Synthesis of Functionalized Benzenoid Macrocycles: An Approach to Accessing Functionalized Cycloparaphenylenes

by

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Abstract

Carbon nanotubes (CNTs) are cylindrically shaped allotropes of carbon with exceptionally good electronic and optical properties. The current state of art for making these CNTs involves heating graphite in a high temperature furnace (above 600 °C). The use of harsh temperatures makes the process unselective and produces CNTs as an inseparable mixture of products. Currently, there is no efficient purification technique for isolating pure CNTs. In order to fully exploit the electronic properties of CNTs, they need to be made as homogeneous and monodispersed structures. Thus, synthetic chemists envisioned using chemical synthesis from the ground-up via a template strategy as a more viable approach to achieve the selective synthesis of uniform CNTs structures with a defined chirality and diameter. This is because the selective synthesis of curved PAHs like [*n*]ciruclenes and CNT substructures could only be accomplished through chemical synthesis. The work described herein focuses on a new approach to accessing highly distorted p-phenylenes, which does not rely on cross coupling reactions and the use of the Burgess reagent as a mild dehydrative aromatization agent, giving access to highly strained benzenoid macrocycles.

Chapter 1: A definition of CNTs, types of CNTs and their properties. A description of the industrial processes used in the synthesis of CNTs and their limitations. The selective synthesis of some curved PAHs like [*n*]circulenes and CNT substructures is described to illustrate the power of chemical synthesis in achieving challenging targets.

Chapter 2: A template approach to the synthesis of uniform, single chirality CNT is described. Various approaches to CPP synthesis have equally been covered as well as the current limitation in the field. A non-cross-coupling approach to bent paraphenylenes have been described, as well as arene bridging strategy tolerable to *ortho* substitutents. Moreover, the use of the Burgess reagent as a powerful dehydrative aromatizing agent to achieve highly distorted paraphenylene and prevent rearrangements is demonstrated. Furthermore, a streamlined approach to access gram quantities of macrocyclic 1,4-diketones from acyclic dialdehydes has been developed which uses mild hydrogenation source, which has provided access to a wide variety of targets not accessible by other methods.

Chapter 3: The synthesis of functionalized benzenoid macrocycles with *ortho* substituents is undertaken and progress towards converting them into functionalized CPPs is reported.

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List of Abbreviations

B3LYP	Becke 3-Parameter (Exchange), Lee, Yang, Parr
BOR	Based on recovery
Bpin	Bis(pinacolato)diboron
C_{60}	Buckminsterfullerene
CNTs	Carbon nanotubes
cod	1,5-cyclooctadiene
CoMoCAT	Cobalt-molybdenum catalyst
CPP	Cycloparaphenylene
CVD	Chemical vapor disposition
DFT	Density functional theory
d.r.	Diastereomeric ratio
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	Diisopropylethyl amine (Hunig's base)
DMA	Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide

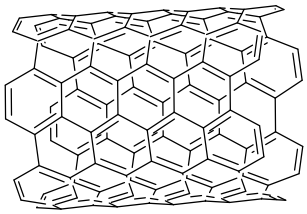
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
equiv	Equivalent
EtOAc	Ethyl acetate
$Fe(CO)_5$	Iron pentacarbonyl
FGI	Functional group interconversion
FVP	Flash vacuum pyrolysis
H-G II	Hoveyda-Grubbs second generation
HiPCO	High pressure carbon monoxide
HK	Hydroxyketone
IPA	Isopropyl alcohol
MOM	Chloromethyl methyl ether
MWCNTs	Multi-walled carbon nanotubes
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance

PAH	Polycyclic aromatic hydrocarbon
PCC	Pyridinium chlorochromate
PhMe	Toluene
PTPP	(3,3")*Para*-terphenylophane
P-TsOH	*Para*-toluenesulfonic acid
RCM	Ring closing metathesis
R_f	Retention factor
r.t	Room temperature
SE	Strain energy
SWCNTs	Single-walled carbon nanotubes
TEM	Transmission electron microscopy
Tf_2O	Trifluoromethanesulfonic anhydride
TLC	Thin layer chromatography
UV	Ultraviolet
UV/Vis	Ultraviolet/Visible
VID	Valence isomerization/dehydrogenation

Chapter 1 : Chemical Synthesis of Carbon Nanotubes (CNTs) and Related Substructures

1.1 Definition of CNTs and Applications

Carbon nanotubes (CNTs) are cylindrical allotropes of carbon composed of sp^2 hybridized carbon (**1.1**).[1] CNTs were first discovered by Iijima in 1991 as rolled up, tubular layers of graphene extracted from the soot of a carbon-arc discharge method.[2] To observe the CNTs, a high resolution image obtained by transmission electron microscopy (TEM) was used. [3,4] This revealed multi-walled carbon nanotubes (MWCNTs), that is numerous sheets of graphene shells separated by approximately 0.34 nm.[2] Two years after the discovery of MWCNTs, Iijima and co-workers synthesized single-walled carbon nanotubes (SWCNTs), which consisted of a single graphite sheet wrapped into a cylindrical tube, by adding a transition metal catalyst to carbon in an arc discharge method.[5, 6] An enormous amount of attention has been given to CNTs since their discovery with respect to synthesis, scalable production, and properties. CNTs possess unique and unusually good electronic and optical properties, making them highly relevant in the fields of materials science and nanotechnology.[7] For instance, due to their high tensile strength, they can be used in device miniaturization as potential nanowires.[7] They have also shown promising medical applications as potential biological sensors for disease detection.[8]



1.1

FIGURE 1.1: An armchair CNT

1.2 Types of CNTs

There are three types of CNTs: armchair, zigzag and chiral CNTs (Figure **1.2**).[9] These CNTs have different properties that arise from the different ways in which a graphene sheet can be rolled up.[9, 10] Rolling up a graphene sheet along the vertical axis (red arrow) generates an armchair CNT (the edge of the CNT has the side view of a "chair" with the seats and arms, see bold area). Armchair CNTs are metallic in nature.[11] Rolling up the graphene sheet along the horizontal axis (purple arrow) generates a zigzag CNT (the edge of the compound has a zigzag form), which has semi-conducting properties. Finally, rolling up the graphene sheet along the diagonal axis (blue arrow) generates a chiral CNT, where there is no symmetrical axis in the molecule. Chiral CNTs can either be metallic or semiconducting.

1.3 Traditional (Industrial) Methods for Making Carbon Nanotubes

CNTs are industrially prepared in the following ways.

1.3.1 Physical Processes

Arc Discharge: An early method used for the synthesis of CNTs, which was first utilized by Iijima.[2] In this method an electric arc is generated between two graphitic electrodes under an inert atmosphere of helium or argon gas. A pressurized chamber containing 10 Torr of methane and 40 Torr argon gas mixtures is used. Two tiny electrodes are installed in the center of the chamber, with a piece of iron installed in a shallow dip at the cathode, made purposefully to support the iron (Figure **1.3**). The arc is generated by passing a direct current of 200 A at 20 V between the two graphitic electrodes under an inert atmosphere, which triggers the vaporization and condensation of some graphite on the iron catalyst, in the cathode, resulting in CNT formation.[2] The arc discharge method used for the collection of the CNTs is similar to that used

for the industrial synthesis of Buckminsterfullerene (C_{60}).2 Nanotubes produced in this way are needle-like with a diameter between 0.7-1.7 nm, and approximately 1 mm in length. The arc discharge technique uses extremely high temperatures (above 1700 °C) and furnishes an inseparable mixture of SWCNTs and MWCNTs.[12, 13a]

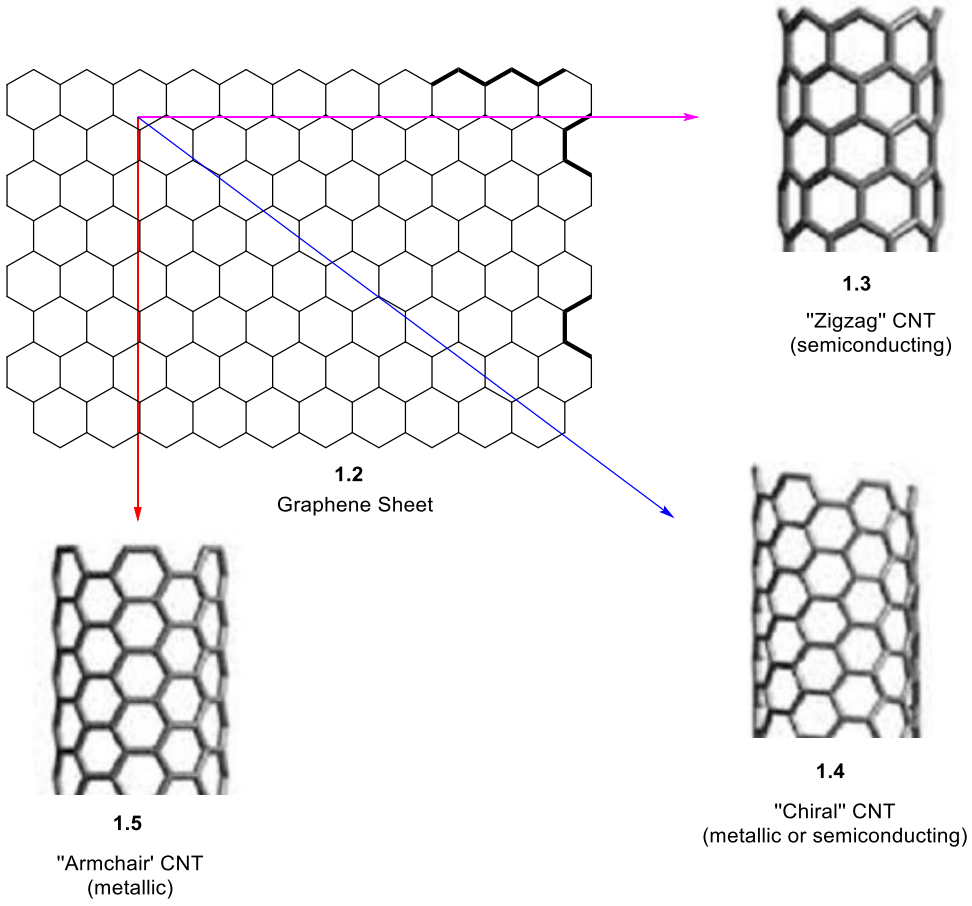


FIGURE 1.2: Types of CNTs (double bonds have been omitted for clarity)

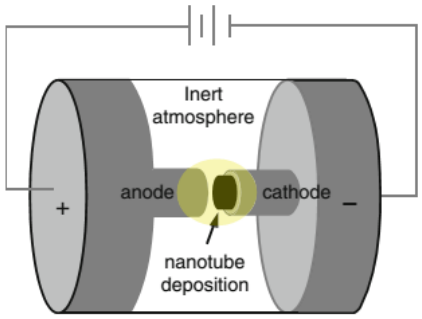


FIGURE 1.3: Schematic representation of arc discharge method for CNT synthesis[13b]

Laser Ablation: This method was discovered by Smalley and co-workers at Rice University in 1995.[10] In this process, a graphite target containing trace amounts of metal catalysts (Ni and Co) is stroked by a pulsed laser in a high temperature (1000-1200 °C) reactor in the presence of an inert gas (helium), which vaporizes the graphite target (Figure **1.4**). This produces CNTs on the walls of the reactor as the vaporized carbon condenses. In some cases, a water-cooled surface is included in the system to ease the collection of CNTs.[10] CNTs produced in this way vary between 10-20 nm in diameter and up to 100 microns in length.[10] This method gives rise to SWCNTs in good yields (70%), but of different chiralities. However, it is neither cost effective nor amenable to large-scale production.[10] The selectivity of the CNTs produced in terms of the length and diameter is achieved by carefully varying the catalyst composition, temperature and other process parameters. For instance, if the graphite target is used alone, without catalyst, only MWCNTs are generated.[10]

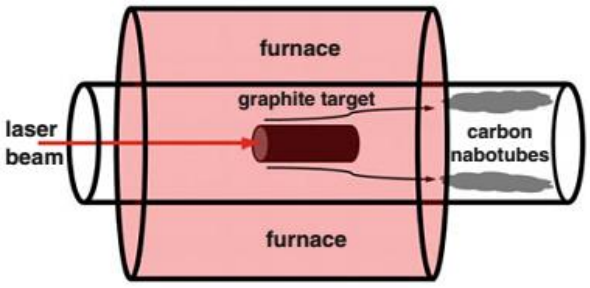


FIGURE 1.4: Laser ablation method for CNT synthesis[13b]

1.3.2 Chemical Processes

Chemical Vapor Deposition (CVD): In this process, a substrate is prepared with a layer of metal catalyst particles, most commonly nickel, cobalt, iron, or a combination of these.[14] Silicon is the most commonly used substrate in CVD, however, alumina and glass can also be used. The metal particles are deposited on the substrate via electron beam evaporation, solution deposition or physical sputtering. Then, a hydrocarbon gas (ethylene, methane or acetylene) and a process gas (ammonia, nitrogen, and hydrogen) are mixed together in a reaction chamber at high temperatures (700-900 °C) and atmospheric pressure, on a heated metal substrate (Figure **1.5**). The process results in CNT formation as the hydrocarbon gas decomposes, grows and is deposited on the substrate (Figure **1.5**).[15] In CVD, the substrate is crucial as it defines the nature and type of CNTs to be formed. Porous silicon material is useful for growing CNTs on large surfaces. The diameters of the nanotubes grown are related to the size of the metal particles. This can be controlled by patterned (or masked) deposition of the metal, annealing, or by plasma etching of a metal layer.[16] CVD is amenable to large-scale production.[16] In the CVD process, SWCNTs are found to be produced at higher temperatures (900-1200 °C) with a well-dispersed

and supported metal catalyst while MWCNTs are formed at lower temperatures (600-900 °C), even in the absence of a metal catalyst.[17]

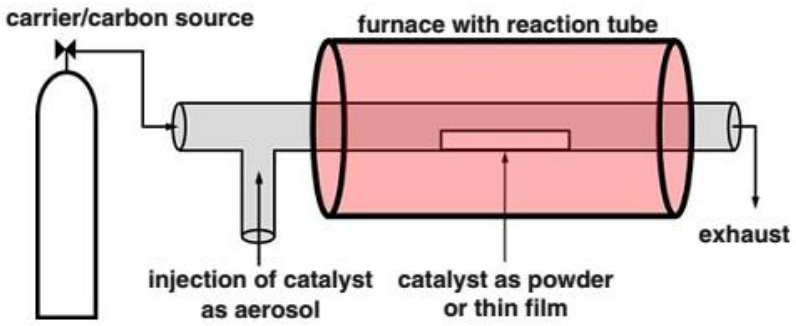


FIGURE 1.5: Schematic representation of CVD method of CNT synthesis[13b]

High Pressure Carbon Monoxide (HiPCO) Process: This method was developed at Rice University in 1999.[18] Unlike other methods, in which the metal catalysts are deposited or embedded on the substrate before the deposition of the carbon begins, in this method, the catalyst is introduced in gas phase. Here, both the catalyst, $Fe(CO)_5$, and the gas, CO, are fed into a furnace, followed by catalytic reaction in the gas phase to form CNTs.[18] This method is suitable for large-scale synthesis, because the nanotubes are free from catalytic supports and the reaction can be operated continuously allowing for the re-use of CO. In the HiPCO method, the thinnest SWCNTs are of very high quality, with few structural defects. A variant of the HiPCO process involves reacting a mixture of benzene and ferrocene in a hydrogen gas flow experiment to form SWCNTs.[19] In both methods, catalyst nanoparticles are formed through thermal decomposition of organometallic compounds, such as iron pentacarbonyl and ferrocene.

Cobalt-Molybdenum Catalyst (CoMoCAT) Process: This process was developed at the University of Oklahoma and involves SWCNT growth by the disproportionation of carbon monoxide (breakdown into C and CO_2) in the presence of CoMo catalyst, at temperatures

between 700-950 °C and a pressure of 10 atm.[20] SWCNTs are produced in large-scale through this method with about 80% selectivity, however, a specific chirality (armchair, zigzag or chiral CNT) cannot be controlled. The synergistic effect of Co and Mo aids in the production of large quantities of SWCNTs. Moreover, the CoMoCAT process is reported to produce SWCNTs with a narrower diameter distribution than HiPCO process, making it more selective.[20]

1.4 Limitations of Traditional (industrial) Methods for Making CNTs

Laser ablation and arc discharge methods require large amounts of energy, as well as very high operating temperatures (1000-1700 °C) rendering these processes uneconomical for large scale production.[2, 10] Moreover, both processes require the use of solid carbon/graphite as target to be evaporated to produce CNTs. It is hard to get large quantities of graphite in industrial processes, limiting their use for large scale production. Furthermore, CNTs prepared in this way are tangled in shape and also produced as mixtures with undesired forms of carbon. CNTs produced from the high temperature chemical processes are not completely selective, and are made with different sizes, chirality and diameters.[16] Purification techniques to isolate a specific type of CNT from the mixtures is deficient. Again, the manufacturing cost of CNTs through these processes is very expensive. For instance, the manufacturing costs for arc discharge, CVD and HiPCO methods are $1,906/g, $1,706/g, and $485/g, respectively.[21] Additionally, the price per gram on the open market vary depending on fabrication methods and the purified quality. These prices ranges from $30/g for CVD with about 60% purity to $7000/g with more than 99% purity.[21]

In order to fully exploit the electronic and optical properties of CNTs, they need to be made as homogeneous structures with defined chirality and diameter. This is where synthetic chemistry, using a controlled bottom-up approach, can be of assistance.

1.5 Synthesis of CNT Substructures

One of the major limitations in the industrial synthesis of CNTs mentioned above involves the use of high temperatures. However, there are some related substructures of CNTs such as C_{60} **1.13** and a [5,5] armchair CNT end cap[22] **1.14** (Figure **1.7**) whose selective synthesis could only be achieved by employing high temperatures-flash vacuum pyrolysis (FVP).[22, 23]

1.5.1 Synthesis of [*n*]Circulenes

The [*n*]circulenes, with the exception of [6]circulene, which is perfectly flat, are curved, or nonplanar polycyclic aromatic hydrocarbons (PAHs) in which the central *n*-sided polygon is entirely surrounded and fused by benzene rings.[23] [5]Circulene (corannulene) (**1.7**)[24] [6]circulene (coronene) (**1.8**)[25], and [7]circulene (pleidannulene) (**1.9**)[26] have been synthesized in the laboratory while, derivatives of [4]circulene[27] (**1.6**) and [8]circulenes (**1.10**) have also been reported.[28] The shapes of these circulenes changes from bowl ([5]circulene) to planar ([6]circulene) to saddle shape ([7]circulene).[24] Of all the [*n*]circulenes, corannulene (**1.7**) has received the greatest amount of attention because it forms an important substructure of CNTs and fullerenes-Buckminsterfullerene (C_{60}) (**1.13**) (Figure **1.6**).[29] It has also served as a key building block in the synthesis of an end cap [5,5]armchair CNT **1.14** and warped nanographenes **1.15** (Figure **1.6**).[22, 30] The name corannulene is derived from the latin word cor = heart and annula = ring and it was first synthesized in 1966 by Lawton and Barth.[31] Although corannulene is industrially accessible via flash vacuum pyrolysis (FVP),[24] in 1999, Siegel and co-workers

improved on their original synthesis and recently reported a ten step approach to **1.7** and its alkyl derivatives which are inaccessible via FVP.[29]

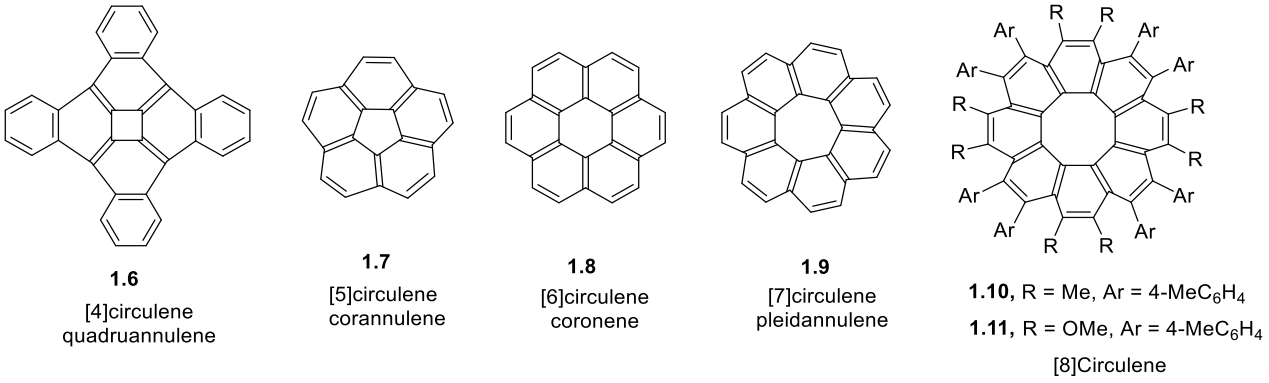


FIGURE 1.6: Well-known [*n*]circulenes prepared by chemical synthesis

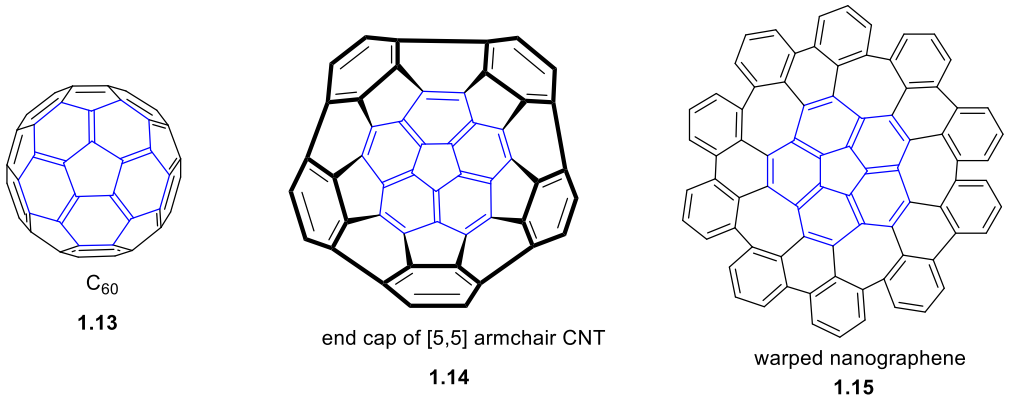
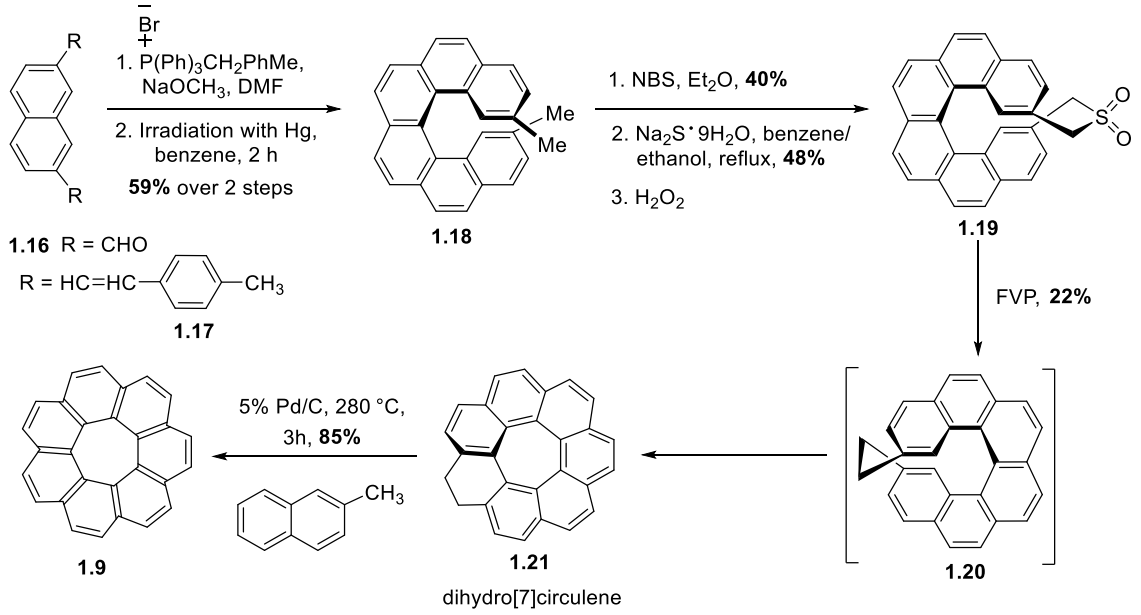


FIGURE 1.7: Corannulene as a key component of curved PAHs

Other [*n*]circulene homologs of great interest are [7] and [8]circulenes. These curved pi-systems can be regarded as graphene molecules containing seven and eight membered rings.[30] [7]Circulene can be mapped onto the surface of a warped nanographene recently synthesized by Scott, Itami and co-workers in 2013.[30] [7]circulene was first prepared by Nakazaki and coworkers in 1983.[32] A modification to the latter synthesis was reported by Kitaura and colleagues in 1996.[33] The synthesis begins with the Wittig reaction of 2,7-

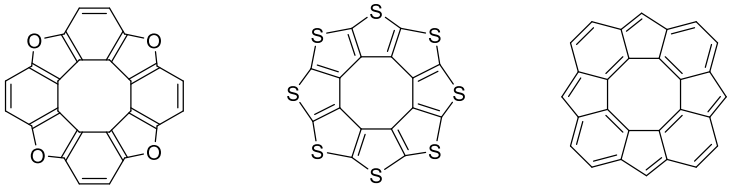
naphthalenedicarboxyaldehyde (**1.16**) with a phosphonium bromide source in the presence of sodium methoxide and dimethylformamide to afford a mixture of diastereomeric alkenes **1.17**. The mixture of alkene isomers was irradiated under a mercury lamp in benzene to produce helicene **1.18** in 59% yield over two steps. Benzylic bromination of **1.18** afforded the dibromide, which cyclized upon treatment with sodium sulfide nonahydrate in refluxing benzene and ethanol to give the hexahelicene sulfide. Subsequent oxidation with H_2O_2 afforded sulfone **1.19**. FVP of **1.19** gave only the dihydro[7]circulene **1.21**. It is speculated that the mechanism of the pyrolysis reaction goes through ethano-bridged hexalicene **1.20**, which later undergoes dehydrogenation to form **1.21**. Finally, **1.21** was converted to [7]circulene (**1.9**) through a dehydrogenation reaction upon treatment with 5% palladium on carbon at 280 °C in the presence of 2-methylnaphthalene as solvent.[33]



SCHEME 1.1: Synthesis of [7]circulene

On the other hand, methyl and methoxy derivatives of [8]circulene **1.10**, **1.28** respectively were synthesized by Wu and colleagues in 2013.[34] Beforehand several planar analogs such as

tetraoxo[8]circulene (**1.22**),[35] octathio[8]circulene (**1.23**),[36] and tetracyclopenta[def,jkl,pqr,vwx]tetraphenylene[37] (TCT) (**1.24**) were reported (Figure **1.8**). The authors reasoned that beginning the synthesis with a tetraphenylene would facilitate access to the desired target, through annulation reactions on the bay region of the tetraphenyl moiety. Iodination of **1.25** with *o*-periodic acid at 90 °C in the presence of molecular iodine, acetic acid, sulfuric acid and water for two days gave rise to a mixture of iodinated regioisomers **1.26** and **1.27**. This reaction places iodine atoms at each bay region, which is subsequently programmed for C-C bond formation. The regioisomers were then subjected to a palladium-catalyzed annulation with diarylethylenes to afford the peri-substituted [8]circulenes **1.10** and **1.28** in good yields. An X-ray structure of the methyl derivative was obtained.

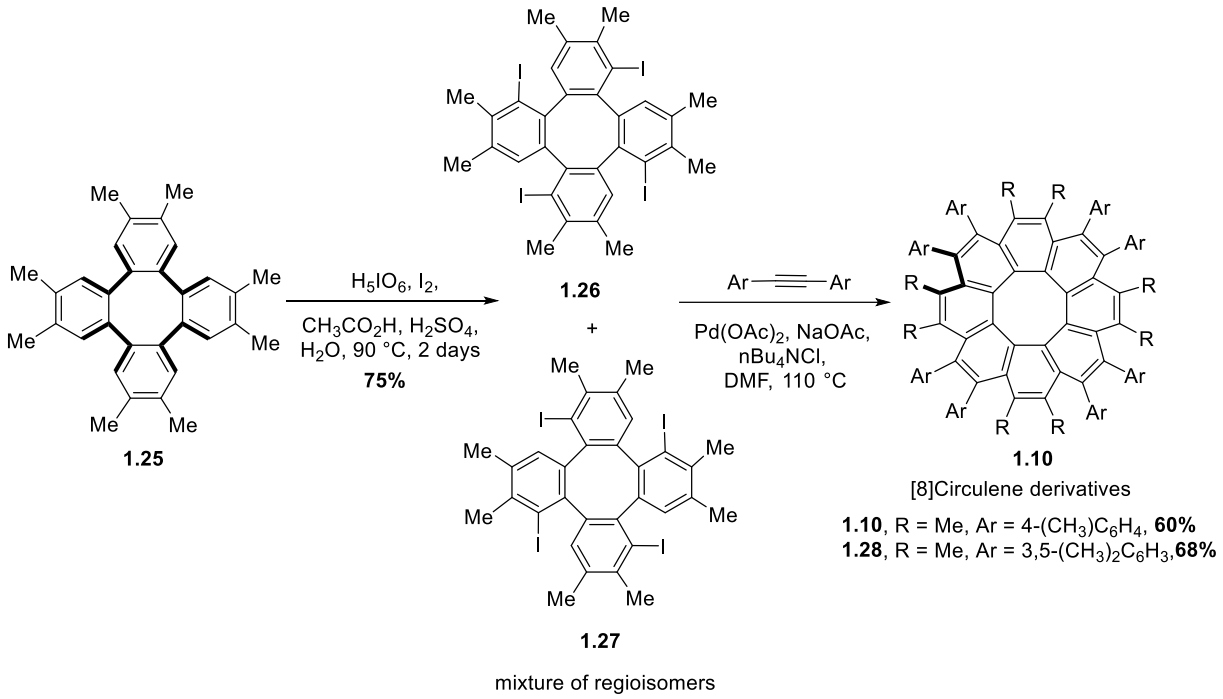


1.22
tetraoxo[8]circulene

1.23
octathio[8]circulene

1.24
TCT

FIGURE 1.8: Well-known analogues of [8]circulene



SCHEME 1.2: Synthesis of derivatives of [8]circulene

1.5.2 Synthesis of Buckminsterfullerene (C_{60})

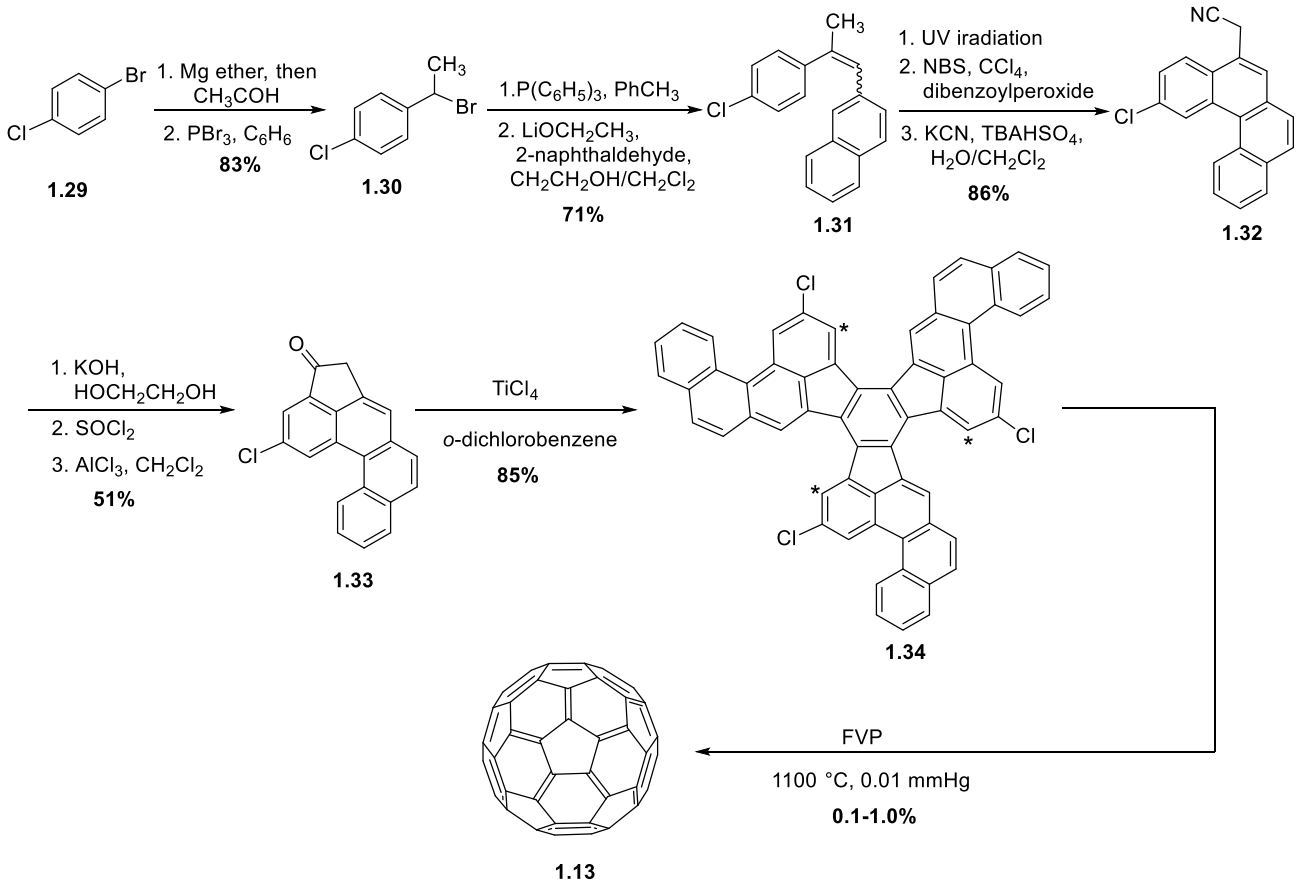
C_{60} (**1.13**), also called Buckminsterfullerene, is an allotrope of carbon with a spherical shape and a cage-like fused-ring structure (truncated icosahedron) similar to a soccer ball.[38] It is made up of 12 pentagons and 20 hexagons all connected with carbon atoms at each corner. Corannulene (**1.7**) is a recognizable bowl-shaped sub-structure of C_{60}. Despite the fact that C_{60} and higher fullerenes can be prepared by laser ablation and arc vaporization of graphite industrially, these methods usually gives rise to a mixture of fullerenes.[39] In 2002, Scott and co-workers reported the selective and stepwise synthesis of C_{60}.[22] The synthesis began with the Grignard addition of the aryl magnesium bromide derivative **1.29** with acetaldehyde (Scheme **1.3**). Converting the hydroxyl group of the secondary alcohol to the bromide was achieved on treatment with PBr_3 to furnish **1.30**. This material was subjected to a Wittig olefination with 2-naphthaldehyde to afford a mixture of *E* and *Z* isomers of **1.31.** The diastereomers of **1.31** were

then subjected to stilbene photocyclization under UV irradiation, followed by NBS bromination and an S_N2 displacement reaction with potassium cyanide to afford compound **1.32** (Scheme **1.3**). It is important to point out that separation of the isomers of **1.31** was not necessary as the *E* isomer interconverted photochemically to the *Z* isomer when subjected to the reaction conditions prior to cyclization. Hydrolysis of compound **1.32** with potassium hydroxide, followed by chlorination with thionyl chloride and a subsequent Friedel Crafts cyclization reaction afforded compound **1.33**. Treatment of **1.33** with titanium tetrachloride in *o*-dichlorobenzene facilitated an aldol cyclotrimerization reaction to produce compound **1.34**. Finally, a FVP reaction of **1.34** at 1100 °C afford the fullerene C_{60} as the only detectable fullerene allotrope. It was argued that having the chlorine atoms at the fjord regions (sites marked by asterisks) of **1.34** would have facilitated the subsequent pyrolysis reaction. However, the authors discovered that having chlorine atoms at those positions introduced considerable strain in the molecule and consequently lowered the yield of aldol cyclotrimerization reaction.[22]

1.5.3 Synthesis of the End Cap of [5,5]Armchair CNT

In 2012, Scott and co-workers reported a three step, selective synthesis of the end cap fragment of a [5,5]armchair CNT (**1.14**)[22] from corannulene (**1.7**). The synthesis commenced with the chlorination of corannulene (**1.7**) with iodine monochloride to afford 1,3,5,7,9-pentachlorocorannulene (**1.35**) as the major product. Treatment of compound **1.35** with 2,6-dichlorophenylzinc (**1.36**) through a 5-fold Negishi coupling reaction gave rise to the decachloride **1.37**. Finally, subjecting **1.37** to FVP brought together the five edges of the molecule to form the [5,5] CNT **1.14**. The CNT end cap was characterized by UV/Vis spectroscopy, NMR spectroscopy, mass spectrometry and X-ray diffraction. The ^{1}H NMR of the compound showed a single resonance at 7.63 ppm while ^{13}C NMR showed six signals as

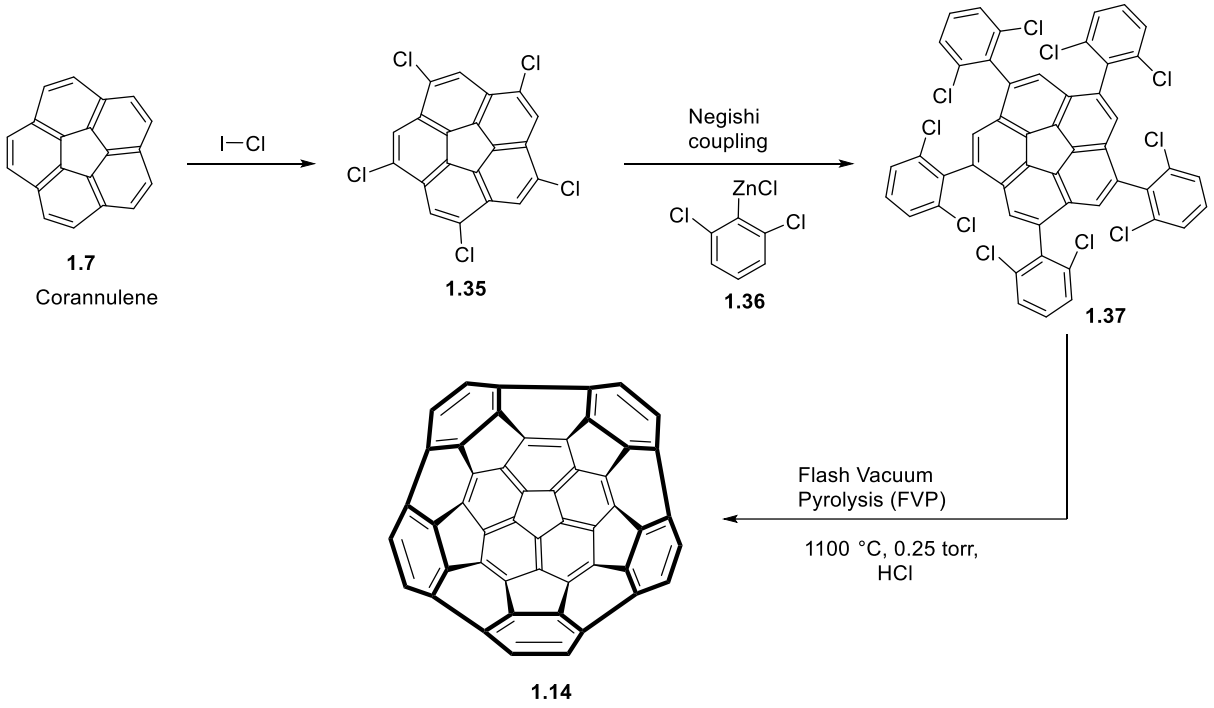
expected. The mass spectrum showed the desired peak, while the UV/Vis revealed absorption maxima at 268 nm and 308 nm. Crystallization of **1.14** from a mixture of carbon disulfide, dichloromethane and hexanes produced crystals suitable for X-ray analysis. Getting an X-ray struccture of **1.14** cleared any ambiguity with regards to its structure and success of the synthesis.



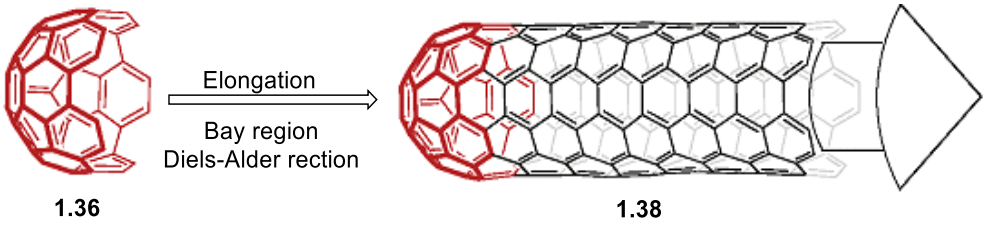
SCHEME 1.3: Selective Synthesis of C_{60} by Scott and colleagues[22]

Ideally, with the successful synthesis of **1.14**, the authors aimed to use the compound as a suitable template for the bottom-up synthesis of uniform diameter, single chirality [5,5]armchair carbon nanotubes (**1.38**) (Figure **1.7**). This is because compound **1.14** had the same diameter as the targeted CNT. However, subjecting **1.14** to a bay region Diels-Alder reaction was

unsuccessful and to date no strategy has been reported to support **1.14** as being a potential template for the ground up synthesis of homogeneous CNTs.



SCHEME 1.4: Synthesis of the end cap of a [5,5]armchair CNT



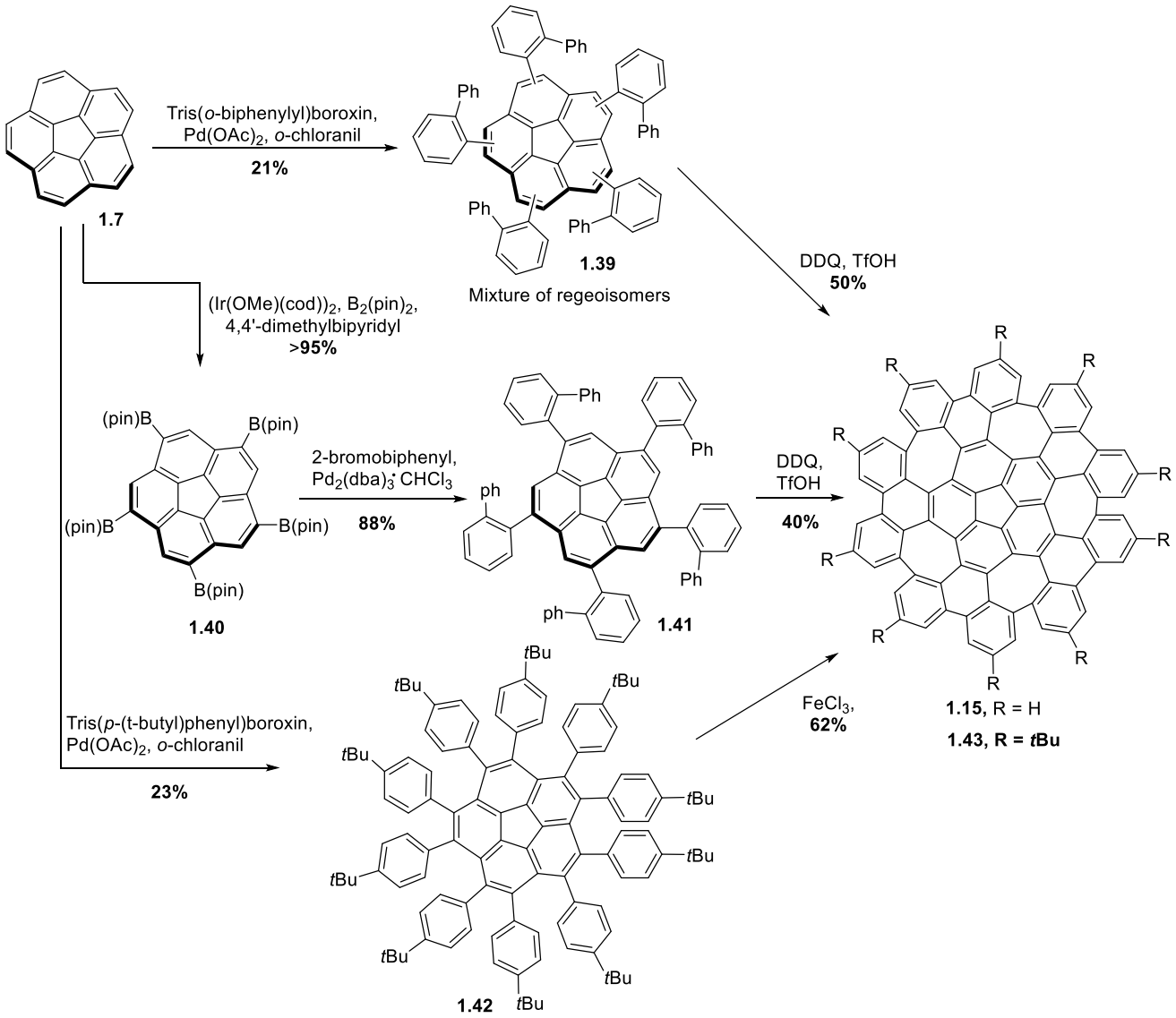
SCHEME 1.5: Approach for the bottom Synthesis of armchair CNT

1.5.4 Synthesis of Warped Nanographene

Graphite is an allotrope of carbon that consists of sp^2 hybridized carbon sheets stacked on top of the other like sheets of paper.[31] Single sheets of carbon are known as graphene.[31] In the last two centuries, several conventional methods based on intramolecular oxidative cyclodehydrogenation (Scholl) reactions have been reported for the synthesis of graphene-like molecules.[39] However, the scope of these synthetic methods have been impeded by incomplete graphitization and structural rearrangement during Scholl reactions.[40]

A warped $C_{80}H_{30}$ nanographene **1.15** made up of five seven-membered rings and one five-membered ring embedded in a hexagonal lattice of trigonal carbon atoms was synthesized by Scott, Itami and co-workers in 2013.[31] The synthesis commenced with corannulene (**1.7**), which was derivatized following three different protocols (Scheme **1.6**).[31] This warped nanographene was characterized by X-ray crystallography. In the first route, corannulene **1.7** was subjected to a palladium-catalyzed C-H arylation with tris(*o*-biphenylyl)boroxin in the presence of *o*-chloranil to produce a mixture of regioisomers **1.39**, which lowered the yield of the reaction. However, the cyclodehydrogenation reaction of **1.39** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of trifluoromethanesulfonic acid afforded the desired warped nanographene **1.15** in 50% yield. In order to circumvent the low yielding direct C-H arylation reaction, **1.7** was subjected to an iridium-catalyzed C-H borylation reaction with bis(pinacolato)diboron to afford compound **1.40** in 95% yield, which was then subjected to a Suzuki-Miyaura coupling with 2-bromobiphenyl to produce **1.41** as a single isomer in 88% yield. Cyclodehydrogenation of **1.41** afforded the desired compound **1.15** in 40% yield. The third route to the synthesis of the warped nanographene involved doing a tenfold palladium-catalyzed C-H arylation reaction with tris(*p*-(*t*-butyl)phenyl)boroxin on corannulene (**1.7**) to produce decakis (4-*t*-butylphenyl)corannulene **1.42**

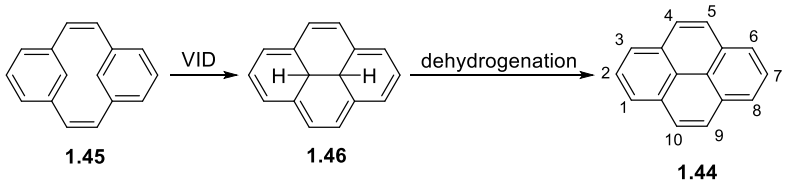
in 23% as the only isomer. Cyclodehydrogenation on **1.42** with iron(III)chloride afforded the warped nanographene **1.43** in 62% yield. The curved structure of these graphene molecules allowed for increased solubility in organic solvents. Astoundingly, the nanographene with the *t*-butyl groups was soluble in hexanes. A major feature of this synthesis was the use of cyclodehydrogenation reactions to furnish strained seven-membered rings.[31]



SCHEME 1.6: Scott, Itami and co-workers synthesis of warped nanographene

1.5.5 Synthesis of Nonplanar Pyrenoid Systems

Pyrene ($C_{16}H_{10}$) (**1.44**) is a compact tetracyclic aromatic hydrocarbon unit, which has been extensively exploited for its electronic and photophysical properties.[41] Its exceptionally long fluorescence lifetime makes it useful as a fluorescent probe in a broad range of applications.[42]



1.45 **1.46** **1.44**

SCHEME 1.7: Structure of pyrene and VID for the synthesis of pyrene

Cyclophanes containing polycyclic aromatic systems such as pyrene have been extensively reviewed.[43a, 44b] Most common are the (2,7)pyrenophanes since it connects the two most distant positions of the pyrene molecule.[44] Valence isomerization/dehydrogenation (VID) reaction of [2.2]metacyclophane-1,9-diene (**1.45**) to furnish pyrene (Scheme **1.7**)[44] is a transformation vital in the synthesis of curved pyrenophanes.44 For instance, VID was used at the final stage to achieve the selective synthesis of a range of teropyrenophanes - an important class of pyrenophanes.[45, 46]

Teropyrenophanes have been identified to contain greater substructure of an armchair CNTs synthesized to date through chemical synthesis. 1,1,7,7-tetramethyl[7](2,11)Teropyrenophane **1.47** represents a large sidewall of the (6, 6) armchair CNTs (Figure **1.9)**.[45] The key reactions to the synthesis of the desired target were the Wurtz coupling of the dibromides to install the first bridge, a McMurry coupling reaction of the dialdehyde to install the second bridge, and finally the VID reaction on the pyrene precursor to furnish the teropyrenophane (Scheme **1.8**).45, [46]

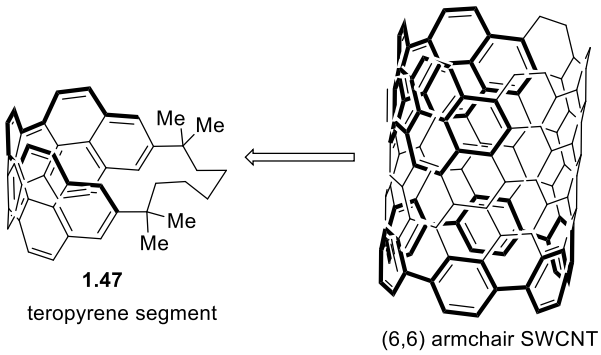
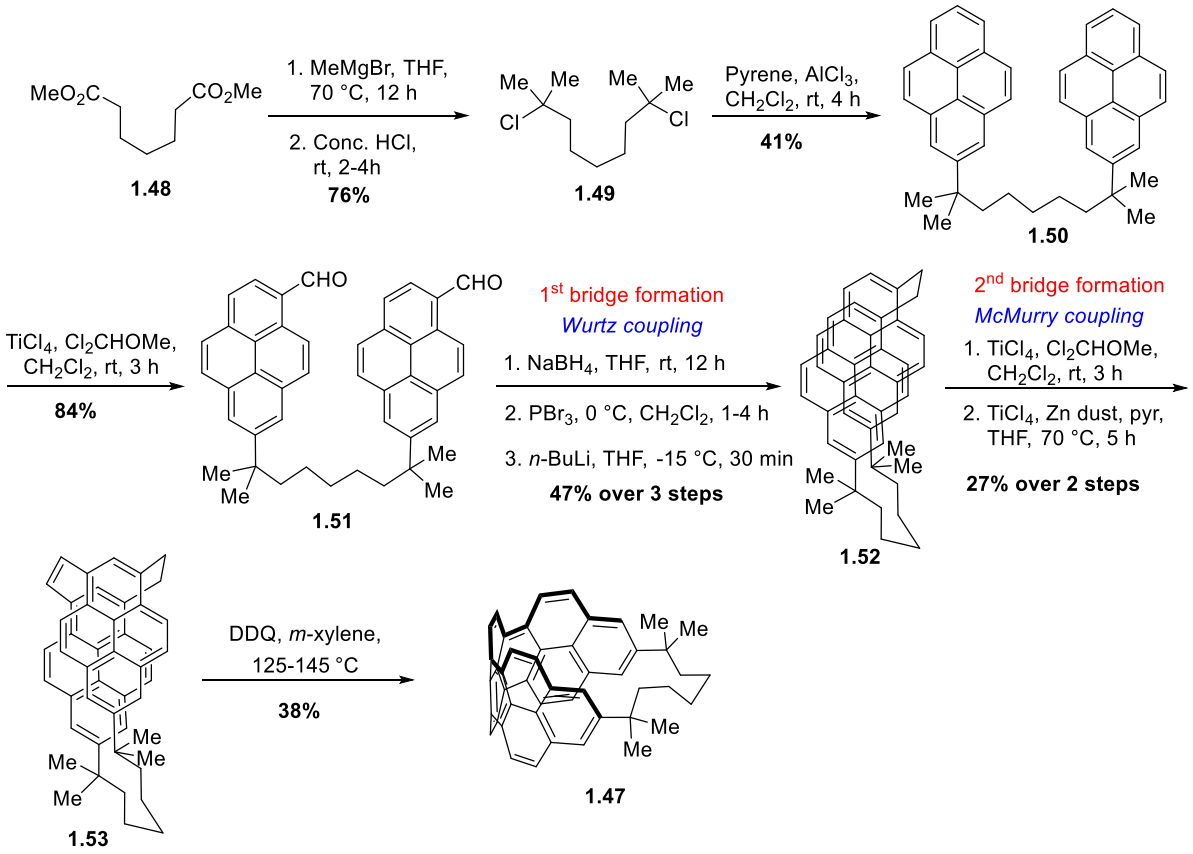


FIGURE 1.9: Representation of teropyrene as as wider PAH segment of [6,6]armchair CNT

The synthesis involved taking advantage of the well-known substitution chemistry of pyrene. In the presence of small electrophiles, substitution occurs at the 1-, 3-, 6-, and 8-positions of pyrene.[47] However, with bulky electrophiles like *t*-butyl groups, substitution occurs uniquely at the 2- and 7-positions.[48] This is because the available nonquaternary sites of pyrene are inequivalent. In this regard, the synthesis began with preparing the *t*-butyl portion. This was achieved via the Grignard addition of methyl magnesium bromide on the ester **1.48** to afford a tertiary alcohol which was then treated with concentrated hydrochloric acid to form the tertiary alkyl chloride **1.49**. Friedel-Crafts alkylation reaction of pyrene with the tertiary alkyl chloride **1.49** tethered two of the pyrene units together at the 2 and 2′ positions to provide compound **1.50**. Subjecting this compound to the Rieche formylation reaction afforded the dialdehyde **1.51**. The aldehyde groups on **1.51** were reduced to the alcohol upon treatment with sodium borohydride and then brominated to afford the dibromides. The dibromides were then engaged in a Wurtz-type coupling reaction to produce the first bridge of the compound and form the cyclophane **1.52**. It is important to mention that in the first reported synthesis of the n = 8 homologue of the teropyrenophane **1.47**, the first bridge was constructed via a McMurry reaction on the aldehydes of compound **1.51** to produce the cyclophane as mixture of *E* and *Z* isomers. However, this approach was unsuitable for the synthesis of the n = 9 homologue as the McMurry reaction

formed predominantly the *E* isomer, which impeded further reaction, since only the *Z*-alkene cyclizes in the next step.45 As such, the authors developed the Wurtz-type coupling as a more general approach. Compound **1.52** was subjected to another Rieche formylation reaction to afford the dialdehyde which was subsequently subjected to McMurry reaction conditions to form the second bridge of compound **1.53**. Finally, treatment of **1.53** with DDQ afforded the desired teropyrenophane **1.54** via a VID reaction. Different homologues (*n* = 8,9) of **1.54** were prepared by varying the length of the ester used in the first step of the synthesis.[45, 46]



SCHEME 1.8: Bodwell synthesis of 1,1,7,7-tetramethyl[7](2,11)teropyrenophane

In summary, well established processes have been designed to produce gram quantities of CNTs and in good yields.[2, 10, 16] However, the harsh temperatures used during these processes

prohibits the selective formation of CNTs with defined chiralities and diameters. Rather, mixtures of SWCNTs, MWCNTs and even deformed (tangled shaped) CNTs are obtained along with other side reactions.[10] Purification techniques to isolate pure CNTs from the mixture are yet to be developed. Due to the different electronic properties exhibited by CNTs, using them as a mixture of compounds in material devices is inadequate. Although harsh temperatures (FVP) have been proven useful in the selective synthesis of challenging CNT substructures such as [5,5] end cap of CNT (**1.14**)[23] and C_{60} (**1.13**)[22], extremely low yields of the desired products were achieved. Additionally, evidence that **1.14** can be used as a potential template for CNT synthesis is yet to be demonstrated.

The efficient, room temperature synthesis of curved PAHs such as [7]circulene (**1.9**), [8]circulene derivatives **1.10**, **1.28**, C_{60} (**1.13**)[22], warped nanographenes[31] **1.15**, **1.43** and teropyrenophanes[45,46] **1.47** from readily available starting materials is proof that chemical synthesis could be used as a powerful tool for the selective synthesis of complex molecular structures. In this perspective, scientists believe that the most viable method for making homogeneous CNT structures, in order for their electronic properties to be fully exploited, is from the ground-up approach via chemical synthesis. It is envisioned that such a synthesis could be achieved by first, designing a macrocyclic template with the exact dimensions (chirality and diameter) of a CNT and subsequently develop new technology to grow up the template and extend it into longer CNTs. The major advantage of the templating strategy over industrial processes lies in the selectivity of the chemical reactions, as they are conducted at lower temperatures, thereby minimizing formation of side reactions. Moreover, chemical synthesis can be optimized and scaled-up once the mechanistic pathway of the reaction is ascertained.[49] An

elaborate explanation of the templating approach to achieve the selective synthesis of homogeneous and monodisperse CNTs will be covered in the next chapter.

Chapter 2 : Benzenoid Macrocycles: Templates for the Bottom-up Synthesis of CNTs

2.1 Bottom-up Synthesis of Armchair CNTs

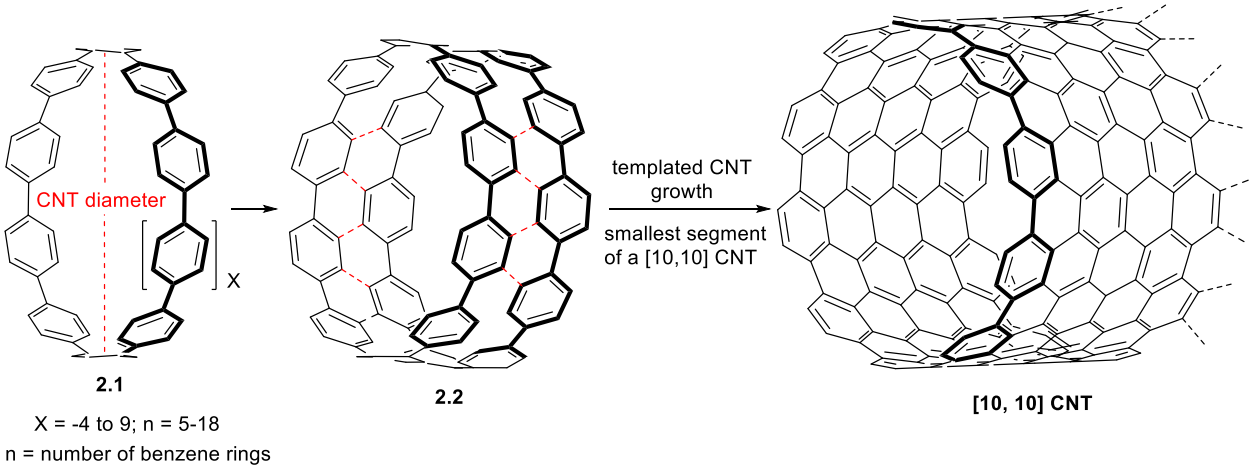


FIGURE 2.1: [*n*]CPPs (diameter defining substructures of CNTs)

The lack of selectivity in the industrial synthesis of CNTs and the absence of suitable purification techniques for the isolation of pure CNT segments has triggered researchers to resort to the use of chemical synthesis as a more viable approach for the uniform synthesis of monodispersed CNTs from the ground-up, by designing a suitable CNT template - a small macrocyclic fragment with identical chirality and diameter as a CNT. The template used here is an [*n*]cycloparaphenylene ([*n*]CPP) **2.1**, which are benzene rings linked at the para position to form a macrocycle, where [*n*] defines the size/diameter of the macrocycle.

The overall idea in the bottom-up approach is to commence with the synthesis of a macrocyclic nanohoop such as an [*n*](CPP) **2.1**, which represents the smallest macrocyclic segment of an armchair CNT. These templates could then be used as potential seeds for the homogeneous synthesis of armchair CNTs, since the [*n*]CPP has the same diameter as the corresponding [*n,n*]CNT (Figure **2.1**). Synthetic methodology/technology could then be

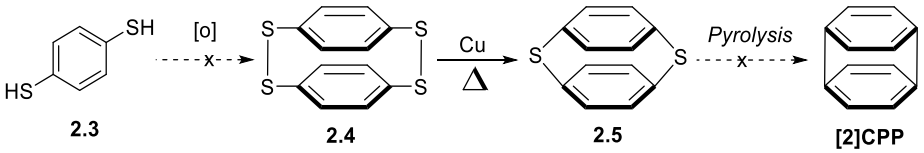
developed to link two or more units of **2.1** together and then closing subsequent bonds to generate the wider segment of the [*n*,*n*]armchair CNT **2.2**. **2.2** could in turn be converted into the [10,10]CNT via a bay region [4+2] cycloaddition reaction. Astoundingly, doing a cycloaddition reaction on one bay region creates another and subsequent Diel-alder reactions will lead to an infinite long CNT.

After establishing a synthetic plan, the next challenge involved synthesizing the macrocyclic CNT template ([*n*]CPP). The difficulty associated with the synthesis of [*n*]CPPs lies in overcoming the strain energy required in bending the benzene rings out of planarity.[49] A synthetic approach that involved sequential buildup of strain was found pivotal to accessing [*n*]CPPs.

2.2 Synthetic Approaches to [*n*]Cycloparaphenylenes (CPPs)

2.2.1 Early Attempted Synthesis of [*n*]CPPs

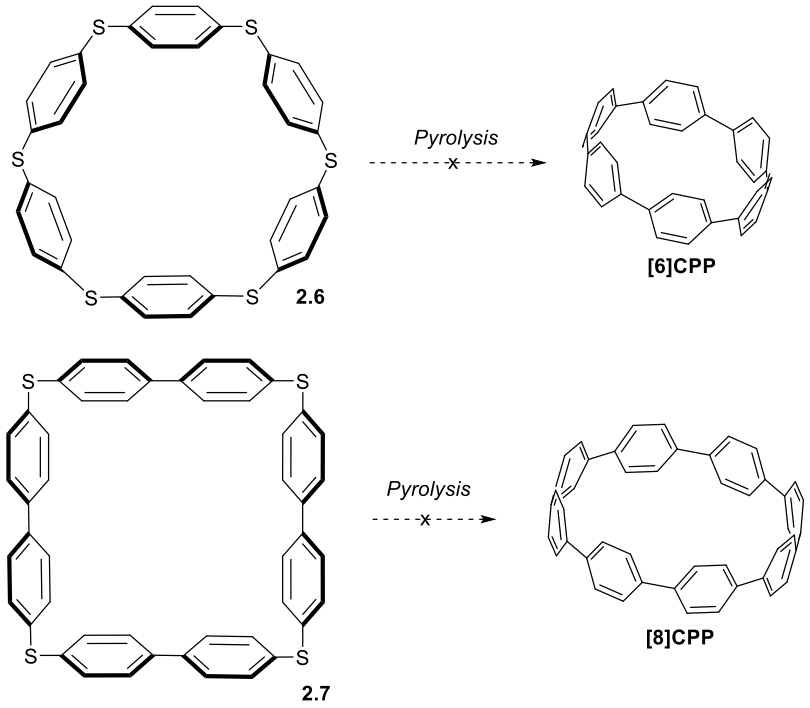
Parekh and Guha in 1934 attempted the synthesis of the highly strained [2]CPP.[50] This was achieved via the oxidation of 1,4-dibenzenethiol **2.3** to form the [2.2]paracyclophane **2.4**. However, copper-mediated desulfurization of **2.4** to afford the [2]CPP only resulted in the partially desulfurized macrocycle **2.5**. All attempts to convert **2.5** into [2]CPP were unsuccessful.



SCHEME 2.1: Efforts towards [2]CPP synthesis by Parekh and Guha

In 1996, Vögtle proposed four different synthetic approaches to access [*n*]CPPs, which were ultimately unsuccessful.[51] In the first route, attempts to access [6] and [8]CPP were pursued

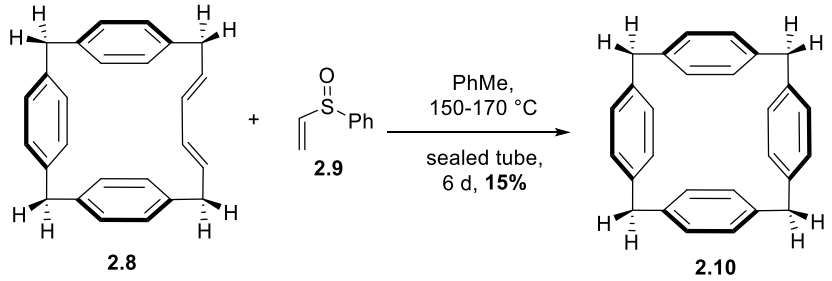
by employing desulfurization reaction of the macrocyclic disulfides **2.6** and **2.7**. This approach is similar to that used by Parekh and Guha. Vögtle proposed that the lower amount of strain energy present in these sulfur-based macrocycles compared to [2]CPP, would make them synthetically more accessible. Preparation of the precursors **2.6** and **2.7** proceeded smoothly and in good yields (60-65%), however, converting these systems into CPPs was not achieved (Scheme **2.2**).



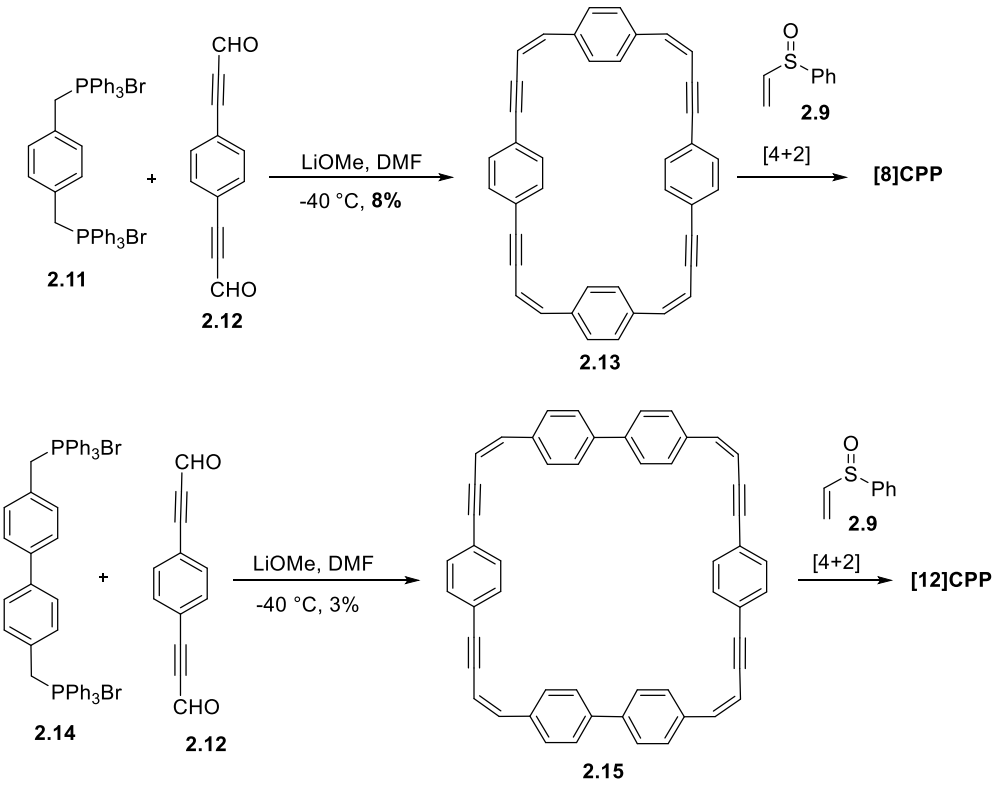
SCHEME 2.2: Vögtle attempted synthesis of [6] and [8]CPP via pyrolysis of macrocyclic disulfides **2.6** and **2.7**.

In the second route, Vögtle examined using Diels-Alder (4+2 cycloaddition) reactions to access [8] and [12]CPPs.[51] Inspired by Miyarahara's successful synthesis of [1_4] paracyclophane (Scheme **2.3**)[52] via a [4+2] cycloaddition between the diene **2.8** and phenyl vinyl sulfoxide **2.9**, Vögtle subjected compounds **2.11** and **2.14** to a Wittig cyclooligomerization with the dialdehyde

2.12 to furnish the macrocycles **2.13** and **2.15**. However, the [4+2] cycloaddition reaction to provide the desired [*n*]CPP did not come to fruition.

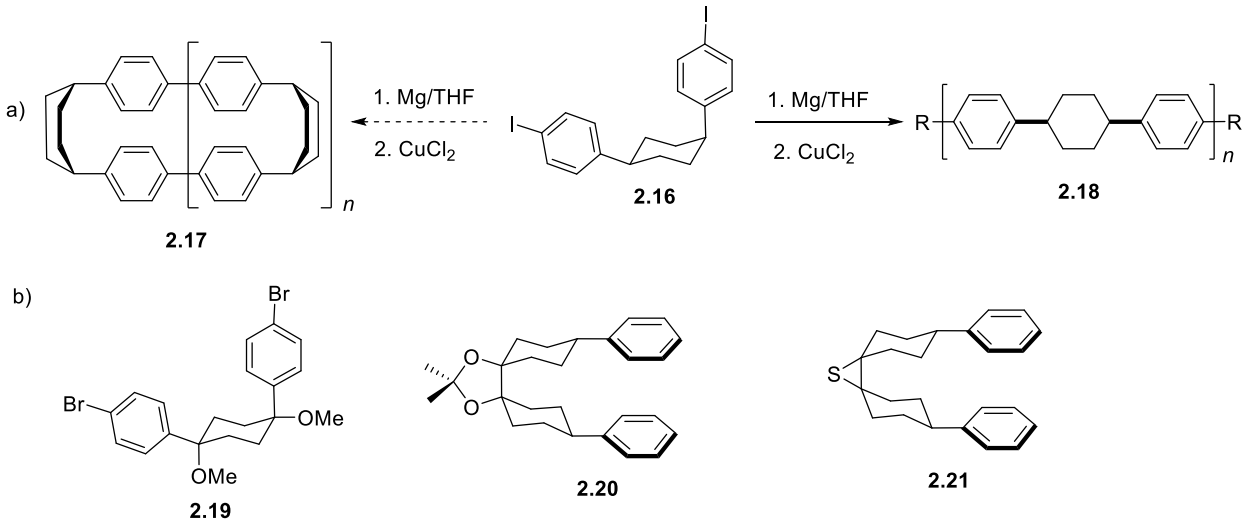


SCHEME 2.3: [4+2] cycloaddition reaction to prepare [1_4]paracyclophane



SCHEME 2.4: Attempted Diels-Alder-based approach by Vögtle as an attempt to the synthesis [8] and [12]CPP.

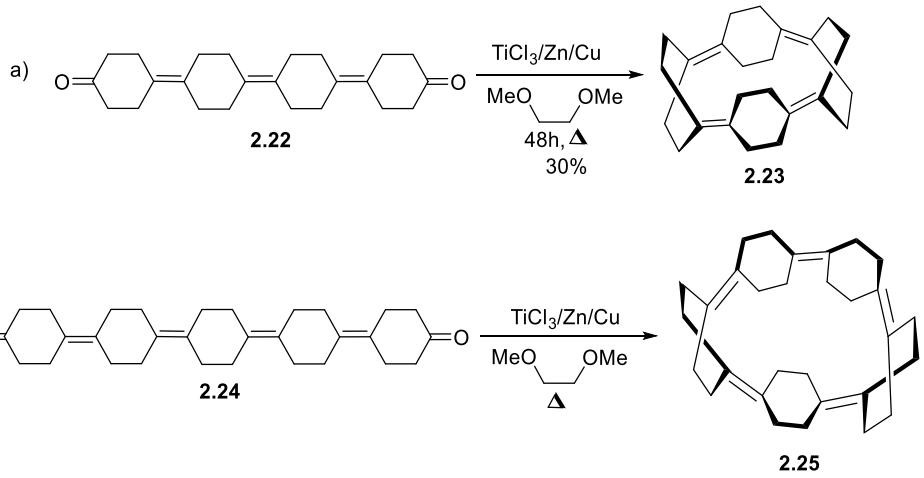
The third route investigated by Vögtle and co-workers to synthesize [*n*]CPPs involved the formation of macrocycles containing cyclohexane and arene rings. The incorporation of cyclohexane rings was to facilitate the synthesis of less strained macrocyclic precursors. Subsequent conversion to the corresponding [*n*]CPP would be accompanied by the gain in aromatic stabilization energy (ASE), which would compensate for strain introduced. Vögtle synthesized the 1,4-*cis*-diaryl cyclohexane **2.16**, but its transformation into the macrocycle **2.17** under Kharasch conditions failed, yielding the linear compound **2.18** instead. Failure of the macrocyclization was attributed to the conformational flexibility of **2.16** in solution. To remedy the situation, a number structurally rigid analogs of **2.16** were synthesized: the dimethoxy derivative **2.19** and the spiro derivatives **2.20** and **2.21**. Attempts at macrocyclization reactions were still unsuccessful.



SCHEME 2.5: a) Unsuccessful macrocyclization of 1,4-*syn*-diaryl cyclohexane; b) Targeted structurally rigid analogs of **2.16** as mean to facilitate the formation of macrocyclic CPP precursors

The fourth and final strategy attempted by Vögtle involved the use of macrocyclic McMurry reaction to access CPP precursors (Scheme **2.6**). Encouraged by the reported successful McMurry reaction-based synthesis of the cyclic tetraene[53] **2.23** from the diketone **2.22**, Vögtle and co-workers embarked on the synthesis of the next higher homolog **2.25** containing five cyclohexane rings as the precursor to [5]CPP. The synthesis of the diketone **2.24** was achieved in good yield (50%), however, reductive cyclization afforded trace amounts of the macrocycle **2.25**, identified through mass spectrometry, which impeded further reactions.

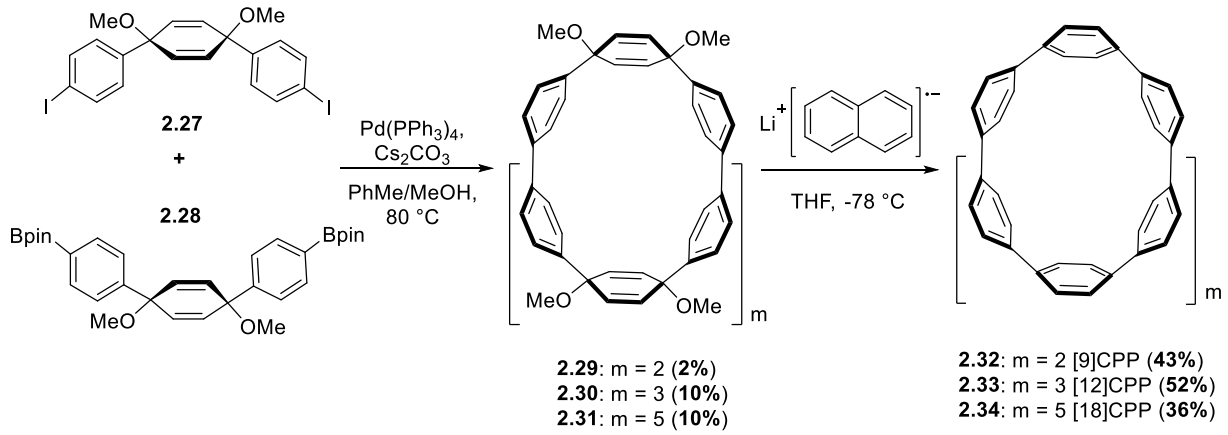
To address the potential of these four approaches, Vögtle speculated the third strategy based on the formation of structurally rigid disubstituted cyclohexane ring to be the most promising. This was quite prophetic given the accomplishments that have been reported two decades later in this field of hydrocarbon synthesis.



SCHEME 2.6: McMurry reaction-based approach to cyclic tetraene **2.23**; b) Attempted synthesis of the cyclic pentaene **2.25**

The first successful synthesis of a CPP was accomplished in 2008 by Jasti, Bertozzi and co-workers, who reported the selective synthesis of [9], [12] and [18]CPP.[54] Their strategy relied on

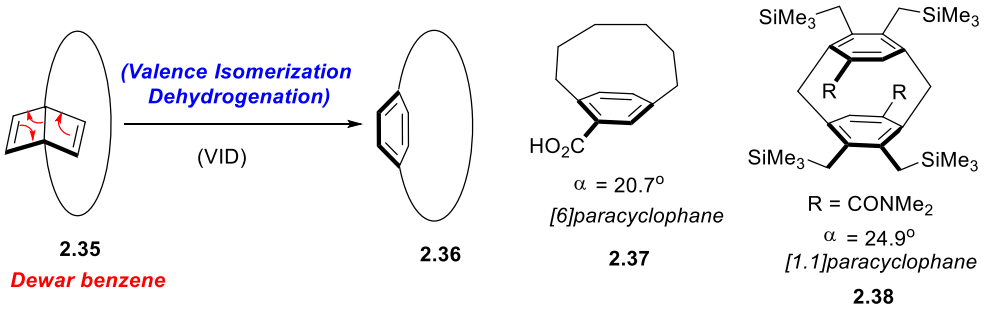
using a 3,6-*cis*-dimethoxy-cyclohexa-1,4-diene **2.27** as a bent pre-arene unit to allow for the sequential buildup of strain during the synthesis (Scheme **2.7**). The pre-arene unit also provided the necessary curvature and rigidity for a successful macrocyclization. The macrocyclic diene was subsequently subjected to reductive aromatization to afford the desired [*n*]CPPs (Scheme **2.7**). Aromatization was facilitated by gain in ASE which compensated the introduction of strain. Bertozzi and co-workers were inspired by the previous reports of Vögtle who identified constrained disubstituted cyclohexanes to be favorable precursors for successful macrocyclization reactions.[51]



SCHEME 2.7: First selective synthesis of [9], [12] and [18]CPP by Bertozzi and co-workers

Until 2014, the best methods for accessing highly distorted *p*-phenylenes was through the VID reaction of Dewar benzene precursors. This strategy was used in the synthesis of highly distorted benzene rings of paracyclophanes such as [6]paracyclophane derivative **2.37** and [1.1]paracyclophane **2.38** Tobe and Tsuji respectively.[55, 56] The degree of distortion of the central arene was quantified by X-ray crystallography. The mechanism of the VID reaction involved rupture of the central C−C bond in the bicyclo[2.2.0]hexa-2,5-diene system to bring about release of strain energy (SE) and a gain in ASE upon destroying the bicyclic system (**2.35**,

Scheme **2.8**) However, VID reactions could only be used to form bent *p*-phenylenes with an α angle of 20° or more. α is the angle of deviation of the *para* carbon atoms from the plane defined by the *ortho* and *meta* carbons in benzene. With the successful synthesis of [*n*]CPPs, it was discovered that reductive aromatization of substituted cyclohexadiene subunits is viewed as a better precursor to highly distorted nonplanar arenes than Dewar benzene, as an α angle of 15.6° was obtained after Jasti and Yamago reported the selective synthesis of [5]CPP[57, 58] , which could not be obtained upon using Dewar benzene as precursor.



SCHEME 2.8: VID reaction to access highly distorted *para*-cyclophanes

2.2.2 A Generalized Approach to [*n*]CPPs

There are four major stages in a CPP synthesis (Figure **2.8**).[59] The first stage involves the synthesis of a bent pre-arene subunit such as **2.39**. The presence of the nonplanar cyclohexadiene units induces curvature into the molecule. In the second stage, a cross-coupling reaction is preformed to link two or more monomers units of **2.39** together to form a larger subunit **2.40**. The third stage involves a macrocyclization reaction in which the previously cross-coupled products (**2.40**) are closed up to form a macrocyclic precursor to **2.41**. The final stage of the synthesis involves aromatization of the pre-arene units to form strained benzene rings, such as those present in **2.42** and thus the [*n*]CPP. Even though the last step requires the formation of a

strained unit, it is facilitated by the gain in aromatic stabilization energy (ASE) which may compensate for the introduction of strain.

