# Synthesis of Novel π-Systems Containing Two Pyrene Units

**Marc MacKinnon**

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**By**

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A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements for

the degree of Master of Science

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May 2014

# Abstract

The research described in this thesis deals with the synthesis of designed π-systems that contain two pyrene units. In Chapter 1 a brief overview of polycyclic aromatic hydrocarbons will be described.

In Chapter 2 the synthesis and characterization of BINOL-like compounds, in which the naphthalene moieties are replaced with pyrenes, is described. Some properties of these compounds are also described.

Over the past several years, the Bodwell group has been involved in the design, synthesis and characterization of pyrene-containing systems, most notably, a series of pyrenophanes. However, all of the pyrenophane examples reported by the Bodwell group have contained only a single pyrene unit. In Chapter 3, the attempted synthesis of a pyrenophane with two pyrene units is described and conclusions presented.

# Acknowledgements

Firstly, I would like to thank my supervisor Dr. Graham J. Bodwell for whom this work would not be possible because of his constant support, advice and encouragement. His mentorship has been invaluable to my growth as a scientist and individual. Whether the discussions were chemistry related or not, they were always lively and informative which left me with a revitalized spirit every time.

I would also like to extend my thanks to Dr. Christopher M. Kozak and Dr. Sunil V. Pansare, my supervisory committee for their attentive reading and review of this thesis.

Thanks are also extended to Ms. Linda Winsor, Dr. Celine Schneider, Dr. Louise Dawe, Dr. Prateek Dongare and Dr. David Thompson for their assistance with mass spectral analysis, NMR analysis, X-ray crystallography and fluorescence measurements. I am also grateful the all the faculty, staff and students of the Chemistry Department.

Finally, I would the express my gratitude to my family for their love and unyielding support over the course of this program.

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# List of Symbols, Abbreviations and Acronyms

| | |
|---|---|
| $\delta$ | units of chemical shift (in NMR) |
| $\Phi$ | quantum yield |
| $\theta$ | bend angle (in pyrenophanes) |
| Å | Ångström(s) |
| Ac | acetyl, $CH_3C(O)$- |
| APCI | atmospheric-pressure chemical ionization |
| Bu | butyl $CH_3(CH_2)_2$- |
| CD | circular dichroism |
| COD | 1,5-cyclooctadiene |
| COSY | correlated spectroscopy |
| dppp | 1,3-bis(diphenylphosphino)propane |
| d | doublet (in NMR) |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL | diisobutylaluminium hydride |
| DME | 1,2-dimethoxyethane |
| DMF | *N,N*-dimethylformamide |
| dtbpy | 4,4'-di-*tert*-butyl-2,2'-bipyridyl |
| EI | electron ionization |
| *ee* | enantiomeric excess |
| Et | ethyl, $CH_3CH_2$- |
| FGI | functional group interconversion |
| h | hour(s) |

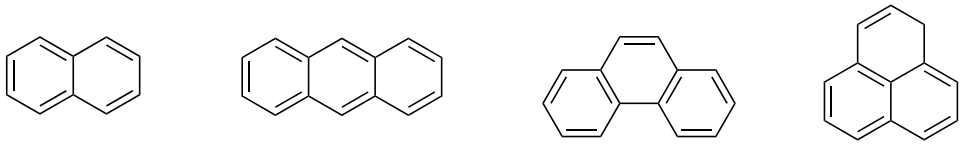
| | |
|---|---|
| HPLC | high-pressure liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| Hz | Hertz |
| *J* | Coupling constant (Hz) (in NMR) |
| LCMS | liquid chromatography-mass spectrometry |
| m | multiplet (in NMR) |
| Me | methyl, $CH_3$- |
| MHz | megahertz |
| min | minute(s) |
| m.p. | melting point |
| NBS | *N*-bromosuccinimide |
| nm | nanometer |
| ns | nanosecond |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| Ph | phenyl, $C_6H_5$- |
| ppm | parts per million |
| PAH | polycyclic aromatic hydrocarbon |
| $R_f$ | retention factor (in tlc) |
| rt | room temperature |
| RCM | ring-closing metathesis |
| t | triplet (in NMR) |
| TBAF | tetrabutylammonium fluoride |

| | |
|---|---|
| Tf | trifluoromethanesulfonyl, $CF_3SO_2$- |
| THF | tetrahydrofuran |
| TMSA | trimethysilylacetylene |
| tlc | thin-layer chromatography |
| VID | valence isomerization-dehydrogenation |

## Chapter 1 – Introduction

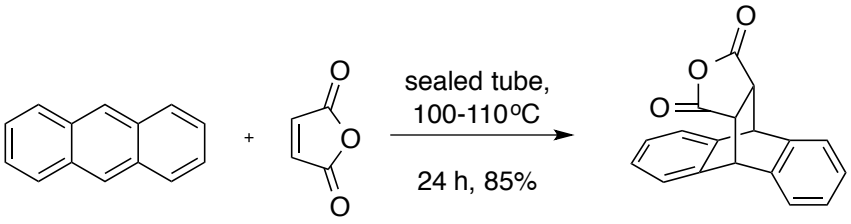
### 1.1 Polycyclic Aromatic Hydrocarbons

When two or more aromatic rings are fused together, they form a class of compounds known as polycyclic aromatic hydrocarbons (PAHs). The simplest PAH is naphthalene (**1.01**), which consists of two fused benzene rings (Figure 1.01). As the number of rings increases, the number of potential fusion patterns rapidly increases. For example, three benzene rings can be fused together in two different fashions to give closed-shell aromatic systems. The two possibilities are anthracene (**1.02**), which is fused linearly, and phenanthrene (**1.03**) (Figure 1.01). An alternative fusion motif, in which each ring shares two bonds, leads to phenalene (**1.04**), but the presence of an $sp^3$-hydridized C atom means that this is not a fully aromatic system. The replacement of the $sp^3$-hybridized C atom with a $sp^2$-hybridized C atom would give either a cation, a radical, or an anion, depending upon how many electrons (0, 1 or 2, respectively) populate the *p* orbital. Anthracene (**1.02**) and phenanthrene (**1.03**) have quite different physical and chemical properties despite their structural similarities. For example, the melting point of anthracene (**1.02**) is 216 °C whereas that of phenanthrene (**1.03**) is only 101 °C.[1] A comparison of their chemical reactivities quickly reveals that anthracene (**1.02**) can undergo a facile Diels-Alder reaction with maleic anhydride (**1.05**) to afford compound **1.06** (Scheme 1.01).[2] However, phenanthrene (**1.03**) has shown no reactivity towards maleic anhydride (**1.05**) under Diels-Alder conditions.



**1.01** **1.02** **1.03** **1.04**

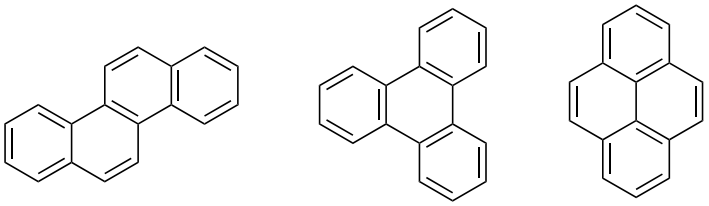
**Figure 1.01** Naphthalene (**1.01**) and three-rings aromatics.




**1.02** **1.05** **1.06**

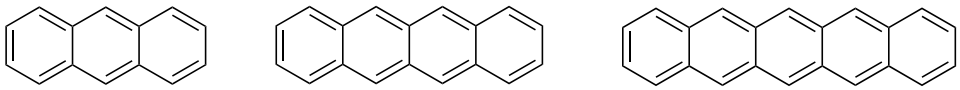
**Scheme 1.01** Diels-Alder reaction of anthracene (**1.02**).

The range of structural diversity increases quickly with additional rings. A few notable examples of four-ring PAHs are chrysene (**1.07**), triphenylene (**1.08**) and pyrene (**1.09**) (Figure 1.02). Similarly, these compounds have markedly different physical and chemical properties. A variety of homologous series of PAHs can be constructed by iterative fusion of additional benzene rings. For example, naphthalene (**1.01**) and anthracene (**1.02**) are members of a subclass of PAHs known as the [*n*]acenes. Structurally, the [*n*]acenes are characterized by a linear fusion of benzene rings. After anthracene (**1.02**) the series continues with tetracene (**1.10**), pentacene (**1.11**) and so on (Figure 1.03). A consequence of increasing the number of benzene rings in this series is that these compounds quickly became sparingly soluble in common solvents. They also become increasingly biradicaloid in character and thus more reactive.



**1.07** **1.08** **1.09**

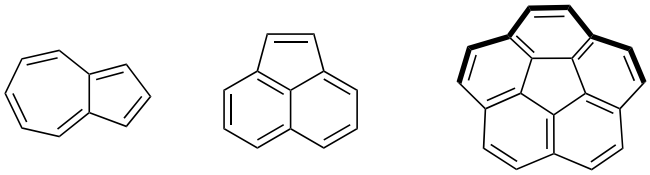
**Figure 1.02** Four-ring PAHs.



**1.02** **1.10** **1.11**

**Figure 1.03** Examples of [*n*]acene series of PAHs.

PAHs do not have to be solely benzenoid, they can contain non-six-membered rings in their core structures. One example is azulene (**1.12**), which is comprised of a seven-membered and five-membered ring, but does not contain a six-membered ring (Figure 1.04). Another example is acenaphthylene (**1.13**), which contains a five-membered ring fused to both six-membered rings of a naphthalene system. A last example, corannulene (**1.14**), introduces the concept of nonplanarity of PAHs, the consequences of which will be discussed in greater detail below.



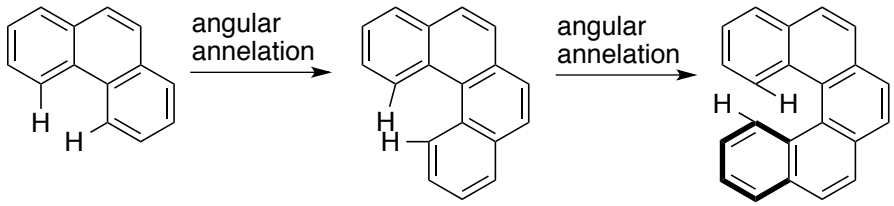
**1.12** **1.13** **1.14**

**Figure 1.04** Non six-membered ring containing PAHs.

PAHs are an area of considerable interest for researchers as novel synthetic targets of academic interest, in applications for materials science and in toxicology. As synthetic targets, they can provide unique challenges to the creativity and resourcefulness of synthetic chemists, not just in terms of constructing the desired carbon skeleton, but also with respect to their purification, isolation and characterization. As with the [*n*]acenes, as planar PAHs grow larger these compounds typically move from low to vanishingly low solubility.

An especially interesting area of PAH chemistry is the synthesis and study of nonplanar PAHs. Once PAHs are forced to deviate from planarity, they often become quite soluble. Organic chemists generally make use of three basic strategies, as outlined by Henning Hopf in his book *Classics in Hydrocarbon Chemistry*:[3] steric effects, architecture and bridging (cyclophanes). If one begins with phenanthrene (**1.03**) and systematically adds benzene rings through angular annelation, eventually the internal hydrogen atoms, that are shown in **1.03** and **1.15** will need to occupy the same space in order for the moleculed to maintain planarity **1.15** (Scheme 1.02). The result of this interaction is the formation of helical structures

**1.16** that form a class of compounds called helicenes. Helicenes are molecules of interest in part due to their inherent chirality and chiroptical properties.[4]

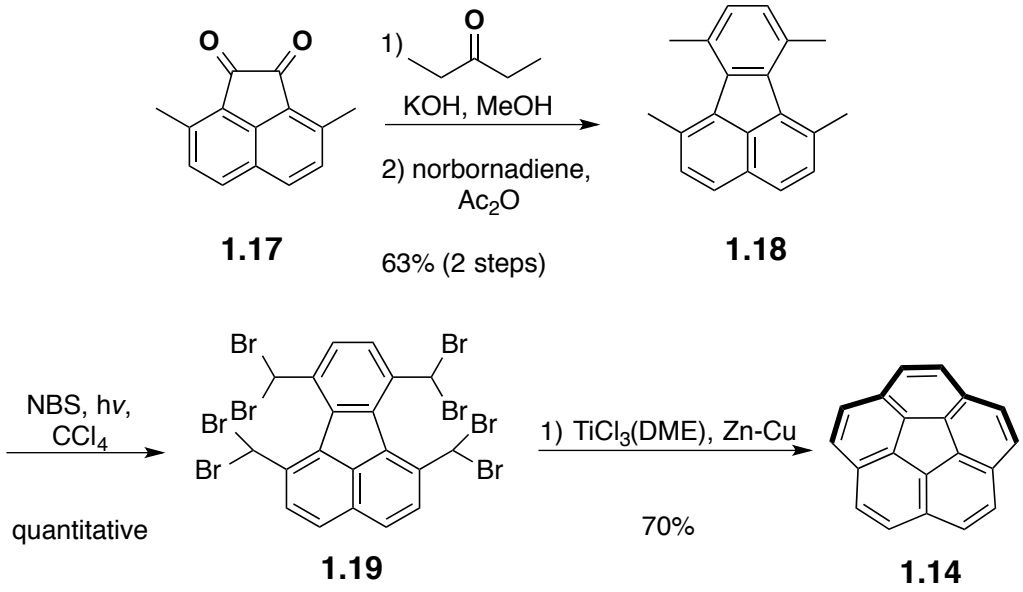



**1.03** **1.15** (+/-) **1.16**

**Scheme 1.02** Angular annelations en route to helicenes.

The second strategy utilized in the formation of nonplanar aromatics is the incorporation of non-six-membered aromatic rings. One class of these compounds, known as the circulenes, are comprised of an inner ring (of varying size), which is surrounded by angularly annelated benzene rings. The most well known example may be corannulene (**1.14**), which has a five-membered ring core. Corannulene has a bowl-shaped geometry and can be viewed as a segment of fullerene $C_{60}$. The first few total syntheses of corannulene (**1.14**) were achieved using a multi-step pathway with low overall yield.[5] A much shorter, high-temperature route was then developed, but this requires specialty apparatus and is not suited to large-scale synthesis.[6] A selected example that demonstrates the subsequent advances in the methodologies utilized in the synthesis of non-planar aromatic compounds is Siegel *et al.*'s report on the solution-phase synthesis of corannulene (**1.14**) (Scheme 1.03).[7] This synthesis starts from 2,7-dimethylnaphthalene, but only the final few steps starting from diketone **1.17** will be reviewed here. Compound **1.17** underwent a

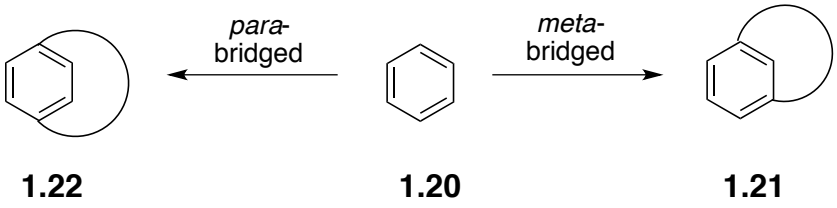
double aldol condensation with 3-pentanone to afford a cyclopentadienone that is then trapped with norbornadiene by way of a Diels-Alder reaction. After a series of retrocycloadditions, fluoranthene derivative **1.18** was obtained in 63% yield. The four methyl groups on compound **1.18** were brominated using *N*-bromosuccinimide and irradiation with visible light to afford octabromide **1.19** in quantitative yield. Compound **1.19** was then reacted with low-valent titanium to directly give corannulene (**1.14**) in 70% yield.




**Scheme 1.03** Siegel *et al.*'s synthesis of corannulene (**1.14**).

The third strategy to generate nonplanar aromatic hydrocarbons is by bridging non-adjacent positions, *i.e.* forming cyclophanes. Taking benzene (**1.20**) as the simplest example, the aromatic system can be bridged in either the *meta* (**1.21**) or *para* (**1.22**) positions (Scheme 1.04). These systems are known as [*n*]metacyclophanes and [*n*]paracyclophanes, respectively. The degree of deviation

from planarity (or bend) is dependent on the length of the bridging unit. The shorter the bridge, the more bent the aromatic unit should be. [*n*]Metacyclophanes (**1.21**) and [*n*]paracyclophanes (**1.22**) were some of the original cyclophanes that appeared in the literature, and contain one benzene ring bridged by alkyl chains of differing lengths.[8] As the field grew and flourished, reports of other cyclophanes that contained more elaborate structures began to appear. For example, cyclophanes with more than one aromatic system, *e.g.* [2.2]paracyclophane (**1.23**), and cyclophanes with multiple bridges, *e.g.* superphane (**1.24**), started being reported (Figure 1.05).[9,10] The range of structural diversity of cyclophanes is potentially limitless and more examples will be reviewed in greater detail in Chapter 3.




**Scheme 1.04** General cyclophane structures.

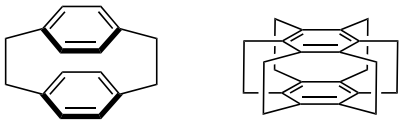


**Figure 1.05** [2.2]Paracyclophane (**1.23**) and superphane (**1.24**).

Polycyclic aromatic hydrocarbons will continue to be a vibrant field of study for many years to come. As long as chemists are asking important questions in

regards to sustainable energy, environmental sensing and others areas, organic and materials chemists will be required for their expertise in the synthesis, characterization and applications of molecules such as these.

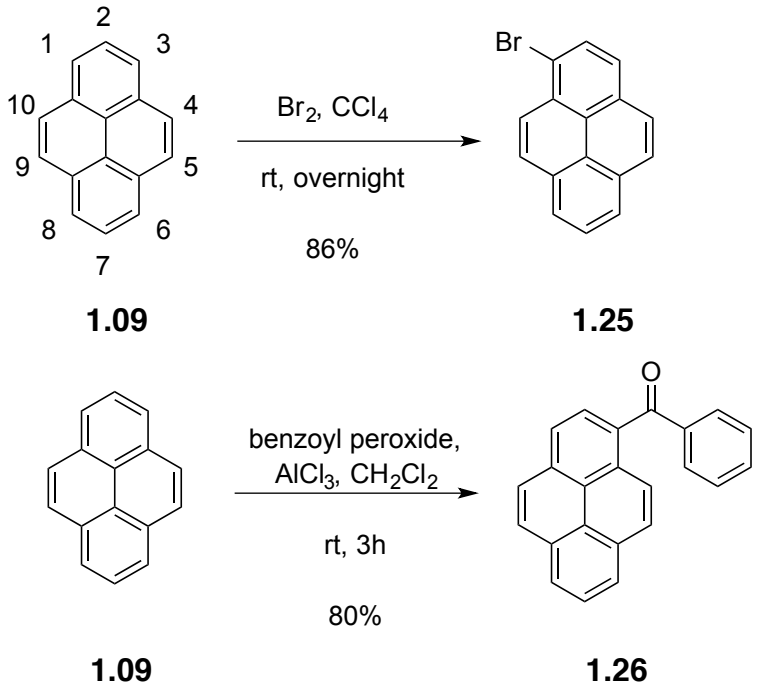
## 1.2 Pyrene: A PAH of Great Importance

Pyrene (**1.09**), a four-ring PAH, is the main aromatic system of focus in this thesis. It is the smallest *peri*-fused benzenoid PAH. Pyrene continues to attract considerable interest in the literature, in part due to its advantageous photophysical and photochemical properties. For example, it has a high fluorescence quantum yield (0.72) and a long-lived excited state (450 ns) in ethanol.[11,12] More importantly, its fluorescence behaviour is highly sensitive to its environment. These properties are responsible for the steadily increasing number of reports of the incorporation of pyrene into materials for organic electronic devices, fluorescent probes, and other applications. In Müllen and co-workers' extensive review on pyrene-based materials, the authors dubbed pyrene as the "gold standard as a molecular probe for exploring microenvironments".[13] Pyrene has also experienced a surge in its use as a building block for novel organic molecules and materials.

### 1.2.1 Mono-Substituted Pyrenes

The chemistry of pyrene is limited, but well documented.[14] The overwhelming majority of electrophilic aromatic substitutions occur at the 1,3,6,

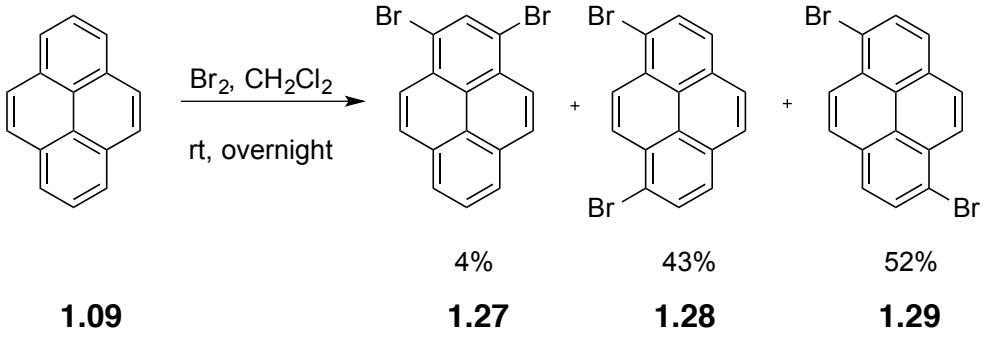
and 8 positions of pyrene, with varying selectivities. Monobromination of pyrene (**1.09**) is possible but can be tedious in practice, as it requires successive crystallizations to isolate the desired product from the disubstituted byproducts. Monobromination is achieved by careful control of the addition of bromine to afford 1-bromopyrene (**1.25**) in 86% yield (Scheme 1.05).[15] Other monosubstituted pyrene systems are constructed using Friedel-Crafts acylation. One example is the reaction of pyrene (**1.09**) with benzoyl chloride to afford compound **1.26** in 80% yield.[16] Other transformations to install mono-functionalization at the 1-position of pyrene are known but will not be reviews further in this thesis. Mono-substitution at the other positions about pyrene (**1.09**) are less common and a few examples will be described later in this thesis.




**Scheme 1.05** Monosubstitution reactions of pyrene (**1.09**) at the 1-position.

### 1.2.2 Disubstituted Pyrenes

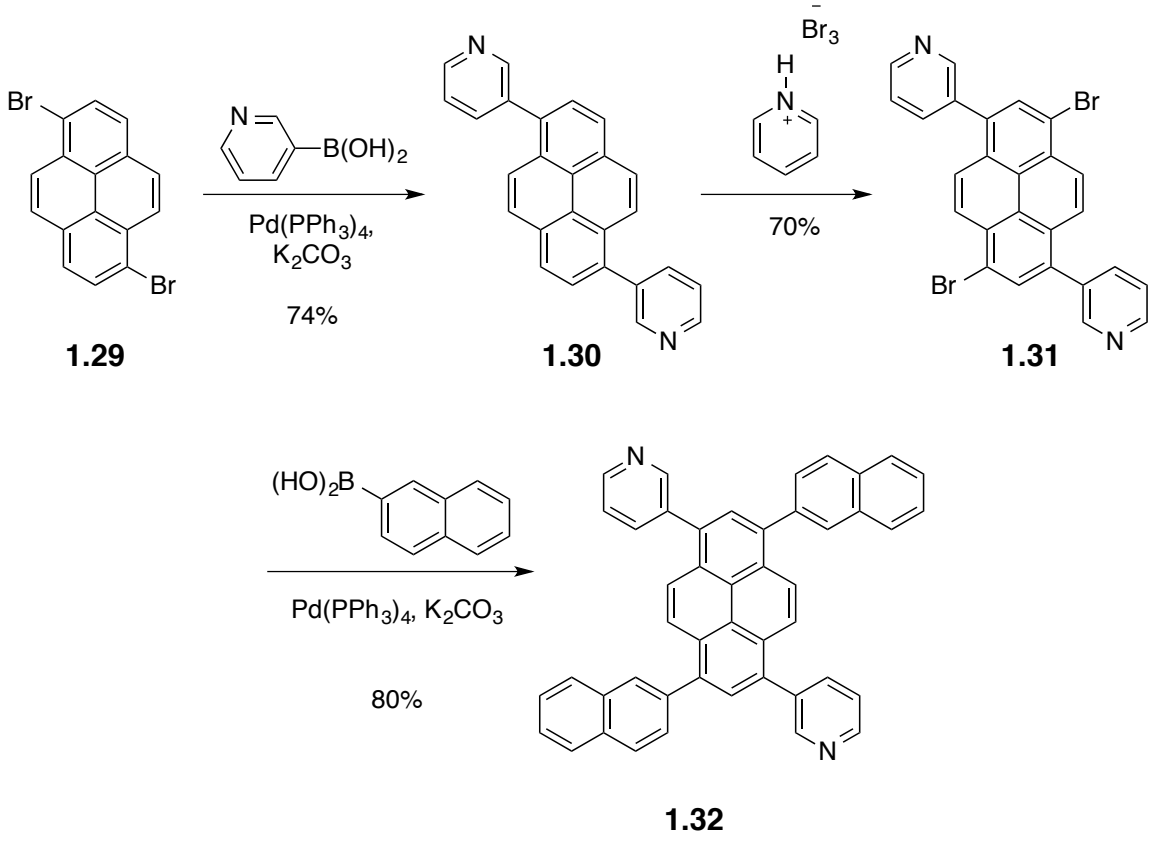
Disubsitution of pyrene (**1.09**) by electrophilic aromatic substitution affords mixtures of isomers arising from 1,3-, 1,6- and 1,8-substitution. These isomers are often difficult to separate. For example, treatment of pyrene (**1.09**) with 2 molar equivalents of bromine affords a mixture of all three possible products; 1,3-dibromopyrene (**1.27**), 1,8-dibromopyrene (**1.28**) and 1,6-dibromopyrene (**1.29**) in 4%, 43% and 52% yields, respectively (Scheme 1.06).[17] This mixture of products can ultimately be separated by successive crystallizations, but this is nontrivial from a practical perspective.




**Scheme 1.06** Dibromination of pyrene (**1.09**).

These dibromo compounds have been used often to incorporate pyrene moieties into larger systems, many of which are used for organic electronics. For examples 1,6-dibromopyrene (**1.29**) was a starting material in the synthesis of compound **1.32** (Scheme 1.07).[18] 1,6-Dibromopyrene underwent a Suzuki-Miyaura cross-coupling reaction to afford compound **1.30** in 74% yield, which was then

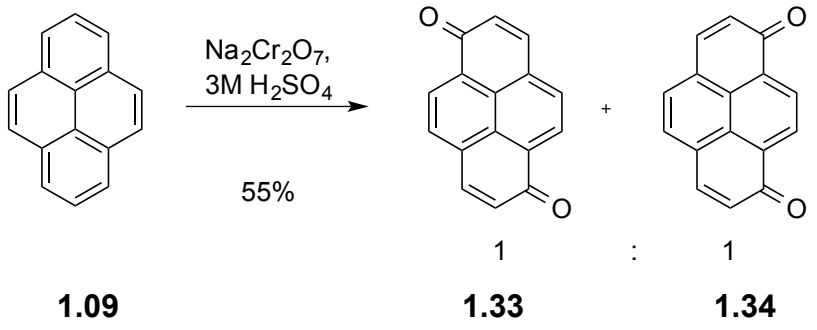
dibrominated, at the expected positions, with pyridinium tribromide to afford dibromide **1.31** in 70% yield. Compound **1.31** was then subjected to a Suzuki-Miyaura reaction to afford the target molecule **1.32** in 80% yield. Compound **1.32** has been used as a transport material in blue organic light emitting diode (OLED) devices.



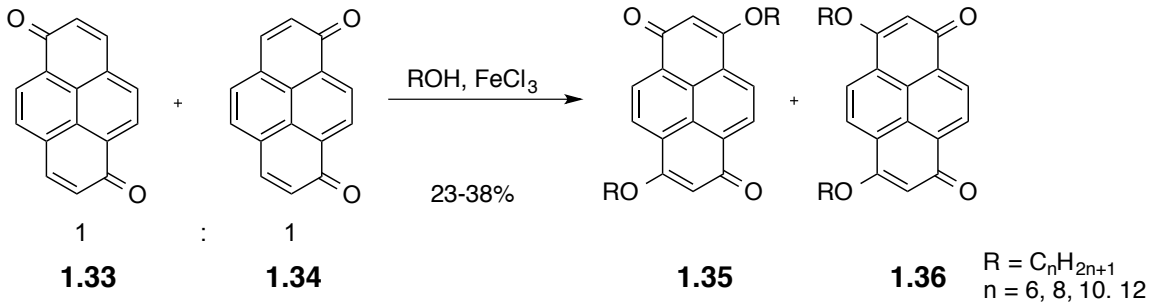

**Scheme 1.07** Synthesis of blue OLED component **1.32**.

Pyrene (**1.09**) can also be selectively oxidized at different positions depending on the oxidation conditions used. If diketones **1.33** and **1.34** are desired, the oxidation of pyrene (**1.09**) with $Na_2Cr_2O_7$ in sulfuric acid are the required conditions (Scheme 1.08).[19] This reaction affords **1.33** and **1.34** in a 1:1 mixture in

55% yield. The two regioisomers are not easily separated, which makes it difficult, but not impossible, to work further with these systems. The mixture of **1.33** and **1.34** was reacted with straight-chain aliphatic alcohols and $FeCl_3$ to afford the corresponding pyrene derivatives **1.35** and **1.36** (R = $C_nH_{2n+1}$, n = 6, 8, 10, 12). These systems formed a new class of π-acceptor discotic liquid crystals (Scheme 1.09).[19]



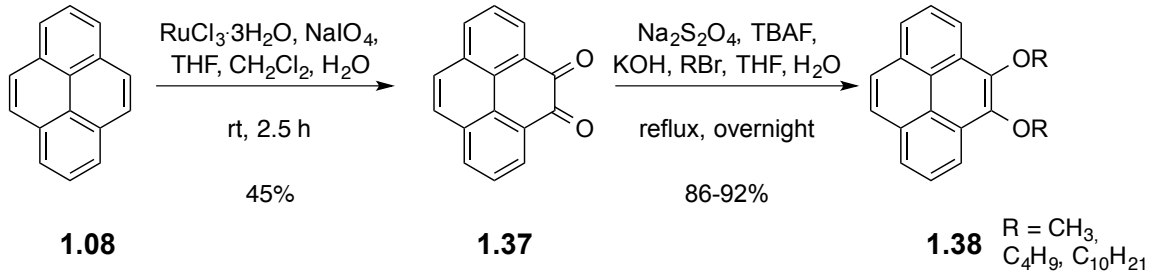

**Scheme 1.08** Oxidation of pyrene (**1.09**) at the 1,6 and 1,8 positions.




**Scheme 1.09** Synthesis of discotic liquid crystals **1.35** and **1.36**.

Using another set of oxidation conditions, pyrene (**1.09**) can be oxidized at the 4 and 5 positions to afford pyrene-4,5-dione (**1.37**) in 45% yield (Scheme

1.10).[20] This system can then be reductively alkylated with alkyl halides (**1.38**) and further functionalized (R = $CH_3$, $C_4H_9$, $C_{10}H_{21}$).



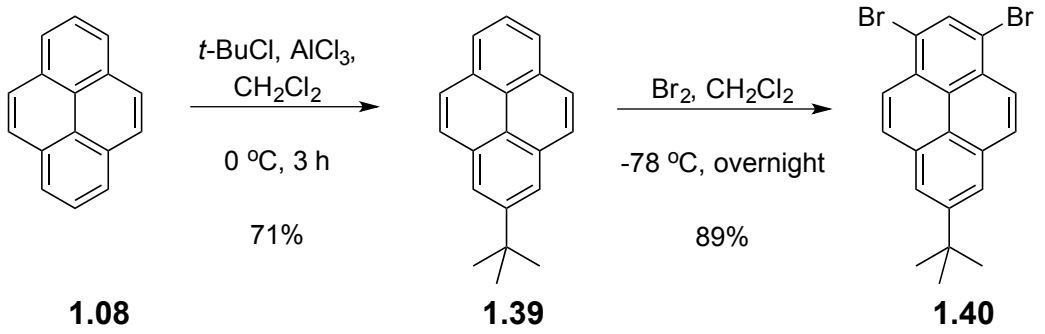

**Scheme 1.10** Oxidation of pyrene (**1.09**) and reductive alkylation (**1.36**).

2,7-Disubstituted pyrenes are also directly accessible and will be reviewed in greater detail later in this thesis.

### 1.2.3 Multi-Functionalized Pyrenes

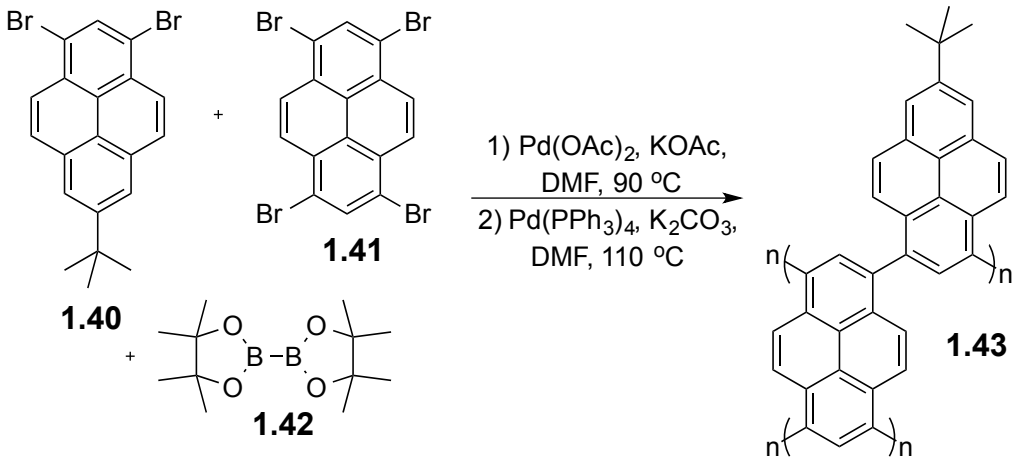
The substitution patterns previously discussed can be combined to give rise, rather quickly, to more elaborate pyrene systems. For example, *tert*-butylation of pyrene (**1.09**) affords 2-*tert*-butylpyrene (**1.39**) in 71% yield (Scheme 1.11).[21] The large size of the *tert*-butyl group causes the Friedel-Crafts alkylation to be disfavoured at the more electron-rich 1,3,6 and 8 positions, which can all be considered to be sterically hindered *peri* positions. Dibromination of compound **1.39** occurs exclusively at the 1,3-positions to give 1,3-dibromo-7-*tert*-butylpyrene (**1.40**) in 89% yield.[21] Due to the presence of the *tert*-butyl group, the two positions

*ortho* to the *tert*-butyl group are essentially blocked by the steric effects exerted. As a result the only two positions easily accessible via electrophilic aromatic substitution are 1 and 3.



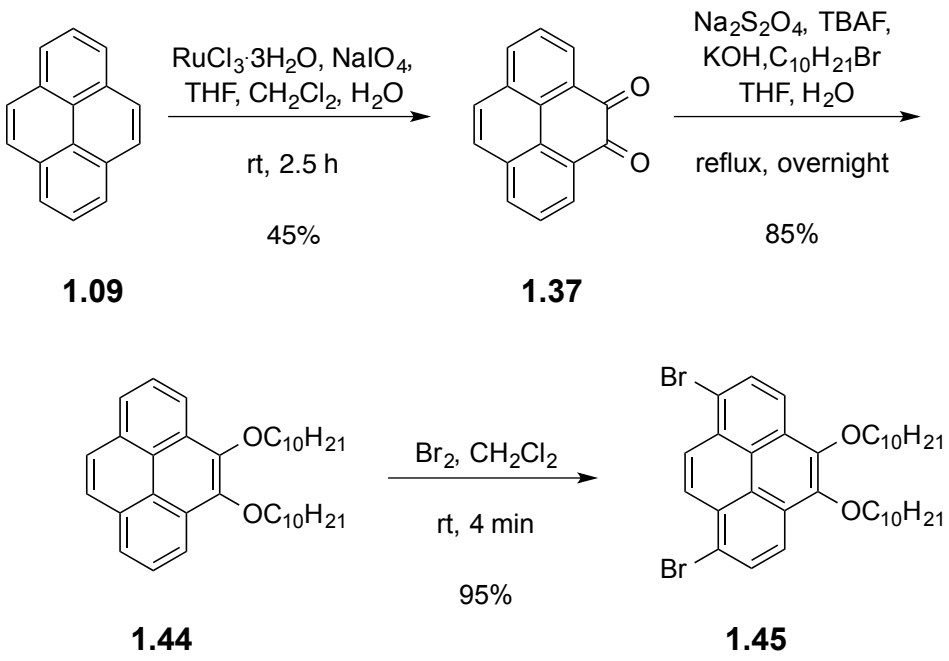

**Scheme 1.11** Dibromination of 2-*tert*-butylpyrene (**1.39**).

Compound **1.40** has been used as a building block in several complex systems. A report by Cooper and co-workers utilized a two-step one-pot coupling reaction (Scheme 1.12).[22] In the first step, an aryl halide/diboron coupling was catalyzed by $Pd(OAc)_2$ to afford the arylboronate derivatives of **1.40** and **1.41**. The authors described the first step as a one-pot "prepolymerization" reaction. The next step was undertaken without isolation of the arylboronates by the addition of $K_2CO_3$ and catalytic $Pd(PPh_3)_4$ to afford polymer **1.43**. When polymer **1.43** was dissolved in common organic solvents (THF, $CH_2Cl_2$, toluene), it produced homogenous green-luminescent solutions.



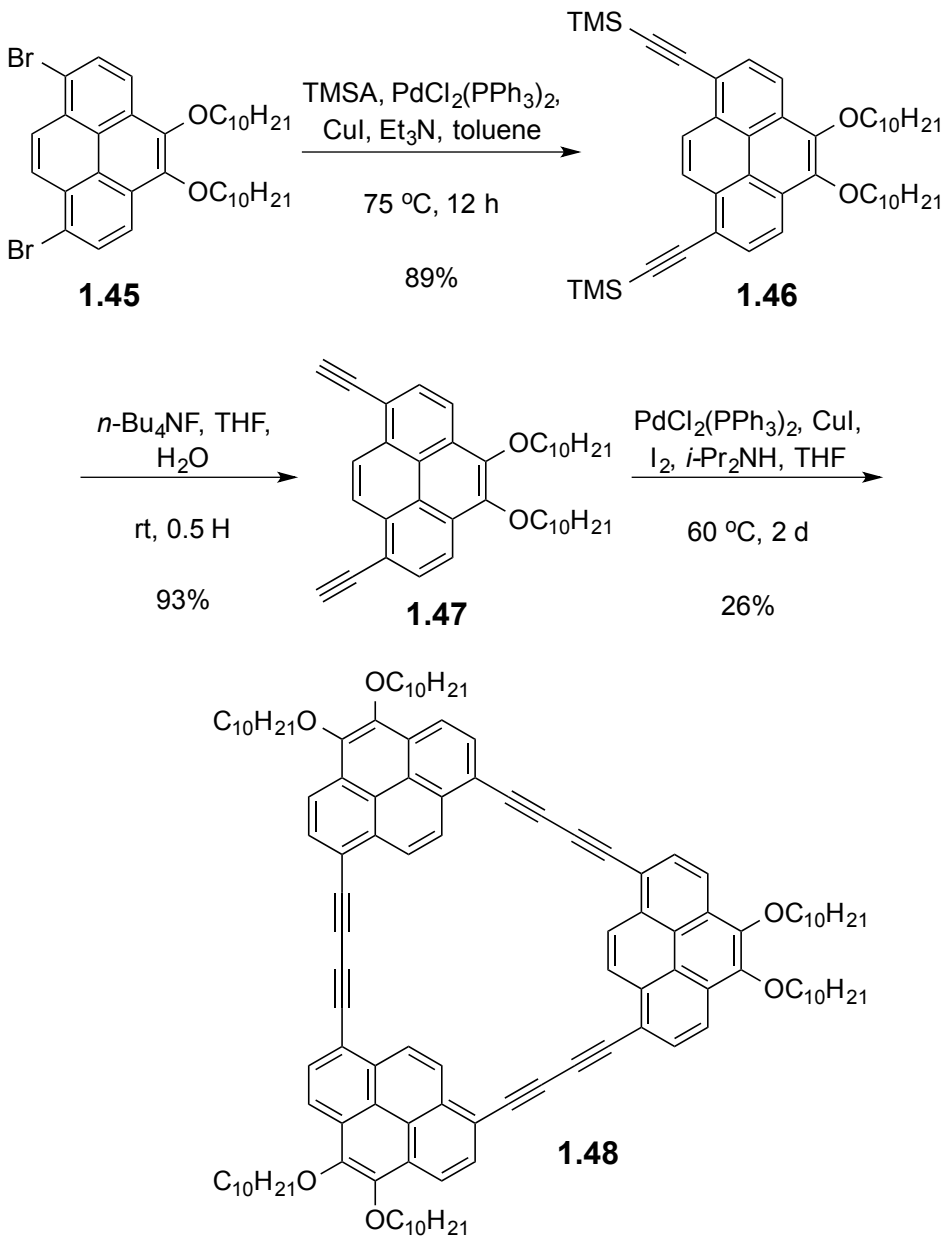

**Scheme 1.12** Synthesis of branched pyrene-based polymer **1.43**.

If controlled dibromination at the 1 and 8 positions is desired, it can be accomplished through another combination of transformations. As previously mentioned, diketone **1.37** can be reductively alkylated with a variety of alkyl halides to form compounds such as **1.44** (Scheme 1.13). Similar to the previous example, the alkoxy groups sterically hinder the *peri*-positions, leaving only what will become the 1 and 8 positions available for electrophilic aromatic substitution. Dibromination of compound **1.44** does in fact afford only the 1,8-dibromo product **1.45** in 85% yield. Compound **1.45** is a useful molecule that has been exploited in the Bodwell group.




