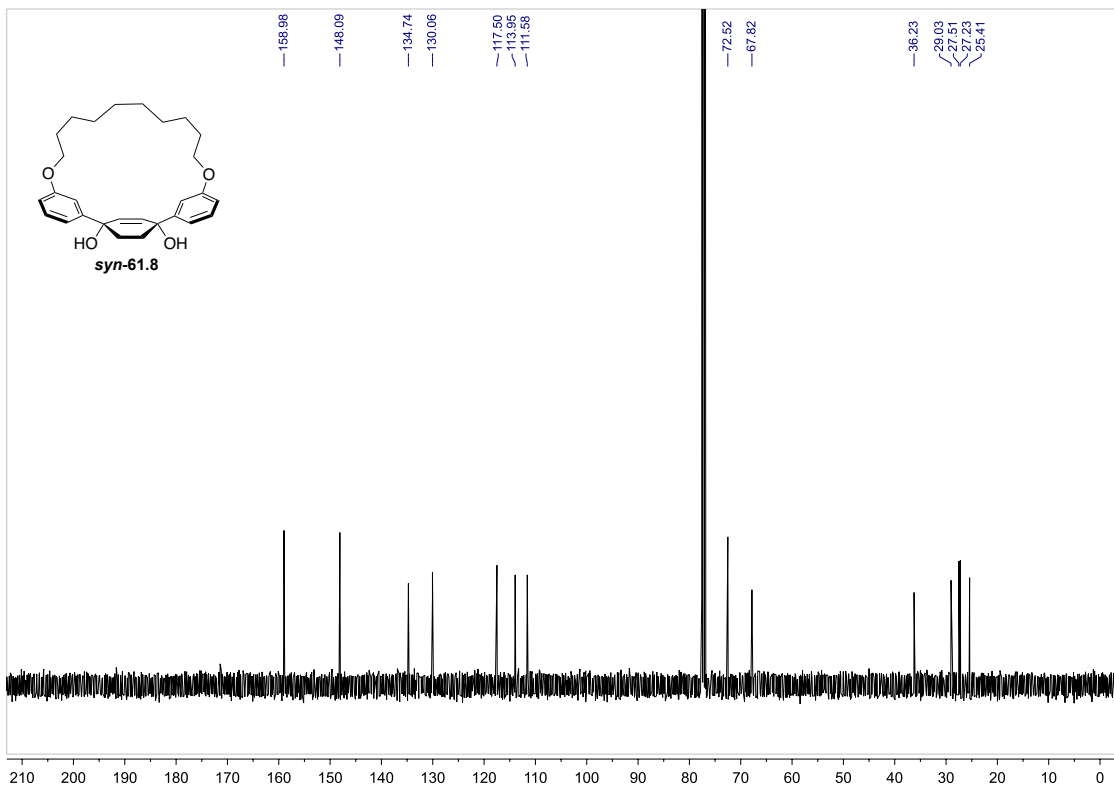
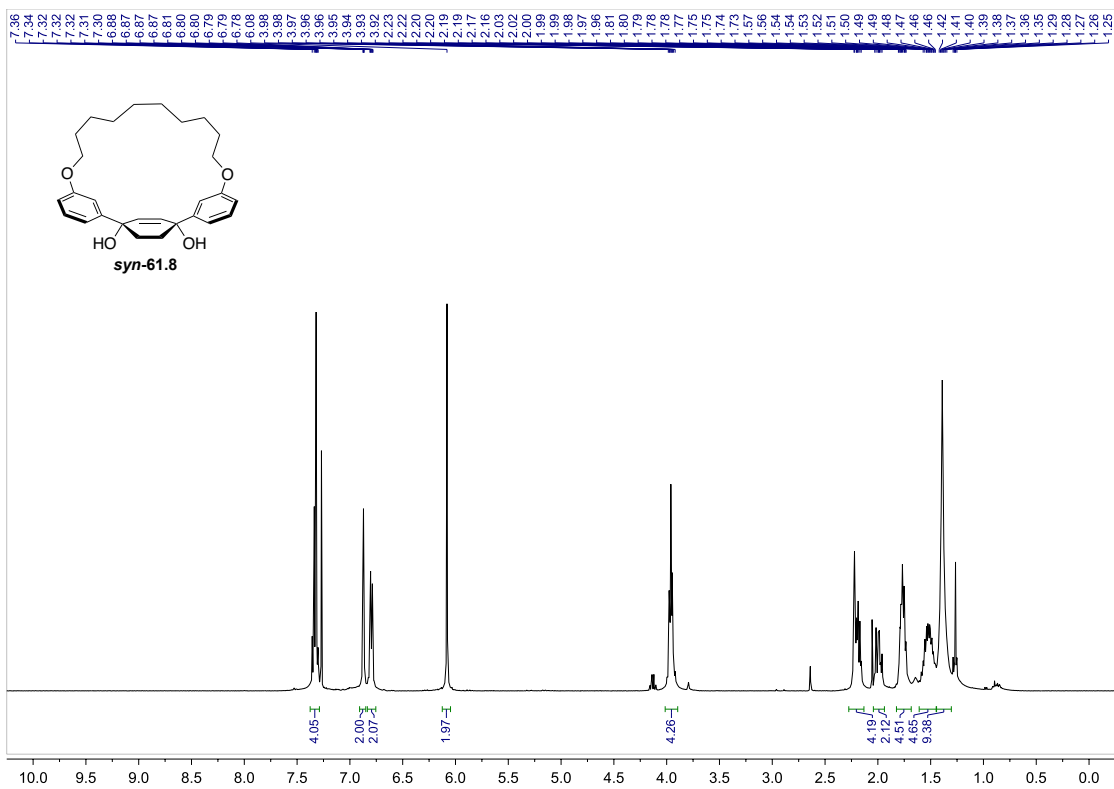


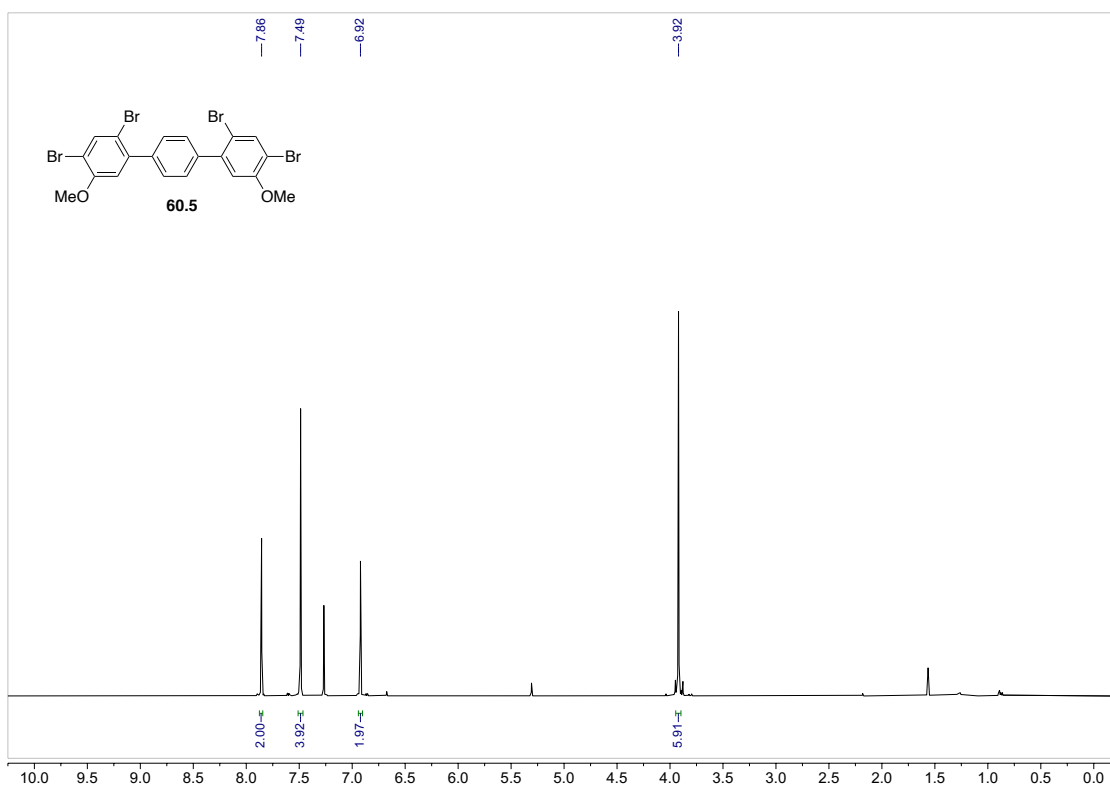
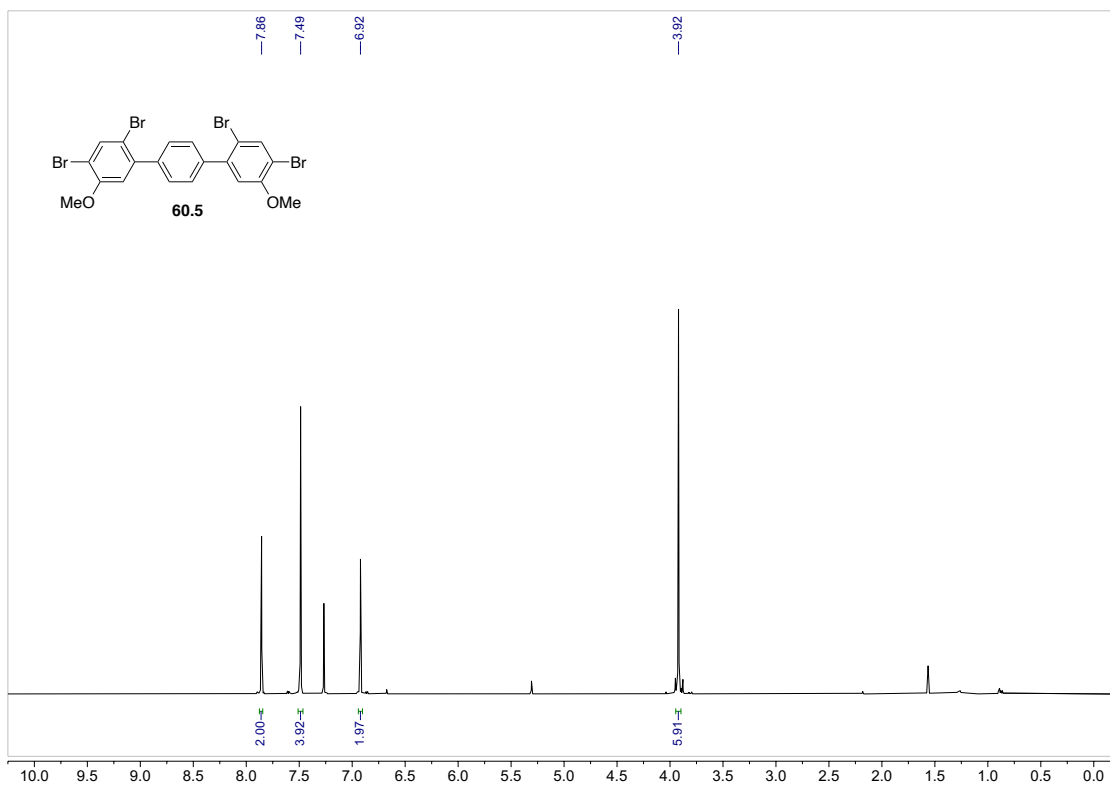


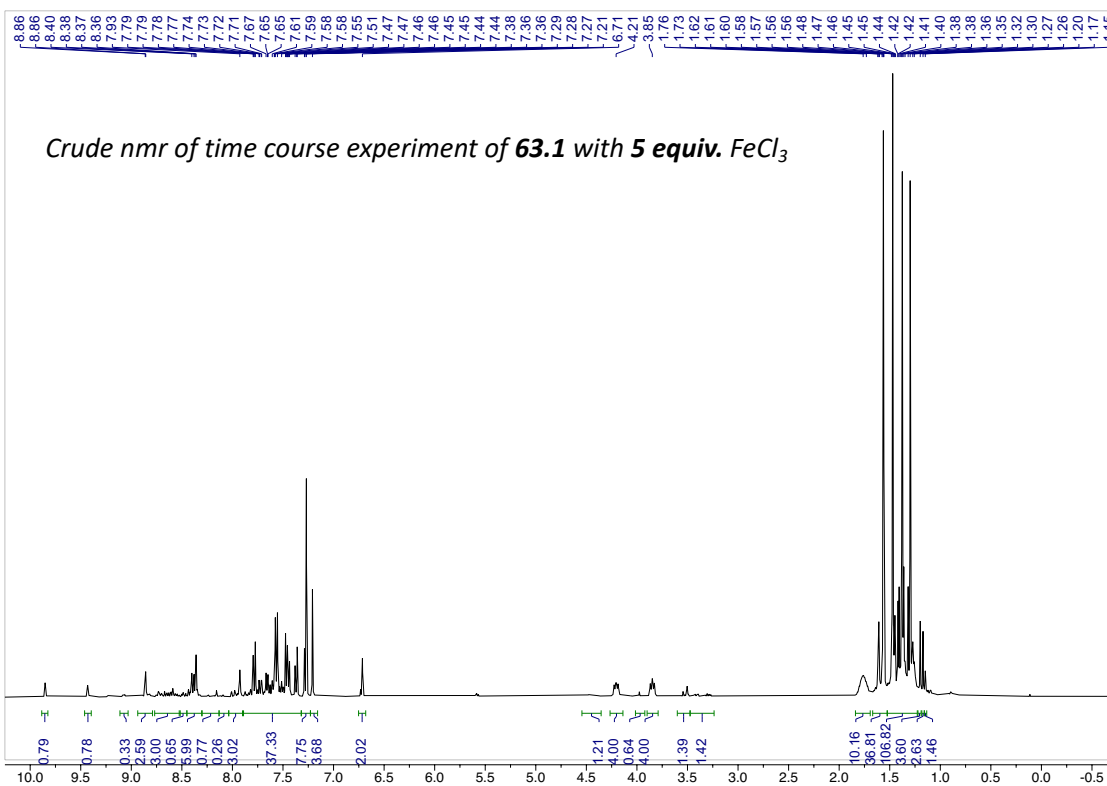
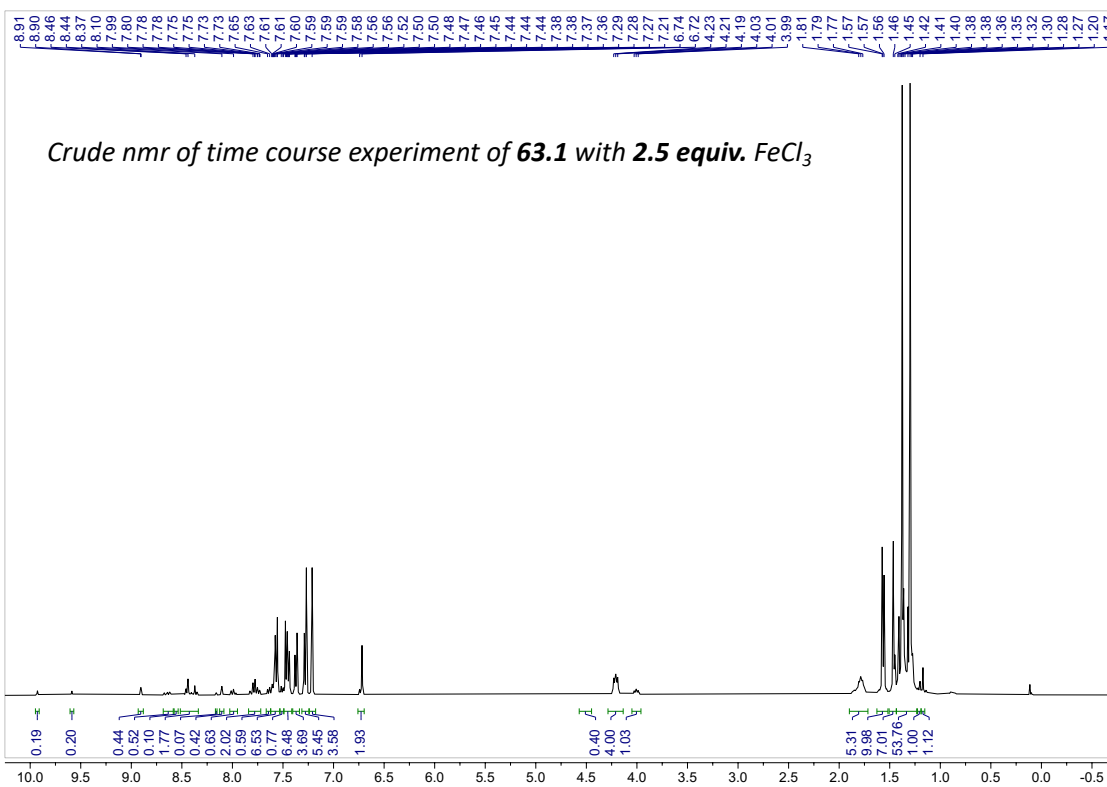


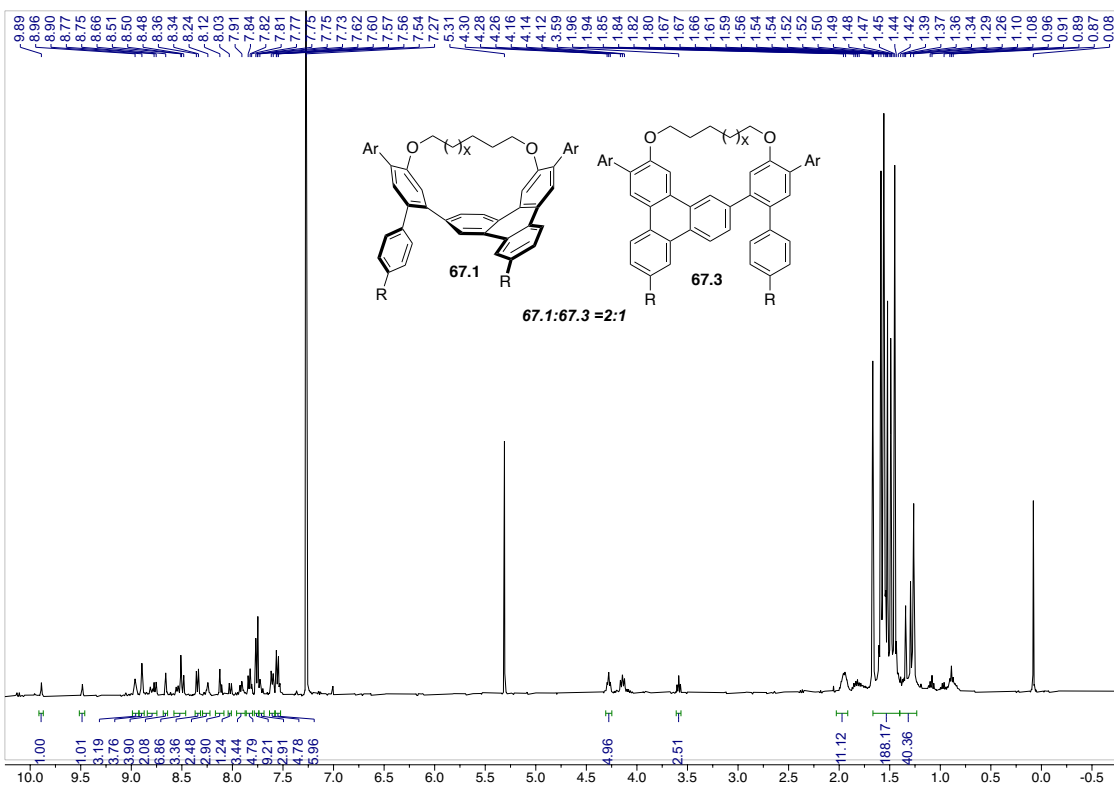
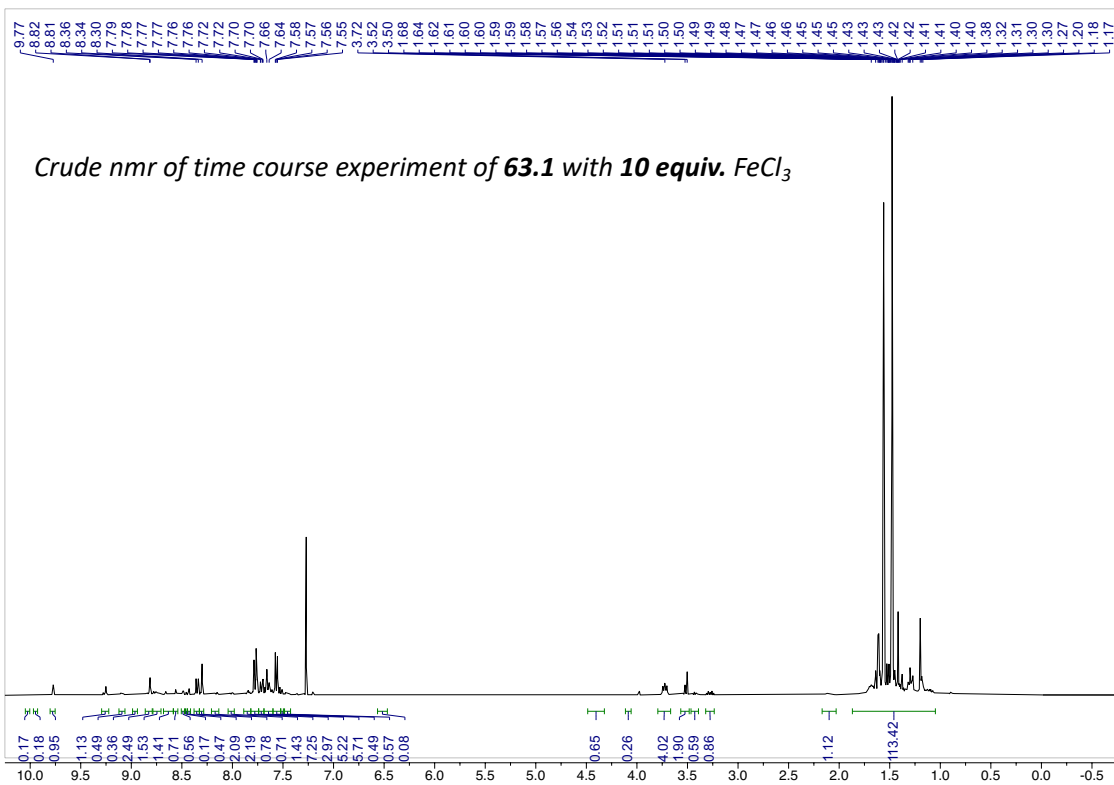












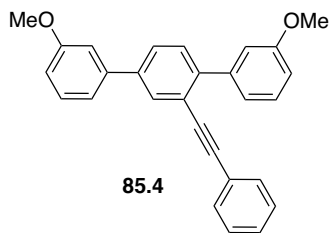
APPENDIX 3:

Supporting Information for

Chapter 3 Pi-extension of Benzenoid Macrocycles via Alkyne Annulation: Synthesis of Chiral, Twisted, and Highly Strained Phenanthrene Units

General Experimental Conditions

All reactions were run in flame or oven-dried (120 °C) glassware and cooled under a positive pressure of ultra-high pure nitrogen or argon gas. All chemicals were used as received from commercial sources, unless otherwise stated. Anhydrous reaction solvents were purified and dried by passing HPLC grade solvents through activated columns of alumina (Glass Contour SDS). All solvents, dichloromethane, toluene, ethanol, and water, that were used in Suzuki and Scholl reactions were purged with nitrogen or argon gas for 30 min prior to use. All solvents used for chromatographic separations were HPLC grade (hexanes, ethyl acetate, dichloromethane, chloroform, methanol, and acetone). Chromatographic separations were performed using flash chromatography, as originally reported by Still and co-workers, on silica gel 60 (particle size 43-60 μm), and all chromatography conditions have been reported as height \times diameter in centimeters. Reaction progress was monitored by thin layer chromatography (TLC), on glass-backed silica gel plates (pH = 7.0). TLC plates were visualized using a handheld UV lamp (254 nm) and stained using an aqueous ceric ammonium molybdate (CAM) solution or vanillin solution (vanillin, ethanol and concentrated H_2SO_4). Plates were dipped, wiped clean, and heated from the back of the plate. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 500 or 600 MHz, calibrated using residual undeuterated solvent as an internal reference (CHCl_3 , δ 7.27 and 77.2 ppm), reported in parts per million relative to trimethylsilane (TMS, δ 0.00 ppm), and presented as follows: chemical shift (δ , ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (J , Hz). X-ray diffraction was recorded on a Bruker D8 VENTURE diffractometer system. Single crystals were obtained from slow evaporation of ethyl acetate. High-resolution mass spectrometric (HRMS) data were obtained using a quadrupole time-of-flight (Q-TOF) spectrometer and electron impact (EI) or electrospray ionization (ESI). Reactions carried out above room temperature were heated using a ceramic heat block unless otherwise stated. UV-visible spectra were recorded on an Agilent HP 8454 diode array spectrophotometer in dichloromethane for all samples. All fluorescence spectra were collected on a Shimadzu RF-5301PC fluorospectrophotometer in dichloromethane with a xenon lamp and a 1 cm width quartz cuvette with an excitation of 480 nm and emission spectrum of 400-600 nm. Optical rotations were measured on a Perkin Elmer 241 Automatic Polarimeter using CHCl_3 as solvent.



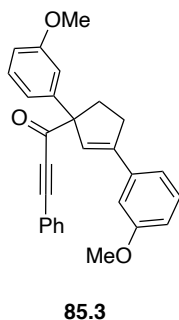
2,5-Bis(3-methoxyphenyl)phenylethynylbenzene (85.4):

Phenylethynylmagnesium bromide (0.84 mL, 1.0 M, 0.84 mmol) was added to a stirred solution of α -ketol **85.1** (48 mg, 0.15 mmol) in dichloromethane (10 mL) at 23 °C. After 17 h, the reaction was poured into water (10 mL) and further diluted with 1 M HCl (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 \times 5 mL).

The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , fil-

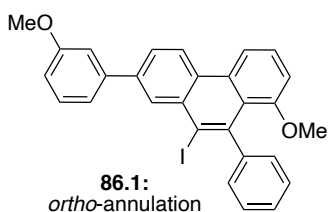
tered, and concentrated under reduced pressure. The residue was dissolved in toluene (5 mL), heated to 80 °C followed by addition of Burgess reagent (110 mg, 0.46 mmol). After 2 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 16 cm; 50% dichloromethane/hexane to 70% dichloromethane/hexane) to yield 2,5-bis(3-methoxyphenyl)phenylethynylbenzene (**85.4**) as white solid (16 mg, 27%) and cyclopentene derivative **85.3** (14 mg, 23%).

2,5-bis(3-methoxyphenyl)phenylethynylbenzene (85.4): $R_f = 0.51$ (60% dichloromethane/hexane); $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 7.90 (d, $J = 1.9$ Hz, 1H), 7.63 (dd, $J = 8.1, 2.0$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.43 - 7.37 (m, 4H), 7.33 - 7.29 (m, 5H), 7.28 - 7.25 (m, 2H) with CHCl_3 , 7.20 (dd, $J = 2.6, 1.7$ Hz, 1H), 7.00 - 6.93 (m, 2H), 3.91 (s, 3H), 3.86 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 160.31, 159.48, 142.88, 141.75, 141.70, 140.28, 131.83, 131.69, 130.15, 129.22, 128.56, 128.47, 127.54, 123.62, 122.19, 122.11, 119.82, 114.98, 113.77, 113.43, 112.97, 92.72, 89.61, 55.64, 55.56. HRMS (ESI-TOF) calc'd for $\text{C}_{28}\text{H}_{23}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 391.1698$ found 391.1695.



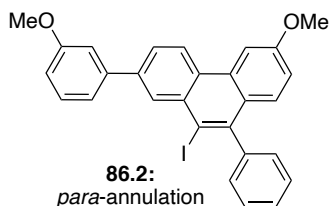
409.1790.

Ynone 85.3: $R_f = 0.21$ (60% dichloromethane/hexane); $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 7.44 - 7.39 (m, 3H), 7.35 - 7.28 (m, 4H), 7.18 - 7.15 (m, 1H), 7.08 (dd, $J = 2.6, 1.6$ Hz, 1H), 6.97 (ddd, $J = 7.7, 1.7, 0.9$ Hz, 1H), 6.92 (dd, $J = 2.5, 1.7$ Hz, 1H), 6.88 - 6.82 (m, 2H), 6.61 (dd, $J = 1.8$ Hz, 1.8 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.28 - 3.21 (m, 1H), 2.95 - 2.81 (m, 2H), 2.21 - 2.14 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 186.45, 160.17, 159.91, 147.41, 144.73, 137.33, 133.28, 130.85, 129.99, 129.69, 128.77, 125.79, 125.77, 120.37, 119.49, 119.01, 113.68, 113.15, 112.59, 112.23, 93.80, 87.64, 71.97, 55.57, 55.54, 34.28, 33.08. HRMS (ESI-TOF) calc'd for $\text{C}_{28}\text{H}_{25}\text{O}_3$ ($[\text{M}+\text{H}]^+$) $m/z = 409.1804$ found

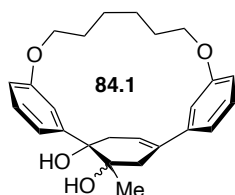


Idodophenanthrene 86.1: Iodine mono chloride (1.0 mL, 10 mg/mL, 0.06 mmol) in dichloromethane was added dropwise to a stirred solution of 2,5-bis(3-methoxyphenyl)phenylethynylbenzene **85.4** (10 mg, 0.02 mmol) at -78°C . After 4h, the reaction was warmed slowly to 23°C and poured into 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 14 cm; 40% dichloromethane/hexane to 60% dichloromethane/hexane) to yield *ortho* **86.1** and *para*-annulated product **86.2** as white solid (12 mg, 99%). From $^1\text{H nmr}$ the ratio of *ortho*:*para* = 1:1.9. Both annulated products were separated by using preparative thin layer chromatography (20 cm × 20 cm; 2000 micron; 60% dichloromethane/hexane) to yield *ortho* **86.1** as white solid (3mg, 23%, isolated yield) and compound *para* **86.2** (5 mg, 39%, isolated yield).