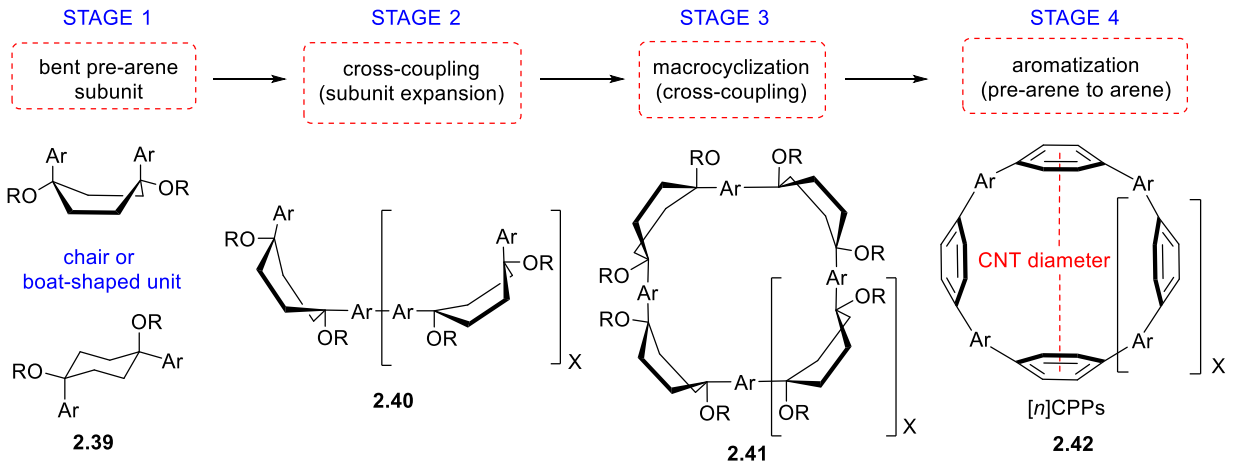


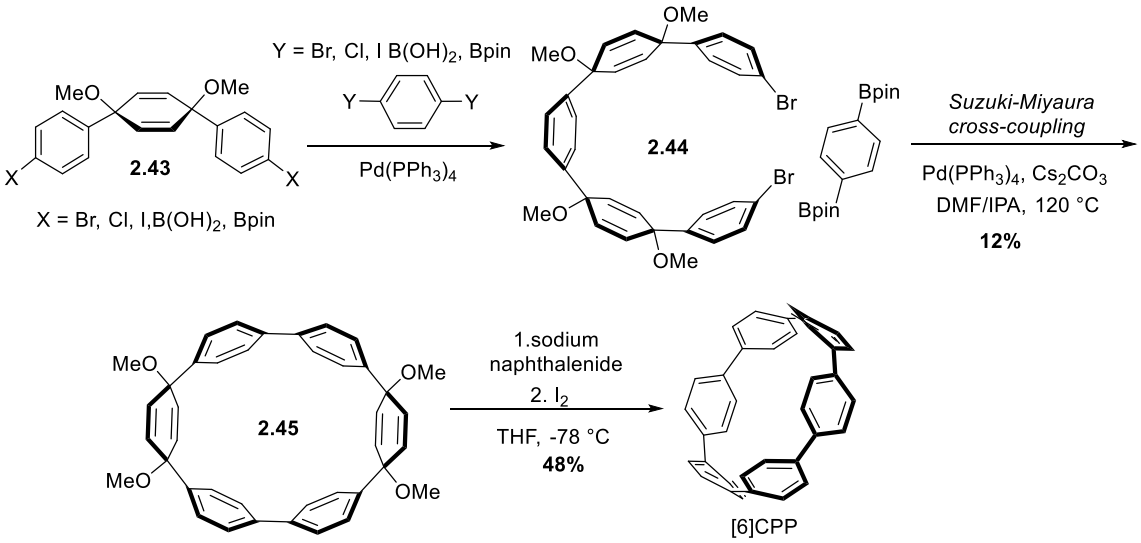
FIGURE 2.2: Synthetic steps to [*n*]CPPs

2.2.3 Different Approaches to CPP Synthesis

The main difference in the reported approaches to [*n*]CPPs lie in the first and last stage of the syntheses.[59] In the first stage, different types of bent (chair or boat) pre-arene subunits are used to pre-organize the molecule for subsequent macrocyclization and in the final stage, the methods used for aromatizing the pre-arene to the arene varies from reductive to oxidative.[59]

Jasti's Approach: Jasti and Bertozzi's first successful and selective synthesis of [*n*]CPPs brought new interest in this area.[54] The strategy used involves the formation of a *syn*-3,6-dimethoxycyclohexa-1,4-diene **2.43** as the bent pre-arene subunit to induce the necessary curvature and pre-organization/rigidity in order to facilitate macrocyclization. Jasti and Bertozzi were inspired by the previous reports of Vögtle (Scheme **2.9**). The main difference was that Suzuki-Miyaura coupling conditions were used for macrocyclization instead of Kharasch coupling conditions and a *cis*-3,6-dimethoxycyclohexa-1,4-diene unit was used instead of a 1,4-

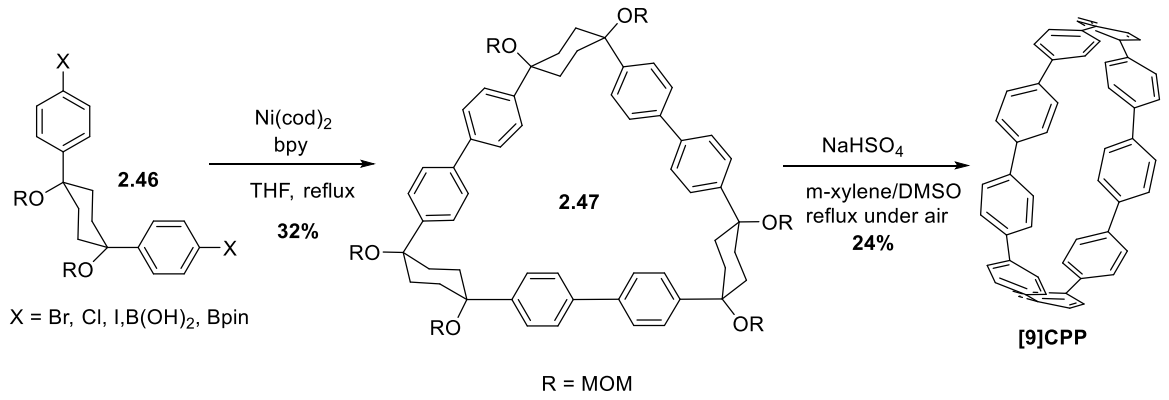
syn-diaryl cyclohexane as reported by Vögtle.[51] The aromatization of the pre-arene to form the corresponding CPP involves a radical mechanism. For instance, in the synthesis of [6]CPP, **2.43** was converted to the dibromide **2.44** via a Suzuki cross-coupling reaction. A second Suzuki reaction with 1,4-benzenediboronic acid bis(pinacol) ester gave macrocycle **2.45** in 12% yields. Treatment of **2.45** with sodium naphthalenide in the presence of iodine afforded the aromatized product, [6]CPP in 48%.[60] This approach by Jasti and co-workers has been successfully employed in the selective synthesis of wide range of CPPs ([5]-[12], [18]), some of which are commercially available.[61] Most notably, it was used to synthesize the smallest CPP, [5]CPP (SE = 119 Kcal/mol), in 2014.[61]



SCHEME 2.9: Jasti strategy to [*n*]CPP synthesis

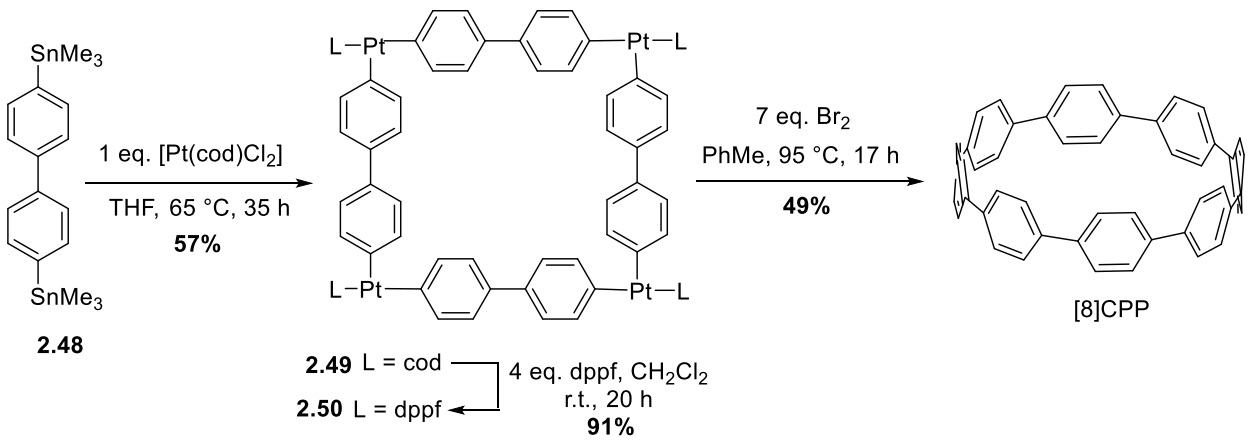
Itami's Approach: Itami and co-workers have used an L-shaped *syn*-1,4-dihydroxy-cyclohexane unit **2.46** to induce curvature into the molecule and alleviate the build-up of strain energy during the macrocyclization (stage 3, Figure **2.2**).[62] The L-shaped subunit is then subjected to a Ni-mediated Yamamoto-type coupling to afford macrocycle **2.47** in 32% yield. Acid-mediated dehydrative aromatization of **2.47** gives [*9*]CPP. Itami's strategy was inspired by

the idea put forth by Vögtle who earlier identified 1,4-disubstituted cyclohexanes to be promising substrates for successful macrocyclization to access [*n*]CPP precursors in 1996 (Scheme **2.5**).[51] This strategy of using L-shaped subunits has been effective in the selective synthesis of [7]-[16]CPP but not smaller and more strained CPPs.[63]



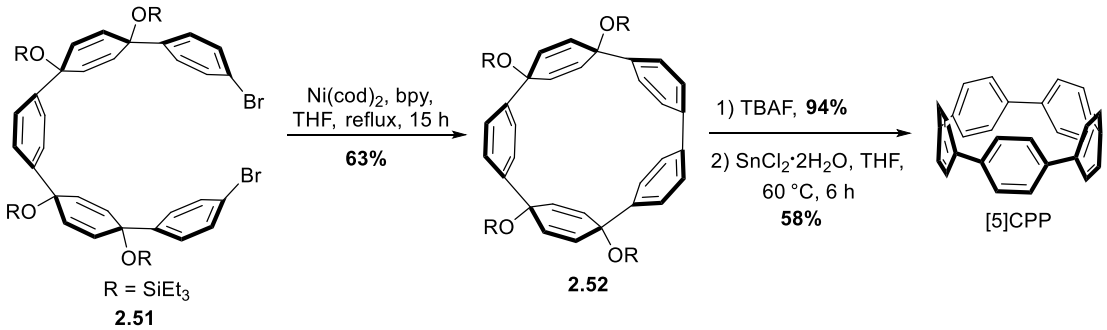
SCHEME 2.10: Itami approach to [*n*]CPPs

Yamago's Approach: Yamago and co-workers have developed two different synthetic strategies for accessing [*n*]CPPs. The first strategy relies on the use of a tetranuclear platinum (II) complex **2.49**, which prefers a square-type geometry that ultimately facilitates macrocyclization and C-C bond formation. Reductive elimination of Pt from the metallocycle by treatment with bromine furnishes the desired [*n*]CPP (Scheme **2.11**). Yamago, just like Jasti and Itami was inspired by the earlier work of Vögtle and co-workers.[51] The idea of using precursors in which all rings are already aromatic and extruding an atom to lead to CPP was earlier tried unsuccessfully by Vögtle.[51] The only difference being that the atom extruded in Yamago's approach was platinum instead of sulfur in the case of Vögtle.[51] This methodology has been vital in the selective synthesis of [6], [8], [9], [11], [12] and [13] CPP.[64]



SCHEME 2.11: Yamago's synthesis of [8] CPP via a square planar platinum (II) complex

In 2014, Yamago reported a second strategy for accessing [5]CPP, the smallest nanohoop synthesized to date. Due to the inability of the Pt-based approach to achieve the desired macrocyclic precursor synthesis, Yamago resorted to the use of a silylprotected 3,6-*cis*-dihydroxycyclohexa-1,4-diene unit **2.51**, akin to the Jasti pre-arene unit, as the precursor to access **2.52** (Scheme **2.12**).[65] The dibromide **2.51** was subjected to a Ni-mediated (Yamamoto) coupling reaction to give **2.52**, followed by reductive aromatization with tin dichloride dihydrate afforded [5]CPP in 58% yield. In 2015, Yamago and co-workers reported an alternate aromatization protocol, which involved the use of $SnCl_2 \cdot H_20$/HCl complex. This method was used to synthesize a series of [*n*]CPPs as well as a gram-scale synthesis of [6]CPP .[66]

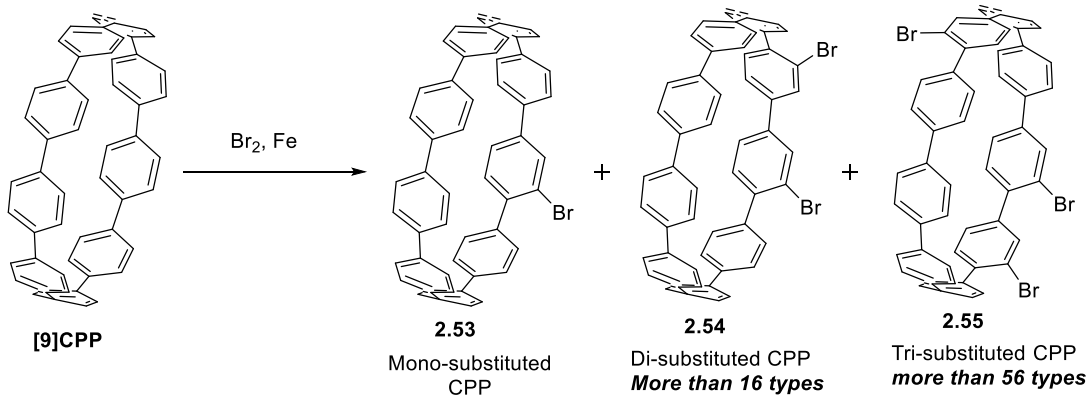


SCHEME 2.12: Yamago strategy to access [5]CPP

2.3 Major Limitations in [*n*]CPP Synthesis

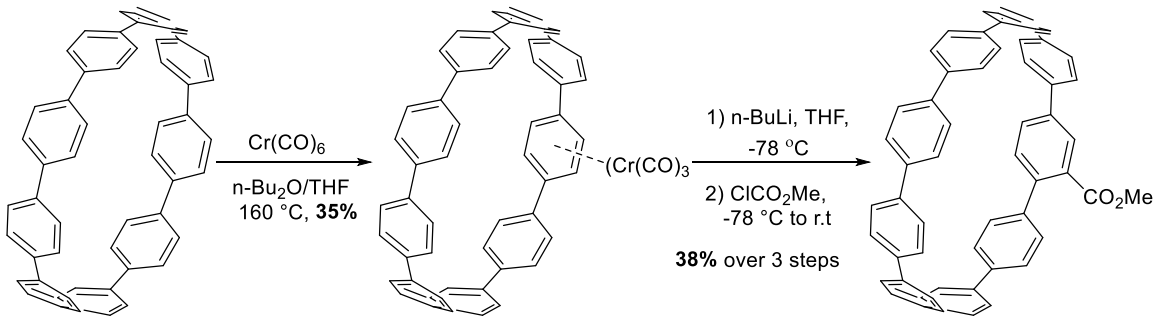
2.3.1 Direct Regioselective (Late-Stage) Functionalization

Despite the fact that several approaches to synthesize [*n*]CPPs have been successful, and numerous optimizations have been reported such that gram-scale quantities of the compound are now accessible, converting [*n*]CPP units into higher order nanostructures such as CNTs is yet to be realized. In this regard, a major limitation is that all benzene rings in an [*n*]CPP are equivalent. As such, selective introduction of functional groups at appropriate positions on the ring is a major synthetic difficulty. For instance, when [9]CPP is subjected to an electrophilic aromatic bromination reaction in the presence of iron as catalyst, a mixture of mono-, di-, tri-, tetra- etc substituted compounds are produced (Scheme **2.13**).[67] Dibrominating the phenylene rings can produce more than 16 different bromination patterns, tribromination can generate more than 56 different product combination and so on and so forth. These mixtures of products are completely inseparable, thus, there is a clear need for alternative approaches/methodologies/strategies to be developed in order to regioselectively functionalize [*n*]CPPs.



SCHEME 2.13: Mixture of products from the electrophilic aromatic substitution of a CPP

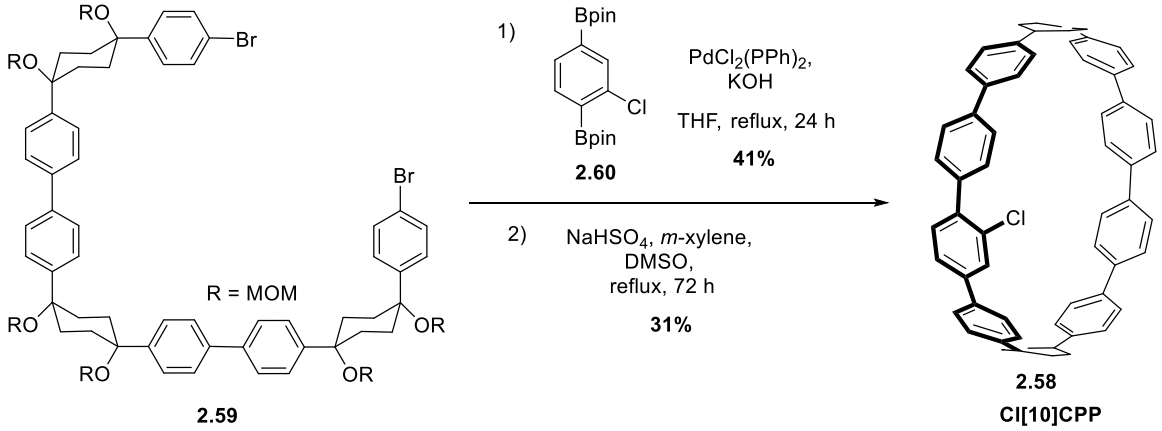
In an attempt to remedy this drawback, Itami and co-workers developed a novel strategy that led to the selective, and late-stage functionalization of [9] and [12]CPP with three different substituents, $SiMe_3$, CO_2Me, and Bpin.[67] This was done via complexation of the [*n*]CPP with a chromium-VI complex in the dark. Due to the extreme sensitivity of the complex **2.56** to light, a one pot reaction was done, where complexation of the metal, deprotonation, nucleophilic substitution and decomplexation were all performed consecutively without purification. In addition, the reaction flasks were wrapped with aluminum foil and the reactions performed in the dark. For example, the reaction of [9]CPP with $Cr(CO)_6$ afforded the complex **2.56** which upon treatment with *n*-BuLi in the presence of methyl chloroformate furnished the substituted [9]CPP **2.57** in 38% overall yield (Scheme **2.14**). The major disadvantage of this approach is the low consumption of starting material, the rapid decomposition of the complex **2.56** upon contact with light and the limited number of functional groups that can be installed, which confines the practicability of the methodology. Moreover, mono-functionalization of CPP alone has not proven to be useful in converting [*n*]CPPs into higher order nanostructures (CNTs).



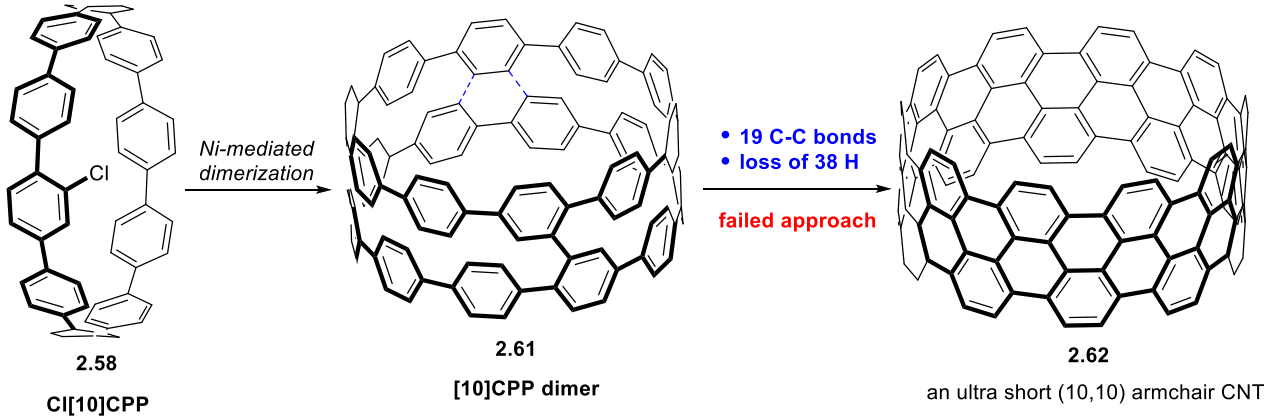
SCHEME 2.14: Late stage functionalization of [9]CPP by Itami and co-workers

In 2014, with the same objective to address the late state functionalization of [*n*]CPPs, Itami and co-workers synthesized a chloro[10]CPP (**2.58**), where the chlorine atom was installed

at the macrocyclization stage (Scheme **2.15**).[68] The chlorine atom was then used as means to link two of the [10]CPP units together to form the [10]CPP dimer **2.61** via a Yamamoto coupling reaction (Scheme **2.16**). Ideally, the authors aimed to convert the dimer into the ultra-short CNT **2.62**, however, their approach failed. The successful synthesis of **2.62** requires the formation of 19 carbon-carbon bonds between unactivated carbon atoms. Clearly, in order for this approach to work, many more functional groups/substituents about the dimer **2.61** are desirable to facilitate carbon-carbon bond formation. This points to a clear limitation in this area of chemical synthesis and the need to synthesize functionalized CPPs units. This represents a very challenging problem for synthetic organic chemistry.



SCHEME 2.15: Synthesis of chloro[10]CPP by Itami and Co-workers



SCHEME 2.16: Dimerization of Cl[10]CPP and attempted synthesis of an ultra-short CNT

2.4 Functionalized CPPs as Better Templates for Armchair CNT Synthesis

The challenges encountered in performing a late stage functionalization on CPPs as described in Section **2.3** above caused researchers to believe that synthesizing substituted CPPs, where the functional groups have been installed at an early stage would serve as a more suitable template for CNT synthesis. As shown in Figure **2.3** below, if macrocyclic nanohoops with complementary functional groups on both sides of the macrocycle, as the case of **2.63**, could be synthesized, then these functional groups could be used to direct subsequent carbon-carbon bond formation and thereby aid in the dimerization, trimerization and so on of the CPP. Closing the edges of the CPP as shown in the cartoon representation would provide a short CNT. In this regard, functionalized CPPs were targeted as better building blocks for the uniform synthesis of CNTs than CPPs alone.

Jasti and co-workers have synthesized arene-linked [8]CPP dimers **2.64** and **2.66** in an effort to build wider segments of SWCNTs (Figure **2.4**).[69] Their strategy called for stitching together proximal carbon atoms and forming the desired C-C bonds. This was ultimately unsuccessful.[69]

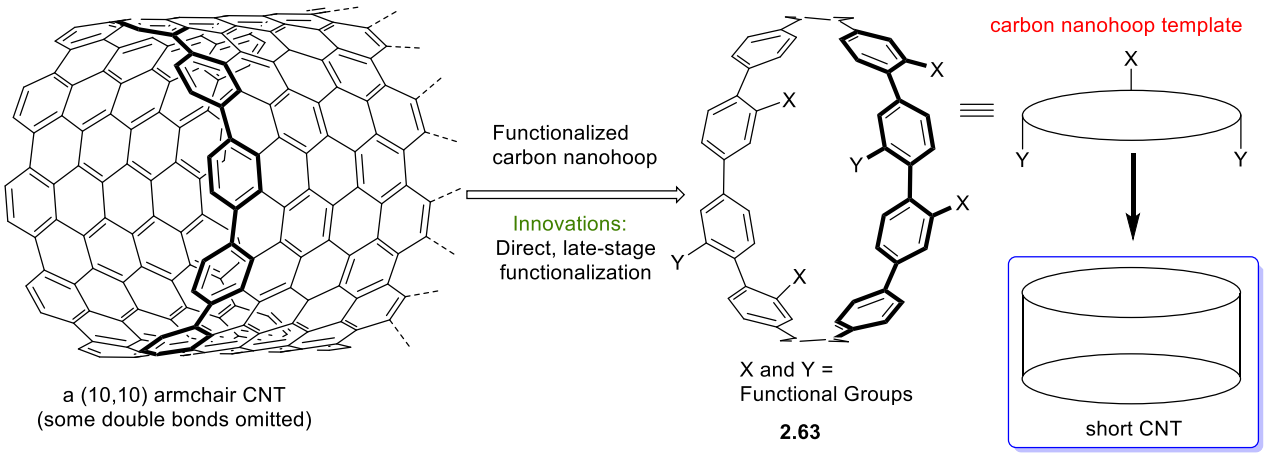


FIGURE 2.3: Functionalized CPPs as better for the homogeneous synthesis of CNTs

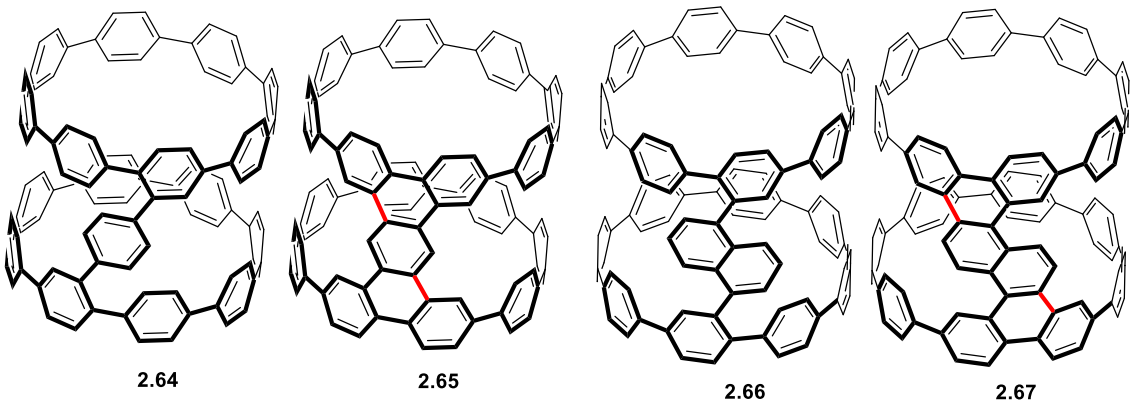
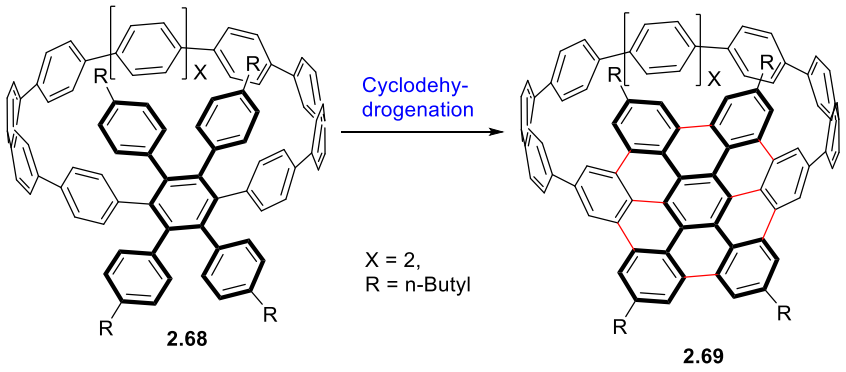


FIGURE 2.4: Phenyl and naphthalene-linked [8]CPP dimers as precursors to the synthesis of wider segments of SWCNTs

In a separate approach, Jasti and co-workers synthesized a tetraphenyl-substituted [12]CPP **2.68**.[70] Their strategy called for an oxidative reaction, namely, a cyclodehydrogenation (Scholl)

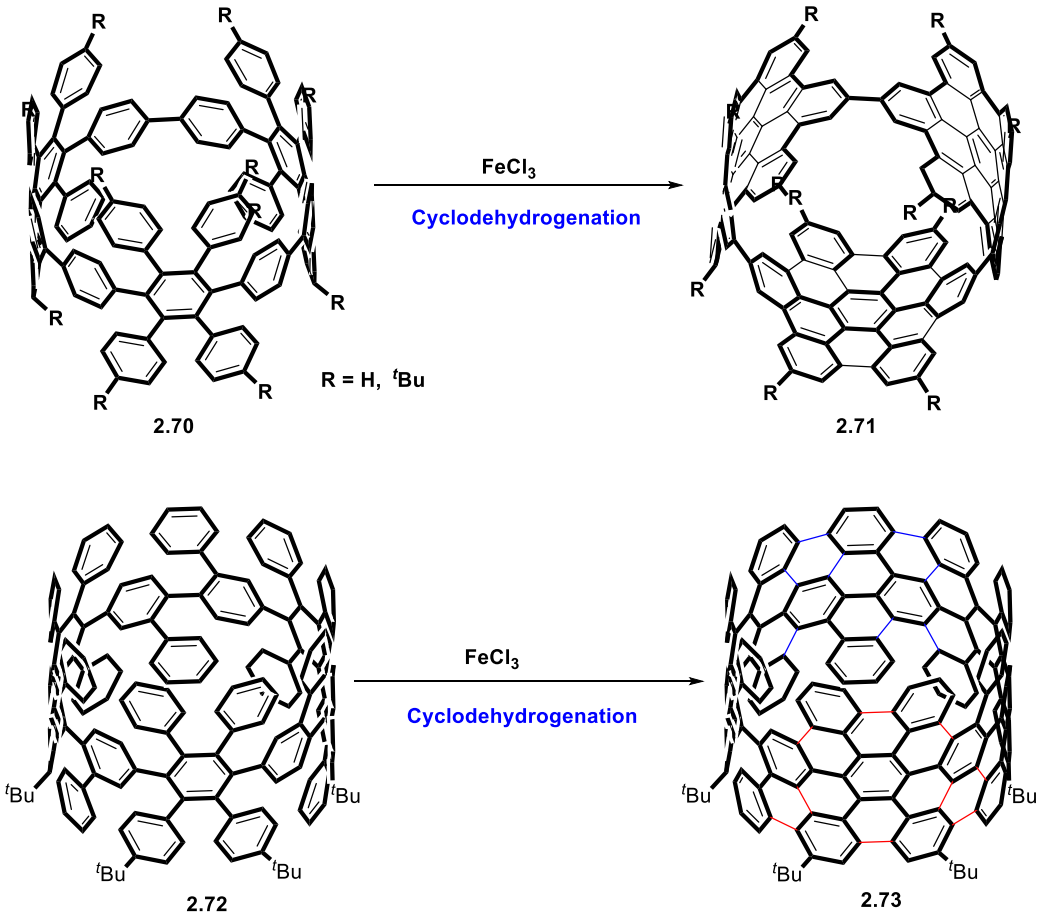
reaction, to afford a pi-extended sidewall segment of a CNT (**2.69**, Scheme **2.17**). To date, Jasti and co-workers have not reported the successful formation of the desired CNT segment.



SCHEME 2.17: Jasti synthesis tetraphenyl [12]CPP

In 2015, Müllen and co-workers synthesized compounds akin to the system desired by Jasti - the partially and fully arylated [9]CPPs **2.70** and **2.72**, respectively.[71] However, the attempted cyclodehydrogenation reactions to furnish the desired CNTs was unsuccessful with both compounds (Scheme **2.18**). In some instances, especially with highly strained homologs, rearrangement of the phenyl ring was observed.

The examples presented in this section demonstrate that there is a clear deficiency in this field of chemical synthesis and a need for synthetic innovations. Moreover, the need to synthesize functionalized CPPs, other than those containing aryl rings, is high as these substituents could be used to direct subsequent bond formation to generate wider CNT substructures.



SCHEME 2.18: Attempted synthesis of ultrashort SWCNT precursors by Müllen and co-workers

2.5 Insight into the Present Research and Generation of Hypothesis

2.5.1 Project Goal and Plan

The main objectives of this thesis are to develop late-stage functionalization reactions on a CPP substructure, and develop a non-cross coupling-based approach to arene-bridged macrocycles that would enable the selective introduction/placement of functional groups for future synthetic manipulations.

In 2012, Jasti and co-workers reported the synthesis and X-ray structure of [6]CPP (Scheme **2.9**).[60] Their studies showed that, unlike all other CPPs, [6]CPP prefers a stacking well-defined orientation in the solid state (Figure **2.5**). The natural organization of the individual nanohoop units may be suggesting that functionalized [6]CPP units may take on a similar stacking arrangement and thus facilitate subsequent C-C bond formation. It is therefore proposed that the synthesis of functionalized [6]CPP molecule would be desirable for CNT synthesis.

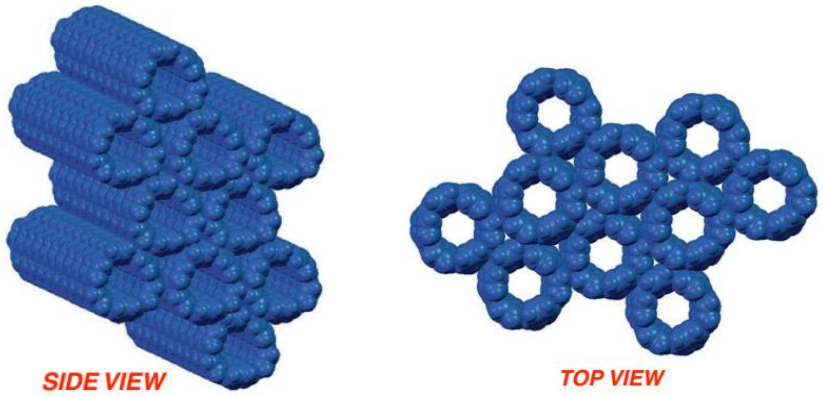
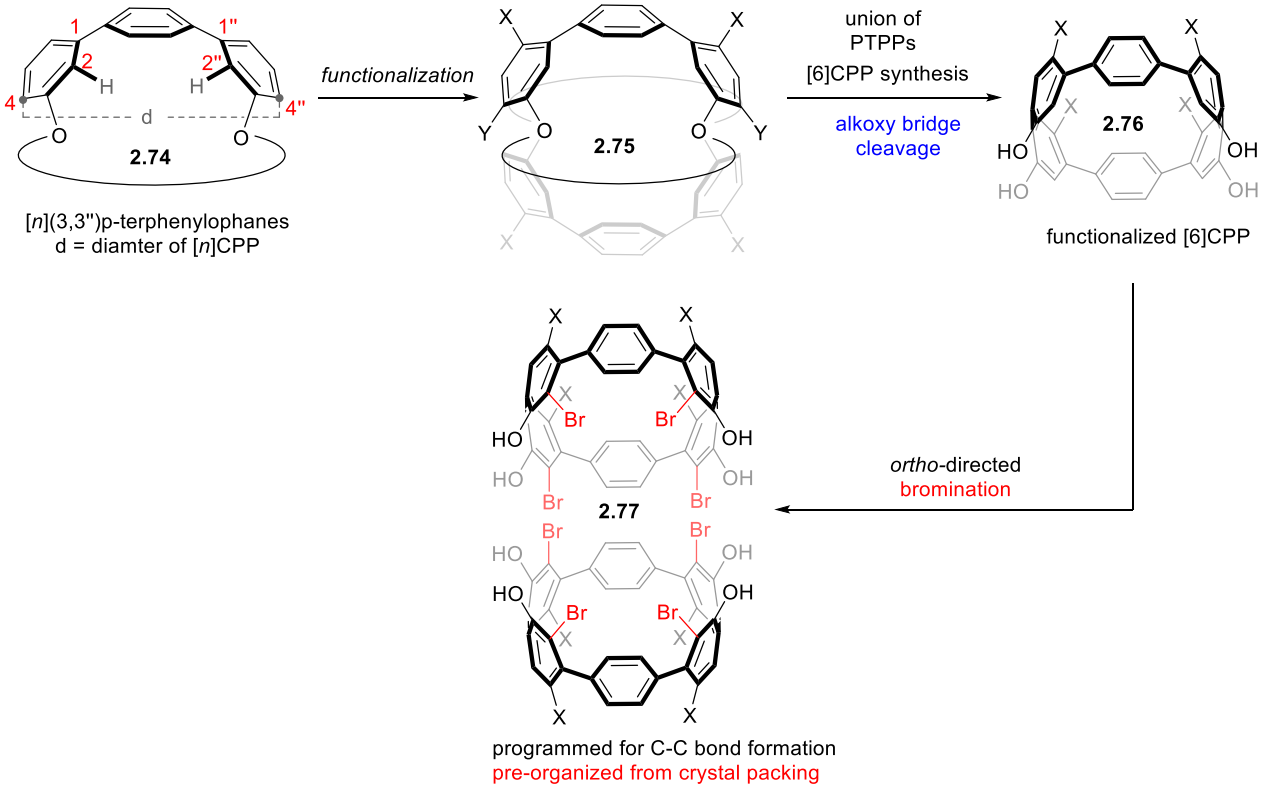


FIGURE 2.5: Solid state structure of [6]CPP

Our plan towards the synthesis of functionalized [6]CPP was to begin with the synthesis of a *p*-terphenylophane (PTPP) **2.74**, which is a substructure of CPP, where we could control the distance between the terminal vertices (4 and 4″ positions) of the PTPP by modulating the number of atoms in the tether. The distance between the 4 and 4″ of the PTPP was envisioned to have the same diameter (8.1 A°) as [6]CPP. The alkoxy bridges were used strategically to impose the curvature/rigidity required for a facile macrocyclization reaction. Secondly, we aimed to develop a strategy that could allow for the selective functionalization of the terminal arene units of the PTPP, preferably at the *para* positions (4 and 4″) by taking advantage of the oxygen atoms at C-3 and C-3″ positions of the *p*-terphenyl system (**2.75**, Scheme **2.19**). Finally, the functional

groups installed at the second stage could subsequently be used as a means to link two of the PTPP units together, thereby cleaving the alkoxy bridges to generate the functionalized [6]CPP - a [6]CPP in which four of the six rings have been substituted **(2.76**, Scheme **2.19)**. The hydroxyl groups that resulted from cleaving the tether could in turn be used to direct *ortho* bromination on **2.76**, thus introducing more functional groups selectively on the CPP unit to generate compound **2.77**. We viewed our approach would give rise to a CPP that is highly functionalized, well organized and programmed for further C-C bond formation and therefore could serve as a more suitable template for CNT synthesis.

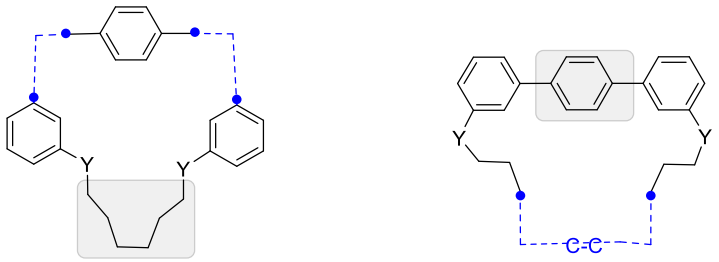


SCHEME 2.19: Synthetic plan to access highly functionalized [6]CPP

The second objective of this work is to develop an arene-bridging macrocyclization strategy that will tolerate the presence of *ortho*-substituents or functional groups at the site of macrocycle

formation. Transition metal-catalyzed cross-coupling reactions to furnish strained biaryl bonds are notoriously difficult transformations in chemical synthesis.[72] Most significantly, the construction of strained macrocycles through biaryl bond formation are more difficult reactions to accomplish.[73] The presence of biaryl bonds in natural products,[74] and molecules relevant to nanoscience[75] has instigated interest in the development of optimized reaction conditions. Transition metal-catalyzed cross-coupling reactions that were successful in forming strained biaryl bonds like in [*n*]CPP synthesis were on systems that had a pre-arene unit incorporated to facilitate macrocyclization.[61, 68] The main difficulty in the synthesis of a strained biaryl macrocycle is the accumulation of strain in the C-C forming reaction to provide the desired end product. There are two scenarios to be considered here. In the first case, the macrocyclization reaction will probably become energetically unfavorable if stretching or elongation of C-C bonds within the alkyl chain is required as a result of macrocycle formation (**2.78**, Figure **2.6**). In the second instance, extremely low yields are obtained [73] if the cross-coupling reaction requires bending one or more arene units to form the macrocycle (**2.79**, Figure **2.6**). The reaction becomes even more difficult when *ortho* substituents are present at the site of biaryl bond formation.[73] This is because not only would macrocyclization involve bending the arene unit which is energetically prohibitive, steric interactions between the *ortho* substituents disfavors the reaction (**2.81**, Figure **2.7**). When more than one biaryl bonds are involved with many more substituents, multiple steric interactions significantly increase the activation energy barrier for the process thereby impeding the reaction progress (**2.82**, Figure **2.7**).

In the course of this research, a new approach to access strained biaryl macrocycles was developed that did not rely on any cross coupling reaction. The detail synthetic endeavor of our strategy will be elaborated in subsequent sections

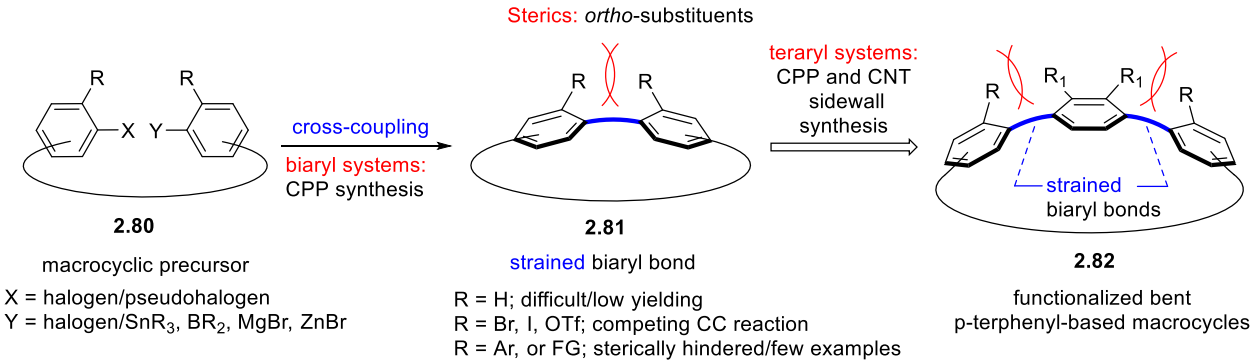


2.78 **2.79**

Scenario 1: *Macrocylization reaction that requires stretching alkyl chain*

Scenario 2: *Macrocyclization that involves bending arene units*

FIGURE 2.6: Strain induced in carbon-carbon forming reactions upon macrocylization



2.80 **2.81** **2.82**

macrocyclic precursor

X = halogen/pseudohalogen
Y = halogen/SnR_3, BR_2, MgBr, ZnBr

strained biaryl bond

R = H; difficult/low yielding
R = Br, I, OTf; competing CC reaction
R = Ar, or FG; sterically hindered/few examples

functionalized bent
p-terphenyl-based macrocycles

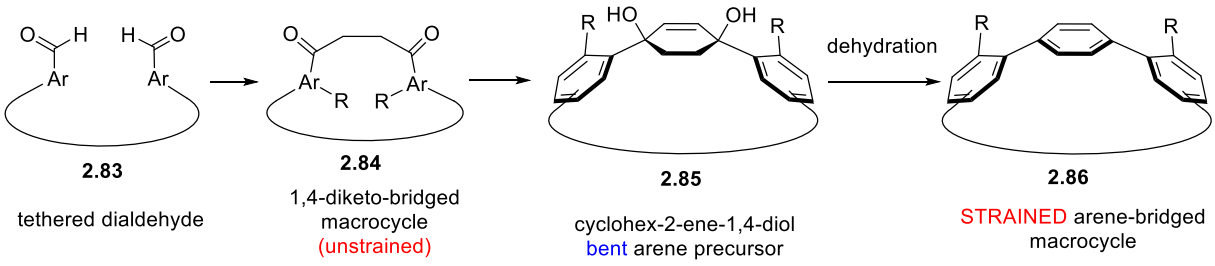
SCHEME 2.20: Limitations of Pd-catalyzed cross-coupling reaction to form strained biaryl macrocycles

2.6 A Non-Cross Coupling Approach to Arene-Bridged Macrocycles: Regioselective Functionalization of CPP Substructures, and the Synthesis of Congested Benzenoid Macrocycles

2.6.1 A Non-Cross Coupling Approach to Strained Biaryl Macrocycles

The limitations of Pd-catalyzed cross-coupling reactions in forming strained biaryl macrocycles, and in particular sterically congested systems with *ortho* substituents have already been addressed (see section **2.5**).

In 2015, Merner and co-workers reported a non-cross coupling-based approach to accessing strained arene-bridged macrocycles.[76] The bridging arene unit was, in turn a bent *para* phenylene ring. The formation of Csp^2-Csp^2 bonds in the macrocyclic system resulted from the conversion of an aldehyde carbonyl group **2.83** to a 1,4-diketone macrocycle **2.84**, and then to a bent arene unit **2.86 (**Scheme **2.21)**. No Pd or Ni-mediated reactions were employed. The potential advantage of this approach is that an aryl halide functional group can be introduced at an early stage in the synthesis and then carried through without any competing intermolecular cross-coupling reactions that would be encountered using the Jasti, Itami and Yamago approaches to benzenoid macrocycles. Furthermore, the use of a 1,4-diketo-bridged macrocycle as surrogate to a bent *para*-phenylene unit (arene-bridge) will circumvent the steric demand associated with the Csp^2-Csp^2 biaryl bond formation (Scheme **2.21**, **2.85** to **2.86**). It has been demonstrated that the dehydrative aromatization reaction of cyclohex-2-ene-1,4-diols is a powerful tool for accessing highly bent paraphenylene units as α angle of 15.6° were obtained from [5]CPP synthesis,[57] which is inaccessible through other precursors like Dewar benzene. In this chapter, work aimed at synthesizing sterically congested and strained arene systems using this method developed by Merner and co-workers will be described.



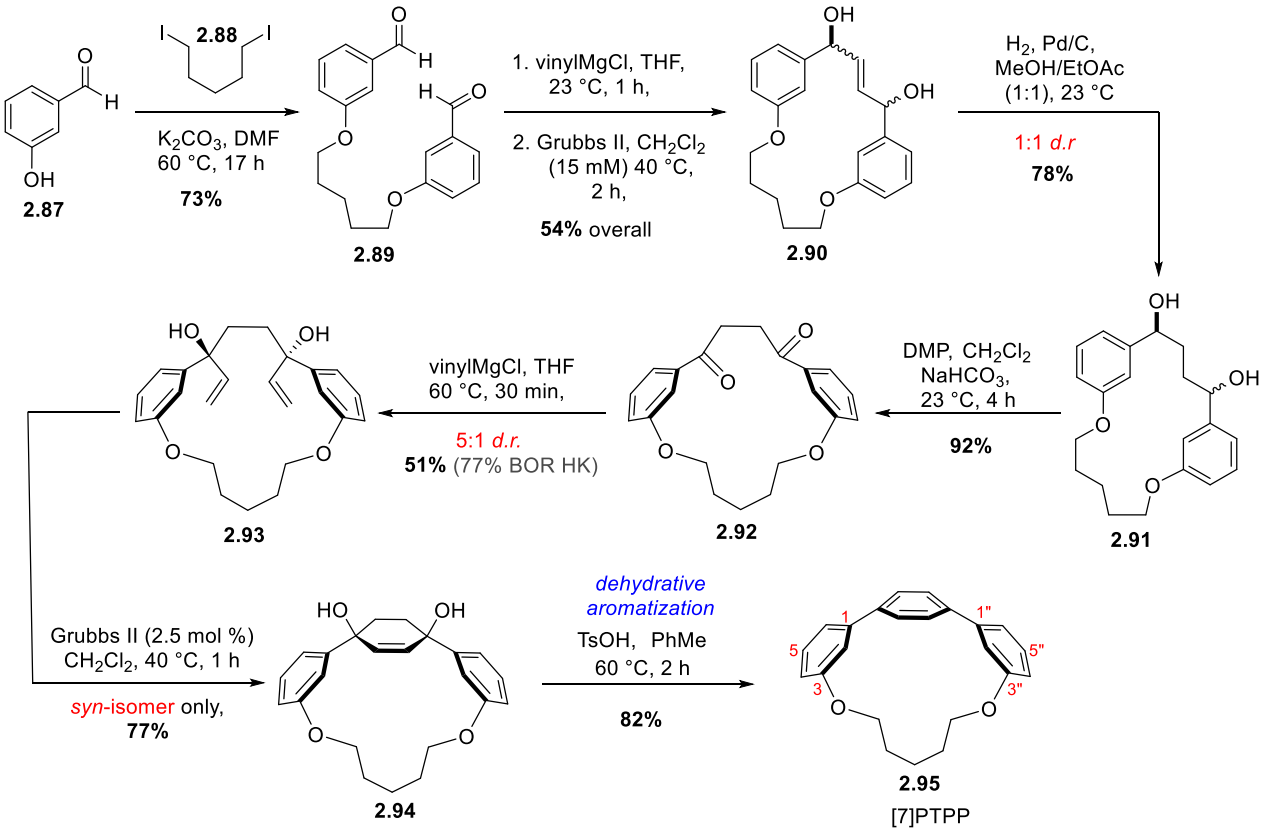
SCHEME 2.21: A non-cross-coupling approach to *ortho* functionalized arene bridged macrocycles

2.6.2 Synthesis of 1,7-dioxa[7](3,3″)-*p*-terphenylophane ([7]PTPP)

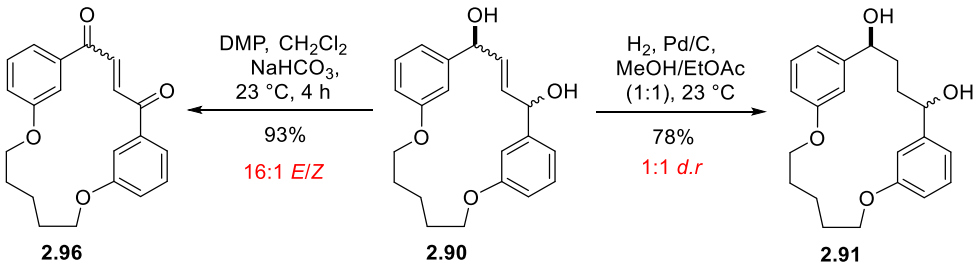
The synthesis began with the alkylation of 3-hydroxybenzaldehyde (**2.87**) with 1,5-diiodopentane (**2.88**) using a standard Williamson ether synthesis to furnish the dialdehyde **3.89** in 73% yield (Scheme **2.22**). The dialdehyde **2.89** was then subjected to a Grignard reaction with vinylmagnesium chloride to give the corresponding diene in 82% yield. A ring-closing metathesis (RCM) reaction of the diene with Grubbs′ second generation catalyst at 15 mM in dichloromethane afforded the macrocyclic diol in 57% yield. The concentration of this reaction is noteworthy, since related macrocyclic RCM reactions require significantly higher dilution (cf 1-3 mM). In fact, this reaction can be run at 40 mM without significant decrease in chemical yield.[77] During the course of our synthetic investigations, it was discovered that purification of the allylic diol product and subsequent RCM reaction was not advantageous with respect to yield and purity of the macrocycle **2.90**. Furthermore, a chromatographic separation was required at the RCM stage. Thus, the Grignard and RCM reactions could be carried out sequentially on a gram scale, with purification at the RCM stage to give a **54%** overall yield.

Analysis of the ^{1}H NMR of macrocycle **2.90** indicated that a mixture of olefin and alcohol isomers were present. Oxidation of **2.90** to the ketone indicated that the *E*/*Z* ratio was 16:1 and catalytic hydrogenation of **2.90** gave 1.1 mixture of diastereomeric alcohols (**2.91**, **2.96**, Scheme **2.23**). The *E*-olefin isomer was determined to be the preferred diastereomer from molecular modeling and later confirmed by X-ray crystallography of a homologous compound (n = 8). The macrocyclic diol **2.91** was then oxidized to the diketone **2.92** in 92% yield. A Grignard reaction with vinylmagnesium chloride on **2.92** afforded an inseparable mixture (5:1 *dr*) of *syn*/*anti* diasteromeric alcohols **2.93** in 51% yield with 34% of the monoreacted hydroxy ketone being isolated. Treatment of the diastereomer **2.93** with Grubbs′ second generation catalyst at 40 mM

concentration gives the cyclization of the *syn*-isomer only to form the cyclohex-2-ene-1,4-diol derivative **2.94** in 77% yield. The uncyclized *anti*-isomer was easily removed from the mixture at this stage due to the R_f difference of **2.94** and *anti*-**2.93** in 1:1 EtOAc/hexanes (R_f (*anti*-**2.93**) = 0.59, R_f (**2.94**) = 0.27). Dehydrative aromatization of **2.94** in the presence of *p*-TsOH acid forms the strained benzenoid macrocycle, 1,7-dioxa[7](3,3″)-*p*-terphenylophane ([7]PTPP, **2.95**) in 82% yield (Scheme **2.22**).



SCHEME 2.22: Synthesis of [7]PTPP



SCHEME 2.23: Determination of diastereoselectivity of macrocycle **2.90**

Recrystallization of **2.95** from a mixture of acetone and dichloromethane produced a single crystal suitable for X-ray analysis. The X-ray structure (Figure **2.7**), clearly indicates that the central arene unit is bent or nonplanar. In cyclophane chemistry, the deformation of benzenoid systems is quantified using the angles α and β.[78] The angle α is the mean deviation of the *para*-carbon atoms C-23 and C-24 of the central benzene ring from the plane defined by C-12, C-13, C-18 and C-19. The angle β is the average angle of distortion of the benzylic carbon atoms C-22 and C-25 from the plane defined by C-23 and C-24 respectively. In the case of **2.95**, the angle α is measured to be 9.9° and the angle β is 18.2°. A mean C-C_{biaryl} bond deviation of 7.0° was observed between the central benzene ring and the two terminal rings. The strain energy of the system was calculated to be 30.1 kcal/mol using DFT calculations carried out at the B3LYP level of theory using 6-31G(d) as basis set. The majority of strain energy resides in the aromatic system, SE aromatic = 21.8 kcal/mol (72%), with 14.5 kcal/mol on the central arene unit.

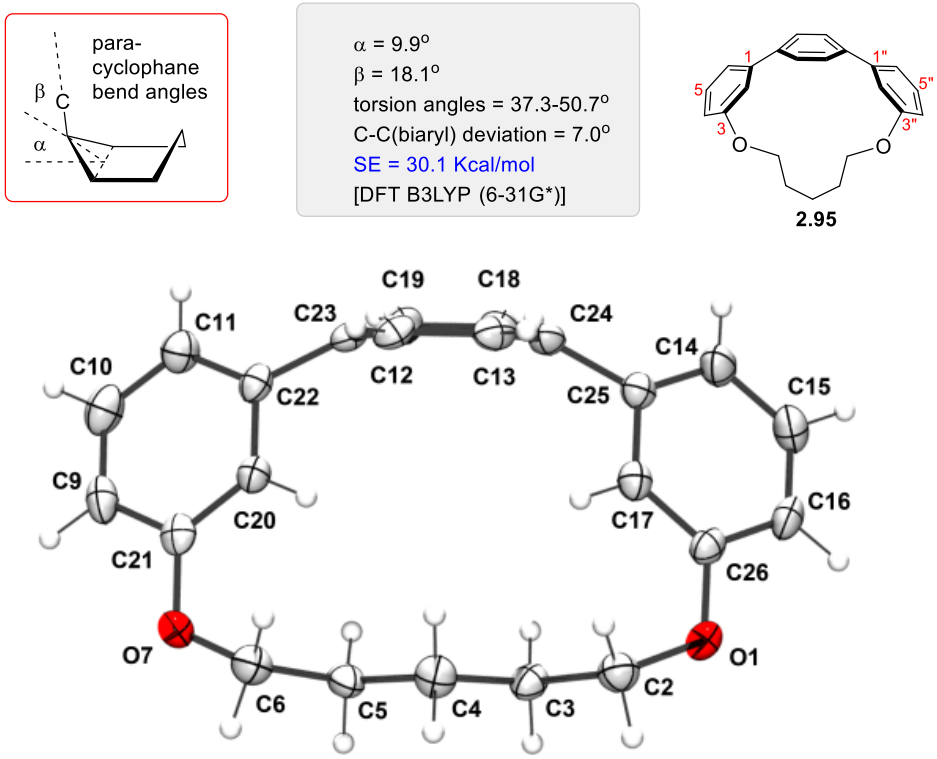
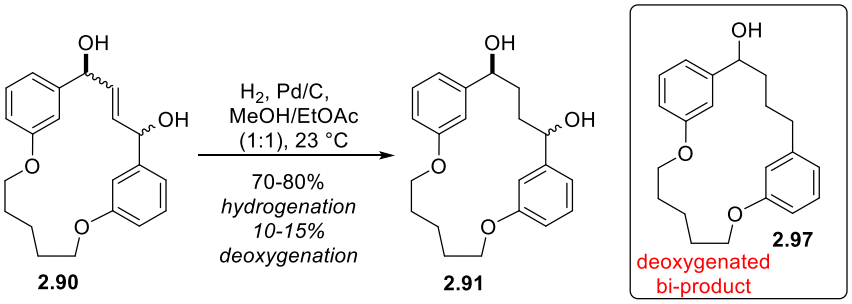


FIGURE 2.7: X-ray structure and computed strain energy of [7]PTPP

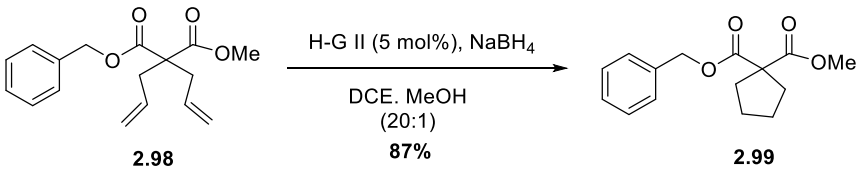
2.7 Streamlined Synthesis of Macrocyclic 1,4-diketone

Upon scaling up the synthesis of [7]PTPP (**2.95**), it was observed that the catalytic hydrogenation of the macrocyclic diol **2.90** produced a significant amount of benzylic deoxygenated product assigned as **2.97** (Scheme **2.24**). This byproduct reduced the efficiency of the large scale synthesis of **2.95** and necessitated a purification (chromatography) step. This reaction in various solvent combinations of methanol, methanol/EtOAc or EtOAc did not suppress the formation of **2.97.**

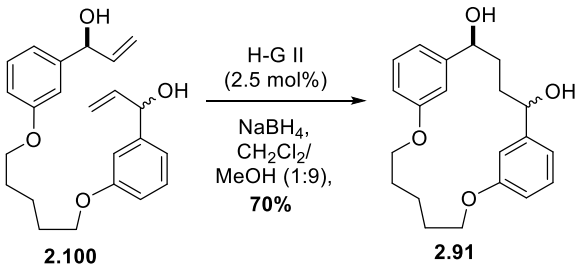


SCHEME 2.24: Deoxygenated byproduct formation on catalytic hydrogenation of **2.90**

To overcome the unwanted deoxygenated bi-product formation (**2.97**), in order to scale-up the synthesis, we explored the possibility of using sequential RCM and transfer hydrogenation reactions. Inspired by the work of Peese and co-workers,[79] who reported the use of H-G II catalyst to perform, first a RCM reaction and then a transfer hydrogenation in the presence of $NaBH_4$ on substrate **2.98** to afford the saturated 5-membered ring compound **2.99** in 87% yield (Scheme **2.25**), we subjected the allylic diol **2.100** to similar conditions. To our delight, the two step process proceeded smoothly without the formation of any bi-product and in good yields (Scheme **2.26**). This result was quite helpful as the overall yield of the two step process was higher than when the RCM and hydrogenation were carried out separately. Also, the low yield observed from the previous synthesis was due to the low solubility of macrocycle **2.90** in dichloromethane, and thus rendered purification tedious, as some of the product was lost on the column. The diol **2.91** was very soluble in dichloromethane rendering separation easier and the reaction higher yielding.



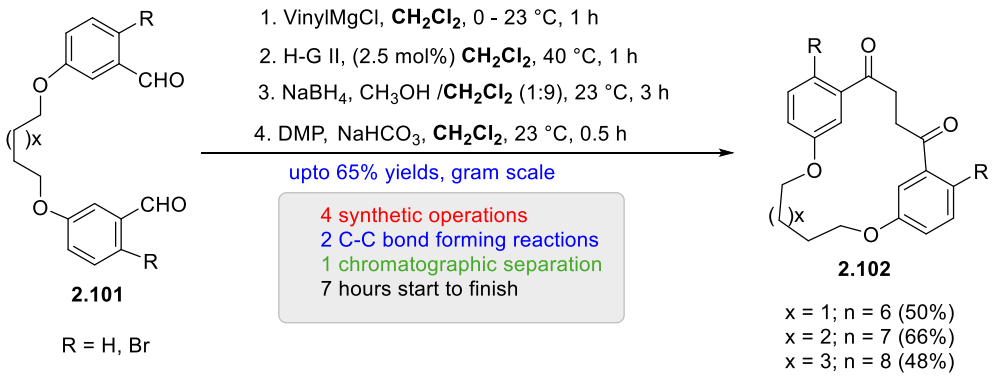
SCHEME 2.25: Successive RCM and transfer hydrogenation with H-G II



SCHEME 2.26: Sequential RCM and transfer hydrogenation

With this preliminary result, we designed a synthetic sequence that would facilitate the gram-scale synthesis of macrocyclic 1,4-diketones from acyclic dialdehydes without purification of any intermediates. Treatment of the dialdehyde **2.101** with vinylmagnessium chloride followed by RCM reaction with H-G II catalyst at 15 mM in dichloromethane produced a mixture olefin isomers, with the *E* isomer being predominant (Scheme **2.27**). The solvent from the RCM reaction was evaporated and the residue dissolved in 9:1 mixture of dichloromethane/methanol (instead of 20:1 as reported by Peese[79] and co-workers) followed by the addition of 3.0-5.0 equivalents of $NaBH_4$ to effect the selective hydrogenation of the double bond. Importantly, this hydrogenation could be done in less than 3 h on grams scale and no benzylic deoxygenation product was formed after analysis by both TLC, NMR and mass spectrometry. Remarkably, only 2.5 mol% of H-G II catalyst was used to effect both the metathesis and transfer hydrogenation, all of which was added at the RCM stage.[80] In order to minimize solvent loss, evaporation of only the desired amount of dichloromethane from the RCM reaction could be effected followed by addition of the required amount of methanol, and the hydrogenation still proceeded smoothly. Moreover, it was discovered that the use of a 9:1 mixture of methanol/dichloromethane during the transfer hydrogenation step enabled the reaction to proceed faster, compared to the 20:1 ratio as reported by Peese[79] and co-workers, which significantly lengthened the reaction time. Lastly, DMP oxidation of the crude diol mixtures, in

the presence of $NaHCO_3$ afforded the pure macrocyclic-1,4-diketones in up to 65% yield. This one pot reaction sequence was very efficient in terms of cost, solvent, time and manpower. This four step protocol involving two C-C bond formation processes could be done in less than 7 h, providing access to about 500-600 mg of the desired macrocyclic 1,4-diketone using less than 500 mL of solvent and about 50 g of silica gel. Also, a single chromatographic separation was required in the last step. Up to date, there is no current reported literature procedure for synthesizing gram-scale quantities of macrocyclic 1,4-diketones in a shorter and more efficient sequence than the one reported by Merner and co-workers.



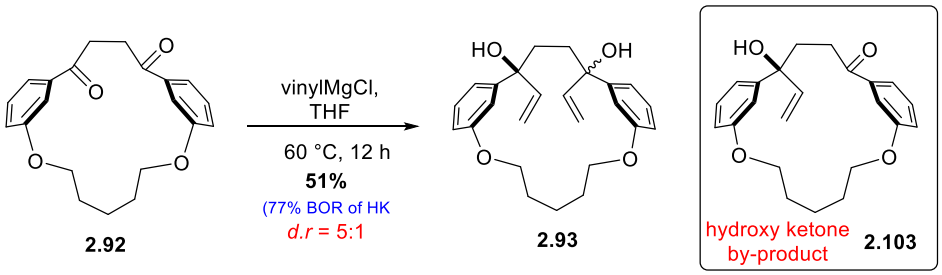
SCHEME 2.27: Streamlined synthesis of macrocyclic 1,4-diketones

Another powerful advantage of the transfer hydrogenation condition using H-G II catalyst is its tolerance to a wide variety of functional groups, notably aryl halides and benzyloxy-brigding groups which are normally hydrogenolyzed during Pd-catalyzed hydrogenation. This tolerance enabled access to the synthesis of wide variety of PTPPs for further synthetic manipulations as will be described in subsequent sections.

2.8 Optimization of Grignard Reaction (Solvent/Size-Dependent Diastereoselectivity)

Another difficulty faced during the scale-up synthesis of [7]PTPP (**2.95**) was the propensity for the formation of a hydroxyketone byproduct **2.103** (mono addition product) (23%)

during the addition of vinylmagnesium chloride to the macrocyclic diketone **2.92**. Formation of HK **2.103** also required a chromatographic step, which ultimately lowered the yield of the reaction (Scheme **2.28**). Addition of excess Grignard reagent did not facilitate the second addition, or improve the chemical yield. When the isolated HK, **2.103** was re-subjected to the same Grignard conditions, all the starting material was not consumed. Also, doing so added an additional step to the synthesis and increased the overall reaction cost.

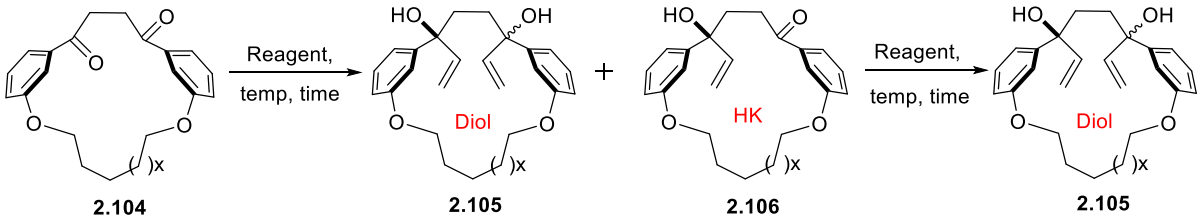


2.92 **2.93** **2.103**

SCHEME 2.28: Hydroxyketone produced as by-product during the Grignard reaction of the diketone **2.92**

It was speculated that addition of vinylmagnesium chloride resulted in deprotonation of the α proton next to the ketone resulting in enolate formation which obstructed further addition. Thus, our first attempt to circumvent enolization was to use a reagent that would increase the acidity of the ketone and cause the Grignard reagent to act more as a nucleophile than a base. In 2006, Knochel and co-workers reported the use of lanthanum (III) chloride salt ($LaCl_3 \cdot 2LiCl$) in Grignard reactions.[81] Their findings demonstrated that the use of this reagent reduced, if not entirely eliminating, undesired by-product formation, in particular the deprotonation of ketones in the presence of Grignard reagents. The diketones **2.104** were then subjected to Knochel conditions at various temperatures. To our pleasure, the reaction proceeded in excellent yield with a high suppression of hydroxyketone formation (Table **2.1**). However, diastereoselectivity

of the allylic diols produced was significantly reduced. Moreover, the diastereomers produced were in favor of the *anti*-isomers (entries 1 and 2, Table **2.1**), which unfortunately does not cyclize in the next RCM stage. The same trend was observed when the addition was done on the hydroxyketone (entry 9 and 10, Table **2.1**). Another observation was that Grignard addition reactions with vinylmagnesium chloride proceed significantly faster and in higher yields and diastereoselectivities than with vinylmagnesium bromide (entry 5 and 6, Table **2.1**). Thou, the Lewis acid suppressed HK formation and improved the yield of diols obtained, the predominant formation of the undesired allylic alcohol was an obstruction to proceed with the synthesis. Therefore, an alternative approach was highly desirable.



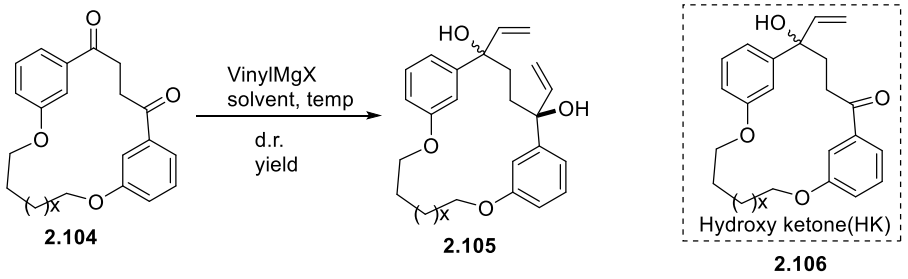
Entry	X(n)	Grignard reagent	Lewis acid	Solvent	Temp (°C)	Time (h)	Syn/ Anti	Diol (%)	HK (%)
1	1 (7)	VinylMgBr	---	THF	60	6	5:1	37	34
2	1 (7)	VinylMgBr	$LaCl_3 \cdot 2LiCl$	THF	23-60	18	1:1	37	---
3	1 (7 HK)	VinylMgBr	---	THF	60	2	4:1	60	---
4	1 (7 HK)	VinylMgBr	$LaCl_3 \cdot 2LiCl$	THF	60	0.08	1.3:1	80	---
5	2 (8)	VinylMgBr	---	THF	60	2	1.3:1	60	35
6	2 (8)	VinylMgCl	---	THF	60	2	2.3:1	68	25
7	2 (8)	VinylMgCl	$LaCl_3 \cdot 2LiCl$	THF	0	0.5	1:1	46	36
8	2 (8)	VinylMgCl	$LaCl_3 \cdot 2LiCl$	THF	23	0.17	1:1.4	90	

9	2 (8)	VinylMgCl	$LaCl_3 \cdot 2LiCl$	THF	60	0.5	1:2	90	---
10	2 (8)	VinylMgCl	$LaCl_3 \cdot 2LiCl$	THF	-78	2	---	---	70

TABLE 2.1: Optimization of Grignard reaction with Lewis acid

The second attempt towards preventing/minimizing enolization of the ketone during Grignard addition involved carrying out the reaction in solvents other than THF. It was observed that better yields and diastereoselectivities were obtained when non-coordinating solvents like toluene or dichloromethane were used in place of THF (Table **2.2**). For instance, for n = 7 homolog the *dr* of the reaction was improved from 4:1 in THF (60 °C) to 6:1 in both toluene (60 °C) and CH_2Cl_2 (40 °C) (entries 5,6,7, Table **2.2**). The yield of the diol obtained were also higher when using CH_2Cl_2 (83%) and PhMe (68%) as solvents than THF (51%). The same trend was observed for n = 8 homolog. Even though the *dr* of the diols was the same in all three solvents for the smallest homolog (n = 6) of the series, better yields were obtained with non-coordinating solvents (toluene (67%) and CH_2Cl_2 (77%). HK suppression was equally enhanced with the non-coordinating solvents. Another important observation from Table **2.2** is that the *dr* of the diols is dependent on the size of the macrocycle, the smaller the macrocycle, the better the *dr*.[80] Overall, dichloromethane was identified as being the ideal solvent for the second Grignard addition as it gives, better *dr* and yield of the diol. Moreover, it is carried out at lower temperatures and it provides highest suppression of HK formation (Table **2.2**). Furthermore, with CH_2Cl_2, the crude reaction products could be carried through to the next stage of the synthesis without purification, and recyclic of solvent. A proposed explanation for the above results has to do with the ability of the oxygen atom in THF to form a coordinate bond with the magnesium of the Grignard reagent, thereby lowering it accessibility to the ketone. Such coordination is not possible with CH_2Cl_2 or

toluene, thereby providing total accessibility of the Grignard reagent to the ketone, resulting in improved yields.



2.104 2.105 2.106

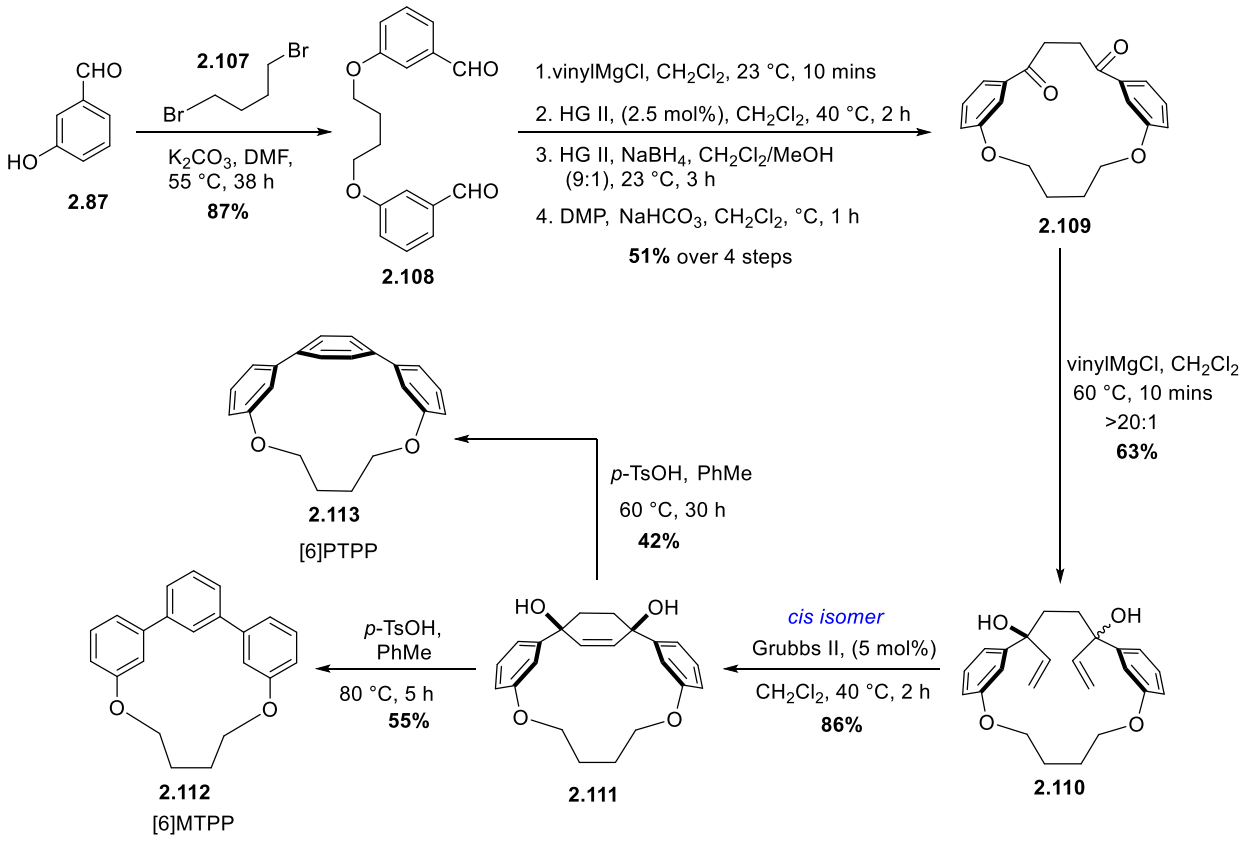
Entry	X(n)	Grignard reagent	Solvent	Temp (°C)	Time (h)	Syn/Anti	Yield(%)	HK(%)
1	3 (8)	VinylMgBr	THF	60	3	1:1	38	41
2	3 (8)	VinylMgCl	THF	60	0.5	2:1	52	26
3	3 (8)	VinylMgCl	PhMe	60	0.4	4:1	75	22
4	3 (8)	VinylMgCl	CH_2Cl_2	40	0.5	4:1	81	10
5	2 (7)	VinylMgCl	THF	60	0.5	5:1	51	5
6	2 (7)	VinylMgCl	PhMe	60	0.5	6:1	68	24
7	2 (7)	VinylMgCl	CH_2Cl_2	40	0.5	6:1	83	11
8	1 (6)	VinylMgCl	PhMe	60	0.5	>19:1	67	5
9	1 (6)	VinylMgCl	CH_2Cl_2	40	0.5	>19:1	77	10
10	1 (6)	VinylMgCl	THF	60	0.5	>19:1	63	15

TABLE 2.2: Size dependent diastereoselectivity and solvent effect on Grignard addition

2.9 Synthesis of 1,6-dioxa[6](3,3″)-*p*-terphenylophane ([6]PTPP)-A More Strained System

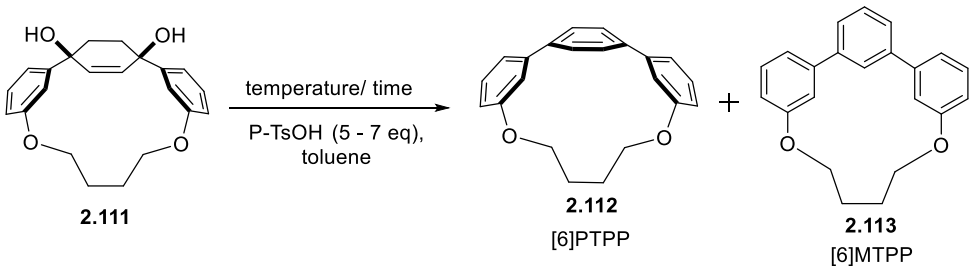
After synthesizing the [7]PTPP (**2.95**) and developing optimized conditions for accessing gram quantities of the compound, we embarked on the synthesis of the smaller homolog [6]PTTP (**2.113**). 3-hydroxybenzaldehyde (**2.87**) was converted to the dialdehyde **2.108** in 87% yield (Scheme **2.29**). The dialdehyde was subjected to the streamlined approach to provide the macrocyclic-1,4-diketone **2.109** in 51% yield. Grignard addition of vinylmagnesium chloride on **2.109** afforded a >20:1 (*syn*:*anti)* mixture of diastereomeric alcohols **2.110**, of which only the *syn*-isomer cyclized on treatment with 5 mol% of Grubb's II catatyst in CH_2Cl_2 at 40 mM to provide cyclohex-2-ene-1,4-diol **2.111** in 86% yield. Formation of the [6]PTPP from the precursor **2.111** was quite challenging. Unlike with the synthesis of [7]PTPP, treatment of **2.111** with *p*-TsOH in toluene at 80 °C did not provide the *para*-linked benzene bridged macrocycle, [6]PTPP **2.113**. Instead, the *meta*-bridged benzene macrocycle [6]MTPP **2.112** was obtained in 55% yield, where the central arene unit was shifted from the *para* to the *meta* position, possibly to relieve strain.[80]

In an attempt to prevent the rearrangement from occurring, the reaction was carried out at a lower temperature (50 °C) with 5-7 equiv. of *p*-TsOH. Formation of [6]PTPP was observed slowly throughout the reaction progress alongside production of intermediates which were not get consumed completely. Upon increasing the reaction temperature, slow formation of [6]MTPP was visible from TLC. It was uncertain whether the rearrangement (formation of [6]MTPP) came from the intermediates or from the [6]PTPP, and at what temperature it does exactly occur.



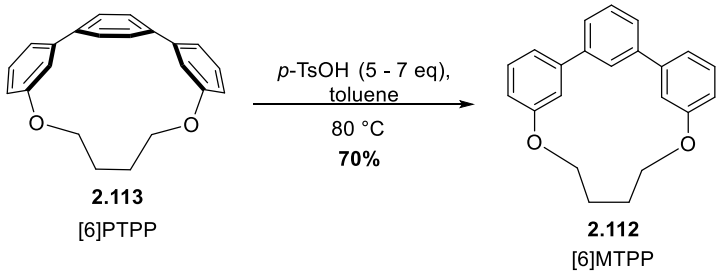
SCHEME 2.29: Synthesis of [6]PTPP and [6]MTPP

In order to ascertain the mechanism and the exact temperature at which rearrangement occurs, five different experiments on the precursor **2.111** were carried out at various temperatures (60, 65, 70, 75 and 80 °C) with 5-7 equivalents of *p*-TsOH (Table **2.3**). The results revealed that rearrangement occurred at 65 °C after heating the reaction for a prolonged time. The higher the temperature, the faster the formation of [6]MTPP, the lower the amount of [6]PTPP and the better the yield of the reaction. Therefore, the mechanistic pathway of the reaction was speculated to go through a series of intermediates to produce the [6]PTPP first which later rearranges to the [6]MTPP.



Entry	Temp (°C)	Time (h/min)	Yield(%)	[6]PTPP/[6]MTPP
1	60	30 h	42	[6]PTPP
2	65	12 h 10 min	37	5.9/1
3	70	7 h	55	8.3/1
4	75	4 h 30 min	55	2.8/1
5	80	2 h 25 min	67	3.1/1

TABLE 2.3: Dehydrative aromatization to ascertain rearrangement temperature



SCHEME 2.30: Conversion of [6]PTPP to [6]MTPP

To ascertain/confirm the mechanistic route, In a separate reaction [6]PTPP was subjected to the same dehydrative aromatization in *p*-TsOH and the compound rearranged to the [6]MTPP (Scheme **2.30**). Recrystallization of the latter in dichloromethane/hexanes provided single crystals suitable for X-ray analysis. Indeed, the X-ray picture shows a meta-arrangement between

the central and the terminal arenes (Figure **2.8**). However, when the isolated intermediates from the reaction were subjected to the same reaction conditions, nothing occurred.

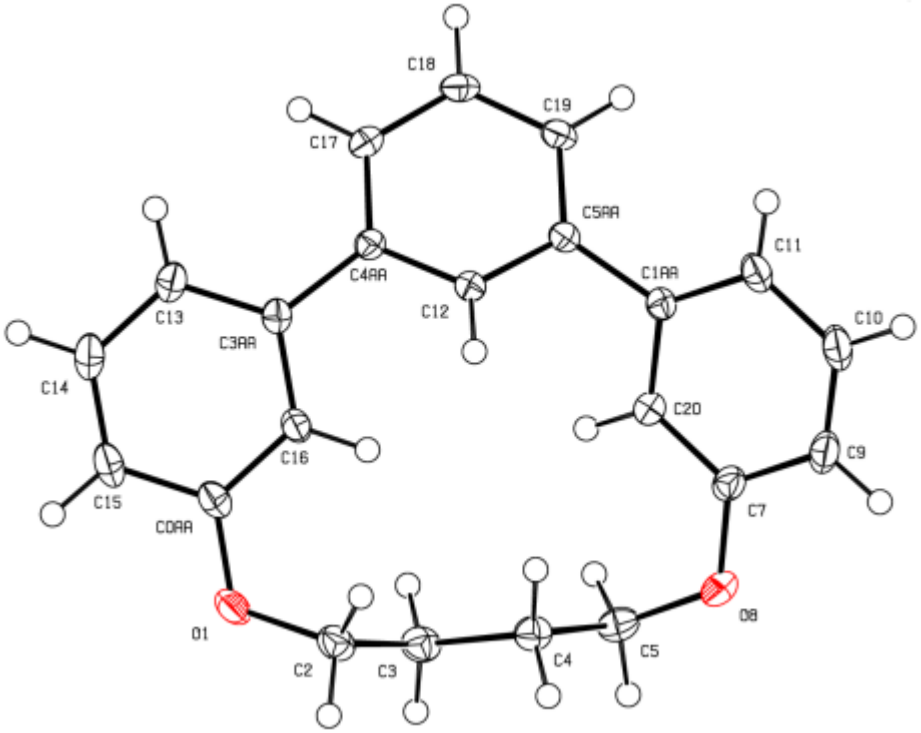
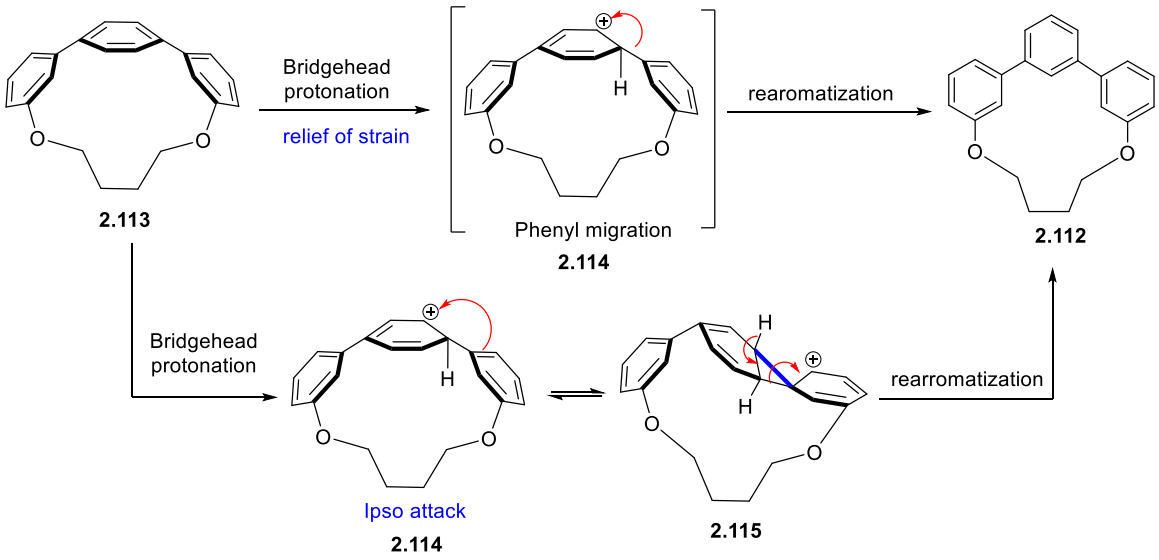


FIGURE 2.8: X-ray structure of [6]MTPP

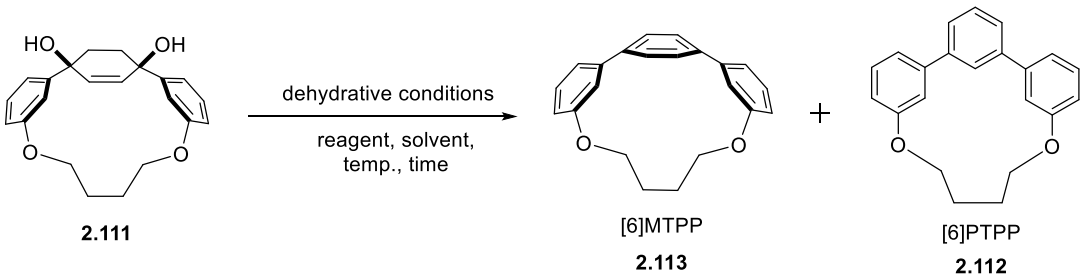
With all the evidence enumerated above, the mechanism of the reaction is proposed to proceed in either of the following two paths (Scheme **2.31**). In the first route, protonation of the central arene unit of **2.113** occurs to attenuate strain, thereby forming intermediate **2.114**. Migration of one of the terminal phenyl rings in **2.114**, followed by rearomatization produces the [6]MTPP (**2.112**) (Scheme **2.31**). In the second route, protonation of the bridged head position in **2.113**, relieves strain and provides intermediate **2.114**. Ipso attack of the olefin unit on the terminal phenyl ring of **2.114** provided intermediate **2.115** which later aromatizes to form **2.112** (Scheme 2.31).



SCHEME 2.31: Mechanism of rearrangement of [6]PTPP to [6]MTPP

In order to overcome any rearrangement during the dehydrative aromatization reaction of **2.111**, alternative aromatization conditions were explored. Treatment of **2.111** with a modified Yamago's aromatization conditions ($SnCl_2 \cdot 2H_2O$) in 1:1 mixture of THF and toluene[82] resulted only in the elimination of a single water molecule to form a partially aromatized product in 56% yield. Subjecting **2.111** to Itami aromatization conditions ($NaHSO_4 \cdot H_2O$)[83] in DMSO/xylene (1:2.7), in the presence of *o*-chloranil at 130 °C afforded the desired [6]PTPP in very low yield (36%) and purity (entry 3, Table **2.4**). Major disadvantages of Itami's conditions are the harsh temperature used and the lengthened reaction time. On the other hand, treatment of **2.111** with trifluoromethanesulfonic anhydride in Hunig's base (DIPEA) and CH_2Cl_2 at 0 °C provided the [6]PTPP in 57% yield. However, when the Tf_2O reaction was carried out at 23 °C, only the rearranged product **2.112** was obtained. This results suggests that the reaction temperature is crucial in obtaining the desired product. Finally, treatment the precursor **2.111** with Burgess reagent in THF at 50 °C provided the desired [6]PTPP in 75% yield after only 10 minutes without any rearrangement. Therefore, Burgess reagent was identified as being mild dehydrative

aromatization reagent to furnish highly distorted PTPP. To examined the potency of Burgess reagent, a more strained homolog [5]PTPP was synthesized by a colleague in the merner group and the aromatization of the precursor proceeded smoothly.



2.111 [6]MTPP 2.113 [6]PTPP 2.112

Entry	Reagent	Solvent	Temp (°C)	Time (h)	[6]PTPP (%)	[6]MTPP (%)
1	TsOH	PhMe	60	10	42	0
2	TsOH	PhMe	80	4	trace	55
3	$NaHSO_4$	DMSO/xylenes	130	31	36	trace
4	$SnCl_2$·H2O	PhMe/THF (1:1)	80	20	0	0
5	Tf_2O	DIPEA, CH_2Cl_2	0	0.17	57	0
6	Tf_2O	DIPEA, CH_2Cl_2	23	0.17	0	57
7	**Burgess**	**THF**	**50**	**0.17**	**75**	**0**
8	Burgess	PhMe	80	0.2	56	0

TABLE 2.4: Mild dehydrative aromatization conditions

Recrystallization of the [6]PTPP **2.113** from a mixture of CH_2Cl_2/hexanes provided crystals suitable for X-ray crystallographic analysis. The X-ray structure of [6]PTPP indicates the central arene unit is nonplanar. The α and β angles were measured to be 12.9°and

21.2° respectively. The strain energy of the system was calculated to be 37 kcal/mol (7 kcal/mol more strain than [7]PTPP) using DFT calculations (Figure **2.9**).

