A Non-Cross-Coupling-Based Approach to Arene-Bridged Macrocycles and Their Use in the Development of Annulative Pi-Extension Methods

by

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Abstract

The synthesis of strained macrocyclic benzene-containing molecules has been an area of interest for decades. However, the synthesis of macrocyclic structures that contain adjacent benzene units linked at their 1 and 4 positions (*i.e.*, a *para*-phenylene unit) has presented a challenge for chemical synthesis. Chemical reactions that are well suited for the formation of biaryl bonds typically fail when called upon to furnish macrocyclic (biaryl-containing) systems. This dissertation deals with the development of a synthetic strategy that avoids the use of venerable biaryl bond-forming reactions, which in turn, has led to the synthesis of regioselectively functionalized biaryl-containing macrocyclic, benzenoid systems.

Chapter 1: A non-cross-coupling-based approach to arene-bridged macrocycles has been described. This strategy involves the conversion of an unstrained 1,4-diketo-bridging unit into strained *para*-phenylene unit. The final macrocyclic target contains a bent *p*-terphenyl unit, which can be viewed as a substructure of an [*n*]CPP. Regioselective bromination of the *p*-terphenyl unit represents a rare example where such a nanostructure can be selectively derivatized.

Chapter 2: The synthesis of homologous series of macrocyclic 1,4-diketones using an optimized three-step reaction protocol has been developed. This streamlined approach affords gram-scale quantities of these 1,4-ketones, which were later converted into a series of highly strained *para*-phenylene-bridged macrocycles. During these investigations, strain-induced rearrangement reactions were encountered during the aromatization of macrocyclic cyclohex-2-ene-1,4-diol units. This was overcome by developing a mild dehydrative aromatization protocol, which employed the Burgess reagent. The application of this macrocyclic 1,4-diketone-based approach to highly strained *para*-phenylene units culminated with the synthesis of macrocyclic system that contains a benzene ring more strained than a monomer unit of [4]CPP.

Chapter 3: An overview of annulative pi-extension (APEX) methods for the synthesis of polycyclic aromatic hydrocarbons (PAHs) is described. A detailed investigation of an oxidative aryl coupling reaction, known as the Scholl, and its application towards APEX of a series of selectively arylated, strained *p*-terphenyl-containing macrocycles is reported. The development of an APEX strategy that involves allylic arylation of selectively functionalized cyclohex-2-ene-1,4-diols is described, as well as reaction mechanisms that explain observed rearrangement reactions.

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List of Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
Ad	Adamentyl
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
BOR	Based on recovered
Bpin	Boronic acid pinacol ester
$B_2(pin)_2$	Bis(pinacolato)diborane
bpy	2,2'-Bipyridyl
C_{60}	Buckminsterfullerene
CNTs	Carbon nanotubes
cod	1,5-cyclooctadiene
CPME	Cyclopentyl methyl ether
CPP	Cycloparaphenylene
CVD	Chemical vapor disposition

dba	Dibenzylidineacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
d.r.	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	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
FC	Friedel-Crafts

$Fe(CO)_5$	Iron pentacarbonyl
FVP	Flash vacuum pyrolysis
G II	Grubbs second generation
GNR	Graphene nanoribbon
HBC	Hexa-*peri*-hexabenzocoronene
HFIP	Hexafluoroisopropanol
H-G II	Hoveyda-Grubbs second generation
HiPCO	High pressure carbon monoxide
HK	Hydroxyketone
HRMS	High resolution mass spectrometry
Ile	Isoleucine
i-Pr	Isopropyl
i-Pr_2NH	Diisopropylamine
IPA	Isopropyl alcohol
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
Me	Methyl
MeOH	Methanol
MOM	Chloromethyl methyl ether

M.S.	Molecular sieves
MsOH	Methanesulfonic acid
MTPP	(3,3")*meta*-Terphenylophane
n-BuLi	*n*-Butyllithium
Nap	Napthalenide
NBS	*N*-bromosuccinimide
NEt_3	Triethylamine
NMR	Nuclear magnetic resonance
PAH	Polycyclic aromatic hydrocarbon
PCC	Pyridinium chlorochromate
PhH	Benzene
PhMe	Toluene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PivOH	Pivalic acid
pp	*Para*-phenylene
PPh_3	Triphenylphosphine
PTPP	(3,3")*p*-terphenylophane
p-TsOH	*para*-Toluenesulfonic acid
pyr.	Pyridine
RCM	Ring-closing metathesis

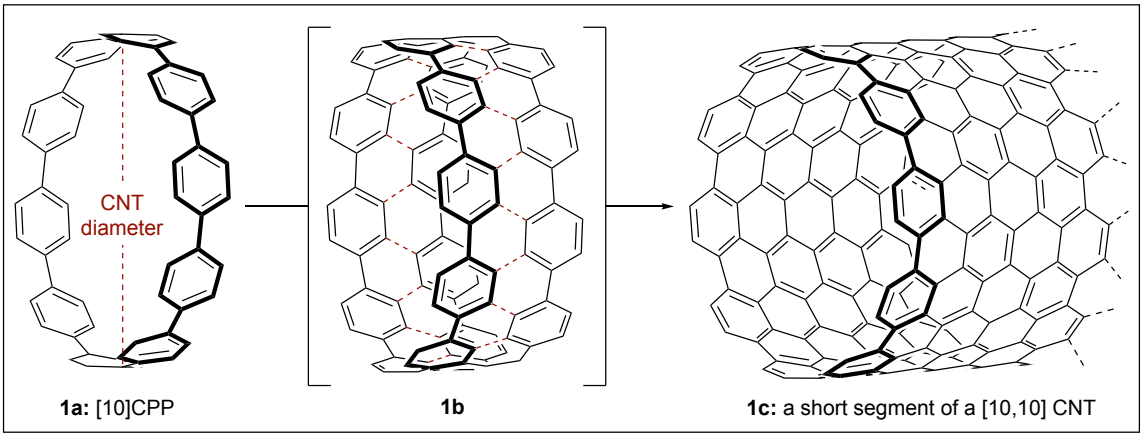
R_f	Retention factor
S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SE	Strain energy
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
TES	Triethylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
Tf_2O	Trifluoromethanesulfonic anhydride
TIPS	Triisopropylsilane
TLC	Thin layer chromatography
TsCl	Toluenesulfonyl chloride
UV	Ultraviolet
UV/vis	Ultraviolet/visible

CHAPTER 1 A Non-Cross-Coupling Approach to Arene-Bridged Macrocycles: Synthesis, Structure, and Direct, Regioselective Functionalization of a Cycloparaphenylene Fragment

1. Introduction

1.1. Cycloparaphenylenes

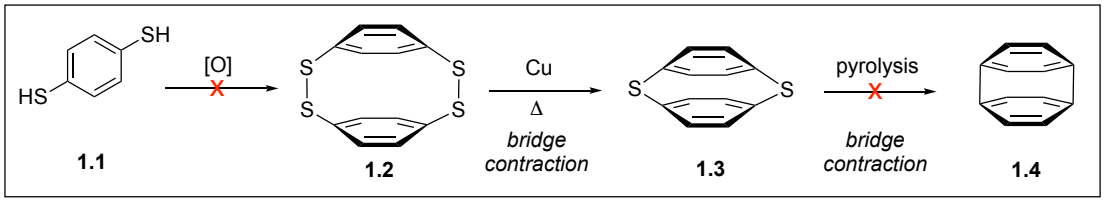
Cyclic molecules that contain only benzene rings connected through *para* (1,4) linkages are known as cycloparaphenylenes (CPPs). These macrocyclic structures represent the smallest possible cyclic subunit of (*n*,*n*) armchair carbon nanotubes (CNTs) (Figure 1.1). As such, [*n*]CPPs have been suggested a diameter-defining templates that could be employed in the bottom-up chemical synthesis of monodisperse CNTs.[1-3] The main challenge associated with the syntheses of the [*n*]CPPs is the introduction large amounts of strain energy (SE) into the macrocyclic structure.



FGURE 1: [*n*]Cycloparaphenylenes - templates for a bottom-up synthesis of CNTs

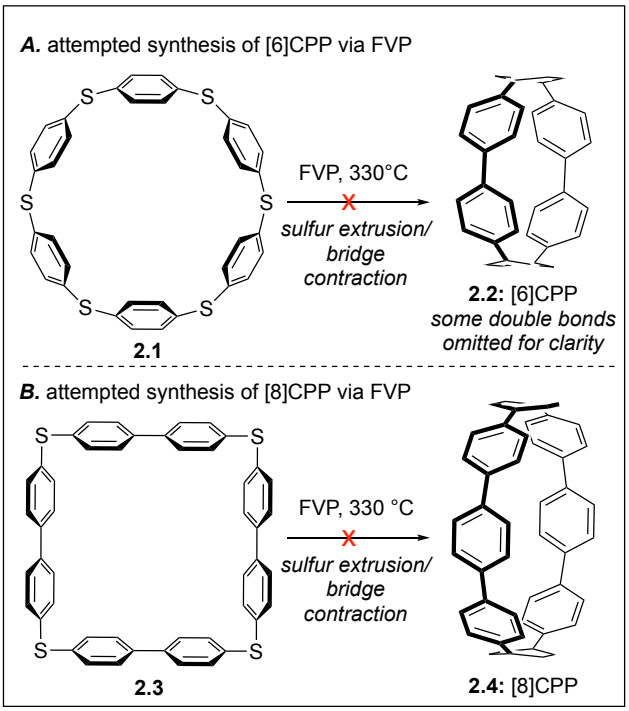
1.1.1 Early attempted syntheses of [n]CPPs

The first synthetic investigation of an [*n*]CPP can be traced back to the 1930s, when Parekh and Guha attempted to the synthesis of [2]CPP (**1.4**, Scheme 1).[4] Their proposal called for the assembly of a [2.2]paracyclophane (disulfide) derivative **1.2**, which was to be subjected to sequential bridge contraction reactions. The main pitfall of this approach was the need to introduce a large amount of strain energy (SE) into the individual aromatic units and the macrocyclic structure of the **1.4**, using relatively weak synthetic methodology. While the pursuit of [*n*]CPPs and related macrocyclic structures remained active for decades, it was not until 2008 that these structures were first synthesized.



SCHEME 1: Attempted Synthesis of [2]CPP (**1.4**) by Parekh and Guha

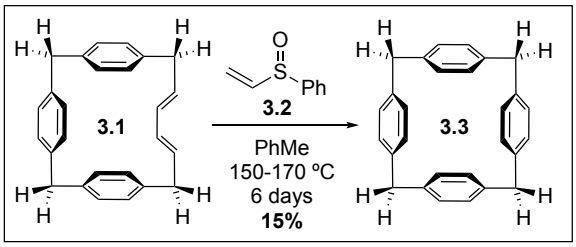
In 1996, Vögtle proposed several different synthetic approaches to [*n*]CPPs, which ultimately proved to be unsuccessful.[5] However, the synthetic strategies developed by Vögtle and co-workers for accessing macrocyclic precursors to the [*n*]CPPs undoubtedly guided future synthetic investigations and the successful syntheses that were reported by the groups of Jasti,[6] Itami,[7] Yamago,[8] and others.[9-10] In fact, the macrocyclization strategies that were developed by the Vögtle group laid the foundation for the aforementioned syntheses.



SCHEME 2: Attempted synthesis of [6] and [8]CPP

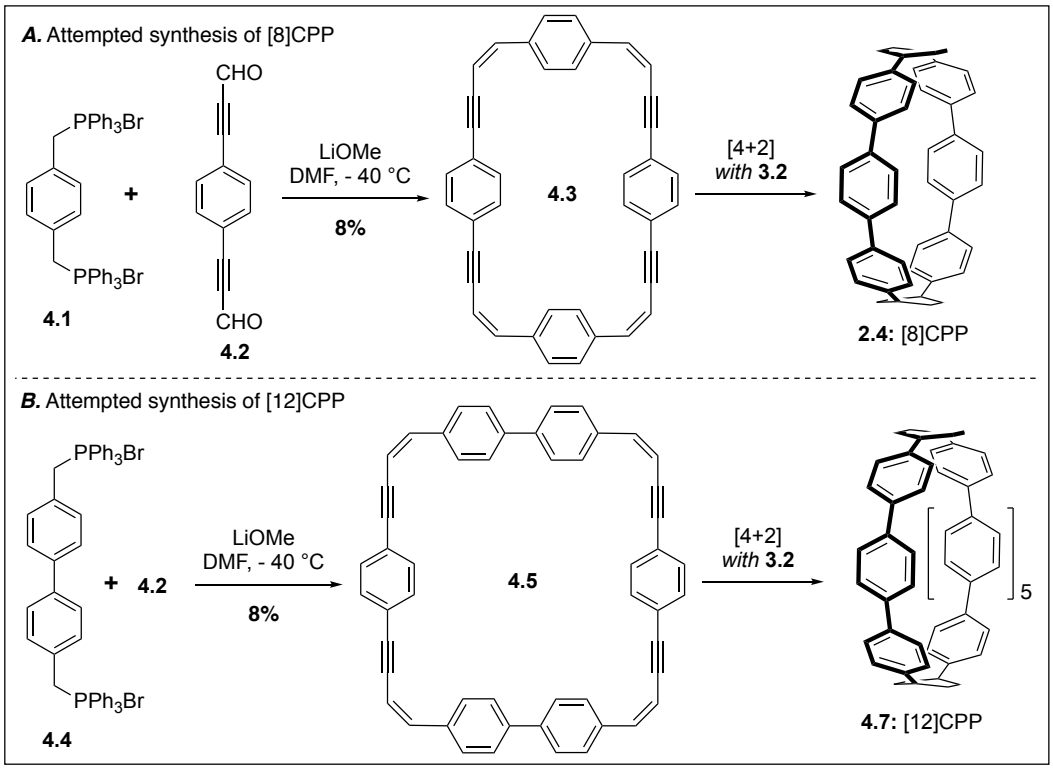
Initial attempts to access to [6] and [8]CPP employed a similar approach to that of Parekh and Gua. The desulfurization of the macrocyclic sulfides **2.1** and **2.3** via flash vacuum pyrolysis was unsuccessful in delivering the highly strained macrocycles[11] Vögtle reasoned that the reduced amount of SE in going from [2]CPP to [6] and [8]CPP could make them easily accessible via this standard cyclophanes-based bridge contraction method.

In a second approach, Vögtle co-workers tried the synthesis of [8] and [12]CPPs by applying Diels-alder (4+2 cycloaddition) reactions inspired by Miyarahara's successful synthesis of [1.1.1.1] paracyclophane[12] via a [4+2] cycloaddition between the diene **3.1** and phenyl vinyl sulfoxide. Vögtle subjected dibromo com-



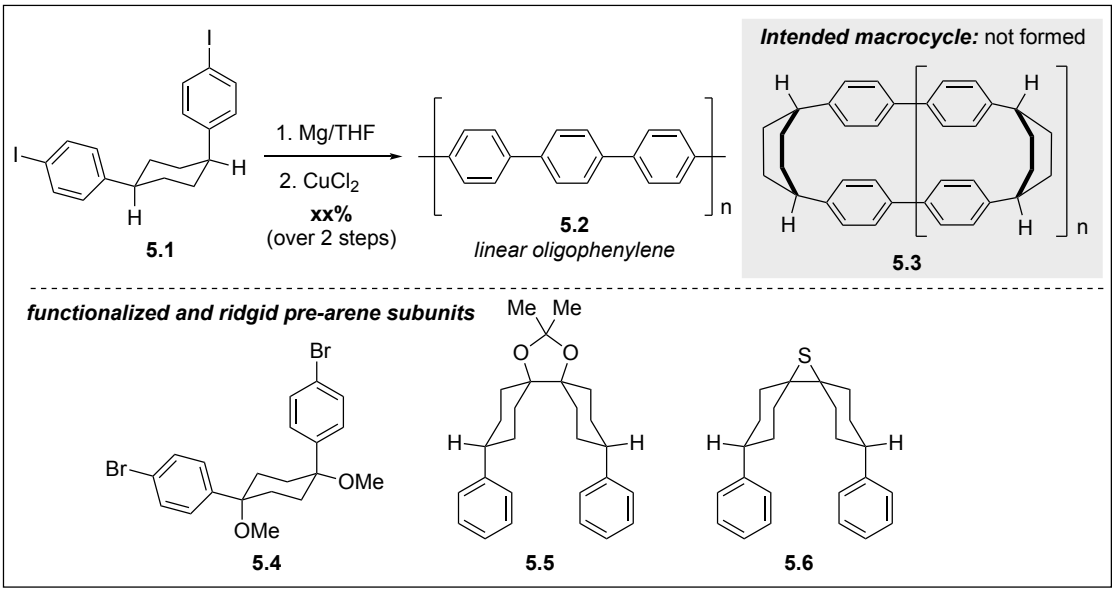
SCHEME 3: [4+2] Cycloaddition in the synthesis of [1.1.1.1]paracyclophane **3.3**

pounds **4.1** and **4.4** to a Wittig cyclooligomerization with the dialkynyl dialdehyde **4.2** to furnish ene-yne macrocycles **4.3** and **4.5.** However, [4+2] with the sulfoxide-based dienophile phenyl vinyl sulfoxide was not capable of installing the remaining four benzene rings to complete the syntheses of [8] and [12]CPP.



SCHEME 4: Attempted syntehsis of [8] and [12] CPP

The third approach investigated by Vögtle to synthesize [*n*]CPPs involved the incorporation of an arene surrogate, or pre-arene subunit. The intention of using the pre-arene subunit was to facilitate the macrocyclization stage of the synthesis. The pre-arene subunit is nonplanar and therefore can accomdate the boat-shaped geometry of the arene to be formed in the last stage of the synthesis of [*n*]CPPs. The hope was that conversion to the corresponding [*n*]CPP would be favored due to a gain in aromatic stabilization energy (ASE), which would, in part, compensate for the increase in SE. To this end, Vögtle synthesized a 1,4-*syn*-diaryl cyclohexane **5.1**, however, its conversion to macrocycle **5.3** under Kharasch conditions failed[13]. Only the linear compound oligophenylene **5.2** was formed. To circumvent the formation of linear oligophenylenes, several more structurally rigid analogs of **5.1** were synthesized including the dimethoxy derivative **5.4** and the spirocyclic derivatives **5.5** and **5.6**. However, attempts to employ these subunits in the construction of macrocyclic precursors of [*n*]CPPs did not come to fruition.



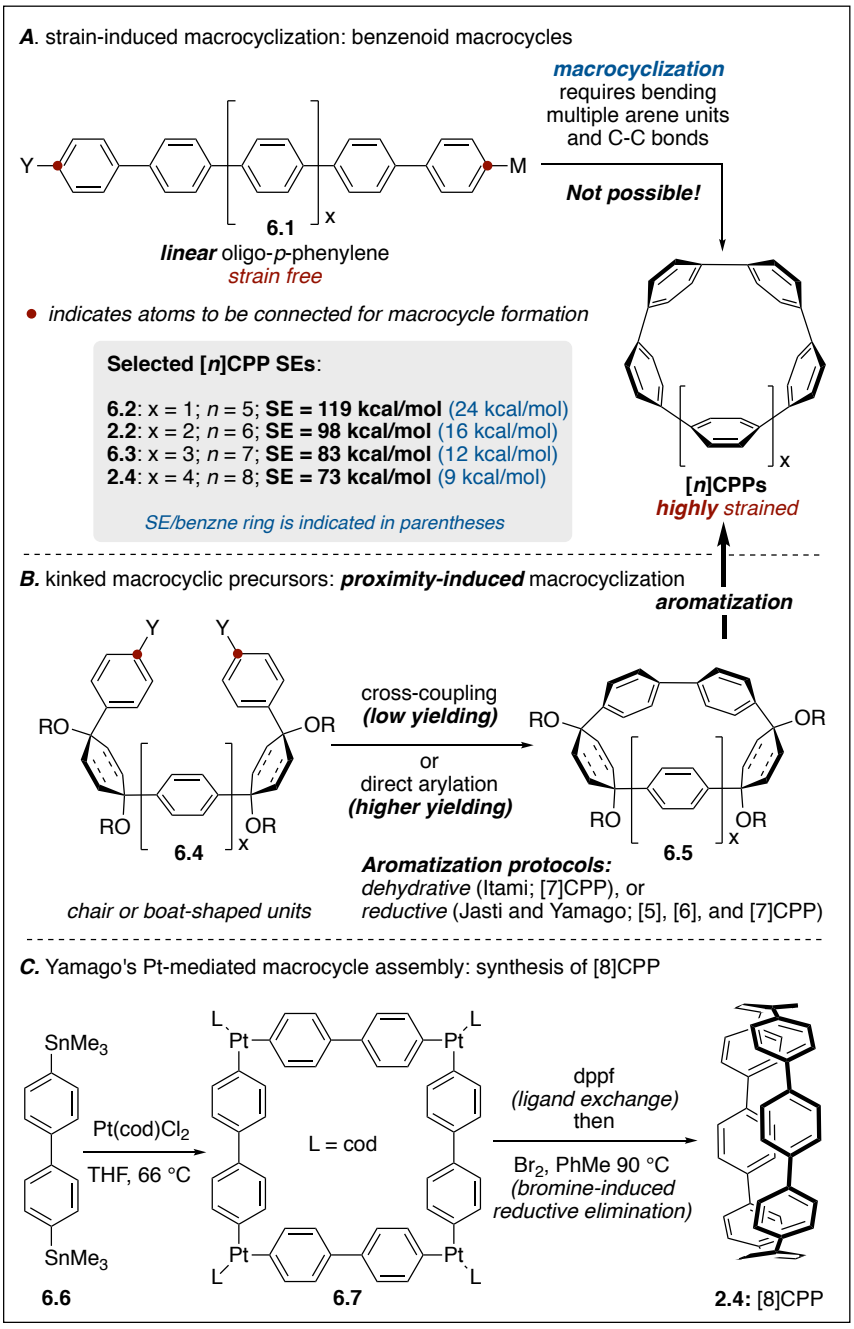
SCHEME 5: Attempted synthesis of [*n*]CPPs by Vögtle and co-workers using pre-arene subunits

While Vögtle never synthesized an [*n*]CPP, his synthetic investigations and development of synthetic strategies for accessing macrocyclic precursors of these highly-strained targets were influential to this field of chemical synthesis. In a concluding remark in one of his later papers, Vögtle speculated the third strategy presented here (Scheme 5), which is based on the formation of a structurally rigid 1,4-*syn*-diaryl cyclohexane ring system, would be the most useful building block in future work aimed towards the synthesis of these molecules. Clearly, the master of cyclophane chemistry had deep insight and his statements, in retrospect, are somewhat prophetic given the advancements made in this field nearly 30 years after his initial comments (see section **1.1.2**).

1.1.2 Successful synthesis of [n]CPPs: From 2008 onward

The major hurdle facing this field of benzenoid macrocycle synthesis, after nearly 70 years of synthetic investigations, was the assembly of suitable macrocyclic precursors that could be subjected to late-stage aromatization. Macrocyclization is a challenging area of chemical syntehsis,[11] and the synthesis of macrocyclic systems that are held together by only biaryl bonds is at the pinnacle of (challenging) macrocyclization reactions. Guided by the early work of Vögtle and co-workers, the research groups of Bertozzi/Jasti, Jasti, Itami, and Yamago were able to develop innovative synthetic strategies for assembling macrocyclic precursors of [*n*]CPPs, and powerful aromatization protocols that enabled the first syntheses of these long sought after targets.

The amount of SE that has to be introduced into a macrocyclic benzenoid systems, such as an [*n*]CPP, can be appreciated when considering connecting the two most remote (para) vertices of an oligophenylene unit (**6.1**, Scheme 6A). This is essentially impossible to achieve at (synthetically) reasonable temperature and pressure. To overcome the challenge of macrocyclization, Bertozzi and Jasti,[6] and later Jasti alone, developed an approach that took advantage of the boat-shape of a cyclohexa-2,5-diene-*syn*-1,4-diol unit (**6.6**, Scheme 6B). Coupled together, the relative stereochemistry and kink of the 6-membered ring, positioned the arene units such that they would be conducive to macrocyclization. Itami and co-workers developed a synthetic approach that capitalized on "L-shaped" cyclohexane-*syn*-1,4-diol units, which is akin to those synthesized by Vögtle. Both groups developed macrocyclization strategies of these subunits and later stage aromatization protocols that featured reductive and dehydrative aromatization reactions, respectively. Yamago and co-workers developed a different strategy in their initial synstheses of [*n*]CPPs, which cleverly exploited the square planar preference of platinum. By linking together four identical biaryl units in a square-



SCHEME 6: Macrocyclization strategies to [*n*]CPPs

like arrangement (**6.8**, Scheme 6C) Yamago and co-workers were able to do the unthinkable and directly bend the 8 planar benzene rings and complete the synthesis of [8]CPP in 2010.[8]

Itami and co-workers have reported the size-selective synthesis of [*n*]CPP (*n* = 7–16) using the transition metal-catalyzed (Pd or Ni) shot-gun method.[14] The key step of these syntheses is the formation of strain-free triangular and square macrocyclic precursors form "L-shaped" building blocks and linear units such as 1,4-disubstituted benzene derivatives. These macrocycles are then been converted to [*n*]CPPs upon an acid mediated aromatization (see Chapter 2 for details). This approach is advantageous for the synthesizing the larger [*n*]CPPs (*n* > 6), however, the synthesis of the smallest [*n*]CPPs, [5] and [6]CPP have never been prepared using the Itami strategy for nanohoop synthesis. On the other hand, the research groups of Jasti, and Yamago have reported the synthesis of the smallest CPPs. The key advantages of their synthetic approachs lie in their macrocyclization and aromatization strategies (discussed below).

1.2 Biaryl bond formation

The development of synthetic methods for the construction of biaryl bonds represents one of the greatest advancements in chemical synthesis over the past 50 years. Rightfully so, the Nobel Prize in chemistry was awarded to Suzuki, Heck and Negishi in 2010 for their pioneering contributions and the development of this area of organic chemistry. Biaryl bonds are found in many important natural products,[15] pharmaceutically relevant[16] and biologically active molecules[17] (see **Figure 2** for selected examples).

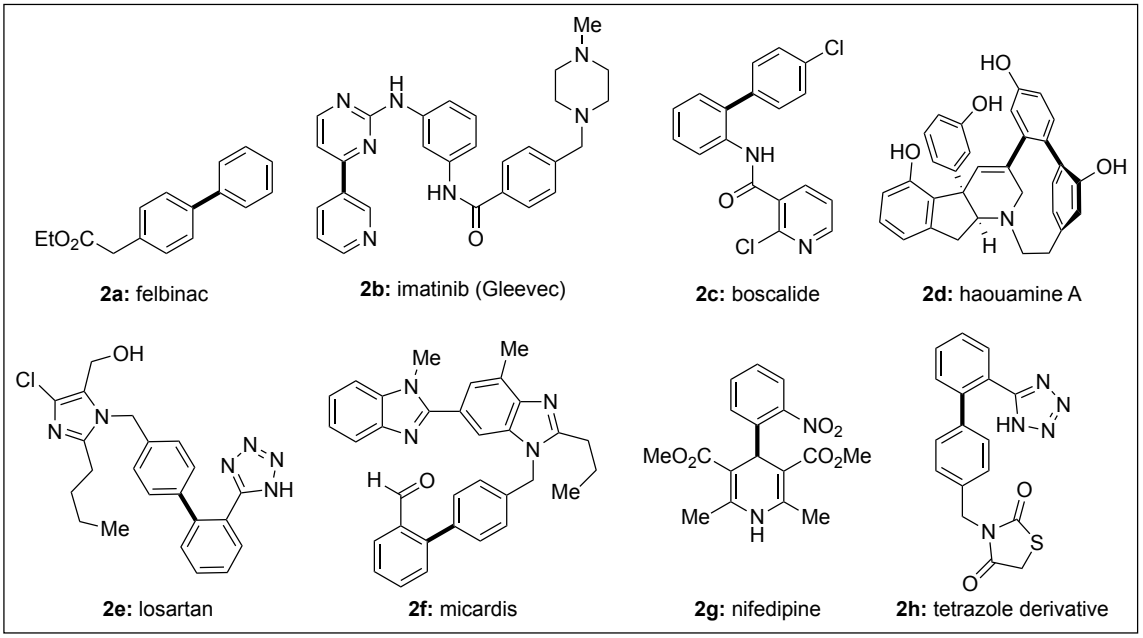


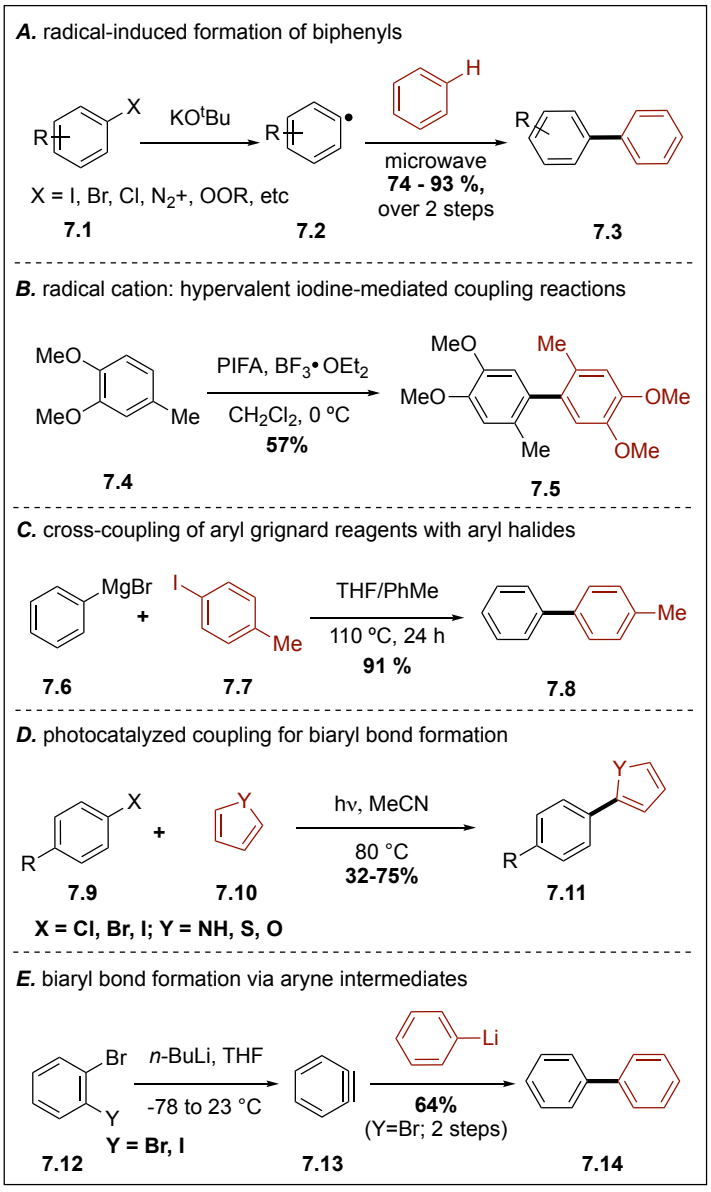
FIGURE 2: Biaryl motifs in medicinally and agriculturally important compounds

Although there exist a variety of routes including non-transition metal mediated coupling reactions for the construction of aryl-aryl bonds, arguably the most common method employed in chemical synthesis for this type of C-C bond formation is transition metal-mediated reactions.[18]

1.2.1 Transition metal "free" cross-coupling reactions

Transition, or simply, metal free cross-coupling reactions are often described as chemical reactions that engage non-identical reaction partners to afford products similar to those that would be obtained from a transition metal-mediated process, where no transition metal catalyst is employed in the reaction.

Although a lot of attention has been given to the development of transition-metal-free coupling reactions and significant amount of efforts have been employed to foster this type of chemistry but still the chemists have not been able to coherently deliver the concept of transition-metal-free coupling reaction.[19] The scope of the "transition-metal-free coupling reactions" seems quite extensive as the definition of the "absence of transition-metal catalysts" is still arguable due to the difficulty of rooting out transition-metal residues from starting materials, reagents, additives or solvents. Often residual amounts of a transition-metal impurity from reagents used in the reaction flask can be responsible for catalyzing the desired reaction. Thus, defining such processes as transition metal free is difficult.



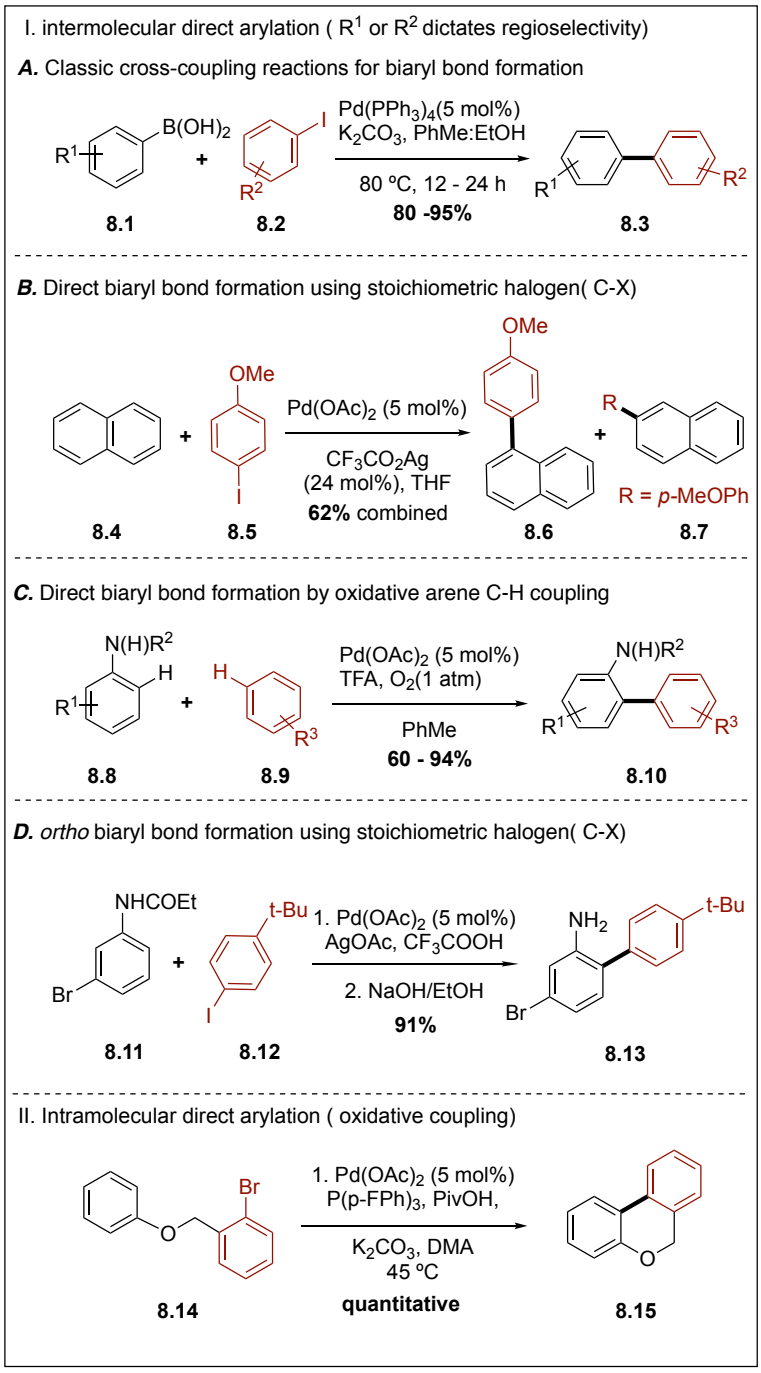
SCHEME 7: Metal free approaches to biaryl bond formation

Chemical reactions that lead to biaryl bond formation that have been categorized as transition metal free processes in-

clude radical induced biphenyl synthesis under microwave irradiation (Scheme 7A),[19] oxidative homocoupling of electron rich arene units in the presence of a Lewis acid and hypervalent iodine reagent (Scheme 7B),[20] thermally induced corss-coupling of Grignard reagents with iodoarenes via a S_NAr-type reactions (Scheme 7C)[21] photo-induced coupling of heterocyclic aromatics with haloarenes (Scheme 7D),[19] and cross-coupling of benzyne with organolithium reagents (Scheme 7E).[22]

1.2.2 Transition metal-catalyzed cross-coupling reactions

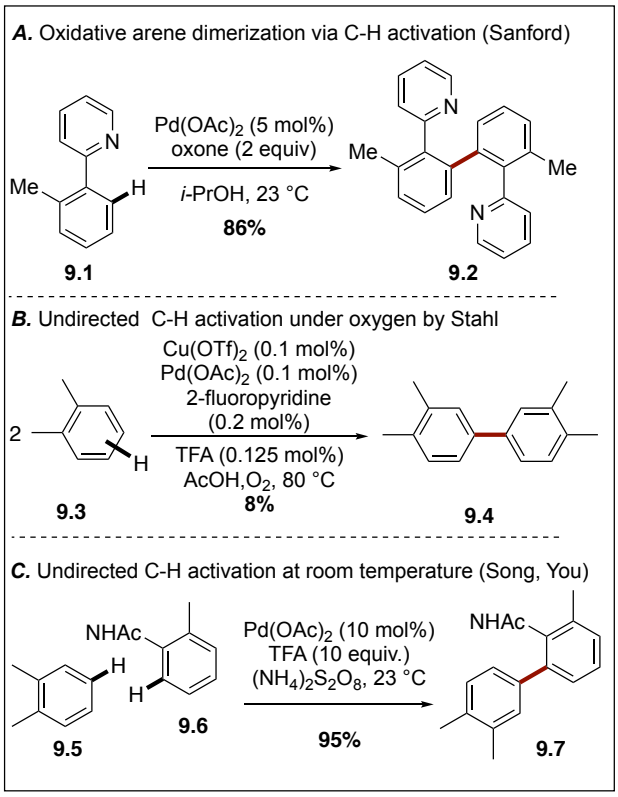
A key focal point of synthetic organometallic chemistry in 1960s, transition metal-catalyzed reactions have been widely developed over the past 50 years.[23] Synthetic innovations, modifications, ligand accelerated processes,[REF] and catalyst development[REF] has led to the expansion of the synthetic chemists' toolbox where dozens of synthetic transformations can be called on to achieve aryl-aryl coupling reactions. These reactions have become so commonplace in chemical synthesis that they are often viewed as straightforward and highly reliable processes. In the early stages of their development, transition metal-mediated cross-coupling reactions required the use of stoichiometric amounts of the metal. Nowadays, aryl-aryl bond formation can be achieved using extremely low catalyst loadings, which has greatly in-



SCHEME 8: Examples of transition metal catalyzed cross-coupling reactions

creased the scope of these reactions. The importance of this class of reactions in pharmaceutical, and polymer industries, and chemical synthesis in general, was recently recognized with awarding the Nobel Prize to Suzuki, Heck, and Negishi for their pioneering contributions to the development of this class of reactions. [24-25]

The development of synthetic methods that capitalize on "activated" C-H bonds of functionalized aromatic compounds has emerged as an arene of significant interest. These reactions do not require stoichiometric amounts of organometallic reagents or aryl halides and by analogy to these functional groups, a C-H bond can be activated in the presence of a metal catalyst and ligand and subsequently functionalized. Selected examples of the C-H activation/functionalization reactions that lead to C(sp^2)-C(sp^2) bond formation are presented in Scheme 9.[26]



SCHEME 9: Examples of C-H activation for C(sp^2)-C(sp^2) (biaryl) bond formation

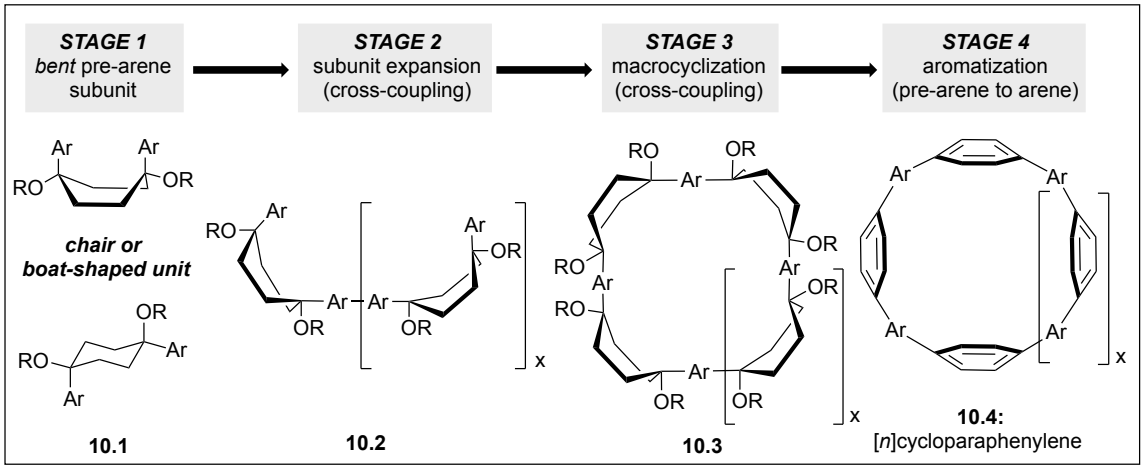
Some metal-catalyzed cross-coupling reactions have been honored as named reactions in organic chemistry. The most common examples of these reactions are those catalyzed by palladium, and the distinction of each named reaction often comes from the nature of the organometallic coupling partner. For instance, cross-coupling reactions involving organoboron[27-28] reagents are known as the Suzuki coupling reaction. Reactions that employ organotin reagents,[29-30] are known as Stille coupling reactions, while those that use Grignard reagents,[31] have been named Kumada coupling reactions. Feringa has pioneered the use of organolithium-[32-33] based reagents in cross-couplings, and the organozinc[34-35]-based Pd-catalyzed process is known as a Negishi coupling. Others include organosilane (Hiyama) reagents.[36] arenediazonium salts (Heck-Matsuda), and the powerful Buchwald-Hartwig amination reaction. In all the aforementioned cases halides or pseudohalides or alkene or arene units are required starting materials.

While numerous synthetic innovations have come in the form of metal-mediated and metal-catalyzed C-C bond forming reactions, there are still several limitations within this class of reactions. In particular, their use in forming strained biaryl bonds and application to macrocycle synthesis has been well-documented.[11] The following section will underscore some of these limi-

tations as they apply to the synthesis of [*n*]CPPs, however, focus will be placed on the development of new metal-mediated and catalyzed process that have addressed the challenge of macrocyclization.

1.2.3 Transition metal-mediated and catalyzed cross-coupling in the synthesis of [n]CPPs

All of the reported syntheses of [*n*]CPPs involve in four major stages in assembling these strained macrocycles (Scheme 10). Stage 1 stage involves the synthesis of a bent pre-arene subunit containing a boat or chair-shaped six-membered ring such as that found in **10.1**. This arylated, bent pre-arene subunit induces curvature, which will accommodate the macrocyclic structure at later stage in the synthesis (Stage 3). Stage 2, involves transition-metal or catalysed cross-coupling reactions linking two or more pre-arene units together to form an elongated, linear subunit. Stage 3 is arguably the bottleneck of this approach, which involves macrocyclization via a metal-mediated or metal-catalyzed reaction. In early approaches to [*n*]CPPs, macrocyclization was achieved through low yielding cross-coupling reactions.[16] As smaller and more strained [*n*]CPPs were targeted, new macrocyclization strategies were developed (see below). The final stage involves aromatization of the pre-arene units to complete the synthesis of the [*n*]CPPs. The devlopment of aromtization stratgies for accesing the highly strained benzenoid units of these and related macrocycles will be discussed in Chapter 2.

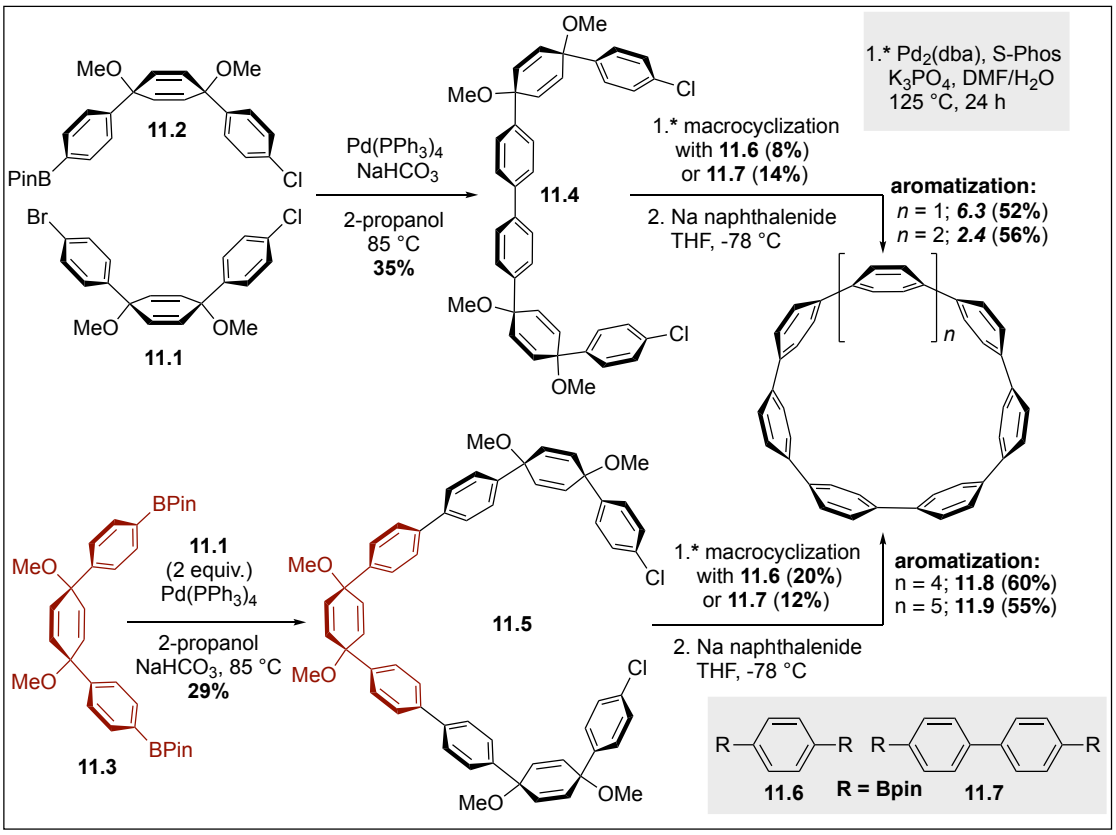


SCHEME 10: General synthetic approaches to [*n*]CPPs

1.2.3.1 Jasti and co-workers selective syntheses of [7]-[12]CPP

In 2012, Jasti and co-workers reported a synthetic approach that utilized sequential Suzuki cross-coupling reactions to selectively assemble macrocyclic precursors of [7]-[12]]CPP and to furnish partially aromatized macrocycles (Scheme 11). The boat-shaped *syn*-1,4-diol was prepared using a diastereoselective strategy developed in the Jasti laboratory.[37-39] Installing both aryl bromide and chloride units was critical to the achieve selective functional group manipulations and

cross-coupling reactions. For example, **11.1** was converted to boronate **11.2** after halogen-metal exchange (C-Br bond), followed by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*i*-PrBpin). Selective Suzuki cross-coupling of the aryl bromide position of **11.1** with boronate ester **11.2** gave dichloride **11.4** in 85% yield. From here, intermolecular, followed by intramolecular, Suzuki cross-coupling of **11.4** with **11.6** or **11.7** furnished macrocyclic precursors to [7] and [8]CPP, which were ultimately subjected to a reductive aromatization reaction with sodium naphthalenide to give the desired nanohoops in 4% and 8% yield, respectively. It should be noted that the low yields obtained over the final two steps of these syntheses are due to the cross-coupling reactions employed in assembling the macrocycles (8 and 14%, respectively, Scheme 11).



SCHEME 11: Orthogonal Suzuki reaction for the synthesis of [*n*]CPP

Using the same general strategy, but different cross-coupling partners, a kinked 9-ring oligomer **11.5** was synthesized upon treatment of **11.3** with two equivalents of **11.1** in the presence of $Pd(PPh_3)_4$ and sodium bicarbonate in 2-propanol at 85 °C. Using identical cross-coupling conditions (for macrocyclization) to insert the reaming arene units of [10] and [11]CPP, followed by reductive aromatization, furnished the benzenoid macrocycles in 12% and 7% yield, respectively over the last two steps (Scheme 11). These short, size-selective synthetic sequences to [*n*]CPPs represented a ground breaking achievement for this field of chemical synthesis, and sim-

ilar reports on size-selective syntheses of [*n*]CPPs would soon follow from the groups of Itami[7, 40] and Yamago.[8, 41-43] These contributions demonstrated that virtually any macrocyclic CNT precursor (or template) could be assembled, however, they also validated that cross-coupling reactions, in general, are low yielding and somewhat limited for macrocyclization that require biaryl bond formation.

1.2.4 Limitations of transition metal-catalyzed cross-coupling reactions in biaryl macrocycle synthesis

Despite their widespread use in chemical synthesis and their importance in construction of C-C bonds, transition metal-catalyzed cross-coupling reactions are not without their limitations. These include costs associated with precious metal catalysts and special ligands, which can often have exotic structures, be even more expensive than the metal catalysts themselves, and challenging to synthesize. Furthermore, most transition metals are considered to be toxic and thus have to be removed from compounds intended for use or to be tested as potential drugs. This can also lead to increased cost when a pharmaceutically relevant molecule hits the market. Transition metal catalysts are often air and moisture sensitive and require tedious reaction protocols for rigorous removal of oxygen and water to ensure that costly ligands and catalysts are not destroyed during the course of the reaction. However, as it applies to this dissertation, and chemical synthesis in general, one of the biggest limitations of transition metal-catalyzed cross-coupling reactions is their poor performance in macrocyclization reactions. This topic has been discussed extensively by Baran and co-workers in an authoritative review article.[11]

In general, transitional metal catalyzed cross-coupling reactions produce low yields, or fail all togther, when there is a need to introduce strain in biaryl containing macrocycles. In terms of synthesizing marcocylic systems that contian both aromatic and alkne units (*i.e.*, cyclophanes) the introduction of strain energy can arise during alkyl bridge formation (Mode 1, Figure 3) or biaryl bond formation (Mode 2, Figure 3). In either scenario there is a need to form C-C bonds with non-deal bond angles and to deform/bend of the arene unit from its native planar conformation. This increase in strain energy contributes to the activation barrier for C-C bond formation, which is often prohibitive. As such, transition metal-catalyzed cross-coupling

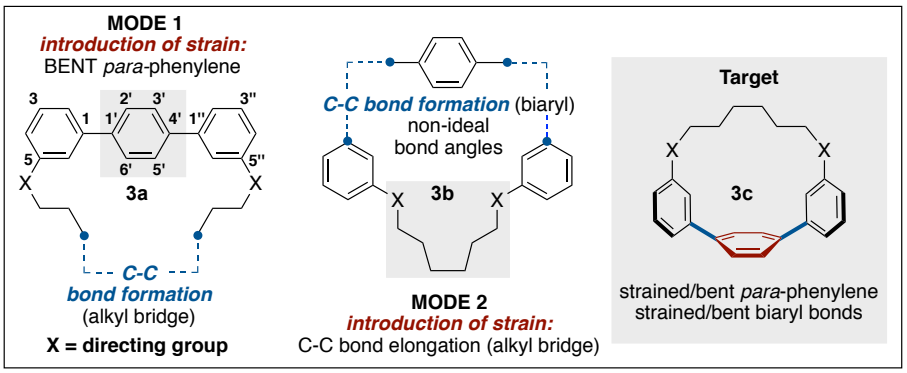
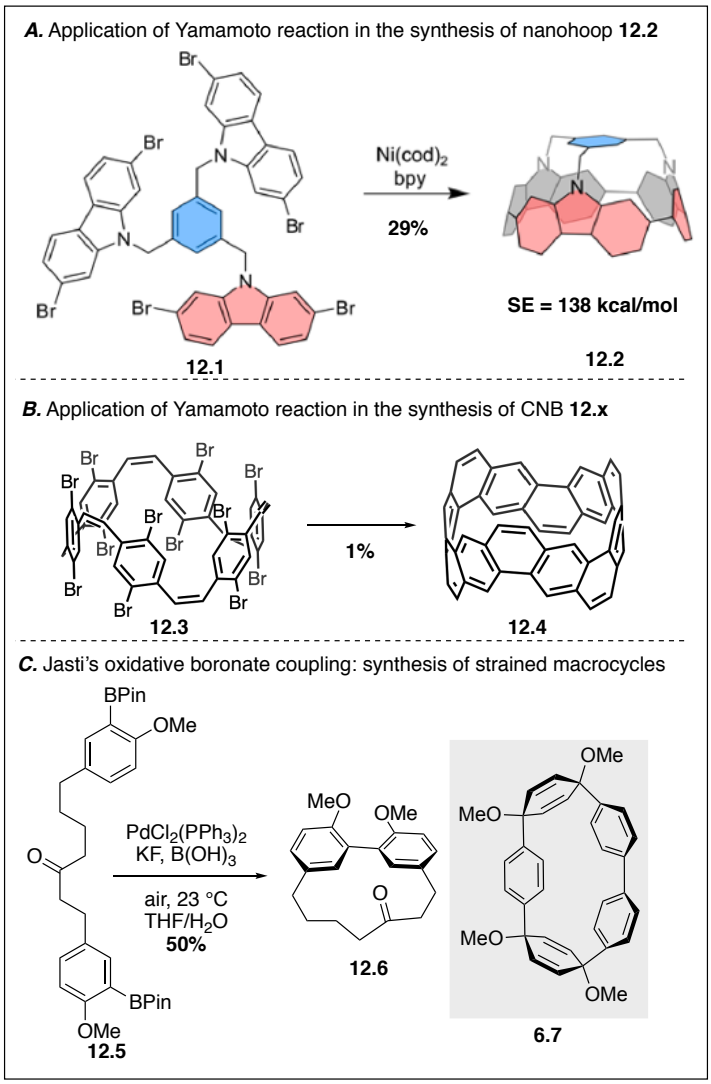


FIGURE 3: Inducing strain in C-C bond forming reactions - macrocycle synthesis

reactions have proven to be weak synthetic tools for this class of macrocycle synthesis. Recent advances in direct arylation methods, discussed below, have provided a clever solution to strained biaryl bond/arene formation; however, these reactions have been limited to highly symmetrical precursors.

1.2.5 Recent advances in metal-mediated intramolecular coupling reactions for biaryl macrocycle synthesis

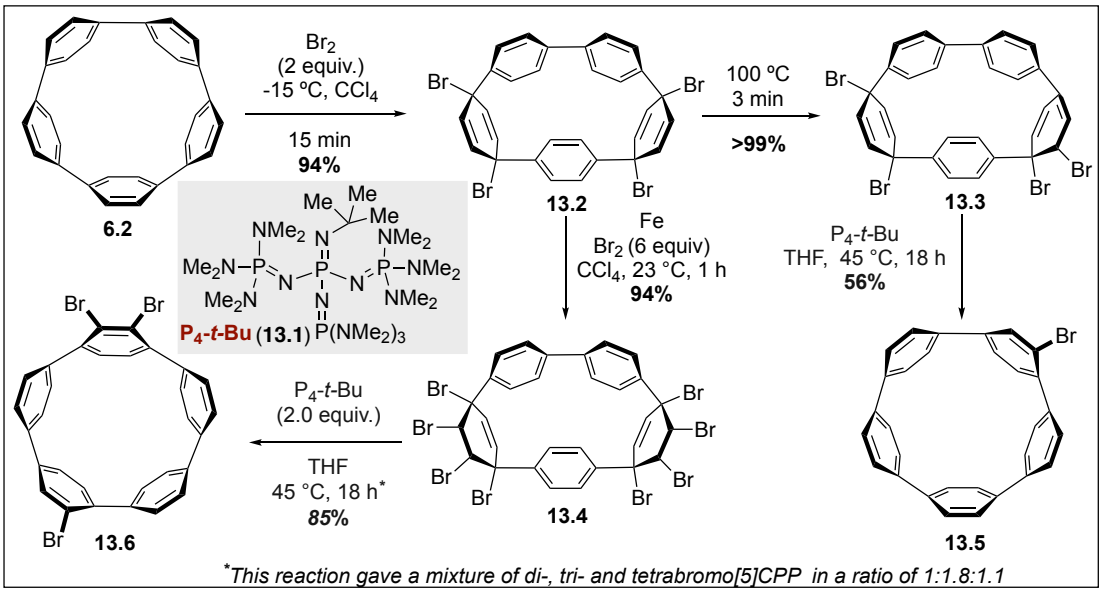
The Yamamoto coupling reaction is powerful intramolecular biaryl bond forming reaction of a aryl bromides and chlorides, which has been used to synthesize strained macrocycles. This reaction is generally performed using stoichiometric amounts of nickel ($Ni(cod)_2$) under anhydrous and oxygen free conditions. This reaction has been employed in the synthesis of carbazole-containing nanohoops (Scheme 12A) and most recently employed in Itami's synthesis of a carbon nanobelt (CNB, Scheme 12B). During their synthesis of [10]CPP,[44] Jasti and co-workers identified the formation of an "undesired" macrocyclic by-product to be that of 6.7 (Scheme 12C), which had formed as a result of oxidative boronate coupling. They would later use this macrocycle to complete the synthesis of [5]CPP (discussed in Chapter 2) and develop and demonstrate the utility of this reaction in the synthesis of several macrocyclic biaryl systems such as 6.7 (Scheme 12C).



SCHEME 12: Yamamoto and oxidative boronate coupling reaction in the synthesis of CPP

While the synthesis of strained, biaryl macrocycles has presented a challenge for venerable Pd-catalyzed cross-coupling reacitions, there are, albeit low yielding, examples were these reactions have been employed. While accessing gram-scale quantities of the [*n*]CPPs and related carbon nanohoops has been

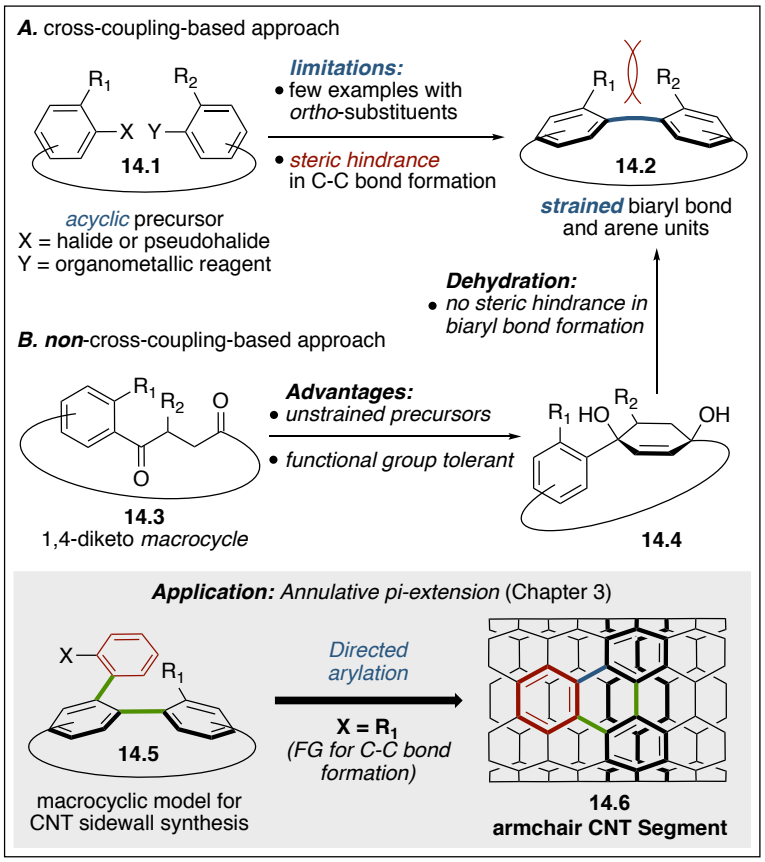
accomplished,[44-46] their use as templates for the bottom-up chemical syntehsis of CNTs has not. This is in large part due to the inability to install functional group handles in the macrocyclic backbone of these nanohoops at late or early stages of their syntheses. In the case of late-stage functionalization of [*n*]CPPs, the major synthetic hurdle involves controlling regiochemistry and separation of constitutional isomers produced. An approach to selective, late-stage monofunctionalization of [9] and [12]CPP has been reported by Itami and co-workers,[47] while the Yamago group has been able to take advantage of strain-relief bromination of highly strained CPPs ([5]-[8]CPP) to afford selectively monofunctionlized derivatives.[48] Bromination of these the CPP takes place via addition and not substitution, and following heating tetrabromide **13.2.** at 100 °C, rearrangement to **13.3** takes place in quantitative yield. Treatment of tetrabromide **13.2** using bromine (6 equiv.) in the presence of Fe powder produced octabromide **13.4**. The tetra- and octabromine adducts were then transformed into mono (**13.5**) di-, tri-(**13.6**), and tetrbromo CPPs using phosphazene superbase, *t*-BuN=P[N=P(NMe$_2$)$_3$] (P$_4$-*t*-Bu, 2.0 equiv.), in THF at −45 ºC. in the case of **13.6**, it was produced as an inseparable mixture with di- and tetrabromides (1:1.8:1 *r.r.*). While selectively monofunctionalized derivatives have been synthesized, the conversion of these derivatives to pi-extended CPPs and carbon nanobelts has not.



SCHEME 13: Selective bromination of [5]CPP by Yamago

One possible solution to the [*n*]CPP functionalization problem, would be to use strategically functionalized arene units at the start of their synthesis. For the purposes of late-stage C-C bond forming reactions that lead to pi-extended derivatives, aromatic units containing halide or pseudohalide substituents *ortho* to the biaryl bonds holding the macrocycle together would be ideal. However, this presents a major challenge for cross-coupling-based synthetic approaches

to these and related benzenoid macrocycles, as the desired biaryl bond formation becomes sterically hindered and much more challenging (**14.1** to **14.2**, Scheme 14A). Furthermore, if these *ortho*-substiutents are halides or pseudohalides, competing intermolecular cross-coupling reactions will come into play and likely dominate product formation. To address these shortcomings of cross-coupling-based approaches, a synthetic approach that would utilize an unstrained macrocyclic 1,4-ketone as a surrogate to a highly strained arene-bridged macrocycle was designed.[49] In this approach (**14.3** to **14.4**, Scheme 14B) substitution of the arene unit *ortho* to the carbonyl unit and/or α-substitution of the 1,4-diketo bridging unit, would ultimately manifest as *ortho*-functional group handles upon formation of the bent arene unit. Since "biaryl bond" formation will take place upon dehydration of a bridged-cyclohex-2-ene1,4-diol (**14.4** Scheme 14B) there will be not steric hindrance associated with this approach. Finally, by avoiding cross-coupling reactions for biaryl macrocycle synthesis, no competing intermolecular (cross-coupling reactions) will be in play. Thus, these *ortho*-functional groups will remain dormant during the course of the synthesis of **14.5**, and can be engaged in C-C bond forming reactions once the strained macrocycle has been assembled. The introduction of functionalized arene units via late-stage cross-coupling reactions will enable the development of annulative pi-extension protocols and the synthesis of CNT sidewall substructures such as **14.6**. the latter is the major focus of Chapter 3 of this dissertation.



SCHEME 14: Potential advantages of a non-cross-coupling-based approach to arene-bridged macrocycles

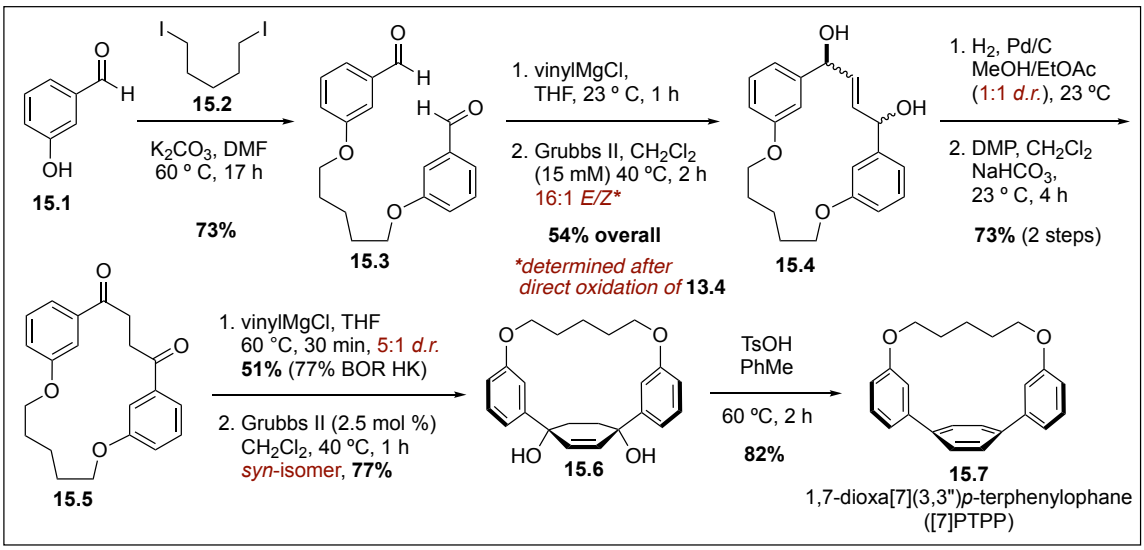
1.3 A non-cross-coupling-based approach to arene-bridged macrocycles

In the section 1.2.4, the limitations of transition metal-catalyzed cross-coupling reactions for strained biaryl bond formation and the synthesis of arene-containing macrocycles with *ortho* sub-

stituents was discussed. To circumvent the problems, an eight-step synthetic protocol was developed to access highly strained benzenoid macrocycles, which featured the conversion of a relatively unstrained 1,4-diketo-bridging unit into a bent *para*-phenylene unit.[49]

1.3.1 Synthesis of 1,7-dioxa[7](3,3")-p-terphenylophane ([7]PTPP)

Alkylation of 3-hydroxybenzaldehyde (**15.1**) with 1,5-diiodopentane afforded dialdehyde **15.3** in 73% (Scheme 15). A Grignard reaction of **15.3** with vinylmagnesium chloride in THF produced an allylic diol, which was directly subjected to a macrocyclic ring-closing metathesis (RCM) reaction without at 15 mM concentration in dichloromethane using the Grubbs second-generation catalyst to afford macrocyclic 1,4-diol **15.4** in 54% yield over 2 steps. This reaction could be carried out on a gram-scale and a single purification at the stage of **15.4** resulted in higher overall yield. Macrocycle **15.4** was produced as a mixture of *syn* and *anti*-1,4-diols, as well as a mixture of alkene diastereomers. The latter ratio was determined to be 16:1 *E/Z* upon direct oxidation of **15.4** to furnish macrocyclic enone. As such, it was necessary to hydrogenate the olefin of **15.4**. This was achieved by catalytic hydrogenation, which confirmed the *syn*/*anti* (*d.r.*) ratio to be 1:1. Oxidation of the resulting saturated 1,4-diol gave macrocyclic 1,4-diketone **15.5 in** 73% yield over 2 steps.



SCHEME 15: Synthesis of 1,7-dioxa[7](3,3")*p*-terphenylophane (**15.7**)

With macrocycle **15.5** in hand, the stage was set to convert the relatively unstrained 1,4-diketo-bridging unit into a strained *para*-phenylene bridging unit. Treatment of **15.5** with vinylmagnesium chloride in THF at 60 °C afforded an inseparable mixture of diastereomeric allylic diols (5:1 *d.r.*) and a separable hydroxyketone (HK) by-product. While the diasteromeric alcohols could no be separated at this juncture, it was reasoned based on molecular modeling that only the *syn*-diastereomer would succumb to a ring-closing metathesis reaction. Indeed, this proved to be the case and when the mixture of allylic alcohols was treated with the Grubbs second-generation cat-

alyst in dichloromethane at 40 °C cyclohex-2-ene-1,4-diol **15.6** (R_f = 0.27, 1:1 EtOAc/hexanes) was isolated in 77%, along with the uncyclized *anti*-diastereomer (R_f = 0.59, 1:1 EtOAc/hexanes). An X-ray crystal structure of **15.6** would later confirm the relative stereochemical assignment of this macrocycle, which was initially made up the basis of the steric hindrance in the RCM reaction (Figure 4). To complete the conversion of the 1,4-diketone to a highly strained *para*-phenylene, **15.6** was subjected to a TsOH-mediated dehydrative aromatization reaction[49] to furnish arene-bridged macrocycle **13.7** in 82% yield.

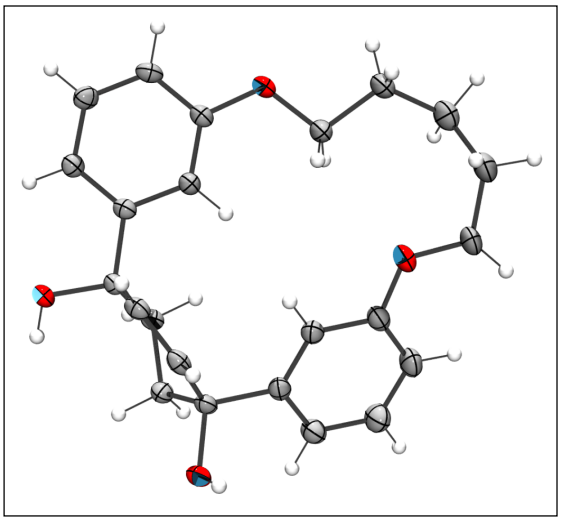


FIGURE 4: X-Ray crystal structure of **15.6**

1.3.2 X-ray crystal structure of 15.7 and its computed strain energy

Fortunately, recrystallization of **15.7** from acetone and dichloromethane provided a single crystal suitable for X-ray crystallography. The crystal structure of **15.7** (Figure 5) indicates that the central benzene ring of the *p*-terphenyl system is distorted from planarity. The *para*-carbon atoms, C-23 and C-24 (crystallographic numbering) of the central benzene ring have a mean deviation angle (α) of 9.9° from the plane defined by C-12, C-13, C-18, and C-19, respectively, and are displaced from the plane by 0.054 Å. The benzylic carbon atoms, C-22 and C-25, are distorted by an average angle (β) of 18.1°. These angles are and akin to those (α and β) used for quantifying the deformation of nonplanar benzene rings in the [*n*]paracyclophanes. [50-51] The average twist (torsion angle) of the teraryl system ranges from 37.3-50.7°, and the mean C-C biaryl bond deviation between the two terminal rings and the central benzene ring is 7.0°. As such, the *meta*-alkoxy bridging group cants the terminal phenyl rings away from the central arene unit. Deviation of the *p*-terphenyl system from its ideal geometry, relative to that of unperturbed 3,3"-dimethoxy-*p*-terphenyl (model compound **15.8**, Figure 5), causes a blue-shift in both the UV-vis and fluorescence spectrum: λ_{max} (**15.7**) = 270 nm (absorption) and 335 nm (emission), λ_{max} (15.8) = 278 nm (absorption) and 339 and 352 nm (emission). The total strain energy present in **15.7** has been estimated using density functional theory (DFT B3LYP (6-31G*)) calculations. Relative to a planar *p*-terphenyl system, the macrocyclic structure of **15.7** has total SE of 29.7 kcal/mol, with 21.8 kcal/mol contained within the bent *p*-terphenyl unit. The central *para*-phenylene ring of **15.7** bears 14.5 kcal/mol of SE, which is slightly more strained than a *para*-phenylene unit of [7]CPP (SE_{pp} = 11.8 kacal), but less than that of a *para*-phenylene unit of [6]CPP (SE_{pp} = 16.3 kcal/mol).[52]

Compound **15.7** can be viewed as cyclophane, and therefore named 1,7-dioxa[7](3,3")*p*-terphenylenophane ([7]PTPP). This numbering is appropriate for a discussion of its substitution chemistry (Scheme 16). In the initial stages of our synthetic investigations, we had envisioned that incorporation of oxygen atoms at the C-3 and C-3"-poistions of the *p*-terphenyl system of **15.7** would allow for selective functionalization of the terminal benzene rings. Furthermore, it was anticipated that the hindered C-2 and C-2"-posiitons would be less susceptible to substitution reactions. Indeed, the ^{1}H NMR spectrum of **15.7** shows that the proton resonance of the (H-2) and (H-2")-positions is considerably shielded at 5.81 ppm – *cf*, 7.20 ppm (δ H-2 and H-2") for 3,3"-dimethoxy-*p*-terphenyl (Figure 5). This indicates that, like the solid phase structure, H-2 and H-2" are directed toward the shielding cone of the central benzene ring in the solution phase.

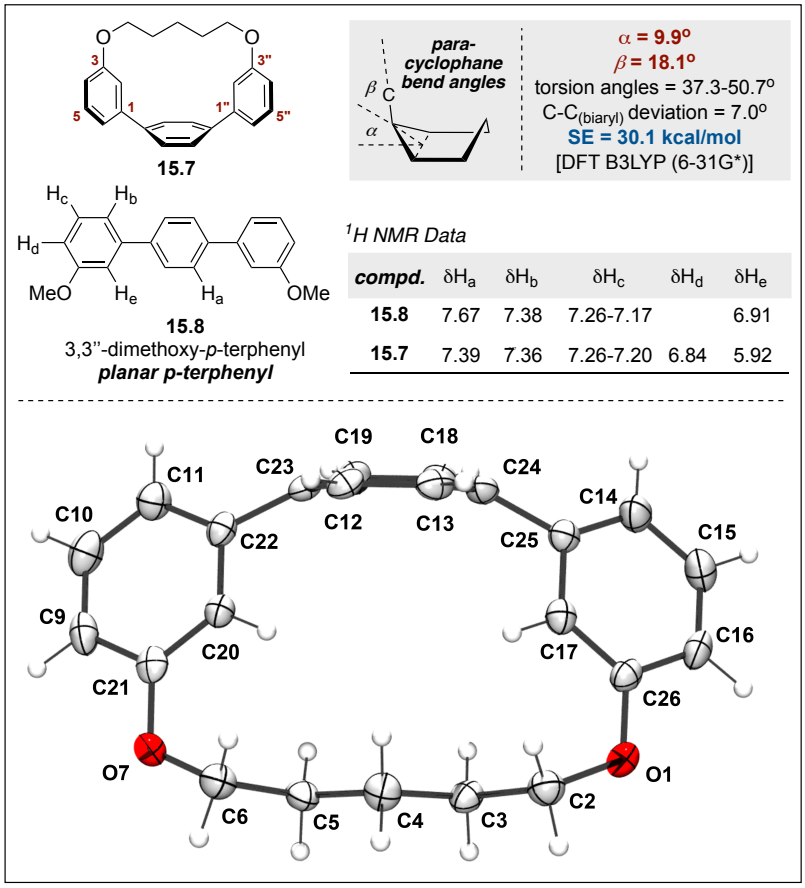
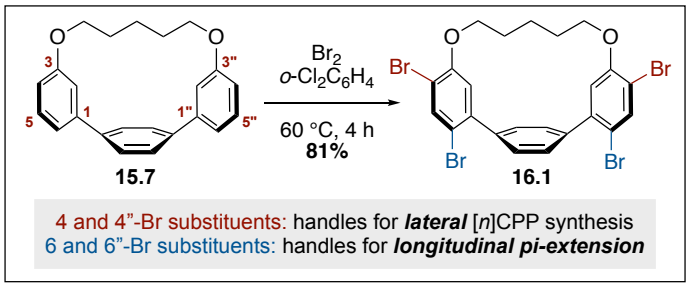


FIGURE 5: X-ray crystal structure (**15.7**) and structural data for **15.7** and **15.8**

1.3.3 Regioselective, late-stage bromination of 15.7

At the time when **15.7** was synthesized, only a single report on the regioselective functionalization of strained benzenoid macrocycles such as the [*n*]CPPs had been reported. Upon η^6 complexation of [9] and [12]CPP with $Cr(CO)_6$ Itami and co-workers[47] reported selective monofunctionalization reactions of these CPPs. However, the introduction of more than one functional group/substituent was not accomplished and cited as problematic. Furthermore, their synthetic method required the absence of light and to avoid decomposition of the metallated CPPs, experiments needed to be conducted in a dark room.

The introduction of an alkoxy bridging group at the 3 and 3"-posiitons of *p*-terphenyl was done so with the intention bending this aromatic unit of the resulting macrocycle, but also to activate the terminal phenyl rings towards electrophilic aromatic substitution. It was hoped that regioselective bromination of 4, 4", 6, and 6"-positions would take place upon treatment of **15.7** with bromine. From ^{1}H NMR spectroscopy and X-ray crystallographic analysis of **15.7** it was reasoned that the 2 and 2" positions of would not undergo bromination due to steric hindrance. Indeed, treatment of **15.7** with an excess of bromine (6.0 equiv.) in *ortho*-dichlorobenzene at 60 °C furnished only the 4,4",6,6"-tetrabrominated product **16.1** (Scheme 16). Such bromination reactions of 3,3"-substituted *p*-terphenyl systems had not been previously reported, and direct halogenation reactions of [*n*]CPPs had been cited as problematic.[47, 53] These site-selective bromination reactions should facilitate future two directional carbon-carbon bond-forming reactions for expanding the terphenyl unit of **15.7** into a PAH system (blue bromine atoms of **16.1**) and connecting the remote (*para*) arene vertices (red bromine atoms of **16.1**) to complete nanohoop or tube construction. The former will be the subject of Chapter 3. The fact that the central, arene unit of **13.7** does not undergo strain relief driven bromination reaction is also noteworthy, especially in view of what Yamago and co-workers later reported for [5]-[8]CPP (see **Scheme 13**, and section 1.2.4)



SCHEME 16: regioselective bromination bent *p*-terphenyl **15.7**

1.4 Concluding remarks: Outlook of the non-cross-coupling-based approach to arene-bridged macrocycles

The objective of this chapter was to develop synthetic approach to strained arene-bridged macrocycles that avoided the use of transition metal-mediated reactions. Such a strategy would address the limitations of cross-coupling reactions in biaryl macrocycle synthesis and provide a means to synthesize strategically functionalized arene units within the macrocyclic framework of these nanohoop subunits. In the case of the former, using a 1,4-diketone bridging unit and a cyclophane-based approach to the synthesis of bent *p*-terphenyl units, we hoped to tackle the synthesis of highly strained macrocyclic systems such as the elusive [4]CPP. In terms of the latter, regioselectively functionalized *p*-terphenyl-containing macrocycles would provide a platform for the development of the annulative pi-extension reactions that convert strained benzenoid systems into strained PAHs that are larger (pi-extended) substructures of carbon nanotube sidewalls. The remaining two chapters of this thesis will describe our efforts in these directions.

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CHAPTER 2 A Mild Dehydrative Aromatization Protocol for Synthesis of Highly Distorted *para*-Phenylene-Containing Macrocycles

2. INTRODUCTION

A dehydrative aromatization reaction of a cyclohex-2-ene-1,4-diol-containing macrocycle under protic acid-mediated conditions, furnished a highly strained arene-bridged macrocycle in Chapter 1.[1] Derived from a macrocyclic 1,4-diketone, the cyclohex-2-ene-1,4-diol represented a new addition to a growing, albeit small, list of arene surrogates that had been recently employed in the synthesis of highly strained benzenoid macrocycles (see below). The main objective of this chapter is to explore the advantages and potential limitations of acid-mediated dehydrative aromatization protocols, by synthesizing increasingly strained *para*-phenylene units. This requires the synthesis of a homologous series of macrocyclic 1,4-diketones and related synthetic intermediates. Furthermore, it was hoped that this aromatization strategy and the non-cross-coupling-based approach to biaryl macrocycles could be applied to the synthesis of selectively functionalized, bent *p*-terphenyl units, which could later be used in the development of annulative pi-extension (APEX) methods.[2] Before describing the results of these investigations, a brief discussion of historically relevant and modern synthetic approaches to the most distorted *para*-phenylenes known would be appropriate.

2.1 The valence isomer approach to highly distorted benzene rings

The synthesis of distorted benzene rings has been ongoing for over 65 years,[3] and the quest to synthesize the most perturbed cyclic 6π system culminated with kinetically stabilized [4]paracyclophane derivatives in 2003.[4] However, this field of chemical synthesis has remained quite vigorous over the past decade. The discovery of natural products containing highly strained *para*-phenylene subunits, particularly the haouamine alkaloids (see below, Scheme 17),[5] and the notion that macrocyclic benzenoid hydrocarbons may serve as templates in the bottom-up chemical synthesis of carbon nanotubes (CNTs)[6-8] has kept the level of interest in new synthetic method development high. It is noteworthy that in both of the aforementioned examples, the bent *para*-phenylene units are part of biaryl macrocyclic systems.

The most distorted benzene rings to be characterized by X-ray crystallography belong to the paracyclophanes. In the case of Tobe's [6]paracylophane derivative **6c**,[9] and Tsuji's [1.1]paracyclophane **6d**,[10] the highly distorted pi-systems were obtained upon valence isomerization of Dewar benzene precursors (Figure 6). For a long time, valence isomerization reactions were viewed as the ultimate method for synthesizing severely distorted aromatic systems. In the case of the Dewar benzenes, rupture of the central C-C bond in the bicyclo[2.2.0]hexa-2,5-diene system (**6a**, Figure 6A), via a 4π electrocyclic ring-opening reaction, brought about a release of

strain energy (SE) upon destruction of the bicyclic intermediate, and a gain in aromatic stabilization energy (ASE) upon forming the arene system. Until 2014, no bent *para*-phenylene ring with an α angle (see Chapter 1 for definition) greater than 15° had been synthesized using a non-valence isomerization approach. The pioneering contributions from the groups of Bertozzi,[11] Itami,[12-16] Yamago,[17-21] and Jasti[11, 22-24] on the synthesis of [*n*]cycloparaphenylenes rejuvenated this area of chemical synthesis, in the context of strained (macrocyclic) benzenoid nanohoops. The 2014 syntheses of [5]CPP[20, 25] re-wrote the record books for the smallest [*n*]CPP homologue. With an average mean plane deviation angle (α) of 15.6° and a total SE of 119 kcal/mol (*ca.* 24 kcal/mol per benzene ring), [5]CPP is by far the most strained of the carbon nanohoops to be synthetized. The synthesis of this impressive nanostructure, and related homologs, has led to the development of powerful aromatization strategies that employ reductive (aromatization) protocols and not valence isomerization reactions (see Schemes 18 and 19).

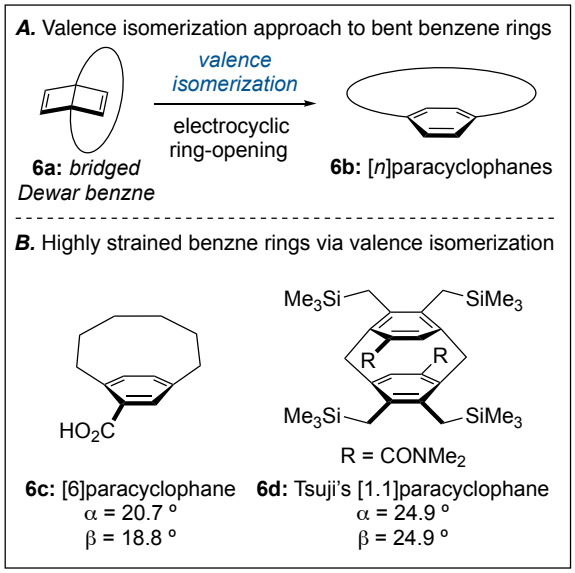


FIGURE 6: Valence isomer approach to the most distorted benzene rings

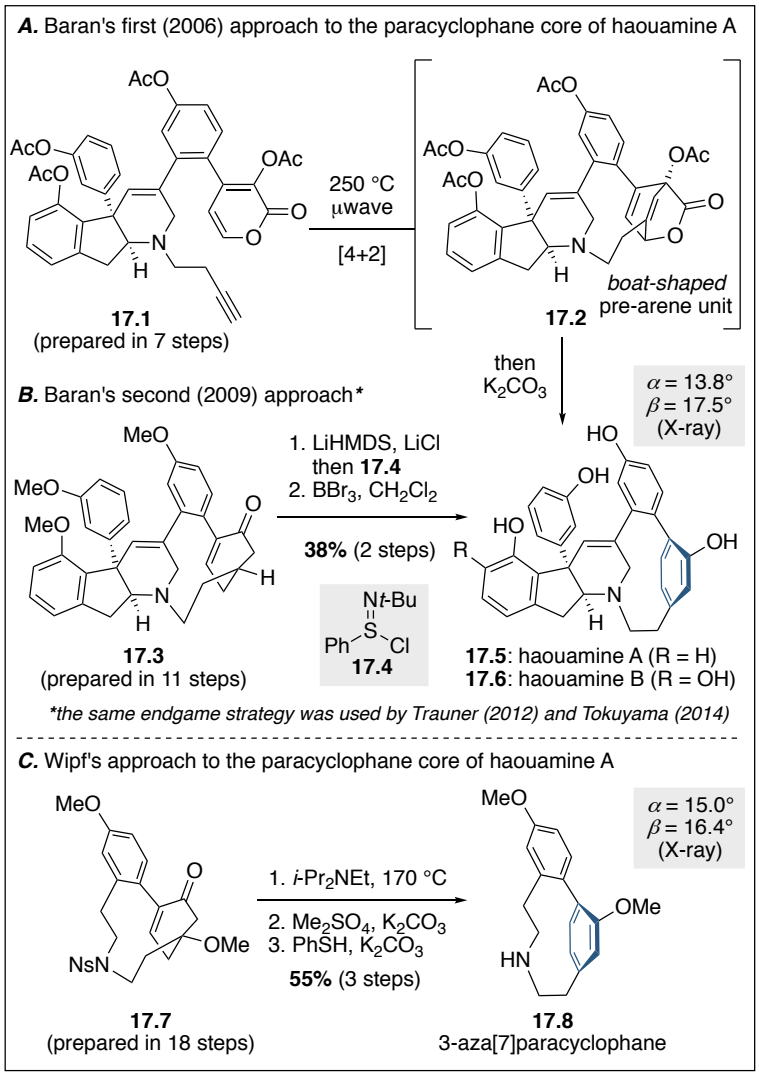
2.2 Recent/modern aromatization protocols for the synthesis of highly distorted *para*-phenylene units containing biaryl bonds

While the valence isomer-based approach to highly strained aromatic systems has proven to be the ultimate synthetic method for synthetizing the most distorted pi-systems known, it has not featured prominently in the synthesis of larger, and more complex macrocyclic targets containing bent *para*-phenylene units. This is likely due to the need to incorporate arene units at the 1 and 4-positions of a macrocycle containing the Dewar benzene unit, and limited synthetic methodology for assembling this strained bicyclic system. The first example of the synthesis of a complex macrocyclic system containing a highly strained (biaryl) *para*-phenylene unit was that of haouamine A. Completing the total synthesis of this natural product required the development of innovative synthetic tactics for assembling the biaryl, bent phenol core. Numerous research groups tried to tackle the synthesis of haouamine,[5, 26-27] with the Baran group emerging as the first to complete the total synthesis of this structurally unique alkaloid.[5] The plethora of formal syntheses and synthetic approaches that have been reported by several groups,[27-29] underscored the limitations of cross-coupling reactions for assembling strained biaryl systems and signaled the need to develop new synthetic technology for accessing the 3-aza[7]paracyclophane core structure of the

haouamines (A and B).

2.2.1 Synthetic approaches to (±)-haouamine A, haouamine A and B, and the 3-aza[7]paracyclophane core of the haouamines

Assembling the complex indeno-tetrahydropyridine **17.1** in racemic form was accomplished by Baran and Burns in short order (7 steps) and relied on the use of relatively straightforward synthetic methodology.[29] At this stage in their synthesis, the pyrone diene and alkynyl units of **17.1** were engaged in an intramolecular Diels-Alder reaction under microwave conditions. The bridged bicyclo[2.2.2]-1-oxaoctan-2-one (cycloadduct **17.2**) that is initially formed upon [4+2]cycloaddition succumbs to a cheletropic elimination of carbon dioxide to aromatize the boat-shaped cyclohexadiene ring system of **17.2**, and afford the bent, biaryl phenol unit of haouamine A (**17.5**) after hydrolysis of the acetate esters (Scheme 17A) in 21% yield over 2 steps. In 2009, Baran and co-workers reported a second (asymmetric) synthesis of haouamine A, which featured an improved endgame strategy for assembling the bent phenol unit of the natural product (Scheme 17B).[29] In this approach, bridged cyclohexenone **17.3**, synthesized over 11 steps, was subjected to dehydrogenative aromatization, upon treatment with LiHMDS and LiCl, and then exposure of the resulting enolate to **17.4**.[30] After global cleavage of the methyl ethers present in **17.3**, haouamine A was afforded in 38% yield over the last 2 steps.



SCHEME 17: Synthetic aproaches to the 3-aza[7]paracyclophane core structure of haouamine A and B

The same dehydrogenative aromatization strategy was employed by Trauner and co-

workers in 2012, when their synthesis of the proposed structure of haouamine B (**17.6**, Scheme 17B, revised structure shown) prompted a structural revision of the natural product.[28] Tokuyama and co-workers corroborated this structural revision through total synthesis, when they completed the synthesis of haouamine B pentaacetae in 2014.[26] A slightly different approach to the 3-aza[7]paracyclophane core of **17.8** was reported by Wipf and co-workers in 2006.[27] Utilizing a familiar bridged cyclohexenone unit, treatment of **17.7** with Hünig's base at 170 °C brought about an elimination of methanol, followed by tautomerizaton of the resulting dieneone to afford a bent phenol, which was subsequently subjected to *O*-methylation and nosyl deprotection to afford **17.8** in 55% overall yield.

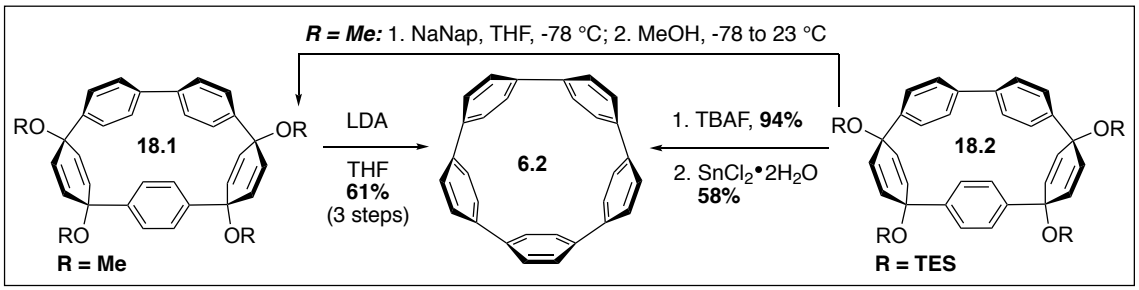
2.2.2 Synthetic approaches to carbon nanohoop and related benzenoid macrocycles: endgame aromatization strategies

In Chapter 1, the pioneering contributions of Vögtle and co-workers in the development of synthetic strategies for accessing macrocyclic systems that could serve as precursors to the, then elusive, [*n*]CPPs was described (section 1.1). The German group cleverly incorporated boat and chair conformations of six-membered rings into linear oligomeric precursors that they had hoped would succumb to macrocyclization, however, this strategy never came to fruition for Vögtle and his team. With the advancement of organometallic chemistry, specifically metal-mediated and catalyzed cross-coupling reactions, several groups would later exploit Vögtle's vision and capitalize on the this strategy.[31]

Jasti and co-workers have reported numerous syntehsese of [*n*]CPPs. These included size-selctive syntheses,[14, 18, 24] gram-scale syntheses,[32-33] the synthesis of dimeric CPPs,[34-35] pi-extended CPPs,[36] and ultimately the syntehsis and X-ray crystal structure of the most strained [*n*]CPP, [5]CPP (SE = 119 kcal/mol).[25, 37] In all of these exmaples, the Jasti group has called upon a a reductive aromatization reaction of a *syn*-1,4-dimethoxy-cyclohexa-2,5-diene unit in the presence of sodium naphthalenide at low temperatures (Scheme 19A). The only instance where this reaction failed to deliver a highly strained *para*-phenylne unit outright, was during the synthesis of [5]CPP. However, this was overcome by performing sequential deoxygenation and elimination reactions (**18.2** (R = Me) to **18.1** to **6.2**, Scheme 18). This stragey has been sucessful in synthetsizing a *para*-phenylene unit with an α angle of 15.6° and SE of 23.8 kcal/mol.

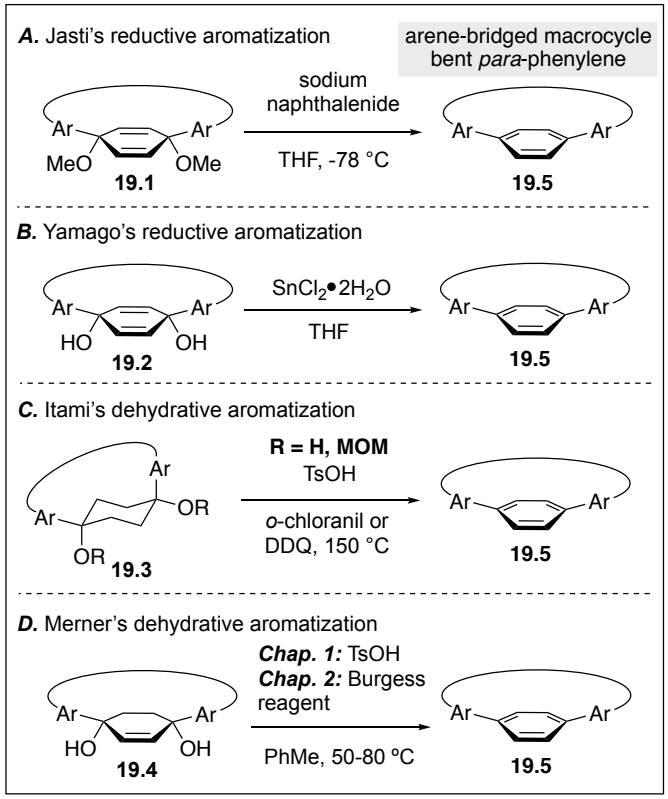
Yamago and workers have also made a substantial contribution to the field of carbon nanohoop synthesis,[18] as well as describing their important photophysical and electrochemical properties,[18, 37] and computing the strain energies of these compounds.[37] Recently, they have devloped a reductive aromatization protocol that differs from that of Jasti and co-workers, in terms of the pre-arene subunit (*syn*-1,4-dihydroxy-cyclohexa-2,5-diene) and reaction conditons (tin(II) chloride dihydrate in THF) employed (Scheme 19B). The crowning achievement of their work in this area came in 2014, when they also reported the synthesis of [5]CPP by employing this aro-

matization method for the first time.[20] They would later showcase the versatility of this methodology in a synthesizing a homologous series of [*n*]CPPs in 2015.[21] It should be noted that Yamago's protocol for reductive aromatization was capable of furnishing [5]CPP directly (**18.2** to **6.2**, Scheme 18), after cleavage of the silyl ethers, and the Jasti group has adopted this strategy in subsequent synthesis of CPPs.[32]



SCHEME 18: Jasti (R = Me) and Yamgo (R = TES) aromatization of **18.1-18.2** - synthesis of [5]CPP

The Itami laboratory is ceredited with being the second gorup to sythesize an [*n*]CPP, when they reported the syntehsis and X-ray crystal structutre of [12]CPP in 2009.[12] Itami and co-worker's strategy for assembling macrocyclic precursors of carbon nanohoops bears a strong resemblance to the attempted synthetic approach of Vögtle's group some 30 years earlier – the use of arylated *syn*-cyclohexane-1,4-diols. A plethora of work has come from Itami and co-workers over the past 9 years with respect to advancing the field of carbon nanohoop,[38] and carbon nanobelt synthesis.[39] In the case of the former, their aromatization of cyclohexane-1,4-diol units relies on a dehydrative followed by dehydrogenation of the resulting cyclohexadiene unit (Scheme 19C). A similar dehydrogenative protocol has been reported by Wang and co-workers, however, the synthesis of the cyclohexdiene units of their macrocyclic precursors involves cycloaddition chemistry.[40] The smallest and most strained [*n*]CPP that Itami and co-workers have synthesized using this aromatization strategy is [7]CPP – α = 11°, SE_{pp} = 11.8 kcal/mol.[16]

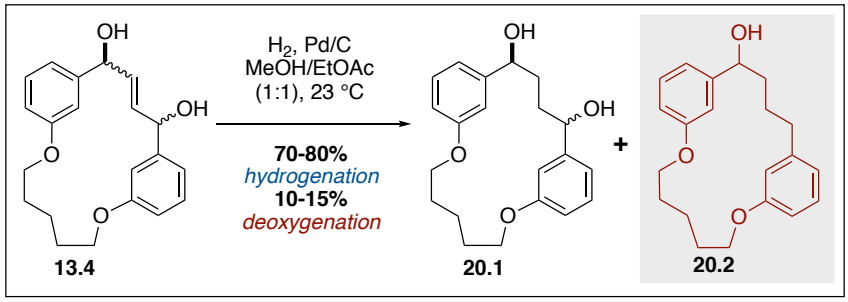


SCHEME 19: Recent approaches to bent *para*-phenylenes

Recently, Merner and co-workers have reported a dehydrative aromatization reaction of a *syn*-cyclohex-2-ene-1,4-diol that is capable of introducing up to 15 kcal/mol of SE in a single *para*-phenylene unit (Scheme 19D, see also: Section 1.3.1, Chapter 1).[1] The remaining sections of this chapter will describe the application of this strategy to the synthesis of a homologous series of macrocycles and the development of modified dehydrative conditions that overcome strain-relief driven rearrangement reactions of these highly strained *para*-phenylene rings.

2.3 Synthesis of a homologous series of 1,*n*-dioxa[*n*](3,3")*p*-terphenylophanes (*n* = 5-8) using a non-cross-coupling-based approach

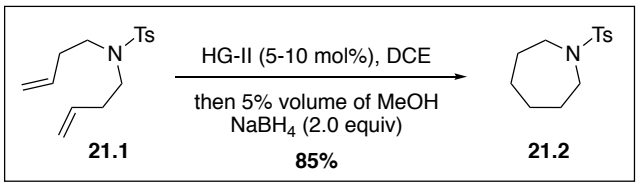
In order to demonstrate the (potential) synthetic utility of the non-cross-coupling-based approach to arene-bridged macrocycles described in Chapter 1, a scalable synthetic route to a homologous series of macrocyclic 1,4-diketones had to be developed. During the first-generation synthesis of **20.1** it was discovered, upon scale up, that a deoxygenation by-product is produced during the hydrogenation of **13.4** (**20.2**, Scheme 20). This presumably takes place via the formation and of a π-allyl-type intermediate that can be formed upon treatment of allylic alcohols with palladium catalysts. While the deoxygenation by-product **20.2** is only produced in 10-15% yield, a chromatographic separation was required. To circumvent this, hydrogenation reactions in EtOAc, MeOH, THF and mixtures of these solvents were attempted. In all cases deoxygenation of **13.4** takes place and an alternative hydrogenation protocol was pursued.



SCHEME 20: Deoxygenation of macrocyclic allylic diol **13.4**

2.3.1 Streamlined synthesis of macrocyclic 1,4-diketones

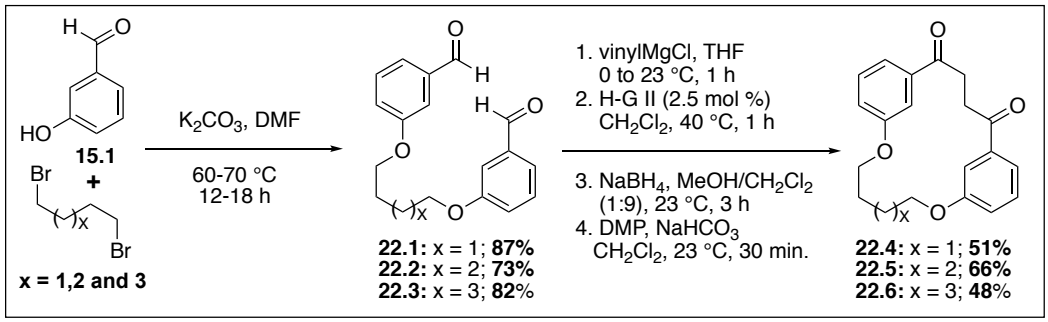
In 2014, Peese and co-workers reported a process for sequential ring-closing metathesis (RCM) and transfer hydrogenation reactions using the Hoveyda-Grubbs second-generation (H-G II) catalyst.[22] This serendipitous discovery came as a result of telescoping the synthesis of a series of heterocyclic analogs that contained ketone units. In an attempt to reduce the ketone units of analogs such as **21.1**, after RCM it was noticed that hydrogenation of the olefin unit produced in the RCM reaction takes place. The Bristol-Myers Squibb team optimized this process such that RCM and transfer hydrogenation reactions would take place in a single reaction flask. For example, diene **21.1** was first subjected to



SCHEME 21: Sequential RCM and transfer hydrogenation

5-10 mol% of the Hoveyda-Grubbs catalyst in 1,2-dichloroethane and upon completion of the RCM reaction, 5% of the total solvent (DCE) volume of methanol and 2.0 equiv. of sodium borohydride was added to the reaction flask. This resulted in smooth reduction of the alkene unit to afford **21.2** in 85% yield (Scheme 21). Inspired by this work, we designed a synthetic sequence that would facilitate the synthesis of macrocyclic 1,4-diketones from acyclic dialdehydes without purification of any synthetic intermediates.

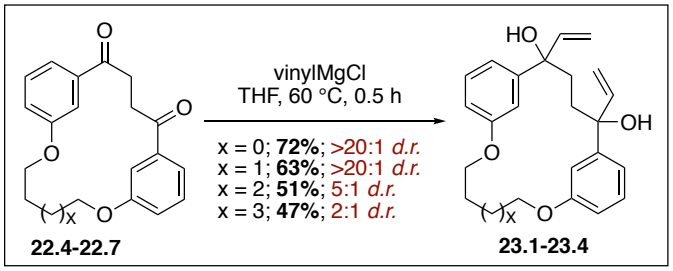
Dialdehydes **22.1**-**22.3** were synthetized using a standard Williamson ether synthesis protocol – potassium carbonate and DMF (Scheme 22). Treatment of the three dialdehydes **22.1**, **22.2** and **22.3** with vinylmagnesium chloride, followed by a H-G II-mediated macrocyclic RCM reaction at 15 mM in dichloromethane afforded the corresponding macrocyclic allylic diols as mixtures of alkene diastereomers, in which the *trans*-configured (undesired) olefin was the major product. After evaporation of the solvent (dichloromethane), the residue was dissolved in 1:9 methanol/dichloromethane and the addition of 3.0-5.0 equivalents of $NaBH_4$ resulted in transfer hydrogenation of the olefin in less than three hours, without any benzylic deoxygenation. It is noteworthy that only 2.5 mol% of the H-G II catalyst was used in both the metathesis and transfer hydrogenation reactions, all of which was added at the RCM stage of the synthesis. Furthermore, the use of a 1:9 vs a 1:19 methanol/dichloromethane solvent mixture, as originally reported by Peese and co-workers,[22] provided much shorter reaction times in the transfer hydrogenation step. Finally, direct exposure of the crude 1,4-diol mixtures to the Dess-Martin reagent, in the presence of $NaHCO_3$, furnished pure macrocyclic 1,4-diketones **22.4**-**22.6** in up to 66% yield over 4 steps (Scheme 22). Running this four-step reaction protocol on a gram-scale provided access to 500-650 milligram quantities of the desired diketone while using less than 500 mL of solvent and 50 g of silica gel for a single chromatographic separation at the 1,4-diketone stage. Furthermore, the desired products can be obtained in less than 7 hours starting from acyclic dialdehydes. We have attempted to develop a more direct synthesis of macrocyclic 1,4-dikeotnes such as **22.5-22.7;** however, we have been unable to find a more efficient and reliable protocol.



SCHEME 22: Streamlined synthetic protocol for the synthesis of macrocyclic 1,4-diketones

2.3.2 Size-dependent diastereoselectivity in Grignard additions to macrocyclic 1,4-diketones

The conversion of the 1,4-diketo-bridging group into a strained 1,4-arene bridge (bent *para*-phenylene) was previously accomplished by employing a three-step reaction protocol. The first of which involved a Grignard reaction with vinylmagnesium chloride. The diastereoselectivity of this reaction was critical to the formation of the desired arene precursor, as only the *syn*-allylic diol was converted to the bridged cyclohex-2-ene-1,4-diol system.[1] After completing the synthesis of a homologous series of macrocyclic 1,4-diketones, it was discovered that the diastereoselectivity of this Grignard reaction is dependent on the size of the macrocyclic system employed. Larger macrocyclic rings (18 and 17-membered) gave lower diastereoselectivities (**23.4**, x = 3, 2:1 *d.r.*; **23.3**, x = 2, 5:1 *d.r.*, Scheme 23), while smaller macrocyclic rings (16 and 15-membered) gave much higher diastereoselectivity (**23.2**, x = 1, >20:1 *d.r.*; **23.1**, x = 0, > 20:1 *d.r.*, Scheme 23). To the best of our knowledge, no studies have been carried out to explore the origin of diastereoselectivity in related macrocyclic systems. We are currently conducting an extensive investigation of this reaction in our laboratory. Selected examples that demonstrate the macrocyclic size, reagent and solvent dependence of this reaction will be presented below.



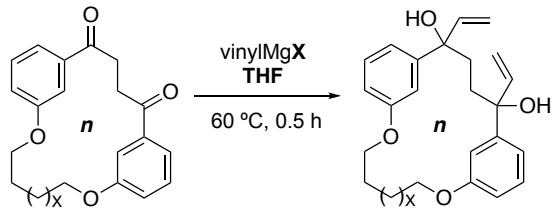
SCHEME 23: Diastereoselctivity in macrocyclic 1,4-diketones

2.3.3 Reagent-dependent diastereoselectivity in macrocyclic 1,4-diketones

During the synthesis of **23.3**, it was discovered that the addition of vinylmagenesium chloride to macrocyclic 1,4-diketone **22.6** gave both higher yield and diastereoselectivity (72%, 5:1 *d.r.*, entry 8, Table 1) when compared to vinylmagnesium bromide (55%, 2:1 *d.r.*, entry 3, Table 1). Re-examining this with the 15, 16, 18, and 19-membered macrocyclic 1,4-diketones prepared above, it became apparent that while the size of the macrocyclic system employed in these reactions has the greatest influence on diastereoselectivity, the of the Grignard reagent used also plays a significant role. All reactions run with vinylMgBr gave lower diastereoselectivity, when compared to those with vinylMgCl (Table 1). In the case of 19-membered diketone **22.8**, the *anti*-allylic diol was favored to that of the *syn*-isomer, when vinylMgBr was employed (1:2 *d.r.*, entry 1, Table 1) and a complete reversal of selectivity was observed with vinylMgCl (2:1 *d.r.*, entry 6, Table 1). The highest levels of diastereoselectivity were observed in the 15 and 16-membered 1,4-diketones, with a maximum of 9:1 and >19: 1 *d.r.* obtained for **22.4** and **22.5** with vinylMgBr and vinylMgCl, respectively. (entries 4, 5, 9, and 10, Table 1). It should be noted that the conversion of 1,4-diketones to 1,4-allylic diols was higher using the more reactive vinylMgCl. To demonstrate that the observed diastereoselectivity is not due to 1,4-asymmetric induction of the

initially formed stereogenic center, upon 1,2-aditon to one of the ketone units, a non-macrocyclic analog **24.1** was synthesized (Scheme 24). Upon treatment of **24.1** with either vinylMgBr or vinylMgCl, afforded both *syn* and *anti*-allylic diols **24.2** in a 1:1 ratio, with 90% and 94% yield, respectively. Interestingly, no hydroxyketone, or monoadditon product was produced when **24.1** was treated with either vinylMgCl or vinylMgBr. This suggested that the "formation" of the hydroxyketone by-product in the macrocyclic examples presented in Table 1, may not be as a result of monoadditon. In fact, using an excess of Grignard reagent in these (macrocyclic) reactions did not improve the ratio of diol to hydroxyketone. Furthermore, adding additional Grignard reagent to reaction once the hydroxyketone had formed (TLC analysis) did not lead to an observable increase in diol formation. This led to the conclusion that the hydroxyketone by-product forms, and is subsequently isolated, as result of enolate formation during the course of the reaction.

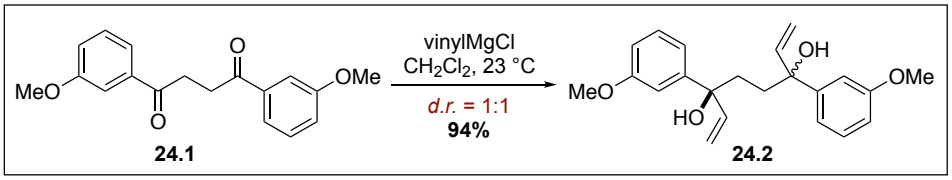
TABLE 1: Size and reagent-dependent diastereoselectivity



***n* = size of macrocyclic ring**

entry	compd.	***n***(x)	**X**	*d.r.* (*syn/anti*)	diol[a] (%)	HK[b] (%)
1	**22.8**	19 (4)	Br	1:2	39	61
2	**22.7**	18 (3)	Br	1:1	48	52
3	**22.6**	17 (2)	Br	2:1	55	45
4	**22.5**	16 (1)	Br	9:1	58	42
5	**22.4**	15 (0)	Br	9:1	50	40
6	**22.8**	19 (4)	Cl	2:1	62	38
7	**22.7**	18 (3)	Cl	2:1	67	33
8	**22.6**	17 (2)	Cl	5:1	72	28
9	**22.5**	16 (1)	Cl	>19:1	70	30
10	**22.4**	15 (0)	Cl	>19:1	72	28

a. ratio determined by ^{1}H NMR analyssi of crude reaction mixtures; ***b.*** HK = hydroxyketone/monoadditon product



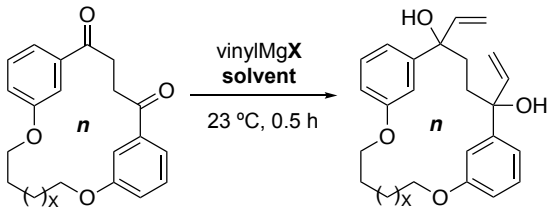
SCHEME 24: Vinylmagnesium chloride additon to acyclic 1,4-diketone **24.1**

2.3.3 Solvent dependence on diastereoselectivity in Grignard reactions of macrocyclic 1,4-diketones

In addition to macrocyclic size and reagent dependence on diastereoselectivity, it was discovered that the solvent also plays an important role in this reaction. Typically, Grignard reactions are run in ethereal solvents such as diethyl ether and THF. Due to the low solubility of the macrocyclic 1,4-diktones studied here in diethyl ether, no comparison of this solvent to THF could be made. However, a comparison of THF to dichloromethane, toluene, and benzene is presented in Table 2.

In general THF gave the lowest diastereoselectivity and poorest conversion of macrocyclic 1,4-diketone to the desired allylic-1,4-diol product (see entries 1, 5, 9, and 13, Table 2). Comparing each macrocyclic system, based on ring size, and their Grignard reactions with vinylmagnesium chloride in the four solvents investigated, we were surprised to find that benzene emerged as the best solvent for these reactions (entries 4, 8, 12, and 16, Table 2). Dichloromethane gave comparable levels of diastereoselectivity to that of benzene (*c.f.*, entries 3 to 4; 7 to 8; 11 to 12; and 15 to 16, Table 2), however, a small amount (*ca.* 5-20%) of hydroxyketone by-product was observed in macrocyclic 1,4-diketones containing a 17-membered ring or larger. Toluene was a better alternative to THF in larger macrocyclic systems (*c.f.*, entries 2 to 1 and 6 to 5, Table 2), but afforded lower levels of diastereoselectivity when compared to that of benzene and dichloromethane, and 15-29% of hydroxyketone was observed in these reactions (entries 2, 6, 10, and 14).

TABLE 2: Solvent dependence on diastereoselectivity



***n* = size of macrocyclic ring**

entry	starting material	*n*(x)	solvent	*d.r.*[a]	diol[b] (%)	HK (%)
1	**21.10**	19 (4)	THF	2:1	62	38
2	**21.10**	19 (4)	PhMe	3:1	71	29
3	**21.10**	19 (4)	DCM	3:1	77	23
4	**21.10**	19 (4)	PhH	4:1	100	0
5	**21.9**	18 (3)	THF	2:1	67	33
6	**21.9**	18 (3)	PhMe	4:1	82	18
7	**21.9**	18 (3)	DCM	5:1	95	5
8	**21.9**	18 (3)	PhH	5:1	100	0
9	**21.8**	17 (2)	THF	5:1	72	28
10	**21.8**	17 (2)	PhMe	5:1	79	21
11	**21.8**	17 (2)	DCM	8:1	91	9
12	**21.8**	17 (2)	PhH	8:1	100	0
13	**21.7**	16 (1)	THF	>19:1	70	30
14	**21.7**	16 (1)	PhMe	>19:1	85	15
15	**21.7**	16 (1)	DCM	>19:1	100	0
16	**21.7**	16 (1)	PhH	>19:1	100	0

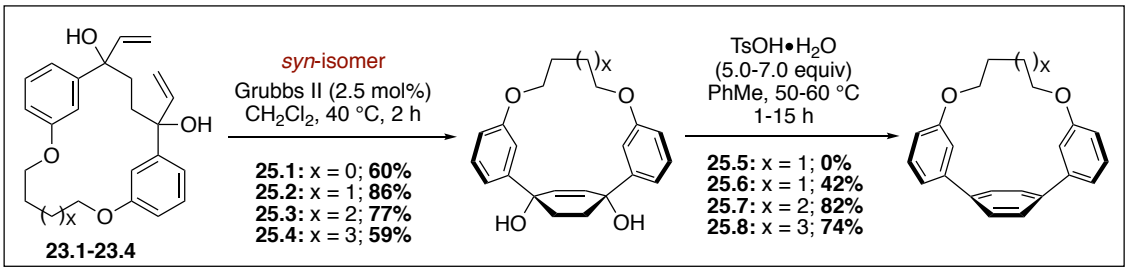
[a] *syn/anti* ratio [b] ratio determined by ^{1}H NMR analysis of crude reaction mixtures;

The general trend that can be gleaned from these experiments is that macrocyclic size is a dominant factor in controlling the diastereoselectivity of these reactions. As the size of the macrocyclic ring containing the 1,4-diekto bridging unit shrinks, the diastereoselectivity of the reaction increases (*n* = 19, 4:1 *d.r.*; *n* = 18, 5:1 *d.r.*; *n* = 17, 8:1 *d.r.*; *n* = 16, >19:1 *d.r.* with benzene as the solvent). In the case of the smallest macrocyclic system investigated (16-membered ring), the level of diastereoselectivity is completely controlled by the size of the macrocycle (entries 13-16, Table 2). Furthermore, for smaller macrocyclic systems there is less hydroxyketone by-product produced. This general trend was observed for all solvents investigated and suggests that enolate formation in the macrocyclic backbone is attenuated for smaller ring systems. This could be due to an increase in strain energy that would result from placing an olefin unit in the 1,4-diketo bridging unit, however, the possibility of the conformational changes with in the macrocyclic framework and the carbonyl becoming more accessible for Grignard addition cannot be ruled out.

The origin of diastereoselectivity in these reactions is currently under detailed investigation in our laboratory, both experimentally and computationally.

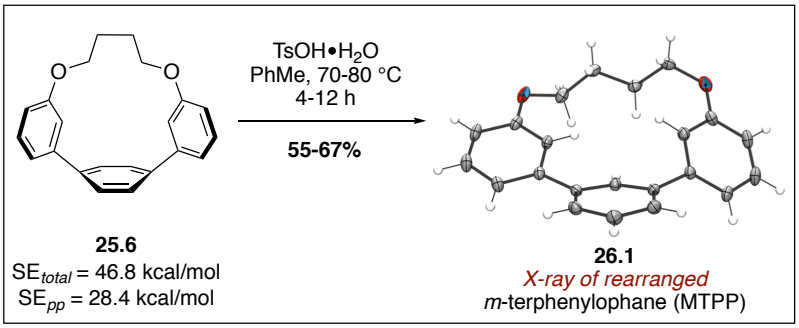
2.3.4 Protic acid-mediated dehydrative aromatization: Strain-Induced rearrangements of highly distorted biaryl para-phenylenes

As mentioned earlier, only the *syn*-diastereomer (major product) of the allylic-1,4-diols produced upon vinylmagnesium chloride addition to macrocyclic 1,4-diketone **22.6** undergoes cyclohexene formation when treated with the Grubbs second-generation catalyst. The inseparable (minor) *anti*-diastereomer could be easily removed after a RCM reaction of this mixture.[23]



SCHEME 25: Synthesis of 1,*n*-dioxa[*n*](3,3")*p*-terphenylophanes (*n* = 6, 7 and 8)

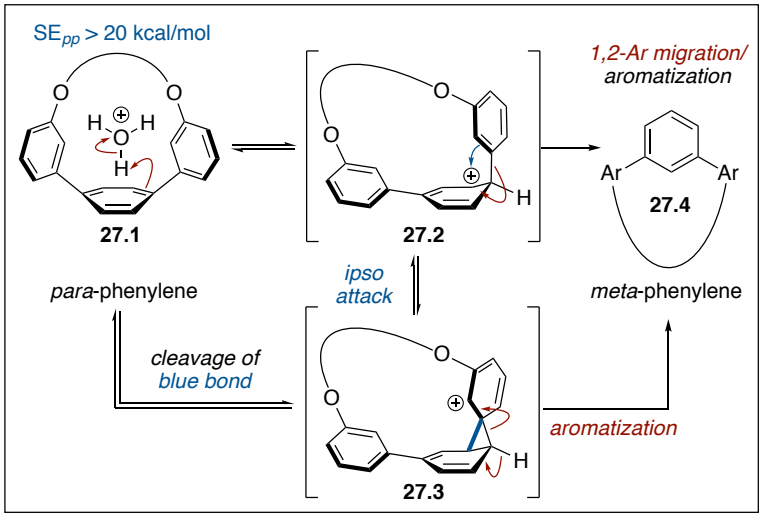
Treatment of **23.1-23.4** with the Grubbs second-generation catalyst completed the conversion of the 1,4-dione unit into a six-membered ring, and the precursor macrocycle for a dehydrative aromatization reaction (Scheme 25). In the case of **25.3** and **25.4**, conversion to the bent *p*-terphenyl systems was high yielding and straightforward using TsOH. For the next smallest macrocycle in the series, **25.2**, clean isolation of the highly distorted *p*-terphenyl system proved to be more challenging and slightly lower yielding at 42%. Controlling the temperature of this reaction was critical to avoid the formation of unwanted by-products, and the reaction *must not* be heated above 60 °C, as the isomeric and less strained (3,3")*m*-terphenylophane (MTPP) derivative is formed. Heating a toluene solution of **25.6** in the presence of 6.0 equivalents of TsOH at 80 °C resulted in clean isomerization to **26.1** (X-ray, Scheme 26), presumably through a strain relief driven protonation of the bridgehead carbon followed by migration of the terminal arene unit.[41] It has been speculated that similar "backbone" rearrangements occur when strained [*n*]CPPs are subjected to protic or Lewis acid-mediated reaction conditions, however, at the time of these investigations no supporting structural evidence had been reported to corroborate such a rearrangement.[42] In the case of the smallest



SCHEME 26: TsOH-induced rearrangement of **25.6** - X-ray of **26.1**

homolog (x = 0), only the rearranged *m*-phenylene containing macrocycle was isolated upon treatment of **25.1** with TsOH in toluene. During the course of this reaction, what was believed to be a partial elimination product, was initially produced under the conditions of TsOH at 60 °C in toluene. This intermediate persisted until the reaction temperature was increased to 70 °C. At this temperature conversion to the desired *para*-phenylene-bridged macrocycle was observed by TLC analysis, however, after 3 hours only the rearranged *meta*-phenylene-bridged isomer was isolated.

It is proposed that *para*-phenylene to *meta*-phenylene bridge migration occurs upon protonation of the bridgehead carbon atom of **27.1**, which relieves strain within the macrocyclic framework and the central arene unit (Scheme 27). An *ipso* attack on the resulting carbocation **27.2** can give intermediate **27.3**. Irreversible 1,2-aryl migration can occur directly from **27.2** (red arrow) or upon re-aromatization and fragmentation of **27.3** (red arrows). Following a different fragmentation pathway of spirocyclic intermediate **27.3**, reversible formation of the *para*-phenylene-bridged macrocycle **27.1** can occur (blue bond cleavage, Scheme 27).

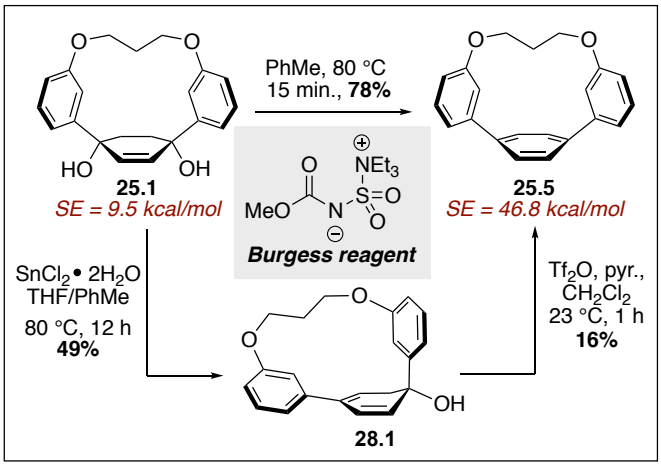


SCHEME 27: Mechanism for the TsOH mediated rearrangement of strained *p*-phenylene to unstrained *m*-phenylene

2.3.5 Development of a mild dehydrative aromatization protocol for the synthesis of highly strained para-phenylene units

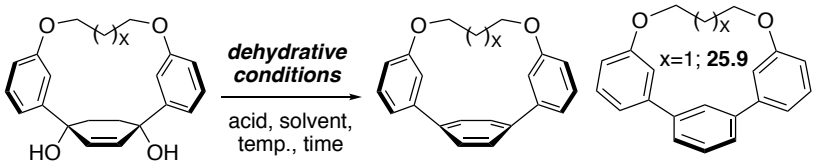
Several different reaction conditions that employ milder acidic reagents were screened to facilitate the synthesis of **25.6** and **25.5** from **25.2** and **25.1**, respectively. Application of $NaHSO_4$ in the presence of *o*-chloranil, which has been used by Itami and co-workers to aromatize cyclohexane-1,4-diol units of [*n*]CPP macrocyclic precursors,[13] gave a low yield of **25.6** with the formation of rearranged isomer **26.1** (entry 4, Table 1). Using a modification of Yamago and co-workers tin(II) chloride dihydrate-mediated aromatization reaction, which was used to successfully synthesize [5]CPP,[20] gave only the partial dehydration product **28.1** in 49% yield (Scheme 28). Furthermore, application of the recently reported $SnCl_2$/HCl ate complex (H_2SnCl_4), did not afford the aromatized product. However, treating **28.1** with Tf_2O in pyridine (Scheme 28 and entry 7, Table 3) gave a 16% yield of the desired *p*-terphenylophane **25.5** (8% from **25.1**, Scheme 28).

Shifting our focus to non-acidic dehydration conditions, we attempted the synthesis of **25.5** by employing the Burgess reagent. Remarkably, **25.5** was isolated in 58% yield upon heating a toluene solution of **25.1** at 80 °C in the presence of the Burgess reagent,[29] without the formation of the rearranged isomer **25.9**. In comparison, heating toluene solutions of the cyclohex-2-ene-1,4-diol (arene) precursors at 80 °C in the presence of TsOH for 30 minutes saw rearrangements occur at the *n* = 7 (**25.3**) homolog stage (Table 1, entry 11). Indeed, subjecting all of the remaining cyclohexe-2-ene-1,4-diol precursors (**25.2**-**25.4**, *n* = 6-8, respectively) to identical reaction conditions, with the Burgess reagent, furnished the desired *p*-terphenyl-containing macrocycles in comparable yields (Table 1, entries 8, 9, 10, and 12). At the time, this represented the first application of the Burgess reagent in the synthesis of a nonplanar aromatic system; however, recently the application of this aromatization strategy has been applied to the synthesis of a bent non-alternant hydrocarbon, dibenzo[*a*,*e*]pentalene by Esser and co-workers.[43]



SCHEME 28: Synthesis of 1,5-dioxa[5](3,3")p-*t*erphenylophane

TABLE 3: Dehydrative aromatization reactions of cyclohex-2-ene-1,4-diols



25.1: x = 1; **25.2:** x = 2
25.3: x = 3; **25.4:** x = 4

p-terphenylophane **(PTPP)**

m-terpheylophane **(MTPP)**

entry	comp.	reagent	solvent	temp (°C)	time (h)	PTPP (%)	MTPP (%)
1	**25.2**	TsOH	PhMe	60	10	42	0
2	**25.2**	TsOH	PhMe	80	4	trace	**55**
3	**25.1**	TsOH	PhMe	70	3	0	**40**
4	**25.2**	$NaHSO_4$	DMSO	130	24	36	trace
5[a]	**25.1**	$SnCl_2$•$2H_2O$	THF/PhMe	80	12	0	0
6[b]	**25.1**	H_2SnCl_4	THF	23	72	0	0
7[c]	**25.1**	Tf_2O	CH_2Cl_2/pyr.	23	0.5	16	0
8	**25.1**	***Burgess***	PhMe	80	0.2	**58**	0
9	**25.2**	***Burgess***	PhMe	80	0.2	**56**	0
10	**25.3**	***Burgess***	PhMe	80	0.2	**68**	0
11	**25.3**	TsOH	PhMe	80	0.2	38	**19**
12	**25.4**	***Burgess***	PhMe	80	0.2	**60**	0
13	**25.4**	TsOH	PhMe	80	0.2	62	0

a. Only the monodehydration product **28.1** (Scheme 28) was formed; ***b.*** H_2SnCl_4 was prepared by mixing $SnCl_2$•$2H_2O$ and HCl; ***c.*** This entry refers to the reaction of **28.1**.

2.3.6 X-ray crystal structure and strain energy of a highly distorted para-phenylene ring

Recrystallization of **25.5** from dichloromethane and hexanes produced a single crystal suitable for X-ray analysis, revealing the highly distorted *p*-terphenyl nucleus and *para*-phenylene ring of the macrocycle. The central *para*-phenylene ring of **25.5** has an α angle of 15.7°, which is comparable to the α angle found in the bent *para*-phenylene units of [5]CPP – *cf*. 15.6° – and is greater than that found in the natural product haouamine A.[5] It is, however, less than that of the mean plane deviation found in compounds **6c** and **6d** (Figure 6, Section 2.1). The β angles found in **25.5** have an average value of 24.6°, with the largest deviation coming in at 26.8°. This is identical to the largest β angle measured in a bent *para*-phenylene unit – Tsuji's [1.1]paracyclophane derivative **6d**. The 1,3-propanoxy bridge of **25.5** severely bends the *p*-terphenyl system from an ideal planar geometry, but also twists and bows the terminal arene units. In fact, the biaryl bonds in **25.5** are canted forward at an average angle of 9.8° (C11–C22–C23 and C14–C25–C24). The overall SE of **25.5** has been computed at the DFT B3LYP level of theory using the 6-31G(d) basis set, and is estimated to be 46.8 kcal/mol. The SE of the *p*-terphenyl system comprises 40.2 kcal/mol of the total SE found in **25.5**, the majority of which is localized on the central arene unit. At 28.4 kcal/mol, the SE of the *para*-phenylene (SE_{pp}) ring is approximately 4.6 kcal/mol greater than that of the average SE/*para*-phenylene unit in [5]CPP – the most strained CPP homolog to be prepared by chemical synthesis. The SE of [4]CPP, which has yet to be synthesized, is predicted to be 144 kcal/mol,[31] giving an average SE/*para*-phenylene of 36 kcal/mol. The synthesis of a macrocyclic precursor of [4]CPP is underway in our laboratory and the synthesis of a smaller homolog of **25.5** is presented in section 2.4. Both of these targets will provide the a significant test of the Burgess reagent-mediated aromatization protocol of macrocyclic cyclohex-2-ene-1,4-diols.

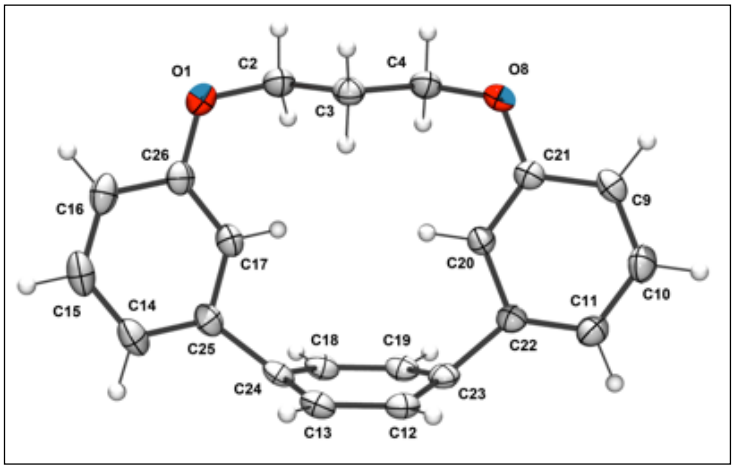
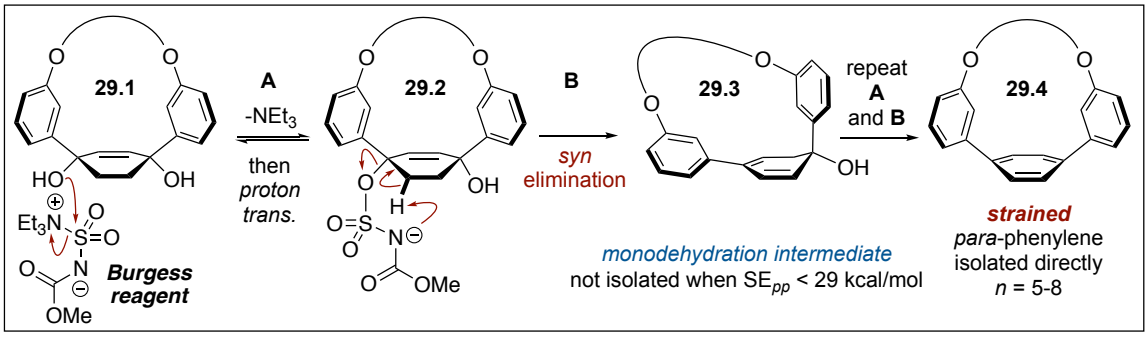


FIGURE 7: X-ray crystal structure of **25.5** (α = 15.7°; β = 24.6°)

2.3.7 Mechanism of the Burgess reagent-mediated dehydrative aromatization

The Burgess reagent (methyl *N*-(triethylammoniumsulfonyl)carbamate) is a mild dehydrating reagent often used to convert secondary and tertiary alcohols into alkenes. Dehydration of primary alcohols has been cited as problematic for this reagent. The Burgess reagent is a neu-

tral, zwitterion, containing a built-in leaving group in the form of triethylammnium and internal sulfamidate-type base. Elimination/dehydration reactions that employ the Burgess reagent are believed to proceed through an intramolecular, *syn*-elimination, or Ei-based, mechanism (Scheme 29).[44]



SCHEME 29: Proposed mechanism of Burgess reagent-mediated dehydrative aromatization

The first step of this mechanism involves activation of the alcohol by formation of a sulfamate-type ester (**29.1** to **29.2**, **A**: Scheme 29). This typically takes place in a hydrocarbon solvent such as toluene. Under thermal conditions, the (sulfamate) ester undergoes decomposition resulting in ionization of a carbon atom bearing the sulfamate group (the rate-determining step) resulting in the formation of an ion pair and rapid transfer of a β-hydrogen resulting in alkene formation. For macrocyclic cyclohex-2-ene-1,4-diols such as **29.1**, dehydration of both alcohol groups takes place very rapidly when the SE of the *para*-phenylene to be formed is less than 29 kcal/mol. Monodehydration product **29.3** was never observed (TLC analysis) or isolated for the *n* = 5-8 homologs synthesized above.

2.4 Synthesis of a benzenoid macrocycle containing a *para*-phenylene ring more strained than a monomer unit of [4]CPP

In 2014, Yamago[20] and Jasti[25] individually reported the synthesis of the smallest CPP, [5]CPP. This macrocyclic compound, containing 5 *para*-linked benzene rings, is predicted to have strain energy (SE) of 119 kcal/mol (23.8 kcal/mol per benzene ring). Prior to its synthesis and subsequent characterization by X-ray crystallography, the benzenoid nature of its structure was called to question.[45] Indeed, the solid state structure obtained by Jasti and co-workers demonstrated that [5]CPP was in fact benzenoid. As mentioned above, the next smallest member of this

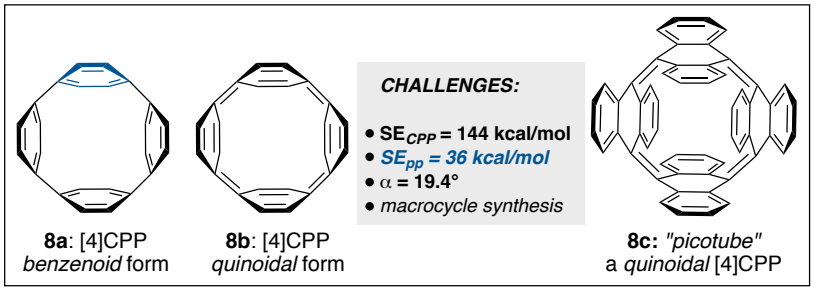


FIGURE 8: [4]CPP (benzenoid) and [4]CPP (quinoid) derivatives

class of carbon nanohoops ([4]CPP), is predicted to have 144 kcal/mol of SE_{pp} = 36 kcal/mol) contained within the macrocyclic structure.[46] This high degree of SE has led many to believe that [4]CPP (**8a**, Figure 8) may not be composed of benzene rings, and may possibly prefer a quinoidal-type structure (such as that of **8b**, Figure 8). This is in part due to the known [4]CPP derivative "picotube" having been shown to be quinoidal. Herges and co-workers reported the synthesis of picotube (**8c**) in 1996,[47] that proceeded through a photochemically induced ring expanding metathesis-based strategy. The precursor hydrocarbon of picotube contained $C(sp^2)$–$C(sp^2)$ π-bonds bonds between adjacent "pre-arene" subunits, and therefore may not represent the best model for [4]CPP. A potentially better suited macrocyclic precursor to [4]CPP is one that contains the requisite $C(sp^2)$–$C(sp^2)$ σ-bonds between adjacent arene and pre-arene units. However, the synthesis of such a macrocyclic precursor is not trivial (Figure 9).