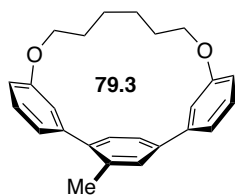
Idodophenanthrene 86.1: $R_f = 0.46$ (60% dichloromethane/hexane); $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 8.74 - 8.70 (m, 2H), 8.40 (dd, $J = 8.8, 8.8$ Hz, 1H), 7.93 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.63 (dd, $J = 8.1, 8.1$ Hz, 1H), 7.48 - 7.38 (m, 5H), 7.35 (dd, $J = 2.6, 1.6$ Hz, 1H), 7.23 - 7.19 (m, 2H), 6.99 - 6.93 (m, 2H), 3.93 (s, 3H), 3.36 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 160.37, 151.07, 143.40, 142.28, 141.00, 133.62, 133.28, 132.57, 130.26, 129.64, 128.96, 128.14, 127.42, 126.84, 126.50, 124.21, 123.47, 120.30, 115.82, 113.63, 113.22, 110.29, 109.49, 56.22, 55.66. HRMS (ESI-TOF) calc'd for $\text{C}_{28}\text{H}_{22}\text{I}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 517.0665$ found 517.0667.



Idodophenanthrene 86.2: $R_f = 0.52$ (60% dichloromethane/hexane); $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 8.71 - 8.63 (m, 2H), 8.11 (d, $J = 2.6$ Hz, 1H), 7.94 (dd, $J = 8.5, 1.9$ Hz, 1H), 7.59 - 7.51 (m, 3H), 7.49 - 7.39 (m, 2H), 7.38 - 7.29 (m, 4H), 7.07 (dd, $J = 9.1, 2.5$ Hz, 1H), 6.99 (ddd, $J = 8.1, 2.6, 1.2$ Hz, 1H), 4.04 (s, 3H), 3.94 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 160.38, 159.01, 145.76, 145.72, 142.35, 140.95, 133.29, 131.90, 130.64, 130.27, 130.19, 129.63, 128.71, 128.06, 127.59, 126.52, 123.67, 120.31, 117.04, 113.68, 113.18, 104.32, 103.62, 55.80, 55.68. HRMS (ESI-TOF) calc'd for $\text{C}_{28}\text{H}_{22}\text{I}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 517.0665$ found 517.0672.



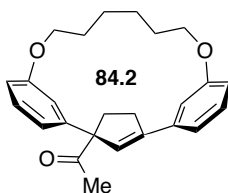
1,2-Diol 84.1: Methylmagnesium chloride (0.03 mL, 3.0 M, 0.09 mmol) was added to a stirred solution of α -ketol **77.1** (6 mg, 0.02 mmol) in dichloromethane (1 mL) at 23 °C. After 3 h, the reaction was poured into water (5 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 \times 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm \times 8 cm; 5% acetone/dichloromethane to 8% acetone/dichloromethane) to yield **84.1** as white solid (4 mg, 64%): $R_f = 0.17$ (3% acetone/dichloromethane); $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.46 - 7.42 (m, 1H), 7.39 - 7.33 (m, 2H), 7.27 - 7.25 (m, 1H), 6.98 - 6.95 (m, 1H), 6.93 (d, $J = 2.6$ Hz, 1H), 6.88 (dd, $J = 8.2, 2.4$ Hz, 1H), 6.81 (dd, $J = 8.1, 2.3$ Hz, 1H), 6.07 (d, $J = 2.1$ Hz, 1H), 4.25 - 4.13 (m, 2H), 3.91 - 3.84 (m, 1H), 3.84 - 3.77 (m, 1H), 2.54 - 2.46 (m, 2H), 2.36 - 2.22 (m, 2H), 2.18 (s, 1H), 2.03 (s, 1H), 1.97 - 1.89 (m, 1H), 1.79 - 1.67 (m, 4H), 1.57 (s, 3H), 1.55 - 1.41 (m, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.12, 158.75, 145.38, 143.18, 138.68, 134.28, 130.53, 129.94, 119.64, 119.05, 116.42, 114.58, 113.42, 112.63, 78.73, 75.93, 69.39, 67.86, 34.77, 28.46, 28.22, 27.57, 26.31, 25.81, 25.20. HRMS (ESI-TOF) calc'd for $\text{C}_{25}\text{H}_{30}\text{O}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$) $m/z = 417.2042$ found 417.2042.



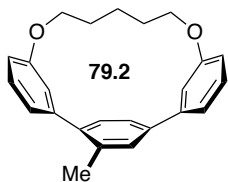
1,8-Dioxa[8]-2'-methyl(3,3'')-p-terphenylenophane (79.3): The diol **84.1** (4 mg, 0.01 mmol) was dissolved in toluene (2 mL), heated to 70 °C followed by addition of TsOH (14 mg, 0.07 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm \times 8 cm; 40% dichloromethane/hexane to 50% dichloromethane/hexane) to yield **79.3** as white solid (3 mg, 82%): $R_f = 0.44$ (50%

dichloromethane/hexane); ^1H NMR (500 MHz, Chloroform-*d*) δ 7.40 - 7.31 (m, 2H), 7.30 - 7.14 (m, 5H and CHCl_3), 6.83 (ddd, $J = 8.4, 2.7, 0.9$ Hz, 2H), 6.05 (dd, $J = 2.8, 1.4$ Hz, 1H), 5.72 (dd, $J = 2.8, 1.4$ Hz, 1H), 4.14 (ddd, $J = 12.4, 9.0, 6.1$ Hz, 1H), 4.07 - 3.97 (m, 2H), 3.86 (ddd, $J = 12.5, 9.4, 4.6$ Hz, 1H), 2.22 (s, 3H), 1.73 - 1.42 (m, 4H), 1.24 - 1.06 (m, 3H), 1.03 - 0.92 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 157.37, 156.93, 144.68, 144.04, 144.00, 142.71, 136.15, 130.58, 130.42, 130.13, 129.85, 125.70, 118.33, 117.43, 116.56, 116.47, 115.79, 69.09, 68.15, 27.98, 27.89, 27.85, 27.61, 20.02.; HRMS (ESI-TOF) calc'd for $\text{C}_{25}\text{H}_{27}\text{O}_2$ ($[\text{M}+\text{H}]^+$) $m/z = 359.2019$ found 359.2011.

Alternative procedure: Diol **84.1** (7 mg, 0.02 mmol) was dissolved in toluene (2 mL), heated to 80 °C followed by addition of Burgess reagent (12 mg, 0.05 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm \times 8 cm; 40% dichloromethane/hexane to 70% dichloromethane/hexane) to yield 1,8-Dioxa[8]2'-methyl(3,3'')-p-terphenylenophane **79.3** as white solid (1 mg, 16%): $R_f = 0.81$ (100% dichloromethane) and by-pdt cyclopentene **84.2** (2 mg, 29%).

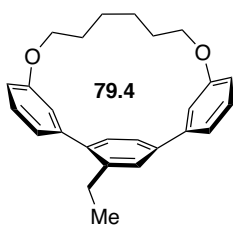


Ketone 84.2: $R_f = 0.14$ (dichloromethane); ^1H NMR (500 MHz, Chloroform-*d*) δ 7.30 - 7.19 (m, 3H and CHCl_3), 7.02 (d, $J = 2.7$ Hz, 1H), 6.90 (dd, $J = 8.8, 8.8$ Hz, 2H), 6.82 (d, $J = 7.9$ Hz, 1H), 6.73 (d, $J = 7.7$ Hz, 1H), 6.37 (d, $J = 2.7$ Hz, 1H), 4.37 - 4.30 (m, 1H), 4.19 - 4.08 (m, 3H), 3.10 (ddd, $J = 12.0, 6.2, 2.7$ Hz, 1H), 2.98 - 2.89 (m, 1H), 2.62 - 2.53 (m, 1H), 2.14 (s, 3H), 2.12 - 2.05 (m, 1H), 2.02 - 1.87 (m, 2H), 1.85 - 1.72 (m, 2H), 1.63 - 1.56 (m, 3H), 1.53 - 1.44 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 207.14, 159.85, 158.78, 148.19, 146.05, 138.02, 130.43, 130.22, 126.98, 119.14, 119.05, 118.33, 116.74, 112.13, 111.46, 71.49, 69.82, 68.52, 34.47, 33.36, 29.07, 28.15, 27.20, 25.31, 25.17.; HRMS (ESI-TOF) calc'd for $\text{C}_{25}\text{H}_{29}\text{O}_3$ ($[\text{M}+\text{H}]^+$) $m/z = 377.2177$ found 377.2103.

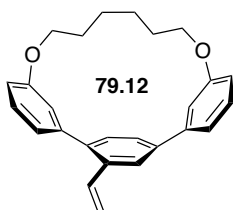


1,8-Dioxa[7]-2'-methyl(3,3'')-p-terphenylenophane (79.2): Methylmagnesium chloride (0.06 mL, 3.0 M, 0.18 mmol) was added to a stirred solution of α -ketol **79.1** (20 mg, 0.05 mmol) in dichloromethane (2 mL) at 23 °C. After 1 h, the reaction was poured into water (5 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 \times 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was dissolved in toluene (2 mL), heated to 60 °C followed by addition of TsOH (45 mg, 0.24 mmol). After 2 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm \times 8 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **79.2** as white solid (10 mg, 53%): $R_f = 0.32$ (90% dichloromethane/hexane) ^1H NMR (500 MHz, Chloroform-*d*) δ 7.36 - 7.31 (m, 2H), 7.29 - 7.27 (m, 2H), 7.25 - 7.20 (m, 3H), 6.78 (ddd, $J = 8.2, 2.7, 0.9$ Hz, 2H), 5.85 (dd, $J = 2.8, 1.4$ Hz, 1H), 5.70 (dd, $J = 2.9, 1.4$ Hz, 1H), 4.12 - 3.96 (m, 4H), 2.31 (s, 3H), 1.54 - 1.46 (m, 2H), 1.21 - 1.11 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 157.82, 157.11, 145.00, 144.74, 144.04, 142.92, 136.80, 131.27, 130.56, 130.43, 129.88, 126.91, 118.27, 118.17, 116.06, 115.45, 115.36, 69.58, 68.49, 27.34, 26.84,

23.43, 20.16. HRMS (ESI-TOF) calc'd for C₂₄H₂₅O₂ ([M+H]⁺) *m/z* = 345.1855 found 345.1843.

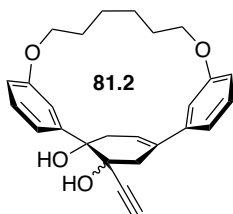


1,8-Dioxa[8]-2'-ethyl(3,3'')-p-terphenylenophane (79.4): Ethylmagnesium chloride (0.05 mL, 2.0 M, 0.10 mmol) was added to a stirred solution of α -ketol **77.1** (6 mg, 0.02 mmol) in dichloromethane (1 mL) at 23 °C. After 3 h, the reaction was poured into water (5 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 \times 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (2 mL), heated to 70 °C followed by addition of TsOH (19 mg, 0.10 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm \times 8 cm; 40% dichloromethane/hexane to 50% dichloromethane/hexane) to yield **79.4** as white solid (2 mg, 34%): *R_f* = 0.48 (50% dichloromethane/hexane); ¹H NMR (500 MHz, Chloroform-*d*) δ 7.36 (ddd, *J* = 10.8, 8.4, 7.5 Hz, 2H), 7.31 - 7.22 (m, 3H and CHCl₃), 7.19 (ddd, *J* = 7.4, 3.1, 1.5 Hz, 2H), 6.87 - 6.79 (m, 2H), 6.05 (dd, *J* = 2.9, 1.5 Hz, 1H), 5.72 (dd, *J* = 2.9, 1.4 Hz, 1H), 4.15 (ddd, *J* = 12.4, 9.1, 6.2 Hz, 1H), 4.08 - 3.95 (m, 2H), 3.83 (ddd, *J* = 12.5, 9.6, 4.4 Hz, 1H), 2.64 - 2.48 (m, 2H), 1.68 - 1.55 (m, 3H), 1.54 - 1.44 (m, 1H), 1.25 - 1.15 (m, 1H), 1.14 (t, *J* = 7.6 Hz, 3H), 1.13 - 1.05 (m, 2H), 1.01 - 0.87 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 157.12, 156.91, 144.83, 144.13, 143.88, 142.63, 142.16, 130.45, 130.43, 129.82, 129.12, 125.57, 118.33, 117.43, 116.80, 116.59, 115.78, 115.78, 69.08, 68.16, 27.95, 27.91, 27.83, 27.63, 26.77, 16.43.; HRMS (ESI-TOF) calc'd for C₂₆H₂₉O₂ ([M+H]⁺) *m/z* = 373.2182 found 373.2168.

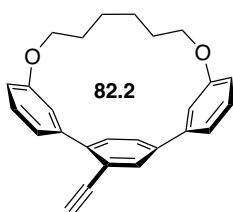


1,8-Dioxa[8]-2'-vinyl(3,3'')-p-terphenylenophane (79.12): Vinylmagnesium chloride (0.04 mL, 1.9 M, 0.08 mmol) was added to a stirred solution of α -ketol **77.1** (10 mg, 0.03 mmol) in dichloromethane (1 mL) at 23 °C. After 3 h, the reaction was poured into water (5 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 \times 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (2 mL), heated to 80 °C followed by addition of Burgess reagent (16 mg, 0.07 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm \times 8 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **79.12** as white solid (2 mg, 21%): *R_f* = 0.48 (60% dichloromethane/hexane); ¹H NMR (500 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 1.8 Hz, 1H), 7.41 - 7.31 (m, 3H), 7.28 (d, *J* = 1.1 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.20 (dt, *J* = 7.3, 1.1 Hz, 1H), 6.87 - 6.80 (m, 2H), 6.67 (dd, *J* = 17.6, 11.0 Hz, 1H), 6.05 (dd, *J* = 2.8, 1.5 Hz, 1H), 5.76 (dd, *J* = 2.8, 1.4 Hz, 1H), 5.72 (dd, *J* = 17.6, 1.1 Hz, 1H), 5.18 (dd, *J* = 11.0, 1.2 Hz, 1H), 4.18 (ddd, *J* = 12.5, 9.1, 6.7 Hz, 1H), 4.05 (ddd, *J* = 12.5, 9.7, 6.5 Hz, 1H), 3.97 (ddd, *J* = 12.8, 9.5, 3.6 Hz, 1H), 3.82 (ddd, *J* = 12.9, 9.9, 3.6 Hz, 1H), 1.70 - 1.58 (m, 2H), 1.53 - 1.43 (m, 2H), 1.25 - 1.11 (m, 2H), 1.09 - 0.99 (m, 1H), 0.96 - 0.87 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 157.12, 157.00, 144.50, 144.13, 143.31, 141.87, 136.18,

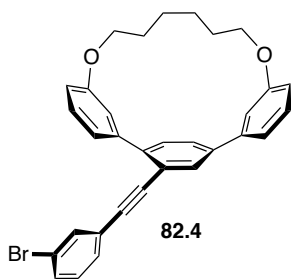
135.09, 130.99, 130.48, 129.99, 127.18, 125.91, 118.32, 117.31, 117.08, 116.64, 116.03, 116.01, 115.18, 68.88, 68.26, 27.93, 27.88, 27.78, 27.56. HRMS (ESI-TOF) calc'd for $C_{26}H_{27}O_2$ ($[M+H]^+$) $m/z = 371.2012$ found 373.2011.



Propargylic-1,2-diol 81.2: Ethynylmagnesium chloride (1.0 mL, 0.5 M, 0.50 mmol) was added to a stirred solution of α -ketol **77.1** (28 mg, 0.07 mmol) in dichloromethane (2 mL) at 23 °C. After 21 h, the reaction was poured into water (10 mL) and further diluted with 1 M HCl (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 \times 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm \times 8 cm; 2% acetone/dichloromethane to 5% acetone/dichloromethane) to yield diol **81.2** as white solid (20 mg, 67%): $R_f = 0.27$ (5% acetone/dichloromethane). 1H NMR (500 MHz, Chloroform- d) δ 7.42 (d, $J = 7.4$ Hz, 1H), 7.33 (dd, $J = 8.0, 8.0$ Hz, 1H), 6.99 (d, $J = 7.6$ Hz, 1H), 6.94 - 6.87 (m, 2H), 6.80 (dd, $J = 8.2, 2.3$ Hz, 1H), 6.12 (d, $J = 2.2$ Hz, 1H), 4.25 - 4.12 (m, 2H), 3.91 - 3.78 (m, 2H), 2.84 (s, 1H), 2.78 (s, 1H), 2.62 - 2.49 (m, 3H), 2.27 - 2.15 (m, 1H), 2.13 - 2.03 (m, 1H), 1.78 - 1.66 (m, 4H), 1.55 - 1.43 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.11, 158.24, 142.39, 141.72, 140.83, 129.97, 129.91, 128.75, 120.11, 119.13, 116.87, 114.65, 113.95, 113.48, 84.75, 77.80, 76.10, 74.87, 69.38, 67.63, 36.60, 28.38, 28.23, 28.15, 25.69, 25.12. HRMS (ESI-TOF) calc'd for $C_{26}H_{28}O_4Na$ ($[M+Na]^+$) $m/z = 427.1885$ found 427.1902.

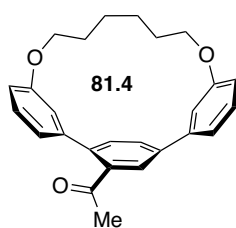


1,8-Dioxa[8]-2'-ethynyl(3,3'')-p-terphenylenophane (82.2): The diol **81.2** (47 mg, 0.12 mmol) was dissolved in toluene (5 mL), heated to 80 °C followed by addition of Burgess reagent (85 mg, 0.36 mmol). After 4 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1 cm \times 16 cm; 60% dichloromethane/hexane to 70% dichloromethane/hexane) to yield **82.2** as white solid (12 mg, 28%): $R_f = 0.29$ (60% dichloromethane/hexane). 1H NMR (500 MHz, Chloroform- d) δ 7.57 (d, $J = 1.8$ Hz, 1H), 7.43 - 7.31 (m, 4H), 7.28 (s, 1H), 7.23 (d, $J = 7.4$ Hz, 1H), 6.91 - 6.78 (m, 2H), 5.98 (d, $J = 2.6$ Hz, 1H), 5.90 (d, $J = 1.8$ Hz, 1H), 4.25 - 3.85 (m, 4H), 3.00 (s, 1H), 1.70 - 1.57 (m, 3H), 1.54 - 1.47 (m, 1H), 1.28 - 0.93 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.08, 145.82, 143.92, 143.48, 142.77, 133.50, 130.52, 130.28, 129.88, 128.67, 121.47, 118.01, 117.29, 117.08, 116.61, 116.36, 116.29, 82.46, 80.48, 68.81, 68.35, 27.91, 27.87, 27.82, 27.64. HRMS (ESI-TOF) calc'd for $C_{26}H_{25}O_2$ ($[M+H]^+$) $m/z = 369.1845$ found 369.1855.



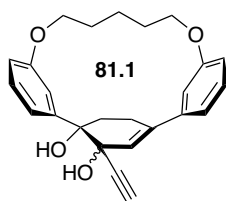
Macrocycle 82.4: 1,8-Dioxa[8]-2'-ethynyl(3,3'')-p-terphenylenophane **82.2** (10 mg, 0.03 mmol) was dissolved in toluene (2 mL) and diisopropyl amine (1 mL) at room temperature. The mixture was purged with nitrogen for 25 min. 3-bromoiodobenzene (**82.3**, 201 mg, 0.71 mmol) was added followed by addition of copper (II) chloride (1 mg, 0.005 mmol) and bis(triphenylphosphine)palladium (II) chloride (1 mg, 0.001 mmol) at room temperature under nitrogen. After 21 h, water (5 mL) was added to the reaction and was further diluted by di-

chloromethane (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **82.4** as white solid (8 mg, 56%): *R_f* = 0.46 (60% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.59 (s, 1H), 7.44 - 7.31 (m, 7H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.20 - 7.10 (m, 2H), 6.92 - 6.83 (m, 2H), 6.01 (s, 1H), 5.93 (s, 1H), 4.17 - 3.93 (m, 4H), 1.67 - 1.50 (m, 4H), 1.23 - 1.00 (m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 157.17, 157.10, 145.57, 144.11, 143.57, 142.93, 134.35, 132.28, 131.52, 130.52, 130.24, 129.93, 129.86, 129.71, 128.95, 125.50, 122.54, 122.30, 118.37, 117.34, 117.23, 116.62, 116.33, 116.29, 91.23, 89.91, 68.87, 68.37, 27.93, 27.90, 27.81, 27.67. HRMS (ESI-TOF) calc'd for C₃₂H₃₁NO₂Br ([M+NH₄]⁺) *m/z* = 540.1538 found 540.1534.



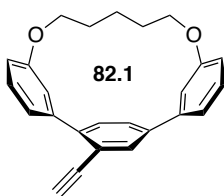
Ketone 81.4: Diol **81.2** (6 mg, 0.01 mmol) was dissolved in toluene (2 mL), heated to 70 °C followed by addition of TsOH (14 mg, 0.07 mmol). After 4 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 90% dichloromethane/hexane to 100% dichloromethane) to yield **81.4** as white solid (4 mg, 74%): *R_f* = 0.21 (100% dichloromethane). ¹H NMR (500

MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 1.5, 1.5 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.44 - 7.29 (m, 4H), 7.28 - 7.26 (m, 1H), 6.90 - 6.83 (m, 2H), 6.01 (dd, *J* = 1.5, 1.5 Hz, 1H), 5.67 (dd, *J* = 1.5, 1.5 Hz, 1H), 4.31 - 4.24 (m, 1H), 4.16 - 4.08 (m, 1H), 4.27 (ddd, *J* = 12.3, 8.2, 8.2 Hz, 1H), 4.12 (ddd, *J* = 12.3, 8.8, 8.8 Hz, 1H), 3.88 (dd, *J* = 12.5, 9.6 Hz, 1H), 3.75 (dd, *J* = 11.3, 11.3 Hz, 1H), 2.30 (s, 3H), 1.75 - 1.60 (m, 2H), 1.48 - 1.19 (m, 4H), 0.97 - 0.77 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 201.21, 157.13, 157.03, 144.05, 143.74, 143.36, 142.97, 139.10, 132.43, 130.74, 130.58, 130.00, 129.75, 117.12, 117.08, 116.85, 116.64, 116.59, 116.45, 68.39, 68.32, 31.11, 27.89, 27.80, 27.77, 27.32. HRMS (ESI-TOF) calc'd for C₂₆H₂₆O₃Na ([M+Na]⁺) *m/z* = 409.1780 found 409.1770.

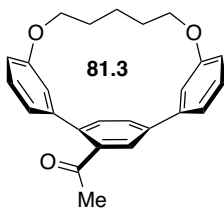


Propargylic 1,2-diol 81.1: Ethynylmagnesium chloride (0.45 mL, 0.5 M, 0.23 mmol) was added to a stirred solution of α-ketol **79.1** (19 mg, 0.05 mmol) in dichloromethane (2 mL) at 23 °C. After 23 h, the reaction was poured into water (10 mL) and further diluted with 1 M HCl (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered,

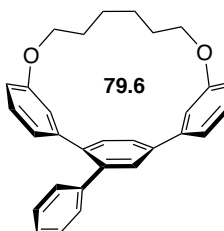
and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 2% acetone/dichloromethane to 5% acetone/dichloromethane) to yield diol **81.1** as white solid (13 mg, 69%): $R_f = 0.12$ (3% acetone/dichloromethane). ^1H NMR (500 MHz, Chloroform- d) δ 7.44 - 7.41 (m, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.34 - 7.28 (m, 1H), 7.26 - 7.21 (m, 1H), 6.94 - 6.85 (m, 3H), 6.81 (d, $J = 7.9$ Hz, 1H), 6.07 (s, 1H), 4.24 - 4.11 (m, 2H), 4.09 - 4.02 (m, 1H), 3.88 - 3.80 (m, 1H), 2.83 (s, 1H), 2.79 (s, 1H), 2.76 (s, 1H), 2.66 - 2.55 (m, 2H), 2.16 - 2.10 (m, 1H), 2.04 - 1.89 (m, 3H), 1.84 - 1.63 (m, 4H), 1.58 - 1.52 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 158.32, 157.99, 142.54, 141.59, 141.33, 129.99, 129.80, 128.39, 120.61, 119.25, 118.36, 115.75, 113.63, 113.60, 84.91, 77.91, 75.93, 74.63, 69.22, 67.93, 36.49, 29.04, 27.71, 26.91, 21.67.



Macrocycle 82.1: Diol **81.1** (7 mg, 0.03 mmol) was dissolved in toluene (2 mL), heated to 80 °C followed by addition of Burgess reagent (13 mg, 0.05 mmol). After 4 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 60% dichloromethane/hexane to 80% dichloromethane/hexane) to yield **82.1** as white solid (2 mg, 31%): $R_f = 0.24$ (50% dichloromethane/hexane). ^1H NMR (500 MHz, Chloroform- d) δ 7.62 (d, $J = 2.3$ Hz, 1H), 7.41 - 7.32 (m, 5H), 7.24 (d, $J = 7.5$ Hz, 1H), 6.80 (dd, $J = 7.5, 2.3$ Hz, 2H), 5.88 (s, 1H), 5.83 (s, 1H), 4.12 - 4.01 (m, 4H), 3.07 (s, 1H), 1.53 - 1.41 (m, 4H), 1.23 - 1.15 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 157.34, 146.07, 144.53, 143.74, 142.80, 134.06, 130.77, 130.62, 130.10, 129.80, 121.96, 118.55, 118.38, 117.65, 116.00, 115.98, 115.87, 82.61, 80.63, 68.96, 68.54, 27.07, 26.83, 23.39.

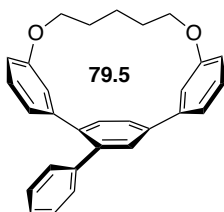


Ketone 81.3: Diol **81.1** (7mg, 0.01 mmol) was dissolved in toluene (1 mL), heated to 65 °C followed by addition of TsOH (18 mg, 0.09 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 90% dichloromethane/hexane to 100% dichloromethane) to yield **81.3** as white solid (5 mg, 75%): $R_f = 0.67$ (4% acetone/dichloromethane). ^1H NMR (500 MHz, Chloroform- d) δ 8.22 (d, $J = 2.3$ Hz, 1H), 7.43 - 7.29 (m, 4H), 7.26 - 7.23 (m, 2H), 6.80 (dd, $J = 8.6, 8.6$ Hz, 2H), 5.86 (s, 1H), 5.55 (s, 1H), 4.35 - 4.18 (m, 2H), 3.95 - 3.87 (m, 1H), 3.71 - 3.64 (m, 1H), 2.36 (s, 3H), 1.69 - 1.58 (m, 2H), 1.32 - 1.24 (m, 2H), 1.22 - 1.15 (m, 1H), 1.06 - 0.96 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 201.29, 157.58, 157.31, 144.55, 143.72, 143.68, 141.06, 132.17, 132.01, 131.35, 130.75, 128.79, 118.64, 117.77, 116.17, 116.01, 115.97, 115.80, 68.65, 68.38, 31.14, 27.00, 26.80, 23.11.



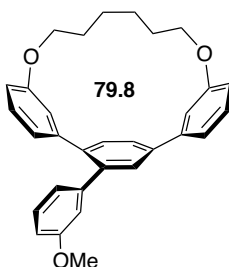
1,8-Dioxa[8]-2'-phenyl(3,3'')-p-terphenylenophane (79.6): Phenylmagnesium chloride (1.6 mL, 2.0 M, 0.32 mmol) was added to a stirred solution of α -ketol **77.1** (15 mg, 0.04 mmol) in dichloromethane (1 mL) at 23 °C. After 2 h, the reaction was poured into water (5 mL) and further diluted with 1 M HCl (2 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3

× 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (5 mL), heated to 70 °C followed by addition of TsOH (47 mg, 0.28 mmol). After 4 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 70% dichloromethane/hexane to 80% dichloromethane/hexane) to yield **79.6** as white solid (12 mg, 73%): *R_f* = 0.50 (80% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 1.7 Hz, 1H), 7.44 - 7.34 (m, 5H), 7.24 (d, *J* = 7.3 Hz, 5H), 7.22 - 7.17 (m, 1H), 6.88 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.69 - 6.60 (m, 1H), 6.12 (d, *J* = 2.7 Hz, 1H), 5.62 (d, *J* = 2.6 Hz, 1H), 4.31 - 4.22 (m, 1H), 4.06 - 3.86 (m, 2H), 3.59 - 3.48 (m, 1H), 1.78 - 1.67 (m, 1H), 1.65 - 1.57 (m, 1H), 1.54 - 1.47 (m, 1H), 1.46 - 1.36 (m, 1H), 1.35 - 1.15 (m, 2H), 1.08 - 0.95 (m, 1H), 0.93 - 0.77 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 156.98, 156.46, 144.42, 144.42, 144.00, 141.93, 141.28, 141.05, 132.11, 130.46, 130.36, 130.17, 129.91, 128.36, 127.22, 126.32, 118.54, 117.38, 116.81, 116.10, 115.39, 68.41, 68.29, 27.99, 27.92, 27.80, 27.63. HRMS (ESI-TOF) calc'd for C₃₀H₂₈O₂Na ([M+Na]⁺) *m/z* = 443.2127 found 443.1987.



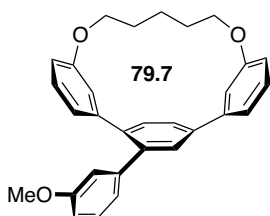
1,8-Dioxa[7]-2'-phenyl(3,3'')-p-terphenylenophane (79.5): Phenylmagnesium chloride (0.05 mL, 2.0 M, 0.10 mmol) was added to a stirred solution of α -ketol **79.1** (6 mg, 0.16 mmol) in dichloromethane (1 mL) at 23 °C. After 4 h, the reaction was poured into water (5 mL) and further diluted with 1 M HCl (2 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL).