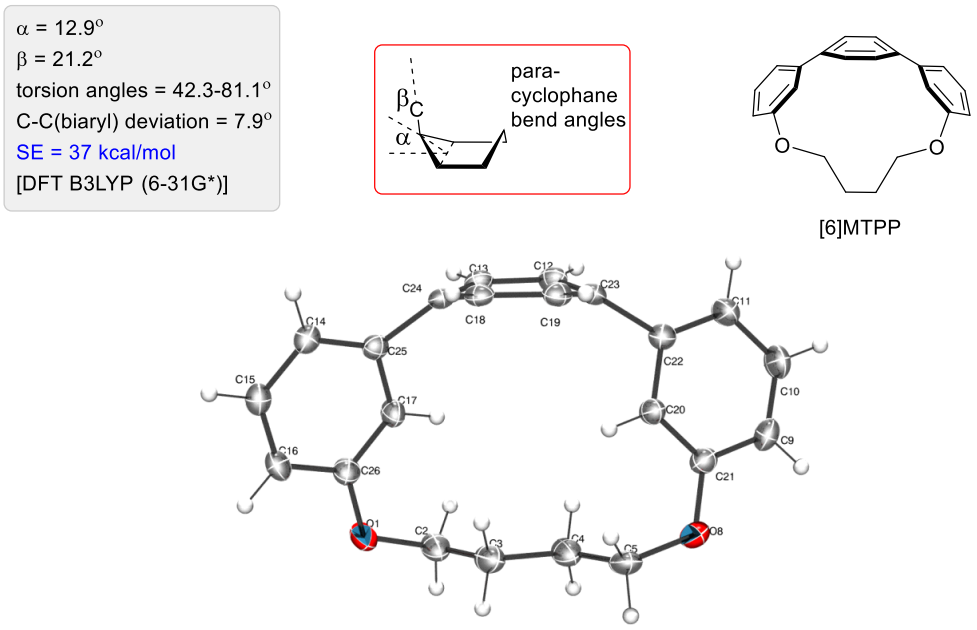
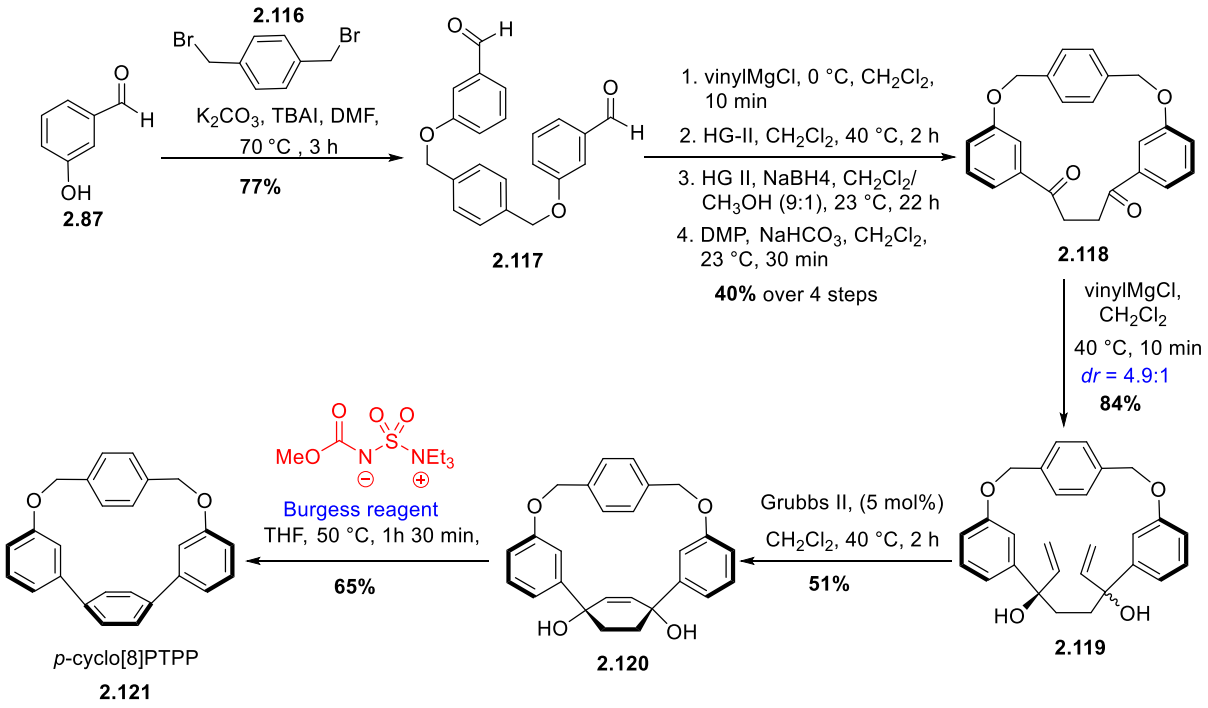


FIGURE 2.9: X-ray structure of [6]PTPP

2.10 Synthesis of *p*-cyclo[8]-*p*-Terphenylophane

The synthesis of this compound was pursued to demonstrate the power of the transfer hydrogenation conditions in providing access to a wide number of targets, one of which is the *p*-cyclo[8]PTPP **2.121** (Scheme **2.33**). Treatment of 3-hydroxybenzaldehyde **2.87** with 1,4-bis(bromomethyl)benzene **2.116** afforded the dialdehyde **2.117** in 77% yield (Scheme **2.32**). One pot conversion of dialdehyde **2.117** to diketone **2.118** via the streamlined sequence was achieved in 40% yield. The transfer hydrogenation condition, using H-G II catalyst was of vital benefit to selectively hydrogenate the olefin in the presence of ether (benzyloxy group). On the contrary, hydrogenolysis of the benzyloxy ether group was observed upon using Pd/C hydrogenation, which obstructed further reaction. Grignard addition of vinylmagnesium chloride to **2.118**

provided a 4.9:1 (*syn*/*anti*) mixture of diastereomeric alcohols **2.119** in 84% yield. Cyclization of the *syn* isomer was initiated on exposure of **2.119** to Grubb's II catalyst to provide the precursor **2.120,** which was subsequently subjected to dehydrative aromatization with the Burgess reagent to afford the *p*-cyclo[8]PTPP **2.121** in 65% yield. In the contrary, treatment of the **2.120** with *p*-TsOH afforded **2.121** in only 32% yield and low purity.



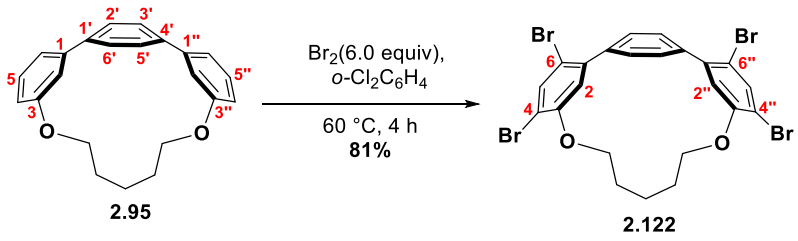
SCHEME 2.32: Synthesis of *p*-cyclo[8]PTPP

2.11 Late Stage/Regioselective Bromination of [7]PTPP

Treatment of [7]PTPP (**2.95**) with an excess of bromine in 1,2-dichlorobenzene at 60 °C resulted in the selective addition of bromine on the terminal arene units, without the relief of strain on the central benzene, provided the tetrabrominated compound **2.122** in 81% yield (Scheme **2.33**).[76] This selectivity arise due to the *ortho* and *para* directing effects of the oxygen atoms at C-3 and C-3″ positions of **2.95**. The oxygen atoms were installed beforehand eventually

to serve this purpose. Bromination of C-2 and C-2″ positions of the terminal arenes was not observed since the protons at these positions are in the shielding cone of the central benzene ring as depicted by the X-ray solid-state structure, thus unreactive (Figure **2.7**). The regioselective bromination of **2.95** was an innovation as there is no precedent for bromination on such systems in the literature. Moreover, regioselective bromination of [*n*]CPPs has been reported as problematic as all the benzene rings in the molecule are equivalent, whereas bromination of the PTPP **2.95** which is a CPP substructure was successful.

Recall, Itami and co-workers used three steps to introduce a single functional group on [9]CPP, which required complexation of the CPP with a chromium complex (Scheme **2.14**). The drawback of his approach was the lengthened reaction sequence, the low yield obtained and the propensity of the complex to decompose upon contact with light. However, with our approach, only a single step was required to introduce four functional groups selectively on [7]PTPP, which is a CPP fragment.



SCHEME 2.33: Regioselective bromination of [7]PTPP

The tetra-brominated compound **2.122** provided us with a handle to either expand the remote (4 and 4″) vertices of the PTPP through cross-coupling reactions and convert it into a CPP (**2.123**, Figure **2.13**) or expand the 6 and 6″ positions into a wider CNT sidewall segment (**2.124**, Figure **2.10**).

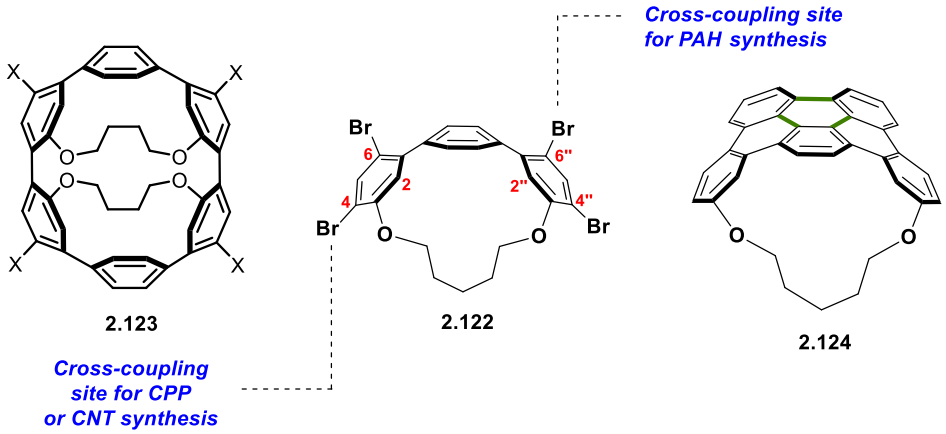


FIGURE 2.10: Extension of [7]PTPP into wider nanostructures

Chapter 3 : Towards the Synthesis of Functionalized [*n*]CPPs

3.1 Synthesis of Functionalized [*n*](3,3")*p*-terphenylophanes: Precursors to Functionalized Cycloparaphenylenes (CPPs)

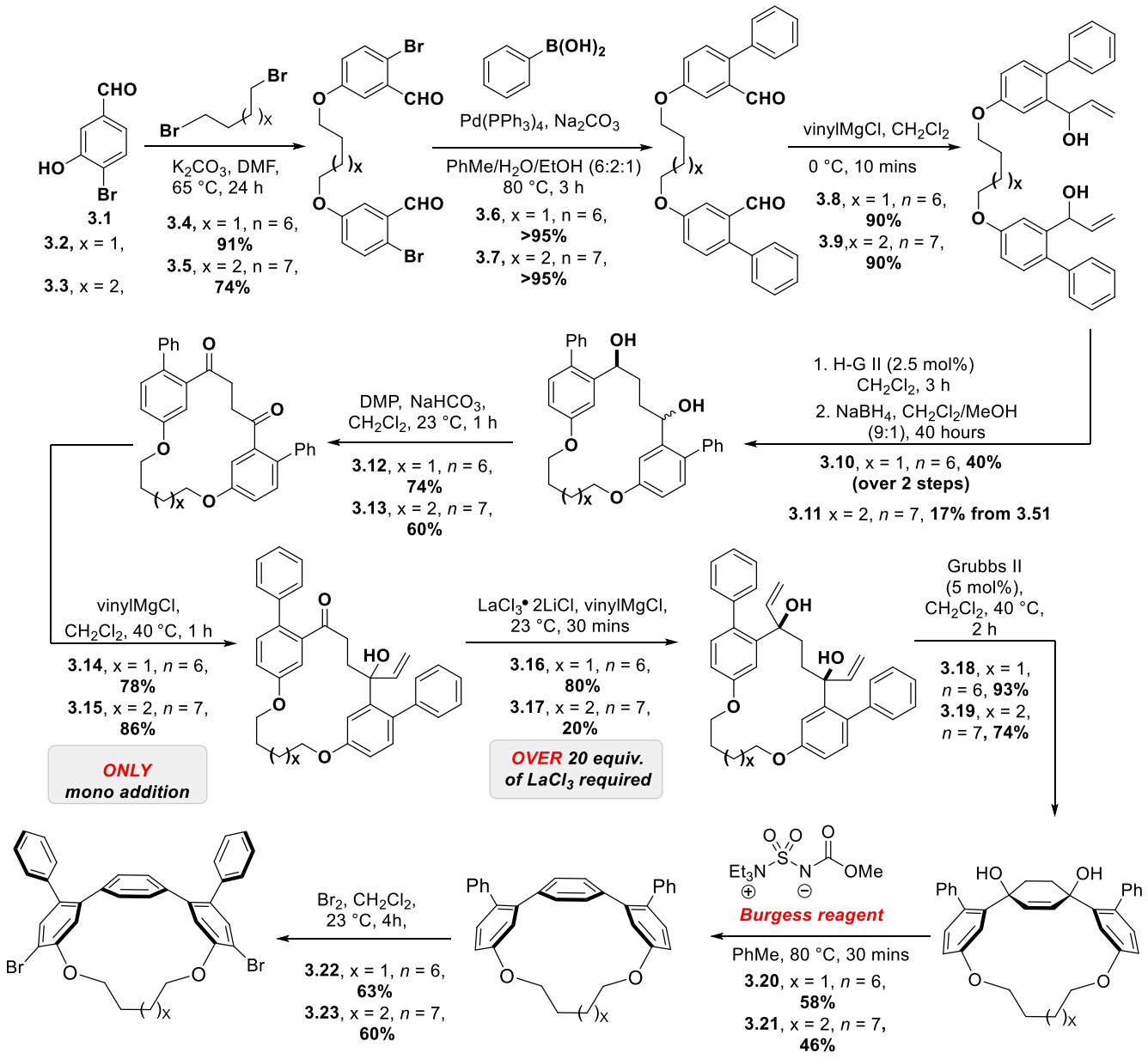
In this project, we were more interested in converting the functionalized PTPP into a functionalized CPP. In order to achieve this, we had to develop a strategy where we could block/substitute the 6 and 6″ positions earlier on in the synthesis so we could brominate the 4 and 4″ selectively later and extend it to accomplish our aim. The substituent placed at the 6 and 6" position was a phenyl ring since it could use later on to cyclize unto the non-planar arene to furnish the CNT side wall **2.124** as earlier anticipated.

3.1.1 Early-Stage Suzuki Reaction: Challenging Grignard

To realize our objective, we began the synthesis strategically with 2-bromo-5-hydroxybenzaldehyde (**3.1**). The bromo-derivative of 3-hydroxybenzaldehyde was used deliberately, the bromine atom was used as a handle to substitute/block the *o*-bridged position with the phenyl group later in the synthesis. The synthesis commenced with subjecting **3.1** to Williamson ether synthesis with 1,*n*-dibromoalkanes **3.2** and **3.3** to afford the brominated dialdehydes **3.4** and **3.5**. At this stage, we had the possibility of either doing an early-stage Suzuki cross coupling reaction to convert the carbon bromine bond to a carbon-carbon bond or carrying the bromine through the synthesis and do a late-stage Suzuki reaction. We proceeded forward to explore the first option. The aryl bromides on **3.4** and **3.5** were subjected to a Pd-catalyzed cross-coupling reaction with phenyl boronic acid to provide the diphenyl dialdehydes **3.6** and **3.7** (Scheme **3.1**). A Grignard reaction with vinyl magnesium chloride on the dialdehydes afforded the dienes **3.8** and **3.9** in 90% yield respectively. The dienes were subjected to a RCM reaction with 2.5 mol% H-G II catalyst at 15mM in CH_2Cl_2 to afford the macrocyclic

diene in low yields. The low yield of this reaction is explained by the formation of a higher molecular weight biproduct during the RCM reaction. Hydrogenation of the macrocyclic diene from the RCM product was quite challenging. We first resorted to the use of catalytic hydrogenation (Pd/C) in a 1:1 mixture of ethyl acetate and methanol and observed a huge amount of deoxygenated biproduct formed, thereby lowering the yields. In an attempt to overcome this, using solely ethyl acetate or methanol as solvent did not solve the problem. The other way to reduce bi-product formation was to use the transfer hydrogenation condition with H-G II and $NaBH_4$ which gave the desired product in good yield. Thus, the two step reaction from **3.6** to **3.10** afforded the alcohols in 40% overall yield for n=6 homolog. For n=7 homolog, the three step reaction from the dialdehyde **3.5** to the diol **3.11** provided a 17% overall yield. Oxidation of the hydroxyl groups in **3.10** and **3.11** to the diketones **3.12** and **3.13** was effected using DMP in CH_2Cl_2. The streamline sequence from the dialdehydes **3.6** and **3.7** to the diketones **3.12** and **3.13** could not be effected due to the side reaction produced at the RCM stage and the closeness in R_f value between the transfer hydrogenated product and bi-product, which rendered separation difficult. Surprisingly, subjecting the macrocyclic 1,4-diketones **3.12** and **3.13** to a second Grignard reaction with vinylmagnesium chloride resulted in only mono-addition to afford the hydroxyl ketones (HK) **3.14** and **3.15** in 78-86% yield. Adding an excess of Grignard reagent either to the diketone or the isolated HK did not trigger a second addition. This observation was attributed to the steric hindrance caused by the phenyl rings (the rings being in the shielding cone of the ketone) thereby blocking addition of the Grignard reagent. Moreover, it was speculated that the Grignard reagent acted as a base thereby deprotonating the alpha proton next to the diketone resulting in enolate formation. In order to circumvent enolate formation and to promote the second addition reaction, we resorted to the use of a lewis acid

($LaCl_3 \cdot 2LiCl$), as it is well known to activate ketone and prevent enolization during Grignard reactions.[81] Thus, treatment of the HK **3.14** and **3.15** with $LaCl_3 \cdot 2LiCl$ and vinylmagnesium chloride in THF afforded the diene **3.16** and **3.17** in 80% yield for n=6 homolog and 20% yield for n=7 homolog respectively. In order for the latter reaction to take place, about 20 equivalence of the lewis acid was required which is not practicable. Also, there was a huge problem of reproducibility of the reaction. This reaction worked twice on the n=6 and n=7 homologs, however, all other attempts were unsuccessful. It is also important to mention that once the reagent is opened from the sealed container, it decomposes, and this could be one of the factors that affected reproducibility. The allylic alcohols **3.16** and **3.17** was then subjected to a second RCM reaction with Grubb's II catalyst to form the cyclohex-2-ene-1,4-diol **3.18** and **3.19** in excellent yields. Aromatization of the latter compounds with *P*-TsOH acid resulted only in the elimination of one water molecule to form the partially aromatized product. However, treatment of precursors with the Burgess reagent gave the desired substituted *p*-terphenylophanes **3.20** and **3.21** in good yields. Having the latter compounds in hand was a huge accomplishment, since it represents the first synthesis of a strained biaryl macrocycle with an *ortho* substituent at the site of macrocycle formation, without using cross-coupling reactions. It was also reported earlier on that the accomplishment of such reactions while relying on Pd-catalyzed cross coupling reactions are extremely difficult and low yielding.[73] Treatment of the PTPPs **3.20** and **3.21** with bromine in CH_2Cl_2 afforded the dibrominated compound **3.22** and **3.23** in good yields.



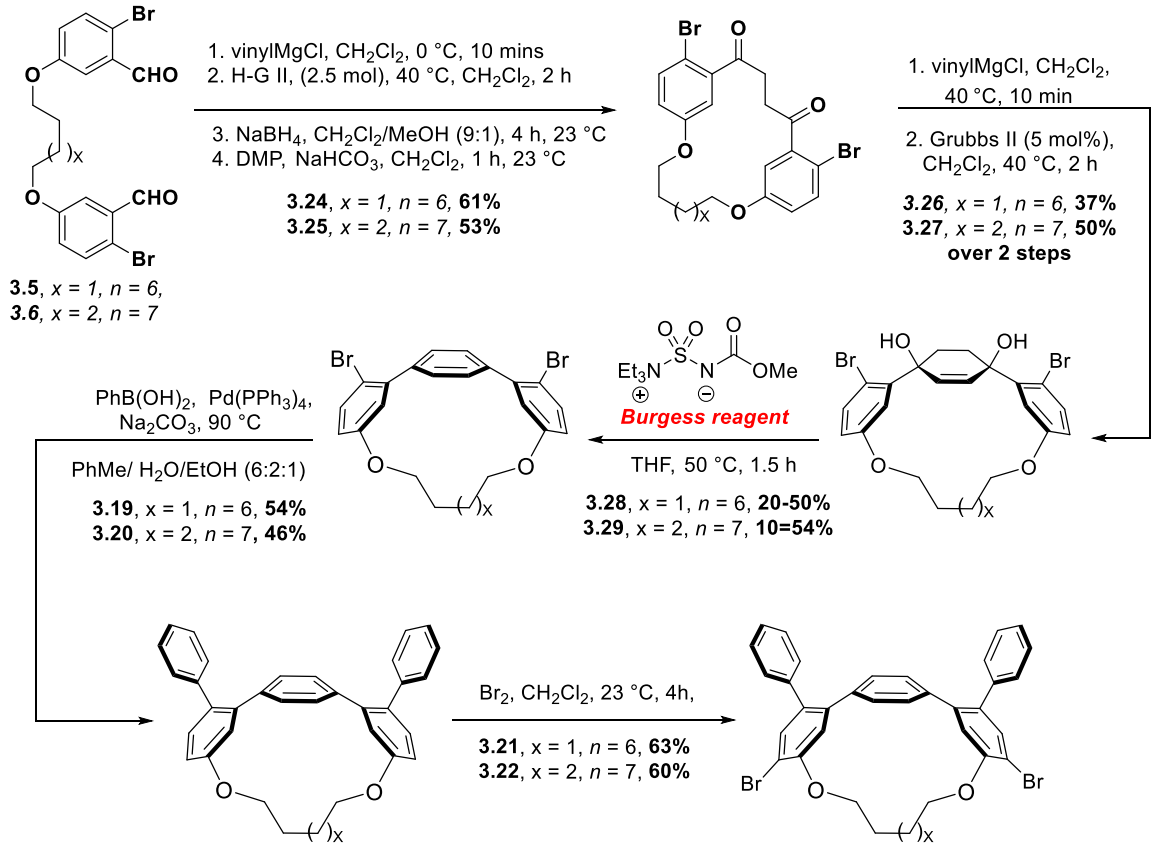
SCHEME 3.1: Synthesis of functionalized [*n*]PTPP (early-stage Suzuki)

3.1.2 Late-Stage Suzuki reaction: Overcoming the problematic Grignard and low yielding Reactions of first-generation approach

The higher molecular weight bi-products formed during RCM reaction of the dienes **3.8** and **3.9** and the reproducibility problem during the second addition of vinylmagnesium chloride

on the HK **3.14** and **3.15** prompted us to consider doing the Suzuki reaction at a later stage of the synthesis in order to overcome the fore stated challenges. In this regard, the bromine atom was carried throughout the synthesis till the formation of the brominated TPPP. The bromo dialdehydes **3.4** and **3.5** were subjected to the one port sequence to afford the macrocyclic-1,4-diketones **3.24** and **3.25** in 50-60% yield (Scheme **3.2**). H-G II catalyst was particular useful in the transfer hydrogenation step as no hydrogeneolyss of the C-Br bond was observed. In the first attempted synthesis of **3.24** and **3.25**, the hydrogenation of the RCM product with palladium on carbon cleaved the C-Br bond, there by hindering further reaction. Grignard reaction on **3.24** and **3.25** with vinylmagnesium chloride followed by RCM with Grubb's II catalyst provided the cyclohex-2-ene-1,4-diols **3.26** and **3.27** in good yields. Aromatization of the latter precursor with Burgess reagent in THF at 60 °C afforded the bromine substituted PTPP **3.28** and **3.29** in low yields. This reaction faced the problem of scale-up. The reaction worked well on a 10 mg scale to provide the desired product in 50% yield. However, repeating the same reaction on a 50 mg scale resulted in a drastic decrease in yield. Also, isolation of the PTPPs **3.28** and **3.29** was difficult as the product had low UV/visible activity and did not stain well in a number of organic stain. Nonetheless, treatment of the bromosubstituted PTPPs **3.28** and **3.29** with phenyl boronic acid provided the phenyl substituted PTPP **3.20** and **3.21** in moderate yield (Scheme **3.2**). Due to the difficulty in isolating **3.26** and **3.27**, we examined the possibility of converting the diol precursors **3.24** and **3.25** directly into the PTPP **3.20** and **3.21**. This two-step reaction provided 50% yield of the desired product when done on 10 mg scale, yet, scale-up and optimization of the reaction was still problematic. Bromination of the PTPPs **3.20** and **3.21** with bromine in CH_2Cl_2 afforded the dibromo-diphenylsubatituted PTPPs **3.22** and **3.23** in good yields. Recrystallization of **3.23** in CH_2Cl_2/hexanes provided crystals suitable for X-ray analysis, for

which the solid-state structure cleared any ambiguity with respect to the success of the synthesis (Figure **3.1**).



SCHEME 3.2: Synthesis of functionalized [*n*]PTPP (late-stage Suzuki)

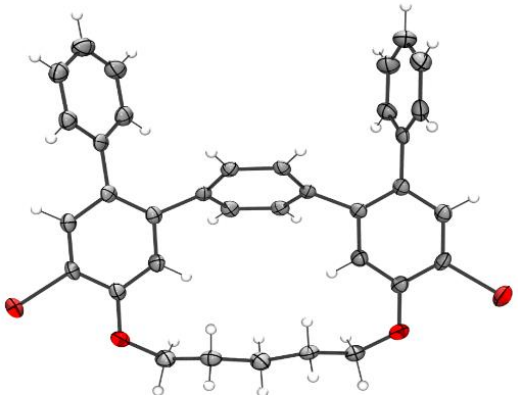


FIGURE 3.1: X-ray structure of diphenyldibromo[7]PTPP **3.22**

The successful synthesis of the bromo-substituted PTPP **3.28** and **3.29** was another accomplishment where a non-cross coupling approach was used in providing strained biaryl macrocycles with *ortho* substituents. As shown in Figure **3.2**, such macrocyclization reactions on planar systems to furnish non-planar biaryl units have not been reported in the literature. This is due to the weakness of cross coupling reactions in forming strained biaryl bonds. Steric hindrance caused by the phenyl rings equally impedes macrocyclization.

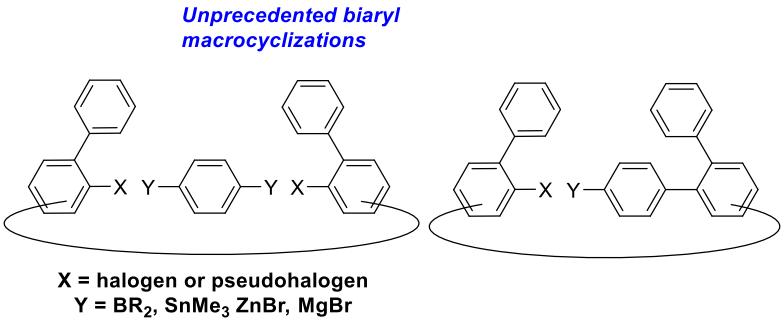
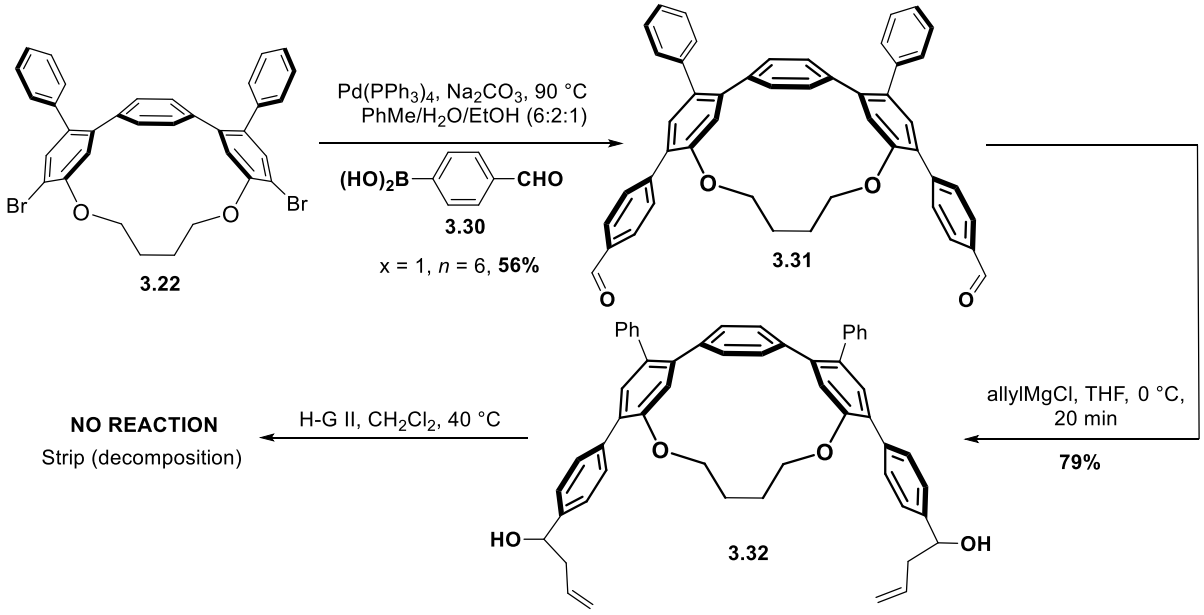


FIGURE 3.2: Unprecedented biaryl macrocyclization

3.2 Attempted Extension of the 4 and 4″ Positions of the Functionalized PTPP 2.122 into a Functionalized CPP

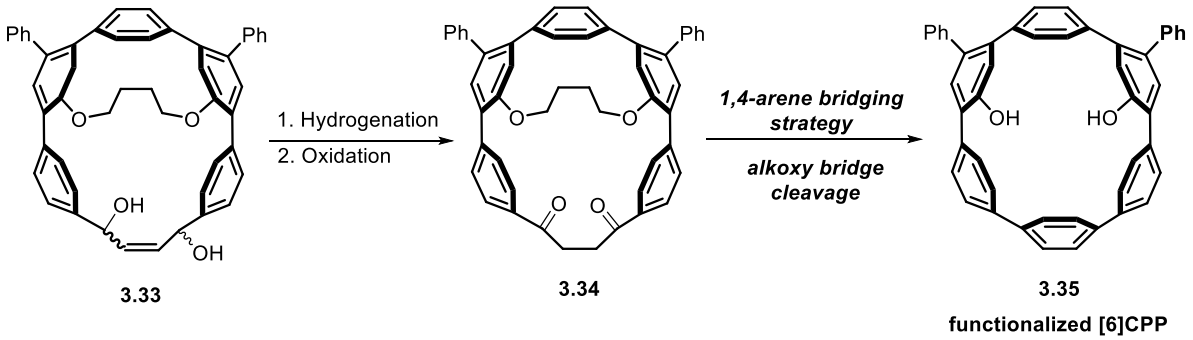
The successful synthesis of **3.22** was a step towards the attainment of our objective. Recall, in section **2.12**, our plan was to selectively substitute/block the 6 and 6″ positions of the PTPP **2.122** early on in the synthesis so we could regioselectively functionalize and extend the para vertices (4 and 4″ positions) into a functionalized CPP. Thus, compound **3.22** has a phenyl ring at the 6 and 6″ positions and bromine atoms at the 4 and 4″ position as intended. The bromine atoms were used as handle to extend those para vertices into a functionalized CPP. Therefore, the aryl bromide on **3.22** was subjected to a Suzuki cross-coupling reaction with 4-formylphenylboronic acid **3.30** to afford the complex compound **3.31**. Treatment of the aldehyde on **3.31** with allylmagnesium chloride in THF provided the diene **3.32** in 79% (Scheme **3.3**).

RCM reaction on the diene **3.32** was unsuccessful, decomposition of the compound was observed from TLC. This was probably due to the amount of strain energy required in forming the second macrocycle (Scheme **3.3**).



SCHEME 3.3: Attempted synthesis of a functionalized [6]CPP

Ultimately, what we aimed to do was to convert the diene **3.32** into the macrocyclic diol **3.33** and later hydrogenate the double bond while oxidizing the hydroxyl group to provide the macrocyclic-1,4-diketone **3.34**. The ketones on **3.34** could in turn be subjected to the 1,4-arene bridging strategy developed earlier to furnish the phenyl ring, while cleaving the alkoxy tether to provide the functionalized [6]CPP **3.35**.

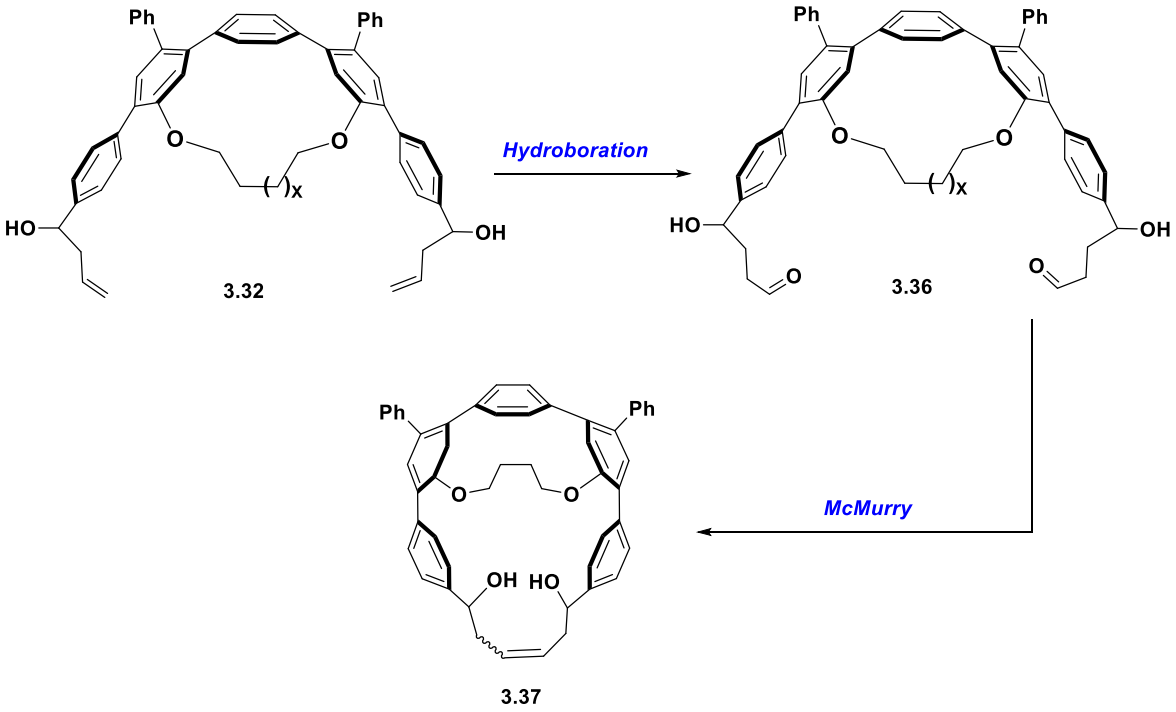


SCHEME 3.4: Foreseen plan towards functionalized [6]CPP

3.3 Future Work

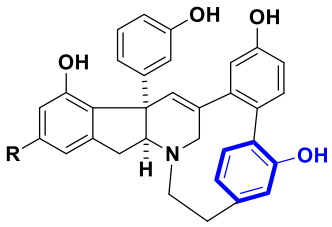
3.3.1 Using McMurry Reaction to Generate the Second Macrocycle

In the near future, we wish to consider using a McMurry coupling reaction to as an alternative approach to forming the second macrocycle of **3.30**, since RCM reaction has proven to be a weak tool. The plan would require conversion of **3.30** to the diketone **3.34** via a hydroboration/oxidation reaction. The diketone group in 3.34 could then be subjected to a McMurry coupling conditions to furnish the macrocycle **3.35**. Is the latter described reactions were successful, similar condition would subsequently be applied to the synthesis of smaller macrocycles.



SCHEME 3.5: Using McMurry coupling as an alternative approach to forming strained macrocycles

3.3.2 Synthesis of Non-Planar Phenols



Haouamine A; R = H, 3.38
Haouamine B; R = OH, 3.39

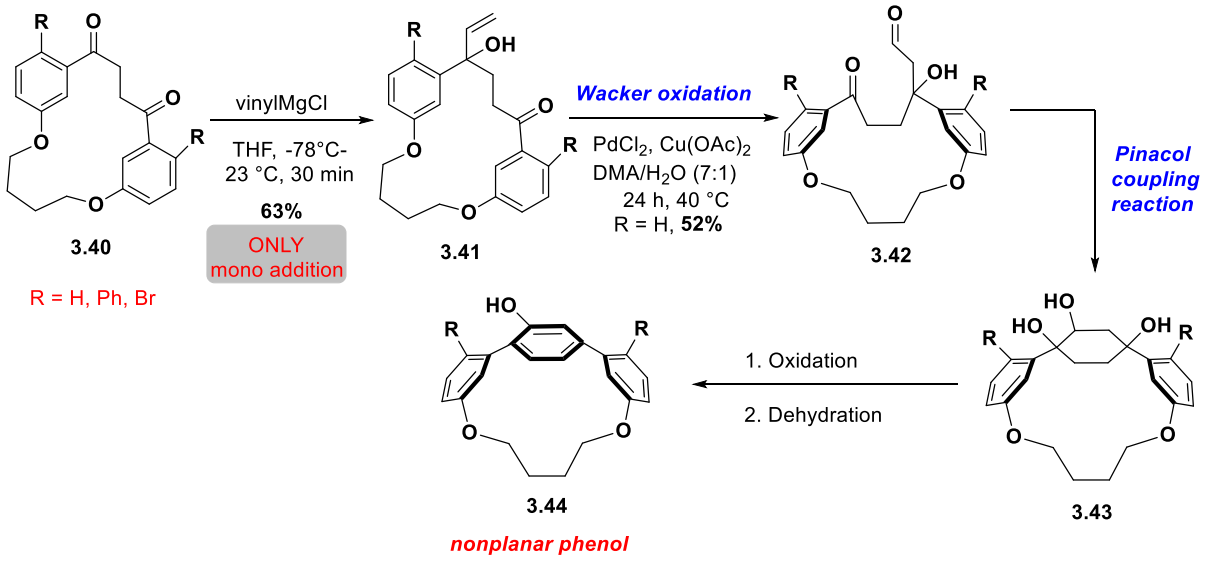
FIGURE 3.3: Structure of haouamine A and B with the non-planar *p*-phenol ring highlighted

The difficulties/challenges encountered in aromatizing the cyclohex-2-ene-1,4-diols **3.26** and **3.27** and reproducibility issue with the Grignard addition on the HK **3.14** and **3.15** prompted us to develop/establish a new route to access functionalized nonplanar phenylenes, more

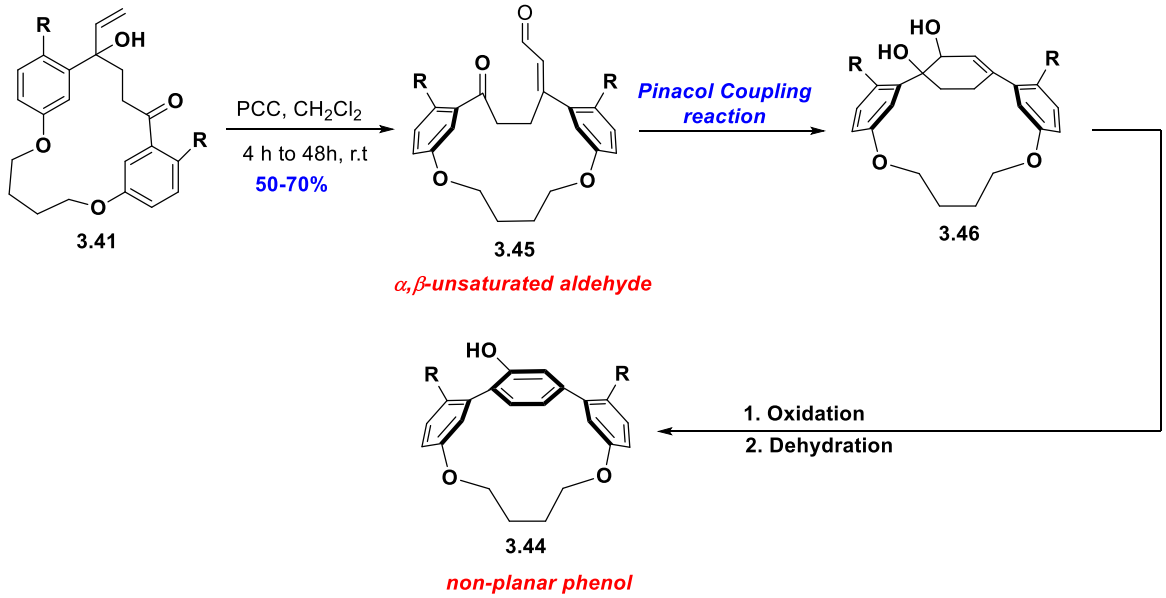
precisely non-planar phenols. We were interested in synthesizing a PTPP with the central non-planar arene unit functionalized. The reason being that, the natural products Haouamine A (**3.38**) and B (**3.39**) which are known to possess potent anticancer activity has as pharmacophore a non-planar phenol moiety (Figure **3.3**). The total synthesis of these natural products up to date has been accomplished by a single research group and only two successful synthesis of the macrocyclic portion of the natural product have been accomplished to date.[84] We aim to use the macrocyclic 1,4-diketone, since we developed a route to easily access gram quantities of the compound as surrogate to the nonplanar phenol.

The plan to access the substituted non-planar phenols **3.44** began with the mono addition of vinylmagnesium chloride on the macrocyclic diketone **3.40** in THF between -78 °C and 23 °C to provide the hydroxyketone **3.41** in 63% yield. The HK **3.41** could either be subjected to a Wacker oxidation or a PCC oxidation to form the corresponding aldehyde. Treatment of **3.41** with palladium dichloride ($PdCl_2$) and copper(II)acetate ($Cu(OAc)_2$) in a 7:1 mixture of dimethylacetamide (DMA) and water (H_2O) at 40 °C for 24 h triggered a Wacker oxidation to take producing the aldehyde **3.42** as the major product in 52% yield (Scheme **3.6**). The aldehyde and the ketone group in **3.42** could then be subjected to an intramolecular pinacol coupling reaction to furnish the macrocyclic diol **3.43.** Oxidation of the primary alcohol with DMP followed by dehydration of the tertiary alcohols of **3.43** was envisioned to produce an enone which will subsequently tautomerize to furnish the nonplanar phenol macrocycle **3.44**. On the other hand, subjecting the HK **3.41** to a PCC oxidation in CH_2Cl_2 at room temperature for about 24 h provided the α,β−unsaturated aldehyde **3.45** in yields between 50 and 70% (Scheme **3.7**). Likewise, the aldehyde and the ketone groups of **3.45** could in turn be exposed to an intramolecular pinacol coupling to furnish the macrocyclic diol **3.46** which after oxidation and

dehydrative aromatization would lead to the non-planar phenol **3.44**. This approach is anticipated to give rise to a variety of substituted nonplanar phenol which could be subsequently used for biological testing.



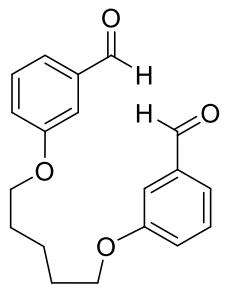
SCHEME 3.6: Access to non-planar *p*- phenols via wacker oxidation



SCHEME 3.7: Access to non-planar *p*-phenols via PCC oxidation

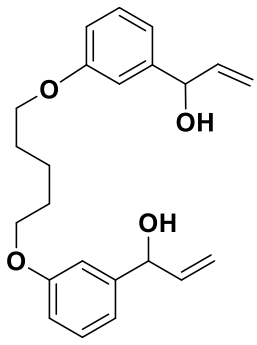
Chapter 4 : Experimental Section

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 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 mm), 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 (d, ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, 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).



2.89

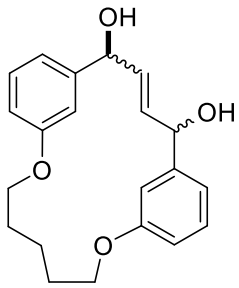
Dialdehyde 2.89: 1,5-Diiodopentane (3.59 g, 11.1 mmol) was added to a stirred solution of 3-hydroxybenzaldehyde (3.01 g, 24.7 mmol), K_2CO_3 (3.41 g, 24.7 mmol) and tetrabutylammonium iodide (0.456 g, 1.24 mmol) in DMF (25 mL). The slurry was heated at 60 °C for 17 h, at which point water (100 mL) and 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 **2.89** 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.



2.130

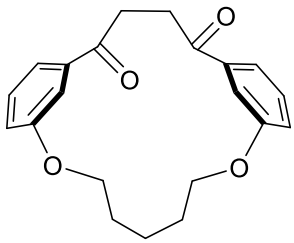
Allylic alcohol 2.130: Vinylmagnesium chloride (1.6 M in THF, 5.4 mL, 8.7 mmol) was added to a stirred solution of dialdehyde **2.89** (1.08 g, 3.48 mmol) in THF (30 mL) at room temperature. After 1 h, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). The resulting 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 **2.130** (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-.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-2(H_2O)+ H]$^+$) *m/z* = 333.1855, found 333.1864.



2.90

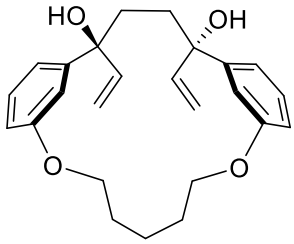
Streamlined synthesis of 2.90: Vinylmagnesium chloride (1.6 M in THF, 5.2 mL, 8.3 mmol) was added to a stirred solution of dialdehyde **2.89** (1.03 g, 3.32 mmol) in THF (30 mL) at room temperature. After 1 h, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). 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 Na2SO4, 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 **2.90** as a white solid (0.605 g, 54% from **2.89**): *Rf* = 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.



2.92

1,4-Dione 2.92: A hydrogen filled balloon was placed over a stirred slurry of 10% wt. Pd/C (0.063g) and allylic diol **2.90** (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 **2.91** as colorless solid (0.432 g, 78%): *Rf* = 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 **2.91** (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 dichloromethane (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 **2.92** 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.

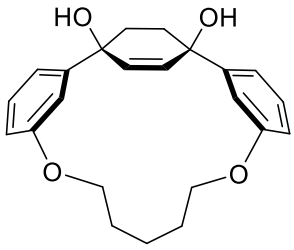


2.93

Allylic alcohols 2.93: 1,4-diketone **2.92** (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 **2.131** (0.060 g, 34%) and allylic alcohols **2.93** (0.098 g, 51%; 77% based on recovery of **2.131**) as a mixture of diastereomers (dr = 5:1). A single column fraction produced pure sample of the major (slower moving) diastereomer, *syn*-(or *meso*) **2.93**: 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.

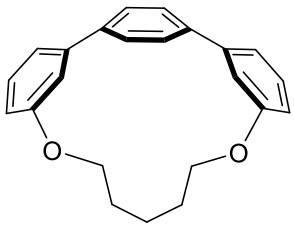
***Anti*-(or *rac*) 2.93**. R_f = 0.22 (1:4 EtOAc/hexanes), 0.59 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.17-7.10 (m, 2H), 6.77 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 2H),

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.



2.94

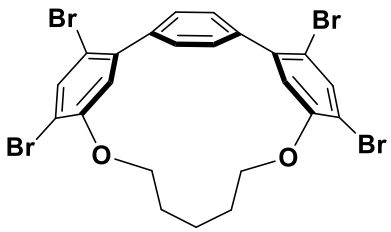
Cyclohex-2-ene-1,4-diol 2.94: Grubbs′ second-generation catalyst (0.0114 g, 0.0134 mmol) was added to a stirred solution of *syn*-**2.93** and *anti*-**2.93** (**dr = 5:1**, 0.101 g, 0.253 mmol) in dichloromethane (7 mL) and the reaction was heated to 40 °C. After 3 h, the solvent was evaporated under reduced pressure and residue was purified by flash chromatography (15 × 1.3 cm, 3:7 EtOAc/hexanes) to give *anti*-**2.93** as a colorless oil (0.017 g, 17%, R_f = 0.59 (1:1 EtOAc/hexanes)) and compound **2.94** 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, CDCl3) 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.



2.95

1,7-dioxa[7](3,3″)p-Terphenylenophane (**2.95**): *p*-Toluensulfonic acid monohydrate (1.22 g, 6.390 mmol) was added to a stirred solution of **2.94** (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

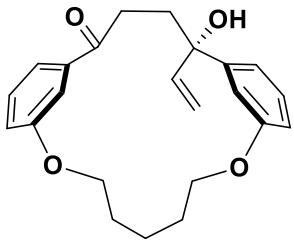
and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The organic extracts were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 1:19 EtOAc/hexanes) to afford **2.95** 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.



2.122

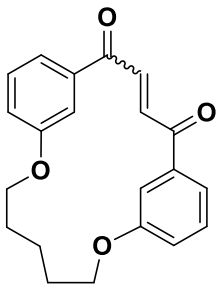
Bromo PTPP 2.122: Bromine (0.105 g, 0.636 mmol) was added to a stirred solution of **2.95** (0.035 g, 0.11 mmol) in 1,2-dichlorbenzene (2 mL). The resulting mixture was heated to 70 °C for 6 h, and then cooled to room temperature under a stream of nitrogen gas. After evaporation of the solvent, the residue 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 MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 1.3 cm, 3:7 dichloromethane/hexanes) to yield tetrabromide **2.122** 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,

42.8, 136.7, 129.7, 120.5, 110.5, 109.6, 69.96, 26.5, 23.4; HRMS (EI) calculated for $C_{23}H_{18}O_2Br_4$ 641.8040, found 641.8038.



2.131

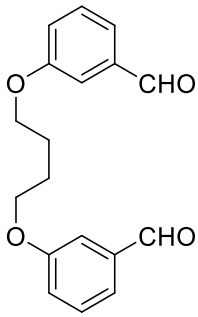
Hydroxyketone 2.131: R_f = 0.29 (3% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.35-7.24 (m, 2H), 7.15 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.08-7.01 (m, 2H), 6.96 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 6.81 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.30 (dd, *J* = 17.3, 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) calculated for $C_{23}H_{25}O_3$ ($[M-(H_2O)+H]^+$) *m/z* = 349.1804, found 349.1793.



2.96

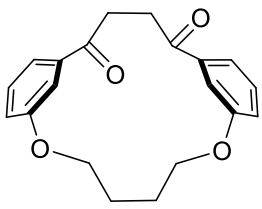
Ene-1,4-dione 2.96: Dess–Martin periodinane (0.235 g, 0.556 mmol) and $NaHCO_3$ (0.0.47 g, 0.56 mmol) were added to a stirred solution of macrocyclic 1,4-diol **2.90** (0.063 g, 0.19 mmol) in dichloromethane (5 mL) at room temperature. After 1 h, a 10% solution of $Na_2S_2O_3$ (10 mL) was added and the reaction was stirred for 10 min. The resulting mixture was extracted with dichloromethane (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 **2.96** 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 337.144.



2.108

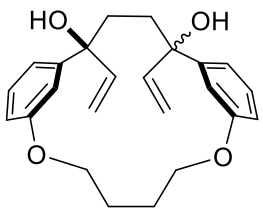
Dialdehyde 2.108: 1,4-Dibromobutane (3.98 g, 18.4 mmol) was added to a stirred solution of 3-hydroxy benzaldehyde (5.00 g, 40.9 mmol), K_2CO_3 (5.66 g, 401.0 mmol) and TBAI (0.76 g, 2.05 mmol) in DMF (40 mL). The reaction was heated at 50 ^oC for 48 h, at which point water (100 mL) and 1 M HCl (50 mL) 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 **2.108** as white solid (4.75 g, 87%): R_f = 0.25 (chloroform); ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 2H), 7.48-7.43 (m, 4H), 7.40-7.39 (m, 2H), 7.19-7.16 (m, 2H), 4.13-4.10 (m, 4H), 2.05-2.01 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.32, 159.68, 137.97, 130.25, 123.72, 122.10, 112.85, 67.87, 26.05; HRMS (ESI) calculated for $C_{18}H_{19}O_4$ ($[M+H]^+$) *m/z* = 299.1283, found 299.1290.



2.109

1,4-diketone 2.109: Vinylmagnesium chloride (1.6 M in THF, 4.6 mL, 7.4 mmol) was added to a stirred solution of the dialdehyde **2.108** (1.00 g, 3.36 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 sodium bicarbonate (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 ^oC, followed by the addition of the

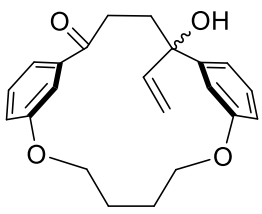
Hoveyda-Grubbs second-generation catalyst (0.046 g, 0.073 mmol). After 1 h, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (34 mL), and sodium borohydride (0.380 g, 10.0 mmol) and Hoveyda-Grubbs second-generation catalyst (0.0065 g, 0.010 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 (4.28 g, 10.1 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 **2.109** as a white solid (520 g, 48% from **2.108**): R_f = 0.39 (3:7 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.41-7.37 (m, 2H), 7.24-7.23 (m, 2H), 7.11 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 2H), 4.21-4.18 (m, 4H), 3.09 (s, 4H), 1.98-1.96 (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.



2.110

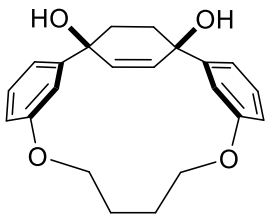
Allylic alcohol 2.110: 1,4-diketone (0.300 g, 0.926 mmol), as a solution in THF (7.5 mL) was added to a stirred 65 °C solution of vinylmagnesium chloride (1.6 M in THF, 1.8 mL, 2.8 mmol). After 30 min, the reaction mixture was poured into water (20 mL) and further diluted with 1 M HCl

(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), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatograph (15 × 2.5 cm, 25% EtOAc/hexane) to give hydroxyketone **2.125** (0.48 g, 15%) and allylic alcohol **2.110** (0.220 g, 63%; 77% based on recovery of hydroxyketone) as an inseparable mixture of diastereomers (dr = 9:1). R_f = 0.22 (25% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20 (m, 2H), 6.94 (dd, *J* = 7.7, 1.1 Hz, 2H), 6.80 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 2H), 6.70-6.69 (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), 4.15-4.01 (m, 4H), 3.08 (s, 2H), 2.01-1.89 (m, 4H), 1.77-1.76 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.71, 146.46, 143.17, 129.17, 118.48, 113.54, 113.30, 112.82, 76.87, 67.51, 36.78, 26.03; HRMS (ESI) calculated for $C_{24}H_{25}O_2$ ([M-(2H_2O)+H]$^+$) *m/z* = 345.1855, found 345.1868.



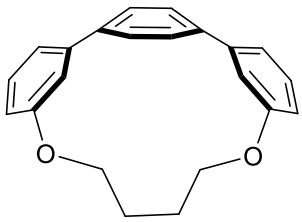
2.125

Hydroxy ketone 2.125: R_f = 0.35 (25% EtOAc/hexane); 7.53 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.36-7.32 (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), 6.95-6.94 (m, 1H), 6.92-6.90 (m, 1H), 6.87 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 6.24 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.31 (dd, *J* = 17.4, 0.8 Hz, 1H), 5.15 (dd, *J* = 10.7, 0.8 Hz, 1H), 4.25-4.19 (m, 2H), 4.18-4.10 (m, 1H), 4.01-3.95 (m, 1H), 2.77-2.69 (m, 1H), 2.69-2.59 (m, 1H), 2.38-2.28 (m, 2H), 2.10-2.05 (m, 2H), 2.05-1.89 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.84, 158.69, 158.60, 145.40, 144.32, 144.30, 137.62, 129.98, 129.75, 120.39, 119.81, 118.31, 115.99, 113.39, 113.37, 113.34, 113.06, 77.08, 69.17, 67.07, 39.20, 33.76, 26.45, 25.81; HRMS (ESI) calculated for $C_{22}H_{23}O_3$ ([M-(H_2O)+H]$^+$) *m/z* = 335.1647, found 335.1657.



2.111

Cyclohex-2-ene-1,4-diol 2.111: Grubbs' second-generation catalyst (0.023 g, 0.026 mmol) was added to a stirred solution of **2.110** (dr = 9:1; 0.200 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 **2.111** 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 7.34-7.26 (m, 4H), 7.06-7.00 (m, 2H), 6.80 (ddd, *J* = 7.7, 2.5, 1.4 Hz, 2H), 6.08 (s, 2H), 4.24-4.14 (m, 2H), 4.05-3.96 (m, 2H), 2.17 (s, 2H), 2.14-1.98 (m, 4H), 1.97-1.80 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.65, 147.78, 134.96, 130.23, 117.60, 114.71, 113.82, 73.26, 69.82, 37.01, 26.99; HRMS (ESI) calculated for $C_{22}H_{23}O_3$ ($[M-(H_2O)+H]^+$) *m/z* = 335.1647, found 335.1641.



2.113

1,6-dioxa[6](3,3')-*p*-Terphenylenophane [6]PTPP: *para*-toluenesulfonic acid monohydrate (0.130 g, 0.684 mmol) was added to a stirred solution of **2.111** (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 chromatograph (15 × 1.3 cm, 5% EtOAc/hexanes) to afford **2.113** as a white solid (0.015 g, 42%): R_f = 0.43 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 4H), 7.34 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.27-7.24 (m, 2H), 6.78 (ddd, *J* = 8.3, 2.8, 1.0 Hz, 2H), 5.31 (dd, *J* = 2.9, 1.5 Hz, 2H), 3.98-3.86 (m, 4H), 1.47-1.38 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.39, 144.88, 144.61, 130.30, 117.76, 115.83,

115.74, 67.36, 22.86; HRMS (ESI) calculated for $C_{22}H_{21}O_2$ ($[M+H]^+$) *m/z* = 316.1463, found 316.1437. Recrystallization from dichloromethane/hexanes gave colorless crystals, suitable for X-ray analysis.

Burgess Reagent Aromatization: [6]PTPP synthesis

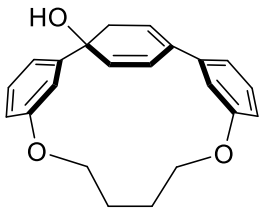
Burgess reagent (0.020 g, 0.085 mmol) was added to a stirred solution of cyclohexene-1,4-diol (0.010 g, 0.028 mmol) in THF (1 mL) and the reaction was heated at 50 °C. After 10 min, the reaction mixture was poured into H_2O (10 ml) and extracted with dichloromethane (2 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a white solid (0.007 g, 75%): R_f = 0.66 (1:4EtOAc/hexanes).

Itami Aromatization [6] PTPP synthesis

Sodium hydrogen sulfate hydrate (0.008 g, 0.06 mmol) was added to a stirred 130 ^oC solution of cyclohexene-1,4-diol (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 21 h, the reaction mixture was cooled to 23 ^oC and a saturated solution of $NaHCO_3$ (10 ml) were added and stirred for 5 min. The reaction mixture was extracted with dichloromethane (2 × 10 mL), and the combined organic phase were 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 [6]PTPP as a white solid (0.0032 g, 36%); R_f = 0.44 (5% EtOAc/hexanes) and trace amounts of the [6]MTPP.

Triflate anhydride procedure: [6]PTPP synthesis

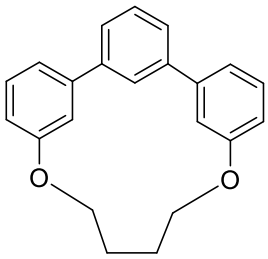
Trifluoromethanesulfonic anhydride (0.025 g, 0.088 mmol) was added dropwise to a stirred 0 °C solution of cyclohexene-1,4-diol (0.010 g, 0.028 mmol) and DIPEA (0.074 g, 0.56 mmol, 0.10 mL) in dichloromethane (1.5 mL). After 10 min, the reaction mixture poured into water (10 ml) and the resulting mixture was extracted with dichloromethane (2 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified using a pipette column in 3:7 CH_2Cl_2/hexanes to give the [6]PTPP as a white solid (0.008 g, 57%); R_f = 0.27 (3:7 CH_2Cl_2/hexanes).



2.126

Yamago aromatization procedure: Mono-eliminated product.

Tin dichloride dihydrate (0.064 g, 0.28 mmol) was added to a stirred 80 °C solution of cyclohexene-1,4-diol (0.010 g, 0.028 mmol) in THF (1 mL) and toluene (1 mL). After 20 h, the reaction mixture was cooled to 23 °C and a 10% solution of NaOH (10 ml) were added and stirred for 3 min. The reaction mixture was extracted with dichloromethane (2 × 10 mL), and the combined organic phase 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 (7.5 × 0.6 cm; 1:9 EtOAc/hexanes) to afford the product **2.126** as a brown oil (0.0052 g, 56%); R_f = 0.11 (1:9 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 2H), 7.26-7.23 (m, 1H), 7.16 (dd, *J* = 2.7, 1.7 Hz, 1H), 6.91-6.86 (m, 2H), 6.84-6.82 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.64 (dd, *J* = 2.7, 1.5 Hz, 1H), 6.40 (ddd, *J* = 9.7, 1.6, 0.7 Hz, 1H), 5.94-5.91 (m, 1H), 5.67 (ddd, *J* = 6.8, 2.9, 1.4 Hz, 1H), 4.23-4.06 (m, 4H), 2.97-2.88 (m, 1H), 2.54 (ddd, *J* = 16.3, 6.9, 1.8 Hz, 1H), 2.06 (d, *J* = 4.5 Hz, 1H), 1.73-1.67 (m, 4H).

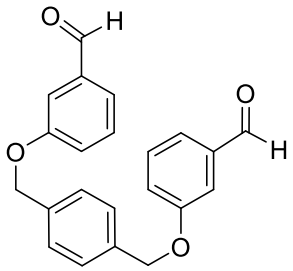


2.112

[6]MTPP 2.112: P-TsOH (0.076 g, 0.40 mmol) was added to a stirred solution of PTPP **2.113** (0.010 g, 0.033 mmol) in toluene (2 mL) and the mixture was heated at 70 °C for 19 h and 80 °C for 5 h. 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 using a pipette column (5% EtOAc/hexanes) to afford **2.112** as a white solid (0.007 g, 70%): R_f = 0.31 (5% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.66 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 4.8 Hz, 4H), 7.33 (d, *J* = 2.7 Hz, 2H), 6.92 (q, *J* = 4.9, 4.1 Hz, 2H), 4.37 – 4.25 (m, 4H), 2.08 (p, *J* = 3.3 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.

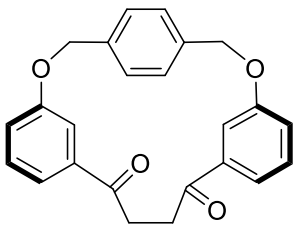
[6]MTPP (2.112): *P*-TsOH (0.071 g, 0.37 mmol) was added to a stirred solution of a mixture of MTPP and PTPP (0.015 g, 0.047 mmol) in toluene (5 mL) at 80 °C. After 20 h, the reaction was cooled to room temperature, water (10 mL) was added, and the resulting mixture was stirred for 5 min. The layers 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 using a pipette column (3:2 dichloromethane/hexanes) to afford **2.112** as a white solid (0.005 g, 33%): R_f = 0.47 (3:2 dichloromethane/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.66 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 4.8 Hz, 4H), 7.33 (d, *J* = 2.7 Hz, 2H), 6.92 (q, *J* = 4.9, 4.1 Hz, 2H), 4.37-4.25 (m, 4H), 2.08 (p, *J* =

3.3 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.



2.117

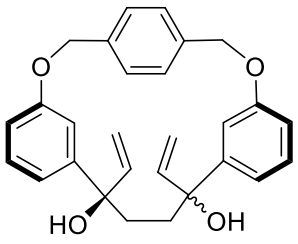
Dialdehyde 2.117: 1,4-bis(bromomethyl)benzene (3.60 g, 13.6 mmol) was added to a stirred solution of 3-hydroxy benzaldehyde (5.00 g, 40.9 mmol), K_2CO_3 (6.63 g, 47.7 mmol) and TBAI (0.505 g, 1.36 mmol) in DMF (70 mL). The reaction was heated at 70 °C for 3 h, at which point water (80 mL) and 1 M HCl (90 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 × 70 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 by flash chromatography (18 × 5.0 cm; dichloromethane, 1% acetone/dichloromethane) to afford the **dialdehyde 2.117** as white solid (3.13 g, 66%): R_f = 0.39 (dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.98 (s, 2H), 7.51-7.45 (m, 10H), 7.27-7.25 (m, 2H), 5.15 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.27, 159.36, 137.97, 136.50, 130.35, 128.04, 124.05, 122.40, 113.24, 70.02.



2.118

Macrocyclic 1,4-diketone 2.118: Vinylmagnesium chloride (1.6 M in THF, 2.6 mL, 4.1 mmol) was added to a stirred 0 °C solution of dialdehyde **2.117** (0.650 g, 1.40 mmol) in THF (14 mL). After 10 min, the reaction mixture was poured into water (30 mL) and further diluted with 1 M HCl (30 mL). The resulting mixture 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (140 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.021 g, 0.035 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 (0.326 g, 8.62 mmol) was added at 23 °C. After 22 h, the reaction was poured into water (50 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (25 mL), and brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (18 mL), followed by the sequential addition of $NaHCO_3$ (0.236 g, 2.80 mmol) and Dess-Martin periodinane (1.19 g, 2.80 mmol). After 30 min., a 10% $Na_2S_2O_3$ solution (30 mL) was added and the reaction was stirred for 5 min. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 15 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, 1:3 EtOAc/hexanes) to afford the 1,4-diketone **2.118** as a white solid (0.209 g, 40% from **2.117**); R_f = 0.26 (3:7 EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 7.7 Hz, 2H), 7.38-7.34 (m, 2H), 7.31-7.23 (m, 6H), 6.71-6.70 (m, 2H), 5.28 (s, 4H), 2.98 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.32, 157.57, 137.52, 136.67, 130.03, 127.60, 123.68, 121.12, 115.83, 71.32, 35.01; HRMS (ESI) calculated for $C_{24}H_{21}O_4$ ($[M+H]^+$) m/z = 373.1440, found 373.1428.

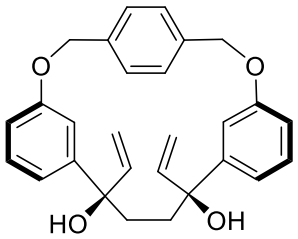


2.119

5:1 *d.r*

Allylic alcohol 2.119: Vinyl magnesium chloride (1.6 M in THF, 0.50 mL, 0.82 mmol) was added to a stirred 40 °C solution of 1,4-diketone **2.118** (0.101 g, 0.271 mmol) in dichloromethane (3 mL). After 10 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

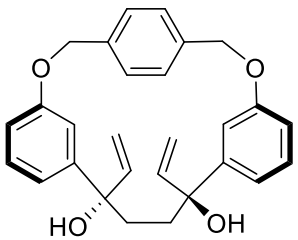
solution of $NaHCO_3$ (20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatography (15 × 1.3 cm, 1% acetone/dichloromethane) to give hydroxyketone **2.127** (0.013 g, 12%) and allylic alcohol **2.119** (0.097 g, 84%; 95% based on recovered hydroxyketone) as a mixture of diastereomers (dr = 5:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 6.2 Hz, 4H), 7.21 (m, 1H), 7.15 (m, 2H), 6.97 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.93-6.86 (m, 2H), 6.73 (dt, *J* = 4.5, 1.3 Hz, 3H), 6.40 (m, 1H), 6.08 (dd, *J* = 17.0, 10.7 Hz, 2H), 5.34 (d, *J* = 4.1 Hz, 1H), 5.32-5.27 (m, 2H), 5.23 (dd, *J* = 9.7, 1.1 Hz, 1H), 5.20-5.14 (m, 3H), 5.14-5.06 (m, 2H), 3.18 (s, 1H), 1.49 (ddt, *J* = 14.9, 11.4, 5.6 Hz, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.77, 147.14, 143.46, 137.22, 129.25, 127.13, 118.07, 116.47, 113.45, 111.43, 76.66, 69.91, 36.29; HRMS (ESI) calculated for $C_{28}H_{25}O_2$ ($[M-(2H_2O)+H]^+$) m/z = 393.1855, found 393.1851.



2.128

meso

Allylic diol (meso): R_f = 0.38 (1% acetone/dichloromethane); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41-7.28 (m, 4H), 7.14 (m, 2H), 6.89-6.84 (m, 2H), 6.74-6.69 (m, 4H), 6.07 (dd, *J* = 17.2, 10.7 Hz, 2H), 5.33 (d, *J* = 14.2 Hz, 2H), 5.25 (dd, *J* = 17.2, 1.2 Hz, 2H), 5.19-5.12 (m, 4H), 2.93 (s, 2H), 1.52 – 1.41 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.80, 147.17, 143.53, 137.24, 129.32, 127.17, 118.06, 116.43, 113.44, 111.50, 76.67, 69.97, 36.30; HRMS (ESI) calculated for $C_{28}H_{25}O_2$ ($[M-(2H_2O)+H]^+$) m/z = 393.1855, found 393.1851.

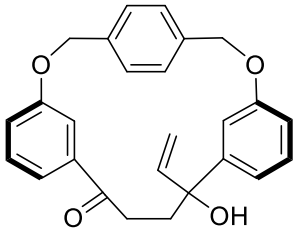


2.129

trans

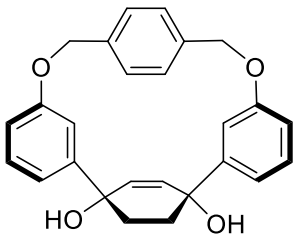
Racemic (trans) product: R_f = 0.27 (1% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 7.19 (m, 2H), 6.94-6.86 (m, 4H), 6.41 (dd, *J* = 2.6, 1.6 Hz, 2H), 6.03 (dd, *J* = 17.2, 10.6 Hz, 2H), 5.31 (d, *J* = 14.3 Hz, 2H), 5.22-5.11 (m, 4H), 5.08 (dd, *J* = 10.6, 1.0 Hz,

2H), 1.76 (s, 2H), 1.53-1.44 (m, 2H), 1.21-1.11 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.37, 146.23, 144.52, 137.19, 129.46, 127.14, 117.36, 116.55, 112.77, 111.37, 76.52, 69.73, 35.47, 29.91; HRMS (ESI) calculated for $C_{28}H_{25}O_2$ ([M-(2H_2O)+H]$^+$) m/z = 393.1855, found 393.1840.



2.127

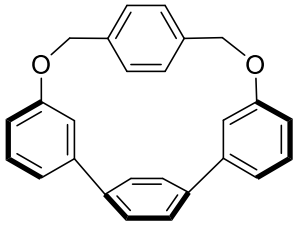
Hydroxy ketone 2.127: R_f = 0.55 (1% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.407.25 (m, 4H), 7.23 – 7.13 (m, 2H), 6.98 – 6.94 (m, 1H), 6.89 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.72 – 6.65 (m, 2H), 6.25 (ddd, *J* = 17.4, 10.7, 2.1 Hz, 1H), 5.40-5.36 (m, 1H), 5.32 (d, *J* = 12.9 Hz, 2H), 5.25 (dd, *J* = 14.1, 2.1 Hz, 1H), 5.18 (dd, *J* = 10.6, 2.1 Hz, 1H), 5.05 (dd, *J* = 14.6, 2.1 Hz, 1H), 2.59 (m, 1H), 2.21 – 2.01 (m, 2H), 1.92 (s, 1H), 1.79 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.40, 158.59, 157.27, 145.32, 144.86, 138.23, 137.48, 137.40, 129.80, 129.58, 128.51, 127.88, 126.90, 126.25, 123.56, 120.56, 118.66, 116.49, 115.82, 113.22, 111.23, 76.12, 72.39, 69.52, 36.03, 33.23; HRMS (ESI) calculated for $C_{26}H_{23}O_3$ ([M-(H_2O)+H]$^+$) m/z = 383.1647, found 383.1628.



2.120

Cyclohex-2-ene-1,4-diol 2.120: Grubbs' second-generation catalyst (0.005 g, 0.0004 mmol) was added to a stirred solution of allylic alcohols **2.119** (dr 4.9:1; 0.077 g, 0.18 mmol) in dichloromethane (2 mL) and the reaction was heated to 40 ºC. After 2 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 2.5 cm, 2:3 EtOAc/hexanes) to give **2.120** as an off-white solid (0.037 g, 51%, 58% based on recovered racemic (trans) product) and (uncyclized) trans-isomer **2.129** (0.013 g, 9%): R_f = 0.14 (2:3 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.30 (m, 4H), 7.29-7.26 (m, 2H), 7.19 (d, *J* = 1.7 Hz, 2H), 7.02-6.98 (m, 2H), 6.17 (d, *J* = 2.1 Hz, 2H), 5.89 (s, 2H), 5.24 (d, *J* = 13.9 Hz, 2H), 5.05 (d, *J* = 13.9 Hz, 2H), 2.12-2.03 (m, 4H), 1.77 (m, 2H); ^{13}C NMR (151 MHz,

$CDCl_3$) δ 157.94, 147.12, 137.41, 134.18, 130.12, 127.55, 127.41, 119.51, 118.48, 114.21, 72.59, 71.79, 35.32; HRMS (ESI) calculated for $C_{26}H_{23}O_3$ ($[M-(H_2O)+H]^+$) m/z = 383.1647, found 383.1629.

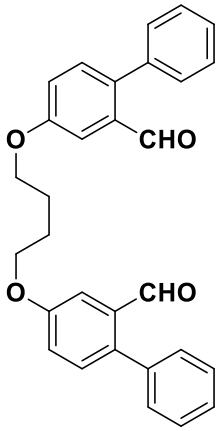


2.121

1,5-dioxa[5](3,3")*p*-terphenylenophane 2.121: *P*-TsOH (0.024 g, 0.13 mmol) was added to a stirred solution of **2.120** (0.010 g, 0.025 mmol) in toluene (2 mL) at 55 ^{0}C. After 5 h, 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 chromatograph (12 × 0.6 cm, 5% EtOAc/hexanes) to afford **2.121** as a white solid (0.0032 g, 32%): R_f = 0.47 (5% EtOAc/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.21-7.19 (m, 2H), 7.08 (s, 4H), 7.01 (s, 4H), 6.95-6.92 (m, 2H), 5.41 (m, 2H), 5.15 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.50, 144.46, 143.27, 137.44, 129.83, 128.86, 125.73, 121.40, 116.76, 115.76, 71.38; HRMS (ESI) calculated for $C_{26}H_{20}O_2$ ($[M+H]^+$) m/z = 364.1463, found 364.1457.

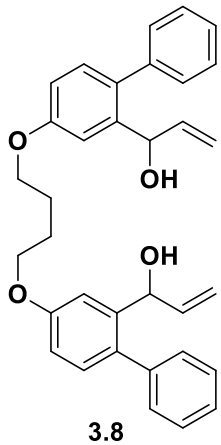
1,5-dioxa[5](3,3")*p*-terphenylenophane 2.121: Burgess reagent (0.027 g, 0.11 mmol) was added to a stirred solution of cyclohexene-1,4-diol (0.015 g, 0.038 mmol) in THF (2 mL) at 60 ^{0}C. After 1 h 30 min, the reaction was cooled to room temperature, water (10 mL) was added, and the resulting mixture 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 $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm, 1:4 dichloromethane/hexanes) to afford **2.121** as a white solid (0.009 g, 65%): R_f = 0.30 (1:4

dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.21-7.19 (m, 2H), 7.08 (s, 4H), 7.01 (s, 4H), 6.95-6.92 (m, 2H), 5.41 (m, 2H), 5.15 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.50, 144.46, 143.27, 137.44, 129.83, 128.86, 125.73, 121.40, 116.76, 115.76, 71.38; HRMS (ESI) calculated for $C_{26}H_{20}O_2$ ($[M+H]^+$) m/z = 364.1463, found 364.1457.



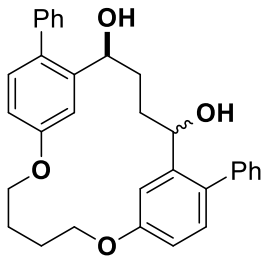
3.6

Dialdehyde 3.6: Benzene boronic acid (0.512 g, 4.20 mmol), Na_2CO_3 (1.06 g, 10.0 mmol) and $Pd(PPh_3)_4$ (0.12 g, 0.050 mmol) were added to a stirred solution of the dibromodialdehyde **3.4** (0.908 g, 2.00 mmol) in toluene (14 mL), EtOH (2.6 mL) and H_2O (5 mL). The reaction was heated at 80 ^{o}C for 3 h, at which point water (50 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 20 mL). The organic extracts were combined and washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm; 4:1 dichloromethane/hexanes) to afford **3.4** as white solid (1.00 g, > 95%): R_f = 0.35 (4:1 dichloromethane/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 2H), 7.53 (d, J = 2.8 Hz, 2H), 7.48-7.42 (m, 6H), 7.40 (s, 1H), 7.39-7.35 (m, 5H), 7.22 (dd, J = 8.5, 2.8 Hz, 2H), 4.19-4.16 (m, 4H), 2.08-2.05 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.57, 158.70, 139.28, 137.68, 134.64, 132.31, 130.43, 128.58, 127.97, 127.35, 122.00, 121.93, 110.73, 110.70, 68.00, 26.09; HRMS (ESI) calculated for$C_{30}H_{25}O_3$ ($[M-(H_20)+H]^+$) m/z = 433.1804, found 433.1823.



3.8

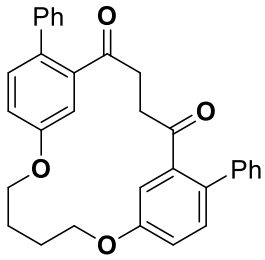
Allylic alcohol 3.8: Vinylmagnesium chloride (1.6 M in THF, 4.0 mL, 6.4 mmol) was added to a stirred 0 °C solution of dialdehyde **3.6** (0.996 g, 2.15 mmol) in THF (22 mL)). After 10 min, the reaction mixture was poured into water (50 mL) and further diluted with 1 M HCl (30 mL). The resulting mixture 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 residue was purified by flash chromatography (15 × 2.5 cm; 3:7 EtOAc/hexanes) to afford the allylic diol **3.8** (0.98 g, 90%): R_f = 0.33 (3:7 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.38 (m, 4H), 7.37 (dd, *J* = 1.7 Hz, 1H), 7.36-7.31 (m, 5H), 7.19 (dd, *J* = 8.4, 1.0 Hz, 2H), 7.15-7.13 (m, 2H), 6.91 (ddd, *J* = 8.5, 2.7, 1.4 Hz, 2H), 6.02 (ddd, *J* = 17.2, 10.2, 4.9 Hz, 2H), 5.34-5.25 (m, 2H), 5.25-5.12 (m, 4H), 4.14-4.11 (m, 4H), 2.09-1.96 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.87, 141.34, 140.68, 140.35, 140.34, 133.88, 131.41, 129.84, 128.28, 127.11, 115.03, 114.11, 112.58, 71.47, 67.71, 26.23. HRMS (ESI) calculated for$C_{34}H_{31}O_2$ ($[M-(2H_20)+H]^+$) m/z = 471.2324, found 471.2305.



3.10

Diol 3.10. Hoveyda-Grubbs second-generation catalyst (0.015 g, 0.025 mmol) was added to a stirred solution of allylic alcohol **3.8** (0.500 g, 0.988 mmol) in dichloromethane (99 mL) at 40 °C. After 2 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 (10 mL), and sodium borohydride (0.284 g, 7.52 mmol) and Hoveyda-Grubbs second-generation catalyst (0.012 g, 0.019 mmol) were added. After 40 h, the reaction was poured into water (40 mL) and further diluted with 1 M HCl (20 mL). The layers

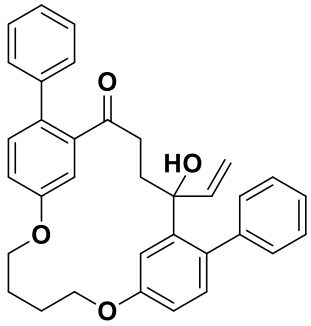
were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm; 0.75% acetone/dichloromethane) to afford compound **3.10** as a light brown oil (0.180 g, 40% over 2 steps): R_f = 0.38 (1% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 10H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.92 (dd, *J* = 8.5, 2.6 Hz, 2H), 6.74 (d, *J* = 2.7 Hz, 2H), 4.67-4.64 (m, 2H), 4.23-4.18 (m, 2H), 4.12-4.07 (m, 2H), 2.13-1.99 (m, 2H), 1.97-1.91 (m, 2H), 1.75 (s, 2H), 1.55-1.48 (m, 2H), 1.38-1.24 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.53, 141.24, 140.70, 135.15, 131.44, 129.88, 128.29, 126.98, 114.66, 111.76, 69.81, 67.16, 33.50, 25.75; HRMS (ESI) calculated for $C_{32}H_{29}O_2$ ($[M-(2H_2O)+H]^+$) m/z = 445.2168, found 445.2152.



3.12

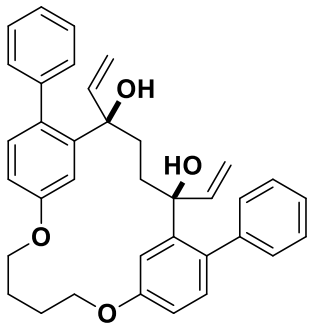
1,4-Diketone 3.12: Dess-Martin periodinane (0.629 g, 1.48 mmol) and $NaHCO_3$ (0.125 g, 1.48 mmol) were added to a stirred solution of 1,4-diol **3.10** (0.331 g, 0.494 mmol) in dichloromethane (5 mL) at room temperature. After 1 h, a 10% $Na_2S_2O_3$ solution (20 mL) was added and the reaction was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, dichloromethane) to afford 1,4-diketone **3.12** as a beige solid (0.243 g, 74%): R_f = 0.53 (3:7 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.33 (m, 6H), 7.29-7.23 (m, 6H), 7.00 (dd, *J* = 8.4, 2.7 Hz, 2H), 6.56 (d, *J* = 2.7 Hz, 2H), 4.24-4.22 (m, 4H), 2.17 (s, 4H), 2.05-1.97 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 207.24, 157.83, 141.35, 140.11, 132.42, 131.26, 129.06, 128.86, 127.77, 116.86, 114.81, 67.62, 58.80, 39.10, 25.17; HRMS (ESI) calculated for$C_{32}H_{29}O_4$

([M+H]$^+$) m/z = 477.2066, found 477.2085.



3.14

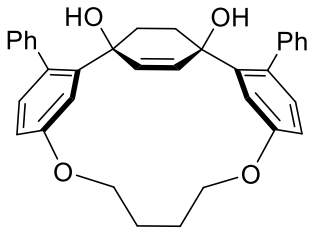
Hydroxy Ketone 3.14*:* 1,4-diketone **3.12** (0.100 g, 0.209 mmol), as a solution in THF (5 mL) was added to a stirred 60 ^{o}C solution of vinylmagnesium chloride (1.6 M in THF, 0.40 mL, 0.63 mmol). After 10 min, the reaction mixture was poured into water (15 mL) and further diluted with 1 M HCl (15 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatograph (15 × 1.3 cm, 15% EtOAc/hexanes) to give hydroxyketone **3.14** as a light brown oil (0.48 g, 15%): R_f = 0.25 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 7H), 7.29-7.20 (m, 5H), 7.05-6.99 (m, 2H), 6.95 (d, *J* = 2.6 Hz, 1H), 6.81 (dd, *J* = 8.3, 2.7 Hz, 1H), 5.96 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.02 (dd, *J* = 17.2, 1.0 Hz, 1H), 4.91 (dd, *J* = 10.6, 1.1 Hz, 1H), 4.28-4.16 (m, 4H), 2.67-2.59 (m, 1H), 2.54-2.44 (m, 1H), 2.16-1.98 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.07, 157.91, 157.88, 145.61, 142.97, 142.78, 141.58, 140.57, 133.54, 133.21, 132.82, 131.95, 128.99, 128.47, 127.79, 127.29, 127.21, 118.25, 115.09, 113.35, 112.93, 110.98, 77.83, 68.98, 67.59, 38.33, 35.33, 26.18, 26.12; HRMS (ESI) calculated for$C_{34}H_{31}O_3$ ([M-(H_2O)+H]$^+$) m/z = 487.2273, found 487.2265.



3.16

Allylic Alcohol 3.16*:* Hydroxy ketone **3.14** (0.045 g, 0.089 mmol), as a solution in THF (3 mL) was added to a stirred 23 ^{o}C solution of Lanthanum (III) chloride (0.6 M in THF, 0.30 mL, 1.8 mmol). After 1 h, the temperature was decreased to 0 ^{o}C and a solution of vinylmagnesium chloride (1.6 M in THF, 0.30 mL, 0.45 mmol) were

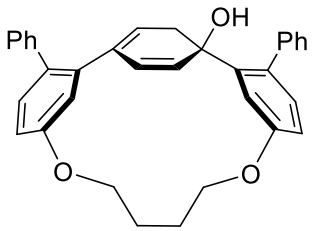
added. After 50 min, the reaction mixture was poured into water (10 mL) and further diluted with 1 M HCl (10 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatography (15 × 1.3 cm, 1:4 EtOAc/hexanes) to give allylic alcohol **3.16** as a brown oil (0.038 g, 80%): R_f = 0.31 (1:4 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.29 (m, 6H), 7.20-7.18 (m, 4H), 7.12 (d, *J* = 2.7 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.82 (dd, *J* = 8.3, 2.6 Hz, 2H), 5.79 (dd, *J* = 17.2, 10.7 Hz, 2H), 4.94 (d, *J* = 17.3 Hz, 2H), 4.78 (d, *J* = 10.7 Hz, 2H), 4.21-4.19 (m, 4H), 2.45 (s, 2H), 2.08-1.99 (m, 4H), 1.93-1.87 (m, 2H), 1.81-1.76 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.91, 144.65, 144.12, 143.11, 133.43, 133.18, 130.36, 127.73, 127.16, 114.00, 113.15, 112.21, 77.92, 68.12, 37.75, 26.44; HRMS (ESI) calculated for$C_{36}H_{33}O_2$([M-(2$H_2$0)+H]+) m/z = 497.2481, found 497.2459.