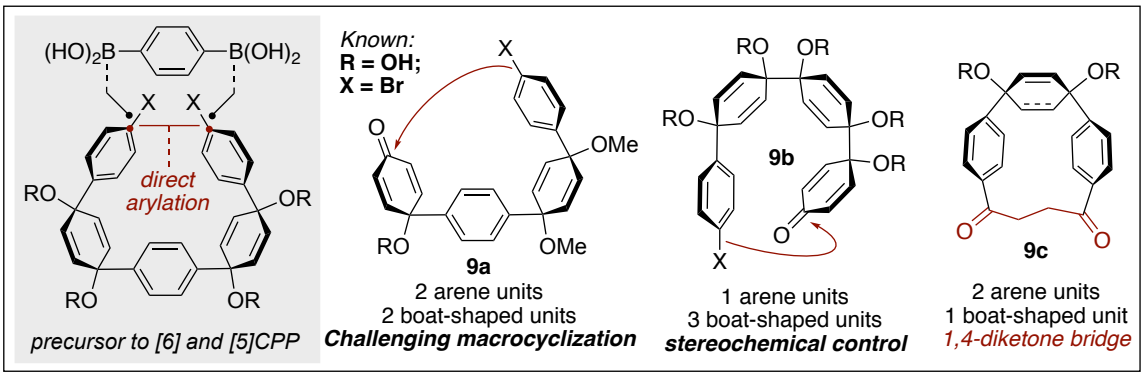


FIGURE 9: Potential synthetic strategies and precursors to [4]CPP

As discussed in Chapter 1, the synthetic approaches used to construct the macrocyclic precursors of [5] and [6]CPP involved a common intermediate (Figure 9).[32] Directed arylation strategies, via Ni (Yamago) and Pd-mediated (Jasti) reactions led to the formation of $C(sp^2)$–$C(sp^2)$ bonds and macrocycle synthesis. Employing the same type of macrocyclization strategy to a smaller precursor molecule poses a significant synthetic challenge. The introduction of boat-shaped, pre-arene subunits in the common precursor and related systems is critical to the success of macrocyclization reactions, as the *syn*-1,4-diol units provide the necessary curvature or kink in the linear acyclic precursors to bring the reacting arene vertices into proximity and facilitate C–C bond formation (section 1.2.3.1, Chapter 1).

The sheer distance between the terminal *para*-vertices of an acyclic precursor containing two arene and two (boat-shaped) pre-arene units will be difficult to overcome, as will competing intermolecular reactions between an aryllithium or Grignard-type reagent (*eg.*, **9a**, Figure 9). Introduction of three boat-shaped units into an acyclic precursor (*eg.*, **9b**, Figure 9) may bring the desired reacting termini closer together, however, controlling the relative stereochemical relationship between all 5 tertiary diol units will be challenging. To address both of these (potential) shortcomings, it is proposed that a cyclophane-based approach where a 1,4-diketo-bridging

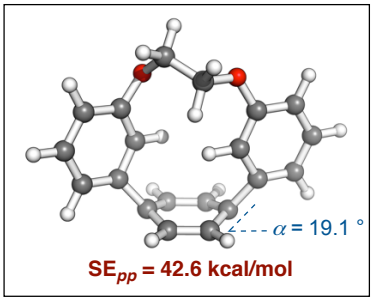
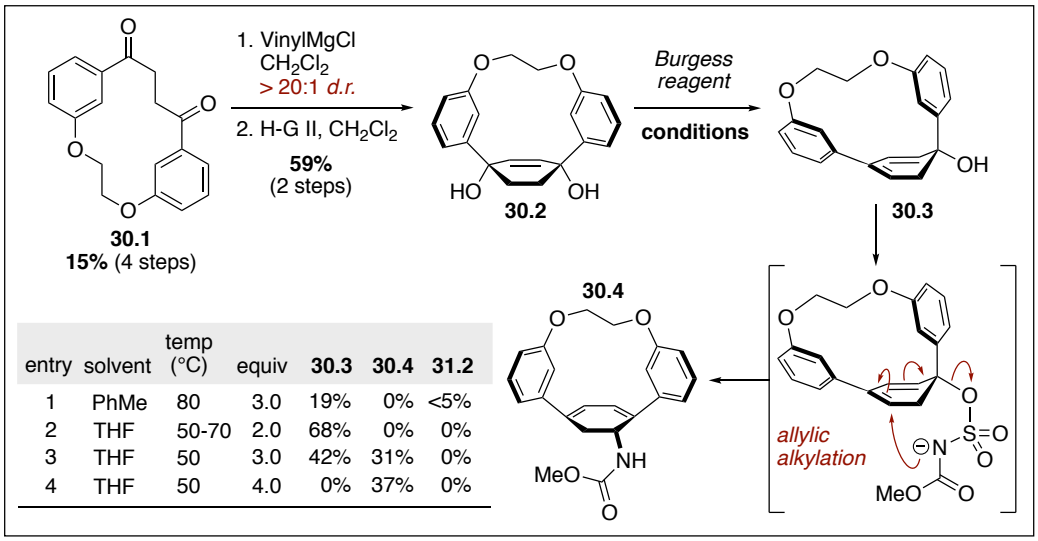


FIGURE 10: DFT structure of [4]PTPP

group spanning two arene units, which are further bridged by a single boat-shaped unit, may represent a viable macrocyclic precursor to [4]CPP (*eg*., **9c**, Figure 9). To validate this approach and to push the limits of the Burgess reagent-mediated dehydrative aromatization strategy described above, we set our sights on the synthesis of a *p*-terphenyl-based macrocyclic system containing a *para*-phenylene unit that is more strained than a monomer unit of [4]CPP (Figure 10). The key feature of which involves the conversion of a macrocyclic 1,4-diketone unit into a highly strained *p*-phenylene system (SEpp = 24.6 kcal/mol; α = 19.1°, Figure 10).

2.4.1 Attempted synthesis of [4]PTPP using a Burgess reagent-mediated aromatization

The synthesis of a macrocyclic 1,4-diketone **30.1** proved to be much more challenging than related homologs. In particular, the alkylation reaction of 3-hydroxybenzaldehyde with 1,2-dibromoethane was low yielding (13% in our hands). Nonetheless, gram-scale quantities of this precursor could be obtained and conversion to the **30.1** using the streamlined approach described above proceed in 15% overall yield (Scheme 30). Similar to what was observed during the synthesis of a homologous 15-membered macrocyclic 1,4-diketone, the ring-closing metathesis (RCM) reaction of the intermediate diene gave a significant amount of a higher molecular weight metathesis by-product. Treatment of **30.1** with vinylmagnesium chloride gave the corresponding *syn*-allylic-1,4-diol as a single diastereomer, which was directly subjected to a second RCM reaction to afford macrocycle **30.2** in 59% yield over two steps. Previously, direct aromatization of cyclohex-2-ene-1,4-diol precursors such as **25.1**, was easily accomplished using the Burgess reagent (dehydrative aromatization reaction) to afford the central *para*-phenylene unit. In the case of the most strained system that had been prepared using this strategy (**25.5**, Scheme 28) 37.0 kcal/mol of SE was introduced into the macrocyclic benzenoid target upon elimination of two molecules of water, affording a *para*-phenylene unit with 28.4 kcal/mol of SE. Subjecting diol **30.2** to the same reaction conditions (Burgess reagent, toluene, 80 °C) gave the monodehydration product **30.3** in 19% yield, with a trace amount (<5%) of the desired 1,4-dioxa[4](3,3")*p*-terphenylophane (**31.2**, entry 1, Scheme 30) being observed by ^{1}H NMR analysis.



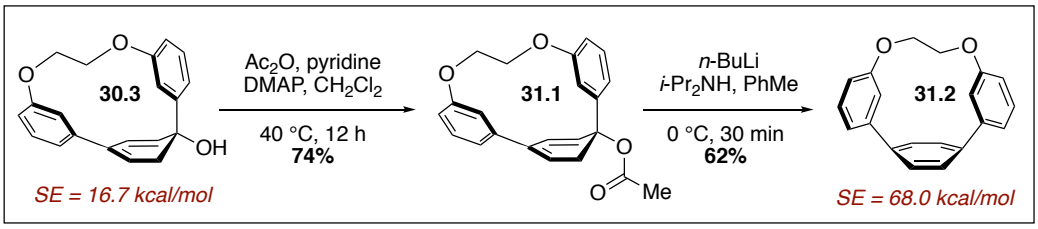
entry	solvent	temp (°C)	equiv	30.3	30.4	31.2
1	PhMe	80	3.0	19%	0%	<5%
2	THF	50-70	2.0	68%	0%	0%
3	THF	50	3.0	42%	31%	0%
4	THF	50	4.0	0%	37%	0%

SCHEME 30: Attempted aromatization of **30.2** using the Burgess reagent

Synthetic efforts from our laboratory revealed that THF can be successfully employed as solvent for Burges reagent-mediated aromatization reaction. Moreover, dehydrative aromatization reactions in THF can be run at lower temperatures than the toluene variation, making the reaction conditions potentially better suited for the formation of increasingly strained *para*-phenylene units. Treatment of **30.2** with 2.0 equivalents of the Burgess reagent in THF at 50 °C for 1 h, led to the formation of monodehydration product **30.3** in 68% yield (entry 2, Scheme 30). Prolonged heating of this reaction and increasing the temperature to 70 °C did not afford any of the desired aromatized macrocycle **31.2**. Increasing the number of equivalents (2.0 to 3.0) of Burgess reagent used led to the formation of **31.3** (42%) and an allylic alkylation product **31.4** in 31% yield (entry 3, Scheme 30). In fact, the addition of 4.0 equivalents of Burgess reagent afforded **31.4** as the sole product of this reaction in 37% yield (entry 4, Scheme 30). It appears that the second dehydration reaction under these conditions is less favorable than the corresponding allylic alkylation reaction. However, the observation that the highly strained *para*-phenylene ring was formed, albeit in trace amount, under dehydrative conditions in toluene led us to pursue an alternative aromatization protocol.

Close monitoring of the dehydration reaction of **30.2**, to afford a trace amount of **31.2** (entry 1, Scheme 30), gave no indication that desired compound was prone to decomposition or rearrangement reactions. However, the low yield of these two products, when compared to previous results and the THF variation of this reaction, was cause for concern. During the final stages of Jasti and co-workers' synthesis of [5]CPP it was necessary to modify their aromatization protocol to furnish the remaining two *para*-phenylene rings of the desired nanohoop. In case of **31.1**, we envisioned a β-elimination of AcOH could be employed to furnish the highly strained aromatized product **31.2** (Scheme 31). Thus, **30.3**, SE = 16.7 kcal/mol, was acetylated to give **31.1** in 74% yield. In order to introduce the remaining 51.3 kcal/mol of SE in the acrocyclic structure of

31.2, a LDA-mediated elimination of AcOH was designed. Indeed, treatment of acetate **31.1** with LDA in toluene at 0 °C gave the desired macrocycle **31.2**. The strain energy induced in this reaction (51.3 kcal/mol) per *para*-phenylene unit generated is greater than that induced during the Jasti synthesis of [5]CPP – *cf.* 43.5 kcal/mol of SE per *para*-phenylene ring synthesized. Incremental increases in SE induction have been paramount to the successful preparation of increasingly strained arenes over the past 50 years. We believe that this strategy of employing iterative elimination protocols can be tailored to the synthesis of increasingly strained systems such as [4]CPP.



SCHEME 31: Synthesis of **31.2** (SE_{pp} = 42.6 kcal/mol) using iterative elimination reactions

2.4.2 Benzenoid structure of the highly strained para-phenylene unit of 31.2*: Spectroscopic and computational evidence*

All attempts to grow suitable crystals of **31.2** for X-ray diffraction studies were unsuccessful. However, the optimized geometry of **31.2** was obtained from density functional theory (DFT) calculations using the B3LYP functional, in combination with the 6-31G(d) basis set (Figure 10). Comparing the deformation angles α and β derived from the X-ray crystal structure of **25.5** (Figure 7), with the DFT-derived values for **25.5**, shows excellent agreement (Figure 10). In fact, it appears that the computationally derived value of α for **25.5** is slightly lower than the experimentally determined value. Thus, in the case of **31.2**, the computational value of α = 19.1° is likely very close to the predicted value of α in [4]CPP (19.4°).[46] One of the major questions surrounding the structure of [4]CPP is whether or not the highly strained *para*-phenylene rings will retain their benzenoid form. In the case of **31.2**, the central arene unit of the *p*-terphenyl system represents a good model for a monomer unit of [4]CPP, and can provide valuable insight into addressing this question. Its computed SE of 42.6 kcal/mol is greater than that of a monomer unit of **8a**, and the boat deformation angle (α) of 19.1° is in good agreement with the computational predicted value of the bent benzene rings of [4]CPP. Furthermore, the biaryl bonds that connect the central *para*-phenylene ring simulate the structure of a monomer unit of [4]CPP and represent a good model of the arene units contained within the macrocycle.

The overall out-of-plane deformation of the central arene of **25.5** is nearly identical to the *para*-phenylene units of [5]CPP, as indicated by their α angles of 15.7 and 15.6°, respectively (Table 4). Despite both of these large deviations from planarity, which impart a great deal of strain on the *para*-phenylene rings (28.4 and 23.8 kcal/mol for **25.5** and **6.2**, respectively), the solid state structures of both **25.5** and [5]CPP (**6.2**) revealed that the C-C bond lengths of the strained arene units are between 1.39-1.40 Å and 1.38-1.40 Å, respectively. Indicating that both rings are indeed benzenoid. The ^{1}H NMR spectrum of [5]CPP shows one signal at δ = 7.86 ppm, which is shifted downfield by 0.22 ppm relative to [6]CPP.[25] The narrowing of the torsional angle between the adjacent phenyl rings, and not the increase in distortion of the arene(s), is cause for this increase in chemical shift. In the case of the [*n*](3,3")*p*-terphenylophanes that have been reported, there is very little deviation in the aromatic resonances observed in the ^{1}H NMR spectra due to the larger torsional angles between the arene units. Protons at the 2 and 2"-positions (a, Figure 11) are generally shifted to higher field as the number of methylene groups in the alkoxy bridging unit decreases. This can be attributed to the increased β angle, which directs these protons towards the shielding cone of the central *para*-phenylene ring. Protons b, c, d, e and f (Figure 11) show virtually no deviation in their chemical shift values, and in the case of **31.2**, its ^{1}H NMR spectrum is nearly identical to that of **25.5**. Coupled with the X-ray structure of **25.5** and identical magnetic susceptibility, these data are suggestive that the highly strained *para*-phenylene ring that is part of a teraryl macrocyclic system, containing a SE greater than 36 kcal/mol and an α angle of 19.1°, is benzenoid. Finally, the computationally derived structure of **31.2** indicates that the C-C bond lengths of the central arene unit are between 1.40-1.41 Å, supporting a benzenoid structure.

TABLE 4: Structral and spectroscopic data **25.5** and **30.2**

metric	**25.5** (expt)	**25.5** (DFT)	**30.2** (DFT)
α (°)	15.7	15.4	19.1
β (°)	24.6	24.5	30.2
δ H_a	5.35		5.29
δ H_b	6.72		6.70
δ H_c	7.25-7.21		7.24-7.21
δ H_d	7.33-7.26		7.31-7.26
δ H_e	7.42		7.43
δ H_f	4.12-3.81		4.20-3.76

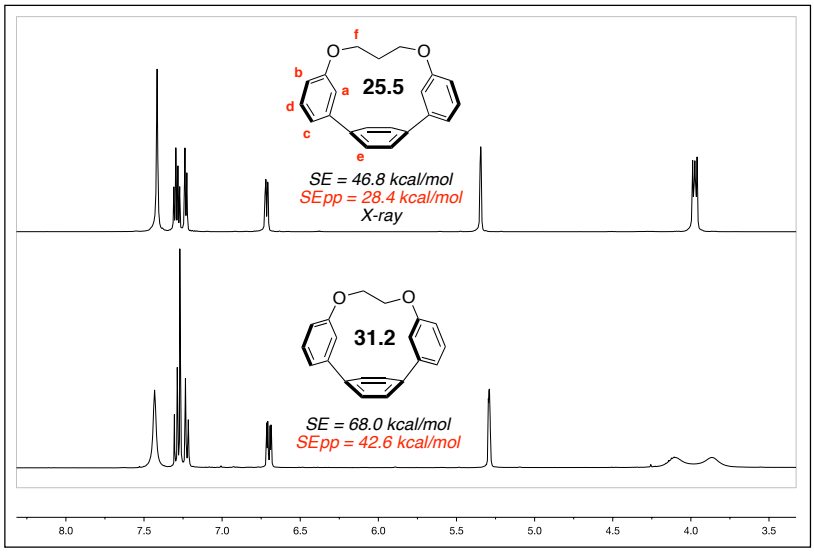


FIGURE 11: ^{1}H NMR spectra ($CDCl_3$) of **25.5** and **31.2**

2.5 Concluding remarks

The development of a streamlined synthetic protocol for the synthesis of macrocyclic 1,4-diketones that can be prepared on a gram-scale, coupled with their conversion into highly strained *para*-phenylene-bridged macrocycles, is a significant accomplishment for this field of chemical synthesis. Overcoming strain-induced rearrangement reactions that occur under acidic conditions using the Burgess reagent for dehydrative aromatization reactions of cyclohex-2-ene-1,4-diols, has expanded the synthetic tool box for strained benzenoid macrocycle synthesis. Furthermore, these studies provide a better understanding of backbone rearrangements that can occur during the course of acid-mediated reactions of these and CPP-based macrocyclic systems. In this regard, the accomplishments of this chapter will guide future synthetic efforts aimed at the development of skeletal building reactions that lead to pi-extended macrocycle synthesis. The latter will be the focus of Chapter 3. Finally, the development of an iterative elimination protocol of a cyclohex-2-ene-1,4-diol to furnish a *para*-phenylene unit that has the same bonding arrangement to that of [4]CPP and is more strained than a monomer unit of [4]CPP, provides cautious optimism that the synthesis of this elusive nanohoop may be possible using a macrocyclic 1,4-diketone as a key synthetic precursor.

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CHAPTER 3 Annulative Pi-Extension (APEX) of Selectively Substituted Benzenoid Macrocycles: An Investigation of the Scholl Reaction and Allylic Arylation

3.1 Introduction

The successful syntheses of CPPs and related macrocyclic nanohoops, which can be used as diameter defining building blocks in the bottom-up chemical synthesis of cylindrical carbon-based nanomaterials, brought much hype and excitement to those engaged in the development synthetic strategies for accessing carbon nanobelts (CNBs) and carbon nanotubes (CNTs). However, 10 years after the initial report by Bertozzi and Jasti and numerous other advancements to this field, including the synthesis of gram-scale quantities,[1-2] and functionalized derivatives of these materials,[3-6] their highly touted use as building blocks for a laboratory synthesis of a CNB or CNT has not come to fruition. This is largely due to a poor understanding of how to connect arene vertices of strained benzenoid systems to unstrained benzene rings. In order to accomplish this, new synthetic methods/technology that are able to mitigate SE and C-C bond formation, to facilitate the conversion of benzenoid systems into polycyclic aromatic hydrocarbons (PAHs), is critical. With this in mind, the main focus of the work discussed in this chapter was to capitalize on the synthetic methods developed in Chapters 1 and 2 and to prepare a series of selectively arylated macrocyclic benzenoid systems that could be subjected annulative pi-extension (APEX) reactions.

3.1.1 Polycyclic Aromatic Hydrocarbons (PAHs)

A class of organic compounds that consist of more than two fused aromatic ring systems. PAHs have attracted immense interest due to their unique structural, electronic and optoelectronic properties. In general, PAHs are colorless, or pale yellow solids and are notorious as one of the most widespread organic pollutants. Some PAHs are suspected to be carcinogenic,[7-8] and directly involved to other human health problems, including immune dysfunction, kidney and liver damage, as well as breathing problems related to asthma like symptoms.[8] They can be found either in natural sources (*e.g.*, oil, the atmosphere, etc.) or formed by incomplete combustion of carbon-containing fuels such as wood, coal, diesel, fat, tobacco, or incense.

Structurally the PAHs are comprised of two or more benzene rings bonded together in a linear, cluster, or angular fashion (Figure 12). PAHs containing up to six fused aromatic rings are often known as small PAHs, and are widely used in scientific studies due to their availability. PAHs containing more than six aromatic rings are known as large PAHs (SHOW SOME EXAMPLES IN THE FIGURE!!!). According to the definition given by the International Union of Pure and Applied Chemistry (IUPAC), the smallest PAHs are phenanthrene and anthracene, which contain only three benzene rings in angular and linear fusion, respectively. PAHs may contain four, five, six, seven- or even lager-membered rings, but polycyclic compounds with embedded five or six-membered rings are most common in terms of availability and stability. PAHs that con-

tain only of six-membered rings are known as *benzenoid* PAHs and are typically planar, unless they belong to the helicene family of PAHs.[9-10] Bending benzenoid-based PAHs is requirement for the bottom-up chemical synthesis of CNTs and the development of synthetic methods to facilitate this bending of larger PAHs, is the focus of this chapter.

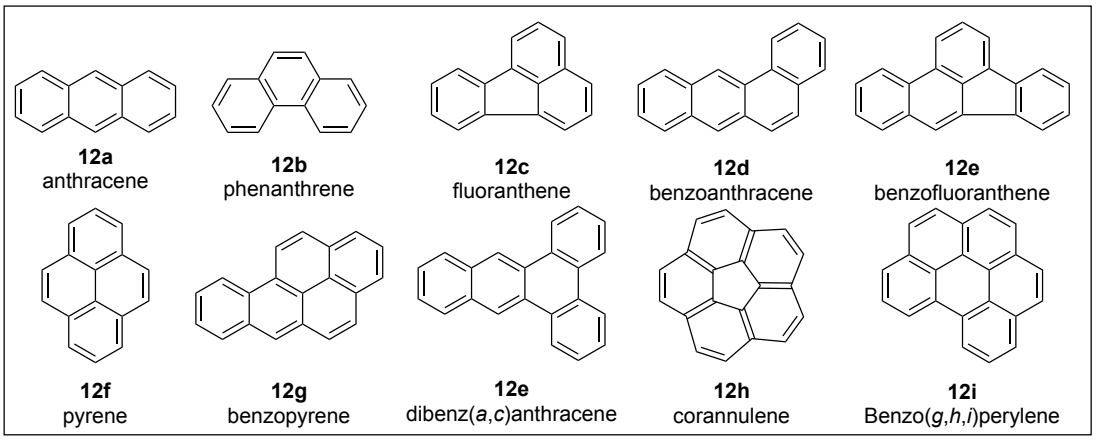


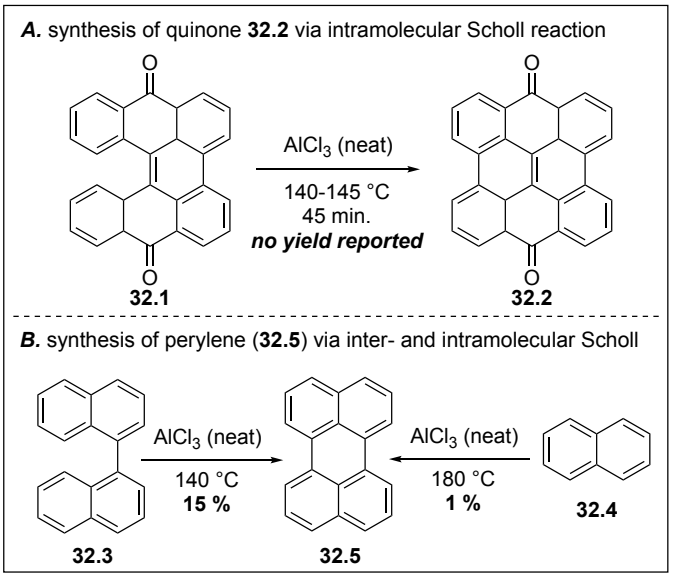
FIGURE 12: Selected polycyclic aromatic hydrocarbons

3.1.2 Synthesis of the benzenoid-based and curved PAHs

The field of polycyclic aromatic hydrocarbon synthesis was largely pioneered by the efforts of Scholl, Clar, and Zander.[11-12] These groups completed the syntheses of numerous PAHs, often requiring forcing reaction conditions, which featured high temperatures and strong oxidants. The characterization and differentiation of isomeric PAHs produced during these syntheses was made possible due to advancements analytical chemistry and improved spectroscopic measurements. Ultimately, this helped future synthetic investigations that led to the selective synthesis of various PAHs under milder reaction conditions. One of the intrinsic properties of the PAHs is their aromaticity, which has attracted a great deal of interest in theoretical chemistry. In fact, numerous theoretical methods have been developed and applied to quantify aromaticity and estimate electronic properties of benzne-based on PAHs (*i.e.,* graphitic-type materials) with increasing size and varying topologies. In turn, this has lead to the development of organic semiconductors, as well as improved electronic and optoelectronic properties of PAHs. Furthermore, well-defined nanostructures resulting from supramolecular self-assembly of PAHs, such as nanotubes and nanowires, have great potential for advancements in nanotechnology. Small PAHs have been isolated from coal tar and catalytic hydrocracking of petroleum, but synthetically many of these PAHs, and modifications thereof, can be prepared in the laboratory. Scholl, Clar, and Zander reported the synthesis of **32.2** and **32.5** using an oxidative aryl-aryl coupling reaction, later to become known as the Scholl reaction, in 1910 (Scheme 32).[12] Since then chemical syntheses and synthetic strategies for accessing these and related PAHs have improved significantly. The most commonly used methods for the synthesis of benzenoid-based PAHs, both planar and nonplanar,

will be discussed in the remaining sections of this chapter.

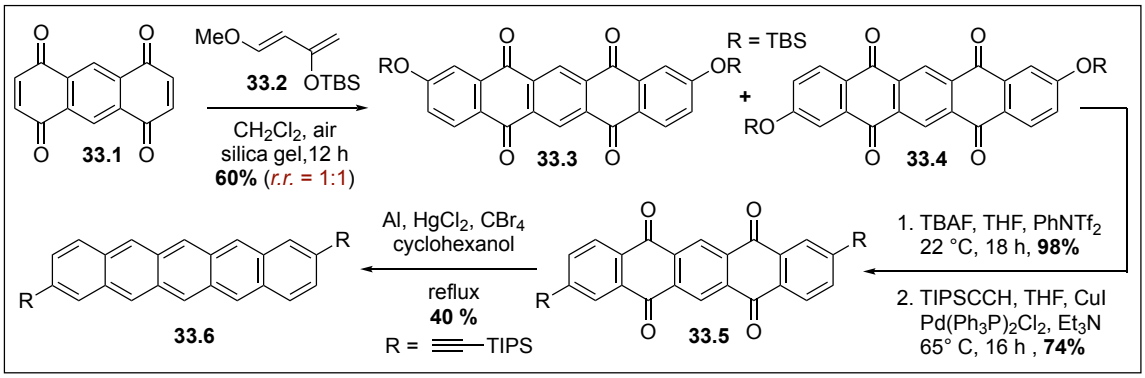
The synthesis of π-extended quinone **32.2** was reported by Scholl and Mansfeld in 1910. Treatment of **32.1** with an excess of (neat) anhydrous aluminum chloride at 140-145 °C produced **32.2** in pure form, however, no yield was reported for this reaction (Scheme 32A). In a follow up publication, the same group reported the synthesis of perylene (**32.5**) from 1,1'-binaphthalene (**32.3**, Scheme 32B) and naphthalene (**29.4**) via intramolecular and inter- followed by intramolecular C-C bond formations, respectively.



SCHEME 32: Early Scholl reactions by Scholl *et. al.*

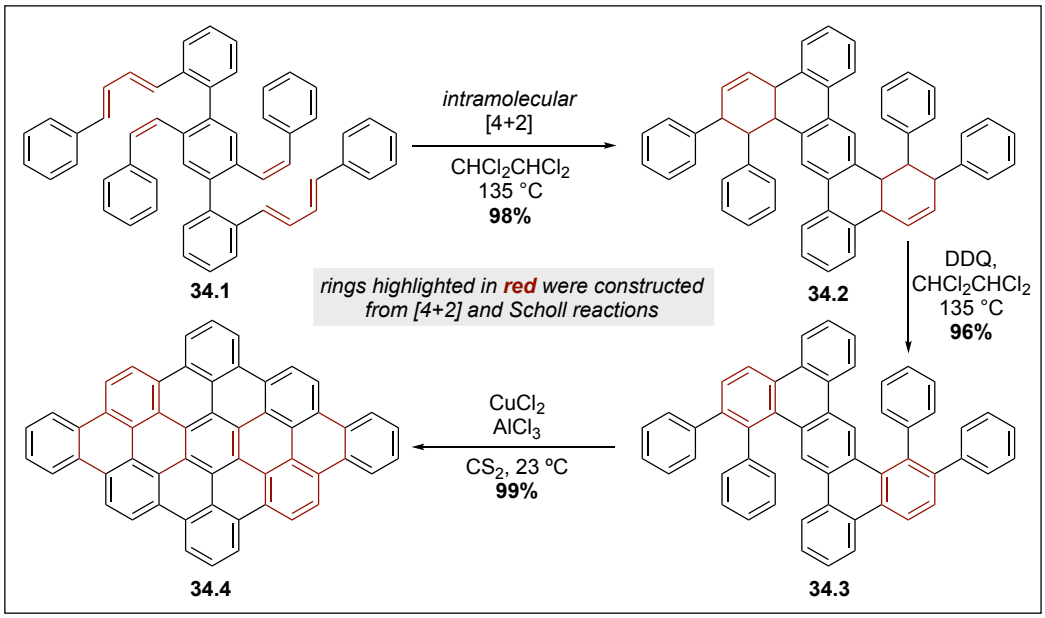
3.1.2.1 Intra- and intermolecular Diels-Alder reactions in PAH synthesis

The Diels-Alder reaction is one of the most efficient synthetic methods for the formation of unsaturated six-membered rings. Typically, this [4+2] cycloaddition reaction is used to synthesize stereochemically rich mono- and polycyclic ring systems, but it is equally useful in annulation reactions that lead to achiral materials, which can be converted in complex PAHs. For example, the double Diels-Alder reaction of anthradiquinone **33.1** with Danieshefsky's diene (**33.2**) affords cycloadducts **33.3** and **33.4** (Scheme 33). After separation, of the constitutional isomers produced in the Diels-Alder reaction, cleavage of the silyl ether and conversion of the resulting phenols to aryl triflates (98% overall yield), a Songashira reaction with triisopropylsilyl acetylene affords **33.5**. The bis-alkyne is then converted to pentacene derivative **33.6** after derivatization and aromatization (Scheme 33).[13]



SCHEME 33: Double Diels-Alder strategy for the synthesis of pentacene **33.6**

Müllen and co-workers have been a dominant force in the area of complex, pi-extended PAH synthesis over the past 30 years. In 1996, they synthesized the highly branched *p*-terphenyl derivative **34.1**, which was subjected to an intramolecular Diels-Alder reaction to afford **34.2** in 98% yield (Scheme 341).[14] Aromatization of the newly installed tetrahydrotriphenylene units in the presence of DDQ, led to formation of **34.3**, which was then subjected to an oxidative aryl coupling reaction to furnish the rhombus-shaped PAH **34.4** containing 60 carbon atoms.

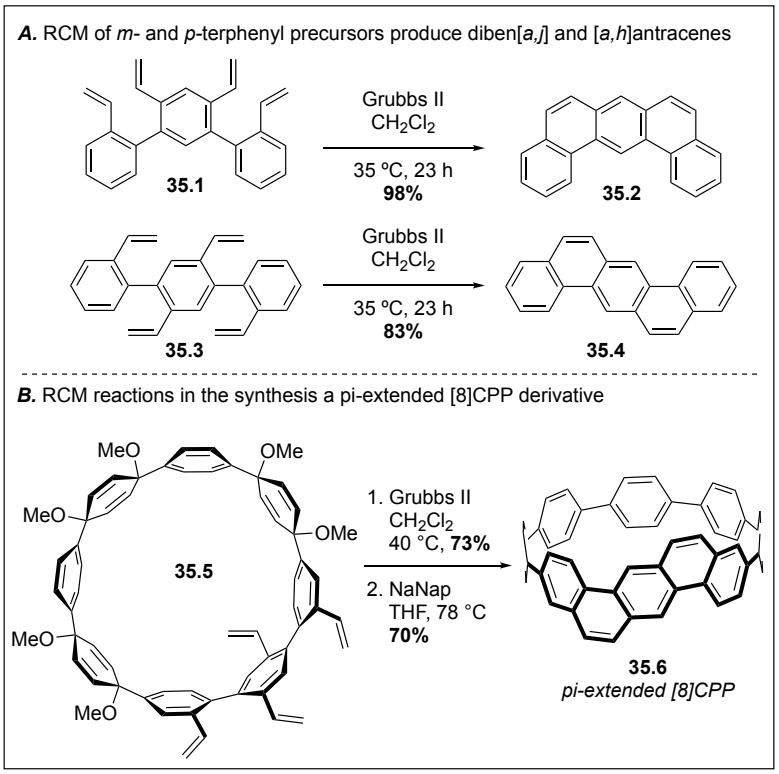


SCHEME 34: Intramolecular Diels-Alder reaction in the synthesis of PAH **34.4**

3.1.2.2 Ring-closing metathesis in PAH synthesis

Olefin metathesis (reactions) that leads to the formation of a cyclic olefin product is known as ring-closing metathesis (RCM). This powerful C-C bond forming reaction has transformed the way chemical syntheses are planned when cyclization or the formation of rings are required. While this reaction has become commonplace in the synthesis of polycyclic natural products, it has also been used in the selective syntheses of benzenoid PAHs. In 2005, King and co-workers

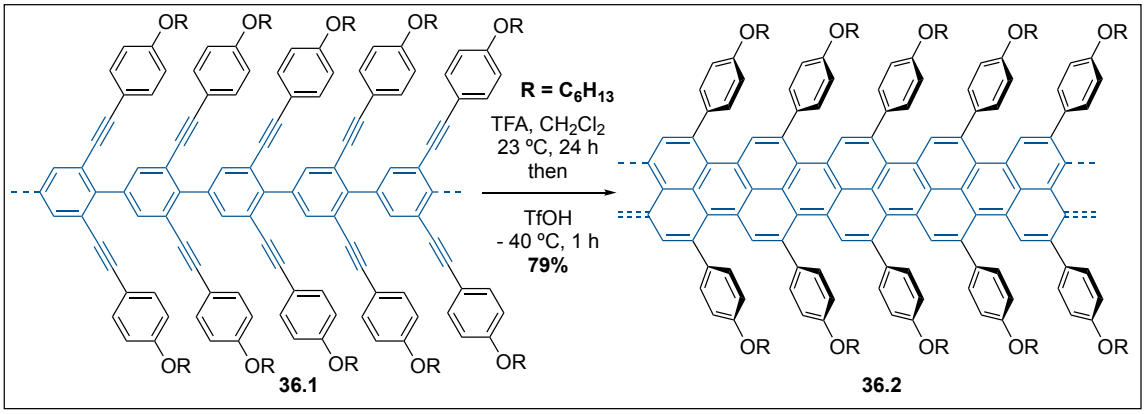
reported one of the first examples were this venerable reaction had been applied to the synthesis of dibenzanthracene derivatives **35.2** and **35.4** (Scheme 35A). Selective synthesis of vinylated *m*-terphenyl **35.1** and *p*-terphenyl **35.3**, followed by a RCM reaction in the presence of the Grubbs second-generation catalyst, gave dibenz[*a*,*j*]anthracene (**35.2**) and dibenz[*a*,*h*]anthracene (**35.4**) in 98% and 83% yield, respectively.[15] In 2016, Jasti and co-workers reported a RCM-based strategy for annulation about the macrocyclic backbone of series of vinylated [*n*]CPPs (**35.**5, Scheme 35B).[16] This was a significant achievement for the field as it represented one of the first examples of the application of RCM in the synthesis of strained, pi-extended systems (**35.6**). Their investigations demonstrated that up to 24 kcal/mol of SE could be introduced into the macrocyclic structure of a CPP precursor.



SCHEME 35: PAH synthesis by the ring-closing metathesis

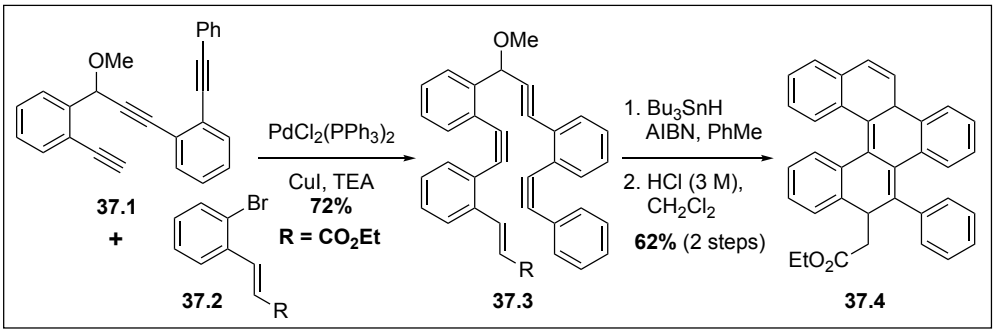
3.1.2.3 Alkyne-based annulation reactions

Recently the groups of Chalifoux and Alabugin have developed new annulation strategies for the synthesis of pi-extended PAHs based on alkyne cyclization reactions. Chalifoux and co-workers have used alkyne benzannulation reactions to synthesize of pyrene-based graphene nanoribbons (GNRs, Scheme)[17-18] Chalifoux synthesized the poly(2,6-dialkynyl-*para*-phenylene) (PDAPP) **33.1** from an aniline derivative by sequential Sonogashira and Suzuki cross-coupling reactions (not shown), and then subjected the poly alkynylated material to a Brønsted acid-promoted alkyne benzannulation reaction to afford GNR **36.2**. This work is significant as **36.2** is highly soluble in a number of common organic solvents, which permitted extensive characterization of these materials. .



SCHEME 36: Alkyne benzannulation reactions in the synthesis graphene nanoribbons (GNRs)

Alabugin and coworkers reported the synthesis of pi-extended PAHs using alkyne-benzannulation via radical cascade reaction.[19-20] Alkyne **37.1**, prepared from sequential Songashira cross-coupling reactions, was subjected to Songashira coupling with aryl bromide **37.2** to afford triyne **37.3** in 72% yield (Scheme 37). Once assembled, **37.3** was subjected to tributyltinhydride and AIBN in toluene, followed by hydrochloric acid to afford **37.4** in 62% yield over 2 steps.

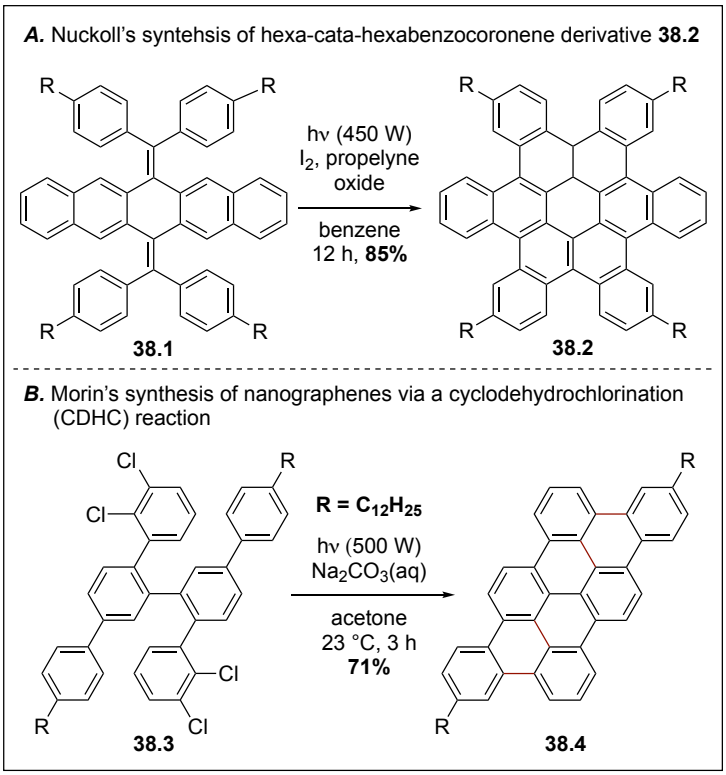


SCHEME 37: Alubugin's alkyne-alkene cascade reaction for PAH synthesis

3.1.2.4 Intramolecular photocyclization of for APEX

Recently, Nuckolls and co-workers have accomplished the synthesis of a distorted hexa-*cata*-hexabenzocoronene derivative **38.2**. Their synthesis involves a series of photo-6π electrocyclization reactions of bis-stilbene derivative **38.1** to afford pi-extended PAH **38.2** in 85% yield (Scheme 38A).[21] In 2016, J. F. Morin reported a new solution-phase strategy for the synthesizing novel nanographenes and GNR-based (PAH) fragments using a photochemical-induced cyclodehydrochlorination (CDHC) reaction of various aryl chlorides (Scheme 38B). The chlorinated precursor **38.3** was prepared by sequential Suzuki cross-coupling reactions, and then irradiated in acetone in the presence of Na_2CO_3 to give **38.4** as a single regioisomer (Scheme 38B). Morin and co-

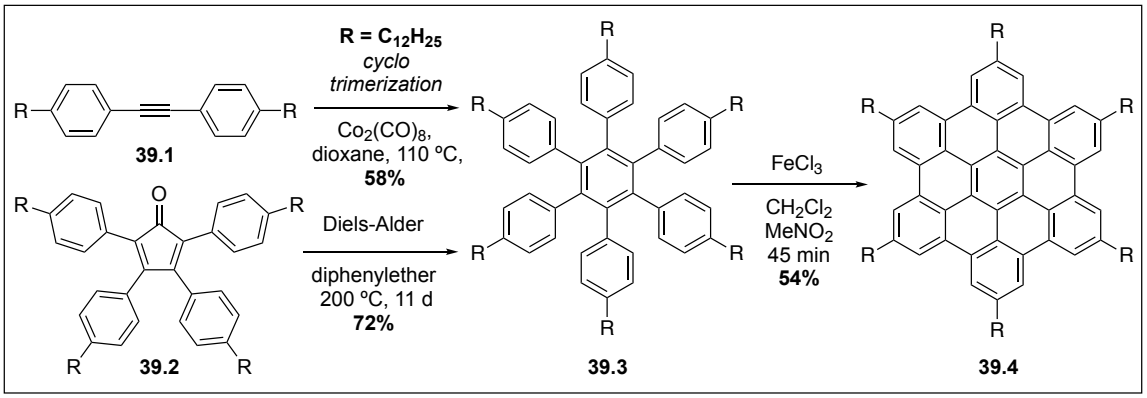
workers have synthesized numerous aryl chloride derivatives and have noted that the CDHC reaction proceeds with remarkable regioselectivity.[22]



SCHEME 38: Intramolecular photocychemical-induced APEX

3.1.2.6 Oxidative cyclodehydrogenation – the Scholl reaction

Lewis acid catalyzed inter- or intramolecular coupling of two aromatic rings via a cyclodehydrogenation reaction is known as the Scholl reaction. This reaction has proved to be a powerful tool to produce unfunctionalized PAHs from relatively simple aromatic precursors. The application of the Scholl reaction in the synthesis of hexabenzocoronene (HBC) **39.4** was reported by Müllen and co-workers in 2008 (Scheme 39). A cobalt-medited [2+2+2] cyclotrimerization of alkyne **39.1** furnished hexaphenylbenzene **39.3** in 58% yield. An alternative and higher yielding (72%) synthesis of **39.3** was accomplished through a [4+2] cycloaddition of **39.1** with **39.2**. Upon treatment of **39.3** with iron(III) chloride in dichloromethane/nitromethane HBC derivative **39.4** was afforded in 54% yield.[23] The synthesis of pi-extended PAHs containing only 6-membered rings has proven to be one of the hallmarks of the Scholl reaction. As will be described in later sections, controlling regioselectivity of these reactions can be difficult and a source of frustration in the chemical synthesis of well-defined graphene-based materials.



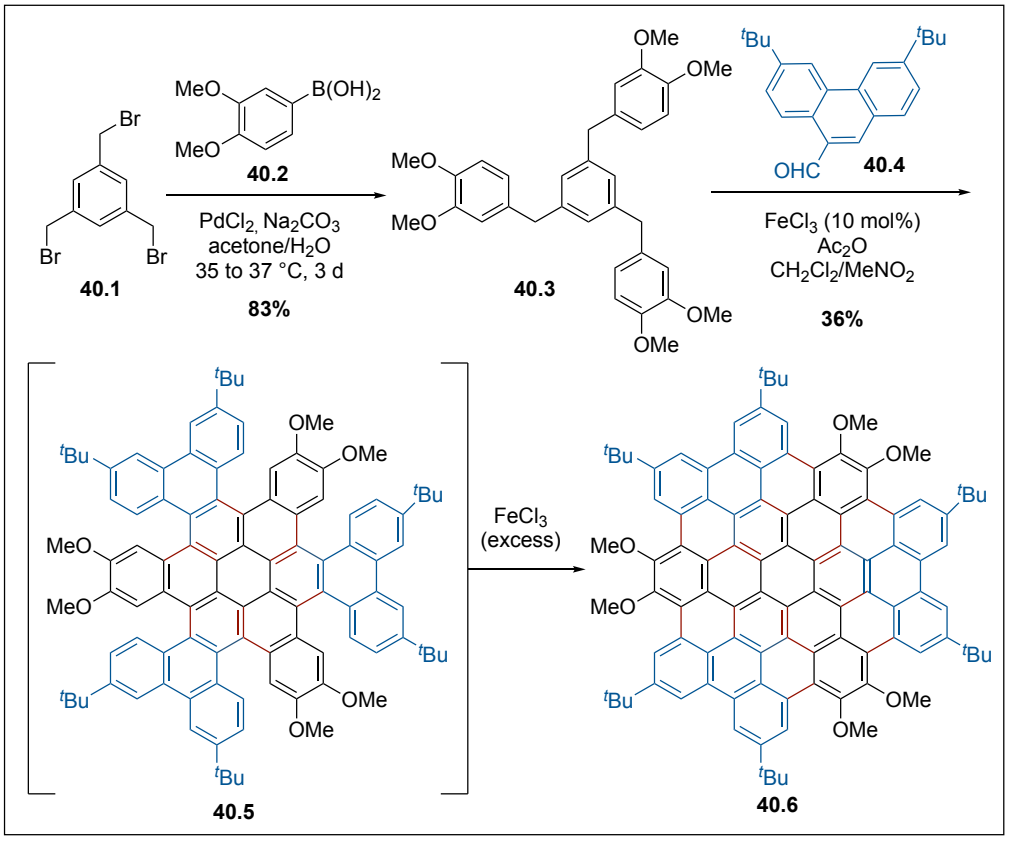
SCHEME 39: Syntheiss of HBC **39.4** via the Scholl reaction

3.1.2 Synthesis of nanographenes and graphene nanoribbons (GNRs) using the Scholl reaction

Graphite is an allotrope of carbon that consists only of sp^2 hybridized carbon sheets stacked on top of one another, like sheets of paper. A single sheet is known as graphene.[24] Graphene nanoribbons (GNRs) have been recognized as promising building blocks for nanoelectronic and spintronic devices in the modern chemistry. Because of their unique properties nanographene have attracted attention from synthetic chemists. Several methods have been reported for the production of the graphene sheets based on chemical oxidation of graphite or heating silicon carbide at extremely high temperatures. The temperatures that are required for these processes make syntheses highly unselective. This lack of synthetic control and harsh conditions strongly restrict the production of graphene in precise size and shape. Several synthetic organic chemistry groups have developed protocols to synthesize graphene-type molecules with well-defined shape and size.[25] However, the synthesis of higher molecular weight nanographene-based materials has presented a problem due to the insolubility of these materials in common organic solvents. Innovative, selective syntheses of GNRs and related materials are discussed below.

3.1.3.1 Wei and co-workers synthesis of a functionalized nanographene 40.6

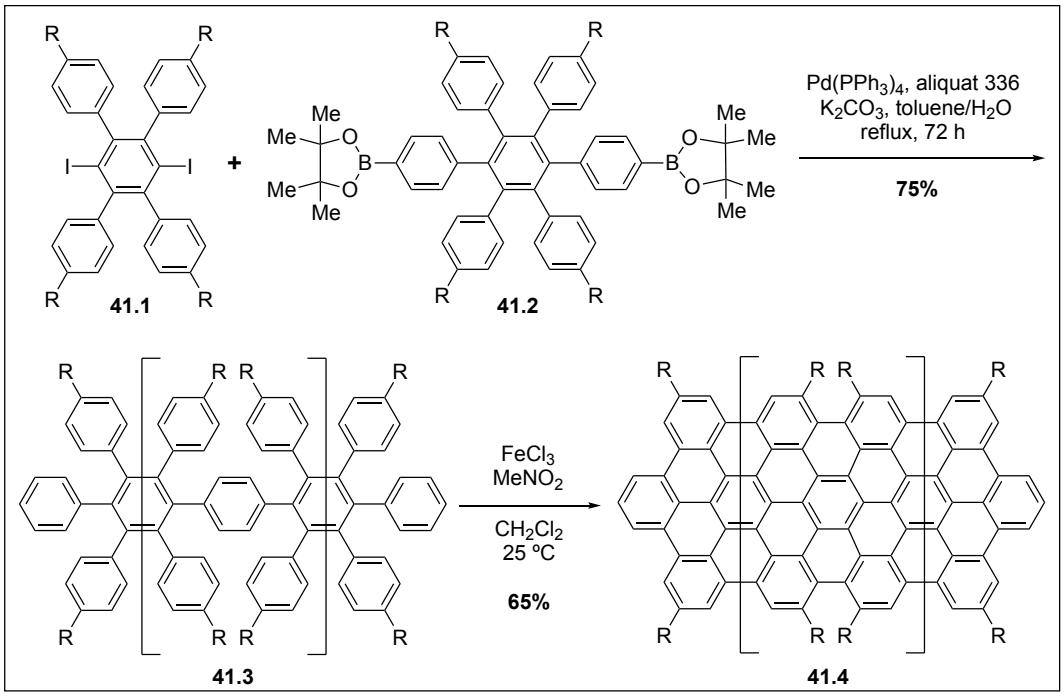
In 2014, Wei and co-workers developed a two-step synthesis of nanographene **40.6** (Scheme 40).[26] The first step involved a three-fold Suzuki reaction on tribromide **40.1** with 1,2-dimethoxyphenyl boronic acid (**40.2**) to give **40.3** in 83% yield**.** Treatment of **40.3** with phenanthraldehyde **40.4** in the presence of iron(III) chloride as an oxidant/Lewis acid and acetic anhydride as dehydrating agent, afforded the nanographene **40.6** in 36% yield. Remarkably, the formation of **40.6** from **40.3** involved a one-pot cascade process that involved Friedel-Crafts hydroarylation, intramolecular alkylation and dehydrogenative aromatization reactions to furnish intermediate **40.5**, followed by intramolecular cyclodehydrogenation (the Scholl reaction) to afford **40.6**.



SCHEME 40: Wei and co-workers synthesis of nanographene **40.6**

3.1.3.2 Mullen's synthesis of a soluble polymeric GNR

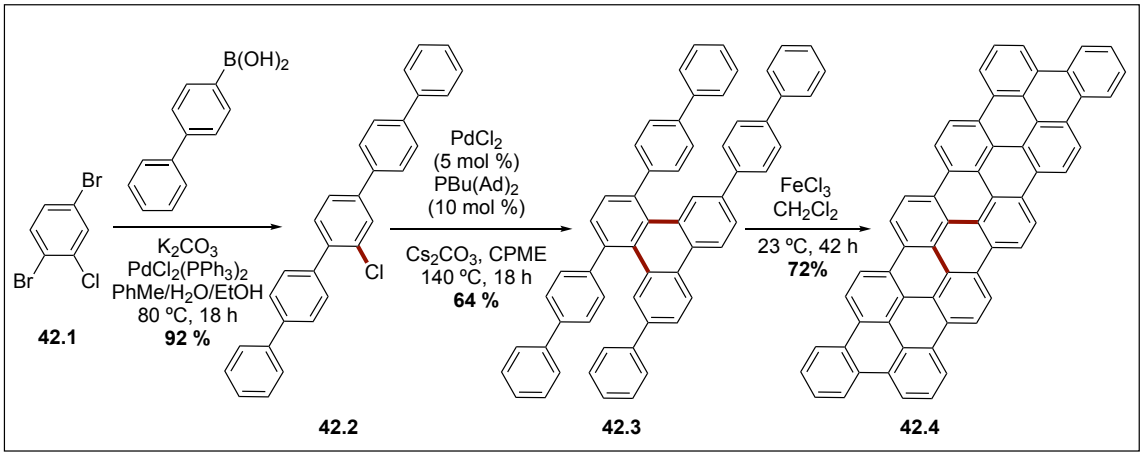
Müllen synthesis of GNR **41.4** began with a sterically hindered Suzuki reaction of diiodide **41.1** and bis-boronate **41.2**, using conditions established for congested cross-coupling reactions to afford (polymeric) polyphenylene **41.3** in 93% yield (Scheme 41). Polyphenylene **41.3** was isolated by soxhlet extraction in acetone and characterized by gel permeation chromatography (GPC) and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS). The soluble polymer material isolated from this purification process was then subjected to a Scholl reaction using iron(III) chloride in niromethane/dichloromethane at room temperature to furnish GNR-based polymer **41.4** as a black solid in 65% yield.[27-28]



SCHEME 41: Müllen's synthesis of graphene nanoribons via Scholl reaction

3.1.3.3 Itami's synthesis of nanographene 42.4 using an annulative-dimerization strategy

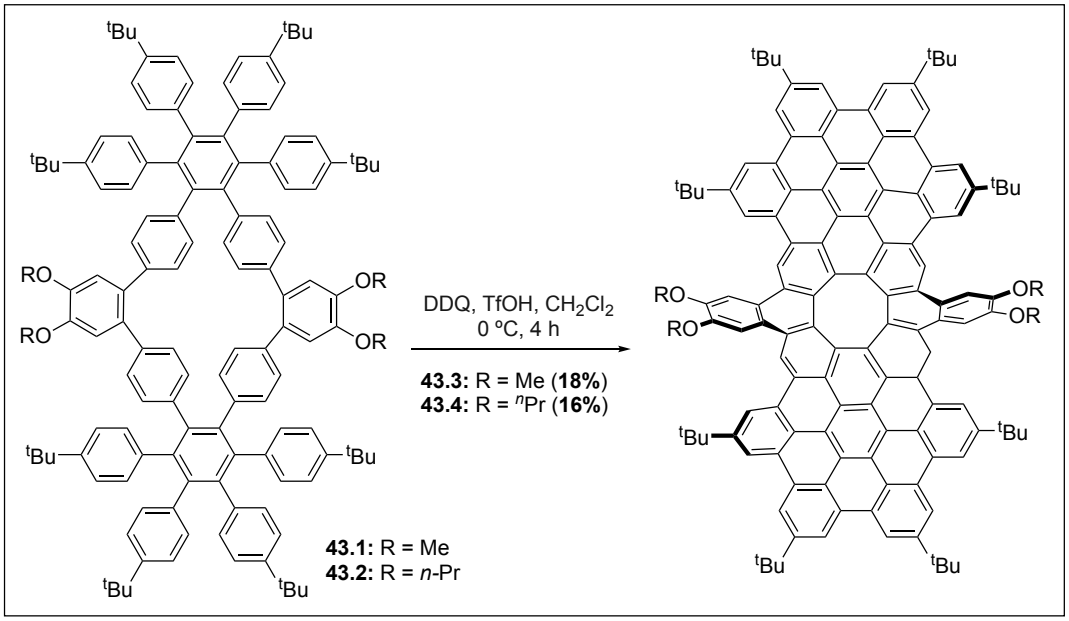
In 2018, Itami and co-workers reported a strategy for the rapid and convergent synthesis of an armchair-edged graphene nanoribbon segment **42.4**.[40] The synthesis commenced with Suzuki cross-coupling of 1,4-dibromo-2-chlorobenzene (**42.1**) with 4-biphenylboronic acid in the presence of $PdCl_2(PPh_3)_2$ catalyst to give chloropentaphenyl **42.2** in 92% yield (Scheme 42). A palladium-catalyzed annulative dimerization of **42.2** afforded triphenylene **42.3** in 64% yield. The direct installation of a triphenylene unit from a relatively simple aryl chloride is a clever and innovative method for partial rung fusion of GNR precursors. Indeed, holding the two petaphenyl units of **42.3** in this manner facilitated subsequent ring fusion/annulation under standard Scholl reaction conditions to furnish the $C_{60}H_{26}$ GNR substructure **42.4** in 72% yield. It is notable that this 60-carbon PAH was synthesized from 1,4-dibromo-2-chlorobenzene in just three steps and 42% overall yield, whilst 11 C-C bonds were formed. This example from Itami and co-workers represents a rare example the synthesis of a fully fused planar nanographene unit without any solubilizing substituents under solution-phase conditions.



SCHEME 42: Itami's synthesis of GNR substructure **42.4** via annulative chlorophenylene dimerization

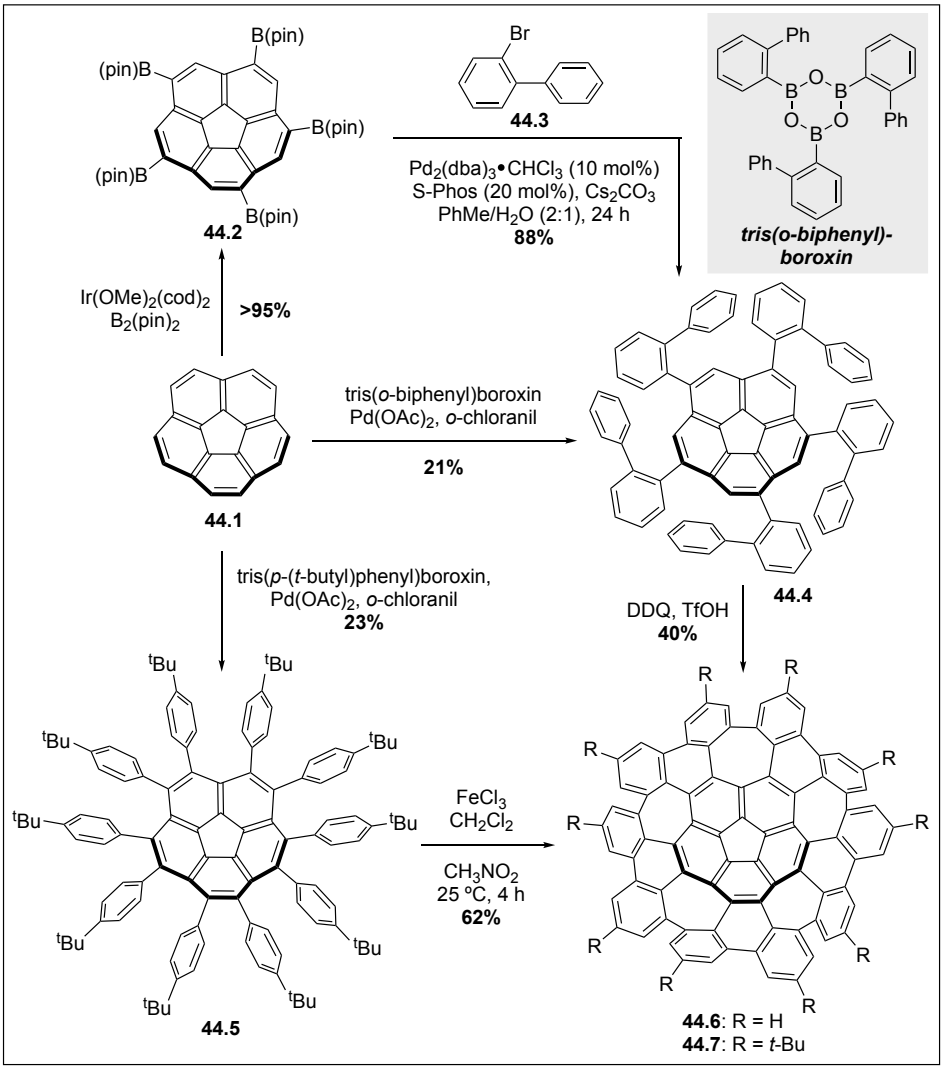
3.1.4 The synthesis of curved aromatic compounds using the Scholl reaction

In 2017, Miao and co-workers reported the synthesis, structure, and properties of a twisted nanographene that contains a central [8]circulene moiety within a polycyclic system of 96 sp^2 hybridized carbon atoms.[38] The macrocyclic precursor **43.1** was synthesized by a Diels-Alder reaction of a macrocyclic diynes and cyclopentadienone derivative to install the hexaphenyl benzene units of **43.1** and **43.2** (Scheme 43). A subsequent Scholl reaction under conditions developed by Rathore and co-workers on macrocycles **43.1** and **43.2** furnished the [8]circulene units of **43.3** and **43.4** after 12 cyclcodehydrogenation reactions in 18% and 16% yield, respectively.



SCHEME 43: Miao's twisted nanographene synthesis using Scholl reaction

In 2013, two giants in field of complex, nonplanar hydrocarbon synthesis, Kenichiro Itami and Lawrence Scott, joined forces to complete the synthesis of a $C_{80}H_{30}$ warped nanographene (Scheme 41). This curved and twisted structure is composed 5 seven-membered rings and 1 five-membered ring, each of which is completely embedded in a hexagonal lattice of trigonal carbon atoms.[24] Their synthesis begins with an Ir-catalyzed pentaborylation of corannulene **44.1** to afford **44.2** in near quantitative yield (Scheme 41). A five-fold Suzuki cross-coupling with 2-bromobiphenyl (**44.3**) with **44.2** gave the propeller-like corannulene derivative **44.4** in 88% yield. [40] Alternatively, **44.4** could be prepared directly from corannulene (**44.1**) upon treatment of the [5]circulene with tris(*o*-biphenyl)boroxin, albeit in much lower yield. Nonetheless, this method provided access to the deca-4-*tert*-butylphenyl derivative **44.5** using a similar boroxin reagent and C-H arylation protocol. In this reaction all 10 non-quaternary positions of **44.1** are substituted directly. With arylated derivatives 41.4 amd 41.5 in hand, the stage was set for a Scholl reaction to install the remaining 10 rings (five 6-membered and five 7-membered) of the targeted warped nanographenes **44.6** and **44.7**. In the case of **44.6**, a Scholl-based cyclodehydrogenation reaction takes place upon treatment of **44.4** with TfOH and DDQ to give to complete its synthesis. Whereas the treatment of **44.5** with iron(III)



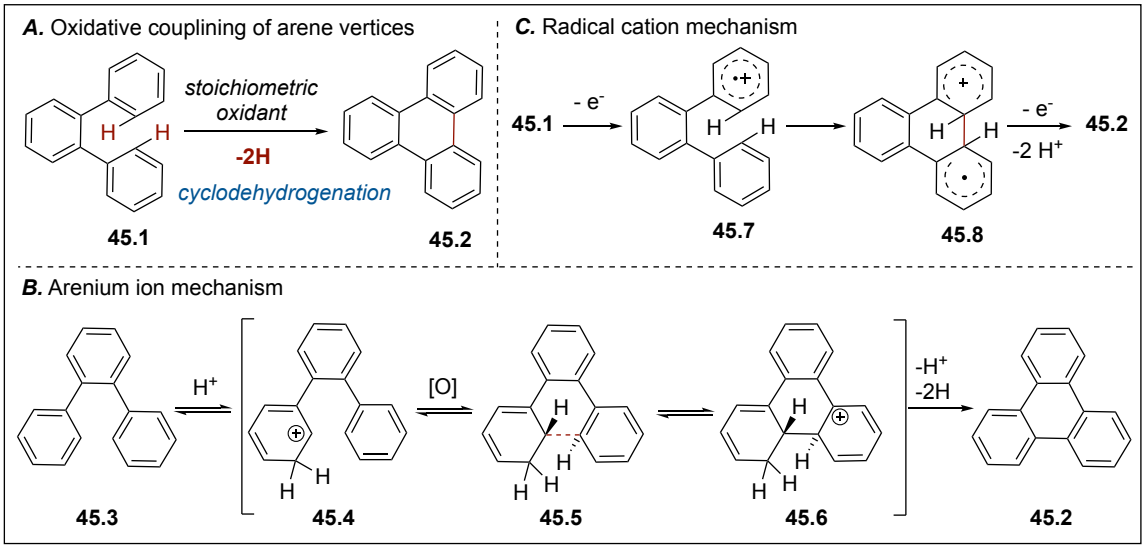
SCHEME 44: Scott and Itami's synthesis of warped nanographenes **44.6** and **44.7**

chloride at room temperature afforded the **44.7** in 62% yield. Owing to their curved structures, these PAHs have increased solubility in common organic solvents compared to planar C_{80} hydrocarbons. It should be noted that the *tert*-butyl derivative **44.6** is soluble in hexanes.

3.2 Mechanism of Scholl reaction

In the early literature, the Scholl reaction was defined as *"a dehydrogenation of aromatic nuclei under the influence of aluminum chloride that results in the formation of a condensed ring system*."[41] Balaban and Nenitzescu later modified this definition to *"the elimination of two aryl-bound hydrogens accompanied by the formation of an aryl-aryl bond under the influence of a Friedel-Crafts catalysts"* (Scheme 45A).[42-43] Baddeley and co-workers were the first to propose that the Scholl reaction may involve the formation of a σ-complex between a Lewis acid an aromatic unit, followed by the formation of an arenium ion, electrophilic attack, and ultimately dehydrogenation (Scheme 45B). Kenner and co-workers were the first to propose a radical cation mechanism for this cyclodehydrogenative reaction (Scheme 45C),[42] which was later supported by Rooney and Pink as well as Clover and co-workers. I t should be noted that in the mechanistic proposals presented in Scheme 45, a proton has been used to represent arenium ion formation for simplicity. In principle, a Lewis acid could serve the same role.

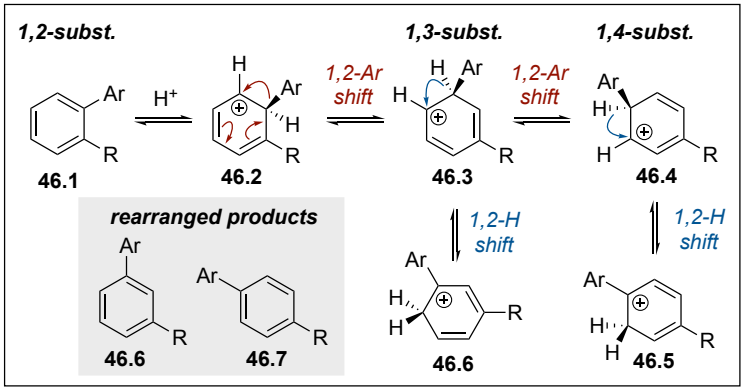
While many groups have put forth mechanistic proposals for the Scholl reaction, it is still poorly understood. In fact, the precise mechanism remains a topic of discussion, which has made this aryl coupling reaction somewhat controversial and, in the opinion of some, notorious in chemical synthesis. However, the reaction continues to be used in the field of complex PAH synthesis, often enabling the synthesis of new members and impressive structures to this family of hydrocarbons (see below).



SCHEME 45: Proposed mechanisms for the Scholl reaction

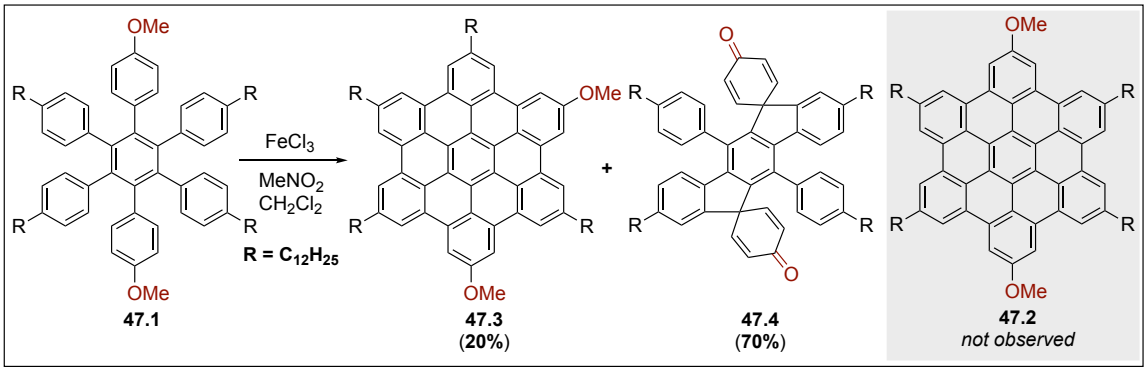
3.2.1 *Problems with the Scholl Reaction: Unpredictable rearrangement reactions*

Typically, oxidants employed in the Scholl reaction are metal chlorides. This can lead to the formation of hydrochloric acid, during the reaction, which can lead to further reactions on the polycyclic substrates formed and the formation undesired, chlorinated products. To circumvent this, it is often necessary to continuously purge the reaction mixture with a stream of an inert gas, such as nitrogen or argon. In addition to this, intramolecular Scholl reactions are susceptible to (unpredictable) rearrangements, which involve 1,2-aryl or 1,2-hydride shifts (Scheme 46). This is due to the formation of cationic intermediates, supporting the arenium ion mechanism. However, rearrangements via a radical cation mechanism are still possible. Selected, unpredictable rearrangement reactions are discussed below.



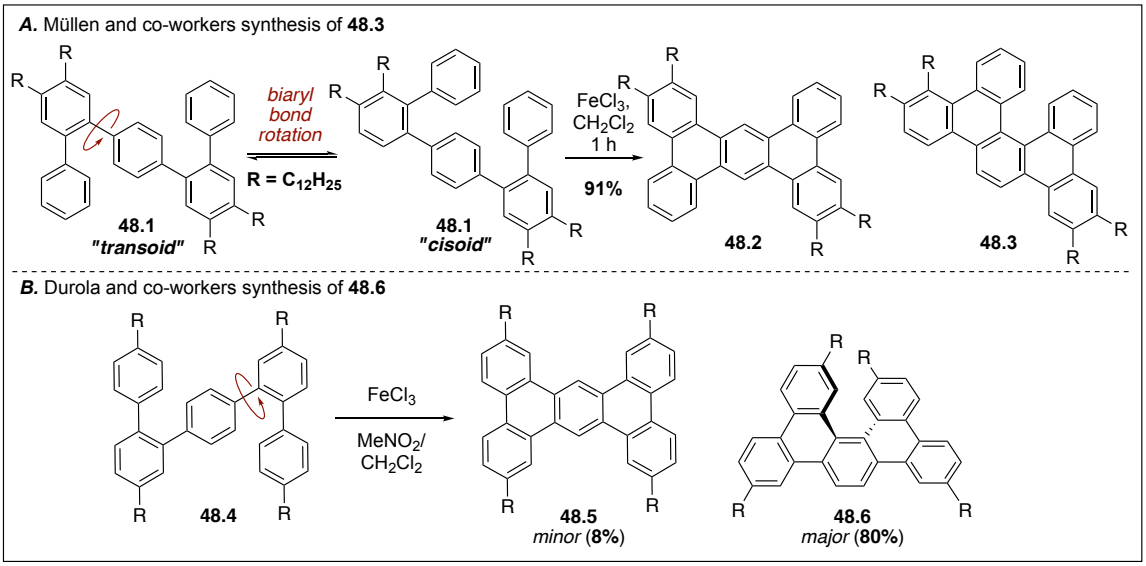
SCHEME 46: 1,2-Ar and 1,2-H shifts in the Scholl reaction

The groups of King and Müllen have conducted extensive studies on the Scholl reaction and its propensity to undergo rearrangement reactions, leading to the formation of undesired constitutional isomers.[44] In 2007, Müllen and co-workers attempted a Scholl reaction-based cyclodehydrogenation of hexaphenyl benzene derivative **47.1** to afford HBC derivative **47.2**. Upon treatment of **47.1** with iron(III) chloride, one of the two *para*-methoxyphenyl units, which are initially 1,4 to each other, end up in a 1,3 orientation in the only HBC product isolated (**47.3**, Scheme 47).[67]



SCHEME 47: Unexpected product formation from the Scholl reaction

Other than being unpredictable with respect to 1,2-Ar or 1,2-H shift reactions and furnishing rearranged products, the Scholl reaction can be somewhat unpredictable with respect to regiochemical outcome of a cyclodehydrogenation reaction. For instance, Müllen and co-workers synthesized *p*-terphenyl **48.1**, with the intention of converting it to the tetrabeznoanthracene derivative **48.2**.[25] The design element here was that the *transoid* cyclization conformer **48.1** would undergo cyclodehydrogenation through a less congested, and thus lower in energy, reaction pathway (Scheme 45A). However, when **48.1** was subjected to Scholl reaction conditions only the undesired constitutional isomer **48.3** was afforded in 91% yield, proceeding through a more congested (*cisoid*) cyclodehydrogenation pathway. In 2011, Durola and co-workers synthesized a similar *p*-terphenyl derivative (Scheme 48B).[35] By placing bulky *tert*-butyl substituents on the aryl units that would undergo cyclization, they surmised that the *cisoid* mode of cyclization, which was dominant in the Müllen investigation, would not be possible for **48.4**, or at minimum, strongly disfavored. Surprisingly, the major product of this reaction was the highly distorted [5]helicene **48.6**, and only a 8% of the desired *transoid* cyclization product **48.5** was afforded. The Durola group has synthesized even more congested *p*-terphenyl derivatives in attempts to favor the *transoid* cyclization, however, the *cisoid* mode of cyclization always dominates the Scholl reaction of these substrates.[36] While this unexpected regiochemical outcome of the Scholl reaction must have come as disappointment to the Durola laboratory, the preference for these *p*-terphenyl systems to undergo a *cisoid*-type cyclization is encouraging for our own investigations of the annulative pi-extension of bent *p*-terphenyl units into curved sidewall segments of CNTs (see section 3.4).



SCHEME 48: Unexpected regiochemical outcomes of the Scholl reaction

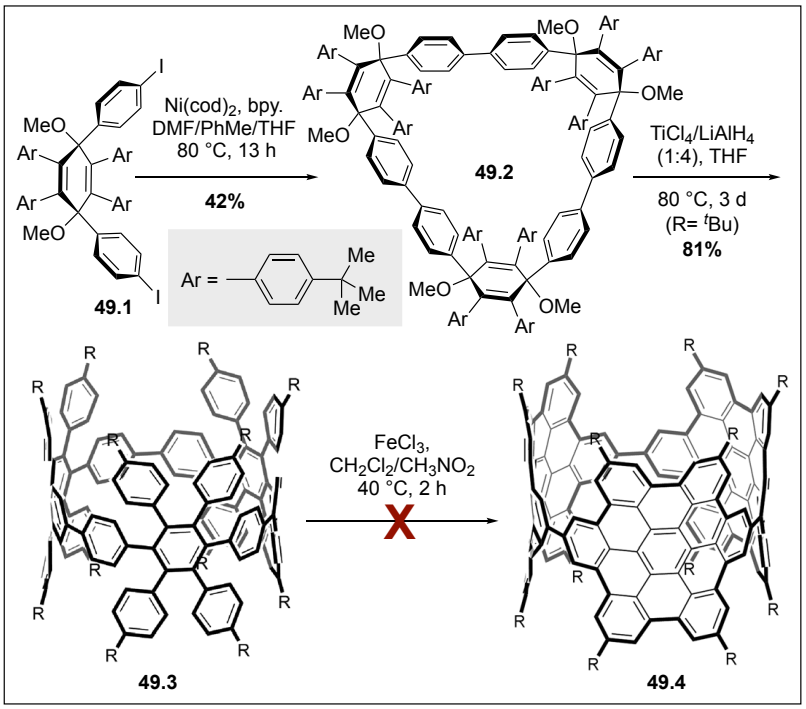
3.2.2 Limited investigations of the Scholl reaction on strained benzenoid systems

Despite the plethora of synthetic work that was been reported over the past 10 years on the syn-

thesis of carbon nanohoops, very little has been reported on the development synthetic strategies for extending these strained benzenoid systems into PAH-containing nanohoops. This speaks directly to synthetic limitations in this field of chemical synthesis. Primarily, easy access to strategically functionalized [*n*]CPPs, which can be subjected to late-stage (synthetic) investigation of annulative pi-extension reactions. What is required for such a study is a homologous series of strained benzenoid macrocycles that can be substituted with arene units for cyclization. Due to the difficulties associated with the selective functionalization of a homologous series of [*n*]CPPs, the development of new synthetic methods to accomplish the conversion of strained benzenoid systems to strained PAH systems has been limited.

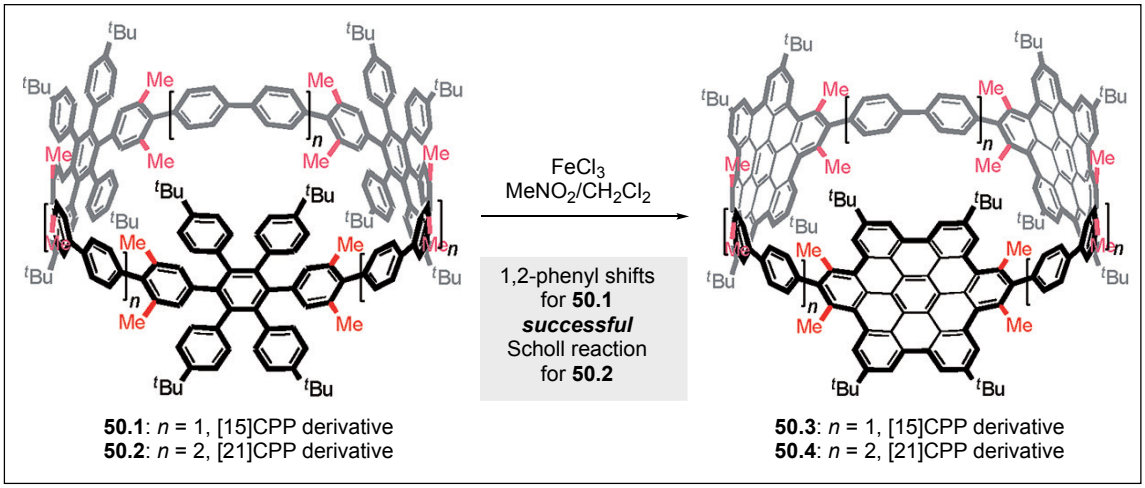
3.2.2.1 Müllen's synthesis and attempted syntheses of HBC-incorporated CPPs

The two most significant reports of attempted cyclodehydrogenation reactions on [*n*]CPPs have come from the groups of Müllen and Jasti. In 2012, Müllen and co-workers described the synthesis of a dodeca-arylated [9]CPP derivative.[33] Starting from 2,3,5,6-tetra-4-*tert*-butylphenyl-*syn*-1,4-diol **49.1**, which was subjected to a $Ni(cod)_2$-mediated Yamamoto reaction, macrocycle **49.2** was isolated in 42% yield (Scheme 49). A reductive aromatization of **49.2** using the low valent titanium reagent generated from $TiCl_4$ and $LiAlH_4$ in THF, furnished the dodeca-arylated [9]CPP derivative **49.3**. Subjecting **49.3** to Scholl reaction conditions did not afford the desired HBC-based nanohoop **49.4**. In 2015, the same group synthesized polyarylated macrocycles containing a [15] or [21]CPP unit (Scheme 50).[39] Strategic incorporation of methyl substituents within the macrocyclic backbone of the large CPPs was designed to prevent 1,2-aryl shift reactions, which had plagued their earlier work. Subjecting **50.1**, a [15]CPP derivative to a Scholl reaction did no result in the formation of **50.3**, but rather products that had undergone 1,2-aryl shift reactions. However, in the case of **50.2**, a [21]CPP derivative, under



SCHEME 49: Müllen's attempted synthesis of [3]HBC nanohoop **49.4**

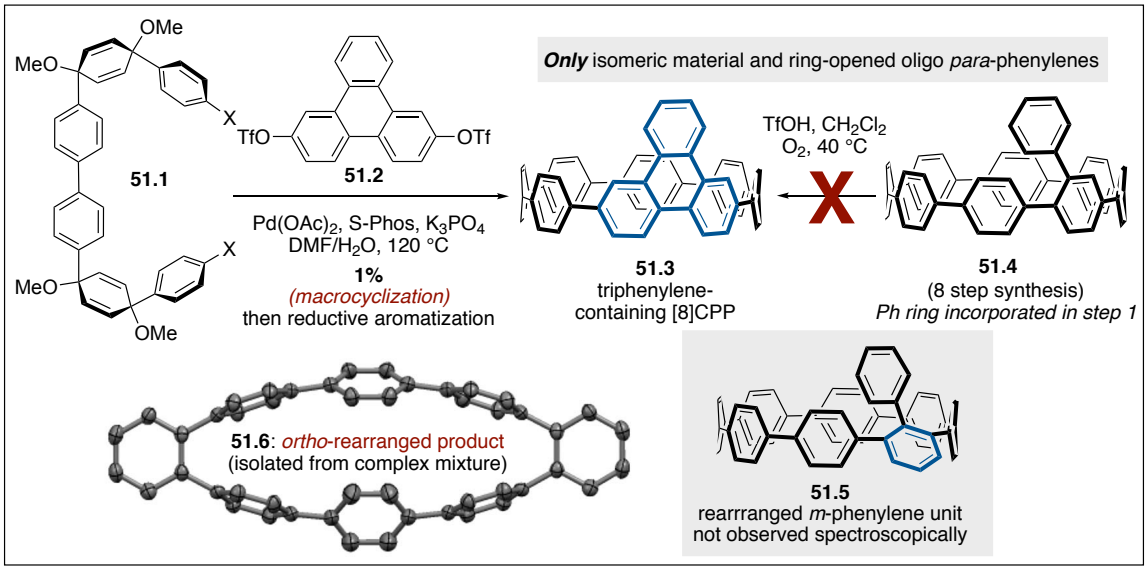
standard cyclodehydrogenation conditions the desired HBC-incorporated [21]CPP derivative **50.4** was formed in 80% yield. The supporting information of the paper provides a ^{1}H NMR spectrum for **50.4**, and the reported yield is calculated from a reaction run on 2 mg of **50.2**.



SCHEME 50: Syntehsis of HBC-incorporated [21]CPP drivative **50.4** using the Scholl reaction

3.2.2.2 Jasti and co-workers attempted synthesis a triphenylene incorporated [8]CPP derivative using the Scholl reaction

In 2016 Jasti and co-workers reported their investigations on the Scholl reaction and its application to annulative pi-extension of a monophenylated [8]CPP derivative **51.4** (Scheme 51).[37] After synthesizing triphenylene-containing nanohoop **51.3** (separately) using bis-triflate **51.2** and **51.1** as key building blocks, [8]CPP derivative **51.4** was subjected to a Scholl reaction using a slight modification of Rathore's conditions.[34] Under these conditions, which circumvent halogenation of the arene units, the desired cyclodehydrogenation to afford **51.3** does not occur. This was confirmed by ^{1}H NMR spectroscopy as an authentic sample off **51.3** was available for comparison. The absence of signature triphenylene signals in the ^{1}H NMR led Jasti and co-workers to conclude that a mixture of rearranged macrocycles containing both *meta* and *ortho*-phenylene-bridging units, as well as ring-opened oligophenylenes were the major by-products of this reaction. No definitive spectroscopic evidence for the formation for a *para* to *meta*-phenylene rearrangement was provided in their study; however, mass spectrometry did indicate that isomeric material to that of **51.5** was obtained. The isolation of a symmetrical macrocycle **51.6** that had undergone dephenylation at the periphery of the macrocycle and to *para* to *ortho*-phenylene bridge migrations supported their hypotheses.



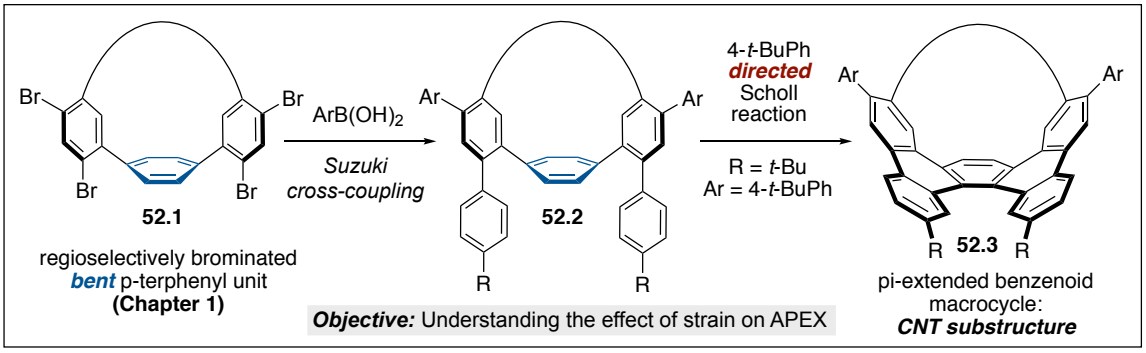
SCHEME 51: Jasti and co-workers attempted synthesis of **51.3** using a Scholl reaction

3.3 Annulative pi-extension of a homologous series of benzenoid macrocycles using the Scholl reaction

One of the key advantages of the non-cross-coupling-based approach to *para*-phenylene-bridged macrocycles described in Chapters 1 and 2, and the mild dehydrative aromatization reaction discussed in Chapter 2, was the possibility of regioselectively functionalizing the bent *p*-terphenyl core of these macrocycles, or directly installing halide or pseudo-halide groups at strategic locations to facilitate late-stage arylation reactions. The synthesis of a homologous series of *p*-terphenyl-containing macrocycles has already been discussed (Chapter 2) and the regioselective bromination of one homolog has been achieved (Chapter 1). In the remaining sections of this chapter the synthesis of selectively mono-, di- and tetraarylated, strained benzenoid macrocycles and the exploration of annulative pi-extension methods that lead to the conversion of bent benzene units to bent PAH units will be discussed.

The main objective of this work is to correlate SE with the success or failure of the desired annulation reaction. In the examples discussed above from the Müllen and Jasti groups,[37] only one or two [*n*]CPPs were subjected to Scholl reactions. This is due to limited synthetic methods for the late-stage functionalization of [*n*]CPPs, which necessitates a multistep synthesis for each [*n*]CPP derivative to be investigated. The later is an onerous task and has limited our understanding of annulation reactions about strained *para*-phenylene rings. The selective, late-stage bromination of a strained *p*-terphenyl-containing macrocycle that was described in Chapter 1 (*eg.*, **49.1**, Scheme 49) will allow us to investigate annulation reactions with numerous nucleophilic arene units onto *para*-phenylene rings for which the bend or SE can be controlled by the length of the alkyl bridging unit within the macrocycle (*eg.*, **52.2** Scheme 52). These studies will enhance our understanding of reaction mechanisms that lead to (possible) rearrangement or

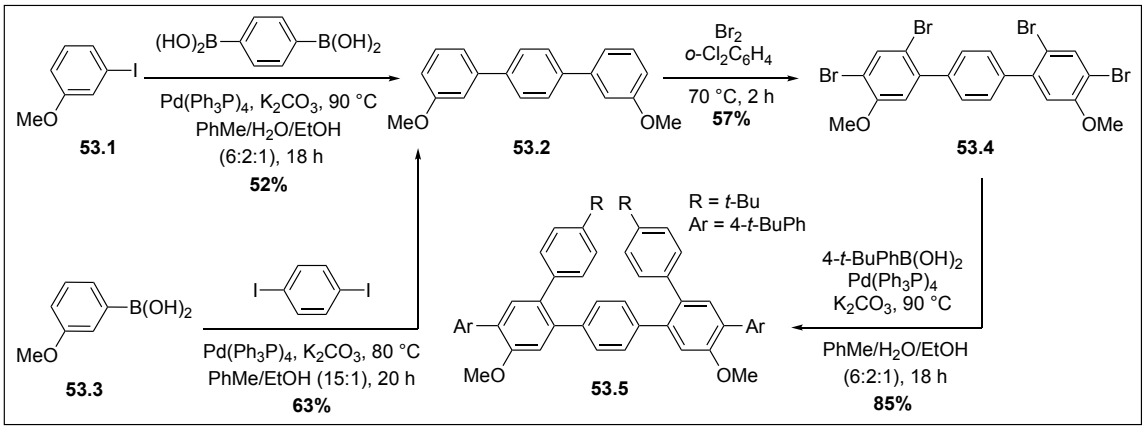
fragmentation reactions en route to pi-extended macrocycles such as **52.3**. The latter will provide the basis of future synthetic method development, if necessary, and guide reaction optimization.



SCHEME 52: Overview of APEX investigation on bent *p*-terphenyl-containing macrocycles

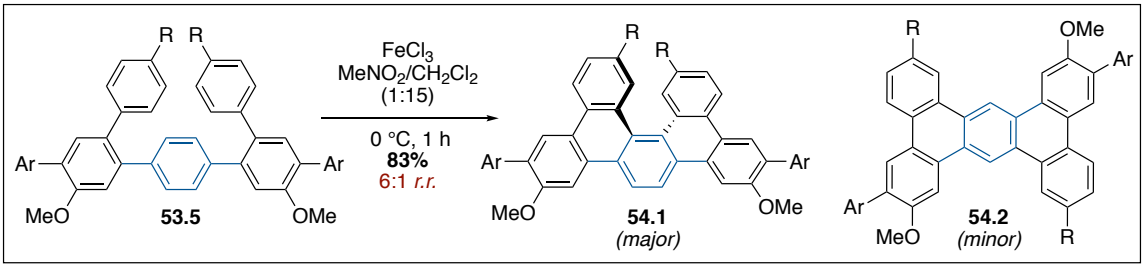
3.3.1 Synthesis of a Model p-terphenyl for the Scholl Reaction

The unexpected propensity for sterically hindered cyclization reactions to take place under Scholl reactions (*cisoid* mode of cyclization, Scheme 48) of substituted *p*-terphenyls, was encouraging for the planned APEX study (see Scheme 52). Both Müllen and Durola had shown that the major products of these reactions were dibenzopicenes, or [5]helicenes, and not the intended tetrabenzoanthracene derivatives (see Scheme 48). This “unexpected” regiochemical outcome is in fact the desired regiochemical outcome of the proposed Scholl reaction-based APEX study. To understand whether or not electronics (alkoxy substituents of on the *p*-terphenyl) has an effect on the mode of cyclization or regiochemical outcome of these reactions, a planar model (*p*-terphenyl) compound **53.5** was synthesized (Scheme 53). 3,3"-Dimethoxy-*p*-terphenyl (**53.5**) was synthesized using two Suzuki cross-coupling-based approaches. The first involved a reaction of 3-iodoanisole (**53.1**) with 1,4-benzenediboronic acid to give **53.2** in 52% yield. Simply switching the cross-coupling partners to 3-methoxyphenylboronic acid (**53.3**) and 1,4-diiodobenzene, with slightly modified reaction conditions, afforded **53.2** in 63% yield (Scheme 53). Treatment of **53.2** with an excess (6-8 equivalents) of bromine in *ortho*-dichlorobenzene at 70 ºC for 2 h, afforded tetrabromo-*p*-terphenyl **53.4** in 57% yield. The tetrabromide was converted to 4,4",6,6"-tetrakis(4-*tert*-butylphenyl)-3,3"-dimethoxy-*p*-terphenyl (**53.5**) in 85% yields using a Suzuki cross-coupling reaction with 4-*tert*-butylphenylboronic acid.



SCHEME 53: Synthesis of model *p*-terphenyl **53.5**

Following a procedure described by Durola and co-workers, $FeCl_3$ (10 equivalents) in nitromethane/dichloromethane (1:15) at 0 °C, the model *p*-terphenyl **53.5** underwent cyclodehydrogenation to afford [5]helicene **54.1** as the major product in 83% yield (Scheme 54). The *transoid* cyclization product **54.2** was produced in only 7% yield. Direct analysis of the crude reaction mixture indicated that the regioselectivity (*r.r.*) of this reaction was 6:1.[45] 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 course of this reaction, and that no 1,2-aryl migrations can be attributed to electronic factors.

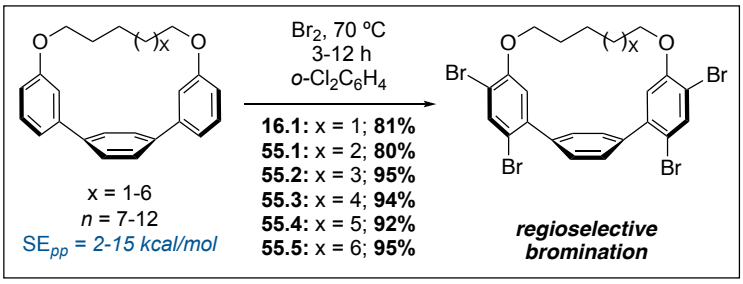


SCHEME 54: Model Scholl reaction of *p*-terphenyl **54.5**

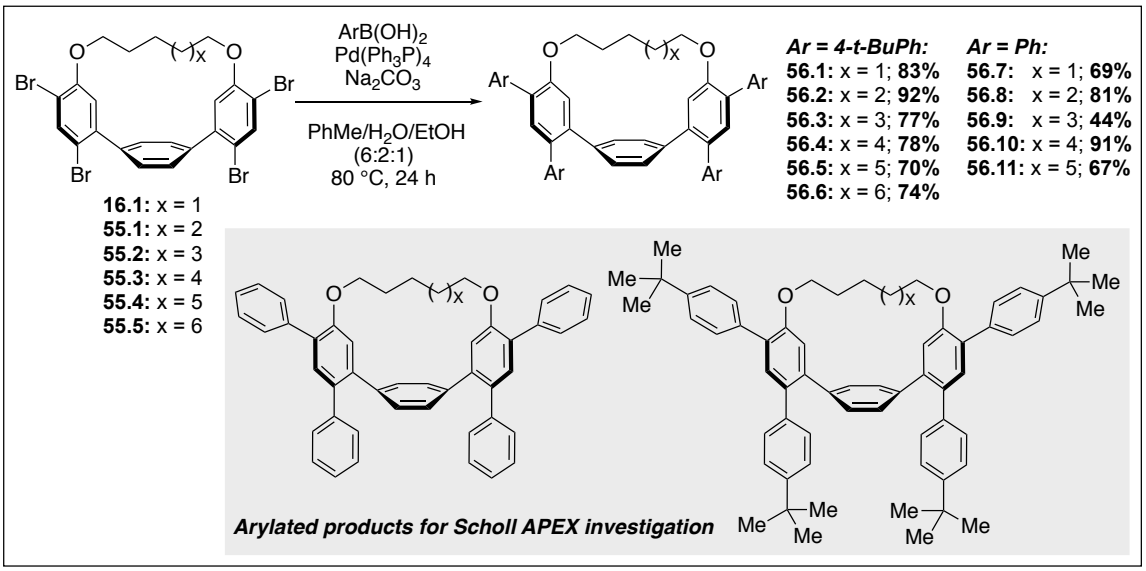
3.3.2 Synthesis of arylated, strained p-terphenyl-containing macrocycles

In Chapter 2, a regioselective bromination of 1,7-dioxa[7](3,3")*p*-terphenylophane to afford tetrabromide **16.1** was presented (see Scheme 16). This bent, *p*-terphenyl-containing macrocycle has 30 kcal/mol of SE, with 15 kcal/mol of SE localized on the central *para*-phenylene (SE_{pp}) ring. Upon completing the synthesis of a homologous series of *p*-terphenyl-containing macrocycles (Chapter 2) six homologs were subjected to identical bromination conditions (*n* = 7-12, see Appendix 3 for synthetic details). Once again, this reaction proved to be completely regioselective, furnishing only tetrabromides **55.1**-**55.5** in 80-95% yield (Scheme 55) with no strain-relief bromination of the central *para*-phenylene rings. With these brominated derivatives in hand, arylation using a Suzuki cross-coupling reaction with 4-*tert*-butylphenylboronic acid and

phenylboronic acid was pursued. Under standard cross-coupling conditions ($Pd(PPh_3)_4$, Na_2CO_3, $PhMe/H_2O/C_2H_5OH$ (6:2:1) at 80 °C), previously reported by Müllen and Durola, the four-fold arylation reactions of bromides **16.1** and **55.1**-**55.5** proceeded in moderate to high yields (Scheme 56). The only exception to this was homolog **55.2**, which gave **56.9** in 44% yield (arylation with $PhB(OH)_2$). It should be noted that these Suzuki reactions involve four C-C bond formations and even in the case of **56.9** the average yield per C-C bond formed equates to 82% per cross-coupling event. Furthermore, increased reaction times, up to 24 hours, resulted in higher yields. The choice to investigate 4-*tert*-butylphenyl and just phenyl substitution initially was based on the success of the former in giving the desired regiochemical outcome under Scholl reaction conditions and the possibility of further cyclodehydrogenation taking place across the fjord region of the anticipated dibenzopicene derivative, in the case of the latter.



SCHEME 55: Bromination of strained *p*-terphenyl macrocycles



SCHEME 56: Synthesis of arylated *p*-terphenyl macrocycles for Scholl APEX investigation

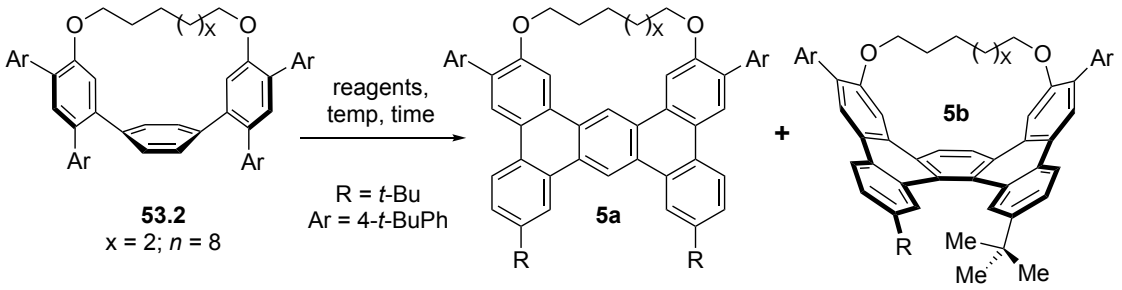
3.3.3 Optimal Scholl reaction conditions of strained p-terphenyl-containing macrocycles

With a series of arylated homologs in hand, focus was placed on finding Scholl reaction conditions that would not see, initial, rearrangement of the *para*-phenylene bridge to a *meta*-phenylene bridged macrocycle. In Chapter 2, a thorough investigation of this strain-relief driven process was described (section 2.3.5), as it applies to dehydrative aromatization of macrocyclic cyclohex-2-

ene-1,4-diols. It was demonstrated that only *para*-phenylene bridged macrocycles containing greater than 20 kcal/mol of SE in the central arene (SE_{pp}) unit succumbed to a protic acid-mediated 1,2-aryl shit in the presence of TsOH. Numerous reaction protocols that facilitate (Scholl-type) cyclodehydrogenation have been reported in recent years. The majority of these involve protic or Lewis acid-mediated reactions, that can be viewed as somewhat harsh or strongly acidic. With this in mind and the knowledge that *p*-terphenyl macrocycle **25.8** (*n* = 8) does not undergo rearrangement at elevated temperatures (up to 80 °C) in the presence of TsOH, initial screening of optimal Scholl reaction conditions were pursued using this homolog.

Under the assumption that a cationic reaction mechanism is operative, the initial intermediate in the Scholl reaction involves arene protonation or coordination of the arene with the Lewis acid. Carbon-carbon bond formation can then take place via a Friedel-Crafts-type reaction to furnish a new a polycyclic intermediate. It is at this stage that (notorious) 1,2-aryl shifts can also take place. Treatment of **56.2** with protic acids (TsOH, entry 1; MsOH, entry 2, Table 5) gave only recovered starting material. An attempt to facilitate direct 6π electrocyclization in the presence of DDQ, also resulted in no conversion of the starting material (entry 3, Table 5). Using the Rathore conditions, MsOH and DDQ in dichloromethane, led to decomposition of the starting material (entry 4). Switching the acid source to TsOH in the presences of DDQ at 60 °C gave only recovery of starting material (entry 5, Table 5). Using identical reaction conditions to those of Jasti and co-workers in their Scholl reaction of [8]CPP derivative **51.4** (Scheme 51) did not result in conversion of the starting material (entries 6 and 7, Table 5). It is surprising that no rearrangement takes place under these conditions, as the *para*-pheneylne under investigation has the same SE as that of the monomer units of **51.4** (SE_{pp} = 9 kcal/mol). However, the macrocyclic system of **51.4** is considerably more strained that of **56.2** (*cf*. 73 kcal/mol to 25 kcal/mol). Switching to Lewis acid-mediated Scholl reaction conditions to $AlCl_3$ (entry 8, Table 5), saw no conversion of **56.2** subjected; however, using the conditions reported by Müllen and Durola, iron(III) chloride in nitromethane/dichlormethane (1:15), did result in the clean conversion of **56.2** to a new PAH-containing macrocycle (entry 10, Table 5). After careful analysis of the ^{1}H NMR spectrum, and comparison to the products obtained from the model study (Scheme 54), it was determined that the new PAH formed was that of **5a** and not the desired PAH **5b**. While the formation of **5a** was not the desired result, we were encouraged by how quickly this product (cleanly) formed under these reaction conditions, and were optimistic that more suitable reaction conditions could be found to facilitate the formation of **5b**. It should be noted that the isolation of **5a** and subsequent characterization by ^{1}H and ^{13}C NMR is, to the best of our knowledge, the first example were a backbone rearrangement product has been isolated cleanly upon attempted annulation onto a strained macrocyclic system.

TABLE 5: Intitial screening of the Scholl reaction with **60.2** (SE_{pp} = 9 kcal/mol)



entry	reagents	equiv.	solvents	time (h)	temp (ºC)	**53.2**[a]	**5a**[a]	**5b**[a]
1	TsOH	8.0	PhMe	14	60	100	0	0
2	MsOH	20.0	CH_2Cl_2	0.5	0-23	100	0	0
3	DDQ	5.0	CH_2Cl_2	16	23	100	0	0
4[b]	MsOH/DDQ	excess/3.0	CH_2Cl_2	0.2	0	0	0	0
5	TsOH/DDQ	5.0/5.0	PhMe	16	60	100	0	0
6	TfOH	4.0	CH_2Cl_2	16	0-23	100	0	0
7	$TfOH/O_2$	5.0	CH_2Cl_2	16	0-23	100	0	0
8	$AlCl_3$	15.0	$CH_2Cl_2/MeNO_2$	15	23-40	100	0	0
9[c]	$FeCl_3$	20.0	CH_2Cl_2	0.5	-20	0	80	0
10	$FeCl_3$	20.0	$CH_2Cl_2/MeNO_2$	0.2	0	0	100	0

[a] Ratio determined from ^1H NMR analysis; [b] (19:1) CH_2Cl_2/MsOH solution was used; [c] 20% of and unidentified by-product was observed.

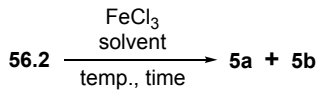
3.3.4 Optimization of the Scholl reaction conditions for APEX of 56.2

4,4",6,6"-Tetrakis(4-*tert*-butylphenyl)-1,8-dioxa[8](3,3")*p*-terphenylenophane (**56.2**) was subjected to an iron(III) chloride-mediated Scholl reaction where the amount of Lewis acid employed, solvent, temperature and reaction time was modified (Table 6). It was hoped that manipulation of these parameters could facilitate the desired cyclodehydrogenation reaction and formation of the desired PAH-containing macrocycle **5b**.

Using the same experimental parameters that had afforded **5a** in near quantitative yield (entry 10, Table 5), the temperature of this reaction was lowered to –78 °C in an attempt to attenuate the rearrangement. This resulted in 0% conversion of the starting material after 2 hours (entry 1, Table 6). Increasing the amount of iron(III) chloride from 20.0 to 40.0 equivalents saw no conversion in the starting material, however, slowly increasing the temperature from –78 to –40 °C resulted in the isolation of **5a** as the sole product of this reaction (entry 2, Table 6). Reducing the amount Lewis acid employed to 10.0 equivalents, shortening the reaction time to 1 hour, and increasing the temperature to 0 °C afforded a 2:1 ratio of **5a** to **56.2** (entry 3, Table 6). When 20.0 equivalents of iron(III) chloride were employed at 0 or 23 °C (entries 4 and 5, respectively, Table 6) complete consumption of **56.2** takes place in less than 15 minutes, to furnish **5a** in 95%

and 83% yield, respectively. Running experiments with fewer equivalents of iron(III) chloride at 0 °C, did not result in complete conversion of the starting material (entries 6 and 7, Table 6). Switching dichloromethane for 1,2-dichloroethane (DCE) required the use of 8.0 equivalents of $FeCl_3$ (entry 8, Table 6) and adding solid potassium carbonate to this reaction, to remove HCl produced during the course of the reaction, did not change the result (entry 9, Table 9). Using a more polar solvent, THF, or combination of THF and dichloromethane resulted in in only recovered starting material (entries 11 and 12, Table 6). These data suggest that the optimal conditions for running future Scholl reactions on more and less strained macrocyclic systems will require between 8.0-20.0 equivalents of iron(III) chloride, reaction times of less than 1 hour and holding the temperature of these reactions at 0 °C.

TABLE 6: Optimization of $FeCl_3$ Scholl reaction of **56.2**



entry	$FeCl_3$ (equiv.)	solvents	time (h)	temp (°C)	**53.2**[a]	**5a**
1	20.0	$CH_2Cl_2/MeNO_2$	2	-78	100	0
2	40.0	$CH_2Cl_2/MeNO_2$	2	-40	0	100
3	10.0	$CH_2Cl_2/MeNO_2$	1	0	33	66
4	20.0	$CH_2Cl_2/MeNO_2$	0.2	0	0	100 (95)
5	20.0	$CH_2Cl_2/MeNO_2$	0.2	23	0	100 (83)
6	2.8	$CH_2Cl_2/MeNO_2$	0.3	0	20	80
7	1.2	$CH_2Cl_2/MeNO_2$	0.5	0	40	60
8	8.0	$DCE/MeNO_2$	1	0	0	100 (85)
9[b]	8.0	$DCE/MeNO_2$	1	0	0	100 (88)
10	2.5	$CH_2Cl_2/MeNO_2$	0.2	0	50	50
11	5.0	CH_2Cl_2/THF	2	0-23	100	0
12	5.0	THF	2	0-23	100	0

a. Ratio was measured by ^1H NMR analysis; ***b.*** 8.0 equiv. of K_2CO_3 was added. Yields in parentheses are isolated yields.

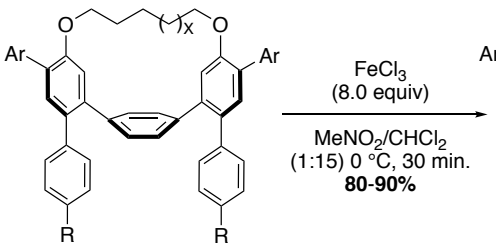
3.3.5 Scholl reactions of strained p-terphenyl macrocycles (n = 7-12)

The six arylated homologs **56.1**-**56.6** synthesized above (Scheme 56) were subjected to a Scholl reaction using 8.0 equivalents of iron(III) chloride in nitromethane/dichloromethane (1:15) at 0 °C. All of these reactions were carried out on a 20-25 mg scale, and to ensure that an accurate amount of $FeCl_3$ was delivered in each experiment, a freshly prepared stock solution of this reagent was used each and every time a set of experiments was conducted. Preparation of this stock solution involved suspending $FeCl_3$ in dichloromethane and then adding nitromethane until all of the Lewis acid had dissolved. This afforded a bright yellow solution that was cooled to 0 °C and stored under argon. Macrocycles **56.1**-**56.6** were dissolved in dichloromethane (5 mM) and cooled to 0 °C. Upon addition of $FeCl_3$ to the macrocycles investigated, a deep green color forms, which is indicative of the formation of a charge transfer complex. It is noteworthy to mention that this color is immediately bleached upon treatment of these reactions with methanol in open air.

After the precise experimental conditions for these reactions had been delineated, all six macrocycles were subjected to identical reaction conditions (see scheme in Table 7). It was not surprising to find that the most strained homolog investigated, **56.1**, afforded the rearranged PAH-

containing macrocycle **5a** (x = 1, *n* = 7; entry 1, Table 7). However, no subsequent rearrangement to an *ortho*-phenylene-bridged intermediate occurs (recall the only product characterized in the Jasti investigation of the School reaction, Scheme 48). The strain energy of the central *para*-phenylene unit of **56.1** is considerably higher than that of **56.2** at 14.8 kcal/mol. Moving to a macrocyclic homolog (**56.3**) containing a less strained *para*-phenylene unit than that of **56.2** (SE_{pp} = 8.4 kcal/mol) produced the same result – **5a** (x = 3, *n* = 9) was isolated as the sole product of this reaction (entry 3, Table 7). Subjecting **56.4** to these Scholl reaction conditions produced a 60:40 mixture (entry 4, Table 7) of two different PAH-containing macrocycles, which were separated using preparative thin layer chromatography. To our delight, the minor component of this reaction was the desired annulation product **5b** (x = 4, *n* = 10), while the major component was that of **5a** (x = 4, *n* = 10). Reacting the remaining macrocyclic homologs, **53.5** (SE_{pp} = 3.8 kcal/mol) and **53.6** (SE_{pp} = 1.9 kcal/mol) with FeCl3 under these conditions produced **5b**, the (desired) product of *cisoid* cyclization, and **7a**, the product of *transoid* cyclization (see **54.2**, Scheme 54), in a 9:1 ratio (entries 5 and 6, Table 7).

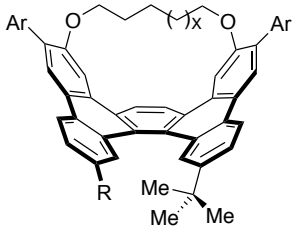
TABLE 7: Scholl reactions of strained *p*-terphenyl macrocyles (*n* = 7-12)



5a
single regioisomer isolated *n* = 7-9
not isolated for *n* = 11-12

entry	x (*n*)	SE*pp* (kcal/mol)	5a[a]	5b	7a[b]
1	1 (7)	14.8	100	100	0
2	2 (8)	9.2	100	100	0
3	3 (9)	8.4	100	100	0
4	4 (10)	6.7	60	40	0
5	5 (11)	3.8	0	90	10
6	6 (12)	1.9	0	90	10

[a] product ratios were determined by ^{1}H NMR;
[b] **7a** is the macrocyclic version of **51.2**
SEs computed at the DFT B3LYP 6-31G level*



5b
isolated for *n* = 10-12
major product *n* = 11-12

The results of these investigations on the Scholl reaction as a method for annulative pi-extension of strained benzenoid macrocycles into strained PAH-containing macrocycles, suggests that appropriately arylated macrocyclic systems containing *para*-phenylene units with less than 4 kcal/mol of SE should succumb to regioselective cyclodehydrogenation. In the case of macrocyclic systems containing *para*-phenylene units with more than 7 kcal/mole of SE, rearrangement reactions should be anticipated. For macrocyclic benzenoid systems containing *para*-phenylene units with 7-4 kcal/mol of SE, a mixture of products may be produced; however, the desired *cisoid* mode of cyclization is possible at this degree of SE.

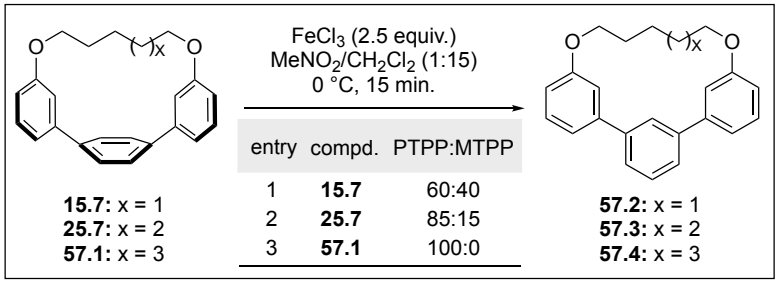
Compared to previous investigations of the Scholl reaction and its use in APEX of [*n*]CPPs, our results provide a better set of guidelines for those considering the synthesis of arylated [*n*]CPP derivatives. For instance, [*n*]CPPs with less than 4 kcal/mol of SE per *para*-

phenylene (SE_{pp}) are those with n >12. Those with SE_{pp} between 4-7 kcal/mol may be subject to rearrangement reactions, and these include [10] and [11]CPP. To the best of our knowledge, arylated derivatives of [10] and [11]CPP have not been reported and subjected to a Scholl reaction-based annulation protocol.

3.3.6 Understanding the reaction mechanism that leads to the formation of rearranged PAH-containing macrocycles 5a (n = 7, 8, and 9)

The clean conversion of **56.1**, **56.2**, and **56.3** to rearranged PAH-containing macrocycle **5a** (n = 7, 8 and 9, respectively), and the absence of any partially cyclized intermediates or further (*ortho*) rearrangement products, led us to conduct a time course ^{1}H NMR experiment of the Scholl reaction on these systems. It was hoped that these studies would provide insight on the mechanism of this rearrangement reaction. The first question that we sought to address was, does a *para* to *meta*-phenylene rearrangement precede cyclization onto the central arene unit? To better understand this, we designed experimental conditions that would result in only partial conversion of the arylated macrocycles **56.1**, **56.2**, and **56.3** to the rearranged PAH **5a**. During the screening process to find suitable Scholl reaction conditions for **56.2** (Tables 5 and 6), it was discovered that 4.0-5.0 equivalents of iron(III) chloride was required per C-C bond formation. Thus, in an attempt to intercept partially cyclized or *meta*-phenylene intermediates that had not undergone complete annulation, we selected the following reaction conditions: 2.5 equivalents of $FeCl_3$, $MeNO_2/CH_2Cl_2$ (1:15), 0 °C, 15 minutes. Furthermore, to probe the extent of a *para* to *meta*-phenylene rearrangement under these conditions, unsubstituted *p*-terphenyl-containing macrocycles, **15.7**, **25.7** and **57.1**, would be subjected to the same reaction conditions. The rationale here is that the central *para*-phenylene units of these compounds is equally strained to that of the arylated derivatives **56.1**, **56.2**, and **563.3**.

Once again our investigations began with **25.7** and **56.2**. Subjecting **25.7** to the conditions described above, resulted in only partial isomerization to the *meta*-phenylene bridged macrocycle **57.3**. The ratio of **25.7** to **57.3** was determined to be 85:15 (*para*:*meta*) based on analysis of the (crude) ^{1}H NMR spectrum of the mixture of compounds afforded (entry 2, Scheme 57 and Figure 13). Subjecting **56.2** to the identical reaction conditions afforded a 60:40 mixture of the rearranged and completely annulated product **5a** (x = 2, n = 8) and unreacted starting material (entry 2, Scheme 58).



SCHEME 57: Extent of *para* to *meta*-phenylene rearrangment

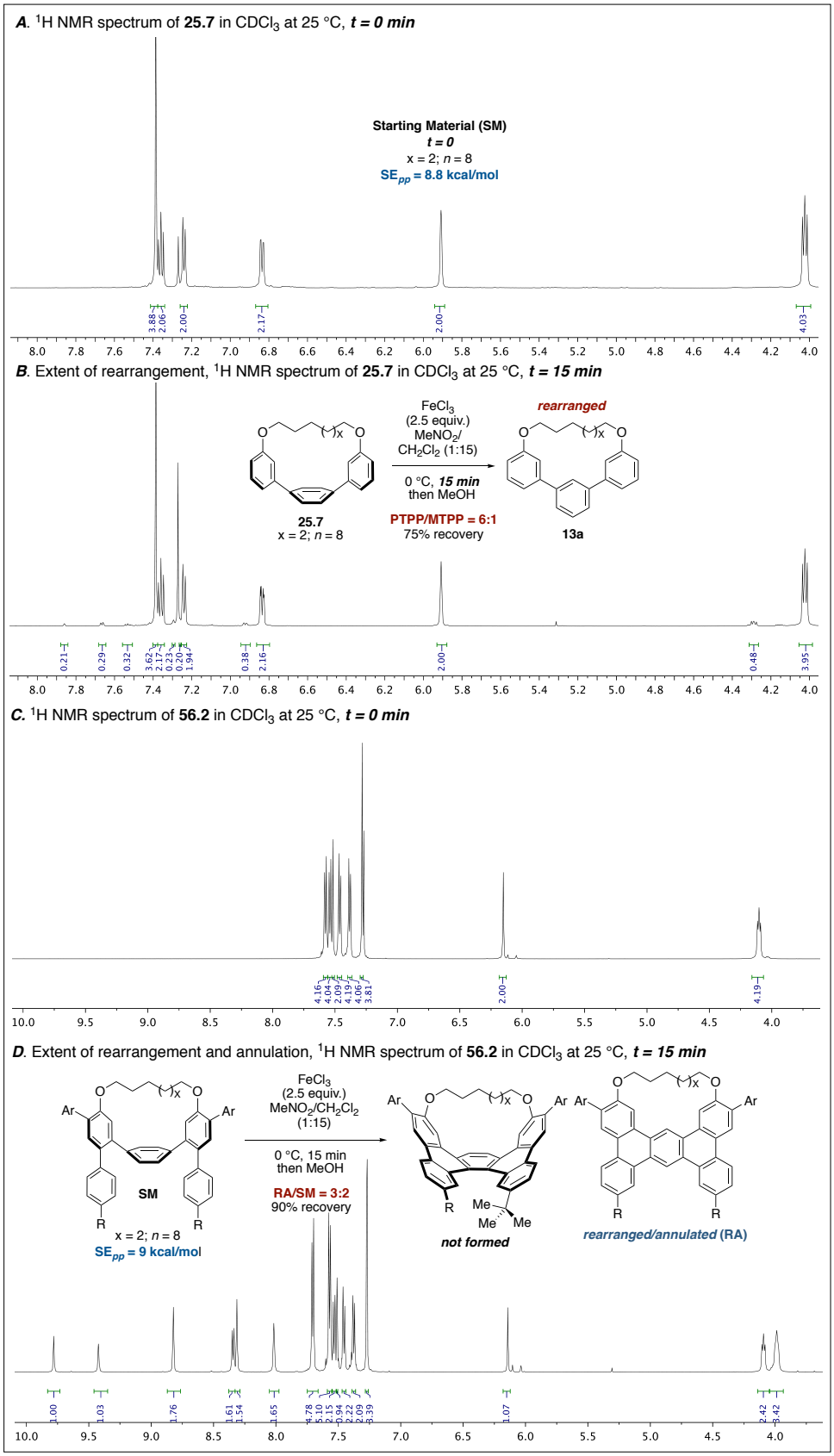
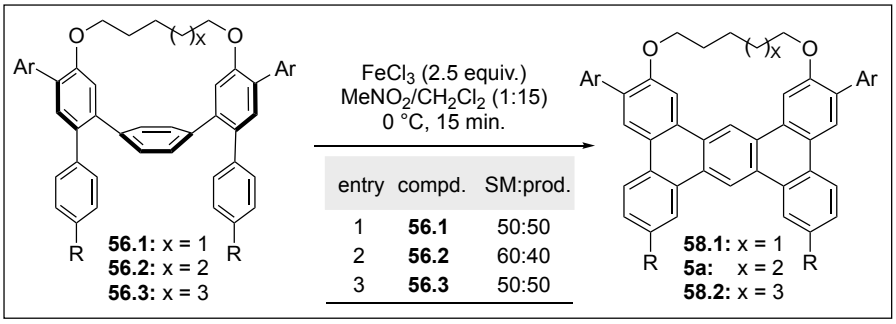


FIGURE 13: Time course ^{1}H NMR analysis of $FeCl_3$-mediated rearrangment reactions of **25.7** and **6.2**

^{1}H NMR analysis of the crude reaction mixture revealed that no partially annulated, partially annulated /rearranged, or related intermediates are formed under these conditions. The reaming macrocycles, **15.7** and **57.1** were subjected to the same Scholl reactions conditions to monitor the extent of *para* to *meta*-phenylene rearrangement of the central arene unit. Not surprisingly, the more strained macrocycle **15.7** (SE_{pp} = 14.7 kcal/mol) produced more of the rearranged macrocycle **57.2** (entry 1, Scheme 57); however, no rearrangement was observed for the less strained macrocycle **57.1** (SE_{pp} = 8.4 kcal/mol; entry 3, Scheme 57). Interestingly, when the arylated derivatives of both of these macrocycles, **56.1** and **56.3**, were subjected to the controlled Scholl reaction conditions, a 50:50 ratio of unreacted starting material (SM) and rearranged products **58.1** and **58.2** was observed. These data seem to suggest that initial rearrangement to of the *para*-phenylene bridge to a *meta*-phenylene bridging units followed by annulation onto the central *meta*-phenylene unit, is not the reaction mechanism (or pathway) that leads to the formation of the rearranged isomer. To probe this transformation further, a computational study using the most strained homolog was pursued.

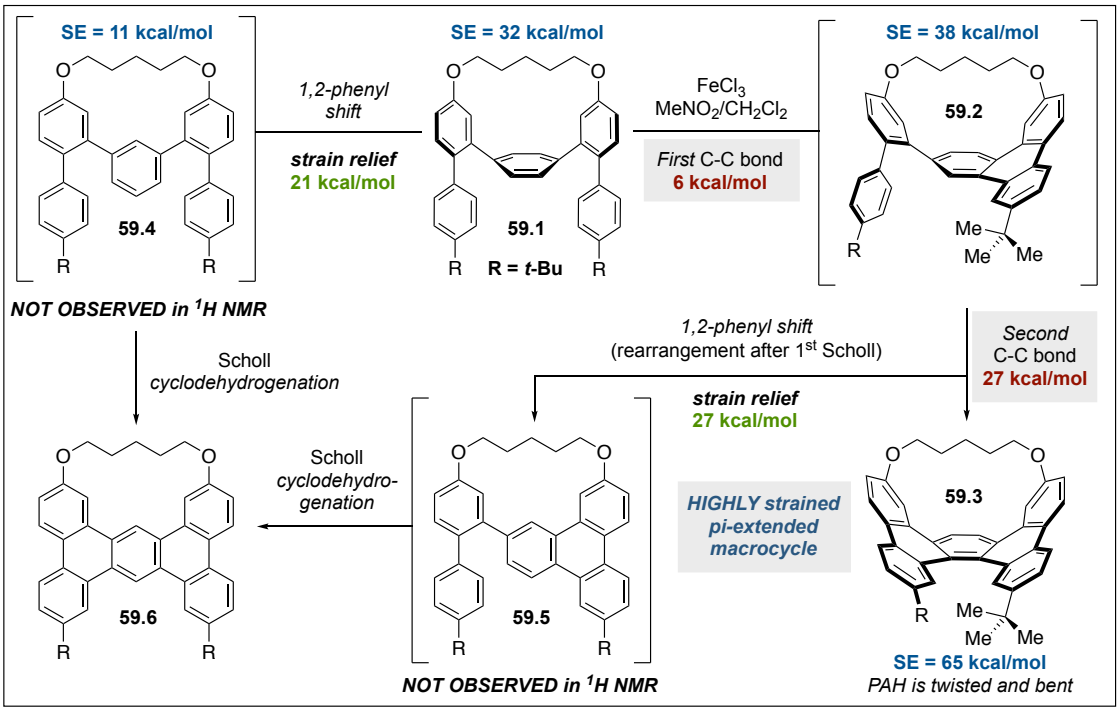


SCHEME 58: Extent of rearrangment/annulation in **58.1**, **5a**, **58.3**

3.3.7 A computational investigation of the origin of rearrangement in the Scholl reaction of a truncated analog of 56.1

Optimized geometries of proposed intermediates that could lead to the formation of the rearranged PAH **5b** (x = 1; *n* = 7) were computed using DFT calculations at the B3LYP level of theory using the 6-31G* basis set. To simplify these calculations, the 4-*tert*-butylphenyl groups at the 6 and 6"-positions, which do not participate in the Scholl reaction, were removed. Macrocycle **59.1**, a truncated analog of **56.1**, contains 32 kcal/mol of SE. A single cyclization/annulation reaction of **59.1** to afford **59.2** introduces an additional 6 kcal/mol of SE into the macrocyclic structure (Scheme 59). 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, the introduction of this amount of SE may be within reach of the Scholl reaction. However, a second annulation reaction to furnish the desired PAH **59.3** requires the introduction of an additional 27 kcal/mol, which is apparently prohibitive for this homolog. A 1,2-phenyl shift from **59.1** to the **59.4**, *i.e.*, *para* to *meta*-phenylene rearrangement would relieve 21 kcal/mol of SE, while a 1,2-phenyl shift from **59.2** to **59.5** would relieve approximately 27 kcal/mol of SE. Due to the absence of **59.4** from the ^{1}H NMR time course experiments and subsequent analysis

described above, we propose that a 1,2-phenyl shift from **59.2** is likely the preferred pathway for this reaction. Furthermore, the fact that *para* to *meta*-phenylene rearrangement does not proceed to the same extent as the formation of macrocycles akin to **59.6** for unsubstituted macrocycles such as **15.7** and **25.7** (Scheme 57) and not at all for **57.1**, is suggestive that rearrangement takes place at the stage of the **59.2**. Despite numerous attempts to synthesize a macrocycle akin to **59.2**, using a monoarylated derivative of **59.1**, and to numerous efforts to isolate this intermediate during Scholl reactions, our mechanistic hypothesis remains somewhat speculative at this juncture. The highly strained structure of the PAH contained in **56.1** is shown in Figure 14.



SCHEME 59: Computationally derived SEs for C-C bond formations during the Scholl reaction of **59.1**

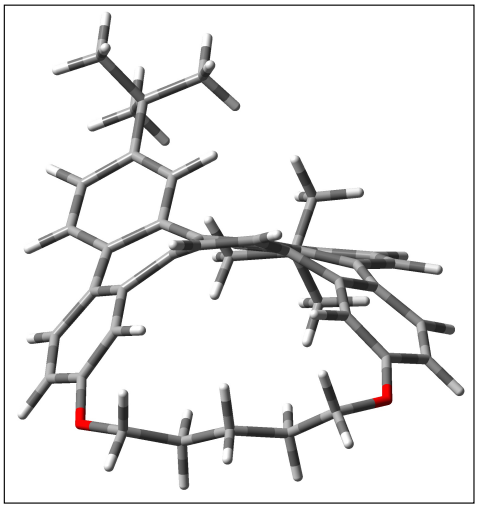
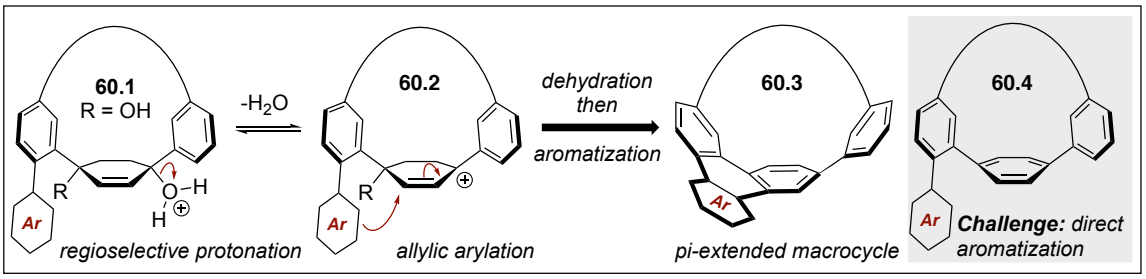


FIGURE 14: Optimized geometry of **59.3**

3.3 Allylic arylation via a Friedel-Crafts-based annulation reaction as a means for APEX

The Friedel-Crafts (FC) alkylation reaction is a versatile synthetic method for C-C bond formation of electron rich aromatic compounds. Despite some of the regiochemical problems that can arise during alkylation of simple aromatic substrates, this reaction remains a staple in chemical synthesis, 135 years after its initial discovery. While intermolecular reactions can be problematic, intramolecular reactions often proceed with high levels of regioselectivity. Friedel-Crafts alkylation reactions typically require powerful Lewis (or protic) acid conditions and stoichiometric amounts of these reagents to initiate the formation of cationic intermediates. This is typically not an issue for most aromatic substitution reactions, however for sensitive substrates, such as those that will be investigated here, mild,[46] and even catalytic,[47-48] reaction protocols have been developed.

The synthetic utility of dehydrative aromatization reactions was the subject of Chapter 2.[49] During these studies, it was discovered that protic acids, such as TsOH, were capable of furnishing moderate to highly strained *para*-phenylene-bridged macrocycles. The major limitation of the protic acid-mediated dehydrative aromatization was the propensity for highly strained arene-bridged systems to undergo rearrangement reactions at elevated temperatures. While this was a limitation of the method, it only occurred when the SE of the *para*-phenylene to be formed was greater than 20 kcal/mol and at temperatures above 60 °C. For less strained *para*-phenylene units, temperatures above 80 °C were necessary to facilitate a strain-relief driven 1,2-aryl migration (Section 2.3.5). As such, it was proposed that the introduction of a nucleophilic arene unit into the macrocyclic backbone of a cyclohex-2-ene-1,4-diol such as **60.1**, and selective activation of the less hindered alcohol group in in this macrocycle could facilitate an intramolecular Friedel-Crafts-type reaction (**60.1** to **60.2**, Scheme 60), which ultimately would lead to annulation and PAH formation after a subsequent dehydration and aromatization reaction (**60.2** to **60.3**). The designed strategy and C-C bond formation would amount to an allylic arylation of **60.1**. A major challenge facing this approach was competing dehydration/aromatization of **60.1** to give **60.1**, however, double dehydration and aromatization of macrocycles akin to **60.1** required heating these reactions above 50 °C. Furthermore, the potential steric hindrance imposed by the arene nucleophile could facilitate regioselective protonation followed by allylic arylation, hopefully, at lower temperatures.



SCHEME 60: Overview of APEX strategy via allylic arylation

3.4.1 Proposed Friedel-Crafts (FC) reaction on non-macrocyclic cyclohex-2-ene-1,4-diol: A planar model compound

In order to test the hypothesis of unhindered alcohol activation followed by nucleophilic attack of the resulting carbocation in a Friedel-Crafts-type reaction, a non-macrocyclic cyclohex-2-ene-1,4-diol (model) substrate **15a** (Figure 15) was synthesized. Retrosynthetically, one can think of numerous approaches to **15a**, however, the choice to proceed through a 1,4-diketone using chemistry developed in our laboratory was deemed to be the most logical starting point, even though it is not the most direct method for acyclic 1,4-diketone synthesis.

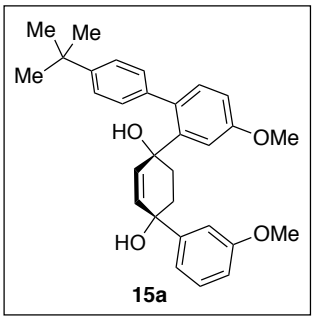
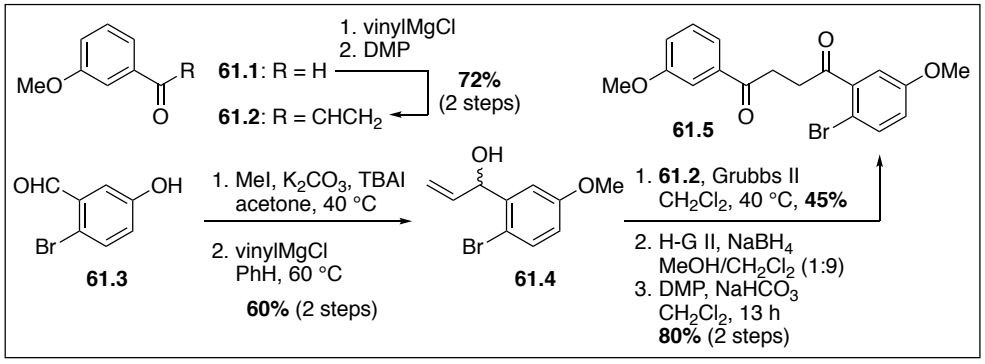


FIGURE 15: model compound

The synthesis of 1,4-diketone **61.5** called for the preparation of different olefin metathesis coupling partners. Thus, enone **61.2**, and allylic alcohol **61.4** were prepared. A Grignard reaction of commercially available *m*-anisaldehyde, followed by direct oxidation of the crude allylic alcohol furnished enone **61.2** in 72% overall yield (Scheme 58). Methylation of **61.3**, followed by treatment of the bromo-*m*-anisaldehyde derivative with vinylmagnesium chloride in benzene at 60 °C gave allylic alcohol **61.4** in 60% yield over 2 steps, which was subsequently subjected to a cross-metathesis reaction with **61.2** in the presence of Grubbs second-generation catalyst. The allylic diol, produced in 45% yield, was then converted to 1,4-diketone **61.5** in 80% yield over two steps, via transfer hydrogenation of the olefin and oxidation of the resulting saturated butane-1,4-diol.

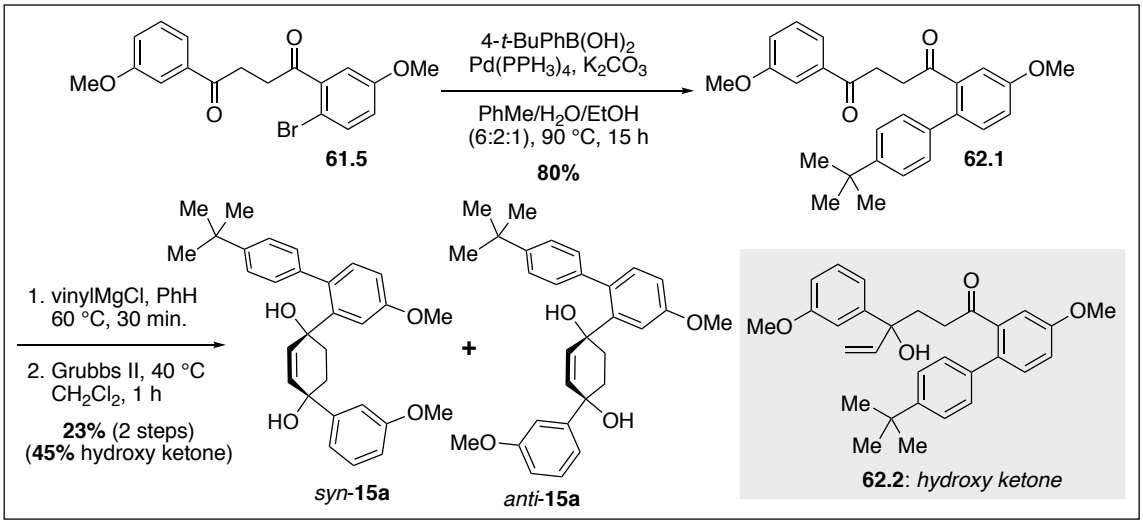


SCHEME 61: Syntheiss of 1,4-diketone **61.5**

With 1,4-diketone **61.5** in hand, completing the synthesis of model compound **15a** first required the installation of a nucleophilic arene unit. In general, cross-coupling reactions can be carried out at virtually any stage in synthetic sequence, however, in the case of tertiary carbinols such as **15a**, protection of the alcohol functional groups is typically required. Thus, bromoketone **61.5** was subjected to a Suzuki reaction with 4-*tert*-butylphenyl boronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) to afford arylated 1,4-diketone **62.1** in 80% yield (Scheme 62). Previous results from our laboratory indicated that Grignard reactions of sterically

hindered 1,4-diketones such as **62.1**, with vinylmagneiusm chloride, produce the desired bis-allylic-1,4-diols in highest yield, when benzene is used as the solvent. Typically, these conditions suppress the formation of a hydroxyketone by-product, which is believed to result from enolate formation, and not mono addition to the 1,4-diketone. Subjecting **62.1** to these conditions resulted in the formation of a 1:1 mixture of diastereomeric alcohols in 25% yield and 45% yield of hydroxyketone **62.2** as a single regioisomer. Re-subjecting **62.2** to a Grignard reaction with up to 6.0 equivalents of vinylmagnesium chloride did not result in the complete consumption of the starting material and afforded a 1:1 mixture of diastereomeric alcohols in 25% yield. A ring-closing metathesis reaction of the combined mixture of diols produced a separable mixture of *syn*-**15a** and *anti*-**15a** in 92% yield.