The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (5 mL), heated to 60 °C followed by addition of TsOH (25 mg, 0.13 mmol). After 4 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 70% dichloromethane/hexane to 80% dichloromethane/hexane) to yield **79.5** as white solid (4 mg, 61%): *R_f* = 0.41 (80% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 1.4 Hz, 1H), 7.61 - 7.57 (m, 2H), 7.39 - 7.28 (m, 5H), 7.26 - 7.21 (m, 4H), 6.83 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.57 (ddd, *J* = 7.9, 2.7, 1.2 Hz, 1H), 6.00 (dd, *J* = 2.8, 1.4 Hz, 1H), 5.55 (dd, *J* = 2.8, 1.4 Hz, 1H), 4.37 - 4.29 (m, 1H), 4.09 - 4.02 (m, 1H), 4.02 - 3.95 (m, 1H), 3.46 - 3.39 (m, 1H), 1.70 - 1.60 (m, 2H), 1.43 - 1.32 (m, 2H), 0.92 - 0.82 (m, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 157.22, 156.90, 144.99, 144.70, 144.40, 142.61, 142.43, 141.11, 132.29, 130.73, 130.37, 130.27, 128.90, 128.79, 128.74, 127.49, 118.66, 117.26, 116.23, 115.67, 114.81, 68.68, 68.49, 27.03, 26.85, 23.52. HRMS (ESI-TOF) calc'd for C₂₉H₂₆O₂Na ([M+Na]⁺) *m/z* = 429.1831 found 429.1842.

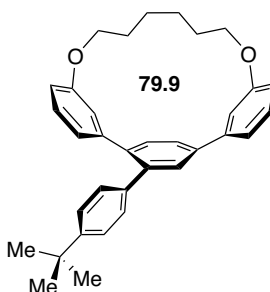


Macrocycle 79.8: 3-*o*-methylphenylmagnesium bromide (0.08 mL, 1.0 M, 0.08 mmol) was added to a stirred solution of α -ketol **77.1** (5 mg, 0.01 mmol) in dichloromethane (1 mL) at 23 °C. After 2 h 30 min, the reaction was poured into water (3 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was

dissolved in toluene (1 mL), heated to 70 °C followed by addition of TsOH (8 mg, 0.04 mmol). After 5 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 70% dichloromethane/hexane to 80% dichloromethane/hexane) to yield **79.8** as white solid (3 mg, 51%): $R_f = 0.69$ (80% dichloromethane/hexane). $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 7.53 (d, $J = 1.8$ Hz, 1H), 7.43 - 7.35 (m, 3H), 7.27 - 7.21 (m, 3H), 7.19 - 7.14 (m, 1H), 7.03 - 6.99 (m, 1H), 6.92 (dd, $J = 2.6, 1.6$ Hz, 1H), 6.87 (ddd, $J = 8.3, 2.7, 0.9$ Hz, 1H), 6.75 (ddd, $J = 8.2, 2.6, 1.0$ Hz, 1H), 6.66 (ddd, $J = 7.7, 2.7, 1.6$ Hz, 1H), 6.11 (dd, $J = 2.8, 1.5$ Hz, 1H), 5.64 (dd, $J = 2.8, 1.3$ Hz, 1H), 4.26 (ddd, $J = 12.5, 9.0, 7.2$ Hz, 1H), 4.04 - 3.89 (m, 2H), 3.71 (s, 3H), 3.57 (ddd, $J = 12.7, 10.0, 2.9$ Hz, 1H), 1.78 - 1.66 (m, 1H), 1.65 - 1.57 (m, 1H), 1.48 - 1.38 (m, 1H), 1.34 - 1.18 (m, 3H), 1.04 - 0.96 (m, 1H), 0.89 - 0.81 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.46, 156.98, 156.50, 144.44, 144.38, 144.02, 142.39, 141.86, 141.09, 132.06, 130.47, 130.24, 129.92, 129.32, 126.42, 122.56, 118.47, 117.38, 117.28, 116.80, 116.11, 115.86, 115.44, 113.03, 68.38, 68.33, 55.44, 28.00, 27.91, 27.79, 27.62. HRMS (ESI-TOF) calc'd for $\text{C}_{31}\text{H}_{30}\text{O}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) $m/z = 473.2100$ found 473.2093.

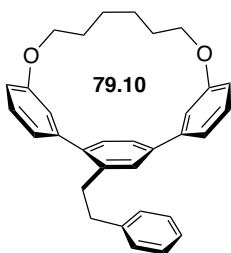


Macrocycle 79.7: 3-*o*-methylphenylmagnesium bromide (0.15 mL, 1.0 M, 0.15 mmol) was added to a stirred solution of α -ketol **79.1** (6 mg, 0.01 mmol) in dichloromethane (1 mL) at 23 °C. After 4 h, the reaction was poured into water (3 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (1 mL), heated to 60 °C followed by addition of TsOH (14 mg, 0.07 mmol). After 5 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 60% dichloromethane/hexane to 70% dichloromethane/hexane) to yield **79.7** as white solid (3 mg, 42%): $R_f = 0.67$ (80% dichloromethane/hexane). $^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 7.84 (d, $J = 1.8$ Hz, 1H), 7.37 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.29 (d, $J = 7.8$ Hz, 2H), 7.26 - 7.20 (m, 5H), 7.11 - 7.08 (m, 1H), 6.85 - 6.77 (m, 2H), 6.58 (ddd, $J = 7.8, 2.9, 1.3$ Hz, 1H), 5.98 (dd, $J = 2.8, 1.5$ Hz, 1H), 5.57 (dd, $J = 2.8, 1.5$ Hz, 1H), 4.32 (ddd, $J = 12.6, 9.5, 7.6$ Hz, 1H), 4.07 (ddd, $J = 12.4, 9.4, 7.6$ Hz, 1H), 3.97 (ddd, $J = 12.5, 10.5, 1.8$ Hz, 1H), 3.46 (ddd, 12.5, 10.5, 1.8 Hz, 1H), 1.70 - 1.58 (m, 2H), 1.44 - 1.29 (m, 2H), 1.09 - 0.97 (m, 1H), 0.92 - 0.82 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.75, 157.22, 156.95, 145.05, 144.67, 144.42, 142.56, 142.48, 142.25, 132.25, 130.73, 130.38, 129.66, 128.87, 122.51, 118.65, 118.51, 117.13, 116.32, 116.22, 115.69, 114.85, 113.03, 68.67, 68.54, 55.46, 27.04, 26.83, 23.51. HRMS (ESI-TOF) calc'd for $\text{C}_{30}\text{H}_{28}\text{O}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) $m/z = 459.1936$ found 459.1947.

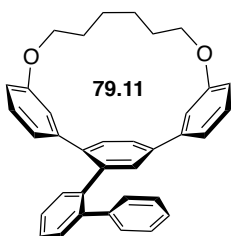


Macrocycle 79.9: *n*-BuLi (0.08 mL, 2.3 M, 0.18 mmol) was added to a stirred solution of 1-bromo-4-*tert*-butylbenzene (72 mg, 0.33 mmol) in tetrahydrofuran under argon at -78 °C. After 0.25 h, α -ketol **77.1** (14 mg, 0.04 mmol) in tetrahydrofuran was added to the reaction at -78 °C, the reaction became yellow. After 4 h, the reaction was slowly warmed to rt and the reaction was poured into water. The layer was separated, and the aqueous

layer extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (3 mL), heated to 70 °C followed by addition of TsOH (30 mg, 0.16 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **79.9** as white solid (6 mg, 34%): *R_f* = 0.47 (60% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 1.9 Hz, 1H), 7.41 - 7.35 (m, 2H), 7.35 - 7.30 (m, 3H), 7.27 - 7.24 (m, 5H), 6.87 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 6.70 - 6.62 (m, 1H), 6.12 (dd, *J* = 2.8, 1.5 Hz, 1H), 5.65 - 5.63 (m, 1H), 4.27 (ddd, *J* = 12.5, 9.0, 7.4 Hz, 1H), 4.00 (ddd, *J* = 12.4, 9.5, 7.2 Hz, 1H), 3.93 (ddd, *J* = 12.4, 9.6, 2.8 Hz, 1H), 3.56 (ddd, *J* = 12.7, 10.1, 2.8 Hz, 1H), 1.78 - 1.57 (m, 3H), 1.53 - 1.48 (m, 1H), 1.47 - 1.41 (m, 1H), 1.28 (s, 9H), 1.24 - 1.18 (m, 1H), 1.11 - 1.00 (m, 1H), 0.88 - 0.79 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 156.97, 156.39, 150.04, 144.72, 144.52, 143.88, 141.76, 140.94, 137.98, 132.27, 130.45, 130.38, 129.91, 129.74, 125.98, 125.31, 118.59, 117.44, 117.38, 116.81, 116.03, 115.27, 68.38, 68.24, 34.69, 31.55, 28.01, 27.92, 27.79, 27.57. HRMS (ESI-TOF) calc'd for C₃₄H₃₇O₂ ([M+H]⁺) *m/z* = 477.2803 found 477.2794.

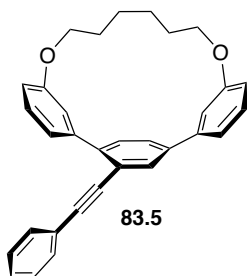


Macrocyclic 79.10: Phenylethylmagnesium chloride (0.12 mL, 1.0 M, 0.12 mmol) was added to a stirred solution of α -ketol **77.1** (12 mg, 0.03 mmol) in dichloromethane (1 mL) at 23 °C. After 21 h 30 min, the reaction was poured into water (3 mL) and further diluted with 1 M HCl (1 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (1 mL), heated to 70 °C followed by addition of TsOH (22 mg, 0.12 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 70% dichloromethane/hexane to 80% dichloromethane/hexane) to yield **79.10** as white solid (5 mg, 37%): *R_f* = 0.44 (60% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.40 - 7.33 (m, 2H), 7.30 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.26 - 7.20 (m, 5H), 7.18 - 7.10 (m, 2H), 7.02 (d, *J* = 7.4 Hz, 2H), 6.87 - 6.81 (m, 2H), 6.07 - 6.03 (m, 1H), 5.75 - 5.71 (m, 1H), 4.13 (ddd, *J* = 12.6, 8.9, 6.1 Hz, 1H), 4.06 - 3.97 (m, 2H), 3.83 (ddd, *J* = 13.0, 9.5, 4.6 Hz, 1H), 2.88 - 2.73 (m, 4H), 1.71 - 1.57 (m, 3H), 1.53 - 1.42 (m, 1H), 1.23 - 1.04 (m, 3H), 1.01 - 0.90 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 157.21, 156.93, 144.66, 144.12, 143.64, 142.46, 141.96, 140.18, 130.52, 130.45, 129.86, 129.73, 128.66, 128.55, 126.16, 125.99, 118.37, 117.39, 116.80, 116.57, 115.93, 115.85, 69.11, 68.13, 38.58, 36.05, 27.95, 27.91, 27.85, 27.63. HRMS (ESI-TOF) calc'd for C₃₂H₃₃O₂ ([M+H]⁺) *m/z* = 449.2496 found 449.2481.



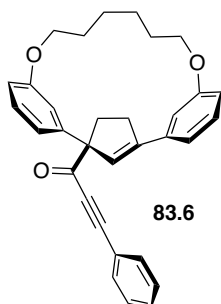
Macrocyclic 79.11: *n*-Butyllithium (0.08 mL, 2.3 M, 0.18 mmol) was added to a stirred solution of 2-bromo-biphenyl (76 mg, 0.33 mmol) in tetrahydrofuran under argon at -78 °C. After 0.25 h, α -ketol **77.1** (14 mg, 0.04 mmol) in tetrahydrofuran was added to the reaction at -78 °C, the reaction became yellow. After 3 h, the reaction was slowly warmed to rt and the reaction was poured into water. The layer was

separated, and the aqueous layer extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (3 mL), heated to 70 °C followed by addition of TsOH (21 mg, 0.11 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **79.11** as white solid (5 mg, 25%): *R_f* = 0.42 (60% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.46 - 7.28 (m, 6H), 7.26 - 7.16 (m, 5H), 7.08 - 6.96 (m, 4H), 6.85 (ddd, *J* = 8.4, 2.7, 0.9 Hz, 1H), 6.58 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.21 (brs, 1H), 6.06 - 5.97 (m, 1H), 5.60 (dd, *J* = 2.9, 1.5 Hz, 1H), 4.26 - 4.16 (m, 1H), 4.04 - 3.89 (m, 2H), 3.65 - 3.55 (m, 1H), 1.77 - 1.65 (m, 1H), 1.63 - 1.56 (m, 1H), 1.53 - 1.47 (m, 1H), 1.46 - 1.34 (m, 1H), 1.29 - 1.18 (m, 2H), 1.05 - 0.87 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 156.95, 144.49, 143.57, 143.53, 141.70, 141.60, 140.34, 132.07, 131.68, 131.05, 130.55, 130.49, 130.35, 129.27, 128.01, 127.76, 127.01, 126.76, 126.69, 118.33, 118.30, 117.63, 117.41, 116.76, 115.97, 115.15, 68.45, 68.31, 27.96, 27.92, 27.83, 27.72. HRMS (ESI-TOF) calc'd for C₃₆H₃₃O₂ ([M+H]⁺) *m/z* = 497.2825 found 497.2481.



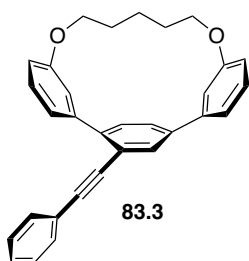
Macrocycle 83.5: Phenylethynylmagnesium bromide (2.3 mL, 1.0 M, 2.30 mmol) was added to a stirred solution of α -ketol **77.1** (213 mg, 0.56 mmol) in dichloromethane (6 mL) at 23 °C. After 23 h, the reaction was poured into water (10 mL) and further diluted with 1 M HCl (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (5 mL), heated to 80 °C followed by addition of Burgess reagent (270 mg, 1.13 mmol). After 5 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 14 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **83.5** as white solid (54 mg, 22%) and burgess by-pdt cyclopentene derivative **83.6** (67 mg, 26%).

Macrocycle 83.5: *R_f* = 0.36 (60% dichloromethane/hexane); ¹H NMR (500 MHz, Chloroform-*d*) δ 7.61 - 7.59 (m, 1H), 7.42 - 7.34 (m, 5H), 7.27 - 7.23 (m, 6H), 6.89 - 6.83 (m, 2H), 6.02 (dd, *J* = 2.8, 1.5 Hz, 1H), 5.97 (dd, *J* = 2.8, 1.4 Hz, 1H), 4.12 - 3.97 (m, 4H), 1.67 - 1.55 (m, 4H), 1.19 - 1.05 (m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 157.12, 157.08, 145.38, 144.02, 143.72, 143.11, 132.29, 131.69, 130.47, 129.83, 129.66, 128.56, 128.49, 128.41, 123.52, 122.99, 118.45, 117.37, 117.31, 116.64, 116.22, 116.19, 92.85, 88.59, 68.86, 68.39, 27.94, 27.92, 27.79, 27.67. HRMS (ESI-TOF) calc'd for C₃₆H₂₉O₂ ([M+H]⁺) *m/z* = 445.2176 found 445.2168.



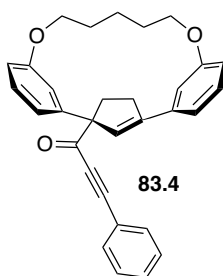
Ynone 83.6: ¹H NMR (500 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 7.6 Hz, 3H), 7.35 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.31 - 7.25 (m, 1H and CHCl₃), 7.23 (s, 1H), 7.21 - 7.15 (m, 1H), 7.05 (s, 1H), 6.94 (dd, *J* = 6.5 Hz, 6.5 Hz, 2H), 6.89 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.85 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.53 (s, 1H), 4.35 (ddd, *J* = 12.3, 8.7, 5.6 Hz, 1H), 4.20 - 4.08 (m, 3H), 3.25 - 3.16 (m, 1H), 3.07 - 2.99 (m, 1H), 2.70 - 2.60 (m, 1H),

2.37 (s, 1H), 2.34 - 2.27 (m, 1H), 2.04 - 1.87 (m, 2H), 1.84 - 1.71 (m, 2H), 1.62 - 1.57 (m, 2H), 1.53 - 1.44 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.44, 159.59, 158.75, 148.06, 145.17, 137.88, 133.23, 130.92, 130.26, 130.19, 128.82, 127.07, 120.34, 119.89, 119.20, 118.39, 116.92, 112.13, 111.82, 93.95, 87.60, 71.48, 69.66, 68.40, 34.54, 33.50, 29.04, 28.08, 25.36, 25.18. HRMS (ESI-TOF) calc'd for $\text{C}_{32}\text{H}_{31}\text{O}_3$ ($[\text{M}+\text{H}]^+$) m/z = 463.2273 found 463.2273.



Macrocycle 83.3: Phenylethynylmagnesium bromide (1.2 mL, 1.0 M, 1.2 mmol) was added to a stirred solution of α -ketol **79.1** (102 mg, 0.28 mmol) in dichloromethane (10 mL) at 23 °C. After 23 h, the reaction was poured into water (10 mL) and further diluted with 1 M HCl (3 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (3 \times 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (5 mL), heated to 80 °C followed by addition of Burgess reagent (140 mg, 0.59 mmol). After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm \times 14 cm; 50% dichloromethane/hexane to 80% dichloromethane/hexane) to yield Ph ethynyl [7]PTPP **83.3** as white solid (28 mg, 23%) and by-pdt **83.4** (34 mg, 27%).

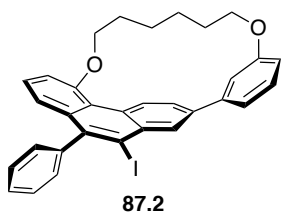
Macrocycle 83.3: R_f = 0.70 (100% dichloromethane); ^1H NMR (500 MHz, Chloroform- d) δ 7.59 (s, 1H), 7.49 - 7.43 (m, 3H), 7.41 - 7.28 (m, 8H), 6.84 - 6.77 (m, 2H), 5.93 (s, 1H), 5.87 (s, 1H), 4.19 - 3.95 (m, 4H), 1.53 - 1.45 (m, 2H), 1.35 - 1.04 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 157.34, 145.48, 144.69, 143.96, 143.08, 133.39, 131.66, 130.75, 130.44, 129.78, 129.20, 128.54, 128.49, 123.53, 123.27, 118.76, 118.41, 118.22, 115.99, 115.82, 115.79, 92.78, 88.61, 69.00, 68.55, 27.10, 26.84, 23.43. HRMS (ESI-TOF) calc'd for $\text{C}_{31}\text{H}_{26}\text{O}_2$ ($[\text{M}+\text{H}]^+$) m/z = 431.2011 found 431.2023.



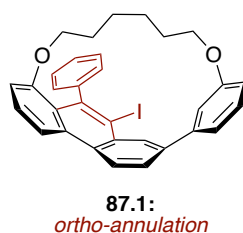
Ynone 83.4: R_f = 0.43 (dichloromethane/hexane); ^1H NMR (500 MHz, Chloroform- d) δ 7.46 - 7.40 (m, 3H), 7.37 - 7.28 (m, 4H), 7.22 (s, 1H), 7.05 (d, J = 2.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.93 - 6.89 (m, 2H), 6.86 - 6.82 (m, 1H), 6.42 (d, J = 2.4 Hz, 1H), 4.39 - 4.30 (m, 1H), 4.24 - 4.04 (m, 3H), 3.22 - 3.12 (m, 1H), 3.03 - 2.93 (m, 1H), 2.65 - 2.53 (m, 1H), 2.27 - 2.19 (m, 1H), 2.13 - 2.02 (m, 1H), 1.92 - 1.73 (m, 3H), 1.55 - 1.48 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.73, 159.30, 158.40, 148.35, 145.41, 138.52, 133.23, 130.90, 130.40, 128.80, 128.45, 120.30, 119.80, 119.40, 118.45, 116.95, 112.98, 111.46, 93.88, 87.76, 71.49, 69.49, 67.67, 34.55, 33.94, 28.54, 27.70, 21.09. HRMS (ESI-TOF) calc'd for $\text{C}_{31}\text{H}_{28}\text{O}_3$ ($[\text{M}+\text{H}]^+$) m/z = 449.2117 found 449.2104.

ICI annulation of macrocycle 83.5: Iodine monochloride (2.8 mL, 6.0 mg/mL, 0.10 mmol) in dichloromethane was added dropwise to a stirred solution of **83.5** (21 mg, 0.05 mmol) at -78 °C. After 4h, the reaction was warmed slowly to 23 °C and poured into 10%

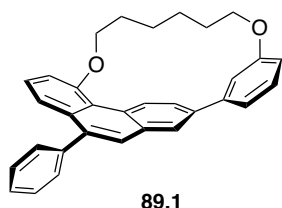
Na₂S₂O₃(aq) solution. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (1.3 cm × 14 cm; 40% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **87.2** as white solid (4 mg, 14%) and compound **87.1** (22 mg, 77%).



Macrocycle 87.2: $R_f = 0.45$ (60% dichloromethane/hexane); ¹H NMR (500 MHz, Chloroform-*d*) δ 9.17 (d, $J = 8.8$ Hz, 1H), 8.29 (d, $J = 1.7$ Hz, 1H), 7.82 (dd, $J = 8.8, 1.7$ Hz, 1H), 7.59 - 7.49 (m, 4H), 7.41 (dd, $J = 8.3, 7.4$ Hz, 1H), 7.36 (ddd, $J = 7.5, 2.2, 1.2$ Hz, 1H), 7.31 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.27 - 7.23 (m, 1H), 7.20 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.07 (dd, $J = 8.2, 1.1$ Hz, 1H), 6.85 (ddd, $J = 8.3, 2.7, 0.9$ Hz, 1H), 6.62 (dd, $J = 2.8, 1.5$ Hz, 1H), 4.31 - 4.21 (m, 2H), 4.09 - 4.01 (m, 1H), 3.26 - 3.20 (m, 1H), 2.22 - 2.12 (m, 1H), 2.08 - 1.96 (m, 1H), 1.82 - 1.72 (m, 1H), 1.61 - 1.56 (m, 1H), 1.53 - 1.43 (m, 2H), 1.42 - 1.31 (m, 1H), 1.24 - 1.13 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 158.19, 157.99, 145.23, 143.17, 141.98, 134.49, 133.05, 131.09, 130.77, 130.53, 129.74, 129.45, 128.85, 128.48, 128.19, 128.08, 127.36, 126.02, 123.86, 122.33, 119.04, 116.56, 116.07, 115.67, 105.99, 75.11, 69.92, 31.20, 27.71, 27.19, 26.67. HRMS (ESI-TOF) calc'd for C₃₂H₂₈O₂l ([M+H]⁺) $m/z = 571.1134$ found 571.1158.

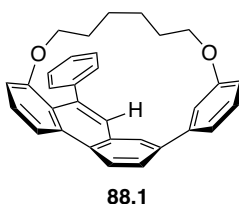


Macrocycle 87.1: $R_f = 0.31$ (60% dichloromethane/hexane); ¹H NMR at rt (500 MHz, Chloroform-*d*) δ 8.26 (d, $J = 1.7$ Hz, 1H), 8.20 (d, $J = 8.6$ Hz, 1H), 8.11 (dd, $J = 8.3, 1.0$ Hz, 1H), 7.57 - 7.50 (m, 2H), 7.49 - 7.39 (m, 3H), 7.37 - 7.31 (m, 2H), 6.94 (dd, $J = 7.6, 1.0$ Hz, 1H), 6.77 - 6.73 (m, 1H), 5.61 - 5.57 (m, 1H), 3.94 - 3.81 (m, 3H), 3.32 (ddd, $J = 11.9, 7.3, 6.1$ Hz, 1H), 1.28 - 1.14 (m, 2H), 0.94 - 0.71 (m, 4H), 0.66 - 0.56 (m, 1H), 0.36 - 0.25 (m, 1H). ¹³C NMR at rt (126 MHz, CDCl₃) δ 157.79, 157.74, 145.51, 143.83, 142.91, 141.67, 136.75, 134.22, 133.87, 130.78, 130.40, 129.90, 129.03, 128.41, 127.64, 122.49, 119.69, 119.63, 116.34, 115.91, 115.57, 101.56, 76.58, 69.48, 29.85, 27.25, 27.20, 25.97. ¹H NMR at -30 °C (500 MHz, Chloroform-*d*) δ 8.28 (d, $J = 1.7$ Hz, 1H), 8.21 (d, $J = 8.6$ Hz, 1H), 8.12 (d, $J = 8.2$ Hz, 1H), 7.92 (d, $J = 7.7$ Hz, 1H), 7.60 - 7.51 (m, 3H), 7.45 (dd, $J = 7.3$ Hz, 1H), 7.42 - 7.34 (m, 3H), 7.01 (d, $J = 7.6$ Hz, 1H), 6.96 (d, $J = 7.5$ Hz, 1H), 6.77 - 6.73 (m, 1H), 5.64 - 5.60 (m, 1H), 3.95 - 3.83 (m, 3H), 3.25 (ddd, $J = 12.6, 7.6, 5.7$ Hz, 1H), 1.26 - 1.12 (m, 2H), 1.01 - 0.91 (m, 2H), 0.90 - 0.80 (m, 1H), 0.79 - 0.60 (m, 2H), 0.28 - 0.17 (m, 1H). ¹³C NMR at -30 °C (126 MHz, CDCl₃) δ 157.51, 157.34, 145.30, 143.48, 142.48, 141.24, 136.51, 133.61, 133.47, 131.94, 130.46, 129.92, 129.43, 129.07, 128.45, 128.22, 127.58, 127.12, 122.44, 119.72, 119.53, 116.42, 115.81, 115.21, 101.44, 77.15, 69.24, 29.63, 26.87, 26.70, 25.37. HRMS (ESI-TOF) calc'd for C₃₂H₂₈O₂l ([M+H]⁺) $m/z = 571.1134$ found 571.1120.

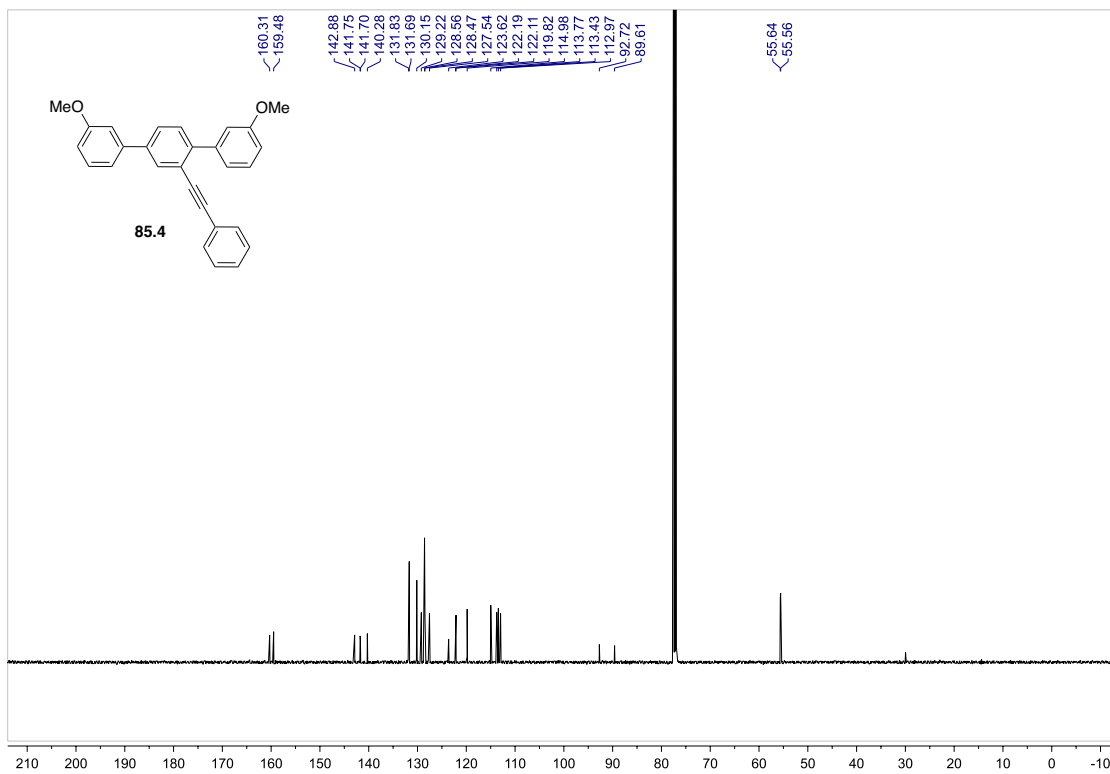
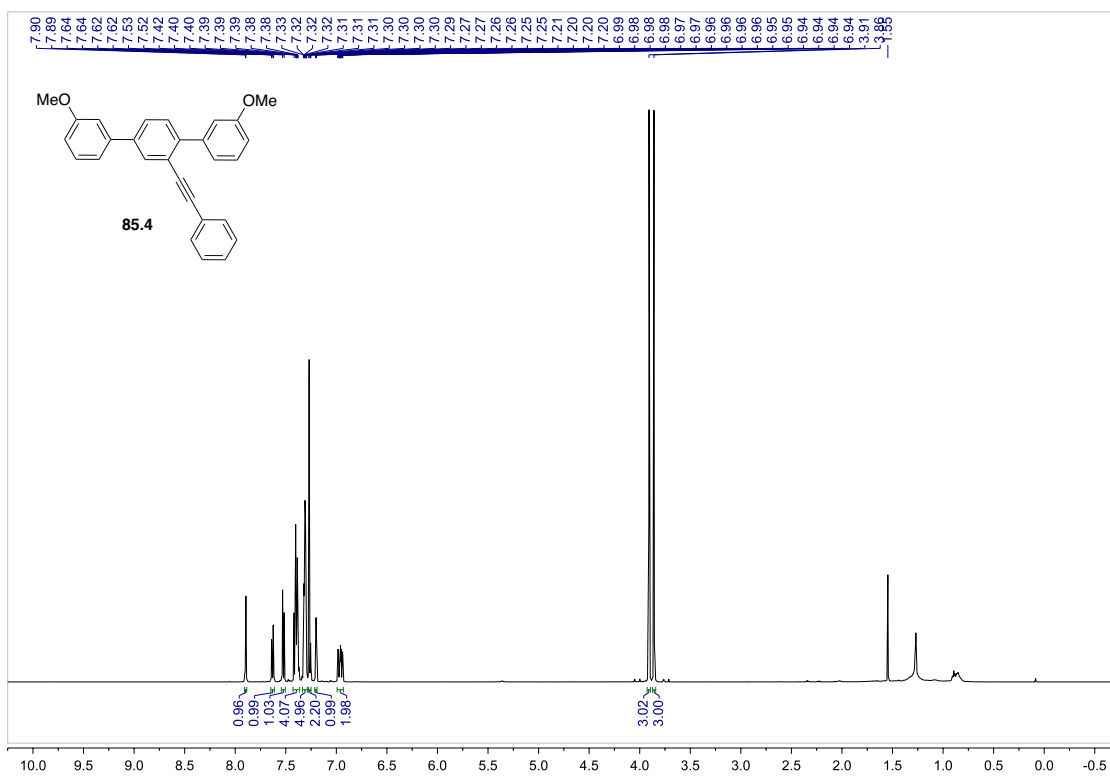