3.18

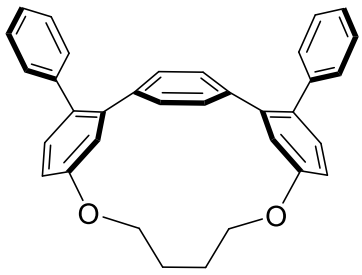
Cyclohex-2-ene-1,4-diol 3.18: Grubbs' second-generation catalyst (0.0030 g, 3.5 × 10^{-3} mmol) was added to a stirred solution of allylic alcohols **3.16** (0.035 g, 0.066 mmol) in dichloromethane (3 mL) and the reaction was heated to 40 °C. After 1 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 1.3 cm, 3:7 EtOAc/hexanes) to give **3.18** as an off-white solid (0.100 g, 88%): R_f = 0.23 (3:7 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 10H), 7.15 (d, *J* = 2.6 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.79 (dd, *J* = 8.3, 2.6 Hz, 2H), 6.12 (s, 2H), 4.23 (dt, *J* = 8.9, 5.8 Hz, 2H), 4.08 (dt, *J* = 9.5, 6.7 Hz, 2H), 2.10 (td, *J* = 14.8, 12.7, 5.7 Hz, 2H), 2.03-1.89 (m, 4H), 1.82 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.98, 144.17, 142.80, 134.85, 133.92, 133.51,

130.19, 128.12, 127.33, 114.93, 113.52, 75.02, 69.97, 36.76, 27.53; HRMS (ESI) calculated for $C_{34}H_{29}O_2$([M-($2H_20$)+H]$^+$) m/z = 469.2168, found 469.2157.



3.47

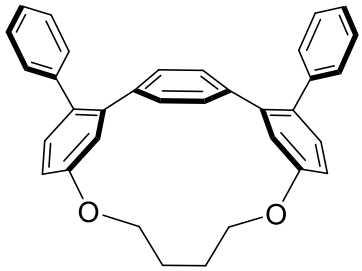
***p*-terphenylenophanediol 3.47:** P-TsOH (0.034 g, 0.18 mmol) was added to a stirred solution of diol **3.18** (0.010 g, 0.020 mmol) in toluene (4 mL) at 55 °C. After 4 h, the reaction was cooled to room temperature, water (10 mL) was added, and the resulting mixture was stirred for 5 min. The layers 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 chromatograph (12 × 0.6 cm, 5% EtOAc/hexanes) to afford **3.45** as a white solid (0.006 g, 62%): R_f = 0.37 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 7H), 7.35-7.29 (m, 4H), 7.27- 7.34 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 5.84 (ddd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 5.64 (dd, *J* = 9.8, 1.5 Hz, 1H), 5.55 (dd, *J* = 9.8, 1.5 Hz, 1H), 4.29-4.07 (m, 4H), 2.76 (ddd, *J* = 16.3, 6.8, 1.7 Hz, 1H), 2.64 (dd, *J* = 16.4, 2.8 Hz, 1H), 2.29-2.20 (m, 1H), 2.15 (s, 1H), 1.93-1.74 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.51, 157.22, 142.81, 141.07, 140.74, 140.43, 139.92, 133.55, 132.25, 131.39, 130.49, 129.41, 128.34, 128.31, 128.24, 127.62, 126.76, 124.84, 117.70, 117.33, 114.21, 111.75, 100.20, 76.74, 40.20, 24.33, 23.49; HRMS (ESI) calculated for$C_{34}H_{29}O_2$ ([M-(H_20)+H]$^+$) m/z = 469.2168, found 469.2188.



3.20

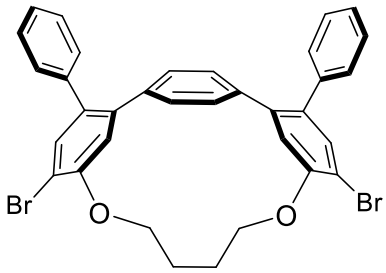
***p*-terphenylenophane 3.20:** Trifluoromethanesulfonic anhydride (2 drops, 0.010 mg, 0.037 mmol) was added to a stirred solution of the PTPP diol **3.18** (0.006 g, 0.012 mmol) in pyridine (0.2 mL)

and dichloromethane (1 mL) at 23 °C. After 15 h, the reaction mixture was poured into water (10 mL) and 1 M HCl solution (10 mL) were added. 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 Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm, 1:9 EtOAc/hexanes) to afford **3.20** as a white solid (0.012 g, 21%): R_f = 0.45 (1:9 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.67 (m, 4H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.42-7.35 (m, 4H), 7.32-7.27 (m, 2H), 7.23 (s, 4H), 6.86 (dd, *J* = 8.6, 2.9 Hz, 2H), 5.43 (d, *J* = 2.9 Hz, 2H), 3.96 (s, 4H), 1.49-1.46 (m, 5H).



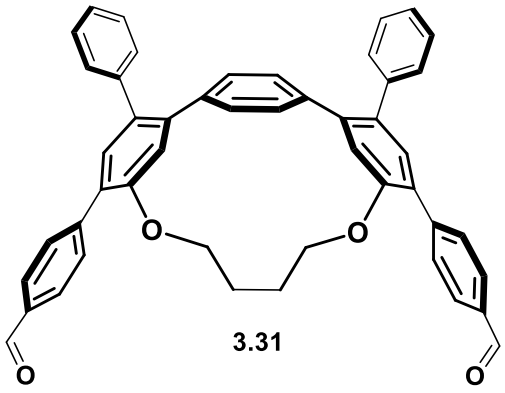
3.20

***p*-terphenylenophane 3.20:** Burgess reagent (0.0094 g, 0.040 mmol) was added to a stirred solution of cyclohexene-1,4-diol **3.18** (0.0033 g, 6.5×10^{-3} mmol) in toluene (1 mL) at 80 °C. After 2 h 30 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm, 1:9 EtOAc/hexanes) to afford **3.20** as a white solid (0.0021 g, 68%): R_f = 0.47 (1:9 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.67 (m, 4H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.42-7.35 (m, 4H), 7.32-7.27 (m, 2H), 7.23 (s, 4H), 6.86 (dd, *J* = 8.6, 2.9 Hz, 2H), 5.43 (d, *J* = 2.9 Hz, 2H), 3.96 (s, 4H), 1.49-1.46 (m, 4H).



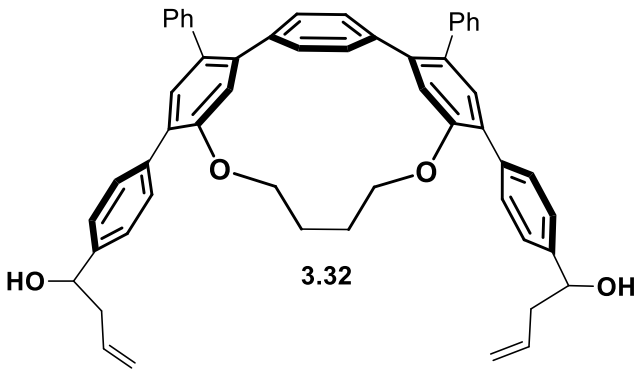
3.22

Brominated PTPP 3.22: Bromine (0.014 g, 0.0080 mg/ml, 0.090 mmol, 1.8 ml) were added to a stirred solution of the PTPP **3.20** (0.0070 g, 0.015 mmol) in dichloromethane (0.5 mL) at 23 °C. After 1 h, a solution of $Na_2S_2O_3$ (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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm, 3:7 dichloromethane/hexanes) to afford **3.22** as a white solid (0.006 g, 64%): R_f = 0.50 (1:1 dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.68-7.65 (m, 4H), 7.40-7.38 (m, 4H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.22 (s, 4H), 5.40 (s, 2H), 4.12-4.00 (m, 4H), 1.53-1.44 (m, 4H).



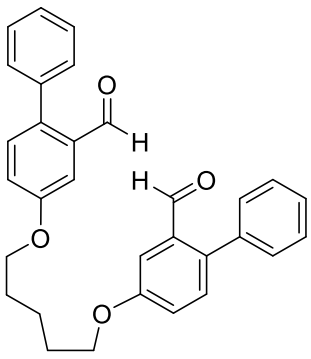
3.31

Aldehyde 3.31: 4-formylphenyl boronic acid (0.013 g, 0.086 mmol), Na_2CO_3 (0.020 g, 0.19 mmol) and $Pd(PPh_3)_4$ (0.001 g, 9 × 10^{-4} mmol) were added to a stirred solution of the dibromophenyl PTPP **3.22** (0.011 g, 0.017 mmol) in toluene (1.3 mL), EtOH (0.2 mL) and H_2O (0.5 mL). The reaction was heated at 90 °C for 17 h, at which point water (10 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm; 1:9 EtOAc/hexanes) to afford **3.31** as white solid (0.005 g, 56%): R_f = 0.22 (1:9 EtOAc/hexanes).



3.32

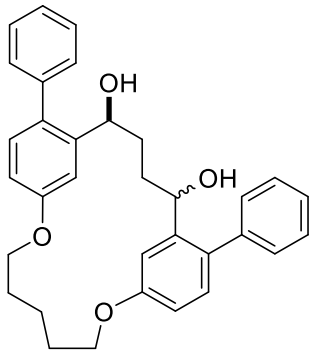
Allylic alcohol 3.32: Allylmagnesium chloride (2.0 M in THF, 0.050 mL, 0.10 mmol) was added to a stirred 0 °C solution of dialdehyde **3.31** (0.006 g, 0.009 mmol) in THF (2 mL)). After 30 min, the reaction mixture was poured into water (5 mL) and further diluted with 1 M HCl (5 mL). The resulting mixture was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm; 3:7 EtOAc/hexanes) to afford the allylic alcohol **3.32** (0.0063 g, 79%): R_f = 0.19 (3:7 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 3H), 7.60 (d, *J* = 8.0 Hz, 3H), 7.54 (s, 2H), 7.45-7.37 (m, 6H), 7.31 (d, *J* = 5.9 Hz, 4H), 5.93-5.83 (m, 3H), 5.58 (s, 2H), 5.20 (dd, *J* = 20.6, 13.5 Hz, 4H), 4.80 (dd, *J* = 8.2, 4.8 Hz, 2H), 4.01 (d, *J* = 6.2 Hz, 4H), 2.66-2.50 (m, 5H), 2.09-1.99 (m, 4H).



3.7

Dialdehyde **3.7**: Benzene boronic acid (1.17 g, 9.60 mmol), Na_2CO_3 (4.84 g, 45.7 mmol) and $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol) were added to a stirred solution of the dibromodialdehyde **3.5** (2.14 g, 4.57 mmol) in toluene (31 mL), EtOH (5.1 mL) and H_2O (10.2 mL). The reaction was heated at 90 °C for 5 h, at which point water (50 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 20 mL). The organic extracts were combined and washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15

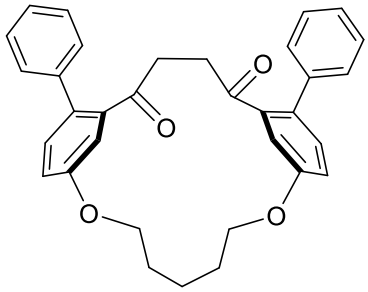
× 2.5 cm; 4:1 dichloromethane/hexanes) to afford **3.7** as white solid (1.00 g, > 95%): R_f = 0.57 (4:1 dichloromethane/hexanes);



3.11

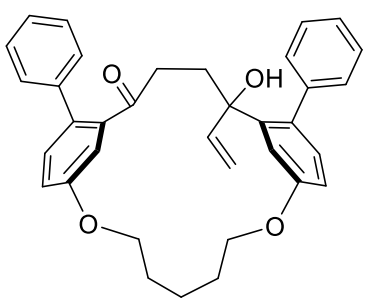
Diol 3.11: Vinylmagnesium chloride (1.6 M in THF, 3.5 mL, 5.6 mmol) was added to a stirred solution of the dialdehyde **3.7** (1.18 g, 2.54 mmol) in THF (25 mL). After 10 min., the reaction was poured into water (40 mL) and further diluted with 1 M HCl (40 mL). The resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with a saturated solution sodium bicarbonate (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The pale yellow residue was dissolved in dichloromethane (180 mL), heated to 40 ^oC, followed by the addition of the Hoveyda-Grubbs second-generation catalyst (0.040 g, 0.064 mmol). After 1 h 30 min, the reaction mixture was concentrated under reduced pressure. The dark brown residue was dissolved in 1:9 methanol/dichloromethane (25 mL), and sodium borohydride (0.768 g, 20.32 mmol) and Hoveyda-Grubbs second-generation catalyst (0.032 g, 0.051 mmol) was added. After 28 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 (3 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 1% acetone/dichloromethane) to afford the diol **3.11** as a white solid (220 g, 17% from **3.7**): R_f = 0.24 (3:7 EtOAc/hexanes), 0.40 (1% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 10H), 7.17 (dd, J = 8.4, 1.9 Hz, 2H), 6.94-6.83 (m, 4H), 4.67 (dd, J = 9.7, 4.5 Hz, 2H), 4.21-4.15 (m, 2H), 4.01-3.96 (m, 2H), 2.05-1.72 (m, 8H), 1.52-1.40 (m, 2H), 1.40-1.26 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ

159.00, 141.39, 140.77, 134.83, 131.54, 131.40, 129.84, 128.27, 126.95, 114.82, 114.60, 111.13, 110.90, 77.54, 77.22, 76.91, 69.96, 69.90, 28.37, 21.99; HRMS (ESI) calculated for $C_{33}H_{31}O_2$ ($[M-(2H_2O)+H]^+$) *m/z* = 459.2324 found 459.2327.



3.13

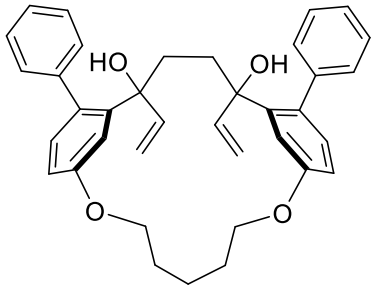
1,4-Diketone 3.13: Dess-Martin periodinane (0.244 g, 0.576 mmol) and $NaHCO_3$ (0.048 g, 0.057 mmol) were added to a stirred solution of 1,4-diol **3.11** (0.095 g, 0.019 mmol) in dichloromethane (5 mL) at room temperature. After 1 h, a 10% $Na_2S_2O_3$ solution (20 mL) was added and the reaction was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 1:4 EtOAc/hexanes) to afford 1,4-diketone **3.13** as a beige solid (0.076 g, 80%): R_f = 0.40 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 6H), 7.24-7.19 (m, 6H), 6.96 (dd, *J* = 8.4, 2.7 Hz, 2H), 6.76 (d, *J* = 2.7 Hz, 2H), 4.11 (t, *J* = 6.5 Hz, 4H), 2.10 (s, 4H), 1.86 (p, *J* = 6.7 Hz, 4H), 1.79-1.67 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 206.94, 158.23, 140.96, 140.09, 132.00, 131.35, 128.83, 127.71, 117.33, 113.75, 113.49, 67.52, 38.47, 26.84, 20.83; HRMS (ESI) calculated for $C_{33}H_{31}O_4$ ($[M+H]^+$) *m/z* = 491.2222 found 491.2221.



3.15

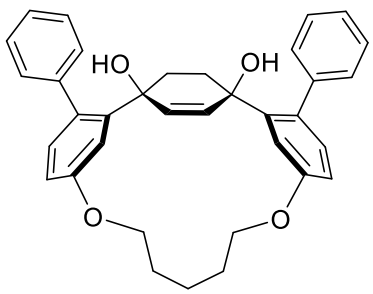
Hydroxy ketone 3.15: 1,4-diketone **3.13** (0.120 g, 0.243 mmol), as a solution in THF (3 mL) was added to a stirred 65 °C solution of vinylmagnesium chloride (1.6 M in THF, 0.50 mL, 0.73 mmol). After 15 min, the reaction mixture was poured into water (20 mL) and further diluted with 1 M HCl (20 mL). The resulting

mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue **3.15** was used without purification as a light yellow oil (0.126 g, 85%): R_f = 0.52 (3:7 EtOAc/hexanes); HRMS (ESI) calculated for $C_{35}H_{33}O_3$ ($[M+H]^+$) *m/z* = 501.2430 found 501.2426.



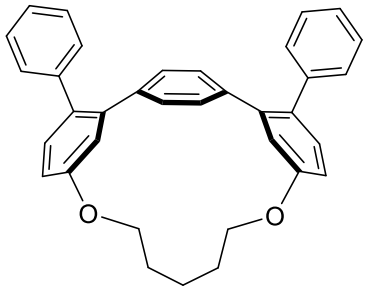
3.17

Allylic Alcohol 3.17: Hydroxy ketone **3.15** (0.110 g, 0.211 mmol), as a solution in THF (3 mL) was added to a stirred 23 °C solution of Lanthanum (III) chloride (0.60 M in THF, 3.6 mL, 2.1 mmol). After 1 h, the temperature was decreased to 0 °C and a solution of vinylmagnesium chloride (1.6 M in THF, 0.40 mL, 0.63 mmol) were added. After 50 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 $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatography (15 × 1.3 cm, 1:4 EtOAc/hexanes) to give allylic alcohol **3.17** as a brown oil (0.022 g, 19%): R_f = 0.24 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 7.22-7.16 (m, 4H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.80 (dd, *J* = 8.3, 2.7 Hz, 2H), 5.79 (dd, *J* = 17.3, 10.7 Hz, 2H), 4.96 (dd, *J* = 17.3, 1.1 Hz, 2H), 4.86 (dd, *J* = 10.7, 1.1 Hz, 2H), 4.24-4.18 (m, 2H), 4.16-4.10 (m, 2H), 3.61-3.58 (t, *J* = 6.6 Hz, 2H), 1.94-1.81 (m, 9H), 1.79-1.68 (m, 7H); HRMS (ESI) calculated for $C_{37}H_{35}O_2$ ($[M-(2H_2O)+H]^+$) *m/z* = 511.2637 found 511.2637.



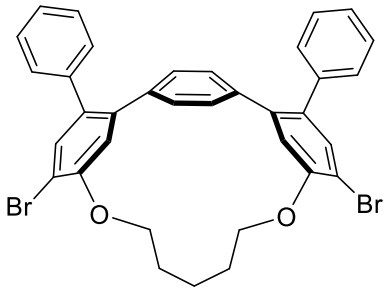
3.19

Cyclohex-2-ene-1,4-diol 3.19: Grubbs' second-generation catalyst (0.0020 g, 1.8×10^{-3} mmol) was added to a stirred solution of allylic alcohols **3.17** (0.020 g, 0.037 mmol) in dichloromethane (1 mL) and the reaction was heated to 40 ^{o}C. After 2 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 1.3 cm, 3:7 EtOAc/hexanes) to give **3.19** as an off-white solid (0.014 g, 74%): R_f = 0.25 (3:7 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 10H), 7.17 (d, *J* = 2.6 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.82 (dd, *J* = 8.3, 2.6 Hz, 2H), 6.11 (s, 2H), 4.22-4.17 (m, 2H), 4.06-3.98 (m, 2H), 2.05-1.89 (m, 4H), 1.86-1.79 (m, 8H).



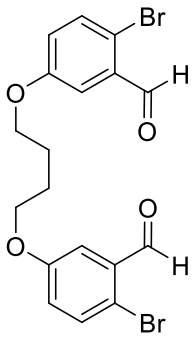
3.21

Compound 3.21: Burgess reagent (0.026 g, 0.11 mmol) was added to a stirred solution of cyclohexene-1,4-diol **3.19** (0.014 g, 0.027 mmol) in toluene (1 mL) at 80 °C. After 1 h 20 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm, 5% EtOAc/hexanes) to afford **3.21** as a white solid (0.06 g, 46%): R_f = 0.24 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.37-7.30 (m, 4H), 7.26-7.22 (m, 2H), 7.15 (s, 4H), 6.85 (dd, *J* = 8.5, 2.8 Hz, 2H), 5.89 (d, *J* = 2.8 Hz, 2H), 4.14-4.06 (m, 4H), 1.61-1.44 (m, 6H).



3.23

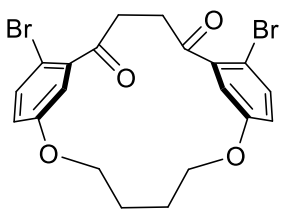
Brominated PTPP 3.23: Bromine (0.0063 g, 0.018 mg/ml, 0.039 mmol, 1.8 ml) were added to a stirred solution of the PTPP (0.0060 g, 0.012 mmol) in dichloromethane (1 mL) at 23 °C. After 1 h, a solution of $Na_2S_2O_3$ (10 mL) was added, and the resulting mixture was stirred for 5 min. The layers were separated and the mixture was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **3.23** as a white solid (0.0059 g, 60%): R_f = 0.53 (1:1 dichloromethane/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 2H), 7.57-7.52 (m, 4H), 7.39-7.31 (m, 6H), 7.13 (s, 4H), 5.87 (s, 2H), 4.23-4.15 (m, 4H), 1.52-1.50 (d, *J* = 6.2 Hz, 6H).



3.4

Dialdehyde 3.4: 1,4-dibromobutane (1.47 g, 4.54 mmol) was added to a stirred solution of 2-bromo-5-hydroxybenzaldehyde **3.1** (2.028 g, 10.09 mmol), K_2CO_3 (1.40 g, 10.1 mmol) and TBAI (0.186 g, 0.504 mmol) in DMF (12 mL). The reaction was heated at 65 °C for 24 h, at which point water (50 mL) and 1 M HCl (50 mL) were added sequentially. The resulting mixture was extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined and washed with a 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 (18 × 5.0 cm; dichloromethane, 40 to 60% dichloromethane/hexanes) to afford the dialdehyde **3.4** as a reddish brown solid (1.80 g, 87%): R_f = 0.25 (2:3 dichloromethane/hexanes): ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 3.2 Hz, 2H), 7.03 (dd, *J* = 8.7, 3.2 Hz, 2H), 4.12-4.03 (m, 4H), 2.06-1.94 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ =

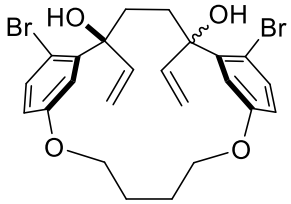
191.99, 158.75, 134.80, 134.13, 123.64, 118.15, 113.47, 68.15, 25.92; HRMS (ESI) calculated for $C_{18}H_{17}O_4Br_2$ ($[M+H]^+$) *m/z* = 454.9494, found 454.9487.



3.24

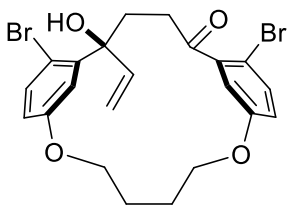
Macrocyclic 1,4-diketone 3.24: Vinylmagnesium chloride (1.6 M in THF, 7.2 mL, 12 mmol) was added to a stirred 0 °C solution of dialdehyde **3.4** (1.75 g, 3.84 mmol) in THF (38 mL). After 10 min, the reaction mixture was poured into water (40 mL) and further diluted with 1 M HCl (40 mL). The resulting mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (256 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.060 g, 0.096 mmol). After 1 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 1:9 methanol/dichloromethane (38 mL), and sodium borohydride (0.290 g, 7.68 mmol) and Hoveyda-Grubb's II catalyst (0.060 g, 0.096 mmol) were added at 23 °C. After 3 h, the reaction was poured into water (40 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), and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (9 mL), followed by the sequential addition of $NaHCO_3$ (0.645 g, 7.68 mmol) and Dess-Martin periodinane (3.260 g, 7.68 mmol). After 30 min., a 10% $Na_2S_2O_3$ solution (20 mL) was added and the reaction was stirred for 5 min. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified

by flash chromatography (15 × 2.5 cm, 7:3 chloroform/hexanes) to afford the 1,4-dibromodiketone **3.24** as a reddish brown solid (1.25 g, 61% from **3.4**); R_f = 0.53 (7:3 chloroform/hexanes): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.79 (dd, *J* = 8.8, 3.1 Hz, 2H), 6.53 (d, *J* = 3.1 Hz, 2H), 4.15-4.04 (m, 4H), 3.23 (s, 4H), 1.91 (t, *J* = 3.1 Hz, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 203.42, 157.84, 141.88, 134.45, 118.20, 115.05, 108.26, 67.63, 38.27, 24.50.



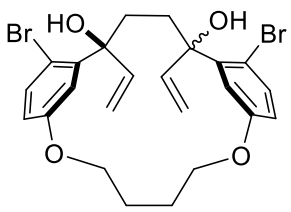
3.48

Allylic alcohol 3.48: Vinyl magnesium chloride (1.6 M in THF, 1.6 mL, 2.5 mmol) was added to a stirred 40 °C solution of 1,4-diketone **3.24** (0.417 g, 0.840 mmol) in dichloromethane (7 mL). After 10 min, the reaction mixture was poured into water (30 mL) and further diluted with 1 M HCl (30 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 × 1.3 cm, 1% acetone/dichloromethane) to give Hydroxyketone **3.49** (0.135 g, 60%) and allylic alcohol **3.48** (0.257 g, 31%; 89% based on recovered Hydroxyketone) as a single diastereomers. R_f = 0.35 (2% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 3.1 Hz, 2H), 6.64 (dd, *J* = 8.7, 3.0 Hz, 2H), 6.41 (dd, *J* = 17.4, 10.7 Hz, 2H), 5.34-5.21 (m, 4H), 4.10-4.05 (m, 4H), 3.95 (s, 2H), 2.27-2.17 (m, 2H), 1.93-1.88 (m, 2H), 1.88-1.80 (m, 4H).



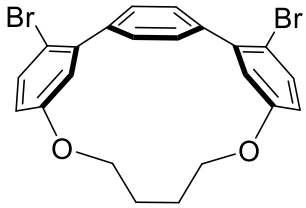
3.49

Hydroxy ketone 3.49: R_f = 0.55 (2% acetone/dichloromethane); HRMS (ESI) calculated for $C_{23}H_{23}O_3Br_2$ ($[M-(H_2O)+H]^+$) m/z = 505.0014, found 505.0009.



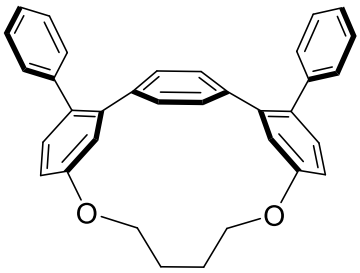
3.26

Cyclohex-2-ene-1,4-diol 3.26: Grubbs' second-generation catalyst (0.010 g, 0.011 mmol) was added to a stirred solution of allylic alcohols II (0.120 g, 0.224 mmol) in dichloromethane (3 mL) and the reaction was heated to 40 °C. After 1 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 1.3 cm, 3:7 EtOAc/hexanes) to give **3.26** as an off-white solid (0.100 g, 88%): R_f = 0.23 (3:7 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 3.0 Hz, 2H), 6.65 (dd, *J* = 8.7, 3.0 Hz, 2H), 6.24 (s, 2H), 4.16-4.06 (m, 2H), 3.99-3.95 (m, 2H), 3.60 (s, 2H), 2.42-2.38 (m, 2H), 2.06-1.99 (m, 4H), 1.87-1.82 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.29, 143.51, 136.21, 134.42, 117.14, 116.65, 111.12, 74.57, 70.80, 33.42, 27.55.



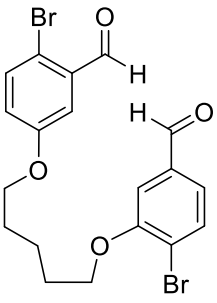
3.28

PTPP 3.28: Burgess reagent (0.014 g, 0.059 mmol) was added to a stirred solution of cyclohexene-1,4-diol **3.26** (0.010 g, 0.020 mmol) in THF (2 mL) at 50 °C. After 10 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm, 5% EtOAc/hexanes) to afford **3.28** as a white solid (0.004 g, 42%): R_f = 0.50 (1:4 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.9 Hz, 2H), 7.42 (s, 4H), 6.68-6.66 (m, 2H), 5.29 (d, *J* = 3.2 Hz, 2H), 3.89 (s, 4H), 2.06-1.98 (m, 4H).



3.20

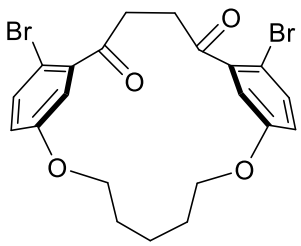
Phenyl PTPP 3.20: Burgess reagent (0.029 g, 0.12 mmol) was added to a stirred solution of cyclohexene-1,4-diol **3.26** (0.020 g, 0.039 mmol) in THF (2 mL) at 60 °C. After 1h 30 min, the reaction was cooled to room temperature, water (10 mL) was added, and the resulting mixture was stirred for 5 min. 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (2 mL), EtOH (0.5 mL) and H_2O (1 mL) and benzene boronic acid (0.014 g, 0.082 mmol), Na_2CO_3 (0.043 g, 0.39 mmol) and $Pd(PPh_3)_4$ (0.0029 g, 1.9×10^{-3} mmol) were added and heated at 90 °C. After 13 h, the reaction mixture was cooled to room temperature at which point water (10 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm; 1:4 dichloromethane/hexanes) to afford **3.20** as white solid (0.010 g, 54%): R_f = 0.14 (1:4 dichloromethane/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.67 (m, 4H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.42-7.35 (m, 4H), 7.32-7.27 (m, 2H), 7.23 (s, 4H), 6.86 (dd, *J* = 8.6, 2.9 Hz, 2H), 5.43 (d, *J* = 2.9 Hz, 2H), 3.96 (s, 4H), 1.49-1.46 (m, 4H).



3.5

Dialdehyde 3.5: 1,5-diiodopentane (2.175 g, 6.715 mmol) was added to a stirred solution of 2-bromo-5-hydroxybenzaldehyde (**3.1**) (3.000 g, 14.92 mmol), K_2CO_3 (2.063 g, 14.92 mmol) and TBAI (0.276 g, 7.462 mmol) in DMF (70 mL). The reaction was heated at 65 °C for 40 h, at which point water (60 mL) and 1 M HCl (60 mL) were added sequentially. The resulting

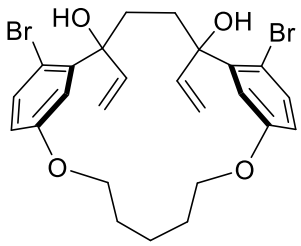
mixture was extracted with ethyl acetate (4 × 50 mL). The organic extracts were combined and washed with a saturated solution of $NaHCO_3$ (60 mL) and brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 5.0 cm; dichloromethane, 60 to 80% dichloromethane/hexanes) to afford the dialdehyde **3.5** as a reddish brown solid (2.33 g, 74%): R_f = 0.36 (4:1 dichloromethane/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 3.2 Hz, 2H), 7.03 (dd, *J* = 8.8, 3.2 Hz, 2H), 4.02 (t, *J* = 6.3 Hz, 4H), 1.92-1.82 (m, 4H), 1.71-1.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.05, 158.84, 134.75, 134.09, 123.67, 118.05, 113.45, 68.44, 28.92, 22.79; HRMS (ESI) calculated for $C_{19}H_{19}O_4Br_2$ ($[M+H]^+$) *m/z* = 468.9650, found 468.9667.



3.25

Macrocyclic 1,4-diketone 3.25: Vinylmagnesium chloride (1.6 M in THF, 1.6 mL, 2.6 mmol) was added to a stirred 0 °C solution of dialdehyde **3.5** (0.400 g, 0.855 mmol) in THF (9 mL). After 10 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 combined organic extracts were washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (86 mL), heated to 40 °C, followed by the addition of Hoveyda-Grubbs second-generation catalyst (0.014 g, 0.021 mmol). After 1 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 1:9 methanol/dichloromethane (9 mL), and sodium borohydride (0.065 g, 1.710 mmol) and Hoveyda-Grubb's II catalyst (0.014 g, 0.021 mmol) were added at 23 °C. After 3 h, the reaction was poured into water (40 mL). The layers were separated and the

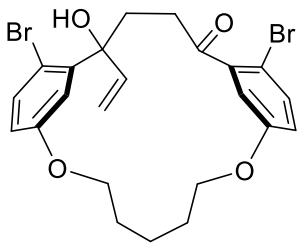
aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (20 mL), and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (9 mL), followed by the sequential addition of $NaHCO_3$ (0.15 g, 1.71 mmol) and Dess-Martin periodinane (0.73 g, 1.71 mmol). After 30 min., a 10% $Na_2S_2O_3$ solution (20 mL) was added and the reaction was stirred for 5 min. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 4:1 dichloromethane/hexanes) to afford the 1,4-dibromodiketone **3.25** as a reddish brown solid (0.223 g, 53% from **3.5**); R_f = 0.30 (4:1 dichloromethane/hexanes): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8 Hz, 2H), 6.75 (dd, *J* = 8.8, 3.0 Hz, 2H), 6.63 (d, *J* = 3.0 Hz, 2H), 3.99 (t, *J* = 6.4 Hz, 4H), 3.30 (s, 4H), 1.77-1.70 (m, 4H), 1.64-1.59(m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.05, 158.09, 141.49, 134.41, 118.65, 115.90, 108.46, 67.87, 37.94, 26.69, 20.88; HRMS (ESI) calculated for $C_{21}H_{21}O_4Br_2$ ($[M+H]^+$) *m/z* = 494.9807, found 494.9793.



3.50

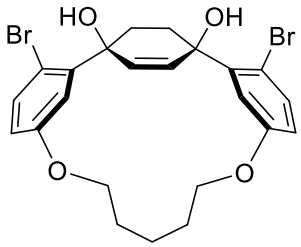
Allylic alcohol 3.50: Vinyl magnesium chloride (1.6 M in THF, 0.60 mL, 0.97 mmol) was added to a stirred 40 °C solution of 1,4-diketone **3.25** (0.160 g, 0.323 mmol) in dichloromethane (4 mL). After 15 min, the reaction mixture was poured into water (20 mL) and further diluted with 1 M HCl (20 mL). The resulting mixture was extracted with dichloromethane (3 × 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 × 1.3 cm, 1%

acetone/dichloromethane) to give Hydroxyketone **3.51** (0.077 g, 46%) and allylic alcohol **3.50** (0.075 g, 42%; 87% based on recovered Hydroxyketone) as a single diastereomers. R_f = 0.28 (1% acetone/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 4H), 6.63 (dd, *J* = 8.7, 3.1 Hz, 2H), 6.55 (dd, *J* = 17.3, 10.7 Hz, 2H), 5.37-5.24 (m, 4H), 4.24-4.09 (m, 4H), 4.03-3.98 (m, 2H), 2.21-2.17(m, 2H), 2.13-2.02 (m, 2H), 1.77-1.59 (m, 5H), 1.59-1.49 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.81, 145.52, 142.45, 141.79, 135.68, 115.69, 115.37, 111.09, 111.06, 77.12, 67.90, 33.81, 27.60; HRMS (ESI) calculated for $C_{25}H_{25}O_2Br_2$ ($[M-2(H_2O)+H]^+$) *m/z* = 515.0221, found 515.0200.



3.51

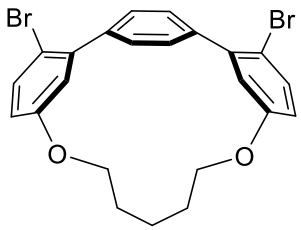
Hydroxy ketone 3.51: R_f = 0.61 (1% acetone/dichloromethane); HRMS (ESI) calculated for $C_{23}H_{23}O_3Br_2$ ($[M-(H_2O)+H]^+$) m/z = 505.0014, found 505.0009.



3.27

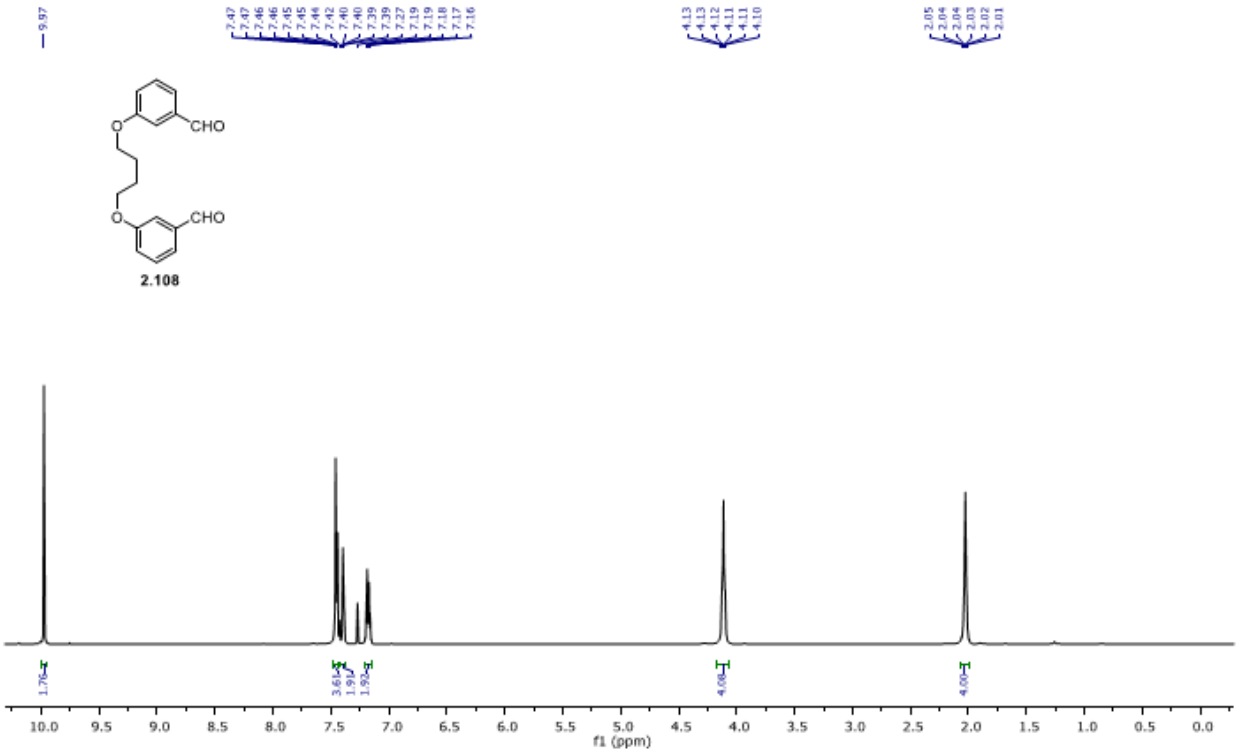
Cyclohex-2-ene-1,4-diol 3.27: Grubbs' second-generation catalyst (0.0080 g, 9.4 × 10^{-3} mmol) was added to a stirred solution of allylic alcohols **3.50** (0.097 g, 0.18 mmol) in dichloromethane (4.6 mL) and the reaction was heated to 40 °C. After 1 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 1.3 cm, 3:7 EtOAc/hexanes) to give **3.27** as an off-white solid (0.076 g, 83%): R_f = 0.23 (3:7 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 3.0 Hz, 2H), 6.67 (dd, *J* = 8.7, 3.0 Hz, 2H), 6.22 (s, 2H), 4.16-4.11 (m, 2H), 3.90-3.84 (m, 2H), 3.54 (s, 2H), 2.47-2.41 (m, 2H), 2.17 (s, 4H), 2.09-1.99 (m, 2H), 1.85-1.78 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.34, 143.60, 136.17, 118.46, 118.34, 116.06, 111.38,

74.27, 69.30, 32.93, 28.54, 21.74; HRMS (ESI) calculated for $C_{23}H_{23}O_3Br_2$ ([M-(H_2O)+H]$^+$) m/z = 505.0014, found 505.0035.



3.29

Bromo PTPP 3.29: Burgess reagent (0.014 g, 0.057 mmol) was added to a stirred solution of cyclohexene-1,4-diol **3.27** (0.010 g, 0.019 mmol) in toluene (2 mL) at 80 ^{0}C. After 3 h, 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 Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 0.6 cm, 5% EtOAc/hexanes) to afford **3.29** as a white solid (0.009 g, 54%): R_f = 0.27 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 1.3 Hz, 4H), 7.48 (s, 2H), 6.67 (dd, *J* = 8.8, 3.2 Hz, 2H), 5.73 (d, *J* = 3.2 Hz, 2H), 4.03-3.96 (m, 4H), 1.56 (s, 4H), 1.53-1.43 (m, 2H).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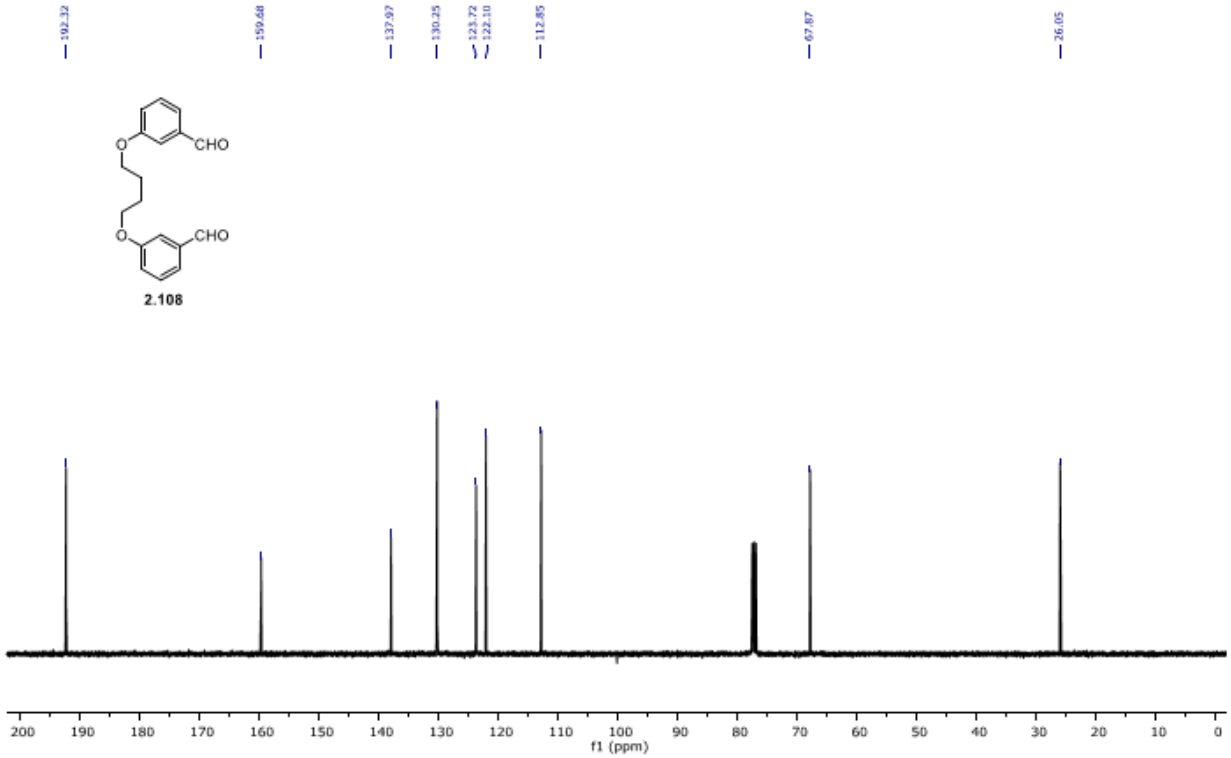
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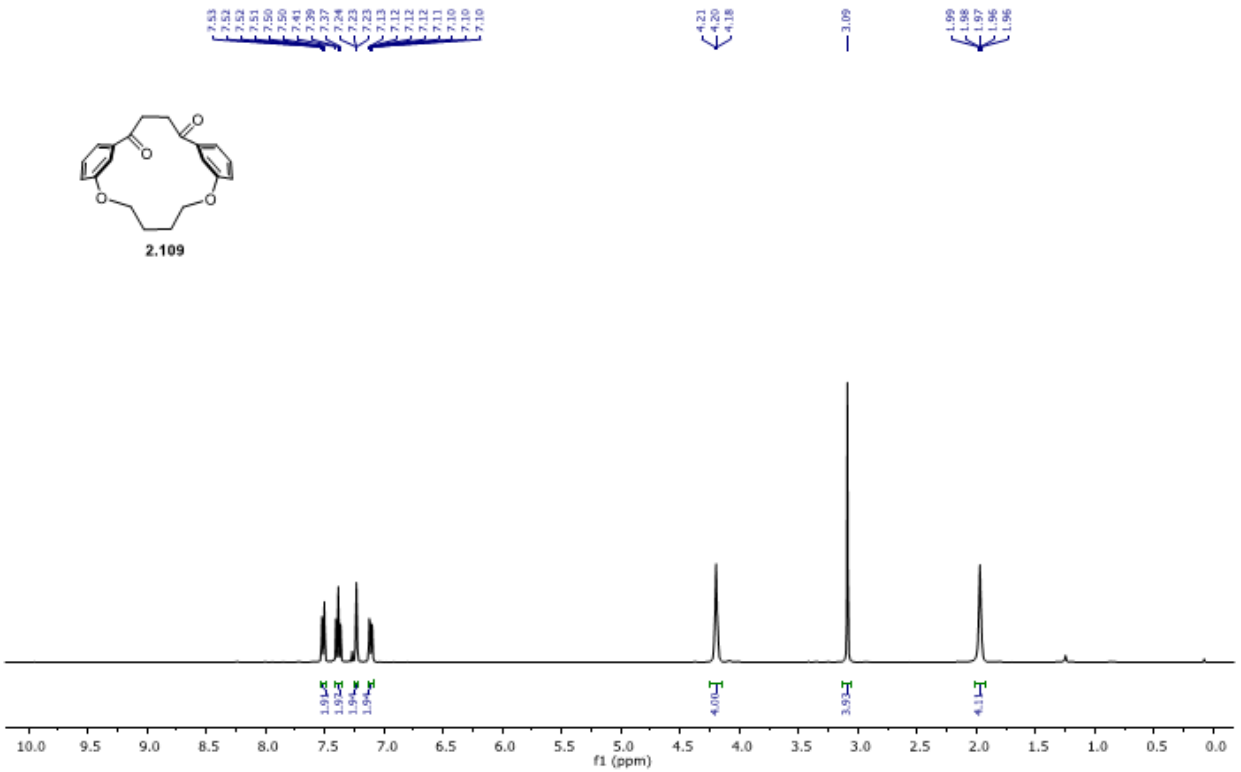
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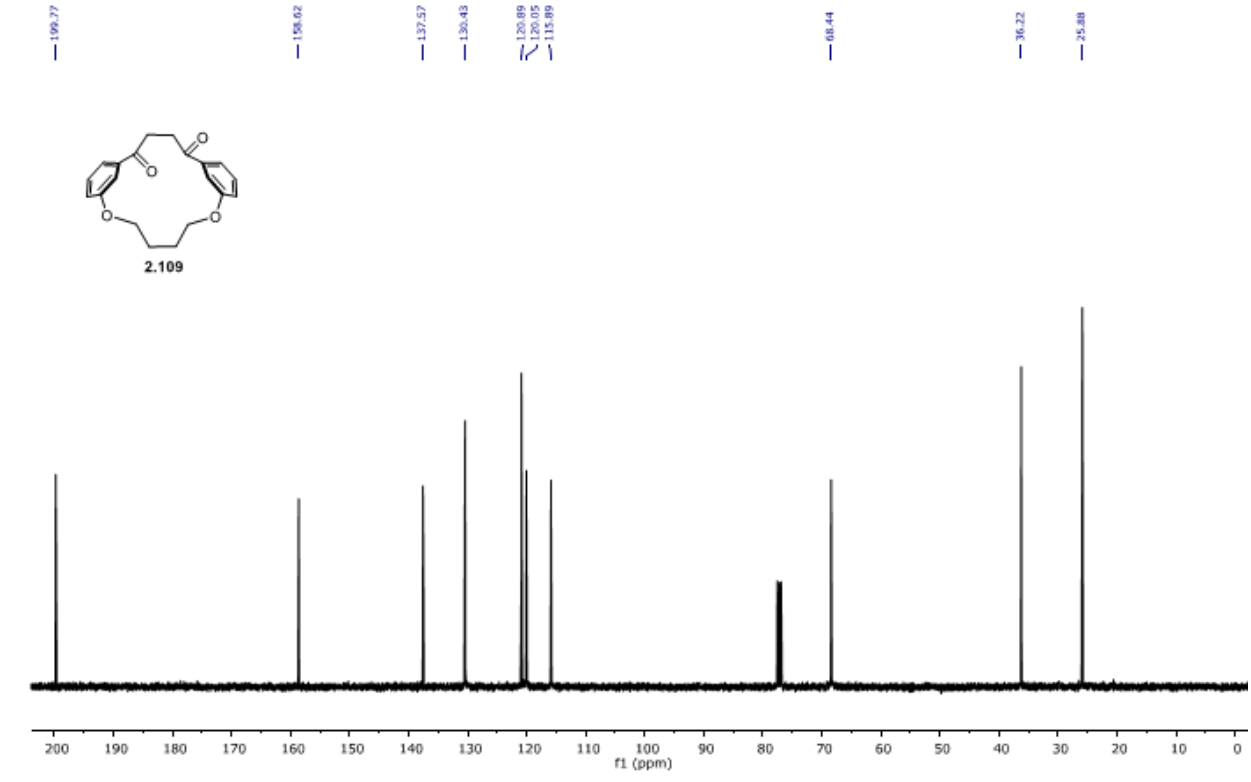
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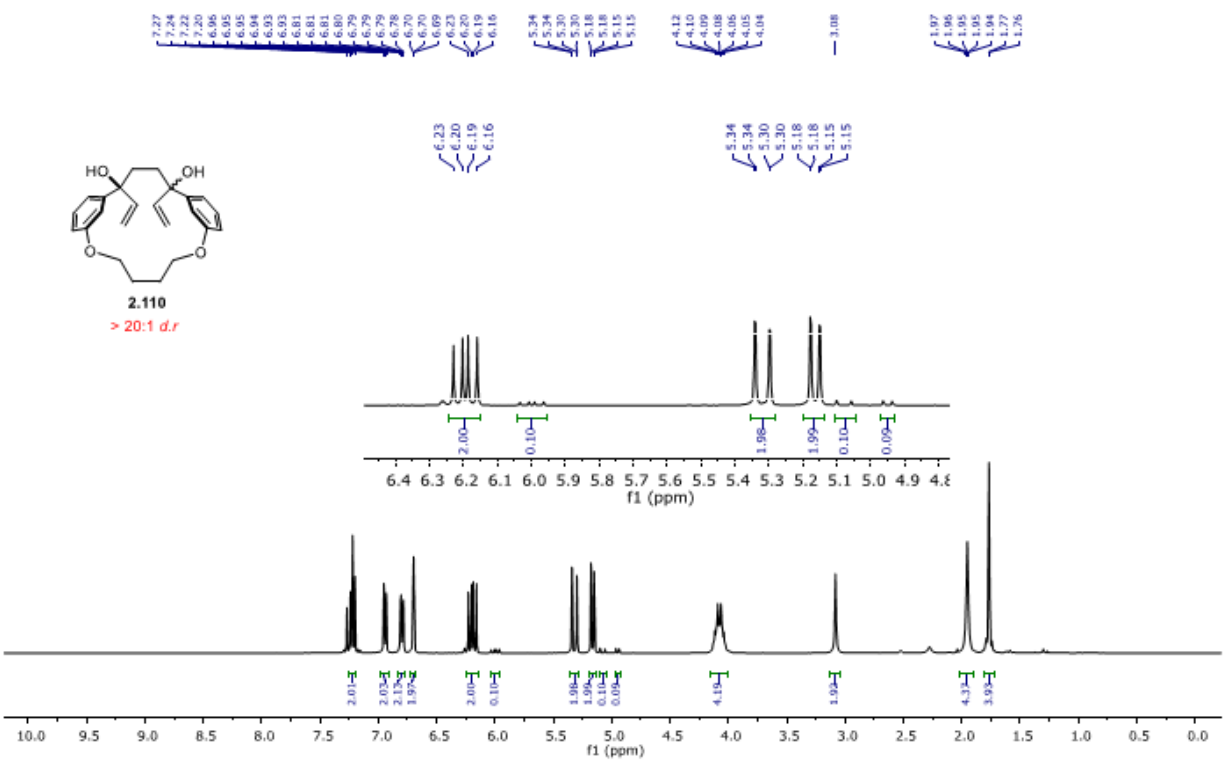
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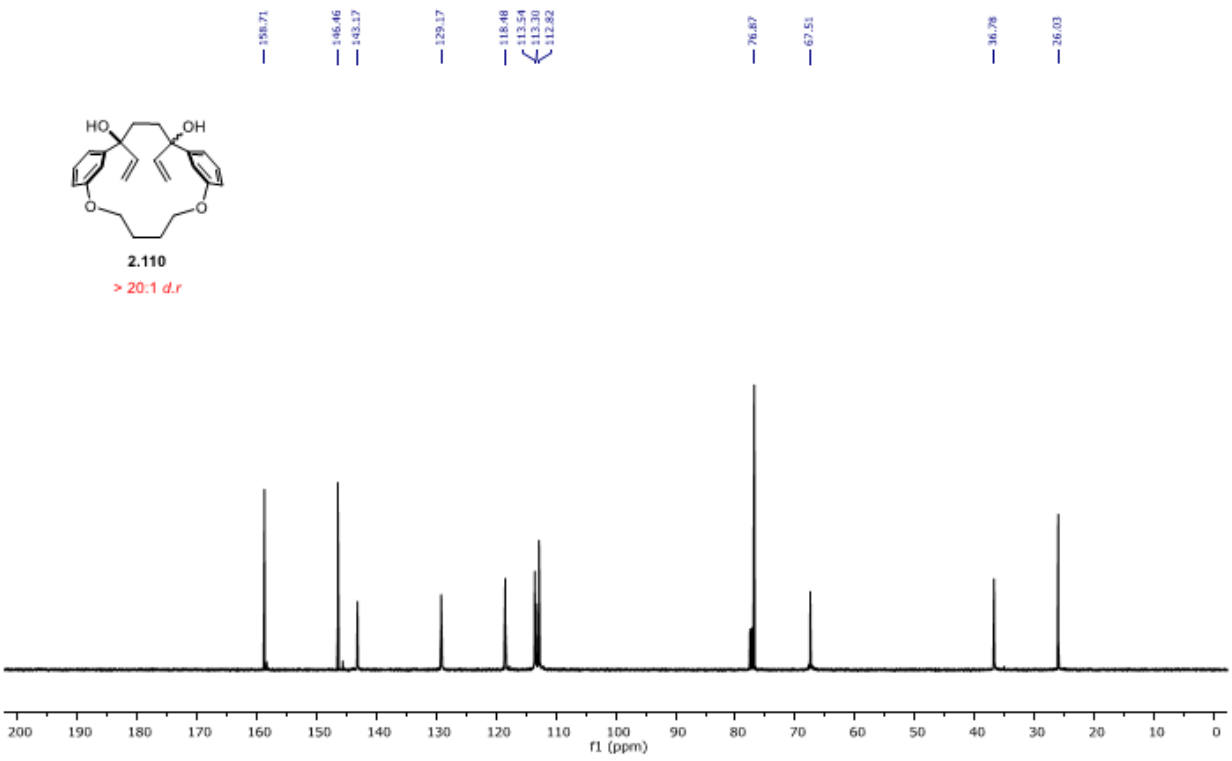
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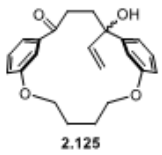

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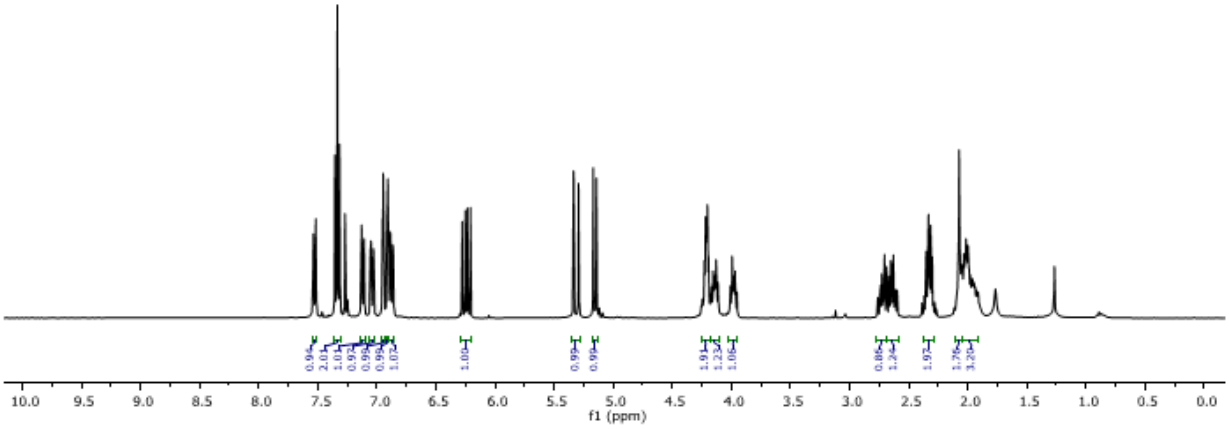
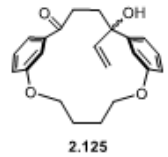
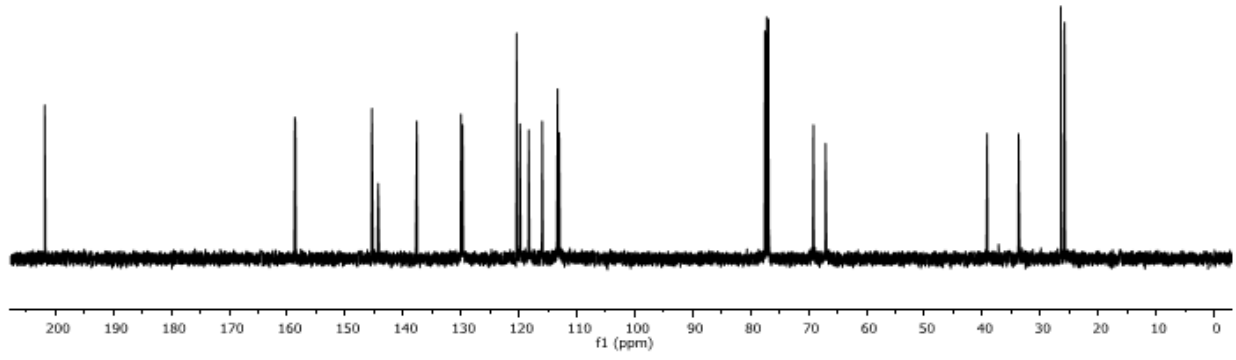
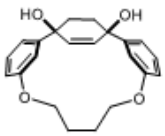


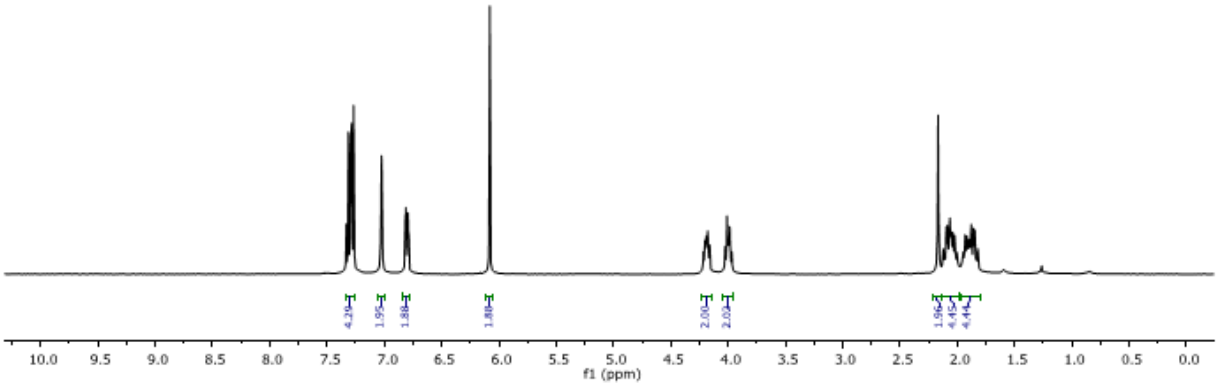


2.125

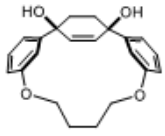




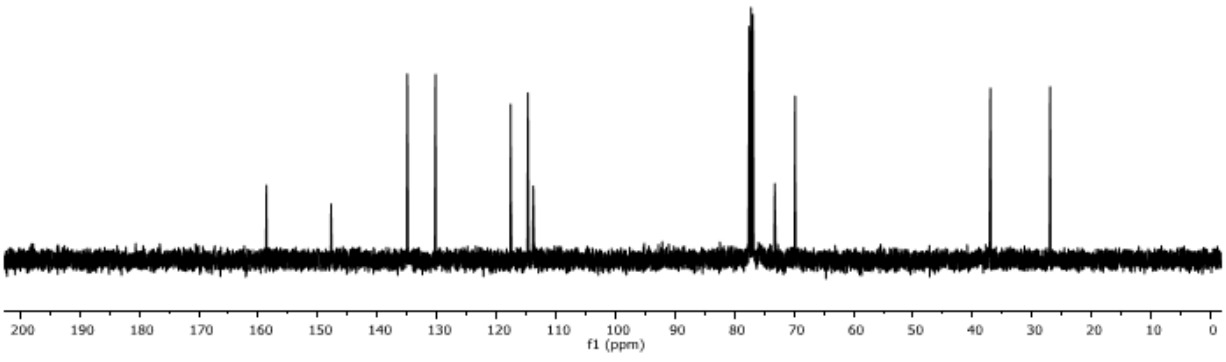
2.111

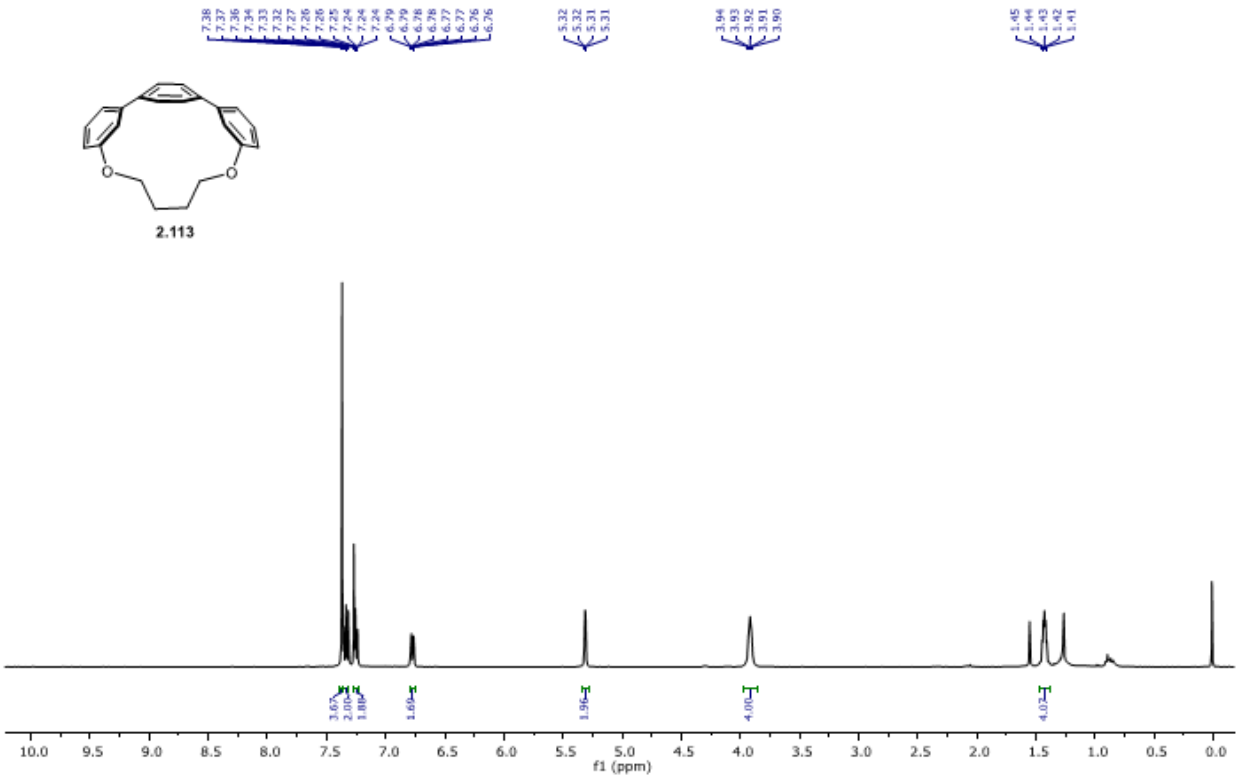

4.29
1.95
1.88
1.88
2.00
2.03
1.96
4.45
4.44
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

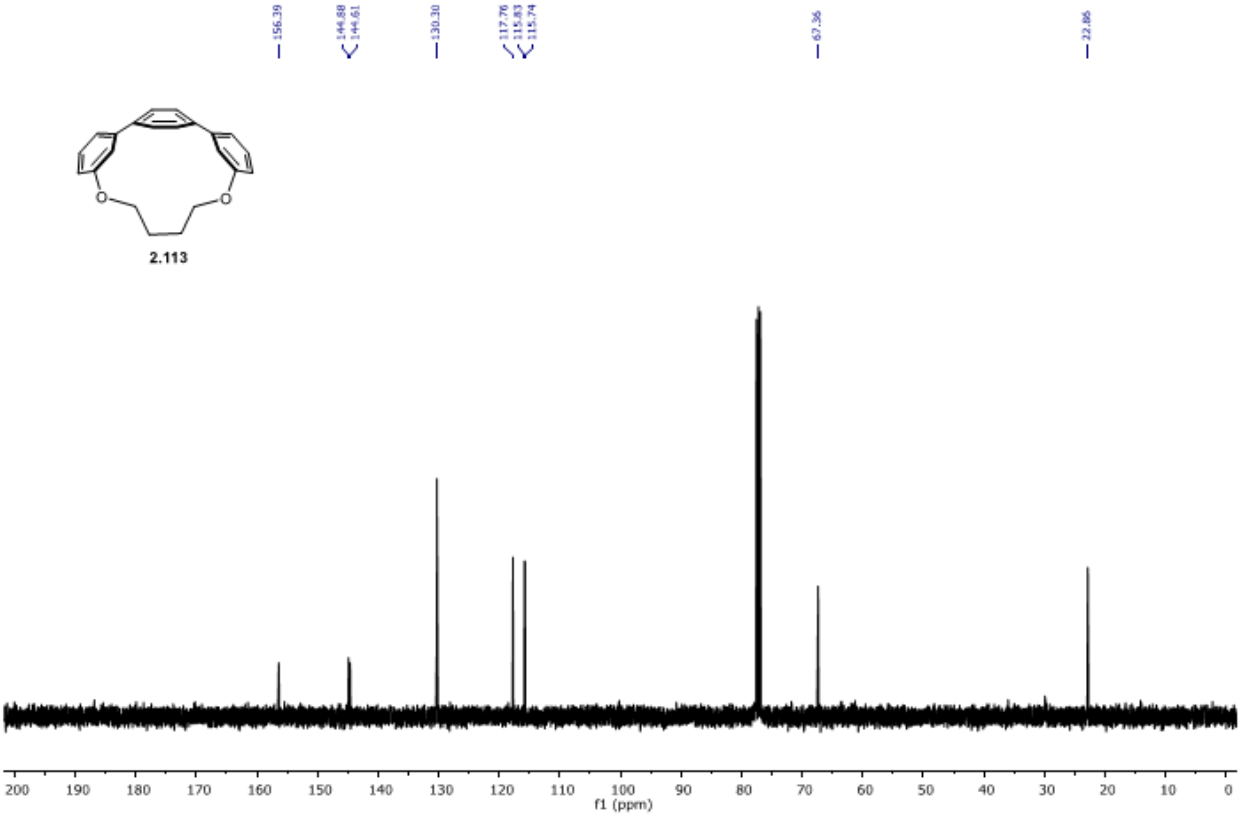

158.65
147.78
134.96
130.23
117.60
114.71
113.82
73.26
69.82
37.01
26.99

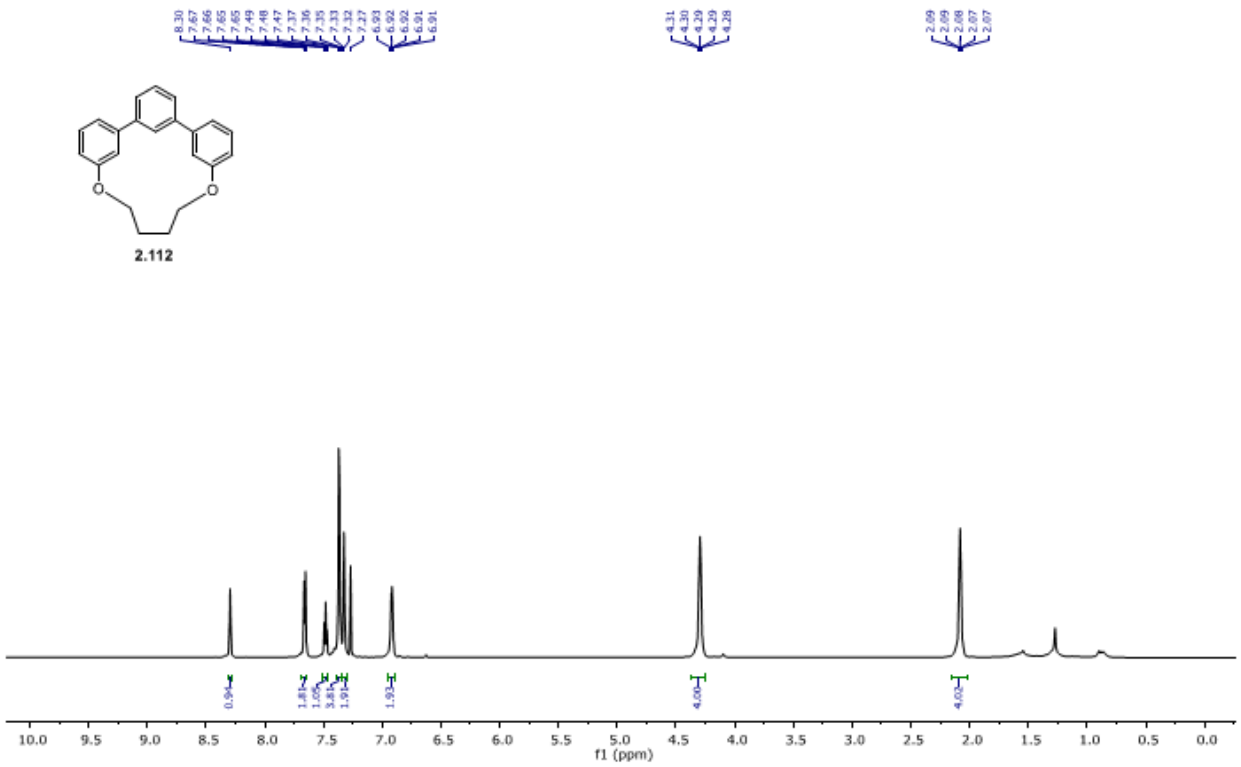


2.111

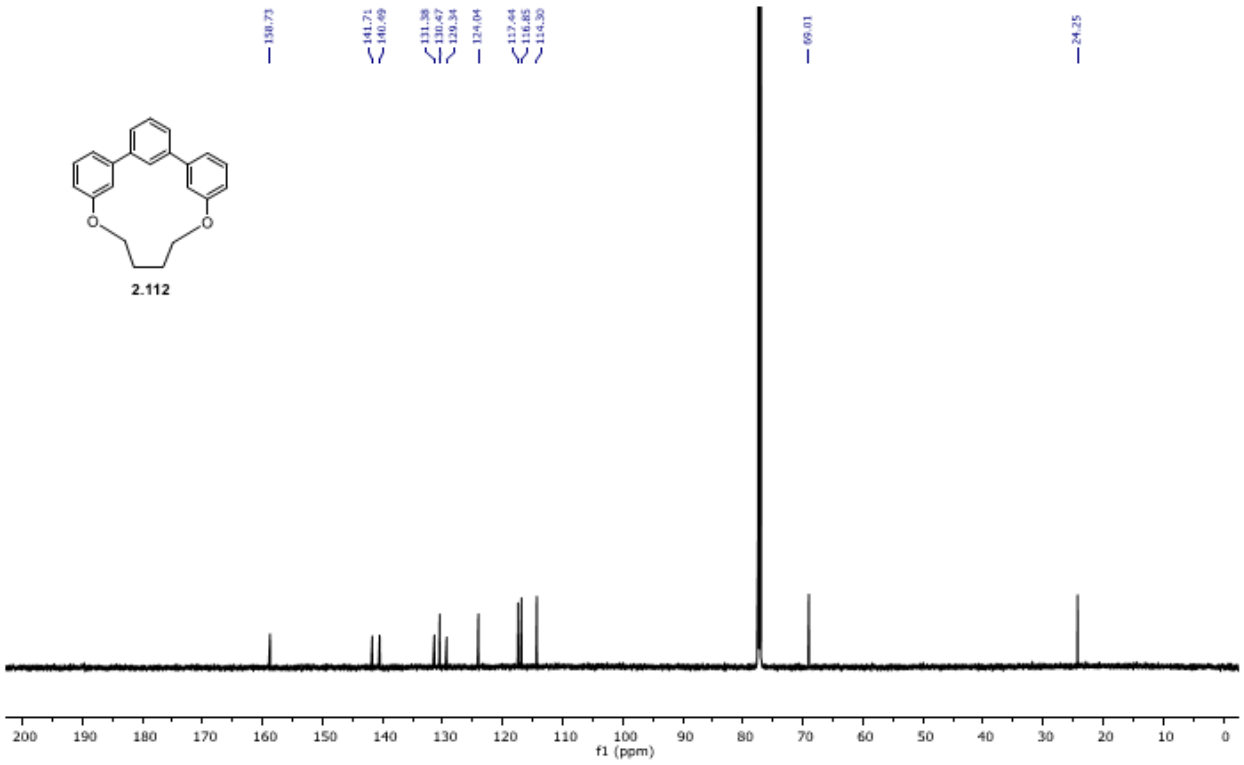

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.38
7.37
7.36
7.34
7.33
7.32
7.27
7.26
7.25
7.24
7.24
7.24
6.79
6.79
6.78
6.78
6.77
6.77
6.76
6.76
5.32
5.32
5.31
5.31
3.94
3.93
3.92
3.91
3.90
1.45
1.44
1.43
1.42
1.41
O
O
2.113
3.67
2.00
1.88
1.69
1.96
4.00
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
f1 (ppm)

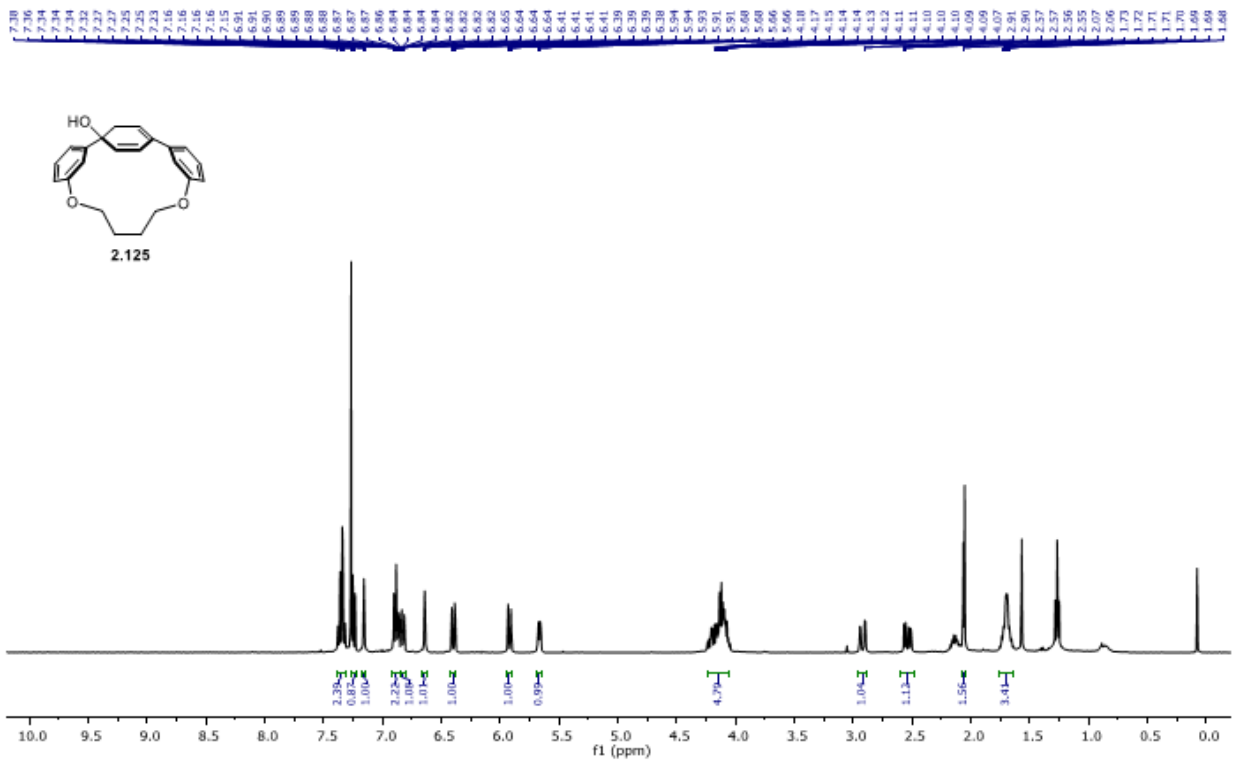

156.39
144.88
144.61
130.30
117.76
115.83
115.74
67.36
22.86
O
O
2.113
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

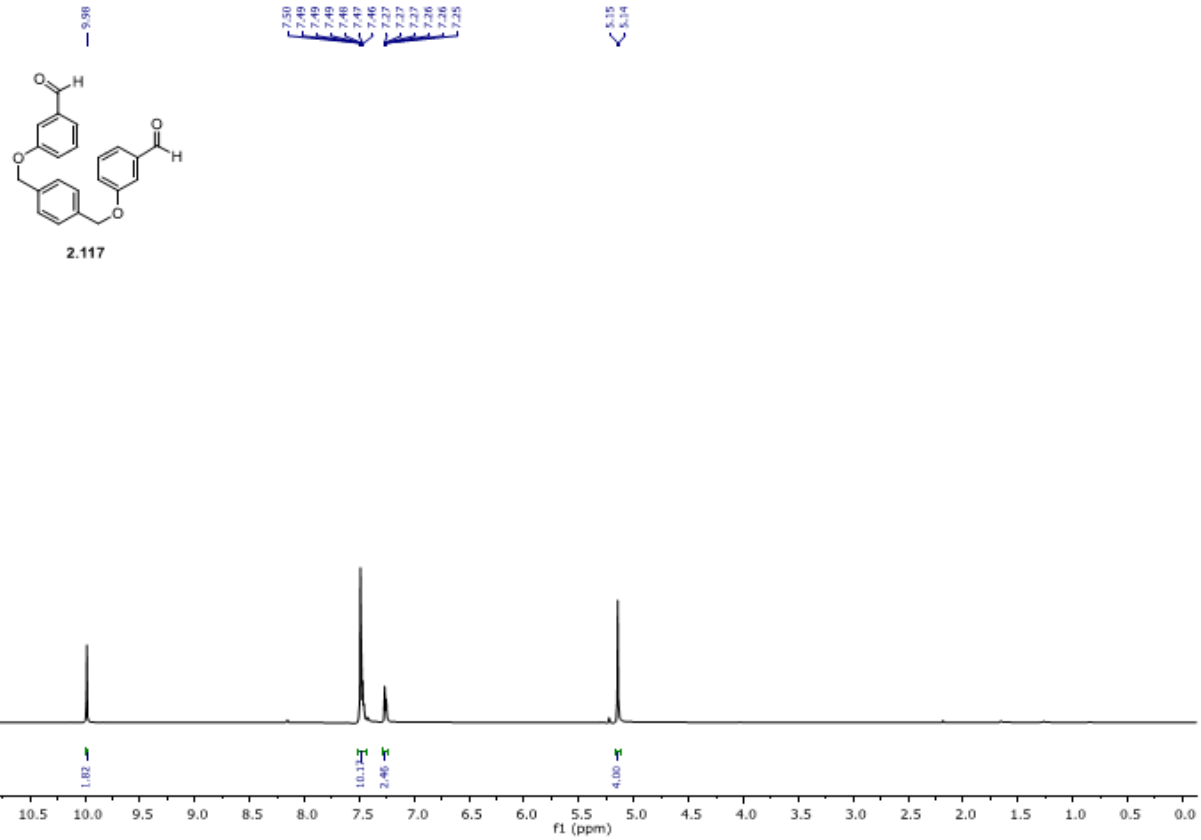

8.30
7.67
7.66
7.65
7.65
7.49
7.48
7.47
7.37
7.36
7.35
7.33
7.32
7.27
6.93
6.92
6.92
6.91
6.91
4.31
4.30
4.29
4.29
4.28
2.09
2.09
2.08
2.07
2.07
0.94
1.81
1.05
3.81
1.91
1.93
4.00
4.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

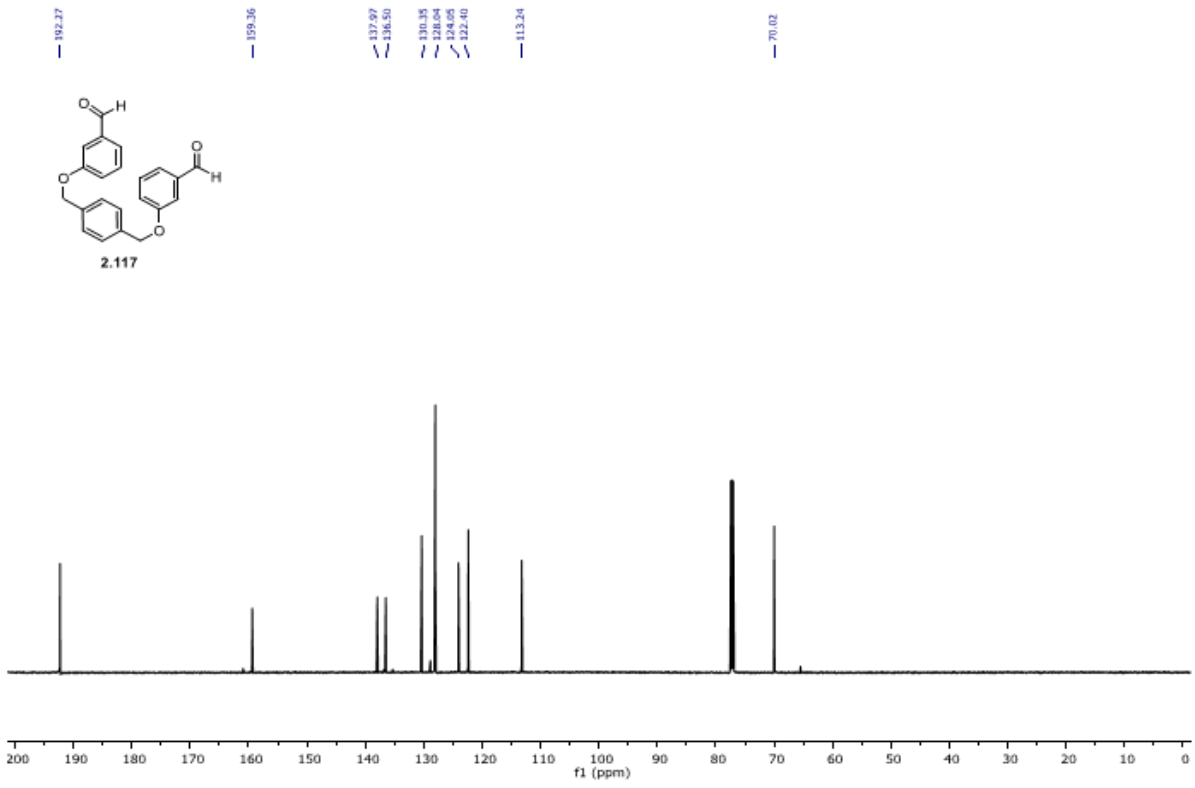
2.112

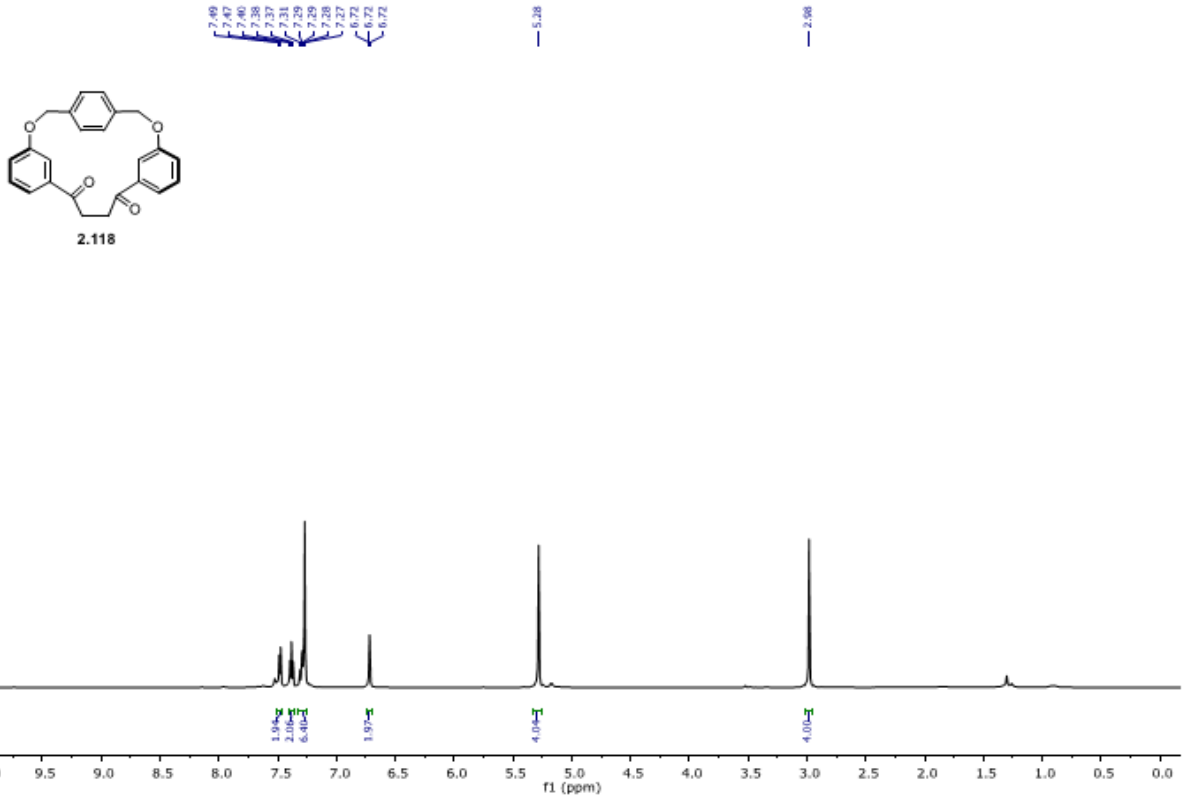

158.73
141.71
140.49
131.38
130.47
129.34
124.04
117.44
116.85
114.30
69.01
24.25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