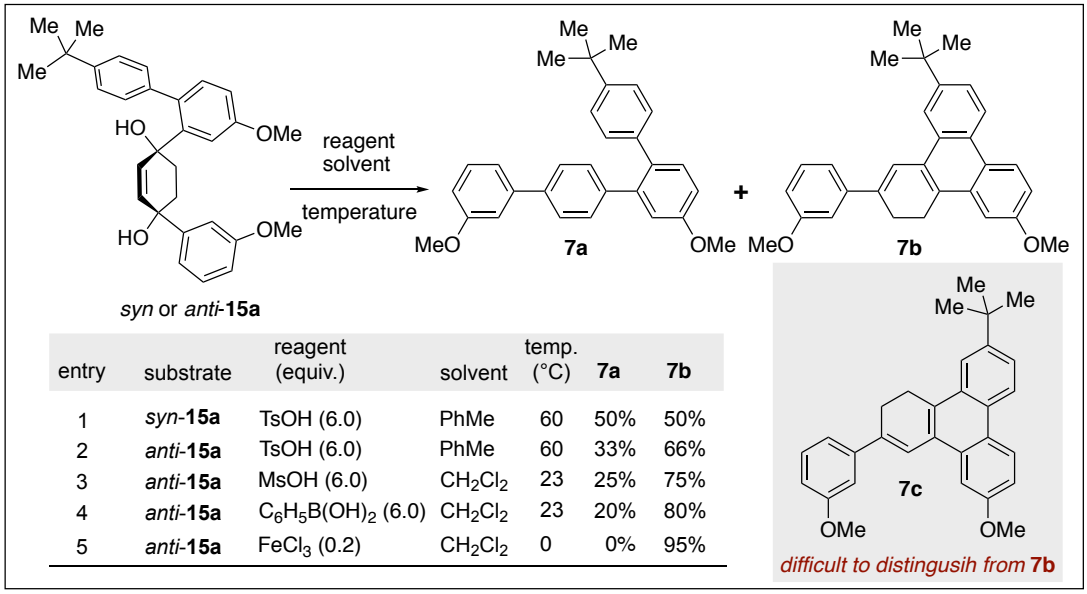
To test the initial hypothesis that regioselective protonation of the least hindered tertiary alcohol present in model compound (**15a**) should facilitate carbocation formation and subsequent nucleophilic attack by the 4-*tert*-butylphenyl group, *syn*-**15a** was subjected to TsOH in toluene. At room temperature, only starting material was observed by TLC analysis. As such, the reaction was heated slowly and once 50 °C was reached, two new products (R_f = 0.39 and 0.49, (1:9) EtOAc/hexanes) had formed with complete conversion of the starting material. By ^{1}H NMR analysis a 1:1 ratio (50% **7a** and 50% **7b**, entry 1, Table 7) of *p*-terphenyl **7a**, and what was presumed to be **7b**, the product of allylic arylation and subsequent dehydration. Subjecting the *anti*-**15a** to the same reaction conditions produced the same products, however, in a 1:2 (**7a**:**7b**, entry 2, Table 7) ratio.



SCHEME 62: Syntheiss of *syn*-**15a** and *anti*-**15a**

Encouraged by these results, reaction conditions that could facilitate allylic arylation or regioselective carbocation formation at lower temperatures were sought. Switching to a slighter weaker sulfonic acid in MsOH (*cf.*, *p*Ka (MsOH) = -1.9 to *p*Ka (TsOH) = -2.8) and changing the solvent to dichloromethane, brought about such a result. In this instance, a 1:3 ratio in favor of

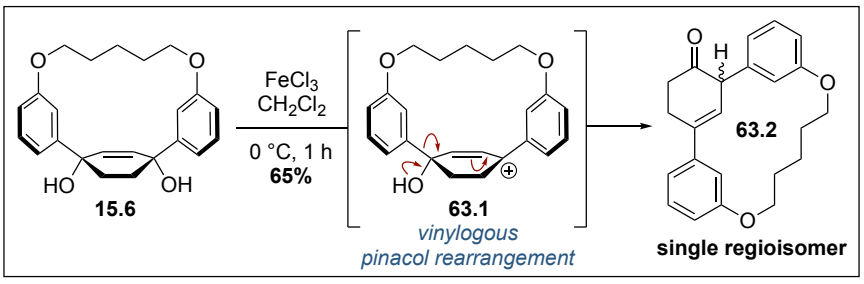
the desired cyclization product **7b** was afforded (entry 3, Table 7). Following conditions that had been disclosed by McCubbin and co-workers for the isomerization of allylic alcohols in the presence of pentafluorophenylboronic acid ($C_6F_5B(OH)_2$), we attempted to employ these in our allylic arylation studies of **15a**. Indeed, treatment of *anti*-**15a** with $C_6F_5B(OH)_2$ provided a slight increase in the formation of **7b** relative to that of the *p*-terphenyl **7a** (1:4, entry 4). At this juncture, it was unclear as to whether the allylic arylation product that had formed was the desired polycyclic system **7b** or a regioisomeric polycycle **7c**, a product that would form as a result of 1,2-aryl migration. Both of these compounds would be virtually indistinguishable by ^{1}H NMR analysis, without having an authentic of one of these two compounds. Thus, the attempted synthesis of **7c** was pursued based on a previous observation form our laboratory.



entry	substrate	reagent (equiv.)	solvent	temp. (°C)	7a	7b
1	*syn*-**15a**	TsOH (6.0)	PhMe	60	50%	50%
2	*anti*-**15a**	TsOH (6.0)	PhMe	60	33%	66%
3	*anti*-**15a**	MsOH (6.0)	CH_2Cl_2	23	25%	75%
4	*anti*-**15a**	$C_6H_5B(OH)_2$ (6.0)	CH_2Cl_2	23	20%	80%
5	*anti*-**15a**	$FeCl_3$ (0.2)	CH_2Cl_2	0	0%	95%

TABLE 8: Allylic arylation of *syn*-**15a** and *anti*-**15a**

During the investigation of dehydrative aromatization reaction protocols for macrocyclic cyclohex-2-en-1,4-diols, it was discovered that treatment of **15.6** with iron(III) chloride in dichloromethane brought about a vinylogous pinacol rearrangement [50] to afford enone **63.2** as single regioisomer (Scheme 63). Since **15.6** is virtually unstrained, the computed SE for the macrocycle derivative is only 9 kcal/mol, the driving force for this reaction was unclear. Thus, it was reasoned that the same type of reaction should occur for a

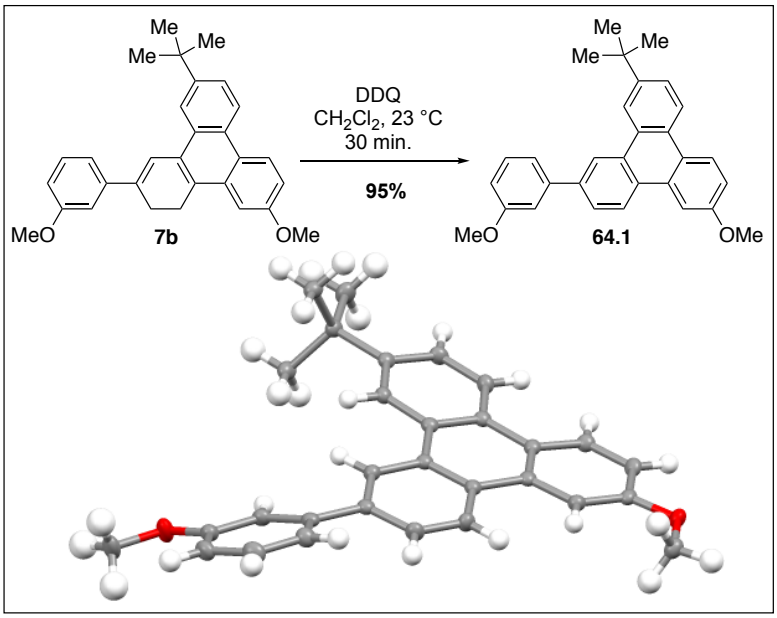


SCHEME 63: Vinylogous pinacol rearrangment in **15.6**

non-macrocyclic analog, such as *anti*-**15a**. In an attempt to form the rearranged polycyclic product **7c**, *anti*-**15a** was subjected to the a catalytic amount of iron(III) chloride in dichloromethane. Surprisingly, an identical, by ^{1}H and ^{13}C NMR analysis, polycyclic compound to that of the protic acid mediated reactions was was produced as the only product of this reaction without the formation of the dehydrated aromatized *p*-terphenyl **7a**.

3.4.2. Elucidation of the polycyclic structure produced in the allylic arylation reaction of anti-15a

Aromatization of the polycyclic product produced during the allylic arylation of *syn* and *anti*-**15a** was accomplished upon treatment of **7b** with DDQ in dichloromethane at room temperature, in near quantitative yield (Scheme 64). Fortunately, recrystallization of 61.1 from dichloromethane and hexanes produced a single crystal that was suitable for X-ray crystallography. The solid state structure of **64.1** confirms that the desired regiochemistry was obtained during the allylic arylation step, and indicates that activation of the least hindered hydroxyl group of 15a is possible under protic and Lewis acidic conditions. Furthermore, this result suggest that the vinylogous pinacol rearrangement observed for **15.6** under the influence of iron(III) chloride is unique to this, and potentially related, macrocyclic system(s). It should be noted that no vinylogous pinacol rearrangement or 1,2-aryl shifts have been observed during our extensive investigation of protic acid mediated dehydrative aromatization reactions of macrocyclic cyclo-hex-2-ene-1,4-diols that produced *para*-phenylene rings with up to 20 kcal/mol of SE. Thus, the application of a protic acid-mediated allylic arylation reaction for APEX of appropriately arylated macrocyclic macrocyclic cyclo-hex-2-ene-1,4-diols seemed promising.



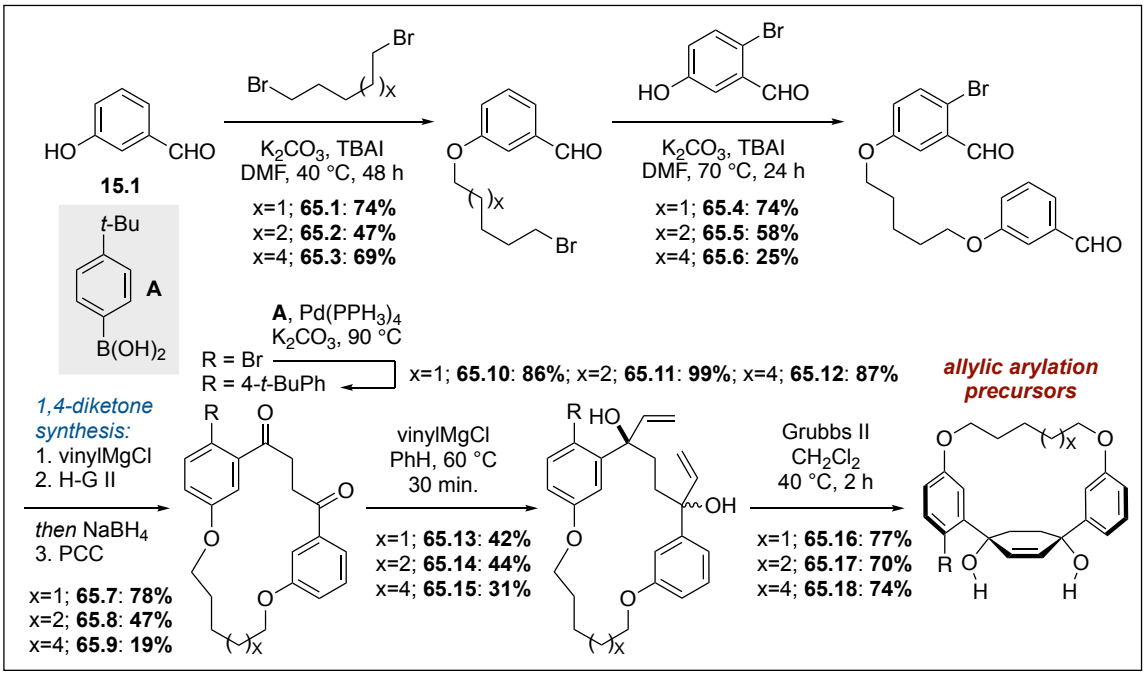
SCHEME 64: Synthesis and X-ray crystal structure of **64.1**

3.4.3 Synthesis of selectively functionalized cyclohex-2-ene-1,4-diols for APEX investigation via allylic arylation

The synthesis of macrocyclic analogs of **15a** is non-trivial due to the *ortho*-substitution of the nucelophilc arene unit. The presence of this substituent attenuates the reactivity of the neighboring carbon atoms in cross-coupling reactions due to steric hindrance. Furthermore, the formation of

tertiary carbinol C-C bonds present in **15a** will require an organometallic addition of a nucleophilic arene to a cyclohexenone-based intermediate. Such nucleophiles typically come from aryl halide derivatives, which will require an *ortho*-dihaloarene as a potential starting material. Halogen-metal exchange or selective metal insertion into one of the C-halogen bonds of an *ortho*-dihaloarene presents a regiochemical challenge, as well as the possible formation benzyne directly. The synthesis of selectively substituted and congested macrocyclic systems such as that found in **60.1** (Scheme 60) was the one of the originally perceived innovations of the non-cross-coupling-based approach to arene-bridged macrocycles discussed in Chapter 1.

The synthesis of three macrocyclic homologs of *syn*-**15a** commenced with the alkylation of 3-hydroxybenzaldehyde (**15.1**, Scheme 65) with three different α,ω-dibromides (x = 1, 2 and 4). Primary bromides **65.1**-**65.3** were then alkylated with 2-bromo-5-hydroxybenzaldehyde to afford dialdehydes **65.4**-**65.6** in 25-74% yield. Subjecting **65.4**-**65.6** to the streamlined synthetic approach for macrocyclic 1,4-diketone synthesis, developed in Chapter 2, afforded bromo-diketones **65.7**-**65.9** in 19-78**%** yield on a gram scale. Treatment of bromo-diketones **65.7**-**65.9** with 4-*tert*-butylphenyl boronic acid furnished arylated ketones **65.7**-**65.9** in 86-99% yield. At this stage the nucleophilic arene unit, which would be later engaged in a Friedel-Crafts-type allylic arylation reaction was installed. The 4-*tert*-butylphenyl derivative was selected as the arene of choice, to overlap with the previously discussed Scholl reaction-based study. A Grignard reaction of **65.10**-**65.12** with vinylmagnesium chloride in benzene at 60 °C afforded a mixture of *syn* and *anti*-allylic



SCHEME 65: Synthesis of monosubstituted allylic arylation precursors **65.16**, **65.17** and **65.18**

diols **65.13**-**65.15** in 31-44%, along with the hydroxyketone by-products in 35-45% yield. Subject-

ing the mixture of allylic diols to a RCM reaction in the presence of Grubbs second-generation catalyst, produced the allylic arylation precursors **65.16-65.18** in 70-77% yield. At this stage the uncyclized *anti*-diols were easily separated and characterized.

Initial investigation of the allylic arylation reaction developed on a model, non-macrocyclic cyclohex-2-ene-1,4-diol was conducted on **65.17**. From previous experience it was known that the non-arylated analog of this macrocycle, which should contain the virtually the same strain energy as **65.17**, does not succumb to any rearrangement reactions during protic acid-mediated aromatization reactions. Thus, it was anticipated that this homolog would proceed along the desired reaction pathway to afford a mixture of the aromatized *para*-phenylene bridged macrocycle **8d** and allylic arylation product **8f** (Table 8). Treatment of **65.17** with TsOH in in dichloromethane at 40 °C resulted in no conversion of the allylic diol (entry 1, Table 8). Switching the solvent to toluene at and running the reaction at room temperature also di not result in conversion of the starting material (entry 2, Table 8), however, heating the reaction to 60 °C resulted in the formation of three new products in a 45:40:15 ratio (entry 3, Table 8). Analysis of crude ^{1}H NMR spectrum of this reaction clearly indicated that a pi-extended macrocyclic system had been produced, due to the presence of a set of downfield signals in the range of 8.0-8.9 ppm along with what was presumed to be the *para*-phenylene bridged macrocycle **8d** and another isomeric annulation product. The formation of the former two compounds is in-line with what we observed during the synthesis of **64.1**. Preparative TLC was required to separate the mixture of products produced in this reaction. The structure of **8d** was unambiguously assigned by ^{1}H and ^{13}C NMR, however, the structures of the other (two) annulation products produced in this reaction could not be unequivocally assigned via NMR analysis. As discussed above in during our initial investigations of this allylic arylation reaction on a model system, the regioisomeric product resulting from a 1,2-phenyl shift, would have very similar, if not identical, NMR spectra. Fortunately, single crystals suitable for

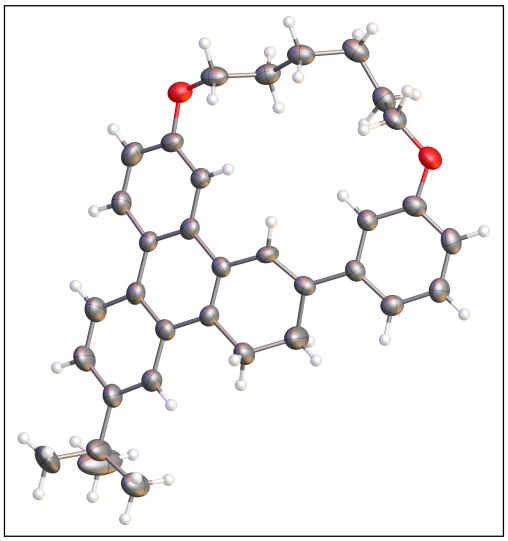


FIGURE 16: X-ray crystal structure of **8e**

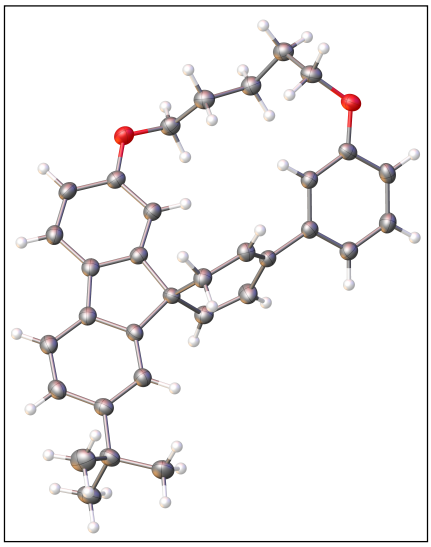


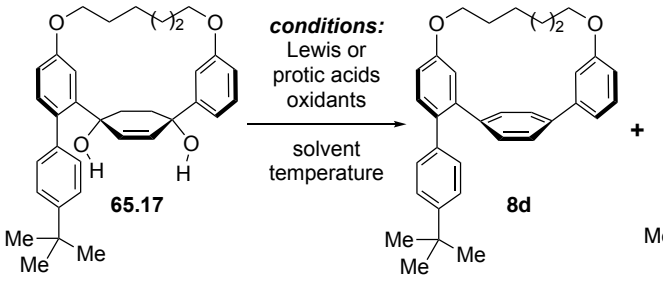
FIGURE 17: X-ray crystal structure of **8f**

X-ray crystallographic analysis were obtained for both of these annulation products.

The major annulation product annulation proved to be that of **8e** (Figure 16). This came as a huge surprise, as the formation of this product has to take place via a skeletal rearrangement of the central cyclohexene ring system, for which no such rearrangement had been observed under protic acid-mediated conditions of analogous, and equally strained, macrocyclic systems. It is proposed that the formation of **8b**, occurs through a vinylogous pinacol rearrangement reaction, followed by annulation onto the proximal ketone unit, and subsequent dehydration of the tertiary carbinol. This is accounts for the observed regiochemistry, but is puzzling given the absence of this type of rearrangement reaction during through investigations of acid-mediated dehydrative reactions on related systems (Chapter 2). The second annulation product proved to be that of **8f** (Figure 17), the product of a spirocyclization onto the more hindered tertiary carbinol position of **65.17**.

Having confirmed the structures of all three compounds produced in the TsOH-mediated arylation reaction, we shifted our focus to finding milder reaction conditions to suppress the formation of **8d** and allow for the desired annulation to take place via activation of the least hindered alcohol, which would in turn circumvent the formation of **8f**. Thus, **65.17** was treated with a slightly weaker protic acid, MsOH. Under these conditions 8d is not formed, however, a 1:1 ratio of 8e and 8f was obtained for all reactions screened (entries 4-6, Table 8). McCubbin and co-workers have reported the use of pentaflurophenylbornic acid as a catalyst to facilitate Friedel-Crafts reactions of teriary allylic alcohols in an S_N2' (allylic arylation) fashion. These conditions were employed on

TABLE 9: Screening allylic arylation conditions for macrocycle **65.17**

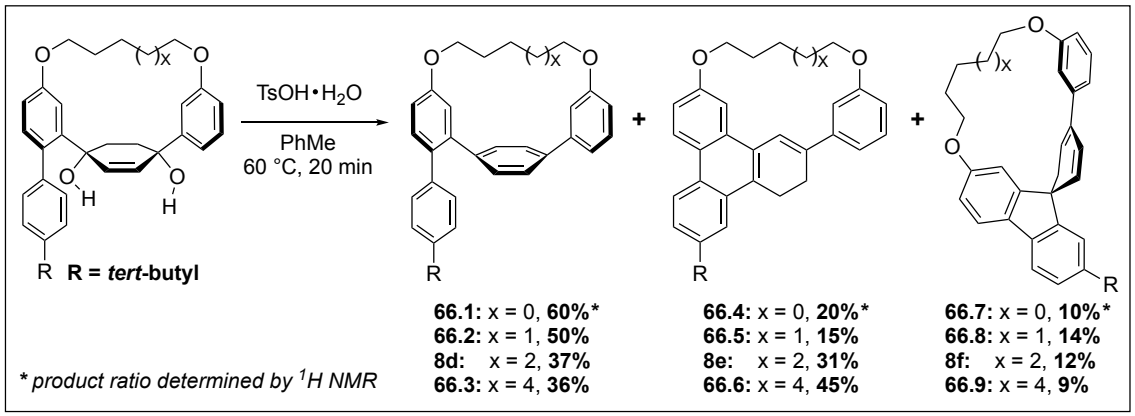


entry	acid (equiv)	solvent	temp (°C)	8d	8e	8f
1	TsOH (5.0)	DCM	40	0	0	0
2	TsOH (6.0)	PhMe	23	0	0	0
3	TsOH (6.0)	PhMe	60	45	40	15
4	MsOH (6.0)	DCM	0	0	50	50
5	MsOH (6.0)	DCM	23	0	50	50
6	MsOH (6.0)	HFIP/PhMe	80	0	50	50
7	$C_6F_5B(OH)_2$ (5.0)	DCM	23	0	60	40
8	Burgess (5.0)	DCM	80	80	20	0
9[a]	BF_3OEt_2 (3.0)	DCM	0	0	35	65
10[b]	$FeCl_3$ (0.2)	PhMe	0	0	50	25
11	TFA (6.0)	PhMe	23	0	0	0
12	$AgSbF_6$ (3.0)	DCM	23	0	85	15

[a] This reaction was run on the *n* = 7 homologue
[b] This reaction gave another 25% of rearranged aromatized product

62.17, however only **8e** and **8f** were produced (entry 7, Table 8). All other protic acid (entry 11) and Lewis acid-mediated reactions (entries 9, 10, and 12) furnished **8e** and **8f**. Treatment of **65.17** with the Burgess reagent gave predominantly the aromatized product **8d**, but surprisingly a trace amount of 8e was detected in the ^{1}H NMR spectrum of the crude reaction mixture (entry 8, Table 7).

Despite the disappointing results obtained from the initial screening of allylic arylation reaction conditions of **62.17**, we proceeded to explore this TsOH-mediated reaction on a series of monoarylated, macrocyclic cyclohex-2-ene-1,4-diols. In doing so, it was discovered that smaller macrocyclic systems (x = 0 and 1; *n* = 6 and 7, Scheme 67) afforded more of the dehydrative aromatization product, *i.e.*, *para*-phenylene formation, than annulated products produced for a larger macrocyclic systems (x = 2 and 4; *n* = 8 and 10, Scheme 67). This is quite puzzling, but nonetheless interesting and will be further investigated by another student in our laboratory.



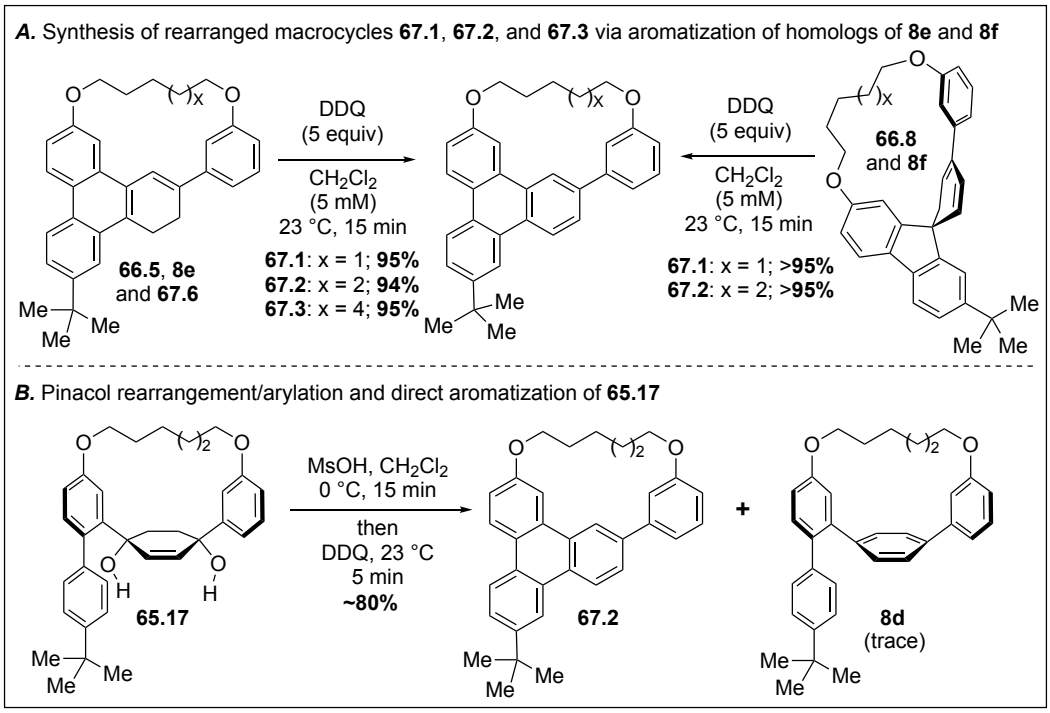
SCHEME 66: TsOH-mediated allylic arylation of a series of macrocycles (*n* = 6, 7, 8, and 10)

3.4.4 Synthesis of a constitutional isomer of 61.1 and comparison of their ^{1}H NMR spectra

Before an X-ray crystal structure of **64.1** was obtained, it was unclear as to whether or not the correct constitutional isomer had formed during the allylic arylation reactions of allylic diols **15a** (see Table 7). Despite the failure for this reaction to provide the correct regiochemical outcome for a macrocyclic homolog of **15a**, the X-ray crystal structure of **8e** confirmed that a rearranged product had indeed formed. As consolation, we were now in a position to obtain ^{1}H and ^{13}C NMR data for both regioisomers and address this issue.

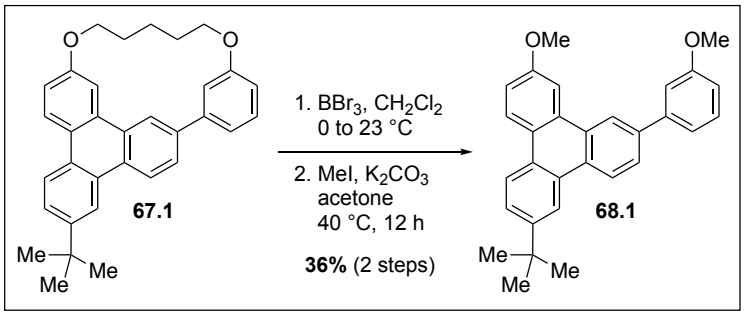
Treatment of macrocycles **66.5**, **8e**, and **66.6** with DDQ in dichloromethane at room temperature for 15 minutes, led to the formation of the aromatized macrocycles **67.1**, **67.2** and **67.3** in near quantitative yield (Scheme 67A). Before an X-ray crystal structure of **8f** was obtained, and it spriocyclic structure was an unambiguously determined, we had attempted to aromatize the "other" annulation product (**8f**) obtained from this reaction under DDQ-mediated conditions. Surprisingly, a compound with identical ^{1}H and ^{13}C NMR spectra to that of **67.2** was obtained. In-

deed, subjecting **66.8**, a smaller macrocyclic homolog, to the same reaction conditions furnished **67.1** in 95% yield (Scheme 67A). A modified one-pot reaction sequence that involved sequential treatment of **65.17** with MsOH to afford a vinylogous pinacol rearrangement, followed by annulation and dehydration, then aromatization with DDQ, afforded **67.2** in 80% yield (Scheme 67B). It is noteworthy, that only a trace amount of the dehydrated aromatized product **8e** was produced in this reaction.



SCHEME 67: Aromatization of the cyclized products from allylic arylation reactions

With these aromatized macrocycles in hand, **67.1** was subjected to dealkylation (bridge cleavage) in the presence of boron tribromide in dichloromethane (Scheme 68). Methylation of the resulting phenol units afforded triphenylene derivative **68.1** in 36% overall yield. The similarities of the ^{1}H NMR spectra of **68.1** and **64.1** can bee seen in Figure 17. Eleven aromatic signals ranging from 7.0-8.8 ppm for **68.1** are observed, while 12 aromatic signals span the same range for **64.1**. Nine of the 12 signals present in **64.1** overlap with those of **68.1**, with all of these signals having virtually the same multiplicity. The subtle difference in chemical shift values of the low field doublets 8.12 and 8.07 ppm for **68.1** and **64.1** cannot be considered diag-



SCHEME 68: Synthesis of **68.1** via alkyl chain cleavage

nostic for either structure. However, the multiplet at 8.77-8.74 ppm of **68.1** (Figure 18A) is separated into a singlet (8.85 ppm) and a doublet (8.64 ppm) in the case of **61.1** (Figure 18B). These signals represent the only noticeable differences in the ^{1}H NMR spectra of the two constitutional isomers. Thus, without an X-ray crystal structure of **64.1**, it would be quite challenging to differentiate these two isomeric triphenylene derivatives with absolute certainty. However, for future investigations of this APEX-based strategy, access to these data will allow for the unambiguous assignment of the PAHs obtained.

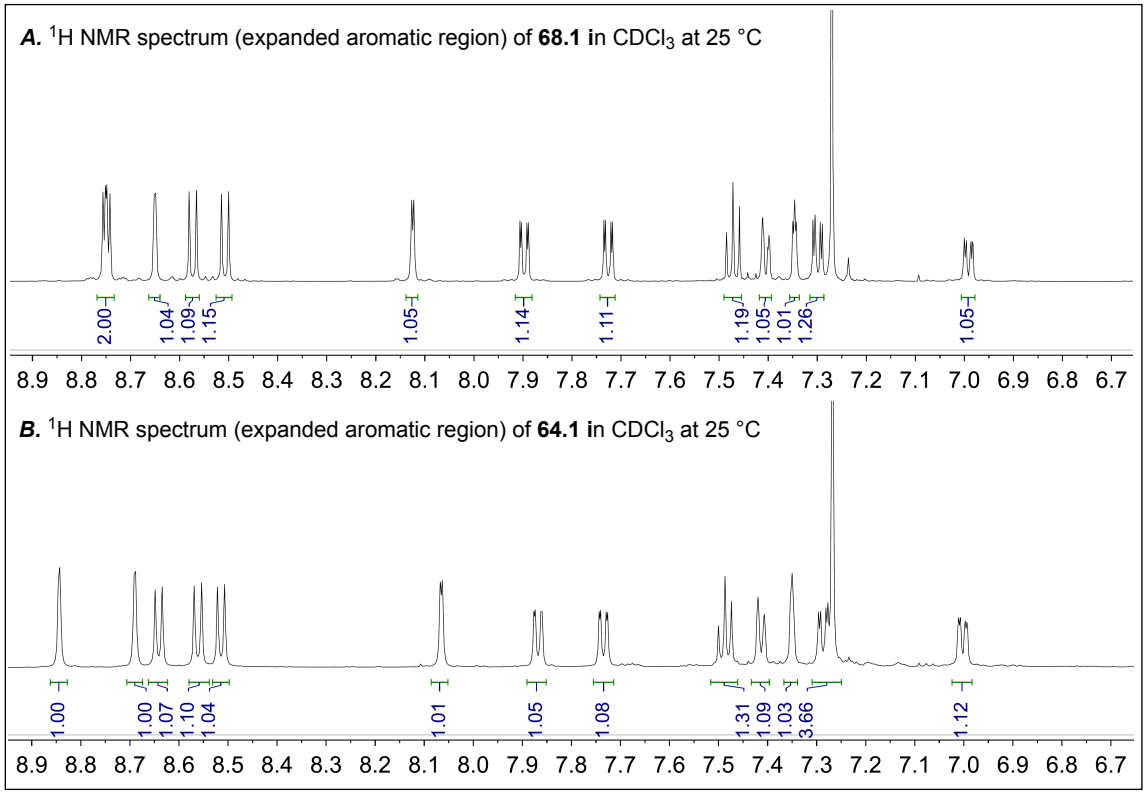


FIGURE 18: Comparison of ^{1}H NMR spectra of allylic arylation products **68.1** and **64.1**

3.5 Concluding remarks and future outlook

The intramolecular allylic arylation of a non-macrocyclic cyclohex-2-ene-1,4-diol holds great promise for rapid synthesis of selectively functionalized polycyclic aromatic hydrocarbons. The success of this reaction with catalytic action of iron(III) chloride makes this reaction well-suited for a multi-component C-C bond forming reactions, where the newly formed triphenylene structure can undergo subsequent annulation in a Scholl-type reaction. Optimization of this process to install the nucleophilic arene units at the stage of a brominated cyclohex-2-ene-1,4-diol make this approach much more versatile for PAH synthesis. The key feature the being the regioselective functionalization of PAHs that are not accessible using cross-coupling reactions and direct

electrophilic aromatic substitution reactions. This project will be continued in our laboratory in the years to come.

The application of this powerful APEX strategy to macrocyclic homologs should be pursued in the context of chemical reactions that do not require the formation of cationic intermediates that are susceptible to the vinylogous pinacol rearrangement. This can be achieved by activation of the 1,4-diol units in a manner that does not require protic or Lewis acid-mediated conditions, or conversion of the alcohol units to a functional groups that serve as leaving groups in a true S_N2'-type reaction. An alternative to this would be the use of chemical reactions that involve formation radical intermediates, which are not prone to rearrangement reactions. Finally, allylic alcohol transposition of the cyclohex-2-ene-1,4-diol unit via an oxidative [3.3]sigmatropic rearrangement reaction to position an enone functional group within the 6-membered ring framework. From here, cyclization in a 1,2 (direct to the carbonyl) or 1,4-additon (Michael-type) reaction could enable the desired annulation event.

In closing, it should be noted that the synthetic challenge associated with development of APEX methodologies that facilitate the synthesis of curved PAHs, particularly those that involve annulation onto strained benzene rings, are considerably more challenging than related strategies that furnish planar PAH systems. The work described in this dissertation speaks to this – strategies that work for model systems cannot always be extended to the actual target system. Furthermore, reaction mechanisms that are not operative in closely related compounds, with identical strain energies, can be operative when simple substitutions are made. The latter is quite intriguing and will be the source of future mechanistic investigations and reaction development in our laboratory.

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Supporting Information for

CHAPTER 1 A Non-Cross-Coupling Approach to Arene-Bridged Macrocycles: Synthesis, Structure, and Direct, Regioselective Functionalization of a Cycloparaphenylene Fragment

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 preformed 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 × 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. ^{1}H 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).

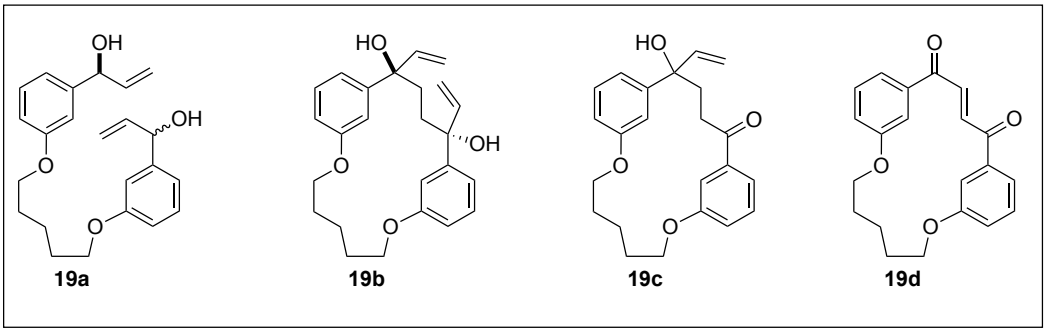
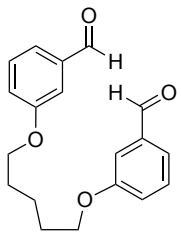


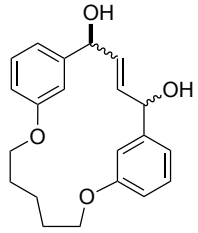
FIGURE 19: Compounds not numbered in Chapter 1 that appear in Appendix 1



15.3

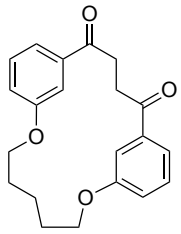
***Dialdehyde* 15.3:** 1,5-Diiodopentane (3.59 g, 11.1 mmol) was added to a stirred solution of 3-hydroxybenzaldehyde (3.01 g, 24.7 mmol), K_2CO_3 (3.41 g, 24.7 mmol) and tetrabutylammonium iodide (0.456 g, 1.24 mmol) in DMF (25 mL). The slurry was heated at 60 °C for 17 h, at which point water (100 mL) and 1 M HCl (50 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash chromatography (15 cm × 5.0 cm; chloroform, 1:19 acetone/chloroform) to afford **15.3** as white solid (2.53 g, 73%): R_f = 0.35 (chloroform); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.98 (s, 2H), 7.48-7.42 (m, 4H), 7.41-7.38 (m, 2H), 7.20-7.16 (m, 2H), 4.06 (t, *J* = 6.4 Hz, 4H), 1.91 (p, *J* = 6.6 Hz, 4H), 1.72-1.66 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.4,

159.7, 137.9, 130.2, 123.7, 122.1, 112.7, 68.1, 29.0, 22.9; HRMS (ESI) calculated for $C_{19}H_{21}O_4$ ($[M+H]^+$) *m/z* = 313.1440, found 313.1432.



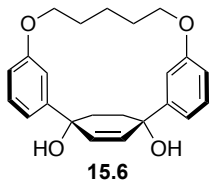
15.4

***Streamlined Synthesis of* 15.4**: Vinylmagnesium chloride (1.6 M in THF, 5.2 mL, 8.3 mmol) was added to a stirred solution of dialdehyde **15.3** (1.03 g, 3.32 mmol) in THF (30 mL) at room temperature. After 1 h, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). The resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (220 mL, 15 mM) and Grubbs second-generation catalyst (0.073g, 0.086 mmol) was added. The reaction was heated to 40 °C for 2 h, cooled to room temperature, and concentrated under reduced pressure. The residue was pre-adsorbed onto silica and subjected to flash chromatography (18 × 2.5 cm, 3:2 EtOAc/hexanes) to give allylic diol **15.4** as a white solid (0.605 g, 54% from **15.3**): R_f = 0.24 (1:1 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.22 (m, 2H), 7.10-7.02 (m, 2H), 6.88-6.76 (m, 4H), 6.06-5.94 (m, 2H), 5.34-5.25 (m, 2H), 4.10-3.95 (m, 4H), 2.00 (s, 2H), 1.89-1.76 (m, 4H), 1.74-1.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 144.53, 132.8, 129.9, 119.2, 114.7, 113.4, 74.0, 68.2, 28.7, 22.0; HRMS (ESI) calculated for $C_{22}H_{23}O_2$ ($[M-(2H_2O)+H]^+$) *m/z* = 319.1698, found 319.1703



15.5

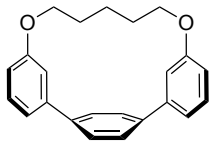
***1,4-Dione* 15.5:** A hydrogen filled balloon was placed over a stirred slurry of 10% wt. Pd/C (0.063g) and allylic diol **15.4** (0.554 g, 1.64 mmol) in 1:1 MeOH/EtOAc (40 mL). After 2 h, the reaction was filtered through a short pad of Celite (4 cm) and the filtrate concentrated under reduced pressure. The solid white residue was subjected to flash chromatography (15 × 2.5 cm, 3:2 EtOAc/hexanes) to give 1,4-diol **20.1** as colorless solid (0.432 g, 78%): R_f = 0.42 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.15 (m, 4H), 6.91-6.76 (m, 10H), 6.71-6.68 (m, 2H), 4.76 (t, *J* = 5.4 Hz, 2H), 4.68-4.54 (m, 2H), 4.20-3.94 (m, 8H), 3.02 (s, 2H), 1.90 (s, 2H), 1.86-1.78 (m, 12H), 1.76-1.64 (m, 6H), 1.55-1.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 159.1, 145.9, 145.4, 129.78, 129.74, 119.8, 118.5, 115.34, 115.24, 112.1, 111.6, 74.63, 73.49, 67.71, 67.62, 34.0, 33.9, 27.9, 27.6, 21.7, 21.4; HRMS (ESI) calculated for $C_{21}H_{25}O_3$ ($[M-(H_2O)+H]^+$) *m/z* = 325.1804, found 325.1816. Dess–Martin periodinane (1.58 g, 3.73 mmol) and $NaHCO_3$ (0.312 g, 3.75 mmol) were added to a stirred solution of 1,4-diol **20.1** (0.420 g, 1.24 mmol) in dichloromethane (15 mL) at room temperature. After 1 h, a 10% solution of $Na_2S_2O_3$ (40 mL) was added and the reaction was stirred for 10 min. The resulting mixture was extracted with dichlormethane (3 × 15 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 1,4-diketone **15.5** as a beige solid (0.384 g, 92%). R_f = 0.27 (1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 2H), 7.39-7.34 (m, 2H), 7.30 (dd, *J* = 2.5, 1.6 Hz, 2H), 7.07 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 2H), 4.11 (t, *J* = 6.2 Hz, 4H), 3.21 (s, 4H), 1.84 (p, *J* = 6.3 Hz, 4H), 1.75-1.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 159.1, 137.7, 130.3, 120.7, 119.6, 115.6, 68.0, 36.1, 27.9, 22.0; HRMS (ESI) calculated for $C_{21}H_{23}O_4$ ($[M+H]^+$) *m/z* = 339.1596, found 339.1598.



15.6

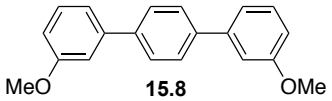
***Cyclohex-2-ene-1,4-diol* 15.6:** Grubbs' second-generation catalyst (0.0114 g, 0.0134 mmol) was added to a stirred solution of *syn*- **18b** and *anti*- **18b** was heated to 40 °C. After 3 h, the solvent was evaporated under reduced pressure and residue was purified by flash chromatography (15 × 1.3 cm, 3:7 EtOAc/hexanes) to give *anti*- **18b** as a colorless oil (0.017 g, 17%, R_f = 0.59 (1:1 EtOAc/hexanes)) and compound **15.6** as an off-white solid (0.071 g, 77%); R_f = 0.27 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.04-6.98

(m, 2H), 6.88-6.81 (m, 2H), 6.05 (s, 2H), 4.18-4.07 (m, 2H), 4.07-3.96 (m, 2H), 2.22 (br s, 2H), 2.18-2.07 (m, 2H), 1.92-1.66 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 147.9, 134.8, 130.2, 117.9, 115.0, 114.1, 73.1, 69.6, 36.7, 28.9, 22.5; HRMS (ESI) calculated for $C_{23}H_{25}O_3$ ([M-(H_2O)+H]$^+$) *m/z* = 349.1804, found 349.1818.



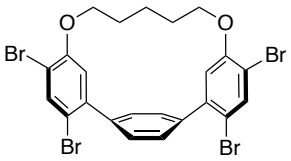
15.7

1,7-dioxa[7](3,3")p-Terphenylenophane (**15.7**): *p*-Toluensulfonic acid monohydrate (1.22 g, 6.390 mmol) was added to a stirred solution of **15.6** (0.390 g, 1.07 mmol) in toluene (50 mL) and the reaction was heated at 50 °C for 4 h and 60 °C for 2 h. After 6 h, a saturated solution of $NaHCO_3$ (50 mL) was added to the reaction. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The organic extracts were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatograph (15 × 2.5 cm, 1:19 EtOAc/hexanes) to afford **15.7** as a white solid (0.288 g, 82%): R_f = 0.32 (1:19 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 4H), 7.35 (dd, *J* = 8.2, 7.4 Hz, 2H), 7.30-7.24 (m, 2H), 6.78 (ddd, *J* = 8.3, 2.8, 1.0 Hz, 2H), 5.81 (dd, *J* = 2.8, 1.5 Hz, 2H), 4.10-4.05 (m, 4H), 1.51-1.42 (m, 4H), 1.21-1.12 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 144.7, 144.1, 130.6, 129.5, 118.7, 115.9, 115.4, 68.5, 26.8, 23.3; HRMS (EI) calculated for $C_{23}H_{22}O_2$ ([M]$^+$) *m/z* = 330.1618, found, 330.1620.



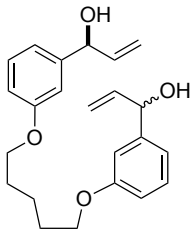
15.8

3,3"-dimethoxy-p-terphenyl (**15.8**)**:** 3-Iodoanisole (0.234 g, 0.13 mL, 1.00 mmol,), 1,4-benzenediboronic (0.066 g, 0.40 mmol) and sodium carbonate (0.424 g, 4.00 mmol) were dissolved in solution of toluene (6 mL), water (2 mL) and ethanol (1 mL), which had been previously purged with nitrogen gas. $Pd(PPh_3)_4$ (0.049 g, 0.04 mmol) was added under stream of nitrogen gas and the reaction was purged again for 5 min. again. The reaction was heated at 90 °C for 18 h and cooled to room temperature at which point H_2O (30 mL) was added. This mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 1:49 Ethyl acetate/hexane) to yield the 3,3"-dimethoxy-*p*-terphenyl as a yellow solid (0.061 g, 52%): R_f = 0.44 (1:19 ethylacetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 4H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.33-7.15 (m, 4H), 6.94 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 2H), 3.90 (s, 6H); ^{13}C NMR (100 MHz)δ 160.02, 142.91, 141.22, 129.93, 128.92, 127.70, 127.60, 127.38, 119.84, 113.01, 112.90, 112.79, 77.06, 55.50, 55.48.



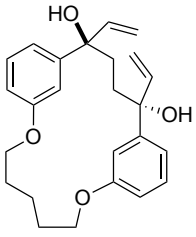
16.1

4,4", 6,6"-Tetrabromo-1,7-dioxa [7](3,3") p-terphenylenophane (**16.1**): Bromine (0.105 g, 0.636 mmol) was added to a stirred solution of **15.7** (0.035 g, 0.11 mmol) in 1,2-dichlorbenzene (2 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 evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL), a 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 (2 × 15 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 residue was purified by flash chromatography (15 × 1.3 cm, 3:7 dichloromethane/hexanes) to yield tetrabromide **16.1** as a white solid (0.052 g, 80%): R_f = 0.48 (1:1 dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.50 (s, 4H), 5.73 (s, 2H), 4.18-4.07 (m, 4H), 1.54-1.43 (m, 4H), 1.18-1.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.4, 143.1, 142.8, 136.7, 129.7, 120.5, 110.5, 109.6, 69.96, 26.5, 23.4; HRMS (EI) calc'd for $C_{23}H_{18}O_2Br_4$ 641.8040, found 641.8038



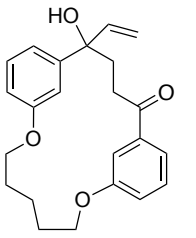
19a

***Allylic alcohol* 19a:** Vinylmagnesium chloride (1.6 M in THF, 5.4 mL, 8.7 mmol) was added to a stirred solution of dialdehyde **15.3**(1.08 g, 3.48 mmol) in THF (30 mL) at room temperature. After 1 h, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). The resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 filtered, and concentrated under reduced pressure. The residue was purified via flash chromatography (18 cm × 2.5 cm; 3:7 EtOAc/hexanes) to afford compound **19a** (1.06 g, 83 %): R_f = 0.26 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 6.98-6.92 (m, 4H), 6.85-6.81 (m, 2H), 6.04 (ddd, *J* = 17.1, 10.3, 6.0 Hz, 2H), 5.36 (dt, *J* = 17.1, 1.4 Hz, 2H), 5.20 (dt, *J* = 10.3, 1.4 Hz, 2H), 5.17 (d, *J* = 5.6 Hz, 2H), 4.00 (t, *J* = 6.4 Hz, 4H), 2.11 (d, *J* = 2.9 Hz, 2H), 1.92-1.81 (m, 4H), 1.72-1.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 144.4, 140.3, 129.8, 118.7, 115.4, 114.0, 112.5, 75.4, 67.9, 29.2, 22.9; HRMS (ESI) calculated for $C_{23}H_{29}O_4$ ($[M-2H_2O]^+$) *m/z* = 333.1855, found 333.1864.



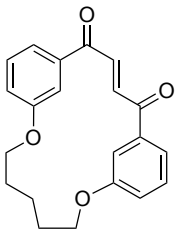
19b

Anti-**19b:** For isolation of this compound, see the experimental procedure below (compound **23.3**): R_f = 0.22 (1:4 EtOAc/hexanes), 0.59 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.17-7.10 (m, 2H), 6.77 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 2H), 6.58-6.52 (m, 2H), 6.08 (dd, *J* = 17.3, 10.6 Hz, 2H), 5.16 (dd, *J* = 17.2, 1.0 Hz, 2H), 5.02 (dd, *J* = 10.6, 1.0 Hz, 2H), 4.07-4.01 (m, 2H), 3.95 (td, *J* = 9.1, 4.0 Hz, 2H), 1.99-1.73 (m, 6H), 1.74-1.50 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 146.2, 145.6, 129.4, 117.4, 113.2, 112.32, 111.3, 76.8, 66.8, 35.7, 28.4, 24.7; HRMS (ESI) calculated for $C_{25}H_{27}O_2$ ($[M-(2H_2O)+H]^+$) *m/z* = 359.2011, found 359.2015.



19c

***Hydroxyketone* 19c**: R_f = 0.29 (3% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.35-7.24 (m, 2H), 7.15 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.08-7.01 (m, 2H), 6.96 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 6.81 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.30 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.39 (dd, *J* = 17.3, 0.9 Hz, 1H), 5.21 (dd, *J* = 10.7, 0.9 Hz, 1H), 4.19-4.02 (m, 4H), 2.91-2.81 (m, 1H), 2.68-2.58 (m, 1H), 2.40-2.23 (m, 2H), 2.03 (s, 1H), 1.92-1.68 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 158.9, 158.8, 145.7, 144.3, 138.1, 129.9, 129.7, 120.4, 120.2, 118.5, 115.0, 113.7, 113.5, 112.7, 76.7, 68.5, 66.7, 37.8, 33.8, 28.2, 27.6, 21.4; HRMS (ESI) calc'd for $C_{23}H_{25}O_3$ ($[M-(H_2O)+H]^+$) *m/z* = 349.1804, found 349.1793



19d

***Ene-1,4-dione* 19d:** Dess–Martin periodinane (0.235 g, 0.556 mmol) and $NaHCO_3$ (0.0.47 g, 0.56 mmol) were added to a stirred solution of macrocyclic 1,4-diol **15.4**(0.063 g, 0.19 mmol) in dichloromethane (5 mL) at room temperature. After 1 h, a 10% solution of $Na_2S_2O_3$ (10 mL) was added and the reaction was stirred for 10 min. The resulting mixture was extracted with dichlormethane (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 1,4-diketone **20d** as a white solid (0.058 g, 92%). R_f = 0.32 (1:4 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2H), 7.49-7.44 (m, 4H), 7.38 (s, 2H), 7.21-7.17 (m, 2H), 4.16 (t, *J* = 6.6 Hz, 4H), 1.94 (p, *J* = 6.7 Hz, 4H), 1.81-1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 159.0, 138.4, 130.9, 121.3, 121.0, 116.0, 69.2, 28.6, 22.5; HRMS (ESI) calculated for $C_{21}H_{21}O_4$ ($[M+H]^+$) *m/z* = 337.1440, found 337.1444.

CHAPTER 2 A Mild Dehydrative Aromatization Protocol for Synthesis of Highly Distorted *para*-Phenylene-Containing Macrocycles

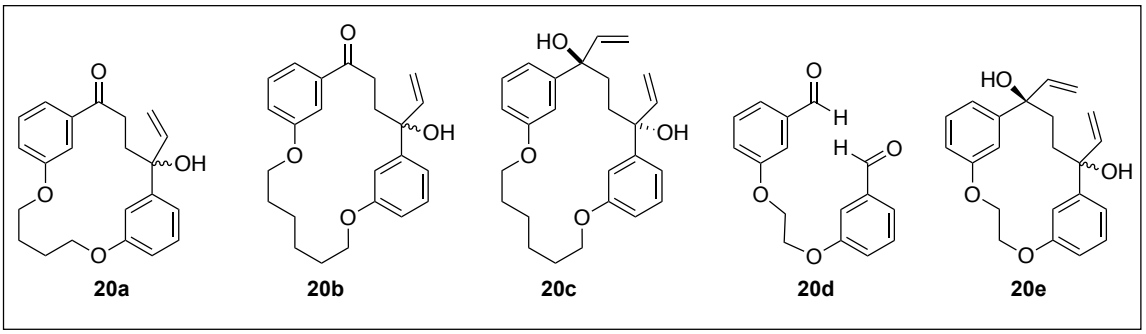
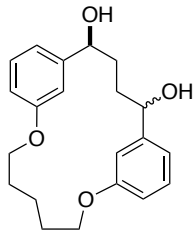
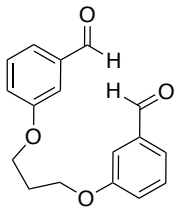


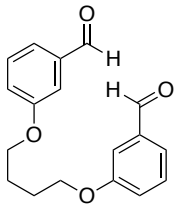
FIGURE 20: Compounds not numbered in Chapter 2 that appear in Appendix 2



***1,4-diol* 20.1:** A hydrogen filled balloon was placed over a stirred slurry of 10% wt. Pd/C (0.063g) and allylic diol **15.4** (0.554 g, 1.64 mmol) in 1:1 MeOH/EtOAc (40 mL). After 2 h, the reaction was filtered through a short pad of Celite (4 cm) and the filtrate concentrated under reduced pressure. The solid white residue was subjected to flash chromatography (15 × 2.5 cm, 3:2 EtOAc/hexanes) to give 1,4-diol **20.1** as colorless solid (0.432 g, 78%): R_f = 0.42 (3:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.15 (m, 4H), 6.91-6.76 (m, 10H), 6.71-6.68 (m, 2H), 4.76 (t, *J* = 5.4 Hz, 2H), 4.68-4.54 (m, 2H), 4.20-3.94 (m, 8H), 3.02 (s, 2H), 1.90 (s, 2H), 1.86-1.78 (m, 12H), 1.76-1.64 (m, 6H), 1.55-1.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 159.1, 145.9, 145.4, 129.78, 129.74, 119.8, 118.5, 115.34, 115.24, 112.1, 111.6, 74.63, 73.49, 67.71, 67.62, 34.0, 33.9, 27.9, 27.6, 21.7, 21.4; HRMS (ESI) calculated for $C_{21}H_{25}O_3$ ([M-(H_2O)+H]$^+$) *m/z* = 325.1804, found 325.1816.

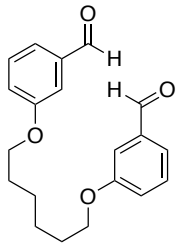


***Dialdehyde* 22.1:** 1,3-Dibromopropane (2.76 g, 13.6 mmol) was added to a stirred solution of 3-hydroxybenzaldehyde (5.00 g, 40.9 mmol), K_2CO_3 (6.50 g, 47.1 mmol) and TBAI (0.375 g, 1.01 mmol) in DMF (75 mL). The reaction was heated at 70 °C for 15 h, at which point water (100 mL) and 1 M HCl (50 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous Na_2SO4, filtered and concentrated under reduced pressure. The residue was purified via flash chromatography (16 cm × 5.0 cm; dichloromethane, and 2% acetone/dichloromethane) to afford **22.1** as colorless oil. (2.80 g, 72%): R_f = 0.27 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 2H), 7.30-7.28 (m, 4H), 7.25-7.23 (m, 2H), 7.06-6.98 (m, 2H), 4.07 (t, *J* = 6.1 Hz, 4H), 2.15 (p, *J* = 6.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.17, 159.44, 137.88, 130.19, 123.70, 121.97, 112.82, 64.60, 29.14; HRMS (ESI) calculated for $C_{17}H_{17}O_4$ ([M+H]$^+$) *m/z* = 285.1127, found 285.1124.



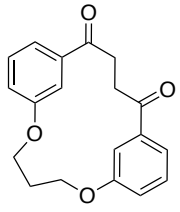
22.2

***Dialdehyde* 22.2:** 1,4-Dibromobutane (3.98 g, 18.4 mmol) was added to a stirred solution of 3-hydroxybenzaldehyde (5.01 g, 40.9 mmol), K_2CO_3 (5.66 g, 41.0 mmol) and TBAI (0.76 g, 2.1 mmol) in DMF (40 mL). The reaction was heated at 70 °C for 48 h, at which point water (100 mL) and 1 M HCl (50 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 5.0 cm; chloroform, 2% to 5% acetone/chloroform) to afford **22.2** as white solid (4.75 g, 87%): R_f = 0.25 (chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 2H), 7.48-7.42 (m, 4H), 7.42-7.37 (m, 2H), 7.21-7.15 (m, 2H), 4.16-4.04 (m, 4H), 2.07-1.99 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.31, 159.67, 137.97, 130.24, 123.72, 122.09, 112.84, 67.87, 26.04; HRMS (ESI) calculated for $C_{18}H_{19}O_4$ ($[M+H]^+$) *m/z* = 299.1283, found 299.1290.



22.3

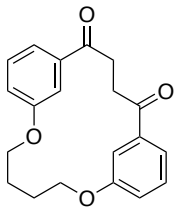
***Dialdehyde* 22.3:** 1,6-Dibromohexane (1.34 g, 5.49 mmol) was added to a stirred solution of 3-hydroxybenzaldehyde (2.03 g, 16.6 mmol) and K_2CO_3 (2.78 g, 20.1 mmol) in DMF (30 mL). The reaction was heated at 80 °C for 4 h, at which point water (75 mL) and 1 M HCl (30 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via flash chromatography (18 cm × 3.8 cm; 9:1 dichloromethane/hexanes, dichloromethane, and 1:9 acetone/dichloromethane) to afford **22.3** as white solid (1.47 g, 82%): R_f = 0.35 (dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.98 (s, 2H), 7.46-7.43 (m, 4H), 7.39 (s, 2H), 7.19-7.18 (m, 2H), 4.05 (t, *J* = 6.4 Hz, 4H), 1.88-1.82 (m, 4H), 1.60-1.55 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.2, 159.6, 137.8, 130.0, 123.5, 122.0, 112.7, 68.1, 29.1, 25.8; HRMS (ESI) calculated for $C_{20}H_{23}O_4$ ($[M+H]^+$) *m/z* = 327.1596, found 327.1595.



22.4

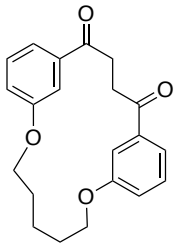
***Streamlined synthesis of macrocyclic diketone* 22.4:** Vinylmagnesium chloride (1.6 M in THF, 2.5 mL, 4.0 mmol) was added to a stirred 0 °C solution of dialdehyde **xx** (0.500 g, 1.76 mmol) in THF (10 mL). After 30 min, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). The resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (150 mL), stirred and heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.040 g, 0.060 mmol). After 2 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 1:9 methanol/dichloromethane (15 mL) and sodium borohydride (0.230 g, 5.88 mmol) was added. After 1 h, the reaction mixture was poured into water (100 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 20 mL) and the combined organic extracts were washed with water (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dichlormethane (20 mL), followed by the sequential addition of $NaHCO_3$ (0.270 g, 3.21 mmol) and Dess-Martin periodinane (1.45 g, 3.20 mmol). After 2 h, a 10% aqueous solution of $Na_2S_2O_3$ (50 mL) was added and stirring was continued for 10 min. The resulting mixture was extracted with dichloromethane (3 × 20 mL). The organic extracts were combined and washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash chromatography (15 cm × 2.5 cm; 3:7 ethyl acetate/hexane) to give 1,4-diketone **22.4** as a beige solid (0.120 g, 22%, over 4 steps): R_f = 0.38 (2:3 ethyl acetate/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.7, 1.3 Hz, 2H), 7.36-7.29 (m, 2H), 7.24-7.20 (m, 2H), 7.10 (ddd, *J* = 8.1,

2.6, 1.0 Hz, 2H), 4.34 (t, *J* = 6.1 Hz, 4H), 3.11 (s, 4H), 2.19 (p, *J* = 6.1 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.85, 159.14, 138.03, 130.43, 121.57, 121.39, 117.10, 66.38, 36.42, 29.09. HRMS (ESI) calculated for $C_{19}H_{19}O_4$ ($[M+H]^+$) *m/z* = 311.1283, found 311.1271



22.5

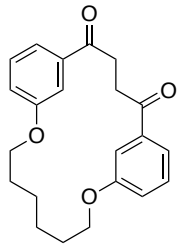
***Streamlined synthesis of macrocyclic diketone* 22.5:** Vinylmagnesium chloride (1.6 M in THF, 4.6 mL, 7.4 mmol) was added to a stirred solution of the dialdehyde **22.1** (1.02 g, 3.42 mmol) in THF (28 mL). After 10 min., the reaction was poured into water (50 mL) and further diluted with 1 M HCl (40 mL). The resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with a saturated solution $NaHCO_3$ (30 mL) and water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (224 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.052 g, 0.083 mmol). After 1 h, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (34 mL), and sodium borohydride (0.380 g, 10.0 mmol) was added. After 3 h, the reaction was poured into water (50 mL) and further diluted with 1 M HCl (20 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (34 mL), followed by the sequential addition of $NaHCO_3$ (0.846 g, 10.1 mmol) and Dess-Martin periodinane (2.91 g, 6.86 mmol). After 30 min., the reaction was poured into water (50 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were washed with water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 3:7 EtOAc/hexanes) to afford 1,4-diketone **22.5** as a white solid (0.551 g, 51% from **22.2**): R_f = 0.38 (3:7 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.42-7.35 (m, 2H), 7.25-7.21 (m, 2H), 7.11 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 2H), 4.22-4.17 (m, 4H), 3.09 (s, 4H), 2.00-1.93 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.77, 158.62, 137.57, 130.43, 120.89, 120.05, 115.89, 68.44, 36.22, 25.88; HRMS (ESI) calculated for $C_{20}H_{21}O_4$ ($[M+H]^+$) *m/z* = 325.1440, found 325.1436



15.5

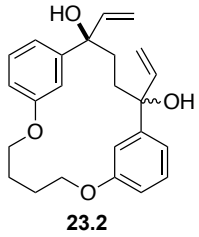
***Streamlined synthesis of 1,4-diketone* 15.5:** Vinylmagnesium chloride (1.6 M in THF, 5.5 mL, 8.8 mmol) was added to a stirred solution of **15.3** (1.24 g, 3.97 mmol) in THF (20 mL). After 10 min., the reaction was poured into water (100 mL) and further diluted with 1 M HCl (50 mL). The resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with a saturated solution $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (220 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.062 g, 0.099 mmol). After 1 h, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (30 mL) and sodium borohydride (0.619 g, 15.9 mmol) was added. After 3 h, the reaction was poured into water (50 mL) and further diluted with 1 M HCl (20 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (30 mL), followed by the sequential addition of $NaHCO_3$ (0.733 g, 8.73 mmol) and Dess-Martin periodinane (3.37 g, 7.89 mmol). After 30 min., the reaction was poured into water (50 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 cm × 2.5 cm; 3:7 EtOAc/hexanes) to afford 1,4-diketone **15.5** as a white solid (0.885 g, 66% from **15.3**): R_f = 0.27

(1:4 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 2H), 7.39-7.34 (m, 2H), 7.30 (dd, *J* = 2.5, 1.6 Hz, 2H), 7.07 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 2H), 4.11 (t, *J* = 6.2 Hz, 4H), 3.21 (s, 4H), 1.84 (p, *J* = 6.3 Hz, 4H), 1.75-1.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.10, 159.05, 137.72, 130.32, 120.70, 119.58, 115.59, 68.01, 36.07, 27.93, 21.98; HRMS (ESI) calculated for $C_{21}H_{23}O_4$ ($[M+H]^+$) *m/z* = 339.1596, found 339.1598.



22.6

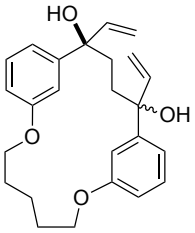
***Streamlined synthesis of 1,4-diketone* 22.6:** Vinylmagnesium chloride (1.6 M in THF, 4.8 mL, 7.7 mmol) was added to a stirred solution of **22.3** (1.19 g, 3.65 mmol) in THF (20 mL). After 10 min., the reaction was poured into water (100 mL) and further diluted with 1 M HCl (50 mL). The resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (40 mL) and water (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (240 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.067 g, 0.107 mmol). After 1 h, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (36 mL), and sodium borohydride (0.652 g, 17.2 mmol) was added. After 3 h, the reaction was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The dark brown residue was dissolved in dichlormethane (30 mL), followed by the sequential addition of $NaHCO_3$ (0.613 g, 7.30 mmol) and Dess-Martin periodinane (3.09 g, 7.30 mmol). After 30 min., the reaction was poured into water (50 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 cm × 2.5 cm; 3:7 EtOAc/hexanes) to afford 1,4-diketone **22.6** as a white solid (0.681 g, 53% from **22.3**): R_f = 0.42 (2:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 2H), 7.43-7.35 (m, 4H), 7.09 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 2H), 4.08 (t, *J* = 5.8 Hz, 4H), 3.20 (s, 4H), 1.87-1.77 (m, 4H), 1.67-1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.67, 159.33, 137.50, 130.36, 120.52, 118.54, 116.23, 67.91, 35.80, 28.24, 25.29; HRMS (ESI) calculated for $C_{22}H_{25}O_4$ ($[M+H]^+$) *m/z* = 353.1753, found 353.1753



23.2

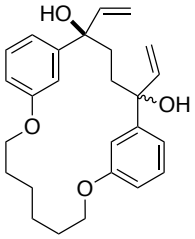
***Allylic alcohol* 23.2:** 1,4-diketone **22.5** (0.298 g, 0.925 mmol), as a solution in THF (7.5 mL) was added to a stirred 65 °C solution of vinylmagnesium chloride (1.6 M in THF, 1.8 mL, 2.8 mmol). After 1 min., the reaction mixture was poured into water (20 mL) and further diluted with 1 M HCl (20 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatography (15 × 2.5 cm, 1:4 EtOAc/hexanes) to give hydroxyketone **19a** (0.048 g, 15%) and allylic alcohol **23.2** (0.220 g, 63%; 77% based on recovered **19a**) predominately as the *syn*-diastereomer (> 20:1 *d.r.*).

***Allylic alcohol* 23.2**: R_f = 0.22 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.17 (m, 2H), 6.98-6.90 (m, 2H), 6.80 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 2H), 6.72-6.64 (m, 2H), 6.19 (dd, *J* = 17.2, 10.7 Hz, 2H), 5.32 (dd, *J* = 17.3, 1.3 Hz, 2H), 5.16 (dd, *J* = 10.7, 1.3 Hz, 2H), 4.15-4.00 (m, 4H), 3.08 (s, 2H), 2.04-1.90 (m, 4H), 1.84-1.65 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.71, 146.45, 143.18, 143.16, 129.16, 129.14, 118.47, 113.54, 113.31, 113.29, 112.81, 76.86, 67.50, 36.77, 26.03; HRMS (ESI) calculated for $C_{24}H_{25}O_2$ ($[M-(2H_2O)+H]^+$) *m/z* = 345.1855, found 345.1868.



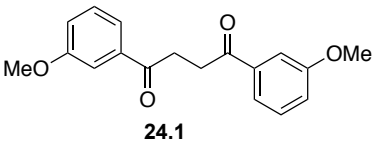
23.3

***Allylic alcohols* 23.3:** 1,4-diketone **22.6** (0.171 g, 0.488 mmol), as a solution in THF (6 mL), was added to a stirred 60 °C solution vinyl magnesium chloride (1.6 M in THF, 1.0 mL, 1.6 mmol). After 30 minutes, the reaction mixture was poured into water (30 mL) and further diluted with 1 M HCl (15 mL). The resulting mixture was extracted with dichloromethane (3 × 15 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatography (18 × 1.3 cm, 1:4 EtOAc/hexanes) to give hydroxyketone **18c** (0.060 g, 34%) and allylic alcohols **23.3** (0.098 g, 51%; 77% based on recovery of **18c**) as a mixture of diastereomers (dr = 5:1). A single column fraction produced pure sample of the major (slower moving) diastereomer, *syn*-(or *meso*) **23.3**: R_f = 0.20 (1:4 EtOAc/hexanes), 0.59 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.12 (m, 2H), 7.03 (dd, *J* = 2.6, 1.7 Hz, 2H), 6.85-6.79 (m, 2H), 6.74 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 2H), 6.18 (dd, *J* = 17.2, 10.7 Hz, 2H), 5.34 (dd, *J* = 17.2, 1.2 Hz, 2H), 5.18 (dd, *J* = 10.7, 1.2 Hz, 2H), 4.10 (dt, *J* = 10.5, 6.2 Hz, 2H), 3.97 (dt, *J* = 10.6, 6.4 Hz, 2H), 3.72 (s, 2H), 1.81-1.71 (m, 8H), 1.70-1.56 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 147.5, 143.3, 129.3, 118.4, 114.3, 113.6, 112.3, 76.8, 67.6, 37.1, 27.8, 21.4; HRMS (ESI) calculated for $C_{25}H_{27}O_2$ ($[M-(2H_2O)+H]^+$) *m/z* = 359.2011, found 359.2023.



23.4

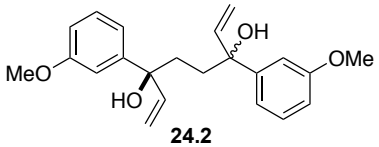
***Allylic alcohol* 23.4:** 1,4-diketone **22.6** (0.560 g, 1.59 mmol), as a solution in THF (10 mL), was added to a stirred 65 °C solution vinylmagnesium chloride (1.6 M in THF, 5.2 mL, 8.3 mmol). After 1 h, the reaction mixture was poured into water (100 mL) and further diluted with 1 M HCl (30 mL). The resulting mixture was extracted with dichloromethane (3 × 30 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The solid residue was purified by flash chromatography (15 × 2.5 cm, 1:4 EtOAc/hexanes) to give hydroxyketone **19b** (0.250 g, 41%) and allylic alcohol **23.4** (0.310 g, 47%; 86% based on recovery of **19b**) as an inseparable mixture of diastereomers (2.3:1 *d.r.*): R_f = 0.14 (1:4 EtOAc/hexanes), 0.59 (1:1 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.19 (dd, *J* = 7.7, 1.7 Hz, 2H), 6.80 (dd, *J* = 8.2, 2.4 Hz, 2H), 6.59-6.54 (m, 2H), 6.08 (dd, *J* = 17.3, 10.6 Hz, 2H), 5.18 (d, *J* = 17.3 Hz, 2H), 5.01 (d, *J* = 10.6 Hz, 2H), 4.11-4.03 (m, 2H), 3.98-3.94 (m, 2H), 2.51 (s, 2H), 2.02-1.94 (m, 2H), 1.93-1.86 (m, 2H), 1.83-1.76 (m, 4H), 1.73-1.56 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2, 146.2, 145.7, 129.4, 117.4, 113.2, 112.3, 111.3, 76.8, 66.8, 35.6, 28.4, 24.7; HRMS (ESI) calculated for $C_{26}H_{33}O_4$ ($[M+H]^+$) *m/z* = 409.2379, found 409.2380.



24.1

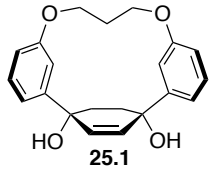
***Streamlined synthesis of 1,4-diketone* 24.1:** Vinylmagnesium chloride (1.6 M in THF, 2.8 mL, 4.4 mmol) was added to a stirred solution of 3-methoxybenzaldehyde (0.400 g, 2.94 mmol) in DCM (10 mL). After 10 min., the reaction was poured into water (10 mL) and further diluted with 1 M HCl (5 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (10 mL) and water (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (44 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.137 g, 0.22 mmol). After 1 h, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (40 mL), and sodium borohydride (0.456 g, 12.0 mmol) was added. After 3 h, the reaction was poured into water (10 mL) and further diluted with 1 M HCl (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with water (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The dark brown residue was dissolved in dichlormethane

(10 mL), followed by the addition of PCC (1.89 g, 8.8 mmol). After 10 hour, silica was added to the the reaction and the slurry was passed through a celite pad, washed with (3 × 20.0 mL) ether and (2× 15.0 mL) dichloromethane and concentrated under reduced pressure. The residue was purified by flash chromatography (15 cm × 2.5 cm; 3:7 EtOAc/hexanes) to afford 1,4-diketone **24.1** as a white solid (0.200 g, 46% after 4 steps): R_f = 0.45 (3:7 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) d 7.65 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 2.5 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 8.3, 2.6 Hz, 2H), 3.87 (s, 6H), 3.46 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) d 198.75, 160.00, 138.28, 129.83, 121.04, 119.98, 112.40, 55.67, 32.96; HRMS (ESI) calculated for $C_{18}H_{18}O_4Na([M+Na]^+)$ *m/z* = 321.1104, found 321.1118.



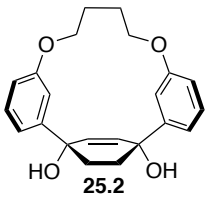
24.2

***Allylic alcohol* 24.2:** 1,4-diketone **24.1** (0.035 g, 0.117 mmol), as a solution in CH_2Cl_2 (2 mL), was added to a stirred 23 °C solution vinylmagnesium chloride (1.6 M in THF, 0.2 mL, 0.293 mmol). After 0.5 h, the reaction mixture was poured into water (5 mL) and further diluted with 1 M HCl (5 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure afforded the colourless oily residue **24.2** (0.039 g, 94%) as an inseparable mixture of diastereomers (1:1 *d.r.*): R_f = 0.15 (1:49 Acetone/DCM) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (td, *J* = 7.9, 4.8 Hz, 2H), 7.01-6.91 (m, 4H), 6.77 (td, *J* = 7.7, 2.4 Hz, 2H), 6.11 (dt, *J* = 17.2, 10.3 Hz, 2H), 5.26 (t, *J* = 17.9 Hz, 2H), 5.12 (dd, *J* = 19.9, 10.7 Hz, 2H), 3.80 (d, *J* = 2.6 Hz, 6H), 2.56 (s, 1H), 2.02 (q, *J* = 5.6, 5.2 Hz, 1H), 1.91 (s, 2H), 1.82 (q, *J* = 5.7 Hz, 1H), 1.27 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.62, 147.34, 147.23, 144.20, 144.04, 129.43, 117.86, 113.04, 112.99, 112.07, 112.03, 111.47, 111.40, 76.83, 76.81, 55.62, 55.37, 35.78, 35.69; HRMS (ESI) calculated for $C_{22}H_{25}O_3([M-(H_2O)]+H]^+)$ *m/z* = 337.1804, found 337.1798.



25.1

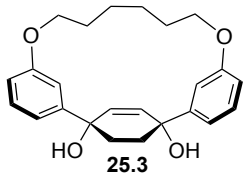
***Cyclohex-2-ene-1,4-diol* 25.1:** Vinylmagnesium chloride (1.6 M in THF, 0.45 mL, 0.70 mmol) was added to a stirred solution of 1,4-diketone **22.4** (0.100 g, 0.322 mmol), in THF (4 mL) at 65 °C. After 30 min., the reaction mixture was cooled to room temperature, poured into water (20 mL), and further diluted with 1 M HCl (10 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (10 mL), the Grubbs second-generation catalyst (0.007g, 0.008 mmol) was added, and the reaction was heated to 40 °C. After 2 h, the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The brown residue was purified by flash chromatography (15 × 1.3 cm, 3:2 EtOAc/hexane) to give compound **25.1** as an off-white solid (0.065 g, 60%); R_f = 0.41 (7:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 4H), 7.03-6.99 (m, 2H), 6.92-6.84 (m, 2H), 6.14 (s, 2H), 4.46-4.30 (m, 2H), 4.29-4.23 (m, 2H), 2.29-2.08 (m, 6H), 1.84-1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.88, 146.95, 142.95, 129.36, 119.04, 115.62, 114.07, 113.62, 76.93, 65.44, 37.24, 27.78; HRMS (ESI) calculated for $C_{21}H_{21}O_3([M-(H_2O)]+H]^+)$ *m/z* = 321.1491, found 321.1493.



25.2

***Cyclohex-2-ene-1,4-diol* 25.2:** Grubbs' second-generation catalyst (0.023 g, 0.026 mmol) was added to a stirred solution of **23.2** (>20:1 *d.r.*; 0.201 g, 0.526 mmol) in dichloromethane (35 mL) and the reaction was heated to 40 °C. After 2 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 2.5 cm, 1:1 EtOAc/hexanes) to give compound **25.2** as an off-white solid (0.159 g, 86%); R_f = 0.27 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 4H), 7.05-6.99 (m, 2H), 6.80 (ddd, *J* = 7.7, 2.5, 1.4 Hz, 2H), 6.08 (s, 2H), 4.26-4.11 (m, 2H), 4.06-3.93 (m, 2H),

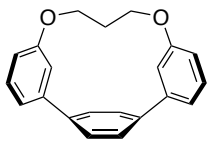
2.17 (s, 2H), 2.14-1.98 (m, 4H), 1.97-1.78 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.64, 147.77, 134.96, 130.23, 117.59, 114.70, 113.81, 73.25, 69.81, 37.00, 26.98. HRMS (ESI) calculated for $C_{22}H_{23}O_3$ ([M-(H_2O)+H]$^+$) *m/z* = 335.1647, found 335.1641.



25.3

***Cyclohex-2-ene-1,4-diol* 25.3:** Grubbs' second-generation catalyst (0.020 g, 0.023 mmol) was added to a stirred solution of **23.4** (2.3:1 *d.r.*; 0.380 g, 0.930 mmol) in dichloromethane (23 mL) and the reaction was heated to 40 °C. After 2 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 x 2.5 cm, 3:7 EtOAc/hexanes) to give compound **25.4** as an off-white solid (0.225 g, 59%, 85% based on recovered *anti*-**23.4**) and (uncyclized) *anti*-**23.4** (0.106 g, 92% recovery).

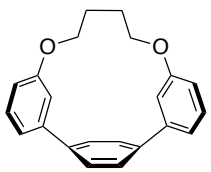
***Cyclohex-2-ene-1,4-diol* 25.3:** R_f = 0.29 (1:1 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H), 6.93-6.88 (m, 2H), 6.80-6.74 (m, 2H), 5.96 (s, 2H), 4.02-3.94 (m, 4H), 2.54 (s, 2H), 2.08-2.03 (m, 2H), 1.86-1.74 (m, 6H), 1.63-1.55 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.83, 147.84, 134.66, 130.13, 117.49, 113.76, 112.62, 72.98, 67.62, 36.33, 27.78, 24.63; HRMS (ESI) calculated for $C_{24}H_{27}O_3$ ([(M-H_2O)+H]$^+$) *m/z* = 363.1960, found 363.1968.



25.4

***1,5-dioxa[5](3,3")p-terphenylenophane* (25.4):** Burgess reagent (0.126 g, 0.530 mmol) was added to a stirred solution of **25.1** (0.044 g, 0.130 mmol) in toluene (2.5 mL) at 80 °C. After 15 min., the reaction was cooled to room temperature, water (20 mL) was added, and the resulting mixture was stirred for 5 min. The layers were separated and the mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 1.3 cm, 1:1 dichloromethane/hexanes) to afford **25.1** as a white solid (0.023 g, 58%): R_f = 0.43 (2:3 dichloromethane/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (s, 4H), 7.33-7.26 (m, 2H), 7.25-7.21 (m, 2H), 6.72 (dd, *J* = 8.3, 2.8 Hz, 2H), 5.35 (s, 2H), 4.12-3.81 (m, 4H), 1.96-1.86 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.25, 145.19, 145.13, 131.75, 130.53, 118.50, 115.48, 115.42, 64.67, 25.16; HRMS (EI) calculated for $C_{21}H_{18}O_2$ (M^+) *m/z* = 302.1307, found 302.1336.

***Alternate procedure for* 25.4:** Trifluoromethanesulfonic anhydride 0.088 g, 0.31 mmol) and pyridine (0.5 mL) were added to a stirred solution of **28.1** (0.020 g, 0.062 mmol) in dichloromethane (2 mL) at 0 °C. After 30 min., the cooling bath was removed and the reaction was warmed to room temperature, poured into water (10 mL), and further diluted by 1 M HCl (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with saturated solution of $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatograph (12 × 0.5 cm, 2:3 dichloromethane/hexanes) to afford **25.5** as a white solid (0.003 g, 16%).



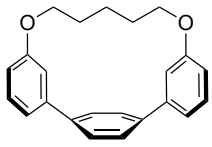
25.5

***1,6-dioxa[6](3,3')p-Terphenylenophane* (25.5)**: *p*-Toluene sulfonic acid monohydrate (0.130 g, 0.684 mmol) was added to a stirred solution of **25.2** (0.040 g, 0.11 mmol) in toluene (6 mL). The reaction was heated at 50 °C for 10 h and then to 60 °C for 5 h. After 15 h, a saturated solution of $NaHCO_3$ (20 mL) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The organic extracts were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 5% EtOAc/hexanes) to afford **25.6** as a white solid (0.015 g, 42%): R_f = 0.43 (5% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 4H), 7.36-7.32 (m, 2H), 7.26-7.24 (m, 2H),

6.78 (dd, *J* = 8.4, 2.7 Hz, 2H), 5.31 (d, *J* = 2.9 Hz, 2H), 3.95-3.89 (s, 4H), 1.46-1.40 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.29, 144.82, 144.55, 130.30, 117.70, 115.81, 115.69, 67.29, 22.77; HRMS (EI) calculated for $C_{22}H_{21}O_2$ (M^+) *m/z* = 316.1463, found 316.1437.

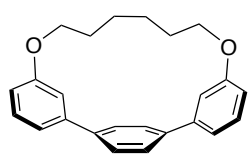
***Alternate procedure for 25.5*:** Sodium hydrogen sulfate monohydrate (0.008 g, 0.06 mmol) was added to a stirred 130 °C solution of **25.2** (0.010 g, 0.028 mmol) and *o*-chloranil (0.035 g, 0.14 mmol) in DMSO (0.75 mL) and xylenes (2 mL). After 24 h, the reaction mixture was cooled to room temperature and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (10 mL) were added. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The corganic extracts were combined, filtered through a pad of Celite (2 cm), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (7.5 × 0.6 cm; 5% EtOAc/hexanes) to afford the **25.5** as a white solid (0.0032 g, 36%). A trace amount of the [6]MTPP isomer was observed in the ^{1}H NMR spectrum of **25.5**.

***Alternate procedure for* 25.5**: Burgess reagent (0.021 g, 0.088 mmol) was added to a stirred solution of **25.2** (0.010 g, 0.028 mmol) in toluene (2 mL) at 80 °C. After 15 min., the reaction was cooled to room temperature, water (10 mL) was added, and the resulting mixture was stirred for 5 min. The layers were separated and the mixture was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 1.3 cm, 1:1 dichloromethane/hexanes) to afford **25.5** as a white solid (0.005 g, 56%).



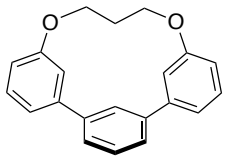
15.7

1,7-dioxa[7](3,3')-p-Terphenylenophane (**15.7**)**:** Burgess reagent (0.050 g, 0.21 mmol) was added to a stirred solution of **15.6** (0.026 g, 0.071 mmol) in toluene (3 mL) at 80 °C. After 15 min., the reaction was cooled to room temperature, water (10 mL) was added, and the resulting mixture was stirred for 5 min. The layers were separated and the mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 1.3 cm, 1:1 dichloromethane/hexanes) to afford **15.7** as a white solid (0.016 g, 68%): R_f = 0.32 (1:19 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 4H), 7.35 (dd, *J* = 8.2, 7.4 Hz, 2H), 7.30-7.24 (m, 2H), 6.78 (ddd, *J* = 8.3, 2.8, 1.0 Hz, 2H), 5.81 (dd, *J* = 2.8, 1.5 Hz, 2H), 4.10-4.05 (m, 4H), 1.51-1.42 (m, 4H), 1.21-1.12 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 144.7, 144.1, 130.6, 129.5, 118.7, 115.9, 115.4, 68.5, 26.8, 23.3; HRMS (EI) calculated for $C_{23}H_{22}O_2$ ($[M]^+$) *m/z* = 330.1618, found, 330.1620.



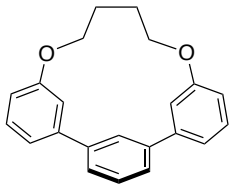
25.6

1,8-dioxa[8](3,3")-p-Terphenylenophane (**25.6**)**:** *p*-Toluene sulfonic acid monohydrate (0.502 g, 2.92 mmol) was added to a stirred solution of **25.3** (0.184 g, 0.484 mmol) in toluene (20 mL) and the reaction was heated to 60 °C. After 2 h, a saturated solution of $NaHCO_3$ (20 mL) was added to the reaction. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The organic extracts were combined and washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (15 x 1.3 cm, 1:1 dichloromethane/hexanes) to afford **25.6** as a white solid (0.120 g, 74%): R_f = 0.41 (1:1 dichloromethane/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 4H), 7.36 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.26-7.20 (m, 2H), 6.84 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 2H), 5.92 (dd, *J* = 2.8, 1.4 Hz, 2H), 4.08-3.99 (m, 4H), 1.62-1.50 (m, 4H), 1.12-1.04 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.86, 144.54, 143.59, 130.21, 128.76, 117.46, 116.63, 115.88, 68.42, 27.81, 27.63; HRMS (EI) calculated for $C_{24}H_{24}O_2$ ($[M]^+$) *m/z* = 344.1931 found 344.1896.



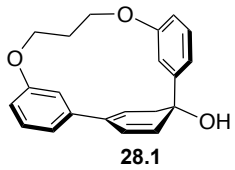
26.1

1,5-dioxa[5](3,3")m-Terphenylophane (**26.1**): *para*-Toluensulfonic acid monohydrate (0.060 g, 0.31 mmol) was added to a stirred 60 °C of **25.1** (0.012 g, 0.038 mmol) in toluene (2.5 mL). After 3 h, the reaction was heated to 70 °C for an additional 1 h, followed by the addition of a saturated solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (7 × 0.5 cm, 1:1 dichloromethane/hexanes) to afford **26.1** as a white solid (0.004 g, 40%): R_f = 0.41 (2:3 dichloromethane /hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.46-7.40 (m, 1H), 7.35-7.29 (m, 2H), 7.28 (s, 1H), 7.07-7.02 (m, 2H), 6.92 (dd, *J* = 8.2, 2.8 Hz, 2H), 4.36-4.19 (m, 4H), 2.65 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.24, 144.91, 142.84, 142.64, 129.70, 127.63, 123.74, 118.28, 117.98, 116.15, 64.23, 24.77; HRMS (EI) calculated for $C_{21}H_{18}O_2$ (M^+) *m/z* = 302.1307, found 302.1336.



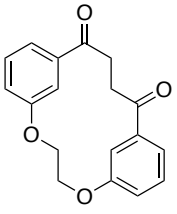
26.2

1,6-dioxa[6](3,3")m-Terphenylophane (**26.2**)**:** *para*-Toluensulfonic acid monohydrate (0.033 g, 0.17 mmol) was added to a stirred 70 °C of **25.2** (0.011 g, 0.035 mmol) in toluene (2 mL). After 12 h, a saturated solution of $NaHCO_3$ (10 mL) was added to the reaction. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (7 × 0.5 cm, 1:1 dichloromethane/hexanes) to afford **26.2** as a white solid (0.060 g, 55%): R_f = 0.31 (5% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33-8.27 (m, 1H), 7.66 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.52-7.45 (m, 1H), 7.40-7.34 (m, 4H), 7.34-7.30 (m, 2H), 6.95-6.89 (m, 2H), 4.36-4.22 (m, 4H), 2.08 (t, *J* = 4.2 Hz, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.73, 141.71, 140.49, 131.38, 130.47, 129.34, 124.04, 117.44, 116.85, 114.30, 69.01, 24.25; HRMS (EI) calculated for $C_{22}H_{21}O_2$ (M^+) *m/z* = 316.1463, found 316.1442.



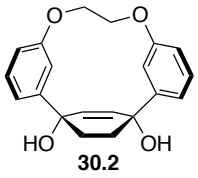
28.1

Monodehydrated compound **28.1:** Tin(II) chloride dihydrate (0.053 g, 0.230 mmol) was added to a stirred solution of **25.1** (0.008 g, 0.023 mmol) in 1:1 THF/PhMe (4 mL) at 80 °C. After 12 h, the reaction was cooled to room temperature and 3 M NaOH (5 mL) was added, followed by dichloromethane (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The off-white residue was purified by flash chromatography (4.0 × 0.7 cm, dichloromethane to 2% acetone/dichloromethane) to give compound **28.1** as colorless solid (0.006 g, 78%); R_f = 0.41 (1% acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 2.5, 1.7 Hz, 1H), 7.34-7.24 (m, 2H), 7.22-7.15 (m, 1H), 6.91 (ddd, *J* = 7.8, 2.6, 1.2 Hz, 1H), 6.84 – 6.80 (m, 1H), 6.79-6.72 (m, 2H), 6.36 (dd, *J* = 9.6, 0.9 Hz, 1H), 6.12 (dt, *J* = 9.6, 1.3 Hz, 1H), 5.66 (ddd, *J* = 7.0, 2.8, 1.4 Hz, 1H), 4.52-4.40 (m, 1H), 4.41-4.15 (m, 3H), 2.97-2.84 (m, 1H), 2.71 (ddd, *J* = 16.0, 7.0, 1.9 Hz, 1H), 2.16 (s, 1H), 2.06-1.91 (m, 1H), 1.88-1.76 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.98, 156.95, 145.10, 142.78, 139.09, 135.73, 130.31, 130.20, 129.11, 124.46, 120.22, 117.53, 116.56, 116.36, 116.05, 111.99, 75.50, 65.96, 64.25, 39.18, 26.69; HRMS (EI) calculated for $C_{21}H_{20}O_3$ (M^+) *m/z* = 320.1412, found 320.1410



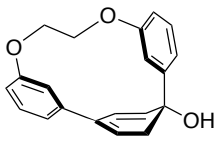
30.1

1,4-diketone **30.1**: Vinylmagnesium chloride (1.6 M in THF, 7.3 mL, 12 mmol) was added to a stirred 0 °C solution of dialdehyde **19d** (1.25 g, 4.63 mmol) in CH_2Cl_2 (35 mL). After 30 min., the reaction mixture was poured into water (100 mL) and further diluted with 1 M HCl (50 mL). The resulting mixture was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na2SO4, and filtered. The resulting solution was diluted with dichloromethane (320 mL), heated to 40 °C, followed by the addition of the Hoveyda-Grubbs second-generation catalyst (0.080 g, 0.13 mmol). After 4 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (15 mL) and sodium borohydride (0.700 g, 18.5 mmol) was added at room temperature. After 1.5 h, the reaction mixture was poured into water (100 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dichlormethane (40 mL), followed by the sequential addition of $NaHCO_3$ (0.840 g, 10.0 mmol) and Dess-Martin periodinane (4.15 g, 9.20 mmol). After 30 min., a 10% aqueous solution of $Na_2S_2O_3$ (50 mL) was added to the reaction and stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 × 50 mL). The organic extracts were combined and washed with water (100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash chromatography (15 cm × 2.5 cm; 3:7 ethyl acetate/hexane) to give **30.1** as a beige solid (0.180 g, 14% over 4 steps): R_f = 0.42 (3:7 ethyl acetate/hexane); ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.70-7.64 (m, 2H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.39 (dd, *J* = 2.5, 1.6 Hz, 2H), 7.23 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 2H), 4.46 (s, 4H), 3.11 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.82, 157.88, 136.80, 131.14, 123.19, 122.04, 113.29, 64.22, 36.02; HRMS (ESI) calculated for $C_{18}H_{17}O_4$ ($[M+H]^+$) *m/z* = 297.1127, found 297.1113



30.2

Cyclohex-2-ene-1,4-diol **30.2**: Grubbs second-generation catalyst (0.018 g, 0.020 mmol) was added to a stirred solution of syn-allylic diol **19e** (0.140 g, 0.397 mmol) in dichloromethane (12 mL) at 40 °C. After 1.5 h, the reaction was cooled to room temperature and the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 1.3 cm, 10-20% acetone/dichloromethane) to give **30.2** as an off-white solid (0.102 g, 79 %); R_f = 0.38 (1:4 acetone/dichloromethane); ^{1}H NMR(600 MHz, $CDCl_3$) δ 7.40-7.32 (m, 4H), 7.22 (br s, 2H), 6.91-6.84 (m, 2H), 5.88 (s, 2H), 4.52 (d, *J* = 7.4 Hz, 2H), 4.17-4.05 (m, 2H), 2.27-2.11 (m, 4H), 2.11-2.00 (m, 2H); ^{13}C NMR(151 MHz, acetone-d_6) δ 157.89, 150.28, 135.07, 130.96, 119.77, 117.67, 112.55, 73.41, 63.95, 37.02; HRMS (ESI) calculated for $C_{20}H_{19}O_3$ ($[M-(H_2O)+H]^+$) *m/z* = 307.1334, found 307.1342

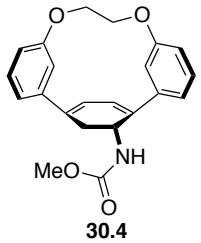


30.3

Dienol **30.3:** Burgess reagent (0.016 g, 0.066 mmol) was added to a stirred solution of **30.2** (0.010 g, 0.033 mmol) in THF (2 mL) at 70 °C. After 2.5 h, the reaction was cooled to room temperature, water (10 mL) was added, and stirred for 5 min. The resulting mixture was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (5 mL), dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5 × 0.7 cm, dichloromethane to 2% acetone/dichloromethane) to afford **30.3** as a colorless solid (0.007 g, 68%): R_f = 0.44 (2% acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.35 (m, 2H), 7.30-7.27 (m, 1H), 7.02-6.95 (m, 2H), 6.95-6.91 (m, 1H), 6.84 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.60-6.54 (m, 1H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.91 (dd, *J* = 9.6, 1.9 Hz, 1H), 5.66 (ddd, *J* = 7.3, 3.0, 1.1 Hz, 1H), 4.54-4.43 (m, 1H), 4.37-4.25 (m, 3H), 2.89 (dd, *J* = 15.5, 3.1 Hz, 1H), 2.43 (ddd, J = 15.5, 7.2, 2.0 Hz, 1H), 2.14 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.11, 156.30, 143.96, 142.12, 142.07, 134.03, 131.13, 130.41, 130.32, 121.60, 120.01, 118.96, 117.73, 116.78, 116.44, 116.15, 76.58, 65.43, 64.45,

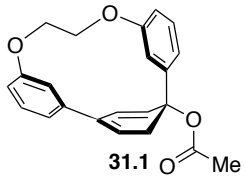
40.29; HRMS (ESI) calculated for $C_{20}H_{19}O_3$ ([M+H]$^+$) m/z = 307.1334, found 307.1342.

***Alternative procedure for dienol* 30.3:** Tin(II) chloride dehydrate (0.625 g, 2.77 mmol) was added to a stirred solution of **30.2** (0.040 g, 0.14 mmol) in 1:1 THF/PhMe (6 mL) at 80 °C. After 24 h, the reaction was cooled to room temperature and 3 M NaOH (10 mL) was added, followed by dichloromethane (10 mL). 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 1.3 cm, 4% acetone/dichloromethane) to give **30.3** as colorless solid (0.025 g, 60%).



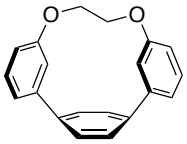
30.4

***Carbamate* 30.4:** Burgess reagent (0.055 g, 0.23 mmol) was added to a stirred solution of **30.2** (0.019 g, 0.058 mmol) in THF (2.5 mL) at 50 °C. After 1 h, the reaction was cooled to room temperature, water (20 mL) was added, and stirred for 5 min. The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10 × 1.0 cm, dichloromethane to 10% acetone/dichloromethane) to afford **30.4** as a white solid (0.008 g, 37%): R_f = 0.39 (10% acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49- 7.45 (m, 1H), 7.43-7.37 (m, 1H), 7.36-7.32 (m, 1H), 7.30-7.24 (m, 1H), 7.03-6.98 (m, 2H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 8.4, 2.7 Hz, 1H), 6.67 (dd, *J* = 9.8, 2.0 Hz, 1H), 6.36 (dd, *J* = 9.9, 1.3 Hz, 1H), 6.27 (dd, *J* = 2.7, 1.3 Hz, 1H), 5.59 (ddd, *J* = 7.3, 3.0, 1.3 Hz, 1H), 4.52-4.35 (m, 2H), 4.33-4.19 (m, 2H), 3.85 (s, 3H), 3.38 (dd, *J* = 15.2, 3.0 Hz, 1H), 2.68 (ddd, *J* = 15.2, 7.3, 2.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.36, 156.49, 150.39, 142.43, 141.13, 138.33, 132.42, 130.37, 130.18, 127.79, 121.36, 120.20, 118.86, 118.71, 117.42, 116.83, 116.49, 96.03, 66.97, 64.36, 54.21, 38.48; HRMS (ESI) calculated for $C_{22}H_{22}NO_4$ ([M+H]$^+$) *m/z* = 364.1549, found 364.1560



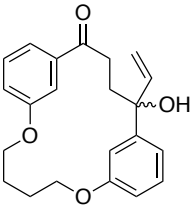
31.1

***Acetate* 31.1**: Acetic anhydride (0.060 g, 0.59 mmol) and DMAP (0.0036 g, 0.010 mmol) were added to a stirred solution of **30.3** (0.030 g, 0.098 mmol) in pyridine (2.5 mL) at 40 °C. After 12 h, the reaction was cooled to room temperature and water (10 mL) was added. The resulting mixture was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were washed brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The solid residue was purified by flash chromatography (10 × 1.3 cm, dichloromethane) to give **31.1** as colorless solid (0.026 g, 74%); R_f = 0.49 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.9 Hz, 1H), 7.30-7.25 (m, 1H), 7.07 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 7.00 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.96-6.92 (m, 1H), 6.90 (ddd, *J* = 8.0, 2.6, 0.9 Hz, 1H), 6.83 (ddd, *J* = 8.3, 2.8, 0.9 Hz, 1H), 6.48 (dd, *J* = 2.9, 1.4 Hz, 1H), 6.37-6.28 (m, 2H), 5.62 (ddd, *J* = 7.3, 3.1, 1.1 Hz, 1H), 4.52-4.42 (m, 1H), 4.35 (dt, *J* = 12.8, 5.5 Hz, 1H), 4.27 (td, *J* = 5.7, 2.9 Hz, 2H), 3.11 (dd, *J* = 15.4, 3.1 Hz, 1H), 2.43 (ddd, *J* = 15.4, 7.2, 1.8 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.05, 157.34, 156.53, 142.53, 141.88, 141.76, 131.30, 130.25, 130.17, 129.03, 120.69, 118.87, 118.79, 117.55, 117.42, 116.33, 116.31, 83.66, 66.09, 64.62, 38.15, 22.30; HRMS (ESI) calculated for $C_{22}H_{21}O_4$ ([M+H]$^+$) *m/z* = 349.1440, found 349.1428.



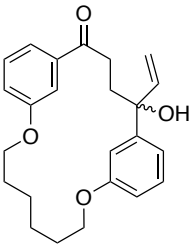
31.2

1,4-dioxa(3,3'')[4]p-terphenylophane (**31.2**)**:** A solution of *n*-butyllithium in hexanes (2.53 M, 0.80 mL, 2.0 mmol) was added dropwise to a stirred solution of diisopropylamine (0.50 mL, 3.6 mmol) in toluene (10 mL) at 0 °C. After 30 min., a solution of **31.1** (0.024 g, 0.066 mmol) in toluene (2.0 mL) was added at 0 °C. After 1 h, the reaction was quenched with water (20 mL), the layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatograph (4 × 0.6 cm, 1:1 dichloromethane/hexanes) to afford **31.2** as a white solid (0.012 g, 63%): R_f = 0.42 (2:3 dichloromethane/hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br s, 4H), 7.31-7.26 (m, 2H), 7.24-7.21 (m, 2H), 6.70 (ddd, *J* = 8.2, 2.9, 1.0 Hz, 2H), 5.29 (dd, *J* = 3.0, 1.4 Hz, 2H), 4.20-3.76 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.25, 145.57, 145.19, 130.59, 117.85, 115.69, 115.63, 62.34 (Only 8 of 9 signals are observed δ 130.59 corresponds to 2 carbons); HRMS (EI) calculated for $C_{20}H_{16}O_2$ (M^+) m/z = 288.1150, found 288.1158



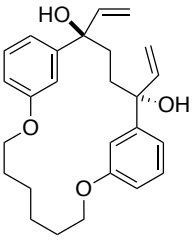
20a

Hydroxy ketone **20a:** R_f = 0.35 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.38-7.30 (m, 2H), 7.12 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 7.04 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 6.96-6.93 (m, 1H), 6.92-6.90 (m, 1H), 6.88 (dd, *J* = 2.5, 1.0 Hz, 1H), 6.86 (dd, *J* = 2.5, 1.0 Hz, 1H), 5.31 (dd, *J* = 17.3, 0.9 Hz, 1H), 5.15 (dd, *J* = 10.7, 0.8 Hz, 1H), 4.27-4.17 (m, 2H), 4.18-4.10 (m, 1H), 4.03-3.93 (m, 1H), 2.79-2.56 (m, 2H), 2.44-2.24 (m, 2H), 2.13-1.88 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.84, 158.68, 158.59, 145.39, 144.29, 137.62, 129.98, 129.74, 120.38, 119.80, 118.30, 115.98, 113.38, 113.34, 113.05, 77.07, 69.16, 67.06, 39.19, 33.75, 26.45, 25.80; HRMS (ESI) calculated for $C_{22}H_{23}O_3$ ([M-(H_2O)+H]$^+$) *m/z* = 335.1647, found 335.1647.



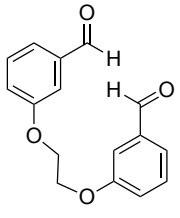
20b

Hydroxy ketone **20b**: R_f = 0.33 (1:4 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58-7.52 (m, 1H), 7.37-7.32 (m, 1H), 7.29-7.24 (m, 1H), 7.21 (s, 1H), 7.12 (s, 1H), 7.06 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.93 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.79 (dd, *J* = 8.1, 2.6 Hz, 1H), 6.26 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 5.17 (d, *J* = 10.6 Hz, 1H), 4.12-3.96 (m, 4H), 2.95 (dt, *J* = 15.5, 7.6 Hz, 1H), 2.57 (dt, *J* = 15.1, 6.6 Hz, 1H), 2.45 (dt, *J* = 14.8, 7.6 Hz, 1H), 2.33-2.19 (m, 1H), 2.09 (s, 1H), 1.97-1.74 (m, 4H), 1.69-1.56 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.35, 159.19, 158.89, 145.49, 144.45, 138.18, 129.74, 129.45, 120.02, 118.67, 118.00, 116.16, 112.99, 112.76, 111.58, 76.61, 67.99, 66.45, 37.18, 33.02, 28.09, 27.90, 24.66, 24.33.



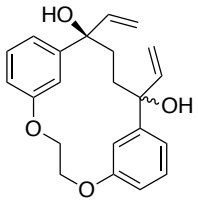
20c

anti-**20c:** R_f = 0.33 (1:4 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 7.15-7.10 (m, 2H), 6.79-6.73 (m, 2H), 6.58-6.52 (m, 2H), 6.06 (dd, *J* = 17.2, 10.6 Hz, 2H), 5.15 (dd, *J* = 17.2, 1.0 Hz, 2H), 5.00 (dd, *J* = 10.6, 1.0 Hz, 2H), 4.03 (dt, *J* = 9.3, 4.8 Hz, 2H), 3.94 (td, *J* = 9.2, 3.9 Hz, 2H), 2.00 (s, 2H), 1.95-1.88 (m, 2H), 1.88-1.80 (m, 2H), 1.79-1.72 (m, 1H), 1.69-1.50 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.15, 146.18, 145.66, 129.43, 117.42, 113.21, 112.31, 111.30, 76.80, 66.75, 35.64, 28.38, 24.71; HRMS (ESI) calculated for $C_{26}H_{33}O_4$ ([M+H]$^+$) *m/z* = 409.2379, found 409.2372.



20d

***Dialdehyde* 20d:** 3-Hydroxybenzaldehyde (12.2 g, 100 mmol) and KOH (5.80 g, 100 mmol) were dissolved in ethanol (125 ml) and solvent was removed under vacuum. The residue was dissolved in DMF (200 ml) and 1,2-dibromoethane (18.5 g, 98.6 mmol) was added slowly. The reaction mixture was heated at 120 °C for 72 h, at which point water (400 mL) and 1 M HCl (100 mL) were added. The resulting mixture was extracted with ethyl acetate (3 × 100 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via flash chromatography (15 cm × 5.0 cm; 0.5%-2% acetone/dichloromethane to afford **20d** as brown solid. (1.80 g, 13%): R_f = 0.48 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 2H), 7.53-7.45 (m, 6H), 7.27-7.23 (m, 2H), 4.43 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.20, 159.19, 137.88, 130.33, 124.23, 122.29, 112.73, 66.72. HRMS (ESI) calculated for $C_{16}H_{15}O_4$ ([M+H]$^+$) *m/z* = 271.0970, found 271.0975.



20e

***Allylic alcohol* 20e:** Vinylmagnesium chloride (1.6 M in THF, 0.79 mL, 1.3 mmol) was added to a stirred solution of 10 (0.150 g, 0.507 mmol), in CH_2Cl_2 (10 mL) at 40 °C in a flame-dried two neck flask. After 30 min., the reaction mixture was poured directly into water (40 mL) and further diluted with 1 M HCl (20 mL). The resulting mixture was extracted with dichloromethane (3 × 15 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid was purified by flash chromatography (15 × 1.3 cm, 5-10% acetone/dichloromethane) to give **20e** as a single diastereomer (0.151 g, 75%): R_f = 0.26, (1:19 acetone/dichloromethane); ^{1}H NMR (400 MHz, CDCl3) δ 7.33-7.24 (m, 2H), 7.13-7.04 (m, 2H), 6.94 (dd, *J* = 8.1, 2.2 Hz, 2H), 6.39-6.27 (m, 2H), 6.20 (dd, *J* = 17.2, 10.8 Hz, 2H), 5.30 (d, *J* = 17.1 Hz, 2H), 5.15 (d, *J* = 10.7 Hz, 2H), 4.45-4.27 (m, 4H), 1.88 (s, 2H), 1.84-1.69 (m, 4H); ^{13}C NMR (101 MHz, CDCl3) δ 158.67, 145.60, 143.29, 129.51, 120.01, 116.74, 114.58, 113.24, 77.39, 68.34, 36.78; HRMS (ESI) calculated for $C_{22}H_{25}O_4$ ([M-(2H_2O)+H]$^+$) *m/z* = 317.1542, found 317.1539.

Annulative Pi-EXtension (APEX) of Selectively Substituted Benzenoid Macrocycles: An Investigation of the Scholl Reaction and Allylic Arylation

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 for 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 × 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. ^{1}H 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, 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).

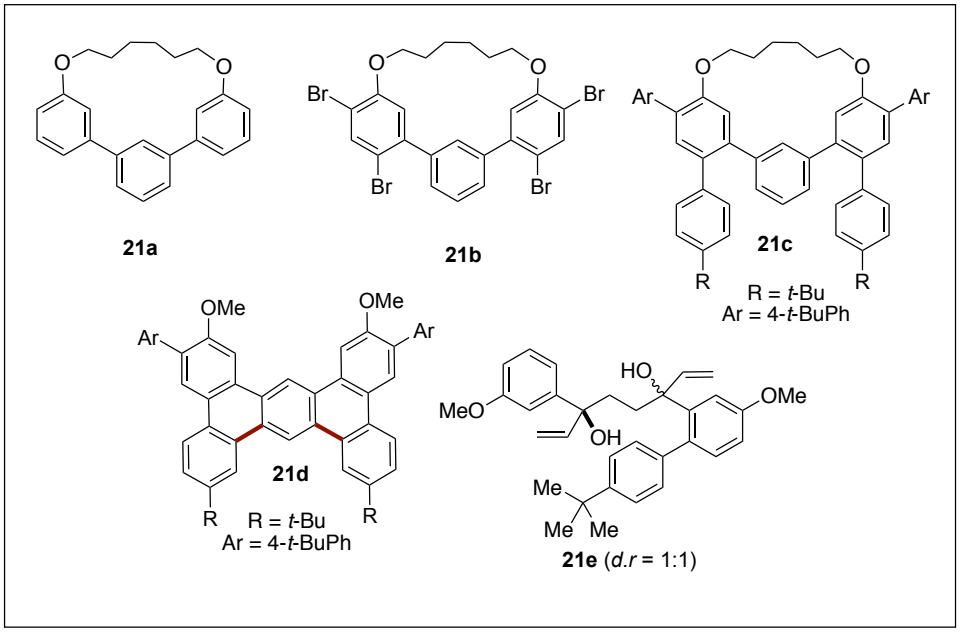


FIGURE 21: Compounds not numbered in Chapter 3 that appear in Appendix 3

General Reaction Procedures

This chapter required the preparation of a series of homologous benzenoid macrocycles, which were regioselectively functionalized using bromination, Suzuki, and Scholl reactions. While the precise experimental conditions for each of these reactions have been listed below, general reaction procedures for these three reactions are also presented.

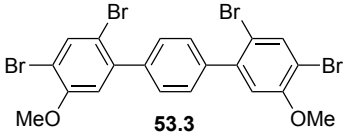
Procedure 1: *Bromination of p-terphenyl-containing macrocycles*

Bromine (8-12 equiv.) was added to a stirred solution of the macrocycle in 1,2-dichlorbenzene (50 mM) and was heated to 80 °C. After 2-6 h the solvent was evaporated under a gentle stream of nitrogen gas while heating at 80 °C and then cooled to room temperature. The residue was dissolved in dichloromethane, and a solution of 5% $NaHSO_3$ was added. The resulting mixture was stirred for 10 min. The layers were separated and the aqueous phase extracted with dichloromethane. The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used directly in a Suzuki cross-coupling without further purification.

Procedure 2: *Suzuki Cross-Coupling Reactions of brominated p-terphenyl-containing macrocycles*
NOTE: All solvents used for these reactions were purged with nitrogen gas for 30 min prior to use.
Sodium carbonate (30 equiv.) and boronic acid (8 equiv.) were added sequentially to a stirred solution of the tetrabrominated macrocycle in a toluene/water/ethanol mixture (6:2:1, 40-50 mM) at room temperature. Tetrakis(triphenylphosphine)palladium(0) catalyst (10-12 mol%) was added while gently passing nitrogen gas over the reaction vessel. The resulting mixture was heated to 90 °C for 2-14 h and then cooled to room temperature, at which point water was added to the reaction. The reaction mixture was extracted with dichloromethane, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/hexanes).

Procedure 3: *Scholl-based cyclodehydrogenation of tetraarylated p-terphenyl-containing macrocycles*
NOTE: All solvents used for these reactions were purged with ultra high pure argon gas for 30 min prior to use.

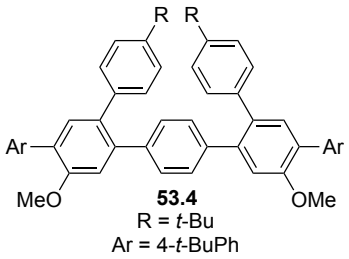
A 0 °C solution of Iron(III) chloride (2.5-20.0 equiv) in nitromethane/ dichloromethane (1:9, *ca.* 100 mM) was added to a stirred 0 °C solution of tetraarylated macrocycle in dichloromethane (5 mM). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon filled balloon was placed over the reaction. After 15-60 min, methanol was added to the reaction. At this stage, the deep green color of the reaction is dissipated. Water was added and the layers were separated. The aqueous phase was extracted with dichloromethane, and the combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered through a 3 cm pad of silica gel, and concentrated under reduced pressure. In most cases, no purification was required, but in instances were purification was necessary, flash chromatography with dichloromethane/hexanes or ethyl acetate/hexanes was employed.



53.3

4,4",6,6"-tetrabromo-3,3"-dimethoxy-p-terphenyl (**53.3**)***:*** Bromine (0.480 g, 3.00 mmol) was added to a stirred solution of 3,3"-dimethoxy-*p*-terphenyl (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 **53.3** a pale yellow solid (0.096 g, 57%): R_f = 0.51 (2:3 dichloromethane/hexane); ^{1}H 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 $C_{20}H_{14}O_2Br_4$ ($[M]^+$) *m/z* = 605.7686, found 605.7662.

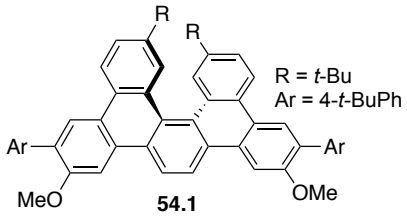


53.4
R = *t*-Bu
Ar = 4-*t*-BuPh

4,4",6,6"-tetrakis(4-t-butylphenyl)-3,3"-dimethoxy-p-terphenyl **(53.4):** Sodium carbonate (0.731 g, 6.89 mmol, as an aqueous solution, 3 mL) and 4-*tert*-butylphenyl boronic acid (0.332 g, 1.85 mmol) were added sequentially to a stirred solution of **53.3** (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 × 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 **53.4** as a white solid (0.160 g, 85%): R_f = 0.42 (1:19 ethyl acetate/hexanes); ^{1}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}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 $C_{60}H_{66}O_2$ ($[M]^+$) *m/z* = 818.5063, found 818.5024.

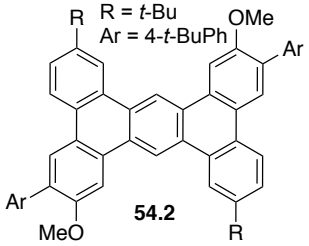
Scholl reaction on Model compound

Tetrabenzo[5]helicene (**54.1**) ***and Tetrabenzanthracene*** (**54.2**)*:* 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 **53.4** (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 transoid tetrabenzanthracene **54.2** as a white solid and cisoid tetrabenzo[5]helicene **54.1** as a pale yellowish solid.



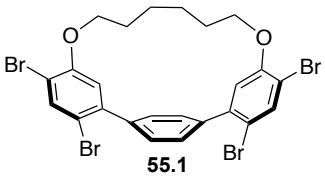
54.1

PAH **54.1** (0.026 g, 65%): R_f = 0.17 (1:19 ethyl acetate/hexanes); ^{1}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}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 $C_{60}H_{62}O_2$ ($[M]^+$) *m/z* = 814.4744, found 814.4788.



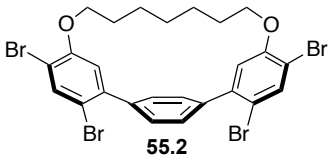
54.2

***PAH* 54.2** (0.003 g, 7%): R_f = 0.30 (1:19 ethyl acetate/hexanes); ^{1}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}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 $C_{60}H_{62}O_2$ ($[M]^+$) *m/z* = 814.4750, found 814.4788.



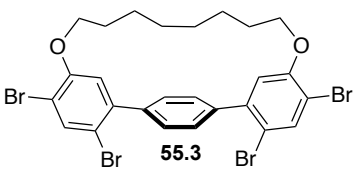
55.1

4,4",6,6"- tetrabromo -1,8 – dioxa [8] (3,3")p-terphenylophane (**55.1**)**:** Bromine (0.368 g, 2.32 mmol) was added to a stirred solution of **25.8** (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), a solution of 5% $NaHSO_3$ (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 $NaHCO_3$ (15 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford **55.1** as a white solid (0.184 g, 97%): R_f = 0.31 (3:7 dichloromethane/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{24}H_{20}O_2Br_4$ ($[M]^+$) *m/z* = 655.8197, found 655.8224.



55.2

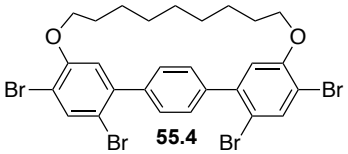
4,4", 6,6"- tetrabromo-1,9-dioxa [9](3,3")p-terphenylophane (**55.2**)**:** Bromine (0.71 g, 4.4 mmol) was added to a stirred solution of [9]PTPP (0.020 g, 0.056 mmol) in 1,2-dichlorobenzene (2.0 mL). The resulting mixture was heated to 70 °C for 6 h and then cooled to room temperature under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL), a 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 extracted with dichloromethane (2 × 15 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 **55.2** as a white solid (0.038 g, > 95%): R_f = 0.34 (3:7 dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{25}H_{22}O_2Br_5$ ($[M+Br]^+$) *m/z* = 748.7537, found 748.7537.



55.3

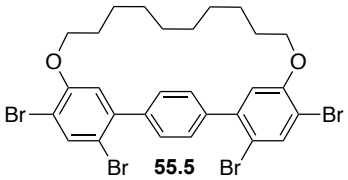
4,4", 6,6"-tetrabromo-1,10-dioxa [10](3,3")p-terphenylophane (**55.3**)**:** Bromine (0.178 g, 1.12 mmol) was added to a stirred solution of [10]PTPP (0.052 g, 0.14 mmol) in 1,2-dichlorobenzene (6 mL). The resulting mixture was heated to 80 °C for 12 h and then cooled to room temperature under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (15 mL), a solution of 5% $NaHSO_3$ (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 $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered,

and concentrated under reduced pressure to yield **55.3** as a white solid (0.090 g, 93%): R_f = 0.37 (3:7 dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) 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 $C_{26}H_{24}O_2Br_5$ ($[M+Br]^+$) *m/z* = 762.7693, found 762.7702.



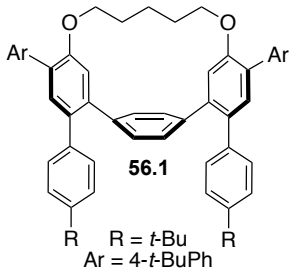
55.4

4,4", 6,6"-tetrabromo-1,11-dioxa [11] (3,3")p-terphenylophane (**55.4**)**:** Bromine (0.150 g, 0.939 mmol) was added to a stirred solution of [11]PTPP (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), a 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 **55.4** as a white solid (0.042 g, 92%): R_f = 0.37 (3:7 dichloromethane/hexanes); ^{1}H 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 (APCI) calc'd for $C_{27}H_{28}O_2Br_5$ ($[M+H+Br]^+$) *m/z* = 778.8006, found 778.7968.



55.5

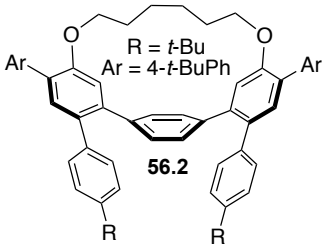
4,4", 6,6"-tetrabromo-1,12-dioxa [12] (3,3")p-terphenylophane (**55.5**)**:** Bromine (0.052 g, 0.32 mmol) was added to a stirred solution of [12]PTPP (0.016 g, 0.040 mmol) in 1,2-dichlorobenzene (2 mL). The resulting mixture was heated to 80 °C for 3 h and then cooled to room temperature under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL), a 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 **55.5** as a white solid (0.029 g, >95%): R_f = 0.40 (3:7 dichloromethane/hexanes); ^{1}H 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 $C_{28}H_{28}O_2Br_5$ ($[M+Br]^+$) *m/z* = 794.7965, found 794.7942.



56.1

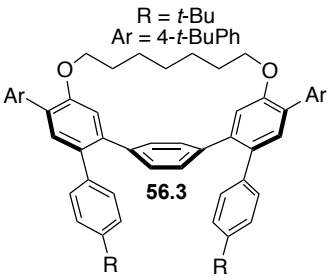
4,4",6,6"-tetrakis(4-t-butylphenyl)-1,7-dioxa [7](3,3")p- ter phenylenophane (**56.1**)**:**Sodium carbonate (0.590 g, 5.55 mmol) and 4-*tert*-butlyphenyl boronic acid (0.272 g, 1.51 mmol) were added sequentially to a stirred solution of **16.1** (0.121 g, 0.185 mmol) in toluene (9 mL), water (3 mL), 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 were 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 Na_2SO_4, filtered, and con-

centrated under reduced pressure. The residue was purified by automated flash chromatography (5-20% ethyl acetate/hexanes) to yield **56.1** as a white solid (0.132 g, 83%): R_f = 0.27 (1:19 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{63}H_{70}O_2$ (M^+) *m/z* = 858.5376, found 858.5389.



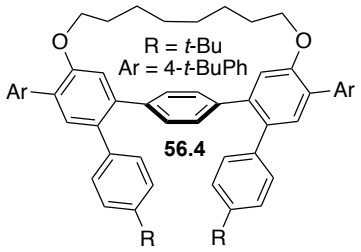
56.2

4,4",6,6"-tetrakis(4-t-butylphenyl)-1,8-dioxa[8](3,3")p- ter phenylenophane (**56.2**)***:*** Sodium carbonate (0.480 g, 4.50 mmol) and 4-*tert*-butylphenyl boronic acid (0.215 g, 1.20 mmol) were added sequentially to a stirred solution of **55.1** (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 Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by automated flash chromatography (5-20% ethyl acetate/hexanes) to yield **56.2** as a white solid (0.120 g, 92%): R_f = 0.39 (1:19 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{64}H_{73}O_2$ ($[M+H]^+$) *m/z* = 873.5611, found 873.5646.



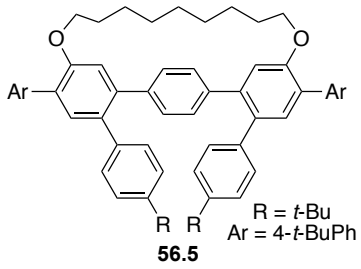
56.3

4,4", 6,6"-tetrakis (4-t-butylphenyl) -1,9-dioxa [9](3,3")p-terphenylenophane (**56.3**)***:*** Sodium carbonate (0.283 g, 2.67 mmol as an aqueous solution, 2 mL) and 4-*tert*-butylphenyl boronic acid (0.125 g, 0.712 mmol) were added sequentially to a stirred solution of **55.2** (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 Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 1:19 ethyl acetate/hexanes) to yield **56.3** as a white solid (0.061 g, 77%): R_f = 0.38 (1:19 ethyl acetate/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{65}H_{75}O_2$ ($[M+H]^+$) *m/z* = 887.5767, found 887.5747.



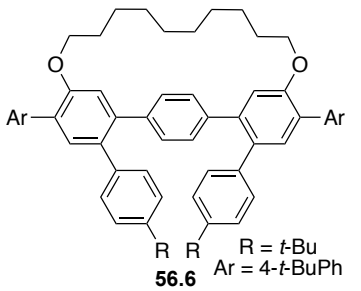
56.4

4,4", 6,6"-tetrakis (4-t-butylphenyl) -1,10-dioxa [10](3,3")p-terphenylenophane (**56.4**)***:*** Sodium carbonate (0.390 g, 3.69 mmol, as an aqueous solution, 2 mL) and 4-*tert*-butylphenyl boronic acid (0.165 g, 0.917 mmol) were added sequentially to a stirred solution of **55.3** (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 Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 25% to 40% dichloromethane/hexanes) to yield **56.4** as a white solid (0.085 g, 78%): R_f = 0.39 (3:7 dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{66}H_{77}O_2$ ($[M+H]^+$) *m/z* = 901.5924, found 901.5881.



56.5

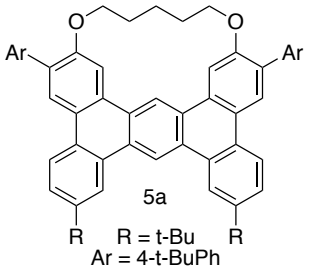
4,4", 6,6"-tetrakis (4-t-butylphenyl) -1,11-dioxa [11](3,3")p-terphenylenophane (**56.5**)***:*** Sodium carbonate (0.111 g, 1.05 mmol, as an aqueous solution, 1 mL) and 4-*tert*-butylphenyl boronic acid (0.052 g, 0.29 mmol) were added sequentially to a stirred solution of **55.4** (0.025 g, 0.036 mmol) 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 Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (14 × 1.0 cm, 10% to 30% dichloromethane/hexanes) to yield **56.5** as a white solid (0.022 g, 70%): R_f = 0.40 (3:7 dichloromethane/hexanes)**;** ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{67}H_{79}O_2$ ($[M+H]^+$) *m/z* = 915.6080, found 915.6035.



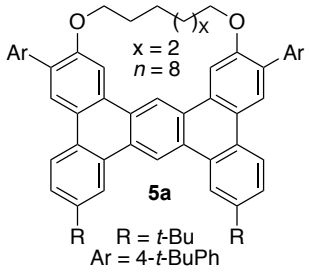
56.6

4,4" ,6,6"- tetrakis (4-t-butylphenyl) -1,12-dioxa [12] (3,3")p-terphenylenophane (**56.6**)***:*** Sodium carbonate (0.110 g, 1.045 mmol, as an aqueous solution, 1 mL) and 4-*tert*-butylphenyl boronic acid (0.061 g, 0.34 mmol) were added sequentially to a stirred solution of **55.5** (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

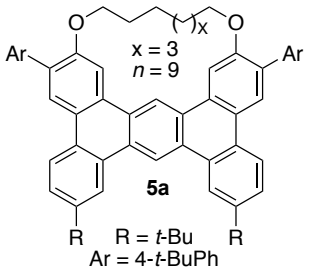
mixture for 3 min. Tetrakis(triphenylphosphine)palladium(0) (0.005 g, 0.004 mmol) was added, and nitrogen gas was once again passed over the reaction mixture for 2 min. The reaction was heated to 90 °C for 7 h and then cooled to room temperature. Once cooled, water (20 mL) was added to the reaction, 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 Na_2SO_4, 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 **56.6** as a white solid (0.028 g, 74%): R_f = 0.41 (3:7 dichloromethane/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{68}H_{81}O_2$ ($[M+H]^+$) *m/z* = 929.6237, found 929.6283.



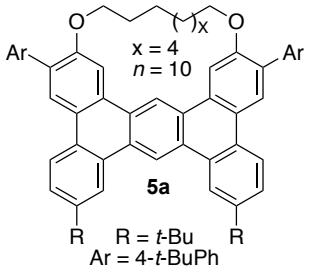
***Tetrabenzoanthracene* 5a:** A solution of Iron(III) chloride (0.088g, 0.054 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **56.1** (0.024 g, 0.028 mmol) in dichloromethane (5 mL). During the addition, a gentle stream of argon gas was passed through the 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 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 crude product was purified by flash chromatography (6 × 1.0 cm, 3:7 dichloromethane/hexanes) to yield **5a** (7) as a white solid (0.021 g, 90%): R_f = 0.37 (3:7 dichloromethane/hexanes); ^{1}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}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 $C_{63}H_{66}O_2$ ($[M+H]^+$) *m/z* = 855.5141, found 855.5167.



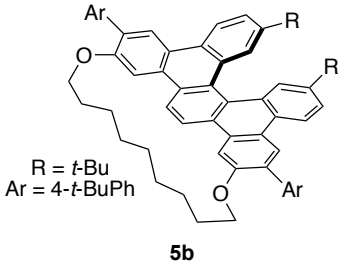
***Tetrabenzoanthracene* 5a:** A solution of Iron(III) chloride (0.092 g, 0.056 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **56.2** (0.025 g, 0.027 mmol) in dichloromethane (5 mL). During the addition, a gentle stream of argon gas was passed through the 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 to the reaction. 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 **5a** as a white solid (0.020 g, 80%): R_f = 0.49 (2:3 dichloromethane/hexanes); ^{1}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}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 $C_{64}H_{68}O_2$ ($[M+H]^+$) *m/z* = 869.5298, found 869.5266.



***Tetrabenzoanthracene* 5a:** A solution of Iron(III) chloride (0.030 g, 0.180 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **56.3** (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 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 (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.0 cm, 3:7 dichloromethane/hexanes) to yield **5a** as a white solid (0.012 g, 80%): R_f = 0.42 (2:3 dichloromethane/hexanes); ^{1}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}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.



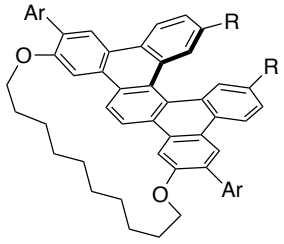
***Tetrabenzoanthracene* 5a:** A solution of Iron(III) chloride (0.031 g, 0.190 mmol) in dichloromethane/nitromethane (9:1) was added dropwise over 30 min to a stirred 0 °C solution of **56.4** (0.012 g, 0.014 mmol) in dichloromethane (3 mL). During the addition, a gentle stream of argon gas was passed through the reaction vessel, after which an argon-filled balloon was placed over the reaction. After 1 h methanol (5 mL) and water (5 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 (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.0 cm, 2% to 5 % ethyl acetate/hexanes) to yield the rearranged dehydrocyclized product **5a** (*n* = 10) as a white solid (0.005 g, 40%): R_f = 0.26 (1:19 ethyl acetate/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.91 (s, 1H), 9.56 (s, 1H), 8.89 (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. and an inseparable mixture of 2 compounds including helicene **5b** (*n* = 10) (0.004 g, 34%), R_f = 0.18 (1:19 ethyl acetate/hexanes);



5b

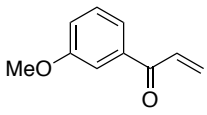
***Tetrabenzo[5]helicene* 5b:** A solution of Iron(III) chloride (0.012 g, 0.07 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **56.5** (0.006 g, 0.007 mmol) in dichloromethane (3 mL). During the addition, a gentle stream of argon gas was passed through the 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 re-

duced pressure. The residue was purified by flash chromatography (5 × 1.0 cm, 3:7 dichloromethane/hexanes) to yield **5b** (11as a white solid (0.005 g, 80%): R_f = 0.32 (3:7 dichloromethane/hexanes); ^{1}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}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 $C_{67}H_{75}O_2$ ($[M+H]^+$) *m/z* = 911.5767, found 911.5812.



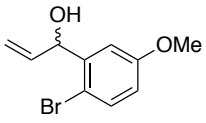
R = *t*-Bu
Ar = 4-*t*-BuPh
5b

***Tetrabenzo[5]helicene* 5b:** 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 **56.6** (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, 1:19 ethyl acetate/hexanes) to yield an inseparable mixture of cisoid and transoid (12:1) products **5b**(12) as a white solid (0.008 g, 80%): R_f = 0.35 (1:19 ethyl acetate/hexanes) ^{1}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}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 $C_{65}H_{75}O_2$ ($[M+H]^+$) *m/z* = 925.5924, found 925.5914.



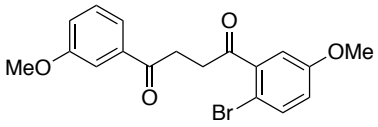
61.2

***Enone* 61.2:** Vinylmagnesium chloride (1.6 M in THF, 2.25 mL, 3.60 mmol) was added to a stirred solution of the 3-methoxybenzaldehyde (0.408 g, 3.00 mmol) in dichloromethane (10 mL). After 10 min., the reaction was poured into water (30 mL) and further diluted with 1 M HC1 (10 mL). The resulting mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with a saturated solution $NaHCO_3$ (20 mL) and Brine (20 mL), dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (12 mL) followed by the sequential addition of $NaHCO_3$ (0.380 g, 4.50 mmol) and Dess-Martin periodinane (2.02 g, 4.50 mmol). After 30 min., the reaction was poured into water (20 mL) the reaction was further diluted with 20 mL $Na_2S_2O_3$(aq) solution and stirred for 5 min. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with water (2 x 30 mL) and brine (20 mL) dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **61.2** (0.350 g, 72 % over 2 steps). The residue was used for next step without chromatography R_f = 0.55 (1:5 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 -7.51 (m, 1H), 7.49-7.46 (m, 1H), 7.39 (dd, *J* = 16.1, 8.3 Hz, 1H), 7.07 (m, 2H), 6.45 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.93 (dd, *J* = 10.6, 1.7 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.76, 159.73, 138.47, 132.20, 130.42, 129.57, 121.31, 119.66, 112.66, 55.43. HRMS (ESI) calc'd for $C_{10}H_{10}O_2$ ($[M]^+$) *m/z* = 162.0681 found 162.0687.