**Scheme 1.13** Dibromination of 4,5-bis(decyloxy)pyrene (**1.44**).

Compound **1.45** has been used in the preparation of shape-persistent macrocycles, such as the 1,8-pyrenylene-ethynylene macrocycle **1.48** (Scheme 1.14).[20] The aryl-bromide connectivities present in **1.45** allow for the quick construction of larger systems through cross-coupling chemistry. In this example, **1.45** was coupled with TMSA under Sonogashira conditions to afford dialkyne **1.46** in 89% yield. This alkyne was then deprotected to afford terminal dialkyne **1.45** in 93% yield. Compound **1.47** was then subjected to oxidative homo-coupling, which give a mixture of different sized macrocycles, the major product being macrocycle **1.48** (26% ).

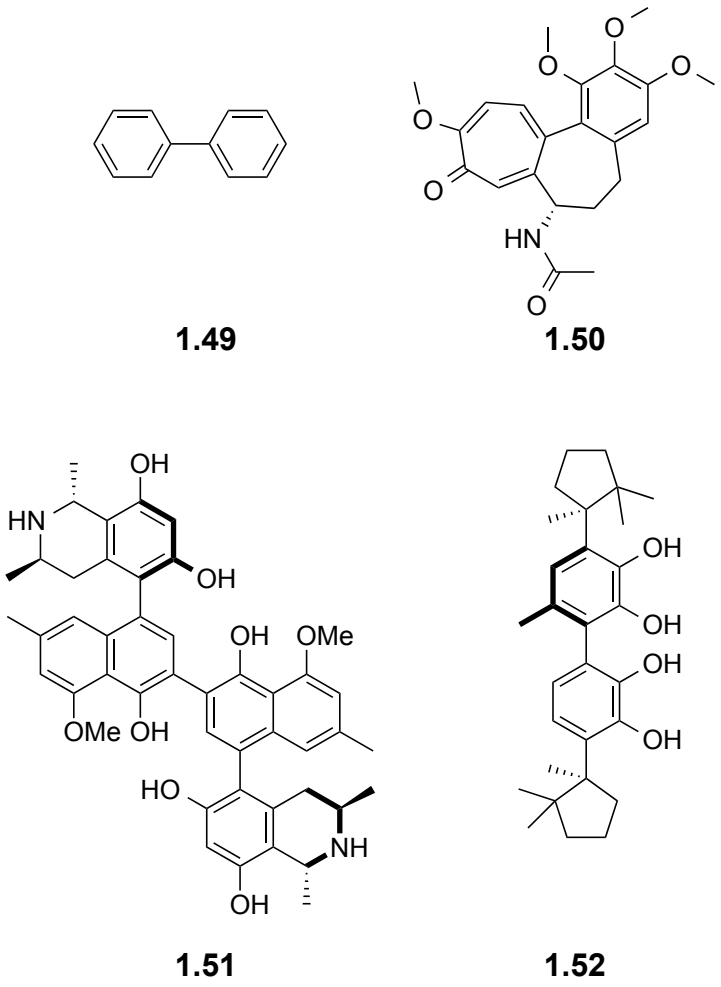



**Scheme 1.14** Synthesis of 1,8-pyrenylene-ethynylene macrocycle **1.48.**

Pyrene (**1.09**) therefore is a molecule of great utility which will be a unifying theme of the work presented in this thesis.

## 1.3 Biaryls

The term biaryl refers to any molecule that is composed of two aryl units. However, the term is more generally ascribed to molecules whose aryl units are connected through a single $sp^2$-$sp^2$ carbon-carbon bond. The simplest example is biphenyl (**1.49**) (Figure 1.06). The aryl-aryl bond that gives rise to biaryls is an important structural element in organic chemistry. It is present in many natural products including some that have shown interesting biological activity. One example, the alkaloid colchicine (**1.50**), which is extracted from the genus *Colchicum*, is used in the treatment of gout.[23] Structurally, it contains a biaryl bond between the phenyl ring and the seven-membered non-benzenoid aromatic tropone ring. Another example of an alkaloid natural product is michellamine B (**1.51**), derived from the Cameroonian liana *Ancistrocladus korupensis*.[24] It has three biaryl bonds and has shown some potential as a potent anti-HIV-1 and -2 agent. One last example of the many possible to choose from is mastigophorene A (**1.52**), which was isolated for the liverwort *Mastigophora diclados*.[25] It is a complex molecule built upon a biphenyl backbone that has shown some activity to stimulate nerve growth.

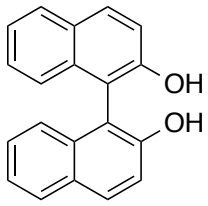



**1.49** **1.50** **1.51** **1.52**

**Figure 1.06** Biphenyl (**1.49**) and selected biaryl natural products.

In addition to the important biaryl natural products, there are equally important non-natural products that are biaryls. The source of importance of the non-natural biaryls is their ability to exhibit atropisomerism. The most well-known example may well be BINOL (**2.01**) (1,1'-bi-2-naphthol) (Figure 1.07). Structurally, BINOL (**2.01**) can be viewed as two 2-naphthol systems coupled at the 1 position. Rotation about the carbon-carbon bond between the two aryl groups is restricted.

This is partly due to steric repulsion of the OH groups that increases the steric strain to an extent that it can no longer freely rotate. The consequence of restricted rotation is that BINOL (**2.01**) belongs to the $C_2$ point group, which is inherently chiral. Its chirality has been exploited to resounding success in the field of asymmetric catalysis when it or its derivatives are utilized as ligands.[26]




**2.01**

**Figure 1.07** Structure of 1,1'-bi-2-naphthol (BINOL) (**2.01**).

## 1.4 References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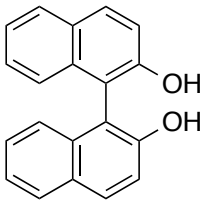
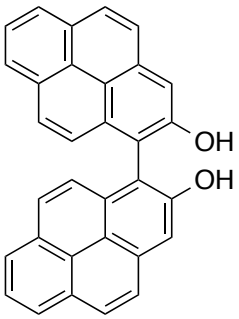
## Chapter 2 - Synthesis of Novel Pyrene-based BINOL Derivatives

### 2.1 Introduction

1,1'-Bi-2-naphthol (BINOL) (**2.01**) is a tremendously important core structure in the field of organic chemistry as evidenced by the abundance of variants and derivatives of BINOL (**2.01**) that have appeared in the chemical literature for the past few decades (Figure 2.01). BINOL (**2.01**) has been known since Pummerer and co-workers first reported its synthesis in 1926.[1] It is chiral by virtue of an axis of chirality that is coincident with the C-C bond that connects the two 2-naphthol moieties. Rotation about this bond is severely restricted, which means that BINOL (**2.01**) is configurationally stable at room temperature. The barrier to rotation has been determined experimentally to be 37.2 kcal/mol.[2] Racemic BINOL (**2.01**) is typically synthesized by oxidative coupling of 2-naphthol (**2.03**)[3] (Scheme 2.01).

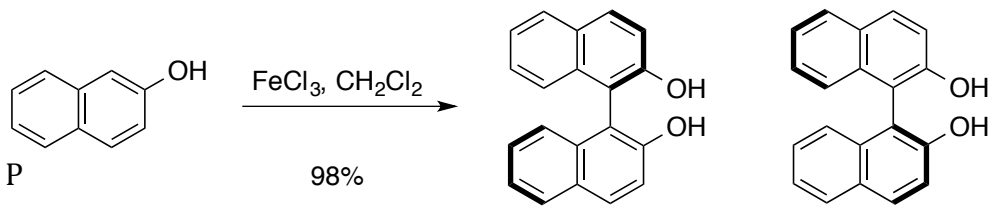



**2.01**




**2.02**

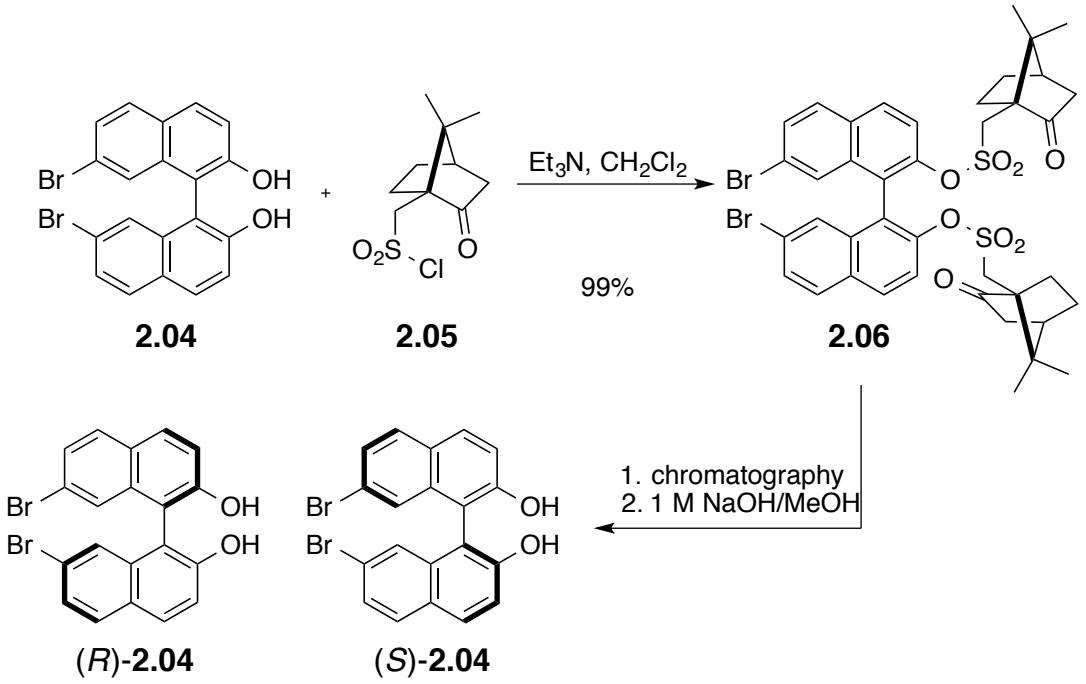
**Figure 2.01** BINOL (**2.01**) and pyrene-based BIPOL (**2.02**).



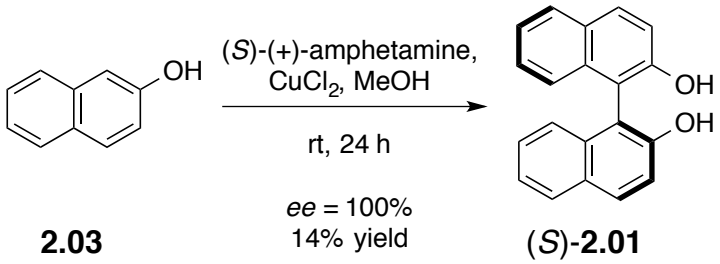

**2.03** (*R*)-**2.01** (*S*)-**2.01**

**Scheme 2.01** Oxidative coupling in the synthesis of BINOL (**2.01**).

Pure enantiomers can be obtained by resolution or by asymmetric synthesis. There are a few different strategies for resolving racemic BINOL (**2.01**) (or derivatives thereof), one of which is the reaction of BINOL (**2.01**) or some variant with (1*S*)-camphor-10-sulfonyl chloride (**2.05**) to afford a mixture of diastereomers (**2.06**) that can be separated by flash column chromatography (Scheme 2.02).[4] Once separated, the pure diastereomers (**2.06**) are hydrolyzed back to enantiomerically pure *R*- or *S*-BINOL derivative (**2.04**). There are also methods for the asymmetric synthesis of BINOL (**2.01**) and derivatives by the use of enantiomeric additives in the oxidative couplings.[5] For example, the reaction of 2-naphthol (**2.03**) with $CuCl_2$ in the presence of (*S*)-(+)-amphetamine stereoselectively (*ee* = 95%) affords (*S*)-BINOL ((*S*)-**2.01**) (Scheme 2.03).



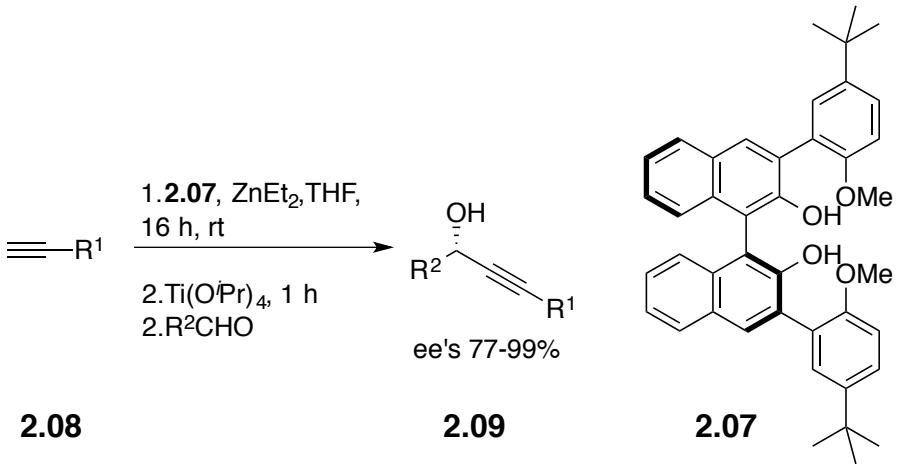

**Scheme 2.02** Resolution of BINOL derivatives (*R*)-**2.04** and (*S*)-**2.04**.




**Scheme 2.03** Asymmetric synthesis of BINOL (**2.01**).

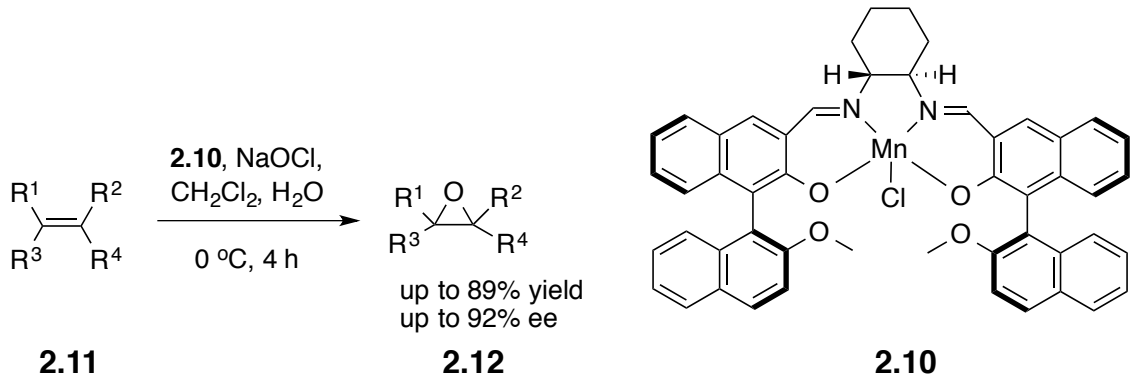
BINOL (**2.01**) and its variants have shown themselves to be very useful compounds that have been used in different applications. The most prevalent application of these compounds takes advantages of their chirality and phenolic functionality. These structural features make BINOL (**2.01**) an attractive ligand in asymmetric catalysis and derivatives continue to appear in the literature on a

consistent basis. The magnitude of the use of these compounds as ligands is highlighted in a 2003 review by Yudin *et al.*[6] The last decade has not seen any slowing in the appearance of BINOL (**2.01**) including these two recent examples. Firstly, Pu *et al.* reported the use of BINOL derivative **2.07** as a ligand for the asymmetric synthesis of propargylic alcohols (**2.09**) from terminal alkynes (**2.08**) (Scheme 2.04).[7]




**Scheme 2.04** Application of BINOL derivative **2.07** in asymmetric synthesis.

A second recent example of BINOL applications in the literature involves BINOL-salen manganese complexes **2.10** in the asymmetric epoxidation of olefins (Scheme 2.05).[8] Complex **2.10** achieves high yields (up to 89%) and high enantiomeric excesses (up to 92%) for the epoxidation of vinylbenzyl compounds.

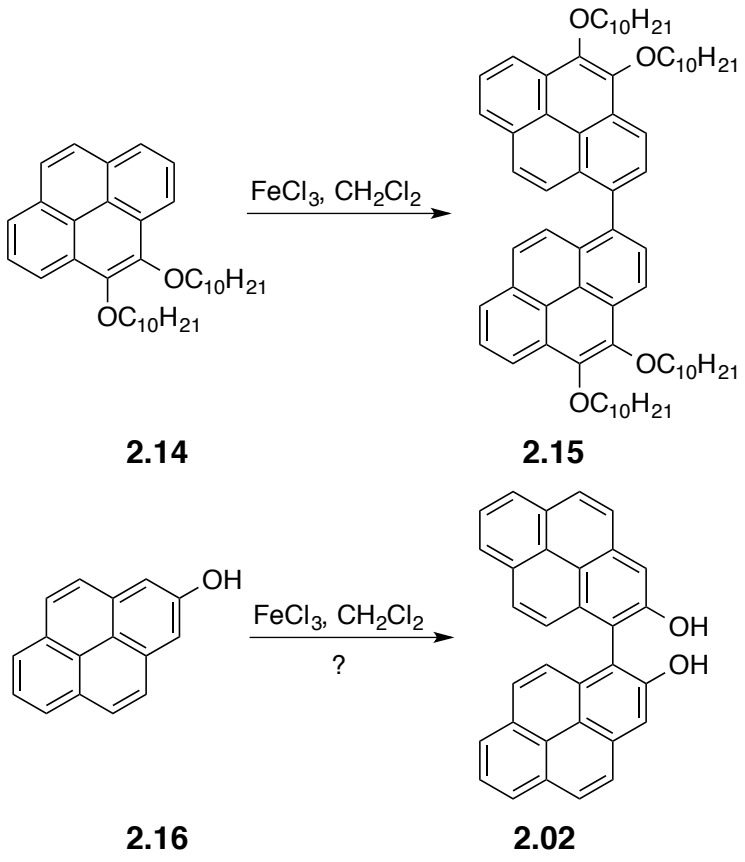



**Scheme 2.05** Application of BINOL derivative **2.10** in asymmetric synthesis.

In the Bodwell group, pyrene is one of the primary molecule of interest. The interest in pyrene originally was in the synthesis of pyrenophanes.[9-12] More recently, attention has also been focused on pyrene itself as a building block for larger cyclophanes and other designed π systems.[13-15] Like BINOL (**2.01**), pyrene (**2.13**) is a molecule of great importance and derivatives appear very frequently in literature. Interest in pyrene stems mainly from the photophysical properties it exhibits. For example, as presented in Chapter 1, pyrene has a relatively high quantum yield of 0.72 ($CHCl_3$)[16] and long lived excited state of 450 ns (EtOH).[17] In addition to these photophysical properties the flouresence behaviour of pyrene is strongly influenced by the environment in which it is measured.[18]

As part of previous studies it was observed that 4,5-(bis)decyloxypyrene (**2.14**) underwent internal Scholl reaction to afford biaryl **2.15**.[19] This begged the question as to whether pyrene-2-ol (**2.16**) would react similarly to give 1,1'-bi-2-

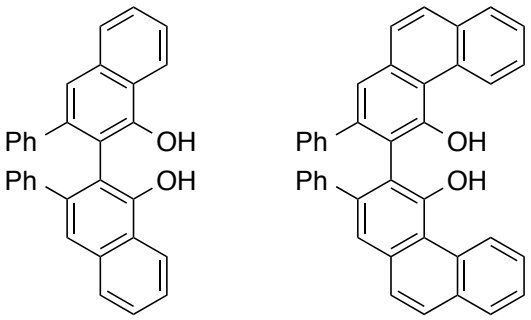
pyrenol (BIPOL) (**2.02**), a molecule that marries two very important core structures, BINOL (**2.01**) and pyrene (**2.13**) (Scheme 2.06).




**Scheme 2.06** Scholl reaction of substituted pyrenes.

Other bis-(hydroxyaryl)s are known, such as VANOL (**2.17**)[20] and VAPOL (**2.18**)[21] but no compounds of that type incorporating pyrene are known (Figure 2.02). BIPOL (**2.02**) would be of interest because it would be expected to be as good a ligand as BINOL (**2.01**) in asymmetric catalysis. It would also be expected to bring "better" photophysical properties to the table because of the presence of pyrene. In this Chapter, the synthesis of BIPOL (**2.02**) and selected derivatives, as well as

preliminary studies of the photophysical properties of some of these compounds are described.

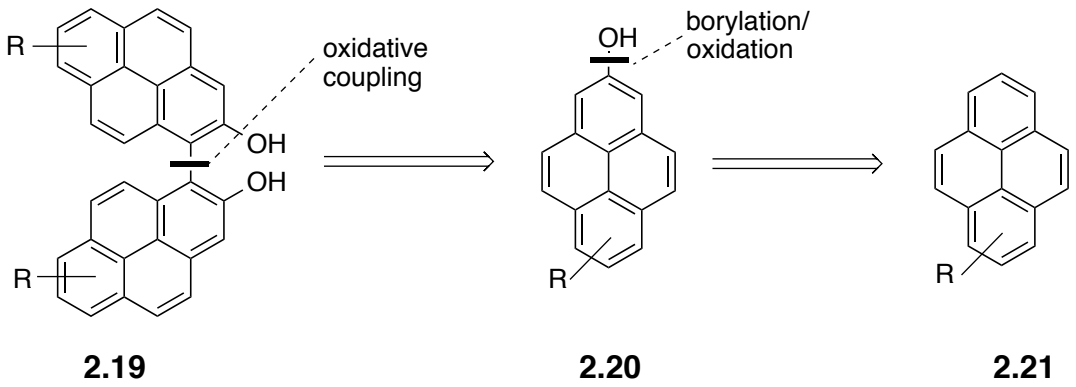



**2.17** **2.18**

**Figure 2.02** Other known bi(hydroxyaryls) VANOL (**2.17**) and VAPOL (**2.18**).

## 2.2 Retrosynthetic Analysis

This retrosynthetic analysis could be applied to all other 2-pyrenols (Scheme 2.07). As alluded to in Scheme 2.06, BIPOL or analog (**2.19**) was envisioned as coming from the oxidative coupling (Scholl reaction) of 2-pyrenols (**2.20**). No 2-substitued pyrenes are commercially available, so the plan for the synthesis of **2.21** was to subject it to Marder's borylation,[22] followed by oxidation.




**Scheme 2.07** Retrosynthetic analysis of pyrene-based BINOL analogs.

## 2.3 Results and Discussion

The first system to be explored, was not the parent BIPOL (**2.02**), but rather the *tert*-butylated derivative 7,7'-di-*tert*-butyl-1,1'-bi-2-pyrenol (**2.21**) (Scheme 2.03). This target was to chosen to lessen any potential solubility problems.

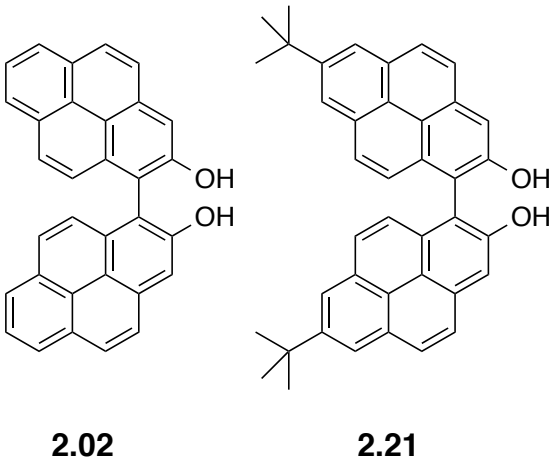
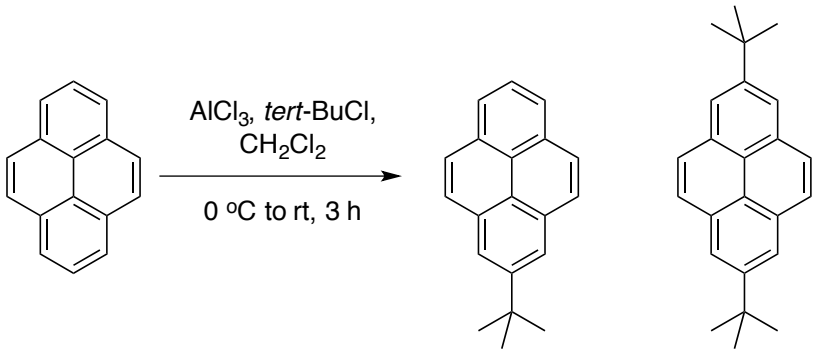



**Figure 2.03** Initial synthetic targets.

The synthetic path toward di-*tert*-butylBIPOL (**2.21**) began with the mono Friedel-Crafts *tert*-butylation of pyrene using 1.1 equivalents of *tert*-BuCl according to a literature procedure, which resulted in the formation of a mixture of unreacted pyrene (**2.13**), 2-*tert*-butylpyrene (**2.22**)**,** and 2,7-di-*tert*-butylpyrene (**2.23**) (Scheme 2.08).[23] The desired mono-*tert*-butylated compound was isolated using a modified procedure for crystallization. Crystallization of the crude product from a methanol solution afforded 2,7-di-*tert*-butylpyrene (**2.23**) in 13% yield. Subsequent crystallization of the concentrated mother liquor from hexanes yielded 2-*tert*-butylpyrene (**2.22**) in 68%

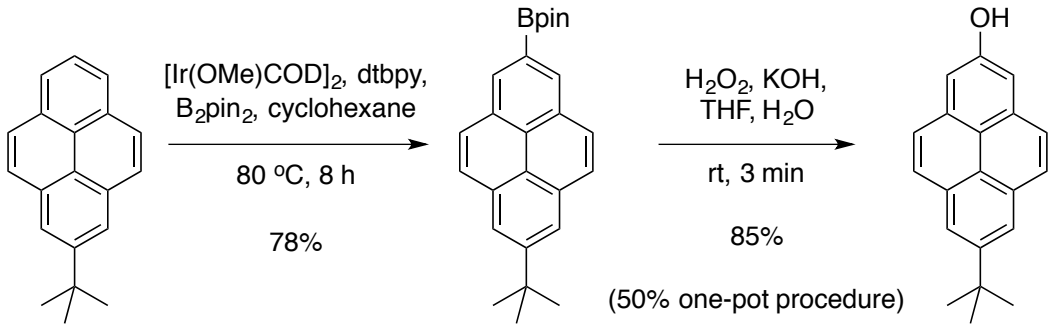



**Scheme 2.08** Friedel-Crafts *tert*-butylation of pyrene (**2.13**).

The introduction of the required hydroxyl functionality was then approached using Marder's borylation methodology. This chemistry, which was first reported by Marder and co-workers in 2005,[22] described the regioselective iridium-catalyzed borylation of pyrene. It was reported that borylation occurs solely at the 2,7-positions of pyrene, to varying degrees, depending on the amount of borylating

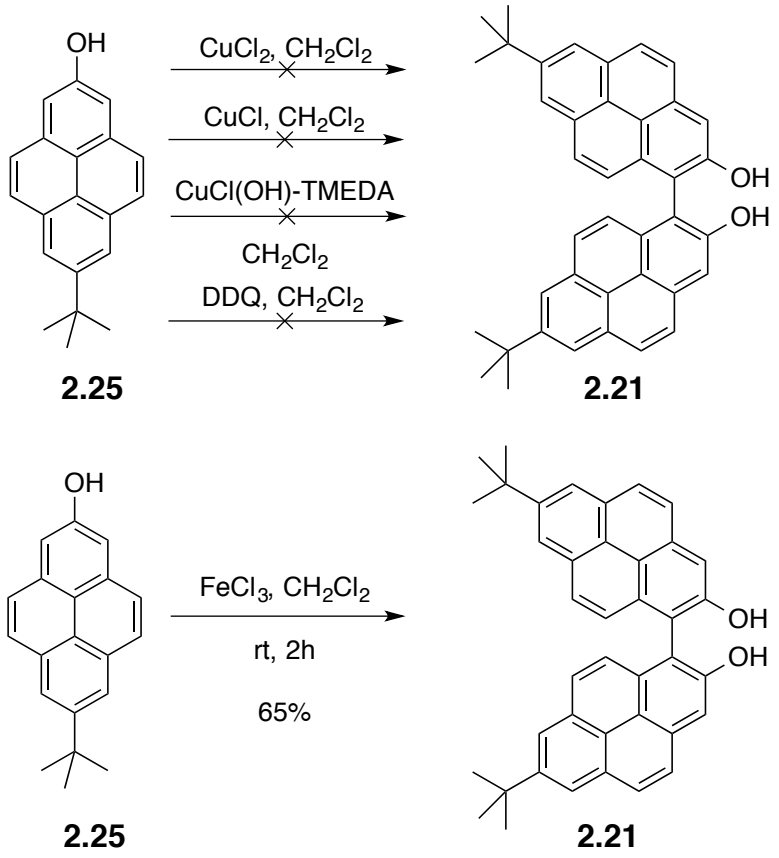
agent used. In theoretical work reported by Sakaki and co-workers on the catalytic cycle of the iridium-catalyzed borylation of arenes, the key intermediate in the rate-determining C-H activation step is sterically crowded.[24] This crowded intermediate translates into selective borylations at the least sterically hindered positions of arenes. The 2 and 7-positions of pyrene are the only two positions on pyrene that are not sterically encumbered *peri* positions.

Starting from 2-*tert*-butylpyrene (**2.22**), only the 7-position is available for borylation as the 2-position is already occupied by the *tert*-butyl group. As expected, completely regioselective borylation was achieved by the reaction of 2-*tert*-butylpyrene (**2.22**) with catalytic amounts of $[Ir(OMe)COD]_2$ (1 mol%) and 4,4'-di-*tert*-butyl-2-2'-bipyridyl (dtbpy) (2 mol%) with bis(pinacolato)diboron ($B_2pin_2$) at reflux in cyclohexane to give exclusively borylated product **2.24** in 78% isolated yield on a scale up to 5 grams (Scheme 2.09). The borylated product could then be oxidized using KOH and $H_2O_2$ to yield the hydroxy compound **2.25** in 85% yield. These two transformations could be accomplished in a one-pot procedure without isolation of the borylated product **2.24**, but the overall transformation suffered from a drop in yield to 50% from 66%.



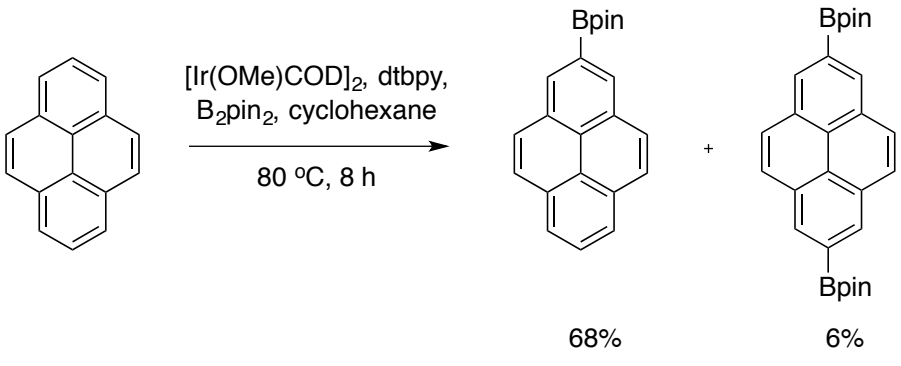

**Scheme 2.09** Synthesis of 7-*tert*-butylpyren-2-ol (**2.25**).

At this point, **2.25** was easily accessible in gram quantities and various oxidants were tested for their utility in inducing the desired oxidative coupling. The reaction of **2.25** with $CuCl_2$[25], CuCl[26], DDQ[27], CuCl(OH)•TMEDA[28] all failed to produce the desired product and either showed no reactivity or led to an intractable mixture of products. However, when $FeCl_3$[29] was used as the oxidant with stirring in open air, the desired product **2.21** was produced in an initial yield of 46% (Scheme 2.10). The yield could be improved to 65% when nitrogen was continually bubbled through the reaction mixture during the reaction to expel HCl generated as part of the reaction. When this reaction was scaled up to gram quantities the yield was not adversely affected. Compound **2.21** was rather soluble in most common organic solvents, such as $CH_2Cl_2$, THF, and ethyl acetate, which made it very easily to manipulate and handle.




**Scheme 2.10** Scholl reaction of 7-*tert*-butylpyren-2-ol (**2.25**).

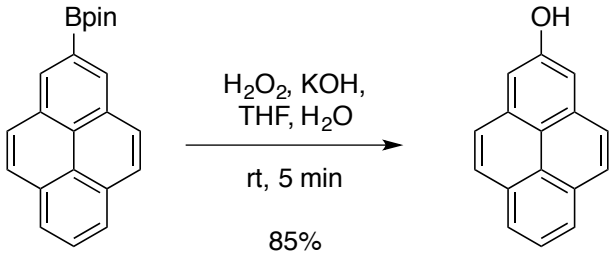
Following this very encouraging result, focus was then shifted to the synthesis of the parent BIPOL (**2.02**). The synthesis began with borylation of pyrene (**2.13**) with catalytic $[Ir(OMe)COD]_2$ and dtbpy (1 mol% and 2 mol% respectively) with $B_2pin_2$ at reflux in cyclohexane to yield 68% of the desired borylated product **2.26** along with 8% of the bis-borylated product **2.27** (Scheme 2.11). These results are identical to those published by Marder and co-workers in their 2005 report for the borylation of pyrene.




**2.13** **2.26** **2.27**

**Scheme 2.11** Borylation of pyrene (**2.13**).

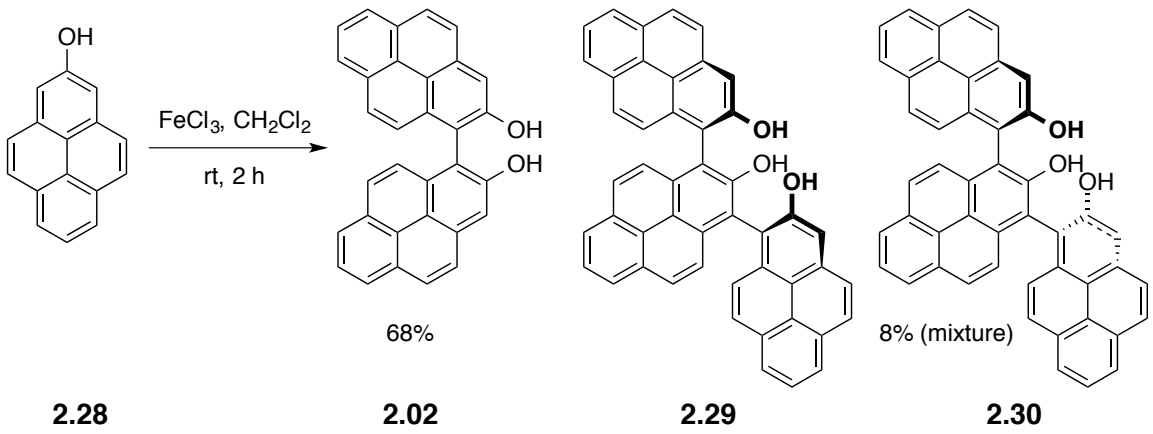
With borylated product **2.26** in hand, it was subjected to the same oxidation conditions as the *tert*-butyl borylated system **2.24** (Scheme 2.12). The hydroxy product **2.28** was obtained in 85% yield. Again, these two transformations could be accomplished using a one-pot procedure without isolation of borylated product **2.26**, but the one-pot transformation proceeded in only 40% yield, compared to 58% for the two-step protocol.




**2.26** **2.28**

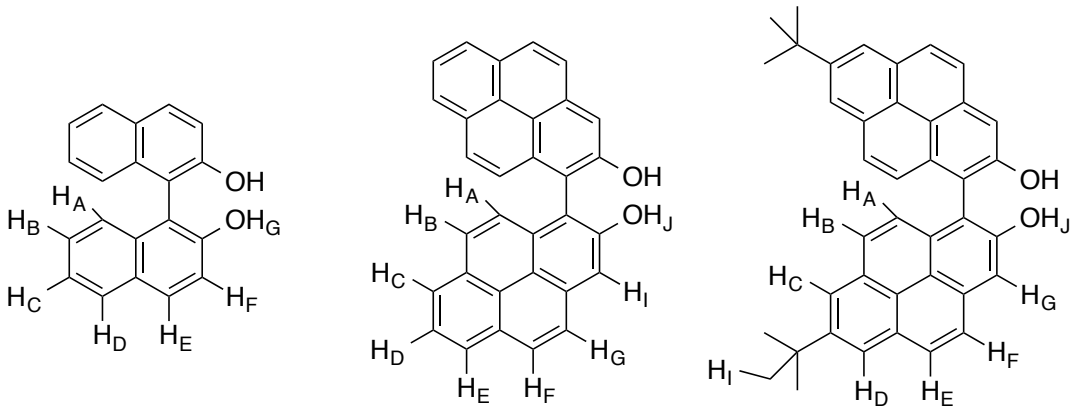
**Scheme 2.12** Oxidation of borylated pyrene **2.26**.

In view of the results of the oxidative coupling of **2.25,** the oxidative coupling of **2.28** was carried out using only $FeCl_3$ (Scheme 2.13). This led to the formation of BIPOL (**2.02**) in 68% yield. Interestingly, small amounts (8%) of the trimer **2.29** and **2.30** are also obtained in 8% yield. Dimer **2.02** was easily separated from trimers **2.29** and **2.30** by column chromatography, but the diastereomeric trimers **2.29** and **2.30** could not be separated and were left as a mixture of stereoisomers. Any concerns about the solubility of BIPOL (**2.02**) were not borne out, as it exhibits good solubility in common organic solvents. It was even modestly soluble in hexanes.




**Scheme 2.13** Synthesis of BIPOL (**2.02**).

In the $^1H$ NMR spectrum of BIPOL (**2.02**) and di-*tert*-butylBIPOL (**2.21**), all protons were assigned unambiguously using COSY-2D and NOE experiments. The labeled protons (Figure 2.04) are tabulated below (Table 2.1). For BIPOL (**2.02**), the signals for $H_A$ stands out in that it is observed at significantly higher field (δ 7.40 ppm) than the corresponding proton in pyren-2-ol (**2.28**) (δ 7.95 ppm).




**2.01** **2.02** **2.21**

**Figure 2.04** Labeled protons of BINOL (**2.01**), BIPOL (**2.02**) and di-*tert*-butylBIPOL (**2.21**).

Interestingly, the upfield shift of $H_A$ (0.55 ppm) is significantly larger than the analogous one (0.16 ppm) for proton $H_A$ in going from 2-naphthol (**2.03**) (δ 7.12 ppm) to BINOL (**2.01**) (δ 6.96 ppm).[30] An identical upfield shift of $H_A$ (0.55 ppm) is observed in di-*tert*-butylBIPOL (**2.21**) (δ 7.47 ppm, compared to δ 7.92 ppm in 7-*tert*-butylpyren-2-ol (**2.25**)).

| **BIPOL (2.02)** | | **Di-*tert*-butylBIPOL (2.21)** | |
|---|---|---|---|
| Proton | Chemical Shift (ppm) | Proton | Chemical Shift (ppm) |
| $H_A$ | 7.40 | $H_A$ | 7.36 |
| $H_B$ | 7.91 | $H_B$ | 7.89 |
| $H_C$ | 8.14 | $H_C$ | 8.19 |
| $H_D$ | 7.97 | $H_D$ | 8.28 |
| $H_E$ | 8.23 | $H_E$ | 8.16 |
| $H_F$ | 8.17 | $H_F$ | 8.09 |
| $H_G$ | 8.11 | $H_G$ | 7.99 |
| $H_I$ | 8.02 | $H_I$ | 1.57 |
| $H_J$ | 5.25 | $H_J$ | 5.22 |

**Table 2.1** Chemical shifts of BIPOL (**2.02**) and di-*tert*-butylBIPOL (**2.24**).

With BIPOL (**2.02**) and its di-*tert*-butylated derivative **2.21** in hand, studies of their chemical and physical properties were undertaken. First, single crystals of BIPOL (**2.02**) suitable for X-ray diffraction studies were obtained by slow evaporation of a 3:1 $CH_2Cl_2$/acetone solution. Suitable crystals of di-*tert*-butylBIPOL (**2.21**) were not obtained. The crystal structure was determined by Dr. L. Dawe (Memorial University) and it was found that acetone was incorporated into the crystal lattice. The unit cell, represented by the capped stick representation in the expanded unit cell (Figure 2.05) contains fractions of molecules. The expanded unit cell shows that two pyrene moieties have slipped face-to-face π-π interactions. The closest contact between the planes is 3.48 Å with a centroid distance of 3.91 Å. The

two pyrene moieties are offset by 1.72 Å. One also notices the ($sp^2$)C-H…π interactions, denoted by the dashed line in Figure 2.05, at a distance of 2.95 Å between the C-H and the centroid.