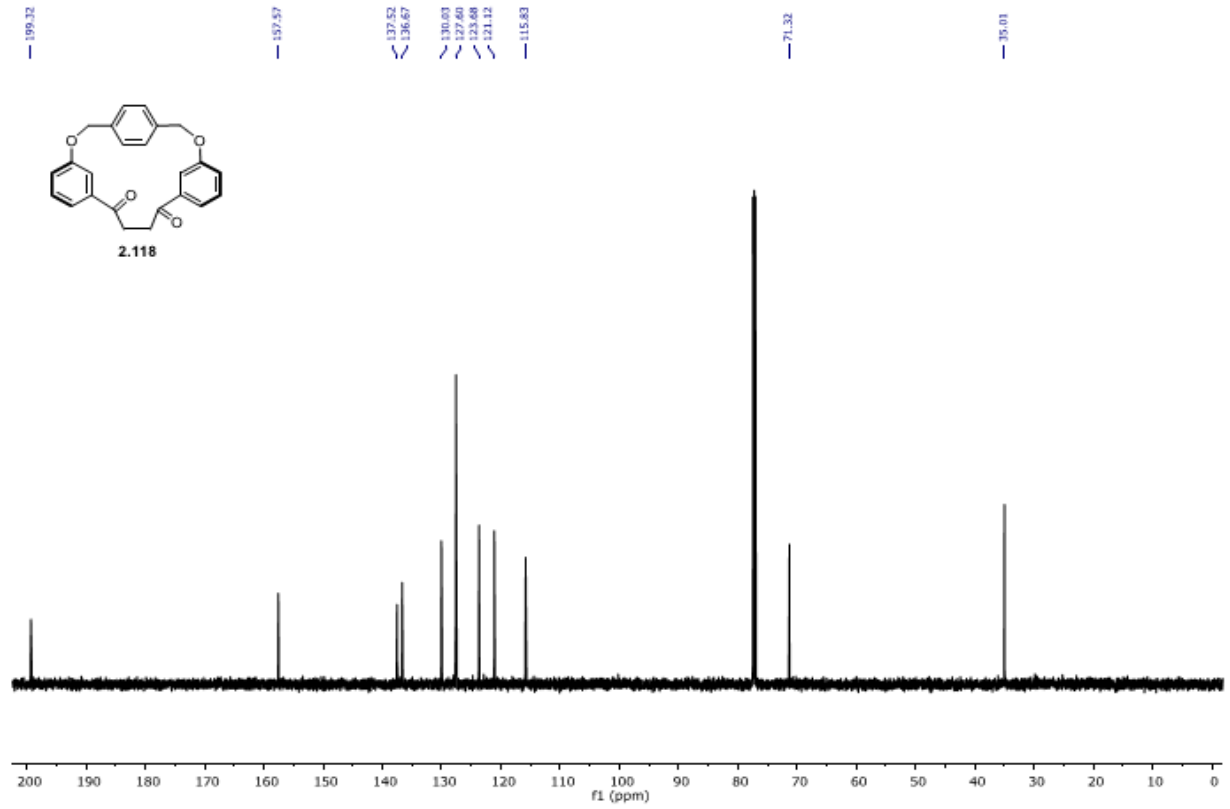
2.112

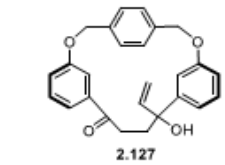

HO
O
O
2.125
2.39
0.87
1.00
2.25
1.08
1.01
1.00
1.00
0.99
4.79
1.04
1.12
1.56
3.41
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


9.98
7.50
7.49
7.49
7.49
7.48
7.47
7.46
7.46
7.27
7.27
7.27
7.26
7.26
7.25
5.15
5.14
O
H
O
O
H
O
2.117
1.82
10.13
2.46
4.00
11.0
10.5
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
f1 (ppm)

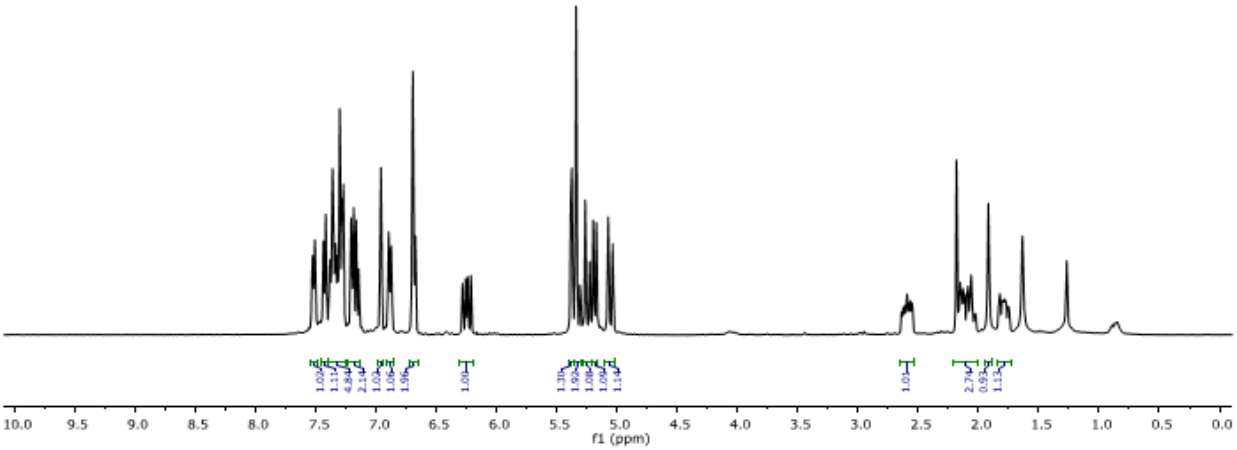

192.27
159.36
137.97
136.50
130.35
128.04
124.65
122.40
113.24
70.02
O
H
O
O
H
O
2.117
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

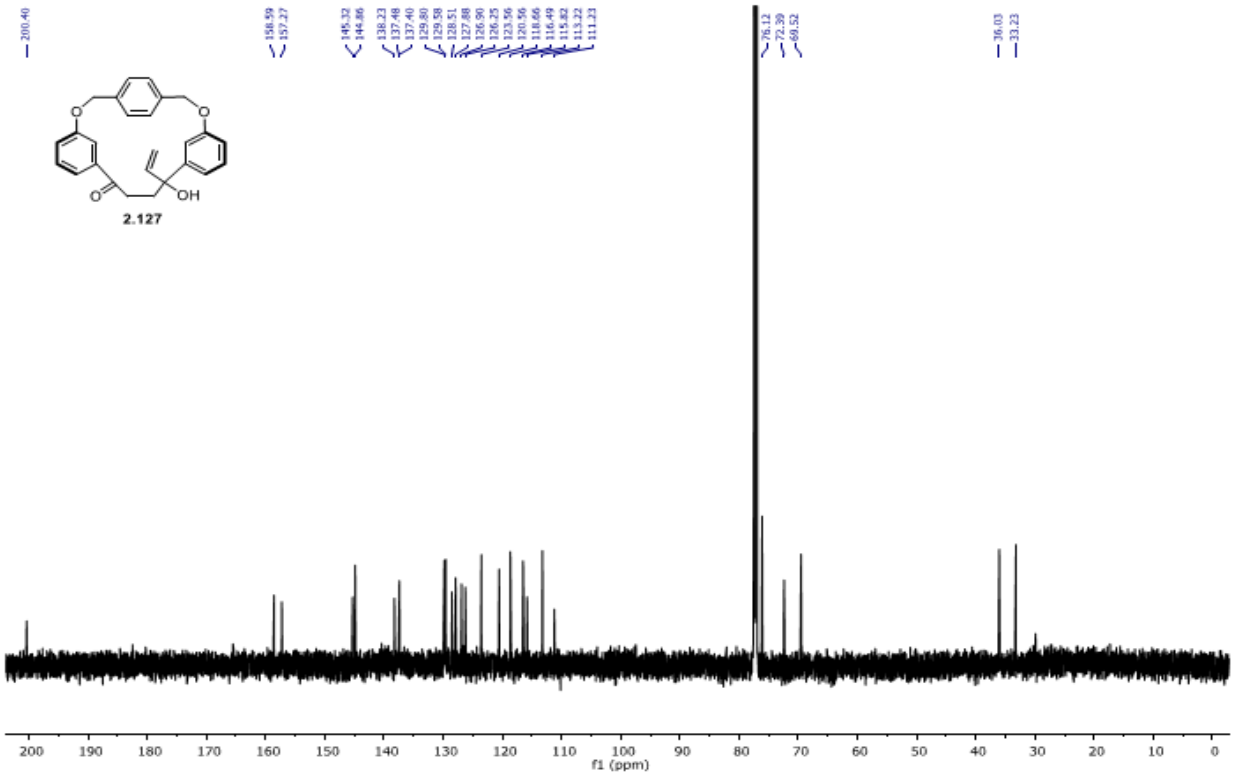

7.49
7.47
7.40
7.38
7.37
7.31
7.29
7.29
7.28
7.27
6.72
6.72
6.72
5.28
2.98
2.118
1.96
2.08
6.40
1.97
4.04
4.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


199.32
157.57
137.52
136.67
130.03
127.60
123.68
121.12
115.83
71.32
35.01
2.118
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

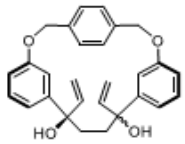


2.127



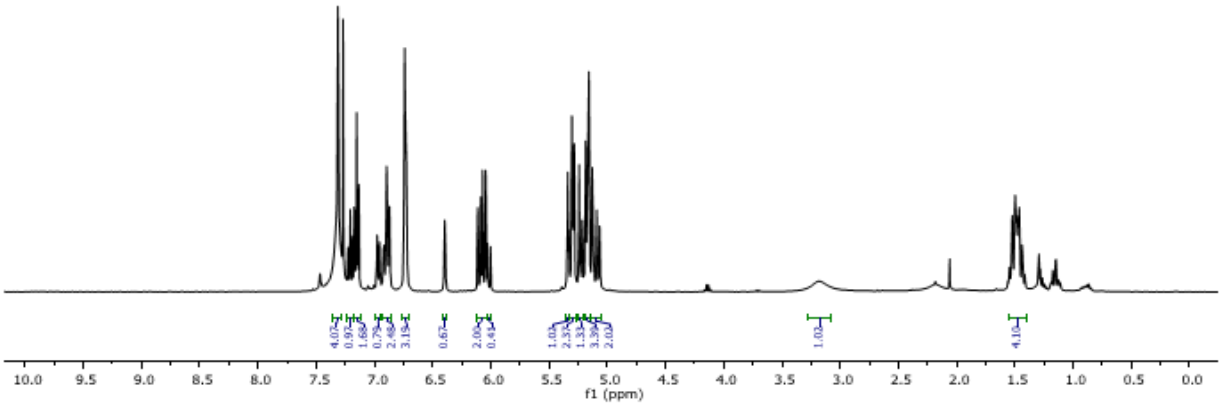


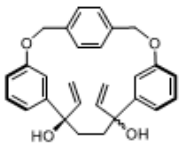
2.127



2.119

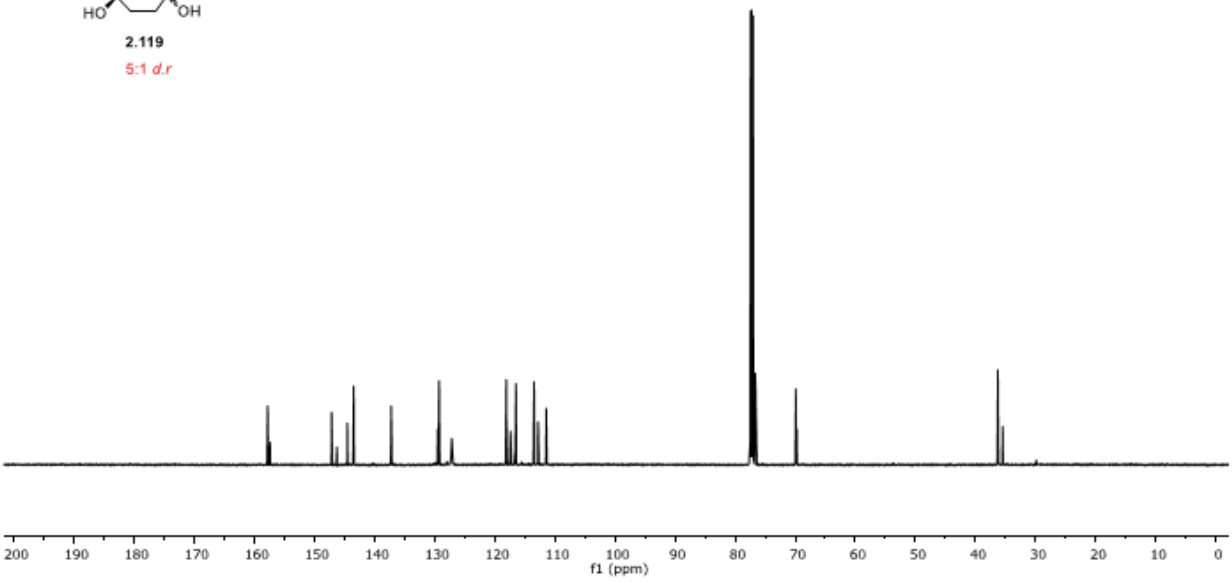
5:1 *d.r*

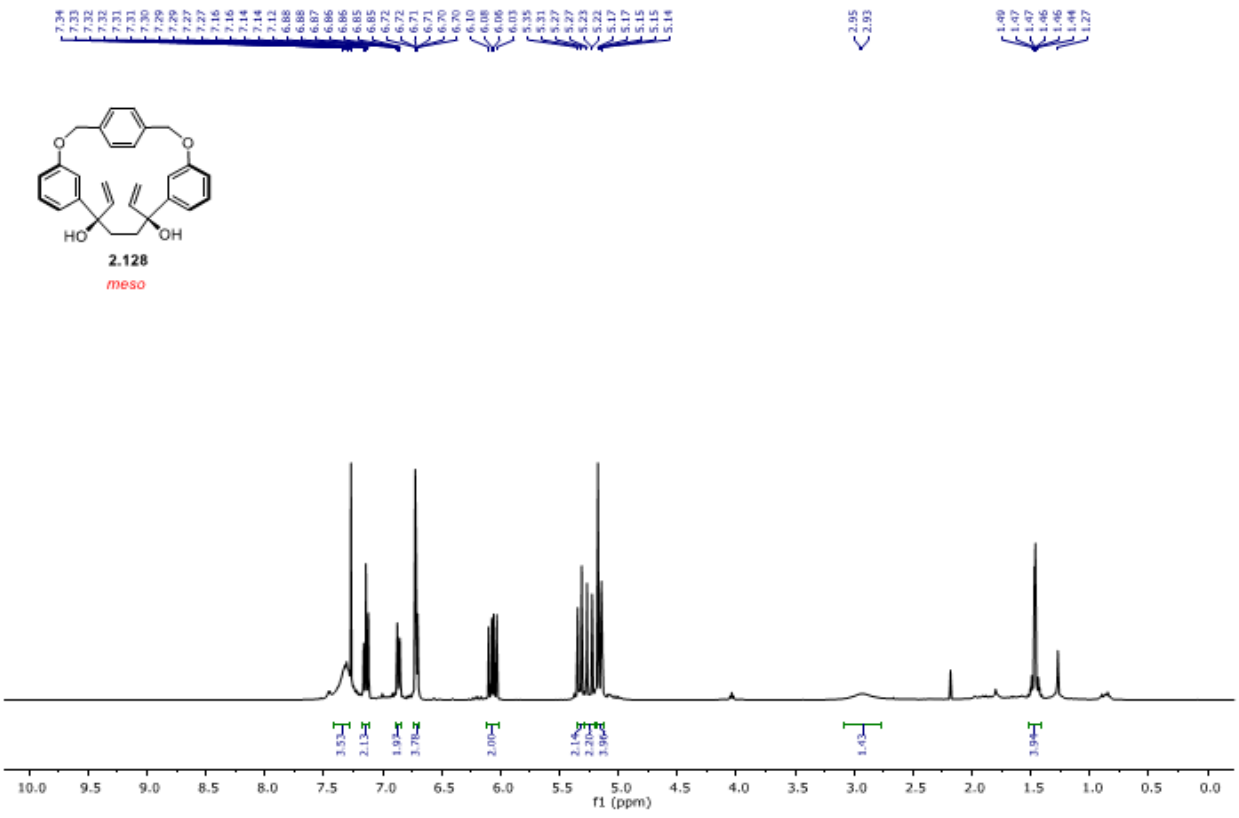


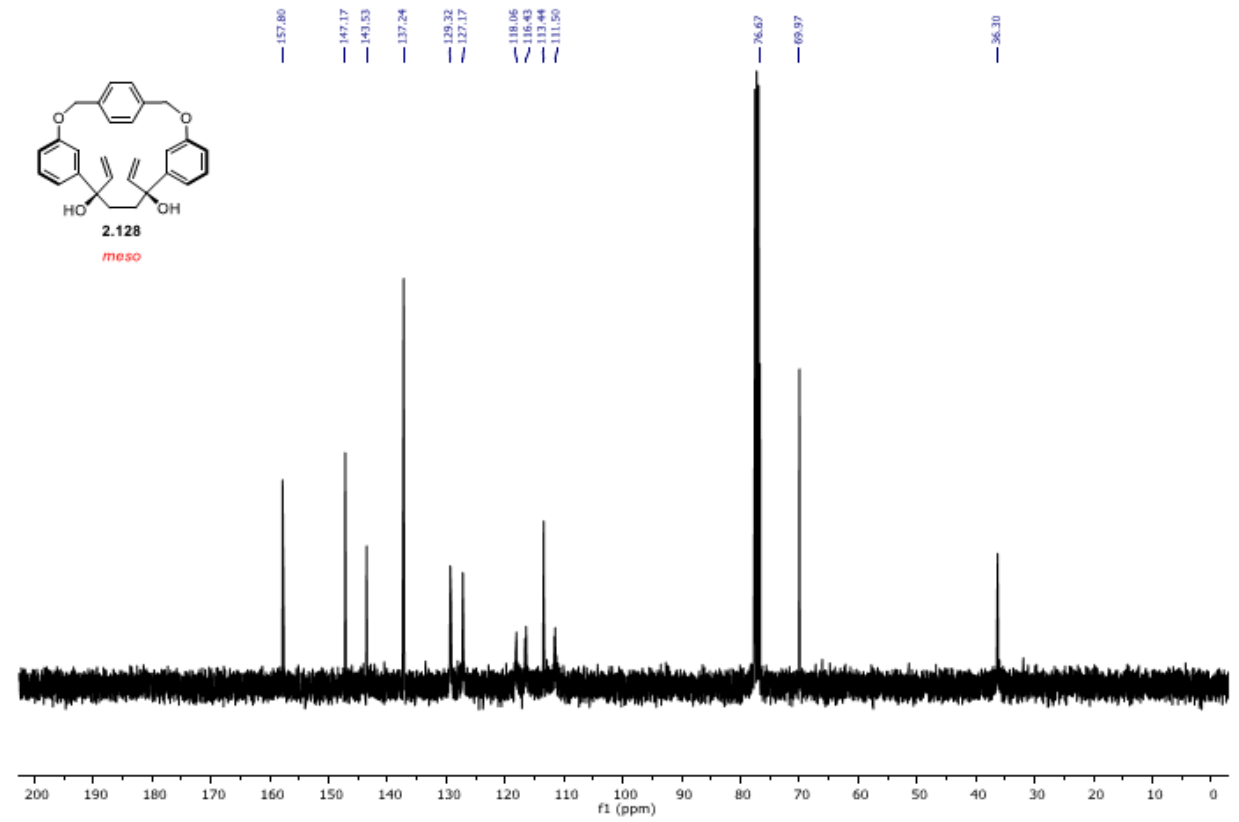


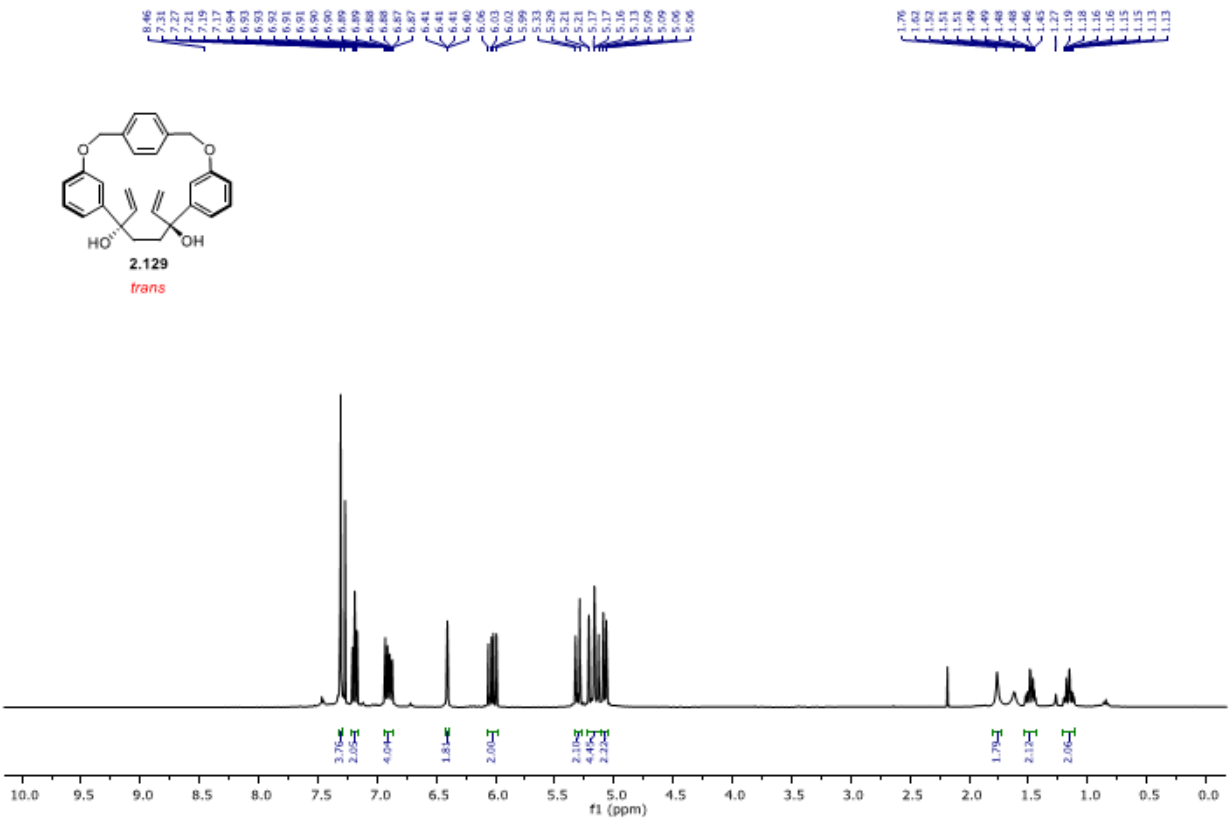
2.119

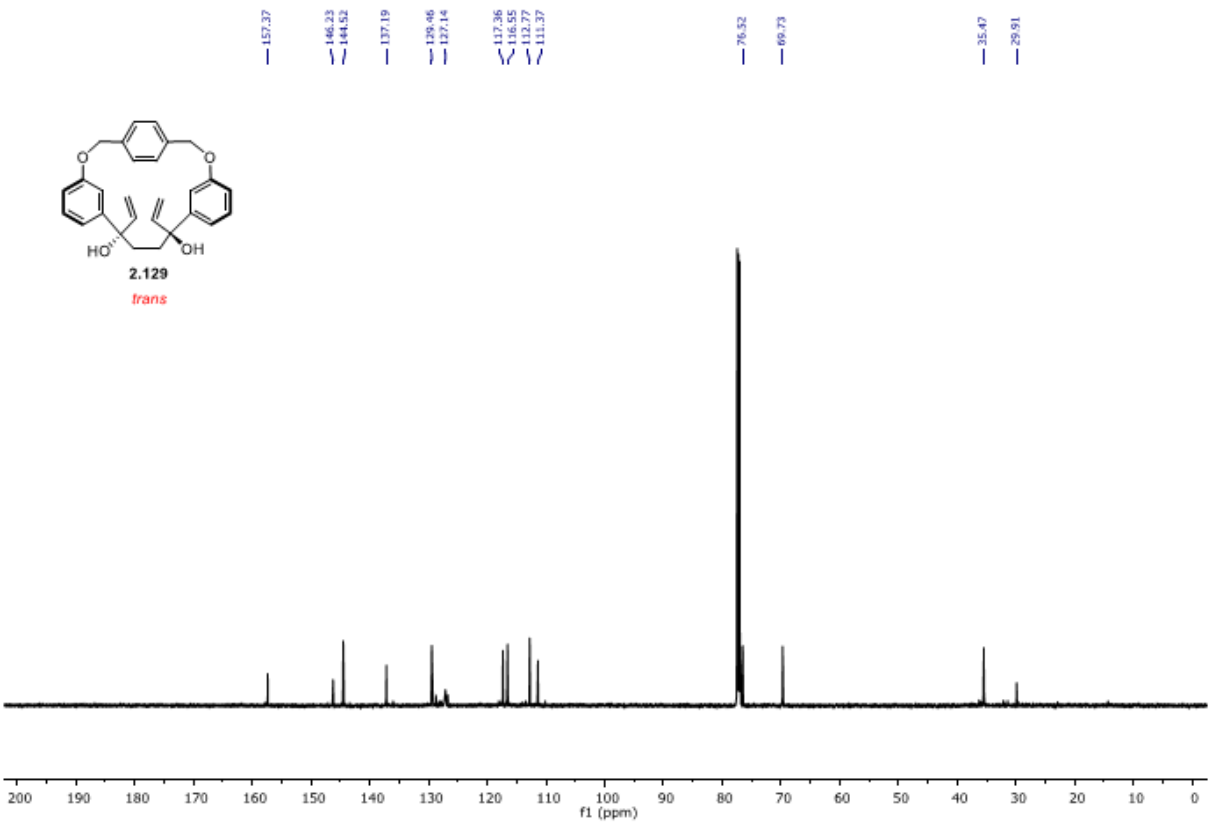
5:1 *d.r*




HO
OH
2.128
meso
f1 (ppm)


HO
OH
2.128
meso
f1 (ppm)

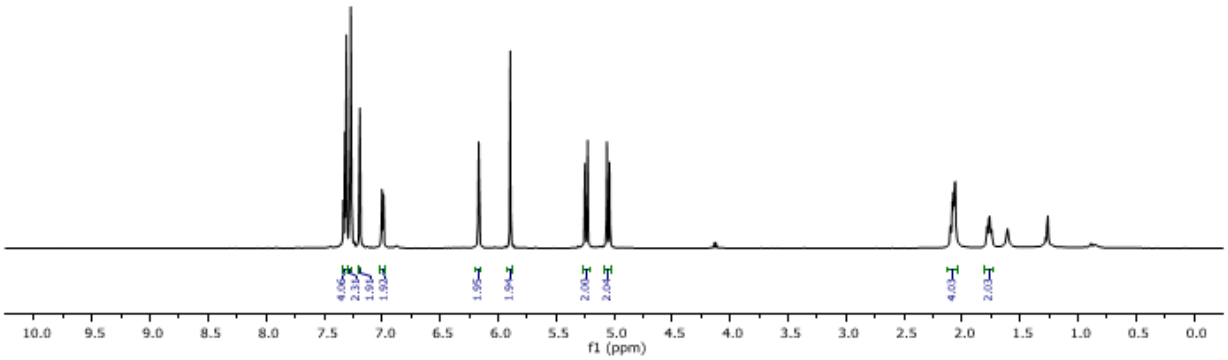

HO
OH
2.129
trans
f1 (ppm)

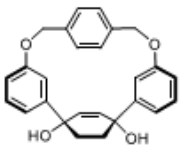

HO
OH
2.129
trans
f1 (ppm)


7.34
7.32
7.31
7.31
7.28
7.28
7.28
7.27
7.26
7.19
7.19
7.01
7.00
7.00
6.99
6.99
6.99
6.99
6.17
6.17
6.16
5.89
5.25
5.23
5.06
5.04
2.08
2.08
2.06
2.06
1.77
1.76

HO
OH

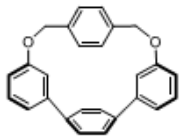
2.120


4.06
2.31
1.91
1.92
1.95
1.94
2.00
2.04
4.03
2.03
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
f1 (ppm)

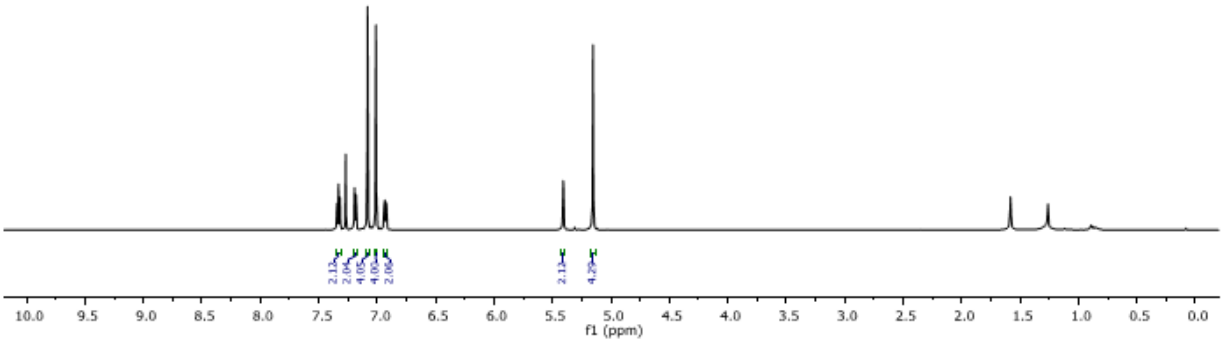

HO
OH

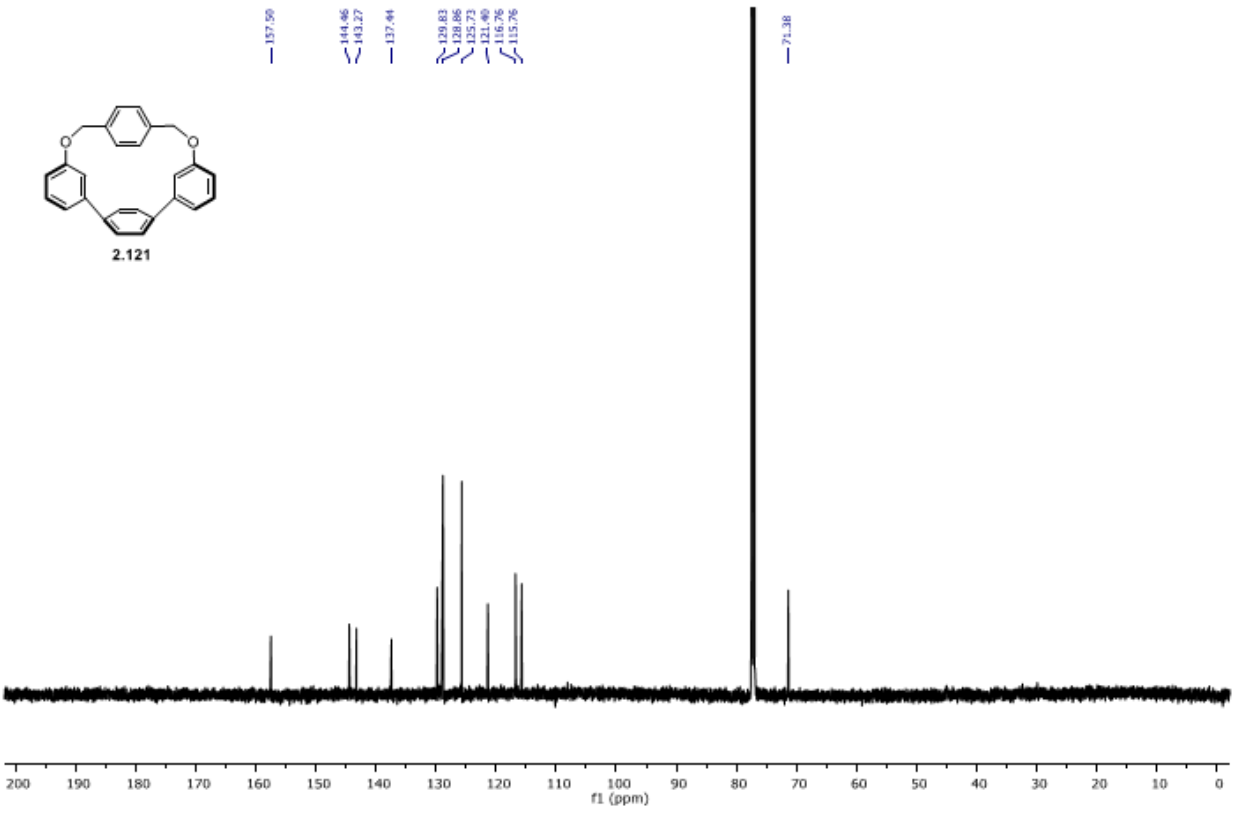
2.120

158.01
147.19
137.48
134.25
130.19
127.62
127.48
119.58
118.55
114.28
72.66
71.86
35.39
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

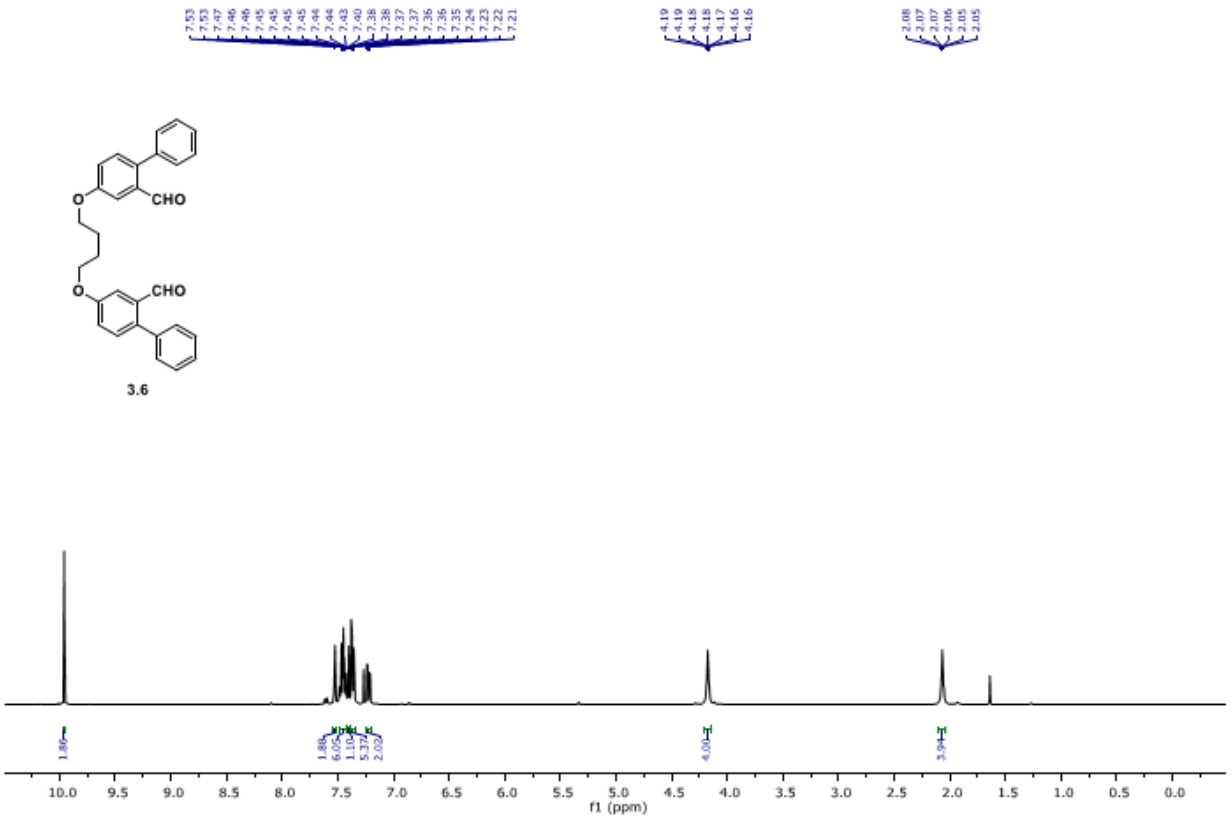


2.121





2.121


7.53
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7.45
7.44
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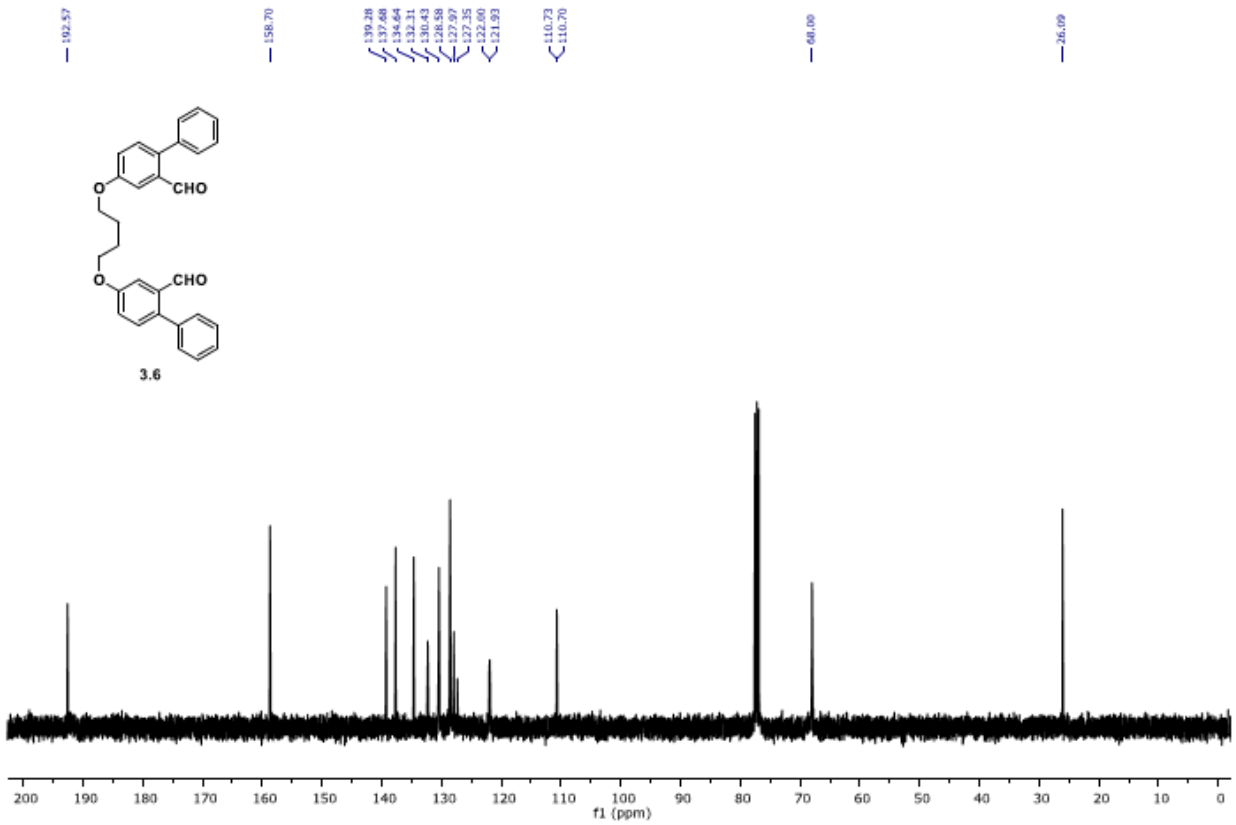
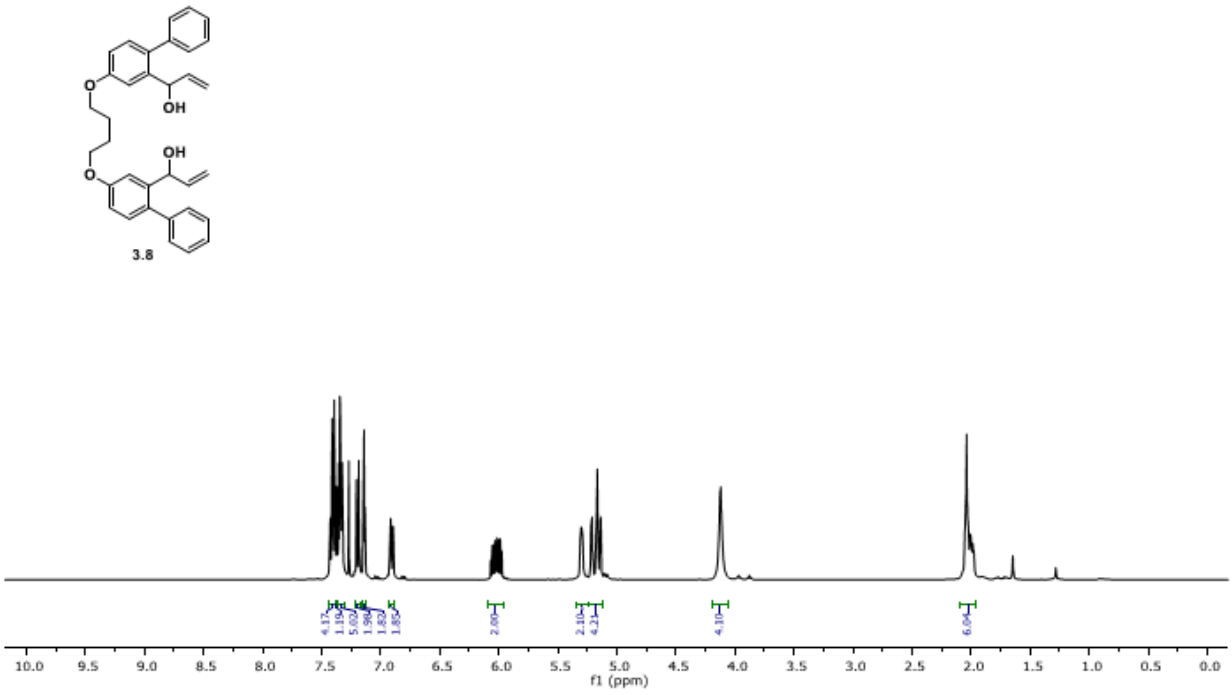
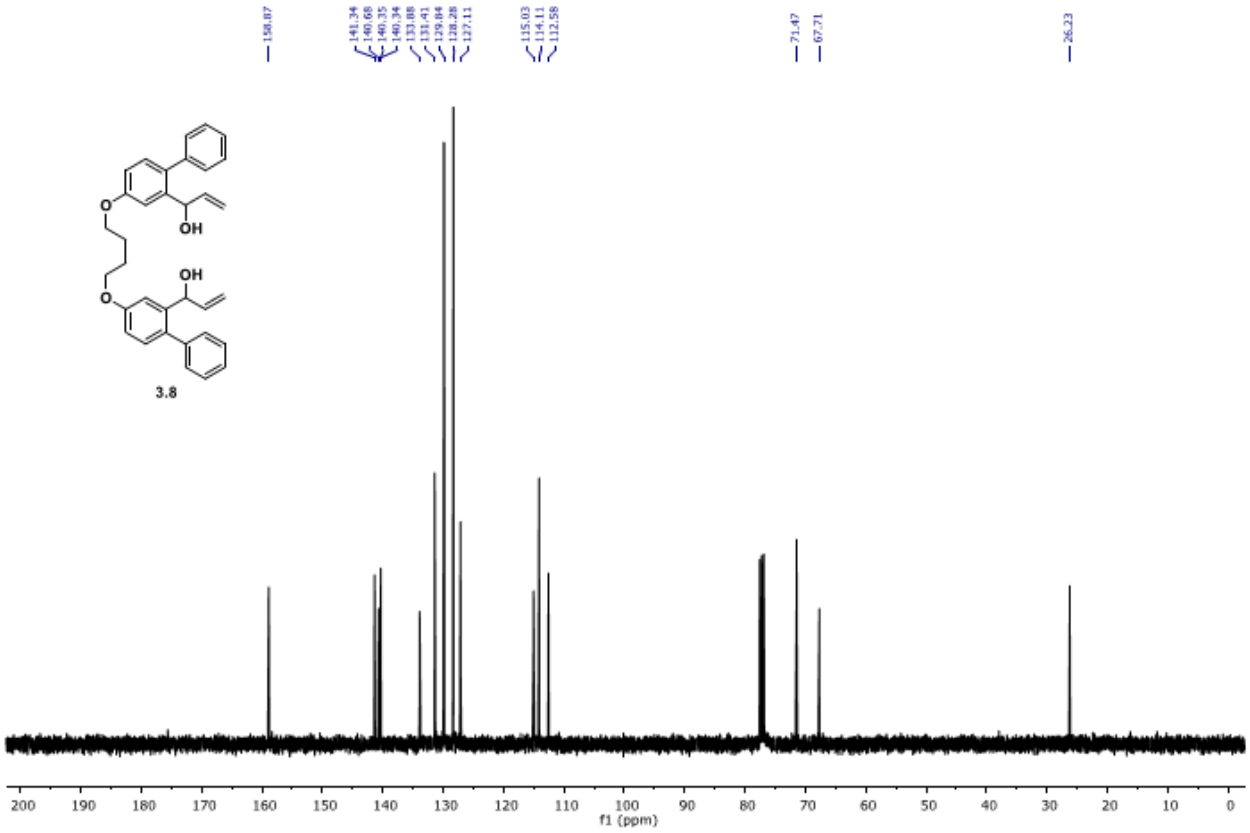
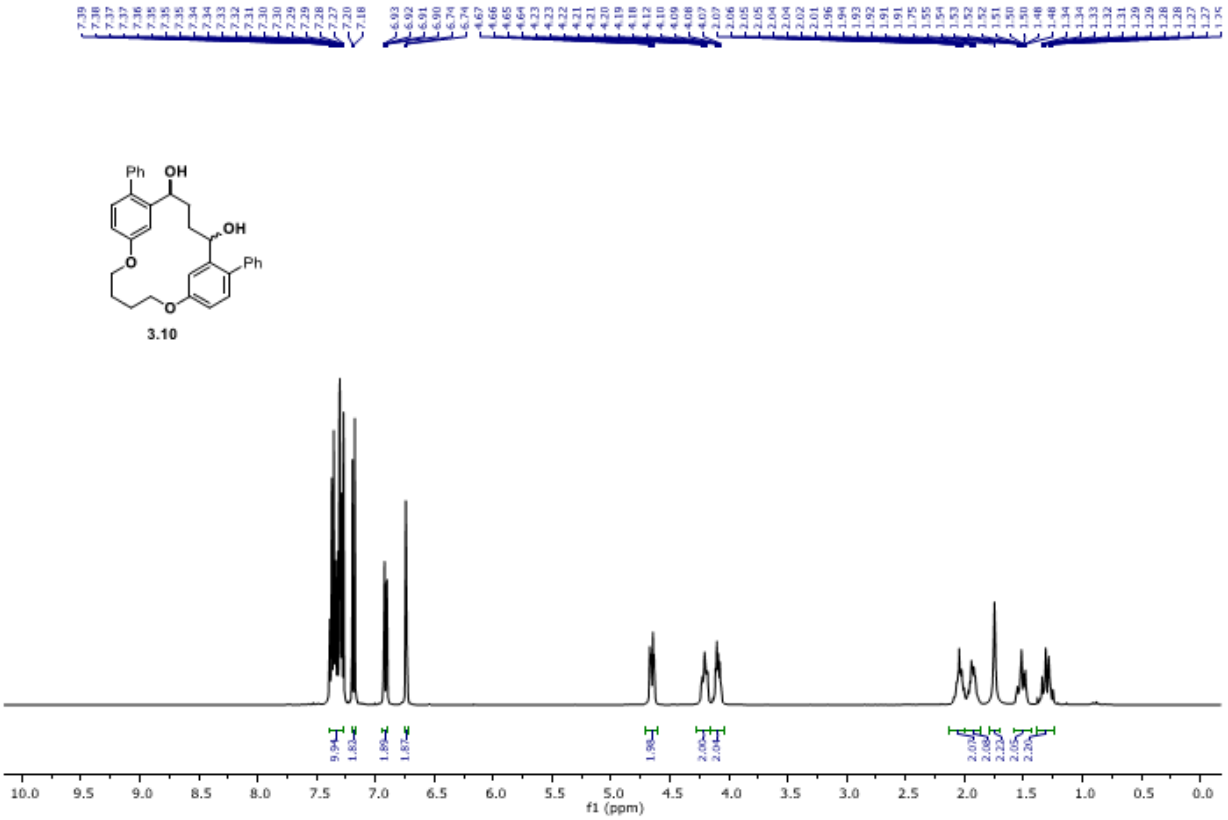
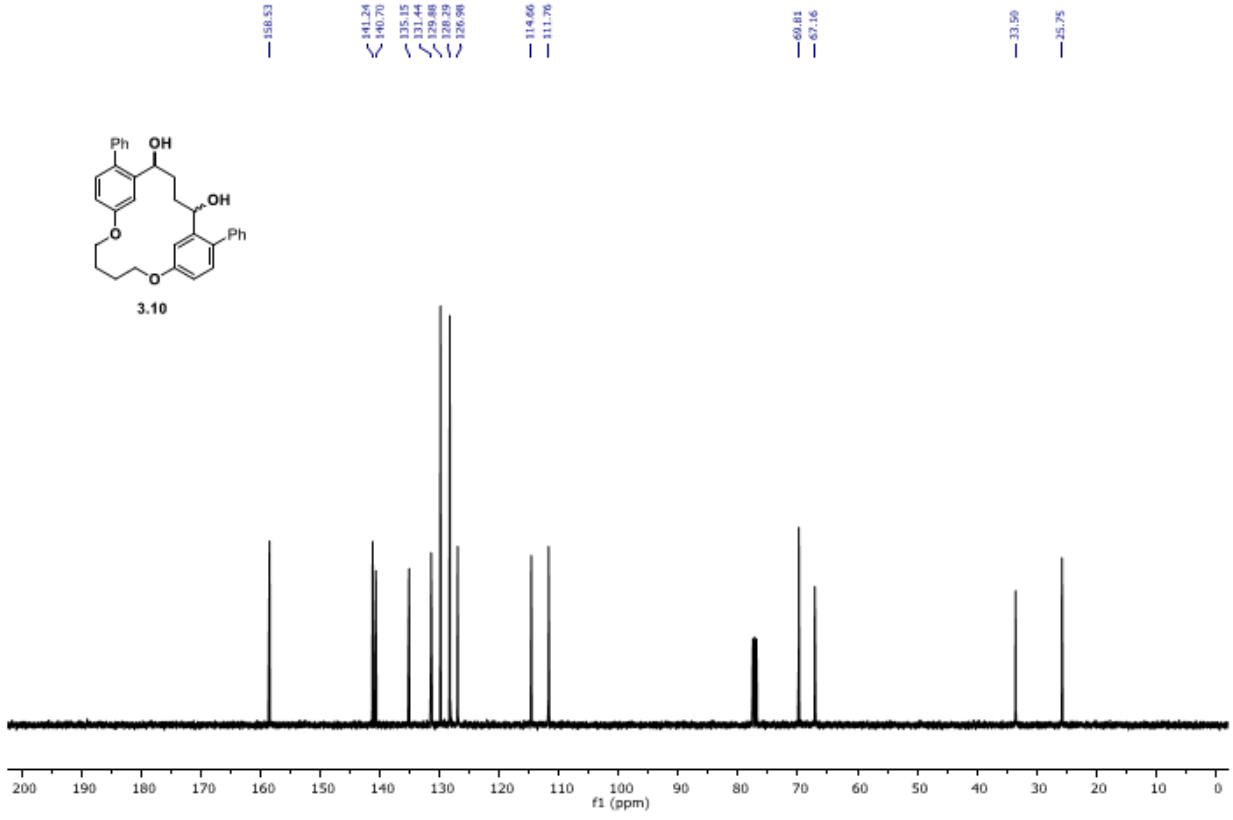
7.43
7.40
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.24
7.23
7.22
7.21
4.19
4.19
4.18
4.18
4.17
4.16
4.16
2.08
2.07
2.07
2.06
2.05
2.05
O
CHO
O
CHO
3.6
1.86
1.88
6.05
1.10
5.37
2.02
4.00
3.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

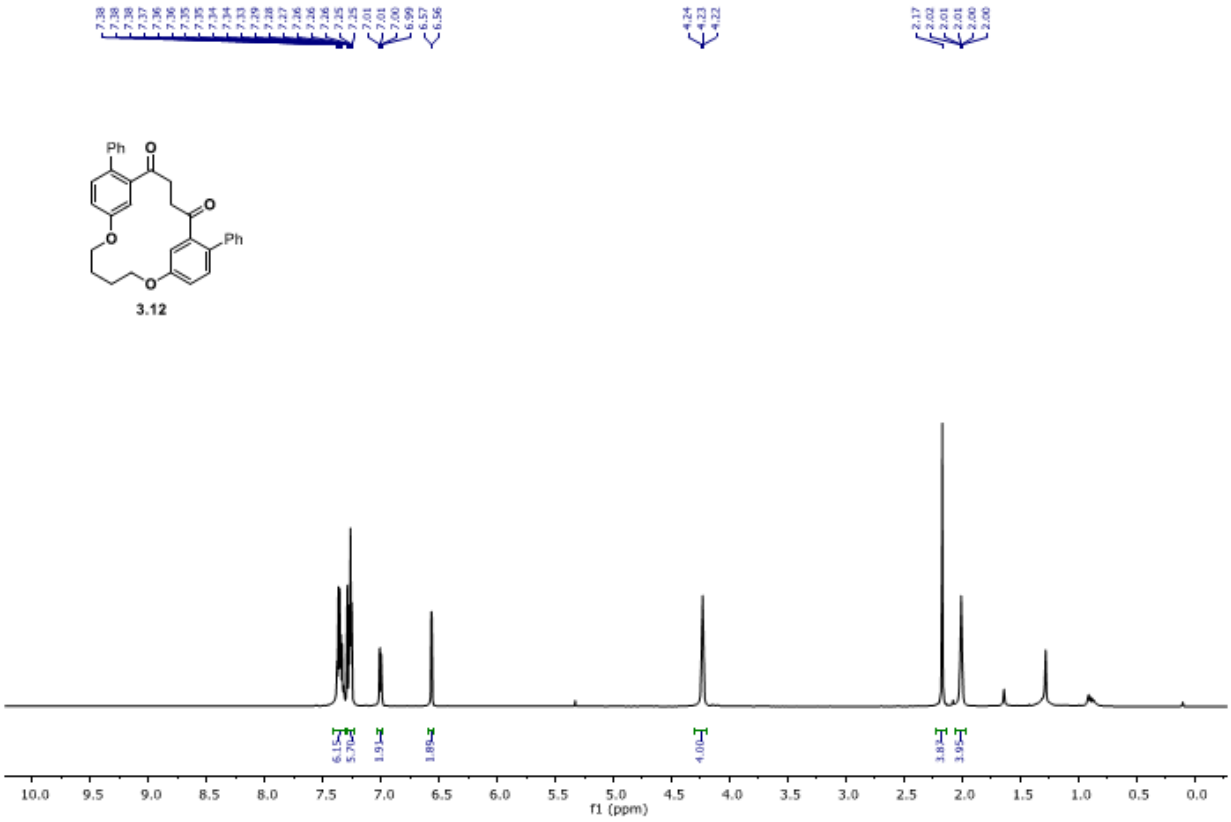

192.57
158.70
139.28
137.68
134.64
132.31
130.43
128.58
127.97
127.35
122.00
121.93
110.73
110.70
68.00
26.09
CHO
CHO
3.6
f1 (ppm)

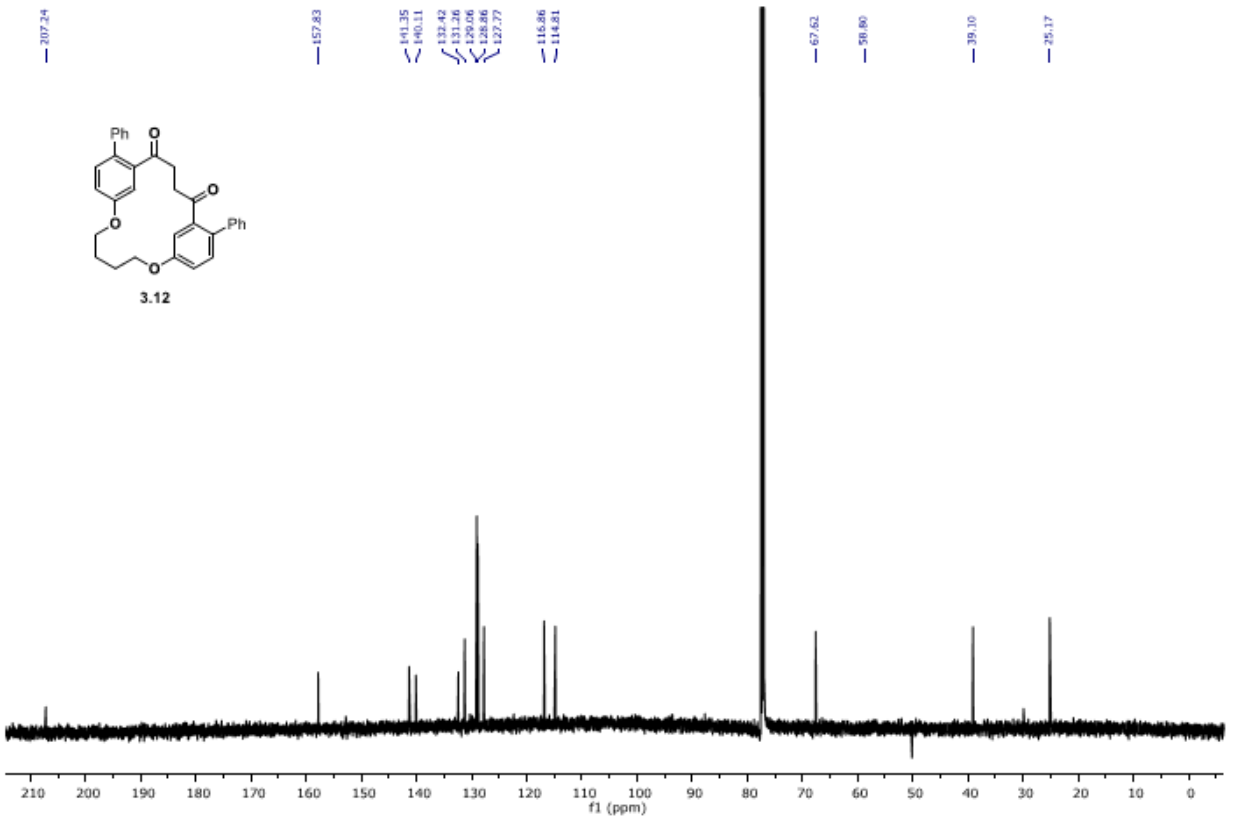

OH
OH
3.8
f1 (ppm)

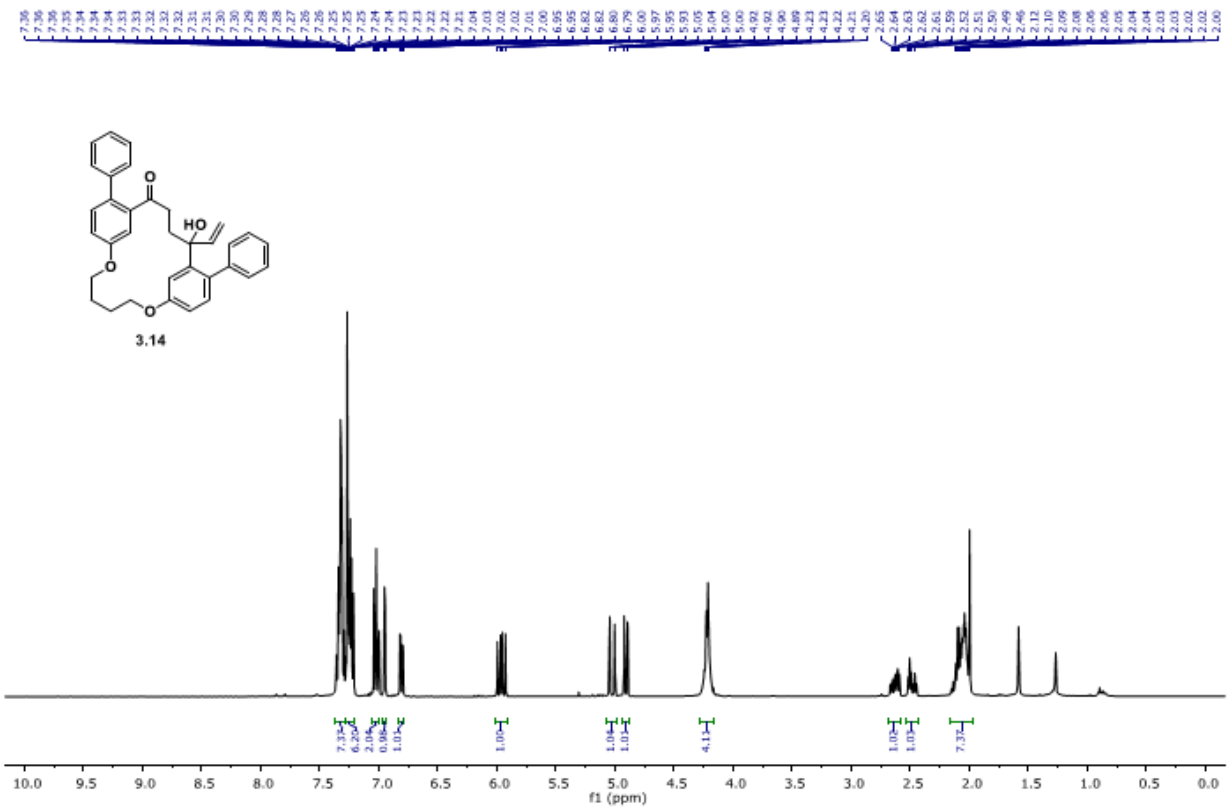

158.87
141.34
140.68
140.35
140.34
133.88
131.41
129.84
128.28
127.11
115.03
114.11
112.58
71.47
67.71
26.23
OH
OH
3.8
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

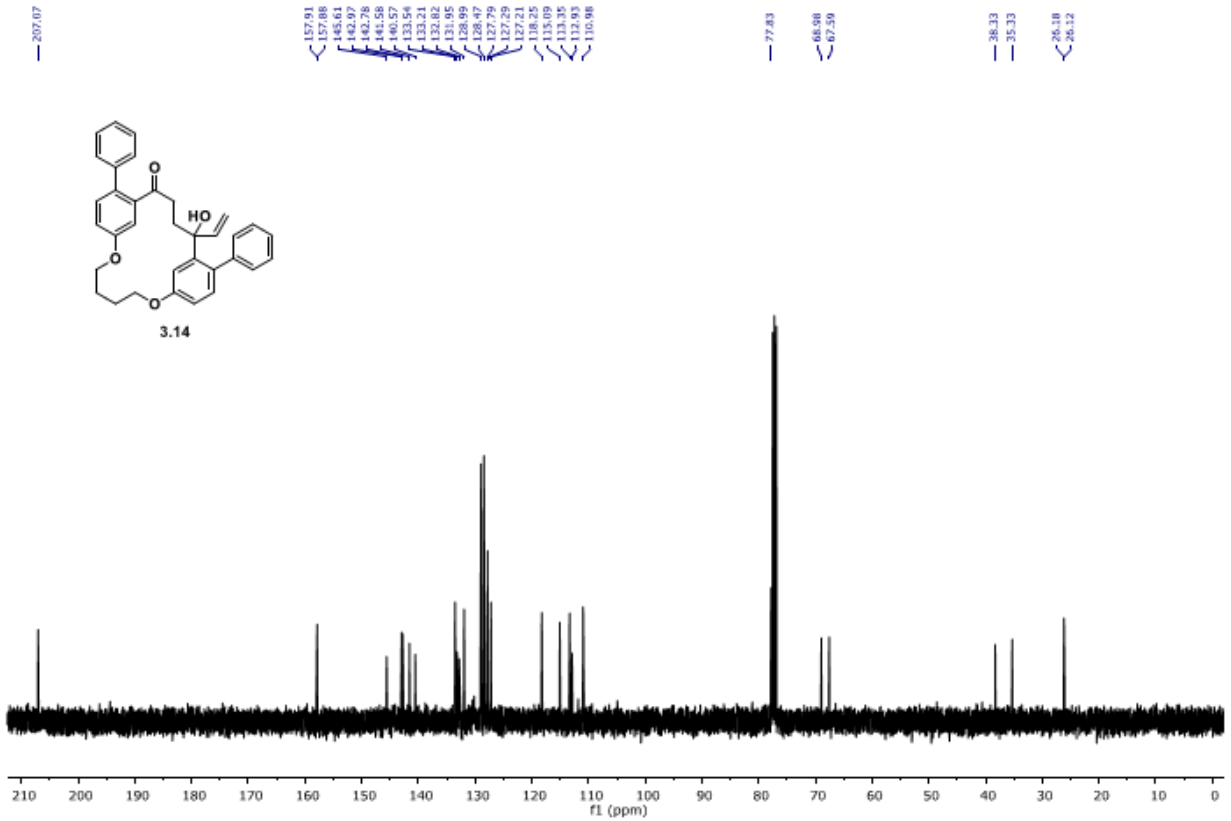

Ph
OH
OH
Ph
O
O
3.10
f1 (ppm)

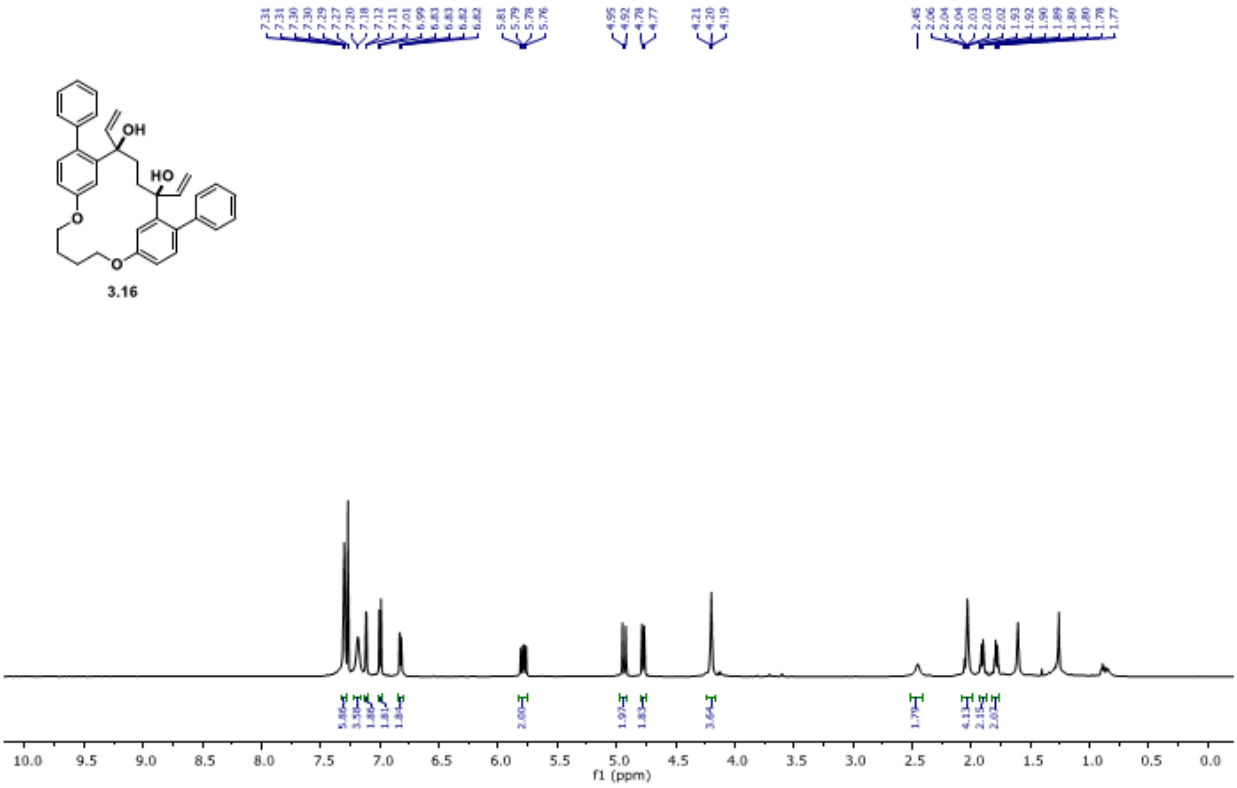

Ph
OH
OH
Ph
O
O
3.10
f1 (ppm)

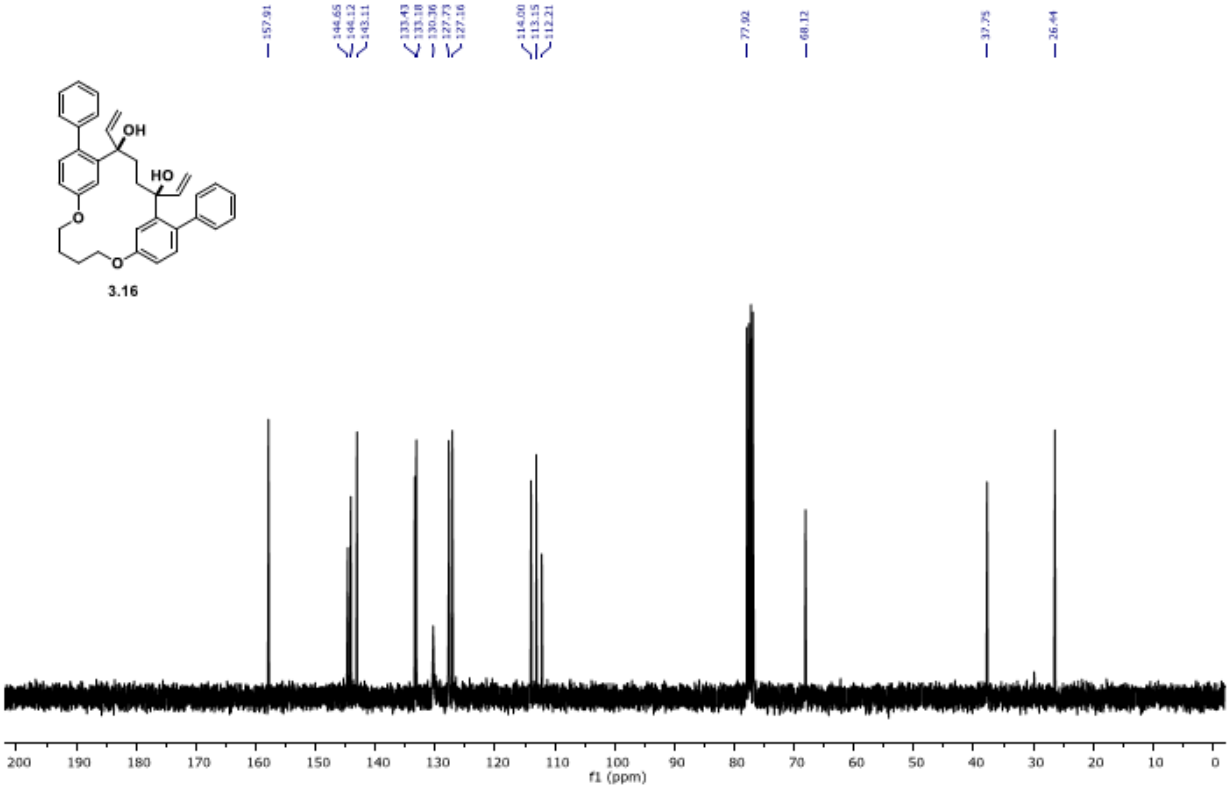

Ph
O
O
O
O
Ph
3.12
f1 (ppm)


Ph
O
O
O
O
Ph
3.12
f1 (ppm)

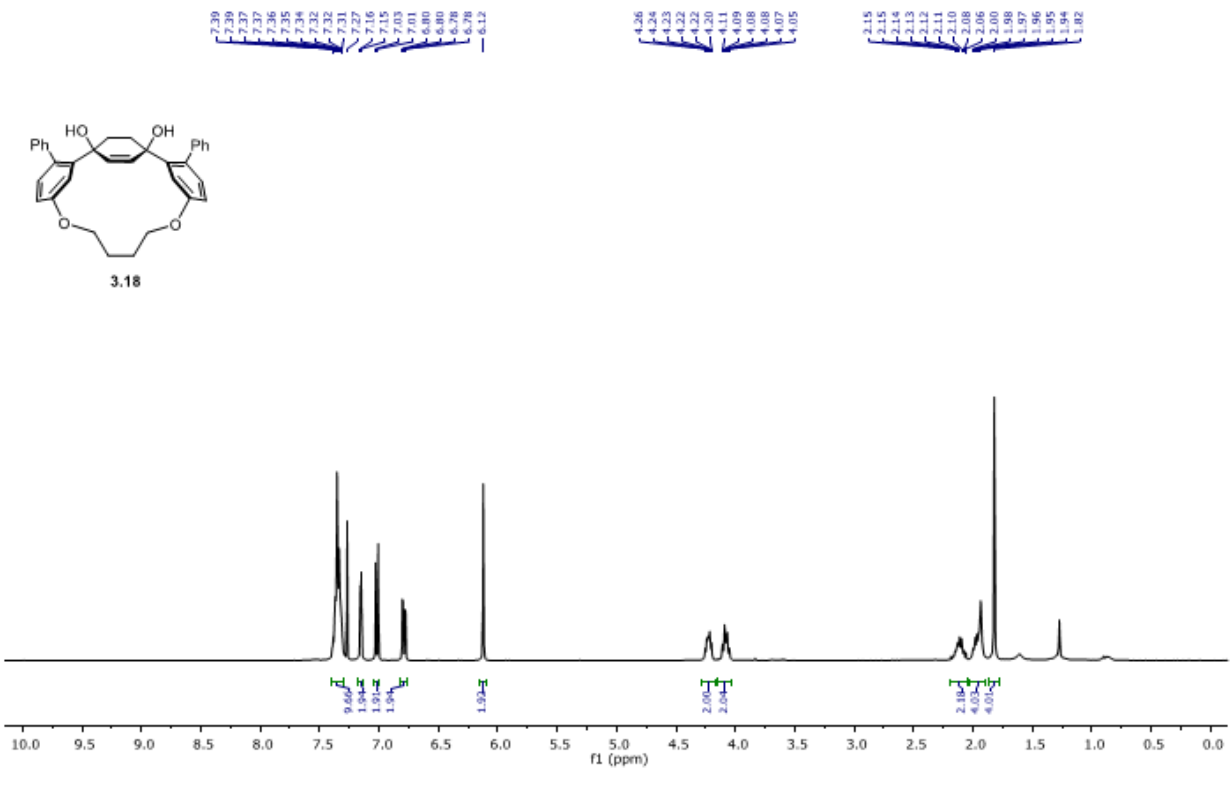

O
HO
O
O
3.14
7.37
6.23
2.04
0.98
1.01
1.00
1.04
1.01
4.11
1.02
1.03
7.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


207.07
157.91
157.88
145.61
142.97
142.78
141.58
140.57
133.54
133.21
132.82
131.95
128.99
128.47
127.79
127.29
127.21
118.25
115.09
113.35
112.93
110.98
77.83
68.98
67.59
38.33
35.33
26.18
26.12
O
HO
O
O
3.14
f1 (ppm)

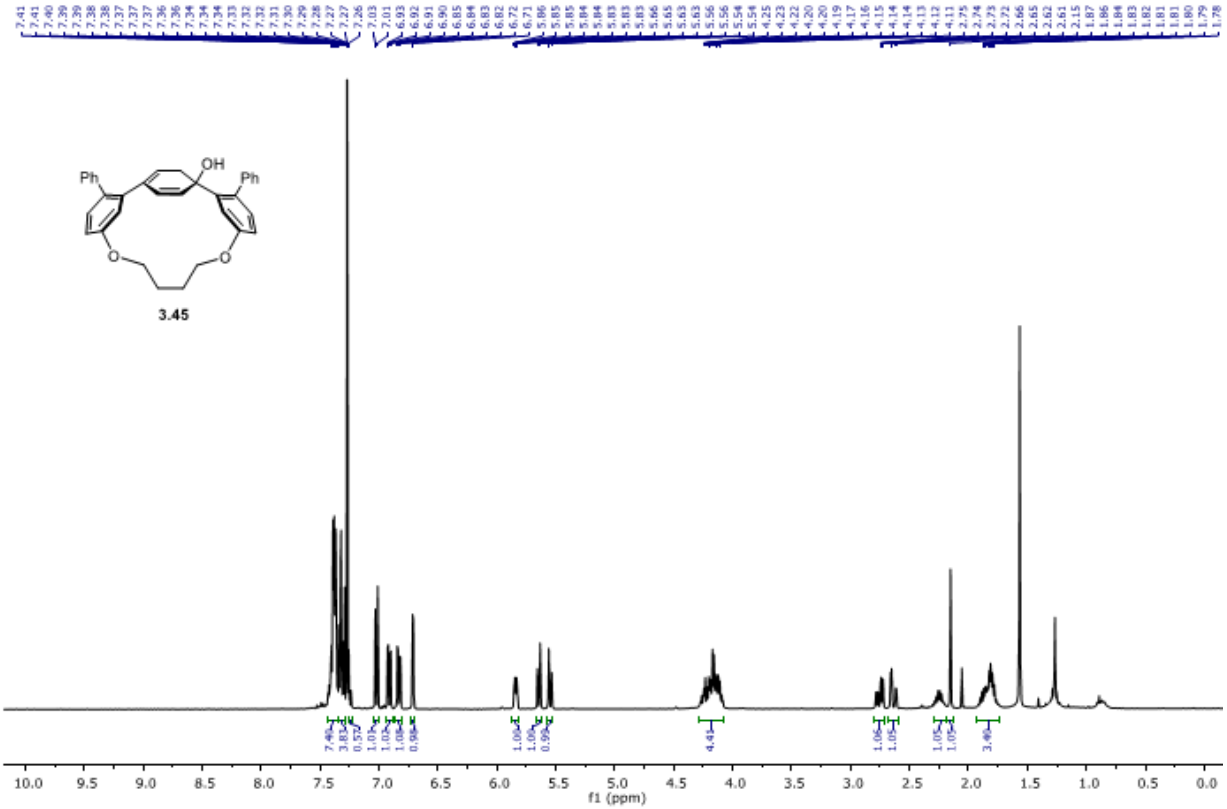

7.31
7.31
7.30
7.30
7.29
7.27
7.20
7.18
7.12
7.11
7.01
6.99
6.83
6.83
6.82
6.82
5.81
5.79
5.78
5.76
4.95
4.92
4.78
4.77
4.21
4.20
4.19
2.45
2.06
2.04
2.04
2.03
2.03
2.02
1.93
1.92
1.90
1.89
1.80
1.80
1.78
1.77
OH
HO
O
O
3.16
5.86
3.59
1.86
1.81
1.84
2.00
1.97
1.83
3.64
1.79
4.13
2.15
2.07
f1 (ppm)

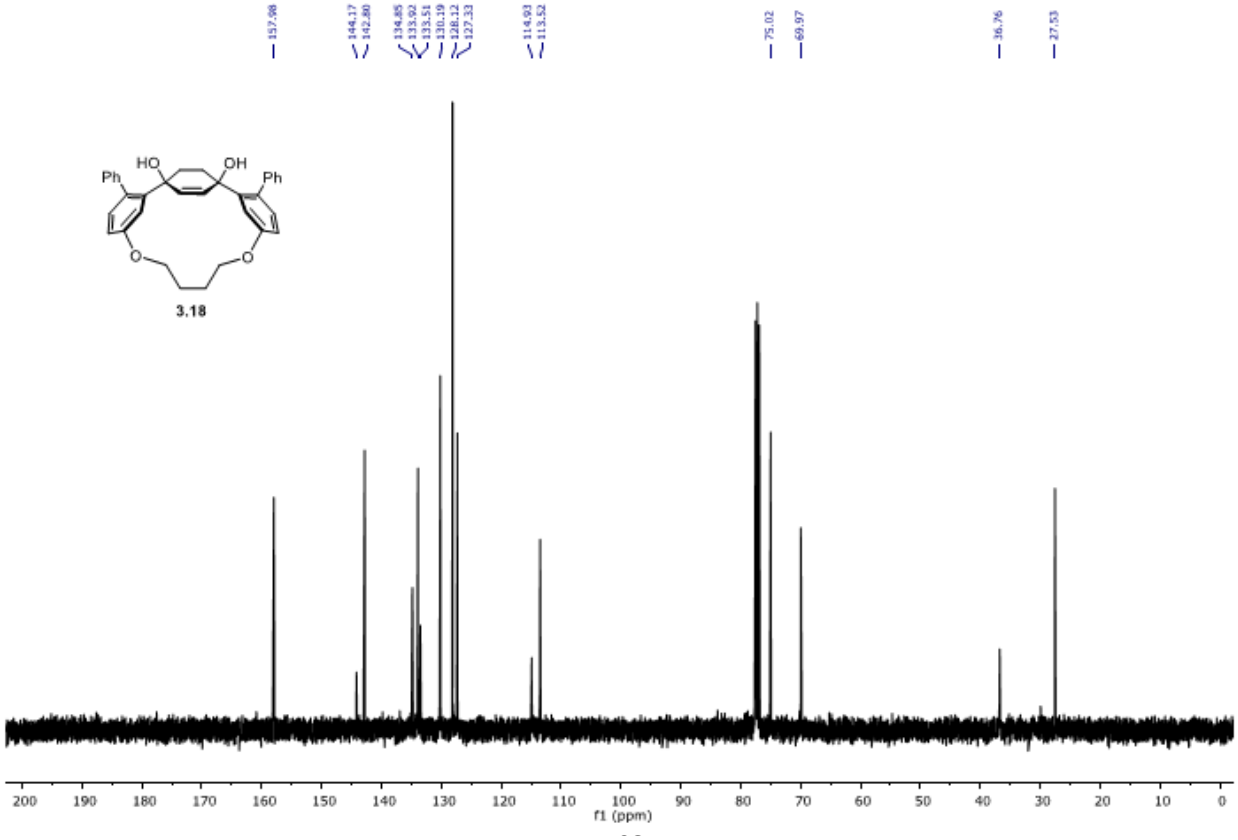

157.91
144.65
144.12
143.11
133.43
133.18
130.36
127.73
127.16
114.00
113.15
112.21
77.92
68.12
37.75
26.44
OH
HO
O
O
f1 (ppm)