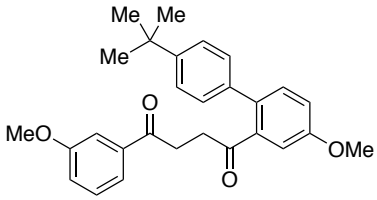
61.4

***Allylic alcohol* 61.4:** Methyl iodide (1.70 g, 12.0 mmol) was added to a stirred solution of 5-bromo-3-methoxybenaldehyde at room temperature. The reaction was heated to 42 °C for 14 h and then cooled to room temperature. Once cooled, water (10 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 × 20 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue (1.2 g, R_f = 0.62;1:4 EtOAc/hexanes*)* was dissolved in dry dichloromethane (30 mL) and vinylmagnesium chloride (1.6 M in THF, 4.15 mL, 6.66 mmol) was added to the stirred solution. After 10 min., the reaction was poured into water (30 mL) and further diluted with 1 M HC1 (20 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with a saturated solution $NaHCO_3$ (20 mL) and Brine (20 mL), dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The pale-yellow residue was purified by flash chromatography (14 x 2.5 cm, 1:5 EtOAc/hexanes) to afford the **61.4** as a colourless liquid (0.800 g, 60%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.72 (dd, *J* = 8.8, 3.2 Hz, 1H), 6.01 (ddd, *J* = 16.5, 10.3, 5.4 Hz, 1H), 5.56 (t, *J* = 4.4 Hz, 1H), 5.45-5.39 (m, 1H), 5.27-5.22 (m, 1H), 3.80 (s, 3H), 2.24 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.20, 142.28, 138.00, 133.31, 115.82, 115.18, 112.88, 112.62, 73.47, 55.47. R_f = 0.50; 1:5 EtOAc/hexanes; HRMS (ESI) calc'd for $C_{10}H_{11}O_2Br$ ($[M]^+$) *m/z* = 241.9942 found 241.9935.



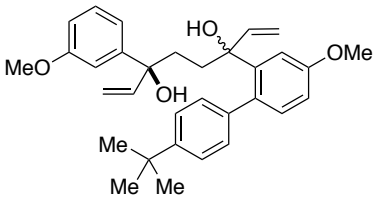
61.5

***1,4-diketone* 61.5:** Grubbs' second-generation catalyst (0.032 g, 0.037 mmol) was added to a stirred solution of allylic alcohol **63.4** (0.180 g, 0.74 mmol) and enone **63.2** (0.300 g, 1.86 mmol) in dichloromethane (7.50 mL) and the reaction was heated to 40 °C. After 48 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 2.5 cm, dichloromethane - 4% acetone/dichloromethane) to afford the cross-metathesis product (0.102 g, 36%, 45% based on recovering starting materials): R_f = 0.17; dichloromethane. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (7 mL), and sodium borohydride (0.061 g, 1.61 mmol) was added followed by the addition of H-G II catalyst (0.003 g, 0.006 mmol). After 2 h, the reaction was poured into water (10 mL) and further diluted with 1 M HCl (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The dark brown residue was dissolved in dichlormethane (10 mL), followed by the sequential addition of $NaHCO_3$ (0.067 g, 0.80 mmol) and Dess-Martin periodinane (0.36 g, 0.80 mmol). After 15 h the reaction was poured into water (10 mL) and further diluted by 10% $Na_2S_2O_3$ (10 mL) and stirred for 10 min. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 cm × 1.5 cm; dichloromethane) to afford 1,4-diketone **61.5** as a white solid (0.082 g, 80 % over 2 steps): R_f = 0.52 (dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.53 (t, *J* = 2.1 Hz, 1H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 12.5, 2.9 Hz, 2H), 6.86 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.46 (dd, *J* = 7.0, 5.6 Hz, 2H), 3.35 (dd, *J* = 7.0, 5.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.77, 198.18, 159.94, 159.02, 142.45, 138.03, 134.50, 129.78, 120.93, 119.94, 117.95, 114.18, 112.36, 108.84, 55.84, 55.60, 36.71, 33.23. HRMS (ESI) calc'd for $C_{18}H_{17}O_4Br$ ($[M]^+$) *m/z* = 376.0310 found 376.0304.



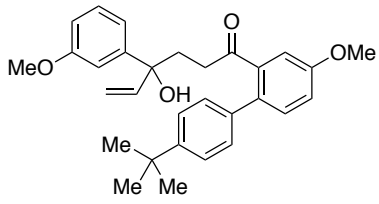
62.1

1,4-diketone 62.1: Potassium carbonate(aq) (2 M, 0.29 mmol.) and Tetrakis(triphenylphosphine)palladium (0) catalyst (0.014 g, 0.012 mmol) were added sequentially to a stirred solution of the monobromo diketone **61.5** in a toluene/water/ethanol (6:2:1) solution (4.5 mL) at room temperature and stirred for 20 min at which point 4-*t*-butylphenylboronic acid (0.064 g, 0.36 mmol) solution in ethanol was added. The resulting mixture was heated to 90 °C for 15 h and then cooled to room temperature. The reaction was washed with H_2O (10 mL) and further diluted by 1 M HCl (10 mL) The reaction mixture was extracted with dichloromethane (3x10 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 cm x 1.3 cm; 1:5 ethyl acetate/hexanes) to afford **62.1** (0.080 g, 80%) as a white solid: R_f = 0.43 (1:5 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.48-7.41 (m, 3H), 7.40-7.32 (m, 2H), 7.29 (s, 2H), 7.11 (dt, *J* = 6.2, 3.0 Hz, 2H), 7.07 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.17 (t, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 6.5 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.52, 198.26, 159.88, 158.91, 150.65, 141.83, 138.09, 137.53, 132.70, 131.61, 129.67, 128.75, 125.69, 120.83, 119.75, 116.96, 112.47, 112.27, 55.71, 55.57, 36.99, 34.71, 33.69, 31.48. HRMS (APCI) calc'd for $C_{28}H_{30}O_4Na$ ($[M+H]^+$+Na) *m/z* = 453.2042 found 453.2052.



21e (*d.r* = 1:1)

Allylic diols 21e: Vinylmagnesium chloride (1.6 M in THF, 0.32 mL, 0.48 mmol) was added to stirred solution of mono(4-*t*-butyl) phenyl-1,4-diketone **62.1** (0.072 g, 0.16 mmol) in benzene (3 mL) at 65 °C. After 30 min., the reaction mixture was poured into water (10 mL) and further diluted with 1 M HCl (10 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. (The diastereomeric ratio was determined from the crude nmr and showed HK:Syn:Anti = 2:1:1) The solid residue was purified by flash chromatography (14 × 1.3 cm, 2-5 % acetone/dichloromethane) to give hydroxyl ketone **62.2** (0.030 g, 40%) and allylic diol **21e** (0.020 g, 25%; 65% based on recovered **62.2**) as an mixture of diastereomers. Diols $R_{f\,=}$ 0.33; 1:19 acetone/dichloromethane; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 10.3, 8.0 Hz, 2H), 7.23 (td, *J* = 7.9, 4.6 Hz, 2H), 7.15 (dd, *J* = 14.0, 7.7 Hz, 2H), 7.10-6.91 (m, 3H), 6.82-6.74 (m, 2H), 6.10-5.95 (m, 2H), 5.24 (ddd, *J* = 21.8, 17.2, 1.3 Hz, 1H), 5.12-4.94 (m, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 2.70 (s, 1H), 2.98 (s, 1H), 2.01-1.80 (m, 3H), 1.77-1.68 (m, 1H), 1.36 (d, *J* = 4.9 Hz, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.68, 158.67, 147.64, 145.93, 145.81, 144.68, 144.15, 143.70, 139.60, 133.58, 133.02, 129.86, 129.84, 129.28, 124.98, 118.04, 117.98, 113.38, 113.32, 113.07, 113.00, 112.81, 112.59, 111.99, 111.57, 111.16, 111.07, 78.51, 78.44, 76.58, 76.56, 55.47, 55.35, 36.15, 36.09, 35.44, 35.40, 34.73, 31.56. HRMS (APCI) calc'd for $C_{32}H_{38}O_4Na$ ($[M+H]^+$+Na) *m/z* = 509.2692 found 509.2690.

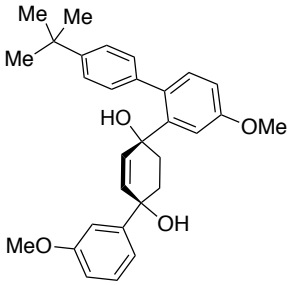


62.2

Hydroxy ketone 62.2**:** R_f = 0.56 (1:19 acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 -7.42 (m, 2H), 7.34-7.25 (m, 2H), 7.25-7.16 (m, 3H), 7.04 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.98-6.91 (m, 2H), 6.86-6.73 (m, 2H), 5.91 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.19 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.03 (dd, *J* = 10.6, 1.2 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 2.42-2.24 (m, 3H), 2.06 (ddd, *J* = 14.4, 8.3, 6.1 Hz, 1H), 1.95 (ddd, *J* = 14.2, 8.2, 6.0 Hz, 1H), 1.63 (d, *J* = 1.7 Hz, 1H), 1.34 (t, *J* = 3.5 Hz, 1H), 1.32 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.70, 158.90, 147.18, 143.55, 137.46, 132.78, 131.54, 129.35, 128.78, 125.82, 117.76, 117.01, 112.93, 112.33, 112.20, 111.36, 76.02,

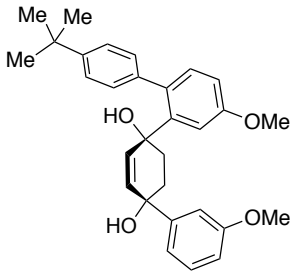
55.73, 55.37, 38.12, 36.53, 34.80, 31.57. HRMS (APCI) calc'd for $C_{30}H_{34}O_4Na$ ([M+H]$^+$+Na) *m/z* = 481.2355 found 481.2359.

Cyclohex-2-ene 1,4- diols* 15a*: Grubbs' second-generation catalyst (0.004 g, 0.005 mmol) was added to a stirred solution of **20j** (0.035 g, 0.072 mmol) in dichloromethane (7 mL) and the reaction was heated to 40 °C. After 1 h, the solvent was removed under reduced pressure and the residue was purified by short silica gel chromatography (6 cm × 1 cm, 2-10 % acetone/dichloromethane to give *anti*-**15a** (0.016 g**, 47%**) as an off-white solid and *Syn***- 15a** (0.014 g; **45%)**



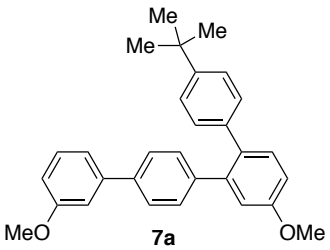
anti-**15a**

Anti-**15a:** R_f = 0.54 (1:9 acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) d 7.49 (d, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 2H), 7.26-7.22 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.98 (t, *J* = 2.1 Hz, 1H), 6.92 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.77 (dd, *J* = 8.1, 2.6 Hz, 1H), 5.88 (dd, *J* = 9.8, 1.5 Hz, 1H), 5.41 (dd, *J* = 9.8, 1.5 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 2.37 (td, *J* = 13.6, 3.3 Hz, 1H), 2.14 (td, *J* = 13.6, 3.3 Hz, 1H), 1.95 (s, 1H), 1.87 (dtd, *J* = 14.2, 3.8, 1.6 Hz, 1H), 1.83-1.76 (m, 1H), 1.61 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) d 159.62, 159.09, 151.05, 149.24, 135.24, 133.02, 132.48, 130.93, 129.26, 124.36, 117.65, 112.21, 112.13, 111.81, 111.02, 71.70, 70.46, 55.55, 55.38, 35.97, 35.53, 34.83, 31.61, 31.56. HRMS (APCI) calc'd for $C_{30}H_{34}O_4Na$ ([M+H]$^+$+Na) *m/z* = 481.2355 found 481.2358.



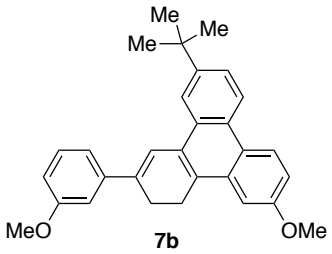
syn-**15a**

Syn- **15a:** R_f = 0.21(1:9 acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H), 7.30-7.22 (m, 3H), 7.15-7.05 (m, 4H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.86-6.78 (m, 2H), 6.05 (d, *J* = 10.1 Hz, 1H), 5.96 (d, *J* = 10.1 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.29 (s, 1H), 2.05 (dd, *J* = 12.1, 6.6 Hz, 3H), 1.96 -1.90 (m, 1H), 1.63-1.59 (m, 1H), 1.36 (s, 9H).^{13}C NMR (151 MHz, $CDCl_3$) δ 159.78, 158.48, 150.45, 147.84, 144.65, 139.36, 135.08, 133.96, 133.80, 132.98, 129.93, 129.49, 125.24, 117.98, 113.55, 113.06, 111.58, 111.45, 74.51, 72.42, 55.48, 55.41, 37.05, 36.36, 34.77, 31.55. HRMS (APCI) calc'd for $C_{30}H_{34}O_4Na$ ([M+H]$^+$+Na) *m/z* = 481.2355 found 481.2359.



7a

p-terphenyl* 7a*: *p*-toluenesulfonic acid monohydrate (0.025 g, 0.12 mmol) was added to a stirred solution of *syn*-**15a** (0.010 g, 0.02 mmol) in toluene (2.5 mL) at 60 °C. After 15 min., saturated solution of $NaHCO_3$ (5 mL) was added to the reaction and stirred for 5 min. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 3 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (20 × 20 cm, 1000 μm, 12% EtOAc/hexanes) to afford *p*-terphenylene **7a** (0.003 g, 30 %): R_f = 0.39 (1:9 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.41-7.33 (m, 3H), 7.27-7.17 (m, 8H), 7.14 (t, *J* = 2.1 Hz, 1H), 7.12-7.03 (m, 3H), 7.03-6.96 (m, 2H), 6.89 (dd, *J* = 8.1, 2.6 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.06, 130.38, 129.94, 129.68, 126.73, 124.99, 119.66, 115.98, 113.29, 112.87, 112.79, 55.63, 55.49, 34.59, 31.56. HRMS (APCI) calc'd for $C_{30}H_{31}O_2Na$ ([M+H]$^+$+Na) *m/z* = 445.2144 found 445.2141.



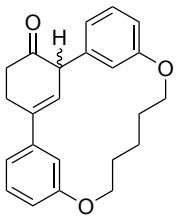
7b

***Allylic arylated product* 7b:** (0.005.2 g, 50 %): R_f = 0.49 (1:9 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 24.1, 8.9 Hz, 2H), 8.23 (d, *J* = 2.0 Hz, 1H), 7.73-7.68 (m, 2H), 7.51 (d, *J* = 2.7 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.32 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.30-7.22 (m, 3H), 6.95-6.89 (m, 1H), 4.01 (s, 3H), 3.92 (s, 3H), 3.35 (dd, *J* = 9.7, 7.6 Hz, 2H), 2.97-2.91 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.03, 158.40, 148.60, 143.26, 138.74, 131.78, 129.80, 128.88, 128.61, 128.16, 127.81, 124.76, 124.67, 124.42, 122.54, 120.82, 118.78, 118.19, 116.00, 112.72, 111.57, 104.99, 77.43, 77.22, 77.12, 77.01, 55.58, 55.55, 35.22, 31.70, 26.52, 25.07. HRMS (ESI) calc'd for $C_{30}H_{31}O_2$ ($[M+H]^+$) *m/z* = 423.2324 found 423.2338.

Alternative procedure for* 7a *and* 7b:*** Methanesulfonic acid (0.005 g, 0.025 mmol) was added to a stirred solution of *anti*-**15a** (0.002 g, 0.004 mmol) in dichloromethane (1 mL) at 23 °C. After 15 min., water (1 mL) and saturated solution of sodiumbicarbonate (1 mL) were added. The layers were separated and the mixture was extracted with dichloromethane (3 × 2 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude nmr showed a ratio of **7a**: **7b** (*p*-terphenyl: FC cyclized product) = 1:3.

Alternative procedure for 7a and 7b: Pentafluorophenylboronic acid (0.007 g, 0.033 mmol) was added to a stirred solution of *anti*-**15a** (0.003 g, 0.006 mmol) in dichloromethane (1 mL) in presence of MS (4 ºA) at 23 ºC. After 30 min, H_2O (2 mL) was added to the reaction. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 2 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude nmr showed a ratio of **7a**: **7b** (*p*-terphenyl: FC cyclized product) = 1:4.

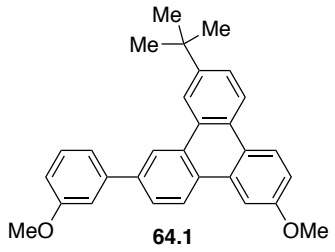
Alternative procedure for 7b: A solution of Iron(III) chloride (0.0001 g, 0.0009 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of *anti*-**15a** (0.002 g, 0.004 mmol) in dichloromethane (1 mL). After 15 min, methanol (1 mL) and water (2 mL) were added to the reaction. The layers were separated and the aqueous phase extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was passed through a short column of silica gel (5 cm x 1 cm) to afford **7b** (0.002 g, 95%) as off white solid.



63.2

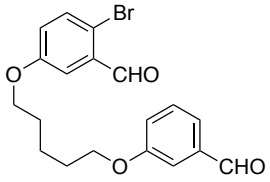
***Cyclohexenone* 63.3** A solution of Iron(III) chloride (0.0026 g, 0.016 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **15.6** (0.012 g, 0.030 mmol) in dichloromethane (4 mL). After 15 min, methanol (2 mL) and water (2 mL) were added to the reaction. The layers were separated and the aqueous phase extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was passed through a short column of silica gel (5 cm x 0.7 cm) to afford **63.2** (0.009 g, 65%.) as off white solide. R_f = 0.55 (1:9 acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 13.2, 7.8 Hz, 3H), 7.13 (t, *J* = 2.1 Hz, 1H), 7.07-6.99 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.90 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.88-6.83 (m, 1H), 6.18 (dd, *J* = 3.7, 1.8 Hz, 1H), 4.38-4.28 (m, 3H), 4.15 (ddd, *J* = 12.7, 8.1, 4.9 Hz, 1H), 4.02 (td, *J* = 11.5, 4.7 Hz, 1H), 3.15 (dddt, *J* = 17.2, 8.5, 6.4, 2.0 Hz, 1H), 2.88-2.78 (m, 1H), 2.71 (ddd, *J* = 14.0, 8.8, 6.7 Hz, 1H), 2.63 (dt, *J* = 13.8, 6.0 Hz, 1H), 2.25-2.14 (m, 1H), 2.08 (ddp, *J* = 15.6, 7.8, 3.8 Hz, 1H), 1.81-1.62 (m, 2H), 1.60-1.45 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.66, 159.17, 158.63, 142.96, 140.16, 130.34, 130.17, 126.12, 122.28, 117.87, 117.62, 117.22, 111.22, 110.81, 67.86,

67.19, 54.02, 36.66, 29.82, 28.24, 27.64, 20.67. HRMS (ESI) calc'd for $C_{23}H_{25}O_3$ ([M-+H]$^+$) *m/z* = 349.1804 found 349.1795.



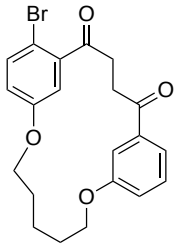
64.1

Model triphenylene* 64.1:* 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone(DDQ)(0.013 g, 0.065 mmol) was added to a stirred solution of **7b** (m) (0.005 g, 0.013 mmol) in dichloromethane (2 mL) at 23 ºC. The reaction turned deep green at this point. After 30 min, H_2O (2 mL) and saturated solution of $NaHCO_3$(2 mL) were added and stirred for 5 min at which point the color changed to light yellow, the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 3 mL). The organic extracts were combined and washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a short column of silica gel (5 cm x 1 cm) to afford **64.1** (0.005 g, quant.) as off white solide. R_f = 0.36 (5% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.69 (s, 1H), 8.64 (d, *J* = 8.5 Hz, 1H), 8.56 (d, *J* = 9.0 Hz, 1H), 8.51 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.87 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.41 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.35 (t, *J* = 2.0 Hz, 1H), 7.03-6.98 (m, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 1.52 (s, 9H). HRMS (ESI) calc'd for $C_{30}H_{29}O_2$ ([M+H]$^+$) *m/z* = 421.2168 found 421.2178



65.4

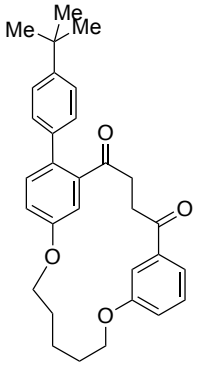
***Monobromodialdehyde* 65.4:** 1,5-Dibromobutane (9.42 g, 40.9 mmol) was added to a stirred solution of 3-hydroxybenzaldehyde (5.00 g, 40.9 mmol), K_2CO_3 (11.3, 81.9 mmol) and TBAI (0.756 g, 2.00 mmol) in DMF (43 mL). The reaction was heated at 40 °C for 28 h, at which point water (50 mL) and 1 M HC1 (50 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 5 cm; 10 % EtOAc/hexanes,) to afford **65.1** as light pink solid (8.18 g, 74%: R_f = 0.40, 1:9 EtOAc/hexane) 5-bromo-3-hydroxybenzaldehyde (2.44 g, 10.6 mmol) was added to a stirred solution of **65.1** (2.88 g, 10.6 mmol), and K_2CO_3 (3.00 g, 21.3 mmol) in DMF (50 mL). The reaction was heated at 60 °C for 26 h, at which point water (40 mL) and 1 M HC1 (40 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 x 25 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 x 5 cm; 2:3 dichloromethane/hexane to dichloromethane) to afford **65.4** as light purple solid (2.73 g, 65 %): R_f = 0.50, 9:1 dichloromethane/hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 1H), 9.98 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.42 (m, 2H), 7.40 (dd, *J* = 12.5, 2.9 Hz, 2H), 7.18 (dt, *J* = 5.9, 2.9 Hz, 1H), 7.04 (dd, *J* = 8.7, 3.2 Hz, 1H), 4.04-4.02 (m, 4H), 1.92-1.85 (m, 4H), 1.68 (q, *J* = 8.5 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.48, 192.13, 159.78, 158.88, 137.97, 134.79, 134.10 130.29, 123.79, 123.75, 122.21, 118.10, 113.45, 112.78, 68.51, 68.16, 29.07, 29.00 22.89 . HRMS (ESI) calc'd for $C_{19}H_{20}BrO_4$ ([M]$^+$) *m/z* = 390.0467 found 390.0450



65.7

***Monobromo diketone* 65.7:** Vinylmagnesium chloride (1.6 M in THF, 7.7 mL, 12.3 mmol) was added to a stirred solution of the dialdehyde **65.4** (1.93 g, 4.92 mmol) in DCM (42 mL). After 30 min., the reaction was poured into water (20 mL) and further diluted with 1 M HC1 (20 mL). The resulting mixture was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with a saturated solution $NaHCO_3$ (30 mL) and water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The pale-yellow residue was dissolved in dichloromethane (330 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.077

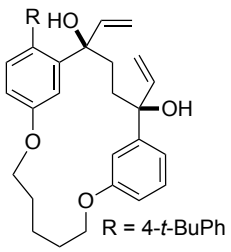
g, 0.123 mmol). After 2 h, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (50mL), and sodium borohydride (0.935 g, 24.6 mmol) was added. After 3 h, the reaction was poured into water (30 mL) and further diluted with 1 M HC1 (20 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The dark brown residue was dissolved in dichloromethane (20 mL), followed by the addition of $NaHCO_3$ Pyridinium chlorochromate (PCC) (3.18 g, 14.8 mmol). After 15 h, silica was added to the the reaction and the slurry was passed through a celite pad, washed with (3× 20.0 mL) ether and concentrated under reduced pressure and concentrated under reduced pressure. The residue was purified by flash chromatography (15 x 3.8 cm, 1:5 EtOAc/hexanes) to afford monobromo-1,4-diketone **65.7** as a white solid (1.45 g, 70 % from dialdehyde **65.4**): R_f = 0.54 (3:7 EtOAc/hexanes. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.24 (m, 3H), 7.20 (s, 1H), 7.05-7.03 (m, 1H), 6.62-6.55 (m, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.86 (t, J = 5.8 Hz, 2H), 3.22 (m, 2H), 3.26-3.16 (m, 4H), 1.80-1.76 (m, 2H), 1.68-1.56 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.54, 199.75, 158.26, 158.16, 141.97, 138.08, 133.63, 129.95, 121.90, 120.58, 116.80, 116.32, 113.19, 107.51, 67.61 , 67.14 , 37.99 , 34.78 , 27.30 , 26.07 , 21.26. HRMS (ESI) calc'd for $C_{21}H_{22}BrO_4$ ($[M+H]^+$) *m/z* = 417.0701 found 417.0681



65.10

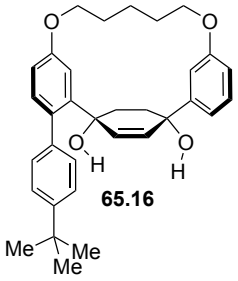
1,4-diketone **65.10**: Potassium carbonate(aq) (0.97 mmol, 2 M, 2 equiv.) and Tetrakis(triphenylphosphine)palladium (0) catalyst (0.070 g, 0.05 mmol) were added sequentially to a stirred solution of the monobromo macrocyclic diketone **65.7** (0.404 g, 0.97 mmol) in a 4.5 mL toluene/water/ethanol mixture (6:2:1) at room temperature and stirred for 20 min at which point 4-*t*-butylphenylboronic acid (0.260 g, 1.46 mmol) solution in ethanol was added. The resulting mixture was heated to 90 °C for 24 h and then cooled to room temperature, at which point the reaction was poured into water (20 mL). The reaction was further diluted with 1 M HCl solution (10 mL). The reaction mixture was extracted with dichloromethane (3× 10 mL), and the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 x 2.5 cm, 15% EtOAc/hexanes) to afford mono-(4-*t*-butyl)-phenyl-1,4-diketone **65.10** as a white solid (0.429 g, 94 %): R_f = 0.27 (15% EtOAc/hexanes) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.26- 7.22 (m, 7H), 7.20-7.15 (m, 2H), 7.04 (ddd, *J* = 8.1, 2.6, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.67 (d, *J* = 2.7 Hz, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.97 (t, *J* = 5.9 Hz, 2H), 2.86 (m, 2H), 2.51 (dd, *J* = 7.6, 5.5 Hz, 2H), 1.83 (p, *J* = 6.3 Hz, 2H), 1.73 (dd, *J* = 8.9, 6.2 Hz, 2H), 1.64 (dd, *J* = 15.0, 7.2 Hz, 2H), 1.36 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.05, 200.08, 158.26, 158.09, 150.94, 140.96, 138.32, 136.87, 131.48, 130.85, 129.81, 128.65, 125.91, 121.49, 120.40, 115.80, 115.07, 113.24, 67.55, 67.05, 38.34, 34.94, 34.80, 31.56, 27.42, 26.34, 21.42. HRMS (ESI) calc'd for $C_{31}H_{35}O_4$ ($[M+H]^+$) *m/z* = 471.2535 found 471.2539.

Allylic diols **65.13*:*** Vinylmagnesium chloride (1.6 M in THF, 1.03 mL, 1.64 mmol) was added to stirred solution of mono(4-*t*-butyl)phenyl-1,4-diketone (0.30 g, 0.66 mmol) in benzene (7 mL) at 65 °C. After 15 min., the reaction mixture was poured into water (20 mL) and further diluted with 1 M HCl (20 mL). The resulting mixture was extracted with dichloromethane (3 × 15 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatography (15 × 2.5 cm, 2-7 % acetone/dichloromethane) to give (0.230 g, 60 %) as an inseparable mixture of Hydroxyketone and *anti*-diol and *syn*-**65.13** (0.90 g, 27%; 87% based on recovered HK and *anti*-diol).



syn-**65.13**

***Syn*-65.13** (0.90 g, 27%; R_f = 0.35 (1:49 acetone/dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.20-7.15 (m, 5H), 6.99 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.73 (m, 3H), 6.23 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.38 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.15 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.09 (m, 3H), 4.01 (td, *J* = 9.8, 9.0, 4.1 Hz, 1H), 3.60 (ddd, *J* = 12.4, 6.8, 3.1 Hz, 1H), 2.38 (m, 1H), 2.18 (m, 2H), 2.07 (m, 1H), 1.96 (dd, J = 14.1, 8.1 Hz, 1H), 1.81 (m, 2H), 1.64 (m, 1H), 1.37 (s, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 157.95, 150.22, 147.86, 145.41, 143.97, 142.74, 139.74, 133.41, 133.07 , 131.67 , 129.88 , 129.16 , 125.26 , 124.72 , 118.43 , 115.00 , 114.18 , 113.97 , 112.71 , 112.57 , 111.45 , 111.25 , 78.02 , 76.64 , 67.81 , 67.65 , 67.56 , 53.61 , 37.34 , 36.53 , 34.69 , 31.56 , 31.54 , 31.51 , 31.11 , 28.08 , 27.91 , 21.60 . HRMS (ESI) calc'd for $C_{35}H_{39}O_2$ ([M-2H_2O+H]$^+$) *m/z* = 491.2950 found 491.2938

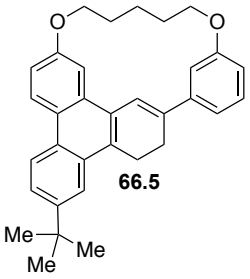


65.16

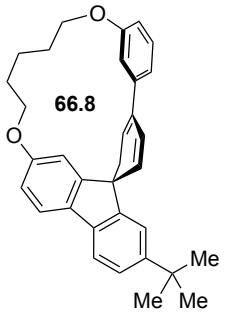
***Cyclohex-2-ene-1,4-diol* 65.16:** Grubbs' second-generation catalyst (0.014 g, 0.016 mmol) was added to a stirred solution of *syn*-**65.13** (0.160 g, 0.295 mmol) in dichloromethane (12 mL) and the reaction was heated to 40 °C. After 3 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 2.5 cm, 1:9 acetone/dichloromethane) to give compound **65.16** as an off-white solid (0.109 g, 77%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.30 (dd, *J* = 8.4, 6.6 Hz, 5H), 7.16 (d, *J* = 2.7 Hz, 1H), 7.01 (m, 2H), 6.79 (m, 2H), 6.10 (d, *J* = 10.1 Hz, 1H), 6.04 (d, *J* = 10.1 Hz, 1H), 4.10 (m, 2H), 3.97 (m, 2H), 2.28 (m, 1H), 2.18 (p, *J* = 2.1, 1.7 Hz, 1H), 1.89 (m, 5H), 1 1.68 (m, 6H), 1.37 (s, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.92, 147.99, 139.30, 135.35, 134.03, 133.30, 130.04, 129.84, 125.30, 117.95, 115.98, 115.05, 113.67 , 112.83 , 75.17 , 72.64 , 69.51 , 69.03 , 37.07 , 36.60 , 34.77 , 31.55 , 28.91 , 28.75 , 22.32 . R_f = 0.31 (1:9 acetone/dichloromethane); HRMS (ESI) calc'd for $C_{33}H_{37}O_3$ ([M-H_2O+H]$^+$) *m/z* = 481.2743 found 481.2755.

General procedure for the Friedel-Crafts Arylation on substituted cyclohex-2-ene-1,4- diol: Protic acid or Lewis acid (xx g, xx mmol) was added to a stirred solution of substituted cyclohex-2-ene-1,4- diols (xx g, xx mmol) in dichloromethane or toluene (xx mL) at different temperatures. After 15 min., water (xx mL) was added and further diluted by adding saturated solution of NaHCO_3 (10 mL) and the resulting mixture was stirred for 5 minutes. The layers were separated and the mixture was extracted with dichloromethane (3 × xx mL). The organic extracts were combined and washed with brine (xx mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography or preparative TLC (1:19 EtOAc/hexanes) to afford the *para*terphenylophane **8d**, rearranged cyclized product **8e** and spirocyclic product **8f** as a white solid.

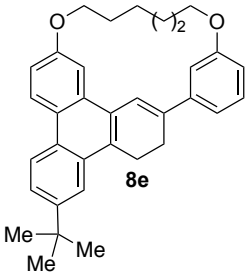
***Cyclized products* 66.5 and 66.8:** Methanesulfonic acid (0.047 g, 0.486 mmol) was added to a stirred solution of **65.16** (0.050 g, 0.097 mmol) in dichloromethane (10 mL) at 0 °C. After 15 min., water (10 mL) was added and further diluted by adding saturated solution of $NaHCO_3$ (10 mL) and the resulting mixture was stirred for 5 minutes. The layers were separated and the mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (16 × 1.3 cm, 1:19 EtOAc/hexanes) to afford the spirocyclic product **66.8** as a white solid (0.018 g, 39%) and the rearranged cyclized product **66.6** (0.22 g, 48 %)



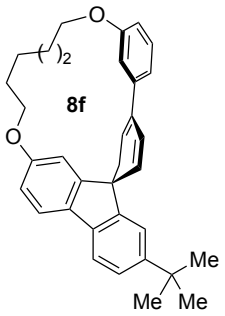
***Macrocycle* 66.5** (0.022 g, 48 %), R_f = 0.31 (1:19 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 8.9, 4.1 Hz, 2H), 8.11 (d, *J* = 2.0 Hz, 1H), 7.78-7.71 (m, 2H), 7.68 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.41 (t, *J* = 2.0 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.16 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.91 (dd, *J* = 8.0, 2.6 Hz, 1H), 4.38-4.25 (m, 4H), 3.44 (t, *J* = 8.5 Hz, 2H), 2.92-2.85 (m, 2H), 2.15 (ddt, *J* = 26.1, 15.2, 7.1 Hz, 4H), 1.65 (q, *J* = 6.9 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.56, 157.61, 148.62, 142.30, 139.89, 130.10, 130.03, 129.47, 129.14, 128.16, 127.32, 124.91, 124.39, 123.94, 123.24, 122.70, 119.65, 118.03, 117.74, 117.58, 110.97, 103.70, 70.05, 68.99, 35.22, 31.69, 27.82, 27.71, 24.96, 24.67, 21.68. HRMS (ESI) calc'd for $C_{33}H_{35}O_2$ ($[M+H]^+$) *m/z* = 463.2637 found 463.2637



***Sprirocycle* 66.8:** (0.018 g, 39%), R_f = 0.43 (1:19 EtOAc/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.9 Hz, 1H), 7.55 (dd, *J* = 8.1, 3.5 Hz, 2H), 7.41 (td, *J* = 4.3, 3.7, 1.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.09-7.04 (m, 2H), 6.91 (m, 1H), 6.87 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.55 (dd, *J* = 9.5, 1.4 Hz, 1H), 6.12-6.08 (m, 1H), 5.91 (dd, *J* = 9.6, 1.3 Hz, 1H), 4.26 (hept, *J* = 6.8, 6.3 Hz, 2H), 4.02-3.98 (m, 2H), 3.29-3.23 (m, 1H), 2.33 (ddd, *J* = 7.5, 6.7, 1.4 Hz, 1H), 1.82 (m, 3H), 1.77 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.72, 158.66, 151.68, 150.37, 150.01, 142.78, 138.73, 138.00, 133.98, 132.05, 130.29, 128.07, 124.79, 123.84, 120.98, 120.88, 118.73, 118.68, 117.46, 116.85, 112.18, 109.62, 69.74, 67.26, 50.41, 36.48, 35.18, 31.85, 28.46, 28.29, 21.64. HRMS (ESI) calc'd for $C_{33}H_{35}O_2$ ($[M+H]^+$) *m/z* = 463.2637 found 463.2644.



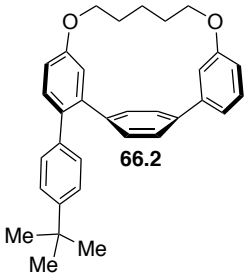
***Macrocycle* 8e:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (t, *J* = 8.3 Hz, 2H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.77-7.65 (m, 3H), 7.51 (t, *J* = 2.0 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.22 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.18 (d, 1H), 6.92 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.46-4.13 (m, 4H), 3.47 (t, *J* = 8.7 Hz, 2H), 3.05-2.77 (m, 2H), 2.20-2.09 (m, 2H), 2.10-1.96 (m, 2H), 1.81-1.60 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.19, 157.97, 148.61, 141.81, 138.45, 130.39, 130.00, 129.82, 129.32, 128.22, 127.15, 124.83, 124.58, 124.09, 122.64, 121.01, 119.68, 118.19, 118.02, 117.99, 109.45, 103.92, 69.95, 68.99, 35.23, 31.68, 28.85, 27.83, 25.83, 25.50, 25.03, 24.81. HRMS (ESI) calc'd for $C_{34}H_{37}O_2$ ($[M+H]^+$) *m/z* = 477.2794 found 477.2801.



***Spirocycle* 8f:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 8.1, 3.4 Hz, 2H), 7.43-7.30 (m, 3H), 7.14-7.07 (m, 2H), 6.99-6.92 (m, 1H), 6.88 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.58 (dd, *J* = 9.6, 1.4 Hz, 1H), 6.15 (ddd, *J* = 6.8, 2.7, 1.4 Hz, 1H), 5.90 (dd, *J* = 9.5, 1.3 Hz, 1H), 4.21 (hept, *J* = 6.1, 5.6 Hz, 2H), 3.86 (h, *J* = 8.4 Hz, 2H), 3.31-3.24 (m, 1H), 2.35 (ddd, *J* = 7.6, 6.7, 1.4 Hz, 1H), 1.87-1.66 (m, 4H), 1.57 (s, 2H), 1.43 (p, *J* = 6.0, 5.3 Hz, 3H), 1.40 (s, 7H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.32, 158.49, 151.61, 150.36, 149.75, 142.46, 137.92, 137.67, 134.05, 131.69, 129.92, 127.34, 124.61, 123.78, 120.84, 120.61, 118.70, 118.47, 116.67, 115.50, 115.29, 108.77, 68.58, 68.53, 50.32, 36.25, 35.01, 31.68, 28.57, 27.98, 24.60, 23.87. HRMS (ESI) calc'd for $C_{34}H_{37}O_2$ ($[M+H]^+$) *m/z* = 477.2794 found 477.2797.

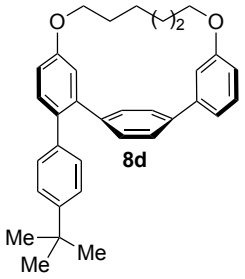
Alternative procedure for 8e and 8cf: *Pentafluorophenylboronic acid* (0.040 g, 0.019) was added to a stirred solution of **65.17** (0.020 g, 0.038 mmol) in dichloromethane (5 mL) in presence of MS (4 ºA) at 23 ºC. After 30 min, H_2O (10 mL) was added to the reaction. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (20 × 20 cm, 2000 μm, 1:9 EtOAc/hexanes) to afford the Spiro cyclic compound **8f** as a yellowish solid (0.006 g, 30 %): R_f = 0.43 (1:19 EtOAc/hexanes); and the rearranged cyclic product **8e** as white solid (0.008, 44 %): R_f = 0.31 (1:19 EtOAc/hexane);

Alternative procedure for 8d, 8e and 8f: *para*-Toluensulfonic acid monohydrate (0.021 g, 0.116 mmol) was added to a stirred 60 °C of **65.17** (0.010 g, 0.019 mmol) in toluene (2 mL) at 60 ºC. After 30 min, H_2O (5 mL) and a saturated solution of $NaHCO_3$ (5 mL) was added to the reaction. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (20 × 20 cm, 1000 μm, 1:9 EtOAc/hexanes) to afford **8f** as a yellowish solid (0.001 g, 14%%): R_f = 0.43 (5% EtOAc/hexanes), *para*-terphenylophane **8d** as white solid (0.003 g, 33 %): R_f = 0.34 (5% EtOAc/hexanes) and the rearranged cyclic product **8e** as white solid (0.001, 14 %): R_f = 0.31 (1:19 EtOAc/hexane).The same procedure was used for the other homologs and the similar results were obtained.



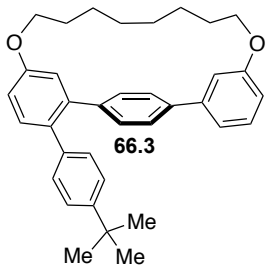
66.2

Macrocycle **66.2:** (0.003 g, 33 %): R_f = 0.34 (5% EtOAc/hexanes) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64-7.58 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.43-7.39 (m, 2H), 7.38-7.25 (m, 6H), 7.20 (d, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.78 (dd, *J* = 8.2, 2.7 Hz, 1H), 5.88-5.83 (m, 2H), 4.15-4.04 (m, 4H), 1.49 (q, *J* = 7.8 Hz, 4H), 1.36 (s, 9H), 1.24-1.14 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.03, 156.58, 149.64, 144.95, 144.72, 143.64, 142.23, 136.98, 131.08, 130.53, 130.07, 130.03, 129.45, 129.27, 125.45, 119.80, 118.49, 116.15, 115.93, 115.35, 77.43, 77.22, 77.01, 68.78, 68.46, 34.69, 31.59, 27.08, 26.66, 23.31. HRMS (ESI) calc'd for $C_{33}H_{35}O_2$ ($[M+H]^+$) *m/z* = 463.2637 found 463.2644.



8d

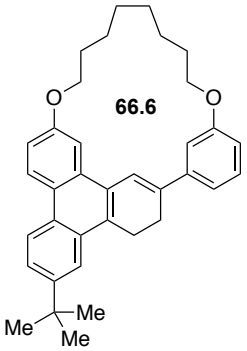
Macrocycle **8d:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54-7.50 (m, 2H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.38 -7.31 (m, 5H), 7.28 (d, *J* = 10.5 Hz, 7H), 7.21 - 7.18 (m, 1H), 6.90 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.83 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.00-5.97 (m, 1H), 5.89 (d, *J* = 2.9 Hz, 1H), 4.03 (dt, *J* = 18.5, 7.3 Hz, 4H), 1.62-1.51 (m, 5H), 1.33 (s, 10H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.81, 156.01, 149.43, 144.53, 144.28, 142.97, 142.12, 137.28, 131.09, 130.51, 130.27, 129.65, 129.43, 128.55, 125.37, 118.46, 117.26, 116.68, 116.64, 115.86, 77.43, 77.22, 77.01, 68.57, 68.27, 34.67, 31.57, 27.91, 27.82, 27.39. HRMS (ESI) calc'd for $C_{34}H_{37}O_2$ ($[M+H]^+$) *m/z* = 477.2794 found 477.2780.



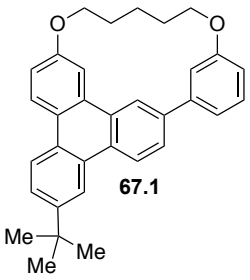
66.3

Macrocycle **66.3:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54-7.50 (m, 2H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.38-7.31 (m, 5H), 7.28 (d, *J* = 10.5 Hz, 7H), 7.21-7.18 (m, 1H), 6.90 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.83 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.00-5.97 (m, 1H), 5.89 (d, *J* = 2.9 Hz, 1H), 4.03 (dt, *J* = 18.5, 7.3 Hz, 4H), 1.62- 1.51 (m, 5H), 1.33 (s, 10H), 1.17 -1.01 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.19, 157.98, 148.63, 141.82, 138.48, 130.39, 130.01, 129.83, 129.33, 128.23, 127.16, 124.84, 124.59, 124.10, 122.65, 121.02, 119.68, 118.20, 118.02, 118.00, 109.46, 103.94, 77.43,

77.22, 77.01, 69.96, 69.00, 35.22, 31.68, 29.92, 28.87, 27.85, 25.85, 25.51, 25.05, 24.82. HRMS (ESI) calc'd for $C_{36}H_{37}O_2$ ([M+H]$^+$) *m/z* = 505.3107 found 505.3107.

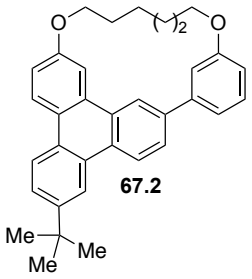


***Macrocycle* 66.6:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (t, *J* = 8.3 Hz, 2H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.77-7.67 (m, 3H), 7.51 (t, *J* = 2.0 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.25-7.16 (m, 3H), 6.92 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.39-4.29 (m, 4H), 3.47 (t, *J* = 8.7 Hz, 2H), 3.00-2.93 (m, 2H), 2.14 (p, *J* = 6.9 Hz, 2H), 2.09-2.00 (m, 2H), 1.77 -1.62 (m, 5H), 1.49 (s, 7H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.19, 157.98, 148.63, 141.82, 138.48, 130.39, 130.01, 129.83, 129.33, 128.23, 127.16, 124.84, 124.59, 124.10, 122.65, 121.02, 119.68, 118.20, 118.02, 118.00, 109.46, 103.94, 77.43, 77.22, 77.01, 69.96, 69.00, 35.22, 31.68, 29.92, 28.87, 27.85, 25.85, 25.51, 25.05, 24.82. HRMS (ESI) calc'd for $C_{36}H_{37}O_2$ ([M+H]$^+$) *m/z* = 505.3107 found 505.3104.



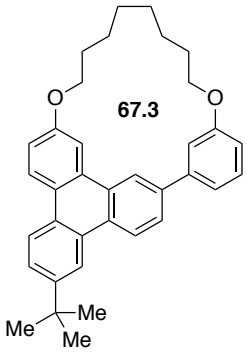
Triphenylene* 67.1:* 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone(DDQ) (0.025 g, 0.11 mmol) was added to a stirred solution of **66.5** or **66.8** (0.010 g, 0.021 mmol) in dichloromethane (5 mL) at 23 ºC. The reaction turned deep green at this point. After 30 min, H_2O (5 mL) and saturated solution of $NaHCO_3$ (5 mL) were added and stirred for 5 min at which point the color changed to yellow, the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a short column of silica to afford **67.1** as a white solid (0.009 g, 95 %): R_f = 0.27 (5% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.71-8.62 (m, 2H), 8.47 (dd, *J* = 15.3, 8.7 Hz, 2H), 8.11 (d, *J* = 2.8 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.74 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.53 (s, 1H), 7.46-7.39 (m, 2H), 7.23 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.97 (dt, *J* = 7.7, 2.0 Hz, 1H), 4.42-4.29 (m, 4H), 2.22 (dq, *J* = 38.8, 7.9 Hz, 4H), 1.74 (p, *J* = 7.8 Hz, 2H), 1.57 (d, *J* = 21.9 Hz, 10H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.31, 158.26, 149.27, 141.54, 138.05, 130.94, 130.57, 129.83, 129.74, 128.39, 127.90, 125.57, 125.00, 124.57, 124.09, 124.02, 123.91, 122.93, 119.57, 118.63, 118.46, 117.26, 111.23, 105.52, 70.75, 68.35, 35.25, 31.73, 28.05, 27.49, 23.00; HRMS (ESI) calc'd for $C_{33}H_{33}O_2$ ([M+H]$^+$) *m/z* = 461.2481 found 461.2465.

Triphenylene* 67.2:* 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.024 g, 0.11 mmol) was added to a stirred solution of a crude mixture of **8b** and **8c** (0.012 g, 0.024 mmol) in dichloromethane (5 mL) at 23 ºC. The reaction turned deep green at this point. After 30 min, H_2O (5 mL) and saturated solution of $NaHCO_3$ (5 mL) were added and stirred for 5 min at which point the color changed to yellow, the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a short column of silica to afford **67.2** as a white solid (0.0011 g, 94 %): R_f = 0.47 (10% EtOAc/hexanes);



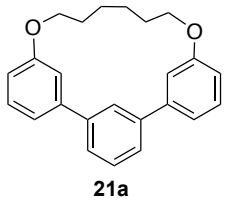
67.2

Triphenylene* 67.2:* ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.83 (d, *J* = 1.9 Hz, 1H), 8.73 (d, *J* = 8.5 Hz, 1H), 8.65 (d, *J* = 2.0 Hz, 1H), 8.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 8.17 (d, *J* = 2.7 Hz, 1H), 8.02 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.58-7.54 (m, 1H), 7.47-7.37 (m, 3H), 7.24 (dd, *J* = 8.9, 2.6 Hz, 2H), 6.97 (dt, *J* = 7.0, 2.5 Hz, 1H), 4.39-4.29 (m, 4H), 2.22-2.13 (m, 2H), 2.13-2.05 (m, 2H), 1.81-1.72 (m, 2H), 1.57 (s, 2H), 1.53 (s, 8H), 1.43-1.28 (m, 2H), 1. ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.31, 158.38, 149.23, 141.77, 138.48, 130.85, 130.46, 129.87, 128.26, 127.84, 125.58, 125.12, 125.00, 124.15, 124.10, 122.87, 122.54, 119.46, 119.15, 119.04, 117.57, 111.23, 105.11, 69.92, 68.62, 35.24, 31.72, 29.43, 27.80, 26.13, 25.73. HRMS (ESI) calc'd for $C_{34}H_{35}O_2$ ($[M+H]^+$) *m/z* = 475.2637 found 475.2642.



67.3

Triphenylene* 67.3:* 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone(DDQ) (0.07 g, 0.03 mmol) was added to a stirred solution of **66.6** (0.003 g, 0.006 mmol) in dichloromethane (2 mL) at 23 ºC. The reaction turned deep green at this point. After 30 min, H_2O (2 mL) and saturated solution of $NaHCO_3$ (2 mL) were added and stirred for 5 min at which point the color changed to yellow, the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 2 mL). The organic extracts were combined and washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a short column of silica to afford **67.3** as a white solid (0.003 g, 100 %): R_f = 0.28 (5% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.7 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H), 8.46-8.40 (m, 2H), 8.36 (d, *J* = 8.9 Hz, 1H), 7.89 (d, *J* = 2.6 Hz, 1H), 7.79 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.71 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.14 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.88 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.65-6.61 (m, 1H), 4.49 (t, *J* = 6.4 Hz, 2H), 4.17-4.11 (m, 2H), 1.72-1.58 (m, 8H), 1.56-1.52 (m, 4H), 1.51 (s, 9H),^{13}C NMR (151 MHz, $CDCl_3$) δ 158.29, 156.31, 149.34, 143.80, 141.77, 131.10, 131.00, 130.29, 129.74, 128.91, 128.47, 127.80, 125.78, 125.43, 123.52, 123.43, 122.85, 122.57, 120.08, 118.43, 116.68, 116.37, 115.90, 108.15, 68.01, 67.98, 35.21, 31.75, 31.40, 30.92, 29.85, 29.30, 27.33, 26.05. HRMS (ESI) calc'd for $C_{36}H_{39}O_2$ ($[M+H]^+$) *m/z* = 503.2950 found 503.2947.

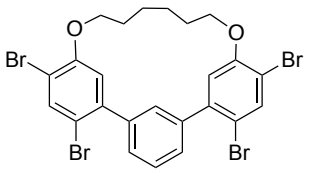


21a

***1,8-dioxa[8](3,3")m-Terphenylenophane* (21a):** Aluminium chloride (0.027 g, 0.20 mmol) was added to a stirred solution of **25.3** (0.045 g, 0.11 mmol) in toluene (20 mL) and the reaction was heated to 80 °C. After 30 min, a saturated solution of $NaHCO_3$ (10 mL) was added to the reaction. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (12 x 1.0 cm, 1:19 EtOAc/hexanes) to afford **21a** as a white solid (0.006 g, 14%): R_f = 0.42 (1:19 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (t, *J* = 1.9 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.32-7.24 (m, 2H), 7.23 -7.13 (m, 5H), 6.83 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 2H), 4.22-4.16 (m, 4H), 1.95-1.87 (m, 4H), 1.59-1.49 (m, 4H), 1.22-1.15 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.77, 141.99, 141.31, 130.18, 129.46, 127.45, 125.20, 118.64, 117.02, 111.06, 67.89, 27.85, 25.50. HRMS (EI) calculated for $C_{24}H_{24}O_2$ ($[M]^+$) *m/z* = 344.1931 found 344.1896.

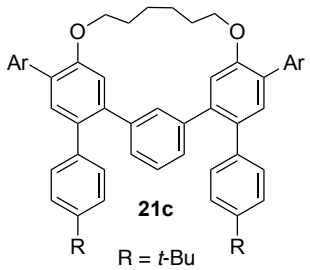
Alternative procedure for *1,8-dioxa[8](3,3")m-Terphenylenophane* (21a): A solution of Iron(III) chloride (0.011 g, 0.066 mmol) in dichloromethane/nitromethane (9:1) was added dropwise to a stirred 0 °C solution of **25.3** (0.100 g, 0.263 mmol) in dichloromethane (20 mL). After 15 min, methanol (5 mL) and water (10 mL) were added to the reaction. The layers were separated

and the aqueous phase was 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 dissolved in methanol (3 mL) followed by adding 1.5 equivalent $NaBH_4$. After 1 hour, the reaction was poured into water (10 mL) and further diluted by adding 1 M HCl (5 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was dissolved in pyridine (2 mL) followed by adding TsCl (0.094 g, 0.494 mmol). The reaction was heated to 80 °C for 12 hours at which point water (10 mL) was added. The reaction was further diluted by adding 1 M HCl(5 mL) solution. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in dichloromethane followed by addition of DDQ (0.100 g, 0.474 mmol) at 0 °C. After 10 min the ice bath was removed and the reaction was run for 1 hour at which point water (10 mL) and saturated solution of $NaHCO_3$ (5 mL) were added. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 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 x 1.3 cm, 1:19 EtOAc/hexanes) to afford **21a** as a white solid (0.020 g, 25% over 3 steps): R_f = 0.42 (1:19 EtOAc/hexanes);



21b

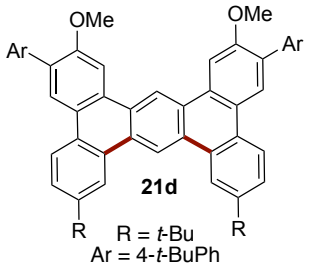
4,4",6,6"-tetrabromo-1,8-dioxa[8](3,3")m-terphenylophane **(21b):** Bromine (0.074 g, 0.464 mmol) was added to a stirred solution of **57.3** (0.020 g, 0.058 mmol) in 1,2-dichlorobenzene (5.0 mL) at room temperature. The resulting mixture was heated to 80 °C for 12 hours and then cooled to room temperature under a stream of nitrogen gas. After complete evaporation of the solvent, the residue was dissolved in dichloromethane (10 mL), a solution of 5% $NaHSO_3$ (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 × 5 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 **21b** as a white solid (0.034 g, 89%): R_f = 0.31 (3:7 dichloromethane/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.68 (dd, J = 7.7, 1.9 Hz, 2H), 7.42 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 6.86 (s, 2H), 4.26 - 4.19 (m, 4H), 1.83 (q, J = 7.3, 5.5 Hz, 4H), 1.50-1.43 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.15, 141.33, 140.60, 137.21, 130.56, 129.01, 127.78, 126.92, 115.73, 111.86, 68.61, 27.43, 25.19. HRMS (EI) calc'd for $C_{24}H_{20}O_2Br_4$ ($[M]^+$) m/z = 655.8197, found 655.8224.



21c
R = *t*-Bu
Ar = 4-*t*-BuPh

4,4",6,6"- tetrakis(4-t-butylphenyl)-1,8-dioxa[8](3,3")m-terphenylenophane **(21c)*:*** Sodium carbonate (0.165 g, 1.56mmol) and 4-*tert*-butylphenyl boronic acid (0.0750 g, 0.416 mmol) were added sequentially to a stirred solution of tetrabromide **20l** (0.034 g, 0.052 mmol) in toluene (3 mL), water (1 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) (0.007 g, 0.006 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 13 h and then cooled to room temperature. Once cooled, water (10 mL) and 1 M HCl (5 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 (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% ethyl acetate/hexanes) to yield **21c** as a white solid (0.030 g, 66%, 59% from 57.3): R_f = 0.39 (1:19 ethyl acetate/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65-7.58 (m,

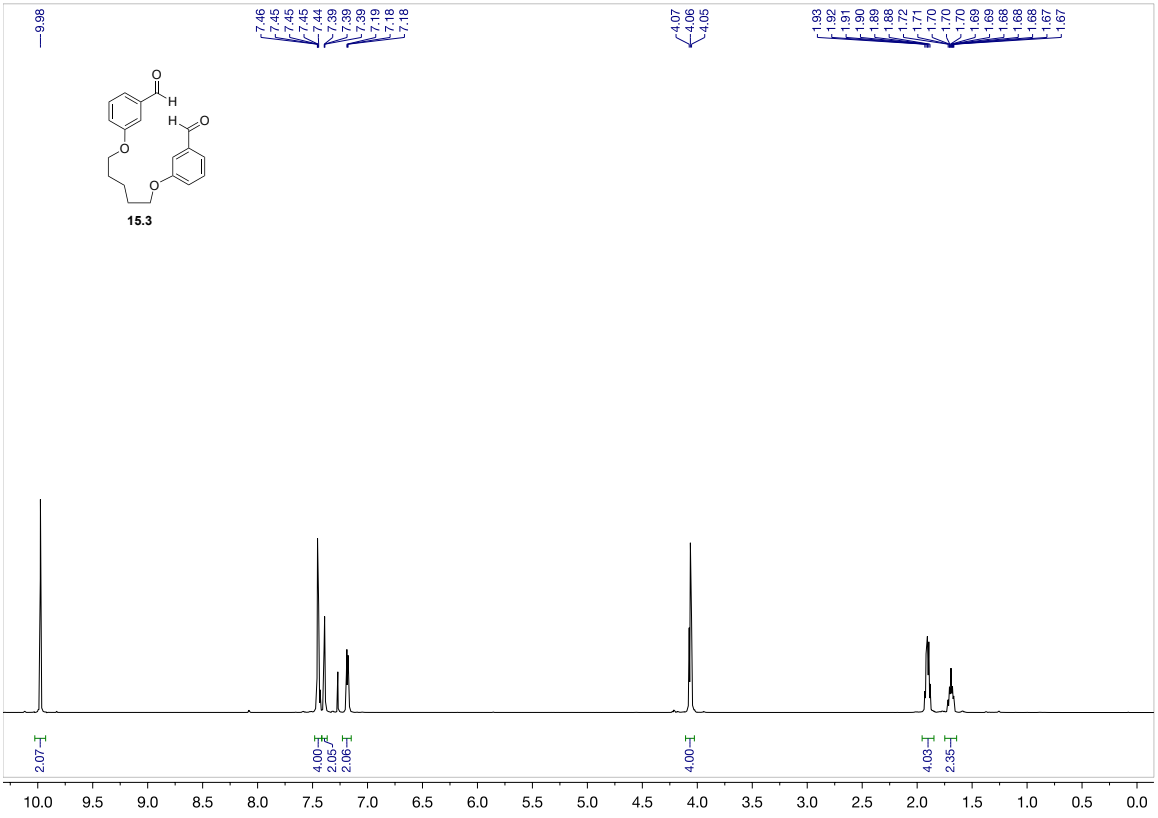
4H), 7.52 -7.44 (m, 6H), 7.33-7.27 (m, 4H), 7.23 (s, 2H), 7.22-7.15 (m, 4H), 6.71 (dd, *J* = 6.9, 1.7 Hz, 2H), 4.38-4.32 (m, 4H), 2.07 (h, *J* = 6.6 Hz, 4H), 1.64-1.63 (m, 4H), 1.40 (s, 18H), 1.36 (s, 18H).[13]C NMR (151 MHz, $CDCl_3$) δ 153.12, 148.64, 148.03, 140.88, 139.05, 136.61, 134.05, 132.10, 131.11, 130.47, 128.62, 128.54, 128.05, 127.03, 123.97, 123.52, 113.74, 66.66, 33.51, 33.33, 30.35, 30.31, 26.66, 24.31. HRMS (ESI) calc'd for $C_{64}H_{73}O_2$ ($[M+H]^+$) *m/z* = 873.5611, found 873.5646.



***Tetrabenzanthracene* 21d:** 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 the rearranged Scholl product **5a** (n = 7) (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-cooled 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 $MgSO_4$, filtered, and concentrated under reduced pressure. The white solid residue was dissolved in acetone (4mL) 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 to the reaction mixture, and the layers were 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 Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5 × 0.7 cm, 3:7 dichloromethane/hexanes) to yield **21d** as a white solid (0.002 g, 35%), R_f = 0.56 (2:3 dichloromethane/hexanes*);* [1]H NMR (600 MHz, $CDCl_3$) 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); [13]C NMR (151 MHz, $CDCl_3$) 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.

Appendix 4

^{1}H and ^{13}C NMR spectra for the new compounds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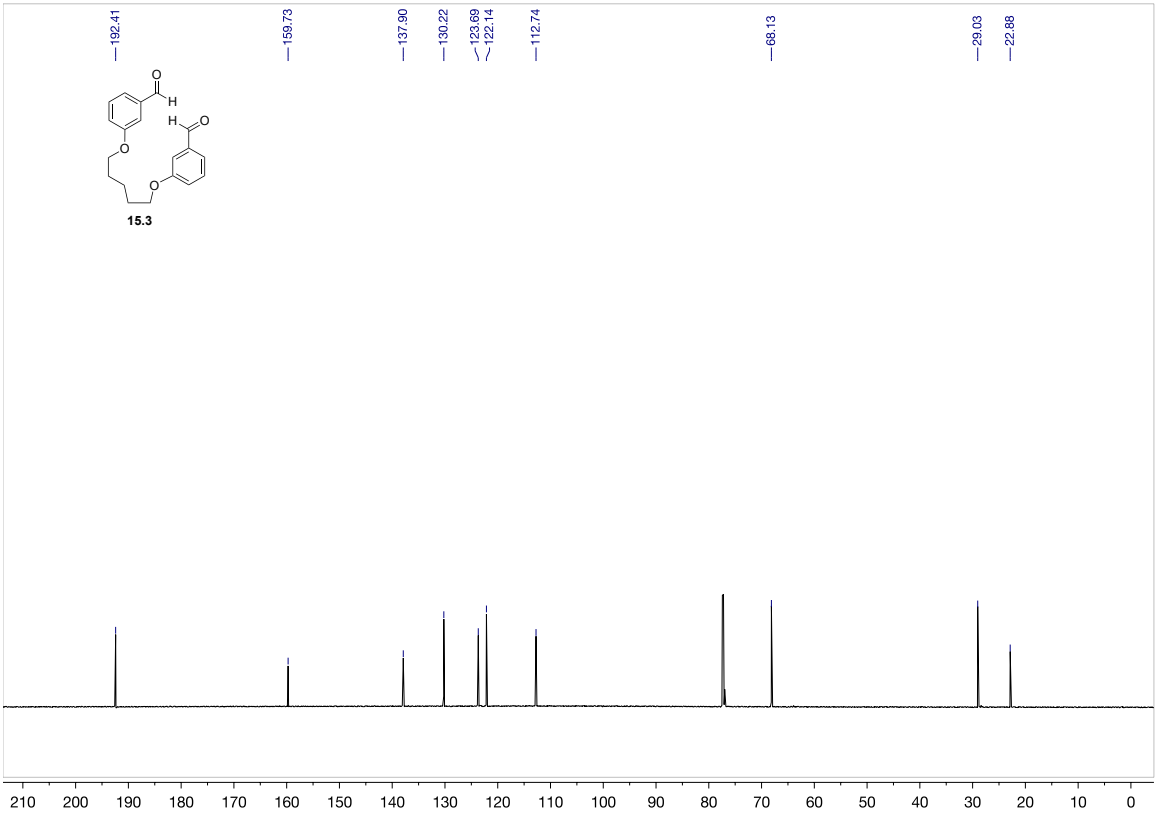
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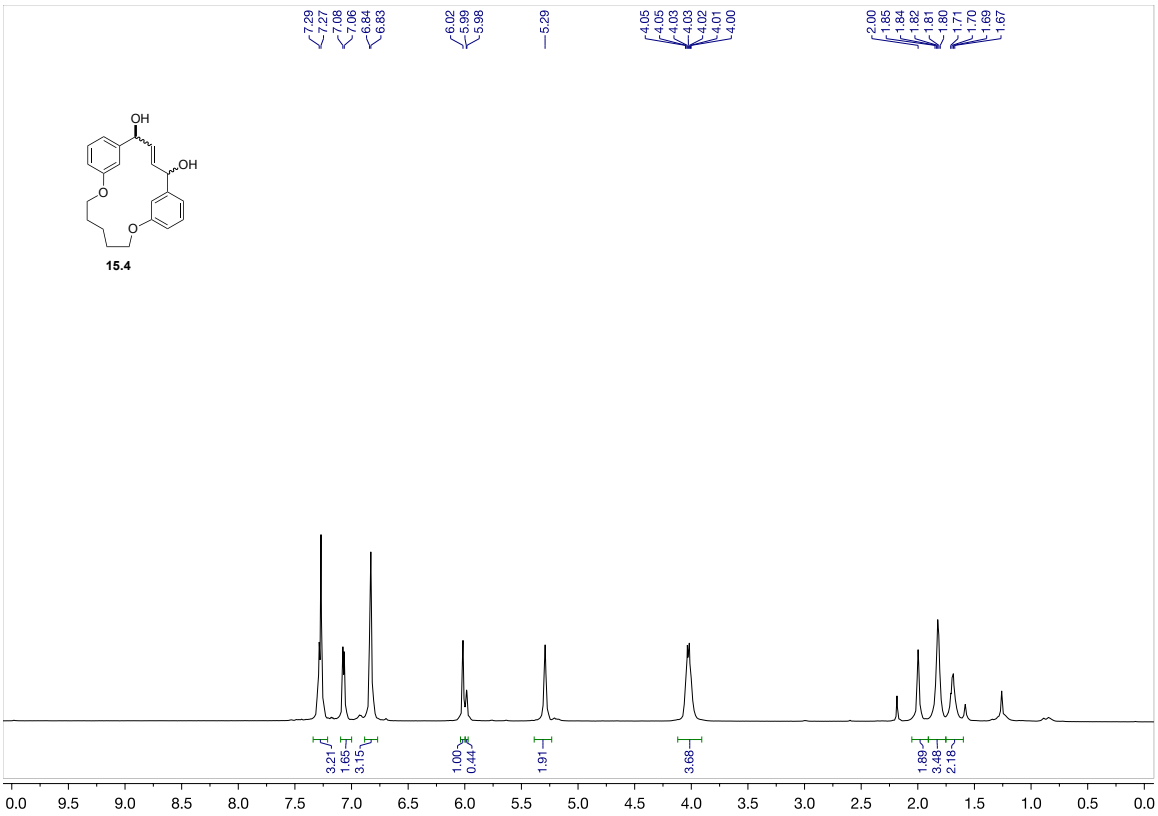
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3.68
1.89
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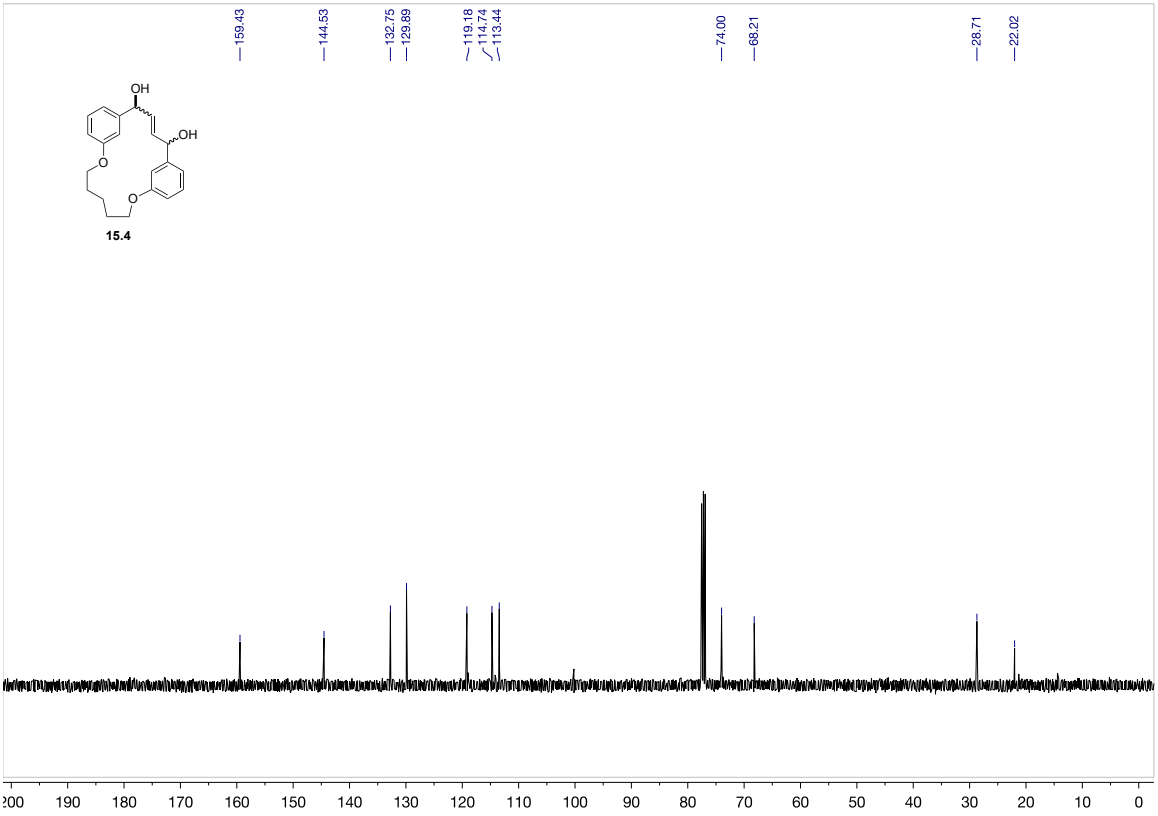
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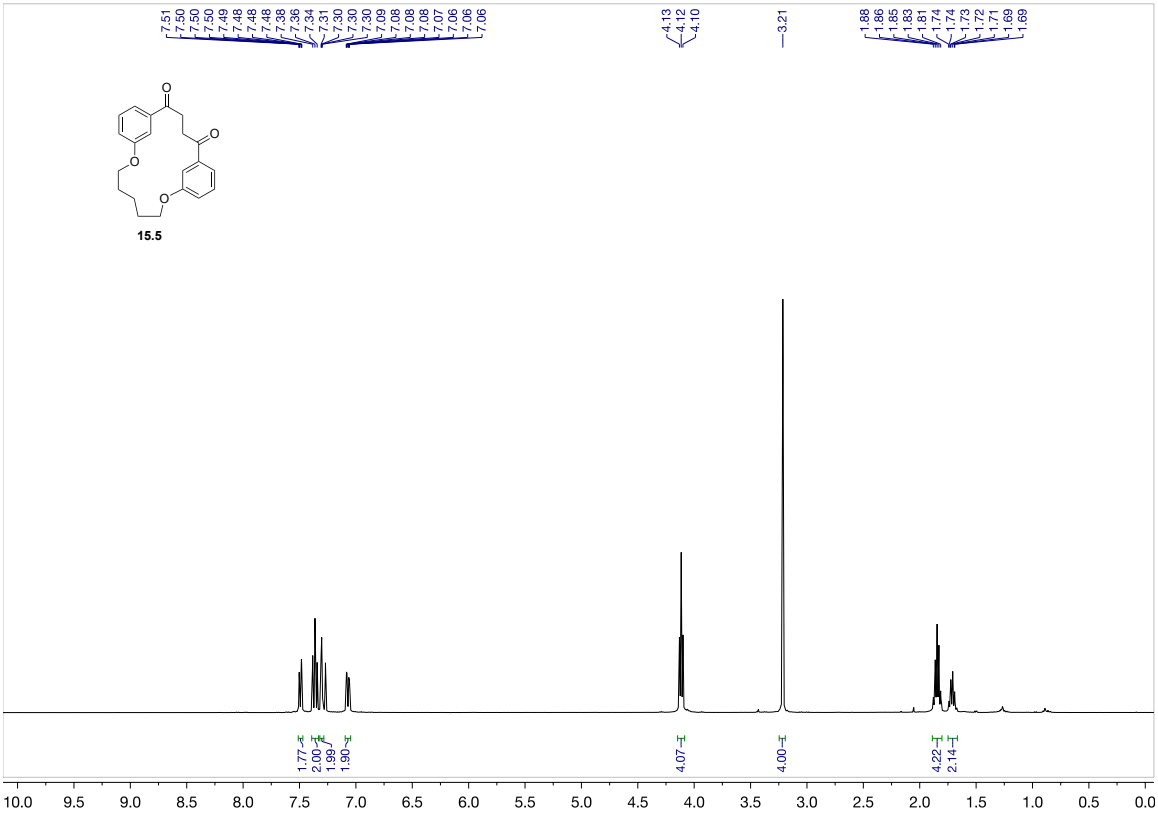
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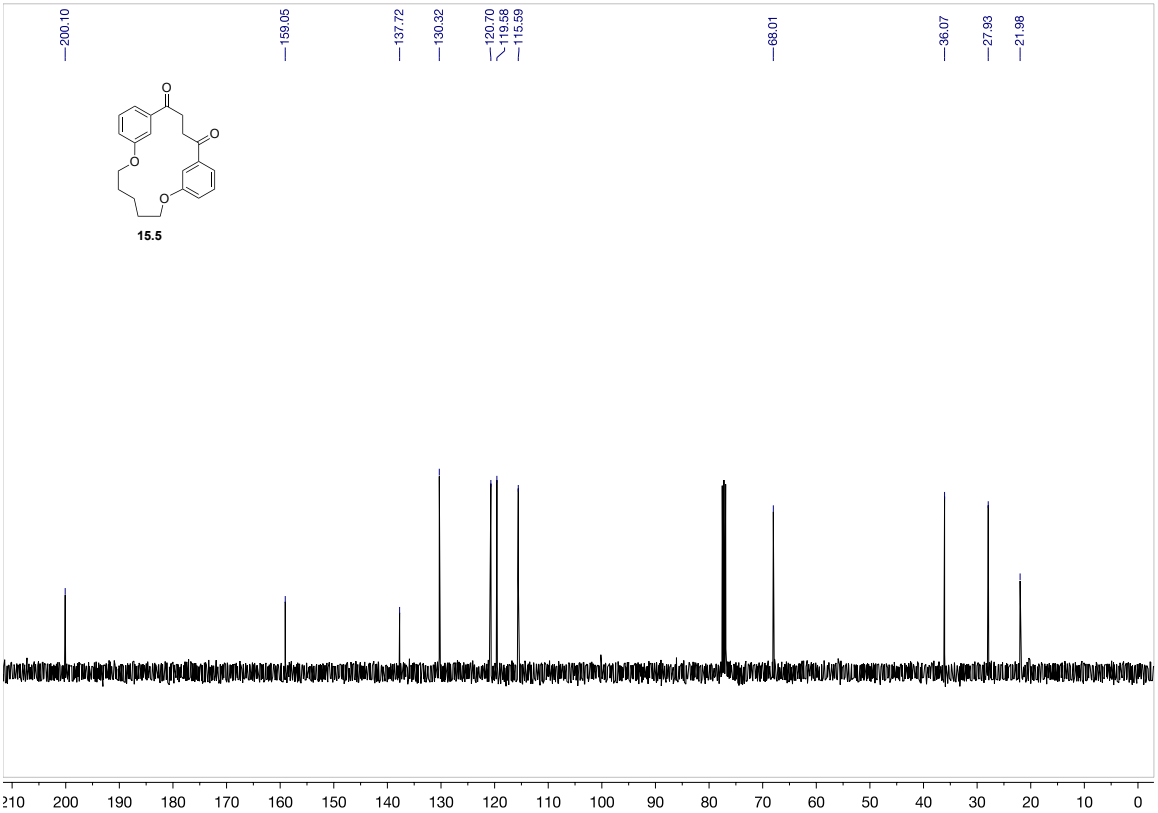
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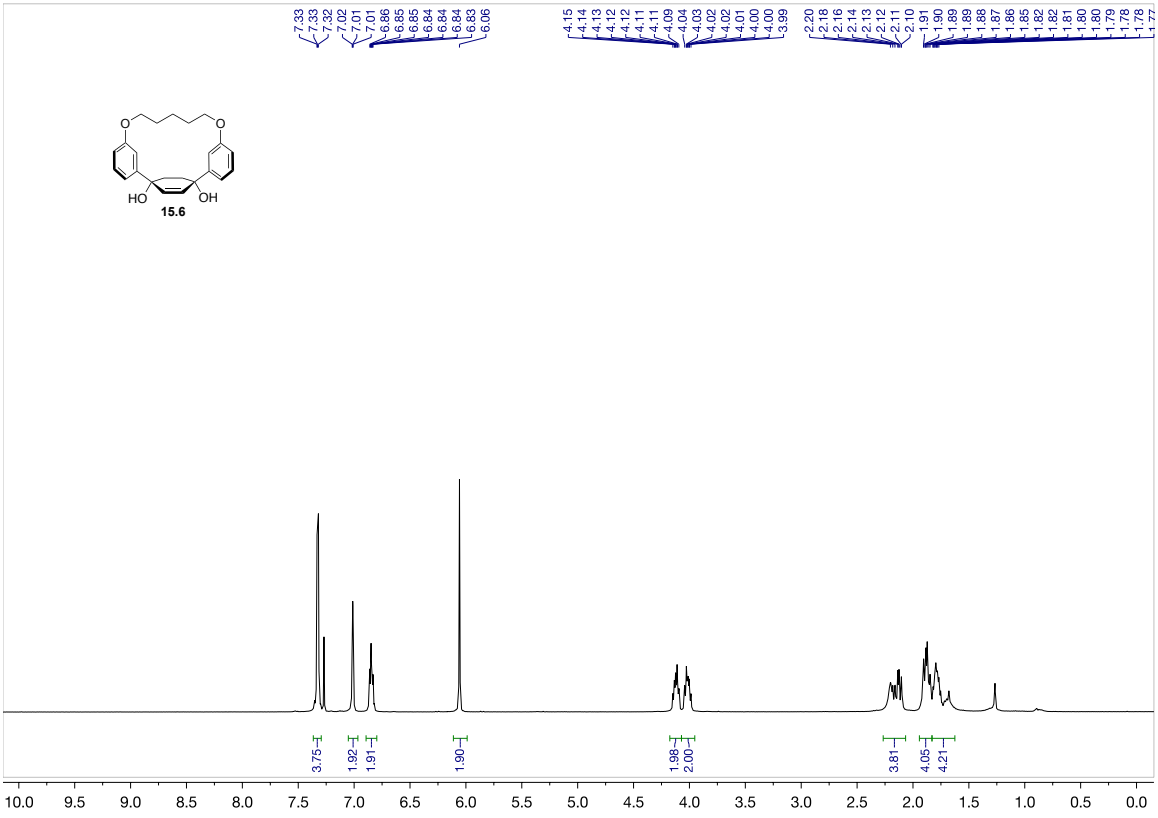
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4.12
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4.09
4.04
4.03
4.02
4.02
4.01
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2.13
2.12
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2.10
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1.89
1.89
1.88
1.87
1.86
1.85
1.82
1.82
1.81
1.80
1.80
1.79
1.78
1.78
1.77
O
O
HO
OH
15.6
3.75
1.92
1.91
1.90
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2.00
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9.0
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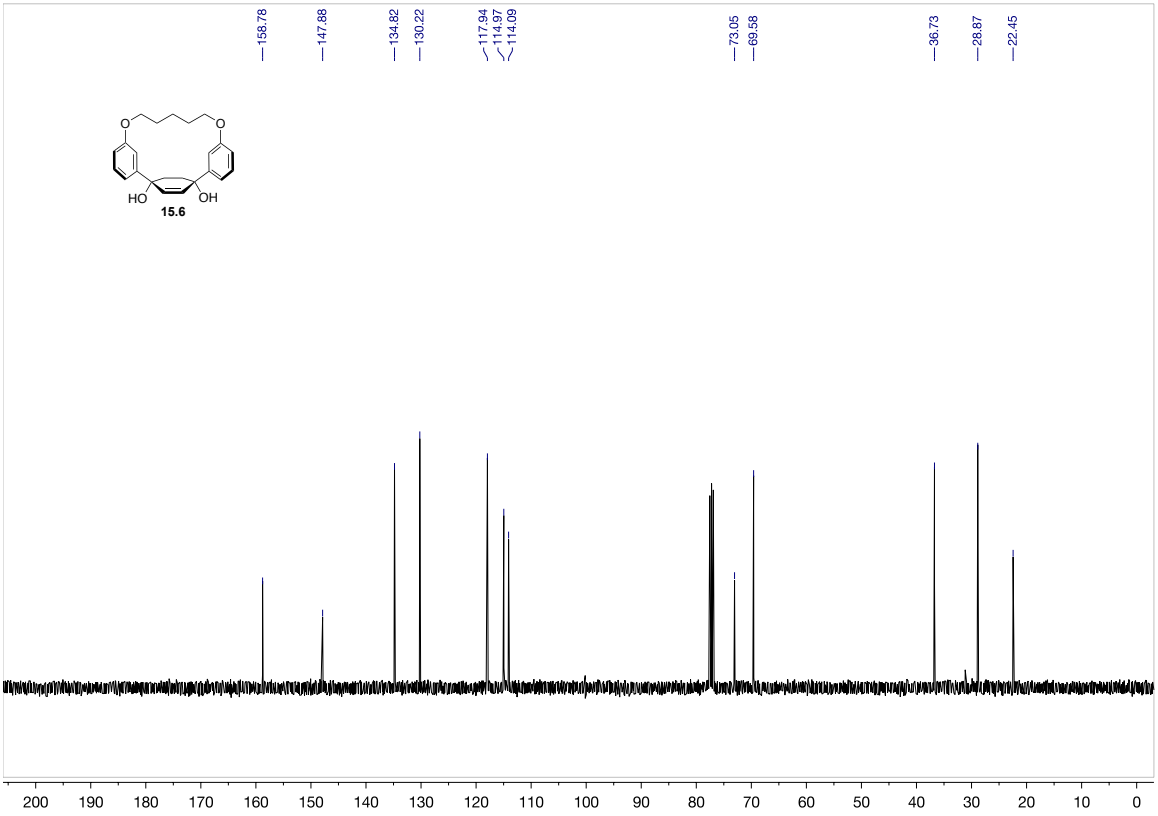
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22.45
O
O
HO
OH
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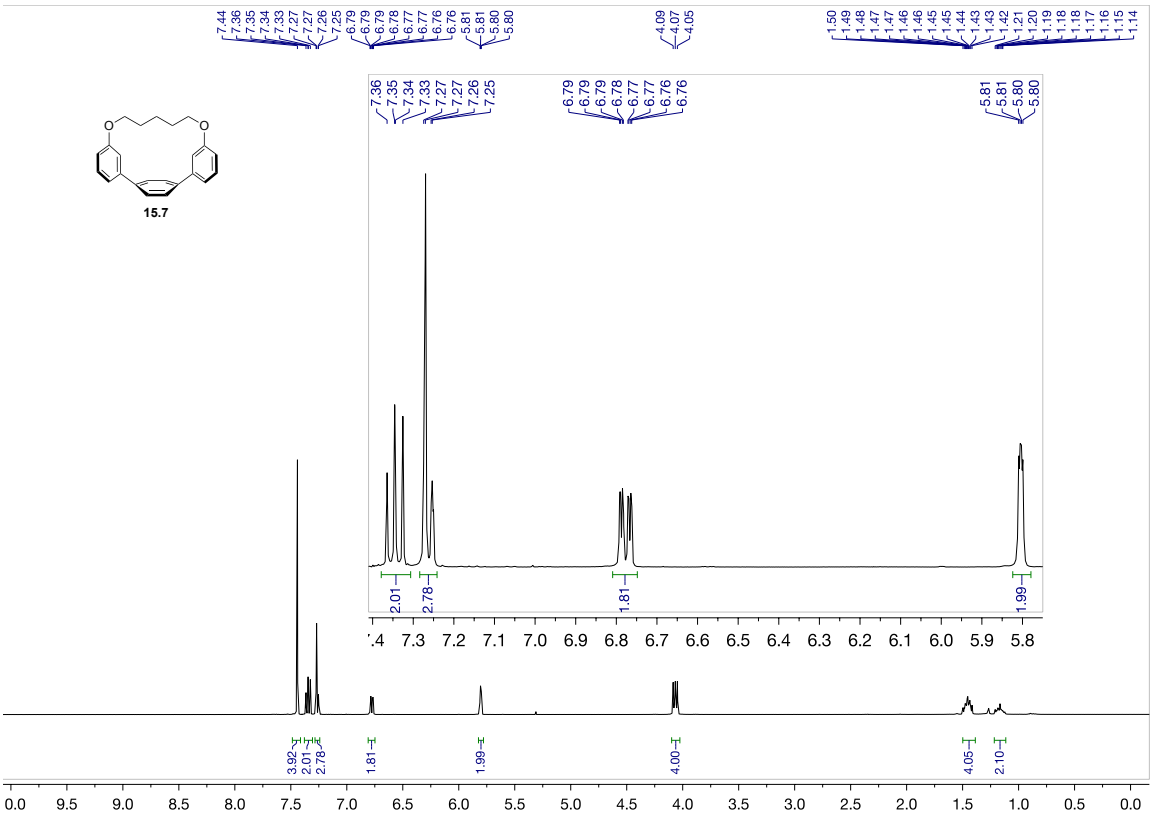
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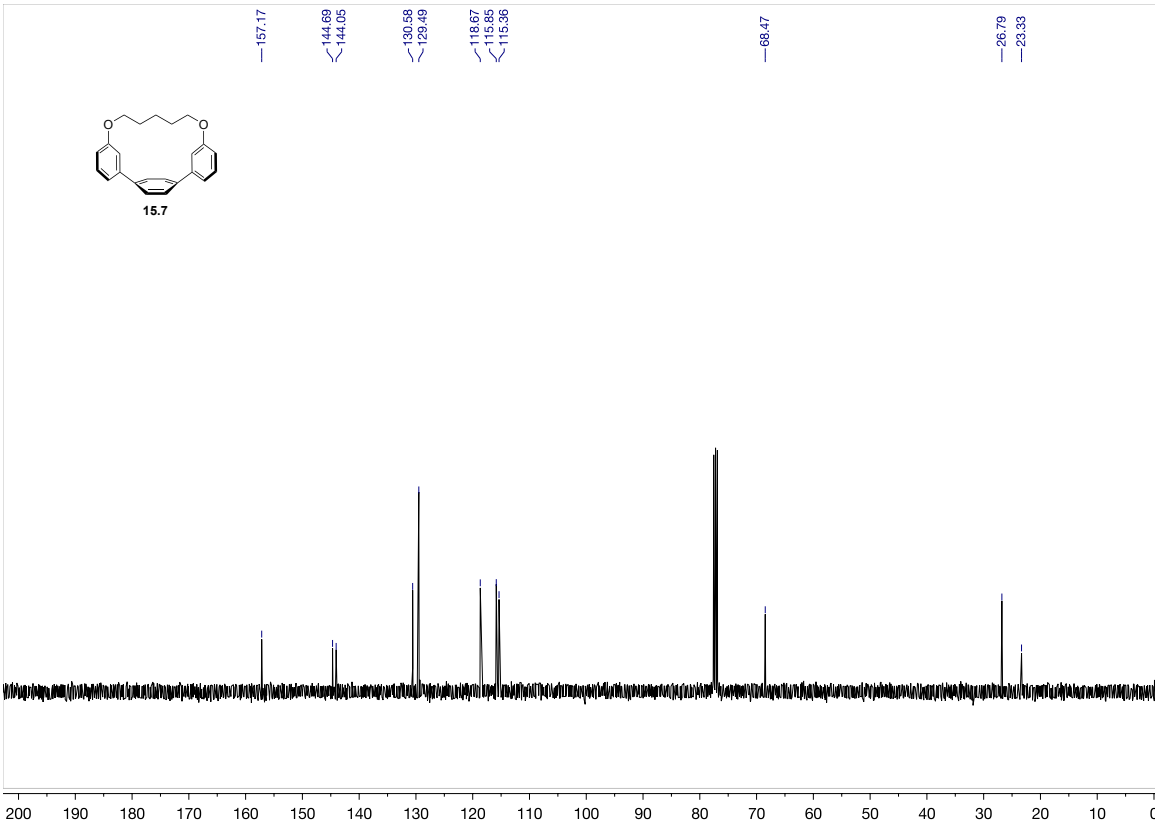
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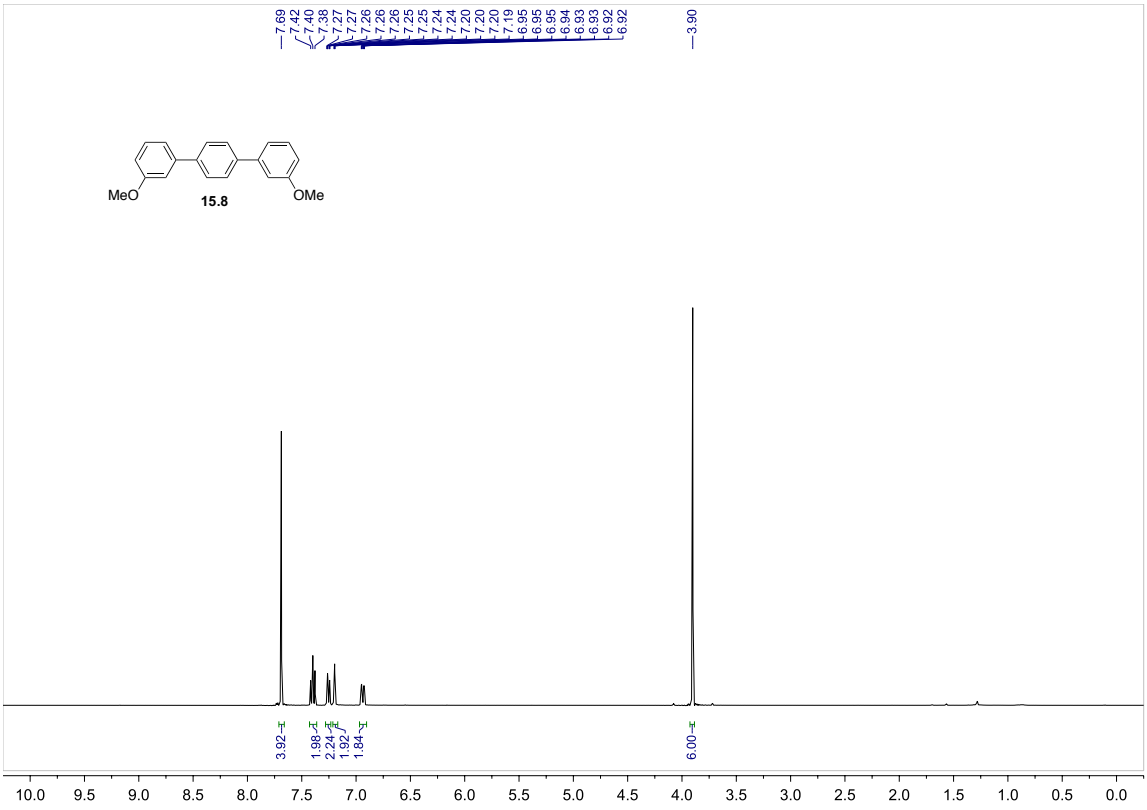
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7.20
7.20
7.19
6.95
6.95
6.95
6.94
6.93
6.93
6.92
6.92
3.90
MeO
OMe
15.8
3.92
1.98
2.24
1.92
1.84
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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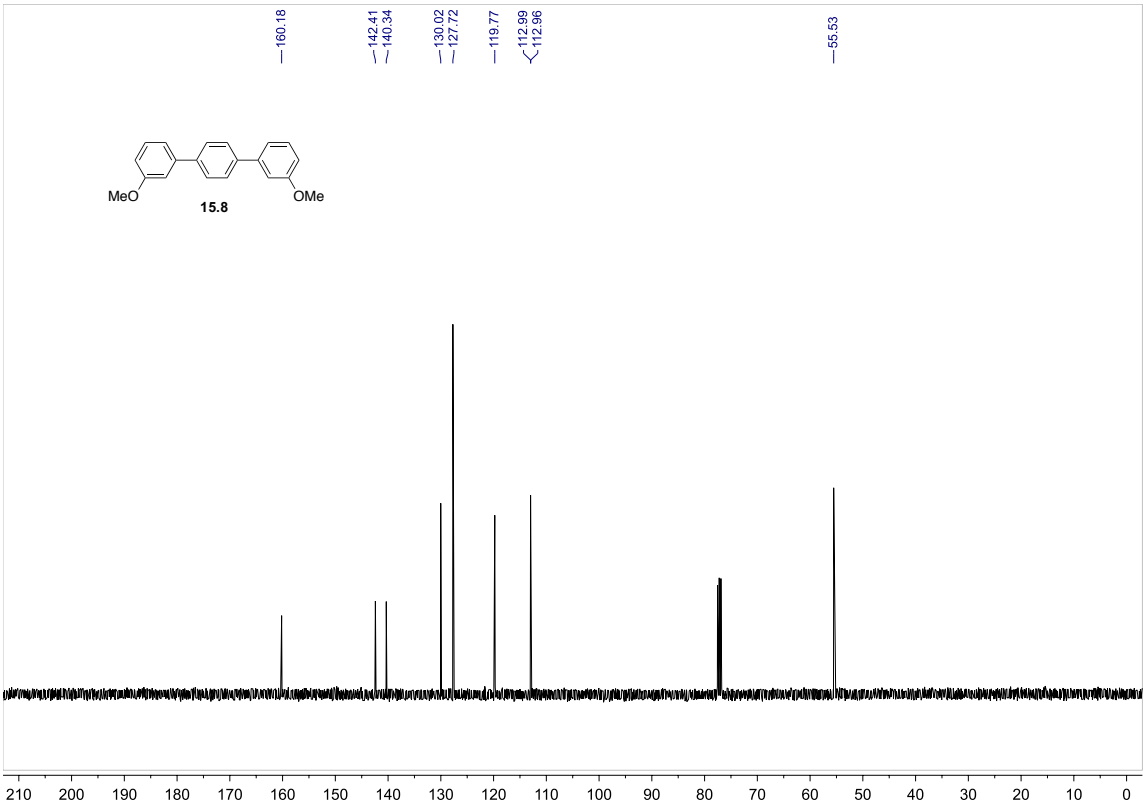
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119.77
112.99
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MeO
OMe
15.8
210
200
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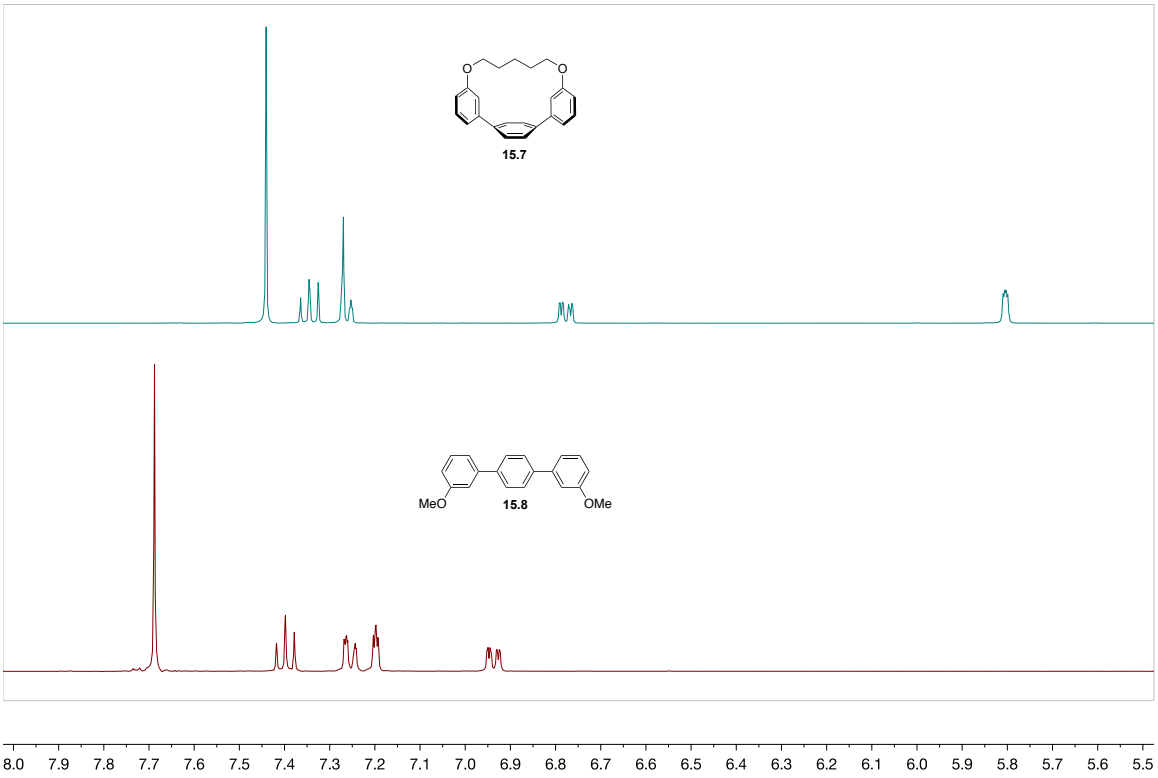
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MeO
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OMe
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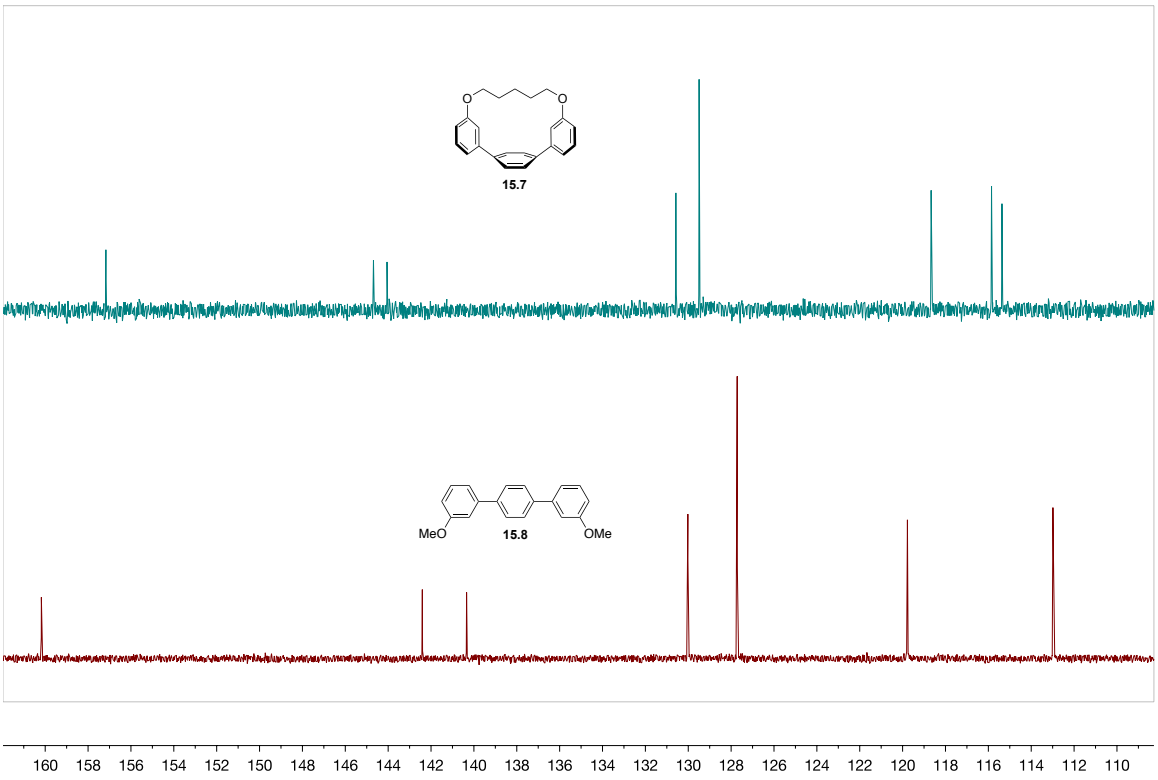
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15.8
OMe
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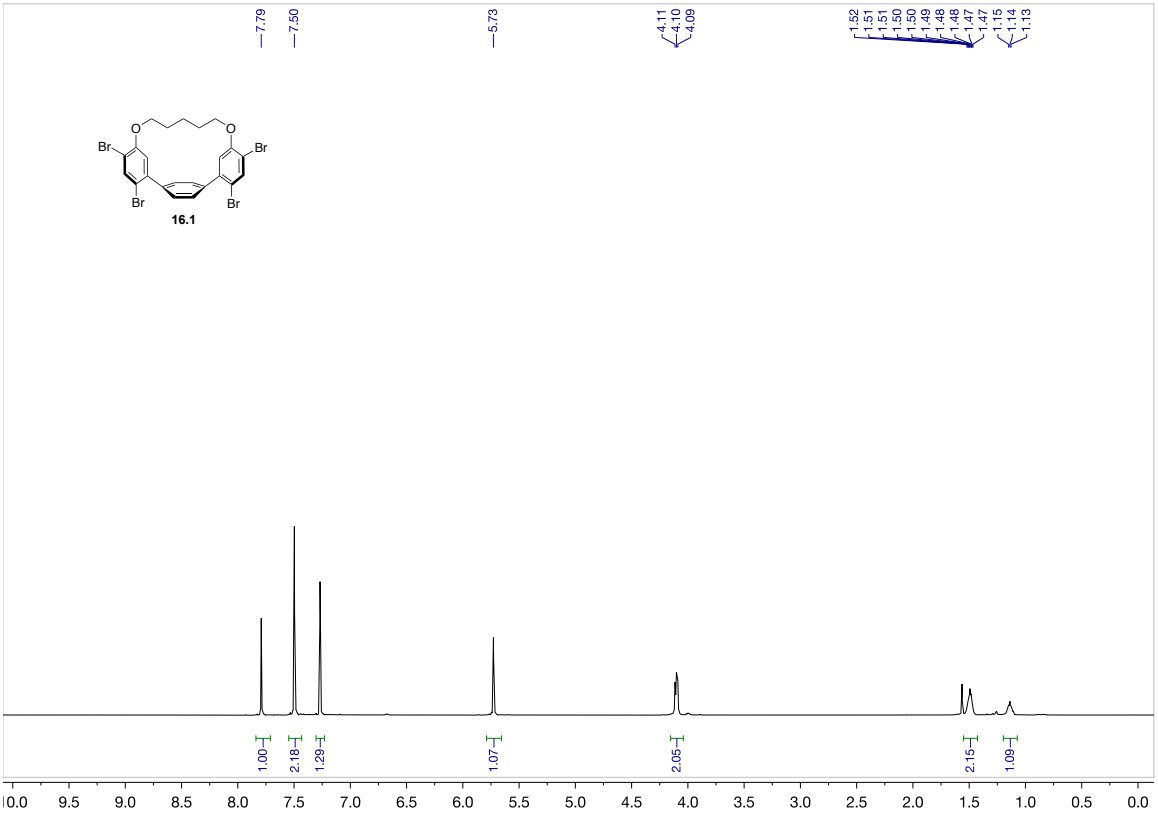
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1.50
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1.48
1.48
1.47
1.47
1.15
1.14
1.13
Br
Br
Br
Br
O
O
16.1
1.00
2.18
1.29
1.07
2.05
2.15
1.09
10.0
9.5
9.0
8.5
8.0
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7.0
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6.0
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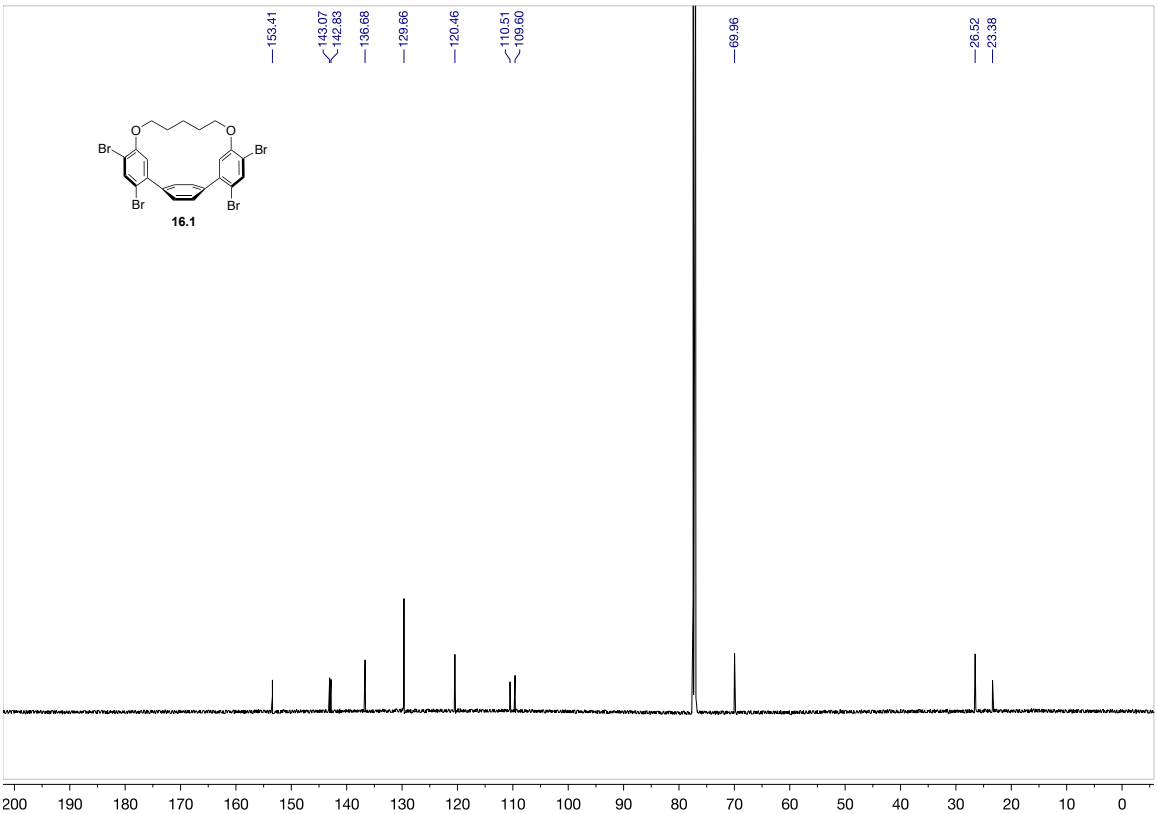
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69.96
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23.38
Br
Br
Br
Br
O
O
16.1
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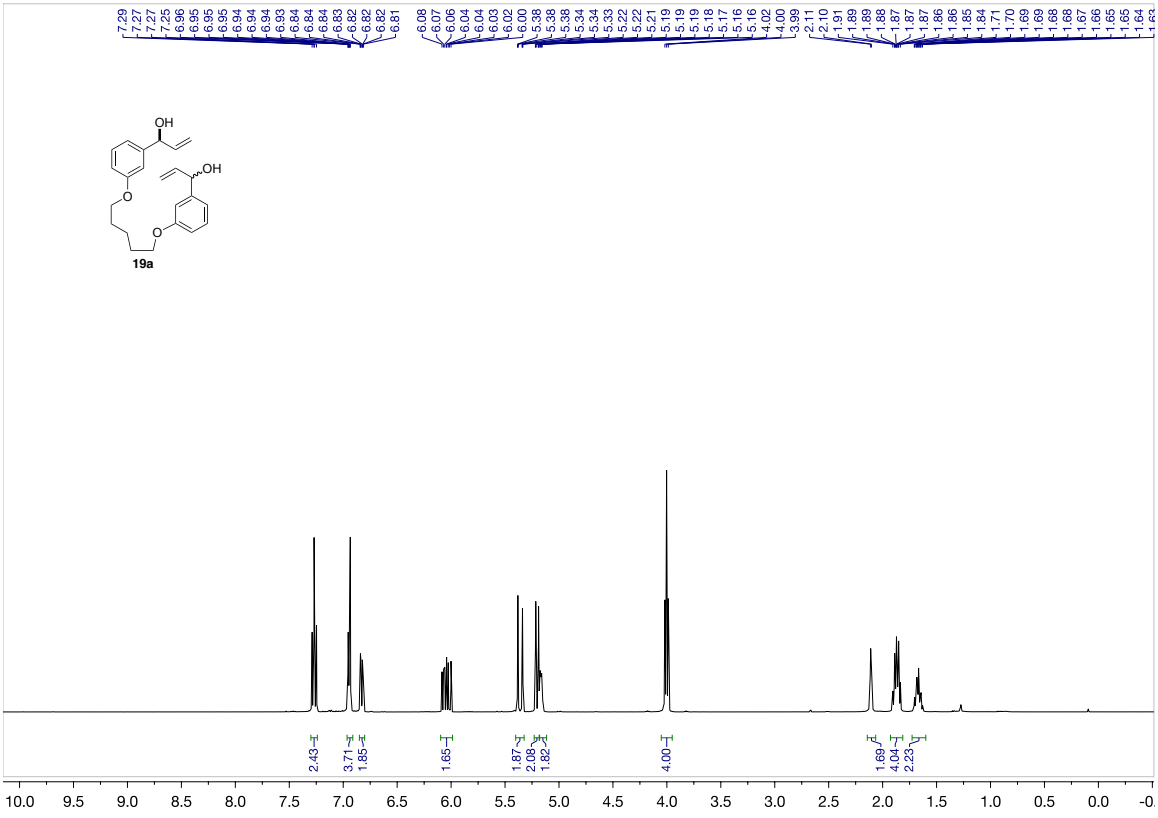
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OH
O
O
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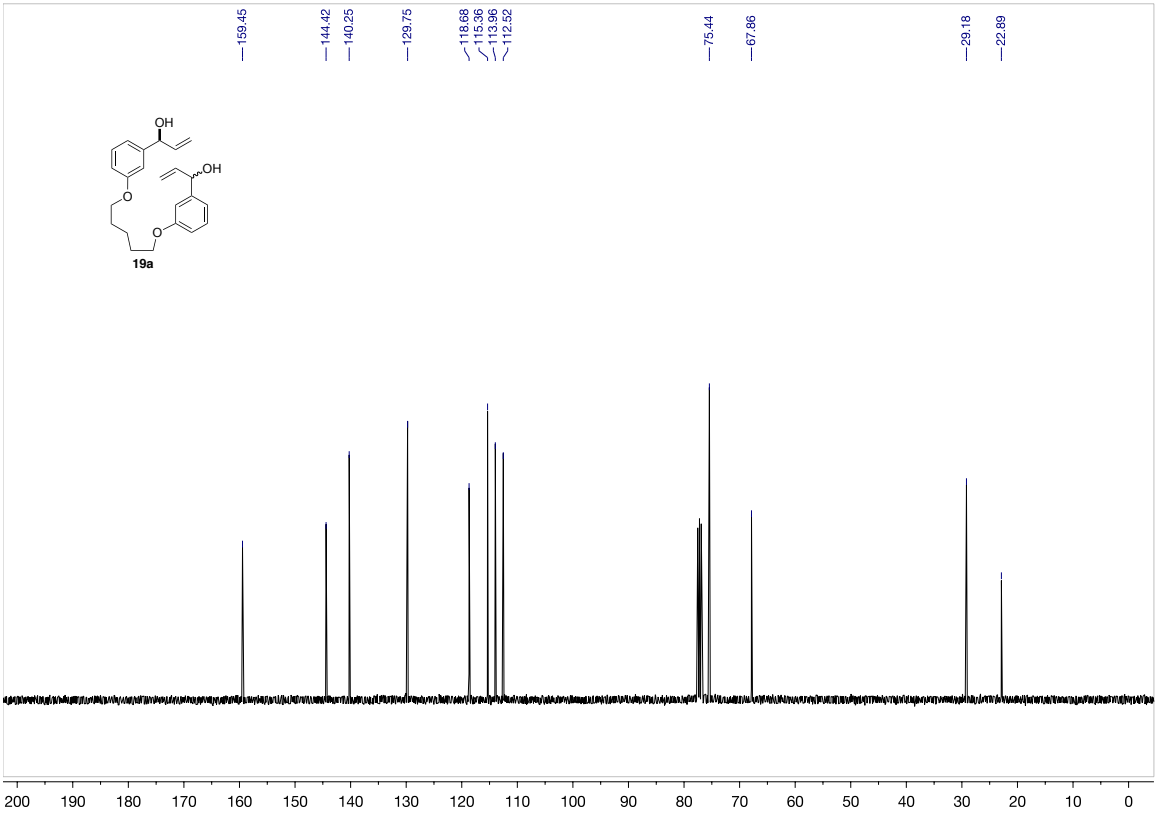
1.65
1.87
2.08
1.82
4.00
1.69
4.04
2.23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113.96
112.52
75.44
67.86
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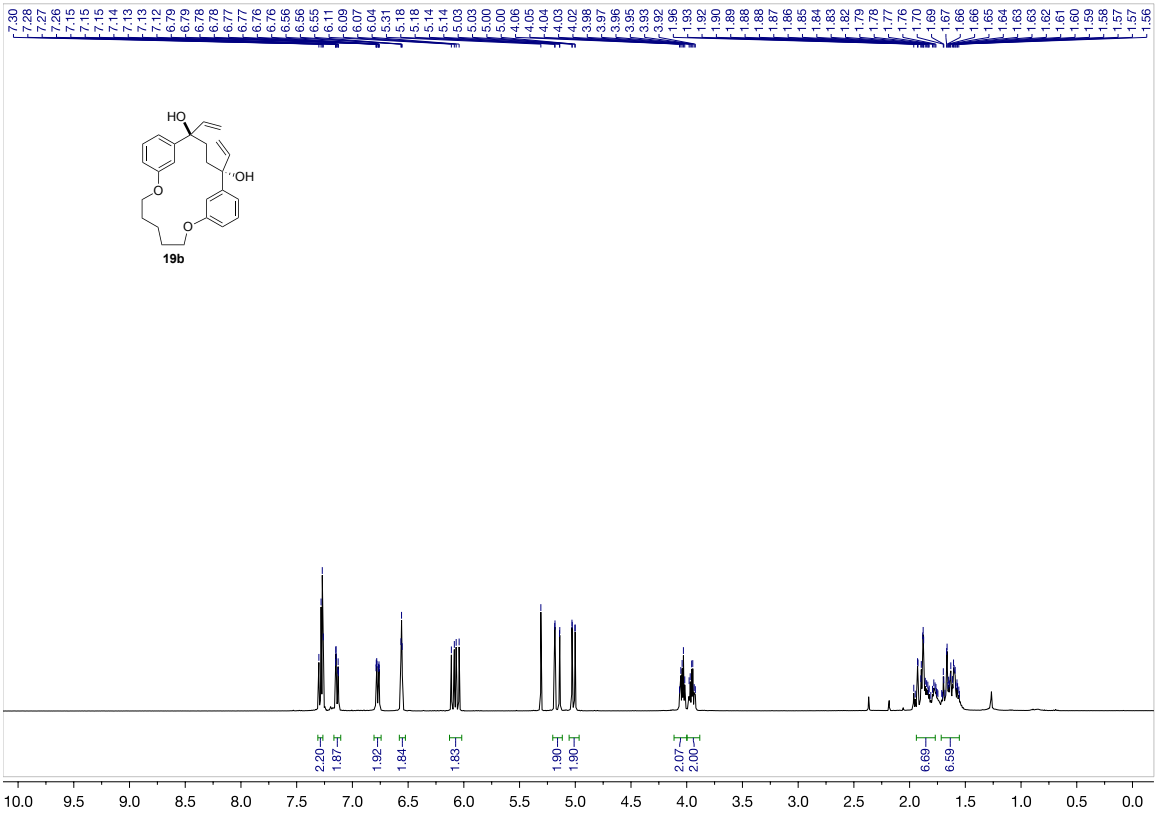
22.89
OH
OH
O
O
19a


HO
OH
O
O
19b
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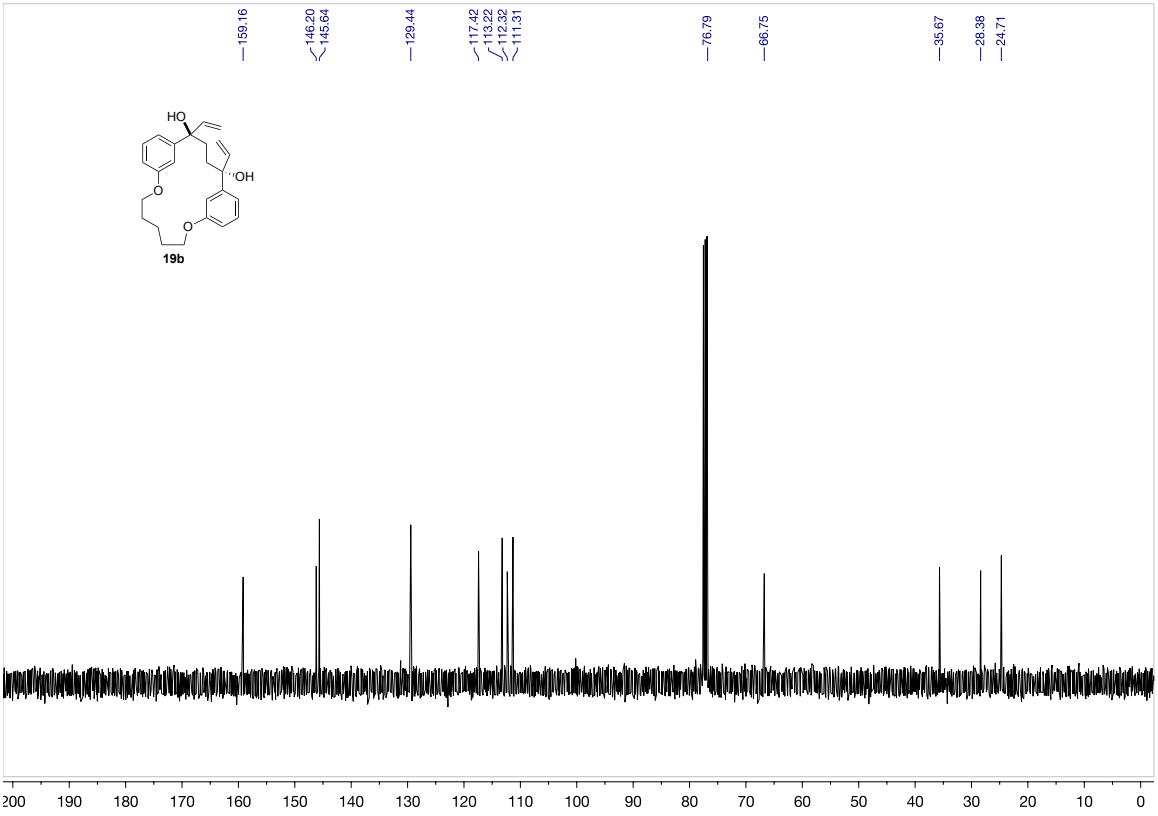
2.20 1.87 1.92 1.84 1.83 1.90 1.90 2.07 2.00 6.69 6.59
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


HO
OH
O
O
19b
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145.64
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117.42
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76.79
66.75
35.67
28.38
24.71
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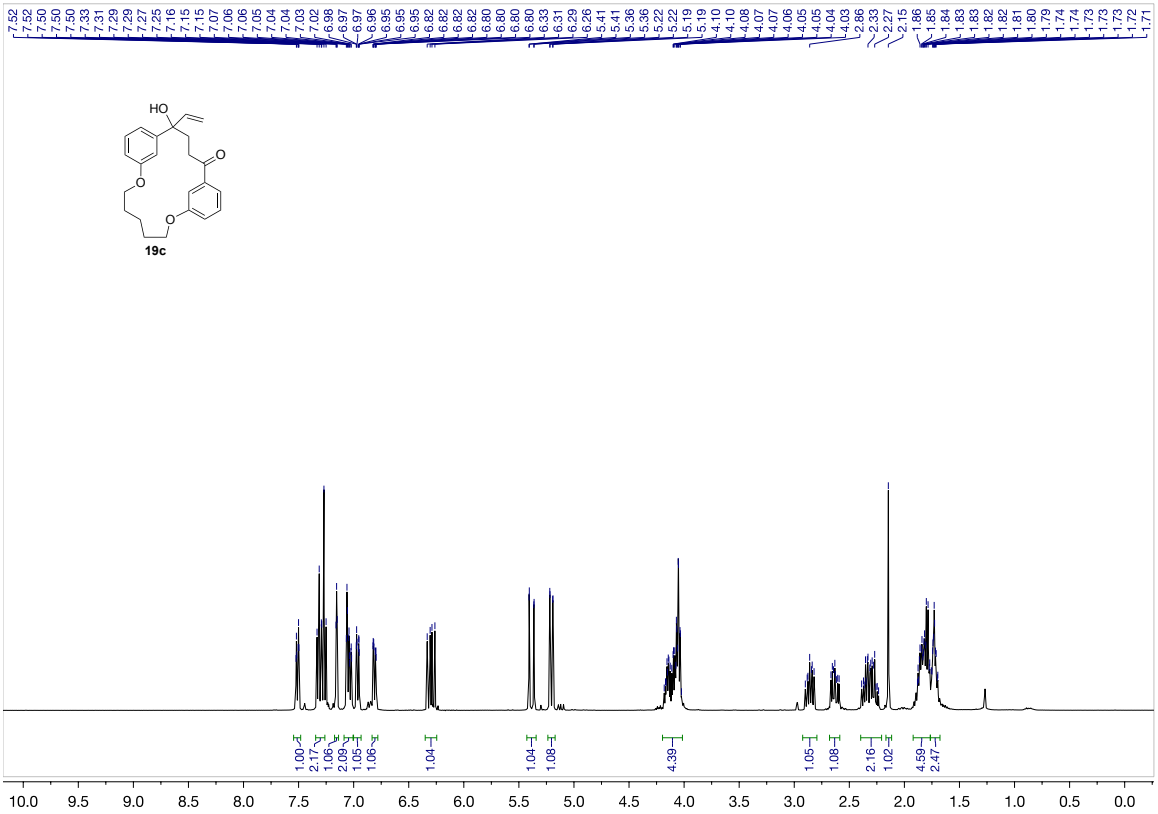
HO
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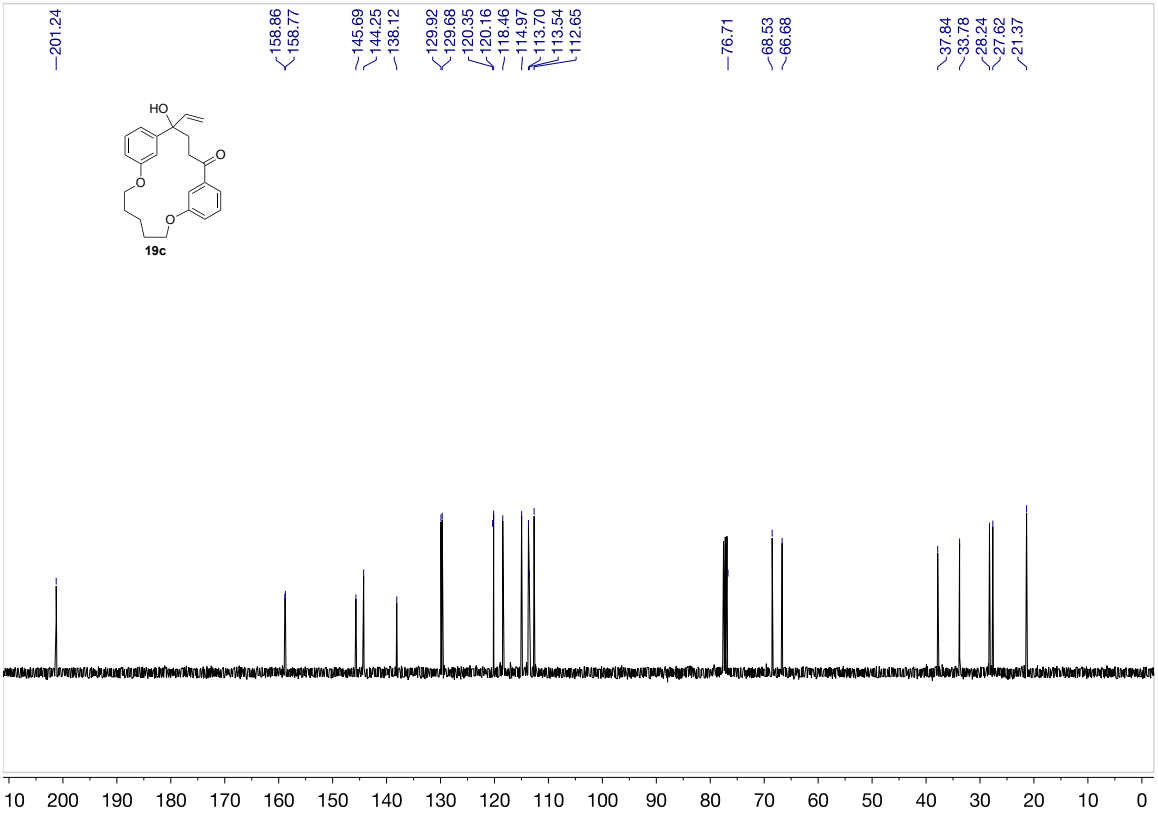
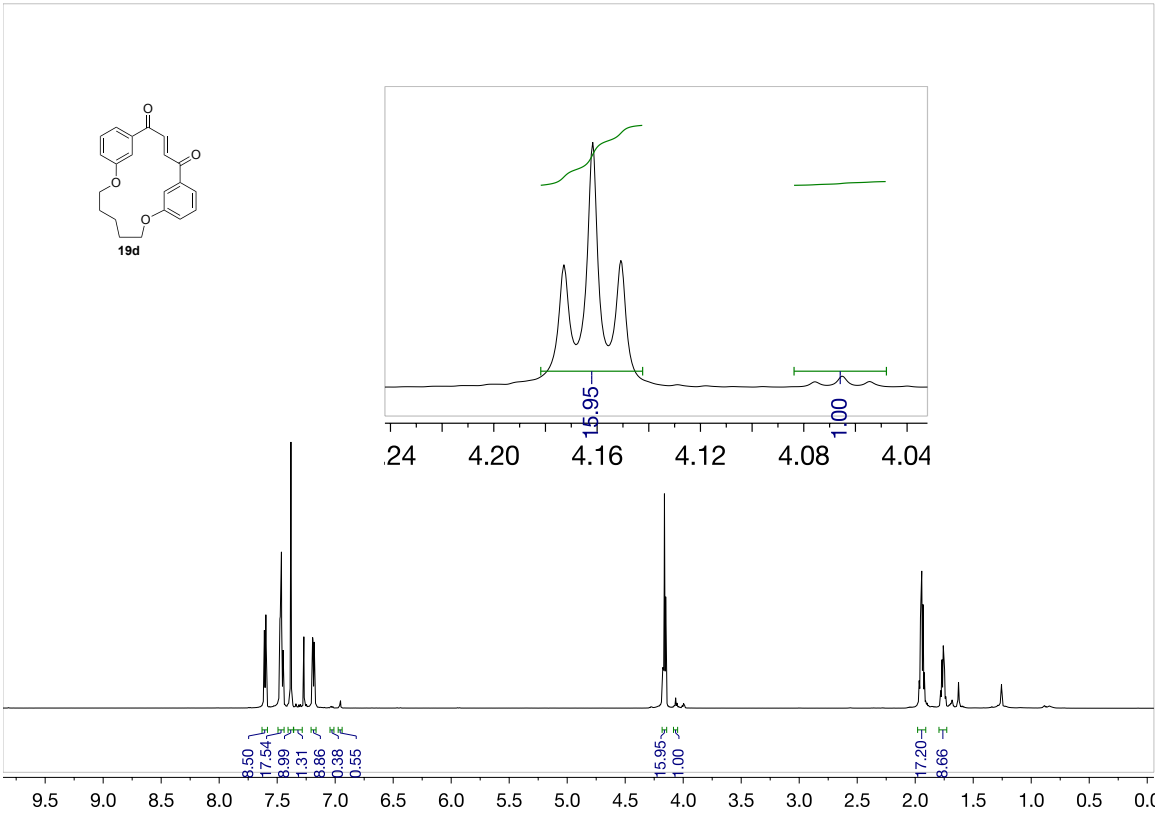
O
O
19c