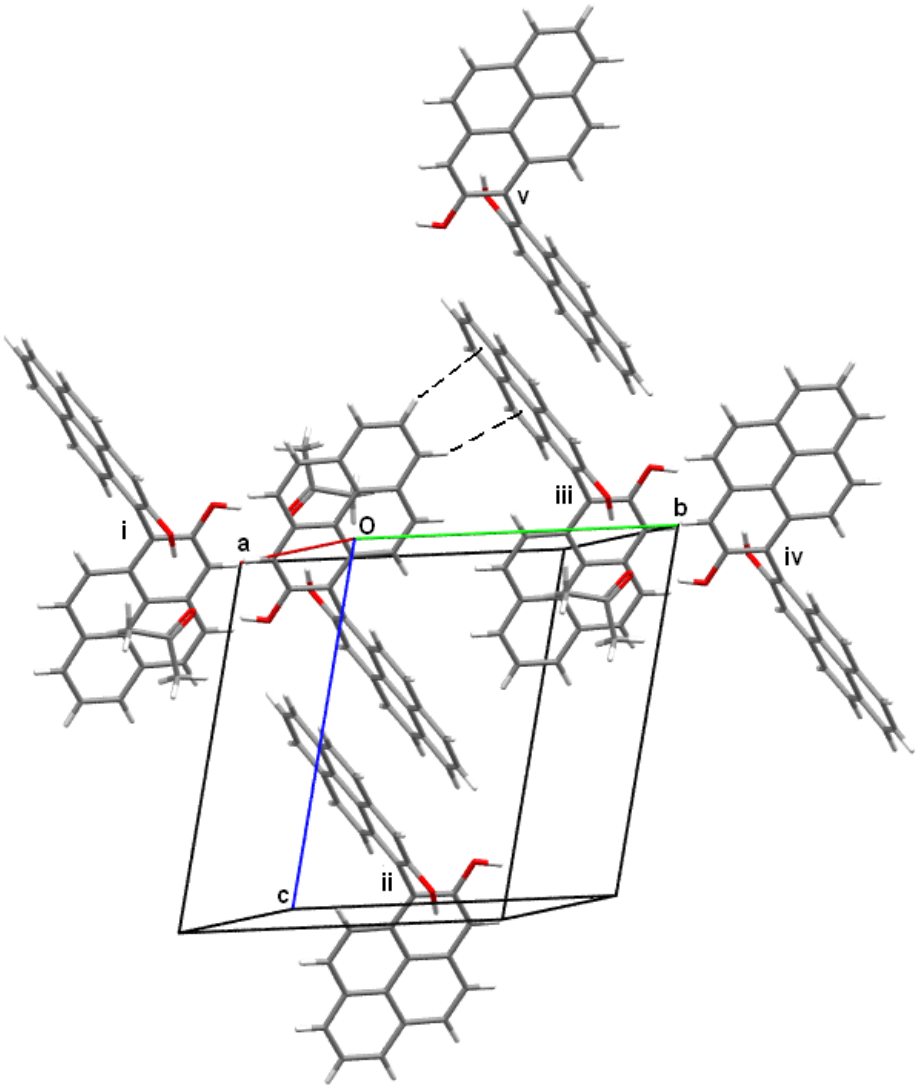



**Figure 2.05** Expanded unit cell of BIPOL (**2.02**).

The asymmetric unit (Figure 2.06) shows one BIPOL (**2.02**) molecule and one acetone lattice solvent molecule. The dihedral angle between the two pyrene

planes was determined to be 103.3°. The two pyrene systems are essentially planar (largest deviation from the the best plane = 0.076 Å). The dihedral angle for BINOL (**2.01**) has been reported to be between 89.9° and 99.7°.[31-32] The two dihedral angles are similar, as one would expect due to the fact that they have similar chiral environments around the axis of chirality.

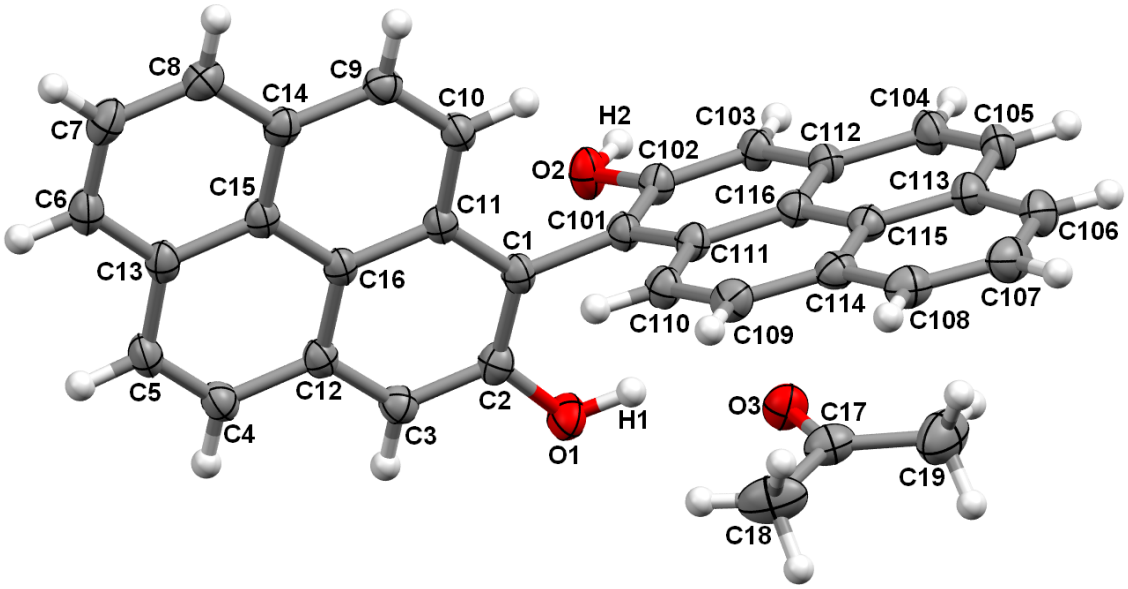



**Figure 2.06** Asymmetric unit of BIPOL (**2.02**).

By applying the symmetry operation (2-x, -y,-z) Figure 2.07 is obtained which shows the intermolecular hydrogen bonded 18-membered supramolecular ring. The ring consists of two hydrogen bond accepting acetone molecules and four OH hydrogen bond donors coming from two BIPOL (**2.02**) molecules of opposite configuration.

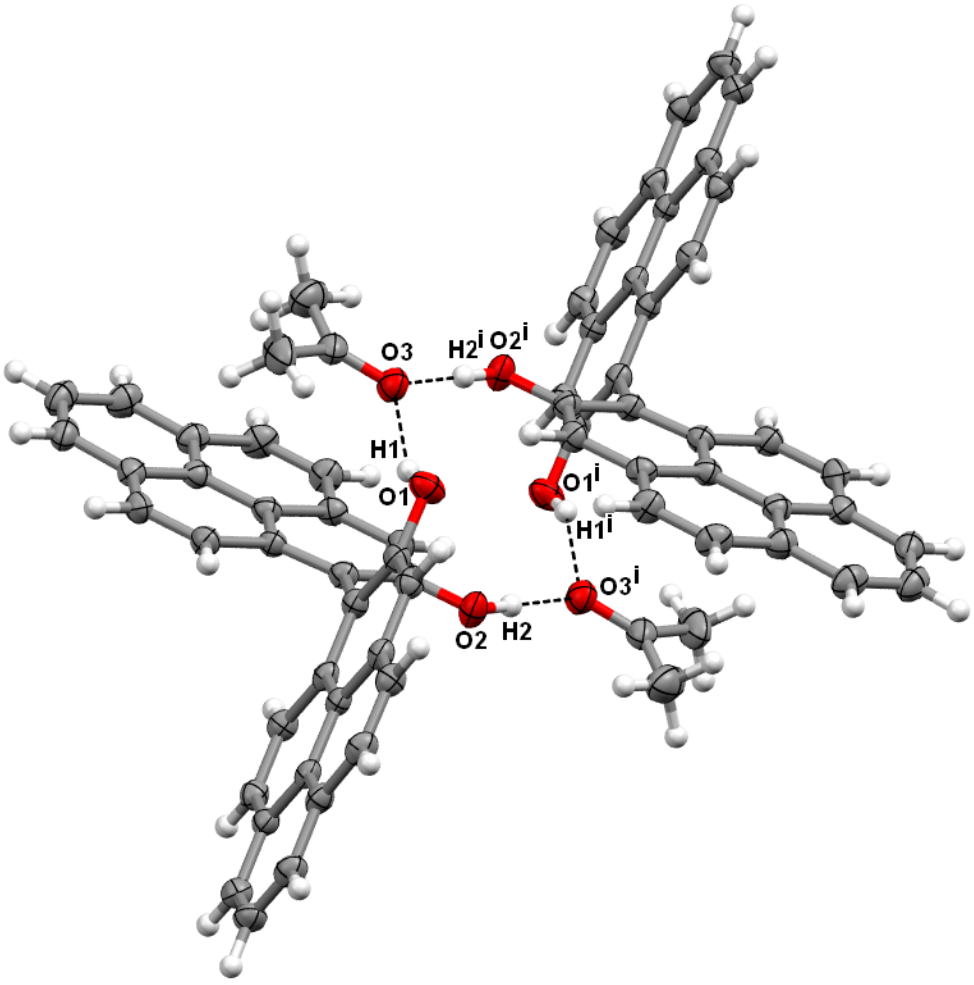
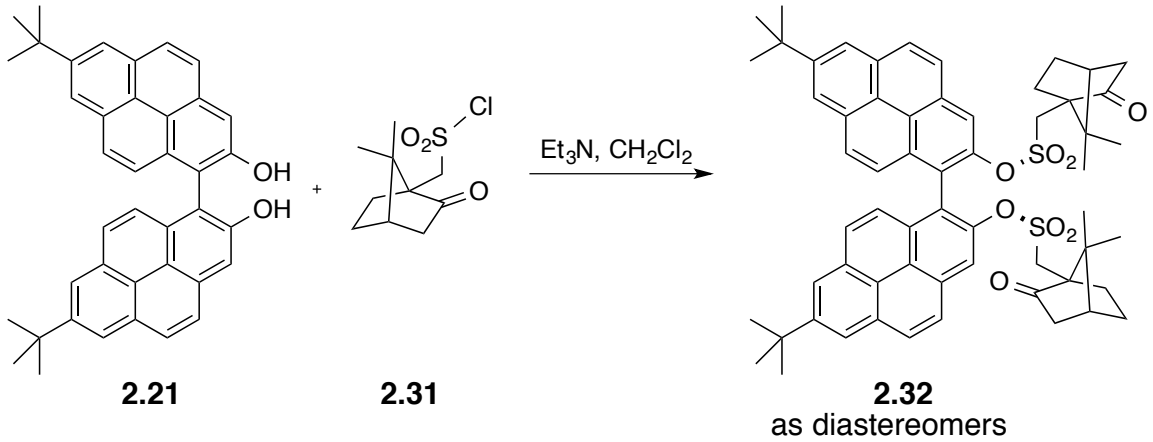



**Figure 2.07** Intermolecular hydrogen bonding in BIPOL (**2.02**).

In order to resolve **2.02** and/or **2.21** numerous classical techniques for the resolution of BINOL (**2.01**) were investigated. Resolution of large quantities of enantiomerically pure samples is one of the key issues that needs to be settled. Ideally, a classical approach to resolution of the enantiomers is necessary to gain access to larger samples of single enantiomers to carry on chiroptical studies or to test there utility as chiral ligands. A couple of attempts at resolution were tested.

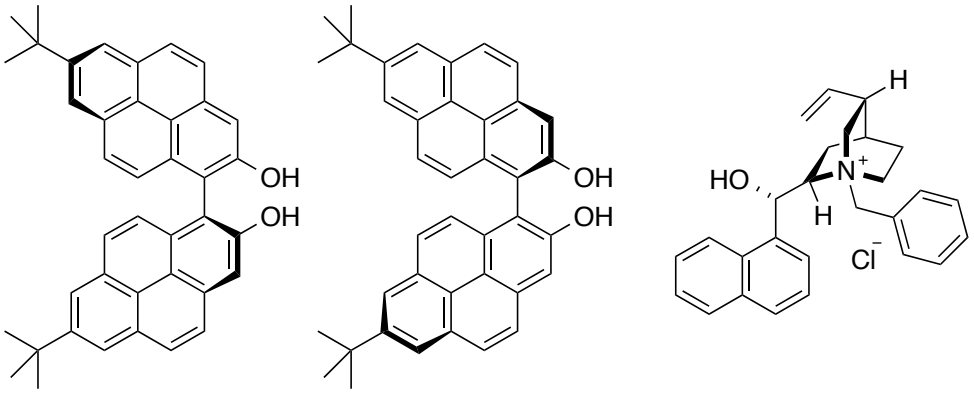
The first procedure pursued was derivatization with both (1*S*)-(+)-camphor-10-sulfonyl chloride (**2.05**) and (1*R*)-(-)-camphor-10-sulfonyl chloride (**2.31**) to afford the mixture of diastereomers (**2.32**) that in theory should be separable by column chromatography (Scheme 2.14).[4] This approach is similar to the one presented earlier in Scheme 2.02. The reaction of BIPOL (**2.02**) and its *tert*-butylated derivative **2.21** with either enantiomer of sulfonyl chloride led to a mixture of products that could not be separated by column chromatography.




**2.21** **2.31** **2.32** as diastereomers

**Scheme 2.14** Derivatization of **2.21** to diastereomers.

A second strategy for optical resolution attempted to selectively crystallize one enantiomer preferentially through molecular complexation with *N*-benzylcinchoninium chloride (**2.33**) (Figure 2.08).[33] Compound **2.33** has been shown to selectively form inclusion crystals with the *R*-enantiomer of BINOL (**2.01**) and precipitates out of solution, leaving the *S*-enantiomer in the mother liquor. The same protocol was applied in an attempt to separate the enantiomers of BIPOL (**2.02**) but no inclusion crystals were obtained.




(*S*)-**2.21** (*R*)-**2.21** **2.33**

**Figure 2.08** Optical resolution by molecular complexation.

Without promising results at this point for classical resolution of **2.21**, a few grams of **2.21** was sent to Lotus Separations LLC in an attempt to separate the two enantiomers by means of chiral HPLC. The enantiomers were successfully separated on an AD-H (15 x 0.46 cm) column using an eluent system of 40% ethanol(DEA)/$CO_2$ at 100 bar with a flow rate of 3 mL/min. The pure enantiomers have yet to have their absolute configurations determined, but the first compound to elute did so in >99% chemical purity and an enantiomeric excess of >98.6%. The second compound to elute was obtained in 99% chemical purity and an enantiomeric excess of >99%. Although the separation was successful, specific rotations were not able to be determined because the amount of pure material obtained was not enough to produce sufficiently concentrated solutions to perform those measurements. Fortunately, there was enough material to obtain a circular

dichroism spectrum (obrained by Prof. R. A. Pascal, Jr., Tulane University) (Figure 2.09).

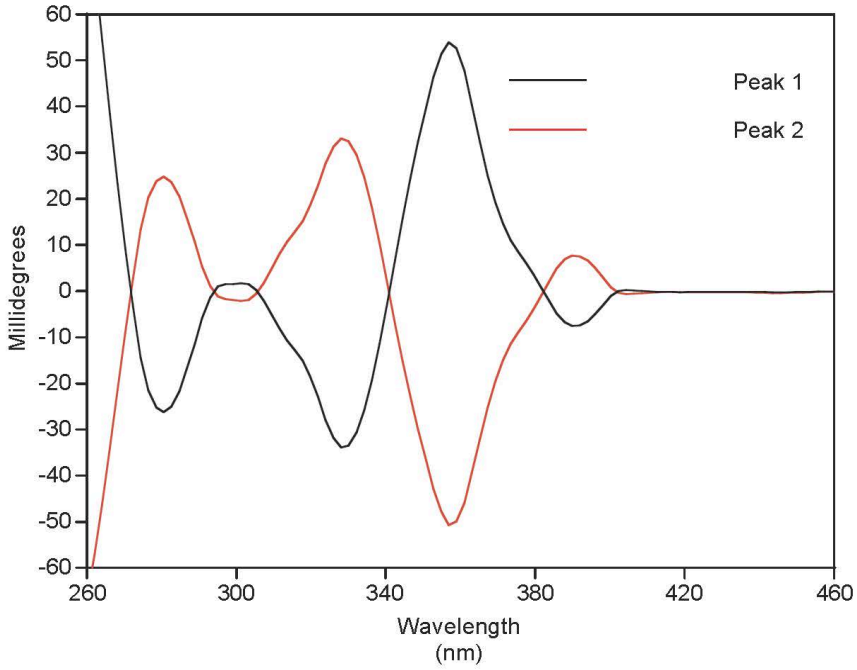



**Figure 2.09** CD spectra of compound **2.21**.

As presented earlier, one of the most important aspects of designing pyrene-based analogues of BINOL is the photophysical properties that the pyrene systems bring along with them. The quantum yields of the hydroxypyrenes, **2.25** and **2.28**, and BIPOL (**2.02**) and the di-*tert*-butylated derivative **2.21**, were measured in collaboration with Dr. D. Thompson (Memorial University). The values are tabulated below along with literature values for various arene, hydroxyarene, biarly, and bi(hydroxyaryl) systems (Table 2.2). When comparing the core arenes benzene, naphthalene and pyrene, it can be seen that the quantum yield increases

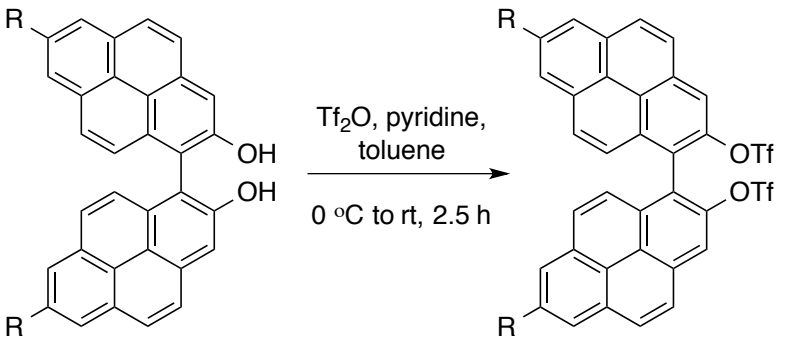
dramatically as aromatic system becomes large (Table 2.2, entries 1-3). Upon moving to the biaryl systems derived from these core arenes, one notices that there is a sixfold increase in going from benzene to biphenyl (Entries 1 and 4), a threefold increase in going from naphthalene to 1,1'-binaphthalene (Entries 2 and 5), and no change in going from pyrene to 1,1'-bipyrene (Entries 3 and 6). In comparing the hydroxyaryl systems (phenol, 2-naphthol, and 2-pyrenol) the addition of an OH group from having a beneficial effect on quantum yield in benzene (Entries 1 and 7), to having little in naphthalene (Entries 2 and 8) and a detrimental effect in pyrene (Entries 3 and 9). Finally, comparison of the hydroxyaryl systems with the corresponding bi(hydroxyaryls) reveals that "self-coupling" of phenol and 2-naphthol (Entries 7,8,10 and 11) results in a drop in quantum yield. Whereas a substantial jump is observed in going from pyren-2-ols to BIPOL (**2.02**) or di-*tert*-butylBIPOL (**2.24**) (Entries 9,12 and 13). One of the potential applications envisioned for these compounds is to replace the BINOL (**2.01**) derivatives that are currently used as fluorescent sensors. One notices the abysmal quantum yield of BINOL (**2.01**) (Entry 12), which makes one imagine that these sensing systems could be greatly improved if compounds with more advantageous photophysical properties. It stands to reason that the excellent quantum yield of BIPOL (**2.02**) would lend itself to higher performance turn-off sensing devices relative to BINOL (**2.01**).

**Table 2.2** Selected quantum yield.

| Entry | Aromatic | Quantum Yield (Φ) | Reference |
|---|---|---|---|
| 1 | benzene | 0.033 | 16 |
| 2 | naphthalene | 0.21 | 16 |
| 3 | pyrene | 0.72 | 16 |
| 4 | biphenyl | 0.18 | 34 |
| 5 | 1,1'-binaphthalene | 0.67 | 34 |
| 6 | 1,1'bipyrene | 0.72 | 23 |
| 7 | phenol | 0.075 | 36 |
| 8 | 2-naphthol | 0.18 | 35 |
| 9 | pyren-2-ol | 0.45 | This work |
| 10 | 1,1'-bi-2-phenol | 0.034 | 35 |
| 11 | BINOL | 0.024 | This work |
| 12 | di-*tert*-butylBIPOL | 0.63 | This work |
| 13 | BIPOL (**2.02**) | 0.65 | This work |

Most BINOL systems that are used as asymmetric ligands or sensors are functionalized at different junctions of the molecule. If BIPOL systems are to be used in such applications, access to similarly functionalized derivatives is of considerable importance. The BINOL systems used most often are derivatives that have been functionalized at the 3 and 3' positions, which are also the 3 and 3' positions in BIPOL (**2.02**). This is most often the site of derivatization because it is the closest to the action; the plane of symmetry and the OH groups. Another common site to functionalize these compounds is the OH group itself. With access to gram quantities of di-*tert*-butylBIPOL (**2.21**) and BIPOL (**2.02**), studies towards their functionalization were undertaken. The first derivatives to be synthesized were triflates (**2.34**) and (**2.35**), which were generated upon reaction of BIPOL (**2.02**) and di-*tert*-butylBIPOL (**2.21**) with trifluoromethanesulfonic anhydride in toluene (Scheme 2.15).[39] The yields of **2.34** and **2.35** were 73% and 95%,

respectively. These triflates are important because they enable cross-coupling to aryls or other heteroarom-based substituents to build onto.

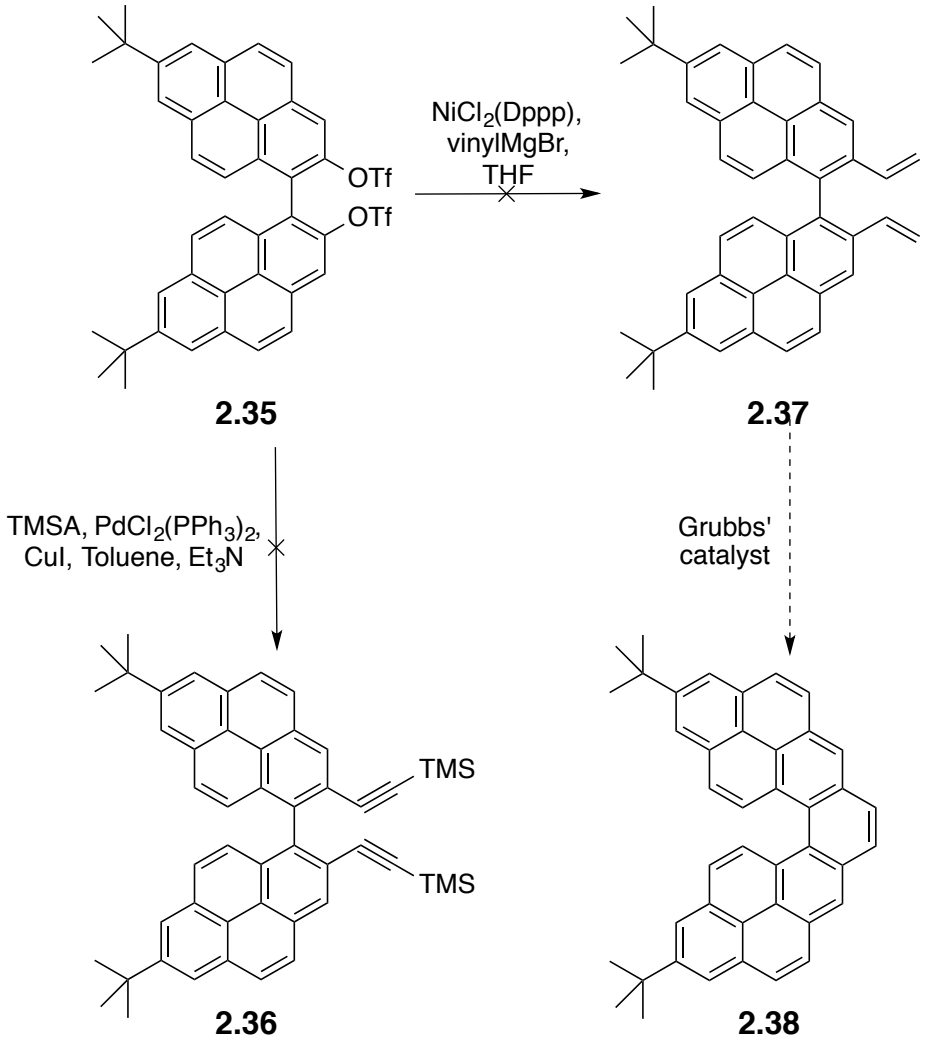



R = H, **2.02**
R = *t*-Bu, **2.21**

R = H, **2.34**, 73%
R = *t*-Bu, **2.35**, 95%

**Scheme 2.15** Triflates of BIPOL systems.

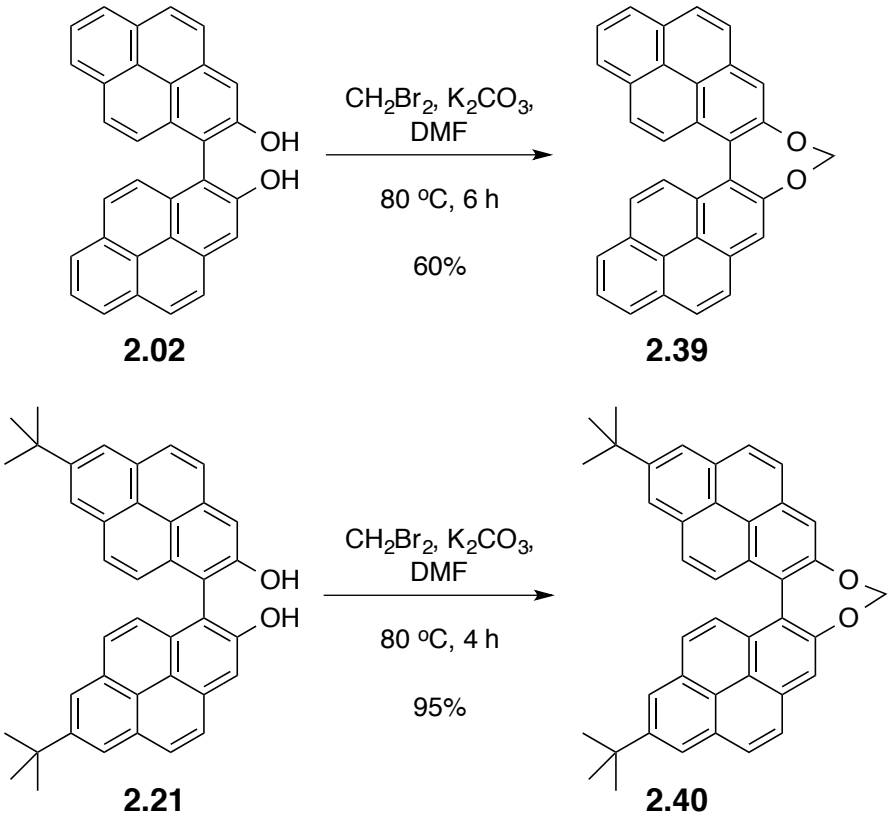
A few cross-coupling reactions were attempted with compound **2.35** (Scheme 2.16). A Sonogashira reaction with trimethylsilylacetylene to obtain **2.36** was explored to unfulfilled results. The reaction of **2.35** with vinylmagnesium bromide and $NiCl_2$(dppp) was also tried, but unfortunately did nor result in any desired reaction products. These reactions were performed as an attempt towards the synthesis of helicenes like **2.38**, by ring-closing methathesis (RCM).[40] Helicenes are privileged structures that exhibit some of the largest optical rotations known. These properties make helicenes useful compounds in nonlinear optics and in the manufacture of high optical rotation materials. Compound **2.37** is set up for RCM, and **2.36** could be transformed into **2.37** by deprotection and catalytic hydrogenation with Lindlar's catalyst. RCM has previously been reported in the synthesis of helicenes starting from BINOL (**2.01**).




**Scheme 2.16** Attempted Sonogashira reaction of triflate **2.35**.

Other chemistry could be performed at the 2-position towards the synthesis of helical systems. For example, tying together the OH groups by a methylene bridge has been shown in BINOL (**2.01**) systems.[41] The resulting helical structures have been shown to exhibit increased chiroptical properties. The reaction of compounds **2.02** and **2.21** with potassium carbonate in DMF yielded the helicene-like methylene bridged **2.39** and **2.40** in 60% and 95% yields, respectively (Scheme

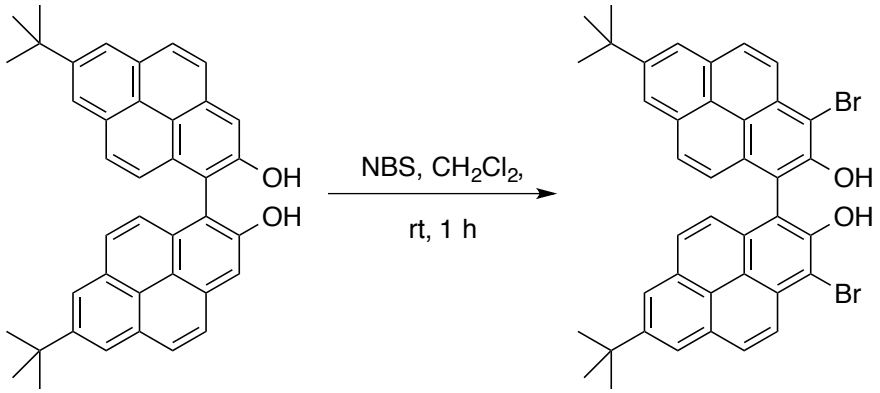
2.17). Resolution has not yet been achieved for these compounds. The two types of 2,2'-substituted derivatives if BIPOL (**2.02**) and di-*tert*-butylBIPOL (**2.21**) could in the future be exploited in the synthesis of larger designed π-systems with tunable properties.




**Scheme 2.17** Helicene-like compounds **2.39** and **2.40**.

After the successful synthesis of BIPOL analogs at the OH positions, the other most common derivatives, the 3,3'-derivatives were explored. The two analogs in which most BINOL-based applications are built from are the dihalide and diformyl derivatives. Two complimentary approaches to generate 3,3'-disubstituted BIPOLs were explored. The first was to oxidatively couple a 3-substituted pyren-2-ol, and

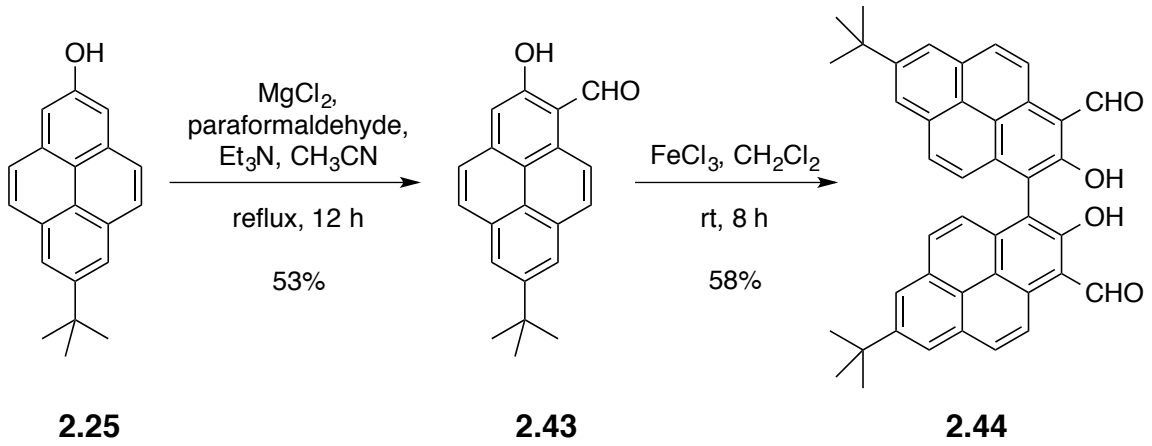
the second was direct functionalization of BIPOL (**2.02**) and di-*tert*-butylBIPOL (**2.21**). Utilizing the later approach, di-*tert*-butylBIPOL (**2.21**) and BIPOL (**2.02**) underwent bromination upon treatment with *N*-bromosuccinimide in dichloromethane. Dibromide **2.41** was thus obtained in 69% yield (Scheme 2.18).




**2.21** **2.41**

**Scheme 2.18** Synthesis of brominated BIPOL derivative **2.41** and **2.42**.

Using the other approach, Skatebøl formylation was employed to convert 7-*tert*-butyl-2-pyrenol (**2.25**) into the corresponding hydroxyaldehyde **2.43** in 58% yield (Scheme 2.19).[42] This compound was then oxidatively coupled using $FeCl_3$ to afford the 3,3'-diformylated product **2.44** in 58% yield.




**2.25** **2.43** **2.44**

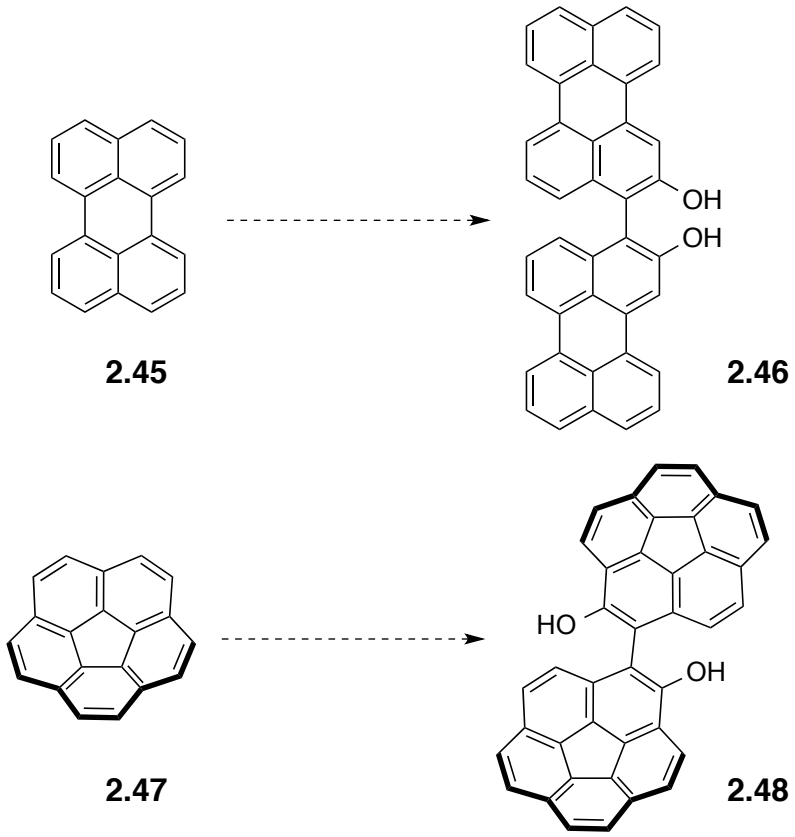
**Scheme 2.19** Synthesis of dihydroxyaldehyde **2.44**.

The accessibility of the dihalide and dihydroxyaldehyde derivative should allow for functionalization in the future that could be used for the synthesis of compounds with properties suitable for application in devices such as sensors.

## 2.4 Conclusion

The first BINOL-like system built on a polycyclic aromatic hydrocarbon backbone with greater than three fused aromatic rings, in this case pyrene, has been successfully synthesized in multi-gram quantities. A number of derivatives have also been synthesized that have the potential for further functionalization to create a wide-range of BIPOL derivatives. A single crystal X-ray structure of **2.02** was obtained and a small-scale resolution of (*S*)-**2.21** and (*R*)-**2.21** was achieved by chiral HPLC. The general strategy of borylation/oxidation followed by oxidative coupling may ultimately prove to be applicable to the synthesis of other new

bis(hydroxyaryls) from larger polycyclic aromatic hydrocarbons, such as perylene (**2.45**) and corannulene (**2.47**) (Scheme 2.20). The corannulene bis(hydroxyaryl) **2.48** is especially interesting because it adds an extra layer of complexity. In addition to axial chirality compound **2.48** there is another chiral factor from the bowl-to-bowl interconversions that corannulene (**2.47**) exhibits.




**2.45** **2.46**

**2.47** **2.48**

**Scheme 2.20** Future work.

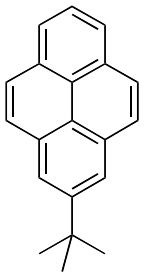
## 2.5 Experimental Section

All chemicals were used as received from commercial suppliers (Sigma Aldrich, Alfa Aesar) without further purification. Organic solvents were removed under reduced pressure by the use of a rotary evaporator and column chromatography was performed using Silicycle silica gel 60, particle size 40-63 μm.

**Instrumentation:**

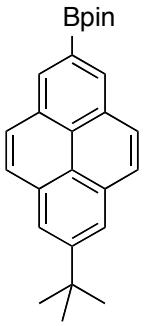
Melting Points were measured using a Fisher-Johns apparatus and are uncorrected. $^{1}H$ NMR (500 MHz) spectra were recorded on a Bruker AVANCE 500 MHz instrument and were measured using $CDCl_3$ as solvent. $^{13}C$ NMR (75 MHz) spectra were recorded at 300MHz on a Bruker AVANCE III and were measured using $CDCl_3$ as solvent. Chemical shifts are reported relative to internal standards: $(CH_3)_4Si$ (δ 0.00 ppm) and $CDCl_3$ (δ 77.23 ppm). Low-resolution mass spectrometric data (LCMS) were determined in an Agilent 1100 series LC/MSD instrument. High-resolution mass spectrometric data (HRMS) were determined on a Waters Micromass GCT Premier instrument. X-ray crystallography was performed using an AFC8-Saturn 70 single crystal X-ray diffractometer from Rigaku/MSC, equipped with an X-stream 2000 low temperature system.

**2-*tert*-Butylpyrene (2.22)**



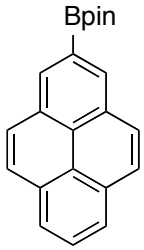
To a 0 °C solution of pyrene (**2.13**) (10.00 g, 49.4 mmol) in $CH_2Cl_2$ (200 mL) was added to 2-chloro-2-methylpropane (5.04 g, 54.4 mmol), followed by addition of $AlCl_3$ (7.91 g, 59.3 mmol) in roughly 3 equal portions within 5 min. The solution was gradually warmed to room temperature and stirred for 3 h. Cold water (100 mL) was added slowly to the reaction mixture. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The yellow residue was crystallized from methanol to yield 2,7-di-*tert*-butylpyrene (**2.23**) (2.02 g, 13%). The mother liquor was concentrated under reduced pressure and recrystallized from hexanes to yield 2-*tert*-butylpyrene (**2.22**) as a beige solid (8.28 g, 65%): $R_f$ = 0.39 (hexanes); m.p. 108-111 °C (lit. 109-110 °C)[23]; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 2H), 8.16 (d, $J$ = 7.6 Hz, 2H), 8.06 (m, 4H), 7.97 (t, $J$ = 7.6 Hz, 1H), 1.59 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 149.21, 131.21, 131.18, 127.78, 127.45, 125.69, 124.93, 124.83, 123.23, 122.41, 35.26, 31.98; LCMS (APCI-positive) *m/z* 259 $[MH]^+$.

**2-*tert*-Butyl-7-pyreneboronic acid pinacol ester (2.24)**



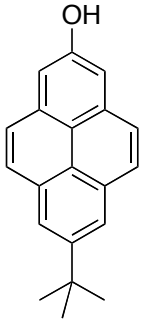

Cyclohexane (150 mL) was purged with $N_2$ for 5 min, after which $[Ir(OMe)COD]_2$ (116 mg, 0.19 mmol), 4,4'-di-*tert*-butyl-2-2'-bipyridyl (99 mg, 0.39 mmol) and bis(pincolato)diboron (5.41 g, 21.3 mmol) were added. The solution was stirred at room temperature for 5 min under a $N_2$ atmosphere, after which 2-*tert*-butylpyrene (**2.22**) (5.00 g, 19.4 mmol) was added. The resulting mixture was heated at 80 °C for 8 h and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (25% $CH_2Cl_2$/hexanes) to afford 2-*tert*-butyl-7-pyreneboronic acid pinacol ester (**2.24**) as an off-white solid (5.79 g, 78%): $R_f$ = 0.37 (25% $CH_2Cl_2$/hexanes); m.p. 238-240 °C (lit. 240-241 °C)[43]; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 2H), 8.20 (s, 2H), 8.06 (d, $J$ = 8.8 Hz, 2H), 8.04 (d, $J$ = 8.8 Hz, 2H), 1.59 (s, 9H), 1.46 (s, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 149.56, 131.46, 131.13, 130.23, 127.63, 127.42, 126.32, 122.83, 122.09, 84.10, 35.28, 31.93, 25.01 (13 of 14 signals observed); LCMS (APCI-positive) *m/z* 385 $(MH)^+$.

**2-Pyreneboronic acid pinacol ester (2.26)**



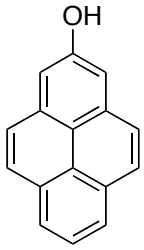

Cyclohexane (100 mL) was purged with $N_2$ for 5 min after which [Ir(OMe)COD]$_2$ (114 mg, 0.19 mmol), 4,4'-di-*tert*-butyl-2-2'-bipyridyl (100 mg, 0.39 mmol) and bis(pinacoloto)diboron (5.51 g, 21.70 mmol) were added. The solution was stirred at rt for 5 min under a $N_2$ atmosphere, after which pyrene (**2.13**) (4.00 g, 19.8 mmol) was added. The resulting mixture was heated at 80 °C for 8 h and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (40% $CH_2Cl_2$/hexanes) to yield 2-pyreneboronic acid pinacol ester (**2.26**) as an off-white solid (3.69 g, 68%): $R_f$ = 0.24 (25% $CH_2Cl_2$/hexanes); m.p. 125-128 °C (lit. 127-128 °C)[43]; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 2H), 8.15 (d, *J* = 7.6 Hz, 2H), 8.10 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 8.00 (t, *J* = 7.3 Hz, 1H), 1.47 (s, 12H); LCMS (APCI-positive) *m/z* 329 $(MH)^+$.

**7-*tert*-Butyl-2-pyrenol (2.25)**



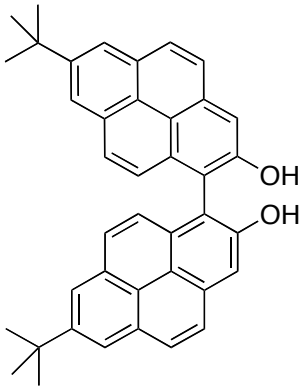

A solution of 30% v/v $H_2O_2$ (20 mL), KOH (666 mg, 11.87 mmol) in $H_2O$ (20 mL) was added slowly to a solution of boronate ester (**2.24**) (2.28 g, 5.93 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 5 min and then poured into $H_2O$ (50 mL). The resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (30% ethyl acetate/hexanes) to yield 7-*tert*-butylpyren-2-ol (**2.25**) as a brown solid (1.38 g, 85%): $R_f$ = 0.32 (20% ethyl acetate/hexanes); m.p 222-224 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 2H), 8.02 (d, $J$ = 9.0 Hz, 2H), 7.91 (d, $J$ = 9 Hz, 2H), 7.60 (s, 2H), 5.18 (s, 1H), 1.57 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) 153.50, 148.05, 132.63, 129.96, 128.42, 126.37, 122.85, 122.62, 120.07, 111.33, 35.15, 31.94; LCMS (APCI-positive) *m/z* 275 $(MH)^+$.