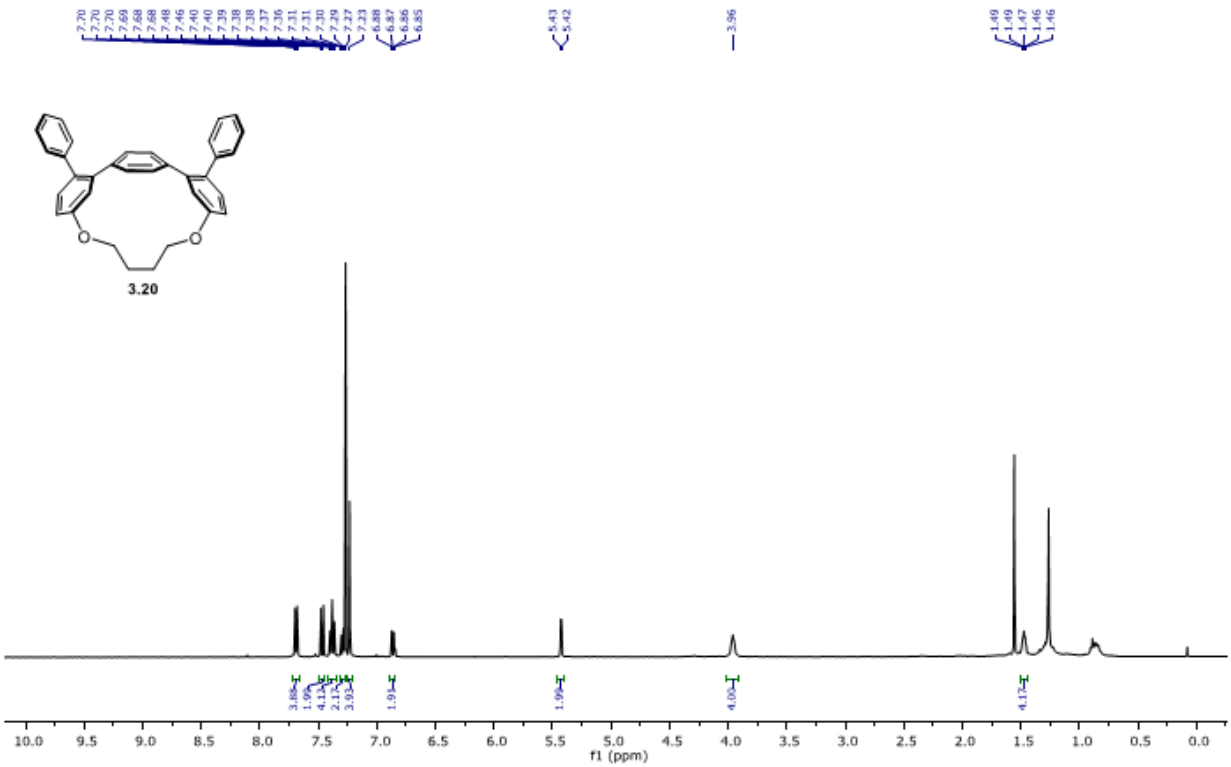
3.16

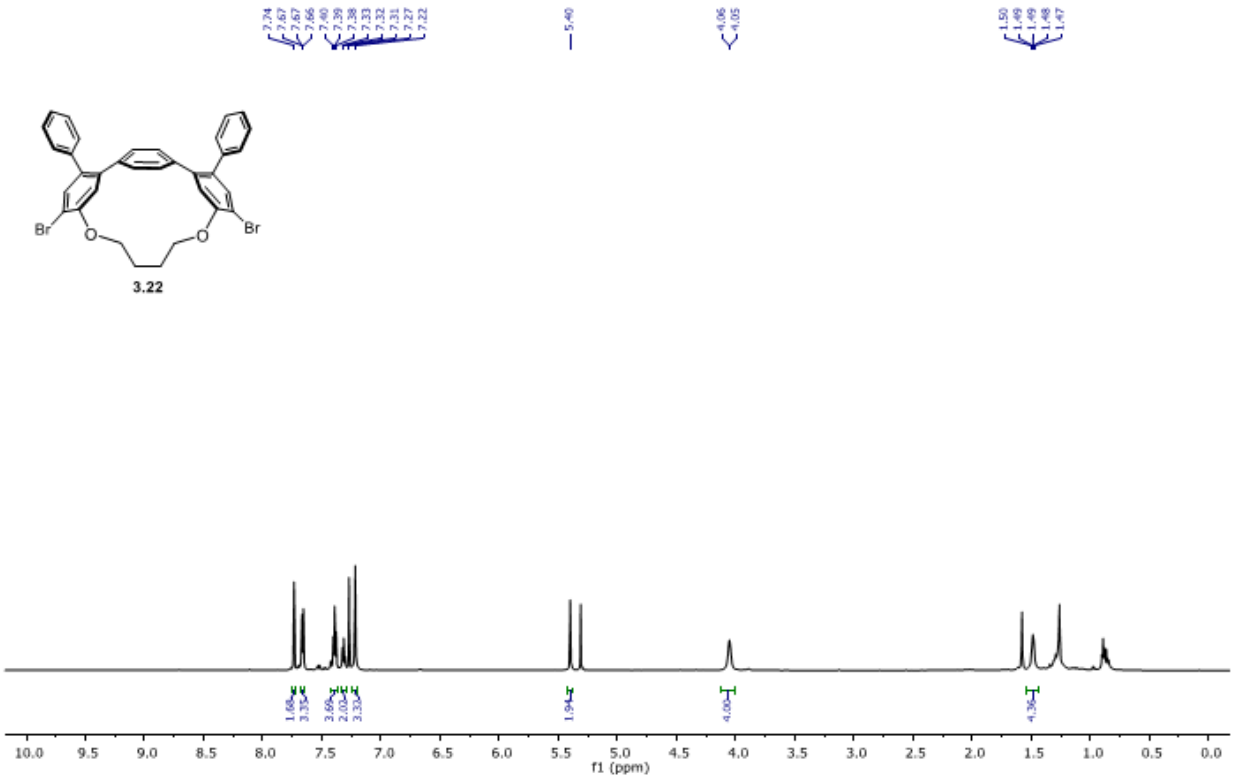

7.39
7.39
7.37
7.37
7.36
7.35
7.34
7.32
7.32
7.31
7.27
7.16
7.15
7.03
7.01
6.80
6.80
6.78
6.78
6.12
4.26
4.24
4.23
4.22
4.22
4.20
4.11
4.09
4.08
4.08
4.07
4.05
2.15
2.15
2.14
2.13
2.12
2.11
2.10
2.08
2.06
2.00
1.98
1.97
1.96
1.95
1.94
1.82
HO
OH
Ph
Ph
O
O
f1 (ppm)

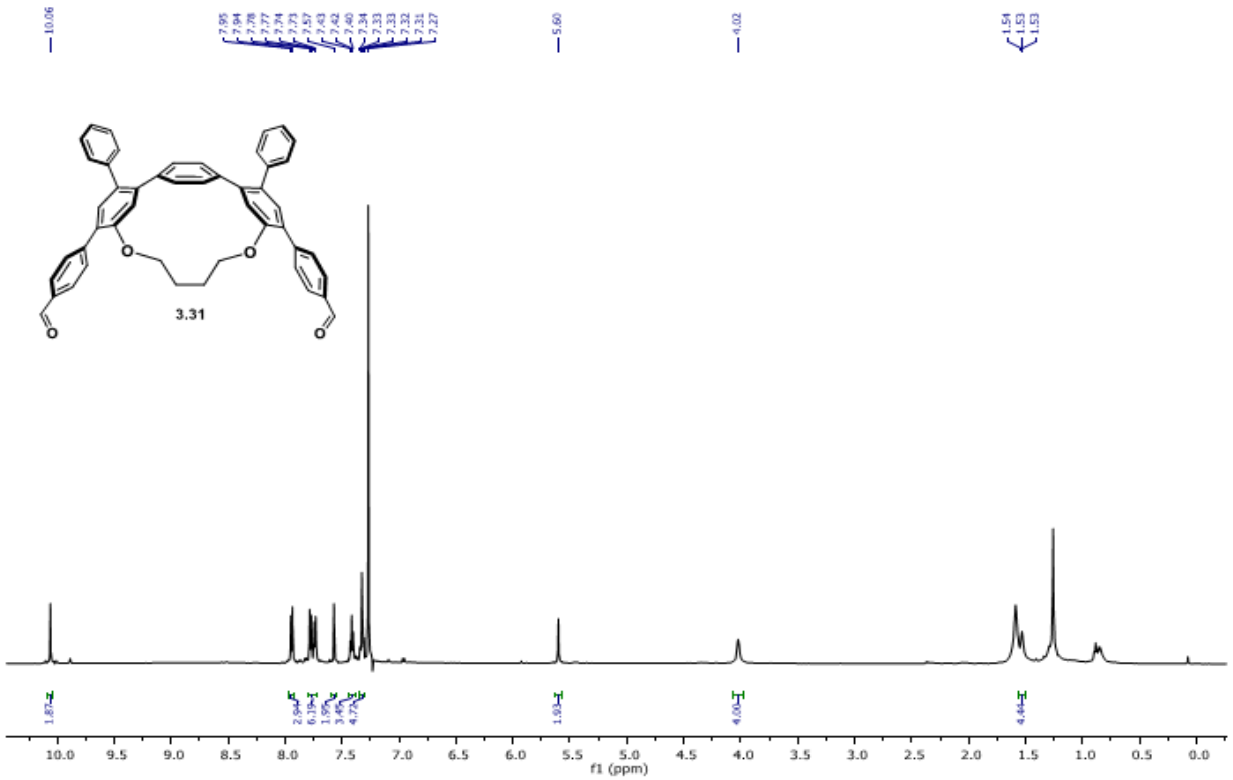
3.18

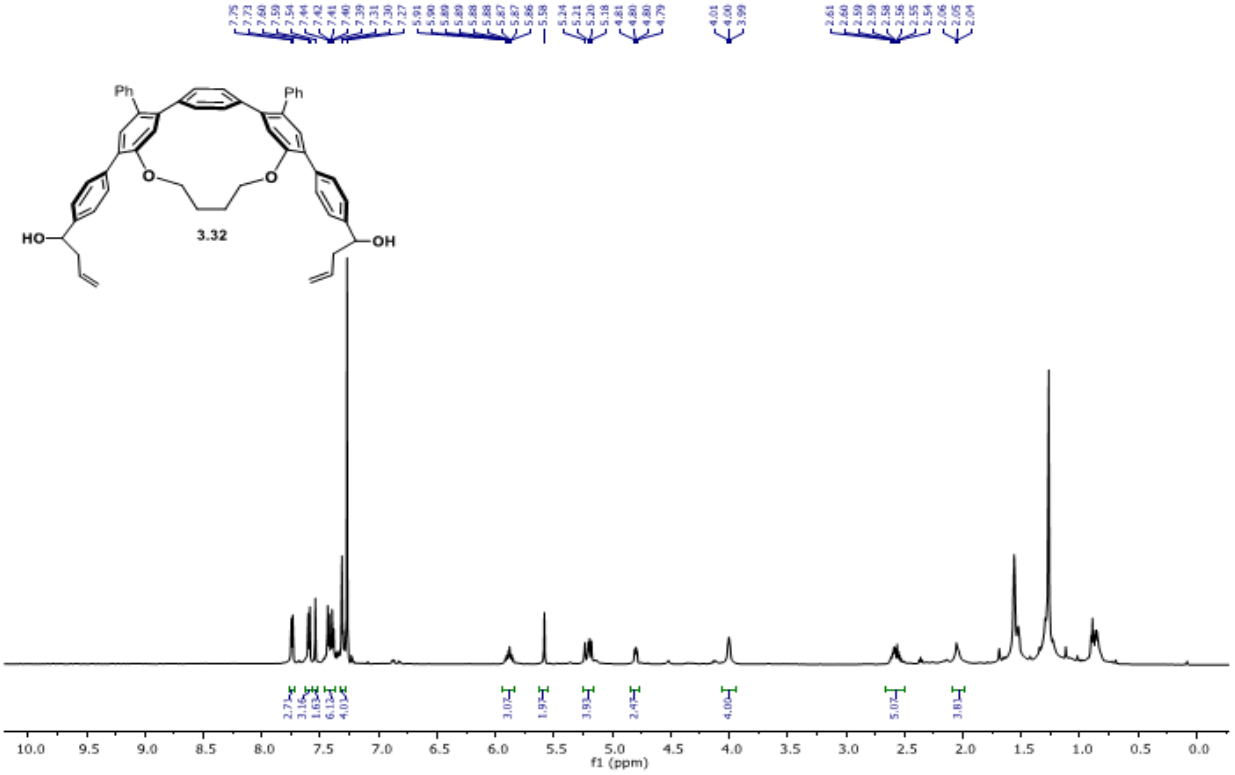

OH
Ph
Ph
O
O
3.45
f1 (ppm)

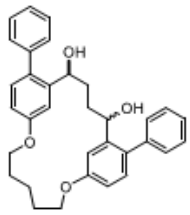

HO
OH
Ph
Ph
O
O
3.18
f1 (ppm)


3.20
f1 (ppm)

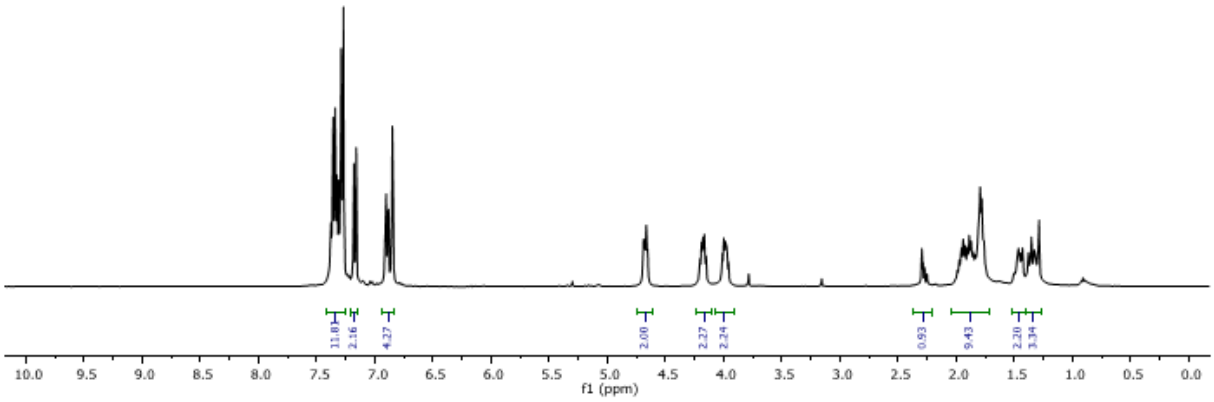

Br
Br
3.22
f1 (ppm)

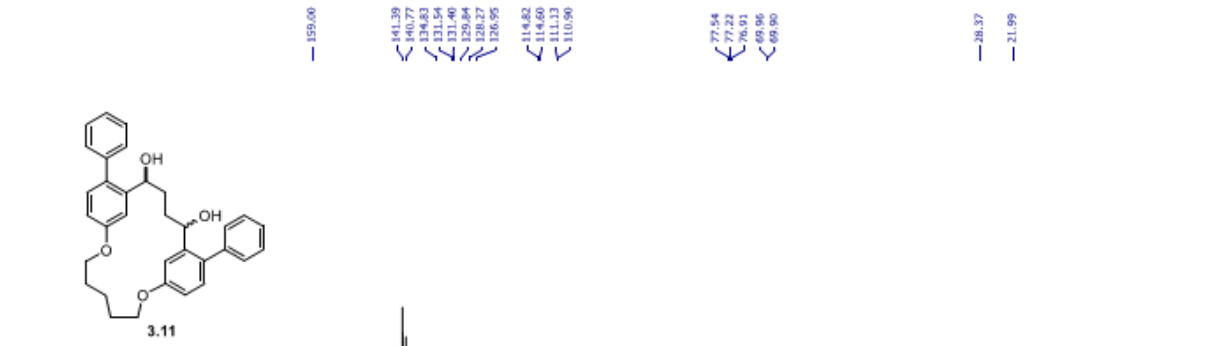

10.06
7.95
7.94
7.78
7.77
7.74
7.73
7.57
7.43
7.42
7.40
7.34
7.33
7.33
7.32
7.31
7.27
5.60
4.02
1.54
1.53
1.53
3.31
1.87
2.94
6.13
1.95
3.46
4.72
1.93
4.00
4.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


7.75
7.73
7.60
7.59
7.54
7.44
7.42
7.41
7.40
7.39
7.31
7.30
7.27
5.91
5.90
5.89
5.89
5.88
5.88
5.87
5.87
5.86
5.58
5.24
5.21
5.20
5.18
4.81
4.80
4.80
4.79
4.01
4.00
3.99
2.61
2.60
2.59
2.59
2.58
2.56
2.55
2.54
2.06
2.05
2.04
Ph
Ph
HO
OH
3.32
2.71
3.16
1.63
6.13
4.01
3.07
1.94
3.93
2.45
4.00
5.07
3.81
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
f1 (ppm)


OH
OH
O
O

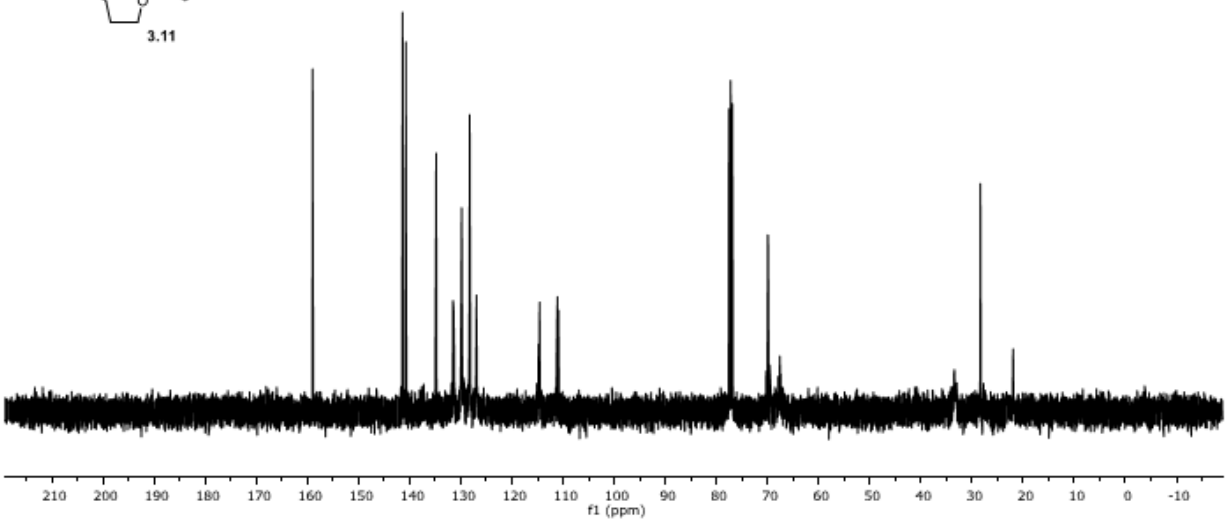
3.11

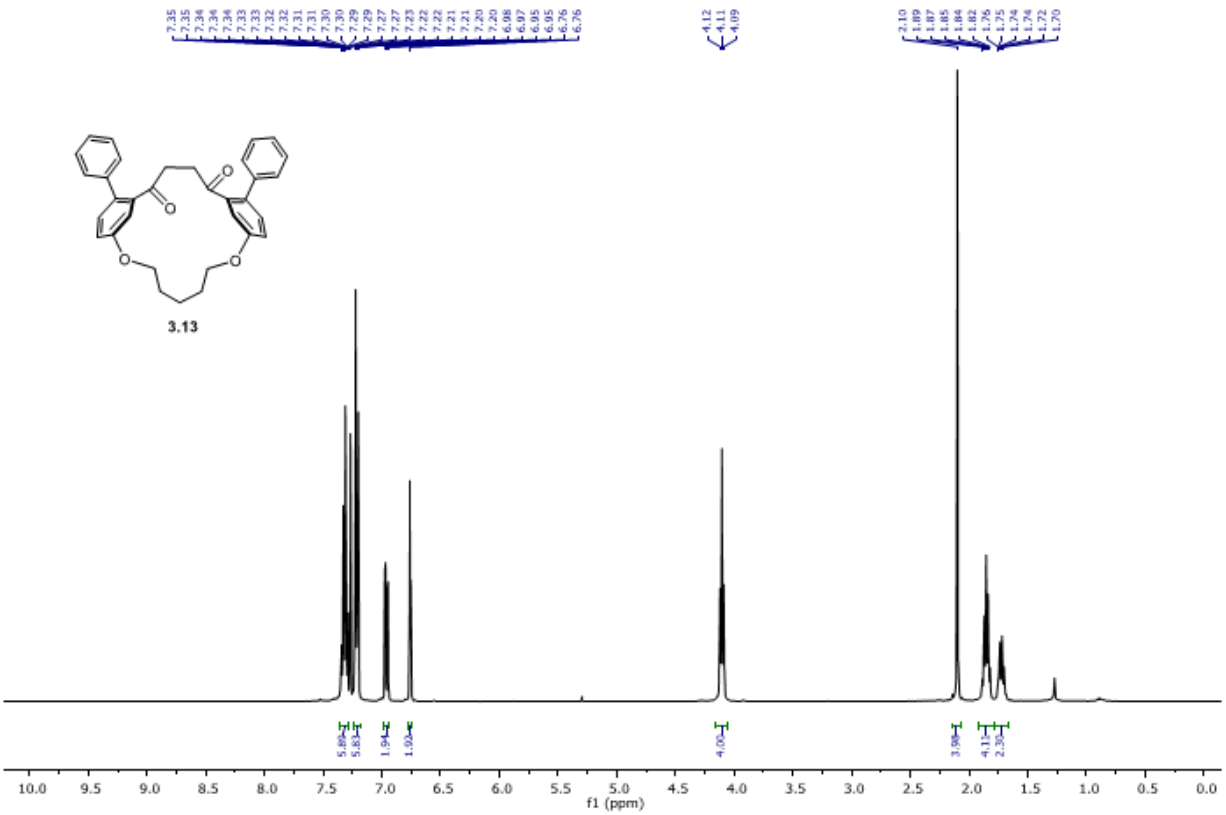

11.81
2.16
4.27
2.00
2.27
2.24
0.93
9.43
2.20
3.34
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

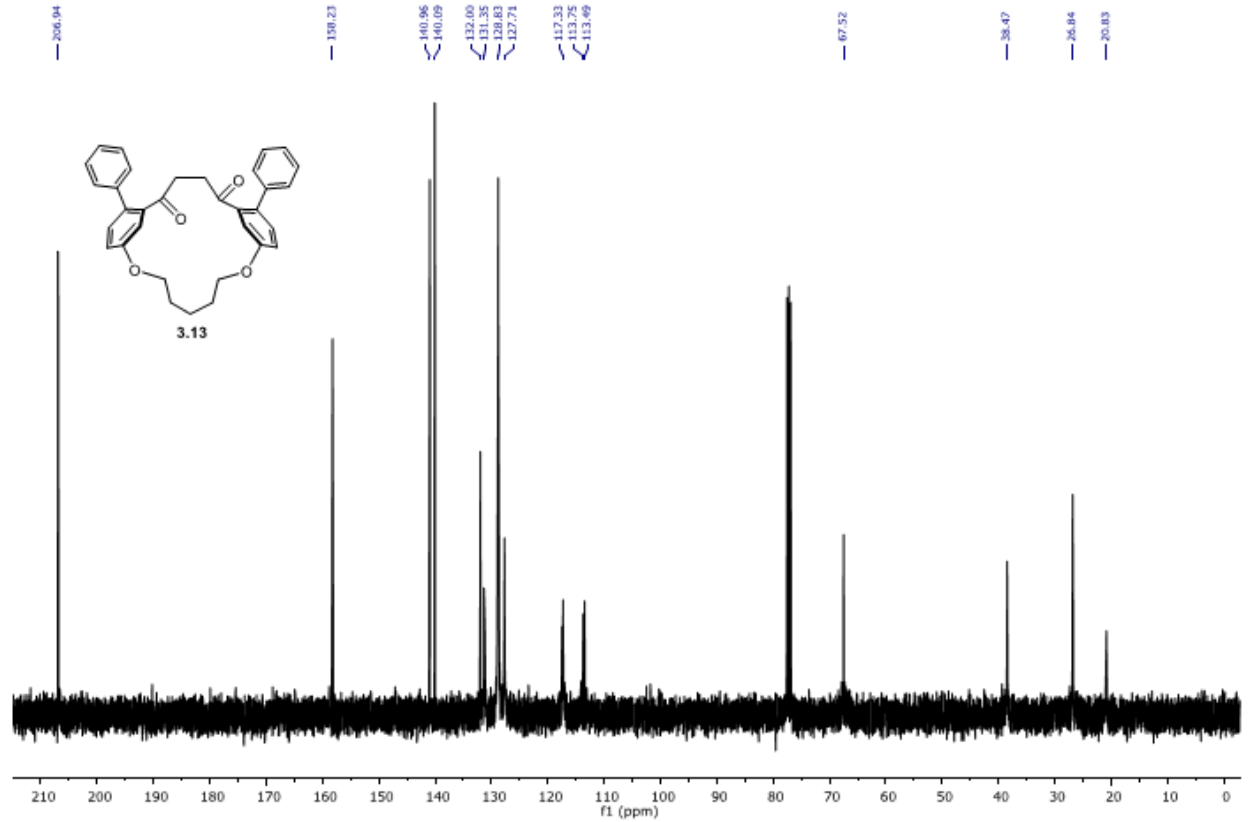

159.00
141.39
140.77
134.83
131.54
131.40
129.84
128.27
126.95
114.82
114.60
111.13
110.90
77.54
77.22
76.91
69.96
69.90
28.37
21.99

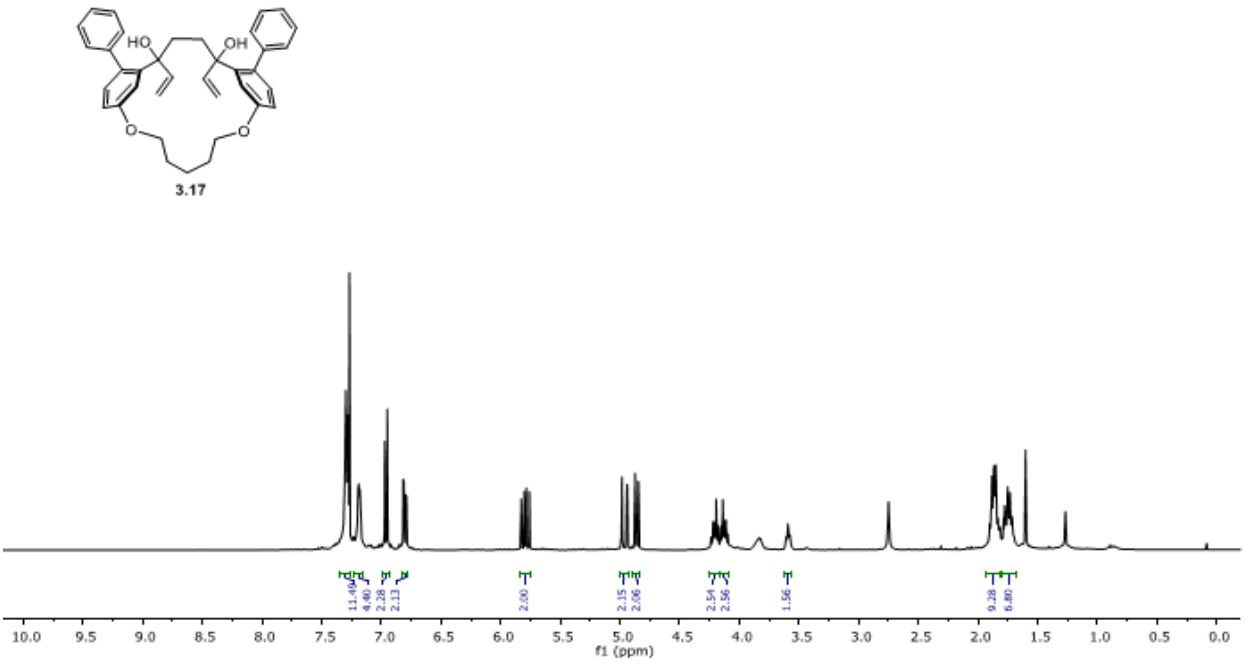
OH
OH
O
O

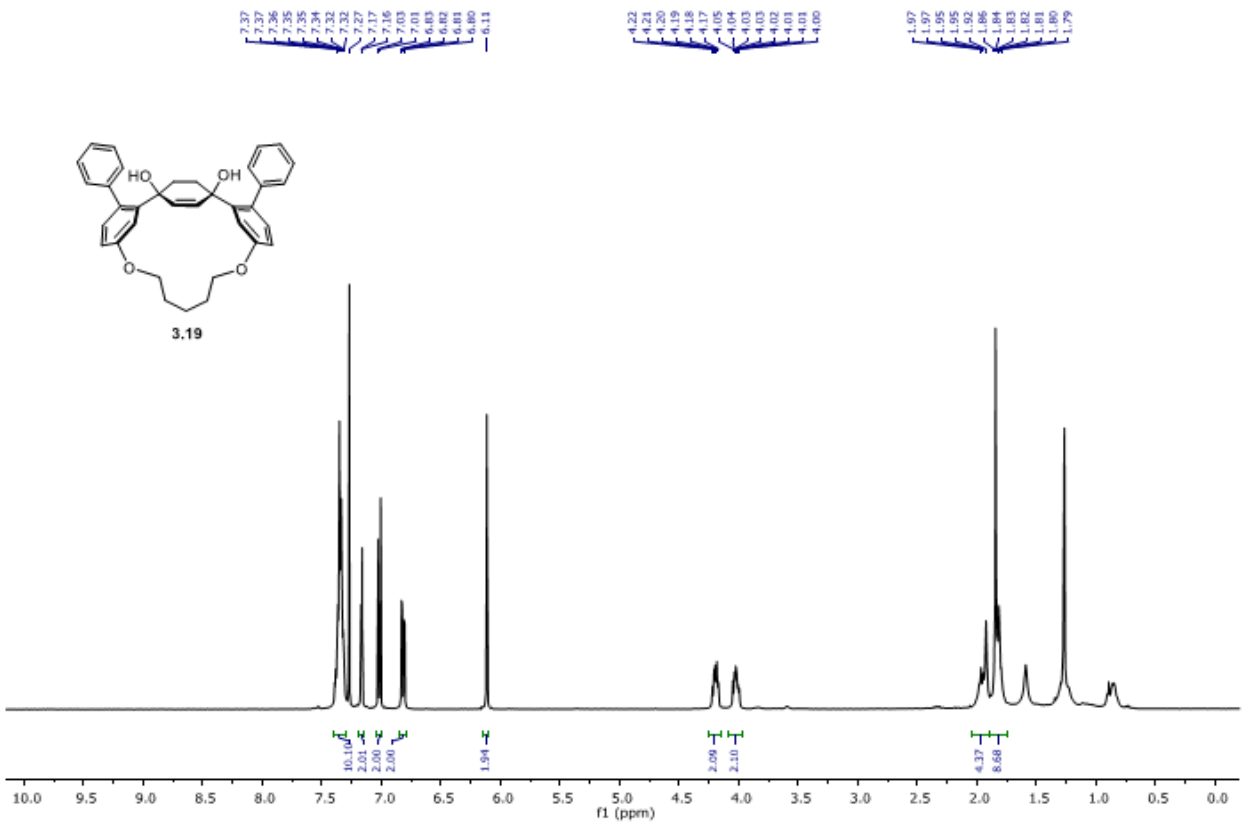
3.11

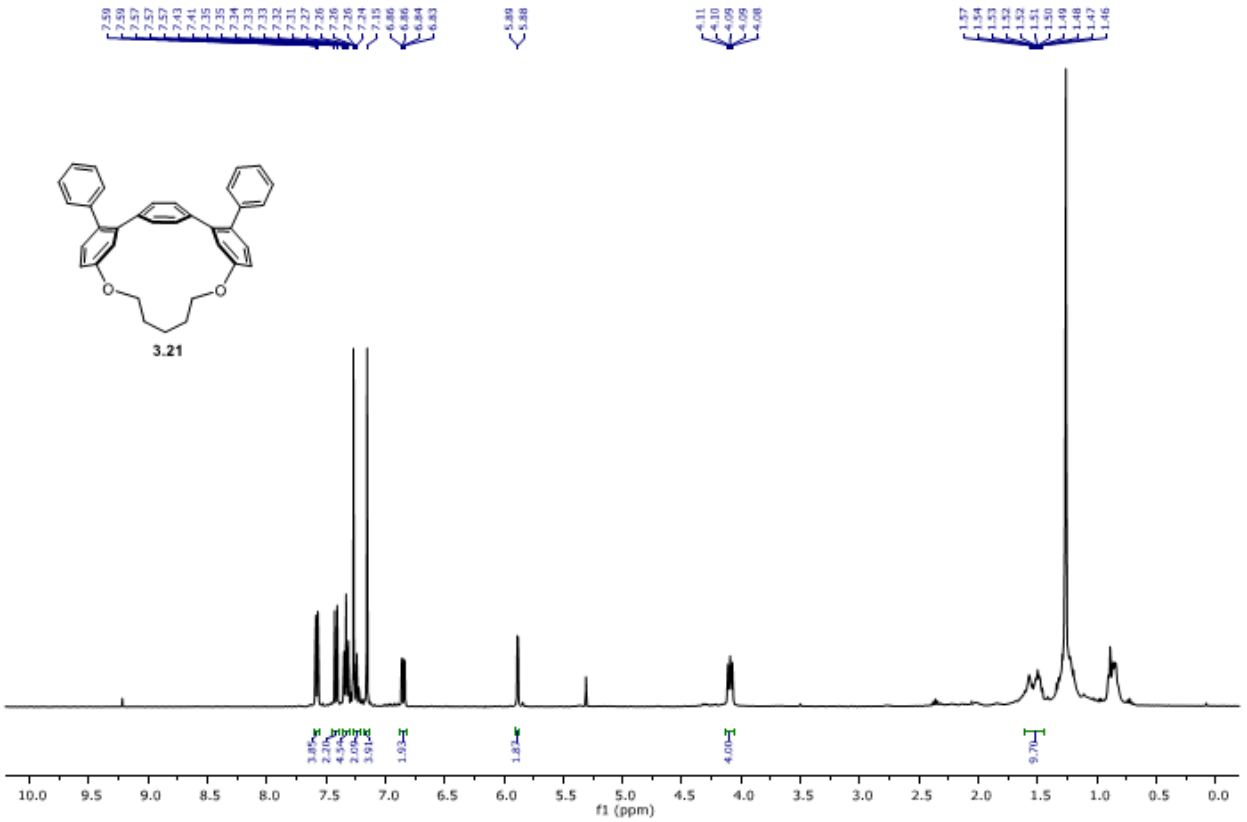

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

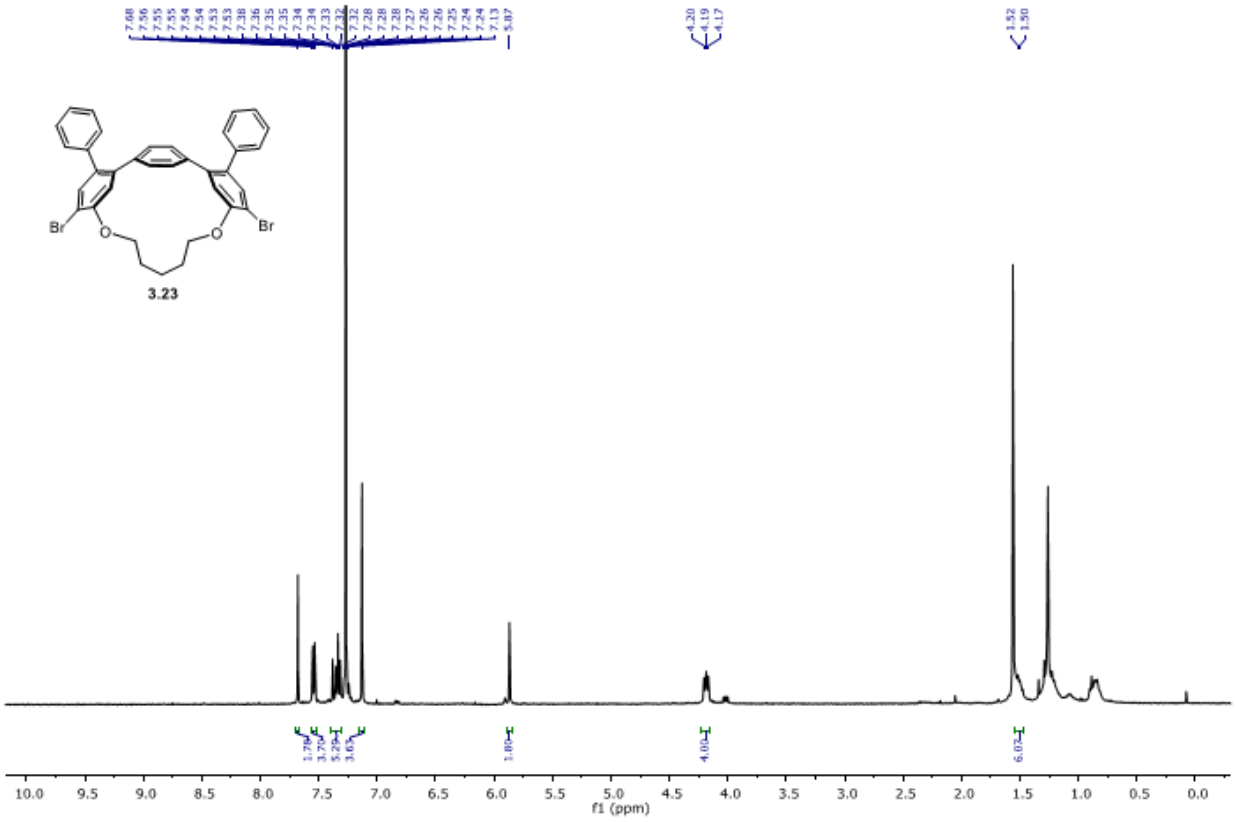

3.13
f1 (ppm)

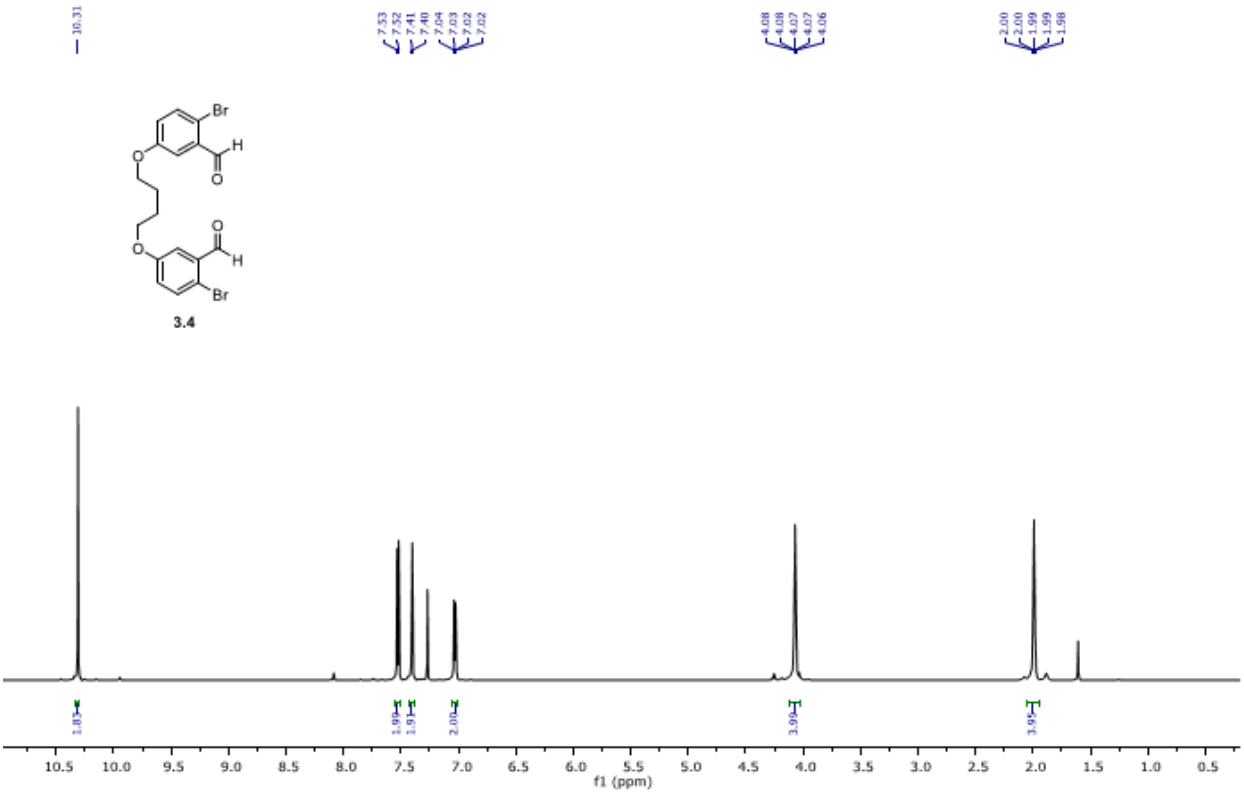

206.94
158.23
140.96
140.09
132.00
131.35
128.83
127.71
117.33
113.75
113.49
67.52
38.47
26.84
20.83
3.13
f1 (ppm)

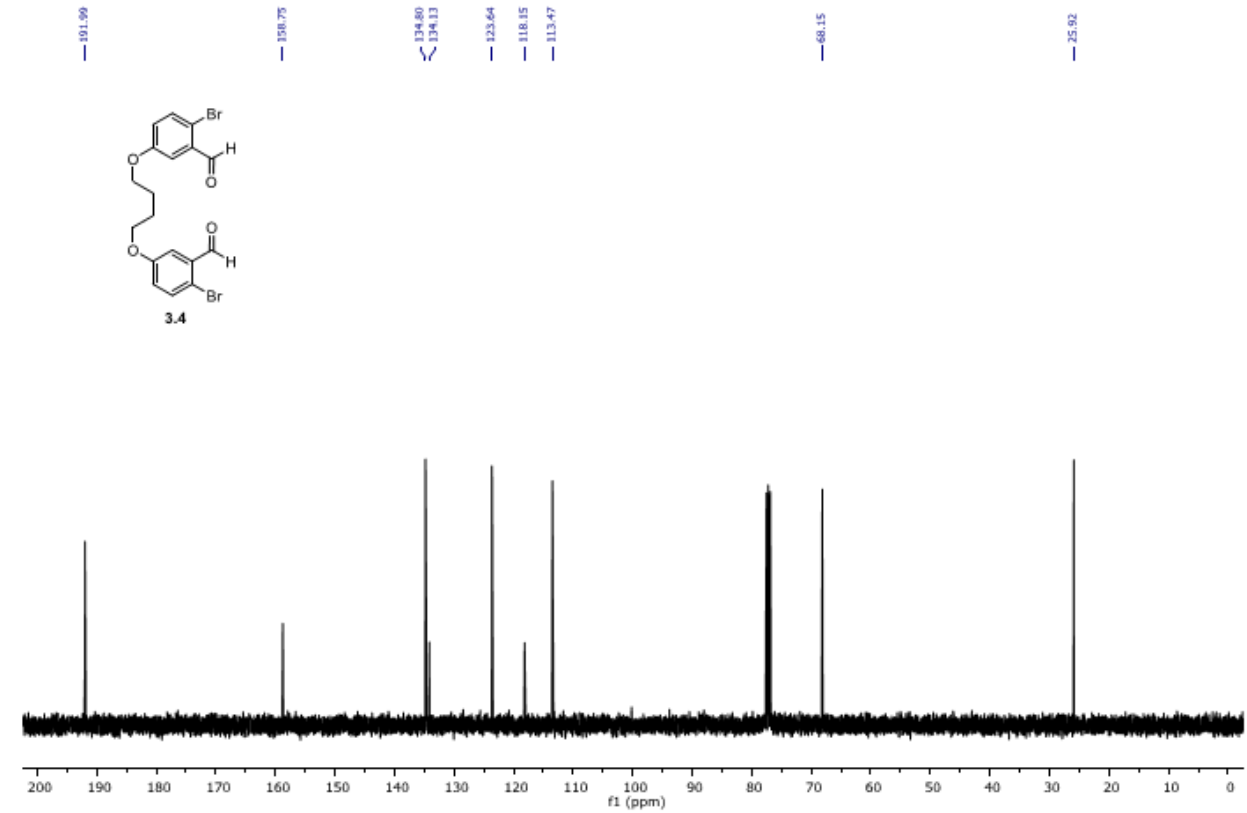

HO
OH
3.17
f1 (ppm)

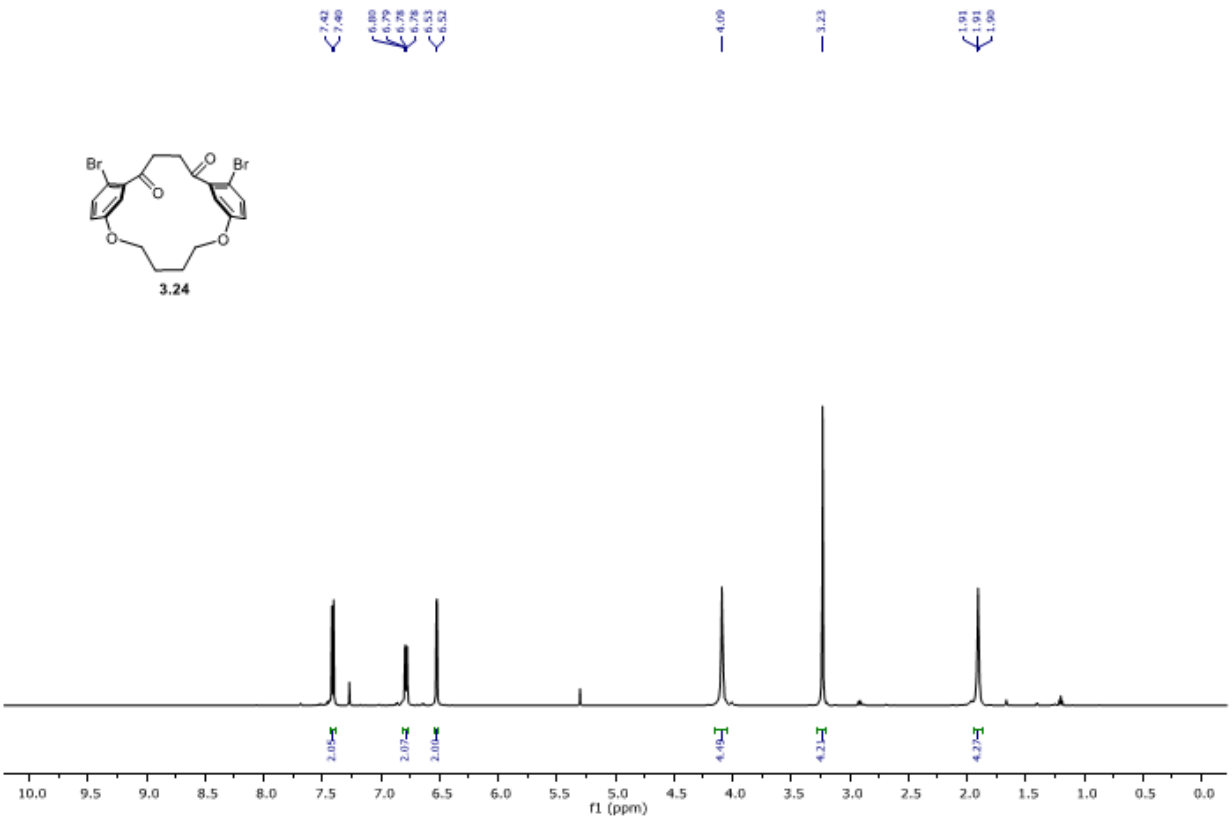

HO
OH
O
O
3.19
f1 (ppm)

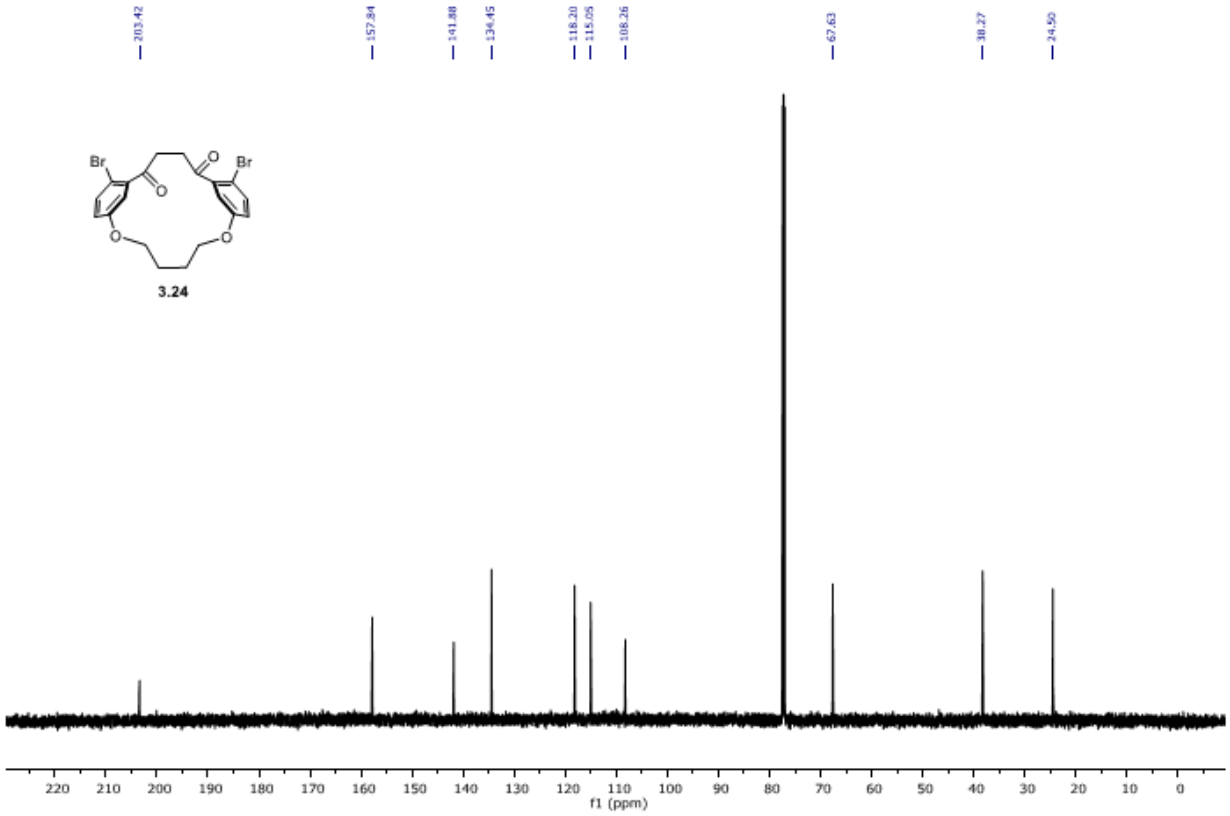

3.21
f1 (ppm)

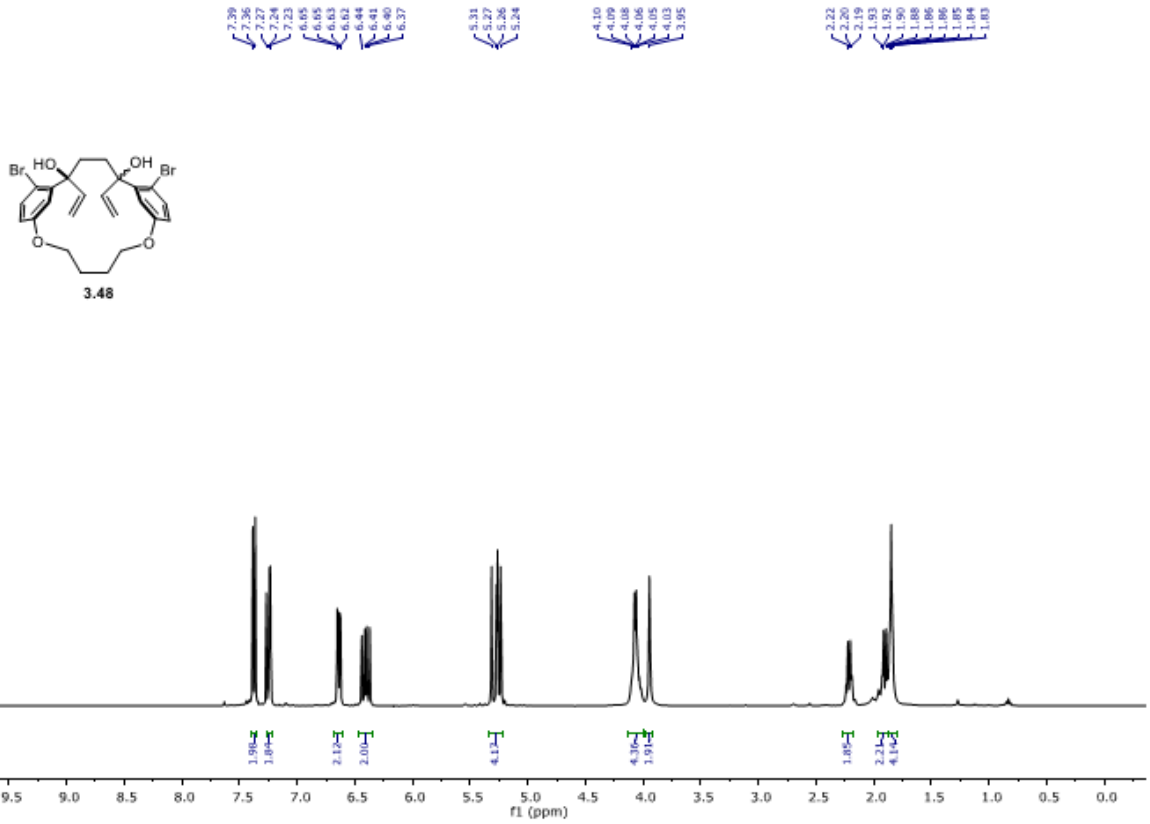

Br
Br
3.23
f1 (ppm)

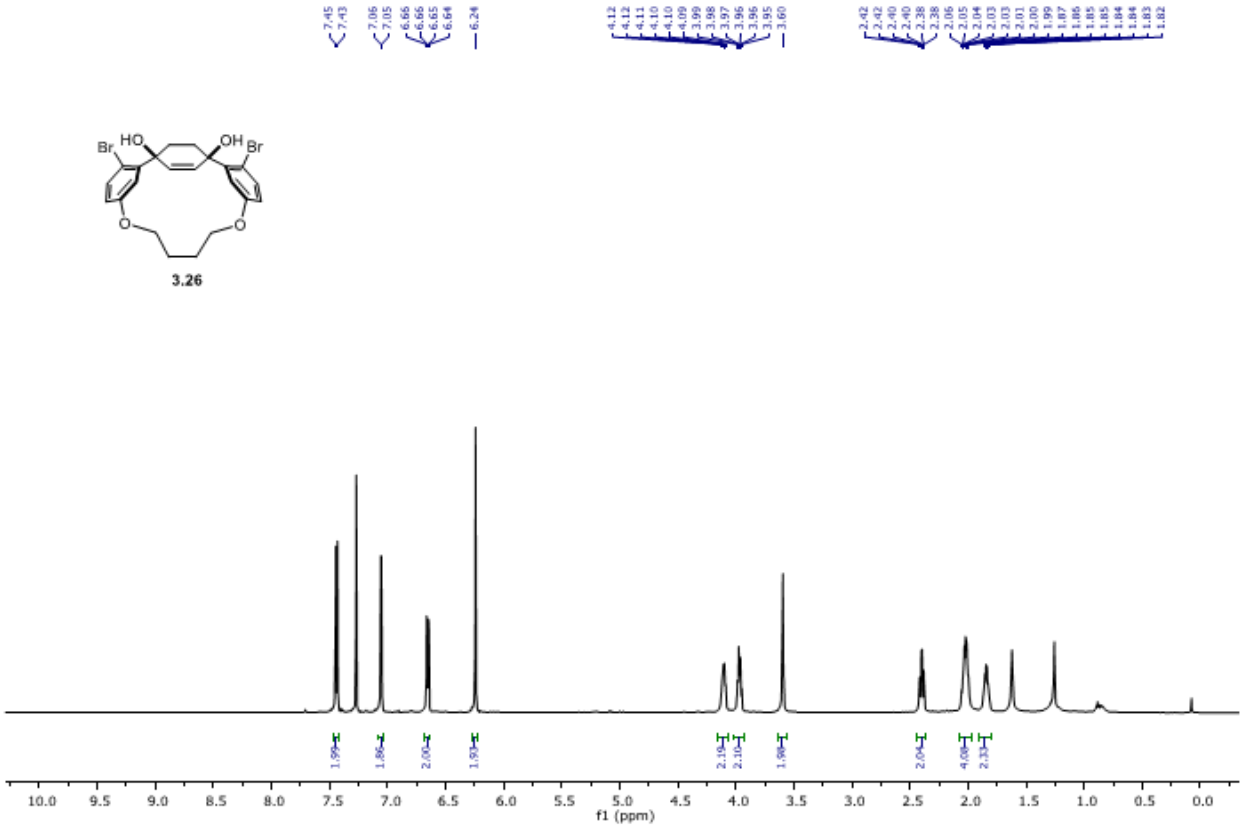

10.31
7.53
7.52
7.41
7.40
7.04
7.03
7.02
7.02
4.08
4.08
4.07
4.07
4.07
4.06
2.00
2.00
1.99
1.99
1.98
Br
H
O
O
O
H
Br
3.4
1.83
1.99
1.91
2.05
3.99
3.95
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

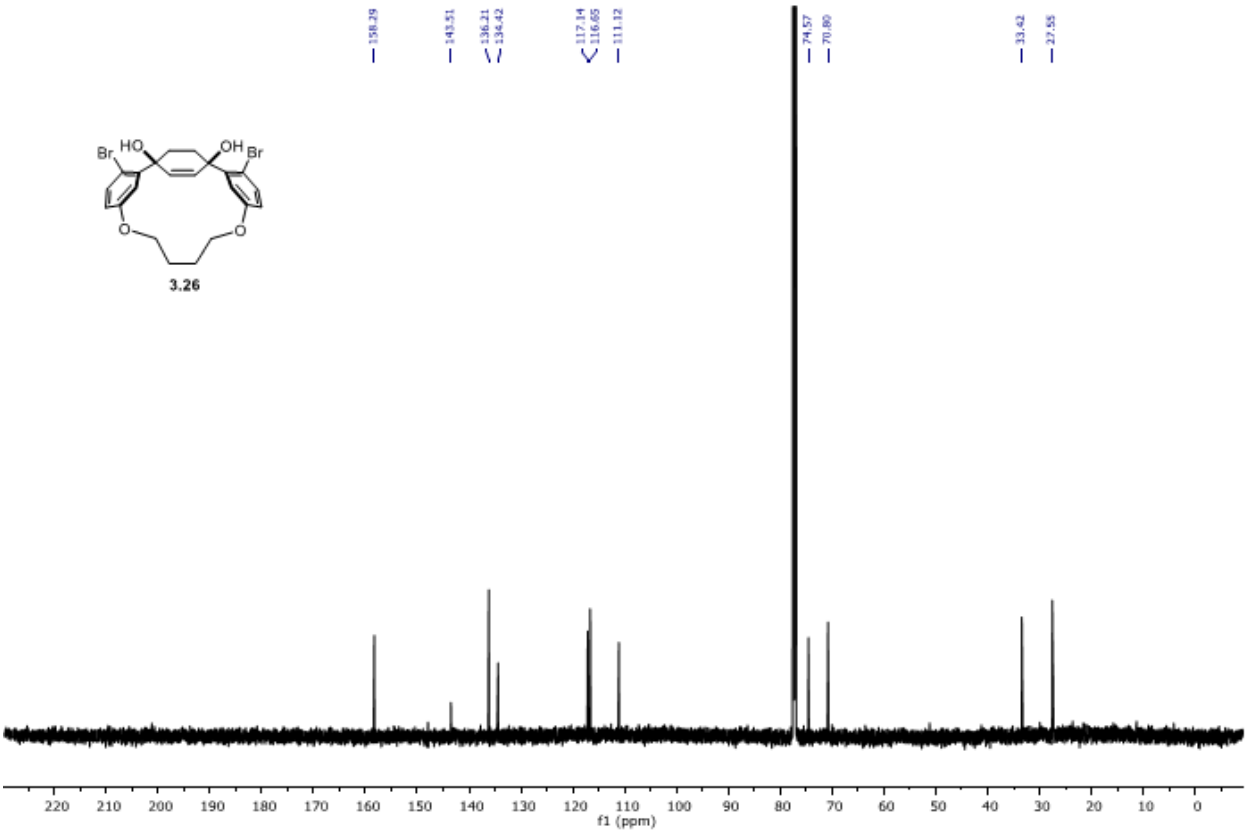

191.99
158.75
134.80
134.13
123.64
118.15
113.47
68.15
25.92
Br
H
O
O
O
H
Br
3.4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

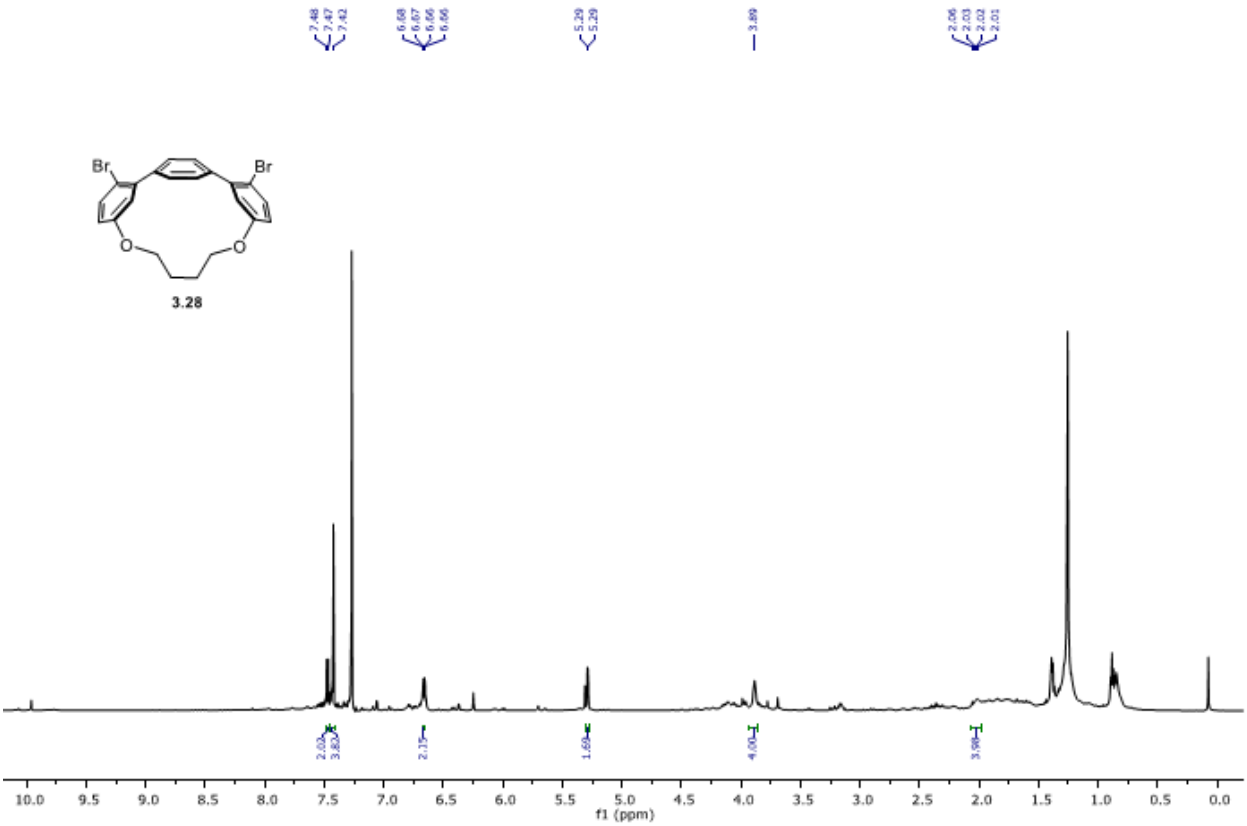

7.42
7.40
6.80
6.79
6.78
6.78
6.53
6.52
4.09
3.23
1.91
1.91
1.90
Br
O
O
Br
O
O
3.24
2.05
2.07
2.00
4.49
4.21
4.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

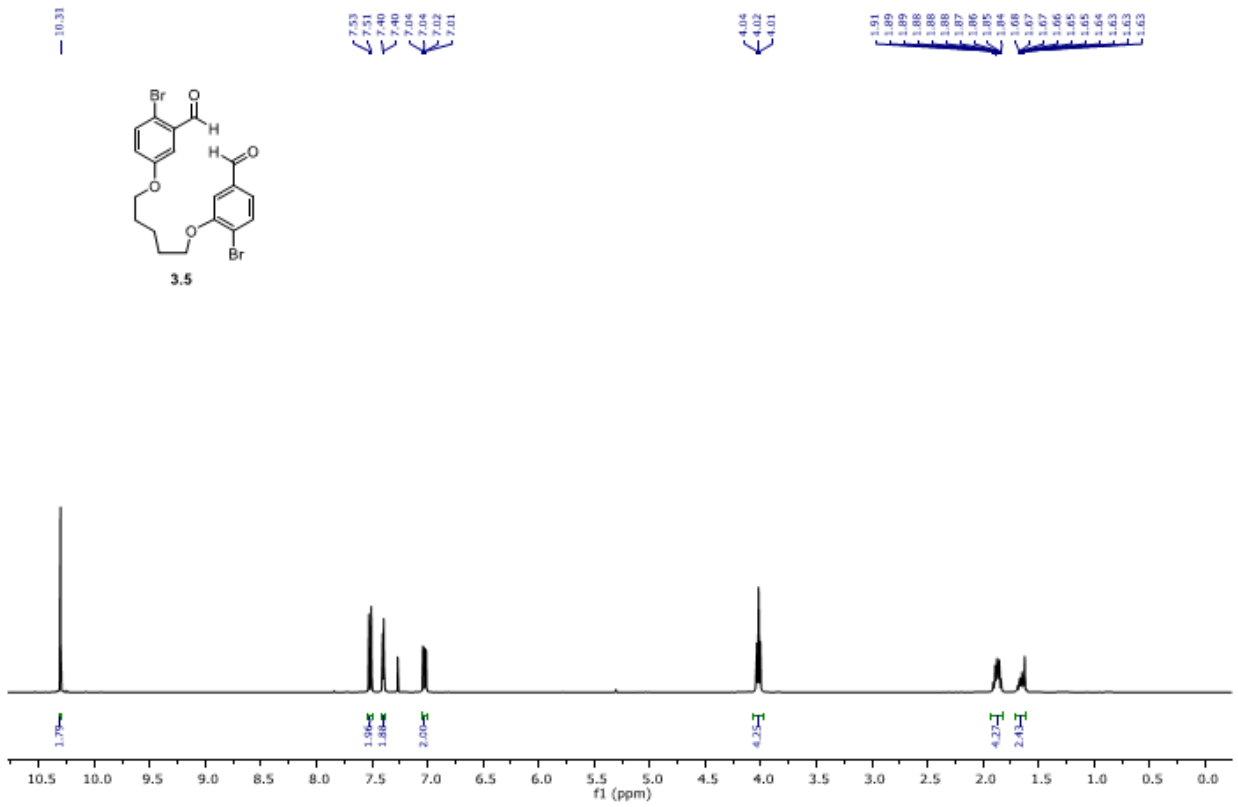

203.42
157.84
141.88
134.45
118.20
115.05
108.26
67.63
38.27
24.50
Br
O
O
Br
O
O
3.24
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.39
7.36
7.27
7.24
7.23
6.65
6.65
6.63
6.62
6.44
6.41
6.40
6.37
5.31
5.27
5.26
5.24
4.10
4.09
4.08
4.06
4.05
4.03
3.95
2.22
2.20
2.19
1.93
1.92
1.90
1.88
1.86
1.86
1.85
1.84
1.83
Br
HO
OH
Br
O
O
3.48
1.98
1.84
2.12
2.04
4.12
4.36
1.91
1.85
2.21
4.14
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
f1 (ppm)


7.45
7.43
7.06
7.05
6.66
6.66
6.65
6.64
6.24
4.12
4.12
4.11
4.10
4.10
4.09
3.99
3.98
3.97
3.96
3.96
3.95
3.60
2.42
2.42
2.40
2.40
2.38
2.06
2.05
2.04
2.03
2.03
2.01
2.00
1.99
1.87
1.86
1.85
1.85
1.84
1.84
1.83
1.82
Br
HO
OH
Br
O
O
3.26
1.99
1.89
2.00
1.93
2.15
2.10
1.98
2.04
4.08
2.33
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
f1 (ppm)


158.29
143.51
136.21
134.42
117.14
116.65
111.12
74.57
70.80
33.42
27.55
Br
HO
OH
Br
O
O
3.26
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.48
7.47
7.42
6.68
6.67
6.66
6.66
5.29
5.29
3.89
2.06
2.03
2.02
2.01
Br
Br
O
O
3.28
2.02
3.83
2.15
1.69
4.00
3.98
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
f1 (ppm)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7.51
7.40
7.40
7.04
7.04
7.02
7.01
4.04
4.02
4.01
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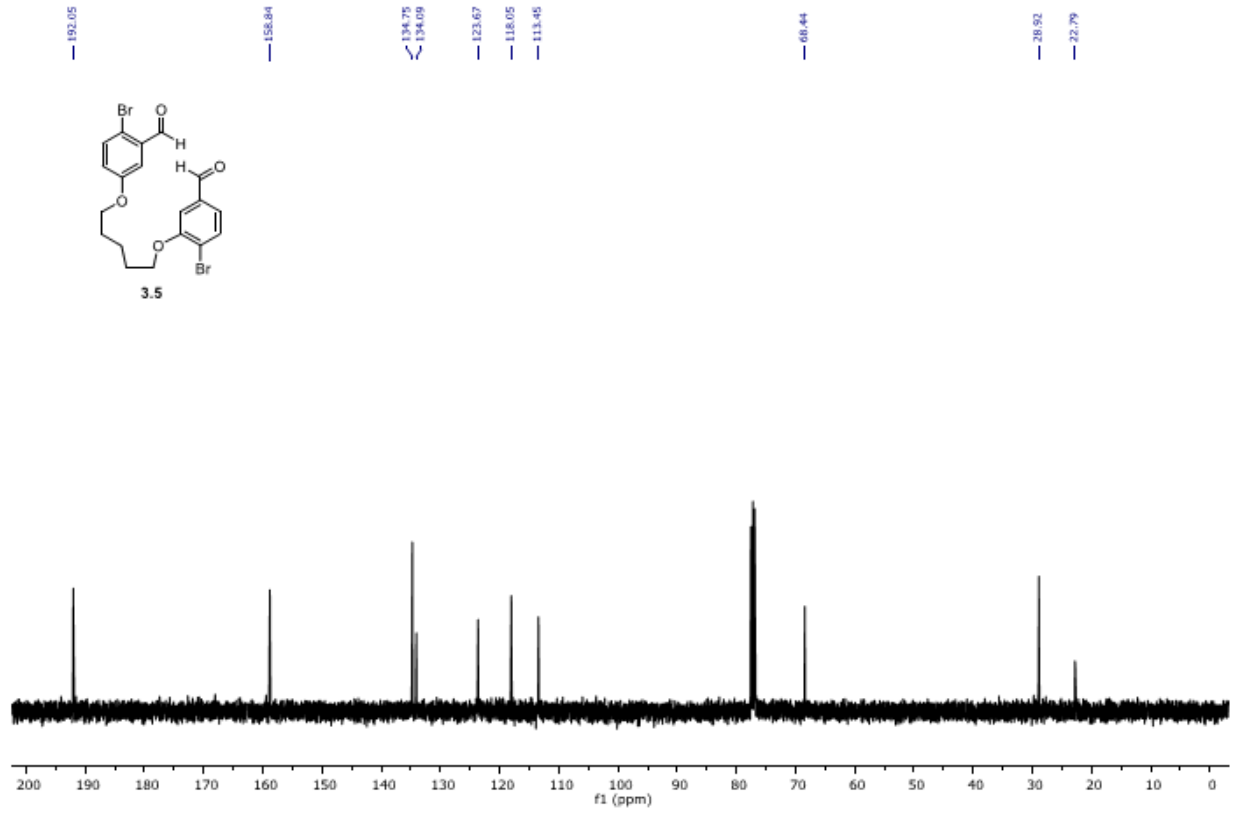
1.89
1.89
1.88
1.88
1.88
1.87
1.86
1.85
1.84
1.68
1.67
1.67
1.66
1.65
1.65
1.64
1.63
1.63
1.63
Br
O
H
H
O
O
O
Br
3.5
1.70
1.96
1.88
2.00
4.25
4.27
2.43
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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134.75
134.09
123.67
118.05
113.45
68.44
28.92
22.79
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H
H
O
O
O
Br
3.5
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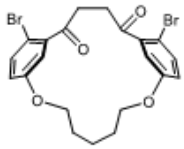
f1 (ppm)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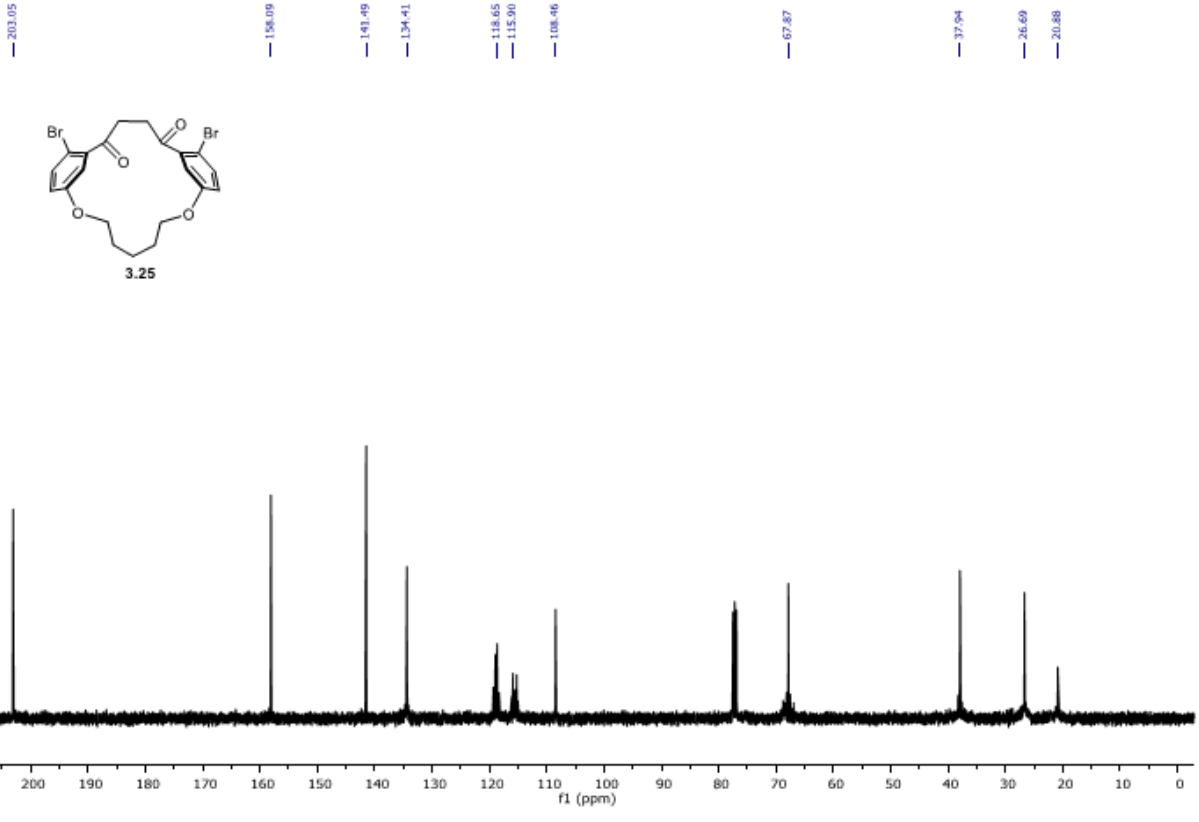
O
O
Br
O
O

3.25

7.37
7.35
6.77
6.76
6.75
6.74
6.63
6.62
4.00
3.99
3.97
3.30
1.77
1.75
1.74
1.72
1.70
1.64
1.62
1.60
1.59
1.85
1.84
1.80
4.00
3.61
3.88
2.31
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
f1 (ppm)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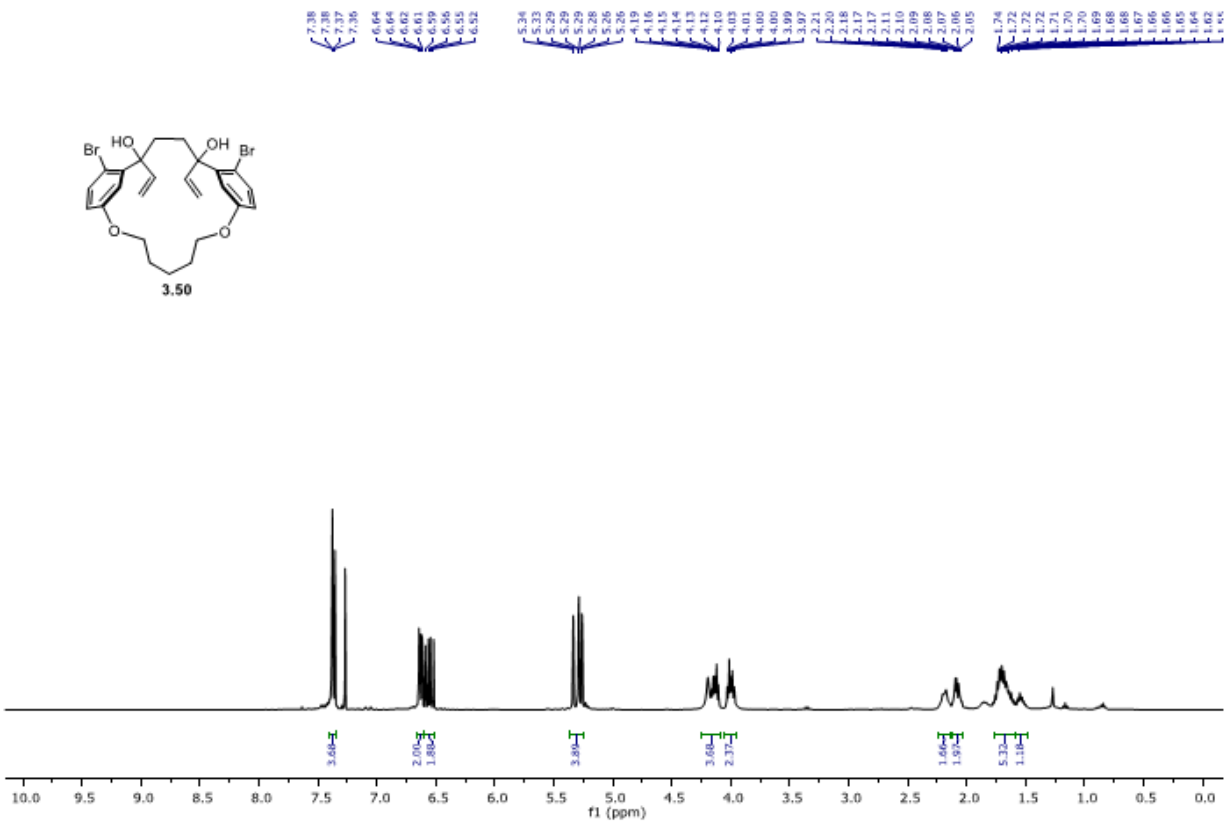
141.49
134.41
118.65
115.90
108.46
67.87
37.94
26.69
20.88
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Br
O
O
Br
O
O

3.25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5.34
5.33
5.29
5.29
5.28
5.26
5.26
4.19
4.16
4.15
4.14
4.13
4.12
4.10
4.03
4.01
4.00
4.00
3.99
3.97
2.21
2.20
2.18
2.17
2.17
2.11
2.10
2.09
2.08
2.07
2.06
2.05
1.74
1.72
1.72
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1.70
1.69
1.68
1.68
1.67
1.66
1.66
1.65
1.64
1.62
1.44
Br
HO
OH
Br
O
O
3.50
3.68
2.00
1.88
3.89
3.68
2.37
1.66
1.97
5.32
1.18
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
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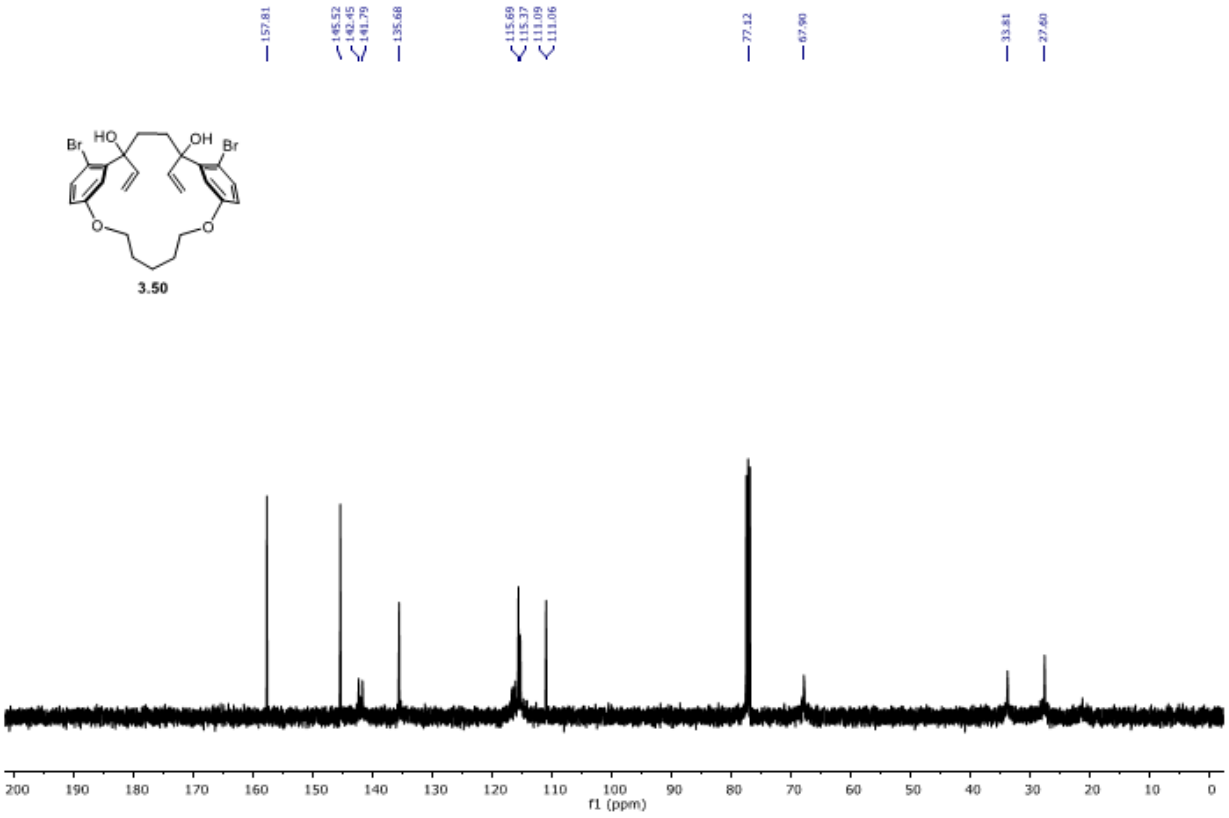
0.0
f1 (ppm)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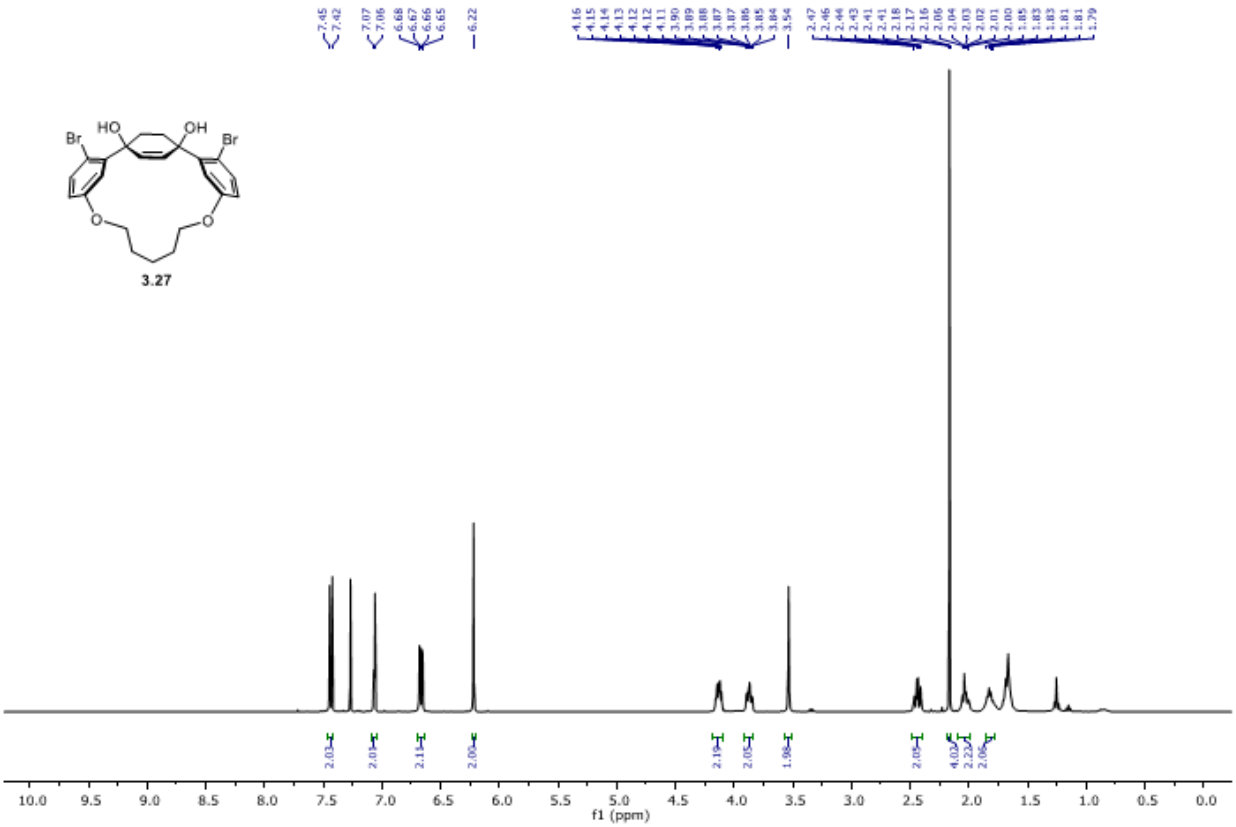
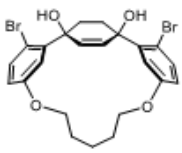
142.45
141.79
135.68
115.69
115.37
111.09
111.06
77.12
67.90
33.81
27.60
Br
HO
OH
Br
O
O
3.50
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


HO
OH
Br
Br
O
O
3.27
f1 (ppm)


HO
OH
Br
Br
O
O

3.27

158.34
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136.17
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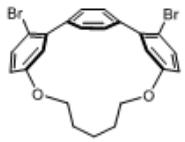
118.34
116.06
111.38
74.27
69.30
32.93
28.54
21.74
f1 (ppm)


Br
Br
O
O

3.29

7.51
7.50
7.48
6.69
6.68
6.67
6.66
5.74
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4.01
4.00
3.99
3.98
1.56
1.52
1.50
1.50
1.49
1.48
1.47
1.46
1.45
1.45
1.44
f1 (ppm)