HO
O
O
O
19c


19d
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4.08
4.04
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17.54
8.99
1.31
8.86
0.38
0.55
15.95
1.00
17.20
8.66
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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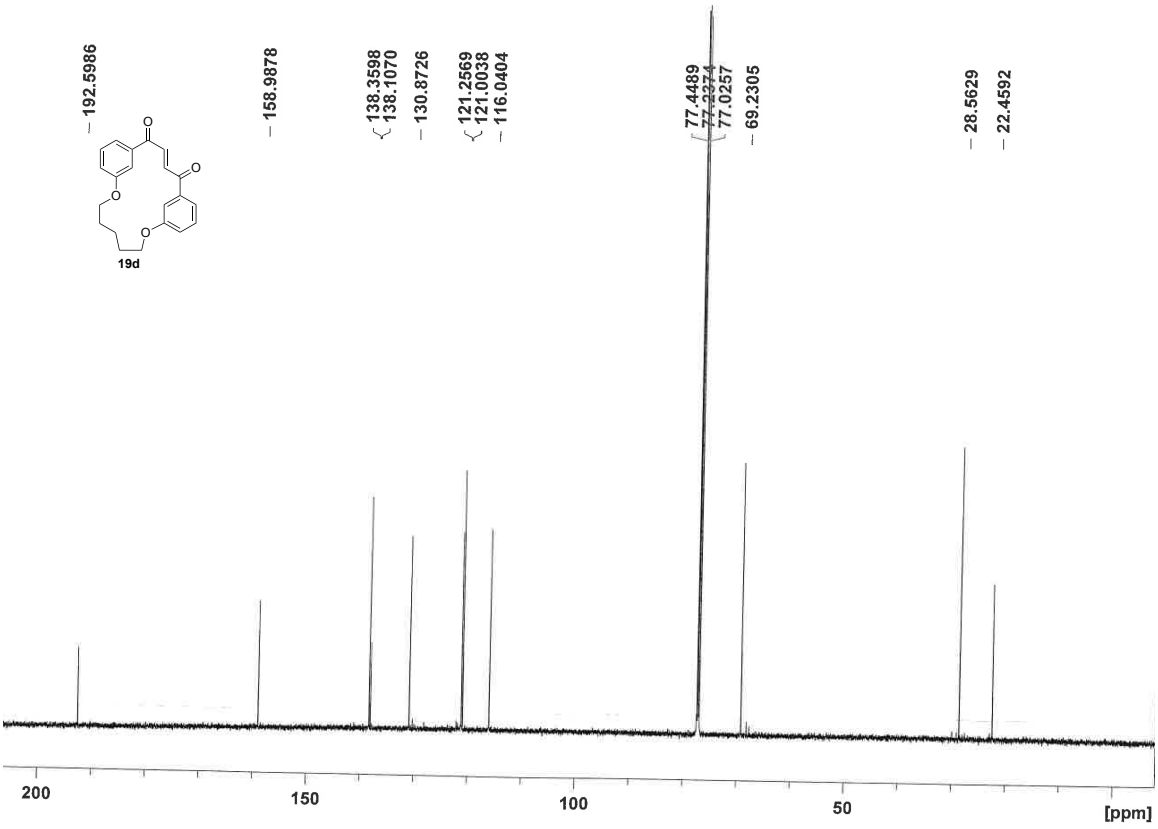
1.0
0.5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121.0038
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77.0257
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22.4592
19d
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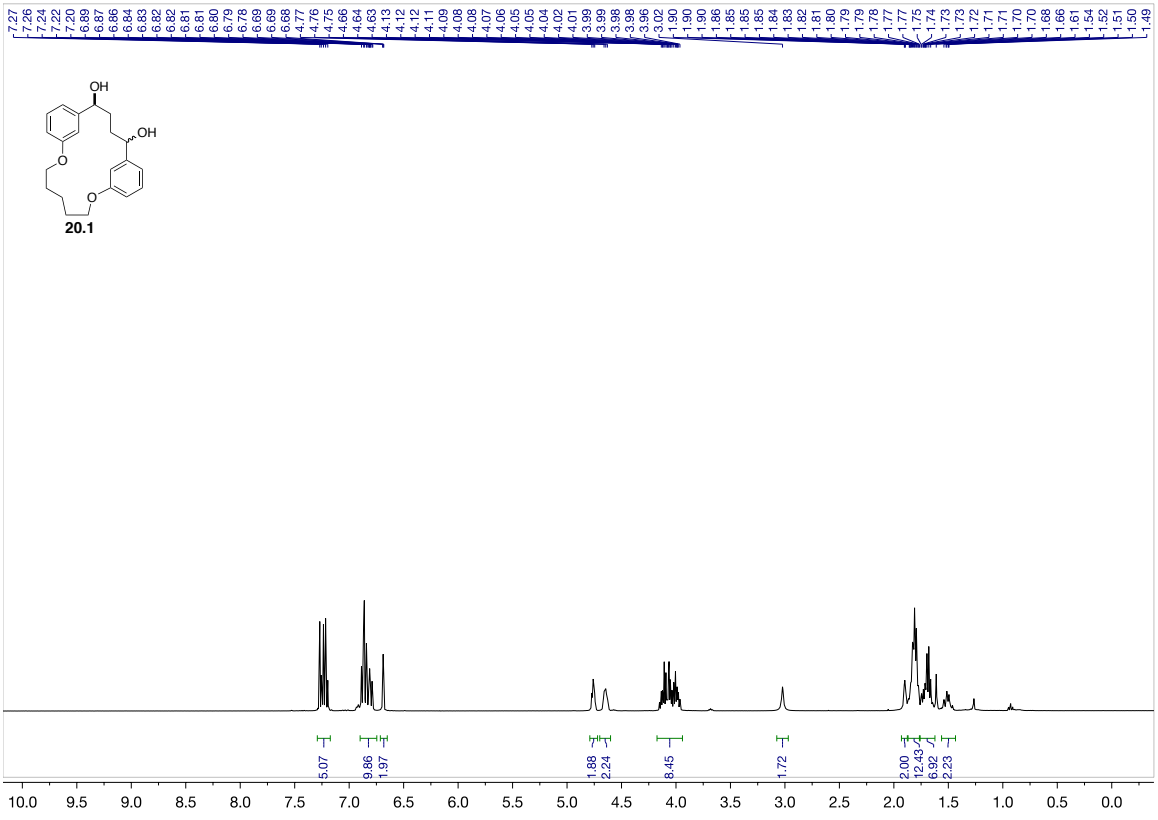
150
100
50
[ppm]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OH
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O
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1.72
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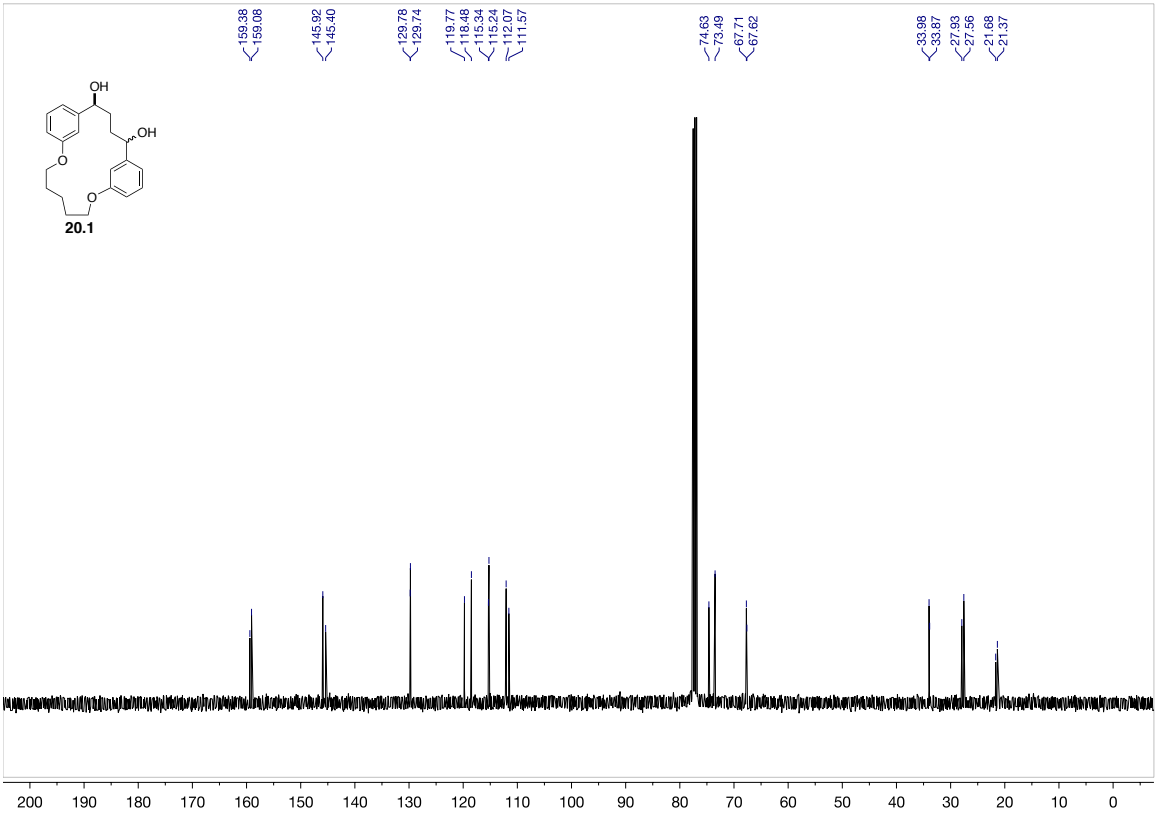
6.92
2.23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O
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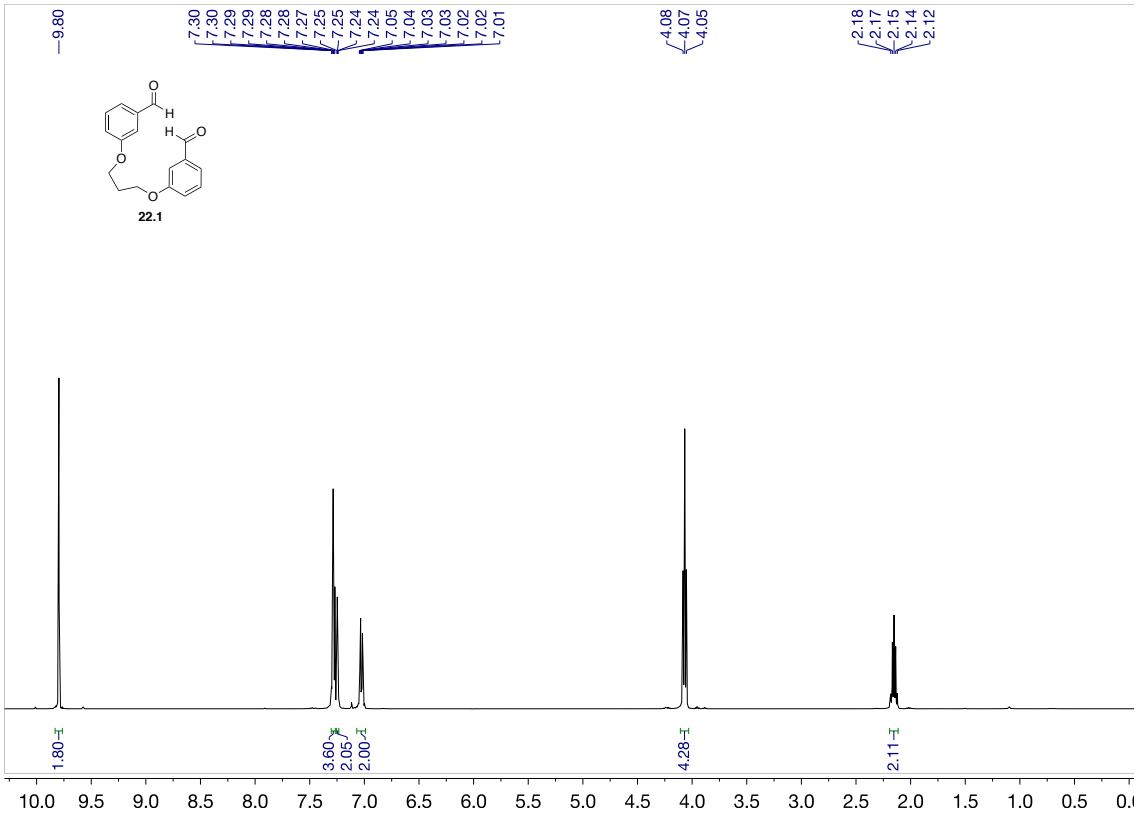
21.37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7.03
7.02
7.02
7.01
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4.05
2.18
2.17
2.15
2.14
2.12
22.1
1.80
3.60
2.05
2.00
4.28
2.11
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9.0
8.5
8.0
7.5
7.0
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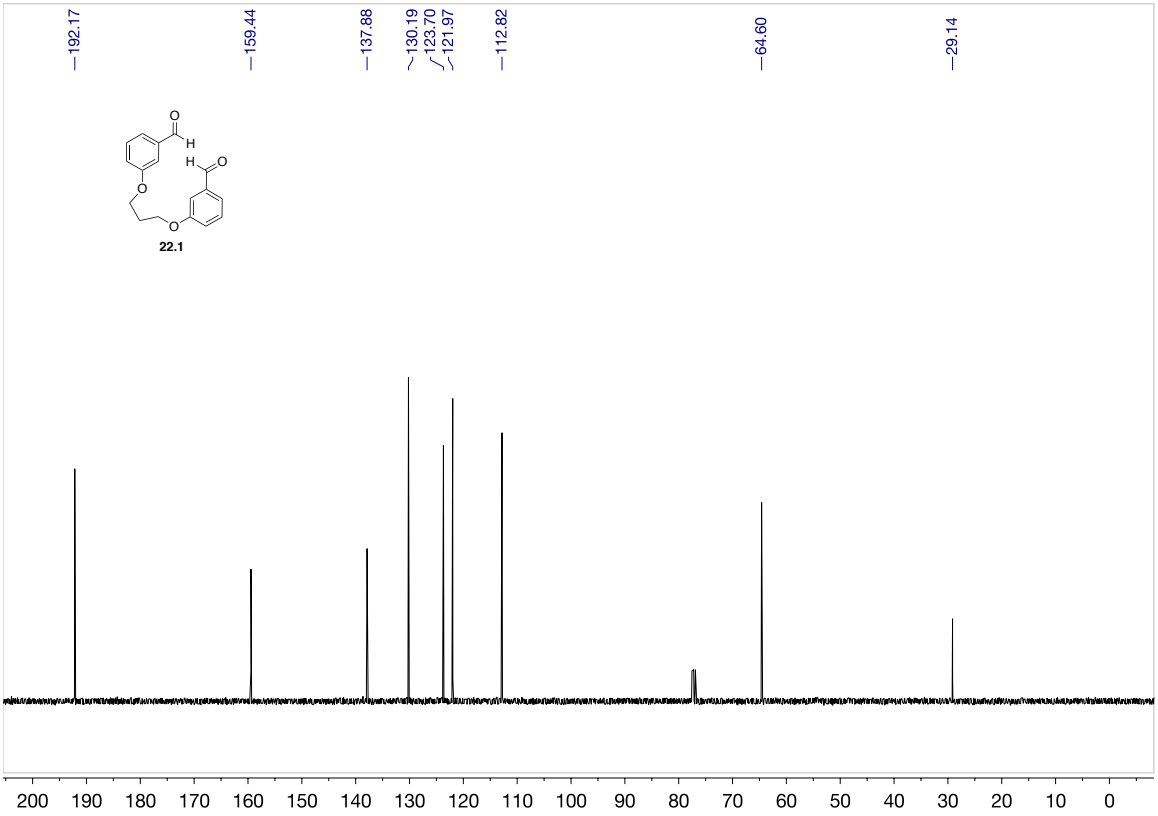
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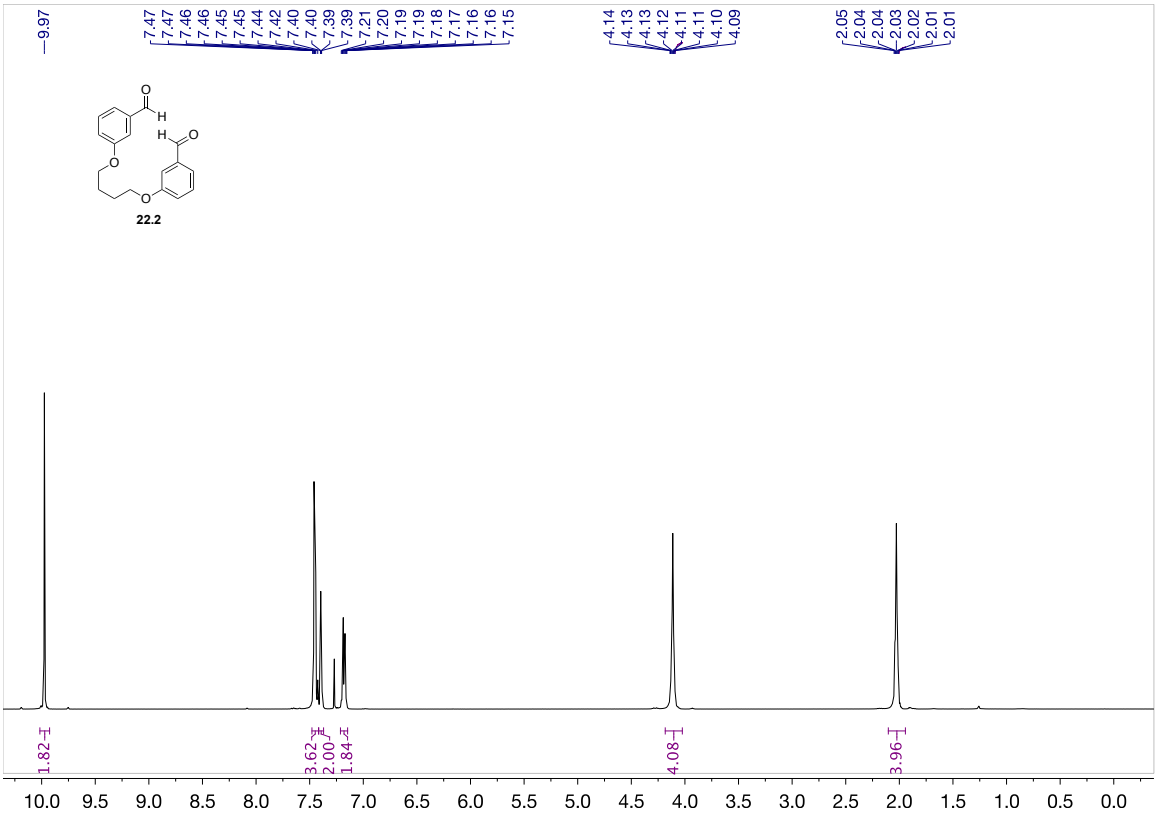
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4.12
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2.04
2.04
2.03
2.02
2.01
2.01
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3.62
2.00
1.84
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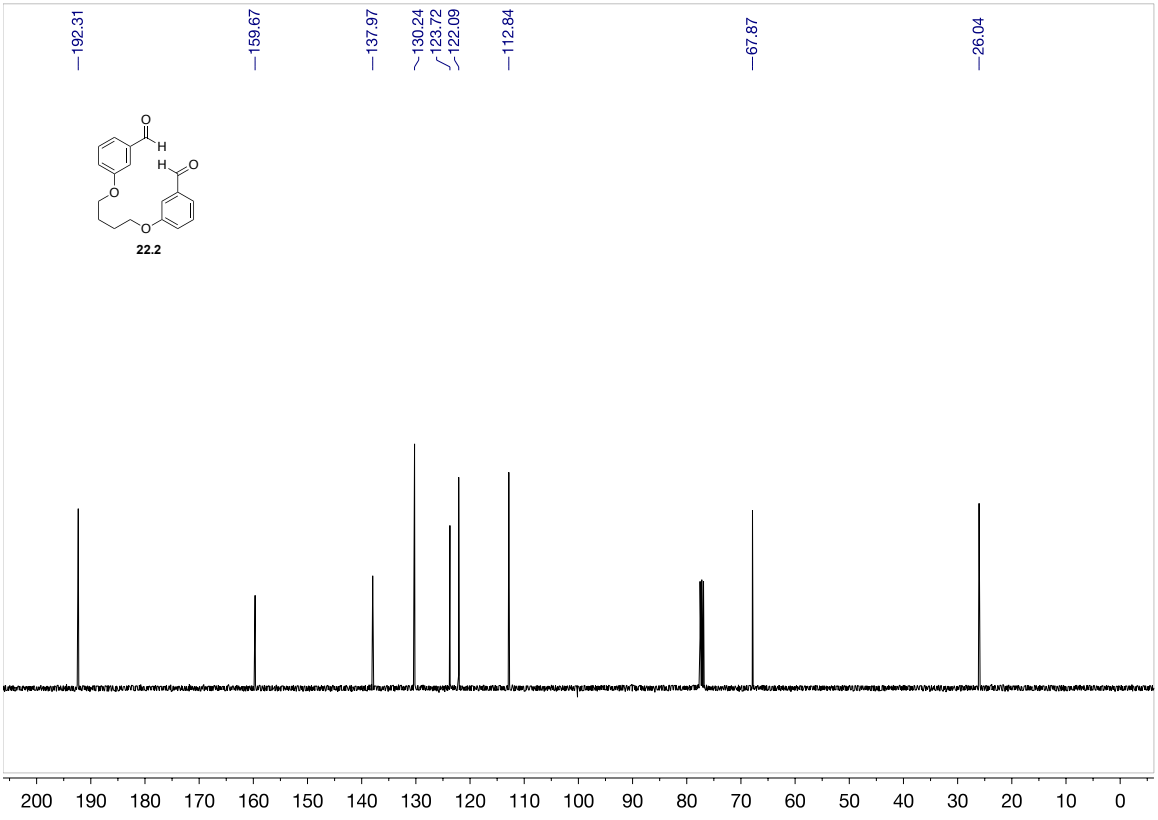
3.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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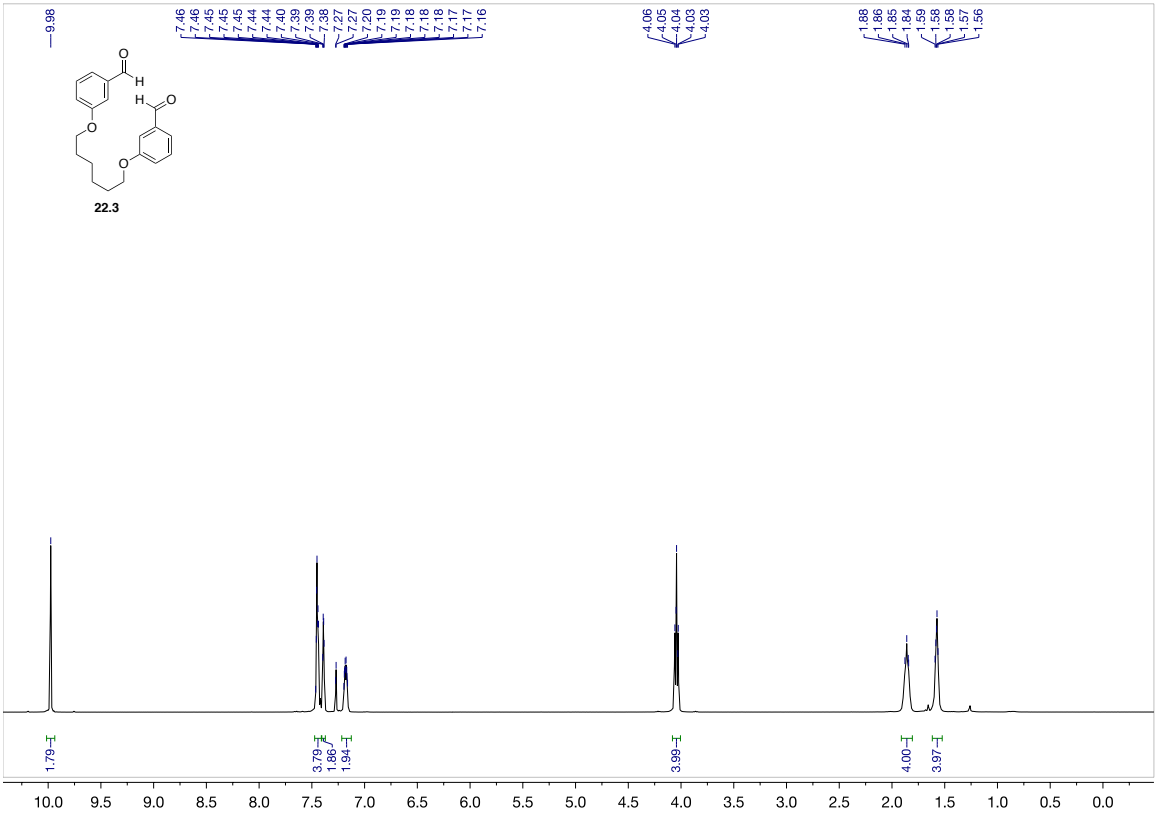
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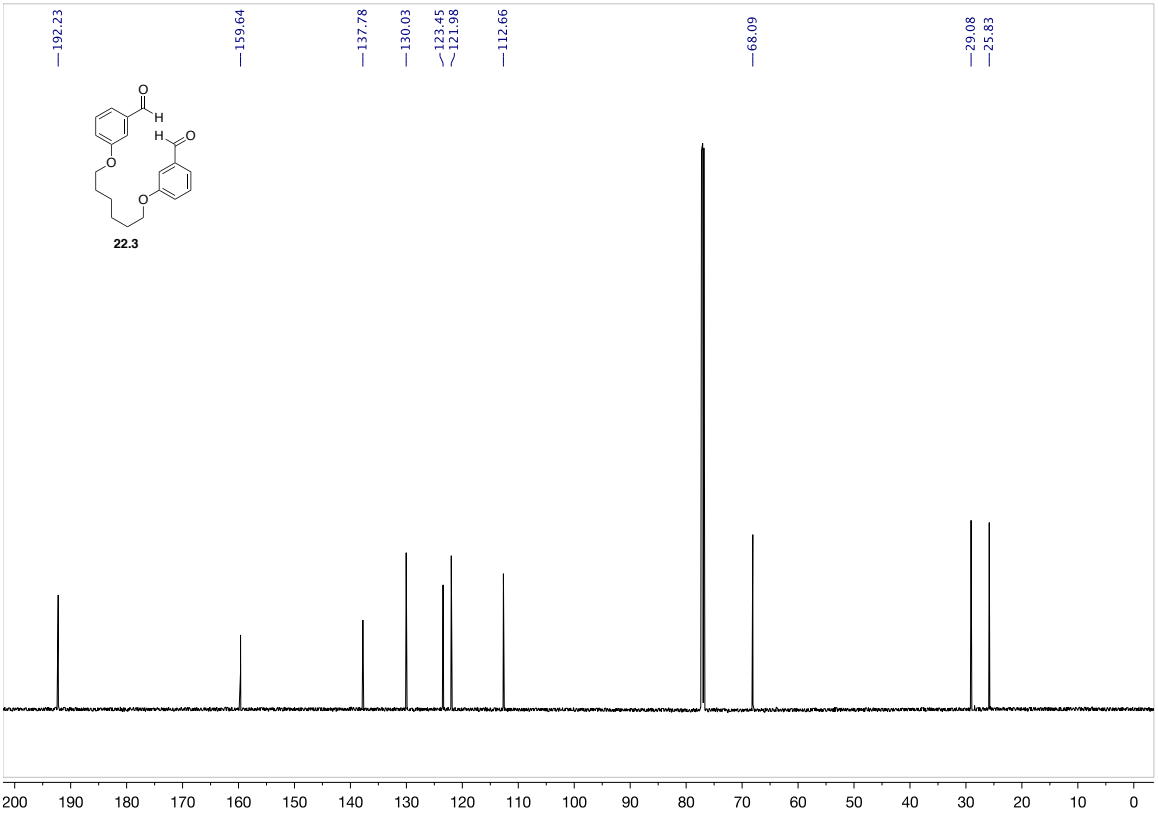
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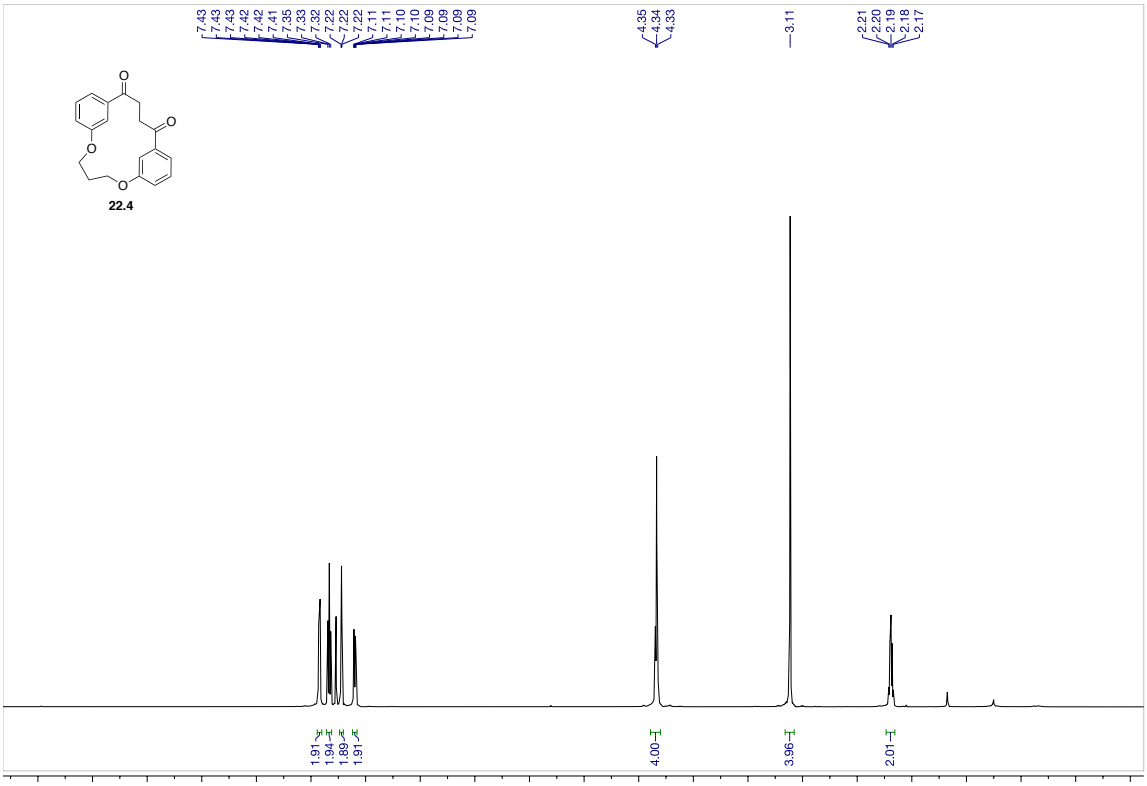
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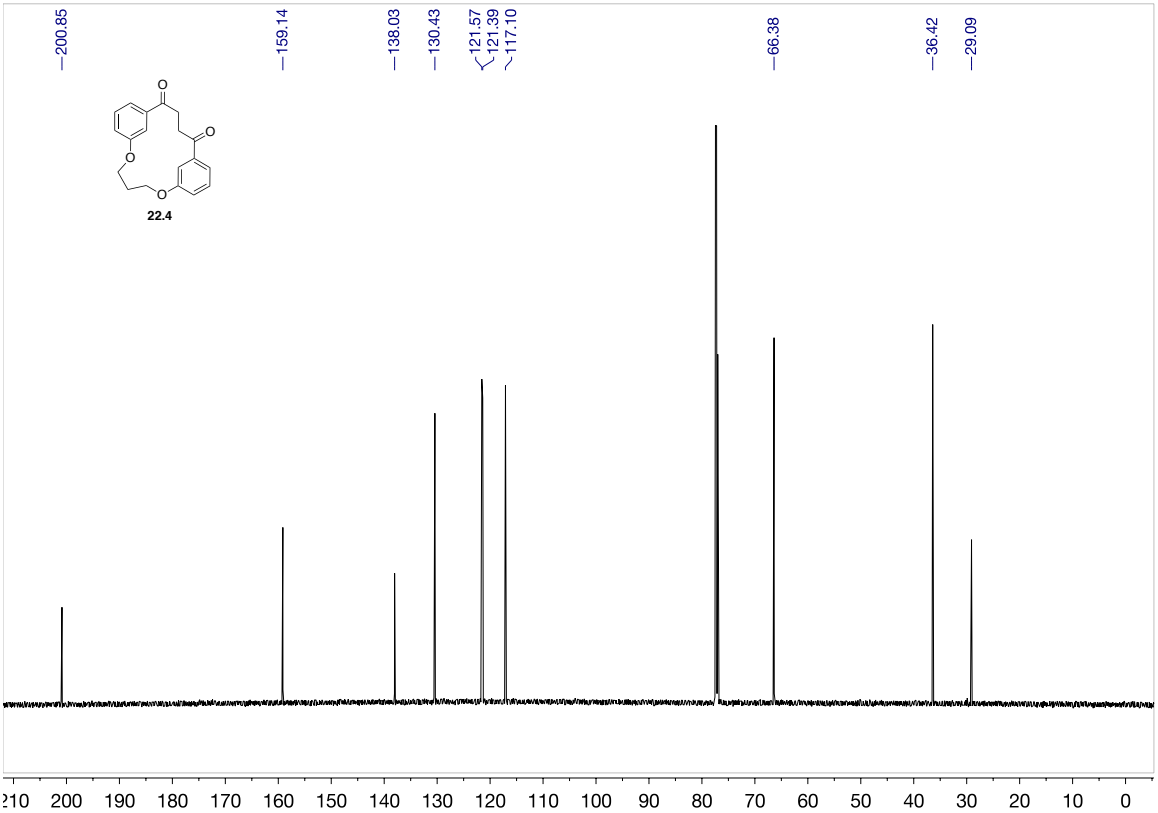
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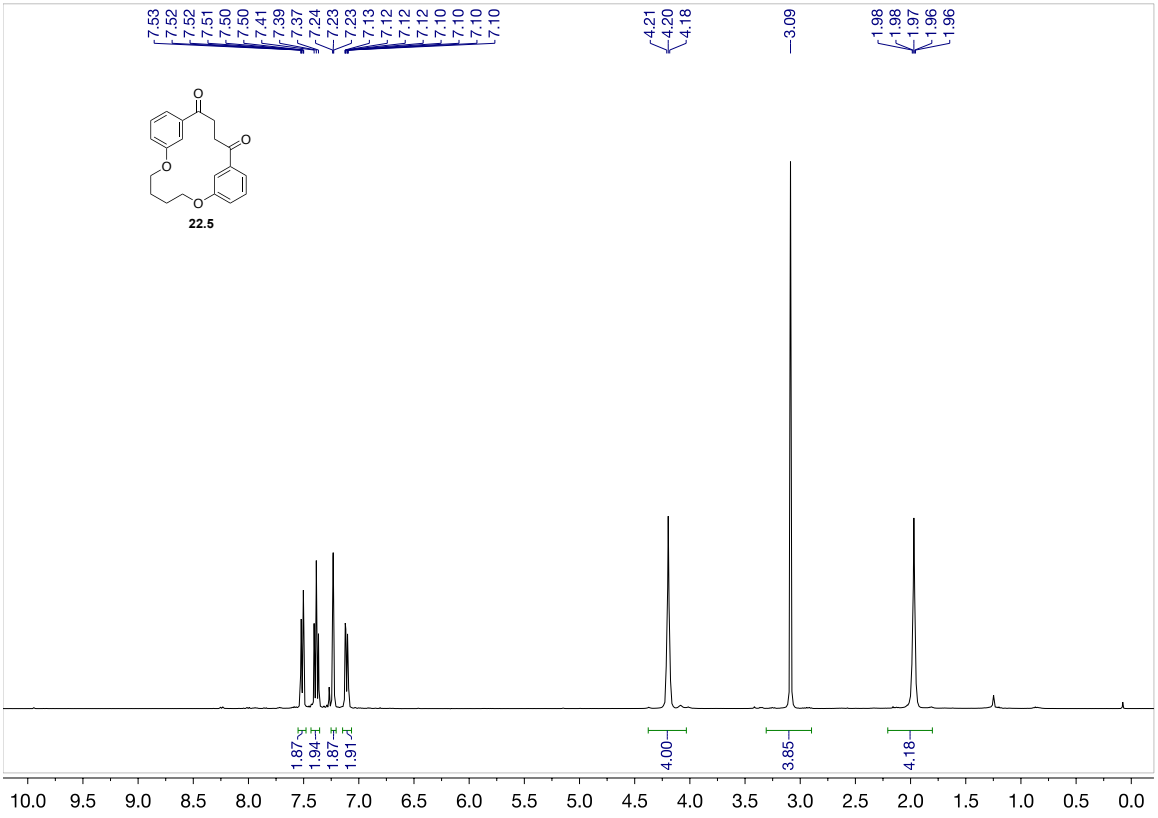
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4.18
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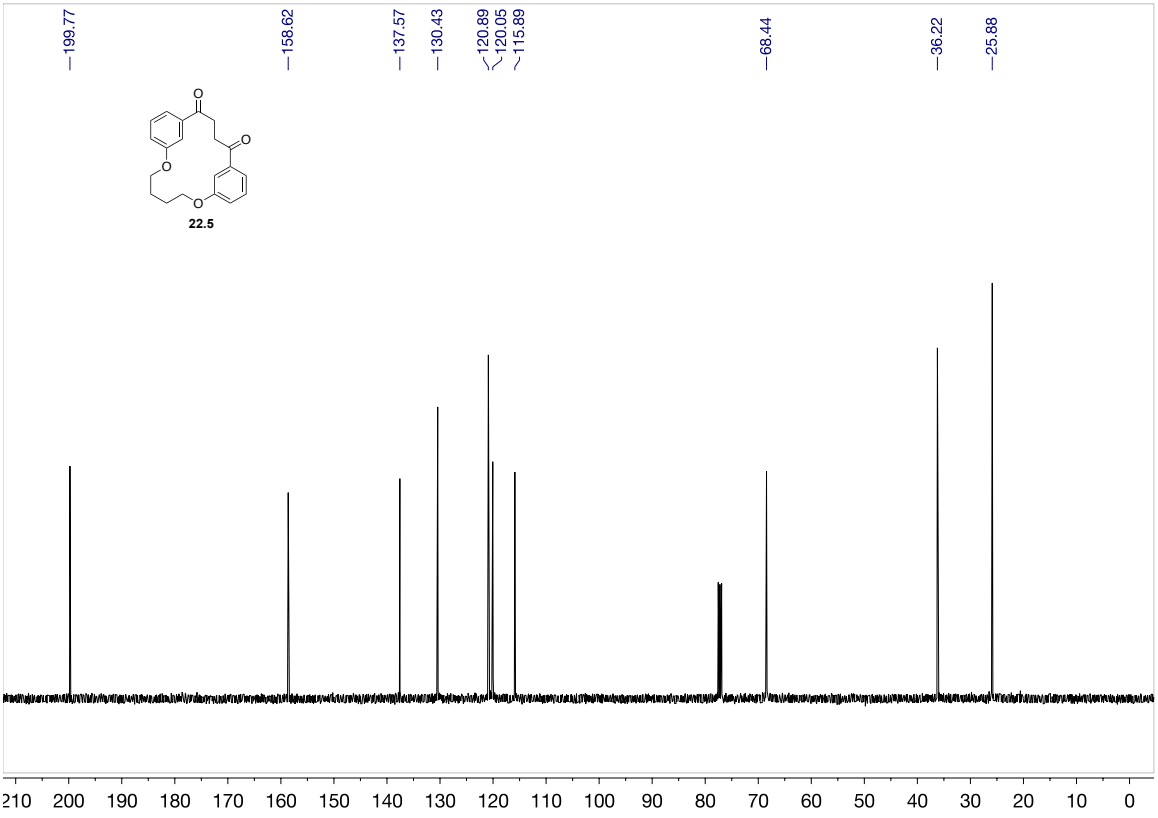
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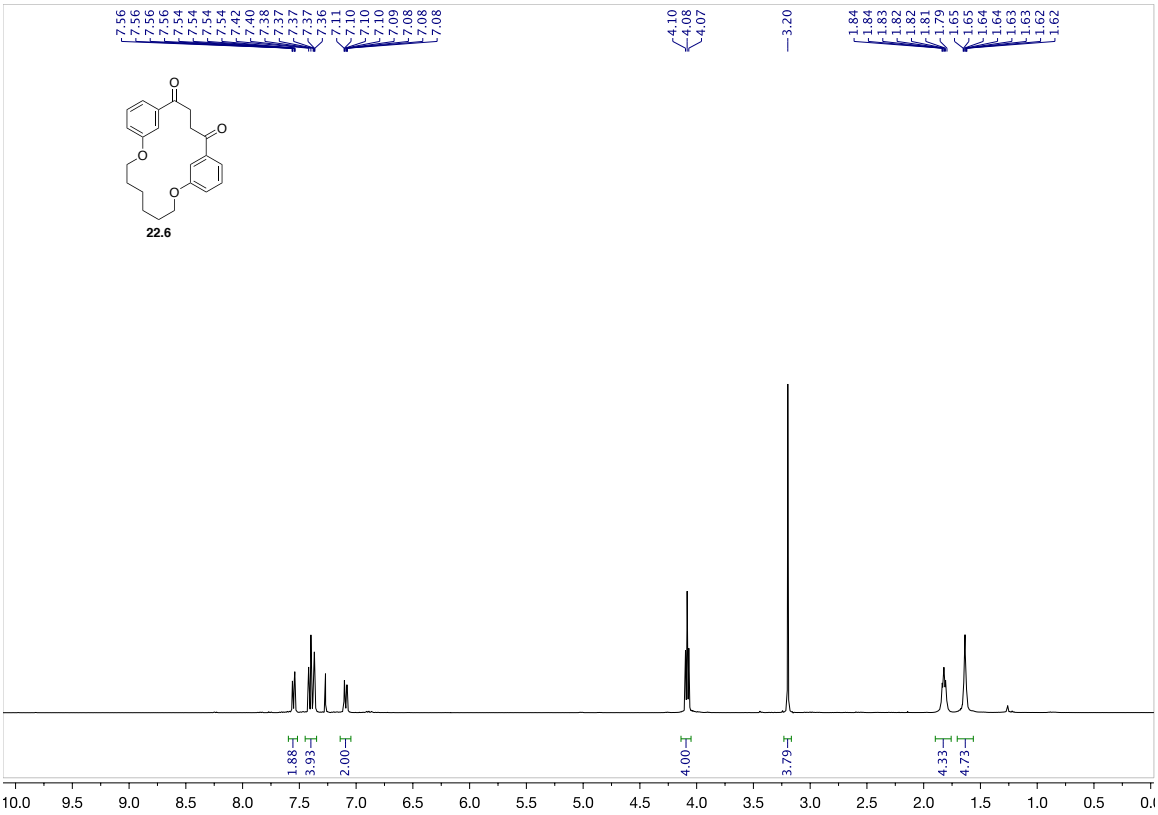
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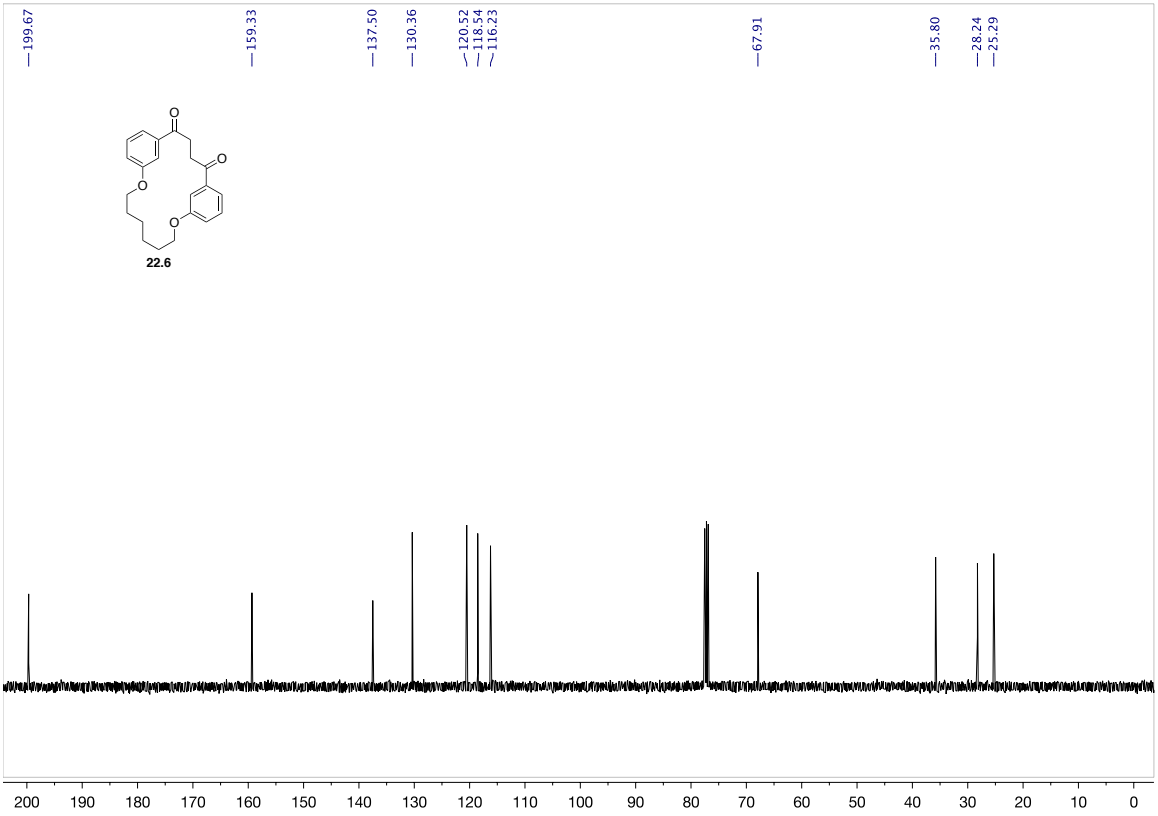
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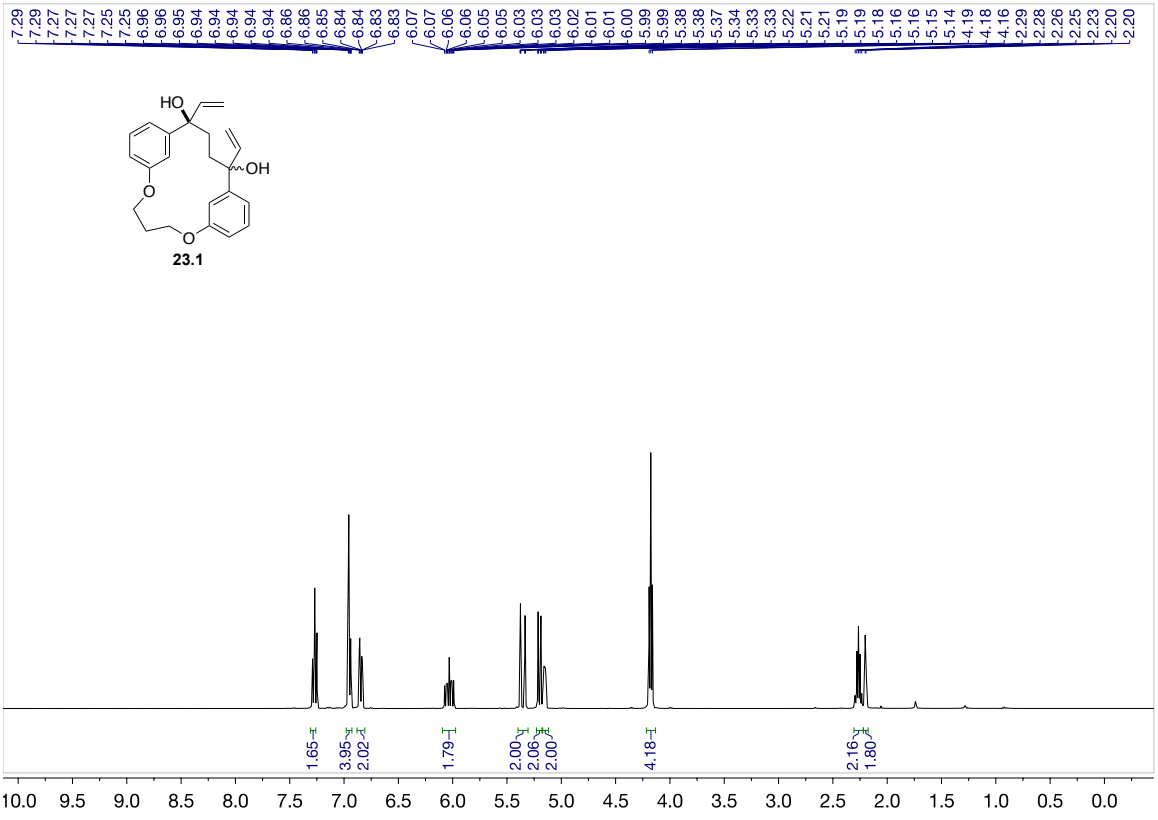
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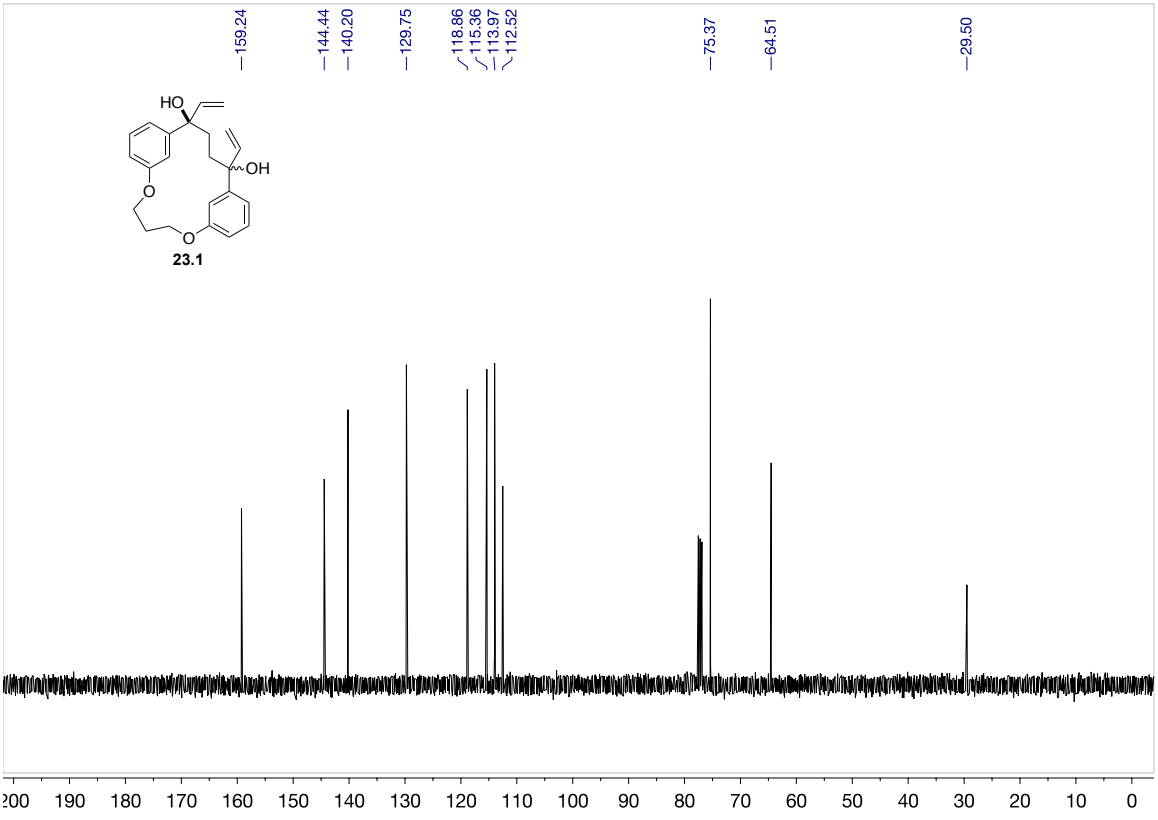
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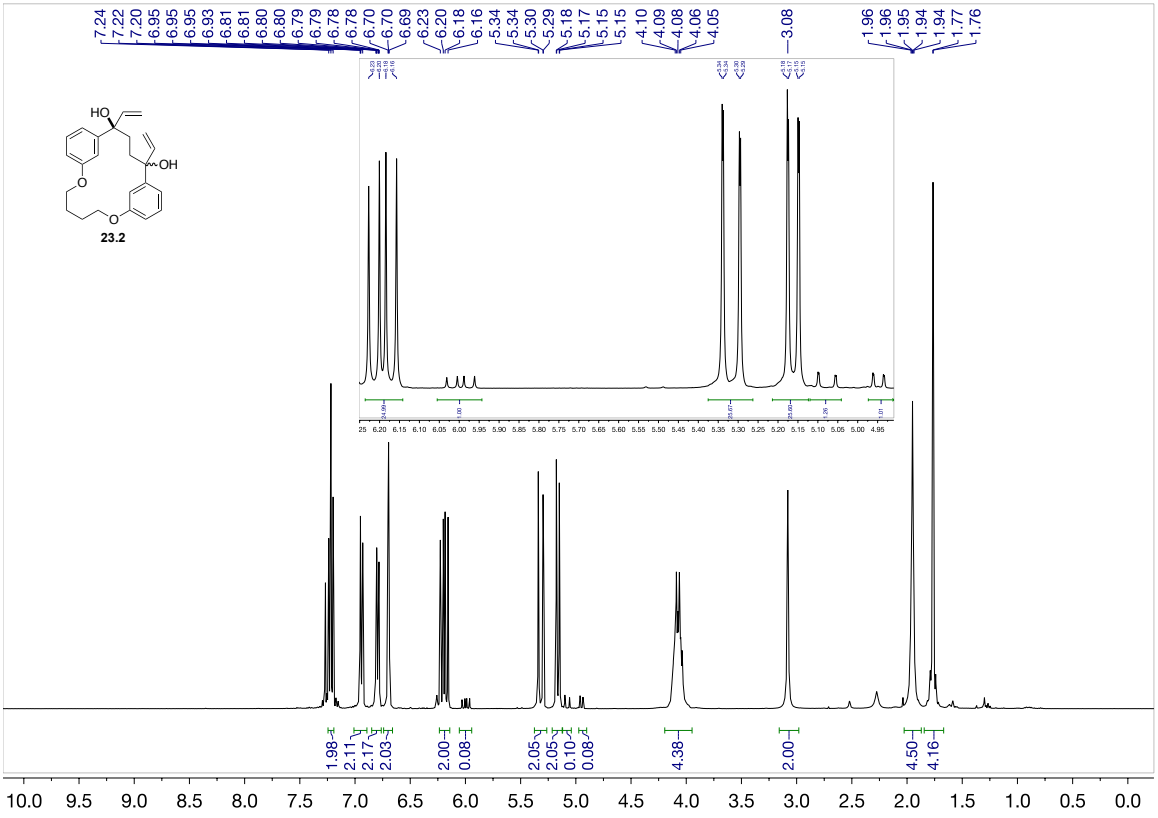
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1.76
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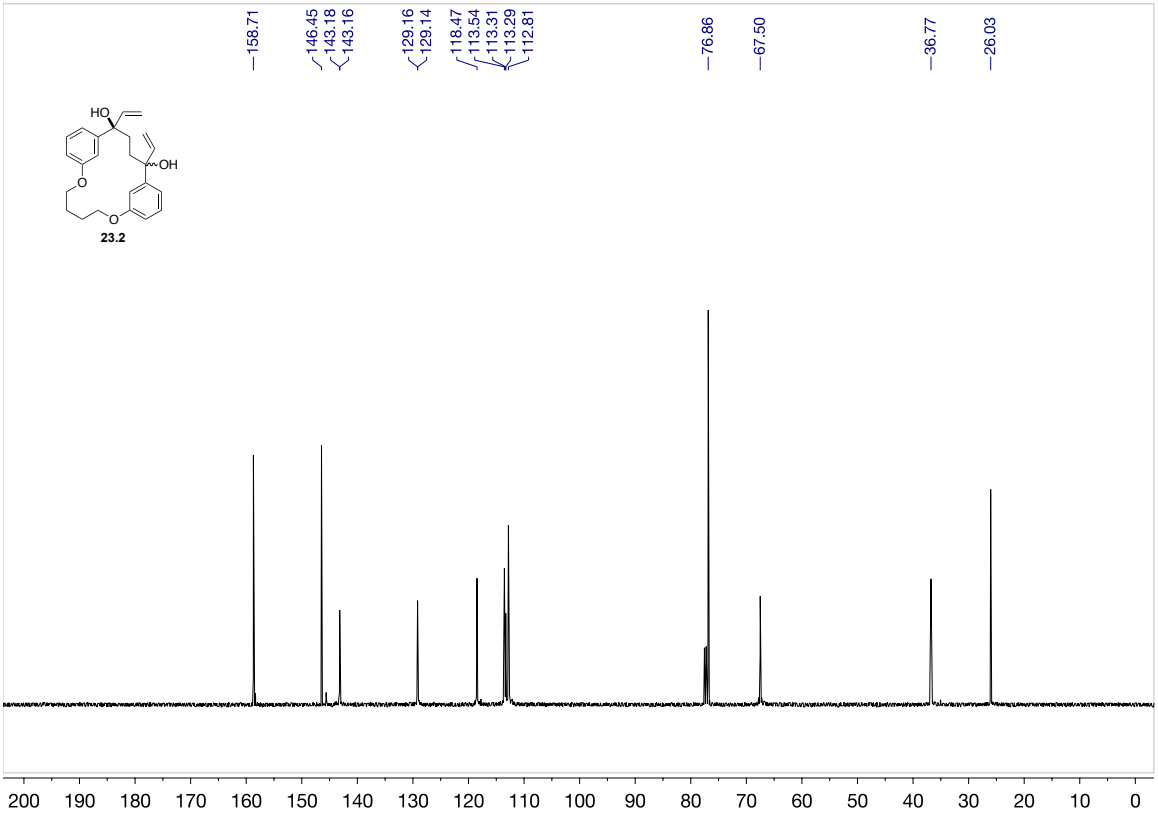
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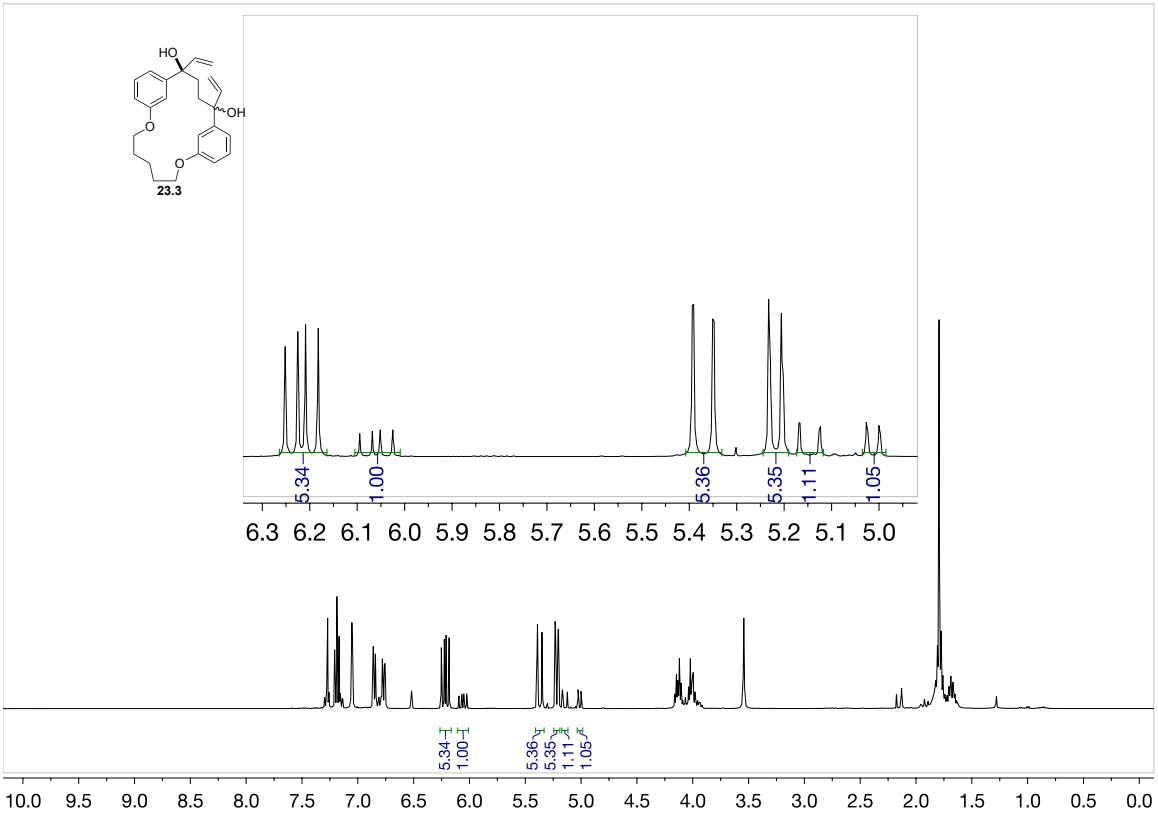
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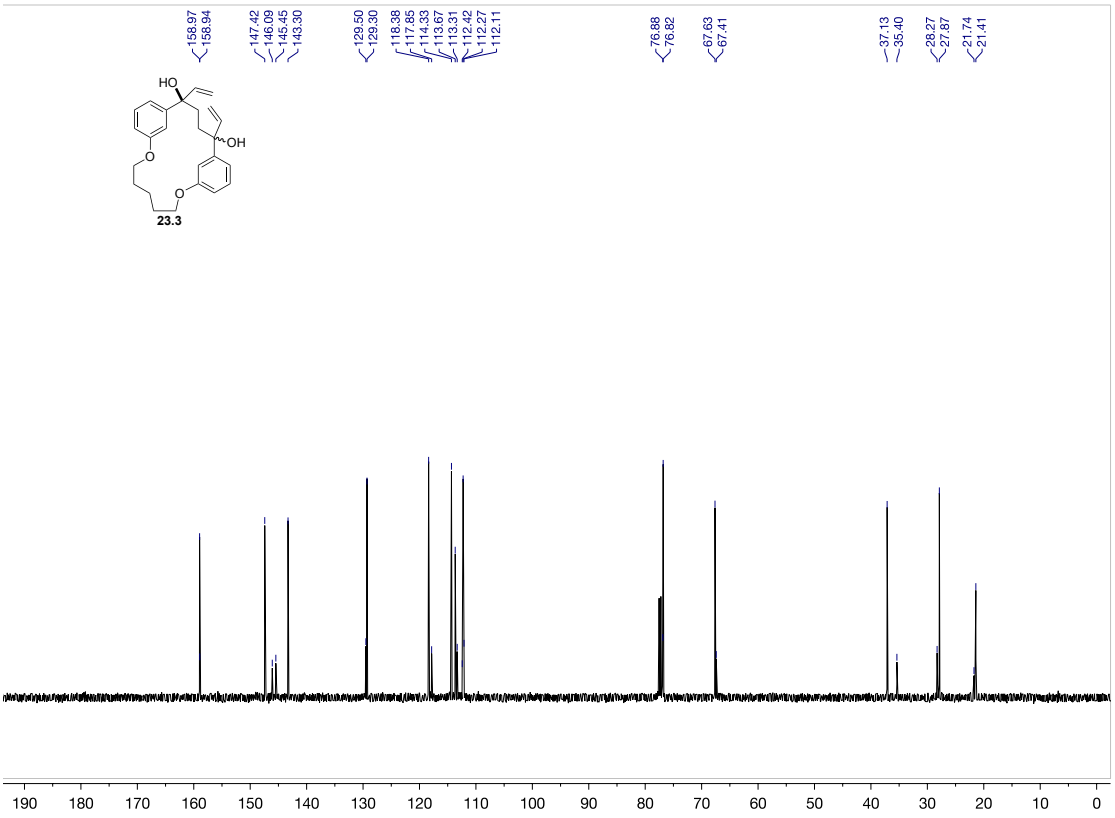
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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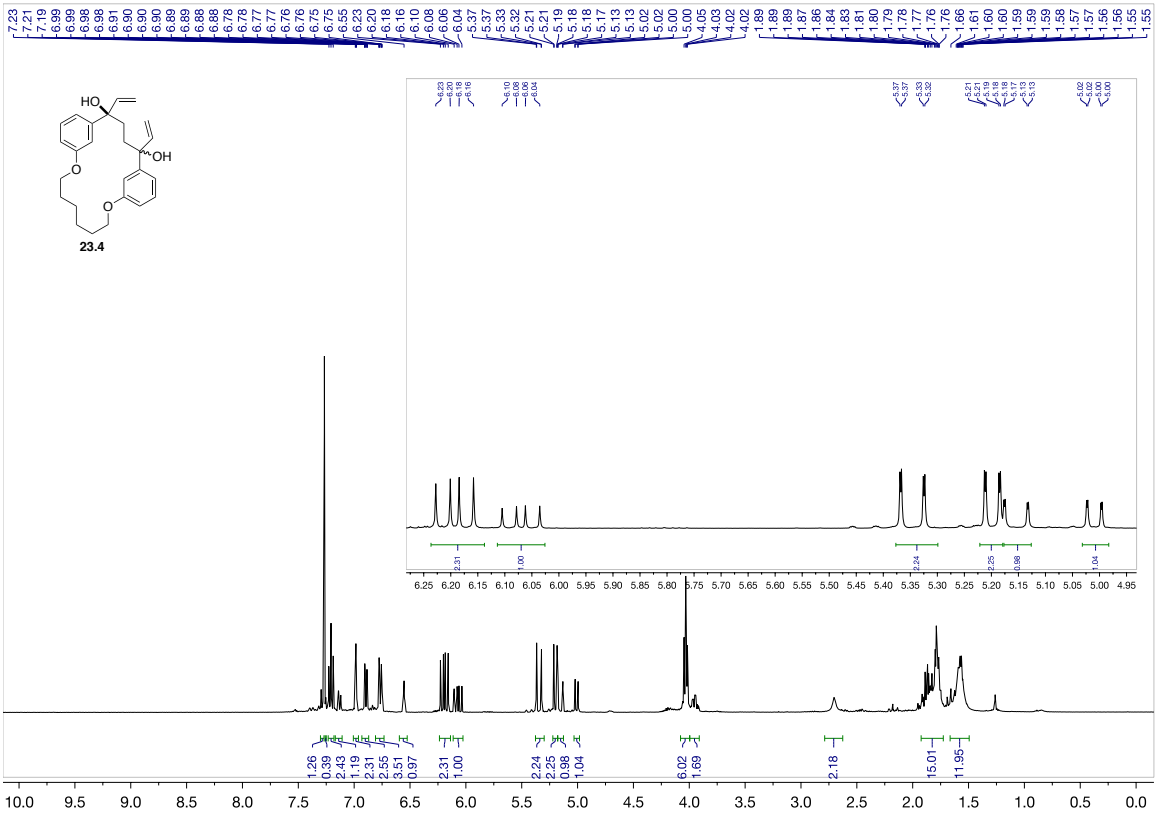
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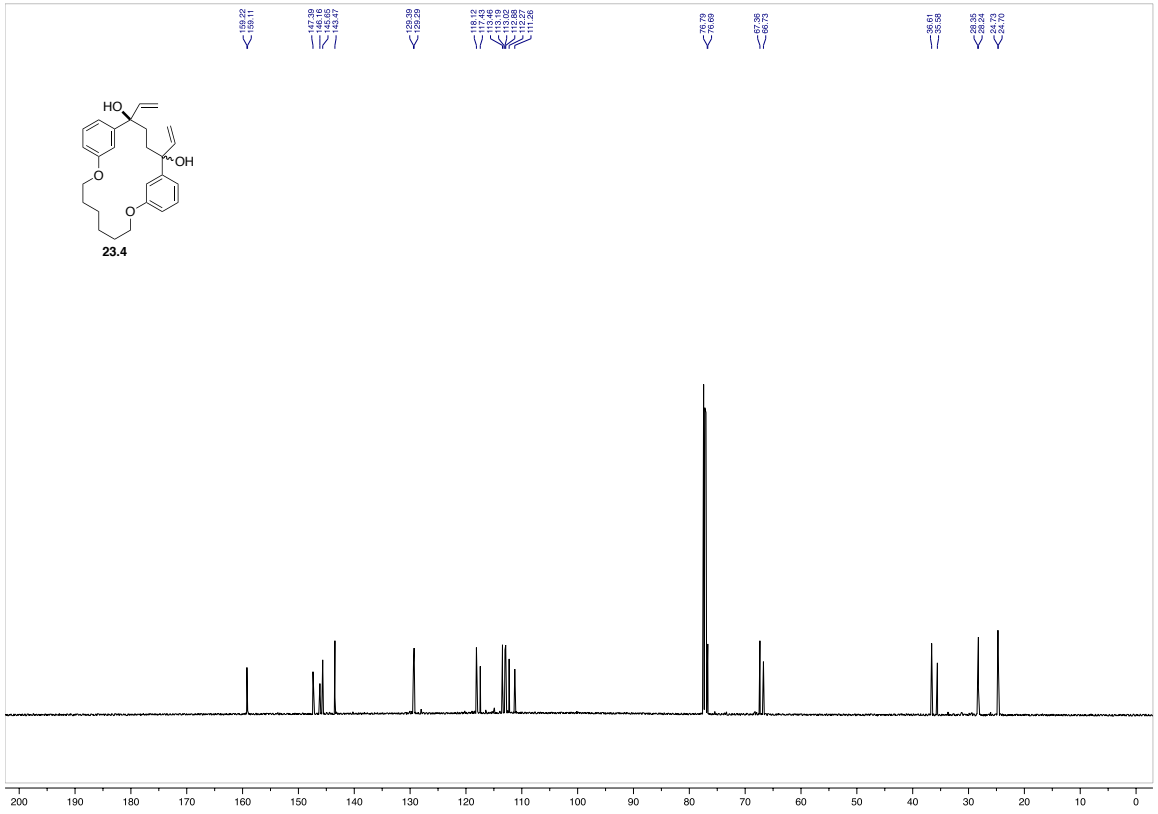
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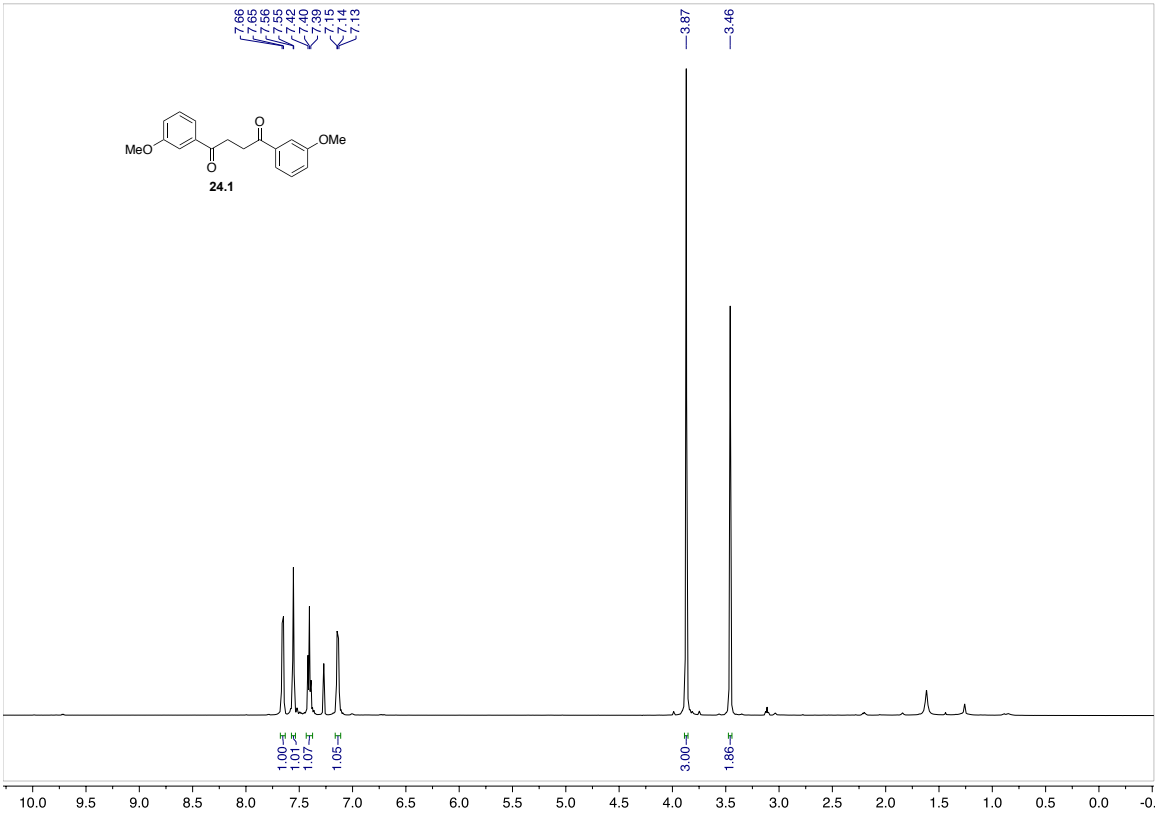
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OMe
O
O
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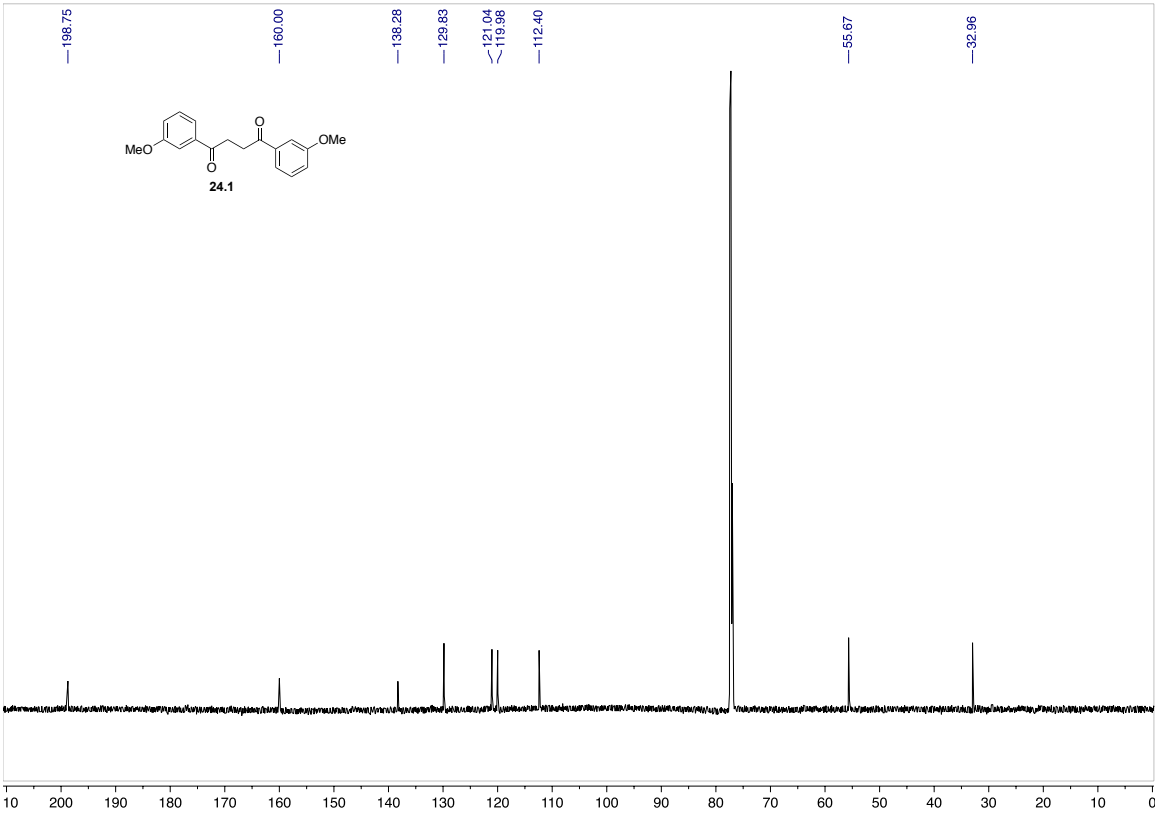
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OMe
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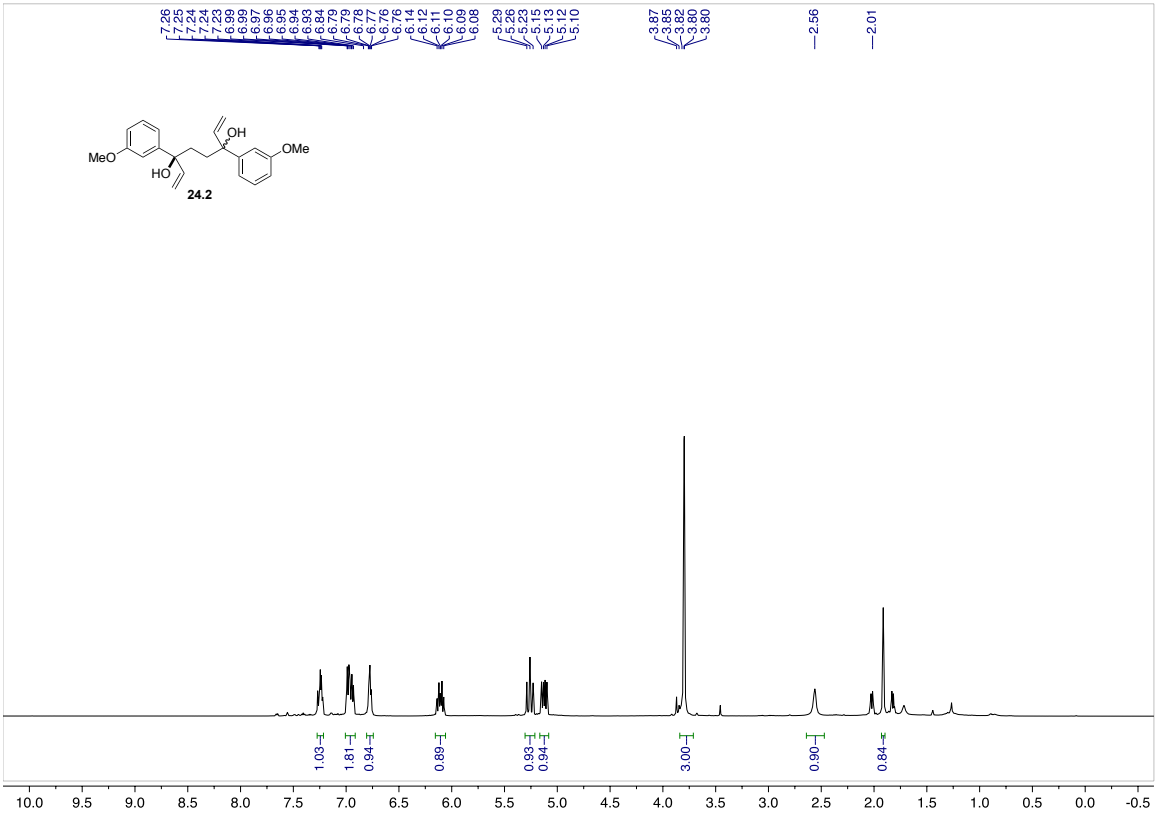
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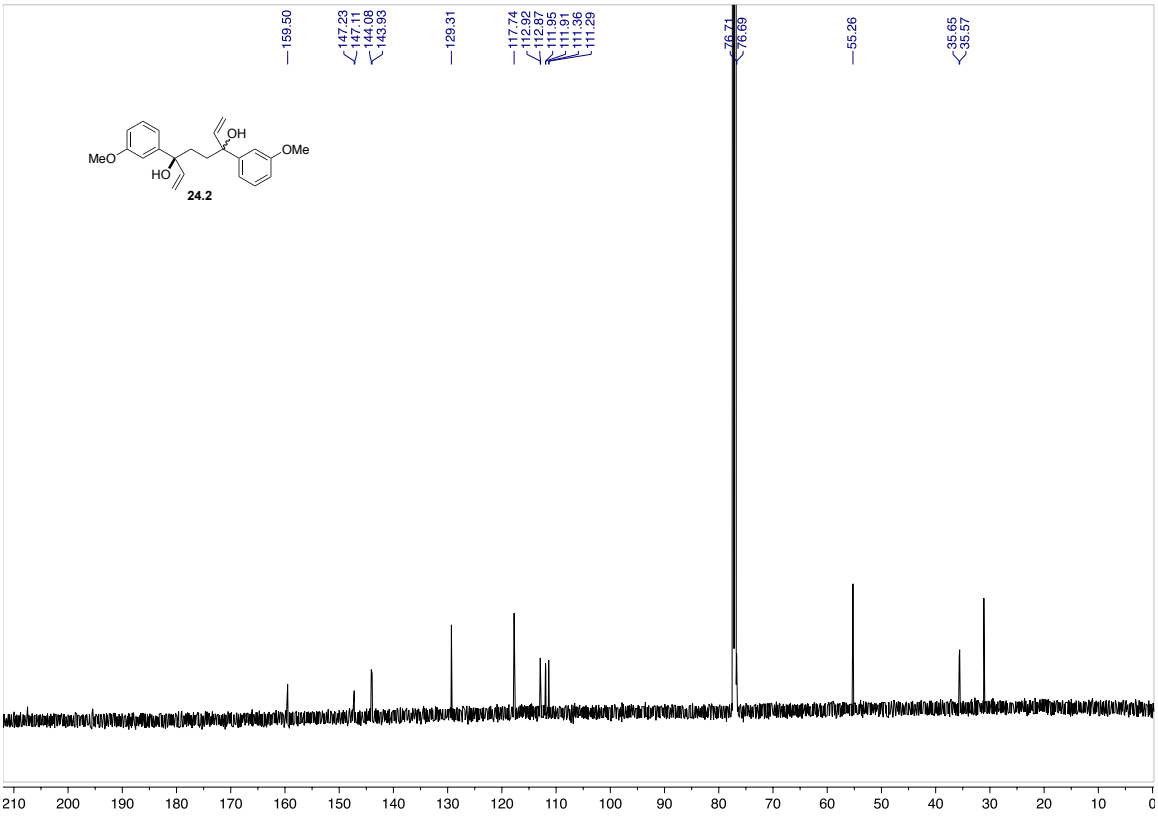
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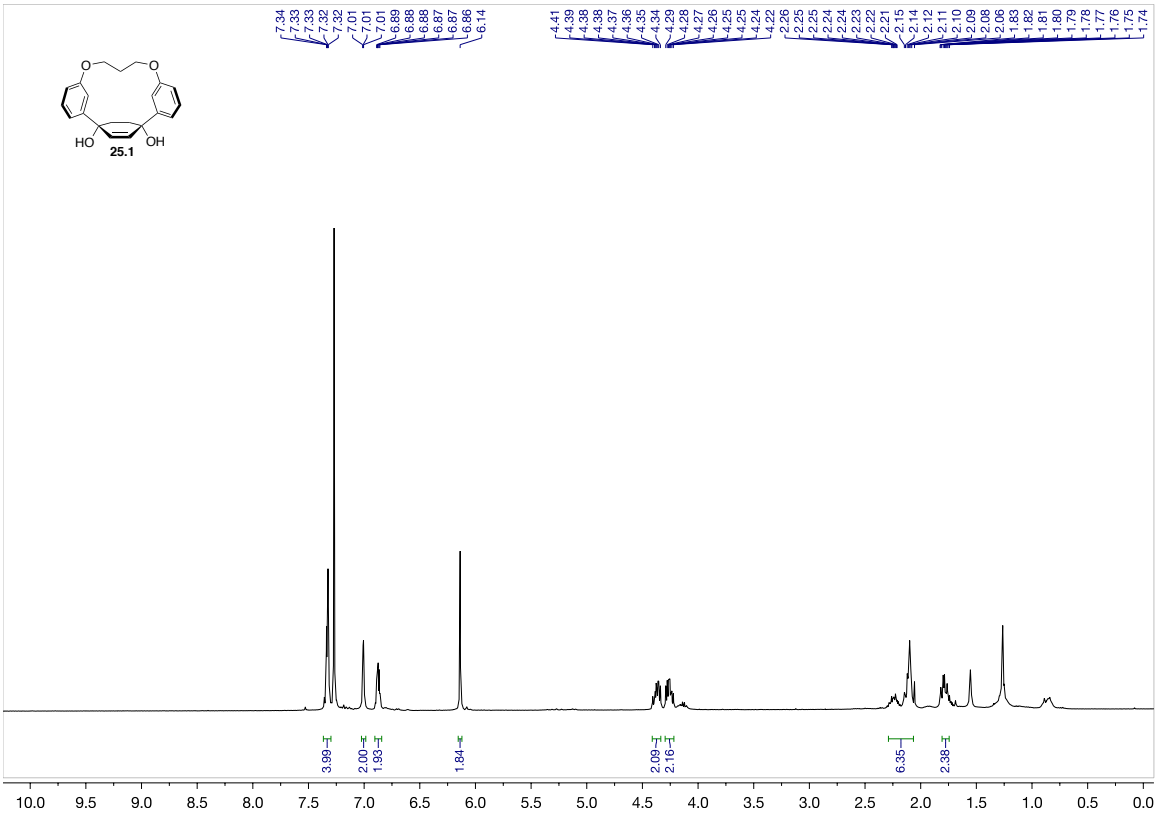
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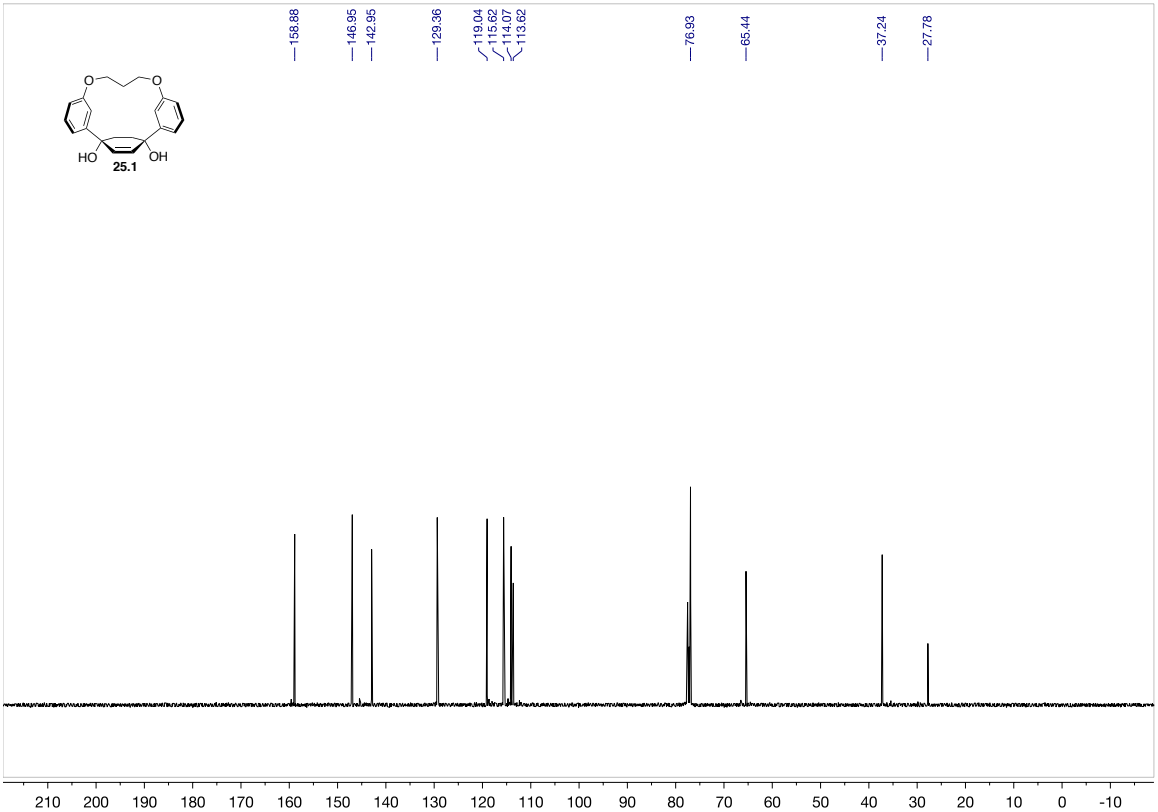
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OH
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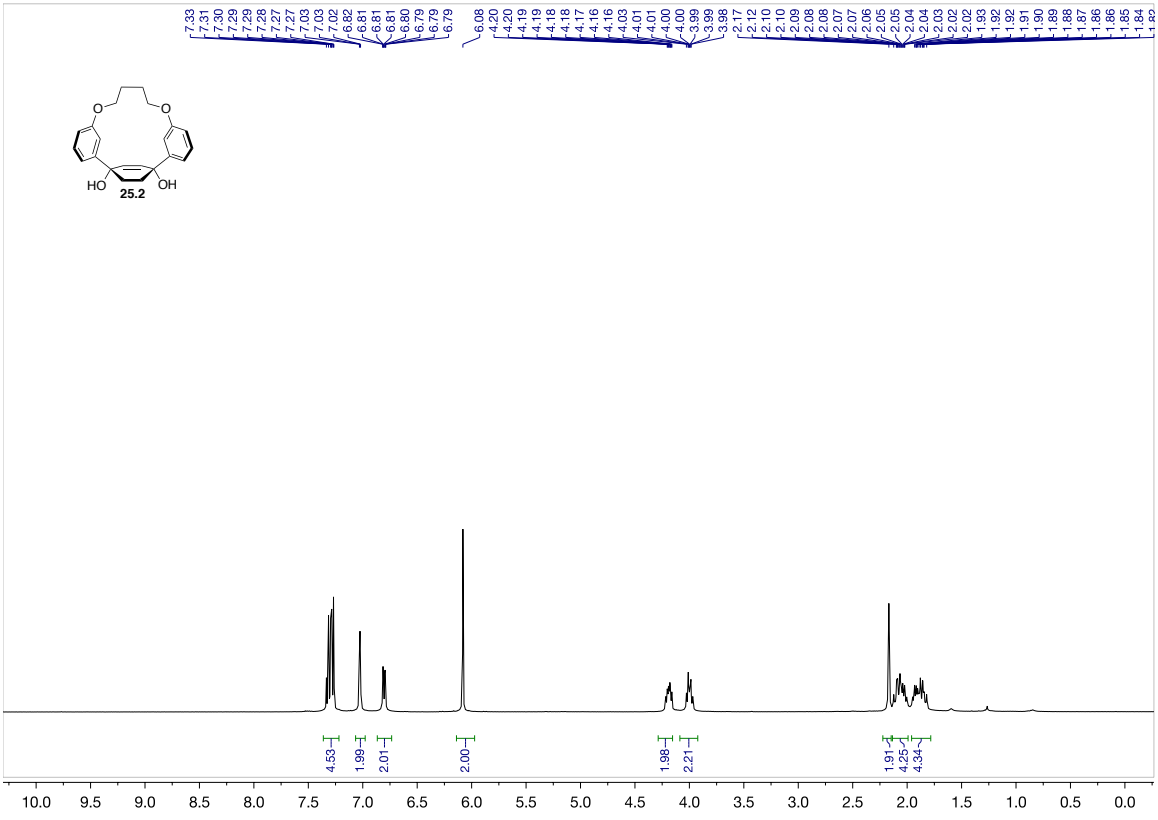
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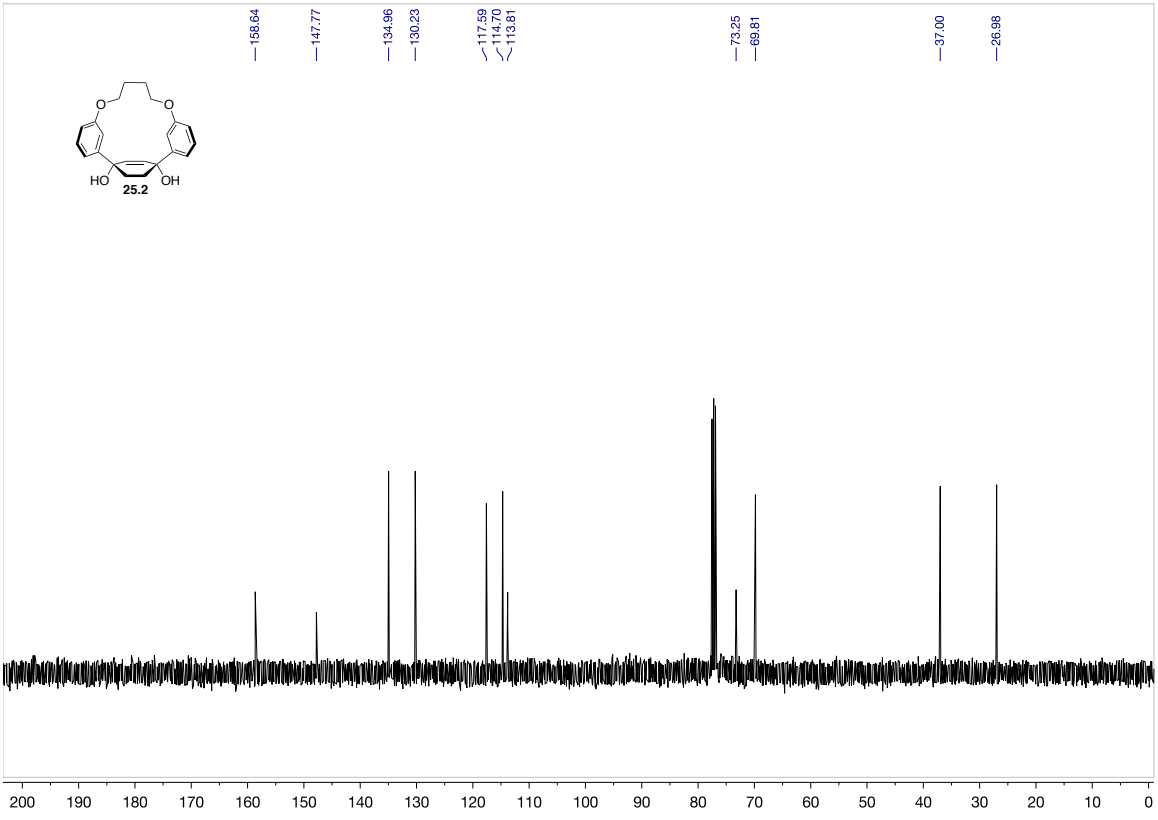
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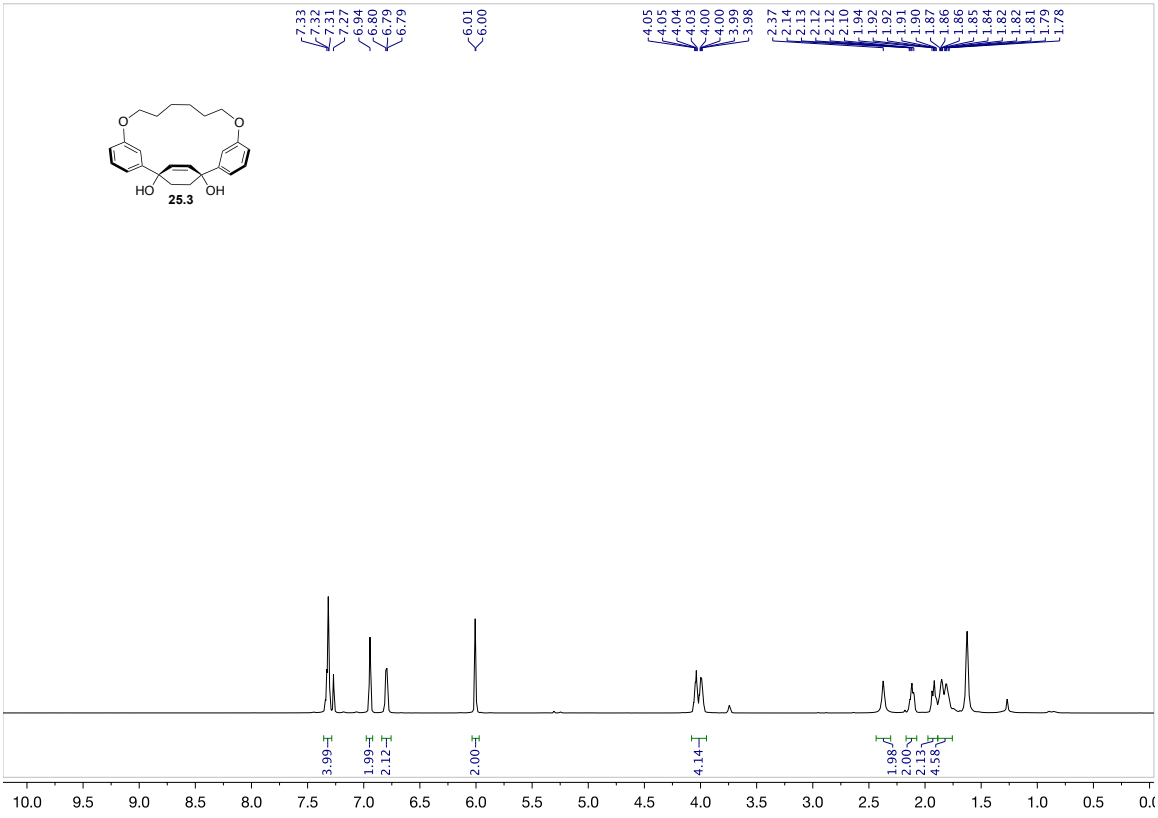
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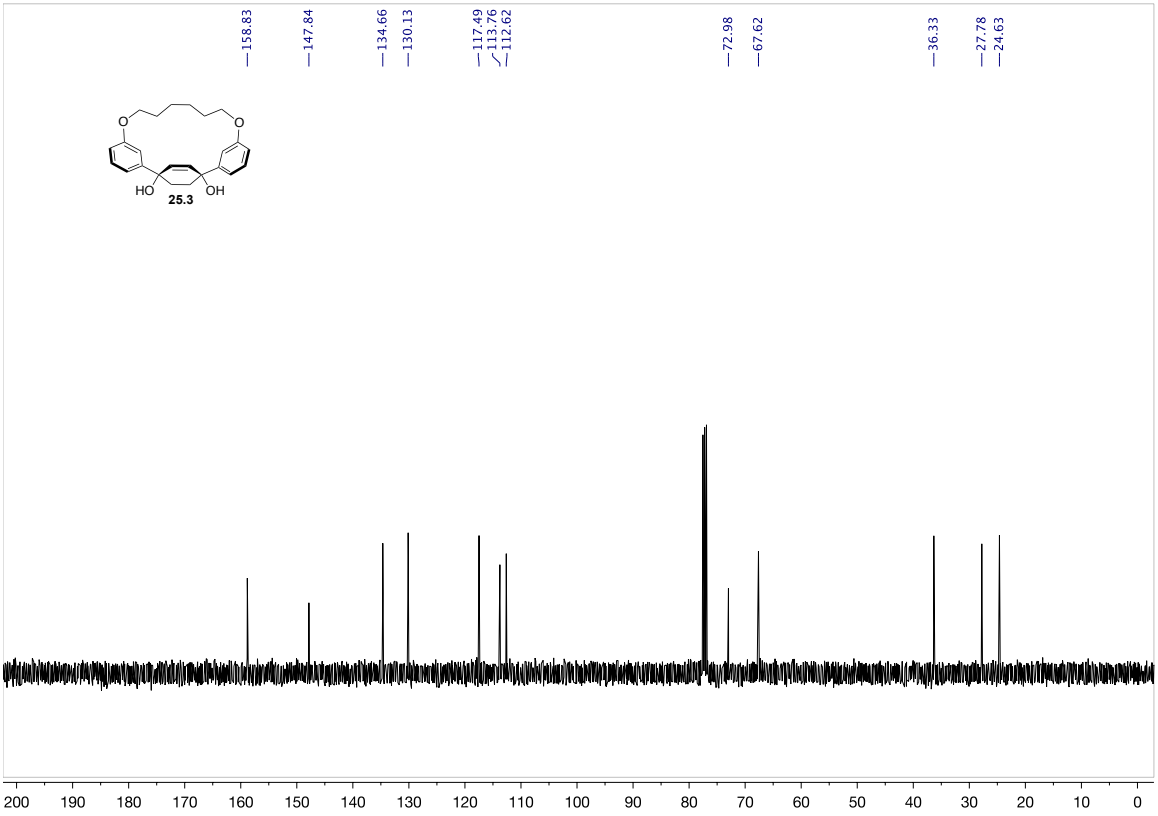
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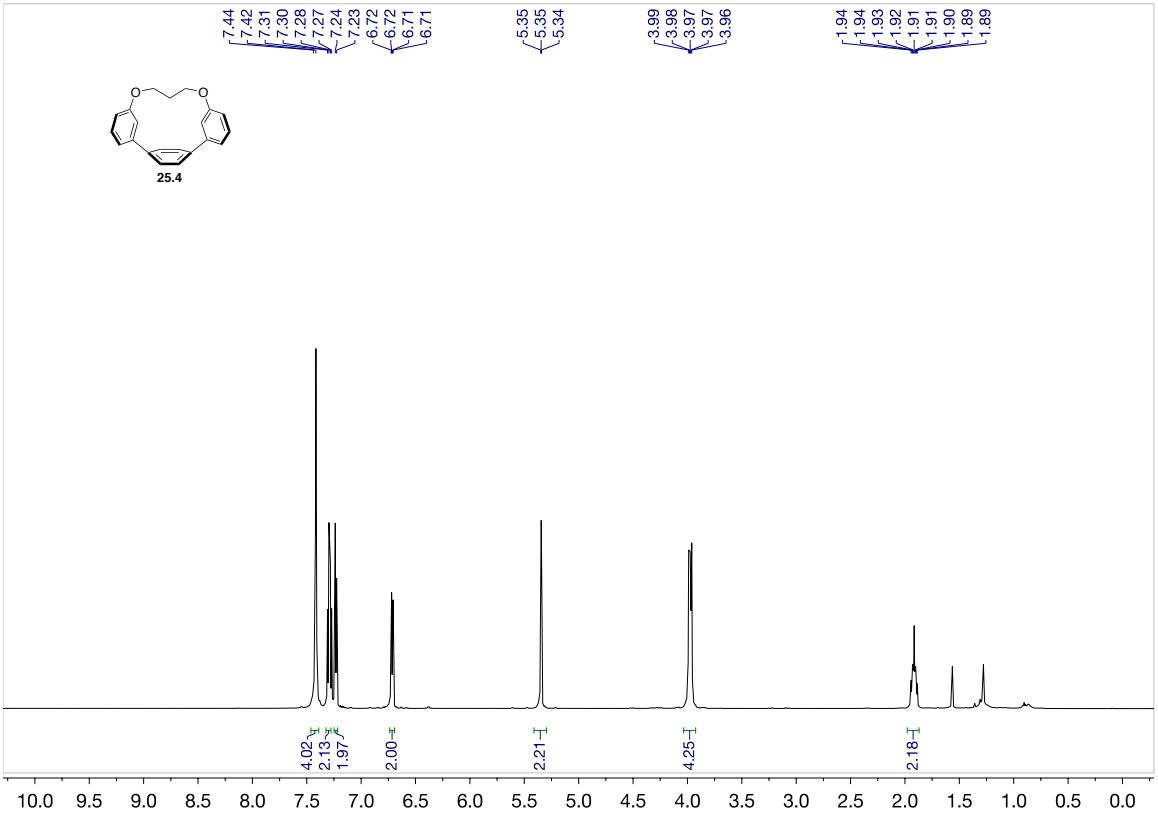
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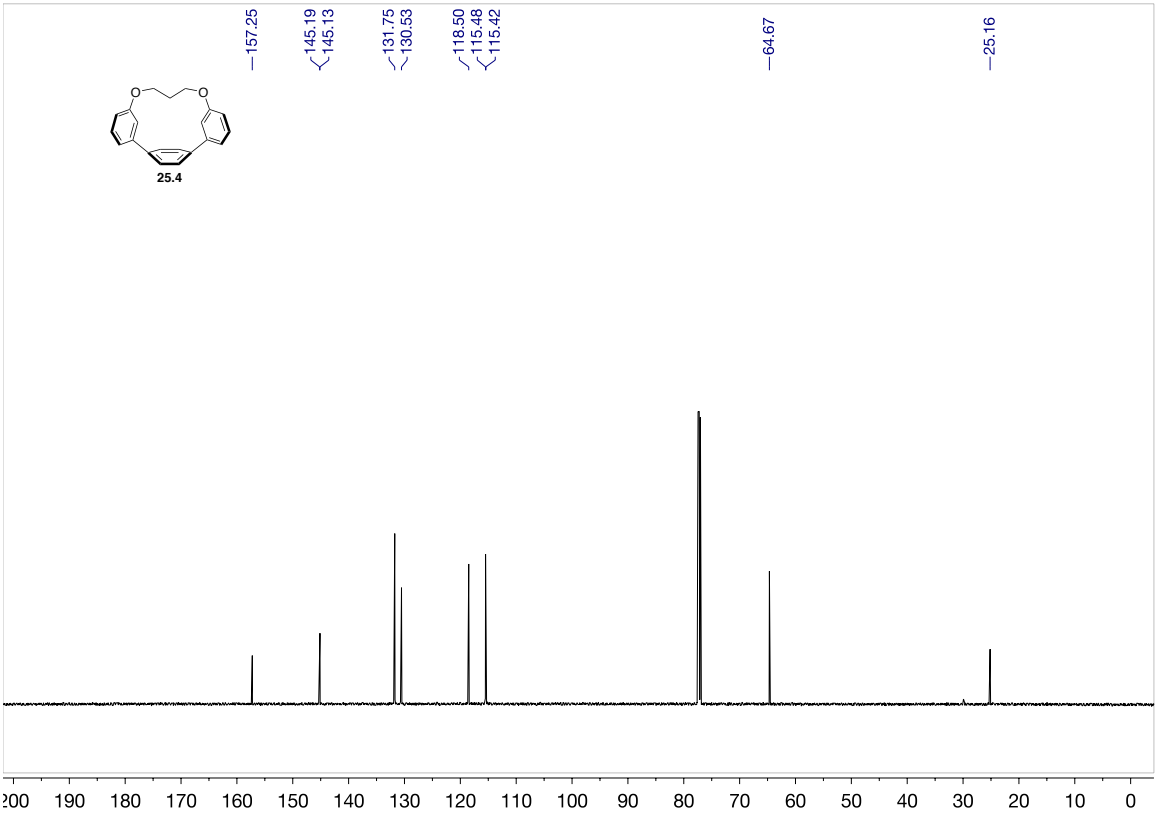
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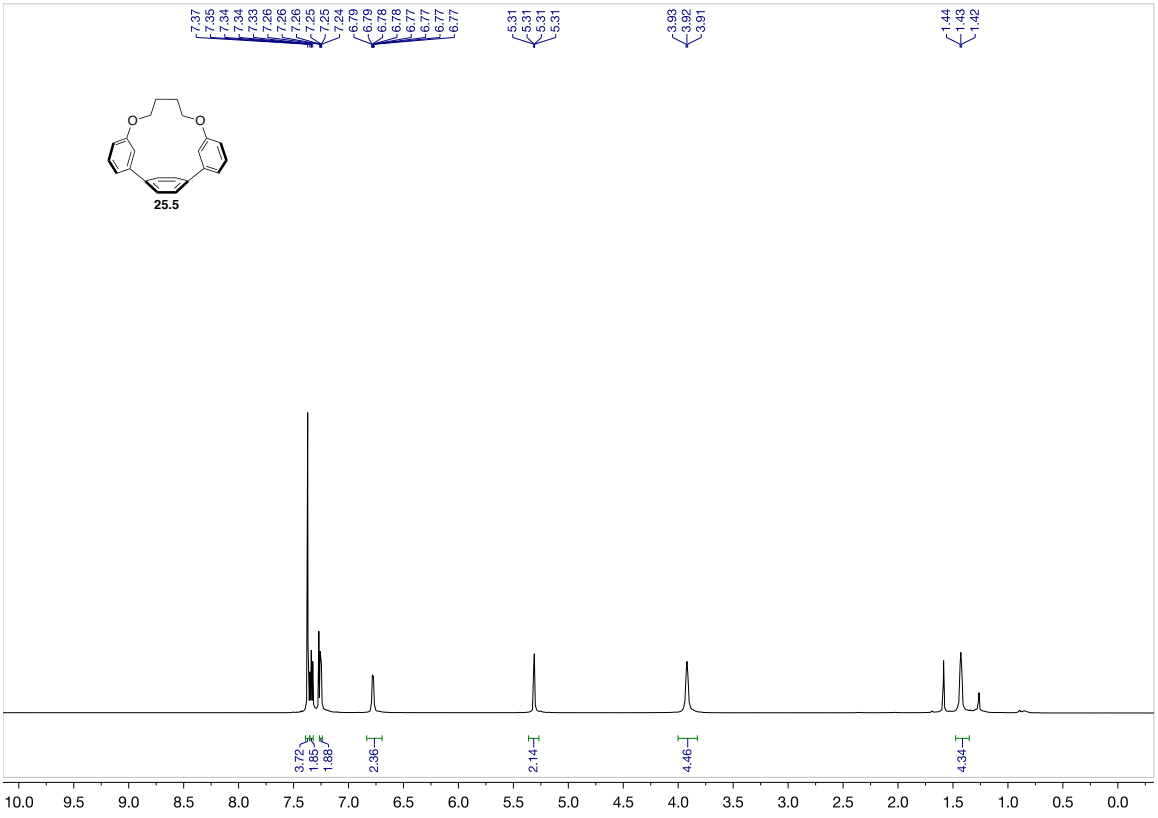
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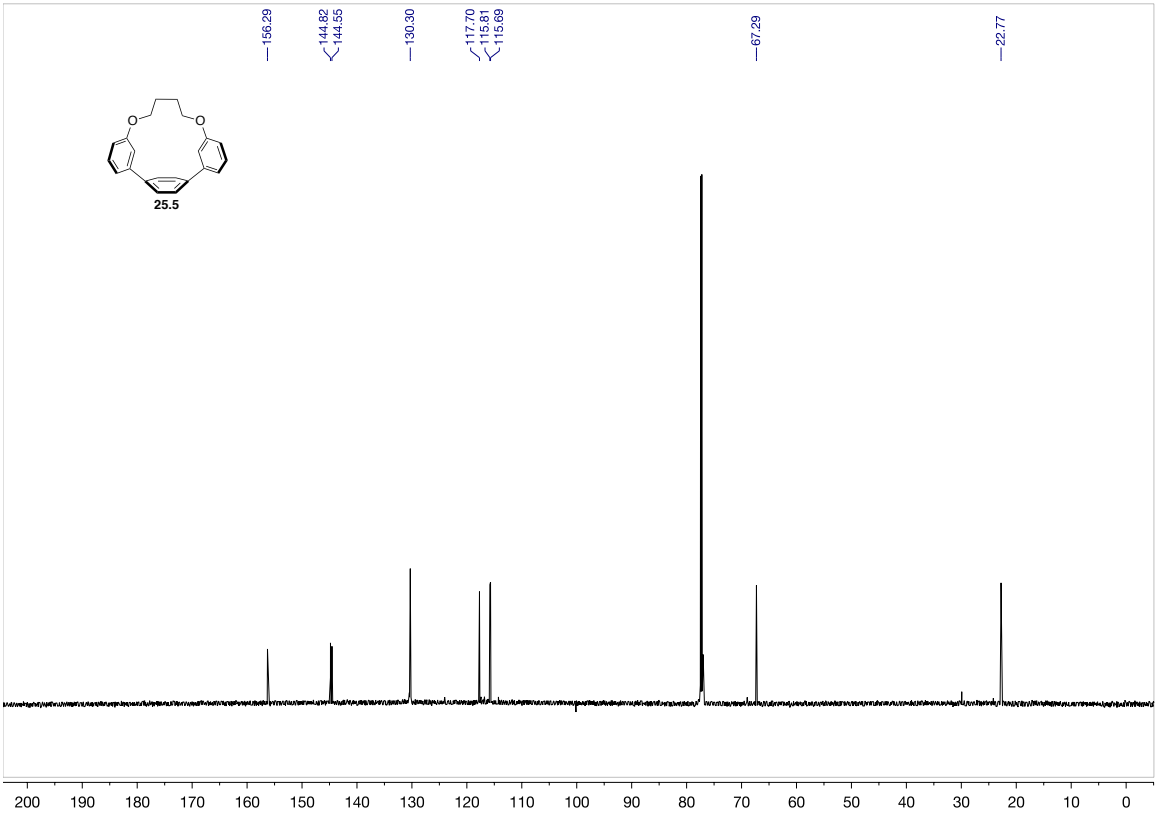
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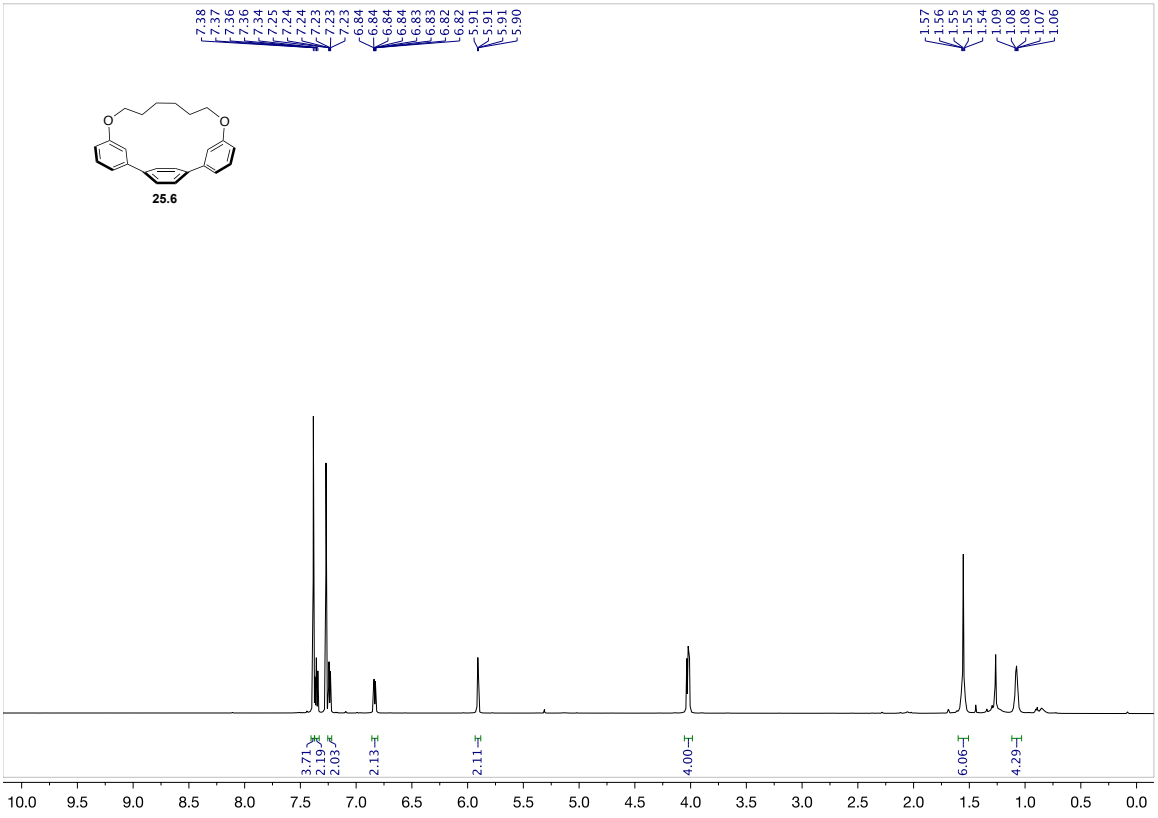
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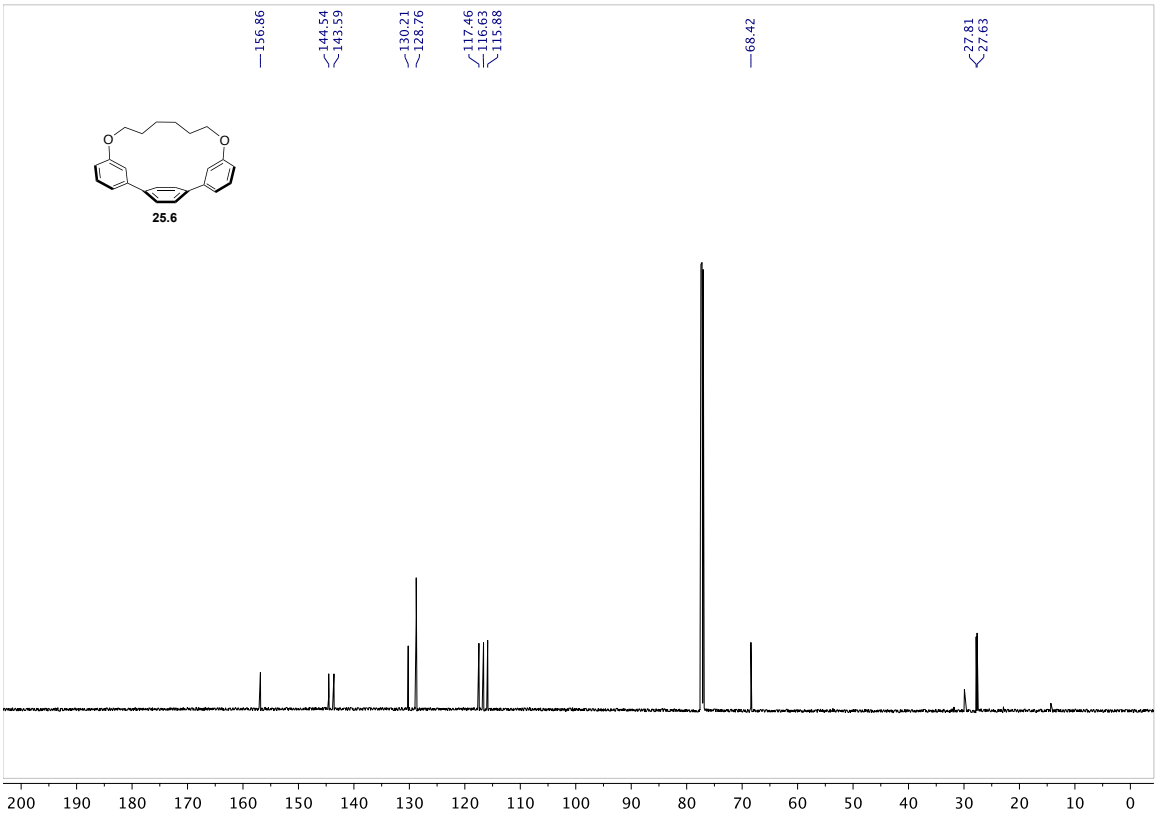
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143.59
130.21
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117.46
116.63
115.88
68.42
27.81
27.63
O
O
25.6
200
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150
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110
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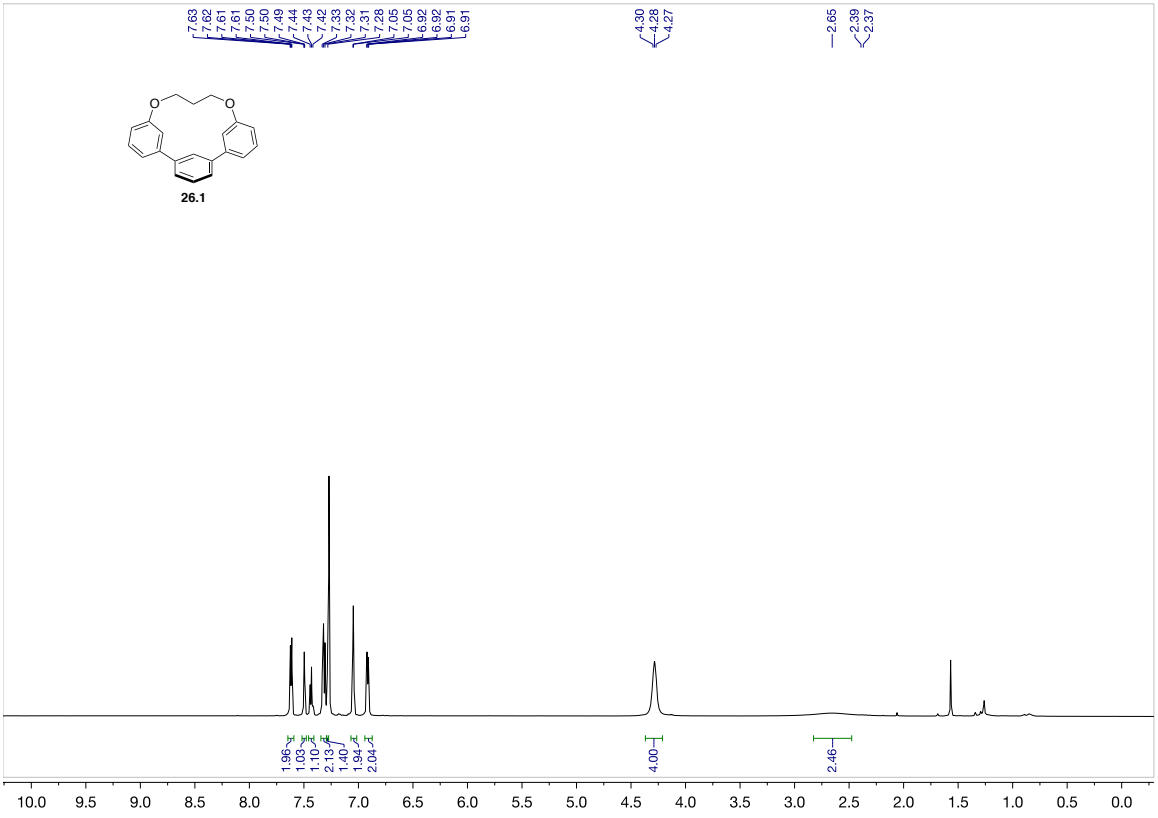
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7.33
7.32
7.31
7.28
7.05
7.05
6.92
6.92
6.91
6.91
4.30
4.28
4.27
2.65
2.39
2.37
26.1
1.96
1.03
1.10
2.13
1.40
1.94
2.04
4.00
2.46
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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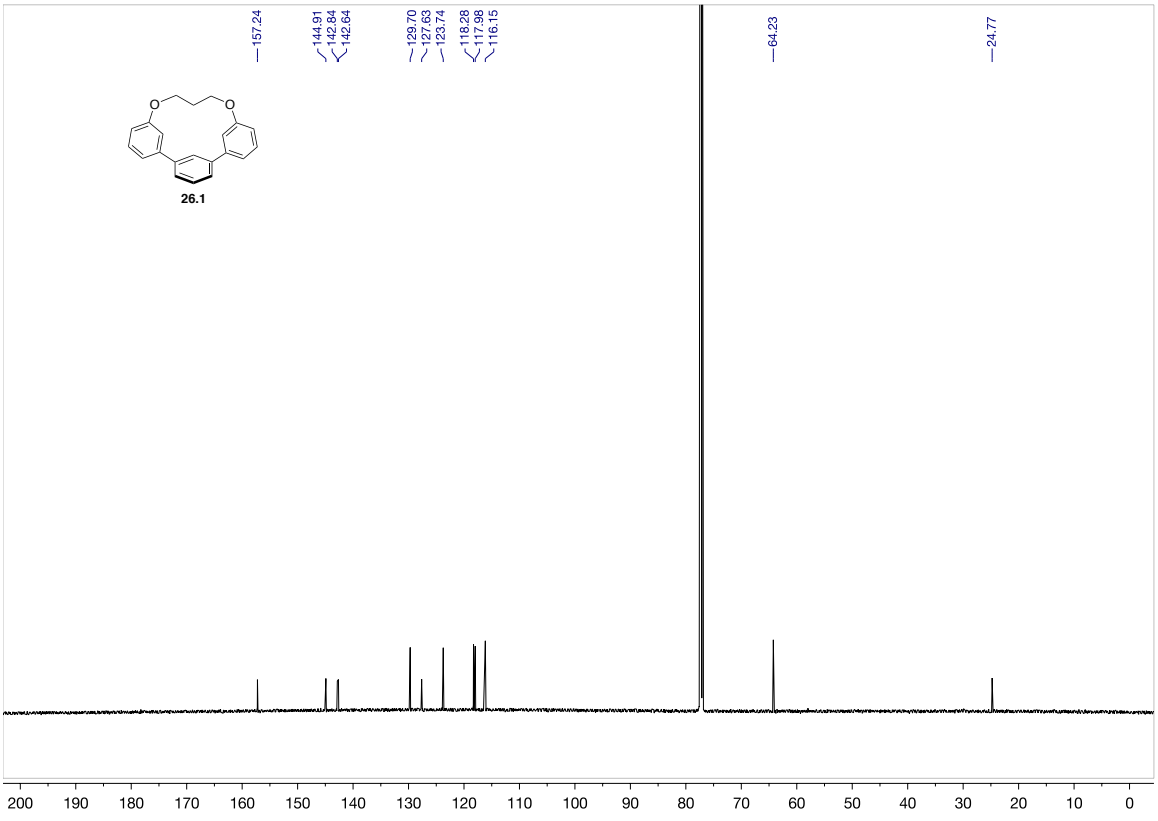
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116.15
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24.77
26.1
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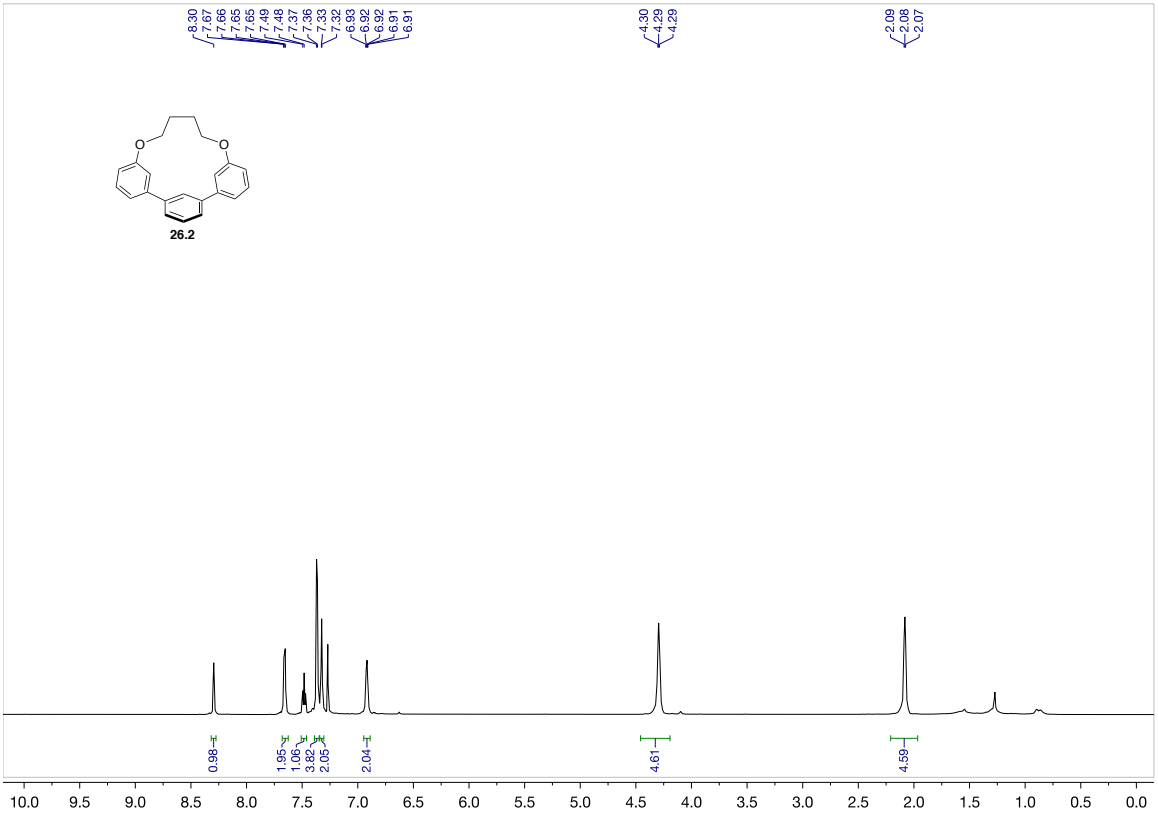
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7.33
7.32
6.93
6.92
6.92
6.91
6.91
4.30
4.29
4.29
2.09
2.08
2.07
26.2
0.98
1.95
1.06
3.82
2.05
2.04
4.61
4.59
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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3.0
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2.0
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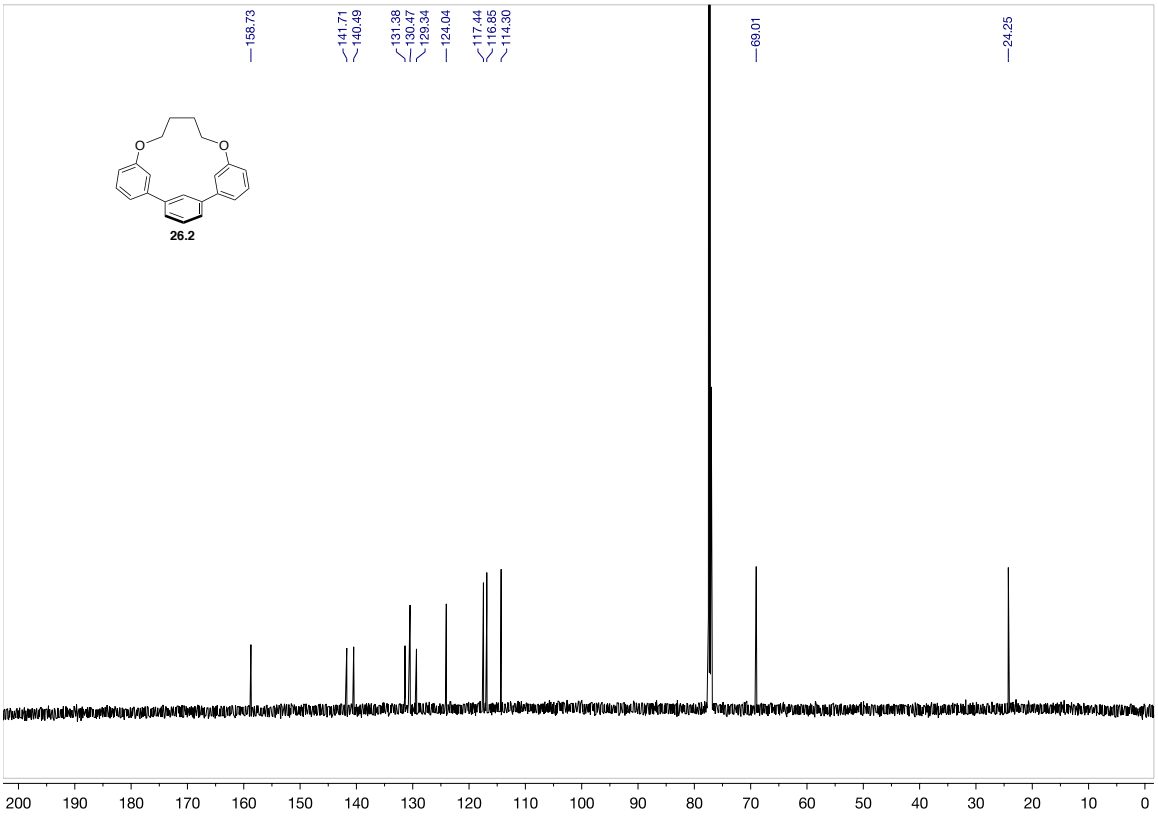
0.0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141.71
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129.34
124.04
117.44
116.85
114.30
69.01
24.25
26.2
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150
140
130
120
110
100
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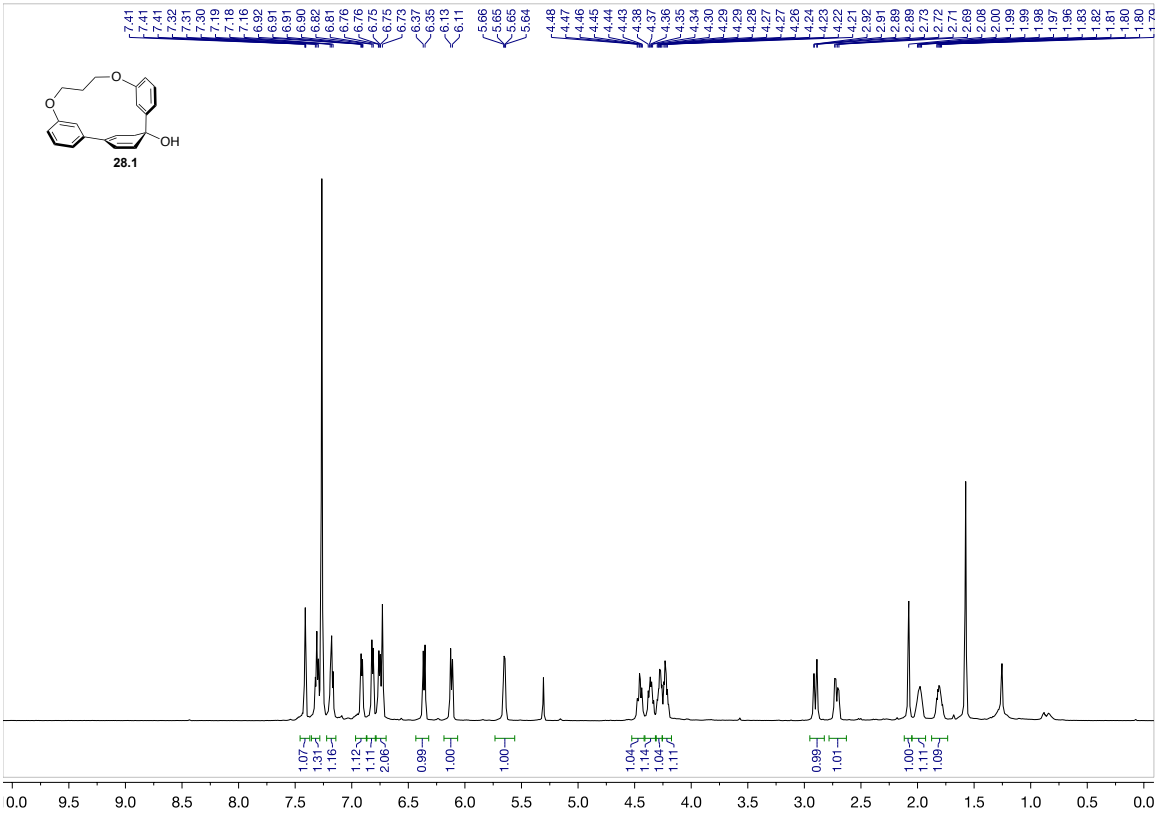
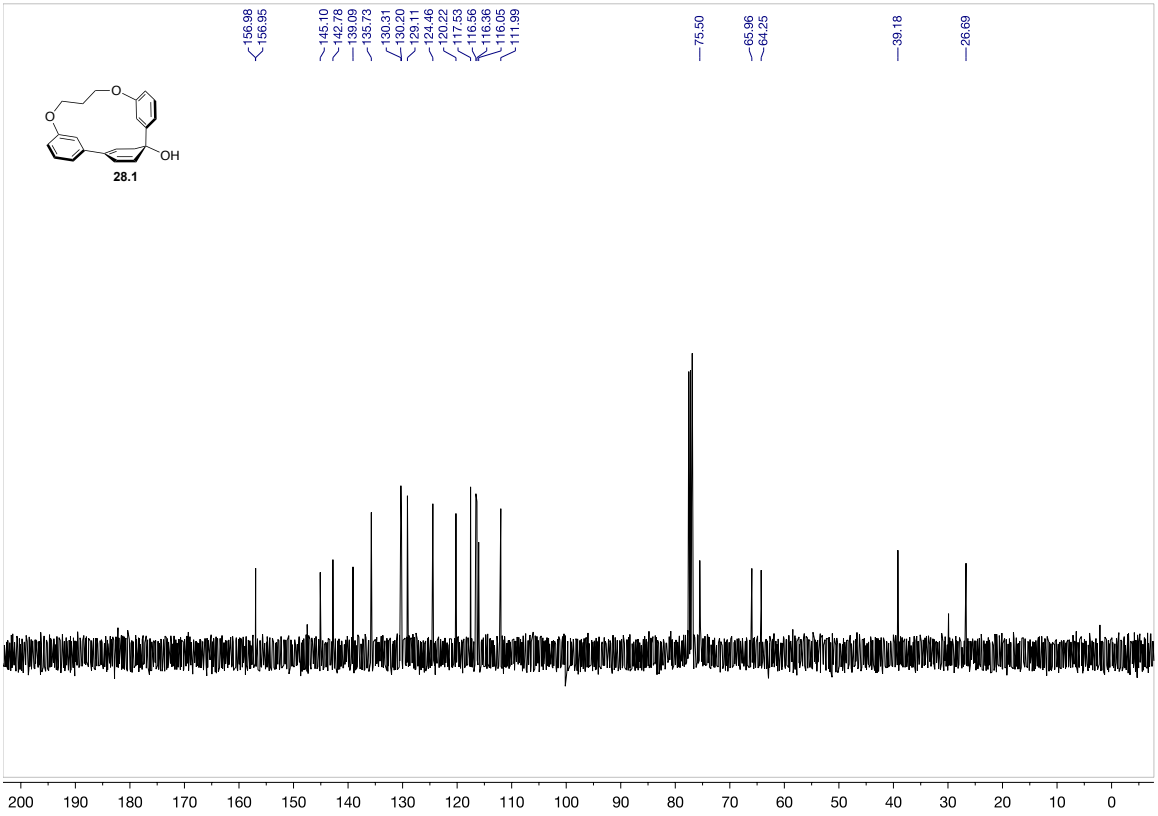
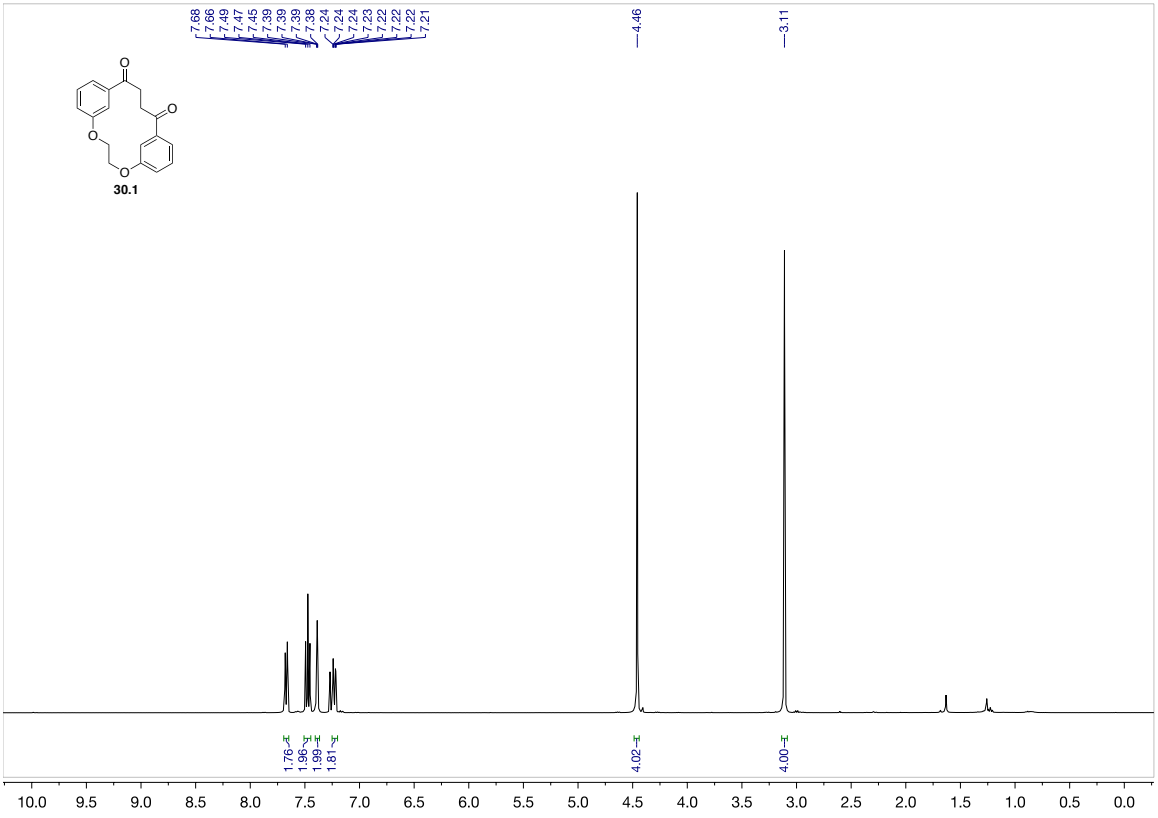
10
0