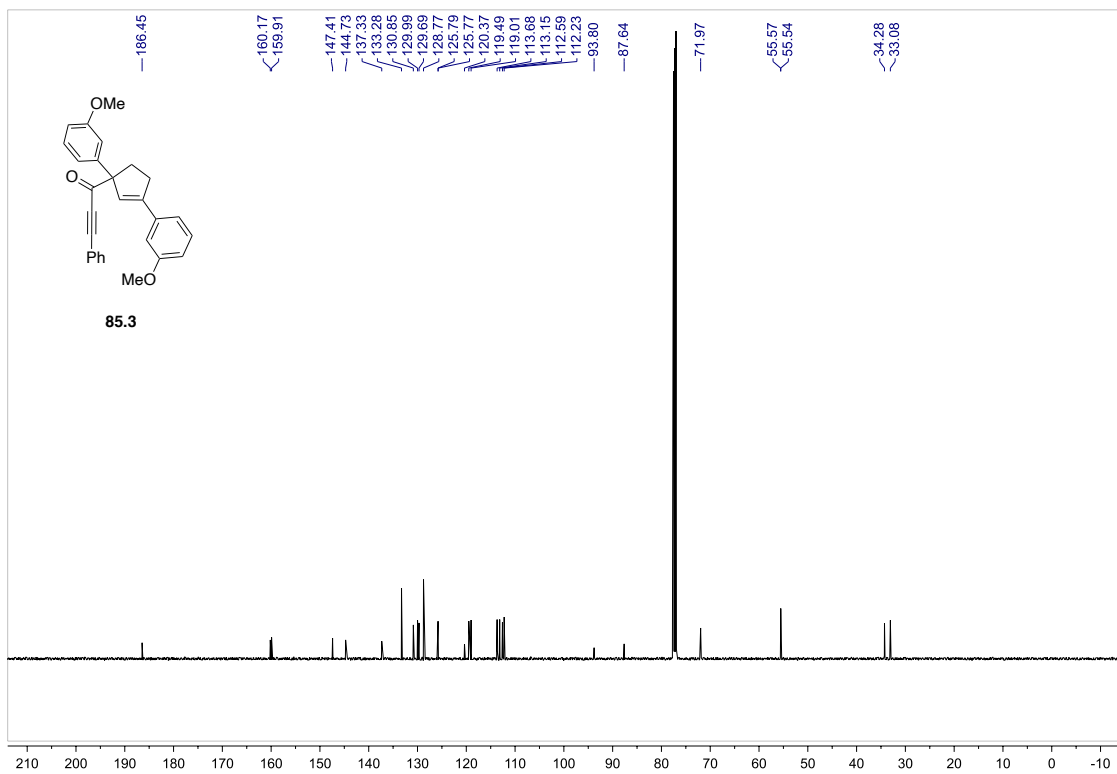
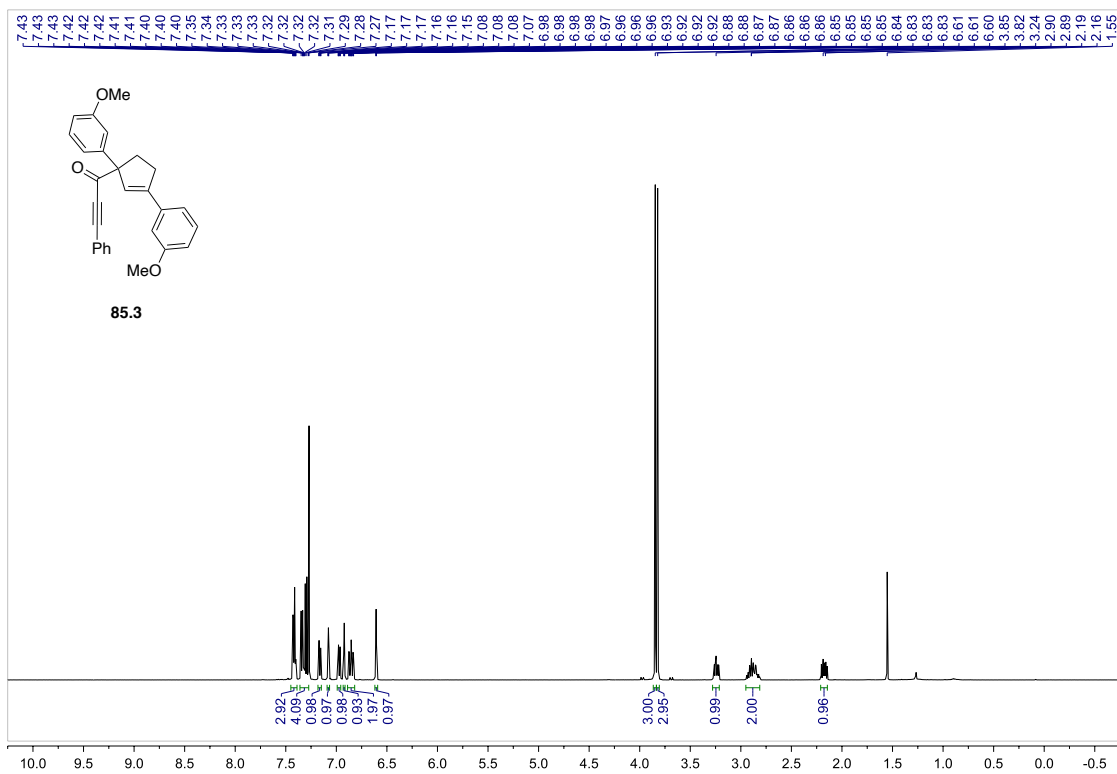
Macrocycle 89.1: To a dry 10 mL round bottom flask was added 3 mL toluene and macrocycle **17 87.2** (4 mg, 0.007 mmol). The mixture was then cooled to -78 °C and then a 2.35 M solution of *n*-butyllithium in hexanes (0.03 mL, 0.04 mmol) was added. After 1 h, methanol (0.5 mL) was added to the reaction. The reaction mixture was allowed to warm to rt and stirred for additional 1 h

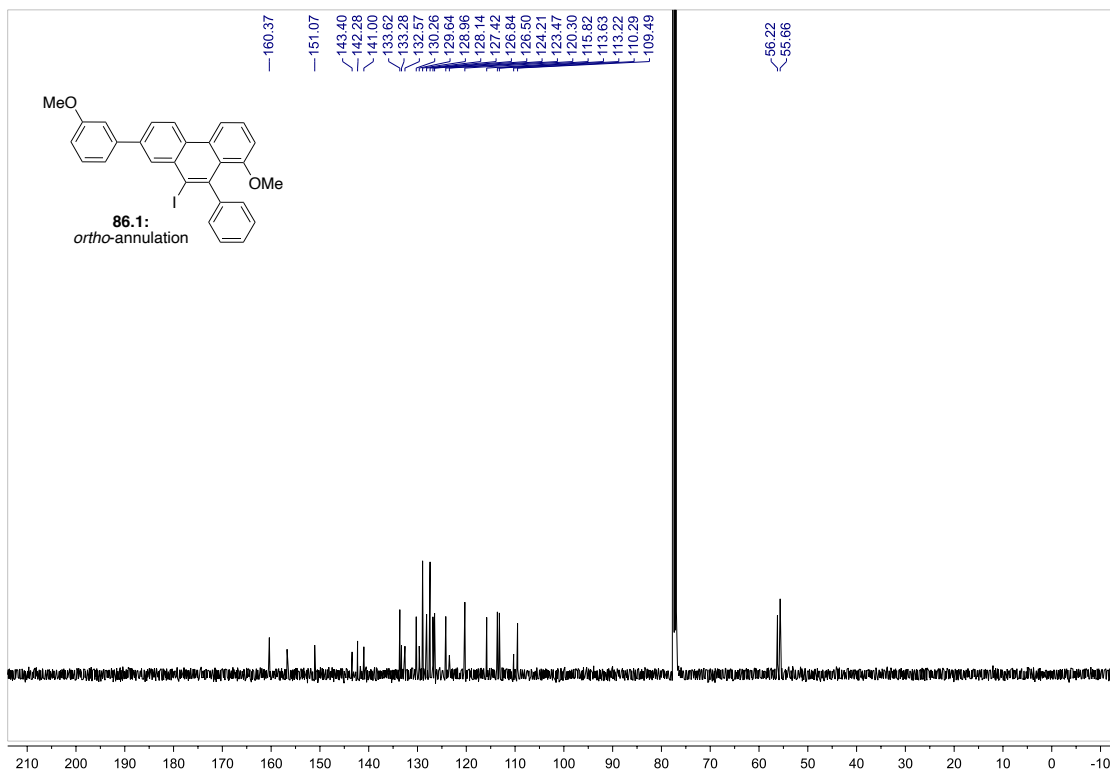
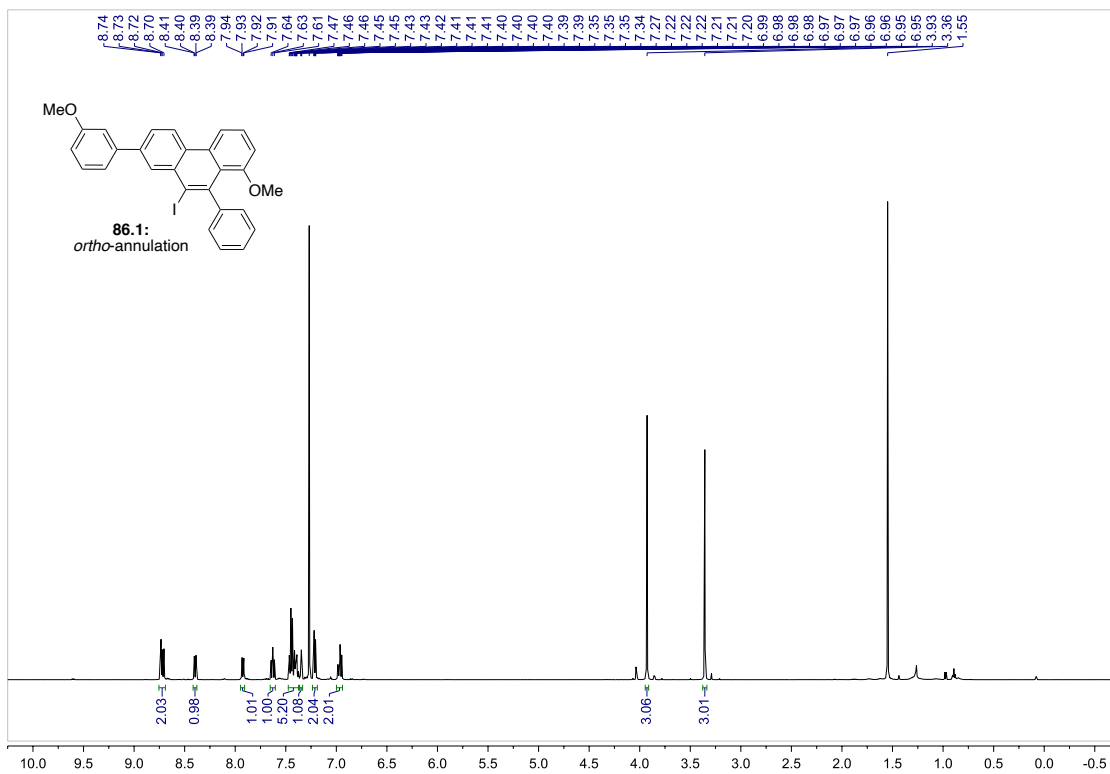
then added water (5mL) with stirring. The mixture was further diluted by addition of 5 mL dichloromethane. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 3 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **89.1** as white solid (3 mg, 96%): *R_f* = 0.29 (60% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 9.25 (dd, *J* = 8.9, 0.8 Hz, 1H), 7.86 (d, *J* = 1.8 Hz, 1H), 7.80 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.63 (d, *J* = 0.8 Hz, 1H), 7.59 - 7.50 (m, 5H), 7.49 - 7.36 (m, 4H), 7.22 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.83 (ddd, *J* = 8.1, 2.8, 0.9 Hz, 1H), 6.62 (dd, *J* = 2.9, 1.5 Hz, 1H), 4.31 - 4.21 (m, 2H), 4.10 - 4.01 (m, 1H), 3.27 - 3.19 (m, 1H), 2.23 - 2.13 (m, 1H), 2.07 - 1.98 (m, 1H), 1.83 - 1.74 (m, 1H), 1.54 - 1.46 (m, 2H), 1.37 - 1.28 (m, 2H), 1.23 - 1.14 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 158.57, 158.16, 143.50, 140.97, 140.86, 139.44, 133.62, 131.36, 130.44, 130.13, 129.76, 128.61, 127.63, 127.15, 127.09, 126.98, 125.41, 124.89, 124.41, 121.02, 119.26, 116.37, 115.78, 115.39, 75.33, 70.09, 31.25, 27.82, 27.39, 26.76. HRMS (ESI-TOF) calc'd for C₃₂H₂₉O₂ ([M+H]⁺) *m/z* = 445.2168 found 445.2154.

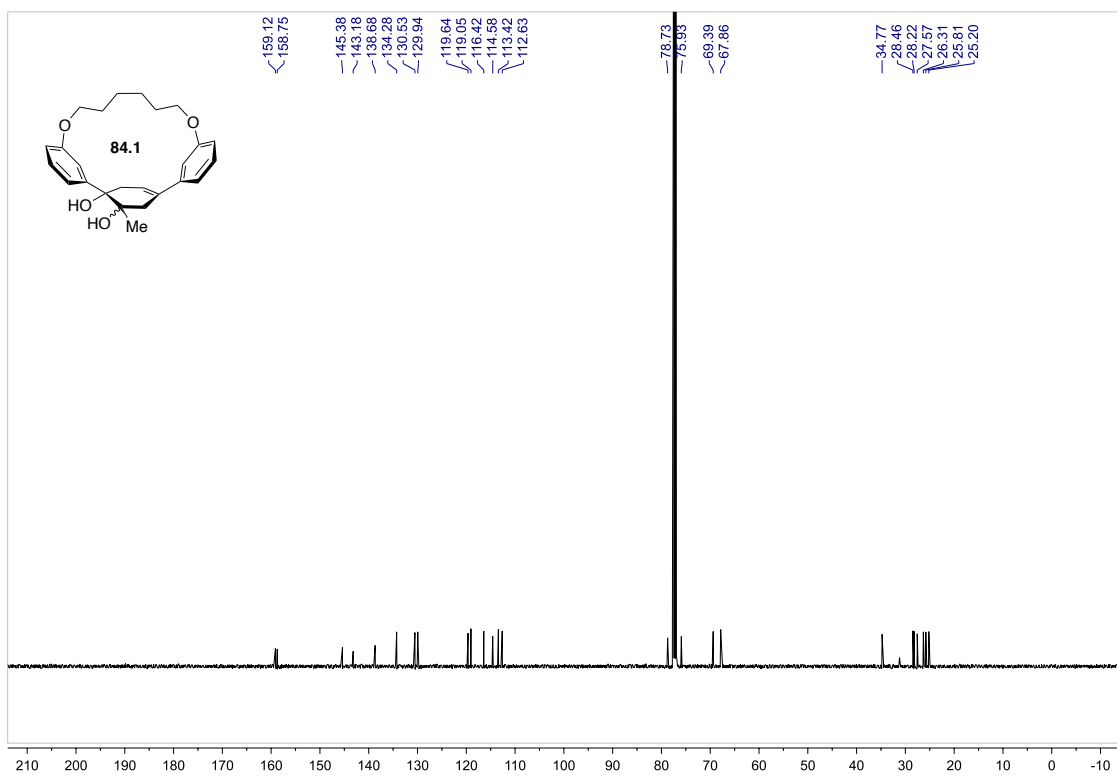
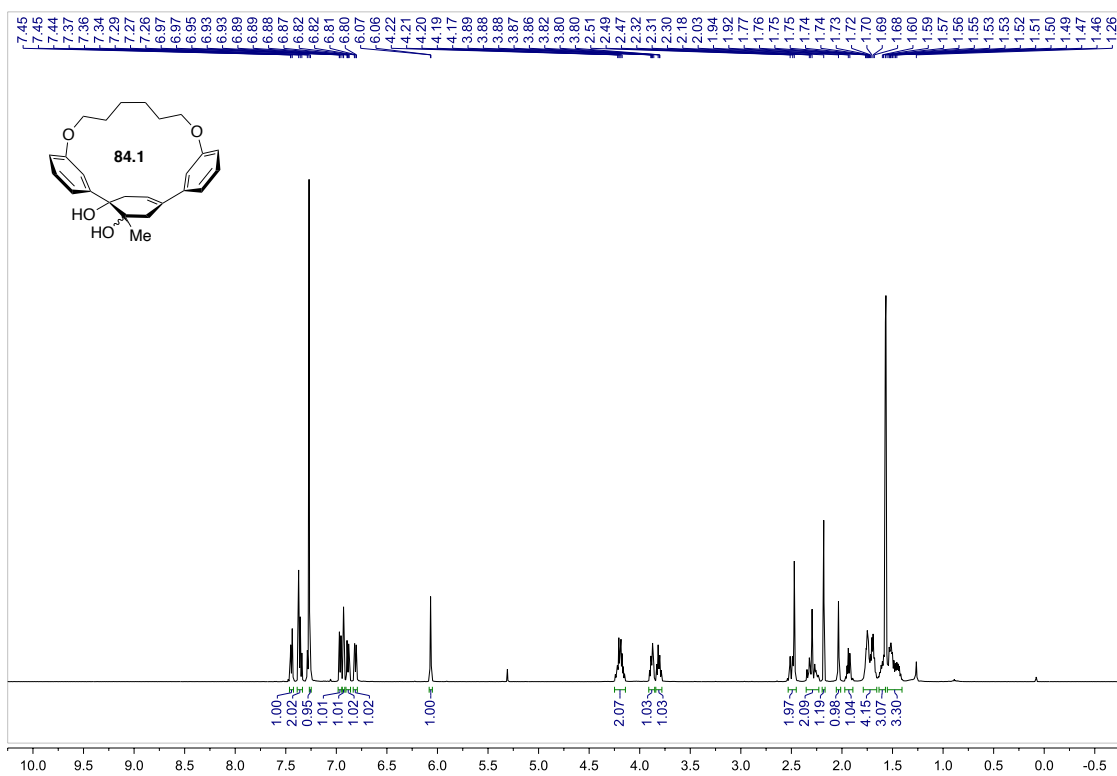


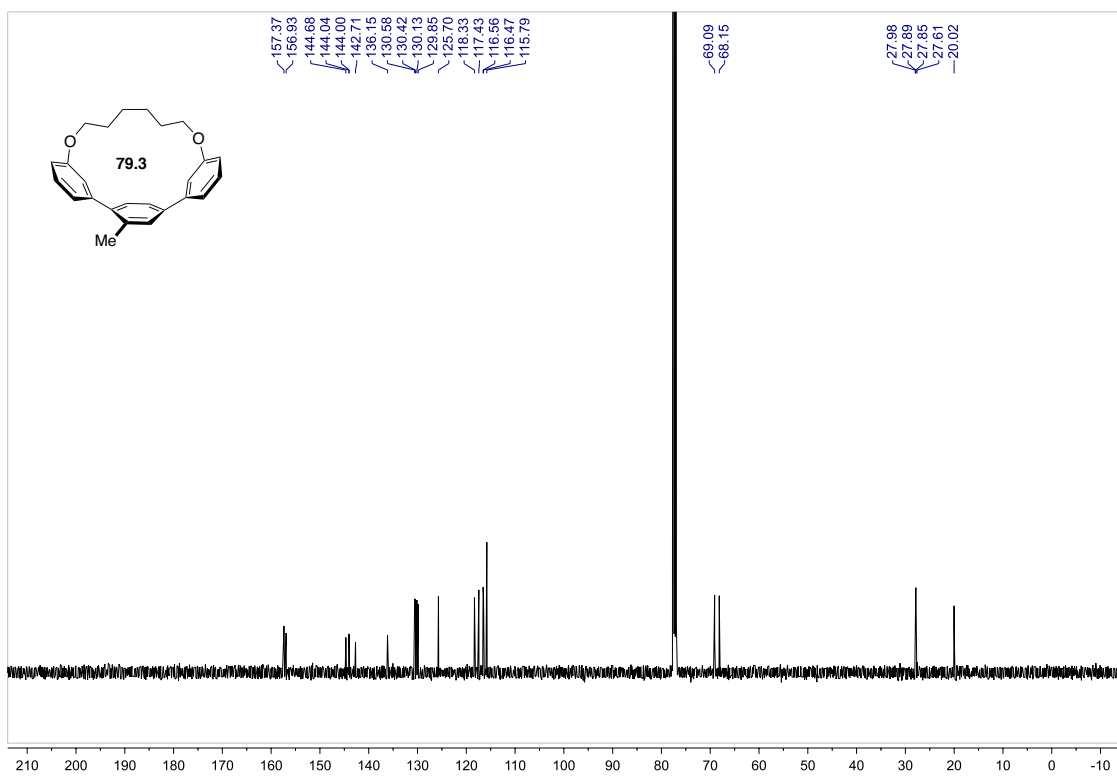
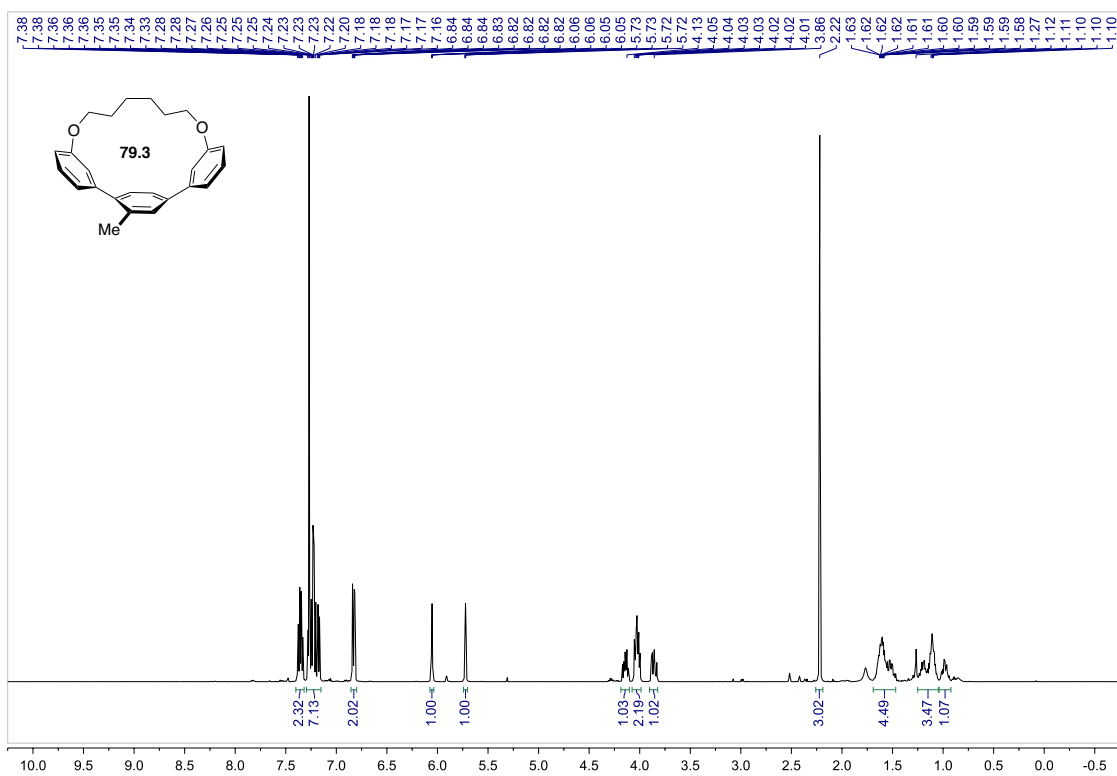
Macrocycle 88.1: To a dry 10 mL round bottom flask was added 3 mL toluene and macrocycle **87.1** (4 mg, 0.007 mmol). The mixture was then cooled to -78 °C and then a 2.35 M solution of *n*-butyllithium in hexanes (0.03 mL, 0.04 mmol) was added. After 1 h, methanol (0.5 mL) was added to the reaction. The reaction mixture was allowed to warm to rt and stirred for additional 1 h then added water (5mL) with stirring. The mixture was further diluted by addition of 5 mL dichloromethane. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 3 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was directly subjected to flash chromatography (0.5 cm × 8 cm; 50% dichloromethane/hexane to 60% dichloromethane/hexane) to yield **88.1** as white solid (3 mg, 96%): *R_f* = 0.29 (60% dichloromethane/hexane). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 8.6 Hz, 1H), 8.23 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.92 (d, *J* = 1.8 Hz, 1H), 7.78 (s, 1H), 7.68 - 7.65 (m, 2H), 7.57 - 7.52 (m, 2H), 7.48 - 7.44 (m, 2H), 7.39 - 7.35 (m, 1H), 7.34 - 7.31 (m, 2H), 7.04 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.75 - 6.70 (m, 1H), 5.58 - 5.56 (m, 1H), 3.90 - 3.83 (m, 2H), 3.81 - 3.73 (m, 1H), 3.33 - 3.26 (m, 1H), 1.23 - 1.14 (m, 2H), 0.87 - 0.82 (m, 1H), 0.76 - 0.62 (m, 2H), 0.57 - 0.37 (m, 2H), 0.25 - 0.15 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 158.20, 157.59, 144.25, 142.43, 141.98, 137.04, 134.52, 133.69, 130.72, 130.29, 128.99, 128.91, 128.51, 128.39, 128.16, 127.33, 125.74, 125.35, 123.14, 119.92, 119.19, 116.99, 115.81, 115.40, 76.02, 69.39, 29.42, 27.30, 27.16, 26.51.