**Pyren-2-ol (2.28)**[43]




A solution of 30% v/v $H_2O_2$ (30 mL), KOH (724 mg, 12.92 mmol) in $H_2O$ (30 mL) was added slowly to a solution of pyrene-2-boronic acid pinacol ester (**2.26**) (2.12 g, 6.46 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 5 min and then poured into $H_2O$ (50 mL). The resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (30% ethyl acetate/hexanes) to yield pyren-2-ol (**2.28**) as a light brown solid (1.20 g, 85%): $R_f$ = 0.24 (20% ethyl acetate/hexanes) m.p. 204-206 °C (lit. 202-203 °C)[43]; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.6 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 7.92-7.96 (m, 3H), 7.64 (s, 2H), 5.16 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 153.71, 132.89, 130.16, 128.28, 126.52, 125.40, 124.98, 124.64, 120.15, 111.53; LCMS (APCI-positive) *m/z* 219 $(MH)^+$; HRMS (EI) calculated for $(M)^+$ $C_{20}H_{18}O$ 274.1358, found 274.1361.

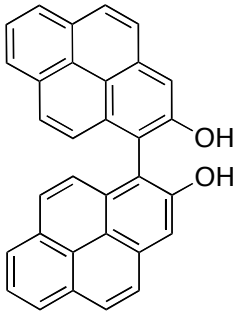
**7,7-Di-*tert*-butyl-1,1'-bipyren-2-ol (di-*tert*-butylBIPOL) (2.21)**




A solution of 7-*tert*-butyl-2-pyrenol (**2.25**) (1.00 g, 3.64 mmol) in $CH_2Cl_2$ (100 mL) was purged with $N_2$ for 5 min, after which $FeCl_3$ (650 mg, 4.01 mmol) was added in one portion. The reaction mixture was stirred at room temperature with constant nitrogen bubbling for 2 h and monitored closely by TLC analysis (20% ethyl acetate/hexanes). After complete consumption of the starting material, the reaction mixture was poured into a 10% aqueous solution of HCl (50 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (15% ethyl acetate/hexanes) to yield 7,7-di-*tert*-butyl-1,1'-bipyren-2-ol (di-*tert*-butylBIPOL) (**2.21**) as a light brown solid (645 mg, 65%): $R_f$ = 0.21 (20% ethyl acetate/hexanes); m.p. 240-244 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.8 Hz, 2H), 8.19 (d, *J* = 1.8 Hz, 2H), 8.16 (d, *J* = 9.0 Hz, 2H), 8.09 (d, *J* = 9 Hz, 2H), 7.99 (s, 2H), 7.89 (d, *J* = 9.1 Hz, 2H), 7.36 (d, *J* = 9.1 Hz, 2H), 5.22 (s, 2H), 1.57 (s, 18H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 152.65, 148.62, 133.72, 131.86, 130.16, 129.80, 129.55, 129.24, 126.61, 123.96, 123.36, 123.13, 122.89, 113.48, 111.91, 35.22, 31.94 (17 of

18 signal observed); LCMS (APCI-positive) *m/z* 545 $(MH)^+$; HRMS (EI) calculated for $(M)^+$ $C_{40}H_{34}O_2$ 546.2559, found 546.2554.

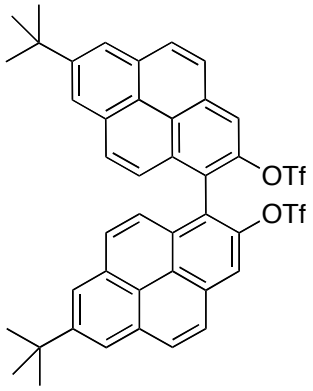
**1,1'-bi-2-pyrenol (BIPOL) (2.02)**




A solution of 2-pyrenol (**2.28**) (1.13 g, 5.18 mmol) in $CH_2Cl_2$ (100 mL) was purged with $N_2$ for 5 min, after which $FeCl_3$ (1.01 g, 1.2 mmol) was added in one portion. The reaction mixture was stirred at room temperature with constant nitrogen bubbling for 2 h and monitored closely by TLC analysis (20% ethyl acetate/hexanes). After complete consumption of the starting material, the reaction mixture was poured into a 10% aqueous solution of HCl (50 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography ($CH_2Cl_2$) to yield 1,1'-bi-2-pyrenol (BIPOL) (**2.02**) as a light brown solid (761 mg, 68%): $R_f$ = 0.48 (40% ethyl acetate/hexanes); m.p. 218-221 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.4 Hz, 2H), 8.17 (d, *J* = 9.0, 2H), 8.14 (d, *J* = 7.7 Hz, 2H), 8.11 (d, *J* = 9.0 Hz, 2H), 8.02 (s, 2H), 7.97 (t, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.2 Hz, 2H), 5.25 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 152.93, 133.98, 132.09, 130.31, 129.95,

129.43, 129.08, 126.76, 126.06, 125.99, 125.45, 124.67, 124.02, 120.58, 113.60, 112.13; LCMS (APCI-positive) *m/z* 435 $(MH)^+$; HRMS (EI) calculated for $(M)^+$ $C_{32}H_{18}O_2$ 434.1306, found 434.1294.

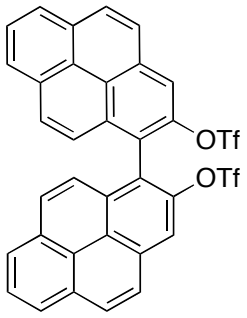
**7,7'-di-*tert*-butyl-1,1'-bipyrene-2,2'-diyl bis(trifluoromethanesulfonate) (2.35)**




Trifluoromethanesulfonic anhydride (500 mg, 0.88 mmol) was added dropwise to a 0 °C solution of di-*tert*-butylBIPOL (**2.21**) (120 mg, 0.22 mmol) and pyridine (70 mg, 0.88 mmol) in toluene (15 mL) under $N_2$.. The reaction mixture was warmed to room temperature and stirred for 2.5h. The solvent was removed under reduced pressure and the residue was taken up in $CH_2Cl_2$ (10 mL) and then poured into a 3 M aqueous solution of HCl (10 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 ×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (5% ethyl acetate/hexanes) to yield 7,7'-di-*tert*-butyl-1,1'-bipyrene-2,2'-diyl bis(trifluoromethanesulfonate) (**2.35**) as a light brown solid (169 mg, 95 %); $R_f$ =

0.66 (20% ethyl acetate/hexanes); m.p. 254-259 °C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 1.8 Hz, 2H), 8.28–8.31 (m, 6H), 8.21 (d, *J* = 8.9 Hz, 2H), 7.96 (d, *J* = 9.3 Hz, 2H), 7.43 (d, J = 9.3, 2H), 1.59 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 150.40, 145.55, 133.11, 132.69, 131.06, 130.52, 130.23, 130.06, 126.66, 125.20, 124.06, 123.98, 123.73, 122.22, 121.05, 120.35, 116.37, 116.10,35.39, 31.89; LCMS (APCI-positive) *m/z* 811 $(MH)^+$; HRMS (EI) calculated for $(M)^+$ $C_{42}H_{32}F_6O_6S_2$ 810.1544, found 810.1328.

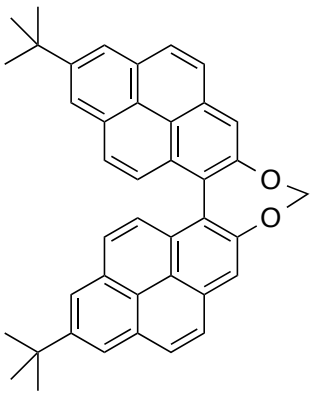
**1,1'-bipyrene-2,2'-diyl bis(trifluoromethanesulfonate) (2.34)**




Trifluoromethanesulfonic acid (260 mg, 0.92 mmol) was added to a 0 °C solution of BIPOL (**2.02**) (100 mg, 0.23 mmol) and pyridine (73 mg, 0.92 mmol) dissolved in toluene (15 mL) under $N_2$. The reaction mixture was warmed to room temperature and stirred for 2.5 h. The solvent was removed under reduced pressure and the residue was taken up in $CH_2Cl_2$ (10 mL) and then poured into a 3 M aqueous solution of HCl (10 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced

pressure. The residue was subjected to column chromatography (10% ethyl acetate/hexanes) to yield 1,1'-bipyrene-2,2'-diyl bis(trifluoromethanesulfonate) (**2.34**) as an off-white solid (116 mg, 73%): $R_f$ = 0.56 (20% ethyl acetate/hexanes); m.p. 238-240 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.31-8.36 (m, 6H), 8.22-8.25 (m, 4H), 8.11 (t, *J* = Hz, 2H), 7.99 (d, *J* = Hz, 2H), 7.47 (d, *J* = Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 145.77, 133.40, 131.77, 131.17, 130.65, 130.08, 129.93, 127.03, 126.82, 126.71, 125.25, 123.99, 123.83, 123.63, 121.17, 116.54 (16 of 17 signals observed); LCMS (APCI-positive) *m/z* 716 $(MH)^+$; HRMS (EI) calculated for $(M)^+$ $C_{34}H_{16}F_6O_6S_2$ 698.0292, found 698.0286.

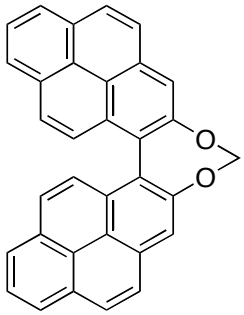
**7,7'-di-*tert*-butyl-1,1'-bipyrene-2,2'-methylenedioxy (2.40)**




A solution of di-*tert*-butylBIPOL (**2.21**) (287 mg, 0.53 mmol) in DMF (20 mL) was purged with $N_2$ for 10 min. Potassium carbonate (440 mg, 3.18 mmol) was added, followed by dibromomethane (276 mg, 1.59 mmol) and the resulting mixture was heated at 80 °C for 4 h. The reaction was poured into water (50 mL) and the resulting mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The

residue was subjected to column chromatography (10% ethyl acetate/hexanes) to yield 7,7'-di-*tert*-butyl-1,1'-bipyrene-2,2'-methylenedioxy (**2.40**) as a light yellow solid (290 mg, 98%): $R_f$ = 0.63 (20% ethyl acetate/hexanes); m.p. 269-252 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 1.8 Hz, 2H), 8.22 (d, *J* = 1.8 Hz, 2H), 8.16 (s, 1H), 8.15 (s, 2H), 7.91 (d, *J* = 9.3 Hz, 2H), 7.74 (d, *J* = 9.3 Hz, 2H), 5.88 (s, 2H), 1.60 (s, 18H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 150.99, 149.04, 132.59, 130.86, 130.29, 130.21, 128.51, 128.21, 126.86, 126.10, 123.03, 123.02, 122.95, 122.74, 116.93, 102.97, 35.23, 31.93 (18 of 19 signals observed); LCMS (APCI-positive) *m/z* 559 $(MH)^+$; HRMS (EI) calculated for $(M)^+$ $C_{41}H_{34}O_2$ 558.2559, found 558.2551.

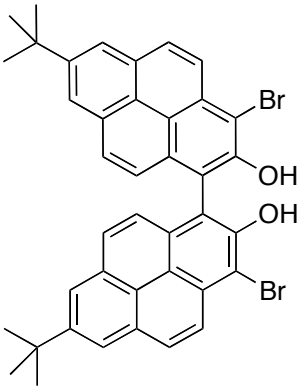
**1,1'-Bipyrene-2,2'-methylenedioxy (2.39)**




A solution of BIPOL (**2.02**) (100 mg, 0.23 mmol) in DMF (20 mL) was purged with $N_2$ for 10 min. Potassium carbonate (191 mg, 1.38 mmol) was added, followed by dibromomethane (120 mg, 0.69 mmol) and heated at 80 °C for 5 h. The reaction was poured into $H_2O$ (40 mL) and the resulting mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (25% ethyl acetate/hexanes) to yield 1,1'-Bipyrene-2,2'-

methylenedioxy (**2.39**) as a yellow solid (54 mg, 50%): $R_f$ = 0.68 (20% ethyl acetate/hexanes); m.p. 224-228 °C; LCMS (APCI-positive) *m/z* 447 $[MH]^+$; HRMS EI calculated for $[M]^+$ $C_{33}H_{18}O_2$ 446.1307, found 446.1308.

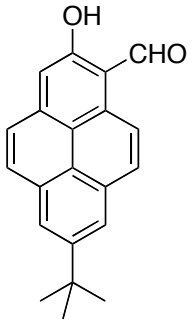
**3,3'-Dibromo-7,7'-di-*tert*-butyl-1,1'-bi-2-pyrenol (2.42)**




*N*-Bromosuccinimide (122 mg, 0.69 mmol) was added in one portion to a solution of di-*tert*-butylBIPOL (**2.21**) (150 mg, 0.27 mmol) in $CH_2Cl_2$ (30 mL) and stirred at room temperature under a $N_2$ atmosphere for 1 h. The reaction mixture was poured into brine (25 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (10% ethyl acetate/hexanes) to yield 3,3'-dibromo-7,7'-di-*tert*-butyl-1,1'-bi-2-pyrenol (**2.42**) as red solid (130 mg, 69%): $R_f$ = 0.56 (20% ethyl acetate, hexanes); m.p. 260-263 °C); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 9.3 Hz, 2H), 8.32 (d, *J* = 1.8 Hz, 2H), 8.29 (d. *J* = 9.3 Hz, 2H), 8.20 (d, *J* = 1.8 Hz, 2H), 7.87 (d, *J* = 9.3 Hz, 2H), 7.34 (d, *J* = 9.2 Hz, 2H), 6.05 (s, 2H), 1.57 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 149.06, 148.78,

131.00, 130.39, 130.02, 129.93, 129.36, 125.27, 124.34, 123.83, 123.61, 122.33, 121.07, 116.84, 108.34, 99.99, 35.22, 31.91; LCMS (APCI-positive) *m/z* 705 $(MH)^+$.

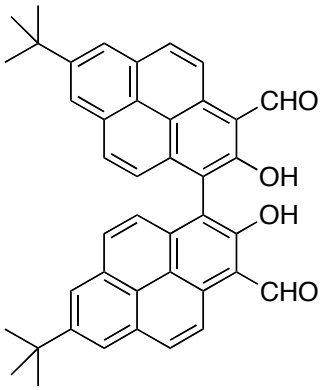
**1-formyl-7-*tert*-butyl-2-pyrenol (2.43)**




A 100 mL round-bottom flask was charged with $MgCl_2$ (958 mg, 10.1 mmol) and flame-dried under reduced pressure. 7-*tert*-Butyl-2-pyrenol (**2.25**) (920 mg, 3.35 mmol) followed by dry acetonitrile (40 mL) and dry $Et_3N$ (2.29 g, 22.61 mmol). Paraformaldehyde (2 g) was added and the reaction mixture was heated at reflux under a $N_2$ atmosphere overnight. The reaction mixture was cooled to room temperature and poured into a 3 M aqueous solution of HCl (50 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (15 % ethyl acetate/hexanes) to yield 1-formyl-7-*tert*-butyl-2-pyrenol (**2.43**) as a bright yellow solid (535 mg, 53 %); $R_f$ = 0.39 (20% ethyl acetate/hexanes); m,p, 202-206 °C; $^1H$ NMR (500 MHz, $CDCl_3$) δ12.53 (s, 1H), 11.15 (s, 1H), 8.69 (d, J = 9.2 Hz, 1H), 8.27 (m, 3H), 8.11 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 7.60 (s, 1H), 1.58 (s, 9H);

$^{13}C$ NMR (75 MHz, $CDCl_3$) δ 193.60, 161.23, 148.91, 139.11,133.70,132.39, 131.21, 129.81, 129.29, 126.59, 125.21, 124.58, 122.66, 119.20, 118.55, 113.11, 112.10, 35.21, 31.85; LCMS (APCI-positive) *m/z* 303 ($MH^+$); HRMS (EI) calculated for ($M^+$) $C_{21}H_{18}O_2$ 302.1307, found 302.1317.

**3,3'-formyl-7,7-di-*tert*-butyl-1,1'-bi-2-pyrenol (di-*tert*-butylBIPOL) (2.44)**




A solution of 1-formyl-7-*tert*-butyl-2-pyrenol (**2.43**) (535 mg, 1.77 mmol) in $CH_2Cl_2$ (75 mL) was purged with $N_2$ for 10 min. after which $FeCl_3$ was added in portion. The reaction mixture was stirred at room temperature with constant $N_2$ bubbling for 8 h. The reaction mixture was poured into a 10 % aqueous solution of HCl (30 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (20 % ethyl acetate/hexane) to yield 3,3'-formyl-7,7-di-*tert*-butyl-1,1'-bi-2-pyrenol (di-*tert*-butylBIPOL) (**2.44**) an orange solid (310 mg, 58 %); $R_f$ = 0.39 (20% ethyl acetate/hexanes); m.p. 264-268 °C; $^1H$ NMR (500 MHz,

$CDCl_3$) δ 12.85 (s, 1H), 11.29 (s, 1H), 8.83 (d, J = 9.2 Hz, 1H), 8.22 (m, 2H), 7.92 (d, J = 1.7 Hz, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 1.57 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 193.85, 159.52, 149.03, 138.49, 134.00, 132.78, 131.47, 129.73, 129.46, 125.40, 124.95, 124.69, 122.84, 118.56, 118.29, 112.00, 35.19, 31.81; LCMS (APCI-positive) *m/z* 603 ($MH^+$); HRMS (EI) calculated for ($M^+$) $C_{42}H_{34}O_4$ 602.2457, found 602.2451.

## 2.6 References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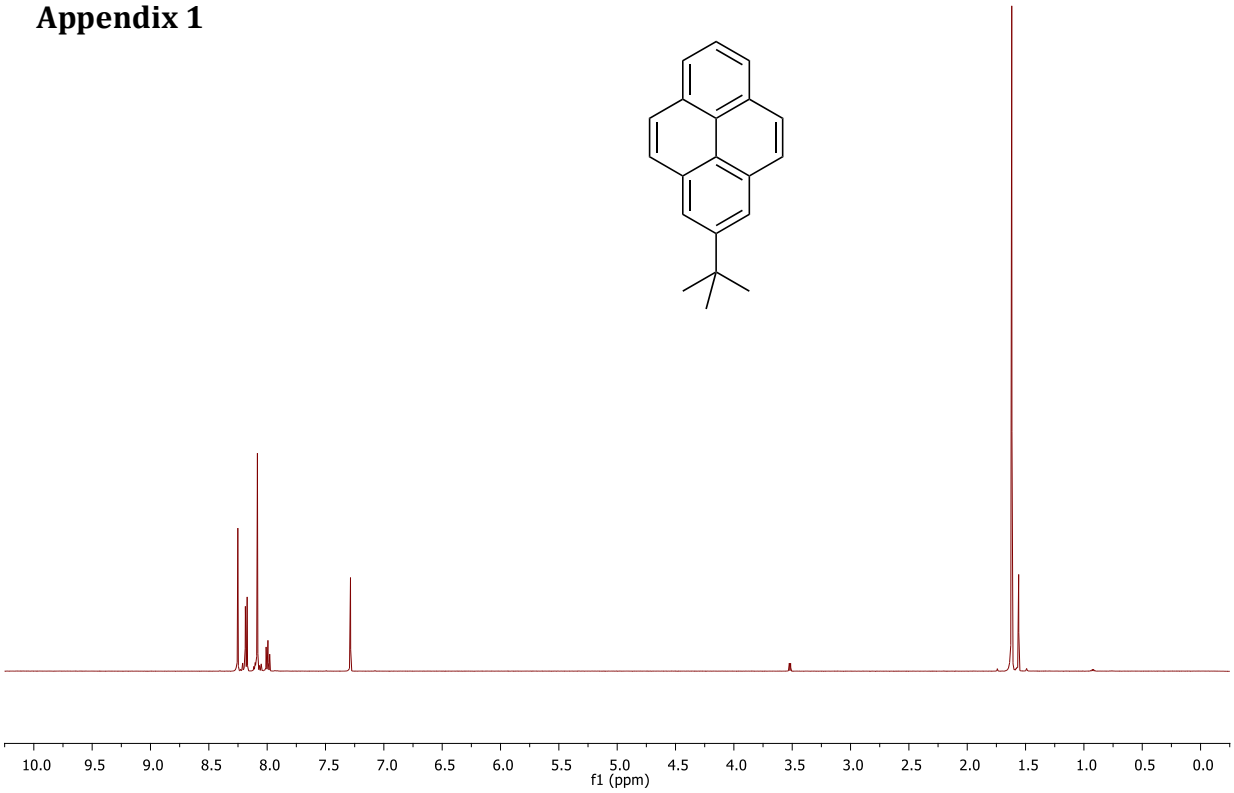
**Appendix 1**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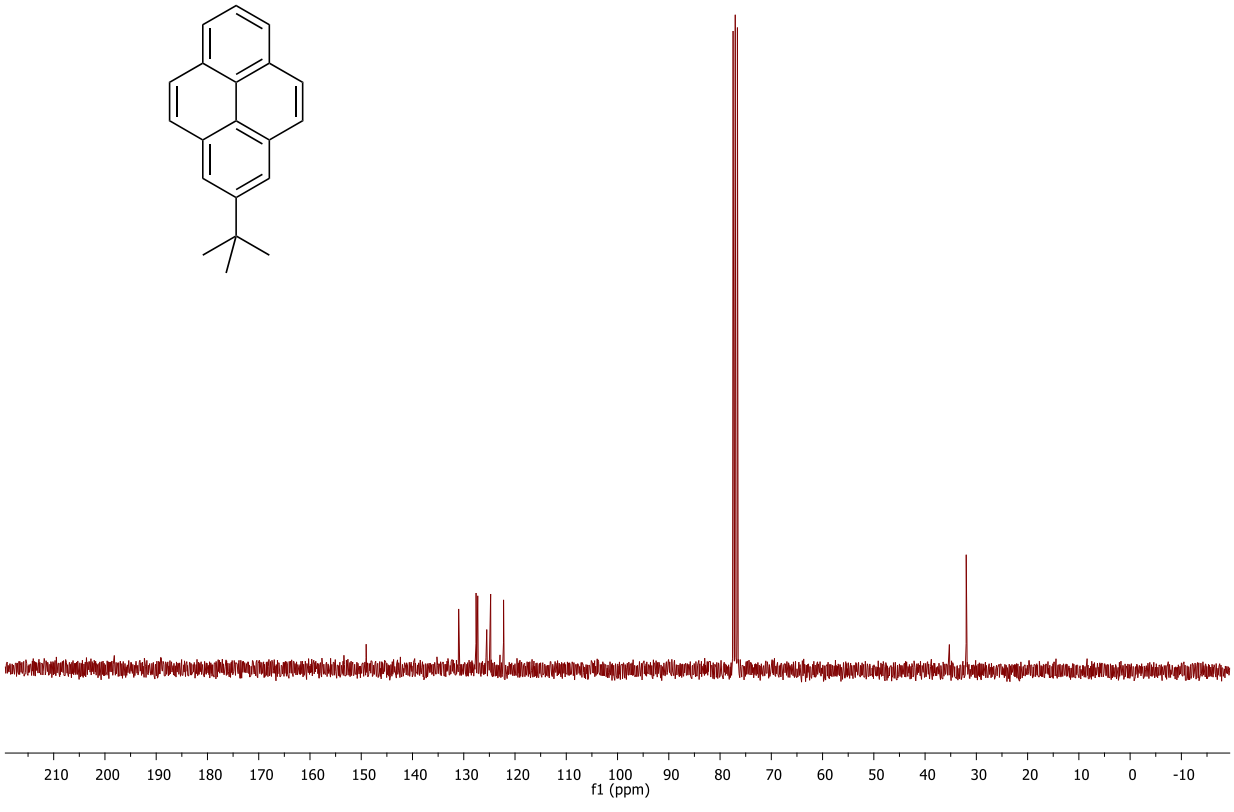
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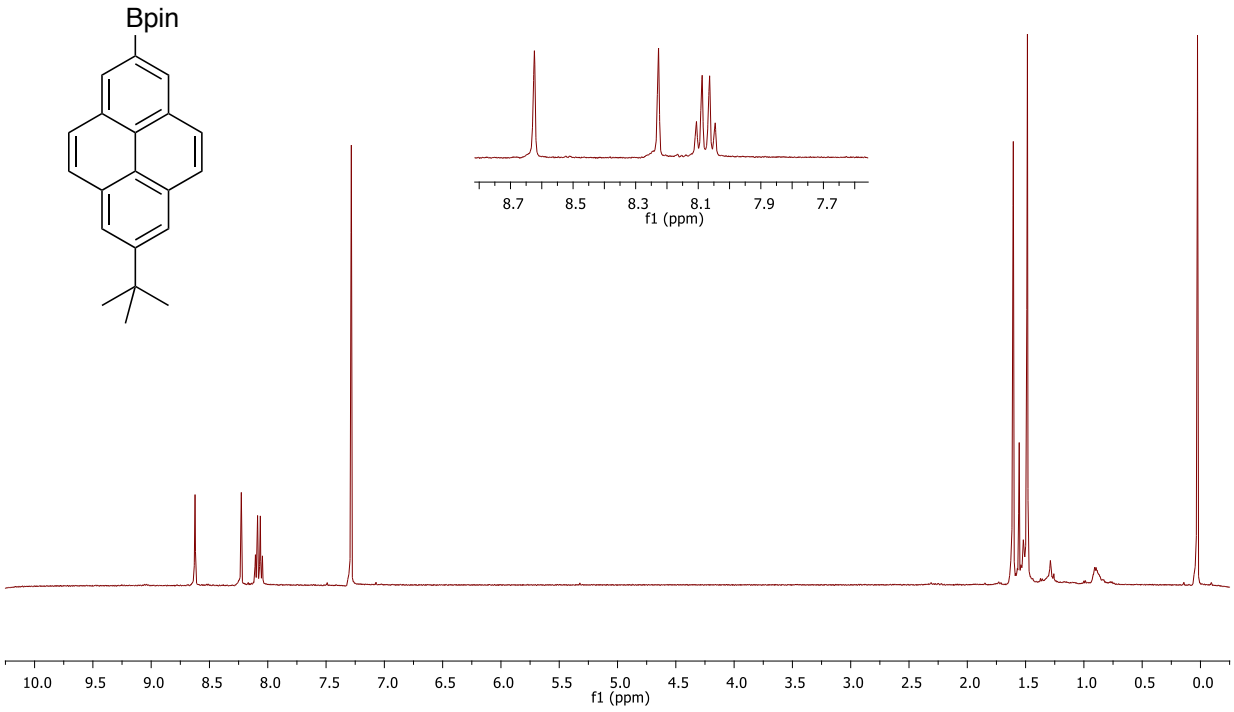
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8.5
8.3
8.1
7.9
7.7
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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1.0
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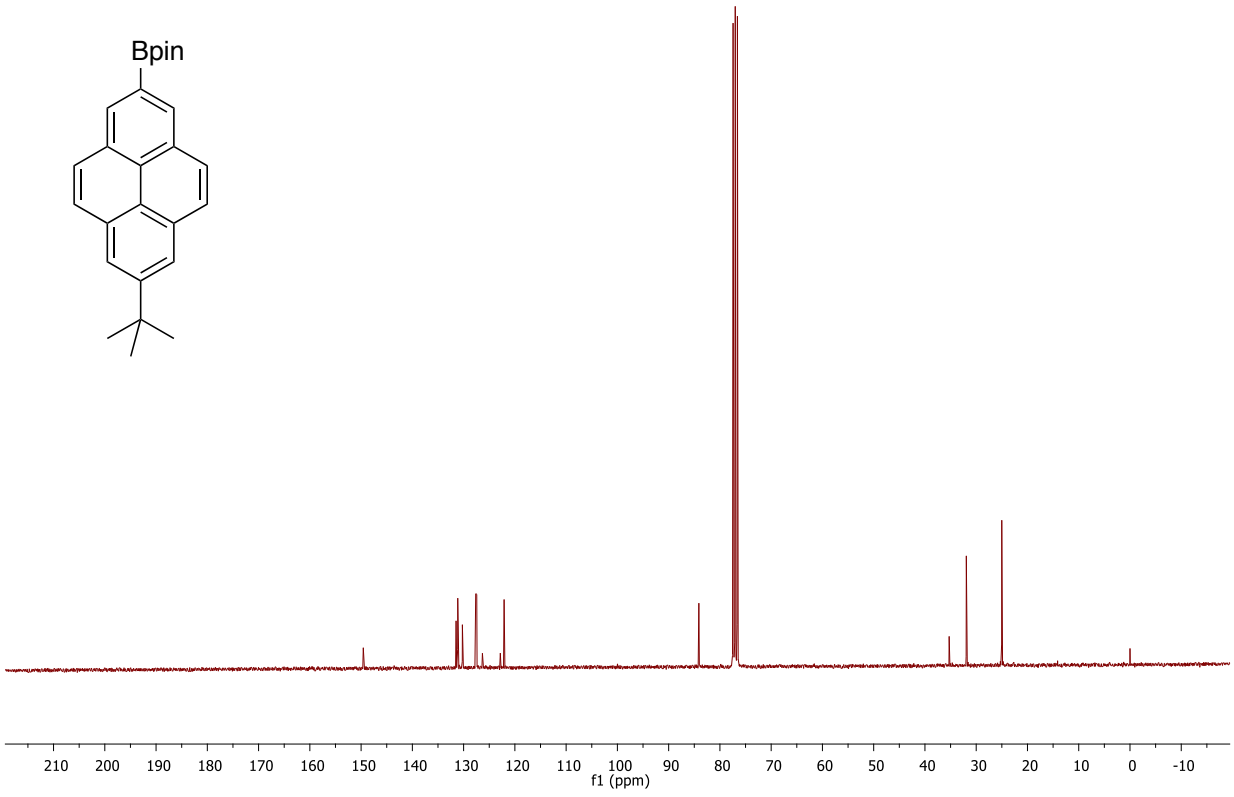
f1 (ppm)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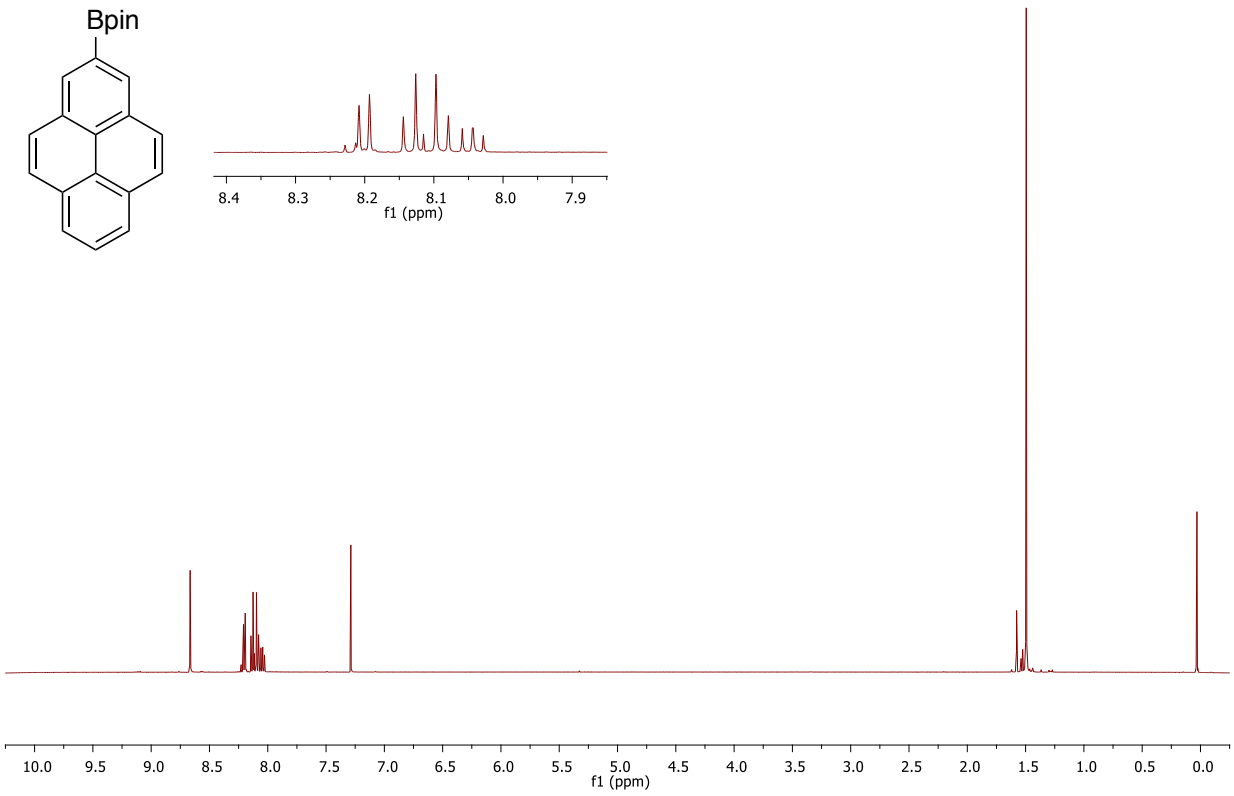
f1 (ppm)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8.2
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8.0
7.9
f1 (ppm)
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9.5
9.0
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6.5
6.0
5.5
5.0
4.5
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2.5
2.0
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1.0
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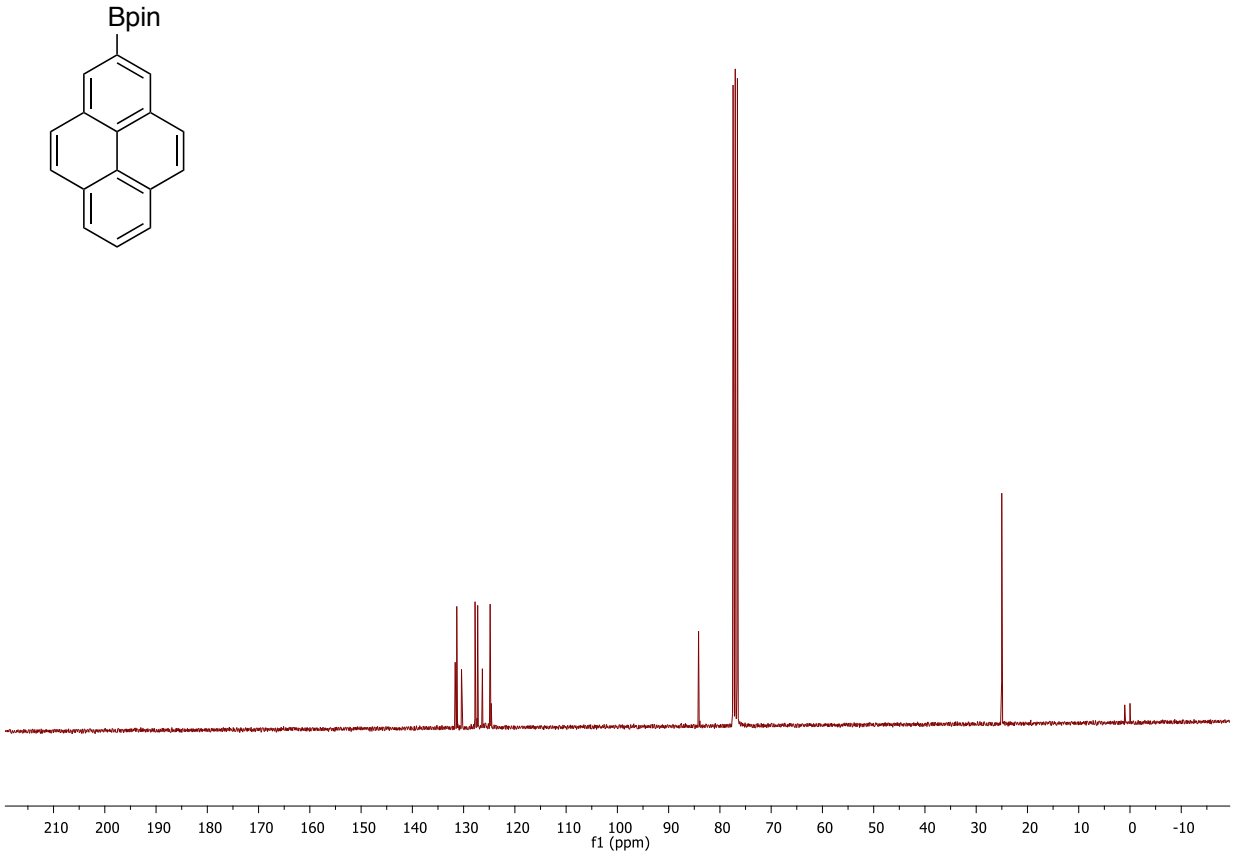
0.0
f1 (ppm)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60
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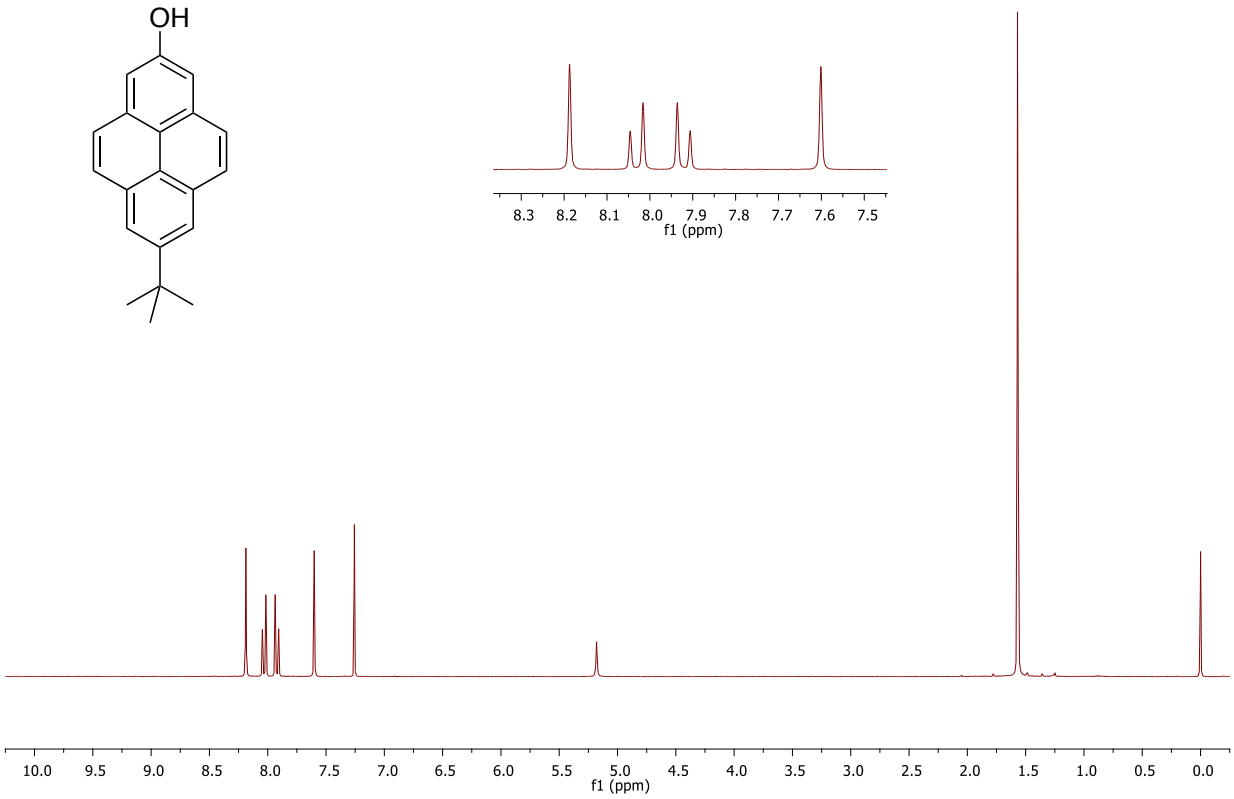
40
30
20
10
0
-10
f1 (ppm)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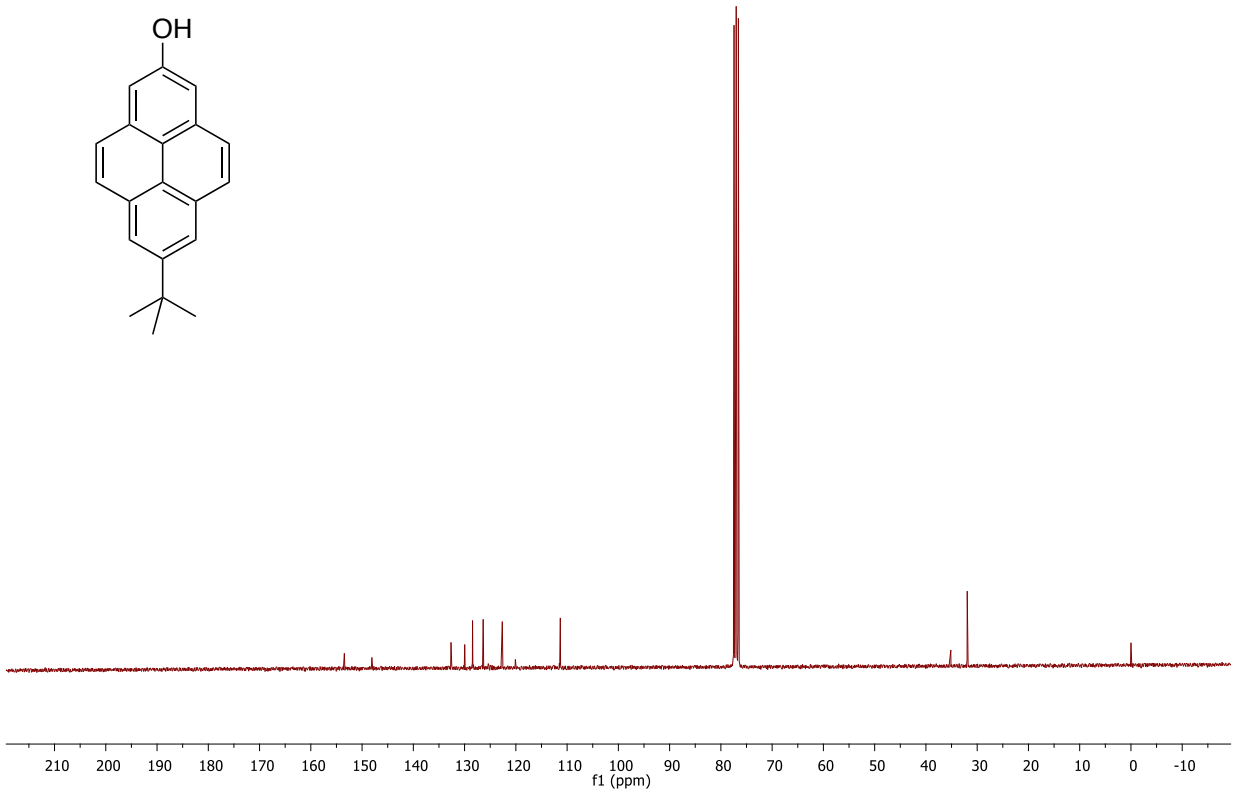
f1 (ppm)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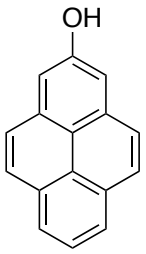
f1 (ppm)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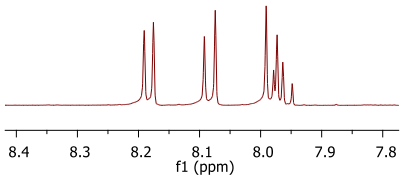
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7.8
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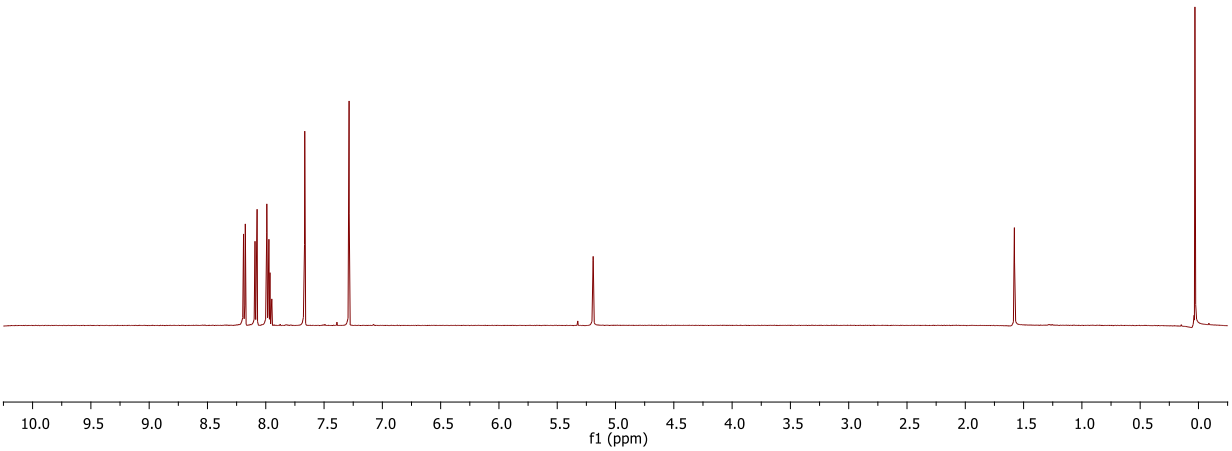
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5.5
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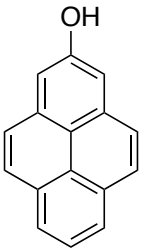
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OH