Crystal Data and Structure Refinement for [7]PTPP Compound 2.95

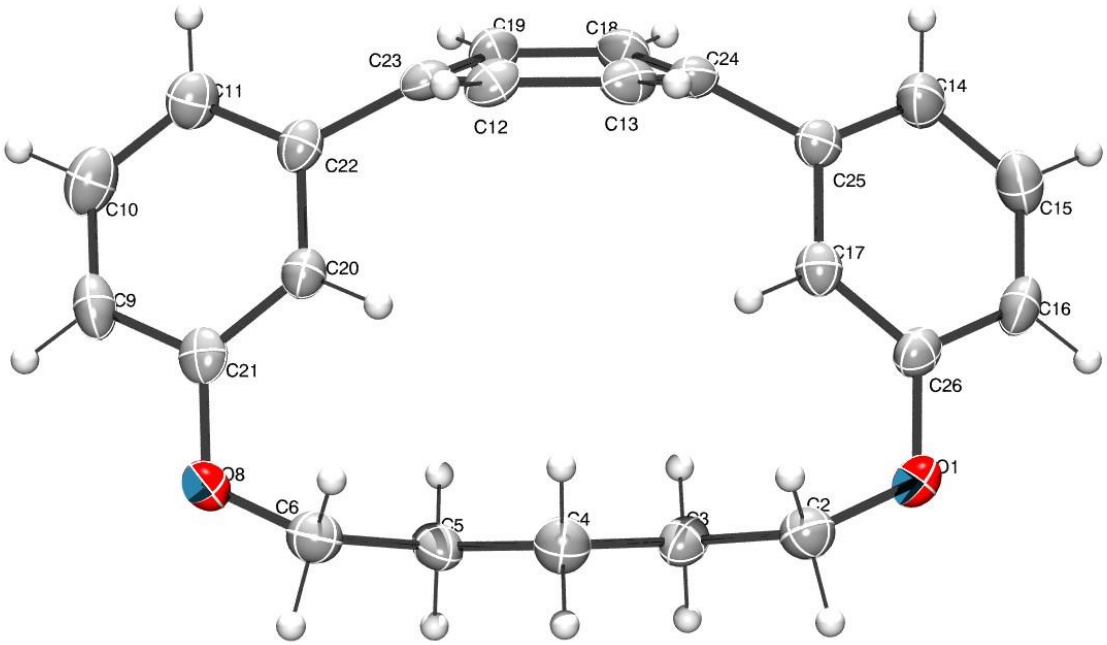
Identification code	**2.95**
Empirical formula	C23 H24 O2
Formula weight	332.42
Temperature	180(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 8.099(3) Å α = 90° b = 13.445(4) Å β = 90° c = 16.407(5) Å γ = 90°
Volume	1786.6(9) Å3
Z	4
Density (calculated)	1.236 g/cm3
Absorption coefficient	0.077 mm-1
F(000)	712
Crystal size	0.05 x 0.08 x 0.10 mm3
Theta range for data collection	1.96 to 22.73°
Index ranges	-8<=h<=8, -14<=k<=14, -17<=l<=17
Reflections collected	10323
Independent reflections	2402 [R(int) = 0.0708]
Completeness to theta = 22.73°	99.9%
Absorption correction	Multis can
Max. and min. transmission	0.9960 and 0.9920
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2402 / 0 / 226
Goodness-of-fit on F2	0.973
Final R indices [I>2sigma(I)]	R1 = 0.0404, wR2 = 0.0680
R indices (all data)	R1 = 0.0587, wR2 = 0.0721
Absolute structure parameter	1.9(10)
Largest diff. peak and hole	0.151 and -0.127

Bond Lengths and Angles for [7]PTPP Compound 2.95

O1-C26	1.371(4)
O1-C2	1.442(4)
O8-C21	1.377(4)
O8-C6	1.440(4)
C16-C15	1.376(5)

C16–C26 1.395(5)

C19–C18–C24 120.6(3)
C18–C19–C23 120.6(3)
C12–C23–C19 117.7(3)
C12–C23–C22 119.8(3)
C19–C23–C22 119.3(3)
C11–C22–C20 119.5(3)
C11–C22–C23 127.7(3)
C20–C22–C23 112.5(3)
C22–C11–C10 119.0(3)
C9–C10–C11 121.4(3)
C26–C17–C25 121.7(3)
C21–C20–C22 121.4(3)
C13–C12–C23 120.6(3)
C12–C13–C24 120.6(3)



X-ray crystal structure of compound **2.95**

Crystal Data and Structure Refinement for [6]MTPP (2.113)

Identification code	**2.113**	
Empirical formula	C22 H20 O2	
Formula weight	316.40	
Temperature	180.45 K	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 12.5333(3) Å	α = 90°
	b = 7.8729(2) Å	β = 91°
	c = 16.2274(4) Å	γ = 90°
Volume	1600.48(7) $Å^3$	
Z	4	
Density (calculated)	1.3130 g/cm^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	672.3	
Crystal size	0.5 x 0.4 x 0.2	
mm^3 Theta range for data collection	4.04 to 74.34°	
Index ranges	-21 ≤ h ≤ 20, -13 ≤ k ≤ 13, -27 ≤ l ≤ 27	
Reflections collected	47977	
Independent reflections	8058 [R(int) = 0.0586, R(sigma) =	
0.0452] Data / restraints / parameters	8058 / 0 / 217	
Goodness-of-fit on F2	1.099	
Final R indices [I>2sigma(I)]	R1 = 0.0682, wR2 =	
0.1560 R indices (all data)	R1 = 0.0984, wR2 =	
0.1826		
Largest diff. peak and hole	0.70 and -0.47	

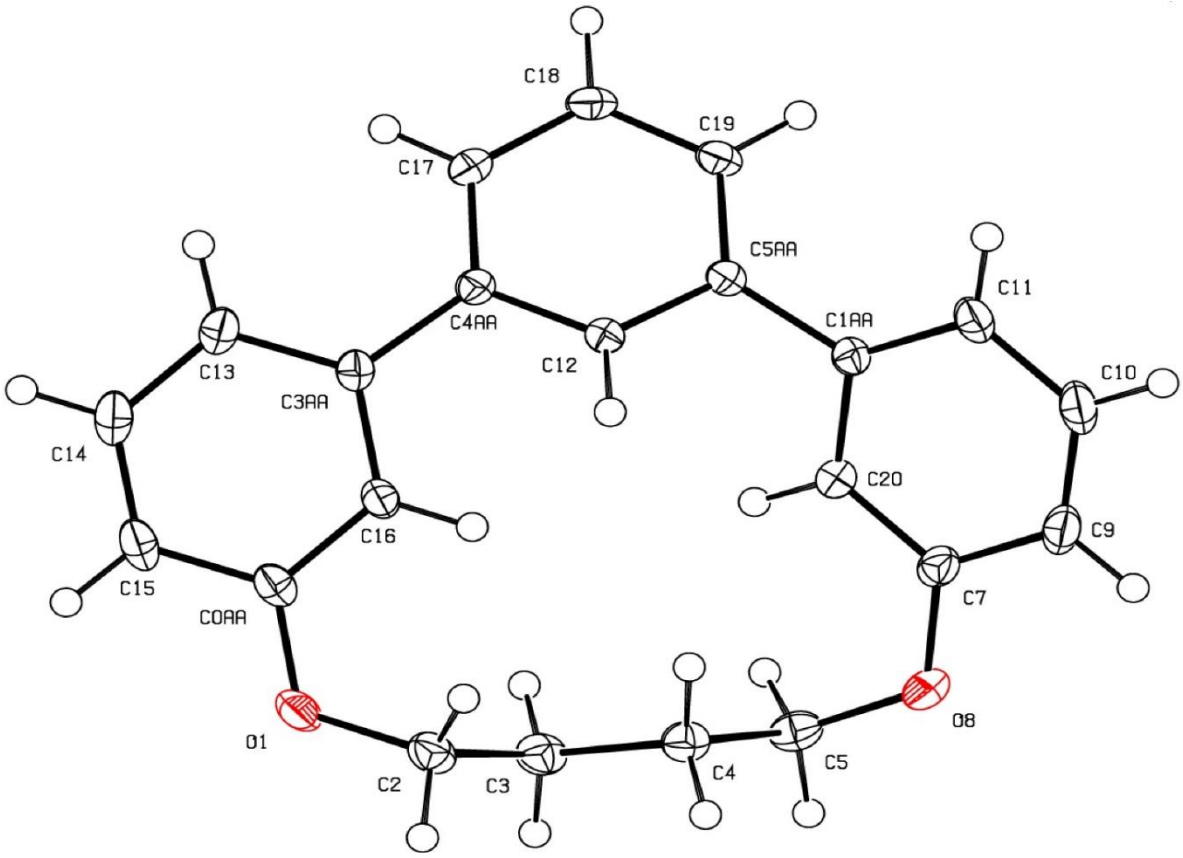
Bond Lengths and Angles for [6]MTPP (2.113)

O1-C0aa	1.371(2)
O1-C2	1.449(2)
O8-C5	1.446(2)
O8-C7	1.374(2)
C15-C0aa	1.402(2)
C15-C14	1.389(2)
C16-C0aa	1.389(2)
C2-C3	1.536(2)
C3-C4	1.536(2)

C4-C5	1.532(2)
C7-C9	1.400(2)
C7-C20	1.391(2)
C9-C10	1.388(2)
C14-C13	1.397(2)
C13-C3aa	1.400(2)
C16-C3aa	1.406(2)
C3aa-C4aa	1.488(2)
C20-C1aa	1.405(2)
C1aa-C5aa	1.490(2)
C1aa-C11	1.395(2)
C5aa-C19	1.401(2)
C12-C4aa	1.399(2)
C4aa-C17	1.402(2)
C17-C18	1.398(2)
C18-C19	1.394(2)
C11-C10	1.399(2)

C2-O1-C0aa	116.75(9)
C7-O8-C5	117.99(9)
C14-C15-C0aa	118.66(11)
C15-C0aa-O1	117.83(10)
C16-C0aa-O1	122.70(11)
C16-C0aa-C15	119.45(12)
C2-C3-O1	114.34(10)
C4-C3-C2	111.52(10)
C5-C4-C3	112.70(11)
C4-C5-O8	112.90(11)
C9-C7-O8	117.14(11)
C20-C7-O8	123.94(11)
C20-C7-C9	118.91(12)
C10-C9-C7	119.77(11)
C13-C14-C15	121.99(11)
C13-C24-C18	119.73(10)
C3aa-C13-C14	117.93(10)
C4aa-C3aa-C13	124.74(11)
C4aa-C3aa-C16	117.09(9)
C3aa-C16-C0aa	122.18(11)
C1aa-C20-C7	121.30(11)
C5aa-C1aa-C20	115.27(18)
C11-C1aa-C20	119.47(11)

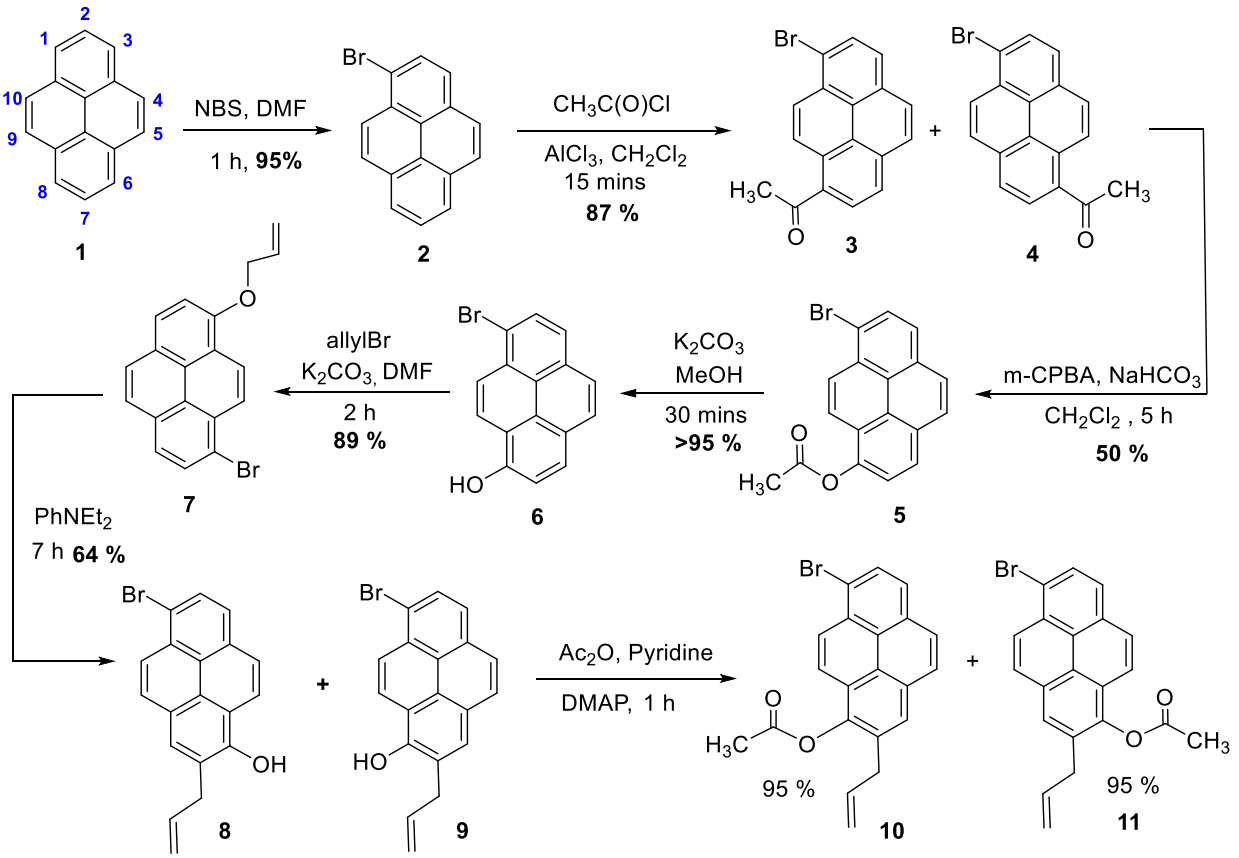
C11-C1aa-C5aa	125.09(11)
C12-C5aa-C1aa	115.29(10)
C19-C5aa-C12	118.34(10)
C4aa-C12-C5aa	123.12(10)
C12-C4aa-C3aa	118.00(10)
C17-C4aa-C3aa	124.22(10)
C17-C4aa-C12	117.21(10)
C18-C17-C4aa	120.09(10)
C19-C18-C17	121.52(11)
C18-C19-C5aa	119.18(12)
C10-C11-C1aa	118.89(12)
C11-C10-C9	121.55(12)



X-ray crystal structure of compound **2.113**

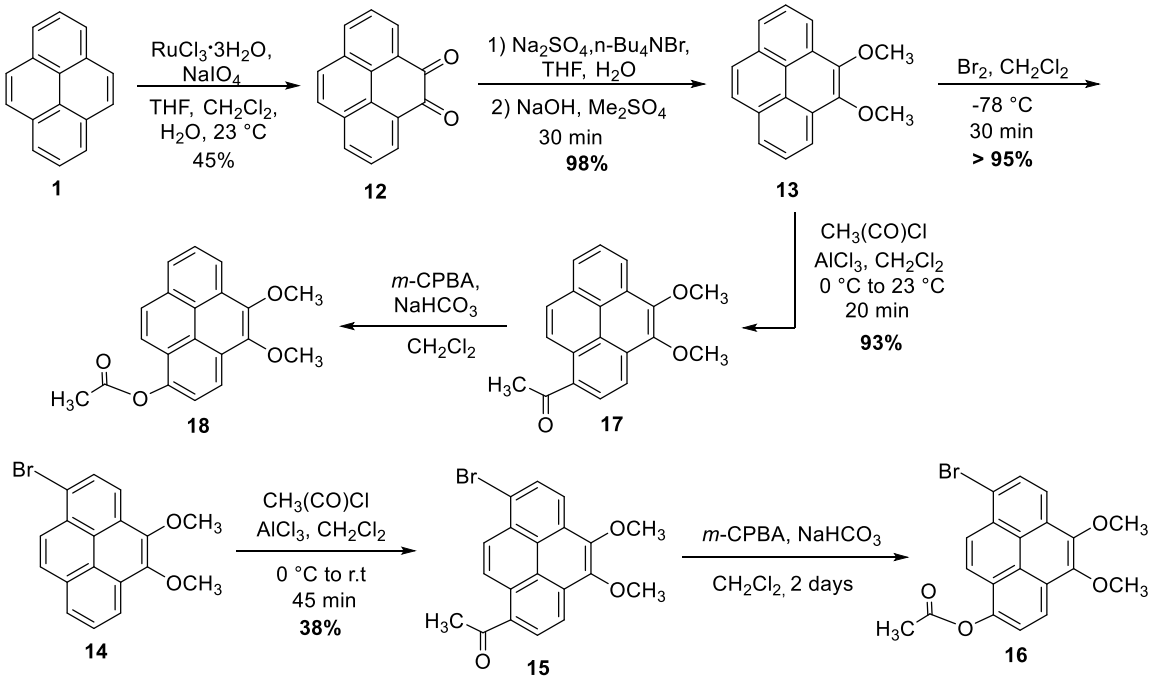
Appendix 1: Selective Substitution of Pyrene

The selective substitution of pyrene has been reported to be difficult from the literature. Most commonly, small electrophiles are known to substitute at the 1-, 3-, 6-, and 8-positions while bulky electrophiles substitute at the 2- and 7- positions.[47, 48] It is difficult to functionalize pyrene at the 1 and 2 positions simultaneously which is mainly what we aimed to achieve by developing a novel synthetic route as described below. The allylic group adjacent to the hydroxyl group was placed strategically to be later used as a handle to link two or more pyrene units together. Reaction sequences explored to achieve the selective substitution of pyrene would be described in subsequent sections.



SCHEME 1: First route to the selective functionalization of pyrene

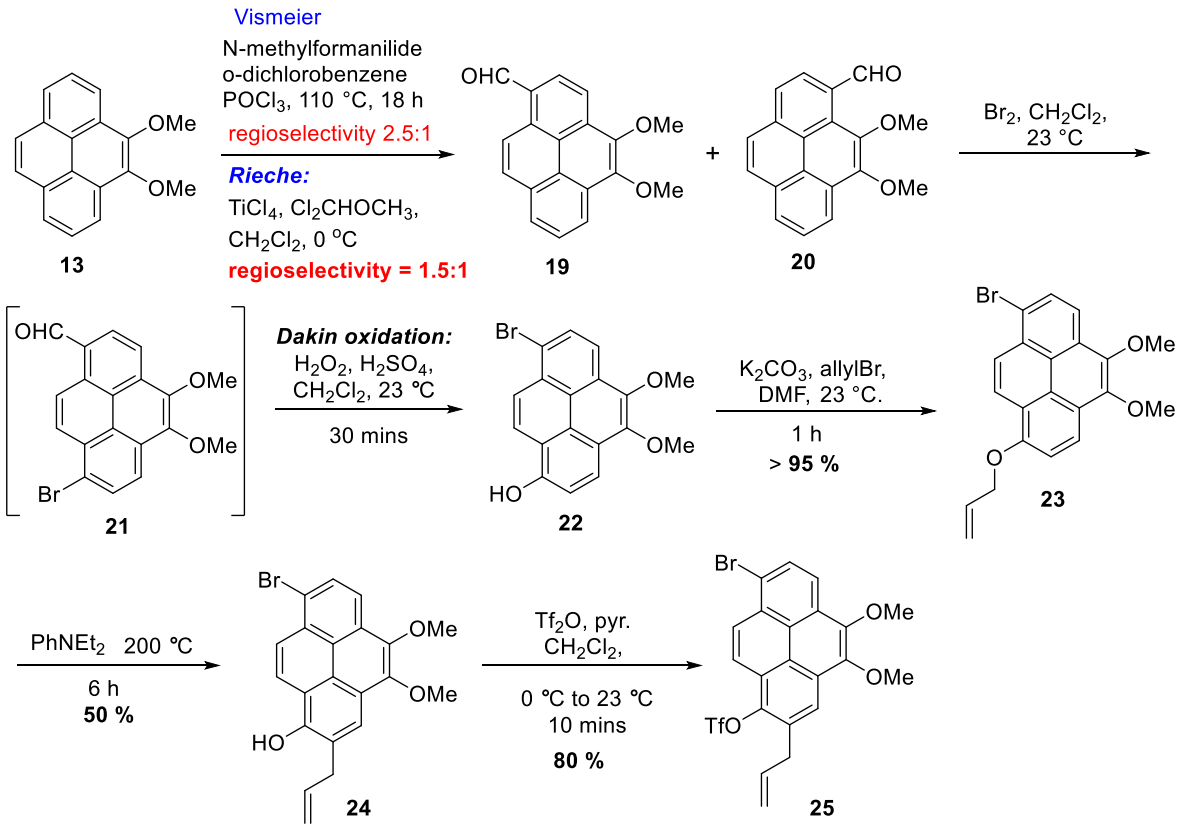
The Synthesis commenced with the NBS bromination of pyrene **1** in DMF to afford 1-bromopyrene **2** in 95% yield. Compound **2** was then treated with acetyl chloride in the presence of $AlCl_3$ to produce a mixture of 8-acetyl-1-bromopyrene **3** and 6-acetyl-1-bromopyrene **4** as an inseparable mixture of isomers in 87% yield. This mixture of compounds were carried throughout the synthesis. *m*-CPBA oxidation of the diastereomeric products with $NaHCO_3$ resulted in the formation of the esters **5** in 50% yield. Cleavage of the ester group with potassium carbonate in methanol formed 1-bromo-8-hydroxypyrene **6** in 95% yield. The hydroxyl group on the latter compounds were then alkylated with allyl bromide to afford a mixture of 8-(allyloxy)-1-bromopyene and 6-(allyloxy)-1-bromopyene **7** in 89% yield. Treatment of the mixture of allylated compounds with *N*,*N*-diethylaniline at 190 °C for 7 h initiated a claisen (3,3-sigmatropic) rearrangement to take place to afford a mixture of 7-(prop-2-enyl)-6-hydroxy-1-bromopyene **8** and 7-(prop-2-enyl)-8-hydroxy-1-bromopyene **9** in 64% yield. At this stage the diastereomers were separable in 10% EtOAc/hexanes but not in 50% CH_2Cl_2/hexanes. Subjecting the hydroxyl groups of **8** and **9** to acetic anhydride in pyridine in the presence of DMAP as catalysts formed the 7-(prop-2-enyl)-8-acetoxy-1-bromopyrene **10** and 7-(prop-2-enyl)-6-acetoxy-1-bromopyrene **11** in 95% yield each.



SCHEME 2: Second route to access functionalized pyrene

The fact that mixture of compounds were carried throughout the synthesis and they could only be separable after the sixth step instigated the development of a novel pathway where substitution could be done on the pyrene backbone selective. Moreover, the regioselectivity of compounds **10** and **11** were indistinguishable by NMR. Thus, in the second route, substitution of the K-region (4 and 5 positions) of pyrene was effected in the first step in order to minimize the number of regioisomers in subsequent steps. Pyrene **1**, was oxidized to 4,5-pyrene-dione **12** in 54%, by treatment with rutheniumtrichloride trihydrate in the $NaIO_4$ as catalyst. The diketone **12** was then oxidized to 4,5-dimethoxypyrene **13** in 98% yield. Brominating compound **13** with one equivalence of bromine in dichloromethane gave a 5:1 mixture of mono and disubstituted bromo-4,5-dimethoxypyrene **14**. Treatment of the mixture with acetylchloride and aluminiumtrichloride in dichloromethane afforded the 1-bromo-8-acetyl-4,5-dimethoxypyrene **15** in 38% yield. The dibrominated compound from the previous step could easily be separated

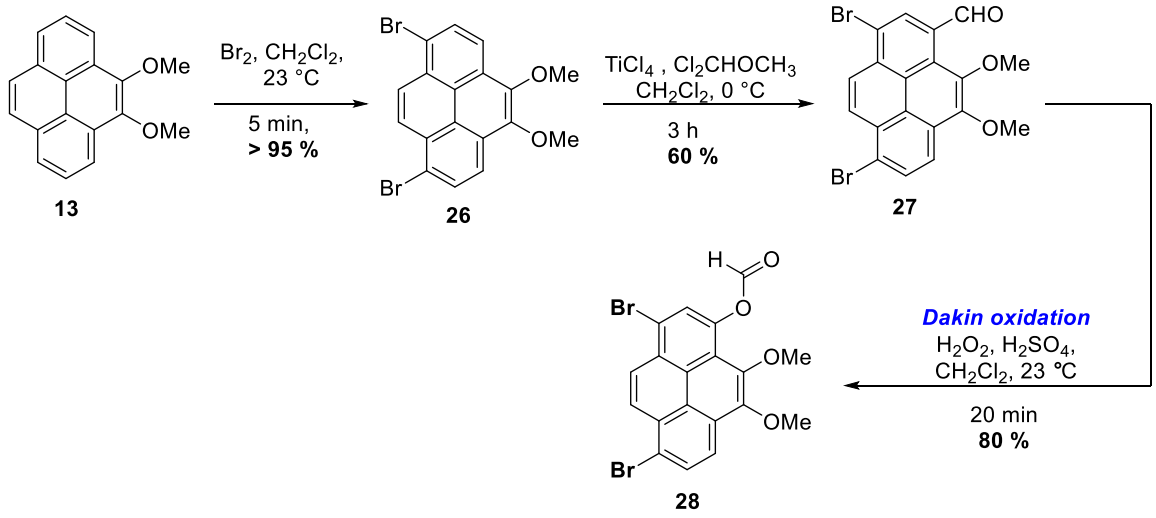
from the mixture via flash chromatography. All attempts to convert the acetyl group of **15** into the ester group on **16** was unsuccessful thereby impeding further reaction. Likewise, the acetylation of **13** into **17** proceeded smoothly and in excellent yield, yet, formation of the ester **18** was ineffective.



SCHEME 3: Third path to selectively synthesize functionalized pyrene

Failure to achieve the Baeyer-villiger oxidation reaction prompted us to consider an alternative route to achieve our goal. The synthesis began with the formylation of 4,5-dimethoxypyrene to afford a an inseparable mixture of aldehydes 4,5-dimethoxy-1-pyrenecarbaldehyde **19** and 4,5 dimethoxybenzene-3-pyrenecarbaldehyde **20**. Vilsmeier formylation conditions afforded a 2.5:1 mixture of **19** and **20** while the Rieche formylation provided just 1.5:1 of products. The latter mixtures were brominated to provide a mixture of

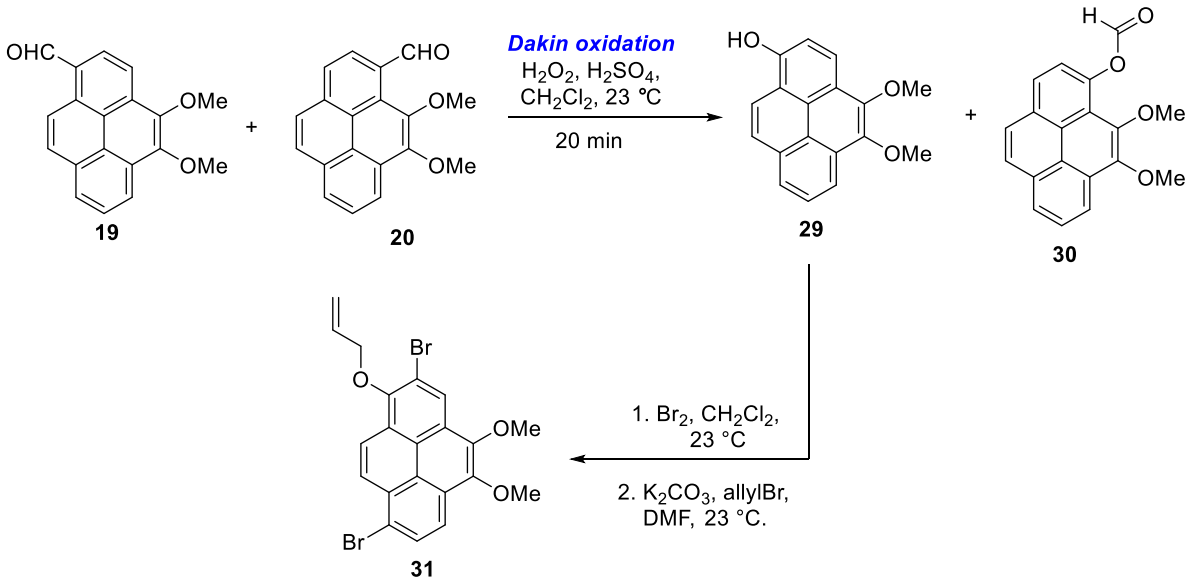
brominated products **21** which were inseparable in a number of solvents. Subjecting **21** to a Dakin oxidation conditions separated the compounds and provided what we assumed to be 1,-bromo-8-hydroxy-4,5-dimethoxypyrene **22**, as one of the products. Treatment of the hydroxyl group in **22** with allyl bromide provided the allylated product **23** which was later subjected to a claisen rearrangement by heating **23** with N,N-diethylaniline at 200 °C to provide compound **24** in 54% yield. Treatment of the hydroxyl group in **24** with trifluoromethanesulfonic anhydride in pyridine and dichloromethane provided the triflated compound **25** in 80% yield. To our surprise, the proton NMR spectrum of 25 revealed it to be two compounds, this observation impeded further reaction. It is speculated that the mixture of products arose during the bromination of the mixture of aldehydes (**19** and **20**), since there was no change in R_f value between the reactants and the products and identifying whether or not the reaction was complete was impossible.



SCHEME 4: Route four to the selective functionalization of pyrene

Another thing we explored was to investigate why selective formylation of 4,5-dimethoxypyrene was difficult and to pinpoint exactly where the formyl group was attached. We began with the bromination of 4,5-dimethoxypyrene to provide the 1,8-dibromo-4,5-

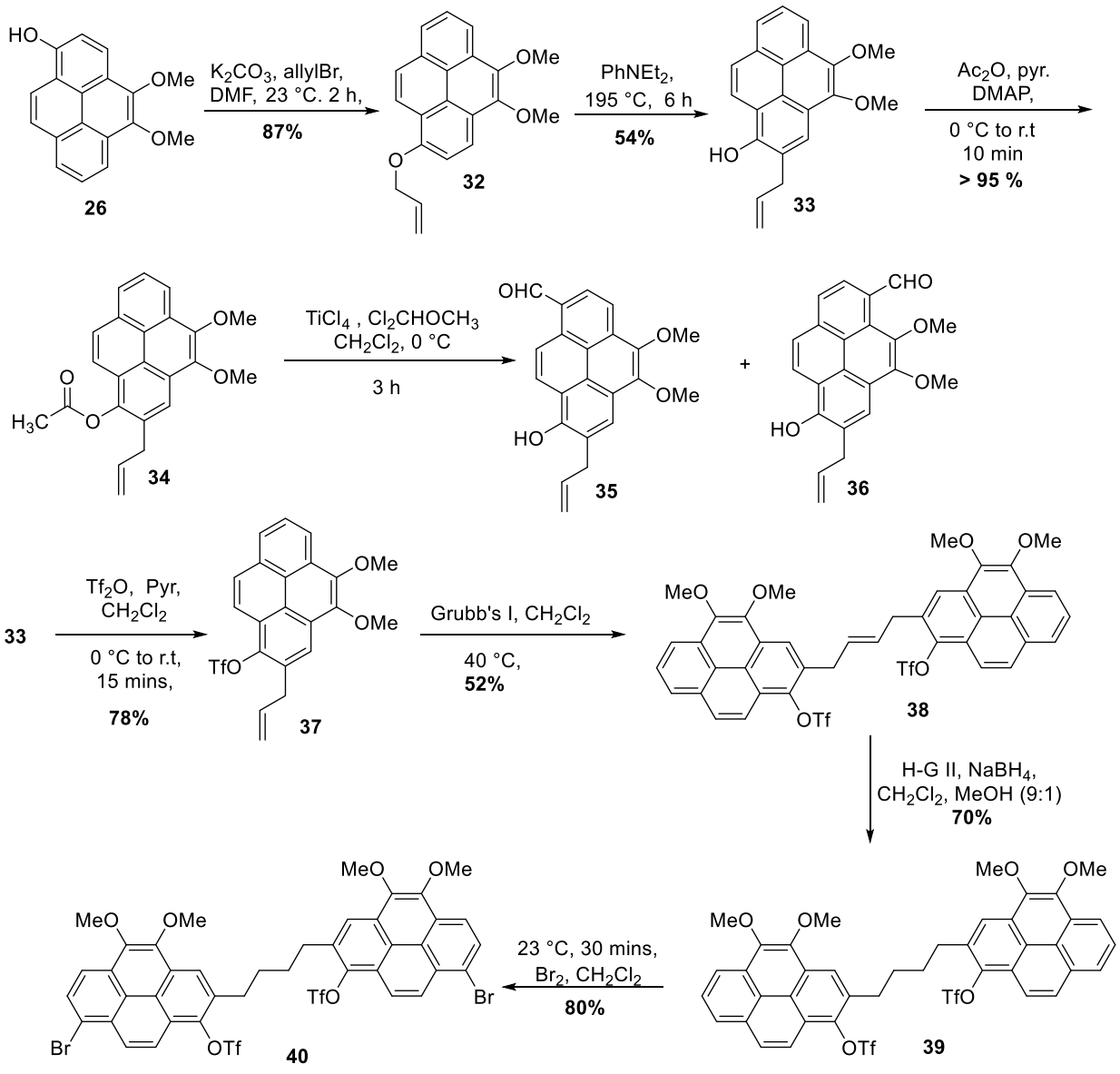
dimethoxypyrene **26** in 95% yield. Then subjecting the dibromide **26** to the Rieche formylation condition provided the 1,8-dibromo-3-formyl-4,5-dimethoxypyrene **27** in 60% yield. Subjecting **27** to the Dakin oxidation conditions provided only the formate derived pyrene **28** in 80% yield. All attempts to cleave the formate group was unsuccessful.



SCHEME 5: Efforts towards the selective substitution of pyrene

The above difficulty motivated us to consider a different route, where a Dakin oxidation on the mixture of aldehydes **19** and **20** was effected to produce the alcohol **29** and the formate **30** which could easily be separated. Bromination of **29** by treatment with bromine in dichloromethane inserted bromine atoms at the 2 and 8 positions. Ultimately, the goal was to substitute the bromine at the 8 position only so that the 2 position could be substituted via a claisen rearrangement. Subjecting the brominated product to an alkylation reaction with allyl bromide furnished the allylated compound **31**. Compound **31** could not be exposed to the desired (3,3) sigmatropic rearrangement because the 2 position was already blocked. It is speculated that

the electron donating nature of the hydroxyl group favored the addition of bromine at the adjacent position (2-position) in addition to the normal substitution at the 8-position.



SCHEME 6: Sixth route to the selective substitution of pyrene

Alternative to brominating the 1-hydroxypyrene-4,5-dimethoxypyrene **26**, we explored the alkylation reaction first. Treatment of the hydroxyl group in **26** with allylbromide in DMF in the presence of potassium carbonate as base provided the 1-allyloxy-4,5-dimethoxypyrene **32** in

87% yield. Heating compound **32** in a dry flask with *N*,*N*-diethylaniline at 195 °C for 6 h triggered a (3,3)-sigmatropic rearrangement to take place to provide 2-(prop-2-enyl)-1-hydroxy-4,5-dimethoxypyrene **33** in 54% yield. The hydroxyl group of **33** could be converted into the ester **34** in 95% yield upon reacting with acetic anhydride in pyridine and DMAP as catalyst. Treatment of **34** with titanium tetrachloride and dichloromethylmethyl ether in CH_2Cl_2 gave a mixture of formylated products **35** and **36**. On the other hand, conversion of the hydroxyl group of **33** into the triflate **37** was accomplished in 78% yield by treatment with trifluoromethanesulfonic anhydride and pyridine and dichloromethane. The allyl group in **37** was used as a handle to link two of the pyrene units together, thus, exposing compound **37** to Grubb's first generation catalyst in dichloromethane at 40 °C instigated a cross metathesis reaction to take place providing the diene **38** in 52% yield. The diene unit in **38** was hydrogenated by treatment with 2.5 mol% of Hoveyda-Grubb's second generation catalyst and sodium borohydride in a 9:1 mixture of dichloromethane and methanol to afford compound **39** in 70% yield. Recrystallization of **39** in dichloromethane/hexanes provided crystals suitable X-ray analysis. Getting a picture of the latter compound cleared any ambiguity with regards to the success of the synthesis. Treatment of **39** with bromine in dichloromethane provided the expected brominated product **40** in good yield. Compound **40** represents the most advanced stage of our synthesis.

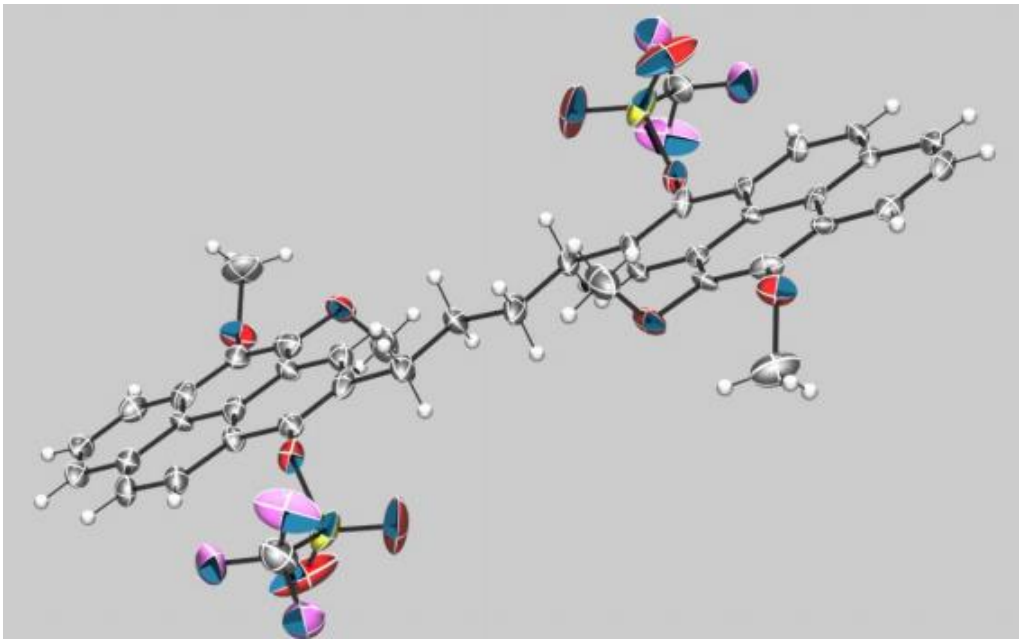
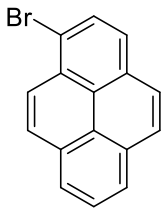


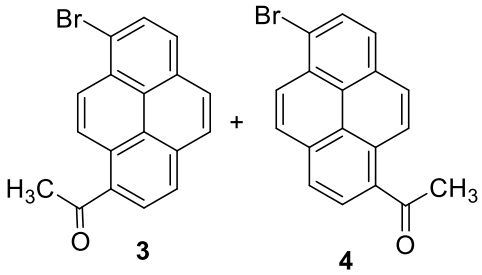
FIGURE 1: X-ray structure of compound **40**

Appendix 2: Selected Experimental Data for the Selective Substitution of Pyrene



2

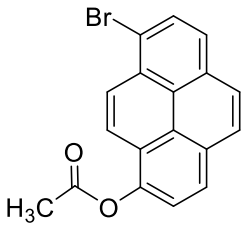
1-bromopyrene (2): To a stirred solution of pyrene (2.00 g, 9.89 mmol) in DMF (20 mL) at r.t. was added *N*-bromosuccinamide (1.848 g, 10.38 mmol). The solution was stirred at r.t for 20 h and monitored by TLC. Afterward, the reaction mixture was poured into H_20 (50 mL), acidified with 1 M HCl (3 × 50 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried ($MgSO_4$), filtered and concentrated. Purification was done by crystallization in boiling ethanol (120 mL); a small amount of CH_2Cl_2 was added slowly to ease the dissolution of the compound for recrystallization. The solution was then filtered using a filter funnel and the filtrate was allowed to slowly crystallize. Three crops of crystals were collected and the third crop was found to be very pure-the 1-bromopyrene and the mother liquor contained a mixture of 1-bromopyrene and pyrene. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.2 Hz, 1H), 8.21-8.16 (m, 3H), 8.11 (d, *J* = 9.2 Hz, 1H), 8.05-8.00 (m, 2H), 7.95 (dd, *J* = 8.5, 7.1 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 131.25, 131.04, 130.68, 130.11, 129.70, 129.06, 127.80, 127.19, 126.60, 126.02, 125.92, 125.83, 125.65, 125.60, 124.09, 120.03.



3 **4**

Compound 3 and 4: To a stirred solution of acetyl chloride (0.26 mL, 3.56 mmol) in dry CH_2Cl_2 (50 ml) at 0 °C was added $AlCl_3$ (0.948 g, 7.11 mmol). The reaction mixture was stirred for 5 min. Later on, 1-bromopyrene (1.00 g, 3.56 mmol) was to the reaction mixture and the solution was stirred for 15 min. Afterward, the solution was poured into ice cold H_2O (50 mL), acidified with 1 M HCl (50 mL), extracted with CH_2Cl_2 (4 × 30 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL), dried ($MgSO_{4)}$, filtered and concentrated. The residue was subjected to column chromatography with 10% EtOAC/hexanes to give compound **3** and **4** as a mixture of

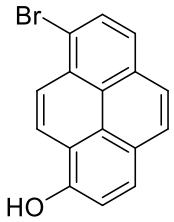
diastereomers (1.00 g, 3.09 mmol) 87%). R_f= 0.45 in 20% EtOAc/hexane.^{1}H NMR (600 MHz, $CDCl_3$) δ 9.02 (d, *J* = 9.6 Hz, 1H), 8.94 (d, *J* = 9.3 Hz, 1H), 8.42 (d, *J* = 9.6 Hz, 1H), 8.35 (d, *J* = 9.121Hz, 1H), 8.12 (dd, *J* = 2.24 Hz, *J* = 2.24 Hz, 2H), 8.18 (d, *J* = 3.42 Hz, 1H), 8.16 (d, *J* = 3.48 Hz, 1H), 8.06 (d, *J* = 7.98 Hz, 2H), 8.02 (d, *J* = 9.3 Hz, 1H). 7.96 (d, *J* = 9.18 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 9.96 Hz, 2H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 200.4, 134.8, 134.5, 133.4, 133.1, 131.6, 131.5, 131.4, 130.7, 130.4, 130.3, 130.2, 130.1, 129.8, 129.4, 129.1, 128.9, 128.7, 128.6, 127.6, 127.45, 127.4, 126.3, 126.25, 126.2, 125.7, 125.4, 125.2, 122.3, 122.2, 33.0.



5

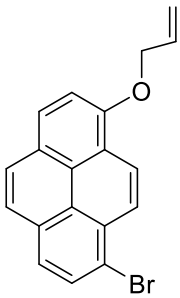
8-acetoxy-1-bromopyrene (3) and its diastereomer: To a stirred solution 8-acetyl-1-bromopyrene (0.760 g, 2.35 mmol) and *m*-CPBA (1.05 g, 4.70 mmol) in CH_2Cl_2 (30 mL) at r.t. was added finely divided powder $NaHCO_3$ (0.988 g, 11.76 mmol). The suspension was concentrated under reduced pressure to a solid residue. When the reaction wasn't complete after 20 min, a small volume of CH_2Cl_2 (5 mL) was added to the reaction mixture and the whole mixture was again concentrated to a solid. After about 3 h, H_2O (15 mL) and $NaHCO_3$ (15 mL) were added and the mixture stirred for 5 min at r.t. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ (15 mL), dried ($MgSO_4$), filtered and concentrated. The residue was subjected to column chromatography in 5% EtOAc/hexane to give compound **5** (0.400 g, 1.18 mmol, 50%). R_f = 0.42 in 50% CH_2Cl_2/hexane and 0.24 in 5% EtOAc/hexane. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 9.42 Hz, 1H), 8.42 (d, *J* = 9.18 Hz, 1H), 8.26 (dd, *J* = 1.92 Hz; *J* = 1.92 Hz, 2H), 8.23 (t, *J* = 7.74 Hz; *J* = 7.86 Hz, 2H), 8.19 (d, *J* = 9.42 Hz, 1H), 8.15 (d, *J* = 9.24 Hz, 1H), 8.11 (d, *J* = 9.12 Hz, 1H), 8.07 (t, *J* = 8.76 Hz; *J* = 9.06 Hz, 2H), 8.03 (d, *J* = 7.86 Hz, 1H), 8.0 (d, *J* = 9.06 Hz, 2H), 7.85 (d, *J* = 8.28 Hz,

2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 170, 145, 130.6, 130.55, 130.4, 129.7, 129.5, 129.4, 129.2, 128.7, 127.8, 127.4, 126.8, 126.7, 126.0, 125.8, 125.78, 125.75, 125.7, 125.6, 125, 123.3, 123, 121.7, 120.6, 120.45, 120.4, 120.2, 30, 20.



6

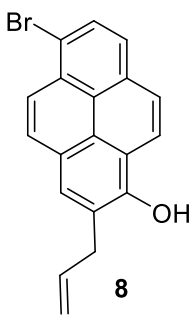
8-hydroxy-1-bromopyrene (6) and its diastereomer: To a stirred solution of compound **5** and its diastereomer (0.400 g, 1.18 mmol) in methanol (40 mL) at r.t. was added K_2CO_3 (0.326 g, 2.36 mmol). The reaction mixture was stirred at r.t. for 30 min. Later on, the solution was poured into ice cold H_2O (50 mL), acidified with 1 M HCl (60 mL), extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with $NaHCO_3$ (60 mL), dried ($MgSO_4$), filtered and concentrated to give compound **6** (0.370 g, 1.25 mmol, > 95%). R_f= 0.17 in 50% CH_2Cl_2/hexane.



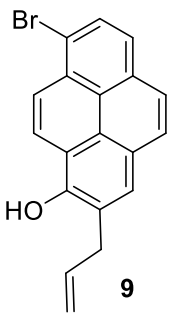
7

Synthesis of 8-(allyloxy)-1-bromopyrene (7) and its diastereomer: To a stirred solution of 8-hydroxy-1-bromopyrene (**6**) and its diastereomer (0.370 g, 1.25 mmol) in DMF (40 mL) at r.t. was added K_2CO_3 (0.258 g, 1.87 mmol) and allyl bromide (16.0 mL, 1.87 mmol). The reaction mixture was stirred for 3 h. Later on, the reaction mixture was poured into H_2O (30 mL) and acidified with 1 M HCl (50 mL). The solution was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with $NaHCO_3$ (500 mL), dried ($MgSO_4$), filtered and concentrated. The residue was subjected to column chromatography in 5% CH_2Cl_2/hexane to give compound **7** and its diastereomer. (0. 378 g, 1.12 mmol, 89%). R_f= 0.75 in 50% CH_2Cl_2/hexane. ^1H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 9.42 Hz, 1H), 8.47 (d, *J* = 9.06 Hz, 1H), 8.33 (d, *J* = 9.42 Hz, 1H), 8.20 (d, *J* = 9.121Hz, 1H), 8.15 (d, *J* = 8.22Hz, 2H), 8.02 (dd, *J* = 2.28Hz, *J* = 2.28Hz, 2H), 7.97Hz (d, *J* = 8.18 Hz, 1H), 7.93-7.85 (m, 4H), 7.76 (d, *J* = 8..82 Hz, 1H), 7.45 (dd, *J* = 3.3Hz, 3.33 Hz, 1H), 6.25 (m, 2H), 5.62 (d, *J* = 17.22 Hz, 2H). 5.45 (dd, *J* = 3.29 Hz; 1.32 Hz, 2H), 4.85

(d, *J* = 5.1 Hz, 4H). ^{13}C NMR (150 MHz, CDCl3): δ 153, 133.3, 131.2, 131.1, 130.3, 130.2, 130.1, 130.05, 128.8, 127.5, 126.2, 125.9, 125.3, 125 (3 signals), 124.8 (4 signals), 123.5, 122.8, 121.5, 120.4, 120.3, 118.9, 118.8, 117.8, 110, 70.

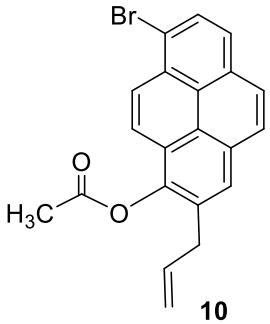


8



9

Compounds 8 and 9: A solution of compound **6** and its diastereomer (0.360 g, 1.07 mmol) in *N*,*N*-diethylaniline (3.6 mL) were heated under reflux at 190 °C for about 6 h. The reaction was monitored by TLC experiments in 50% CH_2Cl_2/hexanes (the compounds appear as one spot) and 10% EtOAc/hexane (the compounds separate into two). After 6 h, the reaction mixture was poured into H_20 (40 mL), washed several times with 1 M HCL solution (4 × 20 mL), extracted with EtOAc (15 mL), the aqueous layer was extracted with CH_2Cl_2. The combined organic phase were washed with a saturated solution of $NaHCO_3$ (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography in 10% EtOAc/hexane to give compound **8** (0.070 g) and **9** (0.064 g) 56% yield. R_f = 0.39 and 0.29 in 10% EtOAc/hexane.HRMS calculated for $C_{19}H_{12}0Br$ $[M-H]^+$ m/z = 335.01, found 335.0123 for compound **8** and 335.0156 for compound **9**.

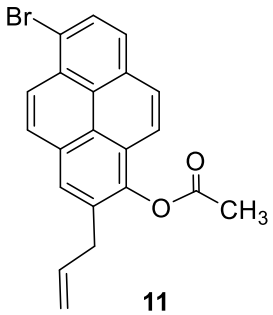


10

7-(prop-2-enyl)-6-acetoxy-1-bromopyrene (10): To a stirred solution of compound **9** (0.064 g, 1.9 x 10^{-1}mmol) in pyridine (2.5 mL) were added acetic anhydride (0.078 g, 7.6 x 10^{-1}mmol), and DMAP (0.010 g, 8.1 x 10^{-2} mmol). The solution was stirred for 30 min at r.t. Later on, the solution was poured in H_2O (20 mL), washed with 1 M HCl (3 × 20 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with $NaHCO_3$ (30 mL), dried ($MgSO_4$), filtered and concentrated to afford compound **10** (0.085 g, > 93%). R_f = 0.50 in 10% EtOAc/hexane. ^{1}H

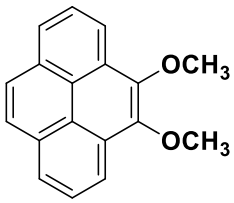
NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 9.4 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 10.7 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.96 (dd, *J* = 11.4, 8.7 Hz, 3H), 6.12 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.30-5.18 (m, 2H), 3.78-3.70 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.74, 143.57, 135.97, 131.08, 130.43, 130.29, 129.61, 129.49, 128.61, 128.22, 126.82, 126.00, 125.92, 125.81, 123.96, 123.86, 120.85, 120.60, 117.12, 35.63, 29.91, 21.04.

7-(prop-2-enyl)-8-acetoxy-1-bromopyrene (11): To a stirred solution of compound **8** (0.070 g, 2.1 x 10^{-1}mmol) in pyridine (3 mL) were added acetic anhydride (0.084 g, 8.3 x 10^{-1}mmol), and DMAP (0.015 g, 1.2 × 10^{-1}mmol). The solution was stirred for 30 min and monitored by TLC.



11

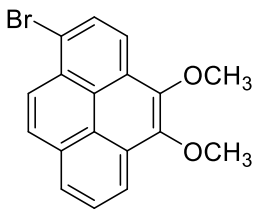
Later on, the solution was poured in H_2O (20 mL), washed with 1 M HCl (3 × 20 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with $NaHCO_3$ (30 mL), dried ($MgSO_4$), filtered and concentrated to provide compound **11** (0.074 g, 93%). R_f= 0.56 in 10% EtOAc/hexane. ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 9.48 Hz, 1H), 8.17 (d, *J* = 8.20 Hz, 1H), 8.04 (d, *J* = 10.68 Hz, 2H), 8.00 (d, *J* = 8.88 Hz, 1H), 7.60 (s, 1H), 7.30 (d, *J* = 2.72 Hz, 1H), 6.10 (m, 1H), 5.20 (m, 2H). 3.70 (d, *J* = 6.64 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.73, 143.57, 135.97, 131.08, 130.43, 130.29, 129.61, 129.49, 128.61, 128.22, 126.82, 126.00, 125.92, 125.81, 123.96, 123.86, 120.85, 120.60, 117.12, 35.64, 29.92, 21.05.



13

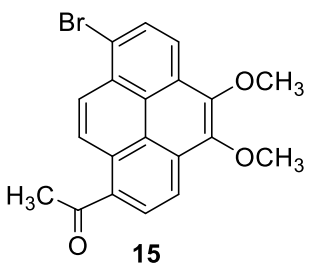
4, 5-dimethoxypyrene (13): To a stirred solution of pyrene-4,5-dione (**12**) (1.00 g, 4.31 mmol) in THF (20 mL) and H_2O (20 mL) were added tetra-*n*-butylammonium bromide (0.420 g, 1.30 mmol) and $Na_2S_2O_4$ (2.27 g, 18.0 mmol). After 10 min, a solution of NaOH (2.08 g, 52.1 mmol) in H_2O (20 mL) was added to the reaction mixture followed by Me_2SO_4 (2.74 g, 21.7 mmol). The red-colored reaction mixture was stirred at room temperature for 30 min. The reaction mixture was

extracted with EtOAc (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined EtOAc extracts were washed water (50 mL) followed by brine (50 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product was subjected to column chromatography (10% CH_2Cl_2/hexane) to yield compound **13** (1.11 g, 98%). R_f (40% CH_2Cl_2/hexane) = 0.48. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.59 (dd, *J* = 7.8, 1.4 Hz, 2H), 8.19 (dd, *J* = 7.7, 1.3 Hz, 2H), 8.12-8.08 (m, 4H), 4.30 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.99, 131.27, 128.53, 127.49, 126.20, 124.64, 123.03, 119.47, 61.34.



14

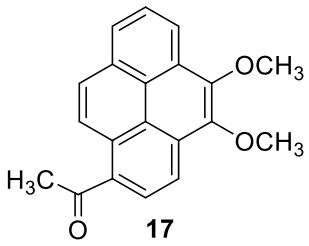
4, 5-dimethoxy-1-bromopyrene (14): To a stirred solution of 4,5-dimethoxypyrene **13** (0.050 g, 1.9 × 10^{-1} mmol) in dry CH_2Cl_2 (5 mL) at -78 °C were added a solution of bromine (0.033 g, 0.21 mmol) in CH_2Cl_2 (1 mL) dropwise over a 6 min period and monitored by TLC. Afterward, the reaction mixture was poured into a solution of $NaHSO_3$ (15 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with H_2O (20 mL), followed by brine (20 mL), dried (Na_2SO_4), filtered and concentrated. R_f = 0.5 in 40% CH_2Cl_2/hexane.



15

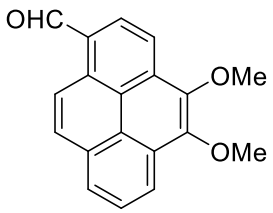
8-acetyl-4, 5-dimethoxy-1-bromopyrene (15): To a stirred solution of 4, 5-dimethoxy-1-bromopyrene (**13**) (0.080 g, 2.3 × 10^{-1}mmol) in dry CH_2Cl_2 (6 mL) at 0 °C was added acetyl chloride (0.074 g, 4.7 × 10^{-1} mmol), followed by $AlCl_3$ (0.125 g, 0.940 mmol). The solution was stirred for 45 min from 0 °C to r.t. while being monitored by TLC. Afterward, the solution was poured into ice H_2O (30 mL), acidified with 1 M HCl (20 mL), extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ (30 mL), then brine (20 mL), dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column

chromatography in 50% CH_2Cl_2/hexane to give compound **15** (0.034 g, 38%). R_f = 0.26 in 50% CH_2Cl_2/hexanes.^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.12 (d, *J* = 9.7 Hz, 1H), 8.55-8.49 (m, 2H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 4.24 (s, 3H), 4.20 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.98, 146.29, 144.19, 131.86, 131.81, 130.84, 129.50, 129.15, 128.31, 128.10, 128.01, 126.67, 123.86, 122.69, 121.42, 121.08, 119.03, 61.50, 61.38, 30.63, 29.93. HRMS calculated for $C_{20}H_{16}O_3Br$ $[M+H]^+$ m/z = 383.0283 found 383.0302.

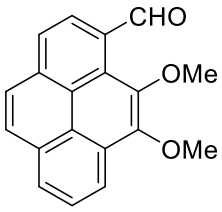


17

4, 5-dimethoxy-1-acetylpyrene (17): To a stirred solution of 4, 5-dimethoxypyrene (0.20 g, 0.76 mmol) in dry CH_2Cl_2 (6 ml) at 0 °C was added acetyl chloride (0.180 g, 2.29 mmol), followed by $AlCl_3$ (0. 610 g, 4.58 mmol). The reaction mixture was stirred for 20 min from 0 °C to r.t. Afterward, the reaction mixture was poured into H_2O (50 mL), washed with 1 M HCl (20 mL), extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ (20 mL), then brine (20 mL), dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography in 80% CH_2Cl_2/hexane to give compound **17** (0.215 g, 93%). R_f= 0.12 in 80% CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.08 (d, *J* = 9.4 Hz, 1H), 8.58 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.24-8.20 (m, 2H), 8.10-8.07 (m, 1H), 4.27 (s, 3H), 4.21 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.26, 146.73, 144.24, 131.79, 131.45, 130.64, 129.91, 129.69, 128.41, 127.68, 126.67, 125.80, 125.13, 123.29, 122.71, 120.85, 118.32, 61.48, 61.38, 30.64; HRMS calculated for $C_{20}H_{16}O_3$ $[M+H]^+$ m/z = 305.1178 found 305.1231

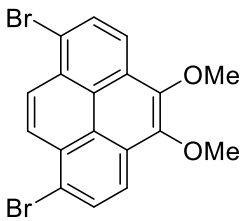


19



20

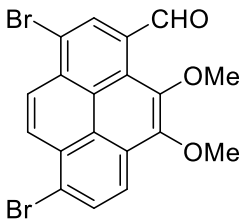
4,5-dimethoxy-1-pyrenecarbaldehyde (19), 4,5-dimethoxybenzene-3-pyrenecarbaldehyde (20): 1,2-dichlorobenzene (6 mL), *N*-methylformanilide (3 mL) and $POCl_3$ (mL) were heated together at 90 °C for 10 min. Later, a solution of 4,5-dimethoxypyrene (3.10 g 11.8 mmol) in 1,2-dichlorobenzene were added and the reaction mixture was heated at 100 °C for 17 h. Afterward, the reaction mixture was poured into H_2O (60 mL), washed with 1 M HCl (50 mL), extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were washed with 1 M HCl (5 × 50 mL), followed by $NaHCO_3$ (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography in 60% CH_2Cl_2/hexane to give a mixture of compounds (**19** and **20**) (3.0 g, 87%). R_f= 0.38 in 60% CH_2Cl_2/hexane. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 11.40 (s, 1H), 10.75 (s, 0.7H), 9.35 (d, *J* = 9.18 Hz, 1H), 8.60 (s, *J* = 7.12 Hz, 0.7 H), 8.56 (d, *J* = 7.2 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 0.7H), 8.44 (d, *J* = 7.98 Hz, 1H), 8.42 (d, *J* = 8.1 Hz, 1H), 8.22 (m, 2H), 8.12 (m, 2H), 8.08 (m, 2H), 8.02 (d, *J* = 8.82 Hz, 1H), 4.26 (m, 4H), 4.18 (s, 1.6H), 4.08 (s, 2.6 H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.65, 195.63, 193.30, 148.15, 147.75, 146.22, 144.28, 134.78, 133.39, 132.04, 131.27, 131.10, 130.98, 130.94, 130.51, 130.00, 128.56, 128.30, 127.98, 127.47, 127.01, 126.80, 126.74, 126.52, 126.45, 126.42, 124.74, 123.37, 123.18, 122.86, 122.84, 122.44, 121.61, 120.85, 118.81, 61.67, 61.55, 61.41, 60.63. HRMS calculated for $C_{19}H_{15}O_3$ $[M+H]^+$ m/z = 291.1021 found 291.1057.



26

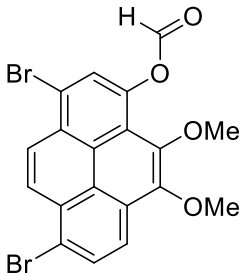
1,8-dibromo-4,5-dimethoxypyrene (26): To a solution of 4,5-dimethoxypyrene (0.12 g, 0.47 mmol) in CH_2Cl_2 (8 mL) were added a solution of bromine (0.165 g, 1.03 mmol) in CH_2Cl_2 (1.40 mL) and the

mixture was stirred at r.t for 15 min. Afterward, the reaction mixture was poured into $NaHSO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with H_2O (20 mL), followed by brine (20 mL), dried (Na_2SO_4), filtered and concentrated to provide compound **26** (0.190 g, >95 %). R_f in 40% CH_2Cl_2/hexanes = 0.51. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 2H), 8.36 (d, *J* = 8.4 Hz, 2H), 8.28 (d, *J* = 8.4 Hz, 2H), 4.20 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.65, 131.00, 129.65, 128.33, 127.67, 123.65, 120.91, 120.30, 61.40.



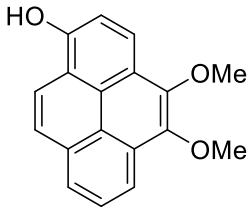
27

1,8-dibromo-4,5-dimethoxy-3-pyrenecarbaldehyde (27): Titanium tetrachloride (0.17 g, 0.90 mmol) and dichloromethyl methyl ether (0.11 g mg, 0.90 mmol) in CH_2Cl_2 (5 mL) were stirred together at room temperature for 10 min. The temperature was decreased to 0 °C and compound **26** (0.19 g, 0.45 mmol) was added to the reaction mixture and stirred together for 2 h from 0 °C to r.t. Afterward, one more equiv. of $TiCl_4$ and Cl_2CHOCH_3 were added and the solution was stirred for an additional hour. Later on, the reaction mixture was poured into H_2O (20 mL) and a saturated solution of $NaHCO_3$ (20 mL) were added and stirred for 5 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL).The combined organic extracts were washed with $NaHCO_3$ (20 mL), dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography in 20% CH_2Cl_2/hexane to afford compound **27**. R_f = 0.10 in 20% CH_2Cl_2/hexane. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.29 (s, 1H), 8.70-8.66 (m, 2H), 8.58 (d, *J* = 9.4 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 4.28 (s, 3H), 4.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.93, 147.66, 145.77, 132.79, 131.88, 131.66, 130.96, 130.05, 129.81, 127.97, 127.74, 124.15, 123.65, 122.20, 122.11, 120.56, 61.78, 60.82, 53.65.

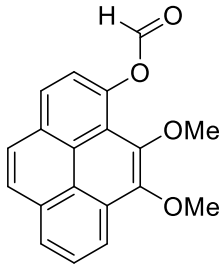


28

3-formyl-1,8-dibromo-4,5-dimethoxypyrene (28): To a solution of compound **27** (0.12 g, 0.27 mmol) in CH_2Cl_2 (8 mL) and MeOH (8 mL) were added conc. H_2SO_4 (4 drops) and 35 % solution of H_2O_2 (4 drops) and the mixture was stirred at r.t for 45 min. Later, the solvent was evaporated under reduced pressure and the residue was taken into CH_2Cl_2 (10 mL) and H_20 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography in 10% CH_2Cl_2/hexanes to give compound **28** (0.10 g, 80%). R_f = 0.17 in 10% CH_2Cl_2/hexane. ^{1}HNMR ($CDCl_3$, 400 MHz) δ 10.13 (s, 1H), 8.39 (d, *J* = 9.4 Hz, 1H), 8.28 (d, *J* = 9.4 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 4.30 (s, 3H), 4.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.51, 145.29, 143.70, 131.29, 130.50, 128.37, 127.84, 124.72, 124.60, 124.57, 123.29, 121.85, 120.19, 119.63, 119.04, 62.34, 61.26.



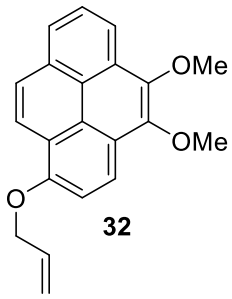
29



30

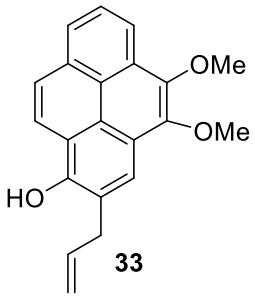
1-hydroxy-4,5-dimethoxypyrene (29) and 3-formyl-4,5-dimethoxybenzene-3-pyrene carbaldehyde (30): To a mixture of 4,5-dimethoxy-1-pyrenecarbaldehyde (**19**) and 4,5-dimethoxybenzene-3-pyrenecarbaldehyde (**20**) (0.500 g, 1.72 mmol) in CH_2Cl_2 (12 mL) and MeOH (12 mL) were added conc. H_2SO_4 (9 drops) and 35% solution of H_2O_2 (9 drops) and the mixture was stirred at r.t for 2 h. Later, the solvent was evaporated under reduced pressure and the residue was taken into CH_2Cl_2 (20 mL) and H_20 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was subjected to

column chromatography in 80% CH_2Cl_2/Hexanes to give compounds **29** (0.35 g) and **30** (0.140 g). R_f of compound **29** and **30** in 80% CH_2Cl_2/Hexanes are 0.15 and 0.62 respectively. Characterization information for compound **30**: ^{1}HNMR ($CDCl_3$, 600 MHz) δ 10.02 (s, 1H), 8.32 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.06 (dd, *J* = 15.4, 8.1 Hz, 2H), 7.99 (t, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 4.32 (s, 3H), 4.16 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.23, 145.62, 143.96, 132.21, 128.75, 127.71, 126.95, 126.50, 124.75, 124.63, 124.55, 124.31, 124.00, 117.77, 115.30, 112.72, 62.18, 61.18.



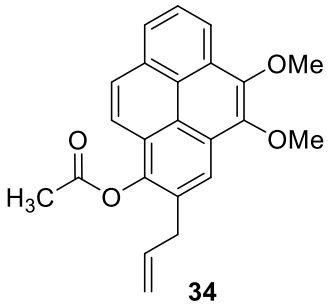
32

Compound 32: To a stirred solution of 1-hydroxy-4,5-dimethoxypyrene (**29**) (0. 50 g, 1.8 × 10^{-1}mmol) in DMF (5 mL) was added K_2CO_3 (0.40 g, 2.8 × 10^{-1}mmol) and allyl bromide (0.33 g, 2.7 × 10^{-1} mmol). The reaction mixture was stirred at r.t for 2 h. Later on, the reaction mixture was poured into H_2O (20 mL) and acidified with 1 M HCl (20 mL). The solution was then extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with 1 M HCl (20 mL) followed by $NaHCO_3$ (20 mL), dried (Na_2SO4), filtered and concentrated. The residue was subjected to column chromatography in CH_2Cl_2 to give compound **32** (0.50 g, 87%). R_f = 0.8 in 100% CH_2Cl_2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 9.1 Hz, 1H), 8.43-8.39 (m, 2H), 8.10 (dd, *J* = 7.7, 1.2 Hz, 1H), 8.07-7.99 (m, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 6.27 (ddd, *J* = 12.2, 10.5, 5.3 Hz, 1H), 5.64-5.58 (m, 1H), 5.44-5.38 (m, 1H), 4.91 (dt, *J* = 5.2, 1.7 Hz, 2H), 4.24 (s, 3H), 4.20 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.61, 145.09, 143.03, 133.56, 131.78, 129.25, 126.53, 126.45, 124.37, 123.93, 123.24, 122.34, 121.39, 120.89, 120.13, 118.84, 117.84, 109.79, 69.93, 61.35, 61.24, 29.93; HRMS calculated for $C_{21}H_{19}O_3$ $[M+H]^+$ m/z = 319.1334 found 319.1348.



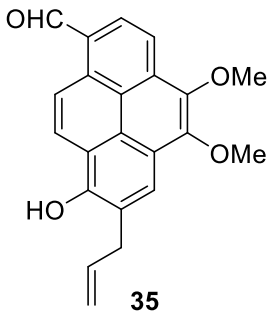
33

7-(prop-2-enyl)-8-hydroxy-4,5-dimethoxypyrene (33): A solution of compound **32** (0.730 g, 2.29 mmol) in *N*,*N*-diethylaniline (5 mL) were heated under reflux at 190 °C for about 3 h. The reaction was monitored by TLC and 4 mL of *N*, *N*-diethylaniline were added again and stirred. After 7 h, the reaction mixture was poured into H_20 (40 mL), diluted with 1 M HCl solution (60 ml), extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phase were washed with 1 M HCl (4 × 20 mL) followed by a saturated solution of $NaHCO_3$ (60 mL), dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography in 10% EtOAc/hexanes to afford compound **33** (0.54 g, 58%). R_f = 0.23 in 10% EtOAc/hexanes.

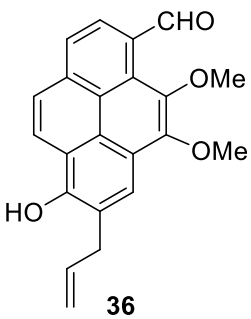


34

1-acetoxy-2-(prop-2-enyl)-4,5-dimethoxypyrene (34): To a solution of compound **33** (0.26 g, 8.0×10^{-2}mmol) in pyridine (3 mL) were added Ac_2O (5 drops) and DMAP (0.20 g, 1.6×10^{-2}mmol). The solution was stirred at r.t for 30 min and monitored by TLC. Later on, the solution was poured in H_20 (20 mL), diluted with 1M HCl (20 mL), extracted with CH_2Cl_2 (2 × 10 mL), washed with 1 M HCl (3 × 10 mL) followed by $NaHCO_3$ (20 mL), dried (Na_2SO_4), filtered and concentrated to give compound **34** (0.030 g, >95 %). $R_f$in 10% EtOAc/hexane = 0.31. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.38 (s, 1H), 8.14 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 8.05-8.01 (m, 1H), 7.95 (d, *J* = 9.1 Hz, 1H), 6.14 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.28-5.18 (m, 2H), 4.22 (s, 3H), 4.21 (s, 3H), 3.76 (dt, *J* = 6.7, 1.6 Hz, 2H), 2.58 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.89, 144.81, 144.68, 142.83, 136.28, 130.82, 130.46, 128.56, 128.47, 126.86, 126.39, 124.91, 123.83, 122.86, 122.83, 120.85, 120.47, 120.06, 116.76, 61.38, 61.36, 36.02, 29.92, 21.07; HRMS calculated for $C_{23}H_{21}O_4$ $[M+H]^+$ m/z = 361.1440 found 361.1430.

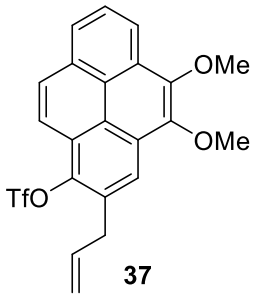


35



36

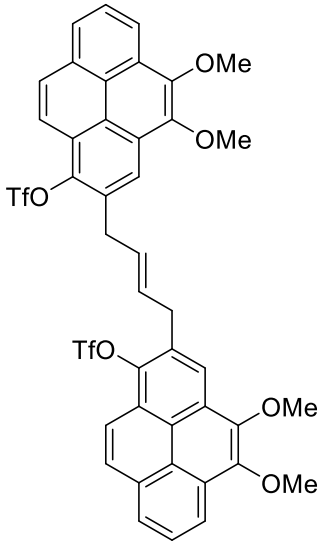
Compounds 35 and 36: A stock solution of titanium tetrachloride (0.32 g, 0.17 mmol) and dichloromethyl methyl ether (0.19 g, 0.17 mmol) in CH_2Cl_2 (3 mL) were stirred together at room temperature for 5 min. The temperature was decreased to 0 °C and compound **34** (30 mg, 8.3×10^{-2} mmol) was added to the reaction mixture and stirred together for 4 h from 0 °C to r.t. while being monitored by TLC. Afterward, 5 drops of $TiCl_4$ and 4 drops of Cl_2CHOCH_3 were added and the solution was stirred for an additional hour. Later on, the reaction mixture was poured into H_2O (20 mL) and a saturated solution of $NaHCO_3$ (20 mL) were added and stirred for 5 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL).The combined organic extracts were washed with $NaHCO_3$ (20 mL), dried (Na_2SO_4), filtered and concentrated to give a mixture of compounds (**35** and **36**). R_f = 0.34 in 20% EtOAc/hexanes.



37

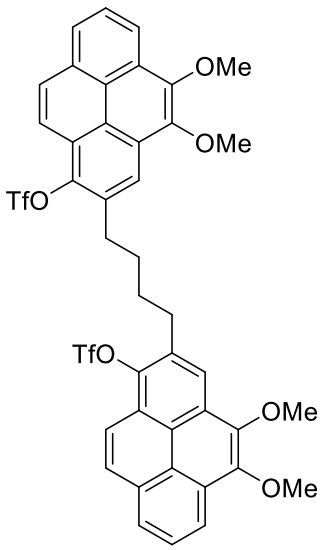
Compound 37: To a solution of compound **34** (0.540 g, 1.70 mmol) in CH_2Cl_2 (30 mL) at r.t were added pyridine (0.27 g, 0.27 mL). The temperature was decreased to 0 °C and trifluoromethanesulfonyl anhydride (0.57 g, 0.35 mL) were added and the mixture was stirred from 0 °C to r.t for 30 min. Later on, the solution was poured in H_20 (20 mL), diluted with 1M HCl (20 mL), extracted with CH_2Cl_2 (3 × 15 mL), washed with 1 M HCl (3 × 15 mL) followed by $NaHCO_3$ (30 mL), dried (Na_2SO_4), filtered and concentrated. The residue was subjected to column chromatography in 5% EtOAc/hexane to give compound **37** (0.59 g, 77%). R_f in 5% EtOAc/hexanes = 0.25. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.42 (s, 1H), 8.29 (d, *J* = 9.2 Hz, 1H), 8.19 (dd, *J* = 8.3, 6.1 Hz, 2H), 8.07 (t, *J* = 7.7 Hz, 1H),

6.18 (ddt, *J* = 16.1, 10.6, 6.6 Hz, 1H), 5.34-5.27 (m, 2H), 4.23 (d, *J* = 3.6 Hz, 6H), 4.01 (dd, *J* = 6.9, 1.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.79, 144.12, 140.14, 135.46, 131.44, 130.48, 129.65, 128.56, 128.53, 126.91, 125.65, 124.67, 122.88, 122.18, 121.29, 120.94, 120.15, 120.10, 117.75, 61.39, 61.38, 53.63, 35.44; HRMS calculated for $C_{22}H_{18}O_5F_6S$ $[M+H]^+$ m/z = 451.0827 found 451.0840.



38

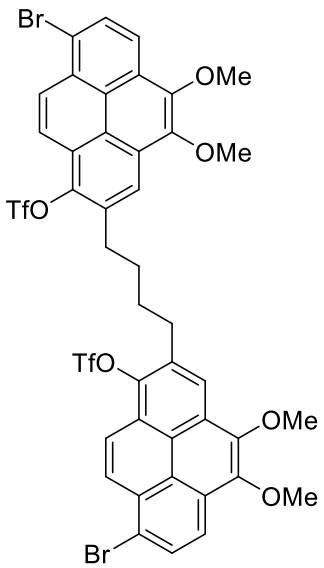
Compound 38: Grubbs' first-generation catalyst (0.025 g, 0.030 mmol) was added to a stirred solution of **37** (0.270 g, 0.599 mmol) in dichloromethane (10 mL) and the reaction was heated to 40 °C. After 21 h, the solvent was removed under reduced pressure and residue was purified by flash chromatography (15 × 2.5 cm, 1:9 EtOAc/hexanes) to give compound **38** as an brown oil (0.110 g, 52% BOR of **37**); R_f = 0.31 (1:9 EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55-8.52 (m, 2H), 8.41 (s, 2H), 8.31-8.27 (m, 2H), 8.21 (dd, *J* = 8.7, 2.2 Hz, 4H), 8.10-8.06 (m, 2H), 6.03 (dd, *J* = 4.8, 3.1 Hz, 2H), 4.19 (s, 6H), 4.10 (s, 6H), 4.05-4.02 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.75, 144.11, 140.05, 131.77, 130.46, 130.18, 129.68, 129.41, 128.58, 128.50, 126.94, 125.68, 124.67, 122.86, 122.15, 121.30, 120.93, 120.16, 61.40, 61.27, 34.37.



39

Compound 39: Hoveyda-Grubbs′ second-generation catalyst (0.010 g, 0.016 mmol) and sodium borohydride (0.025 g, 0.66 mmol) were added to a stirred solution of **38** (0.110 g, 0.130 mmol) in 1:9 MeOH/CH_2Cl_2 (14 mL) at 23 °C. After 40 h, the reaction mixture was poured into water (30 mL) and extracted with dichloromethane (3 ×

10 mL). The combined organic extracts were washed with water (20 mL) and 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; 3:7 CH_2Cl_2/hexane) to afford compound **39** as a light brown oil (0.070 g, 70% BOR of 38): R_f= 0.39 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 7.9, 1.2 Hz, 2H), 8.38 (s, 2H), 8.25 (d, *J* = 9.2 Hz, 2H), 8.21-8.14 (m, 4H), 8.08 (t, *J* = 7.7 Hz, 2H), 4.23-4.15 (m, 12H), 3.35-3.26 (m, 4H), 2.10-2.03 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.75, 144.13, 140.37, 133.57, 130.48, 129.60, 128.56, 128.53, 126.88, 125.66, 124.68, 122.75, 122.24, 121.11, 120.92, 120.17, 61.42, 61.34, 31.44, 30.60.