28.1
OH


28.1
OH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7.47
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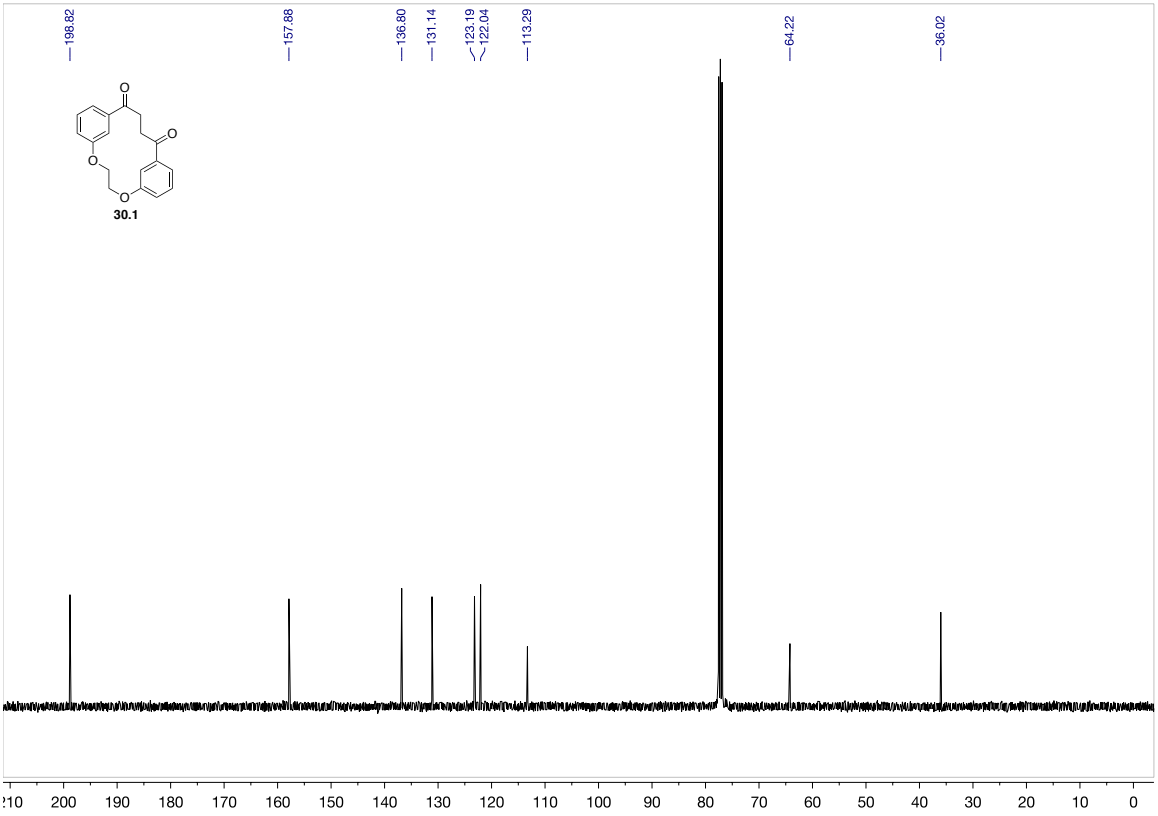
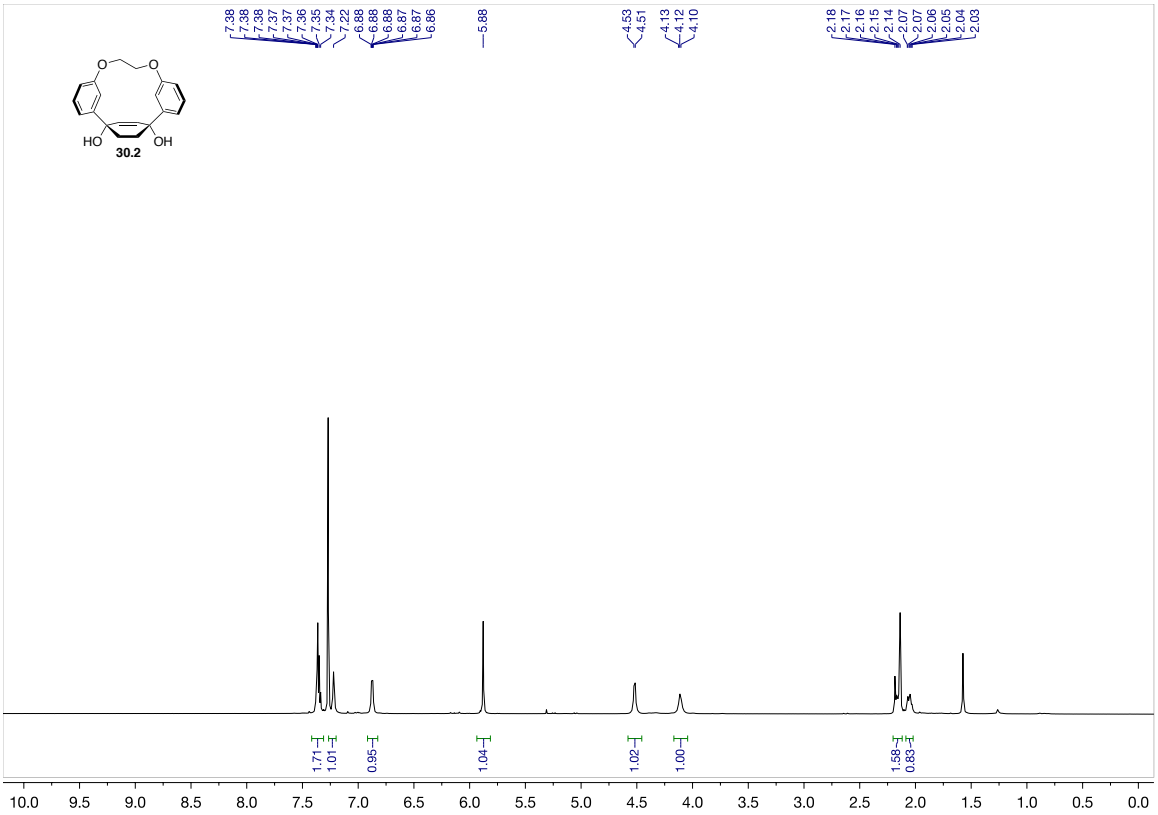
7.39
7.39
7.39
7.38
7.24
7.24
7.24
7.23
7.22
7.22
7.22
7.21
4.46
3.11
30.1
1.76
1.96
1.99
1.81
4.02
4.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


198.82
157.88
136.80
131.14
123.19
122.04
113.29
64.22
36.02
30.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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7.37
7.37
7.36
7.35
7.34
7.22
6.88
6.88
6.87
6.87
6.86
5.88
4.53
4.51
4.13
4.12
4.10
2.18
2.17
2.16
2.15
2.14
2.07
2.07
2.06
2.05
2.04
2.03
HO
OH
30.2
1.71
1.01
0.95
1.04
1.02
1.00
1.58
0.83
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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2.0
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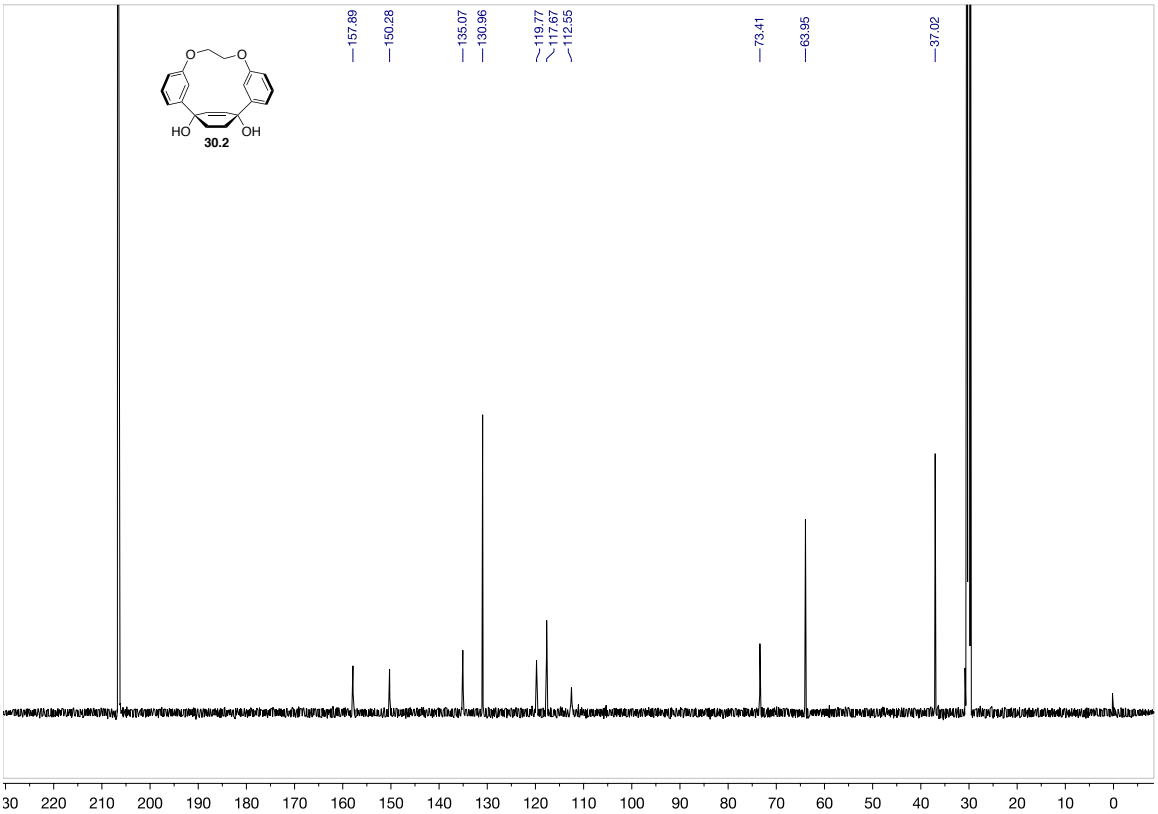
0.0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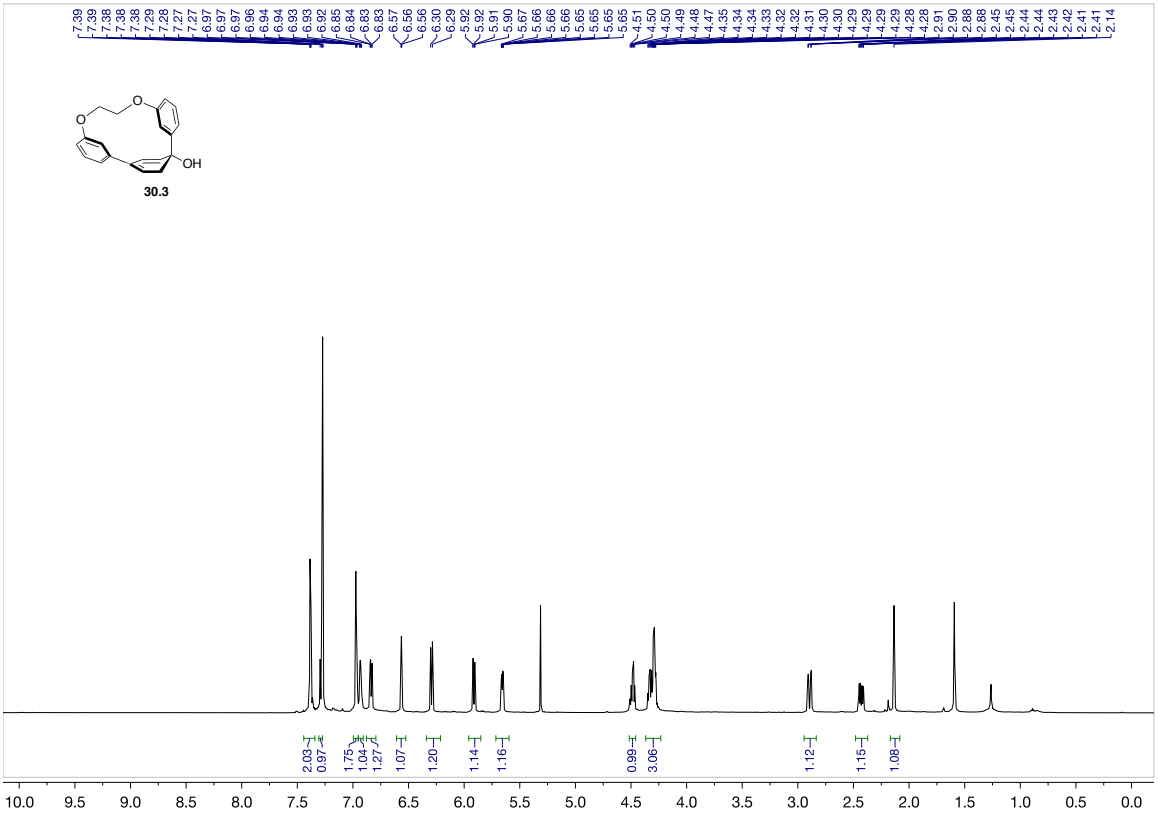
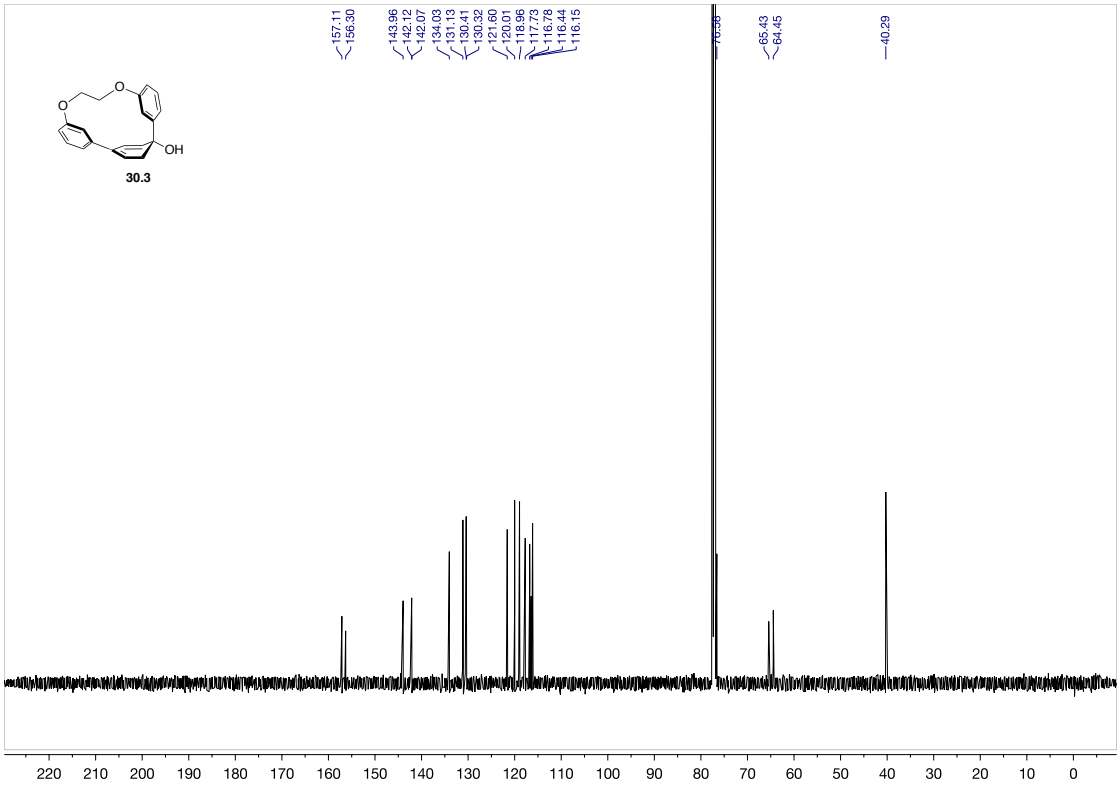
150.28
135.07
130.96
119.77
117.67
112.55
73.41
63.95
37.02
HO
OH
30.2
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


30.3
OH
2.03
0.97
1.75
1.04
1.27
1.07
1.20
1.14
1.16
0.99
3.06
1.12
1.15
1.08


30.3
OH
157.11
156.30
143.96
142.12
142.07
134.03
131.13
130.41
130.32
121.60
120.01
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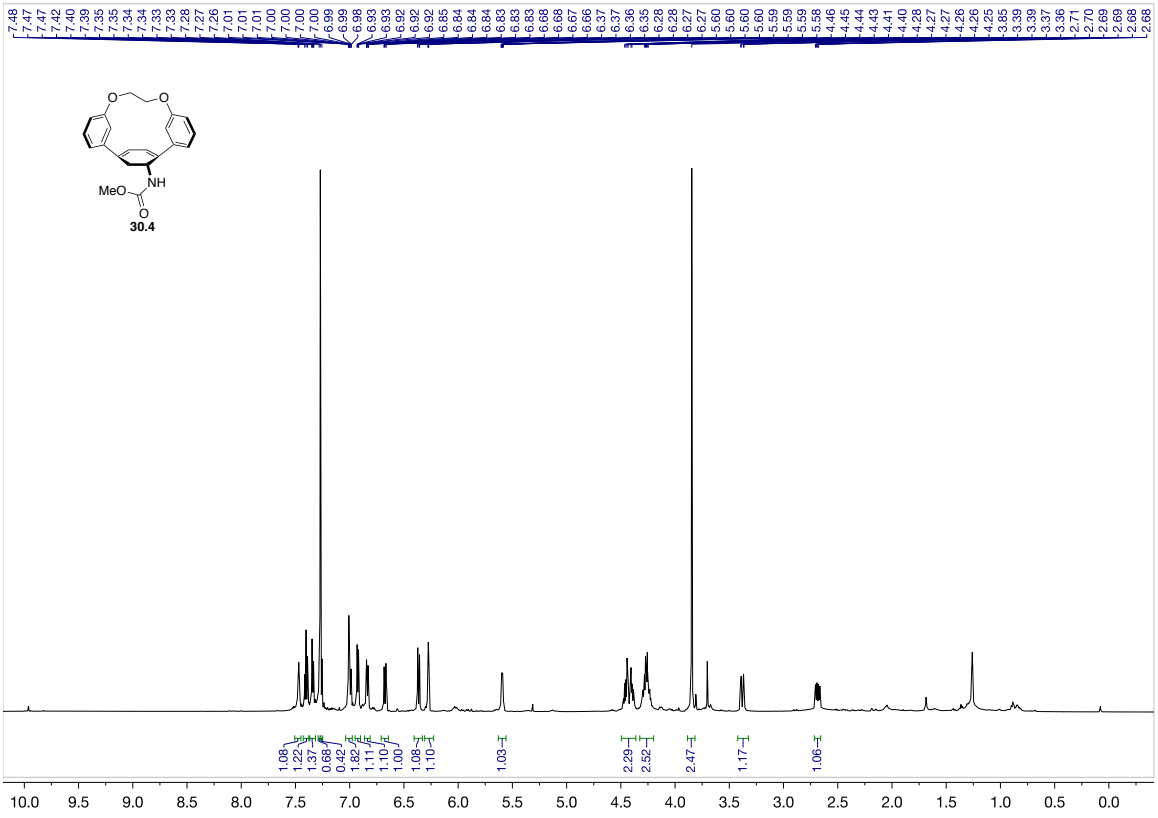
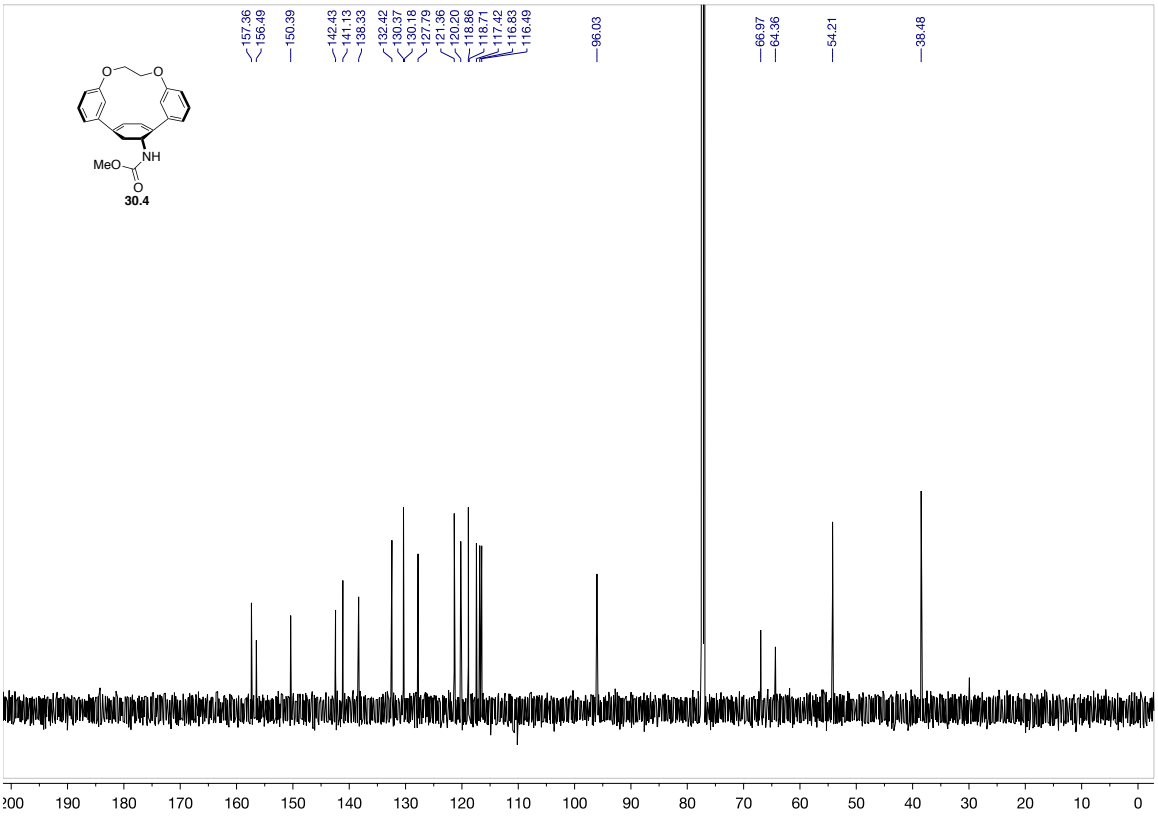
116.78
116.44
116.15
65.43
64.45
40.29


30.4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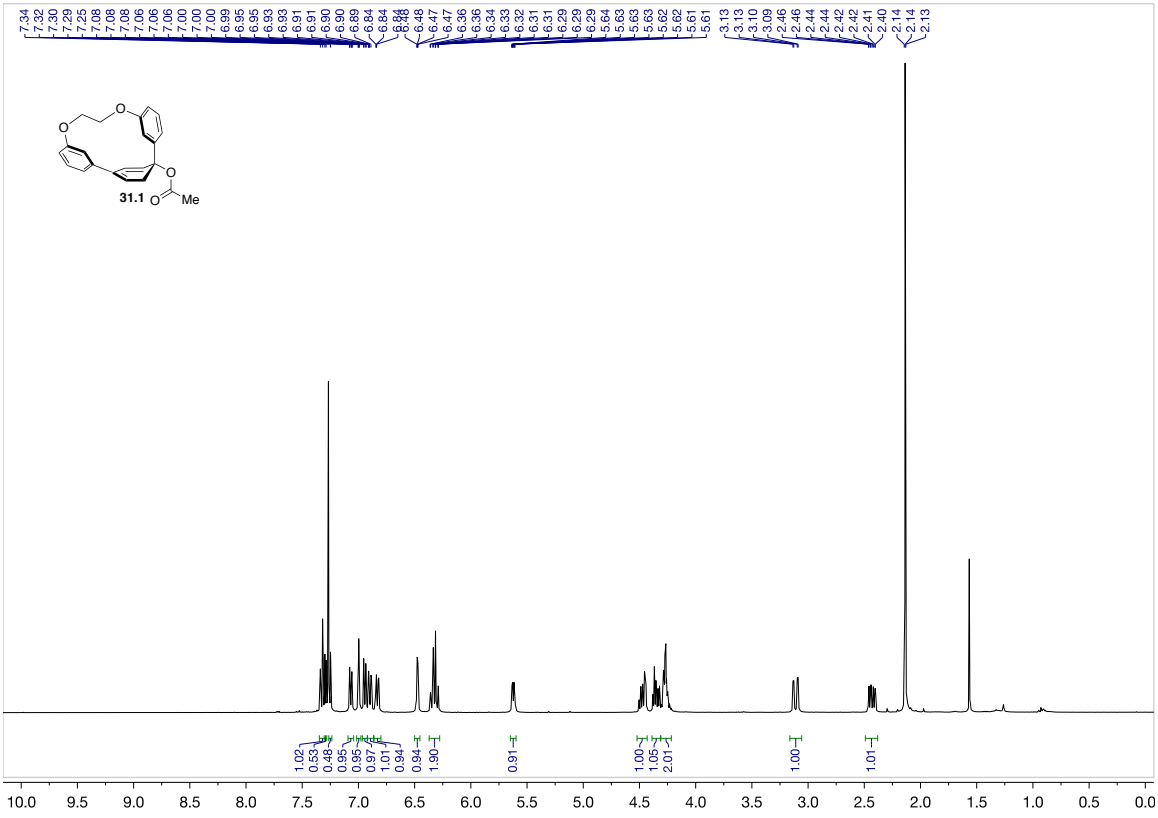
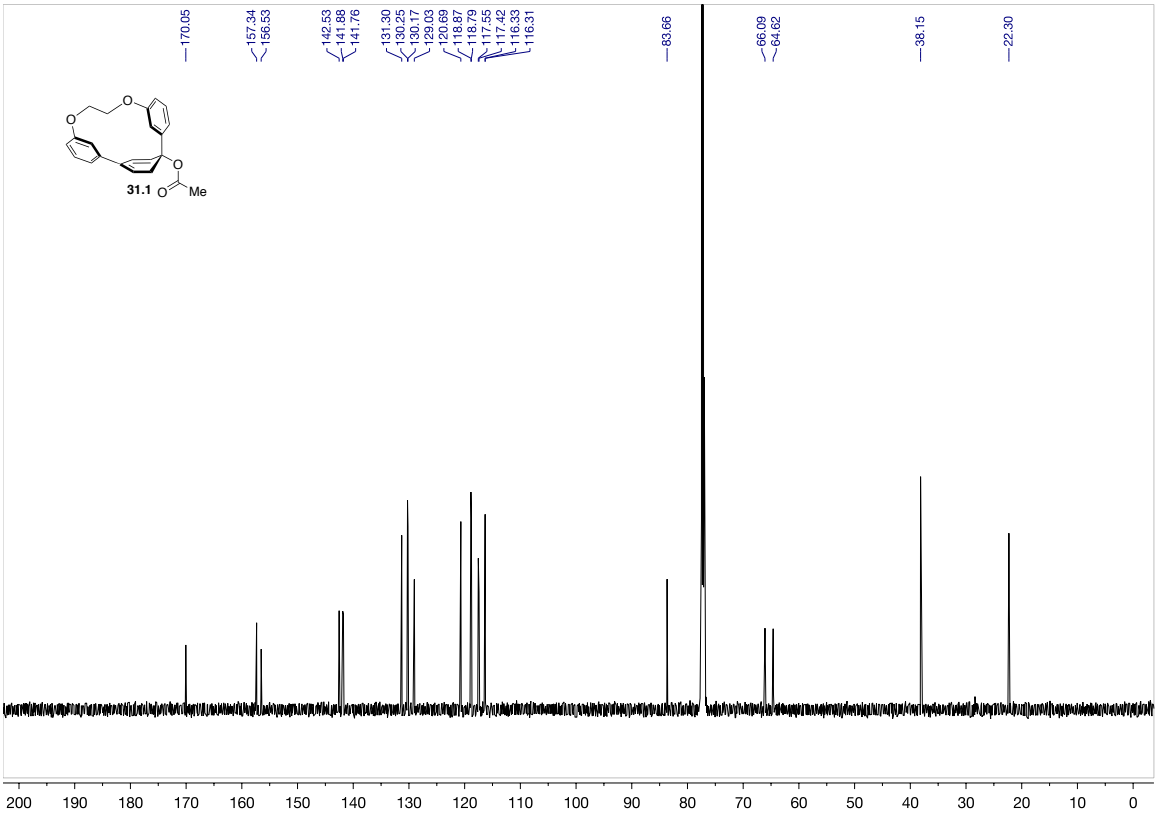
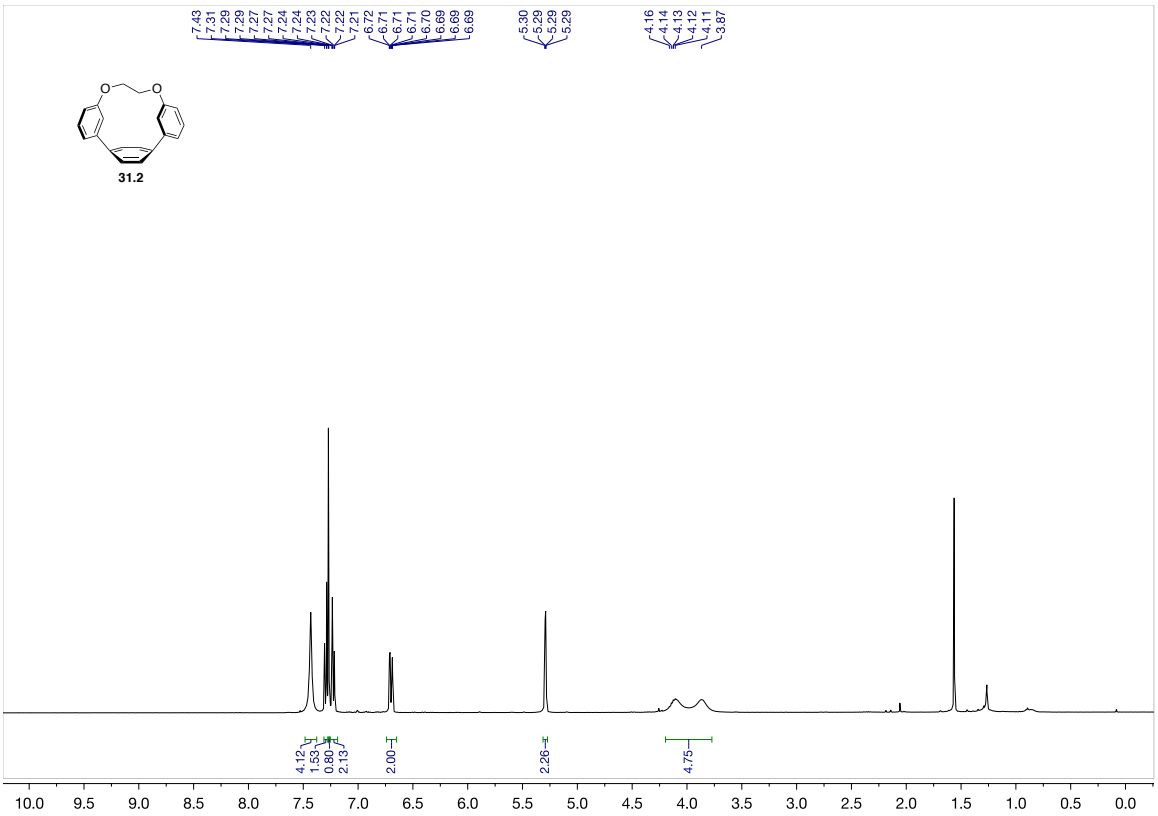

31.1
Me


31.1
Me


7.43
7.31
7.29
7.29
7.29
7.27
7.27
7.24
7.24
7.23
7.22
7.22
7.21
6.72
6.71
6.71
6.71
6.70
6.69
6.69
6.69
6.69
5.30
5.29
5.29
5.29
5.29
4.16
4.14
4.13
4.12
4.12
4.11
3.87
31.2
4.12
1.53
0.80
2.13
2.00
2.26
4.75
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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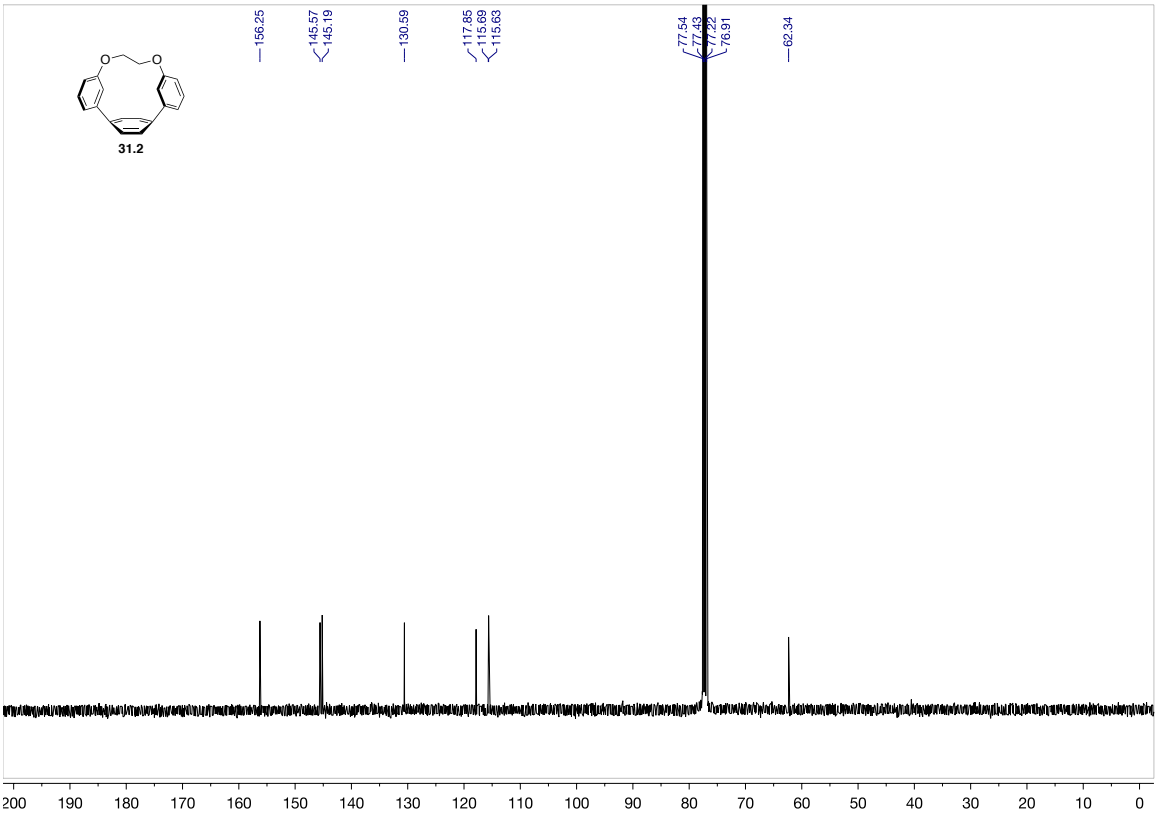
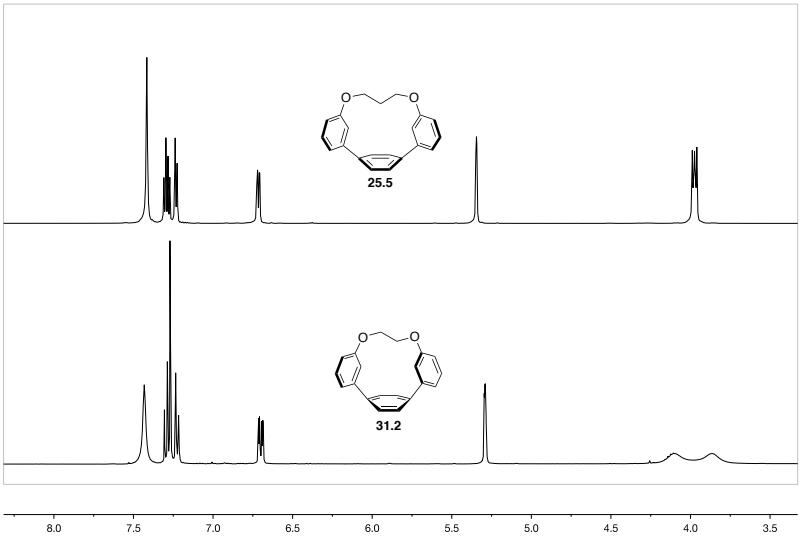
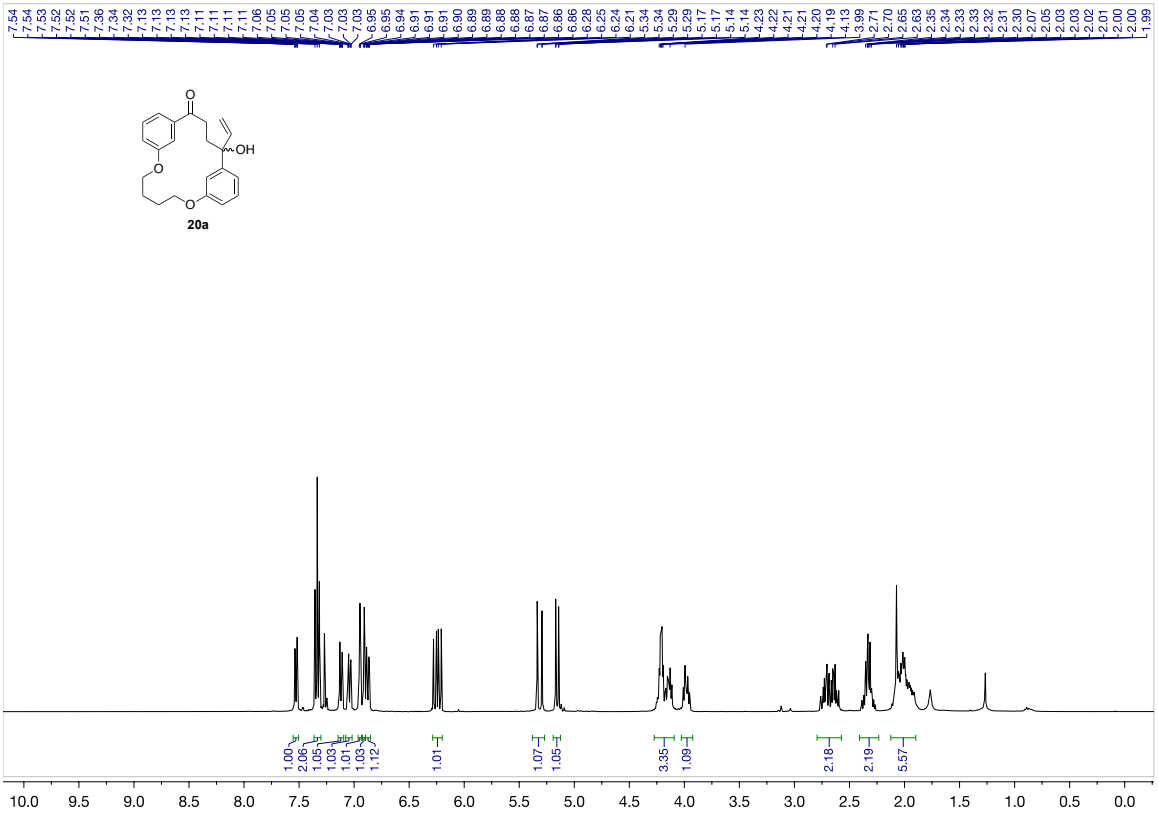
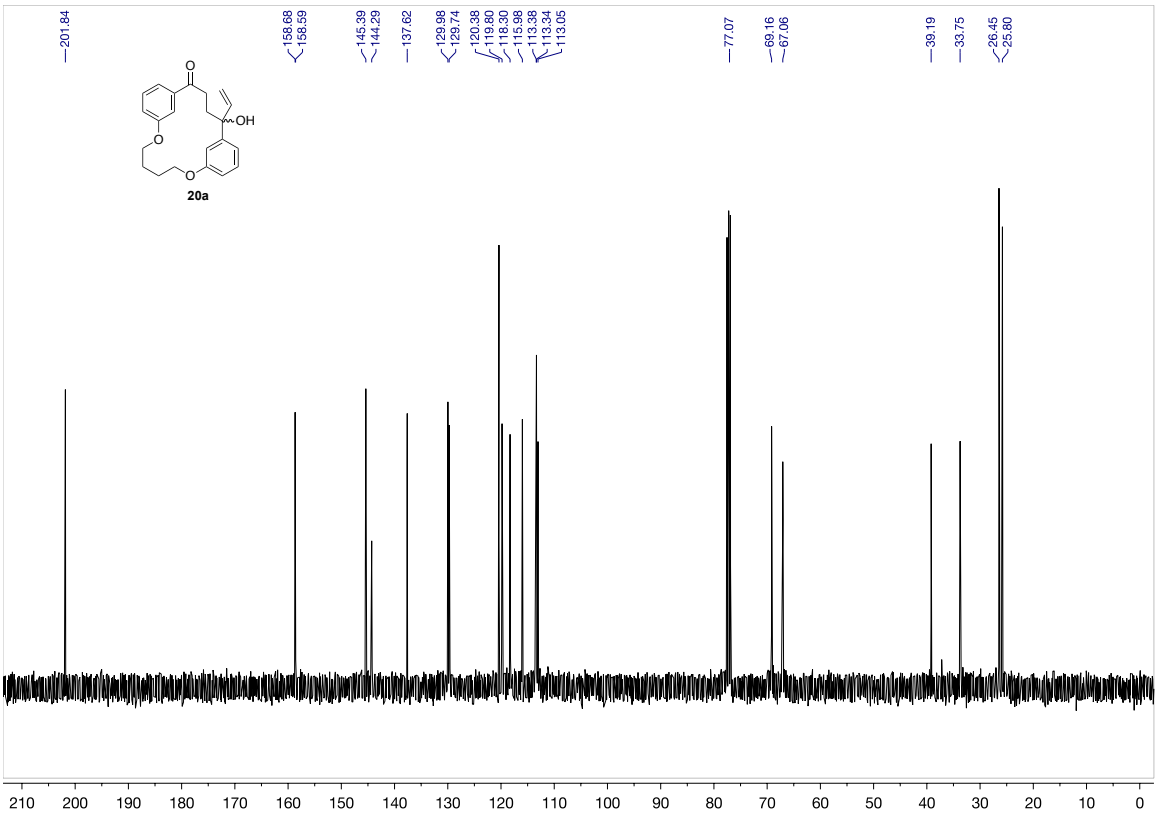
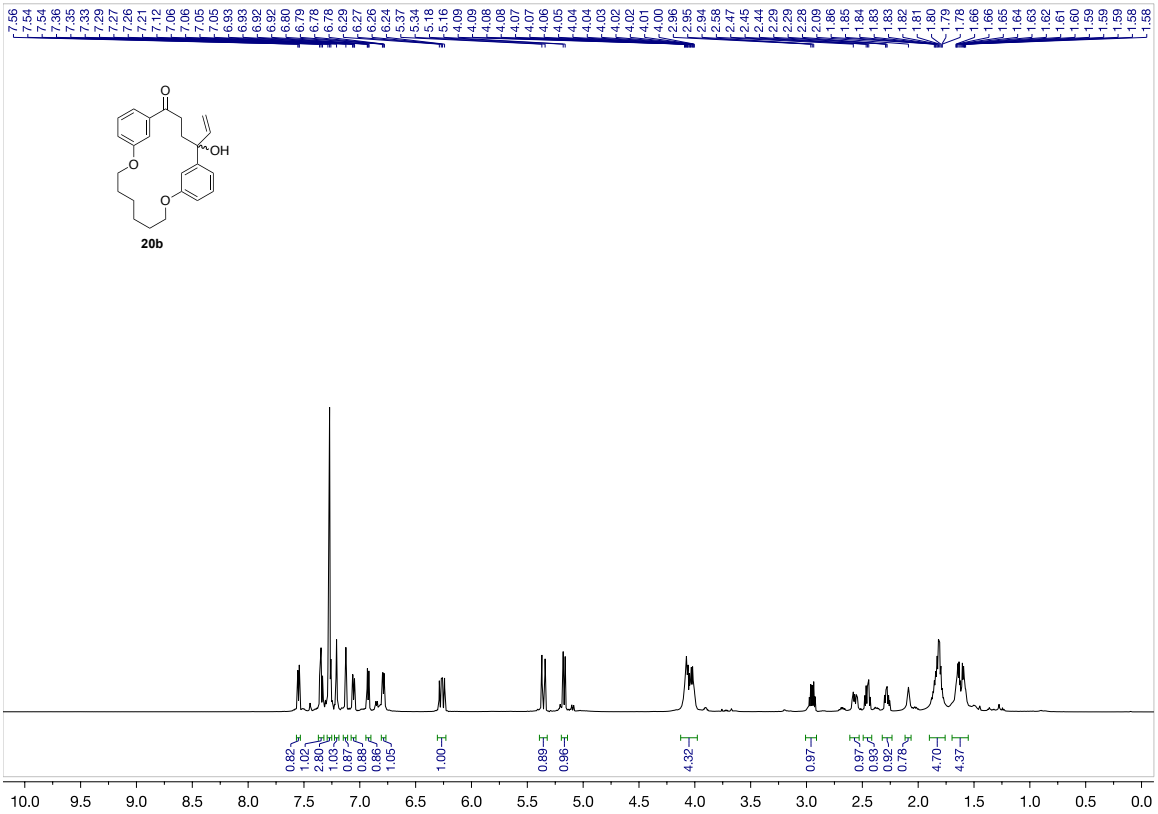
2.0
1.5
1.0
0.5
0.0

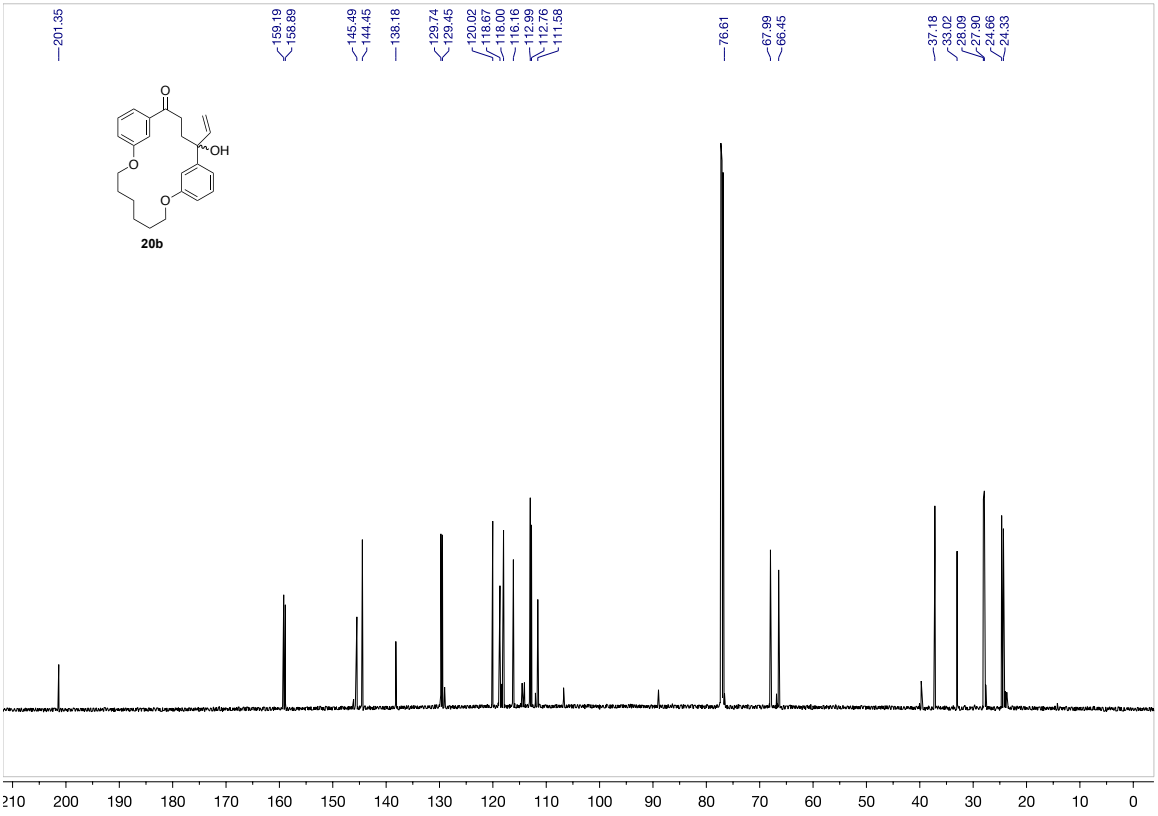

156.25
145.57
145.19
130.59
117.85
115.69
115.63
77.54
77.43
77.22
76.91
62.34
31.2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

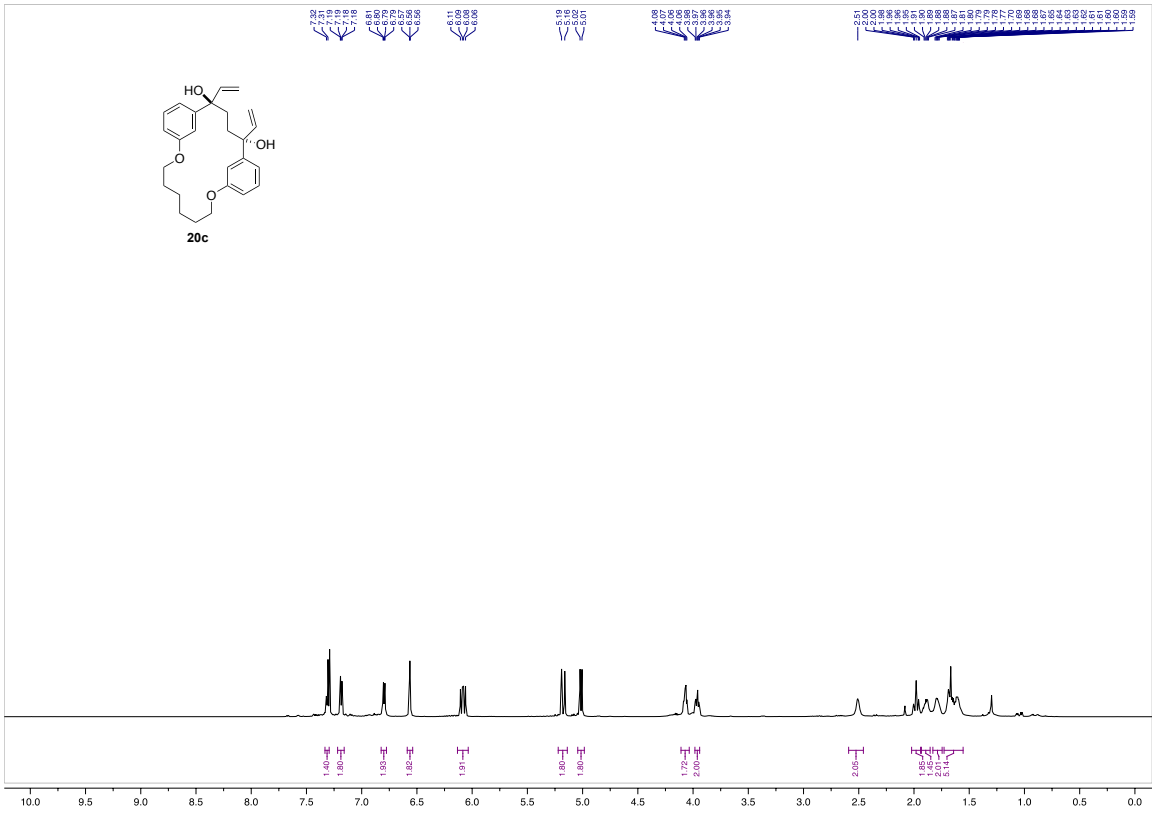

25.5
31.2
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5

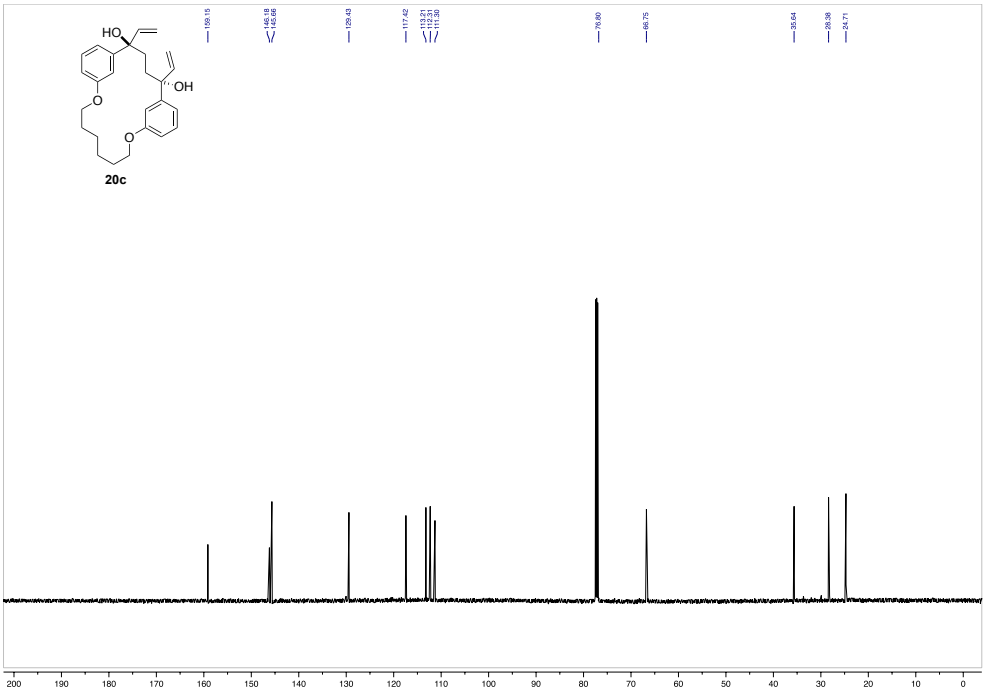

20a

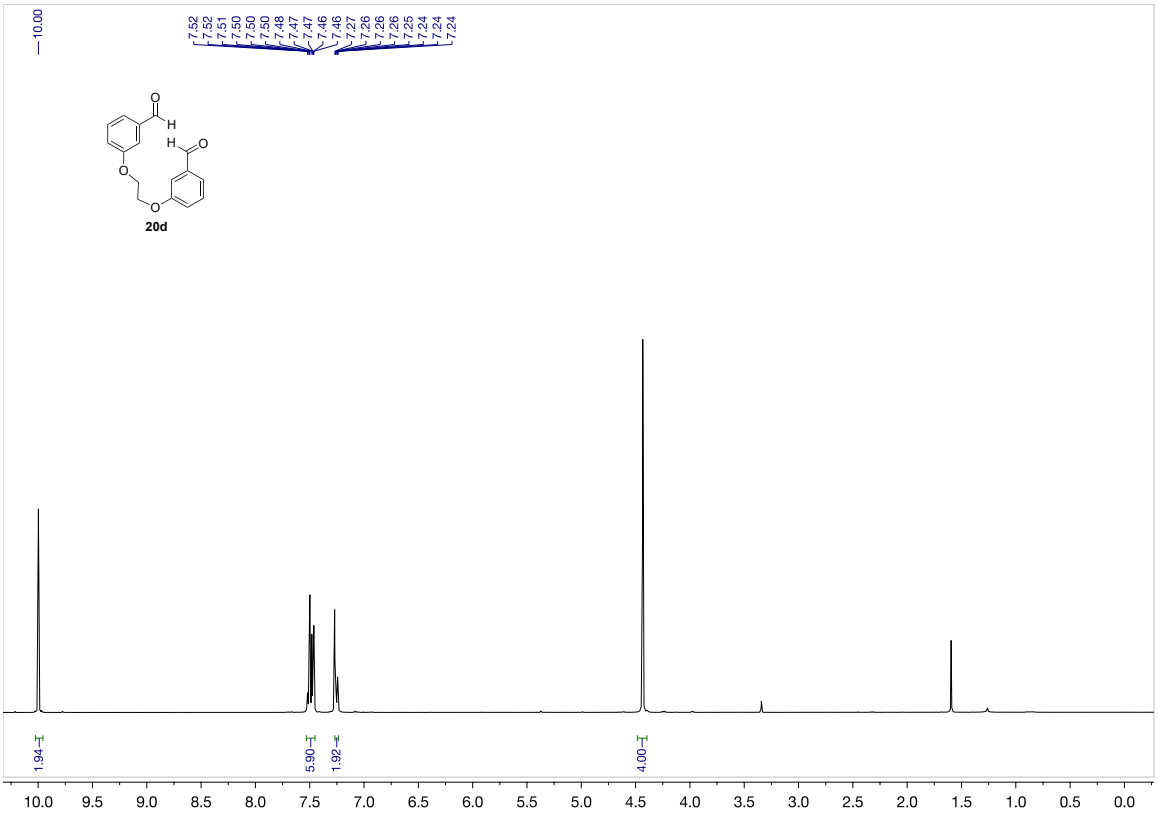

20a

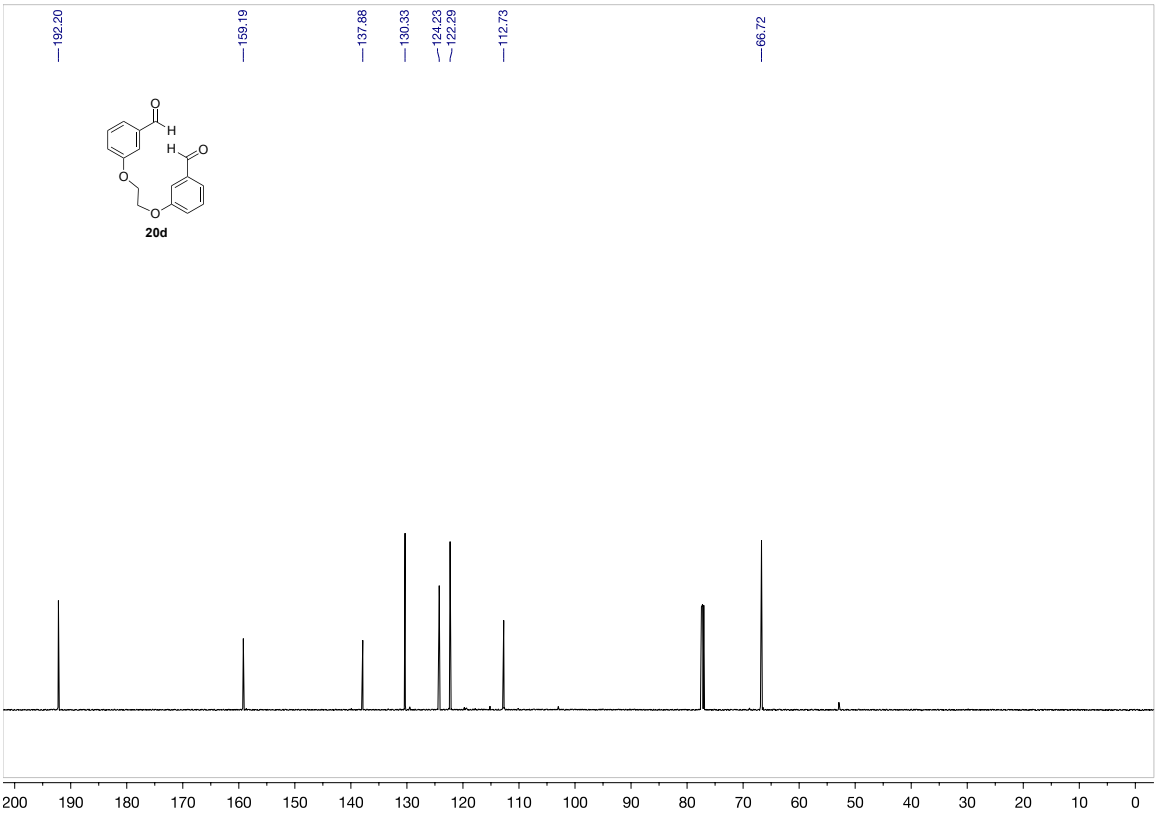

20b


20b


HO
OH
O
O
20c


HO
OH
O
O
20c


10.00
7.52
7.52
7.51
7.50
7.50
7.50
7.48
7.47
7.47
7.46
7.46
7.27
7.26
7.26
7.26
7.25
7.24
7.24
7.24
20d
1.94
5.90
1.92
4.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


192.20
159.19
137.88
130.33
124.23
122.29
112.73
66.72
20d
200
190
180
170
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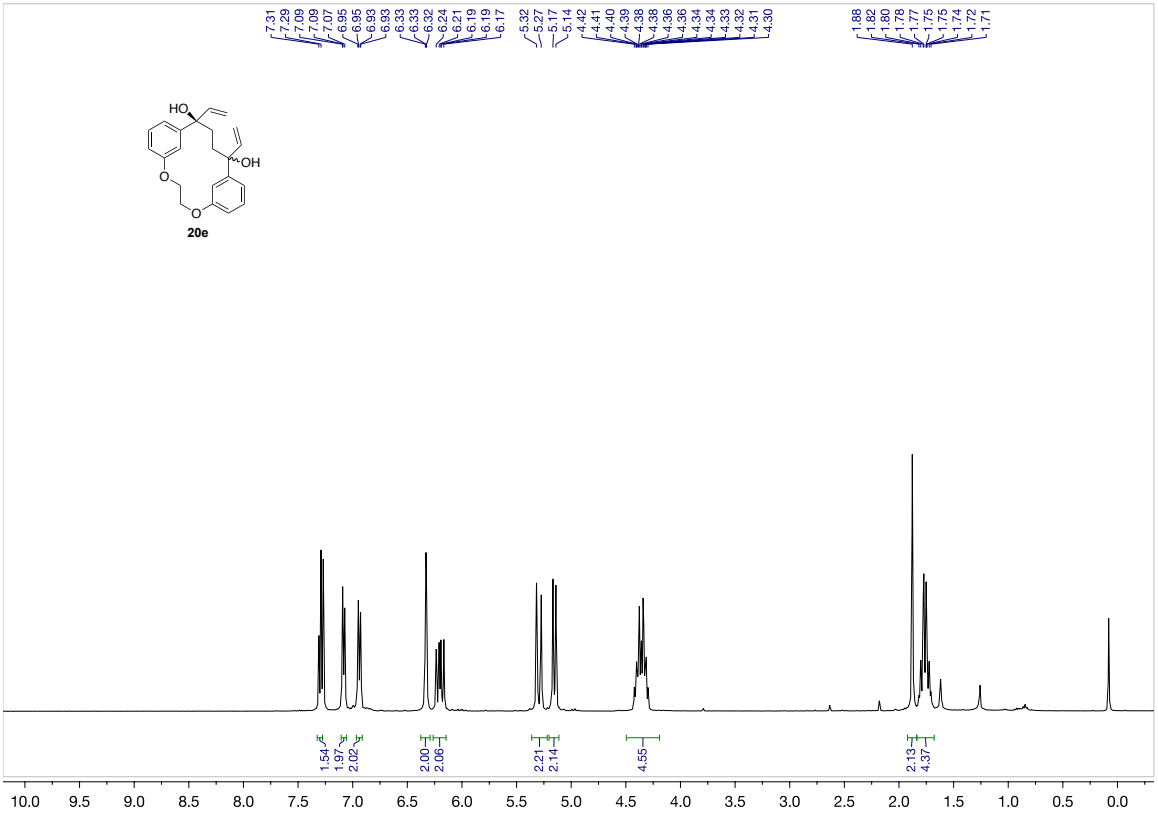
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.31
7.29
7.09
7.09
7.07
6.95
6.95
6.93
6.93
6.33
6.33
6.32
6.24
6.21
6.19
6.19
6.17
5.32
5.27
5.17
5.14
4.42
4.41
4.40
4.39
4.38
4.38
4.36
4.36
4.34
4.34
4.33
4.32
4.31
4.30
1.88
1.82
1.80
1.78
1.77
1.75
1.75
1.74
1.72
1.71
HO
OH
O
O
20e
1.54
1.97
2.02
2.00
2.06
2.21
2.14
4.55
2.13
4.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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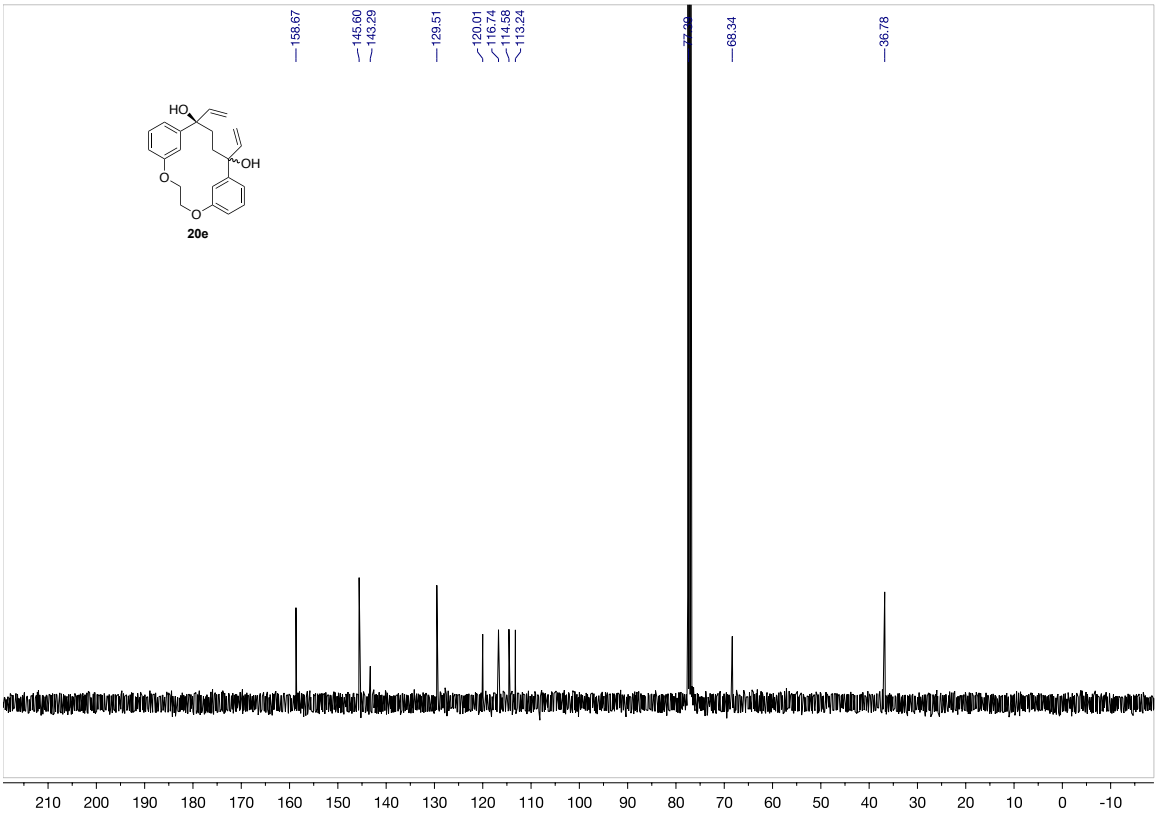
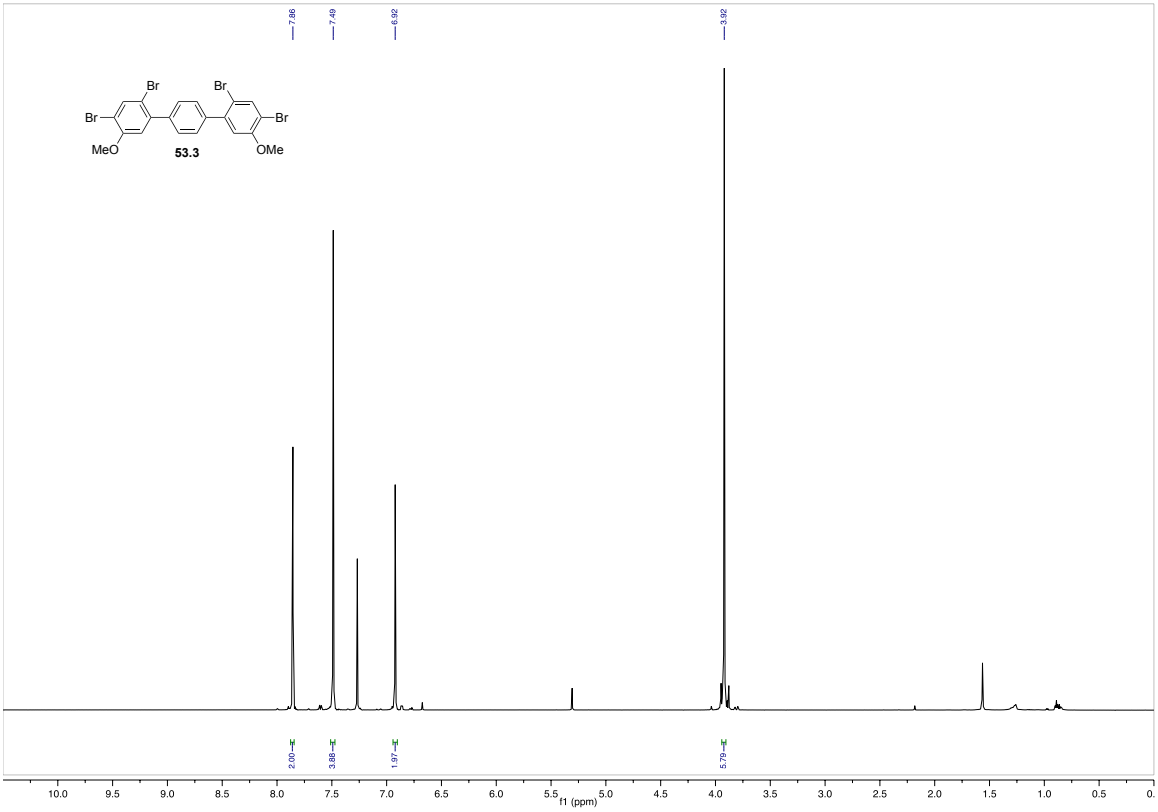
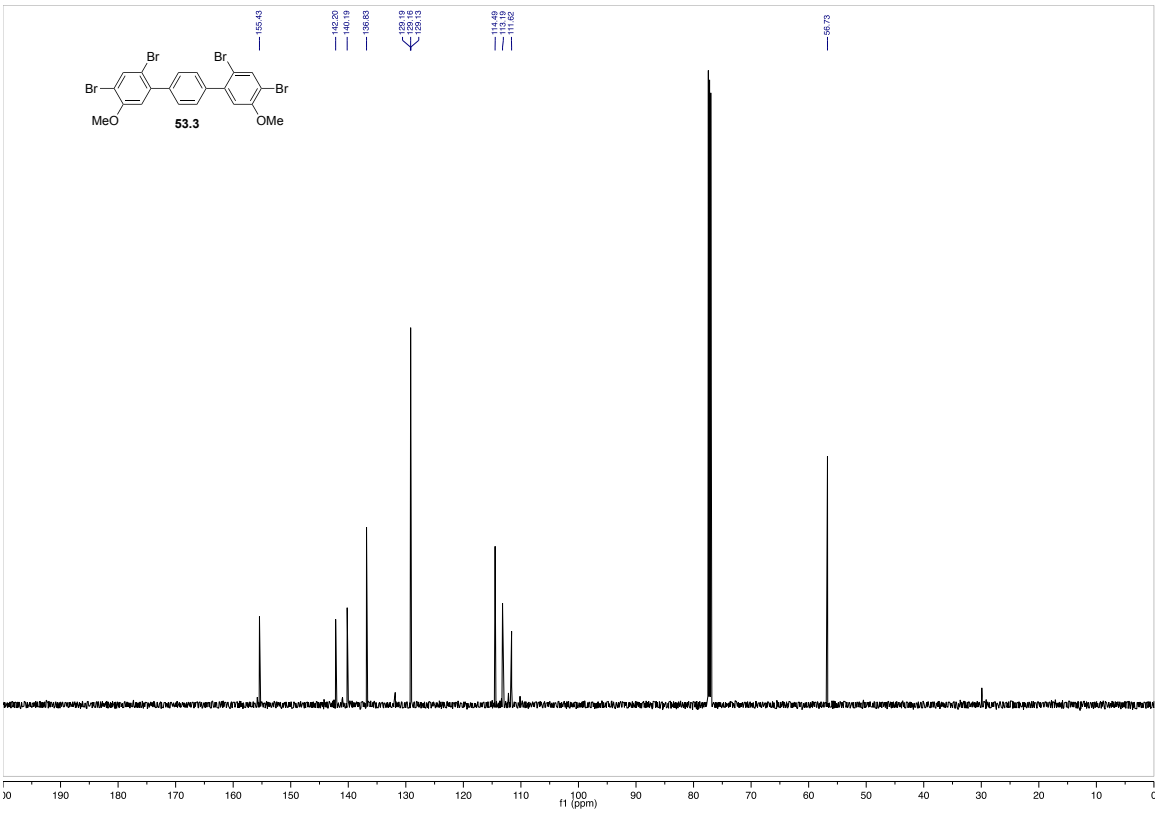
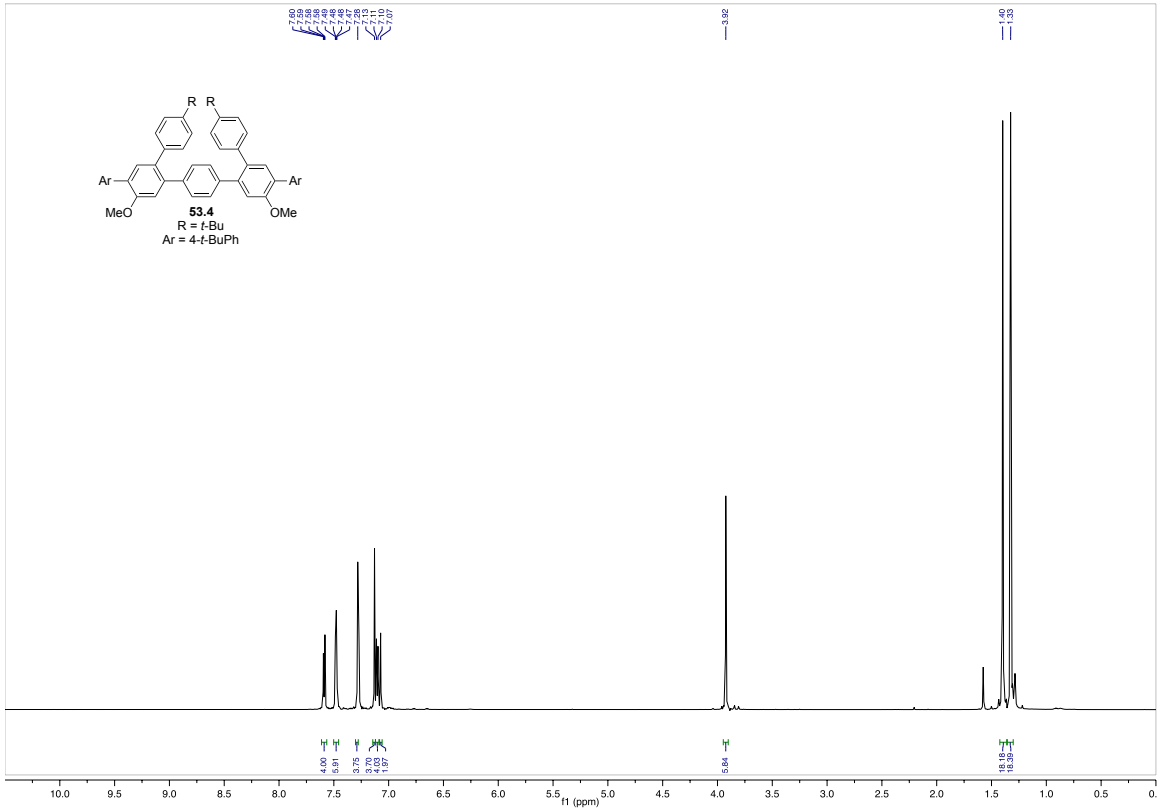
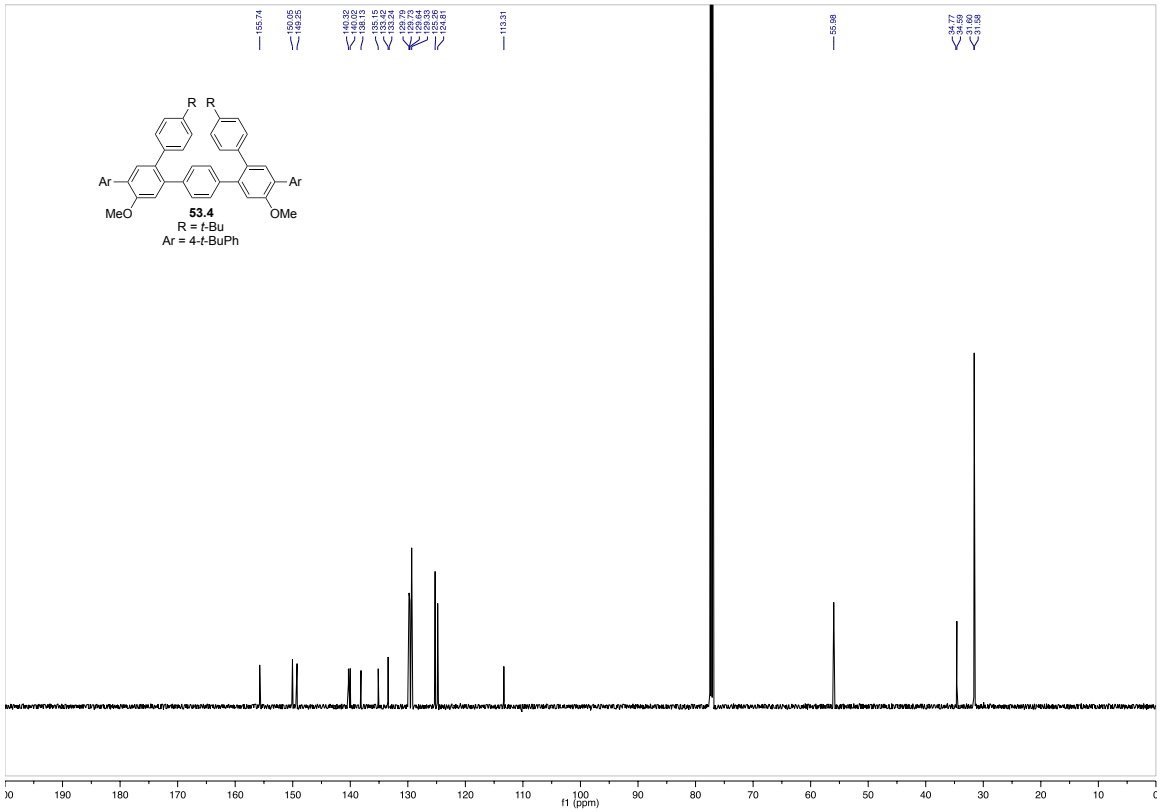
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

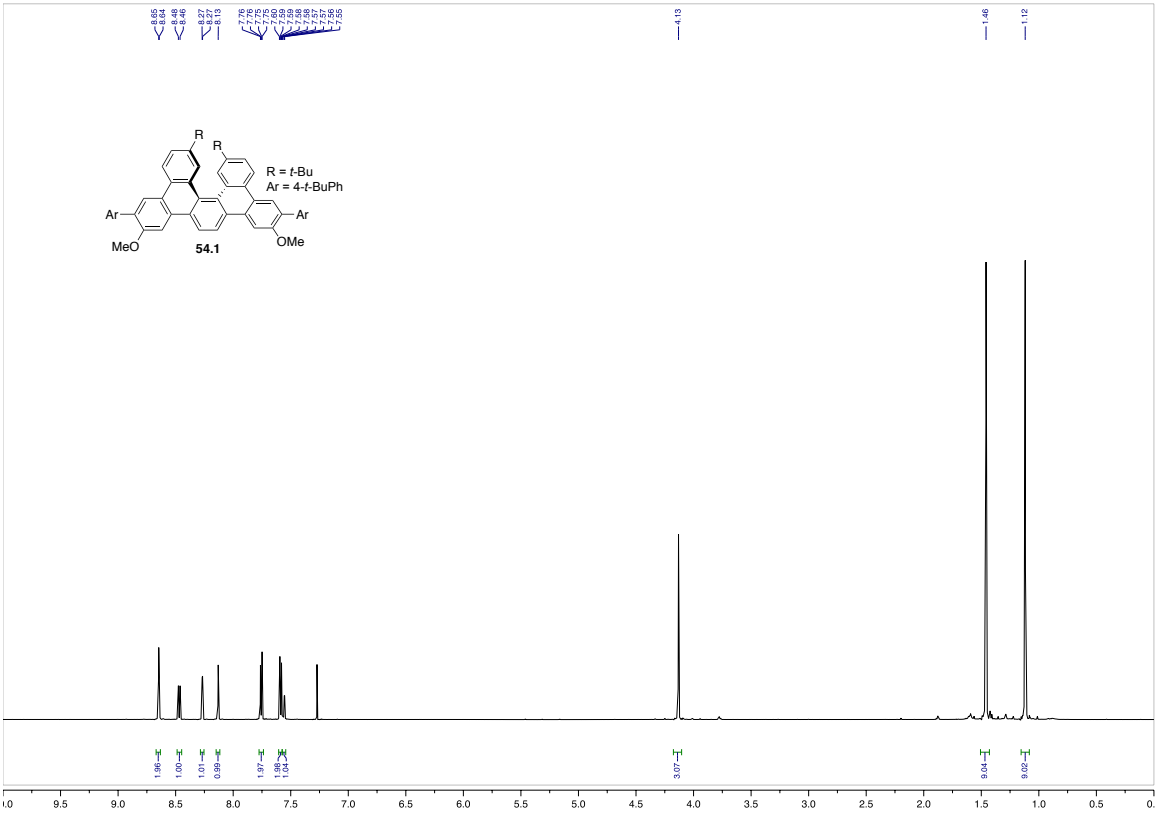

158.67
145.60
143.29
129.51
120.01
116.74
114.58
113.24
77.09
68.34
36.78
HO
OH
O
O
20e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

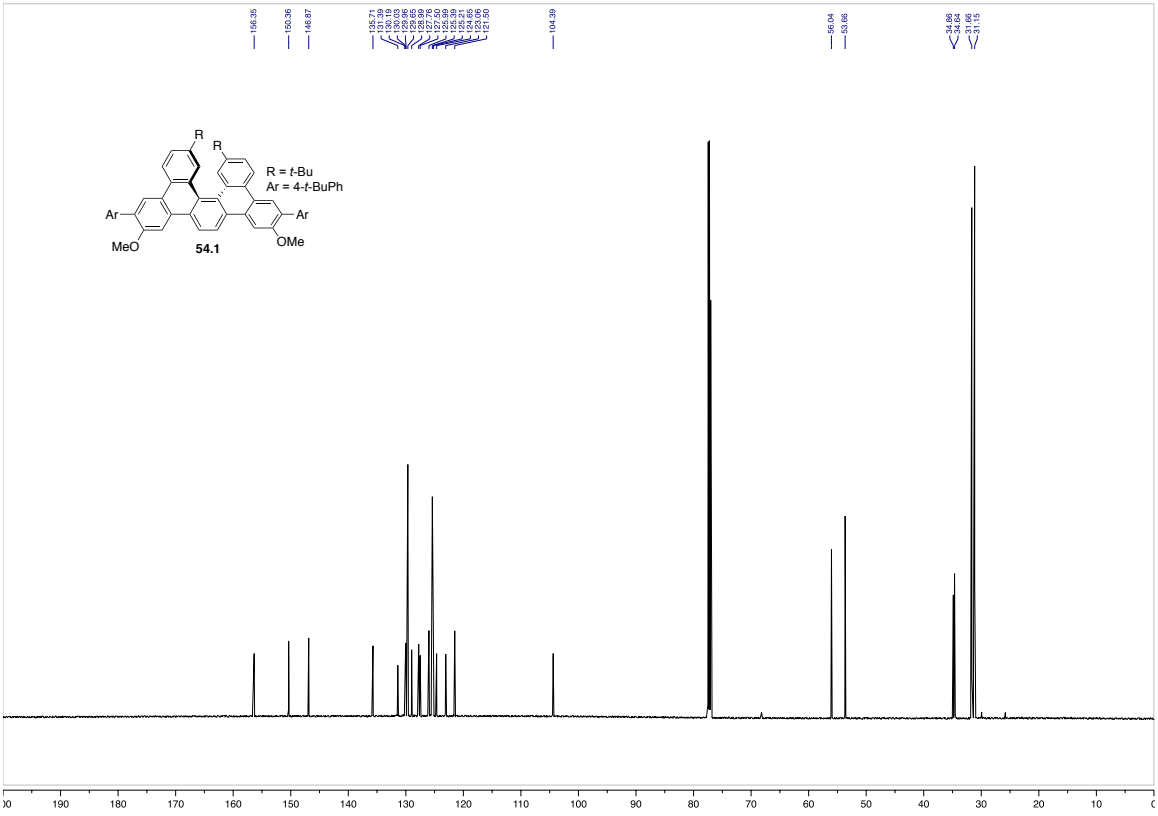

7.86
7.49
6.92
3.92
Br
Br
Br
Br
MeO
OMe
53.3
2.00
3.88
1.97
5.79
f1 (ppm)


155.43
142.20
140.19
136.83
129.19
129.16
129.13
114.49
113.19
111.62
56.73
Br
Br
Br
Br
MeO
OMe
53.3
f1 (ppm)


7.60
7.59
7.58
7.58
7.49
7.48
7.47
7.26
7.13
7.11
7.07
3.92
1.40
1.33
R R
Ar
Ar
MeO
OMe
53.4
R = t-Bu
Ar = 4-t-BuPh
4.00
5.91
3.75
3.70
4.03
1.97
5.84
18.18
18.39
f1 (ppm)


155.74
150.05
149.25
140.32
140.02
138.13
135.5
133.45
133.24
129.79
129.73
129.44
129.33
125.26
124.81
113.31
55.98
34.77
34.59
31.60
31.58
R R
Ar
Ar
MeO
OMe
53.4
R = t-Bu
Ar = 4-t-BuPh
f1 (ppm)


8.65
8.64
8.48
8.46
8.27
8.27
8.15
7.76
7.76
7.75
7.75
7.60
7.59
7.59
7.58
7.57
7.57
7.56
7.55
4.13
1.46
1.12
R
R
R = t-Bu
Ar = 4-t-BuPh
Ar
MeO
Ar
OMe
54.1
1.96
1.00
1.01
0.99
1.97
1.98
1.04
3.07
9.04
9.02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150.36
146.87
135.71
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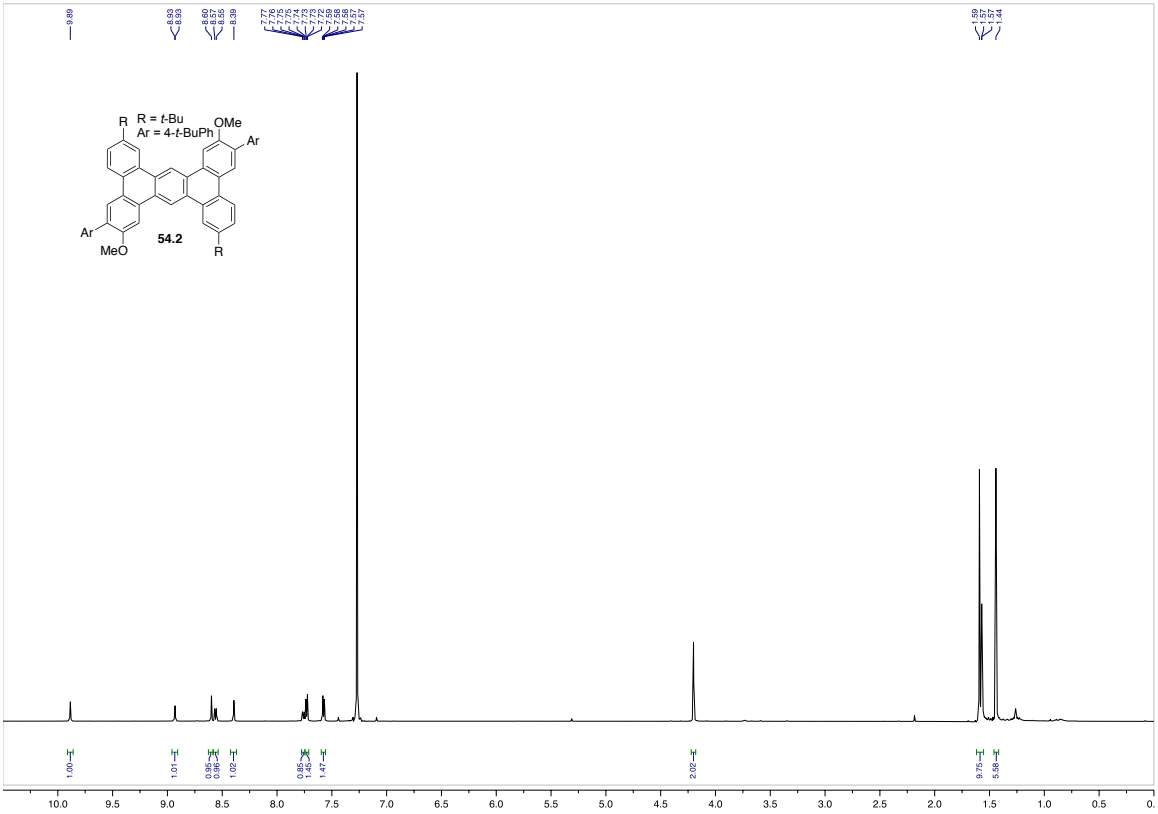
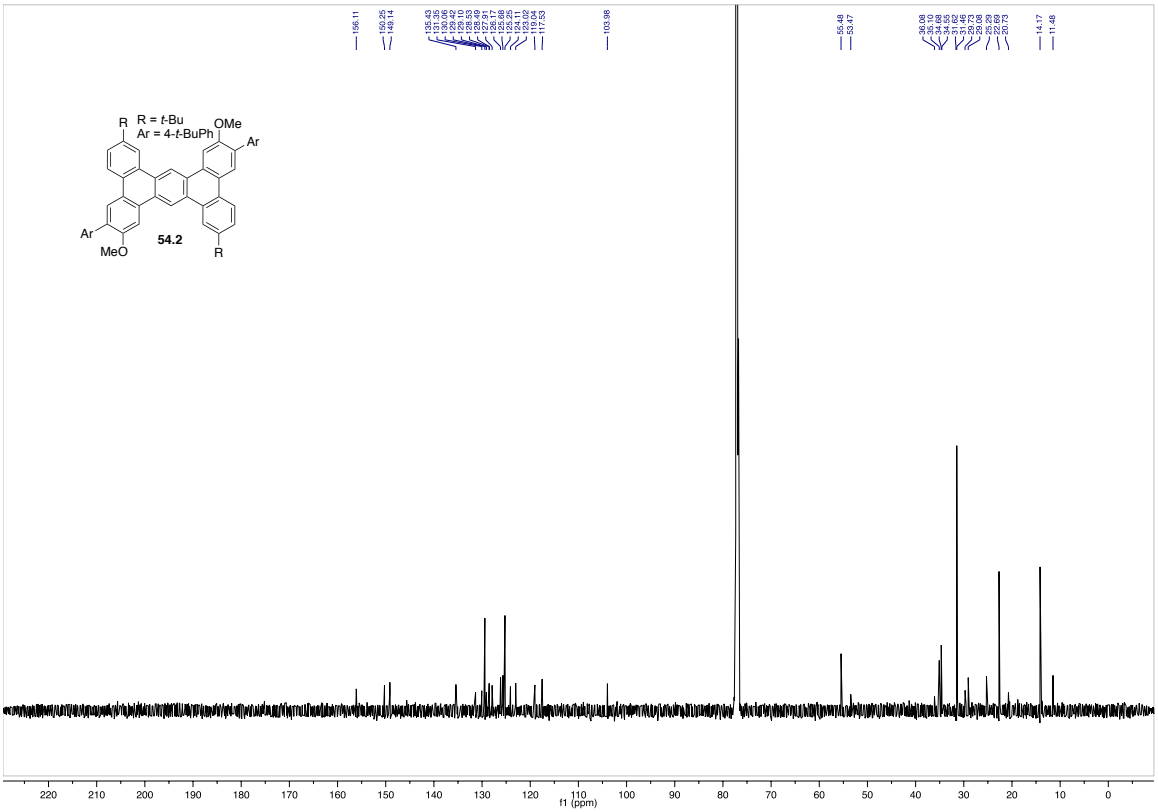
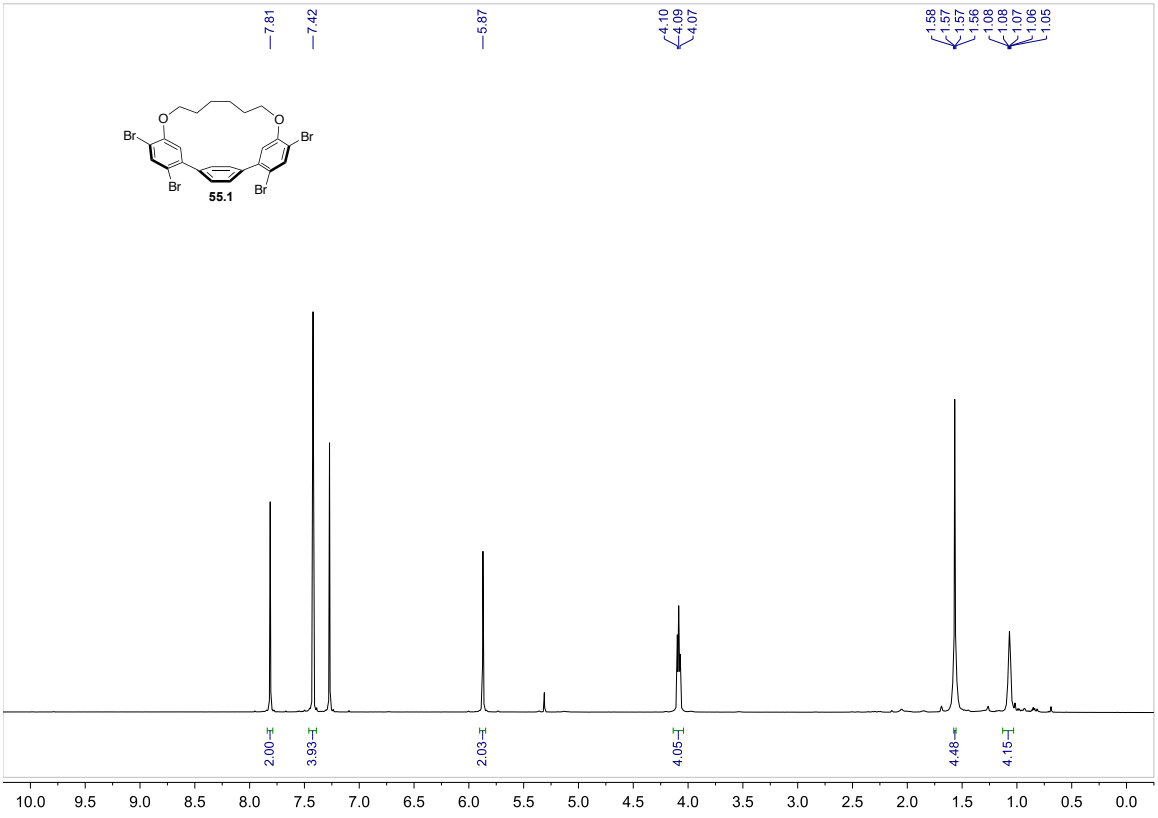
130.13
130.03
129.86
129.60
128.89
127.70
127.50
125.99
125.59
124.21
124.05
123.66
121.50
104.39
56.04
53.66
34.86
34.64
31.66
31.15
R
R
R = t-Bu
Ar = 4-t-BuPh
Ar
MeO
Ar
OMe
54.1


R = t-Bu
Ar = 4-t-BuPh
OMe
Ar
Ar
MeO
54.2
R


R = t-Bu
Ar = 4-t-BuPh
OMe
Ar
Ar
MeO
54.2
R
f1 (ppm)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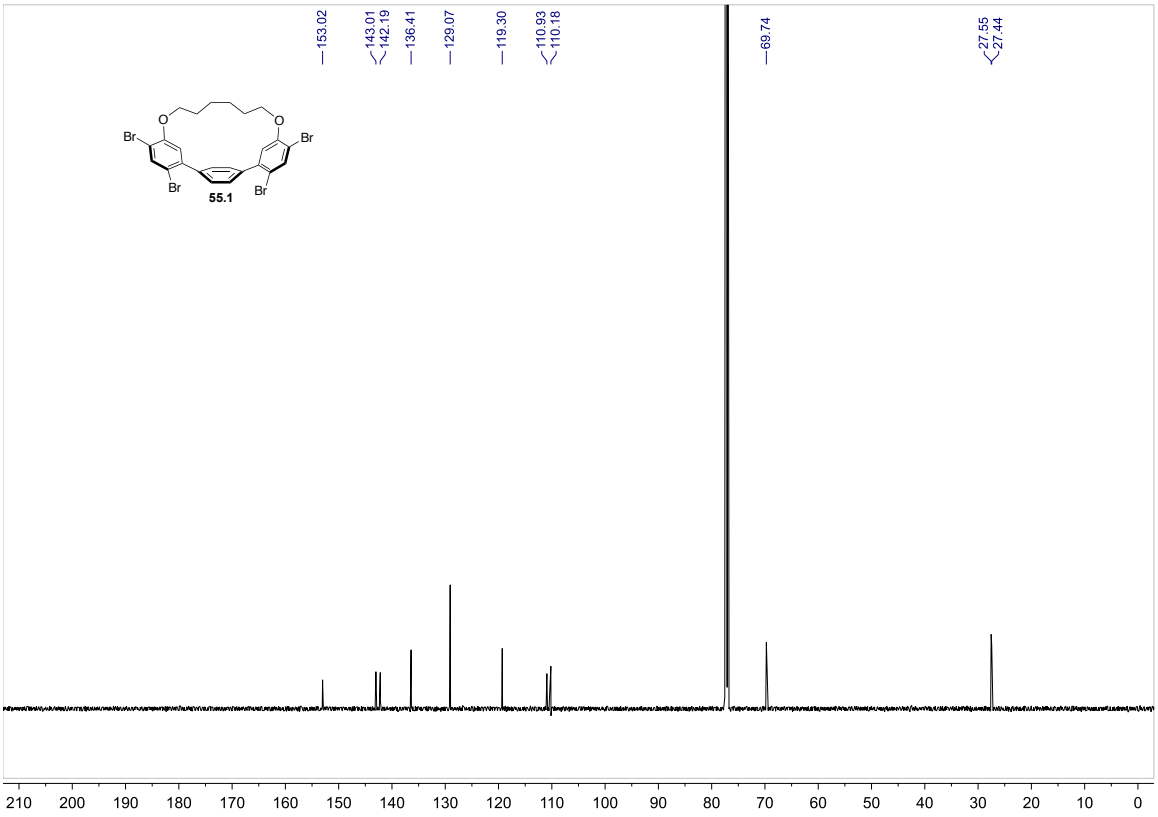
7.42
5.87
4.10
4.09
4.07
1.58
1.57
1.57
1.56
1.08
1.08
1.07
1.06
1.05
Br
Br
Br
Br
O
O
55.1
2.00
3.93
2.03
4.05
4.48
4.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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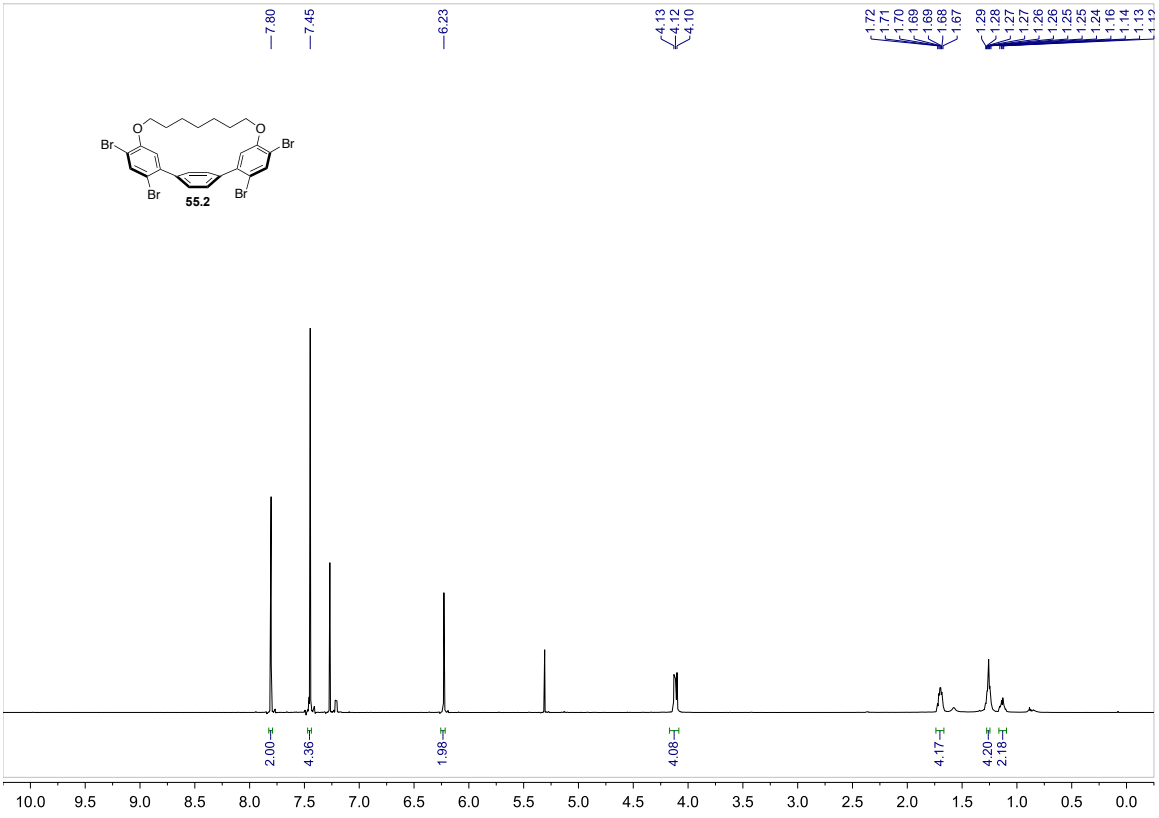
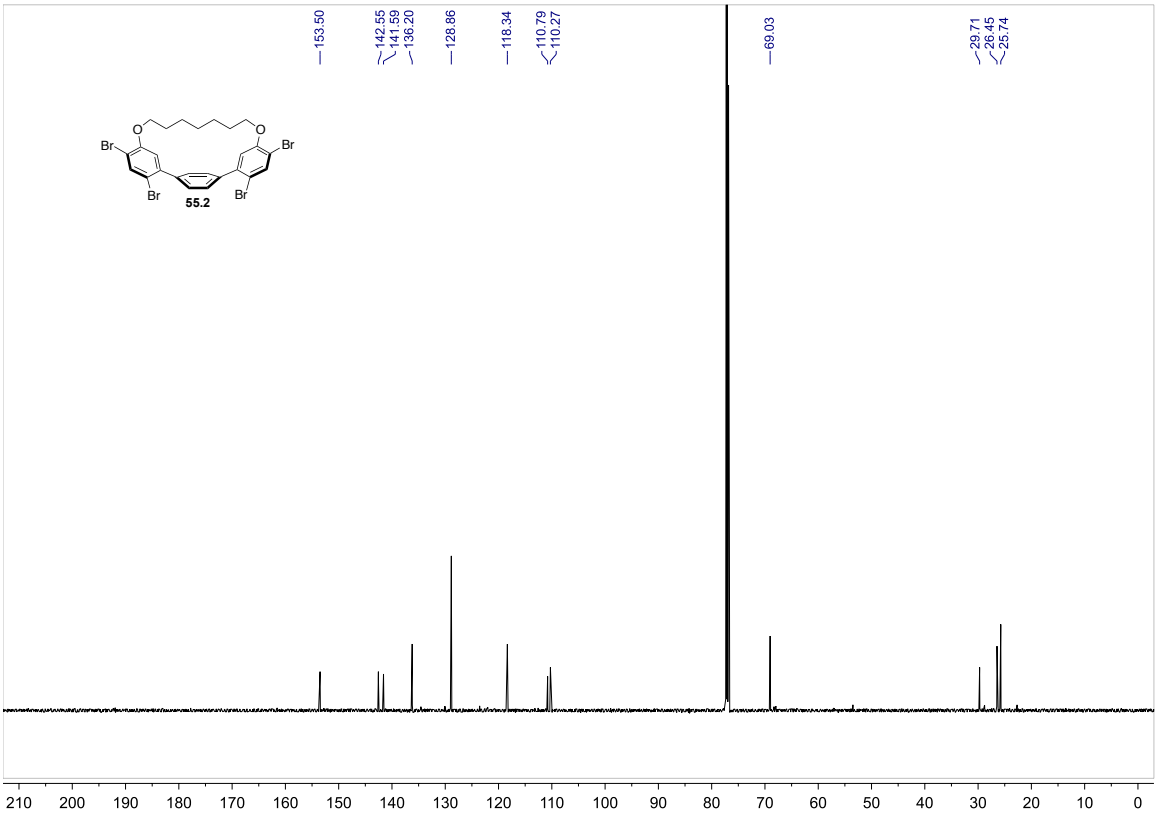
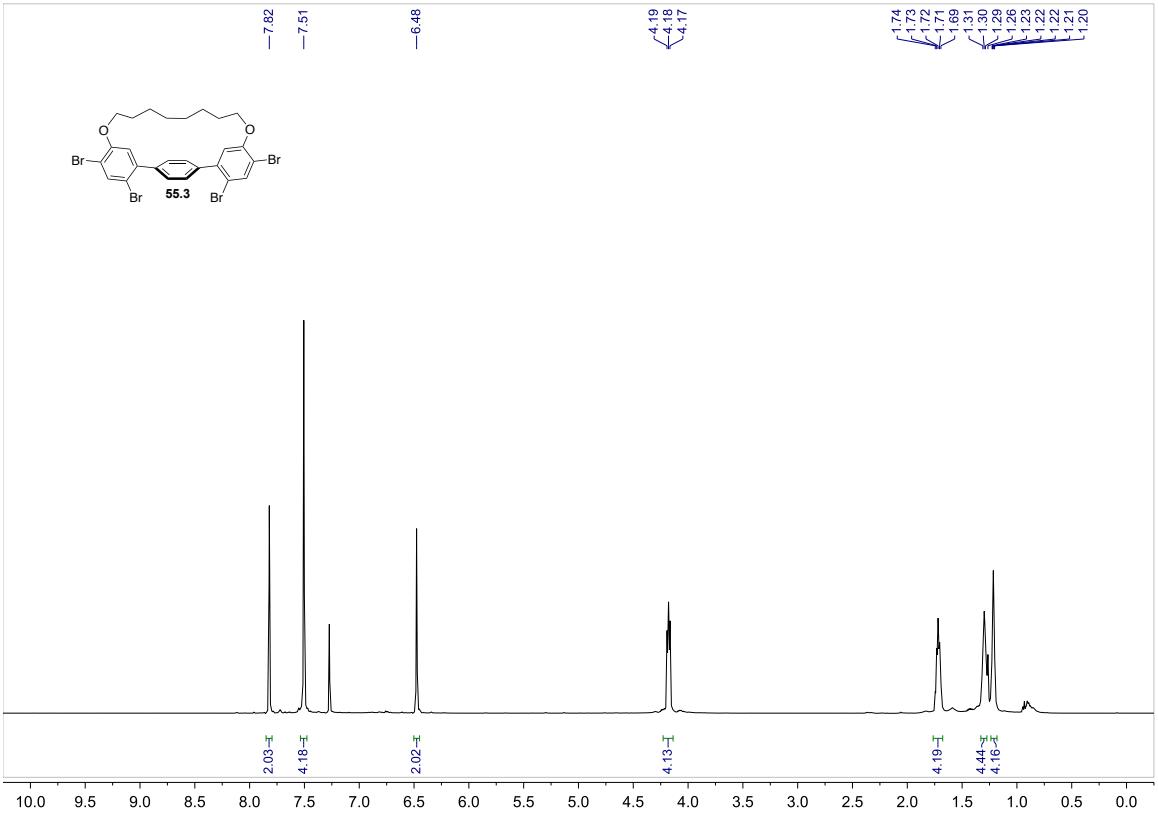
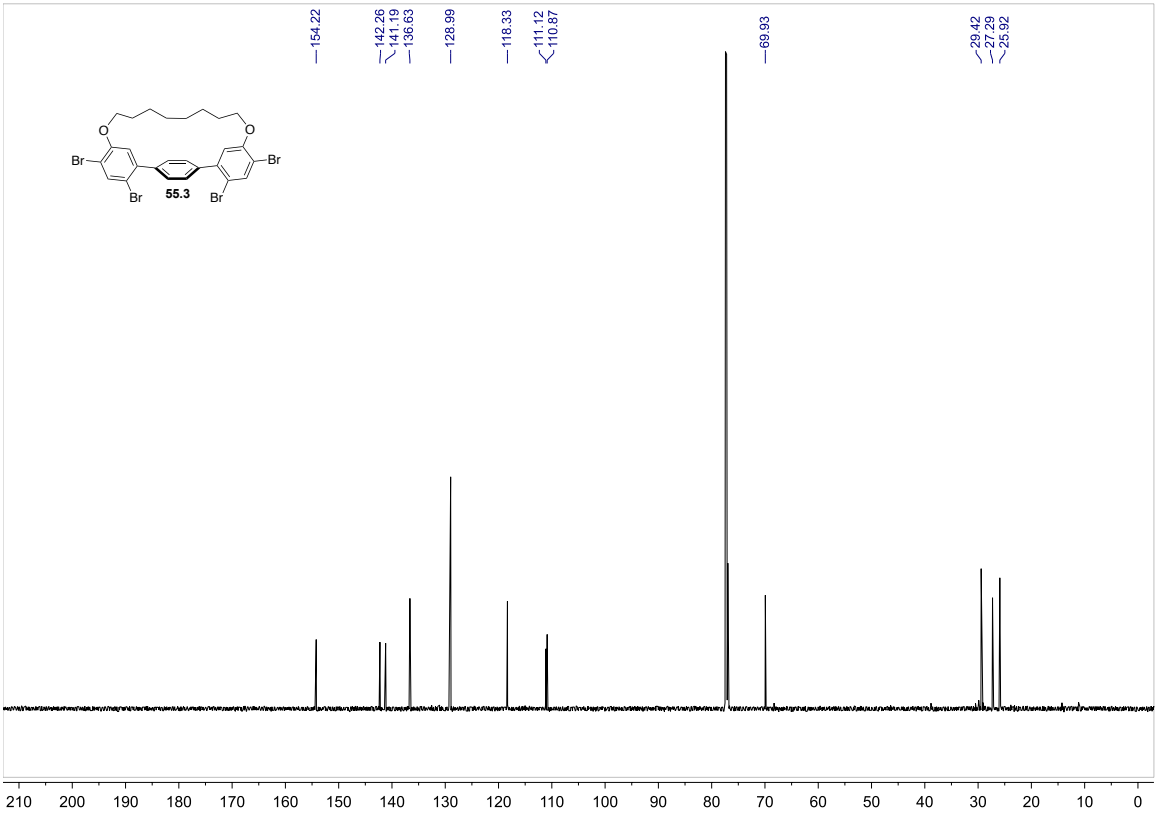
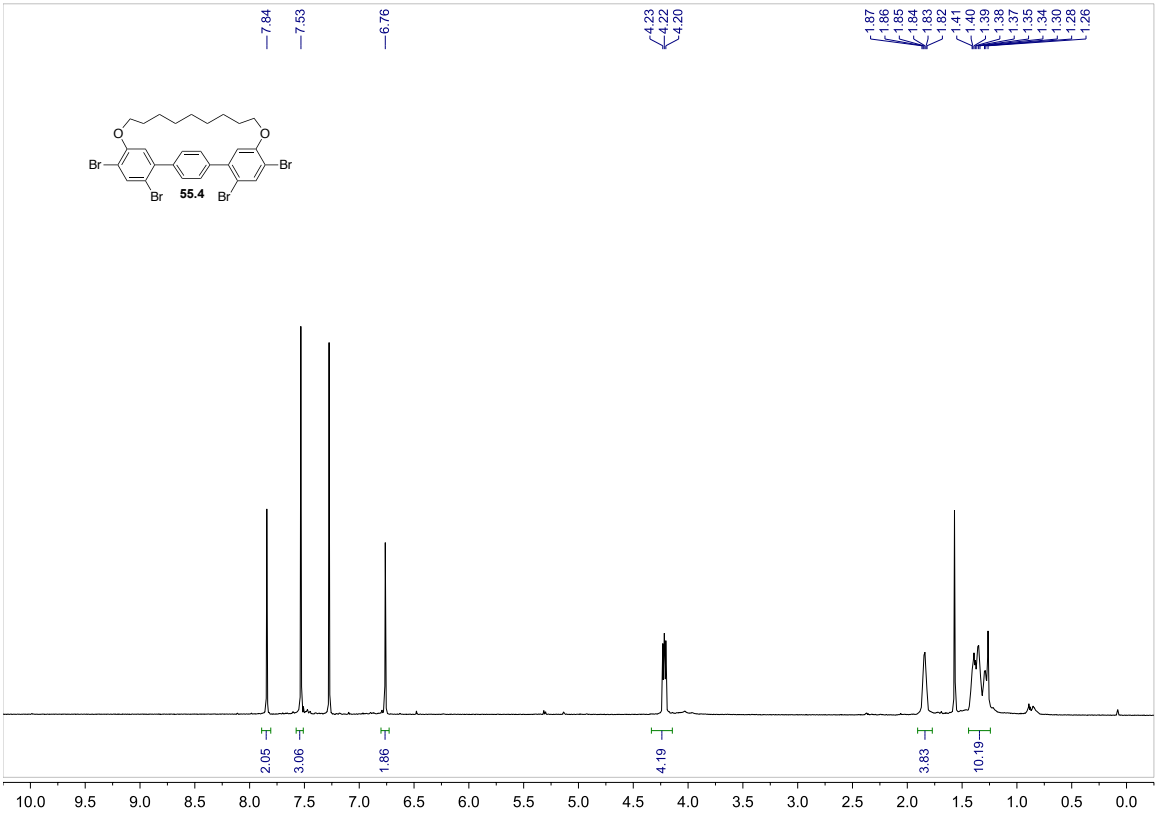
143.01
142.19
136.41
129.07
119.30
110.93
110.18
69.74
27.55
27.44
Br
Br
Br
Br
O
O
55.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

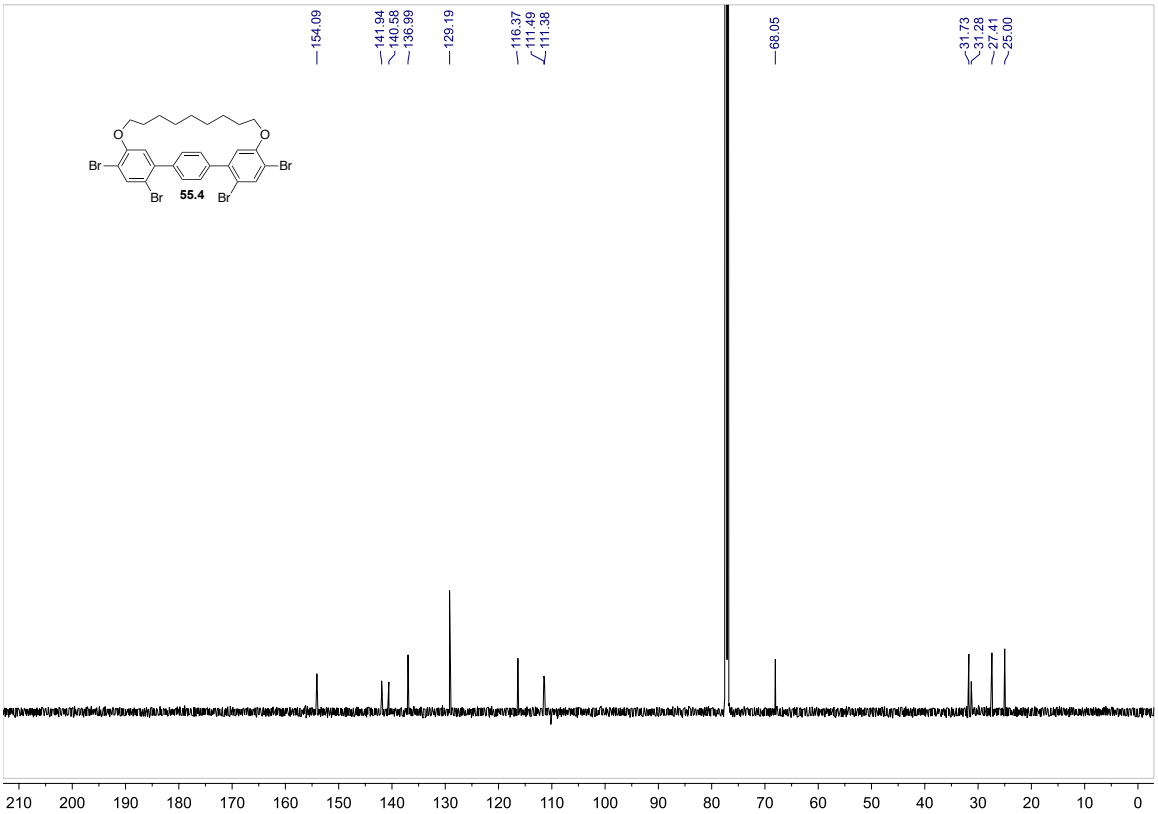

7.80
7.45
6.23
4.13
4.12
4.10
1.72
1.71
1.70
1.69
1.69
1.68
1.67
1.29
1.28
1.27
1.27
1.26
1.26
1.25
1.25
1.24
1.16
1.14
1.13
Br
Br
Br
Br
O
O
55.2
2.00
4.36
1.98
4.08
4.17
4.20
2.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

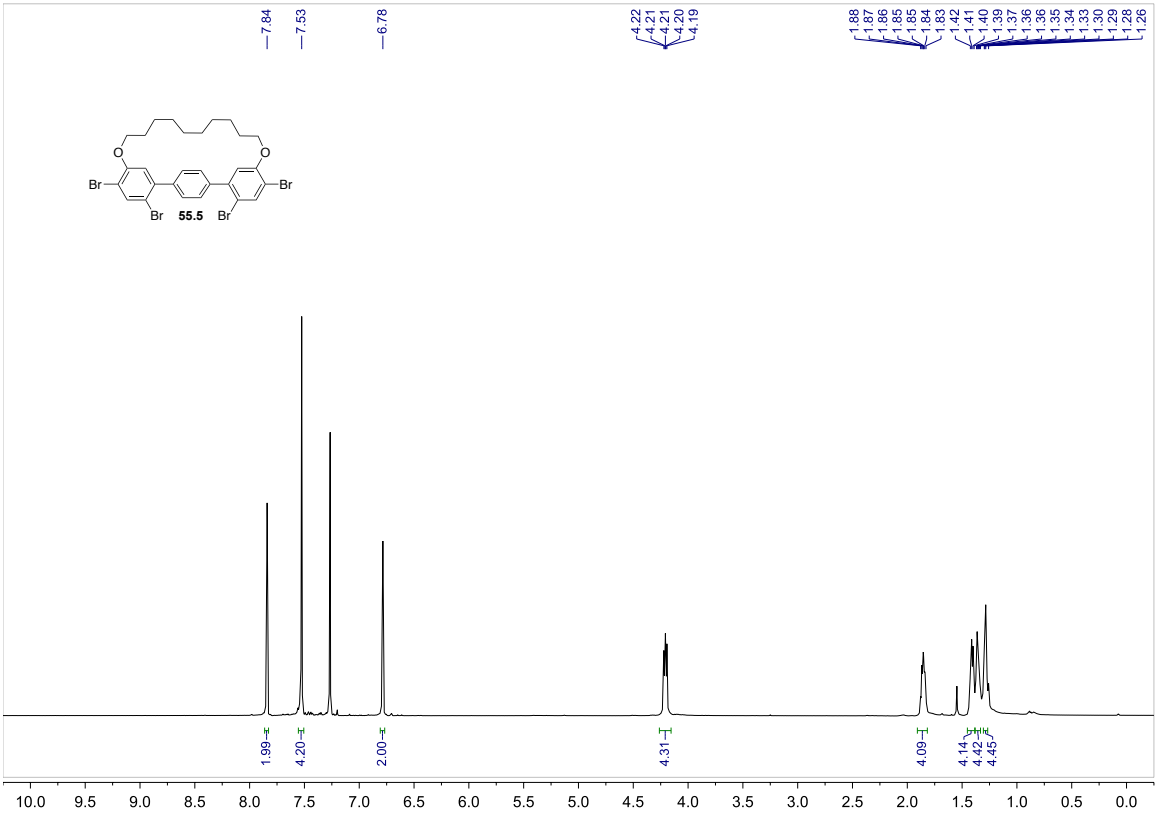

153.50
142.55
141.59
136.20
128.86
118.34
110.79
110.27
69.03
29.71
26.45
25.74
Br
Br
Br
Br
O
O
55.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

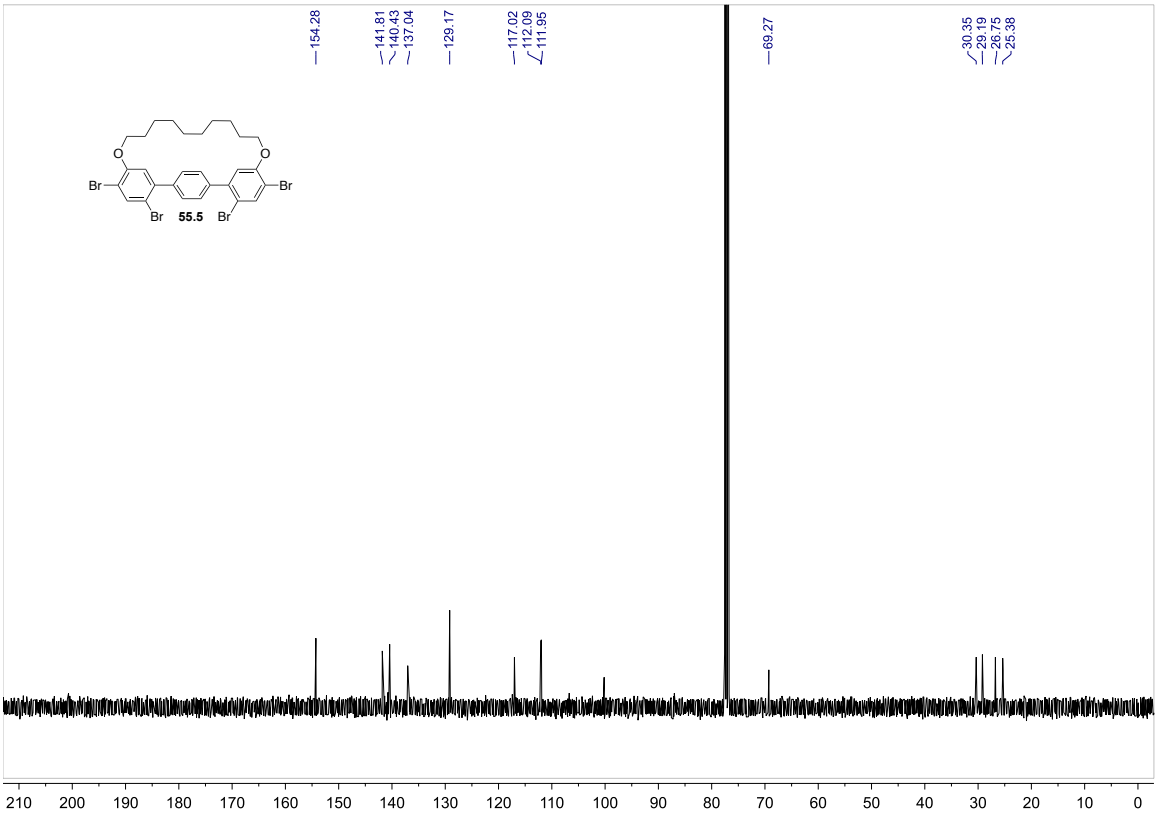

7.82
7.51
6.48
4.19
4.18
4.17
1.74
1.73
1.72
1.71
1.69
1.31
1.30
1.29
1.26
1.23
1.22
1.22
1.22
1.21
1.20
Br
Br
Br
Br
O
O
55.3
2.03
4.18
2.02
4.13
4.19
4.44
4.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

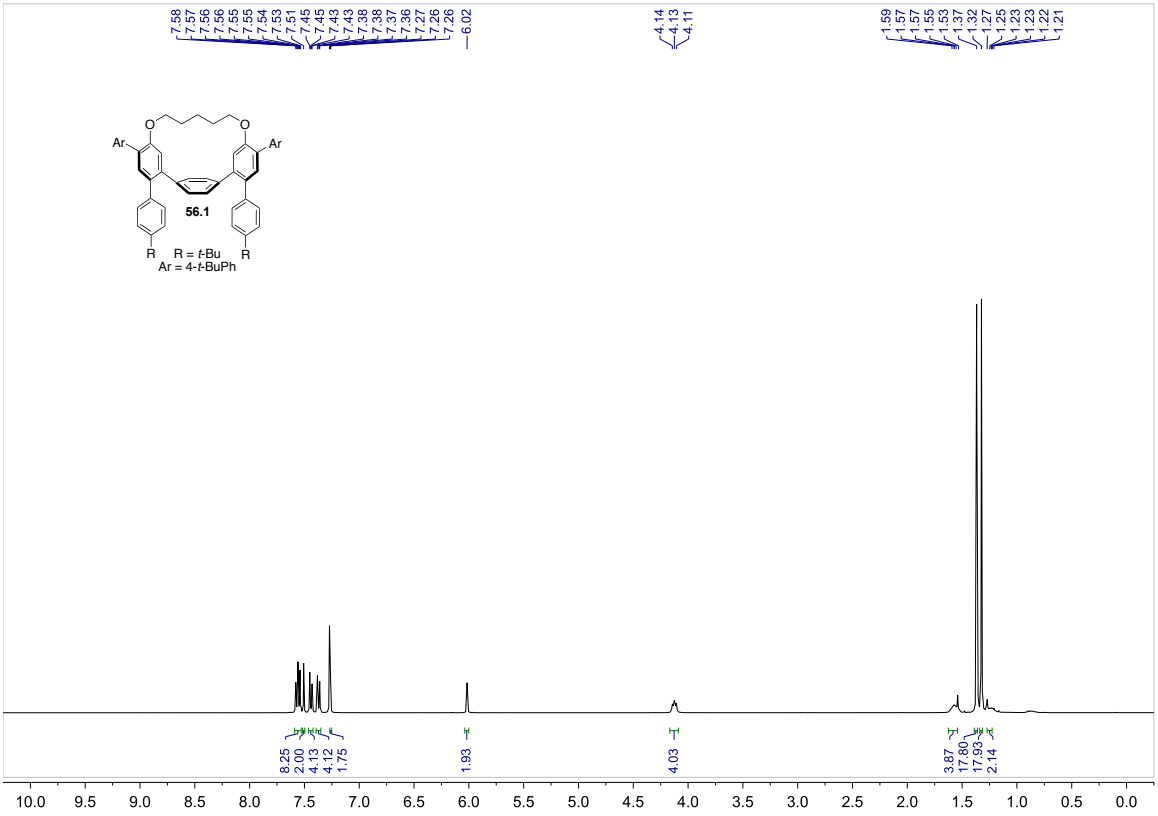

154.22
142.26
141.19
136.63
128.99
118.33
111.12
110.87
69.93
29.42
27.29
25.92
Br
Br
Br
Br
O
O
55.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

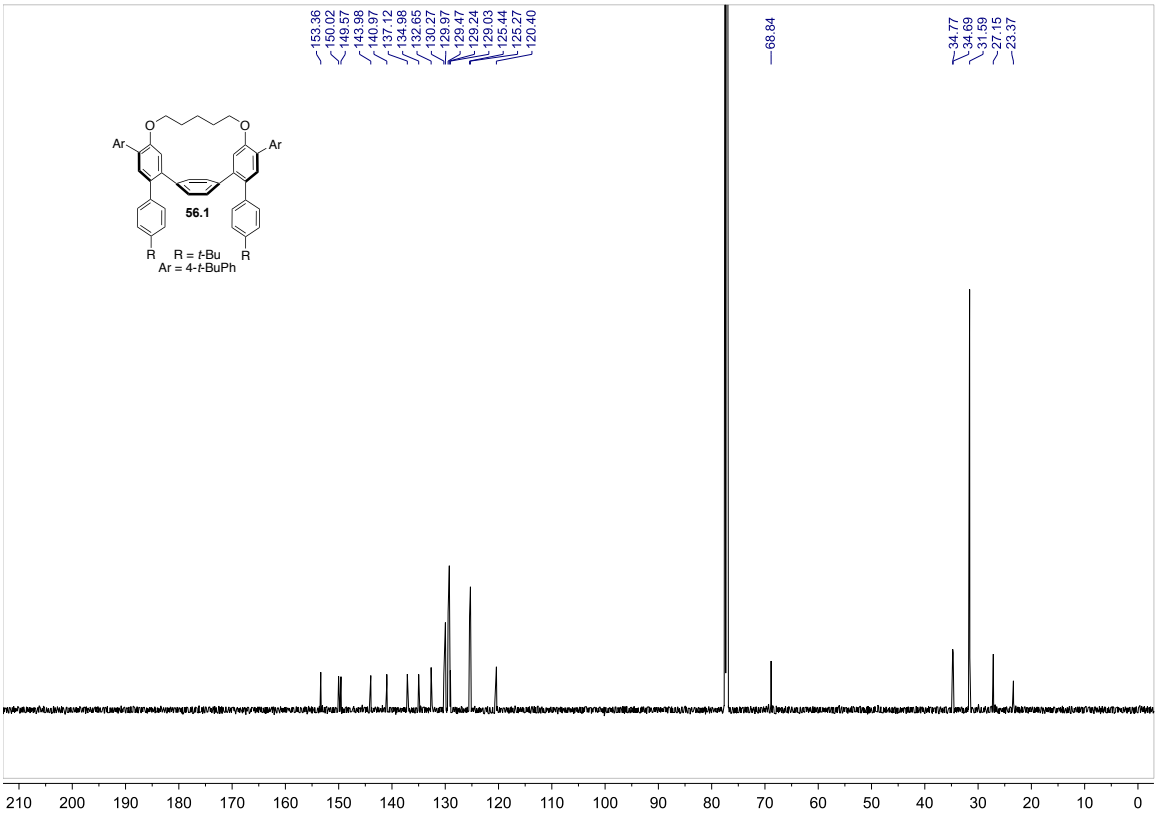

7.84
7.53
6.76
4.23
4.22
4.20
1.87
1.86
1.85
1.84
1.83
1.82
1.41
1.40
1.39
1.38
1.37
1.35
1.34
1.30
1.28
1.26
O
O
Br
Br
Br
Br
55.4
2.05
3.06
1.86
4.19
3.83
10.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


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
O
O
Br
Br
Br
Br
55.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


7.84
7.53
6.78
4.22
4.21
4.21
4.20
4.19
1.88
1.87
1.86
1.85
1.85
1.84
1.83
1.42
1.41
1.40
1.39
1.37
1.36
1.36
1.35
1.34
1.33
1.30
1.29
1.28
1.26
O
O
Br
Br
Br
55.5
Br
1.99
4.20
2.00
4.31
4.09
4.14
4.42
4.45
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