210
200
190
180
170
160
150
140
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120
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100
90
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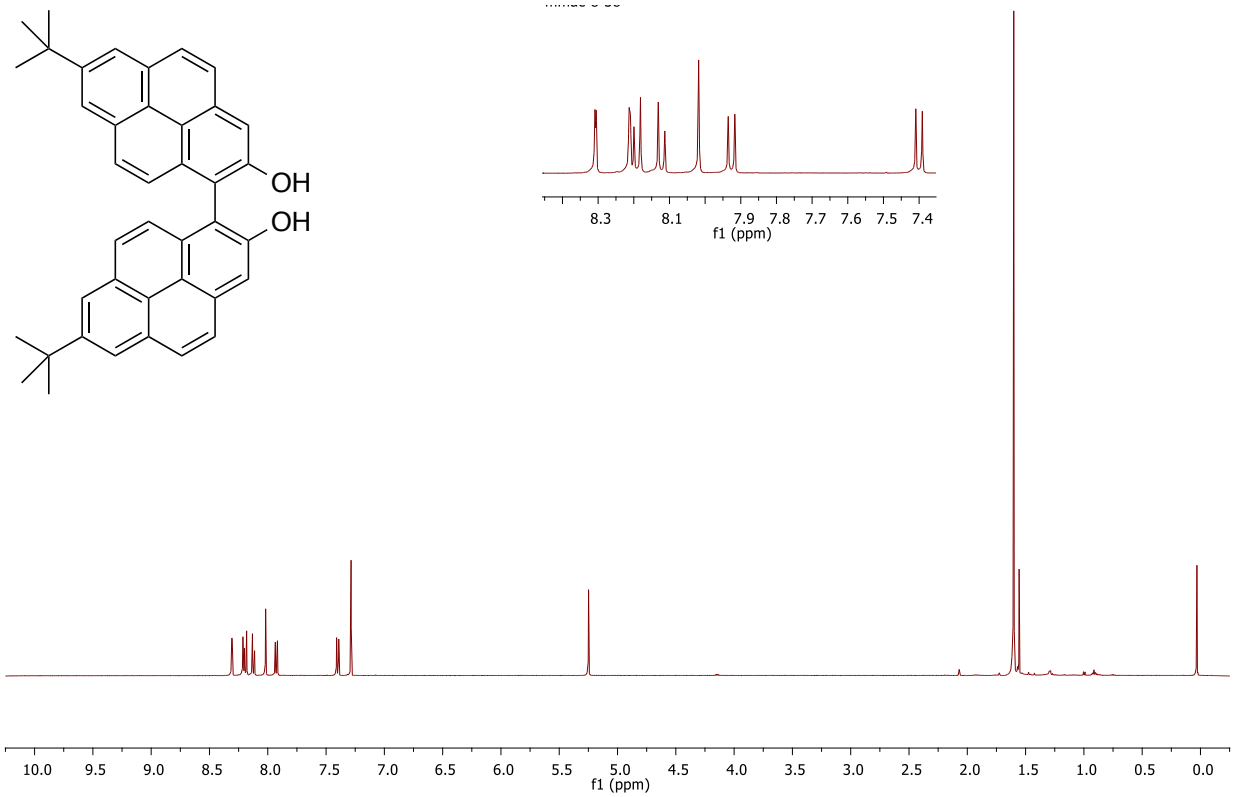
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.8
7.7
7.6
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7.4
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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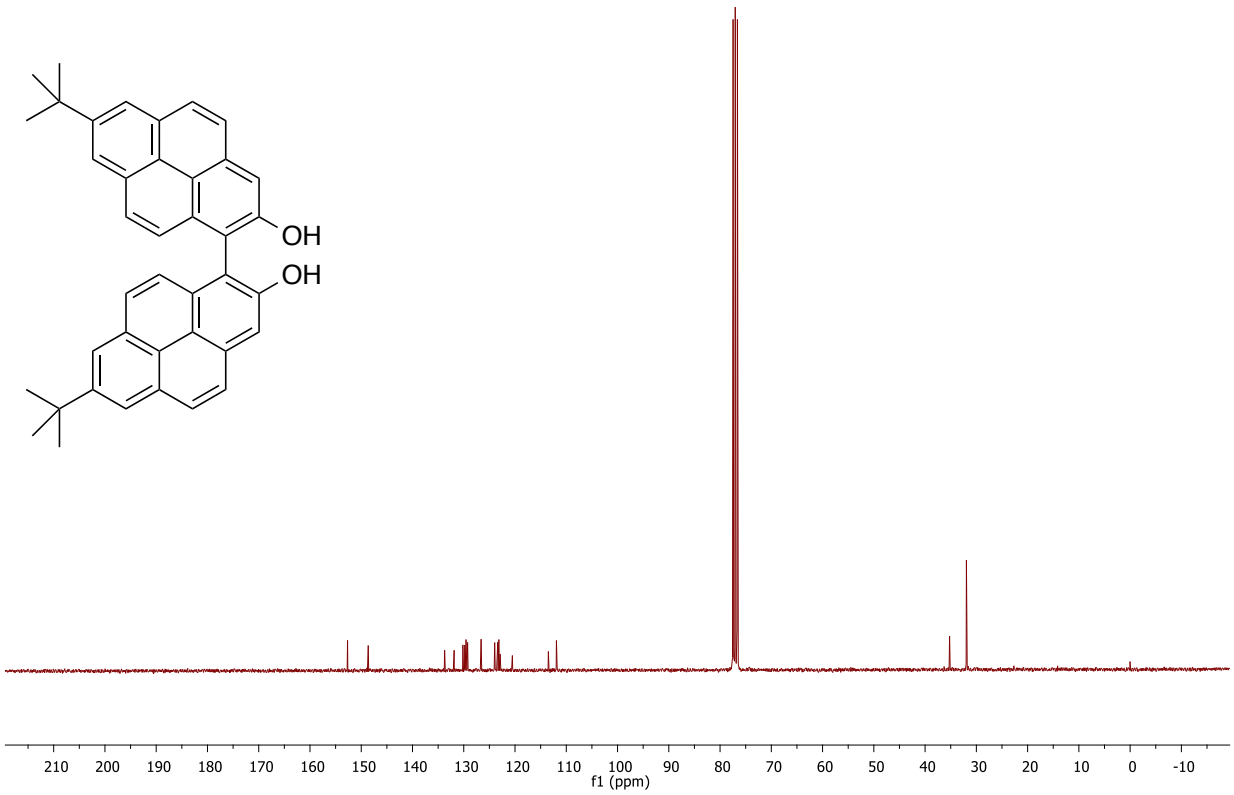
f1 (ppm)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200
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10
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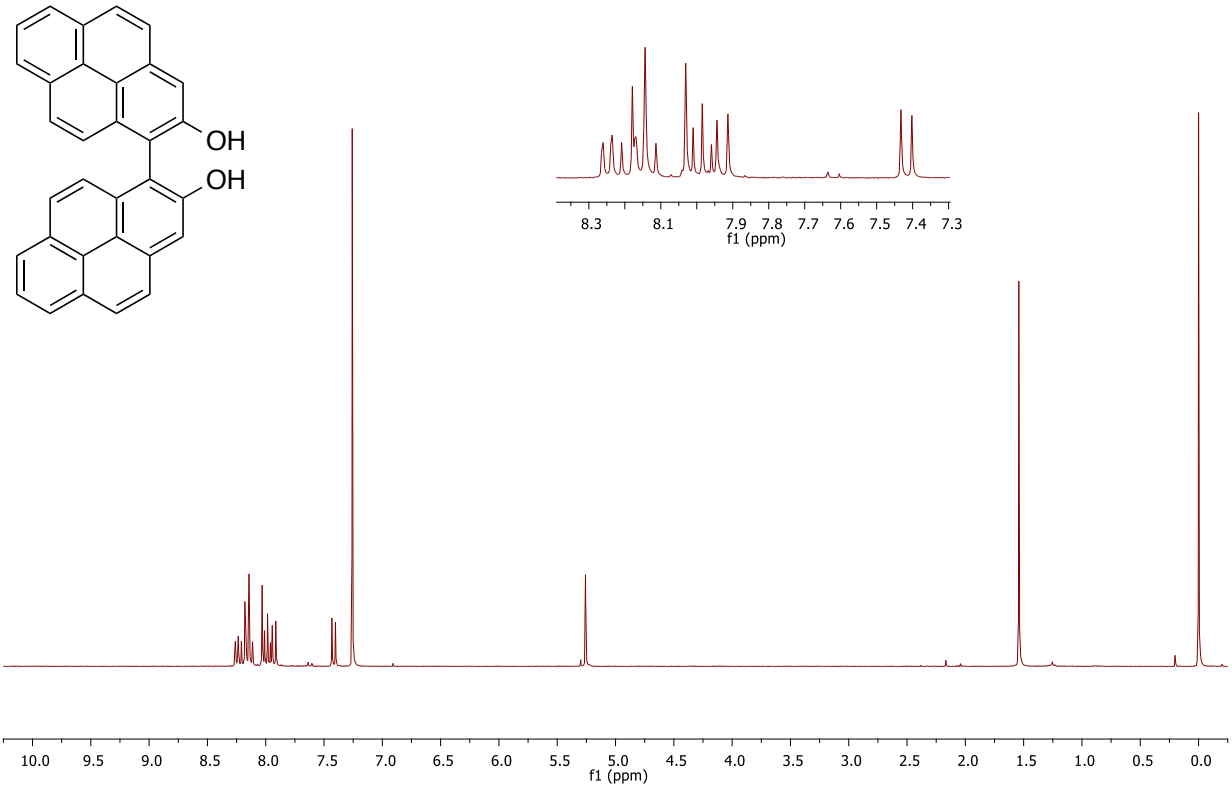
f1 (ppm)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7.3
f1 (ppm)
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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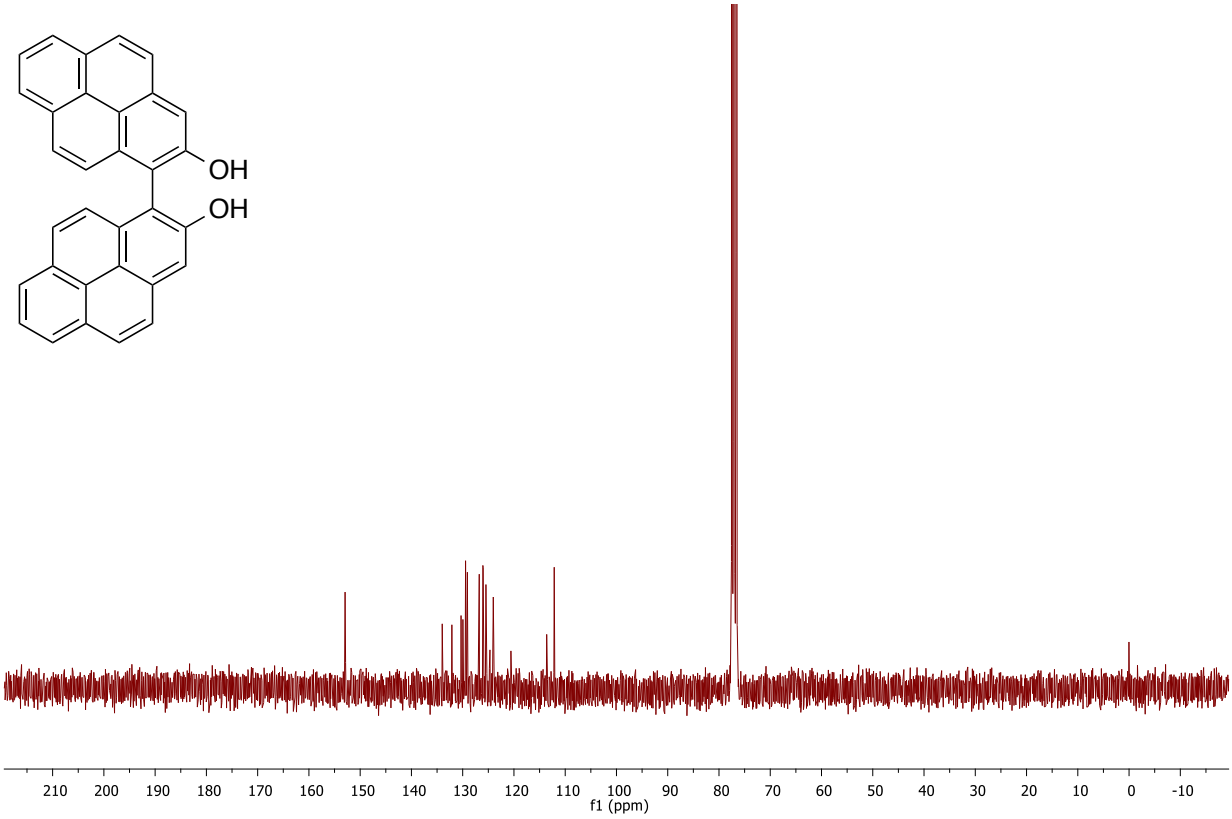
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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200
190
180
170
160
150
140
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100
90
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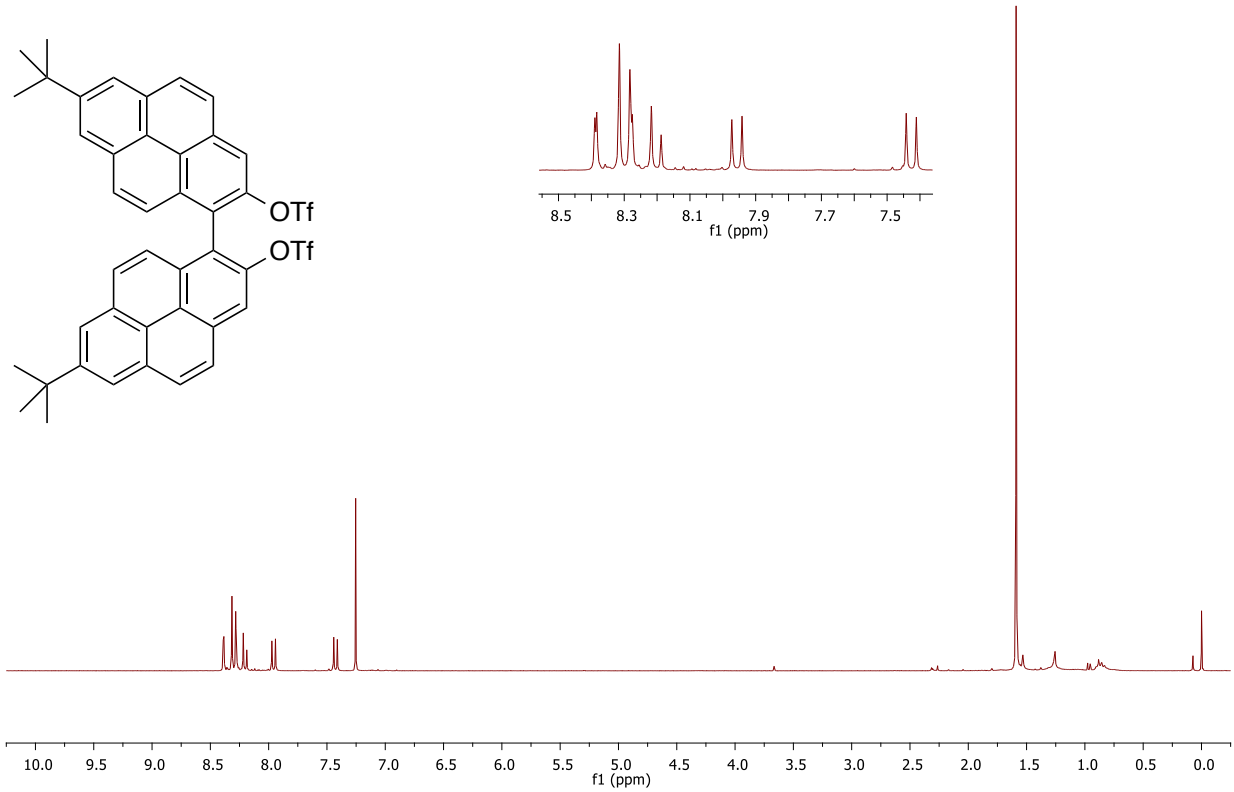
70
60
50
40
30
20
10
0
-10
f1 (ppm)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OTf
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7.9
7.7
7.5
f1 (ppm)
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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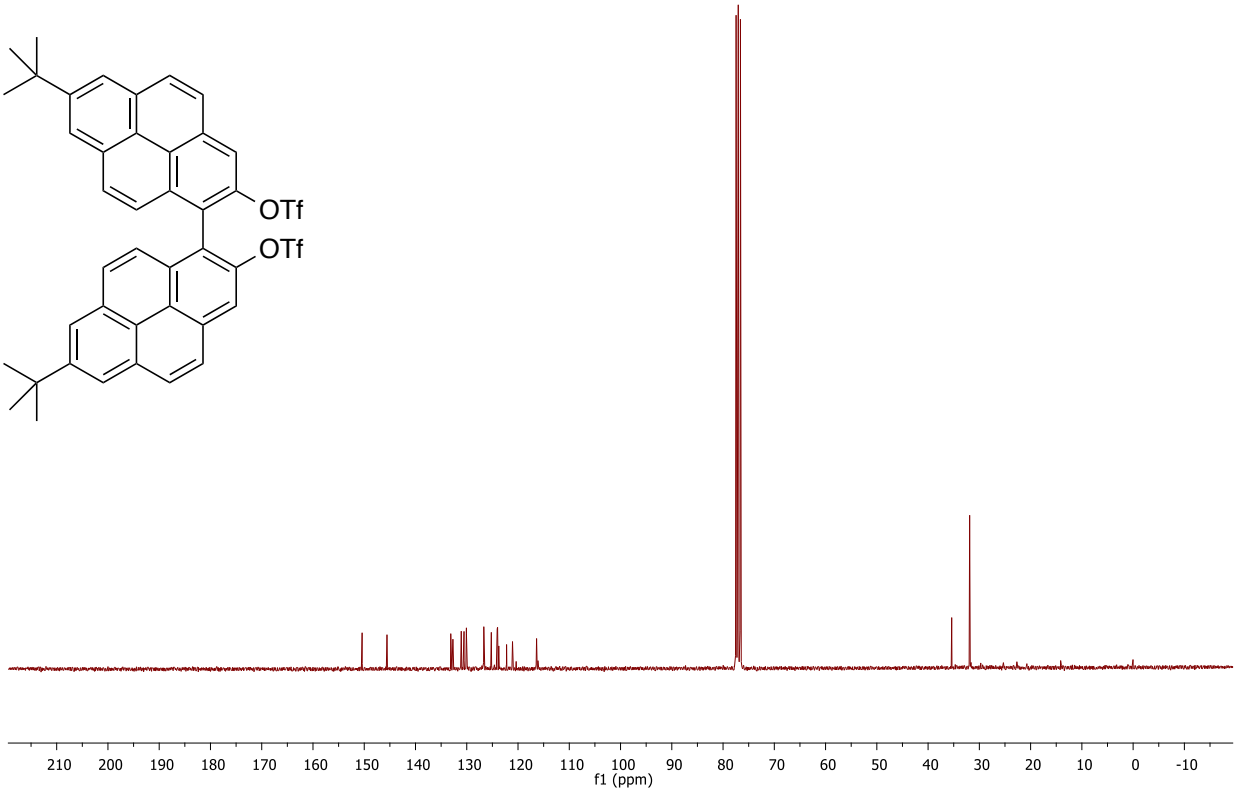
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OTf
OTf
210
200
190
180
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60
50
40
30
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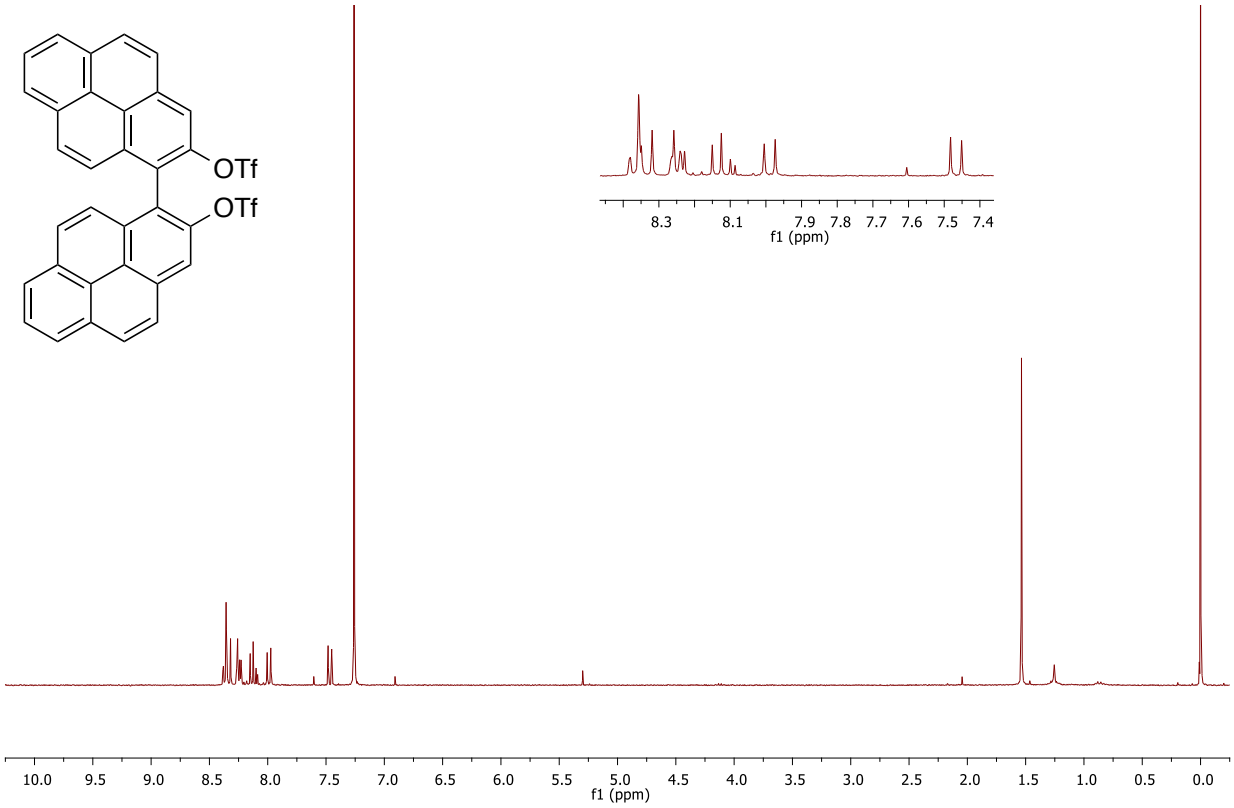
f1 (ppm)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8.1
7.9
7.8
7.7
7.6
7.5
7.4
f1 (ppm)
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9.5
9.0
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
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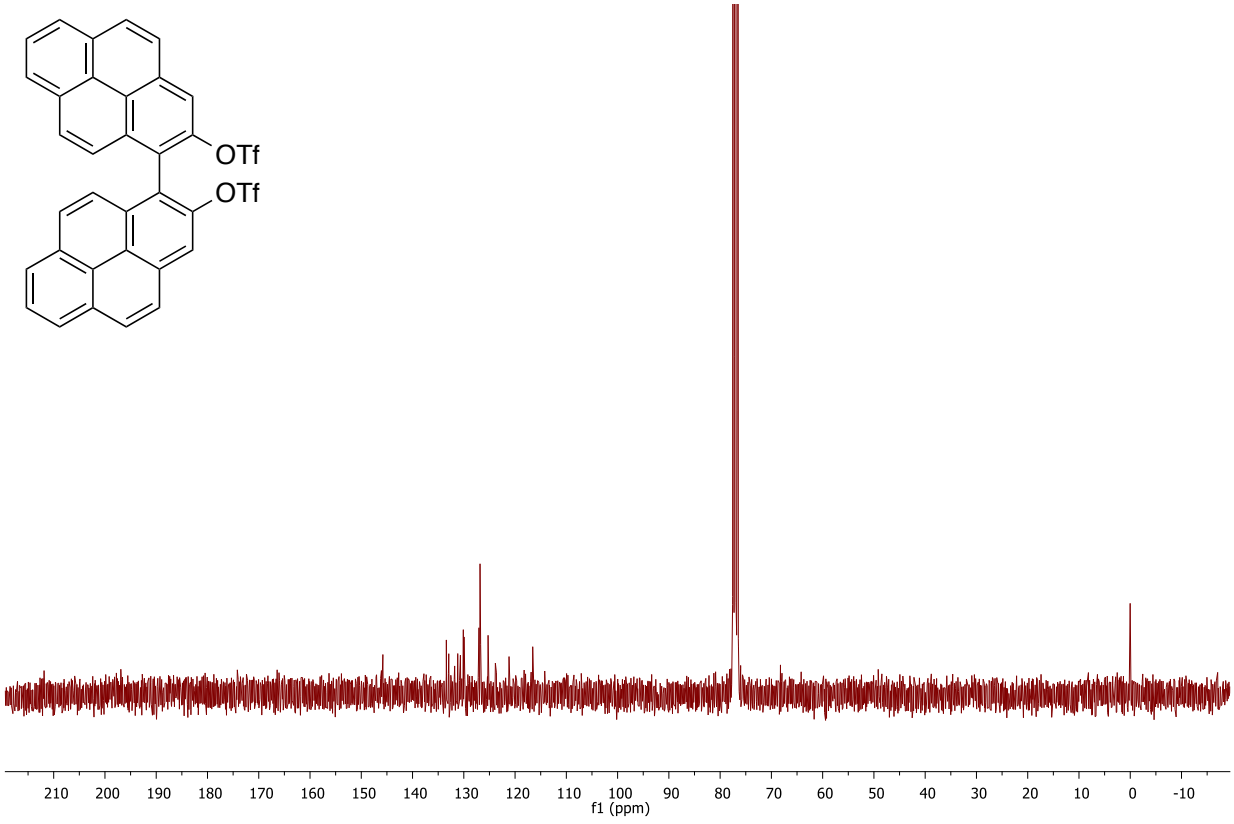
1.5
1.0
0.5
0.0
f1 (ppm)


OTf
OTf
210
200
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180
170
160
150
140
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120
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100
90
80
70
60
50
40
30
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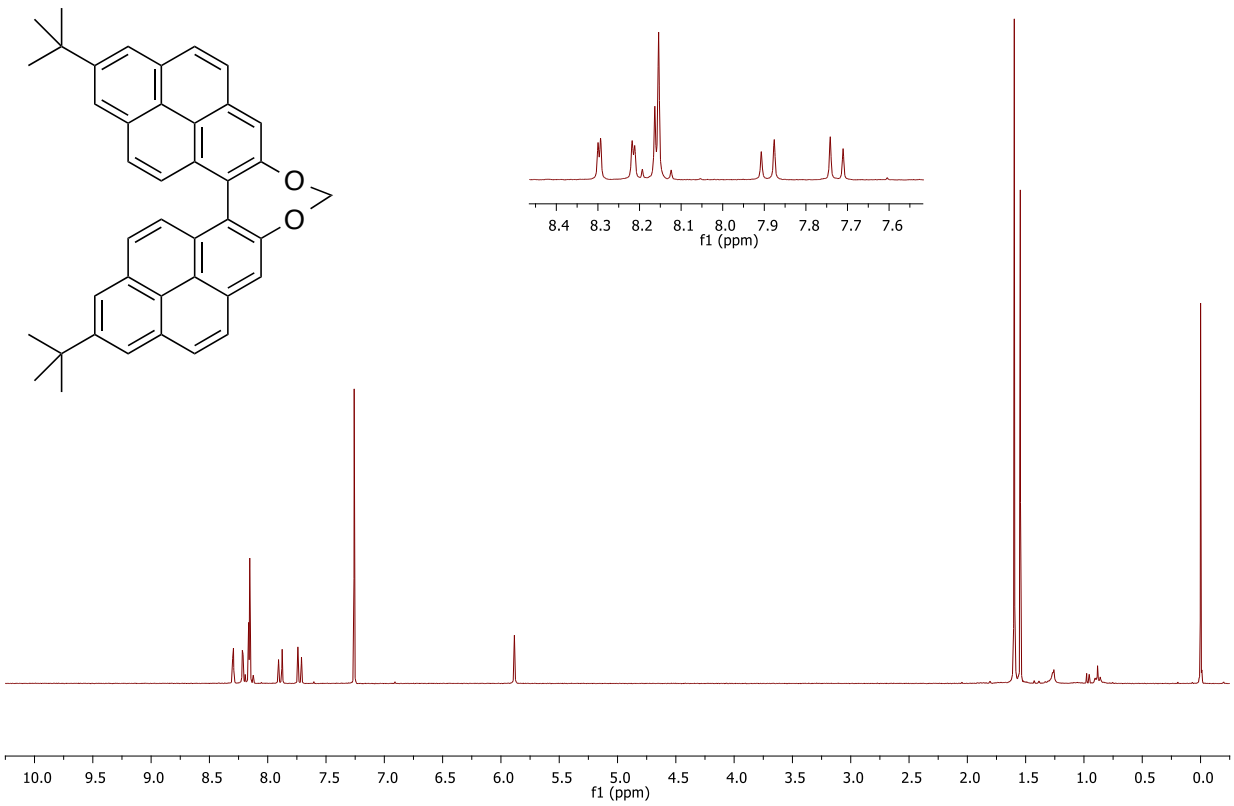
10
0
-10
f1 (ppm)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O
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f1 (ppm)
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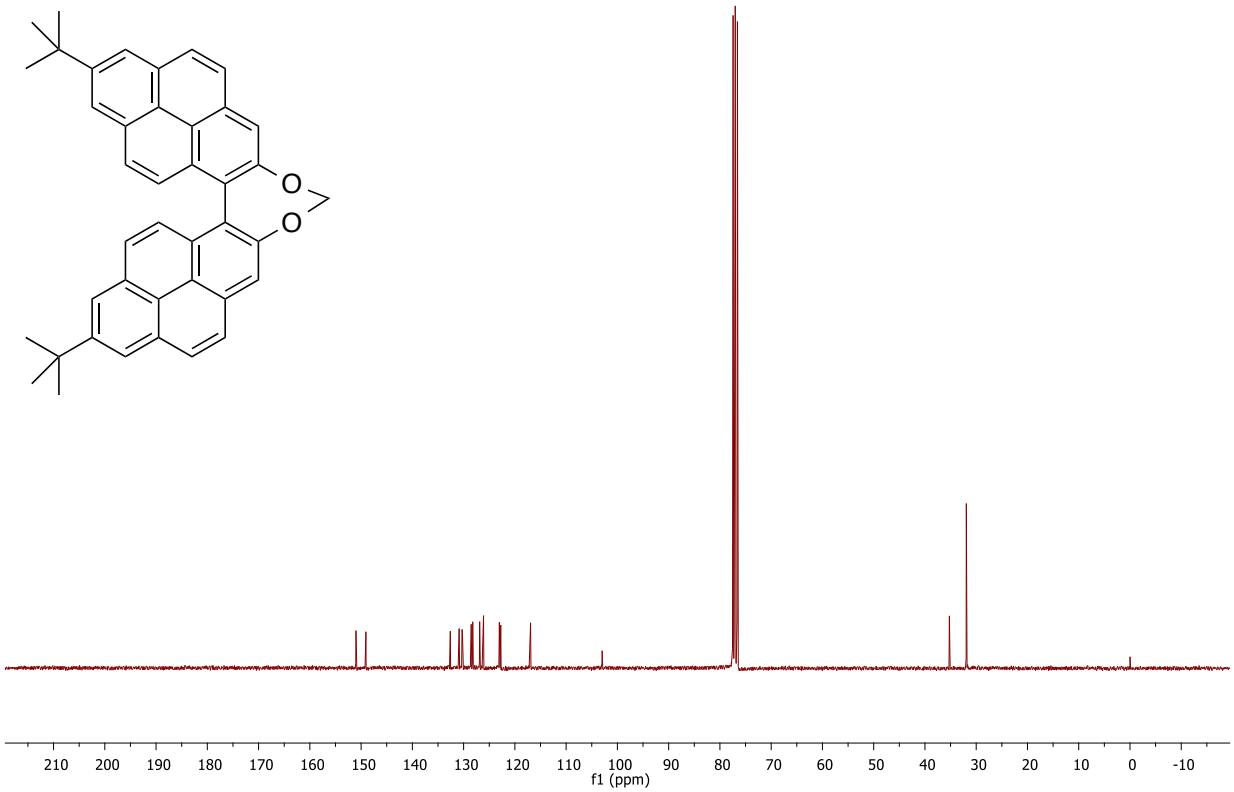
f1 (ppm)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O
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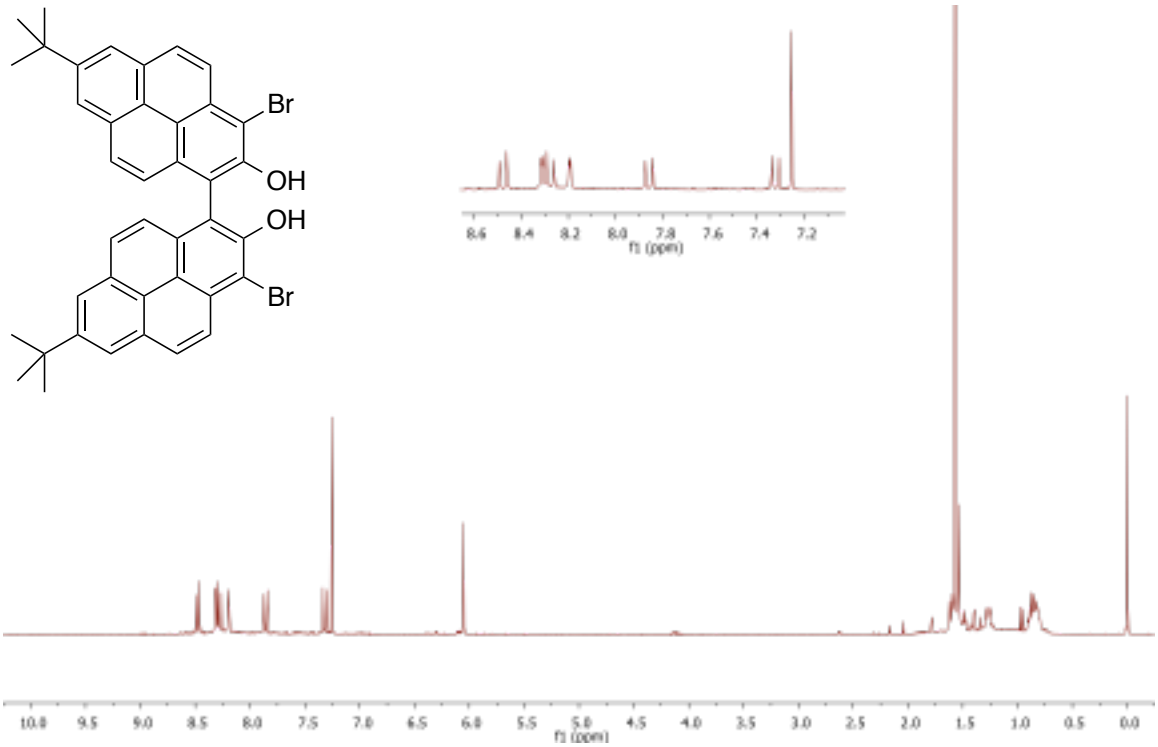
f1 (ppm)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OH
Br
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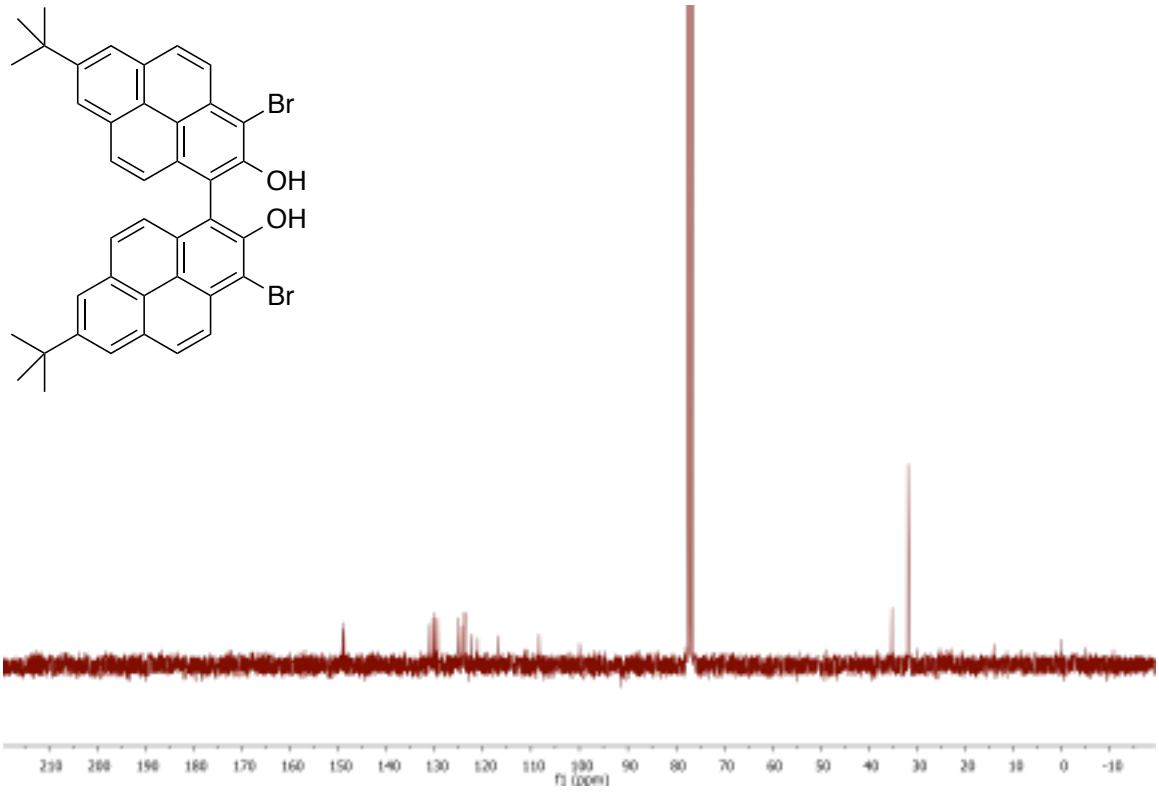
f1 (ppm)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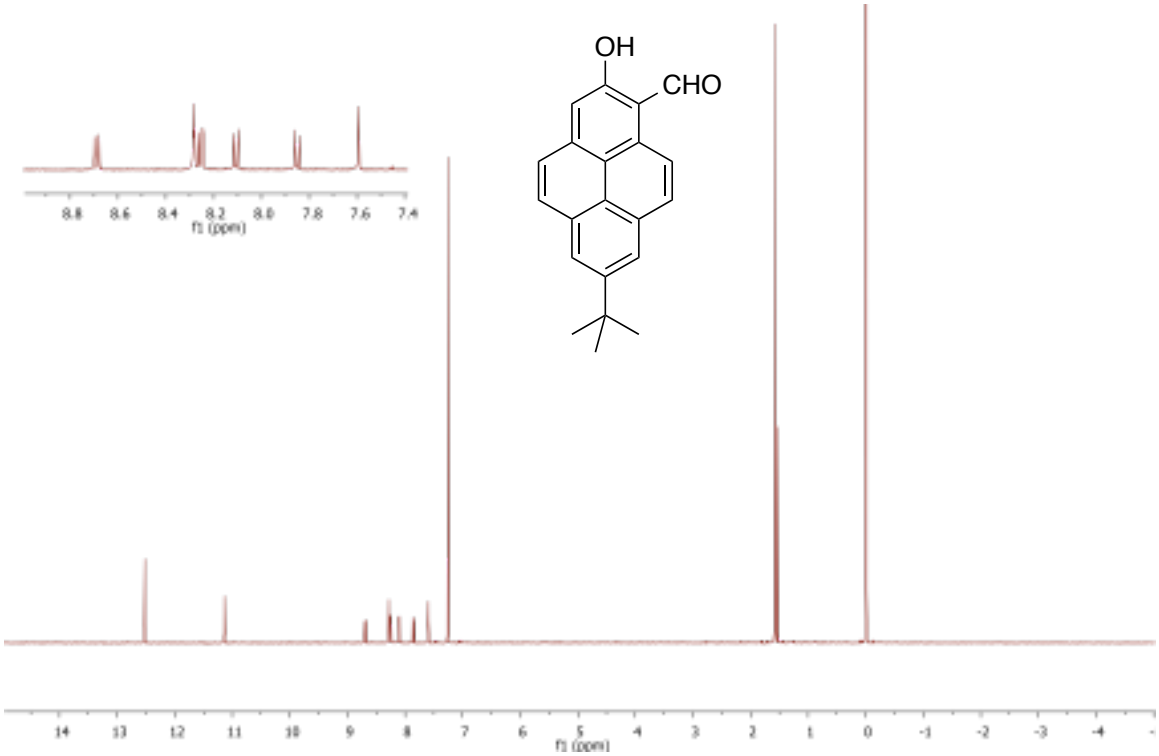
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f1 (ppm)
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2
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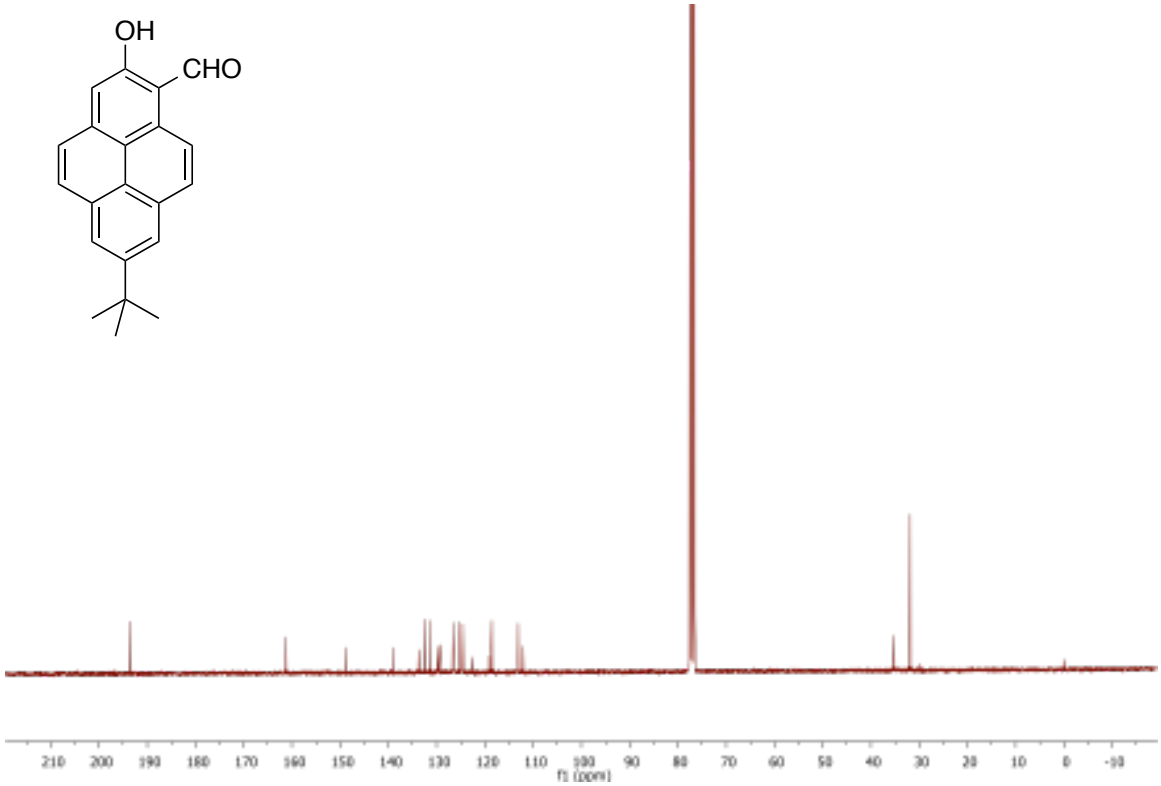
-1
-2
-3
-4
f1 (ppm)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50
40
30
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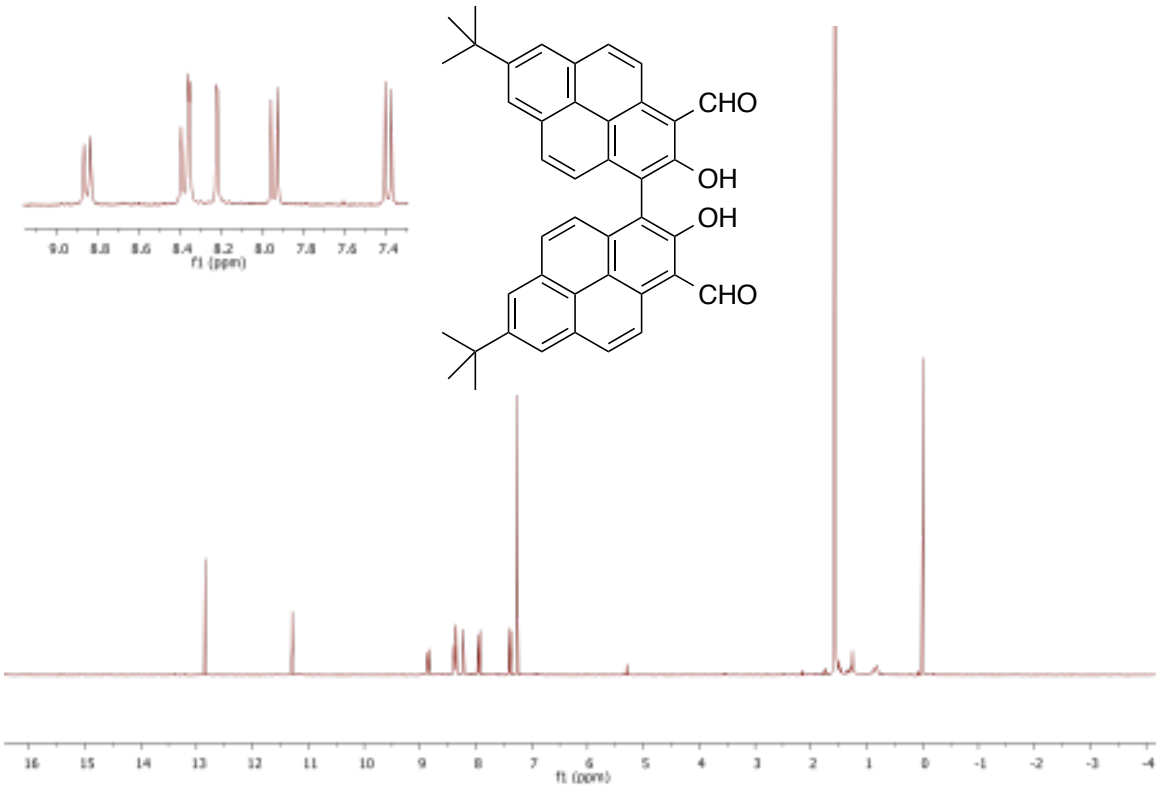
10
0
-10
f1 (ppm)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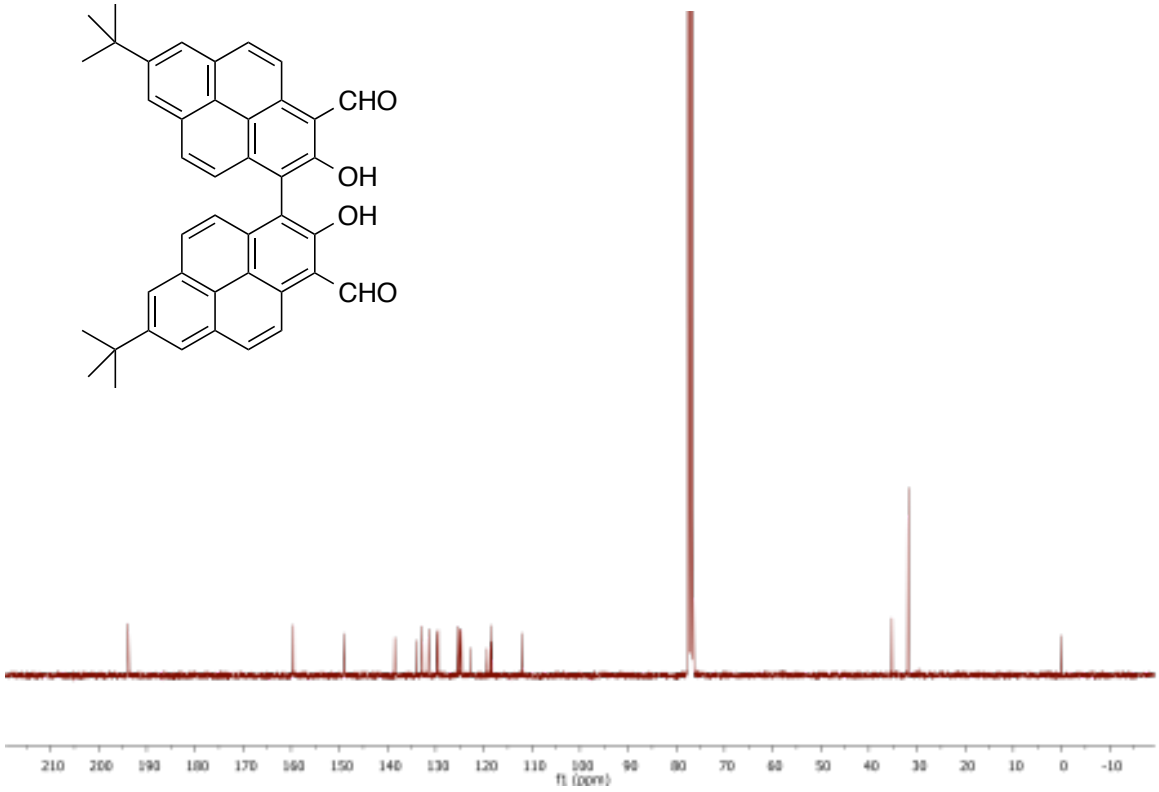
OH
OH
CHO
f1 (ppm)