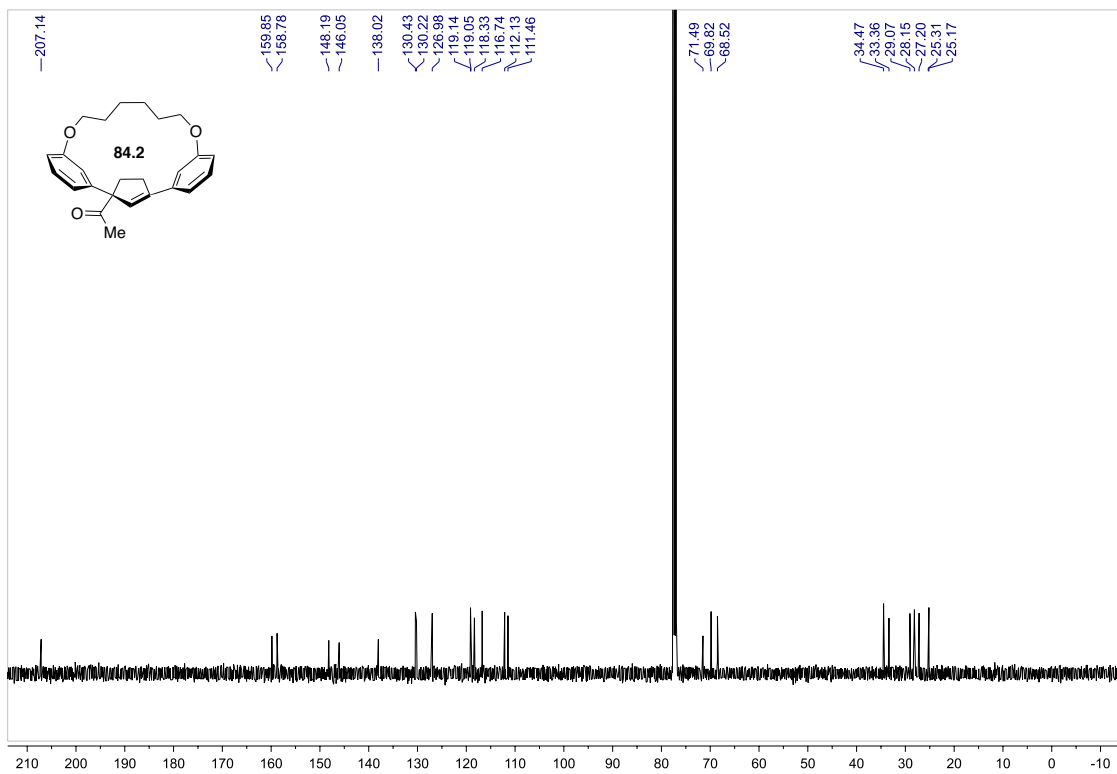
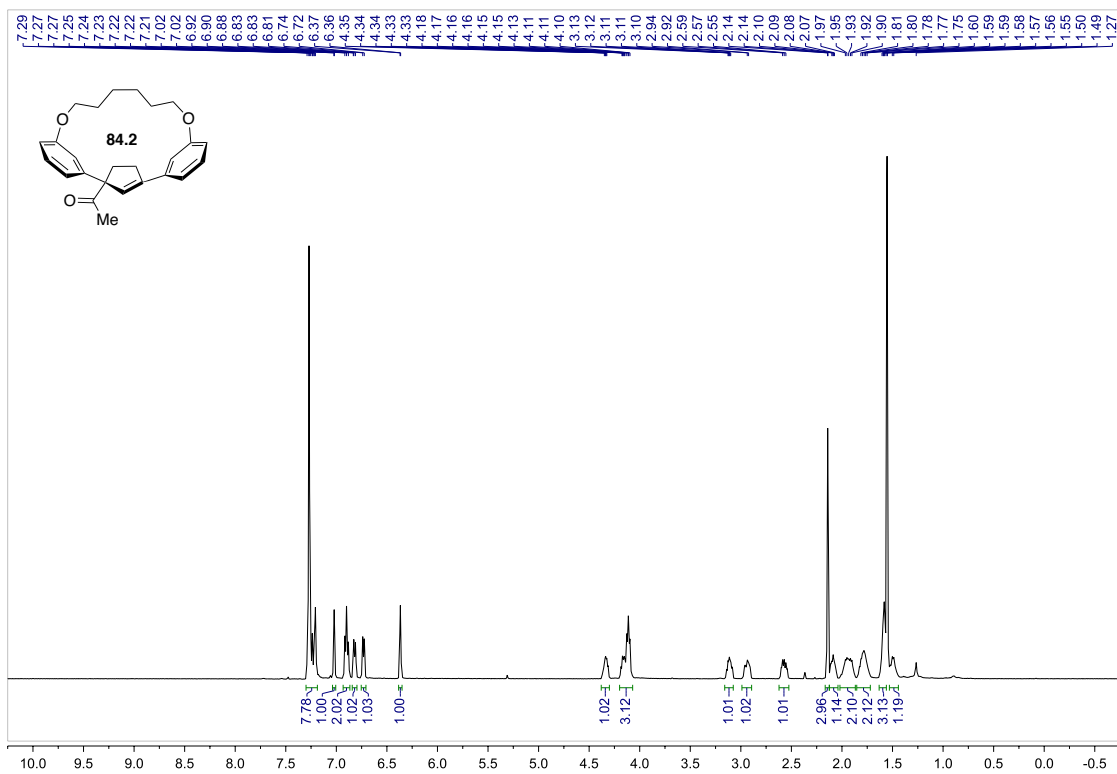


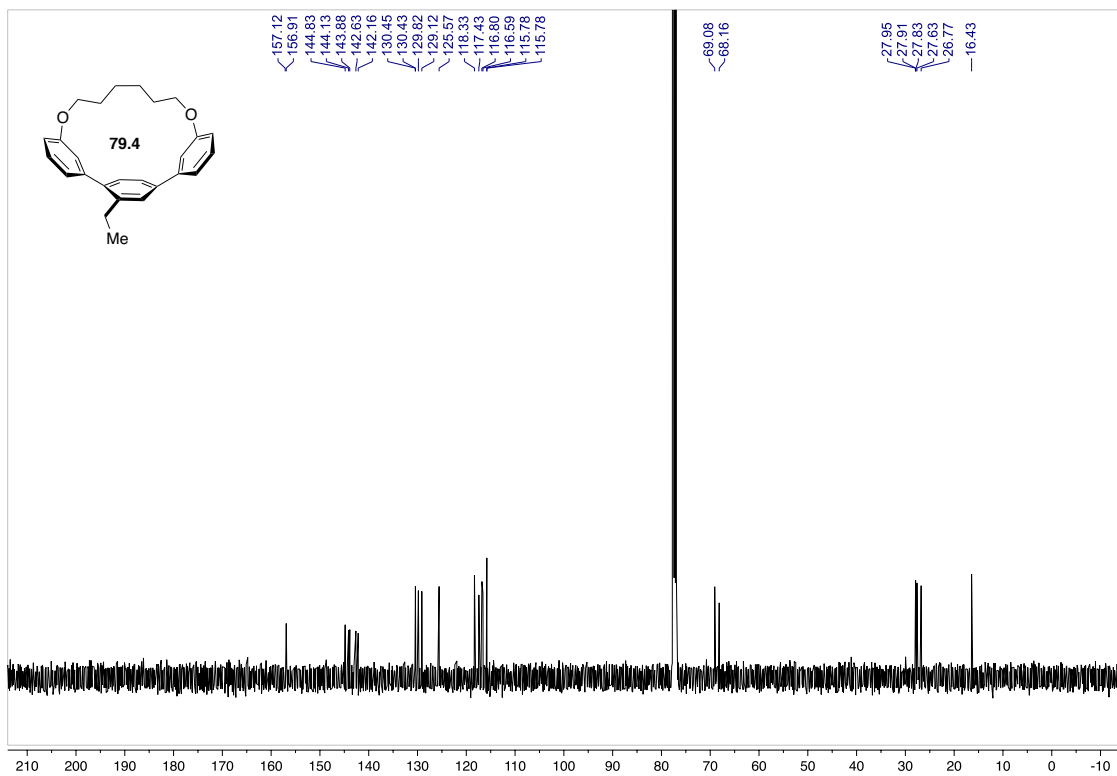
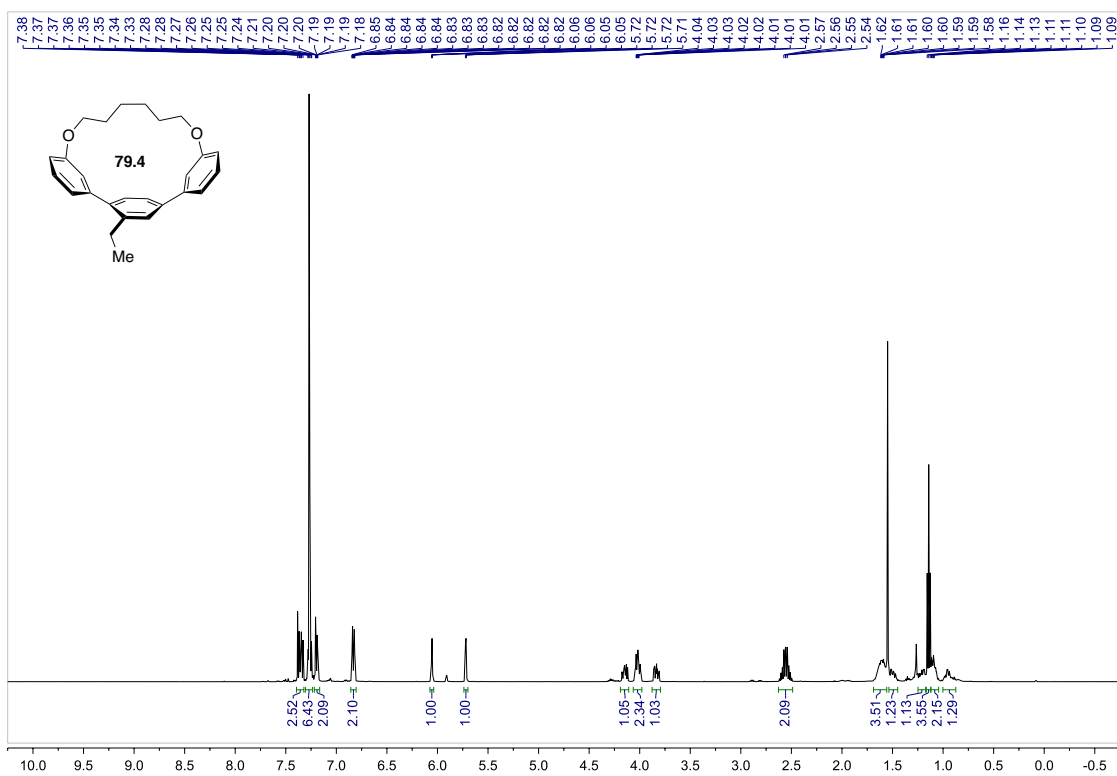


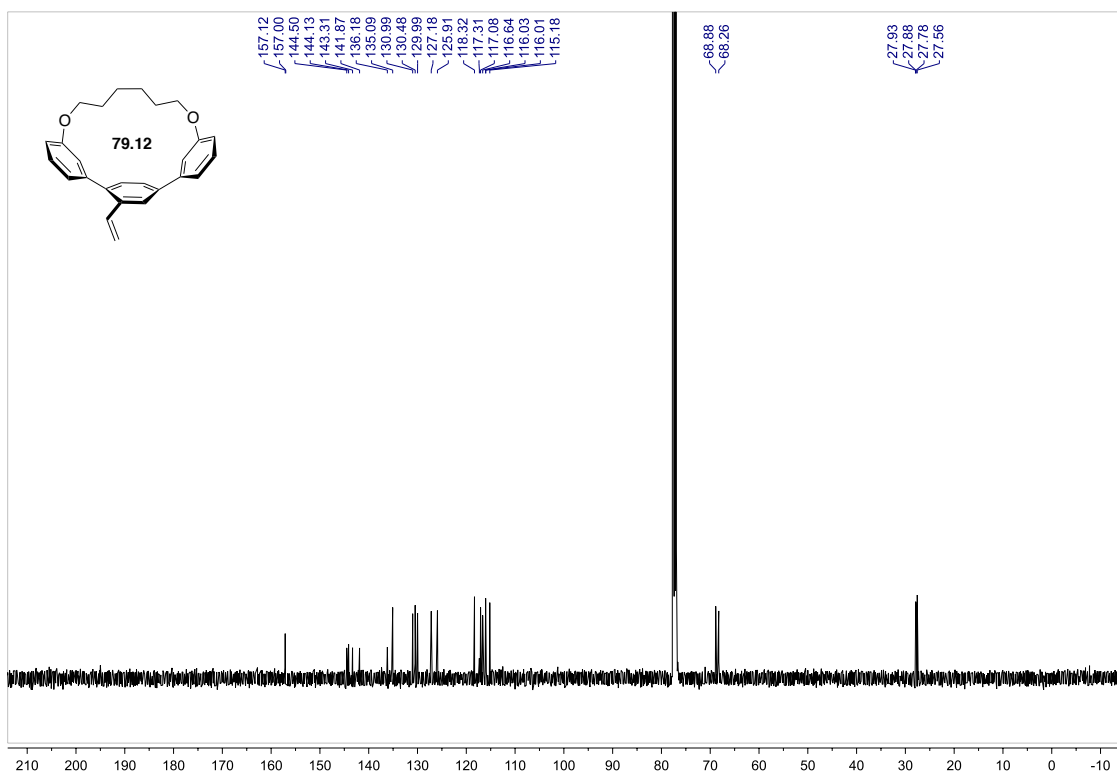
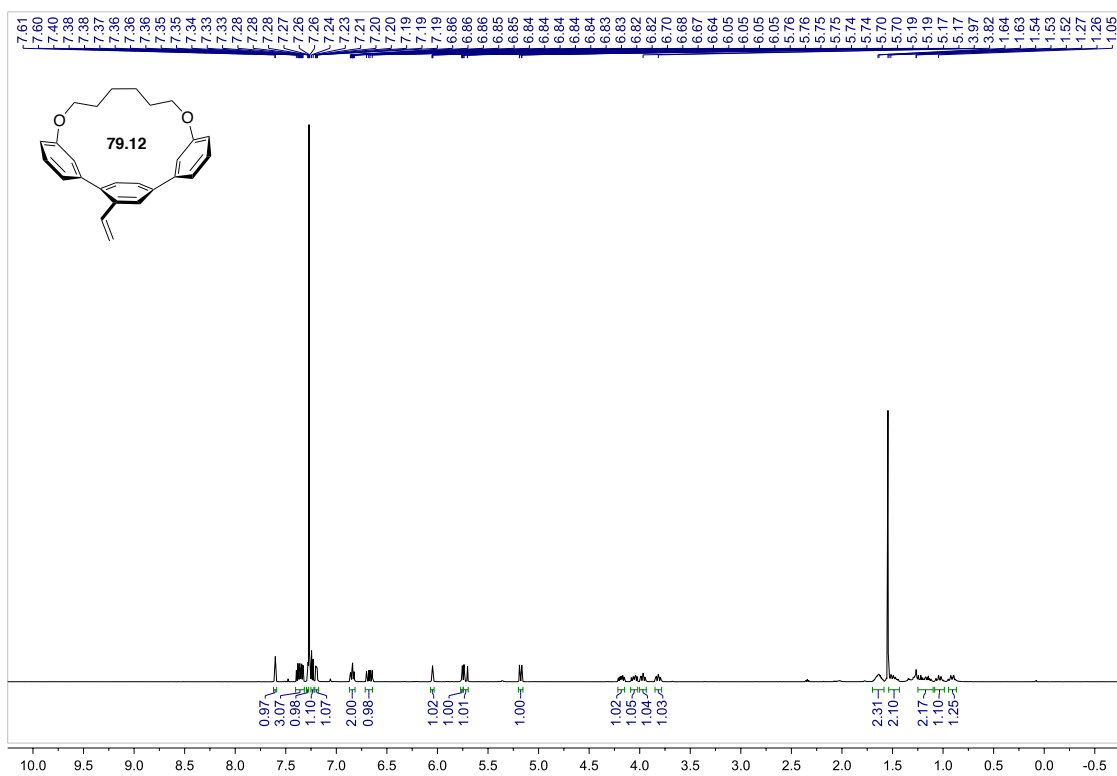


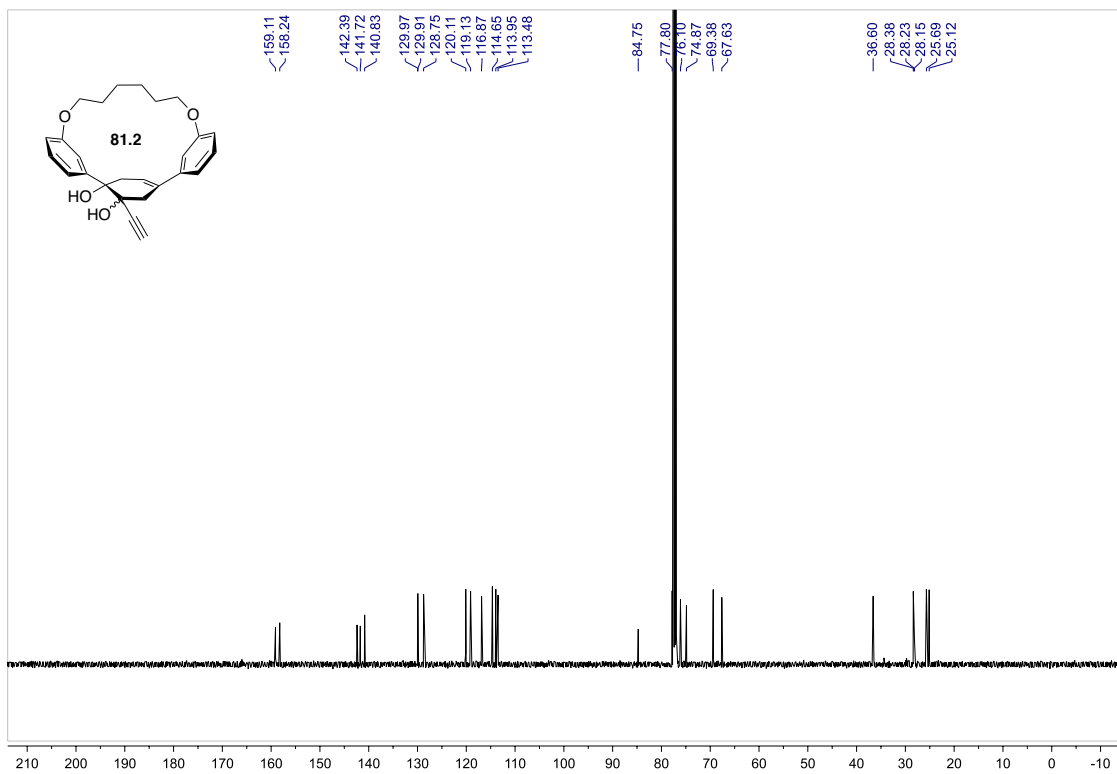
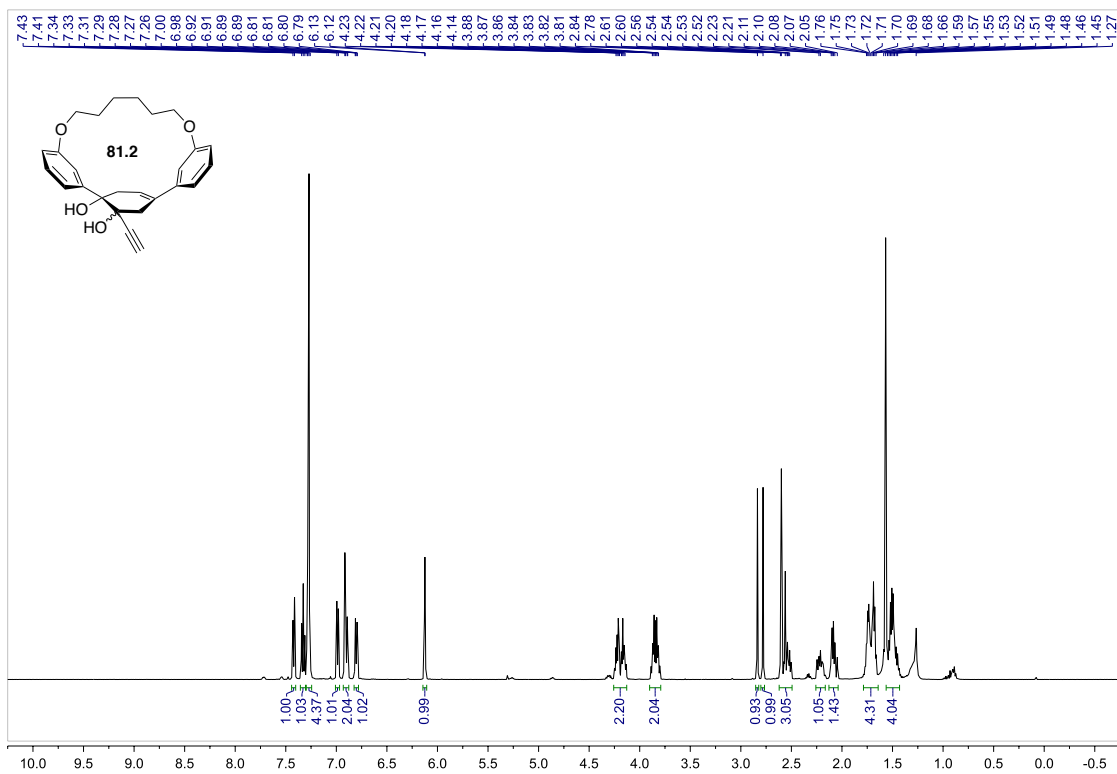


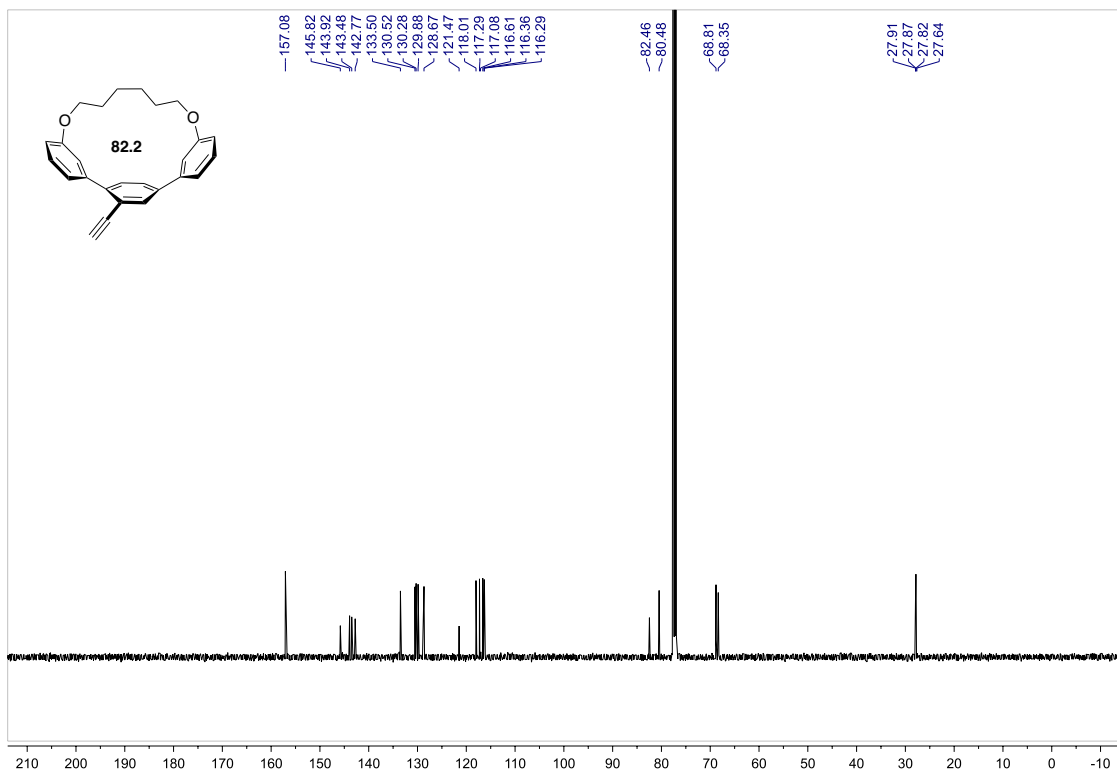
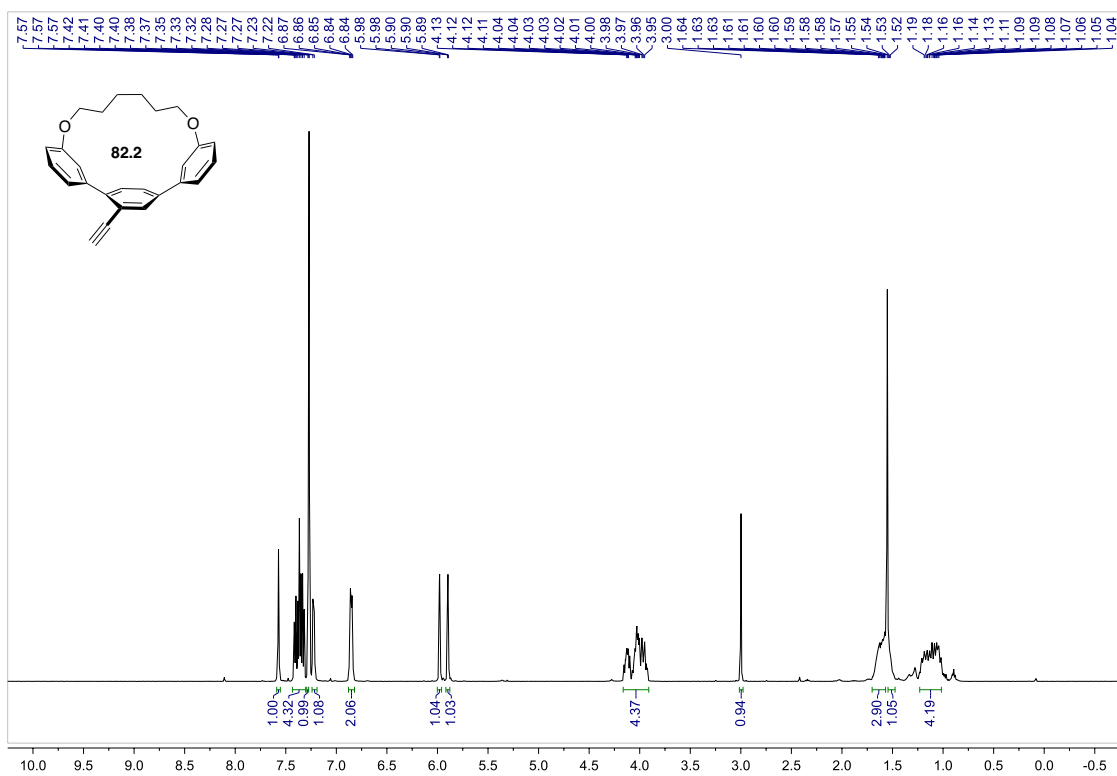


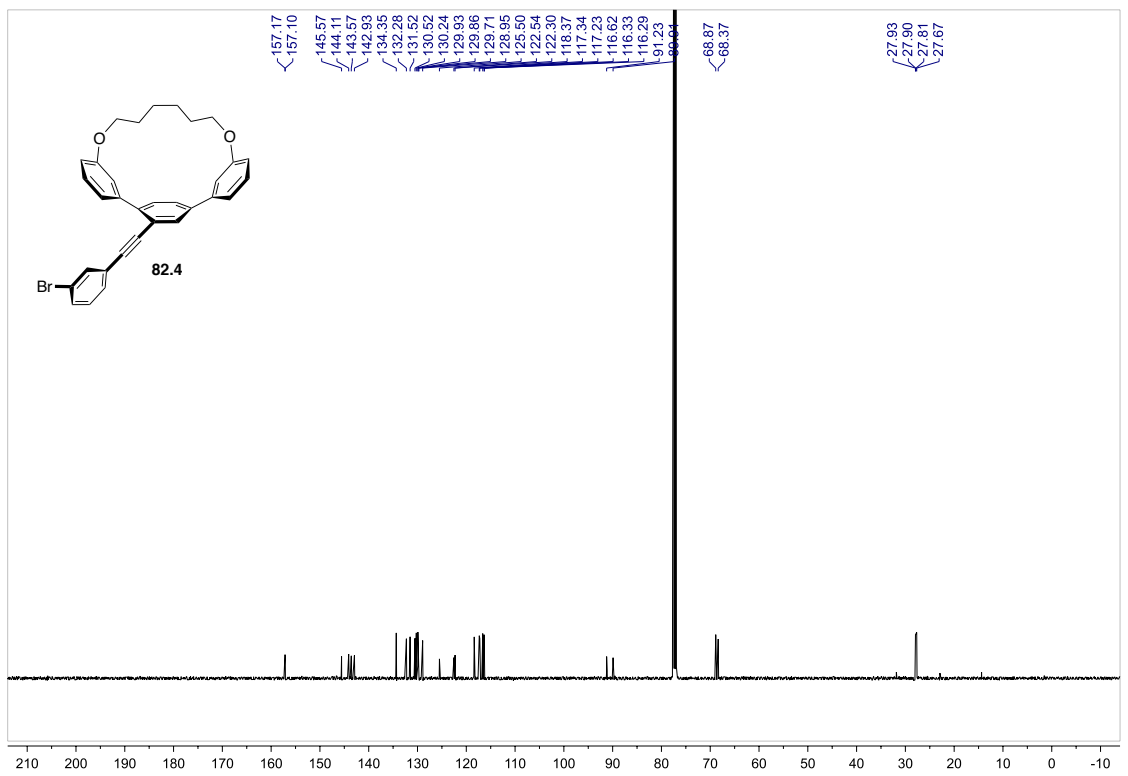
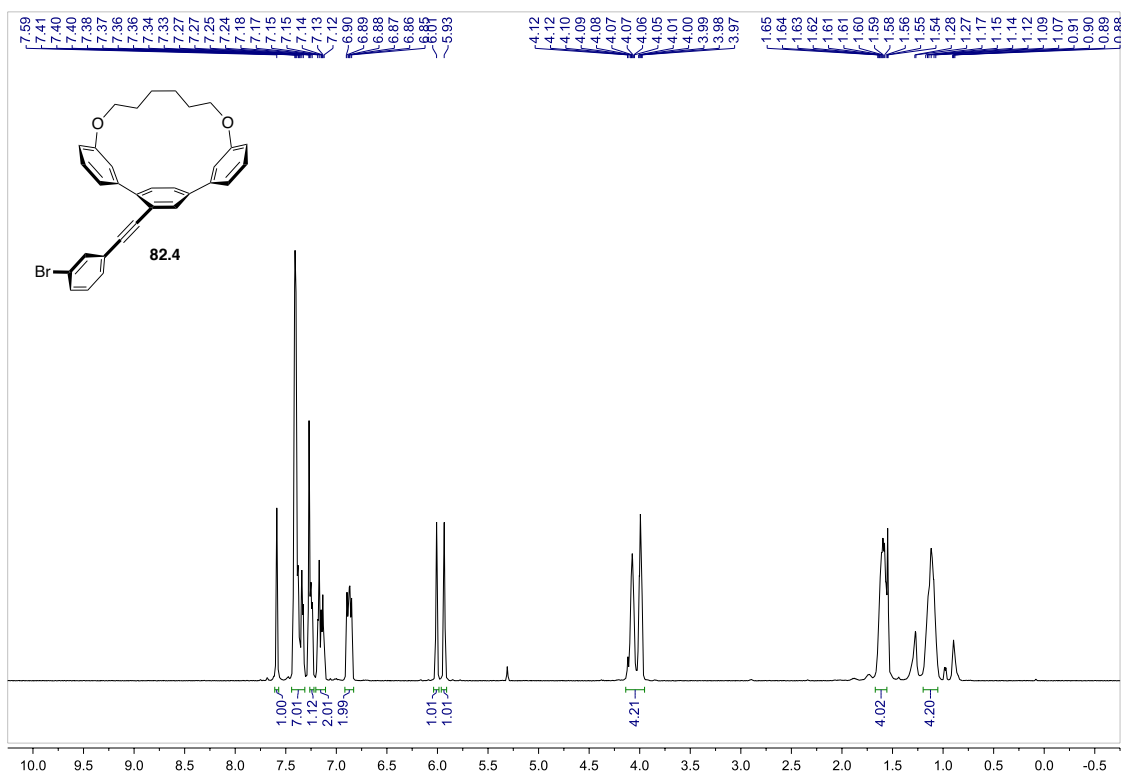