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
O
O
Br
Br
Br
55.5
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.58
7.57
7.56
7.56
7.55
7.55
7.54
7.53
7.51
7.45
7.45
7.43
7.43
7.38
7.38
7.37
7.36
7.27
7.26
7.26
6.02
4.14
4.13
4.11
1.59
1.57
1.57
1.55
1.53
1.37
1.32
1.27
1.25
1.23
1.23
1.22
1.21
Ar
O
O
Ar
56.1
R
R = t-Bu
Ar = 4-t-BuPh
R
8.25
2.00
4.13
4.12
1.75
1.93
4.03
3.87
17.80
17.93
2.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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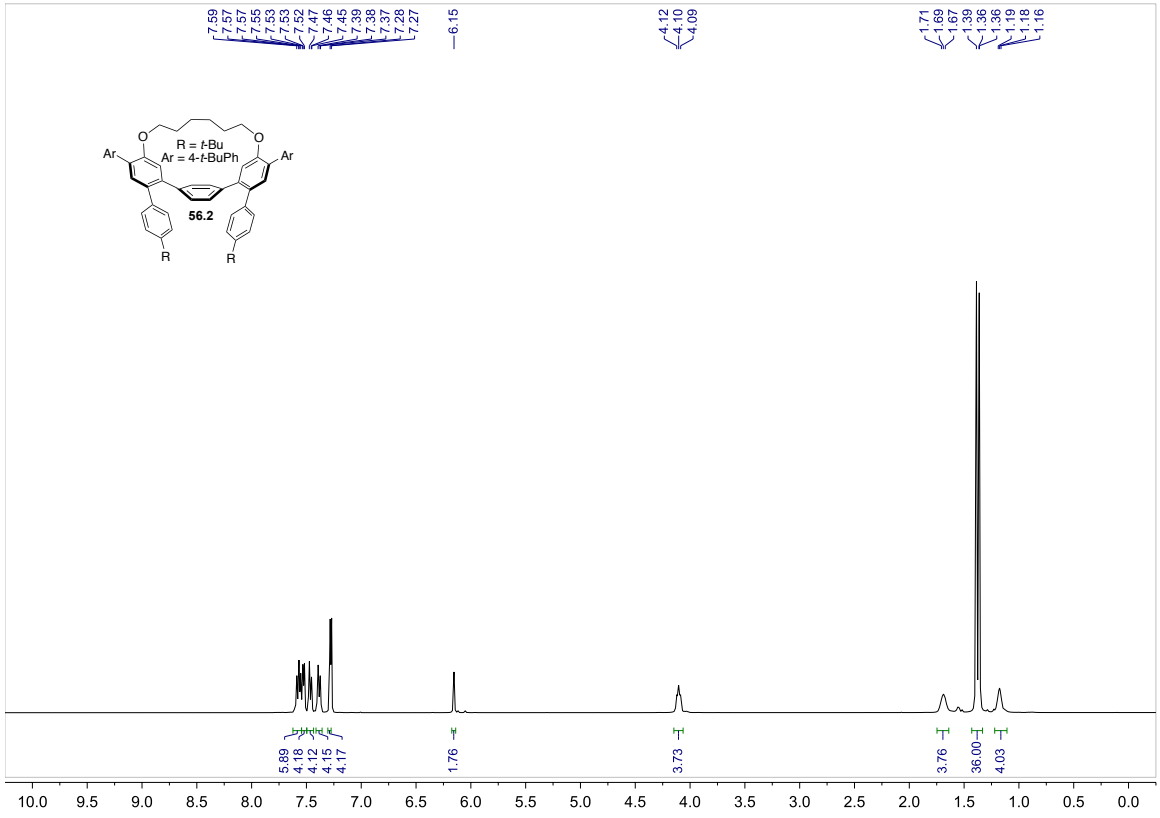
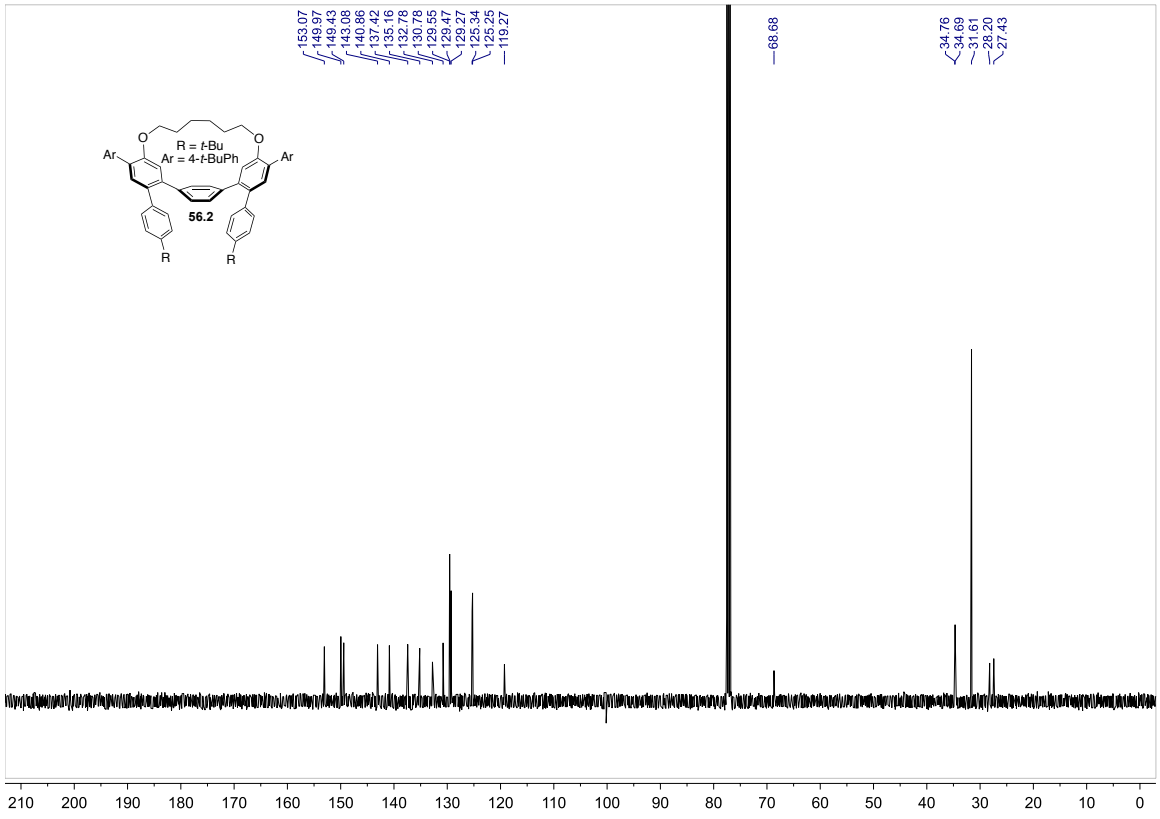
150.02
149.57
143.98
140.97
137.12
134.98
132.65
130.27
129.97
129.47
129.24
129.03
125.44
125.27
120.40
68.84
34.77
34.69
31.59
27.15
23.37
Ar
O
O
Ar
56.1
R
R = t-Bu
Ar = 4-t-BuPh
R
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.59
7.57
7.57
7.55
7.53
7.53
7.52
7.47
7.46
7.45
7.39
7.38
7.37
7.28
7.27
6.15
4.12
4.10
4.09
1.71
1.69
1.67
1.39
1.36
1.36
1.19
1.18
1.16
R = t-Bu
Ar = 4-t-BuPh
56.2
5.89
4.18
4.12
4.15
4.17
1.76
3.73
3.76
36.00
4.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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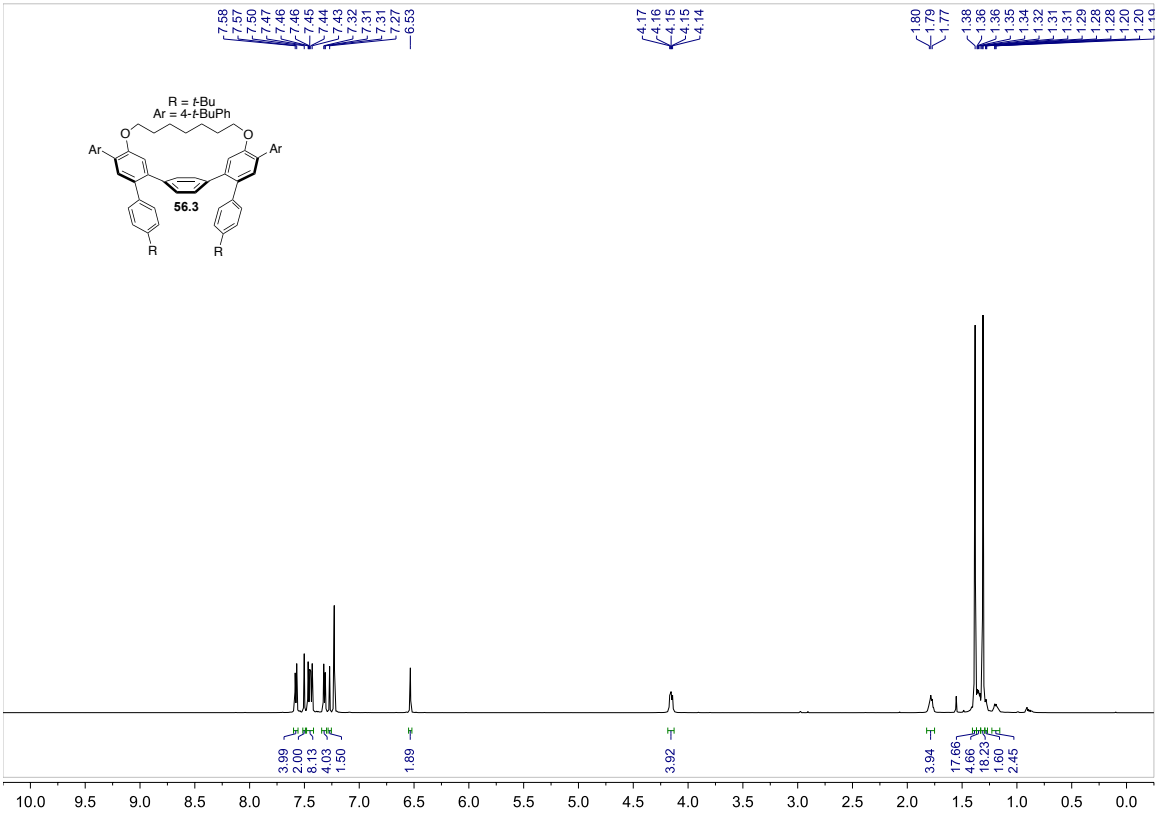
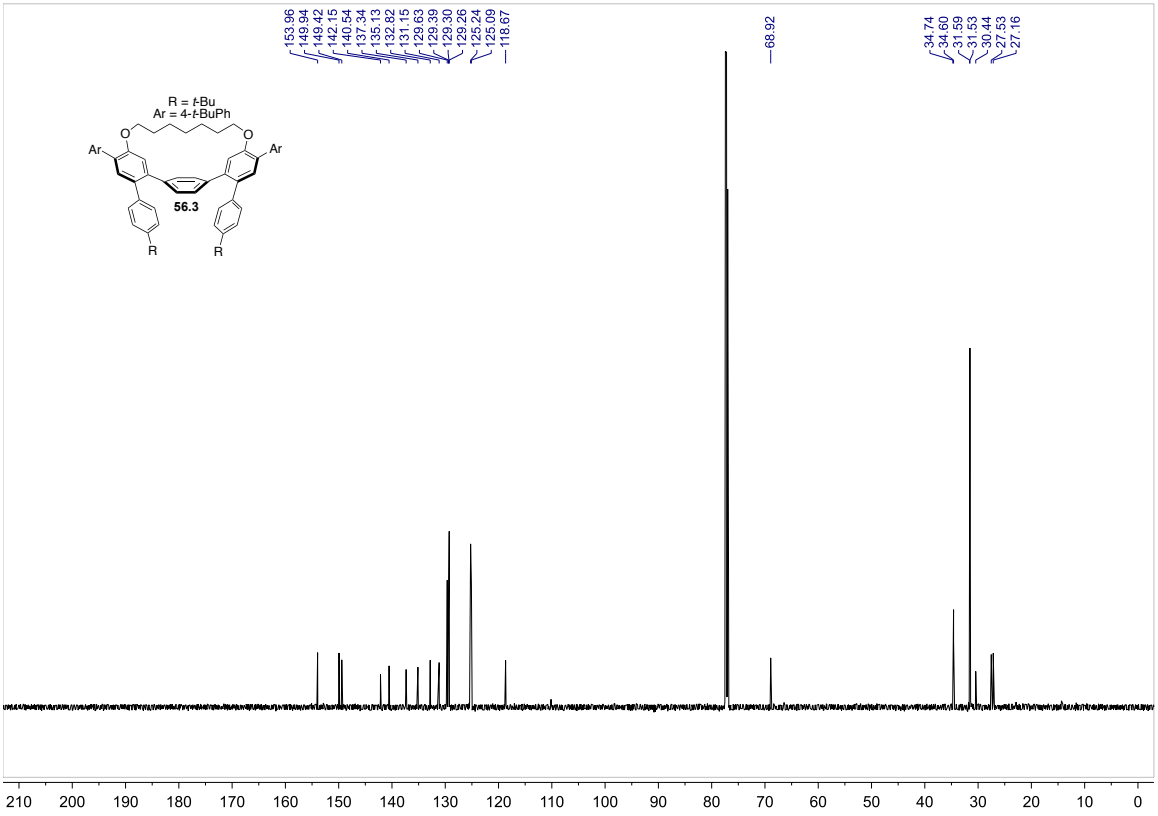
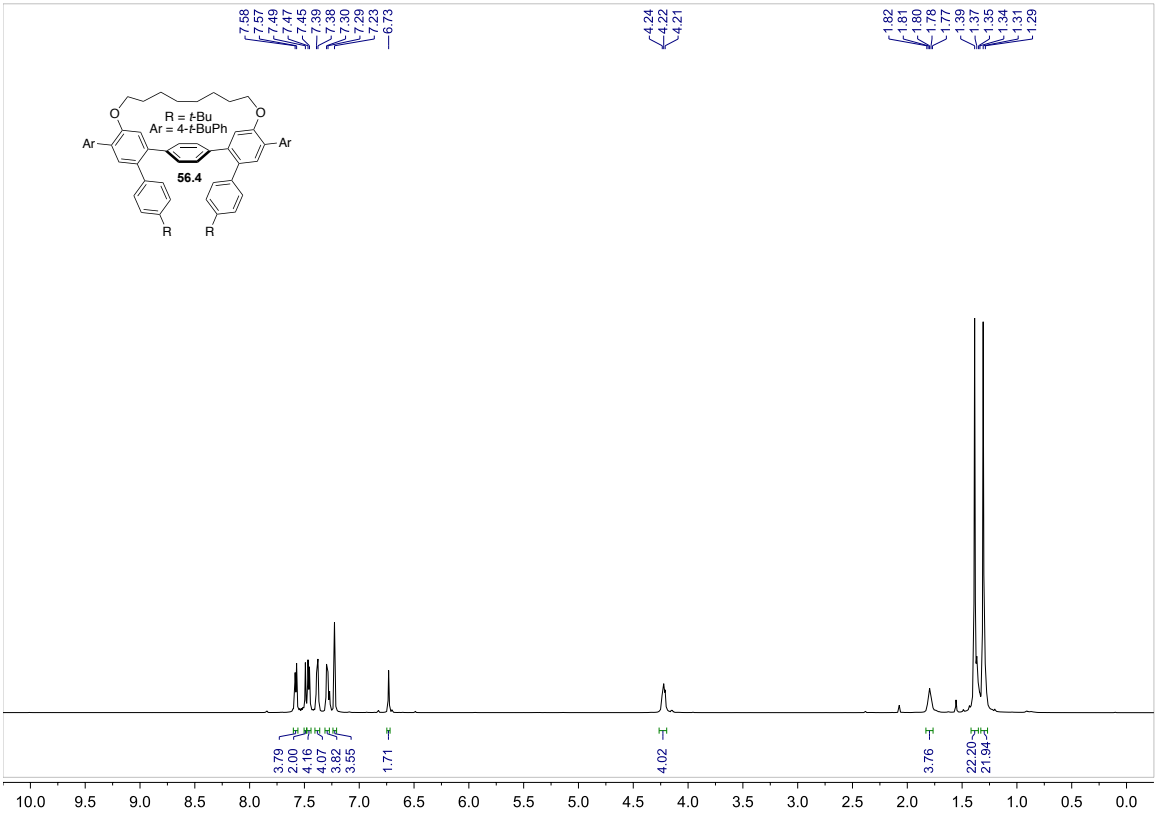
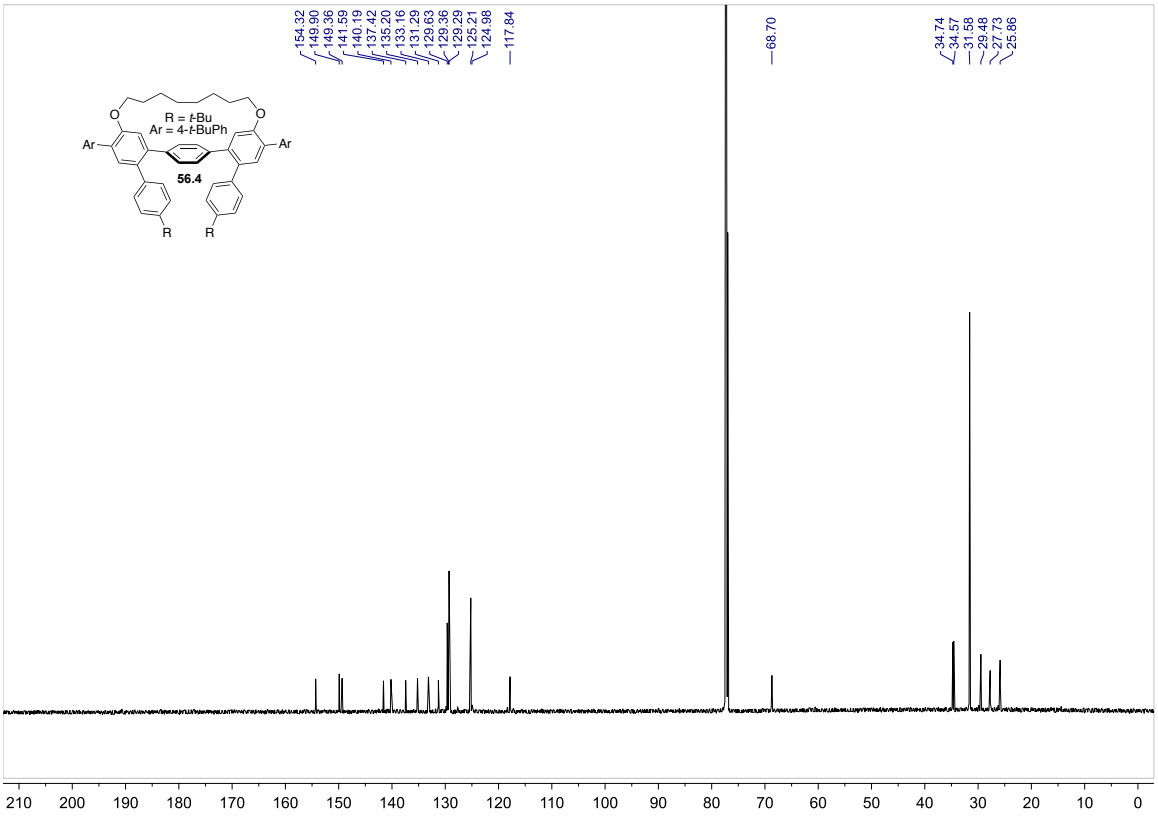
149.97
149.43
143.08
140.86
137.42
135.16
132.78
130.78
129.55
129.47
129.27
125.34
125.25
119.27
68.68
34.76
34.69
31.61
28.20
27.43
R = t-Bu
Ar = 4-t-BuPh
56.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


R = t-Bu
Ar = 4-t-BuPh
56.3
7.58
7.57
7.50
7.47
7.46
7.46
7.45
7.44
7.43
7.32
7.31
7.31
7.27
6.53
4.17
4.16
4.15
4.15
4.14
1.80
1.79
1.77
1.38
1.36
1.36
1.35
1.34
1.32
1.31
1.31
1.29
1.28
1.28
1.20
1.20
3.99
2.00
8.13
4.03
1.50
1.89
3.92
3.94
17.66
4.66
18.23
1.60
2.45


R = t-Bu
Ar = 4-t-BuPh
56.3
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


7.58
7.57
7.49
7.47
7.45
7.39
7.38
7.30
7.29
7.23
6.73
4.24
4.22
4.21
1.82
1.81
1.80
1.78
1.77
1.39
1.37
1.35
1.34
1.31
1.29
R = t-Bu
Ar = 4-t-BuPh
56.4
3.79
2.00
4.16
4.07
3.82
3.55
1.71
4.02
3.76
22.20
21.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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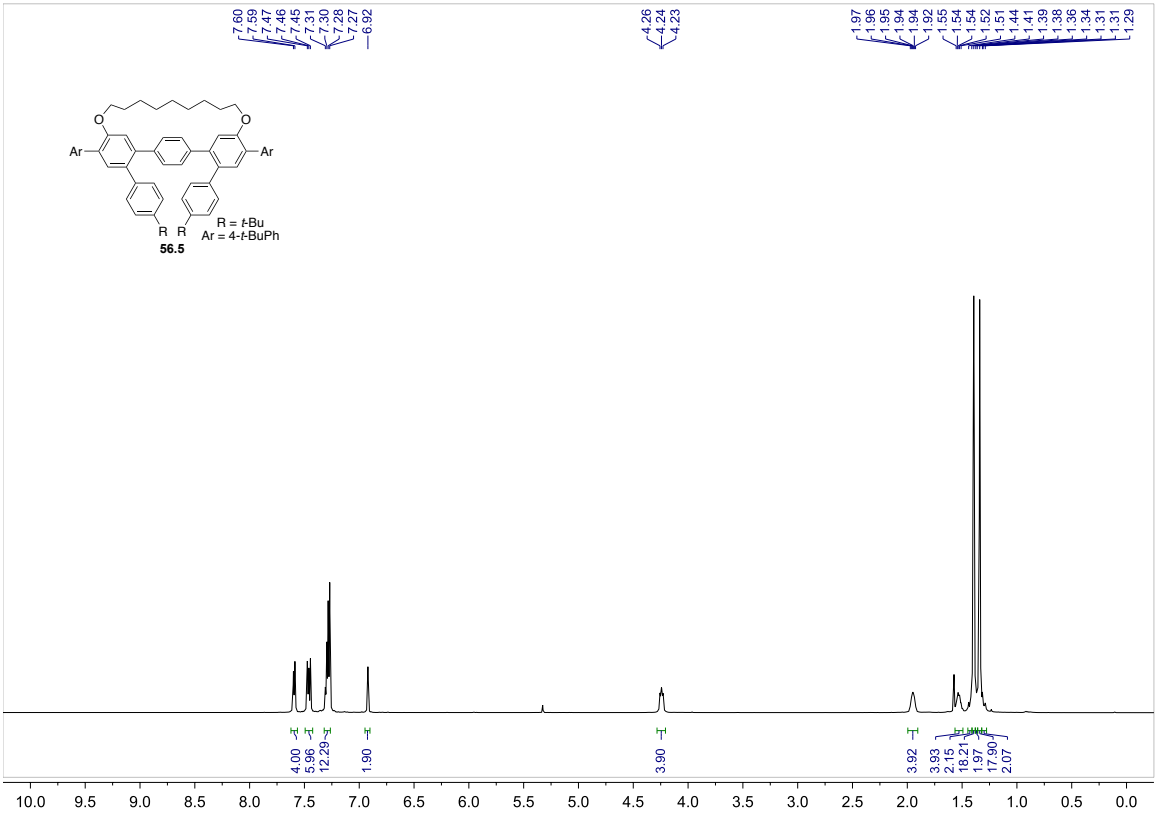
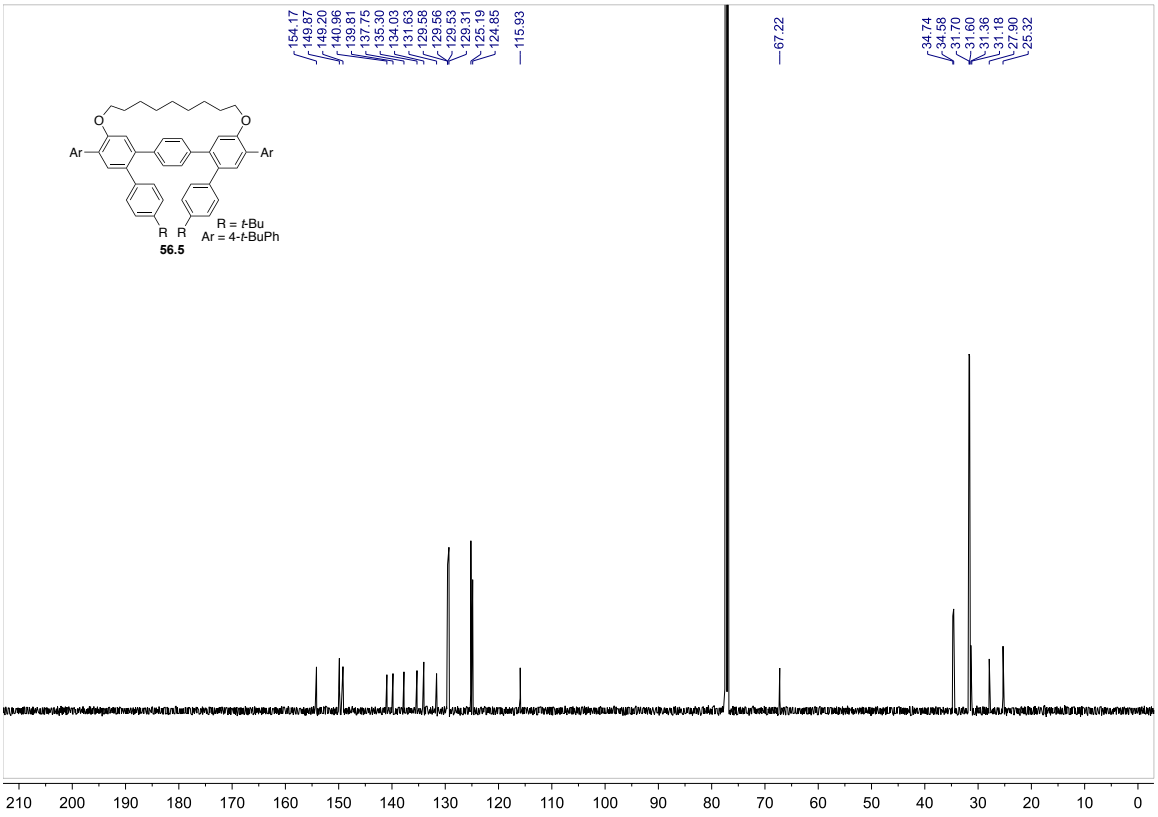
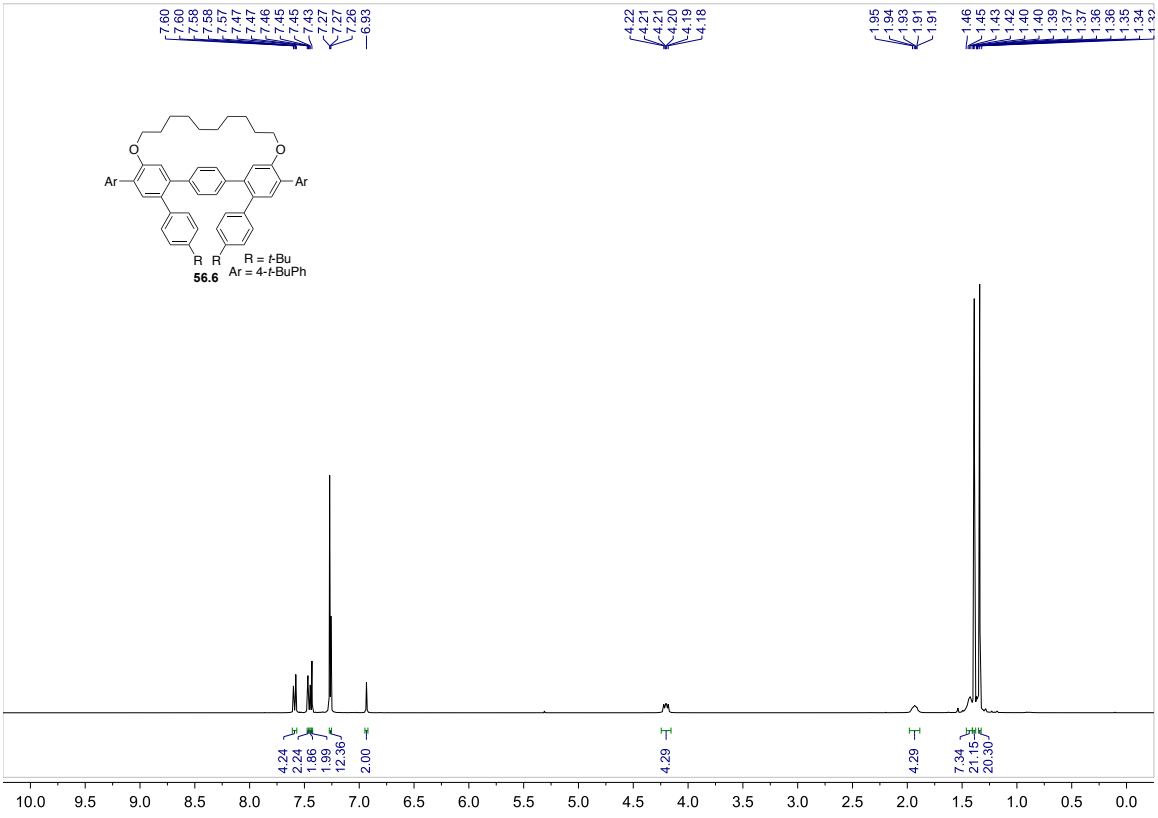
149.90
149.36
141.59
140.19
137.42
135.20
133.16
131.29
129.63
129.36
129.29
125.21
124.98
117.84
68.70
34.74
34.57
31.58
29.48
27.73
25.86
R = t-Bu
Ar = 4-t-BuPh
56.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


7.60
7.59
7.47
7.46
7.45
7.31
7.30
7.28
7.27
6.92
4.26
4.24
4.23
1.97
1.96
1.95
1.94
1.94
1.92
1.55
1.54
1.54
1.52
1.51
1.44
1.41
1.39
1.38
1.36
1.34
1.31
1.31
1.29
Ar
Ar
R R
R = t-Bu
Ar = 4-t-BuPh
56.5
4.00
5.96
12.29
1.90
3.90
3.92
3.93
2.15
18.21
1.97
17.90
2.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


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
Ar
Ar
R R
R = t-Bu
Ar = 4-t-BuPh
56.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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4.18
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1.93
1.91
1.91
1.46
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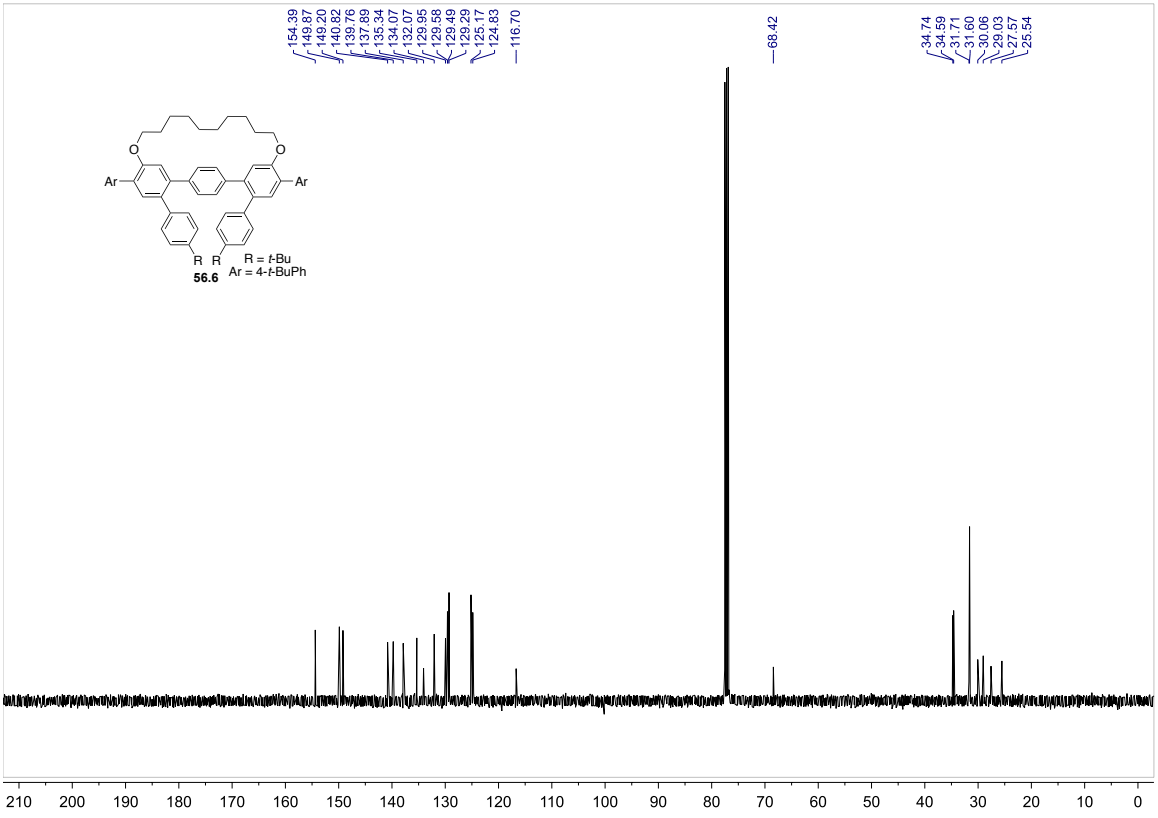
1.43
1.42
1.40
1.40
1.39
1.37
1.37
1.36
1.36
1.35
1.34
O
O
Ar
Ar
R R
R = t-Bu
Ar = 4-t-BuPh
56.6
4.24
2.24
1.86
1.99
12.36
2.00
4.29
4.29
7.34
21.15
20.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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124.83
116.70
68.42
34.74
34.59
31.71
31.60
30.06
29.03
27.57
25.54
O
O
Ar
Ar
R R
R = t-Bu
Ar = 4-t-BuPh
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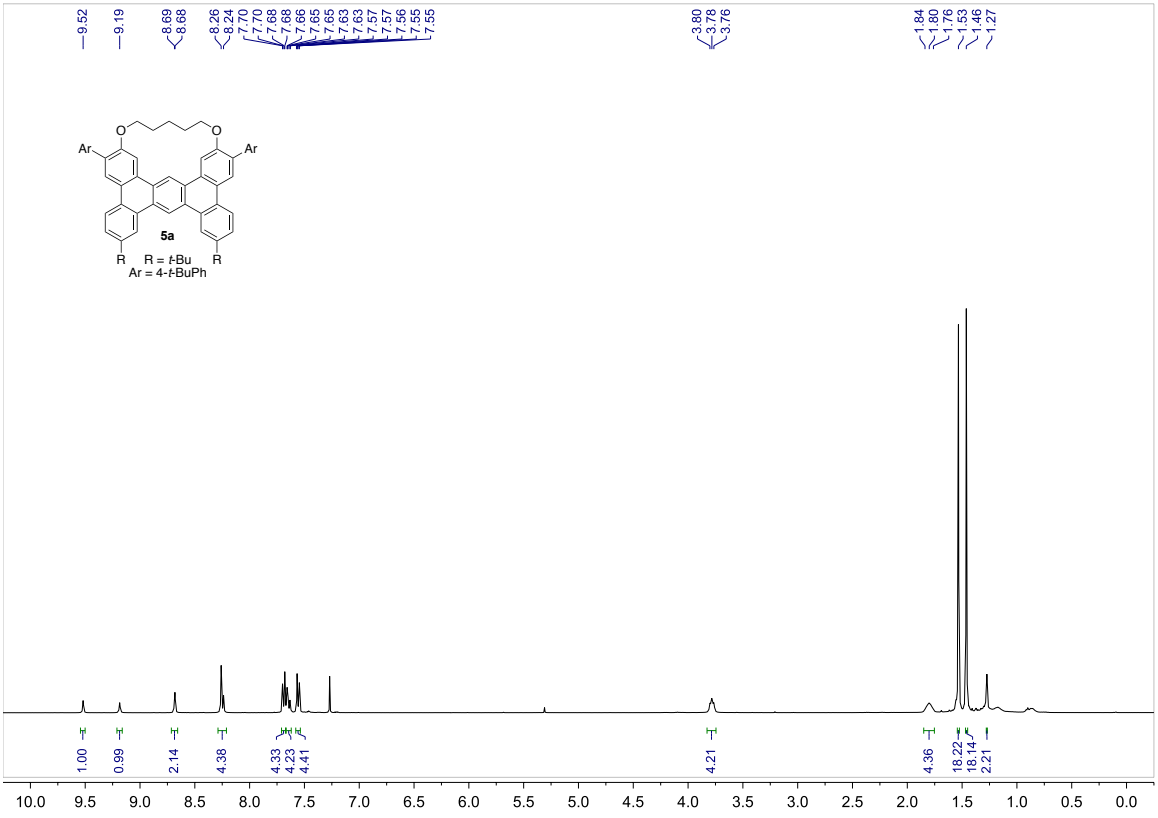
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7.56
7.55
3.80
3.78
3.76
1.84
1.80
1.76
1.53
1.46
1.27
Ar
Ar
O
O
R
R
5a
R = t-Bu
Ar = 4-t-BuPh
1.00
0.99
2.14
4.38
4.33
4.23
4.41
4.21
4.36
18.22
18.14
2.21
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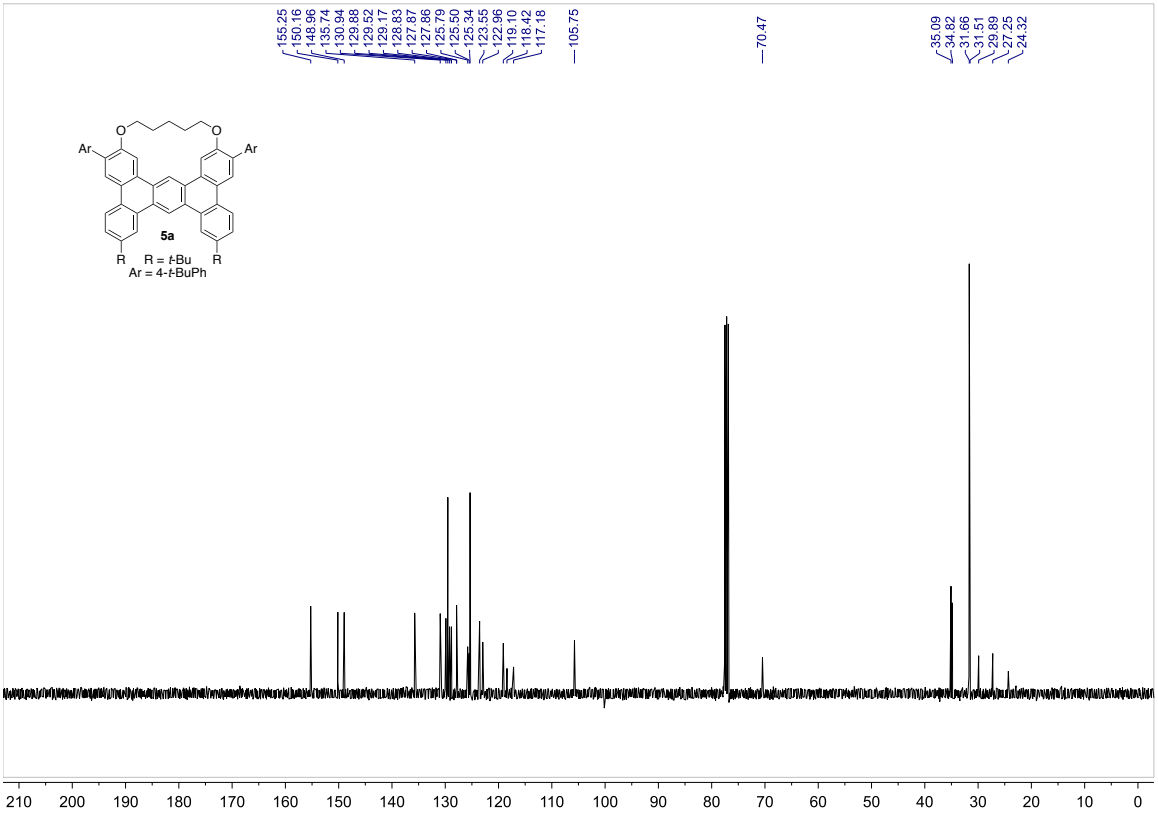
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119.10
118.42
117.18
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34.82
31.66
31.51
29.89
27.25
24.32
Ar
Ar
O
O
R
R
5a
R = t-Bu
Ar = 4-t-BuPh
210
200
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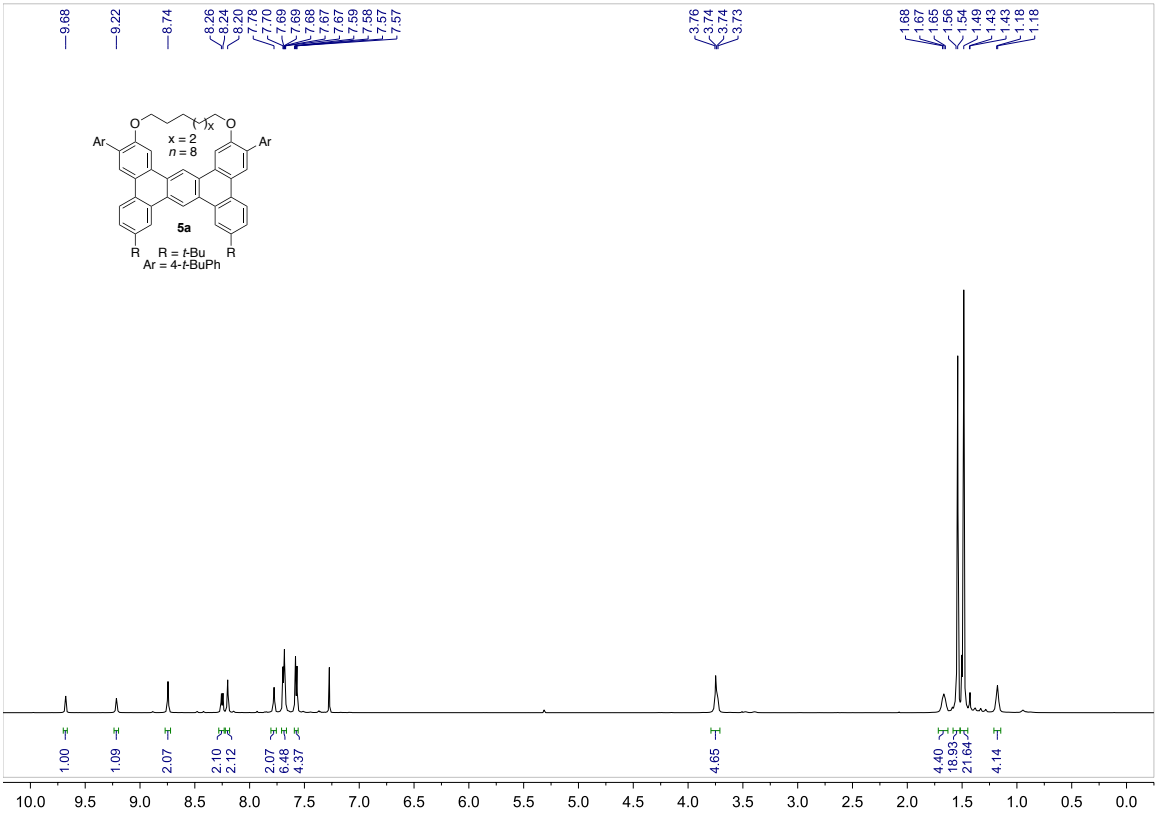
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7.59
7.58
7.57
7.57
3.76
3.74
3.74
3.73
1.68
1.67
1.65
1.56
1.54
1.49
1.43
1.43
1.18
1.18
x = 2
n = 8
5a
R = t-Bu
Ar = 4-t-BuPh
1.00
1.09
2.07
2.10
2.12
2.07
6.48
4.37
4.65
4.40
18.93
21.64
4.14
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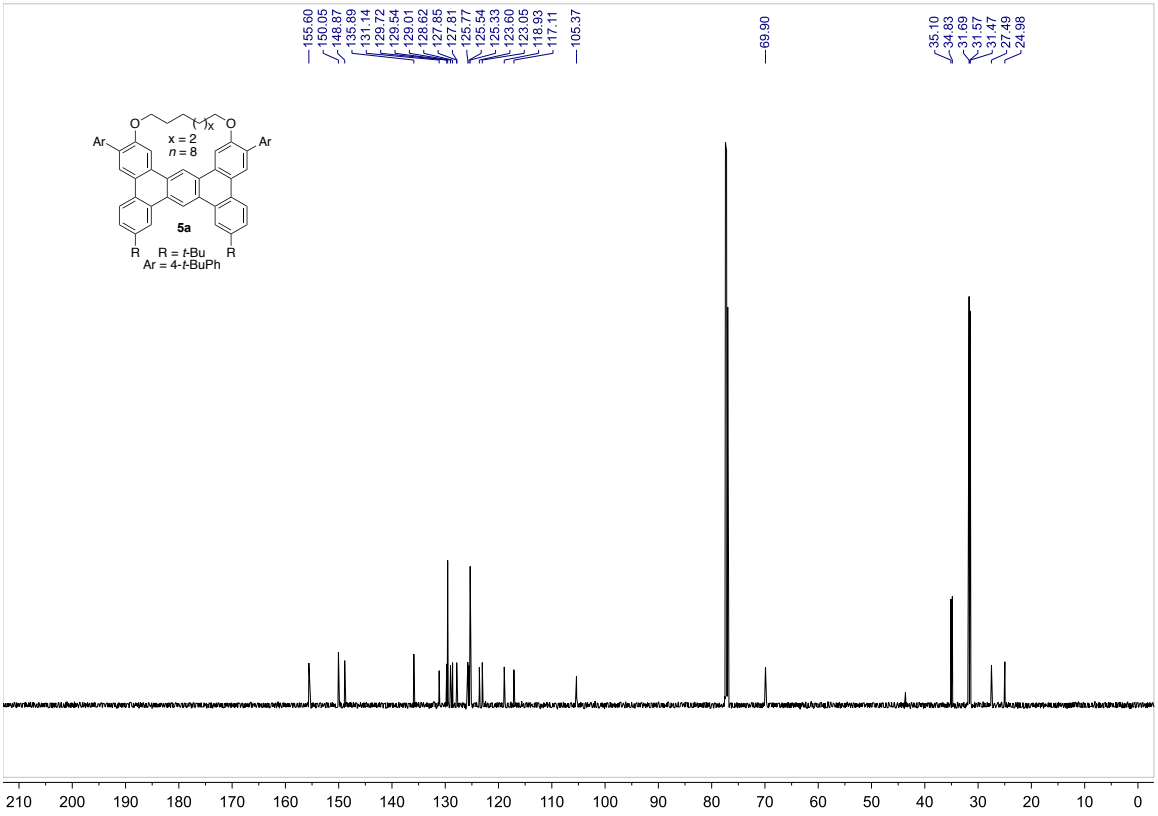
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123.60
123.05
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117.11
105.37
69.90
35.10
34.83
31.69
31.57
31.47
27.49
24.98
x = 2
n = 8
5a
R = t-Bu
Ar = 4-t-BuPh
210
200
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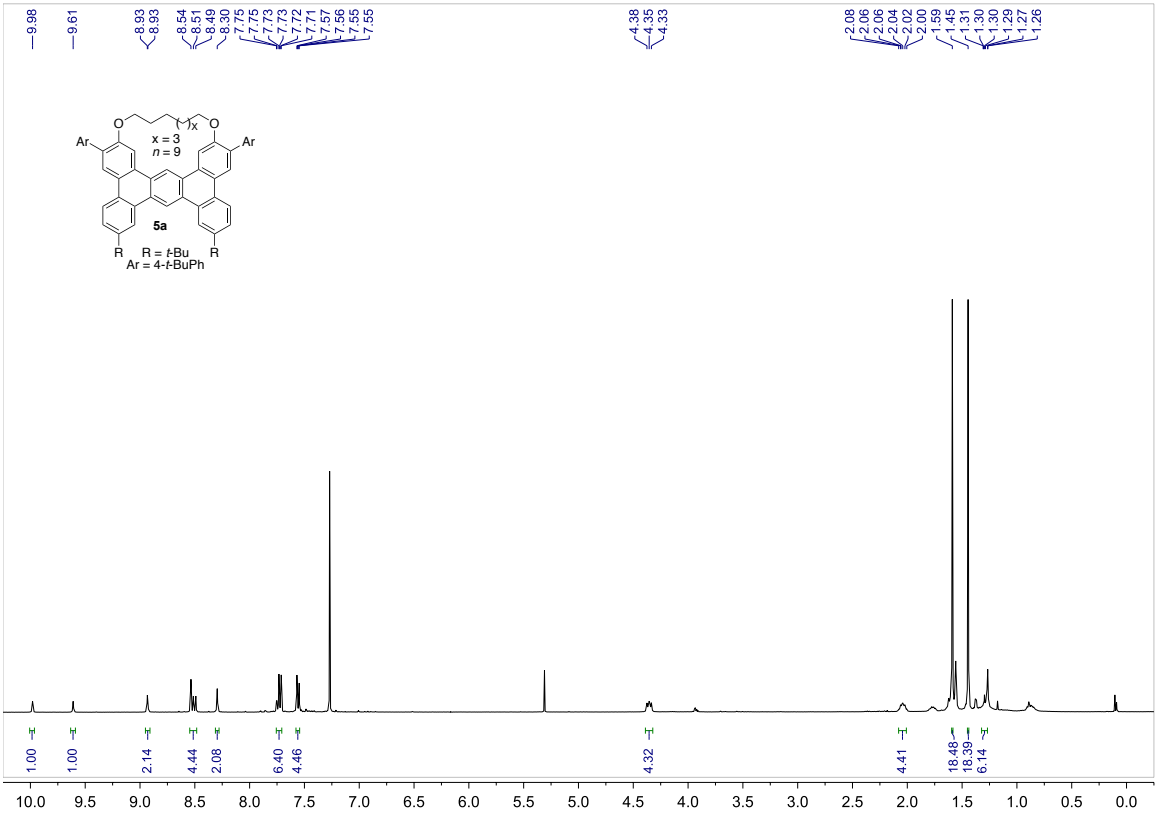
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2.06
2.06
2.04
2.02
2.00
1.59
1.45
1.31
1.30
1.30
1.29
1.27
1.26
x = 3
n = 9
5a
R = t-Bu
Ar = 4-t-BuPh
1.00
1.00
2.14
4.44
2.08
6.40
4.46
4.32
4.41
18.48
18.39
6.14
10.0
9.5
9.0
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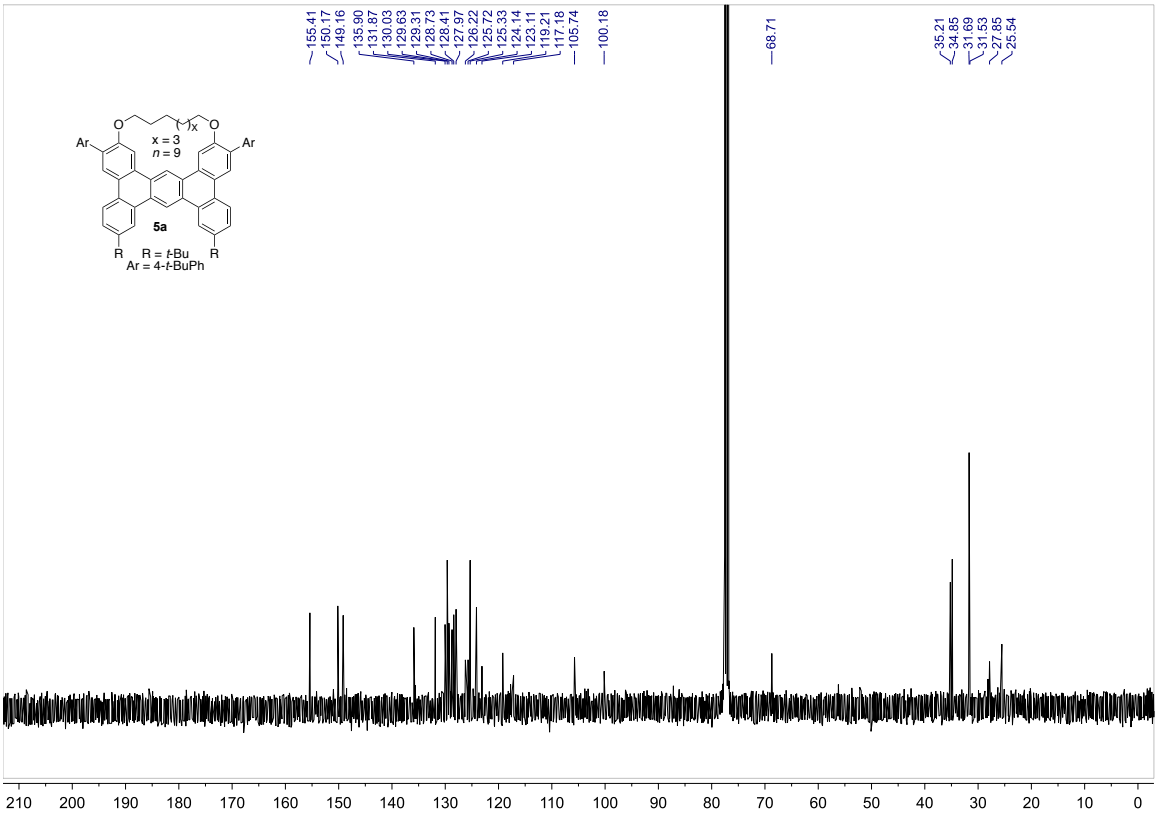
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123.11
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31.53
27.85
25.54
x = 3
n = 9
5a
R = t-Bu
Ar = 4-t-BuPh
210
200
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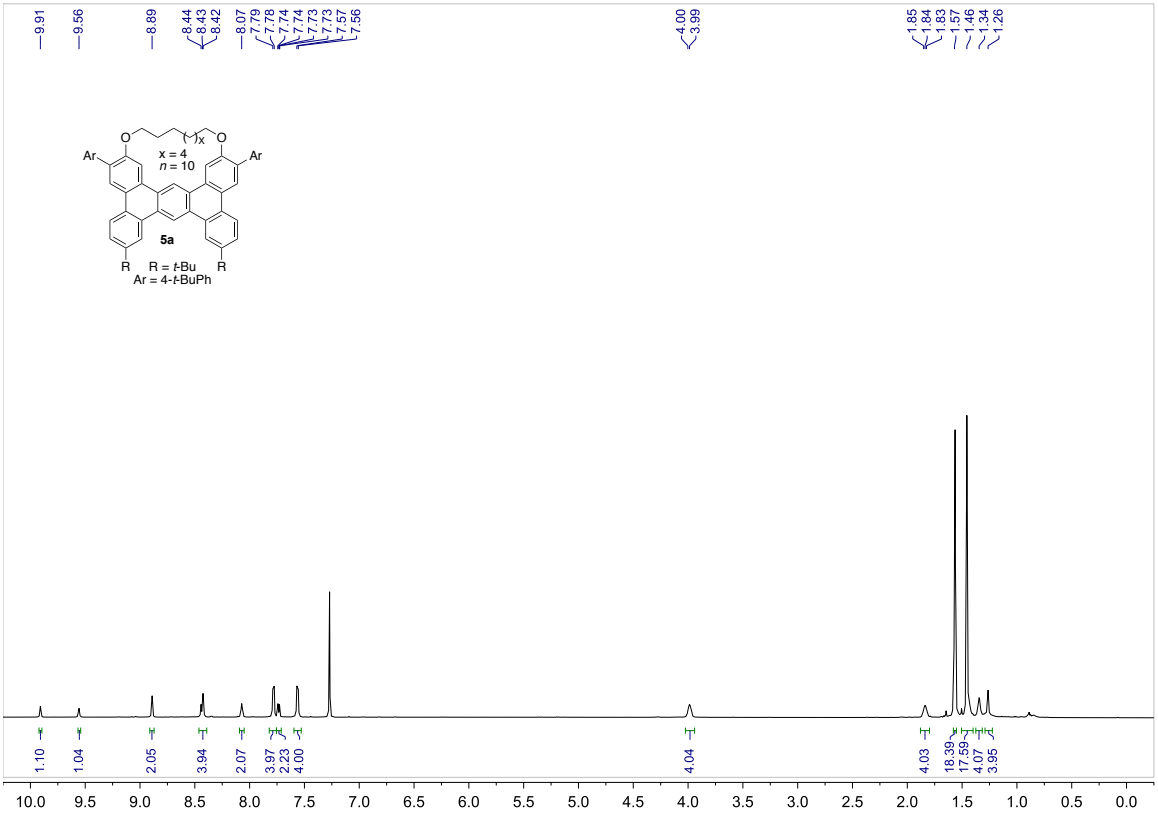
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7.57
7.56
4.00
3.99
1.85
1.84
1.83
1.57
1.46
1.34
1.26
x = 4
n = 10
5a
R = t-Bu
Ar = 4-t-BuPh
1.10
1.04
2.05
3.94
2.07
3.97
2.23
4.00
4.04
4.03
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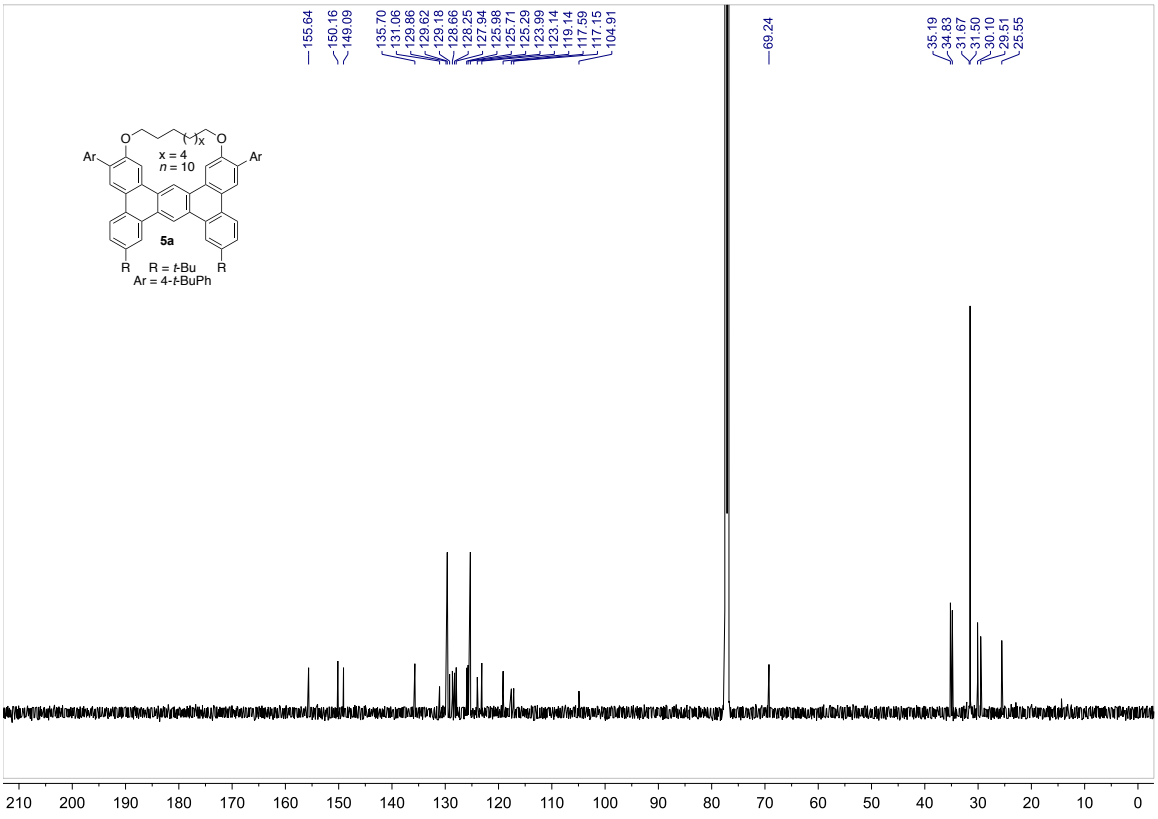
4.07
3.95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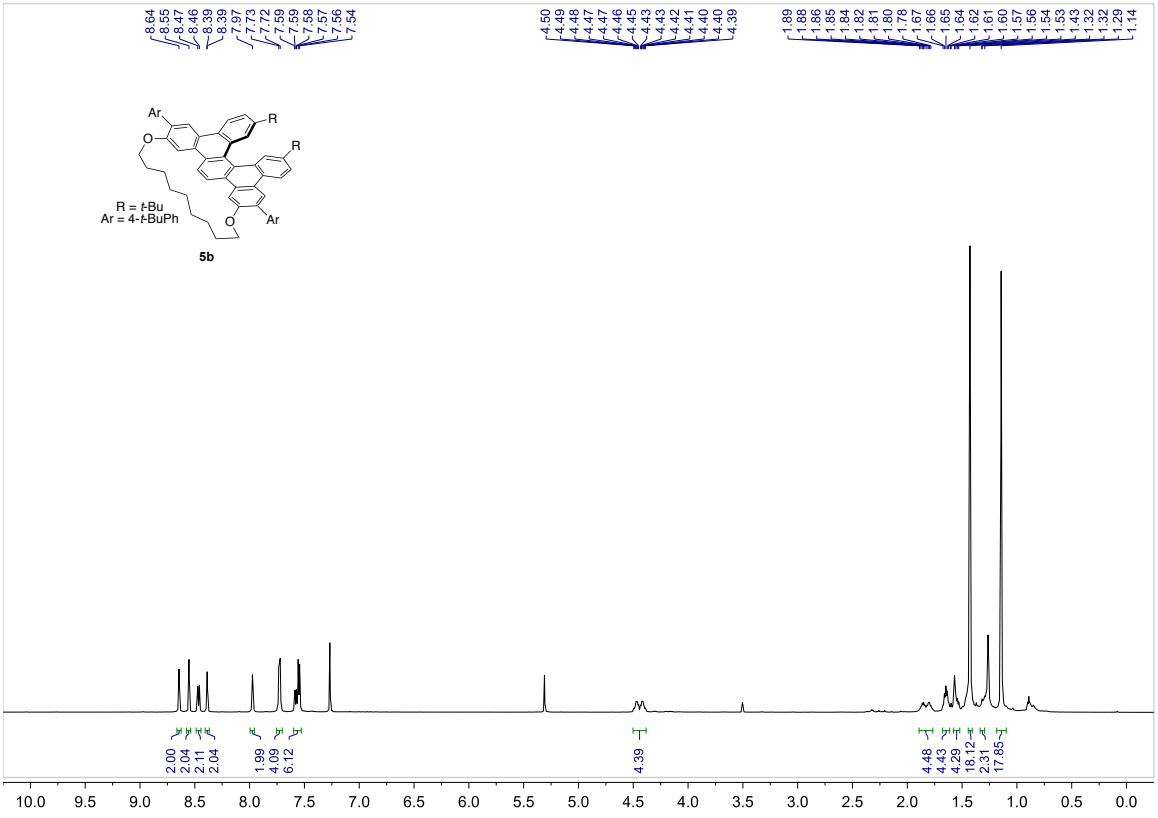
x = 4
n = 10
5a
R = t-Bu
Ar = 4-t-BuPh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1.43
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1.32
1.29
1.14
Ar
O
R
R
R = t-Bu
Ar = 4-t-BuPh
O
Ar
5b
2.00
2.04
2.11
2.04
1.99
4.09
6.12
4.39
4.48
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4.29
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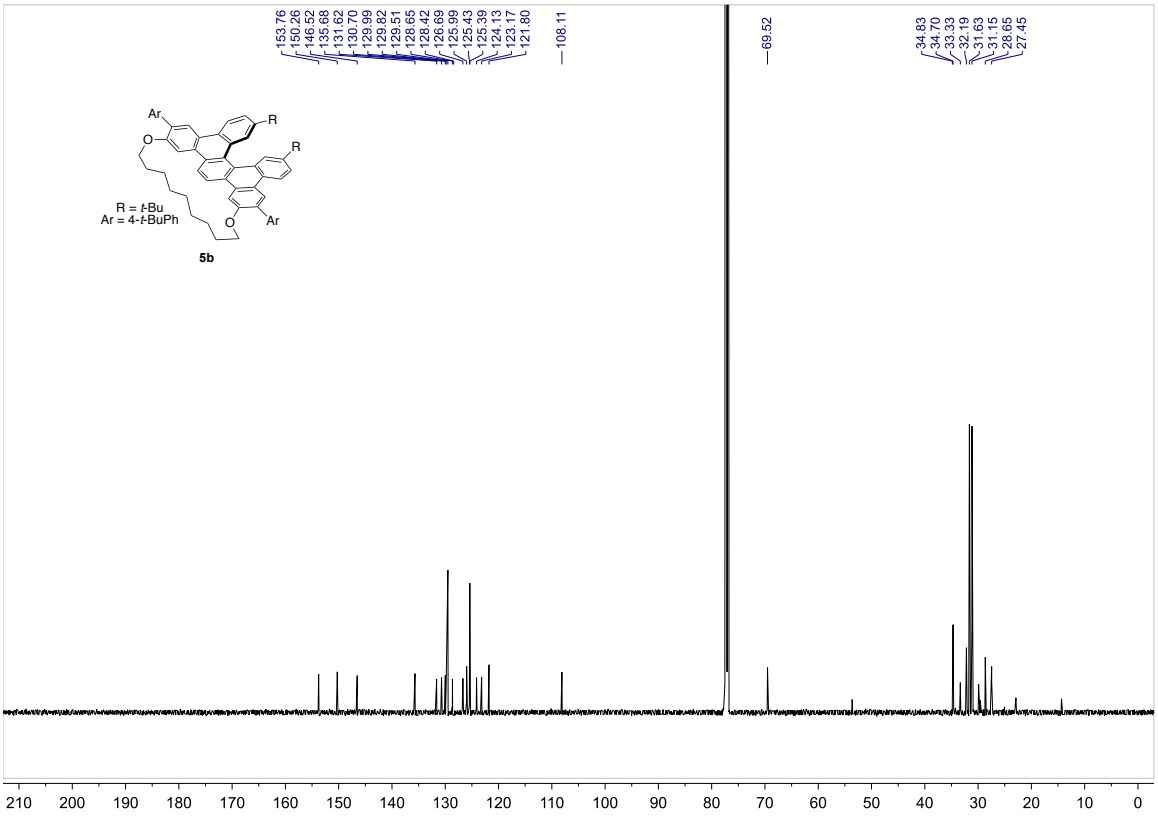
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123.17
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108.11
69.52
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34.70
33.33
32.19
31.63
31.15
28.65
27.45
Ar
O
R
R
R = t-Bu
Ar = 4-t-BuPh
O
Ar
5b
210
200
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180
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100
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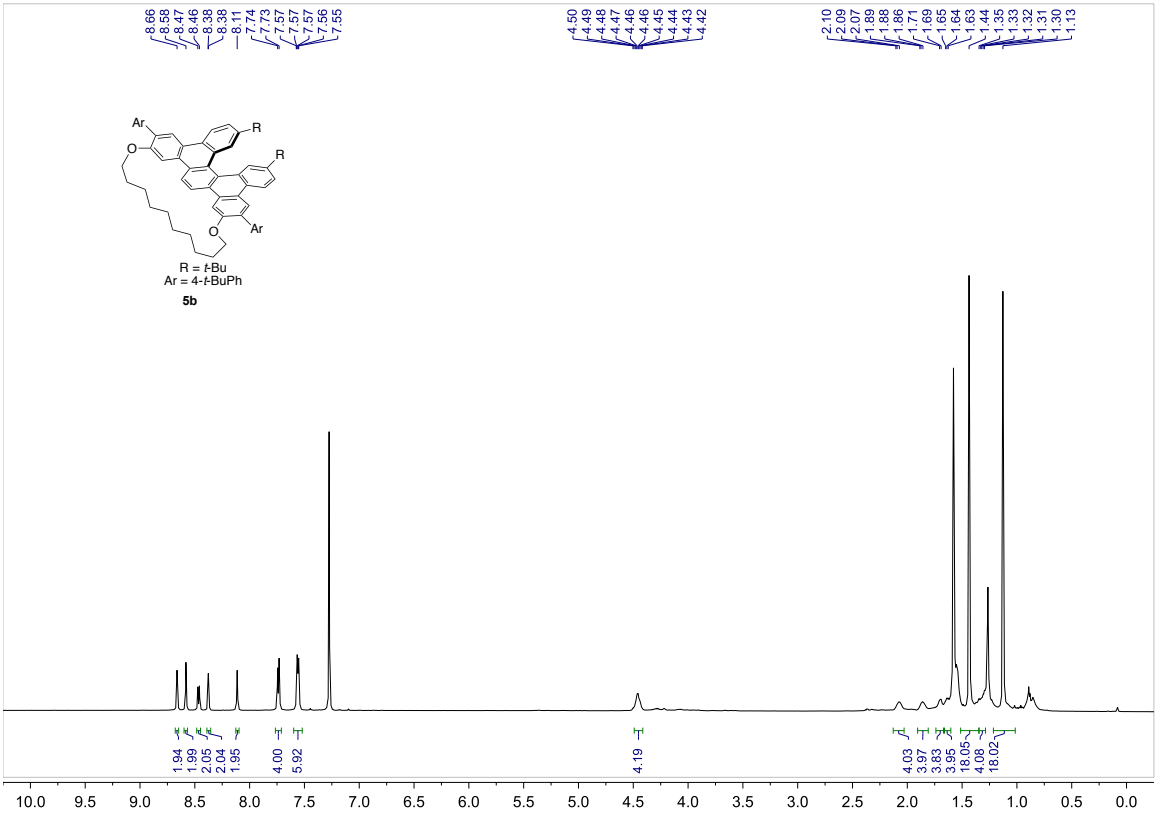
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1.30
1.13
Ar
R
R
O
O
Ar
R = t-Bu
Ar = 4-t-BuPh
5b
1.94
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2.04
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4.03
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3.83
3.95
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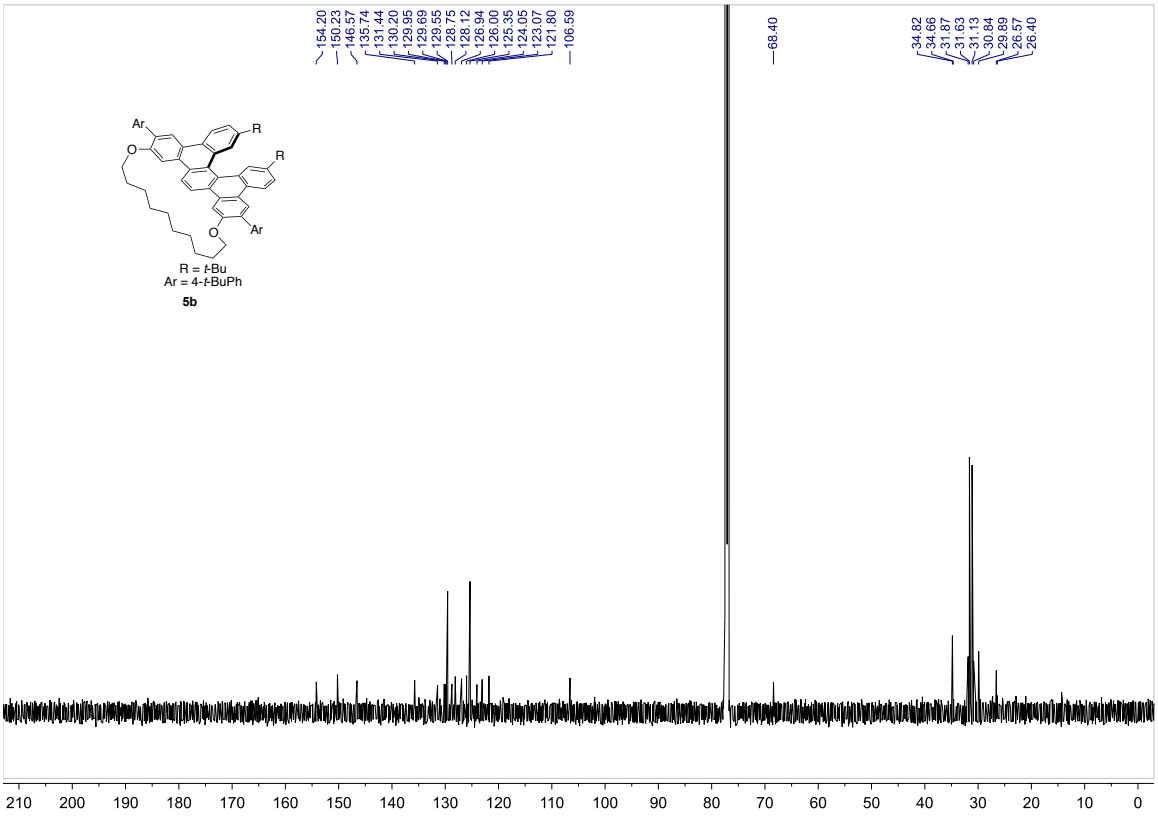
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124.05
123.07
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34.66
31.87
31.63
31.13
30.84
29.89
28.57
26.40
Ar
R
R
O
O
Ar
R = t-Bu
Ar = 4-t-BuPh
5b
210
200
190
180
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150
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100
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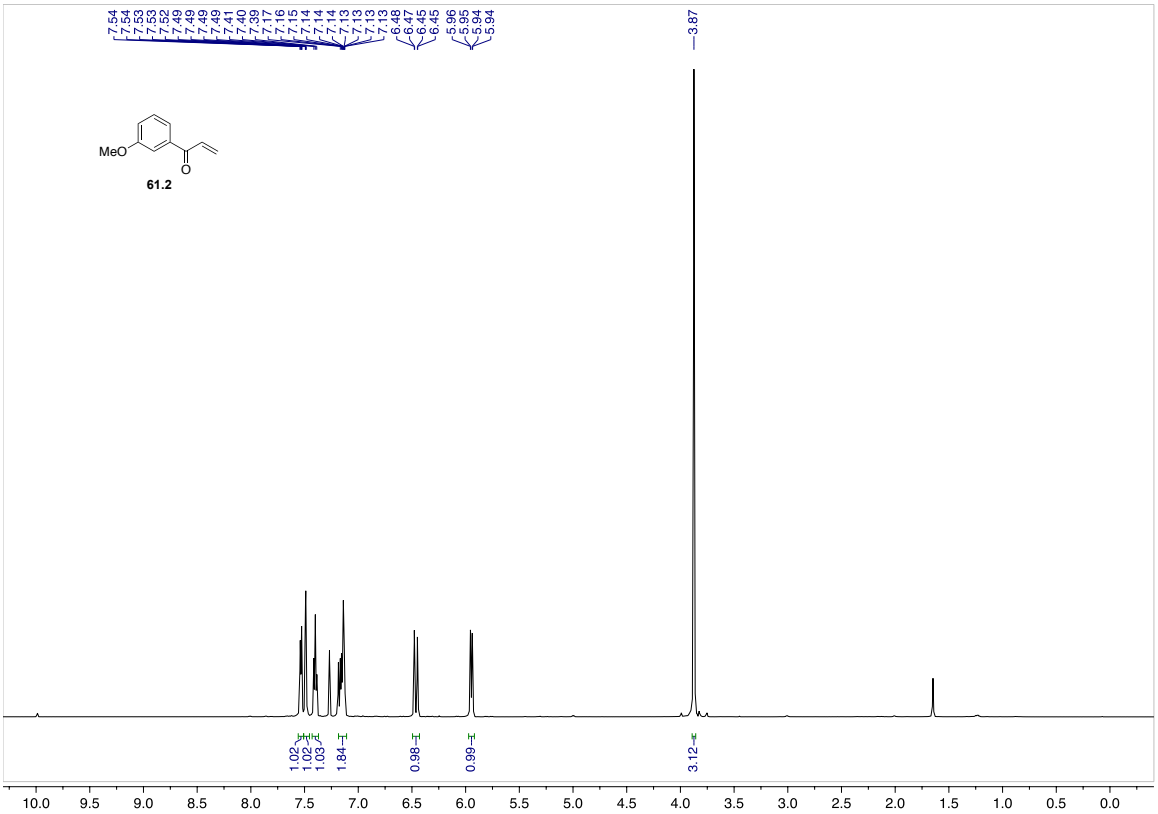
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7.14
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7.13
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6.45
6.45
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5.95
5.94
5.94
3.87
MeO
O
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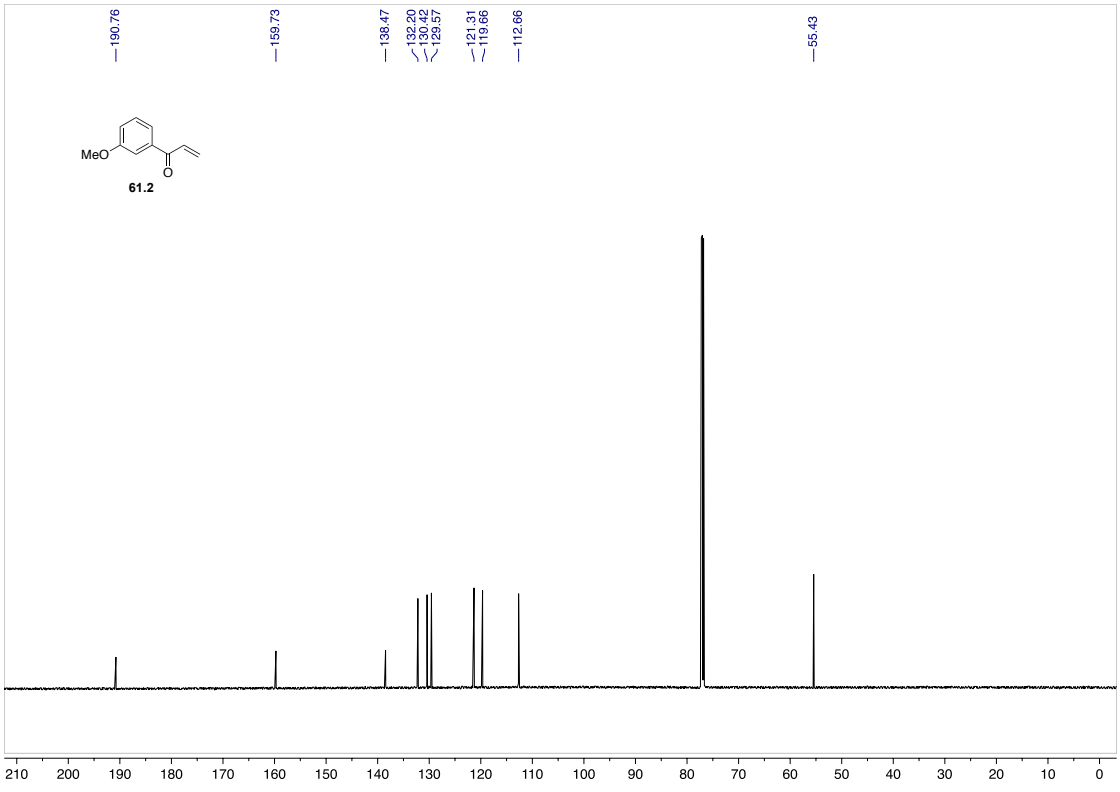
1.02
1.03
1.84
0.98
0.99
3.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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MeO
O
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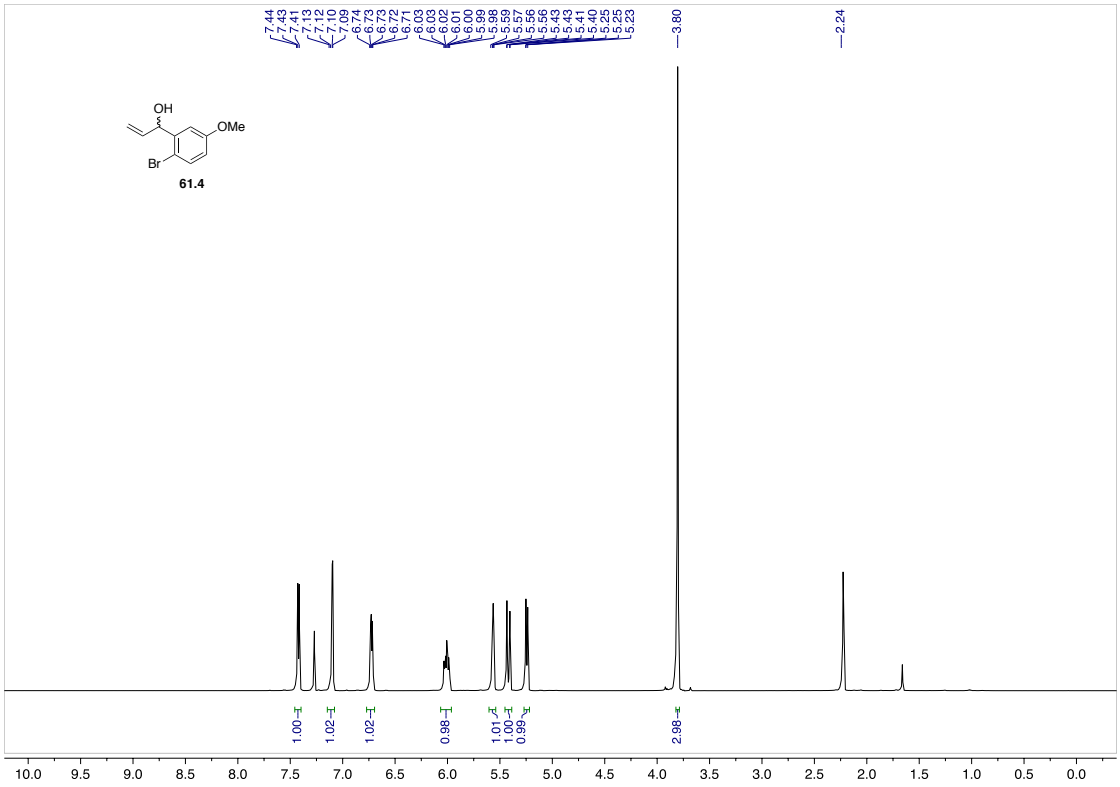
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2.24
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OMe
Br
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1.02
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1.00
0.99
2.98
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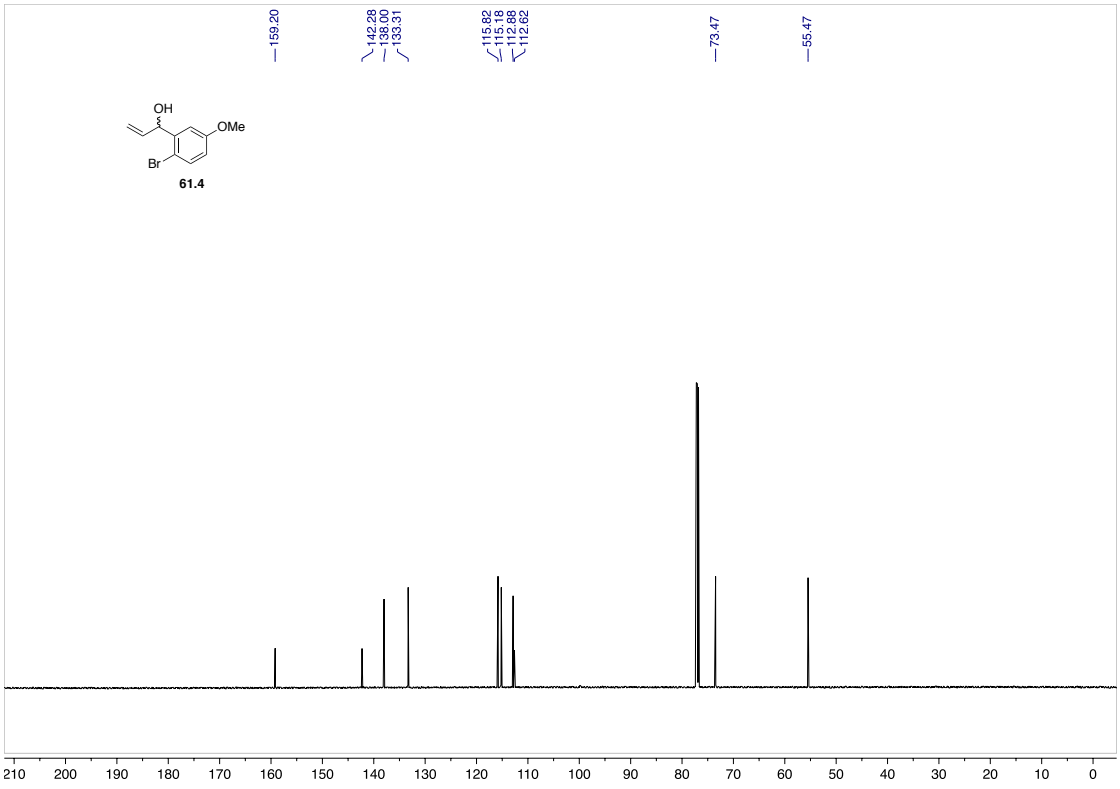
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OH
OMe
Br
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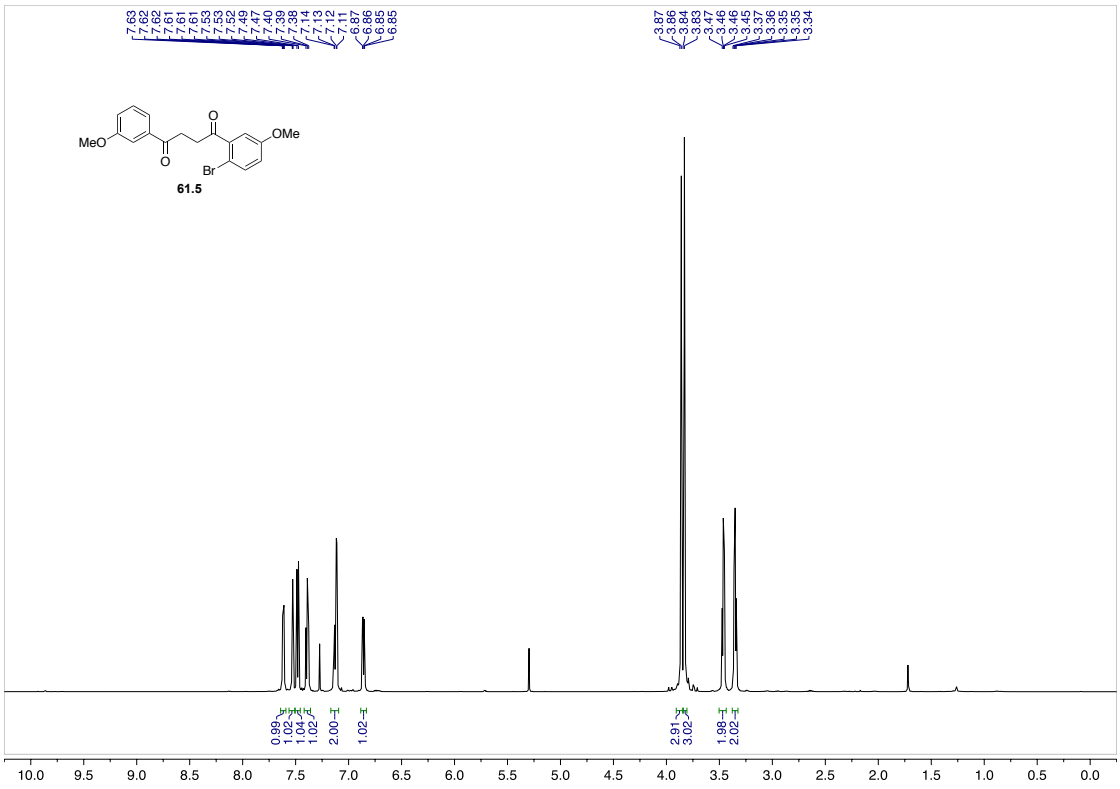
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3.34
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O
O
OMe
Br
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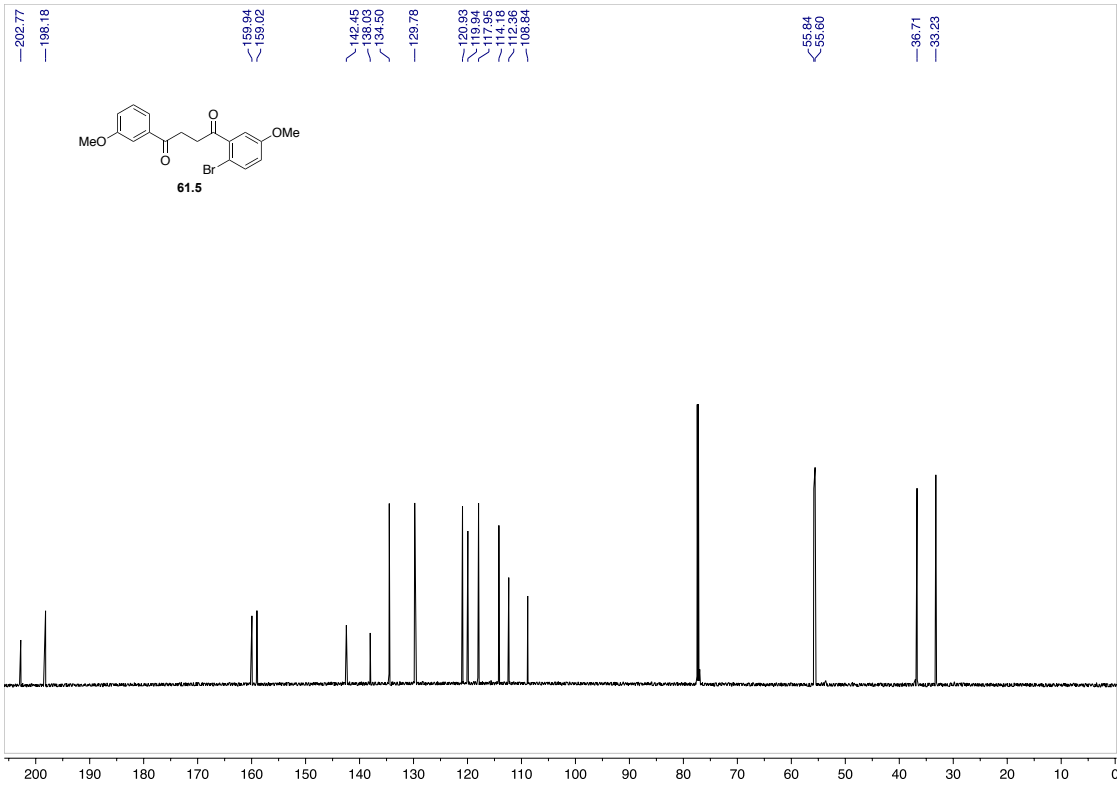
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O
O
OMe
Br
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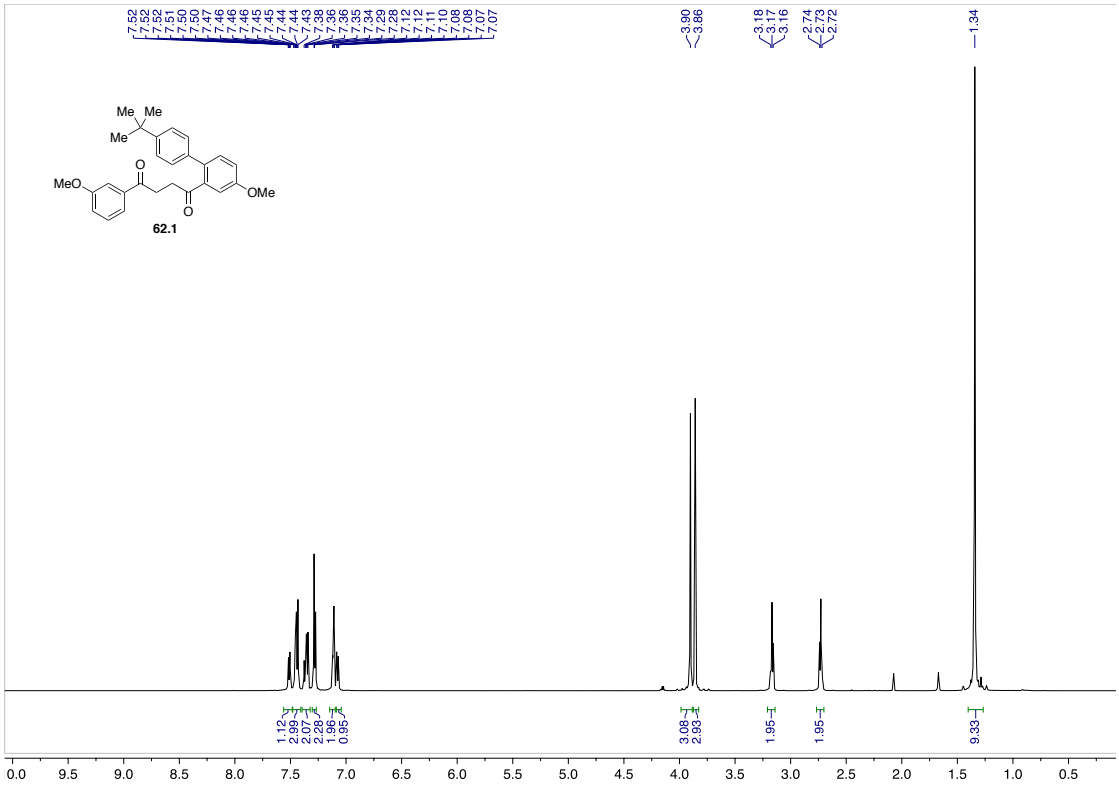
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7.52
7.52
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7.46
7.46
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7.45
7.45
7.44
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7.35
7.34
7.29
7.28
7.12
7.12
7.11
7.10
7.08
7.08
7.07
7.07
3.90
3.86
3.18
3.17
3.16
2.74
2.73
2.72
1.34
Me
Me
Me
O
MeO
OMe
O
62.1
1.12
2.99
2.07
2.28
1.96
0.95
3.08
2.93
1.95
1.95
9.33
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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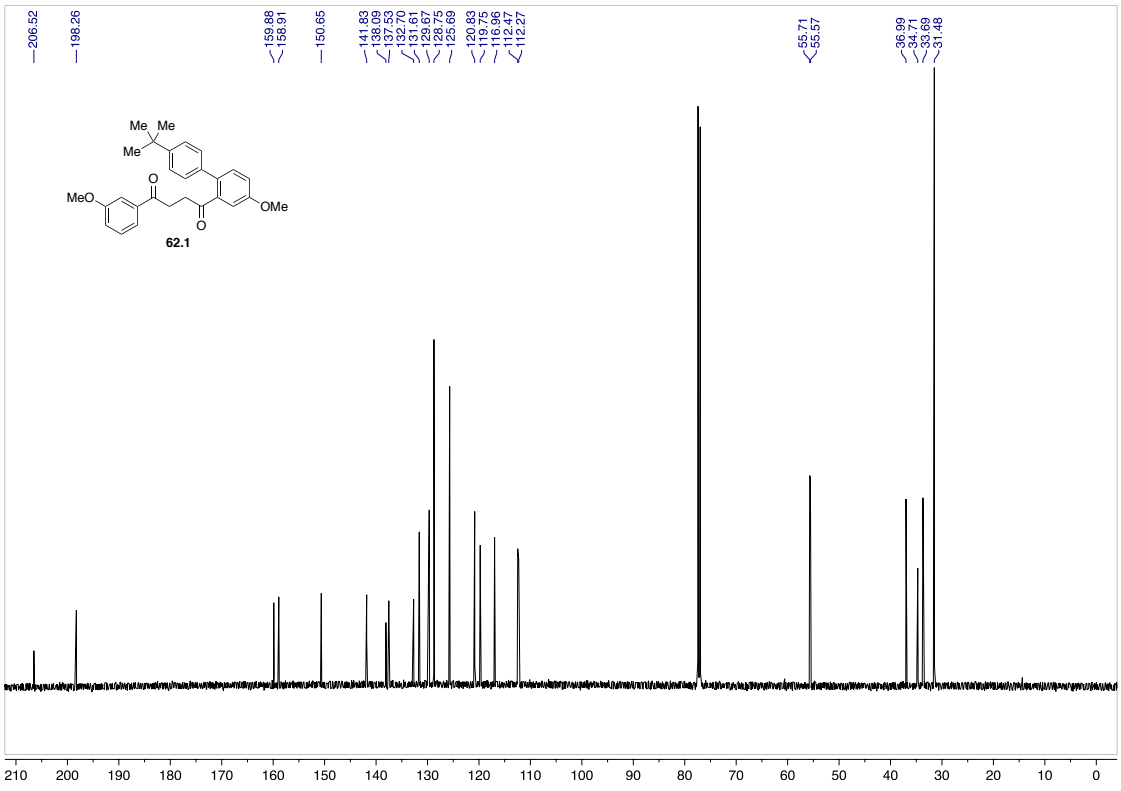
1.0
0.5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125.69
120.83
119.75
116.96
112.47
112.27
55.71
55.57
36.99
34.71
33.69
31.48
Me
Me
Me
O
MeO
OMe
O
62.1
210
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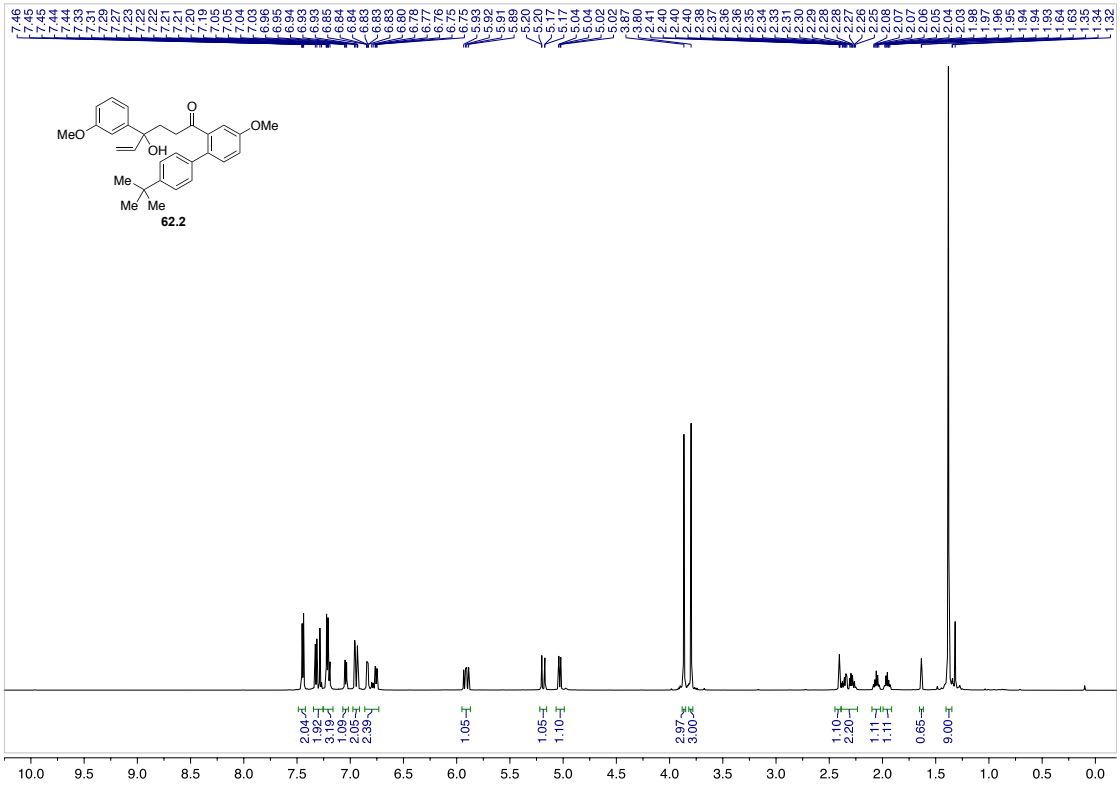
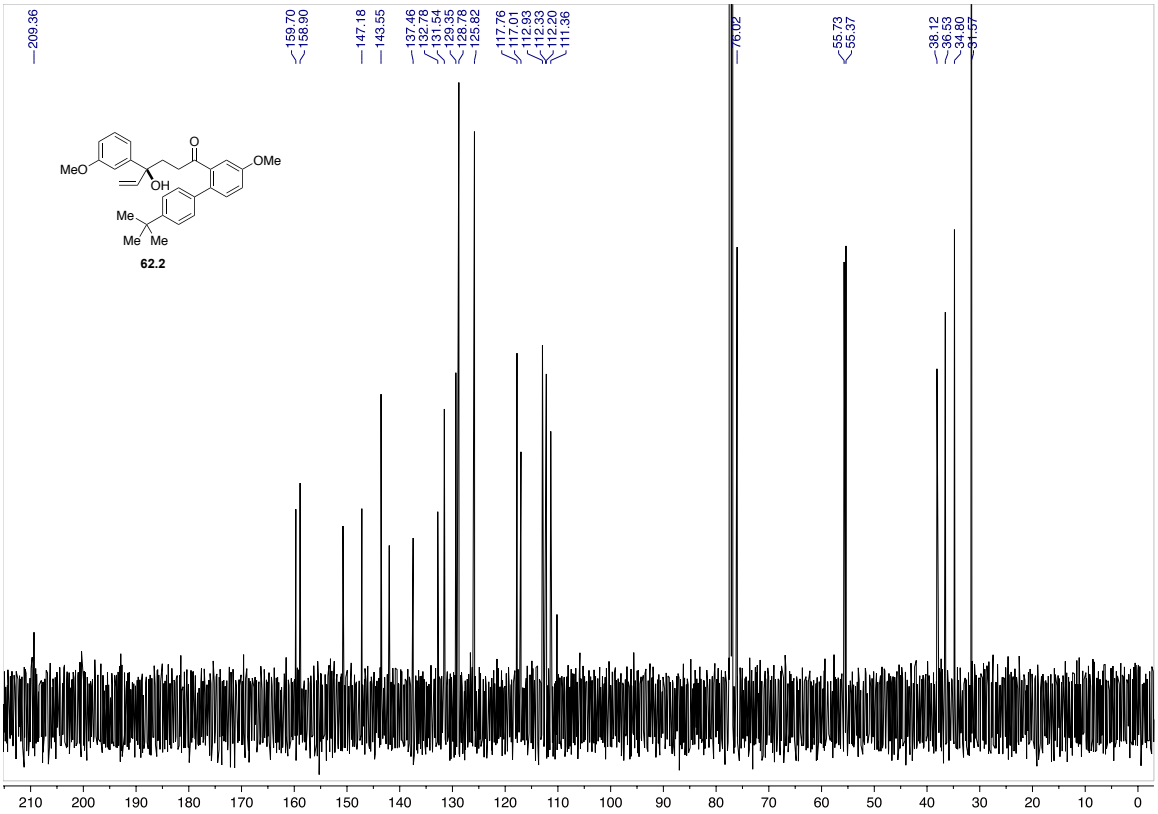
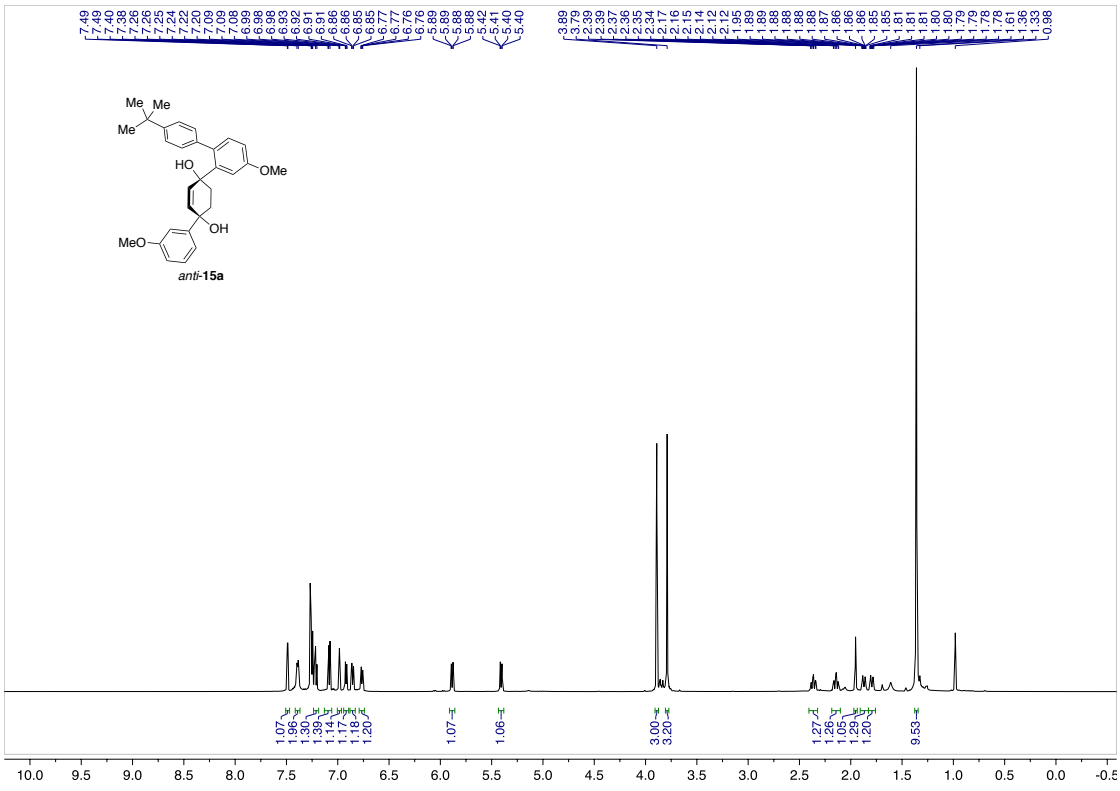
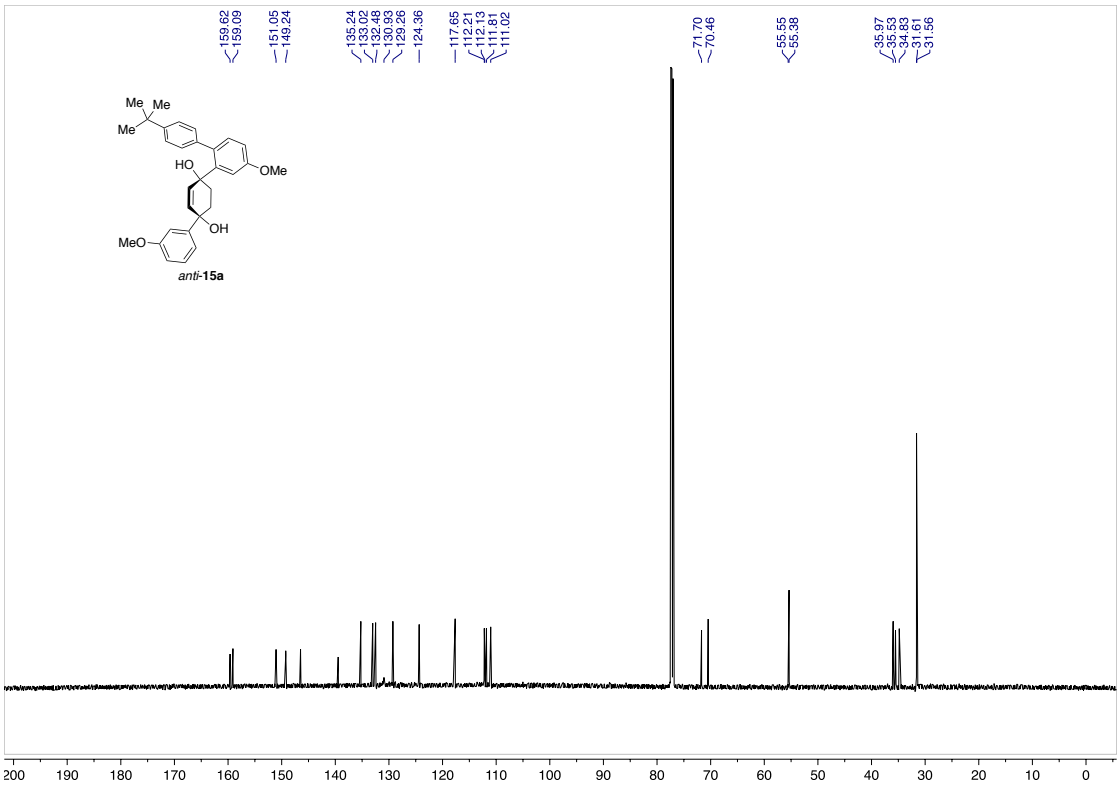
20
10
0


MeO
OMe
OH
Me
Me Me
62.2


MeO
OMe
OH
Me
Me Me
62.2


Me
Me
Me
HO
OMe
OH
MeO
anti-15a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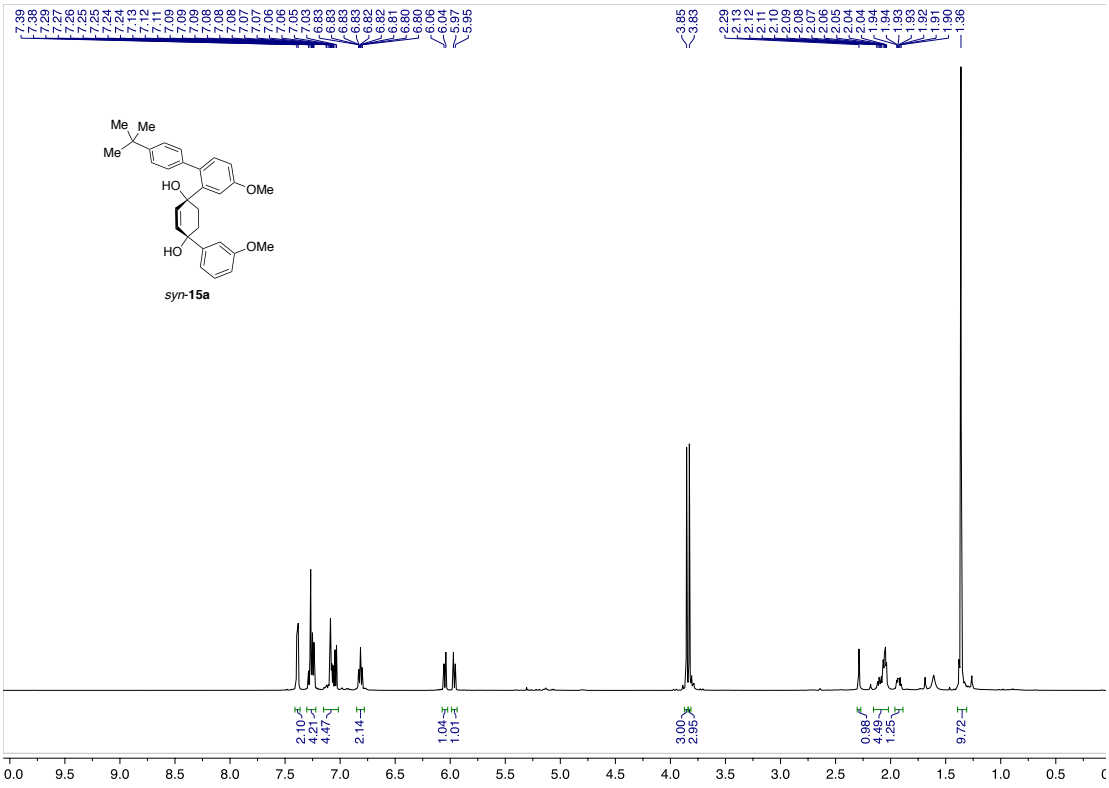
Me
Me
HO
OMe
OH
MeO
anti-15a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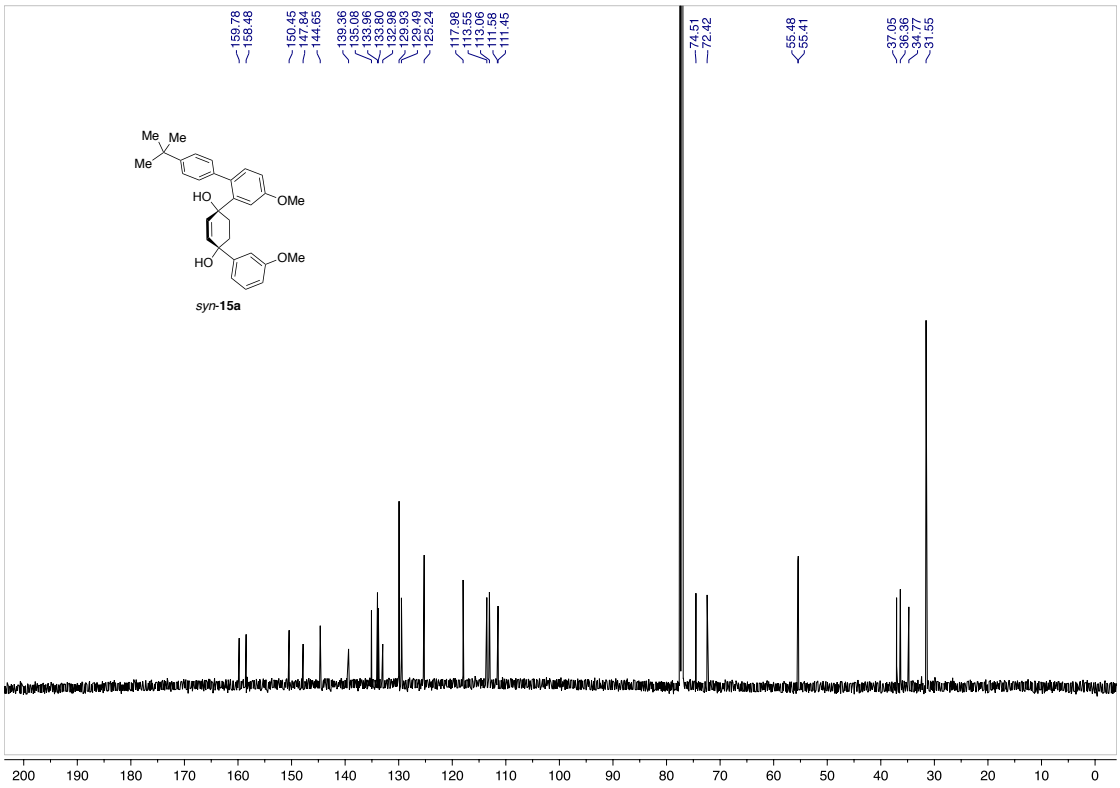
3.85 3.83
2.29 2.13 2.12 2.11 2.10 2.09 2.08 2.07 2.06 2.05 2.04 2.04 1.94 1.94 1.93 1.92 1.91 1.90 1.36
Me Me Me HO OMe HO OMe
syn-15a
2.10 4.21 4.47 2.14 1.04 1.01 3.00 2.95 0.98 4.49 1.25 9.72
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5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74.51 72.42
55.48 55.41
37.05 36.36 34.77 31.55
Me Me Me HO OMe HO OMe
syn-15a
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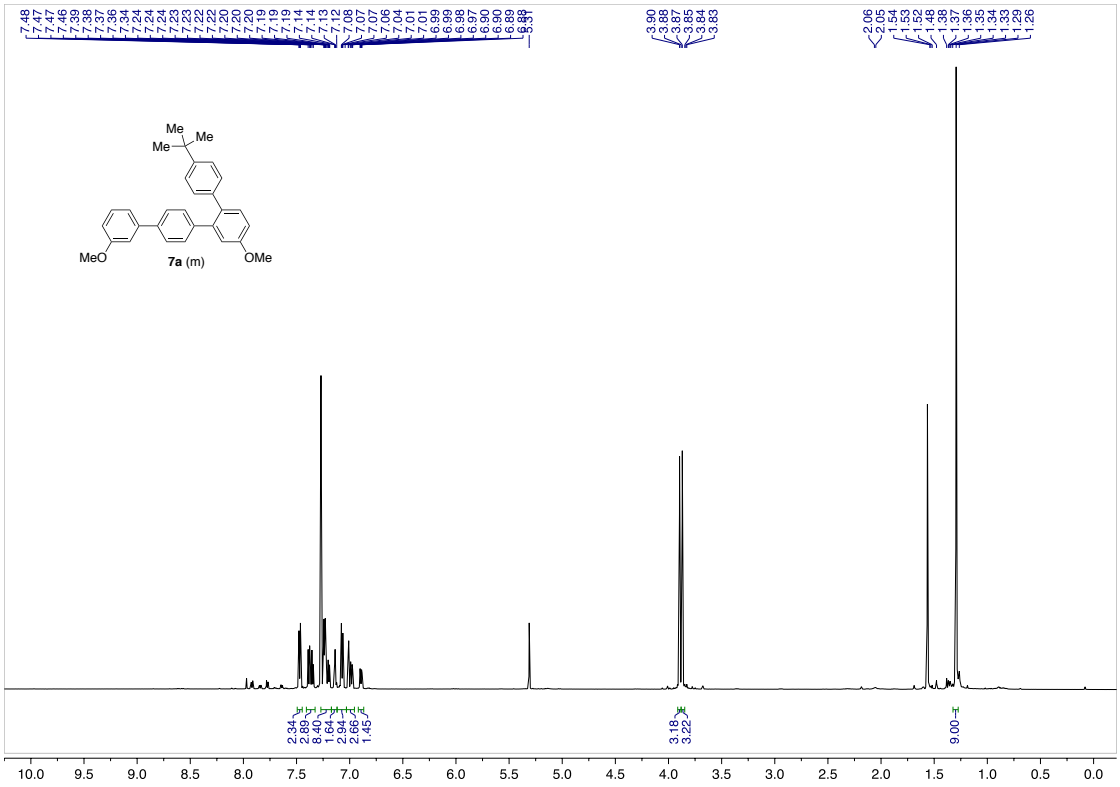
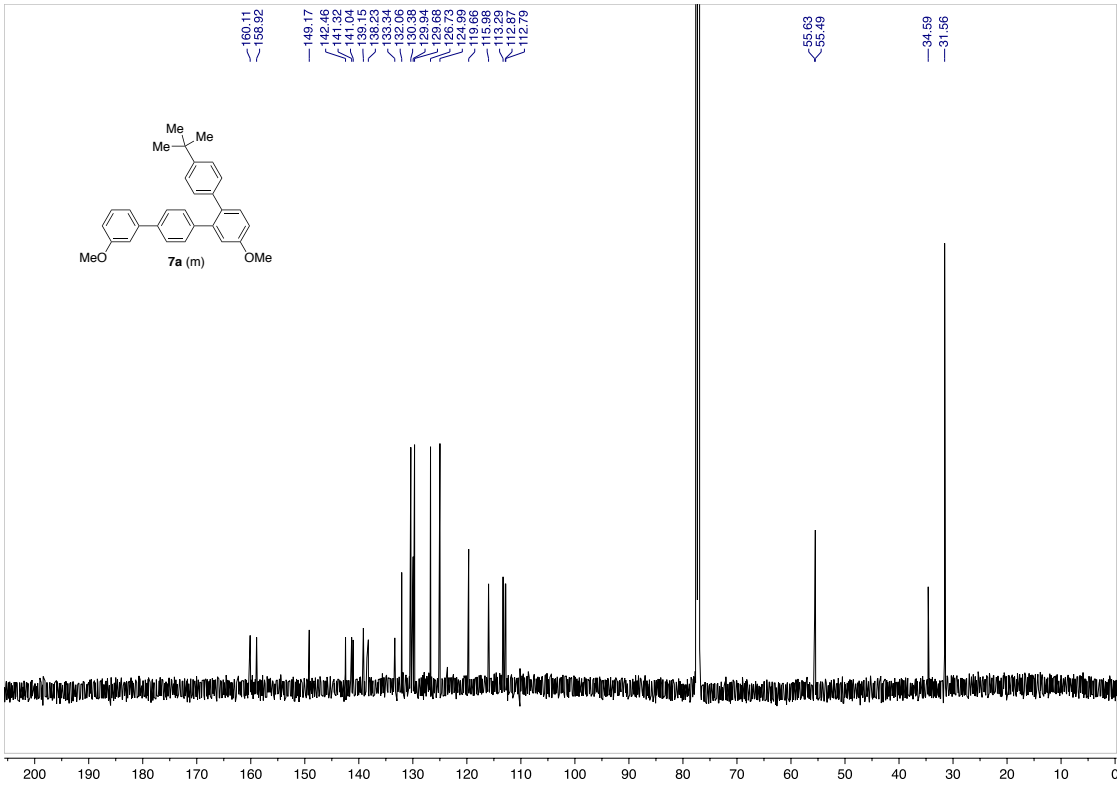
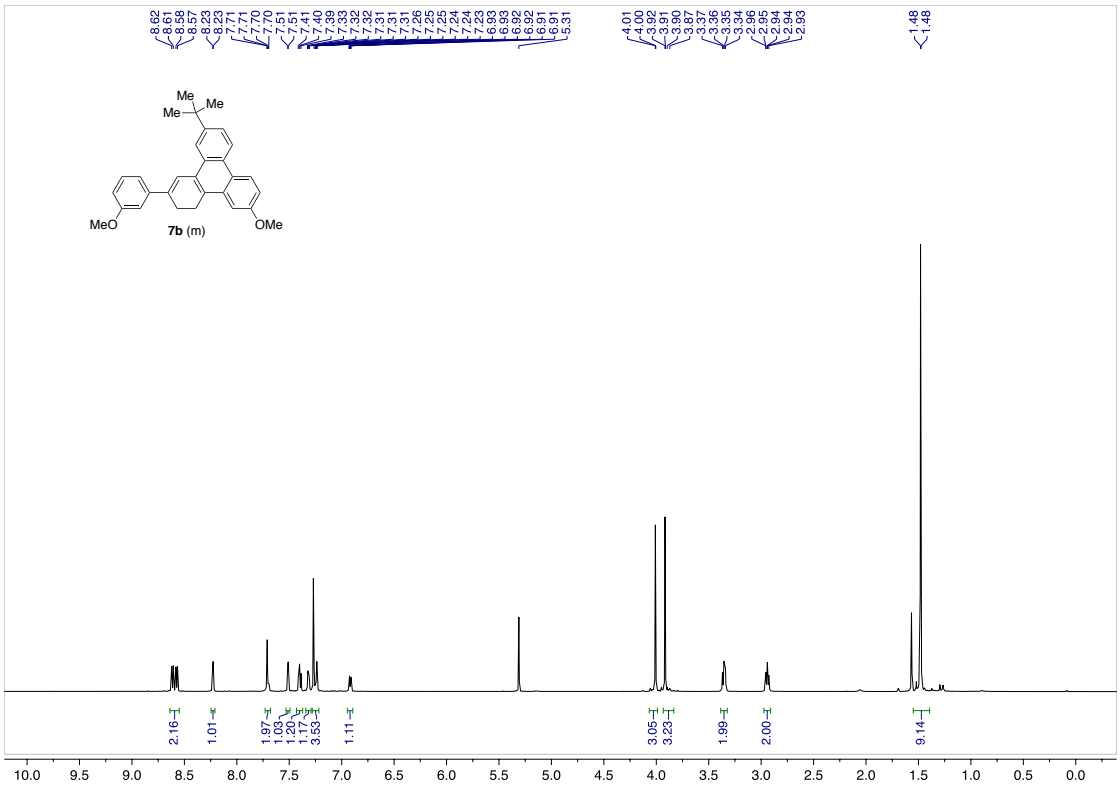