CHO
OH
OH
CHO
f1 (ppm)

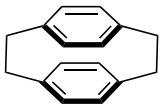
## Chapter 3 - Efforts Towards the Synthesis of a Novel Pyrenophane Containing More Than One Pyrene Unit

### 3.1 Introduction

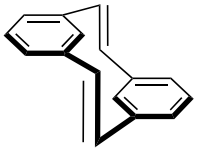
Cyclophanes are a large class of compounds that contain at least one aromatic system bridged by at least one aliphatic *n*-membered (or other type of) bridge.[1] The first example in the literature using the cyclopahane nomenclature was reported by Cram and co-workers in 1951 and was called [2.2]paracyclophane (**3.01**).[2] Numerous other examples have appeared since then, Figure 3.01 e.g. compounds **3.02-3.04**.[3-5] The vast diversity in cyclophanes arises from the open-ended nature of the definition; there can be any number of aromatic systems of any type and there can be as many bridges as allowed by the aromatic systems. The bridges can be of any length and constitution. For example, cyclophanes **3.01** and **3.02** are both doubly bridged, but **3.01** is bridged by two-carbon alkyl chains while **3.02** has unsaturated bridges. Compound **3.03** is still doubly bridged but the two bridges are of different lengths. One is a single carbon methylene bridge and the other is a longer aliphatic chain. Compound **3.04** contains only one aromatic system and one aliphatic *n*-membered bridge.

Cyclophanes can contain multiple bridges and/or aromatic units, so long as they satisfy the general rules of cyclophanes. The bridging unit does not have to strictly be aliphatic as the name implies. It can contain heteroatoms such as oxygen,

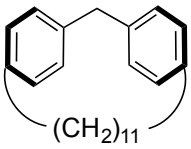
solely $sp^2$ hybridized carbon atoms, or the bridge can be made up of aromatics (i.e. zero bridges or benzannulated unsaturated bridges).



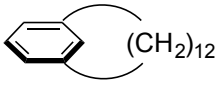
[2.2]paracyclophane (**3.01**)



*anti*-[2.2]metacyclophanediene (**3.02**)




[11.1]paracyclophane (**3.03**)




[12]metacyclophane (**3.04**)

**Figure 3.01** Selected examples of simple cyclophanes.

The Bodwell group has a longstanding and continued interest in the synthesis of cyclophanes in which the aromatic unit is pyrene. This special class of cyclophanes, called pyrenophanes, is of interest due to their unusual structures and properties, especially as they pertain to the pyrene system. As described in the previous chapter, pyrene is widely studied and important due to its photophysical properties. Therefore access to a range of pyrenophanes has enabled the study of the effects of systematically distorting a pyrene unit from planarity on these properties. Depending on the nature of the bridge and its length, the degree and nature of distortion of the pyrene units from planarity changes. The degree of bend

is, for a start, dependent on the length of the tether, the shorter the tether, the higher degree of bend. The bend angle ($\Theta$) in [$n$](2,7)pyrenophanes is defined as the smallest angle formed by the planes formed by the three bolded carbon atoms at the two ends of the pyrene system (Figure 3.02).[6]

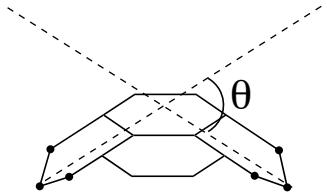
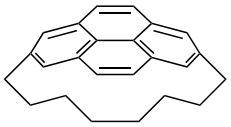
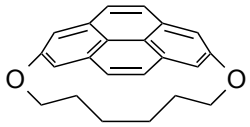



**Figure 3.02** Definition of $\theta$ angles in [$n$](2,7)pyrenophanes.

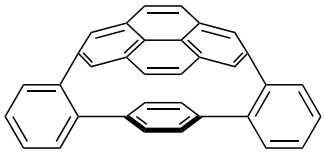
To date, all examples of pyrenophanes reported by the Bodwell group have the unifying structural feature that they all contain a single pyrene moiety. What differentiates these cyclophanes is the nature of the bridge, which to date includes purely aliphatic (**3.05**),[7] oxygen-containing (**3.06**),[8] benzannulated (**3.07**)[9] and mixed aromatic and aliphatic (**3.08**) (Figure 3.03).[10]



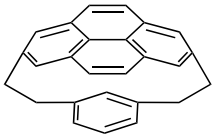
[8](2,7)pyrenophane (**3.05**)




1,8-dioxa[8](2,7)pyrenophane (**3.06**)



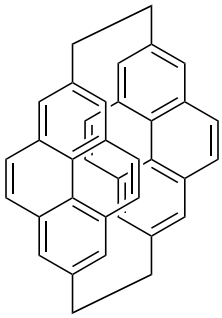
dibenzo[2]paracyclo[2](2,7)pyrenophane (**3.07**)



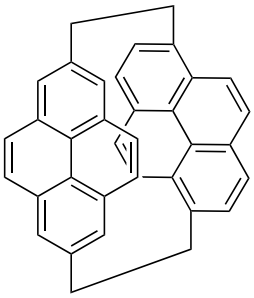
[2]metacyclo[2](2,7)pyrenophane (**3.08**)

**Figure 3.03** Selected examples of pyrenophanes with one pyrene unit.

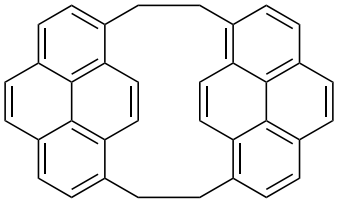
In addition to these examples, there are several examples of pyrenophanes in the literature that contain two or more pyrene units, such as **3.09-3.12** (Figure 3.04).[11-13] In examples **3.09**, **3.10**, and **3.12**, the pyrene units are identical in connectivity and have little (**3.09, 3.10**) or no (**3.12**) distortion from planarity. Example **3.11** contains two pyrene units with different bridging motifs, but both have gentle distortion from planarity.



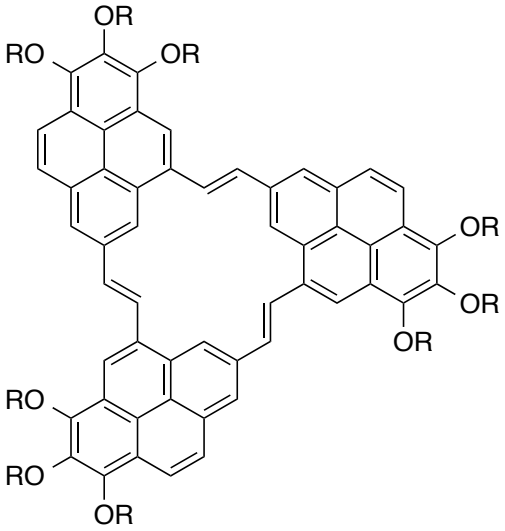
**3.09**



**3.10**



**3.11**

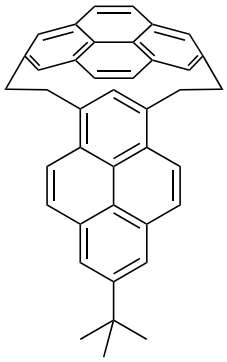



**3.12**

**Figure 3.04** Selected examples of pyrenophanes with two or more pyrene units.

The main goal of the work presented in the chapter was to synthesize a pyrenophane that contains two structurally very different pyrene units and study the interactions between them, *i.e.* target compound **3.13** (Figure 3.05). The pyrene units in **3.13** differ in their connectivity ((1,3) *vs.* (2,7)) and also in their distortion from planarity. Using the structurally related pyrenophane **3.08** as a point of comparison, the pyrene unit in **3.13** with the (1,3) bridging motif would be expected to be essentially planar, whereas the pyrene unit with the (2,7) bridging motif

would be expected to have a bend angle ($\theta$) of *ca.* 97.1°.[14] As such, the two pyrene systems in **3.13** should structurally be almost as different as possible.



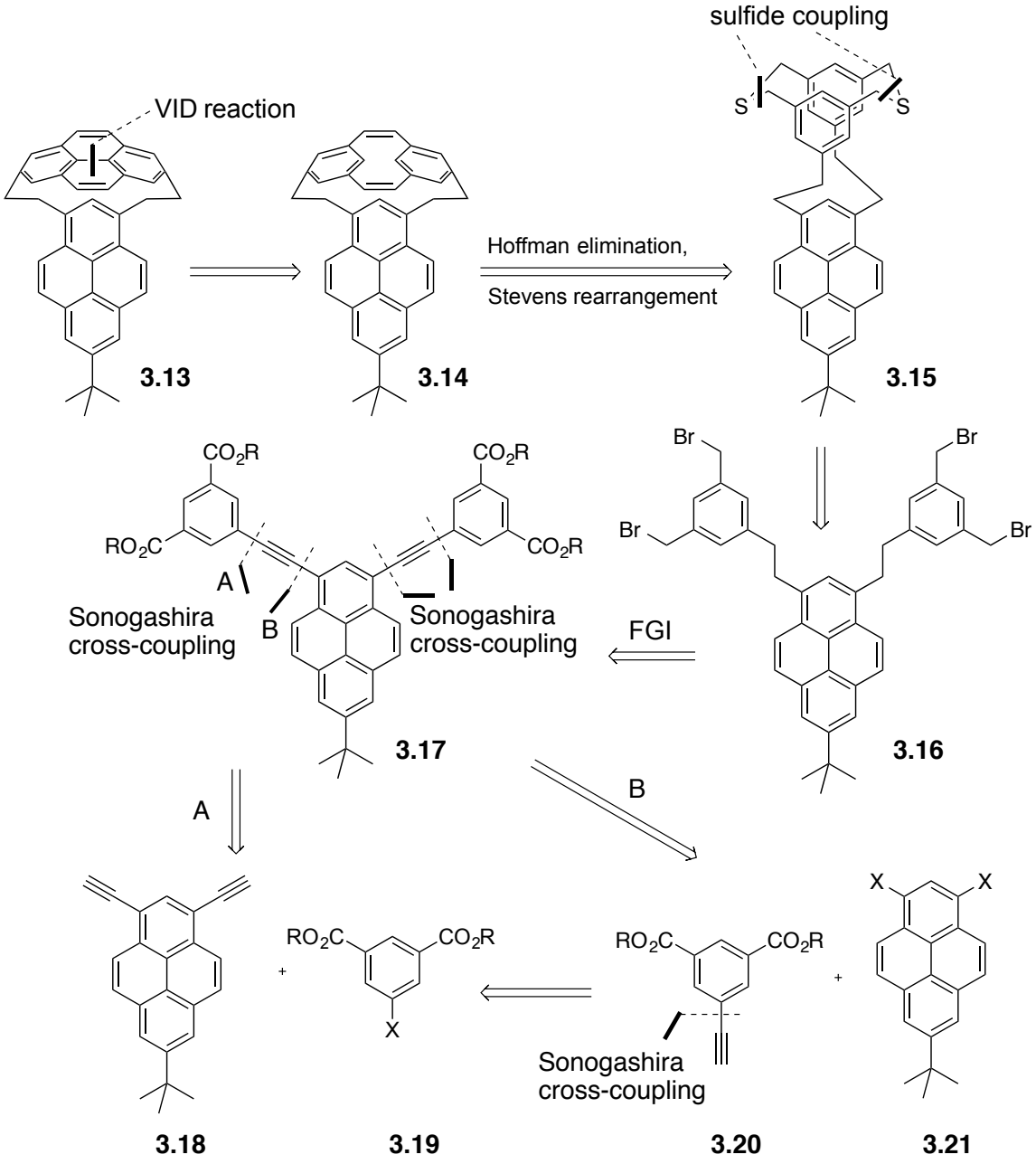
**3.13**

**Figure 3.05** Target pyrenophane **3.13**.

## 3.2 Retrosynthetic Analysis

The retrosynthetic analysis of target compound **3.13** begins with a valence isomerization/dehydration (VID) transform to afford cyclophanediene **3.14** (Scheme 3.01). This is a key step in the synthesis, because the VID reaction accomplishes the formation of the nonplanar pyrene system. It has been employed in numerous pyrenophane syntheses, including those with pyrene systems having similar or even greater bend than the one in **3.08**. Cyclophanediene **3.13** leads back to dithiacyclophane **3.15** via a Hoffman elimination and Stevens rearrangement.[15] Dithiacyclophane **3.15** is the expected product of sodium sulfide coupling of benzylic tetrabromide **3.16**. Functional group interconversion (FGI) leads back to diynetetraester **3.17**, which should be accessible by way of Sonogashira cross-

coupling. Two possible routes, A and B, which lead back to suitable coupling partners were enivisioned. Route A leads back to halo-diester **3.19** which is expected to couple with 1,3-ethynylpyrene **3.18.** Route B involves the coupling of dihalogenated pyrene **3.21** with 5-ethynyl-isophthalate **3.20**.

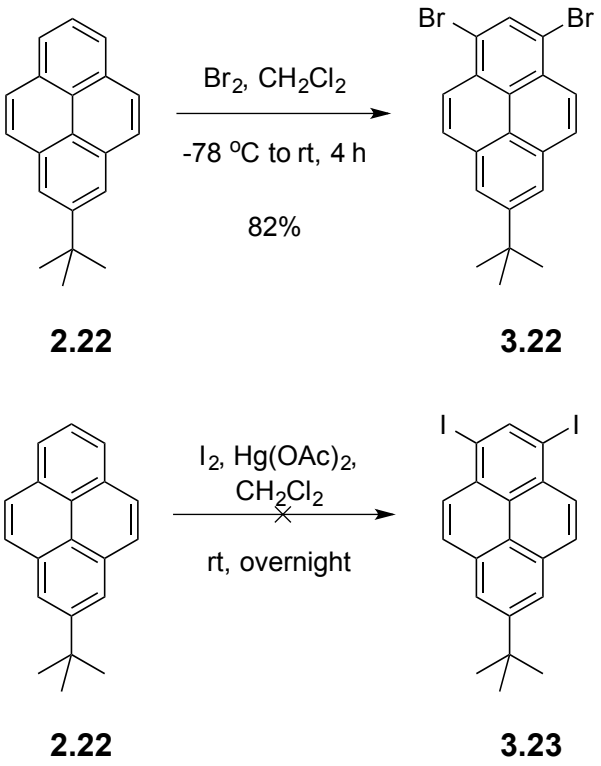



**Scheme 3.01** Retrosynthetic analysis of **3.13**.

### 3.3 Results and Discussion

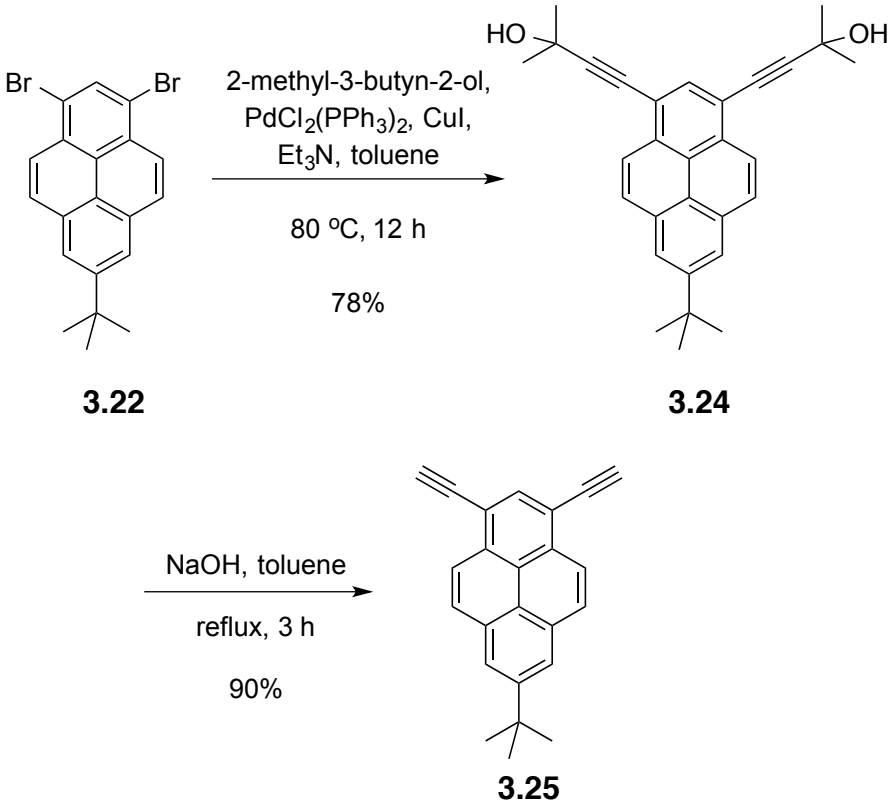
From the retrosynthetic analysis, it can be seen that the Sonogashira coupling of terminal dialkyne **3.18** and halo-diester **3.19** is a key step because all of the carbon atoms that eventually manifest themselves in the target pyrenophane are brought together at this point. The synthesis of compound **3.18** began with Friedel-Crafts *tert*-butylation of pyrene, as described in Chapter 2 (Scheme 2.08), to afford 2-*tert*-butylpyrene **2.22** (68%).[16] Reaction of **2.22** with molecular bromine (2.1 equivalents) at −78 °C afforded 1,3-dibromo-7-*tert*-butylpyrene **3.22** in 82% yield (Scheme 3.02).[17] As described in Chapter 2, pyrene is electronically predisposed to undergo electrophilic aromatic substitution at the 1 ,3, 6 and 8 positions. In the case of **3.22**, bromination occurred solely at the 1 and 3 positions, presumably because the *tert*-butyl group at the 7 position sterically hindered electrophilic aromatic substitution at the 6 and 8 positions. The reaction could be performed comfortably on a 5 g scale and the product could be isolated in pure form by simple crystallization. The synthesis of the corresponding diiodo derivative **3.23** was also considered due to the advantage aryl iodides often exhibit in cross-coupling chemistry.[18] 2-*tert*-Butylpyrene (**2.22**) was treated with molecular iodine and mercury(II) acetate. Thin-layer chromatographic analysis of the reaction mixture showed complete consumption of the starting material **2.22** overnight, but none of the desired product **3.23** was isolated or observed by mass spectrometry. As dexcribed below, dibromide **3.21** proved to be a competent reaction partner under Sonogashira conditions, so other iodination conditions were not investigated.

Nevertheless this is a transformation that would be worth revisiting in the future, as the diiodo compound **3.22** would be expected to be a generally useful compound in the Bodwell group.




**Scheme 3.02** Synthesis of dihalo-2-*tert*-butylpyrenes **3.22** and **3.23**.

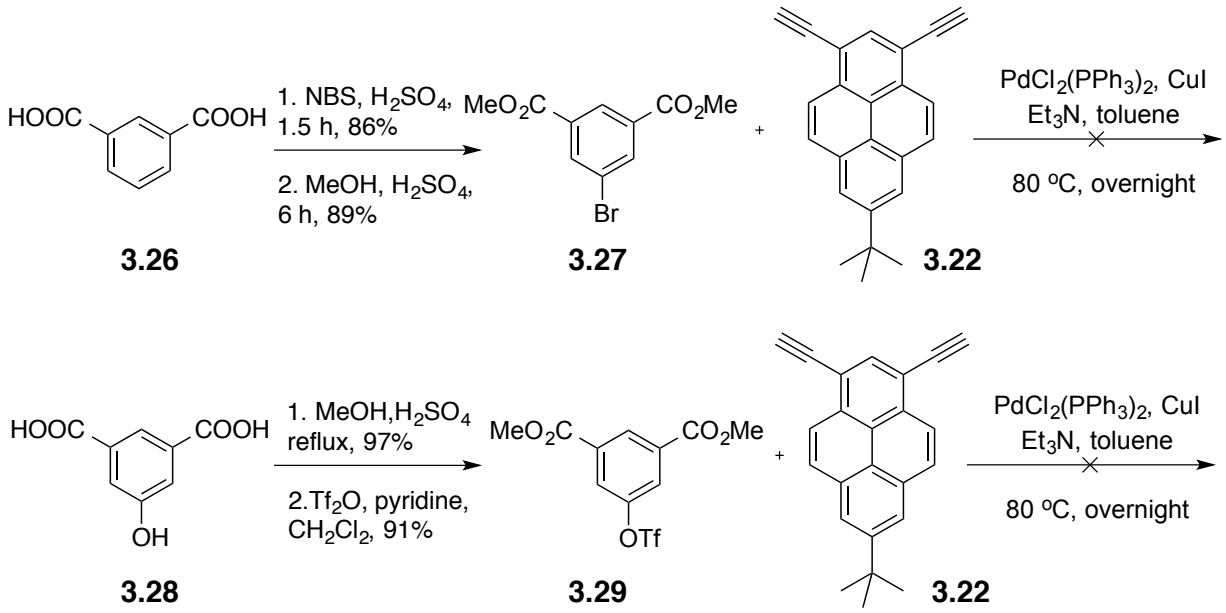
Dibromide **3.22** was subjected to Sonogashira cross-coupling conditions with 2-methyl-3-butyn-2-ol to yield the dialkyne diol **3.24** in 78% yield (Scheme 3.03). Reaction of **3.24** with NaOH in refluxing toluene yielded the terminal dialkyne **3.25** efficiently (90%).[19] Compounds **3.22**, **3.24** and **3.25** all exhibited good solubility in common organic solvents, which made for routine work-up and handling.




**Scheme 3.03** Synthesis of terminal dialkyne **3.25**.

With **3.25** in hand, the stage was set for the second Sonogashira cross-coupling reaction, in which the full complement of carbon atoms required for the construction of **3.13** would be assembled. Three reaction partners (**3.27**, **3.29** and **3.30**) were investigated for their utility in this reaction. The first one was dimethyl 5-bromoisophthalate (**3.27**), which was synthesized in two steps (bromination and esterification) from commercially available isophthalic acid (**3.26**) (Scheme 3.04).[20] Reactions of **3.25** and **3.27** under standard Sonogashira cross-coupling conditions resulted in the consumption of starting dialkyne **3.25** (tlc analysis) but led to the formation of an intractable mixture of products. No evidence of the desired product

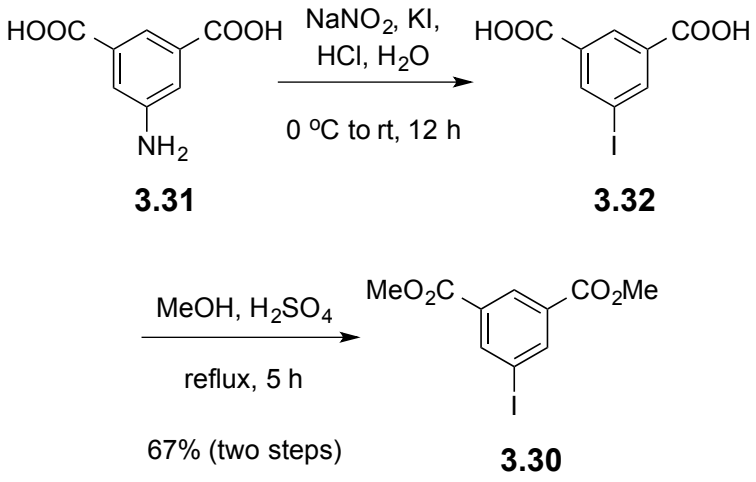
was observed. Focus was then shifted to the use of aryl triflate **3.29** as the coupling partner. This compound was synthesized in two steps (esterification and triflation) from commercially available 5-hydroxyisophthalic acid (**3.28**) (Scheme 3.04).[21] Again, the reaction showed consumption of starting material **3.19** (tlc analysis), but led to the formation of an intractable mixture of products.




**Scheme 3.04** Initial attempts at Sonogashira cross-coupling.

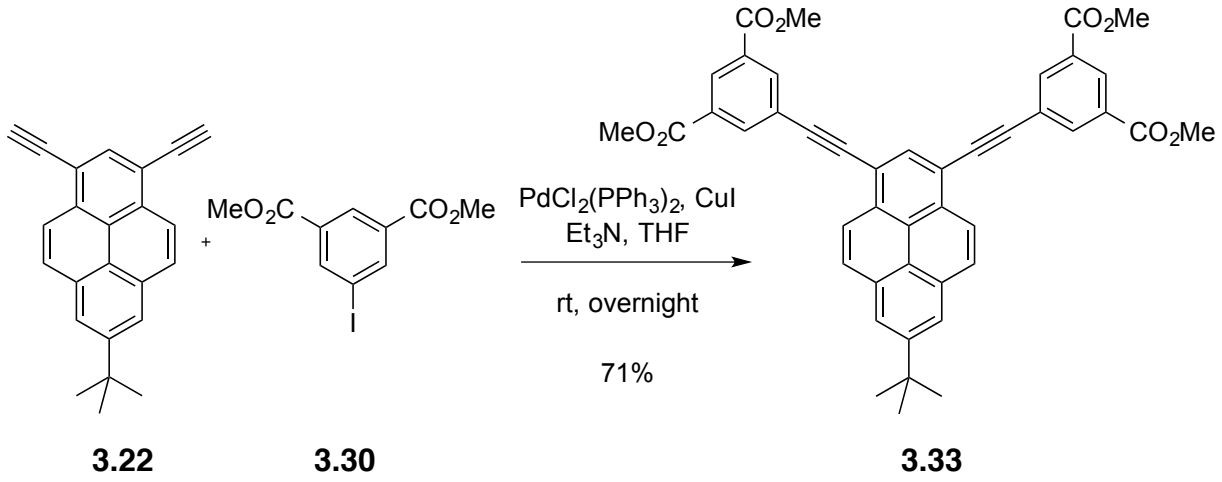
It is well known that aryl iodides are typically more reactive than the corresponding bromides and triflates in cross-coupling reactions and therefore require milder reaction conditions. This being the case, the synthesis of dimethyl 5-iodoisophthalate **3.30** was undertaken. The synthesis of **3.30** started with diazotization of commercially available 5-aminoisophthalic acid **3.31**, followed by the addition of excess potassium iodide to generate 5-iodoisophthalic acid **3.32** (Scheme 3.05). The crude product was then subjected to Fischer-Speier

esterification with methanol to yield dimethyl 5-iodoisophthalic acid (67%, two steps).[22]




**Scheme 3.05** Synthesis of aryl iodide **3.30**.

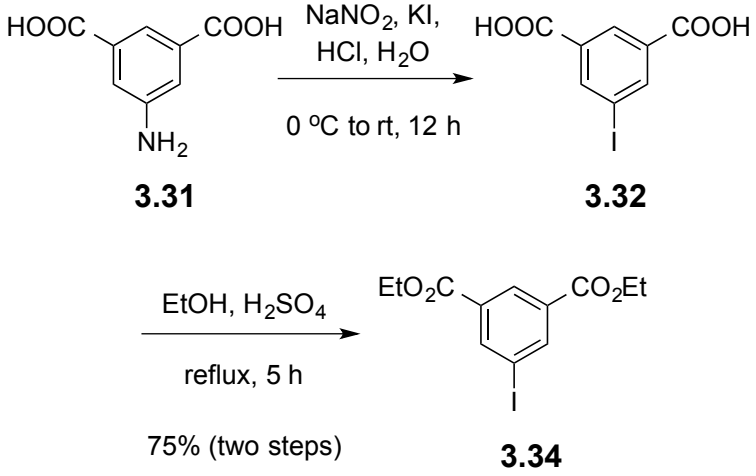
The reactivity of **3.30** under Sonogashira conditions was then investigated. Using the same conditions that were used with bromide **3.27**, but with lower catalyst loading (1 mol% $PdCl_2(PPh_3)_2$ and 2 mol% CuI) compound **3.33** was successfully obtained in 71% yield (Scheme 3.06). Compound **3.33** was isolated in reasonably pure form by suction filtration. It was sparingly soluble in organic solvents such as toluene, THF, $CH_2Cl_2$, $CHCl_3$ and could not be purified further. Although **3.33** was just soluble enough in chloroform to obtain a $^1H$ NMR spectrum, its low solubility rendered the next step in the synthesis (catalytic hydrogenation) essentially impossible. All attempts to perform this chemistry resulted in no reaction.




**3.22** **3.30** **3.33**

**Scheme 3.06** Second Sonogashira cross-coupling reaction.

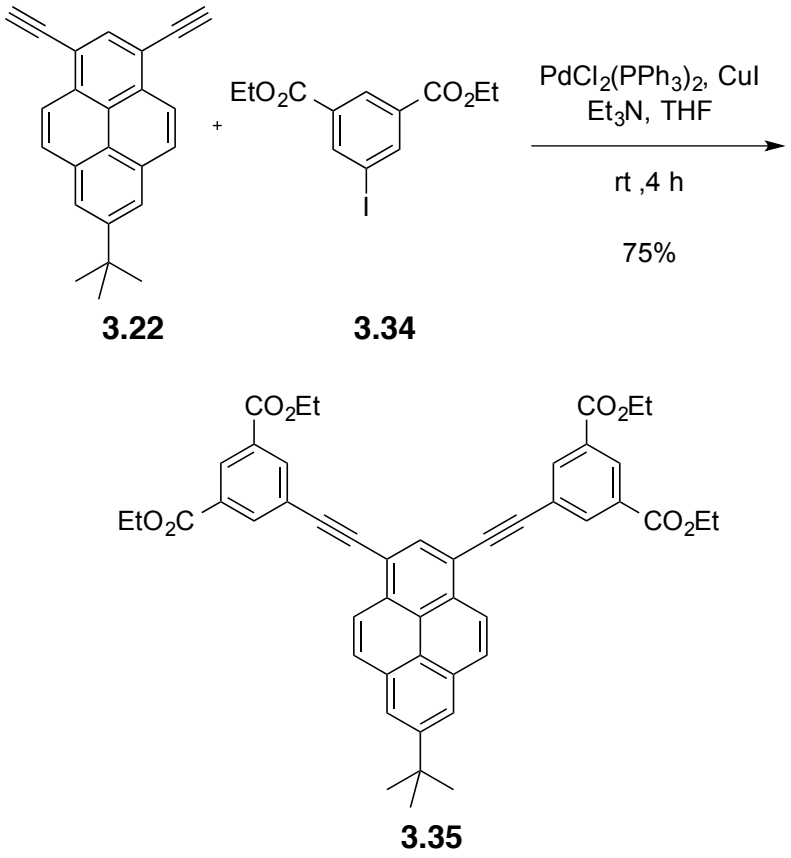
To overcome the solubility issue, the alkyl component of the ester was changed from methyl to ethyl. Diethyl 5-iodoisophthalate (**3.34**) was synthesized in the same fashion as dimethyl 5-iodoisophthalate (**3.30**) except that the Fischer-Speier esterification was performed with ethanol in lieu of methanol (Scheme 3.07). As such, diester **3.34** was obtained in 75% yield over two steps from **3.31**.