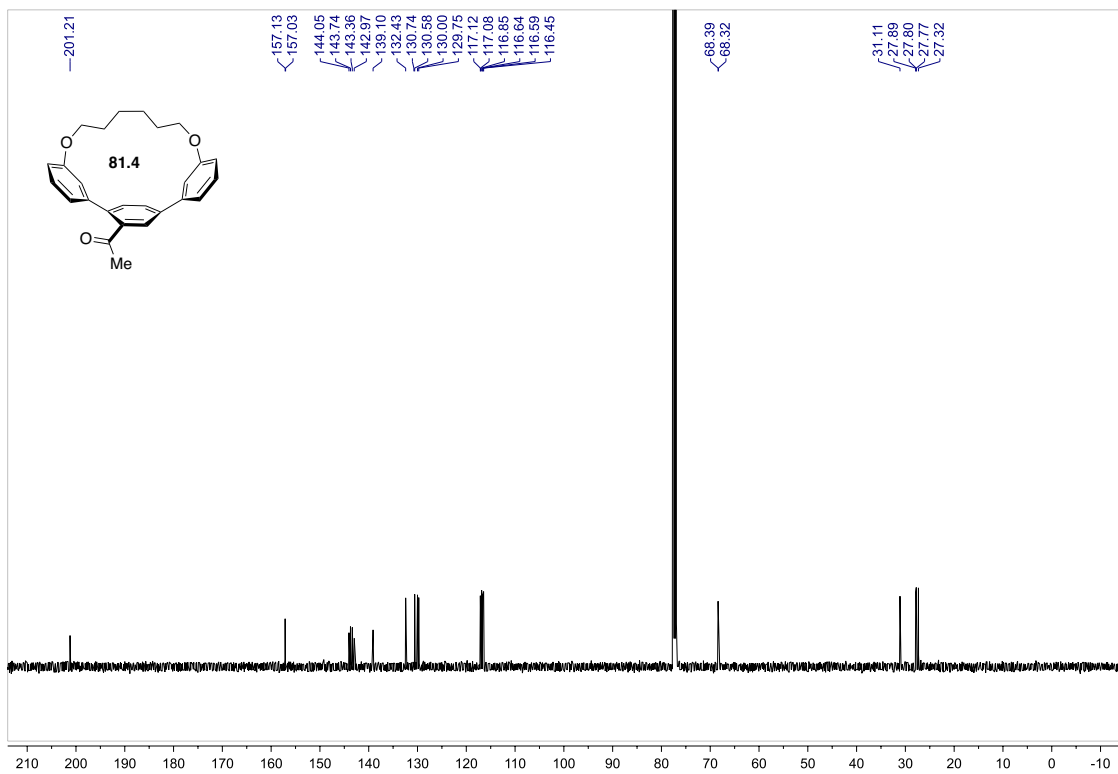
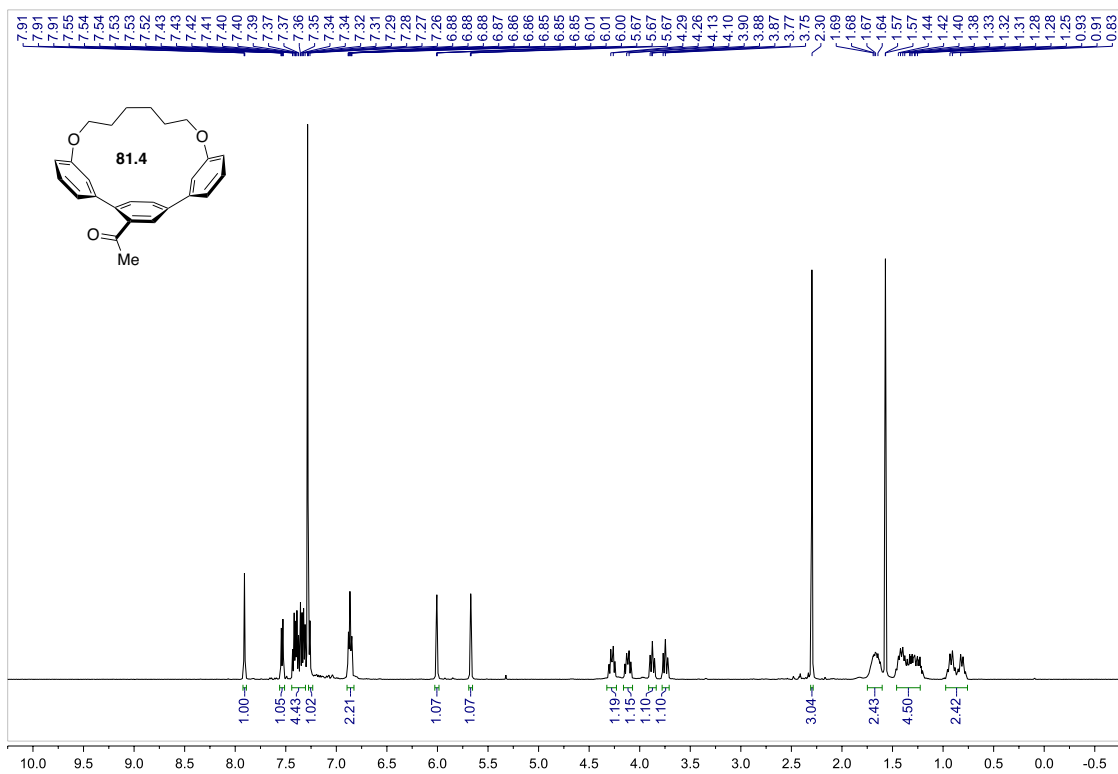


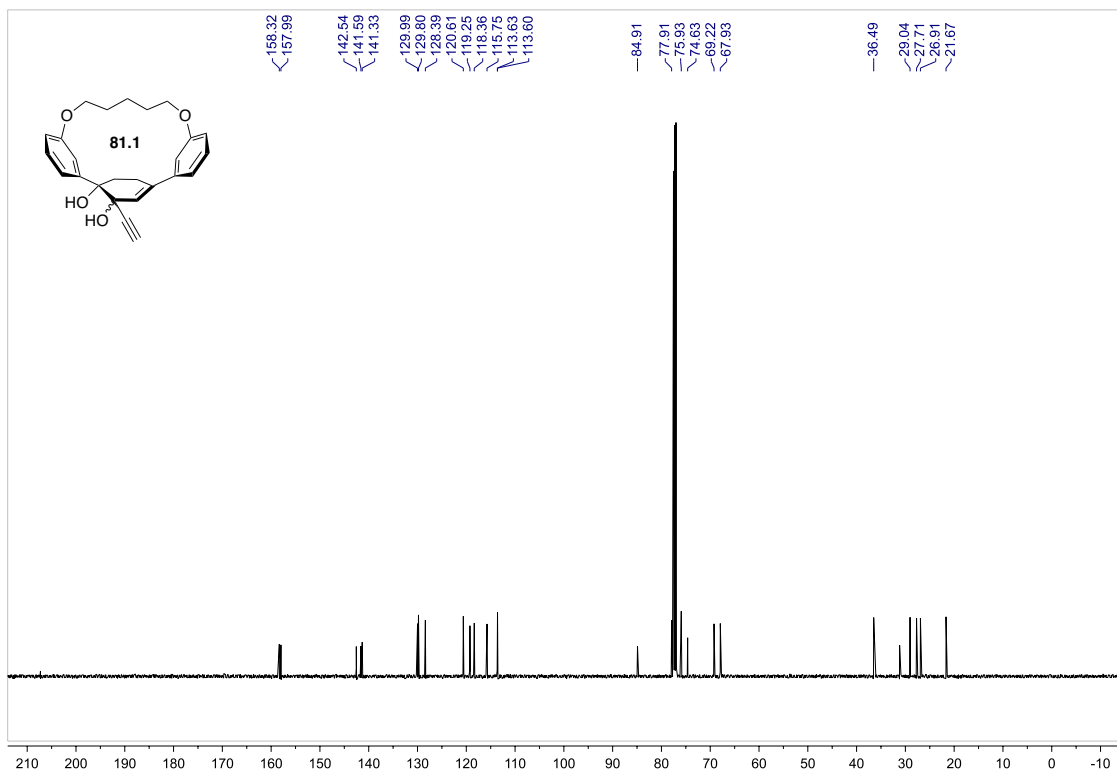
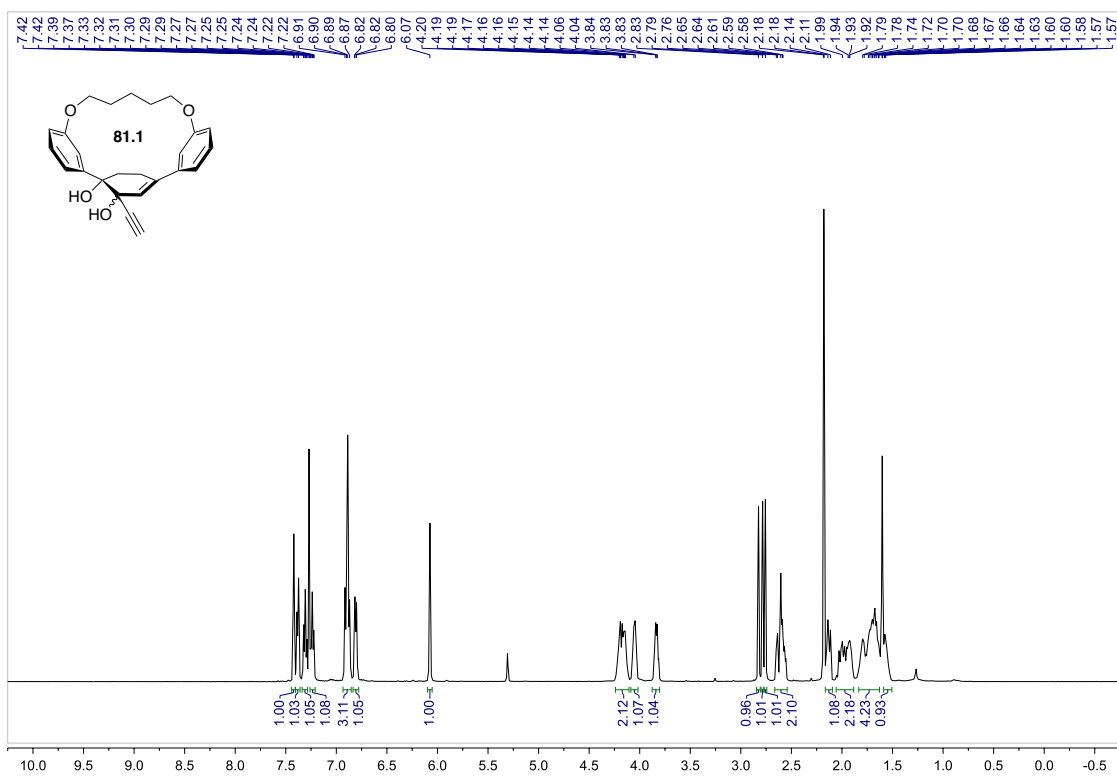


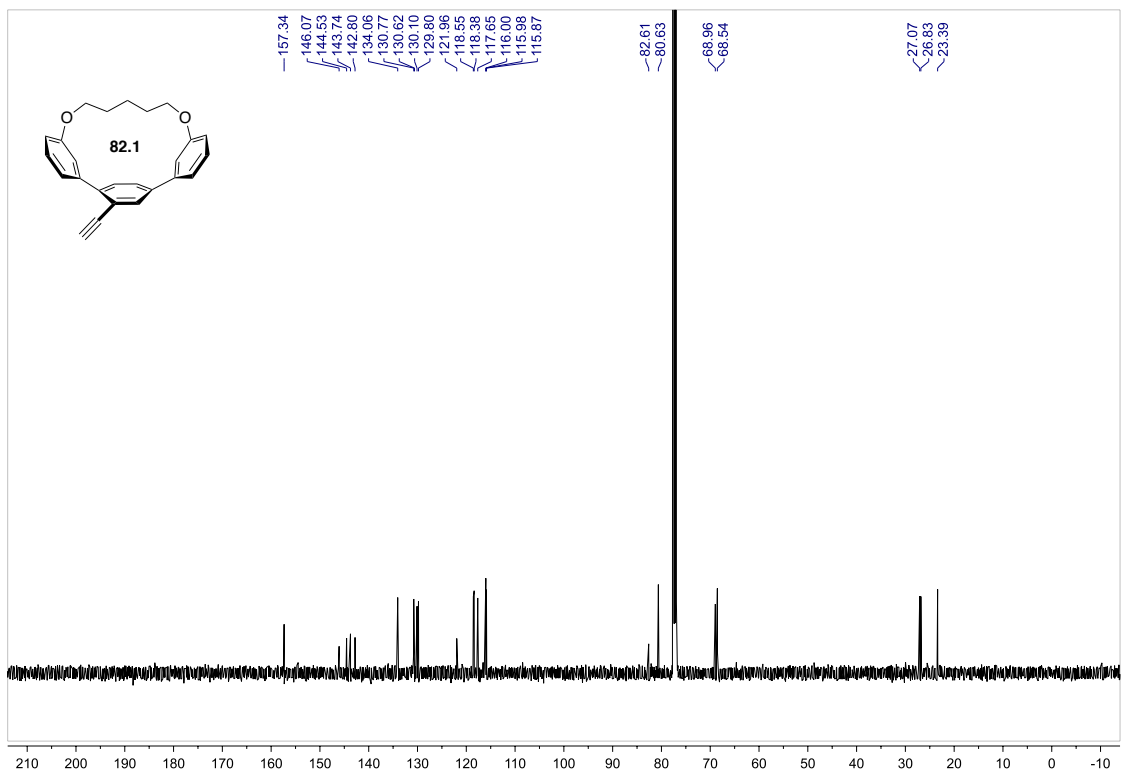
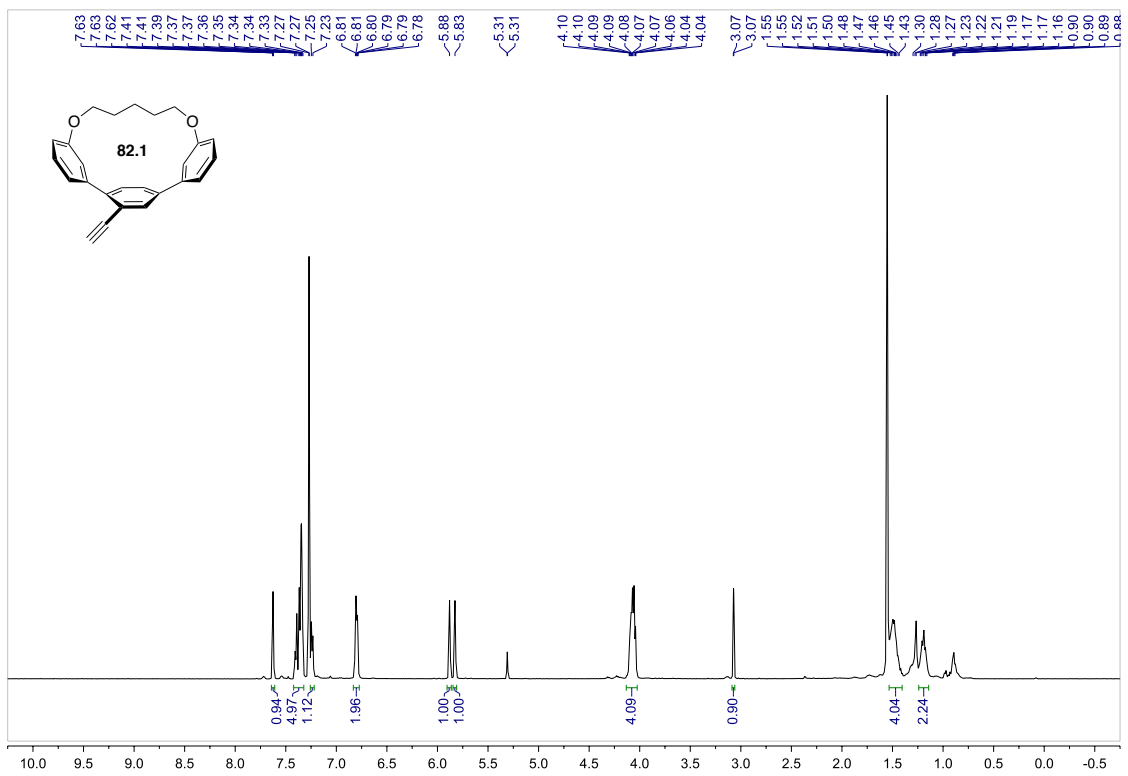


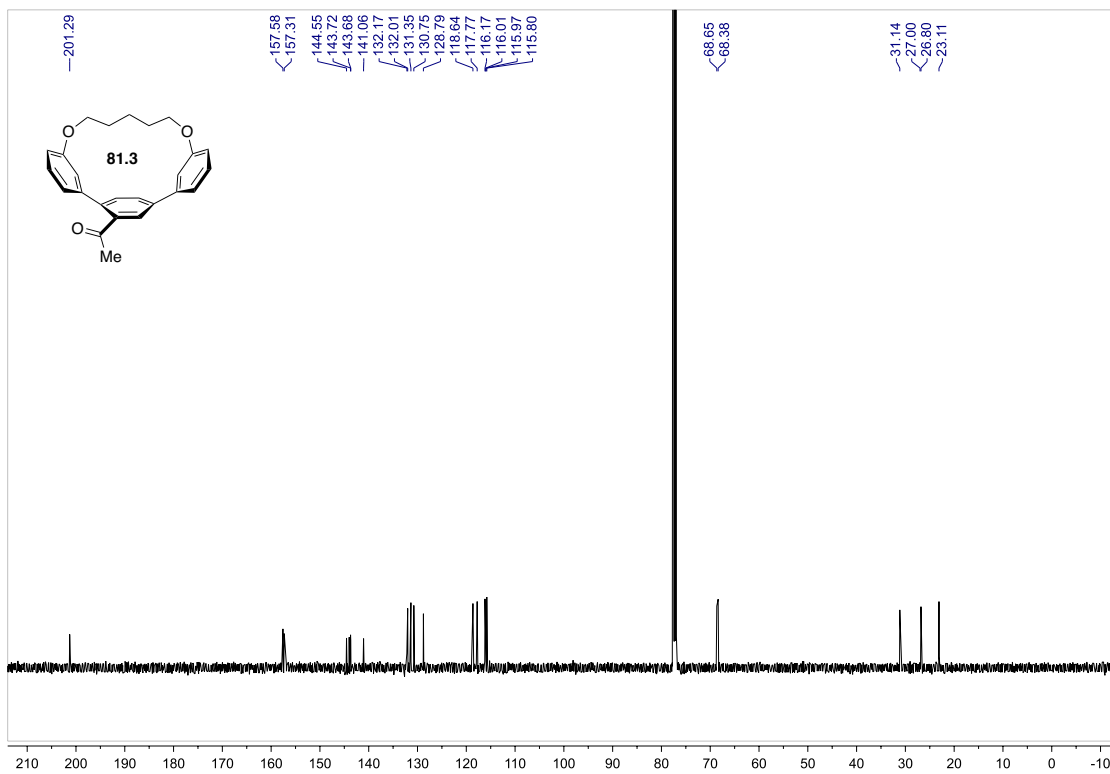
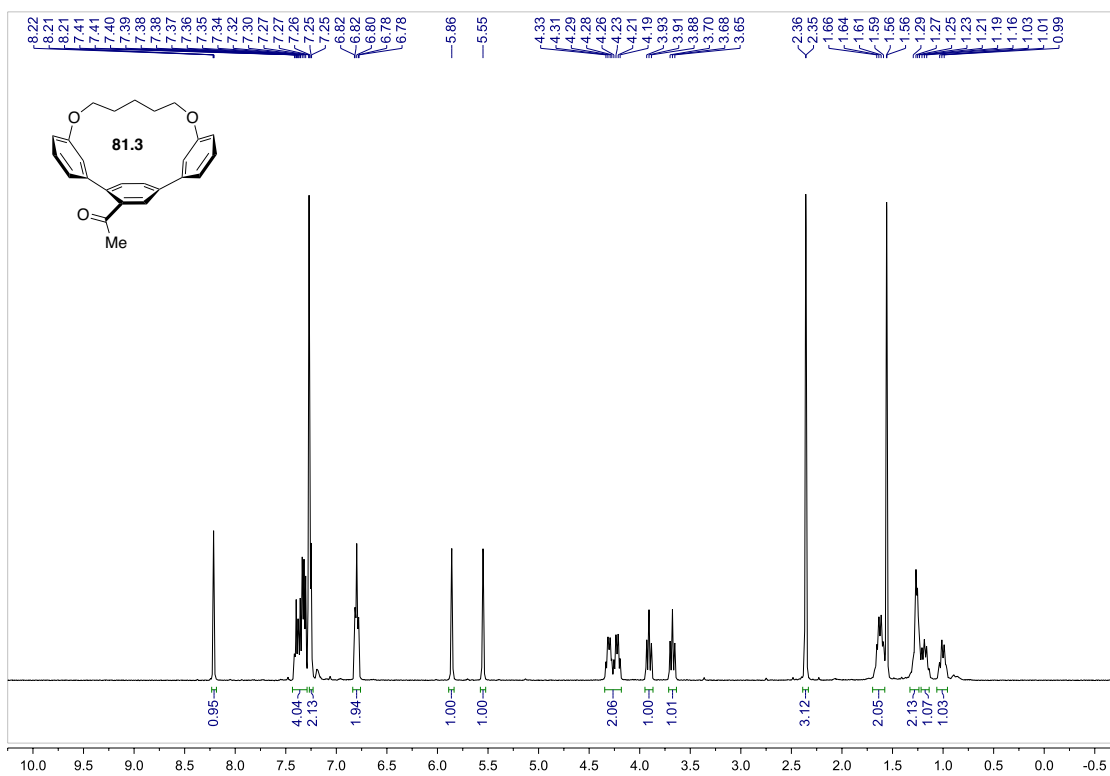


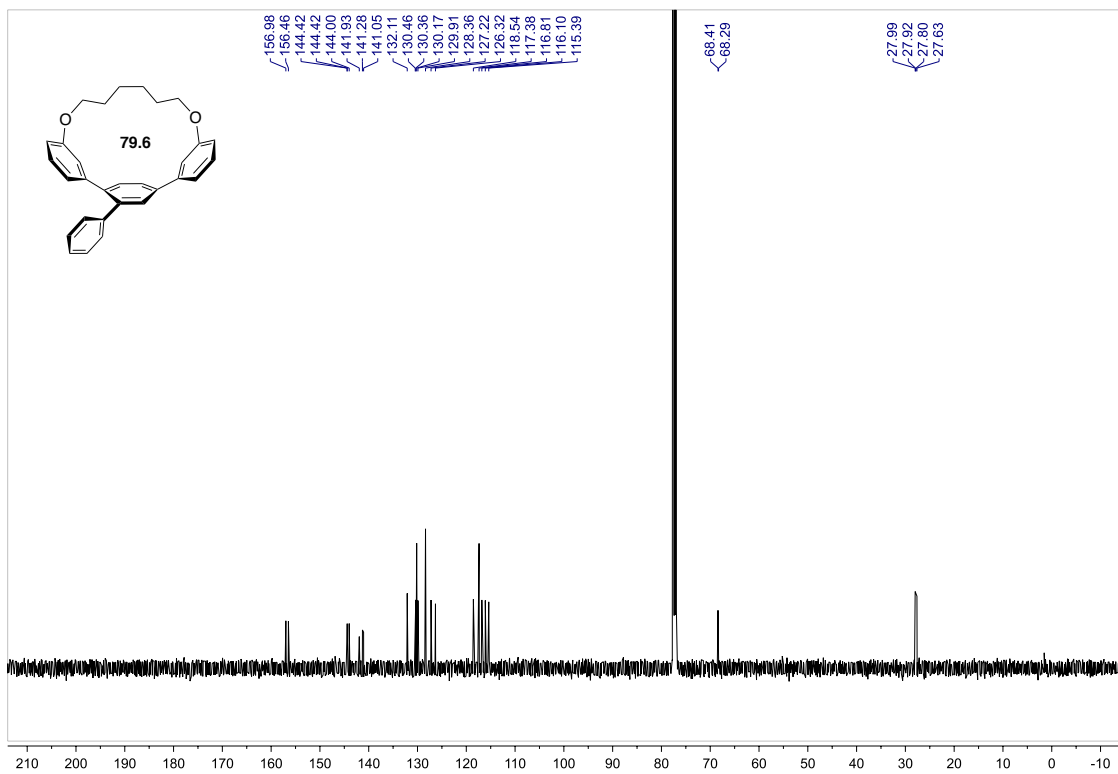
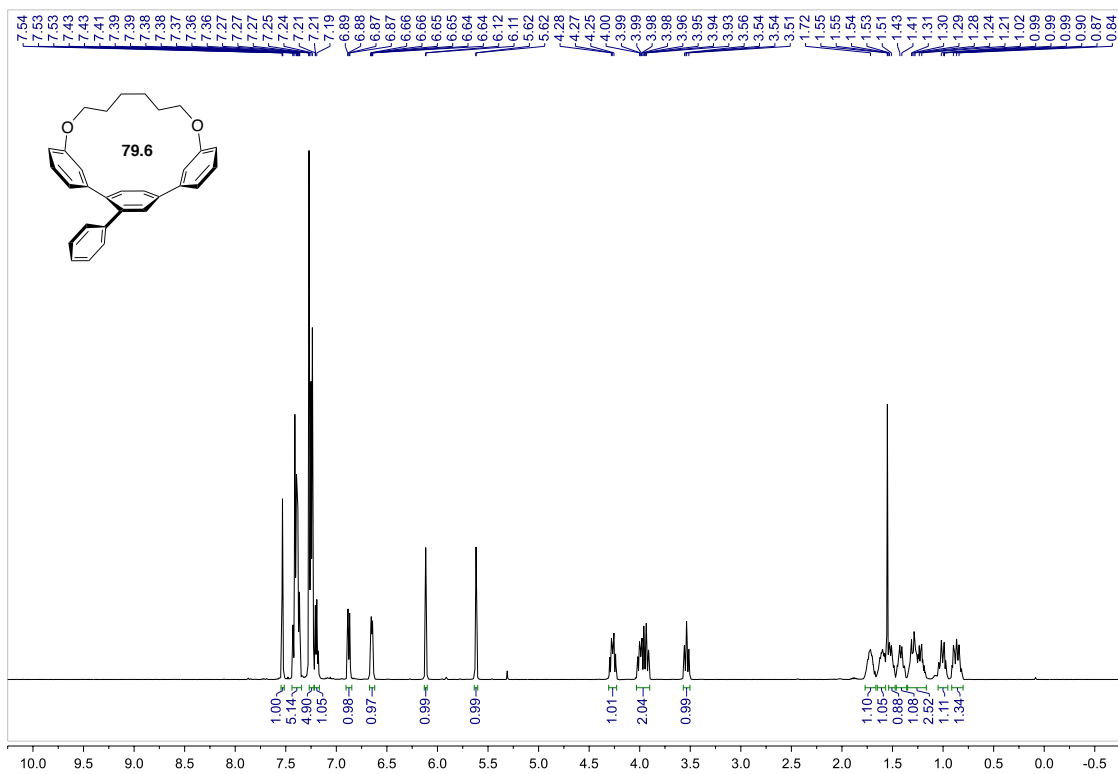


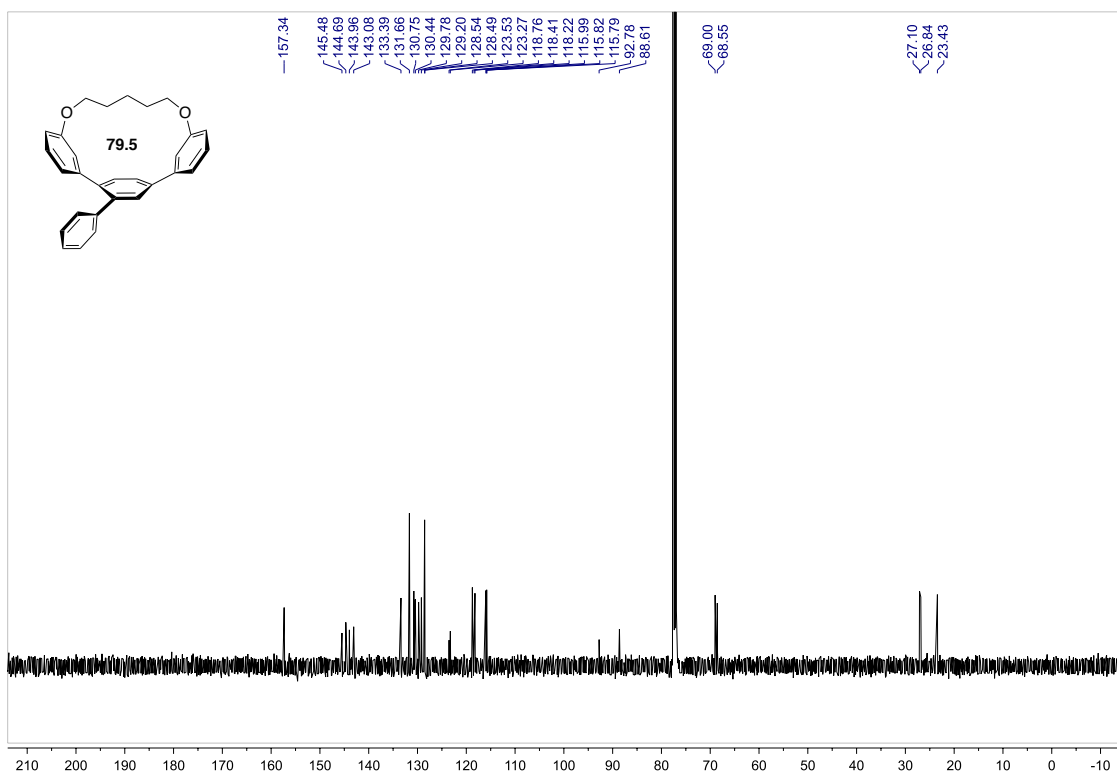
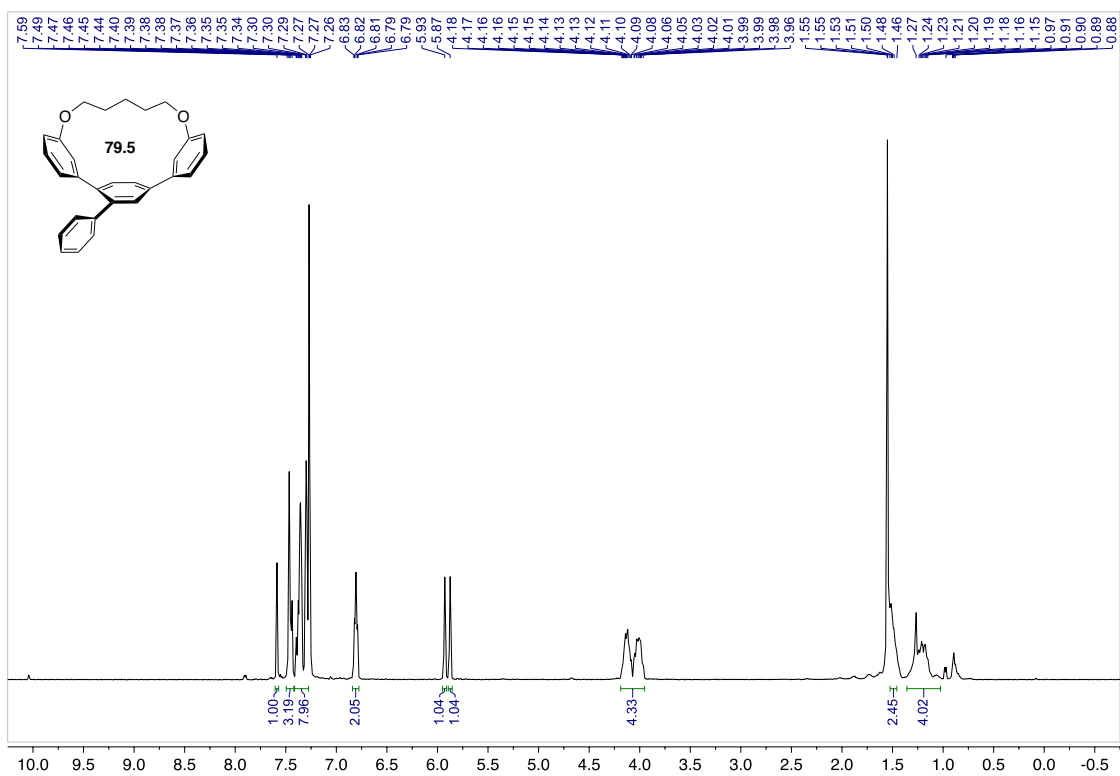