40

Compound 40: Bromine (0.0078 g, 0.049 mmol) was added to a stirred solution of **39** (0.015g, 0.017 mmol) in CH_2Cl_2 (2 mL) and resulting mixture wasstirred at r.t. After 5 min, the mixture was poured into a 5% $NaHSO_3$ solution (10 mL), the layers were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with a H_2O (10 mL) and brine (10 mL), dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (6 × 0.5 cm, 3:7 /hexanes) to yield dibromide **40** as a reddish white solid (0.014 g, 80%): R_f= 0.16 (3:7 CH_2Cl_2/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 9.5 Hz, 2H), 8.40 (s, 2H), 8.36 (d, *J* = 8.4 Hz, 2H), 8.29 (dd, *J* = 8.9, 3.4 Hz, 4H), 4.17 (d, *J* = 2.9 Hz, 12H), 3.30-3.27 (m, 4H), 2.09-2.03 (m, 4H).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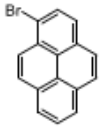
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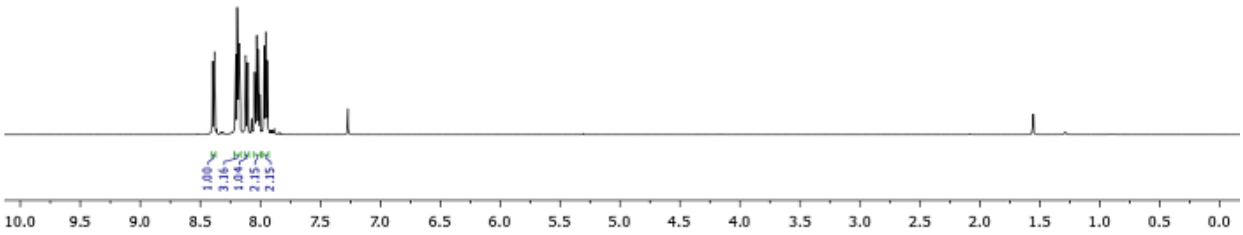
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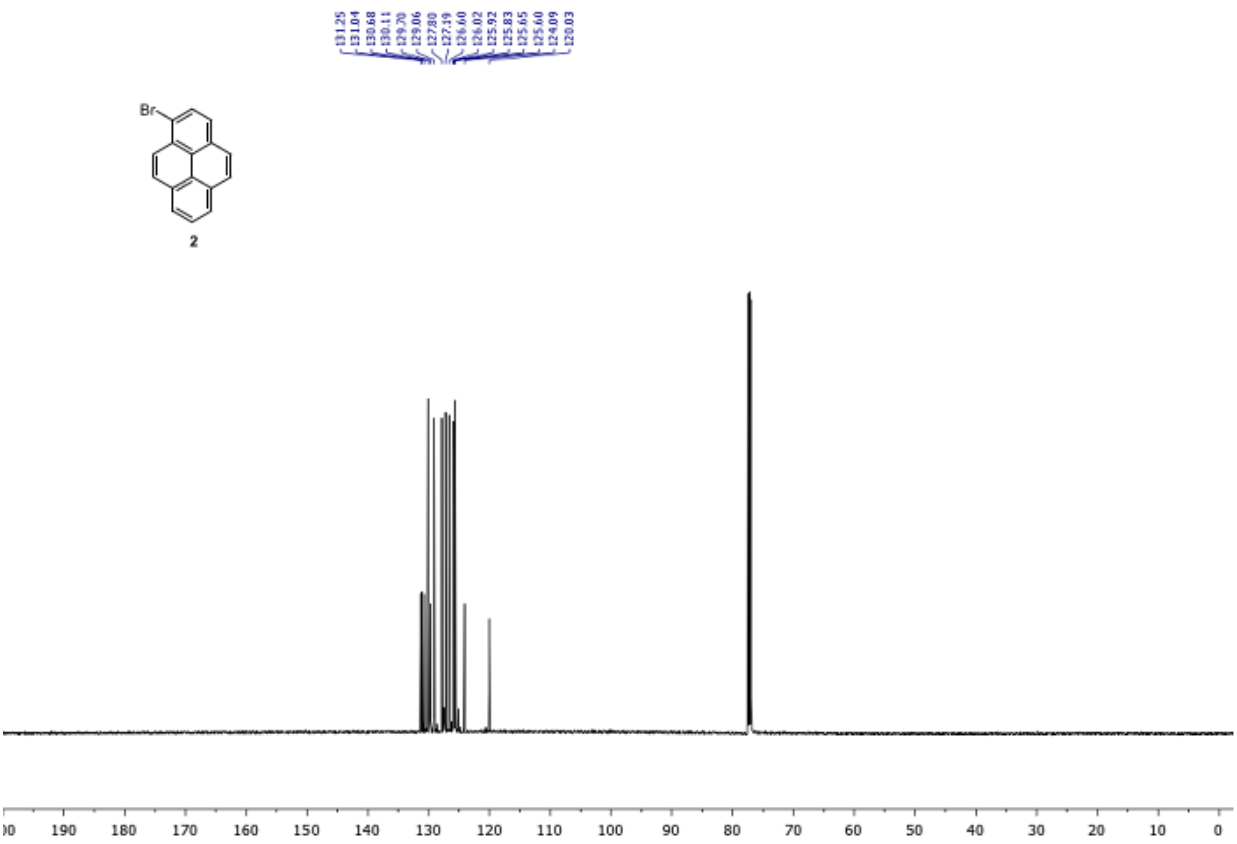
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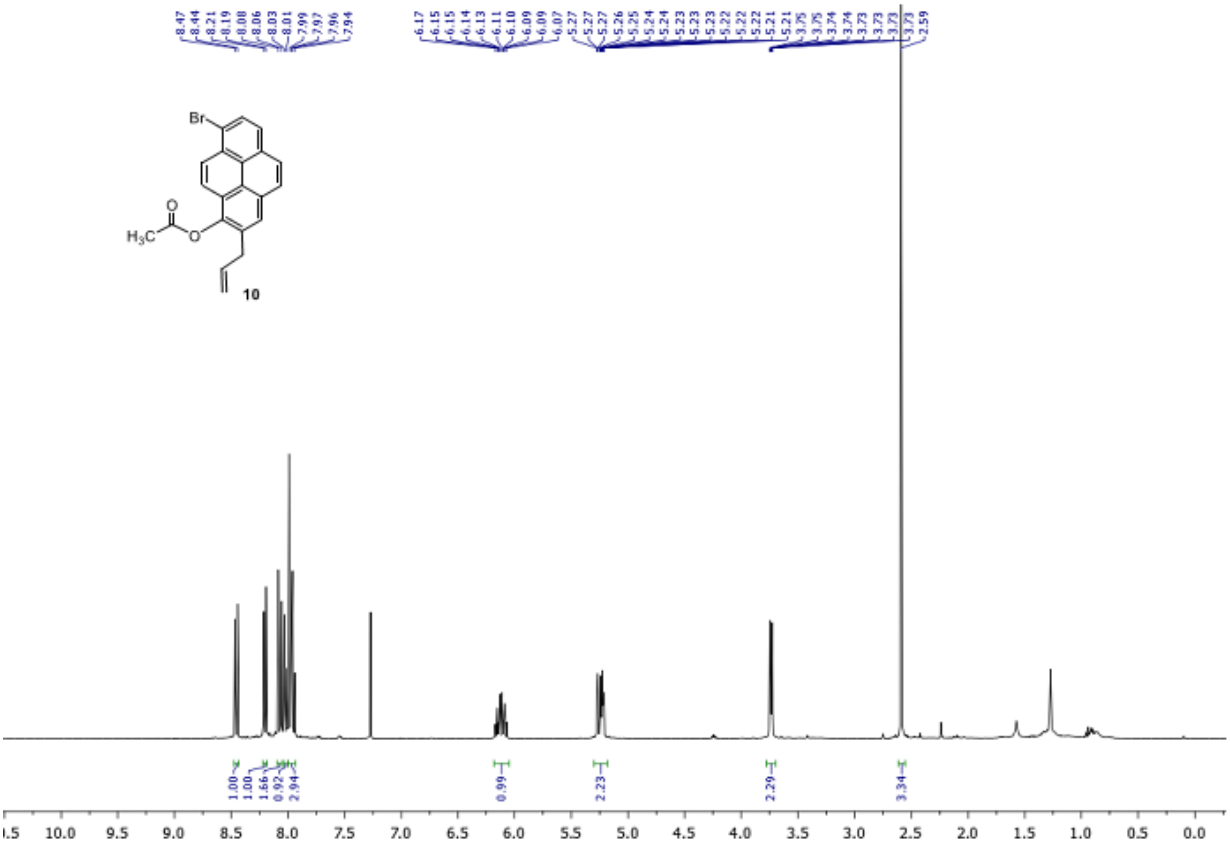
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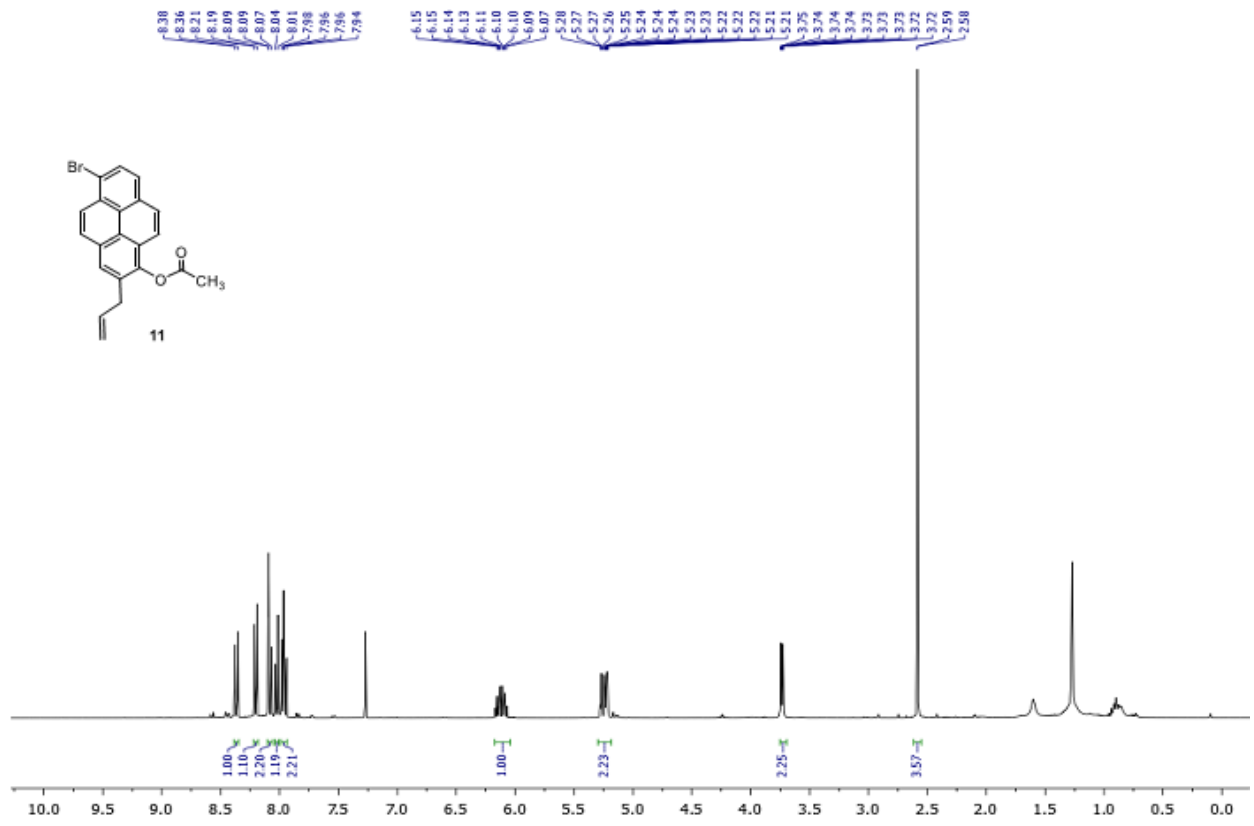
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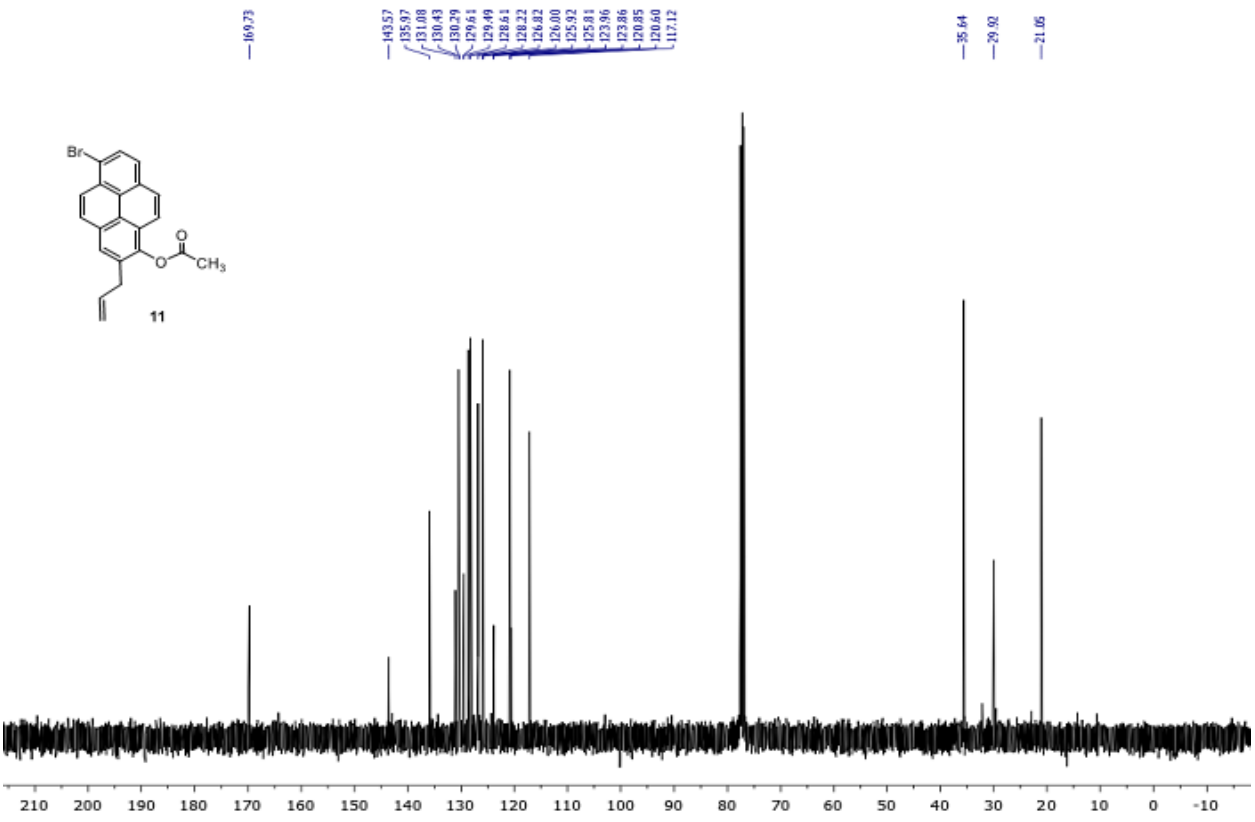
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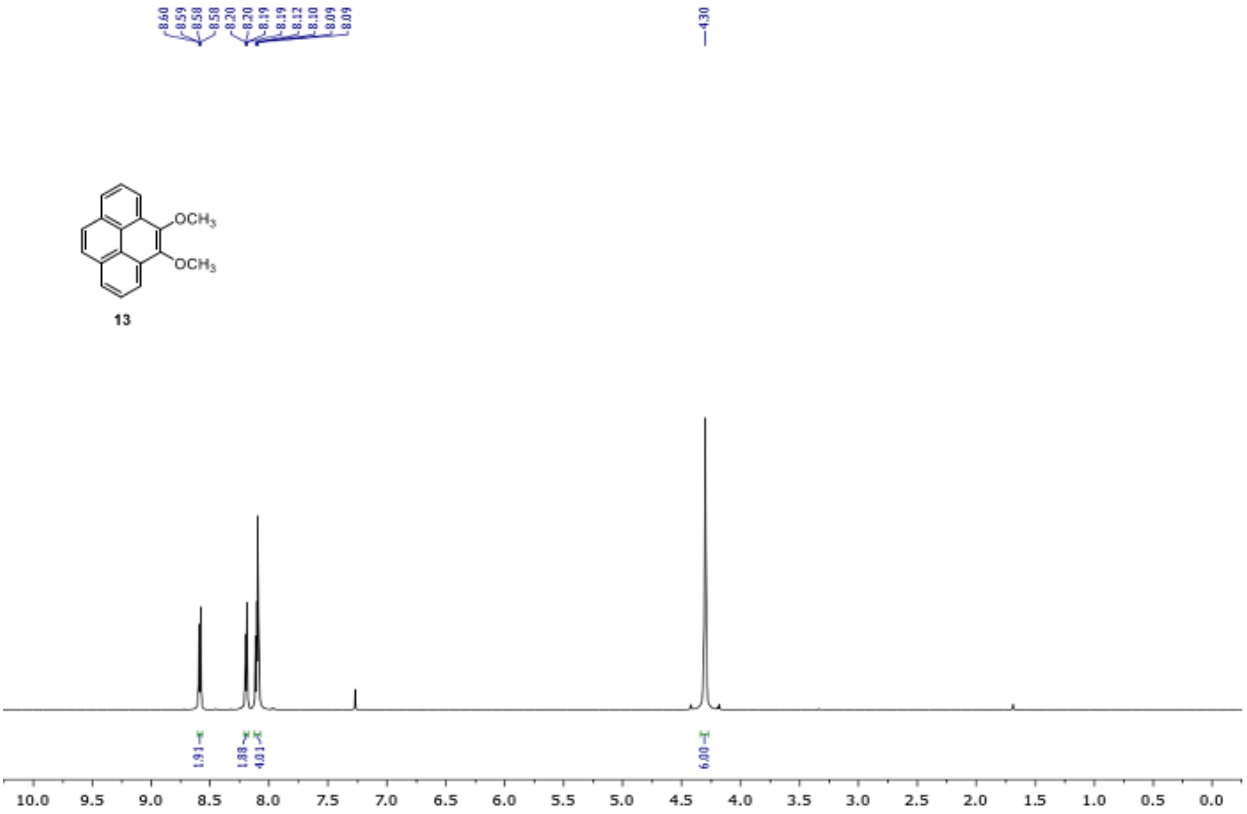
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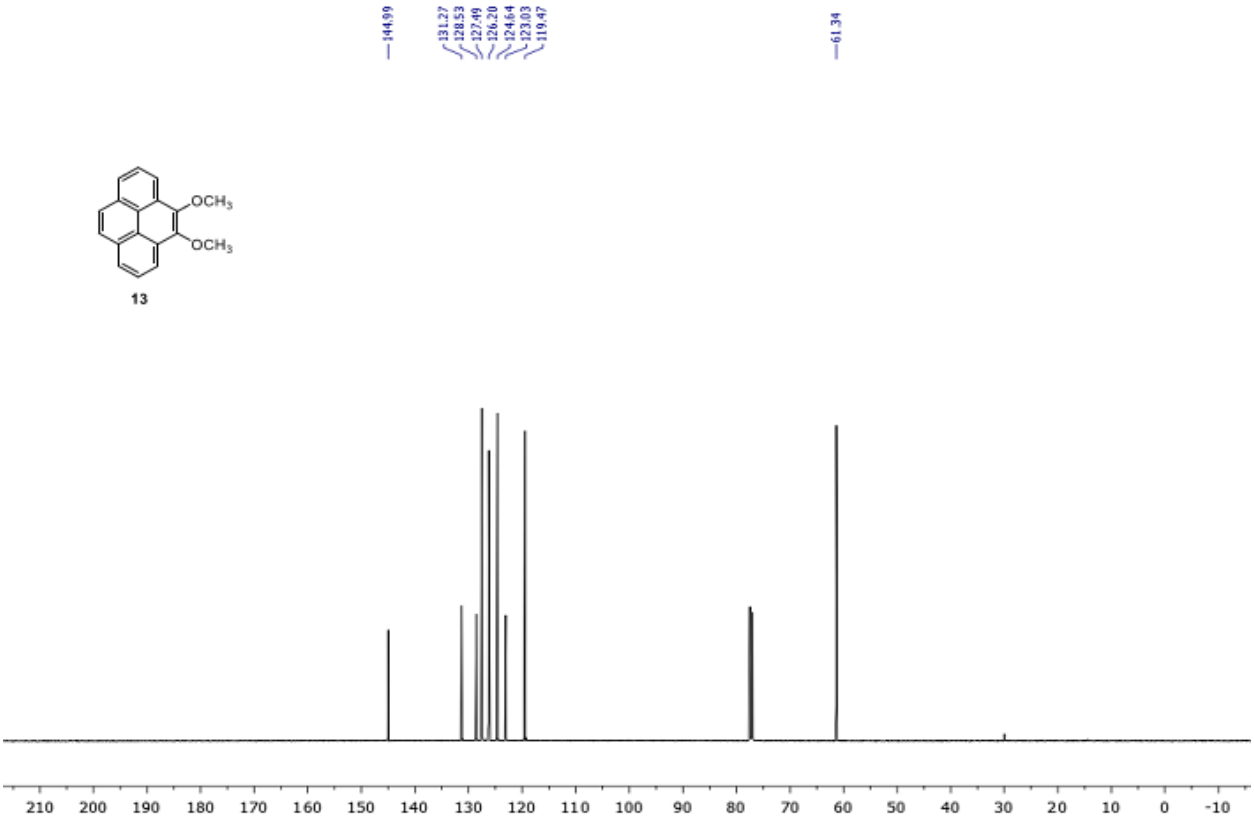
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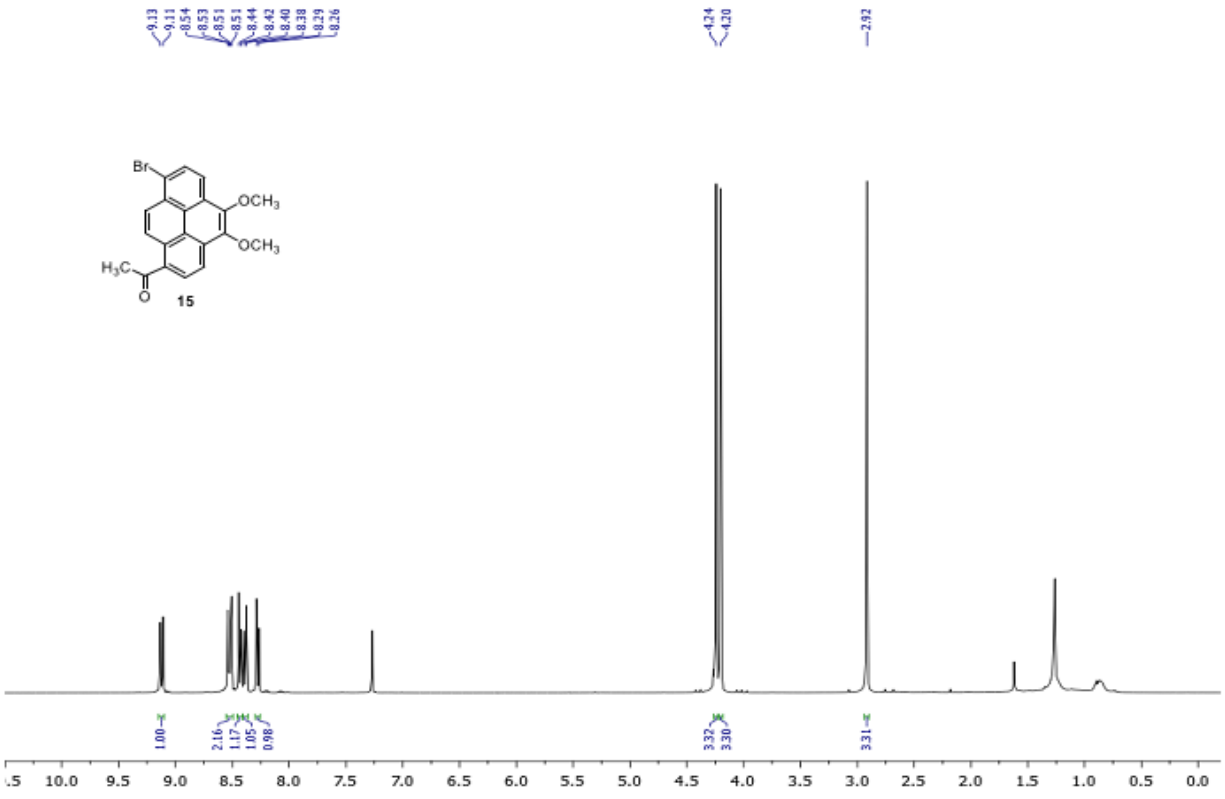
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OCH3
H3C
O
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1.05
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3.31
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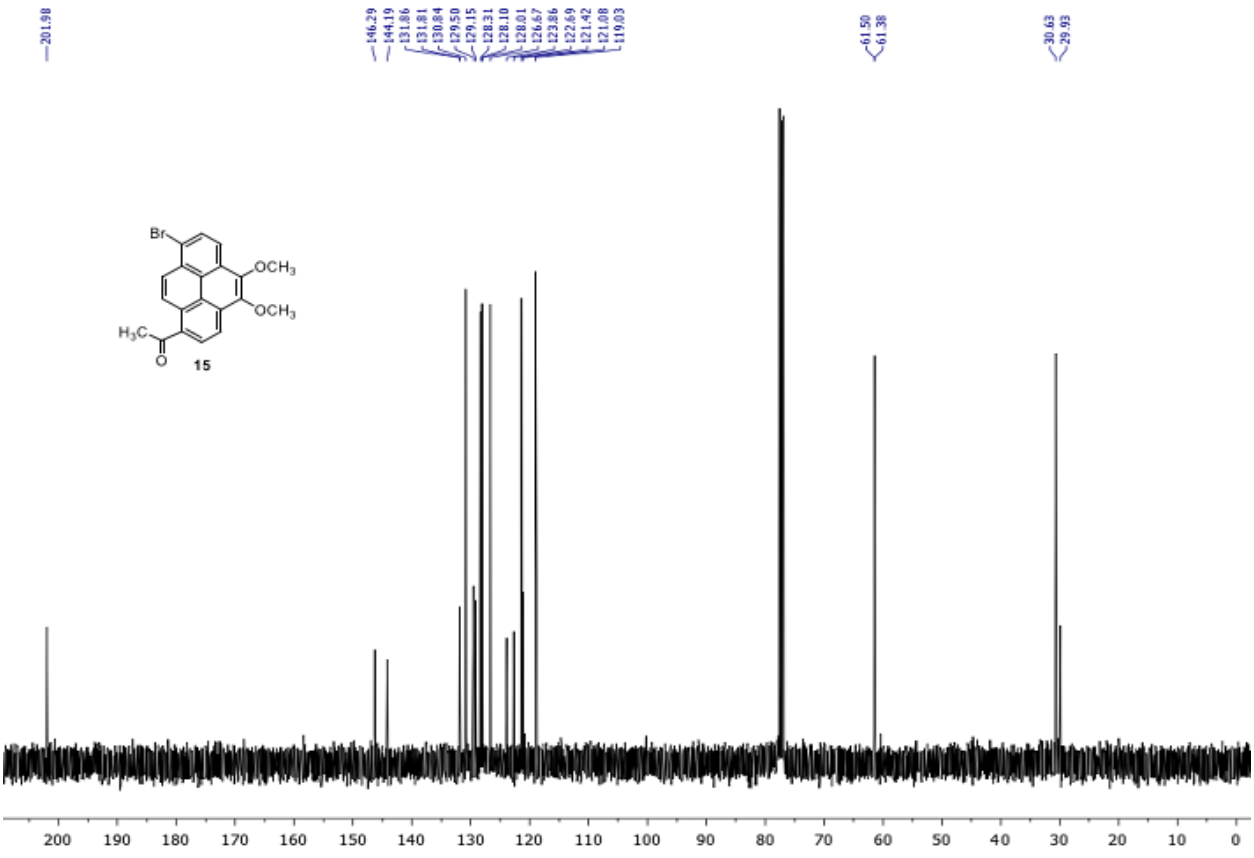
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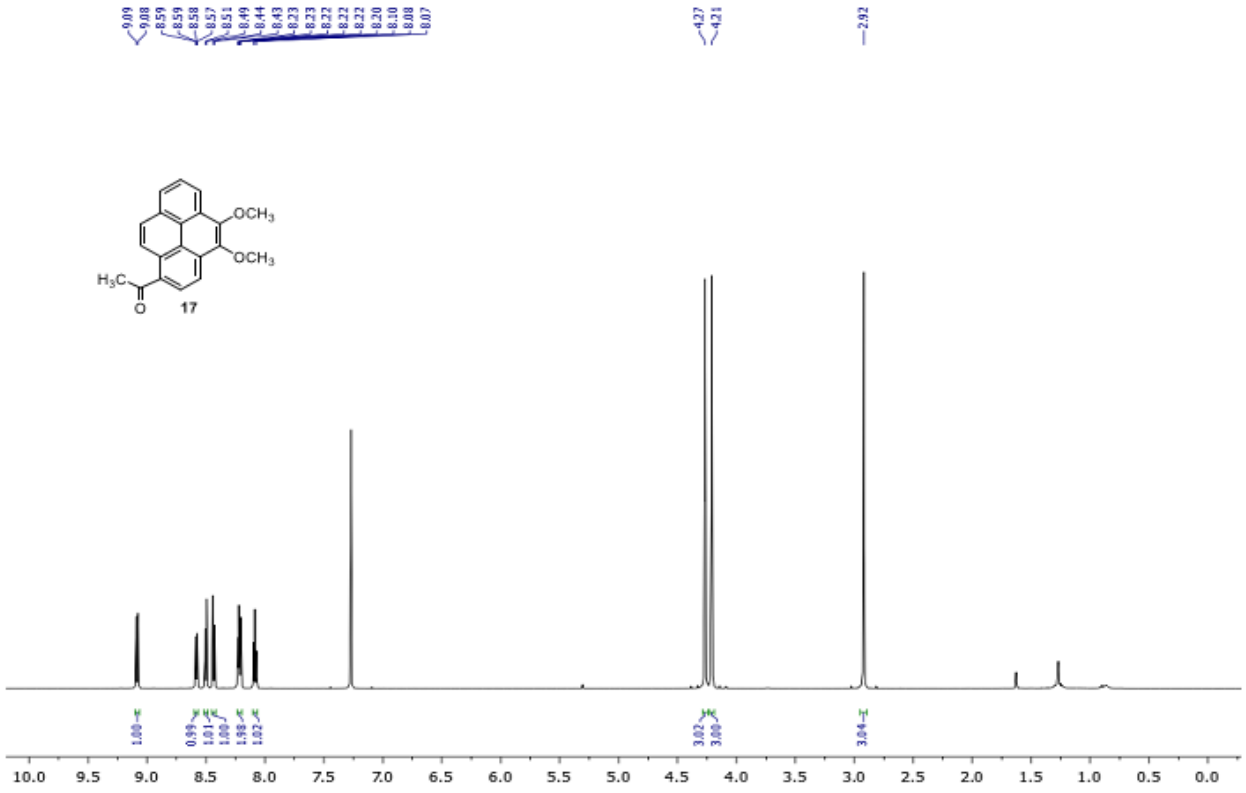
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3.00
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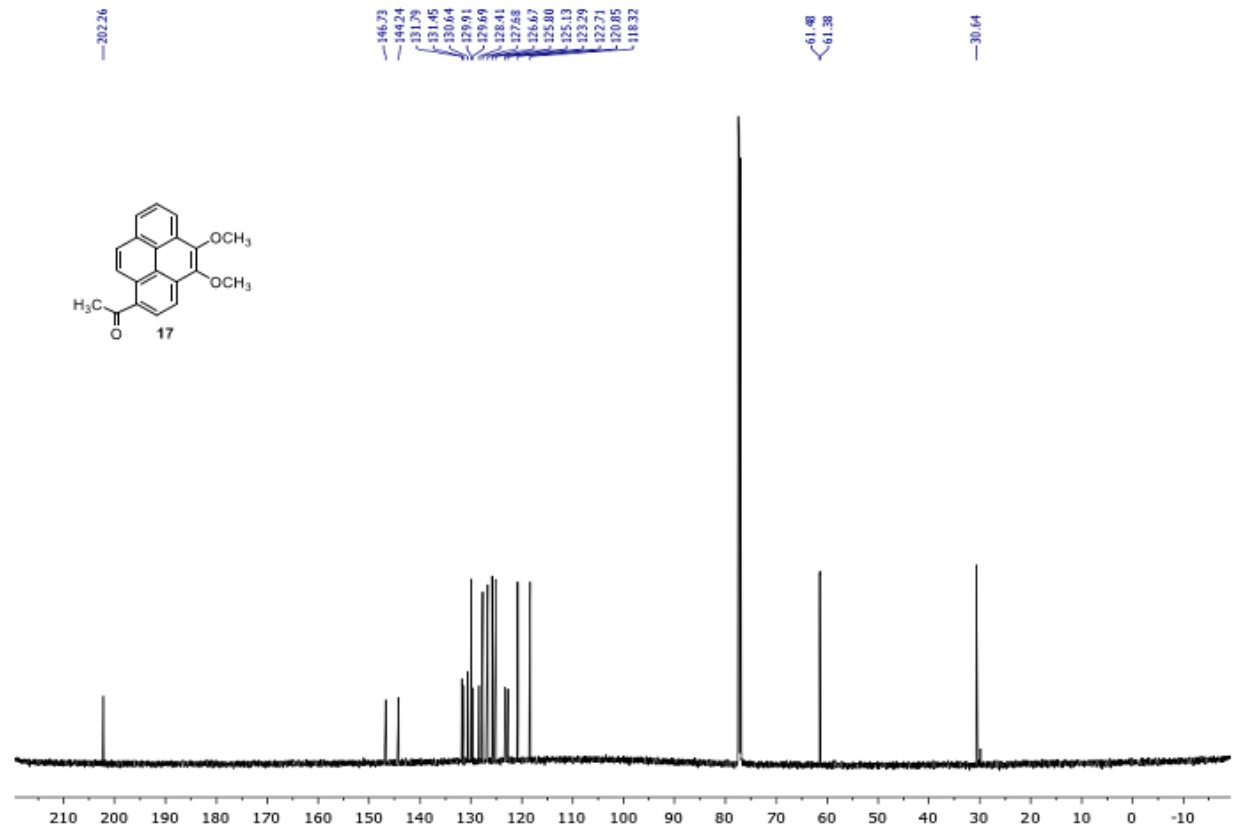
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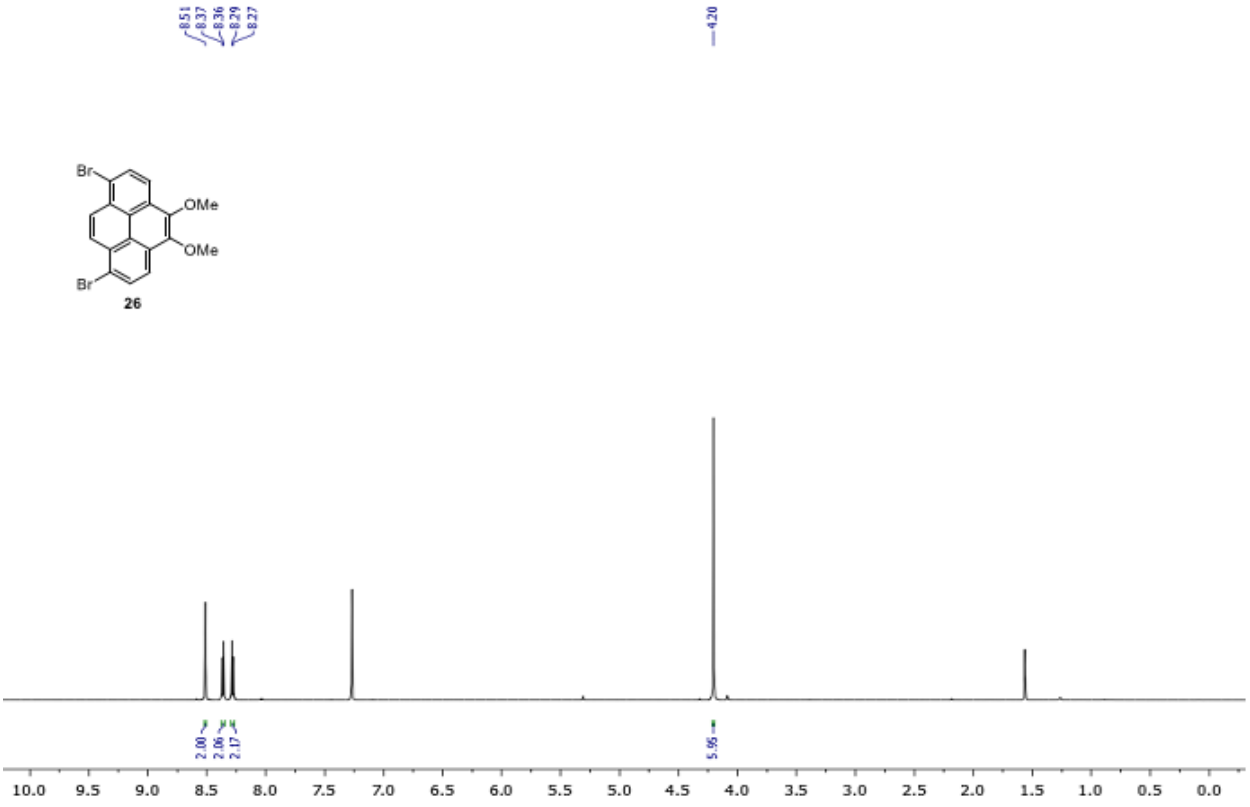
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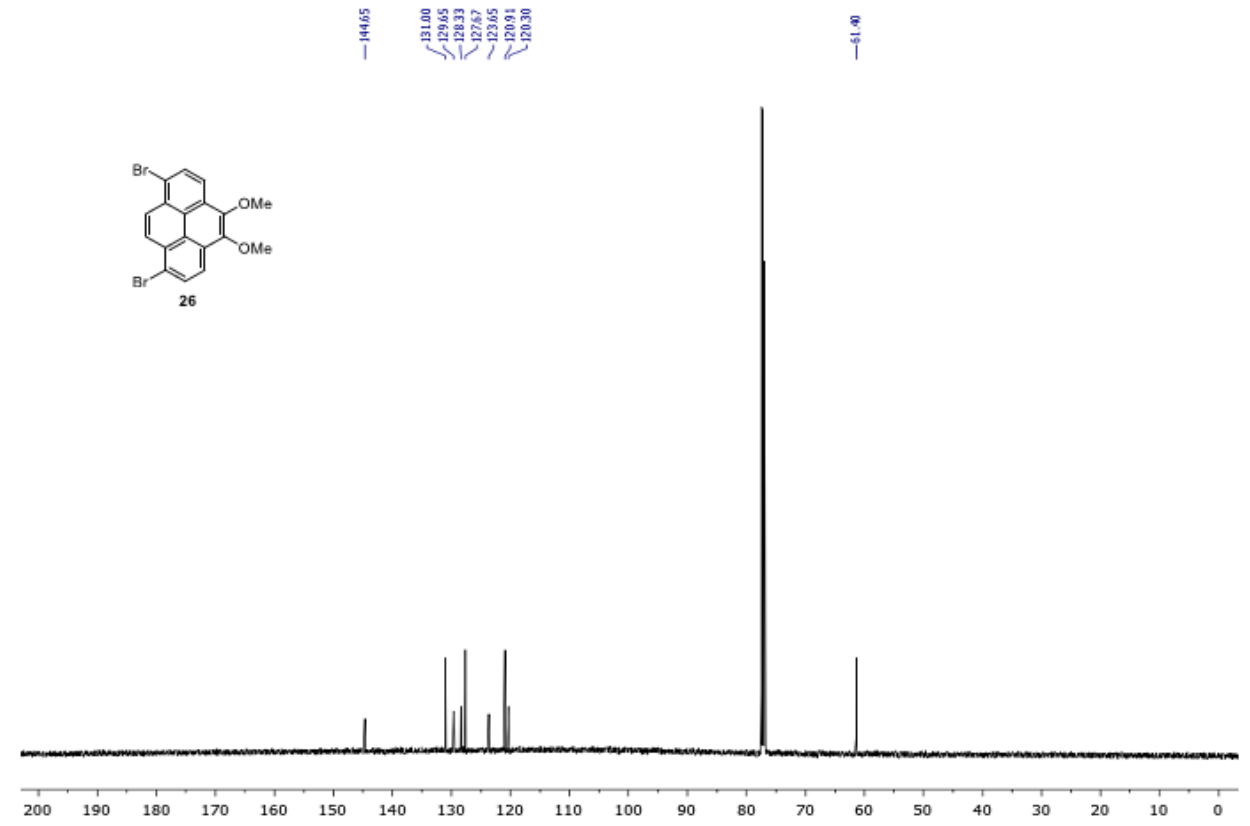
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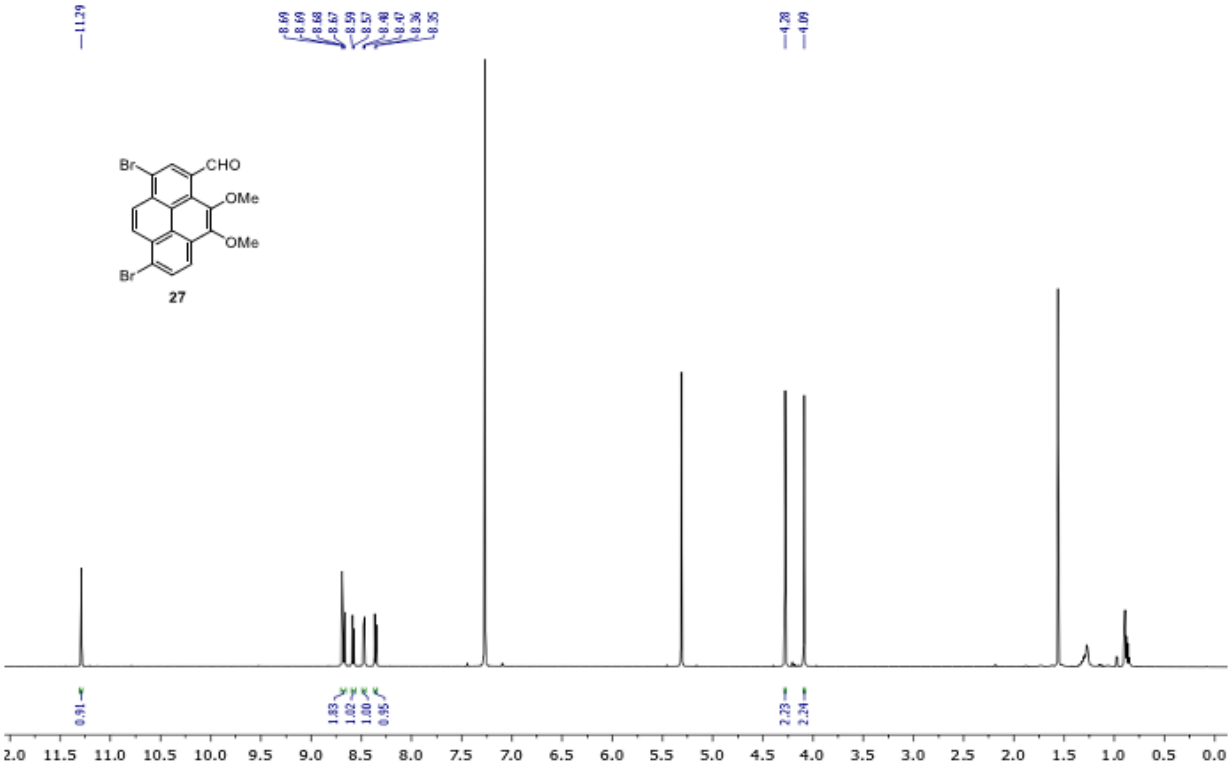
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0.95
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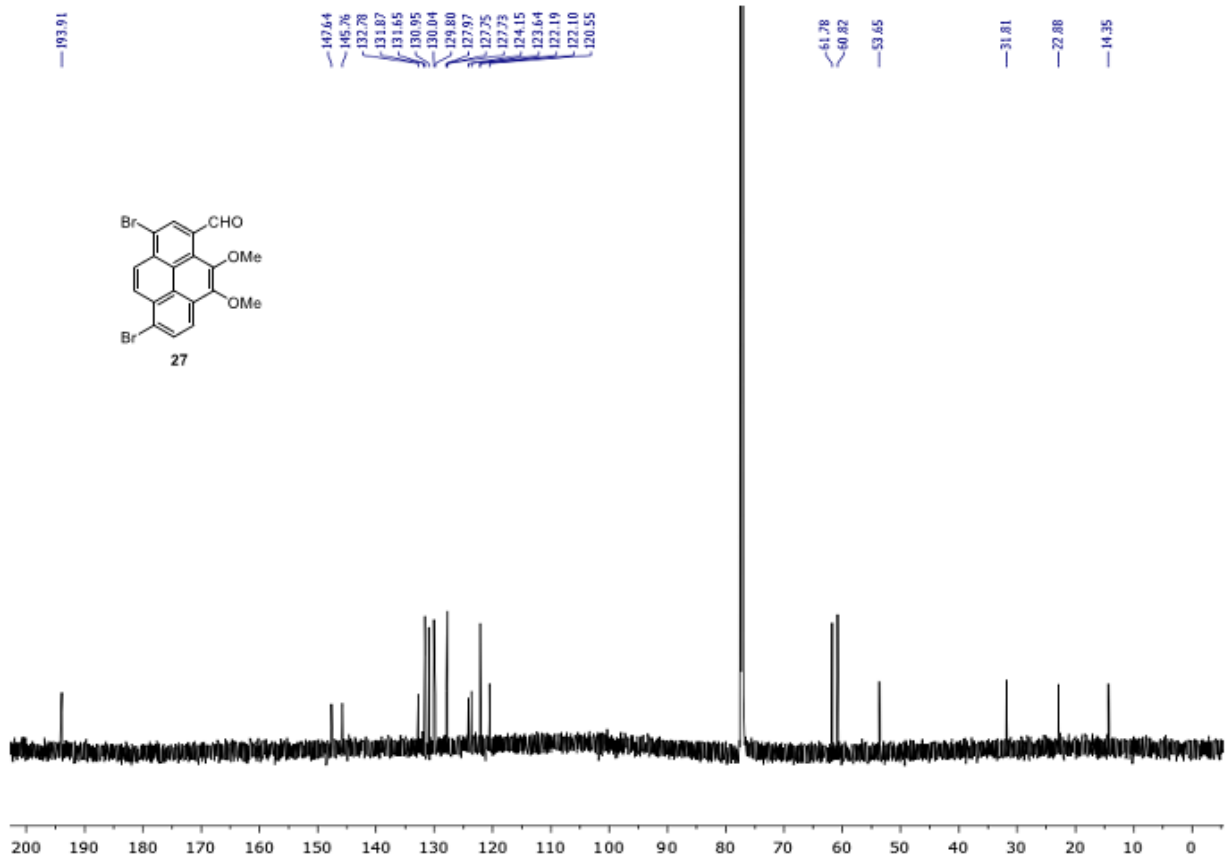
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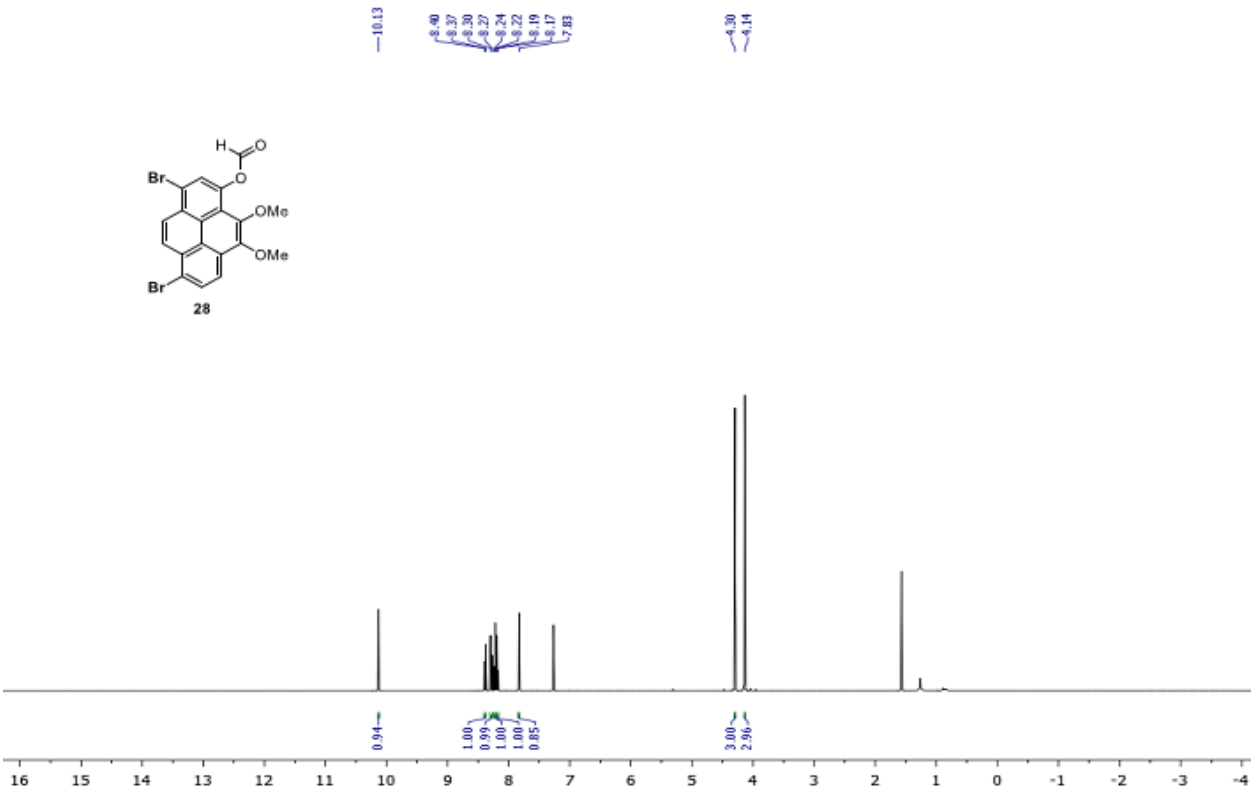
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OMe
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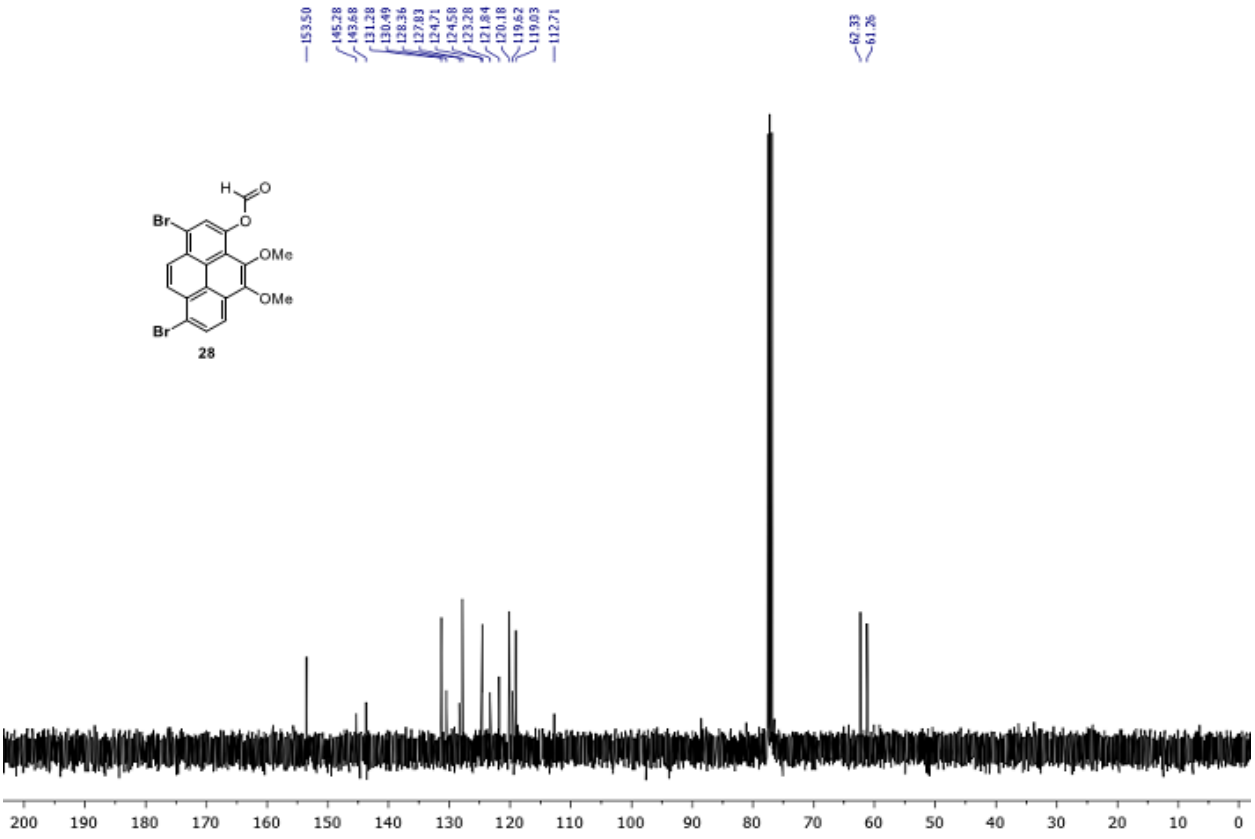
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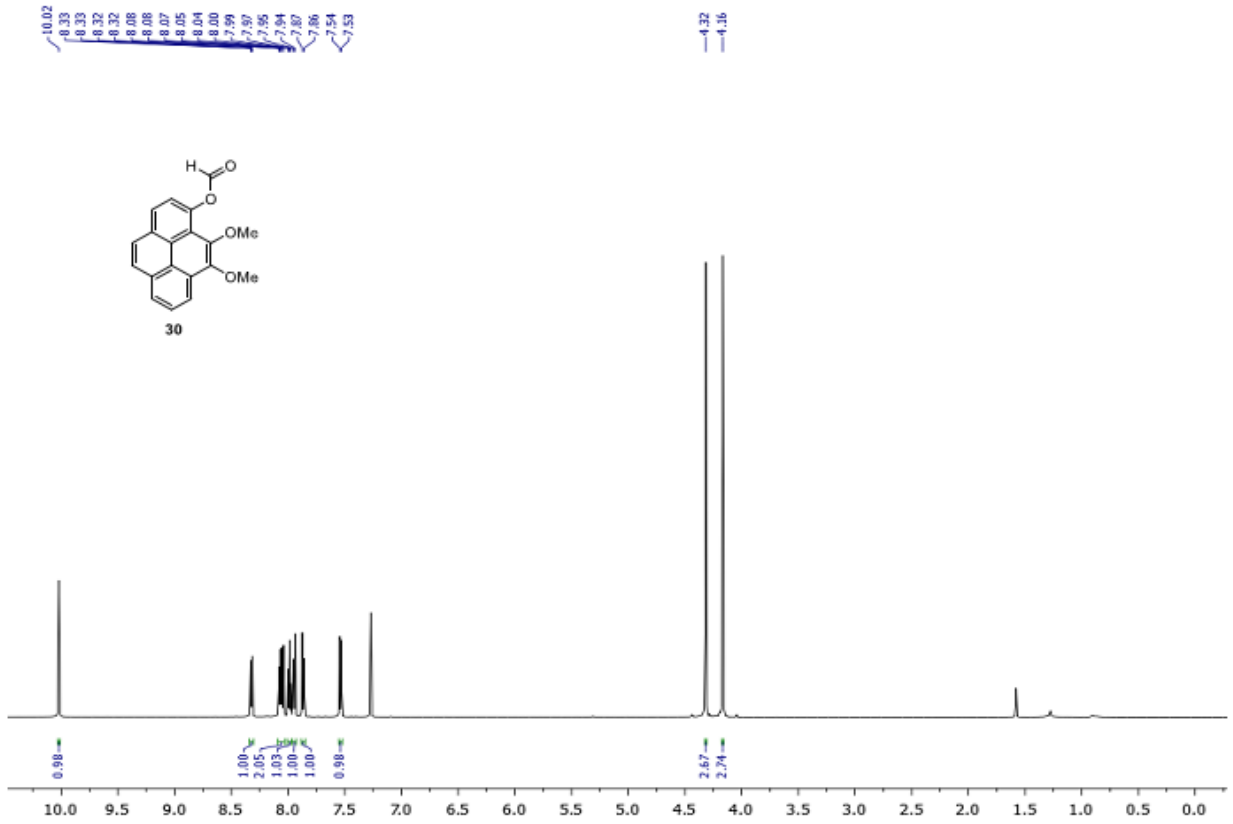
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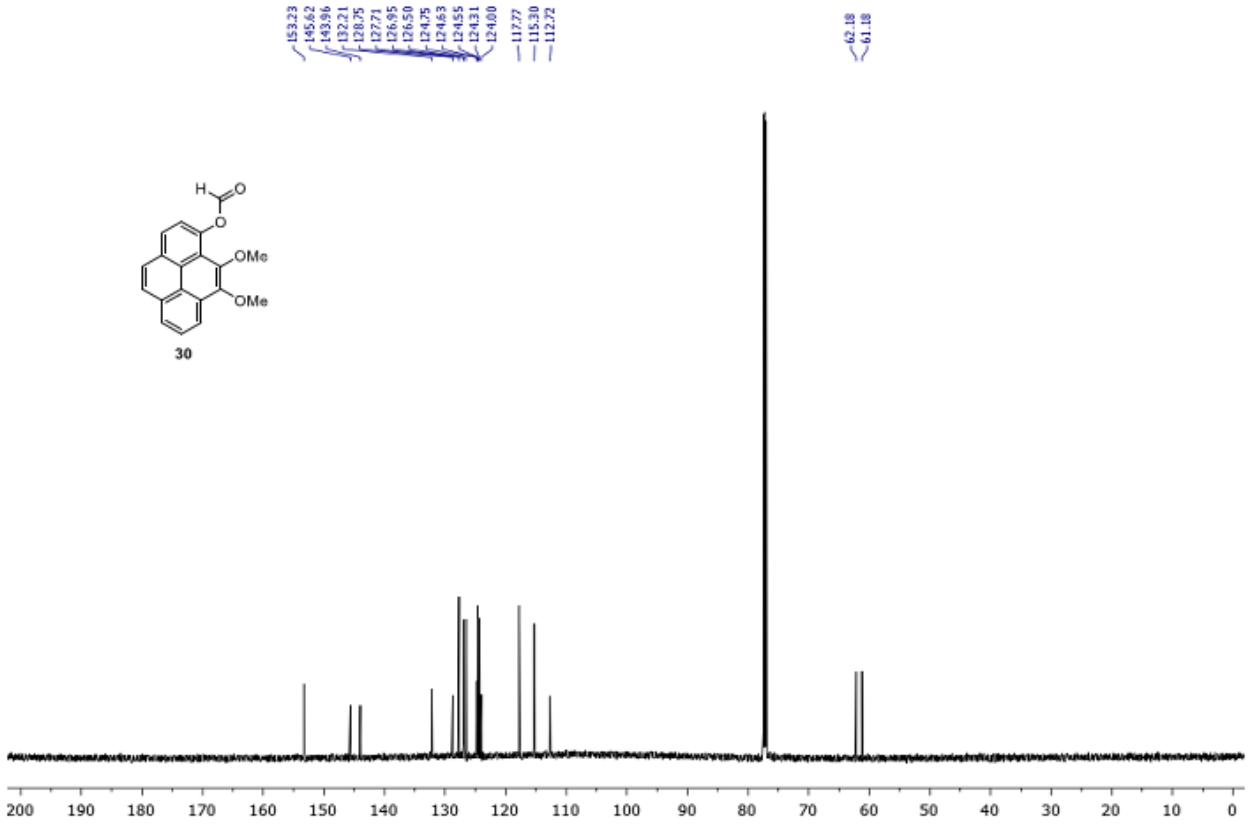
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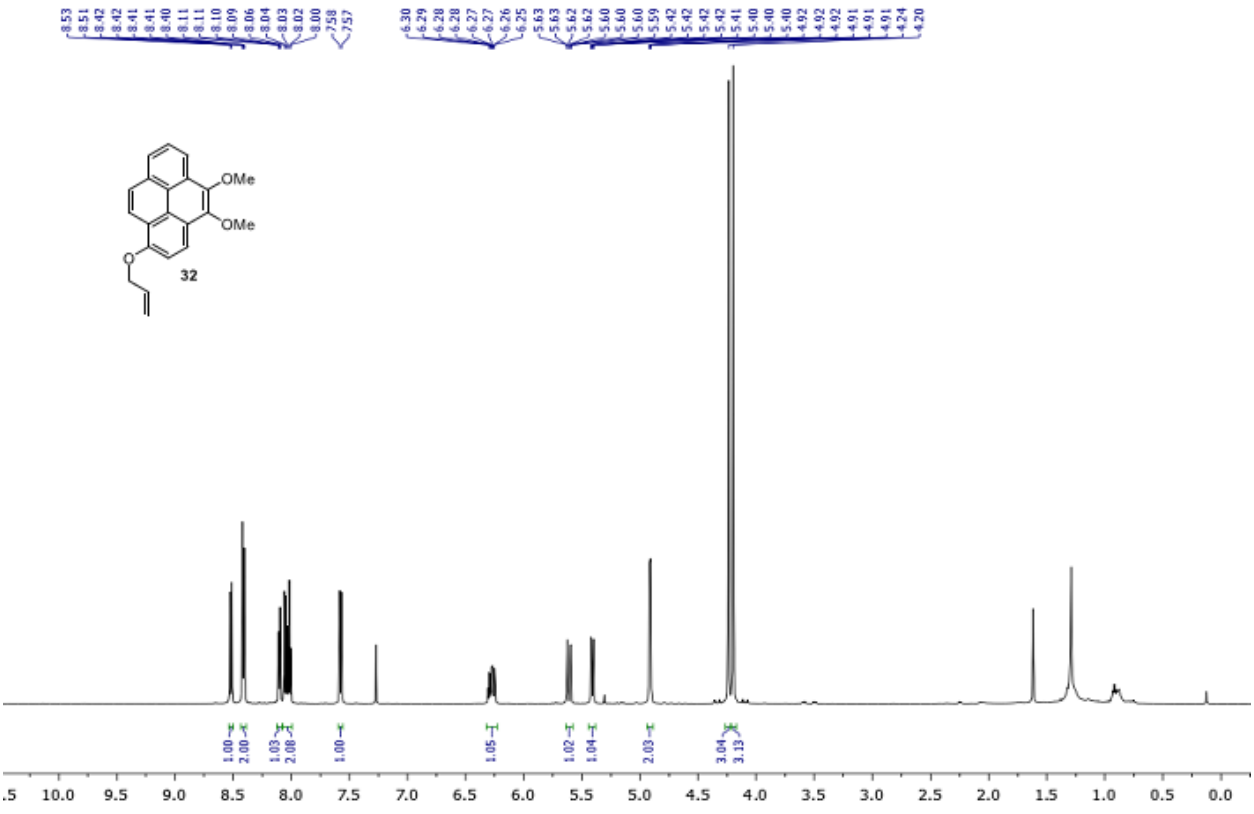
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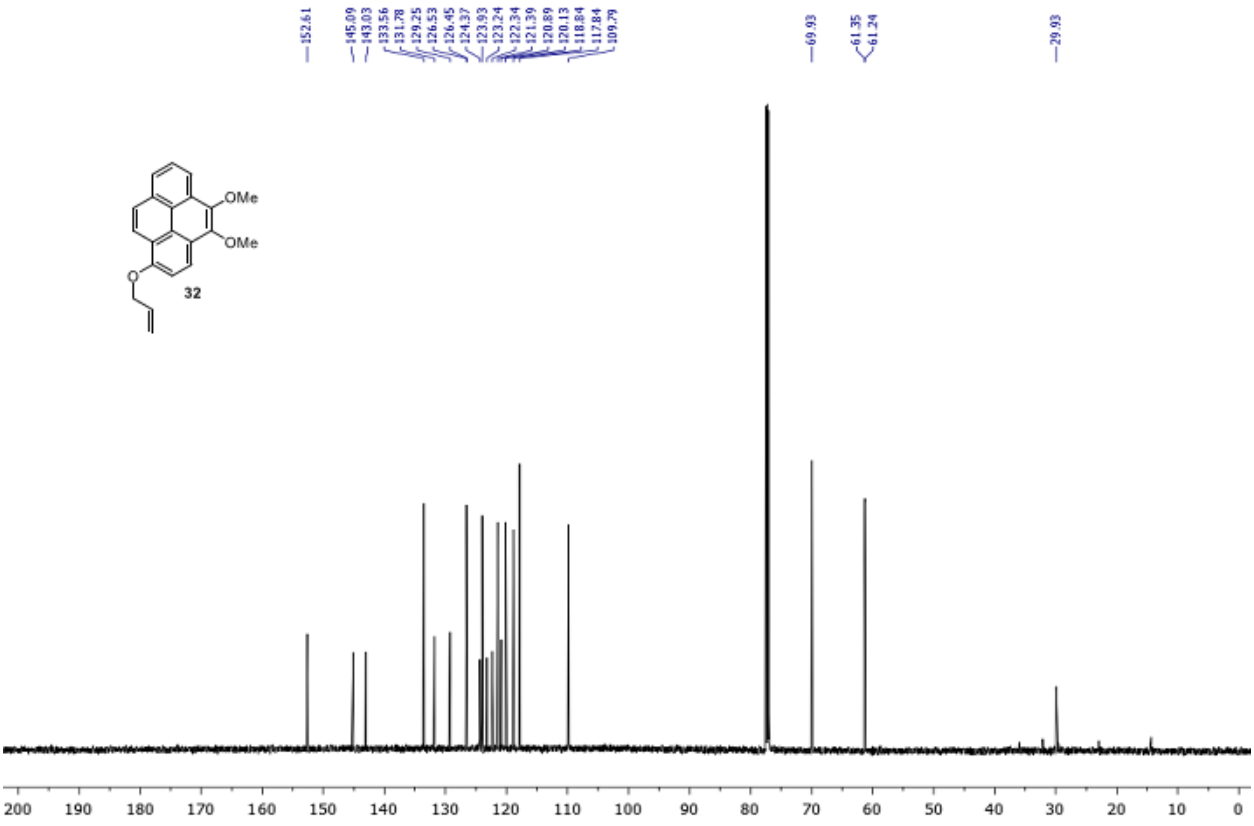
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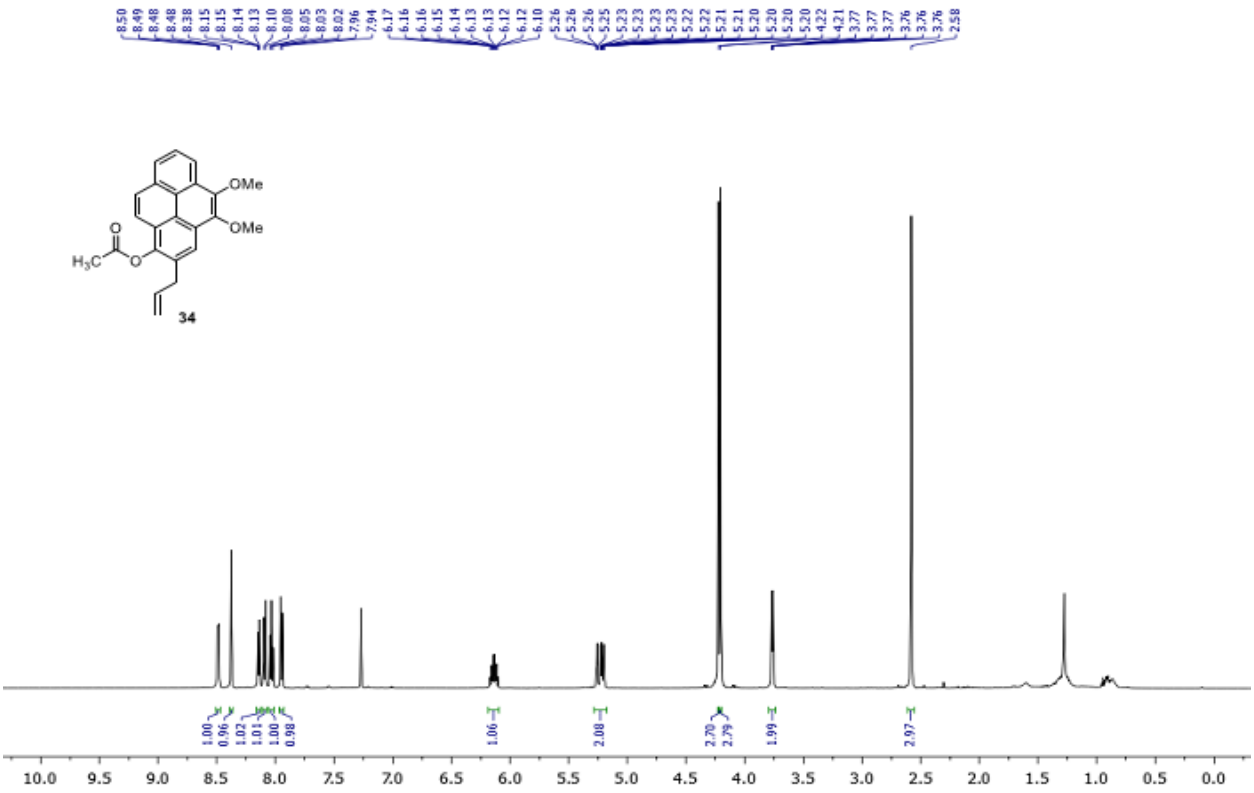
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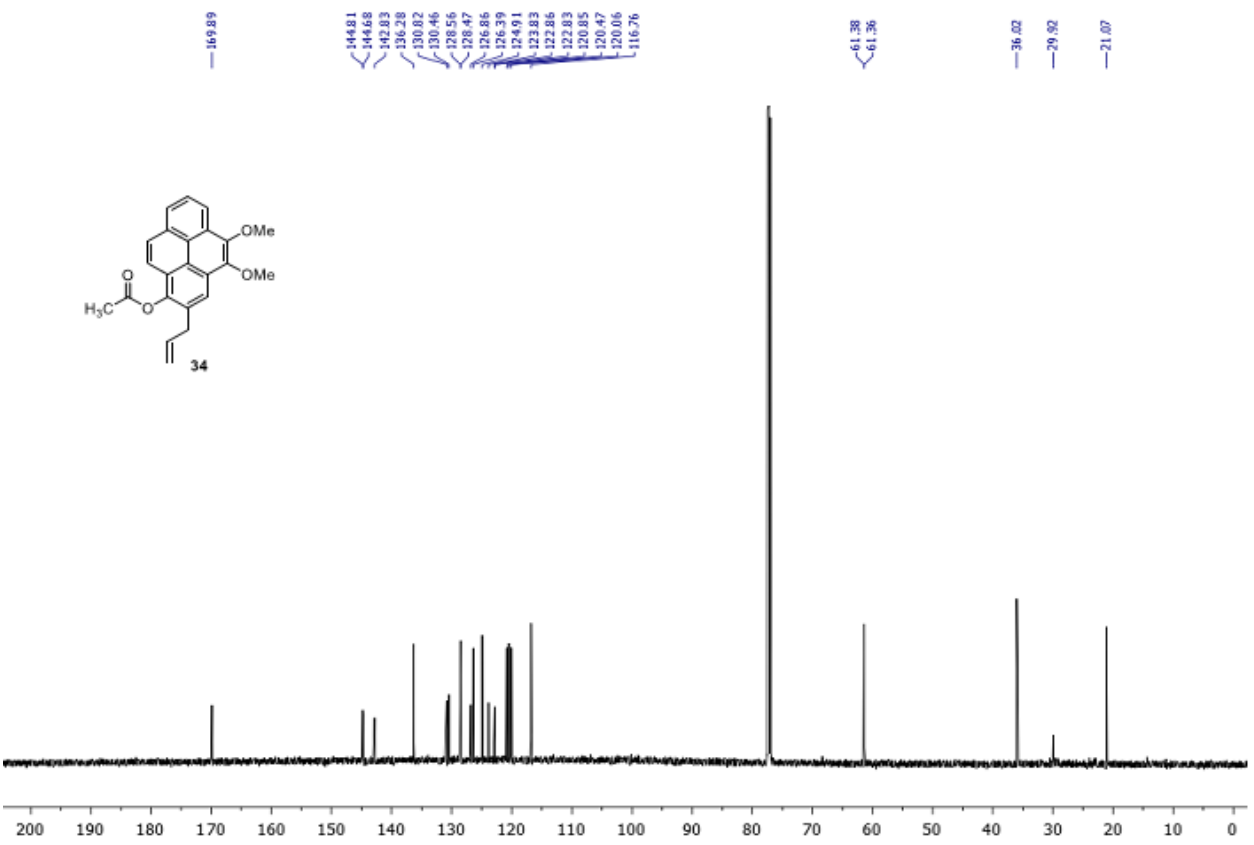
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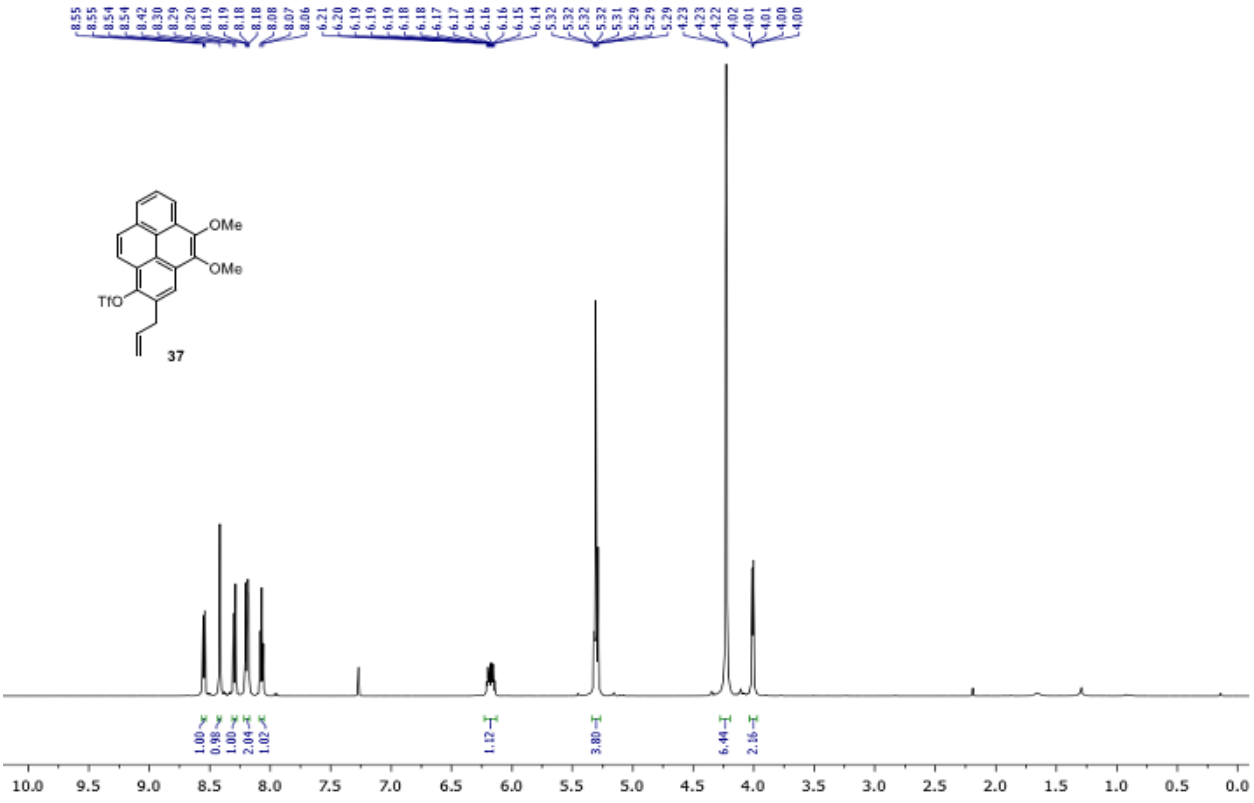
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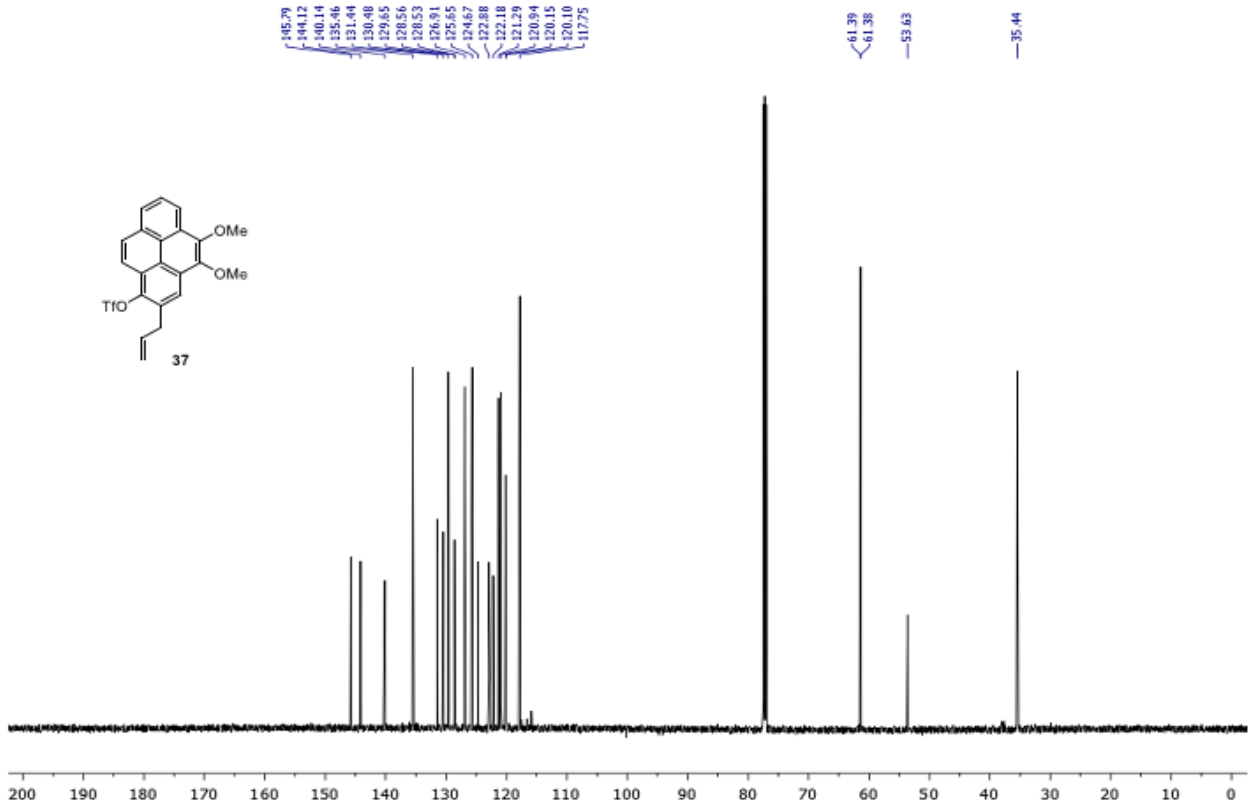
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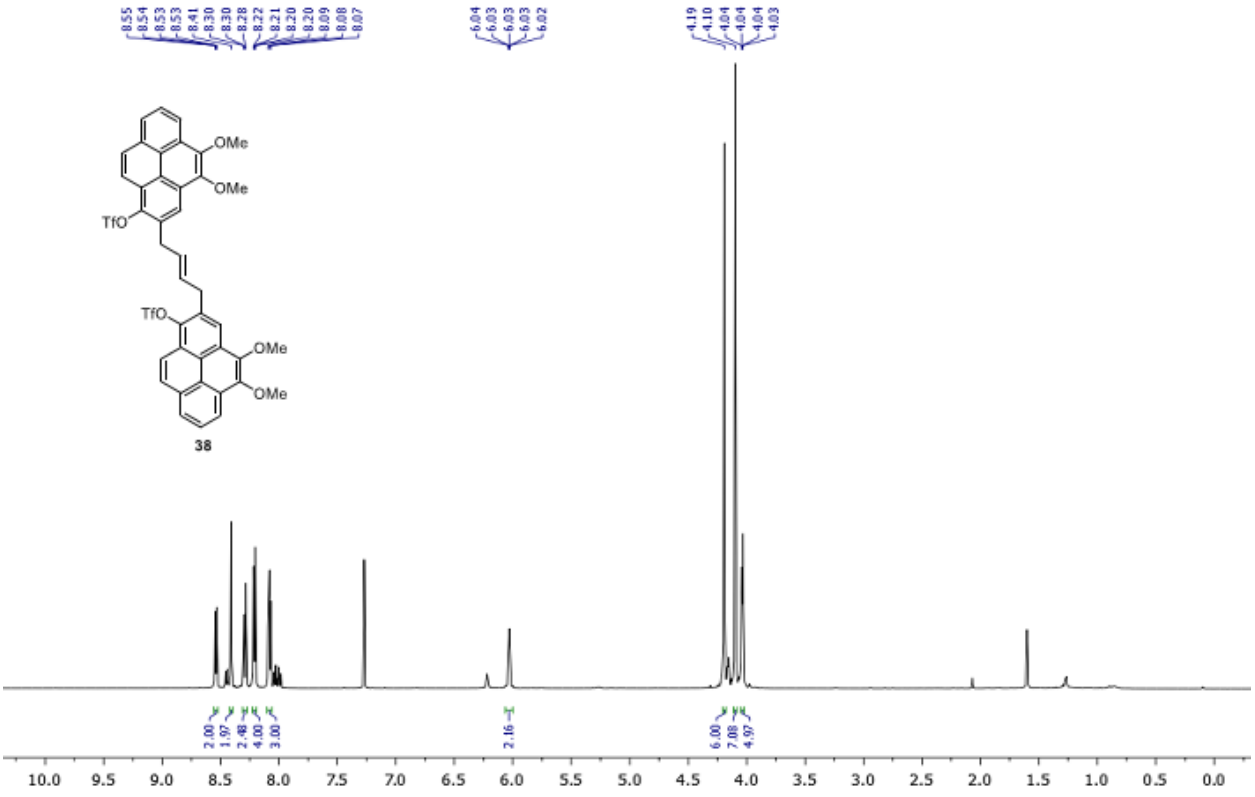
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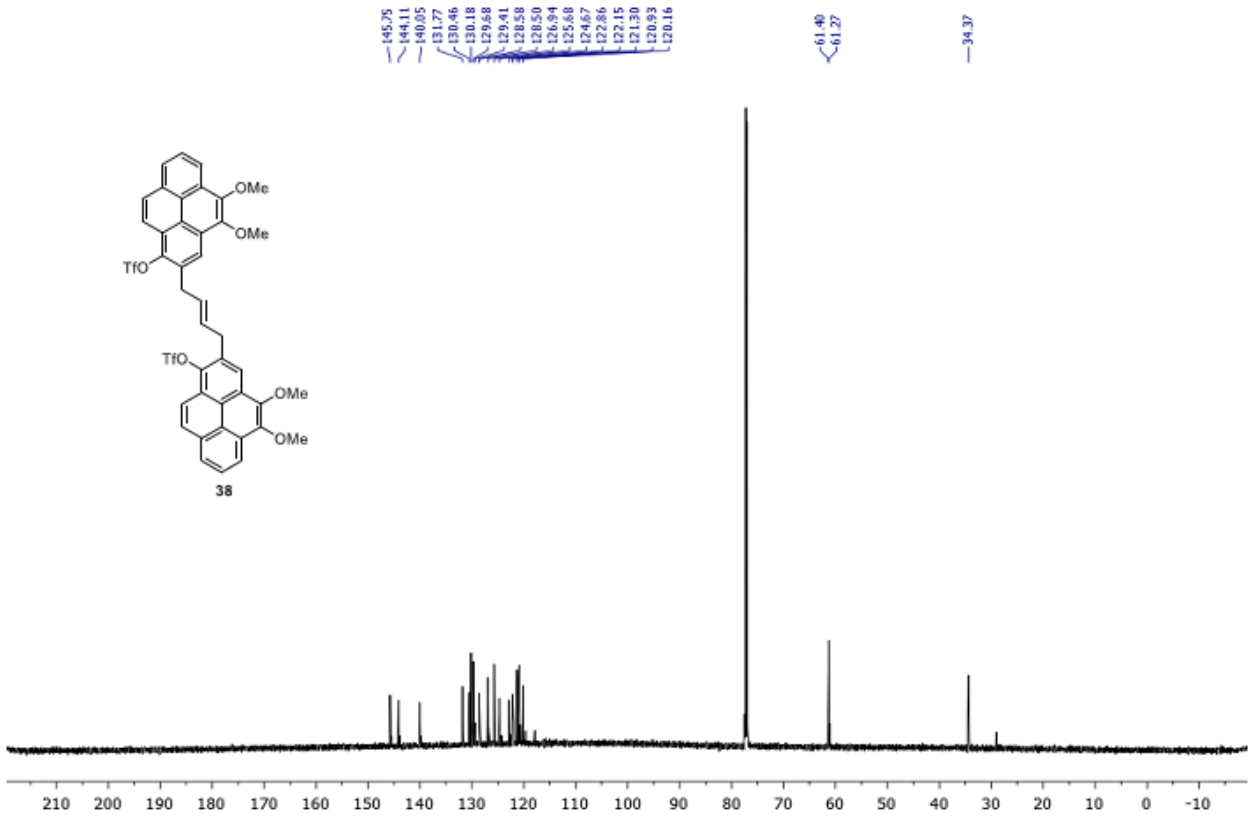
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TfO
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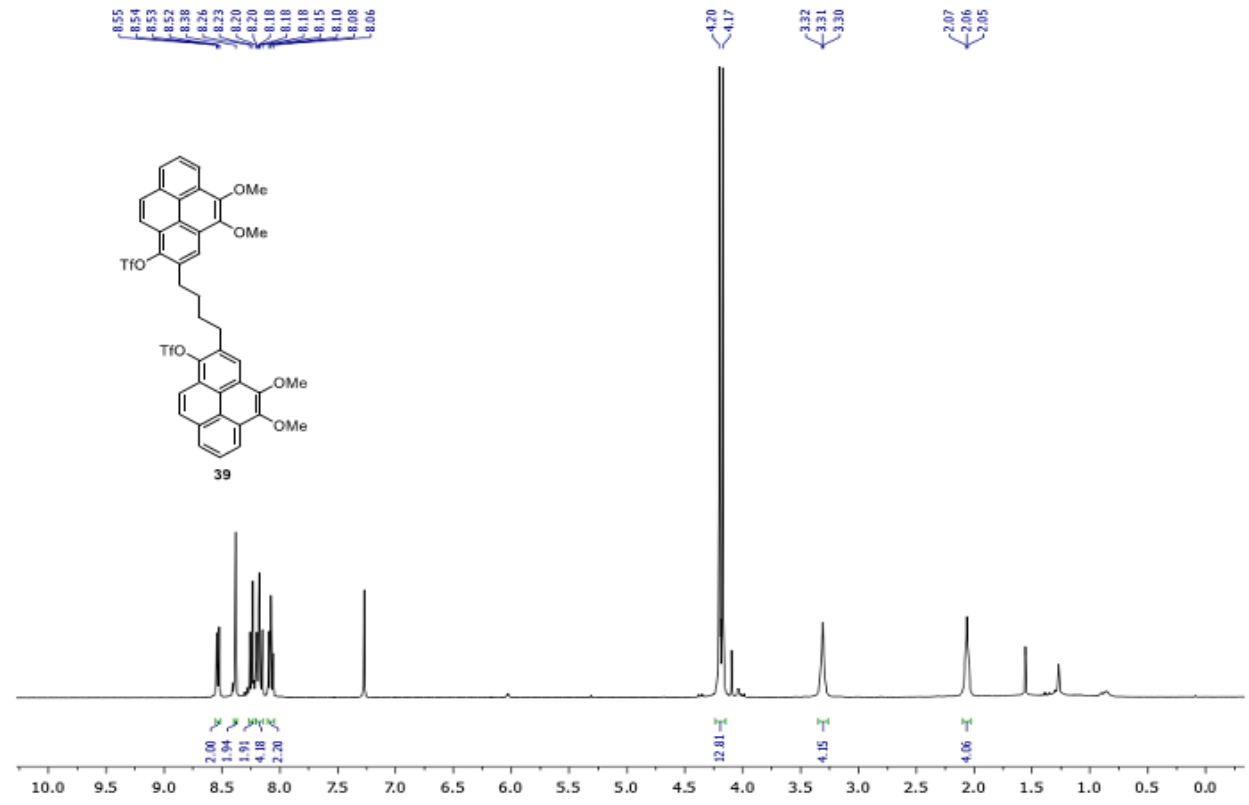
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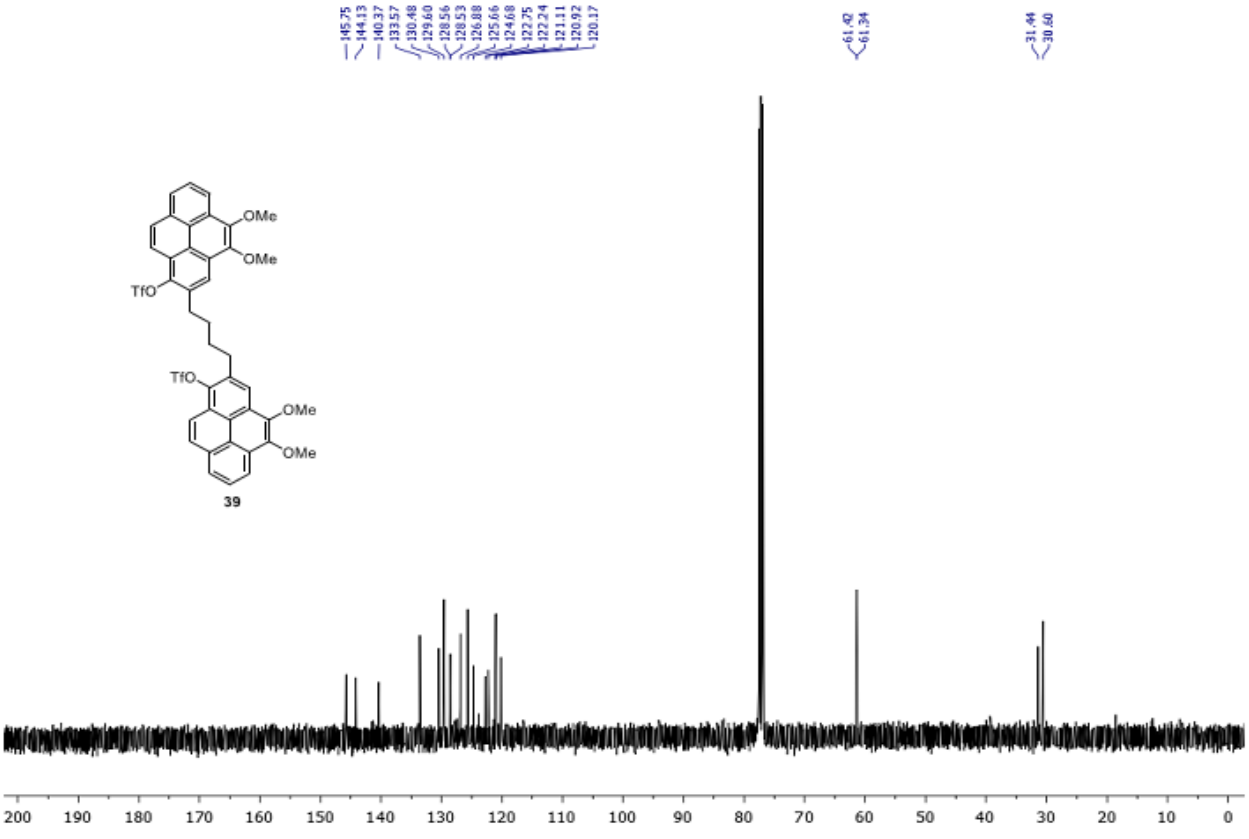
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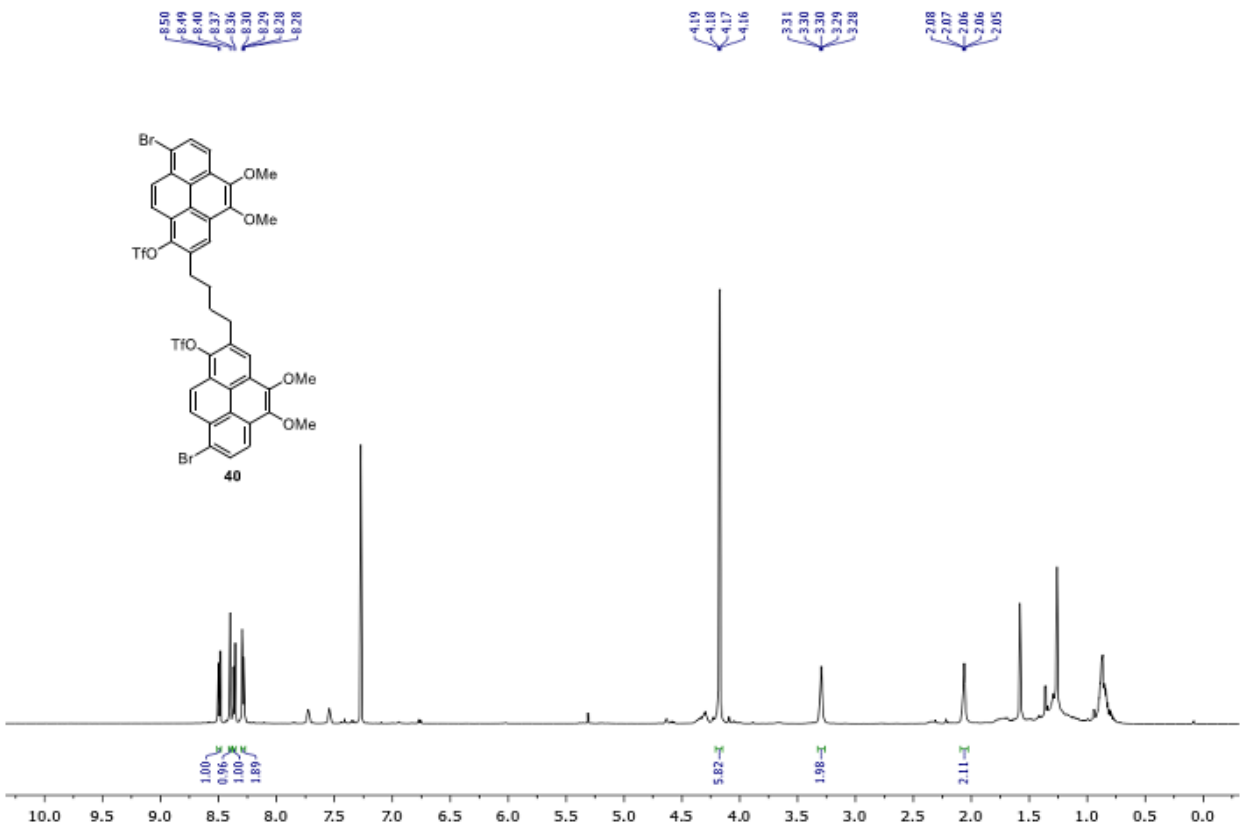
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