**3.31** **3.32** **3.34**

**Scheme 3.07** Synthesis of aryl iodide **3.34**.

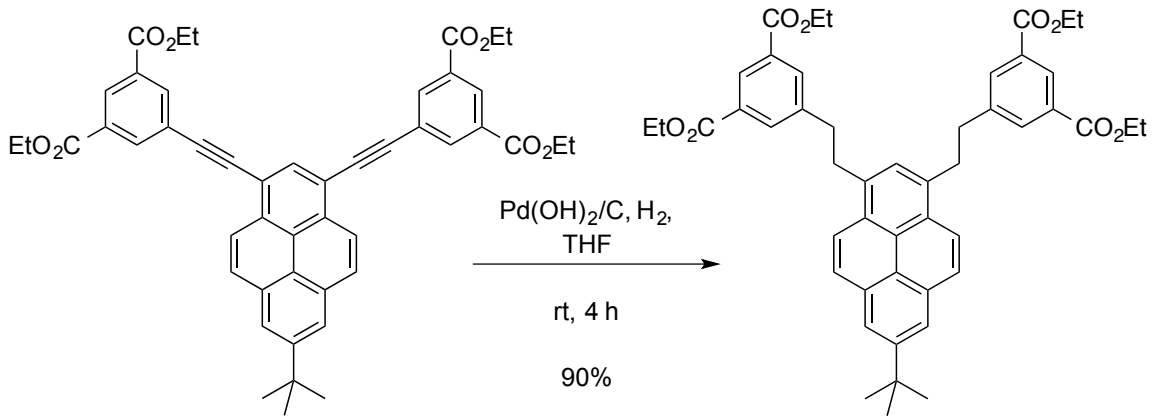
The Sonogashira cross-coupling of dialkyne (**3.22**) with diethyl 5-iodoisophthalate (**3.34**) was then investigated (Scheme 3.08). Gratifyingly, the reaction produced the desired cross-coupled tetraester product **3.35** in 78% yield as a bright yellow solid. Compound **3.35** was also isolated by suction filtration, but could be further purified by column chromatography with chloroform as the eluent. Tetraester **3.35** was found to have rather low solubility in most organic solvents, but was modestly soluble in chloroform and THF. This limited solubility allowed for the next step of the synthesis (catalytic hydrogenation) to be performed comfortably. It is worth reiterating at this point that compound **3.35** contains all of the carbons atoms that ultimately manifest themselves in the target compound **3.13**. Thus the remaining synthetic steps involve functional group interconversions and stitching the atoms together to form the target pyrenophane.




**Scheme 3.08** Sonogashira cross-coupling reaction of **3.22** and **3.35**.

The next step in the planned synthetic pathway was catalytic hydrogenation of **3.35**. Catalytic hydrogenations are generally performed in polar solvents such as methanol, ethanol, ethyl acetate, acetone, THF, DMF or even aqueous acetic acid. The only solvent from this list in which compound **3.35** exhibited any appreciable solubility was THF. Therefore the catalytic hydrogenation was performed in THF (in the presence of Pearlman's catalyst) to yield compound **3.36** in quantitative yield (Scheme 3.09). The hydrogenation reaction was found to be quite sensitive to the cleanliness of the glassware, septum, and stir bar that was used. The reaction

was found to work consistently when the glassware and stir bar were washed with concentrated HCl immediately prior to performing the reaction. The use of a new septum, through which a balloon of $H_2$ gas was connected to the reaction flask was also found to be beneficial.

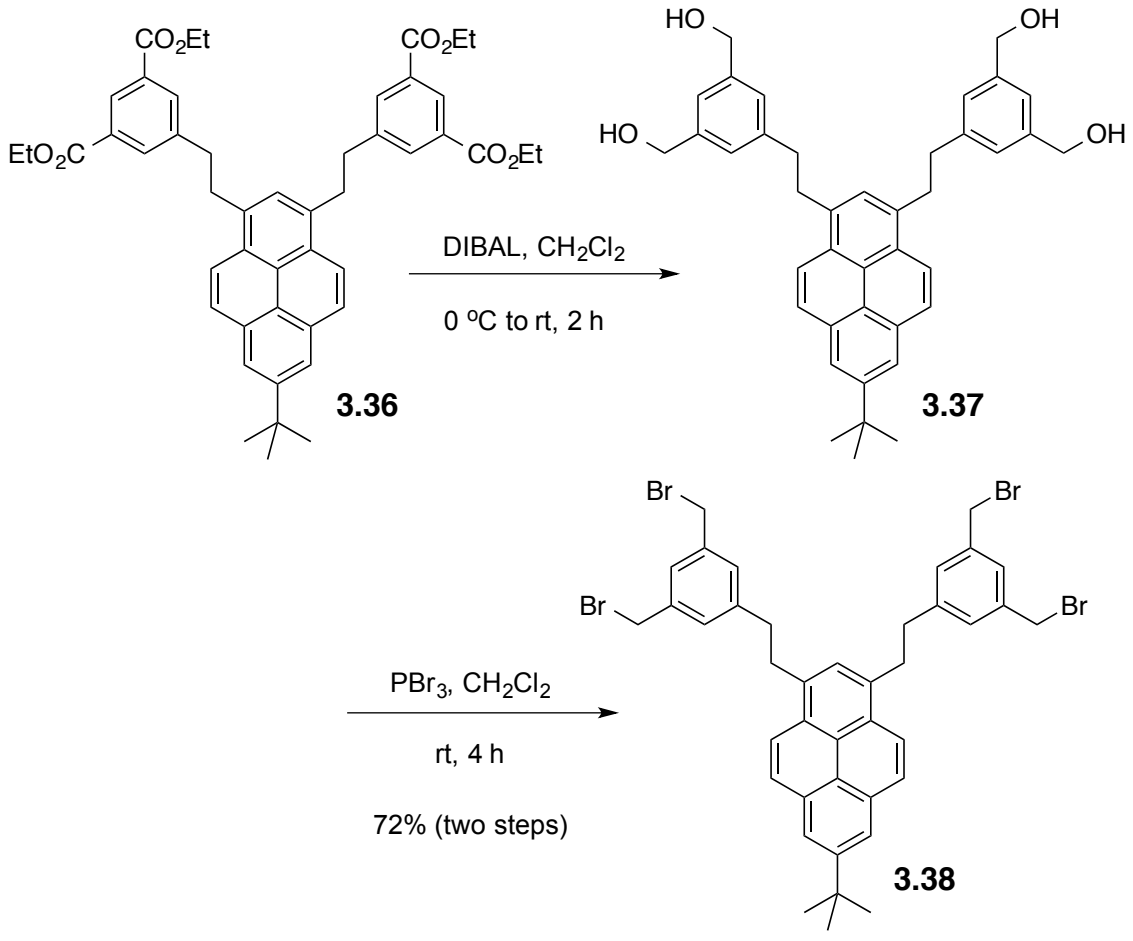



**3.35** **3.36**

**Scheme 3.09** Catalytic hydrogenation of **3.35**.

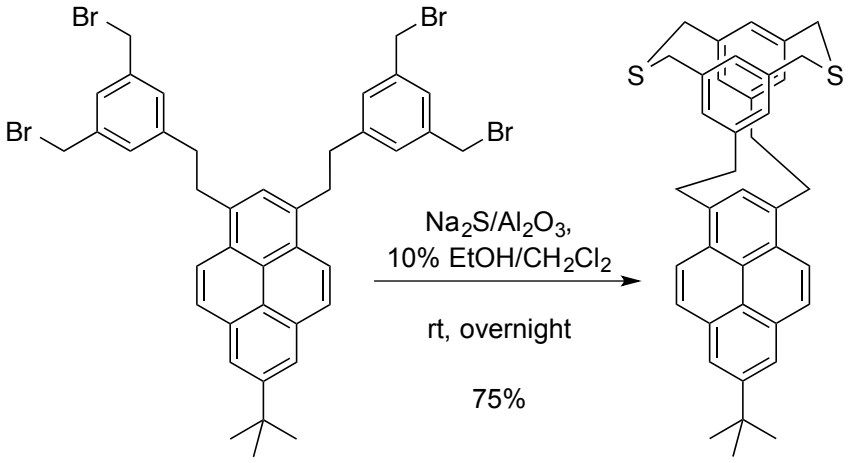
The hydrogenation step served to install the $CH_2$-$CH_2$ units that would eventually become the bridges between the aromatic moieties in the target molecule (**3.13**). The next stage of the synthesis involved functional group interconversion to obtain tetrabromide **3.38**, which was to function as the substrate for cyclophane formation (Scheme 3.10). The first step in this process was the reduction of the ester group in **3.36** to afford the corresponding tetraol **3.37**. This was initially attempted using lithium aluminium hydride, but was found to be difficult, presumably due to problems associated with separating the desired product from the aluminum salts formed during the reaction. Therefore, the use of diisobutylaluminium hydride (DIBAL) was investigated. In this case, the workup

proved to be much easier and the desired product was obtained in a high yield. Although the $^1$H NMR spectrum of the crude product indicated the presence of some impurities, tetra-alcohol product **3.37** was used in the next step without further purification. It had been well established in the Bodwell group that tetra-alcohols related to **3.37** are extremely difficult to purify (*e.g.* by flash column chromatography) and often afforded products in significantly reduced quantities that are no more pure than they were before chromatography. Crude product **3.37** was brominated smoothly with $PBr_3$ in $CH_2Cl_2$ to yield tetrabromide product **3.38** in 72% yield over two steps.




**Scheme 3.10** Synthesis of tetrabromide **3.38**.

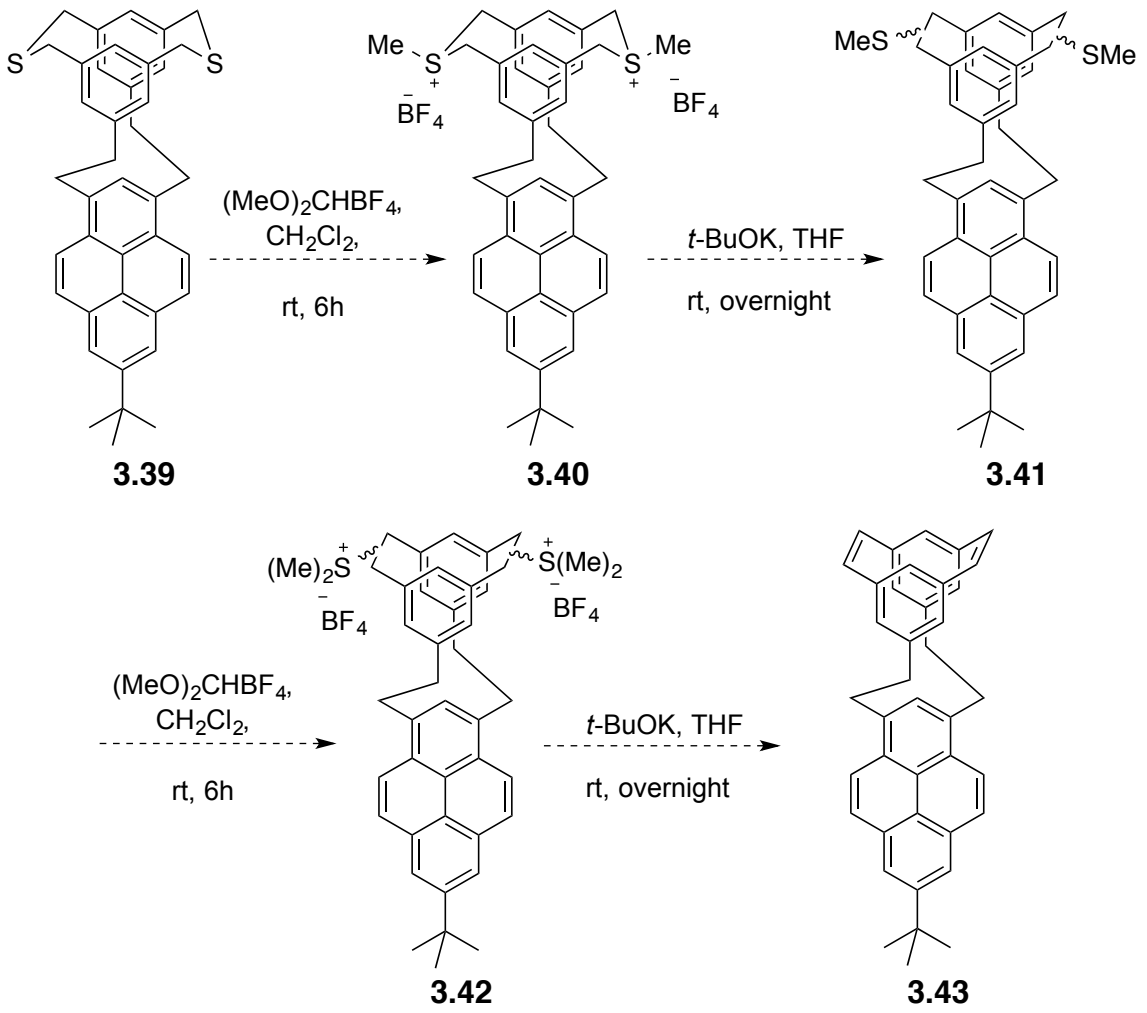
Tetrabromide **3.38** was reacted with $Na_2S/Al_2O_3$[23] under moderate dilution to generate dithiacyclophane **3.39** in 75% yield (Scheme 3.11). The yield is fairly high when compared to those of similar dithiacyclophanes reported by the Bodwell group. Only 5 examples of sodium sulfide coupling from the many reported are higher yielding (83-89%).[24-25] By comparison, the sodium sulfide coupling reaction in the synthesis of the corresponding pyrenophane **3.08** was reported to occur in a 68% yield.




**Scheme 3.11** Sodium sulfide coupling of tetrabromide **3.38**.

Numerous dithiacyclophanes have been transformed into pyrenophanes through a series of well-documented transformations. The first step involves *S*-methylation of the thioether with Borch reagent ($(MeO)_2CHBF_4$), a very reactive source of electrophilic methyl, to yield the bis(methylsulfonium tetrafluoroborate) salt **3.40** (Scheme 3.12). Treatment of the salt **3.40** with a strong base, potassium *tert*-butoxide, induced a Stevens rearrangement to yield compound **3.41** as a

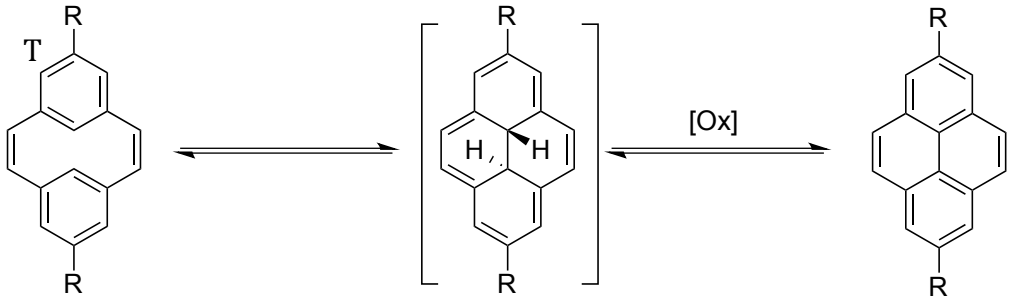
mixture of constitutional and stereoisomers. This step not only contracted the bridges from three atoms to two, but also formed the bond between benzylic carbon atoms and left functionality that can be exploited to install the required double bond. The isomers of **3.41** were not separated because the individual isomers should all lead to the same product. Thioether mixture **3.41** was then subjected to another *S*-methylation with Borch reagent to yield the bis(dimethylsulfonium tetrafluoroborate) salts **3.42**, again as a mixture of constitutional and stereoisomers. Induction of a Hoffman elimination by treatment of salt **3.42** with potassium *tert*-butoxide should afford cyclophanediene **3.43**.[26-27] However, cyclophanediene was never conclusively obtained, even when Borch reagent was freshly prepared before use, and potassium *tert*-butoxide was purified by sublimation.




**Scheme 3.12** Synthetic pathway towards cyclophanediene **3.43**.

The final step in the synthesis of pyrenophane **3.13** involves a valence isomerization-dehydrogenation (VID) transformation which could be achieved in principle by treatment of cyclophanediene **3.43** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[28] Cyclophanedienes **3.44**, in general, undergo valence isomerization to form dihydropyrenes **3.45** (Scheme 3.13). These compounds undergo dehydrogenation in the presence of an oxidant to give a new aromatic pyrene moiety **3.46.** This transformation has been employed as the final synthetic

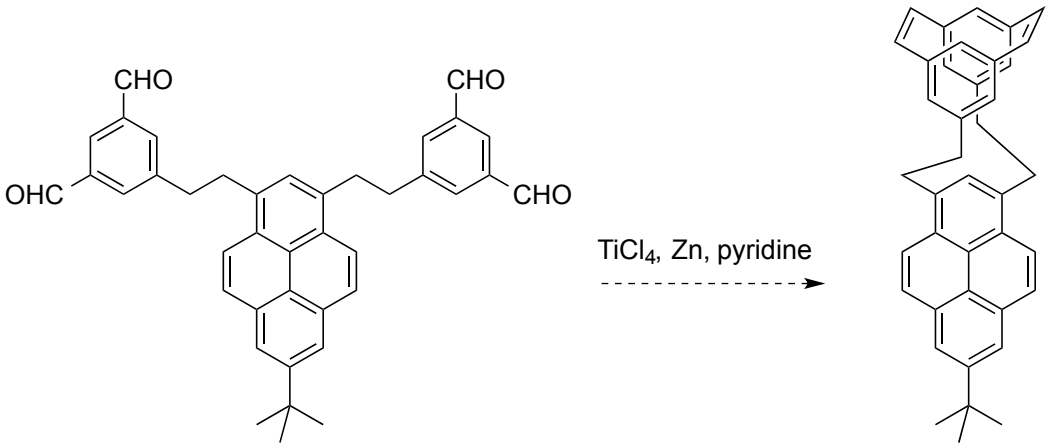
step in the synthesis of the majority of pyrenophanes reported by the Bodwell group.




**3.44** **3.45** **3.46**

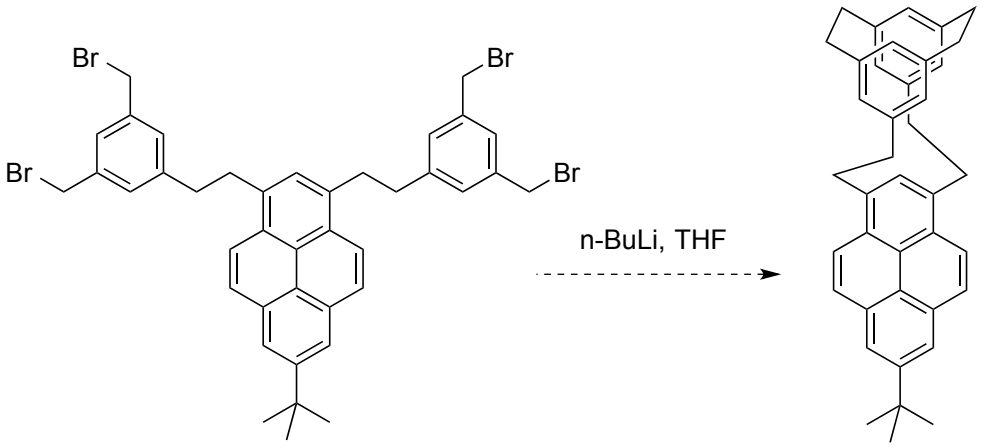
**Scheme 3.13** Valence isomerization-dehydrogenation protocol.

Two other potential strategies for the synthesis of pyrenophane (**3.13**) include the McMurry reaction of a tetraldehyde **3.47** (Scheme 3.14), and Wurtz-type coupling of tetrabromide **3.38** (Scheme 3.15). The McMurry reaction has been successfully employed in the synthesis of teropyrenophanes,[29] but has yet to be described in the synthesis of pyrenophanes. The required tetraldehyde **3.47** would be obtained by oxidation of tetra-alcohol **3.37**. The McMurry reaction is brought about by treatment with $TiCl_4$, zinc and pyridine. The product of this reaction is cyclophanediene **3.43,** which would then be transformed into pyrenophane **3.13** by valence isomerization/dehydrogenation protocol.




**Scheme 3.14** McMurry reaction of tetraldehyde **3.47**.

The other alternate route would involve a Wurtz-type coupling of tetrabromide **3.38** with *n*-BuLi to yield cyclophane **3.48**. Cyclophanes of this type (alkyl bridged) have shown the ability to undergo the valence cyclohydrogenation to form tetrahydropyrene moieties, which can be subsequently dehydrogenated to give pyrenes.[30]




**3.38** **3.48**

**Scheme 3.15** Wurtz-type coupling of tetrabromide **3.38**.

## 3.4 Conclusions

The efforts towards the synthesis of novel pyrenophane **3.13** were reported. The synthesis was successful to the formation of dithiacylcophane **3.39**, but the synthesis of the corresponding cyclophandiene **3.43** proved to be problematic.

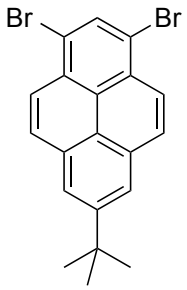
## 3.5 Experimental Section

All chemicals were used as received from commercial suppliers (Sigma Aldrich, Alfa Aesar) without further purification. Organic solvents were removed under reduced pressure by the use of a rotary evaporator and column chromatography was performed using Silicycle silica gel 60, particle size 40-63 μm.

**Instrumentation:**

Melting points were measured using a Fisher-Johns apparatus and are uncorrected. $^{1}H$ NMR (500 MHz) spectra were recorded on a Bruker AVANCE 500MHZ instrument and were measured using $CDCl_3$ as solvent. $^{13}C$ NMR (75 MHz) spectra were recorded on a Bruker AVANCE III 300MHz instrument and were measured using $CDCl_3$ as solvent. Chemical shifts are reported relative to internal standards: $(CH_3)_4Si$ (δ 0.00 ppm) and $CDCl_3$ (77.23 ppm). Low-resolution mass spectrometric data (LCMS) were determined on an Agilent 1100 series LC/MSD instrument. High-resolution mass spectrometric data (HRMS) were determined on a Waters Micromass GCT Premier instrument.

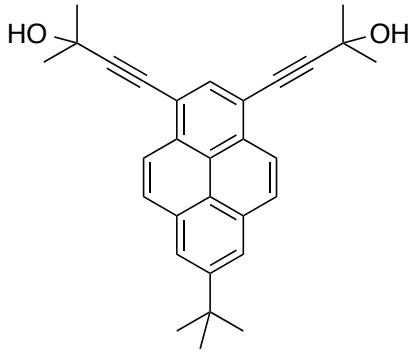
**1,3-Dibromo-7-*tert*-butylpyrene (3.22)**




To a solution of 2-*tert*-butylpyrene **2.22** (3.25 g, 12.6 mmol) in $CH_2Cl_2$ (125 mL) was added a solution of $Br_2$ (4.21 g, 1.35 mL, 26.4 mmol) in $CHCl_2$ (25 mL) dropwise via cannula over a period of 10 minutes. The solution gradually warmed to room temperature and stirred overnight. The reaction mixture was poured into asaturated aqueous $Na_2S_2O_3$ solution (50 mL). The layers were separated and the

aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The off-white residue was recrystallized from boiling hexane to yield **3.22** as a light brown solid (4.30 g, 82 %). $R_f$ = 0.76 (10% $CH_2Cl_2$/hexanes); m.p. 296-298 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.48 (s, 1H), 8.36 (d, $J$ = 9.7 Hz, 2H), 8.30 (s, 2H), 8.17 (d, $J$ = 9.7 Hz, 2H), 1.59 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.47, 132.93, 130.98, 129.42, 129.00, 126.53, 125.65, 123.59, 121.71, 119.20, 35.30, 31.84; LCMS (APCI-positive) $m/z$ 417 $[MH]^+$.

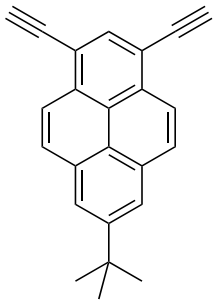
**Dialkyne diol 3.24**




A solution of 1,3-dibromo-7-*tert*-butylpyrene (**3.22**) (4.1 g, 9.8 mmol) was in toluene (50 mL) and $Et_3N$ (50 mL) was purged with $N_2$ for 10 minutes. $PdCl_2(PPh_3)_2$ (344 mg, 0.49 mmol) and CuI (189 mg, 0.99 mmol) were added. The reaction mixture was stirred at room temperature under a $N_2$ atmosphere for 5 minutes, after which 2-methyl-3-butyn-3-ol (4.14 g, 4.8 mL, 49.3 mmol) was added. The reaction mixture was heated to 80 °C and stirred overnight. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The

residue was purified by column chromatography (30% ethyl acetate/hexanes) to yield **3.24** as an orange solid (3.24 g, 78%): $R_f$ = 0.54 (50% ethyl acetate/hexanes); m.p. 228-231 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.42 (d, $J$ = 9.0 Hz, 2H), 8.26 (s, 2H), 8.18 (s, 1H), 8.13 (d, $J$ = 9.0 Hz, 2H), 2.16 (s, 2H), 1.78 (s, 12H), 1.59 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.82, 133.04, 131.64, 130.98, 129.21, 125.05, 124.21, 123.49, 122.19, 116.75, 99.47, 80.56, 66.03, 31.88, 31.71, 31.05; LCMS (APCI-positive) *m/z* 417 $[MH]^+$; HRMS (EI) calculated for $[M]^+$ $C_{30}H_{30}O_2$ 422.2246, found 422.2242.

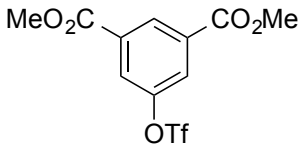
**1,3-diethynyl-7-*tert*-butylpyrene (3.25)**



To a solution of dialkyne diol (**3.24**) (2.5 g, 5.9 mmol) in toluene (75 mL) preheated to 80 °C, powdered NaOH (1.18 g, 29.6 mmol) was added. The reaction mixture was heated at reflux for 3 h then cooled to room temperature. The reaction mixture was poured into $H_2O$ (30 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to yield **3.25** as a orange solid (1.63 g, 90%): $R_f$ = 0.54 (20% ethyl acetate/hexanes); m.p. 190-193 °C;

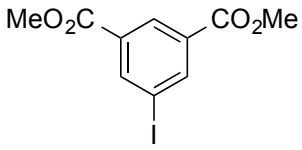
$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.51 (d, $J$ = 9.0 Hz, 2H), 8.30 (s, 1H), 8.28 (s, 2H), 8.17 (d, $J$ = 9.0 Hz, 2H), 3.59 (s, 2H), 1.59 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.95, 133.92, 132.53, 130.91, 129.70, 125.00, 124.06, 123.75, 122.01, 116.07, 82.75, 81.95, 35.32, 31.89; LCMS (APCI-positive) *m/z* 307 $[MH]^+$; HRMS (EI) calculated for $[M]^+$ $C_{24}H_{18}$ 306.1409, found 306.1408.

**Dimethyl-5-trifluoromethanesulfonateisophthalate (3.29)**



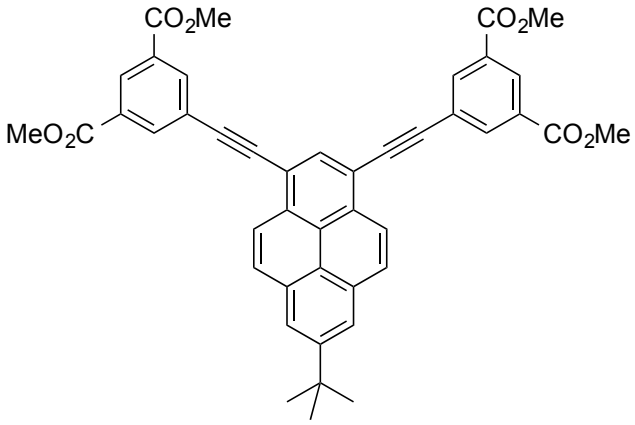

To a 0 °C solution of dimethyl-5-hydroxyisophthalate (5.00 g, 23.8 mmol) in $CH_2Cl_2$ (100 mL) was added pyridine (2.82 g, 2.60 mL, 35.7 mmol) followed by $Tf_2O$ (7.4 g, 4.43 mL, 26.2 mmol) dropwise via syringe. The solution was stirred at 0 °C for 30 minutes. The reaction mixture was poured into a 5% aqueous solution of HCl (30 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 25 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography ($CH_2Cl_2$) to yield **3.29** as a white solid (6.2 g, 76%): $R_f$ = 0.65 ($CH_2Cl_2$); m.p. 67-69 °C (lit. 68.5-69 C); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.70 (s, 1H), 8.12 (s, 2H), 3.99 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.33, 149.29, 133.10, 130.33, 126.53, 120.80, 52.93; LCMS (APCI-positive) *m/z* 343 $[MH]^+$.

**Dimethyl-5-iodoisophthalate (3.30)**



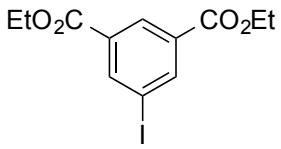

To a 0 °C suspension of 5-aminoisophthalic acid (1.75 g, 9.60 mmol) in $H_2O$ (5 mL) and a 10% aqueous solution of HCl (30 mL) was added $NaNO_2$ (701 mg, 10.16 mmol). The suspension was stirred at 0 °C for 1 h, after which KI (6.37 g, 38.4 mmol) was added portionwise over 10 minutes. The reaction mixture was gradually warmed to room temperature and stirred overnight. The suspension was collected by filtration and washed with cold $H_2O$ (50 mL) to afford crude 5-iodoisophthalic acid. The collected solid was dissolved in MeOH (50 mL) and $H_2SO_4$ (5 mL) and heated at reflux for 5 h. The solvent was removed *in vacuo* and redissolved in ethyl acetate (30 mL) and poured in $H_2O$ (30 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography ($CH_2Cl_2$) to yield **3.30** as a white solid (1.17 g, 67%): $R_f$ = 0.64 ($CH_2Cl_2$); m.p (); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.63 (s, 21H), 8.54 (s, 2H), 3.95 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.84, 142.49, 132.22, 129.90, 93.44, 52.68; LCMS (APCI-positive) *m/z* 321 $[MH]^+$

**Compound 3.33**



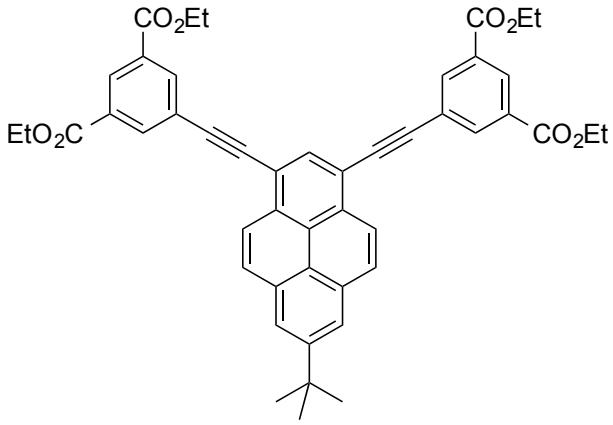

THF (10 mL) and $Et_3N$ (10 mL) were purged with $N_2$ for 10 minutes, after which dimethyl-5-iodoisophthalate (**3.30**) (100 mg, 0.33 mL) and dialkyne **3.25** (262 mg, 0.82 mmol) were added. The reaction mixture was stirred under a $N_2$ atmosphere for 5 minutes. $PdCl_2(PPh_3)_2$ (2 mg, 0.0033 mmol) and CuI (1 mg, 0.0066 mmol) were added. The reaction mixture was stirred at room temperature overnight. The bright yellow precipitate was collected by filtration and washed with MeOH (30 mL)to yield **3.33** (133 mg, 71%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.69 (t, $J$ = 1.6 Hz, 2H), 8.60 (d, $J$ = 9.1 Hz, 2H), 8.54 (d, $J$ = 1.6 Hz, 4H), 8.44 (s, 1H), 8.33 (s, 2H), 8.24 (d, $J$ = 9.1 Hz, 2H), 4.01 (s, 12H), 1.61 (s, 9H).

**Diethyl-5-iodoisophthalate (3.34)**



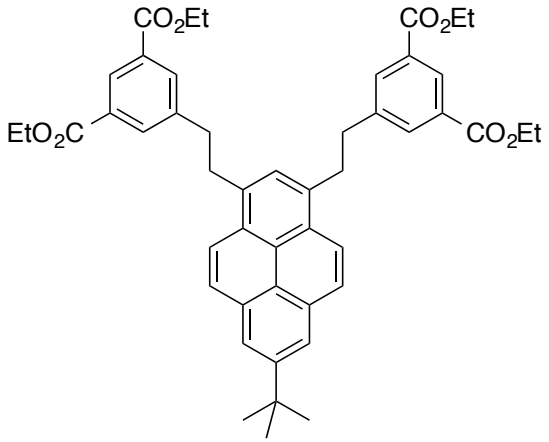

To a 0 °C suspension of 5-aminoisophthalic acid (1.75 g, 9.60 mmol) was suspended in $H_2O$ (5 mL) and a 10% aqueous solution of HCl (30 mL), $NaNO_2$ (701 mg, 10.16 mmol) was added. The reaction mixture was stirred for 1 h, after which KI (6.37 g, 38.4 mmol) was added portionwise over 10 minutes. The reaction mixture was gradually allowed to warm to room temperature and stirred overnight. The suspension was collected by filtration and washed with cold $H_2O$ (50 mL) to afford crude 5-iodoisophthalic acid. The collected solid was dissolved in EtOH (50 mL) and $H_2SO_4$ (5 mL) and heated to reflux for 5 h. The solvent was removed *in vacuo* and redissolved in ethyl acetate (50 mL). The reaction mixture was poured into $H_2O$ (30 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography ($CH_2Cl_2$) to yield **3.34** as a white solid (2.51 g, 75%): $R_f$ = 0.60 ($CH_2Cl_2$); m.p. ; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.63 (s, 1H), 8.53 (s, 2H), 4.40 (q, $J$ = 7.3 Hz, 4H), 1.41 (t, $J$ = 7.3 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.39, 142.32, 132.54, 129.89, 93.39, 61.76, 14.31; LCMS (APCI-positive) $m/z$ 349 $[MH]^+$.

**Compound 3.35**




THF (30 mL) and $Et_3N$ (30 mL) were purged with $N_2$ for 10 minutes, after which diethyl-5-iodoisophthalate (**3.34**) (2.00 g, 2.74 mmol) and dialkyne **3.25** (840 mg, 2.74 mmol) were added. The reaction mixture was stirred under a $N_2$ atmosphere for 5 minutes. $PdCl_2(PPh_3)_2$ (10 mg, 0.027 mmol) and CuI (10 mg, 0.055 mmol) were added. The reaction mixture was stirred at room temperature 4 h. The bright yellow precipitate was collected by suction filtration. The residue was purified by column chromatography ($CHCl_3$) to yield **3.35** as a bright yellow solid (1.55 g, 75%); $R_f$ = 0.42 (20% ethyl acetate/hexanes); m.p. 292-295 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.70 (t, $J$ = 1.7 Hz, 2H), 8.62 (d, $J$ = 9.0 Hz, 2H), 8.55 (d, $J$ = 1.7 Hz, 4H), 8.47 (s, 1H), 8.34 (s, 2H), 8.25 (d, $J$ = 9.0 Hz, 2H), 4.47 (q, $J$ = 7.2 Hz, 8H), 1.59 (s, 9H), 1.46 (t, $J$ = 7.2 Hz, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.25, 150.10, 136.44, 133.24, 132.16, 131.45, 131.03, 130.20, 129.86, 125.11, 124.33, 124.31, 123.97, 122.20, 116.64, 93.19, 89.64, 61.69, 35.35, 31.89, 14.38; LCMS (APCI-positive) *m/z* 747 $[MH]^+$.

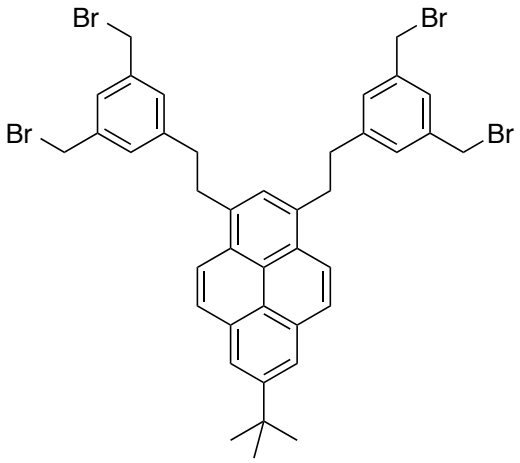
**Compound 3.36**




To an acid washed round-bottom flask was added a solution of **3.35** (1.00 g, 1.34 mmol) in THF (100 mL). The reaction mixture was purged with $N_2$ for 10 minutes. Pearlman's Catalyst $Pd(OH)_2$ (100 mg, 10 w/w) was added portionwise. The reaction mixture was stirred under a $H_2$ atmosphere for 4 h. The reaction vessel was evacuated and filled with $N_2$, then celite was added. The reaction mixture was suction filtered through a plug of celite, and washed with $CHCl_3$ (2 × 30 mL). The filtrate was concentrate under reduced pressure. The residue was purified by column chromatography (20% ethyl acetate/hexanes) to yield **3.36** as a light yellow solid (950 mg, 95%); $R_f$ = 0.49 (20% ethyl acetate/hexanes); m.p. 213-215 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.54 (t, $J$ = 1.6 Hz, 2H), 8.21 (d, $J$ = 9.1 Hz, 2H), 8.20 (s, 2H), 8.08 (d, $J$ = 1.6 Hz, 2H), 8.05 (d, $J$ = 9.1 Hz, 2H), 7.58 (s, 1H), 4.37 (q, $J$ = 7.1 Hz, 8H), 3.59 (m, 4H), 3.19 (m, 4H), 1.59 (s, 9H), 1.36 (t, $J$ = 7.1 Hz, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) (20 of 21 signals observes) $\delta$ 165.96, 149.04, 142.57, 134.58, 133.79, 131.05, 130.99, 128.51, 127.38, 127.21, 125.64, 123.59, 122.87, 122.24,

61.31, 37.69, 35.33, 31.91, 29.43, 14.31; LCMS (APCI-positive) *m/z* 754 $[MH]^+$, HRMS (EI) calculated for $[M]^+$ $C_{48}H_{50}O_8$ 754.3506, found 754.3503.

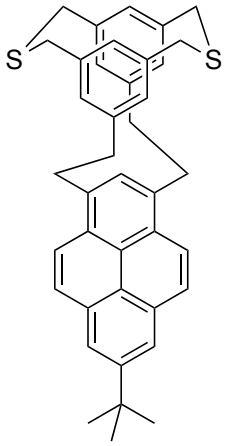
**Tetrabromide 3.38**




To a 0 °C of compound **3.36** (520 mg, 0.69 mmol) in dry $CH_2Cl_2$ (40 mL) and was added DIBAL (11.0 mL, 11.0 mmol) dropwise over a period 5 minutes under a $N_2$ atmosphere. The reaction mixture was gradually warmed the room temperature and stirred for 2 h. The reaction mixture was poured into a 6 M aqueous solution of HCl (30 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield tetraol **3.37** as a white solid (400 mg, quantitative). Crude teraol **3.37** was used without further purification. Crude **3.37** (400 mg, 0.68 mmol) was dissolved in dry $CH_2Cl_2$ (20 mL), to which $PBr_3$ (728 mg, 0.26 mL, 2.72 mmol) was added dropwise. The reaction mixture was stirred at room temperature under a $N_2$ atmosphere for 4 h. The reaction mixture was poured into $H_2O$ (25 mL). The layers were separated and the aqueous layer was extracted

with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (25% $CH_2Cl_2$/hexanes) to yield **3.38** as an off-white solid (412 mg, 72%); $R_f$ = 0.59(20% ethyl acetate/hexanes); m.p. (); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.19 (m, 4H), 8.03 (d, $J$ = 9.1 Hz, 2H), 7.43 (s, 1H), 7.26 (s, 2H), 7.13 (s, 4H), 4.42 (s, 8H), 3.55 (t, $J$ = 8.0 Hz, 4H), 3.05 (t, $J$ = 8.0 Hz, 4H), 1.58 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ ; LCMS (APCI-positive) $m/z$ 839 $[MH]^+$.

**Dithiacyclophane 3.39**




Tetrabromide **3.30** (180 mg, 0.21 mmol) was dissolved in 10% EtOH/$CH_2Cl_2$ (50 mL) and $Na_2S/Al_2O_3$ (372 mg) was added in one portion and the reaction mixture was stirred overnight at rt. The solution was filtered through a plug of silica with $CH_2Cl_2$ as eluent to yield **3.31** as an off-white solid (96 mg, 75%); $R_f$ = 0.42 (30% $CH_2Cl_2$/hexanes); m.p. (); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.28 (d, $J$ = 9.1 Hz, 2H), 8.22 (s, 2H), 8.07 (d, $J$ = 9.1 Hz, 2H), 7.13 (s, 2H), 7.03 (s, 2H), 6.54 (s, 4H), 3.67 (m, 12H), 3.12 (t, $J$ = 5.7 Hz, 4H), 1.61 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 148.80, 140.60,

137.02, 133.62, 131.00, 129.26, 128.72, 127.26, 126.85, 126.53, 123.31, 122.02, 39.03, 35.19, 34.61, 32.23, 31.97; LCMS (APCI-positive) *m/z* 583 $[MH]^+$; HRMS (EI) calculated for $[M]^+$ $C_{40}H_{38}S_2$ 582.2415, found 582.2413.