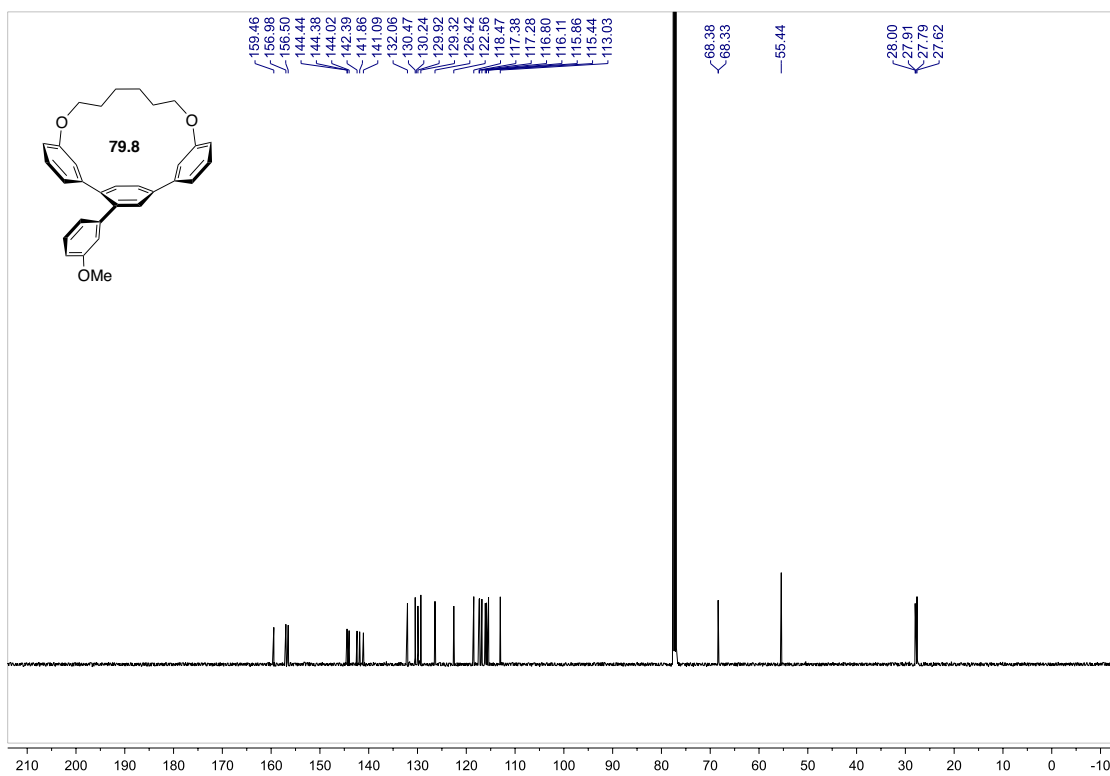
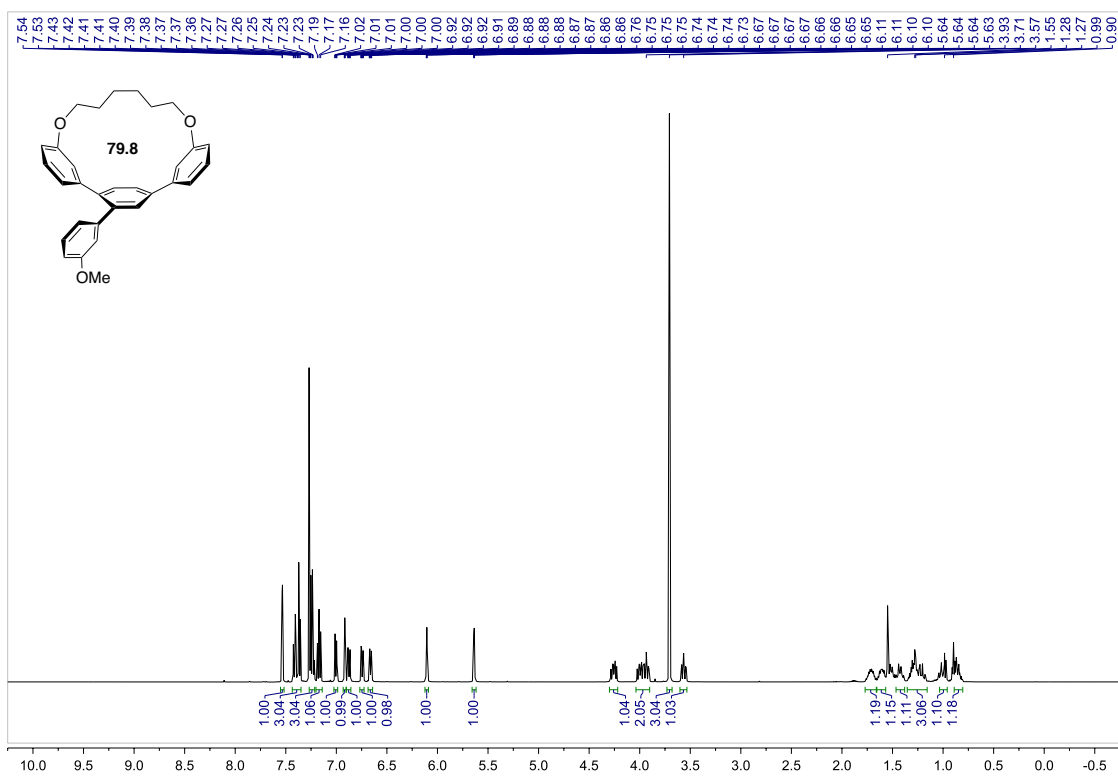


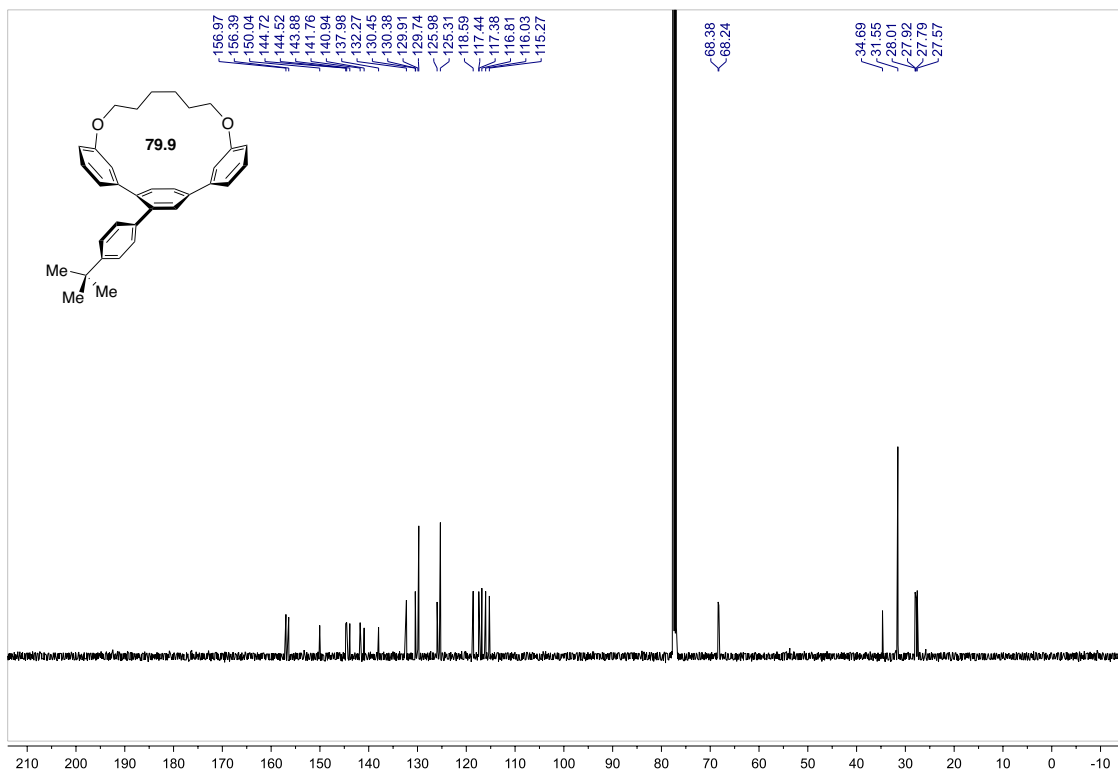
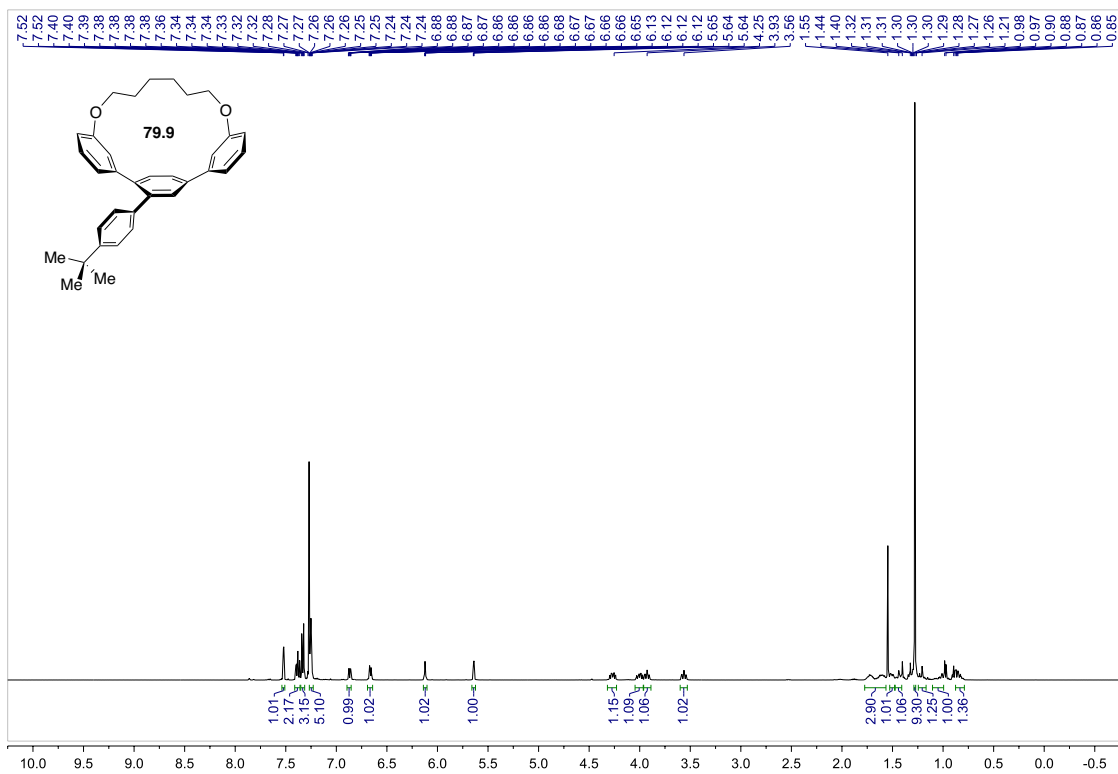


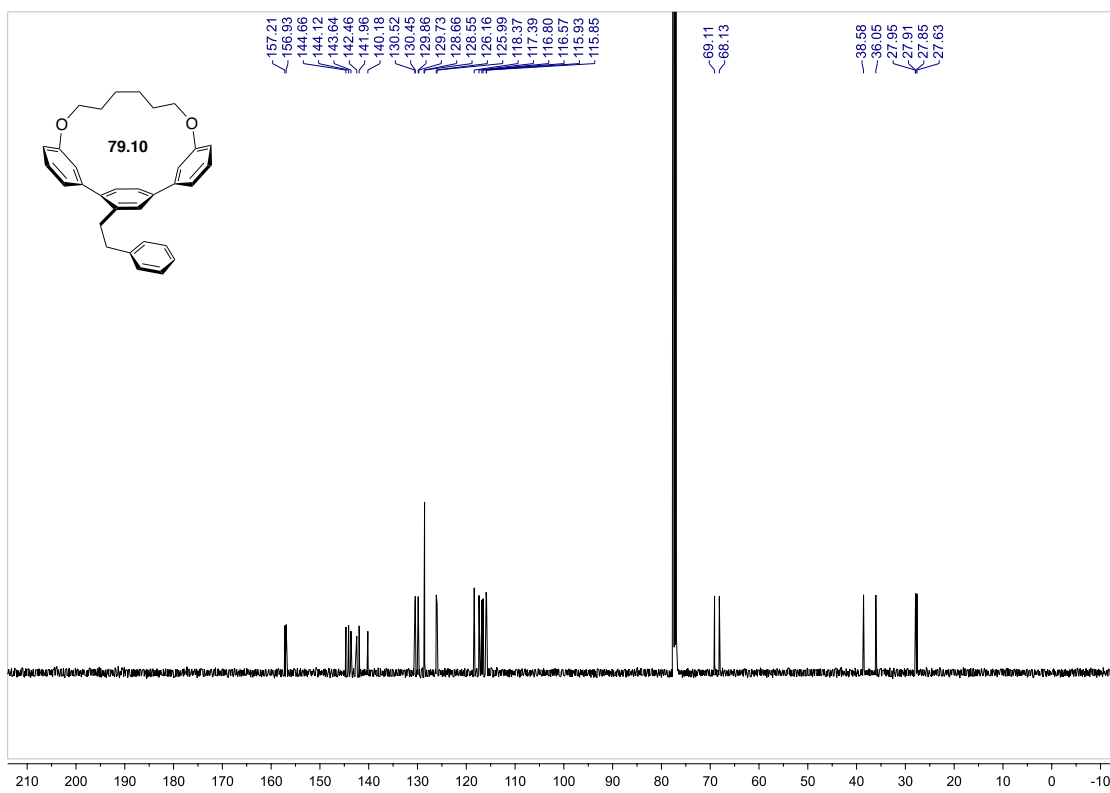
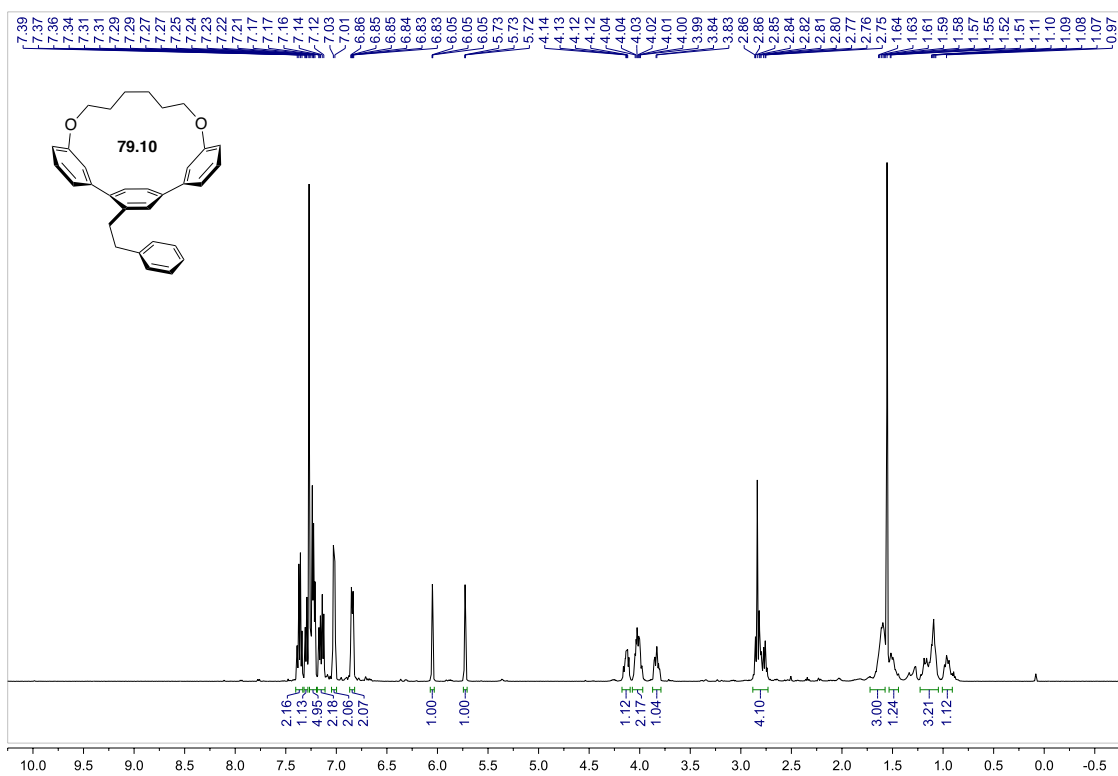


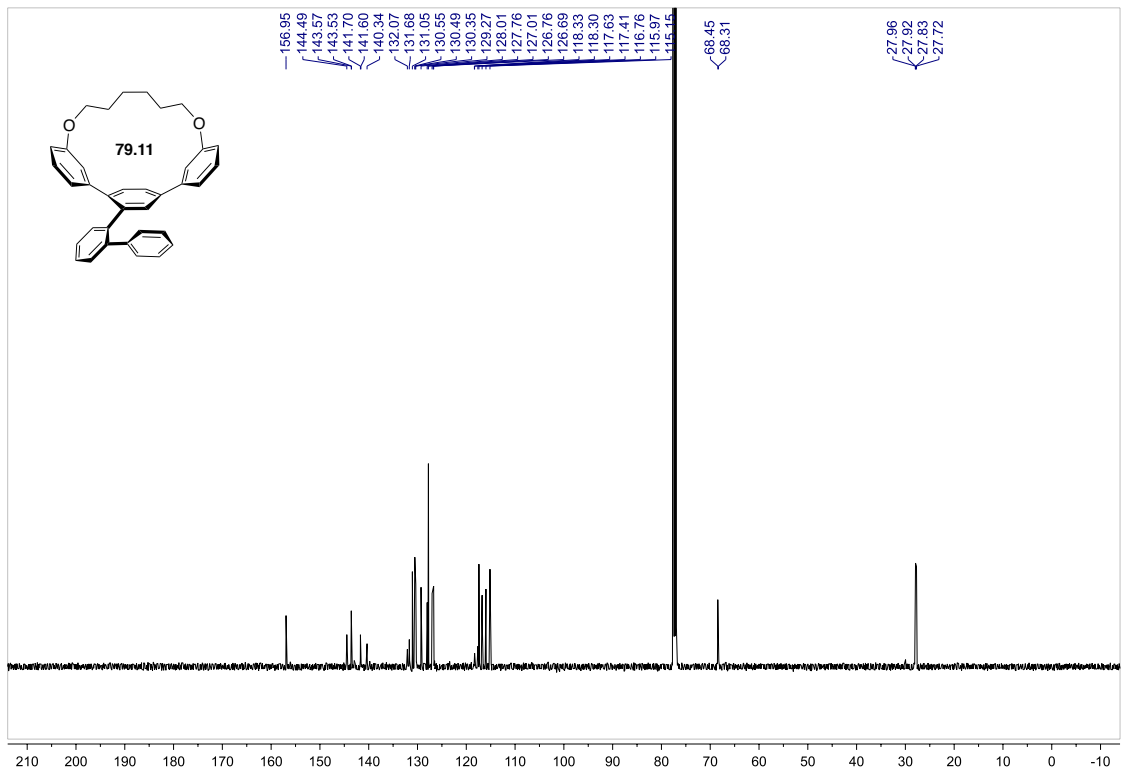
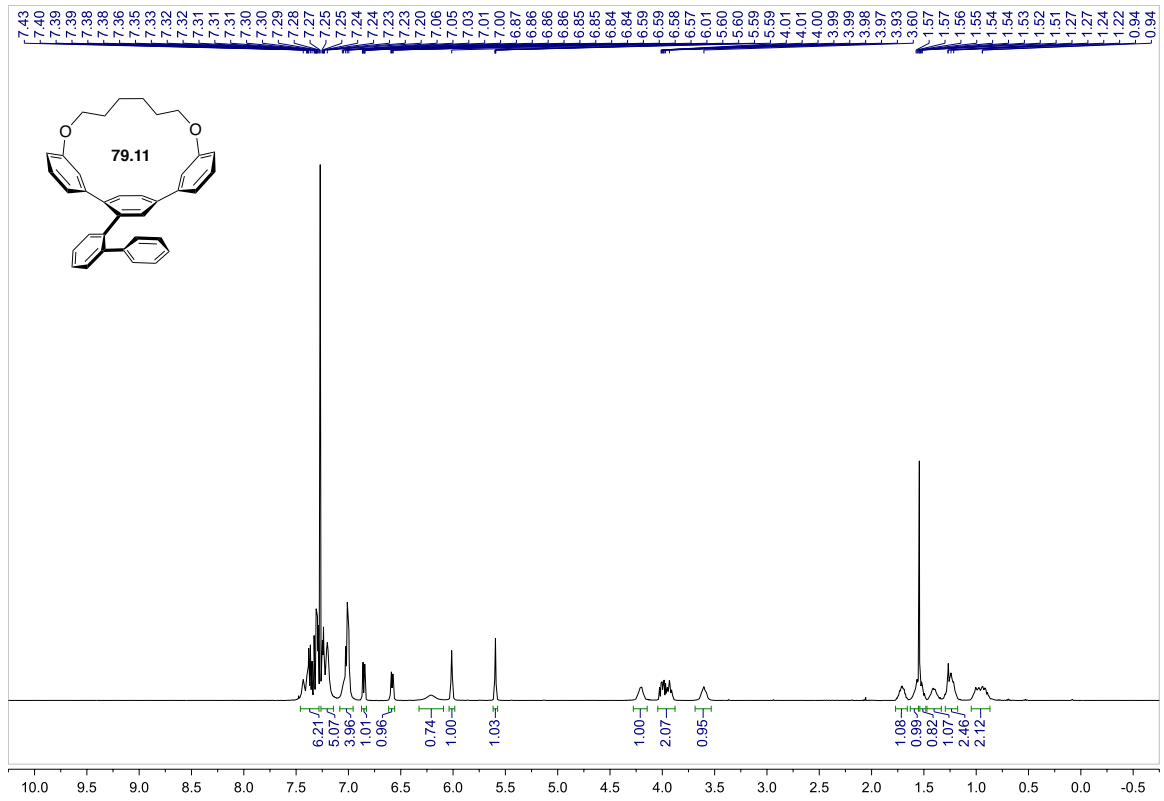


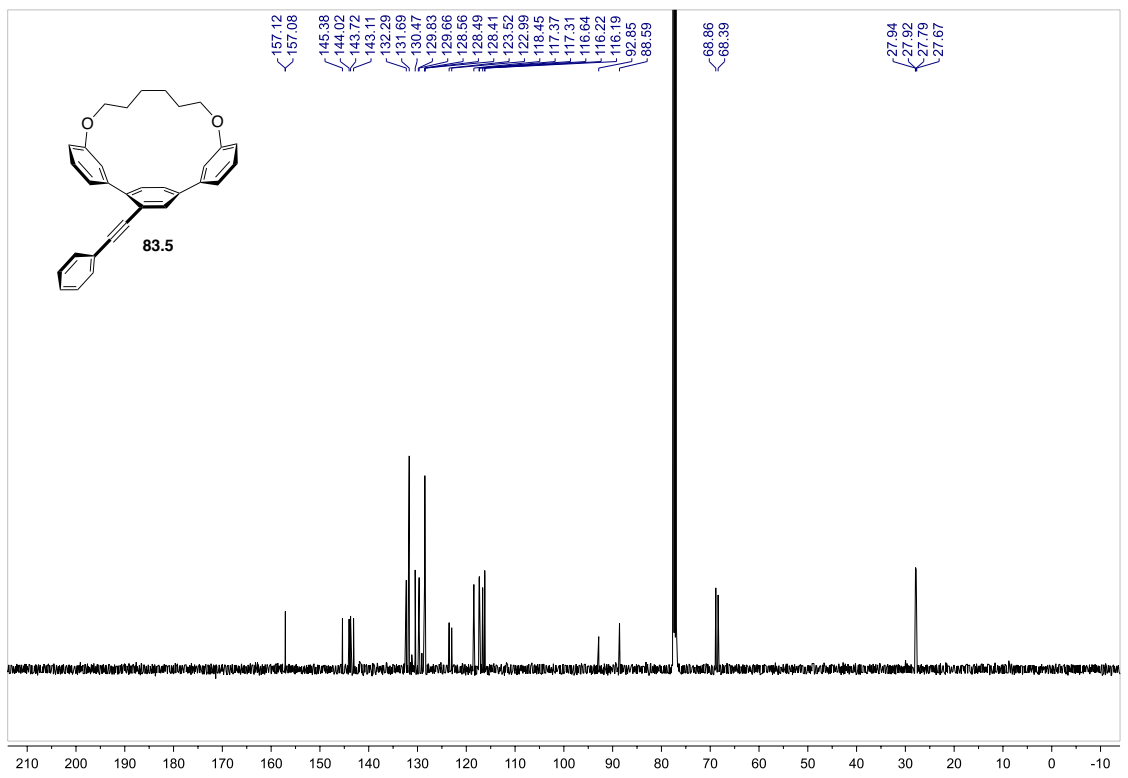
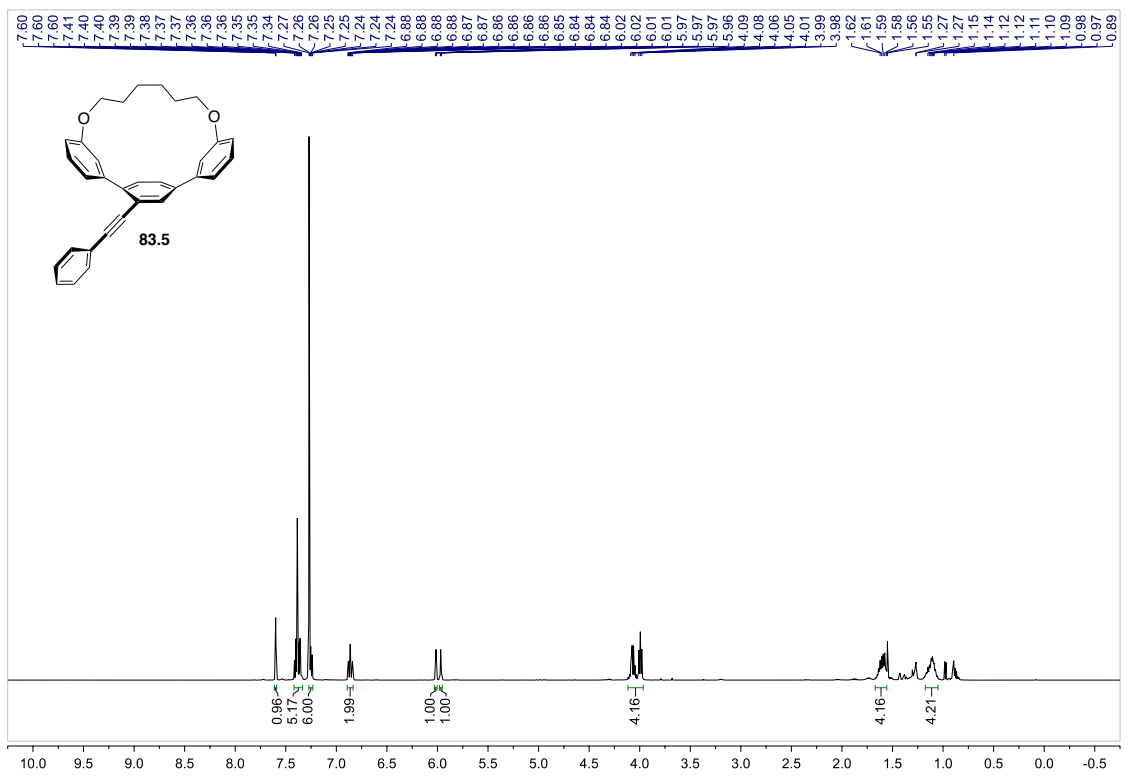