7a (m)
MeO
OMe


7a (m)
MeO
OMe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7.70
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7.51
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7.40
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7.33
7.32
7.32
7.31
7.31
7.26
7.25
7.25
7.24
7.24
7.23
6.93
6.92
6.92
6.91
6.91
5.31
4.01
4.00
3.92
3.91
3.90
3.87
3.37
3.36
3.35
3.34
2.96
2.95
2.94
2.94
2.93
1.48
1.48
Me
Me
Me
MeO
OMe
7b (m)
2.16
1.01
1.97
1.03
1.20
1.17
3.53
1.11
3.05
3.23
1.99
2.00
9.14
10.0
9.5
9.0
8.5
8.0
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7.0
6.5
6.0
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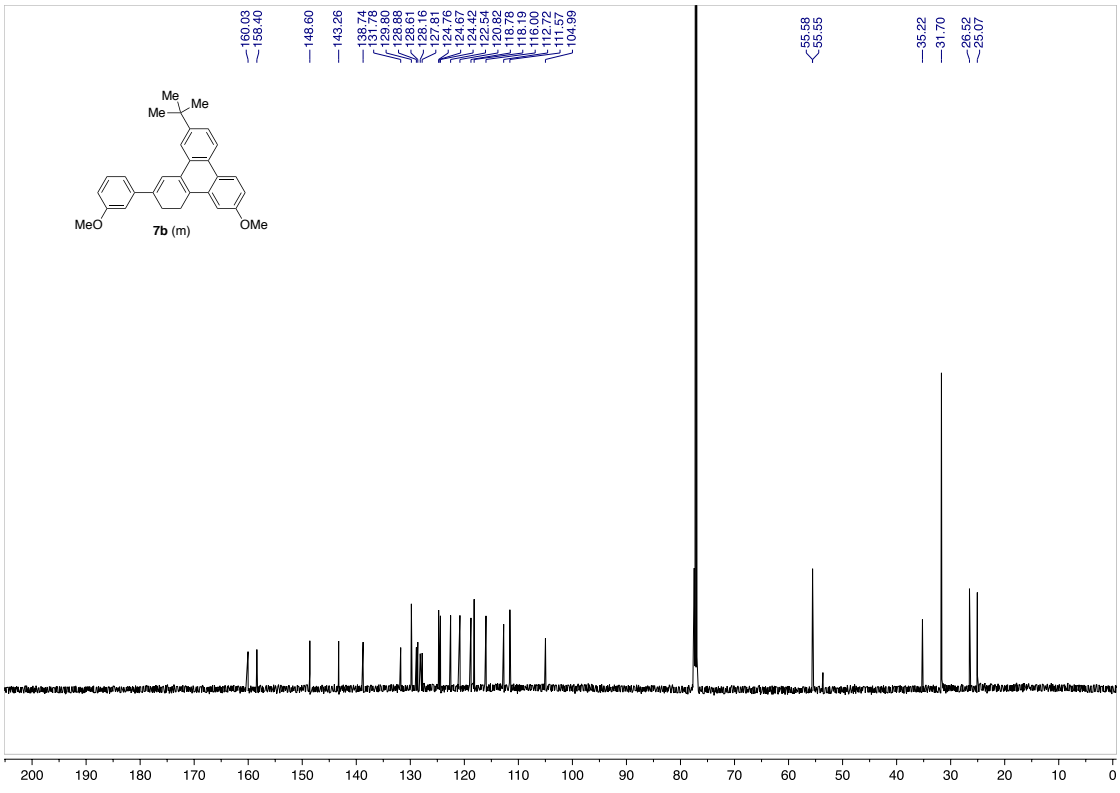
0.0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128.15
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124.67
124.42
122.54
120.82
118.78
115.19
116.00
112.72
111.57
104.99
55.58
55.55
35.22
31.70
26.52
25.07
Me
Me
Me
MeO
OMe
7b (m)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
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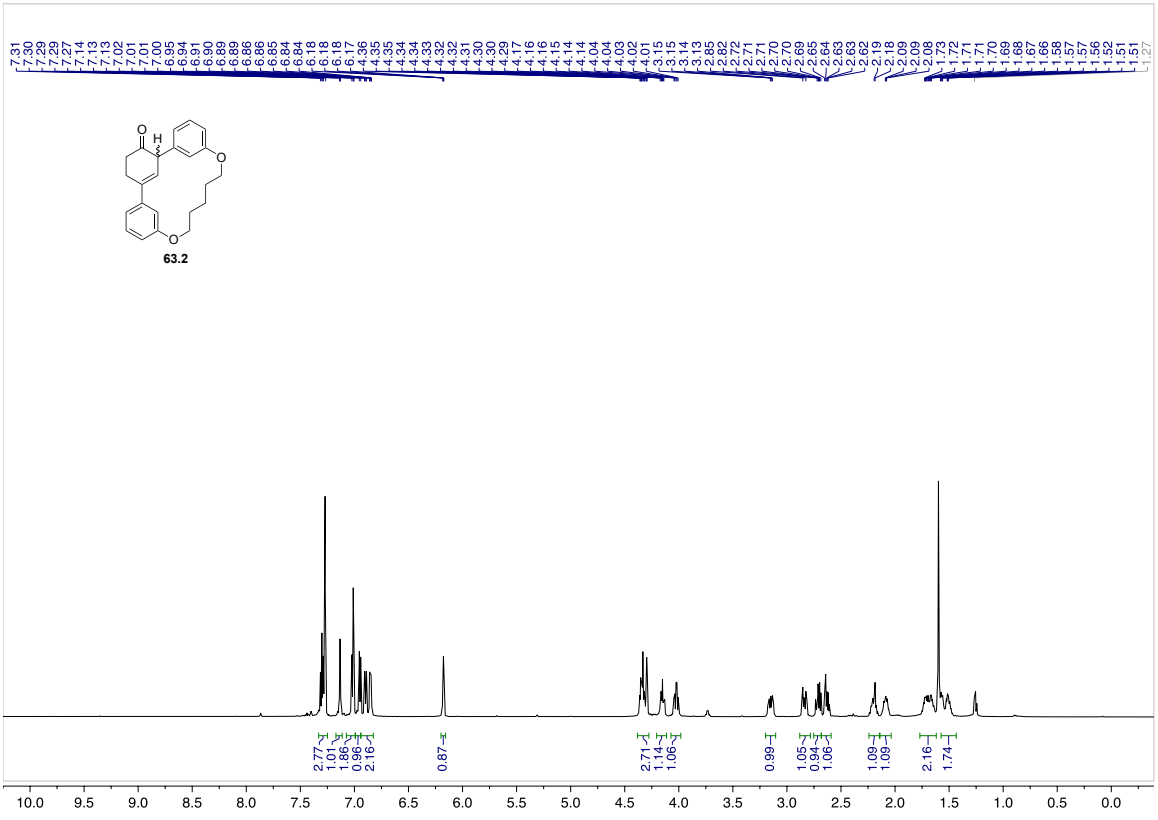
30
20
10
0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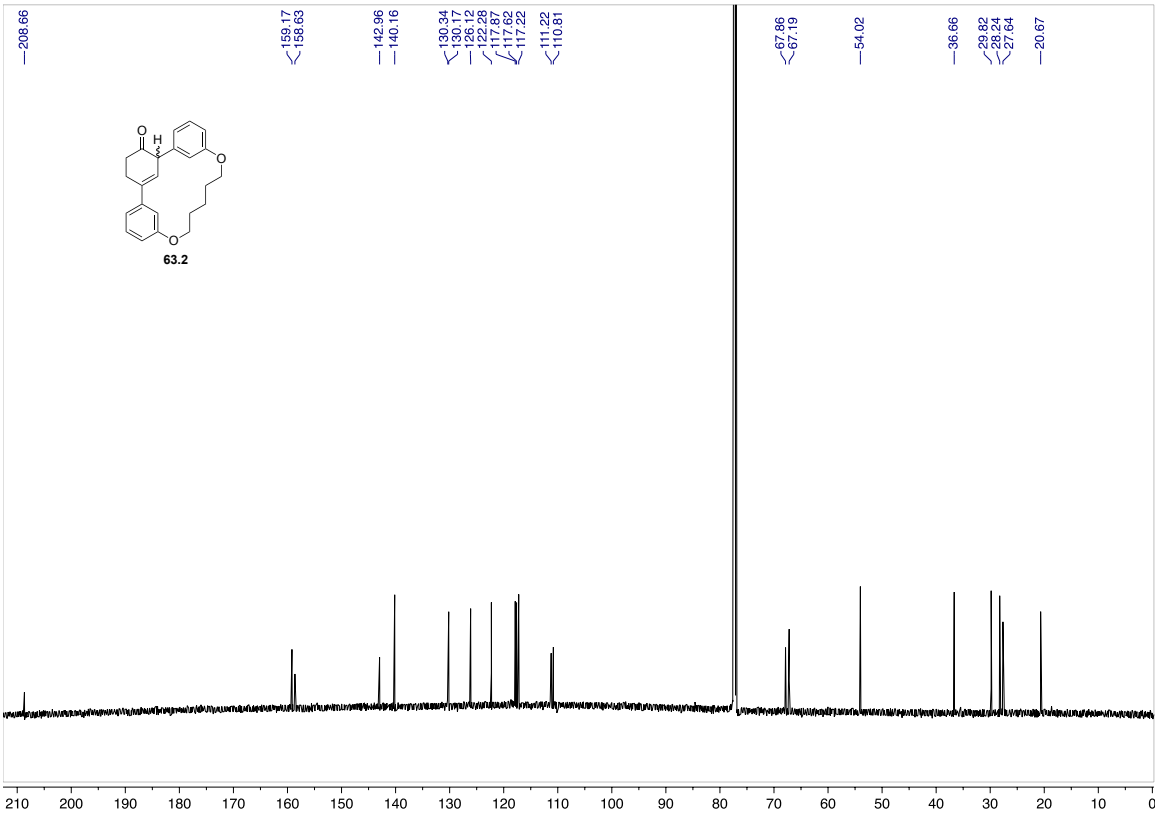
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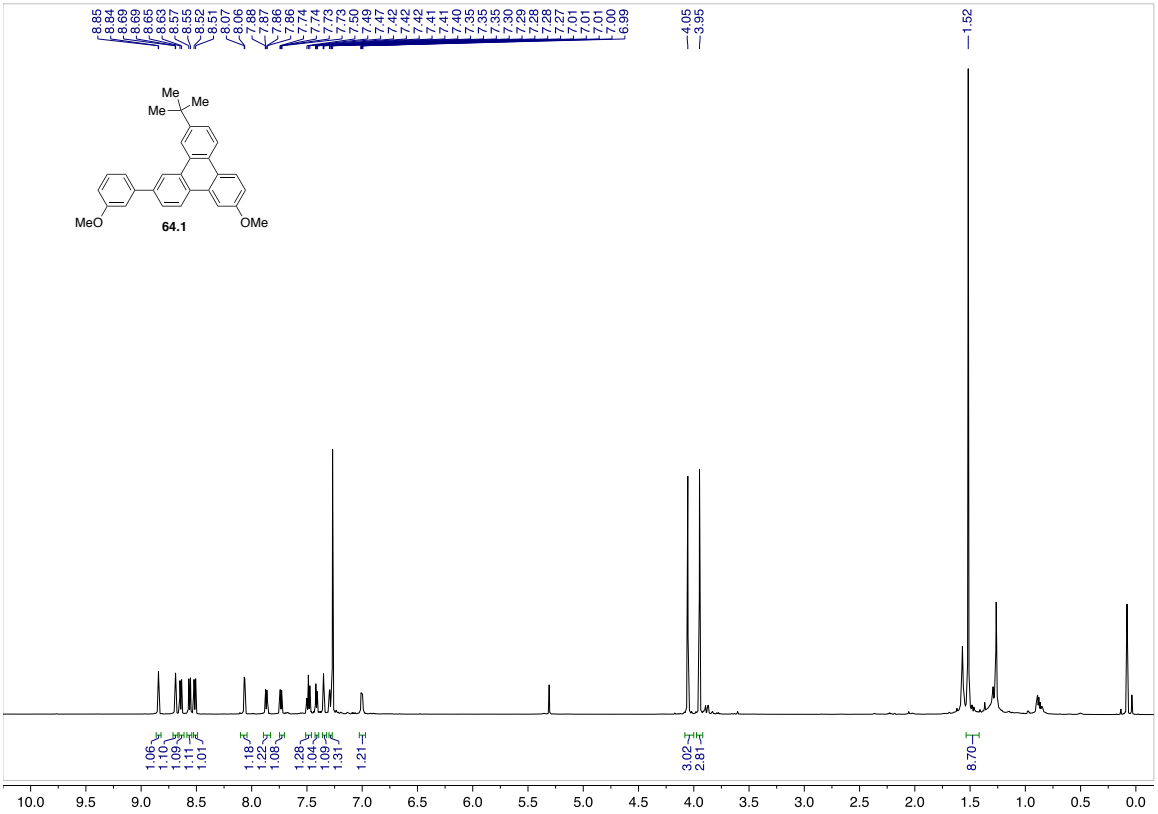
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7.29
7.28
7.28
7.27
7.01
7.01
7.01
7.00
6.99
4.05
3.95
1.52
Me
Me
Me
MeO
OMe
64.1
1.06
1.10
1.09
1.11
1.01
1.18
1.22
1.08
1.28
1.04
1.09
1.31
1.21
3.02
2.81
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10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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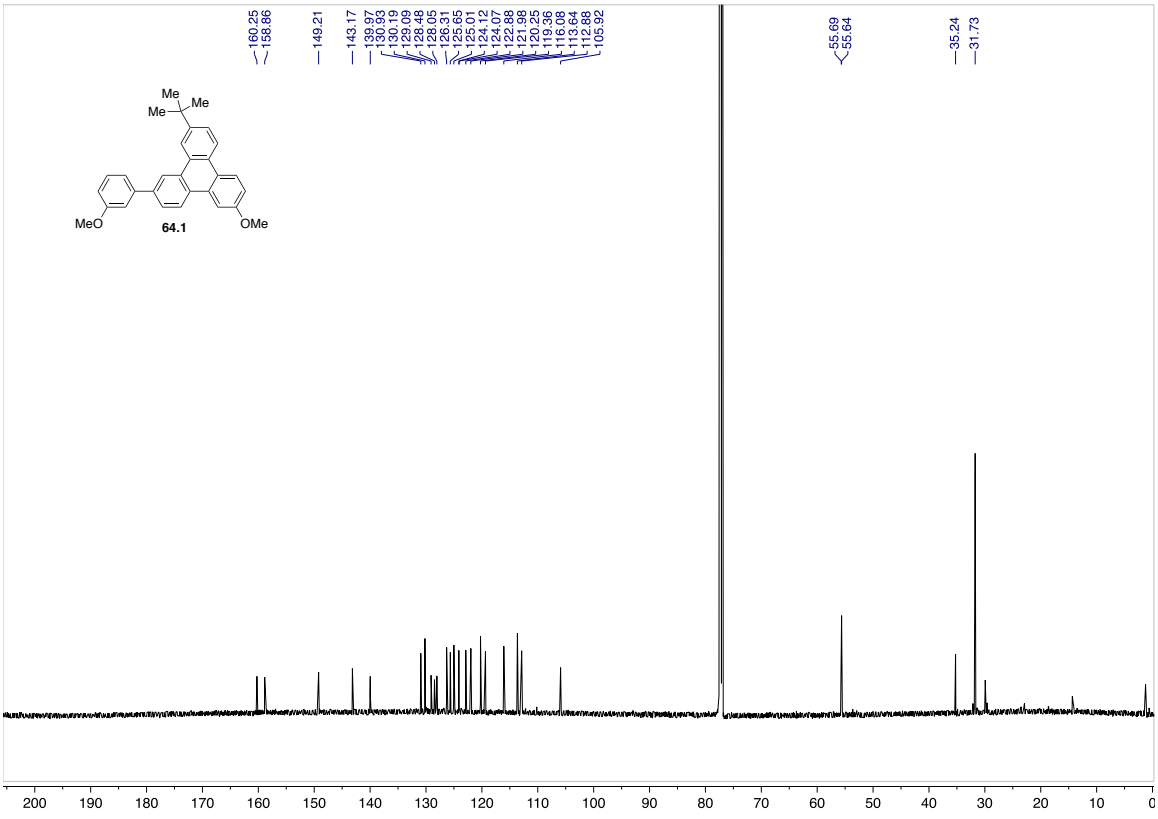
0.0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128.05
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125.65
125.01
124.12
124.07
122.88
121.98
120.25
119.36
116.08
113.64
112.88
105.92
55.69
55.64
35.24
31.73
Me
Me
Me
MeO
OMe
64.1
200
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10
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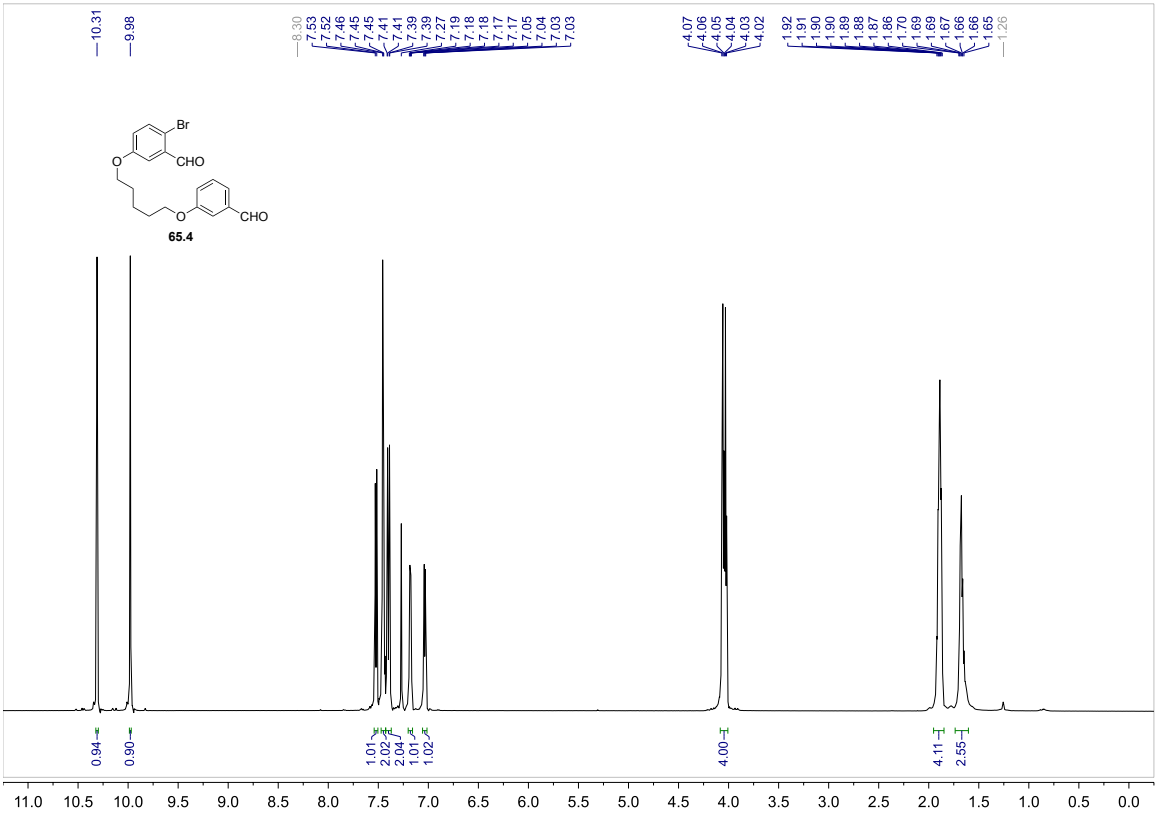
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7.19
7.18
7.18
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7.17
7.05
7.04
7.03
7.03
4.07
4.06
4.05
4.04
4.03
4.02
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1.90
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1.87
1.86
1.70
1.69
1.69
1.67
1.66
1.66
1.65
1.26
Br
CHO
O
O
CHO
65.4
0.94
0.90
1.01
2.02
2.04
1.01
1.02
4.00
4.11
2.55
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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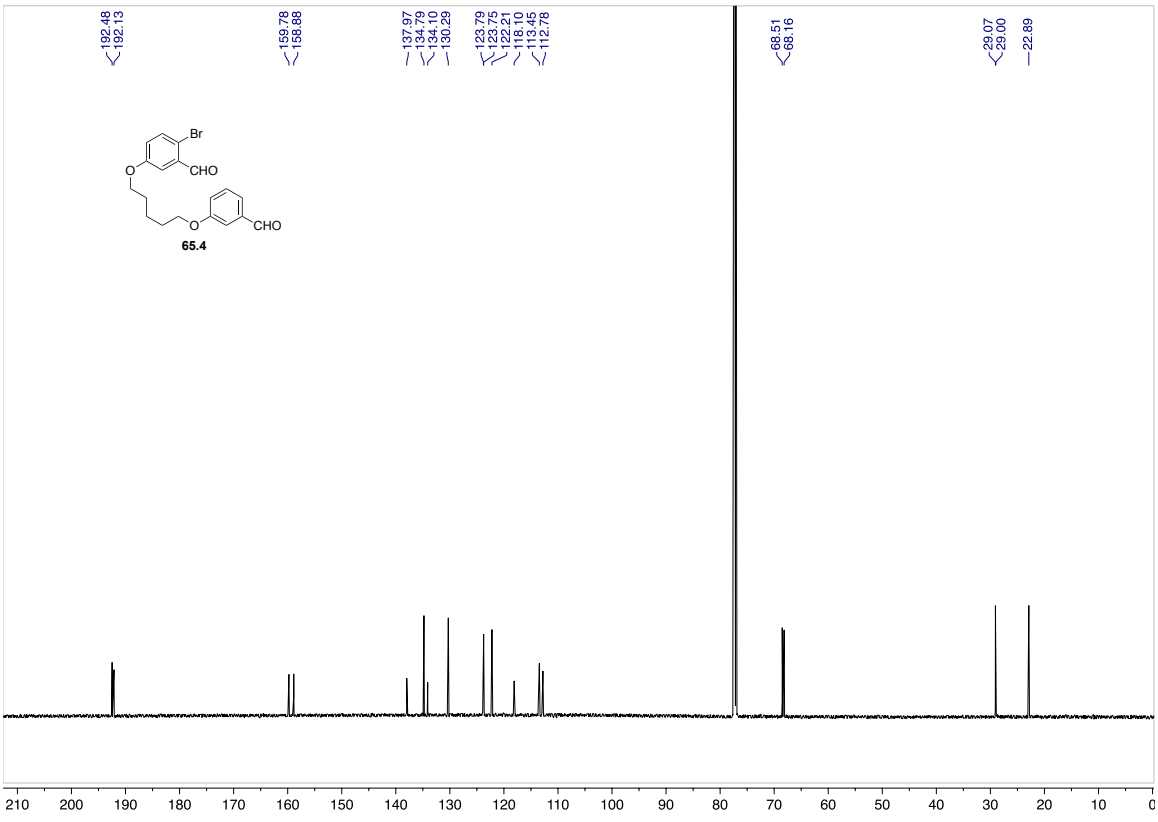
0.0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192.13
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130.29
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123.75
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118.10
113.45
112.78
68.51
68.16
29.07
29.00
22.89
Br
CHO
O
O
CHO
65.4
210
200
190
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150
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10
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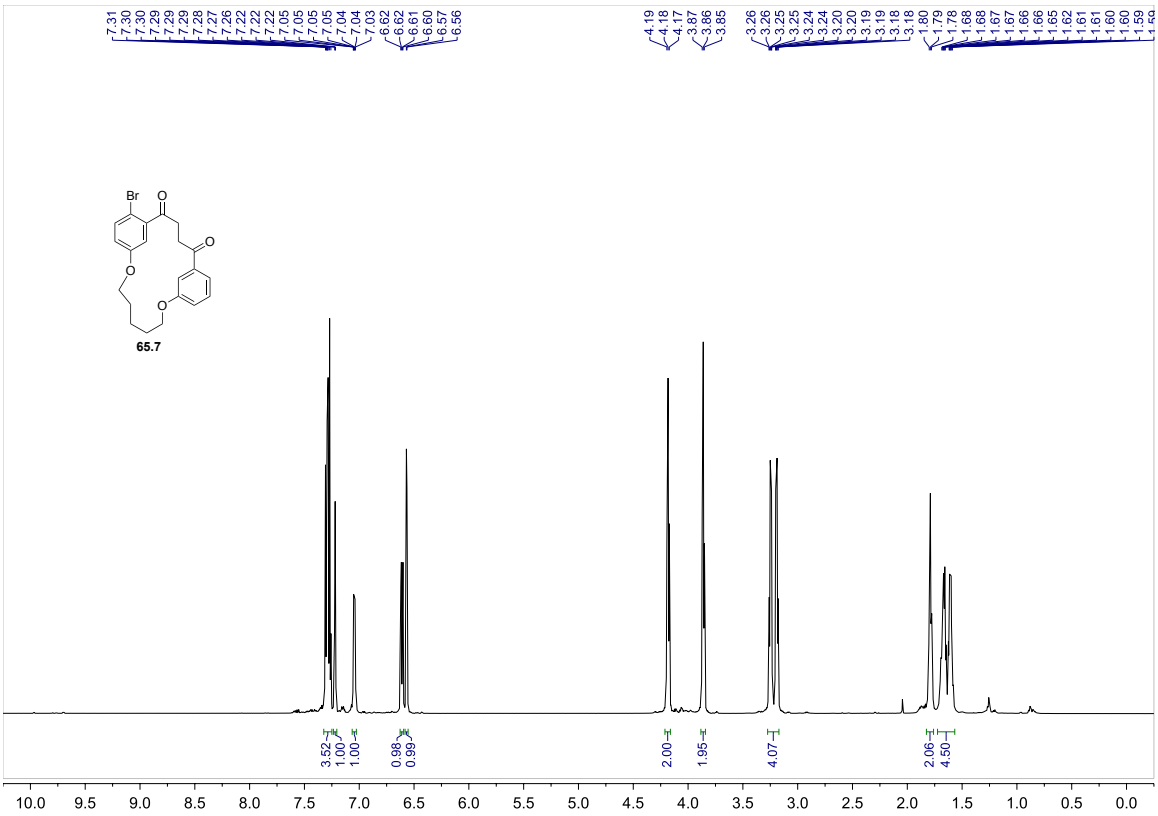
Br
O
O
O
O
65.7
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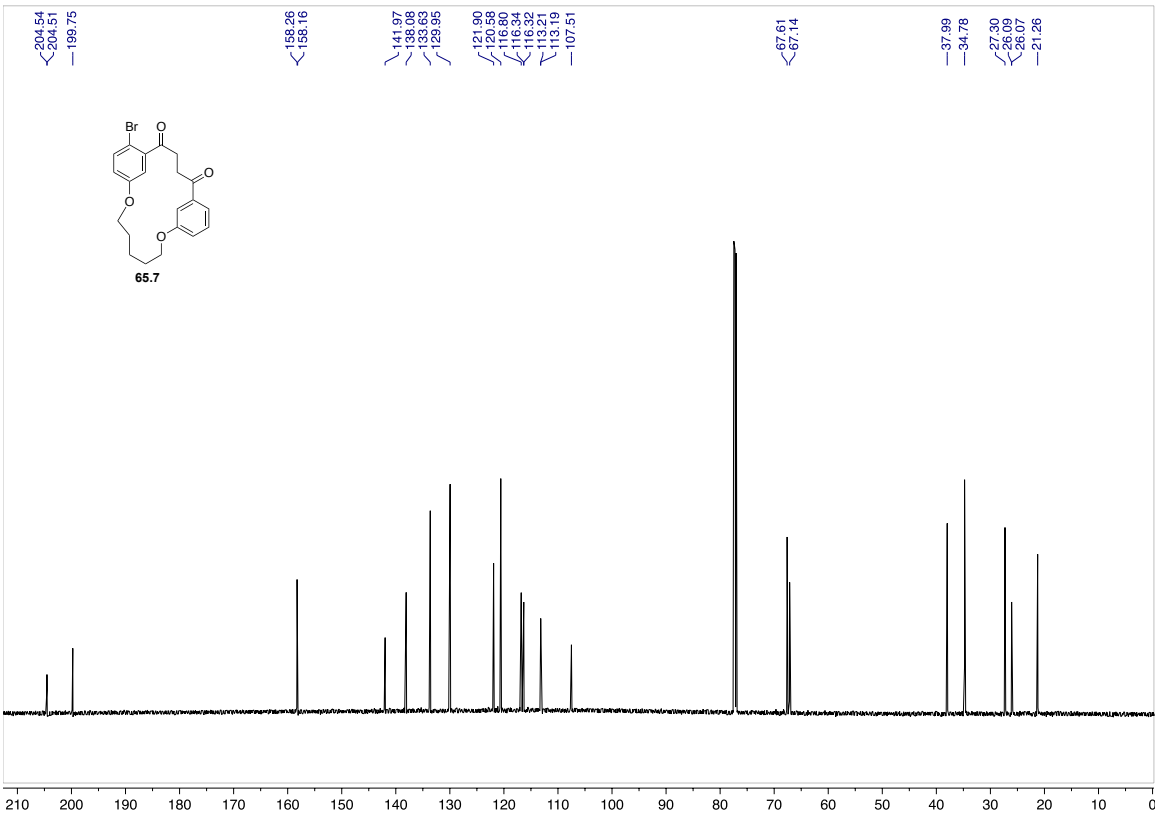
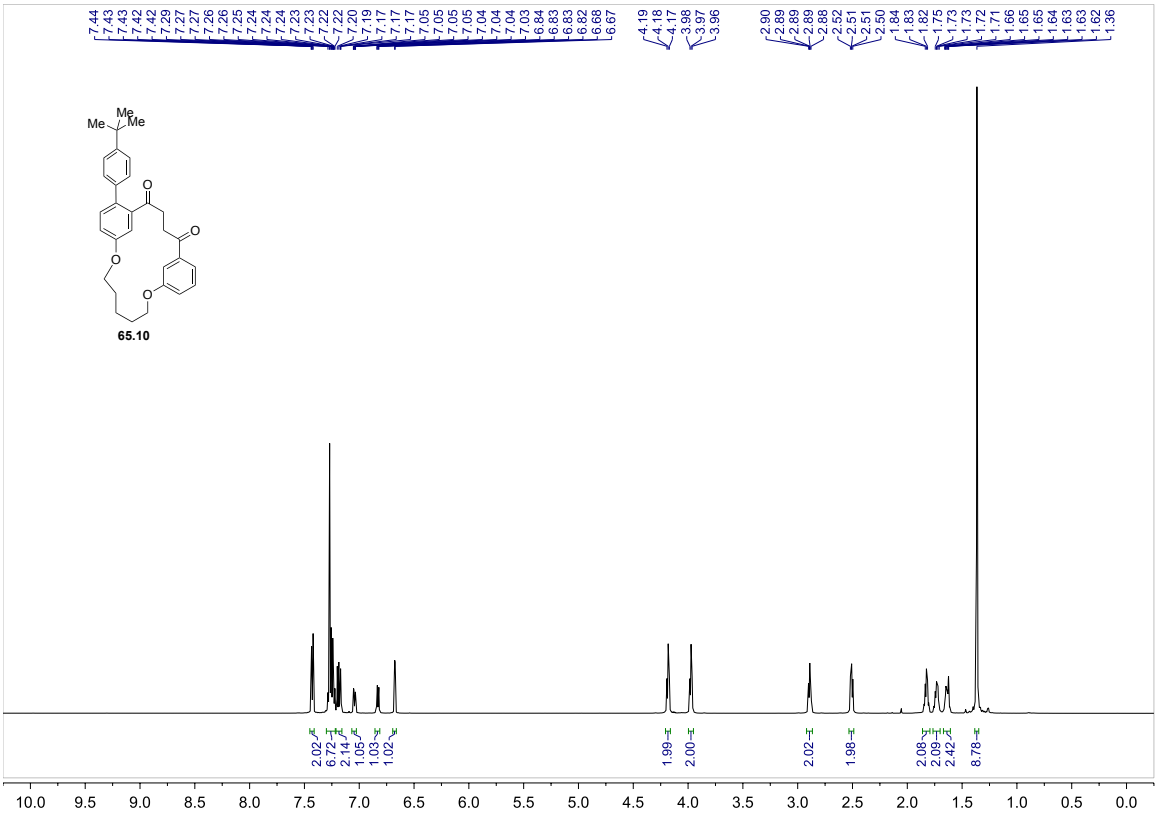
4.19 4.18 4.17 3.87 3.86 3.85 3.26 3.26 3.25 3.25 3.24 3.24 3.20 3.20 3.19 3.19 3.18 1.80 1.79 1.78 1.68 1.68 1.67 1.67 1.66 1.66 1.65 1.62 1.61 1.61 1.60 1.60 1.59
3.52 1.00 1.00 0.98 0.99 2.00 1.95 4.07 2.06 4.50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


Br
O
O
O
O
65.7
204.54 204.51 199.75 158.26 158.16 141.97 138.08 133.63 129.95 121.90 120.58 116.80 116.34 116.32 113.21 113.19 107.51 67.61 67.14 37.99 34.78 27.30 26.09 26.07 21.26
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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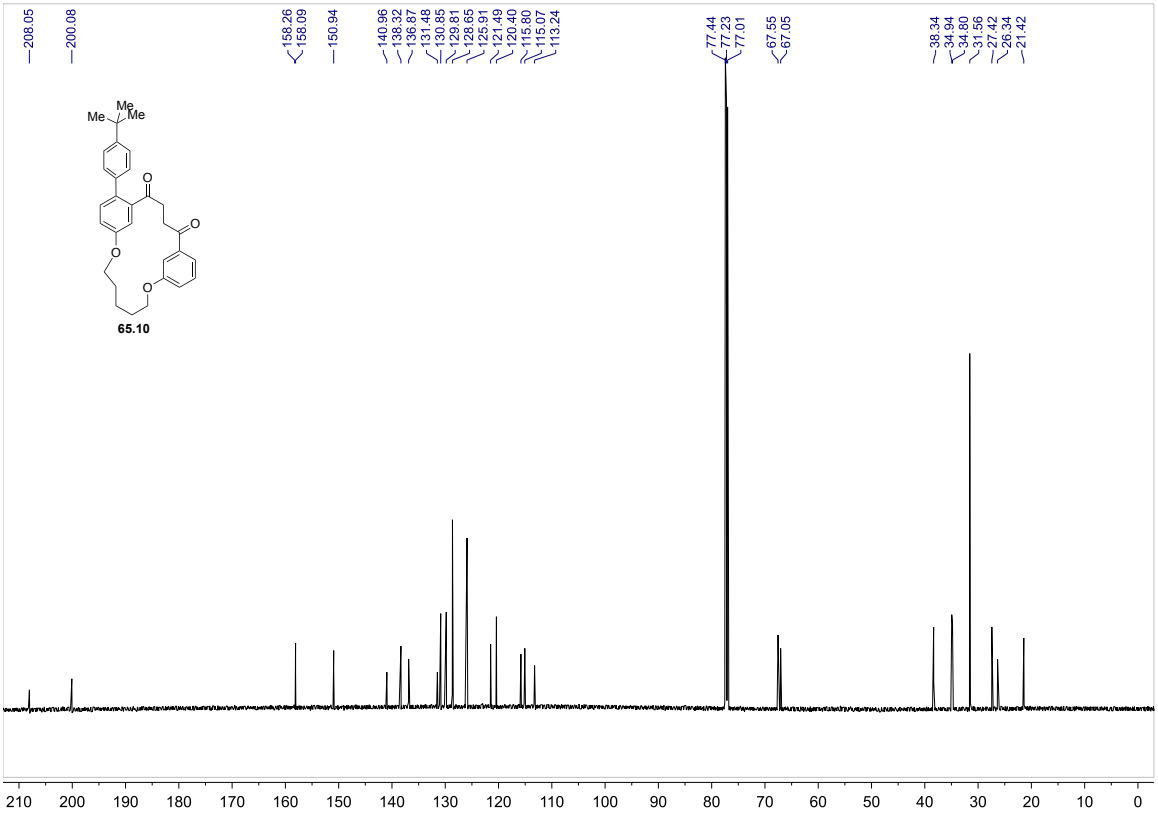
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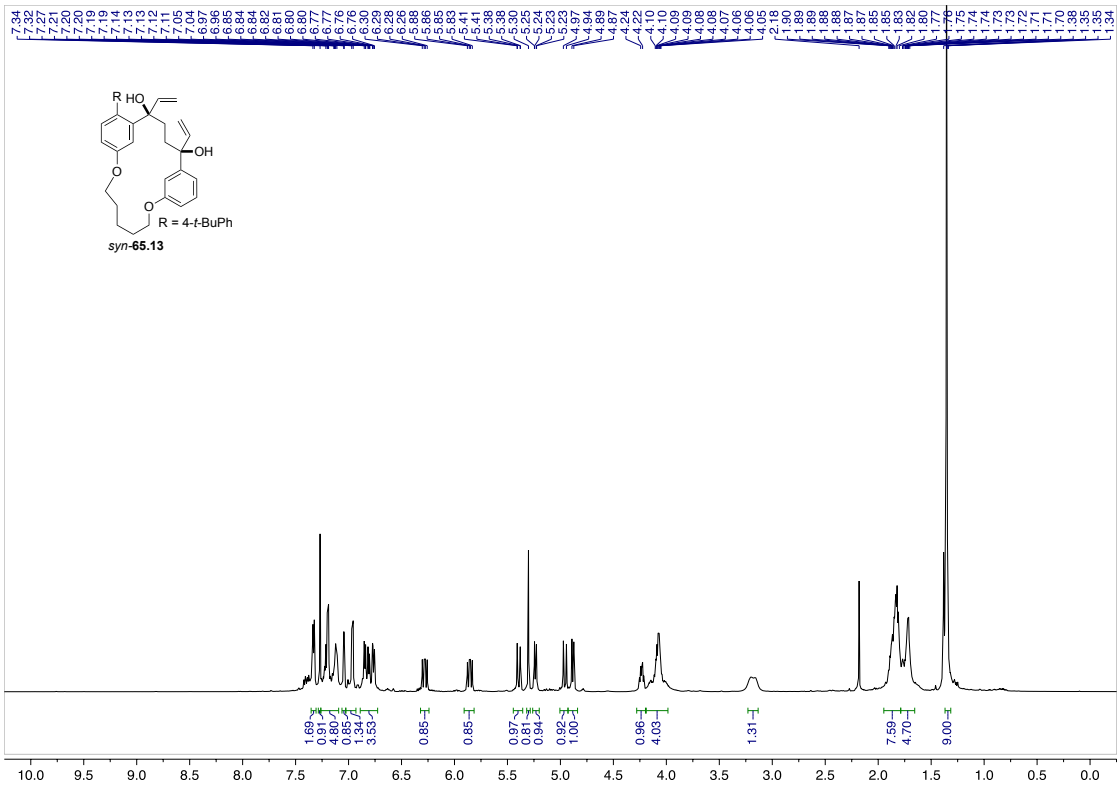
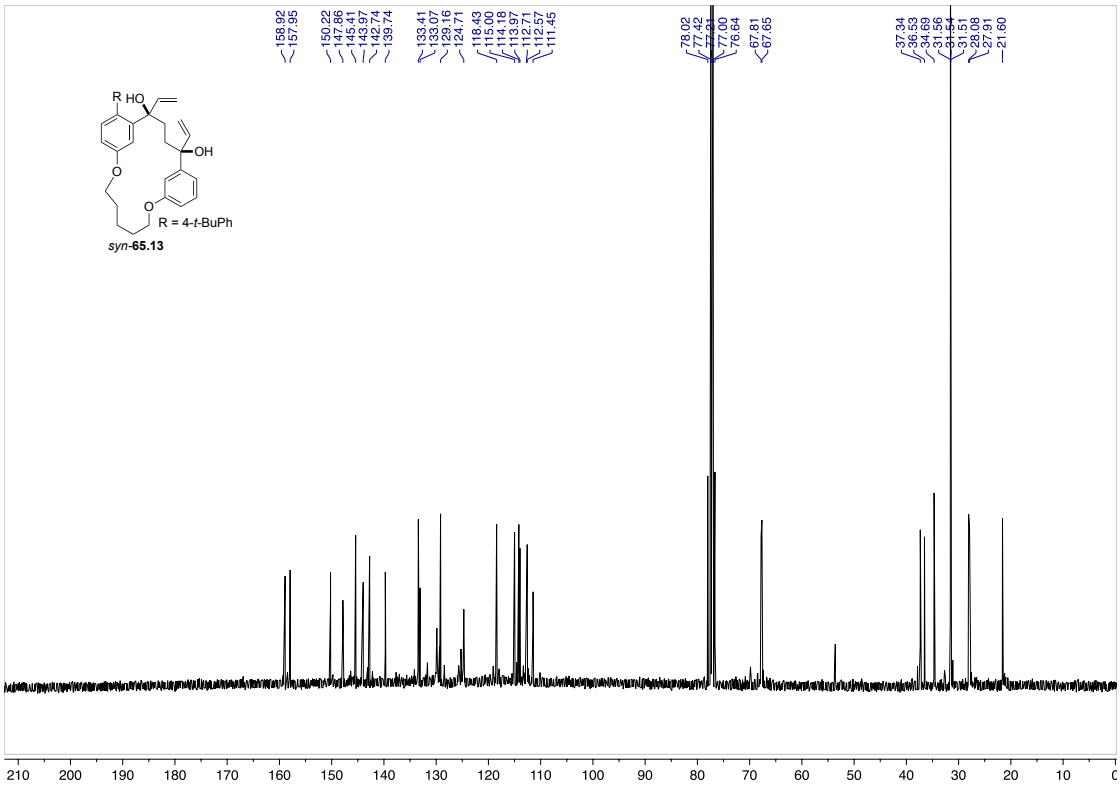
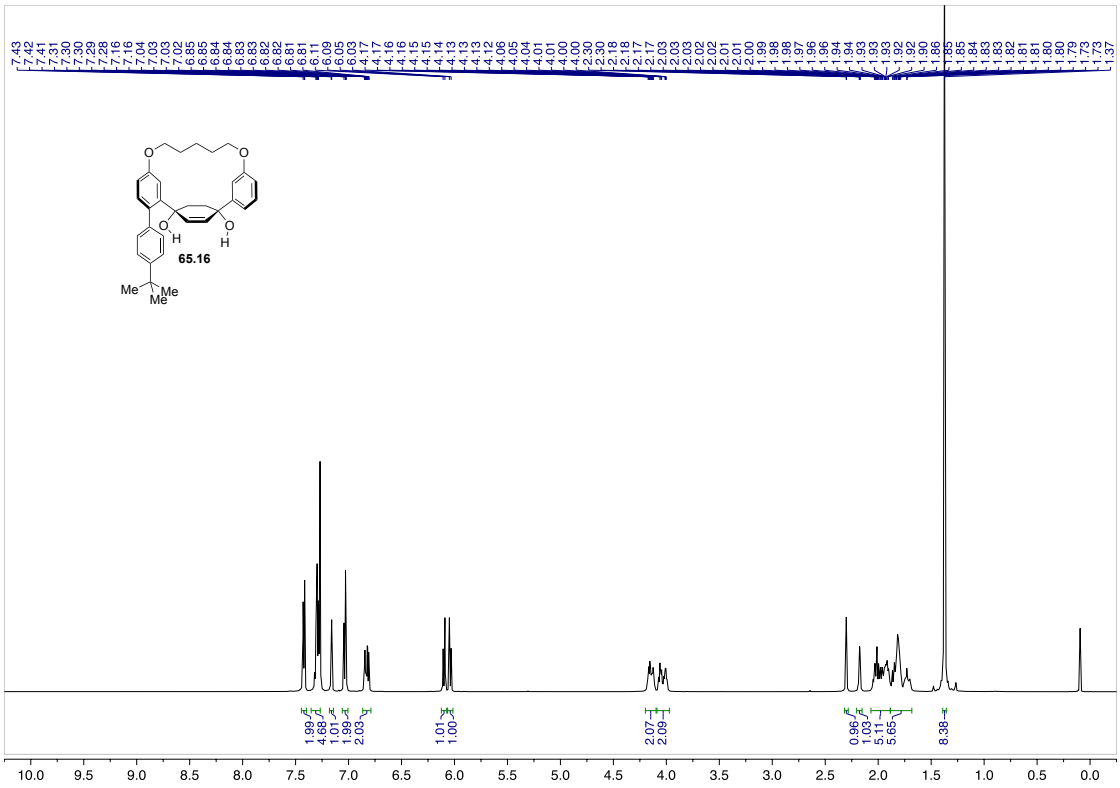

R HO
OH
O
O
R = 4-t-BuPh
syn-65.13


R HO
OH
O
O
R = 4-t-BuPh
syn-65.13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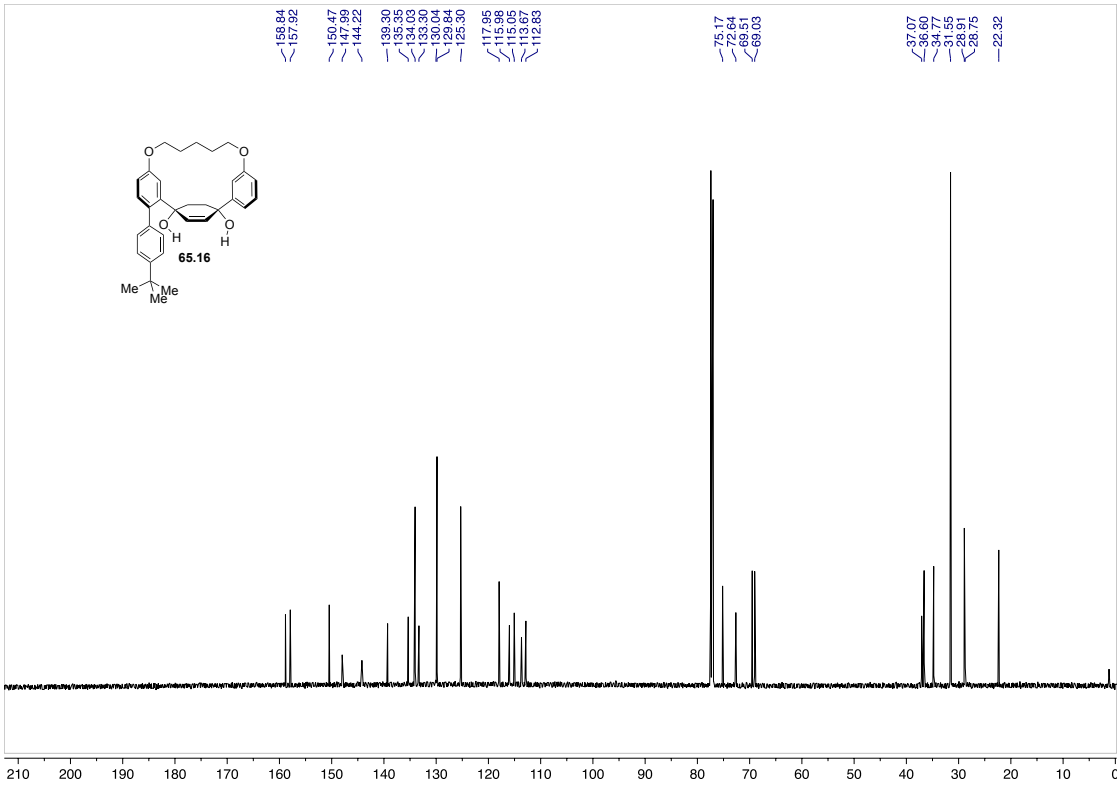
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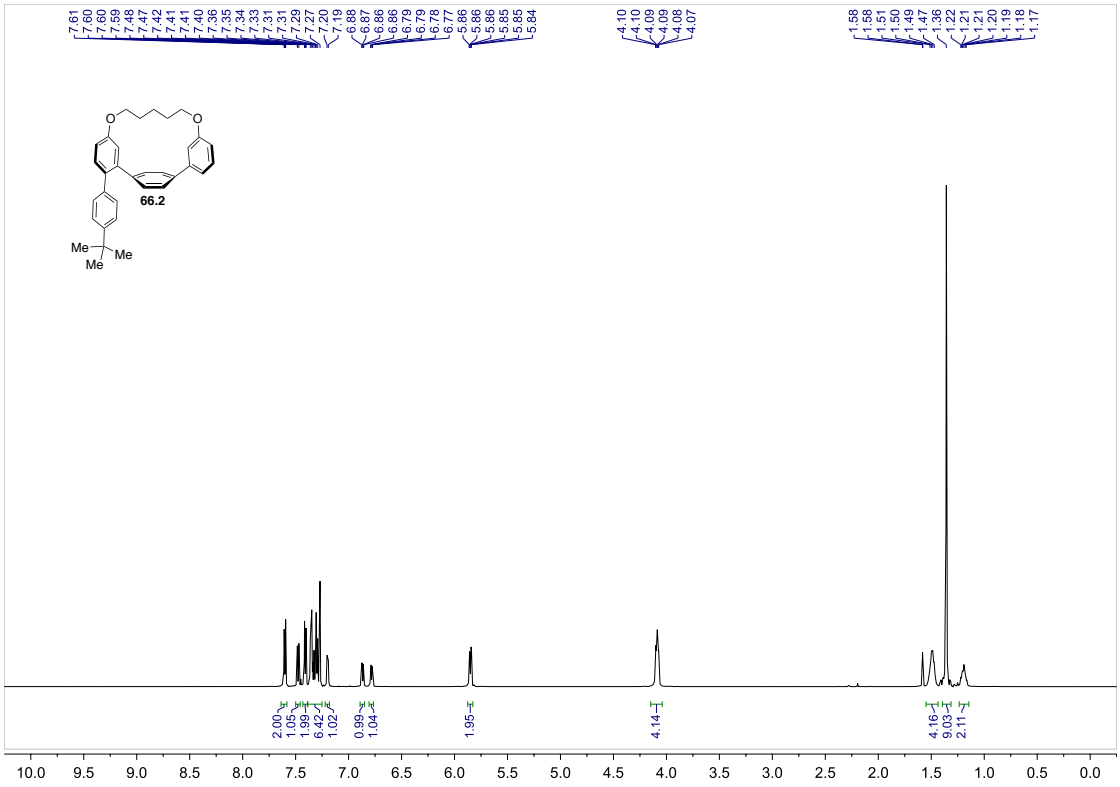
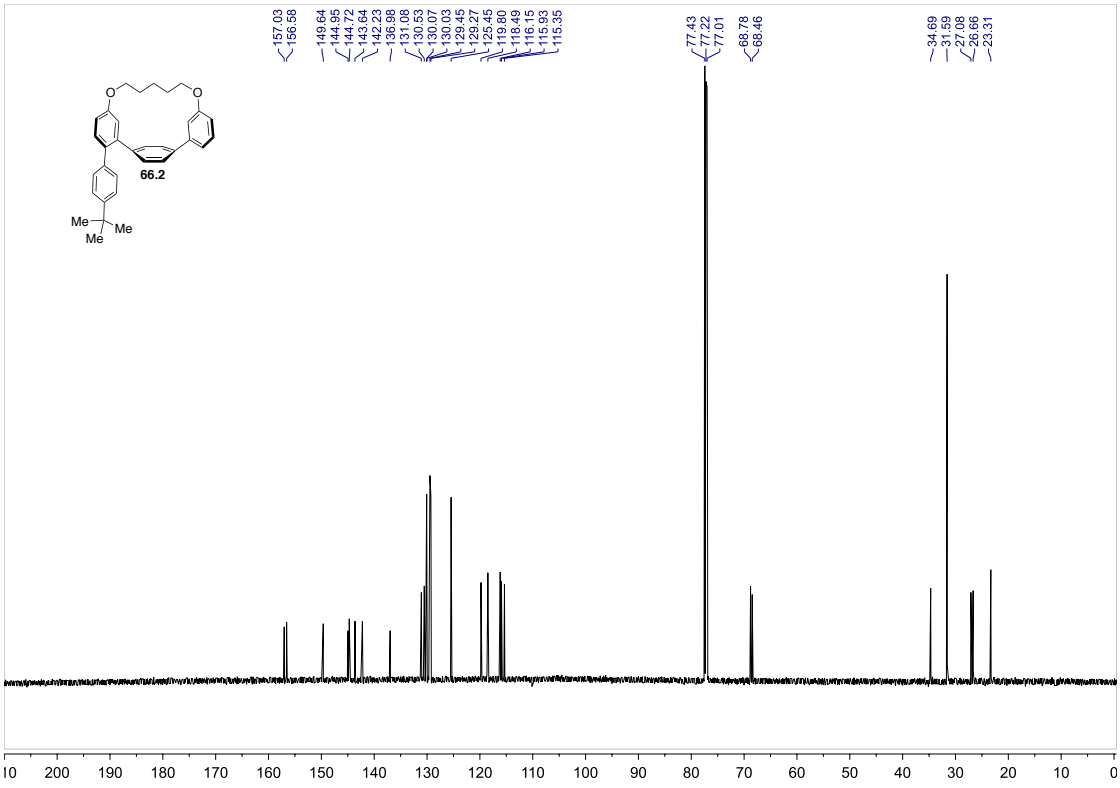

66.2
Me
Me
Me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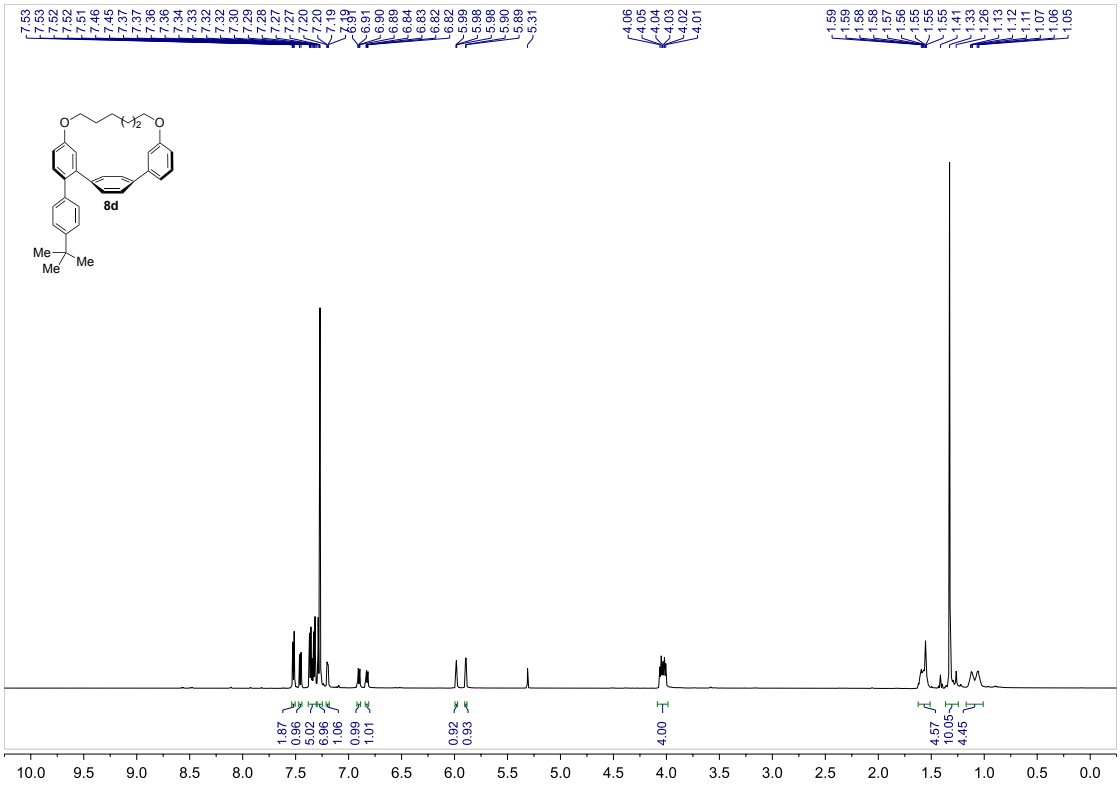
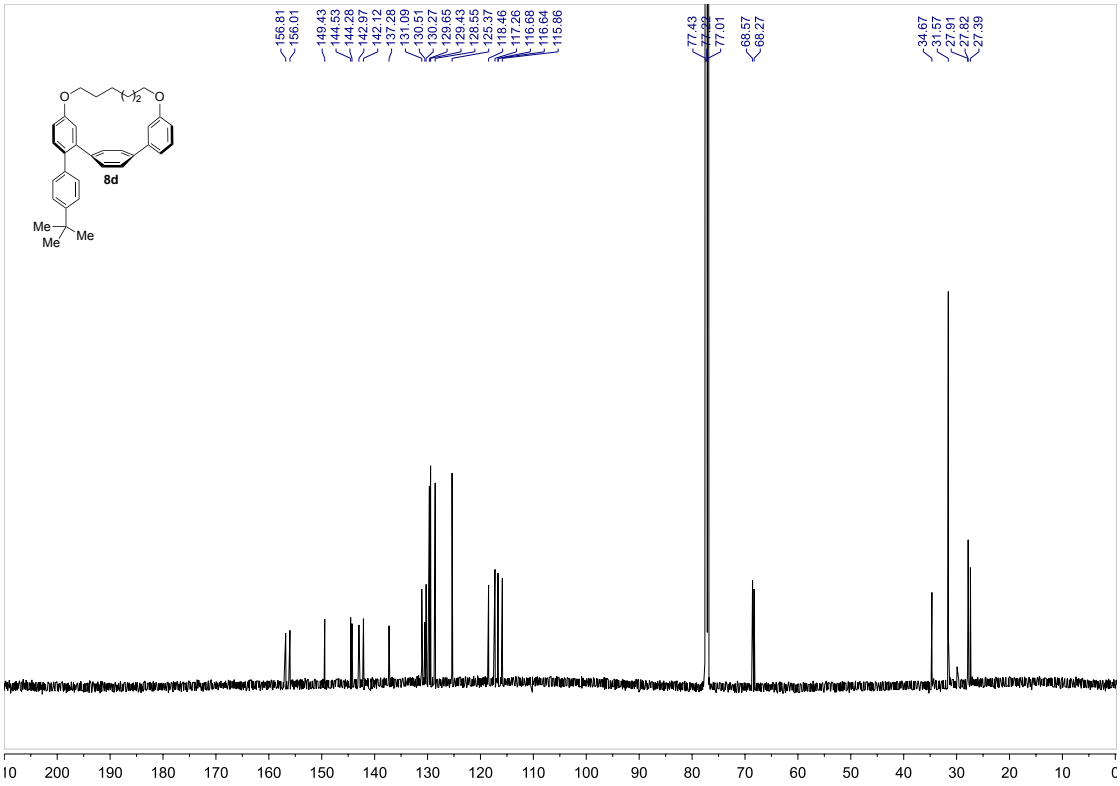
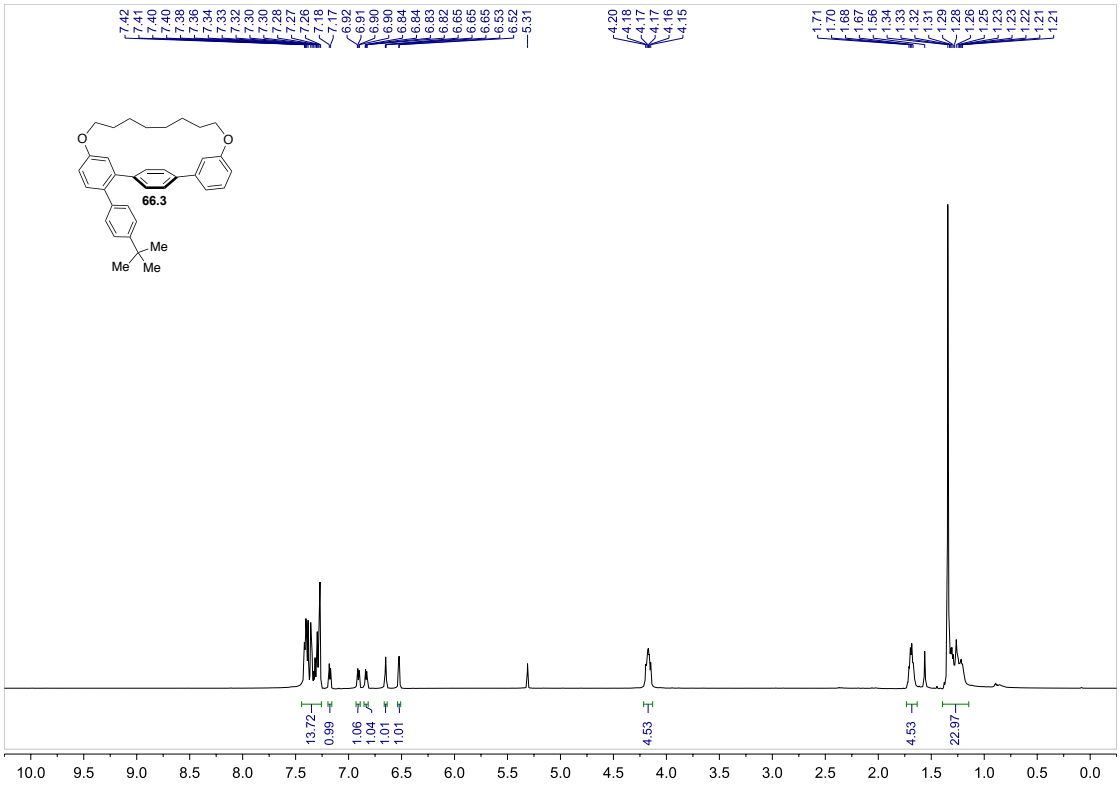
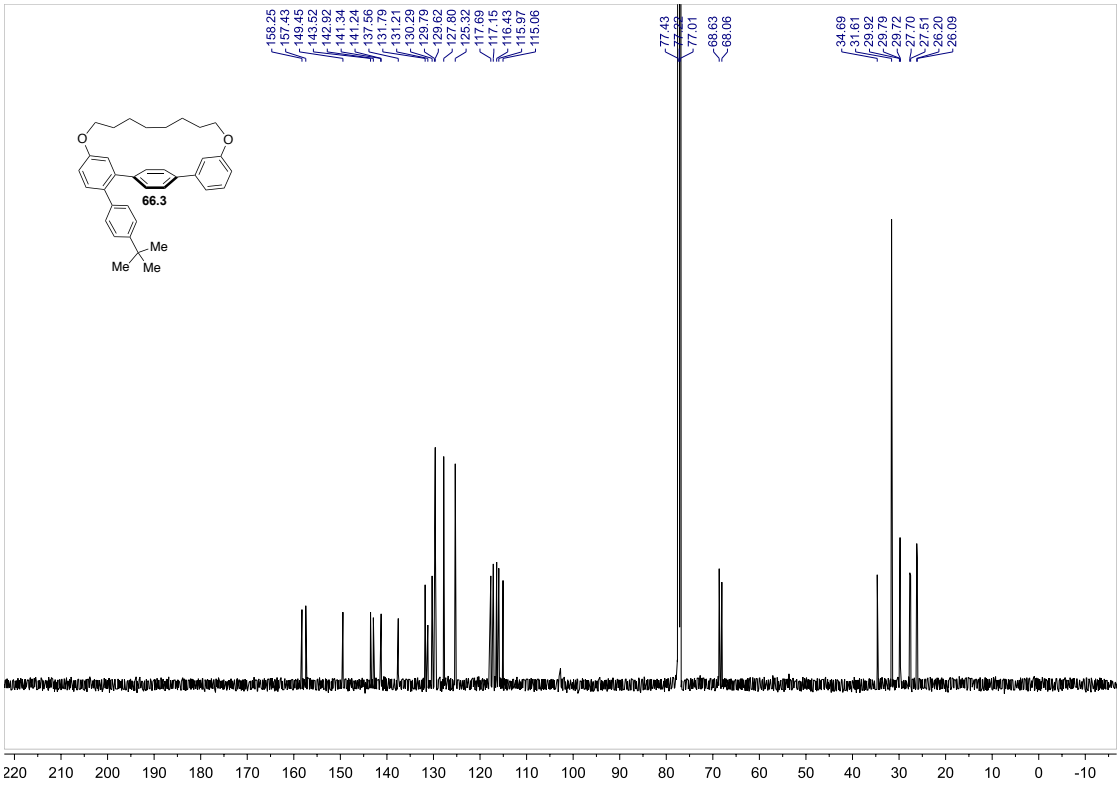

8d
Me
Me
Me


8d
Me
Me
Me


66.3
Me
Me
Me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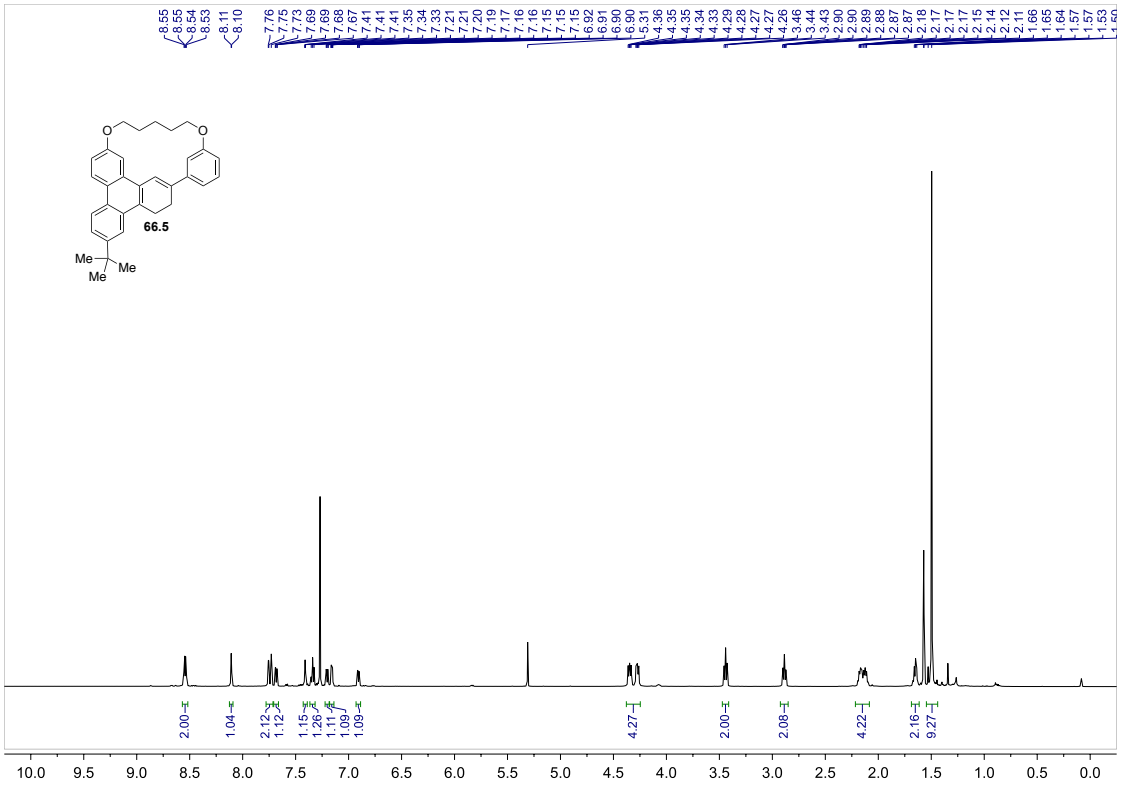
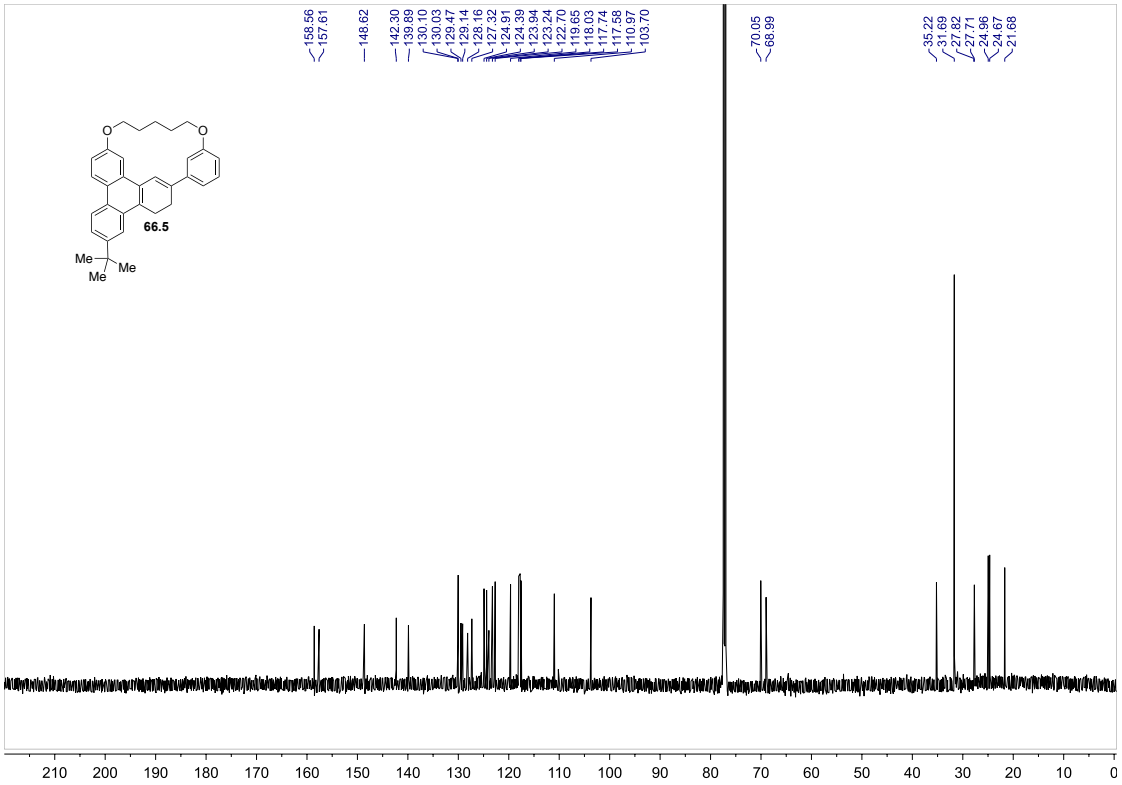
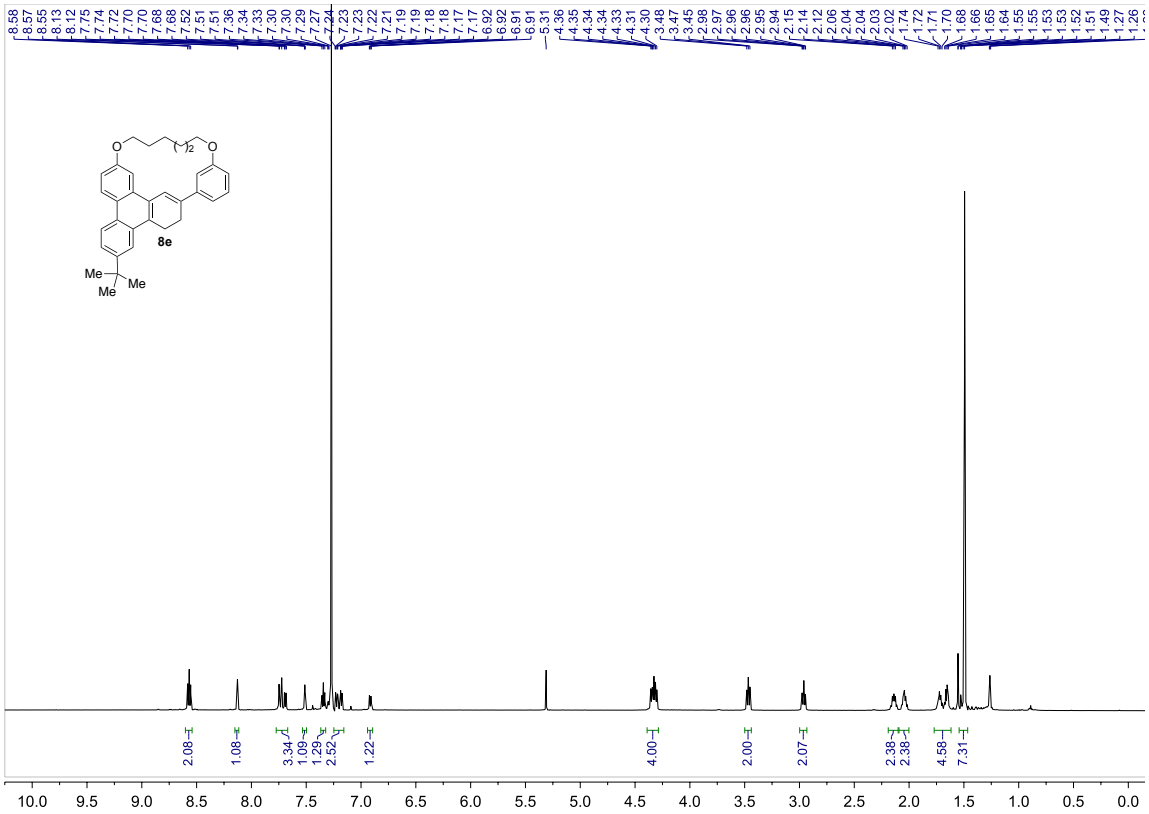
Me
Me
Me


66.5
Me
Me
Me


66.5
Me
Me
Me


8e
Me
Me
Me
2.08
1.08
3.34
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1.29
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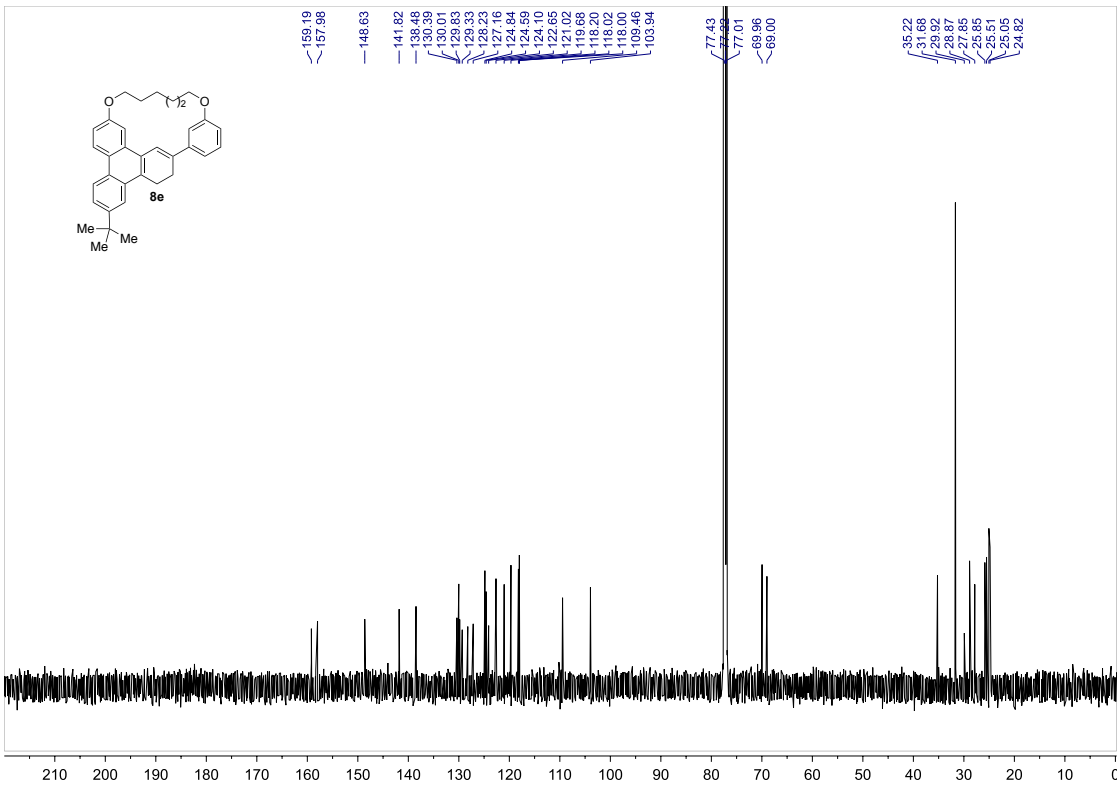
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127.16
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124.59
124.10
122.65
121.02
119.68
118.20
118.02
118.00
109.46
103.94
77.43
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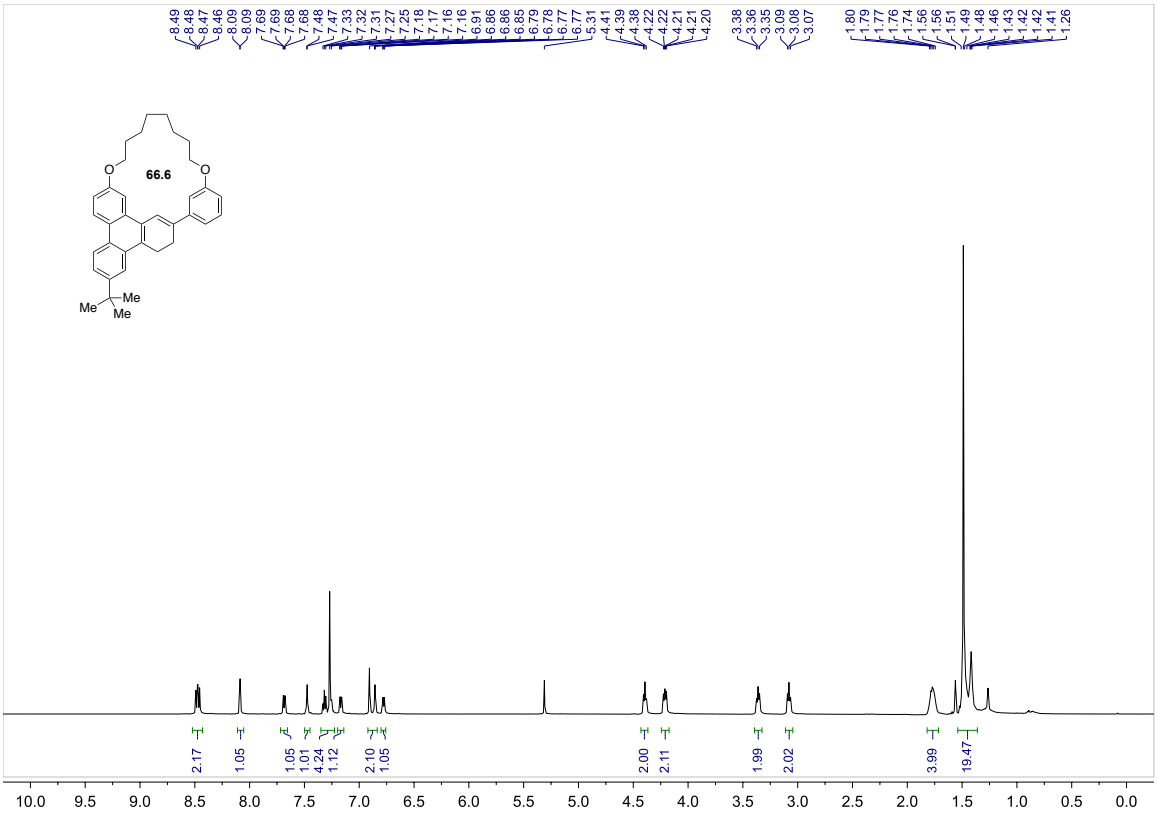
24.82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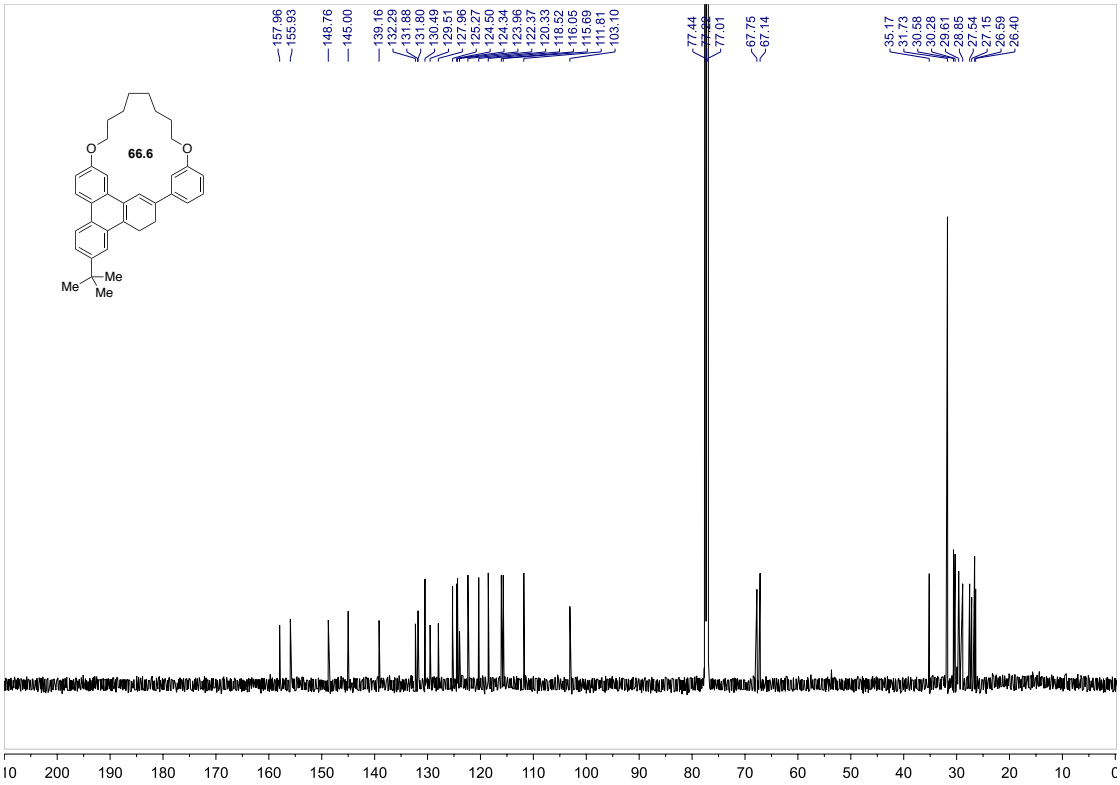
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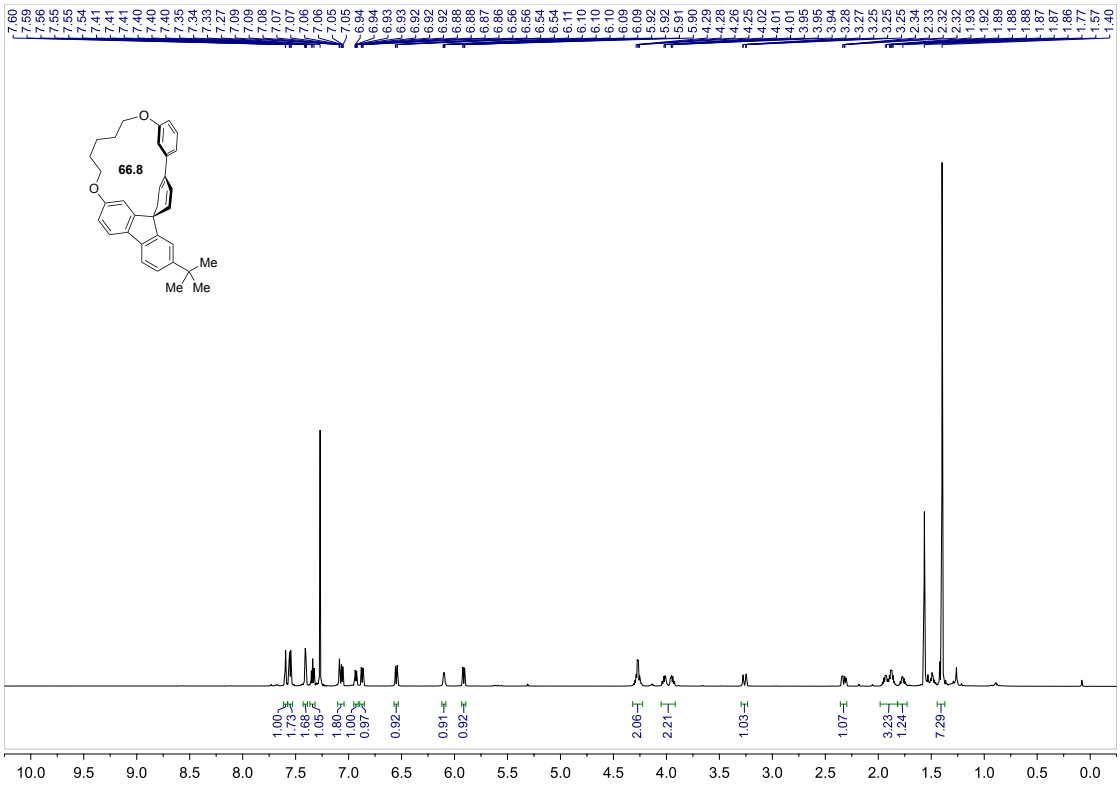
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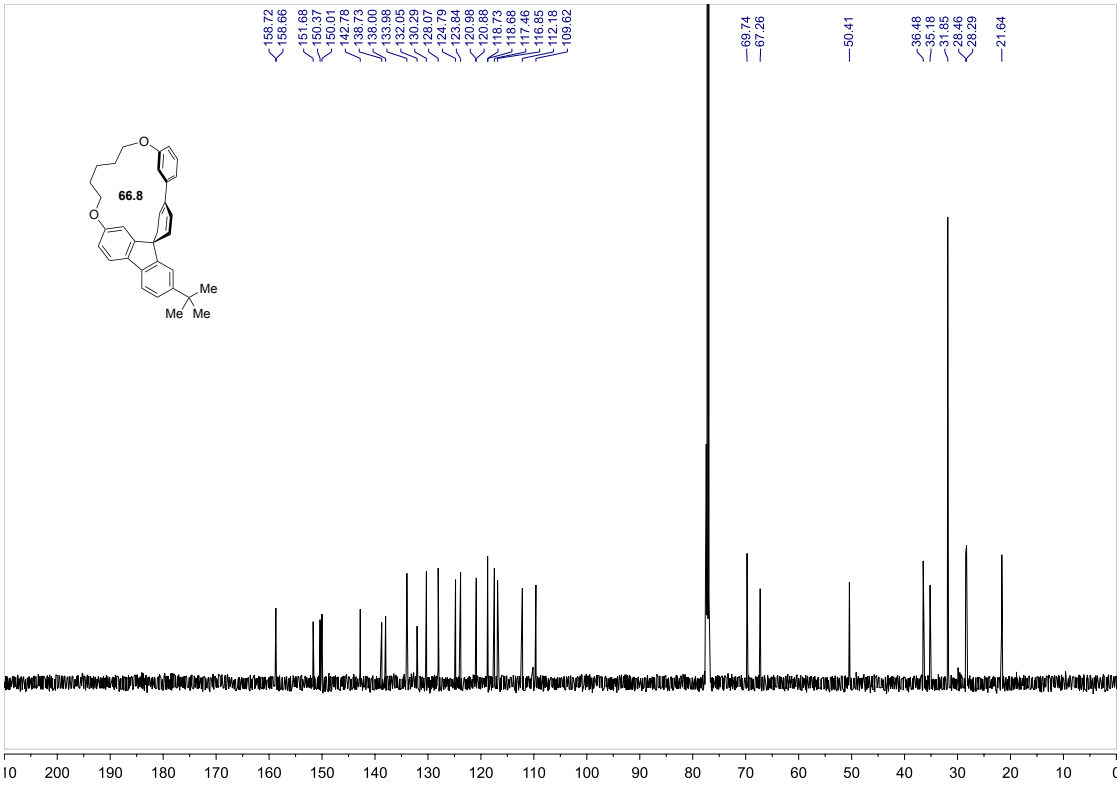
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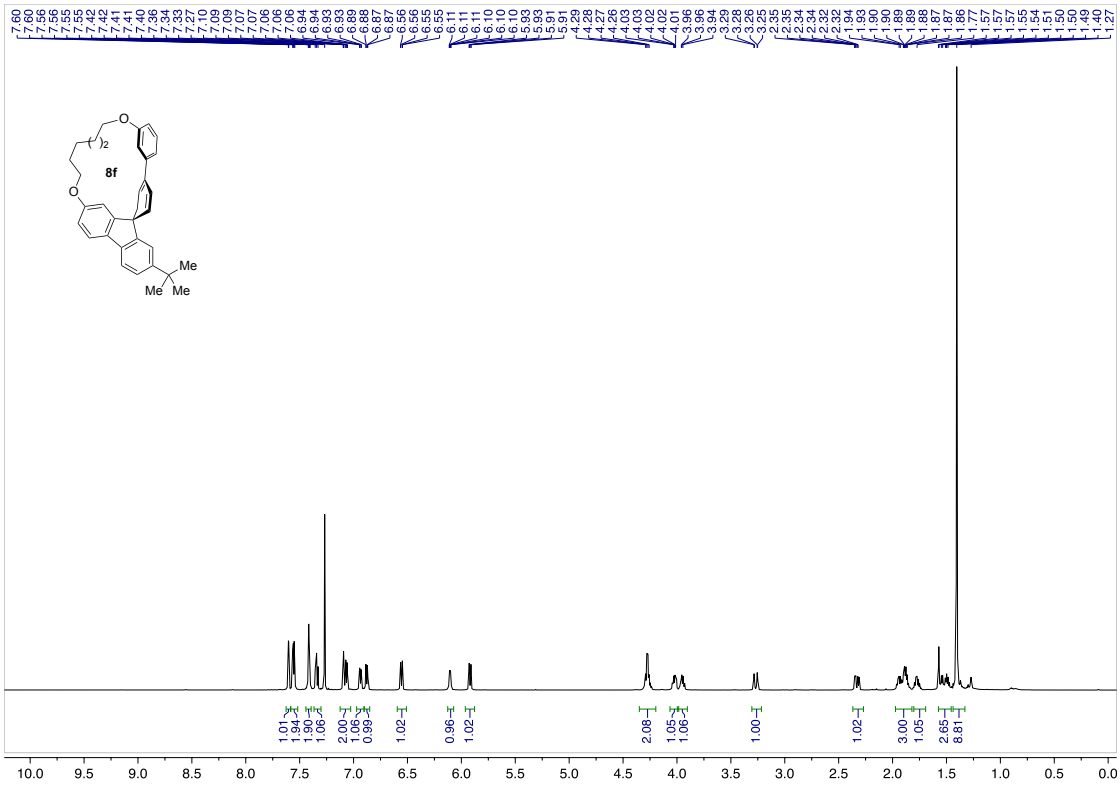
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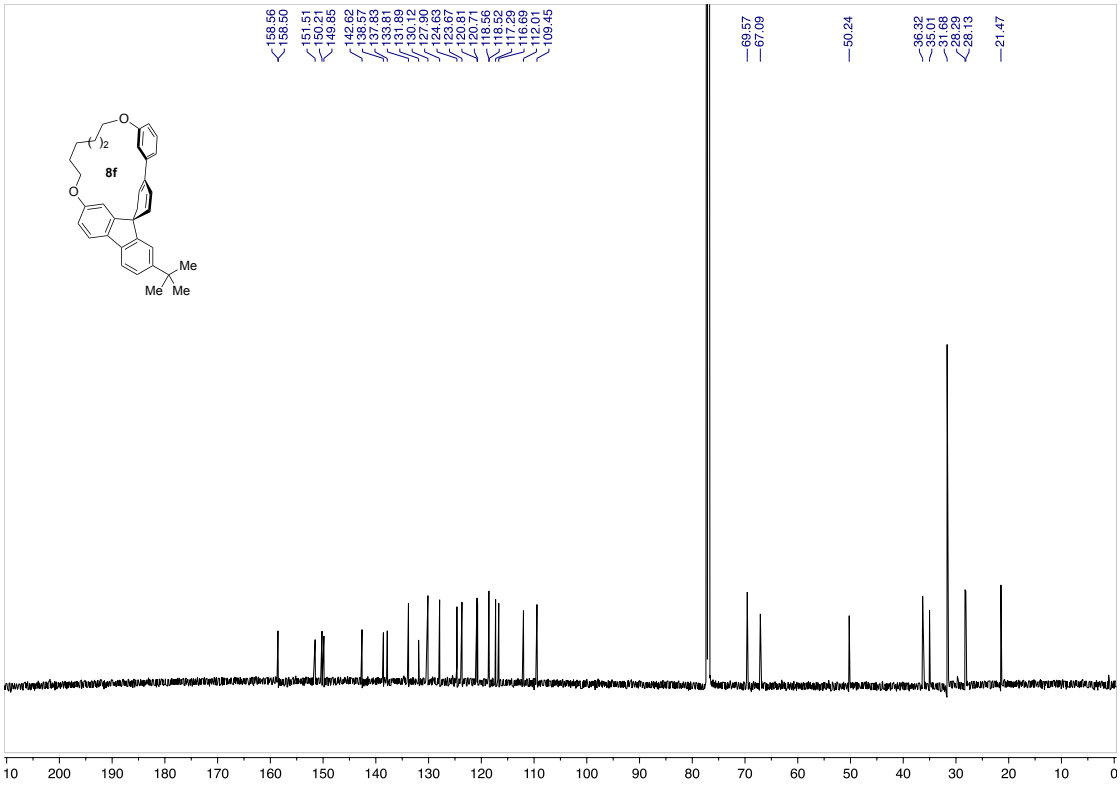
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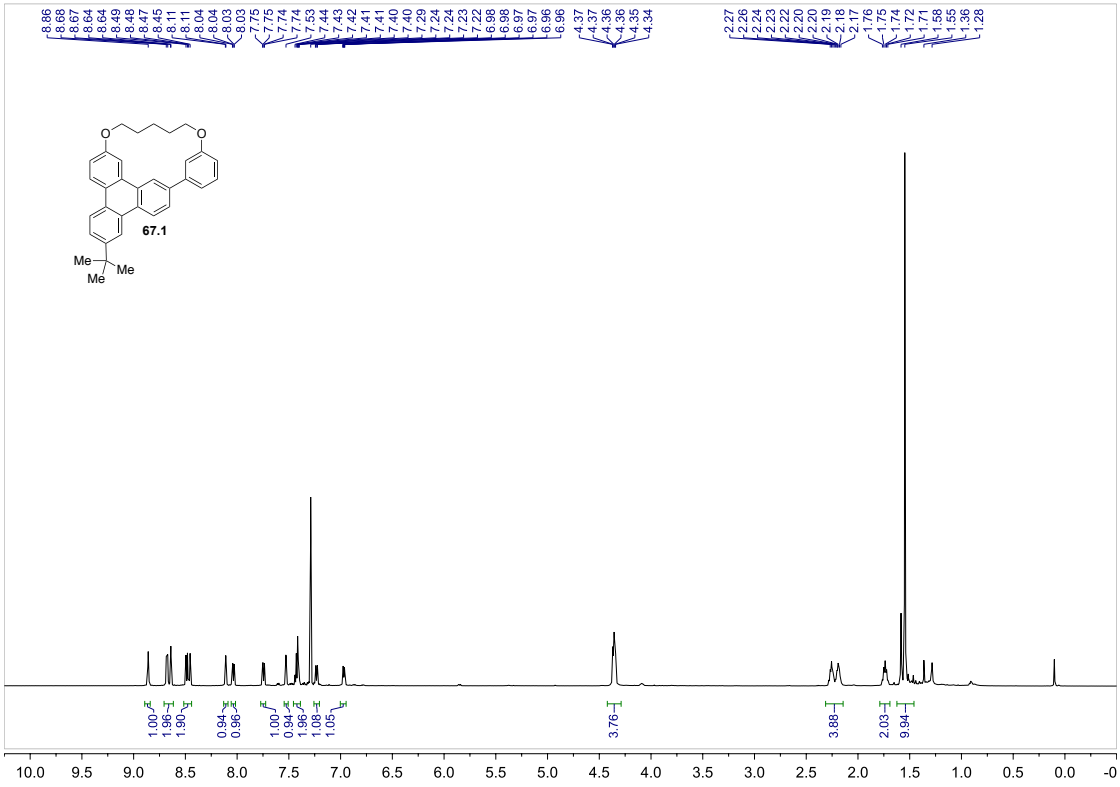
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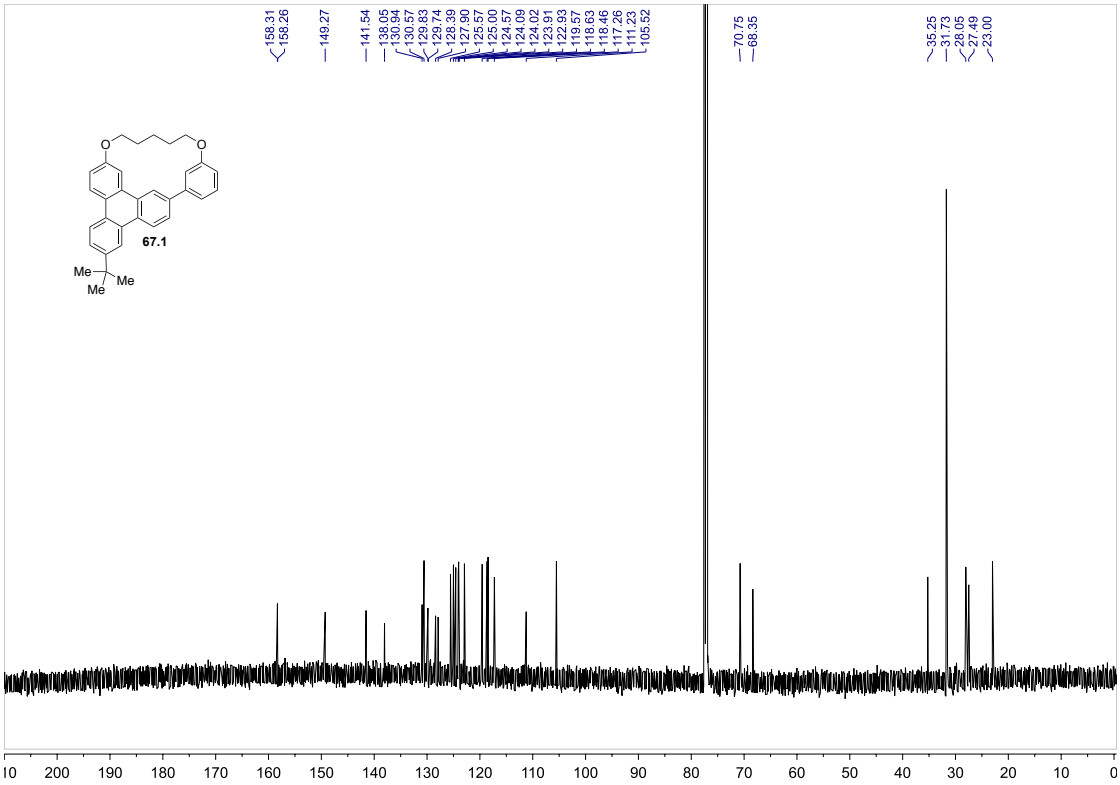
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124.09
124.02
123.91
122.93
119.57
118.63
118.46
117.26
111.23
105.52
70.75
68.35
35.25
31.73
28.05
27.49
23.00
67.1
Me
Me
Me
10
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10
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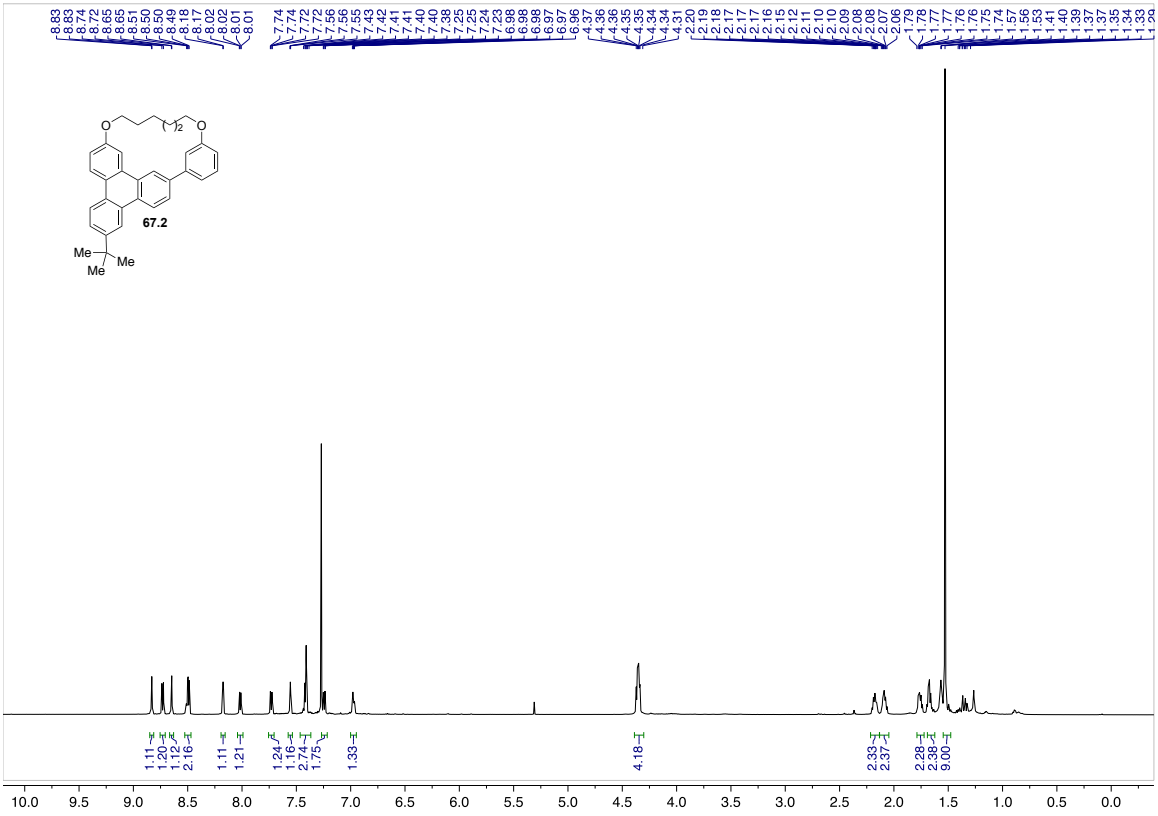
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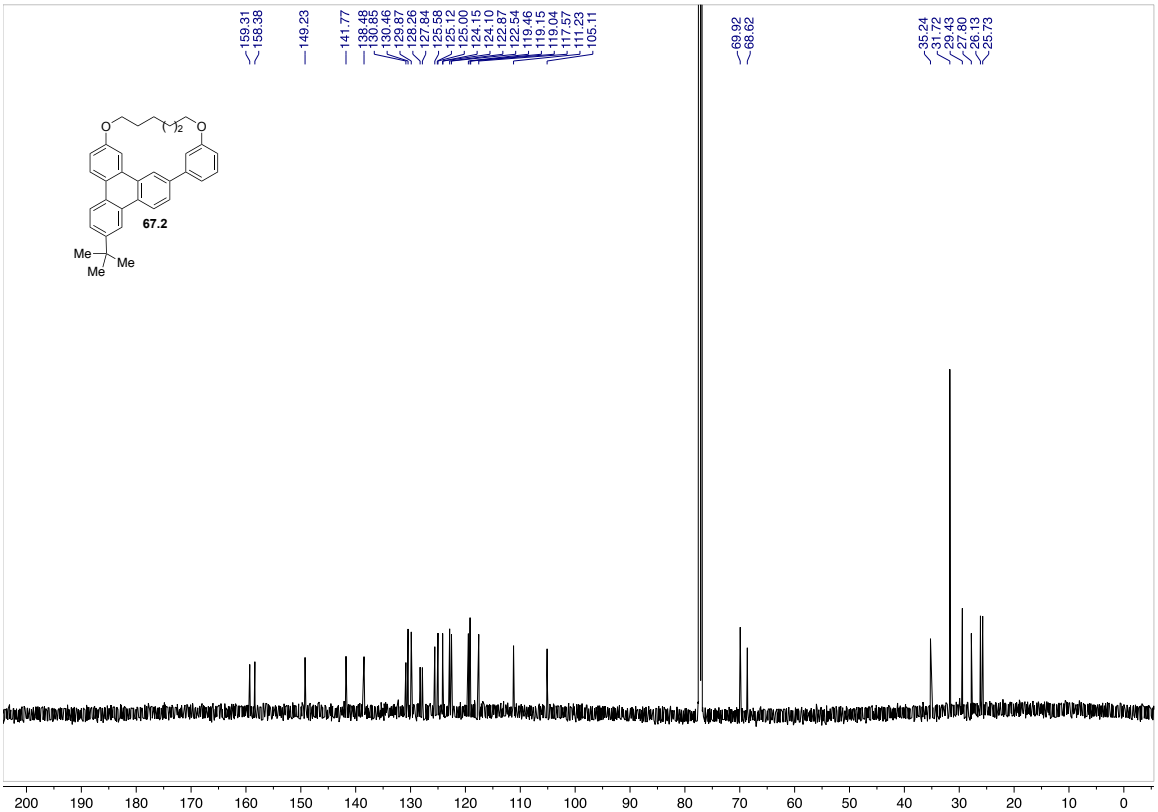
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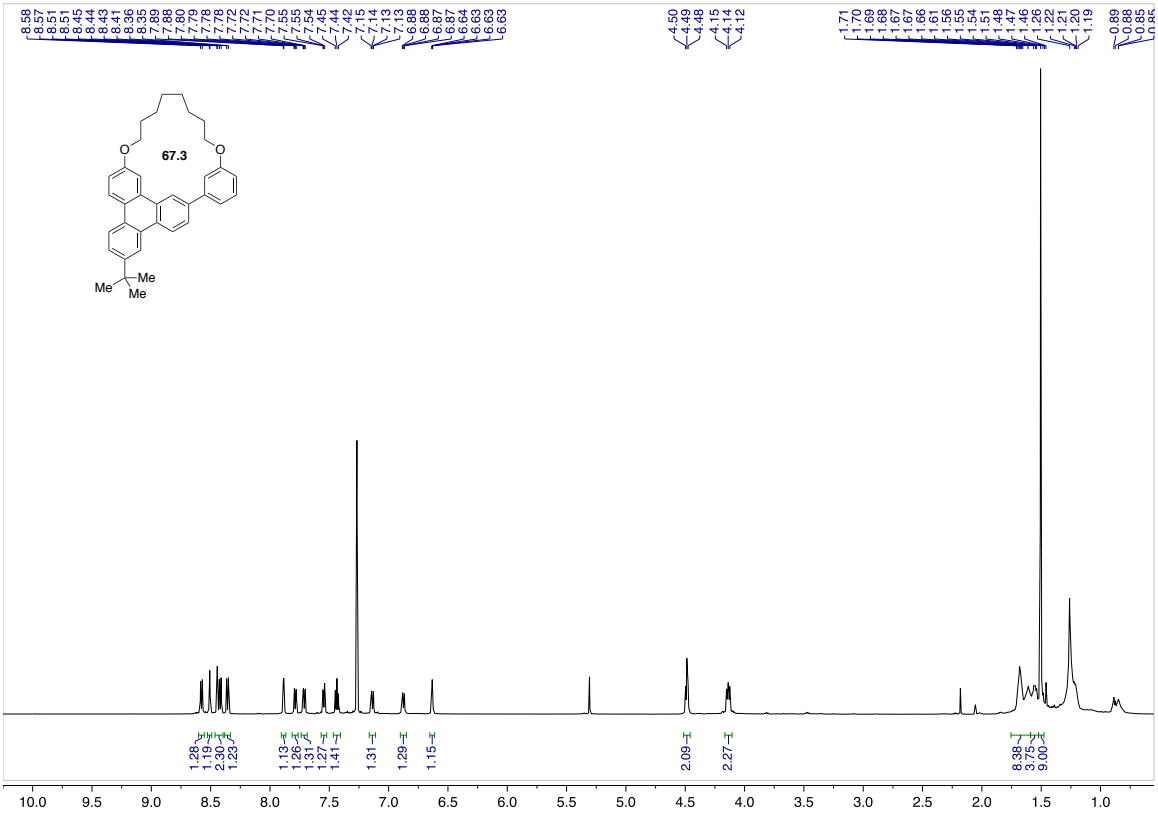
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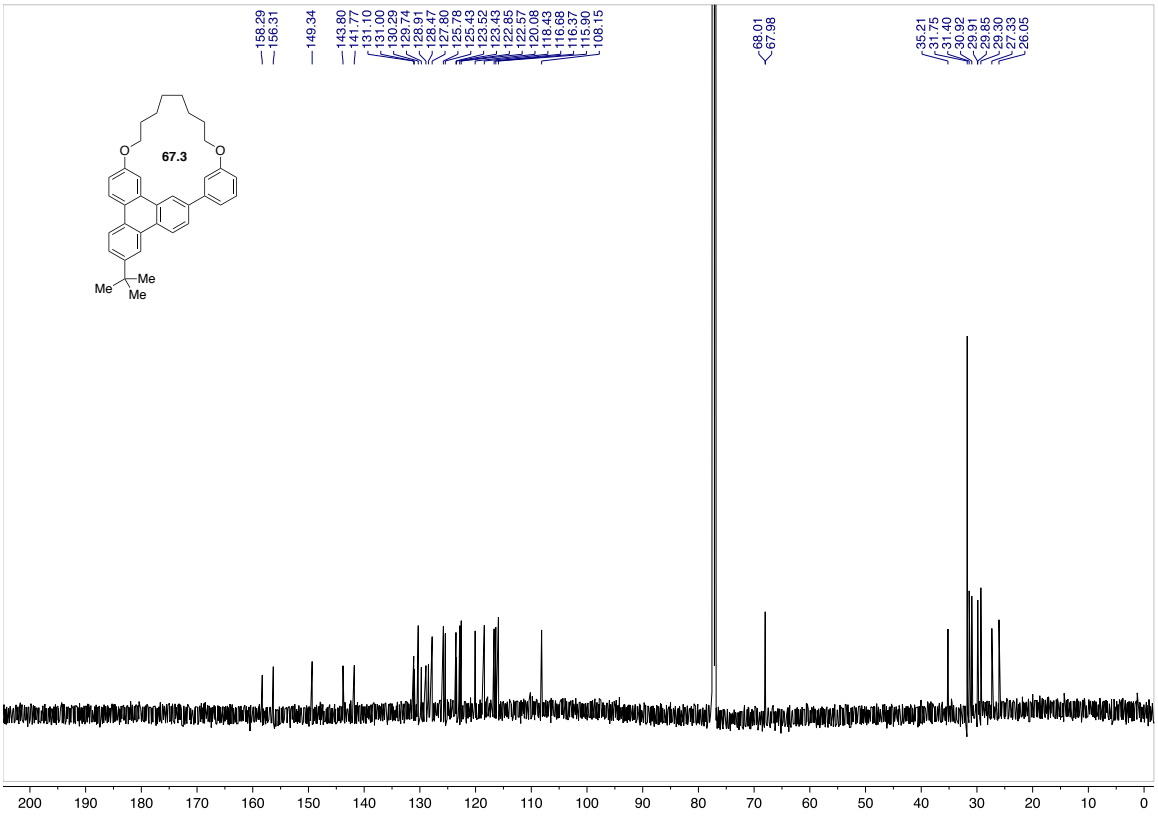
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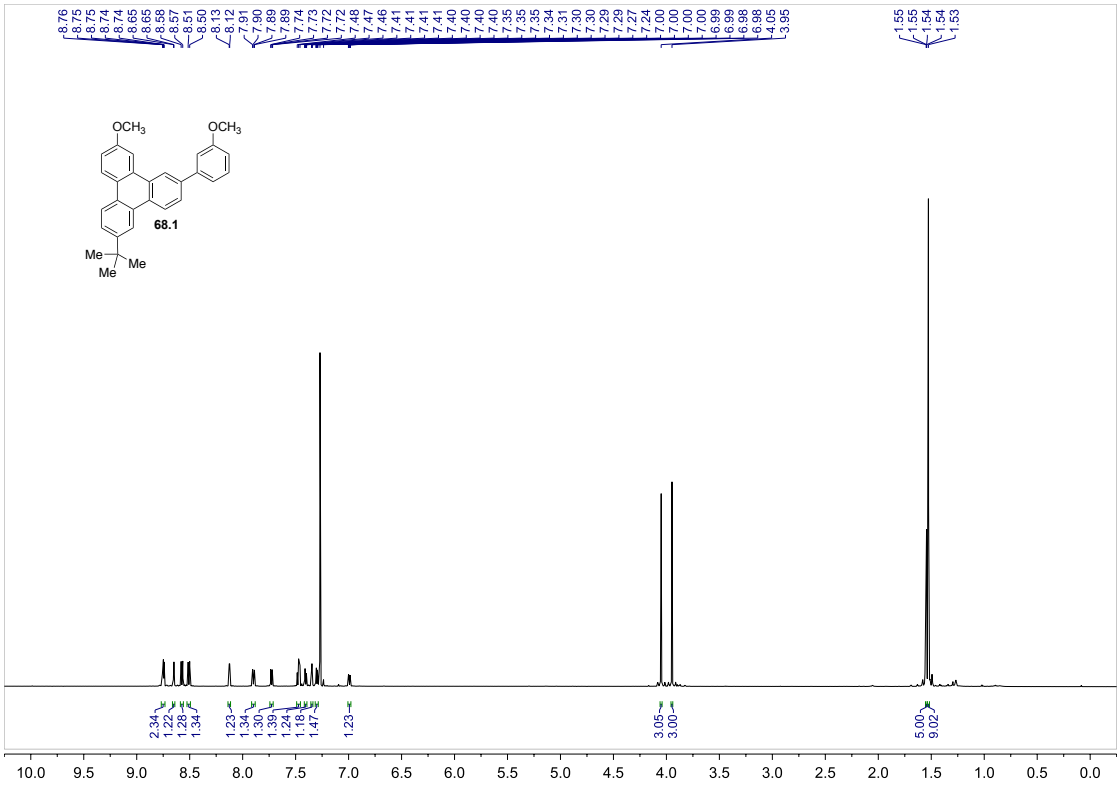
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Me
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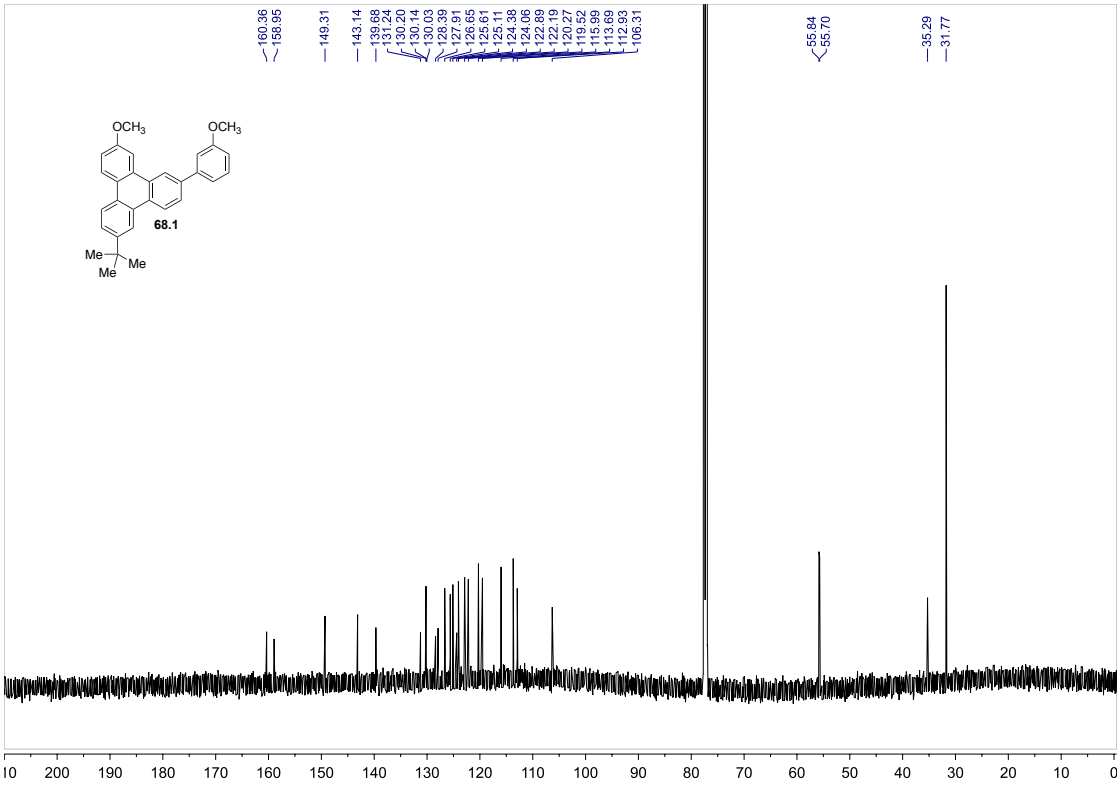
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Me
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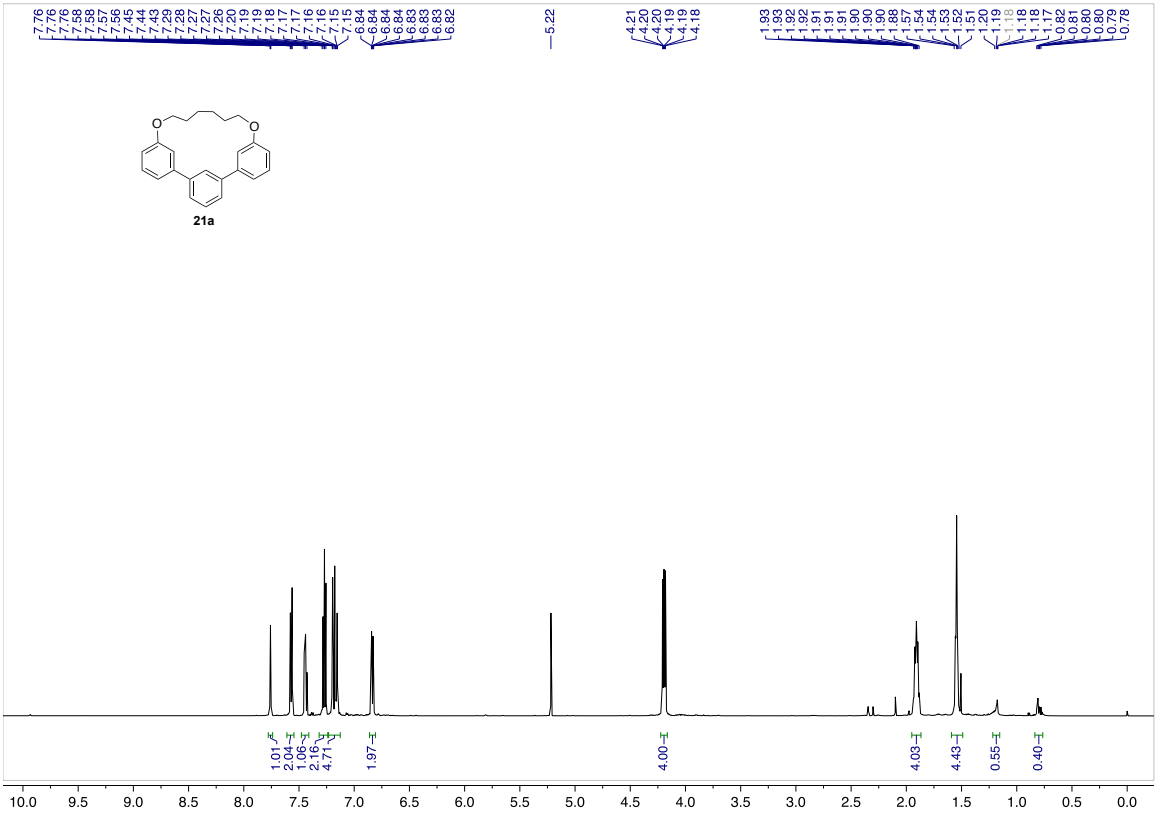
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1.17
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0.80
0.80
0.79
0.78
O
O
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1.01
2.04
1.06
2.16
4.71
1.97
4.00
4.03
4.43
0.55
0.40
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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6.0
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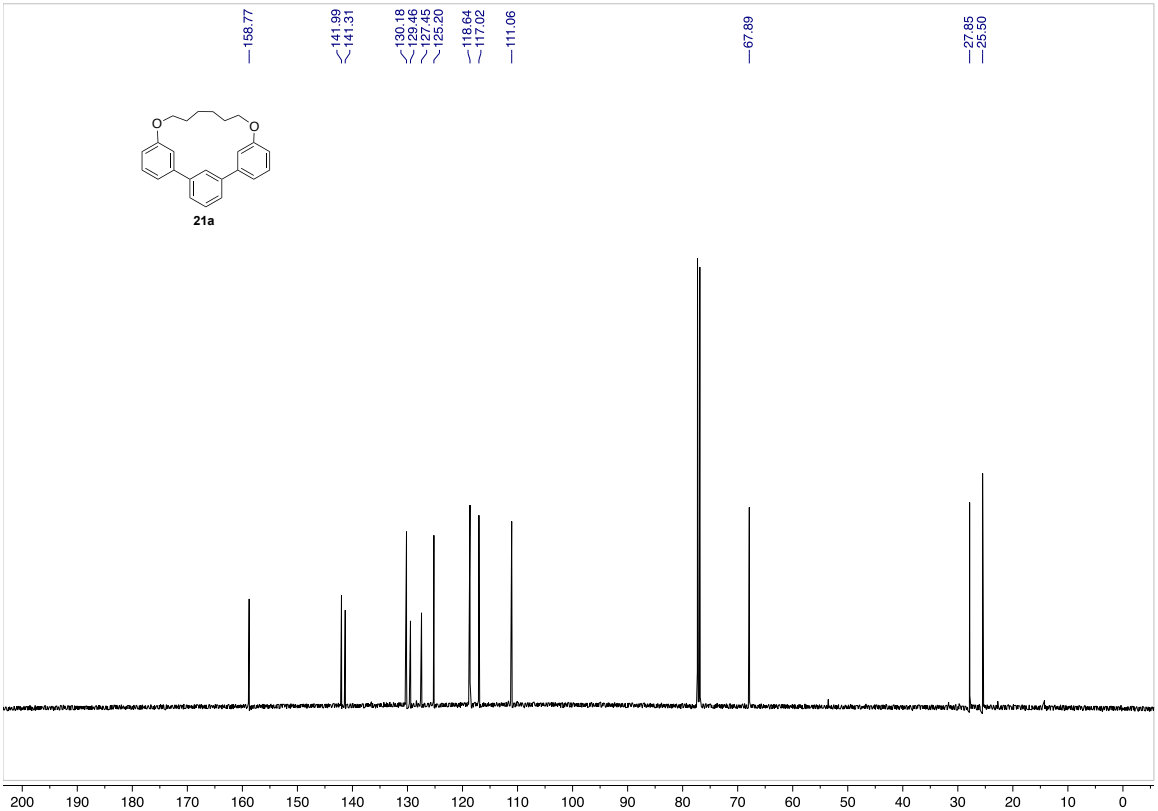
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111.06
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25.50
O
O
21a
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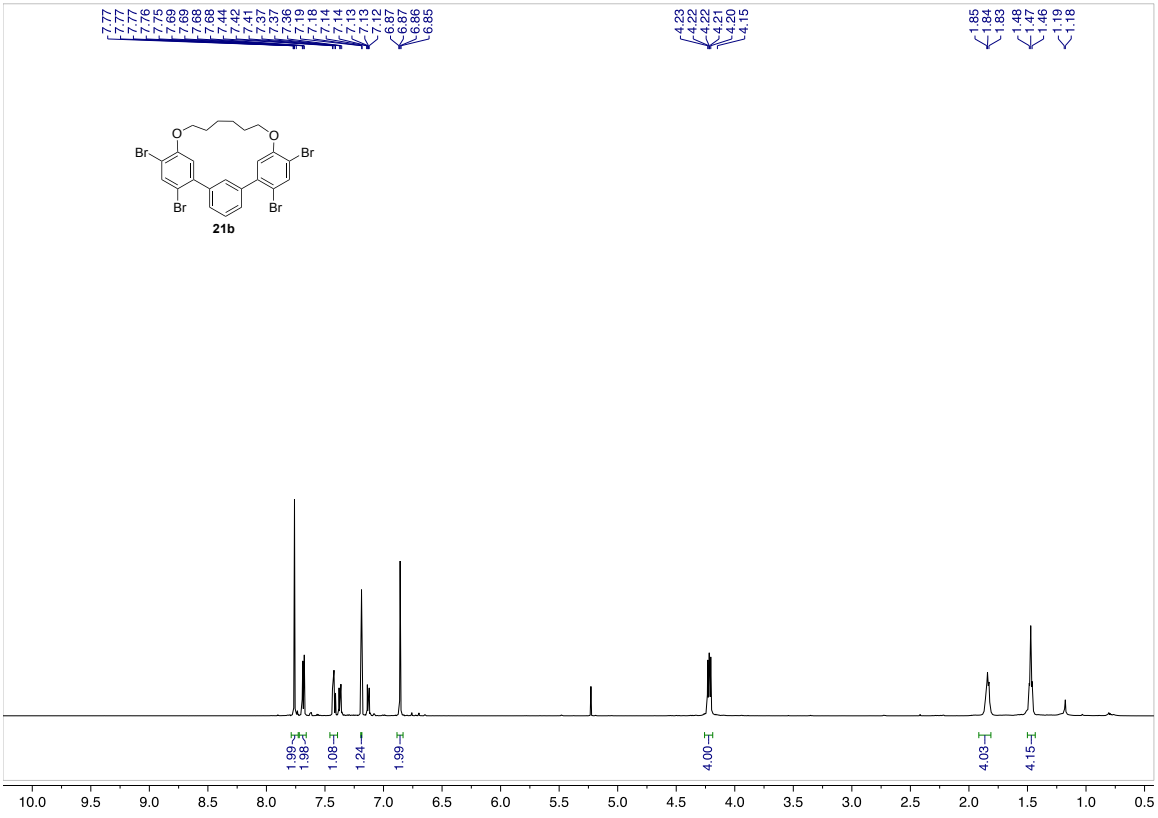
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1.83
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1.19
1.18
Br
Br
Br
Br
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O
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1.08
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4.03
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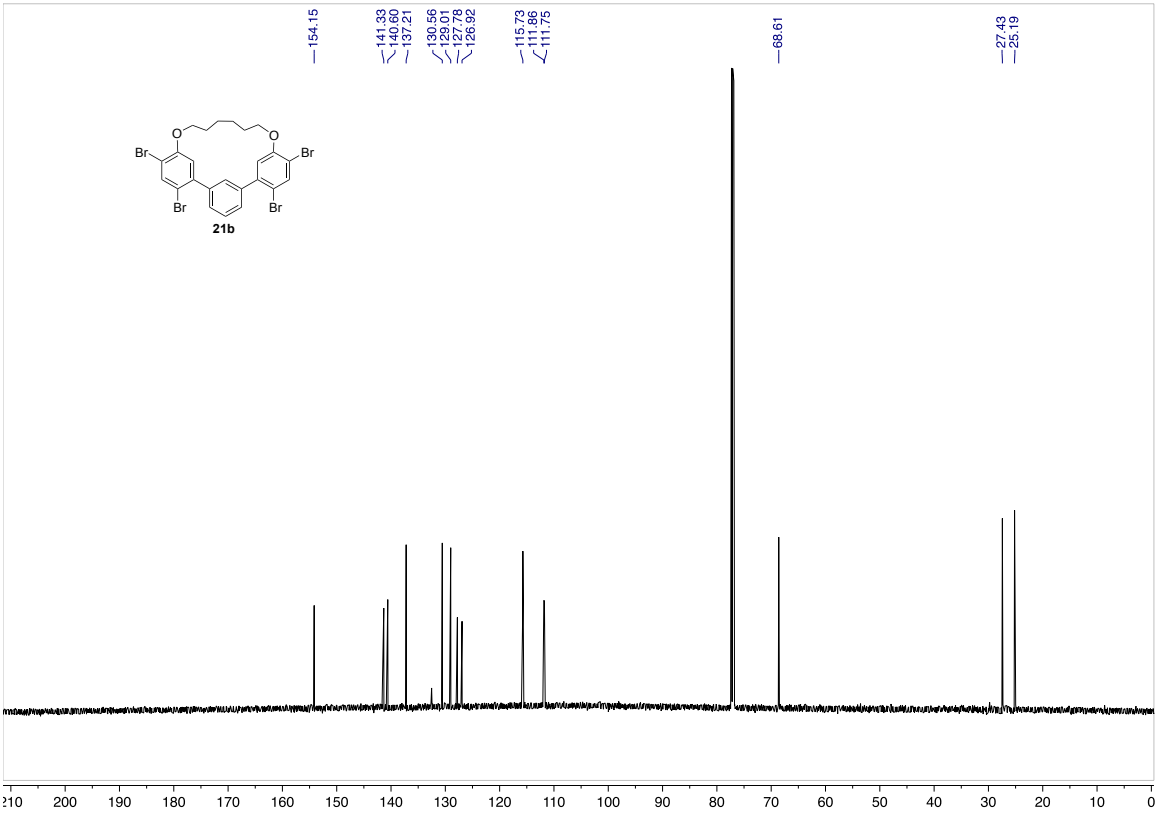
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111.75
68.61
27.43
25.19
Br
Br
Br
Br
O
O
21b
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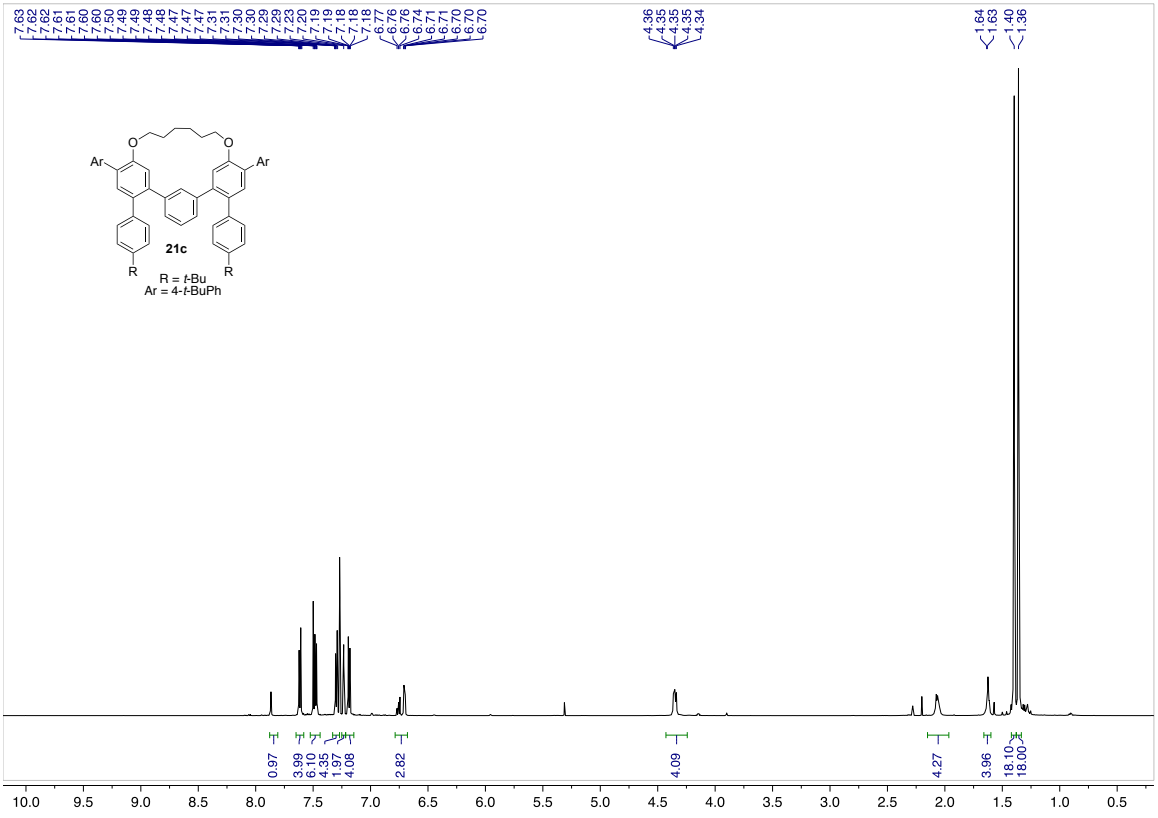
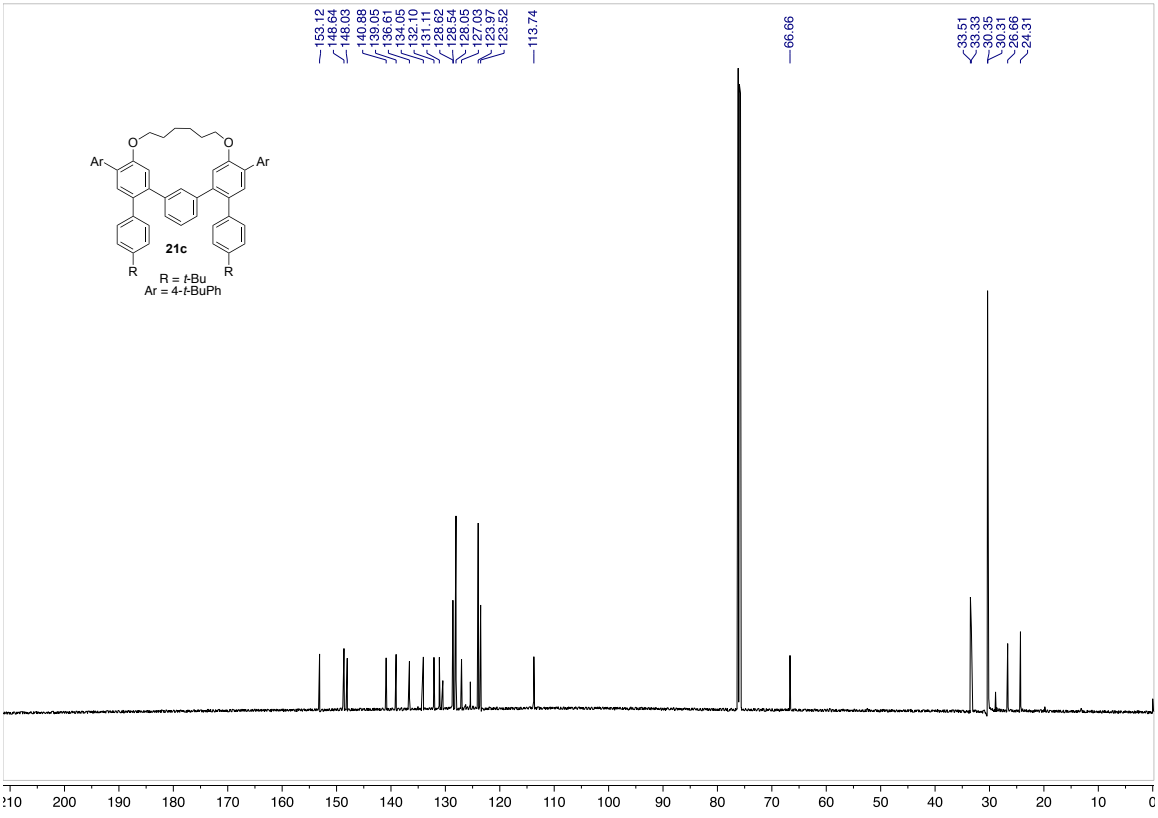
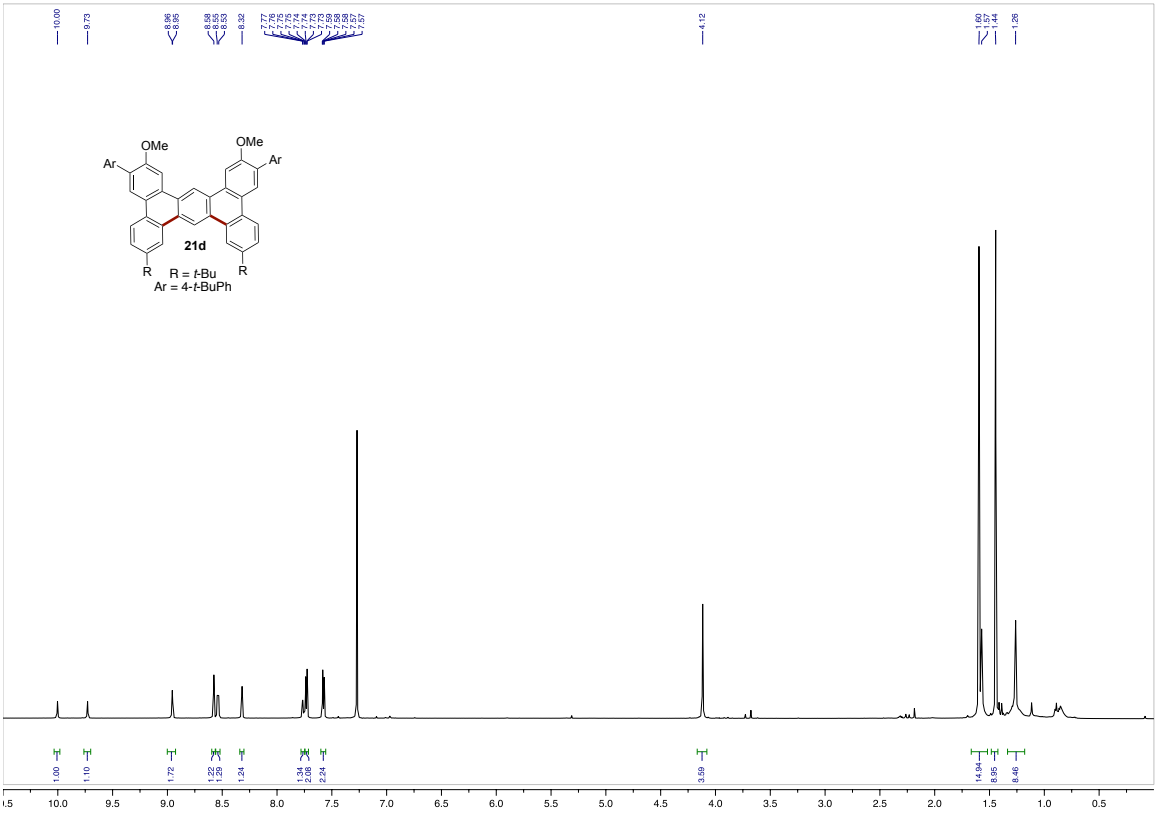
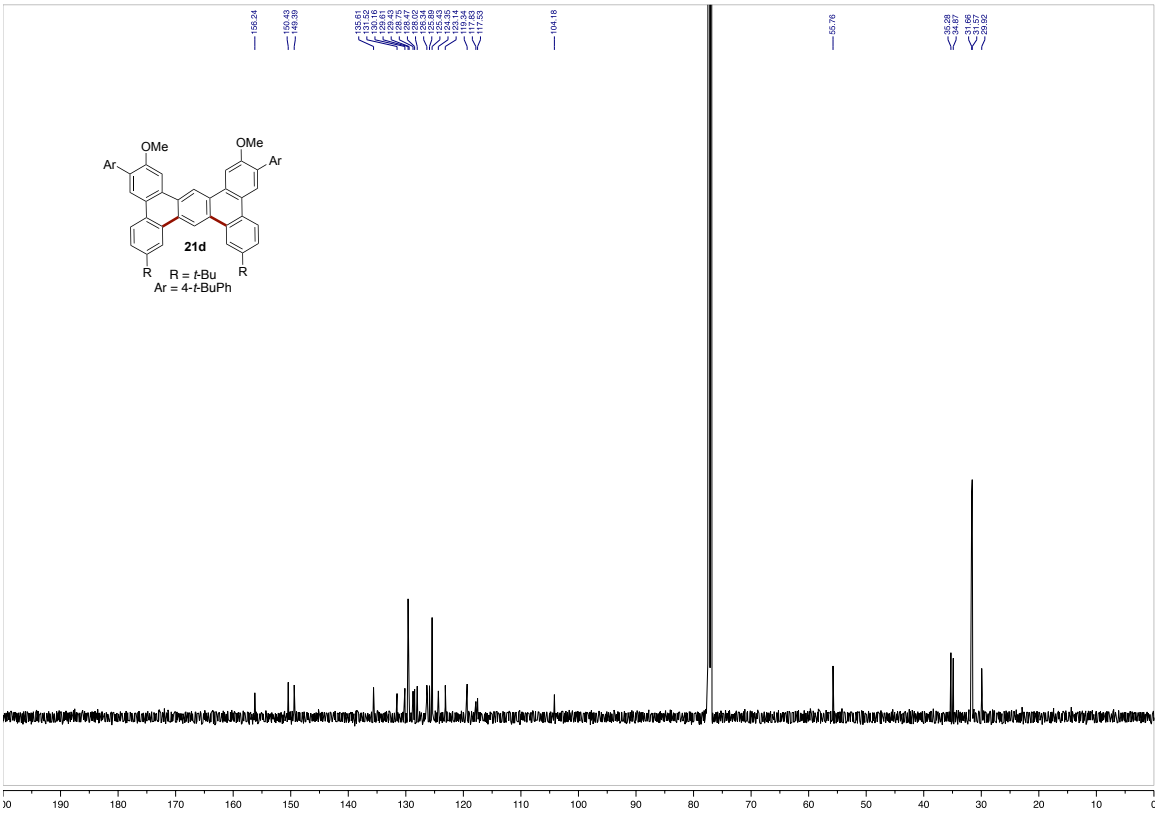
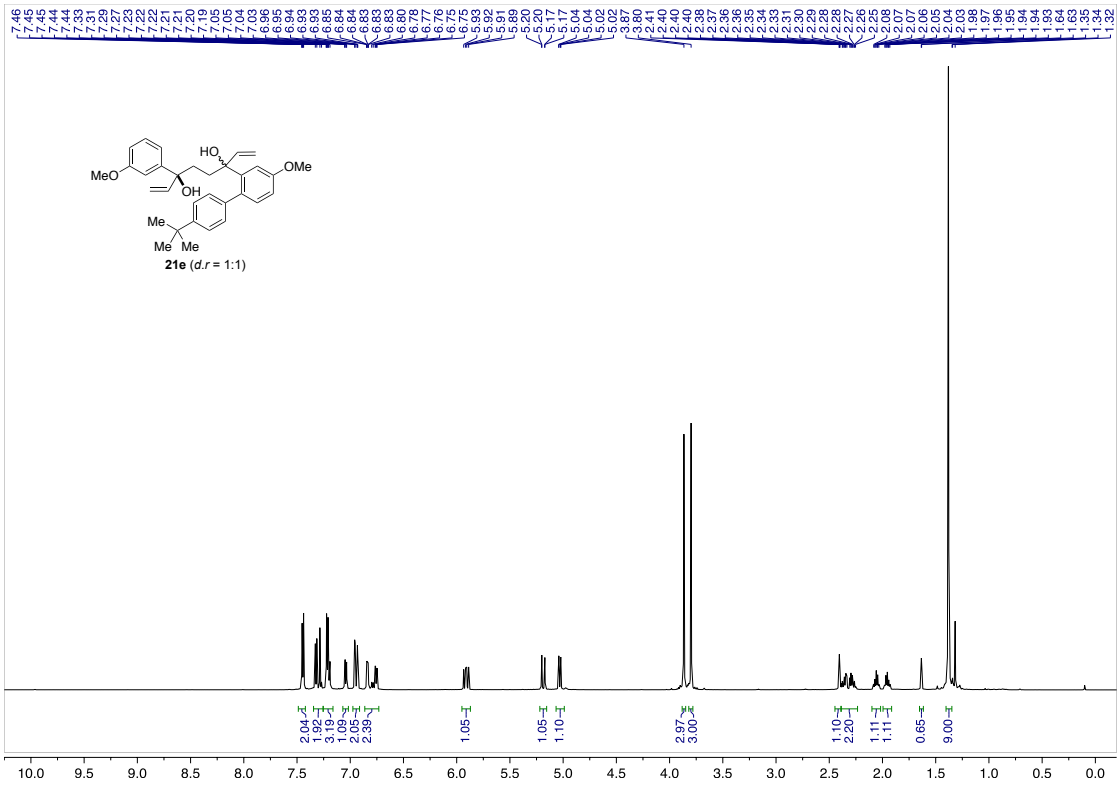
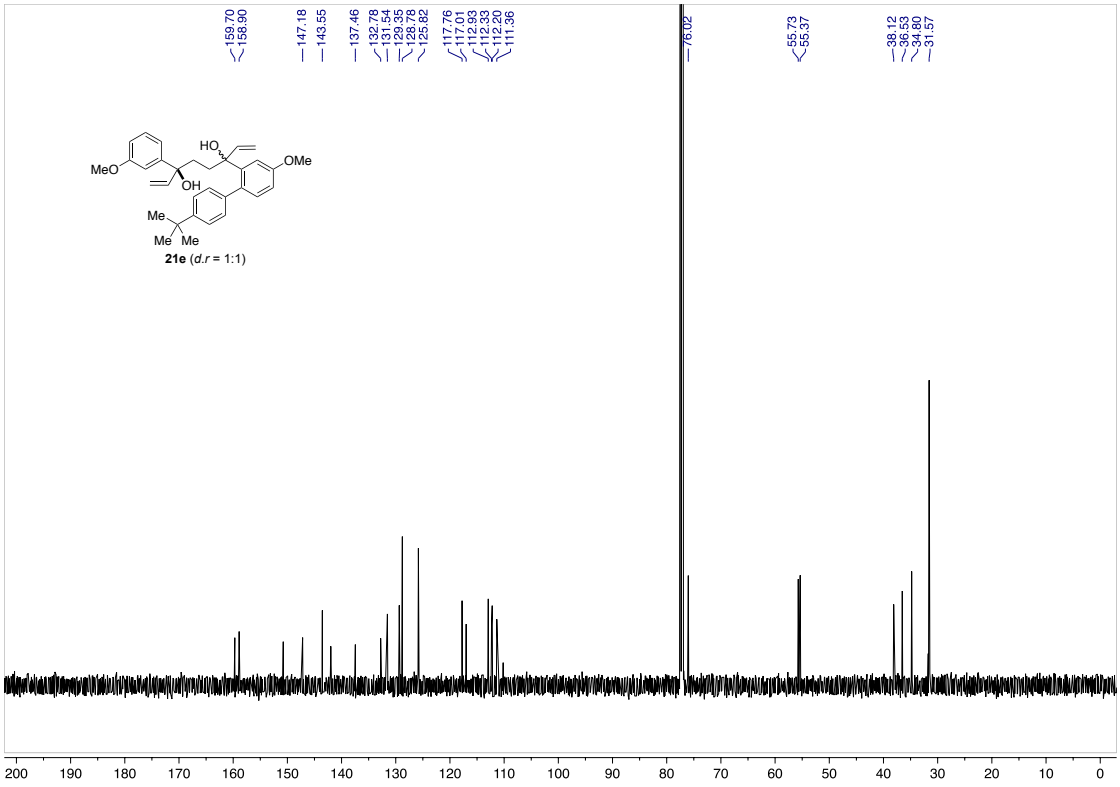

21c
R = t-Bu
Ar = 4-t-BuPh


21c
R = t-Bu
Ar = 4-t-BuPh


OMe
OMe
Ar
Ar
21d
R
R
R = t-Bu
Ar = 4-t-BuPh


OMe
OMe
Ar
Ar
21d
R
R
R = t-Bu
Ar = 4-t-BuPh


HO
MeO
OMe
OH
Me
Me Me
21e (d.r = 1:1)


HO
MeO
OMe
OH
Me
Me Me
21e (d.r = 1:1)

The End