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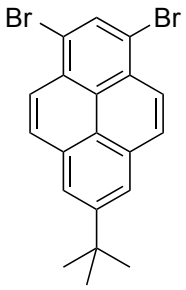
## Appendix 2


Br
Br


8.45
8.40
8.35
8.30
8.25
8.20
8.15
f1 (ppm)
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9.5
9.0
8.5
8.0
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3.5
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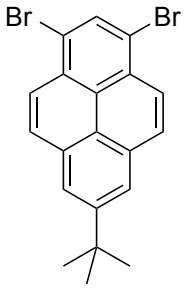
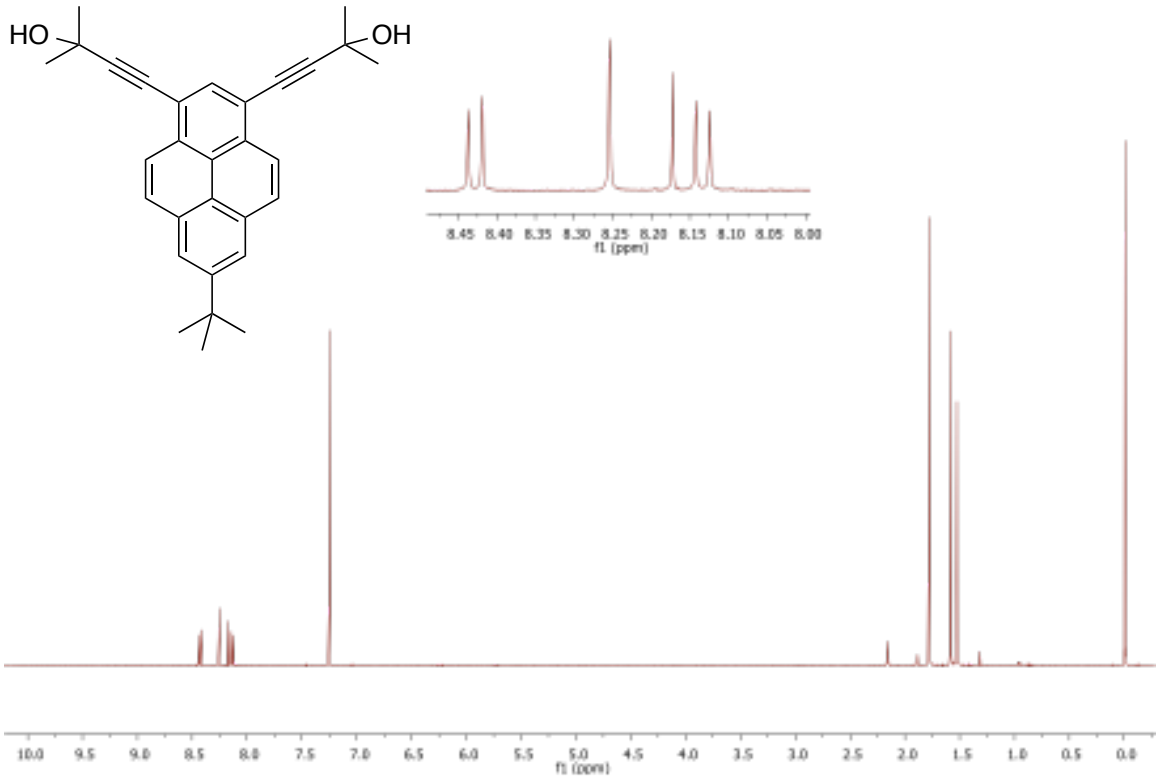
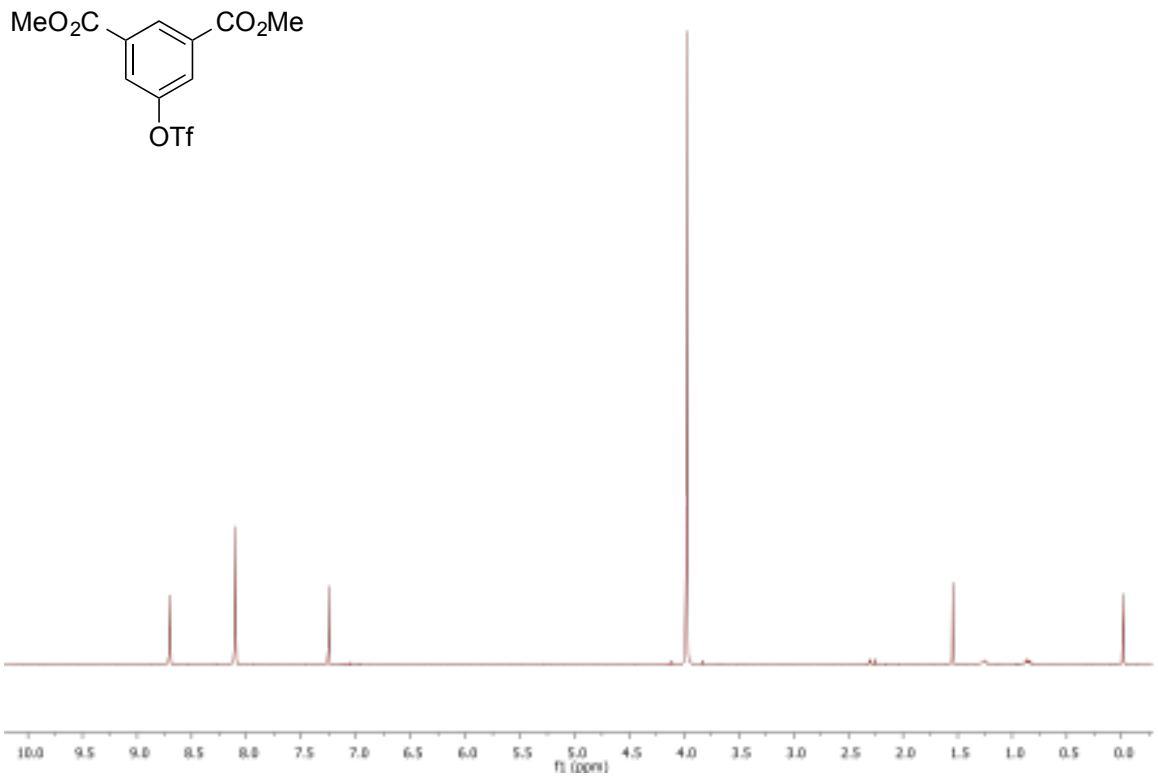
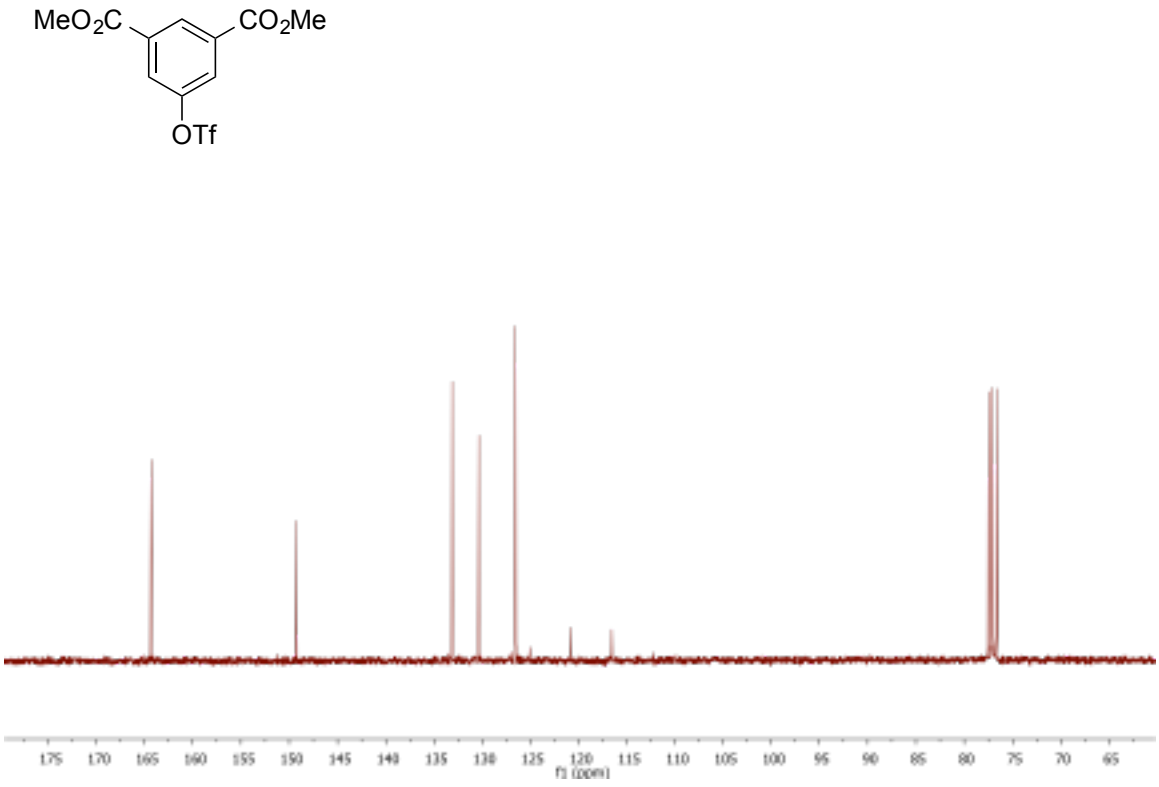
0.0
f1 (ppm)

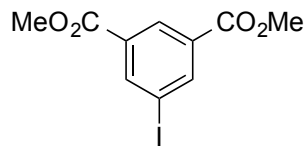

Br
Br

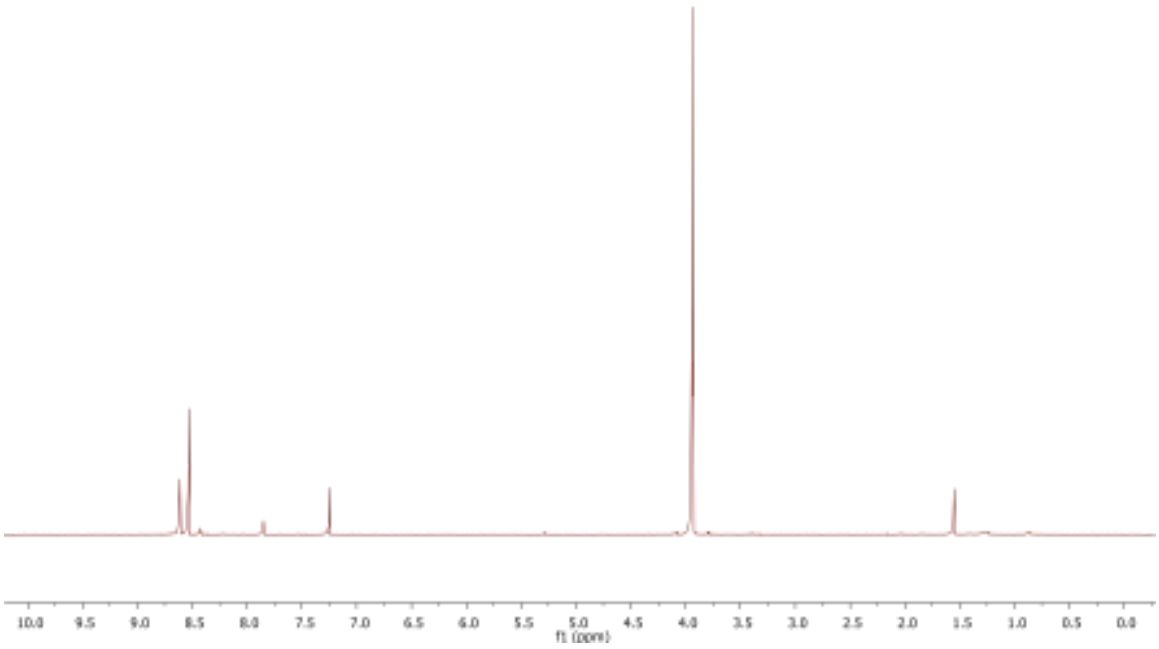

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

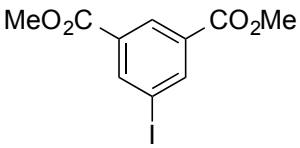

HO
OH
8.45 8.40 8.35 8.30 8.25 8.20 8.15 8.10 8.05 8.00
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


MeO2C
CO2Me
OTf
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)

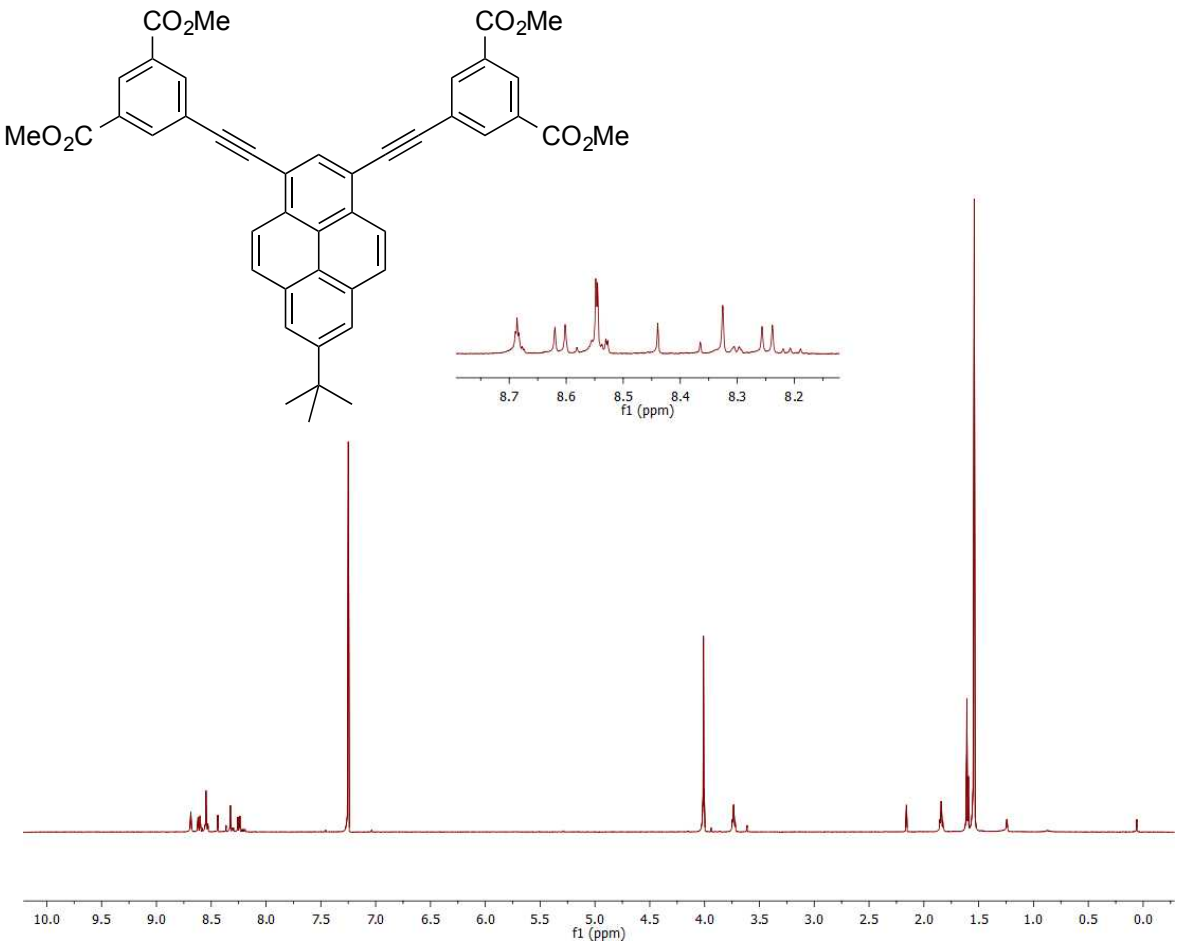

MeO2C
CO2Me
OTf
175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65
f1 (ppm)

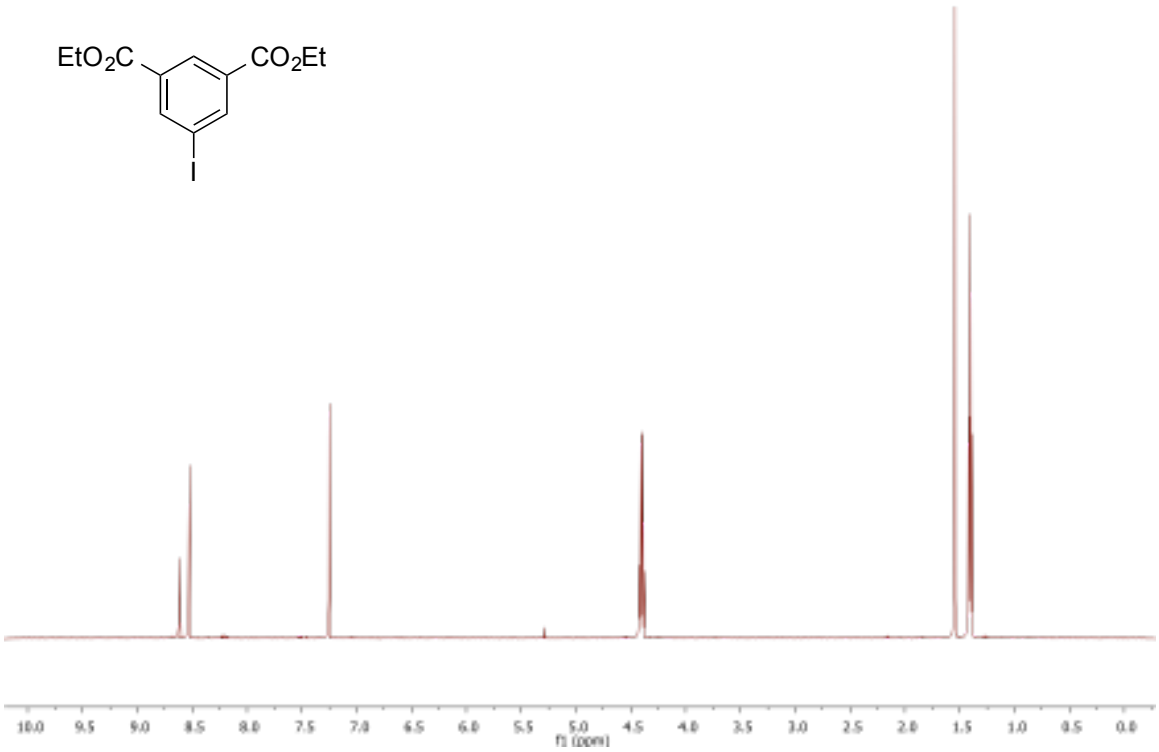

MeO2C
CO2Me
I

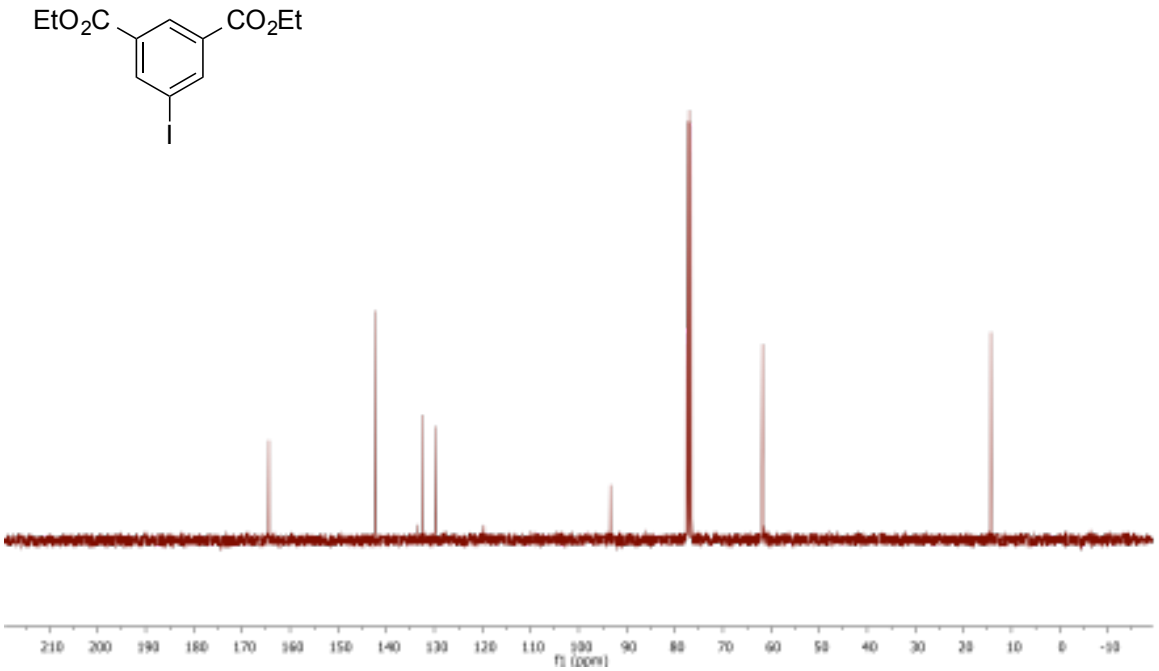

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

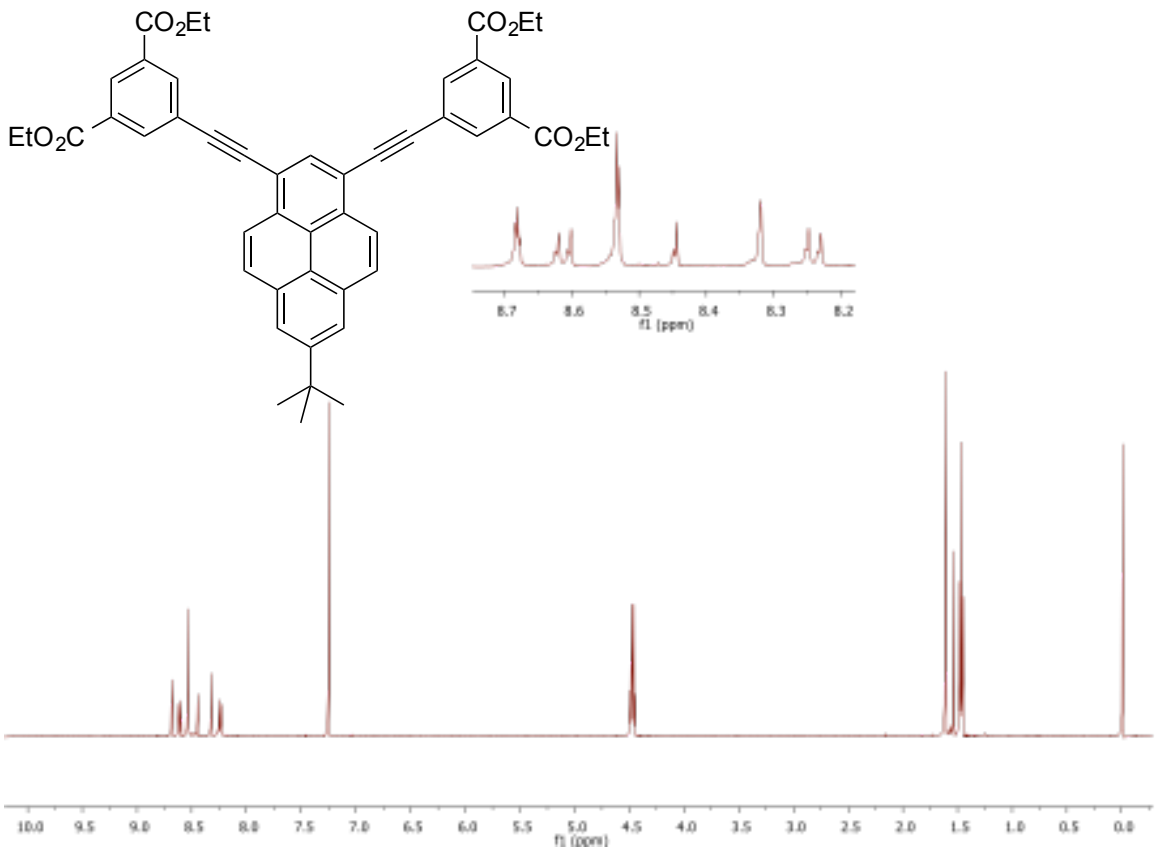

MeO2C
CO2Me
I

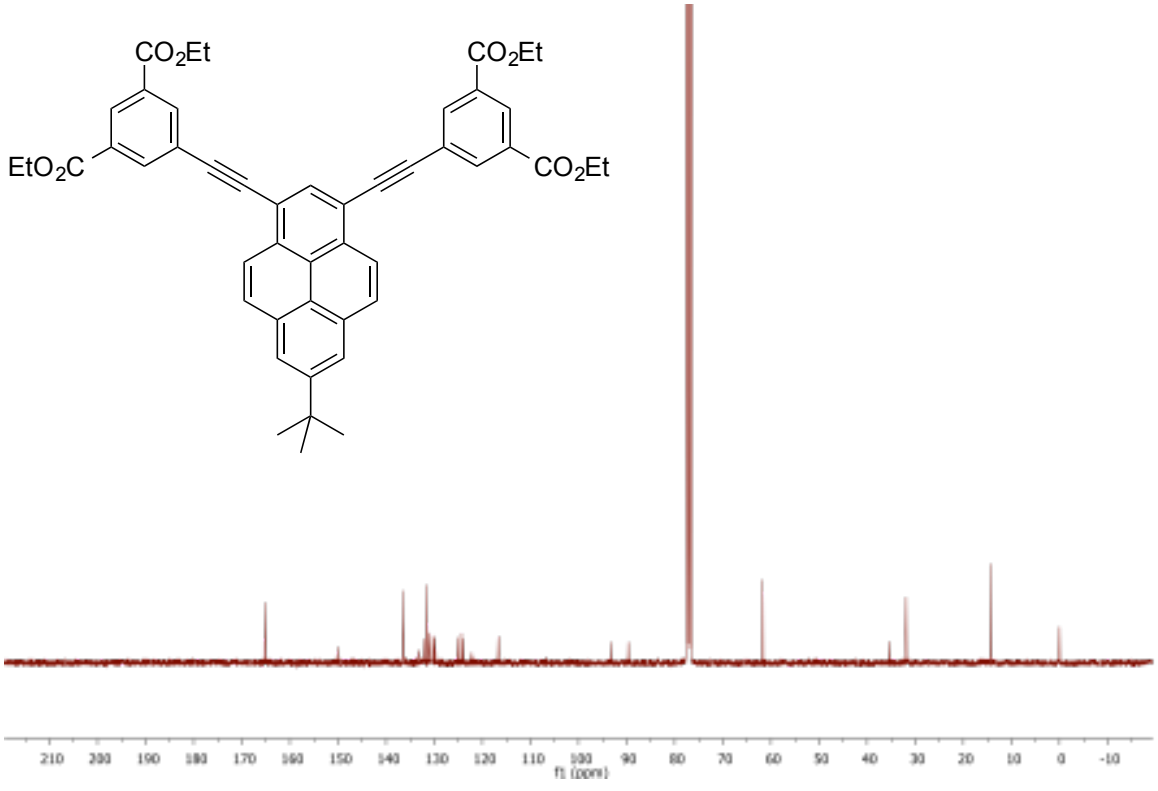

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

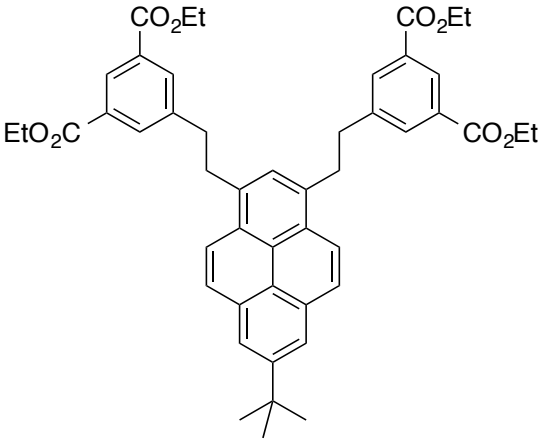

CO2Me
CO2Me
MeO2C
CO2Me
8.7
8.6
8.5
8.4
8.3
8.2
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

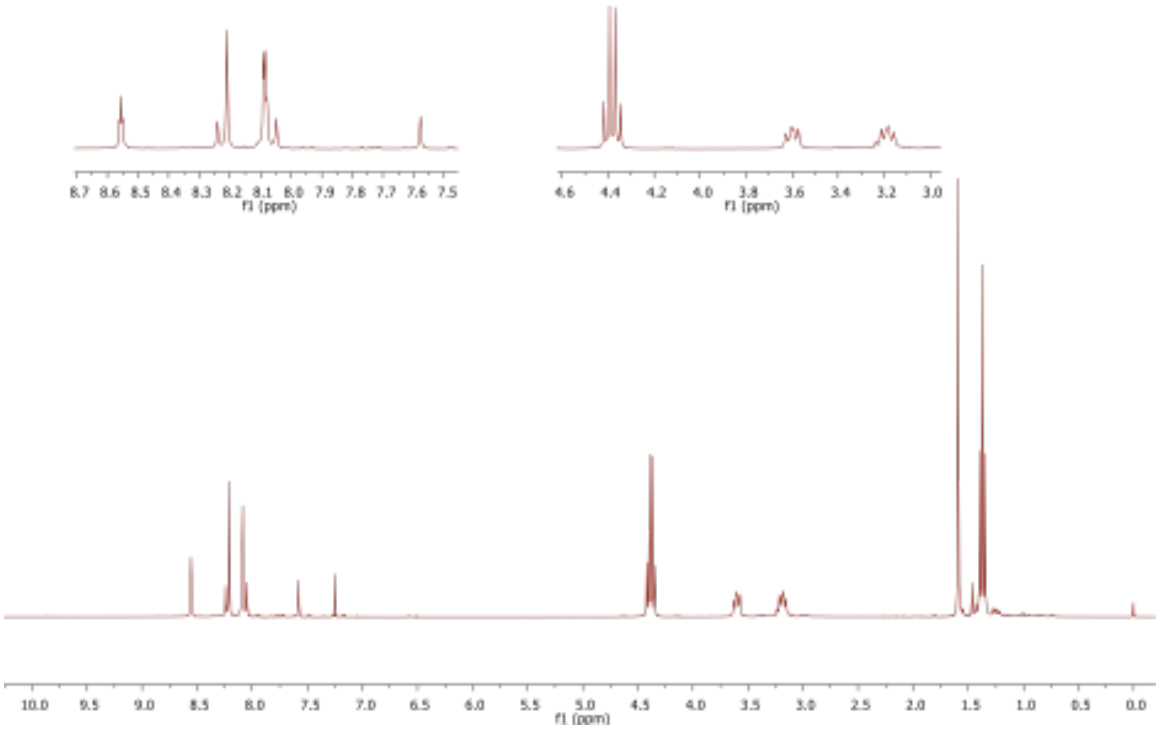

EtO2C
CO2Et
I
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

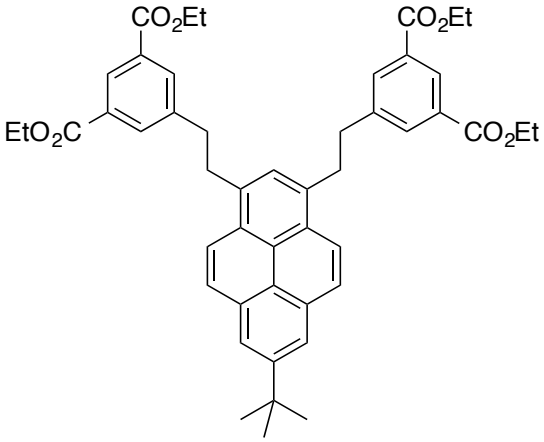

EtO2C
CO2Et
I
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

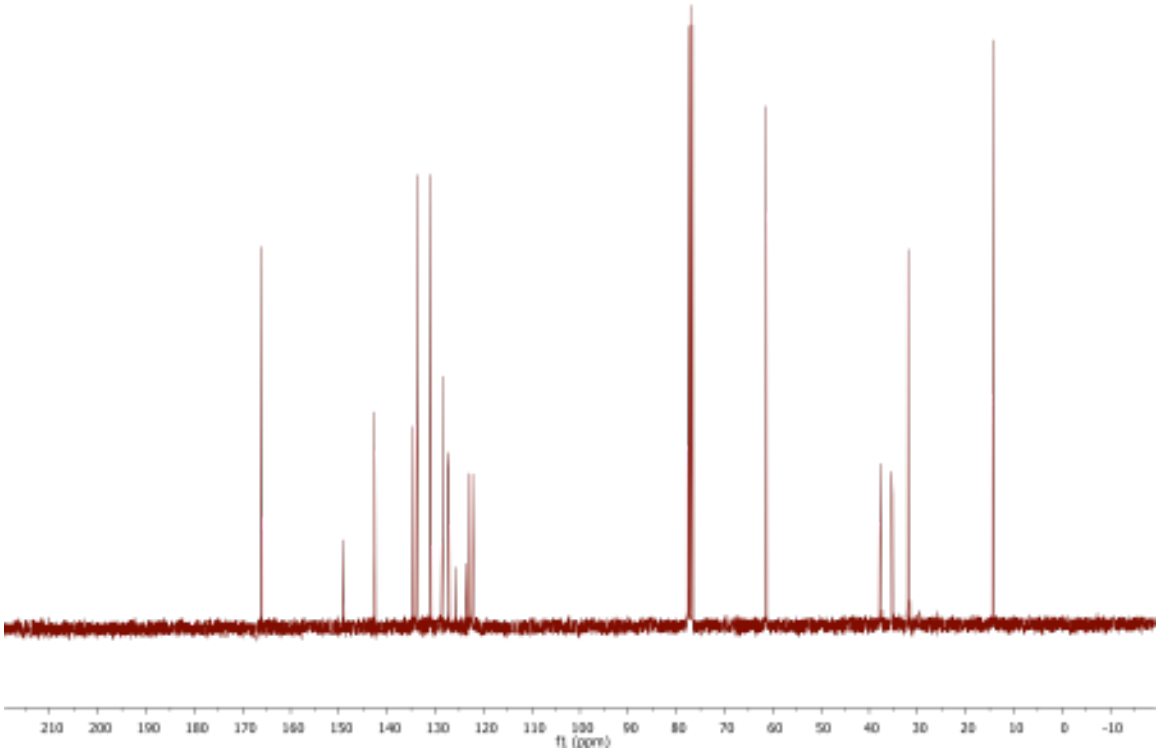

CO2Et
CO2Et
EtO2C
CO2Et
8.7
8.6
8.5
8.4
8.3
8.2
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

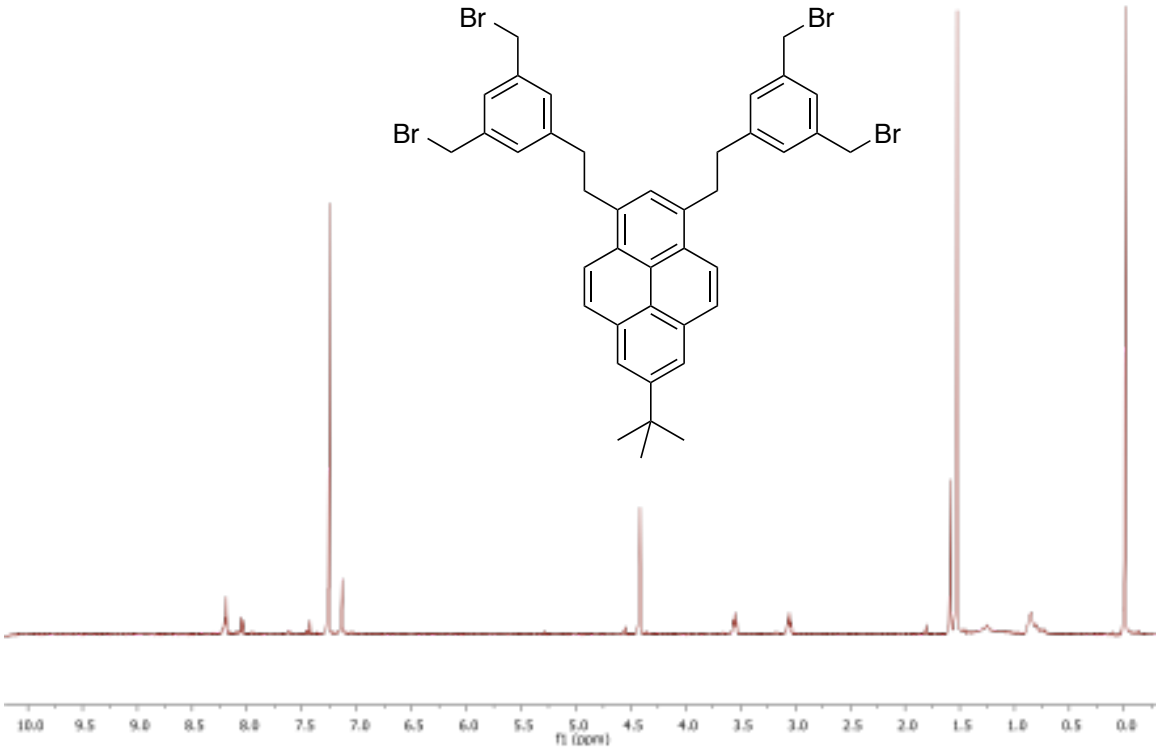

CO2Et
CO2Et
EtO2C
CO2Et
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

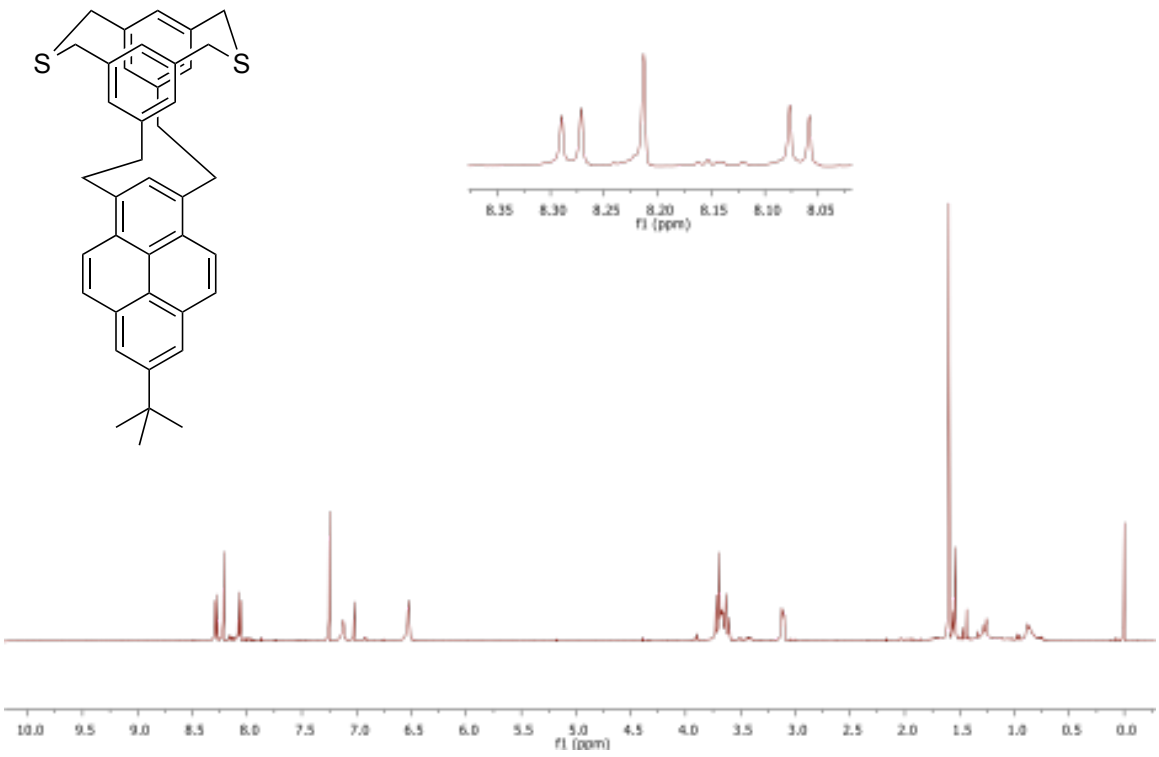

CO2Et
CO2Et
EtO2C
CO2Et

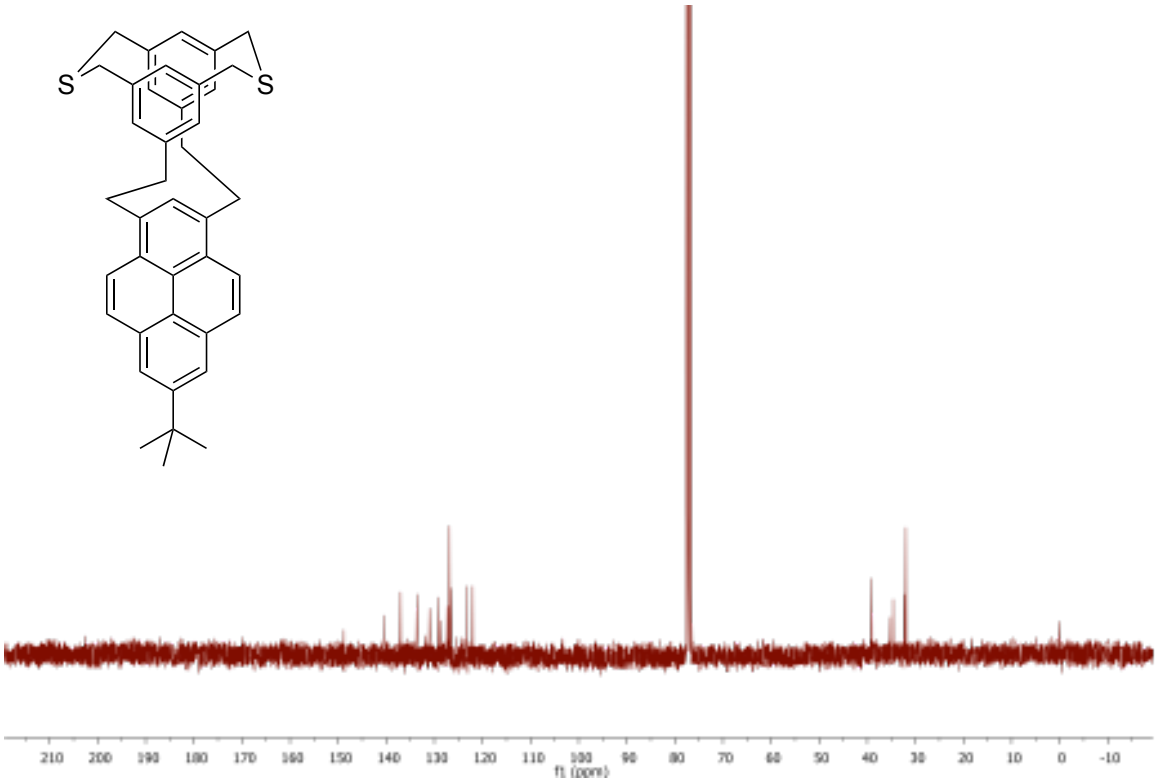

8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5
f1 (ppm)
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CO2Et
CO2Et
EtO2C
CO2Et


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)


Br
Br
Br
Br
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)


S
S
8.35
8.30
8.25
8.20
8.15
8.10
8.05
f1 (ppm)
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)


S
S
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)