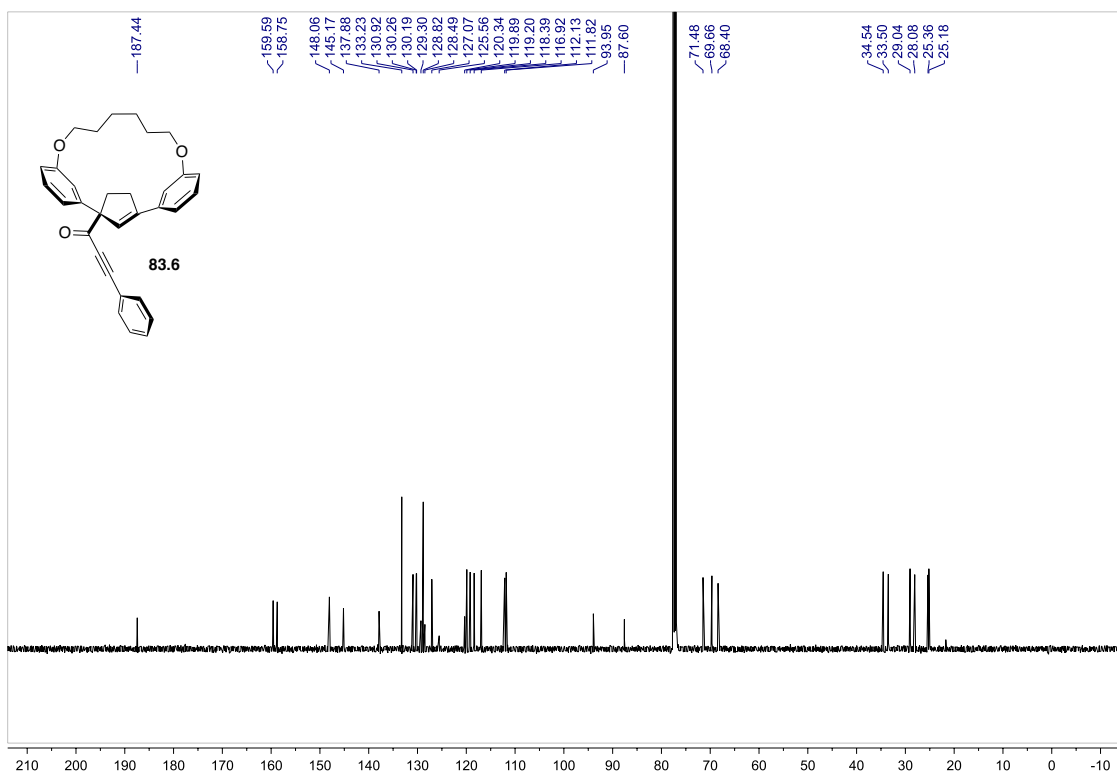
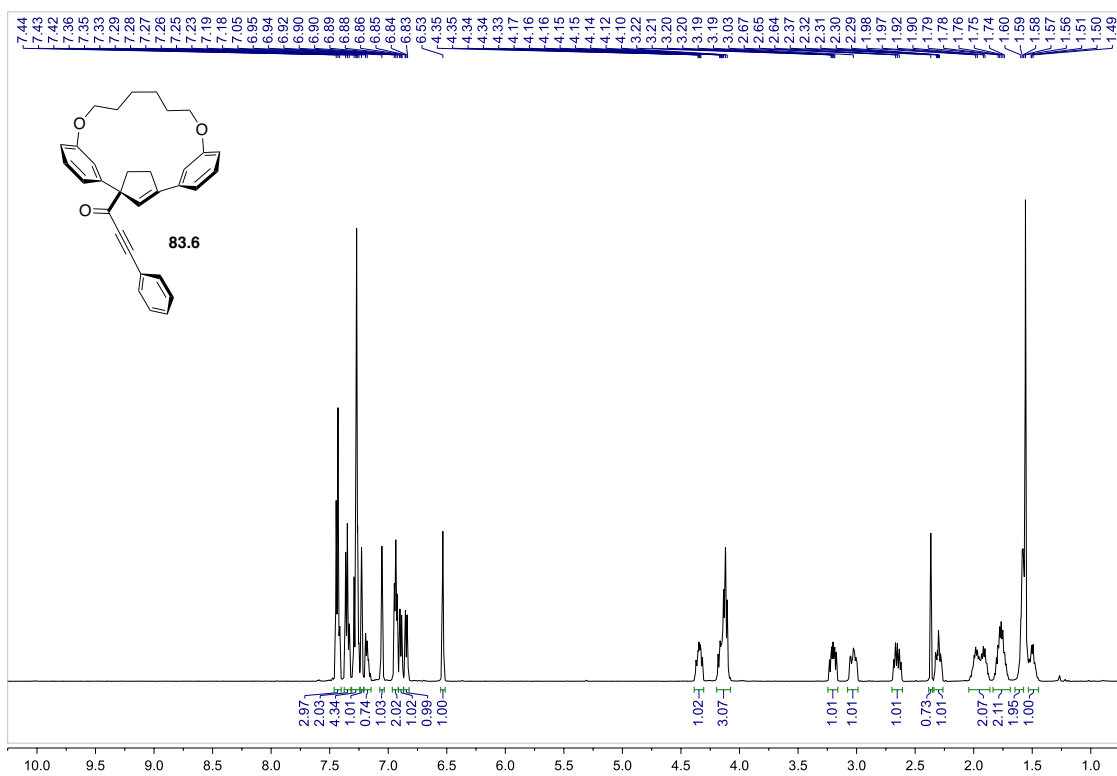


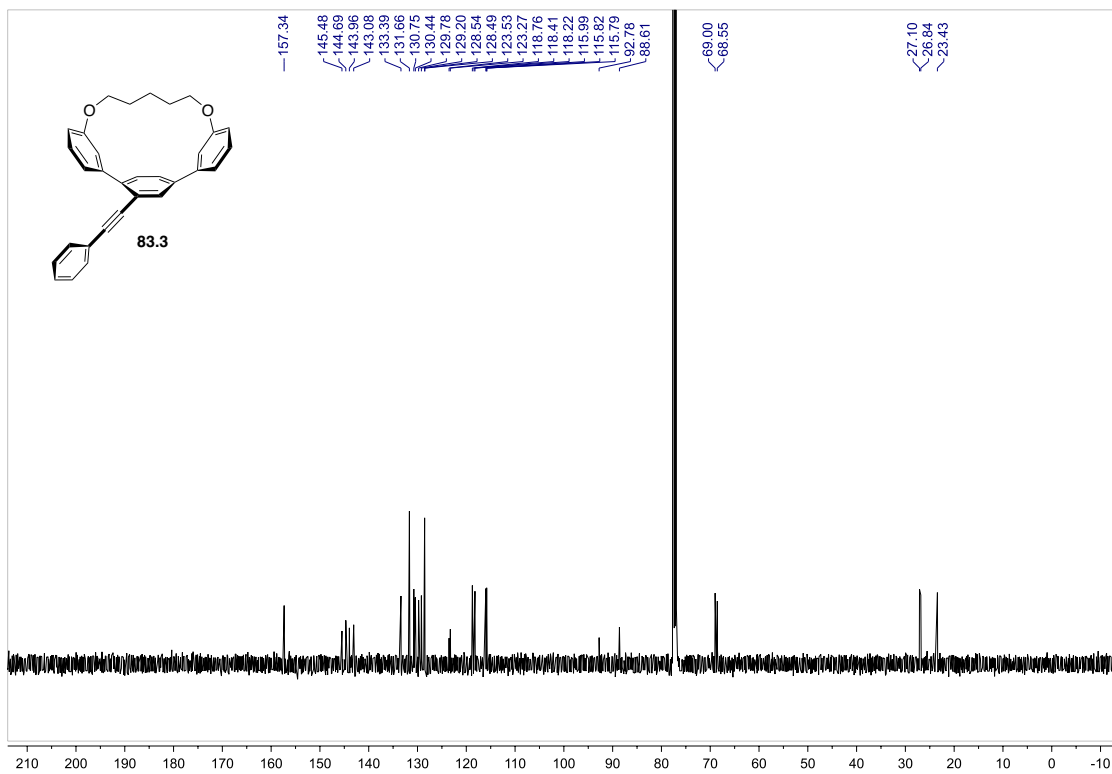
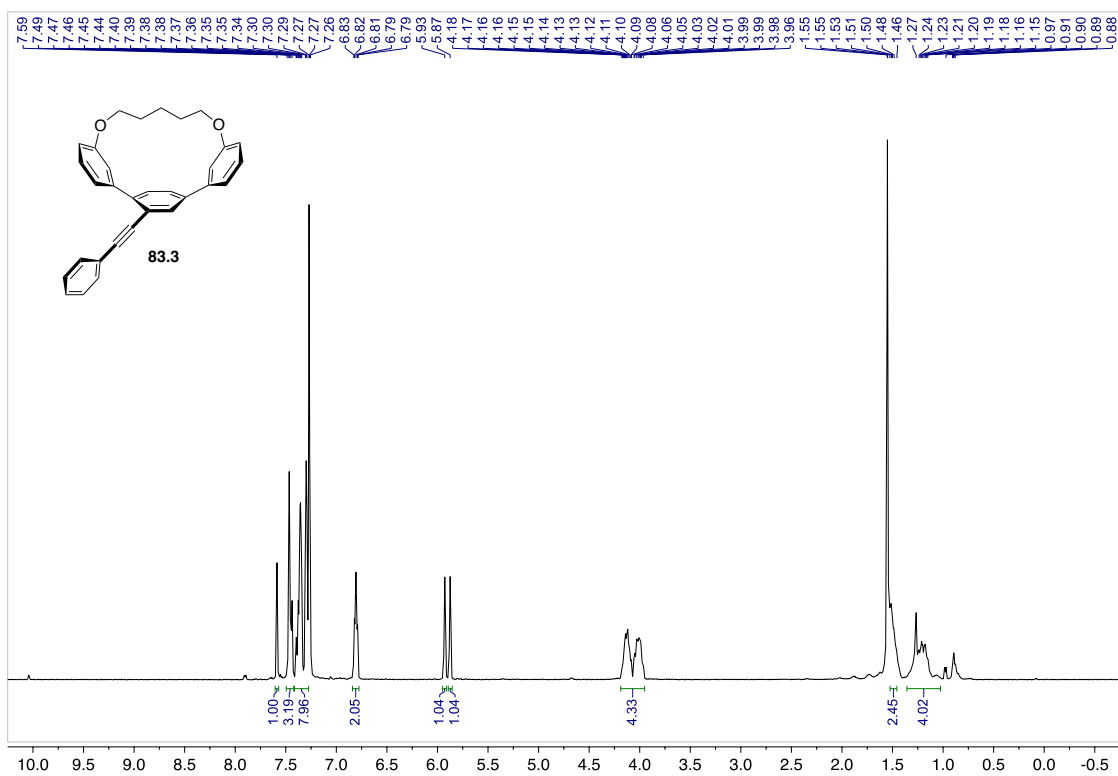


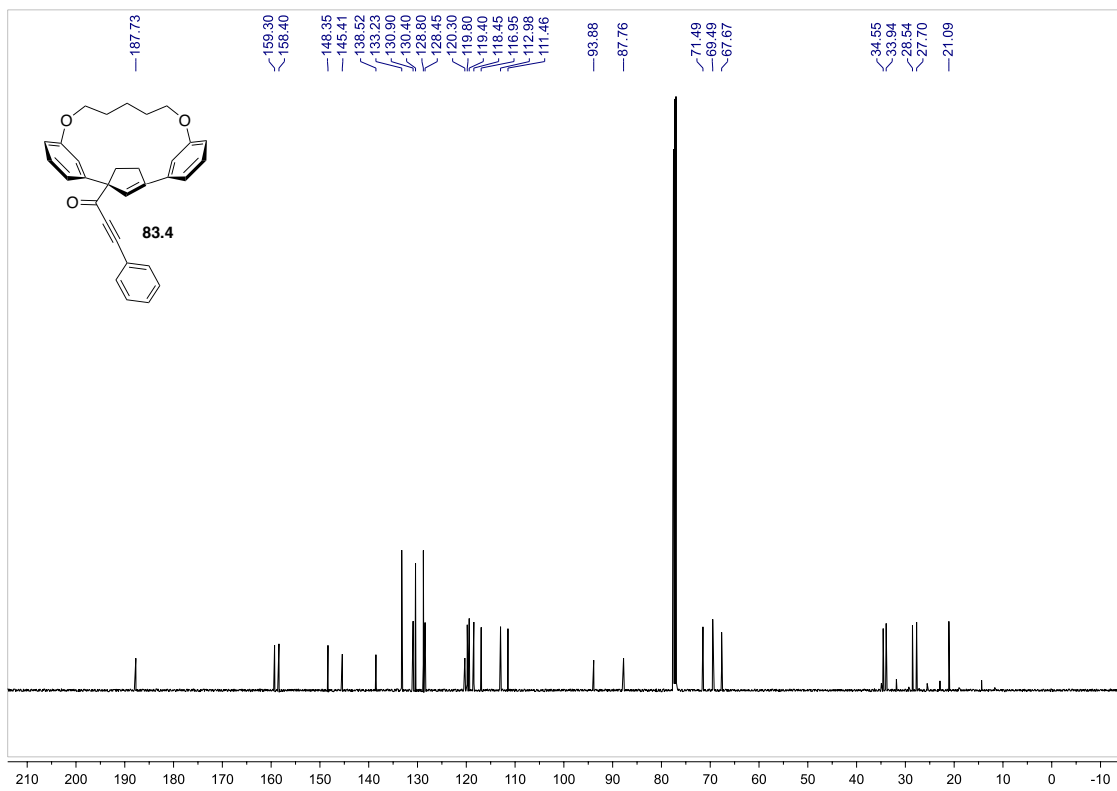
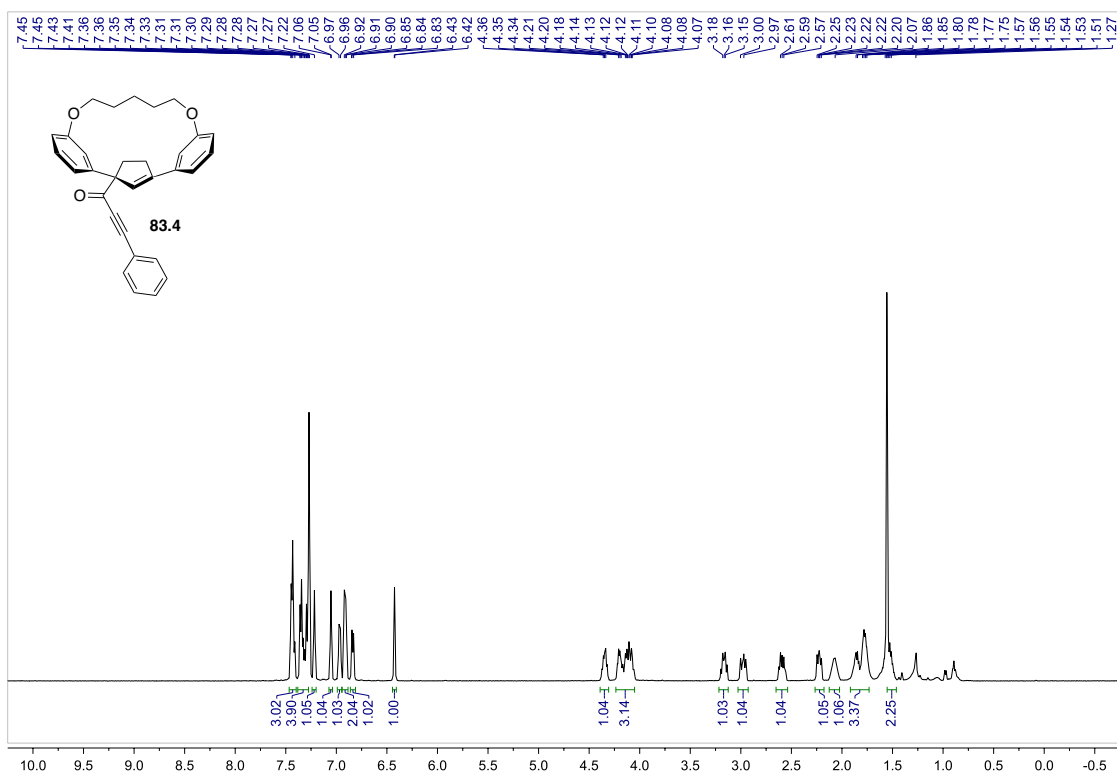


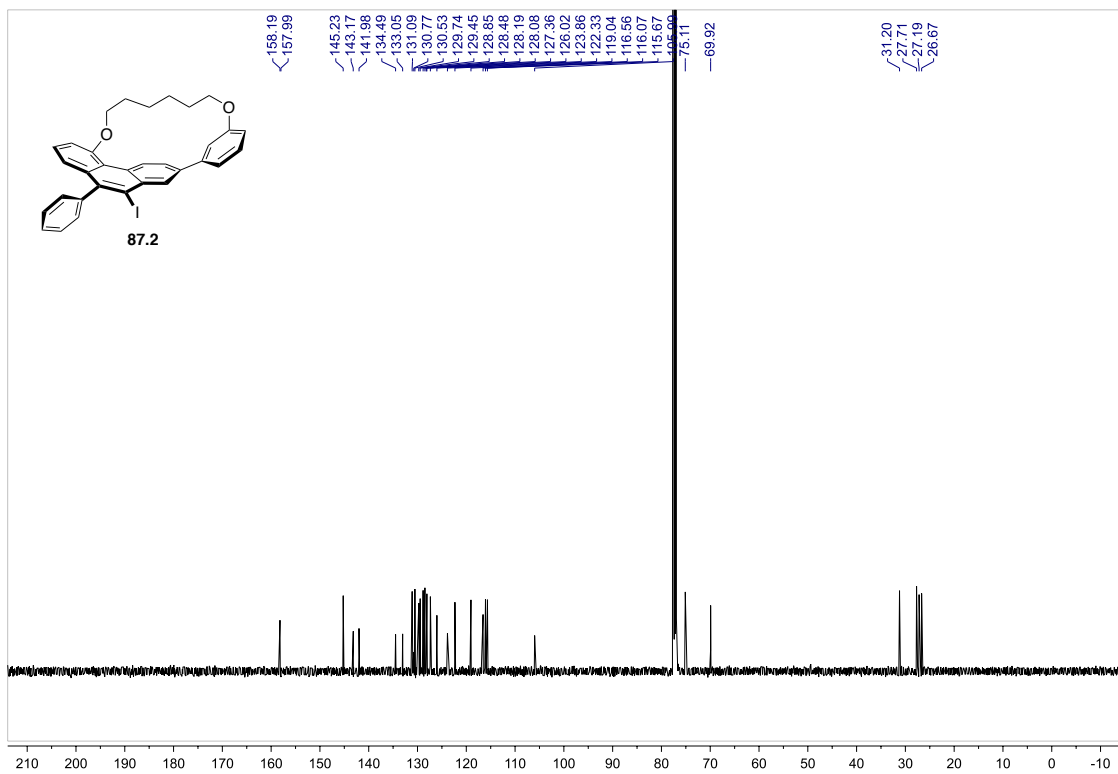
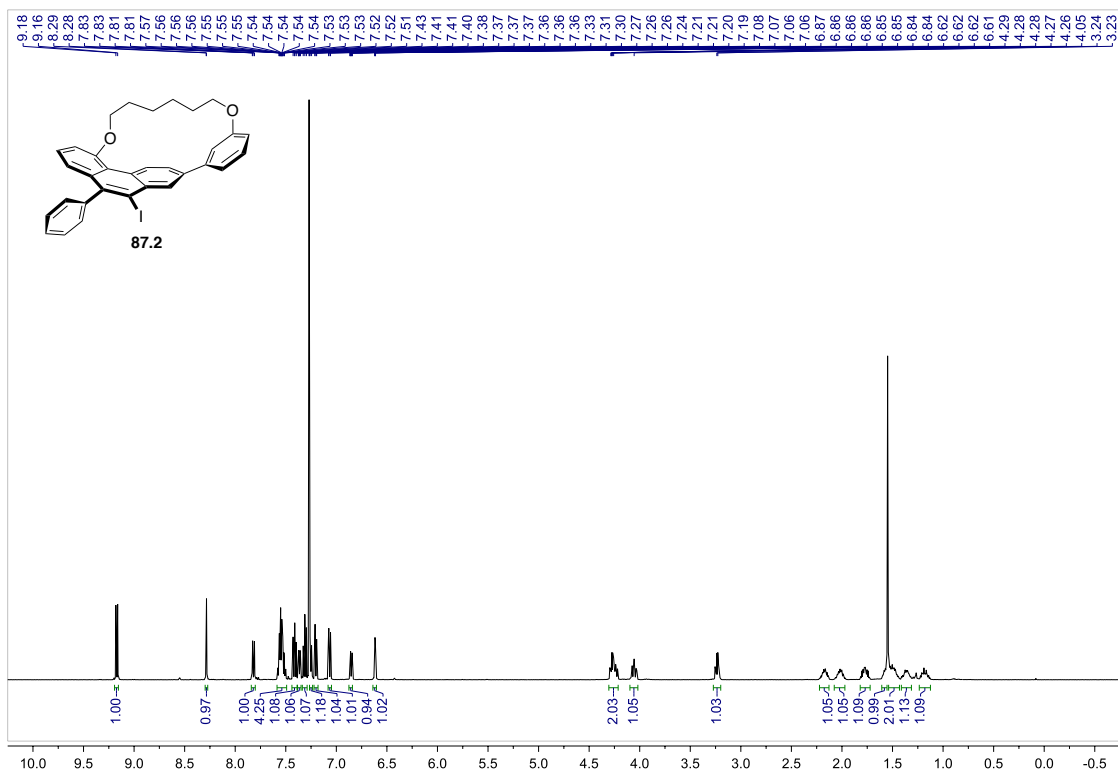


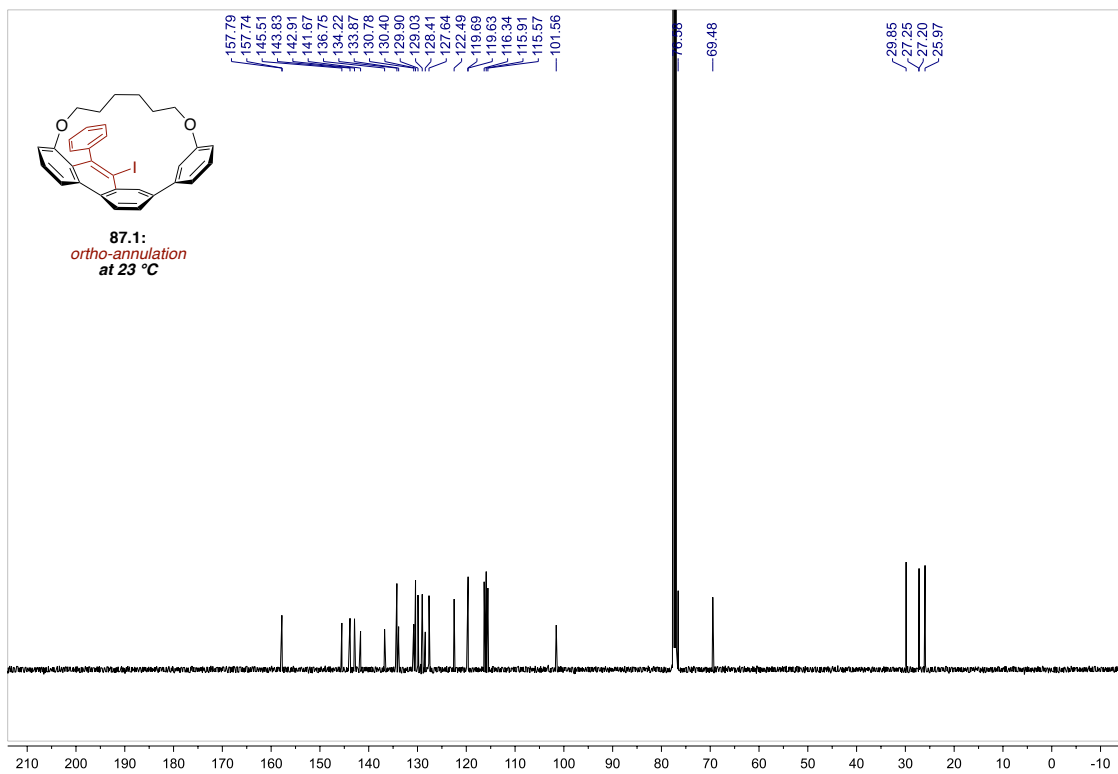
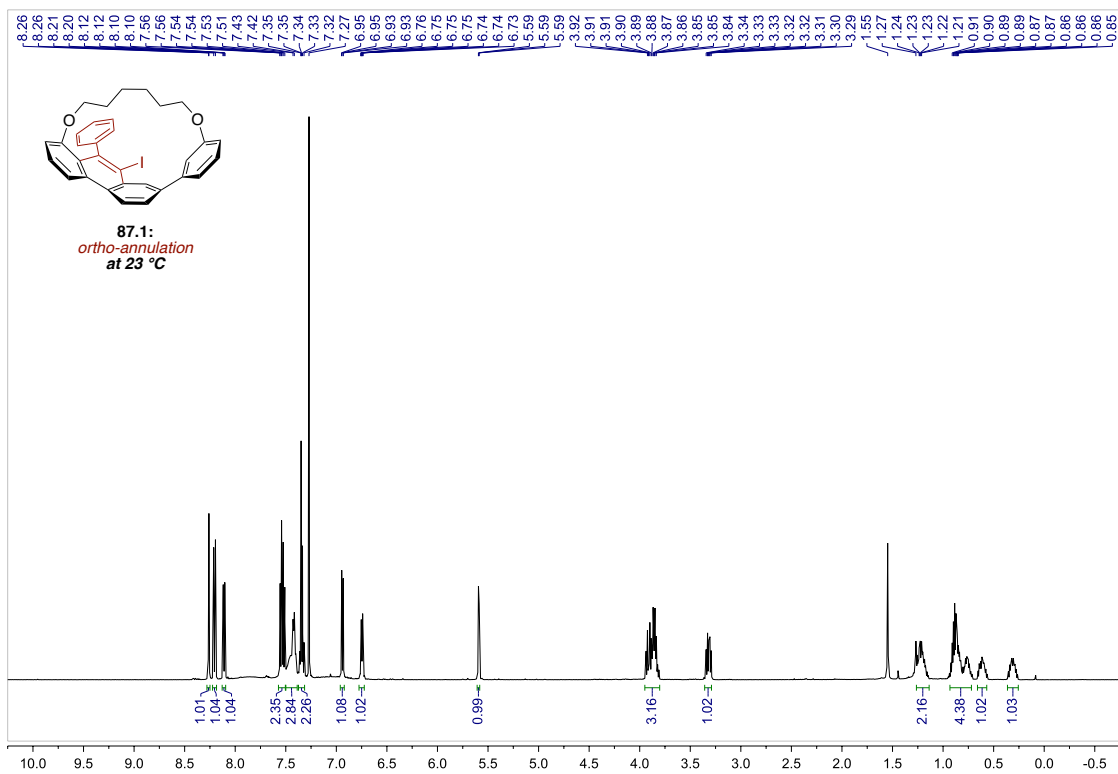


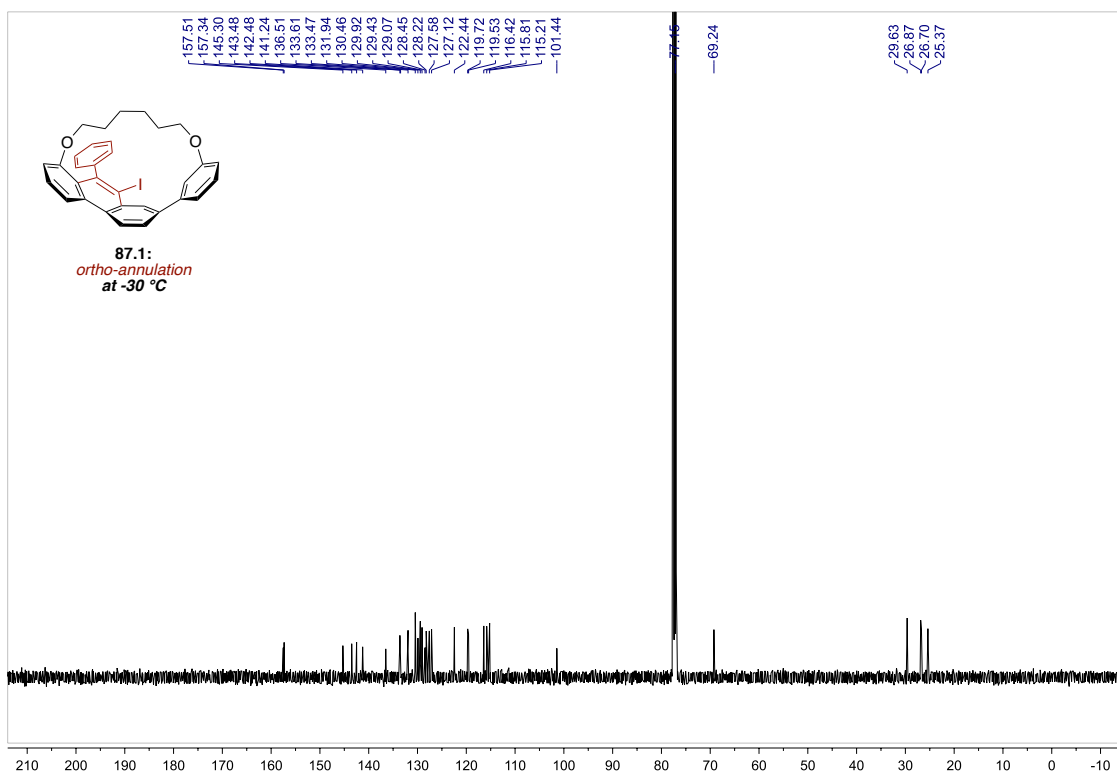
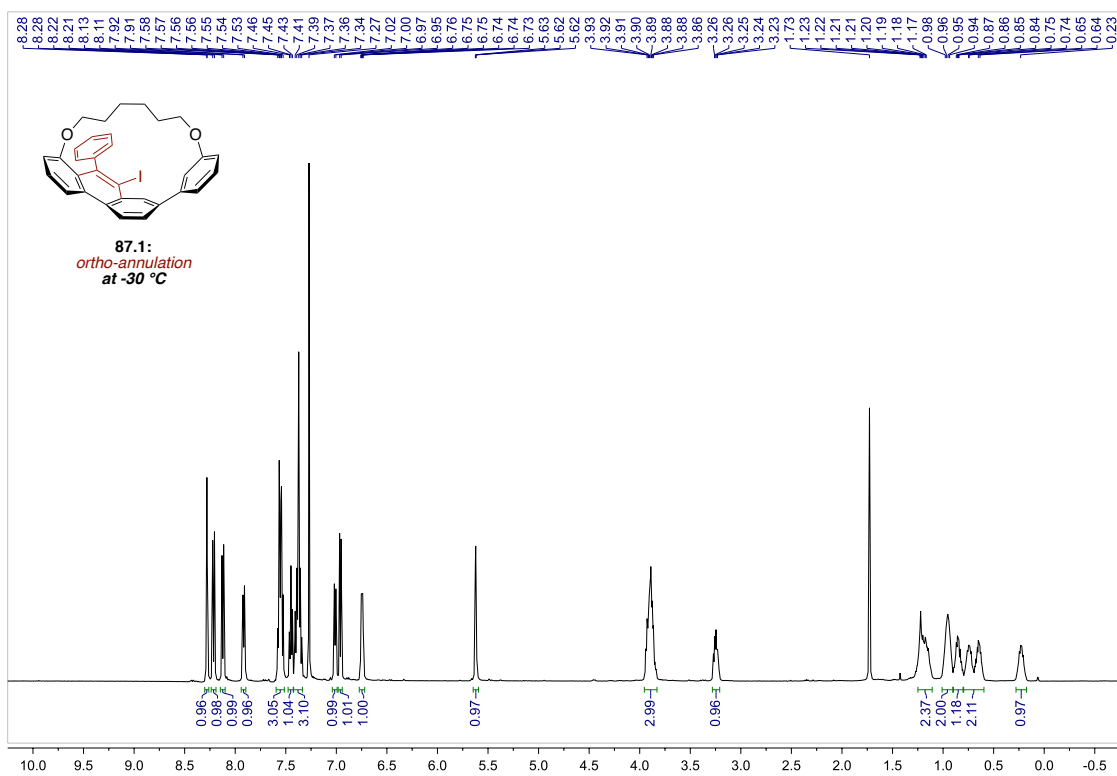












Variable temperature ^1H nmr for ortho-annulated product 87.1.

